SEVENTH EDITION

Rook's TEXTBOOK OF DERMATOLOGY

VOLUMES 1 - 4

EDITED BY

TONY BURNS • STEPHEN BREATHNACH
NEIL COX • CHRISTOPHER GRIFFITHS

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Rook's

Textbook of Dermatology

The Editors. From l to r, Tony Burns, Stephen Breathnach, Christopher Griffiths and Neil Cox standing in front of a portrait of Arthur Rook, the father of the *Textbook of Dermatology*.

Rook's Textbook of Dermatology

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Preface to the Seventh Edition

Over thirty years have passed since the first edition of *Textbook of Dermatology* was published under the leadership of Arthur Rook, Darrell Wilkinson and John Ebling.

Arthur Rook, a wise clinician with an encyclopaedic knowledge of medical literature, and a man of great linguistic talent and enormous energy, died in 1991 (see Preface to the fifth edition).

John Ebling, who continued as an editor to the fifth edition, died in 1992. He occupied a unique position in British dermatology, as a full-time Professor of Zoology, a distinguished research worker and a man of enormous erudition and editorial skills. His breadth of knowledge covered the whole of biology and we owe him a great debt for his tremendous and untiring work over 25 years on this textbook.

The fifth edition, published in 1992, was edited by Champion, Burton and Ebling, with invaluable advice from Darrell Wilkinson. Bob Champion and John Burton continued to lead the editorial team into the sixth edition, published in 1998, and we are indebted to them for their expertise and dedicated hard work for many years.

For this seventh edition, Tony Burns and Stephen Breathnach have been joined by two new editors, Neil Cox and Christopher Griffiths. As always, we would all like to express our gratitude to the three original editors who laid the foundations and provided a framework upon which this book has developed through subsequent editions.

Our aim is to continue to provide a comprehensive reference guide to all recognized dermatological diseases, and to encourage understanding and development of scientific aspects of dermatology, although the book is not intended to provide details of research in the basic sciences.

For this edition, every chapter has been updated, and several have been completely rewritten. There are several new contributors, and a new chapter on AIDS and the skin is a reflection of the impact this disease has had in recent years. We would like to acknowledge our indebtedness to contributors to earlier editions, who have generously allowed some of their original material to be retained for the present edition.

We are also very grateful to all those colleagues who have donated colour photographs, and the origin of these is given in the legend to each figure. Where no acknowledgement is given the figures have been provided by the authors of that chapter.

Our wives and families deserve our thanks for their forbearance and support over many years.

We should also like to thank the staff of Blackwell Publishing for their efforts throughout the production of this edition, in particular Rupal Malde, Nick Morgan, Katrina Chandler and Stuart Taylor. We are once again extremely grateful to Caroline Sheard for her excellent index. Her index for the sixth edition deservedly won the Wheatley Prize (1998). Our heartfelt thanks also go to the team of copy editors and proof readers who, in deciphering and analysing reams of verbiage, are the ultimate refiners of these four volumes.

D.A. Burns
S.M. Breathnach
N.H. Cox
C.E.M. Griffiths

Preface to the First Edition

No comprehensive reference book on dermatology has been published in the English language for ten years and none in England for over a quarter of a century. The recent literature of dermatology is rich in shorter texts and in specialist monographs but the English-speaking dermatologist has long felt the need for a substantial text for regular reference and as a guide to the immense monographic and periodical literature. The editors have therefore planned the present volume primarily for the dermatologist in practice or in training, but have also considered the requirements of the specialist in other fields of medicine and of the many research workers interested in the skin in relation to toxicology or cosmetic science.

An attempt has been made throughout the book to integrate our growing knowledge of the biology of skin and of fundamental pathological processes with practical clinical problems. Often the gap is still very wide but the trends of basic research at least indicate how it may eventually be bridged. In a clinical textbook the space devoted to the basic sciences must necessarily be restricted but a special effort has been made to ensure that the short accounts which open many chapters are easily understood by the physician whose interests and experience are exclusively clinical.

For the benefit of the student we have encouraged our contributors to make each chapter readable as an independent entity, and have accepted that this must involve the repetition of some material.

The classification employed is conventional and pragmatic. Until our knowledge of the mechanisms of disease is more profound no truly scientific classification is possible. In so many clinical syndromes multiple aetiological factors are implicated. To emphasize one at the expense of others is often misleading. Most diseases are to some extent influenced by genetic factors and a large proportion of common skin reactions are modified by the emotional state of the patient. Our knowledge is in no way advanced by classifying hundreds of diseases as genodermatoses and dozens as psychosomatic.

The true prevalence of a disease may throw light on its aetiology but reported incidence figures are often unreliable and incorrectly interpreted. The scientific approach to the evaluation of racial and environmental factors has therefore been considered in some detail.

The effectiveness of any physician in practice must ultimately depend on his ability to make an accurate clinical diagnosis. Clinical descriptions are detailed and differential diagnosis is fully discussed. Histopathology is here considered mainly as an aid to diagnosis but references to fuller accounts are provided.

The approach to treatment is critical but practical. Many empirical measures are of proven value and should not be abandoned merely because their efficacy cannot yet be scientifically explained. However, many familiar remedies old and new have been omitted either because properly controlled clinical trials have shown them to be of no value or because they have been supplanted by more effective and safer preparations.

There are over nine hundred photographs but no attempt has been made to provide an illustration of every disease. To have done so would have increased the bulk and price of the book without increasing proportionately its practical value. The conditions selected for illustrations are those in which a photograph significantly enhances the verbal description. There are a few conditions we wished to illustrate, but of which we could not obtain unpublished photographs of satisfactory quality.

The lists of references have been selected to provide a guide to the literature. Important articles now of largely historical interest have usually been omitted, except where a knowledge of the history of a disease simplifies the understanding of present concepts and terminology. Books and articles provided with a substantial bibliography are marked with an asterisk.

Many of the chapters have been read and criticized by several members of the team and by other colleagues. Professor Wilson Jones, Dr R.S. Wells and Dr W.E. Parish have given valuable assistance with histopathological, genetic and immunological problems respectively. Many advisers, whose services are acknowledged in the following pages, have helped us with individual chapters. Any errors which have not been eliminated are, however, the responsibility of the editors and authors.

The editors hope that this book will prove of value to all those who are interested in the skin either as physicians or as research workers. They will welcome readers' criticisms and suggestions which may help them to make the second edition the book they hope to produce.

Chapter 1

Introduction and Historical Bibliography

D.A. Burns & N.H. Cox

What is dermatology?

Dermatology is defined in the *New Oxford Dictionary of English* as 'The branch of medicine concerned with the diagnosis and treatment of skin disorders' [1]. However, dermatologists do not confine themselves merely to a study of intrinsic disorders of the skin, but must also study internal medicine and the many environmental and occupational factors that so frequently cause skin problems.

A plethora of external factors, including numerous chemicals, can adversely affect the skin in some circumstances. The clinical dermatologist must be knowledgeable about these potential hazards, and this will often require a detailed study of the multiplicity of chemicals, plants, animals, parasites, microorganisms, radiation, climatic conditions, etc., to which the skin is exposed. In many cases, the dermatologist will need to obtain exact details of what is involved in the patient's occupation and hobbies, and many dermatologists build up a considerable knowledge of the different jobs involved in their local industries.

The dermatologist must also have a good knowledge of internal medicine, as most systemic diseases can occasionally affect the skin, either directly or as a result of a complication of the disease or its treatment. Drugs taken by the patient have to be considered by the dermatologist, because the unwanted effects of many drugs include provocation of rashes. This applies not only to prescribed medication, but also to over-the-counter and 'complementary' remedies.

A dermatologist must also pay attention to the psyche, as psychological factors play an important part in dermatology. The skin is of major importance in our 'body image', and the fact that skin diseases are often regarded with revulsion by the general population adds to the distress they cause, so that the psychological disturbance induced by skin problems may be out of all proportion to their 'medical' significance. Sometimes, these psychological problems are exacerbated by the reactions of the patient's relatives, friends or colleagues, and in other cases they are partly accounted for by feelings of guilt or despondency, induced by the belief that skin diseases are due to 'uncleanliness' of some kind (with or without sexual overtones). In recent years, there has been increasing awareness of the impact of skin diseases on social and leisure activities, work and sexual relationships, and questionnaires such as the Dermatology Life Quality Index (DLQI) have been employed to measure the impairment of quality of life (see Chapter 71). In addition, skin diseases not only cause stress or depression, but psychological stress from another cause can exacerbate, or even be involved in causation of, some skin diseases.

Whatever the complexity of these psychological nuances, the dermatologist must be aware of their existence and try to deal with them accordingly. As described later (Chapter 61), some patients have 'skin problems' that are imagined or self-inflicted, and the presentation to the dermatologist seems to be a 'cry for help' with marital or other social problems. In other cases, the dermatological consultation may be a manifestation of an underlying psychological disease such as depression or schizophrenia.

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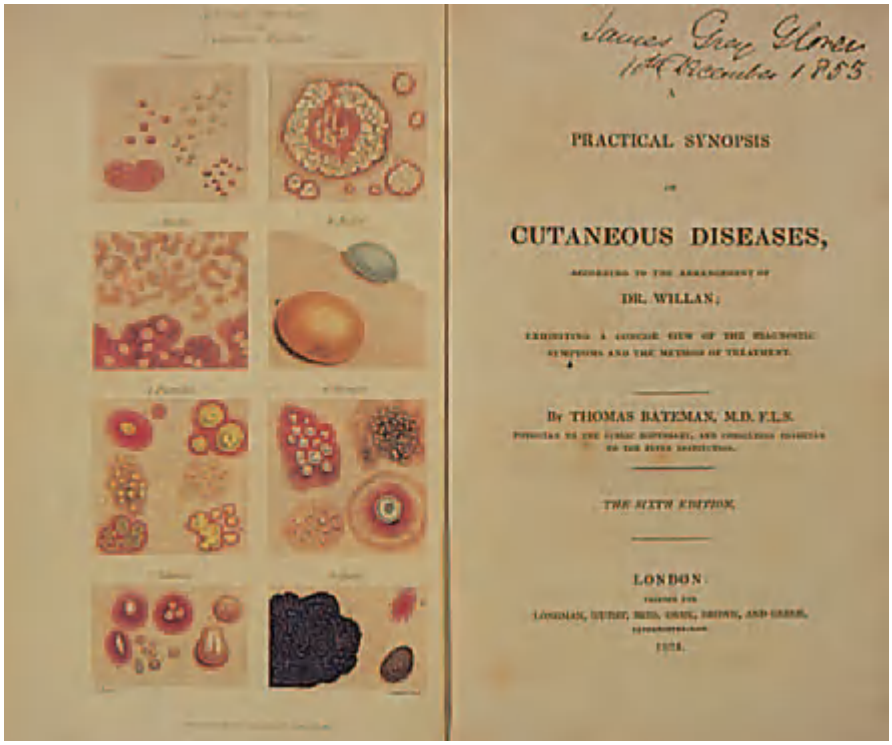
The evolution of dermatology

Skin diseases predate written records, and many of the earliest medical writings deal with dermatological subjects. The history of dermatology is too large a subject to be covered in this book, although a selected historical bibliography is given at the end of this chapter. The development of modern dermatology is briefly outlined below.



PRACTICAL SYNOPSIS

OF

CUTANEOUS DISEASES,

ARRANGED ACCORDING TO THE ARRANGEMENT OF

DR. WILLAN;

EXHIBITING A CONCISE VIEW OF THE DIAGNOSTIC SYMPTOMS AND THE METHOD OF TREATMENT.

By THOMAS BATEMAN, M.D. F.L.S.

THE SIXTH EDITION.

LONDON:

Fig. 1.1 The title page and facing plate from the 6th edition (1824) of Thomas Bateman's *Practical Synopsis of Cutaneous Diseases, According to the Arrangement of Dr Willan*. The plate shows the eight orders of cutaneous eruption in Willan's classification.

Dermatology evolved as a branch of internal medicine during the 19th century. Previously, many diseases of the skin had fallen within the province of the quack or the surgeon, and indeed many of the older surgical textbooks devote much attention to the treatment of skin disease. The physicians of that time were little concerned with the skin, apart from the eruptions of the acute infectious fevers. In the early 18th century, individuals such as Daniel Turner advocated use of preparations applied to the skin as treatment for internal diseases. During the last decades of the 18th century, however, many of the great physicians began to record their observations on the diseases of the skin, and this continued throughout the 19th century. Towards the end of that century, skin diseases, particularly the chronic infections such as syphilis and tuberculosis, formed a significant part of the general physician's practice, and by the beginning of the 20th century some physicians were beginning to specialize in dermatology. This trend towards increasing specialization has continued ever since.

In the first half of the 20th century, dermatology was slow to develop along scientific lines. The emphasis was very much on the clinical description, naming and classification of the numerous skin disorders, and this led to a profusion of synonyms, which are daunting to those attempting to get to grips with dermatological nomenclature. Only empirical treatment was available, and it was often ineffective, messy and malodorous. Dermatology certainly lagged behind some of the other medical specialties in its understanding of basic disease processes. In retrospect, this seems to have been due to two main factors. The first was that most skin diseases could be identified by external examination alone, and therefore seemed to need no further investigation. The second and perhaps more important factor was that most skin diseases could not be investigated by the relatively crude tests that were available at that time. It was only when skin biopsy became a standard technique, with the plethora of pathological knowledge that followed, that an understanding of the pathogenesis of many skin diseases began to emerge.

In the second half of the 20th century, there was an explosion of dermatological knowledge, mainly as a result of the introduction of sophisticated research techniques which not only led to a better knowledge of the pathogenesis and treatment of skin disorders, but also facilitated the development of more targeted treatments. More recently, the techniques of molecular biology have also been applied (Chapter 8), leading to, amongst other things, important developments in genetics and the understanding of mechanisms underlying cancer. As a result, increasing numbers of non-medical scientists are studying the skin, and its accessibility, which paradoxically inhibited investigation in the first half of the 20th century, is now of course very helpful to the research worker.

Dermatological treatment patterns have changed over the last 50 years, and will no doubt continue to do so. Recent advances in treatment include topical immunosuppressants, immune response modifiers and biological therapies for psoriasis. Further sophistication in treatment

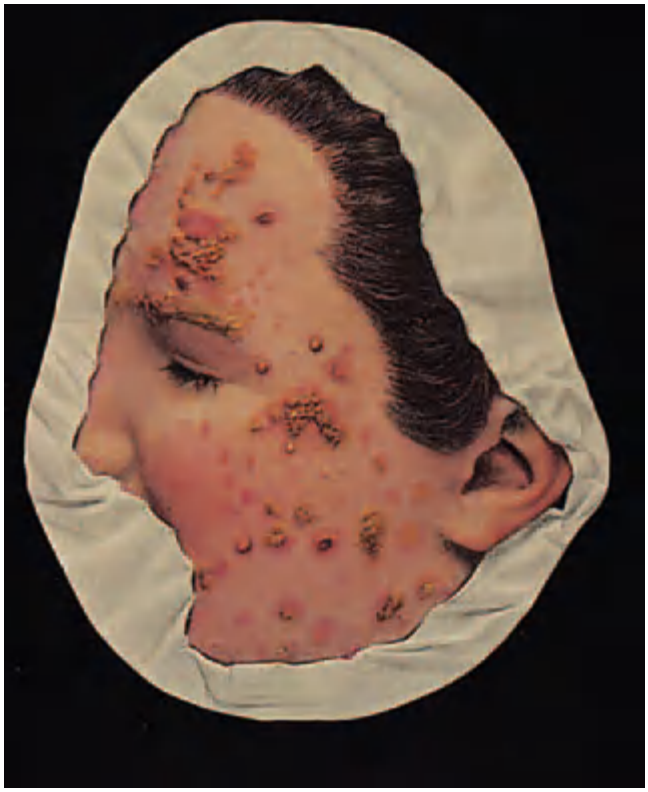


Fig. 1.2 Impetigo contagiosa, from the *Portfolio of Dermochromes* by Professor Jacobi (1903). The English adaptation of the text was performed by J.J. Pringle of the Middlesex Hospital. The majority of the illustrations were of models in the Breslau Clinic.

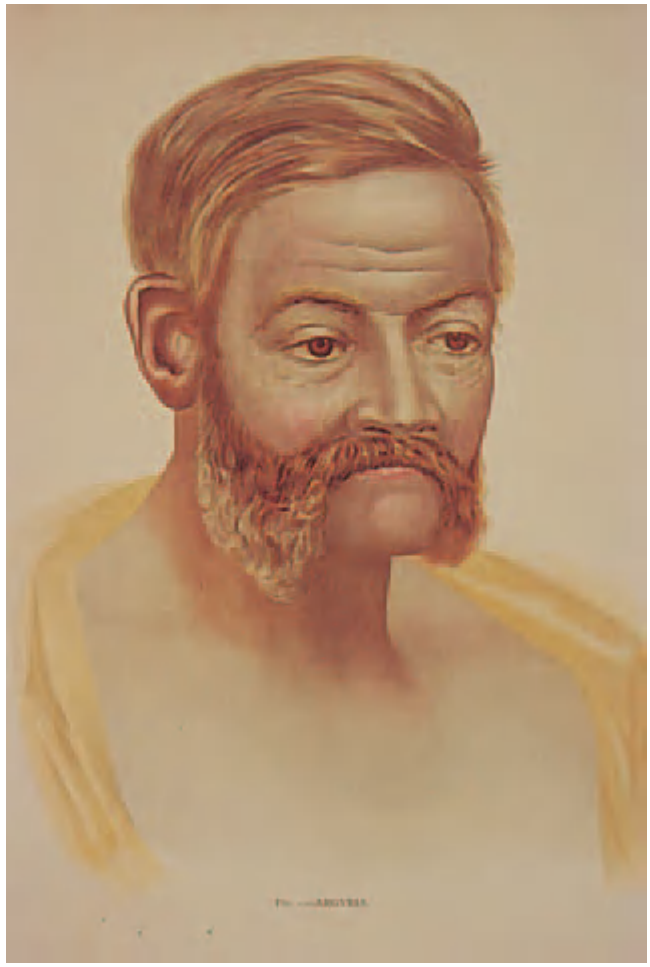


Fig. 1.3 Argyria, from Radcliffe Crocker's *Atlas of Diseases of the Skin*. Henry Radcliffe Crocker (1845–1909), physician to the skin department of University College Hospital, London, made a number of important contributions to clinical dermatology, and was also a pioneer in skin microscopy and the therapeutic use of radium. His textbook *Diseases of the Skin* and the *Atlas of Diseases of the Skin* contributed to his reputation as one of the leading dermatologists of his day.

should parallel increasing knowledge of the roles of inflammatory mediators in disease. Some older treatment modalities, such as radiotherapy, are used much less.

Dermatology is thus changing at an ever-accelerating pace, both in the amount of scientific knowledge and treatments available, and with regard to disease patterns and patients' expectations. Increasing specialization within dermatology is becoming more common, with the expansion of expertise in dermatological surgery, laser therapy, chemosurgery, photobiology, contact allergy, genetic counselling, histopathology, etc. Certainly, dermatologists can no longer be regarded only as general physicians with an interest in the skin, although some training in internal medicine is still regarded as desirable in most countries. In the UK, trainee dermatologists are expected to have completed a minimum of 2 years of general professional training and to have passed a postgraduate examination in general medicine (Membership of the Royal College of Physicians, MRCP) before they can start their specialist training in dermatology. The specialist training entails 4 years in an approved training post, with an annual assessment of progress, on satisfactory completion of which the trainee is awarded a Certificate of Completion of Specialist Training (CCST).

It seems possible that the days of the generalist dermatologist are numbered. Future dermatologists will perhaps regard themselves as dermatological physicians, surgeons or researchers and train accordingly. The future cannot be predicted, but it seems certain that with the increasing sophistication of populations throughout the world, the demand for dermatological expertise is likely to increase.

The dermatologist's work

There are probably at least 2000 different skin conditions that might present to the dermatologist, and most dermatologists treat patients of all ages, from the neonate to the very old.

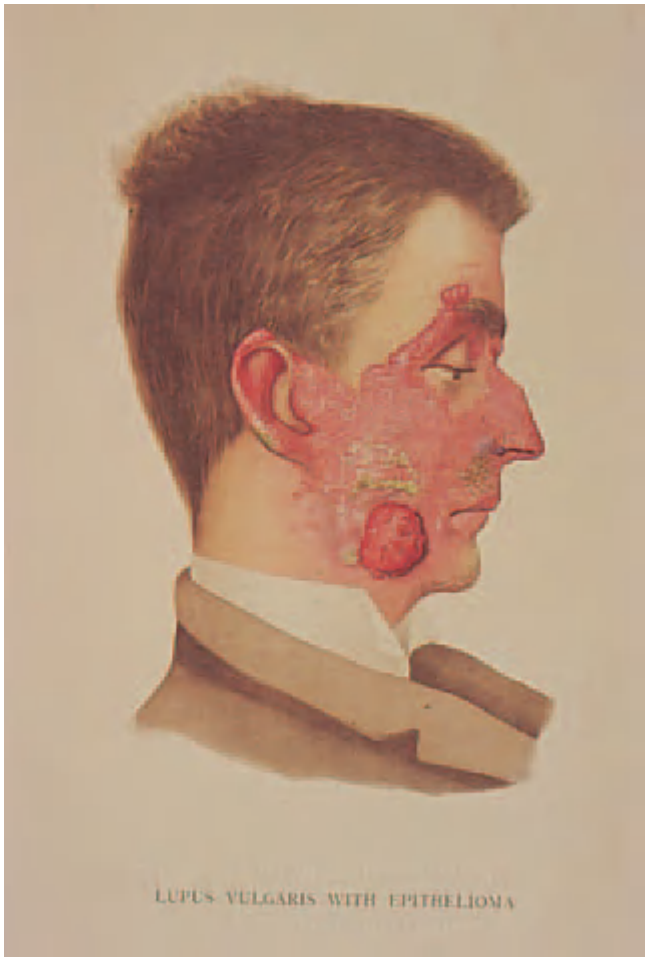


Fig. 1.4 Lupus vulgaris with epithelioma, from Crocker's *Atlas*.

The conditions seen vary enormously in severity. They range from cosmetic problems, such as dry skin or wrinkles, through a huge variety of acute or chronic diseases, which may be disfiguring, itchy or painful, but are rarely fatal, to life-threatening conditions, which, if untreated, may prove fatal within days (e.g. toxic epidermal necrolysis), weeks (e.g. pemphigus), months (e.g. malignant melanoma) or years (e.g. cutaneous lymphoma). In the UK, about 70% of consultations for dermatological problems are related to skin cancer, acne, psoriasis, viral warts and other infections, benign tumours, leg ulcers and various forms of dermatitis [1].

Obviously, the pattern of disease varies from one country to another, and even in the same city the work of dermatologists will differ, depending on their particular interests and expertise and on the social mix of their patients. Involvement with cosmetic procedures, in particular, varies according to the constraints of the health care system in which the dermatologist works.

Space precludes any detailed consideration of the work of dermatologists throughout the world, but in the British system patients are normally first seen by a primary care physician (general practitioner, GP) who refers the patient to the hospital consultant if he or she thinks it necessary or advisable. It has been estimated that around one in seven primary care consultations relates to a dermatological problem [2]. In a semirural practice in Cornwall, England, 21% of patients seen in a 5-year period by one GP had a dermatological diagnosis [3], and the most common skin diseases seen were viral warts, eczema and benign tumours. In another survey of GPs in the Bristol area of the UK, 47% of those replying to a questionnaire managed nearly all skin problems themselves in primary care [4]. The hospital dermatology services are provided by consultant dermatologists and their supporting staff. In the UK at present, each consultant is responsible for a population of around 200 000 persons, although the British Association of Dermatologists recommends a ratio of one consultant per 85–100 000 to cope with the need for specialist advice. About 12.5 people/1000 population are referred to a hospital dermatology department annually [1].

Other countries have different systems and services. In the USA, there is a ratio of 3.3 dermatologists for every 100 000 persons, although there is considerable interstate and intrastate variation in this ratio [5]. For example, it is 1/100 000 in Alaska and 3.9/100 000 in California, and within California varies from 1.26/100 000 in Fresno to 7.66/100 000 in San Francisco. There is continuing concern about provision of an adequate number of trained dermatologists to satisfy increasing demand, and that an increase in the number of dermatologists specializing in surgical and cosmetic procedures might lead to a shortage of those dealing with 'medical' dermatology patients [5–8]. It is also important that planning should take account of the high proportion of women in dermatology, and of the changing roles of nursing staff [9]. There are, of course, other countries from which dermatologists are conspicuously absent.

Many skin diseases, for example warts, acne vulgaris or psoriasis, can be quickly diagnosed by their clinical features, and need little or no further investigation. At the other extreme, there are some patients—for example, those with lymphoma—who need detailed and time-consuming investigations both to confirm the diagnosis and as a basis for treatment.

The most common investigations performed in a dermatology clinic, other than simple blood tests or swabs for microbiology, are skin biopsies. Other investigations include the extraction and identification of scabies mites, the microscopic examination of hairs, patch testing and photo-patch testing (Chapter 20). In occasional cases, special procedures may be needed, such as the examination of pets for animal parasites, or a visit to the patient's workplace or home to search for possible allergens.

The management of this infinite variety of skin disorders ranges from simple reassurance and explanation

Fig. 1.5 Discoid lupus, from Crocker's *Atlas*.

through the gamut of topical and systemic remedies, to the performance or supervision of numerous physical procedures such as ultraviolet irradiation, photochemotherapy, curettage and cautery, surgical excision and laser treatment. Some dermatologists will also undertake complicated and specialized techniques such as prenatal investigation and Mohs micrographic surgery, which may require close collaboration with other specialists, and newer techniques such as photodynamic therapy are finding a niche in the dermatologist's armamentarium.

In addition to this clinical workload in the hospital, UK dermatologists also sometimes undertake 'domiciliary' visits to assess and treat at home patients who for one reason or another cannot attend hospital. All consultant dermatologists in the UK are also involved in administrative and managerial work, audit and continuing medical education. All dermatologists, and not just those few employed by a university, are involved in teaching, whether of nurses, undergraduate medical students, GPs or trainee dermatologists, and a surprising number of National Health Service consultants (i.e. 'non-academics') manage to undertake other commitments such as writing and research.

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General articles

Ancient and medieval dermatology

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Chapter 2

Comparative Dermatology

D.A. Burns

The evolutionary sources of the skin components [1–5]

All organisms have an outer layer that delimits the body and separates it from the environment. Its main functions include protection of the animal against physical damage, including that from radiation, defence against biological invasion, the regulation of the inward and outward passage of materials, and the receipt and transmission of signals to other organisms.

Dermatologists may consider matters relating to other animals unimportant, but an appreciation that many of the structures and much of the biochemistry of skin has an evolutionary history that antedates the origin of the vertebrates not only gives perspective to the human condition but also may provide clues to its understanding and models for its investigation.

Although the anatomy of skin differs greatly between animal classes and shows considerable variety in relation to the exigencies of lifestyle even within groups, it is nevertheless possible to recognize various long-standing elements. Structural materials, such as cross-linked proteins similar to collagen, are found in the most primitive animals. For example, supporting structures of aromatically cross-linked proteins associated with polysaccharides are found in coelenterate polyps, and the cuticles of parasitic worms such as *Ascaris* are composed of collagen proteins linked by disulphide bonds. Among the vertebrates, keratin first seems to have occurred in the lips and in the breeding tubercles of some fish, but similar materials are found in invertebrates.

Glands and pigment cells have an equally long history. The simplest glands are the unicellular goblet cells, which secrete mucus in coelenterates and fish alike. Multicellular glands of various degrees of complexity are ubiquitous.

Melanins, which are pigments produced by the oxidation of tyrosine, are equally widespread and are found, for example, in worms, molluscs, arthropods and echinoderms, as well as throughout the vertebrates.

The questions of most interest in dermatology concern the skin changes, including loss of long hair on the body, which have occurred in hominid evolution. However, the appreciation that the biochemical machinery of human skin was established much earlier makes it relevant first to review briefly the integument in the more primitive forms of life.

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The epidermis and the dermis and their derivatives

Invertebrates

Life began in the sea, just as the human fetus develops bathed in the amniotic fluid. Among the simplest and most archaic animals are the coelenterates, namely the

corals, jellyfish and their allies. Such forms have only two layers of cells: an ectoderm in contact with the aquatic environment and an endoderm lining the gut cavity. The ectoderm may, nevertheless, contain gland cells, stinging cells, pigment cells and sensory cells, and its outer surface may bear microvilli, suggesting an absorptive function [1]. Microvilli are similarly found on the outside of the integument of flukes and tapeworms, which are internal parasites [2,3], and on the amniotic border of periderm of the human embryo.

Marine worms and their relatives in fresh water and on land have a thick cuticle outside their epidermis [4,5]. Arthropods, animals with jointed limbs of which crustacea and insects are examples, have a tough exoskeleton, which has helped some of their forms to colonize land. In crabs and lobsters this cuticle is hardened by the inclusion of calcareous material. Insect cuticle is composed of chitin, a polysaccharide containing amino groups, and protein, which may be tanned or otherwise cross-linked to form a hard natural plastic [6,7]. A coat of wax prevents desiccation of the animals. An obvious disadvantage of the exoskeleton is that growth can only occur if it is periodically shed, a procedure that leaves its owner vulnerable to predation or other damage [8].

One interesting feature of annelid worms is that they bear stiff bristles or chaetae, made of a keratin-like material with properties similar to that of human hair. Although of epidermal origin, chaetae are not composed of aggregated cells produced by an active matrix. Lateral cells may add substance or provide tanning agents, but the bulk of each chaeta is secreted by only a single basal cell [9,10].

Vertebrates

Origins and trends

A continuous evolutionary narrative starts with the vertebrates—animals with a backbone, which is preceded in embryonic development by an elastic rod known as a notochord. The simplest known chordates, which have only notochords and no vertebral column, are the planktonic larvae of sea squirts and a small, bottom-living marine animal known as the lancelet or *Amphioxus*.

Amphioxus has no more than a single layer of epidermal cells, but this is attached to a basal lamina below which is a cutis made up of a jelly-like zone sandwiched between two layers of collagen [11]. This appears to be a simple version, perhaps the forerunner, of the thick dermis that gives support and instruction to the complex epidermis and its elaborate derivatives, scale, feather and fur, in the various vertebrate classes, fish, amphibia, reptiles, birds and mammals.

In all vertebrates, the skin is characterized by an outer stratified epidermis and an underlying dermis, also known as the corium or cutis. The epidermis consists of closely packed cells, which are renewed from the basal layer and which constitute a barrier. The dermis is a connective tissue of mesodermal origin and is made up mainly of extracellular ground substance and collagen fibres manufactured by scattered cells.

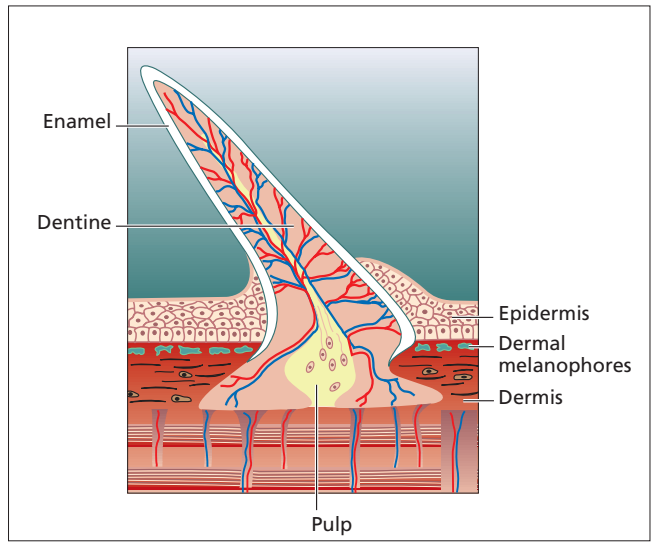

Fig. 2.1 Placoid scale of a shark.

The evolution of the vertebrates and their successful colonization of land are associated with a variety of structures, such as glands, scales, feathers and hair, as well as horns, claws and nails. Some of these, notably the scales of fish, are derived from the dermis or have substantial dermal components. Most, however, are epidermal, although their formation is orchestrated by interactions with the dermis.

Fish [12–14]

With few exceptions, such as eels and some catfish, fish have scales of one type or another. Sharks have placoid scales or denticles, which project from the skin. It is their presence that gives shark leather, or shagreen, its characteristic rough feel. In essence, the placoid scale has the same structure as a mammalian tooth, of which it is regarded as a forerunner (Fig. 2.1). Its bulk is formed by a cone of dentine, of dermal origin, which during its formation becomes capped with enamel deposited by an epidermal enamel organ.

Bony fish have elasmoid scales, consisting of plates of collagen with superficial mineralization. There are two main types. The more primitive cycloid scales found, for example, in the cod and the carp, are thin, large, round or oval, and have smooth, free edges, which overlap and show growth rings (Fig. 2.2). Ctenoid scales, found in perches and sunfishes, differ in having stiff spines on their posterior borders. All elasmoid scales remain covered by a thin layer of dermis and epidermis.

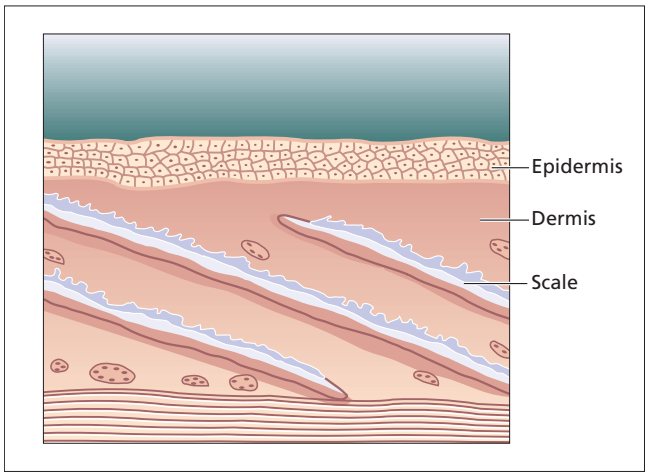

Fig. 2.2 Section of skin of bony fish. The cycloid scales lie below the epidermis.

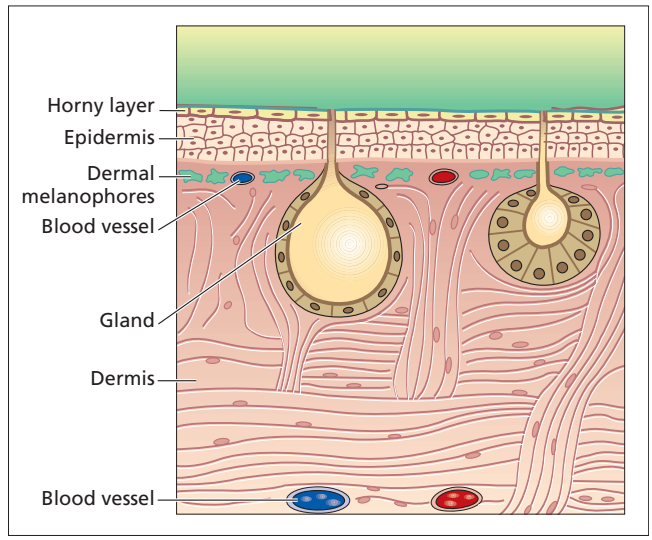

Fig. 2.3 Section of frog skin. Note the flattened superficial horny layer, only one cell deep, which is periodically sloughed as the 'scarf skin', the dermal chromatophores and the multicellular glands.

Unlike mammals or birds, fish do not reach a definitive size at maturity but go on growing throughout life. The problem of increasing the area of the integument is met by cartilaginous fish and bony fish in different ways. In sharks, completed denticles do not increase in size, but denticles continue to be formed *de novo*. Elasmoid scales of bony fish cannot be generated in this fashion but grow throughout life by the addition of step-like rings.

Amphibia [15–18]

Amphibians were the first vertebrates to emerge from the water, although they still depend on it for reproduction. Their epidermis has several layers of cells, which are formed by a basal stratum germinativum and ultimately become keratinized to form a very thin horny layer, only one cell deep in most species, which is intermittently sloughed (Fig. 2.3). Although the amphibia have lungs, they also respire through their moist skin.

Reptiles [19,20]

Reptiles are truly terrestrial, in that they do not need an aqueous environment for the development of their larvae. Their chief problem, prevention of desiccation, is solved by possession of scales, which in essence are overlapping folds of skin. An additional property of scales is that they allow the passage of infrared radiation from the sun. All modern reptiles are dependent on this external source of heat to achieve and maintain a constant body temperature similar to that of mammals.

Reptile scales contain a thick stratum corneum in which waxes are sandwiched between keratinized cells. Snakes and lizards do not, like mammals, renew their epidermis by continuous proliferation and exfoliation of cells. The vertically stratified epidermis is periodically shed as a whole, subsequent to the formation of a complete new generation of epidermal cells below it [21]. Only in rattlesnakes are several generations of scale retained at the tip of the tail.

Birds [22]

The most obvious integumental feature of birds is the possession of feathers of three kinds. The small, almost hair-like filoplumes and the downy plumules provide insulation to conserve metabolically produced body heat, whereas the larger contour feathers, which include those of the wings and tail, have aerodynamic functions.

Feathers are considered to have evolved from reptile scales [23,24] and, like scales, they are periodically moulted and replaced.

The legs and feet of birds bear scales, and some other areas, such as the comb and wattles of the domestic cockerel, are naked. The epidermis of birds, as distinct from its derivatives, is thin, and so is the dermis in most species, although ostrich skin is thick enough to be processable into leather.

Mammals [25–27]

Mammals, in general, are characterized by hair, but not all possess it. The epidermis also produces a range of other derivatives such as quills, claws, nails, hooves and horns. Antlers are made of bone, but they are covered with epidermis, the velvet, when newly grown, and the bony plates of the armadillo are similarly of dermal origin.

2.4 Chapter 2: Comparative Dermatology

Hair, wool and quill are all produced by follicles that are ingrowths of epidermis enclosing a papilla of mesodermal cells in their bases. Hair is not considered to be the homologue of scale or feather. It is more likely that the first hairs to arise in evolution were part of sensory structures between the scales of some ancestral reptile [23,28].

Reptiles with ancestral mammalian features appear in the fossil record over 200 million years ago (Ma) in the Carboniferous period, long before the first dinosaurs. Skin, unfortunately, usually leaves no fossil record. However, the existence of pits in the outer surface of the maxillary bones of some later mammal-like reptiles suggests that these creatures had tactile vibrissae, as similar pits also occur in living mammals.

The fact that groups of three or four primary hair follicles are found in the hinge regions of the reptile-like scales on the tails of modern marsupials and rodents possibly lends support to this view. It is undoubtedly of interest that the keratinization of the tail scales is similar to that in reptiles and birds, whereas typical mammalian keratinization with a granular layer occurs only in the hinge regions [12,23,24]. The evolution of the mammalian pelage may have involved the appearance of numbers of secondary hair follicles and an increase of the hinge accompanied by the loss of scales.

Antlers, as already noted, are formed from bone and are shed annually. The horns of cattle, goats, sheep and antelopes also have a bony core, but this is covered by a layer of dense horn formed by a non-hairy epidermis. Except in the American pronghorn, horns are never shed [25].

Claws, nails and hooves are tough, keratinized derivatives, which develop dorsally on the ends of the digits. They are all formed from an active matrix within a fold of epidermis; the various shapes are produced by differential growth. Nails are found only in primates, but the dorsal skin of the scaly anteater or pangolin is covered with horny scales that are surprisingly similar to nails in structure [12,25].

As distinct from the appendages, mammalian epidermis is of several types. Most furry species, from rodents to sheep, have a thin epidermis, which is only two or three cells deep. Human epidermis lacks a protective pelt and, perhaps in compensation, is somewhat thicker. The epidermis of the palms and soles has a much thicker stratum corneum than skin that bears hair follicles.

The elephant, rhinoceros and hippopotamus all have skins with very thick hyperkeratotic horny layers. Whales, which lack hair, also have a very thick epidermis, although the cells remain parakeratotic, i.e. they retain their nuclei. Whale skin has a highly indented dermal–epidermal junction, which suggests a very high rate of epidermal cell production. The whole epidermis bears a remarkable and striking histological similarity to that of psoriasis.

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Glands

Evolution of glands

Glands are organs that manufacture and discharge their products either by extrusion (*merocrine*) or by complete disintegration (*holocrine*) of their cells.

Simple unicellular glands are found throughout the animal phyla. Primitive examples, in the evolutionary sense, are the mucus glands of coelenterates [1] and the considerable variety of glands in the simple epidermis of annelid worms [2]. Unicellular glands are also plentiful within the stratified epithelium of lampreys and fish [3].

The simplest type of multicellular gland is no more than an aggregation of glandular cells. Many segmented worms, for example, have glandular fields. In earthworms there is a region known as the clitellum (Latin for 'saddle'), which not only secretes a cocoon that can be slipped off like an arm band and sealed but also fills it with a fluid which is of nutritive value in some species [2].

Glands of greater productive capacity can be produced by proliferation of nests of epidermal cells and their growth downwards into the dermis. Such an occurrence can be observed in the larval development of amphibia, providing a model for the evolutionary process, if not a literal recapitulation of it [4].

Glands of vertebrates

Amphibia

Amphibian glands are of a number of types and have various functions, including the production of mucus, poison and even courtship stimulants. The flask-shaped gland of the frog skin is a typical structure (see Fig. 2.3). It is globular, lined with secretory cells, sunk into the dermis, and opens by a neck to the skin surface [5].

Reptiles

Multicellular glands, both holocrine and merocrine, are found in reptiles, although they are usually small and inconspicuous [6]. So-called 'generation glands' in lizards and snakes are connected with the shedding and sloughing cycle [7,8]. Odour-producing glands, used in both courtship and aggression, are present in most reptiles, including turtles and crocodiles as well as lizards and snakes [9]. For example, turtles have chin glands [10] and paired inguinal and axillary musk glands [11], and snakes have sac-like glands at the base of the tail.

Birds

In birds, the only conspicuous glands are the large uropygial or preen glands, although there are also some small tubular glands in the vent region [12]. The uropygial gland is holocrine and secretes an oily material by way of ducts, usually two, which open on a papilla. Histologically, it closely resembles both the mammalian sebaceous glands and the holocrine glands of reptiles. The product of the uropygial gland is transferred by the beak of the bird to the feathers, and is important for their maintenance. It may also serve to regulate the fungal and microbial species on the plumage, contain a scent for intraspecific communication, and perhaps distribute ergosterol for conversion to vitamin D, which is then ingested or absorbed. The gland is hormonally controlled and appears to be sensitive to progesterone [13] and androgens [14].

Mammals

Nearly all mammals have both holocrine and merocrine glands. Only whales lack sebaceous glands, and only whales, elephants, sea cows and scaly anteaters have no tubular glands in their skin.

Merocrine glands occur in many different sites and serve several functions. The tubular glands associated with hair follicles were designated by Schiefferdecker [15] as 'apocrine', on the grounds that secretion involved decapitation of at least some of the cells, as distinguished from 'eccrine' glands in which the cells remain intact. Although electron microscopy has cast doubt on these criteria, the terms remain useful. Alternative designations of 'epitrichial' and 'atrichial' have been proposed, but apocrine glands do not invariably open into hair ducts. In primates, most tubular glands can, in fact, be clearly assigned to one type or the other on histochemical grounds.

A major function of sebaceous and apocrine glands is the production of scent for intraspecific communication. Although sebaceous units occur throughout hairy skin and so, in some species, do apocrine units, they also occur in batteries to form discrete scent organs [16,17]. Such structures are found in most mammalian orders and can occur in almost any area of the body. Some, such as the chin gland of the rabbit, contain only tubular units; there are those, such as the supracaudal gland of the guinea pig, that are purely sebaceous; and others, such as the side glands of shrews, contain units of both kinds. The human axilla contains large hair follicles with functional holocrine and apocrine glands, which constitute a scent organ of this type [18].

Eccrine glands are found in two sites. On footpads, including human soles and palms, they occur in many different mammals, and their main function appears to be to increase surface friction by moistening the keratin. On hairy skin, however, where they function to cool the body by sweating, they occur only in primates and are most abundant in humans.

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Pigment cells

Animal colours [1–3]

Colours abound throughout the animal kingdom. Some, such as the metallic sheen of beetles and the gleam of the feathers in the peacock's tail, are produced by *interference*, i.e. by the reflection of light from both the outer and inner surfaces of a film. So-called structural colours can also be produced by *diffraction*, which accounts for the iridescence of the wet bristles of the 'sea mouse' (*Aphrodita*), or by *scattering* of the shorter waves of white light by very small particles, a phenomenon that produces the pale blue of the clear sky or the bright blue on the mandrill's face. The blue colour of the human Mongolian spot is a similar optical effect (Chapter 38).

Most colours are, however, due to pigments. The most widespread and the most important in humans is *melanin*, which also gives colour to the feathers of blackbirds, black beetles and slugs, and fills the ink sacs of the octopus and the squid. Melanin exists in two forms: black or dark-brown *eumelanin* and reddish or yellow *phaeomelanin*. Both are oxidation products of tyrosine.

Not all brown or black pigments are melanin. Insects and crustacea have *ommochromes*, synthesized from the amino acid tryptophan. A third group are the white, yellow and orange *pterins*, which give colour to the wings of butterflies and to spotted salamanders. Fourth, there are the widespread *carotenoids*, imparting colour to red sponges, goldfish and pink flamingos, for example, as well as to human skin. None can be synthesized by animals; all are acquired by eating plants. Fifth, of particular importance in human skin colouration, is the oxygen-carrying pigment of the blood, *haemoglobin*, which is responsible for the pink tint of white people and the bright red of human lips and baboons' buttocks. This list is not exhaustive. For example, some marine worms contain a green respiratory pigment known as *chlorocruorin*, and a red pigment, *echinochrome*, is found only in sea urchins and in the bones and teeth of the Pacific sea otter which feeds on them. This last material may seem of little interest to dermatologists, except to remind them that human skin colour may be similarly acquired, for carotenaemia is caused by the ingestion of excessive amounts of food rich in carotenoids.

Chromatophores and melanocytes

In many animals, pigment is formed in specialized cells. Pigment cells start their evolutionary history in coelenterates and appear to reach the peak of their variety in each of two unrelated groups: the molluscs and the vertebrates.

Molluscs

Molluscs contain not only melanins and ommochromes but also porphyrins and bilichromes. The squid, cuttlefish and octopus have assemblages of differently coloured pigment cells, or chromatophores, containing yellow, orange, red, red–brown, blue, violet–black or black ommochromes. Underlying these are so-called iridiophores and leukophores, which absorb, reflect and scatter light [4,5]. The chromatophores can be expanded rapidly or

contracted by smooth muscle fibres that are attached to the periphery of each cell. Contraction of the muscle pulls out the cell and its pigment into a flat plate, and relaxation causes the cell and pigment to concentrate into a small dot. The animals are thus able to change colour and pattern to match their backgrounds extremely rapidly. The information about background is obtained through the eye and mediated through colour centres in the brain [6].

Vertebrates in general

The pigment cells of vertebrates differ from those of molluscs in that their size is not controlled by muscle fibres [7]. There are two mechanisms of colour change, each involving a distinctive cell. Short-term *physiological* colour change is brought about by active redistribution of pigment-containing organelles within the boundaries of relatively large cells, which are collectively known as *chromatophores*. Long-term *morphological* colour change results from alterations in the numbers of smaller pigment cells known as *melanocytes*, or in the amount of pigment each produces. The dendritic pigment cell of the human epidermis is an example.

Fish

Fish contain chromatophores in both the dermis and the epidermis, but in most species the dermal chromatophores are the more important [8]. Several types can be distinguished, namely black or brown melanophores, red erythrophores and yellow xanthophores. In each, the pigments, namely melanins, carotenoids and pteridines are contained within organelles. In addition, there are leukophores and iridiophores containing colourless pigments, mainly guanine. Iridiophores cannot translocate the pigment-containing organelles; the guanine is deposited in crystalline platelets. Their function is to produce physical colours by reflection, scattering or diffraction.

There are two modes of regulation: hormonal and nervous. Hormones, in particular the melanocyte-stimulating hormone (MSH) of the pituitary, appear to provide the more primitive mechanism. It is the only one present in lampreys, the prevailing means of control in sharks, and it is retained in the evolution of amphibia, reptiles and mammals. Only in some bony fish does nervous control take over, making it possible, for example, for flatfish such as the flounder to mimic a chequerboard bottom on which it is placed.

Amphibia and reptiles

Amphibia also have both dermal chromatophores, of similar types to those found in fish (Fig. 2.4), and dendritic epidermal melanocytes [9].

The pattern is continued in reptiles [10]. Lizards have a layer of melanophores in the dermis, with two to four layers of iridiophores above them and, more superficially, xanthophores and erythrophores [11,12]. In addition, melanocytes occur in the basal layer of the epidermis and transfer melanosomes into the keratinocytes.

Birds

In birds [13], melanocytes are responsible for transferring eumelanin and phaeomelanin into the feather germ to produce black, grey, brown and related tints, and also to form the dark background for structural blue and interference colours. Carotenoids, also, may be responsible for yellow and red, and sometimes even for green, violet and blue. It is of interest that the pelican can produce cosmetic colouration of the plumage by a rose-coloured secretion from the preen gland.

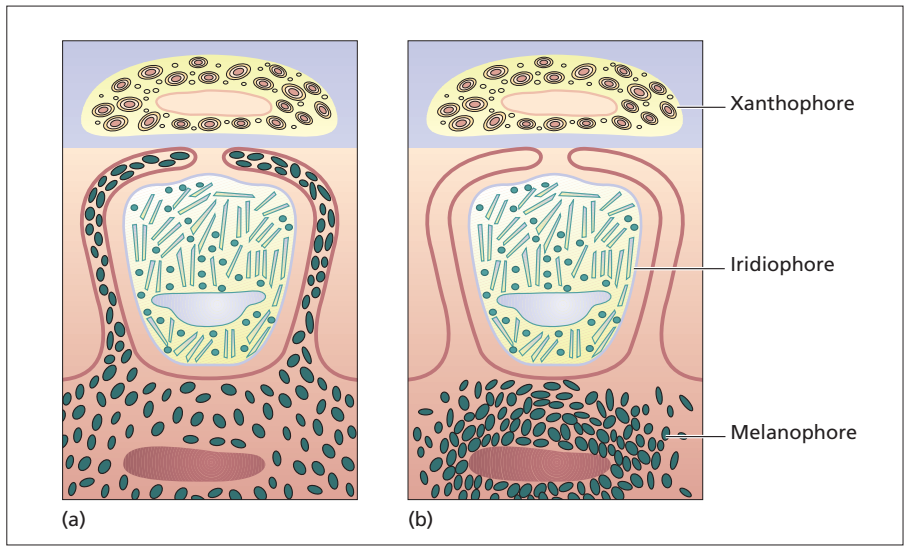

Fig. 2.4 The dermal chromatophore unit of amphibia. Uppermost, just below the basement membrane, is a layer of yellow pigment cells (xanthophores). Immediately beneath are reflecting iridiophores lying over melanophores, which engulf them with dendrites. In adaptation to dark backgrounds, melanosomes fill the dendrites to obscure the reflecting surface (a). When the melanosomes retreat, the dark pigment becomes almost completely obscured by the xanthophores and iridiophores and the animal appears light (b).

The striking white colour of many aquatic birds, for example, the albatross, seagull and swan, is entirely structural. Pigment-free feathers contain irregularly distributed air-filled cavities, which equally reflect all wavelengths of light. Some blue, green and violet colouration, for example that of kingfishers and parrots, is produced by scattering or interference.

Mammals

In comparison with their vertebrate relatives—fish, amphibia, reptiles and birds—and, indeed, many invertebrates, mammals are drab animals. Even the power to perceive colours has been lost in most mammalian orders. Animals as diverse as crabs, octopuses, insects, fish and birds all have colour vision, but dogs are colour blind, and the bull remains indifferent to the redness of the rag even if enraged by the antics of the matador. The evolutionary explanation is that for many millions of years our ancestors were small, insect-eating, nocturnal mammals for which colour vision had no adaptive advantage.

All was not lost forever. Something was retained and something was regained. All mammals retain epidermal melanocytes, and monkeys, apes and humans share with some species of squirrel the power to appreciate colours. The return of colour as an item of social commerce is symbolized, for example, by the rump of the sexually receptive female macaque or the bright-blue scrotum of the vervet monkey.

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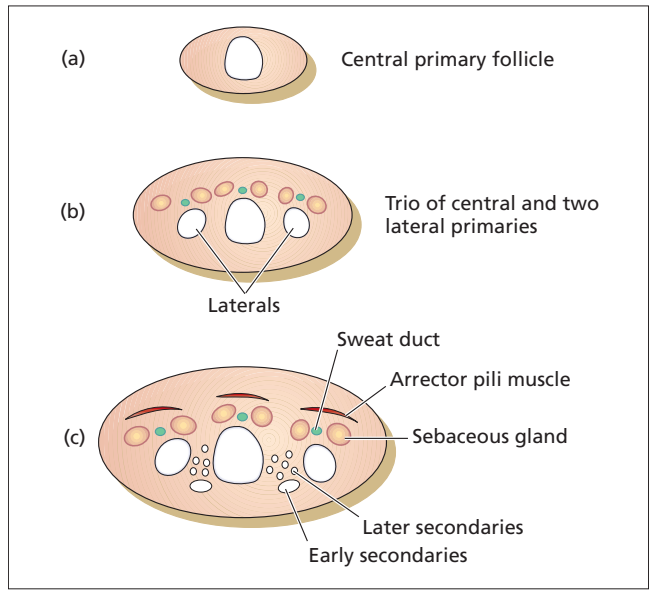

Fig. 2.5 Stages in the development of a follicle group in the sheep.

The skin of mammals

Mammals owe their evolutionary success to many features, and changes in the skin were critical factors. The development of a tough, flexible but impermeable integument enhanced the capacity for movement, especially on land, and the evolution of the hair follicle and its associated structures not only provided the essential insulation against heat loss, but also the glands for suckling the young.

How did the first hairs arise? In the virtual absence of fossil evidence, only speculative answers can be suggested. The most favoured idea [1,2] is that the first hairs were sensory structures, perhaps similar to the tylotrichs of living mammals, between the scales of reptilian ancestors. A model may be provided by the tails of many mammals in which groups of three follicles occur between epidermal scales, as first noted by De Meijere in 1894 [3]. Embryological evidence is certainly consonant with this view. In many mammalian families, the first follicles to develop are those of the whiskers, and in humans, similarly, follicles form on the upper lip, chin and eyebrows long before they take shape elsewhere. Moreover, the development of all follicles in many different mammals involves the formation of trio groups at an early stage, even though the ultimate patterns may greatly vary.

Sheep are the most widely studied and described species [4]. The first central primary follicles appear on the flank of lambs at about 60 days of fetal age (Fig. 2.5). Subsequently, a lateral primary follicle forms on each side of the central to form the trio group. Each of the three follicles has a sebaceous and an apocrine gland, as well as an arrector muscle. After 90 days of gestation, secondary

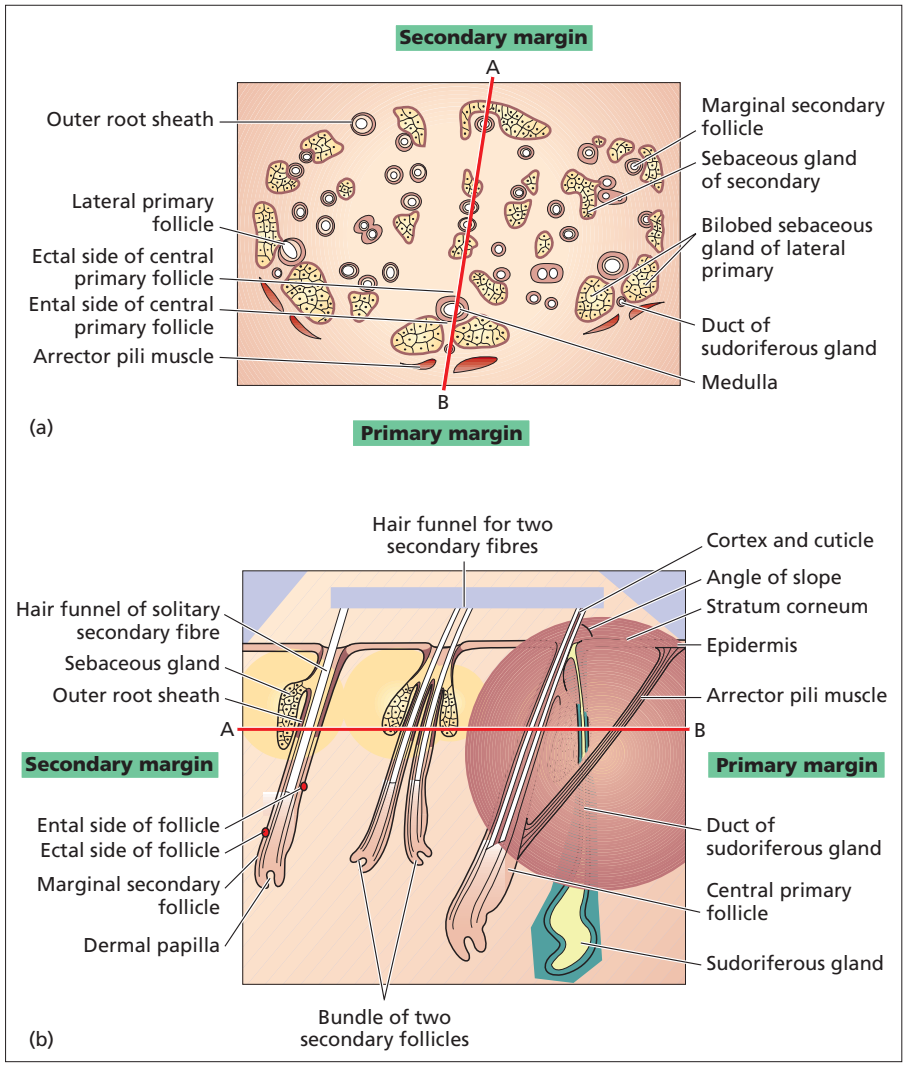

Fig. 2.6 Diagram of a sheep follicle group (a) in transverse section and (b) in longitudinal section. (From Hardy and Lyne [5].)

follicles, lacking apocrine glands and arrector muscles, develop in between the primaries, on the side opposite to that with the glands, to form a group of five follicles, three primary and two secondary. The maturation of these secondary follicles is complete by birth. However, further groups of smaller secondary follicles mature after birth, and these may not have fibres for 2 or 3 months (Fig. 2.6). Primary follicles produce the coarse hairs of the outer coat, whereas secondary follicles form the fine underwool.

Although similar features can be recognized in many other mammals, it has to be admitted that the density and arrangement of follicle types varies greatly between species and between regions of the body. Thus, for example, the duck-billed platypus (*Ornithorhynchus*) an egg-laying mammal considered to be of the most primitive type, has, according to Carter [6], over 600 follicles per square millimetre of skin, with over 30 secondaries to each primary. The mole (*Talpa*) of the order Insectivora, which are considered to be the most primitive of placental mammals, similarly has a high density of follicles, which produce a thick coat of fine hairs. The mouse (*Mus*) has 50–150 follicles per square millimetre, with a ratio of secondaries to primaries of two to five. Four types of fibre have been described in mice and rats [7,8]. The larger monotrichs, awls and auchenes are produced by primary follicles; the finer zig-zags of the underfur grow from secondary follicles. This order of decreasing length is also probably the order of follicle initiation and fibre emergence. Only the vibrissae have emerged by birth (Fig. 2.7).

The coat shows wide variations, related to size and to lifestyle, throughout the mammalian orders. Larger animals in general have a lower density of follicles than the familiar rodents and fur species. For example, horses have 10–15 follicles per square millimetre and use apocrine glands for thermoregulation. Pigs have less than one [6]. The hippopotamus, one of the largest living terrestrial mammals, is hairless except for sparse bristles on the tail, ears and muzzle. This remarkable animal immerses itself in water during the day, but emerges to graze on land at night. The skin is adapted for this habit; thermoregulatory

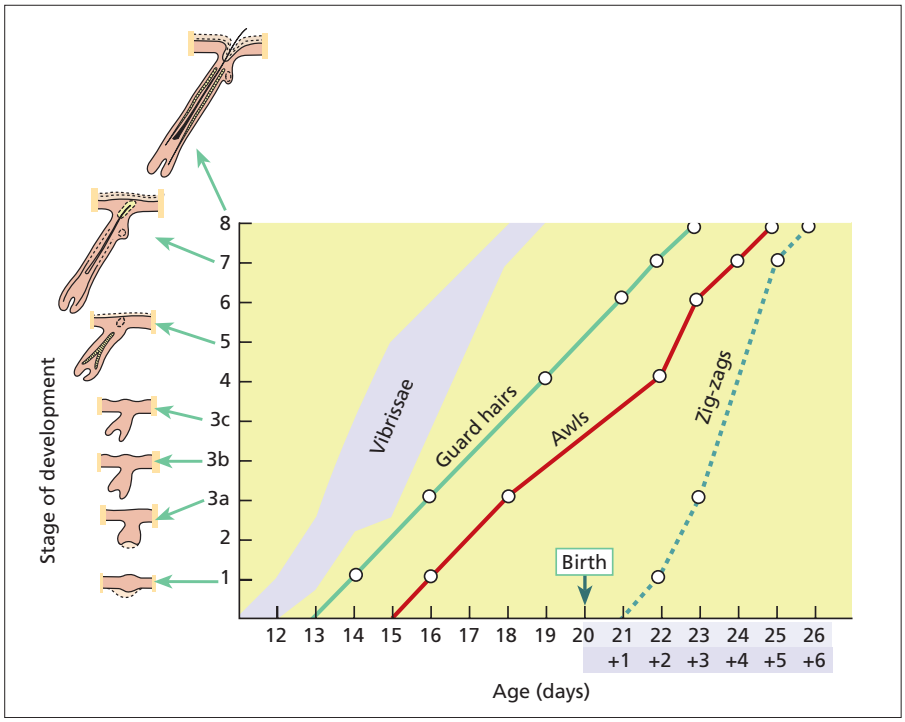

Fig. 2.7 Development of hair follicles in the mouse. Rudiments become evident on the 12th day of gestation, and Hardy [9] recognized 11 stages of development (1–8, with three subdivided). The presumptive dermal papilla, shown by a broken line in stages 1 and 3a, becomes engulfed in stages 3b and 3c. Hardening of the inner root sheath is seen in stages 4 and 5, and keratinization of the growing hair in stages 6 and 7. Eruption occurs at stage 8. At birth, the vibrissae but not the guard hairs or awls have emerged. Rudiments of the zig-zag follicles do not appear until the day after birth.

sweating is not required, but the apocrine glands produce a pink, sticky secretion that dries to form a protective and possibly antiseptic lacquer when the animal is on land.

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The skin of primates

Origins and classification of primates [1–4]

The human species, *Homo sapiens*, is a member of the primates, an order of the class Mammalia. The traditional classification of primates is in two suborders—the Prosimii or so-called 'lower' primates (lemurs, lorises and tarsiers) and the Anthropoidea or 'higher' primates (monkeys and apes). The higher primates are composed of two groups, which had a common ancestor, but evolved separately in the New World and the Old World. A superfamily of the Anthropoidea, the Hominoidea, includes the apes and humans. All primates have a typical mammalian skin. Hair follicles occur over most of the body, and are lacking only on the footpads and other friction surfaces such as the contact areas of the prehensile tails of some New World monkeys or the knuckle pads of gorillas.

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The evolution of Hominoidea [1–6]

Apes and men

The superfamily Hominoidea has traditionally been divided into the Pongidae, to include all the apes, and the Hominidae, to include humans and their recognizable antecedents. Now that the evidence for taxonomic relationships comes not only from fossil history and comparative anatomy but from biochemical analyses such as aminoacid and DNA sequencing, it is generally

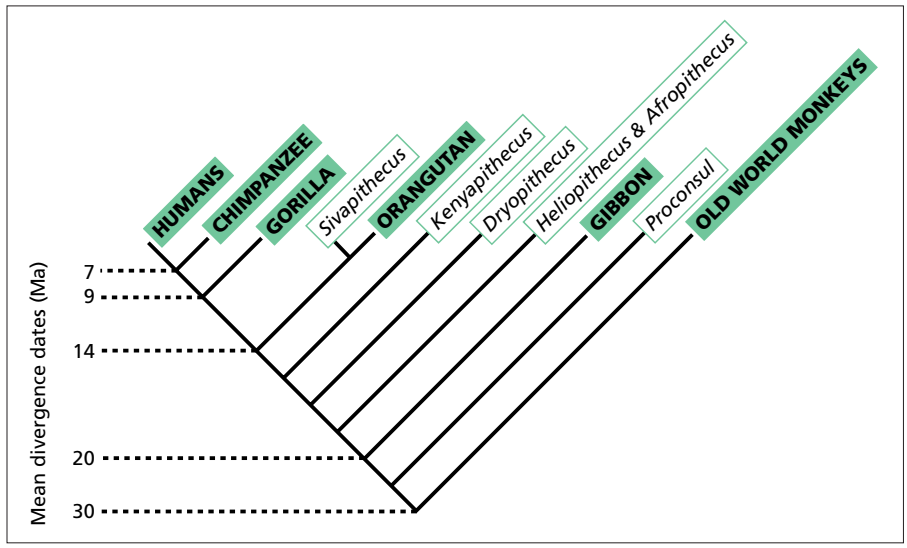

Fig. 2.8 A cladogram showing relationships within the Hominoidea and the divergence dates. Fossil forms are shown in lower case. (From Tattersall *et al*. [2].)

acknowledged that some modern apes are more closely allied to humans than to other apes.

The fossil evidence suggests that the hominids originated in Africa. Among the fossil apes of the Early Miocene, the most favoured candidate as the last common ancestor of both apes and humans is *Proconsul*, of which jaws, skulls and limb bones, assigned to more than one species, have been discovered in Kenya. The genus was named in 1933, and the name refers to a chimpanzee named Consul who then lived at London Zoo [3]. They are dated to around 22–17 Ma. Between 22 and 18 Ma, the gibbons (family Hylobatidae), which are the most primitive of living apes, diverged (Fig. 2.8).

The remaining genera are now put into a single family, the Hominidae, from which one subfamily, the Ponginae, including only the orangutan, diverged some 16–13 Ma, when it left Africa for Asia.

The other subfamily, the Homininae, embraces gorillas, chimpanzees, humans and their fossil relatives. This split also marks the development of different modes of locomotion, from a generalized tree-climbing ancestor. The orangutans suspended themselves in the trees by their arms (brachiation) and the African great apes specialized in terrestrial quadrupedalism (chimp, gorilla) and bipedalism (humans). The mean date for divergence of gorillas was 9 Ma and for the chimpanzee about 7 Ma.

The Australopithecines, which are recognized as human ancestors, and of whom there were several species, occur as fossils from around 4 Ma, but the molecular clock suggests they may be rather older.

Homo: the human genus

The genus to which modern human beings belong was given its title by Linnaeus in 1758, and the line to modern humans is considered to include several species of australopiths and *Homo*. Neanderthal Man is considered to be a variety of *Homo sapiens*.

Homo sapiens

The species now embraces not only the whole variety of human beings in the world today, and closely related forms, but also a range of archaic fossils, including Neanderthals.

'Neanderthal Man' was the name given to parts of a skeleton found in 1856 in a cave in a valley near Düsseldorf, the first indisputable example of a fossil man to be discovered [7].

The Neanderthals had many distinct anatomical features, and the stereotype is well known. They appear to date from the middle Pleistocene and to have spread widely over Europe and western Asia. Their evolutionary position is disputable, for, although in some respects they seem to be an intermediate between archaic and modern *Homo sapiens*, they had many unique characters that are not found in modern peoples. Neanderthals seem to have disappeared about 35 000 years ago, and the reasons for this are not clear—they may have been killed off by more modern *Homo sapiens*, or have interbred with them.

The early populations of modern *Homo sapiens* in Europe are known collectively as 'Cro-Magnons' after the site near Les Eyzies in the Dordogne, France, where what appeared to be a deliberately buried skeleton was disinterred in 1868. The association of the bones with flint tools of the Aurignacean type, and the stratigraphic evidence, dated them to the fourth glaciation period of the upper Pleistocene, overlapping the Neanderthals.

Genetic data support the view that all existing races of *Homo sapiens* arose from a single, relatively recent ancestor, in Africa—the 'single origin model' of human evolution [3–9]. By assuming a constancy of molecular

mutation, it has been estimated that European and Asian populations shared a last common ancestor about 40 000 years ago and, in turn, had common ancestry with an African population about 110 000 years ago. It is probable therefore that modern *Homo sapiens* originated from southern African ancestors during the African middle Stone Age from 120 000 to 40 000 years ago. Asian populations probably reached Australia as early as 40 000 years ago.

The three major geographical varieties of humans—Negroid, Caucasoid and Mongoloid—each with distinctive characteristics of skin and hair, have all become established within this relatively recent era.

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From *Tupaia* to *Homo*: a variety of skins

Tupaioidea

Tree shrews have a thin skin that resembles that of the Insectivora, which are regarded as among the most primitive of living mammals [1]. The hair follicles are arranged in rows rather than in groups and have small but typically mammalian sebaceous glands opening into the pilary canals. Apocrine glands are widespread throughout the hairy skin and are borne by almost every follicle in some regions, although only on every second or third follicle on the scalp, arms and back. Of particular interest is that eccrine sweat glands are found not only in clusters in the soles, palms, fingers, toes, rhinarium and genital skin, but also, in fewer numbers, throughout the hairy skin. In this respect, *Tupaia* appears nearer to the Anthropoidea than the Prosimii.

Tarsiidae

The Philippine tarsier (*Tarsier syrichta*) [2] one of the three existing species, has a thin epidermis, only one or two cells thick, except on the friction surfaces. The dense, woolly pelage is made up of fine hairs similar to those of the Lorisidae. Hair follicles are in groups of six to nine, and each has a sebaceous gland but no arrector muscles. There is one apocrine gland to each hair group, with the duct opening directly to the surface. The friction surfaces have glands that appear to be of the eccrine type. On the lateral sides of the upper lip there are gigantic sebaceous 'labial' glands. Tarsiers have opposable thumbs and big toes, and bear nails on their digits, except for the second and third of the hind limb, which bear grooming claws.

Lorisidae

Varieties of bushbaby [3–5] have similar skins. The epidermis is relatively thin except over the lips, face and scrotum, and for the most part lacks demonstrable melanocytes. The fur is soft and very dense, and the hair follicles are arranged in groups of three or four in the pigmy bushbaby, and four to 26, but usually eight or nine, in the great bushbaby. Sebaceous glands open into the pilary canals. In the pigmy bushbaby, each hair group has one associated apocrine gland; in the great bushbaby there is only one gland in every three to five follicle groups. The ducts open independently of the pilary canals.

The skin of the potto (*Periodicticus potto*) [6,7] resembles that of bushbabies in most respects. The fur is dense and woolly, with sparse coarse hairs projecting 2 cm or more beyond the fur in the cheek, eyebrow and scapular regions. Hair follicles occur in groups of four to 20. Most sebaceous glands are small and open directly to the pilary canals, but they are larger and have ducts in the face, scalp and scrotum. There is usually only one tubular gland to each group of follicles, with the duct opening directly to the skin surface. Eccrine glands are confined to the palms, soles and digital pads.

The slender loris (*Loris tardigradus*) [8] and the slow loris (*Nycticebus coucang*) are similar to other members of the family. The hairy skin of the slender loris is very thin and lacks melanocytes. Hair follicles occur in clusters of four to 20, with small sebaceous glands, which open directly into each pilary canal. There are one or two tubular glands to each hair group and they open directly to the surface. 'Eccrine' glands occur on the palms and soles. Of particular interest is the existence of large apocrine scent glands, the brachial organs, on the medial side of each arm.

Lemuridae

The skin of lemurs has many similarities to that of lorises. In the black lemur (*Lemur macaco*) [9], the ring-tailed lemur (*Lemur catta* [10]), *Lemur mongoz* [11] and *Lemur fulvus* [12], the hair follicles occur in groups of various sizes, and most of the hair groups contain only a single apocrine gland. Both this and the sebaceous glands open directly to the skin surface.

In the black lemur, for example, the hair follicles are in islands of six to 14 and lack arrector muscles. The skin within each island is glabrous, and the sweat and sebaceous glands open directly between the orifices of the

pilary canals. The hairs are of two types, wool and guard hairs, in the ratio of three or four to one. The sebaceous glands are of two types: multiple acinar on the face, lips, scrotum and perianal region, and single acinar elsewhere. There are numerous melanocytes in the sebaceous glands as well as in the epidermis, and the sebum is yellow, brown or black.

Ceboidea

The skins of New World monkeys show considerable variety. Hanson and Montagna [13] considered that of the owl monkey (*Aotus trivirgatus*) to resemble that of prosimians in that it has a thin, fairly unpigmented epidermis. The hair follicles are arranged in elongated clusters of four to 20. Apocrine glands occur over the general body surface and open into the pilary canals, but eccrine glands are confined to the friction surfaces of the hands and feet. Large aggregations of sebaceous and apocrine glands occur in the sternal and subcaudal fields.

In contrast, the woolly monkey (*Lagothrix lagotricha*) [14] has a heavily pigmented epidermis and a near absence of dermal melanocytes, and thus appears to resemble the Old World lutong. At the same time, the hair follicles are formed in clustered groups as in the owl monkey and prosimians. Apocrine glands occur only in the tail and external genitalia.

The red-mantled tamarin (*Saguinus oedipus*) [15] appears to have characteristics of both Prosimii and Catarrhini. The epidermis, like that of the black lemur, is moderately pigmented, but the hair follicles are arranged in linear perfect sets, with one apocrine gland per hair group. Eccrine glands are confined to the friction surfaces, except for some in the brow and pubic region. A similar arrangement of hair follicles and a comparable distribution of apocrine and eccrine glands are found in the pigmy marmoset (*Callithrix pygmaea*) [16].

The glabrous skin of the prehensile-tailed, woolly, golden, spider and howler monkeys resembles that of their palms and soles in possessing eccrine glands. However, in the woolly monkey the glands are restricted to the tail and external genitalia; in the spider monkey they occur in the chest, axilla and back; and in the howler monkey they are present throughout the hairy skin.

The red uacari (*Cacajao rubicundus*) [17] is another New World monkey in which the skin shows many primitive features. Nevertheless, the hair follicles are arranged in independent perfect lines, just as are those of the Old World macaques and baboons. Uacaries are notable because, like the stump-tailed macaque and man, they undergo progressive balding of the scalp (Fig. 2.9). The process starts on the forehead and gradually extends to the frontal, parietal and occipital regions [18]. The follicles do not disappear, but become smaller and produce only vellus hairs. Baldness occurs in both sexes.

Fig. 2.9 *Cacajao calvus*, the white uacari. Uacaris are notable because both sexes undergo progressive balding of the scalp in which the follicles produce only vellus hairs. (Courtesy of Edward Parker, Oxford Scientific Films Ltd.)

Cercopithecoidea

The skins of the various members of the family Cercopithecidae, which include the rhesus monkey [19], the anubis baboon [20] and the lutong [21], have many features in common.

The epidermis is moderately thick in all species. In the rhesus monkey, for example, the stratum germinativum is three or four cells thick, there is a discontinuous stratum granulosum, which is especially well developed on the friction surfaces, and a compact stratum corneum, which becomes deep and dense in the ischial callosities.

The dermis varies with region. The papillary layer is most pronounced in the friction surfaces, the anogenital areas and the scalp.

Melanocytes occur in both epidermis and dermis, but they are not ubiquitous. The rhesus monkey, for example, appears to lack epidermal melanocytes except in the face, eyelids and friction surfaces. The skin is, nevertheless, pigmented in piebald fashion, the colour being derived entirely from melanocytes in the dermis.

In all species the hair follicles occur in linear groups. Each one has one or two large follicles flanked by smaller ones, usually making a total of three or four, although there may be up to seven. The stump-tailed macaque (Fig. 2.10) is of particular interest because all adult males,

Fig. 2.10 *Macaca arctoides*. Adult males of the stump-tailed macaque, but not females, become progressively bald from the forehead backwards. (Courtesy of Mikaail Kavanagh, Oxford Scientific Films Ltd.)

but not females, become progressively bald from the forehead backwards [22].

Sebaceous glands with one or two lobules occur generally, and multilobular glands are found in sites such as the eyelids, lips and external genitalia.

Apocrine glands with their ducts opening into the pilary canals are found throughout the hairy skin. In the anubis baboon [20] there are large apocrine glands sparsely distributed over the body, but forming large fields, which resemble the axillary organs of humans and apes on the chest.

Eccrine glands occur generally on the friction surfaces. However, they are also found throughout the hairy skin.

Hylobatidae

Only in females of the white-browed gibbon (*Hylobates hoolock*) does the skin appear to have been fully described. The epidermis is very thin throughout the general body surface, and when shorn of its black hairs the skin appears pink without apparent pigmentation. However, in the lips, vulva, eyelids, perianal region and pressure surfaces the epidermis is thick and has a good population of melanocytes.

Hair follicles are arranged in groups of three. Sebaceous glands are generally small, but they are larger in the lips, eyelids, vulvar and perianal regions. Most, but not all, open into the pilary canals. Both apocrine and eccrine glands occur throughout the hairy skin, but the apocrine are the more numerous. Unlike humans and the other apes, the gibbon has no axillary organs.

Homininae

Apart from humans, only the skin of the chimpanzee seems to have been described in detail. A study of the gorilla was confined to the male.

The gorilla (*Gorilla gorilla*) [23] has an entirely black skin, with pigment cells crowded into the epidermal ridges, where these are present, and elsewhere distributed uniformly along the basal layer and extending into the pilary canals. The pelage is in general sparse and formed by coarse, deeply pigmented hairs about 4 cm long, except on the cheeks and brow, which are covered mainly by vellus hair. Both the large and small hair follicles are grouped in clusters of two to five.

The sebaceous glands are generally small, but are larger on the cheek and upper lip. Small apocrine glands are sparsely distributed throughout the hairy skin and are always associated with hair follicles. Larger glands occur on the chest, areola, cheek and perianal region, and very large and numerous glands contribute to axillary organs, which closely resemble the human structures. Eccrine glands are found over the entire body, in hair and in glabrous skin.

One other interesting feature of the gorilla is the occurrence of friction pads on the knuckles, an adaptation for their use in walking. These pads resemble the palms and soles in their possession of dermatoglyphic configurations, a thick stratum corneum, an abundance of eccrine glands and numerous tactile end-organs.

The skin of the chimpanzee (*Pan troglodytes*) [24] resembles that of the gorilla and humans (Fig. 2.11). The epidermis is pigmented, with the greater concentrations of melanin in the ridges. The pelage of young animals is fairly dense, but that of adults is usually sparse. In adults, the forehead becomes denuded and animals may go bald. The hair follicles are in groups of two or three, but these become less obvious in the adult.

Sebaceous glands appear, in general, to be smaller than those of humans, although large ones associated with small hair follicles occur on the face. Apocrine glands are widely but sparsely distributed, except in the axillae, where they contribute to axillary organs, the exterior meatus, the upper throat region and the mons. They are surrounded by nerves that contain cholinesterases, and they show phosphorylase activity. Eccrine glands occur throughout the hairy as well as the glabrous skin. Their secretory epithelium is composed of characteristic dark, clear cells.

The skin of *Homo sapiens* will be described in detail elsewhere, principally in Chapters 3 and 4. It is, however, appropriate here to note that in its essentials human skin is similar to that of the gorilla and the chimpanzee. The epidermis is pigmented, but to various extents in different geographical races. The most important evolutionary development is the loss or great diminution in hair, except for that on the scalp, axillary and perineal areas. The scalp may become progressively bald with age, especially in males. Except for the friction surfaces, however, hair

Fig. 2.11 The chimpanzee (*Pan troglodytes*)—the nearest living relative of *Homo sapiens*. (Courtesy of Mike Hill, Oxford Scientific Films Ltd.)

follicles are present. Apocrine gland rudiments form, but they remain vestigial and effectively disappear, except in the axilla, areola and perineum. Eccrine glands occur throughout the body. Both types of tubular gland contribute to axillary organs.

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Comparative anatomy

Eight different patterns of hair-follicle configuration have been discerned (Fig. 2.12), each one characteristic of one or a number of species [1]. Only in gibbons and gorillas have two arrangements, each in different areas of the body, been recognized.

The linear arrangement of repeating subunits of three or more follicles (linear perfect) occurs in tarsiers, the New World Ceboidea and the Old World Cercopithecoidea. Independent perfect lines and imperfect lines are found in a wide range of Old World monkeys and in some apes.

Independent circular clusters appear to be generally characteristic of lemurs, and clustered circular sets of lorises, supporting the conclusion that these Prosimians have deviated early from the main evolutionary line. The elongated clusters of the owl monkey (*Aotus*) add weight to the view that this is one of the most primitive of New World monkeys.

Random and paired groupings occur largely (but not exclusively) in the Hominoidea, suggesting that the hair groupings become less organized with phylogenetic advancement.

Changes in the skin glands are of the utmost importance in the evolution of the Hominoidea. No difficulties arise in relation to the sebaceous glands; they are present in all species of primate just as in nearly all other mammals. Small glands open into hair follicles throughout the hairy skin, and larger, multiacinar glands frequently

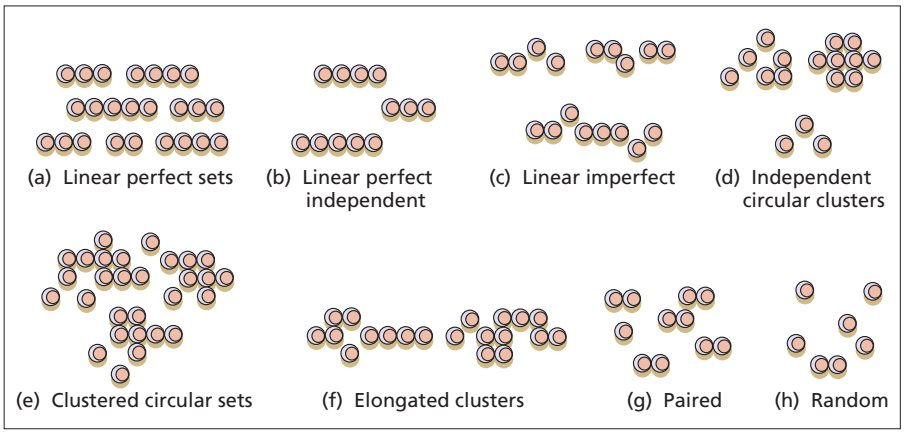

Fig. 2.12 Hair-follicle configurations as discerned by Perkins *et al*. [1].

occur in limited areas or as discrete glands, sometimes in association with tubular units.

The comparative anatomy and evolution of the merocrine glands is less clear-cut. Schiefferdecker's division into apocrine, in which secretion involves decapitation of the apical cytoplasm, and eccrine, in which the cells remain intact, is not entirely satisfactory, as evidence of necrobiotic secretory cycles is often lacking (Chapter 45). In the primates, at least, it is equally unsatisfactory to distinguish between 'epitrichial' glands, which normally develop from the external root sheath and remain attached to the hair follicle, and 'atrichial' glands, which develop from the superficial epidermis and remain independent, because Prosimians have glands which develop from the hair follicle but, in the adult, open separately to the skin surface. Moreover, as in the ring-tailed lemur, similar glands open directly on to the glabrous surfaces.

Broad distinctions can, nevertheless, be made between two types of gland. In humans, apocrine glands are much the larger. They contain cuboidal secretory cells with prominent nuclei and apical caps projecting into the lumen, as well as myoepithelial cells next to the basement membrane. In eccrine glands, three types of cell can be identified: myoepithelial cells, serous or clear cells, and mucous or dark cells. Apocrine glands rarely contain glycogen, lack phosphorylase, are low in succinic dehydrogenase and are not surrounded by cholinergic nerve fibres. Eccrine glands, in contrast, abound in glycogen, phosphorylase and succinic dehydrogenase activity, and are always wrapped with nerve fibres containing cholinesterase.

Montagna and Yun [2] have used these histological and histochemical criteria to describe the tubular glands throughout the primates. The distinctions are fairly clear-cut in Cercopithecidae, but less so in the lower primates. In the anubis baboon [2], for example, the large apocrine glands have thick, coiled secretory segments, rich in alkaline phosphatase but lacking phosphorylase; the eccrine glands have both clear and dark cells and are rich in succinic dehydrogenase and amylophosphorylase. However, there are regional differences. In the white-crowned mangabey, for example, the larger apocrine glands of the external genitalia show greater phosphorylase activity than do those of the hairy skin [3]. In the potto [4], the skin of the scrotum and vulva contains large apocrine glands, which, unlike those of the body surface, are surrounded by nerves rich in acetylcholinesterase.

It is therefore perhaps not surprising that Grant and Hoff [5] found that a dendrogram plot of sweat gland characters separated ceboids from non-ceboids (prosimians plus catarrhines) but otherwise did not correlate with groupings determined by other taxonomic criteria. It seems probable that apocrine glands are of more than one type, and that histochemistry may reveal more about their function than their phylogenetic history.

Eccrine glands should clearly be put into two categories. Those of the friction surfaces are present in many mammalian orders as well as in all species of primates. The fact that in humans the friction surface glands develop at about 3.5 months of gestation, 2 months before those elsewhere, reinforces the view that these are the more archaic. This does not, however, imply that the eccrine glands of the hairy skin are structures only recently acquired by the Hominoidea, for they are also present in *Tupaia* and in all the Old World monkeys. Only the New World monkeys and the Prosimii have diverged from this tradition.

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The trend to nudity

Fossils cannot help in establishing when and why hair was lost in the course of human evolution, and there has been much speculation about the reasons for denudation, including an assumption that the reduction of body hair was a gradual process. It is, moreover, necessary to explain why humans have more highly developed eccrine sweat glands than any other mammal and a dermal blood vasculature far in excess of its own metabolic needs [1,2].

Physical anthropologists have generally neglected skin; for example, a famous book in which Wood Jones [3] documented the anatomical evidence for human arboreal ancestry does not mention it. Darwin [4], however, proposed the hypothesis of *sexual selection*, which was admirably designed to explain why body hair had virtually disappeared in the human species. The idea was, in essence, simple. As mating, in humans at least, and probably in many animals, was a matter of choice for both parties, each would select a partner with pleasing features.

Darwin first argues that from the presence of woolly hair, or *lanugo*, on the human fetus, and of rudimentary hairs scattered over the body in maturity, it could be inferred that humans are descended from some animal which was born hairy and remained so during life. He believed that this loss of hair was an inconvenience and probably an injury 'even in a hot climate, for he is thus exposed to the scorching of the sun, and to sudden chills, especially during wet weather. No one supposes that the nakedness of the skin is any direct advantage to man; his body therefore cannot have been divested of hair through natural selection' [4]. The absence of hair on the body was to a certain extent a secondary sexual character for, in all parts of the world, women are less hairy than men, 'therefore, we may reasonably suspect that this character has been gained through sexual selection'.

A more feasible argument, that hair loss was related to the descent from the trees and the adoption of a bipedal stance, has been advanced by several authors. Morris [5] regarded the achievement of nakedness as a major factor in human evolution. He puts the view that somewhere around 15 Ma a climatic change caused a diminution in the forest strongholds of the early apes. The ancestors of chimpanzees, gorillas, gibbons and orang-utans held on—and their numbers have been diminishing ever since. Human ancestors struck out, and left the forest for the savannah. Their diet changed; insects, eggs, tree frog-utans and small reptiles were added to fruit and nuts. Then they started to hunt mammals. The development of humans as hunters depended on a bipedal stance, which allowed sprinting, and the hands were freed for the making and use of tools and weapons. In parallel with this development of manual skill was enlargement of the brain and increase of mental ability.

Why should nudity have any selective advantage? Morris mentions several proposed explanations, such as a reduction in infestation with ectoparasites and, with particular regard to the female, a role in sexual attraction. He also refers to the suggestion of Hardy [6] that the ancestral hominid went through an aquatic phase, conceding that this nicely explained the existence of the thick layer of subcutaneous fat. Finally, he discusses the most commonly held view that the hairless condition is a cooling device. Although simply removing a hairy coat may not reduce body temperature, as heat can be gained as well as lost, the loss of the heavy coat of hair coupled with a great increase in sweat glands could be a cooling mechanism, not for minute-by-minute living in an intensely hot climate, but for the supreme movements of the chase in more moderate environmental temperatures. In short, hunting was a major factor in bringing about the skin changes.

A similar view is expressed by Brace and Montagu [7], who suggest that, by virtue of their hairlessness and sweat glands, human beings became the only major predators which could function exclusively in broad daylight. Until their advent as a serious menace, the big-game quadrupeds had less to fear from predators during the mid-day heat than at any other time.

Ardrey [8] developed the argument even further. In his view, the expansion of the brain depended on the eating of meat. After claiming that the association of fossil animal bones with hominid remains proved that butchering sites existed almost 2 Ma, long before the development of the brain to human capacity, he cites the statement of Crawford and Sinclair [9] that certain structural fats are essential for the development of the brain and nervous system. The necessary unsaturated fatty acids—linoleic and linolenic—originate in plants, and are concentrated and synthesized into chains by herbivores. Only carnivores, however, can acquire a whole season's storage from a single kill.

The evidence quoted in favour of an aquatic phase in the evolution of the ancestral hominid is that, alone among all primates, the hairs on the human body show precisely the pattern which would be followed by the flow of water over a swimmer. Moreover, *Homo sapiens* resembles other aquatic mammals in its layer of subcutaneous fat, and the erect walk might also be related to wading. The aquatic hypothesis undoubtedly has some attractions. In particular, it must have been easier for hominid ancestors to obtain food from the resources of the sea or even fresh water than by hunting animals larger and faster than themselves. A serious objection, if one is needed, is that the human's heavy endowment of eccrine sweat glands would appear to be utterly superfluous for aquatic life.

Whatever the doubts about the hunting hypothesis, it seems undeniable that the reduction in hair density and

the development of eccrine glands provides a mechanism for keeping cool, perhaps especially for the dispersal of metabolic heat produced by short bursts of muscular activity. These evolutionary events were not, however, recent. Both the gorilla and the chimpanzee have relatively sparse hair in adult life, which suggests that the trend towards hairlessness existed before their divergence 9–7 Ma. Such sparsity could result from a reduction in hair density as well as in hair size, and may simply be related to body size. Thus, Schwartz and Rosenblum [10] concluded from an examination of hair densities in 23 primate species, ranging from the marmoset to the gorilla, that increasingly massive primates have substantially fewer hairs per equal unit of body surface. As the 'equal units' referred to were 'relative hair densities' for which the actual density of hairs per square centimetre had already been divided by the body surface area, the extent of the claimed allometric trend is difficult to assess. However, by estimating the weight of australopithecines from the skeletal remains, the authors conclude that substantial depilation of hominids probably occurred prior to and not after their migration from forest to grassland.

Similarly, eccrine glands did not suddenly replace allegedly more primitive apocrine glands. It may be true that apocrine units function as sweat glands in some large mammals, such as horses, cattle and other ungulates, in which the hairy skin lacks eccrine glands. But the most primitive extant primate, the tree shrew, has both apocrine and eccrine glands in the hairy regions, as do Old World monkeys and apes. The evolutionary change in primates is thus simply a vestigialization of the apocrine glands accompanying that of the hair follicles.

Increase in body size does not explain everything. Viewed by hindsight at least, evolving hominids were preparing to move out of the tropical forests, first to the savannah, and ultimately to fan out globally, even to the edges of the polar seas. This change was accompanied by the adoption of bipedalism. In relation to gain or loss of heat and protection from solar radiation, an upright organism has completely different properties from one on all fours. Thus, Lee [11] has pointed out that a standing human receives on average only two-thirds as much solar radiation as a sheep of equivalent size and less than one-quarter at the noontime peak, and Wheeler [12] has calculated that a quadruped hominid would expose 17% of its total body surface area to direct radiation when the sun is at its zenith, whereas a bipedal hominid would expose only 7%.

Wheeler [12] points out that many mammals are able to keep the brain at a lower temperature than the rest of the body by dissipating heat through a counter-current system. It is exchanged between a carotid rete and the venous blood system, which drains the mucosal linings of the nasal chamber and turbinates, where cooling by evaporation occurs. Primates lack this system, and can only protect the brain from thermal damage by restricting rises in overall body temperature. The thermoregulatory advances in the evolution of *Homo* removed the physiological restraint and made the rapid expansion of the brain possible.

Why does hair persist in certain areas? The male beard is undoubtedly a sexual character, as its production requires high levels of male hormone. Whether as a visual signal it is directed towards females, or other males, or both, is unclear; ethologists have conveniently invented the term 'socio-sexual' to cover such ambiguous situations. Hair on the trunk of males is similarly androgen dependent and must be put in the same category. Pubic and axillary hair also clearly serves a socio-sexual purpose, as it develops, in both sexes, only after puberty. It is probably part of scent-disseminating systems.

Little controversy surrounds the assumption that scalp hair remains to protect bipedal animals from radiation in the mid-day sun. Long hair would similarly protect the shoulders and could, indeed, provide a complete shield for both mother and infant. However, the fact that long, straight scalp hair is generally characteristic only of the Caucasoid and Mongoloid geographical races and Negroids more often have curved or crimped hair would seem to invalidate any sweeping generalizations.

The loss of scalp hair in some adults, particularly males, is not entirely a human propensity, as it is presaged in the uacari, the stump-tailed macaque and the chimpanzee. Montagna [1] has regarded scalp baldness simply as part of the evolutionary trend to complete denudation. But what is important is that baldness, although hereditary, is androgen dependent. It is thus manifested principally in males, notwithstanding that less obvious diffuse hair loss in women probably has a similar aetiology. Does baldness therefore have a direct selective advantage to males alone? Or could its cosmetic disadvantage be linked with some other unidentified benefit?

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Chapter 3

Anatomy and Organization of Human Skin

J.A. McGrath, R.A.J. Eady & F.M. Pope

Components of normal human skin

Human skin consists of a stratified, cellular epidermis and an underlying dermis of connective tissue [1–5]. The dermal–epidermal junction is undulating in section; ridges of the epidermis, known as rete ridges, project into the dermis. The junction provides mechanical support for the epidermis and acts as a partial barrier against exchange of cells and large molecules. Below the dermis is a fatty layer, the panniculus adiposus, usually designated as 'subcutaneous'. This is separated from the rest of the body by a vestigial layer of striated muscle, the panniculus carnosus.

There are two main kinds of human skin. Glabrous skin (non-hairy skin), found on the palms and soles, is grooved on its surface by continuously alternating ridges and sulci, in individually unique configurations known as dermatoglyphics. It is characterized by a thick epidermis divided into several well-marked layers, including a compact stratum corneum, by the presence of encapsulated sense organs within the dermis, and by a lack of hair follicles and sebaceous glands. Hair-bearing skin (Fig. 3.1), on the other hand, has both hair follicles and sebaceous glands but lacks encapsulated sense organs. There is also wide variation between different body sites. For example, the scalp with its large hair follicles may be contrasted with the forehead, which has only small vellus-producing follicles, albeit associated with large sebaceous glands. The axilla is notable because it has apocrine glands in addition to the eccrine sweat glands, which are found throughout the body. Regional variation is further considered below.

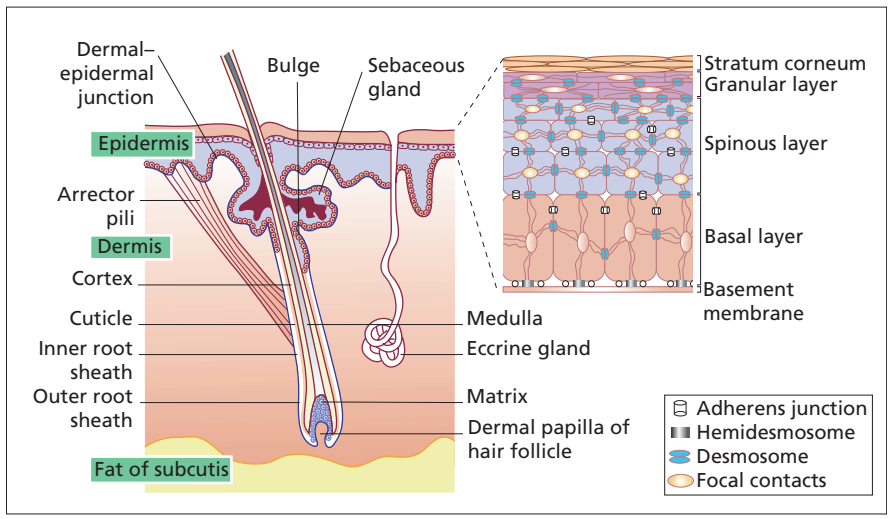

Fig. 3.1 The skin and its appendages.

The superficial epidermis is a stratified epithelium largely composed of keratinocytes that are formed by division of cells in the basal layer, and give rise to several distinguishable layers as they move outwards and progressively differentiate. Within the epidermis, there are several other cell populations, namely melanocytes, which donate pigment to the keratinocytes (Chapter 39), Langerhans' cells, which have immunological functions (Chapter 10) and Merkel cells.

The hair follicles comprise pockets of epithelium that are continuous with the superficial epidermis. They undergo intermittent activity throughout life. During the active phase, the follicle envelops at its base a small papilla of dermis. A bundle of smooth muscle, the arrector pili, extends at an angle between the surface of the dermis and a point in the follicle wall. Above the insertion, the holocrine sebaceous gland opens by a short neck into the pilary canal, and some follicles in certain areas of the body, notably the axilla, have, in addition, an apocrine gland. Also derived from the epidermis, and opening directly to the skin surface, are the eccrine sweat glands, present in every region of the body in densities of 100–600/cm^2.

The basis of the dermis is a supporting matrix or ground substance in which polysaccharides and protein are linked to produce macromolecules with a remarkable capacity for retaining water. Within and associated with this matrix are two kinds of protein fibre: collagen, which has great tensile strength and forms the major constituent of the dermis, and elastin, which makes up only a small proportion of the bulk. The cellular constituents of the dermis include fibroblasts, mast cells and histiocytes (monocyte/macrophages). The dermis has a very rich blood supply, although no vessels pass through the dermal–epidermal junction.

The motor innervation of the skin is autonomic, and includes a cholinergic component to the eccrine sweat glands and adrenergic components to both the eccrine and apocrine glands, to the smooth muscle and the arterioles and to the arrector pili muscle. The sensory nerve endings are of several kinds: some are free, some terminate in hair follicles and others have expanded tips. Only in glabrous skin are some nerve endings encapsulated. Sense organs are described later in this chapter.

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Embryology [1,2]

Origin of the skin

The skin arises by the juxtaposition of two major embryological elements: the prospective epidermis, which originates from a surface area of the early gastrula, and the prospective mesoderm, which is brought into contact with the inner surface of the epidermis during gastrulation [3,4]. The mesoderm not only provides the dermis but is essential for inducing differentiation of the epidermal structures, such as the hair follicle in mammals [5]. Indeed, an influence from the dermis is essential for the maintenance of adult epidermis [6], although organized dermis is not in this instance mandatory, the property also residing in powdered dermis or tendon [7].

The neural crest also makes an important contribution to the skin, namely the pigment cells, although their bulk is small.

The timing of the events during development is summarized in Table 3.1.

Epidermis

The development of the epidermis (and its appendages) relies on specific initiation signals. Although complex, critical events appear to be governed by opposing interplay between the Notch and Wnt (wingless-related) signalling pathways, with β-catenin, Lef1 and Notch peptide all having key roles [9]. Signals from the Sonic hedgehog pathway and bone morphogenetic proteins (BMPs) also are important in early embryogenesis, notably in determining whether cells have an ectodermal or neural fate. Specifically, BMP signalling promotes ectodermal development, while Sonic hedgehog promotes neural tube and

Table 3.1 Morphological events during fetal skin development. (Data from Holbrook and Hoff [8].)

	Month (gestation)					
	1	2	3	4	5	6
Hair peg				+		
Exposed hair					+	
Nail				+		
Sebaceous gland					+	
Apocrine gland						+
Eccrine gland						+
Follicular keratinization					+	
Interfollicular keratinization						+
Non-keratinocytes						
Melanocytes						
Non-functioning			+			
Active				+		
Langerhans' cells				+		
Merkel cells				+		

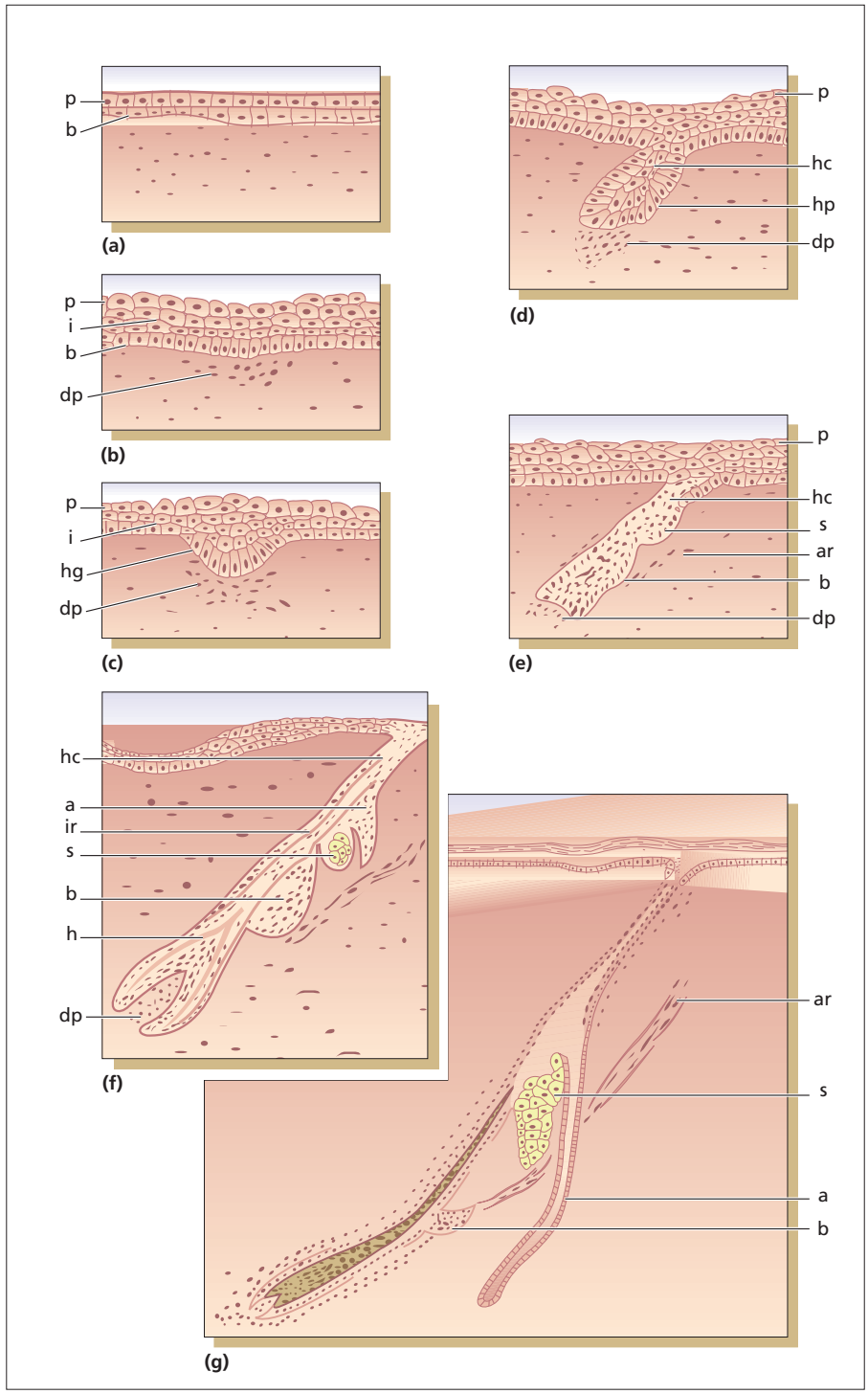

Fig. 3.2 Development of epidermis, hair follicle and associated structures. (a) Section of skin of embryo at about 4 weeks. The periderm (p) is clearly seen, and a basal or germinative layer (b) appears in some areas. (b) Skin at about 11 weeks. The epidermis is made up of basal cells, cuboidal in shape (b), and cells of the stratum intermedium (i) are beginning to appear above them. The periderm (p) consists of a single cell layer. Mesenchyme cells (dp) are beginning to aggregate below a presumptive hair follicle. (c) Hair germ (hg) stage. Basal cells are now columnar and starting to grow downwards. (d) Hair peg (hp) stage. Cells of the so-called 'hair canal' (hc) form a solid strand. (e) Bulbous hair peg. Note the solid 'hair canal' (hc), sebaceous gland rudiment (s), bulge (b) for attachment of developing arrector muscle (ar). (f) Later stage showing apocrine rudiment (a), sebaceous gland (s) now partly differentiated, and bulge (b). The dermal papilla (dp) has been enclosed and a hair (h) is starting to form, with an inner root sheath (ir). (g) Complete pilosebaceous unit of axillary skin from a 26-week-old fetus. The sebaceous gland (s) is well differentiated and the apocrine gland (a) is canalized.

central nervous system (CNS) development [10]. Thus, a complex interaction between these two components, as well as signals from fibroblast growth factors (FGFs) and additional regulatory control mechanisms from the Wnt pathway, underlies the preliminary stages of epidermal development.

In about the third week of fetal life, the epidermis consists of no more than a single layer of undifferentiated, glycogen-filled cells [8]. In a 4- to 6-week-old fetus [2], however, two layers of cells can be distinguished, the periderm or epitrichial layer and a stratum germinativum (Fig. 3.2). The periderm [8] is a purely embryonic structure (Fig. 3.3), which is unique to primates: it is ultimately lost *in utero* as the true epidermis keratinizes beneath it.

Between 8 and 11 weeks (crown to rump length 26–50 mm) a middle layer starts to form (Fig. 3.2). Glycogen is

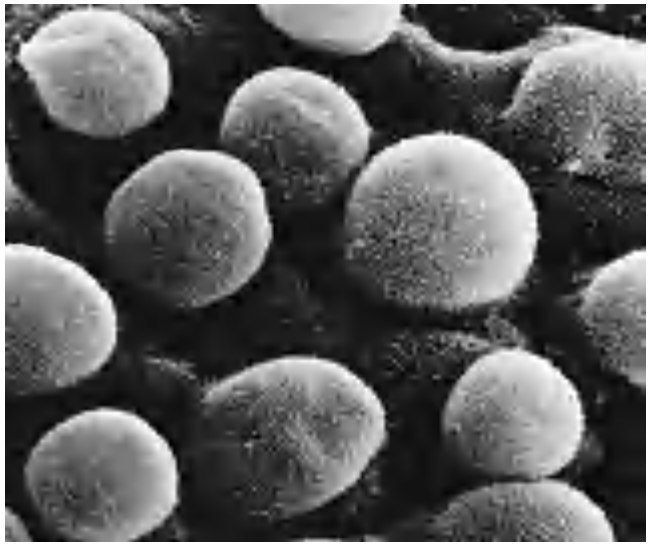

Fig. 3.3 Scanning electron micrograph of an 85–110 day (estimated gestation age) human embryo. Single globular blebs project from the periderm cells. (Courtesy of Professor K.A. Holbrook, University of Florida, Gainesville, FL, USA.)

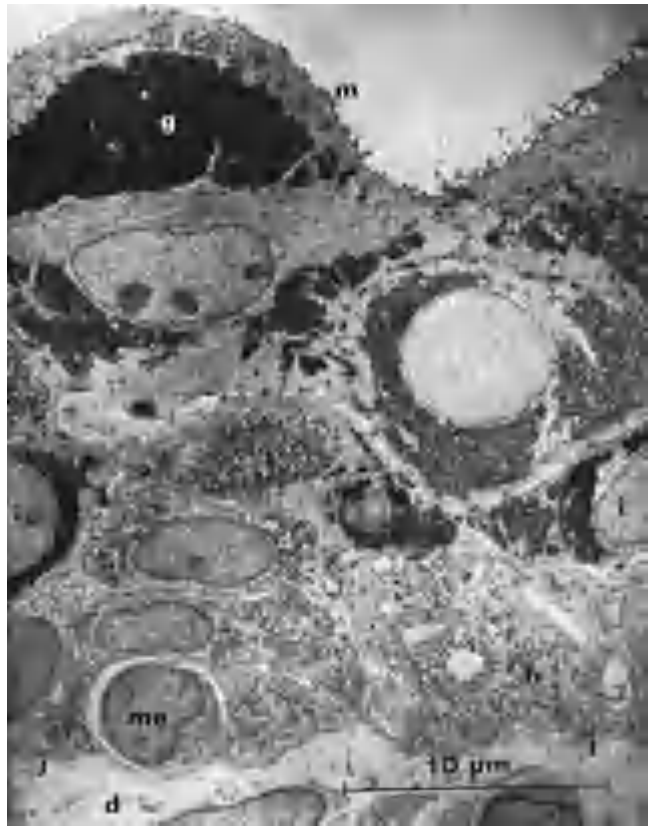

Fig. 3.4 Electron micrograph of the full-thickness epidermis from the back of a 14-week human fetus. Osmium fixation and lead staining. The periderm cells are full of glycogen (g) and have microvilli (m) at their amniotic border. Cells of the intermediate layer (i) also contain glycogen. Basal-layer cells (b) have lost glycogen by this stage. Just above the dermal–epidermal junction (j) is seen a melanocyte (me); the surrounding space indicates that it is a recent immigrant from the dermis (d). (Courtesy of Professor A.S. Breathnach, St John's Institute of Dermatology, London, UK.)

abundant in all layers, and a few microvillous projections occur at the surface of the periderm. The surface cells, as viewed by the scanning electron microscope, are flat and polygonal [11].

By 12–16 weeks (crown to rump length 69–102 mm), there are one or more intermediate layers. These cells contain mitochondria, Golgi complexes and a few tonofilaments, as well as abundant glycogen both within and between the cells (Fig. 3.4). Microvilli become much more numerous.

From this stage onwards, dome-shaped blebs start to project from the centres of the periderm cells (Fig. 3.3). At first the blebs are simple (Fig. 3.4), but later their surface becomes dimpled and infolded. Between 16 and 26 weeks, the intermediate layers increase in number, and by 21 weeks keratohyalin granules appear in the uppermost layer. The elevations of the periderm become cast off into the amniotic fluid, and by 24 weeks the periderm cells start to separate from the embryo. Together with shed lanugo, sebum and other materials, they form the vernix caseosa.

Hemidesmosomal and desmosomal proteins are already demonstrable in the basal keratinocytes at 10 weeks. By 14 weeks, basal keratins are expressed by the basal cells and skin-differentiation keratins are expressed by cells of the middle layer. Filaggrin, the protein of the granular layer, is first detectable at 15 weeks.

The periderm may be no more than a protective investment for the fetus before keratinization of the epidermis. On the other hand, features such as the abundant microvilli, raised blebs, coated- and smooth-membrane vesicles and increasing cell size, suggest it may have an important embryonic function. The microvilli with their 'fuzz' coat of mucopolysaccharide are similar to the modifications of the luminal border of the intestinal mucosa cell. All these considerations suggest that the periderm might be concerned with the uptake of carbohydrate from the amniotic fluid [11].

Hair follicles and apocrine glands

The earliest development of the hair rudiments [12–14] occurs at about 9 weeks in the regions of the eyebrow, upper lip and chin. This represents an initial response to the first of three discrete mesenchymal-epithelial exchanges that orchestrate hair follicle formation [15]. The first sign of a hair follicle is a crowding of nuclei in the basal layer of the epidermis, the so-called primitive hair germ or pregerm stage (Fig. 3.2b). This occurs in response to a primary message from the subjacent mesenchyme. The pregerm passes rapidly into the hair germ stage, the

basal cells become high; the nuclei become elongated and the structure starts to grow downward into the dermis. At the same time, mesenchymal cells and fibroblasts increase in number to form the rudiment of the hair papilla beneath the hair germ. These events are mediated by a second series of signals from the expanding epithelial cells. At this stage it is known as the hair peg (Fig. 3.2d). The outer cells of the hair peg are arranged radially to the long axis, and are columnar in shape, those at the advancing matrix end being conspicuously tall and narrow. As the germ develops, it grows obliquely downwards, and the advancing extremity becomes bulbous, gradually enveloping the mesodermal papilla. Proliferation and differentiation are then enhanced by a third series of signals emanating from the dermal papillae. At this bulbous hair-peg stage, two epithelial swellings appear on the posterior wall of the follicle. The lower one is the bulge to which the arrector muscle becomes attached, and the upper is the rudiment of the sebaceous gland. In many follicles, a third bud later appears above the sebaceous gland; this is the rudiment of the apocrine gland. Such rudiments develop in a large number of the follicles, including some on the scalp, face, chest, abdomen, back and legs, as well as in the axilla, mons pubis, external auditory meatus, eyelids, circumanal area, areola region of the breast, labia minora, prepuce and scrotum, where they survive in the adult.

As the bulbous hair peg grows downwards and differentiates, the first cells of the inner root sheath (IRS) begin to form above the region of the matrix. The matrix continues to burrow deeper, and above the root sheath the inner cells of the follicle grow upwards into the epidermis, to form the hair canal.

The different mesenchymal-epithelial cues involve several signalling pathways including Notch, Sonic hedgehog and Wnt, as well as contributions from FGFs and BMPs. There are also marked changes in certain cell adhesion proteins, notably E-cadherin and P-cadherin [15].

The hair follicles are arranged in patterns, usually in groups of three. It appears that the first follicles develop over the surface at fixed intervals of between 274 and 350 μm. As the skin grows, these first germs become separated, and new rudiments develop between them when a critical distance, dependent on the region of the body, has been reached. Commonly, follicles occur in groups of three, with the hairs arranged on a straight, short line, more or less transverse to the grain or slant of the hair. There is no large-scale destruction of follicles during postnatal development, only a decrease in actual density as the body surface increases; nor do any new follicles develop in adult skin.

Sebaceous glands [16,17]

These are, at first, solid, hemispherical protuberances on the posterior surfaces of the hair pegs. The cells contain moderate amounts of glycogen, but soon the cells in the centre lose this, and become larger and foamy as they accumulate droplets of lipid. The sebaceous glands become differentiated at 13–15 weeks, and are then large and functional. The sebum forms a part of the vernix caseosa. At the end of fetal life, sebaceous glands are well developed and generally large. After birth, the size is rapidly reduced, and they enlarge to become functional again only after puberty.

Eccrine glands [18,19]

These start to develop on the palms and soles at about 3 months, but not over the rest of the body until the fifth month. In embryos of 12 weeks, the rudiments of eccrine sweat glands are first identifiable as regularly spaced undulations of the stratum germinativum. Cells that form the anlagen are oblong, palisading and lie closely together, but otherwise they do not differ from the rest of the stratum germinativum. By 14–15 weeks, the tips of the eccrine sweat gland rudiments have penetrated deeply into the dermis, and have begun to form the coils. In the overlying epidermis, columns of cells that are destined to form the intraepidermal sweat ducts are recognizable. Each column is composed of two distinct cylindrical layers, comprising two inner cells that are elongated and curved so that they embrace the inner cylinder.

The intraepidermal duct appears to form by the coalescence of groups of intracytoplasmic cavities formed within two adjacent inner cells. In the intradermal segment, on the other hand, the lumen appears to form by dissolution of the desmosomal attachment plaques between the cells that compose the inner core of the eccrine duct germ.

Nails [20,21]

Nails begin to develop in the third month. In fetuses at 16–18 weeks (crown to rump length 120–150 mm) keratinizing cells from both dorsal and ventral matrices can be distinguished.

Melanocytes [22]

Melanocytes take their origin from the neural crest. This can be identified in early human embryos, but the elements arising from it soon lose themselves in the mesenchyme, and pigmented melanocytes cannot be identified, even in black skin fetuses, before 4–6 months of gestation. However, dopa-positive melanocytes can be demonstrated earlier.

Langerhans' cells [22,23]

These are derived from the monocyte–macrophage–histiocyte lineage and enter the epidermis at about 12 weeks.

Merkel cells [24]

These appear in the glabrous skin of the fingertips, lip, gingiva and nail bed, and in several other regions, around 16 weeks.

Dermis

It was at one time believed that the mesenchymal cells forming the dermis came from the ventrolateral part of the somite, which for that reason was named the dermatome. Although some cells may migrate from the dermatome and take part in the formation of the skin, most of the dermis is formed by mesenchymal cells that migrate from other mesodermal areas. These mesenchymal cells give rise to the whole range of blood and connective tissue cells, including the fibroblasts and mast cells of the dermis and the fat cells of the subcutis. Nevertheless, a new type of stem cell from the dermis, called skin-derived precursor (SKP) cells, has been identified [25]. Such cells are capable of being converted into several different cell types *in vitro* (e.g. neurones, smooth muscle cells or adipocytes) and might constitute a highly accessible source of pluripotential autologous stem cells.

The embryonic dermis is at first very cellular, and in the second month the dermis and subcutis are not distinguishable from each other. Fibrillar components shortly make their appearance, and regular bundles of collagen fibres are evident by the end of the third month. Later, the papillary and reticular layers become distinct and, at the fifth month, the connective tissue sheaths are formed around the hair follicles. Elastic fibres are first detectable at 22 weeks [26]. Beneath the dermis is a looser tissue characterized by fat islands that begin to form in definite places.

In embryos of 6–14 weeks, three types of cell have been described in the dermis: stellate cells, phagocytic macrophages and a granule-secretory cell, either a melanoblast or a mast cell [27]. From weeks 14–21, fibroblasts are numerous and active, and perineurial cells, pericytes, melanoblasts, Merkel cells and mast cells [28] can be individually identified. Another cell, of bone marrow origin, may be ancestral to the Langerhans' cell and the histiocyte [27].

At first, the undersurface of the epidermis is smooth, but during the fourth month, at the same time as the hair follicle starts to develop, it becomes irregular.

Touch pads become recognizable on the hands and fingers, and on the feet and toes, by the sixth week, and reach their greatest development at the 15th week. After this, they flatten and become indistinct. It is these areas, however, that determine the pattern of dermatoglyphs —the systems of papillary ridges—that take their place [29].

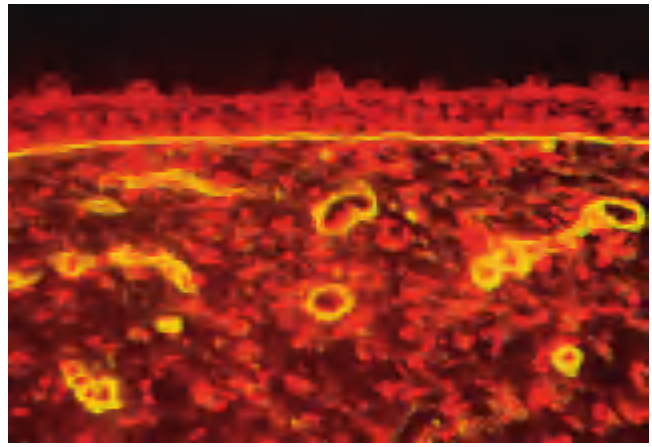

Fig. 3.5 Immunofluorescence photomicrograph showing staining with antitype IV collagen antibody of a section of the skin of a fetus of 15 weeks' gestational age. Note the surface periderm and the bright fluorescence at the dermal–epidermal junction and around the blood vessels. × 250.

Dermal–epidermal junction

A continuous lamina densa of the basement membrane becomes evident in the second month of gestation (Fig. 3.5), and hemidesmosomes appear in the third month [30].

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Epidermis

Structure and ultrastructure [1,2]

The normal epidermis is a terminally differentiated, stratified squamous epithelium (Fig. 3.6). The major cell, making up 95% of the total, is the *keratinocyte*, which moves progressively from attachment to the epidermal basement membrane towards the skin surface, forming several well-defined layers during its transit. Thus, on simple morphological grounds, the epidermis can be divided into four distinct layers: *stratum basale* or *stratum germinativum*, *stratum spinosum*, *stratum granulosum* and *stratum corneum*. The term *Malpighian* layer includes both the basal and spinous cells. Other cells resident within the epidermis include melanocytes, Langerhans' cells and Merkel cells.

The stratum basale (Fig. 3.7) is a continuous layer that is generally described as only one cell thick, but may be two to three cells thick in glabrous skin and hyperproliferative epidermis. The basal cells are small and cuboidal (10–14 nm) and have large, dark-staining nuclei, dense cytoplasm containing many ribosomes and dense tonofilament bundles. Immediately above the basal cell layer,

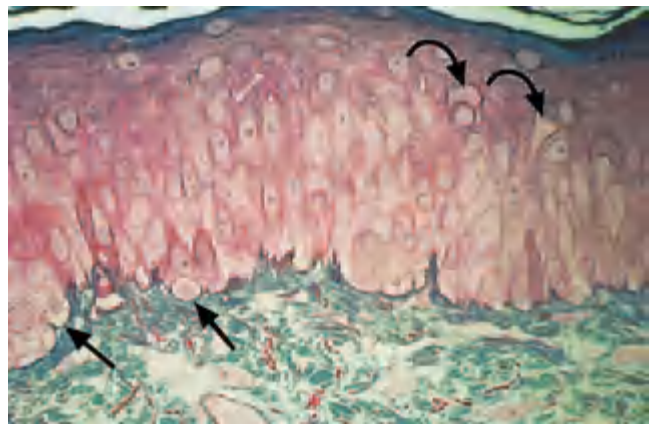

Fig. 3.6 Photomicrograph of a 1-µm-thick plastic section of normal human skin. The tissue was fixed with half-strength Karnovsky's medium and embedded in Epon. This technique allows the cellular components of the epidermis, including keratinocytes, melanocytes (straight arrows) and probable Langerhans' cells (curved arrows) to be clearly resolved. × 400. Basic fuchsin and methylene blue.

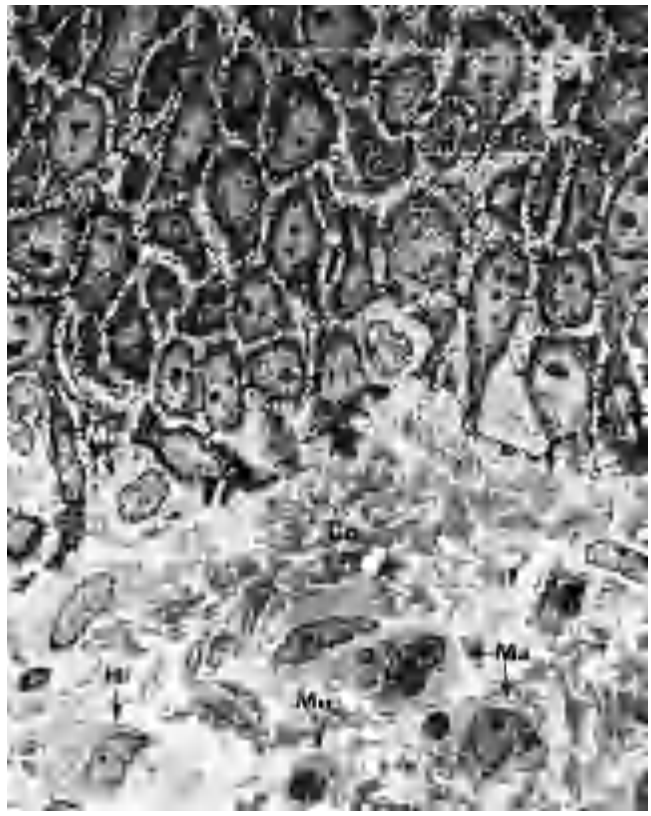

Fig. 3.7 The stratum basale (SB) and part of the stratum spinosum together with underlying dermis of skin from the forearm. Two melanocytes (Me) can be seen between the basal cells of the epidermis. In the dermis, collagen fibres (Co), histiocytes (Hi), monocytes (Mo) and mast cells (Ma) can be identified. ×1400. (Courtesy of Professor A.S. Breathnach, St John's Institute of Dermatology, London, UK.)

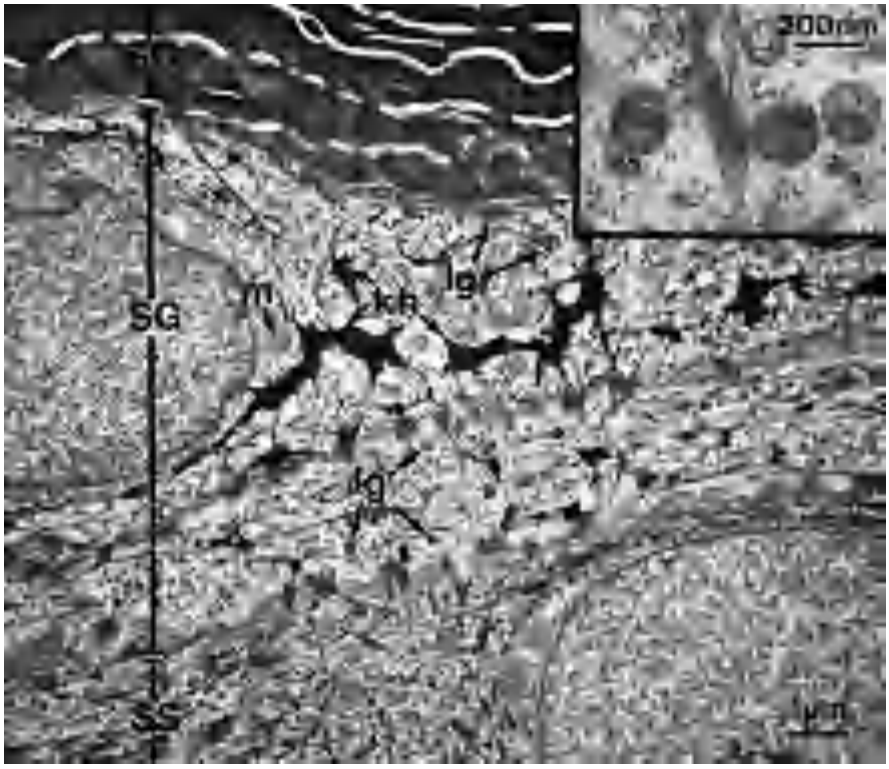

Fig. 3.8 Electron micrograph showing details of upper part of epidermis including stratum corneum (SC), stratum granulosum (SG) and the most superficial cell layer of stratum spinosum (SS). Note the irregularly shaped keratohyalin granules (kh) and the small, round lamellar granules (lg). The latter are present in both SS and SG and are smaller than mitochondria (m). Inset shows details of lamellar granules. See also Figs 3.19 and 3.20. Scale bar = 1 µm.

the epibasal keratinocytes enlarge to form the spinous/prickle-cell layer or *stratum spinosum* (Fig. 3.8).

The stratum spinosum is succeeded by the *stratum granulosum* or granular layer (see Fig. 3.8) because of the intracellular granules of keratohyalin. At high magnification, the dense mass of keratohyalin granules from human epidermis has a particulate substructure, with particles of irregular shape on average 2 nm length and occurring randomly in rows or lattices [3]. The cytoplasm of cells of the upper, spinous layer and granular cell layer also contains smaller lamellated granules averaging 100–300 nm in size, which are known as lamellar granules or bodies, membrane-coating granules or Odland bodies [2] (see Fig. 3.8). These are numerous within the uppermost cells of the spinous layer and migrate towards the periphery of the cells as they enter the granular cell layer. They discharge their lipid components into the intercellular space, playing important roles in barrier function and intercellular cohesion within the stratum corneum.

The outermost layer of epidermis is the stratum corneum (see Fig. 3.8) where cells (now corneocytes) have lost nuclei and cytoplasmic organelles. The cells become flattened and the keratin filaments align into disulphide cross-linked macrofibres, under the influence of *filaggrin*, the protein component of the keratohyalin granule, responsible for keratin filament aggregation [4]. The corneocyte has a highly insoluble cornified envelope within the plasma membrane, formed by cross-linking of the soluble protein precursor, *involucrin* [5], following the action of a specific epidermal transglutaminase also synthesized in the high stratum spinosum [6]. The process of desquamation involves degradation of the lamellated lipid in the intercellular spaces and loss of the residual intercellular desmosomal interconnections. In palmoplantar skin there is an additional zone, also electronlucent, the *stratum lucidum* between the granulosum and corneum. These cells are still nucleated, and may be referred to as 'transitional' cells.

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Intercellular junctions

Several types of cellular junction exist that link adjacent keratinocytes and which are responsible for mechanical,

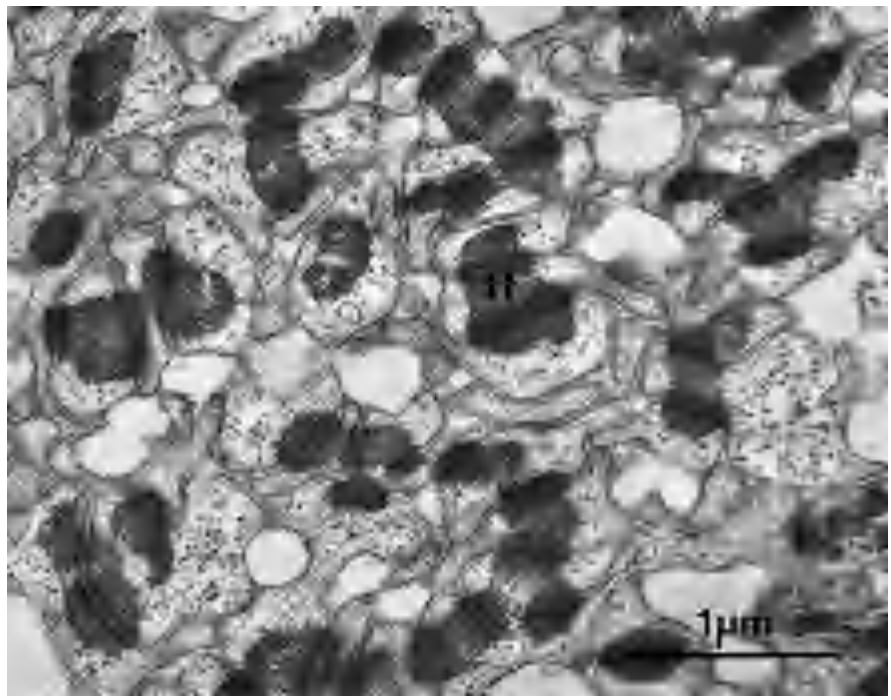

Fig. 3.9 Electron micrograph of desmosomes in spinous layer. These intercellular junctions are closely associated with tonofilaments (tf), many of which, in this view, are cross-sectioned. Scale bar = 1 μm.

biochemical and signalling interactions between cells. These include desmosomes, adherens junctions, gap junctions and tight junctions.

Desmosomes

Desmosomes are the major adhesion complex in epidermis, anchoring keratin intermediate filaments (IFs) to the cell membrane and bridging adjacent keratinocytes, and allowing cells to withstand trauma. The desmosome has a characteristic ultrastructure, in which the cell membrane of two adjacent cells forms a symmetrical junction with a central intercellular space of 30 nm containing a dense line (Fig. 3.9). Plaques of electron-dense material run along the cytoplasm parallel to the junctional region, in which three ultrastructural bands can be distinguished: an electron-dense band next to the plasma membrane, a less dense band, then a fibrillar area. Intermediate filaments loop through this region, and traversing filaments extending between the IFs and globular elements in the cell membrane may be unravelling IF protofilaments or associated proteins [1].

The main components of desmosomes consist of the products of three gene superfamilies: the desmosomal cadherins, the armadillo family of nuclear and junctional proteins, and the plakins [2]. The transmembranous cadherins comprise heterophilic associations of desmogleins and desmocollins. There are three main epidermis-specific desmogleins (Dsg1–3) and likewise for the desmocollins (Dsc1–3), all of which show differentiation-specific expression. For example, Dsg1 and Dsc1 are preferentially expressed in the superficial layers of the epidermis whereas Dsg3 and Dsc3 show greater expression in basal keratinocytes. The intracellular parts of these glycoproteins are attached to the keratin filament network via desmoplakin, plakoglobin and other macromolecules, the nature of which has been gleaned from a combination of yeast two hybrid, coimmunoprecipitation, recruitment assays in cultured cells and immunoelectron microscopy studies [2,3]. These have identified the armadillo protein, plakophilin 1, as an important stabilizer of keratinocyte adhesion in differentiated keratinocytes [4], as well as other site-specific plakin cell envelope proteins, such as envoplakin and periplakin [5,6]. The network of the major interactive desmosomal proteins is depicted in Fig. 3.10.

Further clues to the biological function and *in vivo* contribution to keratinocyte adhesion of these desmosomal components have arisen from various mouse models and human diseases, both inherited and acquired [2]. A summary of recent findings is represented in Table 3.2.

Adherens junctions

Adherens junctions are electron dense transmembrane structures that associate with the actin skeleton, part of the keratinocyte filament network concerned with cell motility, changes in cell shape and cell interactions. The transmembrane component of adherens junctions is E-cadherin, which forms calcium-dependent homophilic adhesive interactions with E-cadherin on opposing cells. The main linkage to the actin cytoskeleton is through α-catenin, although other adherens junction components

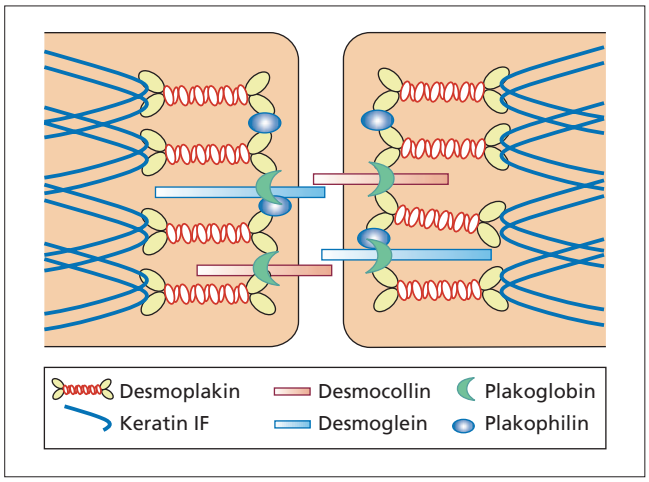

Fig. 3.10 Macromolecular composition of desmosomes linking adjacent keratinocytes. Cells are connected via transmembranous cadherin glycoproteins (desmogleins and desmocollins). Attachment of these molecules to the keratin filament cytoskeleton occurs via a network of desmosomal plaque proteins (desmoplakin, plakoglobin and plakophilin).

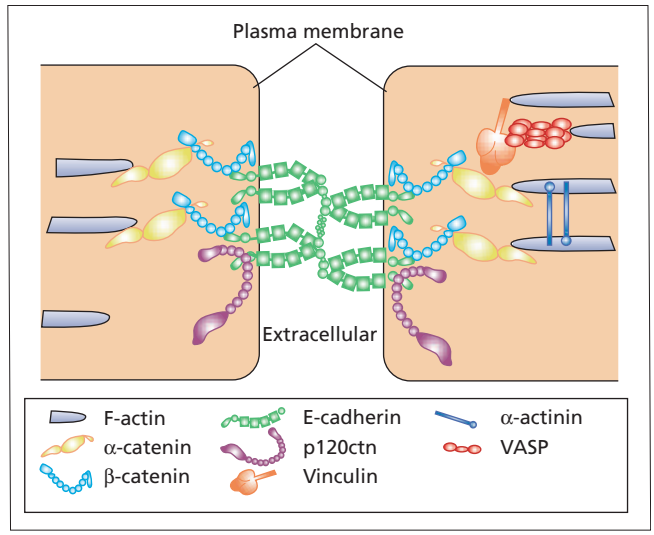

Fig. 3.11 Macromolecular composition of adherens junctions linking adjacent keratinocytes. Cells are connected via transmembranous E-cadherin and linked to the actin cytoskeleton via a network of adhesive proteins including β-catenin, α-catenin and p120ctn.

include p120ctn, β-catenin, plakoglobin (also present in desmosomes), α-actinin, vinculin, VASP (vasodilator-stimulated phosphoprotein), Mena and ZO1 (Fig. 3.11). Apart from forming E-cadherin–catenin complexes, α-catenin also appears to have a role in organizing the entire multiprotein complexity of adherens junctions and in determining the actin-binding and polymerization activities [7]. Clues to the precise function of individual components are gradually being realized through extensive conditional gene targeting and cultured cell

Table 3.2 Mouse models and human diseases related to desmosome genes/proteins.

Mutation/target antigen	Phenotype
Mouse models	
Plakoglobin knock-out	Lethal in early embryonic development (cardiac defects) Later survivors show epidermal fragility
Desmoglein-3 knock-out	Hair loss and epithelial fragility
Epidermally targeted truncated desmoglein-3 transgenic	Flakiness of back skin and paw swelling within 2 days of birth Desmosomes are reduced in number Hyperproliferation and inflammation in some areas
Desmoplakin knock-out	Lethal in early embryos
Desmocollin-1 knock-out	Flaky skin, defective epidermal barrier, hair loss
Inherited human diseases (autosomal recessive)	
Plakoglobin carboxy-terminal truncation	Naxos disease (arrhythmogenic right ventricular cardiomyopathy, keratoderma and woolly hair)
Desmoplakin carboxy-terminal truncation	Cardiomyopathy, keratoderma and woolly hair
Desmoplakin nonsense/missense combination of mutations	Skin fragility, keratoderma, woolly hair
Plakophilin-1 ablation	Skin fragility—ectodermal dysplasia syndrome
Desmoglein-4 ablation	Congenital hypotrichosis
Inherited human diseases (autosomal dominant)	
Desmoplakin haploinsufficiency	Striate palmoplantar keratoderma
Desmoglein-1 haploinsufficiency or dominant-negative mutations	Striate palmoplantar keratoderma
Autoimmune human diseases	
Desmoglein-3	Pemphigus vulgaris
Desmoglein-1*	Pemphigus foliaceus
Desmocollin-1	IgA pemphigus (subcorneal pustular dermatosis subtype)

* Desmoglein-1 is also the target/cleavage site of bacterial toxins in staphylococcal scalded skin syndrome and bullous impetigo.

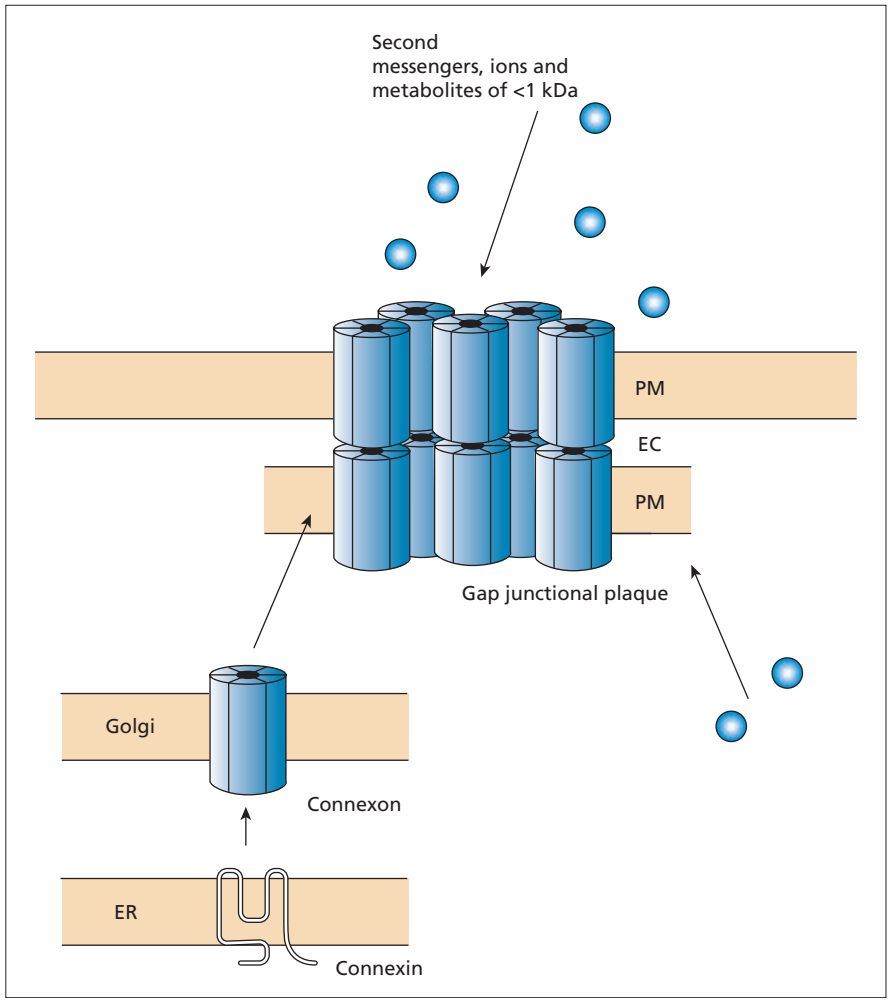

Fig. 3.12 Formation of gap junctions in human skin. In the Golgi network six connexin subunits assemble to form a connexon. The connexon is then transported to the plasma membrane. Other connexons then coaggregate and, in combination with aggregates of connexons on adjacent keratinocytes, a gap junction is formed that allows for the transfer of low-molecular-weight molecules (< 1 kDa) between cells. EC, extracellular; ER, endoplasmic reticulum; PM, plasma membrane.

reconstitution experiments, although the mechanisms regulating the dynamics of adherens junction formation are not yet clear. Nevertheless, the small GTPases of the Rho family appear to be important [8]. Likewise, VASP/Mena proteins have been implicated in the reorganization and polymerization of actin filaments [9]. Aside from actin polymerization, the myosin family of actin motor proteins may also contribute to generating the cellular movement necessary for intercellular adhesion by inducing contraction of actin filaments akin to pulling on a purse string [10]. The dynamics of the actin filament network allow for the extension, protrusion, embedding and anchorage of filipodia into neighbouring keratinocytes. This then encourages formation of adherens junctions and, in turn, permits other cell–cell junctions such as desmosomes to form, thus sealing adhesion between adjacent keratinocytes.

No human skin disorders have been linked to primary abnormalities in the structural components of adherens junctions, although plakoglobin—which may be mutated in Naxos disease (see Table 3.2)—is a component of both desmosomes and adherens junctions.

Gap junctions

Gap junctions comprise clusters of intercellular channels, known as connexons, that directly form connections between the cytoplasm of adjacent keratinocytes (and other cells) [11,12]. Thirteen different human connexins have been described [11]. Connexons originate following assembly of six connexin subunits within the Golgi network that are then transported to the plasma membrane. Here, connexons associate with other connexons to form a gap junction (Fig. 3.12). Homotypic or heterotypic connexins (formed from one or more than one type of connexin, respectively) are possible and the formation and stability of gap junctions can be regulated by protein kinase C, Src kinase, calcium concentration, calmodulin, adenosine 3′,5′-cyclic monophosphate (cAMP) and local pH. The function of gap junctions is to permit sharing of low-molecular-mass metabolites (< 1000 Da) and ion exchange between neighbouring cells, thus allowing intercellular coordination and uniformity [13].

Inherited abnormalities in genes encoding four different connexins (Cx26, 31, 30.3 and 30) have been detected in

several forms of keratoderma and/or hearing loss [12]. Specific connexin-associated genodermatoses include Vohwinkel's syndrome, autosomal dominant and recessive forms of erythrokeratoderma, Clouston's syndrome and *k*eratitis–*i*chthyosis–*d*eafness (KID) syndrome [14].

Tight junctions

Intercellular (tight) junctions are the major regulators of permeability in simple epithelia, but they are also present in skin, with a key role in skin barrier integrity [15]. Tight junctions, including those linking keratinocytes, are composed of transmembrane and intracellular molecules that include occludin, junction adhesion molecule and claudins [16]. As well as controlling permeability, tight junctions also have a role in maintaining cell polarity. Claudins may regulate epidermal permeability either through formation of tight junctions or via direct binding to certain transcription factors. However, a direct link to other transcription factors (e.g. Kruppel-like factor 4, Klf4) or enzymes (e.g. transglutaminase 1), that are known to be involved in regulating epidermal permeability through cross-linking of cornified cell envelope proteins, has yet to be established. Nevertheless, genetic ablation of claudin-1, or Klf4, or transglutaminase 1, in mice has been shown to cause similar patterns of epidermal barrier disruption [15,17,18]. This suggests that both the correct organization of tight junctions in the stratum granulosum and of cornified cell envelopes in the stratum corneum are required for full control of skin permeability.

No human skin disease has been associated with primary abnormalities in tight junction proteins, although abnormal expression of tight junction components, such as occludin, has been noted in a variety of inflammatory dermatoses, including psoriasis [19].

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Organization and kinetics

In adult life, cell division maintains differentiated tissues and replaces lost cells. There are three broad categories of tissues according to proliferative potential. In nerve and skeletal muscle there is no cell division. In other tissues, such as liver, cell division can occur in response to injury—'conditional renewal', which occurs little in normal states. In many tissues including skin and mucosa (stratified squamous epithelia) and gastrointestinal tract (simple epithelia), permanently renewing populations are produced by rapid and continuous cell turnover from a small population of 'stem' cells into differentiated cells having short lifespan. The epidermis has classically been viewed as a stratified squamous epithelium maintained by cell division within the basal layer, which is attached to the epidermal basement membrane. Differentiating cells are gradually displaced outwards through the stratum spinosum to the stratum corneum. The anucleate corneal cells (squames), corneocytes or cornified cells, which protect the viable cell layers, are continually shed from the skin surface, and the rate of production of cells in the basal layer must match the rate of loss from the surface to produce the normal skin thickness, although increased rates of loss and cell division occur in pathological states.

Dynamics of epidermis

Stem cells

Stem cells can be defined as cells that have an unlimited capacity for self-renewal and the ability to generate daughter cells that undergo terminal differentiation [1,2]. However, not all dividing basal keratinocytes are stem cells [2]. It is evident that a stem cell daughter cell that is

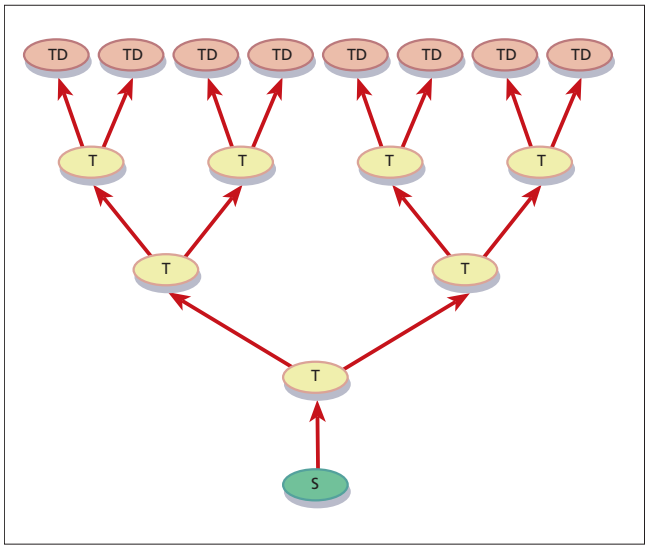

Fig. 3.13 Keratinocyte stem cell and transient amplifying cell division in human skin. Transient amplifying cells (T) are capable of increasing the number of keratinocytes that undergo terminal differentiation (TD) following a single stem cell (S) division. In this example, one stem cell division has resulted in eight terminally differentiated cells.

destined to undergo terminal differentiation can first proliferate and divide a small number of times (perhaps 5–6 mitoses): such cells are known as transient amplifying cells (Fig. 3.13). This expansion of proliferation therefore increases the number of terminally differentiating keratinocytes generated from each original stem cell division. Thus stem cells in the epidermis have a large capacity for proliferation but actually divide infrequently.

Stem cells are located in small clusters in the basal interfollicular epidermis and, in particular, in the bulge region of follicles. Although morphologically similar to other keratinocytes, stem cells are, to some extent, associated with a profile of particular chemical, molecular and biological characteristics. For example, stem cells retain labelling with injected ^{3}H-thymidine or Brdu after repeated cell division. In culture, actively growing clones present after serial passaging are considered to indicate origins from stem cells. Stem cells have also been shown to display increased β1 integrin expression as well as high levels of Notch ligand Delta 1. Other markers with altered expression in epidermal stem cells include the transferrin receptor, the nuclear-export protein 14-3-3σ, and the cytoskeletal keratins, K19 and K15.

Some putative stem cell markers, such as the c-Myc-regulated protein or the psoriasis-associated fatty acid binding protein (PA-FABP), are also expressed in the transient amplifying compartment. The same is true for the transcription factor p63.

Stem cells in the bulge region have the capacity to migrate (e.g. to the base of the hair follicle in follicular regeneration), as well as to differentiate into diverse lineages (e.g. outer root sheath [ORS], IRS, hair shaft, sebocytes and interfollicular epidermis). The precise lineage of terminal differentiation is governed by several local environmental cues. For example, Sonic hedgehog, Wnt and BMP are important in both embryonic and postnatal hair follicle development. Indeed, overexpression of the Wnt signalling component, β-catenin, leads to *de novo* follicle formation in skin. Thus, Wnt signalling appears to be important in making a follicle and Sonic hedgehog in maintaining it. Bone morphogenetic protein signalling influences differentiation of the hair shaft but not the IRS. However, little is known about the control of other adnexal differentiation, although Myc activation may be relevant for sebocyte differentiation.

The mechanisms that control exit from the stem cell compartment are incompletely understood, but clearly several molecular networks and signalling pathways are important in balancing epidermal growth and differentiation. Key components include NF-κB, Wnt/β-catenin, Sonic hedgehog/Patched, p63, 14-3-3σ, α-catenin and β1 integrin.

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Epidermal kinetics

Cell kinetics are complicated in the epidermis by the balance between growth with differentiation and cell death. A differentiated cell may have no proliferative capacity but may be extensively metabolically active, and can increase tissue volume or mass without an increase in cell number. There are a number of kinetic concepts that underly skin biology.

A major concept is that of *turnover time*, which is the amount of time for the whole cell population to replace itself (regeneration time or replacement time). This depends both on the time taken for individual cells to divide, *cell cycle*, and the proportion of basal cells dividing the *growth fraction*.

The *cell cycle* or intermitotic time (Tc) represents the interval between two successive mitoses (M). On histopathology of skin, dividing cells can be recognized by mitotic figures, but a longer period of time is spent between mitoses in interphase. Radiolabelled thymidine is incorporated into DNA, because of the salvage pathway for DNA, only during a specific period of DNA synthesis, the 'S' phase. All proliferating cells go through a cycle (Fig. 3.14), in which mitosis (M) is followed by the interphase or post-mitotic growth phase (G1), a period of active DNA synthesis (S) and a short resting or premitotic

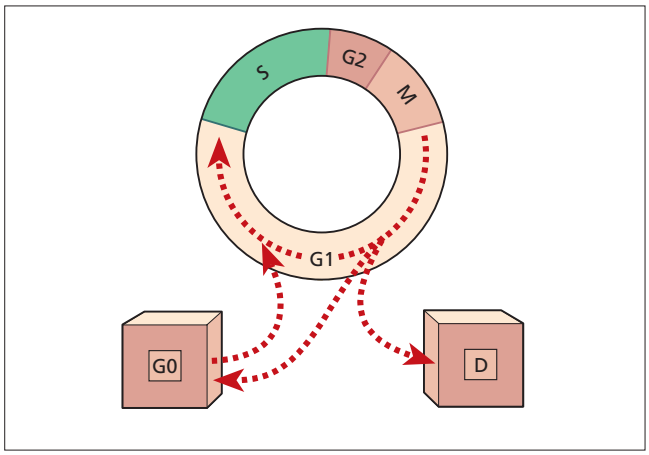

Fig. 3.14 Compartments of a cell proliferation system: M, mitosis, G1, interphase or post-mitotic growth phase; S, DNA synthesis; G2, resting or premitotic phase; G0, stem cells not proliferating; D, cells differentiating.

growth phase (G2). Some basal cells may remain quiescent in the so-called G0 phase, which permits them to re-enter the cell cycle and continue proliferation when required to do so by various stimuli. The balance of cell loss, from death, desquamation and apoptosis, and cell birth, decides the rate of increase or decrease of a cell population.

The *growth fraction* is the proportion of basal cells that are proliferative at any one time: in normal mouse skin this is estimated to be 60% of cells [1]. High proliferative rates can be achieved by a shorter cell cycle, or a higher proportion of proliferating cells, or both.

The proliferative index is familiar as the mitotic index and the flash-labelling index. The *mitotic index* is the fraction of basal or viable cells that is in mitosis at any point, and the *labelling index* is the fraction of basal cells in DNA synthesis. The labelling index is measured by exposing the skin to tritiated thymidine (^{3}HTdR), by intradermal or systemic injection, which is selectively taken up in DNA synthesis or rapidly broken down. This 'flash' labels the cells in S phase, which can then be detected by high-resolution autoradiography. Flash labelling the normal human epidermis labels about 30% of suprabasal cells, so this has to be included in some calculations [2].

These indices are referred to as state parameters, as they reflect the state of a particular component. However, rate parameters reflect the rate at which cells enter any phase. The rate of entry into mitosis is referred to as the *birth rate* in cells per 1000 cells per hour and can be measured by the accumulation of arrested metaphases after application of a stathmokinetic agent such as vincristine or colcemid [3]. The rate of entry into S phase is measured by double labelling, and is equivalent to the birth rate if all cells entering the S phase eventually divide, which is often not the case for keratinocytes in hyperproliferation. It is not known when cells leave the cycle to enter differentiation, as cells expressing involucrin as late markers of proliferation can still undergo scheduled DNA synthesis.

The *epidermal turnover time*, or transit time, has been used to represent the time taken for a cell to pass from basal layer to the surface of the skin, comprising passage through the living compartment to the upper stratum Malpighi and on through the non-viable compartment to the surface. Epidermal transit through stratum corneum can be estimated by injecting radioactive label or fluorescent dye, and measuring their appearance or disappearance at the surface of the skin. In normal skin, the total time is 52–75 days, but this is greatly reduced for psoriatic epidermis.

The best way of measuring the epidermal cell cycle and its component phases is the fraction of labelled mitoses technique, which involves determining the proportion of labelled mitoses after flash labelling with tritiated thymidine. From plotting the curve of the percentage of labelled mitoses with time, the duration of different phases of the cell cycle can be determined. Most cell populations show a distribution of cell-cycle times. *In vitro* studies, including explant cultures and cultures of disaggregated keratinocytes, have now been extensively used to analyse parameters of proliferation. Time-lapse photography can be used to directly measure intermitotic time *in vitro*. Initial colony formation is not dependent on multiplication, as keratinocytes appear to reassociate to colonies of four to six cells before replication, which occurs after 24–48 h. The kinetic parameters also illustrate a diversity of cell-cycle time *in vitro*. Scintillation counting is often used to measure incorporation of tritiated thymidine into DNA, but errors can be introduced by the size of the endogenous thymidine pool, and activity of thymidine-incorporating enzymes.

There are few direct measures of the cell-cycle time in normal skin, but they vary from 50 h (flow cytometry) to 457 h (turnover time). In psoriatic skin, the labelling index is greatly increased; the cell-cycle time is consistently reported to be reduced to around 50 h, and the growth fraction increased to 100% [4]. Keratinocytes *in vitro* have a mean intermitotic time of 22–24 h.

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The regulation of epidermal differentiation

Recent years have seen considerable progress in our

understanding of the patterns of expression of different structural genes in the epidermis and its appendages. However, just how the specific programmes of terminal differentiation are orchestrated at the transcriptional level remains poorly understood.

In skin development, several signalling pathways such as Hedgehog, Wnt and transforming growth factor-β (TGF-β) have been implicated. Indeed, many of these pathways show evolutionary conservation in aspects of epithelial differentiation, proliferation and tumourigenesis. These pathways may be variably activated, both spatially and temporally, leading to a diverse series of transcribed genes. In keratinocyte differentiation, three main classes of transcription factors, AP1, AP2 and Sp1, appear to be relevant, although gene-targeting experiments have shown evidence for functional redundancy. Nevertheless, key elements include the Fos/Jun family of *AP1* genes. *In vitro* studies have also identified several other relevant transcription factors such as basonuclin, C/EBP, Oct6 and Oct11 (POU domain transcription factors), ESE2 (ELF5), Klf4 and retinoic acid receptors (RARs).

Regulation of the nuclear transcription factor NF-κB also appears to be significant in the process of terminal differentiation in epidermis. I kappa kinase alpha (IKKα) is a kinase that, along with IKKγ, phosphorylates and destroys IκB, a cytoplasmic inhibitor of NF-κB. Targeted inactivation of the gene encoding IKKα results in impaired terminal differentiation, although actual levels of NF-κB are normal. It is thought that the defects result from loss of an unknown secreted factor normally dependent on IKKα activity. However, NF-κB activity is abnormal if IKKβ is compromised. IKKβ usually increases NF-κB activity but *IKKβ* gene-targeted heterozygous mice (X-linked gene) display signs of keratinocyte proliferation, skin inflammation and increased apoptosis. The *IKKβ* gene is clearly important in human epidermal physiology too since mutations underlie most cases of incontinentia pigmenti. Overall these *in vitro* data, mouse models and human gene mutations demonstrate that compromising NF-κB perturbs the balance between growth and differentiation in the epidermis (and perhaps also in certain immune response cells).

Terminal differentiation is also influenced by retinoids that act at the mRNA level to inhibit aspects of differentiation and to promote proliferation. These changes are mediated by nuclear RARs and their heterodimeric binding partners, retinoid X receptors (RXRs). Transgenic mice with disrupted RARs have impaired epidermal barrier function and suppressed epidermal differentiation. In addition, targeted disruption of RXRα leads to further changes in epidermal hyperplasia and aberrant terminal differentiation. These mice also have alopecia, indicating a further role for these receptors in hair follicle morphogenesis and cycling.

Growth stimulatory signals [1,2]

Epidermal growth factor (EGF) family

Human EGF is a 6-kDa polypeptide with 53 amino acids that stimulates cell proliferation and differentiation in a wide range of tissues. Transcripts are not found in the epidermis but in the salivary glands and intestinal tract. EGF has been shown to increase the growth and persistence of epidermal keratinocytes *in vitro* via binding to specific cell-surface receptors (170-kDa EGFr1), that have been detected in the basal layer of human epidermis and throughout the epidermis in psoriasis [3]. The EGFr has a large cytoplasmic domain with tyrosine kinase activity stimulating protein phosphorylation, and the cerB1 oncogene encoding truncated receptors acts by mimicking receptor activation [4].

In contrast to EGF, TGF-α, a single-chain 26-kDa polypeptide, is synthesized by epidermal keratinocytes and stimulates keratinocyte growth in an autocrine fashion following binding to the EGFr [5], although keratinocyte lifespan *in vitro* is mainly enhanced by stimulation of lateral migration of dividing colonies [6]. TGF-α can up-regulate its own production, as well as that of EGFr1. Overexpression of TGF-α has been found in suprabasal psoriatic epidermis [7].

Amphiregulin is a unique member of the EGF family of growth factors, with binding affinity for heparin-like glycosaminoglycans (GAGs) [8]. The amphiregulin gene maps to chromosome 4q, and encodes a transmembrane precursor protein, cleaved proteolytically to the active form, which binds to the EGFr. Amphiregulin appears to be a major autocrine keratinocyte growth factor, regulated by cellular GAGs and up-regulated by exogenous EGF and TGF-α, being overexpressed in hyperproliferative skin disease and squamous carcinomas [8,9].

More than 90% of autocrine growth of keratinocytes is mediated through the EGFr [8], but other cytokines synthesized by keratinocytes including interleukin-1 (IL-1), IL-6 and granulocyte–macrophage colony-stimulating factor (GM-CSF) can also stimulate growth [10–12]. Paracrine factors may be produced by dermal fibroblasts and microvascular endothelial cells. Some members of the FGF family stimulate keratinocyte growth, including acidic and basic FGF (bFGF). *Keratinocyte growth factor* (KGF: FGF7), in particular, has a high specificity for keratinocytes and is induced in dermal fibroblasts within 24 h of wounding [13]. Factors produced by leukocytes and macrophages—platelet-derived growth factor (PDGF) [14], TGF-α, IL-1β and tumour necrosis factor (TNF)—induce the *KGF* gene and may induce this rapid response.

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Growth inhibitors for keratinocytes

It has long been suggested that epidermal growth is under the influence of a negative-feedback mechanism. Bullough *et al*. and Elgio *et al*. proposed the existence of growth inhibitors or *chalones* produced by suprabasal cells that slow basal mitosis [1,2]. Recent studies have purified a number of defined growth-inhibitory substances that are produced in skin and may have contributed to activities within the previous crude biological extracts. It is likely that further cytokines with growth-inhibitory activity towards keratinocytes remain to be found, some of which may be site or cell specific.

TGF-β comprises a family of closely related two-chain polypeptides present in normal cells and malignant cell lines [3]. TGF-β1 stimulates fibroblast growth and increases fibrosis, but inhibits growth of keratinocytes [4]. TGF-β receptors are ubiquitous and are likely to be important regulatory molecules in inflammation and repair and in epithelial–mesenchymal interactions.

Interferon-α (IFN-α) and IFN-γ have cytostatic effects on keratinocytes both *in vivo*, following systemic administration, and *in vitro* [5]. Following stimulation with IFN-γ, keratinocytes express class II antigens, predominantly human leukocyte antigen (HLA)-DR, in a dose-dependent manner, but higher doses are cytotoxic to keratinocytes.

TNF-α, a macrophage cytokine, induces neutrophil activation [6], endothelial activation, fibroblast stimulation, endotoxic shock and acute phase protein release, but is also secreted by keratinocytes, especially after UV radiation. TNF is reversibly cytostatic to keratinocytes, but stimulates fibroblast proliferation and cytokine production.

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Apoptosis [1]

Selective cell death is a means of eliminating unwanted cells during normal differentiation, or when cells are damaged [2]. There are two pathways: necrosis, when cells are passively damaged with membrane damage, cell swelling and rupture; and apoptosis, an active process. Apoptosis, a term first introduced in 1972 [3], and also known as programmed cell death, is characterized by nuclear fragmentation and shrinkage of the cells into small fragments that are then phagocytosed by surrounding cells. Intricate control of apoptosis is vital since insufficient cell death will lead to uncontrolled growth, whereas too much apoptosis will result in degeneration or developmental defects. The final pathway leading to cell death often results from mitochondrial permeabilization and activation of caspases and other proteases, but these events can be triggered through numerous mechanisms including signalling induced by DNA damage, responses from the ubiquitin/proteasome pathway, the pro-apoptotic molecule Fas and proapoptotic mediators such as ganglioside GD3. Moreover, these signals can by modified by tumour suppressor genes including p53, p63 and the retinoblastoma tumour suppressor protein, the inhibitor of apoptosis (IAP) gene family, and Fas-ligand.

Alterations in the regulation of apoptosis are relevant to several developmental and malignant skin disorders. For example, mutations in the *p63* gene result in ectodermal dysplasia syndromes and altered responses to UV irradiation. In melanoma, resistance to chemotherapy in some cases may be due to increased antiapoptotic activity [4].

For example, several natural defence processes induced by granzyme B or interactions with TNF family members (e.g. TNF-related apoptosis-inducing ligand, TRAIL) normally function to kill melanoma cells, but melanomas that express high levels of the oncogene bcl-2 may override these protective pathways, making them more resistant to treatment.

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Differentiation

Terminal differentiation of the epidermis *in vivo*

As the epidermal keratinocytes move through the epidermis after losing their attachment to the basal lamina, they undergo the complex process of terminal differentiation to produce the stratum corneum. Most suprabasal cells in the stratum spinosum have lost this ability to divide, and are inevitably committed to differentiation, although they remain metabolically active. The stratum corneum cells (squames or corneocytes) have lost their nuclei and other recognizable organelles, and comprise 65% insoluble cysteine-rich, disulphide cross-linked, fibrous proteins or keratins (Greek *keras* = horn). The series of changes whereby keratin filaments aggregate into bundles through the action of the histidine-rich basic protein filaggrin is the process of *keratinization*. However, keratin IFs characterize all epithelial cells. In addition, epidermal differentiation involves the synthesis of a highly insoluble cornified envelope whose cross-linking is catalysed by a keratinocyte-specific transglutaminase from a precursor protein called involucrin (Greek = envelope).

In addition to formation of keratin macrofilaments and the cornified envelope, changes also occur during terminal differentiation in the expression of intercellular lipids and membrane glycoproteins, including growth-factor receptors, intercellular adhesion proteins (integrins), cell-matrix adhesion proteins and blood-group antigens.

Aside from changes in these structural proteins, terminal differentiation is also influenced by several other factors including expression of desmosome proteins and signalling pathways such as Notch [1] or phosphatidylinositol 3 kinase [2], extracellular matrix protein 1 (ECM1) [3], vitamin D receptors [4], FGF10 [5], cyclo-oxygenase enzymes [6], calcium-sensing receptors [7], sodium channels [8] and small heat shock protein [9].

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Keratin biochemistry, synthesis and changes in epidermis

The filamentous cytoskeleton of all mammalian cells, including epidermal keratinocytes, comprises actin-containing microfilaments approximately 7 nm in diameter; tubulin containing microtubules 20–25 nm in diameter; and filaments of intermediate size, 7–10 nm in diameter (IFs). There are six types of IFs: vimentin within mesenchymal cells; glial filament acidic protein (GFAP) in glial cells; neurofilaments in neurones; desmin in muscle cells; and peripherin in peripheral nerves [1]. The nuclear matrix proteins, nuclear lamins A, B and C, are also IFs. The keratins are the IFs characteristic of all epithelial cells. The polypeptide building blocks of all IFs have a similar backbone structure of a classical α-helical region with heptad repeats, having four separate helical zones with interhelical linker sequences, and non-helical carboxy- and amino-terminals.

Keratins form a family of proteins with more than 30 individual and distinct members, each the product of a distinct and separate gene. The molecular weight of keratins varies between 40 kDa and 67 kDa, and they can be resolved on two-dimensional gel electrophoresis into individually numbered polypeptides: the basic keratins (numbered 1–8) and the acidic keratins (numbered 9–19) [2]. The genes encoding individual keratins fall into two gene families: type I (basic) and type II (acidic) [3]. Keratin expression within cells and tissues can be determined by a variety of techniques: immunohistochemistry using polyclonal antisera and monoclonal antibodies (Fig. 3.15) and *in situ* hybridization probes to analyse the cellular

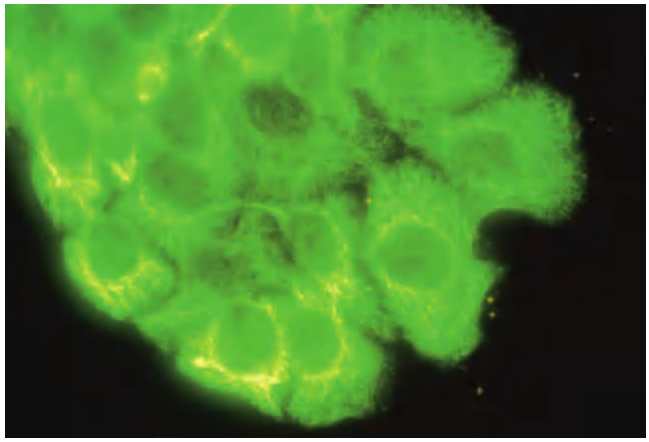

Fig. 3.15 Cells in tissue culture stained by immunofluorescence with monoclonal antibody to keratin intermediate filaments (IFs).

expression of mRNA for the individual keratin genes [4,5]. Synthetic peptides to carboxy-terminal sequences can be used to develop highly specific antibodies [4]. Mapping the tissue distribution of keratins shows co-expression of particular acidic–basic pairs in a cell- and tissue-specific manner [5,6]. Heterodimers are assembled into higher-order protofibrils and protofilaments by an antiparallel stagger of some complexity [7,8]. Simple epithelia are characterized by the keratin pair K8/K18, and the stratified squamous epithelia by K5/K14. In addition, stratified squamous epithelia express up to four other keratin pairs during epithelial differentiation (Fig. 3.16). In skin, suprabasal keratins K1/K10 are characteristic of epidermal differentiation [4]. In the stratum granulosum, release of filaggrin from the keratohyalin granules forms macrofibres. Retinoid levels, growth factors and hormones may regulate keratin gene expression. Mesenchymal signals may also direct or permit intrinsic patterns of keratinocyte differentiation. K19 is expressed in basal keratinocytes of the hair-follicle bulge region at the site of pluripotential stem cells [9]. K9 and K2e expression are site restricted in skin: K9 to palmoplantar epidermis and K2e to superficial interfollicular epidermis. Apart from their structural properties, keratins may also have direct roles in cell signalling, the stress response and apoptosis [10].

In epidermal hyperproliferation, as in wound healing and psoriasis, expression of suprabasal keratins K6/K16/K17 is rapidly induced suprabasally, probably due to previous expression of their mRNAs with post-transcriptional regulation [5]. Mutations in epithelial keratins underly an increasing number of human skin diseases with good correlation of genotype and phenotype, as lesions tend to occur at sites of expression of particular keratins [11,12].

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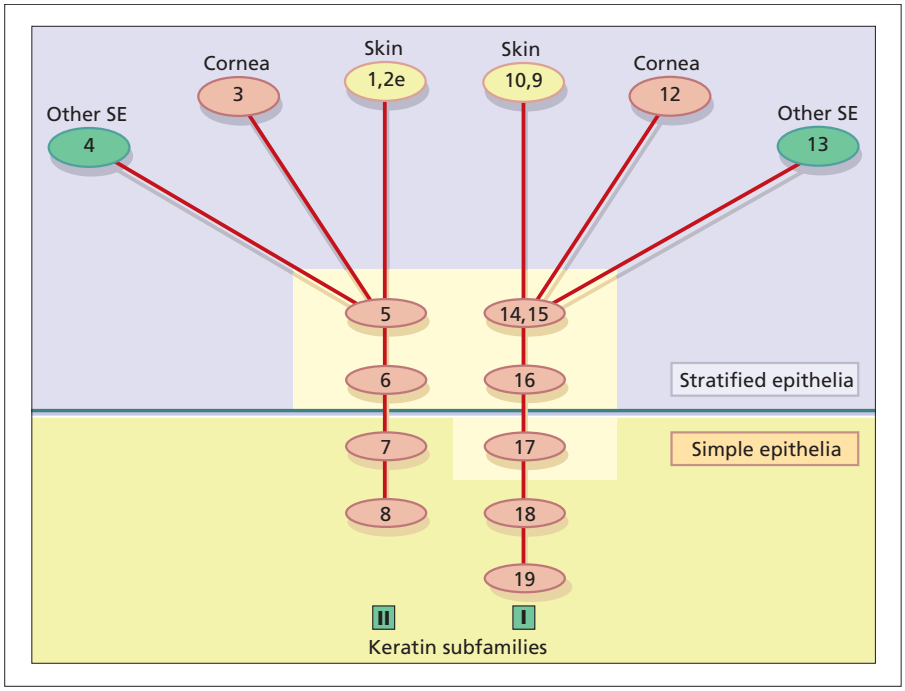

Fig. 3.16 Keratins coexpress in pairs (Moll numbers) according to tissue patterns of differentiation. (From Eichner [6].)

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Hair and nail differentiation

The pilosebaceous units develop from epidermal downgrowths under the influence of specific mesenchymal cell condensations between the 10th and 14th week estimated gestational age. They have complex groups of specialized cell layers with distinctive pathways of differentiation. There are four classes of pilosebaceous unit: terminal on the scalp and beard; apopilosebaceous in axilla and groin; vellus on the majority of skin; and sebaceous on the chest, back and face. The dermal papilla is located at the base of the hair follicle with a rich ECM. Around the papilla are germinative (matrix) cells that have a very high rate of division, and give rise to spindle-shaped central cortex cells of the hair fibre, and the single outer layer of flattened overlapping cuticle cells. In animals, a paracortex and orthocortex can be distinguished, with nuclear remnants distinguishable in the paracortex. A central medulla is seen in some hairs, with regularly stacked condensed cells interspersed with air spaces or low-density cores [1]. The cortical cells are filled with keratin IFs orientated along the long axis of the cell, interspersed with a dense interfilamentous protein matrix. Terminal differentiation of cortical cells is associated with the appearance of a continuous laminated intercellular layer, which appears critical for filament integrity. The cuticular cells are morphologically distinct, with flattened outward-facing cells, with three layers inside the cuticle of condensed, flattened protein granules: endocuticle, exocuticle and 'a' layer.

Around the cuticle is the IRS, which is composed of three distinct layers of cells that undergo keratinization: the IRS cuticle, the Huxley layer and the outermost Henle layer. Differentiation in the IRS involves the development of trichohyalin granules, with 8–10-nm filaments orientated in the direction of hair growth. The IRS moves up the follicle, forming a support for the hair fibre, and degenerates above the sebaceous gland. The outermost layer is the ORS, which is continuous with the epidermis and expresses epithelial keratins, K5/K14, K1/K10 and K6/K16 in the upper ORS and K5/K14/K17 in the deeper ORS (Fig. 3.17).

Normal growth of the hair fibre is 300–400 μm/day, generated by the high rate of proliferation of progenitor cells in the follicle bulb. Compartmentalization within the bulb gives rise to the different layers within the follicle, with the majority of bulb cells forming the IRS. There are three phases of cyclical hair growth: anagen, when growth occurs; catagen, a regressing phase; and telogen, a resting phase (Fig. 3.18). The follicle re-enters anagen, and the old hair is replaced by a new one [2]. It had been assumed that

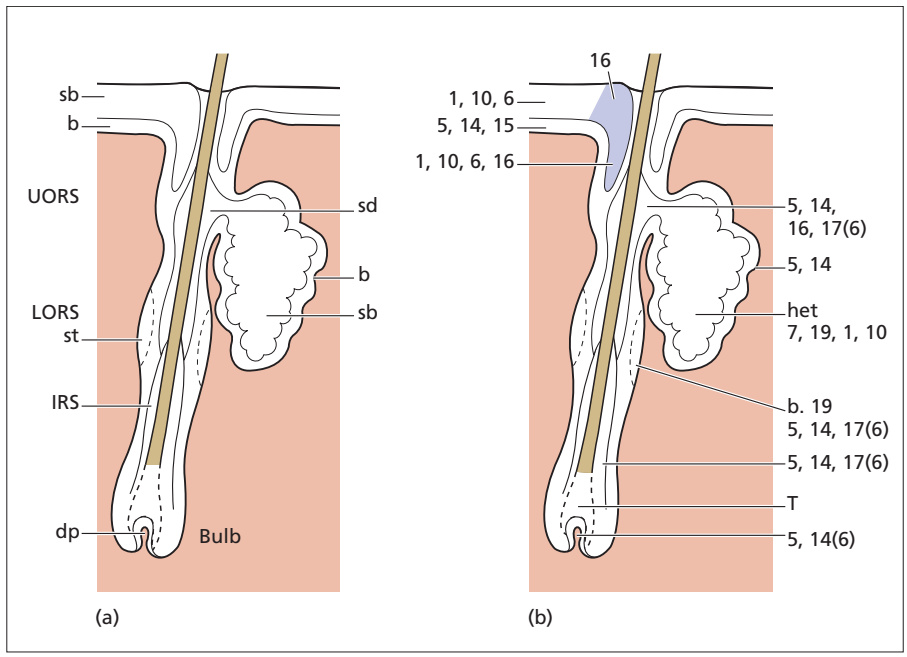

Fig. 3.17 Hair follicle: (a) structure and (b) expression of epithelial keratins (Moll number). b, basal; dp, dermal papilla; IRS, inner root sheath; LORS, lower outer root sheath; sb, suprabasal; sd, sebaceous duct; st, stem cell region; UORS, upper outer root sheath.

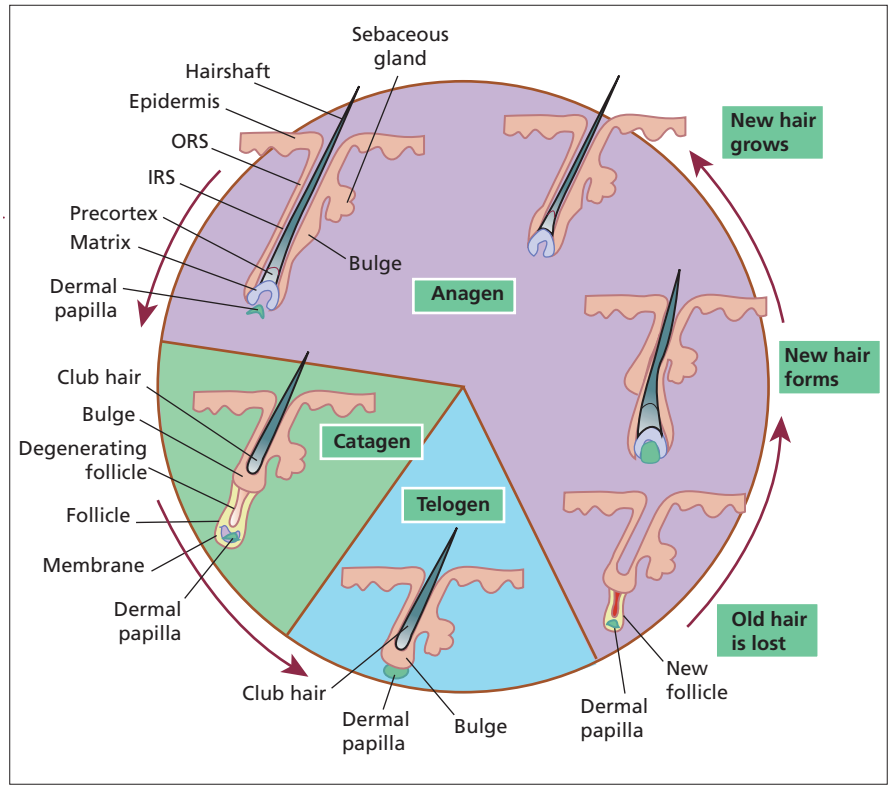

Fig. 3.18 The hair cycle. There are three components to the hair cycle: anagen (where new hair forms and grows), followed by catagen and telogen, and then loss of old hair. The hair cycle is associated with discrete changes in hair follicle anatomy, both in the shape of the follicle and in the subjacent dermal papilla. IRS, inner root sheath; ORS, outer root sheath.

stem cells for the follicle lay in the highly proliferative matrix [3], but recently a slow-cycling (label-retaining) population of basal keratinocytes at the level of arrector pili muscle has been suggested as the pluripotential stem-cell region. Cells in this region express keratin K19 and high levels of β1 integrin [4].

Immediately above the basal layer in the hair bulb, cells undergo a secondary pathway of 'trichocyte' or hair differentiation, and express a further complex group of keratins, the hard keratins [5,6]. Two families of hair keratins, types I and II, are present in mammals, which have distinctive amino- and carboxy-terminals with high levels of cysteine residues, and lack the extended glycine residues of epidermal keratins. The proteins differ from epithelial keratins in position on two-dimensional gels, but form acidic and basic groups: on gel electrophoresis, there are four major proteins in each family and several minor proteins, Ha 1–4 and Hb 1–4 [7]. Recent cloning of the hair keratin genes, which cluster on chromosomes 12 and 17, has shown a greater number of hair keratin genes, *HaKRT1–6* (including 3.1 and 3.2) and *HbKRT1–6*. Mutations in hair keratin genes have been found to be causative for the human disease monilethrix [8]. In addition, keratin 17 null mice also demonstrate varying degrees of alopecia, depending on the age and strain of the mice [9].

The hair keratin-associated proteins are cysteine-rich and glycine tyrosine-rich families [10]. Cysteine-rich proteins were originally called the high sulphur group, but protein fractions with even higher amounts of cysteine were noted and called the ultra-high sulphur keratin proteins, at least five families occurring in both cortical and cuticular cells [4].

A similar pathway of differentiation occurs in nail formation, when hard keratin expression occurs following a pattern of adjacent epithelial keratin expression, in the nail matrix [11]. The nail cells mature from a deep layer at the proximal nail, with cells moving forward and outward, filling up with a complex, hair-like cortex of filaments embedded in an electron-dense interfilament matrix. Nail keratinocytes show marked interdigitations with laminated intercellular cement. The expression of significant amounts of epithelial keratins in nail matrix explains the nail findings in some diseases caused by keratin gene mutations.

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Keratohyalin granules

Keratohyalin granules are highly distinctive cellular inclusions in differentiating epidermis forming the characteristic granules of the stratum granulosum, which disappear in the formation of cornified squames. They are also found in other cornifying epithelia, such as palate and gingiva, but not in non-cornified squamous epithelia. Filaggrin provides the interfilamentous material between keratin filaments in the lower stratum corneum cells; it contributes towards the cornified envelope [1]. Two types of granule can be distinguished in rodent skin by staining characteristics, differential incorporation of radioactive probes and microanalysis. The PF granule is phosphate rich and contains the filaggrin precursor, profilaggrin, and the L granule, which is found at the periphery of the PF granule or independently in the cytoplasm, contains the sulphur-rich protein loricrin [2]. In human interfollicular epidermis, keratohyalin forms dense, irregular, stellate globules of amorphous material along keratin filament bundles and at intersections of such bundles.

Filaggrin is a cationic protein originally isolated from rat epidermis [3–5], and has an unusual amino-acid composition, being rich in arginine, glutamine, glycine, serine and histidine, but lacking non-polar residues. The name results from the recognition that filaggrin was a *fil*ament *aggr*egating prote*in*. Antibodies to filaggrin react with stratum corneum and keratohyalin granules. Filaggrin is derived from a high-molecular-weight precursor profilaggrin, which is insoluble, cannot aggregate filaments and is highly phosphorylated. It comprises of multiple repeats of filaggrin joined by linker peptides. Profilaggrin is dephosphorylated, cleaved by proteases [6], which remove the linker peptides to generate the filaggrin, and which associates with keratin filaments. The degradation of filaggrin produces amino acids that help to retain stratum corneum water [7].

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The cornified envelope

The cornified envelope [1] is rendered highly insoluble by the formation of glutamyl-lysysl isodipeptide bonds between envelope proteins, catalysed by transglutaminases [2]. There are three distinct transglutaminases, but TG1 (keratinocyte transglutaminase) can cross-link envelope proteins in the absence of other enzymes. An increasing number of envelope precursor proteins have been identified.

Involucrin is the best-established envelope precursor, as a preferred substrate of TGk. The protein can be found decorating the cytoplasmic face of envelopes from human plantar epidermis [3]. The involucrin gene has been located on chromosome 1q21–22 in the epidermal differentiation gene complex. Twenty-six per cent of the residues in involucrin are glutamine, but preferential labelling of residue 496 suggests this site initiates cross-linking [4]. The protein is expressed in stratified squamous epithelia, accumulating in the upper stratum spinosum, but is detected in the lower stratum spinosum in benign epidermal hyperplasia, and epibasally in cultured keratinocytes. Regulation of expression appears relatively retinoid insensitive. Involucrin is not always associated with cornification, as it occurs in cornea and is therefore a good marker of epithelial differentiation. Other cytosolic envelope precursors include the family of small proline-rich proteins (SPR1) including *cornifin* [5] or SPR1 and *pancornulins*. There are three closely related subfamilies SPRr1, SPRr2 and SPRr3, originally isolated by differential screening as UV-inducible genes [6]. They all contain internal peptide repeating units of eight or nine amino acids, up to 40% proline. Other envelope proteins include *SKALP/elafin* and *keratolinin/cystatin*, a 36-kDa protein cross-linked by transglutaminase into a 150-kDa multimer [7].

Some precursors of the cornified envelope are delivered by granules. Small, smooth, sulphur-rich L granules were suggested to contain the 315 amino acid, cysteine-rich protein *loricrin*, and accumulate in the stratum granulosum [8]. Loricrin appears to be the major component of the cornified envelope, cross-linked by isodipeptide bonds by the action of epidermal transglutaminase. The human

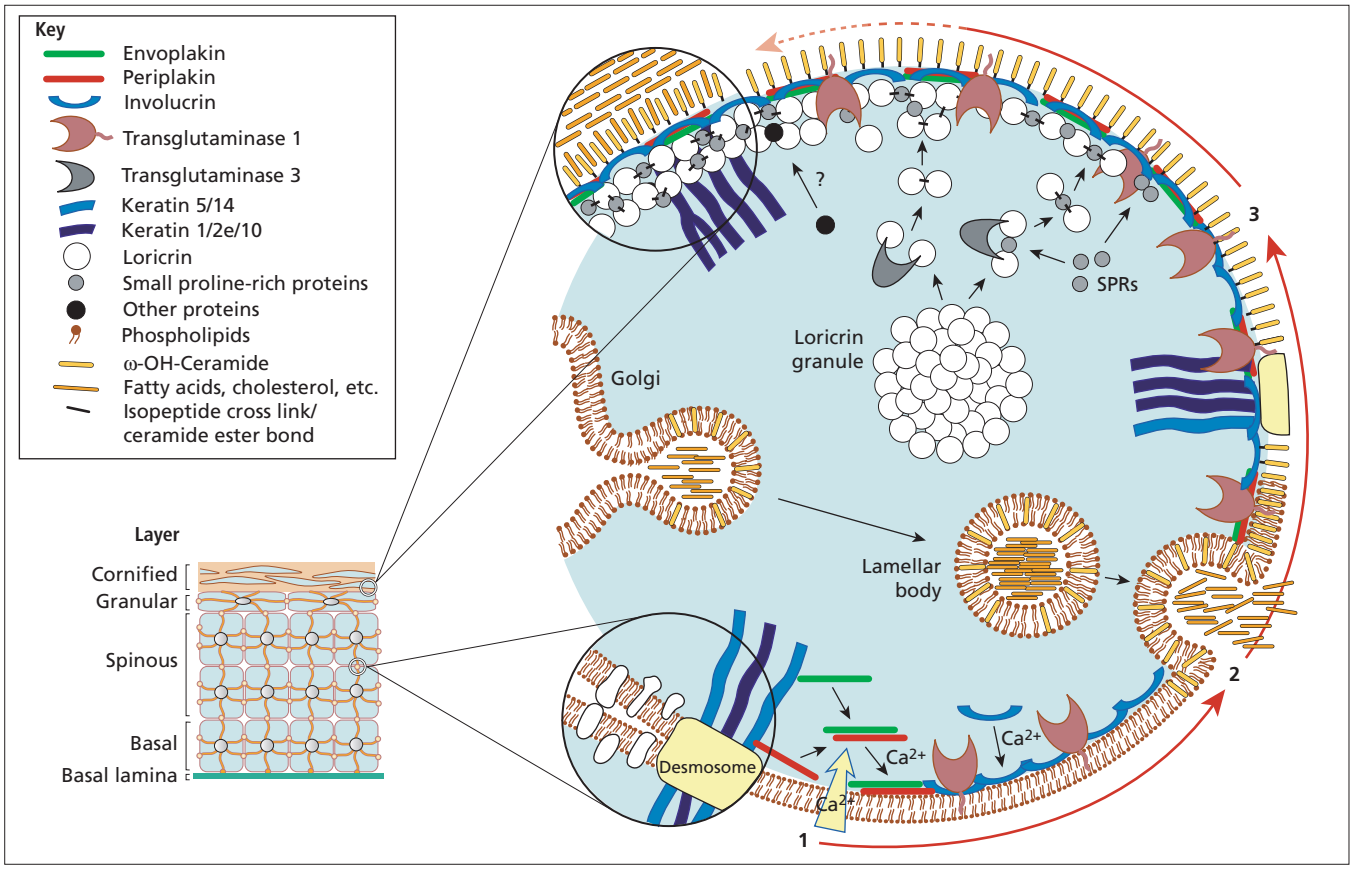

Fig. 3.19 Assembly of the epidermal cornified cell envelope. In response to increasing intracellular calcium, an internal scaffold of desmosomal proteins is made along the plasma membrane. The contents of lamellar bodies (ceramides and other fatty acids, cholesterol and cholesterol esters) are released into the extracellular milieu to form a lipid membrane. The developing envelope is then added to and reinforced by recruitment of various proteins including loricrin, small proline-rich proteins (SPR1), other desmosomal remnants and attached keratin filaments. The resulting cornified cell envelope is durable and flexible and provides important mechanical and barrier functions.

loricrin gene is also located on chromosome 1q21. Expression depends on a high calcium concentration, is associated with keratinocyte differentiation and is down-regulated by retinoids. Profilaggrin in F granules may make a minor contribution to the envelope.

At least three membrane-associated proteins are also envelope precursors: a 210-kDa protein (envoplakin) and a 195-kDa protein (periplakin) detected in human keratinocytes [9]; and a 61-kDa protein found in transformed cells. Envoplakin has recently been cloned and sequenced [10,11], has some homologies with desmoplakin and plectin, and thus may serve as an organizing linker protein.

Transglutaminases [2] catalyse isopeptide bonding between γ-amide of donor glutamine and ε-amino group of acceptor lysine to produce a stable insoluble macromolecule. The transglutaminases consist of a family of distinct enzymes, TGase 1 membrane-associated enzyme in many epithelial tissues, a ubiquitous TGase 2, and TGase 3, which is restricted to epidermal and hair keratinocytes. Both TGase 1 and 3 are thought to be important in constructing the cornified cell envelope during terminal differentiation, although TGase 3 is thought to account for 75% of activity in epidermis.

Formation of the cornified cell envelope (Fig. 3.19) is triggered by a rise in intracellular calcium levels [12]. This leads to cross-link formation between plakins and involucrin catalysed by transglutaminase. Other desmosomal proteins are then also cross-linked, forming a scaffold along the entire inner surface of the plasma membrane. Ceramides from the secreted contents of lamellar bodies are then esterified onto glutamine residues of the scaffold proteins. The cornified cell envelope is reinforced by the addition of a variable amount of SPRs, repetin, trichohyalin, cystostatin α, elafin and LEP/XP-5 (skin-specific protein) [12]. Although most desmosomal components are degraded, keratin IFs (mostly K1, K10 and K2e) may be cross-linked to desmoplakin and envoplakin remnants. Together these assembly and degradation events result in durable, flexible but dead cells that have vital mechanical and water-permeability barrier functions.

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Lipid biosynthesis and barrier function

During epidermal differentiation, there are profound changes in the composition of lipids: in the viable layers phospholipids, cholesterol and triglycerides predominate, but in the upper stratum spinosum and stratum granulosum lipid is synthesized and packaged into lamellated membrane-bound organelles known as *membrane-coating granules*, lamellar granules or Odland bodies (Fig. 3.20). They are found adjacent to the cell membrane with alternating thick and thin dense lines separated by lighter lamellae of equal width, consistent with packing of flattened discs within a membrane boundary. Immunochemistry has confirmed the presence of phospholipids, glycolipids and free sterols. The organelles move towards the plasma membrane as the cells move through the granular layer and cluster at the cell membrane. They fuse with the plasma membrane dispersing their contents into the intercellular space. Polar lipids from the lamellar granules are remodelled into neutral lipids in the intercellular space between corneocytes, forming an important barrier to permeability [1]. The lamellar granules also contain hydrolytic enzymes, lipases and glycosidases, which are responsible for this remodelling [2,3].

Thus, the stratum corneum is rich in ceramides, free sterols and free fatty acids [4]. Linoleate appears to be essential for proper barrier function as an ester-linked residue in acyl ceramides, so in essential fatty acid deficiency substitution of this linoleate by oleate causes a defect in barrier function [5]. The skin is an active lipid-synthesizing tissue, with a daily rate of 100 mg/day. Keratinocytes *in vitro* can synthesize all lipids except essential fatty acids, which have to be obtained from the circulation, so epidermal lipogenesis can be studied in culture.

In human epidermis, nearly all sterol is present as cholesterol. In many cells, cholesterol biosynthesis may be modulated by uptake of exogenous cholesterol, mediated by low-density lipoprotein (LDL) receptors, but these are only present on the plasma membrane of basal keratinocytes, and are rapidly down-regulated on epidermal differentiation [6]. Sterol synthesis is higher in the stratum granulosum, and is thus relatively autonomous and uninfluenced by dietary or circulating sterol levels. Cholesterol sulphate is highest in the stratum granulosum

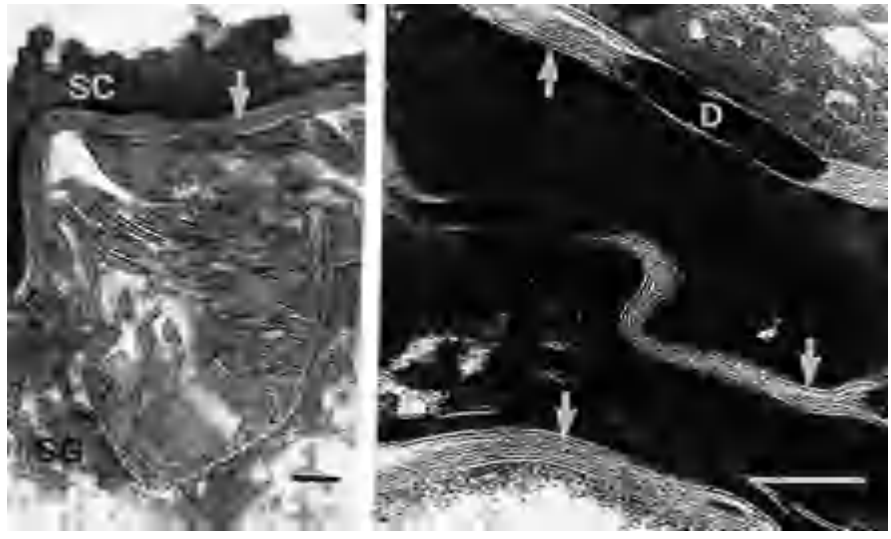

Fig. 3.20 Electron micrograph showing location of epidermal lipids by ruthenium oxide staining. (a) Extrusion of lamellar body lipids or sheets can be seen at the interface between the stratum granulosum (SG) and stratum corneum (SC). Scale bar = 0.1 µm. (b) Sheets of lipid bilayers (arrowed) are present in the intercellular spaces of the stratum corneum. Some regions show a repetitive pattern of staining. D, desmosome. Scale bar = 0.1 µm. (Courtesy of Dr M. Fartasch, Department of Dermatology, University of Erlangen, Germany.)

and corneum, where it is thought to play a role in cell cohesion. In X-linked recessive ichthyosis vulgaris due to steroid sulphatase deficiency, scales contain high levels of cholesterol sulphate giving increased intercellular adhesion [2].

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Keratinocyte integrins

Integrins are a 'superfamily' of cell-surface glycoproteins forming receptors, which mediate adhesion, in both intercellular and cell–substrate interactions. Each integrin consists of a heterodimer of an α (95–130 kDa) and a β (130–210 kDa) subunit; they are transmembrane glycoproteins that interact with actin on the intracellular surface, and the extracellular domains form the ligand binding sites [1]. There are at least 14 α subunits and eight β subunits, ligand specificity being dependent on heterodimer composition. The predominant integrin subunits found in the epidermis are α1, α3, α6, β1 and β4 [2,3], expressed as α2β1, α3β1 and α6β4, predominantly expressed on basal keratinocytes. Other integrins that can be expressed by keratinocytes are αv and α5. Many integrins bind to ECM proteins at sites encompassing the arginine–glycine–aspartate (RGD) sequence and many bind to a specific matrix protein. α2β1 mediates keratinocyte adhesion to types I and IV collagen, α3β1 and α6β4 to laminins and α5β1 to fibronectin. α6β4 is a component of the hemidesmosome complex, and is the receptor for laminins [4,5]. β4 integrin can only combine with the α6 integrin, whereas the α6 subunit can also combine with β1. β4 integrin has a large intracellular domain that includes a connecting segment capable of binding plectin. Other intracellular parts of the molecule bind type XVII collagen and there is a tyrosine activation motif that is necessary for the incorporation of β4 integrin into hemidesmosomes.

When keratinocytes differentiate, they lose adhesion to matrix by loss of integrin expression. Most adherent keratinocytes with high levels of surface β1 integrin expression are thought to contain stem cell populations [6]. There are changes in integrin expression during epidermal morphogenesis and wound healing [7,8], with expression of α1, α3, α6 and β1 in all suprabasal layers. Changes have been noted in basal cell cancer [9]. Suprabasal α6 and β1 have been reported in psoriasis, with variable increased and decreased expression in epidermal tumours [1,3].

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Keratinocytes *in vitro*

The ability to grow keratinocytes through multiple generations has added considerably to our understanding of keratinocyte biology (Fig. 3.21). Initial attempts to grow skin centred on the use of organ cultures and explant cultures, where whole pieces of skin where kept alive and growth was confined to the epibole around the piece or to the plastic around the explant. These cultures have a short life and limited application, as mixed cultures of keratinocytes and fibroblasts are obtained. In 1975, Rheinwald and Green [1] reported the ability to grow pure cultures of keratinocytes from single cell suspension of epidermal cells, using a mesenchymal feeder cell (irradiated mouse 3T3 cells) and serum containing medium. These cells could then be passaged through multiple generations. The technique of keratinocyte culture was improved by added mitogens (EGF and CAMP-elevating agents, including cholera enterotoxin) [1,2]. In the cultures, keratinocytes attach as single cells or small clusters, and then grow at the periphery of the colony while stratifying in the centre. The cells form intercellular desmosomes, and so grow as coherent colonies until confluent stratifying multilayered sheets are obtained. These have poorly formed squames and do not show normal skin morphology, with cells being flattened, attenuated and

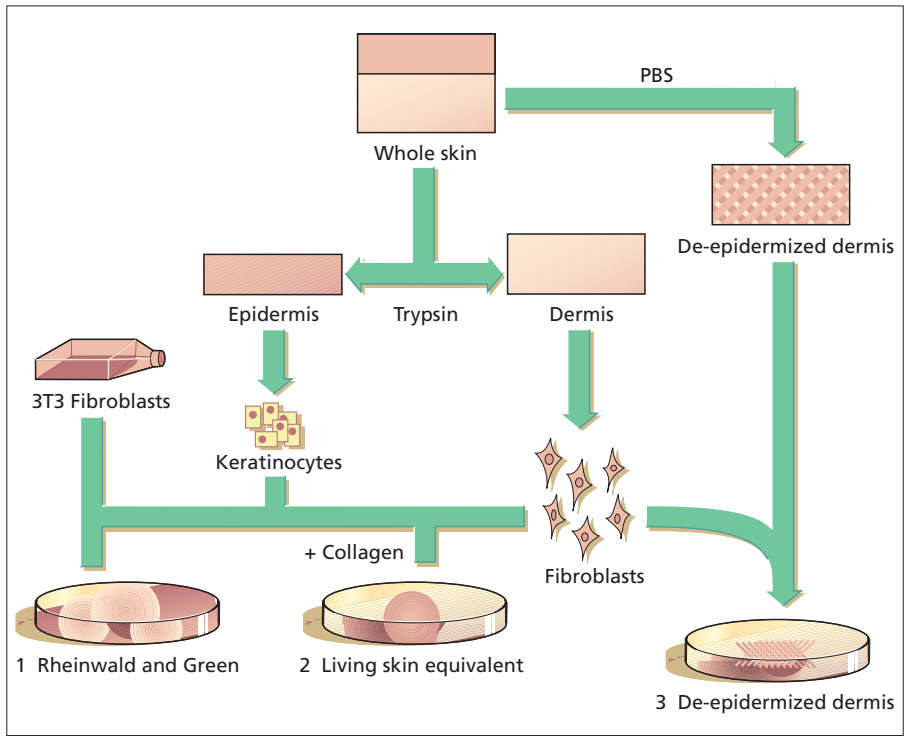

Fig. 3.21 Different methods of culturing skin. PBS, phosphate-buffered saline.

forming no stratum granulosum or stratum corneum. Membrane coating granules and keratohyaline granules are sparse, and the cultures show the same phenotype as regenerating epidermis [3].

Since the fundamental breakthrough of keratinocyte culture, other ways of growing keratinocytes have been developed. The search for a defined serum-free medium has resulted in a low-calcium medium containing many growth factors, which is now commercially available [4]. In a low-calcium (< 0.06 mmol/L) medium the cells fail to form desmosomal interconnections and are spaced out as a monolayer [5]. Although the keratinocytes fail to stratify, they commence terminal differentiation with the expression of involucrin in the larger cells, which move suprabasally when calcium levels are restored (to 1.2 mmol/L). There is no difference in cell proliferation between low-calcium and high-calcium medium. The cell cycle is around 22 h with a growth fraction of 60–70% [6]. These systems are therefore heavily weighted towards hyperproliferation.

The desire to produce a more normal epidermis for experimental purposes has led to the development of complex cultures involving a dermal equivalent or substrate of collagenous gels, including fibroblasts and ECM components [7–9] or de-epidermized dermis [10]. These form organotypical cultures—also termed skin equivalents—sometimes also containing cultured fibroblasts [11]. The cells tend to form a more differentiated epidermis, with stratum corneum and granulosum including keratohyaline and membrane-coating granules. These complex cultures are useful for pharmacological experiments, but they provide little tissue expansion, whereas with the Rheinwald–Green technique 1 cm^2 of skin can generate 1-m^2 culture areas within 6 weeks. This huge population expansion enables application of keratinocyte culture for skin grafting—keratinocyte grafting [12]. The technique has been applied to the treatment of burns and other skin defects, including leg ulcers [13]. Both autologous keratinocytes and allogeneic keratinocytes have been used—keratinocyte autografting and keratinocyte allografting. Although allografts do not survive transplantation [14], they provide a biological dressing and produce wound healing via cytokine release.

In addition to direct clinical application, the development of keratinocyte culture systems has contributed greatly to an increased understanding of factors influencing keratinocyte growth and differentiation, and the release of peptide growth factors and immunological cytokines. The keratinocyte has been shown to play an active part in the skin immune system or SALT (skin-associated lymphoid tissue), both in cellular interactions with Langerhans' cells and epidermotropic T lymphocytes, and in the production of cytokines (Chapter 10). Keratinocytes have been transformed by virus exposure, particularly SV40 [15] and human papillomaviruses, and by oncogene transfections, which have illuminated the processes of skin carcinogenesis. The effects of pharmaceutical agents, particularly retinoids, has been studied *in vitro*. Keratinocytes which have been transfected with human growth hormone genes can release human growth

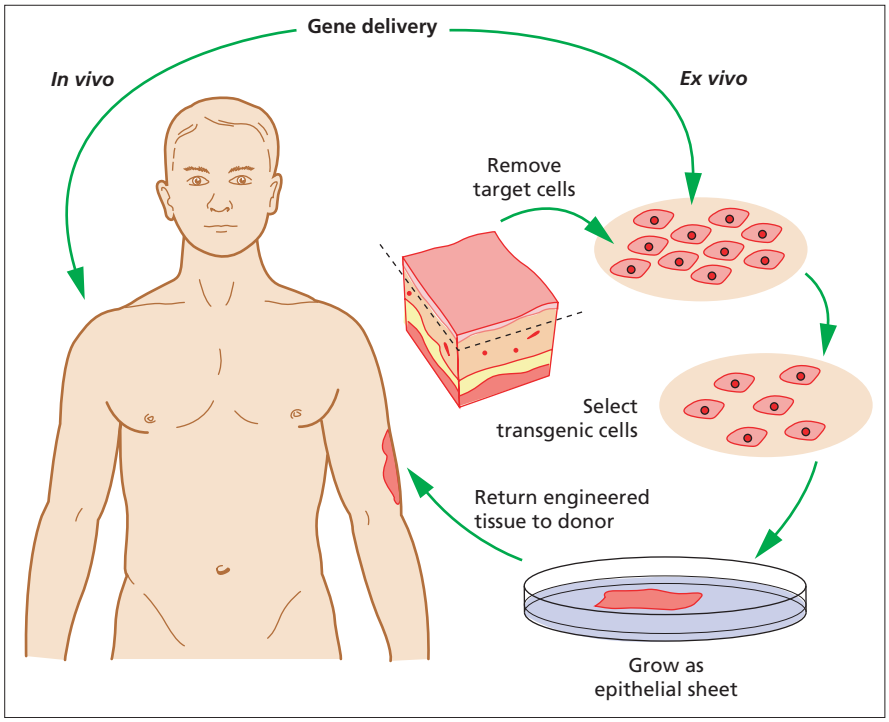

Fig. 3.22 Possible approaches to keratinocyte gene therapy for inherited skin disorders. One approach is direct transfer of genes into skin (*in vivo*) using direct injection of naked DNA or 'gene guns' (ballistic microprojectile accelerators) with the new genes being coated onto small particles of ice or gold. The alternative approach (*ex vivo*), and relevant to most strategies aimed at somatic gene therapy in skin, involves taking a biopsy from a patient, selecting transgenic cells, keratinocyte culture, and grafting of autologous engineered skin back onto the patient.

hormone [16], laying a basis for the use of keratinocytes in gene therapy, perhaps eventually to correct genetic defects such as type VII collagen abnormalities in recessive dystrophic epidermolysis bullosa or laminin 5 pathology in junctional epidermolysis bullosa (Fig. 3.22) [17]. The concept of keratinocyte function has changed over the last 10 years, from a passive cell awaiting terminal differentiation to an active secretory cell having important biochemical and immune functions.

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The dermal–epidermal junction [1]

The dermal–epidermal junction is one of the largest epithelial–mesenchymal junctions in the body. It forms an extensive interface between the dermis and epidermis, and is continuous with the junction between dermis and epidermal appendages. By virtue of its anatomical location and highly complex composition, the dermal–epidermal junction and its major constituent, the basement membrane, have a key role in a wide range of epithelial–mesenchymal interactions including epidermal cell anchorage, adhesion, migration and differentiation. It is also involved in signalling between the ECM and basal cells, and serves as a barrier and filter.

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Ultrastructure of the dermal–epidermal junction

The dermal–epidermal junction encompasses the basal plasma membrane of keratinocytes, melanocytes and Merkel cells and closely related structures, including hemidesmosomes. Hemidesmosomes [1–4] superficially resemble focal thickenings of the basal plasma membrane of keratinocytes. At high magnification, hemidesmosomes (Fig. 3.23) can be seen to have a complicated ultrastructure [1]. The most cytoplasmic portion of the hemidesmosome plaque, or inner plaque, associates with tonofilaments or IFs comprising keratin 14 and keratin 5. The outer plaque is closely associated with the basal plasma membrane. An extracellular component, known as the subbasal dense plate, lies parallel to and just beneath the outer plaque and associated plasma membrane.

Hemidesmosomes have an important role in maintaining adhesion between dermis and epidermis. Hemidesmosome numbers are consistent among individuals, and are not influenced by age, sex or body region [5]. They are similar in skin, gingiva, epidermal cell cultures and cornea.

Immediately beneath the basal plasma membrane is the basement membrane, which consists of three layers: the lamina lucida, the lamina densa and the lamina fibroreticularis [2,6,7]. Distributed throughout the lamina lucida are anchoring filaments, which are often difficult to resolve in electron micrographs, but are most conspicuous in the region of the hemidesmosomes. Anchoring filaments are very fine structures (approximately 3–4 nm in diameter) that are orientated perpendicularly between the lamina densa and basal plasma membrane. The lamina densa is an electron-dense layer that lies parallel to and below the lamina lucida. It usually appears amorphous in skin, although a filamentous substructure has been resolved in other tissues [6]. Anchoring fibrils are the major constituent of the fibroreticular layer of the basement membrane [2,5,8]. These are curved structures, with an irregularly spaced central cross-banding, that insert into the lamina densa and extend into the upper part of the dermis. They may also insert into amorphous bodies in the superficial dermis known as anchoring plaques [8], or, more typically, curve back to have a second insertion in the lamina densa [8,9]. Anchoring fibril numbers vary widely among individuals. Fewer have been found in the arm compared with the leg [5].

Another component of the lamina fibroreticularis is the elastic microfibril [2]. This may occur singly, but is best recognized in a 'bundle' consisting of many microfibrils that extends into the dermis and may enmesh with the microfibrillar system that surround dermal elastin [2]. The main elastic microfibril at the dermal–epidermal junction is fibrillin.

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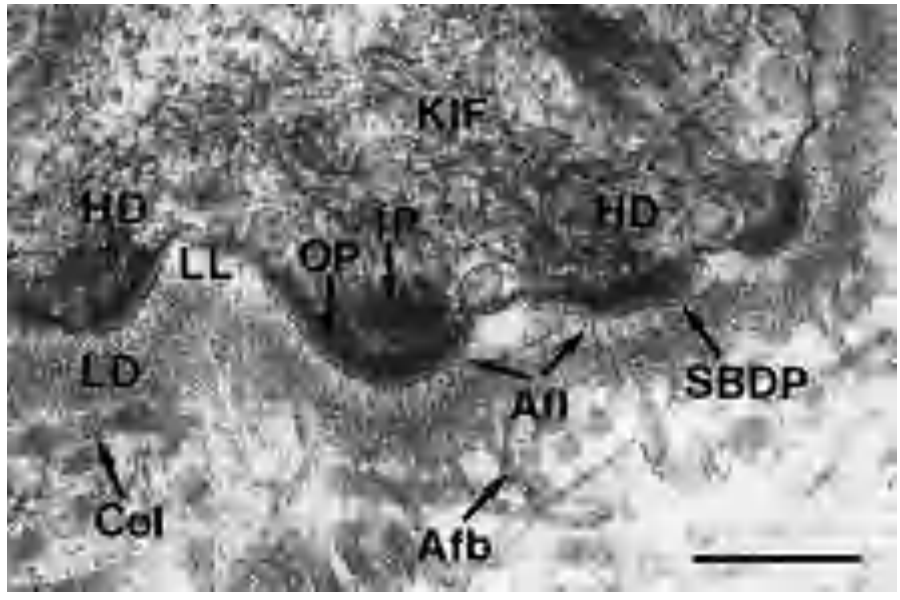

Fig. 3.23 High magnification view of the dermal–epidermal junction showing detail of hemidesmosomes. In this section, inner plaque (IP) and outer plaque (OP) components of the hemidesmosomes (HD) can be resolved. Subbasal dense plates (SBDP) are in the upper lamina lucida (LL) immediately below the outer plaques. Anchoring filaments (Afl) can be seen transversing the lamina lucida and merging with the lamina densa (LD). Anchoring fibrils (Afb) insert into the lamina densa and are closely associated with interstitial collagen (Col) in the papillary dermis. Intracellular tonofilaments or keratin intermediate filaments (KIFs) link up with the inner plaques of hemidesmosomes. Scale bar = 0.25 μm.

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Molecular components of the epidermal basement-membrane zone [1–3]

Our understanding of the nature and function of the different components of the dermal–epidermal junction has progressed enormously over the past few years. This progress has resulted from studies incorporating recombinant DNA strategies, applied both *in vitro* and in transgenic and knock-out mouse experiments, from the production of highly specific monoclonal and polyclonal antibodies, and from improvements in immunocytochemistry enabling precise immunolocalization of antigens at the subcellular level. Important biological functions for many components of the dermal–epidermal junction have also been derived from mutation analysis in DNA from patients with inherited blistering skin diseases. The epidermal basement membrane, in common with other basement membranes, consists of a number of collagenous and non-collagenous macromolecules [1] (Table 3.3). These components have unique capabilities to interact and bind to one another, and to form a matrix that subserves the main functions of the basement membrane, including cell attachment, differentiation and movement.

Type IV collagen is the main structural constituent of the basement membrane (Figs 3.24 & 3.25), and has been immunolocalized mainly to the lamina densa [4]. The two major polypeptides are α1(IV) and α2(IV) with a molecular weight of 180–200 kDa for the α(IV) chains and of 550–600 kDa for the monomeric collagen type IV. The molecule is thought to have heterotrimeric composition of [α1(IV) α2(IV)]. The type IV collagen molecule has a large C-terminal globular domain at one end (Fig. 3.24), and an aminoterminal triple-helical region at the other, through which four molecules are able to bind covalently and form tetramers or 'spiders'. The point of overlap has been referred to as the 7s domain. The spiders are linked by covalent interactions between the C-terminal globular domains (Fig. 3.24). The type IV collagen molecule is able to interact with laminin, nidogen, heparan sulphate proteoglycan (PG), BM-40/SPARC and β1 integrin. Immunolabelling of normal human skin with an antitype IV collagen antibody is shown in Fig. 3.25.

Table 3.3 Molecular components of epidermal basement membrane.

Intermediate filament (IF) components
Keratin 14
Keratin 5
Hemidesmosomal plaque components
Bullous pemphigoid 230-kDa antigen (BP230; BPAG1)
Plectin
Transmembrane components
α6β4 integrin
Type XVII collagen (180-kDa bullous pemphigoid antigen 2 [BPAG2])
α3β1 integrin
Type XIII collagen
Syndecans 1 and 4
Lamina lucida/lamina densa components
Laminin 5
Laminin 6
Laminin 10
Laminin 2
Laminin 1
Lamina densa components
Type IV collagen
Nidogen
BM-40/SPARC
Perlecan
Anchoring fibril components
Type VII collagen
GDA-J/F3 antigen

Type VII collagen (Fig. 3.24) is described elsewhere. Initially, it was recognized that crystallites of SLS collagen were similar to anchoring fibrils [5], and more recently type VII collagen has been immunolocalized to anchoring fibrils (Fig. 3.26).

Of the non-collagenous basement-membrane components, the laminin family of glycoproteins is the best characterized [1,2,6]. The laminins are heterotrimeric molecules, each consisting of an α chain, β chain, and γ chain. More than 10 different laminin isoforms have been described [6], and laminins 1, 2, 5, 6 and 10 are known to occur in epidermal basement membrane.

Nidogen is a ubiquitous 150 kDa glycoprotein comprising three globular domains and a central rod [7]. It acts as a key stabilizer of basement membrane, binding to type IV collagen, perlecan and fibulins [8]. It also has calcium-dependent binding to the γ1 laminin chain. Thus, ligands for nidogen at the dermal–epidermal junction include laminins 1, 2, 6 and 10.

Perlecan is the main PG of basement membranes. It comprises a 500-kDa core domain with heparan sulphate attached to the amino terminus [9]. Perlecan binds to nidogen, dystroglycan and ECM1 [10]. Its functions include stabilization of basement membrane and regulating basement membrane synthesis and turnover through binding cytokines and growth factors.

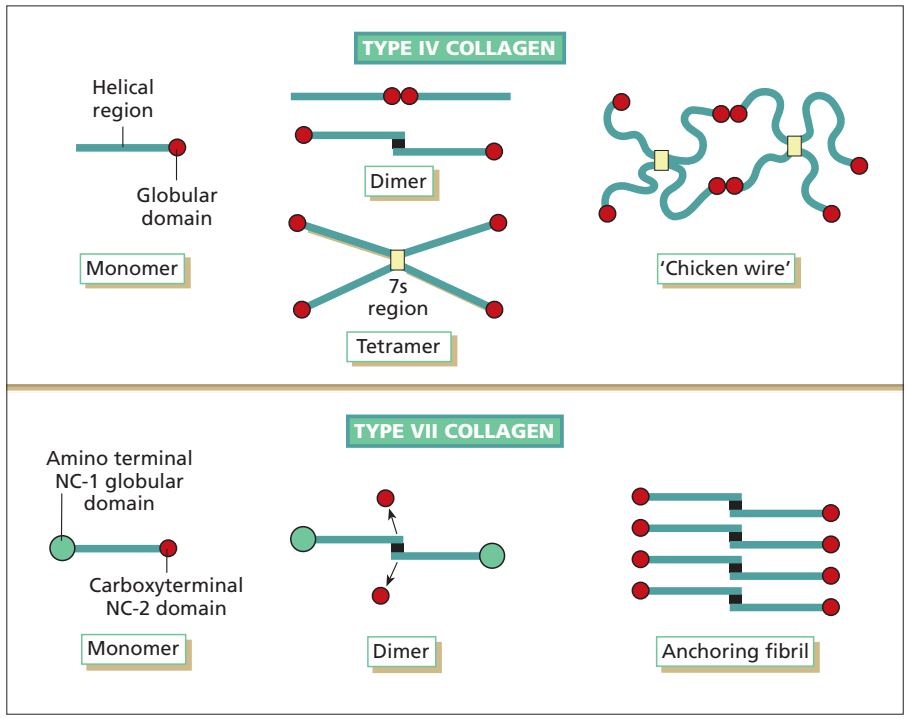

Fig. 3.24 Diagrammatic representation of the molecular organization of types IV and VII collagen.

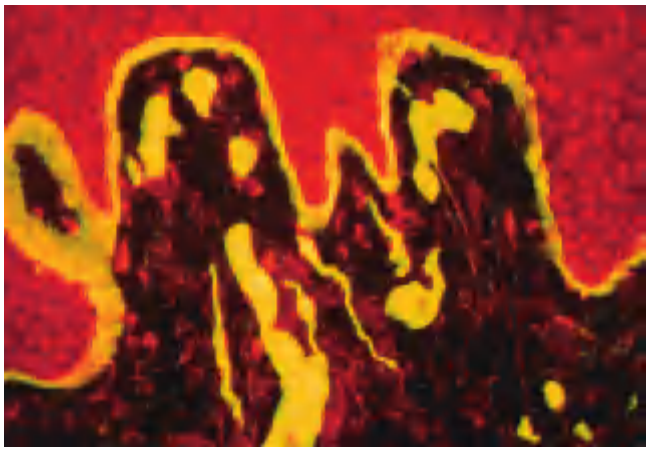

Fig. 3.25 Immunofluorescence micrograph showing staining for type IV collagen in the dermal–epidermal junction and around dermal vessels. × 250.

The major component involved in adhesion between basal cells and ECM is the hemidesmosome-anchoring filament-anchoring fibril adhesion complex (see below).

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The hemidesmosome-anchoring filament-anchoring fibril adhesion complex [1–3]

Hemidesmosomes are thought to form a continuous link between the intracellular keratin filament network and the extracellular basement membrane. Further links are possible with elements in the superficial dermis via the anchoring fibril network. Because of the nature of the different molecules comprising this highly specialized complex, it now seems likely that hemidesmosomes are important not only in adhesion but also as a pathway for signal transduction between the extracellular and intracellular compartments [4,5; reviewed in 3]. Major intracellular (plaque) components of the hemidesmosome include the 230 kDa bullous pemphigoid antigen (BP230

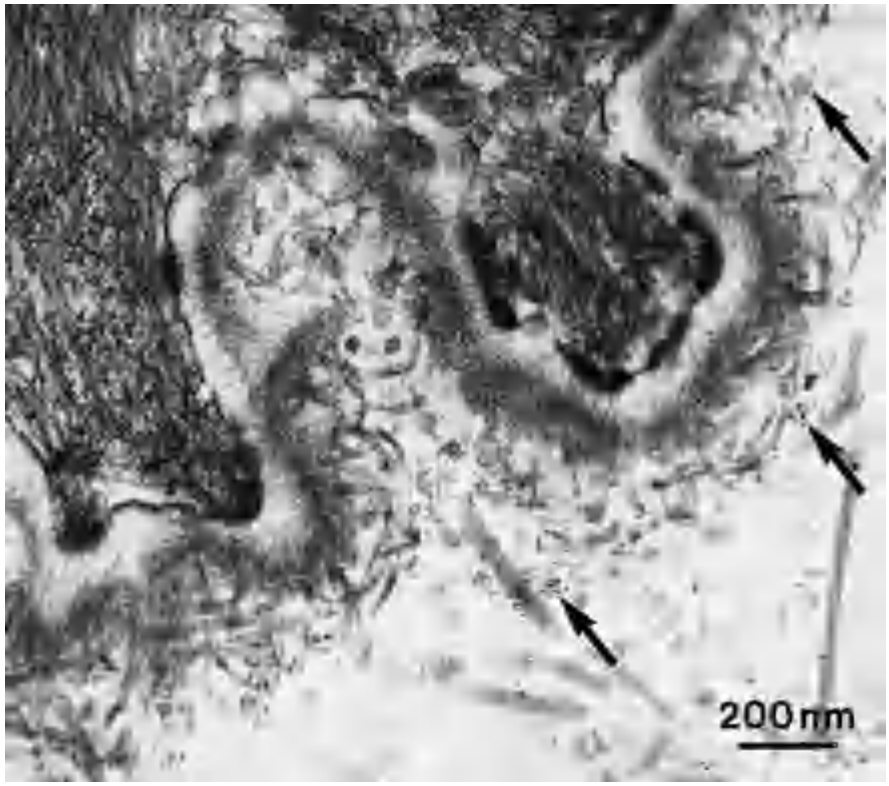


Fig. 3.26 Immunoelectron micrograph showing 5-mm gold labelling of epidermolysis bullosa acquisita antigen (N terminus of type VII collagen) associated with the ends of anchoring fibrils (arrows). (Courtesy of Dr H. Shimizu, Hokkaido University, Japan.)

or BPAG1) [6] and plectin [7] (Fig. 3.27). At least part of these molecules (the C termini) extend into the inner plaque, in a region of the hemidesmosome that would seem, at least spatially, well suited to interact with the keratin filament network. The possibility of such an interaction is strengthened by sequence homology between BP230 and plectin, and with another putative IF-associated protein, desmoplakin [2,8], which is a component of desmosomes but not hemidesmosomes. Plectin has a molecular mass of around 500 kDa. It is widely distributed among different cell types in various tissues, and its localization is not restricted to hemidesmosomes. It has the potential to form links with a variety of cytoskeleton components, including IF-forming proteins, microtubules and microfilaments [7]. HD1 and IFAP300 have also been described as components of the inner hemidesmosomal plaque. However, it appears that these represent either specific variants of plectin that are expressed only in hemidesmosomal inner plaques or unique plectin epitopes expressed only in the context of hemidesmosomes [9,10].

The α6β4 integrin and the 180-kDa bullous pemphigoid antigen (BP180, BPAG2 or collagen type XVII) are both transmembrane components of hemidesmosomes [11–13]. The region spanned by this combination of molecules is quite extensive. The cytoplasmic tail of the β4-integrin subunit contains over 1000 amino acids, and is thought to extend to the inner plaque of the hemidesmosome [14]. It also may have the potential to bind to keratin filaments, perhaps the end domain of keratin 5 (Fig. 3.28).

Immunoelectron microscopy has been used to localize epitopes of different proteins to anchoring filaments, which straddle the lamina lucida between hemidesmosomes and the lamina densa. These anchoring filament-associated proteins include laminin 5 [15,16], laminin 6 [17], the extracellular segment of type XVII collagen [18,19], the linear IgA antigen, LAD-1 (which constitutes part of the extracellular domain of type XVII collagen [20]) and the as yet unknown antigen recognized by 19-DEJ-1 monoclonal antibody [21].

Laminin 5 (previously known as nicein, kalinin or epiligrin) is a member of the laminin family of glycoproteins, of which over 10 distinct isoforms have been described [22]. Each is a heterotrimeric macromolecule with a cruciate structure, consisting of an α chain in part alignment with β and γ chains. Classical laminin, which is ubiquitous in basement membranes, is now known as laminin 1, with the composition of α1, β1 and γ1 chains. Laminin 5 has a more restricted distribution and comprises α3, β3 and γ2 chains. The α3 and γ2 chains undergo post-synthetic processing involving the enzyme BMP-1, leading to a reduction in their molecular weights from around 200 to 165 kDa and from 155 to 105 kDa, respectively. To maintain adhesion, specific interactions between the various structural components of the hemidesmosome-anchoring filament complex, including α6β4 integrin, type XVII

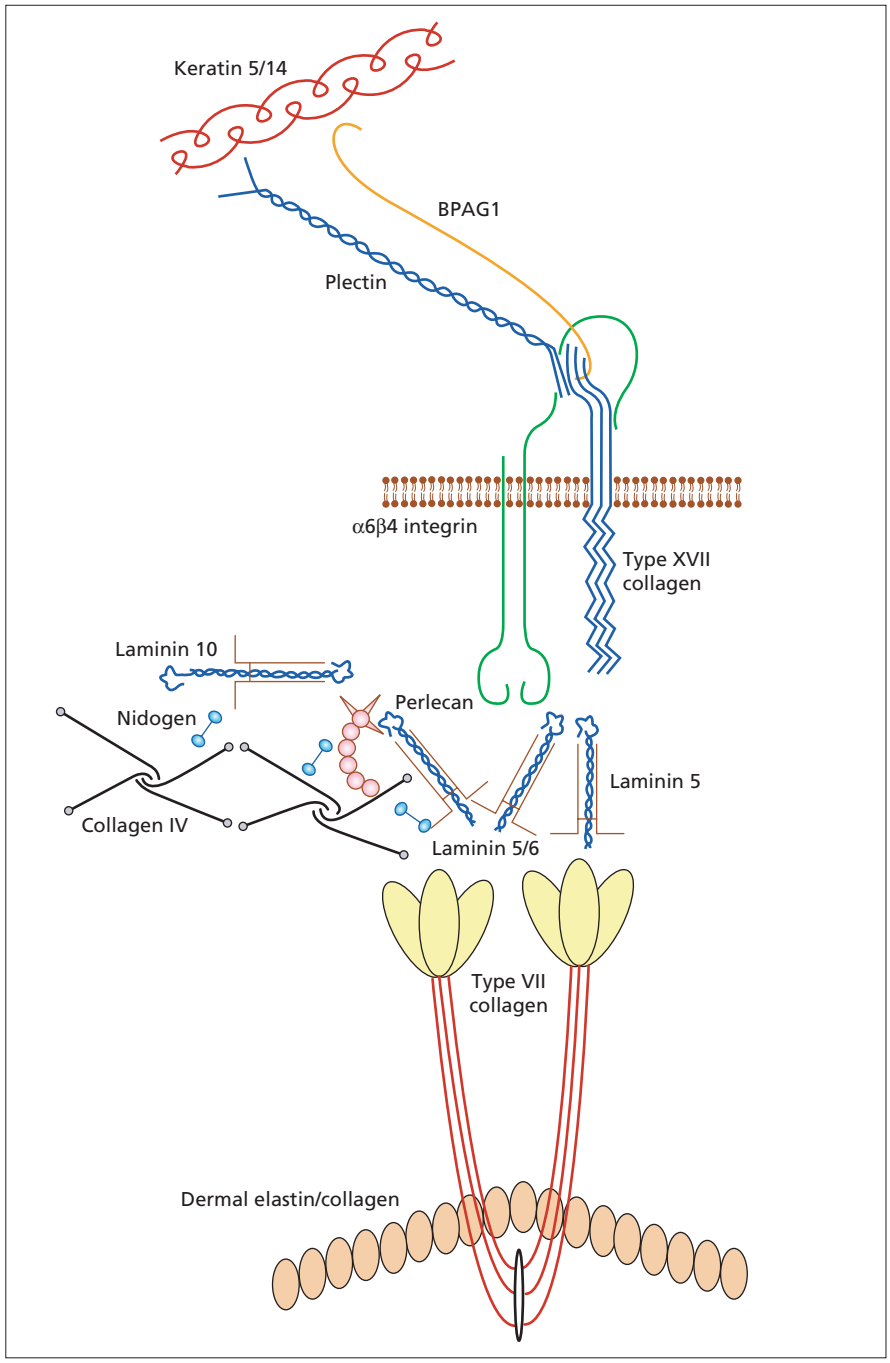
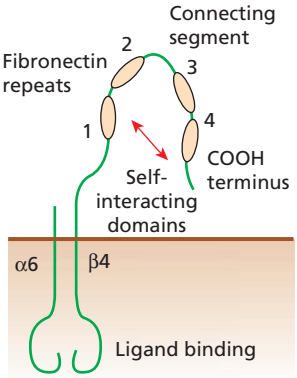


Fig. 3.27 Protein organization and interaction at the dermal–epidermal junction. Keratin filaments in basal keratinocytes are attached to the basal cell plasma membrane through plectin and BPAG1 within hemidesmosomes. Connections between these proteins and α6β4 integrin and type XVII collagen then provide a link to the epidermal basement membrane and bind to laminin 5. Laminin 5 may complex with laminin 6 and secure further adhesion to type IV and VII collagen. Additional protein complexes involving laminin 10, nidogen and perlecan provide further stability to the dermal–epidermal junction.

collagen, laminin 5 and laminin 6, must occur. For example, the intracellular part of β4 integrin binds to both plectin and type XVII collagen; the extracellular part of α6 integrin binds to type XVII collagen; laminin 5 binds to type XVII collagen, type VII collagen and laminin 6; laminin 6 binds to nidogen. Thus, a complex and coordinated meshwork of adhesive proteins (Fig. 3.27) is responsible for maintaining adhesion between the epidermis and the dermis [23].

Type VII collagen is the major, if not sole, component of anchoring fibrils [24]. Type VII collagen molecules are homotrimers consisting of three identical pro-α1(VII) chains. During extracellular assembly of anchoring fibrils, two type VII collagen molecules form an antiparallel dimer through an intermolecular interaction at the overlapping C-terminal ends of the molecule. There is also extracellular processing by BMP-1. Formation of anchoring fibrils comes about through lateral aggregation of multiple type VII collagen dimers [25] (Fig. 3.24).

Cloning of cDNA corresponding to overlapping α1(VII) sequences has shown a complex structure, comprising a central collagenous segment flanked by two globular



Domain	Function
β4 integrin	
COOH terminus	Plectin binding
COOH terminus	Proximal endodomain binding
Connecting segment	Hemidesmosome assembly
Connecting segment	Plectin binding
Connecting segment	Tyrosine activation motif
Connecting segment and 3rd FN repeat	Collagen XVII binding
NH_2 half, endodomain	COOH terminus binding
Exodomain	Extracellular ligand binding
α6 integrin	
Proximal exodomain	Collagen XVII binding
Exodomain	Extracellular ligand binding

Fig. 3.28 The molecular composition, domain organization and function of α6β4 integrin, the main keratinocyte integrin in hemidesmosomes. This integrin is important in hemidesmosome assembly and protein interactions [14].

domains of unequal size [26,27]. The larger N-terminal NC-1 (non-collagenous) domain is about 145 kDa, and contains sequences with homology to cartilage matrix protein (CMP) and to the A domain of von Willebrand factor [28]. In addition, there are nine consecutive fibronectin type III-like domains. Protein modelling predicts that these fibronectin type III-like domains have suction cup-like morphology and represent the main part of type VII collagen responsible for anchoring fibril adhesion. The smaller C-terminal NC-2 domain is about 17 kDa and contains a segment with homology to the Kunitz proteinase inhibitor [29]. The triple helical collagenous domain contains Gly-X-Y repeat sequences, with a 39-amino-acid non-helical interruption. Binding assays suggest a relatively strong affinity between the NC-1 domain of type VII collagen with type IV collagen with a weaker interaction with laminin 5 [25].

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Dermis

[F.M. Pope, pp. 3.33–3.72]

Components of the dermis [1–3]

The dermis, which is bounded externally by its junction with the epidermis and internally by subcutaneous fat, contributes 15–20% of the total weight of the human body. It varies in thickness from about 5 mm on the back and thighs to 1 mm on the eyelids. It is tough and resilient, providing nutriment to the epidermis and cutaneous appendages and cushioning the body against mechanical injury.

It largely consists of a supporting matrix or ground substance, in which polysaccharides and protein coexist and interact to produce hygroscopic proteoglycan (PG) macromolecules, which strongly attract and retain water. Running through and attached to this matrix are several kinds of protein fibre, such as interstitial *collagen*, with great tensile strength, *elastin*, with considerable elasticity, and various other microfibrillar components such as fibrillin (types I and II), microfibril-associated glycoprotein (MAGP), microfibril-associated fibrillar protein (MAFP), collagen type VI and lysyl oxidase. Collagen (see below) represents 75% of the dry weight and 18–30% of the volume of dermis, of which more than 70% is type I collagen and 15% type III collagen. The ratios are reversed in arteries, while bone is composed of almost exclusively collagen type I. Collagen/connective tissue matrix is very complex, and also contains various PGs and adhesive glycoproteins. All interact with various other matrix components and cellular elements to produce a cohesive but variable tissue mix of ECM with differing combinations in tissues such as dermis, bone, blood vessels, etc. Embryonic dermis is a fine, three-dimensional network of collagen and elastic fibres interlaced with abundant PG-rich ground substance; in adults, collagen fills most of the dermal space [4] (Fig. 3.29). The size and arrangement of the collagen fibres distinguishes two main regions. The thin, superficial *papillary dermis* interdigitates with the ridged underside of the epidermis, from which it is separated by a basement membrane. Collagen fibril diameter (in transverse section) increases progressively from the superficial dermis through the mid and lower dermis, increasing from approximately 20 to 70 nm in this interval.

The underlying nine-tenths is called the *reticular dermis*: it blends with the subcutaneous fat. In regions such as the nipple, penis, scrotum or perineum, there are also stress-orientated smooth muscle fibres in the reticular dermis.

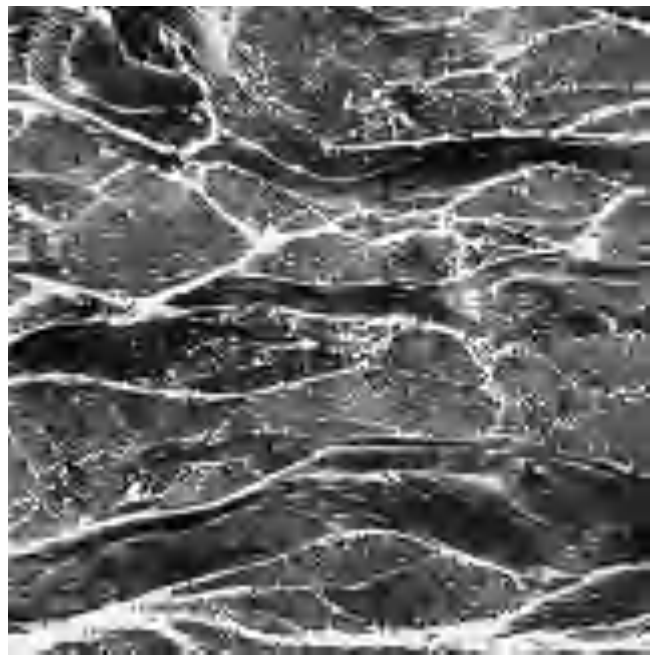

Fig. 3.29 Transmission electron micrograph of a section of dermis from the human forearm showing bundles of collagen fibres sectioned both transversely and longitudinally. × 4900. (Courtesy of Professor A.S. Breathnach, St John's Institute of Dermatology, London, UK.)

Abnormalities of collagen include fibril depletion, and disorganization, as in the hieroglyphic pattern of procollagen peptidase deficiency, the variability of fibrillar diameters in collagen type III deficiency, and highly disorganized fibrillar packing with cauliflower fibrils in type V collagen mutations.

Elastic fibres also form an extensive network, which intermeshes with collagen fibres. They are a complex mixture of proteins; by electron microscopy the central (striped) amorphous material consists of elastin whilst the peripheral microfibrils are more heterogeneous and are formed of components, such as fibrillins 1 and 2, certain microfibril-associated glycoproteins, such as MAGP-1 and -2, microfibril-associated proteins, such as MFAP types 1–3, lysyl oxidase and collagen types VI α1–3. Recently, in 2000, the gene for pseudoxanthoma elasticum (PXE) unexpectedly proved to be an ion transporter related both to the cystic fibrosis sodium CFTR (cystic fibrosis-transmembrane conductance regulator) transporter gene and certain drug resistance phenotypes. The gene contains three distinctive membrane spanning sequences, together with distinctive Walker A and B motifs and nucleotide binding folds (Fig. 3.30). Paradoxically, *ABCC6* mRNA is especially rich in renal and hepatic tissue, whilst homozygous or doubly heterozygous mutations of the gene cause fragmentation of elastic fibres

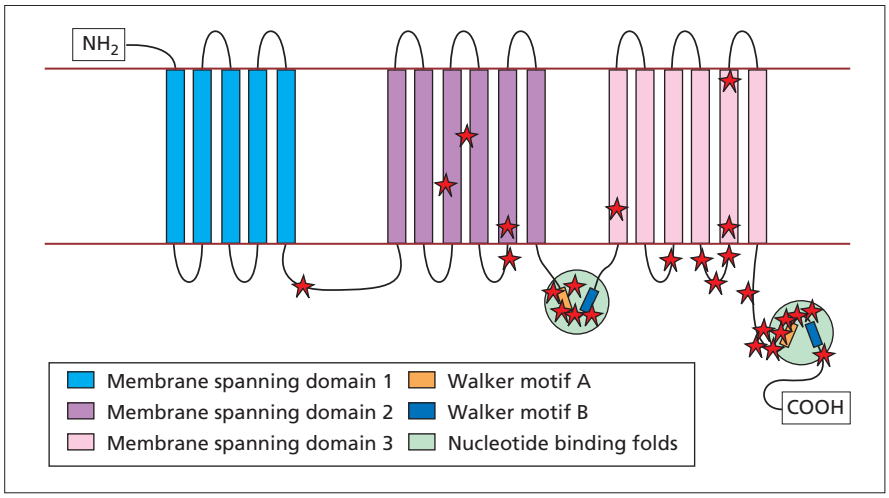

Fig. 3.30 Structure of the *ABCC6* gene showing the characteristic three membrane spanning domains, Walker A and B motifs and the nucleotide binding regions. Many of the starred mutations occur in the transmembrane sequences, or the loops that connect them.

in tissues such as skin, arterial medial walls and the retroretinal Bruch's membarane of the eye. Somehow, errors of *ABCC6* indirectly misassemble elastic fibres, which consequently fragment and bind calcium in skin eyes and arteries [5,6]. This produces the typical flexural rash, premature arteriopathy and early macular degeneration with premature visual loss of PXE. In embryos, the microfibrillar elements precede and act as a scaffold for the more mature elastic fibres. Mature elastic fibres are restricted to the reticular dermis. *Oxytalin* fibres, which probably anchor the basement membrane, extend as small bundles of microfibrils into the papillary dermis [7]. Oxytalin fibres also branch to form a horizontal plexus in the upper reticular dermis; small amounts of stainable elastic matrix are then secreted, to produce so-called *elaunin fibres* [7].

The *fibrillins* are microfibrillar proteins first isolated in 1986, with two or more genes isolated 5 years later. Antifibrillin antibodies detect dermal and vascular elastic fibrils, the ciliary zonules of the lens cornea, vitreous, articular and fibro-cartilage. The anatomical distribution of fibrillin closely parallels that of elastin in the dermis, vasculature, tendons, myotendinous junctions, ligaments, cartilage and lungs. Inherited abnormalities of fibrillin 1 cause Marfan's syndrome, while fibrillin 2 defects have a subtly different distribution, cause congenital contractural arachnodactyly (CCA) (Beals' syndrome), in which the ciliary zonules are normal, whilst impressive tendinous fibrosis causes finger contactures, with accompanying crumpling of the fibrosed external ear cartilage. Unlike Marfan's syndrome, aortic dilatation and rupture is virtually absent.

Other adhesive ECM glycoproteins include fibronectin [8], vitronectin, thrombospondins 1–5 [9,10], tenascins C, R, X and Y [11,12], osteopontin, and the highly diverse α, β and γ laminins [13,14]. The latter not only have mechanical adhesive properties, but also function in embryogenesis, organogenesis, differentiation and cell adhesion, by interactions with integrins, basement membrane collagens and PGs. Fibronectin (cold insoluble globulin), has variably spliced, soluble (in serum) and insoluble (in ECM) forms, of 500 kDa. The multidomain organization and splicing differ in the insoluble and soluble subtypes and a typical RGD binding sequence [8,15] common to most adhesive components. There are interactions with other homologous proteins and certain cellular components via certain integrin receptors [16,17]. The variably spliced domains bind to fibrin, heparin, factor XIIIa, collagen, etc. Fibulins 1 and 2 [18,19] also bind calcium and fibronectin, with distributions in ECM (fibulin 1), and heart, placenta and ovaries (fibulin 2). The fibulin 1 gene is located at chromosome 22, with the fibulin 2 gene on chromosome 3.

Many collagens also contain similar RGD sequences, while some (e.g. collagen type VII) have homologous fibronectin repeats. Vitronectin, thrombospondin and laminin all share RGD sequences but also have sequences with varying combinations of other elements, with EGF, TGF-β and von Willebrand factor homologies. Fibrillin has similar elements, as do some of the PG core proteins.

Proteins such as laminin [13,14], tenascin, vitronectin, nidogen (entactin) and von Willebrand factor share with fibronectin the capacity to modulate cell migration, ECM modelling and skeletal morphogenesis. They may also participate in connective tissue maturation, embryogenesis, wound healing and tumour metastasis, as do many other of the components mentioned earlier.

The predominant dermal cellular elements are fibroblasts, which secrete the ECM proteins mentioned above. Others include mast cells, histiocytes, macrophages, lymphocytes and other leukocytes, and melanocytes. The dermis also contains capillaries, arterioles, venules and lymphatics, as well as peripheral, sensory and motor nerve endings.

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Elastic tissue

Elastic fibres are mixed collections of various distinctive microfibrillar structural glycoproteins, at least one of which is an enzyme, whilst elastin forms the central amorphous centre of the compound elastic fibres. By electron microscopy, they have central amorphous and peripheral microfibrils of 10–13 nm [1], whilst light microscopy shows darkly stained unbranched fibrils which are intermingled and separate from collagen and other matrix elements. Microfibrils either decorate amorphous elastin or occur between individual collagen fibres. Elastin-associated microfibrils include glycoproteins such as fibrillin 1 and 2, MAGP-1, -2 and -3, MFAP-1, -2 and -3, and fibulin 1 and 2 with molecular weights of 25–340 kDa [1–4]. Quite clearly, elastin and elastic fibres differ from other ECM components such as collagen (except type VI) and PGs (see below). They stain with elastic-specific stains such as orcein, and are widespread in tissues such as skin, lungs, alveoli, arteries, veins, the urinary tract, eye (both cornea and suspensory ligament), fibrillar and articular cartilage, and specialized tendons such as the ligamentum nuchae.

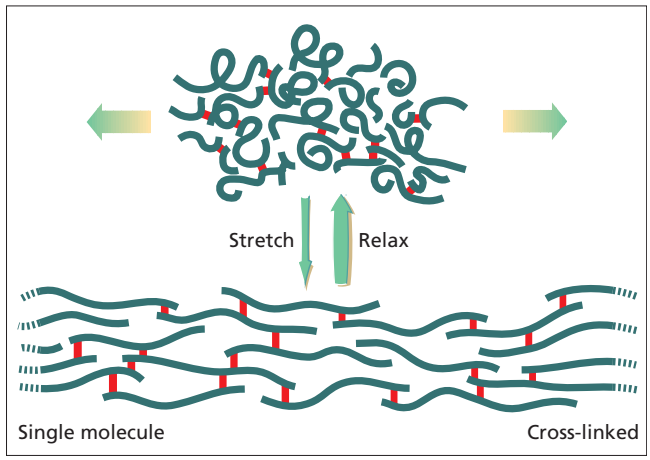

Fig. 3.31 Schematic representation of elastic fibrils in contracted and stretched modes. Cross-linked random coils confer the capacity for extensibility.

Biophysical properties

Elastin possesses a rubbery recoil, allowing the function of expansile tissues such as the aortic arch, which in a lifetime undergoes 1000 million contractions and relaxations. Entropy increases on relaxation but decreases on stretching or expansion. Elastic fibres accommodate these desirable requirements (Fig. 3.31).

Histology and electron microscopy

Elastic fibres have certain characteristic features, on both light and electron microscopy.

Light microscopy [5–7]

On light microscopy with stains such as Weigert's resorcin–fuchsin, Verhoeff's or orcein, elastic fibres are coloured black or dark brown. In contrast, collagen and other connective tissue elements are stained either red or yellow. Oxytalin and elaunin subepidermal microfibrils are closely associated with elastic fibrils in the reticular dermis.

Transmission electron microscopy

Transmission electron microscopy of elastic fibres shows distinctive sheet-like agglomerates, which are several hundred nanometers wide (Fig. 3.32). The peripheral microfibrils include proteins such as MAGP-1, -2 and -3, MFAP-1, -2 and -3, fibulins 1 and 2, and fibrillins 1 and 2, while the central speckled amorphous element contains only elastin. Other proteins, such as collagen type VI α1–3 chains, and lysyl oxidase are also microfibrillar. In the developing embryo, microfibrils precede elastin forming a scaffold upon which mature elastin protein is later

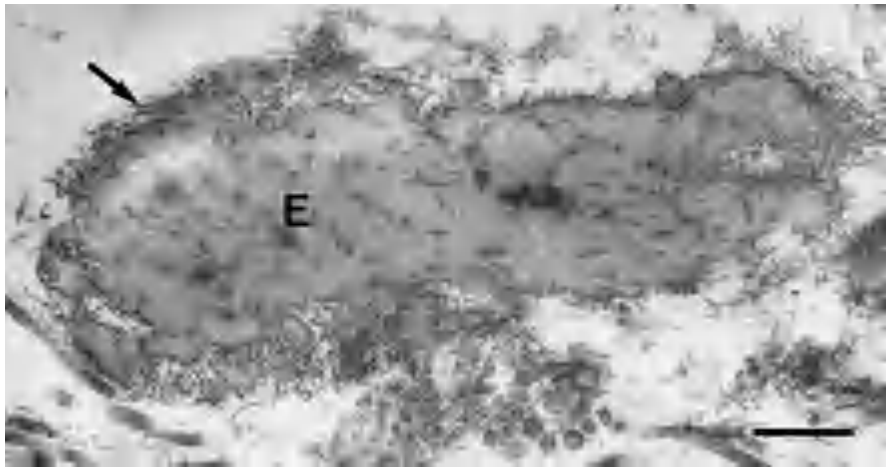

Fig. 3.32 Electron micrograph of an elastic fibre in reticular dermis. The central, mottled component (E) contains elastin, and the microfibrillar network can be seen at the periphery of the fibre (arrow). Scale bar = 0.5 μm.

deposited [1]. Some fibrils behave differently; for example, fibrillin 2 has a subtly different tissue distribution, appears later in fetal development and fulfils a different and non-load-bearing function of elastic fibres [8,9].

Biochemistry and molecular pathology

Since 1984, when the first elastin sequence appeared, all of the other elastin-associated microfibrillar components have also been cloned and sequenced [10–24]. Thus MAGP-1, -2 and -3 and fibrillins 1 and 2 were sequenced between 1991 and 1994 [1,12], closely followed by other constituents, such as the fibulins, the MFAP proteins, lysyl oxidase, lysyl hydroxylase, etc. [13–24]. All are important constituents of mature elastic fibrils. MAGP was first recognized as an ECM component [1]. It formed microfilaments ranging from 3 to 20 nm, which, after denaturing, formed strings of beaded microfilaments on rotary shadowing [4]. Components such as the 340-, 78-, 70-, 31- and 25-kDa proteins were subsequently purified. Other workers identified 128-, 115-, 58- and 36-kDa proteins [12,13]. Fibrillin was then identified as the 340-kDa element and is also microfibrillar. Bressan *et al*. [15] named the 115-kDa component emilin, while Kobayashi *et al*. [16] identified a 58-kDa component of elastin-associated fibrillin. Kielty *et al*. [17–19] showed that fibrillin forms the connecting elements of beaded filaments. The separate, but related, genes (*Fib1* and *Fib2*) were both cloned in 1991 [8,9]. Although MAGP-like glycoproteins are homologous to fibrillin, they are also distinctive and unique. Thus, antibodies to the 31- or 78-kDa proteins both detect part of the 340-kDa fibrillin protein, but do not cross-react [1,13]. Cloning of the relevant genes has clarified this paradox, clearly showing that the protein families have both homologous and non-homologous sequences, which distinguish one from another. More recently, the PXE *ABCC6* gene, rather unexpectedly, has been shown to encode for an ion transporter molecule, analagous to the cystic fibrosis gene. Homozygous or doubly heterozygous muatations somehow disrupt elastic fibril assembly, with consequent fragmention and calcium binding, in tissues such as skin, arterial media and the subretinal Bruch's membrane of the eye, causing the typical PXE clinical phenotype.

Microfibril-associated glycoprotein (MAGP)

Gibson *et al*. [1] first affinity purified and then cloned bovine MAGP, and showed that the 31-kDa protein was not a degradation product of the 340-kDa (fibrillin) protein. Cloning of fibrillins 1 and 2 [11,12] confirmed their distinction from human MAGP [10,20,22], although the latter forms 12-nm microfibrils, which decorate the beaded filaments of fibrillin. Mouse MAGP has two distinctive domains [18]. The N terminus is rich in glutamine, proline and aspartic acid, while the C terminus is cysteine cross-linked, resembling the equivalent fibrillin sequences. The gene has eight introns distributed over 10 kb. It is expressed in lung, pulmonary arteries and heart [11,22]. MAGP-2 and -3 proteins have also been cloned and sequenced. MAGP-1 lies on chromosome 19p36.1–p35, MAGP-2 lies at 12p12.3–13.1, whilst MAGP-3 is located at 15q15–q21, close to the fibrillin 1 (*FBN1*) gene. The microfibril-associated proteins MFAP-1 and -3 are co-associated with, but molecularly distinct from, the MAGP proteins [20–22]. The three MAFP genes have now been sequenced and are located, respectively, close to fibrillin 1 on chromosome 15q15–q21 [10] (*MFAP-1*), and close to fibrillin 2 (*FBN2*) at 5q21–q31, and subsequently, MFAP-2 and -4 [21–24], and mouse MAGP [21] have been sequenced. The deduced protein sequence of MFAP-3 is partially homologous to MAGP-1 and MAGP-2 [23]. Antibodies to MFAP-3 stain ciliary zonules (as does fibrillin 1). Other microfibrillar proteins such as the 78-, 36- and 25-kDa elements have yet to be sequenced, although MFAP-2 may be analogous to the 25-kDa protein. The tissue

distributions of MFAP-1 and -2 also differ substantially. Thus, while MFAP-1 antibodies stain renal glomerulus and mesangium, antibodies to MAFP-2 detect only renal tubular renal basement membrane, implying important functional differences.

Fibrillins 1 and 2

Whilst Gibson *et al*. [1,13] cloned MAGP-1, Sakai *et al*. [25] identified the 350-kDa glycoprotein, fibrillin. Fibrillin antibodies stain elastic fibres in skin and blood vessels and other ECM [26]. Rotary shadowing electron microscopy of fibrillin-containing microfibrils formed from post-confluent Marfan's syndrome fibroblasts showed that they were severely disaggregated [19]. The fibrillin 1 gene [11] and the Marfan's syndrome loci were at 15q15 [12,27,28]. Maslen *et al*. [11] and Lee *et al*. [12] independently cloned a fibrillin cDNA of 10 kb, which was rich in 6- and 8-cysteine repeats. The 6-cysteine repeats resemble EGF [11,12], whilst certain 8-cysteine elements resemble TGF-β. Fibrillin 2 on chromosome 5q causes CCA (Beals' syndrome) [11]. The fibrillin 1 gene has 11 kb of coding sequence spread over 110 kb of genomic sequence split into 65 exons. These include 43 EGF-like calcium-binding regions, four similar but non-calcium-binding repeats and seven TGF-β subunits. Marfan's syndrome mutations frequently cluster in the EGF (calcium-binding) and TGF-β domains. Subsequently Lee *et al*. [12] identified the first mutations and various others quickly followed [29,30]. Nijbroek *et al*. [31] documented 53 mutations including various cysteine substitutions in EGF and TGF-β regions, but also premature stop codons and null alleles. Infantile Marfan's syndrome has mutations clustered between exons 24 and 31. The most structurally disruptive mutations produce the least distorted microfibrils, implying that defective protein structure is more damaging than missing protein. A putative Marfan's syndrome locus at 3p24 is highly controversial [32–34]. Antibodies to fibrillin 1 and 2 differentially stain elastic-containing tissues such as skin, aorta and cartilage. Fibrillin 2 is more widespread than fibrillin 1. In skin, fibrillin 2 is concentrated around hair follicles and sweat glands, and forms connections between the dermis and the overlying basement membrane. Based upon the differential morphological distribution of fibrillin 1 and 2, it has been postulated that fibrillin 1 is load-bearing, and therefore appears early in blood vessels and ciliary zonules. Fibrillin 2, which only appears later in embryogenesis, mainly regulates elastic fibril assembly, but lacks any load-bearing function [9].

Biochemistry and gene structure of elastin

Elastin is highly insoluble and chemically inert [35]. It remains after boiling ligamentum nuchae or aorta in 0.1 mol/L sodium hydroxide at 98°C. Removal of soluble collagen or PG, with 4 mol/L urea or 5 mol/L guanidine, followed by pepsinization and precipitation of microfibrillar proteins, leaves a protein that is rich in glycine, aniline, valine and proline. This suggests an ancient homology with the fibrillar collagens. Both collagen and insoluble elastin have soluble precursors (tropoelastin and preprocollagen). Lysyl 6 oxidase cross-links certain lysines to compounds such as desmosine, isodesmosine, dihydrolysinonorleucine, allylsine and dihydromerodesmosine, with elastin polypeptides cross-linked to form rubbery elastic fibres. Experimental animals fed lysyl oxidase inhibitors produce soluble uncross-linked tropoelastin protein of 72–74 kDa. There are also non-triple-helical Gly-X-Y collagenous homologies which, unlike collagen, are not cross-striated. Instead, elastin monomers cross-link to a deformable rubbery elastomer, distributed in organs such as tendons, lungs and arteries [35].

The elastin gene

Chick, bovine and human tropoelastin/elastin genes have 34 and 36 exons [36–39]. The human gene maps to chromosome 7q11.23 [35,36], coding for a 730 amino acid protein with distinctive hydrophobic and cross-linking cassettes, reminiscent of the fibrillar collagens. As in collagen, each exon ends in a perfect codon, and is followed by the first codon of the next exon. The human gene has 34, rather than the 36, exons of its bovine analogue [39]. Elastin exons are generally small, usually ranging between 27 and 160 bp, and there are similarities to collagen organization [35]. Some intronic sequences also have elastin homologues. In humans, there is alternative splicing of exons 23 and 23a, which significantly alters the geometry and cross-linking of adjacent hydroxylysines to deaminated lysines [32,36]. Elastin mutations cause autosomal dominant and recessive cutis laxa (CL) or PXE [7], Williams syndrome and supravalvular aortic stenosis (SVAS) [40–42]. Both disorders arise from haplo-insufficiency where one copy of the elastin gene has been mutated or deleted [42–45]. The clinical phenotype of Williams syndrome includes generalized ECM features, such as SVAS, mandibular hypoplasia, blubber lips and mental retardation [40,41,45]. Isolated SVAS without Williams syndrome is linked to the elastin locus at 7q11–23 [40,41]. While simple hemizygosity of the elastin gene from small or large intragenic deletions causes SVAS [40,42], those causing Williams syndrome are much larger [43–45]. It is probable that a contiguous deletion syndrome affects adjacent genes, while the defect in SVAS is localized to the elastin gene. The larger Williams syndrome deletions (more than 500 kb) may also affect the contiguous Lim kinase 1 gene, which probably directly influences CNS development and visuospatial capabilities [44,45]. Similarly, more focused elastin mutations cause SVAS, many of which are caused by premature termination

mutations, with nonsense-mediated mRNA decay. SVAS mutations range from clinically benign and undetectable to severe multivessel degeneration [46]. Amongst the various mutational patterns are certain small inframe insertions or deletions, often with duplication or deletion of elastin sequences [47,48]. Contrastingly, single base deletions in exons 32 or 33 cause autosomal dominant CL [49,50], whilst we have recently identified a 24 exon inframe duplication of the elastin gene in a British family with autosomal dominant CL and premature emphysema. This produces an elongated but matrix-incorporated, mutant tropoelastin protein over 55 kDa larger than the normal 72 kDa product. Consequently, there is elastic fragmentation, CL and pulmonary emphysema [51–53]. Furthermore, elastin products are potent chemotactic, proliferative and chemotactic agents, which affect cell proliferation, attachment and migration, and which are potently up-regulated in, and promote the growth of, certain breast and cerebral tumours, especially cerebral astrocytomas.

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Ground substance

Proteoglycan (PG) chemistry

PG families have variable core proteins with attached polymers of unbranched disaccharides (Figs 3.33–3.35). Disaccharide units are usually linked by *O*-linked serine–xylose–galactose–galactose sequences [1–4]. The attached disaccharide polymers vary from few to hundreds in number, making chemical separation by electrophoresis difficult to interpret. Glycosaminoglycans (GAGs) link cell-surface receptors with ECM proteins, such as collagen, fibronectin or fibrin. Biochemically, the GAG chains cluster otherwise unrelated proteins into subsets, which separate similarly by column chromatography. Consequently, the functions of such varied proteins are unusually diverse.

Rules for GAG composition

These may be summarized as follows [1,4].
1 Glycosaminoglycans are linear polymers with alternating pairs of different monosaccharides, such as glucose or galactose, joined in 1–3 or 1–4 linkage.
2 Three common disaccharide combinations are the commonest building blocks from which most GAG sequences are derived.
3 Variably sized polymers have particular post-assembly modifications.
4 Modifications are unpredictable, variable in number, and are catalysed by specific sulphatases or epimerases. They include sulphation, the replacement of *N*-acetyl by *N*-sulphate and the epimerization of D-glucuronic to L-iduronic acid.
5 Individual polysaccharide combinations may have any or none of these changes.
6 In contrast to DNA or protein sequence, such combinations have no information content.

Differences between PG polymers

The derivation and chemical structure of heparin, heparan sulphate, chondroitin, dermatan sulphate, keratan sulphate and hyaluronic acid are shown in Table 3.4 and Fig. 3.33. The differences between constituent polymers are chemically minor [1,4]; they have subtle implications for three-dimensional conformation and molecular interactions [5–9]. For example:
1 Chondroitin/dermatan differ from heparin/heparan only by the substitution of *N*-acetyl galactosamine for *N*-acetyl glucosamine; i.e. essentially by the orientation of a single H-C-OH bond at position 1.
2 Hyaluronic acid differs from keratan both by changing glucuronic acid to galactose and by substituting β1–3-linked glucosamine to β1–4 glucosamine.
3 Similarly, hyluronan (1–3-D-*N*-acetyl glucosamine)$_n$ differs from dermatan and chondroitin sulphate (1–3-D-*N*-acetyl galactosamine) only by the orientation of a H bond.

Relationship of disaccharide side-chains to the various PG core proteins

Aggrecan, a large aggregating cartilage PG, is a good model of PG protein organization [2]. It has a central protein core with certain additional structural motifs and domains (Fig. 3.35). Binding to hyaluronate occurs via link and G1 sequences, with homologous G2 sequences nearby at the N terminus. The C terminus possesses a non-homologous globular sequence with lectin-like properties. Lying between G2 and G3 is the bulk of the core protein, containing near to the N terminus keratan sulphate-rich sequences, which in humans and cattle are attached to certain proline-rich hexapeptide repeats. Keratan sulphation increases with age. Most of the remaining link protein (LP) has serine–glycine sequences for attachment of chondroitin sulphate disaccharide polymers. Of the N terminal 428 amino acids, 117 are serine–glycines. In contrast, only 68 of the 628 C-terminal amino acids have this important combination of attachment sequences. The serine–glycines lie within longer 10 amino-acid motifs. The major part of the core has 1000 chondroitin sulphates (D-glucuronic acid β1–3-*N*-acetyl galactosamine)$_n$ compared with only 30 keratan sulphates (D-galactose β1–3-glucosamine)$_n$. There are also 40 oligosaccharides, most of which are *O*-linked with a few *N*-linked ones. The G1 domain binds hyaluronate (D-glucuronic acid β1–3-D-*N*-acetyl glucosamine β1–4)$_n$, which forms very long disaccharide polymers. Hyaluronate also binds various other PGs through their hyluronate binding domains,

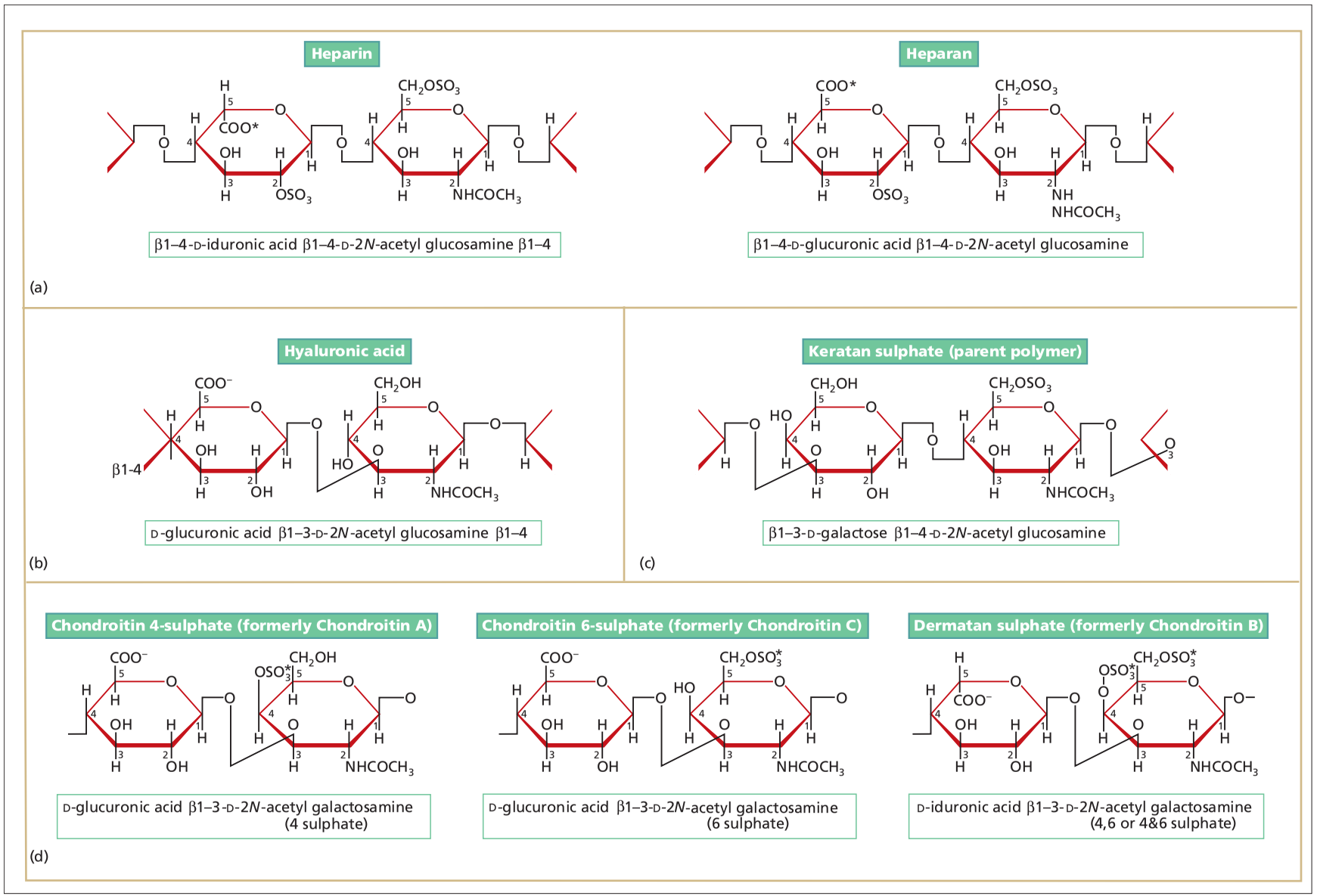

Fig. 3.33 Diagrammatical representation of the glycosaminoglycans (GAGs) which comprise the carbohydrate polymer side-chains of proteoglycan (PG) molecules. These include the arrangements of (a) heparin, (b) hyaluronic acid, (c) keratan and (d) the various chondroitin sulphates; variants include *O*-sulphation at the 6 position of both glucosamine and galactose.

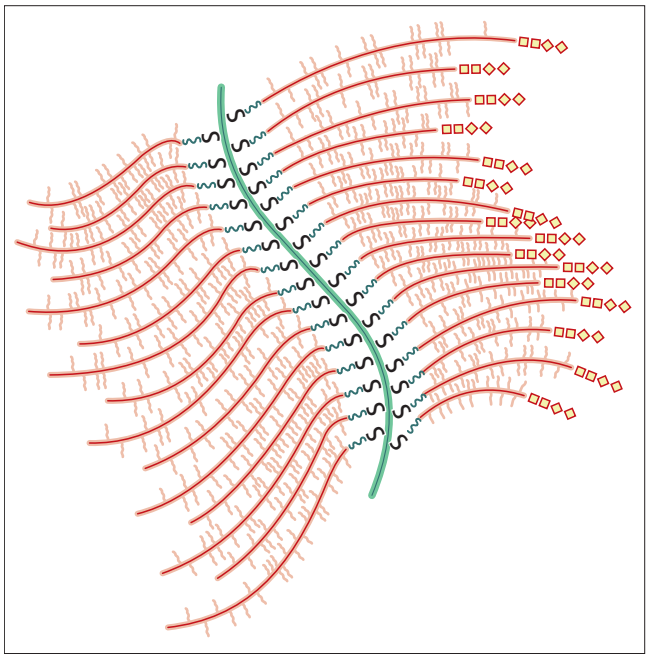

Fig. 3.34 Representation of a typical proteoglycan (PG). The central core (green) is hyaluronate and the link proteins (LPs) are represented by S shapes, joining the protein side-chains and carbohydrate polymers. (Adapted from Stryer [1].)

Fig. 3.35 Diagram of the core protein aggrecan from cartilage, joined by link proteins (LPs) to hyaluronate, with keratan sulphate (KS: blue) and chondroitin sulphate (CS: purple) side-chains: aa, amino acids. (Adapted from Heinegard and Oldberg [2].)

consequently producing compound aggregates with molecular weights of thousands of millions (10^9).

Most PGs are connected to their protein cores by *O*-glycosidic bonds of two galactoses joined to a xylose and serine. The xylosyl transferase reaction occurs in the endoplasmic reticulum and the Golgi, while the galactose and disaccharide links form only in the Golgi. Sulphation occurs just before secretion. Epimerization is also enzymatic and sequence related. Thus, different epimerase enzymes act upon dermatan (D-iduronic acid β1–3-*N*-acetyl galactosamine β1–4)$_n$ than upon heparin/heparan (D-iduronic acid β1–4-D-*N*-acetyl glucosamine α1–4)$_n$.

Classification of PGs [2,7–10]

Latterly, the traditional classification of PGs according to their disaccharide polymers has changed to concentrate upon the nature of their protein cores. This arrangement has both strengths and weaknesses. For example, there is confusion when the same core has different attachments of sugar polymers.

Degradation occurs via GAG receptors and requires endocytosis prior to lysosomal digestion.

Proteoglycan function

The functions of PGs are varied and sometimes unexpected.
1 Very probably, certain carbohydrate or protein sequences have very specific and distinctive functions.

(a) Protein-mediated properties include modulation of fibrillogenesis (decorin, biglycan and fibromodulin)

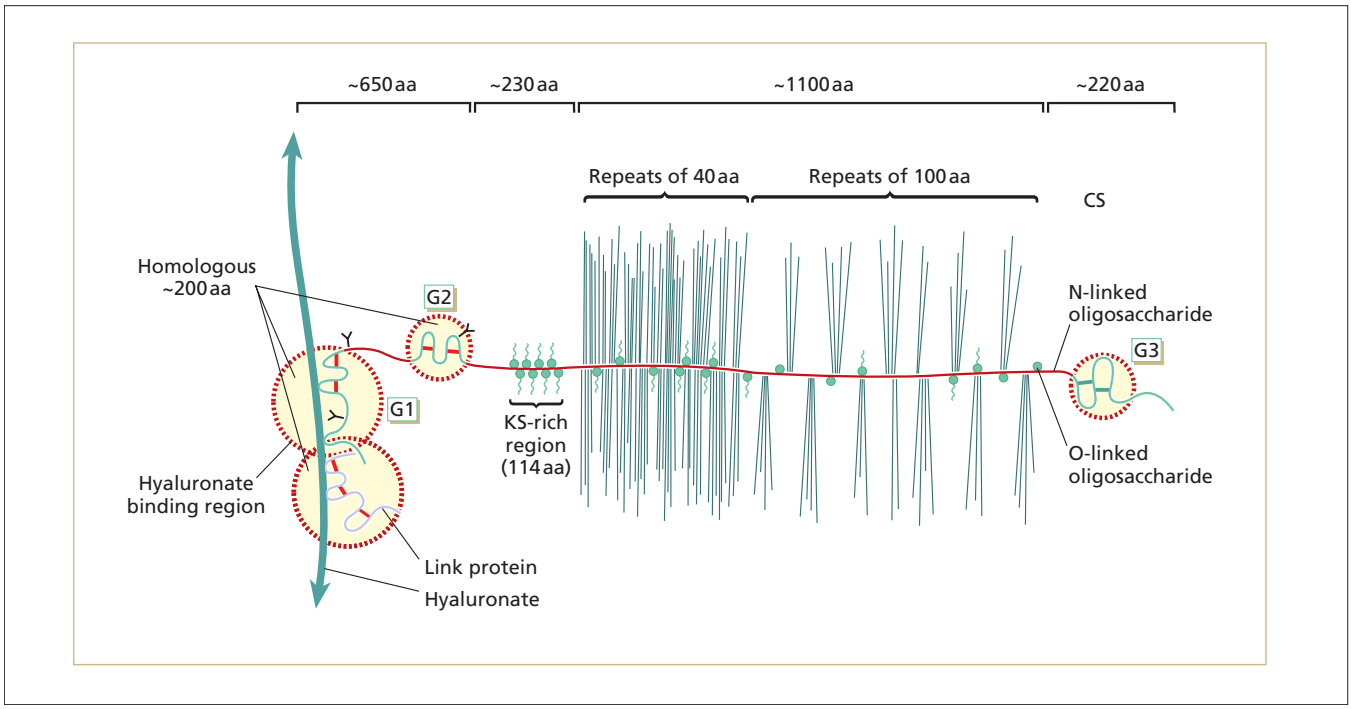

Table 3.4 Glycosaminoglycans.

Name	Parent polymer	Comments
Heparin/heparan sulphate	(D-glucuronic acid β1–4-D-2*N*-acetyl glucosamine α1–4)$_n$	Heparin and heparan differ in extent of sulphation. Heparinase and heparatinase act differently
Chondroitin/dermatan sulphate	(D-glucuronic acid β1–3-D-2*N*-acetyl galactosamine β1–4)$_n$	*Chondroitinase* *ABC* *AC* Cleave: Chondroitin + + Dermatan + –
Keratan sulphate	(D-galactose β1–4-D-2*N*-acetyl glucosamine β1–3)$_n$	
Hyaluronic acid	(D-glucuronic acid β1–3-D-2*N*-acetyl glucosamine β1–4)$_n$	

[8–11], TGF-β binding and hyluronate binding (versican, aggrecan and CD44) [2,12–14].

(b) Contrastingly, sulphated GAGs such as heparan bind basic amino-acid sequences of general formula BBXB or BBXXB; second, binding may be charge dependent as, for example, to other matrix molecules, cell adhesion or growth factors.

(c) An example of disaccharide-dependent binding, is heparin/heparan to antithrombin III [14].

(d) Similarly, highly sulphated PGs bind fibronectin. This is strongest in heparin and progressively weaker with heparan, dermatan or chondroitin.

(e) Carbohydrate length or molecular weight also influence binding. Similarly, some core proteins are stronger interactors than others. Good examples are the hyaluronic acid binding domains and lectin binding domains at different ends of aggrecan core protein. Versican has similar sequences and binding properties. Decorin binds to fibronectin and collagen.

2 Other functions include:

(a) *Cell adhesion*. Cell-surface PG modulates cell adhesion. For example, syndecan has heparan and chondroitin sulphate side-chains, which can bind both collagen and fibronectin. Such PG binding complements and enhances amino acid–RGD binding. Soluble PGs inhibit cell adhesion to collagen or fibronectin, either by blocking the PG attachment site or by steric hindrance of integrin receptors. Core proteins can also mediate cell adhesion [13]. An example is lymphocyte homing receptor, which is homologous to hyaluronic acid and also has sequence homology to the C terminus of versican, possessing similar lectin binding, EGF and complementary regulator sequences (see below).

(b) *Cell proliferation*. Heparin and dextran both inhibit cell proliferation, as does heparan sulphate purified from endothelial cells of hepatocytes. Basic and acidic FGFs bind to heparin/heparan. Binding probably regulates TGF-α or TGF-β release.

(d) *Protease and antiprotease function*. Antithrombin III tightly binds heparin/heparan sulphate. Those proteases that are regulated by antithrombin III, such as thrombin, factors IXa and XIa, are brought into close apposition by heparin/heparan. Their presence accelerates the action of antithrombin as much as 2000-fold. For this reason heparin is a very potent anticoagulant.

(e) *Polypeptide growth factors*. Some PGs are catalytic.

(f) *Cell adhesion*. Neural cell adhesion molecule (NCAM) interacts with cell-surface heparan.

(g) *Lipoprotein uptake*. Hepatocyte heparan sulphate binds lipoproteins via apoE and apoB, thereby immobilizing lipoprotein lipase and hepatic triglyceride lipase to the cell surface.

Classification and gene sequence of extracellular PGs

At least 25 genes specify a range of PG proteins with variable numbers of GAG side-chains. The nomenclature of the latter was described earlier. The first gene was cloned by Krusius and Ruosolahti [13]. They identified the cDNA sequence of a small chondroitin E/dermatan sulphate (D-glucuronic/iduronic acid β1–3-2*N*-acetyl galactosamine) PG (PG40), produced by fibroblasts. The cDNA contained GAG attachment sequences, such as serine–glycine or glycine–serine dipeptides. At the time, the core protein sequence was novel [14,15]. The PG also bound type I collagen and inhibited both collagen and fibronectin-mediated cell attachment. There were also three *N*-glycosylation sites and 12 amino-acid motifs, within which the serine–glycine sequences were implanted. Since then, the field has very rapidly advanced [2,8,11]. PGs may be separated by size, sequence motif, domain distribution, disaccharide attachments and tissue distribution. In practice, PGs form two distinctive subsets: (i) small leucine-rich PGs (SLRPs) and (ii) traditional large molecular PGs, such as versican and aggrecan, with very numerous and densely packed disaccharide polymer side-chains.

Link protein

This glycoprotein is analogous to the G1/G2 regions of aggrecan. It attaches aggrecan to hyaluronic acid core protein (Figs 3.34 & 3.35). Homologous loops in LP and the G1/G2 domains of aggrecan resemble the G3 domain of versican. The biological function of LP is to stabilize

Table 3.5 Proteoglycan (PG) group I. Small leucine-rich proteins (SLRPs).

PG	Protein (kDa)	Glycosaminoglycan (GAGs) disaccharide	Gene location	Tissue distribution
Decorin	36	CS/DS	12q21–23	Bones/tissue
Biglycan	38	CS/DS	Xq28	Cell surface
Fibromodulin	42	KS	1q32	Collagen matrix
Lumican	38	KS	12q21–22	Cornea Gastrointestinal tract Cartilage Muscle
Epiglycan	36	CS/DS		Epiphyseal cartilage

CS, chondroitin sulphate; DS, dermatan sulphate; KS, keratan sulphate.

Table 3.6 Proteoglycan (PG) group II (modular group).

PG	Protein (kDa)	Glycosaminoglycans (GAGs)	Gene location	Tissue
Versican	260–370	CS/DS 10–30	5q13	Blood vessel Brain Skin, cartilage
Aggrecan	220	CS (100)	15q26	Cartilage Brain Blood vessel
Perlecan	400–470	HS/CS	1p36	Bone marrow Cartilage
Agrin	210	HS (3–6)	1q32	Cell membranes Neuromuscular Kidney
Neurecan	136	CS 3–7		Brain
Brevican	100	CS 1–3		Brain
Testican	44	HS/CS	21	Seminal vesicle Testis

CS; chondroitin sulphate; DS, dermatan sulphate; HS, heparan sulphate.

aggregation of aggrecan and hyaluronic acid. Three variants, LP-1, -2 and -3, are variably glycosylated, and the mammalian LPs have 339 amino acids and five disulphide bonds in three loops [2,9,12].

Nomenclature

Instead of the traditional classification by disaccharide polymers, an arbritary protein-core nomenclature has emerged, including small molecules, such as decorin/biglycan and lumican, in group I and larger molecules, such as versican, aggrecan or perlecan, in the modular group (Tables 3.5 & 3.6). This has both order and logic, in comparison to the old carbohydrate method.

Accumulation of PG in human diseases

The mucopolysaccharidoses are a varied group of inherited lysosomal diseases, in which the intracellular accumulation and urinary secretion of PGs is increased from a variety of enzyme deficiencies. Thus PGs such as dermatan, keratan, heparan and chondroitin sulphates accumulate, according to the particular enzyme deficiencies. These include α-L-iduronate (Hurler's and Scheie's syndromes, mucopolysaccharidosis (MPS) types IH and IS), iduronate sulphatase (Hunter's syndrome, MPS type II), heparan *N*-sulphatase (Sanfilippo's syndrome, MPS type III), *N*-acetyl galactosamine-6-sulphatase (Morquio's syndrome, MPS type IV), Maroteaux–Lamy syndrome (aryl sulphatase B, MPS type VI), and β-glucuronidase (Sly's syndrome, MPS type VII) [16]. Most mucopolysaccharidoses are absent at birth but appear during the first 2 years of childhood. The accumulation of PGs produces hepatosplenomegaly, cardiac infiltration, corneal clouding, skin thickening and coarsening and, except for Scheie's, Morquio's and Maroteaux–Lamy syndromes, severe intellectual involvement. In addition, the accumulation of GAGs produces joint contractures, shortened long bones, scoliosis, broadened ribs and spinal deformities. Modern treatment options include bone marrow transplantation, enzyme replacement and substrate restriction, all of which vary in efficacy and indications. For example, enzyme replacement is ineffective in those individuals with CNS accumulation, as they do not cross the blood–brain barrier.

Chromosomal clustering of PG and ECM genes

Particular chromosomal localizations, such as 12q21–q23 (decorin and lumican), 5q13.2 (versican) and 15q21 (aggrecan), are close to other ECM gene loci, such as *COL2A1* (12q13–q14), fibrillin 1 (15q15) and fibrillin 2 (5q15). Elastin microfibrillar components such as *MFPG-1* and -2 also cluster nearby. Similar clusters of other ECM genes suggests functional roles, such as coordinated transcription and regulation of organ or tissue-specific proteins. For example, *COL8A2*, *COL11A1* and agrin cluster at 1p32.

Small leucine-rich PGs [8,9,11,16] (Table 3.5)

SLRPs are a homologous group of PGs sharing N- and C-terminal cysteines with (between six and 12) leucine-rich (LR) repeats. Differences include the presence or absence of tyrosine sulphate (fibromodulin and lumican) and the presence or absence of chondroitin or keratan sulphate side-chains (highest in lumican and fibromodulin and lowest in epiphycan). Despite the overall similarity in domain organization, other shared features include:

1 N termini with chondroitin sulphate/dermatan sulphate attachments (decorin, epiphycan, biglycan);
2 tyrosine sulphate-rich sequences (fibromodulin and lumican) (such differences have implications for matrix and tissue–specific interactions);
3 the N- and C-terminal cysteines are regularly spaced in 20 and 35 amino acid clusters, respectively.

Such LR repeats are shared both with other small PGs and with more members of the LR superfamily. Examples of the latter are RNA splicing and processing enzymes, DNA repair enzymes, embryonic axon synapse and photoreceptor proteins. Others are hormone receptor signal transduction proteins. Whilst a few are membrane bound, most are not. The numbers of LR domains vary from four to 30. Biglycan, decorin, fibromodulin, lumican and PG LR domains have between eight and 12 repeats.

The three-dimensional structure of ribonuclease inhibitor is very well understood and has both A and B repeats (28 and 29 residues, respectively). In contrast, most PGs have 24 repeats [16].

The non-globular and β-sheet structural patterns probably mediate protein–protein interactions.

The ECM binding functions of SLRPs regulate collagen fibrillogenesis and bone modelling through TGF-β1 and -2.

Certain *Drosophila* LR proteins, such as *toll*, *slit*, *connectin* and *chaoptrin*, which are tissue and development (embryo) specific, have very similar properties. Many of the LR repeats of these proteins share the typical N- and C-terminal cysteines but differ slightly from conventional PGs by virtue of slightly different amino-acid motifs (50 rather than 30 amino acids N terminal, but 20 amino acids C terminal) [8,9,16].

Table 3.7 Regulation of decorin and biglycan genes.

	TGF-β	Dexamethasone	Retinoic acid (on chondrocytes)	TGF-α
Decorin	↓	↓	↑	↓
Biglycan	↑	↑	↓	

TGF, transforming growth factor.

Sequence homology

There is evolutionary tree homology between the three groups. For example, the decorin and biglycan genes both have eight exons, of which numbers 3–6 code for the LR repeats. For fibromodulin there is a larger fused exon with this function.

Other features [8,11]

Gene evolution. Even though the LR repeats are 24 amino-acid proteins, it is unclear whether the decorin and biglycan genes arose from ancestral 72-bp DNA sequences. The organization of the existing exon/intron boundaries excludes exon shuffling or gene duplication of the PG genes, even though this mechanism is possible for other LR repeats.

Functions. Decorin regulates collagen fibril diameter by a negative control mechanism. It also probably orchestrates organogenesis and shape, while biglycan is cell-surface distributed.

Promoter functions. The decorin and biglycan promotors are subtly different. While the former has distinctive proximal CAAT, TATA and TNF-α domains, with distal AP1, AP5 and TGF-β elements, biglycan lacks these sequences and has only housekeeping regulatory elements. In keeping with this possibility, it is situated in a CpG island. Very probably, biglycan is switched on permanently, while decorin is a more specialized ECM product and is produced intermittently. The two genes are therefore differentially regulated as shown in Table 3.7.

Other properties. These include the following:

1 decorin specifically inhibits cell proliferation;
2 it is up-regulated in resting cells;
3 SV40 transformation suppresses decorin expression;
4 other transformed cells similarly show suppressed decorin expression;
5 it suppresses the malignant phenotype of colonic cancer cells.

Modular PGs

In contrast to the SLRP group, the modular PGs are larger and more complex. They form two distinct distantly

related subsets; i.e. (i) the hyalolectins, which strongly bind hyaluronan (D-glucuronic acid β1–3-D-2*N*-acetyl glucosamine β1–4), and (ii) those that do not.

Hyalolectins [1,2,9,12,14,15]

Versican and aggrecan are two typical examples. Both the protein and DNA sequences and their joint homologies have been fully clarified. They have very similar N-terminal hyaluronate-binding regions, while their GAG-containing central domains, although analogous, have two separate components in versican, but only one in aggrecan. Both molecules have C-terminal selectin-like sequences, with analagous exon organization. Thus, subtle differences in length allow variable binding functions; at the N terminus they attach to PG, at the C terminus they bind cellular elements, and centrally they have classical disaccharide polymer-binding capabilities. Other similar family members such as neurocan proteoglycan M (PGM) and brevican have adhesive and regulatory functions, while aggrecan and versican function in blood vessel, bone, cartilage, etc. The GAG α and β domains of versican bind to *O*- and *N*-linked carbohydrates, while tissue-specific alternate splicing of various exons fulfils subtly varying functions. The selectin-like C terminus contains dual EGF domains with and without calcium-binding capabilities, as well as C-lectin and complement regulatory protein (CRP) repeats (see below) [14,15].

The single GAG-binding protein of aggrecan has more densely distributed serine–glycine/glycine–serine dipeptides. Other modular PGs such as neurocan and brevican are abbreviated homologues of versican and aggrecan, while the non-modular PGs such as perlecan, agrin and testican have incorporated various other motifs such as SEA (shared with *s*perm protein, *e*nterotoxin and *a*grin), LDL receptor, SPARC (secreted protein acidic and rich in cysteine) and laminin domains III and IV.

Genomic structure and organization of versican and aggrecan

The versican gene (Fig. 3.36) maps to chromosome 5q12–14 and has 15 exons, which span 90 kb of genomic DNA. There is also an alternatively spliced exon of 3 kb, similar to that in chick PGM. The GAG α and β domains are separately coded by exons 7 and 8, respectively. Similarly, exons 3–6 code for the N-terminal hyaluronic acid-binding region, with exons 1 and 2 coding for the promotor region. The EGF repeats are coded by exons 9 and 10, the lectin-binding sites by exons 11–13 and the CRP and untranslated regions by exons 14 and 15 [12–15].

The pattern is highly conserved in other similar PGs. For example, the hyaluronan-binding site is homologous in human and rat aggrecan, rat LP, chick-liver PG and human CD44. Similarly, the selectin domains of versican, aggrecan and human P- and E-selectins also have very strong organizational similarities. The main analogies are illustrated in Fig. 3.37.

The hyaluronan-binding region also codes for an immunoglobulin loop, with homologies to the immunoglobulin superfamily. This contrasts with perlecan, in which numerous immunoglobulin loops are coded by two complete but separate exons, with an intervening phase 0 intron.

Evolution of the hyaluronan-coding domain requires duplication of exons 4, 5 or 6. Parallel, divergent evolution is required to explain the similarity of the hyaluronan-binding regions of human CD44 and tumour suppressor gene (TSG) proteins. Human versican is very similar to chick PGM; both alternatively splice exons coding for the two GAG domains (α and β). Whilst aggrecan is homologous to versican, its denser disaccharide polymers have slightly different serine–glycine and glycine–serine motifs. The versican PG domain is coded by very large, 3.0–5.3-kb, exons, with an equivalent aggrecan sequence of 3.9 kb. The selectin, EGF, lectin-binding and CRP motifs (exons 9–14 of versican) have analogous sequences, but slightly different exon numbers in E-selectin, L-selectin, P-selectin and granulocyte membrane protein.

Both aggrecan and versican have distinct calcium-binding and protein-interacting EGF domains, coded by similarly sized exons differing slightly from those of P- and E-selectin and coagulation factor IX.

The C-type lectin motif (encoded by exons 11–15) is identically arranged in versican and aggrecan. Homologous sequences occur in Kupffer-cell lectin, chicken hepatic lectin, and E- and P-selectin, all of which are calcium binding.

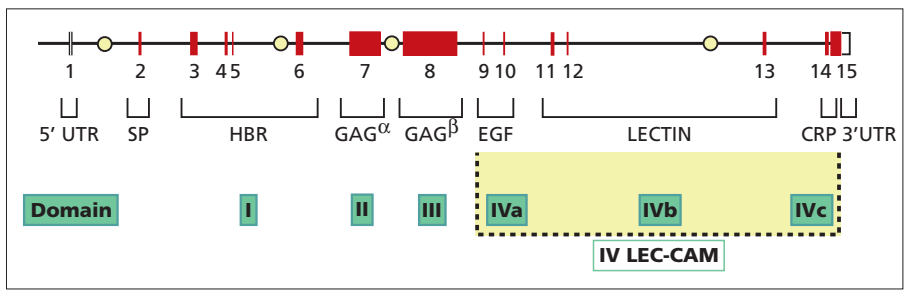

Fig. 3.36 Intron/exon organization of the human versican gene. CRP, complement regulatory protein; EGF, epidermal growth factor; GAG, glycosaminoglycan; HBR, hyaluronan-binding region; SP, promotor region; UTR, untranslated region. (After Dours-Zimmermann and Zimmermann [14].)

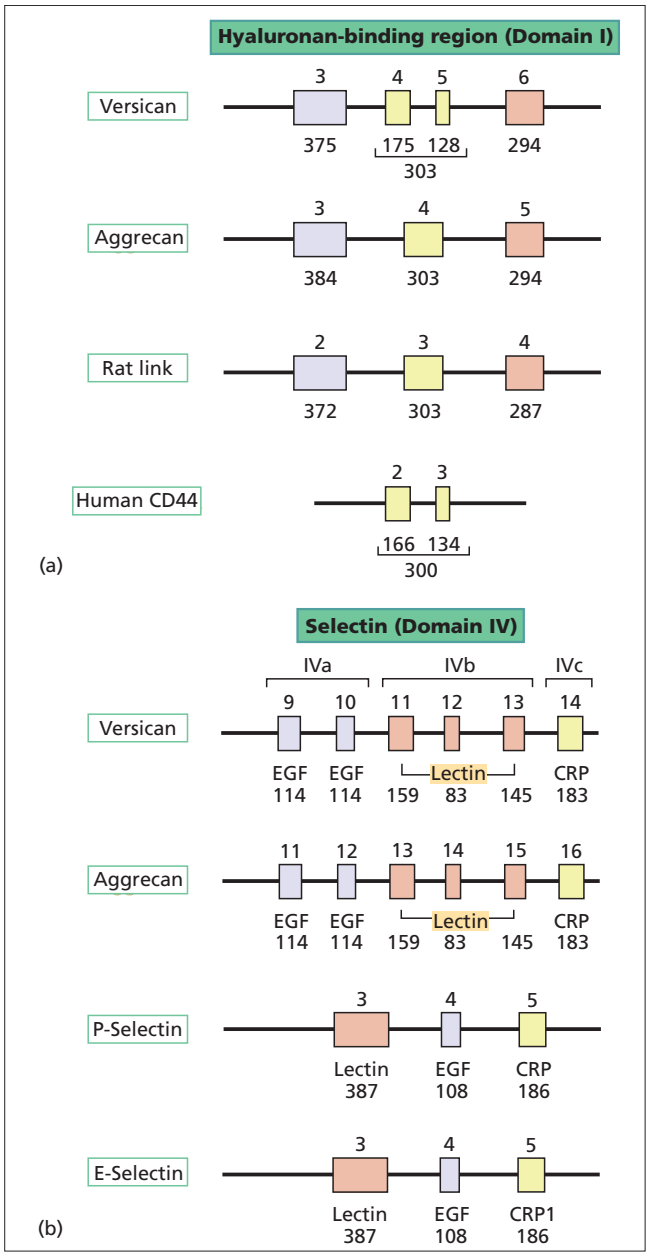

Fig. 3.37 Homology between genes for versican and other related compounds in terms of exon size and organization, at hyaluronan binding (a) and selectin (b) regions. CRP, complement regulatory protein; EGF, epidermal growth factor. (After Dours-Zimmermann and Zimmermann [14].)

Complement regulatory protein

CRP is coded by a single 183-bp exon. Other similar proteins include C4b, factor H and decay-accelerating factor, which have short consensus 60-amino-acid repeats (SCRs), coded by 45–47-bp exon clusters, as in versican and aggrecan. The CRPs interact with C3b or C4b to regulate C3 and C5 convertase in the complement cascade.

Non-hyaluronan-binding PGs [8,11]

These include perlecan, agrin and testican, which, although distinct from the hyaluronan-binding group, also differ substantially from each other. Interestingly, they possess a mixture of protein motifs shared with adhesive glycoproteins such as fibronectin and other ECM components, such as fibrillin, laminin and collagen type VII, etc. Their diversity indicates both functional heterogeneity and the remarkable capacity of nature to shuffle and distribute similar protein domains widely and create combinations with other domains, so producing proteins with differing functions, both within and across animal and plant species alike.

Of this PG subset, perlecan is the most diverse [10,11]. In addition to N-terminal GAG disaccharide polymers, other distinctive sequences include SEA, which is an 80-amino-acid protein regulating carbohydrate binding. Very probably, it is an important recognition signal for Golgi processing of secreted or membrane-bound proteins. The SEA region is adjacent to four LDL-receptor domains, which are followed by laminin III and IV sequences. Next, in marked contrast to hyaluronan-binding PGs such as versican, come 21 consecutive immunoglobulin folds. These have similarities to neural adhesion protein. The four consecutive EGF repeats closely resemble the C-terminal ends of laminin A chains.

The human perlecan gene is located on chromosome 1p36 and has 94 exons occupying 120 kb of genomic sequence. The unusual LDL, laminin and immunoglobulin sequences have close homologies to more specialized members of each respective family. Like aggrecan, the perlecan promotor has housekeeping sequences, quite unlike tissue-specific genes such as the interstitial collagens or versican, both of which have distinctive CAAT and TATA boxes [8,10,11].

Agrin has some motifs similar to domain V of perlecan, thereby sharing homology with laminin G. It also has GAG-rich sequences and a SEA module. The GAG disaccharide polymer is heparan sulphate (D-glucuronic/iduronic β1–4 D-*N*-acetyl glucosamine α1–4)$_n$. Other similar heparan sulphate PGs occur in bovine renal tubules. Additional motifs include follistatin and laminin domain III sequences, resembling laminin β and γ chains.

Genes

Perlecan has 94 exons, spanning 120 kb of genomic DNA, and there is remarkable conservation of incorporated sequences such as LDL with other more conventional members of that family [8,11].

The agrin gene lies on chromosome 1 at 1p32 and its nine follistatin repeats have very probably originated from gene duplications and unequal crossovers. In contrast, the laminin G and EGF sequences of perlecan and agrin are only distantly related [8,10,11].

Functions and properties of agrin

These include the following.

1 It anchors heparan sulphate within basement membranes.

2 It is virtually ubiquitous in basement membranes.

3 The protein core is adhesive for endothelial cells.

4 The protein is constitutive in K562 (bone-marrow-derived) tumour cells.

5 It interacts with other intracellular components, such as nidogen and laminin.

6 There is self-association via the C terminus with laminin G domains and EGF repeats.

7 Other analogues, such as laminin α chains, and *Drosophila* proteins, such as *crumbs*, *fat* and *slit*, regulate larval (embryonic) differentiation, polarization and neural patterning.

8 The binding of growth factors via heparan sulphate side-chains, which mop up and release similar factors such as cytokines and other metabolic regulators.

9 The binding of bFGF and mediators of mitogenesis and angiogenesis.

10 Agrin induces acetyl choline receptors which:

(a) aggregate myotubes;

(b) orchestrate synaptic cleft basement membranes;

(c) the follistatin repeats sequester factors such as PDGF and TGF-β;

(d) the receptor aggregates mediators for laminin G-like clusters and EGF domains.

Membrane-bound PGs

Such PGs interact through their heparan sulphate side-chains, with insoluble or soluble receptors during embryogenesis, malignant tumours and scar formation in wound repair. They include the syndecans and glypicans, which, although not sharing common homologous proteins, utilize similar heparan sulphate side-chain combinations, for signalling purposes.

Syndecans

These are transmembrane PGs with four separate family members (syndecans 1–4), distributed, respectively, in epithelia and plasma cells (syndecan 1), endothelial cells and fibroblasts (syndecan 2), neural crest cells and derivatives (syndecan 3), and universally (syndecan 4). The core proteins share N-terminal heparan sulphate chains at serine-glycine repeats, a trypsin-sensitive site close to the plasma membrane, and highly homologous transmembrane domains to the other three subclasses. Syndecans 1 and 3 contain chondroitin sulphate side-chains as well as heparan sulphate chains, whilst numbers of the latter vary according to their tissue distribution. Amongst their demonstable functions are included the binding of mammary-duct epithelia to fibronectin, thrombospondin and type I collagen, and the interaction of syndecan 4 with actin microfilaments in keratinocyte migration in wound repair. Nearly all adherent cells, especially epithelia, express syndecans close to their cell surfaces. Cleavage of the heparan sulphate containing sequences is mediated extracellularly by the TIMP (*t*issue *i*nhibitor of *m*etallo-*p*roteinase) family of metalloproteinase inhibitors. These cleave the syndecans in their ectodomains, N terminal to their membrane-bound sequences. The shedding of such ecto-domains is regulated in cultured fibroblasts or keratinocytes, but also occurs in embryogenesis, where they then change from acting as membrane-bound receptors to widely diffusable soluble receptors. Competition of these two functions would clearly have paracrine, and sometimes autocrine, roles.

Glypicans

These are also membrane-bound PGs attached to cell surfaces by glycosylphosphatidylinositol (GPI) linkages. Vertebrate glypican core proteins are homologous with at least five subtypes. The family participates in embryogenesis and cell division, and has patterning implications in developing embryos. All of them are cysteine-rich having, like the fibrillar collagens, both N- and C-terminal signal sequences. The C termini contain GAG attachment consensus sequences similar to other PGs.

Glypican 1 is widely dispersed in tissues, such as fetal lung, fetal heart, striated muscle and vascular endothelium, and the basolateral surfaces of certain epithelia. In contrast, glypican 2 is mainly confined to the CNS, where it is enriched in axonal tracts, brain and spinal cord. Glypicans 3 and 4 are enriched in fetal lung, kidney and liver but down-regulated later, whilst glypican 4 is richly expressed in kidney tubular epithelial cells and neuroepithelial cells. The gene for glypican 1 is at 2q35–37, close to the *COL3A1* gene, whilst that for glypican 5 is at 13q32. Glypicans 3 and 4 are X-linked at Xq26. Both monoclonal and polyclonal antibodies are available against glypicans 1, 2 and 3.

In summary, PGs share functions such as growth regulation, tissue differentiation and neuronal outgrowth. Such multidivergent properties promote embryogenesis, tissue regeneration and tumour metastasis or activity. Diseases caused by mutations in some of these functions are also very likely [17,18].

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Histology of the ground substance

The PGs of the ground substance are analogous to the mucins. Histologists had developed empirical staining methods for the latter long before their chemical structure was elucidated.

Methods of fixation, staining and processing have been reviewed [1–3]. Many traditional fixatives remove or denature ground substance, and formalin fixation, freeze drying or use of frozen sectioned fresh tissue are therefore recommended. There are three main types of stain: metachromatic stains, colloidal iron and Alcian blue. In addition, the periodic acid–Schiff (PAS) technique stains certain sugar residues but leaves GAGs unstained. Normal human skin ground substance reacts positively with the first three methods but is PAS negative [4].

Metachromasia means the anomalous staining of the test tissue in a colour different from that of the test dye. This resembles indicator-dye changes with varying pH. Anionic groups such as sulphate, carboxyl and, probably, phosphoric acid esters exhibit this phenomenon with toluidine blue O and azure A, the stains most frequently used.

Colloidal iron staining depends on the attraction of dialysed iron hydroxide to the sulphate groups of GAGs, or the uronic acid of hyaluronic acid, and its subsequent colouration to Prussian blue with acidified ferrocyanide [5].

Alcian blue [6] is an empirical method which supplements colloidal iron or metachromatic stains. It stains substances that are removable by hyaluronidase.

The PAS method [4] involves the oxidation of sections in 0.5% periodic acid, followed by treatment with Schiff's reagent, when compounds containing –CH(OH). CH(OH)– or CH(OH)CO– groups (the hydroxyl groups may be replaced by amino or alkylamine groups) give a purplish red colour. In theory, various sugar derivatives such as glycogen, GAGs, glycoproteins, glycolipids and glycolipoproteins should be detectable. In practice, pure hyaluronic acid and condroitin sulphate are unstained. Other alternatives include the action of dyes, such as cupromeronic blue, which detect PGs linked to collagen fibres.

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Collagen

Collagen refers both to certain fibrous elements of connective tissue, and also to a diverse family of genes coding for specific fibrous proteins. Of Greek origin, the term is synonymous with glue and also gelatine (the denatured form of collagen obtained from animal tissues by boiling and rendering). Collagen fibres are soft and flexible but also strong and inelastic. Their birefringence under polarizing light implies longitudinal stacking [1]. Light microscopy shows unbranched 12–15-μm fibres. Transmission electron micrographs show regularly cross-striated fibrils with a 60–70-nm periodicity [1–4].

Collagen was originally considered a single protein but in 1970 collagen type II was identified; purified from cartilage, it clearly differed from collagen type I [5,6]. Next, collagen type III was purified from skin and blood vessels [7], leading on to the identification of many other collagen types, which now comprise 22 or more proteins, coded by up to 30 genes [8,9], many of which have been cloned and syntenically located in the mouse. The characteristic regularly cross-banded fibrils were identified very early in the history of collagen biology. In particular, they are formed by collagen types I–III, but also characterize collagen types V and XI, the five members comprising the fibrous collagens.

These proteins typically form perfect triple helical α chains, which spontaneously self-assemble into irregularly overlapping staggered fibrils [10]. The geometry of the helically intertwined trimers is such that glycine is internalized on each α-helix, with the accompanying X and Y residues lying externally on the triple helix (Gly-X-Y) [11]. At the N and C termini there are non-helical globular extensions that vary in size between individual fibrous collagens, but in type I collagen are, respectively, 17 (N) and 26 (C) residues long. This contrasts with the 1000 or so residues that form the α-helix. The non-collagenous extensions (propeptides) are cleaved by specific enzymes, leaving behind the triple helix. The specific sequences cleaved by the various N and C propeptidases are known for collagen types I–III.

Since the mid-1970s, numerous other collagen types with distinctive variations have been identified [6,7,12,13]. Not all are typical fibrillar collagens, and are subclassified by α-helical organization and fibril size into traditional (fibrillar) and atypical (non-fibrillar) groups.

Classification of collagens

Historically, collagen proteins and genes have been named in the order of their discovery. Thus, collagen type I, which is the most abundant, was originally detected in bones, tendon and skin. Later, a second similar collagen with distinctive sequence variations was discovered in cartilage [1]. Shortly afterwards, a third variant (collagen type III) was purified from skin (and shown to be abundant and very important for the normal mechanical integrity of arteries, veins and capillaries) [8]. Paradoxically, collagen type I, which is the original model for all other collagen variants, is a heterogeneous molecule containing separate α1(I) and α2(I) chains. The preferred arrangement of collagen type I is a heterotrimer $\alpha1(I)_2$, α2(I). Cartilage collagen $\alpha1(II)_3$ and type III collagen $\alpha1(III)_3$ exist only as homotrimers. Collagen types I and III also co-assemble into compound fibrils in skin, tendons and arteries. Both sorts of fibril contain minority collagens, such as collagen type V (assembling with collagen types I and III) and collagen types IX and XI (which co-assemble with collagen type II). Some of these, such as collagen type IX, form the so-called FACIT (*fi*bril *a*ssociated *c*ollagens with *i*nterrupted *t*riple helices) collagens (see below) [7,8,12,13]. The latter specifically bind to the gap zones of fibrillar collagen types I–III, V and XI and somehow regulate fibre size.

When collagen type IV was first discovered, its numerous triple helical discontinuities were so different from fibrillar collagens that it was considered not to be a collagen at all (in comparison to collagen types I–III). We now know that such interruptions are common in other collagens, such as types VI–X and XII, all of which have distinctive tissue-specific functions, and consequently self-assemble into markedly different crystalloid structures from the typical fibril-forming fibrillar proteins.

Gene structure

Recombinant DNA technology has revolutionized our understanding of collagen genes and proteins. Collagen genes for types I–III and V were consecutively cloned, whilst separate genes coding for α1(I) and α2(I) chains of type I collagen were cloned for the chick before humans [12,14]. The standard nomenclature (*COL1A1* gene for pro-α1(I) protein and *COL1A2* for pro-α2(I)) was applied to all subsequent collagen genes. The genomic organization of *COL1A1* and *COL1A2* is that of an archetypal collagen gene, encapsulating the domain and cassette organization of other fibrillar collagen genes [14]. The mainly globular N- and C-terminal propeptide sequences differ substantially from the central triple helix. This is a repeating polymer of $(Gly\text{-}X\text{-}Y)_n$ (where $n = 333$). Blocks (cassettes) of Gly-X-Y coding exon sequences are all 9 bp multiples, especially of 45, 54, 63, 108 and 162 bp, which strongly implies repeated duplications and deletions of a basic ancestral 9 bp motif [8,12,13]. Alternatively, a 54-bp ancestral gene duplicated to 108 and 162 bp by exon fusion (or intron loss), whilst 45- and 99-bp sequences evolved by asymmetrical recombination.

COL1A1 and COL1A2 N- and C-propeptides are coded by six and four exons, respectively, with the central helix coded by 42 exons [14]. The central helix contains 10% proline or hydroxyproline and 4% lysine or hydroxylysine in the X and Y positions of Gly-X-Y. Continuity of the Gly-X-Y cassettes directly dictates the ordered pattern of helical winding, which starts at the C terminus and then propagates towards the N terminus. Disturbed winding is common in osteogenesis imperfecta (OI) (collagen type I helix), certain chondrodysplasias (collagen type II helix) and vascular Ehlers–Danlos syndrome (EDS type IV) (collagen type III helix). Glycine substitutions are very common. Those nearest the C terminus are both chemically and structurally disruptive, because of their severe interferance with helical winding [13]. Here the best analogy is with a well built, as opposed to a badly constructed, brick wall. Defective badly formed triple helices fail to assemble into a strong structure. Mutant and misshapen bricks make walls that crumble too easily after minor mechanical stress.

The N and C termini of collagen type I also have unique properties, showing varied pathological effects when mutated. Exons 49–52 code for the 3′ C termini of collagen types I–III, which vary between 243 and 247 amino acids. Apart from a short helical (Gly-X-Y) telopeptide sequence, the remainder is globular and is highly conserved in COL1A1, 1A2, 2A1 and 3A1 [8,14]. Whilst exons 49 and 50 may vary, the sizes of exons 51 and 52 are highly conserved between collagen types I–III. Crucially, a

C-propeptide proline both initiates chain assembly and co-association prior to helical winding. Stabilizing disulphide bonds are strategically placed at critical intervals, with very similar lengths (246 and 247 aa) of the pro-α1(I) and pro-α2(I) sequences. Alignment and association of the three C termini is catalysed by a specific enzyme (protein disulphide isomerase, PDI), without which subsequent triple-helical winding could not occur.

In contrast, fibrillar collagen N propeptides gene sequences diverge widely between, and are most complex in, COL2A1 and 5A1/5A2. There are also distinctive differences between the N propeptides of COL1A1 and 1A2. The former codes for an additional 66 amino acids next to the short 48 amino-acid triple helix, while this globular region is omitted in COL1A2. Mutational analysis has provided insights into N propeptide influences upon molecular alignment and subsequent fibril formation. Two classes of mutation cause subtle phenotypical EDS variations. Those with structural mutation of the N propeptide (pNα1 or pNα2) delete the normal enzyme cleavage sites, so that cross-linked lysines fail to align, whilst in other cases in which the enzyme itself is deficient, the cleavage sequence remains. Thus, structural mutants retain abnormally shortened but uncleavable pNα1 or pNα2 extensions (see below), and the enzyme defect retains these extensions on the three chains of the triple helix. Consequently, the abnormally long helices disrupt normal molecular packing of adjacent collagen molecules. The structural errors cause EDS types VIIA and B (in which there are angulated collagen fibrils, and ligamentous and skin fragility), while the enzyme defect causes EDS type VIIC with hieroglyphic fibrils and dermatosparaxis, due to more widespread molecular distortions.

Other similarities at the 5′ and 3′ ends of the genes include regulatory up-stream sequences, such as CCAAT, 80–100 bp 5′ of the *COL1A1* and *1A2* coding sequences. There are also several other important sequences, such as SphI and ApI, which mediate tissue-specific expression and regulation. The *COL1A1*, *1A2* and *3A1* genes also contain enhancer sequences in the first intron (between residues +418 and 1524 of *COL1A2* and +820 and 1602 of *COL1A1*). Very probably, there are other important control elements (analogous to similar β-globin sequences) such as an enhancer at the 3′ end, and a distant locus control region of many kilobases at the 5′ end. The latter remote-controls tissue-specific expression, and may eventually facilitate future gene therapy [12,13].

Structural organization of collagen

The three individual polypeptide left-handed α-helices in the triple helix [10] are each staggered by one amino acid relative to one another. They form a right-handed triple helix with interchain hydrogen bonds between adjacent carbonyl (C–O) and amide (NH) groups.

Fig. 3.38 Transmission electron micrograph of shadowed replica of unfixed, rapidly frozen and surface-sublimated rat-tail tendon showing stepped banding of collagen fibres. × 40 500.

Positive and negative staining

Such type I collagen fibres possess a characteristic banding pattern in transmission electron micrographs [1,3]. Banding patterns differ slightly, depending on whether they are unidirectionally shadowed with gold or palladium (Fig. 3.38), positively stained with phosphotungstic acid (PTA) or uranyl acetate (Fig. 3.39) at acidic pH, or negatively stained with PTA at neutral pH (Fig. 3.40) [1–3]. The D-periodic banding and gap and overlap zones in the negatively stained materials closely correlate with the amino-acid sequence. D-banding originates from the mutual hydrophobic interactions of parallel triple helices (Fig. 3.41). Individual molecules are stacked in parallel, nose to tail (N to C terminally). Gaps separate individual molecules, with overlaps between adjacent triple helices, which are mutually staggered by individual fractions of D. The combined D periods consistently overlap, but also form gaps which together contain 234 amino acids over a distance of 67 nm. Rows of parallel triple helices are axially separated by 0.286 nm [4].

Each triple helix is longitudinally separated from its nearest linear neighbour by 67 nm (234 amino acids). Similarly, every helical α chain is longitudinally staggered from its two companions by one amino acid. Positive staining at acidic pH reflects the axial distribution of charged amino-acid residues in the triple helix. From the C to N terminus these are labelled a1-IV, b1-II, c1-III and d, respectively. The charge distribution from the known gene sequence correlates closely with the positive patterns. PTA or tungstate preferentially stain the positively

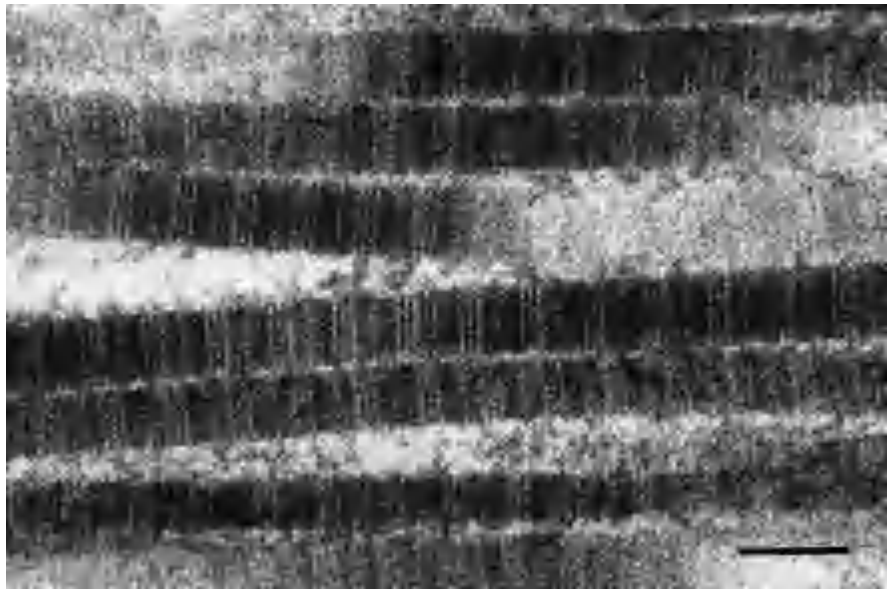

Fig. 3.39 Collagen fibrils in human reticular dermis showing characteristic banding pattern after standard processing and staining (uranyl acetate and lead citrate) for transmission electron microscopy. Scale bar = 0.1 µm.

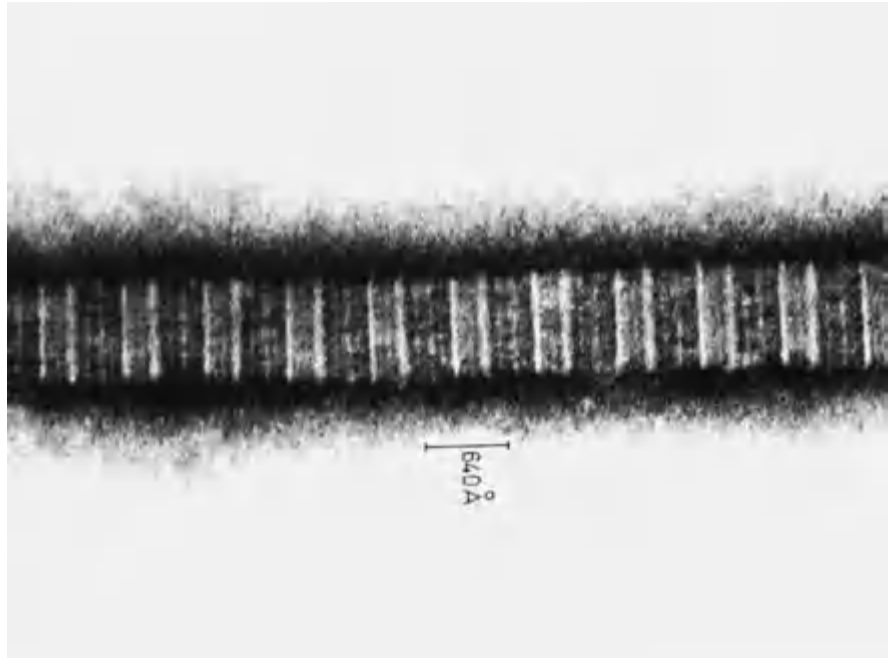

Fig. 3.40 Single fibril of rat-tail collagen, negatively stained with sodium phosphotungstate. One complete period of length 64 nm (640 Å) comprises a light D zone and a dark F zone with a number of interbands. (Courtesy of G.A. Meek.)

charged lysine and hydroxylysine residues. Uranyl salts bind both positive and negative side-chains, depending upon concentration and pH [3]. Negative staining distinguishes dark gap zones and light overlap zones. Computerized bulk distribution corresponds to both positive and negative patterns. Different fixatives will produce varied negative- and positive-staining patterns. Thus, glutaraldehyde particularly modifies negative staining by interfering with charge distribution. It binds lysine, hydroxylysine and histidine, and can also affect positive staining by stain exclusion. Formaldehyde modifies such positively staining. It ignores the positive charges of lysine and hydroxylysine but instead sticks to arginines or histidines. Diimido ester non-selectively stains all of these amino acids.

Segment long-spacing crystallography

The characteristic 60–70 nm cross-striated pattern of native collagen was discovered in 1942 [2]. At neutral pH, a different arrangement, so-called fibrous long-spacing (FLS) collagen, occurs. This has a periodicity of 180–300 nm. At acidic pH, in the presence of adenosine triphosphate (ATP), segment long-spacing (SLS) crystallites precipitate. They vary between 250 and 280 nm in length and stain positively with PTA. SLS fibrils are best examined

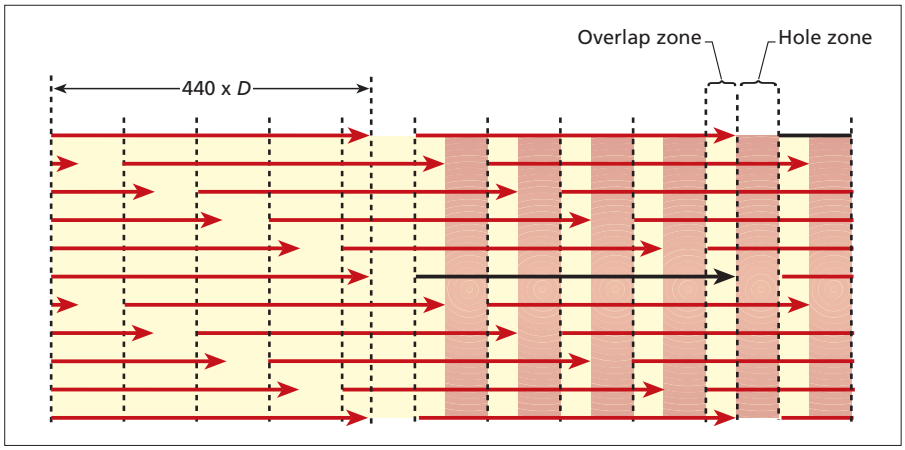

Fig. 3.41 Quarter-staggered packing of individual collagen triple helices. The latter pack nose to tail with respect to one another and are staggered, such as to create gap and overlap zones, visualized as cross-banded dark or light zones, when stained for electron microscopy. Smaller molecules such as FACIT (*fi*bril-*a*ssociated *c*ollagens with *i*nterrupted *t*riple helices) collagens, proteoglycan (PG) or calcium fit into these zones in different interstitial collagens.

after dialysis with ATP, and can be studied in fibroblast culture medium, cell layer or tissue collagens [15]. SLS crystallites have been important in deducing the native staggered axial organization of various interstitial collagens. The distinctive banding patterns of individual collagen products can identify fibrillar collagen types without the need for amino-acid analysis. Positive or negative staining with PTA and uranyl acetate, respectively, stain positive or negative side-chains. Such staining of the various lysine, arginine, glutamate and aspartate residues corresponds to the cross-striation of quarter-staggered collagen type I (α1(I), α2(I)) banding patterns. The charge distribution of each collagen type is almost congruent, although subtly different. Similarly, the fibrillar collagen types I–III and V have an overall similarity of organization (as regards the cross-striation pattern), yet are distinguishable from one another. SLS patterns have allowed the identification of the collagenase cleavage site near the N terminus, and the clear identification of the N- and C-terminal propeptide extensions. Subsequently, Kobayashi *et al*. [16–18] have shown that negative PTA staining of SLS collagen corresponds to the distribution of large hydrophobic amino acids, and positive staining with the polar ionic interactions of up to 58 transverse bands. Molecular mass studies of unstained SLS highlight bands 11, 19 and 37 in collagen type I and bands 15, 17, 19 and 37 in collagen type III. Such type I and III SLS aggregates can reliably be identified in cell cultures [16–18]. Unravelling of the N-terminal portion of the collagen type I triple helix occurred in SLS crystallites produced by a patient with lethal OI caused by a premature hiccup in triple helical winding. The defect was accurately located to lightband numbers 22–34, corresponding to amino-acid residues 460–710 of the triple helix. Such changes can be detected in less than 1 μg of unlabelled collagen protein, an amount easily obtained from fibroblast cultures. Similar SLS aggregates are detected in the cell-layer collagens. Dextran precipitation will artificially promote complete procollagen processing and assembly, providing an opportunity for *in vitro* processing studies [19,20]. As the SLS fibrils of collagens types I–III [16] are clearly distinguished, the fibrillogenesis and lateral interactions of types II and III collagen mutants in diseases such as chondrodysplasia or vascular aneurysms can also be systematically studied in the test tube.

Rotary shadowing electron microscopy

Individual collagen triple helices can also be assessed by electron microscopy. Low-angle rotary shadowing with platinum or tungsten (Fig. 3.38), detects collagen types I and III molecules [21,22]. Rotary shadowing demonstrated a 30–60° kink, lying 70 nm from the C-terminal propeptide of an α1(I) triple helix, of an OI with a glycine–cysteine substitution at residue 748 [23]. Five to 15 per cent of secreted molecules were kinked, and 20–30% of the cell layer collagens were similarly defective. This observation correlated well with the disordered protein chemistry: cysteine–disulphide linked α1(I) chains, disordered thermal stability and defective processing of procollagen to collagen. Unexpectedly, the N-terminal propeptide was excised inefficiently, implying that certain primary helical abnormalities at one position somehow disrupt other parts of the molecule some distance away from the primary mutation [24]. Such kinks are rare in other similar helical substitutions [25–29], which nevertheless sometimes affect collagen processing [30]. Rotary shadowing is therefore useful in visualizing individual mutant collagen molecules. Faulty collagen triple helices could not form normal fibrils by lateral association. Correlation of mutational position, protein stability and molecular architecture with histological and clinical abnormalities may eventually explain disparities between observed clinical phenotype and disturbed protein chemistry.

Rather interestingly, mutational gradients of glycine substitutions are clearest in COL1A1 mutations. The closer to the C terminus, or the larger the substituted amino acid, the more severe the clinical phenotype. Con-

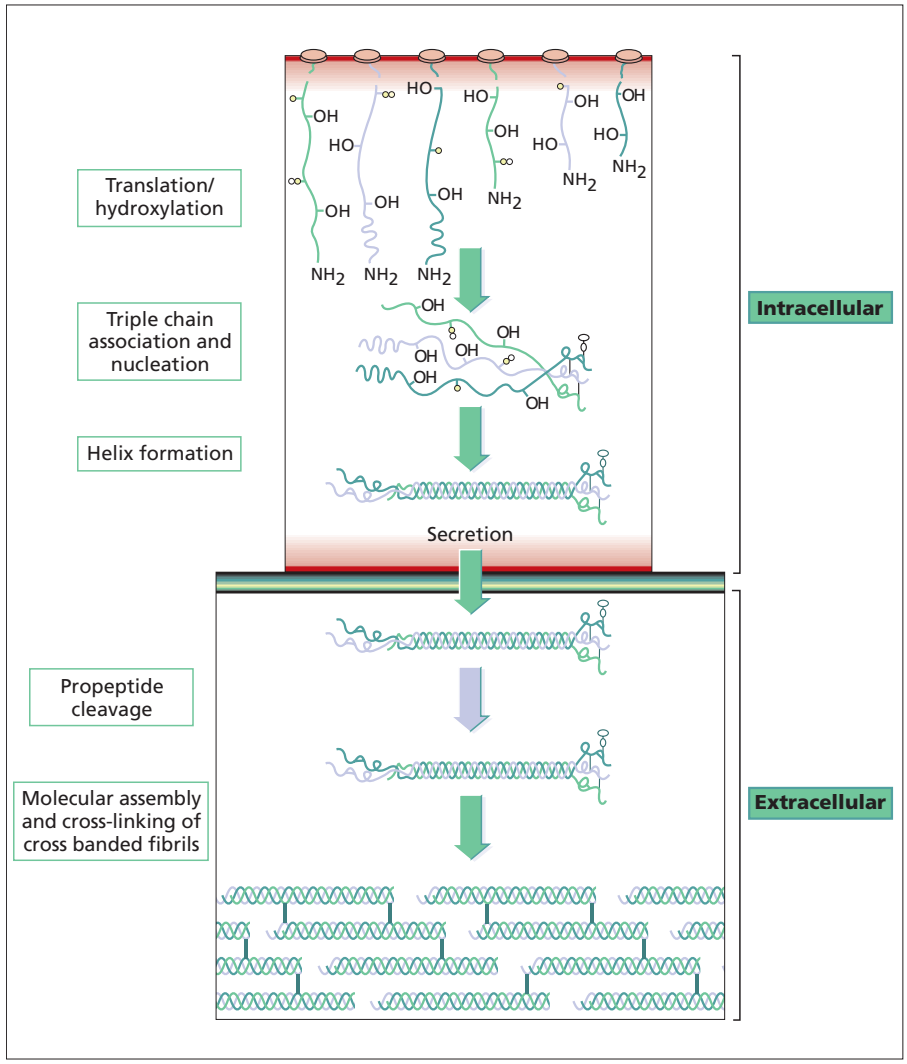

Fig. 3.42 Steps in the production of mature collagen fibrils, from translation at genomic level to the final assembly of cross-banded fibrils in the extracellular matrix (ECM).

trastingly, N-terminal mutations are the mildest. Whilst this general rule closely reflects the clinical phenotypes in OI (COL1A1 and COL1A2), as well as EDS type IV (COL3A1), it correlates very poorly in COL2A1 mutations (such as Kniest, spondyloepiphyseal dysplasia [SED], hypochondroplasia, etc.), and not at all in COL7A1 heterozygous substitutions, in which some glycine mutants are clinically completely normal.

Fibre organization and growth

Fibrils of fibrillar collagen, such as types I–III, spontaneously self-assemble in the ECM (Fig. 3.42), following secretion of procollagen, and the proteolytic removal of the N- and C-terminal propeptides. Triple-helix formation follows the spontaneous apposition of three individual C-terminal propeptides, followed by the ordered helical winding from the C to N terminus of three associated collagen α chains [24]. Until quite recently, the mechanism of the ordered production of quarter-staggered fibres was not well understood. We now know that procollagen aggregation is surface- and not concentration-dependent. Triple-helical fibril formation is now measured *in vitro* after collagen propeptide removal by purified chick N- and C-terminal propeptidases [25–29]. The association kinetics of fibril formation produced by diseased or normal fibroblast cultures can then be compared in a simple test tube assay.

Enzymatically treated (processed) fibrils are centrifuged out of suspension, so allowing the calculation of the concentration and velocity kinetics of fibril formation [25–27]. The morphology of the fibres can be simultaneously monitored either by simple dark-ground illumination or by electron microscopy with positive and negative staining. The distribution of mass within the fibre may be measured by scanning transmission electron microscopy (STEM) [31,32]. The latter has the advantage of using unfixed and unstained samples, which make it artefact-free. The transverse mass distribution is calculated along the growing fibre length [31] and STEM studies of growing

fibril tips show that the mass per unit length increases for 100 D periods close to the growing tip (calculated at 17 molecules per D period). The increase of mass is maximal at the tip and is inversely proportional to the diameter [31]. Interestingly, fibrils formed by removal of the N or C propeptides are short and unipolar, whereas longer bipolar N to N or C to C fibrils occur *in vivo*.

Alternatively, those inherited diseases with faulty removal of the N or C termini can be studied. Uncleaved N-terminal propeptides migrate more slowly by gel electrophoresis than normal α1(I) or α2 chains, and *in vivo* form angulated cutaneous or ligamentous fibrils [31–36].

Consequently, fibril misassembly in various collagen mutations is much better understood. The glycine–cysteine substitution at position 748 referred to earlier [23], which showed kinked fibres by rotary shadowing, produces abnormal collagen fibrils when examined *in vivo* by these methods [29]. When a series of such helical glycine substitutions were examined, including glycine–cysteine 718, glycine–aspartic acid 97 and 883 and glycine–arginine 550 [30], miscleavage of the distant N propeptide occurred, even when the mutated fragment was first removed by vertebrate collagenase. The kinetics of fibril formation were independent of velocity but not of concentration, implying a mysterious conformational disturbance of the N propeptide induced by the distant helical disturbance. Further work has clearly demonstrated bending-back upon itself of the uncleavable and persistent N propeptide in EDS type VIIB [35]. The uncleaved portion of the faulty molecule anonymously fills the gap region of quarter-staggered collagen fibrils, as measured by STEM, even though collagen-positive staining is normal. Probably, a gap-specific binding protein is excluded in EDS type VII, which sometimes produces the specific clinical features such as skin fragility, extreme joint laxity and angulated fibres in transverse section. In contrast, a very close mutation at amino acid 19 of the collagen triple helix, which is coded by exon 7, causes premature osteoporosis with spinal collapse, but no cutaneous fragility. Such distinctive clinical differences must ultimately be explicable in terms of fibril growth, morphology and interactions. The collagen type III propeptide is cleaved by a different enzyme from that which removes the COL1A1, COL1A2 and COL2A1 N termini [37]. Purification of this enzyme would therefore be essential for similar kinetic studies of collagen type III fibril patterns. Collagen type III mutations are just as molecularly diverse as type I errors, but in contrast are consistently life-threatening. They also consistently alter collagen fibril diameter [38,39].

Fibril kinetics

Cleavage with purified N or C propeptidases form hybrid pNα2(I)pCIII, α1(I) and α2(I) collagens. The kinetics of procollagen C (helix + C terminus: pC) type I cleavage, the incorporation of pC collagen type I into fibrils (in the pellet fraction) in the presence of procollagen N (helix + N terminus: pN) III, and the simultaneous incorporation of procollagen III and pC collagen type I in the presence of the C-propeptide, can then be objectively tested. By itself pNIII cannot form fibrils, but pNIII together with collagen type I co-assembles to make smaller fibrils than normal. Furthermore, pNIII deposits on to the surface of type I collagen fibril, and in so doing probably inhibits its rapid polymerization (therefore increasing the lag period and the rate of fibril propagation). Very probably, pNIII coats the type I surface, leaving the growing tips free. This implies that smaller fibres will normally occur in the presence of type III collagen, and in its absence type I collagen fibril diameters vary from large to small, which agrees well with the author's and other workers' empirical observations [36–39]. The increased lag time implies an action early in fibrillogenesis to hinder propagation or fibril growth [37]. It is also consistent with the author's observations of disturbed transverse collagen diameters in various inherited type III collagen mutations. Ordered fibril production may also be impaired if specific molecular interactions with substances such as the various minority collagens are impaired, with consequent misregulation of fibril diameter. Such molecules include the FACITs and collagen types V, XII and XIV (with collagen types I and III). Very probably, other ECM molecules such as PGs, calcium and certain adhesive molecules can also insert into the gap region. More detailed studies of mass distribution with STEM, similar to those of Kadler and colleagues on the packing of the persistent pNα chains of EDS type VII [35], which can measure the mass of gap and other regions, should in future allow the morphological identification of highly specific collagen-binding molecules. Obvious candidates are PGs such as decorin [40,41]. Calcium also specifically binds to the gap region of type I collagen ($\alpha I(I)_2\alpha_2$) but not $\alpha 1(I)_3$ [42]. Possibly, a complex variety of interactive substances bind to the particular fibril domains, raising the possibility of detecting and purifying specific binding proteins. Such studies should clarify the mechanisms of diseases such as OI, osteoporosis and EDS types IV and VII, in which collagen fibril morphology and tissue strength and stability are severely impaired. Disordered binding would be expected in those misassembled fibrils caused by defects in collagen or other connective tissue substrates. Calcium binding to the gap zone should be abnormal in certain abnormalities of bone collagen such as osteoporosis or OI.

Morphological studies

Regularly repeated collagen cross-striations have been clearly described by Chapman *et al*. [2,3] and Kadler *et al*. [29]. There is a succession of positively and negatively

stained bands (labelled a to e) running from the N to C terminus, in which the gap bands d and e alternate with the overlap b bands and intermediate a and c bands. Certain PGs, such as chondroitin, bind to e and d bands in the gaps, whereas keratan sulphate 80 associates independently with bands a and c as judged by keratinase/chondroitinase ABC and AC or hyaluronidase-treated samples [40]. Decorin specifically binds to the e band. The PGs possess variably sized core proteins linked to different glycan combinations. Thus, heparins contain 1–4 glucuronic acid or L-iduronic acid linked to glucosamine. Chondroitin (dermatan) glycans have *N*-acetyl galactosamine-linked 1,4 or 1,3 to D-glucuronic or L-iduronic acid. Similarly, the keratans link *N*-acetyl glucosamine and D-galactose in 1,3 or 1,4 patterns. Rotary shadowing shows a variety of attached core proteins, ranging from tadpole-like ball and sticks to very complex networks. Scott [40,41,43] has carefully studied the interactions of various collagens with PGs by mixing cold collagen solutions at physiological pH and ionic strength with purified PG solutions. This allows affinity association or mixing with either spontaneous or reconstituted fibrils. Kadler's *in vitro* fibrillogenesis methodology [25–27,29,44] could also profitably be explored in this context. Thus, solutions of intact fibril forming collagens at physiological pH and ionic strength will interact with solutions of different GAGs in particular PGs. Collagen can be constituted in a number of ways, such as using cyanogen bromide/sepharin–agarose, cross-linked collagen, reconstituted fibrils, soluble collagen residues or solid phase assays [40]. The various interactions may be monitored by light scattering, turbidometry or electrical birefringence [43,44]. GAGs will electrostatically interact with type I collagen, thereby accelerating fibrillogenesis. Chondroitin and dermatan both inhibit fibrillogenesis but are also incorporated into collagen fibrils. X-ray diffraction or magnetic resonance imaging (MRI) is used to monitor such interactions. Staining with certain anionic substances such as cupromeronic dye or cuproline blue is also useful. Observed patterns include the following.

1 Cupromeronic blue and cuproline blue staining of fibrils, when counterstained with tungstate, clearly demonstrates PGs bound to typical collagen type II fibrils. The distribution of PGs is orthogonal (i.e. lying at right angles to the long axis of collagen fibrils) but D-periodically spaced. Staining is often most marked at the d band, or sometimes the e band in the gap zone. Other PGs will span the gap between adjacent D-spaced filaments, but stain as parallel complexes. Orthogonal PG is usually dermatan sulphate, while the interfibrillar PGs are probably chondroitin sulphate. In annulus fibrosus, chondroitin sulphate forms complete loops at the d1 to e bands. In bone, gap-associated PG is replaced by Ca^{2+}. Interactions of axially bound PGs extend to 1D lengths (thereby encircling one quarter of a collagen molecule). PGs probably participate in the regulation of collagen fibril growth. Other important considerations include, firstly, that collagen/GAG interactions are electrostatic and can be abolished by an increase in salt concentration and, second, that fibrillogenesis is accelerated by dermatan, heparin or PG.

2 Chondroitin and dermatan interact strongly with collagen type I, both electrostatically and as protein–protein associations. The organization of these complex associations has been clarified by MRI rotary shadowing, molecular diagnosis and electron histochemistry [40,41].

Three-dimensional structure of collagen

Techniques such as optical and X-ray diffraction are used to mathematically deduce three-dimensional structural order. In general, X-ray crystallography is used for the computation of the detailed three-dimensional organization of large, complex molecules (such as collagen), while MRI is more suitable for the analysis of smaller molecules up to 20 kDa in size [45]. The primary structure, gene and protein sequence of the interstitial collagen types I–III and V are very well understood. Similarly, their normal two-dimensional structure both *in vivo* (tissue sections) and *in vitro* (fibroblast cultures) has been extensively studied for normal tissues. As mentioned above, positive and negative staining of individual fibres or SLS aggregates by transmission or rotary shadowing electron microscopy have been the standard techniques. Fibril growth can be measured under controlled conditions as described by Kadler *et al*. [25–27,29]. Diffraction methodology (such as X-ray and optical diffraction) applied to suitable collagen preparations, such as tissue sections, collagen fibrils or collagen crystals, allows computation of three-dimensional structure, from which tertiary structure and possible interactions with other connective tissue elements can be further deduced by high-resolution atomic mapping. For X-ray diffraction, monochromatic beams are usually produced from rotary anode generators. If high resolution is essential, higher energy polychromatic beams may be obtained from synchroton rings. Narrow parallel X-rays are directed into specially grown protein crystals, and the consequent diffracted radiation is either collected conventionally on an X-ray film or digitized and stored electronically. Interactions between the beam and electrons from each atom of the sample produce a generalized scattering of X-rays in all directions. In the presence of orderly crystalline geometry of atoms and electrons, the beam produces a characteristic interference pattern, which is directly related and dependent upon three-dimensional crystalline structure. Recently, a 1.9-Å map of collagen type I has been published. Detailed amino acid sequence is essential for the interpretation of such constructs since certain chemical groups such as ONH_2 and CH_3 are indistinguishable at resolutions between 1.7 and 3.0 Å. At this

resolution, amino-acid pairs such as valine and threonine, aspartate and asparagine, and glutamate and glycine look very similar. Similarly, distinguishing between histidine and phenylalanine is also difficult.

X-ray grade crystal growth. Crystallography requires good-quality protein crystals. These must be several tenths of a millimetre in each dimension and also be sufficiently well ordered to produce good quality X-ray diffraction spots. Methods of preparation include hanging drops, sitting drops, dialysis, seeding, batch free, capillary-diffusion and temperature gradient methodologies [46]. All gradually supersaturate the macromolecule of interest, in protein solutions that are well hydrated and at near physiological temperatures and pH. Essentially, highly concentrated protein solutions are crystallized by disruption of hydration shells and reduction of electrostatic shielding [46,47]. Usually a precipitant is required in addition to the protein. Supersaturation and subsequent crystallization follow either gradually increasing precipitant concentrations or saturation with precipitant and varying the temperature or pH. Categories of precipitants include salts (such as ammonium sulphate) and organic solvents (such as ethanol or polyethylene glycol). Hanging-drop methodologies can be used with very small quantities of protein but they produce only very small crystals. The seeding and batch methods require small crystals initially and lots of protein subsequently. Having achieved crystallization (provided the protein under test is well purified), its diffraction patterns can be systematically collected. With small unit sizes (less than 5 nm) diffractometers are suitable, whereas 5–20-nm cells will require an area detector. Higher resolution of more complex structures requires the high flux of a synchroton X-ray source. For diffractometer collection, various options include precession of crystal and film, rotation of the crystal with a stationary film and the Lane method utilizing polychromatic X-rays. Counting methods include diffractometer (crystal and detector both moving) and area detectors with computerized counting. Computer graphics, more powerful X-ray beams and microcomputation have revolutionized the speed, interpretation and analysis of crystallographic data, usually supplemented by the complementary technique of MRI.

Magnetic resonance imaging. The spin of certain ^{7}H, ^{3}C, ^{15}N and ^{31}P atoms have intrinsic magnetic moment, which can be probed by MRI. When such molecules are placed in a strong magnetic field they are excitable at radio frequencies, with the production of one- and two-dimensional spectra. Overtly joined atoms can be identified by correlation spectroscopy (COSY), and atoms that are adjacent in three-dimensional space, even when sited in different parts of the same molecule, are detectable. By 'sequential assignment' any given amino acid has a characteristic set of 'cross-peaks' with a diagnostic fingerprint for any given COSY pattern. In contrast to X-ray crystallography, which provides direct three-dimensional information, MRI produces specific coordinate spatial mapping from which a three-dimensional model can be computed. The two techniques are complementary: MRI being especially useful for studies of dynamic processes such as protein folding, whereas X-ray scanning deduces the fixed structure of the protein in its crystalline state [45].

X-ray diffraction of collagen. Ramachandran and Kartha [48] first described various intrinsic properties of vertebrate collagen fibres, and proposed a right-handed superhelix of three left-handed helical polypeptide chains. They noted a hexagonal unit cell with A = 12–16 Å, C = 9.5 Å (three residues per turn with an invariant glycine in position 1 and with proline often in the third Y position). Rich and Crick [10] modified this model slightly, placing proline as a frequent second position residue but agreeing with a three-chained coil, and postulating a single set of hydrogen bonds. More recent details have been described [4,49–51]. Thus, the collagen helix is very close to 300 nm long and 1.25 nm wide. Recent data show a separation between the tripeptides of 0.289 nm with an azimuthal distance of 8.6 nm (30 amino acids) and P, the pitch of the supercoil being 108°. The essentials of two-dimensional structure as detected by transmission electron microscopy of positively and negatively stained fibres has already been reviewed above, but the three-dimensional structure is still almost unexplored in diseased situations. Electron micrographs of transversely sectioned fibrils show some order of fibre packing, but there is no obvious regularity of structure within the individual fibril. X-ray diffraction, on the other hand, strongly suggests a three-dimensional crystallinity [4]. This varies, depending partly on whether the tissue is wet or dry, and is characterized by strong equatorial Bragg reflections. Such data provide crucial information about lateral associations and disorder and this, together with the two-dimensional details described above, have clearly defined the three-dimensional structure. Essentially, the collagen molecules in any given 68-nm section include four molecules 68 nm long and one of 35 nm. The unit cell is probably quasi-hexagonal without a microfibrillar structure [51]. The molecules are tilted 5° in the lattice at a specific plane forming a molecular crystal. Alternative models have included tetragonal packing with two, five or eight microfibrils. The two-dimensional Hodge–Petruska model postulates equal numbers of the five molecular segments in each (theoretical) 68-nm fibrillar section, with the unit cell being one molecule of five segments.

Most probably, the interpretation of five molecular segments dispersed around the surface of a crystal to form a microfibril pentameter is correct. Other possibilities include the small microfibril or square lattice models of

Fraser. Miller [4] concluded the following: (i) The quasi-hexagonal unit cell is correct and the three-dimensional cell is a triclinic of known dimensions and unit volume containing one collagen molecule. (ii) The molecules are inclined parallel to a specific plane in the lattice with less crumpled triple helices occupying 0.46 D. (iii) The equatorial intensity indicates quasi-hexagonal packing. (iv) The azimuthal inclination of the triple helices have slight irregularities of crystalline structure and correspond to the overlap region. The gap region is less ordered and there are several minor irregularities in the structure, including precise arrangement of D segments within the unit cell, the absolute quasi-hexagonal relationship of the molecules and the precise axial registration and order of the α1(I) and α2(I) chains in the triple helix. Crystallinity therefore implies rather specific molecular interactions.

Covalent cross-links also influence the X-ray diffraction data and link nearest neighbour amino acids between residues 9 and 946 or 103 and 1047. The latter is consistent with the known cross-linkage of cyanogen bromide peptide α1(I) CB3, 5 [52]. This would very probably stabilize the fibril packing, with disturbance produced by molecular abnormalities of these regions.

X-ray diffraction of various collagens and their disorders. Comparatively little work has been done upon the crystal structure of normal connective tissue such as skin, cartilage and arteries. A great deal of detailed information is available upon the three-dimensional organization of type I collagen [4,49–51]. Preliminary data are also available on normal collagen types I–III, and the organization of tissues such as rat-tail tendon, bone and cartilage. Some information has been published on hyperglycaemia-induced cross-linking and ageing, and on the animal disease dermatosparaxis.

Optical diffraction. Standard high-resolution transmission electron microscope pictures have a depth of focus of several thousand angstroms, thereby superimposing numerous three-dimensional images in two dimensions for each tissue slice. Negatively or positively stained electron micrographs are therefore suitable for three-dimensional analysis by optical diffraction [53]. The approximate images are analysed mathematically using classical X-ray diffraction algorithms. Essential steps include selection of good structural images, sampling of optical density by microdensitometry at regular intervals, computation of the Fourier amplitudes and phases, and synthesis of the three-dimensional map. It is a major advantage that phase can be readily calculated from the density of the electron micrograph images, using Fraunhoffer diffraction holography, which is analogous to heavy atom X-ray crystallography. The electron-microscopical two-dimensional image is a projection of the three-dimensional density distribution of all levels lying perpendicular to the beam. By collecting enough projections, a detailed three-dimensional image can be produced. Rotational and screw symmetry reduces the number of images produced, with a rough resolution of 30 Å in a 250-Å field. Unlike X-ray diffraction, in which phase is lost in making the two-dimensional image on a screen or X-ray plate, in optical diffraction the focusing of the electron beam preserves this information. The mathematics and rationale of the methodology has been clearly described [54]. A more modern surveying optical diffractometer suited for this type of approach has also been reported [55], and has generated detailed optical diffraction data and lattice spacings of negatively stained fibrinogen. Optical diffraction has been applied to the elucidation of the three-dimensional structure of *Salmonella typhimurium* flagellar filament [56].

This type of methodology is applicable to the three-dimensional structural analysis of the two-dimensional transversely sectioned electron micrographs of the various inherited collagen disorders. Good examples would be OI and EDS types VIIA and B (*COL1A1* and *1A2*), certain chondrodysplasias (*COL2A1*), vascular EDS (*COL3A1*), and EDS type III (*COL5A1* and probably *5A2*). Similarly, *COL7A1* mutations produce considerable fibrillar disorder, because the fibrils are not quarter-staggered but instead are laterally packed to form naturally occurring SLS fibres.

Other collagens

Non-fibrillar collagens (20+ genes) are both more diverse and numerous than the classical fibrillar types I–III, V and XI (10 genes). Most have globular interruptions to the Gly-X-Y central helix [57]. Such non-collagenous sequences allow molecule shapes other than rod-like, thereby diversifying intramolecular and intermolecular interactions with themselves or other ECM proteins, as basement-membrane proteins and collagen types IV or VII (see below). Others function in eyes, cartilage or blood vessels, whilst other collagenous components act as membrane-bound anchors or even scavenger proteins. Some are particularly important in skin or other tissues such as blood vessels or ligaments, while others resemble similar proteins that interact with certain cartilage matrix components. Collagen types IV and VII differ from the fibrillar and other non-fibrillar collagens by virtue of their large size and extended triple helices. Each of the collagen type IV proteins, which form very complex structural networks, has more than 30 globular interruptions to the Gly-X-Y helix.

Collagens that are neither fibrillar nor basement-membrane related include: (i) those with regular interruptions to the helix (collagen types IX–XII, XV and XVI); and (ii) those without, in which the helix is continuous (collagen types VI, VIII and X).

Basement-membrane collagen (types IV and VII)

Collagen type IV. Although amorphous and not fibrillar, the collagenous nature of basement membrane was first recognized more than 50 years ago by Pirie [58]. He observed both a typical collagenous X-ray diffraction pattern and the hydroxyproline and hydroxylysine ratios of collagenous proteins [57]. Purified collagen α chains from pepsinized lens and glomerular basement membranes differ in size and peptide composition from typical fibrillar collagens. They are also very diverse, containing at least five non-allelic α chains in varied tissues such as skin, lens capsule, glomerular or tubular renal basement membranes, lung, muscle and developing embryos. Even though non-fibrillar, and therefore unable to form SLS fibrils (as do collagen types I–III, V, VII and XI), individual collagen type IV molecules, when rotary shadowed, have long globular extensions at the NC-1 ends. The rat Engelbroth–Holm–Swann (EHS) tumour produces copious basement membrane, from which its chicken-wire (lattice) organization was first deduced [59]. This links individual 7S collagenous N-terminal sequences as overlapping tetramers, formed by four adjacent parallel collagen triple helices in which the 7s elements are parallel, while the triple helices form one arm of four adjacent quadrilaterals [60]. The NC-1 domains attach by multiple disulphide bonds with dimers formed both at the N and the C termini.

Basement membrane collagens α1 type IV and α2 type IV were the first to be characterized. Each is coded by adjacent genes, which are located on chromosome 13q33–q34. They are separated by only 400 kb, and are transcribed in opposite directions from their 5′ promoters, which lie head to head [61]. Thus, COL4A1 and COL4A2 have bidirectional promoters, which are coordinately transcribed from opposite strands, although separated by less than 42 bp in humans (but 130 bp in mice). Subsequently, four additional α chains have been identified (α3–α6 type IV collagen). All of them now have been cloned. Defects of α3–α5 chains of type IV collagen produce variants of Alport's syndrome, a disorder characterized by glomerular basement membrane thickening fragmentation or leakiness, together with deafness from faulty cochlear–epithelial hair-cell degeneration. In all cases, basement membranes at these loci are defective and abnormally permeable, but the clinical phenotypes range from chronic renal failure (with or without deafness) to isolated benign haematuria. The genes coding for α3–α5(IV) collagens, *COL4A3*, *4A4* and *4A5*, are located, respectively, on chromosomes 2q35–37 (α3 and α4) and Xq21–23 [62].

Collagen type VII. Although collagen type VII does form cross-banded fibrils, it is not a fibrillar collagen (such as types I–III, V and XI) by virtue of its larger size, very specific anatomical location and non-quarter-staggered parallel fibril organization. It was first isolated from pepsinized amnion as a contaminant of a collagen type V preparation [63]. The original experiments identified a disulphide-bonded collagen rich in glycine and hydroxyproline, which after reduction formed two α chains longer than either typical interstitial type IV or basement-membrane α chains. It also assembled into novel SLS fibrils [63]. The type VII molecule is 1.5 times longer than normal fibrillar collagen α chains. Unlike the latter, the triple-helical molecules do not form quarter-staggered fibrils, but instead naturally stack laterally, as SLS fibres with a highly ordered and characteristic cross-banded structure. The long central Gly-X-Y helix of 467 nm has only one globular interruption. There is a small globular region (NC-2) at the C terminus, and a large trident-shaped region (NC-1) at the N terminus. Pairs of molecules pack in opposite orientation, overlapping at the NC-2 ends by 60 nm, where they are stabilized by disulphide cross-links. Laterally stacked SLS fibrils have the N termini inserted into, and interacting with, the lamina lucida on the epidermal surface of the basement membrane of the dermis. They also attach to anchoring plaques at the dermal end of the individual collagen type VII (anchoring) fibrils [64].

Chromosomal location and gene structure. The *COL7A1* gene was originally isolated from a human keratinocyte cDNA expression library [65]. The gene sequence showed that, although the NC-2 coding domain is relatively large, it is processed into a smaller mature format. The chromosomal location at 3p21 coincides with autosomal dominant and recessive epidermolysis bullosa dystrophica (EBD), diseases in which anchoring fibril fragility and depletion produce blistering, scarring and separation of stratified squamous epithelium from the dermis. The genomic organization is the most complex of any collagen, with 118 exons distributed over 38 kb. Suitable intronic primers generate 65 amplimers that can be tested for exon mutations [66]. In general, mild autosomal dominant forms of EBD are caused by glycine substitutions or exon skips, while severe recessive EBD is caused by double combinations of stop codon mutations, exon skips and glycine substitutions [67,68]. The NC-2 domain contains 161 amino acids with eight cysteines and a potential Kunitz proteinase site. The cysteines stabilize the antiparallel tail-to-tail association of adjacent (overlapping) antiparallel collagen type VII dimers.

The genomic organization of *COL7A1* has some analogies to the fibrillar collagens. Thus, the collagenous coding region has a cassette format, whereby individual exons begin with a complete glycine codon and end with a Y triplet sequence, and are often multiples of 54 or

45 bp. Furthermore, anchoring fibrils are cross-banded when positively or negatively stained and examined by transmission electron microscopy. Other non-fibrillar collagen exon sizes, in contrast, are rarely 45 or 54 bp derivatives and are usually specified by split codons [66]. The *COL7A1* NC-1 domain also has nine fibronectin III repeats, two domains with similarities to CMP, a von Willebrand factor sequence and an RGD sequence, and must therefore have strong adhesive interactions with various other matrix components. As was predicted from Bentz's original protein data, the collagen helix has a single 39-amino-acid interruption, which is pepsin sensitive. The deduced protein size from the gene sequence is 134 kDa, slightly smaller than the 145 kDa predicted from protein electrophoresis. The difference is probably caused by *N*-glycosylation. In addition to the central 39-amino-acid Gly-X-Y interruption, there are also a further 18 smaller discontinuities. Helical cysteine pairs in the NC-2 domain stabilize the antiparallel assembly. The entire gene has 31132 bp (31.1 kb) with 118 coding exons, with the 5′ signal peptide and peptide cleavage site coded by exon 1. Exons 2–5 contain the cartilage matrix analogue, while exons 6–23 code for the nine consecutive fibronectin III repeats. Exons 24–26 code for the von Willebrand factor regimen and a proline-rich region is encoded by exons 27 and 28. The collagen triple helix is coded by 84 exons, while exon 112 contains the junction between the triple helix and the globular NC-2 domain, which is coded by exons 113–118. The longest globular interruption to the helix spans three exons and 39 amino acids. There are also many helical exons that are multiples of 9 bp.

Non-fibrillar, non-basement-membrane collagens

These are neither classical fibrillar collagens nor are they localized to basement membranes. They include:

1 the FACIT collagens;
2 the short-chain collagens;
3 other filamentous collagens.

***F**ibril-**a**ssociated **c**ollagens with **i**nterrupted **t**riple helices collagens.* Collagen types IX and XII are the prototypes, but other FACITs include types XIV, XVI and XIX. Very recently two more FACITs, type XX, which resembles types XII and XIV, and type XXIII, which occurs in cornea, have been described. Collagen type IX, which was originally copurified from cartilage extracts by differential salt precipitation [69,70], co-assembles and co-associates with fibrillar cartilage collagen (collagen type II), while collagen type XII occurs in tendons, ligaments, perichondrium and periosteum, and is only 60% as long as collagen types II or XI. Rotary shadowing showed a hinged triple helix with intervening globular non-collagenous sequences, which bound to the outside of assembled quarter-staggered collagen type II fibrils.

Three separate collagen genes (*9A1*, *9A2* and *9A3*) code for three distinct, but homologous, type IX proteins. All have analogous NC-1, NC-2 and NC-3 domains interrupting the triple-helical Gly-X-Y collagenous sequences [70]. The NC-3 domain of collagen type IX α2 chains covalently links to chondroitin sulphate/dermatan sulphate PG. The size of the N-terminal NC-4 domain varies widely between the three type IX α chains, while collagen α1 type IX has the largest NC-1 and NC-2 domains.

Collagen type XII has a very similar overall exon–intron structure, though collagen type IX trimers has a much longer NC-3 domain [71]. Rotary shadowing experiments prove that the COL-1 and COL-2 domains of type IX α1 collagen orientate parallel to the fibrillar cross-bands of type II collagen. Contrastingly, the COL-3 domain of α1(IX) collagen projects outwards at an angle. Very probably, collagen type IX subtly regulates interactions between adjacent collagen type II fibres. There are also two alternatively spliced forms of COL9A1. The longer, which includes exons 1–7, occurs only in cartilage. The shorter form deletes exons 1–6 and 7–8, and instead joins a novel variant exon to exon 8. This shorter version of collagen αI(IX) is corneal, while the more abundant longer form is cartilaginous. No doubt, the variable length dictates which particular tissue-specific constituents interact with such collagenous variants, whilst also conferring those subtle structural properties needed for widely differing functions at particular anatomical sites. Perhaps other FACITs play similar roles in specialized tissues such as skin, or blood vessels.

Other FACITs (collagen types XII, XIII, XIV, XVI and XIX). Collagen types XII, XIV and XVI, which are also FACITs, are homologous to collagen type IX [69–72]. Collagen type XIII is less obviously homologous, but has organizational similarities. Collagen type XII cDNA was first identified in chick tendon fibroblasts; its genomic sequence and exon/intron organization closely resembled collagen type IX but lacked an NC-4 domain and instead had a large NC-3 domain. The COL-I helices of types IX and XII are also homologous, whilst the N-terminal globular region of XII is homologous to the NC-4 region of IX. Antibodies locate collagen type XII protein, to tendon, perichondrium and periosteum, implying that just as type IX collagen decorates collagen type II, type XII collagen co-associates with collagen type I.

As skin, bone and cornea completely lack collagen type XII, there must be other homologous FACIT proteins fulfilling similar functions in those tissues. Thus, collagen type XIV is 60% homologous to collagen type XII, and both the cDNA and genomic organization are very similar. Similarly, collagen type XVI is also a FACIT collagen

[72]. Its genomic organization resembles collagen types IX, XII and XIV but is also much more complex, having 10 collagenous and 11 non-collagenous interruptions. It has far more cysteines than any other FACIT, and most of the collagenous regions are imperfect triple helices. Unlike the other FACITs, the non-collagenous regions are small except for the N-terminal one, which has 312 amino acids. The first collagenous domain has substantial homology to various other FACIT molecules. It has 106 amino acids, compared with the 115 and 103 for collagen types IX and XII. The second collagenous domain, COL-2, is 27% identical to the NC-4 of collagen type IX and 17% identical to the NC-3 sequence of collagen type XII. The gene, which is located at 1p31, also resembles the cuticle collagen of the worm, *Caenorhabditis elegans*. Such sequence and structural homology implies specific but subtle interactions with certain other tissue-specific ECM components.

Collagen type XIX. This is also a FACIT collagen, having an 832-amino-acid triple helix distributed in five collagenous domains, interrupted by 20–42 residue non-collagenous sequences [73]. Two of the five COL sequences are analogous to those of collagen type XVI and, like collagen types IX, XII, XIV and XVI, the distribution of the C-terminal cysteines and certain sequences of some non-collagenous domains are also homologous. The C-terminal cysteines span the C-terminal end of the triple helix and the globular non-collagenous C terminus.

There are seven cysteines within the 186-amino-acid N-terminus NC-6 region and two more in the NC-4 sequence. The five collagenous domains have 144, 224, 108, 168 and 70 residues, respectively.

The five collagenous domains of collagen type XIX contrast with two 300-amino-acid residues in collagen types XII and XV and three large collagenous domains in collagen types IX α1–3. Type XV1 collagen has 10 interruptions ranging from 14 to 421 amino acids.

Current evidence suggests that the C termini of collagen types IX, XII and XIV form cysteine-mediated covalent links: in XII and XIV, homotrimers, and in IX α1–3, heterotrimers. The gene, which has a cDNA of 5.6 kb, may be even bigger than the 140 kb *COL13A1* gene [8].

Collagen type XIII [74]. This collagen, which lies on chromosome 10q22, occurs in most connective tissues. It has an unusual N-terminal transmembrane-spanning domain, but lacks a signal peptide sequence. This strongly implies that it is membrane bound rather than secreted. Collagen type XVII, which is basement-membrane associated, is also membrane bound.

Collagen type XVI. This is yet another FACIT [72] with an open reading frame of 1603 amino acids. There are 10 collagenous domains ranging from 14 to 422 amino acids. Except for the 312-amino-acid NC-11 domain, all of the other non-collagenous interruptions are small, varying from 11 to 39 amino acids.

The amino-acid sequence is analogous to collagen types IX, XII and XIV [69,71]. Nearly all the non-collagenous domains have two cysteines separated by two amino acids. The COL-1 domain is exceptional, as the cysteines are four amino acids apart, while the most N terminal is the first amino acid of the triple helix.

The large NC-11 domain has several unexpected homologies with other FACITs, being 27% identical to the NC-4 of α1(IX) and 18% identical to the NC-3 of α1(XII). It is also 20% homologous to the N propeptide of the fibrillar α1(XI) collagen. The gene lies at 1p34.

Collagen types XV and XVIII [75–77]. These two collagens are very similarly organized but differently distributed. The former is largely expressed in kidney, pancreas and adrenal gland, while the latter mostly occurs in lung and liver.

Type XV has significantly more serine–glycine and *N*-glycosylation sequences at the N terminus, and also has a tandem repeat analogous to PG core protein. In this respect it resembles other collagen/PG hybrids, such as types IX, XII and XIV. Collagen type XVIII has no core protein homology and fewer serine–glycine and *N*-glycosylation sequences. Nevertheless, the remaining organization is very similar, with nine collagenous zones in type XV compared with 10 in collagen type XVIII. The first six (from the C terminus) are very similar to size.

In other ways, the frequent non-collagenous interruptions also resemble collagen types XVI and XVII, of which only the former is a FACIT, while the latter is membrane bound. The N-terminal homologies to collagen types V, XI and IX are unexpected. Collagen types XV and XVIII may form a small subgroup of their own [77]. Thus collagen type XVIII has 10 triple-helical regions separated by globular domains and the latter have serine-glycine attachment sequences for PG core-proteins. The gene maps to chromosome 21q22.3 and the C-terminal portion contains endostatin, which is a potent inhibitor of tumour-induced angiogenesis. Apparently, endostatin (collagen type XVIII C terminus) binds to capillary endothelium, with the help of the heparan sulphate chains of glypicans 1 and 4 [78]. Autosomal recessive mutations of *COL18A1* cause Knobloch's syndrome, a disorder similar to the Stickler's syndrome which is characterized by high myopia, vitreoretinal degeneration, macular degeneration and occipital encephalocoele. Mutations uniformly caused low plasma endostatin levels, but collagen type XV is thought to substitute for such deficiencies [79].

Short-chain collagens. These form two subsets: (i) the filamentous microfibrillar collagens (types VI α1–3); and (ii) the true short-chain collagens (types VIII and X).

Filamentous or microfibrillar collagens (collagen type VI). Collagen type VI is rather unusual as it assembles into microfibrils and therefore organizationally resembles fibrillin, lysyl oxidase and certain other microfibrillar proteins, such as MAGP, rather than other conventional collagens. Nevertheless, even though resistant to bacterial collagenase, it has numerous interrupted Gly-X-Y sequences and is therefore truly collagenous. It is cysteine rich, and was originally purified both from human aortic intima and placenta. By rotary shadowing it is 'short chain', forming 105-nm rods with N- and C-terminal globular domains, and has three α chains (two of 140 kDa and one larger one of 250 kDa). The triple helix is a highly disulphide-linked heterotrimer, forming dimers and tetramers, which pack end to end to form 100-nm beaded microfibrils. Sometimes, it appears as so-called mackerel fibres, with a rippled wave-like (seabed) pattern. The latter are also known as Luse bodies, or fusiform or zebra collagen [80]. The triple helix contains 335/336 amino acids and has separate 200-bp von Willebrand domains in both the C and N termini of the α1 and α2 chains. The α3 chain, which is longer, contains nine von Willebrand repeats [81,82]. Autosomal dominant *COL6* mutations cause a mild muscular dystrophy with joint contractures (Bethlem myopathy), whilst double heterozygotes or homozygotes have a more severe congenital muscular dystrophy, otherwise called Ullrich congenital muscular dystrophy. Whilst the milder, autosomal dominant, Bethlem's myopathy form links to the *COL6A1/6A2* locus at chromosome 21q22.3, and the *COL6A3* locus at 2q37, the Ullrich form only has *COL6A2* mutations. As sometimes happens in dystrophic epidermolysis bullosa, Ullrich heterozygotes are clinically normal, in contrast to Bethlem myopathy mutants who are heterozygous affected. As in other collagenopathies, Gly-X-Y substitutions, exon skips and second position errors have been documented (OMIM 158810 and 254090) [83,84]. Deposition of collagen type VI also occurs in the skin of patients with juvenile hyalinosis, although the gene for this disorder is on chromosome 4.

True (non-microfibrillar) short-chain collagens (collagen types VIII and X). These short collagens do not form microfibrils but have a very specific anatomical distribution. Collagen type VIII was originally isolated from aortic and corneal endothelial cells but is not confined to these tissues. Biochemical studies suggest separate α1 and α2 type VIII chains forming hetero- or homotrimers of 60 kDa in a 2 : 1 ratio, similar to type I collagen [85]. A similar 59-kDa homologous homotrimer (collagen type X) can be purified from hypertrophic cartilage, and the two genes are similar enough as to suggest a common evolutionary origin. Both collagen types VIII and X form 130-nm triple helices and have similarly sized globular N- and C-terminal ends.

The *COL8A1* gene has four exons, one of which contains the entire triple helical and C-terminal coding regions and maps to 3q12–13.1. Similarly the *COL8A2* gene also contains the triple helix and C terminus in a single exon and maps to 1p32.3–34.3 [85]. Whilst both proteins occur in vascular endothelium and corneal endothelium (Descemet's membrane), as well as keratinocytes and mesenchymal and the meninges, mutations of *COL8A2* cause certain corneal dystrophies, such as Fuchs endothelial corneal dystrophy and posterior polymorphous corneal dystrophy, both of which require corneal transplantation [86]. So far, there have been no *COL8A1* mutations identified, although given the 2 : 1 protein ratios, they should certainly be clinically very similar and hetero-allelic.

The organization of *COL10A1* resembles *COL8A1* with a small 5′ exon coding for the NC-2 domain and a much larger 3′ exon encoding both the triple helix and the NC-1 domain [87,88]. Collagen type X triple helices assemble into novel polytetrahedral structures, which resemble geodesic domes.

C-terminal mutations of collagen type X cause Schmid-type metaphyseal chondrodysplasia (metaphyseal dysostosis) [89]. The clinical phenotype is consistent with the known tissue distribution of collagen type X and includes short stature, coxa vara and bow legs, but normal facies, hands and feet [89].

Collagen type XVII. Another basement-membrane protein is bullous pemphigoid antigen 2 (BPAG2), a hemidesmosomal protein, which was first identified as an autoantigen in patients with either bullous pemphigoid or herpes gestationis. Unexpectedly, the gene contains a novel collagenous coding region and is therefore distinct from bullous pemphigoid antigen 1 (BPAG1), which is a non-collagenous 230 kDa protein [90,91]. BPAG2 is also homologous to so-called chick corneal collagen. The gene encodes 13 distinct collagenous regions, of which five are 15 amino acids in length, two are multiples of 15 and three others have 12, 18 and 42 amino acids, respectively. All of these could theoretically have evolved by triplet losses or gains, or from crossing over from an ancestral gene coding for 15 amino acids, i.e. 45 bp. The gene also codes for a membrane-spanning sequence with an extracellular collagenous portion, while the N terminus is intracellular. Antibodies to the latter detect human bovine and frog epitopes, while certain *N*-glycosylation sites are conserved between mouse and human genes. Unexpectedly, the N-terminal heptad repeat is the focus for triple helical chain association, which in other collagens occurs from the C-terminal ends. The human cDNA is 4.6 kb and codes for a membrane-bound protein of 1433 amino acids.

Compound heterozygous mutations in *COL17A1* are seen in generalized atrophic benign epidermolysis bullosa, a form of junctional epidermolysis bullosa where blistering occurs at the level of the lamina lucida [92] (Chapter 41).

Table 3.8 Collagenous non-extracellular matrix (ECM) proteins.

Protein	Molecular weight	Function	Structure
Bovine conglutinin	40×10^3	Lectin like. Binds zymosan	Monomer has a central helical stem with a large head; packs as a four-armed unit
Mannose-binding protein	29×10^3 monomer 58×10^3 dimer	Mannose binding (water soluble)	N-terminal collagenous domain is disulphide linked 140 amino-acid terminal carbohydrate binding site 20 repeats of 53–59 amino acids in the collagenous domain Analogous to C1q in terms of the interrupted helix
C1q	Similar to mannose-binding protein	IgG binding	Similar to mannose-binding protein except longer collagenous repeats of 25–27 consecutive Gly-X-Y C terminus binds Fc IgG repeats. Forms a bunch of roses pattern 78 amino acids and collagenous sequence, i.e. 26 triplets with central discontinuity
Macrophage scavenger protein	348 amino acids, 28.3 kDa	Binds low-density lipoprotein receptor	Membrane C terminus, α-helical core and collagenous sequence Collagen helix has 24 Gly-X-Y Y triplets Polar C terminus
Asymmetric acetyl cholinesterase protein		Binds to PG	Long collagenous tail
Pulmonary surfactant apoprotein	28–36 kDa	Binds phospholipids and surfactant. Important for normal lung function	24 Gly-X-Y repeats N-terminal cysteine 5 cysteines in the C terminus Interrupted central triple Gly-X-Y helix homologous to alveolar proteinosis protein

Basement-membrane-associated proteins (collagen types IV and VII and XVII). These collagens either are component basement-membrane proteins or are closely anatomically associated. They include collagen types IV, VII and XVII.

Other collagen-like molecules that are not ECM proteins [93–99]. As with various other proteins such as the immunoglobulin superfamily, nature often uses certain conserved protein motifs for a variety of unrelated functions in differing contexts. Shuffling, mixing and matching is the norm in protein biology and collagenous sequences are no exception. Thus, other triple-helical collagen proteins include C1q, asymmetrical acetylcholinesterase, surfactant apoprotein, conglutinin, mannose-binding protein and the macrophage scavenger receptor, which are good examples of this principle. Even though ECM collagens are defined by their capacity to form supramolecular aggregates, and to be part of ECM, this definition is not consistent at the protein/gene sequence level. These other triple-helical collagenous non-ECM analogues are, in some respects, more collagenous than the short-chain or basement-membrane ECM proteins described above, at least in the sense of infrequent or absent Gly-X-Y interruptions. Nor can they be separated on their membrane-binding properties, as only one non-collagenous and one collagenous membrane-bound sequence exists. Thus, macrophage scavenger protein types I and II and collagen type XVII possess membrane-spanning regions. These differences are probably examples of divergent rather than convergent evolution. Outlines of this diverse group of collagenous molecules are summarized in Table 3.8.

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Metabolism of collagen

Collagenases [1–7]

Collagen is relatively inert metabolically, and usually once laid down it persists for long periods [8]. However, certain tissues and some pathological states exhibit rapid turnover. Half of the collagenous content of the postpartum uterus is resorbed in 24 h [9] and high resorption also occurs from granuloma tissue [10]. In the skin of rodents, a fluctuation during the moult cycle is superimposed on the gradual increase with body growth; the concentration appears to fall sharply prior to and during the early phase of activity of the hair follicles [11]. The possible mechanisms of resorption are not the same for the different collagen types and are subject to specific tissue regulation [4].

Native fibrillar or soluble collagen resists non-specific proteolytic degradation, and is specifically degraded by collagenase at physiological pH, temperature and salt concentrations. The first enzymes that degrade triple-helical collagen at neutral pH were isolated from *Clostridium histolyticum* [12–15].

The first vertebrate collagenases were initially purified from tadpole tails. When explants of metamorphosing bullfrog tadpole tails were cultured upon reconstituted type I native fibrous collagen substrate, they spontaneously digested this substrate [16–18]. It was also possible to show that epidermis and not dermis produced the tadpole collagenase enzyme [16,18].

Later, by similar techniques, human skin cells were shown to produce collagenase [16,19]. Collagenase activity resides in the papillary dermis but not the lower dermis [19,20]. Furthermore, although collagenase is produced by the proliferating epidermis in wound healing, it is not produced in normal epidermis [21]. Collagenase is also produced by neutrophil granulocytes [22,23], activated macrophages [24] and by cultured skin fibroblasts [25].

Table 3.9 The classification of matrix metalloproteinase (MMP) subfamilies, their substrates, molecular weights and chromosomal locations.

Proteinase	Common name	Main substrate	Mol. wt. (kDa)	Chromosomal location
MMP-1	Collagenase-1 (also called fibroblast, interstitial and tissue collagenase)	Collagen	57, 52, 42	11q22.3
MMP-2	72 kDa gelatinase (also called type IV collagenase and gelatinase A)	Cartilage collagen	72	16q13
MMP-3	Procollagenase, stromelysin 1, transin 1, SL1, PTR1	Collagens I, II, III, IX, X	59, 57	11q22.3
MMP-7	Matrilysin, matrin, PUMP-1, -protease		28, 19	11q22.3
MMP-8	Collagenase-2 (neutrophil collagenase)		75, 58	11q22.3
MMP-9	92 kDa gelatinase Gelatinase B		92, 79, 76	20q11.2
MMP-10	SL-2; stromelysin 2	Fibronectin, laminin, nidogen	57, 47, 45	11q22.3
MMP-11	SL-3; stromelysin 3; ST3	Similar to SL1		22q11.2
MMP-12	Macrophage metalloelastase	Elastin	22	11q22.3
MMP-13	Collagenase 3	Collagen	60, 48	11q22.3
MMP-18	Xenopus collagenase 4			
MMP-20	RASL-1	Amelogenin		11q22.3
MMP-23	CA-MMP			
MMP-26	Matrilysin 2 (endometase)	50% identical to MMP-3 and -12	28, 19	11p15
MMP-28	Epilysin			
MT1-MMP	MMP-14 (membrane type 14)	Broad spectrum, including fibrin, fibronectin, tenascin, aggrecan	63, 60	14q11–12
MT2-MMP	MMP-15 (membrane type 15)		72	16q12.2
MT3-MMP	MMP-16 (membrane type 16)		64	8q2
MT4-MMP	MMP-17 (membrane type 17)	Proteolyses MMP-2 enriched in brain tumours	70	12q24.3
MT5-MMP	MMP-24			20q11
MT6-MMP	MMP-25 (leukolysin)	Catalytic domain is 60% identical to MMP-17, resembles MMP-3 and cleaves collagen IV	63	16p13.3

Since then, a very large family of vertebrate collagenases and their relatives has been purified, cloned and sequenced, and presently, in 2003, comprise nearly 20 family members of the so-called matrix metalloproteinase families (*MMPs*) and at least three tissue inhibitors of metalloproteinase (*TIMPs*) (Table 3.9 & Fig. 3.43) [26–28]. The various subtypes cleave not only collagens but also PGs and other ECM constituents, and are members of a larger superfamily of so-called *matrixins*, a diverse group with almost 30 family members active in ECM regulation, as well as in general processes such as inflammation, scarring and wound repair. Other recently discovered metalloproteinases, such as the ADAM-TS family (Fig. 3.44) [29], participate in disorders, such as non-allergic late-onset asthma, with chronic obstructive airways bronchoconstriction, caused by submucosal bronchiolar fibrosis and ECM proliferation. All of them are zinc (Zn^{2+}) binding endopeptidases that degrade certain ECM components, which have a crucial role in all remodelling processes, such as ovulation, pregnancy, embryogenesis, ageing, apoptosis, inflammation and angiogenesis. Yet other MMPs promote tumour metastasis, or affect bone resorption in periodontitis and osteoporosis, hasten the enlargement of arterial aneurysms, or promote fibrotic processes such as hepatic cirrhosis, pulmonary fibrosis, pulmonary emphysema, arthritis, left venticular hypertrophy, nephritis, scleroderma, keloids and post-burns scarring. The original nomenclature and classification was proposed by Nagase *et al*. [28]. Updated information of the entire family group is very easily obtained from OMIM (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM), which lists all the MMPs by subtype and McKusick number (see below). Functionally, it is convenient to subclassify MMPs into those which cleave collagens and those which digest other substances [26,27]. They form distictive subgroups: *collagenases* (primarily, native-collagen-cleaving), *gelatinases* (denatured-collagen cleaving), *stromelysins*, *matrilysins* and *membrane-bound* MMPs. All share common structural motifs, such as an N-terminal signal propeptide domain (which contains a PRCGVPD inhibitory sequence), a catalytic domain (which in the gelatinases contain three head-to-tail repeats homologous to fibronectin gelatin-binding sequences) followed by a flexible hinge region, with a C-terminal haemopexin discoid region (which in the membrane-bound MMPs has additional transmembrane and intracytoplasmic residues, although matrilysin has no haemopexin domain) (Fig. 3.43). Generally MMPs are secreted as inert zymogens,

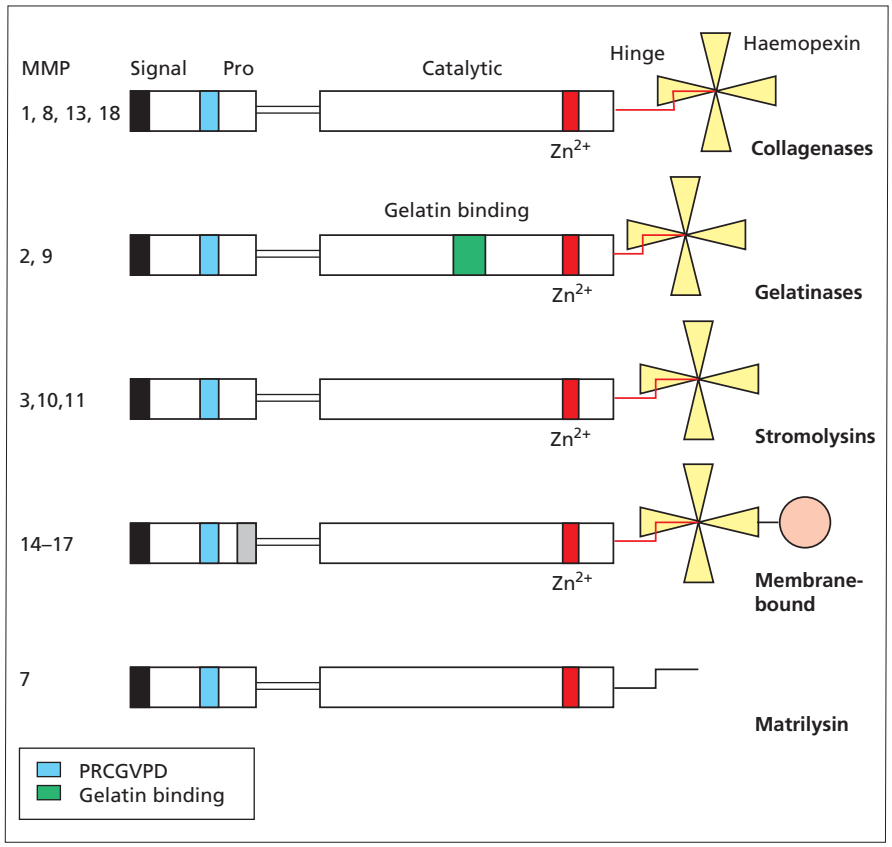

Fig. 3.43 Diagram of the various matrix metalloproteinase (MMP) subclasses. The various signal, propeptide, active catalytic hinge and haemopexin regions are illustrated. MMP-7 is notable for the absence of the haemopexin region, whilst MMPs 14–17 possess membrane-binding sequences N terminal to the haemopexin domain.

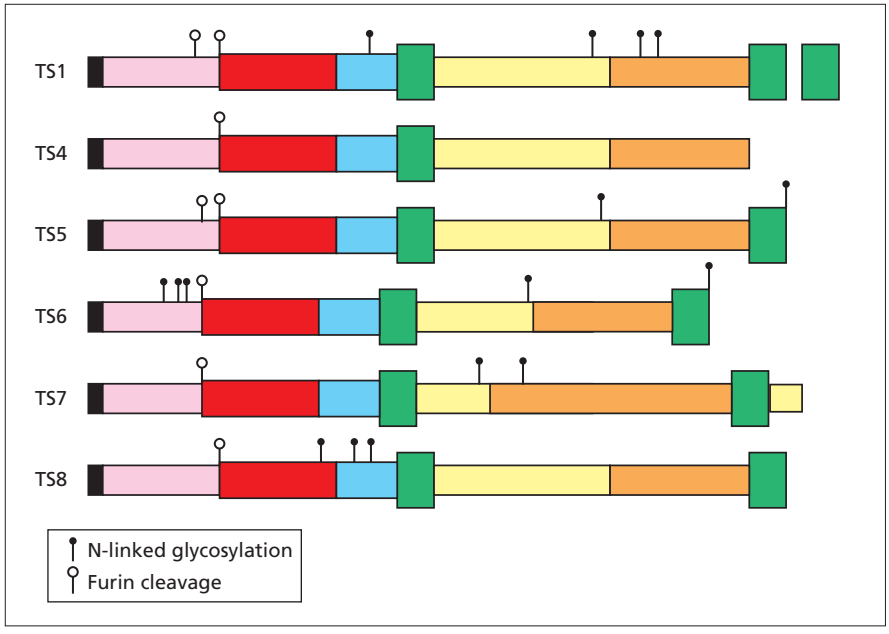

Fig. 3.44 Diagram of various ADAMS-TS families. The catalytic domains analagous to those of the matrix metalloproteinase (MMP) family are shown in red, whilst other important sequences include the thrombospondin type 1 repeat sequences (green), disintegrin-like domains (blue) and cysteine-rich domains (yellow). The signal peptides are shown in black, whilst the propeptides are coloured pink and the spacer domains orange.

which are activated by the piecemeal removal of the propeptide, initiated by disruption of the cysteine–Zn^{2+} switch.

Matrix metalloproteinase nomenclature includes types 1–3, 7–13, 16, 20, 23, 26, 28 and membrane-bound types MT-MMP 1–6. There are no MMP types 4–6, 14, 15, 17–19, 21, 22, 24, 25 or 27.

No less than eight MMPs (types 1, 3, 7, 8, 10, 12, 13 and 20) cluster on chromosome 11q22.3, whilst the others are distributed at 8q13-21, 12q14, 14q11-12, 16q12.2, 20q12-13 and 22q11.2. The intron-exon structure is generally similar, but the two gelatinases contain three extra exons coding for the gelatin-binding repeats. Generally

the catalytic domain is contained in the 3′ end of exon 2 and exons 3 and 4, with the inactive pro-domains coded by the 3′ end of exon 1 and the majority of exon 2. Protein sizes range from 19/28 kDa in the active/inactive forms of matrilysin to 66/72 kDa in the equivalent forms of 72 kDa gelatinase A (MMP-2) and 86/92 kDa in its gelatinase B (MMP-9) relative.

Group 1: native collagen-cleaving MMPs (types 1 [collagenase 1], 8 [collagenase 2] and 13 [collagenase 3])

These cleave native triple-helical fibrillar collagen types I–III. This splits specifically at a glycine–isoleucine–leucine sequence into three-quarter N-terminal and quarter C-terminal fragments, providing a useful mapping strategy in OI, certain chondrodysplasias and EDS type IV. This initial cleavage allows subsequent helical denaturation, followed by generalized digestion by other MMPs. MMP-1 also digests collagen types VII, VIII and X, as well as aggrecan, gelatin and MMP-2 and -9. MMP-3 has similar collagen targets, but also digests elastin, fibronectin, laminin, MMP-7, -8 and -13, as well as aggrecan and gelatin. MMP-8 is very similar to MMP-3, except that it digests no other MMPs, whilst MMP-13 digests fibrillar collagen types I–III, as well as IV, aggrecan and gelatin. Catalytic functions vary between the C- and N-terminal ends (where the proline-rich hinge and haemopexin sequences induce triple-helical cleavage). The conserved histidine residues 50 amino acids from the C terminus, which attach Zn^{2+} at the binding domain, impose substrate specificity, etc. Such relationships of the collagenases can be deduced by grafting this domain into a non-collagen digesting MMP, such as stromelysin or MMP-3 [26,27].

Group 2: gelatinases A and B, denatured-collagen cleaving MMP (types 2 and 9)

These MMPs possess fibronectin type II repeats, which mediate the binding and degradation of denatured collagens and also form enzyme–inhibitor complexes with the inhibitors TIMP-1–3. MMP-2 is smaller than MMP-9 by 20 kDa, but both enzymes are very similarly organized to the collagenases, except for the three extra exons that code for the fibronectin II sequences. The collagen binding sequences are quite distinct from the group 1 MMPs, where they reside at the C termini. Gelatinase A also binds to αv/β3 integrin, whilst gelatinase B binds CD44 at the cell surface. Both also jointly bind TIMP-2 and MT1-MMP as a trimeric complex at the cell surface. Both the self-processing of gelatinase A and the catalytic activation of gelatinase B, by collagenase 1, MMP-3 (stromelysin 1), MMP-7 (matrilysin 1) and trypsin occur *in vivo*, although other enzymes artefactually do so *in vitro*.

Group 3: stromelysins types 1, 2 and 3 (MMP types 3, 10 and 11)

These MMPs have typical propeptide, catalytic and haemopexin domains. The three stromelysins are all *matrixins*, which are a larger group of zincin metalloproteinases and all are activated by cysteine switching of the pro-sequence at the N termini. Thus both stromelysin 1 and 2 have 57 kDa unglycosylated (80%) and 59 kDa glycosylated-aspargine precursors, which are processed to 46–48 kDa and truncated C-terminal 28 kDa subsets. Both also have distinctive insertions of nine amino acids into the hinge regions, which join the catalytic and haemopexin regions. Enzyme activity is promoted by a conserved N-terminal phenylalanine reside. Substrates for the larger 46–48 kDa form include native collagen types III, IV, X and XI, denatured-collagen types I and III–V, and also telopeptides of collagen types I and II. The smaller 28 kDa variants degrade fibronectin, aggrecan and MMP-7, -8 and -13. Other substrates include most serpins, such as α2 macroglobulin, but not α1 antitrypsin, entactin, SPARC and E-cadherin. Stromelysin 3 (MMP-11) is only weakly proteolytic and, in contrast to types 1 and 2 which are extracellularly activated, is intracellularly triggered, in the Golgi. It has diverged substantially from stromelysins 1 and 2, which are almost 80% sequence identical and nearly 90% sequence similar to each other, showing instead only half the identity (40%) and less than 60% similarity. It participates in the metastasis of breast maligancies but is not found in benign breast fibroadenomas. It cleaves gelatin, fibrillar collagens, aggrecan, fibronectin and laminin.

Group 4: matrilysin types 1 and 2 (MMP types 7 and 26)

Like the stromelysins, matrilysin 1 (or PUMP) is a *matrixin* and an ECM-digesting metalloproteinase. It is distinguished from groups 1–3 by lacking both a hinge region and the C-terminal haemopexin domain, and is therefore only 28 kDa (zymogen) and 19 kDa in the active form. It is also confined to glandular epithelium and macrophages, but it was first purified from involuting mammalian uterus. Despite its smallness, it has a wide range of substrates, such as collagen types I, III and V, fibronectin and certain PGs, many of which overlap with those of stromelysin 1. It also occurs in maligant tumour cells, rather than stromal matrix, as is the case with certain other MMPs, such as the stromelysins. Rather surprisingly, it has also been implicated in the macrophage-mediated inflammation and degradation of atheromatous plaques, but might well play a role in macrophage-mediated processes such as pulmonary fibrosis, wound repair or inflammation. Matrilysin 2 (MMP-26) is of similar size and structure, and occurs in placenta, uterus and uterine endometrial tumours. It degrades collagen type IV, gelatin and fibronectin.

Group 5: membrane-type metalloproteinases types 14, 15, 16, 17, 24 and 25 (MT1–6 MMPs)

These are unique amongst the MMP family by being membrane-bound. They are also intracellulary activated (like stromelysin 3) by a propeptide furin convertase, for which they have recognition sequences. They may also be extracellularly activated. MT4-MMP and MT6-MMP do not possess transmembrane sequences but instead are chemically membrane-linked, by a glycosyl–phosphatidyl–sugar bond. The C-termini of all MT molecules possess short intracytoplasmic tails at the C termini. Some of the enzymes form tertiary complexes of MT-MMP, TIMP-2 and proMMP-2 at the cell surface, enabling tumour cells to penetrate vascular and other basement membranes during metastasis. Whilst MT6-MMP is confined to leukocytes, the others are produced by many other cell lineages and tissues, such as liver, heart, skeletal muscle (MT1-MMP), brain, placenta, lung and heart (MT3-MMP), brain, ovary, testis and colon (MT4-MMP). They range from 57 to 72 kDa as zymogens, and from 53 to 62 kDa as activated enzymes. They also exhibit a range of targets, including denatured collagen types I–III, aggrecan, elastin, fibronectin, gelatin and MMP-2 and -13.

Group 6: miscellaneous MMP proteins

This group consists of all other MMPs not already discussed in groups 1–5. These include human macrophage metalloelastase (MMP-12), xenopus collagenase (MMP-18), RASL 1–1 (MMP-19), enamelysin (MMP-20), CA-MMP (MMP-23) and epilysin (MMP-28).

Active macrophage MMP is only 22 kDa, although the inactivated zymogen at 54 kDa is more conventionally sized. In addition to elastin, it also cleaves fibronectin, gelatin and laminin, fibrinogen and α1 antitrypsin. It also promotes macrophage migration into ECM and participates in anerurysm formation and emphysema. Enamelysin also participates in tooth formation, and enamel production in particular.

Summary of MMP's role in disease

Matrix metalloproteinases clearly have a variety of modulating functions in numerous roles of human development. These include *embryogenesis and development* where matrix remodelling is very important, *acute wound healing*, where MMP-1, -3 and -10 are expressed by keratinocytes, *cancer and metastasis*, where MMP-7 promotes tumour invasion in lung, bladder pancreatic and colonic tumours, whilst tumour angiogenesis is promoted by MMP-1, -2, -9 and MT1-MMP. Cutaneous cancers such as basal cell (BCC) and squamous cell (SCC) cancers show increases of MMP-1, -2, -9 and -11 (BCC) or MMP-1 and 10 (SCC). Similarly, some melanomas show increased MMP-2 and decreased TIMP-2. Bullous pemphigoid eosinophils have increased MMP-9, which is also increased in granulomatous disorders such as sarcoidosis and granulomatous necrobiosis. Photodamage by sun exposure increases MMP-1, -3, -7, -9 and -12, whereas in contact hypersensitivity, MMP-2 and -3 are necessary for activation and MMP-9 for resolution of the reaction.

Other non-MMP metalloproteinases

The so-called ADAM-TS family is a very diverse group of metalloproteinases, which contain a disintegrin, a metalloproteinase and thrombospondin. Their properties have only recently been discovered but all possess at least one, and as many as three, thrombospondin type 1 repeats, together with N-terminal metalloproteinase domains adjoining disintegrin sequences, a thrombospondin repeat, followed by a cysteine-rich and then a so-called space sequence. To date, five different family members have been identified, including TS1, TS4 and TS5–TS8 subtypes. As with other MMPs, functions in repair, remodelling and regeneration, arthritis, inflammation and carcinogenesis are likely.

Collagenase and other MMP inhibitors

This is a family of metalloproteinase tissue inhibitors which specifically reversibly inhibit MMPs. Rather like insulin, and perhaps fibrillin, they form very specific intrachain disulphide bonds, which in their case produces a six-loop structure (from 12 completely conserved cysteines) but two-domain secondary structure. Equally importantly, reduction of the disulphide bridges abolishes MMP inhibition. To date, four TIMPs have been cloned and sequenced, of which TIMP-1 diverges considerably from the other three, which are most similar to one another [30,31]. The role of TIMP inhibition of MMP is mediated predominantly through the three N-terminal cysteines, whilst the remaining inhibition is mediated through the interaction between the C termini of the MMP molecule, with the three C-terminal cysteines of the given TIMP. The N terminus is contained within the large loop 1. Matrix metalloproteinase inhibition is mediated through both the N- and C-terminal loops; the latter occupies the MMP active cleft. Other important properties include extracellular secretion, binding to either inactive or active MMPs, and also their tissue specificity.

TIMP-1 and -2 react with the gelatinases (MMP-2 and MMP-9), whilst TIMP-3 is more widespread, occurring in developing embryos, placental tissues, cartilage, muscle and epithelia [31], as well as Bruch's membrane of the retina. The *TIMP-1–3* genes are, respectively, located at Xp11.23–3, 17q25 and 22q12.1–13.2.

TIMP-3 mutations have been described in Sorsby's fundus dystrophy [32], in which a central maculopathy is

caused by lipid accumulation in Bruch's membrane, which is thickened and degenerate. This change should be contrasted with PXE, in which there is elastic degeneration of Bruch's membrane, also with a progressive and debilitating macular degeneration. The Sorsby mutations of TIMP-3 are significant in mutating certain C-terminal cysteines, consequently inhibiting TIMP-3 activity.

Measuring collagen degradation or synthesis

Formerly, extracellular collagen degradation was estimated from urinary hydroxyproline/proline ratios [6]. Although most hydroxyproline derives from the degradation of incorporated fibrillar collagen, an unknown fraction arises from the degradation of newly synthesized but unincorporated amino acid. Urinary hydroxyproline should now be abandoned as a marker of collagen breakdown. Rather, urinary collagen cross-linked peptides provide an accurate estimate of degradation, both of skin, arteries and bone [33,34]. In brief, aldol condensations between adjacent lysines and or hydroxylysines produce a variety of cross-linked peptides, such as allysine/hydroxyallysine between adjacent collagen α chains, so stabilizing the various fibrillar components. Specific lysine–hydroxylsines are cross-linked within the non-helical telopeptide sequences (N terminal) of the collagen triple helix. Reducible cross-links decrease with age, producing instead mainly hydroxylysine aldehydes and trivalent 3-hydroxy pyridinium. In practice, pyrodinoline derivatives such as hydroxylysyl pyrodinoline (HP) or lysyl pyrodinoline (LP) can be directly estimated from urine samples. For example, in EDS type VIA (lysyl hydroxylase deficiency) there is a decreased HP : LP ratio in urinary breakdown products. Hydroxylysyl pyrodinoline derivatives are especially typical of bone, cartilage and dentine, chromatographic quantification of which provides a reasonable estimate of bone breakdown.

Similarly, based upon detailed knowledge of procollagen conversion into collagen, by the removal of the N- and C-terminal propeptides, there are now reliable methods that estimate collagen synthesis in bone, skin, liver and cartilage [34]. Their terminology is as follows:

1 the N- and C-terminal propeptides of type I procollagen are, respectively, named PIN and PIC propeptides;

2 the N- and C-terminal propeptides of type III procollagen are, respectively, named PIIIN and PIIIC propeptides;

3 the equivalent N- and C-terminal propeptides of types II, V and XI collagen would be, respectively, PIIN, PIIC, PVN, PVC, PXIN and PXIC propeptides, although none of these are routinely used in clinical practice.

In brief, the propeptides are stable in serum samples and can also be estimated by a variety of commercial and privately available fluorimetric, HP/LC, or immunoassays. Because of their N-terminal cysteines, PIIIN propeptides are more stable than their PIN equivalents. All of them are cleared by the hepatic reticuloendothelial system and can alter either physiologically or pathologically. A good example of physiological alteration is in puberty, in which the adolescent growth spurt increases the normal PI to PIII ratios from 1 : 1 to nearer 3 : 1, most probably from the disparate increase produced by adolescent bone growth. A very well-known dermatological example is the use of PIIIN levels, rather than liver biopsy, as an idex of hepatic fibrosis induced by methotrexate, in the long-term treatment of chronic psoriasis.

Theoretically, disorders such as OI and EDS types VIIA, B, C and IV, in all of which there are either quantitative deficiencies of either type I collagen (OI) or type III collagen (EDS type IV), or a failure to remove the N-terminal propeptides (EDS types VIIA, B and C), may be usefully screened by these means. Their use in osteoporosis also remains to be explored, as does their role in keloid scarring, scleroderma, pulmonary fibrosis, Paget's disease of bone, myeloma, hyperparathyroidism and degenerative joint disease.

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Changes with ageing [1]

Collagen changes both qualitatively and quantitatively throughout life. The qualitative changes are reflected in decreasing solubility and an alteration in various physical properties [2,3]. For example, in strips of dermis, the temperature at which rapid shrinkage begins and tension develops in isometric contraction both rise with age [4]. Collagen becomes more stable with age.

As observations on animals have been made mainly during their growth phase and those on humans mainly during adulthood and senescence, there has been some confusion about how the concentration of collagen changes. As might be expected, because the skin increases in area and thickness as an animal grows, the collagen content of a complete skin and the amount of collagen per unit area are correlated with body weight [5]. In addition, there is ample evidence, for example from rats, rabbits and cattle, that the actual concentration of total collagen per unit weight of skin increases from birth to adulthood, when it remains stationary. It seems likely that in humans, also, the concentration of insoluble collagen in the skin increases from infant to adult [6]. From early adulthood onwards, however, there appears to be a gradual decrease in the absolute amount of collagen per unit area of skin, and this correlates with the clinical appearance of the skin during ageing. It occurs more rapidly in women than in men [7].

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Fibroblasts [1–3]

Fibroblasts are the most numerous of the cells found in loose connective tissue. The term *fibroblast* should, historically, designate a cell at an early stage of differentiation and *fibrocyte* one that is fully differentiated [4], but in practice many researchers use fibroblast for an actively secreting cell and fibrocyte for an inactive one [2]. Fibroblasts are developed from the mesenchyme, which also gives rise to chondroblasts and osteoblasts. It has been suggested that they may also originate from other mesenchymal elements, such as the vascular endothelium or by transformation of macrophages, and it is possible that differentiated fibroblasts can themselves transform into osteoblasts. Electron microscopy reveals that the fibroblast of developing (as distinct from mature) connective tissue has an abundant cytoplasm, with a well-developed endoplasmic reticulum and prominent ribosomes attached to the membrane surfaces (Fig. 3.45). The Golgi membranes are clearly seen. Such features are characteristic of cells that are engaged in active synthesis and secretion. In studies of the fate of tritiated proline by autoradiography [5], it has been shown that material is first synthesized in the cisternae of the endoplasmic reticulum, and subsequently transferred to the Golgi region, after which it passes out of the fibroblast. Although, historically, the issue has been debated, it now seems generally accepted that fibroblasts are responsible for the manufacture of all the dermal connective tissue elements or their precursors.

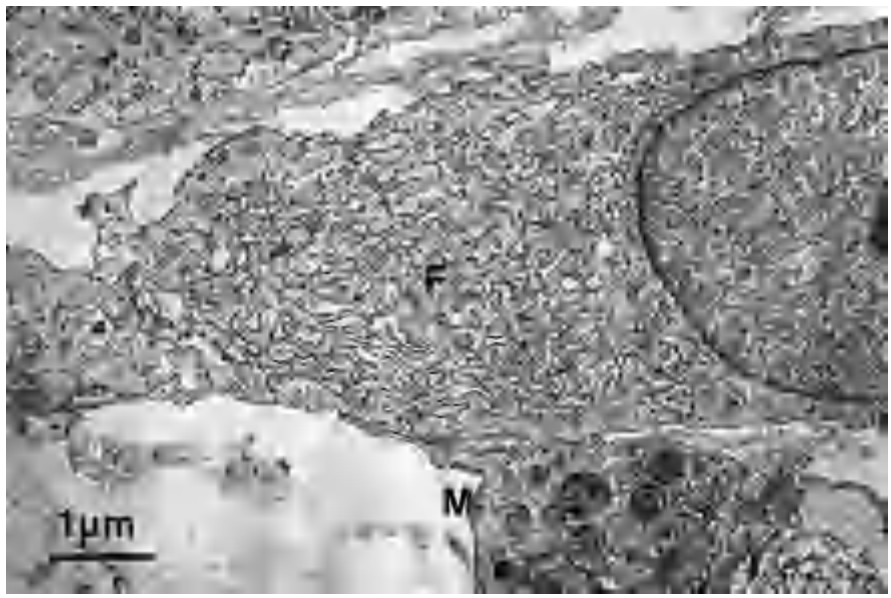

Fig. 3.45 Electron micrograph of an activated dermal fibroblast (F) in a healing wound. Note the prominent rough endoplasmic reticulum in the cytoplasm of this cell. There is an adjacent macrophage (M) with characteristic phagolysosomes, some of which contain ingested melanosomes.

Most researchers have been in agreement with Gersh and Catchpole [6] that fibroblasts are the source of the ground substance, notwithstanding the view of Asboe-Hansen [7] that the mast cell was implicated, on the grounds that it was the only connective tissue cell shown to contain acid mucopolysaccharide. There is evidence, however, from autoradiographic studies that ^{35}S is incorporated into sulphated mucopolysaccharides in the Golgi complex of fibroblasts, and that such substances are secreted [1,3]. The sulphated mucopolysaccharide produced by mast cells, however, is stored within the cell and is mainly heparin.

Human fibroblasts can be shown to produce collagen *in vitro* and there is no doubt that they are the source of the precursor of collagen [8,9]. While the source of elastin is less obvious, it has been clear that elastic tissue never occurs except in the presence of collagen, and in electron micrographs is seen always in the vicinity of fibroblasts [10]. It is now established that tropoelastin, containing a leader sequence of about 25 residues, which is ultimately lost, is synthesized on the rough endoplasmic reticulum in a similar fashion to collagen [11]. The existence of specific elastoblasts has been proposed but never demonstrated [10].

These considerations leave open the question of whether all fibroblasts are identical. Differences between papillary and reticular fibroblasts have been proposed [12], and fibroblasts from human gingiva have been shown to consist of two subpopulations differing in their response to prostaglandin E_2 [13].

Variants from scar tissue have been described. Knapp *et al*. [14] found two types from normal skin and mature scars, one small and spindle shaped (S cell) and one larger, flatter and amoeboid in appearance (A cell). In fibroblast populations derived from keloids, A cells were predominant, and keloid outgrowths often produced a third type, designated the K cell. Other researchers [15] were unable to detect differences in appearance or size distribution between fibroblasts cultured from normal skin and from keloids, although there were differences in response to hydrocortisone [16]. It has been suggested that keloid fibroblasts lack the normal ability to respond to the stresses imposed by wounding, and thus produce badly aligned collagen fibrils [17].

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Langerhans' cells [1] (see also Chapter 10)

Dendritic cells of a form similar to melanocytes, but free from pigment and dopa negative, were first described by Langerhans, who demonstrated their existence in human epidermis by staining with gold chloride [2]. Dendritic cells that are dopa negative but ATPase positive have been found in human epidermis, pilary canals and the ORS of hair follicles [3], as well as in the epidermis of rhesus monkeys [4], guinea pigs [5] and hairless mice [6]. They have also, in the guinea pig, been demonstrated in the oesophageal mucosa and transitional epithelium of the urinary tract [7,8]. Whether all such cells are Langerhans' cells has been questioned, since ATPase activity may not be specific but shared by melanocytes. Thus on ultrastructural evidence, human epidermis appears to have three types of dendritic cells, namely melanocytes, Langerhans' cells and non-specific cells [9] and, similarly, it has been shown that such non-specific dendritic cells are widely distributed throughout the oral epithelium of the rhesus monkey, whereas Langerhans' cells are confined to keratinized epithelia such as the tongue [10]. The pattern of Langerhans' cell migration in skin has been recorded using transmission and scanning electron microscopy [11]; the regulation of migration has also been assessed [12].

Under the electron microscope, Langerhans' cells (Fig. 3.46) share with melanocytes a lobulated nucleus, a relatively clear cytoplasm and well-developed endoplasmic reticulum, Golgi complex and lysosomes. They differ in lacking melanosomes or premelanosomes, and in possessing a characteristic granule which is rod- or racquet-shaped [13–18]. These 'Birbeck' granules have been shown to represent subdomains of the endosomal recycling compartment and form at sites where the protein Langerin accumulates [19].

Using ultrastructural evidence of the presence of the characteristic granules, Langerhans' cells have been identified in the ORS of the human hair and the secretory duct of the sebaceous gland [20] and in the epithelium of the crypts of the human tonsil [21]. The discovery of similar granules in cells in the dermis in histiocytosis X resulted in the renaming of this condition as Langerhans' cell histiocytosis [22–24] (Chapter 52). Langerhans' cells are of mesenchymal origin and originate from bone marrow, as proved by the demonstration that, after destruction of the haemo- and leukopoietic systems of mice by X-rays, injection of bone marrow from F_1 hybrids could re-establish a population of Langerhans' cells [25].

The role of the Langerhans' cell in cutaneous immune reactions as a specialized antigen-presenting cell is considered in Chapter 10.

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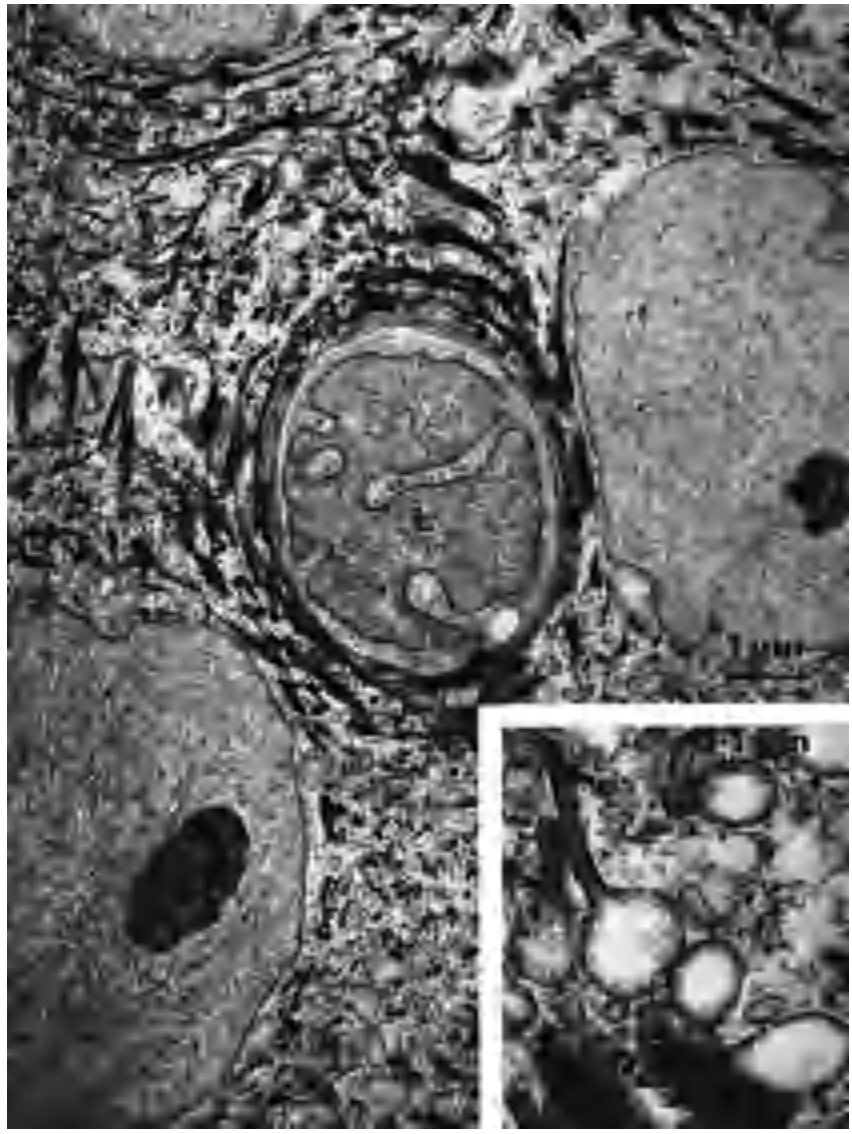


Fig. 3.46 Langerhans' cell (L) with its characteristically indented nucleus, situated between cells of the stratum spinosum of the human epidermis. Inset: Langerhans' cell granules showing racquet-shaped profiles. (Courtesy of Professor A.S. Breathnach, St John's Institute of Dermatology, London, UK.)

Mast cells [1–4]

Mast cells were first described by Ehrlich in 1877 [5] who distinguished them from other connective tissue cells by their ability to stain metachromatically with basic aniline dyes. Mast cells are larger than eosinophils and basophils. They occur in most tissues, but are particularly numerous in skin, bronchus, nasal mucosa and gut.

Mast cells are heterogeneous and fall into two main types—connective tissue and mucosal—which can be differentiated by their morphology, tissue distribution, histochemical characteristics and responses to degranulating agents [6–8]. Solubility of the granules in formaldehyde and content of neutral proteinase, namely tryptase and chymase (chymotryptic proteinase) will vary according to the type of cell [6,7]. For example, human foreskin mast cells contain both proteinases, whereas mast cells in intestinal mucosa and lung contain mainly tryptase [1,6,7].

Human lung mast cells vary in size, numbers of IgE receptors, histamine content and capacity to generate prostaglandin D_2 [7]. Two types of human nasal mast cells may be differentiated histochemically, which resemble either rodent connective tissue or mucosal types of mast cells [9].

There is increasing evidence in support of a haematopoietic stem cell origin for murine mast cells [10], and it appears that human peripheral blood mononuclear phagocytes can give rise to mast cells or mast cell-like cells *in vitro* [11–14]. Human tissue mast cells, including those in skin, have been found to express panhaematopoietic markers, but not antigens typical of either myeloid or lymphoid cells [15]. Further support for mast cell being the progeny of haematopoietic stem cells have been determined from xenotransplantation studies. Specifically, haematopoietic stem cells can proliferate and differentiate into mature mast cells in mouse skin 3 months after

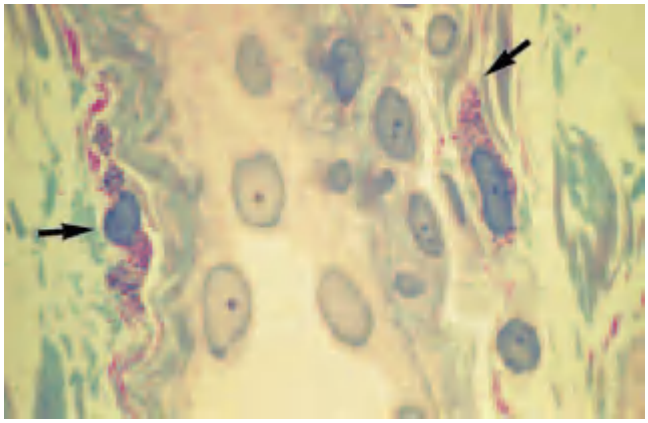


Fig. 3.47 Photomicrograph of semi-thin Epon section showing two spindle-shaped mast cells (arrowed) close to a dermal blood vessel. Methylene blue and basic fuchsin. × 400.

transplantation of human cord blood $CD34^+$ cells [16]. Cytokines such as stem cell factor and IL-6 also promote mast cell proliferation [16].

Mast cells are distributed close to blood vessels, nerves and appendages, and are most numerous in the subpapillary dermis, in the region of the superficial dermal vascular plexus [12,17]. There are about 7000 mast cells per cubic millimetre in normal skin [18]. One study has shown little age-related or regional variation in numbers of mast cells [18], whereas another found considerable differences, with four times as many cells in the facial or genital skin compared with that of the leg or back [19].

Mast cells are present in greatly increased numbers in urticaria pigmentosa, and are also numerous in diverse inflammatory disorders, wound healing and a variety of tumours including neurofibroma and BCC.

Dermal mast cells are ovoid or spindle-shaped, mononuclear or occasionally binuclear, and only rarely show signs of mitosis in normal skin [4]. Their major distinguishing feature is the presence of numerous, round cytoplasmic granules, which stain orthochromatically with alcian blue and safranin or metachromatically with toluidine blue or Giemsa. The cells have an affinity for avidin which has proved useful in examining cells by fluorescence [14] or by staining with an avidin–biotin–peroxidase complex [20,21]. Mast cells are also particularly well demonstrated in 1-µm-thick sections of plastic-embedded tissue stained with Giemsa or with basic fuchsin and methylene blue [12,22] (Fig. 3.47). Carnoy's fixative has been found to be superior to formal-saline for the fixation of human, dermal mast cells [23]. Bouin's fixative and lead subacetate solution are also recommended [4].

At the fine structural level (Fig. 3.48), mast cells are found to possess IFs containing vimentin, in addition to microtubules, Golgi apparatus, mitochondria and lipid bodies [12]. The plasma membrane extends outward to form numerous processes appearing like microvilli in ultrathin sections (Fig. 3.48), but which have been shown by scanning electron microscopy to be fine ridges or folds [24]. The cytoplasmic granules are about 0.6 µm in diameter and surrounded by a perigranular membrane. The ultrastructure of human mast cell granules (Figs 3.48 & 3.49) is highly distinctive and probably species specific. The main component is the lamellae, which are arranged in whorls or scrolls (Fig. 3.49a) and exhibit a banding or cross-striation of approximately 6-nm periodicity. A highly ordered 'paracrystalline' lattice may also occur (Fig. 3.49b). Other granules appear to have largely amorphous or particulate contents. The appearance of mast cell

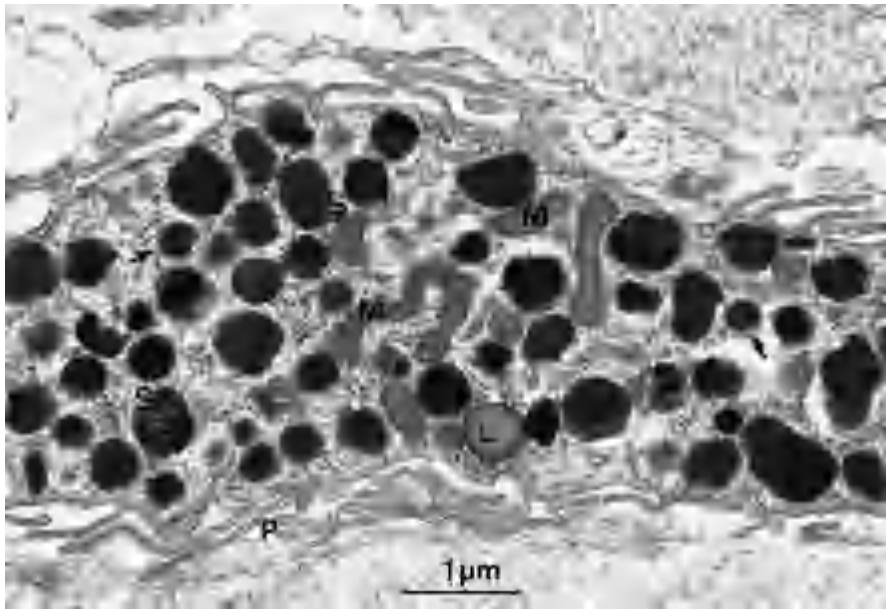
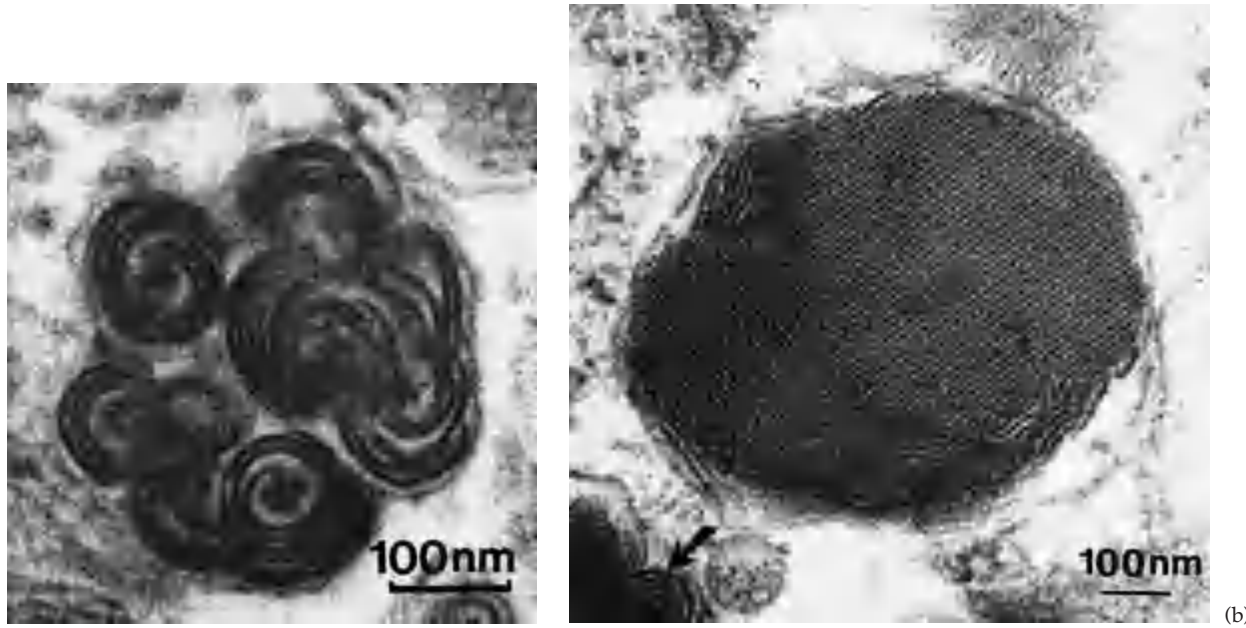


Fig. 3.48 Part of a human skin mast cell on electron microscopy showing characteristic granules, some with scroll-like profiles (S). Arrows indicate perigranular membrane. L, lipid droplet; M, mitochondria; P, peripheral processes.



(a) (b)

Fig. 3.49 High-magnification views of dermal mast cell granules. (a) Typical scroll-like configuration of lamellae, some of which show a cross-banding of regular periodicity. (b) The substructure of this granule is a highly organized lattice. Note the scroll (arrow) in adjacent granule, which is largely excluded from this view.

granules may vary in the same cell or among cells in the same tissues. By contrast, mast cell granules in rats and other species may have a uniformly amorphous composition (Fig. 3.50).

Mast cell granules with a predominantly lattice-type of substructure have been shown, by the use of immunoelectron microscopy, to contain both tryptase and chymase; whereas those with a scroll-like configuration stain only for tryptase [25]. On this basis, it has been suggested that tryptase-containing (mucosal) *T mast cells* and those containing both tryptase and chymotryptase (connective tissue), *TC mast cells*, can be distinguished by their ultrastructure [25].

During the release of mast cell-derived mediators such as histamine, mast cells undergo sequential alterations involving both granules and perigranular membranes [26]. It is not certain whether human dermal mast cells *in vivo* exhibit the same sequence of changes identified in the mouse peritoneal mast cell model, which has been studied extensively *in vitro* [26], but striking intracellular

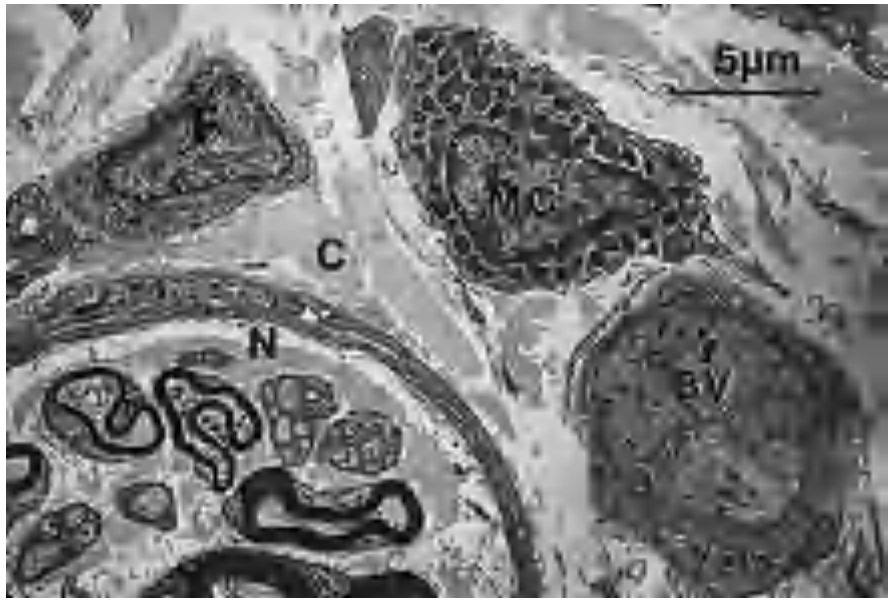


Fig. 3.50 Electron micrograph of a rodent dermal mast cell (MC) close to blood vessel (BV), nerve (N) and fibroblast (F). Note the homogeneous, non-lamellar substructure of mast cell granules. C, collagen.

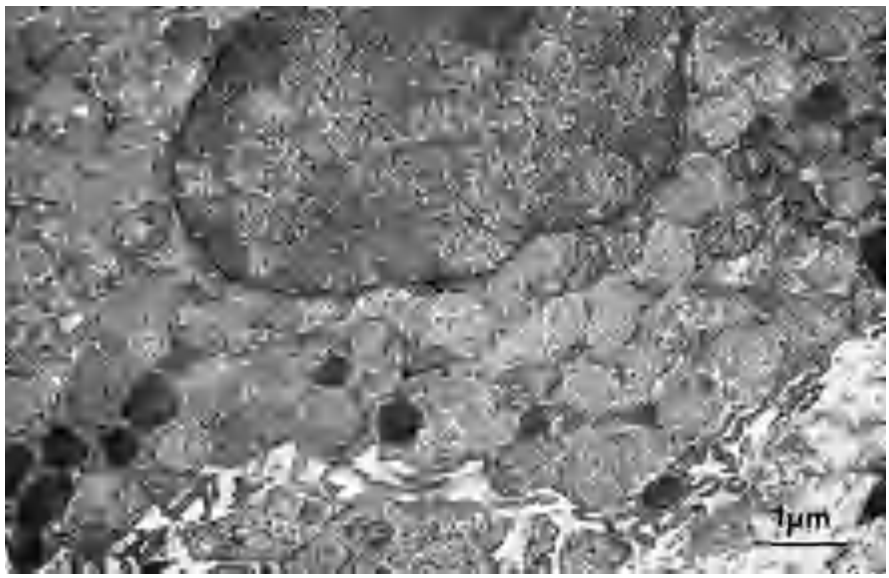


Fig. 3.51 Human dermal mast cell undergoing degranulation. Note that most granules are swollen and have lost their characteristic substructure and density. Note also that granule changes have occurred within the confines of the cell—and very few granules have been discharged into the extracellular space.

modifications can be seen, including swelling and loss in density of granules, and disruption of perigranular membranes and spaces (Fig. 3.51).

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Basophils [1,2]

Human basophils are small, round cells with multilobed nuclei. Like mast cells, they contain prominent cytoplasmic granules, which stain metachromatically with basic aniline dyes [2]. At the ultrastructural level (Fig. 3.52), mature granules usually contain dense particles; however, multiple membrane arrays may also occur [3]. A smaller granule type with a homogeneous content has been reported [3]. Rarely, basophils contain Charcot–Leyden crystals, within either the granules or the cytoplasm [3].

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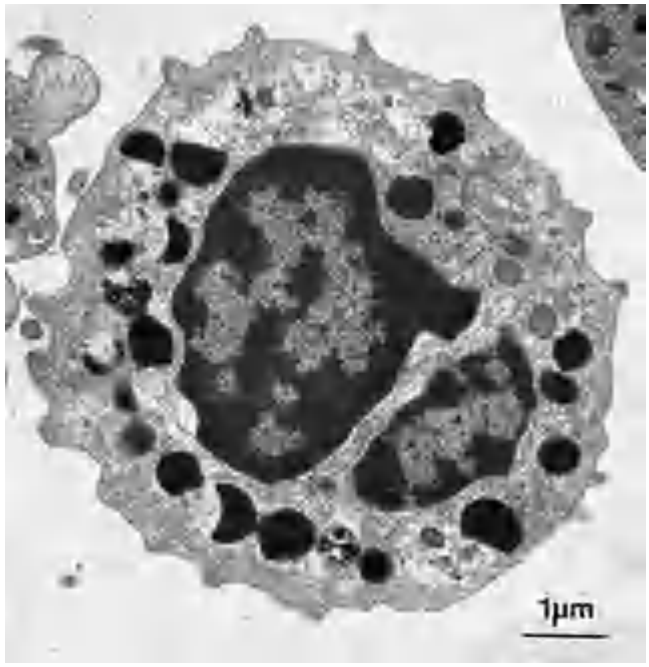

Fig. 3.52 Electron micrograph of a human basophil from peripheral blood. In contrast to a dermal mast cell, this cell is smaller, rounder, and contains a multilobed nucleus. The granules are round or semilunar in shape with a particulate or coarsely reticulate substructure.

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Nerves and sense organs

The skin may be innervated with around 1 million afferent nerve fibres [1–7]. Most terminate in the face and extremities; relatively few supply the back. The cutaneous nerves contain axons with cell bodies in the dorsal root ganglia. Their diameters range from 0.2 to 20.0 µm. The main nerve trunks entering the subdermal fatty tissue each divide into smaller bundles. Groups of myelinated fibres fan out in a horizontal plane to form a branching network from which fibres ascend, usually accompanying blood vessels, to form a web of interlacing nerves in the superficial dermis. Throughout their course the axons are enveloped in Schwann cells (Fig. 3.53) and as they run peripherally an increasing number lack myelin sheaths. Most end in the dermis; some penetrate the basement membrane, but do not travel far into the epidermis.

Sensory endings are of two main kinds: corpuscular, which embrace non-nervous elements; and 'free', which do not [2,3,5–9]. Corpuscular endings can, in turn, be subdivided into encapsulated receptors, of which a range occurs in the dermis, and non-encapsulated, exemplified by Merkel's 'touch spot', which is epidermal.

The most striking of the encapsulated receptors [9] is the *Pacinian corpuscle* [9–14]. It is an ovoid structure about 1 mm in length, which is lamellated in cross-section like an onion (Fig. 3.54), and is innervated by a myelinated sensory axon, which loses its sheath as it traverses the core. The *Golgi–Mazzoni* corpuscle found in the subcutaneous tissue of the human finger is similarly laminate but of much simpler organization. Another classical receptor is the *Krause end bulb*, an encapsulated swelling on myelinated fibres situated in the superficial layers of the dermis (Fig. 3.55). *Meissner corpuscles* [3,6,9,15] are characteristic of the papillary ridges of glabrous skin in primates. They have a thick, lamellated capsule, 20–40 µm in diameter and up to 150 µm long.

Of somewhat different structure are the terminals first described by *Ruffini* [16] in human digits, in which several expanded endings branch from a single, myelinated afferent fibre. The endings are directly related to collagen fibrils [3,17].

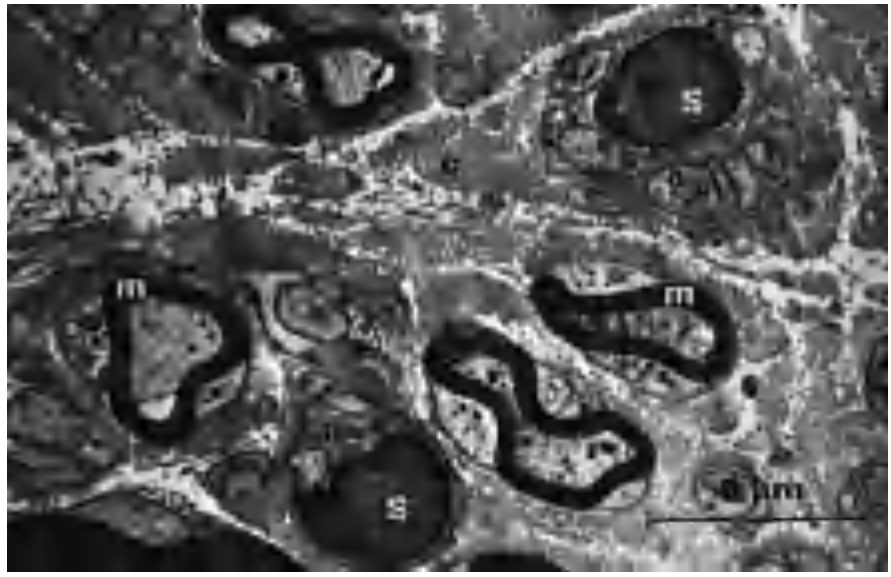

Fig. 3.53 Transverse section of sural nerve of adult human female, showing myelinated fibres (m) and two Schwann cells (S), each associated with a group of unmyelinated axons (a), all set in a bed of endoneural collagen (c). (Courtesy of Professor A.S. Breathnach, St John's Institute of Dermatology, London, UK.)

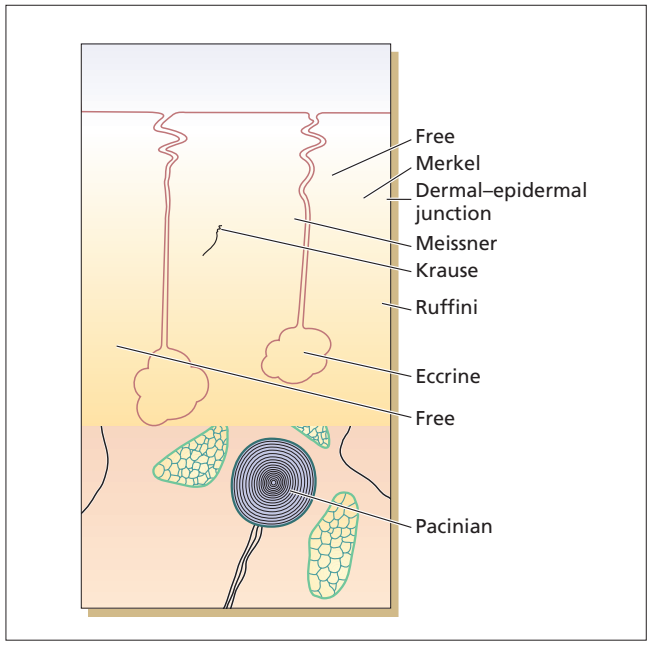

Fig. 3.54 Diagrammatic section showing nerve endings in glabrous skin of fingertip. (From Miller *et al*. [12].)

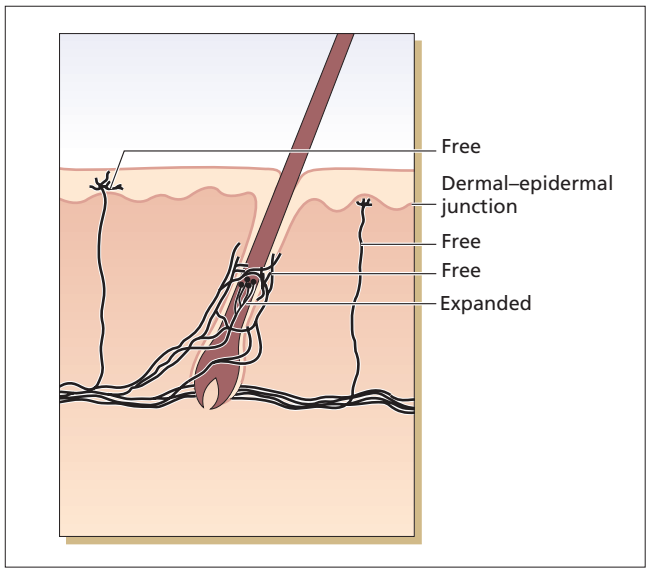

Fig. 3.55 Diagrammatic section showing nerve endings in hairy skin of the human extremities. Free nerve endings are seen in the shallow dermal papillae or between the epidermal cells. The hair follicle is innervated by free endings of the circular fibres and expanded tips of the palisade fibres. (From Miller *et al*. [12].)

'Free nerve-endings', which appear to be derived from non-myelinated fibres, occur in the superficial dermis and in the overlying epidermis [9,12,18,19]. Those in the dermis are arranged in a tuft-like manner and have thus been designated *penicillate nerve endings* [18].

Hair follicles have nerve terminals of varying degrees of complexity (Fig. 3.56). The fine nerve filaments run parallel to, and encircle, the hair follicles, forming a palisade. Each group of axons is surrounded by Schwann cells, and the side away from the glassy membrane appears to be free, lacking any specialized contacts with collagenous fibres [12,21,22]. Sinus hairs, for example the vibrissae of cats and rats, have a much more complex nerve supply, with corpuscular as well as non-corpuscular receptor elements [20,23].

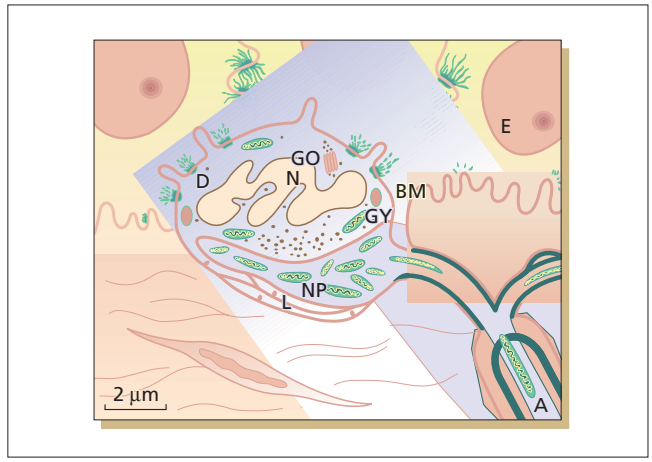

Fig. 3.56 Diagram showing the structure of a tactile cell of a cat and its associated nerve plate. A, myelinated axon; BM, basement membrane; D, desmosome; E, epithelial cell nucleus; GO, Golgi apparatus; GY, glycogen; L, lamellae underlying the nerve plate; N, multilobulated nucleus; NP, nerve plate. Note the granular vesicles in tactile cell near the junction with nerve plate. (From Iggo and Muir [20].)

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Merkel cells

Merkel [1] first gave the name *tastzellen* to certain cells that he found near the base of the rete-peg in the snout skin of the mole. As there were intraepidermal neurites with expanded tips (Merkel discs) adjacent to them, he believed them to be transducers of physical stimuli. Merkel cells [2] have been described in the snout of the oppossum [3], in the fetal sheep [4], in the cat [5] and in human [6–10].

In the hairy skin of the cat [5,11], each touch spot, which is a dome-shaped elevation of the epidermis 0.1–0.4 mm in diameter, is underlaid by a battery of Merkel cells borne on branches of a myelinated axon. Each Merkel cell (Fig. 3.57) has a lobulated nucleus and characteristic granules in the cytoplasm. It is distally embedded in the basal layer of epidermal cells, with which it has desmosomal connections. A nerve plate underlies it [12]. Similar ultrastructural features are seen in Merkel cells of human skin [6–10,13,14], where the spherical granules appear to be membrane limited with a dense central core (Fig. 3.57). Cold receptors identified in the cat's nose [5] appear to be an epithelial cell–neurite complex, analogous to but less distinctive than the Merkel cell system.

There are two hypotheses about the embryonic source of Merkel cells [15]. One postulates that they are derived from the neural crest and migrate into the epidermis along the peripheral nerves [16]. The other assumes that they arise *in situ* and are derived from epithelial cells. Observations on fetal skin in the rat [17] and human [18], on human fetal skin transplanted onto nude mice [14] and on autografts of skin derived from cultured keratinocytes [19] all suggest that Merkel cells originate in the epidermis. These findings would also indicate that the dermal Merkel cells in fetal skin migrate down from the epidermis instead of moving in the opposite direction [20].

Fig. 3.57 Merkel cell in human epidermis. The dermis (d) with collagen fibres is seen in the lower part of the picture. b, basement membrane; de, desmosomes making connections with adjacent basal keratinocyte; g, spherical granules (see inset); n, nucleus of Merkel cell; t, tonofilaments. (Courtesy of Professor A.S. Breathnach, St John's Institute of Dermatology, London, UK.)

Merkel cells contain IFs composed of low-molecular-weight keratin [20,21] rather than neurofilament protein [22], and form desmosomes with surrounding keratinocytes [23].

Human Merkel cells express immunoreactivity for various neuropeptides including *Met*-enkephalin [24] and vasoactive intestinal polypeptide [25], in addition to neurone-specific enolase [26] and synaptophysin-like [27] and pancreastatin-like [28] material. They also contain chromogranin A [29].

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Blood vessels [1–3]

The arteries entering the skin form a deep plexus—the 'fascial' network. From this region vessels rise to the border between the subcutaneous adipose tissue and the corium, and these form a 'cutaneous' network. This gives branches to the various cutaneous appendages, and provides ascending arterioles to supply a subpapillary plexus, which itself forms capillary loops in the papillary layer between the ridges of the dermal–epidermal frontier. From these capillaries the blood is drained by venules which descend to intermediate plexuses [1,2,4–7]. The vasculature is more elaborate than would be necessary solely for nutrition of the skin and temperature control is an important function. It is believed that the amount of blood flowing through the superficial layers of the dermis can be controlled by arteriovenous anastomoses, which act as shunts to short circuit the flow. However, although anastomoses occur in some acral sites, such as the fingertips [3], they have not been found to be regular components of the microvasculature elsewhere [6]. Recently it has been shown that peripheral nerves provide a template that determines the organotypic pattern of blood vessel branching and arterial differentiation: this process is controlled by local secretion of vascular endothelial growth factor (VEGF) [7].

The dermal microvasculature can be divided into a series of adjoining arterial and venous segments. Attempts have been made to delineate these segments using measurements of their diameter [6,8] (Fig. 3.58), but owing to the considerable overlap among these measurements and variations caused by differences in methods of fixation [6], other criteria, such as the nature of endothelium (including size and shape of the cells), and of the periendothelial investment, such as the appearance of the basement membrane, are also necessary to make these distinctions.

The innermost component of the microvessels, in common with other blood vessels, is the endothelium, consisting of adjoining endothelial cells that surround the lumen. Arterioles, except the smallest terminal arterioles, are characterized by a subendothelial layer of elastic tissue. Venules, on the other hand, generally do not have elastic tissue in their walls (Fig. 3.59).

The endothelium of capillaries and of the smallest arterioles and venules is surrounded by pericytes, which appear to share certain characteristics with both endothelial and smooth muscle cells. Capillaries contain a single, discontinuous layer of pericytes, whereas venules may include more than one pericyte layer in their periendothelial investment. Smooth muscle cells are found chiefly in the walls of ascending arterioles, but also within the arterioles of the superficial and deep plexuses and in collecting venules. Smooth muscle cells and pericytes are surrounded by basement membrane, which also encompasses the outer (abluminal) surface of endothelial cells. *Veil cells* are long thin cells, with an attenuated cytoplasm, that more closely resemble fibroblasts than pericytes. They do not have a basement-membrane investment and are situated outside the vessel wall.

At the ultrastructural level (Fig. 3.60), endothelial cells possess many of the common cytoplasmic organelles including Golgi apparatus, rough and smooth endoplasmic reticulum, mitochondria and lysosomes. Micropinocytotic vesicles and pits, of the coated and smooth types, are also evident. Intermediate filaments containing vimentin are present and have been reported to be more abundant on the venous than the arterial side [6]. Dense bodies associated with actin-like filaments of 5–6 nm diameter are found in the endothelial cells of the larger arterioles [5,6], and may have a role in endothelial contraction, a putative function that remains highly contentious.

Weibel–Palade bodies (Figs 3.61 & 3.62) are endothelium-specific inclusions [9,10] that occur more frequently on the

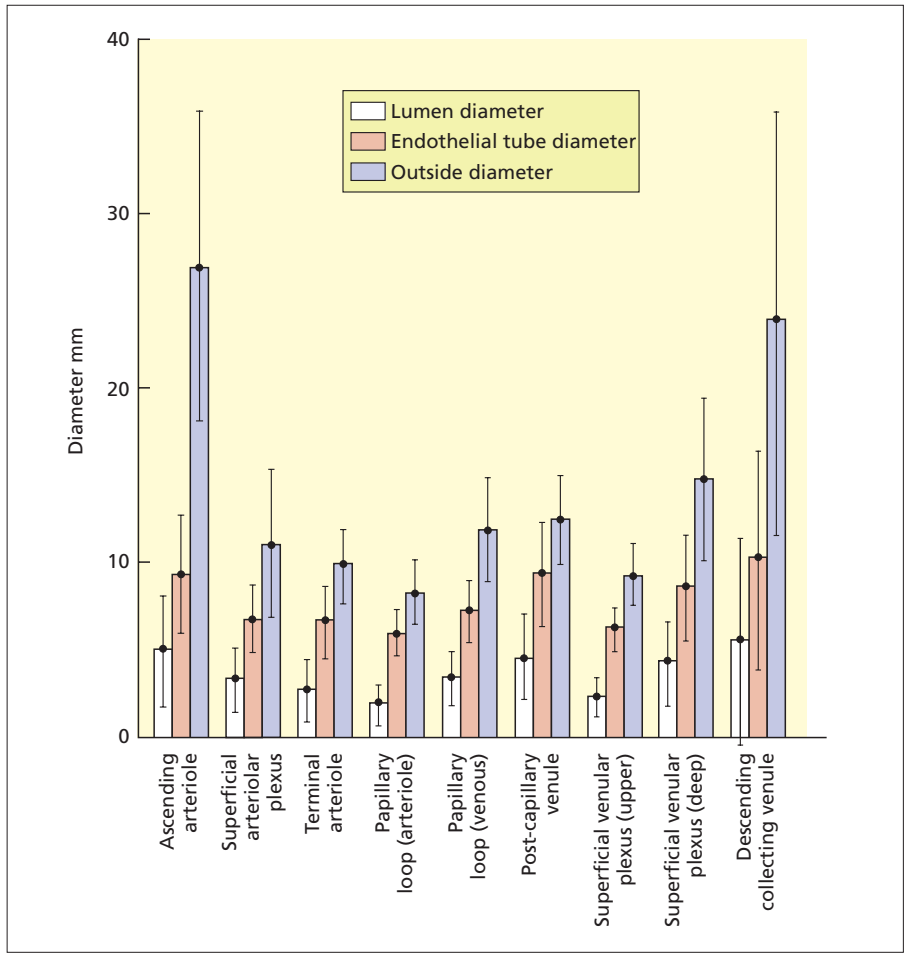

Fig. 3.58 Diagram showing diameters of nine different segments of the dermal vasculature. Bars represent the standard deviation. Note the considerable overlap between adjacent vascular segments. (From Higgins and Eady [6].)

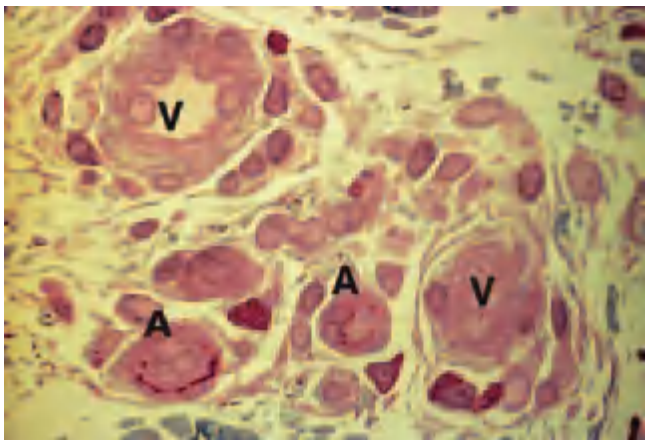

Fig. 3.59 Photomicrograph of 1-μm Epon section of microvessels in reticular dermis. Arterioles (A) can be distinguished from venules (V) by the presence of an elastic lamina, which stains red. Surrounding mast cells can be distinguished by their prominent red/blue cytoplasmic granules. Basic fuchsin and methylene blue. × 400.

venous side of the microvasculature [6]. They are not found in dermal lymphatics but have been reported in larger lymph vessels [11]. Weibel–Palade bodies contain factor VIII-related antigen, von Willebrand factor [10] and GMP-140, a protein that was first described in platelet α-granules [12].

Closed fenestrae (or fenestrations), which allow rapid passage of water and solutes between the circulation and extravascular space, have been observed in capillaries, mainly in the vicinity of epidermal appendages [13] but also in papillary dermis, facing the epithelium [6,14].

A major feature distinguishing arterial from venous microvessels is the ultrastructural appearance of the basement membrane. Venules and venous capillaries have a multilaminated basement membrane, whereas arterioles possess a more homogeneous matrix, lacking the multiple, distinct, electron-dense strands [6,7] (Figs 3.59, 3.60 & 3.62). Vascular basement membrane contains laminin, type IV collagen, fibronectin and heparan sulphate PG [15]. It does not contain BP230 or BP180, type VII collagen or laminin 5, each of which is a component of epidermal basement membrane.

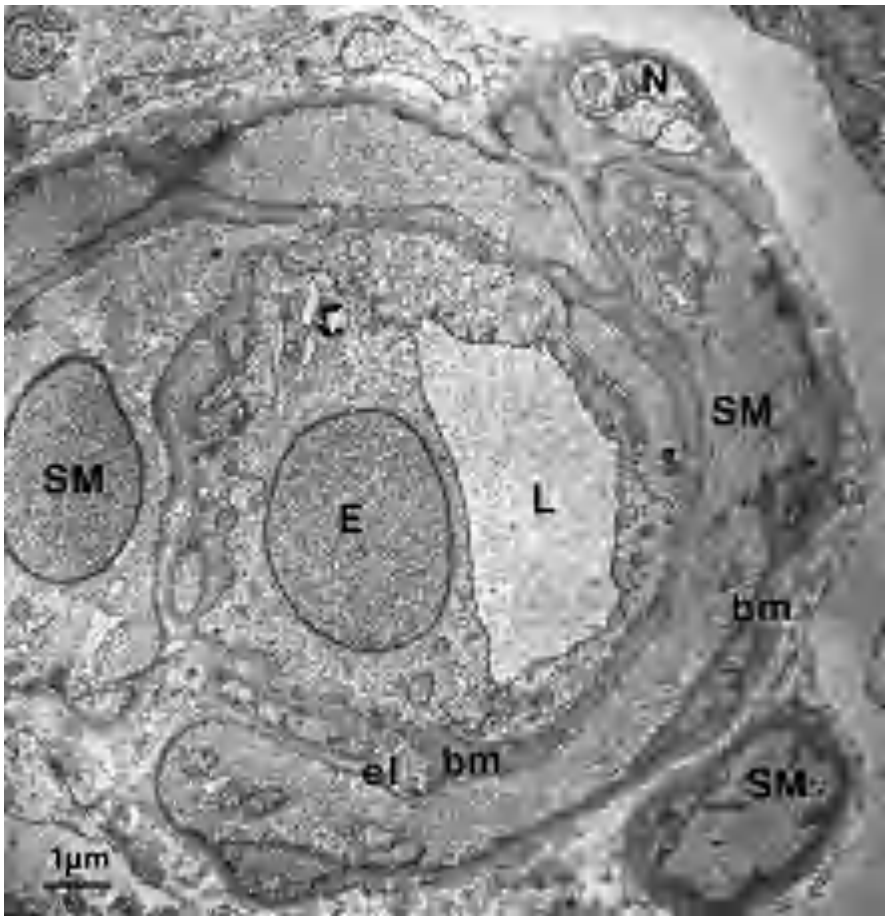

Fig. 3.60 Electron micrograph of a cross-section through a small arteriole. Note the relatively smooth surface of endothelial cells (E) around lumen (L) and the investment of smooth muscle (SM) with associated nerve (N); There is a small amount of elastic tissue (el) among the endothelial basement membrane (bm) which, unlike venular basement membrane, has a uniform density.

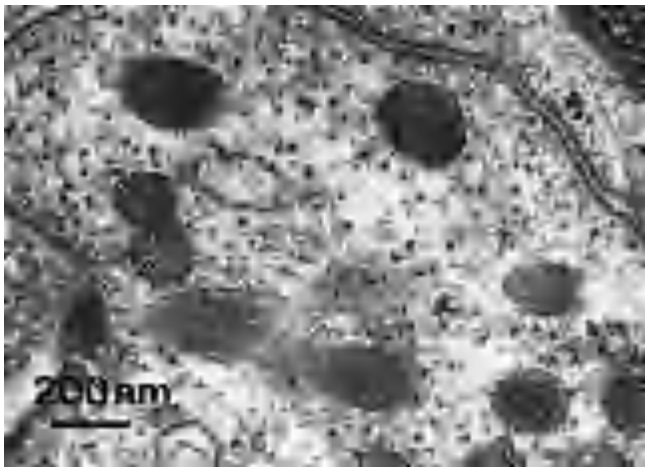

Fig. 3.61 High-magnification view of Weibel–Palade bodies illustrating tubular profiles in cross-section.

A number of endothelium-specific antigens have recently been recognized, and may have a special value in studies on pathology [16,17]. Endothelial cells are the major source of angiotensin-converting enzyme [18] as well as various cytokines and adhesion molecules [16].

The microvasculature is a rich source of enzymes [19] that may be involved in intracellular processes such as endocytosis and vesicular transport. Acid phosphatase has been localized to lysosome-like structures in the endothelium [19], and alkaline phosphatase reactivity has been used extensively to map the distribution and arborization of the dermal vascular network [20] (Fig. 3.63).

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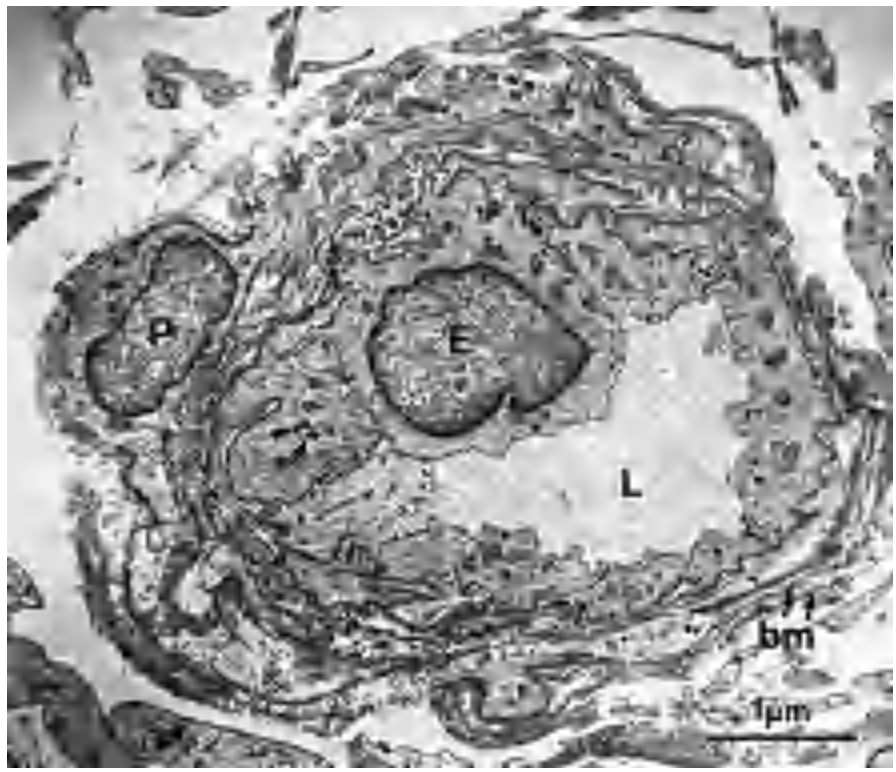

Fig. 3.62 Electron micrograph of a transverse section through a venule. The surface of the endothelial cells (E) facing the lumen (L) is more convoluted than its arteriolar counterpart (see Fig. 3.60). The periendothelial investment consists of pericytes (P) (not smooth muscle) and the basement membrane (bm) contains multiple dense strands. Arrowheads indicate Weibel–Palade bodies.

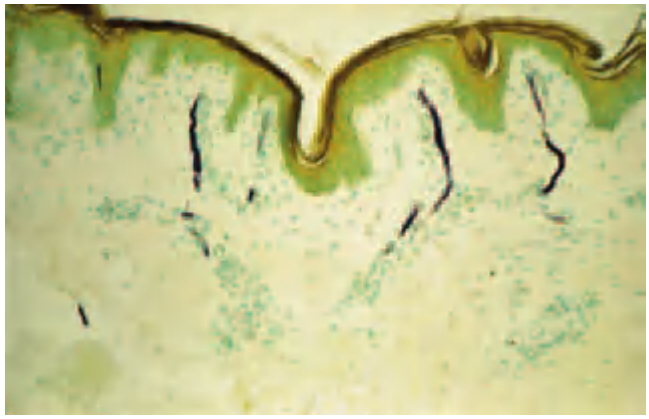

Fig. 3.63 Alkaline phosphatase reaction illustrates arterial microvessels in superficial dermis. × 160.

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Lymphatic system

The lymphatic system (Chapter 51) serves to transport particulate and liquid materials, such as leaked protein, from the extravascular compartment of the dermis. The interconnecting lymphatic spaces arise from terminal bulbs in the papillary layer and ultimately form the system, which drains into the lymph nodes. The vessels have a broad lumen surrounded by a single endothelial layer (Fig. 3.64), which is discontinuous in the terminal components, and rests on an often discontinuous basal lamina [1,2].

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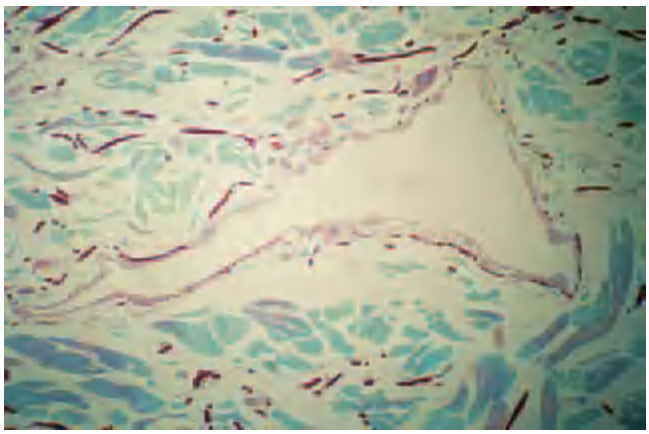

Fig. 3.64 Photomicrograph of a 1-μm plastic section including a dermal lymphatic. Note the attenuated endothelium and the lack of periendothelial cellular investment. The endothelium is surrounded by an elastic tissue mantle (stained purple). Dermal collagen is stained blue. Basic fuchsin and methylene blue. × 400.

Regional variation

The regional diversity of the skin has been graphically described by Kligman [1], who contrasted the tropical rain forests of the axillae with the oily tundras of the face and the comparative deserts of the trunk. Even within each such broad and grossly different zones there are often highly significant structural or functional variations. With modern investigative techniques, we are becoming increasingly aware that no area of skin is identical in all respects with any other, except the corresponding area on the other side of the body. These regional variations are of great practical importance, for they necessarily influence the microclimate on the skin surface, and hence the bacterial flora, and they play a large part in determining the distribution of dermatoses, whether of internal or external origin.

The failure to appreciate the extent and significance of regional variation has been responsible for many false generalizations. Bacteriological, histological or biochemical findings obtained in one region have been assumed to be applicable to the skin as a whole. Histopathological reports based on knowledge of the normal in one region only have frequently been misleading.

A detailed account of the known regional variations would fill a substantial textbook. Here we can consider only certain selected aspects.

1 The thickness of the epidermis. There is marked regional variation in the thickness of the epidermis, in its microanatomy and in its function. The thick epidermis with a compact, thick, horny layer on the palms, soles and other friction surfaces, contrasts with the thin epidermis of the flexures. The thickness of the horny layer influences the resistance of the skin to physical and chemical trauma.

2 The distribution of appendages [2]. The density of hair follicles (Chapter 63) varies greatly and, although the number of follicles remains unchanged until middle life, the changing balance between vellus and terminal hair throughout life frequently alters the surface microclimate of each area.

The distribution of sebaceous glands (Chapter 43), actively functioning in the newborn and from the approach of puberty onwards, modifies the composition of the surface lipid film. The distribution of eccrine and apocrine glands is described in Chapter 45.

3 The distribution of melanocytes (Chapter 38).

4 Variation in the structure of the dermal–epidermal junction [3,4]. The sculpturing of the undersurface of the epidermis shows many totally distinct patterns in different regions of the body. The pattern is modified by the number and type of epidermal appendages, but is determined largely by the mechanical stresses to which each region is subjected.

5 The structure of the dermis. The dermis varies in thickness and in structure according to the functional requirements of each region. The arrangement and size of the elastic fibres have been investigated [5]. Large elastic fibres are especially numerous in the perineal region and around the anus: there are virtually none in the scrotum.

6 Blood supply [6]. Variations in the cutaneous blood supply are considered in Chapter 50. Microangiographic studies [7] have shown strikingly different patterns in regions of distensible skin such as the eyelids in comparison with more rigid areas such as the fingertips.

7 Histamine content [8]. The histamine content of the skin is highest in the region of the eyelids and upper lip and lowest on the chest and abdomen.

8 Percutaneous absorption [9]. Regional differences in percutaneous absorption have not been thoroughly studied. The thickness of the horny layer and its structure are only two of many factors determining the efficacy of the barrier function. The size and distribution of hair follicles obviously influences the capacity for transfollicular absorption.

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Chapter 4

Functions of the Skin

C.B. Archer

Introduction

The skin is arguably the largest immunologically active organ in the body, and its relative accessibility for basic scientific research has allowed much progress in our understanding of its multiplicity of functions. The most obvious functions of the skin are to provide a protective physical barrier between the body and the environment, preventing the inward and outward passage of water and electrolytes, reducing penetration by destructive chemicals, arresting the penetration of microorganisms, and absorbing radiation from the sun. The skin is important in the regulation of body temperature and is designed, to an extent, to respond to mechanical forces; the epidermis has a degree of mechanical strength to withstand damage and the ability to repair itself if damaged, and the dermis provides elasticity in response to mechanical insults.

The immunological functions of the skin depend both on cells in the epidermis and on dermal cellular constituents. Antimicrobial peptides (AMPs) are a diverse group of proteins that are involved as a first line of immune defence by many living things, including plants, insects, bacteria and vertebrates [1,2]. In human skin, AMPs provide a chemical barrier to potentially pathogenic microorganisms. The skin also contains sensory and autonomic nerves and several types of sensory receptors, which detect the incoming stimuli of touch, vibration, pressure, change in temperature (warmth and cold), pain (including heat pain) and itch. As in other animals, human skin has a role in sociosexual communication.

The aim of this chapter is to consider the functions of the skin in relation to its structure. It is important to understand physiological functions of the skin, so that one can plan a logical approach to the management of skin diseases. For example, if a patient has extensive areas of denuded skin, as seen following severe burns or in toxic epidermal necrolysis, the skin is unable to play its usual part in the maintenance of fluid balance and temperature regulation, a clinical situation referred to as 'skin failure' [3]. In addition, a knowledge of the skin as a barrier is important from the point of view of the delivery of topical treatments for skin diseases, and ceramide-dominant barrier-repair lipids have been reported to improve atopic dermatitis [4]. The contribution of bioengineering to present knowledge is also discussed.

It is beyond the scope of this chapter to provide a detailed account of skin biochemistry, and some biochemical functions of the skin are discussed in chapters referring to specific skin diseases. For example, androgen biochemistry is discussed in relation to disorders of the sebaceous glands in Chapter 43, altered cyclic nucleotide metabolism in atopic dermatitis [5] in Chapter 18, and phosphoinositide cell-regulatory abnormalities in psoriasis [6] in Chapter 35. Under the influence of sunlight, the skin is the site of vitamin D synthesis. In addition to its effects on calcium and bone metabolism, vitamin D_3 has antiproliferative and immunomodulatory effects, both of which are likely to be relevant to the treatment of psoriasis with vitamin D analogues (see Chapter 35).

Nails and hair are discussed elsewhere (see Chapters 62 and 63, respectively). Briefly, the scalp hair has a role in heat regulation and in display. Nails are mainly protective, aid in performing delicate tasks and are of cosmetic importance, a more noticeable feature when the nails are either absent or disfigured.

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Barrier functions

The epidermis and stratum corneum as a physical barrier

The skin acts as a two-way barrier to prevent the inward or outward passage of water and electrolytes. The physical barrier is largely situated in the epidermis, isolated epidermis being as impermeable as whole skin, whereas once the epidermis is removed the residual dermis is almost completely permeable. The epidermal barrier is localized to the stratum corneum.

On routine histology, the stratum corneum shows a basket-weave structure, and early investigators therefore believed it to be porous, and considered the barrier must lie below it [1]. In 1953, Blank [2] found that the water permeability of excised full-thickness skin remained unchanged by successive stripping with adhesive tape until the lowest part of the stratum corneum was removed, and proposed that the barrier lay within a thin layer of the innermost region. Subsequently, these observations were considered to be consistent with the belief that there is a uniformly good diffusion barrier throughout all or most of the horny layer [3–5].

The barrier depends on both the cornified material of the keratinocytes and the intercellular material, particularly lipids, regional differences in permeability being related to lipid content and not to thickness of the stratum corneum. A two-compartment model of the stratum corneum as a barrier is currently accepted, in which protein-rich cells, the corneocytes, are embedded within a continuous lipid-rich matrix.

Within the keratinocytes are synthesized both the fibrous proteins of keratin and a histidine-rich protein known as keratohyalin or filaggrin [6,7]. Around each corneocyte is an envelope, formed by cross-linking of the precursors involucrin and keratohyalin, which forms an insoluble exoskeleton and acts as a rigid scaffold for the internal keratin filaments [8,9]. There is evidence that lipids are chemically bound to its surface [10].

The intercellular cement is the product of ovoid organelles, 0.2–0.3 μm in diameter, known as membrane-coating granules, Odland bodies or lamellar bodies [11]. They become identifiable in cells of the spinous layer, and migrate to the cell periphery and fuse with the plasma membrane in the granular layer. They then discharge their contents into the intercellular spaces, which expand to form 10–40% of the total volume of the tissue.

The lamellar bodies originally contain neutral sugars linked to lipids and proteins, hydrolytic enzymes and free sterols, but the composition of the secretion changes greatly as they migrate outwards. Phospholipids, present in the stratum basale, diminish in the stratum spinosum, and virtually disappear at the level of the stratum corneum. However, neutral lipids and sphingolipids, in particular ceramides, are increased in the stratum corneum [12–17]. Cholesterol sulphate increases from the spinous to the granular layer, but is decreased in the stratum corneum.

In parallel with these biochemical events, changes can be observed in the ultrastructure of the intercellular material (Fig. 4.1) [18]. Within the granules, bilayers become arranged to form discs, which represent flattened unilamellar liposomes. The formation of such flattened liposomes has been demonstrated *in vitro* by exposing a mixture of ceramides, cholesterol, palmitic acid and cholesterol sulphate to a hypertonic medium [19,20]. After extrusion into the intercellular space, the discs become arranged parallel to the cell membranes and then fuse to form uninterrupted sheets [21].

In consequence of their origin by fusion of flattened vesicles, the intercellular lamellae of the stratum corneum consist of two lipid bilayers in close apposition [22]. The stratum compactum has been considered to form the principal diffusion barrier. It has also been proposed that in the stratum dysjunctum, the vesicular bodies maintain the patency of the intercellular space, and thus facilitate the absorption of applied substances by a form of shunt mechanism, as well as functioning as a reservoir. Vickers [23] first showed that the horny layer can retain topically applied corticosteroids, and such reservoir effects were later confirmed for hydrocortisone [24] and established for hexachlorophene [25].

In atopic dermatitis, the xerosis and permeability barrier abnormality might have a role in driving disease activity [26]. Both involved and clinically uninvolved skin in atopic dermatitis have impaired barrier function [27], which correlates with a reduction in the stratum corneum ceramide fraction [28]. Emollients do not usually correct the underlying stratum corneum lipid abnormality, but preliminary studies have shown that ceramide-dominant barrier-repair lipids improve atopic dermatitis in children [29].

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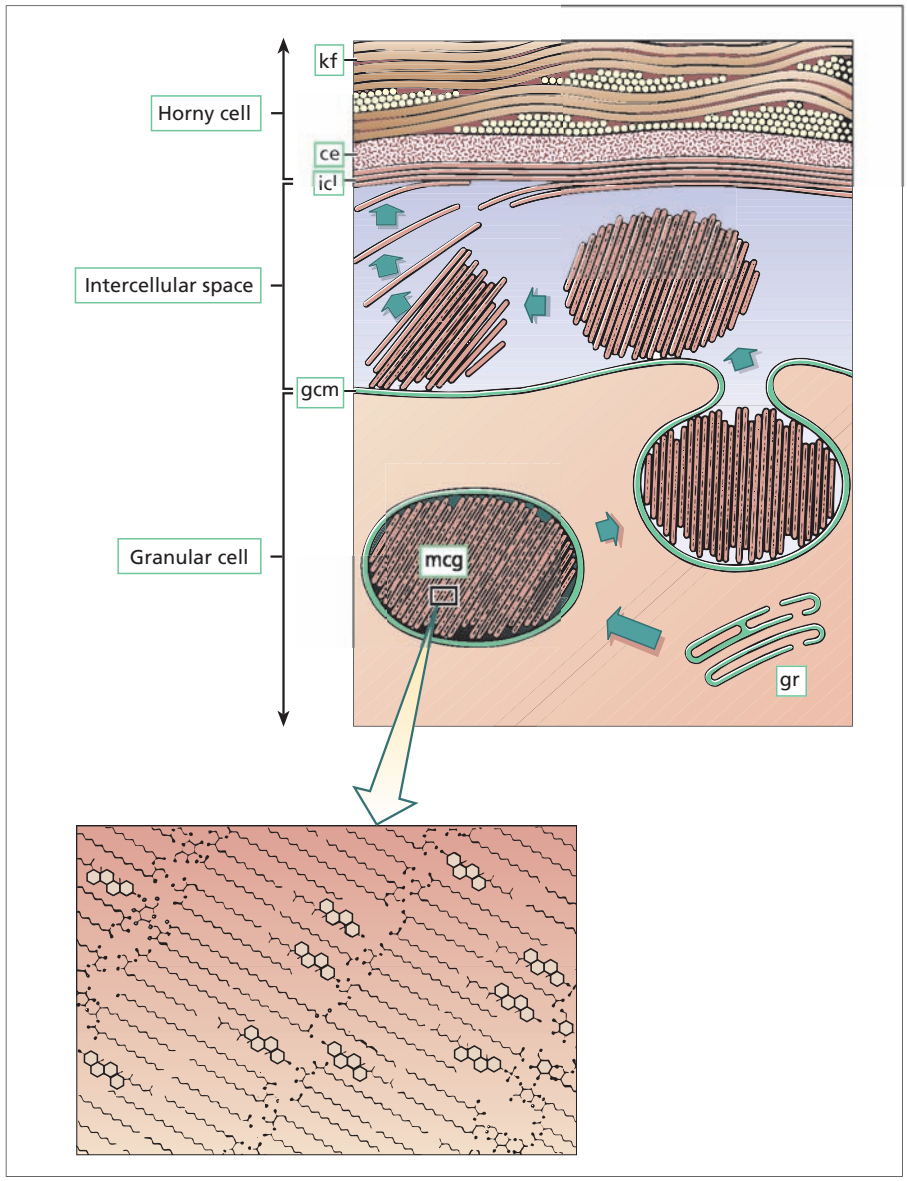

Fig. 4.1 A diagrammatic representation of events in the formation of the epidermal water barrier as seen in electron micrographs. The process includes assembly of a membrane-coating granule or lamellar body (mcg) from the Golgi region (gr) in an epidermal granular cell bounded by a granular cell membrane (gcm); subsequent expulsion of the granule into the intercellular space; and its rearrangement into the intercellular lamellae (icl) that lie parallel with the cell envelope (ce) and the keratin filaments (kf) of the horny cell. The expanded insert shows the proposed arrangement of the acylglucosylceramide molecules (bold) within multiple bimolecular lipid leaflets formed from lipids known to be present in the epidermal granular cells. Hydrogen atoms are omitted from the lipid structures [18]. (Courtesy of P.W. Wertz.)

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Percutaneous absorption

The skin is considered to be a composite membrane, with three anatomically distinct layers [1]: the stratum corneum (10 μm), the viable epidermis (100 μm) and the uppermost papillary layer of the dermis (100–200 μm) each having a different diffusion constant. Even healthy adult human skin allows some permeation of almost every substance, and rates of penetration of different materials may differ by 10 000-fold.

Percutaneous absorption has been studied both *in vivo* and *in vitro*. The penetration *in vivo* of topically applied substances can be assessed by physiological or pharmacological means, or analysed by chemical or histological techniques. Thus, vasoconstriction has been utilized for corticosteroids, vasodilatation for nicotinates, wealing for histamine, sweating for pilocarpine and anaesthesia for local anaesthetics. The application of compounds labelled with radioisotopes and their location through time in layers of stratum corneum, successively stripped by adhesive tape, has been particularly useful. Body fluids, such as blood and urine, can similarly be analysed for substances that have traversed the skin.

In vitro methods usually utilize sheets of whole epidermis or stratum corneum rather than whole skin. Epidermal sheets can be prepared from skin removed surgically, or obtained from cadavers within 48 h of death. The epidermis can be separated by mild heat [2], ammonia vapour [3] or even distilled water. For removal of the Malpighian layer, digestion in 0.2% trypsin [2] or in dispase, a bacterial neutral protease, has been used [4]. The prepared skin material is mounted as a membrane in a diffusion cell between an upper compartment containing a substance, the penetration of which is under study, and a lower compartment containing a buffer solution, which is replenished as samples are removed for analysis at known time intervals, to determine the content of the test substance.

The properties of the skin barrier have a purely physicochemical basis, and do not depend upon the energy-requiring activities of living cells. They are essentially the same *in vitro* as *in vivo*, are unaffected by reversal of the membrane and are maintained long after the skin is removed from the body [5]. Penetrants in weak solutions (although not those at very high concentrations) obey Fick's first law of diffusion, which states that the rate of flow, or flux, is the product of the average concentration of the molecules and their average velocity. In simple terms, the permeability of the barrier for any given penetrant can be completely characterized by the ratio of the flux to the concentration applied, which is known as the permeability constant, and is expressed in length per unit time. The principles of skin permeability and percutaneous absorption have been reviewed in detail elsewhere [1,6–8].

Permeability constants of human and animal skins have been published for a large number of different molecules [6,8]. They vary considerably between species. For example, human skin, which is slightly permeable to water, is relatively impermeable to sodium, potassium and other ions in aqueous solution. In contrast, penetration of various ions through many animal skins is comparatively rapid. Most covalent substances in aqueous solution, such as glucose, urea and the macromolecular human serum albumin, have very low permeability constants in both human and rabbit skin. Others, such as certain aliphatic alcohols, have high constants. Solutes in organic liquids generally show a permeability similar to the solvents themselves. The presence of a solvent is not necessary, for solids dried on the skin continue to penetrate long after a volatile vehicle has evaporated [9]. Thus, for example, application to the scalp of corticosteroids in alcohol may be an effective therapy. In addition, vapours and permanent gases can penetrate skin [10].

The efficiency of the barrier differs between body sites. The scrotum is particularly permeable [11] and the face, forehead and dorsa of the hands may be more permeable to water than the trunk, arms and legs. The palms are particularly impermeable to nearly all molecules except water.

The barrier is affected by many other factors, such as age, environmental conditions and physical trauma, and permeability can be enhanced by various agents, permitting increased access of topically applied drugs.

By virtue of the stratum corneum being adapted to prevent excessive water loss from the body, there is an excellent barrier to the influx of polar molecules, such as water itself. However, many potentially destructive chemicals are non-polar, and the barrier function of the skin slows down penetration of such compounds rather than impeding penetration completely.

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Microorganisms: antimicrobial peptides (AMPs) as a chemical barrier

An intact stratum corneum prevents invasion of the skin by normal skin flora or pathogenic microorganisms. However, both minor injury to the skin, as well as skin diseases, can provide portals of entry to microorganisms, particularly streptococci or staphylococci. The same organisms give rise to different patterns of infection depending, in part, on the nature of the injury. Cellulitis, a dermal and subcutaneous process, may follow a minor abrasion to the skin or tinea pedis affecting the toe webs. Larger abrasions of the skin, as one sees with the lesions of atopic dermatitis (atopic eczema), tend to be associated with superficial infections, such as the crusted lesions of impetigo. In addition, the appendages of the skin can provide a route for infection by some organisms, such as *Staphylococcus aureus* (as seen in folliculitis or a boil) or fungal infections. Colonization with microorganisms occurs more readily in moist areas (flexural sites), and the dryness of the skin surface and continuous shedding of corneal cells help prevent sustained growth of pathogenic organisms.

Sebaceous lipids have been reported to possess antibacterial properties [1], and glycophospholipids and free fatty acids of the stratum corneum have bacteriostatic effects [2], selective for pathogenic microorganisms.

AMPs are a diverse group of peptides that are present on epithelial surfaces such as the epidermis and its appendages as a first line of immune defence by many living things [3,4]. AMPs directly kill a broad spectrum of microbes, including Gram-positive and Gram-negative bacteria, fungi and certain viruses. In addition, these peptides interact with the host itself, targeting events that complement their role as naturally occurring antibiotics.

AMPs can be divided into several categories on the basis of their structures, and most of them include a cationic charge and the ability to interact with bacterial membranes through hydrophobic amino acids. Two major families of AMPs have been characterized in mammals: defensins and cathelicidins.

Defensins are a broadly dispersed family of gene-encoded antibiotics that are subdivided predominantly into the α-defensins and the β-defensins, according to the alignment of the disulphide bridges and their molecular structure [5]. Human neutrophils express a number of distinct defensins, six α-defensins having been identified [6]. Four of these are known as α-defensins 1, 2, 3 and 4 (also referred to as human neutrophil peptides (HNPs) 1–4). The other two α-defensins, known as human defensins 5 and 6 (HD-5 and HD-6), are abundantly expressed in Paneth's cells of the small intestinal crypts and in epithelial cells of the female urogenital tract [3].

In humans, four types of β-defensins have been identified, referred to as human β-defensins (HBDs) 1–4, but it seems that many β-defensins have yet to be discovered [7]. β-defensins have a broad spectrum of antimicrobial activity and act indirectly, being chemotactic for immature dendritic and memory T cells [8], promoting histamine release and prostaglandin D_2 production in mast cells [9,10], and acting as an adjuvant in enhancing antibody production [11]. Human neutrophil α-defensins (HNPs 1–3) also increase the expression of tumour necrosis factor-α (TNF-α) and interleukin-1 (IL-1) in human monocytes that have been activated by bacteria (*Staphylococcus aureus*) [12].

Cathelicidins have been found only in mammals, being limited to a single gene in humans. The human cathelicidin LL-37/hCAP18 was cloned from cDNA isolated from human bone marrow as FALL-39 [13]. The mature AMP is referred to as LL-37 because it begins with two leucine residues and is 37 amino acids long. The term hCAP18 was independently used, because the peptide is a cationic AMP whose mass before proteolytic processing is approximately 18 kDa [14]. The bactericidal activity of human cathelicidin peptide requires proteolytic activation from its precursor by enzymes including neutrophil elastase and proteinase [15]. LL-37 has a broad spectrum of antimicrobial activity and is a chemoattractant for various inflammatory cell types [16,17]. As with the defensins, LL-37 has the potential to participate in the innate immune response both by killing bacteria and by recruiting a cellular immune response.

HBD-2 is present in psoriatic scale [18] and HBD-2 and HBD-3 are increased in keratinocytes from patients with psoriasis [19]. Dermcidin and LL-37 have been found constitutively in sweat gland secretions [20] and HBD-1 and HBD-2 have been demonstrated in ductal epithelia of sweat glands and in normal hair follicles [21]. Other proteins with antibacterial activity in the skin include adrenomedullin [22], cystatin [23] and secretory protease inhibitor [24]. Impaired production of AMPs has been observed in the epidermis in atopic dermatitis, and Th2 cytokines inhibit the expression of HBD-2, one of the AMPs deficient in atopic skin [25].

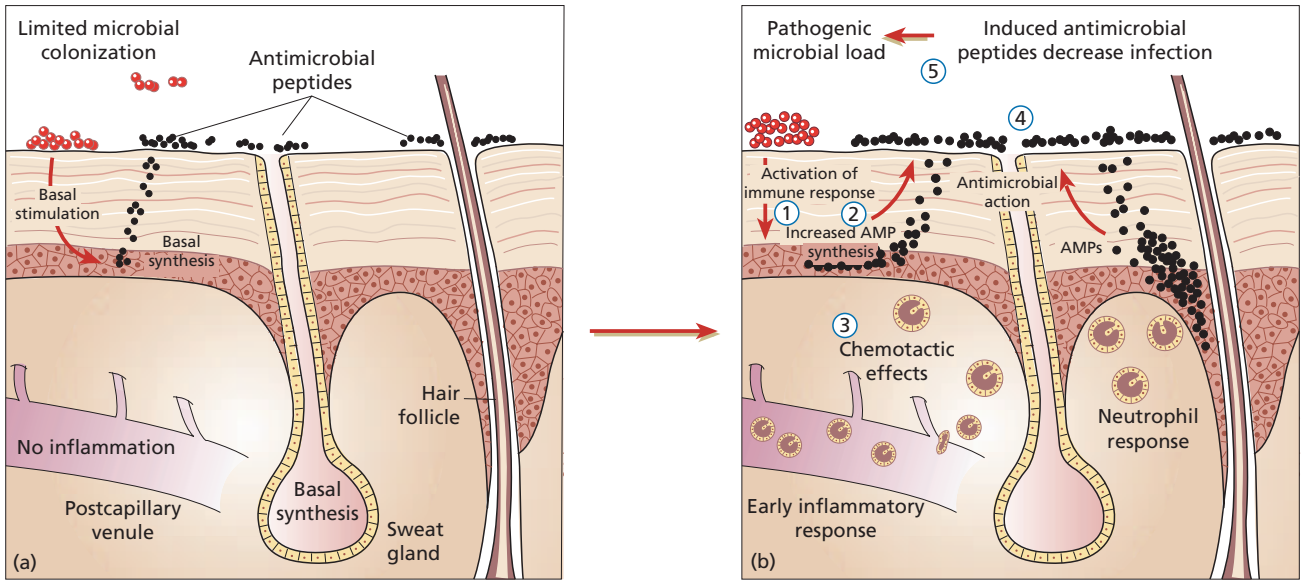

Fig. 4.2 Antimicrobial peptide (AMP) defence. (a) In normal skin, small amounts of AMPs are produced by the epidermis and are concentrated around hair follicles and in sweat. (b) After injury or infection, keratinocytes increase synthesis of AMPs and further AMPs are produced by neutrophils that are recruited as part of the acute inflammatory response. (Modified from Gallo *et al*. [3].)

In normal skin, potential sites of entry of bacteria such as hair follicles and sweat glands produce small amounts of AMPs that provide a chemical barrier to infection where a physical barrier is absent or limited. After injury, the skin responds rapidly with increased production of AMPs from the epidermis and recruited neutrophils (Fig. 4.2) [3].

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Ultraviolet radiation

The sun's radiation is made up of infrared, visible and ultraviolet (UV) light (see Chapter 24), and it is the UV rays that affect the skin. The shorter wavelength UVB rays penetrate the epidermis and are the cause of sunburn and, in the long term, contribute to premature ageing of the skin and the pathogenesis of skin cancer. UVA rays penetrate the skin more deeply and are considered to have an important role in chronic sun damage, particularly skin ageing but also skin cancer development.

The skin has two barriers to UV radiation: a melanin barrier in the epidermis; and a protein barrier, concentrated in the stratum corneum. Both function by absorbing radiation, thereby minimizing absorption by DNA and other cellular constituents. Melanin is synthesized by melanocytes in the basal layer of the epidermis and transferred to surrounding keratinocytes in melanosomes. The partially protective mechanism of delayed tanning [1] is associated with an increase in the number of functional melanocytes, an increase in the number of melanosomes synthesized, and an increased rate of transfer of melanosomes to the keratinocytes. In the long term, there is thickening of the epidermis in response to chronic sun exposure.

Absorption of radiation by epidermal lipids may contribute to protection from UV radiation, in a similar way to that suggested for some low-molecular-weight degradation products of epidermal proteins, including urocanic acid [2]. The role of UV-induced cytokines in the regulation of melanin production is not yet clear [3,4].

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Temperature regulation

The advantage of maintaining a constant body temperature is that the metabolic processes are not directly dependent on changes in the environmental temperature. However, at extremes of ambient temperature, heat may need to be lost or retained. The skin provides a sensory input to thermoregulation and functions to allow heat loss or conservation.

The thermoreceptor cells of the skin are distributed irregularly over the skin, there being warm- and cold-sensitive thermoreceptors. Information on changes in their stimulation in response to changes in temperature is sent to the hypothalamus, leading to either inhibition of sweating or stimulation of shivering [1]. However, the skin thermoreceptors have a relatively minor role in modifying core temperature, and skin temperature has a greater role in mediating behaviour, for example by turning on the heating or putting on extra clothing. At high temperatures, heat pain via nociceptors is perceived rather than warmth.

From an effector point of view, the skin has a major role in thermoregulation of the human body [2]. Heat can be lost through the skin surface by radiation, convection, conduction and evaporation. Of importance in these mechanisms is the rich blood supply of the dermis, which is much greater than that needed for nutrition. The cutaneous circulation is described elsewhere (see Chapters 3 and 50). The essential point about its function, however, is that a system of arteriovenous shunts, which are plentiful in the feet, hands, lips, nose and ears, enables the blood flow to an extensive and more superficial venous plexus to be considerably varied.

In high environmental temperatures, the process of evaporation is considerably enhanced by eccrine sweating.

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Skin failure

Skin failure has been defined by Irvine [1] as 'a loss of normal temperature control with inability to maintain the core temperature, failure to prevent percutaneous loss of fluid, electrolytes and protein with resulting imbalance and failure of the mechanical barrier to penetration of foreign materials'. The term was initially used to bring to the attention of non-dermatologists the need for specialist care in this dermatological emergency. Apart from in thermal burns, skin failure can occur as a consequence of a number of dermatological diseases, including Stevens–Johnson syndrome, toxic epidermal necrolysis, pustular psoriasis and erythroderma of various causes. Depending on the extent of the disease, pemphigus vulgaris, graft-versus-host disease and epidermolysis bullosa are other potential examples.

Used in this specific sense, skin failure is an interesting concept that has not gained common usage. The term is sometimes used in a more general sense to reflect disability in dermatology [2].

Hence, Ryan [2] has included a wide range of skin diseases as examples of 'skin failure', such as hand dermatitis, the development of sunburn and skin cancer in the albino African, and failure of display because of disfigurement. He has emphasized the need for dermatologists and allied health professionals to use a language that can be understood by everyone, particularly patients, when referring to the consequences of skin disease [3].

Both authors [1,2] have drawn attention to the fact that skin failure represents severe loss of function as occurs in other organ systems, for example heart failure, liver failure, renal failure and respiratory failure.

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Mechanical functions

Although the epidermis and subcutaneous fat each have a role in the protective function of the skin, the mechanical properties of the skin related to hard blows with blunt objects depend mainly on the dermis. Skin is elastic to a degree and can, for a few seconds at a time, be stretched reversibly by 10–50%. Skin pulls easily at first. The initial response appears to involve a reorientation of collagen fibres towards the load axis and a decrease in their convolution [1]. The tonus of skin is probably maintained by the elastic fibres, and it seems likely that these fibres provide the small forces that restore the extensibility of slack skin.

Once the initial slack has been taken up, the skin becomes much more difficult to extend. It gradually stretches if it is maintained taut for a long time, as, for example, when using tissue-expanding techniques in skin surgery. This further extension under continued stress is referred to as 'viscous extension', 'viscous slip' or 'creep', and is irreversible. This slip depends on the collagen fibrils. It is unlikely that slipping occurs within the fibril itself; either the individual fibrils slip relative to each other, or whole fibrils do so within the related ground substance. The most probable hypothesis to explain the relative lack of slip is that slip is interfibrillar, that the collagen fibrils are very long and that the interfibrillar substance is highly viscous. It appears that dermatan sulphate is more closely connected to the collagen than hyaluronic acid, and it is probable that this material is the one responsible for restraining the viscous slip.

From these considerations it is clear that disorders in which the skin is hyperelastic, such as Ehlers–Danlos syndrome (see Chapters 3 and 46), must involve a breakdown of the collagen mechanism. The striae seen in adolescence, pregnancy and in situations of excessive systemic corticosteroids, whether administered or as part of Cushing's syndrome, are thought to involve a breakdown of the fibril overlap, so that there is no viscous force to limit further slip.

A further property of skin is that it can be compressed. If a small object is pressed into the skin, a depression is formed that remains after the object is removed; thus, skin becomes moulded round the object exerting the force, and the pressure on any one point is reduced. This compression is primarily because of a flow of ground substance through the dermis between the collagen fibres.

The epidermis itself is relatively strong and holds together under the pressure from blister fluids. On the other hand, the dermal–epidermal junction in human skin is relatively weak. The superficial collagen in the papillary layer appears to be particularly easy to weaken, and many blistering agents appear to act at this level.

By virtue of its protein and lipid constituents, the stratum corneum is a relatively strong elastic tissue. The network of structural proteins allows exogenous forces to spread throughout the tissue. The elasticity of the stratum corneum is also influenced by the degree of hydration of the corneal cell proteins, which in turn depends on the water content of the tissue and by the humidity of the surrounding environment [2]. Stratum corneum proteins, lipids [3,4] and low-molecular-weight by-products of keratohyalin breakdown, referred to as natural moisturizing factors [5], bind and retain water in the stratum corneum, thus maintaining its elasticity.

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Immunological functions

The immunological functions of the skin have been the subject of intense research in recent years, and it is clear that the skin has an important role in immunological host defence, particularly involving those cells residing in (keratinocytes, Langerhans' cells) or passing through (T lymphocytes) the epidermis (see Chapters 9 and 10). The role of AMPs as a first line of defence against microorganisms has been discussed above (see p. 4.5).

Antigens are from either the external environment (exogenous antigens) or are newly formed in the cell itself

(endogenous antigens). T lymphocytes are able to recognize antigen only when it has been presented by specialized cells, termed antigen-presenting cells (APCs) or accessory cells [1–3]. The T cell recognizes the antigen in association with products of the major histocompatibility complex (MHC) gene region of the APC. In helper T cell (Th cell) activation, the antigen moiety is usually presented in the context of MHC class II molecules, whereas most cytotoxic T cells recognize the antigen in association with MHC class I molecules.

Any cell expressing the respective MHC gene product can act as an APC [4] and the predominant APC populations in the MHC class II-dependent antigen-presenting pathway are mononuclear phagocytes [3,4], Langerhans' cells [5–7], B cells [8] and lymphoid dendritic cells [9]. T-cell activation is preceded by interaction of surface molecules, including T-cell antigen receptor (TCR) occupancy by the antigen–MHC complex.

In human skin, most T cells are found in the dermis, usually grouped around postcapillary venules and the appendages. Intraepidermal T cells account for less than 10% of T cells in human skin. Langerhans' cells involved in antigen presentation in damaged epidermis undergo phenotypic and functional changes prior to leaving the epidermis, entering the dermal lymphatics and migrating to the paracortical areas of the draining lymph nodes. At this stage, they present the antigen–MHC complex on their surface to the TCR on either $CD4^+/CD8^-$ or $CD4^-/CD8^+$ naïve resting T cells, and elicit an antigen-specific T-cell response. The T-cell blasts thus generated then seem to preferentially return to the skin sites bearing the antigen.

It will be seen from this brief outline that epidermal cells are intimately involved in the afferent and effector limbs of the immune response. The broader principles of immunology, the mechanisms of immune responses and the implications for clinical dermatology are fully explored in Chapters 9 and 10. As discussed elsewhere, immunological dysfunction probably has a pathogenetic role in a wide range of skin diseases, including the immunobullous disorders, allergic contact dermatitis, atopic dermatitis, psoriasis and cutaneous T-cell lymphoma (mycosis fungoides).

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Sensory and autonomic functions

The skin is innervated by a dense three-dimensional network of highly specialized afferent sensory and efferent autonomic nerve branches. The sensory nervous system detects the sensations of touch, vibration, pressure, change in temperature (warmth and cold), pain (including heat pain) and itch [1,2]. The autonomic nervous system is innervated by postganglionic cholinergic parasympathetic nerves and adrenergic and cholinergic sympathetic nerves. The autonomic system has an important role in maintaining cutaneous homeostasis by regulating vasomotor functions, pilomotor activity and eccrine sweat gland secretion, and is discussed further in Chapter 60.

The sensory nerves are either myelinated A fibres or unmyelinated C fibres, the latter containing sensory and autonomic fibres. The rate of transmission of a nerve impulse is proportional to the diameter of the nerve, and the various types of A fibres are thicker (1–20 μm) than the slow-conducting unmyelinated C fibres (0.2–1.5 μm). The myelinated human cutaneous nerves have been divided into Aβ and Aδ types on the basis of their conduction velocities, corresponding to 35–75 m/s and 5–20 m/s, respectively [2]. In the upper dermis, small myelinated nerves lose their nerve sheaths, and together with the unmyelinated nerves end in either free nerve endings or as specialized sensory receptors, such as Meissner's corpuscles or Merkel's receptors [2].

Much of the research into the sensory functions of the skin was carried out from the 1950s to the 1970s but, since the discovery of neuropeptides with implications for potential pharmacological modulation, there has been renewed interest in this field. Electrophysiological studies showed the existence of functionally specific afferent units [3]. Two major categories of afferent unit have been clearly established: mechanoreceptors and thermoreceptors [4,5]. A third group of pain receptors (nociceptors) respond only to high-threshold stimulation, including mechanical, thermal (heat pain) or chemical stimulation. Within each of these categories some of the afferent units determined functionally can be clearly identified with morphologically distinct structures.

Touch is mediated by mechanoreceptors in the skin, there being two main functional groups [5] according to the way they respond to constant or persistent stimuli. *Slowly adapting* mechanoreceptors respond continuously to a persistent stimulus, whereas *rapidly adapting* mechanoreceptors respond at the onset and frequently at the end

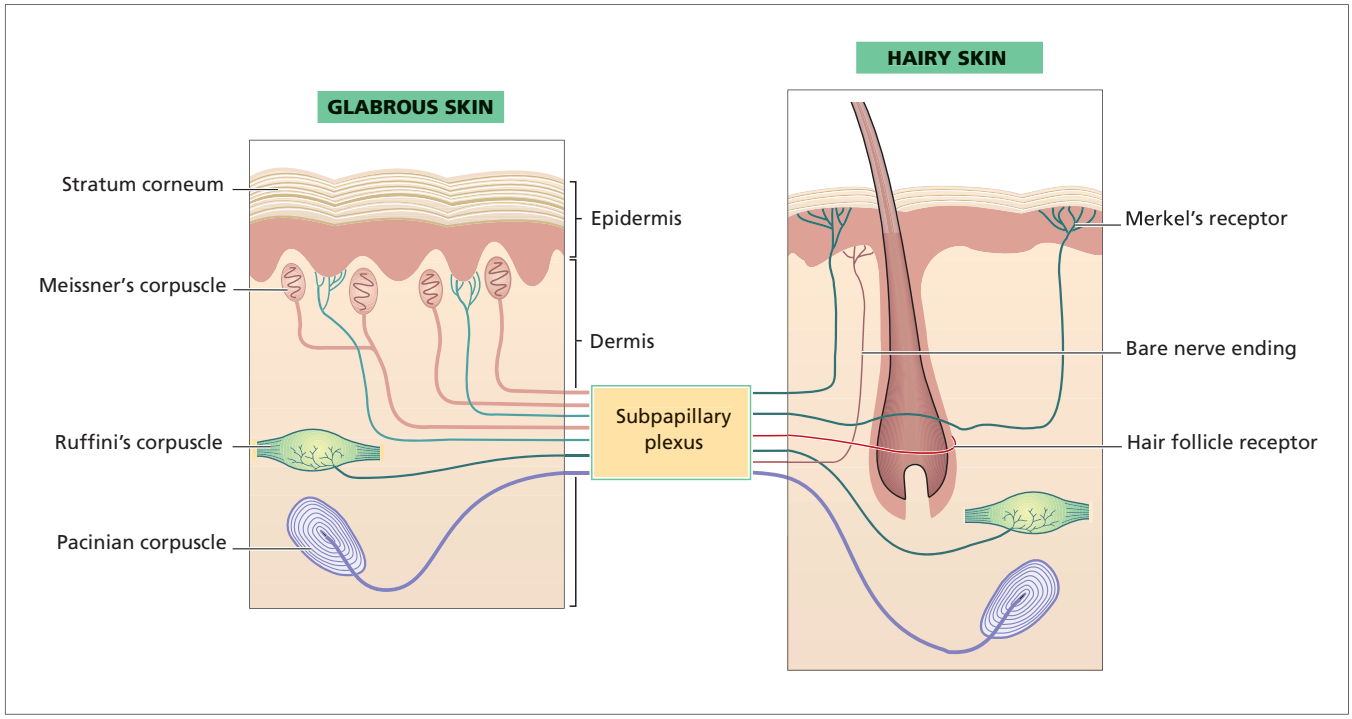

Fig. 4.3 Diagram to show the location of sensory receptors in hairless (glabrous) and hairy skin. The receptors of glabrous skin are Meissner's corpuscles and Merkel's receptors in the dermal papillae, and bare nerve endings. The receptors of hairy skin are hair-follicle receptors, Merkel's receptors, and bare nerve endings. Pacinian corpuscles and Ruffini's corpuscles are situated in the subcutaneous fat and deeper dermis in both glabrous and hairy skin.

of the stimulus, but not throughout the duration of the stimulus.

Glabrous and hairy skins have different types of mechanoreceptor (Fig. 4.3). The predominant mechanoreceptor in hairy skin is the hair-follicle receptor. Glabrous skin (e.g. the hairless skin of the palmar surface of the hands) has two main types of superficial mechanoreceptor: a rapidly adapting receptor, the Meissner's corpuscle; and a slowly adapting receptor, the Merkel's receptor.

Subcutaneous tissue and the deeper dermis beneath both hairy and glabrous skin contain two types of mechanoreceptors: the Pacinian corpuscle, a rapidly adapting receptor; and Ruffini's corpuscle, a slowly adapting receptor. In contrast to the small receptive-field size of Meissner's corpuscles and Merkel's receptors in the upper dermis, the receptive fields of Pacinian and Ruffini's corpuscles are large. When Pacinian corpuscles are tested with uniform or constant-velocity displacement, no impulses result, but sinusoidal displacement (vibration) generates a regular stream of impulses.

The sensations of warmth and cold are mediated by thermal receptors. Two distinct kinds of thermoreceptor [3,6] have been identified in tongue, hairy and glabrous skin of a number of mammals, including humans. Such fibres show a steady discharge dependent on temperature, but no response to non-painful intensities of mechanical stimulation. Temperature sensitivity is punctate, each afferent fibre being connected with a few receptive spots with a diameter in hairy skin of less than 1 mm.

Cold and warmth spots correspond to discrete zones of innervation by cold and warmth receptors. Cold receptors show a frequency rise on sudden cooling, the frequency of firing being proportional to the rate and degree at which the temperature is lowered. Cutaneous cold receptors are activated from approximately 1–20°C below the normal skin temperature of 34°C. Warmth receptors show a steady discharge at constant temperatures in the range 32–45°C, an acceleration of the discharge on warming the skin, small receptive fields and a high sensitivity to temperature change. At temperatures greater than approximately 45°C, heat pain via nociceptors is perceived rather than warmth.

Pain is mediated by *nociceptors*, receptors that respond selectively to stimuli that can damage tissue. Three types of nociceptor can be distinguished. Mechanical nociceptors are activated by strong mechanical stimulation, such as sharp objects. Pricking of the skin gives rise to two kinds of sensation. The initially felt 'pricking' or 'fast' pain is punctate, superficial and local, and this is followed by a more diffuse 'burning' or 'slow' pain [5]. Thermal nociceptors respond to heat or cold. In humans, heat nociceptors respond when the temperature of their receptive field exceeds 45°C, the heat pain threshold. Cold nociceptors respond to cold noxious stimuli. In addition, there are

polymodal nociceptors that respond to several different kinds of noxious stimuli, including mechanical, heat and chemical [5].

Itching [7–10] is closely related to pain and is discussed in detail in Chapter 16.

In addition to classical neurotransmitters such as noradrenaline (norepinephrine) and acetyl choline, peripheral nerves contain neuropeptides. Neuropeptides are released from nerve terminals following depolarization, and have a role in regulating synaptic transmission. A number of neuropeptides have been demonstrated in human skin, including substance P, vasoactive intestinal peptide (VIP), somatostatin, calcitonin gene-related peptide (CGRP), neuropeptide Y and bombesin [11–13]. In addition to acting as neurotransmitters, neuropeptides have a role in the mediation of inflammation in the skin, and are discussed more fully in Chapters 9 and 60.

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Bioengineering and the skin

In recent years, there has been much emphasis on the importance of objective measurement in dermatology and, driven in part by the cosmetics industry, there have been a number of advances in bioengineering technology. Relatively non-invasive bioengineering techniques can be used to assess the functions of the skin either in the resting state or in test conditions (e.g. the use of transepidermal water loss [TEWL] measurement in irritancy testing), or to quantify the response of clinical disorders to treatment (e.g. the use of ultrasound to assess therapeutic responses in chronic dermatoses). Selected aspects of bioengineering and the skin are discussed here. The importance of validation of and comparison between the plethora of similar techniques has been emphasized [1].

TEWL measurement is used to assess the barrier function of the stratum corneum, usually to predict irritancy of substances or to contribute to the assessment of clinical disorders. Various methods have been used, but an open-chamber gradient-estimation method in the form of the *evaporimeter* is preferred, because it allows continuous measurement in ambient air, with little alteration of the microclimate overlying the skin surface [2].

In the past, TEWL was taken to indicate the water vapour passing through the stratum corneum by passive diffusion [3], but currently TEWL refers to the total amount of water loss through the skin, which includes sweating [2]. Many irritants, such as detergents and solvents, damage the skin by impairing the barrier function of the stratum corneum, and TEWL measurement has been reported to be more sensitive in assessing such irritancy effects than visual scoring [4,5], laser Doppler flowmetry, colorimetry and skin thickness by ultrasound A scan [5]. A higher TEWL has been demonstrated in lesional skin of various types of dermatitis [6,7], in psoriatic plaques [8] and in non-lesional skin of patients with atopic dermatitis [9,10].

Cutaneous gaseous exchange, a term preferable to cutaneous respiration, is the absorption of oxygen and the elimination of carbon dioxide through the skin surface [11]. In clinical medicine, transcutaneous oxygen tension (tcPo_2) measurement is used to quantify the adequacy of skin circulation, and to estimate the severity of leg ulceration, because tcPo_2 reflects the degree of oxygen supply by tissue perfusion.

The mechanical properties have been assessed by a number of techniques, designed either to induce a skin deformation and record the resisting force, or to place a load on the skin and measure the resulting deformation. The assessment of vertical forces to the skin is often avoided because this, in part, measures the contribution of the subcutaneous fat, which varies considerably between different subjects and different sites of the body in the same subject [12]. Non-invasive methods include twistometry [12], suction techniques [13], indentometry [14] and ballistometry [15].

TEWL decreases during the ageing process, becoming obvious after the fifth decade [16]. The decrease in TEWL with age is considered to be partly caused by an increased size of corneocytes and increased thickness of the stratum corneum, related to an elevated accumulation of corneocytes resulting from impaired desquamation [17]. Stratum corneum hydration is also decreased in elderly subjects [18,19], the 'dryness' of the skin in the elderly differing from pathologically dry skin, in which there is impaired barrier function.

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Sociosexual communication

The skin, by virtue of its visual appeal, smell and feel, has an important role in social and sexual communication in humans, as it does in other animals. Cosmetics and clothes are used to enhance the appearance and sometimes (but not always) sexual attraction. There are many interesting parallels between humans and other animals, particularly primates, in terms of both visual communication and body odour. The reader is referred to Ebling's fascinating account for further information [1].

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Chapter 5

Diagnosis of Skin Disease

N.H. Cox & I.H. Coulson

Fundamentals of diagnosis

As for any other organ system, diagnosis of skin disease involves a history, examination and sometimes additional tests. The visibility of skin allows an instant diagnosis in some cases, using a variety of visual clues such as body site distribution, colour, scaling and arrangement of lesions. Such apparently effortless pattern recognition is actually quite complex when the individual components are analysed separately [1]. Individuals who examine the skin less frequently often also fail to appreciate the additional value of palpation in determining induration, quality of scaling and temperature changes. This chapter briefly introduces aspects of the history, examination and other diagnostic manoeuvres.

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Disease definition

Most skin diseases do not have a cause which is both identified and unique to that disorder. Conversely, many known causes of skin disease may play a part in several different types of disorder (for example, ultraviolet light may cause or contribute to skin cancers, skin ageing and various patterns of photosensitivity). Current definitions of most skin diseases therefore rely on the presence of a constellation of clinical, histopathological and sometimes immunopathological or genetic features. Even common and important diseases such as psoriasis have no strict and unique diagnostic criteria. The diagnostic stringency required for day-to-day clinical management may differ from that required in epidemiological and therapeutic research, in which it is clearly important to be sure that all studies are actually describing the same entity [1]. In some disorders which remain difficult to classify, such as parapsoriasis [2], numerous names may have been applied over the years and it may be difficult to know exactly what was meant in a previous publication. This problem applies even in atopic eczema, generally considered a fairly straightforward diagnosis, and has significant implications for epidemiological research. Similarly, treatments and prognosis may vary between different types of cutaneous T-cell lymphoma (CTCL), but it is impossible to be certain about the types of CTCL that have been assessed in some studies.

Scientific advances are resolving some of these diagnostic and terminology issues, but many disease definitions in dermatology are still based on a constellation of clinically determined morphological cutaneous features. Some of these have distinct anatomical correlates (e.g. myxoid cyst), a specific external cause (e.g. scabies), or have a known genetic or biochemical defect (e.g. many genodermatoses). Many will have characteristic histological features, although—particularly in the case of inflammatory dermatoses—there are often areas of overlap between disease entities.

In other cases, there may be a number of different cutaneous features or multiorgan involvement which are associated together as a syndrome, such as systemic lupus erythematosus (SLE) or Behçet's disease. A syndrome is

usually defined by the simultaneous presence of a fixed combination of disease indicants, but these may not all be present in an individual case and may not require to be present concurrently; additionally, 'overlap' syndromes can occur where features of two or more related syndromes are present in the same patient. In such instances, making a diagnosis may rely on fulfilling a certain number of criteria—for example, the American Rheumatism Association (ARA) criteria for diagnosis of SLE [3]. This can be further refined by having major and minor criteria in order to achieve a given sensitivity and specificity. In some instances, such as the diagnostic criteria for Behçet's disease, a single diagnostic criterion must be fulfilled (recurrent oral aphthae) together with a given number of minor criteria [4]. In other instances, the number of criteria in each category which need to be fulfilled may vary—for example, in the diagnostic criteria for streptococcal toxic shock, the number of minor criteria that need to be fulfilled depends on the strength of the major criteria which are achieved [5]. All such diagnostic criteria may need to be updated to take into account new diagnostic techniques. However, it should be noted that many such criteria have been derived for confirmation of diagnosis for epidemiological or research reasons, rather than being a prerequisite for clinical diagnosis and management of individual patients.

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The history

It is often possible to make a diagnosis of the type of eruption or lesion by inspection alone, but additional clinical examination techniques are often helpful, such as palpation and rubbing or scratching the skin. However, clinical morphology alone does not usually determine the aetiology of a skin disorder, and a carefully directed history is usually important for both diagnosis and optimal management. The amount of history required, and the sequence of history-taking and examination, may vary depending on the condition and referral information already provided to the dermatologist. Several audit studies and therapeutic guidelines have suggested minimum data sets for the medical history and morphological findings in skin diseases [1,2].

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The presenting complaint

Symptoms. Itch is the prime dermatological symptom, but may be variously described by different patients; there are individual differences in threshold and perception. Intense itch is typical in scabies, atopic dermatitis and lichen planus, whereas psoriasis and pityriasis versicolor usually cause less severe itch for the same degree of body surface involvement.

Other symptoms include sharp pain (e.g. chondrodermatitis of the ear), burning (e.g. chilblains) or tenderness (e.g. erythema nodosum). The site may influence symptoms; for example, urticaria causes itch, but the same pathology affecting the palms often causes pain (because the oedema is deeper and the firmer tissues of the palm cannot distend easily). Both the quality and intensity of symptoms should therefore be recorded.

Symptoms usually parallel overt development of an eruption, but discordance can be diagnostically useful—for example, localized itch preceding herpetic vesicles, or fever and malaise preceding erythema and swelling in cellulitis of the leg or erysipelas.

Duration, evolution, periodicity and previous episodes. The overall duration of a rash or localized lesion is usually apparent to the patient, although there are exceptions; basal cell carcinoma, for example, is often noticed only when it ulcerates, and the patient will therefore underestimate the duration of the lesion. Whether the onset of a rash was sudden or gradual may be diagnostically useful. The overall duration is also of diagnostic help for localized lesions. For example, a presumed keratoacanthoma that is still enlarging after a few months is probably a squamous cell carcinoma; lesions which turn black overnight do so due to intralesional bleeding, not as a result of becoming a melanoma.

More precise details may require carefully phrased questions. In urticaria, the diagnostic feature is that individual lesions change from day to day (usually over a few hours), but the overall duration of the process may be years. Asking the patient about the duration of the eruption needs to distinguish between these two aspects. Similarly, if lesions are not present, then diagnosis may depend on the patient's description, but there are pitfalls; weals are often described as 'blisters', a term which should not be taken at face value, and distinguishing between eruptions triggered by heat or sunlight often causes confusion. It is helpful to ask the patient whether

any particular factors (e.g. dietary items, cosmetics, work chemicals, sunlight) appear to provoke (or alleviate) the condition.

Some dermatoses have a characteristic evolutionary sequence (e.g. pityriasis rosea, in which a solitary larger 'herald patch' precedes the widespread eruption by a few days, or 'pre-pemphigoid' eczematous lesions). Other disorders may demonstrate periodicity; for example, occupational contact dermatitis may improve at weekends or holiday periods, and photosensitivity and airborne contact allergy to plants may be seasonal.

Previous episodes of a similar type are likely to be relevant, but other skin problems may be important even if they do not appear to be the same process. For example, patients with type IV hypersensitivity to fragrance materials might at different times have eyelid rash due to cosmetics, axillary rash due to deodorants, widespread eczema due to soaps or clothing detergents or diffuse facial rash due to airborne perfume agents. In such cases the body site distribution may be confusing, but the sequence of sites affected should be determined, especially the site of initial involvement in the case of rashes.

Previous episodes are also potentially relevant for localized lesions (e.g. patients with two or three previous basal cell carcinomas have a high risk of another, so the level of suspicion may be greater in those with a positive previous history of these lesions).

Previous therapy. Previous treatment and response should be documented to guide future therapy, and to exclude the possibility of the diagnosis being obscured (for example, tinea incognito due to use of topical corticosteroids).

General history

Medical history, medications and dietary history. General medical conditions may have cutaneous features, and should be noted especially in patients with rashes or generalized skin symptoms. Recent illnesses, even if apparently resolved, deserve special attention, as conditions such as urticaria, vasculitis, guttate psoriasis and erythema multiforme can be triggered by viral or bacterial infections in the weeks preceding the onset of the rash. Any recent or current systemic medication should be noted, including regular or intermittent self-medication or that received from relatives or friends, both as a possible cause of drug eruptions and to avoid interactions with treatment prescribed for the skin complaint. Medicament and other allergies may be important, as are drugs which might interact with anaesthetics or cause surgical bleeding.

Dietary history may be important in some individuals, especially those with intermittent urticaria or anaphylaxis. However, diet is often erroneously blamed for skin eruptions.

Family history. This may be important if a genodermatosis is suspected, in disorders with more complex inheritance (e.g. atopic dermatitis, psoriasis), and in some non-inherited disorders in which family contact is important (e.g. scabies, chickenpox).

Occupation and leisure activities. An occupational history may be of importance, both current and previous, particularly in individuals with eczema; a detailed account of processes and chemicals may be required, together with additional testing (Chapters 19, 20 and 21). Hands are the most commonly affected site in occupational dermatitis, and it is useful to record details of hand protection (e.g. gloves, barrier creams) as well as the agents to which the patient is exposed. Hobbies less commonly cause problems, but may involve exposure to a variety of common allergens. Outdoor work or hobbies may also involve exposure to sun, cold or to plant allergens.

Ethnicity and cultural aspects (Chapter 69). Several disorders have a predilection to occur in specific racial groups—for example, the high frequency of sarcoidosis in black patients [1], or prurigo pigmentosa in the Japanese [2]. The morphology of common diseases may be altered by racial pigmentation, and normal pigmentary variations may be apparent. The severity of diseases may appear to be different between races or cultural groups; atopic eczema has been noted to be more frequent in children born in England of Asian or Caribbean origin [3,4]. Cultural differences may be diagnostically important, such as use of hair pomades and skin depigmenting agents, or may influence acceptance and understanding.

Geographical factors. Foreign travel, especially if recent, is a potentially important cause of dermatological disease. The place(s) visited may lead to specific likely diagnoses, and documentation should include any brief stopping-off countries. A long visit increases the risk of significant exposure to environmental agents, but dust-borne spores and insect vectors may be carried in aircraft and potentially alter the natural history of a disorder by allowing exposure outside the anticipated geographical distribution.

Social and psychological factors. The living conditions, economic status and standard of nutrition of the patient may be relevant both as a guide to diagnosis and to ensure compliance with the treatment advised. Specific examples of important social factors include the strong association between cigarette smoking and palmoplantar pustulosis, and the multiple influences of excessive alcohol intake on the severity and therapeutic options in psoriasis. A sexual history is also required in some instances. The effects of skin problems on lifestyle, relationships, costs to the patient and costs to the community from work days lost are important, and it is helpful to know the patient's main

concerns. This applies particularly to chronic skin eruptions, but many patients with discrete lesions primarily want reassurance that they are not malignant. It is unlikely that many skin eruptions are due to 'nerves', but psychological factors can clearly be of importance in aggravating or perpetuating symptoms, and may be the primary abnormality in some instances (Chapter 61).

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Examination of the skin

Most patients referred to the dermatologist have objective changes in the appearance or consistency of the skin. Even those who describe itch without rash often have dry skin or other features that can be elicited, such as dermographism. Most lesions and eruptions can either be diagnosed fully, or at least assigned to a diagnostic category, by clinical examination; indeed, clinical diagnosis is more precise than laboratory tests in many disorders. The ability to elicit and interpret cutaneous physical signs is therefore of fundamental importance in dermatological training.

The patient should always be examined in a good light, preferably daylight, and with magnification of lesions if necessary. Ideally, the entire skin should be examined in every patient, and particularly if the diagnosis is in doubt, as this may reveal lesions that are more easily identifiable and have not been modified by secondary changes. Adolescents and elderly people will often deny the existence of lesions other than those presented for examination, the former because they are unwilling to undress and the latter because they have not seen them.

In the examination of the skin, it is helpful to consider the morphology of individual lesions, their overall pattern and spatial relationship to each other, and their body site distribution. Each of these aspects is discussed more fully below. Specific attention to hair, nails and the mucous membranes is required. Careful description and use of nomenclature aids monitoring of changes during follow-up, and any discussion with colleagues.

Touching the skin is important in most instances, and is discussed in more detail below. Gloves should be worn for examination of the mouth, genital/perineal region, or in the case of infective or infected dermatoses.

Additional simple aids to clinical examination include use of Wood's light, diascopy, dermoscopy, iodine-starch testing to identify sweat duct orifices and hair microscopy.

Individual lesions—nomenclature

The commoner descriptive terms applied to cutaneous lesions are listed below. These definitions are broadly in agreement with those recommended by the Nomenclature Committee of the International League of Dermatological Societies [1]. However, it is important to note that some of these definitions have been challenged subsequently [2–5]. A particular problem that many authors have glossed over is the dynamic aspects of skin disease. For example, some papules (less than 0.5 or 1 cm, depending on the source of the definition) are destined to grow larger and become nodules, whereas others (such as syringomas) rarely do so. Additionally, some eruptions may have essentially similar lesions but whose size may include both papules and nodules. Recording of actual size of lesions, or the range of sizes, is often a more useful clinical record [6].

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Glossary

alopecia—absence of hair from a normally hairy area.
aphtha—a small ulcer of the mucosa.
atrophy—a loss of tissue from one or more of the epidermis, dermis or subcutaneous tissues. There may be fine wrinkling and increased translucency if the process is superficial.
burrow—a small tunnel in the skin that houses a parasite, such as the scabies acarus.
callus—a localized hyperplasia of the stratum corneum.
cellulitis—an inflammation of cellular tissue, particularly purulent inflammation of the deep dermis and subcutaneous tissue.
comedo (pl. comedones)—a plug of keratin and sebum in a dilated pilosebaceous orifice.
crusts (scabs)—crusts consist of dried serum and other exudates.

cyst—any closed cavity or sac (normal or abnormal) with an epithelial, endothelial or membranous lining and containing fluid or semisolid material.

ecchymosis (bruise)—a macular area of haemorrhage more than 2 mm in diameter.

en cocarde (or 'cockade')—a rosette pattern of concentric rings, usually applied to naevi.

erosion—a loss of epidermis, which heals without scarring. It commonly follows a blister.

erythema—redness of the skin produced by vascular congestion or increased perfusion.

excoriation—loss of skin substance, specifically produced by scratching.

exfoliation—the splitting off of the epidermal keratin in scales or sheets.

fibrosis—the formation of excessive fibrous tissue.

fissure—any linear gap or slit in the skin surface.

fistula—an abnormal passage from a deep structure, such as a hollow viscus, to the skin surface or between two structures. It is often lined with squamous epithelium.

gangrene—death of tissue, usually due to loss of blood supply.

guttate lesions—small round or oval lesions distributed as a 'shower' of droplets. Usually applied to a form of psoriasis.

haematoma—a localized tumour-like collection of blood.

keratoderma—a horny thickening of the skin.

lichenification—thickening of the epidermis (and to some extent also of the dermis) in response to prolonged rubbing.

macule—a circumscribed alteration in the colour of the skin. Authorities vary on the issue of scaling causing texture change within the definition.

maculopapular—rash consisting of both macules and papules.

milium—a tiny white cyst containing lamellated keratin.

nodule—a solid mass in the skin, which can be observed as an elevation or can be palpated. It is more than 0.5 cm in diameter. It may involve epidermis and dermis, dermis and subcutis, or subcutis alone. It may consist of fluid, other extracellular material (e.g. amyloid), inflammatory or neoplastic cells.

papilloma—a nipple-like mass projecting from the surface of the skin.

papule—a circumscribed palpable elevation, less than 0.5 cm in diameter. By careful examination it is often possible to determine whether the thickening involves predominantly the epidermis or the dermis and what type of pathological process is concerned. The only distinction between a papule and a nodule is the size, and this is artificial; some lesions characteristically occur at the smaller size of a papule, whereas others typically enlarge from a papule to become a nodule. Recording a finite size is more useful.

petechia (pl. petechiae)—a punctate haemorrhagic spot, approximately 1–2 mm in diameter.

plaque—an elevated area of skin, usually defined as 2 cm or more in diameter. It may be formed by the extension or coalescence of either papules or nodules as in psoriasis and granuloma annulare, respectively. Small plaque is sometimes used for such lesions 0.5–2 cm in diameter.

poikiloderma—the association of cutaneous pigmentation, atrophy and telangiectasia.

pustule—a visible accumulation of free pus. It may occur within a pilosebaceous follicle or a sweat duct or, less often, on glabrous skin. Most commonly due to infections, but some eruptions typically cause sterile pustules.

pyoderma—any purulent skin disease.

scale—a flat plate or flake of stratum corneum. A *collarette* scale is a fine, peripherally attached and centrally detached scale at the edge of an inflammatory lesion. *Furfuraceous or pityriasiform* scales are fine and loose. *Ichthyotic* scales are large and polygonal. Scaling may accompany or follow many inflammatory disorders. Silvery scales are characteristic of processes involving parakeratosis, especially psoriasis. The silvery colour is due to reflection of light at the many air–keratin interfaces and can be altered by wetting the skin.

scar—replacement by fibrous tissue of another tissue that has been destroyed by injury or disease. An *atrophic* scar is thin and wrinkled. A *hypertrophic* scar is elevated, with excessive growth of fibrous tissue. A *cribriform* scar is perforated with multiple small pits.

sclerosis—diffuse or circumscribed induration of the subcutaneous tissues. It may also involve the dermis, when the overlying epidermis may be atrophic. It is characteristically seen in scleroderma, but may occur as a sequel to or in association with many different processes.

sinus—a cavity or track with a blind ending.

target lesions—these are less than 3 cm in diameter and have three or more zones, usually a central area of dusky erythema or purpura, a middle paler zone of oedema, and an outer ring of erythema with a well-defined edge.

tumour—literally a swelling. The term is used to imply enlargement of the tissues by normal or pathological material, or cells that form a mass. It may be inflammatory or non-inflammatory, benign or malignant. The term should be used with care, as many patients believe it implies a malignancy with a poor prognosis.

ulcer (of skin)—a loss of dermis and epidermis, often with loss of the underlying tissues.

vegetation—a growth of pathological tissue consisting of multiple, closely set, papillary masses.

vesicles and bullae—visible accumulations of fluid within or beneath the epidermis. Vesicles are small (less than 0.5 cm in diameter) and often grouped. Bullae, which may be of any size over 0.5 cm, should be subdivided as

multilocular (due to coalesced vesicles, typically in eczema) or unilocular.

weal—a transient area of dermal or dermal and hypodermal oedema, white, compressible and usually evanescent. It is the characteristic lesion of urticaria. It is often surrounded by a red, axon-mediated flare.

Shape of lesions, linear and annular lesions

The shape of each lesion and the pattern in which neighbouring lesions are arranged in relation to each other is often of great significance and may provide an easily recognizable clue to a rapid visual diagnosis. The main shapes, with examples, are listed in Table 5.1. The mechanism or anatomical factor dictating the shape can sometimes be inferred, as in the case of many linear lesions (Table 5.2, Fig. 5.1) or the vascular patterning leading to livedo; in other instances, such as many annular lesions (Table 5.3, Fig. 5.2) and reticulate lesions (Fig. 5.3), this is less clear.

A specific cause of a linear lesion is the Koebner or isomorphic phenomenon [1]. This term is applied when localized non-specific trauma locally provokes lesions of a dermatosis which is usually spontaneously present elsewhere, and usually in a relatively 'active' or eruptive phase. It is particularly characteristic of psoriasis (Fig. 5.4, Chapter 35) and lichen planus, but occurs in several other dermatoses (Table 5.2). Less common dermatoses in which this may occur include erythema multiforme [2], Sweet's disease and scleromyxoedema [3]. The trauma may be mild, and is usually a scratch or similar, although light or heat may do the same. Occasionally, one disease may be responsible for the localization of another, such as granuloma annulare developing at sites of herpes zoster, or psoriasis developing at sites of contact dermatitis; this has been termed the isotopic response [4]. Development of lesions of pyoderma gangrenosum or Behçet's disease at sites of injection of serum or saline (or even just pinprick or venepuncture) is known as pathergy.

Some annular shapes result from centrifugal extension of an infection from the point of inoculation (e.g. tinea corporis with dermatophyte fungi or erythema chronicum migrans in *Borrelia burgdorferi* infection). In others, a spreading neoplastic or inflammatory process leaves central scarring or ulceration, e.g. superficial basal cell carcinoma and discoid lupus erythematosus. In eruptions in which an allergic process is probably involved, the annular configuration is attributed to the refractory state of the central area. In some conditions, annular shapes can be related to the vascular network (see livedo, Chapter 48). Some involve an iatrogenic component, e.g. warts recurring at the margin of a blistered cryotherapy site. However, in many diseases, such as lichen planus, sarcoidosis or psoriasis, there is no satisfactory explanation for the occurrence of annular lesions. In clinical evaluation of annular lesions, it is particularly helpful to consider surface features such as scaling as an aid to identifying epidermal involvement and thus narrowing the differential diagnosis.

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Table 5.1 Main shapes of skin lesions. (Adapted from G.M. White and N.H. Cox, *Diseases of the Skin*, London: Mosby, 2000: 5.)

Shape	Description	Examples
Discoid (nummular)	A filled circle	Discoid eczema, psoriasis
Petaloid	Discoid lesions which have merged together	Seborrhoeic dermatitis on the trunk
Arcuate	Incomplete circles	Urticaria
Annular	Open circles with different central skin compared with the rim	Tinea corporis, granuloma annulare
Polycyclic	Circles which have merged together	Psoriasis
Livedo	Chicken-wire criss-cross pattern	Erythema ab igne, polyarteritis nodosa, other types of vasculitis
Reticulate	Fine lace-like pattern	Oral lichen planus
Target	Multiple concentric rings	Erythema multiforme
Stellate	Star-shaped	Lesions of meningococcal septicaemia
Digitate	Finger-shaped	Chronic superficial dermatosis
Linear	Straight line	Koebner reaction to a scratch in lichen planus or psoriasis (see also Table 5.2)
Serpiginous	Snake-like	Cutaneous larva migrans
Whorled	Swirling pattern	Epidermal naevi, late-stage incontinentia pigmenti

Table 5.2 Anatomical and causative factors in linear lesions. (From C.M. Lawrence and N.H. Cox, *Physical Signs in Dermatology*, 2nd edn, London: Mosby, 2002: 21.)

Determinant of pattern	Examples
Blood vessels	Thrombophlebitis, Mondor's disease (linear thrombophlebitis on the trunk)
	Eczema related to varicose veins
	Temporal arteritis
Lymphatics	Lymphangitis
	Sporotrichosis, fish tank granulomas
Dermatome	Herpes zoster, zosteriform naevus, zosteriform Darier's disease, zosteriform metastases
Nerve trunks	Leprosy (thickened cutaneous nerves)
Developmental, Blaschko lines	Pigmentary demarcation line, linea nigra
	Epidermal naevi, incontinentia pigmenti, hypomelanosis of Ito
	Linear psoriasis, linear lichen planus, lichen striatus
Skin stretching	Striae due to growth spurt (on lower back)
Infestation	Scabies, larva migrans (both usually serpiginous)
External factors	
Plants	Phytophotodermatitis
Allergens	Elastoplast, nail varnish (neck), necklace, waistbands, etc.
Chemical	Caustics, e.g. phenol
Thermal	Burns
Physical	*Trauma to previously normal skin*
	Keloid scar, bruising, dermatitis artefacta, amniotic constriction bands
	Trauma to skin with a pre-existing dermatosis
	Purpura (cryoglobulinaemia, amyloid, vasculitis)
	Blisters (epidermolysis bullosa, porphyrias)
	Koebner phenomenon
	Psoriasis, lichen planus, lichen nitidus, vitiligo, lichen sclerosus, pityriasis rubra pilaris
	Inoculation
	Warts, molluscum contagiosum
	Other mechanism
	Scar sarcoid
Other determinants	Linear scleroderma (limb, central forehead)
	Senear–Caro ridge (on hands in psoriasis)
	Dermatomyositis (dorsum of fingers)
	Flagellate pigmentation due to cytotoxic drugs (e.g. bleomycin)

Pattern of lesions

The arrangement of individual lesions may create a characteristic pattern, such as the grouping of vesicles in herpes simplex—this pattern is so striking that it is applied to other lesions which do not share the same aetiology (herpetiform mouth ulcers).

Useful terminology to describe patterns includes:

Agminate—clustered; used to describe lesions such as acne agminata, where granulomatous lesions cluster around the lids, or agminate naevi, an unusual clustering of melanocytic naevi.

Grouped—characteristic of some infections (herpetic vesicles, molluscum contagiosum, plane warts), flea bites, lichen planus, leiomyomata, lymphangioma circumscriptum (Fig. 5.5).

Satellite—a cluster of lesions around a larger central lesion. May occur due to local lymphatic spread of neoplasm such as melanoma; may occur in chronic bullous disease of childhood/linear IgA disease.

Confluent—lesions merging together, locally or widespread, e.g. pityriasis versicolor.

Scattered, disseminated and exanthematous—for example, many drug eruptions, viral exanthemata.

Spared—patterns of sparing may also be diagnostically important, e.g. islands of sparing occur within the otherwise often confluent orange-red erythema of pityriasis rubra pilaris, sparing within skin folds in papuloerythroderma of Ofuji, or areas shielded by clothing or a wristwatch may be overtly spared in photosensitivity (Fig. 5.6)

Symmetrical—often endogenous (e.g. psoriasis) and *asymmetrical*, often of exogenous cause (e.g. tinea).

Distribution of lesions

The overall distribution of lesions in many common dermatoses may be so characteristic that it is of great assistance in clinical diagnosis, even though the mechanism in most instances is not understood. Even some demarcations that presumably have an anatomical basis are not fully understood, e.g. Wallace's line on the foot or the equivalent on the hand (Fig. 5.7). Important factors in determining the distribution of dermatoses include the following:

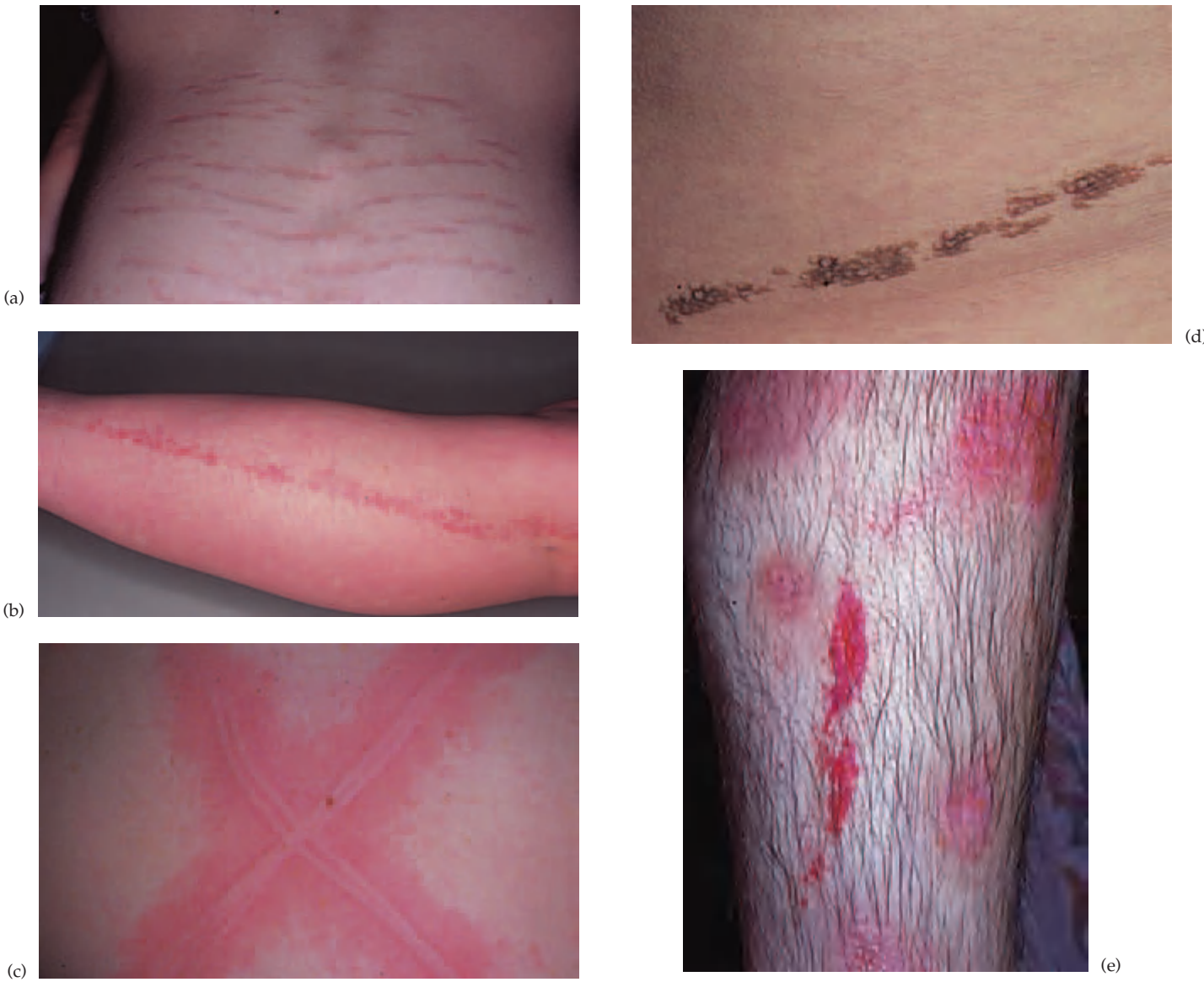

Fig. 5.1 Linear lesions. (a) Growth striae. (b) Lichen striatus. (c) Dermographism. (d) Linear epidermal naevus. (e) Linear excoriations in dermatitis artefacta.

Anatomical factors

—blood supply, e.g. venous eczema
—skin appendages, e.g. acne, hidradenitis
—type of skin, e.g. eruptions may be localized to the glabrous skin of palms and soles
—neural, e.g. herpes zoster
—developmental, e.g. disorders which follow lines of Blaschko (Chapter 12)
—regional variation in the skin surface microenvironment, e.g. erythrasma is usually localized to flexures
—others, e.g. polychondritis is restricted to sites where there is cartilage, affecting ears, nose, joints (and trachea)

External factors

—solar exposure, e.g. photosensitivity disorders
—chemical exposure, e.g. contact dermatitis
—infective, e.g. orf

Colour of skin and of lesions

Normal skin colour is due to melanin, phaeomelanin, haemoglobin, oxyhaemoglobin and carotenoids (Chapter 39). The colour of the skin is greatly modified by the scatter of light, which is responsible, for example, for the whiteness of scale and the blueness of any melanin deep in the dermis, although colour contrast with surrounding skin also alters perception of the colour of skin and subcutaneous structures [1]. The range of colours that may be seen in individual skin lesions is enormous (Table 5.4). Although many red, scaly rashes tend to resemble each

Table 5.3 Examples of annular lesions.

Infections	'Ringworm' dermatophyte infections
	Impetigo
	Erythema chronicum migrans
	Syphilis (secondary, tertiary)
	Leprosy
	Lupus vulgaris
Inflammatory	Psoriasis
	Seborrhoeic dermatitis
	Subacute cutaneous lupus erythematosus
	Lichen planus
	Sarcoidosis
	Granuloma annulare
	Erythema multiforme
	Urticaria
	Serum sickness
	Linear IgA disease/chronic bullous dermatosis of childhood
	Subcorneal pustular dermatosis
	Erythema annulare centrifugum
	Jessner's lymphocytic infiltrate
	Erythema marginatum rheumaticum
Vascular	Purpura annularis telangiectoides
Neoplastic	Superficial basal cell carcinoma
	Mycosis fungoides
Keratinization disorders	Porokeratosis

other, many dermatoses have their own distinctive colour which aids recognition—for example, the orange and yellow-orange palms of pityriasis rubra pilaris and carotenaemia, respectively. Some colours can be logically explained—for example, the purple of lichen planus is due to the redness of inflammation combined with the blue-brown of melanin within the dermis.

Examination of pigmented skin requires a degree of practice, as the physical signs may be modified. Erythema is seen as a dark area, macular or diffuse. Dermal oedema lightens the skin and weals appear pale. Papules may be pale or dark according to the degree of oedema or the presence of acanthosis or hyperkeratosis, which mask pigment. Purpura may be difficult to detect, but may appear jet-black in lighter-pigmented skin. Post-inflammatory depigmentation and hyperpigmentation are exaggerated compared to paler skin—for example, after herpes zoster, syphilis, leprosy, lichen simplex and many other conditions. Normal pigmentary variation between body sites is also more apparent in darker skin, and may cause confusion (for example, dark crease lines on the relatively pale palms); pigmentary demarcation lines may also be visible (Futcher's and Voigt's lines) [2].

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Palpation of the skin

Palpation of rashes or localized lesions imparts additional information about texture, consistency, thickness, tenderness and temperature. Gentle scratching or rubbing alters visibility of scaling and may elicit dermographism. The main 'touch' modalities in examining the skin are:

Simple palpation—to determine texture, etc., as above.

Blunt pressure—for example, to detect oedema, assess capillary refill, identify the dermal defect that occurs in anetoderma.

Linear or shearing pressure—to elicit dermographism, or Nikolsky's sign in pemphigus (Chapter 41).

Squeezing or pinching—to determine localization and consistency of lesions. For example, a pinch of skin can be lifted up over a subcutaneous nodule, whereas squeezing a tethered intradermal process such as a dermatofibroma produces dimpling.

Stretching—may produce blanching of vascular lesions, and helps in visualizing lesions such as 'submarine' comedones, the elastomas of Buschke–Ollendorf syndrome and the glassy edge of a superficial basal cell carcinoma.

Rubbing—may cause release of chemicals; e.g. rubbing a mastocytoma causes urtication and a flare due to histamine release (Darier's sign), rubbing a neuroblastoma causes surrounding pallor due to catecholamine release.

Scratching and picking—scratching scale in psoriasis makes the scale appear more silver in colour by introducing air–keratin interfaces; more vigorous scratching or picking off the scale produces small bleeding points (Auspitz's sign). Neither of these is specific to psoriasis. Removal of crusts overlying nodules may demonstrate the extent of the lesion, and additional diagnostic features, more accurately.

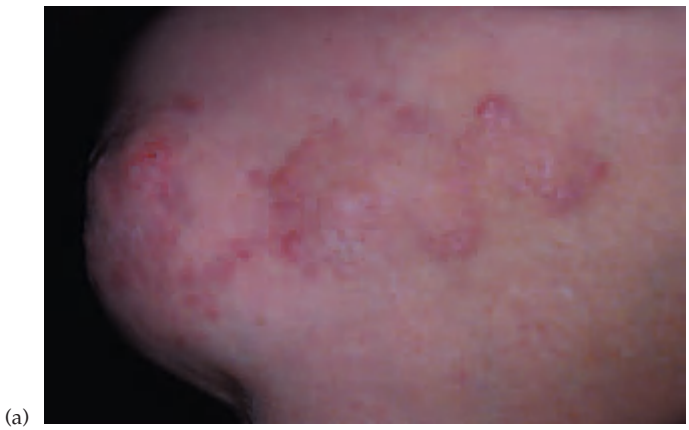
Additional simple clinical examination

Wetting the skin with water or mineral oil (which lasts longer) fills air spaces in scale and allows underlying features to become more visible. In some instances, this just enhances underlying redness—for example, in psoriasis. In other instances, diagnostic features may become apparent to the naked eye (such as Wickham's striae in lichen planus) or with the aid of additional magnification (e.g. use of a dermatoscope to examine pigmented lesions). Soaking of the skin may make the lesions of pitted keratolysis more apparent.

Application of heat or cold may identify specific physical urticarias. Whole-body warming may confirm cholinergic urticaria. Even whole-body cooling has been used, to identify dysarthria as being due to Raynaud's phenomenon of the tongue.

Pinprick sensation may be lost in leprosy.

Paring the skin allows distinction between a wart and a



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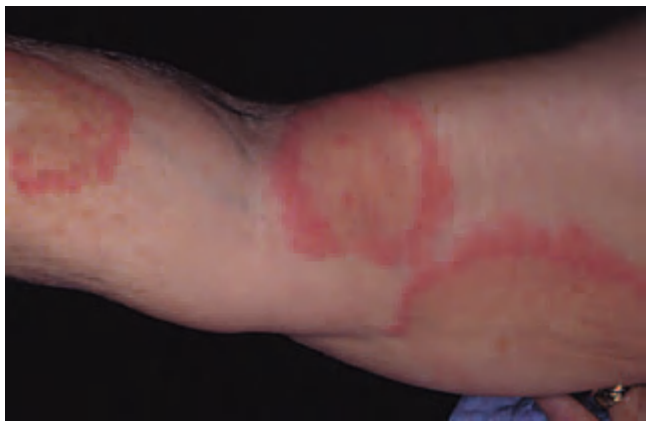

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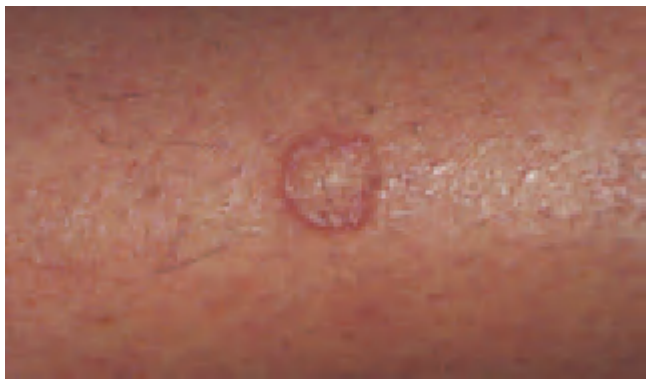

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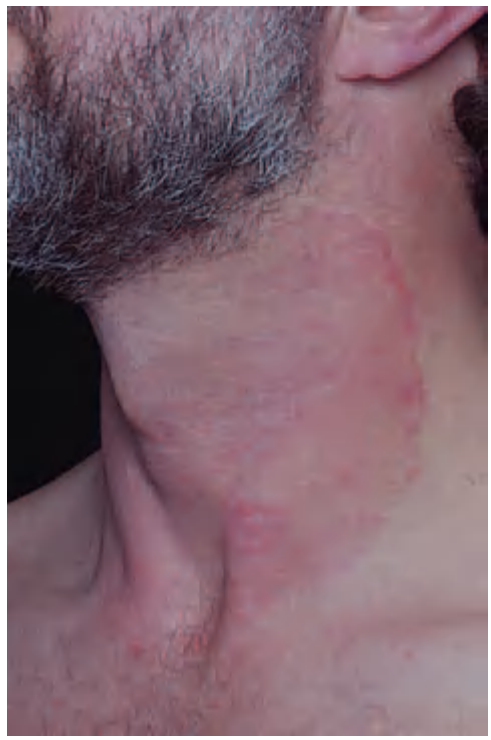

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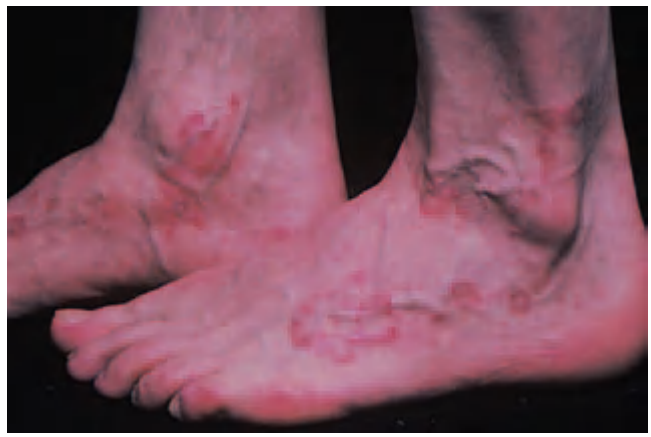


(e)

Fig. 5.2 Annular lesions. (a) Annular perforating granuloma annulare on the elbow. (b) Erythema annulare centrifugum. (c) Annular scale in porokeratosis. (d) Annular lesion of tinea corporis. (e) Annular lichen planus.

corn, or may confirm the presence of old blood in *talon noir* or a haematoma.

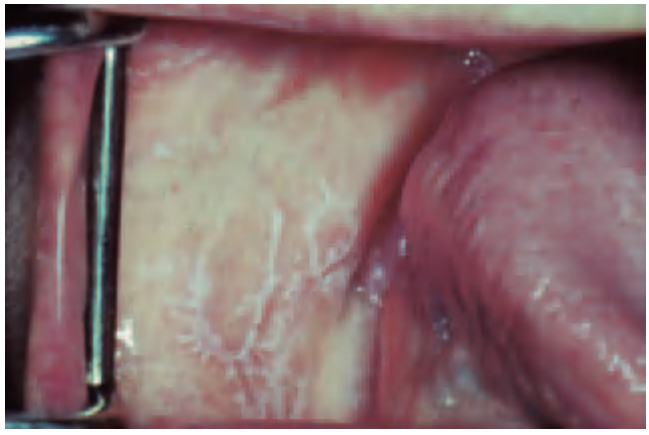
Smell may be useful—for example, in suspecting anaerobic wound infection, or rarities such as trimethylaminuria.

Simple microscopy may be diagnostic for hair shaft abnormalities and for distinguishing between hair casts and head lice egg cases (nits), and is used to detect cutaneous fungal disease.

Additional clinical investigations

Diascopy

Pressing a glass slide or (more safely) a stiff, clear, colourless piece of plastic onto the skin compresses blood out of small vessels, to allow evaluation of other colours. Diascopy is of particular value in detecting granulomatous nodules, which have a translucent brownish colour known as 'apple jelly' nodules (e.g. in lupus vulgaris). In naevus anaemicus, a localized area of vasoconstriction, other pigments are unaltered—diascopy of adjacent skin therefore reveals an identical colour to that of the 'depigmented' area. By contrast, diascopy of skin adjacent to



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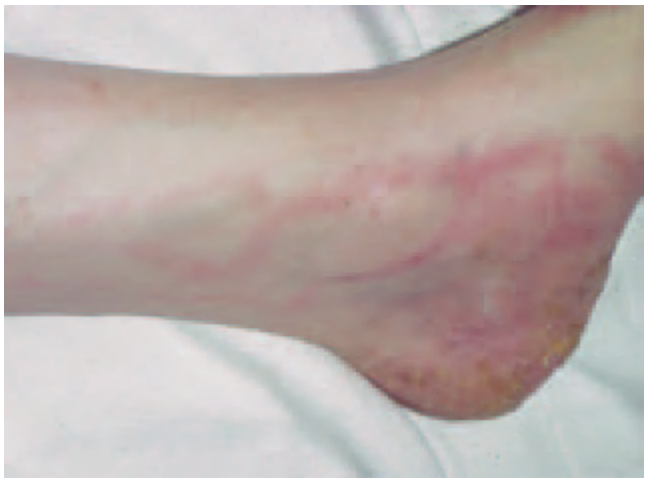

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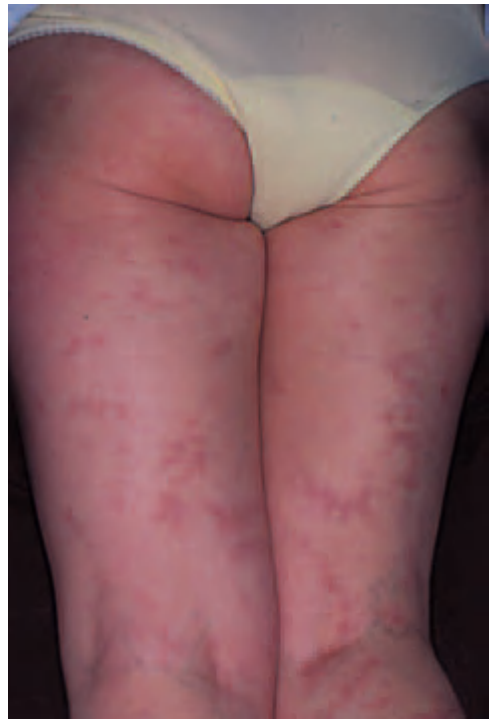

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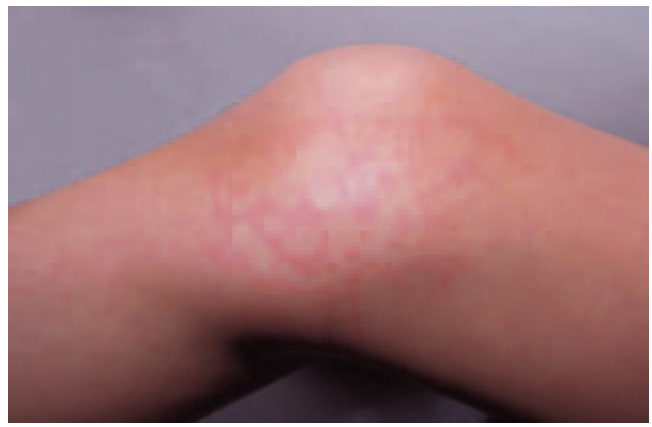

(d)

Fig. 5.3 Reticulate lesions. (a) Reticulate buccal lichen planus. (b) Reticulate lesions in lymphangitis. (c) Broken livedo reticularis in cutaneous polyarteritis nodosa. (d) Reticulate erythema in resolving erythema infectiosum (fifth disease).

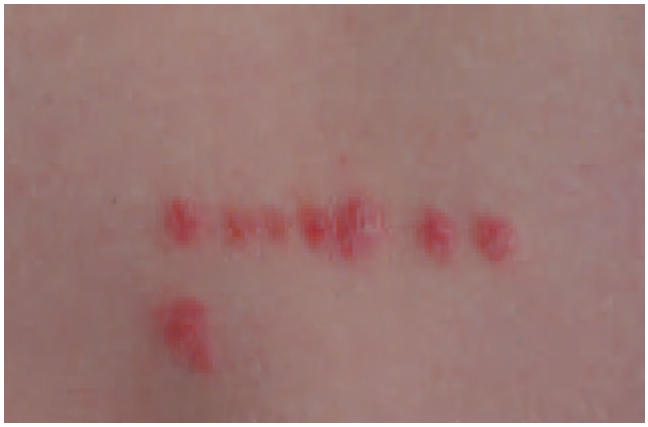

Fig. 5.4 Koebner phenomenon in psoriasis.

vitiligo, in which there is loss of melanin, demonstrates that the vitiligo remains paler. Application of medium pressure to a spider naevus can compress radiating arterioles and allow visualization of pulsatile flow in the feeding vessel.

Wood's light

This is a source of ultraviolet light from which virtually all visible rays have been excluded by a Wood's (nickel oxide) filter. Applications of Wood's light are listed in Table 5.5 [1,2].

Variations in epidermal pigmentation are more apparent under Wood's lamp than under visible light, whereas variations in dermal pigment are less apparent [3]. Thus,

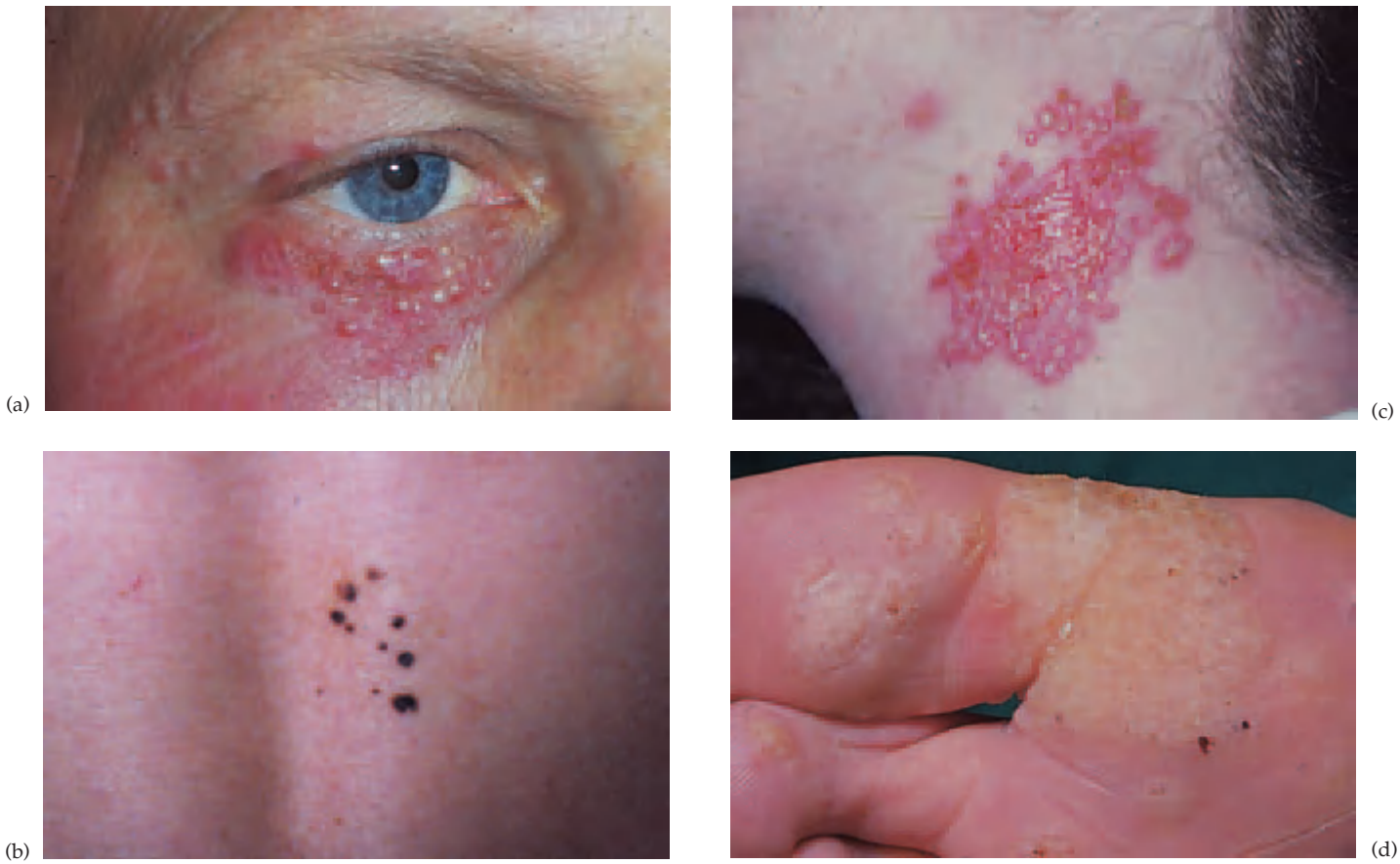

Fig. 5.5 Grouped lesions. (a) Agminate acne. (b) Grouped pigmented areas in a speckled lentiginous naevus. (c) Grouped vesicles in herpes simplex. (d) Grouped lesions within a mosaic plantar wart.

for example, it can be used to distinguish vitiligo from naevus anaemicus. Vitiligo is due to loss of epidermal melanin, and the depigmented areas are greatly exaggerated under Wood's light—naevus anaemicus is due to localized dermal vasoconstriction with normal overlying epidermal pigmentation, and the pallor completely disappears under Wood's light. The ash-leaf macules of tuberous sclerosis are much more prominent under Wood's lamp [3].

Many organisms produce chemicals that fluoresce under Wood's light [4,5] including *Propionibacterium acnes* [6], and *Corynebacterium minutissimum*, the bacterium responsible for erythrasma (Fig. 5.8), and conversion of aminolaevulinic acid to protoporphyrin occurs in several tumours and other skin lesions, leading to the technique of photodynamic diagnosis [7]. Fluorescein can be added to topical agents in studies of their use—for example, to detect areas that are missed during sunscreen application [8]. Wood's light can also be used to view *ex vivo* specimens, such as blood or urine in porphyrias [9], or even

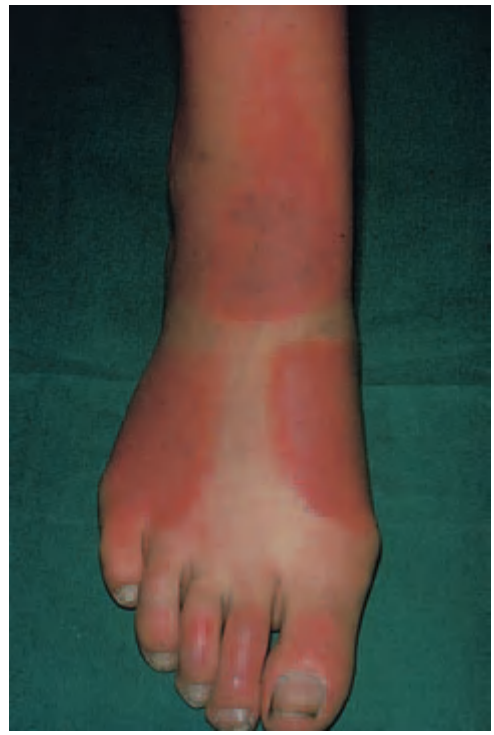

Fig. 5.6 A drug-induced phototoxic eruption showing sparing under the sandal.

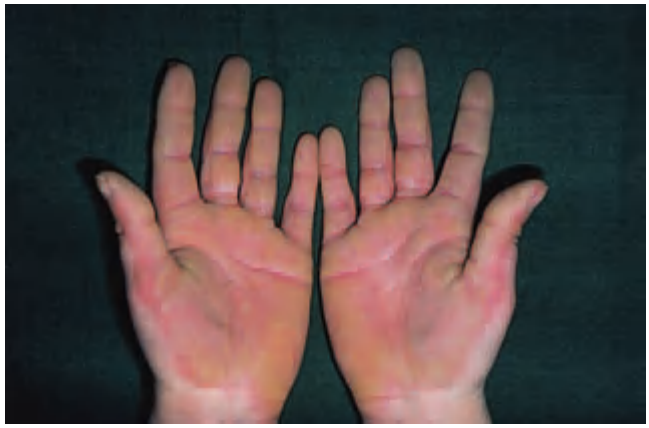

Fig. 5.7 A keratoderma showing abrupt discontinuation at Wallace's line.

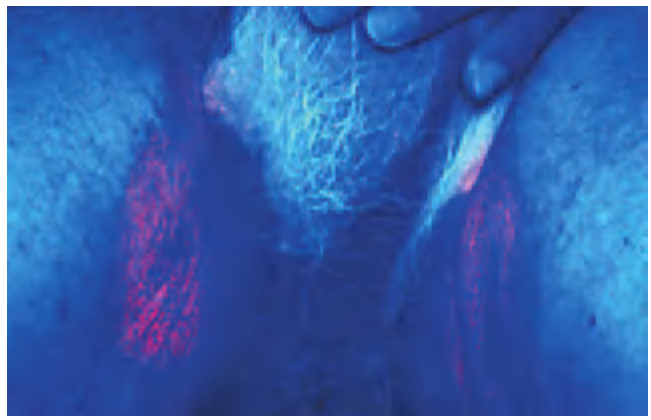

Fig. 5.8 Coral pink fluorescence of groin erythrasma.

inanimate objects, such as clothing from patients with chromhidrosis [10].

There are pitfalls of using Wood's light:

- It is useful to diagnose tinea capitis acquired from cats or dogs, but most fungi do not fluoresce, so a negative test does not exclude the diagnosis.
- There is some reflection of light from any scaly dermatosis, which may be confused with the relatively subtle colour change of pityriasis versicolor.
- Optical brighteners in detergents fluoresce strongly—white shirts and coats may be a considerable distraction.
- Erythrasma fluoresces pink due to porphyrins—it is a reasonably frequent finding that the expected

Table 5.4 Colours of skin lesions. (Adapted from C.M. Lawrence and N.H. Cox, *Physical Signs in Dermatology*, 2nd edn, London: Mosby, 2002: 21.)

Colour	Examples
Black	Melanin, e.g. some naevi, melanoma
	Exogenous pigments, e.g. tattoos, pencil/ink
	Exogenous chemicals, e.g. silver nitrate, gold salts
	Deeply situated blood or melanin, e.g. angiomas, blue naevus
Blue-grey	Inflammatory diseases, e.g. orf
	Drug-induced pigmentation, e.g. phenothiazines, minocycline
Dark brown	Melanin near the skin surface, e.g. most melanocytic naevi
	Exogenous pigments, e.g. dithranol (anthralin) staining
Pale brown	Melanin near the skin surface, e.g. lentigo, freckles
Muddy brown	Melanin in the superficial dermis, e.g. post-inflammatory pigmentation
Purple	Vascular lesions, e.g. angiomas
	Other disorders where telangiectasia is a prominent feature, e.g. lupus pernio (chronic sarcoidosis), dermatomyositis
Dusky blue	Reduced amounts of oxygenated haemoglobin, e.g. poor arterial supply, central causes of cyanosis, methaemoglobinaemia
Violaceous and lilac	Lichen planus, edge of plaques of morphoea,connective tissue disorders, e.g. dermatomyositis
Pink-red	Many exanthemata and common disorders, such as psoriasis
Red-brown	Inflammatory dermatoses, e.g. seborrhoeic eczema, secondary syphilis
	Haemosiderin, e.g. pigmented purpuric dermatoses
Scarlet-red	Lesions with a strong arterial supply, e.g. pyogenic granuloma, spider naevus
	Altered haemoglobin, e.g. carbon monoxide poisoning
Orange	Haemosiderin, e.g. lichen aureus
	Inflammatory disorders, e.g. pityriasis rubra pilaris
Yellow-white/yellow-pink	Xanthomatous disorders
Yellow-orange	Carotenaemia (ingested carotene, myxoedema)
Yellow-green	Jaundice
Green	Exogenous pigment, e.g. copper salts
White-ivory	Lichen sclerosus et atrophicus, morphoea
White (or pale pink, depending on vascularity)	Vitiligo, naevus anaemicus, arterial insufficiency, chemical depigmentation

Table 5.5 Uses of Wood's light.

Fungal infection	Tinea capitis—green fluorescence associated with *Microspora* species and favus (see also Chapter 31) Pityriasis versicolor—yellow
Bacterial infections	Erythrasma, acne—coral pink (porphyrins) *Pseudomonas pyocyanea*—yellowish green (pyocyanin)
Infestations	Scabies—fluorescein solution fills the burrows and can be viewed with Wood's light
Porphyrias (see also Chapter 57)	Urine, faeces and occasionally blister fluid fluoresce in porphyria cutanea tarda; teeth in erythropoietic porphyria; blood in protoporphyria
Pigmentary disorders	Vitiligo is accentuated (see text), dermal pigment becomes less apparent Detection of ash leaf macules in tuberous sclerosus
Drugs and chemicals	Detection in tissues, e.g. staining of teeth or sebum from tetracyclines and of the nails from mepacrine Detection of fluorescent contact or photosensitizers on the skin, or in cosmetics and industrial agents, e.g. ballpoint-pen ink, eosin, furocoumarins, halogenated salicylanilides, pitch ingredients Fluorescein can be added to topical medications to investigate sites of application or of manipulation (e.g. in the investigation of dermatitis artefacta)
Tumours	Red fluorescence can occur in some malignant tumours and other lesions of the skin, especially squamous cell carcinomas. Conversion of aminolaevulinic acid to protoporphyrin IX occurs within tumours as the first step in photodynamic therapy and can be detected with Wood's light
Miscellaneous	Lipofuscins in sweat from patients with chromhidrosis can be identified by Wood's light examination of stained clothing. Research use of fluorescent 'markers' for the investigation of cutaneous penetration and epidermal turnover. Detection of mineral oil on the skin in the assessment of barrier creams

fluorescence is negative if the affected skin has been washed prior to a clinic appointment.

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Clinical microscopy and dermoscopy

Microscopy is an important laboratory technique, discussed briefly later. However, microscopy in a clinical setting also has several uses.

Dermoscopy

This technique, also known as dermatoscopy or epiluminescence microscopy, is an extension of the use of simple magnification. Dermoscopes have built-in illumination, and are applied to the skin surface with a film of oil on the lesion to enhance visibility of subcorneal structures. The technique is mainly used in the diagnosis of doubtful pigmented lesions (Chapter 38). The images may be viewed directly, photographed or recorded digitally for subsequent or sequential analysis. A structured system of analysing the colours and appearances of the structural elements (pigment network, globules and dots, horn cysts and pseudofollicular openings and the vascular patterns visualized) may increase the accuracy of diagnosing malignant melanoma [1]. Scoring systems such as the ABCD dermatoscopy score (assessing *a*symmetry, *b*order *c*olour and *d*ermatoscopic structures) [2] and a 'seven-point check list' [3] have been devised. Computerized image analysis is being developed to aid in distinguishing benign melanocytic lesions from melanoma [4]. Dermoscopes can also be useful in the identification of scabies burrows and mites, and in distinguishing haemangiomas, angiokeratomas, pigmented basal cell carcinomas and seborrhoeic keratoses from melanocytic lesions.

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Identification of scabies mites

Scabies mites can be extracted from the end of a burrow using a needle, with microscopy to confirm the diagnosis. The technique can be useful to convince sceptical sufferers of their infestation. Alternatively, application of mineral oil [1] or 5% potassium hydroxide to an affected interdigital space, followed by light scalpel scraping, reveals the acarus or its eggs. The faecal pellets (scybala) of the mite are also diagnostic, but are dissolved by potassium hydroxide; they remain intact in oil. Burrows can also be removed by a very superficial shave technique, and can be made more apparent by application to the skin of either black ink, or fluorescein with Wood's light visualization. Dermatoscopy (see above) can also be used—the mite appears as a dark triangle shape—or higher-resolution microscopy with a standard light microscope [2]. Outwith the scope of this section, scabies can also be identified using polymerase chain reaction (PCR) to detect mite antigens [3].

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Other simple microscopy procedures

Simple light microscopy is helpful in evaluating hair shaft abnormalities (this, and more complex electron microscopy, are discussed in Chapter 63).

Microscopy of skin scrapings for fungi is discussed in Chapter 31. Scraping the base of a herpetic vesicle with simple Giemsa staining may reveal giant cells (Tzanck smear); molluscum contagiosum can be identified in a similar fashion. Examination of skin pustule smears after fixation and haematoxylin and eosin staining may be useful in the rapid diagnosis confirmation of infantile eosinophilic folliculitis and incontinentia pigmenti; in both conditions, the pustules are filled with eosinophils.

Skin surface biopsies using tape-stripping or adhesive microscope slides pressed onto the skin allows observation of cells of the stratum corneum and of bacteria, fungi such as *Pityrosporon* species, and *Demodex* mites [1–3]. Plastic polymer (Silflo) skin surface impressions may be useful for the study of eccrine gland pore size and numbers.

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Fine-needle aspiration of lymph nodes (FNA)

Aspiration of lymph node tissue using a 25- or 27-gauge needle allows cytological assessment of lymph nodes and is useful in the staging of metastatic malignant melanoma and squamous cell carcinoma of the skin, as well as the assessment of lymph nodes in suspected lymphoma. In patients with palpable lymph nodes and melanoma, the technique has been shown to have high specificity and sensitivity [1]. Combining the technique with flow cytometry can help in the differentiation of lymphoma from reactive and dermatopathic lymphadenopathy [2].

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Commonly used laboratory tests

Numerous special investigations are used to refine a dermatological diagnosis, or for disease or therapy monitoring. Many of these are discussed specifically in relevant chapters—for example, testing for photosensitivity (Chapter 24) or for contact allergy (Chapter 20). The commonest tests which involve additional laboratory processing of samples are as follows:

- Blood tests for haematology or biochemistry. These are used in numerous situations, both diagnostically and for assessing the impact of a skin disease or for monitoring systemic therapy. Many infective disorders or acute inflammatory conditions are associated with neutrophilia or with abnormal results of inflammatory markers such as erythrocyte sedimentation rate or C-reactive protein; eosinophilia is also a feature of several dermatological conditions (Table 5.6).
- Blood tests for immunological studies. For example, in the diagnosis of connective tissue diseases (Chapter 56), IgE and radioallergosorbent test (RAST) in atopic and allergic diseases (Chapters 10 and 18).
- Histology of skin biopsy (Chapter 7). This may include special staining methods, direct immunofluorescence studies and immunocytochemistry. 'Rush' frozen sections may be necessary—for example, during micrographic surgery or in the urgent diagnosis of some blistering conditions [1].
- Other immunological and microscopy studies for bullous diseases, e.g. immunoblotting (Chapter 41), electron microscopy (Chapters 13 and 40).

Table 5.6 Some 'dermatological' causes of eosinophilia (more than 0.44×10^9/L eosinophils).

Atopic disorders, especially asthma and eczema
Parasitic infestations
Worms (intestinal or systemic)
Scabies
Allergy to food or drugs
Tryptophan myalgia syndrome
Collagen vascular disease (especially polyarteritis nodosa and variants), dermatomyositis and eosinophilic fasciitis
Malignancy, especially Hodgkin's disease and eosinophilic leukaemia
Bullous disorders
Dermatitis herpetiformis
Pemphigus
Pemphigoid
Erythema neonatorum
Hypereosinophilic syndrome

- Bacteriology and mycology samples (Chapters 25–31). May include samples for microscopy and culture, serological tests, PCR tests (e.g. for mycobacteria).
- Cytological examination. Usually in the context of FNA from lymph nodes, discussed above.

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Radiological and imaging examinations

These have an important role in dermatology, but less than in many other specialties, because the skin can so readily be seen and felt. Ultrasound [1,2], magnetic resonance imaging [3–5] and even positron emission tomography [6,7], when available, are all used in clinical practice, but more often at present as research tools. They are used, for example, for the accurate assessment of the thickness of lesions in scleroderma, the extent of infection in severe forms of cellulitis or in the assessment of tumours. They also come into their own in the management of diseases like neurofibromatosis, where there may be central nervous system involvement, or in the assessment of muscle change in dermatomyositis. Lymphoscintigraphy may be a useful functional assessment of the lymphatic system of the swollen lower limb (Chapter 51). Doppler assessment of the peripheral lower limb arteries is an essential bedside technique prior to the use of high-compression bandaging in the management of venous leg ulcers (see Chapter 50).

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Skin testing

Substances may be introduced into the skin by a variety of techniques to study pharmacological and immunological [1] reactions under controlled conditions. Such tests are extremely valuable, but details of the type of test and the time at which it is read must correspond to the pathological process under consideration. Interpretation of the relevance of tests, either positive or negative, must always be correlated with the clinical picture. All too often, evidence adduced from tests is either meaningless or misleading.

Absorption of many substances through the intact skin is poor and variable, but direct application to the surface of the skin is used for patch testing. The epidermal barrier may be overcome either by removing it or by introducing the material directly into the dermis. The following techniques for skin testing are most commonly used.

Techniques for skin testing

Epicutaneous tests—patch tests. Patch tests are usually used to detect contact allergy of the delayed hypersensitivity type. They are usually read at 48–72 h and again up to 1 week, but can also be read at 15–30 min to detect contact urticaria. At times, patch testing may usefully be combined with scratch testing. Details of these techniques are discussed in Chapters 19–21.

Intradermal injection

The injection is made into the superficial layer of the dermis through a fine-bore (26- or 27-gauge) needle with its bevel pointing upwards. The quantity that may conveniently be injected varies from 0.01 to 0.1 mL. Precise measurement of smaller quantities is difficult and requires syringes with especially well-fitting plungers and a micrometer screw gauge. For routine clinical purposes, an approximation is sufficient—either 0.05 mL or the amount that just causes a visible weal (0.01–0.02 mL).

The optimal time for reading the reaction naturally varies with the pharmacological agent or the type of immunological reaction. Most such tests are read at either

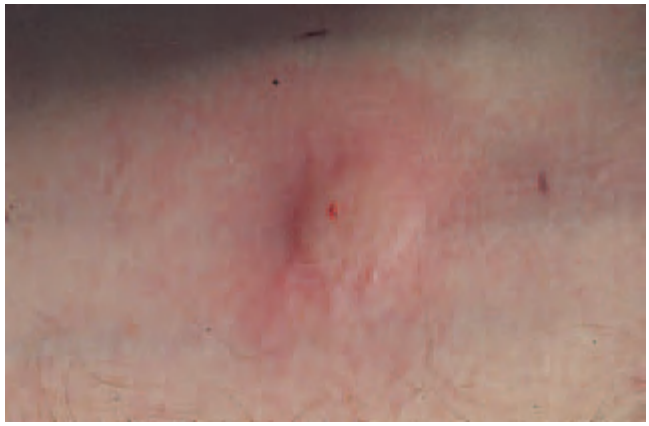

Fig. 5.9 A positive prick test reaction to latex allergen.

15–20 min or at 48 h, but it may be important to read the tests at other times, for example at 4–12 h or after 4 days. The response to be observed at 15 min—for example, after an injection of histamine or after immediate-weal allergy tests—is a weal with a surrounding flare (Fig. 5.9). The weal is a more accurate measure than the flare. When the test is read at 48 h—for example, in the tuberculin reaction—the sizes of the indurated papule and of the erythematous reaction should be observed.

The site of the test is of some importance [2,3]. In general, the whole skin surface is capable of responding to skin tests, but there are regional variations. The back and the flexor aspects of the forearms are most conveniently used. The skin on the ulnar aspect of the forearm is more sensitive than the radial, and the proximal more sensitive than the distal. These differences are not of sufficient magnitude to affect routine testing, but must be taken into account by using symmetrical areas for controls in any accurate quantitative testing.

A test solution must always be compared with a control solution injected in a comparable site at the same time. A positive test may be taken as one that is significantly different from the control. Assessment of what is significant is difficult, and varies with the enthusiasm of the tester. If a difference of less than 5 mm is accepted, reproducible results may not be obtained on retesting [4].

The measurement of a weal is usually made by diameter, although more sophisticated methods such as volume measurements and Doppler flow have been used [5]. If the weal is not circular, an approximation may be made by averaging maximum/minimum diameters, or more accurately the area may be calculated by the formula $D_1 \times D_2 \times \pi/4$, where D_1 and D_2 are the maximum and minimum diameters [6]. For irregular weals, a tracing may be made on squared paper. Pseudopodia should be noted, but for measurement of diameter they are ignored. Attempts to assess the volume of a weal are less satisfactory for routine use.

The size of the weal is not directly proportional to the dose of the active agent, but varies also with the total volume of fluid injected. An approximation of a linear relationship may best be achieved, often only over a narrow range, by plotting the response against the log dose. For accurate quantitative observations, weal diameters below 4 mm or above 15 mm cannot be relied upon.

Antihistamines may greatly inhibit the immediate weal tests. In the case of very long-acting agents, this effect may last as long as 3 weeks. They have no appreciable effect on delayed hypersensitivity patch tests. Moderate to large doses of corticosteroids, in contrast, may somewhat inhibit patch tests, although smaller doses—for example, prednisone 10 mg daily—are not necessarily a contraindication to testing. Steroids do not greatly inhibit the immediate weal tests. When a patient feels faint, any immediate weal test may be completely inhibited.

Prick test

This is a modification of the intradermal injection. A small quantity of the test solution is placed on the skin and a prick is made through it with a sharp needle. This should be superficial and not sufficient to draw blood. The quantity has been estimated as 3×10^{-6} mL [3]. The size of the weal and flare are measured after 15 min (Fig. 5.9). This test gives reproducible results and is convenient for much routine allergy testing. Because of the discrepancy in quantities injected, the testing solutions are made up at different strengths for prick testing and intradermal testing. The intradermal injection of prick-test solutions may be dangerous.

Scratch test

The scratch test resembles the prick test. A linear scratch about 1 cm long, but not sufficient to draw blood, is made through the epidermis. This test gives less reproducible results than the prick test.

Modified prick test

Here, a drop of the test solution is placed on the skin. A needle is then inserted very superficially and almost horizontally into the skin and lifted to raise a tiny tent of epidermis. This test is slightly more sensitive than the ordinary prick test, but gives no more reproducible results.

Skin-window technique [7,8]

The surface of the skin over an area a few millimetres square is scratched off with a scalpel, the test solution applied and the area covered with a coverslip. This is removed at various intervals—for example, 3 h, 6 h, 12 h, 24 h and 48 h—and immediately replaced by another

coverslip. The cells on the coverslip are stained with ordinary haematological stains. The cellular response at varying time intervals can be assessed.

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Immediate weal tests

These tests are used for detecting IgE antibodies. The passive transfer test may be used to detect circulating IgE, but is not recommended because of the risk of serum hepatitis or human immunodeficiency virus (HIV). These antibodies play a role in hay fever, asthma, atopic dermatitis and anaphylactic reactions. They occur especially, but not exclusively, in patients with a personal or family background of atopy. Positive skin tests to a wide variety of antigens are extremely frequent in these patients and must always be correlated with the history. They are principally used in the assessment of hay fever and asthma and have a limited place in the management of atopic dermatitis (Chapter 18). They are disappointing in the diagnosis of urticaria. False-positive and false-negative reactions are common.

Severe systemic reactions and, very rarely, fatalities may occur after correct use of standard testing solutions, and epinephrine (adrenaline) and hydrocortisone injections should always be at hand when skin tests are performed [1,2].

Alternative methods of detecting and measuring circulating antibodies are the RAST and the enzyme-linked immunosorbent assay (ELISA). RAST correlates well with skin testing [3,4]. It is particularly useful in (i) testing very young children; and (ii) with allergens associated with risk on prick testing (e.g. drugs).

The autologous serum test is a technique used in the investigation of chronic idiopathic urticaria whereby the patient's own serum is injected intradermally. It is regarded as being positive if at 30 min there is a weal 1.5 mm larger than at the saline control injection site. Positive reactions are indicative of functional autoantibodies against the high-affinity IgE receptor FcεRI, or against IgE [5] (Chapter 47).

Delayed (4–8 h) tests

The clinical interpretation of tests that are positive at 4–8 h can be difficult. Sometimes, these represent an Arthus reaction, but ideally this should be confirmed histologically. Other such tests represent a delayed variant of the immediate weal (15-min) test.

Intradermal tests for the detection of delayed sensitivity to bacterial, fungal and viral antigens

The tuberculin test. A positive result to the standard strength (10 tuberculin units, TU) is an indication of previous mycobacterial infection, but not necessarily by *Mycobacterium tuberculosis* (especially if the reaction is weak or doubtful). Reactions to 1 TU (1/100 dilution of purified protein derivative (PPD)) are, however, significant. In sarcoidosis, reactions may be wholly negative, or only positive to 100 TU. The minimum size of a positive reaction is taken as 5 mm. An intermediate (24-h) reaction sometimes occurs.

Comparable doses of PPD may vary according to their source. Misleading negative reactions may occur in anergic patients. Tuberculin tests are discussed further in Chapter 28.

The Heaf test. Used in mass testing and in children. It is roughly equivalent to, or perhaps slightly more sensitive than, a dilution of 1 : 100 old tuberculin [6].

Candida antigen is used in a similar manner to the tuberculin test. Depressed reactivity occurs in sarcoidosis and other immunosuppressed conditions. Negative reactions in normal subjects are, however, not uncommon and depend on age and locality.

Trichophytin detects past infection by *Trichophyton* species. Its value is limited.

The lepromin test. This is discussed in Chapter 29.

Histoplasmin, coccidioidin and similar antigenic tests are of most value in areas where these diseases are not endemic. The *Frei test* and *cat scratch fever antigen* are of some value in the UK, where the relevant diseases are comparatively rare. A positive reaction is then significant. Conversely, *Brucella antigen* and *toxoplasmin* are of limited use in dermatological practice.

Delayed-type bacterial antigen tests [7–9]. These are not widely used, partly because their specificity and interpretation are difficult to assess. They consist of standard preparations of bacterial extracts, each probably containing a mixture of antigenic components, which may produce an immediate, or delayed 48-h reaction or an

even later reaction. The normal 48-h response is a papule showing, histologically, a tuberculin-type reaction of lymphocytic type. Occasionally, however, especially in cases of vasculitis, an acute leukocytoclastic reaction occurs within 6–8 h [8] and is fully established at 24–48 h. Sometimes, the reaction is severe enough to produce a sterile abscess. It is tempting to believe that these reactions may be of some significance in conditions such as erythema multiforme, erythema nodosum (streptococcal), allergic vasculitis and, perhaps, pustular psoriasis. However, the antigens at present in use are relatively impure and the reactions may be non-specific. Further careful immunological studies are required.

Long-delayed (6-week) intradermal reactions. These comprise the *Kveim test* and the *Mitsuda test*. They are read at 6 weeks, but biopsy is essential with the Kveim test. Kveim test antigen is no longer available in the UK.

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Oral provocation tests

The administration of a drug, food or chemical by mouth may sometimes be called for to confirm the diagnosis of an eruption or to establish its exact cause. Such tests are used in the following situations.

1 To determine the cause of a drug eruption or to isolate one from a number of drugs or ingredients of a compound drug. It is applicable only when the drug given and the dose chosen are unlikely to provoke a severe reaction in the patient. It may be a valuable method of proving the cause of a fixed drug eruption but should rarely, if ever, be used if the reaction has been of a generalized or acute nature. The subject is discussed in more detail in Chapter 73.

2 In the course of the investigation of food allergens [1–3]. The reintroduction of specific foods, one at a time, is an established part of exclusion, elimination and challenge diets. It is important that the role of the suspect food is subsequently confirmed by reintroducing it in a disguised form to avoid identification by the patient.

The procedure is applicable to patients with atopic eczema (Chapter 18), chronic or recurrent urticaria (Chapter 47) and possibly to some other dermatological conditions that have an allergic basis. However, it must be carried out with care and is only valuable if the tests are properly controlled and the patient is cooperative and well motivated.

3 In establishing the role of additives in chronic urticaria or angio-oedema (Chapter 47). Tartrazine, benzoates and antioxidants have been especially implicated [4–6]. Although oral provocation with increasing test doses of these substances is theoretically simple, the same reservations apply, and the administration of the diets and the 'blind' challenge require time, patience and motivation. Audit has shown that these tests appear to benefit the patient at low cost, but their scientific validity remains uncertain [7].

The role of oral nickel and chromate in the behaviour of endogenous hand eczema has been studied [8,9]. Some authors have produced flares of vesicular hand eczema after oral administration of nickel, but others have been unable to reproduce these results when interspersing test doses with placebo capsules.

Oral provocation with balsam of Peru was used in a series of 221 patients [10]. Flares of an existing dermatitis occurred in 45 patients, only 17 of whom had shown positive patch-test reactions to this substance. Subsequent dietary restriction of flavourings was said to clear or 'markedly improve' the dermatitis in half the patients.

Sublingual food tests are unreliable [11].

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Telemedicine

Considerable clinical experience is needed in order to make correct dermatological diagnoses, and since trained dermatologists are in relatively short supply even in many developed countries, telemedicine—remote consultation via an electronic link—may become an attractive option. It is particularly useful in remote or rural areas where there are no specialists.

Dermatologists have for many years conducted long-range consultations by telephone or by mailing histology slides or clinical photographs, but the unique feature of telemedicine is the two-way electronic network that now allows immediate interactive communication between the patient, the primary care physician and the specialist (so-called real-time teleconsultation). Different parts of the patient can be viewed at various magnifications, and the specialist can ask supplementary questions and advise on the most suitable biopsy sites if necessary. A less satisfactory, but time-efficient, approach is the 'store and forward' system, whereby history details and images taken remotely are reviewed later by a distant specialist. This does not allow simultaneous supplementary history and directed image choice, which may hamper appropriate management.

Several trials have shown that telemedicine can be effective, with high levels of satisfaction reported by patients, GPs and hospital specialists [1–3], although a recent study involving telemedicine in several specialties showed that the visual images were not adequate for the dermatologist [3]. A personal encounter between specialist and patient may offer additional advantages, such as enhanced information about the patient's personality, with more patient participation in decisions and a placebo effect, which can lead to greater compliance [4].

Further technical developments will lead to better visual definition, which will be particularly helpful to dermatologists, and telemedicine clearly has considerable potential for dermatological diagnosis [5,6].

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Chapter 6

Epidemiology of Skin Disease

H.C. Williams

What is epidemiology and why is it relevant to dermatology?

> *Epidemiology is the simplest and most direct method of studying the causes of diseases in humans and many contributions have been made by studies that have demanded nothing more than an ability to count, to think logically and to have an imaginative idea.*
>
> (Sir Richard Doll, 1987 [1])

Many dermatologists still think of epidemiology in terms of describing the prevalence and the age, sex and geographical characteristics of a particular skin disease. Whilst it is true that epidemiology is often used in this fashion to describe the *burden* of disease in human populations, as Sir Richard Doll points out above, epidemiology offers one of the most powerful and direct methods of evaluating the *causes* of skin diseases in human populations. One definition of epidemiology is therefore 'the study of the distribution and causes of diseases in human populations'. In addition to describing the burden and causes of skin diseases in populations, *clinical epidemiology* is concerned with describing the natural history and prognosis of diseases and evaluating interventions which seek to prevent or treat diseases [2]. The term *dermato-epidemiology* refers to the study of the epidemiology of dermatological disorders [3]. Because epidemiological studies are often concerned with making observations about highly complex natural experiments, methods for minimizing bias or adjusting for confounding factors (see glossary) have had to be developed. These new methods, along with the high scientific rigour necessary for designing and interpreting epidemiological studies, are aspects from which all dermatological research can benefit. Epidemiology is therefore relevant to dermatology for the five reasons shown in Table 6.1.

Although epidemiology is often perceived as a novel addition to dermatology, the first epidemiological discoveries in dermatology can be traced back to 1746, when James Lind [4] concluded that scurvy in sailors was related to dietary factors. He then showed, by means of a controlled study, that the disease readily responded to the addition of fresh oranges and lemons in the sailors' diet. In 1914, Joseph Goldberger [5] observed that 8% of 418 patients admitted to the Georgia State Sanatorium developed pellagra, compared with none of the 293 Sanatorium employees. He suggested that pellagra was due to an absence of 'essential vitamins', today recognized as nicotinic acid, and proceeded to test his suggestion in a community trial. Thus, dermato-epidemiology is not such a new subject, and with over 2000 skin disease reaction patterns described, the scope of the topic is vast. This chapter will therefore not deal with the epidemiology

Table 6.1 The relevance of epidemiology to dermatology.

To quantify the burden of skin disease in the community
To identify the causes or risk factors for skin diseases
To describe the natural history, prognosis and disease associations of skin diseases
To evaluate the effectiveness of dermatological health services
To provide a methodological framework for designing and interpreting clinical dermatological research

of specific skin diseases—which will be described where possible under the relevant disease sections—but it will attempt to illustrate the relevance of modern epidemiology to dermatology by using specific examples from dermatology. A glossary of commonly used epidemiological terms and further reading sources are to be found at the end of this chapter.

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Thinking in terms of populations rather than individuals

The community diagnosis

One of the first hurdles to overcome when considering the epidemiology of a skin disease is to think in terms of *populations* rather than *individuals*. Many physicians find this conceptual jump quite difficult, as they are used to dealing with *individual* patients on a daily basis, whereas epidemiological studies refer to *groups* of individuals. Just as molecules, genes and individuals exhibit various aggregate characteristics, entire groups or populations exhibit their own unique characteristics and problems that enable a *community diagnosis* to be achieved [1].

Interesting patterns can occur when one explores the potential implications of treating an entire community (the public health approach) rather than sick individuals who present themselves to doctors (the high-risk approach). Rose [2], for example, showed that a 10-mm lowering of blood pressure distribution as a whole (e.g. from reducing salt intake) would correspond to about a 30% reduction in the total attributable mortality, simply because of the shape of the change conferred on the distribution curve in relation to specific 'disease' cut-off points.

During the scabies epidemics which occurred on the islands near Panama in the 1980s [3], it was found that even the best topical treatments when administered properly had no sustainable impact on the overall prevalence of scabies (which was very high in this population and associated with considerable morbidity from secondary pyoderma). When a *population* approach was adopted, i.e. treating all individuals with a programme of continuing surveillance, the prevalence of scabies fell dramatically to less than 2%, as shown in Table 6.2, and was sustained at that level until the US invasion of Panama interrupted these efforts. Thus, just as individuals become 'diseased', entire populations can become sick [2]. In these situations, a treatment policy based on a population diagnosis is usually beneficial, cost-effective and appropriate [4].

Skin diseases as 'entities' in the population

The concept of considering the health of entire populations also applies to the classification of skin diseases. Typically, dermatologists are preoccupied with deviants at the extreme end of the normal distribution curve who are selected because of disease severity and/or chronicity. Such individuals usually have well-defined physical signs which prompt those studying them to declare them as discrete 'entities' [5,6]. Such distinctions often become blurred when community surveys are undertaken. In a community survey of atopic eczema, for instance [7], it was noticed that indeterminate or borderline cases who had limited areas of dry skin or a single patch of eczematous inflammation were quite common. In these circumstances, perhaps the more relevant question is not 'Has the person got atopic eczema?' but 'How much atopic eczema does the person have?'

The concept of a distribution of disease severity at a population level may also be helpful in evaluating different treatment policies. For example, it has been estimated that a small change in the treatment threshold

Table 6.2 Prevalence of scabies among 756 Kuna Indians on the island of Ticantiki, Panama [3].

Date	Community treatment status	Prevalence of scabies (%)
July 1986	Conventional treatment	33.0
October 1986	Community control and surveillance instituted	0.7
July 1987	Breakdown due to supply problem	3.6
December 1988	Programme running again	1.5
March 1990	US invasion of Panama	12.0

of isotretinoin from severe to moderate cases of acne could result in a 15-fold increase in prescriptions in absolute terms, simply because moderate cases outnumber severe cases by so much [8].

Making comparisons and drawing inferences

Epidemiological reasoning usually progresses in an ordered fashion, starting with a hypothesis that has been suggested by a good clinical observation (e.g. palmoplantar psoriasis seems to be commoner in smokers) or descriptive studies of populations. This hypothesis is then tested in an epidemiological study which gathers and analyses data in a systematic fashion in relation to an appropriate comparison group to see if a statistical association exists. *Analytical epidemiology* is therefore concerned with making comparisons. These comparisons rely upon the uneven distribution of disease within and between populations to shed light on possible causes of ill health. Thus, previous case–control studies [9] showed that smoking was far more common in patients with lung cancer—a finding which led to more sophisticated studies to establish disease causality [10]. If everyone had smoked, it is possible that smoking would not have been identified as a cause of lung cancer.

In the simplest form of epidemiological study, a count is made of the number of cases with a particular skin *disease* (the numerator) within a catchment population (the denominator). The probability or frequency of disease occurrence may then be compared in two or more populations—for example, one exposed to a putative causative agent compared with another which is not. Inferences are then drawn based on the magnitude of the differences of disease frequency between the populations in light of possible *alternative explanations* such as chance, bias and confounding (see glossary). If such associations are genuine, further evidence is usually needed to determine whether they are causal in nature [11]. The whole process brings us one step nearer to the dermato-epidemiologist's ultimate goal—that of preventing skin disease, providing such causes are amenable to individual/public health manipulation. Prevention of skin disease is clearly more desirable than treating diseased individuals (Fig. 6.1).

When referring to an epidemiological study, it is important to make a distinction between the study population chosen for a particular study (e.g. those attending a hospital outpatient clinic) and the target population about whom one wishes to make inferences, as shown in Fig. 6.2.

The prevention paradox

Interventions that confer large population health gains may not confer much benefit to individuals. Thus, in the example of scabies in Panama above [3], although the population's health as a whole benefited greatly, many apparently healthy individuals may have not appreciated being treated for scabies, as it was not known who would have developed scabies in the absence of the prevention programme. Similarly, it is difficult to say which child will benefit from being immunized for tuberculosis in a BCG immunization programme, because events have not yet occurred. This conflict between large gains in the health

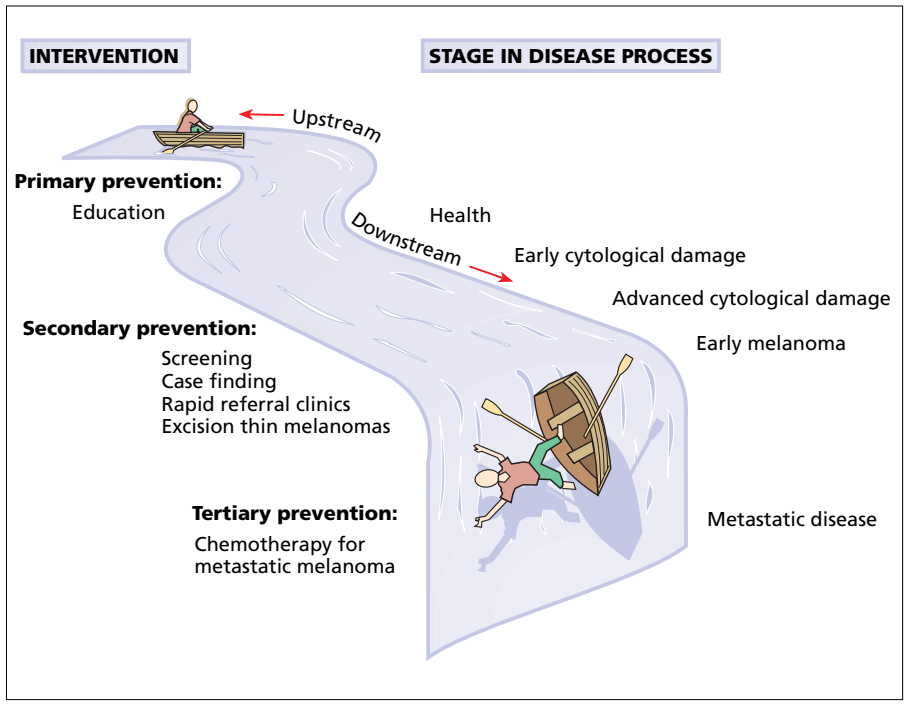

Fig. 6.1 Disease prevention in a serious condition such as melanoma is much more sensible than treating sick individuals with expensive drugs at the end of a long chain of irreversible pathological events.

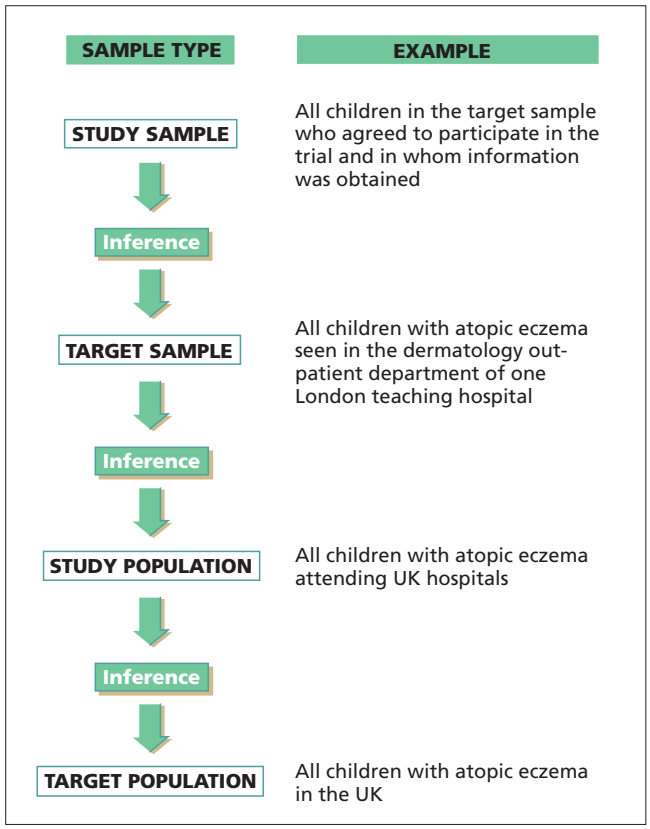

Fig. 6.2 Generalizing the results of a clinical trial of a new treatment for atopic eczema from a study of children attending one hospital department to all children with atopic eczema in the UK requires several jumps of inference.

of entire populations vs. small gains in individuals has been termed the 'prevention paradox' [4]. In the field of contact dermatitis, for example, eradication of a rare but potent contact sensitizer may have a great impact on affected individuals but little impact on the overall total burden of contact dermatitis in the general population. On the other hand, reduction in the amount of contact with formaldehyde, a less potent but far more common sensitizer in the general population, will result in a much larger reduction in the burden of contact dermatitis in that population, simply because far more people are exposed to formaldehyde [12]. As Table 6.3 illustrates, a little bit of harm affecting a lot of people can therefore add up to more than a lot of harm affecting a few people, in *population terms*. The first step when considering the epidemiology of skin disease is therefore to think about *populations* rather than *individuals*.

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How much of a public health problem is skin disease?

The need for a clear disease definition in epidemiological studies

A glance at the dermatological journals makes it clear that the subject matter of most current research is defined—wholly or in part—by diagnostic criteria. But if these criteria are not explicitly stated, are prone to vary from one patient to the next in unpredictable ways, and vary systematically from place to place and time to time, the usefulness of such research is gravely impaired. Although phrases such as 'diagnosed by dermatologists' or 'diagnosed independently by two experienced physicians' and 'all with typical symptoms' may be adequate for dealing with individual patients, they are hopelessly inadequate when describing *groups* of individuals in epidemiological studies [1]. For instance, it has been shown that even experienced physicians are perfectly capable of disagreeing

	Eradication of exposure in:	
	The population	The individual
Rare—Exposure with high relative risk	Small benefit	Large benefit
Common—Exposure with low relative risk	Large benefit	Small benefit

Table 6.3 The prevention paradox: a little bit of harm affecting a lot of people can add up to more than a lot of harm affecting a few people. From Williams [12] with kind permission from Karger, Basle.

Table 6.4 The attributes of a good disease definition for use in epidemiological studies. From Williams [45], with permission.

Validity: it measures what it purports to measure by including cases and excluding non-cases
Repeatability: good replication of the definition between and within observers
Acceptability: to the study population in order to ensure high response rates
Coherence: with prevailing clinical concepts
Easy to administer by field workers
Reflects some degree of morbidity
Comprehensiveness: applicable to a range of ages, ethnic groups and disease severities
Comparability: they should contain elements which allow some comparison with previous studies

with each other over the classical signs of atopic dermatitis [2], and when two agree, a third is capable of disagreeing. What is regarded as 'typical' in London may be nothing of the sort in Lourdes, Lima, Lhasa or Lusaka.

Diagnostic criteria that work well in hospital studies may perform poorly in community studies because of the effect of low disease prevalence on positive predictive value (see glossary) and an increase in borderline cases. The properties of good diagnostic criteria for use in epidemiological studies are summarized in Table 6.4.

Not only is it important to use diagnostic criteria of known validity and repeatability in epidemiological studies, but it is sometimes important to qualify cases identified by such criteria by some measure of disease severity. For example, prevalence surveys of acne in the absence of severity measures are not very helpful in quantifying the disease problem, since physiological acne (non-inflammatory lesions) affects over 90% of adolescents [3]. Again, severity grading systems used in a hospital setting (which are usually non-linear and tend to favour severe and currently active disease) may not be so helpful in separating disease severity in milder community cases, where intermittent disease may be more common.

Impairment, disability and handicap caused by skin disease

Consideration of the three concepts of impairment, disability and handicap may be helpful in separating those effects which result from disordered function from those which are conferred on individuals by society. Impairment refers to the organic lesion produced by a disease, for example a broken limb; disability is the dysfunction which results from that impairment, for example not being able to walk; and handicap is the disadvantage that society confers upon the individual as a result of that impairment, for example unemployment. Handicap in skin disease may not be as explicit as that associated with a broken limb, but the psychological consequences of skin disease,

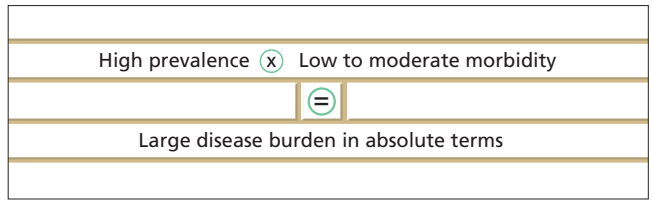

Fig. 6.3 Skin disease is a major public health problem: in public health terms, a little bit of misery affecting a lot of people can add up to more than serious illnesses which affect only a few people.

which include 'failure of display' [4,5], may be just as important. It has been shown that relatively minor skin complaints often cause more anguish to people than other more serious medical problems [4]. Also, because skin disease is so common, a little bit of morbidity affecting a lot of people can add up to far more than a lot of morbidity affecting only a few people. It is this product of high prevalence times moderate morbidity that makes skin disease very important from the public health point of view (Fig. 6.3). Small changes in health policy can have large financial implications, simply because they affect so many people.

One population-based cross-sectional study conducted in the USA on a random sample of 20 479 people examined by dermatologists in 1971–74 [6] has pointed to the magnitude of disability and handicap from skin diseases: skin conditions were reported to limit activity in 10.5 per 1000 of the population aged 1–74 years, or 9% of those persons with such skin conditions. About 10% of those persons with skin complaints considered the condition to be a handicap to their employment or housework, and 1% considered themselves severely handicapped. About one-third of those persons with skin conditions indicated that the condition(s) were a handicap in their social relations. The dermatological examiners rated more than two-thirds of those persons with skin complaints as disfigured to some extent from the condition, and about one-fifth of those were rated moderately or severely disfigured. More than half of those persons with skin complaints reported some overall discomfort from the condition such as itching or burning. An estimated 62.8 per 1000 US civilians (or 56% of those with skin complaints) indicated that the conditions were recurrent, with 49% active in the preceding 7–12 months.

The 1989 UK General Household Survey estimated that 16 per 1000 persons were affected by a long-standing skin disorder sufficiently severe to limit their activities [7]. Another survey of disability amongst 14 000 adults conducted in the mid-1980s found that 1% of complaints causing disability in private households and 2% in communal establishments were due to skin disease [8]. A recent survey of self-reported skin problems in 8000 adults in Uppland, Sweden, found that 20.5% reported skin problems [9]. Those reporting skin problems scored

lower on all eight dimensions of the SF-36, a generic quality-of-life instrument.

Quantification of such disability in monetary terms has not been evaluated. In addition to disability and handicap, some chronic skin diseases such as atopic eczema also incur considerable additional direct costs to families, such as that needed to purchase moisturizers, special soaps, extra laundry expenses, cotton clothing and bedding. The Lothian atopic dermatitis study estimated that the mean cost to the patient was £25.90 per 2 months, while the mean cost to the Health Service was £16.20 in 1994 [10]. Another study has estimated the direct cost of care for patients with psoriasis and psoriatic arthritis in the United States [11].

Routine data which describe the burden of dermatological disease

Generally speaking, routinely published medical statistics on skin disorders are scanty and, when available, are of limited use to the dermatologist in describing the burden of skin disease in the community. Special surveys are usually required to determine the prevalence and morbidity of skin diseases in general or specific skin diseases.

Some routinely published data on skin disease morbidity have limited uses.

1 *Mortality*. Overall mortality is relatively low for skin diseases, accounting for at least 2578 deaths in 1992 in the UK [12] (or 0.46% of deaths from all causes and all ages). Melanoma alone accounted for a total of 1142 deaths in England and Wales in 1992, with 48% of deaths occurring in economically active adults [12]. Mortality statistics of melanoma and non-melanoma skin cancer may be useful in discerning trends over time which may be related to the biology or treatment of these diseases.

2 *Morbidity*. Most routinely published morbidity data refer to those who seek medical help in the primary-care setting. With the exception of a few conditions, such as cellulitis, where incidence and demand are closely related, the extent to which routine morbidity data reflect the burden of dermatological need in the community is unclear. Despite these limitations, routine statistics such as the UK morbidity surveys from general practice [13] are useful in that they provide an estimate of the magnitude and demographic determinants of those who seek medical care.

3 *Skin cancer registration data* (i.e. cases presenting to physicians for the first time who are also reported) are of variable completeness and accuracy [14], but they have contributed some knowledge to understanding secular trends in reported cancer incidence and variations by sex, age and latitude. Special skin cancer registers such as the Scottish Melanoma Group Database [15] and the German Central Malignant Melanoma Registry [16] are examples of more complete databases with stringent controls on data quality.

4 *Other special registers* maintained by groups of enthusiastic individuals exist and may be useful for certain types of epidemiological studies, for example the UK Epi-Derm surveillance system for monitoring occupationally acquired skin diseases, the US National Epidermolysis Bullosa Registry [17], the German *Dokumentationszentrum schwerer Hautreaktionen* for severe cutaneous drug reactions [18] and national registers of sexually transmitted diseases. Other sources of data, such as in-patient and outpatient statistics and prescription data, tell us something about those who present themselves to tertiary medical care. Record-linkage studies may provide useful insights into the determinants of in-patient vs. outpatient care [19].

Special prevalence studies of skin disease in general

Self-reported skin disease

In 1986, the Proprietary Association of Great Britain commissioned a detailed nationwide survey of 1217 adults and the parents of 342 children to determine how British people manage minor ailments and some chronic recurring illnesses [20]. Skin complaints were the commonest ailment reported in the previous 2 weeks, comprising 25% of 6009 adult 'ailments' and 36% of 806 child 'ailments'. In addition to estimating the age- and sex-specific incidence of skin complaints over a 2-week period, the study provides a useful estimate of the proportion of skin complaints that are not considered by the public to be sufficiently severe to seek medical care, and the potential service implication should that threshold change. For example, of the 291 people complaining of acne/spots/greasy skin, 47% took no action, 34% used or bought an over-the-counter preparation, and 12% used medicines prescribed by a doctor, the remaining 7% using home remedies.

Similar proportions of self-reported 'skin disease in the last 2 weeks' have been recorded in two earlier studies [21,22]. A survey of 20 000 randomly chosen residents aged 20–65 years in Gothenburg, Sweden, found that 27% of females and 25% of males reported symptoms of skin disease in the previous 12 months [23]. Another survey of 8000 people aged 20–84 years in Sweden found that 20.5% reported a skin disease and/or use of topical dermatological drugs, with a higher frequency in women (23.3%) than men (17.3%) [9].

Examined skin disease

The Lambeth Study

Only one study in the UK has ever estimated the prevalence of skin diseases in the general population according to some form of physical examination. This study, conducted by Rea *et al*. in 1975 [24], was based on a question-

Table 6.5 Prevalence of examined skin disease expressed as rates per 1000 in a survey of 2180 adults in Lambeth [22]. Prevalence rates have been rounded to the nearest whole number, and 95% confidence intervals for the main findings are shown in parentheses.

	Both sexes		Male		Female	
Skin condition	All grades	Moderate and severe	All grades	Moderate and severe	All grades	Moderate and severe
Tumours and vascular lesions	205	14	142	1	264	27
Eczema	90	61	100	80	81	43
Acne	86	35	109	35	64	35
Scaly dermatoses	85	29	118	39	53	19
Scalp and hair disorders	82	14	79	8	95	18.9
Prurigo and allied conditions	82	39	61	17	95	60
Erythematous and other dermatoses	75	21	31	21	117	22
Infective and parasitic conditions	46	7	48	11	44	3
Warts	34	2	36	—	33	3
Nail disorders	33	19	24	13	42	25
Psoriasis	16	6	24	4	8	8
Mouth and tongue disorders	9	1	15	—	3	1
Chronic ulcer	2	—	4	—	—	—
Any skin condition	555 (496–614)	225 (178–272)	479 (400–559)	213 (147–280)	607 (520–693)	236 (170–302)

naire on skin symptoms which was sent to a stratified sample of 2180 adults in Lambeth, London. All positive respondents and one-fifth of those responding negatively were then interviewed and examined at home by a team of seven doctors and 11 nurses trained in the recognition of common skin disorders. Only exposed skin (face, scalp, neck, forearms, hands, knees and lower legs) was examined, and the overall response rate was 90.5%. Because of difficulties in agreeing on objective criteria for skin disease severity, skin disease was classified into trivial (not justifying medical attention), moderate (justifying medical attention) and severe (needing early medical attention because of severe symptoms or risk of progression), based upon the judgement of the examiner. The key findings of this study were as follows.

1 The overall proportion of the population found to have any form of skin disease was 55% (95% confidence intervals 49.6–61.3%).

2 The overall proportion considered to have skin disease worthy of medical care (i.e. moderate or severe) was 22.5% (95% confidence intervals 17.8–27.2%).

As shown in Table 6.5, the group containing tumours and naevi had the highest overall prevalence (20.5%), but 90% were considered as trivial by the examiners. In the eczema group, on the other hand, with an overall prevalence of 9%, more than two-thirds were graded as moderate/severe, so that the highest prevalence of conditions justifying medical care fell into this group (6.1%). Clear age trends emerged for specific disease groupings, for example acne and warts in younger age groups, although age, sex and social class trends were not found when all forms of skin disease were considered together, since several conditions had trends in opposite directions.

HANES-1

Another detailed cross-sectional study of skin diseases was conducted within the first US Health and Nutrition Examination Survey (HANES-1) [6]. This study, conducted on a representative population sample of 20 749 persons aged 1–74 years from 65 primary sampling units throughout the USA during 1971–74, included a detailed structured skin examination by 101 dermatologists. Clinical findings were backed up by laboratory investigations such as mycology culture and skin biopsy where possible. Key points emerging from this study were as follows.

1 Nearly one-third (312 per 1000 population) had one or more significant skin conditions which were considered by the dermatologist to be worthy of evaluation by a physician at least once.

2 The prevalence of significant skin pathology increased rapidly with age from 142 per 1000 children aged 1–5 years to 362 per 1000 youths aged 12–17 years and to 365 per 1000 young adults aged 18–24 years, due primarily to the increase in acne at puberty.

3 After a slight decline at age 25–34 years, the prevalence of skin pathology again increased steadily, reflecting the increase in chronic diseases such as psoriasis, vitiligo, malignant and benign tumours, actinic and seborrhoeic keratoses.

4 In this study, significant skin pathology was slightly commoner in males.

5 An additional 12.5% of the population was deemed to have a skin condition that was clinically inactive at the time of examination.

Both of these studies therefore suggest that significant skin disease is extremely common. Even though dermatology is characterized by an enormous range of

Table 6.6 Overall prevalence of skin disease in population based studies conducted throughout the world.

Country	Author	Date of survey	Sample size	Study population	Definitions	Overall prevalence of skin disease	Five commonest diagnoses	Comment
UK	Rea [24]	1975	2180	Stratified sample of adults	Examination by team of seven dermatologists and 11 nurses	23%*	Eczema Acne Scaly dermatoses Prurigo Erythematous and other disorders	Only 21% had sought medical advice
USA	Johnson [6]	1971–4	28 043	65 primary sampling units throughout the USA, population aged 1–74 years	Examination by 101 dermatologists	31%†	Diseases of sebaceous glands Fungal diseases Malignant and benign tumours Atopic dermatitis Other eczemas	Detailed survey of usage of health care
Sweden	Larsson [34]	1976	8298	School pupils 12–16 years old in AC county, North Sweden	Examination by dermatologists	Not stated	Acne Verrucae Atopic dermatitis Striae Pigmented lesions	Many children had more than one diagnosis
Faroe Islands	Lomholt [35]	1948	10 984	Survey of seven islands between Norway and Iceland	Examination by dermatologists	5%‡	Eczema Seborrhoeic dermatitis Neurodermatitis Acne Leg ulcer	Part of detailed psoriasis survey
Mexico	Estrada-Castañón [36]	1990	50 000	41 representative communities in Guerrero state (all ages)	Examination by team of dermatologists and nurses	50% of all households included someone with a skin problem	Pityriasis alba Scabies Pyoderma Acne Melasma	60% of skin conditions could be classified into 10 diagnoses
Brazil	Bechelli [37]	1981	9995	School children of 6–16 years in four urban and three rural communities in north-west Brazil	Examination by four dermatologists	26%	Pediculosis capitis Pityriasis versicolor Pyoderma Pityriasis alba Dermatophytosis	Tropical region with 85% relative humidity
Brazil	Romiti [38]	1976	9414	School children aged 5–15 years in Santos municipality	Examination by dermatologist	37%	Infestations Superficial mycoses Viral infections Eczemas Acne	Different disease spectra seen at local dermatology service

Tanzania	Henderson [39]	1991	958	Complete survey of two administrative units at Mvumi village	Examination by dermatologist	49%§	Pyoderma Scabies Pediculosis capitis Dermatophytosis Leg sores	Dry, central plateau
Tanzania	Gibbs [40]	1994	1114	254 randomly selected households from two villages	Examination by dermatologist	27%	Prurigo Scabies Viral warts Pyoderma Papular urticaria	Infectious dermatoses increased in the young. Overcrowding linked with increased skin disease prevalence
Mali	Mahé [41]	1994	1817	Random sample of 30 clusters of children aged less than 13	Examination by dermatologist	34%	Pyoderma Tinea capitis Pediculosis capitis Scabies Mollusca	Pyoderma and scabies significant health problem
Ethiopia	Figueroa [42]	1994	3979	House to house survey in three rural communities	Examination by dermatologist	14%	Ectoparasites Onchodermatitis Dermatophytosis Pyoderma	Only those who considered themselves to have a skin problem were examined
Pakistan	Porter [43]	1980	444	All children aged less than 5 years in three villages in Punjab	Examination by research assistants trained by a dermatologist	36%	Pyoderma (54% of skin disease) Atopic eczema Scabies Warts Other eczemas	Marked variation in prevalence of pyoderma between villages, possibly due to differences in malathion control of insect population

* Thought to justify medical care.
† Significant skin pathology.
‡ Only those who presented themselves spontaneously with a skin disease.
§ Some of those examined might have more than one diagnosis.

disease-reaction patterns, prevalence surveys suggest that the bulk of the skin disease problem is made up of less than 10 disease groups [25]. The prevalence of skin disease documented in these two large population studies [6,24] also suggests that most individuals with skin disease do not seek medical help. Knowledge of this submerged section of the dermatological iceberg is important, as small changes in the population's perception of the need for medical help can have large effects on the delivery of health care.

Caution should be applied to prevalence studies with low response rates, as it cannot be assumed that respondents share the same characteristics as non-respondents. Indeed, a survey of non-respondents to a prevalence survey for skin disease in Australia found that people who did not respond to the initial survey were more likely to have skin cancers than respondents [26]. This important finding emphasizes the need to sample non-respondents in general prevalence surveys of skin diseases.

Surveys limited to children

A large comprehensive survey of examined skin disease in 2491 schoolchildren was conducted in the state of Victoria, Australia, with specific reports published pertaining to warts, atopic dermatitis, acne and tinea pedis [27–30]. Another survey of 1006 primary and secondary schoolchildren in Hong Kong found that 31.3% had one or more skin disorders, 70% of whom did not seek medical attention [31]. A study of 2788 children from eight randomly selected schools in Amman, Jordan, found a similar prevalence of 19.23% [32], and a study which involved a dermatologist examining 1114 children aged 6–12 years in Bucharest, Romania, found a point prevalence of one or more skin diseases of 22.8% [33].

Collectively, these surveys suggest that, like adults, around one-fifth to one-quarter of schoolchildren in urban centres have one or more skin diseases. Skin examination surveys conducted at one point in time (point prevalence surveys) are likely to underestimate the true burden of skin disease in children, since they will miss many children with infectious skin diseases of short duration, such as impetigo.

The burden of skin disease in developing countries

Table 6.6 summarizes studies of skin disease prevalence that have been conducted in developing countries compared with data from some developed countries [6,24, 34–43]. Making comparisons between countries is difficult, as survey methods have differed in terms of population ages, method of sample selection, and classification of diseases. The distinction between any form of skin disease and that which would benefit from medical care is particularly prone to vary according to the views of the dermatologist examiner and the availability of local services. Use of traditional healers is common in developing countries, especially amongst older community members [44]. Some general points can be made regarding the prevalence surveys in these countries: (i) skin diseases are very common; (ii) infections and infestations predominate; (iii) skin diseases are most common among the younger age groups; and (iv) most are easily treated. Making such generalizations is always hazardous, as even within 'developing' countries, urban pockets may occur with a disease spectrum very similar to developed countries.

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What determines the frequency of skin disease in populations?

Risk factors, association and causation

In the first instance, epidemiological studies seek to establish *risk factors* for diseases, i.e. factors which are associated with an increased frequency of disease. When *associations* between skin diseases and risk factors are discovered (e.g. by demonstrating an increased risk of palmoplantar psoriasis in smokers [1]), it should be understood that such *associations* do not necessarily imply *causation*. The association between smoking and psoriasis may simply be a *chance* finding (around one in 20 studies with a P value of less than 0.05 in favour of rejecting the null hypothesis of no association will be wrong due to chance alone), or it could be due to *confounding* (i.e. a third factor such as alcohol, which is independently associated with both smoking and psoriasis [2]). The association could be due to a *bias*—for example, people with psoriasis in hospital may be more likely to recall antecedent events or seek reasons for explaining their illness in comparison with healthy controls [3]. Further analyses or new studies are usually needed to establish whether risk factors are *causative*—for example, by evaluating the strength of the association, biological gradient, relationship in time, the consistency between different studies, biological plausibility, coherence of evidence with external sources, experimental evidence, and specificity of findings as suggested by the Bradford-Hill criteria of causality [4].

The causes of some skin diseases are already established—for example, the herpes simplex virus causes cold sores—but for most dermatological conditions, the causes are unknown. Nevertheless, epidemiological research has already established many *risk factors* for skin diseases which maybe help to serve as pointers to specific causes. Direct manipulation of these risk factors may help in preventing or reducing disease even before the specific cause is found. For example, in the London cholera epidemics of the 1850s, John Snow [5] postulated that the disease was spread by some 'morbid matter' in the water supply and proceeded to intervene by removing the pump handle in Broad Street. This resulted in a dramatic fall in incident cholera cases. All of this occurred some 20 years before germ theory had become established in Europe. Snow's work illustrates one of the beauties of epidemiological research, i.e. that knowledge of pathophysiology is not a prerequisite for determining aetiology.

Even when a causative agent is discovered, for example *Vibrio cholerae*, exposure to this agent does not necessarily imply disease. Of those exposed to cholera during an outbreak, some will die from the disease, some will be very ill, some will be slightly unwell, some will be apparently healthy (but still carry the organism) and some will not be affected at all. The absence of disease in some individuals following exposure is probably due to a whole range of factors such as chance, infecting dose, genetic heterogeneity, and other constitutional and environmental factors which interact together to produce the final clinical picture. This phenomenon of apparent health in the presence of an established harmful exposure has been exploited by individuals in order to avoid modifying their behaviour. One often hears statements such as 'my grandfather smoked 40 cigarettes a day all his life and he did not get lung cancer'. In order to explain such phenomena, we return to the epidemiological concept of *groups* of people

or *populations* and *probability* of disease [6]. On average, groups of people who smoke cigarettes are 10 times more likely to develop lung cancer when compared with those who do not smoke.

It is also important to separate risk factors associated with disease *incidence*, i.e. number of new cases in a given population occurring over a defined period, from those which determine disease *chronicity*, i.e. the determinants of how long a particular disease will last once an individual has it, as the risk factors for each of these aspects may be different. Many dermato-epidemiology surveys have measured the *prevalence* of skin disease when examining risk factors [7], but because prevalence is a function of incidence times chronicity, it is often difficult to say whether these risk factors are important in people developing a disease for the first time, or whether they maintain the disease once established.

Risk factors for skin disease may operate at many different levels. Some may predispose to disease (e.g. a mother with atopic eczema genetically predisposes her child to atopic eczema), some may precipitate disease (e.g. exposure to high levels of house-dust mite may precipitate atopic eczema for the first time), and some may be important in perpetuating that disease (e.g. failure to use prescribed treatments may worsen the course of atopic eczema).

Some of the commonest risk factors for skin disease are discussed below.

Genetics

In addition to a few rare diseases such as epidermolysis bullosa, where specific chromosomal mutations have been closely correlated with different disease phenotypes, several genes may be important in many of the major inflammatory skin diseases. Some genes may be responsible for disease predisposition and some may be responsible for disease severity.

The early environment

There is evidence to suggest that the experience of the fetus *in utero* (e.g. in terms of nutrition) is critical in 'programming' adult diseases such as hypertension and diabetes [8], and *in utero* programming may well operate for many skin diseases such as atopic eczema [9].

The later environment

Age and sex are often included in the descriptive epidemiology of many skin diseases and may point to further risk factors. The marked female preponderance of lichen sclerosus, for example, suggests that hormonal factors may be important in this disease.

Ethnic group may account for some variations in disease rates. Thus, it has been shown that atopic eczema is twice as common in black Caribbean children in comparison with similar white children [10] and, conversely, that mortality from most cancers is less common in black ethnic groups in the UK [11]. Ethnic group, which refers to a way of life encompassing a whole range of dietary and cultural factors, must be distinguished from racial factors [12], which are often more difficult to define because of the considerable mixing of modern populations. Care also has to be taken in lumping many distinct ethnic groups together —for example, combining the diverse cultures of black Africans and black Caribbeans into 'blacks' may be totally inappropriate, both in terms of respecting the identity of the separate cultures and because such lumping together may obscure important epidemiological associations [13]. The term 'race' should not be used in epidemiological studies, as it has no scientific meaning [14]. Migration itself may be an important factor in determining skin diseases; for example, individuals who migrated from China (where atopic eczema is not very common) developed much higher rates of disease (similar to the rates in the local population) after migration to Hawaii [15]. Migrants may not be totally representative of their indigenous peoples, but they may nevertheless show the effect of the environment in determining the frequency of skin disease.

Secular factors may reflect changes in the natural history of skin disease or transient environmental exposures. Thus, the epidemic of melanoma skin cancer has been attributed by some to increased exposure to sunlight over the last 40 years [16]. There is reasonable evidence to suggest that the prevalence of atopic eczema has increased two- to threefold over the last 30 years, but the reasons for this change are less clear [17].

Socio-economic factors may also be crucial in accounting for the distribution of skin disease. In many poorer countries where overcrowding and poor sanitation may occur, infectious or ectoparasitic skin diseases such as secondarily infected scabies or pediculosis are commoner [18,19]. In wealthier countries where such infectious dermatoses are less common, new 'diseases' such as concern regarding the cosmetic appearance of sun-damaged skin or thread veins may preoccupy the population in their quest for a perfect skin. Some skin diseases, such as atopic eczema, also demonstrate a genuine positive social class trend, i.e. higher prevalences in more wealthy groups [7]. Some of this increase in reported eczema may have been due to differences in reporting between socio-economic groups, but other genuine environmental factors such as hygiene, carpets, central heating, family size, or differences in treatment also probably play a part.

Geography and climate are important considerations in describing the frequency of skin disease. Thus, consideration of the marked latitude gradient of melanoma in white-skinned peoples has supported the concept that

exposure to sunlight is an important risk factor for this disease [20]. Paul [21] has drawn attention to the concepts of *macroclimate*, which in the ordinary geographical sense refers to temperature, rainfall and humidity, and *microclimate*, which refers to the immediate domestic and occupational environment a given individual finds himself or herself in. These are discussed further by Marshall [22] and Canizares [23]. The combination of temperature, rainfall and humidity may be crucial to sustain certain infectious disease vectors such as the *Simulium* fly in onchocerciasis, and may for example account for seasonal fluctuations in pyoderma secondary to scabies during the wet season in Lilongwe in Malawi [24].

Occupational factors are occasionally a very important factor for skin disease. Thus, exposure to irritants and contact sensitizers in light and heavy industry accounts for a very large burden of hand dermatitis and lost revenue for both individuals and the state. Certain occupations, for example mining, where workers are constantly exposed to damp conditions, may predispose to fungal infections. Some diseases may occasionally occur in outbreaks from work-related substances, for example chloracne due to dioxins, vinyl chloride disease, and hydroquinone-induced leukomelanoderma. The reader is referred to standard texts of occupational dermatoses and Chapter 21 for further reading [25,26].

Infective agents may directly cause or be suspected to cause many skin diseases. Thus, for a long time, it was suspected that fifth disease was caused by an infectious agent, but it was not until 1983 that human parvovirus B19 was identified as the causative organism [27]. Similarly, there is reasonable circumstantial evidence to suggest that diseases like pityriasis rosea are caused by infectious agents, even though no specific agents have yet been consistently isolated [28].

Dietary factors may be crucial in some skin diseases. As the examples of Lund and Goldberger in the opening section showed, vitamin deficiency states may directly cause skin diseases. Other deficiency diseases with skin manifestations, such as acrodermatitis enteropathica, are completely reversible with administration of the appropriate agent, in this case zinc. Some diseases, such as phenylketonuria and dermatitis herpetiformis, may be transformed by restricting substances which affected individuals cannot handle—for example, phenylalanine and gluten, respectively. Some skin diseases, such as atopic eczema and acute urticaria, may be modified by avoidance of dietary allergens in a proportion of cases. Leisure activities such as gardening or habits such as smoking cigarettes and drinking alcohol may be important risk factors for many skin diseases such as contact dermatitis, psoriasis and porphyria cutanea tarda. Medicines, although intended to alleviate human disease, are a very common cause of cutaneous eruptions, some of which (e.g. toxic epidermal necrolysis) can be fatal.

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Describing the natural history and associations of specific skin diseases

Questions commonly asked by patients with a skin disease are 'How long will it last?' and 'Will it come back again?' Special studies are required to answer these questions, which ideally involve following, over many years, individuals with typical and well-defined disease in terms of morphology and severity [1]. Such prospective studies

are rare in dermatology. Another approach is to identify cases with a specific skin disease from old hospital records and then to trace them in order to find out what has happened to them since they were seen [2]. Studies on the natural history of disease are often difficult to interpret because of incomplete follow-up, the intermittent nature of many skin diseases (leading to the need to distinguish between 'real' and 'apparent' clearance rates) [3] and because the treatment of many diseases has improved with time. Guidelines regarding the attributes of what makes a good follow-up study are summarized elsewhere [4].

Disease associations of specific skin diseases may also give insight into possible causative factors. Thus, the high incidence of laryngeal carcinoma in psoriasis patients might be evidence for the possible role of cigarette smoking in psoriasis [5]. Establishing disease co-occurrence, for example atopic eczema and psoriasis, may also shed light on shared or opposed immunopathological mechanisms [6,7]. Great care has to be exercised in interpreting disease associations generated from hospital sources because, in the absence of an appropriate denominator, many types of bias may occur [8,9].

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Health-services research in dermatology

Broadly defined, dermatological health-services research is concerned with studying how we deliver dermatological health care with the ultimate aim of benefiting patients. Dermatological health services research thus covers a wide variety of service aspects, such as determinants of referrals to hospital departments, evaluation of cost-effectiveness of alternative treatment strategies, quantifying the dermatological needs of the community, evaluating the role of dermatological nurses and exploring economic aspects of screening and other prevention strategies. These diverse studies require a range of quantitative and qualitative research methods, such as focus groups, comparative studies, randomized controlled trials and economic analyses. Research establishes which treatments/services should be used, whereas audit seeks to establish whether health-care providers perform these services to a required standard [1]. As in any other branch of epidemiology, health-services research requires meticulous attention to be given to aspects of study design, which have to be addressed at the design stage. Other pitfalls are discussed further by Chren [2].

Needs assessments in dermatology

In evaluating dermatological health services, certain steps need to be followed [3].

1 Establish the size and nature of the dermatological need based on epidemiological data.
2 Summarize currently available services for that problem.
3 Appraise the evidence for effectiveness of those services.
4 Propose models of care which best fit the epidemiological data and evidence of effectiveness of care within current resources.
5 Propose outcome measures and targets which can be monitored after implementation.

Such an assessment has been attempted for UK dermatological health services by the author [4].

Services available for people with skin diseases

People with skin problems obtain help from various sources, including self-help, advice from pharmacists, advice and treatment from the primary-care team and specialist services. Little research has been conducted to clarify the relative health gain and appropriateness of the various health-care settings for different subgroups of skin disease. The estimated number of people using current dermatology health services in the UK at various entry points, for a population of 100 000 over a 1-year period, is summarized in Table 6.7 [5–10].

Self-help

Although self-help/medication is not traditionally regarded as a health service, the range and availability of over-the-counter skin products is an important element in the equation of balancing need, supply and demand. Around 30% of those with a skin complaint decide to self-medicate, and this proportion is similar for trivial and for moderate to severe disease [6]. Many effective skin treatments are available over the counter in the UK, such as 1% hydrocortisone for mild eczema, topical aciclovir cream for cold sores, topical benzoyl peroxide for acne, and numerous antifungal preparations and wart removers. Pharmacists occupy a key role in advising the public on the use of these products, but whether this advice

Table 6.7 A guide to the number of persons per 100 000 per year using dermatology services. From Williams [4] with permission.

Number with a skin complaint	25 000 (at least 25% of total population) [5]
Number who will self-treat	7500 (30% of those with skin complaint) [6]
Number who will seek advice from GP	14 550* (15% of total population or 19% of all GP consultations) [7]
Number referred to dermatologist	1162 (8% of those attending their GP for skin problems, or 1.2% of the total population) [8]
Number admitted to hospital	24–31 (2–3% of all new dermatology referrals) [9]
Number of deaths due to skin disease	5† (0.4% of all new dermatology referrals) [10]

* Excludes skin neoplasms, viral warts, herpes simplex and scabies.
† Includes people dying from cellulitis, chronic ulcer of the skin and severe drug reactions who might not have been admitted under a dermatologist's care.

is beneficial or whether it simply delays appropriate medical consultation has not been studied adequately in the UK [11]. Self-help groups are often a useful source of advice to those with chronic skin diseases [12].

Primary care

The majority of those with a skin complaint who seek medical help are treated by their general practitioner (GP). In the UK, around 6–8% of all GP diagnoses involve the skin [13,14]. The most recent GP morbidity statistics [7] suggest that 1455 people per 10 000 person-years at risk (approximately 15% per year) consult their GP because of a skin condition in the UK (excluding benign and malignant skin neoplasms and some skin infections). In the US, it has been estimated that around 36.5% of patients attending their GP over a 2-year period had a skin complaint [15].

The range of skin disorders seen in general practice is similar to that in the general population, with relatively few subcategories accounting for the majority of consultations [13,16]. As one would anticipate, proportionally more incident diseases such as skin infections (e.g. impetigo, herpes simplex and viral exanthems) are seen in general practice than in secondary care [7,16].

Secondary care

Although dermatology covers around 2000 disease-reaction patterns, over 70% of specialist activity is concerned with less than 10 main disease categories as shown in Table 6.8 [4]. Age-specific attendance rates are more common in female patients and also increase with increasing age. Around 12% of referrals were considered inappropriate by dermatologists in one UK study [17]. Another UK study showed that even a relatively junior physician with 3 months' dermatology training considered that 26% of 490 consecutive referrals were probably unnecessary [18], and that 75% of these unnecessary referrals belonged to just six disease categories (warts, eczema, naevi, basal cell carcinoma, acne, psoriasis and seborrhoeic warts). There is considerable variation in referral rates to specialist care

Table 6.8 The nine categories of skin disease which account for over 70% of dermatological diagnoses in primary and secondary care. From Williams [4].

Skin cancer (including melanoma)
Acne
Atopic eczema
Psoriasis
Viral warts
Other infective skin conditions
Benign tumours and vascular lesions
Leg ulceration
Contact dermatitis and other eczemas

within the UK and there is some evidence to suggest that much of the regional variation in referral rates may be governed by established patterns of care and the number of available consultants, rather than by any objective dermatological need [4]. Roland and Morris [19] showed no relationship between referral rates for dermatology services and medical need as suggested by standardized mortality ratios or mean number of prescriptions issued by GPs (standardized regression coefficient of 0.1). It should be emphasized, though, that mortality ratios are not a suitable surrogate measure for dermatological need. A strong relationship between dermatology referral rates and the number of dermatology consultants/100 000 population was present, however, in their study (standardized regression coefficient of 0.82, $P < 0.001$).

The relationship between need, supply and demand for dermatological care

Unlike commerce, which aims to balance supply with demand, caring for sick human beings requires consideration of a third factor—that of medical need. Medical need may be defined as the ability to benefit from medical care, demand as that which people ask for, and supply as what the service does or could provide [3,4]. Not all dermatological need is demanded (e.g. a person may be unaware that he or she has an early melanoma), not all that is demanded is needed (e.g. cosmetic removal of all moles), although all that is supplied is usually needed or

demanded. The division between what constitutes reasonable need (e.g. somebody worried that a mole may be cancerous) and demand (e.g. somebody requesting removal of an 'ugly' mole) is especially blurred in dermatology. Defining 'need' in dermatology is therefore quite difficult, and is a process which requires participation of society so that appropriate policies can be set in the light of finite resources.

Two population surveys conducted in the 1970s have produced useful data on the relationship between the need, supply and demand for dermatological care. In a study of 2180 adults in Lambeth who were examined for skin disease [6], it was shown that for those with moderate/severe skin disease, only 24% had made use of any medical service in the previous 6 months. A further 30% had used self-medication. Medical usage was still considerable for those with trivial skin disease, with 10% using medical services and 33% self-medicating.

In the US HANES-1 study [20], there was a considerable mismatch between what the dermatologists considered to represent medical need and what the population were concerned about. Only one-third (31%) of persons with significant skin pathology diagnosed by the dermatologists expressed concern about these specific skin conditions, whereas nearly 18% of those who complained about their skin conditions were not considered to have serious conditions by the dermatologists.

Thus, both of these population studies suggest that, at any one time, around one-quarter to one-third of the population have a skin problem which could benefit from medical care, yet around 80% do not seek medical help. As Savin points out [21], with increased public and professional awareness of effective treatment, this submerged sector of the population is likely to surface and place heavy demands on the current system.

The relationship between need, supply and demand for dermatology services in developing countries may be very different from those in developed countries. Many surveys have shown a high prevalence of need, mainly due to infectious dermatoses [22,23]. There is marked maldistribution of care for people with skin diseases throughout the world, with meagre to absent dermatological services in many countries [24]. Leprosy, onchocerciasis and leishmaniasis are probably the commonest skin diseases worldwide, but the epidemiological research afforded to these diseases is usually scanty. Groups such as the International Foundation for Dermatology work to remedy such inequalities, with the ultimate aim of a healthy skin for all [24]. Getting the right people to the right services is a major challenge. In the state of Guerrero in Mexico, for instance, skin complaints represent the second commonest reason for referral to rural clinics, resulting in a detrimental effect on other important activities such as immunization programmes and antenatal care [25]. In addition to such opportunity costs, this study also showed how much family income is wasted on ineffective treatments for skin infections and scabies.

Systematic reviews and evidence-based dermatology

Reviewing the effectiveness of services in the light of an epidemiologically based needs assessment helps health service planners to distinguish those interventions which confer maximum health gain (e.g. establishment of community leg-ulcer clinics) from those where services are ill-deployed (e.g. specialists involved in the routine treatment of viral warts) [4]. Using published evidence to help us make everyday clinical decisions on disease treatment is something that most physicians aspire to, yet with over 200 journals in dermatology alone [26], keeping abreast of important therapeutic developments in dermatology is difficult. Even enthusiastic teachers place their median reading time at about 2 h per week [27]. Most physicians therefore rely on reviews of the primary research in order to help them make therapeutic decisions in their daily practice. Unfortunately, the quality of such reviews is often suspect, because reviewers have not conducted their review in a systematic fashion with regard to the scientific principles of considering bias and sampling error [28]. Expert therapy reviews published in the top medical journals have been shown to miss important studies and to be far more biased in their conclusions when compared with systematic reviews [29]. Lessons from general medicine have suggested that deficiencies in reviews have meant that advice on some highly effective forms of care have been delayed for many years and other forms of care have continued to be used long after research has shown them to be ineffective or even harmful [30].

Over 20 years ago, the late Professor Archie Cochrane drew attention to our great collective ignorance on the effects of health care and explained how evidence from randomized controlled trials could help the use of resources more rationally, and proceeded to criticize the medical profession for not producing a critical summary by specialty of all relevant trials which is periodically updated [31]. The worldwide Cochrane Collaboration—groups of individuals dedicated to preparing and maintaining systematic reviews of health care—has evolved in response to this challenge [32]. Unlike traditional reviews, systematic reviews employ a structured methodology, which includes: (i) defining the primary objective of the review; (ii) defining the outcome measures; (iii) the systematic retrieval of all (published and unpublished) relevant material; (iv) abstracting the quantitative information; (v) summarizing the evidence; and (vi) interpreting the results. In addition to the benefits of reducing bias by inclusion of unpublished data and by giving more weight to high-quality studies according to predefined criteria, the increased statistical power afforded by the

quantitative pooling of many small studies (meta-analysis) can often provide a clear answer to many small studies which appear at first to be 'conflicting' in their recommendations [33].

Summarizing the effectiveness of various dermatological interventions (be these aimed at preventing new disease, treating established disease or preventing disability) is a time-consuming process. Like any scientific methods, techniques such as meta-analysis have their limitations [34,35]. Several systematic reviews of dermatological intervention have already been conducted, although the poor quality of dermatology trials in terms of unclear entry criteria [36], diversity of outcome measures [37] and inadequate details [38] have served as an obstacle for some reviews. The quality of reporting clinical trials in dermatological journals was poor when reviewed by Bigby *et al*. in 1985 [39]. This situation had changed little in the 1990s [40], although the adoption of the CONSORT guidelines for better clinical trial reporting by several of the top dermatology journals should help to improve the situation [41–43]. An international Cochrane Skin Group formed in 1997 in response to the challenge of providing an up-to-date summary of dermatological health-care interventions [44]. The editorial base of the Cochrane Skin Group coordinates a worldwide voluntary effort in preparing, maintaining and disseminating systematic reviews of health-care interventions in relation to skin diseases and maintains its own specialized register of dermatological clinical trials. Further information about the Cochrane Skin Group is available on the website indicated at the end of this chapter.

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Conclusions

This chapter has demonstrated the fundamental importance that the discipline of epidemiology plays in understanding skin diseases in context, from the clinic to the population. Not only is epidemiology concerned with issues such as describing the incidence, prevalence and human and financial cost of skin disease, but it is also one of the most direct ways of finding out the causes of skin diseases. Finding out causes is important because it may lead to prevention of skin disease on a massive scale. For example, it has been found through a number of epidemiological studies that atopic eczema is less common in large, less economically advantaged families [1,2]. This observation gave rise to the hygiene hypothesis which postulated that increased exposure to microbes and infections in early life might protect against atopy [1,3]. The hygiene hypothesis led to a full-scale randomized controlled trial of lactobacilli cultures given to pregnant mothers and infants, a study which suggested that around 50% of atopic eczema could be prevented by such a measure in infants [4]. Even though this particular study had some potential flaws [5], it nevertheless demonstrates the power of prevention.

I have also shown how application of epidemiological principles has become a backbone to understanding and applying the principles of evidence-based medicine and health services research in relation to dermatology. Although traditional epidemiology may be superseded by genetic epidemiology and other new hybrids as biomedical knowledge develops, there will always be a need for a thorough understanding of the principles of assessing risk and the roles that chance, bias and confounding may play in any study. Similarly, the principles of critically appraising published literature using a framework derived from epidemiology are as basic to dermatological clinical practice as diagnosing skin rashes [6].

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Glossary of epidemiological terms

Measures of disease frequency

Prevalence. The proportion of people with a disease at any one time. *Point* prevalence refers to prevalence at one point in time. *Period* prevalence refers to proportion with a disease (existing and new cases) over a longer period, for example 1 year.

Incidence. The rate of new cases developing over a specified time period, for example the incidence of melanoma in the USA in men in 1983–87 was 6.9 per 100 000 per year [1].

Measures of disease associations

Relative risk. This is the *ratio* of the risk of disease occurring in those exposed to the agent under investigation divided by the risk of those not exposed. It is a measure of the strength of the risk factor.

Attributable risk. This is the *difference* between the incidence rate in those exposed to a factor and the incidence rate in those unexposed. It is a measure of the absolute effect of the exposure.

Risk factor. A factor which increases the risk of disease. This could be a specific exposure, for example asbestos giving rise to mesothelioma, or an attribute such as gender or social class which is indirectly associated with an increased frequency of disease.

Odds ratio. An approximation of relative risk used in case–control studies. It is the ratio of the odds of exposure in cases to the odds of exposure in controls.

Interpreting results

Sampling error. This refers to the variation in values that a given sample could be expected to show by chance alone.

P-value. When referring to the association of a disease with a particular exposure, a *P*-value of < 0.05 means that a value as extreme as that obtained by the study would be expected to be observed by chance in less than one in 20 such studies (or $< 5\%$ of the time). It is convention at this level of significance to reject the null hypothesis of no difference between the compared groups.

*Confidence interval*s. This refers to the range of plausible values for a main study finding. It is based on the size of the sample and the size of the difference between compared groups. For example, the 95% bounds of a relative risk of 2.0 for smoking in a sample of psoriasis sufferers was 1.5–2.5. If the association is a genuine one, this means that the reader can be 95% confident that the true population relative risk resides between the values of 1.5 and 2.5.

Bias. Bias is a systematic error resulting in an incorrect conclusion about the association between an exposure and an outcome. Over 30 types of bias have been described [2], but they fall into two main groups: (i) *selection*, i.e. the two groups to be compared are not comparable in terms of factors in addition to the exposure of interest; and (ii) *information*, i.e. collection of information about the disease and exposure in a fashion that could bias response—for example, those evaluating a new drug were aware of the treatment allocation when assessing patients' response to treatment.

Confounding. This is where the association between an exposure and disease is mixed up with a third factor which is independently associated with both the exposure and the disease, for example the protective effect of prolonged breastfeeding (the exposure) on the development of atopic eczema (the disease) may be due to confounding by parental atopy. The risk of atopic eczema is increased in children born to atopic parents, and atopic parents are more likely to practise prolonged breastfeeding in their infants because they may be more aware of a possible protective effect of breastfeeding.

Association and causation. Association between an exposure and disease does not necessarily imply causation. Other factors such as chance, bias and confounding may explain that association.

Validity and repeatability

Internal validity, for example of a diagnostic test, refers to the extent to which the test measures what it is meant to measure. This is normally measured in terms of sensitivity (proportion of true cases correctly identified) and specificity (proportion of non-cases correctly identified).

External validity refers to the extent to which findings from one particular study (the study population) can be generalized to the target population—for example, to what extent are the favourable results of a clinical trial to test a new oral agent for children with severe atopic eczema attending hospital applicable to children with milder eczema in the community?

Predictive value. When comparing the performance of a test or diagnostic criterion to a gold standard (e.g. clinical diagnosis of melanoma against histological diagnosis), the positive predictive value refers to the probability that someone is a genuine case given a positive test result. Negative predictive value refers to the probability that a person does not have that disease given a negative test result. In addition to sensitivity and specificity, predictive value is dependent on the overall prevalence of the disease being studied [3].

Repeatability. This refers to the extent to which two observations agree with each other. This may be between two observers (interobserver agreement) or between replicate measurements in one observer (within-observer agreement). Repeatability is measured by chance-corrected agreement measures such as the κ statistic [4] or differences between two observers plotted against corresponding means of observations and *not* correlation coefficients [5].

Types of epidemiological study

Observational or descriptive studies. These are studies where the frequency of a disorder is described in terms of its association with various background attributes such as age, sex and ethnicity.

Analytical studies. These set out to test specific hypotheses on the relationship between a potential exposure and disease. These may be *cross-sectional*—for example 'Is atopic eczema more common in black Caribbean children in London compared with white children?'; *case–control*—for example 'Is a history of preceding infection more common in people with pityriasis rosea than in controls?'; or *cohort*—for example 'Are people who are exposed to diesel fumes more likely to develop asthma than those who are not?'

Intervention studies. These are studies in which groups of individuals are allocated to an experimental treatment prospectively. Clinical trials are the commonest examples. Occasionally such trials are conducted at a community level—for example, vaccine trials.

Screening. This refers to the examination of healthy people who would not otherwise have sought medical help for the presence or absence of disease. Principles for evaluating the usefulness of screening are described elsewhere [6].

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Checklist for reading 'epidemiological studies' in dermatology

1 Is there a clear objective(s)?

2 Is the study design appropriate and efficient for the question posed?

3 Have cases (numerators) been clearly defined?

4 Is there a population denominator?
5 Have the main hypotheses and outcome measures been stated a priori?
6 Is there a rationale for the study's sample size?
7 Have potential confounders been considered and measured?
8 Has the study attempted to minimize selection and information biases?
9 Have the data been analysed appropriately?
10 Are the main results clearly presented with confidence intervals?
11 Have subgroups or *post hoc* findings been treated appropriately?
12 Have the authors discussed alternative explanations such as chance, bias and confounding?
13 Are the study's conclusions supported by the main results?
14 Who sponsored the study? Could sponsorship have affected the choice of data and the way they were presented?

Recommended further reading and useful dermato-epidemiology resources

General epidemiology

Schlesselman JJ. *Case Control Studies: Design, Conduct, Analysis*. Oxford: Oxford University Press, 1982.
Hennekens CH, Buring JE. *Epidemiology in Medicine*. Boston: Little, Brown, 1987.
Sackett DL, Haynes RB, Guyatt GH, Tugwell P. *Clinical Epidemiology: a Basic Science for Clinical Medicine*, 2nd edn. Boston: Little, Brown, 1991.

Biostatistics

Kirkwood BR. *Essentials of Medical Statistics*. Oxford: Blackwell Scientific Publications, 1988.
Kahn HA. *Statistical Methods in Epidemiology*. Oxford: Oxford University Press, 1989.
Gore SM, Altman DG. *Statistics in Practice*. London: British Medical Association, 1991.

Systematic review

Chalmers I, Altman D. *Systematic Reviews*. London: British Medical Journal Publishing Group, 1995.
The Cochrane Library. London: British Medical Journal Publishing Group, 1997.

Dermato-epidemiology reports

Chuang TY. Dermatoepidemiology, 1: epidemiologic methods. *Int J Dermatol* 1993; **32**: 251–6.
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Dermato-epidemiology textbooks

Williams HC, Strachan DP. *The Challenge of Dermato-epidemiology*. Boca Raton: CRC Press, 1997. [This contains a comprehensive 'toolbox' section at the start of the book, followed by a summary of the epidemiology of specific skin diseases.]
Williams HC. *Atopic Dermatitis*. Cambridge: Cambridge University Press, 2000. [A textbook dedicated to the epidemiology of atopic eczema].

Epidemiology computer software

Gardner MJ, Gardner SB, Winter PD. *Confidence Interval Analysis (CIA) Version 1.2*. London: British Medical Journal Publishing Group, 1991.
Dean AD, Dean JA, Burton JH, Dicker RC. Epi Info, Version 6: a Word Processing, Database and Statistics Programme for Epidemiology on Microcomputers. Atlanta, GA: Centers for Disease Control, 1995. Available as a free download from http://www.cdc.gov/epiinfo/.

Evidence-based dermatology

Journal reviews

Bigby M. Evidence-based medicine in a nutshell: a guide to finding and using the best evidence in caring for patients. *Arch Dermatol* 1998; **134**: 1609–18.
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See also the 'Evidence-Based Dermatology' section published each quarter in the *Archives of Dermatology* (http://archderm.ama-assn.org/).
There is also a comprehensive section of critically appraised skin topics in clinical evidence published by BMJ Books (http://www.nelh.nhs.uk/clinical_evidence.asp).

Evidence-based medicine

Greenhalgh T. *How to Read a Paper*, 2nd edn. London: BMJ Publishing Group, 1999.
Sackett DL, Straus SE, Richardson SR, Rosenburg W, Haynes RB. *Evidence-Based Medicine: How to Practice and Teach EBM*. Edinburgh: Churchill Livingstone, 2000.

Interest groups/societies

The British Epidermo-Epidemiology Society (BEES). Write to: Ms. Joanne Elliott, Department of Dermatology, Queen's Medical Centre, University Hospital, Nottingham, NG7 2UH, UK, or see website at: http://www.bad.org.uk/groups/bees/index.htm
The European Dermato-Epidemiology Network (EDEN). See website for further details: http://www.dermis.net/org/eden/index.htm.
International Dermatoepidemiology Association (IDEA). Write to current President: Professor Jean-Jacques Grob, Service de Dermatologie, Hôpital Ste Marguerite, 270 Boulevard Ste Marguerite, BP 29, 13009 Marseille Cédex 9, France.

Websites and online resources

- ebderm.org: http://home.cwru.edu/~dxb69/dermatoepidemiology.htm
  An excellent and up-to-date collection of evidence-based dermatology and

dermato-epidemiology teaching curricula/tutorials and links produced by David Barzilai.

- Centre of Evidence-Based Dermatology: http://www.nottingham.ac.uk/dermatology/
  The author's home page, containing a listing of departmental research, tutorials and useful links.
- Centre of Evidence-Based Medicine: http://www.cebm.utoronto.ca/
  Contains a list of useful teaching resources for EBM, along with a glossary of terms and Palm resources.
- Cochrane Skin Group: http://www.nottingham.ac.uk/~muzd/index.htm
  The Cochrane Skin Group home page, containing a list of current skin review titles, protocols and reviews, review abstracts, register for ongoing trials, and methodological support for conducting systematic reviews.
- Cochrane Library: http://www.update-software.com/cochrane/
  Widely acknowledged as the most reliable source of evidence. The Cochrane Library (issue 3, 2002) contains 2557 systematic reviews, 3646 reviews of abstracts of effectiveness and over 350 000 controlled clinical trials (the largest database of trials in the world). It is free online to countries with registered IP addresses (currently England, Ireland, Finland and Norway).
- National Electronic Library For Health—http://www.nelh.nhs.uk/
  Very comprehensive collection of general and specific medical free resources for UK health-care professionals, shortly to incorporate a dermatology virtual branch library.
- NHS health technology assessment reviews: currently, there are two systematic reviews published in full, which are free in the public domain. One is a systematic review of randomized controlled trials for the treatment of atopic eczema (http://www.ncchta.org/execsumm/summ437.htm) and the other deals with systemic treatments for severe psoriasis (http://www.ncchta.org/execsumm/summ440.htm)
- Trainees' curriculum for dermato-epidemiology: http://www.nottingham.ac.uk/~muzidea/aadcurric.htm
  A list of guided reading and questions developed by dermato-epidemiologists from IDEA in conjunction with the American Academy of Dermatology.

Chapter 7

Histopathology of the Skin: General Principles

R. Cerio & E. Calonje

Introduction

As well as clinical examination, microscopic examination of skin tissue is probably the single most important diagnostic ancillary technique used by dermatologists in the management of patients with skin disorders. The correlation of clinical appearances with the dermatopathological findings is not only of direct benefit to individual patients, but has also led to the recognition of many new skin disorders and increased our understanding of the mechanisms of skin disease. The science and art of dermatopathology had its beginnings in early 19th-century Europe with the writings of pioneers like Simon, von Baerensprung, Unna and Gans. It is interesting that these individuals were dermatologists, and this tradition of dermatologists writing about histopathological aspects of skin disease was carried on by researchers such as F. Pinkus, A. Civatte, J. Darier, H. Montgomery, H. Pinkus, W. Lever, and more recently R.K. Winkelmann, E. Wilson-Jones and A.B. Ackermann. In the last century, major contributions to the discipline were made by British dermatopathologists [1,2]. During the last 20 years, the definition of numerous new disease entities and great advances in histopathological and related techniques have led to a wealth of publications on the histopathology of skin disease. Many major reference texts—largely written by dermatologists, but also by individuals trained as pathologists—are now available [3–9].

Close cooperation between the clinician and the diagnostic dermatopathologist is not only desirable, but also essential. The spectrum of skin disease, including rare genetic disorders, infectious diseases, neoplasms and a wide range of inflammatory disorders, is huge, and although in many conditions the histological features are pathognomonic of a particular skin disorder, in others the changes may be characteristic but not specific for one disease. Only by close liaison between the disciplines of clinical dermatology and histopathology can the usefulness and limitations of skin biopsy examination be appreciated. The clinician who reviews the histology of his or her own biopsies appreciates the problems of interpretation of an inadequate biopsy, a biopsy from an inappropriate or unrepresentative lesion, and the effects of artefact caused by undue trauma at the time of biopsy. The pathologist in turn can learn, for instance, that epidermal spongiosis and mild dermal inflammatory changes can represent chronic superficial dermatitis as well as the much commoner subacute eczema. He or she will learn with experience that features once signed out as 'non-specific dermatitis' are in fact specific for certain disorders.

Dermatopathology as a medical specialty is a rapidly expanding discipline, as witnessed by the plethora of recent publications, the development of many national societies for dermatopathology and the many international meetings currently taking place [1]. In several countries, including the UK, examinations such as the Diploma of the Royal College of Pathologists have been set up to assess proficiency in dermatopathology, and this practice is likely to spread. It is hoped that increasing numbers of clinicians and pathologists will become interested and expert in the discipline of histopathology of the skin and discover it to be both exciting and fun.

Table 7.1 Indications for skin biopsy.

Excision of epidermal or dermal neoplasm, whether benign or malignant. Clear margins are required
An incisional biopsy for confirmation of diagnosis of a lesion too big for removal, which will be treated by alternative methods, e.g. more complex surgery, radiotherapy or cryotherapy. Most useful for basal cell carcinoma or *in situ* squamous cell carcinoma (Bowen's disease); avoid in melanocytic lesions, particularly malignant melanoma
An incisional biopsy of a hard-to-categorize skin eruption. Most will be inflammatory; sometimes cutaneous T-cell lymphoma is suspected and two or three biopsies may be necessary
Fresh-tissue incisional skin biopsies for immunopathological study, especially immunofluorescence, in suspected autoimmune dermatoses, e.g. blistering disorders (perilesional skin) or lupus erythematosus (lesional skin)
Simultaneous processing of contiguous incisional biopsies for pathology and for culture of fresh, unfixed tissue when infection is suspected. The tissue can be cultured for various organisms including mycobacteria, deep fungi or examined for protozoa or filarial worms

Biopsy of the skin

A thorough understanding of both the indications for skin biopsy and the various biopsy techniques and their limitations is essential if the histopathologist is to provide the maximum useful information from study of biopsy sections. In addition to light-microscopic examination of paraffin-embedded tissue, material obtained from skin biopsy may be used for a variety of investigative procedures. These include ultrastructural examination, immunofluorescence studies and immunohistochemistry, microbiological studies, tissue culture and molecular biological methods such as *in situ* hybridization and polymerase chain reaction, mainly for immunoglobulin and T-cell-receptor gene rearrangement studies. These various investigative techniques often require specific specimens and transport conditions. The individual undertaking skin biopsy should have a clear idea, before carrying out the procedure, of the studies that are to be performed on the specimen obtained. It should be borne in mind that division of the specimen into many small portions for various techniques such as culture, direct immunofluorescence studies and light microscopy may lead to specimens too small, too unrepresentative or too traumatized to provide useful results.

Of the various indications for skin biopsy (Table 7.1), diagnostic skin biopsy is frequently used to confirm a clinical diagnosis or to aid in the establishment of a diagnosis where a clinical diagnosis is not apparent. Excision biopsy in the treatment of skin lesions, particularly malignant neoplasms and other lesions removed for cosmetic reasons, is often performed. In some situations, even when a clinical diagnosis is not in doubt, a biopsy reassures the patient that the clinician is taking an interest in his or her condition.

The type of biopsy, the selection of the site to be biopsied and the type of lesion to be biopsied where there is a widespread eruption are of utmost importance. Ideally, the lesion biopsied should be an early and untreated lesion and representative of the skin disorder as a whole. If lesions are present at all stages of evolution, such as may be seen in pityriasis lichenoides, it may be appropriate to biopsy more than one lesion. Multiple biopsies are also often helpful in conditions such as early cutaneous T-cell lymphoma, where definite histopathological diagnosis is often difficult. Normal skin should be included with a diagnostic biopsy wherever possible, and the inclusion of perilesional skin is essential when submitting biopsies for direct immunofluorescence studies. In certain conditions such as connective tissue naevi, the changes may be very subtle and comparison with normal neighbouring skin may be very helpful. It is equally important to ensure that the biopsy is deep enough. It is frustrating for the pathologist and clinician alike to receive a specimen with a request form suggesting a diagnosis of panniculitis where sections from the biopsy show only a portion of epidermis and superficial dermis. If lesions are widespread and there is a choice of biopsy sites, it is sensible to avoid areas liable to heal badly, such as areas over bony prominences and the lower limbs, and to avoid cosmetically important areas. Secondary changes in some areas of the body, such as changes of venous stasis in biopsies from the lower legs of older people, may be confusing to the inexperienced diagnostic dermatopathologist, and such sites are also best avoided.

Prior to skin biopsy, written informed consent is normally obtained from the patient, and in all but the smallest biopsies, local anaesthetic—usually 1% or 2% lidocaine (lignocaine) with or without epinephrine (adrenaline)—is injected around the biopsy site. Superficial blebs resulting from injecting local anaesthetic into the skin itself should be avoided. Injection of too much local anaesthetic into one area of the skin can cause a prominent distortion artefact in sections that are prepared from biopsy tissue. The effect of epinephrine on dermal blood vessels and mast cells has probably been overemphasized in the past. However, when biopsying conditions such as urticaria pigmentosa, it may be prudent either to avoid the biopsy site itself and inject the anaesthetic in a circle around it or to use an anaesthetic not containing epinephrine. Epinephrine and other vasoconstrictors should not be used in biopsies taken from the fingers or toes, as occasional intense vasospasm can result in tissue necrosis. Recently, topical anaesthetic gels have been developed as an alternative to injections for removal of superficial skin lesions. These topical anaesthetics are particularly helpful with biopsies performed in children. There are circumstances when skin biopsy is best avoided unless absolutely essential (Table 7.2).

Table 7.2 Relative contraindications to skin biopsy.

Infants	Although local anaesthetic creams/gels make this easier
Upper trunk	In order to avoid keloid formation
Lower legs in elderly patients	Poor healing may occur
Cardiac patients	Valvular disease means there is a potential risk of subacute bacterial endocarditis
	Aspirin/anticoagulants can produce extensive bleeding
Melanoma (incisional) biopsy	Primary excision is preferable to allow proper evaluation and an accurate diagnosis

Table 7.3 Skin biopsy techniques.

Excision	For removal of a single lesion. An elliptical or fusiform-shaped area of skin is removed
Incision biopsy ('wedge')	Similar to excision, but narrower; to include fat in suspected panniculitis. Some normal perilesional skin is included for comparison
Punch biopsy (3–6 mm)	Useful if tissue available is limited, but accurate sampling is essential. A rapid procedure sometimes useful in children
Curettage	For hyperkeratotic lesions, e.g. seborrhoeic keratoses, viral warts, basal cell carcinomas. Usually accompanied by cautery
Shave biopsy	For facial protuberant lesions, e.g. benign intradermal naevi
Snip	For skin tags. Skin snips also for onchocerciasis

Techniques of skin biopsy (Table 7.3) [10,11]

Elliptical surgical biopsy

This is one of the most commonly used diagnostic skin biopsy techniques. Equipment required includes scalpel, fine-toothed forceps, needle holder, scissors and eyeless needle with suture (Fig. 7.1). The use of a skin hook greatly facilitates manipulation of the biopsy specimen and avoids undue trauma. A reasonable size for an elliptical biopsy is about 5 mm, but smaller specimens may be adequate where indicated for cosmetic reasons. Small lesions may be totally excised, but a biopsy of a larger lesion should be at right angles through the margin to include adjacent normal skin. The long axis of the wound should, where possible, follow the natural crease lines of the skin. A full discussion of surgical techniques and suture materials is beyond the scope of this chapter, but there are several excellent reviews [10–12] and aspects of cosmetic dermatological surgery are discussed in Chapter 78.

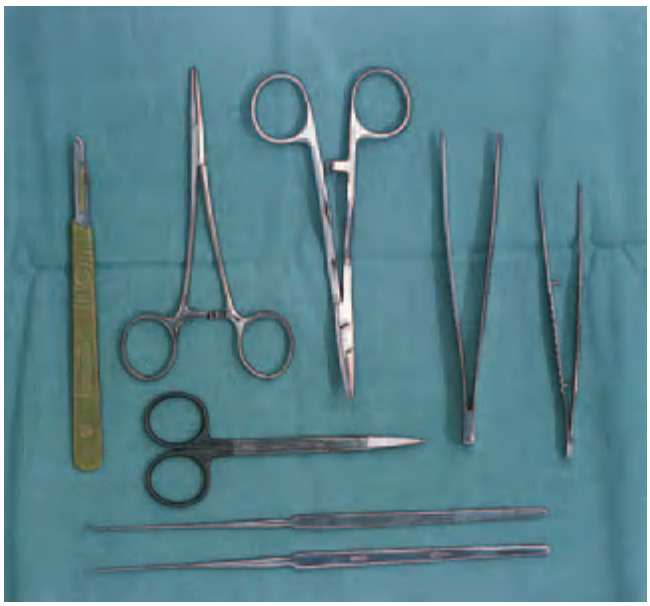

Fig. 7.1 Instruments for skin biopsy, including scalpel, scissors, needle holder and skin hooks.

Punch biopsy

The biopsy punch is a metal cylinder of variable diameter with a sharp cutting edge at one end, usually attached to a plastic handle (Fig. 7.2). The punch is pushed into the skin with a downward twisting movement, and then removed. The tissue specimen is lifted and separated from the underlying tissue, and removed from the biopsy punch.

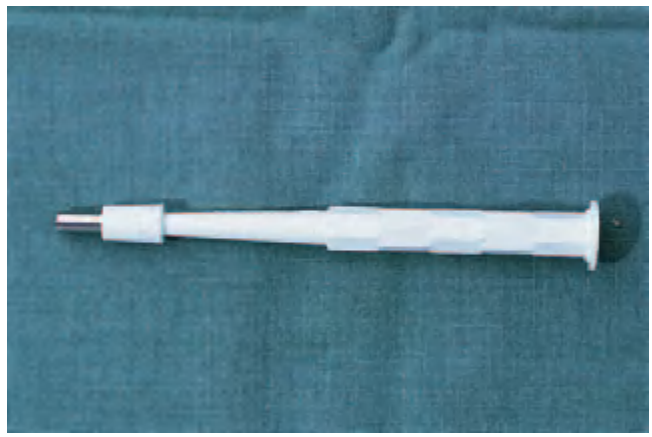

Fig. 7.2 Disposable punch for cutaneous biopsy.

The wound may be left to heal without suturing, the base of the wound being cauterized by electrocautery or some other haemostatic agent. Many operators, however, prefer to insert one or two sutures to secure haemostasis.

Punch biopsies are convenient and quick to use, but it is preferable to use at least a 3-mm punch to obtain a satisfactory specimen. Biopsy punches blunt easily, and therefore disposable punches are recommended. Another problem with small punch biopsies is that the specimen is often difficult to orientate, and most pathologists greatly prefer elliptical excision biopsies for diagnostic interpretation. In general, a punch biopsy should not be used for the diagnosis of cutaneous tumours, and this is particularly true for melanocytic lesions. Nevertheless, punch biopsies do have a place in busy outpatient departments and office practices, particularly for diagnosis and management of small cutaneous lesions.

Curettage [10,13]

The technique of curettage with a sharp-edged Volkmann's spoon or disposable curette followed by cautery is often used for the treatment of small benign and malignant skin lesions, such as viral warts, solar and seborrhoeic keratoses, and basal cell carcinomas. The resulting specimen is often badly fragmented, and it is often impossible to comment on adequacy of removal. A combination of curettage and shave excision has been proposed to overcome this problem [14]. Curettage alone is more useful as a therapeutic procedure than as a technique for providing ideal specimens for histopathological diagnosis. It must be emphasized that all specimens should be submitted for histopathological examination. Haemostasis may be achieved by electrocautery, alginate dressings or using aluminium chloride hexahydrate solution on a cotton bud rolled over the wound.

Shave biopsy

Certain superficial benign papular or nodular lesions may be treated by shaving off the lesion flush with the surface of the surrounding skin. Many sorts of superficial skin lesion may be treated in this way, in particular melanocytic naevi. Although often a useful cosmetic result may be obtained, this technique has several drawbacks. The whole lesion is rarely removed, and recurrence of the lesion is sometimes a problem. In the case of melanocytic naevi, it is known that lesions that recur following partial excision may often demonstrate atypical histopathological features, sometimes leading to an erroneous diagnosis of a malignant lesion [15]. As with the techniques of curettage and punch biopsy, the wounds resulting from the procedure of shave biopsy normally require some form of cauterization or use of aluminium chloride hexahydrate to achieve haemostasis.

Other biopsy techniques

Various other ways of obtaining portions of skin tissue for diagnostic purposes have been described, including needle biopsy, similar to that used for tissue diagnosis of liver disease and lymph-node pathology (see section on cytodiagnosis). The results from such a technique are generally unsatisfactory for skin lesions, and in no way compare with those achieved using more conventional surgical procedures. One technique that has been described particularly in relation to establishing the diagnosis of basal cell carcinoma—for example, prior to considering treatment with radiotherapy—involves use of a dental broach [16]. This instrument is inserted into the suspected tumour and is drawn out; a smear is made from the cells adhering to the shaft of the instrument. The smear is then dried, stained and examined microscopically. Cells of basal cell carcinoma may be identified in the smear, but in the authors' opinion false-negative results are frequent. Various techniques have been described for the study of the detailed anatomy of the skin surface, including the examination of adhesive tape peeled from the skin and the use of various polymerizing adhesives such as cyanoacrylate, which form a replica of the microanatomy of the skin surface [17]. Although in some clinicians' hands these provide useful information in the study of keratinizing disorders such as the ichthyoses, and in disorders of the hair follicle [18], the amount of information they provide is limited. Techniques for slit-skin smears for leprosy and skin snips for onchocerchiasis are discussed in Chapters 29 and 32, respectively.

Information to be provided with the specimen

For the clinician to obtain the optimum help from the pathologist, it is essential that full clinical details be provided. A fully completed histopathology request form should include the following details for each specimen. The patient should be identified by name, sex, age and usually a hospital reference number, or some other identification record number. It is useful to know the patient's racial group, as prominent epidermal basal layer melanin pigmentation may be pathological in some situations, and represents normal skin for other individuals. A brief clinical history of the duration of the skin condition should be provided, together with details of any treatment including topical and systemic therapy. The site of each biopsy taken should be clearly identified on the request form, and accompanied by specimens in separate, individually labelled containers. Unfortunately, it is not uncommon to receive several biopsies from what are thought to be trivial lesions from the same patient in one container. Sometimes it turns out that one of these lesions is histologically malignant and the others are benign, and in these circumstances it may be impossible to determine the site of the malignant tumour.

Details of previous biopsies, and where possible the histopathology report reference numbers, should always be included on a request form, and finally a suggested clinical diagnosis or list of differential diagnoses is helpful. Where possible, abbreviations should be avoided. It may be that many pathologists will recognize the letters PLC as standing for pityriasis lichenoides chronica, but perhaps there would be fewer who would immediately recognize the letters TMEP as representing a form of urticaria pigmentosa.

Finally, but most importantly, the dermatologist or surgeon sending the biopsy material to the pathologist should give some clear indication on the request form from whom the biopsy is being sent, or to whom the report should be forwarded. If some of the simple advice above were more often heeded by clinicians performing biopsies, it would make the life of a dermatopathologist very much easier.

Care of the specimen

Care is required throughout the biopsy procedure, to avoid trauma to the specimen with forceps or any of the other instruments used during biopsy. The use of skin hooks in manipulating the specimen during biopsy is helpful in this respect [19] and, in order to avoid trauma artefact, division of small specimens into multiple smaller portions of tissue for different diagnostic purposes should be avoided. If a specimen is needed for four separate studies—such as paraffin embedding, direct immunofluorescence studies, electron microscopy and microbiological culture—it is often better to take two separate specimens and divide each of these into two portions than to attempt to divide one specimen into quarters. Biopsies taken for ultrastructural studies should be small (of the order of 1–2-mm cubes) to allow for adequate fixation. Once the biopsy specimen has been taken, it should be placed epidermal side uppermost on a small portion of filter paper, to prevent curling, and transferred promptly to the appropriate transport medium.

For routine diagnostic microscopy of paraffin-embedded material, 10% neutral buffered formalin is still the most widely used fixative and is satisfactory for most purposes [20]. Many other fixatives [20,21] and transport media such as Michel's [22] (Table 7.4) are available, and these are indicated for either the study of specific diseases or tissue components, or for the application of specific diagnostic techniques such as immunofluorescence [23]. The use of Michel's medium allows the preservation of antigens for immunofluorescence studies for up to 6 months [24]. By using Michel's medium, specimens may be sent safely without the need for immediate freezing. This medium is also useful for fixation of samples used in immunoelectron microscopy studies [25] and also seems to preserve the antigens relevant for investigation of genetic blistering skin diseases [26]. Table 7.5 gives some details of the more important fixatives and transport media.

Table 7.4 Michel's transport medium for fresh cutaneous tissue.

Ammonium sulphate	55 g in 100 mL buffer
Buffer	1 mol/L potassium citrate (pH 7), 2.5 mL 0.1 mol/L magnesium sulphate, 5 mL 0.1 mol/L ethyl maleimide, 5 mL Distilled water, 87.5 mL Mix 1 : 2 with 1 mol/L potassium hydroxide to pH 7.0

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Table 7.5 Fixatives and transport media for skin biopsy specimens. (Details of most methods are given in Bancroft and Stevens [20].)

Investigative technique	Fixative/transport medium	Comments
Most routine diagnostic studies on paraffin-processed material	10% neutral buffered formalin solution (pH 7)	Most useful fixative for general use
	10% aqueous formalin (unbuffered)	H&E staining generally better than with buffered preparation Formalin pigment a nuisance
	Carnoy's solution (pH 2.8)	Good preservation of nuclear chromatin Haemolyses red blood cells. Use small specimens
Where rapid fixation required	Place specimen in the oven in alcohol	Microwave fixation
When good preservation of mucopolysaccharides is required	Formal saline solution (pH 3.8)	Nuclei badly distorted. Not satisfactory for routine purposes
Demonstration of leprosy bacilli	FMA fixative or Zenker's fluid	Good results for acid-fast bacilli with Wade–Fite stain Mercury deposits must be removed
Transmission electron microscopy and some electron immunocytochemistry	Karnofsky's solution or 2.5% buffered glutaraldehyde solution. Post fixation with osmium tetroxide	Small specimens required, normally no more than 1-mm cube
Immunofluorescence and immunoenzyme techniques	Various. Periodate lysine paraformaldehyde fixation and cold processing useful for some endothelial cell markers	Various fixatives suitable depending on technique and antigen/substance to be identified. Frozen tissue may be required
Transport of specimens for immunofluorescence studies	Michel's medium	Specimen must be thoroughly washed in phosphate-buffered saline before immersion in Michel's medium
Microbiological studies, studies on fat tissue and some immunohistological investigations	Fresh or frozen tissue	Specimens for microbiological examination should be placed in sterile containers and transported to the laboratory as soon as possible

26 Woollons A, Holmes GJ, Gratian MJ, Bhogal BS, Black MM. Michel's medium: a potential alternative to cryoprotection for tissue transport in the investigation of genetic skin diseases. *Clin Exp Dermatol* 1999; **24**: 487–9.

Laboratory methods

Specimen preparation

Frozen sections are not used routinely in dermatopathology, except for Mohs' micrographic surgery (described in Chapter 78) and immunofluorescence. Most antibodies used in diagnostic dermatopathology work adequately in samples fixed in formalin, and except in the context of research, frozen sections are therefore not used on a regular basis for immunohistochemical studies. Frozen sections are used for the diagnosis of autoimmune blistering disorders and also for the diagnosis of blistering genetic skin diseases. Although it has been advocated that autoimmune blistering disorders may be diagnosed with immunohistochemistry performed on samples fixed in formalin, the results are often of inferior quality and interpretation is difficult, leading to false-negative and false-positive results.

Careful identification and preparation of tissue specimens prior to processing is most important. The first requirement is that the biopsy specimen be placed immediately into a fixative solution. Various routine fixatives are employed; most contain 10% formalin. Because a stock solution of formalin consists of 40% formaldehyde, 10% formalin is really 4% formaldehyde. A minimum of 12 h fixation is recommended for most specimens, but small specimens may only need 6 h, and larger specimens a longer period of fixation, to produce optimal results. After fixation, the biopsy tissue is removed from its container, double-checking that the specimen corresponds with details given on the request form, and the pathologist produces a macroscopic description together with details of 'the cut up'.

Special care should be taken where multiple fragments of tissue are present, for example, in specimens obtained by curettage. It may be necessary to pass the contents of the biopsy container through a filter paper to ensure that all relevant portions of tissue are processed and examined. After orientating the specimen, a description should be made of the size and shape of the specimen, and a note made of whether subcutaneous or other tissue is included. A careful description of surface changes is then made, with particular reference to changes of colour and surface texture, such as erosion or ulceration. Any obvious clinical lesion present on the gross specimen should be described. In some surgical specimens, an identification label, such as a skin suture, is left in place in the biopsy specimen by the surgeon, to enable precise orientation of the specimen. This is particularly important when dealing with neoplastic lesions, where clearance of tumour in the margins of the biopsy specimen needs to be assessed.

Prior to sectioning of a gross specimen, especially excised tumours, it is good practice to paint the margins of the biopsy specimen with coloured dyes that are resistant

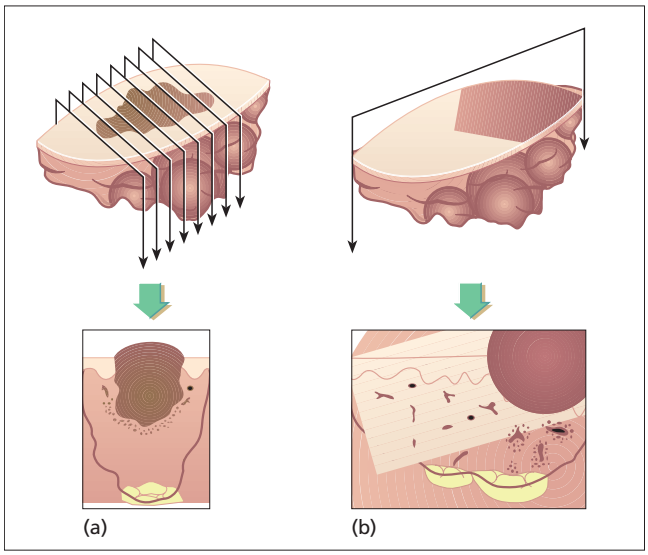
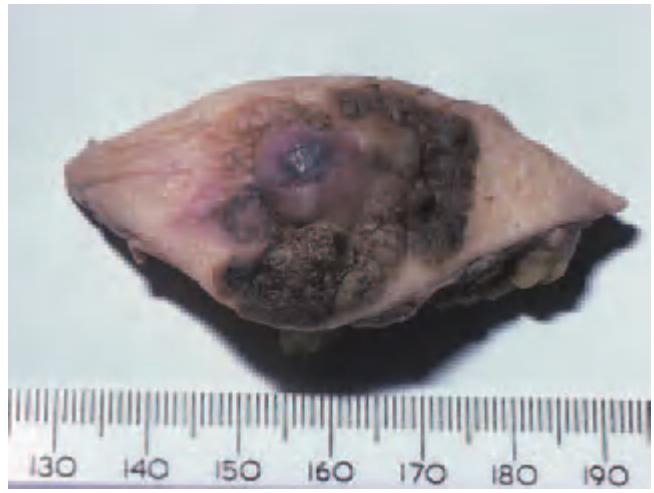
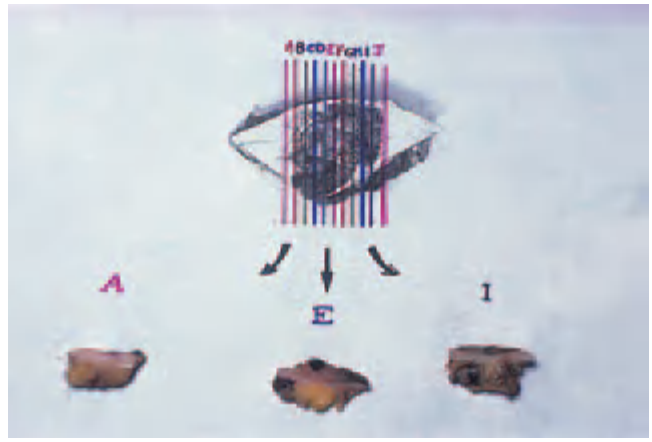


Fig. 7.3 Blocking of elliptical skin biopsy specimens. (a) Neoplastic lesions. Multiple transverse blocks through the whole lesion allow for histopathological examination of the tumour at all levels, and assessment of the narrowest excision margins. (b) Incisional biopsy of inflammatory lesion. Longitudinal blocking is recommended. This allows optimal visualization of the affected and adjacent normal skin.



(a)



(b)

Fig. 7.4 Photocopy procedure for recording the preparation of blocks. (a) The appearance of a macroscopic specimen of malignant melanoma. (b) Transverse blocks are taken from the specimen, and their exact position is recorded on a photocopy made from the surface of the gross specimen.

to tissue processing. Various commercial preparations are available, and one or several colours may be used. If the dye is visible on the final tissue section examined by the pathologist, this implies that no tissue has been lost in processing, and that the edge of the section corresponds to the genuine margin of the biopsy. After painting of the biopsy margins, the gross specimen is then sectioned prior to the preparation of histological blocks. There are various techniques for cutting up a standard elliptical skin biopsy. The ideal method depends to some extent on the nature of the suspected diagnosis. A specimen from an excision biopsy of a benign or malignant skin tumour is better handled by taking transverse blocks through the specimen, so that the narrowest excision margins may be examined. For malignant lesions, particularly for suspected malignant melanoma, ideally transverse blocks should be taken at 2-mm intervals throughout the whole length of the lesion (Fig. 7.3a) [1]. An elliptical biopsy, taken, for instance, from the margin of a patch of inflammatory alopecia on the scalp, is best sectioned longitudinally, so that both normal and abnormal skin can be visualized (Fig. 7.3b). With larger specimens, examination of a selection of transverse blocks made from various portions of the tumour may be adequate for diagnostic purposes. Any biopsy tissue not processed should be labelled, and returned to the fixative in the container and stored. Laboratories have different policies regarding the retention of fixed tissue specimens. Ideally, all specimens should be retained, but limitations of space often mean that most routine specimens can be discarded after a period of a few weeks after the histopathological report has been approved and signed.

In addition to a written description of the gross specimen, and how it has been prepared for blocking, a rough diagram of the specimen is very useful, particularly with larger specimens. This enables clear identification of the portion of the specimen from which various blocks have been taken. An alternative approach for larger specimens, especially when dealing with neoplastic lesions, is to wrap the specimen in clear cling-wrap film and take a photocopy of the surface. This produces an image the same size as the gross specimen, and details of the blocks taken can be recorded directly on the photocopy image (Fig. 7.4).

Very small specimens may be blocked in their entirety after trimming. Other blocking techniques may be used for specific purposes. An example is the blocking of transverse sections of cylindrical punch biopsies of scalp

disorders [2,3]. This technique is particularly useful in the assessment of various forms of inflammatory alopecia, and facilitates the quantitative morphometric analysis of pilosebaceous follicles and the hair itself. The technique also provides a useful method of studying the morphological details of the normal transverse anatomy of follicular structure, including the various phases of the normal hair cycle. Ideally, when investigating a condition presenting with alopecia, two biopsies should be provided: one for vertical sectioning and one for horizontal sectioning. If immunofluorescence studies are required, the specimen for vertical sectioning can be divided into two portions.

Table 7.6 Potential dermatopathological artefacts.

Poor orientation confusing true epidermal and papillary dermis appearance
Formaldehyde fixation vacuolation of epidermis
Scratch marks across tissue due to nick in microtome knife
Tissue carry-over from microtome knife
Foreign bodies, e.g. formaldehyde pigments, suture, *Alternaria*, spores, starch
Polarization of cell nuclear material by electric current in curetted specimens
Clumped mitoses in podophyllin-treated warts
Pyknotic prickle cells from methotrexate- or hydroxyurea-treated patients

Routine tissue processing

Although the skin biopsy specimen may be examined with various techniques, at least a portion of most skin biopsies is routinely processed for light microscopic evaluation of sections from paraffin-embedded tissue. In most modern histopathology departments, the tissue processing is carried out by the use of automated machines. Although it is maintained that superior results may be possible by manual means, this often involves the changing of processing fluids at inconvenient times, and is a time-consuming and labour-intensive procedure. Two main types of automated tissue-processing machine are in use: the traditional carousel type and the enclosed pumped fluid type. Both types of machine have the facility for multiple separate stages in processing. Whether tissue processing is carried out by machine or by hand, after completion of fixation the same basic steps of dehydration, clearing and embedding are involved. The process of dehydration removes aqueous fixative and any tissue water. Clearing refers to the use of a substance such as xylene, which is totally miscible with both the dehydrating agent that precedes it, and the embedding agent that follows it.

For embedding, paraffin wax at 56°C remains by far the most popular material; it is cheap, large numbers of tissue blocks may be processed in comparatively short times, and later sectioning and staining are straightforward. The use of vacuum impregnation in modern and automated tissue-processing machines considerably reduces the overall processing time. At the end of the embedding procedure, paraffin blocks are cut and stained and are then ready for microscopic examination. The dermatopathologist should be aware of relatively common potential artefacts that can cause confusion and misinterpretation (Table 7.6). When urgent preparation of tissue specimens is required, various processing steps can be shortened. The use of very thin portions of tissue, increasing the temperature of the fixative, microwave-fixation techniques [4–6] and shortening the time used for clearing, can all facilitate rapid processing. Alternatively, cryostat sections can be examined. The tetrahydrofurin (dioxane) method for embedding specimens, which also allows for very quick processing and produces sections of a high technical quality, is nowadays rarely used because of concern over toxicity of reagents.

Routine staining techniques, including histochemistry (Table 7.7)

By far the most widely used stain for section from skin biopsies used in histopathology laboratories is haematoxylin and eosin (H&E). This staining technique gives good definition of many cellular and tissue structures in the skin, and is sufficient for the diagnosis of most skin diseases. This stain, however, does not clearly demonstrate certain tissue components, such as elastic fibres, and does not allow differentiation between melanin, haemosiderin and other skin pigments. Special stains are required for these purposes, and also for confirming the nature of abnormal dermal deposits, such as calcium, mucin and amyloid. Another important indication for special staining techniques is the demonstration of microorganisms. Full details of the techniques and applications of special stains used in diagnostic dermatopathology are given in standard reference texts [7–9]. Examples of commonly used staining techniques that are useful in the diagnosis of specific conditions are given below.

The periodic acid–Schiff (PAS) stain demonstrates the presence of carbohydrates, particularly some polysaccharides such as glycogen, and mucoproteins containing neutral mucopolysaccharides. These substances are stained reddish purple by the PAS reaction. Because the cell walls of fungi and yeasts contain neutral polysaccharides, they also stain positively with the PAS reaction. The technique is also useful in demonstrating blood-vessel walls, basement membrane (Fig. 7.5), fibrin deposition and the presence of glycogen deposits, for instance in certain sweat gland tumours, such as clear cell hidradenoma, trichilemmoma and some epithelial lesions of uncertain histogenesis, such as the clear cell acanthoma of Degos. The identification of glycogen can be further confirmed by removal by enzyme digestion with diastase in 1% aqueous

Table 7.7 Some tinctorial stains used in dermatology.

Special stains	Tissue constituent	Appearance
Periodic acid–Schiff (PAS)	Glycogen	Magenta red (diastase sensitive)
	Mucopolysaccharides	Red (fungal wall red)
Van Gieson	Collagen	Red
	Muscle, nerve	Yellow
Congo red	Amyloid	Red with green birefringence
Acid orcein–Giemsa	Elastic fibre	Dark brown
	Collagen	Pink
	Melanin	Black
	Haemosiderin	Green/yellow
	Amyloid	Light blue
	Mast cell granules	Purple
Masson's trichrome	Collagen	Green
	Muscle + fibrin	Red
Aldehyde fuchsin	Elastic fibre	Purple
Gomori's	Reticulin	Black
Alcian blue (pH 4.5, 0.5)	Acid mucopolysaccharides	Blue
Toluidine blue	Acid mucopolysaccharides	Metachromatic purple including mast cells
Perls' Prussian blue	Iron (haemosiderin)	Blue
Masson's Fontana	Melanin	Black
Von Kossa	Calcium salts	Brown/black
Grocott's	Fungus wall	Black
Methenamine silver	Bacteria	
	Gram+	Blue/violet
	Gram–	Red/pink
Ziehl–Neelsen/Wade–Fite	Acid-fast bacilli	Red

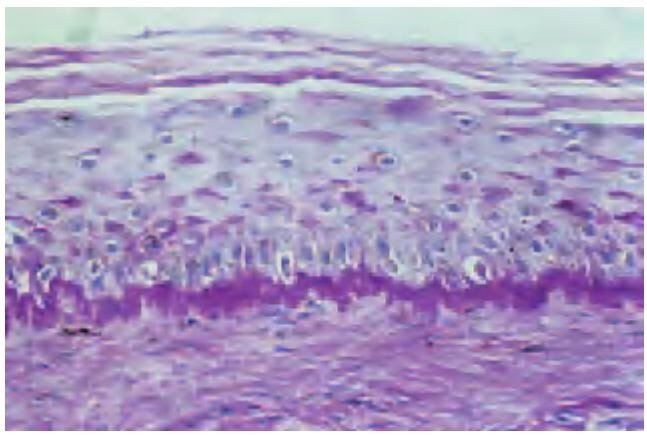


Fig. 7.5 Periodic acid–Schiff (PAS) stain, showing thickening of the basement membrane zone in cutaneous lupus erythematosus.

solution at 37°C for 30 min. Positive staining after the use of diastase indicates the presence of neutral mucopolysaccharides.

The Alcian blue reaction produces a blue coloration in the presence of acid mucopolysaccharides. In addition to demonstrating the presence of mucin in cutaneous mucinoses, the technique is also of value in some cases of extramammary Paget's disease, and occasionally in the demonstration of goblet cells in metastatic carcinoma of the gut. There are small amounts of acid mucopolysaccharide present in the ground substance of normal dermis, and the Alcian blue reaction is very pH-dependent. Care should therefore be exercised in the interpretation of a positive result.

Acid orcein and Giemsa stain was popularized by Pinkus and Mehregan, who recommend its use as a second routine stain [10]. It is a valuable technique which, demonstrates, in addition to structures normally visible with H&E stain, the presence of mast cells, eosinophils, metachromatic substances and elastic fibres. The routine use of the orcein–Giemsa stain often avoids recutting of blocks for other special stains. Orcein itself is a constituent in other staining methods, particularly those used to demonstrate elastic fibres.

Special staining techniques are often essential to differentiate between epidermal and dermal deposits of melanin, haemosiderin and other substances. Masson's ammoniacal silver nitrate technique produces a densely black reaction product with melanin. Melanin deposits appear greenish black with the acid orcein–Giemsa stain referred to above. Iron, which in the context of skin biopsy material normally means haemosiderin pigment, is demonstrated by Perls' Prussian blue reaction, which yields a deep-blue reaction product in the presence of ferric and ferrous iron.

Trichrome stains can demonstrate various elements of connective tissue. Common examples are the van Gieson stain, in which collagen appears red and muscle and

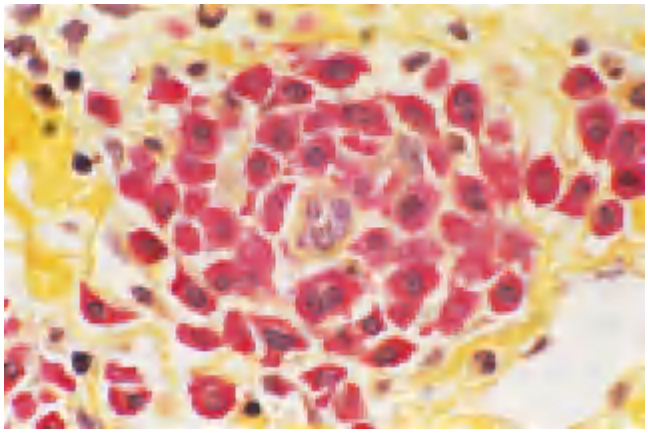


Fig. 7.6 The chloroacetate esterase stain. Mast cells appear red with this technique.

nerves yellow, and Masson's trichrome stain, in which collagen is green and muscle red.

Reticulin fibres are demonstrated by Gomori's silver impregnation technique. This technique is particularly useful in the study of certain cutaneous tumours, including vascular tumours and malignant melanoma. The application of this method to melanocytic lesions may reveal foci of expansile growth undetectable in normal H&E-stained preparations.

Certain types of cell present within the skin may be difficult to recognize on conventional H&E-stained material. Mast cells are best demonstrated either by the use of a metachromatic staining technique, such as toluidine blue, or with one of the few enzyme histochemical methods that may be carried out on paraffin-embedded tissue, such as the chloroacetate esterase reaction. The use of this technique applied to formalin-fixed paraffin sections was described by Leder [11], and mast cells and myeloid white cells are easily identified by their bright pinkish red staining (Fig. 7.6). Other histiocytic and dendritic cells that are difficult to visualize on routinely stained material are best visualized with immunohistochemical methods.

Cutaneous deposits of various naturally occurring and foreign substances often require special staining techniques for their demonstration. The von Kossa method produces a black coloration in the presence of calcium salts, and amyloid deposits may be demonstrated using crystal violet or Congo red. With this latter technique, amyloid deposits stain pinkish red, and under polariscopic examination there is a green birefringence. Another technique useful for the demonstration of amyloid deposits is the thioflavine T method, yielding green fluorescence on examination with a fluorescence microscope. Unfortunately, several of the staining techniques recommended for the demonstration of amyloid are technically unreliable, and none is absolutely specific for amyloidosis. Some cotton dyes other than Congo red, such as pagoda red, have been claimed to be as sensitive as Congo red while being more specific [12]. It is recommended that more than one special stain be used if amyloid is suspected. Occasionally, even with the use of several special stains, amyloid cannot be demonstrated and electron microscopy is necessary for this purpose.

A wide range of techniques is employed for the demonstration of microorganisms in the skin. Reference has already been made to the usefulness of the PAS stain in the demonstration of yeasts and fungi. The silver staining technique of Grocott is also very helpful in the identification of fungal hyphae and yeast bodies. These structures stain black on a pale-green background. Other silver techniques, including the Warthin–Starry technique, are useful in demonstrating spirochaetes, *Bartonella henselae* (the organism that causes bacillary angiomatosis) and *Borrelia* in tissue sections. *Bartonella* may also be demonstrated by the use of a Giemsa stain. The traditional Gram stain demonstrates coccal and bacillary organisms in the skin. Several techniques are available for the demonstration of acid-fast bacilli. The Ziehl–Neelsen method is widely used for the demonstration of mycobacteria, particularly *Mycobacterium tuberculosis.* It is based on the capacity of the lipid-rich cell wall of mycobacteria to take up strong phenol-dye solutions. This dye is retained after differentiation in acid or alcohol. Mycobacteria stain magenta and the background is blue. Auramine–rhodamine is also a sensitive method for demonstrating mycobacteria in tissue sections. Its main drawback is that it requires the use of a fluorescence microscope for interpretation [13]. The Ziehl–Neelsen method should not be used for demonstration of leprosy bacilli. The use of this technique often leads to a false-negative result. The reason for this is that the leprosy bacilli are less acid- and alcohol-fast. The Wade–Fite stain, or a modification of this technique, is more appropriate for identification of leprosy bacilli because it uses minimal treatment with alcohol and acid.

Even with the above techniques, demonstration of small numbers of microorganisms in the skin may be very difficult, and may require the examination of very many sections. Using one of the newer antibody-labelling techniques, with immunofluorescence or immunohistochemical methodology may save some time. Recently, *in situ* hybridization and polymerase chain reaction (PCR) techniques have also been applied to routine skin specimens to confirm the presence of various microorganisms, especially viruses, leishmania and mycobacterial DNA in suspected infected skin [14–22]. PCR is a very valuable tool for confirming the diagnosis in these infections, but very stringent conditions are required to avoid false-positive results. This method is particularly useful in cases with suspicious histology in which special stains and cultures have been negative. It is important to highlight that mycobacterial DNA has been found in cutaneous lesions of nodular vasculitis and papulonecrotic tuberculid [19,23].

While this confirms the relationship between these two entities and tuberculosis, it does not necessarily mean that the finding may be interpreted as evidence of tuberculous infection in the affected sites.

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Immunopathology

There are some situations where even after careful biopsy of an appropriate lesion, expert tissue processing and sectioning, and the use of several special staining techniques, a specific histological diagnosis is still not possible. The use of immunological methods permits the identification of antigens, antibodies and various other cell and tissue components, and has greatly facilitated our ability to achieve a specific diagnosis. Hybridoma monoclonal antibody technology paved the way for the development of numerous antibodies to cell and tissue structures. Further refinement and experimentation with immunohistological techniques has brought this powerful new diagnostic tool within the reach of most histopathology laboratories, particularly with increasing commercial availability of diagnostic cell markers that label routine paraffin sections (Table 7.8).

Immunofluorescence methods

Immunofluorescence is a technique for detecting the presence and position of antigens, antibodies, other cell secretions and cell components in cells or tissue sections. The principle of the technique is that certain fluorochrome dyes exposed to ultraviolet (UV) light emit fluorescent radiation, the colour of which depends upon the particular fluorochrome. When these dyes are conjugated to proteins that are subsequently added to tissue sections, or injected into an animal, the position of the proteins can be traced microscopically by the fluorescence they emit under illumination with UV light with suitable filters.

Two fluorochromes are generally available. Fluorescein is most commonly used. It is best conjugated to protein in the form of fluorescein isothiocyanate, which emits an apple green fluorescence. The second dye is rhodamine RB200, which is conjugated to protein as rhodamine isothiocyanate or sulphonyl chloride; it emits an orange fluorescence.

Preparation of tissues

Tissues to be examined are usually snap frozen in liquid nitrogen, cut in a cryostat at about –20°C, dried and stained without fixation. Sections can be fixed, before staining, in cold acetone or methanol, provided that these agents do not alter the antigenicity of, or dissolve, the substances to be detected [1]. This provision also applies to the technique of cold formaldehyde [2] or alcohol fixation of tissues, and embedding in paraffin for cutting on a microtome at room temperature. The use of acetone, ethanol and methanol enhances tissue preservation, but sometimes increases non-specific staining.

Some antigens can be detected in routine paraffin tissues [3]; others are masked after fixation in formalin, para-formaldehyde or glutaraldehyde and paraffin embedding. Such antigens can be 'retrieved' or revealed, and detection improved, by heat in strictly controlled conditions [4–8]. Heat treatment is by pressure cooker or by microwave. Before treatment, paraffin-embedded sections must be baked overnight at 55°C on charged or silane-coated slides to ensure adherence and then

Table 7.8 Immunocytochemistry panels of cell markers.

1	*Undifferentiated malignancy panel*
	MNF 116 (keratin)
	AE1/AE3 (keratin)
	CAM 5.2 (low-molecular-weight keratin)
	Epithelial membrane antigen (EMA)
	Leukocyte common antigen (LCA)
	S-100
2	*Spindle cell panel*
	As in 1 above plus:
	Desmin
	Smooth muscle actin
	Q bend 10 (CD34)
	Factor XIIIa
3	*Melanocyte panel*
	S-100
	HMB45
	Melan-A
	MIFT-1
	Tyrosinase
4	*Small blue cell panel*
	Chromogranin
	Synaptophysin
	Cam 5.2
	EMA
	CEA
	S-100
	Cytokeratin 20
	CD99
	Desmin
	Muscle-specific actin
	Smooth muscle actin
5	*Lymphoma panel*
	LCA (CD45)
	L26 (CD20) (pan-B-cell marker)
	CD79a (pan-B-cell marker)
	CD2, CD5, CD7 (pan-T-cell markers)
	CD3 (pan-T-cell marker)
	CD4 (T-helper/inducer lymphocytes)
	CD8 (T-cytotoxic/suppressor lymphocytes)
	UCHL (CD45Ro) (pan-T-cell marker)
	Ber-H2 (CD30)
	κ light chain λ light chain
	ALK-1
	Bcl-2
	CD10 (marker of follicle-centre cells)
	Bcl-6 (marker of follicle-centre cells)
	Ki-67 (proliferation marker)
	CD43 (pan-T-cell marker)
	CD56 (natural killer cell marker)
	TIA-1 (marker of cytotoxic granules)
	Granzyme (marker of cytotoxic granules)
	Perforin (marker of cytotoxic granules)
6	*Vascular panel*
	CD31
	Factor VIII
	Q bend 10 (CD34)
7	*Immunofluorescence labelling*
	IgG, IgM, IgA, C3, fibrin (much better results with frozen sections)

All cell markers react on paraffin-embedded sections unless otherwise stated.

dewaxed. The heat retrieval solution is citrate buffer, 10 mmol/L sodium citrate made pH 6.0 by HCl. When heated in a pressure cooker, the slides in open metal racks, well spaced, are placed in hot buffer in the pressure cooker and as quickly as possible heated to 15 lb pressure for 1 min only. Then the pressure cooker is plunged into a sink of cold water. In the more often used microwave method, the slides are placed in Coplin jars containing the same buffer; the jars are placed in an open dish. The dish may contain water but this is not essential. The tissues are heated for variable periods; 15 min is usually adequate. Antigens in skin should not require more than 10 min. After the first and every 5 min after, the fluid in the Coplin jar is replenished with water to replace that lost by evaporation. Unfortunately, the dermis is susceptible to disintegration if heating is excessive, though eccrine and sebaceous glands and larger blood vessels remain. The treated sections are stained by standard methods of immunofluorescence or by immunoenzyme techniques.

Some antigens require protease treatment instead of heat; this is usually indicated on the leaflets accompanying vials of commercial antibodies.

Labelling procedures

Tissue sections must be wetted and treated with protein to block or reduce non-specific binding for at least 30 min. The diluent is phosphate-buffered saline (PBS) +0.1% Triton X100 and protein which may be 0.5% chick albumin, or 0.5–2.0% bovine serum albumin or, rarely, 2–5% of the serum of the same species as the primary antibody. The diluent for the antibody is PBS with 0.1% Triton X100 and 0.5% chick or bovine albumin.

The two principal labelling techniques (Fig. 7.7) are direct staining (Fig. 7.7a), in which sections are incubated with fluorochrome-labelled antibody to detect substances (i.e. the corresponding antigen) in tissues, and indirect staining (Fig. 7.7b), in which unconjugated antibody is incubated with the section, and any bound antibody is detected by the subsequent addition of fluorochrome-conjugated antiglobulin sera. These simple techniques may be modified for more sophisticated investigations by using double staining (Fig. 7.7c) on the same section, one with a fluorescein-labelled antibody, the other labelled with rhodamine or some other fluorochrome-conjugated antibody. Thus, it is possible to detect antigen and antibody in an immune complex (Fig. 7.7c) or a secreting cell and its secretions. Usually, the two-labelled antibodies are derived from different species.

Direct labelling. Direct staining is used to detect substances, including antibody immunoglobulins in tissues (e.g. *in vivo* bound immunoreactants as in pemphigus and pemphigoid), by the addition of fluorochrome-conjugated antibodies (Fig. 7.7a) with subsequent washing to remove

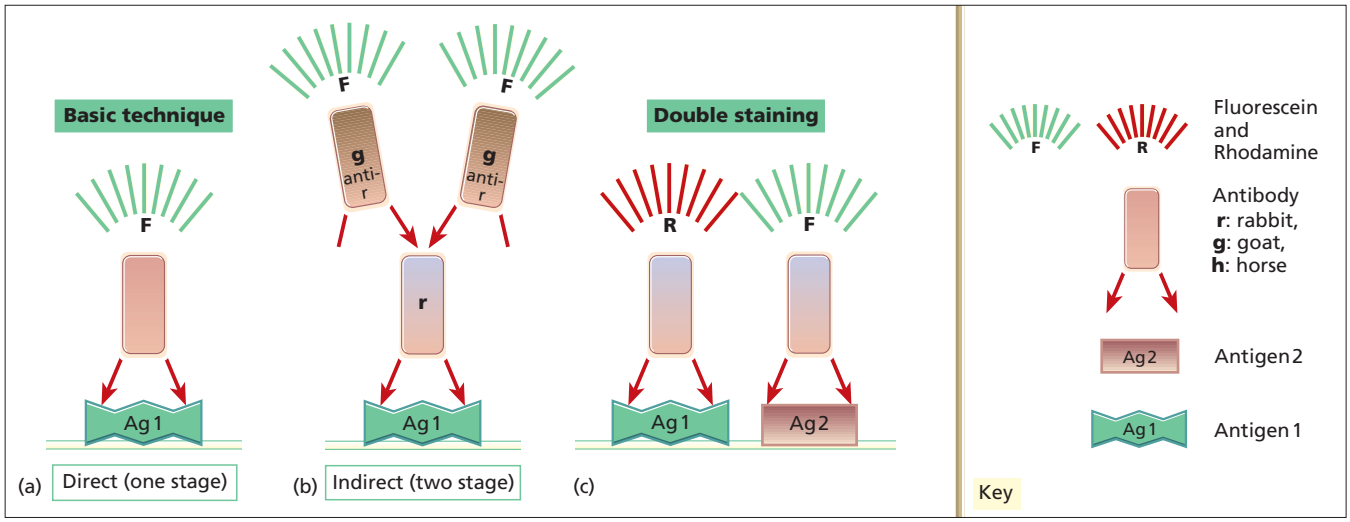

Fig. 7.7 Diagrammatic representation of immunofluorescence techniques.

from the preparation all the conjugated antibody except that fixed to the particular substance. The details of the method are as follows.

1 For critical examination to detect small amounts of antigen, sections treated with the conjugated antibody are maintained in humid conditions overnight at 4°C. For more routine procedures, antibody treatment is for 2–4 h at room temperature in a humid container. The containers must be light-proof.

2 Wash tissue in PBS pH 7 with three changes for a total of 20 min.

3 Mount in commercial antifade mountant fluids.

Indirect labelling. The unconjugated antibody, or primary antibody, is incubated with the specimen to bind to the test antigen; the uncombined surplus is removed by washing, and the preparation stained by a fluorochrome-conjugated antiglobulin serum, i.e. this is the secondary antibody which binds to the primary antibody (Fig. 7.7b). The details of the indirect staining method are as follows.

1 Incubate the tissue with the antibody to the test antigen. This is the primary antibody. Overnight treatment is preferable.

2 Wash in PBS with three changes for at least 20 min.

3 In a light-proof humid container, incubate the sections for 30–45 min at room temperature with the conjugated antiglobulin antibody; this is the secondary antibody, to bind to and label the primary antibody.

4 Wash in PBS for 20 min (three changes) with the least exposure to light.

5 Mount.

Indirect staining with conjugated antiglobulin sera is more sensitive than direct staining with conjugated antibodies, because more conjugated antiglobulin molecules are fixed to antibody in the second stage than are antibody molecules fixed to antigen in the first stage. The method has, however, the disadvantage that it increases the likelihood of non-specific staining.

Results are dependent upon the quality of the antibodies. Monoclonal antibodies, which bind to a small sequence of antigen determinants (epitopes), may have weak affinity and be eluted during washing. False-negative results also occur when the particular epitopes are not exposed; thus monoclonal antibodies to different epitopes of the same antigen vary in their ability to detect the antigen.

Technical limitations

All that glows is not specific fluorescence. The two major sources of error are autofluorescence and non-specific binding.

Control tests. In routine use, the specificity of the conjugated antisera and optimal washing dilution is established and blocking tests are not required, except perhaps in sites of severe inflammation. For critical or experimental studies, blocking tests may be required to prove antibody specificity. Before addition of the conjugated antibody, sections may be treated with normal serum of the same species, or unconjugated specific antibody of the same subclass but against an irrelevant antigen, or unconjugated specific antibody, although this is usually expensive. If the selected pretreatment does not block the binding of the subsequent addition of the test-conjugated antibody, the staining is considered to be antigen-specific. Labelled antisera should be centrifuged before use, to remove any particulate matter, and the glass slides, sections and washing solutions should be free of dust, which readily adsorbs conjugates.

Autofluorescence. Tissues exposed to UV light emit their own fluorescence. In skin, this is not quenched by fixation, and is best controlled by appropriate filters.

Antigen non-specific staining. Non-specific staining refers to fluorescent staining of a section by a labelled antibody, not resulting from a specific antigen–antibody reaction. The causes of non-specific staining and the methods available for removing it are described in detail by Nairn [9].

Appropriate blocking before antibody treatment is essential (see above). The use of optimal dilutions of labelled antibody avoids excess fluorochrome application to the tissue, thus reducing potential non-specific staining. Neutrophils, eosinophils and histiocytes are particularly prone to absorb globulins non-specifically, which accounts for much of the apparently specific fluorescence of inflammatory lesions.

The antigen non-specific binding of fluorescein conjugates by eosinophils can be inhibited by prior treatment of the sections with diaminobenzidine in hydrogen peroxide [10,11].

Another source of confusion is the presence of 'natural' antibodies in the labelled antiserum that combine with sites other than those containing the antigen under examination. This does not apply to monoclonal antibodies and rarely to commercial polyclonal antibody, but they may be present in laboratory-prepared polyclonal antibodies. Natural antibodies are removable by absorbing the antisera with tissue powder from the same species as the tissue under test. Aggregated IgG in the conjugate will also bind non-specifically. Aggregation will occur in conjugates frozen and thawed repeatedly; therefore, conjugates should be stored as small samples and discarded after use. It is advisable to centrifuge the antibody before use.

A peculiarity of immunofluorescence tests on skin is the affinity of the stratum granulosum for antibody–fluorescein conjugates. The nature of this antigen non-specific binding has not been ascertained. Tests on the basic protein or filaggrin peculiar to stratum granulosum cells have not shown this to be the binding substance. However, careful preparation of the conjugates provides reagents with little or no affinity for the stratum granulosum.

Counterstaining. Identification of the particular cells or structures binding labelled antibody may be difficult if there is poor contrast with the background, if there is much autofluorescence and if the specific fluorescent binding is weak. Procedures to identify sites of specific binding are combined phase contrast and immunofluorescence, counterstaining for all the background tissue, or selective stains for nuclei. Counterstains have been used successfully but no one technique is applicable to all preparations. The emission from the counterstain may swamp the specific immunofluorescence if the preparation is thick or the charge affinity is strong, as may occur following the addition of Evans blue or brilliant cresyl violet [9] or of unconjugated rhodamine isothiocyanate to provide contrast to the green specific immunofluorescence. Instead of staining all the structures in a tissue, another counterstain procedure is to use dyes that selectively bind to nuclei to identify cells, for example propidium iodide [12,13], ethidium bromide [14] or *p*-phenylenediamine [15], the latter having the additional advantage of reducing fading of the immunofluorescence.

Photobleaching. Fading or photobleaching is a technical limitation of immunofluorescence. Prolonged or repeated examination reduces the intensity of emission, which also decays if preparations are exposed to sunlight. This fading can be reduced by the addition of *p*-phenylenediamine to the buffered glycerol mounting fluid [16]. This dye was subsequently found to be a useful nuclear counterstain.

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Immunoenzyme methods [1,2]

The immunoenzyme (immunoperoxidase) methods have several advantages over immunofluorescence:
1 Standard microscopes and illumination are used.
2 The preparations are permanent, and the reaction products do not usually fade on repeated examination.
3 Counterstains enable cells containing antigen to be identified with more certainty than using immunofluorescence with dark-ground illumination.
4 Examination is less tiring for the microscopist.
5 The preparations may be examined by electron microscopy.

Technical limitations

Inflammatory lesions may contain endogenous peroxidase activity, and such sections have to be pretreated to remove it [3–5]. Furthermore, it is possible for the antigen to be modified by the pretreatment, with the result that it is more difficult to detect. This mainly applies to examination of lesions. Normal tissues, e.g. those used as a substrate to detect antibodies in a patient's serum, rarely require pretreatment. The problem with endogenous peroxidase is analogous to the disadvantage of autofluorescence in the immunofluorescence preparations.

There is less contrast with immunoperoxidase methods than in slides treated by the immunofluorescence technique, and fine stippling or cytoskeletal structures seen by immunofluorescence are not quite so easily detected by immunoperoxidase. Although immunofluorescence may be more discriminating in detecting small amounts of antigen in cryostat-cut sections, the immunoperoxidase methods, used on paraffin-embedded tissues [6] for antigens that are stable during preparation, provide more definite resolution of the tissue and sites of antigen.

Immunoperoxidase methods have another advantage in being the preferred method to re-examine tissues stored in paraffin blocks after routine histology, provided that the antigens are stable in the fixative and dehydrating agents.

Recent improvements in immunoenzyme techniques have resulted in their application to many investigations. The reagent antibody is conjugated with an enzyme, usually horseradish peroxidase, and the antibody conjugate combines with the antigen in the test preparation. The site of binding is detected by adding a substrate for the enzyme: the degradation of many molecules of substrate leaves a deposit confined to the site of binding. Sites of peroxidase activity appear as dark-brown granular deposits that are seen distinctly in contrast to suitable counterstains, for example methyl green or Mayer's haemalum.

Although the application described is the detection of antigen in tissue sections and cell suspensions or monolayers, the principle of the method is the same as that of the enzyme-linked immunosorbent assay (ELISA).

Chemical conjugation of peroxidase to antibody

Antiglobulins conjugated with peroxidase, and peroxidase–antiperoxidase (PAP) complexes, described below, are available commercially. There are occasions, however, when it is desirable to prepare the conjugated reagents. Peroxidase may be conjugated to antibody by glutaraldehyde [7] or by periodate oxidation.

Use of conjugates

The horseradish peroxidase, conjugated to antibody or to globulin, may be applied to sections to detect antigen by procedures similar to those used for immunofluorescence. There are, however, modifications that increase the sensitivity of the method so that it is equal to, or possibly more sensitive than, indirect immunofluorescence [8–10].

The diagrammatic representation of the procedures seen in Fig. 7.8 shows the different forms of conjugate. Antibody against the antigen to be detected may be conjugated directly with the enzyme (Fig. 7.8a). This is not a very discriminating procedure. The indirect or two-stage procedure, whereby the unlabelled antibody bound to the antigen is detected by antiglobulin conjugated to enzyme (Fig. 7.8b), increases sensitivity by increasing the number of conjugated antibodies binding to the site, and is more versatile, because one conjugated antiglobulin can detect any antibody of that species.

Two other procedures increase the sensitivity of the technique. The antibody bound to the antigen is treated with unconjugated antiglobulin, which in turn is treated with normal globulin of the same species as the first antibody (Fig. 7.8c), for example, a sequence of rabbit antibody, goat antirabbit globulin and then rabbit normal globulin conjugated with peroxidase.

In the second modification, instead of using globulin conjugated chemically with enzyme in the third stage, a PAP complex is added (Fig. 7.8d) [8,10], for example, rabbit antibody to peroxidase, which gives a more discrete, intense reaction product than chemically prepared conjugates of normal globulin–peroxidase, possibly because chemical treatment tends to alter the antigenic determinants of the normal globulin, and to polymerize the peroxidase.

If the antibody applied to the section is human, it is not possible to use a human antiperoxidase antibody in the PAP complex in the third stage. Instead, a baboon antiperoxidase, which is antigenically similar to human IgG, is a satisfactory alternative [11].

The enzyme most frequently used is horseradish peroxidase, which forms a dark-brown product from its substrate. Alkaline phosphatase may also be used, and the

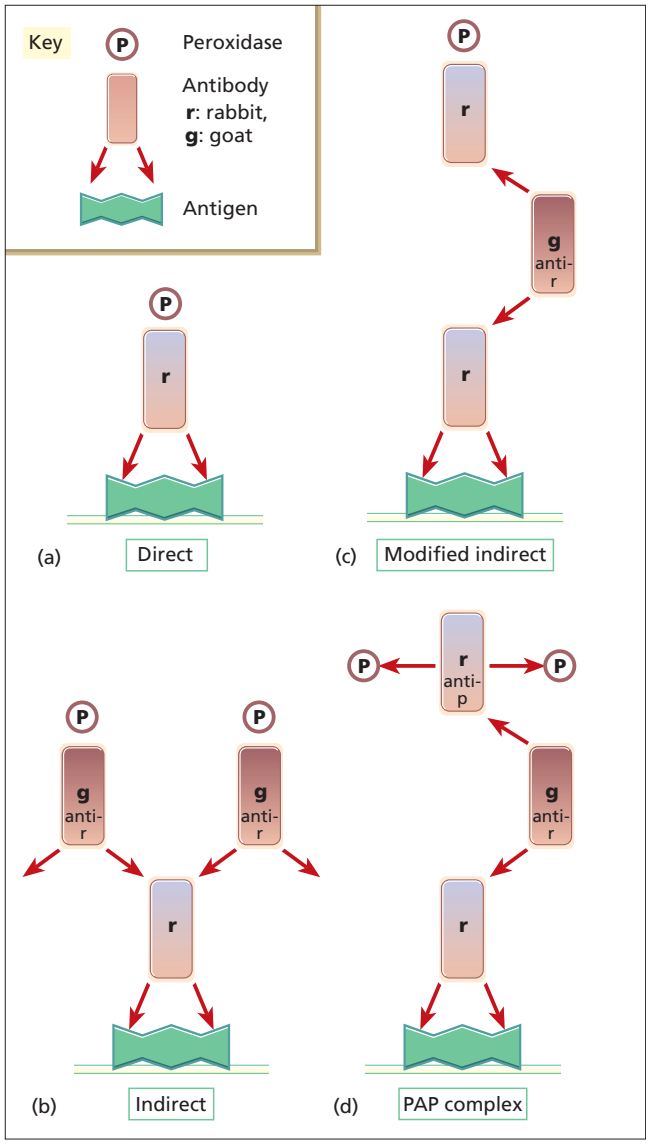

Fig. 7.8 Diagrammatic representation of immunoperoxidase techniques.

reaction product with its substrate is blue. The two enzymes may be used with appropriate antibodies on the same tissue or cells to detect different antigens, and the relationship of one antigen to another (i.e. double staining).

Examination of fixed frozen sections

There are three stages in the procedure:
1 The preparation of the tissue sections.
2 Treatment of the sections with the peroxidase-labelled antibody.
3 Chemical reaction to detect the peroxidase in the tissue.

Preparation and fixation of sections. Sections may be prepared from routine cryostat-cut samples or paraffin-embedded material, and may be treated for antigen-retrieval as described above. Some improvement in cryostat-prepared sections may be achieved by short-term fixation in dilute formalin, as follows.
1 Fix thin slices (2 mm thickness) with 1% formaldehyde in 0.1 mol/L phosphate buffer pH 7.2–7.4 for 30 min.
2 Wash in three changes of 15% sucrose in 0.1 mol/L phosphate buffer pH 7.2–7.4 for 18–24 h at 4°C.
3 Snap freeze in isopentane at the temperature of liquid nitrogen.
4 Cut sections 4–6 µm in a cryostat. Mount on slides, and dry under a fan at room temperature.

Treatment of the sections with antibody. Control for antibody specificity is as described for immunofluorescence. Sections may be treated by the methods described above (Fig. 7.8). The indirect method is probably the most suitable for general use, applying unlabelled antibody, followed by labelled antiglobulin.
1 Moisten section in PBS.
2 Treat with suitable dilution of specific antibody in PBS in a moist chamber at room temperature for 30 min–2 h.
3 Rinse well in PBS: then in two washes of PBS, each for 5 min with gentle agitation. (As the tissues are fixed they are less likely to be washed off the slides than unfixed tissues in the immunofluorescence technique.)
4 Treat with peroxidase-conjugated antiglobulin specific for the antibody applied in step 2. Use at optimum dilution in PBS for 30 min.
5 Rinse well: wash in PBS for 15 min.

Detection of the peroxidase reaction product by staining. The substrate is a carcinogen and should be handled in small quantities with appropriate precautions. It is made up as follows:
- 3′,3′–diaminobenzidine tetra-HCl (DAB), 25 mg
- 0.05 mol/L pH 7.6 Tris–HCl buffer, 50 mL
- 3% hydrogen peroxide (H_2O_2), 0.15 mL

Dissolve the DAB in the buffer and add the H_2O_2 immediately before staining.
1 Slides treated with conjugated antibody or antiglobulin and washed are incubated with the substrate solution for 5–15 min (the longer period is not always an advantage).
2 Wash in tap water for 5 min. (If required, the reaction products may be intensified by 2% osmium tetroxide for 1 h, and the slides then washed.)
3 If required, the slides may be counterstained with methyl green, or Mayer's haemalum.
4 Treat for about 1 min each with 70%, 90% and twice with 100% industrial spirit, followed by two treatments with xylol.
5 Mount with DPX or Permamount.

Controls

It is necessary to confirm that the reaction observed reflects antibody-conjugated peroxidase and not endogenous peroxidase, and that the antibody binding is specific for antigen.

One section should be stained with DAB only; another section with DAB–methanol–H_2O_2, to confirm the absence of endogenous peroxidase.

Paraffin sections

If the antigens to be detected are stable in the fixatives and dehydrating agents, the immunoperoxidase methods may be applied to sections from paraffin-embedded tissue. The best results are obtained when the tissue is prepared for this particular purpose [6,8,12], but tissues prepared routinely for histology may also be examined by this method. The paraffin is removed from the sections with xylol and alcohols; sections are subsequently treated as for frozen sections.

The identity of the cells and tissues containing the antigen is much more easily determined by this method than by cryostat-cut sections, or by immunofluorescence. Immunoglobulins and hormones may be readily detected, but some antigens, such as those of bacteria in vasculitic lesions, tend to be extracted during processing.

Conjugates involving avidin–biotin coupling of antibody and enzyme

Instead of chemical covalent binding of antibody to enzyme to prepare conjugates, the two reagents may be linked non-covalently by the very strong affinity between biotin (a vitamin widely distributed in mammalian tissues) and avidin (a glycoprotein of egg white). Biotin is coupled to the reagent antibody through formation of an intermediate biotin derivative, and the avidin is coupled to the selected enzyme by glutaraldehyde [13]. Each biotin molecule has one combining site for avidin, and avidin has four sites for biotin, although not all of these would combine in a test system. Guesdon *et al*. [13] described two procedures.

1 The antibody–biotin conjugate is incubated with and combines with antigen in the test section or cell. This is followed by addition of peroxidase conjugated with avidin. The avidin binds the peroxidase to any biotin, and subsequent treatment with the substrate for the enzyme reveals the antigen sites (Fig. 7.9a).

2 The antibody–biotin conjugate is used as above to bind to any antigen. Avidin is then added, which becomes strongly linked to the biotin. Then biotin-labelled enzyme is added and the avidin bridges the biotin molecules. As the avidin has a potential four valencies for biotin, there is an enhancement or amplification of the enzyme binding, and therefore greater discrimination of the sites of antigen (Fig. 7.9b).

A further modification has been reported, the avidin–biotin–peroxidase complex (ABC) method (Fig. 7.9c), similar to the PAP method already described. A prepared ABC follows the use of biotin-labelled antiglobulin (to detect unlabelled reagent antibody, or tissue-bound antibody in the tissue). The complex binds through the avidin bridge to biotin on the antiglobulin; the method results in greater intensity of staining [14].

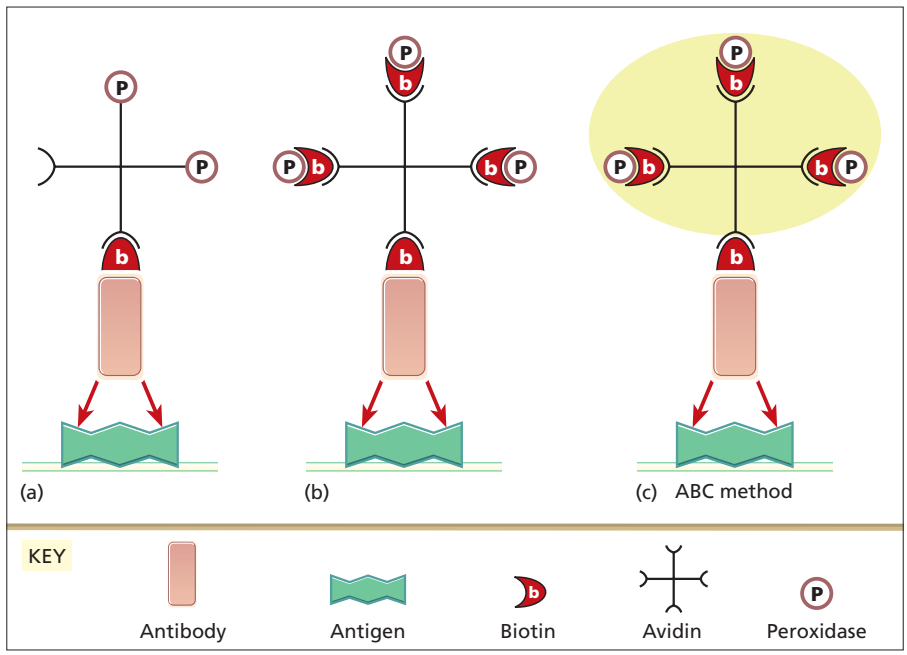

Fig. 7.9 Avidin–biotin staining methods. (a) Antibody coupled with biotin binds with the antigen in tissue. Avidin coupled with peroxidase binds to the biotin on the antibody. Treatment with enzyme substrate reveals the bound peroxidase, and therefore site of antigen. (b) Antibody coupled with biotin binds with the antigen in tissue. Avidin will bind the biotin–antibody complex. Biotin coupled with peroxidase will then bind to the free avidin-combining sites. Finally, treatment with enzyme substrate reveals the bound peroxidase. (c) Complexes (shown within yellow circle) are formed of biotin, coupled with peroxidase, incubated with moderate excess of avidin (ensuring some free avidin combining sites). Antibody coupled with biotin binds to antigen in tissue. The complexes are added to the tissue and the free avidin sites bind to the biotin on the antibody. Finally, treatment with enzyme substrate reveals the bound peroxidase.

As in the other immunodetection techniques, it is necessary to ensure that there is no autologous tissue background activity that will cause confusion when interpreting results. In the biotin–avidin methods, it is necessary to eliminate the possibility of endogenous peroxidase activity as in any peroxidase method. It is also necessary to inactivate endogenous biotin present in tissues that would bind the avidin-labelled reagents. However, overcoming any endogenous activity is a complex multistep activity [15] and is not necessary if the appropriate controls (e.g. tissue treated with the avidin conjugates) show no binding.

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Applications of immunopathology techniques [1,2]

The immunopathological methods described above have revolutionized diagnostic histopathology, and have helped us to recognize, classify and understand the pathogenesis of a wide variety of cutaneous disorders. Although there are many antigens of diagnostic value that are not stable following formalin fixation and paraffin-embedding of tissue, there is still a wide range of antigens that are stable. Refinements to processing techniques, such as the periodate lysine paraformaldehyde technique [3] have increased the range of antibodies and labels that may be used for diagnostic purposes [1,4,5]. A few of the more important areas of diagnostic dermatopathology that highlight the usefulness of immunopathological techniques are described below (Table 7.9). Immunopathological techniques for the diagnosis of connective tissue diseases and autoimmune blistering diseases mainly rely on the use of immunofluorescence methods. Although some have suggested that immunoperoxidase methods are equally reliable in this setting, formalin fixation results in poor preservation of the antigens of interest and false-negative results are frequent. In the last decade, immunofluorescence studies have been increasingly used with success in the diagnosis of genetic blistering diseases particularly, epidermolysis bullosa (see Chapter 40). Samples are fixed in Michel's medium and frozen sections are processed in the same way as samples submitted for the diagnosis of autoimmune blistering disorders.

Table 7.9 Direct immunofluorescence findings in autoimmune blistering disease.

Disease	Pattern and nature of immunoreactants
Pemphigus	Epidermal cell-surface deposits of IgG and C3
Bullous pemphigoid	Linear, homogeneous deposits of IgG (epidermal side on salt-split skin) and C3 at the dermal–epidermal junction
Linear IgA dermatosis	Linear homogeneous deposits of IgA at the dermal–epidermal junction
Herpes gestationis	Linear homogeneous deposits of C3 at the dermal–epidermal junction
Epidermolysis bullosa acquisita	Linear homogeneous deposits of IgG (dermal side on salt-split skin) and C3 at the dermal–epidermal junction
Cicatricial pemphigoid	Linear homogeneous deposits of IgG and C3 at the dermal–epidermal junction
Dermatitis herpetiformis	Focal granular deposits of IgA at the papillary tips
Bullous eruption of lupus erythematosus	Linear homogeneous, or non-homogeneous, deposits of multiple immunoglobulins, C3 and fibrin at the dermal–epidermal junction

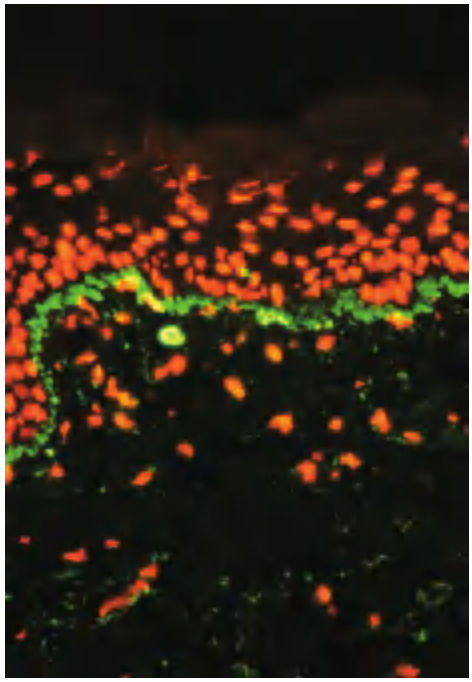

Fig. 7.10 Direct immunofluorescence of lupus erythematosus, showing speckled basement membrane zone deposition of IgM (green); ethidium bromide counterstain (orange). (Courtesy of Mr B.S. Bhogal, St John's Institute of Dermatology, London, UK.)

Lupus erythematosus

The deposition of immunoglobulins and complement at the dermal–epidermal junction is of diagnostic value in patients with lupus erythematosus (Fig. 7.10) and is known as the lupus band test. The presence of immunoglobulins, particularly those other than IgM, at the dermal–epidermal junction in normal non-sun-exposed skin correlates to some extent with the presence of systemic lupus erythematosus and renal involvement. Sequential biopsies may demonstrate the disappearance of a positive lupus band during periods of disease inactivity, and may aid the clinician in the management of the disease. However, this approach is hardly ever used, as it implies repeated invasive procedures and disease activity may be monitored in a simpler way with blood tests. A positive lupus band is usually seen in involved skin in cutaneous lupus erythematosus, but false-positive results may be seen in sun-exposed skin from patients who do not have lupus. Immunofluorescence studies, in conjunction with other serological investigations, have led to the recognition of various important subsets of lupus erythematosus. Examples of this include the high incidence of anti-Ro/SSA and anti-La/SSB antibodies in the sera of patients with subacute lupus erythematosus and neonatal systemic lupus erythematosus [6].

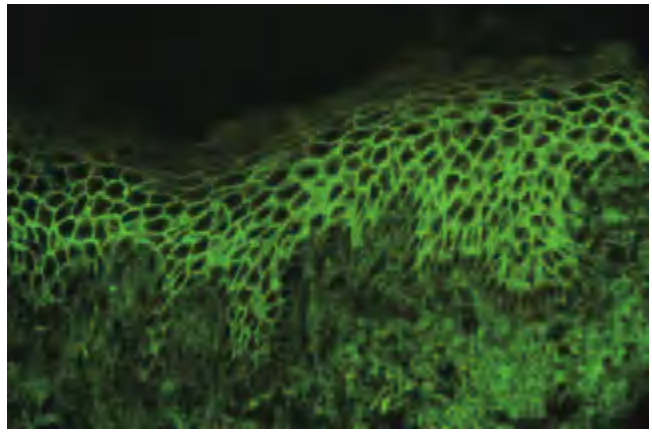

Fig. 7.11 Direct immunofluorescence of pemphigus, showing deposition of intercellular IgG in the epidermis. (Courtesy of Mr B.S. Bhogal, St John's Institute of Dermatology, London, UK.)

Bullous disorders (see also Chapter 41)

The histological diagnosis of the various cutaneous autoimmune blistering diseases should always be confirmed with immunofluorescence studies. Although in many non-autoimmune blistering diseases a diagnosis can be made on the basis of light microscopic features in biopsies from formalin-fixed tissue, in immunological diseases a specific diagnosis is often not possible. In these circumstances, immunofluorescence studies are essential. Other techniques including immunoelectron microscopy and immunoblotting are extremely helpful. The classification and understanding of the pathogenesis of numerous bullous disorders has been greatly facilitated by advances with these techniques. Ideally, tissue for immunopathological examination and serum for indirect immunofluorescence studies should always be taken at the time of a skin biopsy in a patient with an acquired blistering disorder. The biopsy submitted for immunofluorescence should be from perilesional or clinically normal skin. If lesional skin is submitted for immunofluorescence studies, a false-negative result is often obtained. The results of direct immunofluorescence studies on skin biopsies vary considerably depending on the disease being investigated, and the site of the biopsy. Intercellular epidermal deposition of IgG is present in almost all cases of pemphigus (Fig. 7.11). Complement is also frequently present, and IgA and/or IgM may be seen in a smaller percentage of cases. The additional presence of basement-membrane-zone IgG, or the C3 component of complement, points to a diagnosis of pemphigus erythematosus. Linear basement-membrane-zone IgG and complement deposition, and less commonly IgA or IgM, is associated with bullous pemphigoid (Fig. 7.12). Identical results are usually obtained in epidermolysis bullosa

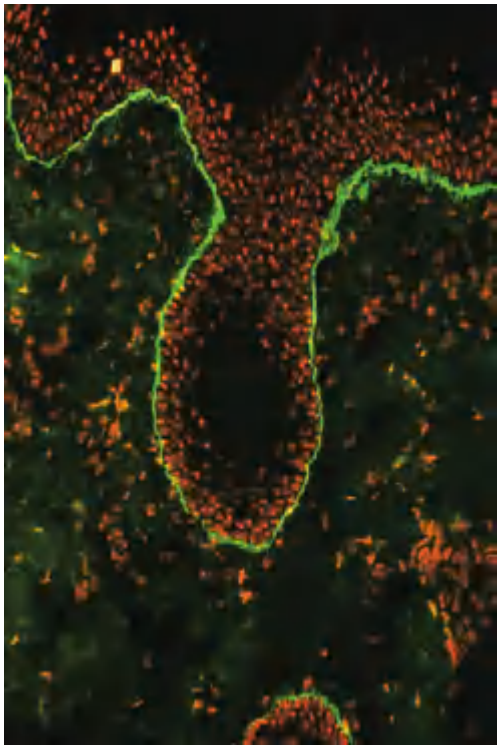

Fig. 7.12 Direct immunofluorescence of bullous pemphigoid, showing linear basement membrane zone deposition of IgG (green); ethidium bromide counterstain (orange). (Courtesy of Mr B.S. Bhogal, St John's Institute of Dermatology, London, UK.)

acquisita. The differential diagnosis is greatly aided by the use of the split-skin technique. In this technique, the exposure of the specimen to 1 mol/L NaCl induces a subepidermal blister. In epidermolysis bullosa acquisita, the immunoreactants line the floor of the blister and in bullous pemphigoid, the immunoreactants line the roof of the blister. With the indirect immunofluorescence technique using patient serum, the detection of linear basement-membrane-zone immunoglobulin antibodies is much more common in the classical form of bullous pemphigoid than in the cicatricial form of the condition, where positive results are obtained in approximately only 10% of cases. The diagnosis of other blistering diseases such as herpes gestationis (pemphigoid gestationis) and dermatitis herpetiformis is also greatly facilitated by immunopathological studies. In addition to direct immunofluorescence examination of skin biopsy material, and indirect immunofluorescence studies carried out on patient serum, the split-skin technique is valuable in the study of most of the subepidermal blistering disorders, enabling localization of the antibody-binding sites to be visualized [7]. Data obtained from such research has shed considerable light on the pathogenesis of many blistering diseases. Since the advent of immunopathological techniques, several new blistering diseases have been categorized. These include linear IgA bullous dermatosis, which is probably identical to some forms of chronic bullous disease of childhood, and epidermolysis bullosa acquisita, where linear basement-membrane-zone immunoglobulin is almost always demonstrable, and circulating antibasement membrane immunoglobulin antibodies may be found in approximately one-quarter of cases investigated. Immunoblotting and related techniques enable specific antigens to be categorized more precisely [8,9] and such techniques are likely to lead to the delineation of new bullous dermatoses in the future.

Cutaneous neoplasms [1,5,10–12]

One of the most useful applications of immunopathology is in helping to determine the line of differentiation of poorly differentiated benign and malignant neoplasms that may arise from the various cellular components within skin and related tissues. The development within the last few years of increasing numbers of antibodies and other labels that can be utilized on formalin-fixed paraffin-embedded material has increased the usefulness of this application. All the antibodies discussed below work well in formalin fixed paraffin-embedded material.

Keratins and other epithelial markers

Cytokeratins represent a group of intermediate filaments known as tonofilaments of variable molecular weight that may be demonstrated in keratinizing and non-keratinizing epithelia [13,14]. They represent the main structural component of the cytoskeleton of epithelial cells. About 30 different keratins have been demonstrated in humans by the use of double-diffusion gel electrophoresis. Their molecular weight ranges from 40 to 68 kDa. Keratins are divided according to molecular weight and their charge properties into acidic (type I) and neutral-basic (type II) [13,14]. They associate as pairs of one acidic and one basic keratin polypeptide molecule with each epithelial cell containing at least one keratin pair. The antibodies against keratins most commonly used in dermatopathology include AE1/AE3, MNF116 and CAM 5.2. They are all cocktails containing several monoclonal antibodies of different molecular weight. CAM 5.2 is a low-molecular-weight keratin antibody, which labels most epithelia, with the exception of stratified squamous epithelia [15]. CAM 5.2 is usually negative in squamous cell carcinoma. It should therefore not be used in the diagnosis of poorly differentiated squamous cell carcinoma, as a negative result is the norm. Positive staining however, may be seen in sebaceous carcinoma, and this is an aid in the distinction between this tumour and squamous cell carcinoma. The main use of CAM 5.2 in dermatopathology is in the diagnosis of Merkel cell carcinoma (primary cutaneous neuroendocrine carcinoma), as tumour cells in this lesion

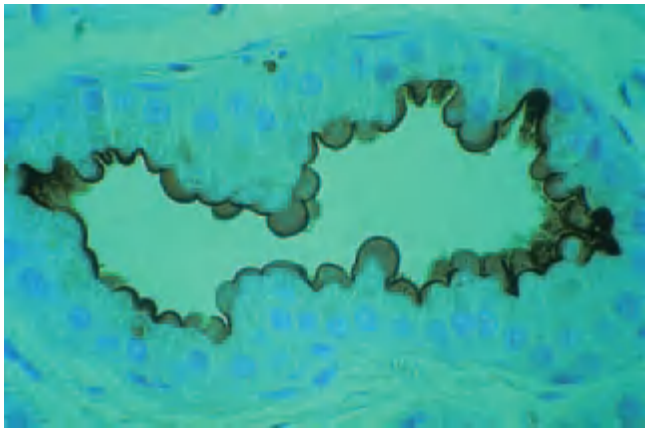

Fig. 7.13 Positive epithelial membrane antigen (EMA) staining of the luminal surface of an apocrine gland. (Courtesy of Dr R. Russell Jones, St John's Institute of Dermatology, London, UK.)

display a typical perinuclear dot-like positivity for this antibody. More recently, a new cytokeratin antibody, cytokeratin 20 (CK-20), has been developed which is very useful in the diagnosis of Merkel cell carcinoma [16,17]. The staining pattern is identical to that of CAM 5.2, and a positive result strongly suggests a primary cutaneous origin rather than a metastatic neuroendocrine carcinoma originating in another organ. Only Merkel cell carcinoma and salivary gland small cell carcinoma tend to be positive for this marker, while neuroendocrine tumours from other organs are consistently negative.

Cytokeratin 7 (CK-7) is a very useful antibody for confirmation of the diagnosis of mammary and extramammary Paget's disease [18]. Tumour cells in the latter stain consistently for this antibody while the surrounding epidermis is negative.

It is important to remember that keratin expression is commonly seen in various sarcomas including epithelioid sarcoma, synovial sarcoma, epithelioid angiosarcoma, and more rarely in other tumours such as leiomyosarcoma and rhabdomyosarcoma.

Epithelial membrane antigens (EMA) [19] are derived from human milk fat globulin membrane, and consist of high-molecular-weight glycoproteins. Antibodies to EMA and related labels react with a range of normal and neoplastic epithelia, and positivity may be found in squamous and ductal epithelia as well as eccrine, apocrine and sebaceous glands (Fig. 7.13). EMA tends to be at least focally positive in squamous cell carcinoma, sebaceous carcinoma and a wide variety of adnexal carcinomas. It is also positive in plasma cells, in epithelioid sarcoma, synovial sarcoma, epithelioid angiosarcoma and in systemic $CD30^+$ large-cell anaplastic lymphoma [20].

Carcinoembryonic antigen is a protein that is normally found in the goblet cells of the small and large intestine. It is found in many adnexal carcinomas particularly tumours displaying ductal differentiation [21]. It is also expressed in many glandular carcinomas arising in other organs. Its main use in dermatopathology is to highlight ductal differentiation in adnexal tumours.

Neuroendocrine markers

Besides CK-20, whose use in the diagnosis of Merkel cell carcinoma has been described before, markers of neuroendocrine differentiation include neurone-specific enolase, chromogranin and synaptophysin.

Neurone-specific enolase is an enzyme described in the brain but also found in neuroendocrine cells [22]. Its use in diagnostic pathology is very limited because of the lack of specificity.

Chromogranin A is part of a family of calcium-binding proteins present in the secretory granules of neuroendocrine cells. This protein is very specific for neuroendocrine differentiation [11].

Synaptophysin is a transmembrane glycoprotein with a molecular weight of 38 kDa and is a specific marker of neuroendocrine differentiation [23].

Melanocytic markers

Over the years, a wide array of markers for melanocytes have been described including S-100, HMB45, Melan-A, tyrosinase and MIFT-1 (microphthalmia transcription factor-1).

It is important to emphasize that no marker allows distinction between benign and malignant melanocytes and that the sensitivity and specificity of different markers is variable. S-100 protein is very sensitive but much less specific than other markers including HMB45, Melan-A and MIFT-1. Melanocytic markers are particularly useful as part of a panel in the differential diagnosis of poorly differentiated malignant tumours. Desmoplastic melanomas are usually positive for S-100 but negative for melanocytic markers such as Melan-A, HMB45 and MIFT-1.

S-100 protein is an acidic protein, originally derived from ox brain, and named because of its solubility in 100% ammonium sulphate. It is a sensitive marker of melanocytes [24–26]. Antibodies to S-100 protein, however, also react with Schwann cells, glial cells, adipocytes, chondrocytes, Langerhans' cells and cells of the eccrine sweat coil, and therefore tumours and hamartomas derived from these cells. S-100 also stains the cells in Rosai–Dorfman disease. S-100 protein is particularly useful in the study of suspected malignant melanoma, as the great majority of, but by no means all, melanomas are positive for this marker [27] (Fig. 7.14). In this context, the technique is particularly valuable in the differentiation of melanoma from other spindle cell neoplasms, and in identifying

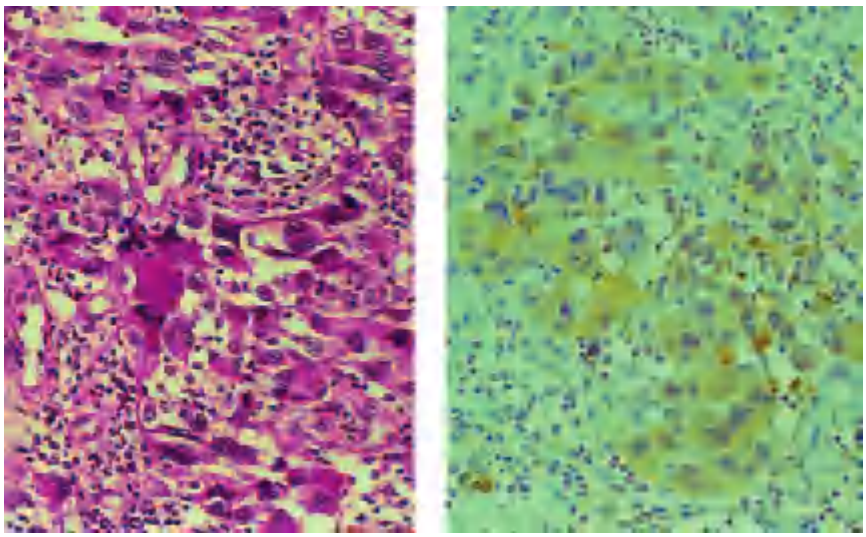

Fig. 7.14 Confirmation of melanocytic origin of large atypical cells in skin biopsy: (left) H&E stain; (right) positive labelling of tumour cells with S-100 antibody.

small deposits of melanoma that may be present in deep dermal tissues, as in determination of accurate Breslow thickness and/or intravascular spread, or the evaluation of spread to sentinel lymph nodes. S-100 is less reliable when used to delineate the epidermal component of a melanocytic lesion. The reason for this is that it also stains Langerhans' cells. More specific markers of melanocytes like Melan-A should be used for this purpose. S-100 is also often focally positive in a number of soft-tissue tumours and should therefore be used as part of a panel of markers in the diagnosis of poorly differentiated tumours.

HMB-45 (gp100) [28–30] recognizes a 10-kDa antigen localized in premelanosomal vesicles. The antibody was developed from an extract of a lymph-node metastasis of melanoma. This antibody does not stain normal adult melanocytes or intradermal naevi. It is a very specific antibody, which is usually negative in desmoplastic melanoma. Around 90% of primary and metastatic melanomas are positive for this marker.

Melan-A (MART-1) [31,32] is a recently described melanocyte marker that recognizes an antigen present in melanoma cells and recognized by $CD8^+$ cytotoxic T lymphocytes. It is a fairly specific marker of melanocytes. Melan-A stains naevi and melanomas, but it tends to be negative in desmoplastic melanoma, spindle cell melanoma and neurotized naevi.

MIFT-1 is the latest addition to the armamentarium of melanocytic markers [33]. This is a nuclear protein involved in the development of melanocytes and in the regulation of melanin synthesis. It stains naevi and melanoma but is usually negative in desmoplastic melanomas. Although it was initially regarded as fairly specific, it has been found to be expressed in macrophages, fibroblasts, lymphocytes, Schwann cells and even smooth muscle cells [34]. Its utility as part of a panel for the diagnosis of difficult tumours is likely to be limited.

Mesenchymal markers

There are many markers of mesenchymal differentiation that are useful in the differential diagnosis of neoplasms particularly those that are poorly differentiated. As with many of the other antibodies discussed so far, the specificity and sensitivity of each of these markers is very variable. What this means is that they should always be used as part of a wider panel of markers. Commonly used markers include vimentin, desmin, smooth muscle actin, muscle-specific actin, S-100, CD34, CD31 and factor VIII-related antigen [11].

Vimentin has a molecular weight of 57 kDa and it is found in all mesenchymal cells and their tumours. It has a very low specificity and can be found in melanomas, lymphomas and even carcinomas. Its value is therefore very limited [35].

S-100 has already been described above. It is a very useful marker for neurofibroma and Schwannoma. While the latter tumour tends to be uniformly positive for S-100, the percentage of tumour cells positive for this marker varies in neurofibroma.

Desmin is a polypeptide with a molecular weight of 53 kDa, and is characteristic of smooth, skeletal and cardiac muscle [36]. In skeletal muscle desmin filaments are found in association with the Z-discs of the sarcomeres and the sarcolemmal attachment plaques. In smooth muscle cells, desmin filaments interconnect the fusiform dense bodies with the plasmalemmal dense bodies. Desmin is very specific for muscular differentiation and it is a useful marker only occasionally reported in other tumours such schwannoma and epithelioid sarcoma [11,37,38].

Actin represents a family of intermediate filaments present in the cytoskeleton of eukaryotic cells. They are contractile proteins involved in the control of motility of muscle cells and non-muscle cells. Actin proteins are

classified according to their amino acid sequences, and six major isoforms have been described. Of the monoclonal antibodies used in diagnostic pathology the most useful ones are HHF35 (muscle-specific actin) and 1A4 (alpha-smooth-muscle actin) [39–41]. The former reacts with skeletal and smooth muscle and the latter only reacts with smooth muscle. Both types of antibody stain myofibroblasts, pericytes and myoepithelial cells [40].

CD34 is a glycosylated transmembrane protein with a molecular weight of 110 kDa. It is normally present on haematopoietic progenitor cells and vascular endothelial cells [42,43]. This marker however, is fairly non-specific and it is expressed in a wide number of soft-tissue tumours including dermofibrosarcoma protuberans (DFSP), neurofibroma and spindle cell lipoma. Its main use in dermatopathology is as an endothelial cell marker and in the differential diagnosis between DFSP and fibrous histiocytoma and its variants, particularly cellular fibrous histiocytoma. CD34 tends to be diffusely positive in the former and negative in the latter [44,45].

One large group of soft-tissue tumours where useful markers are badly needed is the group of fibrohistiocytic tumours. So-called markers of histiocytic cells including alpha-1-antitrypsin and alpha-1-antichymotripsin are very non-specific and have no role in the diagnosis of these tumours. Besides, it appears clear that the so-called fibrohistiocytic tumours usually do not show true histiocytic differentiation. Another interesting polyclonal antibody produced against the blood coagulation transglutaminase, factor XIIIa, seems to be a cell marker for a particular subpopulation of dermal dendritic mononuclear macrophage cells termed dermal dendrocytes [46–48]. A number of positive cells may be identified in very many different types of soft-tissue tumours. However, combined with other markers, FXIIIa is useful in the differential diagnosis between benign fibrous histiocytoma and DFSP. The former is normally rich in factor XIIIa positive cells particularly at the periphery, in contrast to DFSP which is negative [44].

A wide range of endothelial markers now available can identify various vascular tumours. The most useful of these markers are CD31, CD34 and FVIII-related antigen.

CD31 refers to a glycoprotein that belongs to the immunoglobulin supergene family and has a molecular weight of 130 kDa. It is also known as platelet-endothelial cell adhesion molecule type I (PECAM-1) and it stains endothelial cells and some haematopoietic cells. CD31 is the most sensitive marker of endothelial cells [49–51]. However, interpretation should be cautious as CD31 also stains macrophages [52].

Antibodies to factor VIII-related antigen label normal and neoplastic endothelium in routine paraffin sections [53]. This marker, however, may be negative in lymphatic capillaries, and because of the presence of factor VIII-related antigen in plasma and tissue exudates, false-positive labelling may be encountered. None of these endothelial cell markers allows distinction between lymphatic and vascular endothelium. In recent years, a number of antibodies have been described with claims as to their specificity for lymphatic endothelium. These antibodies include vascular endothelial growth factor receptor-3 (VEGFR-3), podoplanin and LYVE-1 (lymphatic vessel endothelial hyaluronan receptor) [54–56]. The first two antibodies have not proven to be specific for lymphatic differentiation in vascular tumours and the final verdict is still awaited on the third.

Metastatic cutaneous tumours

It is important to remember that all tumours that are present in the skin are not necessarily of cutaneous origin. Reference has already been made to several epithelial markers, many of which may be useful in diagnosing metastatic adenocarcinoma. Immunohistochemistry, however, does not usually allow determination of the site of the primary tumour except in a few instances. The latter include prostate-specific antigen in prostatic carcinoma and thyroglobulin in thyroid carcinoma. A recently described marker, thyroid transcription factor-1 (TTF-1), is a 38-kDa nuclear protein expressed in epithelial cells of lung and thyroid. TTF-1 is therefore useful in the diagnosis of cutaneous metastatic tumours [57]. Markers for oestrogen and progesterone receptors are not useful in the diagnosis of metastatic breast carcinoma, because adnexal carcinomas may also be positive for these markers.

Histiocytic markers

CD68 (KP1) is the main marker used to demonstrate histiocytic differentiation in paraffin-embedded material [58,59]. It is an antibody raised against a 110-kDa glycoprotein present in pulmonary macrophages. This antibody stains normal histiocytes, granulocyte precursors, tumour cells in myelomonocytic neoplasms and true histiocytic lymphomas. KP1, however, is not specific for histiocytic differentiation, and expression may be seen in many tumours, including carcinoma, melanoma, granular cell tumours and a variety of sarcomas [60–62].

Lymphoid markers

One of the most difficult areas in diagnostic dermatopathology is the interpretation of heavy lymphoid infiltrates in cutaneous biopsies. The wide range of conditions that may produce a histological picture simulating lymphoma ranges from insect bites, through syphilis, to reactive lymphoid hyperplasia where an aetiological factor cannot be demonstrated. Furthermore, recognition of the number of different varieties of malignant lymphoproliferative disorders that may be encountered in the skin continues to

increase. Very many different markers for lymphocytes and their subsets are now available, and are particularly useful when used as a battery. It should be remembered that histological and antibody-labelling patterns of cutaneous lymphomas do not necessarily mirror their nodal counterparts, and that very few markers are absolutely specific for cells of one lineage. Furthermore, it has to be realized that in the course of a disease process, many lymphoid cell types may lose their antigenic determinants and label in an anomalous fashion. This is particularly common in some forms of advanced cutaneous lymphoma. Nevertheless, with careful interpretation and the use of antibody panels, considerable information can be derived from the use of newer monoclonal antibodies [5].

The rationalization of nomenclature in relation to human leukocyte antigens, the CD (or cluster of differentiation) nomenclature has been a great advance, enabling useful comparison of numerous different monoclonal antibodies developed in different laboratories, and facilitating their classification [5,63]. As in other areas of immunopathology, a further bonus for the diagnostic dermatopathologist is the possibility nowadays of using many of these leukocyte antigen markers in paraffin-processed tissue [64,65]. A full discussion of the applications of immunopathology to the recognition of subsets of lymphocytes in skin biopsies is beyond the scope of this chapter. Useful antibodies available for use on routinely processed material include CD45 (leukocyte common antigen), pan-B-cell markers such as CD20 (L26) and CD79a, and pan-T-cell markers such as CD3, CD2, CD5 and CD7 [66,67]. Determination of the subset of T cells in paraffin-embedded skin biopsies is also possible, as there are commercially available antibodies to CD4 (helper T cells) and CD8 (cytotoxic T cells) T cells [5,68,69]. Immunohistochemistry is also very useful in the determination of clonality, particularly in B-cell infiltrates. Antibodies against kappa and lambda light chains can be used in paraffin-embedded material to demonstrate clonality [5,70,71]. Monotypic Ig light chain expression is very suggestive of a B-cell lymphoma.

Other markers of interest include determinants closely associated with T-cell activation, such as the CD30 antigen. An example of an antibody to the CD30 epitope is Ber-H2, which identifies activated T cells, B cells and Reed–Sternberg cells. In cutaneous biopsies, it is commonly present in examples of lymphomatoid papulosis type A [72] (Fig. 7.15), and lymphomas that are best categorized within the group of large cell anaplastic CD30 positive lymphomas [73,74].

Anaplastic lymphoma kinase (ALK) is a marker of the protein that results from translocation 2;5 between the ALK and nucleophosmin. Its usefulness resides in the fact that this protein is expressed in systemic large cell anaplastic lymphoma, but it is usually not expressed in primary cutaneous large cell anaplastic CD30 positive lymphomas [75,76].

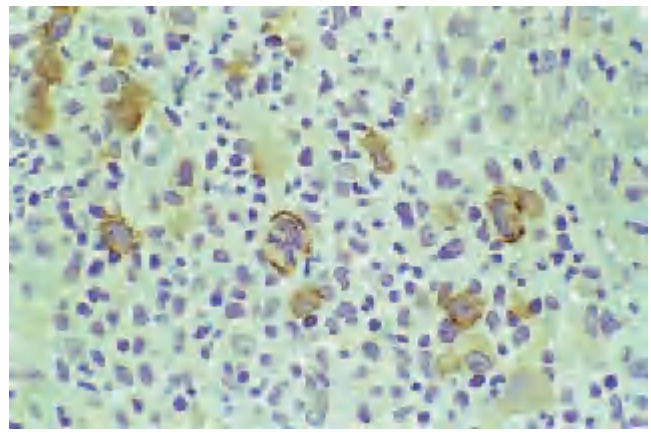

Fig. 7.15 Positive staining of atypical cells in a case of lymphomatoid papulosis with the CD30 marker, Ber-H2. This reaction may be carried out on sections from paraffin-embedded tissue.

CD56 (neural cell adhesion molecule) is expressed in the central and peripheral nervous system, and it is also a marker of natural killer (NK) cells. Its main use in dermatopathology is in the diagnosis of cutaneous NK/T-cell lymphoma [77,78]. Some subcutaneous panniculitis-like T-cell lymphomas may also express this marker [79].

TIA-1, granzyme and perforin are cytotoxic proteins present in the cytoplasmic granules of NK and cytotoxic T cells. Expression of these proteins can be demonstrated in paraffin-embedded material and this is useful in the diagnosis of NK or cytotoxic lymphomas [80,81].

Markers of B follicle-centre cells such as CD10 and bcl-6, although not entirely specific, are useful in demonstrating the presence of these cells in the skin. Positive staining does not indicate that the cells are neoplastic but that they are of follicle-centre origin [5,82–84]. Reactive cutaneous germinal centres are positive for these markers. On the other hand, an infiltrate with follicle-centre cells which are positive for bcl-2 is very suggestive of a follicle-centre cell lymphoma, and usually indicates the presence of a 14;18 chromosomal translocation [5,85]. Many primary cutaneous follicle-centre cell lymphomas, however, do not stain for this marker and the t(14;18) chromosomal translocation is often absent [86]. It is worth remembering that normal reactive T lymphocytes are usually bcl-2 positive and these tend to be prominent in B-cell infiltrates. Normal mantle B cells are also bcl-2 positive.

The field of immunopathology in general, and with relation to the study of lymphoid proliferations in particular, continues to grow apace. In addition to the techniques discussed above, it is likely that within the next few years further information of use to the diagnostic pathologist will be gained from studies of cytokines, adhesion

molecules and similar substances. The correlation of immunophenotypic studies with immunogenotyping using the latest molecular biological techniques is likely to contribute further to our understanding of cutaneous and systemic lymphomas.

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Other special laboratory techniques

Cytodiagnosis and Tzanck smears [1,2] (Fig. 7.16)

Cytodiagnosis in dermatopathology should not be regarded as a substitute for formal biopsy. The technique has been used as an aid to rapid diagnosis of numerous skin conditions, including epithelial tumours, Paget's disease, malignant melanoma, cutaneous lymphomas and skin metastases. In most of these conditions, a diagnostic

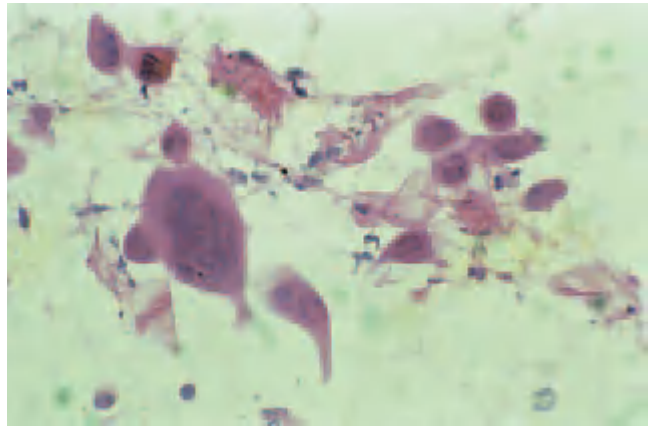

Fig. 7.16 An H&E-stained smear from a lesion of herpes simplex, showing multinucleate giant cells and degenerative nuclear changes.

surgical biopsy rather than fine needle biopsy, is always preferable. Examination of cytological specimens from skin lesions is of most value in bullous disorders, vesicular virus eruptions and basal cell epithelioma.

In blistering disorders, a small, early, uninfected lesion should ideally be selected. The roof of the blister is removed with scissors, and the base of the blister gently scraped with a blunt scalpel so as not to produce bleeding. The material obtained is spread thinly on a glass slide. This is called a Tzanck smear. However, herpes simplex infections cannot be differentiated from herpes zoster using such a simple technique. For cytodiagnosis of suspected basal cell epitheliomas, any surface crust should be removed from ulcerated tumours, and non-ulcerated tumours should be incised with a sharp, pointed scalpel. The incision should be superficial enough to avoid undue bleeding. A sample of tumour is then obtained with either a blunt scalpel or a small curette, and the tissue obtained is pressed between two glass slides. Smears from blisters and basal cell epitheliomas should be fixed immediately for 2 min in absolute alcohol, and stained with H&E. Following rinsing and drying, the smears are cover slipped for microscopic examination.

Microscopic appearances

Bullous disorders. Cytodiagnosis is of most value in pemphigus in its various forms, and in Hailey–Hailey disease, because of the presence of numerous acantholytic keratinocytes. In pemphigus vulgaris, pemphigus vegetans and Hailey–Hailey disease, the cells obtained in the skin smear are usually rounded, and more or less uniform in size, with a relatively large nuclear cytoplasmic ratio. There may be a perinuclear pale halo, with the peripheral part of the cell staining more darkly. In the more superficial forms of pemphigus, including pemphigus foliaceus and Senear–Usher pemphigus, the keratinocytes tend to be more cuboidal in shape, with a small nucleus and more prominent cytoplasm. The cells may contain keratohyalin granules and show evidence of keratinization. Occasional giant cells may be seen, but are quite unlike virus giant cells, which show ballooning degeneration. In addition to the acantholytic disorders mentioned above, occasional acantholytic cells may be obtained in Darier's disease, where dyskeratosis may also be present, and in bullous impetigo. In this latter condition, normally in addition to acantholytic cells there are numerous neutrophil polymorphs and bacteria. The usefulness of cytodiagnosis in subepidermal bullous eruptions is limited, the smear in most instances containing only inflammatory cells. Eosinophils are commonly found in bullous pemphigoid, but may also occur in dermatitis herpetiformis.

Viral disorders. The cytology of herpes simplex, herpes zoster and varicella is often diagnostic because of the presence of characteristic multinucleated giant cells. Keratinocytes of varying size are seen, and as the cell enlarges the nucleus shows some blurring of chromatin pattern and loss of staining. Some of the cells may show condensation of chromatin of the nuclear membrane. The multinucleate giant cells often contain eight or more nuclei, and these nuclei show great variation in size and shape (Fig. 7.16).

Eosinophilic inclusion bodies are very occasionally identified in the herpes virus group of disorders, but commonly examination of many smears may fail to reveal any evidence of this change. Typical ballooning degeneration and giant cell formation as described above does not normally occur in vaccinia or cowpox, but occasionally somewhat enlarged acantholytic cells may be found, and sometimes eosinophilic intracytoplasmic inclusion bodies may be detected. In molluscum contagiosum, characteristic molluscum bodies are easily identified. These are large, rounded, eosinophilic bodies, and may be identified without H&E stain in a potassium hydroxide preparation.

Basal cell carcinoma. In smears obtained from basal cell carcinoma, clumps of closely set oval or round deeply basophilic cells are found. The cytoplasm is usually very scanty and in some cases may not be detectable. The nuclei are finely granular with poorly defined nucleoli, and the cells in the smear are very regular in size and shape. In the presence of significant cytological atypia, an alternative diagnosis, such as squamous cell carcinoma or Bowen's disease, should be considered.

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Electron microscopy

Electron-microscopic examination of cutaneous tissues is performed much less than light microscopy and is nowadays rarely used in diagnostic dermatopathology. Electron microscopy has been replaced by antigen mapping by immunohistochemistry in the diagnosis of many genetic disorders, particularly those in the epidermolysis bullosa group. This technique and its applications are described in Chapter 40. Transmission and scanning electron microscopy have greatly increased our understanding not only of the microanatomy of normal skin, but also of many disease processes. The use of newer embedding materials, has enabled ultrastructural examination to be carried out on single blocks of tissue prepared primarily for light microscopy. With care, even routinely fixed and paraffin-embedded material may produce electron micrographs that provide useful diagnostic information. In recent years, the combination of electron microscopy

with immunopathological techniques, autoradiography and cytochemical methods, has greatly enhanced our knowledge of tissue and cell pathophysiology. The contribution of ultrastructural studies to our understanding of normal microanatomy of skin structures and their variants has been referred to in Chapter 3. Below are listed some of the cutaneous disorders where electron microscopy may be of diagnostic help.

Bullous disorders

The classification and subdivision of bullous disorders has been dramatically advanced by electron microscopy and immunoelectron microscopy. With the electron microscope, it is much easier to separate the varieties of epidermolysis bullosa. In epidermolysis bullosa simplex, the plane of cleavage is within the basal cells. Additionally, tonofilament clumping may be seen. Junctional epidermolysis bullosa has various clinical forms, and, although with the electron microscope there is separation in the lamina lucida zone, junctional epidermolysis bullosa is probably a heterogenous group of disorders. In some forms of this condition, hemidesmosomes are reduced in number, and this may represent a primary defect. In other forms of junctional epidermolysis bullosa, however, hemidesmosomes may be apparently normal. In dystrophic epidermolysis bullosa, again, various abnormalities are observed, but in this case the split is below the lamina densa. Immunoelectron microscopic techniques provide further information in epidermolysis bullosa, and also in some of the other idiopathic blistering disorders. In cicatricial pemphigoid, for instance, immunoreactants may be identified at a lower level in the lamina lucida than in classical bullous pemphigoid. In linear IgA disease, immunoreactants may be found either in the lamina lucida or below it. Sublamina densa deposits of immunoreactants are also seen in epidermolysis bullosa acquisita.

Pigmentary disorders

The quantitative and qualitative evaluation of melanocytes and melanosomes at ultrastructural level can be of great value in the examination of disorders of hyper- and hypopigmentation. In albinism, normal numbers of melano-cytes are present, although melanosomes are immature. In vitiligo, a biopsy from affected skin shows either a complete absence or greatly diminished population of melanocytes. In early stages of vitiligo, some vacuolar degeneration of epidermal melanocytes may be identified.

Cellular identification

In addition to the demonstration of melanocytes, various other cells, both in inflammatory and neoplastic disorders, can be identified clearly with the aid of the electron microscope. The shape of the convoluted nucleus in the peripheral blood from patients with Sézary syndrome is diagnostic. Annulate lamellae, large, dense granules and decapitation secretion are all found ultrastructurally in apocrine secretory cells. Other cellular substructures that may be of diagnostic value are the identification of desmosomes in various epithelia, myofilaments in tumours of muscular origin, the Birbeck granule characteristic of Langerhans' cells, and the Weibel–Palade body found in the endothelial cells of blood vessels.

Identification of dermal deposits

Ultrastructural examination of various forms of amyloidosis shows characteristic deposits of straight, non-branching, non-anastomosing filaments of approximately 6–7 nm in diameter. The apparent increased electron density at their periphery produces a superficial appearance of hollow cylinders. Colloid milia of both the adult and juvenile type may on occasions be confused with amyloid deposition at the light-microscopic level. Ultrastructurally, however, the fibres of colloid milia are of a different thickness to those seen in amyloidosis, and are wavy rather than straight. Other conditions where amorphous hyaline deposits may be seen with the light microscope, such as forms of porphyria and lipoid proteinosis, also have characteristic electron-microscopic appearances.

Viral diseases

Many of the conventional techniques for confirmation of a diagnosis of virus infection, such as virus isolation and culture and the various serological tests, are slow, and the patient has often recovered by the time the diagnosis is established with certainty. Conventional histology either from biopsy or from the scraping of the base of blisters, for instance in herpes simplex or zoster infections, can be useful in experienced hands, but there is quite a high rate of false-negative results. Molecular biological techniques are more specific, especially for identification of human papillomavirus (HPV) infection, but are not widely available. Direct visualization of virus particles with the electron microscope, using a negative staining technique, can give a positive result within half an hour of a lesion being sampled. This technique has become invaluable for confirmation of diagnosis in disorders caused by many of the main families of viruses, particularly lesions such as herpes simplex and zoster, and hand, foot and mouth disease.

Immunogenotyping

In most inflammatory disorders, the lymphocyte population in skin tissue is normally polyclonal, containing progeny of many different parent lymphocytes. In con-

trast, most lymphomas are monoclonal, with cells being derived from the same parent cell. With the development of DNA probes to detect rearrangements of genes encoding for immunoglobulin and T-cell receptor molecules, it has become possible to assess clonality of T- and B-cell populations by immunogenotyping [1–4]. Refinements in technique mean that significant results can now be obtained from relatively small portions of tissue. The PCR technique is now widely used for the study of clonality in cutaneous lymphoid infiltrates. This subject is discussed in detail in Chapter 54.

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Artefacts (Table 7.6)

The microscopic appearance of the end product produced by processing a tissue specimen is in many ways an artificial representation of what is going on in a complex organ at one point in time. The procedures of biopsy fixation and tissue processing produce significant alterations in size, shape and structure of tissue constituents. We tend to think of fat cells as large, round, empty cells with peripheral nuclei, because this is how we are used to visualizing them microscopically. Cysts that normally contain lipid-rich substances, such as those of steatocystoma multiplex, appear relatively empty when sections from paraffin-embedded material are viewed. The clear halo often seen around melanocytes in the lower layers of the epidermis is at least in part an artefactual change. Some routinely observed tissue artefacts are useful for diagnostic purposes. The so-called separation artefact, where dermal connective tissue separates away from islands of basal cell carcinoma, aids us, for instance, in differentiating a basal cell carcinoma from a trichoepithelioma. In addition to these everyday artefacts, there are a wide range of other changes that may be induced accidentally or by poor processing technique. These changes may in some instances mislead the diagnostic pathologist.

Artefacts due to poor biopsy technique

Undue squeezing of the specimen with forceps can produce a marked artefact, causing the connective tissue to become amorphous and basophilic. Considerable distortion of cellular infiltrates is also seen. Toothed forceps

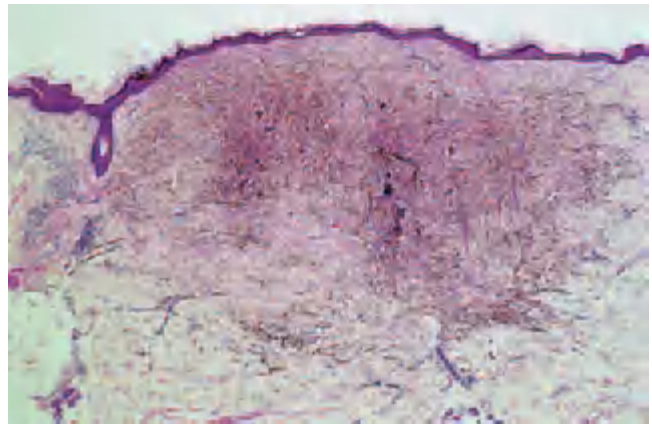

Fig. 7.17 Extensive dermal pigmentation as a result of the application of Monsel's solution.

can produce a hole within the tissue specimen, which, although rarely causing diagnostic confusion, is aesthetically unpleasing. When a small tissue specimen is cut up into even smaller pieces, the pressure produced by the knife at the edge of the smaller biopsy portions may lead to connective tissue and cell distortion. It is far better to carry out several small separate biopsies, perhaps with a punch, from the same area than to try and divide a single specimen after it has been removed from the patient. Various techniques of cautery used to secure haemostasis following either a shave biopsy or curettage can lead to unusual histological appearances. Diathermy produces a bizarre alteration of cellular and nuclear morphology, as well as producing a stringy eosinophilic and homogenized appearance to connective tissue. The haemostatic agent, Monsel's solution (20% aqueous ferric subsulphate), can occasionally produce extensive ferrugination of fibrin, dermal collagen and even striated muscle in skin biopsies [1]. The iron pigment deposition can be very confusing and simulate melanin (Fig. 7.17). Particular problems are encountered where this technique is used following shave biopsy of melanocytic naevi. The deposition of this pigment could lead to an erroneous diagnosis of a malignant melanoma [2]. Artefacts may occasionally be induced by local anaesthetic. The epinephrine contained in some local anaesthetics may result in some degranulation of mast cells, and have minor effects on dermal blood vessels, but these are not normally important problems. A large quantity of local anaesthetic, particularly when injected directly into a lesion or superficially in the dermis, can cause appearances simulating marked tissue oedema, or in the case of a cellular naevus, disruption of the normal architecture of the tumour.

Artefacts related to fixation media

It has already been stressed that adequate fixation of skin-biopsy tissue specimens is needed for optimum

histological interpretation. Specimens that have been fixed for insufficient time show poor definition of cell structure and connective tissue. Cells may appear swollen, and staining of such poorly fixed specimens often produces a rather smudged appearance. Similar results may be seen when the specimen has not been placed in the correct fixative, but rather in some inappropriate solution such as normal saline. Formalin pigment may be precipitated out into the tissues in some skin biopsies, particularly where the biopsies have been fixed in a formalin-containing fixative with an acid pH. Formalin pigment artefact is particularly common in biopsies from tissue containing large amounts of haemorrhage, or tissues heavily congested with blood. Even in neutral buffered formal saline, a long fixation may increase the tendency to formalin pigment production. There are some fixatives, such as Zenker's fluid and Heidenhain's Susa, that contain mercuric chloride. Tissues fixed in these media may develop a granular brownish black deposit. This deposit can be removed normally by treatment in Lugol's iodine followed by sodium thiosulphate.

Artefacts due to blocking and sectioning

One of the most commonly encountered problems is with the orientation of the specimen. Oblique blocking can give a very misleading picture—for example, suggesting that there is pseudoepitheliomatous hyperplasia of the epidermis or psoriasis, when one is in fact dealing with normal skin. Correct and accurate vertical sectioning and blocking is particularly important where measurements are to be made, such as in the assessment of Breslow thickness and Clark's level of malignant melanoma. Occasionally, fragments of a biopsy adhere to the microtome blade and 'knife carry' may occur, with the result that, for instance, a fragment of basal cell carcinoma may be seen just above the epidermis in a section from a histiocytoma. Normally this artefact is easy to spot, but occasionally it can give rise to confusion. Partial blunting of the microtome knife causes uneven thickness of the histological section. This can give a false impression, both of the density of cellular infiltrates and of the qualities of the connective tissue. Irregularities in the microtome knife edge can cause an unaesthetic artefact known as shatter marks. In the presence of very hard or dense foreign material in the tissues, such as calcium, the foreign material may be drawn through the tissue, forming a tear in the resulting sections.

Artefacts due to staining techniques

It should be remembered that the various staining solutions have a very short shelf-life once made up, and that staining solutions that are old produce a very unsatisfactory end-result. It is also quite common for staining solutions to be contaminated with various foreign materials, such as plant hairs [3] or microorganisms, which may appear to be present within the tissue biopsied, when viewed in the finished mounted preparation.

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The approach to microscopic examination of tissue sections

Some understanding of the basic principles of microscopy and careful microscope maintenance are essential for optimal visualization of tissue sections, and ultimately therefore for achieving a correct histopathological diagnosis. Knowledge of the techniques and applications of fluorescence microscopy, interference microscopy and polarized light microscopy is also recommended [1].

Preparing for microscopy

Before using the microscope, some attention should be given to various practical points. Are all the optical surfaces clean? Greasy fingerprints and dust may seriously impair the quality of the image, and before using the microscope all lens surfaces should be cleaned. This may be done with an optical lens tissue. Petroleum spirit is recommended by some manufacturers. Cleaning of objectives with a concave shape can be difficult. A recommended method is to use a small, freshly broken-up piece of expanded polystyrene. It is important that there is no trace of xylene or other organic solvent on an objective treated in this way, or there is a risk of a film of dissolved plastic being left behind.

The microscope light source should be centred, and on most modern microscopes this is easily achieved by a pair of centring screws acting against a spring, or by loosening a screw column and orientating the lamp holder.

The condenser is then adjusted. The aperture diaphragm in the base of the microscope should be closed, and the condenser height adjusted, until the image of the field diaphragm is in focus. The diaphragm should then be centred with adjusting screws. After centring, the field diaphragm should be opened until it just disappears from view. The aperture (substage iris diaphragm) is then adjusted. With experience, this can be done while viewing the image on the slide. Alternatively, an eyepiece can be removed, and while looking down the eyepiece tube the diaphragm is opened until it occupies approximately one-third of the field of view. In this position, the numerical

aperture of the condenser is approximately that of the objective in use, and optimum resolution is achieved.

The slide to be examined should then be viewed with the naked eye. Is the specimen a section of solid tissue, or uniformly spread across the slide, like a tissue or cell smear? The size and shape of sections on the slide should be noted, and it may be possible with naked eye examination to identify several tissues. It is important to note the number of sections mounted on one slide, and whether these are likely to represent sections from the same block, or different blocks mounted together. Finally, before putting the slide on the microscope stage, the name or identification number carried by the slide should be correlated with the details on the clinical request form. When inserting the slide into the microscope, make sure that it is the right way up, otherwise it may be impossible to focus the image with higher power objectives.

Microscopic interpretation

Examination of sections

The normal and recommended procedure is to start with lower power examination of the sections and gradually move up to higher power, detailed examination. Low-power scanning examination with a × 2.5 or × 4 objective provides a wealth of information. Identification of tissues is made, orientation of the specimen is possible, and the main site of any pathological changes is often identified. The basic nature of the pathological changes may also be recognized—for example, whether the main pathology represents a neoplastic or inflammatory process. Low-power scanning of all the material on the slide makes it clear whether all sections are from the same block, or whether they represent different portions of tissue. Low-power examination of biopsy material is the first step in the problem-solving exercise, and is the key to good diagnostic dermatopathology. During low-power examination, the site of biopsy and whether this correlates with the clinical information should be evaluated, and secondly, some attempt at pattern diagnosis should be made.

Site of biopsy and normal histological variation

Without a working knowledge of the differences in skin microanatomy in the different regions of the body, it is very easy to come to a wrong diagnostic conclusion. For instance, the prominent sebaceous glands seen on facial skin, particularly the nose, may lead to a diagnosis of sebaceous hyperplasia, and the normally thick stratum corneum present on the palms and soles may be interpreted as hyperkeratosis. The following notes describe some of the more typical features seen in skin biopsies from specific sites.

Skin from the palms and soles. In biopsies from these sites, there is a fairly thick Malpighian layer with a thickened basket-weave stratum corneum, and a very prominent epidermal rete ridge pattern. Occasionally, specialized nerve endings (Meissner's corpuscles) may be seen in the dermal papillae. Eccrine sweat glands are fairly numerous, but no pilosebaceous follicles are identified. Vater–Pacini corpuscles are characteristically found in the subcutis. They are large specialized nerve endings and have an ovoid or round shape with a typical onion ring appearance.

Skin from the areola of the nipple and the scrotum. In these sites, papillomatosis is a common finding, and in the upper dermis there are often numerous small fascicles and fibres of smooth muscle. In biopsies from the areola and nipple, occasional lactiferous ducts may be identified.

Mucous membranes. Histology of mucosal surfaces often shows fairly thick epithelium lacking well-defined keratinization. Focal mild parakeratosis is often seen. The rete ridge pattern normally associated with glabrous skin is not marked, and the cells of the Malpighian layer are large, pale and typically vacuolated.

Axillary skin. In skin from the axillae, papillomatosis of the skin surface is often marked. Abundant hair follicles are present, as are numerous apocrine glands, which are seen in addition to eccrine glands commonly present in other sites.

Scalp skin. Biopsies from the scalp are normally readily identified by the presence of numerous large hairs with the hair bulbs frequently in the subcutaneous fat.

Facial skin. Facial skin is characterized by the presence of smaller hair follicles than in the scalp and, particularly in the central facial area, large numbers of mature sebaceous glands. The epidermis is very thin and melanocytes are numerous. The rete ridge pattern at the epidermo-dermal junction is often very poorly developed, which makes a distinction between papillary and reticular dermis often difficult to assess. *Demodex* organisms may be seen in the ostia of hair follicles and deeper within the sebaceous glands. Muscle may be identified relatively close to the epidermis in certain areas of the face, such as round the eyes or mouth.

Truncal skin. Skin from the trunk shows no very specific histological hallmarks. However, it is normally quite thick, with the distance between the epidermis and the subcutaneous fat being much greater than in biopsies from other sites. Eccrine sweat glands are normally identified at the junction between the dermis and the subcutaneous fat, and may, in skin from the trunk, appear within the reticular dermis itself. The skin from the back

contains a very thick dermis with thick collagen bundles in which the ground substance is minimal. This normal pattern is often confused with evidence of a sclerosing dermal process such as morphoea.

Low-power histological pattern diagnosis

Having attempted to recognize the site of the biopsy, and having correlated this with the clinical information, the next task is to interpret any abnormal findings and attempt to come to some diagnostic conclusions. Sometimes, the site of the abnormality in the section is immediately obvious on scanning magnification. This then leads one to examine the appropriate area in more detail. When there is no obvious pathology in the section, a useful approach is to examine each identifiable cutaneous structure in turn. For instance, starting outwards with the stratum corneum and working inwards. Is it increased or decreased in thickness? Is parakeratosis present? Is the pattern of keratinization normal producing a basket-weave pattern, or is the stratum corneum compacted? Examination of the epidermis may reveal atrophy or acanthosis, spongiosis or cell atypicality, and may also reveal colonization of the epidermis by inflammatory or other abnormal cells. Various forms of epidermal degeneration may be noted. Some variants of these are described below. A vesicle or bulla may be present within the epidermis or below it.

Moving on to the dermis, is the arrangement of connective tissue fibres in the papillary and reticular dermis normal, or are the collagen fibres thickened and hyalinized? Is there an increase in interstitial oedema fluid, or is there evidence of increased amounts of mucin separating the collagen bundles? Is the elastic pattern normal? Careful examination of all adnexal structures should be made, and then, finally, any dermal infiltrate should be assessed. The density of the infiltrate, the pattern of the infiltrate (diffuse and interstitial and/or focal and localized) and the composition of the infiltrate are important. The position of the infiltrate in the dermis, whether it is predominantly deep or predominantly involves the epidermis, is also worth noting, as is the relationship of the infiltrate to adnexal structures and blood vessels. The blood vessels themselves should also be examined carefully for evidence, for example, of any vasculitic change or dilatation, increased tortuosity or thickening. A search should be made for any abnormal deposits or pigments such as amyloid, calcium or tattoo pigment. When one has some experience in assessing the different structures in a skin biopsy, one soon learns to recognize certain patterns of neoplastic change and inflammation. Ackerman has described a method of pattern diagnosis appropriate for the study of inflammatory diseases [2]. He suggests recognition of nine major patterns of inflammatory change in the skin, ranging from superficial perivascular dermatitis to panniculitis. Having classified the appearances in the section according to one of these patterns, closer examination enables one to come to a more precise diagnosis. Other authors have described similar schemes of microscopy [3]. The system of pattern analysis can be recommended to those new to dermatopathology. More experienced pathologists have almost always developed their own pattern analysis system.

High-power microscopical examination

By the time one has examined a histological section with a $\times 2.5$ objective, a $\times 4$ to $\times 8$ objective depending on personal preference, and a $\times 10$ objective, one should have some idea in most cases of a differential diagnosis. High-power examination with $\times 25$, $\times 40$ or $\times 50$ and sometimes with a $\times 100$ oil-immersion lens, provides an opportunity to confirm one's initial impressions.

Under high-power examination, one examines carefully cells and other structures in the skin in various specific ways. When dealing with neoplastic disorders, the cytology of individual tumour cells, with particular reference to nuclear detail and the variation in size and shape between cells of the same population should be studied. The number of mitotic figures and the number of abnormal mitoses are noted. The pattern of relationship of tumour cells to each other is also an important feature. Loss of polarity of keratinocytes in squamous epithelium is a characteristic feature associated with premalignant epithelial dysplasias, such as Bowen's disease and actinic keratoses, although it can of course also occur in invasive epithelial tumours. The relationship of tumour cells to neurovascular bundles is also important, and the pattern of neoplastic cells in relation to dermal connective tissue should also be evaluated. The so-called Indian-filing pattern of tumour cells lining up one behind another, sandwiched between collagen bundles, is in some contexts suggestive of malignant disease.

In inflammatory conditions under high-power examination, there is an opportunity to try and categorize the different types of cells in the infiltrate. It is important to look over the whole section, as in some areas the infiltrate may be composed of one cell type and in other areas another cell type may predominate. Some infiltrates are composed of almost pure populations of, for example, lymphocytes, and are described as monomorphic, whereas other infiltrates are composed of plasma cells, histiocytes, lymphocytes and eosinophils, and are described as polymorphic. It is only with experience that one becomes confident in recognizing the cytology of cutaneous infiltrates, and one must remember that in some biopsy material, cells may be seen that are impossible to classify by conventional criteria. The following notes describe the more typical appearances of commonly seen inflammatory and related cells, and describe some of the situations where they may be encountered.

Lymphocytes

Lymphocytes originate in the bone marrow and mature through a series of stages both in the bone marrow and the thymus gland, before being released into the peripheral blood and body tissues. The family of lymphocytes is a very heterogeneous one, with many subtypes of lymphocytes. T lymphocytes and B lymphocytes are indistinguishable by normal light microscopy, although on scanning electron microscopy *in vitro* B lymphocytes appear to have rather rougher surfaces than T lymphocytes, and show villous projections. On light-microscopic examination of sections stained with H&E, lymphocytes are roughly 7–12 μm in diameter, and possess small, round, deeply basophilic nuclei, surrounded by a thin rim of cytoplasm, which is usually very difficult to visualize. Numerous immunohistochemical methods are available that readily distinguish T and B lymphocytes, and most of these methods can be carried out using paraffin-embedded sections. In the majority of inflammatory conditions affecting the skin where a significant dermal infiltrate is seen, T cells outnumber B cells. Mature T and B cells are, of course, not the only lymphoid cells that may be found in the skin. In addition to plasma cells (see below), various follicular centre cells and T and B immunoblasts may be seen under certain conditions.

Plasma cells

Plasma cells are responsible for immunoglobulin production. They are a variety of B lymphocyte, approximately 10 μm in diameter, that have a distinct appearance in H&E-stained sections. They have abundant basophilic cytoplasm with a round, eccentrically placed nucleus. The nuclear chromatin is scattered in coarse clumps at the periphery of the nucleus giving it a 'clock face' appearance. Closely adjacent to the nucleus there is a zone of pallor in the cytoplasm, sometimes called the perinuclear hof. This area corresponds to the site where the Golgi apparatus is located. Older plasma cells often contain homogenous eosinophilic globules of varying size within their cytoplasm, known as Russell bodies. Plasma cells are seen in many situations in the skin, particularly in inflammatory conditions affecting hairy areas, near mucous membranes and in the late stages of some granulomas.

Neutrophils

Neutrophils are the most numerous of the circulating white blood cells, comprising in normal individuals 50–70% of the blood leukocytes. They have a multilobed nucleus (3–4), with the lobes connected by narrow bridges of nucleoplasm. The slightly basophilic cytoplasm contains many smallish granules, many of which ultrastructurally correspond to membrane-bound lysosomes. Neutrophils function primarily as phagocytes, and are directed by chemotactic factors, including the complement cascade to noxious materials present in tissue. Such foreign materials include bacteria, fungi and tissues that have been injured. Collections of neutrophils may be seen in the skin in various infectious conditions, such as impetigo and staphylococcal folliculitis, in various inflammatory disorders of unknown cause, such as pyoderma gangrenosum and Sweet's syndrome, and in various vasculitic disorders, including leukocytoclastic vasculitis, granuloma faciale and erythema elevatum diutinum.

Eosinophils

Eosinophils, like neutrophils, originate in the bone marrow, but are rather larger than neutrophils, being 12–17 μm across. The nucleus of the eosinophil is usually bilobed, and the cytoplasm is filled with eosinophilic granules that are larger than the granules found in neutrophil leukocytes. Eosinophils are highly phagocytic, capable of ingesting various bacteria, fungi, immune complexes and inert particles and, like neutrophils, eosinophils contain hydrolytic and proteolytic enzymes contained in membrane-bound granules. Eosinophils are seen in skin biopsies in certain infections, in reactions to insect bites and other foreign bodies, in some drug reactions, and in bullous eruptions such as bullous pemphigoid, and some forms of pemphigus. They are of major importance in the condition known as eosinophilic cellulitis, and may also occur in association with proliferations of cells of the lymphoid series in certain cutaneous T-cell lymphomas.

Histiocytes/monocytes/tissue macrophages

The term histiocyte is used by different authors to mean different things, and is an unsatisfactory term. Monocytes circulating in the blood may be attracted into the skin for the purposes of phagocytosis. They are then called histiocytes or tissue macrophages. However, many other mesenchymal cells and cells of the granulocyte series are also capable of phagocytosis. The appearances of a histiocyte vary considerably. Many of the cells are fairly large with a lightly staining, sometimes vesicular, elongated nucleus. The cytoplasm is usually pale and cell margins may be indistinct. The cells may be dendritic, spindle-shaped or epithelioid, taking on the latter form particularly in epithelioid cell granulomas. The size of histiocytes is also very variable, ranging from 15 to 25 μm. Compared with some of the cells described above, they are less easy to identify, particularly for the novice, in skin biopsies, and immunohistological methods are often necessary to demonstrate histiocyte subsets. Several factor XIIIa-positive, dendritic phagocytes (dermal dendrocytes) are

seen in close proximity to the superficial microvascular plexus. These cells, together with other immune cells, mast cells and endothelial cells, probably collaborate to coordinate antigen presentation, induction of cellular inflammation, wound healing and haemostasis in this microenvironment. Various histiocytes are found in a wide range of inflammatory and neoplastic disorders, but are particularly important in the production of granulomatous inflammation, both in conditions such as granuloma annulare, and in response to cutaneous infection such as mycobacteria.

Giant cells

Many types of giant cell may be recognized in skin tissues. The three best known are the Langhans' giant cell, the foreign-body giant cell and the Touton giant cell. All these giant cells are derived from tissue macrophages, and forms intermediate between the different characteristic types are sometimes seen. The size of these cells varies greatly, but is usually of the order of between 40 and 120 μm. Langhans' giant cells show a characteristic horseshoe distribution of the nuclei arranged at the cell periphery. They are most characteristically seen in sarcoidosis and tuberculosis. Foreign-body giant cells contain a haphazard arrangement of nuclei scattered throughout the cell cytoplasm, and may also contain foreign material. Although typically seen in foreign-body granulomas, they are common in other forms of granulomatous inflammation, and in situations where there is disruption of pilosebaceous follicular structures with keratin release into the dermal connective tissue. Touton giant cells have a central ring of nuclei enclosing a layer of ground-glass cytoplasm, with a peripheral zone of clearer cytoplasm. They are typically seen in some xanthomas and juvenile xanthogranuloma.

It should be noted that many other forms of giant cell are seen, such as the fairly typical giant cell with scattered nuclei, prominent nucleoli and PAS-positive cytoplasm in multicentric reticulohistiocytosis. Not all giant cells are derived from cells of the macrophage series. Multinucleate cells derived from infected keratinocytes may be seen in various virus infections such as herpes and poxvirus infections, and multinucleate cells derived from melanocytes are quite typical of epithelioid and spindle cell (Spitz) naevi (Fig. 7.18).

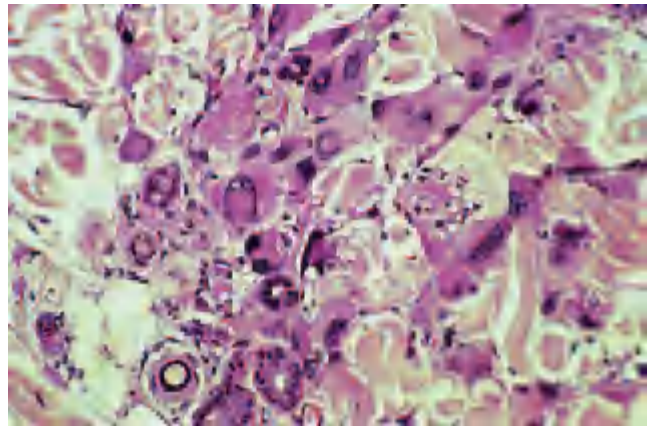

Fig. 7.18 Bizarre multinucleated giant cells from a Spitz naevus.

Mast cells

Mast cells, unlike the white blood cells and some histiocytes, all of which probably originate from the bone marrow, are likely to arise from undifferentiated mesenchymal cells. In normal skin, they are present around small blood vessels in the dermis. They are approximately 9–16 μm in diameter, and they possess a central round to ovoid dark-staining nucleus. The cytoplasm contains small granules that stain metachromatically with such stains as toluidine blue. The granules contain vasoactive substances such as heparin, histamine, and eosinophilic and neutrophilic chemotactic factors of anaphylaxis. Mast cell activation may be triggered by neuropeptides derived from unmyelinated axons that surround perivascular mast cells. This in turn triggers adhesive events between leukocytes and endothelial cells, resulting in angiocentric inflammation.

Although in normal skin the cells tend to have a dendritic morphology, in various pathological conditions, including some forms of urticaria pigmentosa, the cells are larger and polygonal with a central, rounded nucleus. In addition to being found in increased numbers in the mastocytoses, they are also commonly seen in various benign and malignant nerve tumours, and in association with some melanocytic naevi.

Fibroblasts

Fibroblasts are often difficult to identify on routine light microscopy. Their nuclei tend to be oval or spindle-shaped, and with moderately basophilic staining. They are usually found between collagen bundles, and may be prominent in conditions where there is an increase in the production of dermal connective tissue or ground substance, such as morphoea and scleromyxoedema. They may also contribute to the histogenesis of the wide range of so-called fibrocytic tumours that may occur in the skin.

Myofibroblasts

These cells are mainly defined by their electron microscopic appearances and display features intermediate between those of fibroblasts and smooth muscle cells. They are mainly seen in reactive reparative processes

and in neoplasms. Histologically, they have indistinct cytoplasmic margin, pink pale cytoplasm and vesicular nuclei with a single inconspicuous nucleolus.

Smooth muscle cells

Smooth muscle cells occur normally in the skin in the arrector pili muscles, in the tunica dartos of the external genitalia, in the areola of the nipple and in the walls of blood vessels. They are easy to identify by recognizing the normal structures in which they occur and also by their cytomorphology that consists of abundant bright eosinophilic cytoplasm and vesicular nuclei with a single inconspicuous nucleolus.

Rhabdomyocyte (striated muscle cell)

Skeletal muscle occurs in the skin of the neck and of the face. The constituent cells are arranged in bundles and have characteristic cross striations and abundant bright pink cytoplasm.

Schwann cells

Schwann cells are the main constituent cells of nerves. They envelop the neuroaxons and are characterized by a slender hyperchromatic thin nucleus and inconspicuous cytoplasm.

Endothelial cells

A single layer of endothelial cells lines all types of vascular channels in the skin. These cells usually appear flat with inconspicuous cytoplasm and small histiocyte-like vesicular nuclei. However, in most pathological processes, they become more prominent and may appear somewhat hyperchromatic. This, coupled with an increase in mitotic activity, may lead to confusion with malignant cells, particularly in cross-sections, where the normal architecture of the vascular channel is often not apparent.

Pericytes

Pericytes occur as a single layer of indistinct cells around small dermal blood vessels. They are recognized by their location and by positive staining for actin.

Miscellaneous

In addition to closely examining cytology under the high-power objective, the opportunity should also be taken to look carefully for organisms, foreign bodies or deposits of foreign material such as amyloid. Special staining techniques will often be needed to confirm suspicions, and with these stains bacterial, fungal and protozoal organisms may be identified as well as various forms of parasite. The presence of viral organisms can also be inferred by the presence of characteristic cytopathic changes, such as occur for instance with herpesvirus infections and infections with cytomegalovirus. Close examination of nerves and blood vessels should be carried out, particularly in relation to the presence of any organisms or tumour deposits. After examining adnexal structures and the subcutaneous tissues, it is useful to return to low-power examination and attempt to be certain one has not missed any pathology. It is not uncommon to discover more than one abnormality in a tissue section. Patients who develop solar keratoses may also have seborrhoeic warts, naevi and basal cell epitheliomas. Biopsies from patients with acquired immune deficiency syndrome (AIDS) often have multiple pathologies, and one may, for example, see a biopsy of perianal tissue in which there is evidence of cytomegalovirus infection in the endothelial cells, HPV infection of the overlying epithelium and the presence of Kaposi's sarcoma.

The importance of carefully assessing both the low-power pattern of changes in a skin section, as well as a more detailed examination of the cytology of the pathological changes, cannot be too strongly emphasized.

How to produce a histopathology skin report

After carefully carrying out the recommended procedure for low scanning power and high-power examination of a skin biopsy slide, the pathologist will either need more information, or will be in a position to provide a microscopic histopathological report to supplement the report on the gross pathological appearance of the biopsy specimen before processing. If there is very little obvious abnormality, it may be appropriate to cut deeper levels from the tissue block, or even consider blocking any remaining wet tissue that is in storage. If the specimen has been blocked obliquely or, for instance, the epidermis is missing, reblocking will be necessary. Serial sections may be required to determine pathological features that are only focal, such as changes affecting pilosebaceous follicles in a biopsy from the scalp. Special stains may be required for the evaluation of abnormal dermal deposits, to detect the presence of organisms, or to elucidate the nature of various pigments in the biopsy material. Immunohistochemical studies may also be requested in, for example, cases of cutaneous lymphoma or malignant spindle cell tumours. If there is going to be undue delay in these various extra investigations, a preliminary report should always be issued.

Although reporting of histopathology is to some extent a subjective art, and every pathologist will have his or her own idea of what is an appropriate report, a description of the objective histological changes, and either a suggested diagnosis or a differential diagnosis, are always desirable.

In a description of the pathology, it is important never to describe features that are not present, even though they may be consistent with the correct diagnosis. The differential diagnosis suggested by the pathologist should fully take into account the clinical information supplied by the clinician. If the clinician suggests on the request form chronic superficial scaly dermatitis, it would be churlish to sign out the report as subacute eczema without further qualification. In addition to a description of the objective pathological changes and a diagnostic suggestion, it is quite legitimate to add a further comment in certain situations. If the clinician suggests a tumour has been excised, then a comment on the adequacy of excision is obviously useful. Conversely, if the clinician states that this is a diagnostic/incisional or superficial biopsy, it is irritating for the clinician to receive a report stating that tumour extends to one margin of excision.

In some situations where the various histopathological parameters need to be recorded repeatedly in biopsies from specific skin disorders, for example malignant melanoma, specially designed forms facilitate both the recording of information and subsequent computer analysis.

There is some degree of disagreement as to whether it is the role of the histopathologist under any circumstances to make recommendations for treatment, and no general rule can be given on this. If one knows one's clinical colleagues well, it is quite appropriate under certain circumstances to recommend a modest re-excision of the biopsy site, for instance in early superficial spreading melanoma. Some pathologists prefer to make such comments in a separate covering note. With some rarer conditions, particularly if they have serious implications for the patient, a telephone call to the clinician, or again a covering note, may be a reasonable approach. An offer from the pathologist to discuss any interesting case in more detail is often a good idea, and is usually taken up. It is always in the best interests of the patient for there to be a close working relationship between the histopathologist and the clinician.

Finally, it is most important always to appreciate one's own limits of ability. One should never be afraid of asking for a second opinion from a colleague. It has been said that sections from skin biopsies fall into three groups. Firstly, there are those sections where the histological appearances are easy for anyone to interpret and diagnose. Secondly, sections from biopsies, for instance of a very poorly differentiated spindle cell tumour, where one does not know what the diagnosis is, but knows that it is likely that no one else will either. Thirdly, sections where one does not know how to interpret the histological appearances oneself, but does know it is likely that someone else will! Once one is able to divide histological material into one of these three groups, one is already on the way to becoming an accomplished diagnostic dermatopathologist.

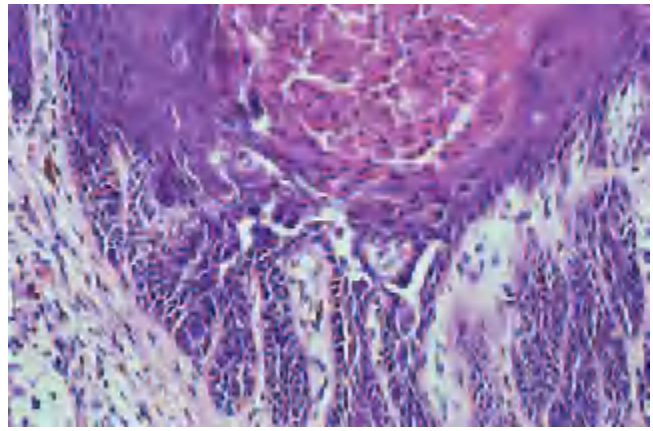

Fig. 7.19 A biopsy from a case of Darier's disease, showing the histological features of parakeratosis, dyskeratosis, acantholysis and formation of villi.

Commonly used descriptive terms in dermatopathology, and their diagnostic significance

Acantholysis

Acantholysis is the term used to describe loss of cohesion between keratinocytes, due to breakdown of intercellular bridges. It results in the formation of intraepidermal clefts, vesicles and bullae. It appears to be the primary pathological change in a group of diseases including pemphigus and its variants, Darier's disease, transient and persistent acantholytic dermatosis and warty dyskeratoma. The site of acantholysis in these disorders is important. In pemphigus foliaceus and pemphigus erythematosus, acantholysis is usually confined to the upper portion of the epidermis, whereas in pemphigus vulgaris the split is formed at a lower level in the epidermis. In benign familial pemphigus (Hailey–Hailey disease), although acantholysis is often focal or incomplete, where it does occur it tends to affect the full thickness of the epidermis.

Acantholysis may also be seen secondary to some other pathological change, where there is alteration or damage to epidermal cells. It may occur, for example, in bullous impetigo, viral disorders, solar keratoses and some forms of squamous cell carcinoma. When acantholysis occurs in these disorders, the term secondary acantholysis is often used to distinguish the process from primary acantholysis, which occurs in pemphigus and related diseases (Fig. 7.19).

Acanthosis

This term is used to describe an increase in number of cells in the Malpighian or prickle cell layer of the epidermis (from the Greek for prickle or thorn). Sometimes, a distinction is made between increased thickness of the epidermis due to enlarged keratinocytes (pseudoacanthosis)

and true acanthosis due to increased numbers of keratinocytes. In practice, acanthosis is commonly used to cover both senses. Increased thickness of the epidermis may result from increased length of rete ridges, as in a psoriasiform tissue reaction, or may effect the whole epidermis, such as in lichenification. Acanthosis is commonly accompanied by other histological changes such as hypergranulosis, hyperkeratosis and papillomatosis.

When reactive epidermal proliferation is marked, the process may simulate an epithelial carcinoma, and in this situation is referred to as pseudoepitheliomatous hyperplasia. Acanthosis may be seen in a wide variety of inflammatory and neoplastic disorders. Some of the common situations where this feature may be seen include the following:

1 Naevoid conditions and localized benign epidermal tumours—for example, keratodermas, epidermal naevi and seborrhoeic keratosis.

2 Virally induced papillomas—for example, viral wart, molluscum contagiosum.

3 Secondary to inflammatory conditions affecting the epidermis, particularly where chronic—for example, persistent friction, lichenification, prurigo and chronic eczema, psoriasis and lichen planus.

4 Secondary to conditions associated with loss of keratinocyte adhesion—for example, the pemphigus group of disorders and Darier's disease.

5 Secondary to conditions associated with the presence of foreign cells within the epidermis, such as malignant melanoma, Paget's disease, mycosis fungoides and Langerhans' cell histiocytosis.

6 Acanthosis is commonly seen overlying a variety of abnormalities in the dermis:

(a) dermal tumours such as fibrous histiocytoma and granular cell tumour;

(b) certain forms of cutaneous infection such as lupus vulgaris and blastomycosis;

(c) overlying dermal deposits of substances such as amyloid, abnormal elastic tissue or in association with foreign bodies; and

(d) in association with chronic oedema, such as chronic lymphoedema of the lower limb and myxoedema.

Anaplasia

This is a term used to describe variations in nuclear size, dense and clumped heterochromatin, and nuclear contour angulation typical of malignant cells, as in metastatic melanoma.

Apoptosis [4]

This is a morphologically distinct type of cell degeneration and death, usually applied to keratinocytes that become homogenous and eosinophilic and are extruded into the underlying upper dermis. These eosinophilic bodies (known as Civatte or colloid bodies), and the process of apoptosis, occur characteristically in lichenoid tissue reactions. A similar process may be observed in many other processes, for example, following UV light exposure, in graft-versus-host disease and in cutaneous lupus erythematosus.

Basal lamina (Chapter 3)

This structure, also known as the basement membrane, is a submicroscopic structure approximately 40 nm in thickness, which extends along the undersurface of the epidermal basal cells. It is not visible with light microscopy. The term basement-membrane zone is sometimes applied to the area that may be visualized with the PAS-staining technique (see Fig. 7.5). This area not only includes the basal lamina itself, but also the lamina lucida and anchoring fibrils.

Bullae

Bullae represent fluid-containing cavities occurring within or below the epidermis. Small bullae are known as vesicles. Determination of the site of bulla formation is most important in histological assessment of skin biopsies. Intraepidermal bullae may arise as the result of spongiosis, as in acute eczema, from reticular and ballooning degeneration seen in association with viral disorders, or from acantholysis or epidermal cell necrosis. Subepidermal blisters usually result either from a defect in the basement membrane region, such as occurs in some forms of epidermolysis bullosa and porphyria, from a disruption of the basement membrane from intense liquefaction degeneration or necrosis of the basal cell layer, such as may occur in bullous lichen planus or bullous lupus erythematosus, or as a result of dermal inflammatory processes involving the upper dermal connective tissue and basement-membrane region. In some conditions, such as erythema multiforme, both subepidermal and intraepidermal factors seem to be involved in bulla formation.

Colloid body

This term, usually regarded as synonymous with Civatte body, describes the homogeneous eosinophilic rounded body resulting from degeneration and death of keratinocytes, particularly in the lower layers of the epidermis. This structure is found in various lichenoid tissue reactions and is involved in the process of apoptosis.

Crust

This term is used to describe collections of inflammatory cells, red blood cells, plasma and fibrin in the superficial

portion of the epidermis. A crust may also contain micro-organisms, and often replaces a partial or total loss of the epidermis itself.

Curlicue pattern

This descriptive term refers to the twisting and curving of dermal fibrohistiocytic cells around collagen bundles, often at the margins of a dermal tumour. The pattern is mainly observed in fibrous histiocytomas. The pattern described by this term is the same as that referred to by the term storiform.

Degenerations

Dermal

Colloid degeneration. Colloid degeneration refers to the deposition of extracellular homogeneous gelatinous material of variable composition. It is typically seen in colloid milium, but may also be found in certain epithelial tumours.

Elastotic degeneration. This describes the degenerative changes that develop with increasing age, particularly in the upper part of the dermis in sun-exposed skin. Early changes include an increase in the number and size of connective tissue fibres staining with elastic stains. In advanced stages of the condition, there are masses of disorganized elastotic fibres occurring, particularly in the upper third of the dermis, and appearing to replace the normal collagen. This elastotic degeneration is normally separated from the epidermis by a narrow band of normal-staining connective tissue. In sections stained with H&E, the elastotic material is basophilic.

Fibrinoid degeneration. This term describes the deposition in tissue of eosinophilic, granular or fibrillary material resembling fibrin. The composition of the eosinophilic amorphous material may vary in different situations, but fibrinogen, plasma proteins, immunoglobulins and dermal ground substance may be components of the material. It is most typically seen in forms of necrotizing vasculitis, and is also found in disorders such as lupus erythematosus and the collagen diseases.

Hyaline degeneration. This term refers to the presence of homogeneous eosinophilic degenerative material in dermal connective tissue, or in relation to blood vessels. The material has a glassy and refractile appearance. Hyaline degeneration occurs in forms of porphyria, lipoid proteinosis and sometimes in lichenoid tissue reactions. Epithelial structures may also show a similar type of change, for instance the tumour cells of cylindroma frequently undergo hyaline change.

Myxoid degeneration. This indicates the deposition or replacement of dermal connective tissue by amorphous, stringy, basophilic material. This pattern of degeneration is seen in localized myxoedema, papular mucinosis, scleredema and dermatomyositis, as well as being seen in various neural, epithelial and adnexal neoplasms.

Epidermal

Ballooning degeneration. This form of degeneration of keratinocytes is associated with marked swelling and pallor of individual cells, with loss of intercellular bridges. A blister forms as a result of the consequent acantholysis. Ballooning degeneration along with reticular degeneration is characteristic of virus disorders affecting epithelia, such as herpesvirus infections.

Hydropic degeneration. This is also known as liquefaction degeneration, and refers to a vacuolar change that affects the basal cell layer of the epidermis. Small droplets and vacuoles develop within and in between basal cells. The process is commonly associated with pigmentary incontinence, and when marked may lead to subepidermal blister formation. It occurs typically in the whole range of lichenoid tissue reactions, including lupus erythematosus, lichen planus, dermatomyositis, poikiloderma atrophicans vasculare and lichen sclerosus (Fig. 7.20).

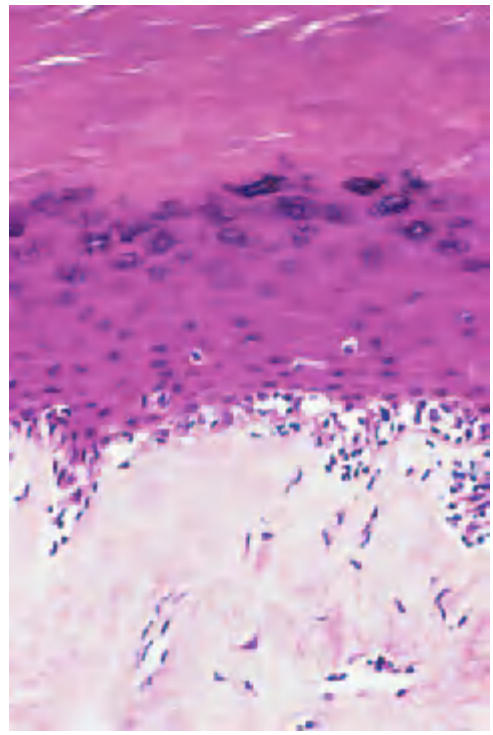

Fig. 7.20 Prominent liquefaction degeneration from a case of lichen sclerosus.

Reticular degeneration. This indicates the development of large, multiple, intraepidermal vesicles, where there remains a ragged network of epidermal cell remnants. As mentioned above, reticular degeneration often occurs in association with ballooning degeneration in acute virus infections of the herpesvirus and poxvirus groups. This pattern of epidermal degeneration may also sometimes be seen in the acute bullous reaction of contact dermatitis.

Desmoplasia

This term describes a pattern of fibrosis or sclerosis of dermal connective tissue, usually in association with an epithelial or melanocytic proliferative lesion. Examples of the use of this term are in desmoplastic trichoepithelioma and desmoplastic malignant melanoma.

Dyskeratosis

This term relates to some abnormality in the process of epidermal cell keratinization. The changes usually consist of nuclear pyknosis and bright pink condensation of the cytoplasm of keratinocytes. The process occurs in two main contexts. Firstly, in malignant and premalignant epithelial lesions, such as squamous cell carcinoma, Bowen's disease and solar keratosis. Secondly, in various forms of acantholytic disorder such as Darier's disease. In this latter condition, specific types of dyskeratotic cell include corps ronds and grains (see Fig. 7.19).

Dysplasia

This term is a confusing one, especially when used to describe atypical melanocytic naevi, because if communication with the clinician is inadequate, it may be interpreted to mean different things. Its use normally reflects some abnormality in cell maturation, cytomorphology or the relationship between cells in epithelial structures. It has the connotation of possible progression to neoplastic disease.

Exocytosis

This term describes the migration of inflammatory cells from the blood vessels of the dermis into the overlying epidermis. The process may be associated with spongiosis, as in eczema, or occur in the absence of spongiosis, such as may be seen in mycosis fungoides. In the later setting, the word epidermotropism is usually preferred.

Granuloma

A granuloma describes circumscribed foci of inflammation containing monocytes, macrophages, lymphocytes and epithelioid cells. Multinucleated giant cells of foreign body, Langhans or Touton type may also be observed. Varying degrees of epidermal hyperplasia, capillary proliferation and dermal fibrosis are common accompanying changes. Granulomatous inflammation occurs in a wide variety of infectious and non-infectious conditions. Many different types of organism ranging from viruses through bacteria to fungi can produce a tissue granuloma. The presence of granulomas in a skin biopsy may indicate a systemic disease, such as sarcoidosis, or a localized dermatosis of unknown cause, such as granuloma annulare or acne agminata. The precise histological appearance of a dermal granuloma depends not only on the underlying cause, but on the period over which the disease has been active, and the immune status of the host.

Grenz zone

This comes from the German word for border, and in dermatopathology is applied to a narrow zone of normal dermis between the epidermis and pathological changes in the underlying dermis.

Hypergranulosis

This refers to an increase in thickness of the granular layer of the epidermis, and is commonly accompanied by hyperkeratosis and acanthosis. It is often seen in chronic lichenification and lichen planus and related disorders.

Hyperkeratosis

Hyperkeratosis refers to increased thickness of the stratum corneum, and may be associated with acanthosis of the Malpighian layer. Hyperkeratosis may occur in various disorders of keratinization, such as the keratodermas and some ichthyotic disorders, and relative hyperkeratosis is quite common in chronic discoid lupus erythematosus. In certain conditions, such as in Flegel's disease, in addition to increased thickness of the stratum corneum there is a change from the normal basket-weave pattern to a compact arrangement of the stratum corneum cells. When assessing the thickness of the stratum corneum, it is important to correlate the histological appearances with the site of the biopsy. The stratum corneum is normally thick on the palms and soles, and very thin, or even absent, around the eyelids and near mucous membrane junctions.

Epidermolytic hyperkeratosis

This particular change, also sometimes referred to as granular degeneration, is a peculiar and characteristic change seen in a number of skin disorders. There is an increase in the thickness of the granular layer, where keratinocytes appear to contain an increased number of

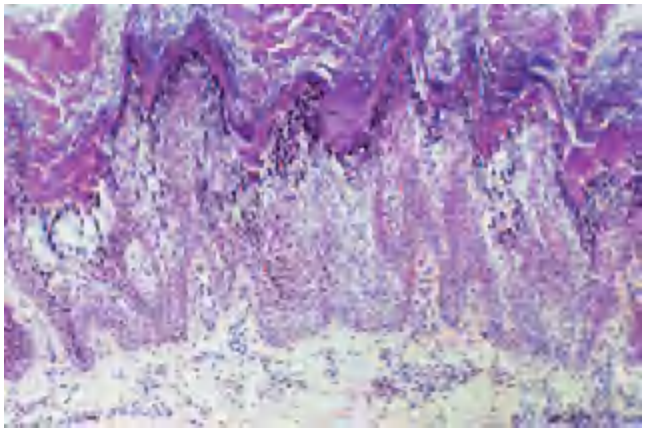

Fig. 7.21 Epidermolytic hyperkeratosis seen in a biopsy from a patient with congenital bullous ichthyosiform erythroderma.

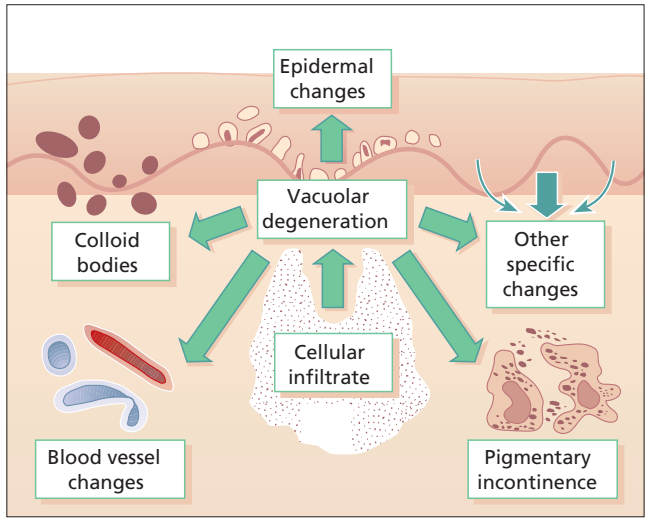

Fig. 7.22 The lichenoid tissue reaction. Various histopathological consequences follow damage to the dermal–epidermal junction. These histopathological changes are seen in a wide variety of lichenoid reactions, ranging from lichen planus to lupus erythematosus, poikiloderma atrophicans vasculare, lichen sclerosus and lichenoid drug eruptions.

keratohyalin granules. Perinuclear vacuolization occurs in this area, and the cell boundaries may be indistinct. The vacuolization may be marked, in some cases appearing to lead to intraepidermal vesicle formation. Although this change is best known as the characteristic histopathological feature of bullous ichthyosiform erythroderma (Fig. 7.21), it also occurs in many other inherited and acquired conditions, including a form of palmoplantar keratoderma, so-called epidermolytic acanthoma, and some forms of linear epidermal naevus. It is also occasionally seen as an incidental finding, either in normal skin or in association with a lesion, such as a naevus, a viral wart or a seborrhoeic keratosis.

Follicular hyperkeratosis

This describes varying degrees of hyperkeratosis and plugging of the ostia of hair follicles, and this change may be associated with the rupture of the follicular wall. It occurs in many conditions including pityriasis rubra pilaris, lupus erythematosus, lichen planopilaris and lichen sclerosus.

Kamino bodies

This term describes the eosinophilic globules seen in the epidermis or in the region of the dermal–epidermal junction in spindle- and epithelioid cell (Spitz) naevi.

Karyorrhexis

This refers to the fragmentation of cell nuclei, and the process may be seen in various forms of neutrophilic dermatoses and cutaneous pyoderma. It is commonly seen in necrotizing vasculitic processes. The term leukocytoclasis specifically refers to the fragmentation of nuclei of neutrophil polymorphonuclear leukocytes. However, the term is sometimes used to refer to fragmentation of other inflammatory cells such as lymphocytes.

Lichenoid tissue reaction

This is a pattern of changes occurring both in the epidermis and especially the dermis, seen in a wide variety of conditions, ranging from lichen planus itself to lupus erythematosus, lichen sclerosus and the poikilodermas. Lichenoid changes may also be seen in some examples of cutaneous drug eruptions. In the upper dermis, there is a band-like infiltrate consisting predominantly of mononuclear cells. This is closely related to the dermal–epidermal junction, which itself may have a saw-toothed pattern. Liquefaction degeneration of the basal cell layer is seen, and colloid body formation may be present. There is often an increase in thickness of the overlying epidermis, affecting both the Malpighian layer and the stratum corneum (Fig. 7.22).

Metaplasia

This term is used to indicate an alteration of one type of tissue into another, such as the formation of bone in certain epithelial tumours, for example pilomatricoma.

Necrobiosis

Necrobiosis is an unsatisfactory term derived from words for life and death. It is applied to certain granulomatous disorders where the dermal connective tissue becomes

homogenized and loses its normal staining characteristics, resulting in mucinous, fibrinoid or sclerotic alteration. The outlines of the normal architecture are usually still present, and the amount of inflammation varies. Changes of necrobiosis are normally surrounded by a palisading histiocytic granuloma. The condition is seen in association with granuloma annulare, necrobiosis lipoidica, rheumatoid nodule and acne agminata.

Necrosis

This term describes the death of cells or tissue.

Necrolysis

This is used to describe the separation of tissue constituents as a consequence on cell death. Epidermal changes of necrolysis are seen in various inflammatory reactions such as erythema multiforme, toxic epidermal necrolysis and necrolytic migratory erythema seen in association with the glucagonoma syndrome.

Papilloma

This term indicates a tumour or tumour-like proliferation exhibiting both papillomatosis and hyperkeratosis. Acanthosis is also present. Examples of skin papillomas include viral warts, seborrhoeic keratoses and some epidermal naevi.

Papillomatosis

This change is characterized by elongation upwards of the dermal papillae, giving an accentuated and sometimes irregular, undulating configuration to the dermal–epidermal junction. The feature is commonly seen in psoriasis, and a wide variety of other inflammatory and neoplastic cutaneous disorders.

Parakeratosis

Parakeratosis can be defined as the retention of keratinocyte nuclei within the horny cell layer. It represents a disturbance of keratinization, and is normally associated with an absence or reduction in thickness of the granular cell layer. The histological feature of parakeratosis is commonly seen in many different forms of inflammatory dermatosis, and is closely associated either with increased epidermal cell turnover or with inflammatory changes in the epidermis itself. It is commonly seen in psoriasis and subacute eczematous reactions, and in conditions such as pityriasis lichenoides where the change reflects an earlier disturbance in the underlying epidermis. In chronic inflammatory conditions where epidermal turnover is unaffected, such as in lichenoid reactions, parakeratosis is rarely seen. Dysplastic epithelial changes, such as those occurring in actinic keratoses and Bowen's disease, are normally accompanied by parakeratosis.

Pigmentary incontinence

This refers to the loss of melanin from cells of the basal layer of the epidermis, and the accumulation of melanin, both free and within dendritic macrophages, in the underlying dermis. It is associated with damage to keratinocytes of the lower epidermis, and is commonly seen in lichenoid tissue reactions. Small amounts of melanin may be seen in the upper dermis in normal pigmented skin.

Pleomorphism

This describes variability in the appearance of cells, and in particular the nuclei of cells of the same type. Although it may be seen in malignant and premalignant conditions, marked pleomorphism may also be seen in benign lesions such as Spitz naevi.

Polymorphism

Conventionally this is used to describe a variation in types of cells in a cutaneous lesion. This term is not the same as pleomorphism.

Pustules and abscesses

These terms are used to describe cavities within the epidermis or dermis formed by collections of neutrophil or eosinophil polymorphonuclear cells. Occasionally, the term is used to describe collections of other leukocytes, as in the term Pautrier microabscesses (see below). Cutaneous pustules may be sterile, or associated with an infectious microorganism. Certain specific types of microabscess and pustule are of diagnostic value in dermatopathology.

Kogoj's spongiform pustule. This describes the multilocular micropustules that form in the superficial portions of the epidermis in pustular psoriasis. They form in a similar manner to Munro microabscesses but the process is more extensive.

Munro microabscesses. These lesions are small collections of neutrophil polymorphs usually found within the stratum corneum. They are normally seen in lesions of chronic established psoriasis, and the other histological features of the psoriatic reaction, such as irregular epidermal thickening and parakeratosis, are normally present.

Papillary tip microabscesses. These are small focal collections of neutrophil polymorphs or occasionally eosinophils, in

the tips of dermal papillae. Although they are characteristic of dermatitis herpetiformis, they may occur in other bullous eruptions such as epidermolysis bullosa acquisita and the bullous form of lupus erythematosus.

Pautrier microabscesses. These small, intraepidermal collections of lymphoid cells in the absence of marked spongiosis are characteristic of mycosis fungoides. The cells within the epidermis may show some degree of nuclear hyperchromatism or atypia. Single cell colonization of the epidermis is more commonly seen than true Pautrier microabscess formation in many cases of early mycosis fungoides.

Subcorneal pustules. Large, subcorneal collections of neutrophil polymorphs usually represent either impetigo or subcorneal pustular dermatosis. Sometimes, the distinction of either of these two conditions from pustular psoriasis may be difficult.

Pyknosis

This term is used to refer to hyperchromatism and shrinkage of the cell nucleus. It is normally associated with cell death, and may be seen in a wide variety of conditions, including epithelial dysplasias, drug reactions and reactions to UV light.

Saw-toothing

This refers to an alteration in the pattern of the dermal–epidermal junction where dermal papillae are expanded and the tips of the rete pegs are pointed. The resulting pattern bears a superficial resemblance to the teeth of a saw and the change is seen in lichen planus and other lichenoid reactions.

Spongiosis

Spongiosis is also known as intercellular oedema, and describes the widening of intercellular spaces between keratinocytes due to fluid accumulation. Spongiosis is the characteristic histopathological change seen in acute and subacute eczematous reactions, but is also seen in a wide variety of other conditions; when spongiosis is marked it leads to intraepidermal vesiculation. Spongiosis of follicular epithelium may be associated with increased mucin deposition in the histopathological reaction pattern known as follicular mucinosis.

Storiform patterning

This is a pattern of proliferation commonly seen in various dermal and soft-tissue tumours, where strands of spindle-shaped tumour cells or even collagen bundles are arranged so as to resemble the pattern seen in woven cloth. The term is also sometimes applied to the presence of strands of spindle-shaped tumour cells or connective tissue cells that appear to extend radially from a central hub, similar to the spokes of a wheel. Cartwheel patterning is probably a better term to describe this particular appearance. Storiform and cartwheel patterning, although commonly referred to in DFSP, are by no means specifically diagnostic (Fig. 7.23).

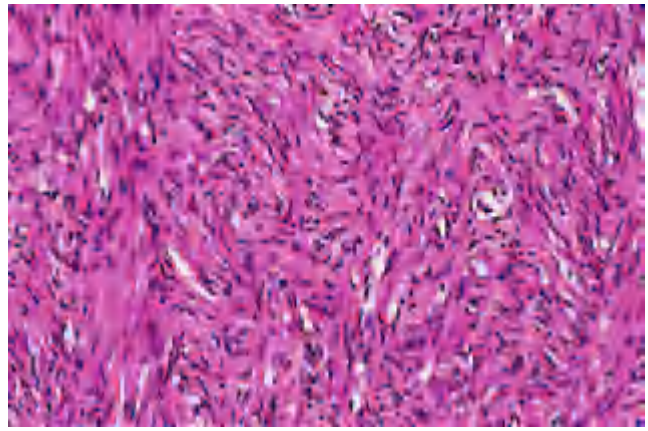

Fig. 7.23 A storiform or woven appearance to the proliferating tumour cells of dermatofibrosarcoma protuberans.

Theque

This term is derived from French and Greek words for a box (*thèque*, θηκη) and is conventionally used in dermatopathology to describe small aggregates or nests of cells, particularly the collections of naevus cells at, and in the region of, the dermal–epidermal junction.

Villi

This term refers to elongated dermal papillae covered usually with a single layer of epidermal cells, and which form the base of a blister cavity that has resulted from the process of suprabasal acantholysis. Villi are seen in the various forms of pemphigus and Darier's disease (see Fig. 7.19), warty dyskeratoma, and transient and persistent acantholytic dermatosis.

Special problems that may be encountered in skin biopsies

Histological sections that reveal little or no abnormality

It is not uncommon for the diagnostic dermatopathologist to come across histological sections where at first sight the appearances resemble normal skin. It may be that the pathological changes have been missed. This can be the

fault of the clinician who has perhaps taken too superficial a biopsy from a lesion of suspected panniculitis, or it can be the fault of the pathologist who has inappropriately blocked the biopsy specimen, or taken too few sections from the material. The importance of studying numerous serial sections in this situation cannot be overemphasized. There are a number of conditions, however, where subtle pathological abnormalities are present, but where a high index of suspicion is needed to make a correct diagnosis. The following list includes some of the more important of these.

Epidermal lesions

Fungal infections. In the presence of patchy epidermal spongiosis and focal overlying parakeratosis, it is always important to exclude the presence of a fungal infection with a PAS stain. Occasionally, a few neutrophil polymorphs may be seen in the upper Malpighian layer of stratum corneum, and this may provide a clue to the correct diagnosis. Pityriasis versicolor may be present in the absence of spongiosis, and is frequently missed.

Ichthyotic disorders. The dominant form of ichthyosis vulgaris is usually characterized by some degree of compact hyperkeratosis, and an absent or attenuated granular layer. If the hyperkeratosis is not significant, the diagnosis may be overlooked. When assessing the stratum corneum, it is always important to look at not only the thickness, but also the quality of the corneocytes. An alteration from the normal basket-weave pattern to a compact cornified layer usually indicates some pathological abnormality.

Porokeratosis. The epidermal changes, usually of atrophy, in the various forms of porokeratosis are often not striking, and the diagnostic cornoid lamella may not be seen on the first sections cut from the block. In diagnostic biopsies, the cornoid lamella may not be present. All forms of porokeratosis may be misdiagnosed, but the disseminated actinic form of the disorder is the most commonly overlooked.

Actinic keratoses. Some flat actinic keratoses may show very little evidence of keratinocyte atypia, and unless a reasonable amount of normal skin is included the biopsy material may be signed out as non-diagnostic.

Pigmentary disorders

Various disorders of epidermal pigmentation may be difficult to diagnose with certainty, particularly if one is not certain of the skin colour of the patient from whom the biopsy has been taken. The loss of pigment in established vitiligo is normally associated with absence or reduction in number of melanocytes. However, in café-au-lait spots and ephelides, melanocytes are normal in number. A melanin stain may reveal a difference between lesional and adjacent skin. In postinflammatory hypo- or hyperpigmentation, the number of melanocytes remains normal with increase or decrease in melanin in basal cells. Often, melanophages are seen in the papillary dermis particularly in post-inflammatory hyperpigmentation.

Dermal deposits

The small amounts of amyloid seen in macular amyloidosis are often difficult to visualize with H&E stain. Special stains are indicated, but the presence of slightly expanded dermal papillae, together with a hint of lichenoid tissue reaction, may alert the pathologist to this possibility. A further useful clue is the presence of scattered apoptotic keratinocytes. The presence of iron pigment in small quantities in the dermis is easily missed, either in common conditions, such as bruising, or in rare situations, such as idiopathic haemochromatosis. A Perls' stain usually highlights iron deposits that have not been detected in slides stained with H&E. The deposits of silver in argyria are often best seen around the basement-membrane zone of dermal sweat ducts.

Connective tissue diseases

Scleroderma, particularly in the late stages, often shows little histopathological abnormality. The coarsening and hyalinization of collagen bundles, with a reduction in the space between them, is often not prominent particularly in the superficial form of morphoea. In the early stages of the condition, there is normally some increase in cellularity around dermal blood vessels. It is always important to try and assess normal skin if there is some present in the biopsy. Similar problems may be encountered with various forms of connective tissue naevi, and abnormalities of elastic tissue such as anetoderma. In atrophoderma, the elastic pattern is more or less normal, but there is a reduction in total thickness of the dermis, which may be difficult to evaluate. A solution to this problem is to obtain an ellipse of skin in which half of the specimen represents clinically normal skin. To indicate the clinically normal skin, the clinician marks the specimen with a stitch.

Dermal infiltrates

Urticaria. In biopsies from urticarial lesions, there may be very little more than slight dermal oedema, which is often difficult to evaluate on processed tissue, together with a slight increase in inflammatory cells around upper dermal blood vessels. It should be remembered that, in normal skin, a few mononuclear cells, fibroblasts and other cells are present in the dermis. A clue to the diagnosis of urticaria is the presence of at least a few eosinophils.

Blue naevus and related disorders. The dendritic melanocytes seen in the dermal melanocytoses, particularly Mongolian spot, are often difficult to recognize without the use of special stains such as the S-100 immunohistochemical marker. The main problem resides in the distinction between melanophages and melanocytes, as most dermal melanocytoses excluding blue naevus contain only few scattered dermal pigmented melanocytes. The use of the immunohistochemical marker for melanocytes such as S-100 is useful, but the product obtained in the detection of the final peroxidase product is usually brown and this is very similar to melanin. This problem can be overcome by bleaching the slide before immunohistochemistry, or by changing the diaminobenzidine for amino-ethyl carbazole, which results in a red product.

Granuloma annulare. In the majority of cases this diagnosis is straightforward, with evidence of a dermal palisading granuloma with necrobiosis. However, in the disseminated form of the condition the changes are often very slight, and may be represented by just a few mononuclear cells dissecting bundles of collagen.

Mast cell disorders. The adult form of urticaria pigmentosa, and particularly its variant telangiectasia macularis eruptiva perstans, frequently shows only a relatively slight increase in numbers of mast cells within the dermis. In these forms of urticaria pigmentosa, the mast cells tend to be rather dendritic or short spindle-shaped. Their granules may not be obvious, and they may resemble normal connective tissue cells, such as fibroblasts. In mastocytoma and some juvenile forms of mastocytosis, the mast cells are larger, rounded cells with central nuclei and are easier to recognize.

Scalp disorders

Unless an adequate biopsy is available for examination, many disorders of the scalp may be difficult to evaluate. Conditions such as telogen effluvium and long-standing alopecia areata show very little sign of inflammation, and diagnosis may have to be made purely on the number of pilosebaceous structures, and the relative number of follicles in different phases of the hair cycle. The study of horizontally sectioned biopsies is the ideal method to study hair follicles with regards to their cycle, pathological alterations and numbers (see Chapter 63).

Conclusion

As mentioned at the start of this chapter, histopathological examination of a skin biopsy taken from an appropriate lesion is a great help in assisting the clinician to come to a correct diagnosis, and therefore to come to a decision regarding management of the patient. Light microscopic examination of sections from skin-biopsy tissue fixed in formalin and embedded in paraffin is likely to remain the single most useful diagnostic technique for the foreseeable future. The wide range of tissue and cytological changes that may be encountered within normal skin and inflammatory and neoplastic conditions mean that considerable experience is required for the dermatopathologist to contribute helpfully to patient management. Many excellent texts are now available on the histopathology of the skin, but there can be no substitute for personal study on a day-to-day basis of as much material as possible under the supervision of an experienced guide. Feedback and communication between clinician and pathologist is essential, and has been perhaps one of the most important factors in the advances in dermatopathology in the last decade. The light microscopist already has a very wide range of additional techniques available to assist in diagnosis and to study the anatomy and physiology of normal and diseased tissues, some of which are outlined above. The numerous new areas of investigation that have developed over the last few years, including molecular biological techniques, such as PCR, *in situ* hybridization and studies on biological response modifiers, cytokines and adhesion molecules, will no doubt continue to further major advances in our understanding of skin in health and disease.

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Chapter 8

Molecular Biology

J.L. Rees

Introduction

There is no single all-embracing definition of molecular biology. However, it is possible, certainly with hindsight, to plot and recognize the growth of a unique blend of biochemistry, genetics and cell biology—the subject we now call molecular biology—which is having a revolutionary impact on all areas of biology, not least clinical medicine. The Nobel Laureate James Watson and colleagues, writing in a preface to one of the standard texts of molecular biology, commented that whereas only 25 years ago it was possible for one individual to know all the important topics in molecular biology, this was no longer the case [1]. This explosion of knowledge is not just due to a revolution in our conceptual understanding, but owes as much to an astonishing expansion in our technical facility to characterize and manipulate nucleic acids. The emphasis on nucleic acid rather than, for example, protein or other macromolecules is important. The caricature of a molecular biologist as somebody who believes that proteins are just an intermediary by which one nucleic acid creates another nucleic acid (whereas, in contrast, biochemists believe that nucleic acids are intermediates that allow proteins to generate yet more proteins), like all good caricatures, only serves to highlight the difference in relative success between gene-based and protein-based strategies: nucleic acid-based approaches have, over the last 10 years, provided a remarkably tractable way in which to solve many medical problems. This may change: development of 'proteomics'—defined as the systematic study of proteins in biological systems, with parallels with genomics—is thought by some to be poised to play a major role in drug discovery. Several features of the organization and structure of nucleic acids go some way to explaining the power of this gene-centred approach to biology. Genetic information is conveyed in a *linear* sequence of only four bases; genes are *colinear* with proteins; and genes themselves are arranged in chromosomes in a fixed *linear* sequence, without which cloning of genes on the basis of position (so-called positional cloning or reverse genetics) would be impossible. What is still extraordinary, and was once not obvious, was how much biologically meaningful information could be revealed by merely understanding the linear base sequence of a particular gene [2].

The development of molecular biology as a discipline has not been a gradual step-by-step process but, by contrast, has faltered at several stages [3,4]. Intellectual landmarks include Avery's work with *Pneumococcus*, demonstrating that nucleic acids (rather than protein) carry genetic information; Watson and Crick's Nobel Prize-winning description of the structure of DNA; and subsequent work by Crick, together with Sidney Brenner and others in the late 1950s and early 1960s, describing how information encoded by DNA was realized in protein structure [1–8]. In the early 1960s, however, there was a hiatus lasting until perhaps the mid 1970s. Both Brenner and Crick have described how in one sense they felt the major intellectual problems—how genes encode macromolecular information and how this is converted into protein—had been solved: consequently they both went to work in new areas, Crick in neuroscience, and Brenner on a host of other biological problems including developmental biology [6,9] for which he was subsequently awarded a Nobel Prize in 2002. At this stage, many of the ground-breaking discoveries, whilst having a general applicability, were experimentally limited to simple organisms such as bacteriophages or bacteria. There were not the experimental tools to allow human genome analysis, and consequently genetic approaches to disease were still beyond reach. In the 1970s, a number of fundamental

advances in an area that would later become known as biotechnology changed this situation [3,4]. The identification and experimental manipulation of plasmids and the identification of restriction, and other DNA-modifying, enzymes heralded a new era in our ability to study the human genome and start utilizing genetic approaches to human disease. In particular, combinations of techniques, together with considerable insight, led to the ability to study those rare but important differences between individuals' protein-coding DNA, which are the cause of most inherited disease. Perhaps counter-intuitively, the detection of variation in non-coding DNA (so-called 'junk DNA') was also to have a great influence; virtually all present-day mapping of disease-causing genes relies on such variation. In addition, an ever-enlarging armamentarium of techniques allowed the increased experimental manipulation of DNA, including the reintroduction of DNA initially into cells, firstly in culture, and later into animals, leading to the development of transgenic technology. This new biology now permeates all areas of clinical medicine, and dermatology is no exception: there has been astonishing progress in identifying the genes for a host of skin disorders. As well as providing and hinting at explanations for the underlying pathophysiology of these diseases, these advances promise an increase in the speed of development of new therapeutic approaches, either those based on genes themselves such as gene therapy, or by allowing a quickening of the pace of drug discovery. Whereas it has been possible for many to continue to feign ignorance of this new biology, those who do so are increasingly consigned to understanding an ever-diminishing fraction of the scientific and clinical literature, and of its limitations.

It is not possible within this chapter to give a comprehensive or even fair treatment of the whole of molecular biology as it applies to dermatology. For those interested, there are some unusually readable (and exciting) books on molecular biology to which the reader is directed [1,4,5,7,8]. Nor can the chapter be viewed merely as a catalogue of genetic disorders of the skin: review of the Online Mendelian Inheritance in Man (OMIM) database suggests that up to one-third of the listed disorders may involve the skin. However, what I will try to do is (i) briefly review the structure of nucleic acids; (ii) explain how the structure of DNA allows the development of a number of techniques, which in turn permits further analysis of the relation between genes and organisms; and (iii) give examples of how molecular biological approaches have been informative for the study of skin disease, including a section on cancer genetics. Finally, a brief treatment is given of the use of molecular biological techniques in diagnosis and therapy.

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Basic molecular biology of the cell

Structure of nucleic acids [1–3]

DNA is an antiparallel double helix in which the backbones of the helix are made from sugar and phosphate groups; these are linked by one of four bases (cytosine, guanine, thymine and adenine) that form hydrogen bonds with a complementary base on the opposing backbone (Fig. 8.1). The primary genetic information is coded by the pattern of these bases. Importantly, and central to the

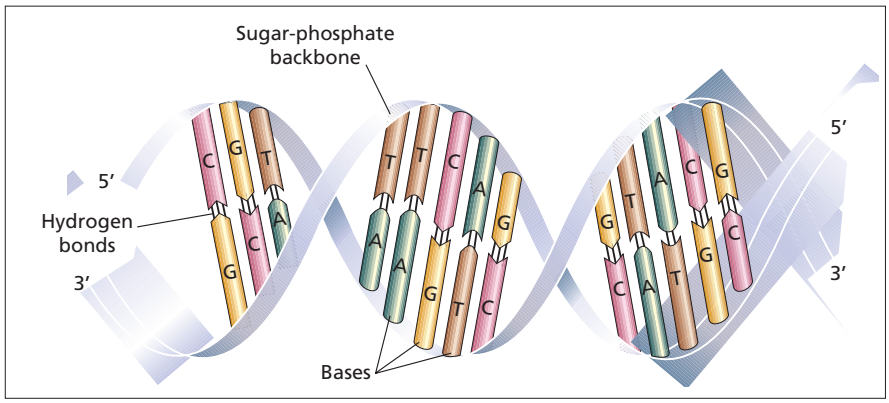


Fig. 8.1 Schematic of the DNA double helix. The backbone of the helix is made up of sugar and phosphate moieties that run in opposite directions (5′→3′ and 3′→5′). The strands are linked by the bases, which pair via hydrogen bonds in a particular fashion, cytosine with guanine, and adenine with thymine. Because of the specific nature of the base pairing, if the hydrogen bonds are broken, each strand can act as a template for the other, such as occurs at transcription of DNA into RNA or when DNA is replicated. It is also evident that because each strand of DNA is complementary to the other, then one strand can be used as a probe for the other.

Watson and Crick model, cytosine always binds with guanine, and adenine with thymine. Because these base pairings are held together by hydrogen bonds only, one can imagine how, if the bonds are broken (such as by treatment with heat), each strand of DNA could act as a template for the opposing strand. Each cell in the human body contains 3 billion bases of DNA arranged on 23 chromosomes. Unless the DNA were organized and packaged in particular ways, the length of DNA in each cell would be 2 m; that from a human body would stretch further than to the moon and back! Surprisingly, perhaps 90% of the DNA on the 23 chromosomes does not appear to code for protein, and is therefore often referred to as 'junk DNA'. Much of this DNA is made up of repeated sequences of DNA, the function of which is unclear. It has, however, been experimentally fortuitous, in that this 'junk DNA' is a rich source of genetic variation between individuals, and forms the basis for genetic mapping of disease traits. Thus for any one chromosome, the genes residing on that chromosome will be diluted by a much larger volume of DNA that does not appear to code for protein. Finding genes is therefore sometimes like searching for a needle in a haystack, even when the area of a chromosome harbouring a gene for a particular disorder has been closely localized by mapping of the disorder in affected kindreds. Not only are genes arranged on chromosomes in an intermittent way, but while genes and proteins are colinear, the DNA that directly codes for particular groups of amino acids is in itself discontinuous on the chromosome, being arranged into introns and exons (Fig. 8.2). With certain important exceptions (which are not central to this description), DNA in every cell in the body is identical in terms of its primary structure. The keratinocyte's DNA is the same as that in a red-cell precursor or a neurone. This immediately raises the problem of how a keratinocyte knows how to make keratins, a red-cell precursor globins and a neurone synapses. How do the different types of cells produce different proteins if they carry identical DNA? DNA is transcribed into RNA, which is then translated into protein. If one were to examine the RNAs produced in these different cell types, one would detect differences. A major area of interest in molecular biology has therefore been in understanding the control of such differences in *gene expression*. This control occurs at two main levels: first, transcription—whether particular RNAs are copied from a particular gene; and second, translation—whether proteins are then made from any particular RNA molecule. Whether a particular gene is transcribed into RNA is determined by the interaction between a variety of proteins in the cell, and by extracellular signals mediated through a number of pathways that interact with RNA polymerases (enzymes that copy DNA into RNA) via the promoter region of the gene. The promoter, located (usually entirely) 5′ to the coding region of the gene ('upstream'), functions akin to an on/off and

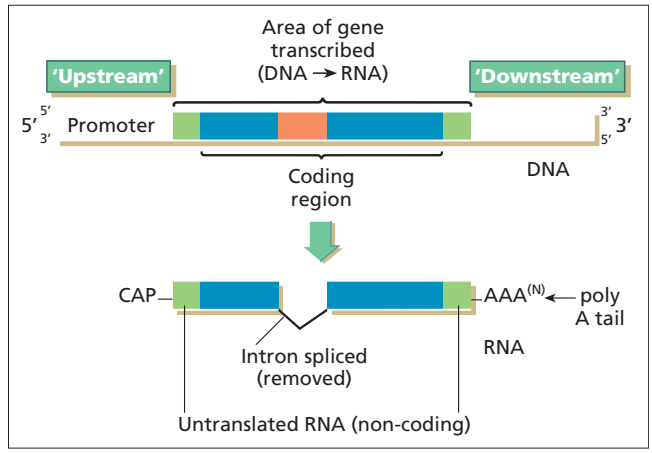


Fig. 8.2 Schematic of a gene and transcription to, and processing of, RNA. The gene comprises the transcribed region, which largely consists of the coding region (including the introns, which will be spliced out and do not code for protein) and the upstream and downstream regions. The promoter region is upstream, although sequences important in determining the level of gene expression in response to a variety of stimuli can be located upstream or downstream. DNA is transcribed into RNA by a DNA-dependent polymerase and the resulting RNA strand processed by removal (splicing) of introns, addition of a string of adenines at the 3′ end (polyA tail) and 'capping' of the 5′ end. Some of the RNA that is transcribed and not spliced out (the untranslated 5′ and 3′ sequences) does not code for protein, but appears to be important for RNA stability and translation into protein. The number of introns is extremely variable: some genes have no introns, whereas others have hundreds of introns, with the length of the introns greatly exceeding the length of the region that directly codes for protein.

volume control on a record player, controlling whether, and how much, gene transcription takes place in response to instructions received from a myriad of pathways. As mentioned above, the gene itself is likely to be discontinuous, such that the RNA produced may contain what are called introns (areas that do not code for protein), which are cut or spliced out once the RNA is made (see Fig. 8.2). The spliced version of the RNA then proceeds to the ribosome (in the cytoplasm) where protein synthesis occurs. Other changes to the RNA also occur, including the addition of a string of adenines (the so-called polyA tail, which appears to be important for the stability of the RNA) and a process termed capping at the 5′ end of the RNA (see Fig. 8.2). The structure of a protein from the same gene may therefore differ in different cells, depending on the splicing and any other changes to the RNA. Throughout this transfer of information, however, it is the linear sequence of bases within and around the gene that appears important in determining the structure of the protein. Within the coding region of the gene, each group of three adjacent bases ('triplet') specifies a particular amino acid. Outside the coding region, although the DNA may not code for protein directly, the pattern of bases, particularly that before the start of a transcription site in

the promoter of the gene, is also important in determining the level of transcription (in response to a variety of stimuli). Primary sequence is therefore more than just a shorthand for the three-dimensional structure of the resulting protein.

Molecular techniques

Extraction of nucleic acid is straightforward. Take a few millilitres of venous blood, or a small skin biopsy, treat with a proteinase overnight, separate the nucleic acid from protein using phenol or chloroform, and then precipitate the several hundred micrograms of DNA with cold alcohol. The resulting DNA can be easily spooled on the bottom of a glass rod or pelleted in a microcentrifuge, and appears as a slightly yellow, sticky substance that can subsequently be dissolved in water and assayed on the basis of its absorption of UV radiation. This isolated DNA is made up of the 3 billion bases of genomic DNA from each cell, multiplied by the 100 million or so cells from which the DNA has been made. However, at this level of analysis, the DNA from different individuals would look much the same. Mere examination with the eye does not provide any insight into the primary base sequence. The technical revolution in the last quarter century allows such analysis. While whole volumes are devoted to describing the techniques of molecular biology, the principles involved are usually straightforward, and it is often possible intuitively to appreciate how and why they work, and to see how they take advantage of the basic structure of DNA.

Restriction enzymes are naturally occurring enzymes that cleave DNA in a sequence-specific manner. They have been identified in a variety of bacteria, where their principal function seems to be to defend bacteria against particular forms of bacteriophage infection (the principle being that particular sequences might occur in an invading organism but not in the host, and that enzymes specific for these sequences would be able to defend the host from invasion). If the DNA isolated from blood or skin, which consists of pieces upwards of 50 kilobases (kb) in length, is suspended in buffer and incubated with a restriction enzyme, the DNA is cleaved into much smaller fragments. The exact size of the fragments depends on the particular restriction enzyme chosen: some might be expected to cut the DNA every few hundred base pairs, whereas others whose target sequence is not so common might only cut once every million base pairs or so. It is therefore possible to characterize the DNA in terms of its primary sequence structure based on the pattern of fragments obtained following restriction enzyme digests. Furthermore, differences between DNA from different individuals (which are particularly common in the non-coding region of DNA) may show up as differences in the size of the fragments following digestion with particular

Fig. 8.3 DNA labelled with ethidium bromide and run through an agarose gel and examined under a UV radiation source. Ethidium bromide intercalates into DNA and fluoresces in response to short-wave UV radiation. The first two tracks show a sample of genomic DNA before and after digestion with a restriction enzyme (note the smearing present in track 2). Track 3 shows the human melanocortin 1 receptor (melanocyte-stimulating hormone receptor) amplified using the polymerase chain reaction (PCR). Tracks 4 and 5 show the PCR, shown in track 3, from two individuals digested with a restriction enzyme that reveals a polymorphism due to a mutation at codon 84 of the melanocortin receptor gene.

restriction enzymes (Fig. 8.3). An important feature of many restriction enzymes is that although their action depends on the presence of a particular sequence of bases, DNA is cleaved in such a way that, with another enzyme known as DNA ligase and a source of energy, it can be stuck together again—'cut and paste' in word-processing terminology. This 'cut-and-paste' facility allows small pieces of DNA (say a couple of kilobases long) that have been cut with the enzyme to be inserted into a vector such as a plasmid. The subject of vectors may appear confusing but, for present purposes, molecular biologists have identified and created a whole range of experimental vehicles that allow the propagation of DNA; very much the workhorses underlying the phrase 'cloning of DNA'. A commonly used vector is a plasmid. Plasmids are naturally occurring, extrachromosomal, circular pieces of DNA found in bacteria. Their medical importance has

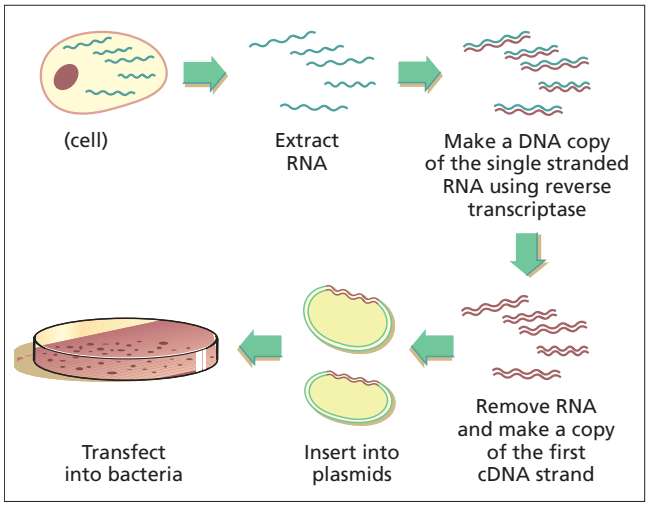


Fig. 8.4 Making a complementary DNA (cDNA) library. RNA (single stranded) is extracted and a cDNA copy of the RNA made using reverse transcriptase. The RNA is then removed, and the first strand of cDNA acts as a template for the second strand of DNA. The short fragments of double-stranded DNA (inserts) are then 'pasted' into plasmids, transfected into a suitable bacterial host, cultured and plated out on agarose. Each bacterial colony will contain a clone of bacteria that contains only one insert. The number of colonies expressing the same insert should reflect the frequency of the RNA species in the cells the library has been made from. Libraries can also be made from genomic DNA, in which case no cDNA synthesis is necessary, but because the desired fragments to be cloned are larger, a variety of other vectors (rather than plasmids) are used.

been that they may carry antibiotic-resistance genes and transmit these from one bacterium to another. Experimental manipulation makes it possible to 'cut and paste' a piece (an 'insert') of DNA into a plasmid, *transfect* the plasmid back into a bacterium, and wherever the bacterium divides, the plasmid and insert will also be copied. Because bacteria can grow in an exponential fashion, this technique allows large amounts of the insert to be produced (cloned).

Additionally, it is possible to restrict (in other words, digest with a restriction enzyme) the DNA isolated from a cell, and 'paste' many of the resulting small pieces of DNA into plasmids (or other suitable vectors), such that each vector will contain only one insert of DNA and that the majority of plasmids would be expected to contain a unique insert. These plasmids can then be transfected back into bacteria, and the resulting collection of bacteria containing many different plasmids comprises a *DNA library*—a representation of a cell's DNA, now in a form that can be cloned, promulgated and used experimentally. An analogous technique can be used for making a complementary DNA (cDNA) library, i.e. a library that represents the RNA species expressed by a particular cell, in which each 'book' corresponds to a particular RNA molecule (Fig. 8.4). Unlike DNA, RNAs are not ordered in the cell in linear arrays like genes on chromosomes, but rather the RNA from a particular cell consists of hundreds of thousands of individual RNA molecules, each of which can be translated into a particular protein. Unlike DNA, RNAs are expected to differ dramatically between different cell types: keratinocytes will produce a large number of RNAs coding for keratins, whereas these would not be seen in a red-cell precursor, which by contrast will be rich in globin RNAs, and vice versa. Because RNA is difficult to manipulate experimentally, the RNA species can be converted using reverse transcriptase into a cDNA—very much the reverse of normal transcription, which converts DNA into RNA—and the resulting DNA inserted into a plasmid, such that the population of plasmids now represents the RNA species in any one cell. The resulting library is known as a cDNA library, 'c' because it is complementary to the RNAs in the original cell.

Southern and Northern blotting

If the DNA extracted from a eukaryotic cell is cut with a particular restriction enzyme, the resulting fragments might be expected to differ between different individuals, the organization of the fragments therefore providing information about any DNA sequence differences. In order to display the DNA, it is possible to order the resulting fragments of DNA by passing them through an agarose gel within an electric field. The charged DNA molecules will migrate through the gel depending on their mass, with the smallest fragments travelling furthest. In terms of strength, the gels used in such gel electrophoresis are not dissimilar to a jelly prepared for a children's party, and they therefore need to be handled with care. However, once the nucleic acid has migrated through the gel, it can be conveniently transferred to a nitrocellulose (or better still a nylon) membrane, in a process called Southern transfer (Fig. 8.5). The DNA is then fixed (cross-linked) to the membrane (which, while looking like a piece of paper, has similar tensile properties to a plastic carrier bag) using UV radiation. Importantly, although the nucleic acid is now covalently bound to the membrane, it is still free to take part in hydrogen-bond reactions. This transfer of DNA from an agarose gel to a membrane is known as Southern blotting, after its inventor Ed Southern; Northern blotting (a pun on Southern!) refers to the transfer of RNA and Western blotting to the transfer of proteins. Because RNAs exist as individual molecules rather than as long arrays on chromosomes like DNA, RNA extracted from cells is fractionated immediately, and does not have to be first digested with restriction enzymes. Following Southern blotting, the DNA attached to the membrane will not be visible to the naked eye, although it is possible to see the DNA when it is size fractionated through an agarose gel by virtue of the fact that dyes such as ethidium bromide intercalate in DNA and fluoresce under UV radiation (see Fig. 8.3). If such a

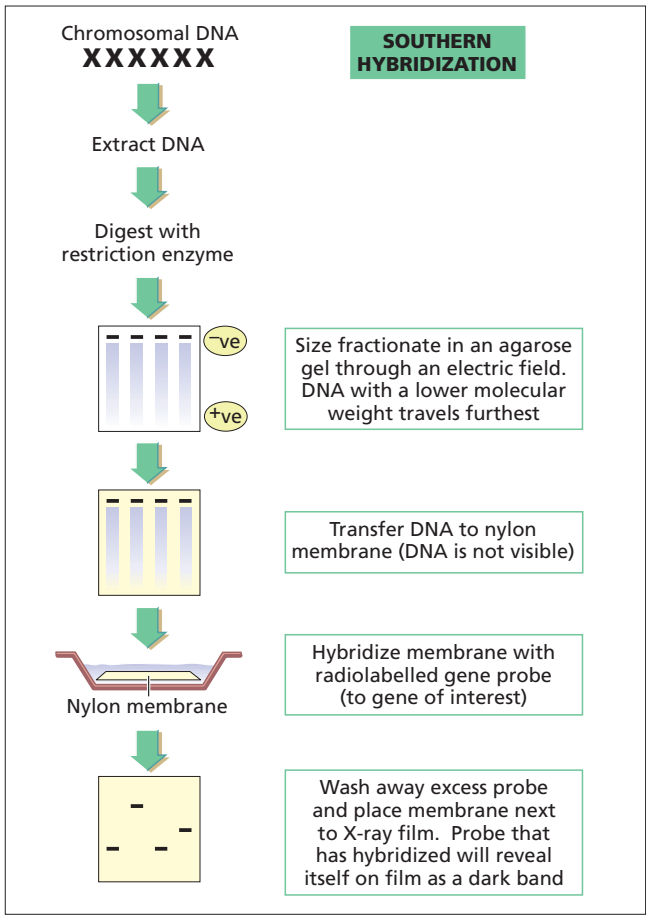


Fig. 8.5 Southern hybridization. Genomic DNA extracted from cells can be cut with a suitable restriction enzyme and then size-fractionated through an agarose gel within an electric field. The DNA in the gel can then be transferred (or blotted) to a nylon (or nitrocellulose) membrane, which is then hybridized with a radiolabelled probe complementary to the target sequence. Following hybridization, the membrane is washed to remove excess probe and sequences that have bound non-specifically. The membrane is then placed next to radiation-sensitive film overnight. Wherever the radiolabelled probe has bound to a complementary sequence, a band will be visible on the film. In this example, DNA from four individuals was run on the gel and hybridized. The differences in the position of the black bands on the autoradiograph reflect that the size of the DNA fragment containing the gene of interest differs between individuals. The most likely explanation for this polymorphism is that the restriction enzyme has cut the DNA differently because of variations in the DNA between the individuals close to, but probably not within, the gene of interest (see text). A similar procedure can be carried out to examine RNA expression and is called Northern (as compared with Southern) blotting. Because RNA molecules exist individually rather than as large chromosomes (as for DNA), no restriction digestion is necessary; the details of the transfer of RNA to a nylon membrane also differ from that needed for DNA. When the membrane is placed next to film, the intensity of the resulting band will reflect the amount of that RNA species in the target cell of interest. More than one band may be seen in a single track, reflecting differences in how the RNA is spliced (there may be more than one splice variant in a particular cell).

gel or membrane is examined, a long smear comprising millions of molecules of DNA will be evident; for most purposes it will be necessary to characterize the DNA further, so that individual genes or stretches of DNA can be examined (see Fig. 8.3). This is usually accomplished by using a radiolabelled gene probe that is complementary to the target of interest, which will bind to the target nucleic acid located somewhere within the smear (and which will comprise only a tiny fraction of the total DNA, for instance one gene out of 100 000).

Imagine that an individual is suspected of harbouring an abnormal keratin gene. As long as the gene of interest has been previously cloned, then it is possible to 'cut and paste' the gene into a plasmid, transfect it into bacteria to amplify the plasmid overnight, and then separate the plasmid DNA from other bacterial DNA, by virtue of the fact that plasmid DNA is smaller than chromosomal DNA. In order to label the gene probe, the plasmid DNA is mixed with the various bases, one of which has been tagged with radioisotope, and a DNA polymerase. Because one of the bases in the mix is radiolabelled, any copied DNA produced will be radioactive. The nylon membrane that contains a smear of eukaryotic DNA can now be mixed (*hybridized*) with the radiolabelled gene probe, which will bind to any complementary sequence it encounters; the keratin probe would therefore be expected to bind to any sequence complementary to it. Following hybridization, the membrane can be washed with salt solutions, to clear any non-specific binding, and placed next to radiation-sensitive film, which when developed should show a band reflecting the binding of the probe to the target sequence on the membrane. If this procedure is carried out in many different individuals, depending on the restriction enzyme used there is a good chance that variations will be seen between these individuals, reflecting sequence differences either in, or close to, the keratin gene. These differences are known as restriction fragment length polymorphisms (RFLPs), which have, until the advent of polymerase chain reaction (PCR) methodology, formed the basis of the mapping of disease-causing genes. Using this assay, a keratin gene that harbours a deletion may also show up as a smaller-than-expected fragment. Alternatively, one might wish to determine the level of expression of a particular RNA species in a diseased skin sample (i.e. how many RNA molecules per cell were present). There are analogous techniques based on Northern blotting, which can be used to study the expression of a particular RNA species. RNAs from various tissues can be size fractionated on an agarose gel, transferred to a nylon membrane, and then probed with the labelled plasmid for a particular keratin gene. Of course, whether any signal is seen will depend on whether that particular cell type expresses keratin RNA. One would not expect to see a positive keratin signal in RNA from red blood cell precursors or fibroblasts.

Furthermore, the intensity of the signal would give some indication of the abundance of any particular transcript. For instance, if cells had been differentially isolated from skin, one might expect that the RNAs for keratins 5 and 14 might be strongly expressed in basal cells in comparison with suprabasal cells, and vice versa for keratins 1 and 10.

The study of gene expression has been revolutionized in the last few years by the development of two new techniques. The first, reverse transcriptase PCR (RT-PCR) makes use of PCR preceded by conversion of RNA to a cDNA copy. The second is the use of microarray technology to study the expression of a large number of RNA species simultaneously. Both these techniques are discussed below.

Polymerase chain reaction

Mention has already been made of the use of DNA or RNA polymerases, enzymes that allow copies of a nucleic acid to be made. For example, a DNA-dependent DNA polymerase will make complementary DNA copies of a DNA molecule, whereas reverse transcriptase is an RNA-dependent DNA polymerase and will therefore make DNA copies of RNA. As well as an energy source and the necessary nucleotide bases, most polymerases require a primer or short sequence of DNA complementary to the strand to be copied, from which to start the synthesis of the complementary copy. The most celebrated use of DNA polymerases is PCR (Fig. 8.6), application of which has revolutionized much of molecular biology and more recently clinical diagnostics. The principle underlying PCR is that if primary sequence information is available for a primer area (usually 15–25 bases long) outside the target area of interest, then once a copy of both strands is made using a DNA polymerase and the resulting daughter strands reanneal, heating the DNA to near 100°C causes the daughter strands to separate again and in turn act as templates for further rounds of replication. The technical breakthrough has been the identification of thermally stable DNA polymerases that are not destroyed by the high temperature needed to separate the complementary strands. Intuitively, one can see that this replication is logarithmic, and therefore PCR allows the amplification of DNA many millionfold. In practice, there are some constraints: amplifying short sequences of 400–500 bases is straightforward but the limit is reached at around 10–15 kb; the extreme sensitivity of the technique can also be a disadvantage, as laboratory contamination can be a major hazard, a drawback which should not be forgotten when PCR is used to diagnose infectious agents in clinical biopsies.

Analogous caveats must apply to the use of RT-PCR. In this technique, RNA is extracted from tissue or cells, converted to its corresponding cDNA and then this cDNA subject to PCR. The technique is extremely sensitive and has been of great use in the study of gene expression patterns in skin pathophysiology. Its utility in skin disease has partly been because of the difficulty of extracting high-quality RNA in suitable amounts for Northern blotting from intact skin (as compared with cell culture). The disadvantages of RT-PCR are that, in the past, reproducibility has been problematic and, because it is so sensitive, RNA species of little biological purpose might be amplified. However, recent developments based on Taqman technology allow a greater quantitative estimation of RNA species, and the technique is now in widespread use.

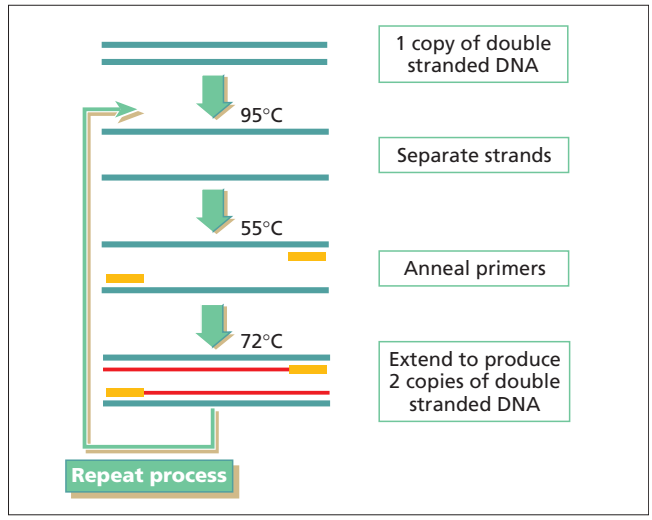


Fig. 8.6 Polymerase chain reaction (PCR). A double-stranded molecule of DNA is denatured into two complementary strands using heat (95°C). Primers are short stretches of DNA, usually 18–25 base pairs in length, complementary to sequences on the separated strands of DNA. For the primers to anneal, the temperature needs to be approximately 55°C, and the presence of a primer is essential for the polymerase (in the presence of the necessary bases and energy) to make complementary copies of each strand of DNA ('extension'). The two double-stranded molecules that are produced can then act as templates for further rounds of replication; hence the term 'chain reaction'. The technical breakthrough that has made PCR so successful was the discovery of polymerases that are so heat stable that they are not destroyed during the denaturation (strand separation) step (such polymerases were found in bacteria that inhabit hot springs).

DNA sequencing

DNA-dependent polymerases also play a central role in the commonest method of sequencing DNA. As long as there is a cloned source of DNA, either from the gene being cloned in a plasmid or from PCR, it is now possible to determine the primary base sequence. Traditionally, this makes use of a DNA polymerase and the four nucleotide bases, only one of which is radioactively labelled. As well as bona fide bases, particular nucleotides ('terminators') are added to the mix; these cause the DNA

Fig. 8.7 An example of a DNA sequence obtained using the dideoxy method of sequencing for which Sanger was awarded a second Nobel prize. References to a full description of the technique are given in the text. Essentially, copies of the template are made using a DNA polymerase only. The presence of dideoxynucleotides (instead of deoxynucleotides as in normal DNA) in the reaction causes the template copies to terminate prematurely. Four such copying reactions are carried out, one for each dideoxy base, such that the reaction terminates where the base was being added. When the products of all four reactions are run out on one gel, then reading across the bands reflects the order of premature termination products, which in turn reflects the primary sequence of the DNA strand being copied. (Courtesy of M. Birch-Machin, Department of Dermatology, University of Newcastle, Newcastle, UK.)

polymerase to fall off the template, resulting in complementary strands that have terminated prematurely. These aborted transcripts will therefore reveal themselves as shorter fragments when the products of the reactions are run on a polyacrylamide gel, resulting in a ladder of lines that will reflect the primary sequence. If separate terminator bases are used in each of the four reactions, one for cytosine, one for guanine, one for thymine and one for adenine, and the resulting four reactions are run out side by side on a gel, then the resulting pattern of radiolabelled prematurely terminated bands will correspond to the primary sequence (Fig. 8.7).

For large-scale sequencing, such as was necessary to sequence the human and mouse genomes, new technology had to be developed. In particular automation coupled with new fluorescent dye labelling allowed previously unheard of rates of DNA sequencing (Fig. 8.8). Radioisotope sequencing is increasingly of historical interest only.

Application of molecular techniques

The utility of the techniques described above has in the recent past been extended in two particular directions. Firstly, it has been possible to marry the approaches of classical genetics and molecular biology to such a degree that mapping of human diseases characterized by a Mendelian pattern of inheritance has now become commonplace; often, the only limiting factor to the identification of disease-causing genes is a paucity of suitable kindreds. Secondly, it has become possible to manipulate genes experimentally such that they can be transfected into either living cells in culture or, more recently, living organisms (transgenic animals).

The principle of mapping of genetic disorders is straightforward and easily grasped: when chromosomes recombine (at meiosis), genes or chromosomal regions that are close together are less likely to be separated than those on opposite ends of the chromosomes [3]. To map human disorders, it is first necessary to construct a genetic map of a chromosome, so that the putative diseased gene can be positioned in relation to other loci on the chromosome. This in turn requires polymorphic loci ordered along each chromosome. Early attempts at linkage of human disorders related particular traits to known protein polymorphisms. This approach was limited because protein polymorphisms are few, and often difficult to detect. By contrast, as mentioned in an earlier section, the majority of human DNA actually comprises DNA that does not code for any particular protein. This so-called 'junk DNA' appears to be under little evolutionary selective pressure, and has therefore provided an excellent vehicle for the delineation and characterization of polymorphic sequences throughout the genome. In particular, recent mapping attempts have made use of hundreds of

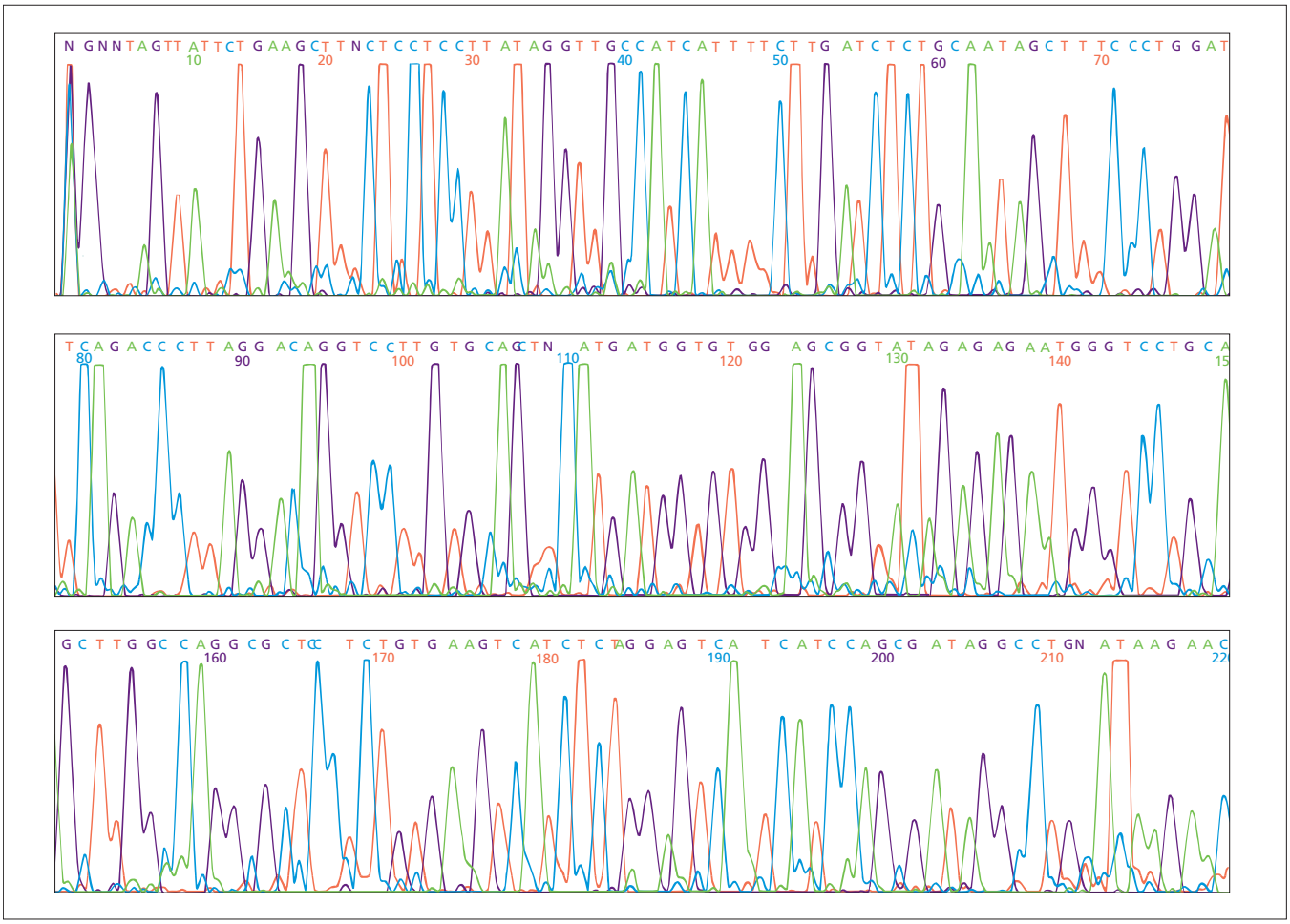
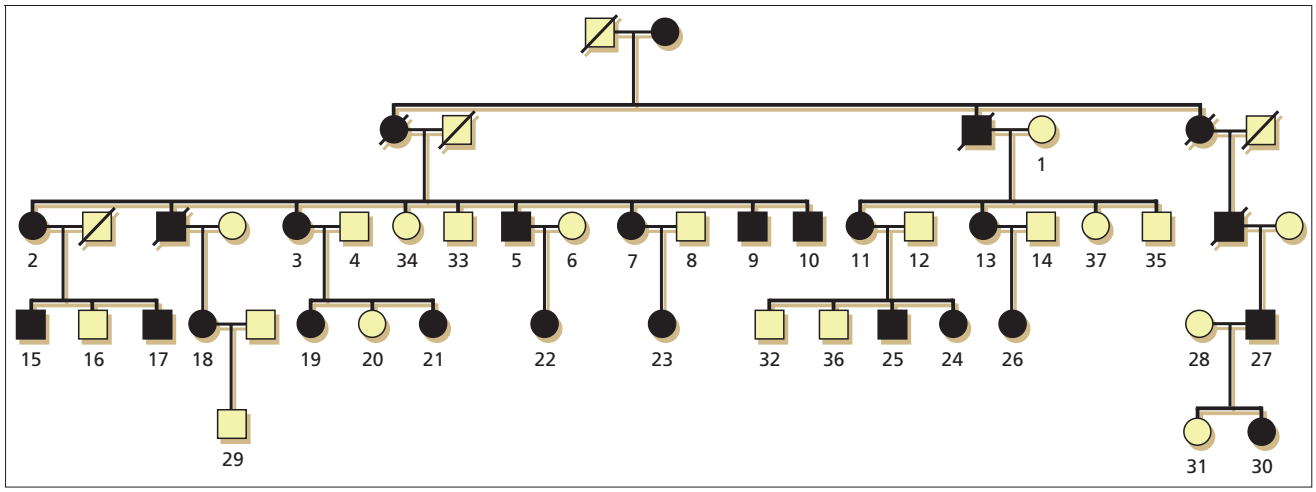


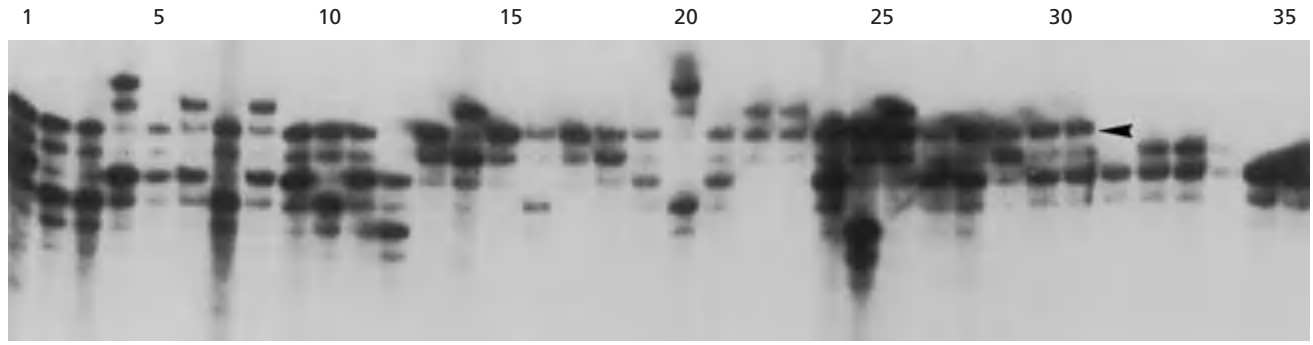
Fig. 8.8 An example of an automated sequence output using fluorescent primers. In this method, each base or primer pair is labelled with a fluorescent dye, the sequencing reaction carried out as described in Fig. 8.7, and the products run in one lane of a gel. A laser beam directed at one point of the gel causes the dyes to fluoresce as the DNA fragments move past, and because the maximum fluorescence occurs at a different wavelength for each of the four dyes, the sequence can be read by computer. (Courtesy of M. Birch-Machin, Department of Dermatology, University of Newcastle, Newcastle, UK.)

thousands of copies of so-called microsatellite DNA dispersed throughout the genome, i.e. at hundreds of loci on each chromosome [4]. These microsatellite loci are each made up of hundreds or even thousands of repeats of a particular core sequence such as $(CA)^n$. The number of repeats is highly variable (polymorphic), such that for many of these loci the chances of an individual's maternal and paternal allele having the same number of repeats is small. Importantly, the DNA outside the repeated sequence is *constant* in all individuals, thereby allowing the design of primer sequences for a PCR reaction. If an individual is polymorphic at one of these loci, PCR analysis using the unique sequence as primer will result in two bands of different length, which can be separated on a polyacrylamide gel: one band originates from the maternal and the other from the paternal chromosome. Analysis using hundreds of such markers up and down each autosome is straightforward and has now been semi-automated. It is now therefore possible with even modest-sized kindreds to track the course of a disease in relation to these markers. If a particular allele at a polymorphic locus always co-segregates with the disease in a kindred, it is likely that the disease is close to that marker (Fig. 8.9).

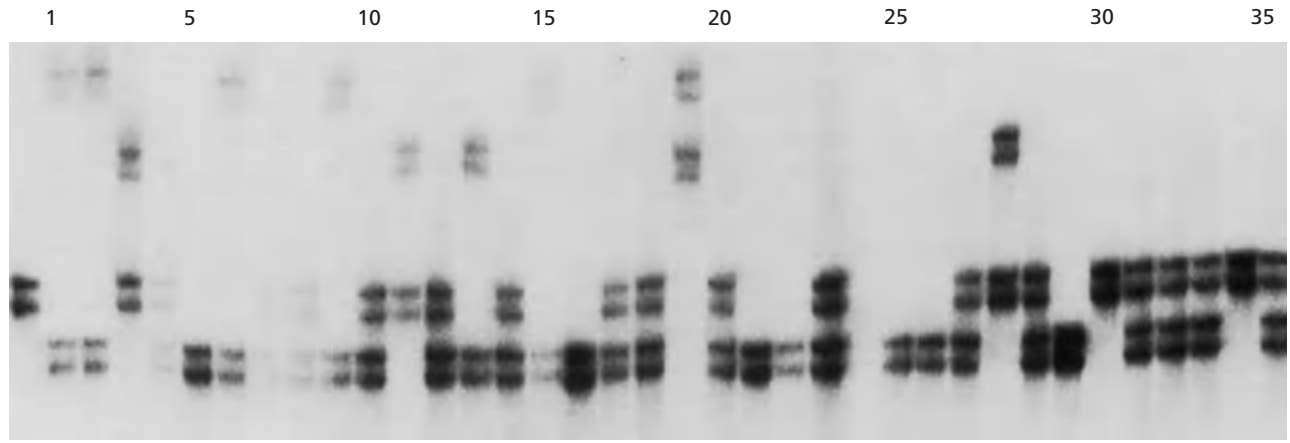
The second direction in which techniques have advanced relates to the ability to take a cloned gene and process it *in vitro* in order to develop functional assays of its function. Although one may associate a particular change in DNA sequence with a particular disease state, at some stage one wants to be able to prove functionally how the mutation leads to disease. The ability to clone DNA in vectors such as plasmids allows the possibility of transferring these plasmids containing the target gene into human cells in the laboratory. If the plasmids are engineered with appropriate regulatory sequences (promoter and related upstream sequences) that will be recognized by eukaryotic cells, the cells may proceed to transcribe genes from



(a)



(b) A A A A A A A A A A A A A A A A A A A A A A A A A



(c) A A A A A A A A A A A A A A A A A A A A A A A A A

Fig. 8.9 Mapping a gene's position using PCR analysis of microsatellite alleles. In this example, a pedigree (a) with pachyonychia congenita was examined with two polymorphic microsatellite markers (b, c) close to the keratin cluster on chromosome 12. The number of persons in the pedigree identify the origin of the DNA samples analysed in the corresponding lane numbers in (b) and (c). Affected individuals in (a) are identified as filled circles or squares, and in (b) and (c) are marked 'A'. For the two markers used, D17S800 (b) and KRT10 (c), most individuals show alleles of different sizes. Arrows mark the position of the allele for each marker segregating with the disease A. Individuals with the disease can be seen always to have an allele of a particular size, suggesting that the disease-causing gene might be close to this marker. Subsequently it was shown that a keratin mutation caused the disease in this kindred (see text). (From Munro *et al*. [20].)

the plasmid in a temporary fashion (*transient transfection*) or, if particular selective markers are encoded by the plasmid, the plasmids may stably integrate into the host nuclear DNA (*stable transfection*). Use of such experimental systems allows examination of the effects of any cloned gene on a cell's phenotype, although experiments can also be performed with different plasmids harbouring different genes, which can then be transfected into the same cells in order to allow an understanding of the various signalling pathways involved in transcriptional regulation of particular genes. In recent years, techniques have moved beyond the ability just to insert DNA into cells in culture to allow the production of transgenic animals, which either carry an additional copy of the gene or, by taking advantage of the presence of endogenous recombinases, allow a particular gene to be deleted. Readers are directed elsewhere for details of these techniques [3]. For instance, imagine one wanted to examine the effects of a particular mutant form of a human keratin gene that had been associated with a particular skin disease. The mutated human gene, once identified, can be cloned and inserted into a plasmid with the appropriate upstream regulatory sequence (promoter), which means that the gene will only be expressed in a particular target situation. Obviously, for this particular experiment one would only wish to express the mutant gene in a physiologically appropriate manner and so ideally its own promoter should be used. Of course it is not necessary to wait for a spontaneous mutant in a human population from which to make a transgenic mouse. One can always mutate a normal human gene and then insert this into a mouse to see what happens. In fact, it was this approach that first suggested that mutations of *K14* or *K5* cause epidermolysis bullosa: transgenic mice in which a mutated *K14* gene was expressed in the basal layer of skin showed a phenotype corresponding to that of epidermolysis bullosa [5].

An added twist to these sort of experiments is that it is possible, by using the appropriate regulatory regions that determine where a gene is expressed, to express a gene in an unphysiological context. This can be experimentally revealing. For instance, β1 integrin is normally expressed in the basal layer of skin, but when transgenic mice are produced in which β1 integrin is expressed suprabasally by expressing the gene under the involucrin promoter, a phenotype resembling psoriasis is seen [6]. Because of the specificity of expression patterns of the various keratin genes, their promoters have been frequently used to regulate the expression of a variety of other genes within skin, including various cytokine genes or oncogenes [7–9]. An alternative transgenic experimental design is that of homologous recombination, in which endogenous recombinases allow wild-type sequence and a mutated vector sequence to be interchanged in embryonal stem cells. These cells can then be used to create chimeric mice, which later can be bred so that they are null for the relevant gene (i.e. they do not have any functional gene on either chromosome) [3]. One difficulty with this approach is that because some gene products serve multiple functions at different stages of development, a null mutation could be embryonically lethal but, given the survival of the embryo, not lethal in the adult. Obviously a knock-out for this gene product would not survive to adulthood and therefore no adult phenotype would be seen. To circumvent this, the technique of CRE-LOX recombination allows a focal knock-out of the gene product (i.e. not in the whole animal) such that frequently the mutation is not embryonically lethal and that some animals will survive into adulthood where a phenotype may be seen in at least part of the animal. Despite the expense and time required, these approaches are extremely powerful, and can go a long way to resolving what the function of a certain gene is at the physiological or whole-animal level or how mutations of a gene contribute to a particular phenotype. This notwithstanding, perhaps the most striking observation in 'knock-out' animals made using homologous recombination is how often such animals are grossly normal. This has inevitably prompted re-examination of the amount of redundancy, and the biological significance of this redundancy, in various biological pathways.

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Strategies for identification of disease-causing genes

Human genetics has sparked a revolution in medical science on the basis of the seemingly improbable notion that one can systematically discover the genes causing inherited diseases without any prior biological clue as to how they function (Lander & Schork [1]).

The spectacular advances in the application of molecular biology to the genetics of human disease have largely been confined to disorders characterized by a simple Mendelian inheritance pattern (such as autosomal dominant or autosomal recessive). Examples include the discovery that mutations in keratin genes can cause a range of skin diseases [2,3] and the identification of *patched* as the tumour-suppressor gene underlying Gorlin's syndrome and sporadic basal cell carcinoma [4–6]. By contrast, for the common dermatoses such as eczema or psoriasis, which show a more complex pattern of inheritance, relatively little progress has been made [7–10]. The reasons for this are obvious: in an autosomal-dominant disorder a single abnormality (in context) is both necessary and sufficient, whereas for polygenic disorders a whole host of genes may interact in a complex way with each other and with the environment. There are two approaches for identifying the causative gene for a disorder that shows a Mendelian pattern of inheritance: positional cloning (originally called reverse genetics) and candidate gene approaches. In many instances, the successful identification of a disease-causing gene relies on a combination of these approaches, and such examples are discussed below.

In the candidate gene approach, a starting point is the suspicion that a particular gene may be implicated in a particular disorder. The candidate gene is then examined for the presence of mutations in an affected kindred. The obvious limitation of this approach is that it only works if understanding of the pathophysiology of a disorder is sufficient to allow a candidate to be identified and if the relevant gene has been cloned. For instance, once the tyrosinase and tyrosinase-related genes were identified, they were obvious candidates to examine for mutation in individuals with albinism or other pigmentary disorders [11]. Mutation detection can be undertaken using a number of strategies, including, of course, DNA sequencing. Often, however, particularly when large genes are examined or a large number of individuals need to be studied, screening techniques are used that, while not providing full sequence information, can detect many, if not all, changes in comparison with the known sequence (e.g. single-stranded conformational polymorphism or heteroduplex scanning) [12]. The disadvantage of the candidate gene approach is that, for many skin disorders, our knowledge of the underlying pathophysiology is so limited that we are unable to identify suitable candidates. Nonetheless, as the technical facility of genetics increases, and knowledge accumulates, this is less of a problem than it once was. For instance, in the previous edition of this book, two examples of this difficulty were quoted: Rothmund–Thomson syndrome and incontinentia pigmenti. Since this previous edition, a combination of research strategies, including testing of likely candidates, has identified genes for these clinical syndromes. Nevertheless, at present the use of mapping and limited positional cloning and scanning of available sequence information remain a useful way of limiting the number of candidates to be examined.

When little is known about the underlying pathophysiology of the disorder, the only viable strategy is that based on positional cloning. This requires a suitable kindred, preferably showing a Mendelian inheritance of the trait, and the use of polymorphic microsatellite markers. Genetic mapping compares the inheritance pattern of the trait with the inheritance pattern of a chromosome region, allowing one to find out *where* a gene is without knowing *what* it is. It is worth remembering, as Lander emphasizes, that in many ways this is the ultimate black box approach [1]. One does not need to know anything about the clinical disorder except being able to diagnose it correctly (a key point, worthy of emphasis); knowledge of the mechanism by which the disease occurs is at least formally superfluous. Although mapping of traits was possible in simple model systems from the beginning of the 20th century, it was only in the 1970s that it was realized that the widespread differences in human DNA (principally the non-coding regions) could form the basis for mapping of human disease [1,13]. Ideally, large kindreds are needed, but if these are not available then it may be possible to analyse several different kindreds, assuming that the same gene causes the disorder in the respective kindreds. This assumption is not always warranted; for instance, mutations of *K5* and *K14* located on different chromosomes both cause epidermolysis bullosa. When numerous loci are examined for linkage to a particular trait, statistical tests are required to determine whether the association between a particular trait and a particular chromosomal position could have occurred by chance. This is conventionally quoted as the log of the odds ratio (lod score), and as a rule of thumb a lod score of at least 3 and preferably higher is required [13]. (A lod score of 3 approaches a similar level of significance as that seen with a conventional statistical test with a value of $P = 0.05$.)

A major brake on the process of gene identification using reverse genetics and subsequent positional cloning had been the difficulty of moving from chromosomal position to the identification of the putative gene underlying the disorder. The Human Genome Project has changed this process considerably. Whereas mapping based on the study of families may pinpoint the disease-causing gene to a couple of million bases, prior to human sequence being available identification of the underlying gene was far from straightforward. For the majority of chromosomal positions this situation has been dramatically improved, because the availability of sequence data allows automated programmes based on bio-informatic algorithms to make predictions about which sequences may code for genes (and which are non-coding), thereby facilitating mutational analysis of candidate genes.

Although candidate gene approaches and positional cloning have been described as alternative approaches, in practice they are often combined, and dermatology has already provided some pertinent examples of such experimental synergism, notably the identification of mutations in keratin genes as the cause of a range of cutaneous disorders. Keratin genes were among the first human genes identified, largely because their expressed RNA represents such a major proportion of the RNA species of a keratinocyte; early cDNA libraries from keratinocytes would consist predominantly of keratin cDNA clones. Similarly, globin was one of the earliest genes identified because it formed such a large part of the RNA species of a red-cell precursor. Despite the high levels of keratin expression in keratinocytes, the raising of antibodies, and numerous studies trying to relate keratin gene expression to disease states, the exact function of keratins remained uncertain. One can imagine two experimental approaches: (i) what disease would result from a mutated keratin ('gene looking for a disease'); and (ii) knowing that keratins are highly expressed in skin, would positional cloning of various skin diseases centre on the known clusters of keratin genes located on chromosomes 12 and 17 ('diseases looking for a gene') [14]? As it turned out, for keratins and epidermolysis bullosa the answer to both these questions was the same, and arrived at within weeks of each other. Mice that had been born harbouring an experimentally mutated keratin showed a phenotype strikingly similar to that seen in epidermolysis bullosa simplex [15]. Almost simultaneously, positional cloning in kindreds mapped the cause of the same disorder literally on top of *K14*, a coincidence too good to ignore [16]. Because *K14* combines with *K5*, it was predicted and subsequently shown that the same phenotype could be produced from mutations in *K5* (even though *K5* and *K14* are located on different chromosomes). Because many keratin genes are clustered on chromosomes 12 and 17, it took little effort to examine whether other inherited blistering disorders might involve other keratin genes. Analysis of kindreds with bullous ichthyosiform erythroderma showed that this disorder also mapped to the keratin cluster and subsequently was found to be due to mutations of *K1* or *K10* [17]. It has been possible to extend this 'phenotypic walking' (by analogy with chromosome walking) even further. Given that bullous ichthyosiform erythroderma is the result of *K1* or *K10* mutations, it was no surprise when ichthyosis of Siemens, a condition with many similarities to bullous ichthyosiform erythroderma, was found to be due to mutations of *K2e* (expression of *K2e* is similar to that of *K1* or *K10*, but more superficial, in keeping with the histological features) [18]. Similarly, some of the cases of palmoplantar keratoderma, where the pattern of blistering is restricted to sites of maximal expression of *K9*, were shown to be secondary to *K9* mutations [19]. However, this process can be taken even further. Patients with pachyonychia congenita show similar involvement of the palms, and a collection of other phenotypic features suggestive of defects in *K17*. Candidate-directed mapping in several kindreds showed linkage to the keratin clusters [20], and pachyonychia congenita has subsequently been shown to arise (depending on the clinical subtype) from mutations of *K17*, *K16* or *K6* [21,22]. Patients with pachyonychia may also show changes in the mouth akin to those of white-sponge naevus and, on the basis of this overlap, mutations of *K4* or *K13* were recently found to underlie white-sponge naevus syndrome [23,24]. Similarly, some patients with pachyonychia have cysts like those seen in steatocystoma multiplex, which in turn can also be caused by mutations of *K17* [25]. Abnormal hair is also a feature of pachyonychia congenita and suggested to some that monilethrix might be secondary to a keratin mutation: candidate mapping studies show that some kindreds of monilethrix do indeed map to a major keratin cluster [26], and the exact keratin gene concerned has recently been identified as that encoding for the hair cortex keratin hHb6 [27]. One could hazard a guess that the keratosis pilaris seen in monilethrix might mean that keratin mutations underlie some independent cases of keratosis pilaris. And so the process continues. The speed at which researchers have uncovered the genes responsible for so many cutaneous disorders attests to the power of the combination of mapping and candidate approaches. There are other examples that one could quote, including the identification of *PAX* mutations as a cause of some cases of Waardenburg's syndrome that relied on the combinations of candidate genes from the mouse and took advantage of the fact that many areas of human chromosomes show syngeny with the mouse (the location of genes on certain chromosomal regions is the same or similar in the mouse and human) [28,29]. Conversely, just as localization of a gene to a particular area followed by examination for possible candidates in this area can speed up the identification of disease-causing genes, it is possible using mapping approaches to quickly exclude some genes as the cause of a disease. For instance, it was always possible that keratin mutations could underlie Darier's disease, yet mapping studies quickly allowed these candidates, like some cell adhesion molecules, to be excluded from consideration [30,31].

Until recently, in the absence of a candidate gene, one of the bottlenecks in the identification of disease-causing genes was the difficulty moving from chromosomal position, which might encompass up to 10 million bases, to identification of the disease-causing gene. This is very much like searching for a needle in a haystack, as the majority of this DNA will be non-coding. These problems, however, have diminished considerably in recent years. This is partly due to a number of collaborative ventures that have made life easier for the experimental gene hunter. First, the number of informative polymorphic markers

spaced at appropriate intervals along the chromosome has increased considerably. Second, there have been concerted attempts to sequence expressed DNA sequences from a variety of tissues and map those expressed sequence tags (EST) to chromosome position [13]. Finally, sequencing of the genome and integration of the sequence with polymorphic markers will allow researchers to move quickly from candidate region to testing for causative mutations in candidate genes in that chromosomal region.

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Complex traits

The term 'complex trait' describes any pattern of inheritance of a phenotype that does not fit a classic Mendelian pattern [1]. Examples in dermatology include atopic eczema and psoriasis. In an absolute sense, the distinction between complex and simple traits is artificial, as even a disorder with an apparently straightforward pattern of inheritance, such as epidermolysis bullosa simplex or Darier's disease, may show variations of clinical phenotype between affected individuals that are the result of other modifying genes or differences in environmental exposure. Nevertheless, the distinction is worthwhile.

Most common skin diseases do not follow a straightforward Mendelian pattern of inheritance. Whereas positional cloning of Mendelian traits has had considerable success, genetic analysis of complex traits is still in its infancy [1]. In some instances, there have been reports of genes that have been thought to underlie particular complex disorders, for instance the major psychiatric conditions, but further work has failed to replicate earlier results. One can see that if a disorder is due to mutations at a number of different loci (i.e. it is polygenic), the influence of any one particular loci will tend to be modest, and conventional linkage analysis may be of limited utility. There are, however, alternative strategies that are being pursued for eczema, psoriasis and other disorders [1,2]. For instance, allele-sharing methods tend to be more robust than linkage analysis, because no underlying model of inheritance is assumed. In allele-sharing methods, one tries formally to demonstrate that the inheritance pattern of a chromosomal region is *not* consistent with random Mendelian segregation (by showing that affected relatives inherit identical copies of the region more often than one would expect by chance). Examples of allele-sharing methods include affected sibling-pair analysis, where the frequency of sharing of particular regions is only compared in siblings affected with the disease (avoiding the problems of incomplete penetrance). Of course, for complex disorders the problem of moving from highlighted chromosomal region to the actual gene is considerably

more difficult than in highly penetrant disorders. This is because co-segregation of a marker and the disease may not be absolute; rather, one has to work with statistical confidence intervals. This raises the question of the number of individuals that need to be examined, because of the absence of the all-or-nothing principle of a gene that is both necessary and sufficient for a particular disease. In this situation, a variety of other strategies including linkage disequilibrium mapping may be needed. Alternative strategies include association studies, which are in effect case–control studies based on the presence of a particular allele in affected and unaffected individuals, for example the association of human leukocyte antigen (HLA)-Cw6 with psoriasis [3]. A recent example of this approach has been the report of an association between particular alleles of the melanocortin 1 receptor and red hair and skin type I [4]. Pedigree analysis suggests that the inheritance of skin colour or hair colour does not follow a classic Mendelian pattern, and therefore pursuing a linkage analysis approach may be difficult. However, if a candidate gene exists, as was the case in this instance, then it is possible to measure the frequency of particular alleles in those with a particular hair colour or skin type. Obviously, the weakness of association studies compared with positional approaches is that for an association study to be performed a clear candidate has to be known. With regards to the association between melanocortin 1 receptor gene variants and red hair, a considerable body of evidence in the mouse and other species suggested that this receptor was a strong candidate for a pigment-determining gene in the human [5,6]. However, there are also significant methodological hazards as for all case–control studies. For instance, any association between melanocortin 1 receptor variants and skin type or hair colour might be confounded by the fact that both the cases and controls may be drawn from different populations. For instance, because those with Celtic ancestry are more likely to have skin type I, any differences between skin type I and skin type IV individuals might reflect other confounding differences between Celtic populations and non-Celtic Anglo-Saxon populations.

How successful, or clinically relevant, the identification of genes that underpin complex disorders such as eczema or psoriasis will be is a topic of debate. The fundamental issue is that of penetrance, i.e. the relation between a particular allele and phenotype. On the one hand, there are those who believe that complex diseases require scaled-up versions of the techniques that have been very successful in the study of Mendelian disorders. This approach admits that the penetrance is lower, but argues that this can be compensated for by larger sample sizes and the range of techniques based around association studies or sibling-pair studies. On the other hand, there are those who argue that many commentators have exaggerated the genetic component to these disorders, at the expense of the environmental precipitants, and more importantly have used inappropriate models to attempt to partition nature and nurture [7]. There also remains a confusion between the use of odds ratios or relative risks and the predictive value of a test. Alleles that carry a moderately increased relative risk (say of three to five) may be interesting mechanistically but will have limited, if any, use as a predictor of clinical state. Interested readers are directed to the articles listed below [8–10].

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Cancer genetics

Molecular biological approaches to understanding the mechanisms underlying cancer, particularly the relation between genotype and phenotype, have been particularly fruitful [1,2]. Interest in the molecular biology of cancer not only reflects the importance of the disease to human health overall but also the intrinsic interest in many of the physiological processes that are deranged in the cancer cell, including cell-cycle control, cell proliferation and differentiation, and the control of cell death. Molecular biological approaches have led to a new conceptual understanding of the genetic contribution to cancer, which can be summarized as follows. First, cancer is a genetic disease in which the accumulation of multiple genetic abnormalities, coupled with the selection of cells for a more and more malignant phenotype, leads to, and correlates with, the clinical behaviour of the tumour. Second, the underlying defective pathophysiological mechanisms in a wide range of human cancers are similar, and increasingly can be seen to relate to a few key cellular pathways, many of which appear to influence whether a cell cycles or not. Third, the same genes are often involved in sporadic tumours as in inherited tumours; for instance, the same gene *patched* is important in Gorlin's syndrome and in sporadic basal cell carcinomas (in the former one

germ-line allele is mutated and the other inactivated somatically, whereas in the latter both alleles are inactivated somatically) [3–5].

Genetic abnormalities in cancer cells can be classified into two types: oncogenes and tumour-suppressor genes [6,7]. Oncogenes are cellular genes that, when mutated, push the cell towards the adoption of a malignant phenotype. In genetic terms they are dominant, and therefore only one mutated copy per cell is enough to observe a different phenotype. Oncogenes were originally identified in animal models in which host genes had been hijacked by viruses and mutated. When these viruses infected animal cells, they contributed towards the adoption of a malignant phenotype. Although the heuristic value of this experimental paradigm has been considerable, and within animal models of cancer viruses are not infrequently implicated, in humans the association between viruses and cancer is weaker, and where it exists, it may not be because viruses harbour oncogenes. Early functional assays for oncogenes relied on extraction of DNA from a tumour, and then transfection of this DNA into cells that had been manipulated experimentally such that they were on the verge of neoplasia. If an oncogene were present, clones of these cultured cells would progress and adopt a malignant phenotype, which could be assayed on the basis of phenotypic characteristics (such as colony formation in soft agar). This sort of assay system is cumbersome, and many more oncogenes in human cancers have been identified either on the basis of homology to known oncogenes in other animal systems or by candidate approaches based on their physiological role. Mutations in oncogenes are rarely involved in inherited cancer syndromes, and appear uncommon in both melanoma and non-melanoma skin cancer. An exception has been the recent report of mutation of a cyclin-dependent kinase in two kindreds with familial melanoma [8]. This finding is of great interest, as it is complementary to the defect seen in the tumour-suppressor gene *p16*, itself a commoner cause of familial melanoma. Cyclin-dependent kinases are important in allowing progression through the cell cycle; *p16* normally acts as a physiological inhibitor of cyclin-dependent kinase, and thus mutations of *p16* remove a brake on cell-cycle control. In families with melanoma harbouring a mutated cyclin-dependent kinase, the kinase is unable to bind *p16*, the net result being functionally equivalent to an absence of *p16*; the difference is that whereas *p16* is recessive, mutation of cyclin-dependent kinase is dominant. Oncogenic mutations of the *ras* family of genes, genes coding for proteins that play a key and wide-ranging role in many signalling pathways, have also been described in both sporadic melanoma and non-melanoma skin cancers [9]. By contrast, abnormalities in the other class of tumour-related genes, namely tumour-suppressor genes, appear far more common in most epithelial malignancies [2,7], including skin cancer [10], and have also been implicated in inherited cancer syndromes involving melanoma and basal cell carcinoma [9,10]. A tumour-suppressor gene is a gene that, when functioning normally, acts so as to protect against the development of the malignant phenotype—the product of the gene possesses *tumour-suppressing* activity. As with oncogenes, many of these genes appear to be involved in interactions with regulatory proteins controlling the cell cycle. Unlike oncogenes, tumour-suppressor genes are (at the level of the cell) recessive, in that homozygous mutation is required for them to lose their normal physiological role. Of particular importance has been the discovery that the same tumour-suppressor genes are frequently implicated in sporadic and familial tumours; mutations of *patched* are the cause of Gorlin's syndrome and sporadic basal cell carcinoma [5].

One aspect of tumour-suppressor genes that is not self-evident is that although these genes are recessive at the level of the cell, when examined in a kindred the trait appears dominant. Based on observations of the epidemiology of retinoblastoma, Knudson [11] proposed a model in which a critical step in the development of tumorigenesis required the inactivation of both maternal and paternal alleles of a particular gene. Importantly, he showed that in an individual inheriting one faulty gene, a second 'hit' leading to loss of the remaining allele (in any particular gene) was far more likely to occur than in an individual who had inherited two wild-type genes. Implicit in this hypothesis was that the same genes were involved in familial and sporadic cancer [11]. This model is illustrated in Fig. 8.10. In Gorlin's syndrome, for instance, those with a family history inherit one abnormality in every cell in the body. If a second hit or mutation occurs (hence the name 'two-hit hypothesis') and if other genetic events are also present, then a tumour may result. In an individual who does not inherit one abnormal copy, a tumour may still result, but in this case both maternal and paternal alleles would have to be somatically inactivated, an event far less likely to occur. This explains why tumours are more common in those who inherit one faulty allele through the germ line. It is of interest to dermatologists that the origin of this idea was first proposed over 50 years ago in order to explain certain aspects of experimental skin carcinogenesis in the mouse [12].

There are a number of mechanisms by which a tumour-suppressor gene can be inactivated: the gene may be mutated; viral proteins may interact with the tumour-suppressor gene product, targeting it for degradation (as happens with some human papillomaviruses); or, quite commonly, the area of the chromosome harbouring the gene may be lost [13,14]. This loss of genetic material can be easily detected using polymorphic PCR microsatellite markers identical to those used in positional cloning, so that instead of two bands—one representing the maternal chromosome and the other the paternal chromosome—

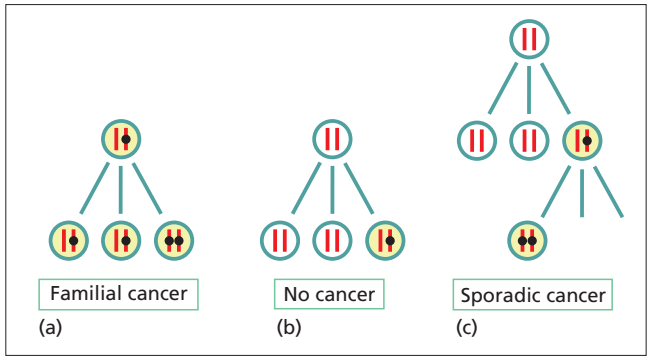

Fig. 8.10 Knudson two-hit hypothesis. Based on the epidemiology of retinoblastoma, Knudson hypothesized that the same genes were involved in familial cancer as in sporadic cancer and that they were recessive at the cellular level—two hits were required to observe a phenotype. Gorlin's syndrome appears to fall into this tumour-suppressor paradigm. A member of a Gorlin's kindred inherits one abnormal germ-line allele (*patched*) in every cell (a). Because tumour-suppressor genes are recessive at the cellular level, the phenotype of all the somatic cells is normal until the remaining wild-type allele is mutated. Once both alleles are inactivated, a rate-limiting step for cancer development has been passed. By comparison, in an individual with no cancer predisposition (b), both germ-line alleles are normal; if an occasional cell undergoes inactivation of one allele, no phenotype will be seen. For a tumour to develop without an inherited predisposition (c), both alleles would have to be inactivated somatically, an event orders of magnitude less likely to occur. This model explains why the frequency of basal cell cancer (in this example) is so much higher in a Gorlin's kindred than in ordinary individuals. Note that despite the gene being recessive at the cellular level, the trait is inherited as a dominant.

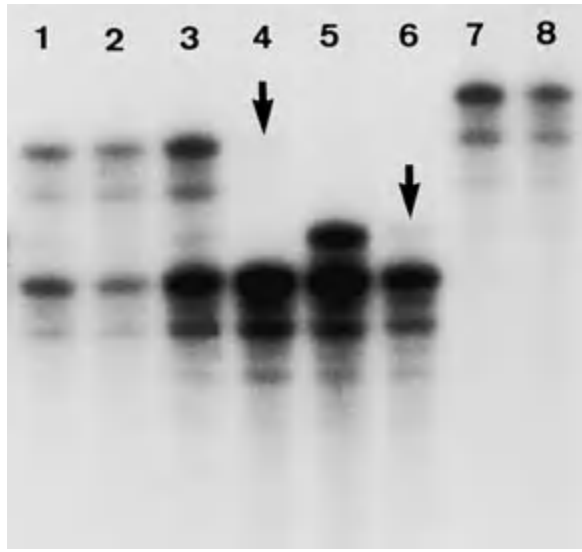

Fig. 8.11 An example of loss of heterozygosity in skin cancer. Polymorphic microsatellite markers have been used to compare tumour and normal skin in order to determine whether chromosomal areas have been deleted. In normal tissue two bands, one maternal and one paternal, are seen. By contrast, in two of the tumours one allele has been deleted (marked ↓; compare tracks 3 and 4, and 5 and 6). The remaining allele is likely to be inactivated by point mutation or by alternative mechanisms.

being visible in the tumour, loss of one allele will be evident as loss of one band (Fig. 8.11). Rarely both alleles will be lost, although it is more common for both alleles to be inactivated by different mechanisms. This loss of genetic material, which is referred to as loss of heterozygosity, is one of the major methods by which tumour-suppressor genes may be identified. There are therefore at least two approaches to the identification of new tumour-suppressor genes. First, one can study an affected kindred and, using conventional positional cloning with polymorphic markers, look for alleles that segregate with the tumour cases. Alternatively, one can study sporadic tumours (tumours occurring in individuals without any family history) and examine DNA for areas of loss of heterozygosity. These approaches of course can be combined, as was the case for the identification of the gene *patched*. Early loss of heterozygosity studies suggested that a candidate gene for basal cell carcinoma resided on chromosome 9q, and subsequent linkage studies in kindreds with Gorlin's syndrome supported these observations. By using positional cloning methodology together with the study of patients harbouring deletions, the underlying gene was cloned (reviewed in [10]). The advantage of loss of heterozygosity studies is that it is not necessary to know the target gene, whereas to detect mutation one obviously needs to know the gene that one wishes to sequence or screen for mutation. On the other hand, loss of heterozygosity is quite common in many epithelial tumours, and it is by no means proven that every area of loss corresponds to a relevant tumour-suppressor gene. Another caveat is that it is still not clear why in certain circumstances the gene is inactivated by mutations, whereas in others inactivation is due to loss of chromosomal material. For instance, in some melanoma kindreds *p16* mutation is common [15], whereas in sporadic melanomas *p16* point mutation is rare (although loss of heterozygosity of the relevant area of chromosome arm 9p is common) [13,16]. It seems possible that for melanoma, as for some other extracutaneous tumours, inactivation of *p16* may occur by changes in methylation status of the gene rather than through any of the mechanisms discussed above. Finally, notwithstanding Knudson's hypothesis, the effects of germ-line inactivation may be very different from those occurring somatically, and the parallel between familial and sporadic tumours may break down.

Besides oncogenes and tumour-suppressor genes, a third category of gene is of relevance to human skin cancer. There are well-known associations between sebaceous carcinoma and a variety of systemic malignancies, particularly colorectal cancer (Muir–Torre/Lynch syndrome) [17]. Work over the last several years has shown that a particular group of genes involved in DNA repair (but

distinct from those genes involved in xeroderma pigmentosum) are important in these disorders [18]. Studies mapping particular forms of non-polyposis coli hereditary colorectal cancer have shown that the microsatellite sequences seem to be frequently abnormal in length, with additional bands being seen following PCR. Positional cloning and candidate gene approaches have shown that a number of human homologues of mismatch repair genes in *Escherichia coli* are at fault in these kindreds, resulting in a decreased ability to repair a particular type of base change. Although these changes in the microsatellite sequences, which originally signalled, and provided insight into, the basis of this disorder, are unlikely to be functionally significant, such failures to repair normal genes, particularly those that have oncogenic potential [19], are thought to contribute to the development of the malignant phenotype.

The rate of identification of cancer-causing genes has intensified. Sequencing of the human genome has also allowed newer approaches. For instance, mutations of the gene *BRAF* have recently been found in over half the malignant melanomas examined. The protein product of this gene is part of the Ras signalling pathway involved in cellular signalling. Identification of this gene followed the new approach based heavily on use of sequence data. Rather than sequencing the whole genome from the tumours, the key signalling pathways were prioritized, and sequencing of all the known genes in these pathways undertaken and compared with germ-line sequence [20].

In broad terms, there seems to be an important correlation between the frequency of genetic abnormality and the clinical behaviour of the tumour [2]. For instance, based on the sorts of analysis described above, it is easy to distinguish between benign tumours such as seborrhoeic keratoses and squamous cell carcinomas, or alternatively between squamous cell carcinomas, keratoacanthomas and basal cell carcinomas [21,22]. However, there are exceptions to this rule that are of interest. For instance, actinic keratoses, despite their relatively banal clinical course, frequently show a greater degree of genetic instability than that seen in squamous cell carcinoma [23]. The explanation for this is not clear at present.

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Putting it all together and future trends

Perhaps one of the most astonishing aspects of the growth in technical prowess of molecular biology has been the way in which, from initial 'boot-strapping' methodology, there has been a rollercoaster of more powerful experimental techniques, allowing increasingly precise and ambitious questions to be answered. For instance, when a gene for a particular disorder has been identified using positional cloning methodology, it is frequently possible to obtain a good idea of the function of that gene, based on either sequence similarity to genes previously identified or knowledge about similar genes in model organisms such as *Drosophila*, mouse or yeast. For instance, *patched*, the gene underlying the naevoid basal cell carcinoma syndrome, once identified, was shown to have a homologue in *Drosophila*, while work in this 'model organism' had already provided important insights into the protein's cellular localization and participation in various signalling pathways [1,2]. As an increasing number of genes and

proteins are characterized and stored in online sequence databases, the power of this process increases. Identification of new genes that do not bear some sequence similarity to known genes is going to become uncommon at some stage. In one sense, the converse of this approach is the way in which sequence similarity may be used to identify new genes. For instance, a whole new family of steroid/thyroid/retinoid hormone receptors have been cloned following screening of cDNA libraries using the oestrogen receptor as a molecular probe [3,4]. The basis of this assay is that complementary pairing between different strands of DNA, if the conditions of hydrogen bonding are relaxed and 'tolerant', can be used to identify not just identical sequences but sequences with varying degrees of similarity. Complementary DNA libraries can therefore be screened with one particular receptor as a probe in order to find 'relatives' of that receptor. PCR analysis allows a different and complementary approach to this procedure: with limited knowledge of the important functional domains of a molecule, degenerate PCR primers can be made that will then amplify homologous sequences from cDNA. This technique has been widely used to identify further members of the transmembrane seven-pass G-protein-coupled family of receptors such as the melanocortin receptor family [5]. The availability of sequencing data from the Human Genome Project has now allowed analogous prediction based on what is described as *in silico* experimentation: human sequence can be screened using a variety of bio-informatic techniques in which expressed sequences can be predicted and similarities to known gene products scored and putative functions suggested.

The ability to transfect genes into cells under experimental conditions has also led to the development of a myriad of experimental techniques [6,7]. For instance, a cDNA of interest may be transfected into cultured cells simply to obtain large amounts of the resulting protein for further analysis. Alternatively, the function of the protein can be studied by examination of changes in behaviour of the cultured cells. Mutated genes, either spontaneously occurring or constructed in the laboratory (usually using PCR-based techniques), can also be transfected, and the influence of these mutations used to map out important domains of the protein's function. A similar assay can be used to study the upstream regulatory regions that are important in controlling a gene's expression. Key regulatory sequences upstream of a gene's start site can be placed in a plasmid vector and transfected into cells. The gene's product itself can be assayed, or more often the gene of interest can actually be replaced with a gene called a 'reporter' that lends itself to experimental analysis. For instance, if one is interested in studying the regions upstream of a gene that are important in determining its expression (i.e. the regions of the promoter that mediate binding to a variety of other cellular proteins and signalling pathways), then one can clone this particular region of the genomic DNA, attach it to a reporter gene that codes for a fluorescent material such as luciferase, and transfect this into cells. The cells can then be treated with a variety of agents to discover whether they are able to induce, or alter, transcription of the reporter gene acting through the promoter sequence under experiment. Such approaches can also be carried out not just in transfected cells but also in transgenic mice, where the natural promoter region of the gene or one that has been experimentally manipulated might be attached to a reporter, a transgenic line created, and the resulting expression pattern studied in mouse embryos. Usually, this system makes use of the expression of β-galactosidase, resulting in (with appropriate development) a blue colour throughout the areas of the embryo where the promoter region is active.

Once a gene is identified, either through positional cloning techniques or from screening based on homology as described above, a number of techniques facilitate studies of the gene's expression and function. Northern blotting relies on complementary base pairing between the strand of the cDNA or RNA used as a probe and the endogenous RNA that one wishes to detect. An application with widespread use in dermatology, and related to Northern blotting but carried out on tissue sections, is *in situ* hybridization. Instead of the hybridization taking place on membranes, tissue sections are prepared and exposed to a cDNA or RNA probe, which is tagged with either a radioisotope or a colour label (as used in immunocytochemistry), and the experimental conditions manipulated such that where there is base pairing between the probe and the target, RNA signal is detected. If radioactive detection systems are used, the probe is labelled with an isotope such as ^{35}S, and the β particles emitted can be detected by dipping the slide (following hybridization) into a radiographic emulsion and waiting for development of the latent image. The end result is that where the probe has sought out and bound to target RNA, silver grains will be seen in the emulsion overlying the cell. Alternative detection systems have also become increasingly popular, particularly those based on the development of colour substrates that allow a more precise cellular localization and also avoid the hazards of working with radioisotopes. In many ways, these colour-detection systems are similar to those familiar from immunocytochemistry, only in this instance the cDNA or RNA probe is actually labelled with a molecule that subsequently binds to antibodies, which are usually in turn attached to other detection reagents. Using this approach, it is therefore possible to study RNA expression using fluorescence or other systems such as biotin and streptavidin, or digoxigenin [7,8] (Fig. 8.12). One particular strength of *in situ* hybridization is that it provides anatomical information about the control of gene expression at the level of

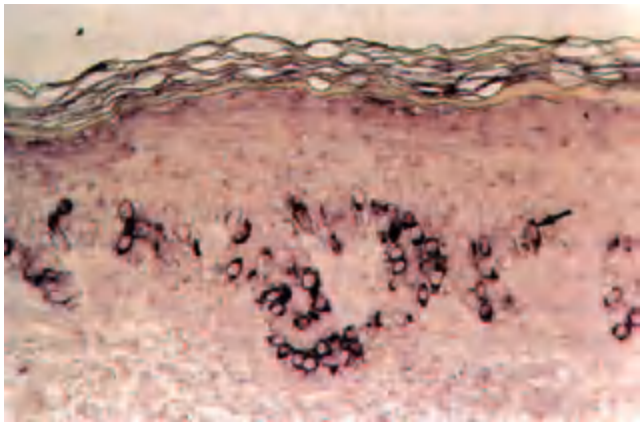

Fig. 8.12 Examples of *in situ* hybridization using a probe that detects histone mRNA, which is expressed during the S phase of the cell cycle. The probe has been labelled with digoxigenin, which affords excellent resolution. The dark stain visible within the lower compartment of the epidermis corresponds to RNA detected within the cytoplasm of the keratinocytes. (Reprinted with permission from Fisher *et al*. [8].)

RNA; in some instances, the gene can be transcribed into RNA but, perhaps surprisingly, little protein may be made. By contrast, immunohistochemistry detects protein expression, and therefore the two techniques can be considered complementary. Molecular biological techniques have also altered antibody technology and consequently the way in which the distribution of cellular proteins can be studied using immunochemistry. For instance, target antigens necessary for the development of polyclonal or monoclonal antibodies can now be made by transfecting the cDNA coding for the desired protein antigen and purifying the resulting overexpressed product [7]. Alternatively, once the cDNA structure is known, short stretches of oligonucleotides can be synthesized and used to immunize mice. Humanized antibodies, which are less immunogenic, can now be made and because they do not attract an immune response themselves may be of therapeutic use. Techniques such as *phage display* bypass the need for immunization of mice or hybridoma technology [7]. Identifying the molecular targets of naturally occurring antibodies is also more straightforward. A collection of cDNAs such as those present in a cDNA library can be cloned into, and expressed on the surface of, bacteriophages. The phage expressing the appropriate antigen can be selected using the antibodies (of unknown specificity) and the phage expressing the particular cDNA purified, allowing identification of the cDNA sequence coding for the antigen to which the antibody has bound [7].

As the pace of mapping and discovery of disease-related genes increases, researchers are increasingly looking to the next stage ahead—what has been referred to as the 'post-genome era'. There are several reasons for this, apart from the continual obsession with technical facility that has characterized the development of molecular biology. First, the rate of mapping of disorders with a defined pattern of Mendelian inheritance is now moving at such a pace that virtually all that limits further progress is the identification of suitable kindreds. Many of the required experimental procedures are already partially automated. It seems likely that the majority of these disorders will therefore be mapped within the next few years. There is also optimism (expressed by some but not all) that even those disorders that show a more complex pattern of inheritance, such as eczema or psoriasis, will also fall to currently available technologies. The identification of the relevant genes should quickly follow identification of the target chromosomal areas, due to rapid progress in sequencing of the human genome and the now industry-led process by which random cDNAs from a variety of cell types are being sequenced and mapped.

However, perhaps the most pressing force driving change is the desire to narrow the gap between the identification of disease-causing genes and the development of therapeutic agents. It is worth remembering that, maybe with the single exception of gene therapy (discussed below), there is no obvious formal scientific procedure that connects the identification of the gene underlying a disorder with the development of a useful and safe pharmacological agent. Of course, one of the great strengths of positional cloning is its ability to identify the gene underlying a particular disorder, based solely on the gene's chromosomal position rather than on any prior knowledge of its physiological or pathophysiological role; this undoubted strength is of little help as far as therapy is concerned. In some instances, however, cloning of the gene does have immediate clinical implications: identification of the genes underlying the inherited bullous disorders means that prenatal diagnosis has become a reality; and identification of the gene underlying the naevoid basal carcinoma syndrome allows identification of those individuals in a kindred at risk prior to the development of the clinical phenotype. For carriers of highly penetrant genes, modification of lifestyle may be appropriate, as for carriers of *p16* mutations who are at high risk of melanoma.

There are other ways in which gene identification improves clinical practice. For instance, it is likely that the apparently heterogeneous group of non-blistering ichthyosiform erythrodermas, some of which are due to transglutaminase mutations [9] and some of which appear not to be, will be classifiable on a more rational basis, once analysis of the separate genes allows a gold standard for measuring genotype against phenotype. This is not to imply that there are no polygenic or environmental influences on the phenotype, such that identical genotypes cannot give rise to different phenotypes or conversely that the same phenotype, as is seen with epidermolysis bullosa, can be due to mutations in different genes.

Although the emphasis in this chapter has been on eukaryotic genetics, rapid progress in prokaryotic genetics also directly impinges on clinical practice. Using PCR-based assays, both in theory and in practice, only one copy of the gene or a single microorganism is required to allow precise identification based on the specificity of amplification of genomic material of the putative infectious agent. PCR-based diagnosis of infectious disease is therefore particularly helpful when the causative microorganisms are relatively inaccessible and present in low numbers, and can implicate viral infection even in the absence of visible viral particles or the ability to culture the virus. For instance, using molecular techniques a novel DNA sequence, related to that of various herpesviruses, was identified in Kaposi's sarcomas from human immunodeficiency virus (HIV)-positive individuals [10]. Subsequent work has implicated a causal role for this virus in Kaposi's sarcomas from both HIV-positive and HIV-negative individuals [11,12]. DNA from mycobacteria or viruses such as human papillomavirus can also be readily detected using PCR techniques. An added bonus is that these techniques can be applied not just to fresh material but also to paraffin-embedded histopathological material that has been routinely collected, and studies can therefore be carried out retrospectively. The extreme power of PCR to amplify starting material many millionfold can also be a weakness, as contamination from other samples or the operator is a significant hazard. Finally, cloning of human genes allows the production in prokaryotes of recombinant pharmaceuticals, such as interferons, and vaccines by genetic engineering.

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Future strategies

Future work relating to the development of new therapeutic strategies lies in two directions: first, the detailed characterization of differences in gene expression; and second, gene-based therapies. In what is becoming known as the 'post-genome era' there are the beginnings of attempts to develop generic and automated approaches to the identification and description of gene expression in different cell types. Just as it has been possible for a number of years to use gel electrophoresis to represent (to a limited degree) the pattern of protein expression in a particular cell type, molecular strategies based on RNA can be used to represent in a global way the activity of a particular cell. One approach has been to use a technique called differential display, which relies on random (or at least almost random) PCR primers being applied to cDNA, with the result that with different combinations of primers thousands upon thousands of bands can be represented on the gel, each of which relates to a particular RNA species [1]. This technique can be used to attempt to identify differences in gene expression between cells from different tissues, or following treatment of a particular cell type with an experimental agent. Bands that are differentially expressed can then be cut out, cloned and the gene studied.

Two overlapping, but complementary, techniques have been developed and are revolutionizing the study of gene expression in biomedicine. The first is known as serial analysis of gene expression (SAGE) [2]. SAGE attempts to describe quantitatively the total production of RNA from a particular group of cells. This technique relies on the specificity of restriction enzymes, and the location of these restriction sites within different cDNA species, to allow one to concatenate small parts of RNA into larger arrays that can then be sequenced. By analogy with computing technology, these 'digtags' (digital tags) can then be counted and estimates made of the proportion of a particular RNA species compared with the total amount of RNA produced by a cell.

An alternative technique, based on advances in the 1990s at Stanford University, has been the development of microarray technology. This technique involves plating at high density a large number of cDNAs on glass slides. Subsequently, target RNA can be fluorescently labelled and hybridized to the glass slides and the signal read as fluorescent intensity. Because there is more than one fluorescent label, the relative intensity of RNA from different tissues or cells that have undergone an experimental intervention can be hybridized at the same time and the readout quoted as the ratio of expression in one sample to that in another (based on the ratio of fluorescence for each probe). This allows the characterization of gene expression from cells in culture or from tissue. For instance, a recent example of this approach has allowed

the gene expression pattern for a large number of genes to be studied in patients with melanoma. With appropriate statistical techniques, the pattern of expression of hundreds of genes has allowed prediction of prognosis beyond that obtained from other conventional histopathological or cell biological variables [3]. As with other recently described techniques aiming to characterize the RNAs produced by a particular cell type, the emphasis is on a generic approach that can be applied to different cells and tissues in different situations, and that facilitates the move from gene back through biochemistry to pharmacology.

Thinking specifically of therapy, there are clear alternative, and perhaps complementary, strategies being pursued. For instance, the development of new small-molecule pharmacological agents is now heavily dependent on molecular biological techniques. In fact, many of the systematic attempts at cloning RNAs from different cell types are being carried out by pharmaceutical companies. The identification of genes, the ability to study gene expression and the ability to produce large amounts of the protein experimentally all facilitate functional studies of protein activity, identification of key domains and characterization of protein structure by crystallography. The identification of the myriad of receptor isoforms for many receptors offers new targets for small-molecule design. The ability to model disease processes in animals also aids pharmacological intervention. For instance, transgenic mice in which the β1 integrin receptor has been placed under the control of the involucrin promoter (resulting in aberrant expression of β1 integrin) have recently been proposed as an animal model of psoriasis [4]. The production of knock-out mice that are null for a particular retinoic acid receptor means that it is possible to study the physiological role of these receptors and their ligands, and also to infer how pharmacological agents with known efficacy are actually working [5]. The approach that not surprisingly has attracted the most attention, and for some raised the greatest hopes, has been the development of therapies directly involving nucleic acids. Defective genes are either replaced or supplemented with a correctly functioning gene, or the products of particular genes antagonized by the introduction of antisense DNA or RNA. Some of these approaches are discussed below.

Gene therapy

Gene therapy describes a range of technologies that have in common the treatment of disease based on the introduction of genes or nucleic acids (including oligonucleotides). Despite the considerable media attention, success has been limited and most work has concentrated on the development of the technology and toxicity assessment [6–8]. Most observers believe that the only unequivocal success for gene therapy has been in the treatment of X-linked severe combined immunodeficiency. However, two children who have been treated with retroviral vectors for this disorder have gone on to develop leukaemia. It seems likely that there is a causal relationship between the therapy and the development of the leukaemia and this finding has caused concern and a slowing down of clinical trials of similar approaches. Nevertheless, the field is young and there are a host of experimental strategies being applied. Some think that cutaneous disorders will lend themselves to gene therapy because of the skin's accessibility and the ability to culture keratinocytes and fibroblasts, treat them *ex vivo* and then reimplant the cells after genetic modification [9,10]. The majority of gene therapy trials so far have been concerned with cancer and many of these have involved gene therapy for melanoma [6]. The exact scientific rationale underlying some of the studies is not always obvious; indeed, where an experimental effect has been seen, it is not always clear why.

Genetic material may be passed to the cell of interest either *in vivo* or *in vitro*. With *in vitro* gene therapy, cells from the individual are cultured, and genetic modification is carried out *in vitro* before returning the cells to the patient. With *in vivo* gene therapy, the manipulation occurs *in vivo*. There are a number of different experimental strategies under consideration. First, it is necessary to dispense the genes or genetic material in an appropriate vector or transfer material. Although naked injection of DNA has been used in experimental animals, and perhaps surprisingly appears to result in low-level transient gene expression, more promising is the use of retroviruses or adenoviruses as targeting vectors. Alternatively, naked genes may be applied within liposomes, which are then taken up by target cells. This latter approach might seem to have considerable potential as far as skin disease is concerned [11]. An alternative strategy is to use antisense oligonucleotides (antisense because they are complementary to the normal sense), which would be expected to bind to the normal-sense RNA for a particular gene and consequently interfere with translation. Despite the theory, and even with appropriate controls, in some experimental systems the effects of such antisense therapy are not always as intended. Antisense genes can also be inserted into vectors such that when they are transcribed (into RNA), they are complementary to the normal wild-type RNA product and therefore might be expected to reduce protein expression. It is even possible to design genes that code for intracellular antibodies, which within the cell could be expected to inactivate particular target proteins.

There have been a number of different approaches suggested for gene therapy of cancer, many of which have been tried on melanoma because of the highly antigenic nature of many human melanomas [7,10]. For instance, it may be possible to insert genes into cancer cells that render the cells sensitive to a particular drug. Alternatively, gene therapy may be aimed not so much at the primary

tumour cell but so as to enhance the ability of the normal immune cells to attack cancer calls. For instance, in melanoma, early gene therapy protocols took a population of lymphocytes called tumour-infiltrating lymphocytes (literally lymphocytes that tend to home-in on tumours), transfected them with tumour necrosis factor-α (TNF-α) and then reinfused them into the patient [12]. The idea was that the tumour-infiltrating lymphocytes would act as a carrier for TNF-α, which when localized to the tumour would lead to tumour regression. Alternative strategies have included adding other cytokine genes to skin fibroblasts and then injecting these fibroblasts with autologous tumour cells into the individual, with the hope that the cytokines produced by these fibroblasts assist the immune system in attacking the tumour cells. Perhaps one of the strangest results that has been described is that in many situations there is what is called a 'bystander effect', i.e. even though not all the tumour cells can be targeted with any particular gene, the death of many of the tumour cells is not a direct effect of the introduction of the gene but merely because many of the cells in the vicinity are cells that have been successfully transfected. This phenomenon offers hope because it is most unlikely that all the tumour cells are going to be successfully targeted with the necessary gene product.

Gene therapy for inherited cutaneous disorders where the primary genetic defect has been identified is attractive to many, and a number of groups are beginning to perform such studies. It is possible to imagine that different sorts of disorders, depending on the particular molecular pathology, may be more or less amenable to therapy. For instance, where there is an enzyme deficiency and the disorder is recessive, even the production of a small amount of enzyme by the insertion of genetic material may be of benefit. For example, such a study on an individual with adenosine deaminase deficiency has been reported, in which T lymphocytes were treated with a retroviral vector containing the deficient gene and then transferred back into the patient [8]. The results are promising, although because the patient received other treatments, the results cannot be considered unequivocal. It might be considered that cutaneous disorders such as steroid sulphatase deficiency or disorders secondary to mutations in transglutaminase (lamellar ichthyosis [13]) might be amenable to similar approaches. Nevertheless, there are a number of technical and conceptual problems which remain. There are concerns about the safety of the vectors being used. Although retroviruses can be altered such that they are incapable of replication in the host, there is always the outside possibility of recombination between the therapeutic form and wild-type retroviruses, such that they may recreate their ability to infect other cells. Adenoviruses may appear less hazardous than retroviruses and are currently being used in a variety of gene-therapy protocols. A disadvantage, however, is that they tend to provoke an immune response, which may limit their clinical effectiveness in the long term. Considerable problems remain in ensuring that the introduced genes continue to be expressed over a long period of time and that insertion does not occur in host genes of importance. Other challenges remain. If one is wishing to treat by gene therapy an inherited autosomal disorder where the mutation causes a loss of function (the mutated protein does not work), the patients will in effect be heterozygous and already produce 50% of the normal protein. Attempts to raise this to the necessary physiological level may be difficult. Alternatively, if a mutation causes a gain of function (the mutant protein takes on a new function not present in the wild-type protein or works so as to inactivate the normal wild-type protein, such as occurs in some of the inherited keratin disorders), simply adding normal protein by gene therapy may not be sufficient.

A final consideration with gene therapy is how generic the techniques can be made. This assumes importance because although studies on cancer using gene therapy have been well funded, to take gene therapy approaches through to the clinic, industrial-scale funding is probably necessary. For many rare dermatological disorders, as for development of new drug-based strategies, it is not clear that the size of the market will justify the necessary investment. A second limitation on application, particularly with respect to dermatological therapy, may be concern about safety. The majority of studies so far have been carried out on cancer patients, reflecting the widespread acceptance of dangerous therapies in disorders that are themselves life-threatening. Obviously, since the vast majority of cutaneous diseases are not life-threatening, one imagines that these sorts of approaches will in the short term be restricted to disorders that are potentially fatal, such as melanoma or some of the inherited blistering disorders.

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Conclusion

Molecular biology and the application of molecular biological techniques to the study of disease have come an astonishingly long way in a short period of time. Disease-causing genes continue to be identified at a significant pace. Molecular biological technology has opened up the study at increased speed of whole areas of medicine, because of both DNA-based diagnostics and an increased facility to carry out classical biochemistry and pharmacology. If nothing else, genomics has set an example that other branches of modern medicine are keen to follow. For instance, proteomics refers to the systematic attempt to characterize and annotate proteome, where proteome is defined as the protein content of a particular unit of biological enquiry such as a cell [1]. It remains possible that nucleic acid-based technologies such as gene therapy may also play an important role in therapy. Nevertheless, there are perhaps cogent reasons for some of the exuberant optimism being bridled with a little caution. Many liken the explosion of knowledge about disease-causing genes to the birth of the science of human anatomy, exemplified by Vesalius' *De Humani Corporis Fabrica*; it was, however, at least another 300 years following publication of Vesalius' masterpiece that visiting a doctor increased one's chances of surviving from any serious disorder. There still remains an enormous gap between the 'anatomy of the cutaneous genome' [2], understanding the pathophysiology of cutaneous disease and the ability to produce successful remedies with the necessary efficacy and low toxicity required for everyday clinical practice. On the other hand, there are some obvious advantages in studying the skin, in that its accessibility lends itself to topical and usually less hazardous therapy. Nevertheless, a look back over the last 30 or 40 years of dermatology suggests that many of the major breakthroughs in therapy have not proceeded from a linear understanding of the cause of a disease but have been arrived at through trial and error, careful clinical observation of agents introduced for therapy of other diseases and intuition [3]. In part, of course, this reflects the reality of the economics of pharmacological development in terms of the market share held by skin diseases. One of the interesting areas to observe over the next few years will be whether molecular-based strategies will alter this state of affairs.

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Chapter 9

Inflammation

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Introduction [1–3]

Inflammation can be defined as a complex body defence response to noxious or dangerous stimuli. Classically, inflammation is associated with the host defence against infectious agents. However, a variety of other exogenous and endogenous stimuli (e.g. ultraviolet light) may induce an acute inflammatory response. Inflammation also constitutes the body's response to injury. Physical stimuli such as heat, cold or mechanical irritation may affect skin homoeostasis and activate the release of inflammatory mediators such as eicosanoids, cytokines, chemokines and neuropeptides.

The inflammatory response comprises various cellular and molecular mechanisms that enable reconstitution of body integrity, and is characterized by successive phases. The initial phase, in which resident cells of the damaged tissue release immediate inflammatory mediators, is clinically silent. In the second phase, a vascular reaction characterized by vasodilatation and increased permeability can be observed. This is in turn followed by a cellular phase, in which inflammatory cells infiltrate the injured microenvironment. As will become clear, the pathogenesis of many skin diseases involves dysregulation of the inflammatory response.

Inflammatory cells, such as neutrophils, seen early in the response, release a variety of mediators, including cytokines or enzymes to remove dead cells, detritus and microbiological organisms and to neutralize toxins. Leukocytes closely interact with endothelial cells, which express adhesion molecules to allow leukocyte emigration into the inflammatory environment. Upon activation, endothelial cells stimulate a plethora of cytokines, chemotactic agents, cell adhesion molecules and selectins. In addition, other important mediators such as kinins, biogenic amines, neuropeptides, nitric oxide, haemoxygenase (HO), various oxygen compounds, growth factors, complement components, prostaglandins, leukotrienes and adenosine diphosphate (ADP) are released, which regulate the inflammatory response. Under normal circumstances, inflammatory effects are rapidly attenuated by anti-inflammatory mechanisms, to protect the body from the consequences of uncontrolled stimulation, and prolonged activation. Several types of resident cutaneous cell can generate inflammatory mediators and their receptors, resulting in termination of cellular responses to released pro-inflammatory molecules and initiation of tissue repair. As a consequence of uncontrolled conditions, an inflammatory response may become chronic, resulting in disease (e.g. in chronic eczema).

The molecular mechanisms underlying the acute and chronic phase of inflammation are different, and only partly understood. Over the last few years, however, our knowledge of the pathophysiology of inflammation and

the mediators involved has expanded substantially. This chapter highlights some of the important recent advances in skin inflammation, and discusses the impact of modern therapeutic strategies on the treatment of cutaneous inflammation. Cellular constituents of the adaptive immune system (T cells, B cells and antigen-presenting cells) are described in Chapter 10. Therefore, the main focus of this chapter is on cells and mediators of the innate immune system, and their role during inflammation.

Characteristics of inflammation

Five characteristic signs of inflammation were described by Celsus centuries ago: redness, heat, pain, swelling and loss of function. However, not all signs may be necessarily observed in all skin lesions during a given inflammatory response.

Redness (Rubor). This reflects the presence of red blood cells or haemoglobin in the skin. Increased redness may follow increased blood flow through superficial dilated vessels, resulting from stimuli leading to vasodilatation, or from obstruction in deeper vessels causing diversion or 'shunting' of blood through more superficial vessels. Redness in the skin may also result from stasis and congestion without increased flow of blood. Such partial stasis increases the chances for leukocytes to emigrate from vessels.

Heat (Calor). This is a usual consequence of increased blood flow through the skin. In acute lesions, the temperature of the skin may increase as a direct result of an elevated local metabolic rate. In chronic inflammation, neither local metabolism nor blood flow may be increased, and the skin may feel cool. Heat loss cannot be correlated exactly with redness, because areas of fast flow may be on the border of a more congested and slow-flowing system. Thus, conduction of heat to the surface of the skin may be considerable over a large deep arteriovenous fistula, while the upper dermis may show all the effects of severe stasis consequent on raised venous pressure.

Pain (Dolor). The sensations that accompany inflammation of the skin include burning, stinging, itching and tenderness, and are thus more variable than in most internal organs. Which of these sensations predominates depends in part on the site, depth, intensity and duration of the inflammatory process. Thus, in urticaria, stinging may accompany transient superficial lesions; itching is the usual sensation in papular urticaria or in wheals resulting from mediator release from mast cells such as histamine. Pain and tenderness may accompany deeper lesions of long duration, as observed in delayed pressure urticaria. Other mediators such as bradykinin and proteases may also induce pain by activating specific receptors on primary afferent neurones.

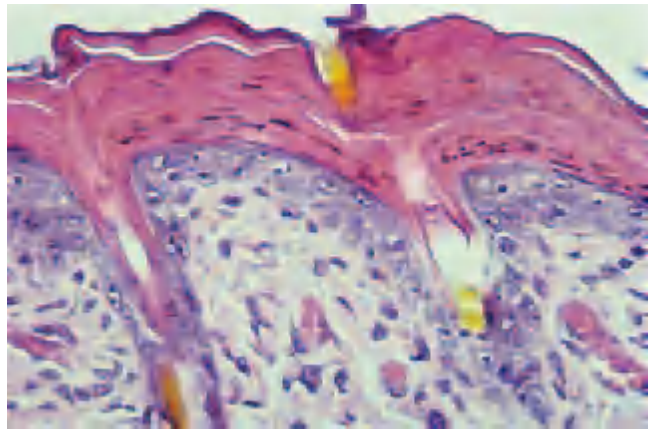

Fig. 9.1 Chemically induced mild irritation of rabbit skin resulting in stimulation, manifested as hyper- and parakeratosis, slight oedema of the epidermis, an occasional neutrophil and capillary hyperaemia. H&E.

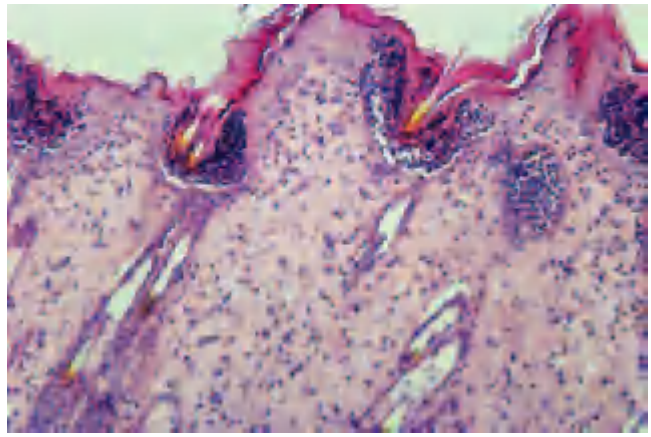

Fig. 9.2 Chemically induced mild irritation of rabbit skin. Example of focal attraction of neutrophils to site of penetration in the hair follicles. Beneath the neutrophil aggregates are small clefts resulting from leukocyte enzyme degradation, below which the follicular epithelium is regenerating. H&E.

Swelling (Tumor). Rapid swelling is caused by oedema, the increased leakage of water and mineral salts (transudate), or proteins (oedema fluid) from blood vessels. This fluid accumulates at the site of inflammation when the rate of exudation from venules and capillaries is greater than the rate of clearance by the lymphatic vessels. In most lesions, swelling is mainly brought about by oedema, or to plasma constituents (e.g. fibrin in delayed hypersensitivity reactions). In chronic inflammation, swelling is also caused by an increase of extracellular matrix components. Even a dense leukocytic infiltration usually does not contribute substantially to swelling, except in the case of abscess or granuloma formation. Neutrophils may accumulate at a site in large numbers within 4 h, but macrophages and lymphocytes, which contribute to a firmer, more persistent swelling, usually accumulate more slowly over 48–72 h (Figs 9.1–9.4). The duration of the leukocyte infiltration

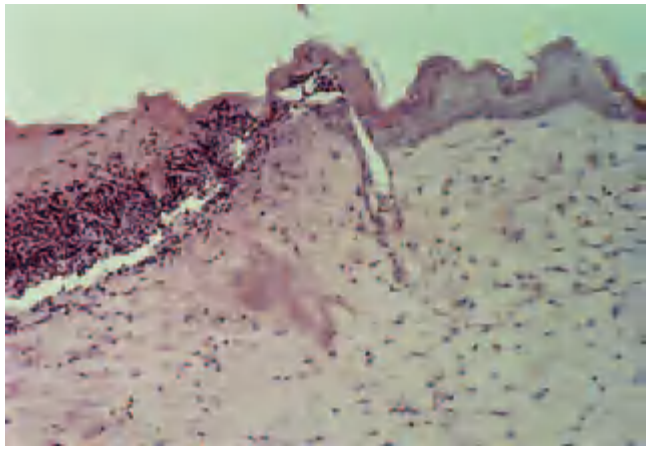

Fig. 9.3 Chemically induced irritation of mouse skin at 24 h. Necrotic epidermis on left. Neutrophil infiltration and proteases forming cleft beneath damaged tissue; the outermost neutrophils are also degenerate. Epidermal cells from outer edge of follicle begin to under-run the separating necrotic tissue. H&E.

Fig. 9.4 Healing irritated mouse skin at 5 days. Necrotic epidermis with neutrophils is sloughed over new stratum corneum and epidermis. Regeneration of follicles in progress. H&E.

depends upon the nature of the causative agent. Tissue hypertrophy with acanthosis, fibroblast proliferation and formation of new blood vessels may also promote more persistent swelling.

Phases of inflammation

Inflammation induced by exogenous or endogenous stimuli can either occur as an acute response or develop into a chronic condition. Normally, the acute inflammatory response is terminated by a variety of negative feedback mechanisms such as receptor antagonists for cytokines or protease inhibitors, for example. Under certain conditions, however, an imbalance in the inflammatory response can lead to persistance of pro-inflammatory stimuli resulting in a chronic condition.

The acute phase (first 6 h) of inflammation consists of a vascular reaction, including vasodilatation, plasma extravasation, oedema formation, activation of endothelial cells and release of early messengers from the injured tissue. Subsequently, the site becomes a target for inflammatory cells charged with eliminating the noxious stimulus. Vasodilatation of small vessels is caused by several mediators, such as kinins (bradykinin), amines (serotonin), prostaglandins (PGE_2) and neuropeptides (calcitonin gene-related peptide), released by platelets, mast cells and sensory nerves, for example. Subsequently, plasma extravasation leads to oedema, which supports the acute inflammatory response. Most of these effects are exerted via the up-regulation of specific receptors such as bradykinin-2 receptor or PGE_2 receptor. In contrast, peptidases released in the vicinity of the vessel wall may inhibit and thereby effectively terminate the vasodilatory response. Macrophages and neutrophils represent the first-line rapid host defence against microorganisms by phagocytosis and killing, until the adaptive immune response is initiated. Subsequently, activated immune cells release cytokines and other mediators in a more directed and effective host immune defence. Moreover, chemokines may be released by most resident cutaneous cells to facilitate recruitment of leukocytes to the site of inflammation. Infectious agents, and the local inflammatory response, activate the complement system, and production of plasma proteins, which destroy pathogenic agents. Finally, the innate immune system also contributes to the effective activation of the adaptive immune response.

The chronic phase of inflammation is characterized by a cellular phase, with recruitment of inflammatory and immunocompetent cells into the site of inflammation. Finally, resident and infiltrated cells collaborate in the phagocytosis and killing of pathogens, removal of debris including necrotic and apoptotic cells, and in the restoration of the tissue. The outcome of the inflammatory response is crucially determined by the removal of the primary pro-inflammatory stimulus. Thus, progression of an acute into a chronic state of inflammation is a result of the persistence of the stimulating agent. Exogenous factors may consist of toxins or pathogens, whereas endogenous factors might be autoantigens, for example. Microorganisms may induce chronic inflammatory states by evading routine immune surveillance, as observed in leishmaniasis or mycobacterial infection. On the other hand, chronic inflammation in pemphigus vulgaris, lupus erythematosus and other autoimmune diseases may result from defective down-regulatory mechanisms.

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Innate defence mechanisms

Antimicrobial peptides

Antimicrobial peptides constitute a novel family of effector molecules with an important role in host defence, inflammation or cytotoxicity, and that may be of potential substantial benefit in the treatment of infectious and inflammatory skin diseases. In humans, peptide antibiotics of three families have been identified: defensins, cathelicidins and histatins. All antimicrobial peptides characterized share the capacity to kill and/or to inactivate bacteria, fungi and enveloped viruses *in vitro*. They apparently kill mammalian target cells and microorganisms by a mechanism involving initial electrostatic interactions with negatively charged surface molecules on target cells, followed by insertion into the cell membrane, permeabilization and formation of voltage-regulated channels. In addition to their antimicrobial and cytotoxic properties, some defensins act as opsonins, while others inhibit signal transduction pathways such as protein kinase C, competitively inhibit receptor activation (e.g. adenocorticotrophic hormone (ACTH) receptor), block steroidogenesis or act as selective chemoattractants for monocytes. Thus, in addition to their capacity to kill microbes, endogenous antibiotic peptides may also contribute to both innate host defence and adaptive immune responses.

Defensins

Defensins are antimicrobial and cytotoxic peptides that consist of 29–35 amino acids, including six invariant cysteines whose intramolecular disulphide bonds cyclize and stabilize them in a triple-stranded β-sheet configuration. They are generated by proteolytic processing from 93–95 amino acid precursor prepropeptides, and can be detected in plants, insects and various mammals [1,2]. The prosegment keeps the peptide in an inactive state; subsequent activation occurs by proteolysis. Matrilysin (MMP-7) was identifed as the enzyme responsible for generation of mature defensin in mice. In the human setting, the situation is less clear, and other enzymes such as trypsinogen-2 may be involved [3]. Interestingly, they make up to 5% of the total protein content in human neutrophils and are also produced by macrophages, keratinocytes and mucosal epithelial cells of the respiratory, digestive, urinary and reproductive systems [4–7]. In mammals, neutrophils are capable of generating and releasing all three classes of defensin. The antimicrobial spectrum of defensins includes Gram-positive as well as Gram-negative bacteria, mycobacteria, *Treponema pallidum*, many fungi and some enveloped viruses. Defensins exert non-specific cytotoxic activity against a wide range of normal and malignant targets, including cells resistant to tumour necrosis factor-α (TNF-α) and natural killer (NK) cell cytolytic factor.

α-Defensins contain three disulphide bridges, and reveal a triple-stranded β-sheet structure with a β-hairpin that contains cationic amino acids. The first human α-defensin was isolated from neutrophils [8] and, so far, six human α-defensins (HNP-1 to -6) have been identified. Human neutrophils generate four α-defensins, termed human neutrophil peptides (HNP) 1–4. They are all localized in azurophilic granules of neutrophil granulocytes, where they are the principal protein and contribute to the oxygen-independent killing of phagocytized microorganisms. In contrast, mouse neutrophil granules do not contain α-defensins. HNP-5 and -6 are primarily found in Paneth's cells of the small intestine and epithelial cells of the female urogenital tract.

*β-Defensin*s were first isolated from cow tongue in 1991, and originally named tracheal antimicrobial peptide (TAP). They contain six cysteine residues connected by three disulphide bridges, spaced differently from those in α-defensins. The genes encoding β-defensins are localized in the same chromosomal region as α-defensins. They consist of 36–42 amino acids, and possess a different disulphide alignment as compared to other defensins. Human β-defensin-1 (HBD-1) is expressed constitutively in epithelial cells of the skin, the gastrointestinal, urinary and respiratory tracts. HBD-2 was isolated from psoriatic skin [9]. HBD-1 and -2 are expressed diffusely throughout different epithelial structures and glandular cells of different tissues. HBD-3 was isolated from psoriatic keratinocytes, and has a potent antimicrobial activity against many skin-pathogenic bacteria [10].

θ-Defensins constitute a novel class of defensins that has recently been isolated from Rhesus monkey neutrophils. The peptide Rhesus θ-defensin-1 is produced by the post-translational ligation of two truncated α-defensins, and demonstrates salt-independent antimicrobial activity. So far, θ-defensins have not been detected in the skin.

Cathelicidins

Peptide antibiotics of the cathelicidin ('cathe-lin' from cathepsin L inhibitor) family contain a highly conserved signal sequence, but show substantial heterogeneity in the C-terminal domain encoding the mature peptide, which can range in size from 12 to 80 amino acid residues. The only human cathelicidin, LL-37/hCAP-18, was originally isolated from human bone marrow [1,2] but is also detectable in inflamed skin. LL-37/hCAP-18 has been found to be regulated by various inflammatory stimuli such as cytokines [11].

Histatins

Histatins are a family of histidine-rich peptides present

in human saliva [12], consisting of approximately 38–32 amino-acid residues. The five members of the histatin family are modulated by post-translational processing. Their antimicrobial activity includes especially strong antifungal effects.

Function of defensins

The expression of defensins is tightly regulated. While the expression of HBD-1 has been found to be constitutive, HBD-2 expression seems to be inducible by infectious and pro-inflammatory stimuli. In the skin *in vivo*, HBD-2 transcripts and peptide levels are found to be up-regulated during infectious diseases [11]. *In vitro*, pro-inflammatory cytokines such as the interleukins IL-1α and IL-1β, and TNF-2, but also lipspolysaccharide (LPS) and microorganisms (Gram-positive and Gram-negative bacteria, and *Candida albicans*) are able to induce hBD-2 production. In addition, the expression of LL-37/hCAP-18 is up-regulated in inflamed skin, and found to be co-localized with IL-6. Interestingly, the LL-37/hCAP-18 gene contains several potential binding sites for transcription factors (acute-phase response factor and nuclear factor for IL-6 expression [NF IL-6]) that are possibly involved in the regulation of inflammation. However, the mechanisms that induce antimicrobial peptides and corresponding signalling pathways can only be speculated upon at present.

Antimicrobial peptides, including defensins, cathelicidins and histatins, have a broad spectrum of activity against Gram-positive and Gram-negative bacteria, as well as against fungi and enveloped viruses. Antimicrobial peptides show synergistic activity with other host defence molecules such as lysozyme and lactoferrin. The microbicidal activity of defensins is based on permeabilization of anionic lipid bilayers and the subsequent release of cellular contents, and destruction of the membrane's electrode potential. A second model describes the aggregation of peptides into positively charged patches resulting in the formation of transient gaps. Additionally, defensin-related cell death has been related to interference with protein synthesis and DNA damage.

So far, the evidence that defensins contribute to innate immunity *in vivo* is largely indirect. Evidence for the host defence function of antimicrobial peptides comes from a study involving MMP7-knockout mice, which showed an increased susceptibility to infections. In addition to their antimicrobial activity, defensins and cathelicidins can bind to LPS and inactivate the biological functions of this endotoxin. Bacterial resistance to antimicrobial peptides is a rare phenomenon. Mechanisms that result in the development of resistance involve modifications of outer cell wall components, such as LPS, teichoic acids or phosphocholine, and the modulation of efflux pumps [2].

Besides their role as endogenous antibiotics, antimicrobial peptides have other functions in inflammation, wound repair and regulation of the adaptive immune system. Human neutrophil defensins have been described to be cytotoxic for various cell types, and to induce cytokine synthesis in epithelial cells, monocytes and T cells. Furthermore, they increase the binding of bacteria to epithelial cells and induce the liberation of histamine from mast cells. Finally, α-defensins are involved in the chemotaxis of monocytes and T cells, the modulation of cell proliferation and B-cell production, and the inhibition of complement activation and proteinase inhibitors [3,13,14]. The human β-defensins have recently been identified as potent ligands for the chemokine receptor CCR6, which is present on dendritic and T cells, therefore suggesting a link between innate and adaptive immunity [15].

There is strong evidence that antimicrobial peptides serve as mediators of host defence, not only by their direct antimicrobial activity but also by their function as inflammatory mediators. Defensins attract inflammatory cells such as neutrophils, B cells and macrophages, and activate epithelial cells including keratinocytes. HNP-1 enhances the phagocytosis of cultured mouse peritoneal macrophages. Human defensins are also able to degranulate mast cells, resulting in the release of histamine and tryptase with consequent recruitment of more neutrophils to the inflammatory sites. In contrast, mast cells release cathelicidin LL-37, which is involved in the killing of bacteria [16].

Neutrophil defensins stimulate IL-8 production, which also helps to recruite more neutrophils to the site of inflammation. This is in accordance with a report that *in vivo* administration of human neutrophil defensins increases the ability of mice to resist local infection by enhancing neutrophil recruitment to infected tissues. Human neutrophil defensins are also reported to bind to complement component 1q [17]. Therefore, it is possible that defensins may participate in the regulation of complement activation. Defensins induce the release of pro-inflammatory mediators such as IL-8, interferon-γ (IFN-γ), IL-6, IL-10 and leukotrine B_4 (LTB_4). On the other hand, defensins might also exhibit anti-inflammatory activities by inducing the secretion of IL-10 [18].

In the skin, defensins such as HBD-2 are up-regulated in psoriasis [9], acne [19] and folliculitis [20]. In contrast, decreased expression and release of HBD-2 and LL-37 was found in lesional skin of atopic dermatitis patients [21]. Interestingly, antimicrobial agents such as LL-37 and HBD-1 are up-regulated in the inflamed skin of newborn infants during erythema toxicum neonatorum [22]. Moreover, growth factors such as insulin-like growth factor-1 and transforming growth factor-α (TGF-α) enhance the expression of hCAP/LL-37 and HBD-3, indicating up-regulation of antimicrobial peptides during wound healing [23]. HNP-1 increases the expression of pro-α-(I)-collagen and decreases MMP-1 release, supporting a role of defensins in wound repair [24]. IL-1 seems to be an important inducer of HBD-2 synthesis in human keratinocytes [25].

Antimicrobial peptides are also involved in adaptive immune responses [2,6,13,14,26]. Defensins have also been shown to modulate the cytokine profile of T cells. For example, HNP-1 and HNP-2 are T-cell chemoattractants, and induce the recruitment of T cells to the sites of inflammation *in vivo*. Human neutrophil α-defensin enhances antigen-specific humoral immune responses, and $CD4^+$ T cells isolated from mice immunized with antigen in the presence of α-defensins displayed higher antigen-specific proliferative responses and elevated production of IFN-γ, IL-5, IL-6 and IL-10 than T cells from mice immunized with antigen alone.

Defensins also modulate dendritic cell function. Human α- and β-defensins are selectively chemotactic for human immature, but not mature dendritic cells. Although *in vivo* neutrophil defensins are stored in azurophilic granules, they can be released into the extracellular environment by neutrophil disruption or degranulation [27]. Murine BD2 has been demonstrated to directly modulate dendritic cell function and maturation [28], indicating that defensins are involved in immunosurveillance. Thus, defensins presumably present at sites of inflammation form chemotactic gradients for immature dendritic cells. Because dendritic cells are crucial for the induction of adaptive immune responses, defensins may directly contribute to antigen-specific immune responses.

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Toll-like receptors

The toll-like receptors (TLRs) are key molecules involved in microbial recognition by the immune system. At present, 10 members of the TLR family have been identified in mammals. They recognize microbial structures such as bacterial LPSs, bacterial DNA and viral double-stranded DNA. There is also evidence that some probiotics that appear to be effective in allergy prevention, may function via interaction with TLRs. The number of ligands for these receptors is growing, and it appears that multiple ligands exist for each receptor. TLRs activate common signalling pathways leading to the activation of nuclear κB transcription factor (NF-κB) and the mitogen-activated protein kinases (MAPKs), which results in the production of pro-inflammatory cytokines. On the other hand, individual TLRs may induce an immune response to a given microbial agent via their specific signalling systems. Thus, TLRs are crucial components of both the innate and adaptive immune response.

TLRs are defined by the presence of a Toll/IL-1 receptor (TIR) domain in their cytosolic regions and an extracellular domain comprising leucine-rich repeats. A key ques-

Table 9.1 Potential use of toll-like receptor (TLR) agonists in various diseases.

Disease/condition	TLR involved	Therapeutic approach	Comments and expected outcome
Acne	TLR-2	Antagonist	Suppression of *P. acnes*-induced cytokine production
Atopic dermatitis	Many	Bacterial vaccine Agonists	Shifting of a Th2 into a Th1 response
Pathogen invasion	TLR-7	Agonist	Reinstatement of cytokine-induced host defence and elimination of viruses
Acute inflammation	TLR-2, -4	Antagonist	Reduction in inflammation by inhibiting TLR-2, -4 expression and HSP-70 release
Chronic inflammation	TLR-2, -4	Antagonist	Reduction in TLR-induced release of inflammatory mediators (heat shock proteins, fatty acids, hyaluronic acids)
Autoimmune disease	TLR-9	Antagonist	Blocking of production of autoantibodies and proliferation of B cells induced by immune complexes containing DNA
Sepsis	Many	Soluble TLRs Antagonists Signalling inhibitors	Ligand neutralization Mediator blockade Receptor blockade

tion concerns signal transduction and whether different responses induced by different TLRs are important for the tailoring of host defence against different microbes. In this regard, two TIR domain-containing adapter proteins, MyD88 and TIRAP/Mal, are of interest. There is evidence from MyD88-deficient mice that MyD88 is an universal adapter for a wide range of TIR domain-containing receptors tested [1], while TIRAP/Mal is implicated in signalling by the LPS sensor TLR-4 but not the bacterial cytosine-phosphate-guanine (CpG) DNA sensor TLR-9 or IL-1 [2,3]. TLRs are expressed on immunocompetent cells and thereby involved in the activation as well as differentiation of dendritic cells and T cells [4]. While undoubtedly important in downstream signalling responses and NF-κB activation, TLRs have not been shown to bind directly to ligands such as LPS or their complexes with LPS binding protein (LBP) [5]. Instead, they bind to CD14, also implicated in apoptotic cell, heat shock protein and fibrinogen clearance. TLRs have recently been found to be expressed on several cells in the skin, including keratinocytes, in addition to immunocompetent cells.

The ligands so far identified that signal through TLR are mainly exogenous, but there are reports of endogenous ligands and of intracellular rather than surface engagement, through which selected TLRs act. Imidazoquinolones such as imiquimod and resiquimod were found to bind to TLR-7 and TLR-8, respectively, and thereby activate macrophages. The resulting secretion of pro-inflammatory cytokines, predominantly IFN-γ, TNF-α and IL-12, was found to be responsible for an immunodeviation towards a T helper 1 (Th1) response required for cytotoxicity and effective antiviral and antitumoral activity. Accordingly, topical imiquimod is successfully used for the treatment of anogenital warts and several types of skin tumour. A similar Th1-inducing effect has been observed for CpG oligodeoxynucleotides (ODN), and was found to be mediated via TLR-9. The efficacy of CpG ODN in the treatment of allergic diseases or as an adjuvant immunotherapy for tumours is currently under study. The potential for using modulation TLRs for therapy of various inflammatory disorders is shown in Table 9.1.

Type 3 complement receptor

Type 3 complement receptor (CR3) is a myeloid cell phagocytic receptor for complement opsonized particles, irrespective of the host or the microbial origin, and also for direct interactions with pathogens such as *Mycobacterium tuberculosis* and yeast-derived zymosan, as well as for host ligands [6]. It is a β2 integrin also known as CD18/CD11b, which has a key role in myelomonocytic cell recruitment to sites of inflammation. The expression of CR3 by macrophages is tissue-selective, and is thus not generated by all macrophages. It is promiscuous in its range of binding of ligands, including intercellular adhesion molecule-1 (ICAM-1) on endothelial cells or platelets, indicating a role at early stages of inflammation and wound healing. Moreover, CR3 contributes to clearance of apoptotic cells. The opsonic phagocytic mechanism differs from that mediated by Fc receptors, and CR3-mediated uptake by macrophages does not trigger release of prostaglandins or reactive oxygen species.

Scavenger receptors

Scavenger receptors (SR) represent a family of structurally unrelated membrane molecules expressed by macrophages and selected endothelial cells, with a broad specificity for polyanionic ligands such as low-density lipoprotein (LDL), suggesting a role in host defence and inflammation. SR-A, for example, contributes to the resistance of the host towards Gram-positive microbial infection *in vivo*. SR-A is also involved in the phagocytic uptake of unopsonized *Neisseria meningitidis* [7]. In contrast, LPS, a previously known ligand of SR-A, is not required for the uptake of *Neisseria* by macrophages, but is responsible for the TLR-4-mediated induction of pro-inflammatory responses. This is associated with an overproduction of

TNF-α and other pro-inflammatory mediators, perhaps resulting from an imbalance between SR-A-dependent clearance of LPS and TLR-4-dependent pathways of secretory stimulation. Thus, the role of SR during inflammation and infection has many interesting features. First, they are able to function as adhesion molecules, but can also mediate endocytosis and phagocytosis of modified-host components and of exogenous ligands (LPS, lipoteichoic acid, and others). The structural basis for receptor–ligand interactions remains unclear. Additionally, the signalling pathways induced by SR-A in the infected cell are poorly defined, and the ligands utilized in many studies can bind to a wide range of SR molecules. Future studies, with the availability of knockout mice for various SR, will help to clarify their role within the innate and acquired immune system and, more generally, in homoeostasis.

Mannose receptor and other C-type lectins

The mannose receptor (MR) is expressed by macrophages, dendritic cells and some endothelial cells. It is a multilectin, which binds mannosy/fucosyl or GlcNAc-glycoconjugate ligands through its Ca^{2+}-dependent carbohydrate recognition domains (CRD) [8]. The ligands are present on several bacteria, fungi, virus-infected cells and parasites. Endogenous self-ligands for CRD include L-selectin, implicated in cell migration and a number of mannose-terminal lysosomal hydrolases [9]. Recent data also suggest novel ligands for MR in peripheral lymphoid organs. Interestingly, macrophages are capable of releasing a soluble form of MR into the plasma. Thus, MR participates in complex functions related to tissue clearance, homoeostasis, immunomodulation and host defence.

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Apoptosis

Apoptosis (Greek: falling, as of leaves from a tree) is a physiological and programmed form of cell death that is characteristic for all nucleated cells. It also modulates the function of leukocytes by directly regulating various effector subtypes. The first step is the induction of endogenous endonuclease activation and proteolysis. In terms of the inflammatory process, recent knowledge indicates that inflammatory cells such as neutrophils, macrophages and dendritic cells are capable of directing the inflammatory response in both pro- or anti-inflammtory directions, depending on the signals that they receive. Thus, apoptosis may be a pro- or anti-inflammatory process, depending on the microenvironment in which this interaction occurs [1].

During the past few years, it has become evident that apoptosis is not a 'neutral' process in inflammatory terms, but is rather an active event in which apoptotic cells become phagocytosed, thereby inducing inflammatory responses. Thus, clearance of apoptotic cells can result in powerful anti-inflammatory and immunosuppressive effects [2]. For example, apoptosis of neutrophils infiltrating damaged tissue may contribute to the termination of inflammation. Accordingly, in the perturbed epidermis, particularly after ultraviolet (UV) light irradiation, apoptotic cell residues are known as Civatte or colloid bodies, or sunburn cells [3]. Recent data, however, also indicate that clearance of apoptotic cells can result in the generation of pro-inflammatory stimuli, which may ultimately lead to chronic inflammation and immune-mediated diseases [4].

During early stages of keratinocyte apoptosis, the nuclei become convoluted and chromatin aggregates on the nuclear membrane, the cell shrinks and separates from the contiguous cells (disaggregation). Fragments of nucleus and small apoptotic bodies ('apical blebbing') are released. They are composed of nuclear remnants, particles of organelles and cytoplasm within a capsule of transglutaminase cross-linked protein resembling differentiated involucrin in keratinocytes. The apoptotic cell residues (e.g. sunburn cells) or bodies may be ingested by professional phagocytes such as macrophages, dendritic cells or neutrophils [5,6].

Apoptosis differs from necrosis in that single or very small groups of cells are affected, there is nuclear pyknosis and condensation of the cytoplasm, and phagocytosis of the residual material without excitation of inflammation, and resolution of organized tissue without major structural change can occur. Nuclear pyknosis occurs in coagulative necrosis, but the change in apoptosis is caused by endonuclease splitting of the DNA, resulting in a 'ladder' pattern on separation in agarose gels, whereas necrotic cell DNA forms an amorphous smear [4]. In the skin, apoptosis is induced during hypoxia, tissue repair, allergic reactions, exposure to toxins and drugs, and after skin radiation with ions or UV light. Thus, apoptosis can be observed as a physiological defence mechansim against 'danger signals' that occur in the skin. For example, distinct subsets of hapten-specific T cells are also capable of inducing apoptosis in autologous keratinocytes, and

nickel-specific $CD8^+$ and $CD4^+$ T-cell subsets can exert a cytotoxic activity against keratinocytes. Finally, glucocorticoids and other immunosuppressants induce apoptotic pathways in several immune cells, thereby contributing to healing during inflammation, autoimmune disease and infection [7–9].

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Major histocompatibility complex

The genetic loci responsible for the rejection of non-self tissues are located in a region known as the major histocompatibility complex (MHC) on chromosome 6. The MHC genes encode for highly polymorphic cell surface structures termed MHC antigens or human leukocyte antigens (HLA). Three classes of molecules (I–III) have been identified. The class I and II glycoproteins, which share a similar overall structure, are involved in antigen presentation. There are three main class I genes (HLA-A, HLA-B and HLA-C) and three main class II genes (HLA-DP, HLA-DQ and HLA-DR). The class III proteins, although encoded by genes residing in the same chromosomal region as those for the class I and II molecules, consist of components of the complement system and molecules that are involved in the processing of antigens, such as the proteasome-like genes and transporter genes [1–3].

Each class I MHC protein is expressed on the cell surface as a dimer composed of two non-covalently linked polypeptide chains (heavy or α-chain associated with a non-MHC-encoded β_2-microglobulin). The peptide-binding capacity of the class I MHC is enormous because each individual carries six different HLA-A, HLA-B and HLA-C alleles, and each allelic gene product is capable of generating a variety of different peptides [1,2].

The class II MHC is highly polymorphic, with the polymorphic residues concentrated in the α_1 and β_1 domains, which are involved in peptide binding. Multimeric receptor forms are also possible for other molecules involved in cognate recognition (e.g. class I MHC, T-cell receptor) and probably increase the avidity of interaction of juxtaposed cells [1–3].

Class I MHC molecules bind cytoplasmic proteins (e.g. viral proteins in infected cells) that are degraded into peptides by a large cytoplasmic proteolytic complex derived from at least two genes in the HLA class II region [4]. Class II MHC molecules bind peptides derived from exogenous proteins that have been internalized in antigen-presenting cells in a coated pit into the endocytic pathway, where antigen degradation generates functional peptides. The resulting peptide–protein complex is then translocated to and expressed on the antigen-presenting cell surface [5].

Under normal circumstances, self-proteins are displayed, leading to a state of tolerant inactivity. However, deleterious intracellular events lead to the display of MHC class I molecules complexed with foreign peptides, activation of $CD8^+$ T cells and the generation of cytolytic T cells. Similarly, extracellular exposure to foreign substances results in the cell-surface display of class II MHC molecules complexed with foreign peptides, leading to the activation of $CD4^+$ T cells, the induction of B cells through helper T-cell activity and immunoglobulin production.

The CD8 class I pathway is associated with internal cellular events. Because virtually all nucleated cells express class I molecules, essentially all cells can act as antigen-presenting cells for $CD8^+$ T cells, providing important protection against harmful intracellular processes such as inflammation, viral infection and neoplasia. The CD4 class II pathway is responsive to external cellular events, but the relative restriction of constitutive class II expression and antigen-presenting capacity to B cells, macrophages, dendritic cells, venular endothelial cells and probably keratinocytes limits the possibilites and consequences of activating $CD4^+$ T cells.

Dysfunction or genetic alterations of MHC alleles have been found in various skin and immune diseases. For example, MHC class I-restricted $CD8^+$ T cells play an important part in the pathophysiology of contact hypersensitivity (CHS). Class I-restricted $CD8^+$ T cells are sufficient for the induction of CHS, supporting the idea that MHC class II-restricted $CD4^+$ T cells down-regulate this inflammatory response. Moreover, $CD8^+$ T cells mediate the skin inflammation through their cytotoxic activity using either the perforin or the Fas–Fas ligand pathway. Thus, cytotoxic $CD8^+$ T cells directly contribute to delayed-type hypersensitivity reactions [6]. Inflammation-associated regulation of MHC function appears also to be crucial in microvascular endothelial cells (HDMEC). For example, cytokines such as IFN-γ or TNF-α, but not IL-1α, increase MHC class I expression on HDMEC [7].

MHC class II antigens have been implicated in the pathophysiology of lichen planus and Behçet's disease. However, histopathological analysis of the skin revealed marked hyperkeratosis of the epidermis and dramatic thickening of the granular layer, with slight infiltration

of inflammatory cells in the dermis, in transgenic mice carrying MHC class I chain-related gene B (MICB) [8]. Moreover, the absence of MHC class II permitted the development of systemic autoimmune effects in a mouse model of acute graft-versus-host disease (GvHD) [9]. In general, variation among individuals in their susceptibility to a variety of autoimmune disorders and a cluster of genes encoding inflammation-related proteins along with MHC genes seems to be crucial for the development of MHC-associated diseases [10].

Modern anti-inflammatory therapeutic strategies are effective in the treatment of MHC-associated inflammatory diseases. For example, recombinant human IL-11 therapy was associated with suppression of mucosal inflammation and concomitant improvement of epithelial resistance and neurally mediated secretion in a model of chronic HLA-B27 colitis; oral treatment of HLA-B27 rats with rhIL-11 reduced myeloperoxidase (MPO) activity in the colon and suppressed clinical signs of diarrhoea [11]. For detailed information on the role of MHC in the adaptive immune response see Chapter 10.

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Cellular components of cutaneous inflammation

Epidermis

To avoid repetition, this chapter focuses on the role of components of the innate immune system during inflammation. The functions of the aquired immune system and dendritic antigen-presenting cells are described in Chapter 10.

Keratinocytes

In the past, the keratinocyte was viewed as a 'brick' in the wall surrounding the body. However, beside their role in producing cytokeratins and lipids, keratinocytes are capable of generating and releasing an armada of different inflammatory mediators. Upon stimulation during inflammation, keratinocytes actively secrete large amounts of cytokines, chemokines, peptides and growth factors, and express receptors for these mediators, as well as several co-stimulatory molecules (Table 9.2).

Keratinocytes respond to both external stimuli and endogenous trigger factors. External stimuli include bacteria, fungi, house-dust mites, viruses, antigens, mechanical stress, UV light or temperature change. Moreover, endogenous inflammatory mediators such as cytokines, neuropeptides, proteases, eicosanoids, nitric oxygen or other free radicals may directly modulate keratinocyte function. Thus, cytokines and other factors derived from keratinocytes may have an important regulatory role in many physiological and pathophysiological conditions in the skin such as inflammation, immune defence and wound healing. Keratinocytes are important regulators of cutaneous inflammation, orchestrating the communication between epidermal and dermal cells and immigrating immune cells, in order to re-establish skin homoeostasis.

The response of keratinocytes to injury may be separated into two phases. In the first phase they produce pro-inflammatory mediators that contribute to the body defence mechanism by reacting to danger signals. In the second phase, keratinocytes induce cutaneous regeneration by activating fibroblasts and proliferation of keratinocytes.

One of the central molecules for the inflammatory response is IL-1. In the skin, IL-1 is mainly synthesized in basal, but also suprabasal keratinocytes, and is released upon various injurious stimuli. IL-1 release can be induced in an autocrine or paracrine fashion by IL-1 itself, or by other cytokines such as TNF-α or IL-6 [1]. Keratinocyte-derived IL-1 can stimulate the release of granulocyte–macrophage colony-stimulating factor (GM-CSF), which serves as a crucial mediator for the activation and differentiation of Langerhans' cells. Keratinocyte-derived cytokines such as TNF-α, IL-1 or IL-6 may enter the circulation and subsequently exert systemic effects such as fever and acute-phase protein production. Keratinocytes also release various chemokines such as CCL-8, CCL-27, RANTES, GRO-α, monocyte chemotactic protein 1 (MCP-1), interferon-inducible protein 10 (IP-10), eotaxin and others, which regulate trafficking of lymphocytes, neutrophils, eosinophils, dendritic cells and mast cells.

Table 9.2 Human *keratinocyte* cytokines and pro-inflammatory mediators.

Agent	Abbreviation
Interleukins	
Interleukin-1α and β	IL-1α and β
Interleukin-3	IL-3
Interleukin-6	IL-6
Interleukin-8	IL-8
Interleukin-18	IL-18
Interferons	
Interferon-α	IFN-α
Interferon-β	IFN-β
Interferon-γ	IFN-γ
Pro-inflammatory mediators	
Tumour necrosis factor-α	TNF-α
Monocyte chemotactic protein-1 CCL27	MCP-1
Epidermal cell lymphocyte chemotactic factor	ELCF
Macrophage migration Inhibitory factor	MIF
Prostaglandin E_2*	PGE_2
Leukotriene B_4*	LTB_4
12-Hydroxyeicosatetraenoic acid	12-HETE
Epidermal proteases	Cathepsins
Serine protease	Trypsinogen
Lysozyme	—
Neuropeptides	SP, NKA
Anti-inflammatory mediators	
α-Melanocyte stimulating hormone	α-MSH
Colony-stimulating factors	
Granulocyte–macrophage colony-stimulating factor	GM-CSF
Granulocyte colony-stimulating factor	G-CSF
Macrophage colony-stimulating factor	M-CSF
Growth regulators	
Transforming growth factor-α	TGF-α
Transforming growth factor-β	TGF-β
Platelet-derived growth factor	PDGF
Basic fibroblast growth factor	bFGF
Vascular endothelial growth factor	VEGF
Endothelin-1	ET-1

* Detection in skin *in vivo*, presumably from the epidermis.

Thus, keratinocytes actively participate in the regulation of many inflammatory skin diseases including psoriasis and atopic dermatitis.

Growth factors such as epithelial growth factor (EGF) also modulate keratinocyte function during inflammation and tissue repair. Recently, an autocrine loop of keratinocyte proliferation and migration was observed during wound healing, which was found to be regulated by the receptor for EGF [2]. Increased TGF-β, basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF) expression levels can be also observed in keratinocytes after injury and inflammatory stimuli, indicating that keratinocytes are autocrine and paracrine key regulators of growth factors during skin inflammation and remodelling. Resting keratinocytes constitutively synethesize TNF-α, which at low concentrations may control keratinocyte proliferation and the maturation of Langerhans' cells. During inflammation and wound repair, keratinocyte-derived TNF-α also participates in the regulation of T-cell activity and dendritic cell functions [3]. Moreover, keratinocyte-derived cytokines such as TNF-α are involved in the regulation of dermal microvascular endothelial cells, via stimulation of the production of cytokines and chemokines, and up-regulation of cell adhesion molecule expression, such as ICAM-1 or vascular cell adhesion molecule (VCAM). Other growth factors generated by keratinocytes are transforming growth factors (TGF-α, TGF-β) and colony-stimulating growth factors (G-CSF, M-CSF, GM-CSF), which exert multiple functions in the skin.

In human keratinocytes, the expression of co-stimulatory molecules such as CD80, which is an important signal for professional antigen-presenting cell and T-cell interactions, is up-regulated by allergens or irritants [4]. In

addition, various inflammatory stimuli up-regulate the expression of MHC molecules such as MHC II or CD1d on keratinocytes, suggesting a role for keratinocytes in antigen presentation [5]. Keratinocytes also provide a source of antigenic proteins to which chemical haptens can conjugate. Lymph node cells from hapten-sensitized mice were found to proliferate in the presence of a keratinocyte extract without hapten [6]. Keratinocyte-derived chemokines also have an essential role during the induction, as well as the elicitation phase of contact hypersensitivity [7].

UV radiation is an important trigger factor that modulates keratinocyte function during inflammation. UV causes DNA damage and, via the activation of the transcription factor NF-κB, induces the production of cytokines, growth factors, proteases and matrix metalloproteinases, which regulate keratinocyte function. Recently, keratinocyte- as well as mast cell-derived cytokines such as TNF-α have been demonstrated to be involved in UV-mediated cutaneous immune responses [8,9]. It was observed that UV failed to induce tolerance in mast cell-deficient mice, and that tolerance occurred if mast cells were triggered to degranulate after activation of the IgE receptor [6]. Recent findings also support a role for NF-κB target genes (IL-1, IL-6, TNF-α, VEGF) in sunburn reactions after UV [10]. Finally, UV also induces the production of suppressor factors, such as IL1-RA, IL-10, TGF-β and α-MSH, which exert an anti-inflammatory and immunosuppressive action. The secretion of these signals following UV usually occurs later, after the initiation of pro-inflammatory mediators, and may therefore reflect mechanisms for the down-regulation of inflammation and the prevention of chronic inflammation [11].

Various microbiological agents such as viruses, bacteria, fungi or house-dust mite antigens, via multiple mechanisms including proteases, proteins and glycoproteins, may also affect keratinocyte functions, ultimately resulting in an inflammatory response. For example, human papillomaviruses (HPV) are known to modulate the expression of signals in keratinocytes that regulate their proliferation, as well as the release of mediators of inflammation. HPV-16 down-regulates IFN-responsive genes and up-regulates NF-κB-responsive genes in keratinocytes, resulting in a modified immune response. Moreover, an HPV-16 protein was found to induce the secretion of chemokines such as IL-8, RANTES, macrophage inflammatory protein-1α (MIP-1α) and IFN-γ-inducible protein. IFN-inducible genes and STAT1 appear to be crucial target genes for keratinocyte-targeting viruses [12]. Thus, keratinocytes may directly alter gene expression in response to pathogens, and thereby influence host resistance to infection and inflammation. Bacterial infections of the skin are another example of the interaction of microbes with keratinocytes. Streptococci and staphylococci frequently infect the skin by using strategies to overcome keratinocyte defence mechanisms. Beside defensins, CD44 appears to have an important role as a receptor for the colonization of keratinocytes by group A streptococci. Thus, receptor-blocking strategies on keratinocytes (e.g. TLRs, CD44) may be novel tools for the treatment of cutaneous infections [13]. In summary, keratinocytes, via the release of mediators and the expression of surface molecules, subserve multiple important functions in the skin during inflammation and infection, tissue repair and autoimmunity.

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Lymphocyte-mediated cytotoxicity

T lymphocytes have a pivotal role in the pathogenesis and pathophysiology of any immune-mediated and inflammatory skin diseases. Many of them, such as psoriasis, atopic dermatitis, contact dermatitis and lichen planus, are T-lymphocyte driven. The crucial role of T cells in the pathogenesis of these diseases is also supported by the finding that deletion of T cells *in vivo* leads to a significant improvement. Depending on the microenvironement, T cells are key players both as effector and regulatory cells. The role of T cells during inflammation and the immune response is extensively discussed in Chapter 10 so this chapter only deals with recent knowledge on the role of perforins in T-cell-mediated cytotoxicity.

T-cell-mediated cytotoxicity is involved at several stages of cutaneous inflammation. Cytotoxic T cells (CTL)

secrete the pore-forming glycoproteins termed perforins, which are able to integrate into the cell membrane, thereby leading to disintegration of target cells. Perforins are markedly up-regulated during infection and inflammatory skin diseases such as atopic dermatitis. Moreover, CTL recognize target cells and present the processed antigen. In contrast, NK cells exert their effects by up-regulating and releasing Fas ligand, which activates Fas on the target cell during inflammation [1]. Thus, in different ways, CTL and NK cells are critically involved in tissue protection during inflammation, infection and tumour growth.

There is evidence that $CD4^+$ T cells are also capable of generating cytolytic activity. Whether they secrete a direct cytolytic factor or exert their effects via an immunoregulatory mechanism is still unclear. However, both Fas- and perforin-dependent cytolytic pathways seem to be possible [2,3].

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Natural killer cells

NK cells or large granular lymphocytes are bone marrow-derived lymphocytes that were originally characterized by their ability to lyse a variety of tumour targets and infected cells, and which share a common progenitor with T lymphocytes. They originally were referred to as null cells, because they display neither T- nor B-cell-specific characteristics. These cells typically express CD56, which is homologous to neural cell adhesion molecule, and sometimes express CD16, a low-affinity receptor for the Fc portion of IgG. CD16 is often associated with the CD3-ζ homodimer found in the T-cell receptor–CD3 complex. NK cells comprise approximately 10% of peripheral blood lymphocytes, and express neither B-cell-specific membrane immunoglobulins nor the T-cell receptor–CD3 complex. However, they may express some T-cell differentiation antigens, such as CD2 and CD8, and myelomonocyte differentiation antigens, such as CD11b, CD11c, CD14 and CD15 [1].

It is well known that NK cells are able to secrete significant amounts of cytokines (IFN-γ and TNF-α) as well as chemokines. In contrast to T- and B-cell responses to antigen, which typically require a proliferation phase, the innate NK-cell response is immediate, implying that NK cells are involved in curbing pathogens during the initial several days of infection. Indeed, there is strong evidence that NK cells contribute to the defence against intracellular bacteria and parasites and that they are crucial for controlling several types of viral infection. Moreover, their antitumour capacity is well established *in vitro* as well as *in vivo* [2–4].

As other cells, NK cells express inhibitory receptors specific for MHC class I proteins and stimulatory receptors with diverse specificities. Thus, they do not require the specialized gene rearrangement machinery that assembles T- and B-cell antigen receptor genes. Nevertheless, NK cells exhibit a clear capacity to discriminate between target cells. In the case of cellular targets, sensitivity to NK cells is correlated in many instances with decreased levels of MHC expression. NK cells are also able to reject MHC-incompatible bone marrow grafts. These observations led to the formulation of the 'missing self' hypothesis, by which NK cells may ignore potential targets expressing normal levels of autologous class I molecules and attack cells that do not. However, 'missing self-recognition' is only one of several modes of NK cell–target cell discrimination [5–9].

NK cells preferentially kill target cells that lack surface expression of MHC class I molecules. This implies the existence of triggering receptors that recognize non-MHC ligands on these target cells. Unlike T lymphocytes that recognize MHC–peptide complexes using clonally distributed T-cell receptors generated by gene rearrangement, NK cells appear to use triggering receptors that do not require this genetic process. These triggering receptors can initiate NK-cell activation and target cell lysis, provided that NK cells are not turned off by activation of MHC class I-specific inhibitory receptors. These data suggest that triggering NK receptors involved in natural cytotoxicity recognize non-MHC ligands expressed not only by abnormal but also by normal cells [10,11].

NK receptors. NK cells are regulated by opposing signals from receptors that activate and inhibit effector functions. Three distinct receptor families, Ly49, CD94/NKG2 and KIR (killer cell-inhibitory cell receptors), are involved in NK-cell recognition of polymorphic MHC class I molecules. Recent studies suggest these inhibitory NK-cell receptors are members of a larger superfamily containing immunoreceptor tyrosine-based inhibitory motif (ITIM), defined as the inhibitory receptor superfamily (IRS). Thus, NK cells are regulated by a balance of signalling via stimulatory receptors, specific for diverse ligands, and inhibitory receptors, specific for MHC class I molecules [12].

Three novel NK-specific triggering surface molecules that are involved in natural cytotoxicity have been identified (NKp46, NKp30 and NKp44). They represent the first members of a novel emerging group of receptors collectively termed natural cytotoxicity receptors (NCRs) [13]. Interestingly, there exists coordinated surface expression

of the three NCRs, their surface density varying in different individuals and also in the NK cells isolated from a given individual. While an altered expression or function of NCR or NKG2D is being explored as a possible cause of immunological disorders, dysfunction has already been associated with a severe form of immunodeficiency. Upon activation of NCRs, NK cells undergo blastogenesis, generate cytokines, enhance cytotoxicity and migrate. In contrast, inhibitory receptors prevent killing of normal cells and limit the production by NK cells of inflammatory cytokines including TNF-α, IFN-γ and GM-CSF.

Another more classic NK-cell receptor is the low-affinity receptor for IgG, CD16 (Fc RIII). The transmembrane-anchored CD16 isoform is expressed on the majority of, but not all NK cells, as well as on activated monocytes and a subset of T cells. Upon CD16-mediated activation, NK cells secrete cytokines [14], mediate antibody-dependent cellular cytotoxicity and may undergo apoptosis as a consequence of Fas ligand-induced cell death [15]. CD2 may be a co-stimulatory receptor that augments primary activation of NK cells.

MHC-specific receptors discriminate among different MHC class I alleles and are expressed in a variegated overlapping fashion, such that each NK cell expresses several inhibitory and stimulatory receptors. Together these mechanisms ensure a self-tolerant and maximally discriminating NK-cell population.

Upon stimulation, NK cells produce high levels of certain cytokines and chemokines. They have a crucial role in the defence against a number of different infectious agents and tumours. The first evidence for this function came from observations that virus-induced interferons (IFN-α and -β) are potent inducers of NK-cell-mediated cytotoxicity, and that NK cells are important contributors to innate defence against viral infections. Since that time, a wide range of other innate cytokines have been detected that mediate biological functions regulating the NK-cell responses of cytotoxicity, proliferation and IFN-γ or TNF-α production. For example, certain viral infections induce IL-12, which elicits IFN-γ production by NK cells, thereby inducing antiviral mechanisms. Thus, after microbial stimulation, NK cells have immediate effects resulting in host defence, especially with regard to viruses. In addition, chemokines such as MIP-1α are capable of stimulating migration of NK cells, probably via binding of the CCR5 chemokine receptor. Other chemokines that activate NK cells are MIP-1β, MCP-1, -2, -3 and RANTES. In addition, numerous cytokines have been found to modulate NK-cell function, including IFN-α and -β, which induce cytotoxic activity, stimulate proliferation and inhibit IL-12 production [13,16].

Unlike T or B cells, NK cells develop normally in *scid* mice or mice with disrupted rearrangement genes, indicating that gene rearrangement is not required for their differentiation or function. NK cells are instrumental in innate immune responses, in particular providing for the early production of IFN-γ and possibly other cytokines necessary to control certain bacterial, parasitic and viral infections. The factors responsible for activation of NK cells during infection have remained elusive, but likely involve soluble factors such as IFN-α and -β, cytokines (TNF-α, IL-12, IL-15) and chemokines, as well as the presence of certain membrane-bound molecules on surrounding tissues. Although positive stimuli are required to activate NK-cell migration and effector function, the process is tightly regulated by inhibitory receptors and cytokines that limit and potentially terminate the response [17–19].

Thus, NK cells serve as sentinels in the immune system, which is constantly assailed by pathogens as well as antigens, and where the achievement of a balance is crucial to permit elimination of pathogens but avoid autoimmunity. For example, the potential for self-aggression is dramatically illustrated by the phenotype of mice with disrupted *CTLA-4* genes. In these animals, CD28 stimulation via CD80 or CD86 in the absence of negative regulation by CTLA4 [20,21] leads to a T-cell lymphoproliferative disease that results in death. Receptors which possess the consensus ITIM (CD22, LAIR-1, gp49, LIR1, gp91/PIR, ILT1/2, ILT3) sequence seem to be crucial in this context [13,19–21].

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Polymorphonuclear granulocytes

The polymorphonuclear granulocytes, basophils, eosinophils and neutrophils, are the mobile attack forces of the allergy army. All arise from haematopoietic precursors, undergo maturation within the bone marrow and are released into the blood as mature leukocytes. Eosinophils and basophils are thought to arise from a common mononuclear stem cell, which is stimulated to divide by the cytokines IL-3 and GM-CSF acting in concert with stromal factors. While the production of these cells is limited in normal conditions, in allergy increased levels of GM-CSF and IL-5 result in their increased production. Both eosinophils and basophils are primarily tissue cells with a very limited lifespan in the blood. For eosinophils, the lifespan in the blood is approximately 24 h and the tissue : blood ratio is about 100 : 1. In contrast, neutrophils are produced constitutively by the bone marrow in large numbers. Because of the large number produced and the relatively short lifespan (less than 24 h), more than half of the work done by the bone marrow is dedicated to the production of neutrophils. In inflammation, increased levels of inflammatory cytokines stimulate enhanced neutrophil production. IL-3, IL-6, GM-CSF and TNF-α are the cytokines that are most likely to be involved.

Basophils

Although representing less than 1% of the circulating leukocytes, basophils can be purified from the blood and have been studied extensively *in vitro*. Like mast cells, basophils stain metachromatically with aniline dyes but can be distinguished from mast cells by their bilobed nucleus.

Structurally and functionally, basophils have a lot in common with mast cells. Perhaps the most important similarity is the presence of FcεRI, the high-affinity receptor for IgE, on their surface. Basophils derived from allergic patients contain up to 500 000 IgE receptors per cell [1]. However, they can be activated by cross-linkage of only approximately 1% of this number [2], making them exquisitely sensitive to allergen stimulation. It has been suggested that IgE on basophils may be in one of two forms, IgE^+ or IgE^-; cells with the former form being activated by IL-3 and histamine-releasing factors [3,4]. Furthermore, like skin mast cells, basophils are activated by the complement fraction, C5a. Other receptors on basophils are for IL-3, IL-4 and GM-CSF, which prolong their survival, and a histamine H_2 receptor, which down-regulates their function. The ease with which basophils can be obtained from patients has led to their widespread use *in vitro* in research and diagnosis of allergic disease (e.g. to detect circulating histamine-releasing autoantibodies in chronic urticaria [5]).

Basophils contain about 1 pg/cell of histamine, which, as in mast cells, is stored in modified lysosomal granules in combination with proteoglycans, predominantly chondroitin sulphate in the case of the basophil. Basophils contain very small amounts of tryptase, but no chymase. On stimulation, basophils generate relatively large amounts of the leukotrienes (LT) LTC_4, but not LTB_4 or the prostaglandin (PG) PGD_2 [6]. Another important function of the basophil is the generation of IL-4 and IL-13, which are critical for switching the B lymphocyte to IgE production [7,8].

In allergic diseases, basophils migrate from the bone marrow, enter the circulation as mature cells and infiltrate tissues in response to inflammatory stimuli. Knowledge of their role within the tissues is largely circumstantial. One reason is that basophils infiltrating an area of active allergic disease are likely to undergo degranulation quite rapidly and therefore be difficult to detect. Another is that until recently it has been difficult to distinguish tissue basophils from mast cells. However, monoclonal antibodies to a basophil granule protein have been described recently [9,10], which should revolutionize basophil research; for example, evidence for basophil recruitment during late-phase allergic response is now unequivocal [11].

Eosinophils

The idea of an association between eosinophils and allergic disease, particularly asthma, has a long history. Until the 1980s, it was thought that eosinophils might be anti-inflammatory. However, with the realization that eosinophil granule proteins are highly toxic, this view changed to one of eosinophils being considered as pro-inflammatory cells. Indeed, many of the features of asthma and related allergic diseases were considered to be mediated by eosinophil products. However, recent studies with anti-IL-5 and IL-12, which ablated eosinophils but failed to relieve asthma [12,13], are now throwing doubt on the pivotal role ascribed to eosinophils in allergic diseases.

Coming from a common precursor, eosinophils and basophils are closely related. Eosinophils, like basophils,

are approximately 8 μm in diameter, have a bilobed nucleus and use the blood merely as a transport system to reach the tissues. The eosinophil cytoplasm contains two types of granule, the most characteristic of which is the core-containing specific granule, which contains the basic proteins. Such granules avidly take up acidic dyes (e.g. eosin), giving eosinophils their characteristic microscopic appearance. The other granule is the so-called 'primary granule', which lacks a core and is of variable size. Also present in the cytoplasm are a number of lipid bodies, thought to be a store of arachidonic acid for eicosanoid synthesis.

The eosinophil membrane is particularly rich in receptors for adhesion proteins, chemokines and cytokines. For example, the coordinated action of IL-5, CCR3 binding chemokines and the adhesion molecules P-selectin and VCAM-1, acting in concert, cause selective recruitment of eosinophils into allergic tissue [14]. Once in the tissues, GM-CSF, IL-5 and eotaxin serve to both prime eosinophils for chemotactic and degranulatory responses and adhesion and cytotoxicity, and to prolong survival. Interestingly, eosinophils produce large quantities of GM-CSF and IL-5, so ensuring their own survival [15]. Eosinophils also possess immunoglobulin receptors for IgA, IgG and IgE, and therefore have wide interactions with the immune system.

The major proteins of the eosinophil granule are major basic protein (MBP), eosinophil cationic protein (ECP), eosinophil peroxidase (EPO) and eosinophil-derived neurotoxin (EDN). To explain their presence, it must be remembered that the allergic response was originally developed as an immune defence system against helminth parasite infestation. All the above proteins are highly toxic to helminths. As they are also potentially toxic to mammalian cells, they may cause tissue damage in allergic responses. In addition, the peroxidase actions of EPO may lead to the generation of toxic oxygenated free radicals.

Eosinophils are probably the major producers of LTC_4 in allergic inflammation. Although this has profound implications for asthma, the importance in allergic responses in the skin is less clear. However, the beneficial effects of leukotriene receptor antagonists in atopic dermatitis [16] and urticaria [17] suggests an involvement.

In peripheral blood and non-inflamed tissue, eosinophils are in a resting state to prevent unwanted tissue damage from eosinophil-derived mediators. In order to become activated, eosinophils must first be primed by exposure to the cytokines IL-5, GM-CSF and IL-3, or the lipid products platelet-activating factor (PAF) and LTB_4. As the majority of these substances are also chemoattractants, the end result is large numbers of degranulating eosinophils and heavy granule protein deposits at sites of allergic inflammation. Such a strategy would be ideal if the target was the surface of a large helminth parasite. However, in allergic skin disease, the stimulus is allergen and not a parasite. Even so, large deposits of extracellular eosinophil granule proteins are found in both urticaria [18] and atopic dermatitis [19,20], with raised MBP levels being found in the circulation [21].

Neutrophils

Neutrophilic polymorphonuclear leukocytes (or neutrophils), are approximately 7 μm in diameter and are easily recognized in conventional cytological preparations by their pinkish cytoplasm and distinctive polymorphic nuclei. When neutrophils are viewed under the electron microscope, a number of heterogeneous granules are obvious. The larger of these, the so-called primary or azurophilic granules, are peroxidase-positive, whereas the smaller ones, the so-called secondary or specific granules, are peroxidase-negative. Other subcellular structures, such as Golgi apparatuses, are scarce.

Neutrophils are the most numerous of the blood leukocytes and represent the first line of defence of the immune system against infection and tissue injury. As a consequence, it is necessary for them to be able to reach an inflammatory site very rapidly. Once released from the bone marrow, the majority of neutrophils are 'stored' intravascularly by the process of margination. It has been calculated for a 70-kg male that the number of marginated neutrophils is approximately 3×10^{10} [22]. The expression of a high density of adhesion proteins on their cell surface allows large numbers of neutrophils to move rapidly from their marginated sites into inflamed tissues. Indeed, evidence of their accumulation may be seen within minutes of a tissue stimulus. Several adhesion proteins have been identified on the neutrophil, the most important being the integrin LFA-1 (CD11a/CD18), which is the ligand for ICAM-1 [23]. In order to move rapidly to an inflammatory site once in the extravascular compartment, neutrophils must also express high levels of receptors for a wide range of chemotactic agents, such as IL-8 and LTB_4 (Fig. 9.5).

Like the other granulocytes, neutrophil mediators may either be preformed and stored in granules or be synthesized *de novo* on cell activation. The preformed mediators are mainly enzymes that facilitate the primary function of the neutrophils—to phagocytose and digest bacteria and other foreign particles. Neutrophil lysosomal granules contain more than 20 enzymes, including proteinases, elastase, gelatinase, collagenase, lysozyme, cathepsin G and defensins [24]. These enzymes may act either intracellularly to digest ingested bacteria or be released into the extracellular environment during inflammation. A further enzyme, myeloperoxidase, facilitates the bactericidal respiratory burst, which is characteristic of neutrophil activation [25]. In this reaction, oxygen radicals, hydrogen peroxide (H_2O_2) and superoxide (O_2^-) generated by the peroxidase converted into the even more toxic hypochloric acid (HOCl) and hydroxyl ($OH^\bullet$) radicals.

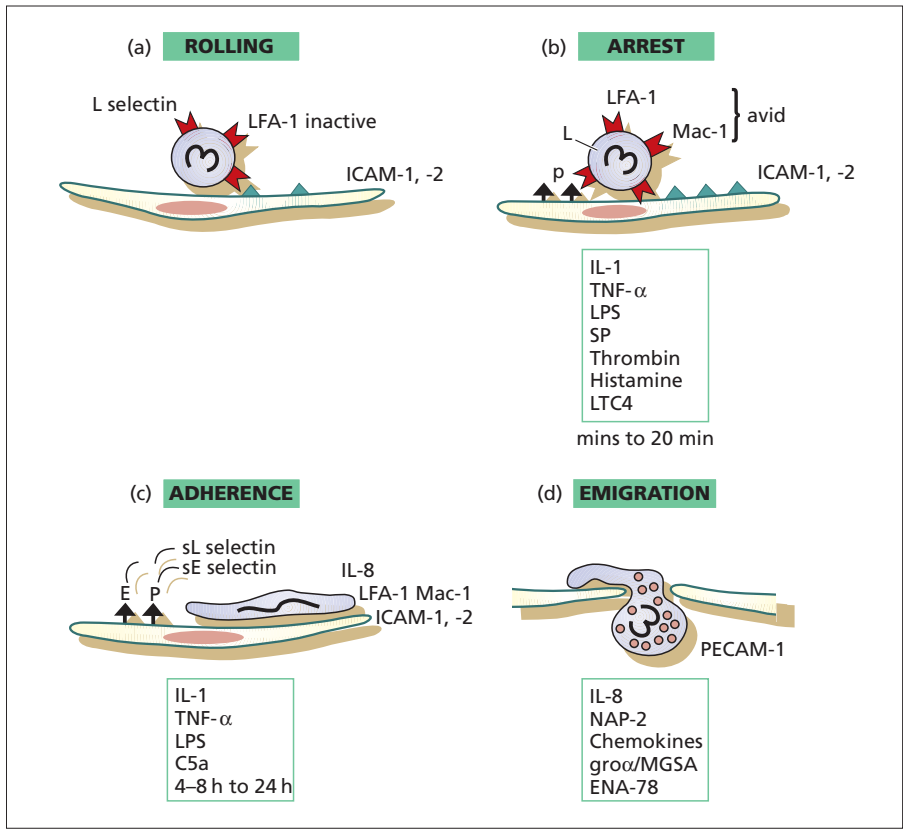

Fig. 9.5 Neutrophil emigration. (a) Rolling: cells roll over the endothelium by brief non-adherent contacts via the selectins, particularly L-selectin. The integrins are non-binding. (b) Arrest: on contact with activated endothelium, selectin binding briefly increases, integrins become avid and intercellular adhesion molecule 1 (ICAM-1) increases on the endothelial surface. (Monocytes and eosinophils also bind via α4β1 to vascular cell adhesion molecule 1 (VCAM-1).) (c) Adherence: the neutrophil flattens on the endothelium, affinity increases and motility response to chemokines is initiated. (d) Emigration: neutrophil leaves vessel through interendothelial cell junction, regulated by integrins, platelet/endothelium cell adhesion molecule 1 (PECAM-1) and chemokines.

Evidence of the capacity of neutrophils to cause tissue damage is, for example, the tissue degradation round an implanted foreign body, such as a splinter, in order to facilitate its rejection as part of the healing process. Pus is an extreme example of neutrophil activity resulting from severe degradation of tissue and of dead leukocytes. However, the potential for neutrophils to cause overt tissue damage is limited by the presence of antiproteinases, such as α_2-antiproteinase, α_2-macroglobulin and antielastins, which penetrate the tissues from plasma during inflammation. Therefore, it is unlikely that neutrophils cause overt tissue damage in the presence of normal levels of antiproteinases. However, in antiproteinase deficiency, as has been suggested is the case in emphysema, the potential for neutrophil-induced tissue damage is enhanced [24].

The primary role of the newly generated mediators appears to be directed to the recruitment of more neutrophils. In the short term, this is facilitated by the synthesis and release of large quantities of LTB_4, a potent neutrophil attractant. *In vitro*, neutrophils certainly have the capacity to synthesize the cytokines IL-1β, TNF-α and IL-8, which would serve to recruit and activate further neutrophils, and IL-6, IL-12 and GM-CSF, which stimulate haematopoiesis of neutrophil precursors. However, bearing in mind that the peak production time for cytokines is often 12–24 h after cell stimulation, the clinical significance of their production in a cell with a tissue lifespan often less than 6 h is questionable.

The potential role(s) of neutrophils in inflammatory diseases is even less clear than that of basophils and eosinophils. In many situations when the neutrophils are present microscopically, it is difficult determine whether their presence is a cause or consequence of the condition. However, there is evidence that damage to the blood vessel wall in cutaneous leukocytoclastic vasculitis is caused by enzymes from activated neutrophils [26]. It has also been suggested that neutrophil elastase is involved in the dermal–epidermal cleavage observed in bullous pemphigoid [27].

The L-selectin molecule is localized to neutrophil microvilli and is cleaved or 'shed' during neutrophil activation, possibly permitting neutrophils to migrate from the intravascular lumen into sites of inflammation. After activation, P-selectin facilitates and supports neutrophil degranulation, superoxide (O_2^{2-}) production, and polarization in response to PAF and bacterial formylated peptides, such as formyl-methionyl-leucyl-phenylalanine (fMLP) [28]. In response to chemoattractant, cross-linking of L-selectin on neutrophils primes cells for increased O_2^{2-} production and calcium influx, and stimulates adhesion. Interaction of neutrophils with endothelial cells also results in increased mRNA levels for TNF-α and IL-8.

Many chemokines, including IL-8 and other chemoattractants such as formyl peptides, complement C5a, LTB_4 and PAF, cause rapid neutrophil adhesion, thereby supporting their emigration from the vasculature [29]. In contrast, the role of various mediators and chemokines in activation of the process of rolling of neutrophils in inflamed venules is still unclear. In certain *in vitro* systems, neutrophil arrest from rolling can be attributed to a single chemoattractant. For example, human umbilical vein endothelial cells (HUVEC) treated with histamine or thrombin support P-selectin-dependent neutrophil rolling and PAF-dependent activation [30]. However, in most inflammatory models *in viv*o, PAF synthesis or receptor antagonists have little or no effect.

Inflammatory or bacterial substances in sufficient amounts may depress the activities of neutrophils, as observed in patients with extensive leg ulcers, for example. Acquired defects in neutrophil chemotaxis are also observed in diabetes mellitus, which may be corrected *in vitro* by the addition of potassium, glucose and insulin. Thus, reduced random movement and response to chemotactic substances may be induced in previously normal neutrophils by severe bacterial infection, without obvious granule changes. This is reversible, because the reduced responsiveness of neutrophils returns to normal during effective treatment. In such cases, it is necessary to differentiate diminished activity induced in mature cells from the normal, lesser activity of immature cells mobilized as a result of the infection.

Abnormalities in neutrophils can have profound effects on resistance to disease. Several defects in enzyme activity have been observed. A deficiency in the H_2O_2–myeloperoxidase–halide system impairs the bactericidal activity of leukocytes. A very good example is chronic granulomatous disease, characterized by recurrent granulomas of skin and lymph nodes, which is associated with defective ability of neutrophils to kill bacteria [31]. An impairment in nicotinamide adenine dinucleotide (NADH) oxidase results in a failure to form H_2O_2 [32], which is critical for effective bactericidal activity. Moreover, deficiency of glucose-6-phosphate dehydrogenase (G6PD) results in the inability to kill catalase-active bacteria.

Several diseases have been revealed to be associated with defects in neutrophil function. In leukocyte adhesion deficiency-I (LAD-I), patients lack CD18 and therefore all β2 integrins; their neutrophils can neither tightly adhere to endothelium nor exit from the circulation in response to infection. LAD-I patients have recurrent skin and mucosal infections, with most patients dying before the age of 10 years [33]. However, qualitative activation rather than quantitative expression of β2 integrins seems to be critical for stimulated neutrophil adhesion [34,35]. Another class of patient has defective carbohydrate fucosylation and lack of expression of Sle x ligands [36]. These 'LAD-II' patients have decreased neutrophil motility *in vitro*, neutrophilia and recurrent bacterial infections. Interestingly, classic drugs such as colchicine have been shown to decrease E-selectin density on endothelial cells and to down-modulate L-selectin expression on neutrophils [37]. Methotrexate inhibits neutrophil adhesion to connective tissues [35]. Corticosteroids lower adhesion molecule expression on both endothelium [38] and neutrophils [39]. Salicylates also inhibit neutrophil adhesion, probably by blocking activation of CD11b/CD18 [40].

Chédiak–Higashi disease is a rare autosomal recessive disease affecting neutrophils and all other lysosomal granule-containing cells in the body. The disease is secondary to mutations in *Lyst*, a gene encoding a cytoplasmic protein involved in lysosomal trafficking [41,42]. The neutrophils contain giant granules resulting from specific and azurophilic granule fusion. Patients have recurrent bacterial infections, neurological disease, partial albinism, platelet dysfunction and early death [33].

Another inherited granule disorder characterized by recurrent bacterial infection is specific granule deficiency, marked by the absence of neutrophil-specific granules and defensins. The disorder is likely secondary to the deficiency of transcription factor CCAAT/enhancer binding protein E, which has a critical role in normal myeloid cell development. Recently, a mutation in the gene encoding this protein has been characterized, and a knockout mouse for this gene has been engineered, showing impaired nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity [43], phagocytosis, intracellular killing and migration [44].

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Mast cells

Mast cells are a heterogeneous group of multifunctional tissue-dwelling cells with roles in conditions as diverse as allergy, parasite infestation, inflammation, angiogenesis and tissue remodelling. The cells were named mastzellen (Greek *mastos*, breast) in 1876 by Paul Ehrlich because he believed that the intracellular granules, which appeared purple in colour when stained with aniline blue dyes, contained phagacytosed materials or nutrients [1]. This change in colour, or metachromasia, we now know to represent the interaction of the dyes with the highly acidic heparin contained within mast cell granules. Mast cells are haematopoietic in origin, entering the circulation from the bone marrow as mononuclear cell precursors that both express mRNA for stem cell factor (SCF) and have SCF receptors (SCFR, CD117) on their cell membranes [2]. From the blood, the precursors migrate into the tissues where, under the influence of local microenvironmental factors, they undergo their final phases of differentiation and maturation into recognizable mast cells. It is pertinent at this stage to distinguish mast cells from basophils, which were originally thought to be circulating mast cells, but are actually related more closely to eosinophils, developing in the bone marrow from granulocyte precursors and entering the circulation only when fully mature [3]. Mast cells and basophils differ in their repertoire of mediators released (Table 9.3).

Mast cells are distinguished immunocytochemically by their neutral protease content, the MC_T phenotype containing only tryptase and the MC_{TC} phenotype containing both tryptase and chymase [4]. MC_T and MC_{TC} mast cells also express different receptors (Table 9.4). Initially, these respective subtypes were suggested to be the equivalents of the 'mucosal' and 'connective tissue' previously described in experimental animals. However, it is now realized that variable amounts of both mast cell subtypes are present within any given tissue, their relative abundance changing with disease (e.g. in allergy or fibrosis). MC_T

Table 9.3 Comparison of mediators formed by human mast cells and basophils.

Mediator/product	Mast cells	Basophils
Histamine	+	+
Leukotriene C_4	+	+
Leukotriene B_4	–	(+)
Prostaglandin D_2 (PGD_2)	+	–
5-HETE	+	–
Thromboxane A_2 (TXA_2)	+	–
Platelet-activating factor (PAF)	+	–
Interleukin-1β	+	
Interleukin-3	+	
Interleukin-4	++	+
Interleukin-5	+	?
Interleukin-6	+	?
Interleukin-8	+	+
Interleukins-9, -10, -13, -14	+	
MCP-1α (chemokine)	+	
TNF-α	++	–
Tryptase/chymase	+	–
Carboxypeptidase	+	–
Heparin	+	–
Nerve growth factor (NGF)	+	
Eosinophil chemotactic factor	+	+
Neutrophil chemotactic factor	+	?

Table 9.4 Receptors identified on the mast cell and basophil membrane.

	Mast cells			
Receptors	MC_{TC}	MC_T	Basophil	Ligand/agonist
FcεR1	+	+	+	IgE
CD32 FcγRI	–	–	+	IgG
CD88				
C5aR	+	(–)	+	C5a
C3aR	–	–	+	C3a
CD25				
IL-1R	+	–	–	IL-1
IL-2R	–	–	+	IL-2
IL-3R	–	+	+	IL-3
IL-5R	–	–	+	IL-5
CDw128 IL-8R	–	–	+	IL-8
GM-CSFR	–	–	+	GM-CSF
Toll-like receptor (TLR)				
TLR1	+	(–)	–	
TLR2	+	–	+	Bacterial peptides
TLR4	+	–	+	LPS
TLR6	+	–	–	Bacterial peptides
Chemokine receptors				
CCR1	+	(–)	(+)	MIP1-α
CCR2	–	–	+	MCP
CCR3	+	(–)	+	MCP
CCR4	+			
CD40L	+	–	+	CD40 : B cells
CD117 c-*kit* (KL)	+	+	(+)	Stem cell factor c-*kit* ligand

GM-CSF, granulocyte–macrophage colony-stimulating factor; IL, interleukin.

appear to be 'immune system-related' mast cells with a primary role in host defence, whereas MC_{TC} appear to be 'non-immune system-related' mast cells with functions in angiogenesis and tissue remodelling rather than immunological protection. However, it should be remembered that both phenotypes express FcRI and may therefore participate fully in IgE-dependent allergic reactions.

In addition, there appears to be a functional heterogeneity between mast cells of different tissues, which is largely unrelated to immunocytochemical heterogeneity. For example, human skin mast cells alone express CD88, the receptor for the anaphylatoxin C5a, allowing them to be activated in complement-mediated disease [5,6]. Also, skin mast cells alone respond to a variety of basic non-immunological secretagogues, including neuropeptides and drugs, such as morphine, codeine and muscle relaxants [7,8]. Interestingly, activation by these agents is incomplete, in that eicosanoid generation does not accompany degranulation [7]. The ability of human skin mast cells, but not those from other tissues, to respond to anaphylatoxins and basic non-immunological secretagogues explains the flushing reactions observed in sensitive individuals in the absence of overt rhinorrhoea or bronchoconstriction. Such responses may also be involved in physical urticarias.

The secretory granule of the human mast cell contains a crystalline complex of preformed inflammatory mediators ionically bound to a matrix of heparin proteoglycan. The mediator most readily associated with the mast cell, the simple diamine histamine, is present in the granules at approximately 100 mmol/L, equivalent to about 1–4 pg/cell. Histamine exerts many effects pertinent to the immediate phase of allergic responses, including initiation of the wheal and flare response [9]. However, these effects are normally of relatively short duration as histamine is rapidly metabolized, usually within 1–2 min, by histamine-*N*-methyltransferase (approximately 70%) and by diamine oxidase (histaminase) (approximately 30%). Interestingly, reduced diamine oxidase activity has been associated with recurrent urticaria [10].

The other 'early phase' mediators released from the skin mast cell are PGD_2 and LTC_4 [11]. While there is little evidence for a role of the former in skin inflammation, the success, particularly in individuals with a variant LTC_4 synthase allele [12], of leukotriene receptor antagonists in atopic dermatitis [13] and urticaria [14] suggests that this eicosanoid may be more important in skin disease than considered previously.

The major mast cell protease is tryptase, an approximately 130-kDa serine protease that is stored in a fully active form in the granule [15,16]. When released into the extracellular environment, the neutral pH allows tryptase to become enzymatically functional as a tetramer bound to

heparin. The properties of tryptase pertinent to the skin include cleavage of the vasodilator calcitonin gene-related peptide (CGRP); a kallikrein-like activity; cleavage of matrix components, including 75-kDa gelatinase/type IV collagen, fibronectin and type VI collagen, and activation of stromelysin, which may, in turn, cleave other matrix components; and mitogenic activity for fibroblasts. While there appear to be no endogenous inhibitors of tryptase, it is likely to have very local effects because, in the absence of heparin, the biologically active tetrameric form of tryptase rapidly dissociates into inactive monomers. In addition to acting as an enzyme in the extracellular space, tryptase and other serine proteinases have been demonstrated to activate specific receptors by proteolytic cleavage (see p. 9.42). In the skin, tryptase activates proteinase-activated receptor-2 (PAR-2), which is constitutively expressed by keratinocytes and myofibroblasts. Upon inflammatory stimuli, endothelial cells, nerves and immune cells up-regulate PAR-2 expression. Interestingly, tryptase mimics various effects of histamine via activation of PAR-2 such as oedema, plasma extravasation, recruitment of neutrophils and induction of pruritus. Thus, beside histamine, tryptase is an important mediator of inflammatory responses, suggesting a role in inflammatory skin diseases such as atopic dermatitis, urticaria and angio-oedema [17,18].

Chymase is a 30-kDa monomeric protease stored in the same secretory granules as tryptase in the MC_{TC} subset of mast cells. Chymase degrades the neuropeptide neurotensin, but not substance P or VIP, cleaves angiotensin I to angiotensin II more effectively than angiotensin-converting enzyme (ACE), and may also contribute to the splitting of the dermal–epidermal junction in bullous pemphigoid [16,19]. Two other proteinases, carboxypeptidase and cathepsin G, have been associated with the MC_{TC} subset of human mast cells. Carboxypeptidase is a unique 34.5-kDa metalloproteinase that removes the carboxyl terminal residues from a range of peptides, including angiotensin, leu^5-enkephalin, kinetensin, neuromedin N and neurotensin. Cathepsin G is a chymotryptic enzyme with a structure seemingly identical to that of neutrophil cathepsin G. When mast cells are activated, chymase, carboxypeptidase and cathepsin G are released together in a 400–500-kDa complex with proteoglycan, and are likely to act in concert with the other enzymes to degrade proteins.

With the recent discovery that polymorphisms in *SPINK5*, a gene encoding for a serine protease inhibitor, is associated with Netherton's syndrome and other allergic diseases [20], the potential role for proteases in skin disease seems to be extending.

Cytokines are responsible for the initiation and coordination of allergic inflammation. It is logical therefore that the mast cell is a source of such cytokines. Of particular note are the NF-κB-dependent cytokines, TNF-α, GM-CSF and IL-8 [21,22] and the Th2 cytokines, IL-4, IL-5 and IL-13 [23,24]. Thus, not only have mast cells the capacity to initiate immediate phase allergic and anaphylactoid reactions and tissue damage, they also have the capacity to stimulate allergic inflammation, which is characterized by the influx of basophils, eosinophils and neutrophils.

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Monocytes and macrophages

The monocyte–macrophage system, formerly known as the 'reticuloendothelial system', represents a heterogeneous family of cell types that vary within different tissues. The range of functions of monocytes and macrophages is summarized in Table 9.5, and their receptor expressing and mediator repertoire is shown in Table 9.6. They all derive from identical progenitors in the bone marrow, where they mature from monoblasts to pro-monocytes. The maturation time is approximately 16 h in the rat and 19–25 h in humans. As mature cells, monocytes may remain in the blood for approximately 2–5 days. Following inflammatory stimuli, monocytes emigrate into the site of inflammation where they differentiate into macrophages or dendritic cells (antigen-presenting cells). During acute inflammation, the rate of monocyte formation may be dramatically increased. Additionally, monocytes adhere to the endothelium and subsequently migrate to the site of inflammation. This is important because resident macrophages show only a poor ability to divide [1,2].

Macrophages rapidly recognize pathogens and 'danger signals' in the connective tissue by means of cell surface receptors [3] such as CD14, mannose receptor, the SR and TLRs (see above). These receptors recognize specific ligands released by microorganisms, leading to intracellular signal transduction pathways and ultimately initiating an immune response. Macrophages also represent an important link to the adaptive immune system by generating immunomodulating cytokines such as interferons. In addition, they release IFN-γ and express MHC class II antigen HLA-DR and may thus stimulate lymphocytes.

Table 9.5 List of major functions of monocytes and macrophages, their receptors and secretory products.

Antitumour activity
Atherogenesis
Control of T and B lymphocytes
Control of dendritic cell function
Coagulation and fibrinolysis
Detoxification
Granuloma formation
Host defence
Metabolism and storage of lipids and iron
Mediation of acute and chronic inflammation
Modulation of keratinocyte function
Processing of antigens
Recruitment of leukocytes
Regulation of haemopoiesis
Release of enzymes for degradation
Scavenging of necrotic debris and effete cells
Wound healing

Table 9.6 List of major products released and receptors expressed by monocytes and macrophages.

Receptors (R)
IgG, IgE, IgA
C-reactive protein
C1q
C3b, C3bi
Fibrin
Fibronectin
Laminin
Transferrin
Heparin
IFN-α, -β, -γ
TNF-α
GM-CSF
Insulin
Insulin-like growth factor
Platelet-activating factor (PAF)
HLA-DR (class II MHC)
Macrophage inhibitory factor (MIF)
IL-2, -3, -4, -8, -10, -13, -16, -19, -23, -26
LTC, LTD_4, LTB_4
PGE_2
Histamine H_1, H_2
CCR4, CCR5
Angiotensin II
Toll-like receptors
α-adrenergic agents
β-adrenergic agents
Cholinergic agents
Products secreted
Atrial natriuretic peptide (ANP)
Lysozyme
Neutral proteases
Acid proteases
Lipases
Collagenase, elastase
α_2-Macroglobulin
α_1-Antiprotease
Complement C1, C2, C4, C3, C5
Factors B and D
NO
Prostaglandins E_2, $F_{2\alpha}$
Leukotrienes B, C, D, E
Thromboxane (TXA_2)
Glutathione
IL-1α, -1β, -1ra, -6, -8, -10, -12, -18
MIF
PAF
TNF-α
IFN-α/β
TGF-β
PDGF
GM-CSF, M-CSF, G-CSF
Respiratory burst reactive oxygen radicals

Macrophages have also been shown to utilize molecules from the complement system to interact with pathogens, and may subsequently undergo apoptosis or become degraded. Under pathophysiological conditions, macrophages may become incorporated into a granuloma or be converted into an epithelioid cell, with an increased ability to synthesize enzymes or other mediators of inflammation. Moreover, macrophages can also be incorporated into a giant cell by fusion with other macrophages. Such pathophysiological chronic inflammatory processes are observed in diseases that may affect the skin, such as tuberculosis, leprosy and sarcoidosis.

Macrophages are professional phagocytes: they recognize pathogens by specific receptors and subsequently phagocytose them. During this active energy-driven process, macrophages generate acidic phagosomes and lysosomal mediators such as oxygen radicals. Macrophage-derived proteolytic enzymes, cathepsins D and G, acid phosphatases or matrix metalloproteinases are released during inflammation. Under normal circumstances, this network of defence molecules is a very effective barrier in the maintenance of tissue homoeostasis. Under pathophysiological conditions, however, when defence mechanisms are impaired, these mediators may also have deleterious effects on the host, resulting in tissue destruction and fibrosis, as observed in various diseases such as arthritis.

Macrophage migration inhibitory factor (MIF) was originally described as a T-cell-derived lymphokine with the potential to inhibit the random migration of macrophages. However, recent reports have shown a much broader tissue distribution of production, including the skin. Recently, a MIF has been localized to many skin cells such as keratinocytes [4], fibroblasts [5] and endothelial cells. An important role for MIF has been reported in several skin diseases such as lupus erythematosus [6], contact hypersensitivity [7], atopic dermatitis [8], psoriasis [9,10], wound healing [11], systemic sclerosis [12], GvHD [13] and sepsis [14,15]. Thus, MIF may represent an important target molecule for the treatment of skin diseases in which macrophages are involved.

The production of arachidonic acid derivatives appears to be crucial for macrophage-mediated responses during inflammation. PGE_2, for example, is involved in lymphocyte activation by macrophages and also inhibits macrophages in an autocrine manner, indicating a negative-feedback system via specific prostaglandin receptors.

Macrophages are major targets for infection by human immunodeficiency virus type 1 (HIV-1). In addition to their role as productive viral reservoirs, inappropriate activation of infected and uninfected macrophages appears to contribute to pathogenesis. These responses establish a complex cytokine network, which may enhance or suppress HIV-1 replication. In addition, dysregulation of macrophage function by gp120–chemokine receptor signalling may contribute to local inflammation and injury and further recruit additional inflammatory and/or target cells [16].

Other receptors expressed by monocytes–macrophages are the proxisome proliferator-activated receptors (PPARs). These are ligand-activated transcription factors that form a subfamily of the nuclear receptor gene family. This subfamily consists of three isotypes, PPARα (NR1C1), -γ (NR1C3) and -β/δ (NRC1C2) with a heterogeneous tissue distribution. PPARs are activated by ligands, such as naturally occurring fatty acids, which are activators of all three PPAR isotypes. In order to be transcriptionally active, PPARs need to heterodimerize with the retinoid-X-receptor (RXR). PPARs have a critical role in lipid and glucose homoeostasis, but lately they have been implicated as regulators of inflammatory responses including in the skin. The first evidence of the involvement of PPARs in the control of inflammation came from PPARα knockout mice, which showed a prolonged inflammatory response. PPARα activation results in the repression of NF-κB signalling and inflammatory cytokine production in different cell types. A role for PPARγ in inflammation has also been reported in monocytes–macrophages, where ligands of this receptor inhibited the activation of macrophages and the production of inflammatory cytokines (TNF-α, IL-6 and IL-1β), although part of the anti-inflammatory effects of these ligands seems to be mediated by a mechanism not involving PPARγ. PPARs also regulate the gene expression of key proteins involved in vascular inflammation. By modulating transcription of pro-inflammatory genes such as cytokines, chemokines, endothelial cell adhesion molecules and metalloproteinases, PPARs directly affect inflammatory events. Together, these findings suggest a role of PPARs in the control of the inflammatory response with potential therapeutic applications in inflammatory diseases such as acne, atopic dermatitis and psoriasis [17–21].

A novel family of monocyte-derived receptors have been described, which seems to be important in the regulation of inflammatory responses. Triggering receptors expressed by myeloid cells (TREMs) belong to a rapidly expanding family of monocyte-derived receptors that include activating and inhibitory isoforms encoded by a gene cluster linked to the MHC. TREM1 and TREM2 activate myeloid cells by signalling through the adaptor protein DAP12. TREM1 triggers phagocyte secretion of pro-inflammatory chemokines and cytokines, amplifying the inflammation that is induced by bacteria and fungi [22].

Macrophages can remain within the tissue in a quiescent resting phase for months until stimulated through ligand binding to one or more of their numerous receptors (Fig. 9.6). They express receptors for IgG (FcγRI, FcγRII, FcγRIII) and complement components C3b and C3bi [23]. They also express receptors for C-reactive protein (CRP),

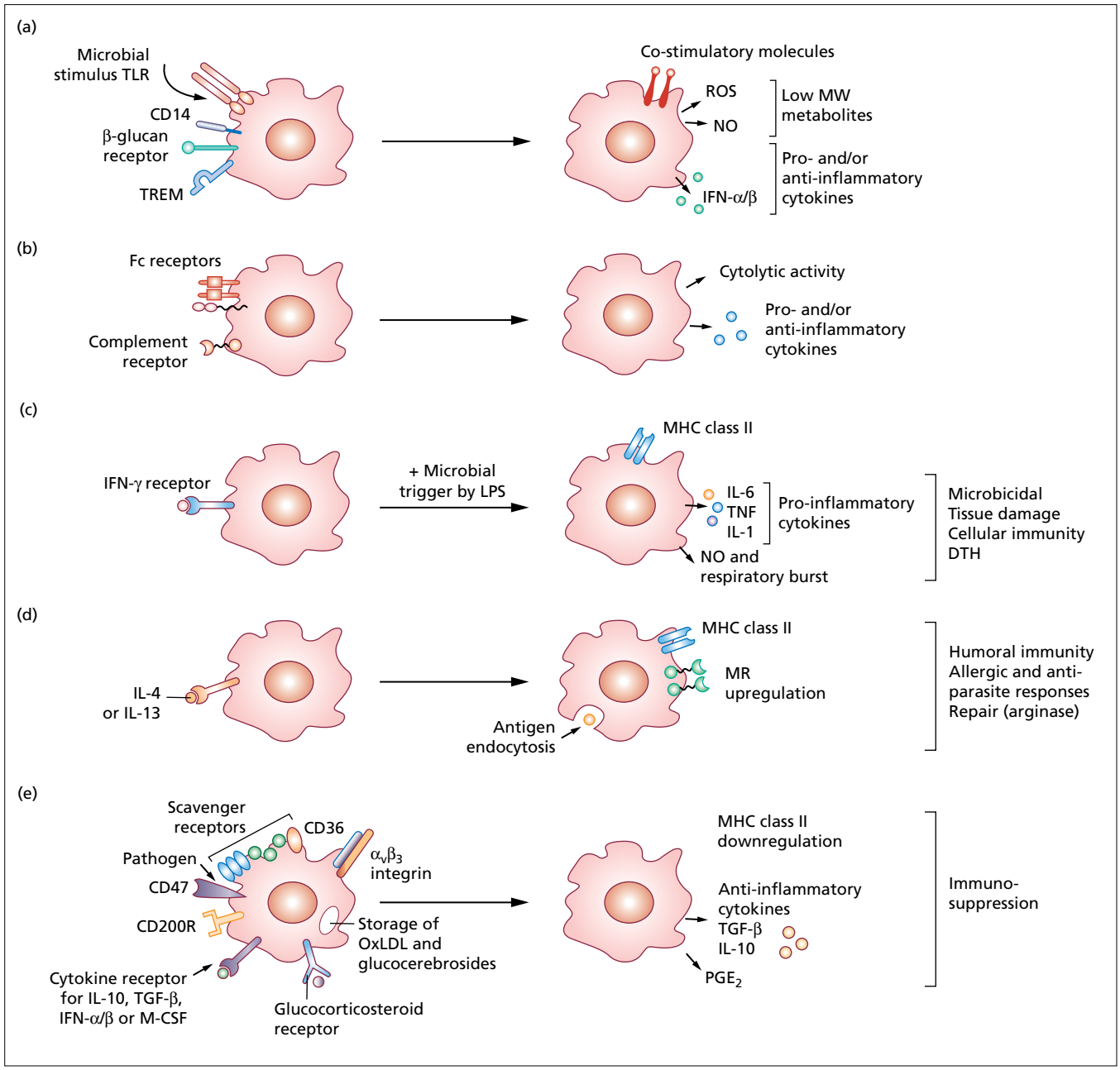

Fig. 9.6 Role of macrophages for innate and acquired immune function. (Modified from Gordon S. Alternative activation of macrophages. *Nature Rev Immunol* 2002; **3**: 26.) (a) Macrophages recognize pattern-recognition receptors such as toll-like receptors (TLRs), CD14–LPS-binding protein and others. These stimuli induce production of pro-inflammatory cytokines such as interferons, nitric oxide and reactive oxygen species. This is followed by a well-tuned anti-inflammatory response. Scavanger receptor (SR-A) and mannose receptor (MR) promote phagocytosis and endocytosis of host and of exogenous ligands. (b) Humoral activation and phagocytosis are mediated by some Fc and complement receptors, whereas other receptors down-regulate these responses. (c) Classical activation is triggered by the priming stimulus IFN-γ, followed by a microbial trigger (e.g. LPS). (d) Alternative activation is mediated by interleukin-4 and IL-13, acting through a common receptor chain (IL-4Rα). (e) Inactivation can be of innate as well as of acquired origin. Uptake of apoptotic cells or lysosomal storage of host molecules generates anti-inflammatory responses. Cellular activity is modulated by interactions of macrophages with T cells, fibroblast or extracellular matrix by activating specific receptors. Glucocorticoids and anti-inflammatory agents can suppress macrophage function. Pathogens can deactivate macrophages thereby contributing to infection. DTH, delayed-type hypersensitivity; M-CSF, macrophage colony-stimulating factor; OxLDL, oxidized low-density lipoprotein; PGE_2, prostaglandin E_2, TGF-β, transforming growth factor-β; TREM, triggering receptor expressed on myeloid cells.

which in blood monocytes induces synthesis of IL-1β and IL-1 receptor antagonist (IL-1RA).

There is evidence for a close interaction between T lymphocytes and macrophages. T-cell-derived IFN-γ both primes macrophages for an enhanced response to other cytokines and activates them to increase oxygen utilization and H_2O_2 formation. It also induces nitric oxide formation, increases phagocytic and tumoricidal activities, initiates or enhances MHC class II membrane antigen expression, and stimulates the synthesis of several cytokines and receptor expression. T-cell IL-2 stimulates macrophages, particularly if they are primed by IFN-γ. Macrophages also synthesize many cytokines such as IL-1, a potent pro-inflammatory signal.

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Fibroblasts

Fibroblasts are part of the connective tissue and the source of most of the extracellular matrix elements in the dermis. Intercellular substrates are mainly composed of collagens and glycosaminoglycans (GAGs). GAGs covalently bind to proteins to form proteoglycans, which are able to bind proteins such as cytokines, chemokines or growth factors in the extracellular space. Collagens or fibronectin can modulate cell–cell interactions between fibroblasts and inflammatory cells. For instance, migrating T cells or mast cells interact with extracellular matrix proteins via β2 integrin activation.

After stimulation, fibroblasts are able to transform into several types of specialized cell such as myofibroblasts, smooth muscle cells, chondrocytes and osteocytes. It is not known if the different phenotypes arise from pluripotential stem cells, or from subtypes with restricted properties of differentiation. Some differentiated fibroblasts can revert to the original mesenchymal state, whereas others persist as mature committed cells. Therefore it is not suprising that fibroblast-derived cartilage and bone may occasionally be found in scar tissue. Under normal circumstances, fibroblasts mature into dermal fibrocytes, and after maturation their function is merely restricted to the synthesis of extracellular matrix proteins such as collagens, elastin and proteoglycans. In the skin, collagens I, III, IV, VII, fibronectin and laminins are of special interest because of their capability to regulate dermal–epidermal interactions via modulating the composition of the basal lamina.

During inflammation, the morphology and properties of fibroblasts are strictly dependent on the surrounding microenvironment. Dermal fibroblasts grown *in vitro* on different substrates (e.g. collagen or laminin) but maintained in the same medium, show differences in morphology, integrin expression and cytokine synthesis. Moreover, dermal fibroblasts cultured in contracting collagen gels form sixfold more PGE_2 than do cells cultured on plastic [1]. Fibroblasts in floating collagen gels are stellate with long cytoplasmic processes [2], and after gel contraction DNA synthesis is reduced [3] and collagenase

synthesis increases [4]. Fibroblasts in anchored (non-contracting) gels are elongated, bipolar and lie along lines of tension [5]. They synthesize DNA, proliferate [3,6] and do not exhibit an increased collagenase synthesis.

Alterations of the extracellular matrix may depend on certain cytokines. Thus, platelet-derived growth factor (PDGF) regulates expression of β1-series integrin chains α2, α3 and α5 in fibroblasts grown on fibronectin and fibrin substrates as in fresh wounds. However, in fibroblasts grown on collagen substrates, PDGF modulates integrin synthesis to resemble that of granulating tissue [7]. Differences in matrix composition alter PDGF receptor phosphorylation [8], and therefore responsiveness to PDGF, one of the most potent mediators controlling fibroblast proliferation and collagen formation. The above clinical evidence of matrix-regulated differences in fibroblast function reflects the *in vivo* situation during wound healing and scar formation, where the environment changes from freshly damaged tissues with fibrin clots in the early stages to organized extracellular matrix in the late stages. Moreover, hypertrophic scars are characterized by a stable phenotype fibroblast, which differs from normal fibroblasts and exhibits a reduced response to epidermal growth factor (EGF) and increased synthesis of collagen [9]. In systemic scleroderma, however, collagen formation is increased, as the α2 chain of the α2β1 integrin is reduced [10]. Similarly, down-regulation of collagen mRNA expression in fibroblasts of systemic scleroderma patients tended to be less than that in controls. This increased potential to form collagen was associated with a decrease in α1β1 integrin [11]. Both α1β1 and α2β1 integrins, but particularly α2β1, recognize collagen I in the dermis, and the reduced integrin expression associated with increased collagen synthesis may reflect defective signalling between fibroblasts and their collagen matrix environment.

Dermal fibroblasts synthesize prostaglandins, leukotrienes and several cytokines, and as resident cells they release pro-inflammatory mediators in an early response to skin injury and growth factors to promote subsequent healing. Fibroblast production of leukocyte activating and/or attracting agents is somewhat in contradiction to *in vivo* histological findings, which rarely reveal accumulations of leukocytes round fibroblasts. Therefore, it is possible that proteoglycan binding of some cytokines results in more diffuse leukocyte infiltration. Fibroblast proliferation is stimulated mainly by PDGF, TGF-β and FGF. Two cytokines, TGF-β and TNF-α, may either stimulate or reduce proliferation, depending upon the state of cell activation [12]. Synthesis of collagen or other connective tissue elements is induced by PDGF and TGF-β, whereas TNF-α may stimulate or repress synthesis [12]. In normal skin, there is an interdependency between fibroblast and epidermal growth and differentiation regulated by cytokines.

Several *in vitro* studies suggest that eosinophils may have a role in fibrosis, remodelling and repair processes associated with IgE-mediated hypersensitivity. Eosinophil-derived TGF-β and IL-13 is temporarily associated with myofibroblast formation and deposition of tenascin and pro-collagen I, suggesting that both inflammatory mediators may contribute to repair and remodelling events of inflammatory skin diseases by modulating fibroblast function [13]. There is also recent evidence of a role for neuropeptides in the modulation of fibroblast functions. Thus, it has been shown that expression and cellular levels of SCF are up-regulated in fibroblasts by substance P [14]. In summary, fibroblasts contribute crucially to the interaction of epidermal and dermal components to maintain skin integrity.

After skin injury, particularly wounding involving the dermis, activated fibroblasts migrate on to fibronectin and fibrin, proliferate and synthesize new collagen to form granulation tissue. Proliferation is gradually reduced as the collagen matures and the wound contracts [6,15]. The forces inducing wound contraction originate in the granulation tissue formed in the wound. The fibroblasts are transformed into myofibroblasts, with several morphological, chemical and antigenic differences to resident mature fibroblasts [16,17]. Myosin in activated cells is phosphorylated to expose actin-binding sites, to form actin–myosin contractile or stress fibres across the cell; via focal contacts and integrins on the cell membrane they exert tension on the matrix. The first formed collagen gel is compacted and modified to form strands of fibres. The fibroblasts migrate to lie along the fibres as seen in normal dermis, at which time they lose their myosin stress fibres although they continue to contribute to the overall tension of the skin.

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Platelets

Platelets are derived from megakaryocytes in the bone marrow and are the major components involved in blood clotting and homoeostasis. Upon injury and inflammation, platelets regulate leukocyte aggregation and adherence to the endothelium, reflected by cell arrest and emigration into the tissue. Using video microscopy, transient platelet rolling on endothelium has recently been observed. Platelets accumulate in the vicinity of an injury, making them available for an immediate response [1]. Moreover, platelets contain a variety of potent inflammatory mediators and growth factors that contribute to normal homoeostasis of blood cells, acute inflammation, tissue repair and immune responses. Accordingly, platelets release mediators such as eicosanoids, ADP, amines, proteolytic enzymes and cationic proteins. They are also a source of serotonin (5-HT), which is released during vascular injury, resulting in enhanced deposition of immune complexes on the endothelium. Thus, the formation of platelet aggregates and the subsequent release of mediators appear to have a role in tissue damage during cutaneous small vessel vasculitis [2].

Platelets are functionally closely associated with all types of leukocytes. Activated platelets secrete chemotactic substances, facilitate the binding of leukocytes to the endothelium as well as their subsequent extravasation, and may influence the inflammatory responses of leukocytes by both stimulation and inhibition. However, platelets also contain an array of potent pro-inflammatory substances, and are therefore effector cells of inflammation. Because of the role of platelets in IgE-dependent killing and eosinophil infiltration, they are currently considered to be directly involved in allergic IgE-mediated reactions [3].

Platelets express several receptors and can be activated by plasma products, immunoglobulins, complement, extracellular matrix components, leukocytes (particularly neutrophils) and endothelial cells. Receptors for soluble agonists include ADP [4], FcγRII [5,6] and complement component C3a [7]. They also express PARs belonging to a novel subfamily of G-protein-coupled receptors with seven transmembrane domains activated by serine proteases [8,9]. PAR-1, -3 and -4 are thrombin receptors in mice (PAR-3, PAR-4) and humans (PAR-1 and PAR-4). During inflammation, PARs become activated by thrombin on platelets, leading to mediator release and regulation of endothelial cell and leukocyte function. PAR-1 is critically involved in angiogenesis and leukocyte transmigration [9].

α11bβ3 (also designated glycoprotein 11b–111a or GP11b–111a) represents an important platelet-specific integrin. Upon activation, it is recruited to the cell surface, where it is capable of binding to thrombin, collagen or laminin [10]. The platelet integrin α2β1 (GP1a–11a) binds collagen [11], α5β1 and α6β1 (GP1c–11a) bind to fibronectin, collagen and laminin, while CD36 (GPIV) binds thrombospondin and possibly collagen [12]. Complement binds to the granule membrane protein 140 (GMP-140). Upon activation, GMP-140 expression is induced on platelets and endothelium, resulting in up-regulation of E-selectin and the promotion of leukocyte adherence [13].

Some receptors may bind to several ligands, and the activating potential of distinct ligands varies. Whereas 'strong agonists' (thrombin, collagen, thromboxane A_2 [TXA_2] and PAF) elicit a direct response, 'weak agonists' (9-ADP, adrenaline [epinephrine], vasopressin and serotonin) depend upon secretion to mediate a full response. Antagonists include PGI_2, PGD_2, endothelium-derived relaxing factor (EDRF) and nitric oxide [14]. Several of these are generated as the result of platelets activating other platelets (TXA_2, ADP and serotonin).

Receptors of normal platelets are either intracellular or, if on the cell surface, do not contact their ligands in undamaged tissue. On activation, rapid exposure and realignment of receptors stimulates second-messenger G proteins, protein tyrosine kinases and phospholipases [14]. The platelets change shape to develop numerous microspicules, which leads to aggregation of platelets and binding to other cells [15]. Platelets are reported *in vitro* to release microparticles that preferentially bind, activate and aggregate neutrophils, increasing expression of the CD11b receptor [16]; *in vivo* this would increase neutrophil–endothelium binding. Platelet–neutrophil interaction promotes formation of leukotrienes and lipoxins, the precursors of which are derived from both cells. Di-HETE is formed by the interaction of platelet 12-lipoxygenase (12-LO) and neutrophil 5-LO; neutrophils release LTD_4 and LTC_4 [17,18]. Such transcellular mediator synthesis results in concentrations of pro-inflammatory lipoxins and leukotrienes at the site of vascular damage. Using 12-LO-deficient mice, a role for platelet-type 12-LO in normal transepidermal permeability barrier function in mice was shown [16]. Other platelet pro-inflammatory

mediators include TGF-α and -β, PDGF and prostaglandins; platelet aggregates in clots are the source of most prostaglandins in the blood during inflammation [19]. PDGF is both a pro-inflammatory mediator by virtue of activating neutrophils and monocytes, and a growth factor inducing tissue repair by regulating fibroblast proliferation, chemotaxis and collagen synthesis.

The expression receptors for immunoglobulins and complement on platelets may contribute to inflammation and to the removal of potential agonists. Thus, via signalling through IgG as well as IgE receptors [3,5,6], the release of pro-inflammatory mediators is enhanced, and the activation of C3a receptors induces release of serotonin and synthesis of thromboxane [6]. The IgG receptors bind IgG–antigen complexes, which are removed from the circulation when the platelet complex is subsequently ingested by phagocytes in the spleen, liver and elsewhere.

Thrombospondin 1 (TSP-1), an adhesive glycoprotein expressed by endothelial cells, fibroblasts and macrophages, has an important role in platelet adhesion, inflammation and cell–cell interaction [20,21]. TSP-1 is upregulated early during tissue injury, and is involved in angiogenesis, inflammation and vascular skin diseases by directly interacting with endothelial cells.

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Mediators of inflammation

The main role of the inflammatory response is the elimination of external noxious stimuli such as irritants, allergens and pathogens, or of endogenous stimuli such as toxic or infectious agents. There is also a necessity to avoid tissue disruption and cell destruction, and to restore tissue homoeostasis. Balance between these potentially opposing requirements is achieved by generating a variety of inflammatory mediators, which may exert their effects in an autocrine, paracrine, juxtacrine or endocrine manner.

A wide variety of distinct mediators including cytokines, phase proteins, kinins, prostanoids, leukotrienes, neuromediators, oxygen, nitrogen and carbon products are involved in the orchestration of inflammation. Importantly, these mediators are not only released by leukocytes and lymphocytes, but also upon activation during injury by almost any cell residing at the site of inflammation. The final outcome depends on the nature, severity and duration of the injurious stimuli, and reflect a cascade of well-tuned interactions between several mediators released by different cell types. Furthermore, the activation and upregulation of specific receptors for each of these mediators is crucial for the outcome of any inflammatory reaction. Occasionally, some mediators can activate more than one receptor and, vice versa, some receptors can be activated by several ligands.

Acute-phase proteins

During the acute phase of inflammation, cytokines such as TNF-α, IL-1 and IL-6 rapidly stimulate the release of proteins from hepatocytes to coordinate tissue integrity. Acute-phase proteins (APPs) are defined as plasma proteins if their serum concentration increases by more than 25% after tissue destruction. They are released by the liver to opsonize pathogens, inhibit protease function and clear cell detritus. APPs such as CRP, mannan-binding lectin, complement proteins, fibrinogen, α_1-antitrypsin, α_1-antichymotrypsin, haptoglobin, serum amyloid A and acid α-glycoprotein may have several pro- or anti-inflammatory activities. Moreover, hormones (e.g. glucocorticoids) are capable of stimulating APP synthesis within hours.

CRP is an APP that can be detected in the serum during infection and tissue damage within 24–48 h. Because CRP correlates well with disease progression, it is a reliable activity marker for inflammatory or infectious processes. It binds phosphorylcholin of LPSs in the cell membrane of bacteria and fungi, activates the classical complement pathway [1], stimulates leukocyte chemokinesis and phagocytosis, and induces a spontaneous vasculitis [2]. It is proposed that one function of CRP is to mobilize cells rapidly to counteract infection, before specific antibody is formed.

Another APP that activates the complement pathway is mannan-binding lectin. Together with the pulmonary surfactant proteins, mannan-binding lectin belongs to the family of 'collectins' that contain a globular lectin-like domain which is able to bind the membrane of pathogens [3,4].

The classic complement pathway is initiated by CRP, heparin, protamine sulphate and DNA, and also by plasmin or trypsin action on C1s. The alternative pathway is initiated by bacterial and endogenous endotoxin and cell debris. Complement C5 is cleaved by leukocyte enzymes, particularly neutral proteases, neutrophil elastase and acidic protease cathepsin G [5]. Epidermal cells contain serine proteinases active at neutral pH, which appear to cleave C5, resulting in a greater neutrophilia than seen in similar tests with plasmin and trypsin [6]. C3 is activated by trypsin and neutrophil elastase. The processes of clotting, generation of kinins and fibrinolysis all activate complement. The pro-inflammatory properties of C5a, C3a and C4a on mast cells and basophils, as anaphylatoxins releasing cell mediators and, in the case of C5a, attracting and activating leukocytes, are described in Chapter 10.

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Cytokines

Cytokines are structurally related polypeptides or glycoproteins that exert their effects at concentrations within the pico- or nanomolar range. Originally, they were regarded as immunocompetent cell-derived immunomodulators. However, recent knowledge demonstrates that a clear-cut differentiation between cytokines, growth factors, neurotransmitters and hormones is not possible. The predominant role of cytokines is to mediate inflammatory and immune responses. Cytokines determine the direction of immune responses and control tissue integrity during injury. Thus, the quality and quantity of cytokine production within the injured tissue determines whether the immune system is directed into a humoral or cytotoxic cell-mediated allergic response. Moreover, cytokines (along with other mediators) determine the switch of the immune system from a pro- to an anti-inflammatory state.

Over the last decades, a large body of knowledge has accumulated on the role of cytokines in cutaneous inflammation. They are ultimately involved in all phases of inflammation. While pro-inflammatory cytokines induce the body response to external or internal danger, anti-inflammatory cytokines are capable of restoring tissue homoeostasis by suppressing inflammatory processes. Various molecular biology and modern immunological techniques have been applied to cytokine research, and the genes for many of these factors have been cloned and characterized in the skin. Together, these studies clearly demonstrate that many cytokines exert pleiotropic functions. For example, IL-1 was originally described as a leukocytic pyrogen, endogenous pyrogen, B-cell-activating factor and lymphocyte-activating factor. Today it is well known that various skin cells, including keratinocytes, use IL-1 to communicate with neighbouring cells in the skin during inflammation [1]. Thus, the IL nomenclature was introduced to replace the older descriptive and often misleading names.

To understand fully the role of cytokines in skin inflammation one has to collate information from human and animal studies as well as *in vitro* and *in vivo* data. The availability of recombinant cytokines and cytokine antagonists was of tremendously benefit in the verification of the specific effects of cytokines *in vivo*. Modern techniques such as genomic and proteomic approaches have given new insights into the regulatory mechanisms underlying the actions of cytokines. Moreover, the use of cytokine and cytokine receptor gene-deficient mice have helped in our understanding of the specific role of these molecules during cutaneous inflammation. It must be appreciated that *in vivo* a cocktail of several cytokines acts simultaneously or sequentially upon the inflammatory microenvironment. Thus, the biological activities of cytokines during inflammation are the sum of well-tuned synergistic and antagonistic processes.

Cytokines use different cell biological mechanisms to modulate inflammation. Some cytokines (e.g. IL-1, IL-2 or IL-4) exert their effects by exclusively binding to cell surface receptors. Others (e.g. TGF-β or IL-6) may additionally interact with components of the extracellular matrix to modulate skin function during inflammation.

Interleukins

Interleukins are polypeptides participating in all normal and reactive cell functions. So far, 27 interleukins have been described and characterized. Some prime cells, making them responsive to other agents, and most act synergistically.

IL-1. The first cytokine detected in the skin was IL-1, originally named epidermal thymocyte-activating factor. Cytokines of the IL-1 family are key players in immunity and inflammation in virtually every organ of the body. Members of the IL-1 family discovered so far include IL-1α, IL-1β, IL-1 receptor antagonist (IL-1RA), IL-1H, IL-1F7b, IL-18 and IL-18BP. They may function as agonistic or antagonistic ligands for the members of the IL-1 receptor (IL-1R) family. IL-1 and IL-18 are structurally very closely related and both are synthesized as biologically inactive precursor molecules lacking a signal peptide. Almost all cells of the body, including keratinocytes, have been found to synthesize many of the IL-1 family members upon stimulation. In some cells, such as macrophages, fibroblasts, endothelial and dendritic cells, IL-1 may also exist in a membrane-bound form.

The currently known 10 members of the IL-1R family are defined as membrane-spanning molecules that consist of at least one immunoglobulin-like domain exterior to the cell and, except for the IL-1RII, a Toll/IL-1R (TIR) domain in the cytoplasm. Type I IL-1R (IL-1R) binds both IL-1α and IL-1β. In addition, a homologue of the IL-1R, known as IL-1R accessory protein (AcP), which has no affinity on its own for either of the IL-1 forms, is required for IL-1 signalling. The second natural IL-1 binding protein is IL-1RII, which has a high affinity for IL-1α, but a much lower affinity for IL-1β or IL-1RA.

IL-1RI is expressed on keratinocytes, fibroblasts, endothelial cells, lymphocytes and other cells. IL-1RII can be detected on B lymphocytes and neutrophils. An endogenous soluble IL-1RA type I acts as a competitive IL-1R inhibitor. There is evidence of differences in responses mediated via each receptor. Cultured keratinocytes predominantly express mRNA for IL-1β, but *in vivo* in normal epidermis IL-1α is also detectable. IL-1 is present in the stratum granulosum, and considerable amounts have been detected in psoriatic scales [1]. However, this is confined to IL-1β, which is functionally inactive, while active IL-1α is reduced [2].

IL-1 is pro-inflammatory, stimulates repair and differentiation, and is an important mediator of immune regulation. It is mitogenic for thymocytes and T cells, inducing IL-2 synthesis and receptor expression, proliferation and release of lymphokines (see Chapter 10). Furthermore, IL-1 is a growth factor for B cells, inducing proliferation and enhancing antibody formation, and it also increases NK cell activity. Macrophages and neutrophils are activated, their enzymes released and prostaglandin synthesis is induced.

It has been contended that, despite the large amounts in epidermis, IL-1 is largely inactive and contributes little to the inflammatory response. Nevertheless, injection of keratinocyte IL-1 and recombinant IL-1 (rIL-1) into mice and rabbits induces oedema, erythema and neutrophil infiltration. There is also evidence that during wound healing, human keratinocyte IL-1 stimulates synthesis of PGE_2 by subpopulations of human fibroblasts, which feeds back to stimulate keratinocyte proliferation and differentiation.

IL-1 is increased in the early phase of numerous skin diseases and induces the release of further cytokines and growth factors, and the recruitment of T lymphocytes, in the inflammatory tissue. IL-1 participates in the regulation of microvascular dermal endothelial cells by the up-regulation of cell adhesion molecules such as ICAM-1 or E-selectin. IL-1 also regulates the expression of ICAM-1 on keratinocytes, thus participating in the recruitment of lymphocytes into the epidermis, and activates IL-6 or NF-κB [2], which may be of considerable relevance in inflammatory dermatoses.

IL-1 is considered to be a key cytokine in the pathogenesis of autoimmune diseases such as pemphigus vulgaris. Increased levels of IL-1α and TNF-α have been detected in lesional skin of patients with pemphigus. Acantholysis of keratinocytes was found to be inhibited by antibodies directed against IL-1α and TNF-α. Furthermore, in IL-1-α and TNF-α receptor-deficient mice, a decreased susceptibility for pemphigus was observed.

IL-2. IL-2, or T-cell growth factor, is an essential mediator for developing an immune response (see Chapter 10). Activated T lymphocytes secrete IL-2 and express IL-2 receptors, resulting in their proliferation and clonal expansion. IL-2 is also an important mediator for the proliferation of B lymphocytes and the activation of NK cells. Furthermore, IL-2 participates in the regulation of T-cell functions in Th1-mediated skin diseases such as psoriasis and cutaneous T-cell lymphoma [3,4]. The role of IL-2 in these diseases has recently been proven by the successful therapeutic use of specific anti-IL-2 strategies.

IL-3. This belongs to the group of haematopoietic colony-stimulating factors (CSF) (see above), and also promotes growth of T-cell lines and mast cells. It is synthesized by T lymphocytes, myeloid cell lines and keratinocytes. Although IL-3 has multi-CSF activity, in the skin it may activate both mast cells, contributing to fibrosis, as seen in scleroderma, and neutrophils, to release oxygen radicals cytotoxic for microorganisms. Moreover, monocyte proliferation, adherence to endothelium and secretion of IL-8 is induced or enhanced by IL-3, as is eosinophil chemotaxis and phagocytosis.

IL-4. Originally named B-cell growth factor, IL-4 acts mainly on immunocompetent cells, and induces proliferation of activated mature T cells, and enhances T-cell cytotoxic properties, but suppresses cytokine formation by Th1 cells, thereby reducing delayed hypersensitivity responses. IL-4 stimulates MHC class II expression (see Chapter 10), and expression of the low-affinity IgE receptor (CD23) on B cells. IgE synthesis is regulated by IL-4 together with IL-13, and is inhibited by IFN-γ and TGF-β. Cytokines such as IL-2, IL-5, IL-6 and IL-9 synergize with IL-4 and IL-13 to enhance IgE production. On macrophages, however, IL-4 decreases CD23 expression. Mast cell growth is stimulated by IL-4, as is the growth of precursor haematopoietic cells, both directly and indirectly, by stimulating G-CSF and M-CSF production in monocytes. IL-4 is important for the differentiation towards a Th2 T-cell subtype. In contrast, cytokines such as IL-12, IL-18 and IL-23 inhibit the differentiation of IL-4-producing T cells. Although IL-4 is generated in high amounts by T cells, there is also evidence that IL-4 is released in the skin by keratinocytes or mast cells. The IL-4 receptor was detected on T and B cells, macrophages, dend-ritic cells, mast cells, fibroblasts and keratinocytes. IL-4 proved to be an essential mediator for the differentiation of dendritic cells [5]. Thus, IL-4 is an important regulator of IgE production and Fcε-receptor expression. *In vivo*, IL-4 has been found to mediate immunodeviation towards Th2 responses and in preliminary studies has been successfully used for the treatment of Th1-mediated skin diseases such as psoriasis.

IL-5. IL-5, a helper T-cell lymphokine (see Chapter 10), induces growth and differentiation of activated B cells, and is a key mediator for the switching of immunoglobulin class synthesis. It is the most important promoter of eosinophil formation and differentiation. Mature eosinophils are activated and their survival is prolonged in parasitic infestations. IL-5 works synergistically with IL-3 and GM-CSF on eosinophils.

IL-6. This is mainly generated by monocytes, bone marrow cells, fibroblasts, endothelial cells, some T cells, B cells and keratinocytes [6]. IL-6 is involved in the regulation of the function of T, B and NK cells, which express both of the IL-6 receptor chains. It has an essential role in the maturation of B cells to produce antibody, and also participates in inflammation by inducing formation of APP by hepatocytes. In T cells, IL-6 mediates activation, growth and differentiation. Thus, IL-6 is an 'early' pro-inflammatory cytokine, induces APP production, and the increased formation of IL-6 by fibroblasts, endothelial cells and keratinocytes stimulated by IL-1 and TNF-α may represent a significant amplifying process in inflammation [7,8]. Despite the finding of increased IL-6 serum levels in autoimmune diseases such as systemic lupus erythematosus (SLE), systemic scleroderma and pemphigus vulgaris, a specific role for IL-6 in any skin disease has not been established.

IL-7. IL-7, synthesized by monocytes and T cells, is a haematopoeitic growth factor, stimulating T- and B-cell proliferation. Moreover, immune functions such as the proliferation of cytotoxic T and NK cells, as well as the activation of monocytes and macrophages, can be triggered by IL-7.

IL-8. This is a member of the CXC subfamily of chemokines (see p. 9.40).

IL-9. This is produced by $CD4^+$ T lymphocytes and was originally described in the murine system as P40, T cell growth factor III (TCGF III) and mast cell growth enhancing activity (MEA). IL-9 is a growth factor for T-helper lymphocytes, mast cells and megakaryoblastic leukaemic cells, and stimulates the development of erythopoietic colonies as well as IL-4-induced IgE production by B lymphocytes. IL-9 transcripts have been detected in Hodgkin's lymphoma and large cell anaplastic lymphoma, suggesting a role for IL-9 in the pathogenesis of these tumours.

IL-10. This was originally described as a cytokine secreted by Th2 cells that inhibited the release of cytokines from Th1 cells [9,10]. Later it was found that IL-10 can be synthetized by Th1 as well as Th2 lymphocytes, and also by cytotoxic T cells, mast cells, B cells and monocytes, the latter being the major source of IL-10 in humans [11].

IL-10 diminishes IFN-γ and IL-2 production by Th1 cells, as well as IL-4 and IL-5 generation by Th2 cells. IL-10 inhibits release of IL-1β, IL-6, IL-8, IL-12 and TNF-α in monocytes, and IFN-γ or TNF-α in NK cells. In monocytes or dendritic cells, IL-10 also down-regulates expression and release of MHC class II molecules, CD23, ICAM-I and the accessory B7 molecule. Thus, IL-10 is an important cytokine for the regulation of antigen presentation and suppression of Th1 and Th2 cytokine production.

The anti-inflammatory effect of IL-10 is a result of the inhibition of pro-inflammatory cytokines such as IL-1, IL-2, IL-6, TNF-α and IFN-γ, and the inhibition of chemokines and chemokine receptors such as IL-8 and CXC-2 receptor. In eosinophils, IL-10 inhibits eosinophil survival and IL-4-induced IgE synthesis, indicating an important role for this cytokine in allergic responses. In contrast, IL-10 activates the proliferation of, and immunoglobulin by production B cells. Thus, IL-10 is also a survival and differentiation factor for B cells. IL-10 contributes to inhibition of cellular and allergic immune responses while stimulating humoral and cytotoxic immune mechanisms [11].

Increased expression of IL-10 occurs in patients with allergic contact dermatitis [12], and IL-10-deficient mice

show a delayed contact by hypersensitivity immune response [13]. Stimulators of keratinocyte IL-10 synthesis include contact allergens and UVB light. The effect of IL-10 is mediated via a specific IL-10 receptor expressed on numerous skin cells. IL-10 has been proposed as a therapeutic target for the treatment of inflammatory diseases such as psoriasis, atopic dermatitis and asthma, and other autoimmune diseases [14,15]. Together with IL-19, IL-20, IL-22, IL-24 and IL-26, IL-10 belongs to a subfamily of cytokines that share a similar structure and biological functions.

IL-11. This stimulates precursor or progenitor haematopoietic blast cell mitosis, and promotes similar activity by GM-CSF, IL-3 and IL-4. It also promotes helper T-cell regulation of B-cell immunoglobulin synthesis. IL-11 induces formation of APPs by the liver, stimulates fibroblast function and supports differentiation of lymphocytes, but depresses differentiation of fat cells. It appears to be involved in cytotoxic immunity and the pathophysiology of asthma.

IL-12. This cytokine is generated by monocytes, macrophages, dendritic cells, B cells, neutrophils, mast cells and keratinocytes. The active form is a heterodimer consisting of a p40 and a p35 subunit. Interestingly, homodimers and monomers of p40 serve as competitive antagonists by binding to the IL-12 receptor without activating the signal transduction cascade. IL-12 is an important activator of NK cells. It further increases IFN-γ production, modulates T-cell functions and inhibits tumour angiogenesis [16]. Other stimulators of IL-12 secretion in the skin include bacteria and UV light. A protective effect of IL-12 on UV-induced DNA damage was demonstrated recently in keratinocytes [17].

IL-13. This is a cytokine with effects similar to IL-4, that is released from T cells, mast cells and keratinocytes [18]. It affects the function of B cells and monocytes, and decreases production of pro-inflammatory cytokines in keratinocytes and endothelial cells. IL-13 also reduces chemokine-induced chemotaxis of T cells. IL-6 expression on monocytes is inhibited by both IL-4 and IL-13 (see Chapter 10).

IL-15. This is thought to be of relevance in the pathophysiology of atopic dermatitis in view of its function in modulation of IFN-γ and IgE synthesis. In human keratinocytes, IL-15 inhibits anti-Fas and methylcellulose-induced apoptosis *in vitro* [19]. Moreover, IL-15 seems to be of significance in the maturation of dendritic cells [20] and activation of NK cells. IL-15 expression can be induced by IFN-α and -β.

IL-16. This is secreted from keratinocytes and Langerhans' cells amongst others, and is an important chemokine for the recruitment of $CD4^+$ T cells, monocytes, eosinophils and Langerhans' cells into inflamed skin. Serological levels of this cytokine correlate positively with the severity of atopic dermatitis [21].

IL-17. This is expressed by numerous immunocompetent cells. In keratinocytes, IL-17 initiates the release of growth-related oncogene-α (GRO-α), GM-CSF, IL-6 and the IFN-γ-induced expression of ICAM-1. In dermal endothelial cells, IL-17 induces IL-1 secretion and up-regulation of cell adhesion molecules. IL-17 activates skin fibroblasts [22] and results in increased IL-6 secretion and collagen synthesis. A pathophysiological role for IL-17 in systemic scleroderma has been proposed [23].

IL-18. Expression of IL-18 has been described in dendritic cells, macrophages, keratinocytes, osteoblasts, microglial cells and fibroblasts. IL-18 mRNA can be stimulated by LPS, GM-CSF and Fas ligand. Keratinocytes also express the receptor for IL-18, indicating autocrine regulation by IL-18 [24]. Functional IL-18 requires activation by an IL-18-converting enzyme (ICE or caspase-1) or proteinase-3.

Together with IL-12, IL-18 is an important activator of IFN-γ stimulation. Our knowledge of the biological effects of IL-18 is rapidly increasing. IL-18 induces maturation of T and NK cells, and stimulates release of cytokines and chemokines. On NK cells, IL-18 increases Fas-mediated cytotoxicity. It also induces IgE production by B cells and synergizes with IL-2 to enhance IL-4 production. In mice, IL-18 also promotes Th2 differentiation. However, the effects of IL-18 on T cells seem to vary, depending on endogenous and exogenous factors such as the maturation state and the micromilieu. In basophils, IL-18 contributes to IL-4 and IL-13 production. Stimulation of macrophages by IL-18 induces cytokine production, such as IL-6 and IFN-γ, TNF-α and IL-1β. IL-18 induces IL-6, IL-8, ICAM-1 and expression of matrix metalloproteinases by endothelial cells.

IL-18-binding protein (IL-18BP) is a secreted protein able to bind IL-18 with high affinity, leading to inhibition of IL-18-induced IFN-γ and IL-8 production and NF-κB activation. Recently, another secreted protein, IL-1H, has been shown to have IL-18 receptor antagonist activity.

Functions in the skin regulated by IL-18 include the migration of Langerhans' cells, Th-cell regulation and wound healing [25]. IL-18 also regulates ICAM-1 expression on microvascular endothelial cells, indicating a role in leukocyte–endothelial interactions during inflammation. IL-18 may be of relevance in the pathophysiology of diseases such as atopic dermatitis [26]. Enhanced expression of IL-18 has been found in patients with lupus erythematosus and psoriasis. Finally, IL-18 seems to be an important regulator of host defence mechanisms against viruses, bacteria, fungi and protozoa.

IL-19. This is a member of the IL-10 family that is released by monocytes and macrophages upon stimulation by LPS and GM-CSF. It can also be released by B cells. IL-19 exerts its effects by stimulating the receptors of IL-20 or IL-22.

IL-20. This exhibits a distinctive homology with IL-10. It is expressed in the skin and trachea and signals via a signal transducer of transcription 3 (STAT-3) pathway. In mice, overexpression of IL-20 genes leads to neonatal lethality with marked abnormalities in the skin, especially of epidermal differentiation. Overexpression of IL-20 in transgenic mice leads to skin lesions similar to psoriasis. Two putative receptors for IL-20 have been identified on keratinocytes. Interestingly, these receptors are highly expressed in psoriasis patients, indicating a potential pathophysiological role for this novel cytokine in psoriasis.

IL-22. This (IL-10-related T-cell-derived inducible factor) is synthesized by $CD4^+$ T and mast cells amongst others, and can be stimulated by IL-9 and LPS [27]. The IL-22 receptor has also been detected in the skin. There are two soluble IL-22 receptor antagonists (IL-22RA1 and -RA2); IL-22RA2 is expressed by immune cells as well as epithelial cells in the skin. However, the exact localization and significance of IL-22 in the skin is still unclear. Although IL-22 belongs to the IL-10 family of cytokines, it mediates acute-phase responses in inflamed tissue and hepatocytes.

IL-23. This recently discovered cytokine is structurally closely related to other mediators such as IL-6, G-CSF and IL-12. Transgenic mice overexpressing IL-23 show an intensive inflammatory infiltrate of lymphocytes and macrophages in numerous organs including the skin [28].

IL-24. This is the fourth member of the anti-inflammatory IL-10 cytokine family. Murine IL-24 is generated by Th2 cells in an IL-4 inducible manner. It has also been found to be generated by differentiated melanoma cells, with anti-tumorigenic activity, and LPS-stimulated monocytes.

IL-26. IL-26, formerly known as AK155, is produced by monocytes and various T-cell types. Our knowledge of its receptor expression, signalling mechanisms, biological effects and relevance to diseases is scant.

IL-27. This novel family member of the long-chain four-helical cytokine family has recently been described [29]. It is a heterodimer protein consisting of an IL-12p40-similar protein (EBI3) and an IL-12p35-similar polypeptide (p28). As an early product of activated antigen-presenting cells, IL-27 is able to induce clonal expansion of naive $CD4^+$ T cells in mice and humans, but not of memory T cells. It acts synergistically with IL-12 on the induction of the Th1- or the NK cell-mediated production of IFN-γ. IL-27 probably binds to the orphan-receptor WSX-1/TCCR, which has a high structural homology with the IL-6–IL-12 receptor family. It is thought that IL-27 is of importance in the proliferation and activation of naive T cells. Thus, this novel cytokine may be involved in the pathophysiology of T-cell-mediated skin diseases, autoimmune diseases and defence against infectious skin diseases.

IL-28 and IL-29. Very recently, novel members of the cytokine family have been cloned in humans, and designated IL-28A, IL-28B and IL-29 [30]. They are distantly related to type I interferons and the IL-10 family because of their capacity to enhance antiviral activity in cells. In addition, IL-28 and IL-29 activate a heterodimeric class II cytokine receptor, defined as IL-28Rβ, and an orphan receptor, designated IL-28Rα. Their distribution and biological function under physiological and pathophysiological circumstances have yet to be determined.

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Interferons

IFNs were originally described as factors that 'interfere' with the replication of virus replication. IFNs are an important protein family of cytokines of great significance in the defence against cancer cells and viral infections. Moreover, IFNs are key regulatory agents with many activities in normal tissue physiology, inflammation and the immune responses, enhancing or depressing the activities of other cytokines.

IFN-α and IFN-β are rapidly released after viral infections upon stimulation by double-stranded RNA. In contrast, IFN-γ is induced indirectly during the inflammatory response against pathogens, but also contributes to host defence. Very recently, a novel member of the type I interferon family has been cloned, defined as IFN-κ [1]. IFN-κ induces the release of several cytokines from monocytes and dendritic cells, and inhibits IL-12 release from monocytes. Synthesis of IFN-κ is inducible by IFN-γ in monocytes and dendritic cells, and IFN-κ can be found in these cells in lesional skin of atopic dermatitis and psoriasis.

The three IFNs, IFN-α from macrophages and B cells, IFN-β from fibroblasts and IFN-γ from activated T cells, have specific receptors and different properties that may act synergistically or in opposition. IFN-α and IFN-β exert their effects by inhibiting virus replication in host cells. Additionally, via binding to IFN receptors, both molecules not only act on infected cells, but also activate defence mechanisms in neigbouring 'healthy' cells in a paracrine manner. Activation of the receptor by IFN-α and IFN-β leads to the induction of intracellular signalling pathways involved in inflammation and host defence. For example, IFN-α and IFN-β activate STATs, P1-kinase and Mx-protein, all factors that increase the resistance of cells to viral replication [2].

IFN-γ alone induces formation of MHC class II molecule HLA-DR on membranes of monocytes and keratinocytes [3–5], while IFN-α and IFN-β induce expression of the MHC class I antigens on many cell types. This leads to optimal antigen presentation to cells of the adaptive immune system such as T cells. IFNs activate NK-cell activity, leading to the successful killing of infected cells. In contrast, INFs save non-infected cells from destruction by NK cells by up-regulating MHC class I molecules on these cells. In addition, IFN-γ up-regulates the activity of a proteinase, cathepsin S, by cultured human keratinocytes [6]. The release of VEGF is induced in keratinocytes and suppressed in fibroblasts by IFN-γ, indicating that this cytokine is involved in the regulation of angiogenesis [7].

IFN-γ augments monocyte secretion of TNF-α and TNF-β, which contribute to the antiviral and antiproliferative properties of IFNs [8], and increases the expression of IL-2R and ligand binding on human leukaemic and normal lymphocytes [9]. All three IFNs augment activity of NK lymphocytes and macrophages [10], and stimulate macrophage synthesis of arachidonic acid products [11]. IFN-α stimulates formation of IgG and IgM by B cells and, although it is not a helper T-cell factor, it enhances the response of helper factor to stimulate antibody formation [12]. Thus, IFNs directly modulate various functions within the innate as well as adaptive immune system.

In inflammatory diseases (e.g. atopic dermatitis), a positive effect of IFN-γ upon the healing of the eczema and pruritus has been documented in non-placebo-controlled single reports. Recent data in mice suggest that mast cells contribute to the regulation of IFN-γ in the inflamed skin [13].

IFN-γ may be of relevance to the pathogenesis of SLE. IFN-γ receptor knockout mice rarely develop lupus nephritis, and overexpression of IFN-γ in the epidermis leads to skin alterations similar to those in SLE. Systemic treatment of inflammatory or infectious skin diseases with IFNs is hampered by side effects such as fever, fatigue and local necrosis [14].

The pro-inflammatory effects of keratinocyte activation by IFN-γ can be inhibited by regulatory molecules defined as suppressors of cytokine signalling (SOCS). SOCS1, SOCS2 and SOCS3 proteins are up-regulated in the epidermis of psoriasis and allergic contact dermatitis but

not in atopic dermatitis patients [15]. They exert multiple anti-inflammatory effects on keratinocytes, such as down-regulation of HLA-DR, ICAM-1, IP-10 and MCP-1.

In summary, interferons not only act as antiviral agents but are also important mediators of inflammatory and immune responses within the skin.

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Tumour necrosis factor

TNF, also defined as cachectin or endogenous pyrogen, is a protein of approximately 17 kDa that exists in a secreted and transmembrane form, and builds dimers or trimers after release into the environment [1]. It is secreted by monocytes and macrophages, mast cells, fibroblasts, smooth muscle cells, endothelial cells, T cells and certain NK cells. It has multiple pro- as well as anti-inflammatory activities, and is also a growth factor in normal physiological regeneration and wound healing [2,3]. Upon stimulation by exogenous factors such as bacterial LPS, staphylococcal toxin, viruses and other organisms, or by endogenous mediators such as C5a, IL-1, IL-2, GM-CSF, substance P, bradykinin and TNF itself, large amounts are released within minutes, and synthesis is rapidly increased. The rate of synthesis is controlled by IFN-γ [4], but several other cytokines may antagonize and influence further release (e.g. TGF-β, IL-6, PGE_2 or vitamin D_3). TNF-α is activated after processing at the cell membrane by a transmembrane enzyme, TNF-α converting enzyme.

TNF binds to three types of receptor, TNF-R1 (CD 120a, p55) and TNF-R2 (CD 120b, p75), which are expressed by almost all cells and bind both TNF-α and TNF-β, and TNF-R3 which is only synthesized by human hepatocytes and which binds TNF-α. Each receptor appears to mediate different cellular responses [5]. TNF receptors also belong to the superfamily of death receptors which induce apoptosis (e.g. in keratinocytes and leukocytes during cutaneous inflammation; see p. 9.8).

The soluble forms of the receptors, released from cell membranes, neutralize both forms of TNF, thereby preventing systemic effects resulting from local inflammation [6]. The soluble receptors occur in the blood and urine of normal persons, and in markedly increased amounts during various inflammatory disorders and sepsis [6–8]. TNF-binding proteins (TBPs) are also capable of regulating TNF function after release into the extracellular space.

TNF has many biological properties, shared with IL-1, with which it is closely associated, and which synergistically enhances TNF activity. It induces septic shock and fever [9], cachexia [10] and is a potent mediator of inflammation, increasing macrophage and neutrophil chemotaxis, phagocytosis, cytotoxicity and respiratory burst activity [11–16]. The protective role of TNF is supported by the observation that mice that lack the gene for TNF do not develop septic arthritis but cannot resist systemic infection [17]. Thus, an important role of TNF is to protect tissues by localizing inflammation. On the other hand, once infection becomes systemic, TNF may have deleterious effects leading to sepsis and shock [16]. Some of these effects may result from its ability to stimulate synthesis of many other cytokines and mediators, including IL-1, GM-CSF, PDGF, TGF-β, prostaglandins and leukotrienes.

TNF-α exerts numerous effects in the epidermis. Toxins and haptens as well as UV light induce the release of TNF-α from keratinocytes. TNF receptors are involved in the regulation of keratinocyte apoptosis [18]. TNF-α also induces intensive expression of ICAM-1 in keratinocytes. Via activation of NF-κB and C/EBPβ, TNF-α regulates the synthesis of cytoskeletal proteins participating in epidermal responses to inflammation or wound healing. In contrast to its many tissue-damaging properties, TNF is also a growth factor, stimulating fibroblast proliferation and synthesis, and shows synergy with EGF, by increasing the EGF receptor, PDGF and insulin [2].

In endothelial cells, TNF promotes leukocyte adherence by increasing expression of E-selectin, ICAM-1 and VCAM, probably via activation of the transcription factor NF-κB. TNF-α is also a potent activator of neutrophils, leading to the regulation of cell recruitment, chemotaxis, degranulation and release of cytokines and oxidative burst mediators.

TNF-α probably exerts a direct effect on Langerhans' cells and type IV hypersensitivity reactions. The pathophysiological relevance of TNF-α has been demonstrated in various models of infection, inflammation and autoimmune disease [19,20].

Syndromes exist that are linked to TNF-receptor type I dysfunction. For example, TNF-receptor-associated periodic syndrome (TRAPS) is a rare hereditary syndrome accompanied by prolonged attacks of periodic fever and severe localized inflammatory reactions. This disease is based on a dominantly inherited mutation within the TNF type I receptor. This defect leads to decreased levels of soluble TNF receptor, resulting in an unopposed TNF-α reaction clinically evident as a prolonged inflammatory response [21].

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Cytokine suppressors and inhibitors

In addition to pro-inflammatory cytokines, certain cytokines including IL-1RA, TGF-β and members of the IL-10 family exert potent anti-inflammatory effects.

The physical state of cytokines in body fluids has rarely been determined. Detection of a cytokine by immunological techniques indicates only its presence, not its potential activity. The cytokine may be coupled to a substance that prevents binding to the specific receptor. Coupling may occur as: (i) dissociable complexes with a protective lipoprotein that releases the cytokine to react with its receptor; (ii) firmly bound complexes of cytokine and a carrier protein that interferes with receptor linkage [1,2]; or (iii) complexes of cytokine with its specific soluble receptor that blocks interaction with cell receptors [3].

Anti-inflammatory cytokines exert their effects by:

1 Regulation of cytokine secretion, and differences in the agonists stimulating secretion
2 Regulation of cytokine receptor expression
3 Receptor competition of different cytokines
4 Soluble binding factors and/or inhibitors
5 Regulation of proteases that activate the cytokine proform (converting enzymes).

IL-1RA and IL-18RA

IL-1 receptor antagonist (IL-1RA) is naturally secreted during inflammatory processes, and its production and release is modulated by many cytokines such as IL-4, IL-6, IL-13 and TGF-β. IL-1RA is important in potentially inhibiting the deleterious effects of IL-1 during the inflammatory process.

Two types of specific blocking agent for IL-1 activity have been identified. The first is a soluble receptor without a transmembrane structure that binds to free IL-1, inactivating its binding site. The second, IL-1RA, is an inactive IL-1 homologue that blocks receptor sites on cells.

IL-1α or IL-1β activity normally follows binding of the cytokine to the IL-1 type I receptor on all responding cells [4]. Other cells, B cells and neutrophils, have another IL-1R, type II receptor [5]. It has been suggested that the IL-1RII receptor can be shed from cells and bind with free

IL-1, blocking its ability to couple to cell-bound IL-R1. An alternative inhibitory molecule is an inactive homologue of IL-1, IL-1RA, which binds to cell receptors without inducing a signal. The inert homologue therefore blocks the receptor, preventing later binding of active IL-1 [6–9]. This type of antagonist is peculiar to IL-1. It is secreted mainly by monocytes and macrophages, but also by neutrophils and fibroblasts. It has been designated secreted interleukin-1 receptor antagonist (sIL-1RA).

Keratinocytes, fibroblasts and monocytes are capable of generating an intracellular form of IL-1RA. Knowledge about its function is still scant. Other cytokine receptors may occur in a soluble form; most of these have blocking and/or inhibitory activity [3].

Both the IL-1α and the IL-18 precursor require cleavage into an active mature molecule by an intracellular cysteine protease termed IL-1α converting enzyme (ICE), which is also known as capsase-1. Thus, ICE inhibitors may limit the activity of IL-1α as well as IL-18. IL-1RA is a physiological antagonist that has a similar structure to IL-1α and IL-β, and thus competes with the binding of the natural ligand to the receptor. IL-18BP is a naturally occurring antagonist that is able to bind IL-18 with high affinity and to neutralize its activity, but not that of IL-1. Recently, another IL-18 antagonist, IL-1H, was discovered, which has sequence homology with IL-1RA, and binds IL-18R but not IL-1R. IL-1F7b shares sequence homology with IL-18 and binds IL-18Rα but has no IL-18-like agonistic or antagonistic activity. IL-F7b binds to IL-18BP and subsequently may block IL-18Rα, which ultimately results in the inhibition of IL-18 activity.

A non-receptor soluble protein that may function as a protective carrier protein or inhibitory substance is α_2M [10]; it is a carrier for IL-1, IL-6 and PDGF [10,11], but inactivates IL-2 and FGF [10]. Other soluble inhibitors, mainly directed against IL-1, have been found in the medium of UV-exposed keratinocyte cultures, and in the sera of UV-exposed mice and humans. The identity of these substances, and a related epidermal cell contra-IL-1, which blocks the activity of IL-1, is still to be determined.

TGF-β

TGF-β belongs to a family of peptides involved in growth and differentiation in almost all cells. It is involved in the regulation of extracellular matrix proteins and pathophysiological processes such as fibrosis, wound healing and scar formation. Within the immune system, TGF-β down-regulates the function of T cells, B cells, monocytes and NK cells. T cells undergoing apoptosis release TGF-β, leading to immunosuppressive effects in the inflammatory micromilieu [12]. TGF-β also diminishes mast cell function by inhibiting mast cell proliferation and IgE synthesis. TGF-β reduces the synthesis of IL-1 and IL-2. TGF-β, secreted in an inactive form, can bind weakly after exposure to acid pH in wound fluid to epidermal growth factor receptor (EGFR) on keratinocytes and endothelium, and compete with the stimulating molecules EGF and TGF-β, thereby reducing keratinocyte and endothelial proliferation.

IL-10 family of cytokines

Because of their similarity to IL-10 function, interleukins IL-10, IL-19, IL-20, IL-22, IL-24 and IL-26 have been grouped together as the IL-10 family. IL-28 and IL-29 share similarities to both type I interferons and IL-10 cytokines. Their function and role during inflammation and immune response are as described above.

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Chemokines

Chemokines constitute a large family of soluble chemotactic cytokines with four conserved cysteines linked by disulphide bonds. Four subfamilies, CXC, CC, CX3C and C chemokines, are distinguished according to the position of the first two cysteines. So far, more than 40 chemokines have been defined and characterized (Table 9.7). Most chemokine genes encode for proteins of approximately 90–125 amino acids. The different chemokine subfamilies are clustered on different chromosomes [1].

The main characteristic of chemokines is their potential to activate and attract leukocytes. Thus, chemokines have a pivotal role during inflammation and immunity. Interestingly, while CXC chemokines mainly attract neutrophils and lymphocytes, CC chemokines are capable of attracting monocytes, eosinophils, basophils and lymphocytes, but not neutrophils.

Table 9.7 Nomenclature for human chemokines. (From Keystone Chemokine Conference, Keystone, CO, USA, January 18–23, 1999.)

Systematic name	Human ligand	Mouse ligand	Chemokine receptor(s)
CC chemokine/receptor family			
CCL1	I-309	TCA-3, P500	CCR8
CCL2	MCP-1, MCAF	MCP-1, JE	CCR2
CCL3	MIP-1α, LD78α, LD78β, AT464.1, AT464.2, GOS19-1, GOS19-2	MIP-1α	CCR1, CCR5
CCL4	MIP-1β, AT744.1, AT744.2, Act-2, G-26, HC21, H400, LAG-1	MIP-1β	CCR5
CCL5	RANTES	RANTES	CCR1, CCR3, CCR5
CCL6	Unknown	C10, MRP-1	Unknown
CCL7	MCP-3	NC28, FIC, MARC	CCR1, CCR2, CCR3
CCL8	MCP-2, HC14	MCP-2	CCR2, CCR3
CCL9, CCL10	Unknown	MRP-2, CCF18, MIP-1γ	Unknown
CCL11	Eotaxin	Eotaxin	CCR3
CCL12	Unknown	MCP-5	CCR2
CCL13	MCP-4, NCC-1, CKβ-10	Unknown	CCR2, CCR3
CCL14	HCC-1, HCC-3, NCC-2	Unknown	CCR1
CCL15	HCC-2, MIP-1δ, NCC-3, MIP-5, LKN-1	Unknown	CCR1, CCR3
CCL16	HCC-4, NCC-4, LEC, LMC	LCC-1	CCR1
CCL17	TARC, dendrokine	TARC	CCR4
CCL18	DC-Ck1, PARC, MIP-4, AMAC-1	Unknown	Unknown
CCL19	MIP-3β, ELC, exodus-3, CKβ-11	MIP-3β	CCR7
CCL20	MIP-3α, LARC, exodus-1	MIP-3α	CCR6
CCL21	6Ckine, SLC, exodus-2, TCA-4	6Ckine	CCR7
CCL22	MDC, STCP-1, DCtacin-β	ABCD-1	CCR4
CCL23	MPIF-1, MIP-3, CKβ8, CKβ8-1	Unknown	CCR1
CCL24	Eotaxin-2, MPIF-2, CKβ-6	Unknown	CCR3
CCL25	TECK	TECK	CCR9 (GPR9-6)
CCL26	Eotaxin-3	Unknown	CCR3
CCL27	CTACK/ALP	CTACK, ALP	Unknown
CXC chemokine/receptor family			
CXCL1	GRO-1, GROα, MGSA-α	GRO (KC)	CXCR2 > CXCR1
CXCL2	GRO2, GROβ, MIP-2α, MGSA-β	GRO (KC)	CXCR2
CXCL3	GRO3, GROγ, MIP-2β	GRO (KC)	CXCR2
CXCL4	PF4	PF4var1, PF4alt	Unknown
CXCL5	ENA-78	LIX	CXCR2
CXCL6	GCP-2	CKα-3	CXCR1, CXCR2
CXCL7	NAP-2	Unknown	CXCR2
CXCL8	IL-8, MDNCF, NAP-1, NCF	Unknown	CXCR1, CXCR2
CXCL9	Mig, Humig	Mig	CXCR3
CXCL10	IP-10	crg-2, mob-1	CXCR3
CXCL11	I-TAC, H174, b-R1	Unknown	CXCR3
CXCL12	SDF-1α, SDF-1β, PBSF	SDF-1α/β	CXCR4
CXCL13	BLC, BCA-1	BLR1L, Angie	CXCR5
CXCL14	BRAK/bolekine	BRAK	Unknown
CXCL15	Unknown	Lungkine	Unknown
C chemokine/receptor family			
XCL1	Lymphotactin, SCM-1α, ATAC	Lymphotactin	XCR1
XCL2	SCM-1β		XCR1
CX3C chemokine/receptor			
CX3CL1	Fractalkine, neurotactin	Fractalkine	CX3CR1

MDC, macrophage-derived chemokine; TARC, thymus and activation-regulated chemokine.

The classic role of chemokines is to attract leukocytes to the site of inflammation. For instance, $CD34^+$ dendritic cells (DCs) secrete ligands for chemokine receptors such as CCR1, CCR5, CCR6, CXCR4 or CCR9 to enter the target tissue. After maturation in epithelial tissues such as the epidermis, DCs change their phenotype by up-regulating CCR7, for example, to traffic to lymph nodes [2].

In addition to attracting leukocytes, chemokines also modulate leukocyte–endothelial interactions. They promote transendothelial emigration by supporting the binding of cell adhesion molecules with integrins (e.g. linkage of VCAM with α4β1 integrin on monocytes, eosinophils and basophils) or the binding of L-selectin to E-selectin on neutrophils. CC chemokines may also induce the syn-

thesis and release of inflammatory mediators such as histamine from basophils [3,4] or leukotrienes.

The effects of chemokines are mediated via binding and activating heptahelical G protein-coupled receptors. Chemokine activation instantly leads to rearrangement of the cell cytoskeleton, and activation of intracellular second messengers and integrins. Chemokine activation in neutro-phils or monocytes results in the generation of inflammatory agents such as lipid mediators, NO, prostaglandins, amines, proteases and oxygen radicals [5]. RANTES and MIP-1α also release histamine from basophils [6].

Besides their specific ligand–receptor interaction, chemokines may also adhere to extracellular matrix proteins and the apical surface of endothelial cells. This appears to be crucial for the migration of leukocytes to sites of inflammation. For example, CXCL8 and CCL19 attach to the endothelial cell surface, thereby stimulating transmigration [7]. In contrast, glycosaminoglycans such as heparan sulphate are capable of inactivating chemokine effects on endothelial cells [8].

Chemokines bind and activate chemokine receptors, which comprise a large family of seven transmembrane receptors. They are expressed by numerous cell types and modulate not only inflammation, but also embryogenesis and innate as well as adaptive immune responses. Chemokine receptors have been implicated in the pathophysiology of several diseases such as HIV infection, malaria, psoriasis and wound healing [9]. Moreover, viruses such as herpesvirus and poxvirus encode for chemokine receptors, thereby entering their hosts, indicating an important role for chemokines in certain infectious diseases [10].

In the skin, a special subset of memory T cells normally bears cutaneous lymphocyte-associated antigen (CLA), with resultant selective trafficking of these cells to the skin. The CLA protein seems to be crucial for T-cell interaction with the endothelium, the extracellular matrix and other cell types in the skin. Approximately 80–90% of T cells found in lesional skin in cutaneous inflammation express CLA. In contrast, in non-cutaneous sites of inflammation CLA^+ T cells constitute only approximately 5% of lesional T cells. During contact dermatitis, specificity to skin-associated allergens such as nickel or house-dust mite allergens is restricted to CLA^+ T cells [11].

CC chemokines

RANTES. RANTES, an acronym for regulated upon activation, normal T cell expressed and secreted, attracts basophils, eosinophils, lymphocytes and monocytes. It induces granule release and leukotriene synthesis in basophils and eosinophils, and histamine release from basophils. The activity is enhanced by priming with IL-5. It is formed by macrophages, fibroblasts and T cells. RANTES is one of the more potent chemokines in inflammation and allergy, and is believed to be an important mediator of tissue eosinophilia. RANTES mRNA has been detected in skin of atopic subjects 6 h after challenge by antigen, and the secreted protein is present in atopic dermatitis skin scales [12].

Macrophage inflammatory protein 1a. This is formed by monocytes, fibroblasts, activated T and B cells, and attracts monocytes, lymphocytes, basophils and eosinophils. When bound to endothelial cells, it is reported to increase binding of $CD8^+$ T cells. In mice, it releases histamine from mast cells and basophils, but histamine release from human basophils is little above control amounts.

Macrophage inflammatory protein 1b. This is closely related to the α-form and shares many of its properties. It has been reported to increase adhesion to endothelium by $CD8^+$ T cells, or adhesion of $CD4^+$ cells, by α4β1 integrin–VCAM binding.

Monocyte chemotactic proteins. MCPs are capable of attracting T cells, DCs and NK cells. They are also potent attractants of monocytes and modulate expression of adhesion molecules. MCP-2 and MCP-3 also attract eosinophils. MCP-1 and MCP-3 attract basophils, and induce histamine release and synthesis of LTC_4. Recently, MCP-2 has been reported to be as potent as MCP-3 in activating eosinophils and basophils [13]. These proteins contribute to leukocyte infiltration of damaged tissue, possibly especially in atopic disorders. Antibodies against MCP-1 rendered animals less susceptible to delayed-type hypersensitivity, indicating a potential therapeutic strategy for the treatment of allergic reactions in the skin.

Eotaxin. Eotaxin, a potent chemokine for eosinophils [14], has more than 50% amino acid homology with the MCP mediators. It has been detected in the epithelium of nasal polyp biopsies and possibly contributes to the eosinophilia of allergic inflammation. Eotaxin attracts T cells and eosinophils to the skin in patients with atopic dermatitis. In eotaxin-deficient mice, allergen-induced attraction of eosinophils seems to be impaired; this effect, however, appears to be compensated for by other chemokines at later stages [15].

CCL27. This is a skin-associated CC chemokine member that binds the receptor CCR10 with high affinity. CCL27–CCR10 interactions are critical for skin-homing CLA-bearing memory T cells [16,17]. Recent data suggest that CCL27 directly contributes to cutaneous inflammation. For example, patients with psoriasis, atopic dermatitis and contact dermatitis express CCR10 on $CD4^+$ T cells, fibroblasts and endothelial cells. Cutaneous application of CCL27 attracts lymphocytes into the skin [18].

CXC chemokines

IL-8. The first chemokine to be defined was IL-8, which is the most potent chemokine for attracting neutrophils. IL-8 binds to and activates CXCR-1 and CXCR-2. CXCR-1 (IL-8R1) is exclusively activated by IL-8, while CXCR2 (IL-8R2) can also be activated by GRO-α, GRO-β, GRO-γ, NAP-2, ENA-78, GCP-2.

GRO-a. This product of a growth-regulated gene, which also has melanoma growth-stimulating activity (MGSA), attracts and activates neutrophils. It is formed by monocytes, fibroblasts, platelets, endothelial cells and melanoma cells. Increased amounts occur in psoriatic scales, together with IL-8 [19].

NAP-2. This is a product cleaved from a basic protein derived from platelet granules. It attracts neutrophils, induces influx of calcium ions, degranulation and the respiratory burst [20].

Interferon-inducible protein 10. IP-10 is induced by IFN in monocytes, activated T cells, fibroblasts, endothelial cells and keratinocytes. It attracts monocytes and T cells and promotes T-cell binding to endothelium; it may contribute to the cell changes of delayed hypersensitivity [21]. Neutrophil attraction is doubtful.

Epithelial neutrophil activating peptide 78. ENA-78 attracts and activates neutrophils with resultant release of their granules and mediators. It is synthesized by type II alveolar epithelial cells stimulated by IL-1, by neutrophils, monocytes, endothelial cells and vascular smooth muscle cells stimulated by IL-1 or LPA; ENA-78 mRNA has been reported in platelets. ENA-78 has been detected in lungs infiltrated by neutrophils in adult respiratory distress, and increased amounts are found in the sera of patients with rheumatoid arthritis [22].

Chemokine receptors

So far, five CXC receptor subtypes have been defined, 11 for CCR and 1 for CX3C chemokines. Most receptors can be activated by more than one chemokine, and several chemokines bind to more than one receptor [1,9].

IL-8 was the first chemokine to be demonstrated in 1987. Later, the first chemokine receptors for IL-8, defined as CXCR1 and CXCR2, were characterized. They are expressed by T cells, activated eosinophils, mast cells, basophils and dendritic cells, suggesting a role for IL-8 during acute inflammation and innate immunity. Both CXCR1 and CXCR2 can be activated by IL-2. CXCR1 appears to be the dominant receptor for chemotaxis, phospholipase D production and superoxide generation after IL-8 or NAP-2 activation. CXCR2 mediates neutrophil chemotaxis in response to low-concentration NAP-2 and GRO-α. Interestingly, human herpesvirus (HHV) and HHV8 both express functional CXCR2 receptors, although the significance of this remains unclear [23]. CXCR3 is a receptor for T-cell activation. It binds I-TAC, Mig and IP-10. Eotaxin and MCP-4 also bind CXCR3, but with lower affinity. CXCR3 is expressed mainly by Th1-type T cells and $CD45RO^+$ memory T cells. In sarcoidosis, virtually all T cells express CXCR3. CXCR4 has been detected on most haematopoietic cells such as B cells, DCs, Langerhans' cells, macrophages and T cells. Moreover, CXCR4 has also been identified as an HIV virus co-receptor, in that the glycoprotein gp120 from the HIV envelope binds to CXCR4 in the presence of CD4 [24]. However, CD4 independent association of gp120 to CXCR4 has also been shown. Thus, CXCR4 may be involved in HIV infection and HIV neurotoxicity. CXCR5 is a B-cell chemokine receptor. After T-cell activation, CXCR5 is up-regulated on memory and/or effector T cells via the chemokine BCA-1, suggesting a role in T–B cell interaction.

CCR1. This is a receptor for several chemokines such as MIP-1α, RANTES, MCP-2, MCP-3, MIP-5, MPIF-1 and HCC-1. MIP-1β and MCP-1 are also poor agonists. CCR1 is expressed by T cells, especially memory $CD45RO^+$ T cells. CCR1 knockout mice do not acquire spontaneous infections, but show increased mortality when infected with *Aspergillus fumigatus*, indicating a role for CCR1 in neutrophil-mediated diseases [25]. This receptor also appears to regulate granuloma formation and Th1–Th2 cytokine balance. Recent data indicate that CCR1 is a receptor that can modulate inflammatory responses either positively or negatively, depending on the microenvironment.

CCR2. This is a leukocyte MCP-1 receptor expressed by monocytes, dendritic cells, NK cells and T cells, B cells and basophils. Mice lacking CCR2 develop normally but do not recruit macrophages in an experimental inflammation model. They fail to clear infections, have smaller granulomas and show defective recruitment of monocytes–macrophages to the site of inflammation. These results indicate a role for CCR2 in macrophage function. CCR2 may be also involved in HIV infection [1,3,9,24].

CCR3. This is the receptor for chemoattractants on eosinophils and may thus be important during allergic inflammation and hypersensitivity. This receptor can be activated by MIP-1α, MIP-1β and eotaxin, RANTES, MCP-3, MCP-4, MIP-5 and the TAT protein of HIV. Eotaxin appears to be the most potent agonist of CCR3. CCR3 can also be detected on basophils, mast cells, Th2-type T lymphocytes and DCs. Eotaxin knockout mice showed only weak responses after ovalbumin challenge. Using animal models, neutralization of eotaxin resulted in a partial blockade of eosinophilia after allergen challenge [26].

CCR4. This is expressed by Th2 T lymphocytes and can be activated by macrophage-derived chemokine (MDC) and thymus and activation-regulated chemokine (TARC). This receptor may be involved in dendritic cell function, trafficking of T cells to the lymph nodes and T-cell transmigration, as well as homing of memory T cells to inflamed skin [27].

CCR5. This has become well known as a major HIV-1 co-receptor that controls susceptibility to HIV-1 infection and disease [9]. CCR5 is expressed by T lymphocytes and macrophages as well as Langerhans' cells. CCR5 can be activated by MIP-1α, RANTES, MIP-1β and MCP-1. MCP-3 however, appears to be an CCR5 antagonist. CCR5 knockout mice appear healthy. A role for CCR5 in down-modulating T-cell-dependent immune responses has been suggested. CCR5 is one of the first receptors for which use of receptor antagonists has been advocated in clinical trials in humans, in HIV infection [28].

CCR6. This mediates responsiveness of memory T cells to the chemokine LARC. CCR6 seems to be important for the migration of memory T cells and dendritic cells to secondary lymphoid organs. The chemokine MIP-3α has been shown to regulate the homing of Langerhans'-type dendritic cells to the epidermis by activating CCR6. The CCR6 ligand LARC can be released by macrophages, dendritic cells and endothelial cells. However, the human β-defensin 2 (HBD-2) has also been shown to functionally bind CCR6. HBD-2 is produced by enterocytes during infection and functions as an antimicrobial factor. It also attracts DCs and memory T cells via CCR6 activation. Together, these results indicate a role for this receptor as a link between the innate and adaptive immune systems [29].

CCR7. This is a homing receptor for B cells, T cells and DCs across high endothelial venules. CCR7 is activated by the chemokines ELC and SLC, which are expressed in the T-cell area of lymphoid tissues but not in the B-cell area. This is supported by the finding that CCR7 knockout mice show defective B- and T-cell homing, whereas defective T-cell development is not found.

CCR8. This is critically associated with the function of Th2 lymphocytes. Reports of the activation of CCR8 by various agents such as TARC and MIP-1β are controversial. Interestingly, CCR8 can be activated by viral chemokines from molluscum contagiosum [30]. CCR8 has also been described as an HIV-1 co-receptor.

CCR9. This is a recently described receptor that can be activated by TECK, a chemokine for dendritic cells, T cells and activated macrophages. It appears to be involved in the development of T cells within the thymus.

CCR10. This is a receptor for the skin-associated CC chemokine CCL27 (CTACK) that attracts skin-homing memory T cells to the site of inflammation [16].

CCR11. This is a receptor for MCP-1, MCP-2 and MCP-4. It has been described in the heart, small intestine and the lung.

CX3CR1. This is a receptor that is crucially involved in cell–cell adhesion and leukocyte trafficking. Its ligand fractalkine is a transmembrane protein that activates CX3R1 on neutrophils, monocytes, NK cells and T lymphocytes. This receptor has also been described as a co-receptor for HIV-1. Its role in the skin, however, is currently unknown.

A crucial role for chemokines and chemokine receptors in cutaneous inflammation has also been observed in several studies in which the relevant genes have been deleted by homologous recombination. For example, CXCR2 gene-deficient mice are incapable of mobilizing neutrophils *in vivo* [31]. Further results showing that CXCR2 ligand neutralization leads to impaired reactions during skin inflammation suggest a potential therapeutic strategy for the use of chemokine receptor antagonists in inflammatory skin diseases such as psoriasis. CXCR2 knockout mice show defective neutrophil recruitment, an altered temporal pattern of monocyte recruitment and altered secretion of IL-1β, indicating a role for this chemokine receptor in wound healing [32].

Recent data suggest a role for chemokines in angiogenesis. IL-8 (CXCL8) has been shown to act as a growth factor in malignant melanoma. Melanoma cells overexpress certain chemokines that activate CXCL8, indicating an autocrine tumour-promoting effect of this chemokine. Many chemokines, including CCL20/MIP-3α, have been demonstrated to display antimicrobial activity comparable to defensins.

Chemokines may also be involved in the modulation of angiogenesis during tumour growth. For instance, CXCL8 (IL-8) and CXCL10 (IP-10) are angiostatic factors, while CXCL12 (SDF-1) has been shown to act as an angiogenic factor *in vivo* [2,7,9,33]. Interestingly, CXCL12 and VEGF appear to act synergistically to regulate angiogenesis. Other chemokines such as CXCL4, CXCL9 and CXCL10 decrease angiogenesis, thereby inhibiting tumour growth. A role for chemokines in regulating blood vessel formation during chronic inflammation and injury awaits further clarification.

In summary, recent data indicate a crucial role for various chemokines in cutaneous inflammation, and receptor antagonists may prove useful in the treatment of several skin diseases including inflammation, autoimmunity, allergy, infection and tumour growth.

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Proteases

Proteases constitute the largest family of enzymes, and comprise approximately 5% of the human genome, making them the largest protein family in humans. Although not known to be involved in multiple processes, proteases have in the past been regarded purely as destructive enzymes that merely degrade peptides. Proteases are in fact involved in almost all biological processes, such as embryogenesis, cell cycling, growth and differentiation, coagulation, inflammation, tumourigenesis, hair growth, secretion and tissue repair, and also assist in cell–cell communication [1–4].

Proteases can be devided into five groups, depending on the type of molecule that mediates catalytic work (serine, threonine, cysteine, aspartyl, metalloproteinases). It is important to realize that the effect of a protease is irreversible, because hydrolysis cannot be reversed. Therefore, proteases are maintained in a precursor state (zymogen) and become activated only when needed. Proteinases are involved in inflammatory processes that are not appropriately regulated. Significant tissue destruction and impairment of repair mechanisms may occur after proteinase activation, or dysfunction of protease inhibitors. One of the best examples of a crucial part played by a protease-regulated system is the blood coagulation cascade. Another example is programmed cell death (apoptosis) in which cysteine proteases (caspases) are critically involved [5].

In the skin, exogenous proteases such as Der p3 or Der p9 from house-dust mite, bacterial (e.g. V8 protease from staphylococci) or fungal proteinases (aspartyl proteases) are capable of triggering the inflammatory response in the epidermis or dermis. Among the keratinocyte-derived enzymes that may contribute to inflammation are acid phosphatase, cathepsins (acid proteases) B, C and D, mainly distributed in lysosomes with acid phosphatase, and neutral serine proteinases such as squamous cell tryptic enzyme (SCTE), squamous cell chymotryptic enzyme

(SCCE) and trypsin IV. Interestingly, enteropeptidase, the enzyme that cleaves trypsinogen and thereby activates trypsin, can be functionally expressed by keratinocytes. Keratinocytes also respond to protease inhibitors, indicating a complete proteinase-regulated machinery within the epidermis. Another enzyme, plasminogen activator, is generated throughout the epidermis, with a predominance within the granular layer.

Hereditary angio-oedema, characterized by episodic localized angio-oedema of the skin or mucosa, results from heterozygous deficiency of a protease inhibitor from the plasma, C1 esterase inhibitor (C1INH). C1INH seems to be involved in preventing excessive vascular permeability, and is an important modulator of inflammatory responses via regulation of complement activation.

Converting enzymes, such as IL-1 converting enzyme or pro-hormone convertase, are important proteinases in the switching of a pro-form of a molecule to the active state. They are especially important during the inflammatory process, where dysfunction of such enzymes may result in a disease state.

Acid phosphatase occurs in large amounts, relative to other acid hydrolases, particularly in the upper keratinizing layers of the epidermis. It probably participates in nucleic acid degradation. Hyperplasia of human skin induced by UV radiation and vitamin A application is associated with increased acid phosphatase. This increase, which also occurs in the stratum corneum, has found applications as a test for weak irritants; severe irritants result in a loss of acid phosphatase. Mild irritation of rat skin results in an increase of acid phosphatase, maximal on the third day, coinciding with acanthosis and thickening of the stratum granulosum.

Acidic protease cathepsins B, C and D occur in human epidermis. Tests in rabbits show that cathepsin D has a major role in intracellular protein digestion, and if released may degrade extracellular protein. Following irritation, proteases first degrade damaged cells on release of lysosomal enzymes, then there is activation of complement or Hageman factor, or cleavage of fibrin, inducing attraction of leukocytes, which further the inflammatory changes. A neutral protease in human skin, also present in fibroblasts, neutrophils and lymphocytes, has been shown to cleave complement and stimulate neutrophil chemotaxis in mice [6]. Thus, damage to the epidermis will initiate generation of chemotactic substances by release of proteolytic enzymes and by activation of other APPs, resulting in infiltration by neutrophils and further inflammation.

Tryptase is released by mast cells during inflammation, allergic reactions and tissue repair, and stimulates the release of pro-inflammatory cytokines (IL-6, IL-8), growth factors (GM-CSF) and other inflammatory mediators (NO, prostaglandins) [7–9]. Another protease released by mast cells during inflammation is chymase. This enzyme seems to be important as a regulator of vascular responses, leukocyte recruitment and the regulation of extracellular matrix proteins. Thus, chymase may be involved in the pathophysiology of allergic reactions, inflammation and tissue repair [10].

Many proteases are integral components of vital signalling networks. Besides their role as catalysts for extracellular matrix proteins, certain serine proteases have been demonstrated to activate specific receptors. The first protease-mediated receptor system identified was the thrombin receptor (PAR-1) [11]. Two other thrombin receptors were characterized: PAR-3 and PAR-4 [12]. Thrombin not only plays an essential part in the coagulation cascade, but additionally activates platelets and endothelial cells, thereby contributing to inflammation and tissue repair. PARs are G protein-coupled receptors with seven transmembrane domains. After activation, PARs mediate several responses involved in inflammation, such as release of cytokines, prostaglandins, NO or chemokines. Up-regulation of cell adhesion molecules on microvascular endothelial cells can be also mediated via PARs, indicating a direct role of proteases on leukocyte–endothelial interactions during inflammation [7]. *In vivo*, PAR-2 can be activated by skin-derived proteases such as tryptase and trypsin IV, leading to pruritus, oedema, plasma extravasation, up-regulation of cell adhesion molecules and promotion of the transendothelial migration of neutrophils [13–16]. Thus, activation of PARs affects all aspects of acute and chronic inflammation.

Plasminogen activation on the cell surface depends on the activation of urokinase type plasminogen activator (uPA) and its receptor. Such protease receptor families are defined as plasminogen activator receptors (also abbreviated PAR receptors). In contrast to the other PARs, these receptors are single-transmembrane receptors with protein kinase activity. One receptor, uPAR (urokinase receptor) can be activated by binding of urokinase and vitronectin [17]. Once activated on endothelial cells, urokinase receptors mediate adhesion, proliferation and migration of inflammatory cells. For example, uPAR has been demonstrated to be highly expressed on leukocytes during HIV infection, and soluble uPAR (suPAR) in the serum is an effective predictor of survival in HIV infection [18]. In the skin, uPAR has been implicated in the pathophysiology of pemphigus acantholysis [19]. uPA also activates metalloproteinases, thereby contributing to vascular damage [20]. The uPA–uPAR system is completed by the existence of plasminogen activator inhibitors (PAIs). Together, the orchestrated interaction of uPA, uPAR and PAI appears to have an essential role during inflammation, angiogenesis and cancer [21]. It is well known that protease inhibitor deficiency, or dysfunction, such as with α_1-antitrypsin, may result in airway disease [22]. An important recent finding has been that certain protease inhibitors are involved in cutaneous inflammation and disease. SPINK5, encoding

the putative multidomain serine protease inhibitor LEKTI, was recently identified as the defective gene in Netherton's syndrome [22]. LEKTI is strongly expressed in the granular and uppermost spinous layers of the epidermis, and in differentiated layers of stratified epithelia. Loss of LEKTI expression in the epidermis seems to be a diagnostic feature of Netherton's syndrome.

Protease inhibitors have been found to be effective drugs. For example, inhibitors of ACE and neutral endopeptidase may be involved in cutaneous inflammation. Moreover, HIV protease inhibitors are effective in the treatment of this infectious disease. Together, the key role of proteases in many organs including the skin and the immune system makes them attractive targets for future drug developments [23–26].

In summary, proteases along with their inhibitors and receptors have an essential role in skin homoeostasis and pathology. A well-tuned orchestra of these enzymes seems to be crucial for the maintenance of many inflammatory responses in the skin such as oedema, plasma extravasation, recruitment of leukocytes, cell–cell communication, extracellular matrix degradation, angiogenesis, cytoprotection, post-inflammatory pigmentation, spongiosis and keratinocyte desquamation. The significance of proteases to the treatment of skin diseases will be better understood once effective protease inhibitors, protease-receptor antagonists (or agonists) are available in the future.

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Matrix metalloproteinases

Matrix metalloproteinases (MMPs) constitute a family of multidomain zinc endopeptidases that contain a catalytic domain with a common metzincin-like topology (Table 9.8). They are involved not only in extracellular matrix degradation, but also in a number of other biological processes. Classically, MMPs are known as key players in the regulation of the extracellular matrix (ECM), by mediating the responses of cells to their environment. By causing the proteolytic degradation or activation of a cell and the ECM, these proteases influence cell migration, proliferation and cell survival. They have overlapping activities principally on collagen, fibronectin, laminin and elastin. The activity is tightly controlled, being stimulated by inflammatory mediators or growth factors such as IL-1, TNF-α, TGF-β, EGF, FGF and PDGF, and repressed by TGF-α and IL-4. The extracellular activity is inhibited by four different tissue inhibitors of metalloproteinases (TIMP-1–TIMP-4) and by the less selective α_1-antitrypsin (α_1-proteinase inhibitor) and α_2-macroglobulin [1–4].

Twenty-eight matrix metalloproteinases (MMP-1–MMP-28), grouped according to domain structure as gelatinases, collagenases, stromolysins and matrilysin, are zinc-dependent endopeptidases present in small

Table 9.8 Vertebrate matrix metalloproteinases (MMPs).

MMP	Name	Group	Substrate
MMP1	Collagenase-1	Collagenases	Collagens I, II, III, VII, VIII, X, gelatin
MMP2	Gelatinase-A	Gelatinases	Collagens I, II, III, IV, V, VII, X, XI
MMP3	Stromelysin-1	Stromelysins	PG core protein, laminin, fibronectin
MMP7	Matrilysin-1	Matrilysins	Collagens I and IV, elastin, fibronectin, entactin, tenascin, aggrecan, vitronectin, decorin, versican, osteopontin, E-cadherin, Fas ligand, pro-TNF-α
MMP8	Neutrophil collagenase	Collagenases	Collagens I, II and III, aggrecan
MMP9	Gelatinase-B	Gelatinases	Collagens IV, V, XI and XIV, gelatin, elastin, fibronectin, vitronectin, laminin, aggrecan, versican, decorin
MMP10	Stromelysin-2	Stromelysins	Collagens III, IV and V, gelatin, elastin, fibronectin, aggrecan
MMP11	Stromelysin-3	Stromelysins	Collagin IV, gelatin, fibronectin, laminin, insulin-like growth factor-binding protein (IGFBP)
MMP12	Macrophage elastase	Metalloelastases	Collagens I, IV and V, gelatin, elastin, fibronectin, vitronectin, laminin, entactin, osteonectin, aggrecan
MMP13	Collagenase-3	Collagenases	Collagens I, II, III, IV, VI, IX, X and XIV, gelatin, fibronectin
MMP14	MT1-MMP	MT-MMPs	Collagens I, II and III, gelatin, fibronectin, tenascin, vitronectin, laminin, entactin, aggrecan, perlecan
MMP15	MT2-MMP	MT-MMPs	Fibronectin, tenascin, entactin, laminin, aggrecan, perlecan
MMP16	MT3-MMP	MT-MMPs	Collagen III, gelatin, fibronectin, vitronectin, laminin
MMP17	MT4-MMP	MT-MMPs	Gelatin, fibronectin, fibrillin
MMP18	Collagenase-4 (Xenopus)		
MMP19	RASI-1	Other MMPs	Collagen IV, gelatin, tenascin, fibronectin, aggrecan, entactin, laminin
MMP20	Enamelysin	Other MMPs	Amelogenin, aggrecan
MMP21	XMMP (Xenopus)		ND
MMP22	CMMP (chicken)		ND
MMP23	CA-MMP	Other MMPs	ND
MMP24	MT5-MMP	MT-MMPs	ND
MMP25	MT6-MMP	MT-MMPs	Collagen IV, gelatin, fibronectin
MMP26	Endometase, matrilysin-2	Matrilysins	Collagen IV, gelatin, fibronectin
MMP27			ND
MMP28	Epilysin	Other MMPs	ND

ND, not determined.

amounts in resting tissue, which are increased in normal tissue remodelling, and pathological changes including tumour infiltration and tissue repair. Secreted forms can be distinguished from transmembrane forms. Both forms have been implicated in proteolytic regulation of cell communication. TIMP-3 seems to be an inhibitor of the function of so-called ADAMs (adamalysin-like proteinases with metalloproteinase and desintegrin-like domains). Moreover, matrix-associated ADAMs exist that have a thrombospondin-like domain (ADAM-TS). In addition to TIMPs, ADAMs appear to be crucial regulators of MMP activity during skin homoeostasis and disease. For example, TACE, ADAM-10 and ADAM-9 have been shown to be functionally expressed in keratinocytes. Activation of these ADAMs resulted in increased shedding of transmembrane collagen XVII from keratinocytes, indicating that it represents a substrate for ADAMs, thereby regulating extracellular matrix function in the skin during inflammation or blistering diseases [5].

MMP activity seems to be enhanced in patients with inflammatory skin diseases such as psoriasis [6], and MMP-9 activity can be enhanced in human keratinocytes by UV irradiation [7]. Moreover, matrix metalloproteinase gelatinase B (MMP-9) coordinates and effects epithelial regeneration during healing, as demonstrated in a mouse model [8]. MMP-1 also directly influences its own up-regulation by elastin peptides in cultured fibroblasts [9], and fibroblast themselves are capable of generating MMP-2 and MMP-9 [10]. Increased levels of MMP-1, MMP-2 and MMP-13 were observed in lesional skin of inflammatory skin diseases such as stasis dermatitis. In contrast, TIMP-1 and TIMP-2 levels were diminished, indicating that MMPs are directly involved in the regulation of skin remodelling and inflammatory responses during stasis dermatitis [11].

There is little difference in the enzymes present in tissues in acute and chronic wounds, the major enzymes being MMP-2 and MMP-9 (gelatinases and pro-collagenase) and MMP-1 (collagenase) [12,13]. Keratinocyte formation of collagenase occurs rapidly (within 4–6 h) during wound healing, reaching a maximum in uncomplicated wounds on days 3–5, and then declining by about day 9 when repair is complete. Collagenase digests native collagen to short peptide chains, which become susceptible

to degradation by other non-specific proteases. At the wound edges, collagenase prepares the extracellular matrix bed for keratinocytes, and may contribute to keratinocyte migration [14–17]. There is also a decrease in the amount of TIMPs, the inhibitors of MMPs, in chronic wounds [15,18]. In addition, cytokines and tissue degradation products also contribute to impairment of healing. Fluid from acute wounds stimulates fibroblast proliferation, proteinase expression, matrix element formation and contains the cytokines PDGF and βFGF [19,20].

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Lysosomal mediators

Many mediators of inflammation, particularly tissue-destructive enzymes, are derived from cellular lysosomes. Released into the cytoplasm, they result in autolysis. Extracellularly, they degrade tissue elements (e.g. collagen and elastin) and dead cells [1,2]. The enzymes also activate further mediators of inflammation in plasma or tissue fluids (e.g. the generation of kinins from kallikrein induced by the trypsin-like activity of the lysosomal proteases). Such proteases can also cleave complement C3 to activate the alternative pathway of complement.

Lysosomes are found in nearly all living cells, and comprise a semipermeable membrane surrounding a small vacuole, which contains acidic hydrolases and other enzymes and substances. There is some variation in the lysosomal substances to be found in each type of cell [1,2]. In the developing neutrophil, lysosomes are derived from the Golgi complex; in macrophages and some other cells including keratinocytes, it is believed that they are derived from the rough endoplasmic reticulum and are transferred to special areas of the smooth endoplasmic reticulum situated within the Golgi complex.

Epidermal cells have lysosomes that contain acid phosphatases, aryl sulphatase, several proteases including the acidic protease cathepsin D, and other enzymes [3–5]. One of the difficulties in examining these enzymes is the presence of inhibitors, which inactivate enzymes of the epidermal cells, and of the dermis and plasma.

The lysosomes participate in the phagocytic functions of epidermal cells, particularly active during regeneration after wounds. They are also involved in pigmentation, as melanosomes are transferred to keratinocytes by a process analogous to phagocytosis. Epidermal cell lysosomes are involved in keratinization, responses to UV light and neoplasia [3,6]. Lysosomes also appear to be involved in sebaceous secretion, as they enlarge and rupture in the process of cell disintegration.

During inflammation, as induced by a cantharidin blister, the increase in extracellular acid phosphatase and protease is attributed to release from epidermal lysosomes, because it occurs before leukocyte infiltration and is more concentrated locally than in serum. The leukocytes, particularly neutrophils, entering the lesion may be attracted by chemotactic substances generated by the activity of acid or neutral proteases, which cleave complement, kallikrein or Hageman factor. A neutral proteinase extracted from rabbit skin induced wealing within 15 min and acute neutrophil infiltration within 18 h when injected into the skin of rabbits, indicating the possible participation of epidermal cell lysosome enzymes in inflammation [7].

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Respiratory burst and oxygen-dependent cytotoxicity

At high concentrations, free radicals and radical derived, non-radical reactive species are hazardous for living organisms and damage all major cellular constituents. However, at moderate concentrations, NO, superoxide anion and related reactive oxygen species (ROS) play an important part as regulatory mediators in signalling processes. Many of the ROS-mediated responses actually protect cells against oxidative stress and re-establish 'redox homoeostasis'. Higher organisms, however, have also evolved the use of NO and ROS as signalling molecules for other physiological functions. These include regulation of vascular tone, monitoring of oxygen tension in the control of ventilation and erythropoietin production, and signal transduction from membrane receptors in various physiological processes. Activation is caused by membrane stimulation, phagocytosis, immune complexes or aggregated immunoglobulins, both IgG and IgA, and IFN-γ. The generated oxygen radicals may exist only for seconds; they are potent toxic agents, although their contribution may not always be significant [1–4].

NO and ROS are typically generated by tightly regulated enzymes such as NO synthase (NOS) and NADPH oxidase, or from less well-regulated sources such as the mitochondrial electron-transport chain. The massive production of antimicrobial and tumoricidal ROS in an inflammatory environment is called the 'oxidative burst' and has an important role as a first line of defence against environmental pathogens. The physiological relevance of NADPH oxidase as a defensive agent is suggested by the observation that mice lacking the NADPH oxidase components gp91phox or p47 exhibit reduced resistance to infection [5–7].

Various forms ('species') of activated oxygen and intermediates exist: superoxide anion O^-, a precursor of toxic products, H_2O_2, MPO particularly formed in phagocytes, and hydroxyl ($HO^\bullet$) and singlet oxygen ($^\bullet O_2$) radicals, which give rise to chemiluminescence. Oxygen (O_2) alone is not toxic. H_2O_2 in small amounts is a normal cell signal molecule. Both may be converted to reactive factors. H_2O_2, particularly in the presence of iron, is converted to the very reactive hydroxyl radical $HO^\bullet$. The $HO^\bullet$ mediates a chain reaction with lipid and cyclic peroxides as the end-products, and causes cell death and membrane lysis. Furthermore, the superoxide anion of the human monocyte oxidizes low-density lipoprotein and converts it into a cytotoxin, which damages fibroblast cell lines [8].

In mitochondria, ROS are generated as undesirable side products of the oxidative energy metabolism. An excessive and/or sustained increase in ROS production has been implicated in the pathogenesis of autoimmune diseases, cancer, diabetes mellitus, atherosclerosis, neurodegenerative diseases, rheumatoid arthritis, ischaemia/reperfusion injury, obstructive sleep apnoea and many other diseases. In addition, free radicals have been implicated in the mechanism of skin ageing. There is growing evidence that ageing involves, in addition, progressive changes in free radical-mediated regulatory processes that result in altered gene expression. Finally, a crucial role of oxygen-dependent cytotoxicity in cutaneous carcinogenesis, with a decreased control of DNA synthesis and cell division, has been described [9,10].

There is a growing evidence that oxidative stress has a pivotal role in various diseases such as inflammation, tumour growth, metabolic diseases, atherosclerosis and thrombosis, and infection such as HIV. 'Mitochondrial oxidative stress' seems to be crucial in metabolic diseases and cancer, resulting in a pro-oxidative shift in the systemic thiol–disulphide redox state and elevated ROS production. In contrast, during 'inflammatory oxidative conditions', an excessive stimulation of NADPH oxidase activity by cytokines or other agents can be observed. Here, increased ROS levels or changes in intracellular glutathione levels are often associated with pathological changes indicative of a dysregulation of signal cascaded and/or gene expression, exemplified by altered expression of cell adhesion molecules [11,12].

During inflammation, NO and ROS are capable of killing microorganisms, thereby contributing to host defence. The generation of their activities is associated with the respiratory burst when cells are exposed to foreign substances. In the skin, UV radiation may—alone or following exposure to phototoxic or photoallergic chemicals—induce the activation of NO and ROS species, leading to the production of various inflammatory mediators, including cytokines and kinins. During psoralen therapy in psoriasis, the skin is exposed to UV radiation, which leads to the production of radicals. Similar effects are observed in patients with porphyria who have been exposed to UV light. In general, the poly (ADP-ribose) polymerase (PARP) pathway appears to have an important role in the regulation of inflammatory processes in the skin [13]. Some of the inflammatory activity of monocyte–macrophages, neutrophils and eosinophils is caused by free radicals. There is growing evidence that the biochemical basis for the mechanism of action of dithranol at the molecular level is related to the redox activity leading to the production of active oxygen species, which include singlet oxygen, and superoxide anion and hydroxyl

radical [14]. ROS molecules have also been implicated in regulating leukocyte–endothelial interactions. For example, adhesion of neutrophils to endothelial cells involves the stimulation of ICAM-1, and L-selectin via ROS activation [15,16].

There also exist important physiological aspects of redox regulation. The production of superoxide and NO, respectively, by these enzymes is strictly regulated by cytokines and other inflammatory mediators. Subsequently, the resulting oxidative species act as secondary messengers to control a variety of physiological responses such as vascular relaxation or hormone production [17].

Enhancement of signal transduction pathways by stimulation of ROS leads to up-regulation of expression or receptors involved in inflammation, such as the angiotensin II receptor and the EGF receptor. Furthermore, H_2O_2 has a relatively long half-life and may directly cross the cell membrane to modulate cell function. For example, ROS from activated macrophages and neutrophils may contribute decisively to the activation of antigen-specific immune responses to pathogens. Signalling pathways involving JNK, p38 MAPK, and the transcription factors AP-1 and NF-kB are particularly responsive to redox regulation. Thus, various intracellular signalling cascades are modulated by ROS molecules [18–20].

The production of ROS by non-phagocytic NADPH oxidase isoforms also plays a part in the regulation of the intracellular signalling cascade within non-phagocytic cells, including fibroblasts. Moreover, activated macrophages and neutrophils can produce large amounts of superoxide and its derivatives via the phagocytic isoform of NADPH oxidase. Stimulated neutrophils and macrophages also generate singlet oxygen by reactions that involve either MPO or NADPH oxidase, respectively. Importantly, physiologically relevant ROS concentrations can also modulate redox-sensitive signal cascades and enhance immunological functions of lymphocytes [21,22].

With regard to achieving a balanced inflammatory response, the activity of free radicals has to be rapidly terminated. Therefore, various endogenous and exogenous molecules rapidly inactivate the function of extracellular oxygen species, such as superoxide dismutase, catalase and glutathione peroxidase, free α-tocopherols and antioxidants.

In summary, ROS generated by many cells in the immune system and the skin can modulate inflammation and infection. Clinical interventions with ROS-modulating agents may help to attenuate oxidative stress that is directly attributable to inflammation.

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Nitric oxide

Over the last few years, NO has been established as a versatile factor in the immune system. NO is involved in the pathophysiology and control of inflammation, infectious diseases, autoimmune processes, tumorigenesis and chronic degenerative diseases, and may be of considerable

Table 9.9 Pathophysiological role of nitric oxide in human skin.

Disease	Functions
Contact dermatitis (CD)	Modified expression in allergic and irritant contact dermatitis NOS expression in irritant CD: focal staining in epidermis and dermis
Atopic dermatitis	Clinical application of NOS inhibitor for atopic dermatitis Enhanced staining in the spongiotic area of the epidermis and of the perivascular region (inflammatory cells?)
Acute urticaria	NOS expression co-localized with inflammatory cytokines and CD23
Psoriasis	iNOS mRNA and IL-8 mRNA co-localize in keratinocytes of psoriatic skin Overexpression of iNOS in keratinocytes of psoriatic lesions NO may account for reduced incidence of infections in psoriasis
Lupus erythematosus (LE)	iNOS expression in cuneous and systemic LE. Aberrant timing of UVA-induced iNOS expression in LE patients Enhanced NO production, endothelial and keratinocyte iNOS production in LE patients
Systemic sclerosis (SSc)	Increased iNOS and eNOS expression by endothelial cells in SSc Enhanced iNOS synthesis in SSc patients Increased NO production and iNOS synthesis in mononuclear cells, endothelial cells and fibroblasts in lesional skin of SSc
Stevens–Johnson syndrome (SJS)/ toxic epidermal necrolysis (TEN)	Expression of iNOS in inflammatory cells of SJS and TEN
Sunburn erythema	Topical application of NO inhibitors protect from UVB-induced erythema UVB acts as a potent stimulator of eNOS and xanthine oxidase in human keratinocytes
Leg ulcers	Increased NOS expression in chronic leg ulcers Increased NOS activity in diabetic foot ulcers (macrophages)
Burn injury	Enhanced NO production in burning skin lesions Expression of iNOS in burn wounds (keratinocytes, capillary endothelium)
Tinea pedis	Successful treatment with a NO-liberating cream (acidified nitrate)
Molluscum contagiosum	Successful treatment with a NO-liberating cream (acidified nitrate)

eNOS, endothelial nitric oxide synthase; iNOS, inducible nitric oxide synthase; NO, nitric oxide; NOS, nitric oxide synthase.

importance in a variety of skin diseases (Table 9.9). Originally, NO was perceived as a product of macrophages activated by cytokines and generated from the amino acid L-arginine by the enzymatic activity of inducible NO synthase (iNOS or NOS2). It is now known that NO functions are considerably more complex. NO has a wide distribution in immune cells such as dendritic cells, eosinophils and neutrophils, Kupffer cells, macrophages, mast cells, microglial and NK cells, as well as in other cells that may be involved in immune reactions, such as chondrocytes, endothelial cells, epithelial cells, hepatocytes, mesangial cells, Schwann cells and vascular smooth muscle cells [1,2]. Furthermore, additionally to iNOS, different isoforms of NO synthase have been identified—endothelial NOS (eNOS or NOS3), neuronal NOS (nNOS or NOS1), both also known as constitutive NOS (cNOS)—that all operate within the immune system and catalyse the same reaction, conversion of L-arginine to NO [2]. Importantly, the activity of NO is not restricted to the site of production. As a gas it is highly diffusable and the ability of NO to form complexes allow this molecule to bridge long distances. Circulating nitrite (NO_2^-), a stable product of the NOS reaction, can be reduced to $^{\bullet}NO$, which is the substrate for the peroxidase pathways of eosinophils and neutrophils, leading to the formation of novel NO-derived oxidants at distant sites [3,4]. Therefore, NOS-negative immune cells can both produce NO and become targets of NO action.

The expression of iNOS is regulated by cytokines, while nNOS and eNOS, constitutively expressed in the cell, are activated by elevation of intracellular Ca^{2+} concentration and binding of calmodulin. In low concentrations, NO itself activates NF-κB and up-regulates iNOS, whereas high concentrations exert the opposite effect and may help to suppress NO overproduction. All three NOS isoforms are only active as homodimers. Another factor that determines NOS activity is the availability of its substrate, arginine. Generation of NO (e.g. by macrophages) depends on extracellular L-arginine even when an adequate level of intracellular arginine is present [2,5].

NO possesses many signalling functions. In the immune system, use of NOS inhibitors, NO donors and NOS knockout mice have provided evidence that NO triggers a broad spectrum of processes. NO inhibits the adhesion of platelets and leukocytes to endothelium [6], but the underlying mechanisms are not understood. It has been shown that NO variably down-regulates the expression of endothelial cell adhesion molecules such as E-selectin,

P-selectin, ICAM-1 and VCAM-1 [7,8]. NO can inhibit the expression of integrins such as LFA-1 on neutrophils [6,9,10] and, interestingly, influence the chemotactic response of leukocytes by modulating the production and activity of chemokines [2,11–13]. Additionally, NO signalling is involved in differentiation, proliferation and apoptosis of immune cells. In the thymus, deletion of T-cell receptor-activated double-positive thymocytes is, amongst other things, dependent on thymic stromal cell released NO [14–18].

Analysis of experimental autoimmune arthritis (EAA), encephalomyelitis (EAE), uveitis (EAU) and nephritis (EAN) in rodents has provided evidence that iNOS functions as a negative feedback regulator of autoimmune Th1 cell responses and thereby protects the host against immunopathological sequelae [1,19]. However, it has to be pointed out that results obtained with iNOS knockout mice, and mice treated with NOS inhibitors, do not support this view [19–21]. A possible explanation derives from work by McCartney-Francis *et al.* [21] on the streptococcal cell wall-induced arthritis model in rats, in which eNOS and nNOS appear to mediate the acute and chronic erosive joint disease, whereas iNOS helped to limit inflammation. Furthermore, a protective anti-inflammatory function of iNOS has been demonstrated in a T-cell-dependent and B-cell-mediated myasthenia gravis-like autoimmune disease [22], in local carrageenan-induced pleurisy [23] and in TNF-induced shock in mice [24].

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Histamine

Histamine (2-[4-imidazolyl]ethylamine) was the first mediator of anaphylaxis to be identified, in 1932. Its pharmacological description as an endogenous substance was even earlier, in 1910 [1]. Histamine is synthesized from histidine by the specific enzyme L-histidine decarboxylase (HDC). It can be generated by some neurones, mast cells, basophils and platelets, where it is intracellularly stored in vesicles, and rapidly released upon stimulation. However, it has been shown that HDC is inducible in a variety of tissues by a mechanism coupled with the cytokine network, leading to non-classical histamine generation. Histamine, like tryptase, is one of the mediators rapidly released from mast cells during inflammation and hypersensitivity. However, recent knowledge clearly indicates that histamine is not the only inflammatory mediator released by mast cells.

Histamine exerts a powerful effect on blood vessels, causing smooth muscle contraction, vasodilatation and plasma extravasation from capillaries. Classically, histamine is released upon an antigen–antibody reaction with IgE bridging on the cell surface of mast cells. Further studies have shown that histamine release can be also triggered in an IgE-independent manner (e.g. by direct interaction of molecules with cell membrane-associated G proteins or transmembrane lipid mediators). Release of

high concentrations of histamine, as during immediate-type hypersensitivity, leads to systemic shock symptoms such as vasodilatation, oedema, smooth muscle contraction, decreased blood pressure and subsequent cardiopulmonary dysfunction. Histamine characteristically mediates itch responses, especially at the beginning of an inflammatory response by activating histamine receptors on cutaneous sensory nerves. Interestingly, histamine does not appear to be the crucial mediator of itch in atopic dermatitis patients. Thus, different mediators seem to be responsible for mediating pruritus in different inflammatory skin diseases. For example, cytokines or proteinases released during the inflammatory response may activate nerve fibres [2].

Additionally, histamine can exert direct effects on immune cells, endothelial cells and primary efferent nerve fibres via activation of histamine receptors. Four histamine receptors (HRs) have been cloned and characterized so far, which belong to the G protein-coupled receptor family with seven transmembrane domains (H_1–H_4).

Except for H_3R, which is exclusively expressed in the brain, histamine receptors are widely distributed in humans. Thus, H_4R is located in the thymus, small intestine, liver spleen, colon, bone marrow, and on peripheral blood leukocytes [3]. H_1R is found to be expressed by tissues including mammalian brain, retina, airway, skin [4], genitourinary tract, vascular smooth muscle, adrenal medulla, liver, endothelial cells, astrocytoma cells, cerebral microvessels and lymphocytes [5]. H_2R shows a similar expression pattern to H_1R, being detected in mammalian brain, pulmonary system, cardiovascular system, intestine, skin [4], endocrine and exocrine glands [6] and the immune system, in T cells [7,8], macrophage–monocytes and lymphocytes [9].

In the skin, histamine receptor-1 is localized on fibroblasts [10] and endothelial cells [11], and both H_1R and H_2R are expressed on keratinocytes [12,13]. After histamine activation, H_1R mediates several vascular responses, such as increased vascular permeability, vasodilatation and constriction of smooth muscle cells. H_2R exerts various effects on immune cells, such as mediator release from basophils, neutrophils and lymphocytes. Interestingly, H_2R augments T-suppressor cell activity, whereas H_1R activates regulatory T cells with contradictory effects. H_3R function is implicated in neuroregulation in the central nervous system.

Histamine action can be terminated by receptor down-regulation, enzymes and suppressor factors. One of the latter is histamine suppressor factor (HSF), synthesized by activated lymphocytes. Histamine also stimulates the formation by monocytes of two substances inhibiting lymphocyte migration [14]. Apart from these direct activities, histamine also enhances expression of cell receptors, and either inhibits the outgrowth of epidermis from skin slices *in vitro* or stimulates it, depending upon concentration [15]. Thus, histamine may contribute to both pro-inflammatory and to regenerative changes in the tissue, depending on the concentration of histamine, of degrading enzymes and of the receptor repertoire of the cells involved.

Histamine formation and release is regulated by several factors other than IgE, such as cytokines, prostaglandins, leukotrienes and neuropeptides. In contrast, histamine activity regulates formation of cytokines. For example, IL-1, IL-3, IL-5 and IL-8 are capable of increasing histamine synthesis and release. Histamine, through the H_2 receptor, reduces formation of IL-1 and TNF-α from endotoxin-stimulated cells in human monocytes [16]. Histamine inhibits formation of IL-2, the critical interleukin promoting formation of T-cell clones, and possibly indirectly through IL-2 inhibition it also reduces IFN-γ activity [16]. Histamine also stimulates IL-6 synthesis [16]. Thus, histamine contributes to cytokine participation in inflammation and allergy. Some cytokines are potent histamine-releasing agents, particularly the chemokine MCP-1, and to a lesser extent RANTES, MIP-1α and MIP-1β [17].

It been shown recently that histamine regulates T-cell and antibody responses by differential expression of H_1 and H_2 receptors [8]; histamine enhances Th1-type responses by triggering the histamine receptor type 1, whereas both Th1- and Th2-type responses are negatively regulated by H_2R via the activation of different intracellular signalling pathways. In mice, deletion of H_1R results in suppression of IFN-γ and dominant secretion of Th2 cytokines (IL-4 and IL-13). Mutant mice lacking H_2R showed up-regulation of both Th1 and Th2 cytokines. Mice lacking H_1R displayed increased specific antibody responses, with increased IgE and IgG1, IgG2b and IgG3, compared with mice lacking H_2R. These findings indicate an important regulatory mechanism in the control of inflammatory and immune functions through release of histamine [8].

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Platelet-activating factor

PAF (1-*O*-alkyl-2-acetyl-sn-glycero-3-phosphocholine) is a phospholipid with diverse biological functions, particularly during inflammation. It is rapidly synthesized on stimulation, probably by activation of phospholipase A_2 hydrolysing fatty acid acyl groups as in arachidonic acid, followed by reacetylation. PAF binds to and activates a specific PAF receptor that is expressed by many inflammatory cells. Inactivation of PAF is regulated primarily by the rate of degradation, which is catalysed by PAF-acetylhydrolase. Beside its role as an inflammatory mediator, PAF is also capable of functioning as a hormone and transmitter in the nervous system. PAF is formed concomitantly with other arachidonic acid derivatives, the prostaglandins and leukotrienes.

In humans, PAF is synthesized by monocyte–macrophages, neutrophils, eosinophils, endothelial cells, mast cells, basophils and platelets, in response to immunological, infective or acute inflammatory mediators.

PAF stimulates platelet aggregation, and synthesis and release of mediators [1], such as serotonin, thromboxane and PAF, within minutes of activation. In neutrophils, PAF induces chemokinesis (activated mobility), chemotaxis (attraction), secretion of lysosomal products, synthesis of 12-HETE and LTB_4 and initiation of the respiratory burst [2,3]. In addition, PAF activates monocytes, in which PAF signals NF-κB translocation to the nucleus and alterations in gene expression and other functional responses [4]. Eosinophils are particularly responsive to PAF, especially *in vivo*, as are endothelial cells, in which PAF mediates contraction with resultant transient increased vascular permeability in post-capillary venules, followed by a late phase of erythema. In humans, intradermal injection has been shown to induce local eosinophilia [5] and a significant neutrophilia with a late-phase erythema [6].

PAF signals the priming and activation of leukocytes at the cell surface of activated human microvascular endothelial cells after activation. Moreover, PAF and the cell adhesion molecule P-selectin are coordinately displayed on the plasma membranes of stimulated human endothelial cells. P-selectin tethers the leukocyte to the endothelial cell, which allows PAF to bind to its receptors on the endothelial cell and on the polymorphonuclear leukocyte. This constitutes a form of juxtacrine signalling that may be a general way to spatially restrict the actions of a potent pleiotropic mediator such as PAF [7].

The PAF-receptor belongs to a subfamily of G protein-coupled receptors with seven transmembrane domains. It is expressed by many immune cells as well as epithelial cells. PAF-induced signalling is mediated via NF-κB and protein kinase C.

PAF-transgenic animals show increased mortality when challenged with endotoxin, develop melanocytic tumours of the skin, and have increased bronchial hyperreactivity. In the skin, PAF is involved in growth of melanocytic tumours and is known to mediate skin inflammation [8].

Dysregulated signalling by PAF may result in disease states. For example, developmental deficiency of PAF acetylhydrolase may lead to unregulated pro-inflammatory signalling by PAF in infants with neonatal necrotizing enterocolitis [9]. Dysregulated signalling by PAF also contributes to the severity of asthma in patients genetically deficient in PAF acetylhydrolase.

Recently, strategies with exogenous recombinant PAF acetylhydrolase or PAF receptor antagonists demonstrated that PAF is a juxtacrine signalling molecule at the surfaces of activated human platelets, which—like endothelial cells—are critical in cell–cell interactions in inflammatory and thrombotic responses [10].

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Prostaglandins and leukotrienes

Prostaglandins and thromboxanes

Prostaglandins (PG) and thromboxanes (TX) comprise a diverse family of autacoids, whose synthesis is initiated by cyclo-oxygenase-mediated metabolism of the unsaturated 20-carbon fatty acid arachidonic acid to the endoperoxide intermediates, PGG_2 and PGH_2 [1]. Prostaglandins were first discovered in the 1930s by Von Euler, who investigated the blood pressure lowering potential of compounds from semen. Prostaglandins are products of cyclo-oxygenase activity on arachidonic acid, and to a much lesser extent other unsaturated fatty acids, and through intermediate products release PGE_2 and PGD_2 by different isomerases, and $PGF_{2\alpha}$ by a reductase. They are synthesized by many cell types. This leads to generation of five bioactive prostanoids: TXA_2, PGD_2, PGE_2, PGF_2 and PGI_2. These mediators are involved in processes such as inflammation, tumour growth and cardiovascular homoeostasis. Thus, cyclo-oxygenase-inhibiting agents are of potential use in a wide range of diseases. Each of the prostanoids is generated via activation of specific synthetases. Because prostanoids are either chemically or metabollically unstable, it is believed that they exert their effects very locally [2].

After release, they exert their effects by binding and activating a subfamily of eight heptical G protein-coupled receptors, defined as EP (four subtypes for PGE_2) and FP, DP, IP or TP for PGF_2, PGD_2, $PGI_{2\alpha}$ and TXA_2, respectively [3]. All these are extremely potent mediators of inflammation, active at very low concentrations. Although each receptor subtype shows the highest affinity to the prospective ligand, cross-reactivity between the family members can be observed [4]. Moreover, splice variants of certain PG receptors can be observed, leading to altered receptor function and probably disease. PG receptors signal via stimulation of IP-3, diacylglycerol, and inhibition of adenylyl cyclase or Gi.

Prostanoids and their receptors are widely distributed and have a biological role in many cell types. Prostanoids may exert synergistic but also contradictory effects on specific cell types, such as epithelial cells or smooth muscle cells. In the airways, for example, PGE_2 has a relaxing effect, whereas $PGI_{2\alpha}$ is a potent vasoconstrictor. PGE_2 shows strong immunosuppressive effects on T cells and facilitates IgE switching in B cells by synergistically acting with LPS or IL-4. $PGI_{2\alpha}$ contracts smooth muscle, and induces broncho- and vasoconstriction. It also inhibits PGE_2-mediated cutaneous permeability.

Thus, $PGI_{2\alpha}$ counteracts PGE_2 activity. In normal tissues, concentrations of both mediators seem to be balanced. Under pathophysiological conditions, however, the vasodilatator PGE_2 is increased, resulting in pro-inflammatory effects. In contrast, this balance is restored during tissue regeneration.

In the skin, PGE_2 induces vasodilatation and potentiates the pro-inflammatory effects of histamine, serotonin and bradykinin, inducing oedema, plasma extravasation, pruritus and pain [5]. Moreover, PGE_2 has important immunoregulatory functions by decreasing proliferation of Th1 cells or by stimulating the synthesis of IFN-γ [6]. This has clinical implications; for example, in patients with atopic dermatitis, who show increased synthesis of PGE_2 in peripheral blood monocytes, decreased Th1 lymphocyte proliferation and reduced synthesis of IFN-γ. PGE_2 also contributes to the synthesis of IL-4, thereby regulating IgE synthesis and affecting the Th1–Th2 balance [7,8].

In vivo, prostaglandins contribute to cutaneous inflammation, such as contact dermatitis or UV-induced inflammation, and potentiate the itch induced by histamine.

Prostacyclin (PGI_2), the common designation of epoprostenol, is the main metabolic product of arachidonic acid in vascular tissue, particularly in the endothelium [9]. It is an unstable substance with a half-life in blood of 2–3 min. PGI_2 is the most potent endogenous inhibitor of platelet aggregation, and also disperses aggregated platelets, inhibits thrombus formation, increases cutaneous bleeding time and is a strong vasodilator.

12-HETE and 15-HETE are products of arachidonic acid, converted by the 12- and 15-lipoxygenase enzymes via intermediate peroxy forms. Both are formed by fibroblasts and keratinocytes. 12-HETE is pro-inflammatory, attracting neutrophils, eosinophils and monocytes *in vitro*, and aggregates leukocytes [10]. It stimulates epidermal DNA synthesis. When applied to skin, 12-HETE induces erythema followed by neutrophil and monocyte infiltration, but not eosinophil infiltration [11]. Physiological amounts occur in psoriatic skin and after UV irradiation. As it is much less potent than LTB_4 and other chemoattractants, the significance of 12-HETE in lesions is unknown. 15-HETE is the main arachidonic acid metabolite in homogenized dermis, and is almost certainly derived from fibroblasts; it inhibits mitogen-induced DNA synthesis by T lymphocytes and 12-HETE formation by platelets and keratinocytes. It is therefore anti-inflammatory, regulating the pro-inflammatory changes mediated by 12-HETE. Keratinocytes also form 15-HETE, but the significance of this to control 12-HETE production appears unknown [12–14]. Pharmacological and genetic approaches have further defined the role of prostaglandin receptors in inflammation and immune response. EP2-deficient

mice show a loss of PGE_2-induced bronchodilatation, and EP3-deficient mice demonstrate impaired febrile responses to pyrogens and mucosal integrity. A decreased inflammatory response can be observed in EP4- and IP-deficient mice, indicating a direct role of this receptor during inflammation [15,16]. PGI_2, via IP activation, seems to be critically involved in acute oedematous responses [17]. PG receptors such as IP, EP1, EP3 and EP4 are expressed by sensory neurones and contribute to pain during inflammation.

Allergic responses are associated with an increase in prostanoid secretion. PGD_2 is a major PG released by mast cells during allergen challenge, and is abundantly produced in atopic diseases such as atopic dermatitis and asthma.

In addition to PG transmembrane receptors, the nuclear peroxisome proliferator-activated receptor-γ (PPARγ) has been identified as a prostanoid receptor. Interestingly, PPARγ can inactivate NF-κB, thereby modulating inflammatory responses [18].

Prostanoid synthesis critically depends on the action of cyclo-oxygenase. Two isoforms exist: COX-1 and COX-2. Whereas COX-1 is localized in the endoplasmatic reticulum and close to the plasma membrane, COX-2 can be found in the perinuclear region. COX-1 is constitutively expressed by most cells but can be slightly increased by growth factors, cytokines or tumour-promoting agents [19]. Although COX-1 was not thought to be involved in inflammation, COX-1-deficient mice display reduced experimentally induced inflammation such as ear oedema and allergic airway disease. COX-2 expression is inducible by various factors such as cytokines, growth factors and endotoxins. Surprisingly, COX-2-deficient mice do not exhibit marked differences in inflammatory responses as compared to wild-type mice. Thus, COX-1 may contribute more to inflammation than previously thought. Overexpression of the COX-2 gene in epithelial cells resulted in increased adhesion to the extracellular matrix, diminished E-cadherin expression, enhanced Bcl-2 levels and enhanced resistance to butyrate-induced apoptosis. Moreover, COX-1 appears to be essential for endothelial tube formation, whereas COX-2 is essential for the production of angiogenic factors. Thus, cyclo-oxygenases exert several effects on endothelial cells during inflammation and tumour growth [20].

Recently, a number of PG receptor compounds and COX-2 inhibitors have been developed. Most of these compounds are not selective but activate or inactivate several receptor subtypes [21,22]. The classic COX-inhibitor, aspirin, blocks both, but preferentially COX-1 over COX-2. In contrast, COX-2 inhibitors such as rofecoxib and celecoxib are effective anti-inflammatory agents, while showing considerably less gastrotoxicity than COX-1 inhibitors and other non-steroidal anti-inflammatory drugs.

Leukotrienes

Cleavage of arachidonic acid by 5-lipoxygenase (5-LO) releases a product that on further degradation results in several chemically related leukotrienes. The leukotrienes [21–24] are divisible chemically and biologically into two substances: LTB_4 and LTC_4. These may be further transformed into metabolites LTD_4 and LTE_4. They are formed by many cell types [21,22]. LTB_4 aggregates, attracts and stimulates chemokinesis of polymorphonuclear leukocytes, and induces exudation of plasma, but is relatively weak at contracting smooth muscle. Leukotrienes induce prolonged contraction of smooth muscle, and hence constriction of small airways. They stimulate mucus secretion and induce post-capillary oedema. LTB_4 has been isolated from the skin of patients with psoriasis and atopic dermatitis.

The 5-LO pathway leading to leukotriene formation plays a pivotal part in the pro-inflammatory cascade during inflammation [22]. For example, LTB_4 promotes neutrophil chemotaxis and adhesion to vascular endothelium through specific integrins. The cysteinyl leukotrienes cause plasma leakage from post-capillary venules and enhance mucus secretion. LTD_4 and another 5-LO-derived eicosanoid, 5-oxo-ETE, are eosinophil chemoattractants. The use of murine models in which specific genes such as '5-lipoxygenase' of the leukotriene pathway have been deleted by homologous recombination firmly support their crucial role in allergic inflammation.

5-LO has been identified as an inducer of ROS production in lymphocytes. However, our knowledge on the physiological relevance of this in redox signalling is still incomplete. The oxidized metabolites generated by 5-LO have been found to change the intracellular redox balance and to induce signal transduction pathways and gene expression. LTB_4 controls cytotoxic effector T-cell recruitment to inflamed tissues [23]. Moreover, Th2 cytokines coordinately regulate IgE-dependent cysteinyl leukotriene production by human mast cells; IL-4 induces leukotriene C4 synthase expression, and thereby regulates T-cell–mast cell interactions [24–26].

Leukotrienes exert theit effects by binding and activating specific heptical G protein-coupled receptors (GPCRs). Four receptor subtypes have been cloned and characterized. The high-affinity B-LT1 receptor on leukocytes binds LTB_4 in the subnanomolar range, and stimulates neutrophil secretion. Two subtypes of cysteinyl leukotriene receptors, CysLT1 and CysLT2, mediate the actions of LTC_4 and LTD_4. CysLT1 is found on airway smooth muscle cells and vascular endothelial cells, and promotes bronchoconstriction and up-regulation of endothelial cell adhesion molecules. However, our knowledge of the role of leukotrienes receptors under physiological and pathophysiological conditions in these tissues is far from complete.

The lipoxins are chemically and functionally different from the leukotrienes. Although LXA_4 and LXB_4 are similar in structure, these mediators display biological activities that are quite distinct. LXA_4 interactions with neutrophils involve binding sites that are not recognized by LXB_4 [27,28]. LXB_4 is a potent agonist for stimulating proliferation and differentiation of granulocyte–monocyte colonies from human mononuclear cells [29], and increases the S-phase in the cell cycle and enhances nuclear protein kinase C activity [30]; such effects have not been reported for LXA_4. However, both LXA_4 and LXB_4 selectively stimulate human peripheral blood monocytes [31] and enhance growth of myeloid progenitor cells [32].

There is increasing interest in a potential therapeutic effect of leukotriene modifiers or antileukotrienes such as 5-LO inhibitors (zileuton [Zyflo]) and CysLT1 receptor antagonists (zafirlukast [Accolate] or montelukast [Singulair]). They have been used clinically in long-term studies in asthma therapy [33]. However, there is still much debate about their clinical efficacy. Their effectiveness in exercise-induced asthma and aspirin-intolerant asthma is well documented. Clinical trials show bronchodilatory effects beyond those provided by β-agonists, as well as reduced eosinophil numbers in the sputum. On the other hand, a number of non-responding patients have been observed. This may be explained—at least in part—by non-leukotriene-dependent asthma mechanisms or by pharmacogenetic factors. Thus, leukotriene modulating agents may provide novel tools for the treatment of certain inflammatory diseases. For instance, a steroid-sparing benefit in mild to moderate asthma was described. However, whether antileukotriene agents may be of help for the treatment of inflammatory skin diseases such as urticaria and allergic reactions is still unclear [34].

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Table 9.10 Neuromediators in the skin; sources and target cells of neurotransmitters/neuropeptides.

Neuromediator	Receptor	Source	Target cells/function
Acetylcholine	Nicotinergic and muscarinergic acetylcholine receptors	Autonomic cholinergic nerves, keratinocytes, lymphocytes, melanocytes	Innervation of sweat glands and arteriovenous anastomoses; keratinocyte and lymphocyte differentiation; proliferation, adhesion; migration
Catecholamine, noradrenaline	Adrenergic receptors	Autonomic adrenergic nerves, keratinocytes, melanocytes	Innervation of blood vessels, arrector pili muscles; pain transmission; regulation of activity of natural killer cells and monocytes; apoptosis induction in lymphocytes
Substance P	Tachykinin (neurokinin) receptors (NK1-, NK2-, NK3R)	Sensory nerve fibres	Mediates skin erythema, oedema, pruritus; up-regulates cell adhesion molecule expession on keratinocytes and endothelial cells; release of Il-8, TNF-α, histamine, leukotriene B4, prostaglandin D_2
Neurokinin A	Tachykinin (neurokinin) receptors	Sensory nerve fibres	Up-regulation of keratinocyte nerve growth factor expression
VIP	VPAC receptors	Sensory nerve fibres Merkel cells	Sweat secretion, vasodilatation; proliferation, migration of keratinocytes; histamine release from mast cells
PACAP	VPAC receptors	Autonomic and sensory nerve fibres, lymphocytes, dermal endothelial cells	Vasodilatation, immunomodulatory effect on T cells and macrophages; modulates mast cell function, inhibits antigen-induced apoptosis on mature T lymphocytes, down-regulates pro-inflammatory cytokines and chemokines in T cells, up-regulates cytokines and cell adhesion molecules in dermal microvascular endothelial cells
CGRP	CGRP receptors	Sensory nerve fibres	Keratinocyte and endothelial cell proliferation, stimulates cytokine production
POMC	Melanocortin receptors	Melanocytes, keratinocytes, endothelial cells, Langerhans' cells, mast cells, fibroblasts, monocytes, macrophages	Antagonizes effects of pro-inflammatory cytokines (IL-1α, IL-1β, IL-6, TNF-α, endotoxins); up-regulates Il-10; releases histamine from mast cells; regulates dendritic cell function

Neuromediators

Accumulating evidence indicates the existence of an interactive network between the cutaneous neuronal system, the neuroendocrine axis and the immune system. Neurocutaneous interactions influence a variety of physiological and pathophysiological biological functions in the skin, such as development, growth, differentiation, immunity, inflammation, pruritus and wound healing (Table 9.10). Different types of cutaneous nerve fibre release neuromediators and activate specific receptors on target cells in the skin, such as keratinocytes, mast cells, Langerhans' cells, microvascular endothelial cells, fibroblasts and infiltrating immune cells, thereby modulating inflammation.

Cutaneous neuropeptides and neurohormones include a large family of small peptides such as substance P, CGRP, somatostatin, vasoactive intestinal peptide (VIP), pituitary adenylate cyclase activating peptide (PACAP), melanocyte-stimulating hormone (MSH) and β-endorphin. Moreover, neurotrophic factors such as nerve growth factor may affect the skin. Such neuromediators can be released from both sensory and autonomic nerve fibres, which terminate predominantly in the dermis but also in the epidermis, and thus are in close anatomical proximity to a variety of different cutaneous cell types during inflammation. Additionally, several skin cells generate neuropeptide receptors during the inflammatory response. Most of them belong to the G protein-coupled heptical transmembrane receptor family coupled to heterotrimeric G proteins. Because sensory neurones also express specific receptors for neuropeptides, prostaglandins, histamine, neurotrophins, proteases and cytokines, an interactive communication network between sensory nerves and immune cells likely exists during cutaneous inflammation [1–3]. Some neuropeptides have been demonstrated to be also capable of direct activation of intracellular G proteins. Endopeptidases such as neutral endopeptidase (NEP) or ACE are transmembrane molecules that regulate neuropeptide function by degradation, thereby leading to the inhibition of neuropeptide function. They have also been shown to modulate neurogenic inflammation by limiting the effects of neuropeptides in the skin [4]. Hence, a complex network of neuromediators, neurotransmitter receptors and peptidases exist to regulate cutaneous inflammation.

The axon reflex response in the skin is complex and is dependent on the anatomical distribution of the cutaneous axon reflexes and release of different types of neuropeptide [4]. In the skin, at least 30% of the cutaneous afferent nerves belong to a subtype of sensory nerves with

dual sensory afferent and efferent function, which mediate neurogenic inflammation. Capsaicin-sensitive C-fibres, and to a lesser extent Aδ–fibres, are not only capable of transporting impulses to the central nervous system (orthodromic signal) but also release neuropeptides (antidromic signal), which result in inflammatory activities in the skin. Neuropeptides released from cutaneous nerves are capable of acting on target cells via a paracrine, juxtacrine or endocrine pathway. These target cells express specific neuropeptide receptors that are appropriately coupled to an intracellular signal transduction pathway, or ion channels that, when activated, may result in activation of biological responses such as erythema, oedema, hyperthermia and pruritus. Because of their anatomical association to cutaneous nerves, mast cells and their released products appear to play an important part in mediating neuronal antidromic responses in the skin, although the precise role of these cells in cutaneous inflammation remains to be determined.

Substance P (SP), for example, strongly induces inflammatory responses and pruritus. TNF-α release from human skin may be also induced by SP. SP is capable of mediating secretion of histamine and TNF-α from mast cells, which results in vasodilatation via activation of H_1 receptors on vascular smooth muscle cells. It may also induce the release of leukotrienes and prostaglandins. Acute immobilization stress triggers skin mast cell degranulation via SP, corticotrophin-releasing hormone and neurotensin [5]. This ties in with the frequent observation that stress, via release of certain neuropeptides, may trigger skin mast cell degranulation and influence cutaneous inflammation and pruritus. Previous studies using tachykinin NK1R antagonists indicate that cutaneous oedema can be modulated by SP via NK1R activation, and is independent of histamine effects [6].

Neuropeptides may also regulate vascular responses in the skin during inflammation. For example, PACAP is a potent vasodilatator and oedema potentiator in rabbit skin, and mediates plasma extravasation in rat skin [7,8]. PACAP is a relatively new member of the VIP–secretin-peptide family, present in autonomic and sensory nerve fibres of the spinal cord and dorsal root ganglia, where it may influence inflammation and nociception [9]. Recently, PACAP was detected in cutaneous nerve fibres coexisting with VIP, substance P or CGRP, respectively, all of which may play a part during cutaneous inflammation. PACAP produces a long-lasting depression of a C-fibre-evoked flexion reflex in rats [10]. PACAP may also be involved in immunomodulation, down-regulating pro-inflammatory responses such as IL-2 or IL-6, and up-regulating anti-inflammatory mediators such as IL-10 [11], indicating that PACAP may have a role in neurogenic inflammation of the skin.

The neuropeptide CGRP has been shown to modulate immune responses and inflammation *in vitro* and *in vivo*. In general, CGRP predominantly mediates anti-inflammatory and neurotrophic effects. CGRP regulates Langerhans' cell function [12], and increases the phagocytotic ability of macrophages, indicating a regulatory role of CGRP on monocyte–macrophage–dendritic cell function. CGRP also stimulated adhesion of human neutrophils and monocytes to HUVEC and dermal microvascular endothelial cells [13]. In addition, CGRP potentiated the accumulation of neutrophils and oedema formation induced by IL-1 [14], and induced mast cells to release TNF-α, which resulted in inflammatory effects on surrounding skin cells [15].

Somatostatin (SOM) is an inhibitor of immune responses and inflammation [16]. Additionally, it is regarded as a predominantly antiproliferative molecule, having cancer-inhibiting properties mediated by tyrosine phosphatases and inhibitory effects on proliferation of T lymphocytes [17]. The inhibitory effects of SOM may not be generalized, because SOM also stimulates histamine release of human skin mast cells. SOM and the SOM analogue angiopeptin also decrease adhesion by monocytes to unstimulated and IL-1-stimulated endothelial cells by a cyclic adenosine monophosphate (cAMP) dependent mechanism that does not involve ICAM-1. SOM may therefore attenuate recruitment of distinct leukocyte subpopulations during the initial phase of inflammation [18]. There is evidence for the participation of SOM in the pathophysiology of atopic dermatitis and mastocytosis [19–21].

Another molecule with anti-inflammatory potential is α-MSH. α-MSH belongs to the family of pro-opiomelanocortin (POMC) peptides. POMC peptides are widely distributed in the skin and are expressed by melanocytes, keratinocytes, microvascular endothelial cells, Langerhans' cells, mast cells and fibroblasts, as well as by immune cells such as monocytes and macrophages. Post-translational processing of a POMC pro-hormone generates up to eight different POMC peptides after cleavage by pro-hormone convertase 1 and 2 (PC1, PC2). α-MSH has direct immunoregulatory and anti-inflammatory effects on several cutaneous cells *in vitro* and *in vivo*. For example, α-MSH antagonizes the effects of pro-inflammatory cytokines such as IL-1α, IL-1β, IL-6 and TNF-α [22], suggesting that the immunosuppressive capacity of α-MSH is also mediated through its effects on monocyte and macrophage functions. α-MSH down-regulates the production of pro-inflammatory cytokines and accessory molecules on antigen-presenting cells, while production of suppressor factors such as IL-10 is up-regulated by α-MSH [23]. It is well established that α-MSH ameliorates contact hypersensitivity leading to hapten-specific tolerance by inducing anti-inflammatory cytokines. Thus, α-MSH may inhibit cutaneous inflammation.

The neurotransmitters acetylcholine (ACh) and noradrenaline (NA) (norepinephrine) are also involved in

inflammatory processes in the skin. ACh is released by autonomic nerves, but can be also produced by melanocytes, keratinocytes [24] and lymphocytes. It regulates different activities in keratinocytes such as proliferation, adhesion, migration and differentiation. ACh was shown to be crucial to sustain the viability of keratinocytes *in vitro*, and cholinergic drugs were capable of modulating keratinocyte function such as adhesion and motility. Both choline acetyltransferase and acetylcholinesterase appear to regulate the function of ACh in keratinocytes. Intracutaneous application of ACh has been demonstrated to modulate various inflammatory responses [25].

ACh and its derivatives exert their effects by activating nicotinergic or muscarinergic cell surface receptors. The nicotinic receptors for ACh are transmembrane ion channels. Muscarinic receptors belong to a subfamily of G protein-coupled heptical receptors, defined as m_1, m_2, m_3, m_4 and m_5 receptors. Muscarinergic as well as nicotinergic receptors are widely expressed and are involved in epithelial differentiation, cell survival of keratinocytes, and inflammation [26–28].

Catecholamines, their regulating enzymes and adrenergic receptors (ARs) have been detected in nerve fibres, keratinocytes [29] and melanocytes [30,31]. They regulate the activity of certain lymphocytes (NK cells) and monocytes, and induce apoptosis in lymphocytes. In contrast, catecholamine release may be also induced by lymphocytes such as T and B cells. During delayed-type hypersensitivity, NA may also serve as an immunoenhancing agent. α- and β-ARs have been detected in human skin. AR agonists inhibit TNF-α release from mast cells [32], and are potent inhibitors of the IgE-mediated release of tryptase mediators from human mast cells *in vitro* [33]. α and β ARs may also regulate important vascular responses in the skin such as vasoconstriction. Decreased levels of β ARs were observed in lesional and non-lesional skin of psoriasis patients [34], whereas increased levels of α ARs were observed in arterioles of patients with scleroderma [35]. NA is able to increase LPS-induced IL-6 production in human microvascular endothelial cells via ARs. Recent data suggest that catecholamines, in addition to CGRP, regulate Langerhans' cell function in the skin [36]. Together, these results clearly indicate a role for classic autonomic neurotransmitters during inflammation and the immune response.

Capsaicin (*trans*-8-methyl-*N*-vanillyl-6-nonenamide), a vanillyl-alkaloid found in chilli peppers and other solanaceae, has been used as an anti-inflammatory agent for many years. Topically applied, capsaicin elicits a rapid sensation of burning pain by selectively activating sensory C-fibres, and triggers a cascade of inflammatory events such as erythema, and release of pro-inflammatory mediators in skin and mucosa. While capsaicin at lower concentrations activates sensory nerves to release neuropeptides, repeated application renders nerves in the treated area insensitive to further stimulation at higher concentrations. This is probably caused by capsaicin receptor-mediated depletion of neuronal-derived neuropeptides within a certain subdivision of sensory nerves [37].

Chronic application of capsaicin leads to neurotoxic effects in sensory nerves, causing involution of nerve termini. Thus, constant application may have an anti-inflammatory and antipruritic effect in the skin. These effects are at least in part mediated by activation of the capsaicin (vanilloid) receptor transient receptor potential vanilloid-1 (TRPV1) [38]. TRPV1 is a non-selective cation channel with six transmembrane domains, now defined as a member of the transient receptor potential (TRP) family. The receptor can be directly activated by exposure to heat, protons and the cannabinoid anandamide (conditions seen in inflammation and injury). In the skin, TRPV1 is expressed by sensory nerves and keratinocytes, and may thus induce the release of neuropeptides, prostaglandins (PGE_2) and cytokines such as IL-8. Moreover, TRPV1 is up-regulated in keratinocytes of patients with atopic dermatitis, indicating a role of TRPV1 and its ligands in cutaneous inflammation.

Recent data suggest that proteases as neuromediators contribute to cutaneous inflammation by activating PARs. Activation of PARs by thrombin or mast cell tryptase results in vasodilatation, extravasation of plasma proteins and infiltration of neutrophils [39], by releasing neuropeptides such as CGRP and SP from sensory nerve endings. Thus, mast cells may regulate inflammatory responses in the skin by communicating with sensory nerves, not only via histamine receptors, but also via PARs. In the skin, PARs are localized in keratinocytes, endothelial cells, nerve fibres and myoepithelial cells of sweat glands. Mast cells themselves express PAR-2, indicating a potential autocrine regulatory role for tryptase in cutaneous neurogenic inflammation via activating PAR-2. *In vivo*, PAR-2 mediates oedema, plasma extravasation and up-regulation of cell adhesion molecules, and promotes the transendothelial migration of neutrophils [40], in part by a neurogenic mechanism. Finally, PAR-2 mediates pro-inflammatory responses and itch, indicating a role of PAR-2 during the pruritic response in inflammatory skin lesions [41].

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Vasculature and inflammation

Adhesion molecules

Intercell and cell–substrate adhesion is an essential function of cell membranes. Adhesion molecules participate in every cell activity, although they may be latent (not expressed until the cell is stimulated) as in platelets, or expressed very transiently, as for the selectins, binding leukocytes and endothelium, or over a longer duration, as for the integrins binding basal keratinocytes to the basement membrane. Tissue growth, differentiation and repair is regulated by adhesion molecules; leukocyte recruitment and function is also dependent upon adhesion molecules. A leukocyte may sequentially express several different surface molecules during its passage through the endothelium to the site of damage, and during its period of activity at the site. Adhesion molecule expression is complex, associated with or induced by the contiguous cells or substrate, cytokines and chemokines. Adhesion molecules are classified as members of the integrin family, the selectin family and the immunoglobulin superfamily.

Integrins

Integrins, first recognized by Hynes in 1987 [1], are the best studied of all cell adhesion receptors. Integrins and their ligands are critical to tissue development, immune responses, leukocyte trafficking, cancer metastasis and haemostasis.

Table 9.11 Integrin β1 and β2 families regulating cell–cell and cell–extracellular matrix binding.

	Family	α: CD number	Ligands	Integrin occurrence/responding cells
VLA-β1				
α1β1	VLA-1	CD49a	Laminin, type IV collagen	Fibroblasts
α2β1	VLA-2	CD49b	Laminin, collagens	Keratinocytes (basal), fibroblasts, platelets
α3β1	VLA-3	CD49c	Laminin, collagen, fibronectin	Fibroblasts, keratinocytes (basal)
α4β1	VLA-4	CD49d	Fibronectin VCAM-1	Fibroblasts, leukocytes (not neutrophils), Langerhans' cells
α5β1	VLA-5	CD49e	Fibronectin	Fibroblasts, endothelium, platelets, macrophages, keratinocytes
α6β1	VLA-6	CD49f	Laminin	Fibroblasts, keratinocytes
α7β1			Laminin	
α8β1				
α9β1			Fibronectin, VCAM-1	Fibroblasts, leukocytes, Langerhans' cells
α10β1			Collagens	Fibroblasts
α11β1			Collagens	Fibroblasts
αvβ1		CD51	Fibronectin, vitronectin	Fibroblasts, keratinocytes
LEUCAM-β2 (mainly cell–cell)				
α1β2	LFA-1	CD11a/CD18	ICAM-1, -2, -3	Leukocytes
αmβ2	Mac-1	CD11b/CD18	ICAM-1, fibrinogen, C3bi	Leukocytes
αxβ2	p150.95	CD11c/CD18	Fibrinogen, C3bi	Leukocytes, endothelium
αdβ2			ICAM-3	Macrophages

See text for abbreviation definitions. β1 integrins stated to bind to basal keratinocytes may be expressed weakly in suprabasal cells of normal epidermis; expression is increased during inflammation. LEUCAM, leukocyte (cell) adhesion molecules.

Integrins are α- and β-heterodimers but are of considerable diversity, there being eight β chains and 18 α subunits; one α subunit non-covalently links with one β subunit [2], assembling into 24 distinct integrins (Table 9.11). Some α subunits (e.g. αv) may link with more than one β-chain, enabling binding to different substrata (e.g. vitronectin, fibronectin or collagen); recognition is specific for the tripeptide sequence Arg-Gly-Asp (RGD) [3]. Ligand substrates have been identified experimentally. *In vivo*, it is probable that there is diversity in adhesion molecules; a cell may vary expression of integrins depending upon the nature either of the substrate or the stimulus [2].

In addition to their roles in adhesion to extracellular matrix ligands, integrins act as links between the intracellular cytoskeleton and extracellular milieu. All integrins, apart from α6β4, link to actin, whereas the β4 subunit with its large (1000 amino acid compared to 50 amino acid) cytoplasmic domain links to intermediate filaments. Ligation of integrins initiates a plethora of signal transduction events that serve to modulate cell behaviour, including proliferation, apoptosis, gene expression, polarity and differentiation [4]. Many integrin-stimulated pathways are similar to those triggered by growth factor receptors. Knockout mice studies have helped elucidate the specific non-redundant function of each of the 24 integrins. Indeed, genes for all eight β subunits and 14 of the 18 α subunits have been knocked out and each subsequent phenotype is distinct. The phenotypes range from perinatal lethality (α3, α6, α8, αv, β4 and β8) to defects in leukocyte function (αL, αM, αE, β2 and β7), inflammation (β6) and angiogenesis (α1 and β3) [5].

The β1 chain integrins, also known as VLA (very late antigens of activation, being late in appearance on T-cell activation) bind cells to substrates (Table 9.11). The β1 integrins have important cell–cell and cell–membrane linking functions in the epidermis. The distribution of integrins in epidermal cultures is fairly consistent. The α2, α3, α5 and β1 chains are present in basal cells, particularly at cell–cell junctions; α6β4 tends to be most strongly expressed on the base of the basal cells, as is αvβ1, which is weakly and irregularly expressed. These two integrins bind to fibronectin, laminin and vitronectin of the basement membrane [3–8]. If the culture substrate in the initial stages of development is changed from laminin to collagen, the dominant integrin in the basal–substrate zone changes from α3 to α2β1 [6]. The half-life of integrins in culture is 12–15 h. Disappearance of integrins in suprabasal cells occurs because they are not replaced, and is associated with terminal differentiation. Upward cell migration from the basal layer involves loss of adhesion to the basement-membrane proteins, which precedes the decrease and loss of the α5β1 integrins and fibronectin [9,10].

In normal epidermis *in vivo*, the greatest expression of integrins is on the basal cells, either at cell–cell contacts, where α2 and α3β1 are particularly found, or the basal cell–basement-membrane interface, with α3β1 being strongly expressed and αvβ1 and α1β1 being less evident [6,11,12]. Integrin α6β4, a laminin receptor, is strongly expressed in hemidesmosomes [13]. Opinion varies about the presence of α5 on normal basal cells, or the persistence of integrins in the suprabasal layers; discrepancies in the literature may be a result of different epitope specificities

of the test antibodies, or to activation of the skin before or during sampling. The β1 chain persists on the cell surface in suprabasal layers, but at a lower level than on basal cells [3,6]. Reported identification of α2β1 and α3β1 on suprabasal cells of normal epidermis [6] may be caused by recognition of the β1 chain rather than the α chains. As described in the culture studies on α5β1, there is first loss of binding to the extracellular matrix components and then loss of the integrin during differentiation [10], with possibly greater persistence of the β1 cell–cell links.

During epidermal wound healing, there is increased expression in the wound of α2β1, α3β1, α5β1, αvβ4 and α6β4 [11,14,15]; some differences in relative expression have been reported during repair of punch-biopsy wounds [15] as compared with suction blisters [11]. The migrating keratinocytes in punch-biopsy repair strongly express α3 and β1, α6 and β4, and after day 2 α5 activity is increased. The α3 and β1 pattern extends into the unwounded peripheral tissue [15]. In suction-blister repair, the blister roof expresses clusters of several α chains and β1 and β4 chains. On day 2, the migrating keratinocytes express the normal basal cell pattern. By day 6 in the healed hyperproliferative suprabasal epithelium, α2, α3, α6 and β1 are present, and there are low amounts of αv. The α5 and β4 integrins are confined to the basal layer, and in the case of β4 also to the next layer. The staining pattern distal to the wounds is normal [11]. These changes reflect the more rapid upward and lateral migration of hyperproliferative keratinocytes, and synthesis of extracellular substances (e.g. fibronectin and vitronectin). Changes in the granulating basement membrane of full epidermal thickness wounds [15] stimulate formation of the corresponding integrins. In 7-day wounds, formation of fibronectin and tenascin is associated with expression of αvβ6, and of the specific integrins beneath the basal cells at the dermal interface [16]. Hyperproliferation of epidermal keratinocytes in psoriasis is associated with discrete clusters of suprabasal α6 and β1 [8], and also with α3 and α5, particularly at the rete ridges [17].

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Avidity of integrins (β2)

Cell migration, and cell–cell or cell–substrate binding in tissue repair, are associated with increased cell adhesion, integrin avidity and cytoskeleton actin polymerization. Members of the β2 integrin leukocyte cell adhesion molecule (LEUCAM) subfamily (also known as CD11/18) are expressed on most leukocytes, becoming inactive when they are 'resting'. Leukocyte function associated antigen-1 (LFA-1) (CD11a/CD18;α1β2) illustrates the changes in conformation and increase in binding sites after activation of the cell. The adhesion molecules of mobile non-activated leukocytes do not bind to endothelial cell ligands, thus avoiding spontaneous cell aggregation and vascular damage. On leukocyte activation, rapid changes in LFA-1 promote binding to the endothelial ligands (immunoglobulin superfamily members) ICAM-1 and ICAM-2, resulting in leukocyte arrest at the site, emigration or local inflammatory change [1,2]. New epitopes appear in the α and β chains [3,4] and there is an influx of calcium ions resulting in an increase in expression of the binding sites [2,5]. Strong support for the importance of β2 to leukocyte trafficking and inflammation comes from the phenotypes of mice lacking one or more β2 integrins on their ligands (e.g. skin infections), and the genetic disease leukocyte adhesion deficiency (LAD) which results from mutations in the gene for β2 integrin. LAD patients suffer from leukocytosis and failure to recruit leukocytes to sites of infection [6]. Blockade of β2 integrins is a highly promising line of biological therapy for skin inflammation, particularly psoriasis [7].

Low-avidity integrins are not closely associated with the cytoskeleton, but upon ICAM-1 contact stimulation,

Table 9.12 Selectin family.

Molecule	Cells	Function	Activation
P-selectin			
CD62P GMP 140 PADGEM LECAM-3	Platelets, endothelial cells	Links neutrophils and monocytes to platelets and endothelium	Thrombin, histamine oncostatin M, IL-4, IL-13, free radicals, peroxides
E-selectin			
CD26E ELAM-1 LECAM-2	Endothelial cells	Links neutrophils, monocytes, and CLA^+ T-cell subsets to endothelium	IL-1β, TNF-α, LPS, substance P
L-selectin			
CD62L LAM-1 LECAM-1 $Gp90^{MEL}$ DREG	Neutrophils, basophils, eosinophils, monocytes, lymphocytes	Leukocyte rolling on endothelium. Transient arrest	Constitutive activation by endothelium

membrane protein kinase C (PKC) initiates phosphorylation of the cytoskeletal proteins, and the α and β chains of LFA-1. This results in reorganization of the vinculin, talin and α-actinin molecules that link actin fibrils to the cell membrane and the integrin, and induces polymerization of the actin fibrils, thereby increasing the cytoskeleton matrix essential to the adaptation of the cell to its environment. The changes in conformation result in increased avidity of the integrins [1,2]. Leukocyte activation results in high-avidity transformation of LFA-1, coupling to the actin intermediate proteins, and polymerization of the actin fibrils, which stabilizes binding to ICAM-1 and promotes adherence to the endothelium. Activation of integrins also stimulates cell synthesis of cytokines and receptors to chemokines, contributing to cell emigration.

Mac-1 (CD11b/CD18) on the membranes of neutrophils eosinophils and monocytes has a wider range of ligand binding than LFA-1 although it has the same β2 chain (Table 9.11). In normal cells it is inactive but, like LFA-1, the binding affinity for the endothelial cell membrane and other ligands becomes expressed on leukocyte stimulation.

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Selectins

Selectins are calcium-dependent transmembrance glycoproteins with an amino-group terminal portion that binds to sialylated carbohydrate counter-receptors on other cells. Selectin binding is a key transient link between leukocytes and vascular endothelium, thereby mediating the initial steps of leukocyte tethering and rolling. The selectin family comprises three members: P-, E- and L-selectin—which are clustered on chromosome 1 (Table 9.12) [1]. Each selectin has a lectin-like domain at the amino (NH_2) terminal followed by an EGF-like domain and consensus repeats.

P-selectin. P-selectin (CD62P, GMP-140, PADGEM, LECAM-3) is stored intracellularly in the α-granules of platelets and Weibel–Palade bodies of endothelial cells [2,3]. Surface expression of P-selectin on endothelium follows fusion of Weibel–Palade bodies with the plasma membrane. This follows stimulation by histamine, IL-4, IL-13, oncostatin M or thrombin [4–6]. Expression of P-selectin occurs rapidly, within 30 min. Transient expression on endothelium contributes to early leukocyte recruitment [7]. More sustained expression of P-selectin occurs when platelets and endothelium are activated by thrombin, histamine or free radicals, resulting in adhesion of platelets to neutrophils or monocytes and further adhesion of leukocytes, which is enhanced by PAF [8–10]. Once expressed on the cell surface P-selectin is rapidly internalized by endocytosis [11].

The main ligand for P-selectin is P-selectin glycoprotein ligand-1 (PSGL-1) expressed on myeloid, lymphoid and dendritic cells [12]. P-selectin–PSGL-1 binding is crucial to

neutrophil rolling, in that targeted gene disruption of PSGL-1 abrogates this process [13]. The other P-selectin ligand is CD24, which can mediate cell rolling on inflamed endothelium independent of PSGL-1 [14]. Recently, it has been shown that adhesion of P-selectin to leukocytes activates intracellular signalling pathways [15]. For instance, adhesion to T lymphocytes leads to tyrosine phosphorylation of proteins including paxillin [16].

Soluble P-selectin has been detected in plasma but its role is uncertain.

E-selectin. E-selectin (CD62E, ELAM-1, LECAM-2) is synthesized and expressed solely by endothelium and, unlike P-selectin, is not constitutively expressed. Expression is transcriptionally regulated by TNF-α, IL-1 LPS and substance P [17–19]. Following stimulation, peak expression of E-selectin occurs within 4 h and wanes in 24–48 h [20]. E-selectin ligand-1 (ESL-1), the main receptor for E-selectin, is expressed only on myeloid cells [21]. Both PSGL-1 and L-selectin are able to bind E-selectin [22,23]. Leukocytes do not require activation to bind to E-selectin, but as a result of binding there is activation of the β_2 integrin LFA-1 receptors on neutrophils [24]. E-selectin differentiates between neutrophil and eosinophil binding through differences in amount and dimeric form of ESL-1, eosinophil binding is about half that of neutrophils [25].

E-selectin expression is detectable on dermal endothelium in all inflammatory dermatoses, indeed it is preferentially expressed in skin [26]. Cutaneous lymphocyte antigen (CLA) is a glycoprotein molecule expressed on T cells that home specifically to the skin [27]. The expression of CLA by T cells is dependent on induction of glycosylation enzymes that modify pre-existing PSGL-1 during transition of T cells from non-activated to memory phenotype [28,29]. T cells in inflammatory skin disease express CLA, whereas T cells in non-cutaneous inflammation are mainly CLA-negative [28]. The skin specificity of E-selectin–CLA binding makes this an attractive target for biological therapy of inflammatory skin disease [30]. However, a systemically administered antibody directed to E-selectin was ineffective in the treatment of psoriasis [30]. A soluble form of E-selectin is released, which can also induce β2 integrin expression on neutrophils. Levels of soluble E-selectin in plasma are increased in scleroderma, polyarteritis nodosa, SLE, psoriasis and atopic dermatitis [31]. Correlation between levels of soluble E-selectin and disease activity has been observed in atopic dermatitis, psoriasis and palmoplantar pustulosis [32,33]. Whether soluble E-selectin has any direct pathogenic role in psoriasis or is merely a reflection of skin inflammation is debatable.

L-selectin. L-selectin (CD62L, LAM-1, LECAM-1, $gp90^{MEL}$, DREG) is constitutively expressed on the surface of leukocytes during maturation, and expression persists until binding of leukocyte to endothelium [34]. L-selectin is important in the initial phases of leukocyte–endothelial cell binding (Fig. 9.5). L-selectin is unique in that it is the only selectin known to be involved in trafficking of lymphocytes into lymphatic tissue. Upon leukocyte activation (binding), L-selectin is shed from the cell surface [35]. During the later stages of the inflammatory response L-selectin is an important mediator of neutrophil recruitment [36]. Four L-selectin ligands have been identified to date:

1 *Glycosylation-dependent cell adhesion molecule-1* (GlyCAM-1): a secreted protein not found on high endothelial venules (HEV)

2 *Mucosal adressin cell adhesion molecule-1* (MadCAM-1): important in tethering and rolling of lymphocytes in the HEV of Peyer's patches in the gut

3 *CD34*: has a role in lymphocyte rolling in the tonsil

4 *Sgp200*: as for the other two selectins, PSGL-1 may also be a ligand for L-selectin.

Although selectins were originally investigated as adhesion molecules, there is now considerable interest in their role as signalling molecules. For instance, activation via cross-linking of L-selectin on leukocytes leads to up-regulation of surface expression of β1 and β2 on naïve but not memory T cells, and calcium flux in peripheral blood mononuclear cells [37–39]. In neutrophils in particular, L-selectin cross-linking leads to activation of MAP kinases involving Erk 1 and 2 activation [40].

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Immunoglobulin superfamily

CAM are the ligands or counter-receptors for the integrins (Table 9.13). They have one or more immunoglobulin-like domains, hence the designation immunoglobulin superfamily, and have repeat sequences resembling those of fibronectin. Their chief function is to bind leukocytes to cells expressing them, or to endothelium to facilitate vascular emigration, or to cytokine-activated fibroblasts and keratinocytes, to aggregate leukocytes at sites of inflammation.

ICAM-1 has five immunoglobulin-like domains, and is expressed weakly on normal endothelium, but is much increased by stimulation by IL-1, TNF-α or the complement component C5a [1]. On other cells (e.g. keratinocytes and fibroblasts) ICAM-1 is not expressed constitutively, but appears following stimulation by TNF-α or IFN-γ. ICAM-2, present constitutively on endothelium, is not increased by inflammatory stimulation. The third member, ICAM-3, contains five immunoglobulin-like domains and is expressed constitutively by resting monocytes, lymphocytes and epidermal Langerhans' cells [2]. Its expression is increased upon stimulation (e.g. treatment *in vitro*) and binds with LFA-1 (CD11a/CD18). ICAM-1 contributes to leukocyte adhesion via the LFA-1 and Mac-1 β2 integrins (Table 9.13) [3]. The related VCAM-1 molecule expression is increased after cytokine stimulation, and binds the α4β1 integrin mediating extravascular migration, principally of monocytes and eosinophils. Another variant, the platelet–endothelial cell adhesion molecule (PECAM-1 or CD31), is found in platelets and at the intercellular junctions of endothelium, where it contributes to leukocyte passage from blood vessels (Fig. 9.5) [4].

Like the selectins, the extracellular regions of ICAMs and VCAM are released into tissue fluids in a soluble form (sICAM-1, sVCAM). *In vitro* studies of ICAM-1 indicate that its soluble form is released from blood mononuclear

Table 9.13 The immunoglobulin superfamily of adhesion molecules.

Adhesion molecule	Cells	Ligand/counter-receptors	Cells
LFA-3 (CD 58)	Most cell types	CD2	T lymphocytes
ICAM-1	Endothelium Fibroblasts Activated leukocytes Activated keratinocytes	LFA-1 (α1β2) Mac-1 (αnβ2)	Leukocytes Monocytes
ICAM-2	Endothelium	LFA-1	Leukocytes
ICAM-3	Activated leukocytes Dendritic cells Langerhans' cells	LFA-1	Leukocytes
VCAM-1	Endothelium Macrophages Dendritic cells Fibronectin	VLA-4 (α4β1)	Leukocytes (not neutrophils) Langerhans' cells
PECAM-1	Platelets, leukocytes Endothelium	PECAM-1, CD31	

cells, but not from epithelium, fibroblasts or endothelium. In normal persons, up to 450 ng/mL sICAM-1 is detectable in serum, but this may be increased two- or threefold in inflammation (e.g. in disorders such as diabetes, idiopathic pulmonary fibrosis and liver disease); sICAM-1 is also detectable in the synovial fluid of patients with rheumatoid arthritis [5]. sICAM-1 is significantly elevated in the serum of a number of dermatological diseases including atopic dermatitis, psoriasis and metastatic melanoma [6–8] and correlates with clinical severity in untreated disease. sICAM-2 does not exist. sICAM-3 is increased in the sera of patients with psoriasis and atopic dermatitis but is less relevant than sICAM-1 to disease activity [9]. sVCAM is present in normal sera, and is increased in cancer and inflammation, including rheumatoid arthritis. Serum levels of sVCAM are elevated in advanced cutaneous melanoma, localized scleroderma, systemic sclerosis and SLE [10–12]. The role of soluble adhesion molecules is poorly understood—they may compete in cell–cell binding or they may activate cells that possess the cognate ligand.

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Adhesion molecules regulating leukocyte emigration

Leukocyte emigration at a site of inflammation is regulated by a complex sequence of interacting changes. A leukocyte rolling over endothelium is arrested by an activated endothelial cell, binds to it, and passes through an endothelial intercellular junction, attracted by chemokines and other chemotactic agents [1–4], a process known as the endothelial cell–leukocyte adhesion cascade (Fig. 9.5).

Neutrophils, eosinophils and monocytes in the blood may flow mid-stream, or roll down the endothelium, when both leukocytes and endothelium are unstimulated. Contact between the rolling leukocyte and endothelium is regulated by constitutive L-selectin (neutrophils) or by L-selectin and α4β1 integrins (eosinophils and monocytes).

On contact between the leukocyte, and endothelium activated by TNF-α, IL-1, IL-4 or LPS endotoxin, the leukocytes are rapidly activated. Differences in the integrins expressed in the leukocyte types contribute to the selectivity of the resulting leukocyte infiltrate. The initial adhesion is enhanced by other products resulting from endothelial activation: thrombin, histamine, bradykinin, H_2O_2 and LTC_4. Similarly, neutrophils become further activated by endothelial inflammatory products, particularly PAF, enhanced by platelet aggregation.

The rolling activated neutrophil is arrested by the activated endothelium. The L-selectin molecules are shed. P-selectin from endothelium and platelets is rapidly mobilized, linking the neutrophil to the endothelium; adherence is enhanced by E-selectin on the endothelium binding to sialyl Lewis groups on the neutrophils (Fig. 9.5).

Arrest is followed by firm adhesion, during which the neutrophil spreads on the endothelium, adhesion forces are progressively increased, and the neutrophil begins to respond to chemokines and other attraction agents. A rapid change occurs in the conversion of LFA-1 integrins to an avid state, to bind with ICAM-1 and ICAM-2 on the endothelium, which increases expression of ICAM-1. A second β2 integrin, Mac-1, also has functional increased activity and binds to ICAM-1 only (Fig. 9.5).

Adherence changes to migration as the neutrophil responds to IL-8, neutrophil activating peptide-2 (NAP-2), growth-regulated gene/melanoma growth stimulating activity (GRO/MGSA), C5a and other attraction agents. Vascular emigration is most evident in the post-capillary endothelium, but occurs elsewhere in the venous system with sufficient loss of vessel wall integrity. Emigration appears to be mediated by the neutrophil flowing over the ICAM molecules and inserting itself into an intercellular junction, where PECAM-1 is localized; this appears essential for passage of the cell (Fig. 9.5).

Emigration of monocytes and eosinophils is similar, but with some differences in the adhesion molecules and chemokines involved. The α4β1 integrin is expressed constitutively, and contributes to leukocyte rolling, and also to adhesion by binding to VCAM-1 [2]. Monocytes express all three of the CD11/CD18 β2 integrins, and also some ICAM-1 [5]. This may regulate the binding of monocytes to unstimulated endothelium, but adhesion to and emigration from stimulated endothelium is much stronger [5]. A greater number of chemokines contribute to monocyte and eosinophil emigration than emigration by neutrophils, particularly RANTES, MIP-1α, MCP-2 and MCP-3, and additionally MIP-1β and MCP-1 attract monocytes.

Detailed knowledge of the adhesion molecules has an application in the development of blocking ligands, which may offer the potential for control of tissue damaging inflammation.

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Adhesion molecules on activated keratinocytes

Leukocytes emerging from blood vessels move through tissue and bind to activated cells by the same adhesion molecules. ICAM-1 is expressed on fibroblasts, activated thymic epithelial cells and activated keratinocytes [1–4]. As for endothelial cells, ICAM-1 is inducible on fibroblasts by IL-1, IFN-γ and TNF-α, which are cytokines activated or released in damaged tissue [4,5].

Normal keratinocytes do not express ICAM-1 when examined by usual immunohistochemical methods, although extremely small amounts are detectable by immunoelectron microscopy; this expression may be sufficient for normal leukocyte and Langerhans' cell migration but avoids leukocyte-mediated damage [6]. The expression of ICAM-1 on keratinocytes is induced by IFN-γ and TNF-α, which are products released by lymphocytes infiltrating inflamed skin [7]. Activated lymphocyte IFN-γ induces keratinocyte expression of ICAM-1 and HLA-DR, promoting inflammatory and allergic epidermal responses [8,9]. ICAM-1 expression is induced in the basal and lower suprabasal layers; decreased expression in the upper layers is associated with greater differentiation and formation of involucrin [10]. When ICAM-1 is found in the upper suprabasal layers, it probably reflects the presence of relatively undifferentiated hyperproliferative epidermis. Among the disorders in which keratinocytes express ICAM-1 are allergic contact dermatitis [11–13], irritant contact dermatitis [14], psoriasis [15,16], lichen planus, bullous pemphigoid, exanthems and urticaria [17].

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Endothelin 1

Endothelin 1 (ET-1) was first identified as an endothelial cell product [1] and contributes to endothelial turnover and integrity. It is also synthesized by keratinocytes [2]. ET-1 is mitogenic for fibroblasts [3], smooth muscle cells including vascular cells [3,4], melanocytes, in which cells it also stimulates tyrosinase activity [5], and renal mesangial cells.

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Growth factors from cells other than keratinocytes

Potent cytokines stimulating regeneration of skin are synthesized by cells of the dermis. TGF-α and TGF-β, PDGF and βFGF are synthesized by several types of cell, and the epidermis probably contributes only a small proportion of that synthesized in a healing lesion. Other potent cytokines are EGF, insulin-like growth factor-1 (IGF-1), IGF-2, FGF, αFGF and βFGF.

Chapter 10

Clinical Immunology, Allergy and Photoimmunology

G.P. Spickett & T. Schwarz

Overview of structure and function of immune system

[G.P. Spickett, pp. 10.1–10.29]

The immune system plays a key role in the protection of the organism against infection and has evolved in parallel with pathogens, which seek to circumvent the organism's defensive strategies. The structure and function of the immune system is complex, rivalled in complexity only by the nervous system with which it shares considerable structural and functional homology. Both organs extend through the body and are reliant on chemical mediators to transmit complex information between cells. There are complex links between the two systems, manifest by shared receptors and common mediators. The immune system is divided into innate and acquired immunity, which between them provide both immediate defence and long-term immunological memory. Both systems are interlinked to provide effective protection against infection. Disease can arise through immunodeficiency, malignancy and deviation (autoimmunity and allergy).

Traditionally, the immune system is divided into two parts, the innate or non-adaptive and acquired or adaptive, the difference being in the ability of the acquired immune system to learn from exposure to pathogens. The requirement for the innate system is to provide generic protection during the time required for the acquired immune system to generate a specific response. The main feature of the adaptive system is long-lived specific immunological memory. The two parts are linked through shared mediators (cytokines and chemokines) as well as shared receptors. In many respects, both systems amplify the other's response through released mediators.

In a short chapter it is not possible to give an in-depth view of all aspects of the immune system and the interested reader is directed to more detailed sources of information. A brief overview of the immune system follows as an introduction to the clinical aspects later in the chapter.

Innate immunity

Innate immunity describes all the body's defensive strategies that do not have the capacity for learnt responses or immunological memory. The system includes surface defences, soluble mediators and non-specific cells. These do not operate in isolation but are closely integrated with acquired immunity. Figure 10.1 gives an overview of the main features and how they are integrated.

Non-specific defence mechanisms

The non-specific defence mechanisms include the

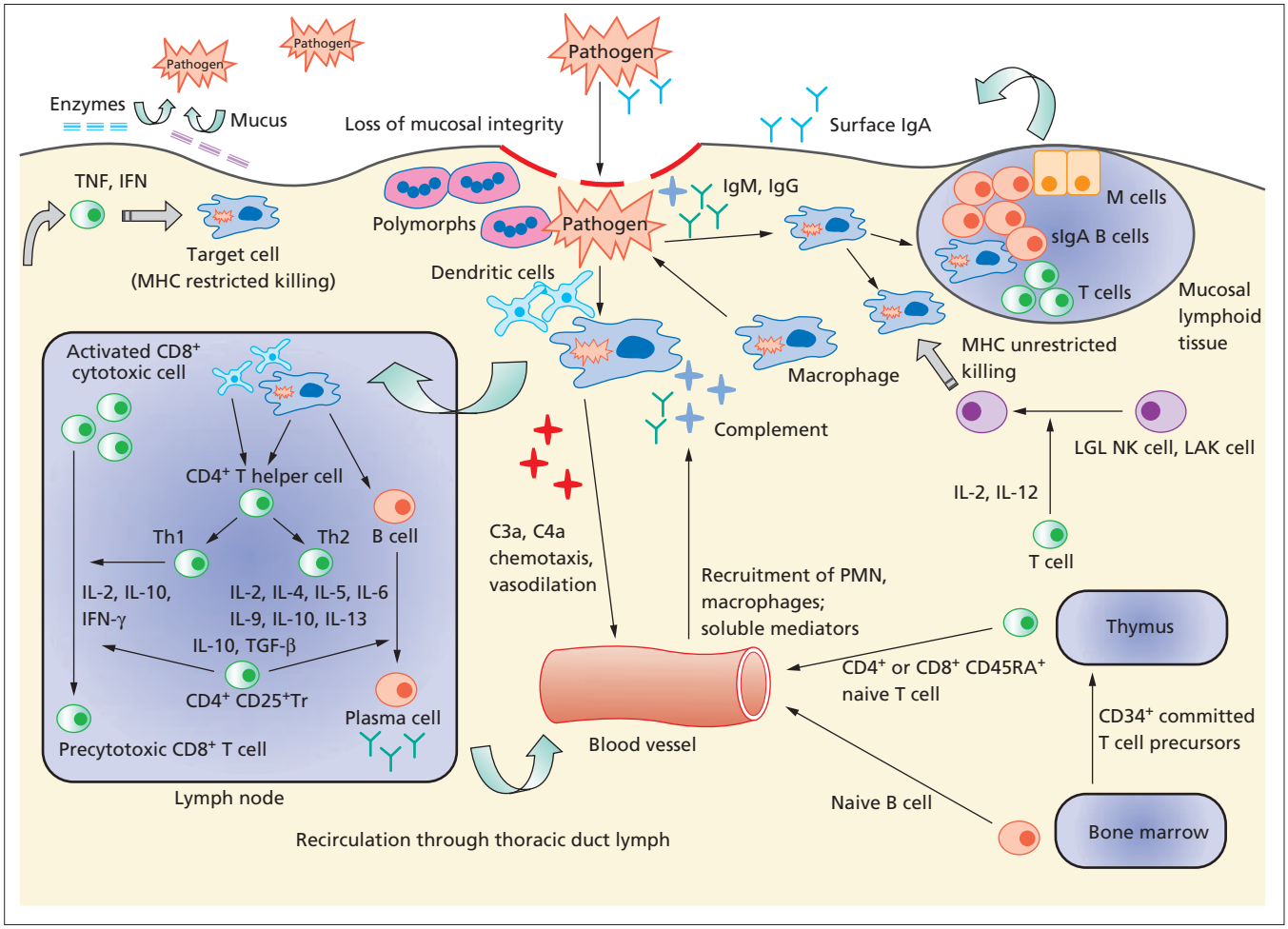

Fig. 10.1 Integration of the various aspects of the immune system, both innate and acquired, in dealing with pathogens. IFN, interferon; IL, interleukin; LAK, lymphokine-activated killer; LGL, large granular lymphocyte; TGF, transforming growth factor.

structural design of the organism, aimed at reducing the capacity for microorganisms to gain entry. These include the structure of the skin itself, together with the secretions that it produces; enzymes in tears and other secretions, such as lysozyme and complement, that have a bactericidal effect; stomach acid, which is extremely effective at reducing bacterial counts entering the upper gastrointestinal tract; and surface mucus in the respiratory tract, which traps bacteria and allows them to be removed by the ciliary escalator. The importance of these mechanisms is demonstrated in illnesses where these protective mechanisms are disrupted, for example burns lead to easy passage of bacteria into deeper tissues; Sjögren's syndrome, with reduced secretions in eyes, mouth and lungs, is accompanied by increased bacterial infections at all these sites; achlorhydria, either due to gastric atrophy or induced by drugs such as proton-pump inhibitors, is associated with reduced resistance to enteric infections and also to *Candida*; cystic fibrosis and ciliary dyskinesia both disrupt the interaction between mucus and cilia and lead to progressive and severe lung disease due to infection. These examples clearly demonstrate that these non-specific features play a significant role in host defence and cannot be replaced no matter how effective other aspects of the innate and acquired immune systems might be.

Soluble factors

The main soluble factors involved in host defence are the components of the complement and kinin cascades, which are linked through shared regulatory components also with the clotting cascade. There are three pathways of complement activation (Fig. 10.2): the classical pathway, triggered by interaction of an antibody–antigen complex with C1q; the lectin pathways, triggered by binding of mannose-binding lectin (MBL) to mannose residues on bacterial surfaces; and the alternate pathway, triggered by interaction of lipopolysaccharides of appropriate surface charge with alternate pathway proteins. The alternate pathway is also responsible for the 'tick-over' low-level activation of the complement system. All three pathways

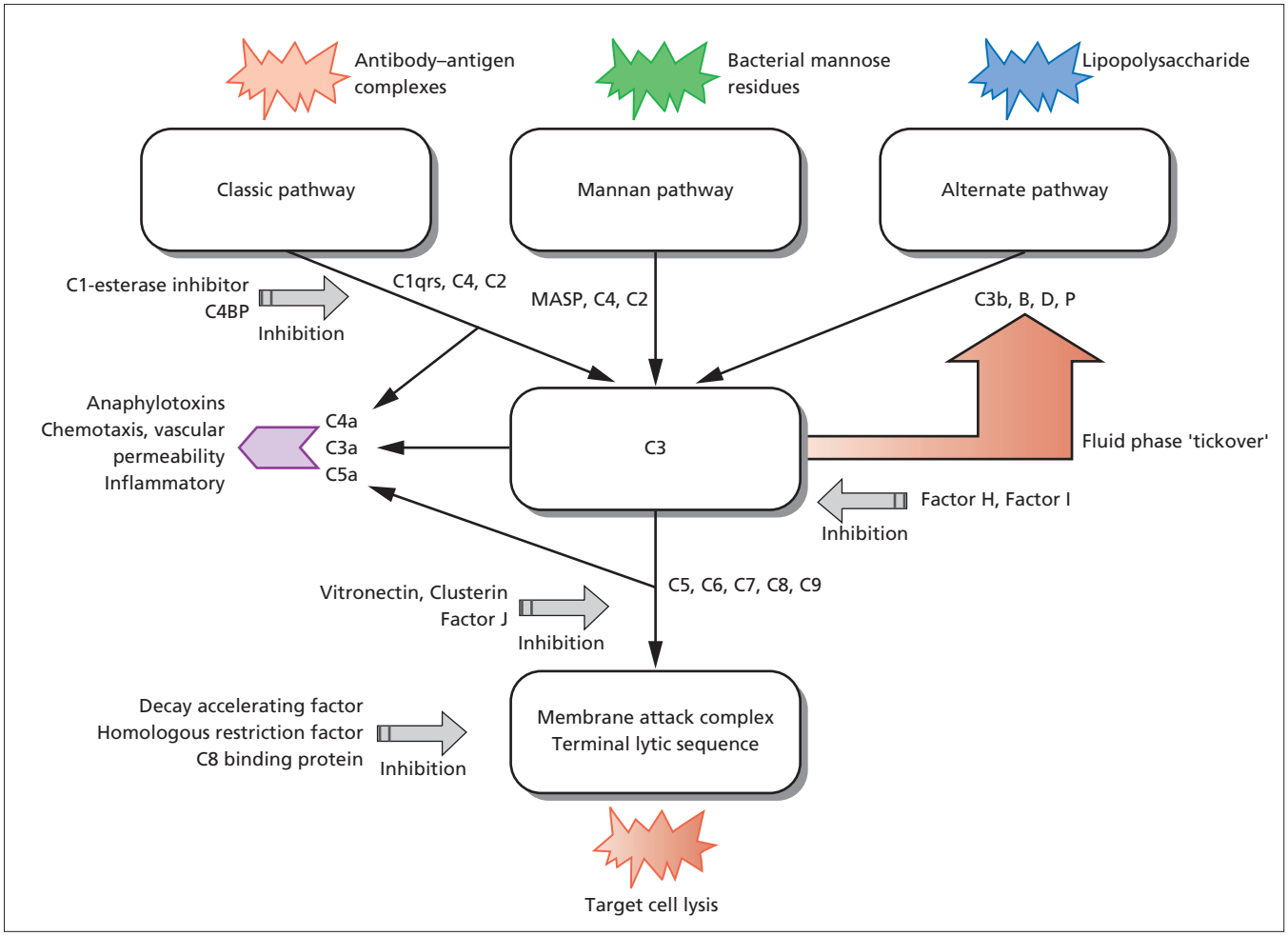

Fig. 10.2 Pathways of complement activation and their control. MASP, mannan-binding protein associated serine protease.

converge at the level of C3 to activate the terminal lytic sequence, which inserts a pore comprising the C5–8 proteins and polymerized C9. These pore-forming proteins are structurally very similar to the proteins produced in natural killer (NK) cells and cytotoxic T cells. Complement is a major opsonin, and the presence of C1q and C3 on bacterial surfaces increases phagocytosis through binding to complement receptors. Activation of the complement system also increases recruitment of phagocytic cells by the split products released during activation, i.e. C4a, C3a and C5a, the anaphylatoxins, which increase vascular permeability and are chemotactic for neutrophils. A specific receptor for C5a (CD88) has been identified that activates cells via tyrosine phosphorylation and MAP kinases.

Complement receptors play a crucial role in linking the innate and acquired systems. Complement receptor 1 (CR1, CD35) is widely expressed on neutrophils, macrophages, follicular dendritic cells and B cells. Its presence on phagocytic cells is directly coupled to the process of phagocytosis, while on follicular dendritic cells it plays a pivotal role in antigen trapping and therefore persistence of antigen for subsequent presentation to T cells and B cells to maintain immunological memory. On B cells it is involved in activation and also in presentation of antigen to T cells. It is present on erythrocytes and is therefore involved in the removal of immune complexes to the spleen for subsequent phagocytosis and destruction. CR2 (CD21, EBV receptor) is expressed mainly on B cells, and forms part of the B-cell antigen receptor complex with surface immunoglobulin, CD19 and the immunoglobulin α chain (CD81). CR2 binds C3 degradation fragments iC3b and C3d, and co-ligation of these with antigen to the B-cell receptor reduces the threshold for B-cell activation 100-fold. CD21 is also essential for the development and maintenance of B1 ($CD5^+$) B cells, which are involved in the spontaneous production of IgM and play a role in recognition of lipid antigens. It is also a receptor for soluble CD23, an autocrine B-cell growth factor involved in IgE production. CR3 and CR4 are β integrins, expressed on phagocytic cells and directly involved in signalling for phagocytosis.

The complement system is an enzymatic cascade of proteases, with each step providing amplification. There are key checkpoints at which regulatory proteins act to ensure that the process is controlled. C1-esterase inhibitor inhibits C1r and C1s and also mannan-binding protein (MBP)-associated serine protease from the lectin pathway, as well as acting as a regulatory protein in the clotting and kinin cascades. Factor H is an inhibitor of C3 and C4-binding protein inhibits activated C4; these are both large molecules with multiple binding sites and are therefore capable of inactivating multiple activated complement proteins simultaneously. Both also act as co-factors for factor I, an inhibitor of activated C3 and C4. Deficiency of factor H has been associated with haemolytic–uraemic syndrome. Newly described regulators of the terminal lytic sequence include vitronectin, clusterin and factor J, which interact mainly with C5b67. Host cells also have regulatory proteins (CD55, decay-accelerating factor; CD59, homologous restriction factor 20; C8-binding protein) expressed on their surface to prevent accidental bystander destruction. In paroxysmal nocturnal haemoglobinuria, there is a somatic clonal mutation in the *pig*A gene that prevents these proteins from being expressed through disruption of the transmembrane glycolipid tail, leading to production of erythrocytes susceptible to complement-mediated lysis.

Deficiency of nearly all components of the complement system has been described, and most lead to increased susceptibility to infection, particularly with *Neisseria* species. The significance of MBP deficiency is uncertain, as deficiency alleles have been identified in healthy subjects. It is thought likely that MBP deficiency is only clinically important when other aspects of the humoral immune system are defective.

The kinin cascade is also a critical pathway in inflammation, particularly in rhinitis and asthma, and also in generation of angio-oedema in hereditary angio-oedema. The end-product of the cascade is bradykinin, which acts through specific bradykinin receptors on smooth muscle, endothelial cells, neurones and synovial cells. C1-esterase inhibitor and α_2-macroglobulin inhibit activated kallikrein and therefore inhibit bradykinin production; C1-esterase inhibitor also inhibits factor XIa in the clotting cascade and Hageman factor in the kinin cascade. Carboxypeptidase N breaks down bradykinin to des-arg-bradykinin, which retains some vasoactive properties: deficiency of carboxypeptidase N has been reported as a cause of angio-oedema. Des-arg-bradykinin is inactivated by angiotensin-converting enzyme (ACE), which explains why angio-oedema and cough are common complications of therapy with ACE inhibitors. Experimental drugs such as icatibant and FR173657 are available that block bradykinin receptors, and may therefore have a major role in the management of angio-oedema.

The pentraxin family of molecules includes C-reactive protein (CRP) and serum amyloid A (SAA). These are acute-phase proteins and bind directly to microbial polysaccharides as well as matrix proteins. CRP also scavenges DNA released from dead cells by binding to chromatin. It binds to C1q, thus facilitating the removal of the DNA–immune complex. CRP is clearly an essential molecule, as deficiency has never been reported.

Defensins are newly described small polypeptide molecules with a direct ability to lyse bacteria. The α-defensins are produced in neutrophils and also in gastrointestinal Paneth cells, while the β-defensins are produced by epithelial cells of the airway and the urothelium.

Many cells of the innate system produce inflammatory compounds derived from the arachidonic acid pathway. These include the prostaglandins, thromboxanes and leukotrienes. These agents have a diverse array of inflammatory properties, including increasing vascular permeability, local blood flow, chemotaxis of neutrophils and smooth muscle constriction, and effects on platelets. The different metabolic pathways include mutually antagonistic agents, prostacyclins and lipoxins. Abnormalities of the enzymes of the synthetic pathways for prostaglandins account for the adverse effects of aspirin in some individuals. The pharmaceutical industry has been active in producing inhibitors of leukotriene synthesis, inhibitors of lipoxygenase (Zileuton) and 5-lipoxygenase activating protein being the most effective, while drugs such as montelukast and zafirlukast are leukotriene antagonists that are effective in asthma but also in urticaria and other inflammatory conditions.

Cellular components

Polymorphonuclear leukocytes (neutrophils) play a critical role in the immediate defence against bacteria. They develop in the bone marrow under the influence of the specific cytokines SCF, IL-3, G-CSF and GM-CSF. The bone marrow contains a large reserve pool of mature cells, which can be released by stress such as infection; 60% of bone marrow capacity is devoted to neutrophil production. Neutrophils remain in the circulation for only a few hours before emigrating into tissues. Abundant expression of leukocyte adhesion molecules, such as L-selectin, P-selectin and cutaneous lymphocyte antigen (CLA), ensures the margination of neutrophils along the endothelial surface. In the presence of activating and chemotactic factors binding to specific surface receptors such as *N*-formylmethionine-containing peptides derived from bacteria, platelet-activating factor (PAF), the chemokines MIP-1α, RANTES and IL-8, and the anaphylatoxins C3a and C5a, adhesion to the endothelium takes place. This process involves integrins of the CD11/CD18 family, with subsequent emigration and migration of neutrophils to the site of inflammation, following the chemotactic gradient. Phagocytosis is stimulated by binding of antibody to

Fc receptors and complement to complement receptors, leading to the formation of the phagocytic vacuole. Fusion of the vacuole with the primary neutrophil granules then exposes the bacterium to an array of enzymes and bactericidal proteins, including myeloperoxidase, lysozyme, elastase, cathepsin G, proteinase-3, azurocidin and α-defensins. Three types of granule are recognized: specific granules containing the enzymes, gelatinase granules containing predominantly gelatinase and NADPH oxidase, and secretory granules. Inducible enzyme systems also contribute, producing nitric oxide and superoxide. The oxidative burst that forms superoxide is produced by the NADPH oxidase system, a multicomponent enzyme. Genetic deficiencies of the subunits of this enzyme cause the X-linked and autosomal forms of chronic granulomatous disease. In X-linked chronic granulomatous disease (63% of cases) mutations occur in the gp91-phox protein, while the autosomal forms are due to mutations in p47-phox, p22-phox and p67-phox. Myeloperoxidase is responsible for the production of hypochlorous acid, a potent oxidizing agent formed from hydrogen peroxide and chlorine; myeloperoxidase deficiency has been reported and leads to increased infections. Neutrophils have multiple bactericidal pathways, so defects in one pathway will not necessarily lead to failure to kill bacteria. Neutrophils are also biosynthetically active, secreting an array of cytokines and chemokines, including tumour necrosis factor (TNF)-α, IL-1, IL-12, interferon (IFN)-γ, transforming growth factor (TGF)-β and IL-8, that amplify the inflammatory response.

Macrophage–monocytes are the mononuclear phagocytic cells, also derived from the bone marrow and under similar differentiation control to neutrophils. They are longer lived than neutrophils and are actively migratory, being found in all tissues in the body. Control of migration is similar to neutrophils, although there are a range of chemokines specifically involved in recruitment, such as MCP-1, MDC, PF4 and MIP-1α. As well as expressing complement and Fc receptors, enabling them to phagocytose immune complexes, they also express an array of scavenger receptors, including lipopolysaccharide (LPS) receptor, CD14 and Toll-like receptors (TLR), which bind LPS complexed with soluble CD14. Other TLR bind proteolytic cleavage fragments from the complement and kinin systems. Activation through TLR leads to oxidative burst and release of the cytokines IL-1 and TNF-α, which drive the systemic inflammatory reaction, stimulating the acute-phase response and causing pyrexia via effects on the hypothalamus. Macrophages have similar enzyme systems to neutrophils, although the activity of the NADPH oxidase system is lower. Macrophages can act as antigen-presenting cells (APCs) and major histocompatibility complex (MHC) class II antigens on the cell surface are upregulated by activation. These cells play an essential role in type IV delayed-type hypersensitivity reactions, as part of granuloma formation, often with cell fusion to create multinucleate giant cells. This is mediated through IFN-γ. Mutations in the IFN-γ receptor, leading to either non-expression or expression but loss of function, have been associated with increased susceptibility to mycobacterial infection, due to failure of macrophage function despite good T-cell immunity. Defects in the receptor for IL-12, which is involved in the induction of IFN-γ, also lead to a similar clinical picture.

Macrophages, together with dendritic cells, form an essential bridge between the innate and acquired immune systems. Phagocytosis of antigen by macrophages leads to internalization, digestion of antigen and re-expression of derived peptides on the cell surface bound to MHC class II antigens. This provides essential stimulation to $CD4^+$ T cells. Dendritic cells do have a direct phagocytic capacity but acquire antigen through transfer from macrophages, with which they form tight complexes during the immune process.

Eosinophils are derived from the same bone marrow lineage as neutrophils, but differentiate under the influence of IL-5. Their main role in host defence is against parasitic infections. Their granules contain eosinophil peroxidase, the Charcot–Leyden crystal protein, a cytotoxic phosphatase, eosinophil cationic protein (ECP), major basic protein and eosinophil-derived neurotoxin. The latter is an important mediator of the neuropathy seen in Churg–Strauss syndrome. Eosinophils have surface receptors for IgE (low affinity, CD23), IgG Fc receptors and complement receptors. Recruitment to sites of inflammation is through similar use of selectins and integrins. The anaphylatoxins and PAF are chemotactic and there are specific eosinophil chemoattractants of the chemokine family, eotaxin-2 and eotaxin-3. Activation of the eosinophil leads to an oxidative burst and production of leukotrienes as well as an array of cytokines, including IL-1, IL-6, TNF-α and the chemokine IL-8, thus promoting an acute inflammatory reaction. Release of eosinophil granule components contributes to the lung damage in asthma, and promotes the chronic phase of inflammation through the release of cytokines active on lymphocytes. MHC class II is expressed, indicating that the cells can also function as APCs.

Mast cells are derived from a distinct lineage of bone marrow cells and express high levels of high-affinity IgE receptors on their surface. Mast cells also express receptors for C3a and C5a, as well as multiple chemokine receptors, ensuring that they are attracted to sites of inflammation regardless of the initiating event. Similar adhesion molecules are expressed as on neutrophils and eosinophils. Their granules contain large amounts of histamine, heparin, tryptase and TNF-α. Cross-linking of the IgE receptor by allergen triggers degranulation. Mast cells produce both leukotrienes and prostaglandins, contributing to the inflammatory response, and also synthesize

IL-3, IL-4, IL-5 and GM-CSF. Mast cells in lung and gastrointestinal mucosa can be differentiated from those in skin and gastrointestinal submucosa by the presence of chymase in the latter.

Basophils are circulating cells with similar properties to tissue mast cells and have high-affinity receptors for IgE. Despite this, they are derived from the same bone marrow precursor as eosinophils, whereas mast cells are a distinct lineage. Basophils circulate for several days in the bloodstream. They produce leukotrienes but not prostaglandins. Basophils are about a 100-fold more sensitive to activation via the IgE receptor compared with mast cells, and are also more sensitive to non-IgE stimuli, including *N*-formyl-methyonyl-leucylphenylalanine (fMLP), C3a and C5a, and phospholipase A. They appear to be involved in the late phase of allergic reactions in tissues and produce IL-4 and IL-13, which increase synthesis of IgE. Interestingly, the release of these cytokines is dependent on the calcineurin pathway, which can be inhibited by ciclosporin A and tacrolimus, accounting for the effectiveness of these drugs in treating allergic reactions.

NK cells are large granular lymphocytes derived from bone marrow precursors. Their granules contain perforin, a cytotoxic protein closely related to complement proteins of the terminal lytic sequence. Although of lymphocyte lineage, these cells do not express CD3/T-cell receptor (TCR) complexes on their surface, nor do they rearrange their TCR genes. Some cells express CD8, but mainly they express CD16, a low-affinity IgG Fc receptor, and CD56, a variant of the neural cell adhesion molecule. They express a range of specific NK-cell receptors, including NKp46 and NKG2D (binds to MHC class I chain-related A and B molecules, MICA and MICB), and cytotoxicity is enhanced by exposure to IL-2. It is thought that the default for NK cells is to kill cells that they come into contact with, unless the cells express sufficient levels of MHC class I antigens to interact with killer-inhibitory receptors (KIRs) expressed on the surface of NK cells. Binding of MHC class I to KIRs is independent of the presence of bound peptide. There are a variety of different KIRs, some of which recognize non-classical MHC antigens (HLA-E, HLA-G). This reactivity explains the abundance of NK cells in the placenta that express high levels of non-classical MHC, NK cells being involved in tolerance to the fetal allograft. Expression of IgG receptors enables them to kill antibody-coated targets via antibody-dependent cell-mediated cytotoxicity. They produce IFN-γ, TNF-α and GM-CSF, contributing to the acute inflammation and stimulating T-helper type 1 (Th1) responses in the acquired system (see below). NK cells contribute to tumour surveillance, seeking out cells with reduced class I expression, and also provide protection against viral infections, as viruses often block surface expression of MHC class I antigens, preventing T-cell recognition. Very rare primary NK-cell deficiency has been reported, with increased susceptibility to all types of herpesviruses. Functional abnormalities of NK cells are seen in the X-linked lymphoproliferative syndrome, due to SLAM—associated protein (SAP) deficiency, and in Chédiak–Higashi syndrome.

Acquired immunity

The key features of the acquired immune system are (i) the responses that develop are specific to a particular pathogen or antigen; and (ii) there is long-lived immunological memory that persists after the first encounter. This is manifest in the antibody responses to antigen on first exposure, where the response is small and comprises predominantly IgM (primary immune response), whereas re-challenge after a suitable interval leads to a large and predominantly IgG response (secondary immune response). The process is accompanied by an expansion of the antigen-reactive cells, together with the generation of long-lived memory B cells. A similar process takes place in T cells. During the process somatic mutation takes place in the antigen receptors to enhance the affinity of the receptor for the antigen. The immune system is a dynamic surveillance system, with constant recirculation of the constituent cells through the bloodstream, tissues and lymphoid tissue. The lymph nodes and spleen remain the primary sites of encounter with antigen-bearing APCs and are also the sites of major antigen-driven proliferation. The recirculation process is tissue specific and targeted through specific receptors expressed on vascular endothelium.

Components of acquired immunity

The key components of the acquired immune system are the B cells, which produce antibody, and the T cells, which serve helper, cytotoxic and regulatory functions. Both have specific receptors based on recombination of multiple genes to give an enormous range of potential specificities. Both cell types use the recombinase-activating genes (*RAG-1* and *RAG-2*) to carry out this process. The antigen receptors on T and B cells differ in their recognition requirements. Antibody binds to conformational epitopes in whole molecules and these will not usually be contiguous, but are represented as surface binding sites on the target molecule. In contrast, the TCR recognizes short linear peptide sequences (7–15 amino acids), only in the context of binding of the peptide to MHC antigens. These linear sequences may be anywhere in the molecule but are usually deeply buried within the structure and not accessible on the surface. This means that B cells can be stimulated by free antigen whereas T cells in the main require processed antigen, presented by antigen-presenting cells (APCs) such as macrophages and dendritic cells. As B cells themselves express MHC class II antigens, they can function as APCs, presenting peptides to $CD4^+$ T cells

in return for help through T-cell cytokine production. Both T-cell and B-cell antigen receptors occur in clusters with co-receptor molecules, which confer additional recognition functions (complement, MHC class), and transmembrane signalling molecules linked to cascades of intracellular enzymes. Activation signals are usually delivered by phosphotyrosine kinases, while inhibitory signals dephosphorylate tyrosine.

B lymphocytes develop in the marrow and then migrate to secondary lymphoid tissue, where they encounter antigen. Antigen-stimulated B cells develop into plasma cells, producing quantities of serum immunoglobulins that are representative of the surface antibody receptor of the cell. B cells exist in two forms, B1 and B2, distinguished by their pattern of surface antigens. B1 cells have low/absent surface IgD, CD45, CD23 and can be $CD5^+$ (B1a) and $CD5^-$ (B1b). B1 cells are long-lived cells producing naturally occurring low-affinity antibodies, usually IgM, against bacteria and autoantigens. Early in life a high percentage of cells are B1, but this falls with age; however, it is this population that is expanded in most chronic lymphocytic leukaemias. B2 cells are 'conventional' B cells and have high levels of surface IgM and IgD as well as CD45 and CD23, but do not express CD5.

Serum immunoglobulins comprise five classes, IgM, IgD, IgG, IgA and IgE (in order of expression), determined by the heavy chain. Each can have either κ or λ light chains. IgD functions primarily as a surface receptor and has no known function as a secreted molecule. High levels have been associated with a syndrome of recurrent fevers, arthritis and infections (hyper-IgD syndrome) that appears to be caused by a defect in mevalonate kinase. IgM exists as a membrane receptor and as a soluble pentameric form, in which the five IgM molecules are joined by a J chain. IgM is the antibody produced in the first phase of an immune response. IgG exists as four subclasses, and comprises by concentration the major serum immunoglobulin. IgG1 and IgG3 are mainly antiprotein antibodies, while IgG2 is mainly antipolysaccharide. IgG4 is present only in low concentrations and its precise role is uncertain, although it and other subclasses do not necessarily give rise to clinical disease; measurement of IgG subclasses is therefore not a useful predictor of underlying humoral immune deficiency. In Sjögren's syndrome, IgG1 is preferentially increased in the polyclonal elevation of IgG seen in this condition; the other subclasses are relatively reduced. IgA exists in two forms, IgA1 (the predominant serum form) and IgA2. IgA is the antibody of mucosal surfaces, and is secreted in the form of dimers and trimers, with an associated J chain. In the process of secretion, which involves active transport through the epithelial cells mediated by the poly Ig receptor, a secretory piece is added, which slows the rate of breakdown. Secretory piece deficiency has been reported very rarely. In the absence of IgA, IgG and IgM can be transported to the mucosal surface and provide effective protection. Thus selective IgA deficiency may be asymptomatic in respect of infection, although it increases the risk of developing a range of autoimmune diseases, including coeliac disease and connective tissue diseases. IgE is primarily involved in antiparasite immunity, acting as a passively adsorbed receptor on mast cells and basophils. Serum concentrations are extremely low in comparison with the other classes of immunoglobulins.

Mature T cells develop in the thymus from T-lineage committed precursors derived from bone marrow. In the thymus, the process of development of functional TCRs takes place in an analogous way to the process in B cells. As well as the TCR, the cells also develop the co-receptor molecules of the CD3 complex (five separate chains) and CD4 and CD8 surface expression. In the periphery, T-cell function is defined to a certain extent by expression of CD4 and CD8, which define the class of MHC recognized. $CD4^+$ T cells are 'helper-effector cells', which recognize predominantly MHC class II antigens and thus interact mainly with a restricted array of MHC class II-positive cells, such as B cells and APCs, or other cells which may have induced class II, e.g. thyrocytes during thyroiditis. Functions ascribed to $CD4^+$ T cells include provision of T-cell help through cognate interactions and cytokine release to B cells and also cytotoxicity towards class II-bearing targets. $CD8^+$ T cells recognize MHC class I antigens, which are expressed on all cells except erythrocytes, and are particularly involved in the recognition of virally infected targets. These cells are actively cytotoxic, using the same enzymes found in NK-cell granules (perforins and granzymes). T cells also perform regulatory functions, cross-suppressing other types of T cells (see below).

Structure and development of the immune system

Although diffused throughout the body, the immune system functions as an integrated organ in much the same way as the nervous system, with which it shares a number of key molecular concepts. However, the immune system has an enormous task as the surface area of the skin is about 2 m^2, that of the lung 100 m^2 (the size of a football pitch) and that of the gastrointestinal tract 400 m^2 (four football pitches!). The mucosal surfaces have to be 'painted' with a contiguous film of secreted IgA. This explains why the total daily production of IgA is tenfold higher than that of IgG, even though the serum level of IgA is five times less than that of IgG.

Primary lymphoid tissue

The primary lymphoid tissue comprises the sites in which lymphocytes and other cells involved in immunological function develop. In humans this comprises the yolk sac

and fetal liver during embryogenesis, with seeding of pluripotent precursors to the bone marrow. These stem cells may be either $CD34^+$ or $CD34^-$, although in clinical transplantation CD34 is used to enrich for stem-cell activity. B-cell development takes place in the bone marrow while committed T-cell precursors, which are $CD7^+$, migrate to the thymus. In birds the bursa of Fabricius and in lagomorphs the sacculus rotundus and the appendix are specific organs involved in the generation of B cells and are analogous to the thymus. However, humans do not appear to have homologous structures. In all these organs there is a complex interaction between stromal epithelium and developing immunocytes, with production of key growth factors by the epithelial cells and presentation of self-antigens involved in tolerance induction.

B-cell development takes place in the bone marrow in humans, with 10^9 new B cells produced each day. During the process of B-cell development, the immunoglobulin genes undergo rearrangement to form the basis of the enormous repertoire of antibodies. This process is dependent on the presence of the recombinase enzymes *RAG-1/RAG-2*. Recombination occurs first in the heavy-chain genes, involving the V, D and J regions. There is a significant wastage as 50% of cells fail to produce viable recombinations. Initially the cells produce a membrane form of the μ heavy chain, which appears on the surface, coupled with the surrogate light chains, V pre-B and λ5. At the same time the invariant chains Igα and Igβ are also produced and combine on the surface as part of the receptor complex. The role of the surrogate light chains is purely to allow expression of the heavy chain and to permit the continued development of the B cell, with recombinations of the κ and λ light chains, and the expression of a fully formed receptor. During this process, the other components of the receptor complex (CD19 and CD21) also appear, and cells become dual positive for surface IgM and IgD. B-cell development is a complex process, and defects in some of the essential enzymes and genes have been identified as causing primary immunodeficiencies. These include deficiencies of surrogate light chain, μ chain, Igα BLNK (B cell linker protein) and BTK (B cell tyrosine kinase), which give B-lineage specific defects, while *RAG-1/RAG-2* defects cause severe combined immunodeficiency (SCID) due to their involvement in TCR rearrangement. Use of knock-out mice has enabled rapid strides to be made in the assessment of the enzymes critical to B-cell development. It is likely that further genetic abnormalities will be described in humans.

Within the thymus, committed T-cell precursors undergo rearrangement first of their TCR β genes; *RAG-1/RAG-2* are critical for this process. In order for the gene product to be expressed a surrogate α chain, invariant TCR pre-α, is produced that permits the next stage of α-chain rearrangement. A small proportion of cells produced do not express αβ TCR but express γδ TCR. Failure to rearrange a functioning β chain leads to cell death. It has been calculated that the process of gene rearrangement can lead to 10^8 potential recombinations. Numerous genes are involved in the control of this process, including *Ikaros* and *Notch-1*. During this process, expression of CD44 (hyaluronate receptor) is lost and expression of CD25 (low-affinity IL-2 receptor) is gained. Cells then express CD3 and both CD4 and CD8 (dual-positive cells), and lose one or the other as development proceeds to become either $CD4^+$ or $CD8^+$ T cells. The enzyme ZAP-70 kinase is essential to this process and genetic deficiency of this enzyme leads to failure of production of $CD8^+$ T cells and reduced numbers of $CD4^+$ T cells; this disorder is a variant of SCID. The T cells then leave the thymus as naive T cells. During the process of T-cell development two key processes take place: positive selection of T cells that recognize self-MHC, and negative selection of those that recognize self-peptides. As the recombination process is essentially random, the majority of developing T cells do not develop appropriate TCRs. Cells that do not recognize MHC die by 'neglect' while those that recognize self-peptides are stimulated to proliferate and die (activation-induced cell death or apoptosis). Accordingly the thymus has a huge turnover of T cells, the majority of which die *in situ*. Any failure in the process of eliminating self-peptide reactive T cells contributes to later development of autoimmune disease.

Failure of thymic development has been described and is due to as yet uncharacterized gene defects located at chromosome 22q11, which control the development of the branchial arches and pouches; this leads to failure of T-cell production as well as cardiac abnormalities. The severe form with immunodeficiency is recognized as DiGeorge's syndrome, analogous to the nude mouse mutation. However, milder variants without immunodeficiency are also identified: velocardiofacial syndrome and conotruncal anomaly face syndome.

Although early dogma denied the possibility of extrathymic generation of T cells, it is now clear that certain specific classes of T cells can develop independently of the thymus. These include intestinal intraepithelial lymphocytes, which are usually γδ TCR^+ and often express an unusual homodimeric ααCD8. Extrathymic γδ TCR^+ cells appear to have specificity for non-protein phosphate-containing antigens, particularly triphosphate nucleic acids and hydrocarbon phosphates derived from mycobacteria. Recognition of these antigens does not appear to require conventional processing and the cells can recognize whole antigen.

Secondary lymphoid tissue

Spleen

The largest lymphoid organ is the spleen, containing about 25% of the body's lymphocytes, and comprises

white pulp surrounding central arterioles (peri-arteriolar lymphoid sheath) and red pulp through which blood is filtered. Red pulp contains sinusoids with abundant macrophages, which are important in stripping off immune complexes bound to the surface of red cells and also for removing aged red cells. The white pulp comprises both T and B cells and also contains follicles comprising mainly B cells. In primary follicles the B cells are predominantly resting cells, whereas in secondary follicles a change in morphology identifies the presence of germinal centres, where active B-cell development takes place in response to antigenic stimulation. This process is stimulated by the presence of APCs and activated T cells expressing high levels of CD40 ligand (CD154). The marginal zone occurs at the interface of red and white pulp and contains a distinct population of B cells, expressing surface IgM but little IgD.

Lymph nodes

Lymph nodes occur in chains beginning at the extremities and are linked by lymphatic channels that eventually coalesce to form the thoracic duct, which drains into the left subclavian vein. Flow along the lymphatics is centripetal, draining lymph containing antigen, inflammatory mediators and cells to regional lymph nodes and thence to the general circulation. Lymph enters the cortex of the node, filtering through the kidney-shaped node to leave by the medulla. The cortex comprises the mainly B-cell area with primary and secondary follicles, as in the white pulp of the spleen, while the medullary area comprises mainly T and B cells in the process of emigration from the node. However, T cells and APCs are spread through the whole structure of the lymph node and the paracortical area surrounding the B-cell follicles is rich in T cells, macrophages and dendritic cells. Specialized follicular dendritic cells are found in the follicles and are responsible for holding antigen on their surface to provide continuous stimulation of B cells recruited into the follicle. These cells have abundant Fc receptors for IgG and use passively bound antibody to sequester antigen in abortive endocytic vacuoles called iccosomes, which protect it from proteolytic degradation. This feature explains why antibody levels decline but not usually to zero after a secondary immune response, as there is continuous restimulation from the sequestered antigen.

Specialized lymphoid tissue is present in the upper respiratory tract, including the tonsils and adenoids (Waldeyer's ring). These are particularly rich in B cells and have a structure similar to lymph nodes. Absence of tonsillar tissue in a small child should always raise suspicion of a B-cell deficiency, particularly a genetic abnormality such as X-linked agammaglobulinaemia, in which mature B cells cannot be produced. The tonsils atrophy in early adult life and it is most unusual to see persistent tonsillar tissue in adults over the age of 25. The gut is well supplied with lymphoid tissue in the form of Peyer's patches, located in the lamina propria, particularly around the ileum, and containing many follicles. Isolated follicles also occur scattered through the lamina propria. The surface epithelium overlying the follicles and Peyer's patches is modified with the presence of M cells, which take up particulate antigen and express MHC class II antigens. Peyer's patches contain all the elements found in peripheral lymph nodes, except that a high proportion of the differentiated B cells express IgA. As well as the defined structures, the lamina propria also contains large numbers of free-ranging lymphocytes, including IgA^+ B cells, and specialized intraepithelial lymphocytes, mainly $CD8^+$ or $CD4^-CD8^-$ T cells. However, there is an increased proportion of $\gamma\delta$ TCR^+ cells with cytotoxic activity. The lymphoid structure in the lower respiratory tract is less well developed, although small aggregates similar to Peyer's patches may be found. The difference is related to the burden of microbes in the two sites, as the lung under normal conditions is relatively free of infection, with most foreign material trapped in the upper airway or removed by the mucociliary escalator.

In the skin there are Langerhans' cells, scattered through the stratum malpighii. These are potent APCs, migrating in the lymph to the regional lymph nodes to stimulate B and T cells and secreting IL-1 and chemokines. Keratinocytes are also directly involved in immune responses through the production of cytokines, including IL-1, IL-6, TNF-α and TGF-β. As noted below, blood vessels in the skin express specific receptors for recruiting skin-homing lymphocytes that express CLA.

Lymphocyte trafficking

A key feature of immune function is the traffic of lymphocytes and other cells involved in the immune response from sites of storage or rest to sites of inflammation. As an estimate of the size of the population of cells on the move, the total number of lymphocytes is estimated at 10^{12} while 10^{11} are in circulation at any one time. Recruitment of lymphocytes into secondary lymphoid tissue occurs through specialized vessels in lymph nodes, the high endothelial venule (HEV); 80% of the lymphocytes enter lymph nodes using the HEV, with the remaining 20% arriving in afferent lymph from tissues. Entry is controlled by expression of L-selectin (CD62L) on the lymphocyte and its cognate receptor on the HEV. The integrins of the lymphocyte function antigen (LFA-1) family are also crucial in neutrophil trafficking but are less so for lymphocytes, which can use other cognate pairs; clinical deficiency of LFA-1 family members leads to an inability of neutrophils to leave the circulation. A range of different receptors occurs on lymphoid tissue in different tissues and the skin that allow selective recruitment of either naive cells or cells that have

been primed to antigens occurring in these locations. For example, binding of L-selectin to the mucosal addressin MAdCAM causes recruitment of naive cells to Peyer's patches, while the interaction of an $\alpha_4\beta_7$ integrin with MadCAM and vascular cell adhesion molecule (VCAM)-1 recruits naive cells to Peyer's patches but memory cells to the lamina propria of the gut. Interaction of CLA and E-selectin on endothelium in skin recruits memory cells to the skin. Binding of lymphocyte very late antigen (VLA)-1 to VCAM-1 attracts lymphocytes to inflammation, as does interaction of lymphocyte CD44 with hyaluronate. Chemokines and their receptors are also involved, such as secondary lymphoid chemokines, which bind to T cells bearing CCR7; fractalkine, expressed on HEV is also a potent chemoattractant for T cells. T and B cells have discrete and non-overlapping patterns of chemokine responses, and are therefore recruited to different areas within the lymph nodes. Many other molecules involved in cellular adhesion have been identified and it is thought that other molecular pairs exist which confer additional tissue specificity on lymphocytes. Once memory cells are recruited in one area, they are thought to retain that homing response for the reminder of their life.

As well as deficiencies of LFA-1 such as leukocyte adhesion molecule deficiency (LAD)-1, clinical examples of other adhesion molecule deficiencies have been described. LAD-2 is caused by a defect in fucosylation that leads to an inability of the receptors for selectins to bind to their cognate molecules, causing recurrent infections, neutrophilia and mental retardation. These patients can be treated successfully with oral fucose. A clinical deficiency of E-selectin has also been described, with recurrent infections but no neutrophilia.

Lymphocyte function, activation and regulation

Antigen presentation

Professional APCs, including macrophages and dendritic cells, undertake antigen presentation to T cells and B cells that express MHC class II antigens constitutively and to other cells on which class II can be induced by inflammation. Although dendritic cells are not phagocytic, they can take up processed antigen transferred from macrophages via pinocytosis in clathrin-coated pits and receptor-mediated endocytosis. Antigen presentation through the class II (or exogenous) pathway targets antigen to the $CD4^+$ T cells. Newly synthesized class II molecules are directed to the endosomal compartment by the invariant chain Ii where they are loaded with peptides. A peptide sequence in Ii called CLIP blocks the peptide-binding groove in the class II molecule until it reaches the endosome, where the enzyme DM removes it. The peptide-binding groove in class II is open-ended, allowing peptides to overhang the ends, provided that the correct sequence binds in the middle. Once loaded, the class II molecule is transferred to the cell surface. The process is a continuous one, and class II is recycled off the surface and can be reloaded with peptide.

Antigen presented via the class I (or endogenous) pathway is loaded in a different compartment, the endoplasmic reticulum, with proteolysis taking place in proteosomes in the cytosol and governed by ubiquitin. The peptide-binding groove on class I has closed ends, which means that the peptide has to be exactly the right length and sequence to bind. Trimming of over-length peptides is carried out in the cytosol by leucine aminopeptidase. The proteins involved in peptide loading are the TAP (transporter associated with antigen processing) proteins. Once correctly loaded, the class I molecule is inserted in the endoplasmic reticulum membrane in association with calnexin and then with β_2-micoglobulin. Finally, a large multimolecular complex is formed and transported to the Golgi body and then to the surface membrane. Any class I molecules not loaded with peptide are destroyed prior to transfer to the Golgi. Evidence for recycling is less clear than for class II.

A third pathway of antigen presentation exists, based on the non-MHC molecular family CD1, which is coded separately from MHC but has similarities to class I, including the use of β_2-micoglobulin as a light chain. CD1 molecules also present antigen to T cells, although the antigens are predominantly lipids, particularly those derived from mycobacteria. At least four isoforms are known, each with different lipid specificities. Loading of CD1 molecules with lipid takes place in the endocytic pathway.

B cells

Mature B cells leaving the bone marrow circulate through the blood and tissues or enter lymph nodes directly via HEVs, where they form the follicles. On encounter with antigen and with T cells recognizing components of the same antigen, the B cells are stimulated to proliferate and to develop further to plasma cells. Two further key processes are involved: class switching, in which the B cell changes the heavy chain associated with a given antibody binding specificity; and somatic hypermutation, which permits an increase in affinity of the antibody (affinity maturation).

Class switching allows the immune system to develop IgG and IgA responses from the initial primary IgM response. This process depends on the interaction of CD40 on the B cell with CD40 ligand (CD154) on activated T cells. Genetic defects in CD154 lead to the X-linked hyper-IgM syndrome, where there is failure of the class switch and IgG and IgA antibody are not produced but high levels of IgM are produced. CD40 is also expressed on APCs and hence T-cell function is also impaired, leading to the typical occurrence of opportunistic infections such

as *Pneumocystis carinii* pneumonia and cryptosporidiosis. One of the enzymes involved in class switching is activation-induced cytidine deaminase (AID); mutations in this enzyme give rise to autosomal hyper-IgM syndrome. Other enzymes involved are the Ku family of DNA phosphokinases, which are targets in the autoimmune process in systemic lupus erythematosus (SLE).

Affinity maturation only takes place in B cells proliferating in the germinal centres, and occurs at hotspots within the variable regions of heavy and light chains, targeting residues that form part of the antibody-binding site. The process is random, and it appears that the enzyme AID is also involved in this process. The process is actively driven by exposure to antigen: cells that hypermutate to produce antibodies of lower affinity are less stimulated and will therefore cease to proliferate, whereas those with higher affinity will continue to receive positive feedback stimuli.

Memory B cells have a different phenotype from naive B cells, expressing high levels of CD27, a member of the TNF-receptor gene family. Conversion to memory phenotype is dependent on the CD40–CD40 ligand interaction in the presence of IL-4. Subsequent activation of memory B cells can take place through interaction of CD27 with its ligand, CD70, expressed on activated T cells; IL-2 and IL-10 augment this process. Naive B cells can be induced to plasma cell formation through OX40 and its interaction with OX40 ligand on T cells.

B-cell responses to antigen have been divided on the basis of requirement for T-cell help. T-dependent antigens include most proteins; T-independent (TI) antigens are mostly polysaccharide antigens. TI-1 antigens include LPS and endotoxin, which at low doses stimulate B cells directly to produce specific antibody, but at high doses stimulate polyclonal B-cell proliferation through interaction with specific receptors. TI-2 antigens such capsular polysaccharides only stimulate specific antibody production. For all TI responses, however, responses are greater in the presence of T cells, so T-cell independence is relative.

Regulation of B-cell activation takes place through negative feedback loops of cytokines produced by activated B cells. It is also thought that the production of idiotypic antibodies, i.e. antibodies that bind to the antigen-binding site of other antibodies, form complex regulatory networks that down-regulate antibody production. Rheumatoid factors are antibodies that recognize the Fc regions of other antibodies; these also appear during infections and are thought to play a role in control of the immune response, presumably by forming immune complexes, which are known to switch off antibody production when present in high concentrations. This explains why antibody responses to antigens are much reduced in small children when maternal antibody is still present. This normal occurrence of rheumatoid factors during the immune response explains why measurement of rheumatoid factors as a diagnostic screening test is usually unhelpful unless a patient has obvious clinical rheumatoid arthritis.

T cells

Recent T-cell emigrants from the thymus are naive and are distinguished by expression of high levels of CD45RA. After antigen exposure the phenotype changes, with reduction in CD45RA and expression of CD45RO. CD45RA and CD45RO are isoforms of the leukocyte common antigen CD45 and are generated by alternate splicing of the RNA transcript. Exposure to antigen via the TCR/CD3 complex must occur in the context of the appropriate co-stimulatory molecules for T-cell activation to occur. If exposure to antigen occurs in the absence of co-stimulation, then non-responsiveness to the antigen is generated (anergy) or the cell is switched to the apoptotic pathway. The best-known co-stimulatory molecule is T-cell CD28. This interacts with B7.1 (CD80) and B7.2 (CD86) expressed on APCs. As noted above, interaction between CD40 and CD40 ligand is also important. ICOS is another T-cell co-stimulatory molecule that interacts with B7RP-1 to activate T cells. Conversely, a related T-cell molecule, cytotoxic T lymphocyte-associated antigen (CTLA)-4, binds to B7.2 and leads to inhibition of T-cell activation. Surface receptors for cytokines are also required for T-cell activation. Mutations in the common γ chain for cytokine receptors leads to SCID. The intracellular kinase cascade is complex, and is being unravelled through studies on knock-out mice and human genetic immunodeficiencies. The kinase JAK-3, linked upstream to cytokine receptors and downstream to STAT kinase, is critical since defects in this molecule also lead to SCID. Other defects in intracellular signal transduction occur in Wiskott–Aldrich syndrome, where mutations in the *WASP* gene interfere with signalling through the rho-GTPases; ataxia telangiectasia, in which a phosphatidylinositol 3-kinase is defective; and the X-linked lymphoproliferative syndrome in which the defect is in the SAP protein. Intracellular calcium is essential for activity of some of the kinases and this is controlled via the calcineurin pathway, which provides the target for ciclosporin A and tacrolimus, immunosuppressive drugs that prevent T-cell activation.

Apoptosis plays a key role in the control of lymphocyte activation and the prevention of autoimmunity. Two processes exist: apoptosis triggered by lack of signals (intrinsic cell death pathway, controlled by Bcl) and apoptosis triggered by activation via CD95. CD95 is expressed on T cells activated via the TCR/CD3 complex. Interaction of CD95 ligand with CD95 (fas) on the T cell activates the caspase pathways and leads to DNA fragmentation. The importance of this pathway is demonstrated in the Canale–Smith syndrome, in which there are defects in the apoptotic pathways at the level of either CD95 or the caspases. The syndrome is characterized by excessive

uncontrolled lymphoproliferation accompanied by features of autoimmunity.

$CD4^+$ Th cells have been divided on the basis of cytokine production, and latterly chemokine receptor expression, into Th1 and Th2 cells. Th1 cells are involved primarily in 'help' for cytotoxic or cell-mediated T-cell responses, while Th2 cells are predominantly responsible for the support of antibody-mediated responses, including IgE-mediated allergic responses. There is cross-regulation of the two subsets, with Th1 cytokines down-regulating Th2 cells and vice versa. Th1 cells produce IL-2 and IFN-γ, while Th2 cells produce IL-4, IL-5, IL-9, IL-10 and IL-13. Th1 responses require signalling through the IL-12 receptor and the IFN-γ receptor; in the absence of function in these pathways, Th1 responses essential for handling mycobacteria are abolished and recurrent infection occurs. Polarization of naive $CD4^+$ T cells to either a Th1 or Th2 response occurs through the release of cytokines from the cells of the innate system, such as macrophages, NK cells, mast cells, eosinophils and basophils. Conversely, the cytokines released by activated Th1 and Th2 cells further stimulate the innate cells. IL-9 appears to have an important role in governing the class switch in B cells to IgE production. In evolutionary terms, the Th2–IgE axis plays an important role in the control of parasitic infections, particularly worm infections of the bowel. One proposal for the increasing prevalence of allergic disease suggests that the disappearance of parasitic worm infections in developed countries releases the IgE system to respond inappropriately to other antigens.

$CD8^+$ cytotoxic T (Tc) cells have also been divided into two populations based on cytokine production: Tc1 produce IFN-γ, while Tc2 produce IL-4 and IL-5. Two discrete mechanisms are used by Tc cells for killing targets recognized via interaction of target cell class I with the CD3/TCR/CD8 complex. Co-stimulation is required for optimum killing activity, especially via CD2 and LFA-1 (CD11a/CD18). The first pathway triggers cell death in the target using the fas–fas ligand pathway of apoptosis, as discussed above. The other pathway uses granzyme and perforin, exocytosed from granules in the Tc. Perforin forms pores in the target cell membrane and allows the entry of granzymes into the cell, which complete cell destruction. Under certain circumstances $CD4^+$ T cells can also be shown to possess cytolytic activity.

A third class of T cells has been described that plays an important role in down-regulation and control of activated T cells. These are sometimes called Th3 or T-regulatory cells, not to be confused with the old concept of 'suppressor cells'. The role of CTLA-4 in inhibiting activation has already been noted. IL-10 and TGF-β produced by these T cells is also inhibitory. No clear phenotype has been identified, but these cells, in some models, are $CD45RB^{hi}$. $CD4^+CD25^+$ T cells have also been shown to be suppressive. As fas is also up-regulated during T-cell activation, this provides another mechanism for control of the immune response.

Overview of immunological disease

Immunological disease can arise as a result of genetic deficiency of key components, hyperreactivity (allergy/hypersensitivity), immune deviation (autoimmunity) and immunological malignancy. In addition, there are changes in immunological function arising from extremes of age, malignancy in other organs, pregnancy and environmental exposures (e.g. cigarette smoke, drug administration).

Understanding immune-mediated disease is dependent on understanding both the development and function of the immune system. However, multiple mechanisms may be active. For example, in primary immunodeficiencies due to genetic defects, there is often aberrant immunological development that leads to autoimmunity and eventually in many cases to lymphoid malignancy.

Immunodeficiency

Immunodeficiency is subdivided into primary and secondary (Tables 10.1–10.3). Over the last 10 years an increasing number of genetic abnormalities of the immune system have been described. A key feature is the lack of correlation between the genetic abnormalities and the clinical phenotype. In some cases this is due to the redundancy within the immune system, allowing compensatory mechanisms to provide protection. Some immunological diseases that are classified as 'primary' do not yet have a clearly defined genetic basis, such as common variable immunodeficiency, selective IgA deficiency and specific antibody deficiency. Most primary immunodeficiencies are rare, in contrast with secondary immunodeficiency, which is common and becoming increasingly so due to widespread use of immunomodulating drugs to control immune-mediated disease.

Primary immunodeficiency

Primary immunodeficiency is defined as immunodeficiency due to genetic defects or where no secondary cause can be identified. Advances in molecular genetics over the last 10 years have meant that clinically well-described syndromes have been identified genetically, increasing our understanding of the immune system through natural knock-out experiments. This has also led to a re-evaluation of some diseases, for example X-linked hyper-IgM syndrome, previously thought to be a B-cell defect, is now known to be a T-cell defect impairing B-cell development.

The type cell or protein affected by the defect determines the likely clinical sequelae. In most cases this will include infection, although other problems such as autoimmunity and malignancy also arise.

Table 10.1 Summary of immune defects.

B-cell defects
X-linked agammaglobulinaemia
μ-chain deficiency; surrogate light-chain deficiency
SWAP-70 deficiency
Hyper-IgE syndrome (includes secondary neutrophil disorder)
CD79a (Igα chain) deficiency
BLNK deficiency
T-cell defects
Wiskott–Aldrich syndrome (*WASP* gene mutations)
Ataxia telangiectasia (*ATM* mutations)
Chronic mucocutaneous candidiasis (AIRE, FOXP3 deficiency)
X-linked hyper-IgM (CD40 ligand deficiency); autosomal hyper-IgM syndrome
Cartilage–hair hypoplasia
Idiopathic CD4 T-cell lymphopenia
Combined defects
Severe combined immunodeficiency (*RAG-1*/*RAG-2* mutations, common γ-chain deficiency; CD3ε deficiency)
Adenosine deaminase deficiency
Purine nucleoside phosphorylase deficiency
DNA repair defects (DNA ligase IV); Bloom's syndrome; xeroderma pigmentosum
Canale–Smith syndrome (autoimmune lymphoproliferative syndromes; fas, fas-ligand, caspase deficiencies)
X-linked lymphoproliferative syndrome (SAP deficiency; includes NK disorder)
MHC class I and MHC class II deficiency
Neutrophil defects
Chronic granulomatous disease (X-linked, autosomal)
Cyclic neutropenia
Leukocyte adhesion molecule deficiency (LAD-1, LAD-2)
Chédiak–Higashi syndrome (including NK cells)
Complement defects
C1–9 deficiency, properdin deficiency
C1-esterase inhibitor deficiency
C4-binding protein deficiency
Factor H deficiency
Unclassified
Common variable immunodeficiency
Selective IgA deficiency
Specific antibody deficiency
Hyper-IgD syndrome (mevalonate kinase deficiency); periodic fever syndromes (TNF-receptor associated protein deficiency)

Investigation for primary immunodeficiency is an increasingly complex field and specialist advice from an immunologist interested in this type of disorder is required at an early stage to assist with both diagnosis and management.

Secondary immunodeficiency

Secondary immunodeficiency represents the most likely type of immunodeficiency that will be encountered by clinical practitioners. The causes are extensive but can be categorized according to primary triggers. In most cases the effects are on T and B cells, although some triggers lead to damage to neutrophils and other parts of the innate immune system, leading to a more complex immunodeficiency. The dermatological manifestations tend to be cutaneous infection and an increase in cutaneous neoplastic change, often at multiple sites. Investigation may be required to prove the cause, but in most cases identification of the primary cause is enough to explain the problem.

Autoimmunity and allergy (hypersensitivity)

These represent overactivity of the immune system. In the case of allergy this is directed against external antigens (allergens), while in autoimmunity the targets are host antigens. Gell and Coombs originally classified the pathogenic mechanisms and no one has produced a better classification since (Table 10.4). However, it is worth noting that pathological reactions frequently involve more than one mechanism so the classification represents a simplification of the true nature of immunological disease.

Allergic disease

Atopic disease in particular is now thought to be a complex phenomenon, with both immediate type I and delayed type IV mechanisms active at different times within the evolution of the disease process. This applies particularly to asthma and has important ramifications for therapy. Previously, treatment has focused on the immediate responses in the airway, while ignoring the T-cell-mediated damage, which is not apparent until secondary lung fibrosis occurs due to T-cell-stimulated collagen deposition. Thus although good initial control is obtained, the disease gradually progresses to irreversible lung disease. Adapting treatment to deal with all the pathogenic mechanisms involved is therefore critical.

In clinical practice, classification of a disease is dependent on demonstrating the presence of appropriate components of the immune response, such as allergen-specific IgE, autoantibodies and complement abnormalities. However, detection of abnormal T cells is more difficult, except in the context of patch-testing for contact hypersensitivity.

The development of allergic disease is multifactorial. In principle, however, allergens are no different to any other antigen in the way in which they are processed and presented to T cells. The propensity to develop a Th2–IgE response appears to be genetically controlled, although more than one gene is involved. Candidate genes include those for the Th2 cytokines IL-4, IL-5 and their receptors, IgE and MHC antigens. Allergic reactions are commoner in developed countries, although allergic sensitization occurs in all populations. However, in communities in developing countries it appears that the cytokines

Table 10.2 Dermatological consequences of some primary immunodeficiencies.

	Key clinical features	Dermatological features
B-cell defects		
X-linked agammaglobulinaemia	Bacterial infections of upper and lower respiratory tracts, joints, gastrointestinal tract	Cutaneous bacterial infection
Common variable immunodeficiency	Bacterial infections of upper and lower respiratory tracts, joints, gastrointestinal tract; autoimmunity; granulomatous disease, lymphoma; nodular lymphoid hyperplasia	Cutaneous bacterial infection, vitiligo, alopecia, cutaneous granulomas
Hyper-IgE syndrome	Eczema, staphylococcal infections of skin and lung (pneumatoceles), osteopenia	Extensive impetigo, recurrent boils
T-cell defects		
Chronic mucocutaneous candidiasis (including APCED: autoimmune polyendocrinopathy, candidiasis and ectodermal dysplasia, due to *AIRE* gene mutations)	Chronic candidiasis; endocrinopathy; systemic infections with bacteria, mycobacteria and herpesviruses	Candidiasis of nails, Norwegian scabies
Wiskott–Aldrich syndrome (mutations in *WASP* gene)	Thrombocytopenia, small platelets, recurrent bacterial and viral infections, eczema, lymphoma	Eczema (distribution atypical compared with atopic eczema); often infected; cutaneous viral infections, papillomavirus, molluscum contagiosum (both extensive)
Ataxia telangiectasia	Cerebellar ataxia (progressive), cutaneous telangiectasia, viral and bacterial infections	Cutaneous viral infections, papillomavirus, molluscum contagiosum (both extensive); telangiectasia (conjunctivae, ears especially)
Cartilage–hair hypoplasia	Short-limbed dwarfism, fine hair, recurrent bacterial infections	Abnormal (fine) hair
Combined immunodeficiencies		
Severe combined immunodeficiency (all variants)	Early onset of infections: bacterial, viral, fungal	Rashes (Omenn variant, maternofetal engraftment)
DNA repair defects (xeroderma pigmentosum, Nijmegen breakage syndrome)	Malignancy, recurrent infections	Keratoses, cutaneous malignancy
Neutrophil disorders		
Chronic granulomatous disease	Bacterial and fungal infections	Cutaneous bacterial infections, ulceration of mouth
Cyclic neutropenia	Bacterial and fungal infections	Cyclic mouth ulceration (gingivitis)
Rare disorders		
Chédiak–Higashi syndrome and Griscelli's syndrome	NK cell defect, abnormal neutrophils, recurrent infections, lymphohistiocytosis	Silver streaks in hair, oculocutaneous albinism
Dyskeratosis congenita	Malignancy, bone marrow failure, recurrent infections (bacterial) with hypogammaglobulinaemia	Cutaneous pigmentation, nail dystrophy, oral leukoplakia
Anhidrotic ectodermal dysplasia	Respiratory infections	Hypohidrosis, abnormal dentition
Papillon–Lefèvre syndrome	Recurrent bacterial infections, impaired neutrophil function	Hyperkeratosis and pyoderma
Complement disorders		
C2 deficiency	SLE-like disease, recurrent bacterial infections	Extensive cutaneous lupus erythematosus
C1-esterase inhibitor deficiency	Angio-oedema	Angio-oedema without urticaria
C4-binding protein deficiency	Angio-oedema, features of Behçet's syndrome	Angio-oedema, ulceration

NK, natural killer; SLE, systemic lupus erythematosus.

produced as a result of endemic infections suppress the clinical manifestations of allergic disease. Where food allergens are concerned, it appears that exposure at times when the immune system is relatively immature in the first 2 years of life can lead to inappropriate responses. This may be augmented by the fact that many of the foods concerned contain naturally occurring lectins (e.g. wheat-germ agglutinin, peanut agglutinin), which have profound proliferative effects on lymphocytes. Exposure to infections in early childhood also has a protective effect against the development of allergic disease, as demonstrated in German children brought up on farms (hygiene hypothesis). Changes in the way we live are also important, for example the move to centrally heated, double-glazed houses with poor ventilation and fitted carpets provide optimum growth conditions for house-dust

Table 10.3 Causes of secondary immunodeficiency.

Infection
Human immunodeficiency virus
Epstein–Barr virus and other herpesviruses
Measles, rubella, influenza
Chronic bacterial sepsis, tuberculosis
Parasitic and protozoal infections
Drugs
Immunosuppressive drugs: corticosteroids, cyclophosphamide, azathioprine, ciclosporin A, tacrolimus, sirolimus, mycophenolate (all affect T- and B-cell function)
Biologicals: anti-CD3, anti-CD4, anti-CD52, anti-TNF (Etanercept)
Anticonvulsants: phenytoin, valproate, carbamazepine (hypogammaglobulinaemia, neutrophil dysfunction)
Carbimazole (agranulocytosis)
Chloramphenicol, penicillins (aplastic anaemia)
Transfusion therapy (blood components, including intravenous immunoglobulin)
Malignancy
Lymphoma, leukaemia, myeloma and other plasma cell dyscrasias, myelofibrosis (neutrophil dysfunction)
Solid tumours
Physical
Irradiation
Plasmapheresis, immunopheresis
Surgery (especially if thoracic duct damaged)
Medical/metabolic
Diabetes mellitus, glycogen storage disease (neutrophil dysfunction)
Chronic renal failure
Protein-losing enteropathy
Myotonic dystrophy
Nutritional deficiency (iron, zinc, vitamin B_{12})
Miscellaneous
Asplenia
Burns
Toxins (alcohol, cigarettes, solvents)
Extremes of age (prematurity, old age)
Pregnancy

TNF, tumour necrosis factor.

mites. Keeping pets indoors also contributes, although there is some evidence that keeping pets can have a protective effect against pet allergy. Other environmental factors include changes in diet, for example peanuts are now a common source of protein whereas they were rarely consumed 30 years ago, and the contribution of pollution, especially diesel fumes.

Autoimmune disease

Autoimmunity can arise through failure of the initial negative selection process for T and B cells or it can occur through the breaking of peripheral tolerance. As pathogens have evolved in parallel with humans, they have developed antigenic structures similar to those present in their preferred host, in order to reduce the risk of elimination by the immune system. Accordingly there is a risk that the immune response may generate both antibodies and effector T cells that are cross-reactive with self components, for example coxsackieviruses and diabetes mellitus, *Klebsiella* and HLA-B27$^+$ arthritis. Evolutionary selection pressure will determine that individuals who can respond to pathogens with an effective immune response will survive, even though this may be at a later cost of autoimmune disease. The pathogen will eliminate those whose immune response fails. The need to present such antigens then drives the evolutionary pressure on the selection of certain MHC haplotypes in stable populations and accounts for the widely differing patterns of MHC antigens in different parts of the world. Today's long-distance travel means that this equilibrium is disturbed: individuals are exposed to pathogens whose antigens cannot be presented effectively because those infected do not possess the appropriate MHC molecules. Other genes also contribute to the generation of autoimmunity, for example there is an increased incidence of autoimmunity in complement deficiencies and a high

Table 10.4 Gell and Coombs classification of immunological reactions.

Gell and Coombs classification	Immunological mechanisms	Examples of clinical disease
Type I (immediate hypersensitivity)	Allergen-specific IgE, mast cells, histamine, leukotrienes, Th2 cells, cytokines involved in IgE production (IL-4), eosinophil production (GM-CSF, IL-3, IL-5)	Anaphylaxis, urticaria (some types), allergic rhinoconjunctivitis, asthma (immediate but not chronic)
Type II	IgG-antibody mediated, direct effects (complement-mediated lysis), Th2 cells	Antibody-mediated autoimmune disease (thyroid, haemolytic anaemia, thrombocytopenia, myasthenia gravis, etc.)
Type III	Immune complex disease, IgG and IgM antibodies, complement, complement receptors	Serum sickness, SLE (abnormal complement, complement receptors), complement deficiency (abnormal immune complexes)
Type IV (delayed hypersensitivity)	T-cell mediated, Th1 cells, cytokines (IL-2, IFN-γ, TNF-α), macrophages, CD8$^+$ cytotoxic T cells	Contact (delayed-type) hypersensitivity, eczema, graft rejection

GM-CSF, granulocyte–macrophage colony-stimulating factor; IFN, interferon; IL, interleukin; SLE, systemic lupus erythematosus; TNF, tumour necrosis factor.

incidence of autoimmunity in defects of apoptosis such as fas deficiency and caspase deficiency. Autoimmunity may also be triggered by the release of sequestered antigen from privileged sites (e.g. the eye) and by the generation of neoantigens by chemicals and toxins (e.g. autoimmune haemolytic anaemia caused by penicillins). One suspects that the root cause of most autoimmune diseases will be infection, although like a hit-and-run accident the culprit is long gone even though the effects of the 'accident' may be lifelong.

Immunity at extremes of age

The immune system is incompletely developed at birth: while all the components are present, the acquired immune system requires antigen exposure to develop the full repertoire of both T- and B-cell antigen receptors through recombination and somatic mutation and class switching. While this process takes place, protection is provided for the first 6 months of life by maternally transmitted antibody, transferred across the placenta by an active process in the last trimester. Breastfeeding also provides important amounts of IgA for protection of the gut. Stimulation to the acquired system can be provided by either natural infection or programmes of immunization. However, virulence factors in certain classes of bacteria, notably pneumococci, *Haemophilus influenzae* and *Neisseria meningitidis*, are capsular polysaccharides. These antigens are difficult for the immune system to recognize in the first 2 years of life, hence the high incidence of invasive disease caused by these organisms in this age group. Normally the bulk of antipolysaccharide antibody is IgG2 subclass. Interestingly, this defect can be bypassed by covalently conjugating the polysaccharide antigen to a protein, with the immune system producing a protective but mainly IgG1 antibody response to the polysaccharide. As the immune system ages, this inability to recognize polysaccharide antigens returns and there is a second peak of disease in the older population.

Ageing of the immune system is not chronologically related. Studies of the immune system in the elderly have been hampered by the need to define healthy elderly, free of other illness and medication. In fact the immune system remains remarkably effective, with good vaccine responses in the healthy elderly. However, protection of at-risk groups is less effective by virtue of their coexisting disease. Thus targeting influenza vaccine at those with, for example, chronic respiratory disease or chronic lymphocytic leukaemia targets the vaccines at those least able to respond. It was previously assumed that beyond the age of about 25 years, the ability of the immune system to reconstitute from thymus and bone marrow declined rapidly. However, newer evidence has shown that thymus is capable of functioning well into old age, albeit with a reduced capacity for generation of mature T cells. Much of the immune dysfunction of the elderly is related to other disease processes, either directly or through their treatment. Immune regulatory function becomes less effective with age and this is manifest by increasing levels of rheumatoid factors and other autoantibodies, usually in the absence of clinical disease. Low-level monoclonal gammopathies also develop due to failure to suppress antibody-producing clones at the end of an immune response. These may remain stable for decades, although the current view is that all will eventually develop into myeloma, given sufficient time.

Immunity and malignancy

The immune system has an important role to play in immune surveillance for malignancy through the activities of NK cells (see above) and in control of established tumours through infiltrating cytotoxic T cells. Tumours often escape immune surveillance and cytotoxicity by loss of key antigens on the cell surface or production of immunosuppressive mediators. Tumours of the immune system, either lymphomas (including chronic lymphocytic leukaemia) or myelomas, have a direct effect on immunological responsiveness, with reduction in humoral immunity especially and an increase in bacterial infections. In the case of lymphomas, the abnormalities of humoral immune function may persist for years after apparently curative therapy. The importance of the acquired immune system in tumour control is well demonstrated by the significant increase in cutaneous tumours seen in patients treated with immunosuppressive drugs such as ciclosporin and cyclophosphamide over long periods.

Overview of diagnostic testing for immunological and allergic disease

Accurate immunological diagnosis depends on access to appropriate immunology laboratory services. Such services need to be run to high quality standards, verified by external peer review inspection. In the UK this is carried out by Clinical Pathology Accreditation (CPA). Laboratories are inspected at regular intervals to ensure compliance with agreed standards. These standards verify the organization, testing and reporting of laboratory testing. Participation in external quality assurance for the tests offered is essential, although rarely requested tests may not have national schemes in place. Under these circumstances the laboratory must satisfy itself that it is taking reasonable steps to quality assure the results. In all cases laboratories should run internal controls with defined parameters and only report results when these internal controls meet their predetermined values. Clinical governance standards require clinicians to assure themselves that they are using appropriate diagnostic services. Where academic departments are providing in-house tests for diagnostic clinical

use, they have the responsibility, under product liability legislation, for any errors or problems arising from the assay. It is essential therefore that scrupulous internal quality control data are collected, together with validation data.

Good clinical practice requires that test selection should be appropriate to the disease under investigation. The laboratory is responsible for selecting the most appropriate methodology and ensuring that clinicians have a clear understanding of the performance of the test, through derivation of normal ranges appropriate to the population under study and interpretative comment. Each laboratory for each test should define normal ranges, although in practice nationally established ranges may be used. Ranges should be adjusted for age, sex and racial background.

Immunochemistry

Immunochemistry covers the measurement and identification of serum proteins, including abnormal ones. Usually this is undertaken using automated analysers, which are readily quality controlled. International standards have been established for all major serum proteins, and there are long-established external quality assurance schemes. Results in principle should vary little from laboratory to laboratory.

Allergy tests (Table 10.5)

Total IgE and allergen-specific IgE are readily measured in the diagnostic laboratory. However, total IgE levels correlate poorly with the allergic symptomatology; elevated levels suggest inheritance of the atopic tendency but do not predict the form this may take. Levels greater than 1000 kU/L are usually seen in atopic eczema. Levels more than 50 000 kU/L are seen in the hyper-IgE syndrome. However, levels in the range 10 000–50 000 kU/L may be seen in either condition and the differential diagnosis is then dependent on associated clinical and immunological features. Levels of total IgE within the normal range do not exclude severe allergic disease, although this is usually mono-allergenic. Total IgE levels are geometrically rather than normally distributed and there is considerable variation in ranges with age. It is essential to check that the laboratory has reported the appropriate range for age.

Allergen-specific IgE can be detected by many techniques, although the earliest technique was the radioallergosorbent test (RAST): this acronym has entered common usage as a term for allergen-specific IgE. Few, if any, laboratories use this technique now, having moved to colorimetric or fluorimetric assays. These assays tend to be expensive. Direct testing by skin prick is cheaper and is the preferred method of testing, provided that staff experienced in the technique are available. Results of skin prick testing are operator dependent. Correlation between skin prick testing and RAST is dependent on the allergen. For inhalant allergens and strongly allergenic food allergens, such as shrimp, peanut and tree nuts, there is good correlation. In the case of fruit allergens, as seen in the oral allergy syndrome, RAST results are unreliable and should not be used. Of those patients with latex allergy, 15% will have negative RAST results. RAST for drug allergy, with the exception of suxamethonium, is also unreliable and skin prick or intradermal testing is required. Newer assays include the Flow-CAST, and assays of stimulated histamine release compare well in some respects but are very expensive in comparison with existing tests. Allergy testing should be targeted to allergens identified on the basis of clinical symptoms, as routine screening with extended panels often leads to positive results of uncertain clinical significance, which is confusing to clinicians and patients alike. Very high total IgE levels (> 1000 kU/L) have always been suspected of causing false-positive reactions in RAST, especially to food allergens, although most modern assays seem to be less susceptible to this effect. Biological cross-reactivity is also common, where similar allergenic proteins occur in many species of plant or animal. This may be clinically relevant, for example prawn allergy in patients allergic to house-dust mite, or irrelevant, as in the detection of IgE to wheat

Table 10.5 Allergy tests.

	Advantages	Disadvantages
Skin prick tests	Cheap Results available in 15 min Useful positive and negative reinforcement Can be used with *ad hoc* allergens (e.g. fresh foods, drugs)	Cannot be done in patients receiving antihistamines, calcium channel blockers, phenothiazines, or those with extensive eczema Inadvisable as first-line test in patients with suspected anaphylaxis to test reagents (except where resuscitation facilities available) Requires skilled staff for reproducible results
Radioallergosorbent test (RAST)	Clinically useful for inhalants and some foods only Automated analysis Can be used in patients where skin prick testing is contraindicated	Expense (staff and analyser) Results not immediately available No reinforcement of clinical message Not suitable for many allergens (fruits, drugs)
Flow cytometric tests	Research tools	Very expensive, labour-intensive

Table 10.6 Patterns of immunoglobulins.

Pattern of immunoglobulins and electrophoresis	Clinical associations
IgG, IgA, IgM all low; electrophoresis shows agammaglobulinaemia	X-linked agammaglobulinaemia (children), light-chain myeloma (elderly), gross unselective nephrotic syndrome (all serum proteins reduced), burns, immunosuppressive drugs (excess), acute severe bacterial infection
IgG and IgM normal, IgA absent; electrophoresis normal	IgA deficiency; may be associated with IgG subclass deficiency and specific antibody deficiency. Also associated with gluten sensitivity (dermatitis herpetiformis, coeliac disease), connective tissue diseases
IgG and IgA low/absent, IgM normal/low; electrophoresis shows reduced γ region	Common variable immunodeficiency, protein-losing enteropathy; selective nephrotic syndrome (albumin reduced)
IgG and IgA low/absent, IgM high/normal; electrophoresis shows reduced γ region	Hyper-IgM syndrome, acute viral infection (repeat in convalescence)
Raised IgG; IgA and IgM low; electrophoresis shows monoclonal band on background of reduced γ region	IgG myeloma, lymphoma
Raised IgA; IgG and IgM low; electrophoresis shows monoclonal band on background of reduced γ region	IgA myeloma
Raised IgM; IgG and IgA low; electrophoresis shows monoclonal band on background of reduced γ region	Waldenström's macroglobulinaemia, lymphoma
IgG, IgA and IgM low; electrophoresis shows monoclonal band on background of reduced γ region	IgD or IgE myeloma, light-chain myeloma with free light chains in serum (also think of AL amyloid)
Raised IgG, normal/raised IgA, normal IgM; electrophoresis shows polyclonal increase in γ	Chronic infections (bacterial, viral), chronic inflammatory disease (RhA, SLE), sarcoidosis, autoimmune hepatitis
Very raised IgG (predominantly IgG1), raised IgA and IgM; electrophoresis shows polyclonal increase in γ	Sjögren's syndrome, hypergammaglobulinaemic purpura
Very raised IgM, normal IgG or IgA; electrophoresis shows polyclonal increase in γ region with or without small IgM bands	Primary biliary cirrhosis
Very raised IgA, normal/raised IgG, normal IgM; polyclonal increase in γ with β–γ bridging	Liver disease, especially cirrhosis due to alcohol

RhA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

in patients allergic to grass pollen. Interpretation of results is therefore dependent on a clear understanding of the patient's history.

Mast cell tryptase is a useful marker of mast cell degranulation and can therefore be used to discriminate between acute allergic reactions and non-immunological mimics. It is a stable protein whose levels remains elevated for up to 24 h after a reaction and is easily and reliably measured on a clotted blood sample. ECP has also been used to demonstrate activation of eosinophils, particularly in the context of asthma, where it has been proposed as a useful marker of chronic eosinophilic inflammation. Unfortunately it is less stable than mast cell tryptase, and has a strict sampling protocol involving timed centrifugation, which renders it useless for diagnostic use.

Mast cell tryptase is also helpful in suspected mastocytosis, although 24-h urinary methylhistamine is probably more sensitive, albeit more awkward to collect. At present, the only commercial assay for urinary methylhistamine has been withdrawn by the manufacturer.

Immunoglobulins (Table 10.6)

Automated analysers, using nephelometry or turbidimetry, can measure serum immunoglobulins and IgG subclasses accurately and reproducibly. The only indications for measurement of these parameters are the investigation of suspected immunodeficiency, liver disease, lymphomas and plasma cell dyscrasias. Normal ranges must be age specific and in adults the range for IgM is also modified by sex, with the lower limit of normal for IgM being higher in females than males. Measurement of immunoglobulins should always be accompanied by electrophoresis, both as an internal quality control and also to permit the detection of paraproteins (monoclonal immunoglobulins). If the latter are detected, then immunofixation should be carried out to identify the nature of the band, and urine requested for analysis for free light chains (Bence Jones proteins). Paraproteins may react abnormally with antisera used for the quantification, leading to falsely low or high results. This may be due to polymerization of the paraproteins or the presence of monomeric, as opposed to pentameric, IgM. Paraproteins should therefore also be quantified by scanning densitometry.

Cryoglobulins and cryofibrinogen

Cryoglobulins are abnormal immunoglobulins that precipitate at a higher temperature than normal (Table 10.7). Normal immunoglobulins may precipitate from serum that is cooled to 4–6°C, but cryoglobulins precipitate at temperatures found in the extremities, i.e. above 26°C,

Table 10.7 Cryoglobulins.

Type	Composition	Associations
I	Monoclonal immunoglobulin	Myeloma, Waldenström's macroglobulinaemia, lymphoma
II	Monoclonal immunoglobulin with rheumatoid factor activity, precipitate contains both monoclonal and polyclonal immunoglobulins	Myeloma, Waldenström's macroglobulinaemia, lymphoma, mixed essential cryoglobulinaemia (HCV infection), subacute bacterial endocarditis, connective tissue diseases
III	Polyclonal immunoglobulins with rheumatoid factor activity	Chronic infections, chronic inflammatory diseases

HCV, hepatitis C virus.

causing obstruction to small blood vessels and a vasculitic-looking rash on cooler parts of the bodies, typically the hands and feet but also nose and ears. The higher the temperature at which they precipitate, the worse the symptoms will be. The appearance of cutaneous vasculitis on extremities, particularly in cooler weather, should always raise suspicions of cryoglobulins. The detection of a type II cryoglobulin in the absence of evidence for myeloma should raise the possibility of hepatitis C infection; complement C4 is invariably markedly reduced. Pyroglobulins are extremely rare and precipitate when the temperature is raised. Cryofibrinogen is an abnormal fibrinogen precipitated by cold; the significance of cryofibrinogen is less certain, but it is often associated with malignancy. Cryoglobulins are often confused with cold agglutinins, which are antibodies that agglutinate erythrocytes in the cold and are strongly associated with *Mycoplasma* infection.

Detection of cryoglobulins requires a clotted blood sample to be taken and kept at 37°C until clot retraction has taken place; in practice this means transporting samples in a vacuum flask containing water at 37°C. Cryofibrinogen can be detected in samples containing ethylenediamine tetra-acetic acid (EDTA); heparin should not be used because some fibrinogens are heparin insoluble.

Specific antibodies

Specific antibodies to bacterial, viral and fungal allergens are useful diagnostic tests for the assessment of the appropriateness of the humoral immune response. Tests can be carried out to exposure antigens and to deliberate challenges with vaccines (no live vaccines should be used in patients with any form of known or suspected immunodeficiency). The use of polysaccharide antigens such as pneumococcal capsular polysaccharide is particularly valuable as a robust test for humoral immune deficiency, as failure of responsiveness may occur even when total immunoglobulins and IgG subclasses are normal.

Precipitating antibodies to fungi are useful as diagnostic tests for fungal infection, although chronic mucocutaneous candidiasis is often accompanied by very high levels of *Candida* precipitins despite poor or absent T-cell responses, demonstrated by delayed hypersensitivity testing or *in vitro* antigen-specific T-cell proliferation (see below).

Complement assays

Complement components C3 and C4 are usually measured routinely by nephelometry or turbidimetry and can be assayed rapidly. Both are acute-phase proteins and will rise in chronic infection or inflammation by about 10%. C4 null alleles are common, resulting in reduced C4; as there is an ancestral gene duplication there are two C4 genes (four alleles), C4A and C4B. As a rule of thumb, two null alleles give a C4 level at the lower end of the normal range, while three null alleles give a level of half the lower end of the normal range, assuming there is no excess consumption. Factor B, from the alternate pathway, can be measured by automated analyser, although in routine practice this adds little useful clinical information. MBP from the lectin pathway can also be readily measured but the clinical utility is uncertain, except in the investigation of recurrent infections, where deficiency in MBP may be a co-factor with other immunological deficiency.

There is no role for measurement of immune complexes. Immune complexes can be readily detected in normal healthy individuals and the assays are difficult to standardize. Measurement of stable complement breakdown products such as C3d is more valuable as a determinant of complement turnover (Table 10.8).

Investigation of complement component deficiencies, which are associated with increased susceptibility to neisserial infection and atypical SLE-like disease, should be undertaken with haemolytic assays of complement that test both the classical and alternate pathways: CH_{100}/CH_{50} and $APCH_{100}$/$APCH_{50}$. These assays demonstrate intact complement cascade pathways through lysis of red cells. In the case of CH_{100}/CH_{50}, antibody-coated red cells are used to fix complement via the classical pathway; for the alternate pathway $APCH_{100}$/$APCH_{50}$, guinea pig erythrocytes are used, which can uniquely bind the alternate

Table 10.8 Patterns of complement abnormalities.

Complement pattern	Associated conditions
C3, C4 raised	Acute phase: infection, inflammation
C3, C4 reduced, C3d increased	Increased complement turnover via classical pathway (antibody or MBP mediated)
C3 reduced, C4 normal/high, C3d increased	Increased complement turnover via alternate pathway (endotoxin) Post-streptococcal glomerulonephritis (up to 6 weeks); C3 nephritic factor (> 6 weeks: type II membranoproliferative glomerulonephritis)
C3 normal, C4 reduced, C3d normal	C4 null alleles, C1-esterase inhibitor deficiency, C4-nephritic factor, mixed essential cryoglobulinaemia (HCV)

HCV, hepatitis C virus; MBP, mannan-binding protein.

pathway components. Both tests rely on an intact terminal lytic sequence. Both tests must be done in parallel to identify the site of any deficient component. Reduced haemolytic function will be seen where there is excessive complement consumption, although absent haemolysis will be found where there is a component deficiency. The exception is C9 deficiency, which permits slow haemolysis via the membrane attack complex C5–8. This deficiency is rare in Caucasians but is common in Japan. Individual components can then be measured depending on which part of the complement cascade is likely to be affected. It is difficult to identify C2 deficiency, which often presents with atypical cutaneous lupus (Ro antibody positive), because active lupus without C2 deficiency will reduce C2 levels due to activation of the classical pathway by antigen–autoantibody complexes. Ideally one needs to carry out testing at a time when clinical disease is quiescent, although this is often difficult to achieve.

C1-esterase inhibitor deficiency leads to a clinical syndrome of angio-oedema *without* urticaria, i.e. hereditary angio-oedema, an autosomal dominant condition. There is no value in screening patients for C1-esterase inhibitor deficiency where typical urticaria is seen. Patients with hereditary angio-oedema all have reduced C4 levels even between attacks; during attacks, C4 levels become undetectable. Measurement of C1-esterase inhibitor is therefore unlikely to be helpful if C4 is normal. Individuals with type I hereditary angio-oedema (85%) have a non-functioning C1-esterase inhibitor gene, while in type II (15%) there is a point mutation at the enzyme active site, leading to loss of function of the protein. Both immunochemical and functional assays for C1-esterase inhibitor are available. Angio-oedema has also been reported as a consequence of the rare deficiency of C4-binding protein.

Acquired angio-oedema may be seen in the older population, in association with the presence of paraproteins or autoimmune disease. In such cases checking for autoantibodies associated with SLE and measuring immunoglobulins and performing serum electrophoresis will give clues to the underlying diagnosis. C2 levels are said to be reduced in hereditary angio-oedema but normal in acquired angio-oedema, but this is not reliable.

Acute-phase proteins

Measurement of acute-phase proteins is an essential part of the investigation of sick patients. Measures of the acute phase include erythrocyte sedimentation rate (ESR), plasma viscosity, CRP, orosomucoid (α_1-acid glycoprotein), SAA and albumin. However, these measures are *not* interchangeable, and more than one marker is usually required. Albumin is a negative acute-phase protein, i.e. serum levels decrease during the inflammatory process. Transferrin behaves similarly. Most other proteins increase during an inflammatory process, although the increase may only be of the order of 10%, for example C3 and C4. In selecting suitable measures for clinical use, it is essential to choose markers that are easily measurable (preferably with automated equipment) and cheap and which have a wide dynamic range, i.e. there is a large difference between normal and abnormal values. The ESR has a dynamic range of 15 (10–150), while the CRP has a dynamic range of 100 (4–400). SAA has a similar dynamic range to CRP but is a less widely available and more expensive test, so has little additional value. Orosomucoid has a dynamic range of 2 so is unsuitable for routine use, although it has been previously supported as a more specific marker in inflammatory bowel disease. There is, however, no evidence that it performs better than CRP. Plasma viscosity has been promoted as equivalent to ESR but also has a poor dynamic range (2); its use is specifically for investigation and monitoring of hyperviscous states occurring in myeloma, especially IgA myeloma, and Waldenström's macroglobulinaemia.

Contrary to popular belief, CRP and ESR are not interchangeable. The relationship between ESR and CRP is similar to that between HbA_{1c} and glucose. The ESR rises only slowly after the onset of an acute insult and remains raised for several weeks after, being largely dependent on serum fibrinogen levels, a long-lived circulating protein. CRP on the other hand rises within hours and has a short half-life (6–8 h), meaning that levels also fall rapidly after a successful therapeutic intervention. Accordingly, CRP is appropriate for day-to-day monitoring, whereas ESR changes little in this time frame. At any given time,

CRP gives a picture of events of the previous 12 h, while ESR clarifies events of the previous 2 weeks. There are diseases, such as active SLE, where the two markers move asynchronously, with a significantly elevated ESR but little if any rise in CRP, unless infection is also present. Occasional patients have been described whose CRP range is reset, so that their acute-phase response takes place within the 'accepted' normal range. This is seen sometimes in giant cell arteritis, and makes monitoring difficult.

Detection of autoimmunity

Detection of the presence of autoantibodies can be performed by direct or indirect immunofluorescence (usually the cheapest and easiest method), solid phase assays, enzyme-linked immunosorbent assay (ELISA) and radioimmunoassay and, in some cases, flow cytometry. In all cases it is essential that the assay system has an appropriate threshold to reduce the risk of false-positive results. A number of autoantibodies may be found at low levels in apparently healthy individuals (e.g. rheumatoid factors, anti-Ro antibodies) and the prevalence of incidental positives rises with increasing age.

Nuclear and related antigens

A very large range of nuclear antigens have been identified as targets for autoimmune processes. Not all of these have identifiable clinical utility. Table 10.9 identifies the most important antigens and their clinical significance. Most of these can be detected by immunofluorescence using either rodent tissue or a human epithelial cell line (Hep2) (Fig. 10.3). Hep2 cells have the advantage of having a large nucleus in which patterns of staining can be readily identified. Genetically modified Hep2 cells are also available, engineered to have higher levels of expression of Ro antigen. Rodent tissue tends to have low levels of Ro antigen and it is also saline soluble so can be lost during the staining procedure. When rodent tissue was used exclusively for the detection of antibodies to nuclear antigens, this loss of Ro accounted for the high percentage of patients classified as antinuclear antibody-negative lupus. The increased use of Hep2 cells has significantly reduced the number of lupus patients in whom no antinuclear antibodies can be detected. Antibodies to extractable nuclear antigens were originally identified by counter-current immunoelectrophoresis; however, with the availability of cloned recombinant antigens, solid

Table 10.9 Nuclear and related antigens.

Staining pattern on rodent liver and Hep2 cells	Antigens recognized	Clinical associations
Homogeneous nuclear staining	dsDNA	SLE
	Histones (H2A, H2B)	SLE, drug-induced LE
	Mi-2	Steroid-responsive dermatomyositis
Fine speckled nuclear staining	Ro (52 kDa, 60 kDa antigens, distinguished using immunoblotting)	Sjögrens's syndrome, SLE
	La (48 kDa protein)	Primary Sjögrens's syndrome, SLE
Coarse speckled nuclear staining	U1-RNP	Undifferentiated connective tissue disease (anti-dsDNA and anti-Sm negative)
	Sm (B′/B and D proteins shared between U1, U2 and U4–U6 RNPs)	SLE
	Nuclear matrix (coarse speckles indicates multiple proteins)	SLE, undifferentiated connective tissue disease
Atypical speckled nuclear staining	Scl-70	Systemic sclerosis (severe form)
Nucleolar staining	RNA Pol I (speckled nucleolar staining)	Diffuse systemic sclerosis
	PM-Scl (PM-1) (homogeneous nucleolar staining)	Myositis–scleroderma overlap
	Fibrillarin (clumpy nucleolar staining)	Systemic sclerosis (lung and heart but few joint problems)
Cell-cycle-specific nuclear speckles	PCNA	SLE
Centromere (dividing cells)	CENA, CENB, CENC	Limited scleroderma (CREST syndrome)
Fine cytoplasmic speckled staining	tRNA synthetases (Jo-1, PL-7, PL-12, EJ, OJ)	Myositis (antisynthetase syndrome)
Coarse cytoplasmic speckled staining	Signal recognition peptide	Myositis
Ribosomal staining	rRNP	SLE (nephritis)
	Ribosomal P protein	SLE (cerebral)

CREST, calcinosis, Raynaud's phenomenon, (o)esophageal involvement, sclerodactyly, telangiectasia; dsDNA, double-stranded DNA; LE, lupus erythematosus; PCNA, proliferating cell nuclear antigen; RNP, ribonucleoprotein; SLE, systemic lupus erythematosus.

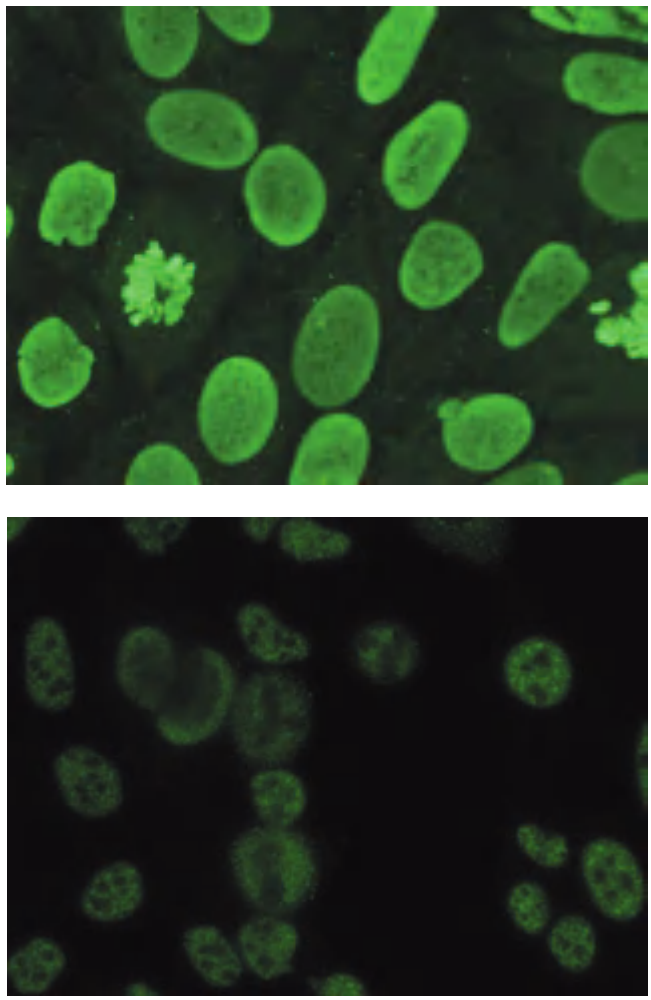

Fig. 10.3 (a) Homogeneous antinuclear antibody demonstrated by indirect immunofluorescence on Hep2 cells. (b) Coarse speckled pattern seen with anti-RNP antibodies on Hep2 cells.

phase assays are widely used to identify specificities of nuclear antibodies. The wide variety of different assays has meant that there is often no good agreement between the different assays and there is no currently accepted 'gold standard'. Similar problems have arisen with antibodies to double-stranded DNA (dsDNA), although here the gold standard has been the Farr assay; ELISA does not always produce satisfactory results due to degradation of dsDNA to single-stranded DNA or reverse-wound DNA (Z-DNA). Immunofluorescence on *Crithidia* has been proposed as a suitable test for dsDNA as its kinetochore contains pure dsDNA. The assay is, however, relatively insensitive and is now less widely used.

Detection of antibodies to nuclear components is diagnostically valuable. However, with the exception of antibodies to dsDNA, serial monitoring of antibody titres or arbitrary ELISA units provides no clinically useful information. Changes in levels of dsDNA antibodies do have some predictive value: a rising titre frequently heralds relapse, while a falling titre is usual where therapy has been successful. However, the absolute value has no relevance to disease activity. It is likely that there are subgroups of dsDNA antibodies, as not all patients with SLE develop renal disease. Currently available diagnostic tests do not yet distinguish these different anti-DNA antibodies.

The significance of the titre of an antinuclear antibody is dependent on the age of the patient: low-titre and clinically insignificant antibodies are seen in healthy elderly patients; conversely, low-titre antibodies are often significant in children. Laboratories should provide age-specific ranges.

Antinuclear antibodies of varying specificities and sometimes in high titre have been reported in association with infection, especially adenovirus and Gram-negative bacteria. Antibodies to dsDNA are rarely found under these circumstances. It is critically important to interpret the laboratory results in the light of the full clinical picture. Similarly, antibodies can appear in association with malignancy. In some cases, these markers are useful identifiers of paraneoplastic phenomena (anti-Hu, anti-Yo, anti-Ri in neurological disease).

ANCA antigens and the diagnosis of vasculitis

The detection of antineutrophil cytoplasmic antibodies (ANCA) has been an important step forward in the diagnosis of autoimmune vasculitis. The substrate for detection is ethanol-fixed human neutrophils. Other fixation techniques such as formaldehyde and acetone are not reliable and should not therefore be used. Three patterns are recognized: cytoplasmic granular staining (C-ANCA), atypical cytoplasmic staining (X-ANCA) and perinuclear staining (P-ANCA). As the latter can be difficult to distinguish from nuclear staining, Hep2 cells should also be used as a control for the presence of nuclear antibodies. Target antigens have been identified: proteinase 3 is the main target antigen for C-ANCA and myeloperoxidase is the main antigen for P-ANCA. Solid phase confirmatory assays are now available for these antigens. Other target antigens that have been identified include cathepsins, lactoferrin and neutrophil elastase. It is important to identify X-ANCA, as laboratories frequently confuse this pattern (which is not associated with antibodies to proteinase 3) with a true C-ANCA.

Of patients with Wegener's granulomatosis, 85% have C-ANCA, 10% P-ANCA and 5% will be seronegative. Of patients with Churg–Strauss syndrome, 10% have C-ANCA and 60% P-ANCA. In microscopic polyangiitis, 45% have C-ANCA and 45% have P-ANCA.

ANCA may also be seen in non-vasculitic conditions, including inflammatory bowel disease and sclerosing cholangitis. Prolonged neutrophil activation, as in infection, may also cause ANCA to appear, for example in cystic fibrosis. Careful interpretation of results is therefore

required. It appears that ANCA do not appear as part of the ageing process, and therefore their detection in the elderly is likely to be significant. There is no correlation between disease severity and ANCA titre, although rising titres are thought to herald relapse. IgA ANCA have been reported in some IgA-related vasculitides such as Henoch–Schönlein purpura and IgA nephropathy, although the significance of this is uncertain.

Rheumatoid factor

As previously noted, rheumatoid factors are seen as part of the normal immune response to infection. They also occur in the ageing population, without clinical significance, and as a specificity of monoclonal proteins (often with cryoglobulin properties). Although the assay is widely requested, its utility as a screening test is nil. Its major value is as a predictor of severe extra-articular disease in those patients with known clinical rheumatoid arthritis, where high levels of rheumatoid factors are predictive.

Other organ-non-specific antigens

Immunofluorescence using composite tissue blocks containing kidney, liver and stomach will also identify other organ-non-specific antibodies such as mitochondrial antibodies (primary biliary cirrhosis), liver–kidney microsomal antibodies (drug-induced hepatitis), ribosomal antibodies (see Table 10.9), smooth muscle antibodies (autoimmune hepatitis) and gastric parietal cell antibodies (pernicious anaemia).

Organ-specific antigens (including skin)

Organ-specific autoantibodies can be detected by direct immunofluorescence on biopsies and also by indirect techniques using animal tissues (primate or rodent). These include autoantibodies against endocrine tissues, as seen in the autoimmune polyglandular syndromes, some of which are associated with chronic mucocutaneous candidiasis (Table 10.10).

Autoantibodies to skin (see Chapter 41) are detected on primate oesophagus by indirect immunofluorescence. Titres and serial monitoring do not appear to have any great clinical significance. The same substrate is also used to detect endomysial antibodies of the IgA class, as a diagnostic test of high sensitivity and specificity in gluten-sensitive enteropathy, including dermatitis herpetiformis. As coeliac disease is associated with an increased incidence of IgA deficiency, screening for IgA deficiency is required; under these circumstances, IgG endomysial antibodies carry the same diagnostic significance. The target antigen has been identified as tissue transglutaminase, and solid phase assays for antibodies to this enzyme are available. There is no evidence that these are diagnostically superior to endomysial antibodies. Gliadin antibodies (IgG and IgA) are non-specific tests that should not be used for the diagnosis of gluten-sensitive enteropathy. Endomysial antibodies disappear gradually when strict gluten avoidance is instituted, but reappear after gluten challenge; they are therefore valuable as a tool to monitor compliance.

Autoimmunity in urticaria

It has been claimed that a significant proportion of patients (up to 35%) with chronic urticaria may have autoantibodies to the α subunit of the IgE receptor, and a further 5–10% may have autoantibodies to IgE itself. Unfortunately the solid phase assays used to demonstrate the presence of these autoantibodies have lacked appropriate controls. Studies using immunoblots have confirmed that such autoantibodies may occur but have shown them to be commonly present in low concentrations in the serum of otherwise healthy individuals and also at higher titre in patients with blistering skin diseases and connective tissue diseases. Their clinical utility is doubtful and there are no commercial validated assays available.

A small proportion of patients with chronic urticaria have hypocomplementaemic urticarial vasculitis. These patients have systemic features and may also suffer from angio-oedema, ocular inflammation and chronic obstructive pulmonary disease in the absence of a smoking history. It may be associated with evidence of an underlying connective tissue disorder. C3 and C4 are usually reduced and autoantibodies to the collagenous region of C1q can be demonstrated, although these are also found in

Table 10.10 Autoimmune syndromes.

Syndrome	Major criteria	Minor criteria
Type I (autoimmune polyendocrinopathy, candidiasis, ectodermal dysplasia)	Candidiasis, adrenal failure, hypoparathyroidism	Gonadal failure, alopecia, malabsorption, chronic hepatitis
Type II (Schmidt's syndrome)	Adrenal failure, thyroid disease, type I diabetes mellitus	Gonadal failure, vitiligo, non-endocrine autoimmunity (myasthenia gravis)
Type III	Thyroid disease	Type I diabetes mellitus *or* pernicious anaemia *or* non-endocrine autoimmunity (myasthenia gravis)

patients with SLE (especially if glomerulonephritis is present) who do not have urticarial lesions. However, all patients with clinical features of hypocomplementaemic urticarial vasculitis have the antibody. Routine assays are available for anti-C1q antibodies, although these are prone to interference from immune complexes and DNA fragments.

Cellular tests

Delayed-type hypersensitivity testing

In vivo testing for type IV reactions is commonly practised in dermatology departments in the form of patch testing for contact dermatitis. This is a useful and reliable test, and is the type IV counterpart of skin prick testing. Allergens are applied under aluminium discs taped to the back for 48 h and then removed. Allergen-specific T cells are then recruited by allergen-bearing APCs in the epidermis, accumulating over the next 48–72 h. The infiltrate is palpable, and there is often blistering and inflammation at the site due to cytokine release and recruitment of inflammatory cells. In the case of photo-allergy, allergens are applied in duplicate, with one panel being exposed to UV light after removal of the discs, while the duplicate panel is protected from light.

Variants of this type of test include the well-known Heaf test for T-cell immunity to *Mycobacterium tuberculosis*, in which a multipronged applicator introduces purified protein derivative (PPD) into the dermis. Similar tests are used by clinical immunologists to test for T-cell immunity to *Candida* and other protein antigens, as part of the work-up for suspected T-cell immunodeficiency. Access to antigens in a form suitable for (unlicenced) clinical use limits the usefulness of this type of testing.

Cell marker analysis (whole blood) (Table 10.11)

Lymphocyte subpopulations in peripheral blood are readily measurable. This test is carried out by flow cytometry, ideally using a single platform instrument capable of producing absolute counts for the major lymphocyte populations. There is a wide range of available surface markers, but in clinical practice a relatively restricted panel provide all the required information. This type of testing has no intrinsic diagnostic value in the absence of a clear clinical question, such as whether a child has immunological features compatible with SCID. Testing lymphocyte subsets is often carried out as a surrogate (without informed consent) for retroviral disease. As well as being ethically unjustified, this is inappropriate because changes in $CD4^+$ T cells are seen in a wide range of acute and chronic viral infections as well as in acutely sick patients and are not specific to human immunodeficiency virus (HIV) disease. In patients with known HIV infection, monitoring of cell counts provides important information on risks of opportunistic infections, as different infections appear at different points in the decline of the $CD4^+$ T-lymphocyte count. Monitoring is also important in assessing the immune reconstitution seen in response to treatment with highly active antiretroviral therapy. Patients on immunosuppressive therapy with cytotoxic agents should in the first

Table 10.11 Surface markers on leukocytes.

Surface marker	Cell type	Examples of abnormalities
CD19 (or CD20)	B lymphocytes	Absent in X-linked agammaglobulinaemia, BLNK deficiency and B^- SCID; reduced in common variable immunodeficiency
CD16/56	NK cells	Elevated in acute infections; rare deficiency reported
CD3	T cells	Reduced/absent in severe combined immunodeficiency
CD4	T helper cells	Reduced in viral infections including HIV
CD8	T cytotoxic cells	Raised in acute/chronic viral infections; reduced/absent in ZAP-70 deficiency
CD25	IL-2 receptor	Expression measured on $CD4^+$ cells as marker of T-cell activation (inflammation and infection)
MHC class II (DR common)	Constitutively expressed on B cells, activation marker on T cells	Measured on $CD4^+$ cells as marker of T-cell activation (inflammation and infection); absent in class II MHC deficiency
MHC class I (W6/32, common)	All nucleated cells	Absent in MHC class I deficiency
CD45RA	Naive T cells	Monitoring reconstitution post BMT
CD45RO	Memory T cells	Monitoring reconstitution post BMT
CD11a,b,c/CD18	Adhesion molecules (lymphocytes, neutrophils)	Leukocyte adhesion molecule deficiency type I
CD15	Adhesion molecule (macrophages, neutrophils)	Leukocyte adhesion molecule deficiency type II
CD21/CD35	Complement receptors (with CD11b, c) on phagocytic cells and B lymphocytes	Complement receptor deficiency

BLNK, B-cell linker protein; BMT, bone marrow transplantation; HIV, human immunodeficiency virus; IL, interleukin; MHC, major histocompatibility complex; NK, natural killer; SCID, severe combined immunodeficiency.

instance be monitored with absolute lymphocyte counts obtained from a standard full blood count, but if very low counts occur then checking the subpopulations is helpful for determining whether any additional prophylaxis against infection is required.

It is important to remember that analysis of peripheral blood lymphocytes provides a snapshot of lymphocytes in transit only, and gives no information about immunological processes going on in other tissues. Furthermore, there are circadian changes in blood lymphocytes, so the timing of samples has a significant effect on cell counts; this is particularly important for serial monitoring.

More extensive panels are used for the identification of leukaemias and this is usually done in parallel with examination of bone marrow. Here absolute counts are not necessary as the phenotype of the bulk population is required.

In vitro proliferation assays

In vitro T-cell function testing is complex, labour-intensive, time-consuming and difficult to quality control. Lymphocytes must be purified from blood by density gradient centrifugation and set up in sterile culture for periods of 3–7 days. Accordingly, its use is restricted to diagnosis and monitoring of primary immunodeficiencies. Abnormalities in these assays are not necessarily translated into clinical symptoms. The gold standard is still tritiated thymidine uptake. Alternative methods using flow cytometry have been developed based on analysis of cellular DNA content and expression of activation markers such as CD69 and transferrin receptor, but these do not provide the same information or have the same clinical correlations as tritiated thymidine incorporation. Panels of polyclonal stimuli are used that activate T or B cells at different points in the cascade, enabling the cellular location of defects to be identified. These include phytohaemagglutinin A, pokeweed mitogens and concanavalin A, plant lectins that bind to oligosaccharides on cell surface proteins; anti-CD3 (± IL-2), which mimics activation via the TCR; and phorbol esters, which activate the intracellular enzyme protein kinase C in the presence of calcium (calcium ionophores are used). Antigen can also be used but as the frequency of antigen-specific T-cell precursors in peripheral blood is very low, responses are very small compared with polyclonal stimuli. Typically, *Candida* antigens, tetanus toxoid and viral antigens such as those from herpes simplex virus (HSV), cytomegalovirus (CMV) and varicella-zoster virus (VZV) are used.

Results are expressed in counts per minute (cpm) and also as a stimulation index (SI) calculated by comparing the control incorporation with the stimulated incorporation. It is essential that a medium control is always performed and that a normal healthy control is run in parallel as a reagent check. There is a large range of normal responses and laboratories should develop their own acceptable ranges. However, as a general principle polyclonal stimuli should give an SI greater than 10, while for antigen an SI of 2–4 is acceptable.

Other functional assays have been developed for the flow cytometer, including assays for apoptosis, valuable in the Canale–Smith syndrome, and activation-induced expression of CD40 ligand (CD154), valuable in the X-linked hyper-IgM syndrome.

Neutrophil function tests

Robust assays exist for the identification of defects of neutrophil oxidative metabolism. The historic assay is the nitroblue tetrazolium reduction test, which was performed as a slide assay. This has been modified by the application of similar fluorescent dyes for use on the flow cytometer. Similarly, flow cytometric assays exist for measuring neutrophil and macrophage phagocytosis, using fluoresceinated opsonized bacteria. However, these assays are highly susceptible to the clinical state of the patient, and abnormal results are obtained in patients with active or recent infection. Assays of neutrophil chemotaxis are described but these are impossible to standardize and there is such a wide range of 'normal' results that interpretation of clinical results is no better than guesswork.

Cytokine assays

Measurement of cytokines by solid phase assays is well established as a research tool. However, measurement of cytokines in clinical material has not been shown to be diagnostically helpful as the assays are unreliable when used in this way, mainly due to the natural occurrence of soluble cytokine receptors and anticytokine antibodies in body fluids that interfere with binding. The use of surrogates such as CRP is more robust. Cytokine production *in vitro* can be used as an adjunct to T-cell proliferation assays. Intracellular cytokine production can be measured using the flow cytometer, and cytokine production can be tied to particular cell types by simultaneous surface staining with monoclonal antibodies. There seems to be little gain in clinically useful information over and above that derived from lymphocyte subset analysis.

Molecular immunology

The use of molecular genetic techniques to identify immunoglobulin and TCR gene rearrangements has been essential in developing the understanding of lymphoproliferative conditions. These techniques can be as easily applied to solid tissue extracts as to peripheral blood cells. Flow cytometric methods have also been used to identify clonality of T cells in peripheral blood by examining Vβ chain usage with panels of monoclonal antibodies.

Immunological therapy

Immunological therapy has for many years rested on a small group of cytotoxic drugs supplemented with corticosteroids. These remain important, but advances in our understanding of basic immunology and parallel technical advances have opened the door to new and exciting immunological therapies with potentially fewer side effects. Nonetheless, steroids and cytotoxics will remain important for the foreseeable future.

Corticosteroids

These have both anti-inflammatory and immunosuppressive effects. The anti-inflammatory effect is mediated by increased production of lipomodulin, an inhibitor of phospholipase A_2, the enzyme essential to the formation of the arachidonic acid pathway metabolites involved in inflammation (leukotrienes and prostaglandins). Phagocytosis is also inhibited, and production of IL-1 and TNF-α is reduced. At higher doses, steroids are lymphotoxic, via increased apoptosis. Lymphocyte proliferation is inhibited and cytokine production is reduced, especially by Th1 cells.

Methotrexate

Methotrexate is a folate antagonist, used in weekly (low) doses as an immunosuppressant. It is converted to long-lived intracellular polyglutamate metabolites, which are potent inhibitors of dihydrofolate reductase; this accounts for the cumulative toxicity. However, it is not clear if this activity accounts for the immunosuppressive and anti-inflammatory activities. One suggested mechanism is blockade of transmethylation reactions, with increased lymphotoxic concentrations of *S*-adenosyl-homocysteine (one of the toxic metabolites that accumulates in adenosine deaminase deficiency, a cause of SCID). Another postulated mechanism involves the inhibition of aminoimidazole carboxamide ribonucleotide (AICAR) transformylase, which leads to an increase in cellular AICAR riboside, which also inhibits adenosine deaminase and leads to an increase in adenosine, a powerful inhibitor of lymphocyte proliferation and cytokine production that acts via specific adenosine receptors.

Azathioprine

Azathioprine, a pro-drug of 6-mercaptopurine, inhibits DNA synthesis and also the purine salvage pathway. Its conversion to thio-IMP suppresses the conversion of IMP to AMP, and metabolism of thio-IMP to thioguanine leads to the latter's incorporation into, and consequent damage to, DNA. Azathioprine has a broad range of immunological activities: reduced NK-cell function, reduction in $CD8^+$ T cells, inhibition of lymphocyte proliferation and cytokine production, inhibition of antibody responses (primary > secondary) and impaired neutrophil chemotaxis. Side effects are related to levels of the enzyme thiopurine methyltransferase (TPMT). Patients with a homozygous deficiency of TPMT are highly susceptible to prolonged bone marrow toxicity from even tiny doses of azathioprine, whereas heterozygotes can tolerate reduced doses of the drug with care. Checking red cell TPMT levels before treatment allows identification of those who will develop severe toxicity so they can be spared a trial of therapy. Long-term use may cause a persistent profound lymphopenia and severe hypogammaglobulinaemia.

Other drugs operating on these pathways are fludarabine and cladribine. These have been mainly used in the treatment of haematological malignancies, but their potent immunosuppressive effects are likely to be of considerable value in managing autoimmune disease, with appropriate tailoring of the doses.

Mycophenolate mofetil

Mycophenolate is a potent inhibitor of the enzyme IMP dehydrogenase and therefore works on both *de novo* purine synthesis as well as purine salvage, i.e. the same pathways affected by azathioprine. Its range of effects is therefore very similar to azathioprine. In addition, the reduction in the guanine nucleotide pool decreases the synthesis of oligosaccharide chains on surface receptors involved in adhesion and migration.

Cyclophosphamide

Cyclophosphamide is a pro-drug converted by the liver into phosphoramide mustard, an alkylating agent that acts on guanine residues in DNA and which increases cross-linking of DNA strands, thus preventing DNA replication and transcription. It is a potent inhibitor of lymphocyte proliferation, reducing antibody production, particularly primary antibody responses. It is more active against $CD4^+$ T cells, and has minimal effects on NK cells. Significant lymphopenia occurs on treatment with cyclophosphamide, and prophylactic antibiotics to prevent opportunistic infections are recommended.

Leflunomide

This is a pro-drug that is converted *in vivo* into a potent inhibitor of the enzyme dihydro-orotate dehydrogenase, an enzyme required for the synthesis of pyrimidines. It prevents lymphocyte proliferation. As T cells are dependent on *de novo* synthesis of pyrimidines, they are uniquely sensitive to leflunomide. At high doses it is also thought to

inhibit tyrosine kinases, inhibiting the cascade linked to the IL-2 receptor. It has a very long half-life, as it is highly protein bound.

Hydroxychloroquine and mepacrine

The actions of the antimalarials are not entirely certain, although they reduce the production of cytokines, particularly the pro-inflammatory cytokines IL-1, TNF-α and IFN-γ. They are also concentrated into lysosomes, where they alter the pH and interfere with antigen processing.

Thalidomide

Thalidomide is a potent inhibitor of TNF-α production by monocytes, interfering with gene transcription. It also decreases adhesion molecule expression and inhibits IFN-γ production through preferential stimulation of Th2 cells. Oxpentifylline has similar but weaker properties.

Ciclosporin, tacrolimus and sirolimus

Ciclosporin binds to cyclophilin, an intracellular peptidyl-prolyl *cis-trans* isomerase, and the resulting complex inhibits cytoplasmic calcineurin, a calcium-activated serine–threonine phosphatase. This in turn prevents dephosphorylation of NF-AT (nuclear factor of activated T cells), which normally binds to DNA to enhance the transcription of IL-2 and other cytokines, and CD40 ligand in activated T cells. Dephosphorylation prevents the normal translocation of NF-AT from cytoplasm to nucleus, and inhibits the production of IL-2 and other molecules normally associated with activation of T cells. T cells are particularly sensitive to the effects of ciclosporin, because of low levels of calcineurin. NK cells and B cells are also affected by ciclosporin. The effect is reversible, so overenthusiastic immunosuppression can be rapidly reversed if required. Monitoring of trough blood levels is possible and enables doses to be accurately controlled; levels required for control of autoimmune diseases are lower than those required to prevent allograft rejection.

Tacrolimus binds to a similar peptidyl-prolyl *cis-trans* isomerase, FKBP12, and this has a similar effect on calcineurin. Clinically and immunologically, the effects of tacrolimus are similar to those of ciclosporin.

Sirolimus (rapamycin) also binds to FKBP12, but appears to inhibit an enzyme called mTOR, which is involved in transmission of signals via the IL-2 receptor. Sirolimus and ciclosporin appear therefore to be able to act synergistically by inhibition both of IL-2 production and signalling via IL-2.

Topical formulations of these drugs and related novel compounds are now being introduced for use in immunologically mediated skin disease.

Biological therapy (monoclonal antibodies, chimeric molecules, cytokines, cytokine antagonists, intravenous immunoglobulin)

There has been great interest in the use of monoclonal antibodies for the treatment of disease. The first agent used clinically was a murine anti-CD3 (Muromonab), although its use was limited by its murine origin, which usually led rapidly to the development of neutralizing antibodies. However, it was recognized as a potent immunosuppressive agent and used in clinical allograft rejection. Genetic engineering of monoclonal antibodies now allows the murine binding site to be inserted into a human immunoglobulin framework, while retaining its original specificity. This reduces but does not completely abolish the antimouse response. Antibodies to the panleukocyte antigen CD52 are potent immunosuppressive agents (Campath), producing a prolonged lymphopenia. Many surface molecules are now the targets of experimental monoclonal antibody therapies. Particular targets of interest are the co-stimulatory molecules B7–CD28 and CD40–CD40 ligand. Because of its inhibitory nature, CTLA-4 has also been used in the form of a hybrid fusion molecule with human immunoglobulin.

An alternative strategy has been to target the cytokines or their receptors. The most effective examples of this have been the use of the humanized anti-TNF monoclonal antibody Infliximab and the TNF-receptor Ig Fc fusion protein etanercept, both of which are highly active in suppressing TNF-based inflammatory reactions such as Crohn's disease and rheumatoid arthritis. There has been concern, however, that use of these agents may increase autoimmunity and also susceptibility to infection, particularly mycobacterial infection. Other cytokine antagonists, such as the naturally occurring IL-1 receptor antagonist, which binds to IL-1 receptor but does not signal, are also being tested in clinical trials. Other targets for monoclonal antibodies in trials include IL-6 and IL-8.

There is a long history to the administration of cytokines in pharmacological doses, starting with IL-2, as adjuncts to chemotherapy for malignant disease. However, the benefits have been small and the side effects considerable. There may be some benefit from IL-2 in common variable immunodeficiency, used in a pegylated form to lengthen the circulating half-life, and in acquired immune deficiency syndrome (AIDS), to improve T-cell function. Administration of IFN-γ has been shown to be beneficial in chronic granulomatous disease, although the precise mechanism of action is unclear. IFN-α is valuable in treatment of chronic hepatitis C infection, with best results coming from combination therapy with the antiviral ribavirin. On the whole, however, cytokine therapy has been a disappointment. This is partly due to the considerable cytokine redundancy, with overlapping

functions from multiple cytokines, and partly because most of the cytokines act as short-range messengers; also, the total cytokine and chemokine milieu that a cell experiences determines its response. The same cytokine may therefore have different effects depending on which other cytokines are present. This scenario is difficult to replicate by pharmacological administration of single cytokines.

High-dose intravenous immunoglobulin is widely used as an immunomodulatory agent for autoimmune disease. It is likely that multiple mechanisms of action are involved, including modulation of cytokine release and function, antiproliferative effects, suppression of antibody production via idiotypic antibodies, inhibition of complement-mediated tissue damage and Fc receptor blockade. Problems with this type of therapy are that it is in short supply and has to be derived from human material, which poses risks of infection; the risks of transmission of prion disease are as yet unquantified. It has been widely used, including the treatment of bullous skin diseases, resistant urticaria and atopic dermatitis. None of these uses are yet licensed. In a shortage, priority for supplies should be given to its use in licensed indications and in properly conducted clinical trials.

Physical therapy (plasmapheresis, photopheresis, irradiation, immunoadsorption)

Plasmapheresis provides a rapid way of removing pathogenic autoantibodies. However, it must be combined with immunosuppressive therapy, as there is usually a rebound increase in autoantibody levels immediately following plasmapheresis. Modifications of plasmapheresis include the use of specific immunoadsorption columns in the extracorporeal circuit. These columns comprise a biocompatible substrate to which either protein A or specific antigen is coupled, enabling specific antibodies to be removed without removing essential antibodies necessary for host defence against pathogens. A further development is the use of photopheresis, in which psoralen-like drugs are administered and the extracorporeal circuit is then irradiated with UV light; this provides a potent method of suppression of lymphocytes. The main drawback of these methods is the need for expensive equipment and trained staff.

Low-dose irradiation is also immunosuppressive in doses below those used in the management of malignant disease. This can prove valuable where there is localized immunological disease, for example locally aggressive Wegener's granulomatosis.

Allergy therapy

The mainstay of symptomatic allergy relief is the reduction of mediator output by the use of steroids and mast-cell stabilizing drugs such as disodium cromoglycate and nedocromil, and the antagonism of released mediators by the use of antihistamines and leukotriene antagonists.

Reduction or abolition of allergic reactivity can be undertaken by specific allergen immunotherapy, using purified and standardized allergen extracts. The precise mechanism by which tolerance is induced is unclear. Initially, IgE levels increase before declining slowly. IgG4 antibodies are also produced and may have a blocking role. Alterations in T-cell function are also likely. The process is slow and optimum schedules have yet to be established. Maintenance therapy is required usually for several years. Most therapy is given by injection but there is some evidence that the sublingual route can be used, albeit requiring much larger doses of allergen. It is, however, very effective for seasonal allergic rhinitis due to grass and tree pollens, and is also effective for house-dust mite, cats (but not dogs) and venoms. There is some risk of anaphylaxis and therefore the treatment is suitable only for hospital use by experienced personnel. Current trials are investigating the use of peptides derived from key allergens as a way of inducing T-cell tolerance and therefore abolishing the IgE response. The peptides induce tolerance when injected because they are not presented in the correct way with co-stimulation. This effect may be enhanced by co-administration of IL-12 or IL-18, which induce IFN-γ and bias the immune response towards Th1.

Monoclonal antibodies to IgE have also been introduced into clinical trials with some success. These have been tested first in asthma, where the effects are modest, probably because non-IgE mechanisms are also prominent, but are likely to be more effective in rhinitis. Significant reductions in circulating IgE levels have been documented.

Transplantation

Stem cell transplantation after bone marrow ablative therapy as a treatment for severe autoimmune disease refractory to conventional immunosuppressive therapy is now being undertaken. Diseases include juvenile chronic arthritis and other severe connective tissue diseases such as scleroderma.

Further reading

The field of immunology is a colossal one and provision of up-to-date references in a textbook that takes 2 years from submission to publication is impossible. Accordingly, the list below indicates useful immunological references that provide more detailed discussion of the topics covered. Use of PubMed and Medline to obtain the latest information is strongly recommended.

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Photoimmunology

[T. Schwarz, pp. 10.29–10.37]

It is more than 25 years since the discovery that ultraviolet (UV) radiation can influence the immune system. Since then, numerous studies in the field of photoimmunology have tried to identify the biological impacts of UV-induced immunosuppression and the underlying mechanisms. The immunosuppressive effects of solar radiation are mostly due to medium-wavelength UV (UVB, 290–320 nm). Accordingly, the vast majority of photoimmunological studies have used UVB. There is recent evidence that long-wavelength UV (UVA, 320–400 nm) can also affect the immune system, although its effects are less pronounced. Hence, in this section the term UV refers mostly to UVB. If other spectra (e.g. UVA or UVC) have been used, they are mentioned specifically.

UV radiation induces local and systemic immunosuppression

Initial evidence that UV radiation influences the immune system was provided by the observation that UV radiation inhibits the immunological rejection of transplanted tumours. Skin tumours induced by chronic UV exposure in mice are highly immunogenic since they are rejected following transplantation into naive syngeneic hosts [1]. However, if the recipient animal is treated with immunosuppressive drugs, the inoculated tumours are not rejected but grow, implying that the rejection is immunological in nature. Rejection can also be prevented when the recipient mice are exposed to UV radiation instead of immunosuppressive drugs, clearly indicating that UV radiation can act in an immunosuppressive fashion (Fig. 10.4).

A similar effect can be observed in another immunological *in vivo* model, namely the induction of contact hypersensitivity (CHS). CHS represents a particular kind of delayed-type hypersensitivity response, induced by epicutaneous application of low-molecular-weight chemical compounds. Since these substances have to bind to proteins to exert antigenic features, they are called haptens. Painting of haptens on areas of skin that have been exposed to low doses of UV radiation (~ 1 J/m^2) does not induce CHS, whereas administration of the same compound to an unexposed site causes a normal CHS response [2]. Inhibition of CHS induction by UV radiation is associated with a reduction in the number of Langerhans' cells at the site of exposure [2,3]. Langerhans' cells are the key APCs in the skin and thus this finding indicates that UV radiation interferes with antigen presentation. Since the areas of hapten application and UV exposure are identical, this type of immunosuppression is called local (Fig. 10.5).

Local immunosuppression seems to be genetically determined in mice since suppression is only observed in particular strains (e.g. C3H/HeN, C57BL/6), while other strains (C3H/HeJ, Balb/c) respond with normal sensitization despite UV exposure. Accordingly the former are called UV-susceptible, the latter UV-resistant [4]. The phenotypic traits of UV resistance and susceptibility are inherited in a polygenic fashion; the relevant loci for polymorphic alleles are LPS and TNF-α [5]. Accordingly, TNF-α appears to be involved in the inhibition of CHS by low-dose UV radiation, since UV-mediated local

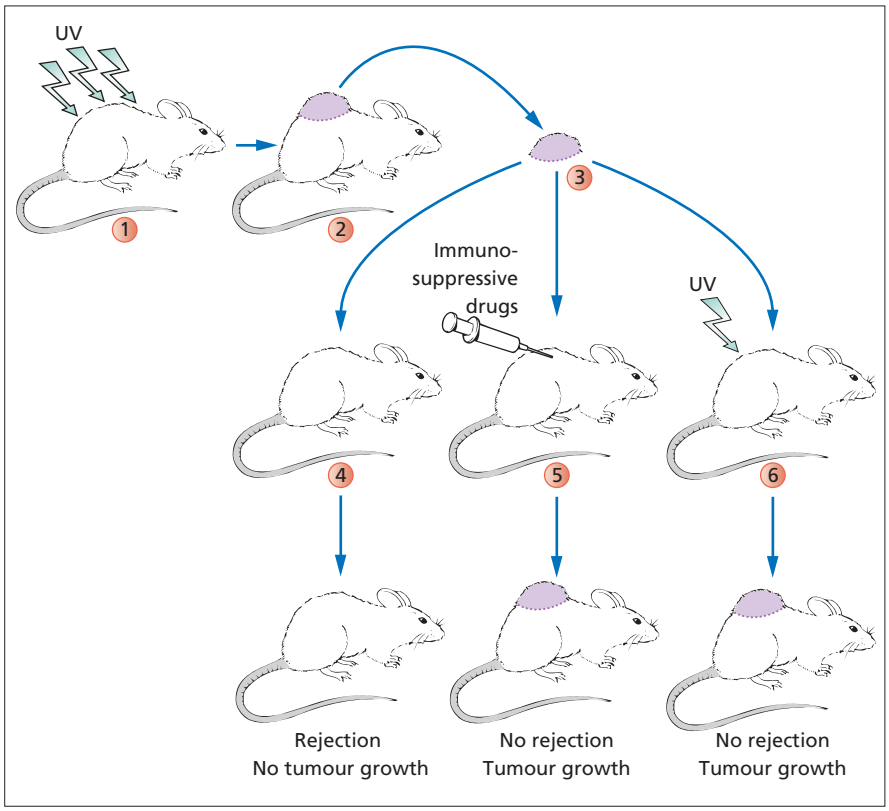

Fig. 10.4 UV radiation inhibits the rejection of immunogenic skin tumours. Chronic UV exposure (1) induces skin tumours (2). Upon transplantation (3), these tumours are rejected by naive syngeneic recipient mice (4). If recipient mice are treated with immunosuppressive drugs (5) or exposed to UV radiation (6), these tumours are not rejected but grow.

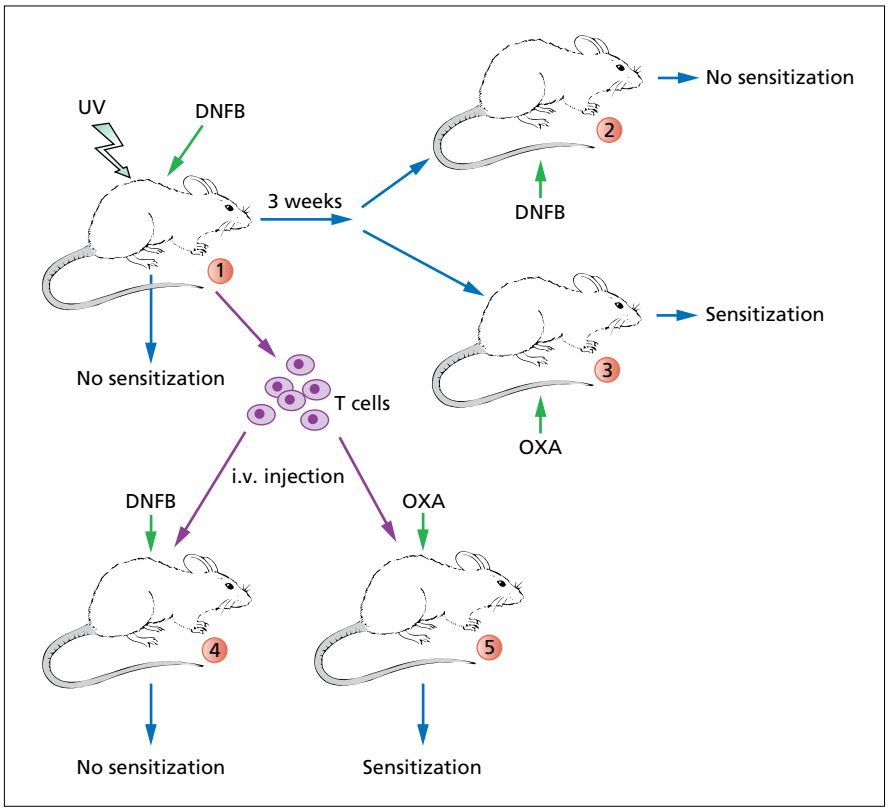

Fig. 10.5 UV radiation induces hapten-specific tolerance that can be adoptively transferred. Application of the hapten dinitrofluorobenzene (DNFB) on to UV-exposed skin does not result in sensitization (1). Reapplication of DNFB to non-UV-exposed skin of the same mice 3 weeks later again does not cause sensitization (2), indicating that tolerance has developed. However, animals can be sensitized against the unrelated hapten oxazolone (OXA), indicating that tolerance is hapten-specific (3). Intravenous injection of T cells obtained from mice that received DNFB on UV-exposed skin inhibits sensitization against DNFB of recipient mice (4). However, recipients can be sensitized against OXA (5), indicating that transfer of suppression is hapten-specific.

immunosuppression can be inhibited by the injection of neutralizing antibodies to anti-TNF-α [6]. However, since TNF-receptor-deficient mice can be immunosuppressed by UV radiation additional factors, other than TNF-α, might be involved in UV-induced local suppression [7].

Higher doses of UV in the range of 2 kJ/m^2 can also affect immune reactions initiated at distant non-UV-exposed sites. Accordingly, CHS cannot be induced in mice exposed to high doses of UV radiation even if the hapten is applied at unirradiated sites [8]. This type is called systemic immunosuppression. Systemic immunosuppression is certainly mediated by mechanisms other than local immunosuppression. The question as to how UV radiation could interfere with the induction of an immune response at a distant non-UV-exposed area of skin has remained unanswered for a long time. It is now clear that UV radiation stimulates keratinocytes to release immunosuppressive soluble mediators, which enter the circulation and cause systemic immunosuppression.

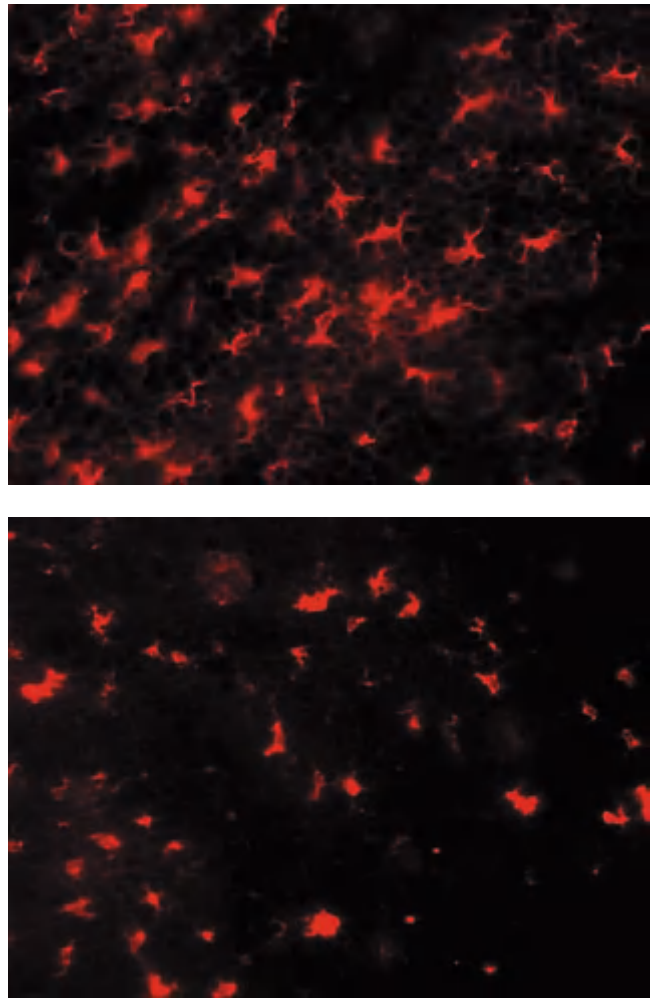

Fig. 10.6 UV radiation depletes Langerhans' cells from the epidermis. (a) In a sheet preparation of normal murine skin, numerous Langerhans' cells can be detected by staining with an antibody against MHC class II (Ia) molecules. (b) The number of Langerhans' cells is remarkably reduced upon UV exposure (2 J/m^2).

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Effect of UV radiation on antigen presentation

Within the epidermis, dendritic Langerhans' cells are the major APCs [1]. Exposure of skin to UV radiation results in a profound depletion of Langerhans' cells, which seems to be responsible for inhibition of the induction of CHS following UV irradiation [2] (Fig. 10.6). Depending on the UV dose applied, the disappearance of Langerhans' cells may be due to emigration out of the epidermis and/or the induction of apoptotic cell death. In addition, UV radiation suppresses the expression of MHC class II surface molecules and adenosine triphosphatase (ATPase) activity in Langerhans' cells [3]. Both markers, particularly MHC class II, are used to identify Langerhans' cells in the epidermis. Furthermore, UV radiation alters the antigen-presenting capacity of Langerhans' cells [4]. Inhibition of expression of the adhesion molecule intercellular adhesion molecule (ICAM)-1 by UV radiation may be responsible for impaired adherence of Langerhans' cells and T cells. Accordingly, inhibition of antigen presentation by UV radiation has been proven both *in vitro* and *in vivo*. Injection of antigen-loaded Langerhans' cells or dendritic cells that have been exposed to UV radiation does not result in sensitization, while injection of antigen-pulsed cells mounts an immune response [5]. In addition, UV-exposed APCs are unable to induce a response *in vitro*, e.g. proliferation in the mixed leukocyte reaction [6]. *In vitro*, UV exposure differentially affects Langerhans' cells in their capacity to stimulate different subsets of CD4$^+$ T-cell clones. While UV-treated Langerhans' cells are unable to stimulate T-cell clones of the Th1 type, their ability to stimulate Th2 clones is unaffected [7]. This may explain

why UV radiation preferentially suppresses Th1-mediated immune responses.

Other APCs such as human peripheral blood-derived dendritic cells exposed to UV radiation and splenic dendritic cells from UV-treated mice have also been found to be significantly impaired in their ability to stimulate allogeneic T cells. This indicates that UV-induced suppression of APC function is not specific for Langerhans' cells. UV radiation suppresses the expression of the co-stimulatory B7 surface molecules CD80/86. CD80/86 are expressed on Langerhans' cells and other APCs and play an important role in interactions between APCs and T cells. UV radiation down-regulates the expression of CD80 and CD86 on human Langerhans' cells *in vitro* and of CD80 on blood-derived dendritic cells *in vitro* [8,9]. Reactive oxygen species may also be involved in the impairment of APC function by UV radiation since the antioxidative enzyme catalase prevents the inhibitory effect of UV radiation [10]. Antigen presentation, however, may also be suppressed indirectly by UV radiation via the release of immunosuppressive cytokines and neuropeptides such as IL-10 or calcitonin gene-related peptide, respectively [11]. In addition, the photoproduct *cis*-urocanic acid interferes with antigen presentation.

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UV radiation induces immunological tolerance

Application of haptens on to UV-exposed murine skin does not result in the induction of CHS. If the same contact allergen is applied several weeks later to an area of skin that was not exposed to UV radiation, again no CHS response is induced [1]. This indicates that the initial application of the hapten on to UV-exposed skin induces long-term unresponsiveness (see Fig. 10.5). However, the mice are not generally immunosuppressed by the initial UV exposure since an immune response against another, unrelated, hapten can be perfectly induced in these animals. This indicates that the immunological unresponsiveness caused by UV radiation is hapten-specific, a state called hapten-specific tolerance. Induction of UV-mediated tolerance can be observed also in the model of systemic immunosuppression [2]. Long-term immunosuppression by UV radiation can also be observed in the tumour transplantation model. UV exposure suppresses rejection of transplanted skin tumours. If mice are treated for several weeks with repeated doses of UV radiation and then treatment is stopped, the animals remain susceptible to tumour challenge for at least 1 year, perhaps for the rest of their lives [3]. UV-induced tolerance appears to be mediated via the generation of hapten-specific T-suppressor cells.

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UV radiation induces T cells with regulatory/suppressor activity

UV radiation-induced hapten-specific tolerance appears to be due to the induction of T cells with inhibitory/suppressor activity. Injection of splenocytes, from mice that have been tolerized by application of a hapten on to UV-exposed skin, into naive syngeneic mice renders the recipients unresponsive to this particular antigen [1]. Immune responses against other non-related antigens are unaffected (see Fig. 10.5). Transfer of suppression is mediated via T cells since depletion of T cells from splenocytes is associated with a loss of transfer. Thus, sensitization in combination with UV exposure induces the generation of T cells with hapten-specific suppressor activity. Transfer of tolerance can be observed in both local [1] and systemic [2] models. Nevertheless, different types of T cells seem to be involved. In the systemic form of UV-induced suppression, transfer of tolerance is mediated by the induction of antigen-specific $CD3^+CD4^+CD8^-$ suppressor cells [3]; in the local form of suppression, both $CD4^+$ and $CD8^+$ cells appear to be involved. These differences may be due to the different systems used dependent on the strain of mice,

the type of haptens and the UV doses applied. When UV-induced suppressor T cells are transferred intravenously not into naive but into sensitized mice, the immune response in the recipients is unaffected [4]. This indicates that suppressor T cells only suppress sensitization but are not active once antigen-specific memory T cells have been induced and thus are not suppressive during the elicitation of an immune response.

Although the adoptive transfer experiments appear convincing, attempts to purify and clone these transferred cells have been unsuccessful. For this reason, the term 'suppressor T cell' was almost banned in general immunology and the entire concept of UV-induced tolerance and suppressor cells drawn into question by many immunologists [5].

The subject of suppressor T cells experienced a renaissance by the finding that chronic activation of both human and murine $CD4^+$ T cells in the presence of IL-10 induces $CD4^+$ T-cell clones that release high levels of IL-10, low levels of IL-2 and no IL-4 [6]. These antigen-specific T-cell clones suppress the proliferation of $CD4^+$ T cells in response to antigen, and prevent a T-cell-mediated colitis in an immunodeficient mouse model of this condition [6]. This $CD4^+$ T-cell subset is referred to as T-regulatory cell 1 (Tr1). These cells exhibit very low proliferative capacity, and offer an explanation as to why cloning of regulatory/suppressor T cells may be difficult or even impossible.

Another subset of $CD4^+$ regulatory T cells is characterized by the constitutive expression of the α chain of the IL-2 receptor (CD25). After antigen-specific activation, $CD4^+CD25^+$ T cells suppress immune reactions both *in vitro* and *in vivo* in an antigen-non-specific way [7]. There is also evidence that $CD4^+CD25^+$ T cells may be involved in the mediation of UV-induced tolerance. The area of regulatory T cells is currently one of the most extensively studied subjects in general immunology and future studies will increase knowledge about mediation of tolerance and active suppression. Whether these T cells are termed suppressor or regulatory seems to be more a semantic issue. The term 'regulatory T cell' is usually preferred since the existence of these cells is becoming accepted even by those investigators who previously denied the existence of suppressor T cells.

The detailed mechanism by which UV-induced regulatory/suppressor T cells mediate suppression still remains to be determined. There is evidence that particular surface molecules like CTLA-4 [8] and the apoptosis-related receptor CD95/Fas [9,10] may be critically involved. NK T cells appear to play a role in UV-induced suppression of tumour immunity [11]. UV-induced NK T cells suppress a delayed-type hypersensitivity reaction against tumour antigens. In addition, they support the growth of inoculated UV-induced tumour cells which are rejected in normal mice. This indicates that NK T cells may play a critical role in regulating the growth of UV-induced skin cancers.

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UV radiation induces the release of immunosuppressive mediators

The finding that mice exposed to higher doses of UV radiation cannot be sensitized, even when the antigen is applied to an area of skin which has not been exposed to UV [1,2], clearly indicates that UV radiation has the capacity to suppress the immune system in a systemic manner. How the events occurring at the irradiated site lead to a suppressed response to an antigen applied at a distant area of non-UV-exposed skin remained unresolved for some years. Keratinocytes have been recognized as a potent source of various soluble mediators, including immunostimulatory and pro-inflammatory cytokines. Cytokine release by keratinocytes can be effectively induced by UV radiation [3]. UV radiation, however, may also stimulate the release of immunosuppressive mediators since intravenous injection of supernatants obtained from UV-exposed keratinocytes into naive mice renders the recipients unresponsive to hapten sensitization [4]. Therefore, UV-induced keratinocyte-derived immunosuppressive mediators may enter the circulation and inhibit immune responses at areas of skin not directly exposed to UV radiation, explaining the phenomenon of systemic immunosuppression.

Several mediators seem to be involved in UV-induced immunosuppression. The major player appears to be IL-10. IL-10, whose release by keratinocytes is induced by UV radiation [5], abrogates the ability of Langerhans' cells

to present antigens to Th1 clones and even tolerizes them [6]. Injection of IL-10 into an area of skin where hapten has been applied prevents the induction of CHS and induces hapten-specific tolerance [7]. In turn, injection of an anti-IL-10 antibody into UV-irradiated mice prevents systemic UV-induced suppression of the induction of delayed-type hypersensitivity [5]. Furthermore, IL-10 induces a shift from a Th1 to a Th2 response; this may explain why UV radiation inhibits primarily Th1 immune reactions and favours development of Th2 reactions [8].

IL-12 is a cytokine that induces a Th1 immune response and may be regarded as a counterbalance to IL-10 [9]. Thus, it is not surprising that IL-12 has the capacity to prevent UV-induced immunosuppression. Injection of IL-12 before UV exposure enables sensitization even if the antigen is applied on to UV-irradiated skin [10–12]. Even more importantly IL-12 is able to break established UV-induced tolerance, since injection of IL-12 into UV-tolerized mice renders these animals susceptible to the antigen against which they were tolerized [10,12]. Other soluble mediators besides IL-10 that appear to be involved in UV-induced immunosuppression include TNF-α [13,14], IL-4 [15], prostaglandin E_2 [15], calcitonin gene related peptide [16] and α-melanocyte-stimulating hormone [17].

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Involvement of urocanic acid in UV-induced immunosuppression

Urocanic acid (UCA) is an epidermal chromophore involved in mediating UV-induced immunosuppression [1]. UCA is generated in the metabolic pathway of the essential amino acid histidine. It accumulates in the epidermis because epidermal cells are devoid of the necessary enzymes to further catabolize UCA. Two tautomeric forms of UCA exist: *trans* (E)-UCA and *cis* (Z)-UCA. The predominant isoform in the epidermis is *trans*-UCA. Upon UV exposure, UCA is photoisomerized from *trans*- into *cis*-UCA. Tape-stripping of the epidermis, which removes the majority of UCA, prevents UV-induced suppression of the induction of CHS, indicating that *cis*-UCA is involved in photoimmunosuppression [2]. Furthermore, injection of *cis*-UCA partially mimics the immuno-inhibitory activity of UV radiation [3]. Vice versa, anti-*cis*-UCA antibodies restore particular immune responses after UV exposure [4]. *cis*-UCA also inhibits the presentation of tumour antigens by Langerhans' cells [5]. This effect can be reversed by IL-12 [6]. In addition, injection of *cis*-UCA antibodies reduces the incidence of UV-induced skin tumours in a photocarcinogenesis model, indicating the involvement of *cis*-UCA in the generation of UV-induced skin cancer [6].

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UV radiation induces immunosuppression in humans

The vast majority of studies in the field of photoimmunology have been performed *in vivo* in animal, usually murine, models. Although numerous *in vitro* studies have been performed with human cells, the key questions are whether the observations made in animal models are relevant to humans and whether humans are immunosuppressed by UV radiation in a similar fashion. In fact, UV radiation appears to suppress the induction of CHS. Even tolerance can be induced, although according to one study only in 10% of people [1]. Tolerance was hapten-specific, since the individuals revealed pronounced CHS responses upon subsequent immunization with another, unrelated hapten [1]. Other studies reported that a higher proportion of subjects developed tolerance when the hapten was applied on areas of skin exposed to erythemogenic doses of UV [2]. However, it is certain that some people can be immunosuppressed by UV radiation. This implies that as in the murine system UV-susceptible and UV-resistant individuals may exist. It remains to be determined whether the UV-susceptible population is at higher risk of developing skin cancer. Indeed, sensitivity to sunburn appears to be associated with susceptibility to UV radiation-induced suppression of cutaneous cell-mediated immunity in humans [3]. Recently, UV-induced immunosuppression has started to be used as a tool to evaluate the potency of sunscreens [4,5].

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Molecular targets mediating UV-induced immunosuppression

Nuclear DNA is a perfect chromophore for both UVB and UVC radiation. UV radiation primarily induces two types of DNA lesions: pyrimidine dimers and (6-4)-photoproducts. Thus UV-induced DNA lesions have been regarded as the major and, for a long time, the only molecular target through which UV radiation exerts its biological effects. UV-induced DNA damage also appears to be critically involved in signalling photoimmunosuppression. The first functional evidence for this assumption was provided by an opossum model that has the ability to remove UV-induced DNA damage via photoreactivation, a DNA repair process induced by visible light [1]. Application of haptens on to UV-exposed skin of these animals does not result in the induction of CHS. In contrast when the animals are exposed to visible light, which induces DNA repair immediately after UV irradiation, sensitization is inducible, indicating that UV-mediated DNA damage is a major trigger for photoimmunosuppression [1].

This conclusion is supported by studies using DNA repair enzymes applied topically in a liposome-based cream. Application of T4N5 endonuclease, a bacterial DNA repair enzyme, restores the immune response when applied immediately after UV exposure [2]. Similar findings were obtained in humans when the repair enzyme photolyase was applied topically [3]. In addition, UV-induced release of the immunosuppressive cytokines IL-10 and TNF-α can be inhibited and reduced, respectively, by the application of T4N5 endonuclease [4,5]. Furthermore, lower doses of UV radiation are required to obtain equal suppression of an immune response in mice deficient in DNA repair (XPA knock-out mice) when compared with wild-type mice that exhibit normal DNA repair capacity [6]. Together, all these data strongly support DNA damage as an important inducer of UV-induced immunosuppression.

Despite clear-cut evidence for the crucial role of UV-induced DNA damage in photoimmunosuppression, there are indications that UV radiation may also affect cytoplasmic and membrane targets [7]. UV radiation can directly trigger surface receptors by inducing either their oligomerization [8] or phosphorylation [9]. UV radiation may also mediate its immunosuppressive effects by affecting targets at the cell membrane, since it prevents both IFN-γ and IL-2 from exerting particular biological effects via interference with the signal transduction of these two important immunostimulatory cytokines [10,11]. In addition, the involvement of *cis*-UCA indicates that UV-induced immunosuppression can be mediated independent of DNA damage. The relative contribution of the extranuclear signalling pathways in photoimmunosuppression remains to be determined, since UV-induced DNA damage appears to be the predominant signalling event.

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UVA-induced immunosuppression

The biologically most active part of the solar spectrum is UVB (290–320 nm) since it is primarily responsible for the induction of inflammation, carcinogenesis and immunosuppression. Hence, it is perhaps unsurprising that the vast majority of photoimmunological studies have used UVB sources. However, this does not mean that UVA has neither biological effects nor the ability to modulate the immune system.

Recently, an increasing number of studies have addressed the photoimmunological properties of UVA. Similar to UVB radiation, broad-band UVA (320–400 nm) can suppress the induction of CHS in the murine model; however, in contrast to UVB, UVA has to be dosed daily for 4 weeks [1]. Under these conditions UVA exposure can induce tolerance [1]. An oxidative pathway appears to be involved in UVA-induced immunosuppression since UVA-mediated inhibition of antigen presentation can be prevented by the addition of glutathione, which exhibits antioxidative properties [2]. Besides reactive oxygen species, nitric oxide may also contribute to the modulation of the immune response by UVA since inhibitors of nitric oxide prevent UVA-induced depletion of Langerhans' cells from the epidermis [3]. When comparing the effect of solar-simulated, UVB and UVA radiation on the suppression of the immune response to recall antigens in humans, UVB radiation appeared to be less immunosuppressive than solar-simulated radiation but followed the same time course. In contrast, UVA radiation-induced immunosuppression turned out to be transient, becoming less effective with subsequent UVA exposures, indicating that an adaptive mechanism may exist [4]. In a similar vein, under particular conditions UVA radiation even appears to abrogate or prevent immunosuppression from UVB radiation [5]. This effect seems to be mediated via IFN-γ [6].

Studying the immunosuppressive effects of UVA is more complicated than UVB since UVA can be separated into UVA-2 (320–340 nm) and UVA-1 (340–400 nm). This has to be taken into account when comparing studies. In the broad-band UVA range (320–400 nm), the immunosuppressive properties are mostly allocated to the short-wave UVA-2, since this spectrum is more related to UVB radiation. However, there are also indications that UVA-1 may affect the immune system since UVA-1 exposure of human skin results in Langerhans' cell depletion and reduction of epidermal APC function [7]. Further studies addressing the photoimmunological effects of UVA-1 are urgently needed since UVA-1 has been advertised as completely free of side effects, which appears not to be the case. More recently, UVA-1-induced immunosuppression has been used to determine the UVA-1 filtering capacity of sunscreens [8].

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Implications of UV-induced immunosuppression

The biological implications of UV-induced immunosuppression may be several-fold. In experimental models it has been demonstrated that UV radiation can inhibit the protective immune response against viral, bacterial and fungal infections. The infectious agents most frequently used to study these phenomena are HSV, *Listeria*, *Leishmania*, mycobacteria and *Candida* [1]. Based on these studies there is clear-cut evidence that UV radiation can

compromise an immune response against these agents in both a local and a systemic fashion. These models have contributed in an essential way to the further understanding of how UV radiation suppresses the immune system. However, from daily clinical practice we know that acute and severe exacerbations of infectious diseases following solar exposure are extremely rare in humans. The only exception is HSV infection in which recurrences are frequently observed after solar exposure. Therefore, at this stage, the clinical implications of UV-induced immunosuppression for infectious diseases may be limited.

The immune system not only protects against infection but also against malignancy. Transformed cells, particularly in the early stages, can be recognized as 'foreign' and attacked by the immune system (tumour immunology). This may specifically apply to both non-melanoma skin cancer and malignant melanoma. There is clear evidence of an association of susceptibility to skin cancer and immunosuppression. Chronically immunosuppressed individuals, like transplant patients, exhibit a significantly increased risk of developing skin cancer [2]. This risk certainly increases with cumulative UV load. In addition, the ability of UV radiation to negate host defences against skin tumours has been convincingly demonstrated in various experimental animal models [3]. Furthermore, restoration or even enhancement of an immune response, e.g. by topical or systemic application of immunomodulators (interferons, imiquimod), has become an established alternative therapeutic option for the treatment of skin cancer. Taken together, the immunosuppressive impact of UV radiation is probably much more relevant for carcinogenesis than for the exacerbation of infectious diseases.

It is striking that UV radiation at low doses can suppress an immune response [4]. Thus, one may speculate that a certain degree of immunosuppression may be beneficial. The skin is an organ that is constantly exposed to potential allergens; in addition autoimmune responses may be generated within the skin [5,6]. Hence, it is tempting to speculate that a certain degree of regular immunosuppression by daily solar exposure may prevent the induction of these immune responses.

However, the immunosuppressive effects of UV radiation can also be exploited therapeutically. Phototherapy is a major therapeutic strategy in the treatment of inflammatory skin disorders (see Chapter 24). Although the mechanisms underlying the beneficial effects of solar/UV exposure in certain diseases remain to be determined, it is obvious that the immunosuppressive properties are essential in this respect [7]. Accordingly, the majority of dermatoses (e.g. psoriasis and atopic dermatitis) that can be treated with immunosuppressive drugs respond favourably to phototherapy.

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Chapter 11

Wound Healing

J.A. McGrath & S.M. Breathnach

Biological aspects of wound healing

[S.M. Breathnach, pp. 11.1–11.10]

Introduction

Maintaining skin integrity is vital for humans and animals to protect against dehydration, bleeding and ingress of microorganisms. In order to do this, animals have evolved a sophisticated mechanism of wound healing to plug the gap quickly, re-epithelialize over the defect and rapidly replace the lost dermis with new matrix. The final product is not normal skin, for adult human skin does not regenerate, but rather is a repair in the form of a scar, which is visible on the skin surface.

Adult wound repair consists of a series of overlapping stages [1], beginning with aggregation and degranulation of platelets, blood clotting and the formation of a fibrin plug (eschar), which initially fills the wound. This is followed by the inflammatory phase, where initially polymorphonuclear leukocytes appear, which stimulate the recruitment of monocytes, macrophages and lymphocytes that kill microorganisms and secrete a wide variety of growth factors and cytokines, which modulate the remaining wound healing response. These immune cells invade the fibrin-filled wound space and, together with fibroblasts and blood vessels from the deep fascia and surrounding dermis, begin to lay down a temporary matrix of granulation tissue consisting initially of a proteoglycan-, glycosaminoglycan- and fibronectin-rich tissue, which serves as a guiding substratum for the migrating and proliferating cells. Cellular behaviour and coordination of the wound response is controlled during this granulation phase by a wide range of growth factors, extracellular matrix molecules and their receptors. There are extensive cell–cell and cell–matrix interactions. The CXC chemokine interferon-γ (IFN-γ) inducible protein-9 acts as a mediator of epidermal–dermal communication during wound repair [2]. Epidermal cells proliferate and move down the edge of the wound until they reach the new granulation tissue, where they dissect between the overlying fibrinous eschar and the underlying granulation tissue to close the wound. At the same time, the wound contracts predominantly by forces exerted by contractile elements contained within myofibroblasts. The transitory granulation tissue phase ends as immune cells, fibroblasts and endothelial cells undergo apoptosis, while the remaining fibroblasts lay down collagen (mostly types I and III), a process that continues for some time. In the final remodelling stage of wound healing, the matrix is remodelled with a decrease in the relative levels of fibronectin, glycosaminoglycans, proteoglycans and type III collagen and an increase in the levels of predominantly type I collagen, which is organized into thick bundles and extensively cross-linked to form the mature scar.

Acute wound healing proceeds quickly and with few problems in the vast majority of cases. Clearly, the speed of wound healing depends upon many factors, including the size of the wound (incisional or excisional), blood supply to the area, presence of foreign bodies and microorganisms, age and health of the patient, nutritional status of the patient, drugs that the patient may be taking and a variety of systemic diseases. Oxygen plays a critical part in wound healing [3,4], as does nitric oxide [5,6]. Leptin may be another regulator of wound healing [7]. Wound healing is subject to regulation by a large number of different cytokines and growth factors [8,9]. Oestrogens promote wound healing, while androgens inhibit it [10–13]. Opioid peptides may also favour wound healing [14].

Sometimes, the wound-healing process does not proceed normally and chronic wounds result. The most common forms of chronic wounds in humans include venous ulcers, diabetic ulcers and pressure sores. In each of these cases there is normally an underlying pathology, such as venous insufficiency in the case of venous ulcers, or abnormal microvascular patterns and high blood sugar levels in diabetic ulcers. These underlying pathologies create a situation whereby the wound-healing response cannot go to completion. Thus, for example, in the case of venous stasis ulcers, there is often a chronic ischaemia–reperfusion injury resulting in high levels of local cytokines, complex cuffs forming around the blood vessels and increased levels of wound proteases, particularly elastase, and decreased levels of protease inhibitors such as tissue inhibitor of matrix metalloproteinases (TIMP) [15–17]. In the case of diabetic ulcers, there are often extensive abnormalities in the microcirculation, thickening of the blood vessel wall, thrombi and areas of focal necrosis [18]. In such chronic wounds, it is necessary to treat the underlying pathology if long-term non-recurrent healing of the ulcer is to be achieved. Understanding the molecular pathogenesis of these chronic wound-healing states can lead to novel therapeutic targets for pharmacological intervention (e.g. exogenous administration of protease inhibitors or fibronectin).

The wound-healing response can also be disrupted by excessive healing (adverse scarring), which is represented at the extremes by hypertrophic scars or keloids. These excessive wound-healing states result from the abnormal deposition of connective tissue within the healing wound, such that the scar is elevated and may extend beyond the boundaries of the original wound. Excessive scarring shows a clear genetic basis with racial tendencies (e.g. it is more common in black and oriental people than it is in white people).

Finally, the acute wound-healing response varies with the age of the individual. Wounds made on very early embryos heal by complete regeneration, while wounds made on later embryos or early fetuses (in the middle trimester of pregnancy) display scar-free healing but absence of regeneration of dermal appendages. Comparison between postnatal and fetal wound healing has revealed differences in inflammatory response, cellular mediators, cytokines, growth factors, extracellular matrix modulators, tyrosine phosphorylation patterns and homoeobox gene expression [19,20]. Wounds in children and young adults often heal quickly with excessive scarring, while elderly patients show specific disruptions in the wound-healing cascade, such as elevated levels of proteases, altered ratios of growth factors and their receptors and a slower rate of healing but often with enhanced quality (reduced scarring). Age-related changes in the inflammatory reponse to wounding have been reported [21]. Wounds heal more quickly if patients are relieved of stress [22].

Despite the fact that the various phases of wound healing overlap, it is convenient to consider the principal cellular and molecular mechanisms regulating the basic biology of wound healing under three phases: inflammation and the immune response, re-epithelialization, and angiogenesis and matrix remodelling.

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Inflammation and the immune response

Following wounding, there is almost immediate release of inflammatory mediators from damaged cells, degranulating platelets or resident tissue macrophages and mast

cells. Furthermore, wounding causes a transient permeabilization of cells near the wound margin, with the rapid exchange of extracellular and intracellular ions, resulting in the switching on of early response genes in such cells within seconds following wounding. These mediators initially cause arteriole dilatation, resulting in an increased blood flow into the wound area. This process is further aided by growth factors such as vascular endothelial growth factor (VEGF), which causes hyperpermeability of endothelial cells [1]. This results in an influx of fluid and plasma components into the wound space, while inflammatory cells adhere to the vascular endothelium and migrate through the vascular wall into the wound. Neutrophils are the predominant initial inflammatory cells recruited to the wound, which together with platelets release a complex mixture of cytokines and growth factors. These stimulate the further influx of monocytes and lymphocytes, the proliferation of monocyte precursors within the wound and their differentiation into mature macrophages [2]. The chemokine CXCR2 has been shown by studies in knockout mice to be important in the neutrophil and monocyte recruitment as well as in wound closure [3].

Platelets respond very quickly, and when they reach the wound they adhere through selectin and integrin receptors [4], degranulate and release a variety of factors, including thromboxanes, prostaglandins, 12 lipoxygenase products, serotonin, adhesive glycoproteins including fibrinogen, Von Willebrand factor, fibronectin and thrombospondin and growth factors including platelet-derived growth factor (PDGF), epidermal growth factor (EGF) and transforming growth factor-β1 (TGF-β1). These factors both contribute to the initial fibrin plug that closes the wound and modulate subsequent cellular behaviour, including attachment, migration, proliferation and matrix deposition. However, wound closure, angiogenesis and collagen synthesis are not significantly impaired in thrombocytopenic mice [5].

These signals from the wound site, together with changes in vascular permeability, cause leukocytes to pavement in the blood vessels, undergo rolling and attachment to activated endothelial cell selectins and integrins [6–8]. Neutrophils, recruited early in wound healing, are responsible for destroying invading bacteria by phagocytosis and release of free oxygen radicals and proteolytic enzymes, which may cause further tissue damage and inflammation. Once in the wound, neutrophils may be activated by cytokines such as granulocyte–macrophage colony-stimulating factor (GM-CSF) and tumour necrosis factor-α (TNF-α), complement or proteases such as thrombin. The neutrophils do not subsequently re-enter the circulation but are eliminated by macrophage phagocytosis or apoptopic cell death, following by phagocytosis by surrounding cells and macrophages [9]. The lifespan of neutrophils in the wound depends on the presence of survival factors, such as GM-CSF and interleukin 2 (IL-2). Monocytes and macrophages are recruited in large numbers to the healing wound as neutrophil numbers begin to decline. Classic studies by Leibovich and Ross [10] demonstrated the importance of these cells in wound healing; experimental depletion of wound macrophages resulted in prolonged inflammation and delays in fibroblast proliferation, matrix deposition and subsequent wound closure. By contrast, exogenous application of blood-derived monocytes to wounds can result in accelerated healing. The transition from a resting to an active state in monocytes and macrophages is controlled by cytokines such as TNF-α and IFN-γ, as well as bacterial products such as lipopolysaccharide. Monocytes and macrophages produce a range of cytokines in response to pro-inflammatory signals, including TGF-β and TGF-α, and fibroblast growth factor (FGF) 1 and 2. The interactions between these growth factors and monocyte/macrophage differentiation/activation is complex and often self-regulatory. Thus, TGF-β1 acts as a pro-inflammatory cytokine early in the wound-healing phase, as it is chemotactic to immature monocytes, which are recruited to the wound site, and synthesize and secrete more TGF-β1 (TGF-β1 has a self-inducing response element within its promoter). However, TGF-β1 is anti-inflammatory to mature or activated monocytes/macrophages, because it inhibits their activation and modulates receptor expression [11,12]. Thus, it can be seen that the same growth factor, TGF-β1, can have completely opposite effects, depending on the state of differentiation/activation of the cell, which in turn may be regulated by other growth factors or extracellular matrix molecules. Wound healing is delayed in immunodeficient TGF-β1 knockout mice [13].

In addition to the production of cytokines, wound macrophages also produce a range of extracellular matrix molecules, which, together with fibrinogen and fibrin from the blood clot, matrix molecules from degranulating platelets, recruited fibroblasts and endothelial cells, form the granulation tissue or provisional matrix. This provisional matrix is rich in molecules, such as fibronectin, vitronectin, thrombospondin, tenascin and proteoglycans such as dermatan, chondroitin and heparan sulphate. It acts as an early scaffold for the re-establishment of the dermis and for the migration of epidermis as it promotes both cell migration and proliferation [14]. Regulation of this provisional matrix is complex, and achieved partially through control at the transcriptional level, for example with alternative splicing of the primary transcript for fibronectin resulting in embryonic-like cellular fibronectins being deposited within the wound space, which better facilitate cell migration and proliferation [15].

Pro-inflammatory cytokines such as TNF-α and IFN-γ can stimulate the production of chemokines by endothelial cells [16]. These chemokines (e.g. IL-8, IL-10, PF-4,

MIP-1α, MIP-1β, RANTES and MCP-1) attract lymphocytes to the wound area, and may have a role in the progression of healing to fibrosis [17]. These lymphocytes include both B and T lymphocytes, and there is growing evidence that the particular type of T-lymphocyte response (Th1 or Th2), each characterized by a different profile of cytokine secretion, may be one of the factors underlying abnormal fibrosis and scarring. Human γ/δ T lymphocytes express and synthesize connective tissue growth factor (CTGF), known to regulate fibrogenesis and wound healing [18]. The type of T-lymphocyte response itself may be determined by the profile of growth factors in the early wound. Thus, for example, natural killer (NK) cell migration out of blood vessels is promoted by VEGF but inhibited by FGF-2 [19]. IL-6 also has a crucial role in wound healing, probably by regulating leukocyte infiltration, angiogenesis and collagen accumulation [20].

These early inflammatory responses are vital to the wound-healing process: clearing the wound of foreign antigens such as bacteria, and supplying combinations of growth factors and extracellular matrix molecules, which orchestrate the subsequent healing of the provisional matrix by providing the signals and scaffold for fibroblast, endothelial and keratinocyte influx. Inflammatory cells such as monocytes and macrophages decrease towards the end of the inflammatory phase, largely through apoptosis resulting from diminution of the levels of survival factors (e.g. specific cytokines and matrix molecules) [21].

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Re-epithelialization

During the inflammatory period, the process of re-epithelialization commences, with consequent alterations in the differentiation and kinetics of surrounding keratinocytes [1]. These surrounding keratinocytes alter their differentiation state and adhesion profile, become migratory, move across the provisional wound matrix, protect themselves against the hostile elements within the wound matrix (e.g. proteases, reactive oxygen species), proliferate to provide replacement cells and, once temporary epithelial cover is established, redifferentiate back into a normal epidermis with stem cells in the correct spatial orientation.

Following wounding, there is immediate stimulation of the tyrosine phosphorylation of numerous cellular proteins, with activation of p21ras, mitogen-activated protein kinases, extracellular signal-regulated kinases 1/2, c-Jun NH2 terminal kinase, and p38 mitogen-activated protein kinase, and consequent increased phosphorylation of their respective substrates, c-jun and activator transcription factor 1 [2]. Syndecan appears to be important in keratinocyte activation [3]. TNF-α stimulates transcription of the PPARβ (peroxisome-proliferator-activated receptor β) gene via an activator protein-1 site in its promoter and it also triggers the production of PPARβ ligands in keratinocytes, with subsequent up-regulation of the expression of integrin-linked kinase and 3-phosphoinositide-dependent kinase-1, which phosphorylates protein kinase B-α (Akt1) [4]. Akt1 activity suppresses apoptosis and ensures the presence of a sufficient number of viable keratinocytes at the wound margin for re-epithelialization. GM-CSF [5], IL-1 and keratinocyte growth factor-2, also described as FGF-10, stimulate keratinocyte growth [6,7]. Keratinocytes in the basal layer some 300–400 cell diameters away from the wound margin proliferate extensively; such proliferation peaks within 1–2 days post-wounding and then falls back again to reach basal levels about 14 days post-wounding. Suprabasal cells derived from this extensive

proliferation roll over the attached basal cells to form new basal cells at the wound margin, a process repeated by successive basal cells until re-epithelialization is complete. Keratinocyte growth factor activates keratinocyte migration and stimulates hyaluronan synthesis, which also promotes keratinocyte migration [8]. p38 signalling is important in keratinocyte outgrowth from human skin explant cultures [9].

Keratinocytes at the wound edge undergo crawling and spreading, while wound contraction and sliding of the epithelial sheet by actin cable formation also contribute to wound closure and re-epithelialization. The migrating keratinocytes initially form an invading spur that moves downwards between the eschar and normal dermis, digesting the granulation tissue *en route*. Once beneath the eschar and necrotic tissue, keratinocytes from behind the front edge of the spur move bilaterally towards each other across the top of the newly formed wound matrix. Thus, the keratinocytes effectively dissect the fibrinous eschar from the underlying granulation tissue, a process achieved in part by the predilection of the keratinocyte to attach and migrate on fibronectin but not on fibrin or fibrinogen [10]. Fibrin promotes keratinocyte migration indirectly by exposing plasminogen to migrating cells, and also selectively disrupts adhesion of differentiated keratinocytes [11].

The keratinocytes that migrate to close the wound show extensive phenotypic changes. The K1 and K10 cytokeratin filaments of the cytoskeleton, which hold the differentiated keratinocyte in a rigid suprabasal phenotype, are replaced by the flexible cytokeratins K6 and K16 [12]. Expression of these cytokeratins is strongly stimulated by growth factors such as EGF, TGF-α and TGF-β present at high levels within the provisional matrix [13]. As the keratinocytes migrate, they express collagenases and urokinase-type plasminogen activator, an enzyme that converts the inactive proteases secreted by granulocytes and fibroblasts such as plasminogen and procollagenase into their active forms [14–16]. Up-regulation of urokinase plasminogen activator induced by hypoxia results in increased keratinocyte migration [17]. This up-regulation is mirrored by the concurrent up-regulation of plasminogen-activator inhibitors, which control the extent of plasminogen activation [18]. This suggests a key role for the plasmin–plasminogen system in wound healing, an assertion given experimental weight by wound-healing studies on mice with targeted disruption of the plasminogen gene [19]. These mice show substantial delays in wound re-epithelialization and the aberrant persistence of fibrin within the wound matrix, demonstrating the importance of the plasminogen–plasmin system for fibrin removal during wound healing. The wound-healing phenotype could be reconstituted by addition of exogenous plasminogen or by deletion of the fibrinogen gene.

Cells migrating through the granulation tissue express different integrins. Thus, α5, β1, αV and β5 integrins, the primary keratinocyte receptors for fibronectin and vitronectin, are up-regulated in migrating keratinocytes during re-epithelialization [20]. Expression of these integrins may be induced by TGF-β1 [21]. These integrin switches on both keratinocytes and fibroblasts surrounding the wound are in part responsible for the early lag phase in wound healing, as the cells become primed to enter the provisional matrix. Once re-epithelialization is complete, the keratinocytes switch from the vitronectin/fibronectin receptor (αVβ5) to the tenascin/fibronectin receptor (αVβ6), a switch that may be involved in the redifferentiation of the epidermis, as the β6 integrin has been associated with epithelial remodelling during development and tumourigenesis [22].

A number of growth factors promote keratinocyte proliferation and migration, including FGF-7, FGF-1 and FGF-2, insulin-like growth factor-1 (IGF-1), EGF, TGF-α and hepatocyte growth factor (HGF) [23]. These factors are up-regulated usually in the dermis near the sites of keratinocyte proliferation, while the proliferating keratinocytes up-regulate receptors for such growth factors [24]. Furthermore, these factors stimulate enhanced re-epithelialization when added exogenously to wounds [25–29]. Equally, keratinocytes produce a large number of cytokines and growth factors including interleukins, TGF-β and TGF-α, EGF, PDGF, GM-CSF and TNF-α [30]. Co-culture and other experiments demonstrate that keratinocytes can stimulate growth-factor production by underlying dermal cells, and that such factors then act back on the epithelial cells themselves. Thus, a complex set of reciprocal epithelial–mesenchymal interactions is continuously ongoing during the wound-healing process. For example, keratinocytes can stimulate FGF-7 production by underlying dermal cells, which then acts specifically on the overlying epithelial cells via the FGF-7 receptor. The FGF-7 is up-regulated in dermal cells at the wound edge, while the receptor is up-regulated in the overlying epidermis [31–33].

The migrating keratinocytes must also markedly alter their adhesive interactions with each other. Alteration in the expression of cell adhesion molecules and desmosomes is effected by the cytokine profile, but probably the earliest signal to change keratinocyte adhesive interactions is the rapid shift in extracellular ionic balance that occurs post-wounding. Thus, damage to cells causes an alteration in the ratios of magnesium and calcium ions, which induces keratinocytes to adopt a migratory phenotype [34].

In normal skin, the basement membrane separates the epidermis from the dermis. Following wounding, this dermal–epidermal junction must be reconstituted as part of the re-epithelialization process. Basal lamina components, such as type IV collagen, laminin and heparan sulphate, are synthesized and deposited into the

dermal–epidermal junction by both the fibroblasts and the keratinocytes. It is thought that most of the molecules are contributed by the fibroblasts, while the keratinocytes organize the molecules into their correct structure and orientation [35]. The early basement membrane is often punctate and poorly organized, but the molecules are deposited synchronously with re-epithelialization. Maturation and organization of the basement membrane, including the establishment of hemidesmosomes and type VII collagen anchoring fibrils, occur later after the epithelial cells are present; the basement membrane is thought to be of predominantly epithelial origin [36].

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Angiogenesis

Neovascularization is an important part of granulation tissue formation, and is stimulated early in the inflammatory process. Angiogenesis, in response to tissue injury, is a dynamic process that is highly regulated by signals from both serum and the surrounding extracellular matrix (ECM) environment [1,2]. VEGF, angiopoietin, FGF and TGF-β are among the most potent angiogenic cytokines. Laminins are the major non-collagenous ECM constituents of endothelial basement membrane produced by human dermal microvascular endothelial cells. Laminin 10 is highly expressed in blood vessels around skin wounds. Laminin 8 promotes dermal endothelial cell attachment, migration and tubule formation. Integrins

with either β1 or αv subunits are the major cellular surface receptors for ECM molecules and mediate the interactions between cells and ECM during wound angiogenesis.

During angiogenesis, endothelial cells degrade the vessel basement membrane and surrounding matrix, migrate, proliferate and form new blood vessels [3]. Thus, angiogenesis results from sprouting of existing dermal vessels surrounding the wound. In larger wounds, there is also evidence for *in situ* vasculogenesis caused by the differentiation of angioblast precursors derived from the blood [4]. Growth factors involved in the stimulation of angiogenesis *in vivo* include FGF-1 and FGF-2, VEGF, neuropilin-1, EGF, TGF-α, TGF-β1, TGF-β2 and TGF-β3, activin, PDGF and CTGF [5–11]. These growth factors act by increasing the expression of proteases or protease activators at the leading edge of the endothelial cells, by stimulating endothelial cell proliferation and by increasing vascular permeability [12,13]. Matrix metalloproteinases may have both pro- and antiangiogenic activities [14]. Many angiogenic growth factors are potentiated by heparin. Adequate revascularization of the wound is essential for healing; ineffective angiogenesis results in impaired wound healing. Indeed, it is the appearance of the capillary loops that gives the provisional matrix its red granular appearance, from which is derived the name granulation tissue. At the end of the provisional matrix phase, the numbers of blood vessels within the healing wound decrease by a process of apoptosis, probably induced by depletion of vascular survival factors, such as VEGF, and the appearance of pro-apoptopic factors such as TGF-β [15].

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Fibroblast recruitment, matrix synthesis and scarring

The fibroblasts migrate into, and proliferate within, the provisional wound matrix, depositing as they do additional extracellular matrix molecules [1]. Most wound fibroblasts are derived from proliferation of fibroblastic stem cells in the deep dermis and the septae of the underlying fat; relatively few cells are derived from the margins of the surrounding dermis. Like the keratinocytes, they alter their integrin profile, expressing receptors for fibronectin and down-regulating receptors for collagen during the early phases of migration [1,2]. During the early stages of provisional matrix deposition, collagen synthesis in the surrounding unwounded skin is suppressed, while fibronectin synthesis is enhanced [3]. Fibroblasts within the provisional matrix secrete and assemble a complex extracellular matrix. Initially, this consists predominantly of fibronectin, proteoglycans and glycoproteins, but later consists of mature type I collagen bundles. The ratio of collagen types during wound healing varies, the early wound being characterized by elevated levels of type III collagen, whereas later in healing type I collagen predominates. Minor collagens, such as types 12 and 14, as well as proteoglycans such as decorin, are also present in the early healing wound and play a key part in collagen fibril organization. The degree of collagenous cross-linking also varies with time after wounding: the early wound has fewer and more immature cross-links compared with the later wound, which has extensive mature cross-links resulting in a more insoluble collagenous matrix. Many growth factors stimulate fibroblast proliferation, migration and extracellular matrix synthesis, including the TGF-β family [4,5], IGF-1, PDGF [6] and CTGF. These growth factors act in various ways—autocrine, paracrine, intracrine and matricrine—to regulate many of the events during dermal healing. There is extensive cross-talk between the extracellular matrix-derived signals and growth factor signalling in this process. Thus, for example, clustering of integrin receptors on the fibroblast leading edge leads to associated clustering of growth factor receptors, which then interact with the growth factors bound to the matrix.

The early granulation tissue is characterized by specialized fibroblasts called myofibroblasts, which show elevated levels of α-smooth muscle actin, and are morphologically

and functionally intermediate between fibroblasts and smooth muscle cells [7]. These myofibroblasts are induced by growth factors such as TGF-β1 but interestingly not by TGF-β3. Myofibroblasts may contribute to the contractile forces involve in wound contraction, and their persistence can lead to abnormal scar contracture. Normally, myofibroblasts are preferentially eliminated during the apoptopic phase of wound healing that results in resolution of the granulation tissue [8]. The Smad family of proteins mediates signal transduction of the TGF-β superfamily, and TGF-β induces fibroblast contraction necessary for efficient wound healing [9]. Turnover of the extracellular matrix is facilitated by a range of proteases and protease inhibitors, including plasmin, matrix metalloproteinases, hyaluronidase and elastase [10]. Levels of these active proteases are carefully and focally controlled both by growth factors and by proteolytic inhibitors such as TIMP and syndecans [11]. IL-10 is an inhibitory factor for the remodelling of the ECM during wound healing [12].

As healing proceeds, the numbers of fibroblasts, endothelial and inflammatory cells decrease, and the predominantly collagenous matrix becomes organized into thicker, more heavily cross-linked bundles. This marks the establishment of the mature scar. Scars continue to remodel for a long time after wounding, and cannot be considered to be in a steady-state condition until at least 2 years post-wounding—often longer. Cutaneous scarring is defined as a macroscopic disturbance of the normal structure and function of the skin architecture, resulting from the end-product of a healed wound [13,14]. Scarring may manifest itself as an elevated or depressed site, with an alteration of skin texture (e.g. hard), colour (e.g. hypermelanotic), vascularity, nerve supply, reflectance and biomechanical (e.g. elasticity) properties. Histologically, dermal scars are characterized by thickened epidermis with a flattened dermal–epidermal junction, and an abnormal organization of the dermal matrix into parallel bundles of scar-tissue collagen, as opposed to the normal basket-weave appearance of dermal collagen. The scar collagen fibres are usually smaller, more densely packed and often have higher proportions of type III collagen and fibronectin compared with surrounding normal skin. Elastin appears early in the wound-healing process but then disappears (presumably because of the activity of elastase) to reappear again later in the scar [15]. However, the elastin is abnormally organized into fragmented and chaotic structures, as opposed to the normal elastin fibre arcades that characterize normal dermis [15]. Epidermal appendages such as hair follicles and sebaceous glands never regenerate in a scar, although experimental addition of dermal papillae fibroblasts to a wound can induce hair follicle formation [16]. Proliferative scarring or chronic wounds may result from overexpression or dysregulated activity of the fibrogenic isoforms of TGF-β [17–19]. All three isoforms of TGF-β, and its receptors, are strongly expressed in adult wounds, but not in fetal wounds, which do not scar [20]. Hypertrophic scars contain increased numbers of epidermal Langerhans' cells [21], and keloid scars may have elevated levels of VEGF [22].

The severity of scarring can be assessed clinically using visual analogue scales, and the severity of macroscopic scarring correlates with histological abnormalities predominantly in the epidermis and in the papillary dermis [23]. Interestingly, experimental studies show that the morphology and severity of scarring is established early in the wound-healing process [24–27]. Thus, addition of antiscarring therapies, such as neutralizing antibodies to TGF-β1 or exogenous TGF-β3, have to be applied at the time of, or shortly after wounding to demonstrate their maximum antiscarring effects many months later [24–27]. It is likely that this timing reflects the underlying biology; early alterations to the cytokine profile can have profound effects later on by influencing autocatalytic and amplification processes. Furthermore, manipulation of the cytokine profile in the early phases of wound healing, when there are only a small number of signalling systems, is likely to produce more dramatic effects than subsequent manipulations later in wound healing, when a large number of interacting and functionally redundant cytokine signalling networks have been established. These biological data have considerable clinical significance. Thus, it is likely that scar-preventing therapies will be applied at the time of, or shortly after wounding (in most cases they will be applied topically by the physician), and only a small number of applications may be required. The current antiscarring therapies include neutralizing antibodies to TGF-β1, TGF-β2 and TGF-β3 itself, or prevention of TGF-β activation by mannose-6-phosphate [24–27]. Scarring is a major clinical problem resulting in adverse cosmesis, loss of function particularly if over joints, and interference with growth in children. Furthermore, scarring is a major clinical problem in nearly every organ or tissue; for example, scarring in the eye (cornea or retina) can lead to blindness, scarring in the central nervous system (CNS) inhibits neuronal reconnection, scarring in the abdomen and pelvis often leads to strictures and adhesions, and scarring in muscle and joints leads to adverse function and ankylosis. Interestingly, the principles of antiscarring therapy based on manipulation of the proportion of proscarring versus antiscarring cytokines appear to hold good for all body systems, as well as for chronic human fibrotic diseases, such as glomerulonephritis or liver fibrosis, indicating that studies in the skin may have a wider clinical application.

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Age-related changes in wound healing

Wounds even of a very substantial size created in certain lower vertebrates (e.g. amphibians) heal by complete regeneration. By the same token, wounds made in early (first-trimester) embryos also heal by complete regeneration [1]. However, these wounds tend to be made before the skin has established even a simple differentiated structure. During the second trimester, experimental studies in numerous animals have shown that late embryonic and early fetal dermal wounds heal with the absence of scarring, but without the regeneration of dermal appendages such as hair follicles or sebaceous glands [2–4]. This scar-free embryonic wound healing then gradually turns into a scarring healing phenotype during the last trimester and after birth. Wounds in children and young adults heal quickly but with poor scars (excessive scarring). There are many differences between scar-free embryonic wound healing and scar-forming adult wound healing, such as alterations in matrix components, cellular proliferation and differentiation, immune cell recruitment and growth factor profiles [4]. However, the real question is, which of these cellular and molecular differences between scar-free and scar-forming healing are central to the scar-free phenotype, and which are simply epiphenomena [5]? One major difference is the degree of inflammation elicited in an embryonic wound that heals in a scar-free fashion [4,6]. The embryonic and fetal immune system is not as well developed, and consequently there are far fewer inflammatory cells at the wound site; those that are present are at different stages of differentiation and activation compared with adult wound healing. Consequently, the growth factor profile at the embryonic wound site is different, with reduced levels, for example, of TGF-β1 and TGF-β2 [3]. These observations of scar-free fetal healing have led to experimental studies of adult wounds to try and mimic the fetal situation [7–9]. Exogenous application of neutralizing antibodies to TGF-β1 and TGF-β2 or exogenous addition of TGF-β3 or mannose-6-phosphate, which prevents activation of TGF-β1 and TGF-β2, to the recently created wound (just before, at the time of, or shortly after wounding) results in adult incisional wounds that heal with reduced or absent scarring [7–9]. These interesting experimental findings have now been translated into putative human therapies, which are undergoing evaluation in clinical trials.

Interestingly, ageing during adult life also brings alterations to the wound-healing process [10]. Many studies of human age-related changes in the wound-healing profile are methodologically flawed because of failure to control for concurrent morbidity and disease [10]. However, experimental investigations on health status in defined human subjects of varying ages have shown profound alterations in the wound-healing process with age [10]. Elderly subjects heal their wounds more slowly, with a reduced inflammatory response, an altered cytokine profile and an increased level of active proteases [11–16]. Of major interest is the observation that, in normal ageing skin, the levels of proteases such as matrix

metalloproteinases and elastase increase, while the levels of proteolytic inhibitors (e.g. TIMP) decrease, tipping the balance towards proteolytic digestion of the dermis [13–15]. This may account for some of the age-related changes seen in normal skin structure. It may also predispose certain individuals to ulcer formation, as chronic venous ulcers are characterized by an excessive proteolytic profile [13]. By contrast, the quality of wound healing in elderly subjects is markedly improved: there is reduced scarring. In part, this correlates with the altered inflammatory and growth factor response, which to some extent mimics that seen during embryonic life [11,12]. These ageing studies have also shown marked differences between how males and females heal their wounds, and between the healing of pre- and postmenopausal females [17]. In general, postmenopausal women heal more slowly but with a better scar quality than premenopausal women [17]. Exogenous therapeutic addition of topical oestrogen to the healing wounds of postmenopausal women causes a marked acceleration of wound healing and reverses the age-related changes in speed and quality [17]. Thus, topical and systemic hormonal treatment of healing wounds is a therapeutic strategy to accelerate healing in the elderly.

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Clinical aspects of wound healing

[J.A. McGrath, pp. 11.10–11.25]

Acute wounds result from a breach in the integrity of the skin, which occurs with incisional and excisional surgical wounds and traumatic skin injury including burns. At a cellular level, acute wounding results in activation of mitogen-activated protein kinase pathways and activator-protein 1 [1].

Healing by primary intention refers to wounds where the edges have been brought into apposition by sutures, which is possible when there is a good blood supply and no contamination or necrotic debris. Optimal healing requires the wound edges to be everted, carefully aligned and free from tension. Epidermis will cross the gap by 24 h, but by 5 days the tensile strength is only about 5% that of normal skin. Thus, sutures help to take some tension off the wound. Buried absorbable sutures are helpful in reducing dead space and supporting the wound for longer, as the tensile strength is still only about 20% that of normal skin at 3 weeks [2].

Healing by secondary intention occurs when a wound is allowed to heal from the edge without surgical closure [3], so re-epithelialization is a crucial process. The depth of the wound is critical to the manner of healing. In a partial thickness wound, not only will part of the dermis remain intact, but retention of critical regions of hair follicles and other skin appendages will also provide a rapid source of epidermal regeneration. The density of skin appendages therefore influences the rate of healing. In contrast, full-thickness wounds will have lost dermal and appendageal components and can only be healed from the wound edge, requiring a stimulation of granulation tissue; a mixture of proliferating microvasculature, fibroblasts and the deposition of matrix components. Wound contraction occurs after 1–2 weeks, via activated fibroblasts or myofibroblasts, which decreases the surface area to be closed. Different body sites vary in the results of secondary intention healing, concave surfaces being better than convex, and the face being better than extremities.

In open wounds, the normal water-retaining properties of the skin are lost, and the inflammatory exudate on the surface dries to form a crust or scab. This acts as a barrier to external infection, but it prevents epidermal migration across the surface of the wound. A wound that is kept moist by an appropriate dressing will epithelialize faster

than a wound that has been allowed to form a crust. Accelerated epithelial healing under an occlusive non-permeable dressing is associated with a gelatinous coagulum containing fibrin and fibronectin, which provides a suitable matrix for epidermal cell migration [4].

Tertiary healing or delayed primary closure [5] involves allowing some healing by secondary intention and then closing the wound primarily. This may be indicated when infection is present and needs to be cleared by antibacterial treatment, or skin grafting is intended. Delaying primary closure in this way reduces morbidity, but does not delay the development of wound strength [6]. Indeed, there is some evidence that by the 60th day, wounds healed by delayed primary closure are considerably stronger than those closed immediately [7]. This may be because of better oxygenation and blood flow with delayed closure [8].

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Burns

Thermal injuries affecting the epidermis only are known as first-degree burns but, when the dermis is involved, second-degree (partial thickness) and third-degree (full-thickness) burns are incurred. The extent of injury is determined by the rule of nines [1,2]. The head and upper limbs are each 9% of the total body surface area (TBSA), whereas each lower limb, the anterior and posterior trunk is 18% TBSA. A minor burn is either superficial or involves less than 20% TBSA. The speed of healing of dermal burns depends on the number of viable hair follicles and other appendages. Deep burns result in severe scarring and contractures, so surgical practice has evolved to excise burn wounds and close with a skin graft as soon as practicable. Full-thickness burns are chalky white or charred, dry and anaesthetic, whereas more superficial burns are non-blanching, erythematous, wet and extremely painful.

Wound healing in burns is affected by particular complications of the burn injury in the cutaneous vasculature [3]. The depth of burns tends to increase after 24–48 h as a result of progressive vascular occlusion. Thermal injury produces a zone of coagulative necrosis surrounded by an area of hyperaemia, as histamine release after burning gives initial vasodilatation followed by bradykinin-mediated vasoconstriction. Leukocyte adhesion to vessel walls produces progressive thrombotic occlusion, which causes extension and deepening of the burn. Continued leukocyte activation leads to free-radical-mediated tissue damage, and produces prolonged inflammation for 1–4 weeks, which prevents healing. Release of proteases from leukocytes, keratinocytes and macrophages also delays healing by inactivating growth factors, and by destroying newly regenerating tissue.

In a circumferential burn, early escharotomy may be needed to prevent ischaemia. Otherwise, after removal from the heat source for thermal burns, or copious washing for chemical burns, early wound management [4] involves application of a suitable dressing for 2–3 days until the wound depth is clarified. One per cent silver sulfadiazine cream is widely used in burns units, but biological dressings such as human allografts or porcine heterografts are very effective in reducing pain. Occlusive dressings may be helpful on small burns, but are not practical for large-surface-area burns.

Surgical excision down to bleeding with immediate grafting is the treatment of choice on any burn not likely to heal in 2–3 weeks. Tangential excision and split-thickness sheet or mesh grafts are used. Significant blood loss (200 mL/1% TBSA) from these procedures must be replaced. Pressure garments are widely used to prevent excessive scarring, as are silicone gel sheets and occlusive membranes.

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Chronic wounds

The series of biological events that close any defect in the skin may be impaired by factors interfering with inflammation, angiogenesis, re-epithelialization and wound remodelling. Most wounds will have a tendency to heal, however long standing, but this process may be very slow and suffer from many complications. Recurrent injury over a previous scar, as in a leg ulcer or pressure sore, and recurrent breakdown following healing, can give rise to chronic skin wounds or ulcers that appear to have lost the capacity to heal. Although the mechanisms of skin

ulceration are understood, the biological profile of the chronic wound is not clear.

The chronic wound environment may, for example, be deficient in stimulatory growth factors, growth factor receptors or proteolytic enzymes required for growth factor activation, or may be overproducing any of these factors [1,2]. Growth activation in the edge of a wound bed is particularly associated with overexpression of TGF-α, heparin-binding epidermal growth factor (HB-EGF) and EGF receptor [3]. The chronic wound may produce a hostile microenvironment to cells requiring activation in the wound-healing process. Chronic wound fluid has been shown to decrease proliferation of fibroblasts, endothelial cells and keratinocytes, in contrast to acute wound fluid, which stimulates growth [4]. Wound fluid from venous ulcers contains active collagenases and degraded fibronectin and vitronectin, and decreases cell adhesion. Fibrin accumulates in chronic wounds (unlike acute wounds), and forms complexes that may bind or inactivate other molecules such as growth factors.

Metalloproteinases (MMPs) are pro-enzymes requiring activation [5]. Three classes of MMPs are collagenases, gelatinases and stromelysins, single-chain proteins the production of which is stimulated by soluble factors and matrix proteins, and inhibited by TIMP [6,7]. There may be abnormalities of MMPs and TIMP in the chronic wound [2,8,9]. Collagenases are probably important in tissue remodelling following healing. Keratinocytes in the edge of a chronic wound are stimulated to produce collagenase by type I collagen.

Keratinocytes in chronic wounds fail to migrate across a wound bed despite a hyperplastic epithelium, and may lack specific matrix proteins in the wound bed to permit cell movement. Keratinocytes migrate most effectively on fibronectin, usually present in the wound bed, and on type I and IV collagens, but not on laminin [10]. Keratinocyte mesenchymal interactions therefore require a vascularized appropriate matrix, and they are impaired in chronic persistent wounds.

The chronic wounds that pose the most significant clinical problems are chronic leg ulcers and pressure sores. These wounds are also of high economic importance, as caring for them consumes a huge amount of health care resources [11].

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Leg ulcers

Leg ulcers are becoming more common as the population ages, as they particularly afflict the elderly. Prevalence figures suggest up to 1% of the population in Europe is affected. The health care cost of non-healing ulcers is immense, in view of the high use of community nursing resources. The most common cause of leg ulcers (80–90%) is chronic venous insufficiency, with arterial disease and diabetic neuropathy accounting for the majority of the remainder (Table 11.1).

Venous ulcers result from valve incompetence in the perforating veins connecting superficial and deep venous systems, so that venous pressure does not fall during exercise and as a result capillary proliferation occurs [1]. An increased permeability to macromolecules produces a pericapillary fibrin cuff, which binds growth factors and matrix proteins and may impede oxygenation [2]. Trapped leukocytes occluding capillaries may add to tissue ischaemia through the release of inflammatory mediators that increase vascular permeability [3]. The skin develops purpura resulting from extravasated red cells, and pigmentation from collections of haemosiderin and melanin. Eczematization is followed by induration and dermal fibrosis giving 'lipodermatosclerosis'. Ulceration then develops above the malleoli as an irregular craggy area, which initially heals but has a high recurrence rate. The

Table 11.1 Causes of leg ulcers.

Venous (chronic venous insufficiency)
Arterial
Atherosclerosis
Hypertensive
Trauma (+ above)
Mixed arteriovenous
Vasculitis (arteritis and allergic vasculitis)
Pyoderma gangrenosum
Bacterial infections (including tropical ulcer, acid-fast bacilli, ecthyma)
Malignancy
Vasospastic (including sickle cell anaemia, cryoglobulinaemia)

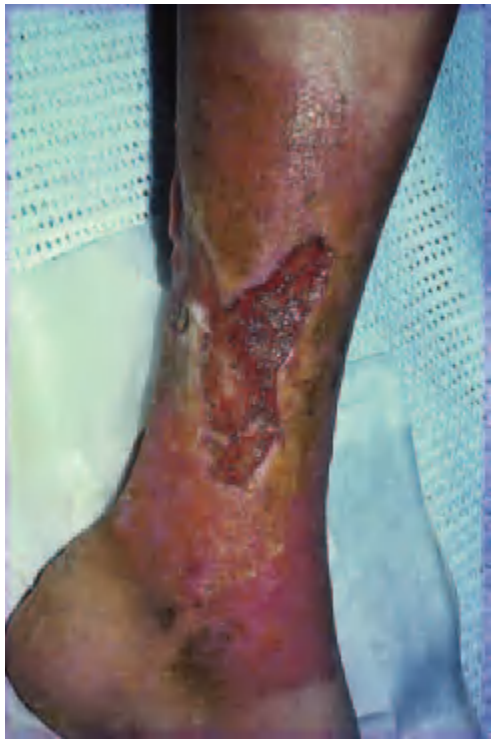

Fig. 11.1 Chronic venous ulcers with surrounding chronic edge.

resultant scarring, repeated episodes of infection and chronic lymphoedema tend to promote the chronicity of ulceration [4,5] (Fig. 11.1). The most important factor in the aetiology of venous ulcers is venous hypertension, resulting from valve incompetence, loss of calf muscle pump, or both. Venous thrombosis may also lead to venous hypertension. In familial cases of venous leg ulcers there may be an inherited resistance to activated protein C, leading to thrombosis and subsequent ulceration. Most cases of activated protein C resistance are caused by a specific mutation in exon 10 of the clotting factor V gene, known as the factor V Leiden mutation [6]. Less commonly, a polymorphic variant in the prothrombin gene (G20210A) may also be associated with increased risk of venous leg ulceration [7].

Arterial ulceration tends to occur in patients with other symptoms and signs of peripheral vascular disease, such as intermittent claudication, rest pain and loss of pulses. The ulcers are punched out with a demarcated border, usually with a dry base, and tend to occur at acral sites such as the tips of toes or over bony prominences. Ischaemic ulcers are extremely painful, especially at night. They may have a livid haemorrhagic edge, or a necrotic surface.

Diabetic ulcers are most commonly associated with diabetic neuropathy, although microvascular occlusive disease may also contribute [8–11]. They often result from unnoticed injury on the plantar surface of the foot, particularly over bony prominences, and are prone to infection. Healing tends to be slow and difficult to achieve with underlying osteomyelitis, so amputation is an unfortunately common outcome. Neuropathy may be associated with paraesthesia, anaesthesia and pain. Light touch, vibration and then position sense is usually lost in the affected foot. Little is known about how endothelial and metabolic abnormalities in diabetes affect wound repair. Hyperglycaemia may affect neutrophil activity. Loss of neuropeptide homoeostasis may be relevant, as intact neurosensory activity is essential for inflammation.

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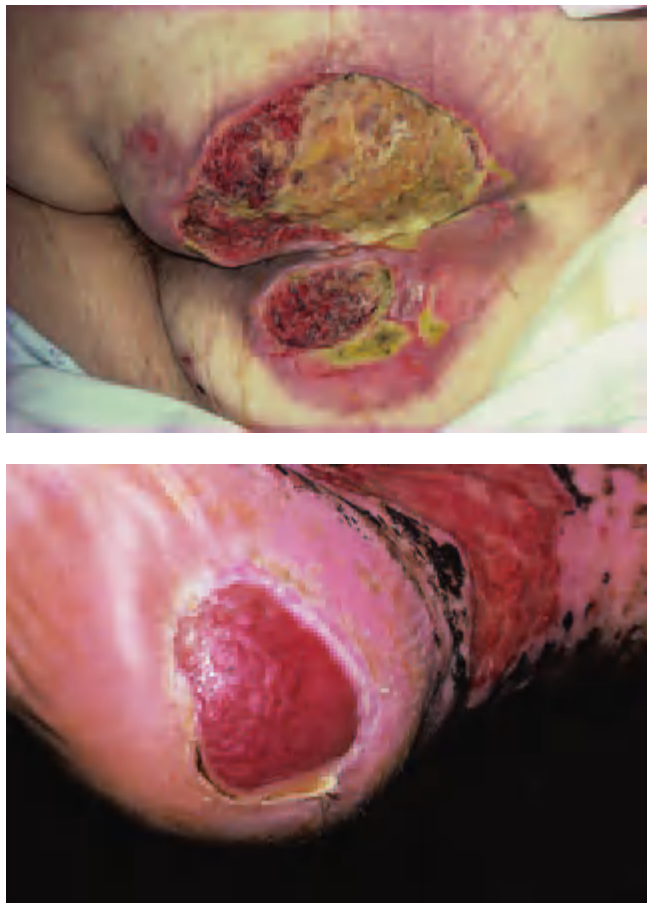
Pressure ulcers

Pressure ulcers are areas of local necrosis developing when soft tissue is compressed between a bony prominence and a rigid external surface [1–4]. The mean capillary pressure in healthy individuals is 25 mmHg, and external compression with pressures of 30 mmHg will occlude blood vessels so that tissues become anoxic and undergo ischaemic necrosis. Toleration of high tissue pressures depends on the patient's health and the extent and time of application, but short intervals of pressure relief will allow longer resistance. Any patient who is severely and acutely ill can develop pressure sores, because dehydration and hypotension will add to tissue destruction. Patient immobility is the major risk factor, but loss of sensory perception, including loss of consciousness, will contribute; the elderly infirm and neurologically disabled being most affected with pressure sores. General ill health, ischaemic heart disease, peripheral vascular disease, low blood pressure and high temperature all increase risk. Patients with poor nutrition, particularly with hypoalbuminaemia and low vitamin and zinc levels, have an increased risk of full-thickness ulceration. Drugs that suppress sensation, mobility or blood flow may be

Table 11.2 Staging of pressure sores.

I	Redness not resolving on relief of pressure
II	Loss of skin layers including epidermis and partial thickness of dermis
III	Full thickness with loss of subcutaneous tissue
IV	Full thickness with penetration to fascia, muscle, bone



(a)

(b)

Fig. 11.2 (a) Full-thickness sacral pressure sore with necrotic debris (stage III) in a patient with neurological coma. (b) Full-thickness heel pressure sore: clean and granulating in an immobile elderly patient.

aggravating factors, as is incontinence. Mattress positioning and quality can contribute. Relieving shear forces by positioning and protecting skin with lubricant or suitable dressings (e.g. polyurethane films) to prevent sticking is therefore essential.

The depth of ulcer is used to classify pressure sores, and there are a number of classification systems (Table 11.2). Eighty per cent are superficial and 20% deep, but even superficial sores will progress if left unrelieved. The most common sites are the areas of highest compression in the supine patient: 60% of all sores are over the sacrum (Fig. 11.2a), while the ischial tuberosities, greater trochanter and heel (Fig. 11.2b) account for 15%. Less common sites are elbows, knees, ankles and occiput. Heels erode when individuals sit immobile with heels supported. Early active mobilization not only relieves pressure, but also increases blood flow and muscle tone. When pressure is relieved, sores go through a process of débridement, where necrotic slough forms a hard dry black eschar. This later separates by natural proteolysis, followed by wound contraction, re-epithelialization and scar remodelling. The pathology of the pressure ulcer shows wedge-shaped infarcts of the subcutaneous tissue, capillary obstruction by microthrombi, and endothelial cell swelling and necrosis, with widespread inflammation.

Infection and osteomyelitis may follow wound breakdown, but significant tissue infection will be associated with redness, heat, oedema and tenderness, and systemic features such as leukocytosis, fever and pain, with an offensive exudate. Rapid débridement is particularly important in those at increased risk of infection, such as diabetics and the immunosuppressed.

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Complications of wound healing

Hypertrophic scarring

Keloids and hypertrophic scars are abnormal fibrous reactions to trauma, inflammation, surgery or burns in predisposed individuals, particularly in Afro-Caribbean skin, and most occur between the ages of 10 and 30 years. Hypertrophic scars remain restricted to the original wound, but keloids extend beyond the original wound and rarely regress. Trauma, skin tension and hormones are aetiological factors. Most keloids commence within a year of trauma in areas of highest skin tension: on the upper back, shoulders, anterior chest and upper arms. Reducing wound tension by orientating the wound along lines of relaxed tension may reduce scar formation. Familial predisposition to keloid formation is suggested by reports of recessive and dominant inheritance, but no human leukocyte antigen (HLA) association or polymorphic variants in TGF-β genes have been found [1]. Some skin diseases give keloidal scarring, including acne conglobata, acne keloidalis nuchae, hidradenitis suppurativa and certain infections such as chickenpox.

Keloids present clinically because they are disfiguring, painful or pruritic, especially when actively growing. The clinical course is variable, with keloids appearing from

weeks to months after the initiating lesion, growing to exceed the wound limits and then stabilizing. Suppurative necrosis occasionally complicates the lesion from vascular damage or pilosebaceous occlusion, particularly in acneiform lesions. Keloids seldom regress spontaneously, but may soften in the elderly.

Hypertrophic scars are distinguished from keloids by growth course and outcome. They occur soon after the trauma or inflammation, are limited to the site of the wound and regress in months to years, but may be difficult to distinguish from keloids in their early actively growing phase. Pathological distinction is not easy. Normal healing involves fibroplasia following the inflammatory phase. In keloids, this is progressive and forms nodular vascular proliferations surrounded by fibroblasts. These nodules transform into avascular collagenous bundles with persistent swirls of fibroblasts; myofibroblasts are prevalent in active keloids. The collagen bundles are randomly aligned and not orientated to the skin surface, whereas in normal scars the bundles lie parallel to the epithelial surface. There are suggestions from *in vitro* studies that abnormal collagen cross-linking, degradation or regulation by TGF-β may be involved in the pathogenesis [1–4]. Other cellular changes identified include alterations in α1β1 integrin collagen receptor expression [5] and in the regulation of fibroblast apoptosis [6]. *In vitro* studies also suggest that keloid keratinocytes may also influence keloid fibroblasts (and normal fibroblasts) to increase procollagen I and III gene and protein expression [7].

Treatment of keloids and hypertrophic scars initially involves intralesional corticosteroid injection, although hypopigmentation and local subcutaneous atrophy are possible local side effects. Mechanistically, triamcinolone acetonide has been shown to directly stimulate basic fibroblast growth factor (bFGF) expression and to inhibit TGF-β1 production [8], changes that are both recognized to reduce scarring. However, repeated injections of corticosteroids are always necessary, and seldom completely successful. Surgical therapy with excision or enucleation has a high recurrence rate in the absence of adjunct therapy, such as intralesional steroids, radiotherapy, pressure devices, silicone gels or other less proven agents including intralesional IFN-γ, IFN-α2 and retinoids. Prevention by minimizing trauma and surgery in predisposed individuals is important, as most treatments are unsatisfactory, although surgery combined with radiation has the lowest recurrence rates [9]. Other possible treatment options include laser therapy (585-nm pulsed-dye or Nd : YAG), electron beam irradiation, cryotherapy, intralesional 5-fluorouracil, intralesional verapamil and topical imiquimod [10–16]. *In vitro* studies suggest that the anti-inflammatory drug lysine acetylsalicylate also decreases proliferation and extracellular matrix gene expression (procollagen I and II) in keloid fibroblasts [17].

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Wound infection

Traumatic wounds may contain necrotic eschar and non-vital tissue or foreign material, which predisposes to bacterial contamination. Colonization of wounds with microorganisms can give a local concentration of organisms without overt tissue infection, which nonetheless mediates adverse events in the wound following binding of microorganisms to tissue, multiplication of organisms and triggering of a host immune response. Wounds that contain more than 10^5 bacteria per gram of tissue are likely to lead to clinical infection [1]. Bacteria compete for metabolites (glucose and oxygen), release toxins and proteases (leading to cell damage), and activate complement (prolonging inflammation). Patients with systemic problems

such as diabetes mellitus, steroid therapy, increasing age, local ischaemia and immunosuppression are more prone to develop infection. Fibronectin in the wound bed is known to predispose to bacterial adhesion.

Chronic wounds are especially prone to infection [2–5], partly because of the underlying pathology and the common presence of necrotic debris, where superinfection with Gram-negative and anaerobic organisms gives a characteristic offensive odour. There is no evidence that bacterial contamination will delay healing [6], but systemic antibiotic treatment will be required for evidence of tissue cellulitis, with spreading redness, oedema, pain and tenderness around the wound. Wound swabs are commonly positive for Gram-negative bacilli, particularly *Pseudomonas* and *Proteus*, and the other common pathogen is *Staphylococcus aureus* (56% leg ulcers and 51% pressure sores [2]). The isolation of *Bacteroides* may be associated with impaired healing. Bacterial counts are often elevated under occlusive dressings, and there is no good explanation for the low incidence of clinical infection, although limiting exogenous pathogenic organisms by the barrier of the dressing may play a part [4,7,8]. In recent years, emergence of multiple antibiotic resistance of methicillin-resistant strains of *Staphylococcus aureus* (MRSA) has become a major clinical problem worldwide [9]. At a cellular level, the key determinant of the broad-spectrum beta-lactam resistance in MRSA strains is the activity of the penicillin-binding protein 2a (PBP2a) [10].

Patients with chronic wounds are frequently treated with oral antibiotics when suspected of clinical infection, which predisposes to the development of organism resistance. Widespread use of ciprofloxacin for its anti-*Pseudomonas* activity has given rise to resistant isolates from leg ulcers [5].

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Other local factors influencing wound healing

Dessication of the wound allows the formation of a dry eschar, leading to slower re-epithelialization. Indeed, covered acute wounds resurface up to 40% faster than those exposed to the air [1]. A moist wound environment also encourages more rapid angiogenesis and dermal repair [2–4]. Occlusion of chronic wounds may also increase healing rate over the first 4 weeks.

Haematoma formation may impede wound healing because of local tissue hypoxia as well as providing a medium for accumulation and growth of bacteria and other microorganisms [5]. Haemostasis is therefore important in surgical procedures, as is good wound handling because crushed tissue or over-tight sutures may cause ischaemia and promote inflammation and secondary infection.

Foreign bodies in wounds tend to lower pH, reduce oxygen tension and activate complement, thereby delaying wound healing [2,5].

Contact dermatitis may develop to a variety of topical antimicrobial preparations applied to wounds, especially to neomycin [5]. Less common allergens include gentamycin, hydrogen peroxide and hexachlorophene. Potential sensitizers include ethyl alcohols, chlorhexidine, quarternary ammonium compounds and benzoyl peroxide. Superimposed contact dermatitis usually delays wound repair and some vehicles of topically applied medications may also affect epithelialization [6].

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Wound healing and ageing

Wound healing in the elderly progresses more slowly, and it is thought that all phases of the wound-healing process are affected, with decreased proliferative responses, delayed angiogenesis, delayed remodelling and slower re-epithelialization [1–6]. Age-related reductions are seen in keratinocyte and fibroblast migration (especially in poorly oxygenated wounds), integrin function, actin cytoskeletal organization and inflammatory chemokine responses [7–10]. Incisional wounds in older individuals have a lower tensile strength, and postoperative surgical

dehiscence rates are higher [11]. However, elderly patients do successfully heal after major surgery, such as open heart surgery, and so the differences from younger individuals are not contraindications to surgical procedures. Other factors adversely affecting wound healing, such as peripheral vascular disease, cardiac problems and poor nutrition, are also more likely to occur in the elderly.

Superficial wounds heal more slowly among the elderly: dermabrasion (healed in 10 days for 25-year-olds and 21 days for 75-year-olds); suction blisters on the forearm (3.6 weeks mean for the young and 5.4 weeks for the elderly to return completely to normal) and split-thickness wounds, such as donor sites, all show the same pattern. Meshed autografts greatly accelerated healing (10 days) compared with vaseline gauze (10–36 days) in the treatment of donor sites in the elderly, which suggests that reducing the need for re-epithelialization is of considerable benefit [12]. New techniques of wound healing, such as cultured epidermal grafts, are particularly applicable to the elderly, but care must be taken to treat vigorously underlying medical conditions.

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Systemic factors affecting wound healing

Systemic diseases, including vascular disorders (e.g. congestive cardiac failure, hypertension, atherosclerosis, venous insufficiency or lymphoedema), as well as metabolic disorders (e.g. chronic renal failure, chronic liver disease or diabetes mellitus) may all interfere with wound healing.

Underlying unrecognized or untreated diseases may also retard healing. For example, ulceration of the skin may result from ischaemic necrosis secondary to a primary vasculitis such as polyarteritis nodosa, rheumatoid vasculitis or neutrophilic inflammation such as pyoderma gangrenosum. Although the early stages of such lesions often have a prominent haemorrhagic component, they may result in indolent chronic ulcers. The site and distribution of lesions are often a clue to the underlying pathology, as are signs of inflammation, haemorrhage or undermining of the edge. Vasculitic lesions particularly affect acral sites and areas of impaired vascularity, and signs of livedo or palpable purpura may be present. Although lesions in necrotizing venulitis may be in the stasis areas, they will also occur on arms, legs and buttocks. Active treatment of the underlying disease will often stimulate surprisingly rapid healing, and intralesional steroids in the edge of a chronic wound help even chronic pyoderma gangrenosum lesions. Genetic abnormalities may also contribute to impaired wound healing, in particular abnormalities of connective tissue, as found in Marfan's syndrome, Ehlers–Danlos syndrome and prolidase deficiency.

Malignancy may be relevant to impaired wound healing, either because of ulceration occurring within a tumour or because malignancy arises on a background of chronic ulceration. Non-melanoma skin cancers, both basal cell and squamous cell carcinomas, may ulcerate. Many of these lesions will be on sun-exposed sites, but they may be extensive in patients exposed to carcinogens, and lesions on the legs may be misdiagnosed, although this is a common site of actinic lesions in women. A malignant ulcer will continually grow in size, be irregular in shape and usually have a thickened edge. The site may be atypical for a chronic ulcer, which provides an important clue. A diagnostic biopsy of the edge should always be considered in any ulcer increasing in size. Excision and grafting will often be required on the lower leg. Malignant change can develop in a chronic non-healing ulcer, and will cause failure to heal and progressive enlargement. Again suspicion is raised by changes in the ulcer edge and size, and a diagnostic biopsy is indicated. Malignancy arising in chronic ulcers following burn injuries is referred to as Marjolin's ulcer; the tumour is usually a squamous cell carcinoma [1].

Protein malnutrition is a major factor affecting wound healing, and malnourished patients have an increased risk of surgical complications [2]. Surgery, trauma or sepsis may lead to relative protein deficiency and a negative nitrogen balance. Angiogenesis is inhibited, and fibroblast proliferation and collagen synthesis are impaired; these abnormalities are reversed on protein replacement. Nutritional support also maintains immune function, decreases the risk of infection and facilitates wound healing, especially in cancer patients. Serum levels of albumin, transferrin and IGF-1 are indicators of the status of protein stores [3].

Vitamin deficiency may have adverse effects on wound healing, particularly in the case of vitamins A, C and K. Vitamin A modulates cell differentiation and can reverse inhibitory effects of glucocorticoids on healing of some wounds. Lack of vitamin A also compromises epithelialization, collagen synthesis and inflammation [4]. Vitamin C deficiency seriously impairs the speed and strength of wound healing because of markedly reduced collagen synthesis, formation of fragile capillaries and decreased resistance to infection [5]. Vitamin K is essential in the synthesis of blood clotting factors II, VII, IX and X. Deficiency of vitamin K impairs haemostasis and may result in haematoma formation.

Trace element deficiency usually occurs in combination with other deficiencies, particularly in chronic malabsorption and alcoholism. Zinc is a component of many coenzyme complexes, and severe deficiency results in abnormal lymphocyte function, increased susceptibility to infection and delayed wound healing [6]. Zinc-deficient wounds are also abnormally weak. Although zinc metabolism and distribution may be abnormal in patients with non-healing leg ulcers, zinc supplementation probably only accelerates healing in zinc deficiency. Iron deficiency interferes with wound healing by causing anaemia and tissue hypoxia, but also interferes with bacterial killing, increasing the risk of wound infection. Clearly, most deficiency states are multiple and it is difficult to distinguish which deficiency is causing the problem in healing. Local nutritional problems are also of importance in consideration of delayed healing, and loss of an adequate blood supply accounts for the bulk of the 'non-healing wounds' seen in clinical practice, including decubitus ulcers and ulcers of the lower legs resulting from various types of vascular disease.

Drugs, such as corticosteroids, reduce DNA synthesis in the epidermis and induce morphological changes in fibroblasts [7,8]. In addition, it is well established that they induce dermal atrophy (probably by inhibiting synthesis of collagen) and retard re-epithelialization. It is therefore not surprising that long-term administration of these drugs either systemically or topically impedes the healing of wounds, and predisposes both to wound dehiscence and to chronic ulceration. Other drugs such as anticoagulants, cytotoxic agents, aspirin, colchicine, penicillamine, ciclosporin and phenylbutazone [9–11] may have adverse effects on wound healing, from direct effects on cells taking part in the healing process (as in cytotoxic agents), effects on vascularization or the enhancement of infection.

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Principles of treating wounds

Measurement

There are a number of essential measurements that are required to assess the primary pathology, such as Doppler studies of arterial pressure. However, progress in ulcer treatment is difficult to assess clinically at visits, often by multiple different health care personnel, and accurate wound measurement is required to establish the area, shape and volume of the wound. Serial photography and computerized planimetry are not possible to use in standard practice in the community, so tracings on plastic films are widely used. Deep flask-shaped pressure ulcers are particularly difficult, but the volume of fluid under an occluding membrane can be roughly measured. Research studies use laser Doppler assessment of blood flow, ultrasound measurement of depth and direct measurement of arterial or venous pressures.

Compression bandaging

Compression bandaging and elastic stockings are of proven benefit in reversing the effects of chronic venous hypertension, by raising the local hydrostatic pressure and reducing superficial venous pressure [1–4]. Indeed, a systematic review of venous leg ulcer compression bandaging trials has found that compression increases ulcer healing rates compared with no compression, that multilayered systems are more effective than single layer dressings, and that high compression is more effective than low compression [5]. The compression increases flow velocity, and results in the restoration of fibrinolysis and breakdown of fibrin cuffs. The optimal external pressure of 35–40 mmHg may not be tolerated, but lower pressures may enhance ulcer healing. It is essential not to deliver such levels of pressure to an ischaemic leg, as necrosis or gangrene may result [6], and so Doppler pressures should be measured and the ankle brachial pressure index must be greater than 0.8. Traditional crêpe bandaging,

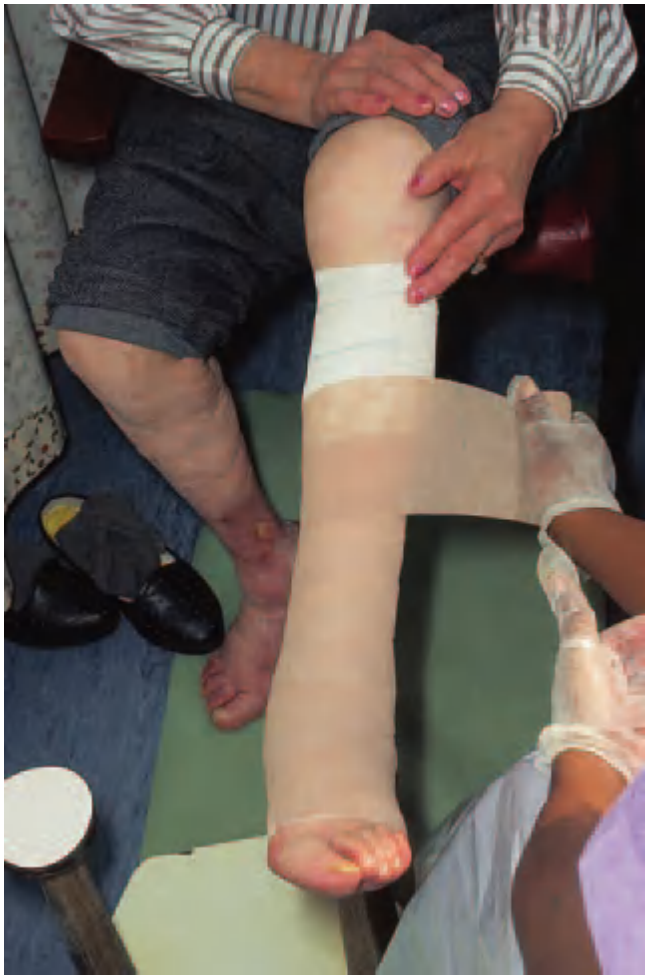

Fig. 11.3 Application of a four-layer bandage.

etc., provides little external compression, but newer short-stretch and high-performance bandages are much more effective. There is variation in pressure according to the technique of the user. A large community programme tested a four-layer bandaging technique (Fig. 11.3) designed to deliver sustained consistent compression for a week between dressing changes (crêpe/Velband/Elset/Coban) [1]. The excellent healing rate (80% of ulcers in 12 weeks) in this study has led to the widespread adoption of the technique in the UK, but the success rates depend on the local clinical profile; specialist wound-care units often collect patients who have failed all conventional treatments.

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Organization of wound-care services

The delivery of currently available wound-care management is not uniform, and many basic items, such as a wide range of compression bandages, are not readily available in the community. There has therefore been a movement to provide wound-care units, with an integrated hospital-based wound clinic interacting with primary care clinics in the community, thus upgrading community nursing. Wound-care nurse specialists are playing a major part in developing these services. They should improve wound-healing rates in the community and also ensure that only patients with wounds requiring special expertise, such as skin grafting, vascular surgery or medical treatment, are referred to more expensive hospital facilities.

Topical therapy

Antiseptics. As clinical infection was thought to retard wound healing, it has been common practice in the past to use antiseptic antibacterial agents to cleanse wounds. However, the advent of systemic antibiotics for infection control has led to a reappraisal of antiseptic usage, as they have now been shown to retard re-epithelialization and slow healing [1,2].

Saline dressings can be used to irrigate and clean a wound, removing cellular and bacterial debris, and are safe but pharmacologically inactive. Hexachlorophene and chlorhexidine are tissue toxic, and painful to apply to open wounds. Hydrogen peroxide is rapidly broken down to give molecular oxygen and, as with sodium hypochlorite, is rapidly inactivated by tissue exudate, although the physical effervescence may help surface débridement. Povidone–iodine solution is also toxic in high concentrations, but can maintain bactericidal activity at low concentration. As iodine can cause contact dermatitis, it should be used with caution.

Silver sulfadiazine compounds are widely used in burn care, being effective against *Staphylococcus aureus* and *Pseudomonas aeruginosa*, and possibly having an effect by enhancing epithelialization [3].

Antibiotics. Topical antibiotics have also been used to reduce tissue infection in wounds and are often incorporated into dressing materials, but they are frequent causes of contact dermatitis, particularly neomycin and gentamycin. Use of systemic antibiotics for true tissue infection is now preferred, particularly with the development of antibiotic-resistant organisms. Mupirocin appears to

sensitize infrequently but, as it may be effective in multi-resistant *Staphylococcus aureus* (MRSA), it should not be generally used. Topical antibiotic use should be strictly limited.

Benzoyl peroxide. In the pig, the application of 20% benzoyl peroxide suspension in a lotion base greatly increased the rate of re-epithelialization [4], whereas a 50% suspension retarded healing. Wounds treated with 20% benzoyl peroxide show a pronounced giant cell infiltrate and a highly vascular granulation tissue, and it has been suggested that the ability of benzoyl peroxide to enhance wound healing is related to its ability to attract macrophages and histiocytes into the wound. It may also be related to the release of molecular oxygen, as hyperbaric oxygen is known to facilitate healing in superficial and full-thickness wounds.

Traditional. Honey mixed with butter was applied to wounds by the Ancient Egyptians as 'Balm of Gilead', and both honey and cane sugar are still used by traditionalists as wound dressings [5,6]. Cane sugar containing sucrose, which is not metabolized outside the gastrointestinal tract, prevents bacterial growth by decreasing the available water, and it has also been claimed that it might stimulate granulation tissue [7]. A systematic review of randomized trials of topical honey in superficial burns and wounds has concluded that confidence in a conclusion that honey is a useful treatment for superficial wounds and burns is low, but that there was biological plausibility [8].

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Wound débridement

When there has been ischaemic necrosis or progression in a chronic ulcer, necrotic debris may accumulate on the surface of a wound. Surgical débridement under local or general anaesthetic may be required to promote healing. Medical treatment for hydrating the slough, so it can be removed easily, can be performed by application of aqueous (or potassium permanganate) compresses or continual irrigation. Interactive hydrogel and hydrocolloid dressings may be beneficial. Proteolytic enzymes such as streptokinase must be used carefully to prevent damage to viable epithelia, but newer agents are more specific. The two enzymes most commonly used in Europe are fibrinolysin/desoxyribonuclease and collagenase. Studies in necrotic ulcer animal models have shown the effectiveness of collagenase in wound débridement but no clinical efficacy for fibrinolysin/DNAse in this model [1]. Proteolytic enzymes derived from Antarctic krill have also been shown to be effective in wound débridement [2]. Maggots have made a recent reappearance on the therapeutic scene [3]. Sterile maggots of the green bottle fly, *Lucilia (Phaenicia) sericata*, are used for débridement. Up to 1000 maggots are introduced into the wound and left for 1–3 days. One advantage of this therapy is that the maggots effectively separate necrotic from living tissue, thereby making subsequent surgical débridement much easier [4].

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Wound dressings

Wound dressings protect the surface of wounds and prevent bacterial and viral contamination of healing wounds. Studies have shown that occlusive dressings maintaining a moist environment have beneficial effects on wound healing through accumulation of endogenous growth factors in wound fluid, and other biological effects on angiogenesis, generation of granulation tissue and re-epithelialization [1–5]. The main concern about wound occlusion has been a perceived increased risk of tissue infection, and indeed occlusion of wounds can lead to higher bacterial counts. However, rates of tissue infection are low and there appears to be no impairment of re-epithelialization [6].

Synthetic dressings are divided into several categories, based on physical properties. These comprise: polyurethane films, hydrogels, hydrocolloids, foams and alginates. In addition, newer dressings have emerged that have specific clinically relevant qualities. These include: collagens, hydrofibres, antimicrobial dressings, débriding agents, odour-absorbing dressings, biosynthetic dressings and hyaluronic acid dressings [7]. Clinical indications for optimal selection of appropriate dressings are outlined in Table 11.3.

Table 11.3 Selection of appropriate wound dressings.

Types of wound	Suitable dressings
Acute	
Abrasions, lacerations	Films, hydrocolloids, thin foams
Catheter or cannula sites	Films
Burns	Hydrocolloids, hydrogels, biosynthetic dressings
Donor sites	Films, hydrocolloids
Dermabrasion, chemical peels	Hydrogels
Surgical wounds	Films, hydrocolloids, hydrogels, alginates
Chronic	
Venous ulcer	
Heavy exudates	Foams, alginates, hydrofibres
Moderate exudates	Hydrocolloids, foams
Mild exudates	Hydrogels, hydrocolloids
Malodorous	Foams, alginates, hydrocolloid charcoal
Arterial	Hydrogels
Neuropathic	
Moist	Hydrogels, alginates, hydrofibres
Dry	Hydrogels, hydrocolloids
Pressure ulcers	
Stage I	Films, thin hydrocolloids
Stage II–III	Hydrocolloids, foams, hydrogels, débriding agents
Stage IV	Alginates, hydrofibres, débriding agents

Films (e.g. Opsite®, Bioocclusive®, Tegaderm®) are thin polyurethane transparent sheets. They are often coated with adhesive to stick to the margins of the wounds. Films are useful for superficial wounds or as dressings around catheter sites (wounds that are only mildly exudative as they cannot absorb exudate). Care must be taken when removing film dressings because new epithelium can easily be stripped [8–10].

Hydrogels (e.g. Intrasite®) are translucent jelly-like non-adhesive materials that maintain a moist environment. They are semi-permeable to gas and water vapour and are available as sheets, impregnated into gauze or in spray bottles. They are suitable for mildly exudative wounds because they absorb only a small amount of exudate, and a secondary dressing is required. Hydrogels often have a soothing and cooling effect because the cross-linked polymers tend to entrap water and reduce the skin surface temperature by up to 5°C.

Hydrocolloids (e.g. Granuflex®) comprise an opaque mixture of adhesive absorbent polymers and gelling agents such as sodium carboxymethylcellulose. They adhere well to the wound edge and have an impermeable polyurethane backing. Hydrophilic particles in the dressing interact with the wound exudate to form a yellow gel next to the wound. This can be confused with a purulent wound discharge, but the acidic microenvironment forms an antibacterial and antiviral barrier and is helpful in wound débridement. Hydrocolloid dressings can adhere to any dry or moist site, allowing the patient to bathe or shower. Side effects from these dressings include an increased amount of granulation tissue and tissue maceration [11,12].

Foams (e.g. Allevyn®) are absorbent opaque polyurethane sheets that are permeable to gas and water vapour. They may be of variable thickness and are suitable for moderately or heavily exudative wounds, although foam dressings may stick and be difficult to remove if the exudate dries out.

Alginates (e.g. Kaltostat®) are made from brown seaweed and are highly hydrophilic, changing from fibrous to gel form on absorbing water. Indeed, alginates can absorb up to 20 times their own weight. The ingredients include calcium salts of alginic, mannuronic and guluronic acids. When exposed to sodium-rich solutions (such as wound exudate) calcium and sodium ions interchange resulting in increased amounts of free calcium. This leads to amplification of the normal wound clotting cascade. Alginates are available in sheets or rope forms and are suitable for dressing heavily exudative wounds, deep wounds and cavities. In addition, they can be easily moved without damage to the wound surface when well hydrated [12].

Collagen dressings are made from cowhide and are available as sheets, pads, particles or gels. Sometimes they are also combined with alginates or hydrogels. These dressings accelerate wound healing by providing a collagenous matrix to enhance cell migration during wound healing.

Hydrofibres are extremely absorbant, up to three times more so than alginates. The absorbant material is composed of carboxymethyl cellulose fibres that form a soft gel when exposed to heavily exudative wounds.

Antimicrobial dressings are designed to counter the antihealing effects of bacterial colonization in chronic wounds. While it is recognized that topical antimicrobials

in high concentration interfere with wound healing, antiseptics such as povidone–iodine 0.001% have been shown to maintain bactericidal activity but without any cytotoxic effects on the healing wound. Slow-release iodine preparations such as cadexomer–iodine are suitable for chronic venous ulcers [13]. Silver compounds have also been shown to prevent chronic wound colonization by bacteria.

Débriding dressings in the form of chemical or enzymatic looseners can be used to remove necrotic tissue, often to supplement hydrocolloid dressings.

Odour-absorbing dressings are based on activated charcoal that absorbs bacterial breakdown products. These dressings are often combined with foam, alginate or hydrocolloid dressings.

Biosynthetic dressings comprise a polyurethane film or silicone membrane with collagen peptides added as a biological component. These dressings are suitable for temporary coverage of burns wounds.

Hyaluronic acid dressings are made of biodegradable absorbent bipolymers that form a hydrophilic mesh with the wound exudate. Hyaluronic acid accelerates granulation tissue formation and re-epithelialization and these dressings help stabilize the clot and attract inflammatory cells crucial to the wound-healing process.

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Other pharmacological agents

Fibrin cuffs around cutaneous microvasculature are associated with impaired fibrinolysis; therefore stanozolol, an anabolic steroid that enhances fibrinolysis, was suggested as an agent to treat lipodermatosclerosis [1]. Although early studies suggested improvement, there is no evidence of benefit in established ulceration.

Pentoxifylline also increases fibrinolysis, decreasing blood viscosity, increasing red cell deformity and inhibiting platelet aggregation, and limited studies suggest benefit (e.g. at a dosage of 400 mg three times daily in chronic venous ulcers [2]).

Prostaglandins E1 and I2, calcium-channel blockers such as nifedipine, and serotonin antagonists such as ketanserin, show conflicting results in peripheral vascular disease and venous ulceration [3]. Some calcium-channel blockers may also have a direct effect on keratinocyte migration [4].

Ascorbic acid is a co-factor for proline hydroxylase necessary for collagen synthesis, but it is of doubtful benefit in patients who are not vitamin-deficient. In accordance with the Pauling concept that most individuals do not have enough vitamin C in their diet, large dietary supplements of ascorbic acid were given to a group of patients with pressure sores in a double-blind study; considerable increase in the rate of healing was noted in the treated group [5]. Ascorbic acid has also been shown to have an important function in the preparation of *in vitro* skin substitutes, with direct effects on epidermal barrier formation, basement-membrane integrity and the quality of skin contracture after grafting [6].

The precise role of zinc in wound healing is at present unclear. Early studies claiming that systemic zinc therapy accelerated wound healing in humans and other animals have been supported by some workers and refuted by others [7]. This discrepancy may be partly explained by studies that have shown that systemic zinc reduces the healing time in patients with venous and arterial leg ulcers, but only if the patients are initially zinc-deficient. Topical zinc is also unlikely to have a major effect [8,9]. Nevertheless, zinc does appear to have an important antioxidant role in skin [10], and mutations in the zinc transport gene, *SLC39A4*, have recently been demonstrated in the zinc-deficiency disorder, acrodermatitis enteropathica, an autosomal reccessive condition associated with chronic superficial skin ulceration and poor wound healing [11].

Treatment of wounds with oxygen has been considered to be helpful in some wounds, although recent studies have focused on the state of the redox environment of wounds and the role of nitric oxide in wound repair [12,13]. Nitric oxide is a small radical, formed from the amino acid L-arginine by three distinct forms of nitric acid synthase. The inducible form (iNOS) is synthesized in the early stages of normal wound healing, and experimental knockout of the gene leads to delayed wound healing. By contrast, improved wound healing can be obtained by the addition of nitric oxide or arginine to wounds. Nitric oxide has also been shown to regulate collagen synthesis,

cell proliferation and wound contraction [12]. Although not yet of practical therapeutic value, manipulation of nitric oxide in skin may have future pharmacological relevance to improving normal or abnormal wound healing.

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Skin grafts

Pinch grafts and split-thickness skin grafts

For pinch grafts, small (2–3 mm^2) pieces of partial thickness skin can be removed under local anaesthetic, as an outpatient procedure or by a specialist nurse within the home, and planted across the wound bed to form islands for re-epithelialization with greatly increased healing (Fig. 11.4). The time-consuming nature of the procedure is the major problem, but repeated grafts can be performed, and the donor sites heal very rapidly. The approach may benefit both arterial and venous leg ulcers, and its suitability for primary care settings has been demonstrated [1].

For split-thickness skin grafts, a large sheet of partial thickness skin is removed using a dermatome. The plane of cleavage may be variable, either within the papillary or reticular dermis. The graft is usually meshed before application as this tends to reduce the chances of the graft subsequently detaching as a result of the wound exudate. Split-thickness skin graft donor sites are often painful.

In vitro-prepared skin grafts

The feasibility of growing human keratinocytes in culture was first established in 1975 [2] and the possibility of expanding a small donor site up to 10 000-fold led to the application of cultured keratinocytes for grafting [3]. Grafts established from the patient's own skin (autografts) or from allogeneic donors (allografts) have subsequently been formulated for clinical use (Fig. 11.5).

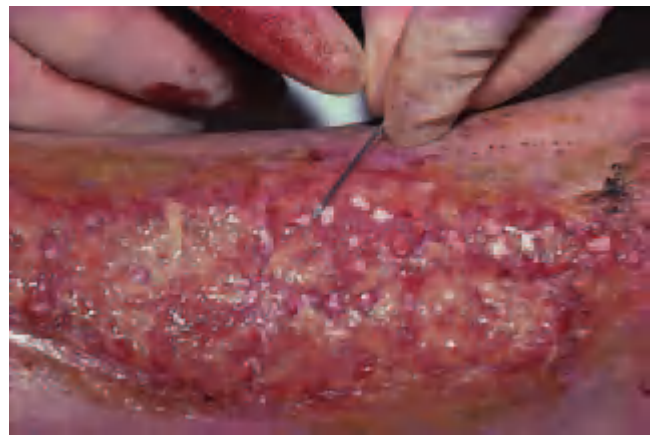
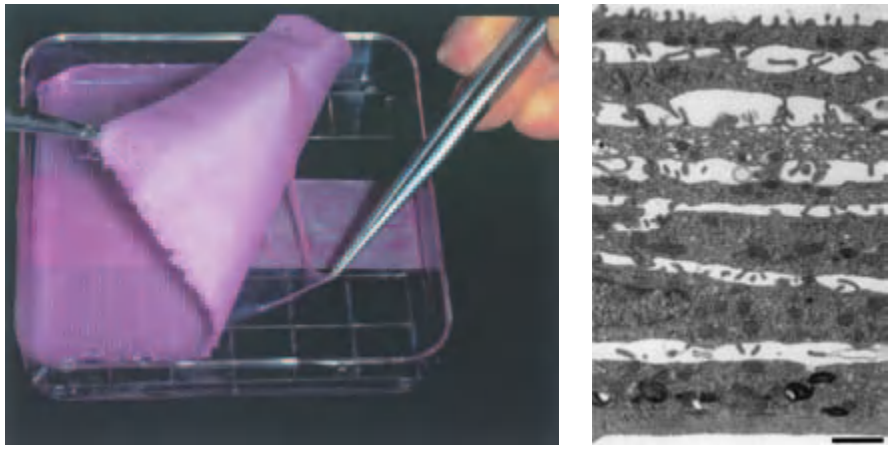


Fig. 11.4 Application of pinch grafts to a leg ulcer.

The earliest clinical use was to treat major burns patients, and the translucent sheets became a permanent stable epidermis, visible after 12–14 days [4]. The resulting graft remained fragile, and remodelling of the dermis occurred only slowly [5]. The incorporation of a dermal connective tissue in the graft on the wound bed appears to enhance graft take [6]; therefore areas of take are now much improved. Cultured epidermal autografts have also been used to treat deep dermal naevi [7], vitiligo and chronic leg ulcers [8], where repeated grafting from passaged cultures is a major advantage. The use of polymer delivery systems, such as hyaluronate membranes, allows earlier grafting than previously possible. Epithelial cell grafts can also be used in the oral cavity [9], mastoid cavity [10], urethra [11] and genital mucosa. Allografts of cultured keratinocytes do not survive long term [12–14], but have been shown to have a wound-healing effect in chronic leg ulcers [15], probably because of the production of appropriate growth factors and extracellular matrix proteins. Keratinocyte allografts have also been used in tattoos [12], donor sites [12], burns [13] and facial dermabrasion wounds.

Keratinocytes can also be subcultured onto a complex matrix or dermal substitute to form skin equivalent cultures, varying from fibroblast-contracted collagen gels [16] to de-epidermalized dermis. These have been used to treat burns, tattoos and leg ulcers and patients with junctional epidermolysis bullosa [17]. Allogenic skin equivalents also appear to promote healing of chronic ulcers, and a number of these products are now commercially available.



(a) (b)

Fig. 11.5 (a) Cultured keratinocyte allograft prepared for clinical use. (b) Ultrastructure of allograft.

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Growth factors to augment wound healing

All cells involved in the wound-healing process (inflammatory cells, epidermal keratinocytes and mesenchymal cells) can synthesize a wide range of membrane-bound and free growth factors, whose effects are mediated by specific growth factor receptors for each family of growth factor. Growth factors are multifunctional and have differing effects on different cell types, and can induce expression of other cytokines and their receptors in an autocrine and paracrine fashion. Growth factor activity can also be regulated via ECM components and proteolytic activation, so the net result of growth factor profiles in a wound bed will differ temporally according to the cascade of cytokine release and also with the wound type. The addition of exogenous growth factors in pharmacological amounts may have measurable effects in wound-healing models, but can be disappointing in the clinical arena, as complex synergistic and antagonistic effects may result in a different net result [1–4]. Furthermore, bacterial superinfection of wounds may completely obliterate any possibility of a useful therapeutic response from the exogenous growth factors.

In animal models, a number of growth factors have positive effects on granulation tissue formation and angiogenesis, including PDGF, FGFs [5] and TGF-β. PDGF and TGF-β have also been shown to increase tensile strength of a wound [6]. EGF appears to enhance epithelialization as well as having mesenchymal effects [7–9]. Growth factors appear to have measurable effects but are of dubious clinical benefit. EGF, for example, demonstrated a 15% acceleration in healing in donor sites. A crude extract of platelet releasate has also been reported to enhance wound healing [10]. Conversely, use of the antiparasitic drug, suramin, which is known to inhibit binding of TGF-β, PDGF, bFGF and EGF to receptors, has been shown to retard wound repair. PDGF is currently the only licensed recombinant growth factor for treating recalcitrant wounds, and its usefulness in the management

of chronic neuropathic diabetic ulcers has been demonstrated in clinical trials [11].

Endogenous overproduction of growth factors may be associated with poor long-term cosmesis or impaired wound healing, and therefore neutralizing the effects of growth factors may be a desirable therapeutic intervention. The role of TGF-β in mediating scarring has been blocked in animal models by neutralizing antibodies and binding agents such as mannose-6-phosphate [12]. The potential clinical usefulness of these agents is currently being evaluated in normal and abnormal scar formation.

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Chapter 12

Genetics and Genodermatoses

J.I. Harper & R.C. Trembath

Genetics and disorders of the skin

Progress in the field of genetics in medicine continues at an astonishing rate. Most of the known single-gene disorders (e.g. genodermatoses) have at least been mapped to a particular chromosomal region and, in ever-increasing number, the causal genes have been isolated and studied (Table 12.1). In contrast, progress towards unravelling the molecular genetic basis of the more common and complex disorders (e.g. psoriasis and atopic eczema) has been somewhat slower. However, recent progress with the human sequencing effort together with radically improved computerized analytical strategies offer the prospect of progress in understanding the pathogenesis of these important dermatological disorders. The extraordinary rate of such developments has contributed to the parallel progress in understanding of the fundamental aspects of human skin characteristics. In combination, this revolution offers enormous opportunity and excitement for future research, together with the prospect of improved therapies for skin disease.

The Human Genome Project, an international effort to describe the entire human genetic sequence (3×10^9 bases), has hit targets ahead of expectation, and the recent release of the first draft [1] has necessitated a radical readjustment of the likely number of human genes within the genome (35 000–40 000), representing half the number predicted at the time of publication of the last edition of this book [2]. The genome sequences of a range of other organisms, including the nematode worm *Caenorhabditis elegans*, the fruit fly *Drosophila melanogaster* and the mouse, have now been completed. These act as important models for exploring gene structure and function in relation to tissues or the whole organism and have been extensively investigated in relation to a number of important genodermatoses.

The Internet provides the most satisfactory window on all this activity and a number of the more informative sites are listed below.

- UK Human Genome Mapping Project Resource Centre (http://www.hgmp.mrc.ac.uk). Access to a wide range of databases and resources for genetic studies, including links to PubMed.
- The National Center for Biotechnology Information (http://www.ncbi.nlm.gov). Main entry point for information about the Human Genome Project.
- Mutation Database, Cardiff (http:// www.uwcm.ac.uk/uwcm/mg/hgmd0.html).
- Online Mendelian Inheritance in Man (OMIM) (http://www.ncbi.nlm.nih.gov/omim/). OMIM is a catalogue of the 6000 known human Mendelian characters with skin manifestations, and was created by Dr Victor McKusick of Johns Hopkins Hospital, Baltimore, USA. OMIM is an excellent starting point for acquiring up-to-date information on human Mendelian characters or *phenotypes*. Each character is given a six-digit MIM number, which is widely used to identify inherited disorders in the medical literature. The first digit of the MIM number indicates the mode of inheritance (historical): 1, autosomal dominant; 2, autosomal recessive; 3, X-loci or phenotype; 4, Y-loci or phenotype; 5, mitochondrial loci; and 6, autosomal loci or phenotypes added after 1994.

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12.2 Chapter 12: Genetics and Genodermatoses

Table 12.1 Human genes relevant to dermatology. Compiled from *On-line Mendelian Inheritance in Man* OMIM™: the online version of McKusick's catalogue of Mendelian disorders [www.ncbi.nlm.nih.gov/omin/].
MIM no.: identification number of the entry in Mendelian Inheritance in Man that describes the locus and the phenotypes related to genes at the locus.
Gene symbol: symbol approved by the Nomenclature Committee of the Human Gene Mapping Workshops and their successor organization.

Chromosome site	MIM number	Disease	Gene symbol	Gene/gene product
1p36	155600	Malignant melanoma, cutaneous	155600 *CMM*, *MLM*, *DNS*	Cutaneous malignant melanoma/ dysplastic naevi
1p36.3–p36.2	225400	Ehlers–Danlos syndrome type VI	153454 *PLOD*, *PLOD 1*	Procollagen-lysine, 2-oxoglutarate 5-dioxygenase (lysine hydroxylase)
1p35.1	133200	Erythrokeratoderma variabilis	603324 *GJB3*, *CX31*, *DFNA2*	Gap junction protein, β3
1p35.1	133200	Erythrokeratoderma variabilis with erythema gyratum repens	605425 *GJB4*, *CX30.3*	Gap junction protein, β4
1p34	176100	Porphyria cutanea tarda/ hepatoerythropoietic porphyria	176100 *UROD*	Uroporphyrinogen decarboxylase
1p21–p13.3	600193	Waardenburg's syndrome type 2B	600193 *WS2B*	Waardenburg's syndrome type 2B
1q21	177900	Psoriasis, susceptibility	603935 *PSORS4*	Psoriasis susceptibility 4
1q21	603165	Atopic dermatitis, susceptibility	605803 *ATOD2*	Dermatitis, atopic, 2
1q21	247100	Lipoid proteinosis	602201 *ECM1*	Extracellular matrix protein 1
1q21	604117 602036	Vohwinkel's syndrome with ichthyosis Erythrokeratoderma progressiva symmetrica	152445 *LOR*	Loricrin
1q21	146700	Ichthyosis vulgaris	135940 *FLG*	Filaggrin
1q21.2	151660 176670	Familial partial lipodystrophy Hutchinson–Gilford progeria	150330 *LMNA*	Lamin A/C
1q22	176200	Porphyria variegata	600923 *PPOX*	Protoporphyrinogen oxidase
1q25–q31	226700 226650	EB junctional, Herlitz type EB generalized, atrophic, benign	150292 *LAMC2*, *LAMNB2*, *LAMB2T*	Laminin,γ2 (nicein, 100 kDa; kalinin, 105 kDa; BM600, 100 kDa)
1q31	226450	EB inversa, junctional	226450 *EBR2A*	EB 2A, junctional Herlitz
1q32	226700 226650	EB junctional EB, generalized, atrophic, benign	150310 *LAMB3*	Laminin, β3 (nicein, 125 kDa; kalinin, 140 kDa; BM600, 125 kDa)
1q32	604536	Ectodermal dysplasia/skin fragility syndrome	601975 *PKP1*	Plakophilin-1
1q42	173870	Xeroderma pigmentosum	173870 *ADPRT*, *PPOL*	ADP-ribosyltransferase NAD(+)
1q42.1–q42.2	214500	Chédiak–Higashi syndrome	606897 *CHS1*, *LYST*	Lysosomal trafficking regulator
2q11–q13	129490 224900	Ectodermal dysplasia, hypohidrotic, AD Ectodermal dysplasia, hypohidrotic, AR	604095 *EDAR*, *DL*, *ED3*, *EDA3*	Ectodysplasin-1, anhidrotic receptor (*downless* mouse, homologue of)
2q21	133510	Xeroderma pigmentosum, group B Trichothiodystrophy	133510 *ERCC3*, *XPB*	Excision repair, cross-complementing rodent repair deficiency, complementation group 3
2q31	600121	Rhizomelic chondrodysplasia punctata, type 3	603051 *AGPS*, *ADHAP*	Alkylglucerone-phosphate synthase

(*continued*)

Table 12.1 (*cont'd*)

Chromosome site	MIM number	Disease	Gene symbol	Gene/gene product
2q31	130050 130020	Ehlers–Danlos syndrome type IV Ehlers–Danlos syndrome type III	120180 *COL3A1*	Collagen III, α1 polypeptide
2q31	130000	Ehlers–Danlos syndrome type I	120190 *COL5A2*	Collagen V, α2 polypeptide
2q32	278250	Wrinkly skin syndrome	278250 *WSS*	Wrinkly skin syndrome
2q34	601277	Ichthyosis, lamellar, type 2	607800 *ABCA12*, *ICR2B*, *LI2*	Ichthyosis congenita IIB
2q34	225310	Ehlers–Danlos syndrome type X	135600 *FN1*	Fibronectin-1
2q35	193500 148820	Waardenburg's syndrome type I Waardenburg's syndrome type III	606597 *PAX3*, *WS1*, *HUP2*, *CDHS*	Paired box homeotic gene 3
Chr 2	226730	EB junctional, with pyloric stenosis	147556 *ITGA6*	Integrin, α6
3p25	278720	Xeroderma pigmentosum, group C	278720 *XPC*, *XPCC*	Xeroderma pigmentosum, complementation group C
3p21.3	131750 226600 131850 132000 131705 604129 607523	EB dystrophica, AD EB dystrophica, AR EB, pretibial EB dystrophica, Bart type Transient bullous dermolysis of newborn EB pruriginosa Toenail dystrophy, isolated	120120 *COL7A1*	Collagen VII, α1 polypeptide
3p21	275630	Chanarin–Dorfman syndrome	604780 *ABHD5*, *CGI58*, *IECN2*, *NCIE2*	Comparative gene identification 58
3p14.1–p12.3	193510 103470 103500	Waardenburg's syndrome type IIA Waardenburg's syndrome/ocular albinism, digenic Tietz syndrome	156845 *MITF*, *WS2A*	Microphthalmia-associated transcription factor
3q12	121300	Coproporphyria	121300 *CPO*	Coproporphyrinogen oxidase
3q21	603165	Atopic dermatitis, susceptibility	603165 *ATOD1*	Dermatitis, atopic, 1
3q21	177900	Psoriasis, susceptibility	604316 *PSORS5*	Psoriasis susceptibility 5
3q21–q28	127550	Dyskeratosis congenita, AD	602322 *TERC*, *TRC3*, *TR*	Telomerase RNA component
3q24	203300	Hermansky–Pudlak syndrome	606118 *HPS3*	HPS gene 3
3q27	604292 106260 103285 603543	Ectrodactyly, ectodermal dysplasia, cleft lip/palate (EEC) syndrome 3 Hay–Wells syndrome ADULT syndrome Limb–mammary syndrome	603273 *TP73L*, *TP63*, *KET*, *EEC3*, *SHFM4*, *LMS*	Tumour protein p63 (tumour protein p73-like)
4p16.3	134934	Crouzon's syndrome with acanthosis nigricans	134934 *FGFR3*, *ACH*	Fibroblast growth factor receptor-3
4p16	225500	Ellis–van Creveld syndrome	604831 *EVC*	Ellis–van Creveld syndrome gene
4p	177900	Psoriasis, susceptibility	601454 *PSORS3*	Psoriasis susceptibility 3

(*continued overleaf*)

Table 12.1 (*cont'd*)

Chromosome site	MIM number	Disease	Gene symbol	Gene/gene product
4p12	164920	Piebaldism Mastocytosis with associated haematological disorder	164920 *KIT*, *PBT*	Hardy–Zuckerman 4 feline sarcoma (V-*kit*) oncogene
4p15.1	604517	Lipodystrophy, familial partial, with decreased subcutaneous fat of face and neck	604517 *PPARGC1*	Peroxisome proliferator-activated receptor γ, co-activator-1
4q12	607685	Hypereosinophilic syndrome, idiopathic	173490 *PDGFRA*	Platelet-derived growth factor receptor, α polypeptide
4q21	147060	Hyper-IgE syndrome	147060 *HIES*	Hyper-IgE syndrome
4q23	181600	Huriez syndrome	181600 *TYS*, *HRZ*	Sclerotylosis
5p	606574	Oculocutaneous albinism type IV	606202 *MATP*, *AIM1*	Membrane-associated transporter protein
5q13.3	139150 608354	Basal cell carcinoma Capillary malformation—AV malformation	139150 *RASA1*, *GAP*, *CMAVM*	Ras p21 protein activator 1 (GTPase activating protein)
5q21–q22	175100	Gardner's syndrome	175100 *APC*, *GS*, *FPC*	Adenomatous polyposis coli
5q23	225410	Ehlers–Danlos syndrome type VIIC	604539 *ADAMTS2*, *NPI*	Disintegrin-like and metalloproteinase with thrombospondin type 1 motif, 2 (procollagen IN-proteinase)
5q23.3–q31.1	219100	Cutis laxa, recessive, type I	153455 *LOX*	Lysyl oxidase
5q31–q33	603165	Atopic dermatitis, susceptibility	605845 *ATOD6*	Dermatitis, atopic, 6
5q32	256500 147050	Netherton's syndrome Atopy	605010 *SPINK5*, *LEKTI*	Serine protease inhibitor, kazal type, 5
5q35.2–q35.3	130070	Ehlers–Danlos syndrome, progeroid form	604327 *B4GALT7*, *XGALT1*, *XGPT1*	Xylosyl protein 4-β-galactosyltransferase, polypeptide 7
5q35.3	153100 602089	Lymphoedema, hereditary, type I Haemangioma, capillary, infantile, somatic	136352 *FLT4*, *VEGFR3*, *PCL*	Fms-related tyrosine kinase-4 (vascular endothelial growth factor receptor-3)
Chr 5	608233	Hermansky–Pudlak syndrome	603401 *AP3B1*, *ADTB3A*, *HPS2*	Adaptor-related protein complex 3, β1 subunit (adaptin, β3a)
Chr 5	216400	Cockayne's syndrome 1	216400 *CKN1*	Cockayne's syndrome 1, classical
6p21.3	142857	Pemphigoid, susceptibility	142857 *HLA-DR1B*	Major histocompatibility complex class II, DR β1
6p21.3	146520	Hypotrichosis simplex of scalp	146520 *HTSS*	Hypotrichosis simplex of scalp
6p21.3	177900	Psoriasis, susceptibility	177900 *PSOR1*	Psoriasis susceptibility 1
6p21.3	606408	Ehlers–Danlos syndrome due to tenascin X deficiency Ehlers–Danlos syndrome, hypermobility type	600985 *TNXB*, *TNX*, *TNXB1*, *TNXBS*, *TNXB2*	Tenascin X
6p21.3	193200	Vitiligo, susceptibility	193200 *VTLG*	Vitiligo
6p21.2–p12	147050	Asthma and atopy, susceptibility	601690 *PLA2G7*, *PAFAH*	Phospholipase A2, group VII (platelet-activating factor acetylhydrolase)
6p21.1–p12	278750	Xeroderma pigmentosum, variant type	603968 *POLH*, *XPV*	DNA polymerase η

(*continued*)

Table 12.1 (*cont'd*)

Chromosome site	MIM number	Disease	Gene symbol	Gene/gene product
6p24	125647 605676 607655	Keratosis palmoplantaris striata II Dilated cardiomyopathy with woolly hair and keratoderma Skin fragility—woolly hair syndrome	125647 *DSP*, *KPPS2*, *PPKS2*	Desmoplakin
6p22–p21	600901	Fanconi's anaemia, complementation group E	600901 *FANCE*, *FACE*	Fanconi's anaemia, complementation group E gene
7q11.2	123700	Cutis laxa, AD	130160 *ELN*	Elastin
7q11.2–q21.3	129900	Ectrodactyly, ectodermal dysplasia, cleft lip/palate 1 (EEC) syndrome 1	129900 *EEC1*	Ectrodactyly, ectodermal dysplasia, cleft lip/palate 1
7q22.1	166200 166210 259420 130060	Osteogenesis imperfecta, three clinical forms Ehlers–Danlos syndrome type VIIA2 Marfan's syndrome, atypical	120160 *COL1A2*	Collagen I, α2 polypeptide
7q31.1–q31.3	150240	Cutis laxa, marfanoid neonatal type	150240 *LAMB1*	Laminin, β1
8p23	606662	Waardenburg's syndrome type IIC	606662 *WS2C*	Waardenburg's syndrome type IIC
8p21	146550	Hypotrichosis, Marie Unna type	146550 *MUHH*	Hypotrichosis, Marie Unna type
8p21.1	266510	Refsum's disease, infantile form	170993 *PXMP3*, *PAF1*, *PMP35*, *PEX2*	Peroxisomal membrane protein-3, 35 kDa
8q24	131950	EB, Ogna type	131950 *EBS1*	EB simplex 1, Ogna
8q24	226670	Muscular dystrophy with EB simplex	601282 *PLEC1*, *PLTN*	Plectin-1, intermediate filament binding protein, 500 kDa
8q24.12	190350 190351	Trichorhinophalangeal syndrome, type I Trichorhinophalangeal syndrome, type III	604386 *TRPS1*	Zinc finger transcription factor TRPS1
8q24.3	268400	Rothmund–Thomson syndrome	603780 *RECQL4*, *RTS*, *RECQ4*	DNA helicase, RecQ-like, type 4
8q24.3	201100	Acrodermatitis enteropathica	607059 *SLC39A4*, *ZIP4*	Solute carrier family 36 (zinc transporter), member 4
8qter	248300	Meleda's disease	606119 *SLURP1*, *MDM*	Secreted LY6/uPAR-related protein-1
9p23	203290 278400	Albinism, brown Albinism, rufous	115501 *TYRP1*, *CAS2*, *GP75*	Tyrosinase-related protein-1
9p21	155601 155755 606719	Melanoma, cutaneous malignant, 2 Melanoma and neural system tumour syndrome Pancreatic cancer/melanoma syndrome	600160 *CDKN2A*, *MTS1*, *P16*, *MLM*, *CMM2*	Cyclin-dependent kinase inhibitor 2A (p16, inhibits CDK4)
9p21	601606	Trichoepithelioma, multiple familial	601606 *MFT*, *TEM*	Trichoepithelioma, multiple familial
9p21–p12	250250	Cartilage–hair hypoplasia	157660 *RMRP*, *RMRPR*, *CHH*	Mitochondrial RNA-processing endoribonuclease
9p13	602956	Fanconi's anaemia, complementation group G	602956 *XRCC9*, *FANCG*	X-ray repair, complementing defective, in Chinese hamster, 9
9q22.3	109400	Basal cell naevus syndrome	601309 *PTCH*, *NBCCS*, *BCNS*, *HPE7*	*Patched*, *Drosophila*, homologue of

(*continued overleaf*)

Table 12.1 (*cont'd*)

Chromosome site	MIM number	Disease	Gene symbol	Gene/gene product
9q22.3	278700	Xeroderma pigmentosum, group A	278700 *XPA*	Xeroderma pigmentosum, group A
9q31	132800	Epithelioma, self-healing, squamous 1, Ferguson-Smith type Basal cell carcinoma	132800 *MSSE*, *ESS1*	Epithelioma, self-healing, squamous 1, Ferguson-Smith type
9q31	109400	Basal cell naevus syndrome	109400 *NBCCS*, *BCNS*	Naevoid basal cell carcinoma syndrome
9q34	191100 606690	Tuberous sclerosis 1 Lymphangioleiomyomatosis	605284 *TSC1*, *LAM*	Hamartin (tuberous sclerosis 1 gene)
9q34.1	187300	Hereditary haemorrhagic telangiectasia 1	131195 *ENG*, *END*, *HHT1*, *ORW*	Endoglin
9q34.1	161200 137750	Nail–patella syndrome Nail–patella syndrome with open-angle glaucoma	602575 *LMX1B*, *NPS1*	LIM homeobox transcription factor 1, β
9q34.2–q34.3	130010 130000	Ehlers–Danlos syndrome type II Ehlers–Danlos syndrome type I	120215 *COL5A1*	Collagen V, α1 polypeptide
10pter–p11.2	266500	Refsum's disease	602026 *PHYH*, *PAHX*	Phytanoyl-CoA hydroxylase
10q11	133540 278800	Cockayne's syndrome 2, type B De Sanctis–Cacchione syndrome	133540 *ERCC6*, *CKN2*, *COFS*	Excision repair, cross-complementing rodent repair deficiency, complementation group 6
10q22	603553	Haemophagocytic lymphohistiocytosis, familial, 2	170280 *PRF1*, *HPLH2*	Perforin
10q22.1	176801	Gaucher's disease, variant form	176801 *PSAP*, *SAP1*	Prosaposin (sphingolipid activator protein 1)
10q23.1	203300	Hermansky–Pudlak syndrome	604982 *HPS1*	HPS gene 1
10q23.31	158350	Cowden's disease	601728 *PTEN*, *MMAC1*	Phosphatase and tensin homologue (mutated in multiple advanced cancers 1)
10q24.1	601859	Autoimmune lympho-proliferative syndrome Squamous cell carcinoma, burn scar-related, somatic	134637 *TNFRSF6*, *APT1*, *FAS*, *CD95*	Tumour necrosis factor receptor superfamily, member 6
10q24.3	226650	EB, generalized, atrophic, benign	113811 *COL17A1*, *BPAG2*	Collagen XVII, α1 polypeptide
10q25.2–q26.3	263700	Porphyria, congenital erythropoietic	606938 *UROS*	Uroporphyrinogen III synthase
10q26	123500 123150 123790 101600 101200	Crouzon's syndrome Jackson–Weiss syndrome Beare–Stevenson cutis gyrata syndrome Pfeiffer's syndrome Apert's syndrome	176943 *FGFR2*, *BEK*,*CFD1*, *JWS*	Fibroblast growth factor receptor 2 (bacteria-expressed kinase)
11p15.5	130650	Beckwith–Wiedemann syndrome	600856 *CDKN1C*, *KIP2*, *BWS*	Cyclin-dependent kinase, inhibitor 1C (p57, Kip2)
11p15	603467	Fanconi's anaemia, complementation group F	603467 *FANCF*	Fanconi's anaemia, complementation group F
11p15	605561		605561 *PKP3*	Plakophilin 3
11p12–p11	278740	Xeroderma pigmentosum, group E, DDB-negative subtype	600811 *DDB2*	Damage-specific DNA-binding protein 2, 48 kDa
11q11–q13.1	106100	Angio-oedema, hereditary	606860 *C1NH*, *HAE1*, *HAE2*	Complement component-1 inhibitor

(*continued*)

Table 12.1 (*cont'd*)

Chromosome site	MIM number	Disease	Gene symbol	Gene/gene product
11q12–q13	278740	Xeroderma pigmentosum, group E, subtype 2	600045 *DDB1*	Damage-specific DNA-binding protein 1, 127 kDa
11q12–q13	147050	Atopy	147050 *IGER*, *APY*	IgE responsiveness, atopic
11q13	147138	Asthma, atopic, susceptibility	147138 *MS4A2*, *MS4A1*, *FCER1B*	Membrane-spanning four domains, subfamily A, member 2 (Fc fragment of IgE, high affinity I, receptor for, β polypeptide)
11q14–q21	203100 103470 606952	Albinism, oculocutaneous, type IA Waardenburg's syndrome/albinism, digenic Albinism, oculocutaneous, IB	606933 *TYR*	Tyrosinase
11q14.1–q14.3	245000 245010	Papillon–Lefèvre syndrome Haim–Munk syndrome	602365 *CTSC*, *CPPI*, *PALS*, *PLS*, *HMS*	Cathepsin C
11q21	604391	Ataxia telangiectasia-like disorder	600814 *MRE11A*, *MRE11*, *ATLD*	Meiotic recombination 11, *Saccharomyces cerevisiae*, homologue A of
11q22.3	208900	Ataxia-telangiectasia Lymphoma, B cell non-Hodgkin's, somatic	607585 *ATM*, *ATA*, *AT1*	Ataxia-telangiectasia mutated (includes complementation groups A, C, D and E)
11q23–q24	225060 225000 225000	Ectodermal dysplasia, Margarita Island type Zlotogora–Ogur syndrome Cleft lip/palate ectodermal dysplasia syndrome	600644 *HVEC*, *PVRL1*, *PVRR1*, *PRR1*	Herpesvirus entry mediator C (poliovirus receptor-related 1; nectin)
11q23.3	176000	Porphyria, acute intermittent Porphyria, acute intermittent non-erythroid variant	176000 *HMBS*, *PBGD*, *UPS*	Hydroxymethylbilane synthase
12p11	602861		602861 *PKP2*	Plakophilin-2
12q11–q13	146800	Ichthyosis bullosa of Siemens	600194 *KRT2A*, *KRT2E*	Keratin-2A
12q11–q13	600231	Palmoplantar keratoderma, Bothnia type	600231 *PPKB*	Palmoplantar keratoderma, Bothnia type
12q11–q14	600376	Hereditary haemorrhagic telangiectasia 2	601284 *ACVRL1*, *ACVRLK1*, *ALK1*, *HHT2*	Activin A receptor, type II-like kinase 1
12q13	158000	Monilethrix	602153 *KRTHB1*, *HB1*	Keratin, hair, basic, 1
12q13	158000	Monilethrix	601928 *KRTHB6*, *HB6*	Keratin, hair, basic, 6
12q13	113800 600962 607602 148700 146590 607654	Epidermolytic hyperkeratosis Keratoderma, palmoplantar, non-epidermolytic Cyclic ichthyosis with epidermolytic hyperkeratosis Keratosis palmoplantaris striata Ichthyosis hystrix, Curth–Macklin type Keratosis palmoplantaris striata III	139350 *KRT1*	Keratin-1
12q13	193900	White sponge naevus	123940 *KRT4*, *CYK4*	Keratin-4
12q13	131900 131760 131800 131960	EB simplex, Koebner type EB simplex, Dowling–Meara type EB simplex, Weber–Cockayne type EB simplex with mottled pigmentation	148040 *KRT5*	Keratin-5

(*continued overleaf*)

Table 12.1 (*cont'd*)

Chromosome site	MIM number	Disease	Gene symbol	Gene/gene product
12q13	167200	Pachyonychia congenita, Jadassohn–Lewandowsky type	148041 *KRT6A*	Keratin-6A
12q13	167210	Pachyonychia congenita, Jackson–Lawler type	148042 *KRT6B*	Keratin-6B
12q13.11–q13.2	108300 132450	Stickler's syndrome type I Epiphyseal dysplasia, multiple, with myopia and deafness	120140 *COL2A1*	Collagen II, α1 polypeptide
12q23–q24.1	124200 101900	Darier's disease Acrokeratosis verruciformis	108740 *ATP2A2*, *ATP2B*, *DAR*	ATPase, Ca^{2+} dependent, slow twitch, cardiac muscle 2
12q23.2–q24.1	175900	Porokeratosis, disseminated, superficial, actinic, 1	175900 *DSAP1*	Disseminated superficial actinic porokeratosis 1
12q24.1	163950 115150	Noonan's syndrome 1 Cardio-facio-cutaneous syndrome LEOPARD syndrome	176876 *PTPN11*, *PTP2C*, *SHP2*, *NS1*	Protein tyrosine phosphatase, non-receptor-type, 11
13q11–q12	124500 148350 148210 602540	Vohwinkel's syndrome Keratoderma, palmoplantar, with deafness KID syndrome Hystrix-like ichthyosis with deafness	121011 *GJB2*, *CX26*, *DFNB1*, *PPK*, *DFNA3*, *KID*, *HID*	Gap junction protein, β2, 26 kDa (connexin 26)
13q12	129500	Ectodermal dysplasia 2, hidrotic	604418 *GJB6*, *CX30*, *DFNA3*, *HED*, *ED2*	Gap junction protein, β6 (connexin 30)
13q12	605068		605068 *WASF3*, *WAVE3*, *SCAR3*	Wiskott–Aldrich syndrome protein family, member 3
13q12–q14	603165	Dermatitis, atopic, susceptibility	605844 *ATPD5*	Dermatitis, atopic, 5
13q12.3	227660 605724	Fanconi's anaemia, complementation group B Fanconi's anaemia complementation group D1	600185 *BRCA2*, *FANCB*, *FANCD1*	Breast cancer-2, early onset
13q33	278780	Xeroderma pigmentosum, group G	133530 *ERCC5*, *XPG*	Excision repair, complementing defective, in Chinese hamster, number 5
14q11.2	242300 242100 242300	Ichthyosis, lamellar, AR Ichthyosiform erythroderma, congenital Self-healing collodion baby	190195 *TGM1*, *ICR2*, *LI1*	Transglutaminase 1 (K polypeptide epidermal type I, protein-glutamine γ-glutamyltransferase)
14q32.1	219100 123700	Cutis laxa, AR Cutis laxa, AD	604580 *FBLN5*	Fibulin 5
15q11.2–q12	203200	Albinism, oculocutaneous, type II Albinism, ocular, AR Albinism, brown oculocutaneous	203200 *OCA2*, *P*, *PED*, *D15S12*, *BOCA*	Pink-eye dilution, murine, homologue of (oculocutaneous albinism II)
15q21	214450	Griscelli's syndrome, type 1	160777 *MYO5A*, *MYH12*, *GS1*	Myosin, heavy polypeptide kinase
15q21	214450	Griscelli's syndrome, type 2	603868 *RAB27A*, *RAM*, *GS2*	Ras-associated protein RAB27A
15q21.1	154700	Marfan's syndrome	134797 *FBN1*, *MFS1*	Fibrillin-1
15q24–q25.1	604416	Pyogenic sterile arthritis, pyoderma gangrenosum, and acne (PAPA syndrome)	606347 *CD2BP1*, *PSTPIP1*, *PSTPIP*	
15q25.1–q26.1	607728	Porokeratosis, disseminated, superficial, actinic, 2	607728 *DSAP2*	Disseminated superficial actinic porokeratosis 2
15q26.1	210900	Bloom's syndrome	604610 *RECQ2*, *BLM*, *BS*, *RECQL3*	DNA helicase, RecQ-like, type 3

(*continued*)

Table 12.1 (*cont'd*)

Chromosome site	MIM number	Disease	Gene symbol	Gene/gene product
16p13.3	180849	Rubinstein–Taybi syndrome	600140 *CREBBP*, *CBP*, *RSTS*	CREB-binding protein
16p13.3	600273	Polycystic kidney disease, infantile, severe, with tuberous sclerosis	600273 *PKDTS*	Polycystic kidney disease, infantile, severe, with tuberous sclerosis
16p13.3	191100 606690	Tuberous sclerosis 2 Lymphangioleiomyomatosis, somatic	191092 *TSC2*, *LAM*	Tuberin (tuberous sclerosis 2 gene)
16p13.3–p13.13	278760	Xeroderma pigmentosum, group F	133520 *ERCC4*, *XPF*	Excision repair, complementing defective, in Chinese hamster, number 4
16p13.1	264800 177850	Pseudoxanthoma elasticum, AR Pseudoxanthoma elasticum, AD	603234 *ABCC6*, *ARA*, *ABC34*, *MLP1*, *PXE*	ATP-binding cassette, subfamily C, member 6
16p12.1–p11.2	147781	Atopy, susceptibility	147781 *IL4R*, *IL4RA*	Interleukin-4 receptor
16p22.1–q22.3	276600	Tyrosinaemia, type II	276600 *TAT*	Tyrosine aminotransferase, cytosolic
16q24.3	227650	Fanconi's anaemia, complementation group A	227650 *FANCA*, *FACA*, *FA1*, *FA*, *FAA*	Fanconi's anaemia, complementation group A
16q24.3	153000 153400 153200 153300	Lymphoedema and ptosis Lymphoedema–distichiasis syndrome Lymphoedema, hereditary II Yellow nail syndrome	602402 *FOXC2*, *FKHL14*, *MFH1*	Forkhead box C2
17p13.2–p13.1	606545	Ichthyosis, lamellar, 5	606545 *LI5*	Lamellar ichthyosis 5
17p11.2	270200	Sjögren–Larsson syndrome	270200 *ALDH3A2*, *ALDH10*, *SLS*, *FALDH*	Aldehyde dehydrogenase 3 family, member A2 (fatty aldehyde dehydrogenase)
17q25	177900	Psoriasis, susceptibility	602723 *PSORS2*, *PSS1*	Psoriasis susceptibility 2
17q11–qter	226730 226650 131800	EB, junctional, with pyloric atresia EB,generalized, atrophic, benign EB, hands and feet	147557 *ITGB4*	Integrin, β4
17q11.2	193520 601321	Neurofibromatosis, type 1 Watson's syndrome Neurofibromatosis–Noonan syndrome	162200 *NF1*, *VRNF*, *WSS*, *NFNS*	Neurofibromin (neurofibromatosis type 1)
17q12–q21	144200	Epidermolytic palmoplantar keratoderma	607606 *KRT9*, *EPPK*	Keratin-9
17q12–q21	131900 131760 131800 601001	EB simplex, Koebner type EB simplex, Dowling–Meara type EB simplex, Weber–Cockayne type EB simplex, recessive	148066 *KRT14*	Keratin-14
17q12–q21	167200 600962	Pachyonychia congenita, Jadassohn–Lewandowsky type Non-epidermolytic palmoplantar keratoderma	148067 *KRT16*	Keratin-16
17q12–q21	167210 184500	Pachyonychia congenita, Jackson–Lawler type Steatocystoma multiplex	148069 *KRT17*, *PC2*, *PCHC1*	Keratin-17
17p13.1	242100	Ichthyosiform erythroderma, congenital, non-bullous, 1	607206 *ALOXE3*	Arachidonate lipoxygenase 3
17q21	601214	Naxos disease	173325 *JUP*, *DP3*, *PDGB*	Junction plakoglobin

(*continued overleaf*)

Table 12.1 (*cont'd*)

Chromosome site	MIM number	Disease	Gene symbol	Gene/gene product
17q21–q22	113800	Epidermolytic hyperkeratosis	148080 *KRT10*	Keratin-10
17q21–q22	193900	White sponge naevus	148065 *KRT13*	Keratin-13
17q21.31–q22	166200 166210 259420 166220 130000 130060	Osteogenesis imperfecta type I Osteogenesis imperfecta type II Osteogenesis imperfecta type III Osteogenesis imperfecta type IV Ehlers–Danlos syndrome type I Ehlers–Danlos syndrome type VII	120150 *COL1A1*	Collagen I, αl polypeptide
17q25	148500	Tylosis with oesophageal cancer	148500 *TOC*, *TEC*	Tylosis with oesophageal cancer
17q25	603165	Dermatitis, atopic, susceptibility	605805 *ATOD4*	Dermatitis, atopic, 4
17q25	177900	Psoriasis, susceptibility	602723 *PSORS2*, *PSS1*	Psoriasis susceptibility 2
17q25	226400	Epidermodysplasia verruciformis	605828 *EV1*, *EVER1* 605829 *EV2*, *EVER2*	EV gene 1 EV gene 2
18q11.2	226700 226650	EB, junctional, Herlitz type EB, generalized, atrophic, benign	600805 *LAMA3*, *LOCS*	Laminin, α3 (nicein, 150 kDa; kalinin, 165 kDa; BM600, 150 kDa; epilegrin)
18q12.1–q12.2	148700	Keratosis palmoplantaris striata I	125670 *DSG1*	Desmoglein-1 (pemphigus foliaceus antigen)
18q12.1–q12.2	125671		125671 *DSG2*	Desmoglein-2
18q12.1–q12.2	169615		169615 *DSG3*	Desmoglein-3 (pemphigus vulgaris antigen)
18q21.3	177000	Protoporphyria, erythropoietic Protoporphyria, erythropoietic, recessive, with liver failure	177000 *FECH*, *FCE*	Ferrochelatase
19p13.3	175200	Peutz–Jeghers syndrome	602216 *STK11*, *PJS*, *LKB1*	Serine/threonine protein kinase-11
19p13.2	147670	Diabetes mellitus, insulin-resistant, with acanthosis nigricans	147670 *INSR*	Insulin receptor
19p13.2–p13.1	604781	Ichthyosis, non-lamellar and non-erythrodermic, congenital	604781 *INLNE*	Ichthyosis, non-lamellar and non-erythrodermic, congenital, AR
19p13	177900	Psoriasis, susceptibility	605364 *PSORS6*	Psoriasis susceptibility 6
19p12–q12	604777	Ichthyosis, lamellar, type 3	604777 *LI3*	Ichthyosis congenita III
19q13.2–q13.3	278730 601675 214150	Xeroderma pigmentosum, group D Trichothiodystrophy Cerebro-oculo-facio-skeletal syndrome	126340 *ERCC2*, *EM9*	Excision repair, cross- complementing rodent repair deficiency, complementation group 2
Chr 19	602077	Ectrodactyly, ectodermal dysplasia, cleft lip/palate (EEC) syndrome 2	602077 *EEC2*	Ectrodactyly, ectodermal dysplasia, cleft lip/palate 2
20p	603165	Dermatitis, atopic, susceptibility	605804 *ATOD3*	Dermatitis, atopic, 3
20q13.2	174800 300800	McCune–Albright syndrome Albright's hereditary osteodystrophy	139320 *GNAS*, *GNAS1*, *GPSA*, *POH* *PHP1B, PHP1A, AHO*	GNAS complex locus [guanine nucleotide-binding protein (G protein), α stimulating activity polypeptide 1]

(*continued*)

Table 12.1 (*cont'd*)

Chromosome site	MIM number	Disease	Gene symbol	Gene/gene product
22q11.2–q12.2	203300	Hermansky–Pudlak syndrome	606682 *HPS4*	HPS gene 4
22q12.2	101000	Neurofibromatosis, type 2 Schwannoma, sporadic Neurolemmomatosis	607379 *NF2*	Neurofibromatosis type 2 (bilateral acoustic neuroma); *Merlin*
Xp22.32	308100	Ichthyosis, X-linked/placental steroid sulphatase deficiency	308100 *STS*, *ARSC1*, *ARSC*, *SSDD*	Steroid sulphatase, microsomal (arylsulphatase C, isozyme S)
Xp22.31	309801	Microphthalmia with linear skin defects Microphthalmia, dermal aplasia and sclerocornea	309801 *MLS*, *MIDAS*	Microphthalmia with linear skin defects
Xp22.3	302950	Chondrodysplasia punctata, XLR	300180 *ARSE*, *CDPX1*, *CDPXR*	Arylsulphatase E
Xp22.3	300500	Ocular albinism, Nettleshop–Falls type	300500 *OA1*	Ocular albinism 1, Nettleshop–Falls type
Xp22.3	300650	Ocular albinism with sensorineural deafness	300650 *OASD*	Ocular albinism with sensorineural deafness
Xp22.3–p22.2	311200	Oral–facial–digital syndrome	300170 *OFD1*, *CXORF5*	OFD1 protein
Xp22.2–p22.13	308800	Keratosis follicularis spinulosa decalvans	308800 *KFSD*	Keratosis follicularis spinulosa decalvans
Xp11.23–p11.22	302960	Chondrodysplasia punctata, XLD	300205 *EBP*, *CDPX2*, *CPXD*, *CPX*	Emopamil-binding protein
Xp11.23–p11.22	301000	Wiskott–Aldrich syndrome	300392 *WAS*, *IMD2*, *THC*	Wiskott–Aldrich syndrome
Xq12–q13	309400 304150	Menkes' disease Occipital horn syndrome Cutis laxa, neonatal	300011 *ATP7A*, *MNK*, *MK*, *OHS*	ATPase, Cu^{2+} transporting, α polypeptide
Xq12–q13.1	305100	Ectodermal dysplasia 1, anhidrotic	300451 *ED1*, *EDA*, *HED*	Ectodermal dysplasia 1, anhidrotic
Xq22	301500	Fabry's disease	301500 *GLA*	Galactosidase, α
Xq24–q27	301845	Bazex syndrome	301845 *BZX*	Bazex syndrome
Xq24–q27.1	307150	Hypertrichosis, congenital, generalized	307150 *HTC2*, *HCG*, *CGH*	Hypertrichosis, congenital, generalized
Xq28	305000	Dyskeratosis congenita 1	300126 *DKC1*, *DKC*	Dyskerin
Xq28	308300 300291 300301	Incontinentia pigmenti, type II Ectodermal dysplasia, hypohidrotic, with immune deficiency Ectodermal dysplasia, anhidrotic, lymphoedema and immune deficiency	300248 *IKBKG*, *NEMO*, *FIP3*, *IP2*	Inhibitor of κ light polypeptide gene enhancer in B cells, kinase of, γ (NF-κB essential modulator)
Xq28	308050	CHILD syndrome	300275 *NSDHL*	NAD(P)H steroid dehydrogenase-like protein
Chr X	300268	Angioneurotic oedema, hereditary, X-linked	300268 *HAEX*, *HAE3*	Angioneurotic oedema, hereditary, with normal C1-inhibitor concentration and function

AD, autosomal dominant; ADULT, acro-dermato-ungual–lacrimal–tooth syndrome; AR, autosomal recessive; CHILD, congenital hemidysplasia with ichthyosiform erythroderma and limb defects syndrome; EB, epidermolysis bullosa; XLD, X-linked dominant; XLR, X-linked recessive.

Nosology of genetics in skin disease

The terms 'familial', 'inherited' and 'congenital' are frequently misunderstood and misused. *Familial* refers to the clustering of a disorder, with more close relatives affected than predicted by the population prevalence of the condition. *Inherited* disorders require the transmission of genetic variants from one generation to the next. The term *congenital* simply means that the character was present at or detectable before birth; such abnormalities may not be genetically determined, and include developmental defects due to environmental infectious agents (e.g. rubella) and deformations arising from physical insults (e.g. amniotic bands). Only a proportion of inherited disorders reveal themselves at birth (i.e. are congenital), with many having their onset in later life. Such age dependence may result from a wide number of factors, including maturation of cells or tissue-specific functions, exposure to exogenous agents or accumulation of a noxious substance. A further and important example of adult age of onset is provided by hereditary cancer syndromes, such as neurofibromatosis (NF) type 2, in which a second mutation impacting upon the normal allele of a so-called *tumour-suppressor gene* (e.g. *Merlin*) is required to lead to tumour formation. Such a mutation occurs as a 'somatic' change.

Of the inherited skin abnormalities, the largest group is the single-gene disorders, which require an alteration in the function of a gene and are known commonly as the genodermatoses. The inheritance patterns for classical genodermatoses are illustrated in Figs 12.1–12.4. Each disorder is relatively uncommon, and more detailed descriptions of a number of important examples are presented in this chapter and elsewhere. Predisposition to the more common skin disorders, including atopic eczema and psoriasis, is determined by the action of more than one gene, with significant evidence for further modulation by environmental factors. Such disorders display complex patterns of clustering in families, and are referred to as *multifactorial*. Chromosomal abnormalities, either in number (*aneuploidy*) or form (*translocation*, *complex rearrangements* or *microdeletions*) are important to the clinician, particularly if the patient presents a range of abnormalities including mental retardation. However, chromosomal anomalies rarely present solely with dermatological problems and hence are only briefly mentioned.

The study of rare disorders, including the genodermatoses, has also provided insight into fundamental aspects of human genetic principles and mechanisms. Essential terms and principles are described, with the intention of helping the reader understand relevant genetic concepts referred to throughout this book and to aid in the interpretation of the rapidly emerging literature in this field [1–4].

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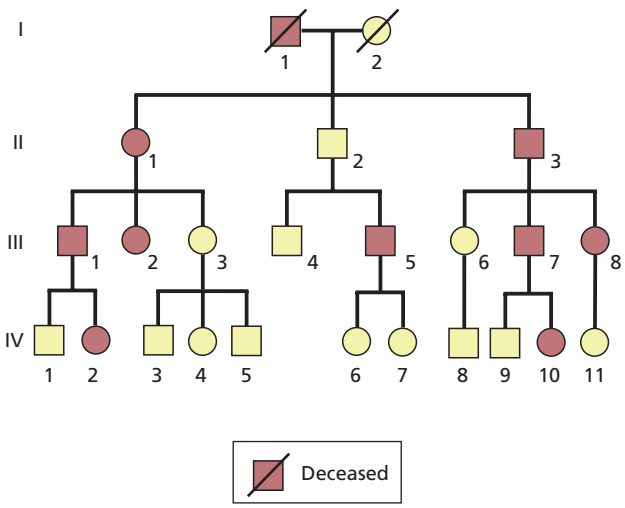
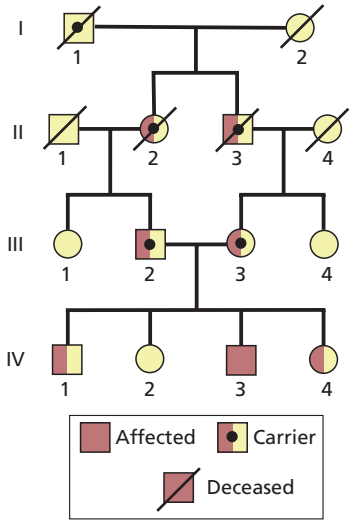


Fig. 12.1 Autosomal dominant (AD) inheritance.

1 AD disorders affect both males and females.
2 Affected individuals are heterozygous for the abnormal allele.
3 Affected person will usually have an affected parent, apart from the recipients of new *de novo* mutations.
4 On average, 50% of the children of an affected parent will be affected.
5 The age of onset and severity of a disorder may be variable and the affected individual may remain without signs or symptoms well into adult life.
6 Some AD disorders show reduced penetrance, i.e. a person who inherits the gene does not develop the disorder, e.g. individual II2. In this situation an unaffected individual cannot be completely reassured that he or she will not transmit the disorder to their children.

Examples:
acute intermittent porphyria
epidermolysis bullosa (some forms)
ichthyosis (some forms)
neurofibromatosis
tuberous sclerosis
hereditary haemorrhagic telangiectasia



1. AR disorders affect both males and females.
2. Affected individuals are homozygous for an abnormal allele and typically are born to unaffected parents.
3. On average, 1 in 4 of the children of heterozygous parents will be affected.
4. Typically, no family history is seen.
5. Consanguinity increases the risk of an AR disorder because both parents are more likely to carry the same mutant allele, inherited from a common ancestor.
6. The offspring of an affected person will be healthy heterozygotes and can be affected only if the other parent is also a gene carrier. This is unlikely except in consanguineous marriages or in ethnic groups in which particular alleles are common (e.g. isolated populations).
7. AR disorders are often severe; for example, many of the inborn errors of metabolism are AR.

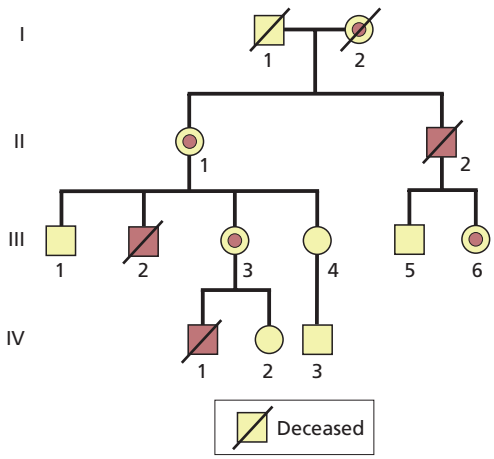
Examples:
epidermolysis bullosa (the more severe forms)
ichthyosis (the more severe forms)
acrodermatitis enteropathica
phenylketonuria
xeroderma pigmentosum

Fig. 12.2 Autosomal recessive (AR) inheritance.

Principles of medical genetics

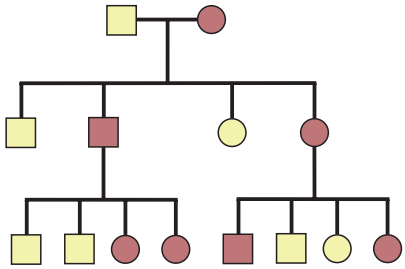
Inherited characteristics are transmitted from one generation to the next by chromosomes, composed of double-helix strands of DNA. A *gene* is a sequence of bases in DNA encoding a polypeptide. The precise position of the gene on a genetic map is known as its *locus*. In females, the 46 chromosomes found in most somatic cells present in homologous pairs; hence two copies of every gene exist, one maternal and the other paternal in origin. In males, the Y chromosome only pairs with the X chromosome at the pseudo-autosomal region. *Meiosis* is the process of cell division by which male and female gametes (germ cells) are produced. Alternative genes at a single locus are called *alleles*. An individual with two different alleles at a particular locus is *heterozygous*; where both alleles are identical,

Fig. 12.3 X-linked recessive (XLR) inheritance.



1. Usually only males are affected.
2. The disorder is transmitted through healthy female carriers; occasionally a heterozygous female may show some features of the condition (as a result of non-random X inactivation).
3. A female carrier will transmit the disorder to half her sons, and half her daughters will be carriers.
4. When a male is affected, all his daughters will be carrier heterozygotes.
5. The trait cannot be transmitted from father to son.
6. An XLR condition should be considered when the family history indicates affected males in different generations of the same family. Family history is not always positive as new *de novo* mutations are fairly common.

Examples:
anhidrotic ectodermal dysplasia
Fabry's disease
Menke's syndrome
ocular albinism



1 An XLD disorder will give rise to a disorder in both hemizygous males and heterozygous females.
2 Affected males will transmit the disorder to their daughters, but not to their sons.
3 Affected females will transmit the disorder to half their sons and half their daughters.
4 In some disorders the condition is lethal in hemizygous males; so only female patients are encountered in clinical practice.

Examples: incontinentia pigmenti
X-linked form of oro-facial-digital syndrome

Fig. 12.4 X-linked dominant (XLD) inheritance.

the individual is described as *homozygous* at that locus. Genes on the X chromosome are not one of a pair in males and when such a gene is abnormal in a male, the term *hemizygous* is used. Nuclear DNA accounts for 99.995% of the total genetic pool. As with all complex mammalian genomes, the human sequence is made up of considerable amounts of repetitive DNA (Fig. 12.5). The total number of genes is now estimated to be approximately 35 000, with an average size, including introns, of between 10 and 15 kb.

An allele is regarded as *dominant* (Fig. 12.1) if it manifests as a phenotype when present on only one member of the chromosome pair (heterozygous state) and as *recessive* (Fig. 12.2) if it must be present at both corresponding loci (homozygous state) before it can exert its full effect. Hence, it is apparent that the terms 'dominance' and 'recessivity' refer to a phenotypic characteristic rather than a gene [1].

Those genes borne on chromosomes other than the sex chromosomes (X and Y) are known as *autosomal*. Characters controlled by genes borne on the X or Y chromosomes are termed *sex-linked* (Figs 12.3 & 12.4). The Y chromosome is much smaller than the X chromosome. The great majority of sex-linked genes are exclusive to the X chromosome, having no active counterpart on the Y chromosome. For these traits the term 'recessive' applies to males who carry only one (mutant) allele. Females who carry X-linked mutations are typically heterozygous and

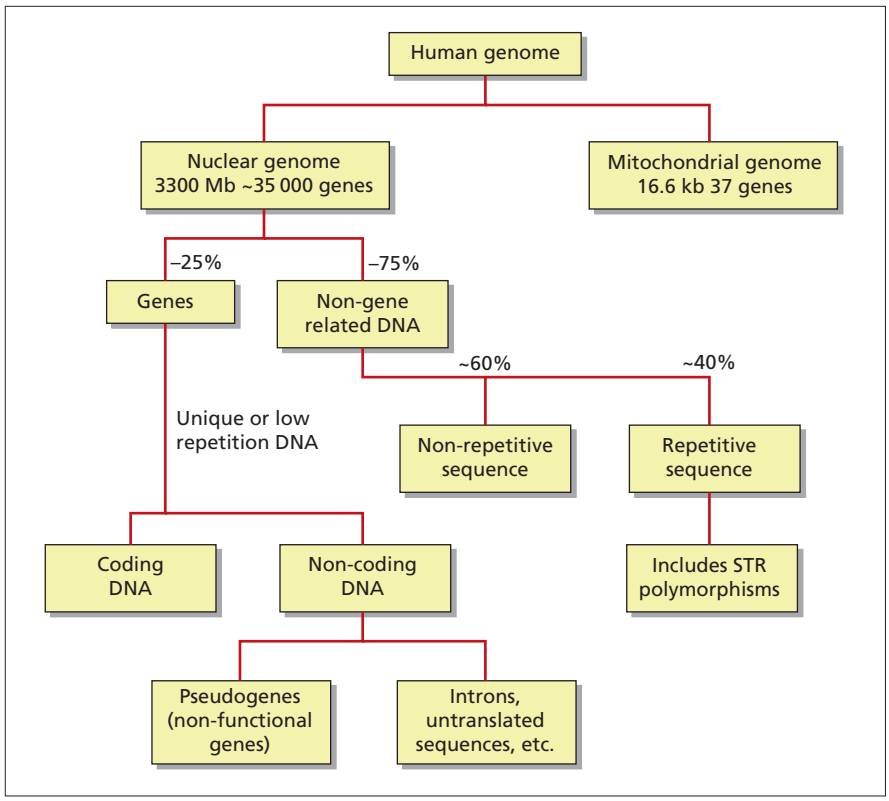


Fig. 12.5 Human genome organization.

with rare exceptions, including markedly skewed X inactivation, display no clinical abnormalities.

A region of homology sufficient for pairing between the X and Y chromosomes exists on the end of the short arm of the X chromosome, known as the *pseudo-autosomal region*, enabling sex-linked transmission comparable to autosomal traits [2]. Genes that are Y-linked are primarily involved in male sex determination (e.g. *SRY* gene controlling the testis determining factor) or spermatogenesis. Girls affected with MIDAS syndrome (microphthalmia, dermal aplasia and sclerocornea) and showing anomalies of the genitalia may display an *SRY*-positive status, indicating a translocation between the pseudo-autosomal region of Xp and Yp [3]. Hairy pinnae is another phenotype that is Y-linked [4].

The effects of a mutant allele are not necessarily constant; the degree to which the effects are variable is a measure of the *expression* of the character in question, and the frequency with which a gene produces any effect at all is a measure of its *penetrance*.

In addition to nuclear DNA, mitochondria contain a circular chromosome comprising 14 protein-coding regions [5]. The mitochondrial DNA codes for enzymes involved in the respiratory chain and oxidative phosphorylation. Mitochondrial disorders are essentially muscular, neurological and ophthalmological diseases and transmission is almost exclusively matrilineal [6].

Genetic heterogeneity

Genetic heterogeneity is the term used to describe clinically similar disorders (phenotypes) that result from different genetic defects. The concept of genetic heterogeneity is important for several reasons: (i) disorders that appear the same can be due to entirely different molecular defects, with a different natural history and requiring different treatment; (ii) for accurate genetic counselling, as defects may have different inheritance patterns; and (iii) because genetic heterogeneity plays a significant role in common complex disease states. Different alleles at the same locus (allelic) and genes at different loci (non-allelic) can give rise to similar phenotypes. Recognizing this, one can differentiate similar disorders by careful clinical distinction, as Wells and Kerr [7] did in distinguishing between autosomal dominant and X-linked ichthyosis. The use of both clinical findings and family history has helped to delineate heterogeneity in the epidermolysis bullosa and Ehlers–Danlos syndromes. Xeroderma pigmentosum illustrates phenotypic homogeneity but with marked genetic heterogeneity, with at least seven different genetic variants.

Mutations and disease

Most mutations are spontaneous and unexplained; however, certain factors such as mutagenic chemicals and ionizing radiation can increase the rate. In the absence of such agents, the mutation rate is of the order of 1 bp substitution for every 10^9–10^{10} bp replicated. If a mutation occurs in a somatic cell (*somatic mutation*), only the descendants of that cell are affected and there will be no transmission of the abnormality to further generations. Only mutations occurring in the gametes or their precursors can be transmitted to offspring.

Normally, replication of DNA is accurate but mutations can occur, either induced by exposure to mutagenic agents or spontaneously through errors in the process of DNA replication and repair during meiosis.

Mutations that impinge on the function of a gene most commonly occur within the coding regions (exons) and may alter the amino-acid sequence and hence structure and function of the protein (Fig. 12.6). In addition to gross structural chromosomal changes, submicroscopic alterations including substitutions (replacement of a single nucleotide by another), deletions (loss of one or more nucleotides) and insertions (addition of one or more nucleotides) may occur. Single-base substitutions, often referred to as point mutations, have been most extensively characterized (see Cardiff Human Mutation Database). The majority are either missense or nonsense mutations. These mutations alter a codon so that either a different amino acid is encoded (missense), or a codon specifying an amino acid in a normal individual is altered to code for the stop codon TGA, leading to premature termination of the protein (nonsense). Deletions and insertions (up to 20 bp of DNA) other than multiples of three will lead to disruption of the reading frame for RNA translation, resulting in a frameshift mutation and premature termination (Fig. 12.6). Point mutations may also affect splicing, the process by which mature messenger RNA (mRNA) is produced from RNA that has been transcribed directly from the gene [1].

Two-hit progression to tumour formation

Through pioneering observations on the familial and sporadic occurrence of rare tumours, Knudson [8] proposed that germ-line mutation of one allele of a tumour-suppressor gene, while required to explain an autosomal dominant pattern of inheritance, was not in itself sufficient to lead to tumour formation. Hence, in a target tissue, acquired mutations known as somatic mutations need to occur and lead to complete loss of function of the gene. Molecular genetic evidence to support this important concept has recently emerged for a number of disorders, including NF1 and tuberous sclerosis.

Contiguous gene syndromes

Large genome deletions may involve several neighbouring

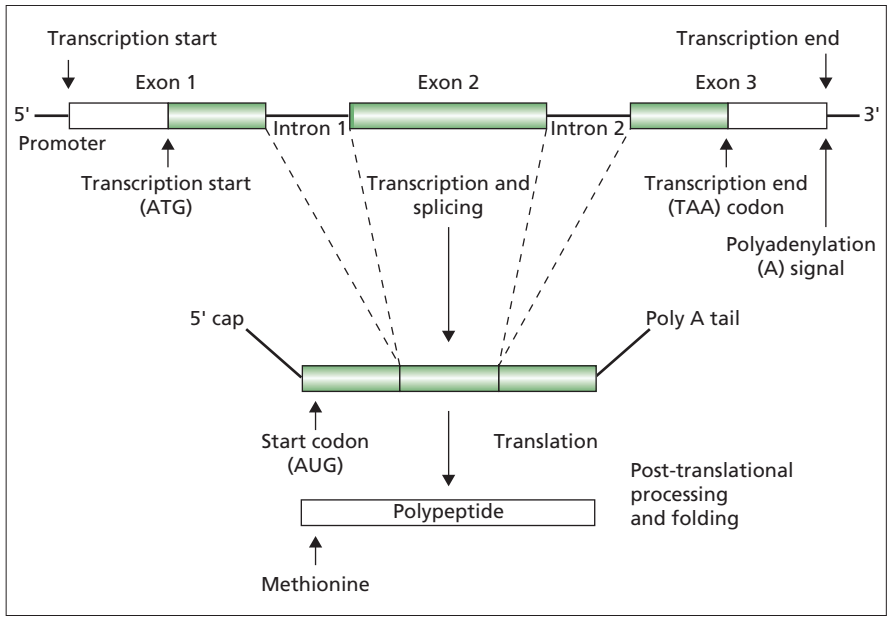


Fig. 12.6 Features of a typical human structural gene.

genes, for example a well-established 'set' of contiguous gene disorders involve the steroid sulphatase locus (Xp22.3). Deletions of different sizes and location within Xp22.3 give varying combinations of X-linked ichthyosis, Kallman's syndrome (hypogonadotrophic hypogonadism and anosmia), chondrodysplasia punctata, ocular albinism, mental retardation and short stature [9].

Functional impact of mutations and polymorphisms

Mutations exert their effects by leading to a loss or gain of function of the gene's protein product. In general, loss-of-function mutations lead to either reduced activity or complete loss of the protein. Gain-of-function mutations result in either increased levels of expression or the acquisition of a new function of a protein. The term 'mutation' has traditionally been applied to genetic variation causative of a Mendelian disorder. As further studies are undertaken to unravel the genetic contribution of common and complex disorders, understanding the subtle functional consequences of all genetic variation, including polymorphisms, will be increasingly important [1].

High-throughput genetic analysis

Studies of human genetic disease have been substantially facilitated by the introduction of rapid and increasingly low-cost methods of DNA analysis. Genome-wide screens of polymorphic markers and global analysis of gene transcripts can readily be achieved. DNA microarray represents one emerging technology likely to impact on the application of molecular genetics to clinical dermatology. A microarray or DNA chip represents multiple DNA sequences immobilized on a solid surface, using either a photolithographic process or simple 'spotting' of DNA sequences onto a glass slide. Such chips allow high-throughput parallel analysis, which can be used to uncover point mutations in single genes or larger genomic deletions, as well as detecting changes in gene expression associated with disease states or response to treatment.

Mosaicism, lyonization and the lines of Blaschko

Mosaicism [13] describes an individual with two or more cell lines of different genotypes derived from the same zygote. In health, all females exhibit functional mosaicism with regard to their X chromosomes. One of the two X chromosomes in the cells of normal females undergoes inactivation at an early stage of embryonic development (12–16 days after fertilization), a process known as lyonization [10]. The inactive X remains condensed as a densely stained mass of chromatin known as the Barr body. For each somatic cell it is random whether the paternal X or the maternal X is inactivated, but the choice is fixed for all subsequent descendants of that cell. Thus, a female has a mixture of two populations of cells, some of which have an active paternal X chromosome and some of which have an active maternal X chromosome. The relative proportions vary from female to female (even in identical twins) due to the randomness of the inactivation process. As a result of lyonization, the heterozygous state of various X-linked gene defects may give rise to a mosaic pattern of cutaneous lesions, which conforms to the system of lines on the skin first described by Blaschko in 1901 [11] (Fig. 12.7). The original description by Blaschko referred to a 'system of lines on the human skin which the

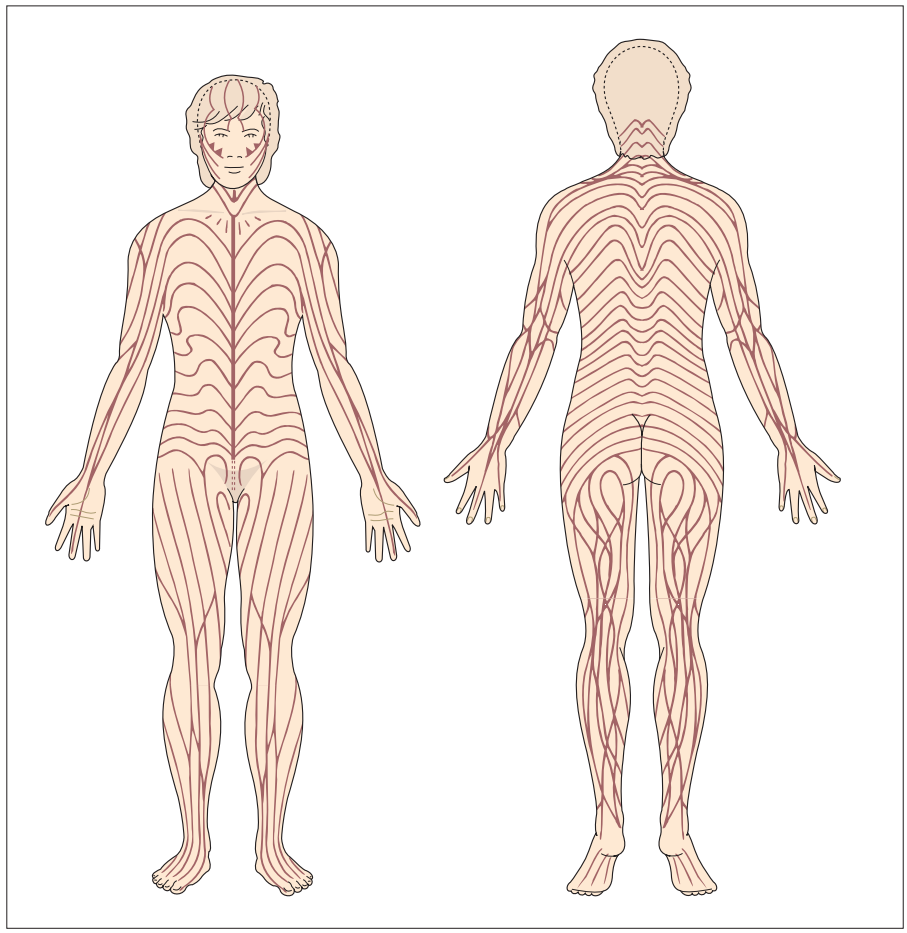


Fig. 12.7 Blaschko's lines as illustrated in his 1901 article 'A system of lines on the surface of the human body which the linear naevi and dermatoses follow'.

linear naevi and dermatoses follow'. Many naevoid skin lesions display an arrangement following these lines. The lines do not correspond to any known nervous, vascular or lymphatic structures, but represent the developmental growth pattern of the skin [12].

Many genetic skin diseases reflect mosaicism, with mutation occurring after fertilization (post-zygotic). Important features to be considered in mosaicism and their impact on phenotype relate to the proportion of cells that harbour the mutation and tissue distribution. In general, the greater the proportion of cells that are abnormal, the greater the severity of the resultant phenotype. Furthermore, phenotype is influenced by the portion of mutant cells in a specific tissue. If a mutation has little impact on the normal function of the tissue, the phenotypic consequences are likely to be minimized. Women heterozygous for the gene of X-linked recessive ichthyosis do not display any mosaic pattern of skin changes, and it has been suggested that some genes on the X chromosome may escape inactivation [13,14].

It is likely that all naevi reflect genetic mosaicism [15]. Streaky or patchy pigmentary skin changes may be a clue to the presence of mosaicism. The pigmentary patterns associated with mosaicism are reviewed by Happle [16].

Gonadal mosaicism and recurrence risk

An autosomal dominant trait may occur in more than one sibling, even though both parents are apparently unaffected. This phenomenon may be explained by gonadal mosaicism, due to the presence of a mutation in germ-line but not somatic cells [17]. Evidence of gonadal mosaicism exists in tuberous sclerosis [18], bullous ichthyosiform erythroderma [19] and NF1 [20]. Gonadal mosaicism for the X-linked disorder incontinentia pigmenti has been reported in a healthy male [21].

Genomic imprinting

This term is used to describe the phenomenon whereby a DNA sequence derived from one parent acts in a different way compared with that derived from the other parent [22,23]. Imprinting (coding or non-coding) carries a signal or imprint that indicates to nuclear transcription machinery the parent of origin for that sequence. For the majority of the human genome, no distinction is made between paternal and maternal copies, with the exclusion of polymorphic variation. The molecular basis of imprinting is thought to be methylation, the process whereby a methyl

group (CH_3) is added to DNA nucleotides (typically cytosine). Methylation is usually associated with reduced levels of expression of a gene, and for certain genes is applied exclusively to either the paternal or maternal copies. Examples of dermatological disorders subject to imprinting include familial glomus tumour [24] and Albright's hereditary osteodystrophy [25], and the phenomenon may also play a role in the genetic basis of atopy [26,27] and psoriasis [28].

Uniparental disomy

For the vast majority of individuals, one chromosome of a pair has been inherited from each parent. Rarely, uniparental disomy may occur when an offspring receives both copies of a chromosome pair from one of its parents. For some chromosomes this results in recognizable phenotypes, for example uniparental disomy of the maternal copies of chromosome 15 leads to Prader–Willi syndrome. For other chromosomes, uniparental disomy does not appear to be of obvious phenotypic value, unless by chance the identical chromosomes harbour a recessive mutation, which would then be present in the homozygous state [29,30].

Twin spotting

This hypothesis has been proposed, based on the genetic concept of somatic recombination, to explain the frequent coexistence of two separate and distinct naevi, for example a telangiectatic naevus and naevus anaemicus and phacomatosis pigmentovascularis [31–33]. Twin spotting has been extensively studied in plants and animals.

Genome sequence and analysis of inherited disorders

Completion of the human genome sequencing effort has led to phenomenal progress in gene mapping techniques, with thousands of DNA markers now available, each defined and covering all chromosomes. The reagents have greatly facilitated linkage studies within families with Mendelian disorders. Linkage analysis questions whether each DNA marker co-inherits with the disease more often than expected by chance. The statistical test of linkage is the logarithm of the odds (lod) score. A lod score of 3 or greater is accepted as significant evidence of linkage, whereas a score of –2 excludes linkage at that location. The traditional DNA marker is a *restriction fragment length polymorphism* (RFLP) analysed by Southern blotting of restricted (digested) DNA, with the fragments detected by a radioactive probe. Most genetic markers are now detected rapidly by polymerase chain reaction (PCR)-based methods of analysis, exploiting an abundant class of DNA sequence variation known as simple tandem repeats or single nucleotide polymorphisms. *Gene tracking* is the term given to the use of a known linkage between a marker and a disease locus to predict the genotype at the disease locus in a particular family member, such as in asymptomatic carrier testing or prenatal diagnosis. Linkage studies are just the first step in positional cloning of a disease gene. Table 12.1 details genes of relevance to dermatology. For more detailed reviews of the subject the reader is referred to Chapter 8 and reference [1].

Genetic linkage, linkage disequilibrium and disease association

Alleles at gene loci residing close to each other on the same chromosome remain linked in transmission so long as the chromosome remains intact; however, during reduction division (meiosis), such linkages may be disrupted if *crossing-over* occurs. The closer two gene loci are situated on a chromosome, the less likely they are to be separated by crossing-over and the more likely they are to be inherited together. Two such gene loci are said to be linked and it is possible to demonstrate genetic linkage in a family using appropriate genetic markers. When two alleles occur together more frequently, or less frequently, in a population than would have been expected from the individual allele frequencies, they are said to be in *linkage disequilibrium*. This may arise as a result of a recent mutation or for a particular combination of DNA sequences, which may have, for example, a selective advantage and hence achieve disequilibrium by natural selection. Linkage disequilibrium is one important cause of disease association.

The nail–patella syndrome is a clinical example of a disorder that shows genetic linkage with the blood group ABO locus; the ABO and the disease gene loci are both situated on chromosome 9. Because of eventual crossing-over, over a number of generations recombination will occur, leading to different affected families; alternatively, independent mutations causing nail–patella syndrome may arise *de novo*. Thus, there is genetic linkage between the loci for blood groups and nail–patella syndrome, but no association with a particular blood group. Genetic linkage is a phenomenon demonstrable within families. In contrast, association due to linkage disequilibrium is a phenomenon demonstrated by comparing a population of affected individuals with a control population [1].

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Histocompatibility antigens and disease association

Human leukocyte antigens are glycoproteins on the cell surface of most nucleated human cells. These differ in subtle ways from person to person and uniquely fingerprint each person's cells. These fingerprints allow a person's immune system to recognize if a given cell is its own. The importance of the human leukocyte antigen (HLA) system has been highlighted by the need to match donors and recipients in the transplantation of human tissues.

The HLA region is located on the short arm of chromosome 6, referred to as the major histocompatibility complex (MHC). A person inherits HLA as a set, one set (haplotype) from each parent. There are at least four or five genetic loci that produce HLA, termed A, B, C, D and DR (in order of their discovery not their location), and their gene products are called HLA-A, HLA-B, HLA-C, HLA-D and HLA-DR. Each locus has multiple allelic determinants (polymorphism). Each allele at each locus controls an antigen, which is identified by a number placed after the letter of that series, for example HLA-A1, HLA-B5. The letter 'w' in front of a number indicates that its specificity was studied in an international workshop, and continues to undergo further definition.

HLAs that code at the A, B and C loci are determined by serological cytotoxicity methods, whereas those occurring at the D locus are detected by the mixed lymphocyte reaction. The HLA-DR antigens are serologically determined and are similar, if not identical, to the D locus antigens. DNA-based methods for typing at all HLA loci are now available.

The association of an HLA with a given disease means that there is a higher incidence of that antigen in a group of patients with the disease than in a group of people without the disease. There are various ways in which the presence of a particular HLA might be involved in the pathogenesis of a disease.

1 *Molecular mimicry*. An infective agent may have a similar configuration to the HLA, so that the agent is then not attacked by the body's defence system. Alternatively, the agent might differ only slightly from the HLA, so that antibodies are produced that attack both the infective agent and the cells containing the HLA, thus inducing autoimmune damage.

2 *Receptor effects*. Many chemicals, including drugs and toxins, bind to the cell surface before they are taken into the cytoplasm. Since HLAs are present on the cell surface, they could modify the binding of these potentially toxic substances, and the specificity for such binding may be determined, at least in part, by DNA variation for HLA molecules.

3 *Genetic linkage*. The HLA may be close to another gene on the same chromosome that produces a disease, either directly (e.g. due to an enzyme deficiency) or indirectly due to an effect on the immune response, which may be abnormally enhanced, leading to autoimmunity, or abnormally decreased, leading to infection.

The association between an HLA and a particular disease is rarely absolute. Ankylosing spondylitis is strongly associated with the B27 antigen, but some patients with this disease are B27 negative and many patients with B27 do not develop ankylosing spondylitis. There are many

Table 12.2 Some skin diseases known to be associated with particular human leukocyte antigens (HLA).

Disease	Antigen	Relative risk
Dermatitis herpetiformis	B8	15
	Dw3/DRw3	> 15
Pemphigus	DRw4	10
Reiter's disease	B27	35
Behçet's disease	B5	10
Psoriasis	B13	4
	B17	5
	B37	5
	Cw6	12
	Dw7	10
Psoriatic arthropathy (central)	B27	10
Psoriatic arthropathy (peripheral)	Bw38	9

There is a genetic predisposition to pemphigoid (herpes) gestationis; 90% of patients express either HLA-DR3 or HLA-DR4 [5].

possible explanations for this, including the role of environmental factors or triggers, such as chemicals or infective agents, in disease causation. Non-HLA-linked genes are probably also important, including some that may confer resistance to disease. The relative risk is the numerical answer to the question 'How many times is a person with a given HLA phenotype more likely to develop a given disease than a person without that HLA phenotype?' The relationship between HLA and skin disease is the subject of several reviews [1–4] (Table 12.2).

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Genetic counselling [1–3]

Advice to parents or prospective parents must be based on an accurate diagnosis and a detailed family history. It is essential to establish a diagrammatic representation of the family pedigree. Genetic counselling depends upon the recurrence risk to parents of having an affected child. The risk that any pregnancy will produce a child with a serious abnormality is about 1 in 50 (2%). A risk greater than 10% is high, whereas a risk of less than 5% is considered low. However, the impact such a risk has upon a couple or extended family depends on the severity of the disorder and any prior experience relatives may have of a condition. The offspring and recurrence risks for known forms of Mendelian disorders are illustrated in Figs 12.1–12.4.

Many different definitions of genetic counselling have been proposed, but all include the concept of a process of communication, where patients or relatives are informed of the probability of developing or transmitting a genetic disorder. This process should also include discussion about the consequences of such disorders and the possibilities for disease prevention. Hence, it is apparent that counselling is a complex process that requires a range of skills, which increasingly includes integration of complex information regarding DNA analysis. However, it remains important to realize that it is the burden of disease rather than the precise numerical value of risk that concerns most patients and prospective parents. Genetic counselling has recently emerged as a distinct specialty in medicine and many dermatology centres work in close collaboration over the provision of accurate and comprehensive advice.

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Chromosomal disorders

Chromosomal disorders may be due to abnormalities of chromosome number or structure and may involve autosomes or sex chromosomes. Somatic cells are *diploid*, with a complement of 46 chromosomes, whereas gametes (ova and sperm) are *haploid*, with only 23 chromosomes following reduction division in meiosis. Numerical abnormalities that involve the gain or loss of one or more chromosomes are known as aneuploidies. Structural chromosome rearrangements result from chromosome breakage with subsequent reunion in a different configuration. They may be balanced or unbalanced, depending on whether or not gain (or loss) of genetic material occurs. Approximately 7.5% of all conceptions have a chromosomal disorder, but most of these are spontaneously aborted, so the birth frequency is 0.6%. Among early spontaneous abortions, the frequency of chromosomal disorders is 60%, whereas in late spontaneous abortions and stillbirths the frequency is 5%. Chromosomal abnormalities generally cause multiple congenital malformations. Children with more than one physical abnormality, particularly if retarded, should undergo chromosomal analysis as part of their investigation. Chromosomal disorders are incurable but can be reliably detected by prenatal diagnostic techniques. Amniocentesis or chorionic villous sampling should be offered to women whose pregnancies are at increased risk, namely women over the age of 35 years and couples with an affected child.

Autosomal chromosome defects

Down's syndrome [1–3]

SYN. MONGOLISM

Down [1] described this syndrome in 1866. In 1959 it became the first recognized chromosomal anomaly [4]. It is the most common autosomal abnormality, with a frequency of about 1 per 700 live births [5].

Aetiology [2]. Most cases (95%) result from trisomy of chromosome 21, in which the extra chromosome is derived by non-disjunction at meiosis usually from the mother; the incidence of this type rises with maternal age. Less common, and clinically indistinguishable, is the type that shows no relation to maternal age and is sometimes familial. The affected child has the normal number of 46 chromosomes but one of the clinically normal parents carries a translocation of part of chromosome 21. A few patients are themselves mosaics and tend to have less marked physical stigmata and higher intelligence [6].

Pathology. Congenital heart defects are common and the brain is small with flat convolutions. Renal tract anomalies are less common.

Immunological defects are frequent. Autoimmune disease is common in Down's syndrome, T-cell function is impaired and the atopic state is often associated [7]. There is an increased risk of developing acute leukaemia, usually under the age of 5 years.

The lichenified patches of skin show no distinctive pattern, with hyperkeratosis, acanthosis and a dermal inflammatory infiltrate.

Clinical features [8]. The facial appearance often permits a clinical diagnosis. The head is small, the face flat, the nose short and squat and the ears small and misshapen. The eyes are usually conspicuously mongoloid, with slanting palpebral fissures. The eyelids are thickened and the eyelashes short and sparse. Epicanthic folds are frequent in early childhood but tend to become less noticeable with age. The iris tends to be hypoplastic and may show light areas in its outer third (Brushfield's spots). The limbs are stumpy and the joint ligaments lax. The fingers are short and cone-shaped and are sometimes webbed. The little finger is often curved. The presence of these features varies in affected individuals, and a diagnostic index has been proposed [9].

Mental retardation is a serious complication: the IQ is usually less than 50, and if it is not mosaicism should be suspected. Congenital heart malformations, especially endocardial cushion defects, are present in 40%, and duodenal atresia may occur. Other complications include cataracts (2%), epilepsy (10%), hypothyroidism (3%), leukaemia (1%), atlantoaxial instability (2–3%) and recurrent respiratory infections. When serious malformations are present, death during infancy is usual, but otherwise life expectancy is little reduced. Down's syndrome accounts for about one-third of all moderate and severe mental disability in children of school age. Most will walk and develop simple language. Puberty is often delayed and incomplete, with adult heights about 150 cm. Presenile dementia commonly supervenes after 40 years of age.

The skin is normal at birth and in early childhood is soft and velvety [8,10]. Between the ages of 5 and 10 years it becomes increasingly dry and less elastic, and by the age of 15 over 70% show generalized xerosis of mild to moderate degree, with evidence of accelerated skin ageing [11]. Patchy lichenification is present in some 30% under 10 years and more than 80% over 20 years of age. The patches resemble lichen simplex and most commonly occur on the upper arm, the wrists, the fronts of the thighs, the back of the ankle and the back of the neck, and are probably correctly regarded as manifestations of atopic dermatitis, the incidence of which some authorities [10] have considered to be low.

A chronic follicular papular eruption of the presternal and interscapular regions is frequently present, consistent with *Malassezia* folliculitis. In a clinical trial, oral itraconazole produced a significant clinical improvement accompanied by a decrease in the skin *Malassezia* count, but relapse occurred when therapy was discontinued and was accompanied by a return of the *Malassezia* yeasts [12].

The hair may be normal but is often fine and may be hypopigmented. The prevalence of alopecia areata is high and it tends to be extensive and persistent [7,13]. The teeth are hypoplastic and late to erupt. Fissuring and thickening of the lips are frequent and increase in prevalence and severity with age [14]. The tongue is scrotal in almost all cases. Elastosis perforans serpiginosa [15,16] and syringomas, especially in adult females with Down's syndrome [17,18], occur more often than in normal subjects.

Skin infections, angular cheilitis, chronic blepharitis and a purulent nasal discharge are common. There is a high prevalence of onychomycosis [7,19]. The cheeks are often red. The peripheral circulation is poor, acrocyanosis is frequent and livedo reticularis is often conspicuous throughout the year, on the thighs, buttocks and trunk.

Dermatoglyphic features include a single flexion crease on the fifth finger, the simian palmar crease and an increased incidence of ulnar loops on the fingers.

There is no evidence that the prevalence of other dermatoses is significantly different in individuals with Down's syndrome compared with individuals with mental retardation from other causes. Psoriasis runs its normal course, although an unusual hyperkeratotic form has been described [20]. Acral lentiginous melanoma has been described in association with Down's syndrome [21].

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Trisomy 18 [1–3]

SYN. EDWARDS' SYNDROME

This is the second most common multiple malformation syndrome. It occurs in about 1 per 3000 live births; 95% of affected fetuses abort spontaneously. Parental nondisjunction at either the first or second meiotic division results in the extra copy of chromosome 18. Rarely, a parental translocation is responsible. Occasionally, mosaicism is seen with a milder phenotype and can give rise to pigmentary skin changes, as seen in hypomelanosis of Ito [4,5]. The syndrome comprises severe mental deficiency, a characteristic skull shape with a small chin and prominant occiput, low-set malformed ears, clenched hands with overlapping index and fifth fingers, single palmar crease, 'rocker-bottom' feet and a short sternum. Malformations of the heart, kidneys and other organs are frequent. Cutaneous features include cutis laxa of the neck, hypertrichosis of the forehead and back, and capillary haemangiomas. Fingerprints show a distinctive low-arch dermal ridge pattern. Death within a month occurs in 30%. Only 10% survive beyond the first year and these infants show profound developmental delay.

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Trisomy 13 [1–4]

SYN. PATAU'S SYNDROME

The incidence of trisomy 13 is 1 per 5000 live births. Nondisjunction at either the first or second meiotic division in either parent may cause trisomy 13. In about 20% of cases, one parent is a translocation carrier. In about 5% of patients, mosaicism is present. The characteristic features of the syndrome are mental retardation, sloping forehead reflecting underlying holoprosencephaly (a developmental defect of the forebrain), eye defects including microphthalmia or anophthalmia, cleft palate and cleft lip, low-set ears, 'rocker-bottom' feet, cardiac defects and a variety of other visceral abnormalities. Survival for more than 6 months is unusual. Cutaneous features include vascular anomalies, especially of the forehead, hyperconvex nails and localized defects of the scalp. Cutis laxa of the neck has also been reported. The palm print shows a distal palmar axial triradius.

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Other autosomal abnormality syndromes

Although the syndromes to which these autosomal abnormalities give rise include distinctive craniofacial malformations, they do not exhibit constant or frequent dermatological features, apart from abnormal dermatoglyphics. Other chromosomal disorders are reviewed elsewhere [1,2].

Chromosome 4, short-arm deletion syndrome [3]

These children have microcephaly, mental retardation, hypospadias and multiple malformations, such as cleft lip and/or palate, low-set ears and pre-auricular pits. There are scalp defects in some cases.

Chromosome 5, short-arm deletion syndrome [4–6]
SYN. CRI DU CHAT SYNDROME

This is a clinically heterogeneous syndrome. The patients are mentally deficient microcephalics with a cat-like cry. In some cases a pre-auricular skin tag accompanies low-set malformed ears. There may be premature greying of the hair.

Long-arm 18, deletion syndrome [7]

Hypoplasia of the mid-face gives these children deep-set eyes. The antihelix is very prominent and there are multiple skeletal and ocular abnormalities. Eczema has been reported to occur in 25% of cases.

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Sex chromosome defects

Turner's syndrome [1,2]

Turner's syndrome is defined as a gonadal dysgenesis due to a missing or structurally defective X chromosome. In 1938, Turner described this syndrome in seven girls [1].

Aetiology [2]. The frequency of Turner's syndrome is 1 per 2500 female births [3]. In some 80% of cases there are 45 chromosomes with an X0 sex chromosome complement. Such cases are chromatin negative in buccal smears. It is assumed that the missing chromosome was lost before or at fertilization. The incidence of 45X was reported to be increased in the offspring of teenage mothers [4], but in a study from Denmark there was no significant relation between mother's age and risk of Turner's syndrome [5].

Most of the remaining 20% of cases are chromatin positive. Some have 46 chromosomes but with partial deletion of one X chromosome [6]. Such individuals may not differ significantly in their phenotype from the common X0 but they may appear more normal [7]. Other cases have shown mosaicism of various types (XX/X0 or XXX/X0) [8].

Pathology [8]. In place of the normal gonads, ovarian streaks are present that are composed of stroma-like cells and quiescent germinal epithelium without follicular activity or germ cells. However, both follicles and germ cells have occasionally been present.

Lymphangiographic studies have shown hypoplasia of cutaneous and subcutaneous lymphatics [9].

A lack of feedback inhibition by hormones from the defective ovaries produces elevated levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) in the serum by 5 days of age [10].

Clinical features [7,11–13]. Turner's syndrome results in early spontaneous loss of the fetus in over 95% of cases. Severely affected fetuses who survive to the second trimester can be detected by ultrasonography, which shows cystic hygroma, chylothorax, ascites and hydrops.

Growth failure is a consistent finding at birth in infants with Turner's syndrome, which begins in early gestation and is well established by mid-pregnancy [14]. The diagnosis may be suggested in the newborn by redundant neck skin and peripheral oedema. However, the diagnosis is usually made later as a result of investigation for short stature and primary amenorrhoea.

The characteristic clinical features of Turner's syndrome include small stature; a broad shield-shaped chest with widely spaced nipples; a wide carrying angle of the arms; a webbed neck (pterygium colli); a low posterior hairline; low, misshapen ears; high, arched palate; cutis laxa, especially on the neck and buttocks; short fourth, and sometimes fifth, metacarpals and metatarsals; hypoplastic nails; and a tendency to keloidal scar formation.

Individuals with Turner's syndrome have increased numbers of melanocytic naevi and therefore have an increased risk for melanoma [15]. Lymphangiectatic oedema of the hands and feet may be present at birth and clear in the first 2 years. Skeletal abnormalities are a common feature [6], but are also very variable. Among the most frequent are cubitus valgus, kyphoscoliosis and epiphyseal defects and pathological fractures. Cardiovascular abnormalities [16] are present in some 25% of cases, especially coarctation of the aorta. Ocular defects, squints or ptosis, are also a feature of some cases. Intelligence is usually normal, although a few girls have educational problems.

Endocrinological investigations reveal an increased output of pituitary gonadotrophins accompanied by low oestrogen levels. Thus there is usually primary amenorrhoea

with failure to develop full secondary sexual characteristics. Some patients menstruate and, exceptionally, may be fertile. Adrenal androgens are present, and pubic and axillary hair may be present in the absence of other manifestations of normal pubertal development. A few examples are known [17] in which otherwise typical Turner's syndrome (X0 chromosome complement) is accompanied by some degree of genital virilization and hirsutism.

Diagnosis. Diagnosis may be made prenatally by amniocentesis [5]. The somatic abnormalities may suggest the diagnosis in infancy or childhood, but if they are inconspicuous or absent, the diagnosis may be unsuspected until puberty. Increased urinary excretion of FSH supports the diagnosis, which can be confirmed by examination of buccal smears supplemented by chromosome studies.

Treatment. Oestrogen replacement will allow the development of secondary sexual characteristics but does not seem to influence stature or infertility. Treatment with human growth hormone may improve the ultimate adult height; long-term, randomized, controlled studies are in progress [18]. Melanocytic naevi may grow more rapidly during growth hormone therapy [19]. Therefore, individuals with Turner's syndrome, especially those on growth hormone therapy, should have periodic skin examinations and be advised on the regular use of sunscreens [15].

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Klinefelter's syndrome [1,2]

Aetiology. The frequency of Klinefelter's syndrome is 1 per 600 male births [2]. In buccal smears the nuclei are chromatin positive and indistinguishable from those of the normal female, but in cultures there are seen to be 47 chromosomes with an XXY sex chromosome complement [3]. The differentiation of the developing gonad proceeds along male lines but the testis fails to develop fully, and many seminiferous tubules are replaced by fibrous tissue. Leydig cells are present in normal or increased numbers.

Clinical features [1,2,4–6]. There are no clinical manifestations before puberty, which occurs at the normal age. The testes are small and fail to produce adult levels of testosterone, which leads to poorly developed secondary sexual characteristics and infertility. Hair growth on the trunk, limbs and face tends to be below average. Psychiatric disorders are common but mental deficiency is not. Some patients retain eunuchoid body proportions. They are tall, obese and may develop gynaecomastia. Associated features include osteoporosis [7] and taurodontism (vertical enlargement of the molar pulp chamber) [8]. Various minor dermatoglyphic changes have been recorded [9].

An association between systemic lupus erythematosus (SLE) and Klinefelter's syndrome has been postulated [10], and this is interesting in view of the fact that SLE is more frequent in women than men and that oestrogens may provoke SLE in some patients [11]. In a case report of SLE in a hypogonadal male with Klinefelter's syndrome treated with testosterone in doses sufficient to normalize the serum level of this hormone to the adult male range, haematological and serological abnormalities, including elevated levels of anti-DNA antibodies and depressed complement levels, returned to normal within 9 months of increasing the testosterone dose [12].

There are two reports of incontinentia pigmenti in boys with Klinefelter's syndrome [13,14]. As incontinentia pigmenti trait is usually lethal in males, it has been proposed that the second X chromosome protects against fetal death.

Patients with Klinefelter's syndrome have an increased risk of developing leg ulcers, especially in combination with hyperpigmentation or atrophie blanche [15,16]. Some authors have attributed the cause of leg ulceration to venous insufficiency, others have implicated increased

activity of plasminogen activator inhibitor 1 [17]. It seems likely that androgens may protect against the development of leg ulcers, because ulcers are more common in women than men, and it may be relevant that men who do develop leg ulcers tend to be taller, heavier and less fertile than age-matched control subjects [18].

Testosterone replacement therapy will improve secondary sexual characteristics, but infertility is the rule, except in mosaics.

Diagnosis. The association of gynaecomastia with small testes and otherwise apparently normal genitalia should suggest the diagnosis, which is supported by finding an increased urinary excretion of gonadotrophin. The diagnosis is confirmed by chromosome studies.

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Other abnormalities of the sex chromosomes

XXYY [1]

These individuals show many of the main features of Klinefelter's syndrome, including sparse body hair. Additional features reported are multiple cutaneous angiomas, acrocyanosis and early peripheral vascular disease.

XYY syndrome [2]

These patients are phenotypic males, often tall and with, perhaps, an increased incidence of severe acne (see Chapter 43). They may be mentally retarded, and have a reputation for aggressive behaviour [3], not accepted by all authorities. There is no evidence of increased secretion of FSH or LH [4].

XXXXY syndrome [5]

These patients, of low birth weight, are slow to grow physically and are mentally defective. There are multiple skeletal defects of which limited elbow pronation is the most characteristic. The ears are large, low-set and malformed. There is hypogenitalism. No consistent dermatological defects are reported, but some patients have hypotrichosis.

Fragile X syndrome [6–8]

Fragile X syndrome is associated with a folate-sensitive fragile site in band Xq27.3 due to a triplet DNA repeat that is expanded and unstable. Subjects have mental retardation and mild dysmorphic features, with mild connective tissue abnormality that leads to fine skin, hyperextensible joints and flat feet. Males are more commonly affected than females. The disorder is common, with about 1 in 2000 children affected.

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Noonan's syndrome (MIM 163950) [1,2]

This syndrome, which occurs in both sexes, phenotypically resembles Turner's syndrome but the karyotype is

usually normal (46XY or 46XX) [1,3]. Chromosomal abnormalities have been found in only a few cases. One such child had both Noonan's syndrome (NS) and DiGeorge's syndrome, with a deletion within chromosome 22q11 [4]. Many cases appear to be sporadic, although autosomal dominant inheritance has been frequently reported [5].

Clinically, the patients are of short stature and have a broad short neck, which may be webbed. The facies shows a characteristic association of hypertelorism, blepharoptosis, epicanthic folds and a small chin. Skeletal defects are frequent. Congenital heart defects, such as pulmonary stenosis and cardiomyopathy, may be present. Intelligence may be normal but some degree of mental retardation is usual. Children with NS tend to be clumsy, stubborn, irritable and have communication difficulties [6]. In 70% of males, the testes are undescended. Lymphoedema of the feet and legs is common and more severe than in Turner's syndrome [7]. Orbital oedema is sometimes seen and can be an unusual presentation of NS [8]. Widespread leukokeratosis of the lips and gingiva has been described [9]. The hair is usually coarse, light coloured and curly, with a low posterior hairline. Downy hypertrichosis may occur on the cheeks or shoulders. Pubic hair is scanty in the male and beard growth is poor [10]. Ulerythema oophryogenes may be a cutaneous marker for NS [11,12]. Evidence has now emerged that one form of NS, that which maps to 12q24.1, is due to mutations in *PTPN11*, a gene encoding the non-receptor protein tyrosine phosphatase SHP2, which contains two Src homology-2 (SH2) domains [13]. Tartaglia *et al.* [13] found that mutations in the *PTPN11* gene accounted for about half the patients studied. Mutations in the neurofibromin gene (*NF1*), which is the site of mutations causing classic NF1, have been found in neurofibromatosis–Noonan syndrome. Acute leukaemia has been reported in a few cases of NS [14]. After germline mutations in *PTPN11* were demonstrated in NS, a search has been performed for defects in *PTPN11* in myeloid disorders, including cases of juvenile myelomonocytic leukaemia (JMML) in children with NS. Specific mutations in *PTPN11* associated with isolated JMML occur as somatic changes and have never been observed as germ-line defects, leading to speculation that these molecular defects have a greater functional impact and may be associated with embryonic lethality.

Patients with overlapping features of NF1 and NS have also been described (see p. 12.32).

In contrast with Turner's syndrome, short stature and infertility are not constant features. The diagnosis of NS must be suspected in all patients labelled as Turner's syndrome if they are of normal height, mentally retarded, have a cardiac valve defect or manifest normal gonadal function. Individuals with NS who are of short stature may benefit from treatment with growth hormone [15].

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Familial multiple tumour syndromes

The neurofibromatoses

The neurofibromatoses comprise several distinct genetic disorders that lead to the formation of tumours surrounding nerves and a variety of other pathological features, the two main forms being NF1 and NF2. The most common type (NF1) is characterized by multiple café-au-lait macules and the occurrence of neurofibromas along peripheral nerves. The second type (NF2) is characterized by the occurrence of vestibular schwannomas (acoustic neuromas), usually bilateral, as well as meningiomas and other tumours of the nervous system. The spectrum of these disorders has been reviewed [1–6].

Neurofibromatosis 1 (MIM 162200)

SYN. VON RECKLINGHAUSEN'S NEUROFIBROMATOSIS

Definition, history and aetiology [7–9]. In 1882, Friedrich von Recklinghausen published a monograph describing this disease and pointing out that the skin tumours were derived from peripheral nerves [10]. In retrospect, Virchow [11] first reported a family with more than one affected member. It is now recognized that NF1 is an inherited neuroectodermal abnormality, characterized by

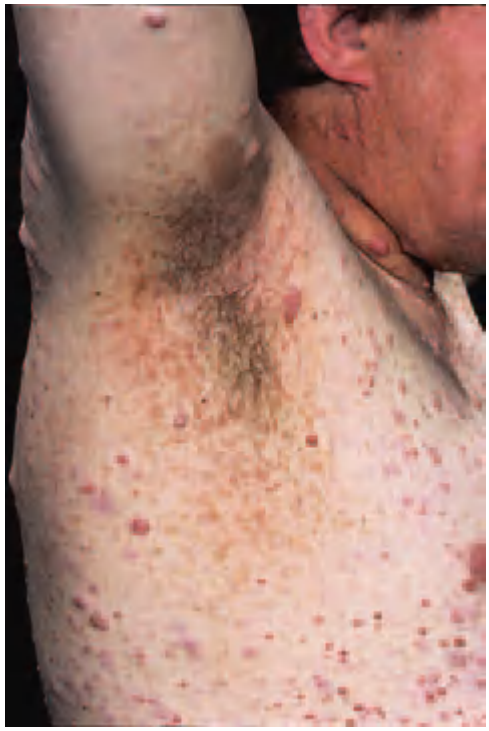

Fig. 12.8 Neurofibromatosis: axillary freckling and multiple neurofibromas.

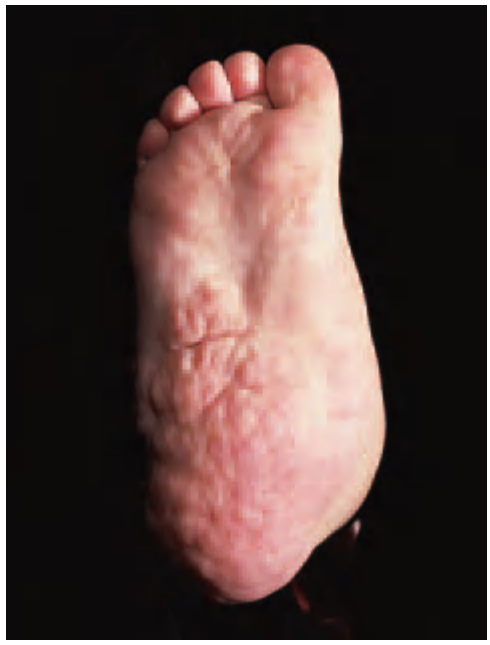

Fig. 12.9 Neurofibromatosis: extensive neurofibroma of the foot.

the presence of six or more café-au-lait spots, axillary freckles, multiple neurofibromas and Lisch nodules (pigmented iris hamartomas) (Figs 12.8–12.10). The mode of inheritance is autosomal dominant, with 100% penetrance by the age of 5 years [9,12]. Sporadic cases result from a high gene mutation rate [7–9]. The prevalance has been estimated at about 1 in 2500–3300 births [9]. Incomplete or monosymptomatic forms are frequent.

Fig. 12.10 Neurofibromatosis: Lisch nodules (pigmented iris hamartomas).

The gene for NF1 is located on chromosome 17 [13,14]. The *NF1* gene has now been cloned and encodes a protein named neurofibromin [15–17]. The gene spans 335 kb and has at least 59 exons, producing four major alternatively spliced transcripts. It is widely expressed in a variety of human tissues. The neurofibromin protein shows significant regions of similarity to the GTPase-activating protein and is capable of down-regulating Ras activity. The majority of *NF1* germ-line mutations alter the reading frame or insert a premature stop codon. No hotspot for mutation has been identified. The impact of these mutations is to reduce the amount of neurofibromin produced by cells. Further investigation supports the contention that the *NF1* gene acts as a suppressor of tumour activity, with a variety of somatic inactivating mutations identified in neurofibromas, in keeping with the classical Knudson 'two-hit' hypothesis of tumour genesis. The random acquisition of somatic mutation partly explains the delayed age of onset of the tumours associated with NF1 and the variability of expression [18]. Mouse models with disrupted *NF1* genes have been shown to have an increased susceptibility to certain tumours, giving further support to the role of the *NF1* gene as a tumour suppressor [19,20]. Neurofibromin has been shown to be present in both keratinocytes and melanocytes in normal adult human skin [21].

Mast cells are increased in neurofibromas and may be involved in the development and growth of these tumours by producing several growth factors, such as histamine and tumour necrosis factor-α (TNF-α) [22,23].

Pathology. Cutaneous neurofibromas are derived from peripheral nerves and their supporting structures, including neurilemmal cells. Ultramicroscopically, they are seen

to consist of arborizing Schwann cells in collagenous interstitial tissue. The fibroblast-like cells in cutaneous neurofibromas are thought to be derived from factor XIIIa and HLA-DR-positive connective tissue cells in peripheral nerves [24]. In both café-au-lait spots and clinically unaffected skin, giant pigment granules are sometimes found in epidermal cells and melanocytes [25–29]. They are rarely found in McCune–Albright syndrome, and never in normal skin. They can, however, be found in other conditions, and their presence cannot be regarded as pathognomonic.

Clinical features [7,8,30–32]. A diagnosis of NF1, according to the National Institutes of Health Consensus Development Conference Statement [33], is based on two or more of the following criteria:
1 six or more café-au-lait macules of over 5 mm in greatest diameter in prepubertal individuals and over 15 mm in greatest diameter in postpubertal individuals;
2 two or more neurofibromas of any type or one plexiform neurofibroma;
3 freckling in the axillary or inguinal regions;
4 optic glioma;
5 two or more Lisch nodules;
6 a distinctive osseous lesion such as sphenoid dysplasia or thinning of the long bone cortex with or without pseudoarthrosis;
7 a first-degree relative (parent, sibling, offspring) with NF1 by the above criteria.

Café-au-lait macules are sharply defined, light-brown patches that vary in size from 0.5 to 50 cm, although the majority are 10 cm or less in size. Café-au-lait spots are the first feature of the disease to appear in all children [8,34]. In a population study, parents noted café-au-lait macules for the first time at 4 years of age or less in all affected children and within the first year of life in 82%. The macules increase in size and number during the first decade. Blue–red macules and pseudoatrophic macules also occur [35].

Cutaneous neurofibromas (or mollusca fibrosa) are soft lilac-pink tumours, sessile and dome-shaped, sometimes pedunculated, most numerous on the trunk and limbs; hundreds may be present, ranging from a few millimetres to several centimetres in diameter. In women, they are prominent on the areola of the breast. Small firm nodules may develop in relation to peripheral nerves. The *plexiform neurofibroma* is a diffuse elongated fibroma along the course of a nerve, frequently involving the trigeminal or upper cervical nerves and usually noticeable within the first 2 years of life. *Elephantiasis neurofibromatosa* is a similar diffuse neurofibromatosis of nerve trunks associated with overgrowth of the subcutaneous tissue and of the skin, which is wrinkled and pendulous and may produce gross disfigurement. Neurofibromas may also involve the viscera and blood vessels.

Freckling occurs frequently in the axillae, when it is virtually pathognomonic [36]. It is present in about 70% of affected subjects and appears a little later than the café-au-lait spots, the youngest case in one series being 3 years old [34]. It may also occur in other intertriginous areas.

There may also be darker pigmented patches over an underlying plexiform neurofibroma, and if these extend to the midline, it may indicate that the tumour involves the spinal cord [37].

Lisch nodules (pigmented iris hamartomas) appear as dome-shaped lesions found superficially around the iris on slit-lamp examination. They occur in over 90% of patients and increase with age [8,34]. They are asymptomatic but help to confirm the diagnosis. They do not occur in segmental or bilateral acoustic NF [31].

Oral lesions are present in 5–10% of cases, as papillomatous tumours of palate, buccal mucous membrane, tongue and lips, or as macroglossia, which is usually unilateral [38].

Kyphoscoliosis occurs in 2% of cases and the early-onset, high-level lesions may progress inexorably, leading to cardiorespiratory disease, unless aggressive surgery is performed. Pseudoarthrosis involving the tibia or radius occurs in 1%, but may be asymptomatic [31].

Short stature and macrocephaly [39] are also features of the condition.

Other organs. The severity of cutaneous involvement gives no reliable indication of the extent of the disease in other organs. Between 25 and 30% of children may exhibit learning difficulties [34,40] and physical development may be impaired. Speech impediments, hypertelorism and headaches are also common [31,41]. Endocrine disturbances of many types may be associated [42]: precocious puberty, acromegaly [43], Addison's disease, hyperparathyroidism, gynaecomastia and phaeochromocytoma. Renovascular hypertension may occur in children [44,45]. Osteomalacia when present is the result of a congenital defect of the renal tubules.

Involvement of the lower urinary tract [46] may give rise to urinary symptoms. Constipation occurs due to dysfunction of the colonic musculature. Gastrointestinal lesions may also cause recurrent haemorrhage or obstruction.

There is a high prevalence of cardiovascular abnormalities [47,48] and NF1 can be complicated by pulmonary hypertension [49].

Neurological manifestations are found in some 40% of patients [38,50]. The most common solitary intracranial tumour

is an optic nerve glioma; astrocytomas and schwannomas also occur. Tumours may arise in peripheral nerves and within the spinal cord. Intracranial tumours may cause epilepsy, although fits may occur in the absence of any demonstrable focal lesion.

Sarcomatous change within a neurofibroma varies from 1.5 to 15% of cases, more often in deeper than in cutaneous lesions [34,51]. It is rare before the age of 40 years, but has occurred in early childhood. Growth is often slow and metastasis late, but local recurrence is frequent. In contrast, malignant peripheral nerve sheath tumours are highly aggressive [52]. Malignant change may occur simultaneously in several lesions. Enlargement or pain should suggest the possibility of malignant change, although rapid enlargement may follow haemorrhage.

Other malignant diseases associated with NF include Wilms' tumour, rhabdomyosarcoma, several types of leukaemia [53], retinoblastoma [54] and malignant melanoma [55].

Pruritus may be a symptom of NF. The presence of large numbers of mast cells in the skin in this condition, and the response of the itching to antihistamines, suggest that histamine is the cause of the pruritus [37]. In addition, a beneficial effect of the mast cell blocking agent ketotifen has been reported [22].

Epidermodysplasia verruciformis has been reported in a man with NF1 [56].

Course and prognosis [7,31,38,57]. The course of the disease varies considerably in individual patients and the majority will never develop major complications. Characteristically, café-au-lait spots are present at birth or, more commonly, develop in early childhood. Cutaneous neurofibromas appear during childhood and increase rapidly in number at puberty. However, lesions may be present at birth and become progressively more extensive. Although early onset and rapid progression before puberty usually indicate a poor prognosis, minimal cutaneous involvement in the young child does not necessarily imply a favourable course, although many cases remain limited. Extensive involvement of the urinary or gastrointestinal tract or the central nervous system carries a poor prognosis. Very rarely, the disease may be so extensive at birth as to be incompatible with survival.

Pregnancy, in which unexplained hypertension frequently occurs, sometimes appears to induce rapid progression of existing lesions and the development of new ones [31,58].

At presentation, a detailed clinical assessment is essential and must include examination of all other members of the family. Investigations should include a neurophysiological assessment, a skeletal survey, audiography and slit-lamp ocular examination. Parents and siblings should also have their eyes examined for the presence of Lisch nodules. It is recommended that individuals with NF1 have an annual clinical review, which must include measurement of blood pressure. Further investigations will depend upon the detection of complications. Magnetic resonance imaging (MRI) should be performed in children who have macrocephaly or who demonstrate focal neurological signs or symptoms. Routine cranial imaging is the subject of debate. The detection of an asymptomatic brain lesion will increase patient and parental anxiety and would not alter clinical management. Patients with NF should be monitored by a number of different specialists, with one physician acting as the coordinator. The ideal situation is a multidisciplinary clinic, now established in a number of centres.

Long-term follow-up information on cohorts of NF1 patients has shown a reduced life expectancy related to the development of malignancy and other complications, such as hypertension due to renal artery stenosis or phaeochromocytoma [59–61].

Diagnosis. Diagnosis is established on the basis of clinical criteria. Molecular genetic testing is feasible, but the large size of the gene and wide range of pathogenic mutations have so far impeded the development of a clinical diagnostic test [62]. Cutaneous neurofibromas are clinically and histologically distinctive, although a plexiform neurofibroma in an infant can clinically resemble a congenital melanocytic naevus. Café-au-lait spots, usually the earliest manifestation in children, are present in 10–20% of normal individuals and about 35% of patients with McCune–Albright syndrome [7,25]. If only one or two are present, they have little diagnostic significance in the absence of other signs or of a family history of the disease; if six or more are present, the probability of NF is high. Identification of the *NF1* gene means that prenatal/presymptomatic diagnosis for this disease is now possible, with greater than 95% accuracy in families with a suitable structure [34]. However, in a disorder showing such varied expression and complications, the decision to undergo prenatal diagnosis is far from clear. Prenatal diagnosis is not an option for approximately 50% of cases who represent new mutations.

Treatment. Treatment is symptomatic. The more disfiguring lesions can be excised if not too diffuse [63]. Carbon dioxide laser surgery is a treatment modality for cutaneous neurofibromas, but hypertrophic and atrophic scars can result and a preliminary test treatment is recommended [64]. Surgery is also indicated when an increase in size and pain suggests possible malignant change. Epilepsy should be thoroughly investigated, as neurosurgical relief is sometimes practicable. Prolonged follow-up with routine checks every 6–12 months is advisable.

NF1 has a significant impact on quality of life through alteration of health and appearance [65]. Adolescence is a particularly difficult time when neurofibromas may grow in response to hormonal changes.

Genetic counselling is important. Informing families about the varied complications of NF1 is a difficult counselling task, and there is a fine balance between providing adequate information and causing unnecessary alarm. It should be made clear to patients that 50% of their children are likely to be affected and the disease may be severe. First-degree relatives (e.g. siblings and offspring) who have no stigmata of the disease are unlikely to carry the gene and the risk for their offspring is small but not absent, as gonadal mosaicism has been observed.

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Neurofibromatosis 2 (MIM 101000)

SYN. BILATERAL ACOUSTIC NEUROFIBROMATOSIS

This condition was originally considered to be part of the spectrum of von Recklinghausen's disease but is now recognized as a separate entity, because of its distinct genetic basis and natural history [1,2]. Genetic studies have confirmed that the gene for NF2 is located on chromosome 22 [3]. The *NF2* gene, localized on chromosome 22q11.21, encodes a protein known as s*chwannomin*, which appears to be important in the linking of cytoskeletal proteins to membranes. Mutations distributed throughout the 17 exons of the *NF2* gene have been reported in different families. Loss of the normal (wild-type) allele is characteristically found when examining tumour tissue. Such events arise as somatic mutations and conform to the tumour suppressor 'two-hit' hypothesis originally proposed by Knudson [4,5].

NF2 is characterized by bilateral vestibular schwannomas (acoustic neuromas), as well as other central nervous system tumours of meningeal and glial origin. Café-au-lait spots and cutaneous neurofibromas may be seen, but are usually few in number and much less common than in NF1. The mean age of first symptoms in a UK study was 22.6 years (range 2–52 years) and the mean age of diagnosis 27.6 years (range 5–66 years); 10% presented before the age of 10 years [6]. Cataracts were present in 81% of patients in the series of Parry *et al*. [7], of which most were posterior subcapsular cataracts.

Diagnostic criteria for NF2 [6,8] are as follows.

1 Bilateral vestibular schwannomas, either proven histologically or seen by MRI with gadolinium enhancement.
2 A parent, sibling or child with NF2 and either:
(a) unilateral vestibular schwannoma; or
(b) one of the following—meningioma, glioma, schwannoma, posterior subcapsular lenticular opacities, cerebral calcification.
3 Unilateral vestibular schwannoma and one of the following: meningioma, glioma, schwannoma, posterior subcapsular lenticular opacities, cerebral calcification.
4 Multiple meningiomas (two or more) and one of the following: glioma, neurofibroma, schwannoma, posterior subcapsular lenticular opacities, cerebral calcification.

It is recommended that annual clinical screening of at-risk individuals is performed from early childhood and should include skin and ophthalmological examinations. Annual 'acoustic screen' MRI should be performed from the age of 15 years unless symptoms necessitate earlier scanning [8]. When a mutation is identified in an affected individual, it can be used as a presymptomatic test within the family [9]. The first application of preimplantation genetic diagnosis for NF2 has been reported [10].

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NF1, juvenile xanthogranulomas and juvenile chronic myeloid leukaemia

The association of juvenile xanthogranulomas with NF1

has been noted in many patients [1]. It is now recognized that children with NF1 and juvenile xanthogranulomas have a 20–32-fold higher risk for juvenile chronic myeloid leukaemia than do patients with NF1 who do not have juvenile xanthogranulomas [2]. Juvenile chronic myeloid leukaemia is a rare type of leukaemia and accounts for about 1–2% of childhood leukaemias. There is some debate as to the validity of this association.

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Segmental neurofibromatosis [1–7]

This condition is characterized by café-au-lait spots, cutaneous neurofibromas and sometimes visceral neurofibromas, limited to a circumscribed body segment. The condition probably represents a somatic mosaicism of the *NF1* gene. Rubenstein *et al.* [8] reported two patients with segmental NF in which signs of generalized NF appeared in a single member of the next generation. It is difficult, in the the light of these and other anecdotal examples, to reassure patients with apparent segmental NF that there is no risk of NF1 occurring in their offspring, although the risk is small.

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Café-au-lait spots and pulmonary stenosis (MIM 193520) [1,2]

SYN. WATSON'S SYNDROME

In three families, café-au-lait macules were associated with pulmonary stenosis and low intelligence. Some affected individuals also had freckling in the axillae, perineum and elsewhere. There was no other evidence of NF [2]. Café-au-lait spots are present in about 60% of patients with this syndrome [1]. Allanson *et al.* [3] demonstrated linkage with markers for the *NF1* gene, and Tassabehji *et al.* [4] identified an *NF1* mutation in a family with features of Watson's syndrome and NS. The pathogenesis of this distinct phenotype is as yet unclear.

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Neurofibromatosis–Noonan syndrome (MIM 601321)

Patients with features of both NF1 and NS have been described, although considerable variability of phenotypic expression exists. Whether a specific NF–NS phenotype exists is unclear at present. In a survey of the Noonan phenotype in a series of NF1 patients, it was concluded that this was not a distinct syndrome [1]. In a case report and review of the literature, Buehning and Currey [2] document two studies of NS families with no proven linkage to the *NF1* gene [3,4] and two studies of patients with NF1 and some features of NS that showed molecular abnormalities at the *NF1* locus [5,6]. Their own patient with NF–NS did not have any demonstrable mutation or deletion at the *NF1* site [2].

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Diffuse neurofibroma [1]

Diffuse neurofibroma is a newly recognized distinct clinical entity. A report of four adult cases [1] described 3–8-cm, hard, sclerotic plaques with an irregular surface but without protruding nodules, present for 1–12 years. Histologically, the tumours consisted of spindle cells with wavy fibrillar cytoplasm and elongated nuclei. Electron

microscopy and special stains confirmed their neural origin. Excision revealed infiltration well beyond the clinical margins, and malignant transformation in one. Early diagnosis is important, as prompt surgical treatment is recommended.

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Tuberous sclerosis complex (MIM 191100)

SYN. EPILOIA; BOURNEVILLE'S DISEASE

Definition, history and aetiology. Tuberous sclerosis complex (TSC) is now the preferred name for the condition previously known as tuberous sclerosis and represents a genetic disorder of hamartoma formation in many organs, particularly the skin, brain, eye, kidney and heart. The characteristic skin lesions are angiofibromas, the shagreen patch, periungual fibromas and 'ash-leaf' white macules, classically, although not invariably, seen in association with epilepsy and mental retardation. The term 'complex' emphasizes the multisystem involvement and variable expression of the disease.

TSC was first recognized in the 19th century [1]. Rayer [2] gave the first description of the fibrovascular papules, and Bourneville [3] reported the case of a mentally retarded girl who also suffered from hemiplegia and epilepsy. He did not recognize her facial eruption or kidney tumour as being part of the disease. Sherlock [4] coined the now outmoded term 'epiloia', indicating the diagnostic clinical triad of *epi*lepsy, *l*ow *i*ntelligence and *a*denoma sebaceum.

Early population studies greatly underestimated the prevalence of TSC. More recent studies have shown the incidence to be 1 in 10 000 in the Oxford region [5] and 1 in 27 000 in the west of Scotland [6]. Osborne *et al*. [7] have estimated that the birth incidence may be in the region of 1 in 5800, which makes TSC one of the more common single-gene disorders.

The inheritance of TSC is determined by a single autosomal dominant gene, showing variability of expression, even within a single family. Genetic linkage studies first mapped the *TSC* gene to chromosome 9 [8,9]. It is now recognized that about half the TSC families are linked to 9q34 (*TSC1*) and the other half to 16p13 (*TSC2*) [10,11]. The proportion of families who do not link to either chromosome 9 or 16 is small. The *TSC1* gene has not yet been cloned. The *TSC2* gene encodes a protein named tuberin. Tuberin shows one area of homology to the catalytic domain of the GTPase-activating protein Rap1. Rap1 is a member of the same group of GTPases as *ras* and is involved in the regulation of cell proliferation and differentiation. This suggests that some of the biological functions of tuberin and neurofibromin are similar. Loss of tuberin activity is thought to lead to activation of Rap1 in tumours of patients with TSC [12]. Further support for a tumour-suppressor role comes from the study of loss of heterozygosity for the *TSC1* and *TSC2* gene regions in various hamartomas from TSC patients [13–15]. No obvious phenotypic differences have been found between families linked to *TSC1* and *TSC2* [16]. Analysis of deletions of the *TSC2* locus has identified one specific correlation, namely severe polycystic kidney disease [17].

Approximately 60–70% of TSC cases are thought to be the result of new mutations, but before genetic counselling of the normal parents of an affected child, both parents should be fully investigated, including Wood's lamp examination, computed tomography (CT) [18], renal ultrasound or intravenous pyelography, and expert ophthalmological examination. A study using these tests showed that about 30% of 'normal' parents had TSC [19].

Pathology [20]. The defect in organogenesis may affect almost any tissue. Most of the lesions are hamartomas, and in many organs the cells resemble embryonic cells, suggesting that the defect occurs at an early stage in life. In many lesions, for example angiomyolipoma of the kidney, there is malformation of vascular and mesenchymal tissue. In other lesions, the aberrant cells are uniform. The lesions are slow-growing and tend to produce symptoms by pressure effects, although sometimes there is haemorrhage from a vascular lesion.

Most of the cutaneous lesions show an excess of collagen. The shagreen patches show no other change and cannot be identified on the histological findings alone. The angiofibroma (formerly misnamed adenoma sebaceum) consists of hyperplastic blood vessels and sebaceous glands of immature hair follicles. Collagen synthesis is increased in the angiofibroma, although total collagen content is decreased, suggesting that there may be an increased turnover of collagen [21]. Histopathology of the periungual fibromas shows a distal part with loose collagen and many blood vessels and a larger proximal part composed of dense collagen bundles and fewer capillaries [22]. The white ash-leaf-shaped macules contain abnormal melanocytes with reduced tyrosinase activity [23] and electron microscopy shows defective melanization of melanosomes [24,25].

The characteristic tuberosclerotic nodules of glial proliferation may occur anywhere in the cerebral cortex, basal ganglia and ventricular walls, but are rare in the cerebellum, medulla or cord [20]. Gliomas are not uncommon and almost always develop in the striothalamic region. Renal tumours of embryonic type, usually multiple, subcapsular and benign, are found in about 80% of cases at post-mortem but are frequently asymptomatic. The angiomyolipoma is the characteristic lesion but cystic renal disease also occurs [26]. The so-called congenital

Table 12.3 Clinical features of tuberous sclerosis complex (TSC).

Major features
Facial angiofibromas or forehead plaque
Non-traumatic ungular or periungual fibroma
Shagreen patch (connective tissue naevus)
Multiple retinal nodular hamartomas
Cortical tuber*
Subependymal nodule
Subependymal giant cell astrocytoma
Cardiac rhabdomyoma, single or multiple†
Lymphangioleiomyomatosis and/or renal angiomyolipoma‡
Hypomelanotic macules (more than three)
Suggestive features requiring further investigation
Multiple randomly distributed pits in dental enamel
Hamartomatous rectal polyps§
Bone cysts§
Cerebral white matter radial migration lines*¶
Gingival fibromas
Non-renal hamartoma§
Retinal achromic patch
'Confetti' skin lesions
Multiple renal cysts§
Skin tags
Positive family history in first-degree relative

* When cerebral cortical dysplasia and cerebral white matter migration tracts occur together, they should be counted as one rather than two features of TSC.
† On echocardiogram.
‡ When both lymphangioleiomyomatosis and renal angiomyolipomas are present, other features of TSC should be present before a definitive diagnosis is assigned.
§ Histological confirmation is suggested.
¶ Radiographic confirmation is sufficient.

rhabdomyoma of the heart is an abnormal and premature differentiation of embryonic myocardium into atypical Purkinje cells. The lungs may show interstitial fibrosis or fibroleiomyomatosis with cystic changes [27–29]. Lymphoblastoid cell lines and fibroblasts from patients with TSC are abnormally sensitive to radiation and radiomimetic chemicals [30].

Clinical features [31–36]. The characteristic features of the syndrome are skin lesions, mental retardation and epilepsy, but these show very wide variation in age of onset and severity. Onset before the age of 5 years with cutaneous changes or with epilepsy is usual, although the disease may remain latent until adolescence or adult life. Diagnostic criteria determined by a committee of the US National Tuberous Sclerosis Association [37,38] have since been modified [39]. A definitive diagnosis of TSC requires two major features (Table 12.3). Brain MRI or non-enhanced CT, renal ultrasound or echocardiogram may be necessary.

Skin lesions are found in 60–70% of cases. Lesions of four types are pathognomonic.

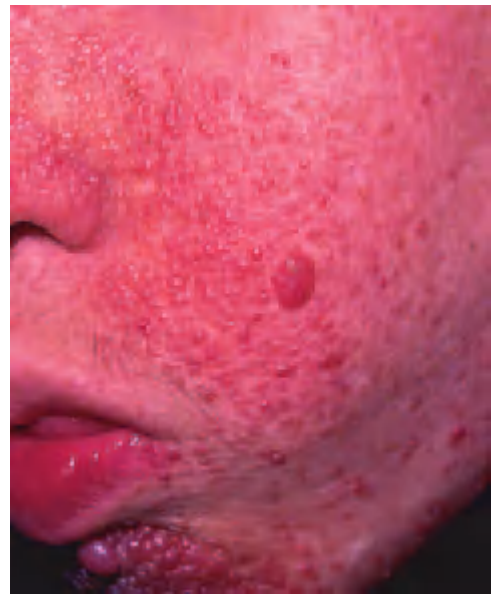

Fig. 12.11 Tuberous sclerosis: angiofibromas.

1 Angiofibromas (Fig. 12.11) may rarely be present at birth or develop in infancy, but usually appear between the ages of 3 and 10 years, and sometimes later. They often become more extensive at puberty and then remain unchanged. Firm, discrete, red-brown, telangiectatic papules, 1–10 mm in diameter, extend from the nasolabial furrows to the cheeks and chin, and are occasionally found in the ears. They may be numerous and conspicuous, and very rarely may form large cauliflower-like masses. In many cases they are easily overlooked, being confined to a small area on each side of the nose or the chin.
2 Periungual fibromas (Koenen's tumours) appear at or after puberty as smooth, firm, flesh-coloured excrescences emerging from the nail folds. They are usually 5–10 mm in length, but may be very large. This can be the only clinically evident abnormality.
3 The shagreen patch is an irregularly thickened, slightly elevated, soft, skin-coloured plaque, usually in the lumbosacral region.
4 White ovoid or ash-leaf-shaped macules [23,40–42] 1–3 cm in length, most easily detectable by examination under Wood's light, are frequently present on the trunk or limbs. They are a valuable physical sign, as they may be found at birth or in early infancy, some years before other signs of the disease develop, and may suggest the correct diagnosis in infants with convulsions. However, it is important to appreciate that hypopigmented macules are seen in 2–3 per 1000 of apparently normal newborn babies and therefore alone their presence is not indicative of TSC [43].

Other cutaneous manifestations include firm fibromatous plaques, especially on the forehead [44] and scalp (Fig. 12.12), soft pedunculated fibromas around the neck and axillae, and poliosis [45].

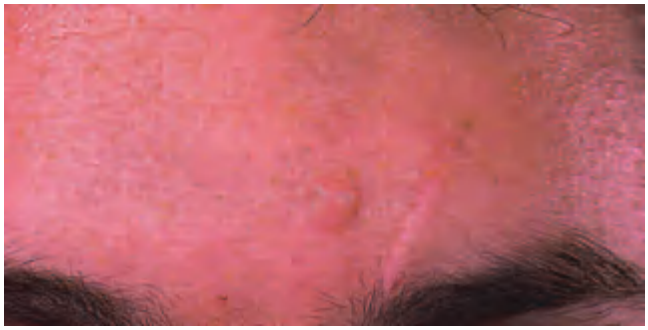

Fig. 12.12 Tuberous sclerosis: fibromatous nodule on the forehead.

Fibromatous tumours are occasionally present on the gums and palate and rarely are found on the tongue, larynx and pharynx [46]. Small pits commonly occur in the tooth enamel in adult patients; although less obvious in the deciduous teeth, these pits have been used as an early diagnostic sign in children with TSC [47].

Mental deficiency is present in 60–70% of cases and may be progressive, but if mental development has been normal throughout childhood subsequent deterioration is uncommon [34]. Some cases have presented gross behaviour disorders, although they have been of normal intelligence. Psychotic symptoms, including schizophrenia, sometimes develop [48], and we have known patients in mental hospitals with depression or schizophrenia to be correctly diagnosed after the discovery of TSC in a near relative.

Epilepsy [49] is seen in almost all mentally retarded patients and in some 70% of those with average intelligence. It usually begins in infancy or early childhood, thus often preceding the skin lesions by many years. Less frequently, the onset of epilepsy is delayed until puberty or adult life. The attacks may be focal and often become progressively more frequent and severe, but there may be long remissions. Intracranial malignant change occurs in a few patients. Symptoms and signs of raised intracranial pressure usually result from obstruction by a tumour at the foramen of Monro. Very rarely, cord lesions produce focal neurological signs.

Ocular signs [50,51] occur in 50% of cases but may be hard to detect. Retinal phacomas are seen as white streaks along the vessels or as small rounded tumours near the disc. Pigmentary and other retinal abnormalities can occur. Symptoms are rare but there may be scotomas or amaurosis. Hypopigmented spots in the iris also occur and these may be analogous to the ash-leaf macule in the skin [52].

Cardiac and renal tumours are often asymptomatic unless by reason of their size or site. Cardiac rhabdomyomas, detected by echocardiography, occur in over 50% of infants [53–55]. These tumours may result in early death; however, recent evidence suggests that in the majority these tumours regress in early infancy and again in adolescence [55]. Prenatal detection of these tumours is now possible by fetal echocardiography [56,57]. Renal involvement includes angiomyolipoma [58], a benign tumour of the renal parenchyma and, less commmonly, renal cysts [59,60]. Rarely, the presenting symptoms may be of renal origin, usually haematuria [61].

Pulmonary changes [28] are rare and seldom cause symptoms, but if extensive can result in increasing dyspnoea and recurrent spontaneous pneumothorax. They occur much more frequently in females and tend to become clinically manifest in the second decade [27,29]. They may result in death from tension pneumothorax or cor pulmonale. The rare association of TSC with chylothorax resulting from lymphangiomyoma appears to be significant [62].

Gastrointestinal tumours may occur [63]. These are usually hamartomatous colonic polyps. Colonoscopy should be considered in the investigation of patients with TSC.

Endocrine and other metabolic disturbances may be present [64]. Most frequently reported are pituitary–adrenal dysfunction, thyroid disorders and premature puberty.

Associated abnormalities. These include primary localized gigantism [65,66] and diffuse cutaneous reticulohistiocytosis [67].

Partial forms. In some cases, only one component of the syndrome is clinically evident, although post-mortem findings in such cases often show involvement of other organs. Unilateral, multiple, facial angiofibromas have been reported in two patients and the authors hypothesized that this represented a mosaic form of TSC [68].

Radiological findings [69] may be as follows.

Skull. Calcification is seen on plain skull X-ray in about 50% of patients, although it is not usually apparent until later childhood or adult life. Investigation should now include CT and MRI [70]. The characteristic CT findings include periventricular (subependymal) nodules, parenchymal hamartomas (cortical tubers), ventriculomegaly and, rarely, subependymal giant cell astrocytomas. The typical CT appearance of TSC consists of calcified periventricular nodules that project into the lateral ventricles and hypoattenuated parenchymal lesions. MRI is more sensitive in the detection of parenchymal lesions. The periventricular lesions may not be seen initially and can progress to calcified lesions with time. This is also true of the parenchymal lesions.

Hands and feet [71]. Cyst-like lesions of the phalanges and irregular thickening of the cortex of metatarsals and metacarpals have been reported, and similar lesions localized in vertebrae, pelvis or long bones are not uncommon.

Lungs. There may be irregular reticulation of the lung fields, not radiologically distinguishable from other types of interstitial fibrosis.

Kidneys. Investigation includes ultrasound and CT [72]. Angiography is helpful in differentiating renal hamartomas from other lesions [73].

Electroencephalographic findings. The proportion of cases showing abnormal findings is high and increases with age, but there is no diagnostic pattern.

Course and prognosis. The expectation of life for a severely affected infant is poor: 3% die in the first year, 28% under 10 years and 75% before age 25 years. Death is usually due to epilepsy or intercurrent infection, but occasionally it is due to a tumour, cardiac failure or pulmonary fibrosis. The prognosis for the older child or young adult with the cutaneous stigmata and epilepsy is unpredictable. Each case must be investigated in detail and individually assessed.

Diagnosis [36]. The telangiectasia and the lack of comedones and pustules distinguish angiofibromas from acne vulgaris. The firm, skin-coloured papules of epithelioma adenoides cysticum must also be differentiated. The full syndrome presents few problems. Difficulties arise in infancy when the classical triad is not evident. The identification of white ash-leaf-shaped macules under Wood's light, in the presence of unexplained epilepsy, retinal phacomas, or radiological or electroencephalographic findings, or a positive family history will help establish the diagnosis. The partial forms are often unsuspected until post-mortem. Any child of a person diagnosed as having TSC has a 50% chance of inheriting the disease. Family screening and genetic counselling should be carried out by referral to a clinical genetics service. DNA testing is available in 85% of cases and should be discussed. Gonadal mosaicism is possible in around 3% of families where parents are not known to have overt TSC. Prenatal diagnosis is not an option for the 60–70% of cases who represent new mutations.

Treatment. The cosmetic appearance may be improved by removing angiofibromas with the pulsed dye vascular laser (wavelength 585 nm). The more papular/nodular lesions are best treated with the carbon dioxide laser in the first instance [74]. The treatment of lesions in other organs is unsatisfactory, and surgical procedures may be required for relief of symptoms. Neurosurgery should be considered when epilepsy is uncontrolled by drugs and there is a fixed, circumscribed, electroencephalographic focus [75].

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Gardner's syndrome (MIM 175100)

Aetiology. The syndrome comprises multiple epidermoid cysts, fibrous tissue tumours, osteomas and polyposis of the colon; its inheritance is determined by an autosomal dominant gene of variable expressivity [1–4]. Gardner's syndrome is located on chromosome 5q, near bands 5q21–q22 [5,6]. It is now thought that Gardner's syndrome and familial polyposis coli are allelic disorders, caused by mutation in the *APC* (adenomatous polyposis coli) gene.

Congenital hypertrophy of the retinal pigment epithelium is a frequent finding in Gardner's syndrome and is a valuable clue to the presence of the gene in persons who have not yet developed other manifestations [7,8].

Turcot's syndrome, in which polyposis of the colon is associated with malignant tumours of the central nervous system [9], was present in the uncle of a patient with gastric polyposis and multiple epidermoid cysts [10]. It has been suggested that Turcot's syndrome represents a variant of Gardner's syndrome.

Pathology. The pathology and natural history of the polyposis are essentially similar to familial polyposis coli. The syndrome in which polyposis of the colon is associated with perifollicular fibrosis is probably distinct [11]. Several groups have reported the association of hepatoblastoma with polyposis coli [12,13].

Histology and immunohistochemistry of cutaneous cysts suggest that these are derived from follicular stem cells [14].

Clinical features [3,11,15–17]. Polyposis of the colon or rectum usually arises during the second decade, but may occur in early childhood. It is present in about 50% of cases by the age of 20 years. There are few symptoms and intussusception is not a feature. Malignant change develops some 15–20 years later in over 40% of reported cases.

The variable expressivity of the gene must be remembered when a family is investigated [18]. Cutaneous and skeletal changes may be present without polyposis, and polyposis may be present when one or more of the other features of the syndrome is lacking [19].

Epidermoid cysts, which may be numerous, are usually irregularly distributed on the face, scalp and extremities, and are less frequent on the trunk. They may first appear between the ages of 4 and 10 years, but often considerably later, and are ultimately present in almost all cases.

Osteomas develop mainly in the maxilla, mandible and sphenoid bones, but also in other bones of the skull and, less frequently, in the long bones. They are usually small, multiple and present in some 50% of cases. The age of onset is often not accurately known, but they may be present at puberty.

Fibromas or desmoid tumours are less frequently present. They are usually poorly localized tumours in incisional scars of the abdomen, but may occur at other sites. Fibrosarcomas have also been associated with the syndrome. Fibromatous growths of the mesentery may be discovered at operation, and severe peritoneal scarring may follow surgery. A very large desmoid tumour extensively involving the chest wall and the left anterior abdominal wall has been described in a patient with a family history of Gardner's syndrome. The desmoid arose at the site of a thoracotomy scar following the removal of a large aneurysm of the left atrial appendage 5 years before [20].

Lipomas in the subcutaneous tissues, and in other organs, have frequently been noted.

Leiomyomas of the stomach or ileum, or retroperitoneal tissue, are sometimes present.

Diagnosis. Because multiple epidermoid or sebaceous cysts may be inherited as an isolated abnormality and may thus have no sinister significance, their discovery is an indication for a detailed family history and a careful examination for osteomas, including radiological examination of the skull, and for other dermal tumours. The cutaneous lesions are an important indicator of possible asymptomatic polyposis.

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Cowden's syndrome (MIM 158350)

SYN. MULTIPLE HAMARTOMA SYNDROME

Definition. In this rare disorder, multiple hamartomatous lesions of ectodermal, endodermal and mesodermal origins are associated with a predisposition to malignant tumours, particularly of the breast. Cowden was the name of the family in whom the disease was first described [1].

The condition is characterized by mucosal and cutaneous papillomatosis and fibromatosis, with fibrocystic breast disease in the female and thyroid goitre or adenoma.

Aetiology. Inheritance of the disease is determined by an autosomal dominant gene of variable expressivity. Germline mutations of the *PTEN1* gene located on chromosome 10 have been identified in a proportion of kindreds.

However, Cowden's syndrome, like so many other inherited disorders, shows locus heterogeneity, with some families developing the disease due to heterozygous mutation of the transforming growth factor (TGF)-β type 1 receptor, known as bone morphogenetic receptor type 1 (*BMPR1A*). Both genes encode proteins required in regulation of cell proliferation, and loss of the wild-type allele has been detected in tumour tissue, in accord with the Knudson 'two-hit' hypothesis [2]. About 100 cases have been reported [3].

Pathology [4,5]. The skin lesions around the mouth, eyes and chin are trichilemmomas [6]. The breast lesions are fibroadenomas, which are liable to undergo malignant degeneration. A unique fibroma on the face and other sites has been described [5,7], composed of broad acellular collagen bundles in a lamellar or whorl-like pattern with occasional giant cells. This has been referred to by Barax *et al.* [3] as 'Cowden's fibroma'. An immunohistochemical study of the sclerotic fibroma has shown strong staining with an antibody directed at human type I procollagen [8]. There is a report of amyloid in association with multiple hamartoma syndrome [3].

Clinical features [9–14]. Mucocutaneous lesions have been present in all reported cases of this disease, but they have varied in their distribution, extent and age of onset. Skin-coloured lichenoid papules up to 4 mm in diameter, tending to coalesce to give a cobblestone appearance, are distributed on and around the eyes and mouth. On the dorsa of hands and wrists are lesions like those of acrokeratosis verruciformis. On palms and soles and on palmar and plantar aspects of fingers and toes are small translucent keratoses. Multiple angiomas and lipomas have been found in several cases. Malignant melanoma has occurred [15].

Verrucous and papillomatous lesions are seen in some patients on the labial and buccal mucosa, fauces and oropharynx, and may extend to the larynx.

In a series of 21 patients [14], craniomegaly was noted to be the most frequent extracutaneous finding, affecting 70% of patients.

Of the many other abnormalities that have been reported in this syndrome, the most frequent involve the thyroid and breasts. Approximately 30% of reported female cases developed breast cancer [14]. Fibrocystic disease of the breast sometimes leads to massive hyperplasia. Goitre or thyroid adenoma is present in many cases and thyroid carcinoma has been reported [7,9]. Adenocarcinoma of the uterus has been reported in 6% of women with multiple hamartoma syndrome [14]. Less frequent associations include adenoid facies, high-arched palate, vitiligo, café-au-lait spots, skeletal abnormalities, retinal glioma, pseudotumour cerebri, gastrointestinal polyposis and various gynaecological disorders (menstrual irregularity, uterine fibroids). An association with renal cell adenocarcinoma and primary neuroendocrine carcinoma of the skin (Merkel cell carcinoma) in one patient has been documented [16].

Ruschak *et al.* [17] described a patient with this syndrome who had a deficiency of T-lymphocyte function, with recurrent cellulitis and abscess formation, and the eventual development of acute myeloid leukaemia.

Differential diagnosis. The combination of clinical and histological findings is pathognomonic. It seems possible that the skin lesions have in the past been confused with Darier's disease, and some cases may have been reported as TSC with mucosal involvement [7]. The relationship between Cowden's syndrome and gingival fibromatosis with hypertrichosis [18] is uncertain, but they are probably separate conditions.

Treatment. Cosmetic surgery may be helpful. The possibility of carcinoma of breast or thyroid must be borne in mind. Female patients with this syndrome should avoid oestrogen therapy and should have frequent breast investigations, including mammography, or even prophylactic mastectomy [19].

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Table 12.4 The ectodermal dysplasias. (Modified from the classification of Freire-Maia and Pinheiro [5].)

Subgroup 1-2-3-4
Hypohidrotic ectodermal dysplasia, X-linked (Christ–Siemens–Touraine syndrome)
Hypohidrotic ectodermal dysplasia, autosomal recessive
Rapp–Hodgkin syndrome
Ectrodactyly–ectodermal dysplasia–cleft lip and palate (EEC syndrome)
Rosselli–Gulienetti syndrome
Alopecia–onychodysplasia–hypohidrosis–deafness
Basan's syndrome
Greither-type ectodermal dysplasia
Xeroderma–talipes–enamel defect
Ankyloblepharon–ectodermal dysplasia–cleft lip and palate (AEC syndrome)
Anonychia with flexural pigmentation
Tricho-onychodental dysplasia
Subgroup 1-2-3
Hidrotic ectodermal dysplasia (Clouston's syndrome)
Tricho-dento-osseous syndrome
Trichorhinophalangeal syndromes I and II
Schöpf–Schulze–Passarge syndrome
Chondro-ectodermal dysplasia (Ellis–van Creveld syndrome)
Tricho-odonto-onychial dysplasia
Odonto-onychodysplasia with alopecia
Schinzel–Giedion syndrome
Fried's tooth and nail syndrome
Hypodontia and nail dysgenesis
Dermo-odontodysplasia
Odontotrichomelic syndrome
Salamon's syndrome
Coffin–Siris syndrome
Ectodermal dysplasia with pili torti and syndactyly
Dwarfism–alopecia–pseudoanodontia–cutis laxa
Subgroup 1-2-4
Hypohidrosis–diabetes insipidus syndrome
Subgroup 1-2
Oral–facial–digital syndromes I, II, III and IV
Oculodentodigital dysplasia
Berlin's syndrome
Sensenbrenner's syndrome
Johanson–Blizzard syndrome
Subgroup 1-3
Tricho-oculo-dermo-vertebral syndrome
Curly hair–ankyloblepharon–nail dysplasia syndrome
Subgroup 1-4
Kirman's syndrome
Subgroup 2-3-4
Hypoplastic enamel–onycholysis–hypohidrosis
Subgroup 2-3
Nail dystrophy–deafness syndrome
Dento-oculo-cutaneous syndrome
Subgroup 2-4
Sandman–Andra syndrome
Ectodermal dysplasia with cataracts and hearing defects
Subgroup 3
Oto-onycho-peroneal syndrome
Deafness, onychodystrophy and digital anomalies
Subgroup 4
Hypohidrosis with neurolabyrinthitis

1, hair defect; 2, tooth defect; 3, nail defect; 4, sweating defect.

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Ectodermal dysplasias

Nomenclature. The ectodermal dysplasias are a heterogeneous group of disorders, the classification of which has been substantially reviewed as a consequence of molecular genetic studies. Weech [1] used the term to describe certain heritable developmental disorders of tissue derived from the ectoderm but, with time, many new syndromes were described in which the term was loosely used. Freire-Maia [2,3] suggested limiting the term 'ectodermal dysplasia' to those disorders with a primary defect in hair, teeth, nails or sweat gland function. Solomon and Keueur [4] discussed the problem of classification, and suggested limiting the term to disorders that are congenital, nonprogressive and diffuse. The number of distinctive syndromes in which there is a defect in one or more epidermal appendages is now so large (more than 150) that Freire-Maia and Pinheiro [5–7] proposed a provisional classification based on which ectodermal derivatives are affected. According to their classification, '1' indicates hair dysplasia, '2' dental dysplasia, '3' nail dysplasia and '4' sweat gland dysplasia. The different subgroups are referred to either by the combination of these numbers or by their Greek names, for example 1-2-3-4 is tricho-odonto-onychodyshidrosis. Although this classification is unsatisfactory in many respects, it has helped in imposing some order on a heterogeneous and complex group of disorders. The principal syndromes and some of the rarer disorders are detailed in this section (Table 12.4).

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Hypohidrotic ectodermal dysplasia, X-linked (MIM 305100) [1–4]

SYN. CHRIST–SIEMENS–TOURAINE SYNDROME; ANHIDROTIC ECTODERMAL DYSPLASIA

Definition. Hypohidrotic ectodermal dysplasia is characterized by partial or complete absence of sweat glands, hypotrichosis and hypodontia.

Aetiology. Hypohidrotic ectodermal dysplasia was first described in 1848 by Thurnam [5] and later in the 19th century by Darwin [6]. It was assigned to the X chromosome in 1921 by Thadani [7], who later reported that carrier females could manifest signs of the condition. The inheritance of this syndrome is determined by an X-linked recessive gene [8,9]. Linkage studies have mapped this disorder to Xq12–q13.1 [10,11], and it is caused by mutation in a novel transmembrane protein with a suggested role in epithelial–mesenchymal signalling [12]. It has been proposed that decreased expression of the epidermal growth factor receptor plays a causal role in the hypohidrotic ectodermal dysplasia phenotype [13]. The incidence of hypohidrotic ectodermal dysplasia was estimated by Stevenson and Kerr [14], based on prevalence in Oxfordshire, to be 1 per 100 000 births. Several hundred cases, of which over 90% are males, have been reported in many different races. The complete syndrome does not occur in females, but female carriers may show dental defects, sparse hair, reduced sweating and dermatoglyphic abnormalities [2,15].

Pathology [16,17]. The epidermis is thin and flattened and eccrine sweat glands are absent or rudimentary, or few and poorly developed. The reduction in the number of sweat glands, hair follicles and sebaceous glands is variable. Large and clinically visible sebaceous glands were, however, present on the faces of two affected twins [18]. Dermal connective tissue usually appears grossly normal, but collagen and elastic fibres may be fragmented or sparse. In some cases, mucous glands are absent in the upper respiratory tract and in the bronchi [3]. Salivary glands show inflammatory changes and ectasia of ducts [19]. An interesting finding was sparsity of amniotic fluid at birth [20]. The cell-mediated immune response may be depressed and the serum IgE level elevated as in the atopic state [21].

Clinical features. The essential features of the syndrome are absent or reduced sweating, hypotrichosis and total or partial anodontia. In the more complete forms the appearance of the patient is distinctive, with prominent frontal ridges and chin, saddle nose, sunken cheeks, thick everted lips, large ears and sparse hair. The skin is smooth, soft, dry, finely wrinkled (especially around the eyes) and appears prematurely aged.

Absent or reduced sweating causes heat intolerance, and affected individuals may present with unexplained fever in infancy or childhood [22]. Extreme discomfort can follow exertion or eating hot foods. Thyroid medication may also induce hyperpyrexia [8]. Happle and Frosch [23] demonstrated that sweat testing of the back reveals a pattern consistent with Blaschko's lines and explained this phenomenon on the basis of lyonization.

The temporary and permanent teeth may be entirely absent, or there may be a few teeth present. The incisors and/or canines are characteristically conical and pointed (Fig. 12.13). The jaws develop normally even in complete anodontia, but the gums may be atrophic [17]. The mouth may be dry from hypoplasia of the salivary glands and the lacrimal glands may also be deficient. Otorhinolaryngological features include atrophic rhinitis, persistent foul-smelling nasal discharge and crust formation, chronic respiratory infections and hearing problems [24,25]. Poor development of mucous glands in the gastrointestinal tract may result in dysphagia and, more rarely, stomatitis and diarrhoea. Aplasia or hypoplasia of the breasts is occasionally noted.

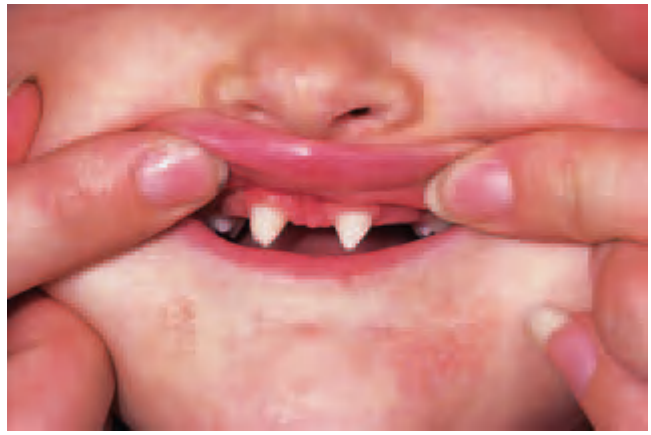

Fig. 12.13 Conical teeth in X-linked hypohidrotic ectodermal dysplasia.

Alopecia is often the first feature to attract attention, but it is seldom total. The scalp hair is sparse, dry, fine and usually remains short. The structure of the shaft may be abnormal. The eyebrows are sparse or absent, but the lashes are usually normal. The beard, pubic and axillary hair are often sparse and other terminal hairs on trunk and limbs may be absent.

The nails are abnormal in about half the cases and may be brittle, thin or ridged, but are seldom grossly deformed.

Ocular abnormalities are unusual, although corneal and lenticular opacities have occurred [8,26]. Atopic eczema and asthma are often present [3,24].

General physical development may be somewhat stunted, but sexual development is usually normal; primary hypogonadism is occasionally associated [27]. Mental development is retarded in 30–50% of cases but usually not greatly. The expectation of life is normal or only slightly reduced.

Partial forms should be sought among the relatives of known cases and are found mainly among carrier females. The conical pointed teeth are the key feature of the syndrome and may be the only obvious abnormality. In other cases, they may be associated with congenital alopecia, and defective sweating, if present, may be detectable only on appropriate testing [28].

Associated abnormalities. In one family, the typical syndrome was associated with Friedreich's ataxia in four brothers [29]. In another, Horner's syndrome of central type with nystagmus was evidence of a developmental defect of the brainstem [30].

Diagnosis. The diagnosis is rarely made until the child is old enough for deficiencies of hair and teeth to arouse parental anxiety, but should be suspected in unexplained hyperthermia. The characteristic facies is pathognomonic but may not be recognized in infancy. Assessment of the dental status of the child and siblings may establish the diagnosis. In the older child with the full syndrome, the diagnosis is unmistakable. In partial forms, the pointed conical teeth provide the most reliable indication and should suggest the need for sweat testing and a skin biopsy.

Treatment. Little can be offered except advice concerning restriction of physical exertion, choice of suitable occupation and avoidance, if practicable, of warm climates. Special schooling and psychological support may be needed. Regular dental supervision is essential and dentures may be required at an early age [19]. The use of DNA-based mutational analysis now offers the opportunity for prenatal diagnosis [31].

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Hypohidrotic ectodermal dysplasia, autosomal dominant and recessive types (MIM 129490 and MIM 224900)

A number of cases of hypohidrotic ectodermal dysplasia have been reported in which autosomal recessive inheritance of the syndrome seems probable [1–3]. Phenotypically, the features are indistinguishable from those of the X-linked form, except that the complete syndrome occurs in both sexes. It has been claimed that the sweating deficiency is less severe in the autosomal recessive form. Sweat glands are reduced in number but are not absent [1]. Dominant and recessive inheritance patterns are due to different types of mutation of the same gene, located at 2q11–q13. The *ED3* gene encodes a protein with a single transmembrane domain, shows many features in keeping with the TNF receptor family of genes, and shows strong homology to the *downless* mouse mutant [4].

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Hidrotic ectodermal dysplasia (MIM 129500)

SYN. CLOUSTON'S SYNDROME

Definition. Hidrotic ectodermal dysplasia is characterized by nail dystrophy, associated with defects of the hair and keratoderma of palms and soles.

Aetiology. Several reports have described an extensive kindred of French extraction, which migrated to Canada, Scotland and the USA [1–6]. The inheritance of the syndrome is determined by an autosomal dominant gene; the homozygous state may be lethal. A molecular defect of keratin was proposed but linkage to known keratin genes has been excluded [7]. The gene responsible for hidrotic ectodermal dysplasia maps to the pericentromeric region of chromosome 13q and the *ED2* gene has been shown to be a member of the gap junction family known as connexin 30 (*GJB6*) [8]. These proteins mediate the direct diffusion of ions and metabolites between the cytoplasm of connecting cells. It is of interest that mutations in the connexin proteins have also been associated with inherited forms of hearing loss, and a number of families with both deafness and hidrotic ectodermal dysplasia have been reported.

Pathology. Hyperkeratosis resulting from reduced desquamation is most evident on palms and soles. Biophysical and biochemical studies of the hair give findings consistent with the hypothesis that there is depletion of matrix protein and disruption of, or a failure to form, disulphide bonds in the remaining keratin. Ultrastructural studies of hair [9,10] have shown disorganization of hair fibrils with loss of the cuticular cortex.

Clinical features [1,4,11–13]. Dystrophy of the nails is the key feature of the syndrome and in some 30% of those affected there may be no other obvious defect. The nails are thickened, striated, often discoloured and grow slowly. Less often they are short, thin and brittle. Persistent paronychial infections are frequent and may partially or completely destroy the matrix. The skin is thickened beneath the free edges of the nails, over the finger joints and knuckles, and sometimes over the knees and elbows. Diffuse hyperkeratosis of the palms and soles, extending in varying degree to the sides of the dorsal aspects, is frequent and may be severe; fissuring is sometimes troublesome.

In the complete forms, scalp hair is very sparse, fine, pale and brittle or completely lacking. It may be more or less normal in infancy, but seldom remains after puberty. The eyebrows are thinned or absent, especially in their outer two-thirds, and lashes are few and small. Vellus and pubic and axillary hair are sparse or absent. One affected woman developed numerous eccrine poromas [14].

The teeth are often normal [15]; they show no characteristic defect but may be poor, with early caries. The skull is sometimes thickened and there may be tufting of the terminal phalanges of fingers and toes [6].

General physical development is normal but affected individuals may be shorter than unaffected siblings. Genital maturation and expectation of life are unaffected. Mental development may be retarded but is often normal.

In one family, five members with this condition developed bilateral premature cataracts [16].

Diagnosis. The presenting manifestation may be alopecia, palmoplantar keratoderma or the unsightly and often painful nail changes. The diagnosis is established by the nail dystrophy in a patient with normal facies, no specific dental defect and normal sweating.

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Rapp–Hodgkin syndrome (MIM 129400) [1–3]

In this autosomal dominant syndrome, hypohidrosis is severe enough to result in intolerance of heat. Hair is sparse, light in colour and of 'steel-wool' texture, and may

show pili torti [4] or pili canaliculi [5]. The nails are narrow and dystrophic. Other abnormalities include small stature, cleft lip or palate, and hypospadias. A high forehead, narrow nose, small mouth and maxillary hyperplasia give a distinctive facies. The dentition is poor, with conical teeth and hypodontia. The lacrimal puncta may be aplastic. One case associated with palmar keratoderma has been described [6]. Rapp–Hodgkin syndrome seems to overlap with both the ectrodactyly–ectodermal dysplasia–clefting (EEC) syndrome [7] and the ankyloblepharon–ectodermal dysplasia–clefting (AEC) syndrome [8,9].

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EEC syndrome (EEC1, MIM 129900; EEC2, MIM 602077; EEC3, MIM 604292) [1–3]

The association of ectrodactyly (lobster-claw deformity of the hand) (Fig. 12.14) with cleft lip and palate, transmitted as an autosomal dominant trait, was originally described by Cockayne in 1936 [4]. The EEC syndromes are characterized by locus heterogeneity, with families displaying autosomal dominant inheritance and the genes mapping to 7q11.2–q21.3 (*EEC1*), chromosome 19 (*EEC2*) and 3q27 (*EEC3*). Of these, the only gene so far characterized is that for *EEC3*. Mutations in *p63*, which shows strong homology to *p53*, a well-known tumour-suppressor gene, have been identified. The majority of the *EEC3*-causing mutations are amino-acid substitutions that lead to the production of a protein that is defective in its ability to bind to DNA and thereby regulate the expression of other genes [2]. As a clear example of the correlation between the functional impact of a mutation and the observed clinical phenotype, other missense mutations of the *p63* gene affect the sterile alphamotif (SAM) domain and are predicted to impinge on *p63*-mediated protein–protein interactions. These mutations have recently been reported in a range of congenital ectodermal dysplasias (see below).

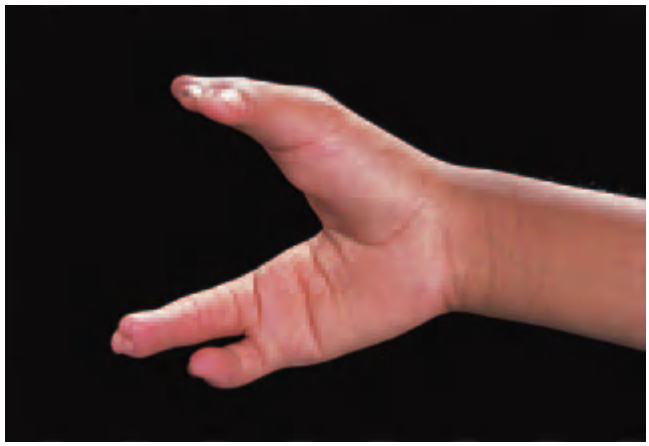

Fig. 12.14 EEC syndrome: typical lobster-claw deformity of the hand.

The main clinical features of the EEC syndromes are ectrodactyly, sparse wiry hypopigmented hair, peg-shaped teeth with defective enamel, cleft lip and palate, and lacrimal duct stenosis. The normal mucosal covering of the laryngeal folds is absent, and the voice tends to have a breathy quality, as it does in anhidrotic ectodermal dysplasia [5]. Conductive deafness is associated with clefting. Although ectodermal dysplasia is a feature, there are numerous sweat glands on the skin biopsy, and sweating may be normal in some patients [6]. In a study of 25 Brazilian patients, 13 had genito-urinary anomalies [7]. Corneal scarring and blindness are serious complications [8,9]. Absence of meibomian glands has been noted [10]. Hamartoma of the tongue in an infant was documented by Hanna *et al*. [11]. The EEC syndrome can be associated with hypothalamic–pituitary dysfunction [12].

Not all the defects are present in every patient. Anodontia was the sole clinical feature in a mother who had two children with ectrodactyly, one of whom had a cleft lip and palate [13].

Multidisciplinary management is essential, with the early involvement of a clinical geneticist. Cleft lip and palate can be detected by ultrasound examination prenatally, which may be of value in the genetic counselling of affected families [14]. At present, molecular genetic analysis is confined to those harbouring *p63* mutations.

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ADULT (*a*cro-*d*ermato-*u*ngual–*l*acrimal–*t*ooth) syndrome (MIM 103285) [1]

A family of seven affected individuals has been reported with an autosomal dominant syndrome that closely resembles EEC syndrome. Linkage studies suggest that the related ADULT syndrome is also caused by mutations in the *p63* gene. The main manifestations are hypodontia and/or early loss of permanent teeth, ectrodactyly, obstruction of lacrimal ducts, onychodysplasia and excessive freckling.

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AEC syndrome (MIM 106260) [1–3]

SYN. HAY–WELLS SYNDROME

The inheritance of this syndrome is determined by an autosomal dominant gene of variable expressivity. The syndrome is due to mutation in the SAM domain of the *p63* gene product [4]. The essential features are ankyloblepharon (fused lid margins), ectodermal defects and cleft lip and palate. Hair may be absent, but if present is sparse and coarse with electron microscopic appearances resembling those of Marie–Unna hypotrichosis. The nails are absent or dystrophic and the widely spaced, pointed teeth are soon shed. Sweating is diminished. The nasal bridge tends to be broad and the maxilla sunken. Denuded skin at birth and chronic scalp erosions complicated by infection are common features of this syndrome [5].

Some cases have other defects, including lacrimal duct stenosis, ptosis, microphthalmia, supernumerary nipples, syndactyly, deformities of the auricle, interventricular septal defect and Waardenburg's syndrome.

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Rosselli–Gulienetti (cleft lip/palate) syndrome (MIM 225000) [1]

The inheritance of this syndrome is probably determined by an autosomal recessive gene. Hypohidrosis accompanies slight frontal bossing and some depression of the nasal bridge. The scalp hair is often fine, dry, sparse and light in colour; the nails are dystrophic and teeth are few and small. Other features are cleft lip and palate, syndactyly and defects of the external genitalia. There may also be popliteal web formation. The disorder includes both Zlotogora–Ogur syndrome and Margarita Island ectodermal dysplasia, and was assigned to chromosome 11q23 by linkage mapping [2]. This was followed by a positional cloning approach to identify the gene as *PVRL1*, encoding nectin-1, an immunoglobulin-related transmembrane cell–cell adhesion molecule that is part of the NAP cell adhesion system. Nectin-1 is also the principal cell surface receptor for α-herpesviruses. Suzuki *et al*. [2] speculated that the high frequency of this syndrome on Margarita Island in the Caribbean Sea might have resulted from resistance of heterozygotes to infection by these viruses.

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Alopecia–onychodysplasia–hypohidrosis–deafness [1]

This is a distinct syndrome of autosomal recessive inheritance. An affected child may be born bald and remain so, apart from the few thin yellow hairs on the scalp. Teeth are small, the fingernails are normal, but the toenails are thick and dystrophic. There is hypohidrosis and also hyperkeratosis of the palms and soles, knees and elbows and, to some extent, on the skin generally, except on the

head and neck. There may be severe sensorineural deafness, and also defects of other organs.

REFERENCE

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Basan's syndrome (MIM 129200) [1]

This autosomal dominant syndrome is characterized by hypohidrosis and dryness of the skin and the mucous membranes of the mouth and vulva. Severe dental caries develops early. Body hair, eyebrows and eyelashes remain sparse throughout life. There may at first be a normal quantity of scalp hair but of coarse texture: it is shed during the second decade. The nails are thick and short. The dermatoglyphic pattern is unusual or absent and there are single palmar flexion creases. The family described by Jorgenson [2] had a similar, if not the same, condition.

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Greither-type ectodermal dysplasia [1]

Hypohidrosis is accompanied by almost total alopecia, with loss of teeth, corneal and lenticular opacities, dystrophic nails and the transgredient form of palmoplantar keratoderma.

Greither's syndrome is a separate entity (see p. 12.65).

REFERENCE

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Xeroderma–talipes–enamel defect [1]

SYN. MOYNAHAN'S SYNDROME

Two siblings born to consanguineous parents were reported with congenital hypohidrosis, nail dystrophy, cleft palate, bilateral talipes and mild mental deficiency with electroencephalographic abnormalities. The teeth were yellow and malformed due to an enamel defect. At least six other members of the family had defective tooth enamel without the other features of the syndrome.

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Anonychia with bizarre flexural pigmentation (MIM 106750) [1]

In this autosomal dominant syndrome, fingernails and toenails are absent from birth and the palmar and plantar skin is dry, thin and peeling. Sweating is diminished. The hair is coarse and sparse in the frontovertical region. There is early dental caries. The diagnostic feature is the presence of mottled hyperpigmentation and hypopigmentation in the axillae, groins and natal cleft.

REFERENCE

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Tricho-onychodental dysplasia [1]

Tricho-onychodental dysplasia is a rare syndrome characterized by taurodontic molars, defective enamel and dentine dysplasia. There are few teeth, widely spaced, and deciduous teeth tend to persist. Nails, particularly toenails, are thin with longitudinal striations and cracks. There is hypohidrosis with a risk of hyperthermia.

REFERENCE

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Tricho-dento-osseous syndrome (MIM 190320)

Definition and aetiology. The inheritance of tricho-dento-osseous (TDO) syndrome, first described in 1966 [1], is determined by an autosomal dominant gene. There is enamel hypoplasia, with enlarged pulp chambers of all teeth, tight curly hair, and bone and nail defects. Three distinct clinical variants are recognized (TDO-I, TDO-II, TDO-III). The gene maps to the chromosomal region 17q12.3–q22 and is a member of the distal-less homeobox gene family known as *DLX3* [2]. This family of genes is involved in transcriptional regulation of gene expression, which may help explain the pleiotropic manifestations of the clinical disorders.

Pathology [3]. Hair from one case showed no abnormality on light microscopy, and its stress–strain characteristics were normal. The serum acid phosphatase level is increased [2]. In TDO-II dentin is dysplastic, whereas it is normal in TDO-I.

Clinical features [3,4]. TDO-I [3] is characterized by kinky or curly hair, dolichocephaly (due to premature fusion of cranial sutures, especially the sagittal), enamel hypoplasia, increased dental caries, radiodense bones and occasionally brittle nails.

Individuals with TDO-II [5] show sparse as well as curly hair, more striking nail changes, and thickening and sclerosis of the calvarium [6]. The nails may show splitting of their superficial layers. Dental eruption is delayed in TDO-I and precocious in TDO-II.

Shapiro *et al.* [7] described a family that differed from both of these (TDO-III); affected persons showed macrocephaly and obliterated diploë and no long-bone sclerosis. Physical and mental development were normal.

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Trichorhinophalangeal syndrome I (MIM 190350)

Aetiology. The first description of trichorhinophalangeal syndrome (TRPS)-I was in 1966 [1]. The disorder is determined by an autosomal dominant gene of variable expressivity. Women are affected more frequently than men. Sanchez *et al.* [2] described a complex chromosome rearrangement in a boy with TRPS-I. Fryns and Van den Berghe [3] reported a patient with TRPS-I and a small interstitial deletion of 8q24.12. Buhler *et al.* [4] described a case of TRPS-I with a mosaic deletion of that band. Detailed analysis of both microdeletion families and the use of linkage studies led to the isolation of the *TRPI* gene, with a range of mutations predicted to result in premature truncation of the protein product. *TRP1* encodes a zinc-finger protein, which functions as a transcription factor. Mutations of the *TRP1* gene have also been reported in additional families with features like TRPS-I but characterized by significant brachydactyly (known as TRPS-III and designated MIM 190351) [5].

Clinical features [1,6–10]. A large, pear-shaped nose is conspicuous above a high philtrum, with slight maxillary prognathism and mandibular hypoplasia. A peculiar tubercle of normal skin below the lower lip is a reliable indicator of the syndrome when seen in a person with a pear-shaped nose. Brachyphalangeal dysostosis gives rise to fusiform swelling of the proximal interphalangeal joints and angulation of the fingers [11].

The hair is fine, brittle and sparse, but the degree of alopecia varies considerably. The eyebrows are dense at their medial ends but sparse laterally. In some patients, the nails are thin and brittle. The stature is short, although growth hormone production is normal [12].

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Trichorhinophalangeal syndrome II (MIM 150230) [1–3]

SYN. LANGER–GIEDION SYNDROME

This syndrome has similarities to TRPS-I, particularly with regard to facies, bulbous nose and sparse hair. Distinguishing features are multiple exostoses, microcephaly and loose/redundant skin. Less consistent features include hyperextensible joints, mental retardation and delayed speech. TRPS-II represents a typical contiguous gene defect, with visible cytogenetic deletions, associated with the loss of a number of genes including the *TRP1* gene. Cytogenetic evaluation of a child presenting with significant mental retardation and the clinical appearance of TRPS-I is mandatory. Analysis of some parents will reveal a balanced parental translocation. All reported cases are sporadic [1].

REFERENCES

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Schöpf–Schulz–Passarge syndrome (MIM 224750) [1–3]

Cystic eyelids, palmoplantar keratoderma and hypotrichosis are associated with marked reduction in the number of teeth and with brittle and furrowed nails. The inheritance is autosomal recessive, although one report was consistent with segregation of an autosomal dominant trait, suggesting that this is a heterogeneous disorder [2]. The frequent occurrence of benign and malignant tumours of the palms and soles has been noted [2]. Lipid biochemical investigation of stratum corneum has shown a decrease in the ceramide fraction and an increase in free fatty acids [2].

REFERENCES

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Chondro-ectodermal dysplasia (MIM 225500)

SYN. ELLIS–VAN CREVELD SYNDROME

Aetiology. This rare syndrome is determined by an autosomal recessive gene [1,2]. Ossification is delayed in the primary centres but occurs prematurely in the secondary centres in the carpals and phalanges, with consequent progressive distal shortening of the extremities. The largest kindred was investigated by McKusick *et al.* [3] in an inbred religious isolate, the Old Order Amish, in Pennsylvania. The gene maps to chromosome 4p16 and encodes a protein with 992 amino acids. Mutations that predict premature truncation of the putative protein do not manifest in the heterozygous carrier. In contrast, several missense mutations have been reported in the milder condition, Weyers' syndrome (acrodental dysostosis, MIM 193530), which appears as an autosomal dominant condition.

Pathology. Skeletal histopathology in fetuses with chondro-ectodermal dysplasia shows chondrocytic disorganization of the physeal growth zone [4].

Clinical features [3,5–8]. The principal features of the syndrome are chondrodysplasia and polydactyly, ectodermal dysplasia and congenital defects of the heart. Short arms or legs on a normally proportioned trunk with lumbar lordosis, genu valgum and an extra digit on the ulnar side of the hand are the most obvious of the multiple skeletal abnormalities.

The teeth are small and defective and may be peg-shaped, and the sulcus between the upper lip and the gum may be obliterated. The upper lip is short and bound down by multiple frenula [9]. The nails are small, thin, short and ridged. The hair is usually normal, but may be sparse and brittle. Sweating and sebaceous activity are normal.

Occasionally, there may be abnormalities in the liver, kidneys [7], urinary tract and central nervous system [10].

Over one-third of cases die in the first 2 weeks of life. If infancy is survived, the expectation of life is not greatly reduced, except in those cases with severe cardiac defects [11].

Christian *et al.* [1] reported the unusual case of an infant with both Ellis–Van Creveld and Dandy–Walker syndromes and with homozygosity for an unusually long segment of the long arm of chromosome 9. McKusick [12] observed hydrocephalus and the Dandy–Walker anomaly in two Amish cases of Ellis–Van Creveld syndrome.

Mahoney and Hobbins [13] proposed fetoscopy and ultrasound as methods of prenatal diagnosis. In a study of three pregnancies terminated at 22–23 weeks because of ultrasound confirmation of short limbs and growth retardation, radiology showed that each fetus had acromelic and mesomelic shortness of long bones with smooth round metaphyses, vertically short iliac bones, short ribs and normal vertebrae. Other findings noted at post-mortem were polydactyly in all three cases, congenital heart defect in two and an abnormal frenulum in one [4].

Diagnosis. Defective teeth and nails, and extra digits in an achondroplastic dwarf are not easily confused with any other syndrome. Mutations of the gene may be investigated using molecular genetic analysis [14].

Polydactyly and congenital heart defects also occur in trisomy 13 (Patau's syndrome).

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Tricho-odonto-onychial dysplasia

The inheritance of this syndrome is autosomal recessive. The hair is dry, brittle and sparse, with alopecia of the crown of the scalp. Enamel hypoplasia affects deciduous and permanent teeth and there is a variable degree of nail dystrophy. Other defects include supernumerary nipples, palmoplantar hyperkeratosis, pigmented naevi and a mixed hearing defect [1].

A different syndrome with aplasia cutis of the scalp and poikiloderma has been described in one patient as the tricho-odonto-onycho-dermal syndrome [2].

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Schinzel–Giedion syndrome (MIM 269150) [1,2]

The cutaneous features of this autosomal recessive syndrome include generalized hypertrichosis, delayed tooth eruption, narrow deep-set triangular nails, and telangiectases over the nose and cheeks, with simian creases and dermatoglyphic changes. Other features include mental and physical growth retardation, epilepsy, spasticity, recurrent bouts of apnoea, bone anomalies, high-arched palate, atrial septal defect, abnormal pinnae, anteverted nostrils, hypertelorism and hypoplastic nipples.

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Fried's tooth and nail syndrome [1]

In this autosomal recessive syndrome, the hair is fine and short, the teeth are few and peg-shaped and the nails are thin and dystrophic.

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Odonto-onychodysplasia with alopecia [1]

In this rare syndrome there is almost total alopecia, small widely spaced teeth, brittle fingernails with a tendency to infection and thick spoon-shaped toenails. Other features include myopia, bilateral webbed toes, supernumerary nipples, irregular areolae, hypertrophied Montgomery glands, palmoplantar hyperkeratosis and simian creases.

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Hypodontia and nail dysgenesis [1–4]

The condition is inherited as autosomal dominant with variable expressivity. There are few teeth and these are conical and widely spaced. There are small, dystrophic or spoon-shaped nails, which grow slowly. The hair is fine and brittle, and the lips are everted.

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Odontomicronychial ectodermal dysplasia

Described by Pinheiro *et al*. [1], this condition is characterized by precocious eruption and shedding of deciduous dentition, precocious eruption of secondary dentition with short rhomboid roots, and short, thin, slow-growing nails. It probably results from an autosomal recessive gene.

REFERENCE

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Odonto-onycho-dermal dysplasia

Originally described by Fadhil *et al.* in 1983 [1], odonto-onycho-dermal dysplasia was described in two unrelated inbred Lebanese families, who showed telangiectatic atrophic patches on the face, sparse hair, conical or widely spaced teeth, hyperkeratosis of the palms and soles, and dystrophic nails. Zirbel *et al.* [2] reported a boy who was similarly affected with persistent atrophic malar plaques [2].

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Dermo-odontodysplasia [1,2]

This syndrome was originally reported in a white family, affecting 11 subjects over four generations, presumably by autosomal dominant inheritance. The skin is dry and thin, with simian creases, and the teeth are small and poorly developed with persistence of the deciduous teeth. The nails are dysplastic and brittle, and the hair is thin, dry and slow growing, with areas of alopecia on the crown.

REFERENCES

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Odontotrichomelic syndrome [1–4]

This probably autosomal recessive syndrome is characterized by severe hypotrichosis, few and small conical teeth, and hypoplastic or absent areolae. There is cleft lip and extensive tetramelic dysplasia. Growth is retarded.

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Salamon's syndrome (MIM 278200) [1,2]

This syndrome, probably of autosomal recessive inheritance, is characterized by sparse brittle hair, which is readily shed. Pili torti and other hair-shaft defects are present, the teeth are few and small, the nails are dystrophic, and numerous ophthalmic defects can occur. The facies has features of classical hypohidrotic ectodermal dysplasia but sweating is normal.

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Coffin–Siris syndrome (MIM 135900) [1–5]

The syndrome is characterized by mental retardation; coarse facial features with sparse scalp hair; bushy eyebrows; low nasal bridge, anteverted nostrils and thick lips; absent fifth fingernails and toenails; short distal phalanges; lax joints; delayed eruption of the teeth, which are small; microcephaly; retarded growth; and multiple skeletal abnormalities. The inheritance is autosomal dominant with variable expression [2]. McGhee *et al.* described an 11-year-old girl with Coffin–Siris syndrome and a *de novo*, apparently balanced reciprocal translocation t(7;22)(q32;q11.2). The 7q break-point in this patient was very similar to a previous report with a balanced translocation t(1;7)(q21.3;q34) [4,5]. Together, these patients provided evidence that the 7q32–q34 region contains the gene responsible for Coffin–Siris syndrome. The condition should be distinguished from Coffin–Lowry syndrome (see p. 12.56), which is a completely unrelated syndrome due to a defect in the *RSK2* gene on the X chromosome.

REFERENCES

1 Coffin GS, Siris E. Mental retardation with absent fifth fingernail and terminal phalanx. *Am J Dis Child* 1970; **119**: 433–9.
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Ectodermal dysplasia with pili torti and syndactyly [1]

This autosomal recessive syndrome is characterized by sparse hair, eyebrows and lashes, with pili torti, severe dental dysplasia and yellow thickened nails, lordosis, high-arched palate and syndactyly.

REFERENCE

1 Wiedemann HR, Grosse FR, Dibbern H. *Caracteristicas das Sindromes Em Paediatra. Atlas de Diagnóstico Diferencial*. Sao Paulo: Editora Manole, 1978: 174–5.

Dwarfism–alopecia–pseudoanodontia–cutis laxa [1]

The cutaneous features of this rare autosomal recessive syndrome include generalized atrichia, unerupted teeth of both dentitions, hyperconvex nails and cutis laxa with fragile skin, which is slow to heal. Other features include dwarfism, deafness, glaucoma, keratoconus, micrognathia, protruding lips, prominent supraorbital ridges, depressed nasal bridge, delayed bone maturation, skeletal abnormalities, hepatosplenomegaly, choanal atresia and hypoplastic mammary glands.

REFERENCE

1 Wajntal A, Epps RR, Mendonça BB *et al*. Nova sindrome de displasia ectodérmica: nanismo, alopecia, anodontia e cutis laxa. *Ciênc Cult* 1982; **34** (Suppl.): 705.

Hypohidrosis with diabetes insipidus [1]

SYN. FLECK'S SYNDROME

Hypohidrosis, hypotrichosis and anodontia are combined with diabetes insipidus, syndactyly, coloboma and disturbed haematopoiesis.

REFERENCE

1 Fleck F. Klinische Beobachtungen einer ungewöhnlichen, sporadischen Form von ektodermal-mesodermer Keimblattdysplasie. *Dermatol Wochenschr* 1955; **132**: 994–1007.

Oral–facial–digital syndromes

Four distinct clinical variants of oral–facial–digital (OFD) syndrome are recognized: OFD-I, OFD-II, OFD-III and OFD-IV.

Oral–facial–digital syndrome type I (MIM 300170)

SYN. PAPILLON–LÉAGE SYNDROME

Aetiology. This syndrome is present in about 1.5% of children with cleft lip or palate [1]. The familial incidence suggests X-linked dominant inheritance, lethal in the male [2–4], so that all affected patients seen are female. Wahrman *et al.* [5] described the condition in an XXY male. To identify the gene responsible for OFD-I, Ferrante *et al*. [6] analysed several transcripts that mapped to Xp22 and found mutations in the *CXORF5* gene. They investigated three familial and four sporadic cases of OFD-I. In the sporadic cases, they found a missense (*de novo*), a nonsense, a splice site and a frameshift mutation. RNA *in situ* studies on mouse embryo tissue sections showed that the Ofd1 protein is developmentally regulated and is expressed in all tissues affected in OFD-I syndrome.

Clinical features [3,7–9]. The profile is usually distinctive, with a short upper lip and hypoplastic alae nasi on a hooked pug nose. The frenula of upper and lower lips and tongue are hypertrophied. The tongue is bifid or multilobed and often shows small tumours, which lie within the clefts and are shown histologically to contain aberrant mucous glands and nests of smooth muscle [10]. Clefts of the hard and soft palates are frequent. The teeth may be widely separated and misplaced, and may develop early and atypical caries.

Deformities of the hands are regularly present, either a trident hand or varying combinations of brachydactyly, syndactyly and polydactyly.

The hair is often dry, coarse, lustreless and brittle. There is a variable degree of alopecia. Fine scales may be conspicuous on the scalp and the upper part of the face. Numerous milia may be seen on the face, ears and dorsa of the hands; some may erupt to leave scars.

Polycystic disease of the kidneys and liver has been present in some cases [4,10–12].

About half the patients are mentally retarded. Towfighi *et al.* [13] reported a variety of central nervous system malformations in OFD-I.

Extreme variability of expression of this syndrome has been observed [12]. Some affected individuals may show only minor oral or digital malformations. Dermatoglyphic studies are then of value in diagnosis [12,14]. Anneren *et al.* [15] suggested that irregular mineralization of the bones of the hands and feet is an important feature of OFD-I that distinguishes it from OFD-II.

REFERENCES

1 Gorlin RJ, Psaume J. Orodigitofacial dysostosis: a new syndrome. A study of 22 cases. *J Pediatr* 1962; **61**: 520–30.
2 Tucker CC, Finley SC, Tucker ES *et al*. Oral–facial–digital syndrome with polycystic kidneys and liver: pathological and cytogenetic studies. *J Med Genet* 1966; **3**: 145–7.
3 Majewski F, Lenz W, Pfeiffer RA *et al*. Das oro-facio-digitale Syndrom. Symptome und Prognose. *Z Kinderheilk* 1972; **112**: 89–112.
4 Whelan DT, Feldman W, Dost I. The oral–facial–digital syndrome. *Clin Genet* 1975; **8**: 205–12.
5 Wahrman J, Berant M, Jacobs J *et al*. The oral–facial–digital syndrome: a male lethal condition in a boy with 47-XXY chromosomes. *Pediatrics* 1966; **37**: 812–21.
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8 Vissian L, Vaillaud J-C. Le syndrome oro-facio-digital. A propos d'un onzième cas dans une même famille. *Ann Dermatol Syphiligr* 1972; **99**: 5–20.
9 Larralde-de-Luna M, Raspa ML, Ibargoyen J. Oral–facial–digital type 1 syndrome of Papillon–Leage and Psaume. *Pediatr Dermatol* 1992; **9**: 52–6.
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14 Doege TC, Campbell MM, Bryant JS *et al*. Mental retardation and dermatoglyphics in a family with the oral–facial–digital syndrome. *Am J Dis Child* 1968; **116**: 615–22.
15 Anneren G, Arvidson B, Gustavson KH *et al*. Oro-facio-digital syndromes I and II: radiological methods for diagnosis and the clinical variations. *Clin Genet* 1984; **26**: 178–86.

Oral–facial–digital syndrome type II (MIM 252100)

SYN. MOHR'S SYNDROME

This genetically distinct syndrome is inherited as an autosomal recessive trait. First described by Mohr [1], features include polydactyly, syndactyly and brachydactyly, a lobate tongue, cleft palate, a normal or flaring alveolar ridge, and a broad bifid nasal tip. Rimoin and Edgerton [2] reported three affected siblings (two male and one female), and suggested that this syndrome should be called OFD-II. In addition to the different mode of inheritance, Mohr's syndrome shows none of the skin and hair changes seen in X-linked OFD-I, but does show conductive hearing loss and bilateral polysyndactyly of the halluces, not present in OFD-I. Gustavson *et al*. [3] reported two affected sisters. Balci *et al*. [4] reported two sisters with Mohr's syndrome from a consanguineous family. At post-mortem, in addition to the typical physical abnormalities of Mohr's syndrome, the fetus showed natal teeth and absence of the olfactory nerves, two features not previously reported in this syndrome. The authors stressed the role of early ultrasonographic examination as a means of prenatal diagnosis.

REFERENCES

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2 Rimoin DL, Edgerton MT. Genetic and clinical heterogeneity in the oral–facial–digital syndrome. *J Pediatr* 1967; **71**: 94–102.
3 Gustavson KH, Kreuger A, Petersson PO. Syndrome characterized by lingual malformation, polydactyly, tachypnea, and psychomotor retardation (Mohr syndrome). *Clin Genet* 1971; **2**: 261–6.
4 Balci S, Guler G, Kale G *et al*. Mohr syndrome in two sisters: prenatal diagnosis in a 22-week-old fetus with post-mortem findings in both. *Prenat Diagn* 1999; **19**: 827–31.

Oral–facial–digital syndrome type III (MIM 258850)

Sugarman *et al*. [1] reported a new form of OFD syndrome in two sisters. Features are mental retardation, eye abnormalities, lobulated hamartomatous tongue, dental abnormalities, bifid uvula, postaxial hexadactyly of hands and feet, pectus excavatum, short sternum and kyphosis. One of the sibs showed 'see-saw winking'. Inheritance is presumed autosomal recessive.

REFERENCE

1 Sugarman GI, Katakia M, Menkes JH. See-saw winking in a familial oral–facial–digital syndrome. *Clin Genet* 1971; **2**: 248–54.

Oral–facial–digital syndrome type IV (MIM 258860)

Baraitser [1] suggested the existence of a fourth type of OFD but recognized that considerable overlap of the features of the various forms gives rise to difficulties in precise clinical differentiation. The autosomal recessive mode of inheritance and severe tibial dysplasia differentiate type IV from type I.

REFERENCE

1 Baraitser M. The orofaciodigital (OFD) syndromes. *J Med Genet* 1986; **23**: 116–9.

Oculodentodigital dysplasia (MIM 164200)

SYN. OCULO-DENTO-OSSEOUS DYSPLASIA

This rare syndrome is determined by an autosomal dominant gene of variable expressivity [1–4].

The characteristic features of the syndrome are small eyes with microcornea, enamel hypoplasia and camptodactyly. The small, closely set, sunken eyes, small mouth with overlapping upper lip and the thin nose without alar flare produce a distinctive facies. There may also be malformations of the iris, hypertelorism, etc. Syndactyly of toes and fingers is associated with camptodactyly of the radially deviated fifth fingers. The teeth are yellowish.

In some cases, the scalp hair is sparse, dry and lustreless and fails to grow to its normal length. Eyebrows and eyelashes may be sparse or absent.

Paznekas *et al*. [5] analysed the connexin-43 gene (*GJA1*) located on chromosome 6q21–q23 as a candidate for oculodentodigital dysplasia and identified mutations in all 17 families studied; 16 different missense mutations and one codon duplication were detected. These mutations may cause misassembly of channels or alter channel conduction properties.

REFERENCES

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5 Paznekas WA, Boyadjiev SA, Shapiro RE *et al*. Connexin 43 (GJA1) mutations cause the pleiotropic phenotype of oculodentodigital dysplasia. *Am J Hum Genet* 2003; **72**: 408–18.

Berlin's syndrome [1]

This syndrome was described in two brothers and two sisters with stunted growth, 'bird-like' legs and severe mental retardation. The fine, thin, dry skin showed mottled pigmentation and leukoderma ('leopard skin'). The facies, with a flat saddle-shaped nose, thick lips and fine wrinkling around the eyes and mouth, recalled that of the Christ–Siemens type of ectodermal dysplasia. The dentition was delayed and incomplete. There were no vellus hairs.

REFERENCE

1 Berlin C. Congenital generalised melanoleucoderma associated with hypodontia, hypotrichosis, stunted growth and mental retardation occurring in two brothers and two sisters. *Dermatologica* 1961; **123**: 227–43.

Johanson–Blizzard syndrome (MIM 243800)

In this distinctive syndrome [1–4], which is probably due to autosomal recessive inheritance, there is congenital aplasia cutis of the scalp, sparse hair, deafness, absence of the permanent teeth buds and hypoplasia of the alae nasi. Other features include short stature, microcephaly, mental retardation, hypotonia, malabsorption due to pancreatic insufficiency, primary hypothyroidism and abnormalities of the genitalia and rectum. An association with diabetes has been reported [5].

REFERENCES

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4 Baraitser M, Hodgson SV. The Johanson–Blizzard syndrome. *J Med Genet* 1982; **19**: 302–3.
5 Nagashima K, Yagi H, Kuroume T. A case of Johanson–Blizzard syndrome complicated by diabetes mellitus. *Clin Genet* 1993; **43**: 98–100.

Tricho-oculo-dermo-vertebral syndrome (MIM 601701) [1]

In this syndrome, the hair is sparse, dry and brittle, the nails are dystrophic and there is plantar keratoderma. There is kyphoscoliosis with short stature, cataract and other ocular defects.

REFERENCE

1 Alves AFP, dos Santos PAB, Castelo-Branco-Neto E *et al*. An autosomal recessive ectodermal dysplasia syndrome of hypotrichosis, onychodysplasia, hyperkeratosis, dwarfism, kyphoscoliosis, cataract and other manifestations. *Am J Med Genet* 1981; **10**: 213–8.

Curly hair–ankyloblepharon–nail dysplasia syndrome (CHANDS) (MIM 214350) [1]

This syndrome, believed to be of autosomal recessive inheritance, includes curly hair and the presence at birth of fused eyelids. The nails are hypoplastic, but sweating and teeth are normal.

REFERENCE

1 Baughman FA. CHANDS: the curly hair–ankyloblepharon–nail dysplasia syndrome. *Birth Defects* 1971; **VII**: 100–2.

Kirman's syndrome [1]

The original description was of a female with anhidrosis, almost total alopecia and severe mental retardation. Nails, teeth and breasts were normal.

REFERENCE

1 Kirman BH. Idiocy and ectodermal dysplasia. *Br J Dermatol* 1953; **67**: 303–7.

Hypoplastic enamel–onycholysis–hypohidrosis (MIM 189500) [1]

SYN. WITKOP–BREARLEY–GENTRY SYNDROME

The original description of this autosomal dominant syndrome included 10 members of a family.

There are defects of the teeth, nails and scalp. The skin is generally dry, with keratosis pilaris on the limbs. Hair is normal, but there is patchy scaling and crusting of the scalp. There is onycholysis and subungual hyperkeratosis. The teeth show a hypoplastic type of enamel defect with multiple unerupted teeth, which undergo absorption within the alveolus. There is a marked degree of facial hypohidrosis.

Jumlongras *et al*. [2] found linkage between this tooth-and-nail syndrome and polymorphic markers in the region harbouring the *MSX1* gene on chromosome 4p16 in a three-generation family [2]. Direct sequencing and restriction enzyme analysis demonstrated a heterozygous stop mutation in the homeodomain of *MSX1*. The precise function of this gene is as yet unknown but these findings clearly demonstrate its importance in ectodermal development.

REFERENCES

1 Witkop CJ, Brearley LJ, Gentry WC Jr. Hypoplastic enamel, onycholysis and hypohidrosis inherited as an autosomal dominant trait. A review of ectodermal dysplasia syndromes. *Oral Surg* 1975; **39**: 71–86.
2 Jumlongras D, Bei M, Stimson JM *et al*. A nonsense mutation in MSX1 causes Witkop syndrome. *Am J Hum Genet* 2001; **69**: 67–74.

Nail dystrophy–deafness syndrome [1]

SYN. ROBINSON'S SYNDROME

This syndrome, probably of autosomal dominant inheritance, combines widely spaced coniform teeth and small dystrophic nails with sensorineural deafness. Some affected individuals also have polysyndactyly and increased sweat chloride levels. The hair is normal.

In another family with congenital deafness and onychodystrophy, the inheritance appeared to be autosomal recessive [2].

REFERENCES

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2 Feinmesser M, Zelig S. Congenital deafness associated with onychodystrophy. *Arch Otolaryngol* 1961; **74**: 507–8.

Dento-oculo-cutaneous syndrome [1]

There may be taurodontia, pyramidal or fused molar roots. The fingernails are dystrophic, with longitudinal ridges and distal splitting. There are pigmented and indurated areas over the interphalangeal joints of the fingers. The philtrum is thick and wide, and there is ectropion of the lower lids.

REFERENCE

1 Ackerman JL, Ackerman AL, Ackerman AB. A new dental, ocular and cutaneous syndrome. *Int J Dermatol* 1973; **12**: 285–9.

Sandmann–Andra syndrome [1]

This type of ectodermal dysplasia was present in three generations of a family. Inheritance was of autosomal dominant type. The patients were hypohidrotic and the number of teeth was considerably reduced.

REFERENCE

1 Sandmann H, Andra A. Beitrag zum Krankheitsbild der ektodermalen Dysplasie. *Z Kinderheilk* 1959; **82**: 238–55.

Ectodermal dysplasia with cataracts and hearing defects (MIM 154780) [1]

SYN. MARSHALL'S SYNDROME

This rare syndrome comprises mild defects of the teeth and sweating, with cataracts and deafness. Some patients also have other ocular defects. The facies is abnormal, with a short depressed nose and underdeveloped maxilla. This disorder has clinical overlap with Stickler's syndrome and mutation analysis of the *COL11A1* and *COL2A1* genes has confirmed that some cases of these disorders are allelic [2].

REFERENCES

1 Marshall D. Ectodermal dysplasia. Report of kindred with ocular abnormalities and hearing defect. *Am J Ophthalmol* 1958; **45**: 143–56.
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Oto-onycho-peroneal syndrome (MIM 259780) [1]

SYN. PFEIFFER'S SYNDROME

Two brothers have been reported in whom abnormal 'crumpled' pinnae were associated with partial or complete aplasia of the nails and fibulae.

REFERENCE

1 Pfeiffer RA. The oto-onycho-peroneal syndrome. A probably new genetic entity. *Eur J Pediatr* 1982; **138**: 137–320.

Deafness, onycho-osteodystrophy and mental retardation (MIM 220500)

SYN. DOOR SYNDROME; TRIPHALANGEAL THUMBS WITH ONYCHODYSTROPHY

At least three families have been reported in which sensorineural deafness was associated with absent or hypoplastic fingernails and toenails, triphalangeal thumbs and great toes, mental retardation and epilepsy. The inheritance appears to be autosomal recessive [1], although Goodman *et al.* [2] described a family with dominant inheritance.

REFERENCES

1 Cantwell RJ. Congenital sensorineural deafness associated with onycho-osteo dystrophy and mental retardation (D.O.O.R. syndrome). *Humangenetik* 1975; **26**: 261–5.
2 Goodman RM, Lockareff S, Gwinup G. Hereditary congenital deafness with onychodystrophy. *Arch Otolaryngol* 1969; **90**: 474–7.

Hypohidrosis with neurolabyrinthitis [1,2]

SYN. HELWIG-LARSEN–LUDWIGSEN SYNDROME

Sweat glands are absent or reduced in number in this autosomal dominant syndrome. There are no dental or hair anomalies. Neurolabyrinthitis develops between the ages of 35 and 45 years.

REFERENCES

1 Helwig-Larsen HF, Ludwigsen K. Congenital familial anhidrosis and neurolabyrinthitis. *Acta Derm Venereol (Stockh)* 1946; **26**: 489–505.
2 Reed WB, Stone VM, Boder E *et al*. Hereditary syndromes with auditory and dermatological manifestations. *Arch Dermatol* 1967; **95**: 456–9.

Other ectodermal syndromes

The following syndromes are not strictly speaking ectodermal dysplasias, but they may be conveniently considered in this section.

Simple anhidrosis [1]

Very rarely, the complete absence of sweat glands may be inherited as an isolated defect, the epidermis being otherwise normal.

Knuckle pads, leukonychia and deafness (MIM 149200) [2]

SYN. BART–PUMPHREY SYNDROME

This rare syndrome is characterized by the association of knuckle pads, sensory deafness and leukonychia, all of which are present from early childhood. In some patients, palmoplantar keratoderma may develop later.

Deafness, with vitiligo and muscle wasting [3]

Two patients in one family have been described with early sensory deafness, vitiligo and marked muscle wasting of the hands, feet and legs.

Amelo-cerebro-hypohidrotic syndrome [4]

SYN. KOHLSCHÜTTER'S SYNDROME

This rare condition has been reported mainly from Germany and Switzerland. There may be X-linked or autosomal recessive inheritance. The syndrome is characterized by thin, yellow, hypoplastic tooth enamel and severe epilepsy in childhood, with progressive spasticity and mental retardation. The sweat and sebaceous glands are decreased in number. Most, if not all, patients have been male and most died in the first decade.

Hyperhidrosis, premature canities and premolar aplasia [5]

SYN. BÖÖK'S SYNDROME

In 18 patients in one family, aplasia of the premolar teeth was associated with premature greying of the hair and, in most patients, hyperhidrosis of the palms and soles. Inheritance was via an autosomal dominant gene.

Keratitis, ichthyosis and deafness (MIM 148210) [6–8]

SYN. KID SYNDROME

In 1915, Burns [9] described a patient with generalized keratoderma, keratitis and deafness. Skinner *et al.* [8] proposed the term 'KID syndrome'. Ichthyosis is usually present at birth, and erythematous and verrucous plaques may develop. These are well marginated with a serpiginous outline. There is also severe diffuse hyperkeratosis of the palms and soles with a characteristic reticulate surface pattern. Perioral furrows may also be seen, and leukoplakia has occurred in some patients.

Severe sensory deafness develops at birth or within the first 2 years of life. Photophobia and diminished visual acuity is reported in about 75% of patients, and this is due to a vascularizing keratitis. The condition may progress to blindness.

About half the patients have an increased susceptibility to cutaneous infections, but laboratory tests have failed to show any immunological defects [8].

In 50% of cases, there is hypotrichosis affecting the scalp, eyebrows and eyelashes. Dystrophic nails and diminished sweating have also been reported, and the condition is easily confused with hypohidrotic ectodermal dysplasia. It is thought to be inherited as an autosomal recessive trait. Richard *et al.* [10] have provided compelling evidence that KID syndrome is caused by heterozygous missense mutations in the gap junction connexin-26 gene, *GJB2*. In each of 10 patients with this syndrome, they identified a point mutation leading to substitution of conserved residues in the cytoplasmic amino terminus or first extracellular domain of connexin 26. One of these mutations was detected in six unrelated sporadic cases and also segregated in one family with vertical transmission of KID syndrome. These findings indicated the presence of a common recurrent mutation and established KID syndrome as an autosomal dominant disorder. Detailed functional analysis revealed that the mutant connexin 26 was incapable of inducing intercellular coupling *in vitro*. Decreased host defence and increased carcinogenic potential in KID syndrome illustrates that gap junction communication plays a crucial role not only in epithelial homeostasis and differentiation but also in immune response and epidermal carcinogenesis.

Growth retardation, alopecia, pseudoanodontia and optic atrophy (MIM 230740)

SYN. GAPO SYNDROME

A girl born to related parents was normal at birth but then developed hydrocephalus, almost complete hair loss, papilloedema and secondary optic atrophy [11]. Growth was retarded, and by the age of 9 years her facies was abnormal, with low-set ears, high-arched palate and pseudoanodontia (teeth were present but unerupted). A similar patient has been reported by Anderson and Pindborg [12]. To date, 15 cases have been documented [13].

Craniofacial dysostosis with hypertrichosis and hypodontia [14]

Two sisters who complained of ulcerated feet were found to have craniofacial dysostosis, hypertrichosis, hypodontia,

and ocular and cardiac defects. The condition had some similarities to the Treacher Collins type of mandibulofacial dysostosis.

Coffin–Lowry syndrome (MIM 303600) [15,16]

This condition shows dominant inheritance, but males are more severely affected. The facies is distinctive, with sunken eyes, a thin nose, sparse hair and thick prominent lips. There is severe mental retardation, short stature and hand anomalies, and the skin is loose and easily stretched. Skin biopsy shows intracytoplasmic inclusions suggestive of a lysosomal storage disorder. Molecular genetic studies have shown that Coffin–Lowry syndrome is caused by mutations in the *RSK2* gene, which is located on the X chromosome and encodes a ribosomal protein kinase [16].

Palmoplantar and perioroficial keratoderma with corneal epithelial dysplasia [17]

A boy has been reported with palmoplantar keratoderma, nail dystrophy, perioral keratoderma and bilateral corneal epithelial dysplasia leading to severe corneal scarring and impaired vision.

Polycystic brain associated with ectodermal dysplasia [18]

This is a neurocutaneous syndrome comprising brain cysts, irregular retinal pigment epithelium, thin hair, dystrophic nails and dental abnormalities.

Scalp–ear–nipple syndrome (MIM 181270) [19]

Scalp–ear–nipple syndrome is a rare autosomal dominant condition that causes aplasia cutis congenita of the scalp, alteration of the shape of the external ear, and hypoplasia of the nipple. Dental changes include widely spaced or missing secondary teeth; some patients have partial syndactyly of fingers and toes.

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Syndromes associated with DNA instability

Xeroderma pigmentosum (MIM 278730 and 278700)

Definition [1]. Xeroderma pigmentosum (XP) is a rare autosomal recessive disease characterized by photosensitivity, pigmentary changes, premature skin ageing, neoplasia and abnormal DNA repair. Some patients with XP also have neurological complications.

Aetiology. The initial report of this disorder was made by Hebra and Kaposi in 1874 [2] and the term 'xeroderma pigmentosum', meaning pigmented dry skin, was introduced in 1882 [3].

XP is found worldwide in all races with an equal sex incidence. It occurs with a frequency of approximately 1 in 250 000 in Europe and the USA [4]. In Japan, the frequency has been reported to be higher (1 in 40 000) [5].

Inheritance is autosomal recessive; parents of affected individuals, who are thus obligate heterozygotes, are clinically normal. The genetic heterogeneity of the syndrome, suspected on clinical grounds, has been confirmed by experimental studies. There are at least eight different subtypes that are recognized, designated complementation groups A–G and XP variant (Table 12.5).

Cleaver first reported in 1968 [6], and in subsequent studies [7–9], that fibroblasts from most patients with typical XP lack the normal capacity to repair UV radiation damage to DNA. In 1970, Epstein *et al.* [10] showed that

Table 12.5 Nucleotide excision repair disorders. (Data compiled from published literature by A.R. Lehmann, Genome Damage and Stability Centre, University of Sussex, UK.)

Complementation group	Gene	Chromosome localization	Size of gene product (amino acids)	Activity	Comments
Xeroderma pigmentosum (XP)					
XP-A	*XPA*	9q22	273 (31 kDa)	Binds damaged DNA	Common; severe skin and neurological abnormalities
XP-B	*XPB*	2q21	782 (89 kDa)	Helicase. Part of TFIIH	Rare; only three kindreds, two with XP/CS, one with TTD
XP-C	*XPC*	3p25	940 (106 kDa)	Damage recognition	Common; severe skin abnormalities
XP-D	*XPD*	19q13	760 (87 kDa)	Helicase. Part of TFIIH	Common; severe + neurological abnormalities; also includes two cases of XP/CS and most cases of TTD
XP-E	*XPE*	11p12	427 (48 kDa)	Damaged DNA binding	Rare; mild features
XP-F	*XPF*	16p13	905 (103 kDa)	Nuclease subunit with ERCC1	Rare; fairly mild
XP-G	*XPG*	13q33	1196 (133 kDa)	Nuclease	Rare; severe + neurological abnormalities; half of cases have XP/CS
*Cockayne's syndrome (CS)**					
CS-A	*CSA*	5q12–q31	396 (44 kDa)	Transcription-coupled repair	Rare
CS-B	*CSB*	10q11	1493 (168 kDa)	Transcription-coupled repair	Common
Trichothiodystrophy (TTD)					
Most TTD patients are in XP-D group, one family in XP-B group, and one unique family in a separate TTD-A group. Gene not yet identified. Note that some TTDs have no repair defect. They cannot therefore be assigned to a complementation group					

* CS also found rarely in combination with XP in XP-B, XP-D and XP-G groups.

DNA repair was defective *in vivo*. Approximately 80% of patients with XP show a defect in the initiation of DNA excision repair of UV photoproducts [11–13]. In these patients, it has since been shown that repair replication is reduced in all cell types examined: epidermal cells, dermal fibroblasts, lymphocytes, conjunctival cells, corneal cells, liver cells and basal cell carcinoma cells [14]. It has also been demonstrated in amniotic fluid cells and used successfully for prenatal diagnosis of XP [15].

The unscheduled DNA synthesis assay (following UV irradiation of the cells in culture) is the standard laboratory method for diagnosis of XP [16].

In 1972, De Weerd-Kastelein *et al*. [17], by using cell fusion techniques, demonstrated genetic heterogeneity in the XP repair defect. Cultured fibroblasts from two different patients with XP are fused so that their nuclei coexist in the same cytoplasm (forming a heterokaryon). If both nuclei have the same defect, then the heterokaryon shows defective DNA repair after UV irradiation and the patients are in the same complementation group. If the nuclei have different defects, then each will supply what the other is lacking and DNA repair within the heterokaryon will be normal. The two patients are then said to be in different complementation groups. Within this group of patients, seven distinct complementation groups are recognized (A–G).

Nucleotide excision repair [18–20]. This process, whereby damaged DNA is removed and replaced with new DNA using the intact strand as a template, involves the products of some 30 genes [21]. The genes involved in nucleotide excision repair (NER) have now been cloned (Table 12.5). The excision repair cross-complementing (ERCC) genes are so called because of their ability to complement DNA repair in mutant rodent cells. The names of the XP genes have superseded those of the corresponding ERCC genes. The complete process of NER has now been reconstructed [22] (Fig. 12.15). The initial step in the process involves recognition of the damaged DNA by the XP-C protein together with its partner HR23B [23]. This results in the recruitment of the dual function transcription factor TFIIH, composed of at least six subunits including XP-B and XP-D proteins, which both have helicase activity. These helicases open out the structure at the damaged site. The exact function of the crucial XP-A protein is not clear, but it seems to have a role in verifying the positions of the other proteins on the damaged structure. This enables the structure-specific nucleases to incise the DNA. ERCC1-XP-F and XP-G are both structure-specific nucleases, which cut the DNA on either side of the damage. The repair-synthesis step requires DNA polymerase ε (polε), the replication accessory factor proliferating-cell nuclear antigen (PCNA) and replication factor C (RFC); the new DNA is then joined to the old by DNA ligase. As well as these proteins, the incision reaction is stimulated by the product of the *XPE* gene, which is the smaller subunit of a dimeric protein that binds specifically to UV-irradiated DNA and is thought to assist in the early recognition of cyclobutane pyrimidine dimers.

Subsequent studies have shown that a deficiency of NER is also associated with Cockayne's syndrome (CS) and trichothiodystrophy.

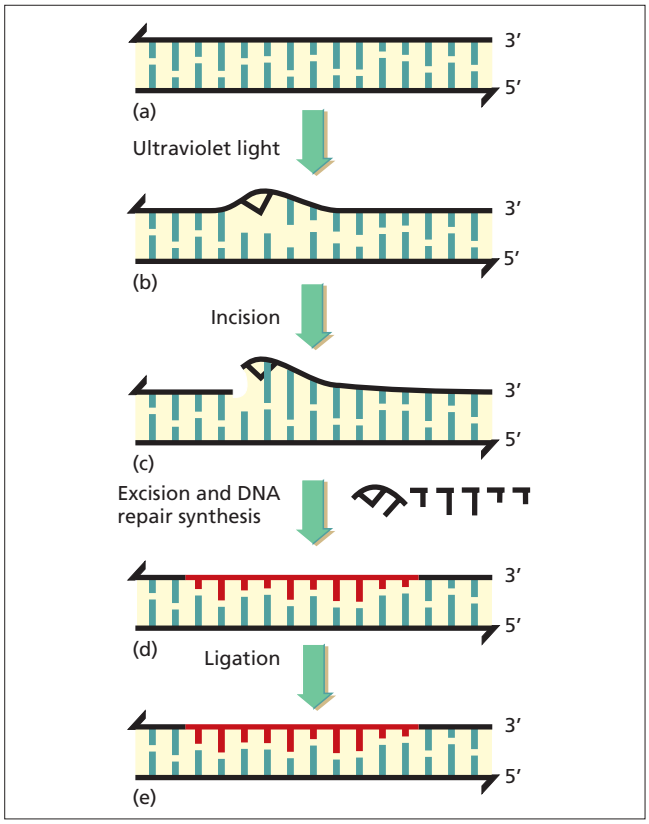

Fig. 12.15 Excision repair of pyrimidine dimers. Distortion in DNA double helix by pyrimidine dimer is located (b), the damaged strand excised (c), the dimer removed together with neighbouring nucleotides and the gap filled with new DNA (d); ligation (e) completes repair. (From Pawsey *et al.* [1].)

XP variant [24]. The other 20% of patients, called XP variants, have normal NER [25] but have a defect in an alternative repair process, known as post-replication or daughter-strand repair. XP variants have a defect that manifests as a reduced molecular weight of newly synthesized DNA in UV-irradiated cells and a delay in the production of intact high-molecular-weight DNA strands following UV irradiation [26]. Further, XP-variant fibroblasts are uniquely sensitive to caffeine inhibition of increase of molecular weight of newly replicated DNA after UV treatment [27]. The protein missing in XP variants is a novel DNA polymerase, designated polη, which is able to replicate DNA past UV-induced cyclobutane thymine dimers and some other types of DNA damage, in most cases inserting the 'correct' nucleotides opposite the damaged bases [28]. This property of polη contrasts with that of the DNA polymerases that carry out normal DNA replication. The latter are extremely accurate, but are blocked by most types of DNA damage.

Despite the substantial increase in our understanding of the genetics, it is still far from clear how these defects relate to the clinical diversity. The various subtypes of XP show clinical and epidemiological differences. The majority of patients in group C, which is most common in Europe and the USA, show no neurological defects. Patients in group A tend to develop neurological disease before the age of 7 years, whereas those in group D tend to develop neurological damage after this age [29].

Skin photosensitivity. XP is very variable in expression of sun sensitivity. The inconsistency noted in tests for light sensitivity no doubt reflects the heterogeneity of the syndrome. Some cases of the typical form show a papular and vesicular reaction, mainly to light in the 290–320 nm range [30]. The minimal erythema dose is lower than normal at most wavelengths [31].

XP and neoplasia. Cultured dermal fibroblasts from XP patients exhibit increased UV-induced mutagenesis. The neoplasms in XP patients, which occur predominantly on sun-exposed surfaces, are thought to be the result of UV-induced mutations [16]. Indeed, skin tumours from XP patients carry mutations bearing a 'UV signature' in the *p53* and *PTCH* genes [32,33]. UV exposure also triggers a complex series of signal transduction pathways that result in immunosuppression of the skin, which may well be an important factor [34,35].

Pathology. The histological changes in the fully developed case in the atrophic stage closely resemble those of senile skin. The epidermis is thin and flattened, and the dermal collagen shows basophilic degeneration. Irregular proliferation of rete pegs, heavily laden with pigment, is a distinctive feature. The keratoses and the various types of malignant tumour that ultimately complicate all but the mildest cases show no special histological characteristics.

Electron microscopic studies [36,37] show shrinkage of keratinocytes and their nuclei, and abnormalities of nuclear morphology. Melanocytes are also abnormal, with polymorphic melanosomes, and there may be giant pigment granules in melanocytes or keratinocytes. There are also abnormalities of desmosomes, the endoplasmic reticulum and mitochondria. The dermal fibroblasts appear to behave like macrophages and engulf melanosomes within vacuoles [37].

In hypopigmented macules the melanocytes are scanty, but Langerhans' cells are numerous [38].

Clinical features [4,39] (Fig. 12.16). The skin is normal at birth; the first symptoms are noticed between the sixth month and the third year in over 75% of cases, but may appear in very early infancy or in later childhood. Although the disease advances relentlessly and in orderly fashion through its successive stages, the rate of progression is unpredictable and bears no constant relationship to the age of onset. Most cases beginning in early childhood have reached the tumour stage before the age of 20 years,

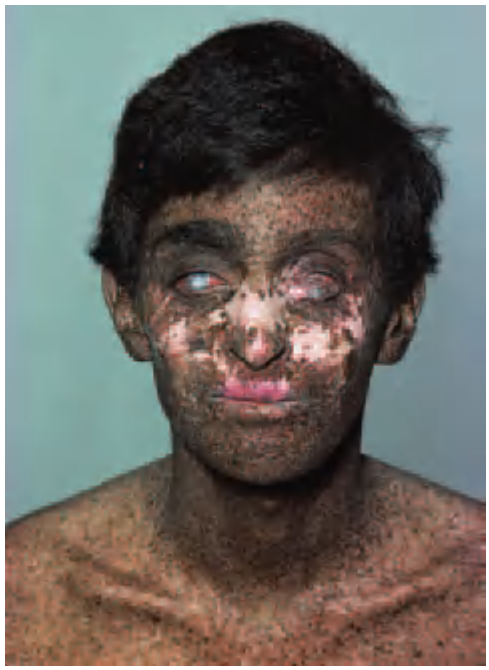

Fig. 12.16 Xeroderma pigmentosum. (From Harper J. *Handbook of Paediatric Dermatology*, 2nd edn. Oxford: Butterworth-Heinemann, 1990.)

although a few run a more benign course and some cases of later onset may develop multiple tumours within a few years.

Freckling and increasing dryness on light-exposed surfaces are usually the earliest manifestations; they may follow an acute sunburn or more persistent erythema. The freckles appear first on the face and hands and later on other exposed parts, the neck and the lower legs, the lips and the conjunctiva; in severe cases the trunk is affected. Varying in colour from light to dark brown and in size from a pinpoint to a centimetre or more, they may fuse to form irregular patches of pigmentation. Fading at first in the winter months, they soon become permanent. As they increase progressively in number, telangiectases and small angiomas appear interspersed among them. Telangiectases and angiomas on unexposed skin and on the lingual and buccal mucous membrane have been reported. Small, round or irregular, white, atrophic spots are soon added to the picture. Some follow crusted vesiculobullous lesions; others arise independently. Superficial ulcers, healing with difficulty, leave disfiguring scars, and contractures may produce ectropion and obliterate the outline of the eyelids. Keratoacanthomas may form, even in the mildest cases, and resolve spontaneously in a few months. Actinic keratoses are frequent; they may separate spontaneously or may undergo malignant change.

The first malignant tumours may develop as early as the third or fourth year. Basal cell carcinoma is common and large numbers, sometimes pigmented, may appear over the course of years. Squamous cell carcinoma is also common. Squamous cell carcinoma of the anterior tongue, the portion that may be exposed to UV radiation, has been reported [40]. Melanomas arise and may be multiple; they may lead to early death from widespread metastases or may run a benign course, even in adults, although histologically malignant. Other malignant tumours, such as angiosarcoma and fibrosarcoma, may rarely occur.

The disease is often fatal before the age of 10 years, and worldwide two-thirds die before 20 years of age. These statistics have improved in those countries where children are adequately protected from the sun. Multiple metastases of squamous cell carcinoma or melanoma are one cause of death. However, many patients die from infection, to which they are abnormally susceptible, or from neurological complications [41]. Survival beyond middle age is sometimes possible in mild cases or with adequate treatment. Striking interfamily variation in expectation of life has been reported.

Ocular lesions [4,39]. The eyes are affected in some 80% of cases. Photophobia and conjunctivitis are common early symptoms. Ectropion and destruction of the lower lids expose the bulbar conjunctiva, and symblepharon and ulceration may occur. Pigmented macules on the conjunctiva are common. Vascular pterygium, corneal opacities and epitheliomas of the lids, conjunctiva or cornea may develop.

Neurological complications. Neurological abnormalities occur in approximately 20% of XP patients [39], with one or more of the following: mental retardation, areflexia or hyporeflexia [42], spasticity, ataxia, sensorineural deafness, dysphasia and abnormal electroencephalographic findings. Patients with neurological abnormalities usually have group A and D disease, although a few have been reported with group C and XP variant disease [39]. There is a positive correlation between the severity of neurological involvement and the sensitivity of XP fibroblasts to killing by UV radiation [4]. It is possible that DNA repair mechanisms are essential for maintaining the normal function of neurones, and progressive damage, perhaps caused by ingested or endogenous chemicals, might cause premature death of susceptible neurones.

De Sanctis–Cacchione syndrome [43–45]. This term has been applied to the association of XP with microcephaly, severe mental deficiency, dwarfism, hypogonadism, deafness, choreoathetosis and ataxia. Post-mortem findings show cerebral and olivopontocerebellar atrophy from neurone loss, without primary damage to white matter, or gliosis.

Associated abnormalities. XP patients are often of small stature and poor physical development.

XP with CS. Rarely, CS can be found in combination with XP in XP-B [46], XP-D [47], XP-G [48,49] and CS-B [50].

XP and SLE. An 18-year-old woman with the typical cutaneous and ocular changes of XP-C developed arthritis, anaemia and a high antinuclear antibody titre [51].

Dominant form of XP. An autosomal dominant form of XP was described in a Scottish kindred by Anderson and Begg [52]. These patients had a mild clinical course.

Diagnosis. In the fully developed case, the diagnosis is unmistakable. The mild or early case must be differentiated from ordinary freckling. Other forms of photosensitivity and premature ageing must be excluded. These include progeria, acrogeria, Rothmund–Thomson syndrome, Bloom's syndrome, CS, Hartnup's syndrome and hydroa vacciniforme.

Prenatal diagnosis by amniocentesis is possible [53], but for some families molecular genetic techniques are now available and allow for an earlier and more reliable result. DNA-based prenatal carrier detection for XP-A in a chorionic villous sample has been successfully performed [54].

Treatment. As soon as the diagnosis is established, patients must be protected from sunlight by every possible means. They must not go outdoors during daylight hours, except in the early morning or evening, and even then they should wear two layers of clothing and a broad-brimmed hat. All uncovered skin surfaces must be protected by a total sun-block cream, and sunglasses with side shields should be worn. UV radiation is harmful up to at least 320 nm, and some fluorescent lights can emit radiation below this wavelength. Chemical light screens can combine a cosmetic and protective function.

Early and adequate excision of all tumours is essential, and is to be preferred to radiotherapy because of the atrophic and degenerate state of the skin. Topical 5-fluorouracil may be useful for early or premalignant lesions. Chemical peeling and dermabrasion can also be helpful [55]. Plastic surgery and grafting of large areas of facial skin may sometimes be required [56].

There is now substantial evidence to suggest that oral retinoids reduce the occurrence of skin cancer in XP [57–59]. A trial of prophylactic therapy should therefore be considered.

The eyes may need to be treated with artificial tears, soft contact lenses or even corneal transplant. The relatives of known cases should be carefully examined and tested [30] so that mildly affected individuals may be detected at the earliest possible stage.

A recent clinical trial used the microbial enzyme T4 endonuclease V applied regularly as a topical liposome lotion. This enzyme is able to bypass the defect in XP cells. Employed over a period of 1 year, it significantly reduced the onset of both new basal cell carcinomas and actinic keratoses [60].

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Cockayne's syndrome (MIM 216400)

Definition. An inherited syndrome characterized by short stature, mental deficiency, photosensitivity, disproportionately large hands, feet and ears, ocular defects and extensive demyelination.

Aetiology [1]. This rare syndrome affects the sexes equally; inheritance is determined by an autosomal recessive gene. Skin fibroblasts are abnormally sensitive to UV irradiation [2–4]. Unlike XP, the global NER process occurs normally in CS cells *in vivo* and *in vitro*. However, CS cells are defective in an important subpathway of NER. Following DNA damage, it is of prime importance for the cell to remove damage from actively transcribed regions of DNA, and in human cells repair is more rapid in transcribed than in untranscribed regions. This preferential repair is referred to as transcription-coupled repair, and it is this rapid preferential repair that is specifically defective in CS cells [5]. The associated failure of cells to restore normal levels of RNA synthesis after UV irradiation [6] has provided a means for carrying out complementation tests on CS cells and two complementation groups have been identified, CS-A and CS-B [7] (Table 12.5). The products of the two known CS genes, *CSA* (chromosome 5) and *CSB* (chromosome 10q11–q21) are envisaged to fulfil a transcription-coupled repair function [8]. CS can rarely be found in combination with XP (see p. 12.60).

Clinical features [9–11]. Although very early onset has been reported in a significant minority of cases, the child usually appears normal for the first year, when facial erythema in the butterfly distribution develops after exposure to sunlight. This provokes repeated exacerbations, which may be febrile. The sensitivity to light is eventually lost, but not before mottled pigmentation and atrophic scars have given the patient a prematurely senile appearance, which is enhanced by the progressive loss of subcutaneous fat on the face and the sunken eyes. The skin

elsewhere shows little change, although the long limbs and disproportionately large hands and feet are often blue and cold. The association of these striking features with large protruding ears has suggested a fanciful resemblance to Mickey Mouse. The hair is usually normal but may be sparse and has sometimes been prematurely grey.

Physical and mental development are greatly retarded and the child remains dwarfed, although sexual maturation occurs in some cases [12]. Optic atrophy, retinal degeneration and cataracts [13] lead to loss of vision, and progressive deafness is usual but variable in degree. Skeletal deformities [14] and limited joint movement increase the child's disabilities. There is extensive diffuse demyelination of the peripheral nerves and the central nervous system [10]. Survival beyond the second decade is unusual, although two affected brothers, aged 42 and 55 years, have been reported [15].

Diagnosis. Progeria has frequently caused confusion, since dwarfism and a prematurely senile appearance are characteristic of both syndromes, and in both the child appears normal in its first year. The light sensitivity, ocular defects, normal hair and disproportionately large extremities are typical of CS. In Rothmund–Thomson syndrome, the cutaneous changes begin in early infancy and affect the buttocks and extremities as well as the face. In Bloom's syndrome, the erythema of face and hands is associated with growth retardation, but mental development is normal. The condition is distinguished from XP by the unusual facies, the demyelination with delayed nerve conduction velocity, the lack of cutaneous malignancy [10] and the normal level of global NER. Prenatal diagnosis is possible by amniocentesis [16,17] or from chorionic villous samples, using the RNA synthesis recovery test.

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Bloom's syndrome (MIM 210900) [1]

SYN. CONGENITAL TELANGIECTATIC ERYTHEMA AND STUNTED GROWTH

Definition. The syndrome is characterized by telangiectatic facial erythema, short stature, a distinctive facies, abnormal immune response and predisposition to malignancy.

Aetiology [2,3]. Bloom's syndrome is determined by an autosomal recessive gene. Males are affected more frequently than females and the majority have been Jewish. Cultured lymphocytes and fibroblasts from patients show a high incidence of chromosomal aberrations; cultures from parents have sometimes shown similar changes [4]. Cells with abnormally high rates of sister-chromatid exchange are uniquely characteristic of Bloom's syndrome [2,5]. The gene for Bloom's syndrome (*BLM*) has been mapped to chromosome 15q26.1 [6,7] and has been identified as a DNA helicase [8,9]. This helicase is thought to be involved in resolving abnormal structures that can arise during DNA replication.

Clinical features [2,10–14]. Bloom's syndrome patients bear a striking resemblance to each other. They have a narrow, slender, delicate facies with a relatively prominent nose. The essential features are erythema of the face and stunted growth (both prenatal and postnatal). The telangiectatic erythema develops during infancy or early childhood as red macules or plaques, which may simulate lupus erythematosus. They are most numerous on the 'butterfly' area of the nose and cheeks, but may involve the margins of the eyelids, the forehead and the ears, and sometimes the dorsa of hands and forearms. There may be slight scaling. Exacerbation after exposure to sunlight is usual but not invariable, and light may also provoke bullae, bleeding and crusting of the lips.

Birth weight is low, and growth disturbance is proportionate and of moderate degree. The build is slender and the skull dolichocephalic (head circumference disproportionately smaller compared with height).

Other associated abnormalities include [13,15] café-au-lait patches, clinodactyly, syndactyly, congenital heart disease, annular pancreas and a high-pitched voice, possibly due to the craniofacial anatomy and high-arched palate. Many associated developmental defects have been reported.

Testicular atrophy is common and adult male patients appear to be infertile. Although the tubular elements of the testes function poorly, the androgen-secreting portions are spared, thus permitting normal puberty [16]. Fertility in female patients remains unknown, although one female patient had a full-term pregnancy [17].

There are no impairments of neurological development; however, most under-perform at school [18]. Some develop unusual personality features and behavioural patterns secondary to their unusual appearance and small size [12].

The mortality from neoplastic disease, particularly acute leukaemia, during the second or third decade is significantly increased [3–5,19]. Cancers of the types and sites seen in the general population arise frequently and unusually early. They are predominantly internal rather than cutaneous malignancies [14]. Reported associations include B-cell lymphoma [20] and Wilms' tumour [21].

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Poikilodermatous syndromes

Dyskeratosis congenita (MIM 305000)

SYN. ZINSSER–COLE–ENGMANN SYNDROME

Definition. Dyskeratosis congenita (DKC) is a rare inherited disorder characterized by atrophy and pigmentation of the skin, nail dystrophy, leukoplakia, bone marrow failure and a predisposition to malignancy.

Aetiology. The syndrome is rare, but widely distributed. It was first described in 1906 by Zinsser [1], and later by Cole *et al.* [2] and Engmann [3]. Most reported cases have been in males, although the full syndrome [4] and partial forms with only pigmentary changes [5,6] have occurred in females. The available pedigrees suggest that it is usually determined by an X-linked recessive gene, localized to Xq28 [7]. Using a positional cloning strategy, the gene was subsequently identified with five different missense mutations in five unrelated patients. *DKC1* is highly conserved across species barriers and is the ortholog of rat *NAP57* and *Saccharomyces cerevisiae CBF5*. The peptide, referred to as dyskerin, contains several motifs and multiple phosphorylation sites. By analogy to the function of the known dyskerin genes in other species, involvement in the cell cycle and nucleolar function has been predicted for the protein [8]. Autosomal dominant inheritance has also occurred [9–11].

Pathology [9]. The cutaneous changes are not pathognomonic and are unimpressive. The epidermis is flattened; the dermis is vascular and contains pigment-laden macrophages and an inconstant lymphocytic infiltrate. The connective tissue is usually normal.

Clinical features [9,11–17]. The essential features of the syndrome are atrophy and pigmentation of the skin, nail dystrophy and oral leukoplakia. The nail changes are usually the first to appear. Between the ages of 5 and 13 years, the nails become dystrophic and are shed: they may be reduced to horny plugs or be completely destroyed. There may be recurrent episodes of suppurative paronychia.

The pigmentary changes may appear simultaneously or 2 or 3 years later, and reach their full development in 3–5 years. Fine, reticulate, grey–brown pigmentation is most conspicuous on the neck (Fig. 12.17) and thighs, but involves the greater part of the trunk. The skin is atrophic, and telangiectases may be sufficiently numerous to give a

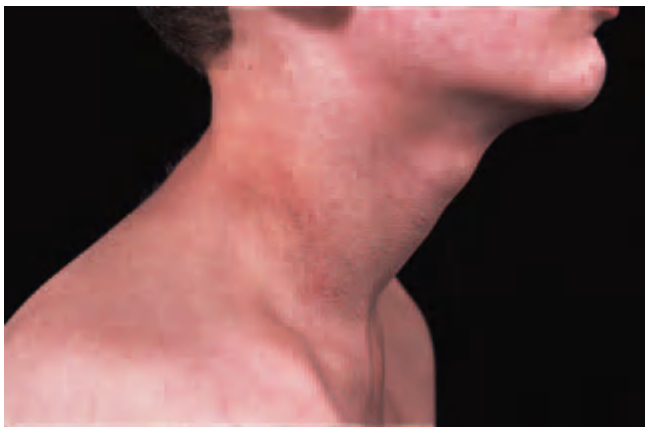

Fig. 12.17 Dyskeratosis congenita: reticulate pigmentation on the neck.

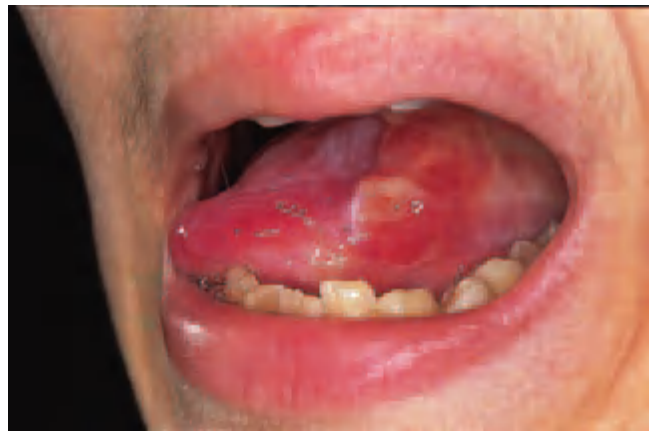

Fig. 12.18 Dyskeratosis congenita: the development of leukoplakia.

poikilodermatous appearance. The skin of the face is red and atrophic, with irregular macular pigmentation, while that of the dorsa of the hands and feet is diffusely atrophic, transparent and shining. The palms and soles may be thickened and hyperhidrotic, and may form bullae with trauma.

A 9-year-old girl with DKC was reported who had, in addition to the known manifestations of the disease, tufts of hairs on the limbs and an early onset of keratinized basal cell papillomas on her trunk [18].

The onset of the mucous membrane lesions may coincide with, or follow, the nail and skin changes. Small blisters and erosions of the lingual and buccal mucous membranes are succeeded by irregular patches of leukoplakia (Fig. 12.18). Similar changes on the tarsal conjunctiva may obliterate the lacrimal puncta, resulting in excessive lacrimation and soreness and scarring of the lids, and anorectal or urethral leukoplakia may produce stenosis. Similar changes may occur throughout the gastrointestinal tract and on the urogenital mucous membranes. Gastrointestinal complications include oesophageal stricture and portal hypertension [19]. Another recognized complication is interstitial pneumonia [20].

General physical and mental growth is sometimes retarded. Intracranial calcification may occur [21]. The teeth tend to be defective and irregularly implanted, and periodontal disease and early caries are usual. The hair may be normal but is sometimes sparse and dry. Premature canities and cicatricial alopecia [15] have occasionally been noted. Various immunological defects have been reported [10,22].

Malignancy. The incidence of carcinoma in the areas of leukoplakia appears to be high; it may prove fatal between the ages of 30 and 50 years. Carcinoma has also developed on other mucosal surfaces and in atrophic skin. Other neoplasms reported include pancreatic carcinoma and Hodgkin's disease. In a review of 104 cases [14], 12% had developed one or more tumours at the time of reporting (mean age of patients at reporting was 21 years).

Haematological abnormalities [6]. Many cases have shown blood dyscrasias, myeloid aplasia, refractory anaemia or pancytopenia. Haematological manifestations are usually added to the clinical picture from the age of 10 years. The resulting infection or haemorrhage is an important cause of death [22]. Rarely, neutropenia can be an early finding [23].

Prognosis. The prognosis is usually poor, for either the blood dyscrasia or carcinoma may prove fatal. However, in some patients only nail dystrophy and pigmentation are present [21], and in such cases the expectation of life is normal.

Diagnosis. Because of the relatively late onset of the characteristic features of this syndrome, their relationship is often overlooked for some years [16]. Rothmund–Thomson syndrome has often been confused. Here, erythema of the face, buttocks and limbs in infancy is progressively succeeded by poikiloderma. Nail changes are unusual and leukoplakia does not occur. In anhidrotic ectodermal dysplasia the dental changes, distinctive facies, sparse or absent hair and normal nails provide points of differentiation.

Treatment. The aplastic anaemia associated with DKC can be successfully treated by allogeneic bone marrow transplantation; however, this approach does not reverse the other systemic manifestations of the syndrome [24,25]. Granulocyte colony-stimulating factor has been used successfully to improve haematological parameters in the short term [23,26].

Retinoids have been reported to cause regression of lesions in leukoplakia [27] and so may reduce the incidence of malignancy.

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Greither's syndrome [1]

This syndrome, reported in two brothers, has many features in common with DKC but appears to be distinct. Warty keratoses are irregularly distributed over the dorsa of the hands and feet and on the legs. The soles show large islands of keratoderma. Poikiloderma, with a prominent pigmentary component, is conspicuous on the face, hands, arms, feet and legs. The nails and hair are normal.

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Rothmund–Thomson syndrome (MIM 268400)

SYN. POIKILODERMA CONGENITALE

Aetiology. Rothmund–Thomson syndrome is a rare hereditary disorder, occurring predominantly in females (1.4 : 1) and determined by an autosomal recessive gene [1–3]. The initial description by Rothmund [4] referred to children with cataracts and a peculiar degeneration of the skin. Thomson [5] described sisters with similar skin changes and subsequently [6] labelled the disorder as 'poikiloderma congenitale'. Cataracts were not a feature of his cases. Taylor [7] reviewed the literature and proposed the eponym of Rothmund–Thomson syndrome. The spectrum of clinical features suggests some degree of genetic heterogeneity. There have been several reports of various karyotypic abnormalities, including trisomy 8 mosaicism [8,9]. Reduced DNA-repair capacity and increased sensitivity to UVC have been reported in individual patients [10,11]. Genes responsible for Werner's syndrome and Bloom's syndrome have been identified as homologues of *Escherichia coli RecQ*, which encodes a DNA helicase that unwinds double-stranded DNA into single-stranded DNA. Kitao *et al*. [12] have reported three patients with Rothmund–Thomson syndrome who carried two types of compound heterozygous mutations in a further member of this family, known as *RECQL4*. The fact that the mutated alleles were inherited from the parents in one affected family and were not found in ethnically matched controls suggest that mutation of *RECQL4* at 8q24.3 is responsible for at least some cases of Rothmund–Thomson syndrome.

Pathology [13]. In childhood, the histological changes are flattening and atrophy of the epidermis, with oedema of the dermal–epidermal junction. There may be some vasodilatation and perivascular lymphocytic infiltration in the dermis. In the adult, the exposed skin shows the combination of fragmentation of elastic tissue in the dermis with patchy Bowenoid dyskeratosis of the epidermis.

Clinical features [2,7,14–20]. The skin appears normal at birth. The earliest lesions usually develop between the third and sixth month, but sometimes as late as the second year. Plaques of erythema and oedema, or more transitory

diffuse erythema, are succeeded by varying combinations of atrophy, telangiectasia, pigmentation and depigmentation. The pigmentation, dull brown in colour, irregularly macular or reticulate, develops later than the atrophy and telangiectasia on which it is superimposed, although it may extend much beyond these areas, especially on the neck and trunk, where it may be the only change. On the face and hands telangiectasia predominates. Ultimately the lesions closely resemble chronic radiodermatitis.

The cheeks are first and most severely involved, but the forehead, chin and ears seldom escape. The hands, forearms and lower legs are next affected, and the buttocks and thighs are frequently involved. Light sensitivity is a feature of many cases, and exposure to sunlight may extend the distribution of the eruption on the upper trunk; however, it is not limited to light-exposed skin, and the poikiloderma may develop without preceding erythema. Light sensitivity may be so severe that a bullous response is elicited, and although this tends to diminish after early childhood, it may persist into adult life [13,18].

Once they have reached their full development in early life, the skin lesions tend to remain unchanged, but in many cases keratoses develop on exposed skin from adolescence onwards, and large warty keratoses of hands, wrists, feet, ankles and elsewhere may restrict the patient's activities [21]. Squamous carcinoma may develop in the keratoses or in the surrounding atrophic skin [2].

Scalp hair is often sparse and fine, and may be absent. Eyebrows and eyelashes and pubic and axillary hair are often sparse or absent. Nails are normal or small and dystrophic. Teeth are often normal, but microdontia and early caries have been reported.

Bilateral cataracts have developed, usually between the fourth and seventh year, in about 40% of reported cases, and are more frequent in some families than in others.

Physical development is frequently retarded; most patients are of small stature and some are dwarfs. The dwarfism is proportionate, with slender delicate limbs, small hands and feet, and short stubby fingers. The skull may be small and the features bird-like, sometimes with a saddle nose. Hypogonadism of slight or severe degree is frequent and the incidence of hyperparathyroidism appears also to be increased [22]. The association of Rothmund–Thomson syndrome and Addison's disease has also been reported [23].

Skeletal abnormalities include radial ray defect [24], which may present as thumb hypoplasia with an abnormal radial head, or complete absence of the radius. There is a recognized risk of osteosarcoma, especially in the bones of the lower leg, which can present in childhood [19,25–27].

Other associations reported include myelodysplastic syndrome [28], malignant eccrine poroma [29], malignant fibrous histiocytoma [30] and annular pancreas with duodenal stenosis [31].

Individuals with Rothmund–Thomson syndrome are usually of normal intelligence. Life expectancy depends on the development of an associated malignancy; otherwise it appears to be normal.

Associated features. Amino-aciduria has occasionally been reported, but has been of no consistent type. One patient had osteogenesis imperfecta [32].

Diagnosis. The essential features in differential diagnosis are the age of onset, the distribution of the lesions and the combination of atrophy, telangiectasia and mottled pigmentation, most intense on light-exposed skin but not necessarily confined to it.

In Werner's syndrome, the skin changes are essentially sclerodermatous, and both skin and ocular lesions develop later than in Rothmund–Thomson syndrome. In DKC, reticulate pigmentation develops between the ages of 5 and 13 years, and is most marked on the neck, trunk and thighs. Atrophy and telangiectasia may appear later. The nail changes are constant and severe. In progeria, the child is often small but otherwise normal during the first year; thereafter development is retarded. The scalp hair, eyebrows and eyelashes are lost and the skin assumes an increasingly senile appearance. In CS, light sensitivity is a conspicuous feature after the first year, but there is no poikiloderma. Hypohidrotic ectodermal dysplasia should be identified by the association, in variable combinations, of conical teeth, hypotrichosis and partial or complete anhidrosis. The skin is atrophic but not poikilodermatous. XP should not cause confusion. In mild forms, only freckle-like macules are present; in mild forms of Rothmund–Thomson syndrome telangiectasia is the conspicuous feature. Telangiectasia, often irregular, linear and present at birth, is a feature of focal dermal hypoplasia. In Bloom's syndrome, erythema, and not poikiloderma, is the essential change. Congenital poikiloderma is a feature of other hereditary syndromes (see below).

Treatment. Protection against sunlight is important. Careful supervision is essential to ensure detection of carcinoma. Low blood concentrations of vitamin A have been found in patients with dyskeratoses [1], and in one case the lesions improved with retinoids [33]. Telangiectasia, especially on the face, can be improved significantly by treatment with the vascular pulsed dye laser [34].

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Acrokeratotic poikiloderma of Weary [1]

This syndrome, probably determined by an autosomal dominant gene, appears to be a distinct entity. Ten members of a family were affected. The main clinical features were (i) a vesiculopustular eruption of hands and feet in infancy and childhood; (ii) extensive eczema from around 4 months to 5 years; (iii) persistent poikiloderma, sparing only the face, scalp and ears; and (iv) warty papules on hands, feet, elbows and knees.

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Kindler's syndrome [1,2]

Kindler's syndrome is an autosomal recessive disorder characterized by neonatal blistering, sun sensitivity, atrophy, abnormal pigmentation and fragility of the skin. It has been considered to be a variant of acrokeratotic poikiloderma of Weary. Linkage and homozygosity analysis in an isolated Panamanian cohort and in additional inbred families mapped the gene to 20p12.3. Loss-of-function mutations were identified in the *KIND1* gene encoding kindlin-1. Kindlin-1 is a human homologue of the *Caenorhabditis elegans* protein UNC-112, a membrane-associated structural/signalling protein that has been implicated in linking the actin cytoskeleton to the extracellular matrix.

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Other poikilodermatous syndromes

These include the diffuse and atrophic macular dermatosis of Stevanovic and hereditary sclerosing poikiloderma of Weary (see Chapter 46).

Miscellaneous syndromes

Bazex–Dupré–Christol syndrome (MIM 301845)

SYN. BDC SYNDROME; BAZEX SYNDROME; FOLLICULAR ATROPHODERMA AND BASAL CELL CARCINOMAS

First described by Bazex *et al*. in 1964 [1,2], the mode of inheritance is now known to be X-linked dominant with evidence of linkage to Xq24–q27 [3]. This represents the

identification of a gene presumed to be involved in hair follicle development and skin tumour formation. Several large family pedigrees have been studied [4–7]. The essential features are follicular atrophoderma, present from birth, and the development of multiple basal cell carcinomas of the face from adolescence onwards. In infancy and childhood, milia are often present. The follicular atrophoderma affects the dorsa of the hands and feet, and sometimes large areas on the extensor surfaces or lower back are affected. The exaggerated follicular funnels ('ice-pick' marks) are caused by deep and lax follicular ostia rather than a true atrophy. The basal cell carcinomas present as lightly pigmented papules, which resemble melanocytic naevi.

Inconstant features include facial hypohidrosis with or without generalized hypohidrosis [8]; hypotrichosis, which in males is diffuse and affects all scalp hairs, whereas females tend to have normal hairs intermingled with abnormal hairs; and hair-shaft abnormalities, like pili torti and trichorrhexis nodosa [6,9]. The condition is easily distinguished from Gorlin's syndrome (see Chapter 36). It must not be confused with a completely different disorder, acrokeratosis paraneoplastica, a cutaneous marker of malignancy that has also been labelled as Bazex syndrome [10].

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Focal facial dermal dysplasia (MIM 136500)

The focal facial dermal dysplasias are a genetically heterogeneous group of disorders characterized by congenital, bitemporal, round, scar-like lesions with or without associated facial anomalies. Kowalski and Fenske [1] proposed a classification for this group of disorders: type 1, autosomal dominant; type 2, autosomal recessive; and type 3 with other facial features (Setleis' syndrome).

Brauer [2] originally reported a large kindred in which the inheritance was autosomal dominant. The facial lesions were described as scar-like and varied in size. Hair was absent in the lesions and no sweating could be demonstrated. Apart from the temporal defects, no other abnormalities were noted.

Setleis *et al.* [3] subsequently described five children from three apparently unrelated Puerto Rican families with scar-like defects on each temple and other features: (i) an aged, leonine appearance; (ii) eyelashes that were either absent from both eyelids, or in multiple rows on the upper eyelids and absent on the lower; (iii) eyebrows that slanted sharply upwards and outwards; (iv) puckered skin around the eyes; (v) a scar-like median furrow on the chin; and (vi) a nose and chin that felt rubbery. Histology revealed a thin epidermis and dermis with little elastic tissue and absence or scarcity of adnexae. Inheritance was assumed to be an autosomal recessive trait.

Jensen [4] described two northern English families with temporal scars and eyelash abnormalities, one with autosomal dominant inheritance and the other autosomal recessive.

McGeoch and Reed [5] documented 31 affected persons in six generations of an Australian family with pigmented atrophic lesions on the temples and linear radiating depressions on the forehead. In addition, clefting and hairless depressions on the chin were described. Autosomal dominant inheritance was clearly demonstrated.

The genetic basis for this group of disorders is unclear. Ward and Moss [6] reported an affected 14-month-old boy, his sister and mother. They all had similar facial features, with sparse lateral eyebows, a prominent upper lip and down-turned mouth. Additional features in the baby included medial epicanthal folds and skin dimpling on one side of the chin. Inheritance was presumed to be autosomal dominant and they proposed that focal facial dermal dysplasia and Setleis' syndrome are a single disorder.

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Focal dermal hypoplasia (MIM 305600)

SYN. GOLTZ SYNDROME

Definition and aetiology. Focal dermal hypoplasia is a rare multisystem condition in which developmental defects of the skin are associated with ocular, dental and skeletal abnormalities. Approximately 200 cases have been reported, although the incidence is likely to be underestimated, as mildly affected subjects may go unrecognized. Most affected individuals have been female, and X-linked dominant inheritance with lethality in males has been proposed as the likely mode of inheritance [1]. Rare male cases [2] could reflect half chromatid mutations [3].

Pathology [4,5]. The foci of dermal hypoplasia show extreme reduction in thickness of the dermis, so that subcutaneous fat is situated almost immediately beneath the epidermis. There is debate [3] about whether the defect is primarily an atrophy of the dermis, with secondary fat 'herniation', or a complex developmental abnormality of connective tissue causing both dermal hypoplasia and the development of fat hamartomas [6]. The frequent presence of dermal elements, including collagen and elastin fibres, below the superficially situated fat and the ultrastructural demonstration of immature adipocytes within the fat tend to support the latter view.

Ishii *et al*. [5] reported a histopathological study of focal dermal hypoplasia and concluded that the adipose tissue in the dermis was the result of dermal dysplasia and not hypoplasia.

The papillomas show markedly acanthotic epithelium overlying a core of vascular connective tissue.

Clinical features [3,4,7–10]. Findings vary from easily overlooked mild skin atrophy to severe limb deformity and life-threatening complications. Skin involvement has been present in all but two of the reported cases [11] and is usually regarded as essential for the diagnosis. It remains possible that undiagnosed gene carriers occur with non-cutaneous features alone.

The typical skin lesions, which are present at birth, consist of asymmetrical linear streaks of atrophy and telangiectasia. The linear patterning follows Blaschko's lines. In racially pigmented skin, the lesions may be hypopigmented or hyperpigmented rather than erythematous. Soft reddish-yellow nodules represent the so-called 'fat herniations' (Fig. 12.19). Raspberry-like papillomas are common on the lips, perineum and at other sites, including the ears, fingers, toes, buccal mucosa and oesophagus [12]. Multiple giant papillomas have been reported [13]. In addition, generalized dryness of the skin and pruritus may be features. Nails may be absent or dystrophic. The hair is usually sparse and brittle, and there may be patchy alopecia of the scalp or pubic area. A case of focal dermal hypoplasia presenting as congenital localized alopecia has been reported [14].

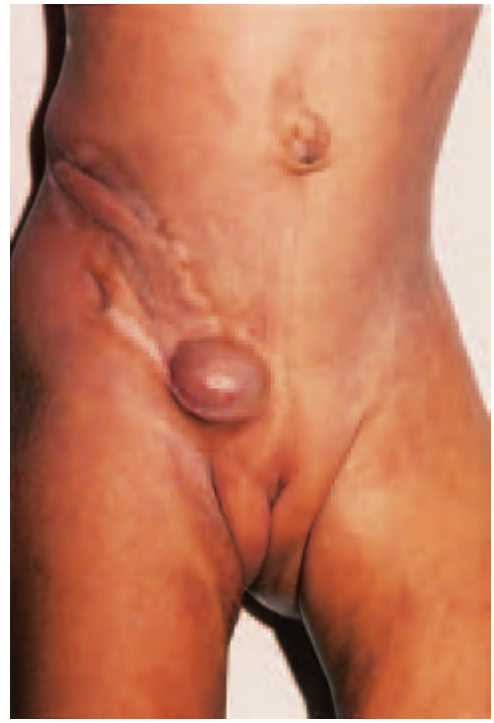

Fig. 12.19 Focal dermal hypoplasia: herniation at the site of skin atrophy.

Short stature and slender build are usual, and mental development is sometimes retarded. The facial features are characteristic: the skull is small and rounded, the chin is pointed and the facial outline is triangular, with protruding ears. The alae nasi may be asymmetrical and notched. Face, trunk and limbs may be asymmetrical. Other skeletal malformations include scoliosis, but most characteristic is syndactyly, polydactyly or absence of one or more digits. A 'lobster-claw' type of deformity may result. Two girls have been reported with overlap features of focal dermal hypoplasia and EEC syndrome [15]. Ocular defects [12,16,17] are frequent and include microphthalmos, anophthalmos, coloboma, strabismus, keratoconus and corneal opacification.

Intestinal malrotation and mediastinal dextroposition have been described in association with focal dermal hypoplasia [18].

On radiological examination, osteopathia striata, seen as fine, parallel, vertical, radio-opaque stripes in the metaphyses of the long bones, are found in a large proportion of cases [19,20]. This finding is not pathognomonic, but is present in approximately 20% of gene carriers and can be a useful feature, particularly if the condition is suspected in minimally affected subjects [3]. Expansile bone lesions are also seen in some cases [21,22]. Osteochondroma of the humerus was diagnosed in a 12-year-old girl with focal dermal hypoplasia [23].

Diagnosis. The presence of the lesions from birth and the association of linear streaks of atrophy and telangiectasia with soft fatty nodules and malformations of the digits confirms the diagnosis. MIDAS syndrome (*mi*crophthalmia, *d*ermal *a*plasia and *s*clerocornea) has been reported as distinct from focal dermal hypoplasia [24,25].

Treatment. These children often require reconstructive surgery. Intubation for general anaesthesia must be undertaken cautiously, as papillomas may be present in the upper respiratory tract [26].

The telangiectatic skin lesions can be improved cosmetically with the vascular pulsed dye laser.

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Nail–patella syndrome (MIM 161200)

SYN. HEREDITARY OSTEO-ONYCHODYSPLASIA (HOOD) SYNDROME

The nail–patella syndrome was first described by Turner in 1933 [1] and Aschner in 1934 [2]. It is determined by an autosomal dominant gene of variable expressivity but high penetrance. Linkage between the ABO blood group and nail–patella loci has been established [3,4] and the gene is located on chromosome 9q34.1 [5]. Mutations in the presumed transcription factor *LMX1B* cause nail–patella syndrome. Dreyer *et al.* [6] found *de novo* heterozygous mutations in the *LMX1B* gene in three unrelated patients with nail–patella syndrome. Functional studies showed that one of these mutations disrupted sequence-specific DNA binding, whereas the other two mutations resulted in premature termination of translation.

The syndrome combines nail and skeletal defects [7–12]. The nails are dystrophic in 95% of cases, either from birth or early childhood. The thumbnails are most severely involved and may be absent or small, thickened and depressed. Nails of other fingers, and sometimes of the toes, may also be affected. The lunula may be triangular.

In only 20% of cases is there aplasia of the patella, but in another 70% there is subluxation of the patella. Other skeletal defects include the presence of posterior iliac horns [13,14], clavicular horn [15], dislocation of the radial heads, scoliosis and thickened scapulae [16–18].

Hyperpigmentation of the pupillary margin of the iris (Lester iris) occurs in 45% of cases.

Various renal abnormalities have been recorded, including glomerulonephritis, renal dysplasia and Goodpasture's syndrome [19–22]. In cases with glomerulonephritis, there is damage to the basement membrane, with deposition of C3 and IgM in the mesangium. Electron microscopy of the skin has shown thickening and redundancy of the epidermal basement membrane, and it has been postulated that there may be a generalized defect in basement membranes [16]. Drut *et al.* [23] studied the kidneys of an 18-week spontaneously aborted fetus of a mother with nail–patella syndrome. Ultrastructural examination of the kidney showed irregular thickening of basement membranes with subendothelial fibrillar electron-dense deposits. Immunofluorescence showed fibrinogen deposition in glomerular basement membranes.

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Clubbing of the fingers and toes (MIM 119900)

SYN. HIPPOCRATIC FINGERS; ACROPACHY

Definition. A swelling of the soft tissues of the terminal phalanx of a digit that obliterates the angle between the base of the nail and the digit. This can be quantified by a shadowgram technique [1].

Hypertrophic osteoarthropathy (HOA) is often associated with clubbing, but the prevalence of these two conditions in different diseases is very different. HOA can occur without clubbing, and whereas clubbing is almost universal in cyanotic congenital heart disease, HOA is very uncommon in this condition. Until further evidence is available, they should be considered as separate entities [2].

In thyroid acropachy, clubbing is associated with thickening of the soft tissues of the hands and feet, and periosteal new bone formation occurs in the hands and feet rather than the long bones [3–5].

Aetiology. Clubbing may occur early as a hereditary defect in otherwise healthy individuals. An autosomal gene of variable penetrance and expressivity is probably responsible [6,7], and there is suggestive evidence [8] that hereditary predisposition may play some part in the more common acquired forms.

The acquired form is associated with cyanotic congenital heart disease, bronchopulmonary disease, subacute bacterial endocarditis, cirrhosis, ulcerative colitis, Crohn's disease, chronic diarrhoea and malabsorption [9–11]. Clubbing does not occur in animals other than humans.

Pathology and pathogenesis. Increased fibrous tissue separates the nail from the phalanx, and there may be perivascular lymphocytic infiltration. The bone is not usually affected, but spurs of bone may occasionally form on the terminal phalanx. Many studies have shown that the blood flow to clubbed fingers is increased, except in hereditary clubbing [11]. The flow returns to normal if the clubbing improves after elimination of the causative pathology. It is possible that the increased blood flow travels through the central Suquet–Hoyer canals of the digital arteriovenous anastomoses. There is at present no single satisfactory theory to account for the hyperaemia and soft-tissue overgrowth, and there may be several mechanisms. Four hypotheses have been proposed [11].

1 A *circulating vasodilator*, which is normally inactivated by the lungs, could account for the clubbing due to those cases of cyanotic heart disease in which venous blood bypasses the lungs. Possible vasodilators include ferritin [1,11,12], prostaglandins [13], bradykinin and 5-hydroxytryptamine [14]. It has been suggested that mast cells might release vasoactive mediators that cause clubbing, although mast cells are not increased in clubbed digits [15].

2 *Tissue hypoxia* could account for some cases, and the occasional occurrrence of clubbing following frostbite, trauma and SLE may be due to vascular occlusion [11].

3 *Neural factors* have been postulated to account for the link with gastrointestinal disease, and the development of clubbing in Crohn's disease after vagotomy [6].

4 *Genetic factors* may explain why clubbing, which is secondary to acquired diseases, does not occur in every case of that disease. Acquired clubbing and inherited clubbing can occasionally occur in the same family [16].

Clinical features [8]. The normal nail projects from the digit at an obtuse angle of about 160°, most clearly seen

on the thumbs. In clubbing, this angle is obliterated, and sometimes reversed. The nail plate usually shows increased curvature in one or both planes and the volume of the distal phalanx may be increased.

In hereditary clubbing, these changes begin gradually at, or soon after, puberty and commonly involve all fingers and toes. Rarely, they may be evident in infancy or early childhood [16].

In acquired clubbing, the onset is also usually insidious and may occur at any age, but even in severe cyanotic congenital heart disease it is seldom noticeable before the second year. It may be bilateral or unilateral, or may affect only one or two digits. In malignant pulmonary disease, the onset may be rapid and painful.

Diagnosis. The distinction between hereditary and acquired clubbing may be of great clinical significance, for clubbing may precede any other evidence of pulmonary neoplasm by many months. Hypertrophic osteoarthropathy always shows bone and often joint changes, and clubbing is merely one feature of the syndrome. Familial osteoarthropathy [17], a manifestation of avascular necrosis of phalangeal epiphyses, presents before puberty as enlargement and impaired mobility of interphalangeal joints.

Pseudoclubbing may be produced by the shortening of the fingernail, which accompanies osteolysis of the terminal phalanges, such as has occurred in workers engaged in the polymerization of vinyl chloride [18].

Unilateral or unidigital clubbing is usually due to a vascular abnormality, such as an aneurysm in the affected limb. Unilateral clubbing can also be caused by neural damage, for example Pancoast's tumour, or prolonged hemiplegia.

Treatment. The secondary form may show some regression if the provocative disease is treated [19].

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Pachydermoperiostosis (MIM 167100)

(see also Chapter 46)

Definition and terminology. Pachydermoperiostosis is a syndrome characterized by hypertrophic changes involving predominantly the skin and bones of the extremities. The term 'cutis verticis gyrata' describes a folded hyperplasia of the scalp that may accompany pachydermoperiostosis but also has other causes.

Aetiology [1,2]. *Primary pachydermoperiostosis* (syn. Touraine–Solente–Golé syndrome) is a rare developmental defect that has been reported in many races and which occurs predominantly in males. Its inheritance has been attributed to an autosomal dominant gene of variable expressivity [3]. Further studies should include a radiological survey of relatives. No chromosomal abnormality has been demonstrated.

Secondary pachydermoperiostosis (syn. secondary hypertrophic osteoarthropathy) may also depend on a hereditary factor, but is usually provoked by severe pulmonary disease, adenocarcinoma or epidermoid carcinoma of the bronchus, pleural mesothelioma, bronchiectasis, lung abscess or, less often, carcinoma of the stomach, oesophagus or thymus. In cyanotic congenital heart disease with clubbing, bone changes rarely develop.

Pathology [2,4]. Proliferative periostitis of the leg bones, especially in the diaphyses of the tibia, fibula, radius and ulna, leads to diffuse irregular periosteal ossification, increasing the circumference of affected bones without increasing their length. In severe cases, almost all bones may be involved, and ligaments, tendons and interosseous membranes may ossify. Abnormal ossification of the skull has been reported [5]. In the early stages, but not the

later stages, there is increased blood flow to the clubbed fingers [6,7]. The skin shows hypertrophy of collagen and of epidermis and epidermal appendages, and an increase of acid mucopolysaccharide.

Clinical features [2,8–11]. Primary pachydermoperiostosis usually begins soon after puberty. The skin of the face, forehead and scalp becomes grossly thickened and thrown into folds. The pattern of folds and furrows on the forehead and cheeks, and the heavy thickened eyelids, stamp the patients with a uniform expression of weariness and despair. The folding of the scalp produces one of the forms of cutis verticis gyrata. The skin of the hands and feet is also thickened, but usually not folded. Sebaceous activity is greatly increased on the face and scalp, and hyperhidrosis of hands and feet may be troublesome.

Thickening of the phalanges and of the bones of the limbs produces spade-like hands and feet on ungainly cylindrical arms and legs. The fingers and toes are clubbed. Acro-osteolysis of the fingers and toes may occasionally occur [7].

In one family, four members suffered from pachydermoperiostosis and peptic ulcer due to hypertrophic gastropathy (Ménétrier's disease) [12].

Skin and bone changes become progressively more severe for 5–10 years and then usually remain unchanged throughout life; exceptionally, they may continue to progress and the degree of sebaceous hyperplasia may become extreme. Sparse facial and pubic hair and gynaecomastia are present in some cases, but evidence of endocrine disturbance is equivocal. Many patients are mentally retarded, some of them severely. Expectation of life is reduced in such patients, although reliable figures for the less severely affected are not available. Working capacity is low.

Secondary pachydermoperiostosis occurs predominantly in men aged 30–70 years. The bone changes are the most obvious feature, develop more rapidly, and are often painful. The skin changes may be absent and are often relatively mild. If the primary disease can be treated effectively, the bone and skin changes will regress.

Radiological changes. The greatest periosteal thickening is seen in the diaphysis of metatarsals and metacarpals and the long bones of the limbs. There is some thickening of the cortex (Fig. 12.20).

Diagnosis. The primary and secondary forms of pachydermoperiostosis must be differentiated by the age of onset, the rate of progression and the presence of a pulmonary lesion. Although skin changes are more frequent in the primary form, their presence does not exclude a tumour.

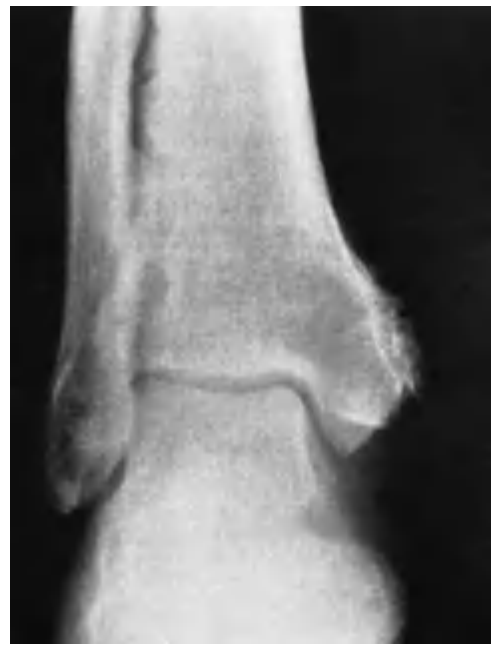

Fig. 12.20 Pachydermoperiostosis: radiograph of the ankle. (Courtesy of Dr J. Savin, Edinburgh, UK.)

In acromegaly, the facial skeleton, jaw and skull as a whole are enlarged, and visual defects may be detectable. In thyroid acropachy, enlargement is confined to hands and feet, and exophthalmos and pretibial myxoedema are often present, with other signs of hyperthyroidism.

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Acromegaloid phenotype with cutis verticis gyrata and corneal leukoma (MIM 102100) [1,2]

SYN. ROSENTHAL–KLOEPFER SYNDROME

In this rare syndrome, inherited via an autosomal dominant gene, there are acromegaloid facial features, for example a large jaw, but the sella turcica is normal in size. The horn-like projections of the lateral half of the supraorbital ridge are characteristic. There may be hyperplasia and folding of the facial skin. The scalp is enlarged, causing gyrate folds in the skin. The dermal ridges in the palms are split longitudinally. During the first decade of life, the cornea becomes opaque, often bilaterally. No endocrine abnormality has been detected.

The condition must be distinguished from cerebral gigantism (Sotos' syndrome) in which there is increased height and weight, with acromegalic features, large hands and feet, and mental retardation [2].

REFERENCES

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Short stature with pleonosteosis and periarticular fibrosis (MIM 151200) [1]

SYN. LÉRI'S SYNDROME

This rare condition is determined by an autosomal dominant gene. There is precocious and excessive ossification of the bones of cartilaginous origin (pleonosteosis), with short stature and mongoloid facies. From childhood onwards there is progressive periarticular fibrosis, especially in the hands. The palms and soles are thickened, with accentuated skin creases. There may be flexion contractures of the digits, broad thumbs and genu recurvatum.

REFERENCE

1 Rukavina JG, Falls HF, Holt JF *et al*. Léri's pleonosteosis. A study of a family with a review of the literature. *J Bone Joint Surg* 1959; **41A**: 397–408.

The craniosynostoses

Craniosynostosis is the premature fusion of skull sutures in the neonate causing craniofacial malformation, often in association with other abnormalities. More than 100 syndromic forms of craniosynostosis have been described [1]. Most notable are the eponymously named, autosomal dominantly inherited syndromes of Apert, Crouzon, Pfeiffer, Saethre–Chotzen and Beare–Stevenson. There have been significant advances in understanding the genetic basis of many of these disorders, especially in relation to fibroblast growth factor receptor genes (Table 12.6).

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Table 12.6 The main craniosynostosis syndromes.

Syndrome	Other features in addition to craniosynostosis	Chromosomal localization	Gene	Reference
Apert	Mid-face malformations, syndactyly of hands and feet, acne	10q26	*FGFR2*	[2]
Crouzon	Proptosis, acanthosis nigricans (AN)	10q26	*FGFR2* *FGFR3* (with AN)	[3] [4]
Pfeiffer	Broad halluces and thumbs	8p/10q26	*FGFR1/FGFR2*	[5,6]
Saethre–Chotzen	Ptosis, facial asymmetry, low hairline	7p21	*TWIST*	[7,8]
Beare–Stevenson	Cutis gyrata	10q26	*FGFR2*	[9]

FGFR, fibroblast growth factor receptor gene; *TWIST*, the human counterpart of the murine *Twist* gene, a basic helix–loop–helix transcription factor.

Apert's syndrome (MIM 101200) [1–4]

SYN. ACROCEPHALOSYNDACTYLY

Apert's syndrome is characterized by craniosynostosis, mid-facial malformations and symmetrical syndactyly. In a group of nine cases [5], all the seven who had reached puberty had severe or moderately severe acne vulgaris of unusually wide extent, with comedones on the arms and forearms as well as in the commonly affected sites. In a report by Henderson *et al.* [6], severe acne in two patients with Apert's syndrome responded well to isotretinoin therapy. Immunohistochemical studies of the skin showed no difference in the number of cells expressing androgen receptors between the patients with Apert's syndrome and controls. Other reported cutaneous associations with Apert's syndrome are hyperhidrosis [7] and oculocutaneous albinism [8].

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Crouzon's syndrome (MIM 123500) [1]

SYN. CRANIOFACIAL DYSOSTOSIS

Crouzon's syndrome is characterized by craniosynostosis, maxillary hypoplasia, shallow orbits and ocular proptosis. Acanthosis nigricans is recognized to occur in some patients with Crouzon's syndrome [2].

REFERENCE

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Pfeiffer's syndrome (MIM 101600)

In 1964, Pfeiffer [1] described a syndrome comprising craniosynostosis, broad thumbs, broad great toes and, in some, partial soft-tissue syndactyly of the hands. Other features may include umbilical hernia, malpositioned anus, bifid scrotum, widely spaced nipples, proptosis of eyelids, pre-auricular tag, absent external auditory canals, bifid uvula, supernumerary teeth and gingival hypertrophy. This is evidence of genetic heterogeneity.

REFERENCE

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Saethre–Chotzen syndrome (MIM 101400)

First recognized by Saethre in 1931 [1] and by Chotzen in 1932 [2], this syndrome is characterized by a broad and variable pattern of malformations, including craniosynostosis, low-set frontal hairline, facial asymmetry, ptosis, deviated nasal septum, brachydactyly, partial cutaneous syndactyly, especially of the second and third fingers, and various skeletal anomalies.

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Beare–Stevenson cutis gyrata syndrome (MIM 123790) [1]

Beare–Stevenson cutis gyrata syndrome is characterized by the furrowed skin disorder of cutis gyrata, acanthosis nigricans, craniosynostosis, craniofacial dysmorphism, digital anomalies, umbilical and anogenital abnormalities and early death.

REFERENCE

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Shprintzen–Goldberg syndrome (MIM 182212)

SYN. MARFANOID FEATURES AND CRANIOSYNOSTOSIS

This syndrome comprises a marfanoid phenotype with craniosynostosis. Associated features include scaphocephaly, facial dysmorphism, arachnodactyly, inguinal and umbilical hernias, and mental retardation [1]. Similar patients with normal mental development have been described [2,3]. Another patient had arachnodactyly, camptodactyly, clover-leaf skull, microcephaly, hydrocephaly, hypoplasia of the corpus callosum and choanal atresia/stenosis [4].

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Curry Jones syndrome (MIM 601707) [1]

Five children were described with a striking asymmetrical facial appearance, craniosynostosis, pre-axial polysyndactyly, agenesis of the corpus callosum and unusual skin with streaky areas of atrophy. The gut and mucous membranes were involved in two of the patients.

REFERENCE

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Craniosynostosis and porokeratosis (MIM 603116)

A child with craniosynostosis and porokeratosis has been described [1]. In addition, he had hypospadias, anterior position of the rectum and incurving of the fourth toe bilaterally. Since the publication of the case report, a similarly affected sibling has been born, with the implication that this is a 'new' syndrome.

REFERENCE

1 Judge MR, Michaels M, Sams VR *et al.* Disseminated porokeratosis in an infant with craniosynostosis. *Br J Dermatol* 1990; **123**: 249–54.

Cranio-ectodermal dysplasia (MIM 218330)

SYN. SENSENBRENNER SYNDROME

Sensenbrenner *et al.* [1] described an autosomal recessive syndrome of dolichocephaly, frontal bossing and antimongoloid palpebral fissures, hypertelorism, rounded cheeks and inverted lower lip, the teeth being grey, small and widely spaced, and the hair short and fine. The clinical features and neurosurgical management of a 9-month-old girl have been reported [2]. There have been other reports of craniosynostosis associated with different hair and bone abnormalities [3] and with short thin hair, dental abnormalities and short limbs [4].

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SCARF (skeletal abnormalities, cutis laxa, craniostenosis, ambiguous genitalia, retardation, facial abnormalities) syndrome (MIM 312830)

Koppe *et al.* [1] reported two male maternal first cousins with a previously unreported pattern of malformations, including lax skin, joint hyperextensibility, umbilical and inguinal herniae, craniosynostosis, pectus carinatum, several abnormally shaped vertebrae, enamel hypoplasia and hypocalcification of the teeth, facial abnormalities and wide webbed neck, ambiguous genitalia, multiple nodular liver tumours, and mild psychomotor retardation. The possibility of X-linked recessive inheritance was proposed.

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Sakati syndrome (MIM 101120)

Sakati *et al.* [1] described a syndrome consisting of acrocephalopolysyndactyly, short limbs, congenital heart defect, ear anomalies and skin defects. The ears were dysplastic and low set. A unilateral ear tag was noted. Patches of alopecia with atrophic skin were present above the ears. Linear scar-like lesions were observed in the submental area. The palate was narrow and arched, the neck short, the hairline low and the genitalia small.

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Cornelia de Lange syndrome (MIM 122470)

SYN. TYPUS AMSTELODAMENSIS; AMSTERDAM DWARF

Aetiology. This syndrome was originally described in 1933 by Cornelia de Lange [1]. The cause is unknown. Most cases are sporadic, and it is difficult to reconcile the pedigrees of the occasional familial cases [2] with a pattern of inheritance, although it is probably autosomal dominant. Some features of the syndrome have occurred

in relatives [3,4]. Cornelia de Lange syndrome has been described in twins [5]. There is a high incidence of chromosomal abnormalities, although these are not consistent [6]. The dup(3q) syndrome simulates Cornelia de Lange syndrome but is probably fundamentally distinct [7,8].

Clinical features [2,6,9–14]. The child is underweight at birth and short stature becomes increasingly evident. Respiratory and feeding difficulties are frequent in infancy and the cry is feeble, low-pitched and growling. Mental retardation is usual, and is often severe.

The face is distinctive—grim, mask-like and expressionless—with a long upper lip and small nose with depressed bridge and anteverted nostrils. The eyebrows are bushy and confluent, and the eyelashes long and delicate. The lips are thin and the angles of the mouth turn down towards a receding chin. The teeth are widely spaced. The head, hands and feet are small, and a variety of skeletal anomalies may be present, usually of the upper limbs, including webbing and hyperextensibility of the digits. A distinctive radiological abnormality is a short, broad first metacarpal [15].

The hairline is low on the neck and forehead and there is hypertrichosis, which may be prominent on the forehead, the sides of the face, the back and shoulders and the extremities [16]. Marbling of the skin is conspicuous and persistent, and the skin around the eyes and nose may show a bluish tinge.

The nipples and the genitalia are sometimes hypoplastic.

The expectation of life is generally poor and most patients die in infancy or childhood, often from infections to which they are susceptible. However, some mildly affected individuals have shown relatively normal development [12].

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Facio-digito-genital syndrome (MIM 305400 and 100050) [1–3]

SYN. AARSKOG SYNDROME

The inheritance is X-linked recessive. There are no pathognomonic features, but the condition is characterized by short stature and abnormalities of the face, digits and genitalia.

The facial changes include anteverted nostrils, a long philtrum, broad nasal bridge, hypertelorism and a 'widow's peak'. Various defects in the eyes and ears have been reported. The hands are short and broad, often with syndactyly and a simian line. There is a characteristic scrotal fold that extends dorsally to surround the base of the penis (the 'scrotal shawl'). Cryptorchidism and inguinal hernia also occur. Many patients also have skeletal defects and learning difficulties.

Positional methods have been used to clone the gene that is mutant in Aarskog syndrome. Pasteris *et al.* [3] isolated yeast artificial chromosome (YAC) clones spanning the t(X;8) break-point associated with the disorder. The *FGDY* gene contains more than 19 exons spanning 100 kb. The predicted length of the FGDY protein is 961 amino acids: it has strong homology to Ras-like Rho/Rac guanine nucleotide exchange factors and contains a cysteine-rich zinc finger-like region and two potential SH3-binding sites. Mutations in *FGDY* may result in perturbed signal transduction and, consequently, developmental growth anomalies.

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Dubowitz syndrome (MIM 223370) [1,2]

This is an autosomal recessive condition in which there is low birth weight, slow growth, microcephaly, mental retardation and characteristic facies, with sparse hair, high sloping forehead, broad nasal bridge, ptosis, epicanthic folds and micrognathia. The voice is high pitched and hoarse. Eczema, vomiting and diarrhoea may occur.

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Rubinstein–Taybi syndrome (MIM 180849) [1–3]

SYN. BROAD THUMB–HALLUX SYNDROME

Aetiology. Rubinstein–Taybi syndrome is due to a deletion at chromosome 16p13.3 [4–7], restricted to a region that contains the gene for the human CREB-binding protein (CBP), a nuclear protein that participates as a co-activator in cyclic AMP-regulated gene expression [8]. The occurrence of some features of the syndrome in relatives of patients has been interpreted as suggesting autosomal recessive inheritance. The majority of cases have been sporadic, although it has been reported in monozygotic twins [9,10]. Gillies and Roussounis [11] reported two families: in one, two siblings were affected; in the other, the uncle of the index case was affected and other members of the family were judged to show varying degrees of expression of the disorder.

Clinical features. The essential features of this complex and variable developmental syndrome are mental deficiency, small head, retarded somatic growth, broad thumbs and great toes, antimongoloid palpebral fissures, a high narrow palate and crowded irregular teeth [12]. The nose is often beaked and the ears may be malformed and low set.

A capillary naevus of the forehead or nape has been noted in over 50% of cases, and about the same proportion are said to develop hypertrichosis, especially of the back. The eyebrows may be heavy and highly arched, and the eyelashes long. Dermatoglyphic abnormalities are common. Patients with Rubinstein–Taybi syndrome seem to be prone to develop keloids [13–15]. There have been individual case reports of Rubinstein–Taybi syndrome associated with multiple pilomatricomas [16] and piebaldism [17].

Approximately one-third of cases have cardiac defects and the use of neuromuscular blocking agents such as succinylcholine during anaesthesia can provoke cardiac arrhythmias [18].

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Marinesco–Sjögren syndrome (MIM 248800) [1,2]

Aetiology. The inheritance of this rare syndrome is determined by an autosomal recessive gene that has recently been shown to be allelic with the congenital cataracts–facial dysmorphism–neuropathy (CCFDN) syndrome. These disorders are caused by mutation in an as yet unidentified gene at 18qter [3].

Pathology. Degenerative changes occur in the central nervous system and are most severe in the cortex of the cerebellum [4,5]. There may also be involvement of the peripheral nervous system [6] and a myopathy [7,8]. Microscopy of the hair shows distinctive features [9]. The shafts show fractures, trichoschisis and points of impending fracture. In polarized light, irregular birefringence is seen. The internal root sheath fails to keratinize fully, and alkaline phosphatase activity persists above the normal level.

Clinical features [4,5,10,11]. Cerebellar ataxia is apparent as soon as the child begins to walk, and is associated with rotary and horizontal nystagmus and with dysarthria. Mental and physical development are retarded. Congenital cataracts and a variety of skeletal defects are commonly present. The teeth are malformed and the lateral

incisors may be absent. The nails are thin and fragile. The hair is sparse, fine, short, fair and brittle.

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Seckel's syndrome (MIM 210600)

Definition and aetiology. The syndrome, defined but not first described by Seckel [1], is one of several to which the term 'bird-headed dwarfism' has been applied [2]. Its inheritance appears to be determined by an autosomal recessive gene. A distinct form of this syndrome [3] has been provisionally named the Montreal type. At least one form of Seckel's syndrome (SCKL1) can be caused by mutation in the gene encoding ataxia-telangiectasia and Rad3-related protein, which maps to chromosome 3q22.1–q24. Another locus for Seckel's syndrome has been mapped to chromosome 18p11–q11 [4].

Clinical features [2,5,6]. The constant features are growth retardation, microcephaly, mental deficiency, and a prominent beak-like nose dominating an otherwise hypoplastic face with large eyes. Skeletal defects are frequent [7,8]. The hair may be sparse and prematurely grey. The brain shows a grossly simplified cerebral structure.

Pigmentary changes, including streaks of brown pigmentation on the neck, groin and axillae, have been reported in a patient with Seckel's syndrome. Histological examination revealed pigment incontinence [9].

In the Montreal type [3], additional features include wrinkled and redundant skin of the palms, ptosis and cryptorchidism.

Diagnosis. The syndrome must be differentiated from others in which there is intrauterine dwarfism. Molecular genetic studies can be offered to families with known mutations in the *SCKL1* gene.

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Russell–Silver syndrome (MIM 180860) [1–9]

This syndrome is a distinct form of intrauterine growth retardation associated with asymmetry. Over 150 cases have been reported; most are sporadic, although several familial cases have been described with the suggestion of heterogeneity [8]. Various chromosomal abnormalities have been found, with approximately 10% of cases showing maternal uniparental disomy for chromosome 7 [9].

The essential features are low birth weight at term, a relatively large head, shortness of stature, significant asymmetry, and elevated urinary gonadotrophins giving rise to premature sexual development [7]. Inconstant features are café-au-lait spots and other pigmentary changes, short incurved fifth fingers, syndactylism of the toes and a triangular face with down-turned corners of the mouth. The features are less marked in adult life.

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Beckwith–Wiedemann syndrome (MIM 130650) [1–4]

SYN. EMG SYNDROME (EXOMPHALOS–MACROGLOSSIA–GIGANTISM)

This is a rare familial disorder, although most cases are sporadic and the aetiology is unknown. Inheritance is thought to be autosomal dominant with incomplete penetrance. Chromosome abnormalities have been reported, in particular relating to chromosome 11 [4]. It has been suggested that a placental endocrine defect may produce visceromegaly, which leads to various other complications.

The characteristic cutaneous changes are ear-lobe grooves and circular depressions on the rims of the helices, but the full syndrome includes macroglossia, omphalocele (umbilical hernia), visceromegaly (liver, spleen, pancreas, kidney, etc.), anomalies of intestinal rotation, neonatal hypoglycaemia, somatic gigantism, microcephaly and facial naevus flammeus. Many other metabolic and anatomical abnormalities have also been recorded, including immunodeficiency and a zosteriform rash at birth.

The hypoglycaemia, which is severe and resists simple therapy, is due to excessive insulin production by the enlarged pancreas. In some cases, pancreatectomy may be necessary to save the baby.

Children with this syndrome have an increased risk of developing hepatoblastoma, rhabdomyosarcoma and Wilms' tumour.

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Cartilage–hair hypoplasia (MIM 250250)

SYN. METAPHYSEAL CHONDRODYSPLASIA OF MCKUSICK

This syndrome was first identified in the inbred Old Order Amish communities of the USA, among whom it occurs in around 1 in 700 live births; it is determined by an autosomal recessive gene [1]. The syndrome is not confined to these communities and its prevalence is high in Finland [2].

A high degree of dwarfism is associated with multiple skeletal deformities resulting from metaphyseal dysostosis. Sexual development is normal.

The hair is sparse, short, of very fine calibre and lighter in colour than in unaffected siblings, and is often very brittle [2–4]. Some affected individuals are almost bald. The filamentous and matrix proteins of the hair have no gross structural defects; decreased reactivity of some disulphide bonds may account for its abnormal biophysical and biochemical properties [3,5].

All patients show immunological defects, although only a proportion of them have increased susceptibility to infections. They have a decreased number of circulating T and B lymphocytes, although the immunoglobulin levels are essentially normal [2,6]. T-cell function is depressed, and studies of continuous T-cell lines have shown impaired interleukin-2 production and utilization, suggesting the presence of a G1-phase defect in the activation of T cells [7]. There is, however, preservation of spontaneous natural killer cell activity, and as not every patient suffers recurrent infections, this disease offers a unique model for studying the *in vivo* requirements for normal immunocompetence [8]. Using a positional cloning strategy and mutational analysis, Ridanpaa *et al*. [9] showed that mutations in the *RMRP* gene are responsible for this syndrome. Mitochondrial RNA-processing endoribonuclease cleaves mitochondrial RNA complementary to the light chain of the displacement loop at a unique site. The enzyme is a ribonucleoprotein whose RNA component is a nuclear gene product. The RNA component is the first RNA encoded by a single-copy gene in the nucleus and imported into mitochondria. The *RMRP* gene is untranslated, i.e. it encodes an RNA not a protein.

There are at least three other conditions in which metaphyseal chondrodysplasia occurs in association with immunodeficiency, but the hair is normal in these [6].

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Popliteal pterygium syndrome (MIM 119500)

SYN. CLEFT LIP/PALATE; MUCOUS CYSTS OF THE LOWER LIP; POPLITEAL PTERYGIUM; DIGITAL AND GENITAL ANOMALIES

The first case was described by Trelot [1], but it was not until 1968 that Gorlin *et al.* [2] suggested the name 'popliteal pterygium syndrome'. Features of the syndrome include [3–5] popliteal pterygium (usually bilateral), intercrural pterygium, hypoplasia or agenesis of digits, valgus or varus deformities of the feet, syndactyly, cryptorchidism, absent or cleft scrotum, inguinal hernia, hypoplasia or aplasia of the labia majora, cleft lip and/or palate, lower lip pits, congenital bands of mucous membranes between the jaws, and filiform adhesions of the eyelids. Cunningham *et al.* [4] have reviewed the urological manifestations. The syndrome is inherited as an autosomal dominant trait and is known to show interfamilial and intrafamilial variable expressivity [5–7]. There is possibly an autosomal recessive form with more severe manifestations [8].

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Van der Woude syndrome (MIM 119300) [1]

SYN. CLEFT LIP/PALATE WITH MUCOUS CYSTS OF THE LOWER LIP

This is an autosomal dominant condition in which there are lower lip pits, cleft lip and/or palate and hypodontia [2]. The penetrance is close to 100%, with variable expression [3,4]. Bocian and Walker [5] described a patient with congenital lower lip pits, who had an interstitial deletion of chromosome 1q. Wienker *et al.* [6] excluded linkage to a number of marker loci. Janku *et al.* [3] traced the syndrome through seven generations. Lip pits, the most common manifestation, were present in 88% of the affected cases and were the only manifestation in 64%. The pits, which vary from mere depressions to deep channels, may secrete small quantities of viscous saliva. Cleft lip/palate occurred in 21%. Other developmental defects, for example syndactyly, are sometimes associated. The recognition of lip pits, or a family history of lip pits, is important for genetic counselling [7].

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Beals–Hecht syndrome (MIM 121050) [1–3]

SYN. CONTRACTURAL ARACHNODACTYLY

This condition, inherited as an autosomal dominant with variable expressivity, is characterized by tall stature, arachnodactyly and multiple congenital joint contractures of the fingers, knees, hips, elbows and ankles. The contractures tend to improve by adulthood. The ears are almost always 'crumpled'. Kyphoscoliosis is an inconstant feature. The condition must be distinguished from Marfan's syndrome (see Chapter 46) and from arthro-ophthalmopathy (Stickler's syndrome) [4].

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Deafness and ear pits (MIM 125100) [1,2]

A dominantly inherited condition in which pre-auricular pits are associated with congenital deafness. The pinna may be normal or deformed, but there is a small pit anterior to the helix that frequently becomes infected and discharges. Injection of a radio-opaque dye may show that the pit communicates with the middle ear. The pits are bilateral and may be multiple.

In some cases, there may also be branchial cysts or cervical fistulae, and fleshy pre-auricular appendages also occur.

Repeated infections of the ear pit may be an indication for surgical excision, but it is important to ensure that the pit does not communicate with the middle ear or a deep sinus tract may ensue.

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Dowling–Degos disease (MIN 179850) [1,2]

SYN. RETICULAR PIGMENTED ANOMALY OF THE FLEXURES

This rare condition is inherited via an autosomal dominant gene [3,4]. It usually presents in adult life (most frequently in the fourth decade) as numerous, small, round pigmented macules that resemble freckles. The axillae and groins are the usual sites, although other areas may be involved, including the intergluteal and inframammary folds, neck, scalp, trunk and arms [5]. Involvement of the genitalia, particularly pigmented lesions of the vulva, has been described [6]. Pigmentation is symmetrical and progressive, but is otherwise asymptomatic. The degree of pigmentation varies, but in some patients the lesions are almost confluent, giving a brown or black lace-like pattern.

Other features that may be present include scattered comedo-like lesions (dark dot follicles) and pitted acneiform scars near the angles of the mouth. One report described Dowling–Degos disease mimicking chloracne [7]. Dowling–Degos disease may be associated with hidradenitis suppurativa [8,9]. Occasional cases have been reported with mental retardation or trichilemmal cysts [10].

The histology is diagnostic, with a distinctive form of acanthosis, characterized by an irregular elongation of thin branching rete ridges, with a concentration of melanin at the tips. The condition involves the follicular infundibulum, and in some cases there is follicular plugging. The melanocyte count is normal [11].

These clinical and histological changes were memorably summarized by Wilson-Jones and Grice [12] as 'demonstrating dusky dappled disfigurements and dark dot depressions, and disclosing digitate downgrowths delving dermally'.

The histology distinguishes the disease from conditions such as acanthosis nigricans, multiple basal cell papillomas, epidermal naevi and the axillary freckles of neurofibromatosis.

It has been suggested that the Dowling–Degos disease as described above may be only one part of a spectrum of conditions that are characterized clinically by variable degrees of reticulate pigmentation, follicular plugging, pitted scars and facial erythema, and histologically by digitate budding and proliferation of the epidermis and follicular walls [10]. This would include some autosomal dominant conditions previously reported under different titles, such as Kitamura's acropigmentatio reticularis [13–18] and Haber's syndrome [19,20]. The latter is characterized by a rosacea-like eruption with keratotic plaques and pitted scars [21].

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Chronic, infantile, neurological, cutaneous, articular (CINCA) syndrome (MIM 607115)

This syndrome was originally described by Ansell *et al.* in 1975 [1], and later termed CINCA syndrome by Prieur *et al.* [2]. It is characterized by a progressive arthropathy,

an urticarial rash usually present from birth, uveitis and mental retardation. Central nervous system involvement and deafness occur, although not necessarily apparent at presentation. Other features include short stature, delayed fontanelle closure, frontal bossing and a broad nasal bridge. Radiological findings are epiphyseal abnormalities, periosteal elevation along the shafts of the long bones and early patella ossification.

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Dermo-chondro-corneal dystrophy (MIM 221800)

SYN. FRANÇOIS' SYNDROME

In 1949, François [1] described a brother and sister with the following features: firm nodular skin lesions on the dorsa of the hands and on the nose and ears; osteochondrodystrophy of the bones of the hands and feet, resulting in limitation of movement; and corneal dystrophy with white or brownish opacities. Since then, there have been other case reports [2–5], suggesting autosomal recessive inheritance.

A non-familial case of dermo-chondro-corneal dystrophy was reported in a 45-year-old woman who had severe involvement of the gingival and palatal mucous membranes [6]. Histology of an early skin lesion showed spongiocytes (large fibroblastoid cells), and in older skin nodules there was compact fibrous tissue with few cells and scarce vascularization. The authors proposed that this disorder was related to an abnormality of fibroblasts, with hyperproduction of type III collagen.

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Oto-palato-digital syndrome (MIM 304120 and 311300)

Dudding *et al*. [1] first described this as a new syndrome, although the case reported by Taybi [2] probably had the same condition. It comprises short stature, distinctive facial appearance, cleft palate, hearing loss, and multiple skeletal abnormalities including short thumbs and short big toes. Wide spacing of the toes creates a resemblance to the foot of a tree frog. Inheritance is thought to be X-linked.

Fitch *et al*. [3] reported an infant with oral, cranial, facial and limb abnormalities in 1976. They presented a follow-up of their original patient in 1983 [4] and pointed out similarities to the oto-palato-digital (OPD) syndrome; they proposed that this be called OPD-II syndrome.

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Congenital scalp defects with distal limb anomalies (MIM 100300)

SYN. ADAMS–OLIVER SYNDROME

There have been a number of reports [1–4] linking congenital scalp defects, often involving the underlying bone, with limb malformations ranging from hypoplasia of the fingers and toes to absence of the lower extremities below the knees. The inheritance pattern is unclear but is probably autosomal dominant with variable expression.

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Acromial dimples (MIM 102350)

Dimples overlying the acromial process of the scapula have been observed in families, consistent with autosomal dominant inheritance [1–3].

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Cleft palate–lateral synechia syndrome (MIM 119550)

Fuhrmann *et al.* [1] described a new syndrome of cleft palate combined with multiple cord-like adhesions between the free borders of the palate and lateral parts of the tongue and floor of the mouth. Gassner *et al.* [2] reported the disorder in a mother and child.

REFERENCES

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Cardio-acro-facial syndrome (MIM 122850)

SYN. RABENHORST'S SYNDROME

Grosse [1] described a syndrome comprising ventricular septal defect and pulmonary stenosis, narrow face with micrognathia, high and narrow nose with prominent septum, microstomia, attached earlobes and minor malformations of the hands and feet.

REFERENCE

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Flynn–Aird syndrome (MIM 136300)

In 10 members of five generations of a family, Flynn and Aird [1] observed a neuroectodermal syndrome with similarities to the syndromes of Werner, Refsum and Cockayne. Clinical features included skin atrophy, ulceration, alopecia and dental caries.

REFERENCE

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Lacrimo-auriculo-dento-digital (LADD) syndrome (MIM 149730)

Hollister *et al.* [1] described a syndrome affecting a Mexican man and five of his eight children, the features of which were nasolacrimal duct obstruction, hypoplasia or aplasia of the lacrimal puncta, cup-shaped ears, hearing loss, hypodontia with enamel dysplasia, and various digital malformations.

REFERENCE

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Laryngo-onycho-cutaneous syndrome (MIM 245660) [1–3]

SYN. SHABBIR'S SYNDROME; LOGIC SYNDROME

Laryngo-onycho-cutaneous syndrome is an epithelial disorder confined to the Punjabi Muslim population. Shabbir *et al.* [1] described 22 patients from 12 families in Pakistan. The features included hoarseness, nail dystrophy and chronic skin ulceration, especially on the face. Inheritance is autosomal recessive. Similarity to junctional epidermolysis bullosa has been previously noted [3]. More recently, the gene has been localized to 18q11.2, the laminin α3 gene (*LAMA3*), in which loss-of-expression mutations cause the lethal skin blistering disorder Herlitz junctional epidermolysis bullosa. In laryngo-onycho-cutaneous syndrome there is N-terminal deletion of laminin α3a, confirmed by immunoprecipitation of secreted proteins from keratinocytes [4].

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FG syndrome (MIM 305450)

The FG syndrome is an X-linked recessive syndrome comprising a number of congenital anomalies and mental retardation, first described by Opitz and Kaveggia [1]. The major features are mental retardation, mild facial dysmorphism, 'cowlicks' of the hairline, congenital hypotonia, relative macrocephaly and constipation [2]. Elia *et al.* [3] reported a boy with FG syndrome, who also had gingival hyperplasia and keloids.

REFERENCES

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Future directions

Every attempt has been made to provide an up-to-date overview of progress in the field of clinical and molecular genetics relevant to contemporary dermatological practice. However, no other field of medicine is changing more

rapidly than our understanding of the genetic basis of human diseases. The interested reader is strongly encouraged to consult the online information sources described, as these sites are continually updated.

It is also clear that significant ethical issues have emerged through such progress and great care will need to be taken to ensure that fundamental principles of privacy and confidentiality are maintained in the provision of excellence in medical care, particularly when issues relate not only to the individual seeking advice and treatment but also in relation to the extended family. It is also evident that prospects for improvement in therapeutic options for the amelioration of these disorders has never been greater.

Chapter 13

Prenatal Diagnosis of Genetic Skin Disease

R.A.J. Eady & J.A. McGrath

Introduction

Recent developments in clinical and molecular genetics and in fetal medicine have had an important role in the diagnosis, management and prevention of hereditary diseases and congenital abnormalities. Congenital malformations, single-gene defects and chromosomal abnormalities are increasing in their relative importance as causes of infant mortality and morbidity. In the USA, each year, 3–5% of more than 3 million live-born infants are affected by congenital defects or hereditary disease, and approximately 20% of all infant deaths today are the result of such disorders [1]. A total estimate of single-gene disorders could be between 1.3 and 1.7%, whereas chromosomal abnormalities with imbalance affect at least 0.5% of infants [2]. Such figures do not account for 'wastage' or the loss, by spontaneous abortion, of embryos and fetuses affected by developmental abnormalities. The impact of birth defects on society at large is thus very great, not least as a financial burden. Equally important is the effect on individual sufferers and families at risk of genetic disease.

Today, any couple planning to have a child cannot afford to ignore these new advances [3]. Prenatal diagnosis with appropriate counselling should be an integral part of the management of individuals or couples at risk of having children with a congenital or genetic disorder. Access to genetic counsellors is important for anyone seeking information about these risks, and the available options after the risk has been determined.

The purpose of prenatal diagnosis is the detection or exclusion of a hereditary disease or congenital defect *in utero*. The option of an elective abortion of affected pregnancies can help parents at risk of having affected children to produce normal offspring. A consequence of early prenatal diagnosis is that many pregnancies can proceed to term with the delivery of a normal child, instead of being terminated on the basis of a high risk.

The prenatal diagnosis of several genodermatoses is now well established. Over the past 20 years the techniques used have changed from being heavily reliant on the analysis of fetal skin biopsy samples acquired during the second half of the mid-trimester, to the examination of DNA from first-trimester chorionic villus samples [4]. Preimplantation genetic diagnosis is a further option that has more recently been introduced [5].

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Methods in prenatal diagnosis

Previously, the techniques were largely limited to the detection of morphological or immunohistochemical abnormalities in fetal skin biopsies [1,2]. In addition, amniotic fluid and its cells may be used for diagnosing a variety of metabolic diseases with skin involvement. Fetal skin cells may also be used in the prenatal diagnosis of conditions that do not usually concern dermatologists. The biochemical analysis of skin-derived amniotic fluid

cells is discussed below. Fetal skin is also a potentially valuable source of fibroblasts, endothelial cells and Schwann cells.

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Amniocentesis

Usually performed at about 16 weeks' gestation, amniocentesis is a convenient and relatively safe method of obtaining amniotic fluid and its cells for morphological, cytogenetic, biochemical or molecular (DNA) analysis. Amniotic fluid cells are derived from fetal epidermis, alimentary and genitourinary mucosa, and amnion. Gosden *et al*. [1] recognized at least 10 different types of amniotic fluid cell from normal fetuses. The proportion of viable cells derived from fetal epidermis is undetermined and may be no more than 10%. Examples of diseases that can be diagnosed *in utero* using amniotic fluid or cells include those exhibiting abnormalities of DNA synthesis and repair, usually in response to ultraviolet (UV) radiation (Table 13.1) [2–10], and inherited metabolic disorders, of which more than 100 have been diagnosed prenatally [11]. The demonstration of the primary protein defect in cultured amniotic fluid cells has the advantage of great reliability, but the disadvantage of a rather long waiting period for the parents, because the cultivation of sufficient fetal cells usually takes about 2–3 weeks [12].

Forming a major group in this second category are the storage diseases associated with a specific enzyme abnormality, such as Fabry's disease [13] or Farber's disease [14]. Other metabolic disorders that can be detected or excluded in the fetus include congenital erythropoietic porphyria [15], acute intermittent porphyria [16], X-linked ichthyosis [17] and Menkes' disease [18]. Raised maternal serum and amniotic fluid concentrations of α-fetoprotein have been reported in association with fetuses affected with epidermolysis bullosa (EB) simplex [19], or with EB and pyloric atresia [20].

Direct biochemical assays of chorionic villus samples obtained during the first trimester (see below) are feasible for nearly all enzyme defects that would otherwise be studied using amniotic fluid cells. In some cases, cultivation of chorionic villus cells is mandatory, otherwise direct examination is possible [12]. The prenatal diagnosis of Sjögren–Larsson syndrome has been based on the identification of a deficiency of the enzymes fatty aldehyde dehydrogenase and fatty alcohol oxidoreductase in cultured amniotic fluid cells or chorionic villus cells [21].

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Table 13.1 Diseases exhibiting abnormalities of DNA or RNA synthesis or repair, or chromosomal instability.

Disease	Demonstrable abnormality
Bloom's syndrome	High numbers of sister chromatid exchanges in AFC [2]
Xeroderma pigmentosum	Abnormal DNA repair in AFC after UVR [3–5]
Cockayne's syndrome	Abnormal DNA repair [5], colony-forming ability [6] or RNA synthesis [7] of AFC in response to UVR
Fanconi's anaemia	Diepoxybutane-induced chromosomal breakage in AFC [8] and cultured trophoblast cells [9]
Ataxia telangiectasia	Clastogenic factor in AF and high spontaneous chromosomal breakage rate with translocation in AFC [10]

AF, amniotic fluid; AFC, amniotic fluid cells; UVR, UV radiation.

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Ultrasonography

With the introduction of equipment capable of high-resolution and real-time operation, the potential information to be gained from ultrasound images of the fetus and other uterine contents is considerable. Ultrasonography is a powerful tool for the detection of central nervous system and skeletal disorders. The structural abnormalities present in a fetus affected with hereditary skin disease are usually microscopic and beyond the resolution of this technique. However, the 'snowflake sign' in the amniotic cavity may be a marker of fetal skin sloughing in certain disorders, including the form of epidermolysis bullosa that is associated with pyloric atresia [1,2] and a rare type of ichthyosis (see below).

Ultrasonography has been used successfully for fetal sexing [3] and in the diagnosis or detection of a variety of disorders including cutis gyrata syndrome [4], osteogenesis imperfecta [5], a thoracic cystic malformation associated with skin oedema [6], a benign facial skin tumour [7], a vascular abnormality [8], Neu–Laxova syndrome [9], Ellis–van Creveld syndrome [10] and harlequin ichthyosis [11]. Ultrasonography also has a key role in monitoring amniocentesis and fetoscopy, and is now largely used on its own (without fetoscopy) for fetal tissue sampling, including fetal skin biopsy.

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Fetoscopy

This technique involves the insertion of a fibreoptic endoscope into the pregnant uterus (Fig. 13.1), using sedation and local anaesthesia, normally at 16–20 weeks' gestation. The main indications for fetoscopy are to enable direct visualization of the uterine contents, fetal blood sampling (usually from the umbilical cord) and tissue biopsy (e.g. from skin, liver or fetal tumour) [1,2]. Direct inspection has been of special value in identifying defects of facial features, limbs and digits, head and spine, anterior abdominal wall and genitalia, and has been used in prenatal exclusion of Cornelia de Lange syndrome and Goltz's syndrome [1,2]. Fetoscopy has also been used for taking samples of hair from the fetal eyebrow for the diagnosis of trichothiodystrophy [3].

The rate of fetal loss as a result of fetoscopy, in experienced hands, has been estimated at less than 5% [2]. Because other non-invasive methods for fetal imaging, such as high-quality ultrasonography, are constantly improving (see above), fetoscopy now has a more limited use. However, the newer microendoscopes are less invasive than the older, larger instruments, and may be preferred when direct inspection of the uterine contents is still required [4].

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Fetal skin biopsy

This can be performed either with the aid of a fetoscope to visualize the fetus or, as is now becoming more widely practised, by relying solely on high-resolution imaging by modern ultrasound scanners. The samples are literally pinched out of the skin using a fine gauge forceps (Figs 13.1 & 13.2).

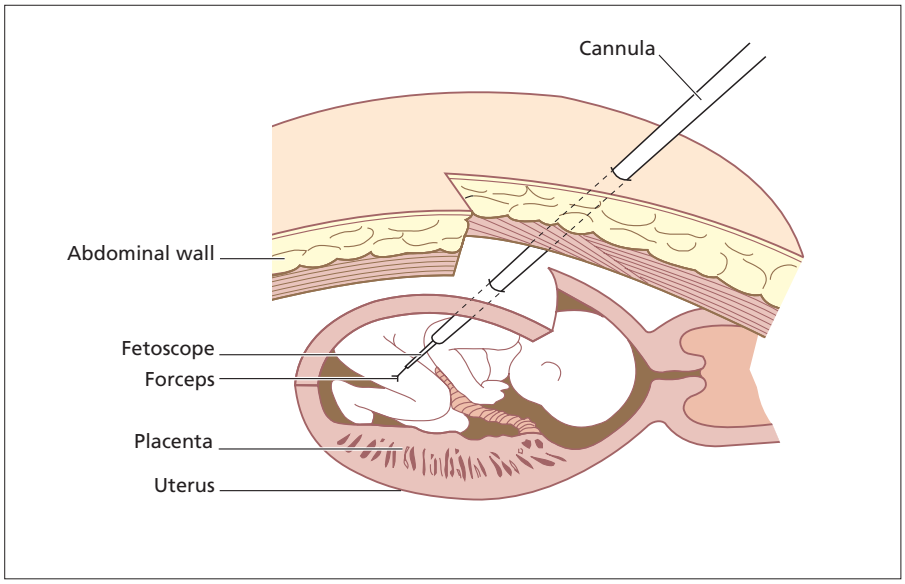

Fig. 13.1 Illustration of fetoscopy and fetal skin biopsy procedure.

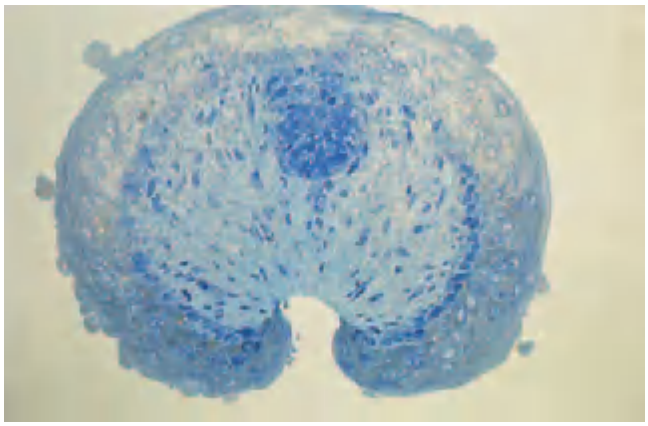

Fig. 13.2 Photomicrograph of semithin section of normal fetoscopic skin sample at 18 weeks' gestation (× 295).

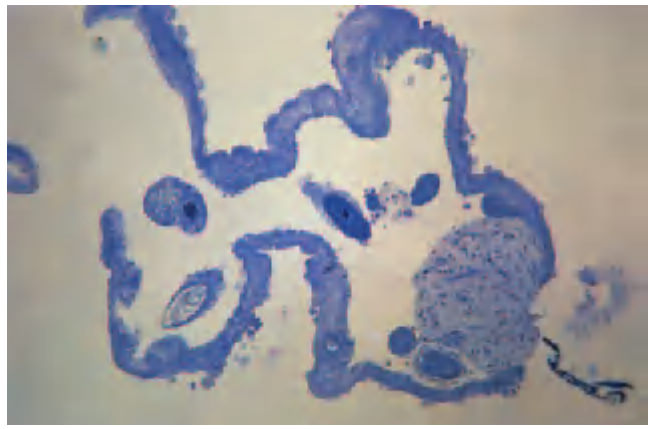

Fig. 13.3 Photomicrograph of fetoscopic skin sample from 18-week fetus affected with recessive dystrophic epidermolysis bullosa. Note extensive dermal–epidermal separation. Subsequent electron microscopy confirmed that the split was beneath the level of the lamina densa. Richardson's stain (× 150).

Light and electron microscopy

Fetal skin biopsy has been used to diagnose a variety of diseases associated with characteristic, if not specific, histological or ultrastructural changes [1–6]. The conditions include EB of the junctional [7] and dystrophic [8] types. The diagnosis is made at 15–18 weeks' gestation by finding a split in the dermal–epidermal junction by light microscopy (Fig. 13.3). The precise level of cleavage should then be determined by electron microscopy. Dermal–epidermal separation occurs in the lamina lucida of the epidermal basement membrane, and is associated with a hemidesmosome abnormality in Herlitz junctional EB (Fig. 13.4) [7], whereas in the dystrophic forms, separation takes place beneath the lamina densa [8]. Prenatal diagnosis of the Dowling–Meara form of EB simplex has also been made by light- and electron-microscopic demonstration of intraepidermal separation associated with clumping of keratin filaments [9].

Bullous congenital ichthyosiform erythroderma (epidermolytic hyperkeratosis) can be diagnosed at 20 weeks' gestation by detection of epidermal vacuolation and abnormal cellular inclusions (Fig. 13.5) [10] or, more specifically, highly characteristic tonofilament clumps in both fetal epidermal and amniotic fluid cells (Figs 13.6 & 13.7) [11,12]. Other types of ichthyosis amenable to this method of prenatal diagnosis include lamellar ichthyosis [13], Sjögren–Larsson syndrome [14] and harlequin ichthyosis [15,16]. For the latter, multiple skin samples are usually taken at 19–22 weeks' gestation from the scalp or other sites bearing hair follicles where the pathognomonic ultrastructural changes can be found (Figs 13.8a,b).

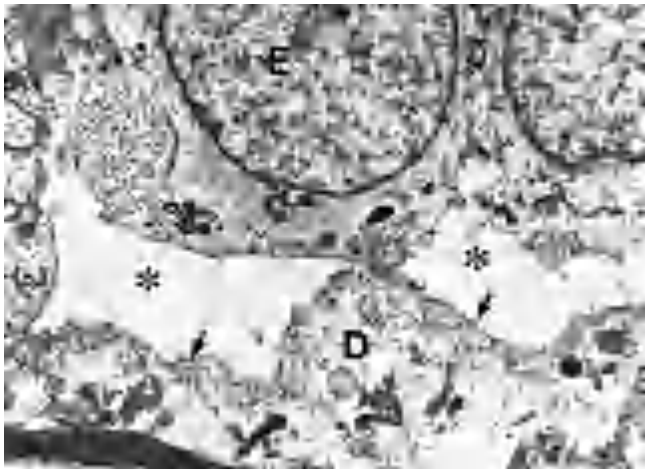

Fig. 13.4 Electron micrograph showing separation at level of lamina lucida (asterisks) between epidermis (E) and dermis (D) in fetal skin affected with junctional epidermolysis bullosa. Arrows indicate lamina densa at base of the split (× 6000).

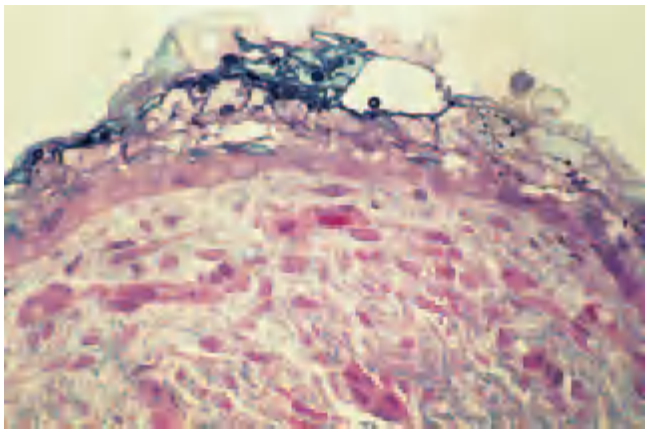

Fig. 13.5 Photomicrograph of semithin section of skin sample from 20-week fetus affected with bullous congenital ichthyosiform erythroderma. Note that severe vacuolation of the intermediate cell layers is present, even before the stratum corneum is formed. Periderm blebs are still evident at the epidermal surface (× 380).

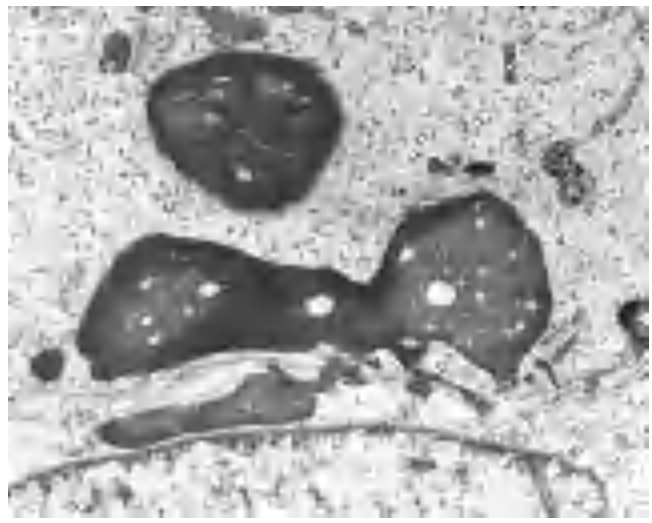

Fig. 13.6 Electron micrograph showing tonofilament clumps within epidermal cells of 20-week fetus affected by bullous congenital ichthyosiform erythroderma (× 17 500).

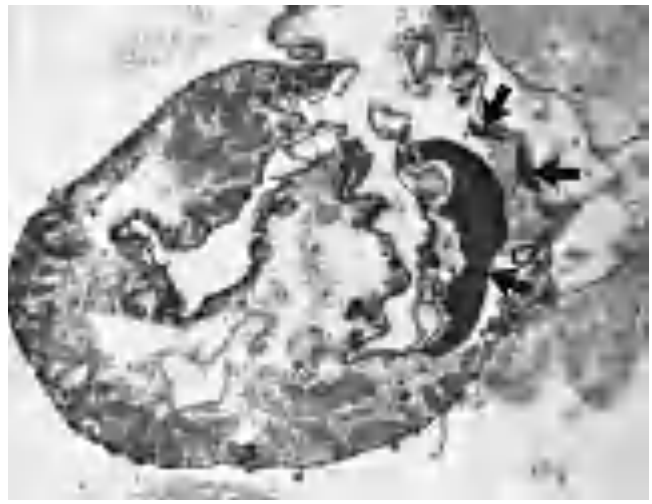

Fig. 13.7 Amniotic fluid cell derived from same fetus whose skin is shown in Figs 13.5 and 13.6, containing characteristic tonofilament clumps (arrows) (× 6720).

Another disorder in this group is a rare autosomal recessive form of ichthyosis in which the newborn is at high risk of asphyxia from aspiration of amniotic fluid with a high content of desquamated skin cells. This little-known skin disorder previously described as 'ichthyosis congenita type IV' [17] is characterized ultrastructurally by stacks of presumably lipid-rich membrane profiles in the cytoplasm of cells of the early keratinizing epidermis of the affected fetus (Fig. 13.9) and in amniotic fluid cells. A 'snowflake' type of appearance in the amniotic cavity may be seen by ultrasonography during the second trimester (D. Griffin, 1998, personal communication).

Ectodermal dysplasia [18] and tyrosinase-negative oculocutaneous albinism [19–21] have also been diagnosed at about 20 weeks' gestation using similar methods.

With rapid processing of the biopsy samples [21], the electron-microscopic findings can be reported within 24–48 h of obtaining the specimen in the laboratory.

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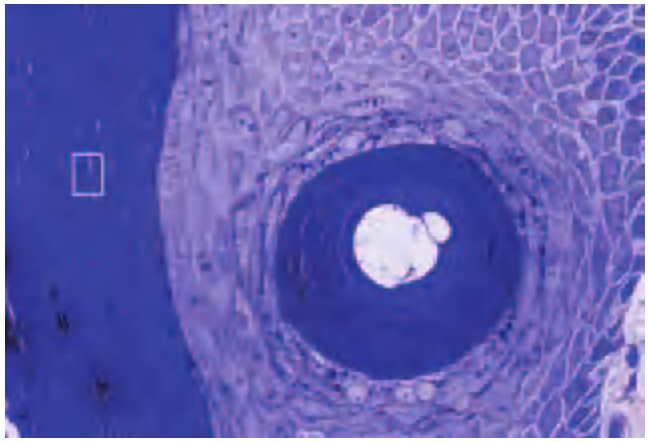
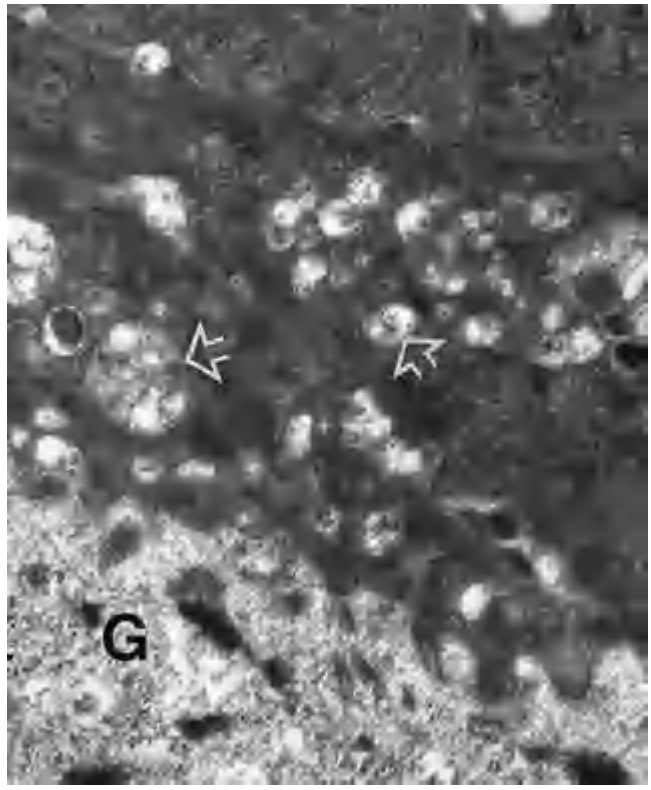
(a)





(b)

Fig. 13.8 Harlequin ichthyosis in a 22-week fetus. (a) Photomicrograph showing hair follicle abnormalities. Note intracellular inclusions (box) in newly cornified cells (× 240). (b) Electron micrograph showing detail of the abnormal inclusions (arrows), which are pathognomonic for this disorder. G, stratum granulosum cell (× 22 400).

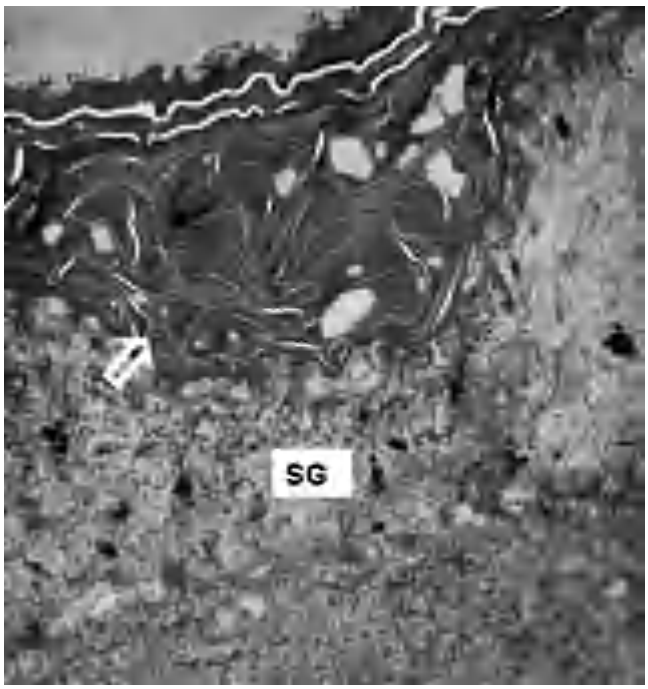


Fig. 13.9 Desquamative ichthyosis. Abnormal membrane structures (arrow) are present in the upper part of the epidermis, including the stratum granulosum (SG).

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Antibody probes [1]

A group of monoclonal antibodies reacting with components of the normal basement membrane zone has been invaluable, not only in the search for candidate genes and proteins in EB but also for diagnosis and prenatal diagnosis, especially when used with immunofluorescence microscopy (see Chapter 40). LH7.2 monoclonal antibody, which binds to the amino terminus of the type VII collagen molecule [2], has been used for the rapid prenatal diagnosis of recessive dystrophic EB (Hallopeau–Siemens) using indirect immunofluorescence microscopic analysis of skin samples from an 18-week fetus at risk for the disease [3] (Fig. 13.10). Using similar methods, a number of other monoclonal antibody probes may also be applied to EB diagnosis. These include GB3 (anti-laminin 5) and 19-DEJ-1 (anti-uncein) for the Herlitz form of junctional EB [4,5], anti-α6 and β4 integrin antibodies for the form of junctional EB associated with pyloric atresia [6,7], anti-bullous pemphigoid antigen 180 (BP180 or collagen XVII) for non-Herlitz junctional EB (generalized atrophic benign EB) [8] and anti-plectin for EB simplex associated with muscular dystrophy [9].

When fetal skin samples are being examined with these monoclonal antibodies, further sections from the same biopsies should be incubated with an anti-type IV collagen antibody to establish that the epidermal basement membrane is present and intact. This procedure may also be used for antigen mapping, to determine the level of splitting in the dermal–epidermal junction (see Chapter 40).

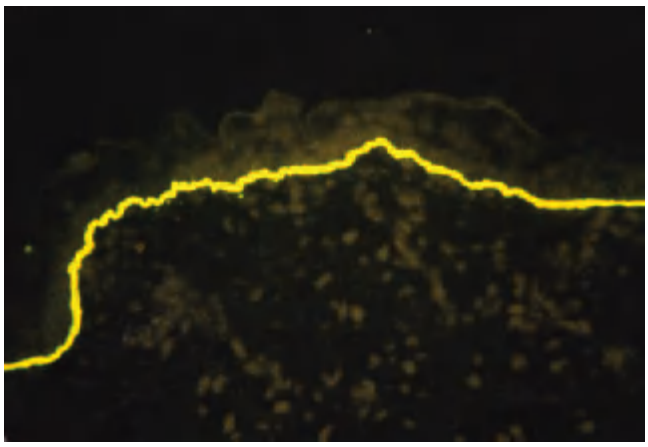

Fig. 13.10 Immunofluorescence photomicrograph of fetal skin at 15 weeks' gestation showing bright linear staining at the epidermal basement membrane using LH7.2 monoclonal antibody, which is directed against the amino-terminus of type VII collagen (× 264). Skin affected with severe recessive (Hallopeau–Siemens) dystrophic epidermolysis bullosa shows an absence of staining with this antibody.

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Complications of fetal skin biopsy

Sampling error, inadequacy of samples for analysis, and difficulty in interpreting the morphological and immunohistochemical features can pose problems, according to the experience of the obstetrician and microscopist. Artefact caused by the biopsy procedure, and by processing the very small fetal skin samples, can be severe or mimic true pathology [1]. In one series of 83 pregnancies examined for a variety of genetic skin disorders, there were no sampling failures or incorrect diagnoses [2]. Complications such as sepsis or fetal death could not be directly related to the procedure, although these risks must be considered. Scarring has been reported [3], but it is rarely severe. Often, the biopsy sites are inconspicuous in healthy infants born at term, after a negative prenatal diagnosis. The rate of fetal loss may be no more than 1% over the background incidence of spontaneous abortions [4].

In summary, in experienced centres, fetal skin biopsy for the prenatal diagnosis of EB in particular, has enjoyed

an excellent track record, with a high degree of sensitivity and specificity of the analytical techniques used. However, the procedure is invasive, which will always be a concern to both the medical team and the patient.

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Current indications for fetal skin biopsy

DNA-based techniques, first used in the early 1990s for the diagnosis and prenatal diagnosis of different genetic skin diseases, have now largely replaced fetal skin biopsy for the prenatal diagnosis of these disorders (see below). However, there is still a role for fetal skin biopsy in the prenatal testing of at-risk pregnancies, mainly for the following indications:

1 Where the causative gene is unknown but prenatal diagnosis has been shown to be possible in similar cases using fetal skin biopsies.

2 Where the causative gene is known, but informative DNA markers are unavailable, perhaps because an affected offspring had died before appropriate DNA samples could be obtained.

3 Where previously attempted DNA-based prenatal diagnosis has been equivocal or technically unsatisfactory.

DNA techniques

Fetal tissue sampling

A major disadvantage of both amniocentesis and fetal skin biopsy is that the parents have to wait until the middle of the second trimester before the procedure can be undertaken. A further delay of up to 4 weeks is required for cytogenetic or enzyme studies of amniotic fluid cells. A positive diagnosis may lead to a late termination, after fetal movements have been felt, which is always distressing. Direct DNA analysis has had an enormous impact on prenatal diagnosis of monogenic disorders, chiefly because it can exploit the rapid advances in gene mapping and sequencing, and because it removes the need to examine tissues in which the gene in question is expressed [1]. Theoretically, there is no limit to how early in pregnancy the diagnosis can be made. The main limiting factors for prenatal diagnosis include reliable access to the fetus with minimum risk to its viability, and the precision of the DNA tests. These new approaches enable diagnosis of genetic diseases in the fetus when the cause of the disease is unknown, and even when the disease locus is not fully determined [1]. Methods are now being developed for detecting genetic defects in eight-cell embryos, before implantation in the uterus (see below), or even in gametes, before fertilization.

After implantation of the embryo, the chorionic plate derived from the trophoblast layer of the blastocyst attaches to the uterine wall. Chorionic villi are of fetal origin and therefore a useful source of fetal DNA, as are amniotic cells that are released from various fetal epithelia [2]. Chorionic villus biopsy can be performed either transcervically or by the transabdominal route [3].

These methods allow for approximately 10–50 mg of tissue to be biopsied or aspirated. The risk of fetal loss following chorionic villus sampling (CVS) (performed after 10 weeks) is approximately 1.7% [4]. Initially, some reports suggested that CVS might increase the risk of severe limb reduction defects and the hypoglossia–hypodactyly syndrome [5], but this has not been borne out in subsequent more extensive international studies [6]. Nevertheless, it is recommended that CVS is not performed before 10 weeks. Tissue obtained from the CVS needs to be cleaned under a dissecting microscope to exclude maternal cells (decidua, blood) that could contaminate polymerase chain reaction (PCR) or biochemical analyses. It is also important that villi are collected in an appropriate medium. For example, the presence of heparin in the collection fluid may inhibit the activity of the Taq polymerase enzyme that is fundamental to PCR amplification. Chorionic villi can also be cultured for subsequent diagnostic confirmation of the findings obtained from direct analysis of the villi.

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Use of DNA methods for prenatal testing in specific disorders

In the preparation for DNA-based prenatal testing, DNA samples should be available from both parents and the

affected family member to screen for the pathogenic mutations. The possibility of *de novo* mutations (a frequent cause of the Dowling–Meara form of EB simplex, for example), non-paternity, uniparental disomy and germline mutations must all be considered in determining the suitability of the prenatal test. Table 13.2 lists the disorders for which prenatal testing has been performed. Further details about the genetic and other aspects of these diseases can be found in the respective chapters describing them more fully. Because the two most requested indications for prenatal testing are Herlitz junctional EB and Hallopeau–Siemens dystrophic EB, a fuller account of the prenatal diagnosis of EB [1–9] is singled out here.

Because mutations in only one gene (the type VII collagen gene, *COL7A1*) are known to cause both recessive and dominant forms of dystrophic EB, prenatal diagnosis can be performed by linkage analysis using a combination of intragenic and flanking markers for the gene locus on chromosome 3p21. These genetic markers can be combined with microsatellite markers for haplotype analysis in predicting whether the fetus carries one, two or neither mutant *COL7A1* allele (Fig. 13.11). A potential pitfall of haplotype analysis using polymorphic markers is the possibility of the occurrence of a *de novo* mutation or parental germline mosaicism in one of the alleles inherited in a previously affected sibling [6]. To increase the accuracy of the test, DNA analysis of pregnancies at risk of recessive dystrophic EB should also, where possible, be based on direct mutation screening of both *COL7A1* alleles [6]. Under optimal conditions, the DNA analysis of key family members, including testing for informative polymorphic and microsatellite markers, in addition to mutational analysis, can be completed within 2 weeks. The analysis of fetal DNA can subsequently be accomplished within 48 h after its receipt in the laboratory [6].

Because junctional EB shows considerable molecular heterogeneity (see Chapter 40), DNA-based prenatal diagnosis of this disorder is dependent on direct mutation analysis instead of genetic linkage. In pregnancies at risk for the Herlitz form of junctional EB, prenatal testing includes analysis of the three laminin 5 genes, *LAMA3* [1], *LAMB3* [2] and *LAMC2* [3].

Mutations in other genes encoding molecular components of the hemidesmosome-anchoring filament complex are also known to cause subtypes of EB. For example, mutations in the α6 or β4 integrin chains underlie a form of junctional EB associated with pyloric atresia [4] and defects in the collagen XVII gene, *COL17A1*, cause a non-Herlitz form of junctional EB (see Chapter 40). Mutations in the plectin gene, *PLEC1*, cause EB simplex associated with a congenital muscle disorder (see Chapter 40). Prenatal diagnosis has also been achieved in fetuses at risk for the Dowling–Meara form of EB simplex by DNA sequence analysis of the keratin K5 and K14 genes [9].

DNA analysis has been used for prenatal diagnostic testing in several other hereditary disorders with cutaneous manifestations, several of which are included in Table 13.2.

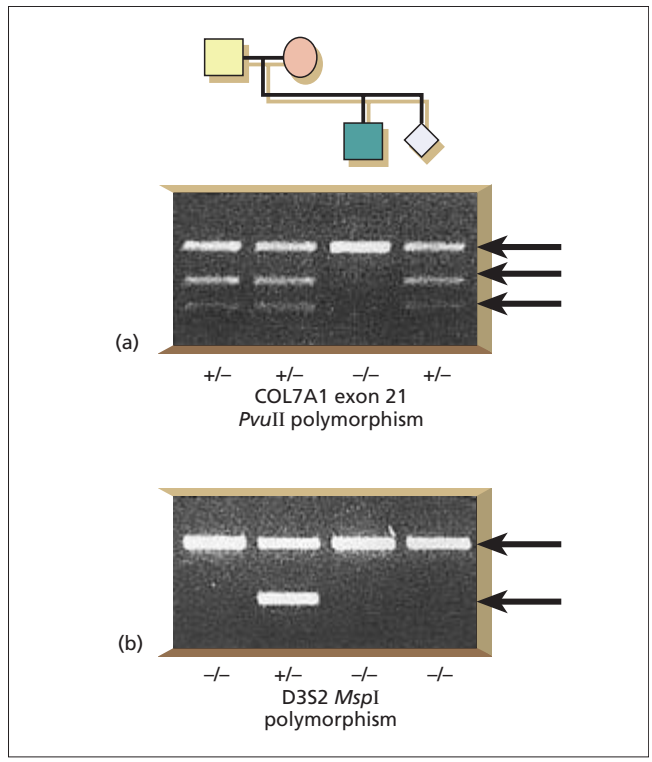

Fig. 13.11 Prenatal exclusion of dystrophic epidermolysis bullosa by linkage analysis. (a) *Pvu*II restriction endonuclease digestion for an intragenic *COL7A1* polymorphism in exon 21 shows a +/– haplotype in the maternal, paternal and fetal DNA in contrast to a –/– haplotype in the previously affected child's DNA. (b) *Msp*I restriction endonuclease digestion for a flanking polymorphism (D3S2) shows a +/– haplotype in the maternal DNA in contrast to a –/– haplotype in the paternal, previously affected child and fetal DNA. These findings indicate that the fetus has inherited the normal paternal *COL7A1* allele and the mutant maternal *COL7A1* allele, and is therefore predicted to be an unaffected carrier of one mutant *COL7A1* allele. (From McGrath *et al*. [7].)

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Table 13.2 DNA-based prenatal diagnosis.

Genodermatosis	MIM	Protein (*Gene*)	Gene locus	Reference(s)
Junctional epidermolysis bullosa (Herlitz)	226700	Laminin 5 α3 chain (*LAMA3*)	18q11.2	[1]
		Laminin 5 β3 chain (*LAMB3*)	1q32.2	[2]
		Laminin 5 γ2 chain (*LAMC2*)	1q25.3	[3]
Junctional epidermolysis bullosa (with pyloric atresia)	226730	β4 integrin (*ITGB4*)	17q25.1	[4]
Dystrophic epidermolysis bullosa (recessive)	226600	Type VII collagen (*COL7A1*)	3p21.33	[5–7]
Dystrophic epidermolysis bullosa (dominant)	131750	Type VII collagen (*COL7A1*)	3p21.33	[8]
Epidermolysis bullosa simplex (Dowling–Meara)	131760	Keratin 14 (*KRT14*)	17q21.2	[9]
Bullous congenital ichthyosiform erythroderma (Epidermolytic hyperkeratosis)	113800	Keratin 10 (*KRT10*)	17q21.2	[10]
Pachyonychia congenita (type 1)	167200	Keratin 16 (*KRT16*)	17q21.2	[11]
Netherton's syndrome	256500	Serine protease inhibitor (*SPINK5*)	5q33.1	[12]
Lamellar ichthyosis	242300	Transglutaminase 1 (*TGM1*)	14q11.2	[13,14]
Sjögren–Larsson syndrome	270200	Fatty aldehyde dehydrogenase (*FALDH*)	17p11.2	[15]
Ehlers–Danlos syndrome type VI	225400	Lysyl hydroxylase I (*PLOD*)	1p36.22	[16]
Oculocutaneous albinism (tyrosinase-negative, OCA1A)	203100	Tyrosinase (*TYR*)	11q14.3	[17,18]
Congenital erythropoietic porphyria	263700	Uroporphyrinogen III cosynthetase (*UROS*)	10q26.2	[19]
Ectrodactyly, ectodermal dysplasia, clefting (EEC) syndrome	129900	TP63 (*p63*)	3q28	[20]
Smith–Lemli–Opitz syndrome	270400	Sterol δ7-reductase (*DHCR7*)	11q13.4	[21]
Mucopolysaccharidosis (Hunter, type II)	309900	Iduronate-2-sulphatase (*IDS*)	Xq28	[22]
Sialidosis (type II)	256550	Lysosomal alpha-*N*-acetyl-neuraminidase (*NEU1*)	6p21.33	[23]
Infantile neuronal ceroid lipofuscinosis (INCL)	256730	Lysosomal palmitoyl-protein thioesterase (*CLN1*)	1p32	[24]
Late-infantile neuronal ceroid lipofuscinosis (LINCL)	204500	Lysosomal tripeptidyl peptidase I (*CLN2*)	11p15.4	[25]
Thanatophoric dysplasias (types I, II)	151210	Fibroblast growth factor receptor 3 (*FGFR3*)	4p16.3	[26]
Achondroplasia–hypochondroplasia	100800	Fibroblast growth factor receptor 3 (*FGFR3*)	4p16.3	[27]
Conradi–Hunermann–Happle syndrome	302960	Emopamil binding protein (*EBP*/*CDPX2*)	Xp11.23	[28]

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Preimplantation genetic diagnosis

For some couples, termination at any stage of pregnancy is unacceptable. Others may find the stress of abortion after skin biopsy prenatal testing in the mid-trimester or even after chorionic villus biopsy in the first trimester is too great to bear, especially if they have experienced a termination previously. Preimplantation genetic diagnosis is an alternative method that is able to provide information about the genetic status of an early embryo [1]. The procedure involves assisted conception techniques to generate embryos *in vitro* (Fig. 13.12). A single cell is then sampled as tissue representative of the whole embryo (Fig. 13.13) and is analysed for the presence of a specific gene or chromosomal abnormality. Only embryos found to be free of a specific genetic defect are then implanted in the uterus. The first successful birth following preimplantation genetic diagnosis (to exclude cystic fibrosis) was reported in 1992 [2]. Subsequent use of this methodology for genetic skin diseases has been limited, but a small number of cases have been reported [3–5].

Fig. 13.12 *In vitro* fertilization using intracellular sperm injection (ICSI), as a prerequisite for preimplantation diagnosis. (Courtesy of the Assisted Conception Unit, Guy's and St Thomas' Hospital, London, UK.)

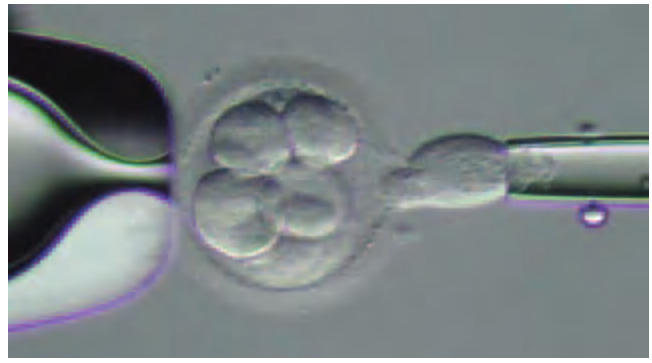

Fig. 13.13 Biopsy of a single cell from a blastocyst (3-day-old embryo) for preimplantation diagnosis. (Courtesy of the Assisted Conception Unit, Guy's and St Thomas' Hospital, London, UK.)

The methods used for preimplantation genetic diagnosis continue to evolve [1], but each test has to be individually optimized, for example in the selection of buffers to digest the single embryonic cells and also in the design of the PCR protocols [6]. A single cell can usually be removed from an eight-cell cleavage-stage embryo without affecting subsequent development [1]. The procedure is generally performed about 3 days after *in vitro* fertilization. Nested PCR techniques can be sufficiently reliable to amplify DNA from a single cell (containing just two copies of a particular gene) isolated from an eight-cell embryo [1,4,5,7]. Fluorescence *in situ* hybridization for the detection of X and Y chromosomes may be used to determine the sex of embryos [1,3]. This may be useful where there is a known risk of transmission of an X-linked disorder to a male embryo, especially in the absence of a specific diagnostic test.

Methods are currently being developed to separate X- and Y-bearing spermatozoa, which, if effective, could theoretically be used instead of sexing an embryo. Some DNA tests on unfertilized eggs are also possible by analysis of the first polar body, which is one of the products of the first meiotic division [1]. Pregnancy rates after preimplantation genetic diagnosis vary with the type of disorder and the experience of the practitioners involved, but data gathered from several centres on approximately 1200 cycles for the period 1999–2001 showed an overall clinical pregnancy rate of 22.4% per embryo transfer [8].

Preimplantation diagnosis is very much more complex than most methods of prenatal diagnosis, and the costs are also higher. Nevertheless, the method has been successfully used for a small number of conditions in the few centres currently able to offer this means of diagnosis. In time, preimplantation diagnosis will become more widely available for couples at risk of having children with certain genodermatoses, such as the junctional or more severe forms of recessive dystrophic EB. However, regulation of preimplantation genetic diagnosis varies throughout the world, and this method of prenatal testing is not permitted in several countries (e.g. Argentina, Austria, Switzerland or Taiwan) and is restricted in others (e.g. France or Germany) [1].

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Ethical aspects of prenatal diagnosis

Present and future trends in prenatal and preimplantation diagnosis are bound to raise questions concerning moral, ethical, legal and economic aspects of these procedures [1,2]. Major questions concern the degree of fetal abnormality and the consequent level of physical or mental disability that may be considered as a justification for abortion [3]. These questions are important for those working in all branches of medicine, including dermatology. The recommendations of a Royal College of Physicians' working party on prenatal diagnosis [4] provides a useful summary of the major issues. Guidelines that should be stressed include those stating that prenatal diagnosis should be undertaken within the general principles of informed consent, including the possibility that after testing the question of terminating the pregnancy may have to be faced. Further, the choice of option and outcome following prenatal diagnosis should be made by informed couples: they are the best judges of what should be done.

Genetic tests are now available for disorders that generally might be regarded as mild, certainly in comparison with those associated with greater clinical severity or worse prognosis. For example, prenatal testing is now possible for the Weber–Cockayne form of EB. However, such a test has not yet been reported, probably because it has not been requested. Before long, it may be possible, in certain families, to carry out prenatal testing for psoriasis or atopic eczema. Most doctors and nurses may feel that aborting a fetus that has tested positive for one of the 'milder' disorders is unjustified [5]. However, society might say that any couple at risk has the right to know what options are available and possibly the right to have prenatal diagnosis with the intention of terminating an affected pregnancy. How these issues are to be resolved based on moral, ethical and legal considerations is by no means clear and will continue to be debated, along with other major issues involving genetic testing [6], created or influenced by recent advances in biomedical technology and reproduction medicine.

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Chapter 14

The Neonate

D.J. Atherton, A.R. Gennery & A.J. Cant

Skin disorders in the neonate

[D.J. Atherton, pp. 14.1–14.50]

Nomenclature

The neonatal or newborn period is the first 4 weeks of extrauterine life, whereas infancy is the whole first year.

Infants born alive before the 37th week of gestation (i.e. 37 weeks after the first day of the mother's last menstrual period) are considered to be premature or preterm. Infants born with a birth weight of less than 2500 g are considered to be low birth-weight infants; this state may be the consequence of prematurity, a less than expected rate of intrauterine growth (small for gestational age), or a combination of both. The term intrauterine growth retardation is used when birth weight is low for gestational age; such infants are commonly described as dysmature or small-for-dates.

Infants born after 42 weeks' gestation are described as post-term, irrespective of birth weight. This expression is often used synonymously with postmature. Because the true period of gestation may not be known exactly by dates, the diagnoses of prematurity, smallness-for-dates and maturity are made principally on clinical grounds; the relevant cutaneous features are considered later.

Skin function in the neonate

Barrier function

Great interest has focused on skin barrier function, both in preterm and full-term neonates, because of the evidence that both are at high risk of toxicity from topically applied substances [1].

It is believed that the normal full-term infant has a completely functional stratum corneum, with fully developed barrier function [2–6]. Toxicity resulting from percutaneous absorption in the full-term neonate is more often therefore related to: (i) the greatly increased ratio of surface area to volume; (ii) the frequent presence of occlusive

conditions, such as exist under waterproof nappy covers; and (iii) high ambient temperatures and humidity, than to any impairment of barrier function *per se*.

There is, in contrast, definite evidence of impaired barrier function in preterm infants, especially those of less than 34 weeks' gestation, mirroring the anatomical immaturity of the epidermis and stratum corneum [3–5,7–11]. Percutaneous absorption correlates inversely with gestational age, but barrier function appears to improve rapidly after birth in the preterm infant, and will generally be normal by the end of the second or third week after birth [3,5,10,12].

It is clear that nothing should be applied to the skin of any baby without careful consideration of the potential hazards of percutaneous absorption, particularly in those with skin diseases. In the case of small, preterm neonates, one should be hesitant to apply anything at all to the skin. The best documented hazards relate to aniline dyes [13], hexachlorophene and related antiseptics [14–17], alcohol [18–21] and corticosteroids [22]. A number of other substances should never be used in neonates, especially not in preterm neonates; these include neomycin [23], boric acid [6,24–26], resorcinol (e.g. in Castellani's solution) [27,28], γ-benzene hexachloride [6,29], benzyl alcohol [30], benzyl benzoate [6], urea [31] and salicylic acid [6,32]. Antiseptics such as chlorhexidine [7] and iodine [33–35] should be used with the greatest caution. Care should also be taken with agents used to launder, sterilize or mark nappies and bed linen [13,36–39], also with mothballs used in their storage [40].

In view of the risk, it is of concern that a study undertaken in the USA a few years ago revealed that parents had applied over 48 different chemicals in over-the-counter preparations to the skin of their 1-month-old babies [41].

Conversely, the increased permeability of the skin in the preterm neonate has potential value for percutaneous administration of drugs [42].

Transepidermal water loss is greatly increased in preterm compared with full-term babies [3,43–45]. The resulting outward passage of water can lead to high rates of heat loss by evaporation, which may even exceed the baby's resting rate of heat production. These losses can be reduced by increasing the ambient humidity [43,46], although this leads to an increased risk of infection, by covering the child with a plastic bubble blanket [47,48], a Perspex shield [49], or by applying a lipid barrier [50,51].

It has been shown that oxygen absorption and carbon dioxide excretion rates through intact skin during the first few days of life are inversely correlated with gestational age [52]. There is, however, no increase in gas exchange in full-term neonates compared with adults, and rates in preterm neonates rapidly fall within 2 weeks of birth to those observed in full-term neonates. These studies raise the possibility of utilizing this increased gas permeability of preterm neonatal skin to deliver oxygen in the respiratory distress syndrome, particularly where there is severe pulmonary hypertension, when adequate oxygenation is exceedingly difficult to achieve.

It is possible that immaturity of the skin also predisposes the premature neonate to penetration of the skin by microorganisms leading to systemic infection. This may be the reason that the premature infant with congenital cutaneous candidiasis is at greater risk of disseminated candidiasis [53].

Eccrine sweating

A full complement of anatomically normal eccrine sweat glands is present by the 28th week of gestation [54], but these appear to be functionally immature in neonates born before the 36th week, in terms of their responses to intradermal injection of acetylcholine and epinephrine (adrenaline) [55], and to thermal stress [56]. However, responsiveness usually develops in such babies by 2 weeks after birth [55,57]. Neonates born after the 36th week of gestation sweat in response to thermal stress from birth [58,59], although such sweating is initially relatively inefficient as a thermoregulatory mechanism. Care must therefore be taken not to overheat any neonate, but particularly the preterm neonate, and although severe overheating leading to hyperpyrexia is probably rare, lesser degrees of iatrogenic overheating appear to be common and may even induce apnoeic attacks [60].

The forehead appears to be the principal site of thermally induced sweating in the neonate [59]. The palms and soles, however, are sites of 'emotional' sweating, occurring in response to arousal, which appears to be well developed at birth in full-term but not preterm neonates [56]. The rate of such 'emotional sweating' can provide a measure of stress in small babies [61].

Sebaceous gland secretion

The secretions of the fetal sebaceous glands make a significant contribution to the vernix caseosa [62]. Sebum secretion rates are high in neonates compared with older pre-adolescent children [63], and it is assumed that this sebaceous gland activity reflects stimulation by placentally transferred maternal androgen, particularly by dehydroepiandrosterone [63]. Sebaceous gland activity decreases from about the end of the first month to reach a stable level by the end of the first year [63].

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The appearance of neonatal skin

A variety of skin lesions commonly seen in the newborn are regarded as 'physiological'. Their frequency has been studied by several authors, and varies somewhat in different racial groups [1–5].

At birth, the skin is covered with a whitish, greasy film, the *vernix caseosa*. The vernix may cover the entire skin surface, or it may be present only in body folds such as the groins. It normally dries rapidly and starts to flake off within a few hours of birth. The vernix appears to be comprised of lipids [6,7]. Little is known of its function, though recent evidence of its content of the pepide antibiotic LL-37 and of lysozyme support an antimicrobial role [8]. Its colour may reflect intrauterine problems, such as haemolytic disease of the newborn and post-maturity, both of which result in golden yellow staining. Fetal

distress *in utero* may lead to staining of the vernix by the bile pigments present in meconium.

Peripheral cyanosis (or acrocyanosis) is a feature of the newborn, particularly the full-term newborn, and is usually particularly marked on the palms and soles and around the mouth. In the absence of cyanosis of warm central parts such as the tongue, this may be regarded as normal during the first 48 h or so. It is made more obvious by hypothermia, and is improved by warming.

A few hours after birth, many babies develop a striking generalized hyperaemia usually known as *erythema neonatorum*, which fades spontaneously within 24–48 h.

In as many as 15% of neonates, a vivid colour difference may appear along the midline at some time during the first week of life [9–12]. This phenomenon occurs when the baby is lying on its side, the upper half of the body becoming pale, the lower half a deep-red colour, with a sharp midline demarcation between the two. The duration of the attack is highly variable, but generally is between half a minute and 20 min. If the baby is turned on the other side, the colour change may reverse. An individual neonate may have only a single episode, or it may recur on several occasions. This curious phenomenon has been called *harlequin colour change*. It appears to have no pathological significance in the great majority of cases, and is considered to reflect immaturity of hypothalamic centres responsible for the control of peripheral vascular tone [9]. If it persists beyond the end of the fourth week, it may be associated with hypoxia due to cardiovascular anomalies [13].

Newborn infants who are subjected to cooling will show distinct marbling of the skin. Although this more or less disappears on rewarming, many normal neonates demonstrate faint marbling, even under optimal environmental conditions. The marbling comprises a reticulate blue vascular pattern, which has often been called *cutis marmorata*. This response is a physiological one, and may be seen throughout infancy. *Cutis marmorata telangiectatica congenita* is an entirely distinct vascular developmental disorder, and is easily distinguished (see Chapter 15). Cutaneous marbling may be seen in older children with a variety of disorders, particularly athyrotic (congenital) hypothyroidism [14], the de Lange syndrome, the Adams–Oliver syndrome, in trisomy 18, trisomy 21, homocystinuria and the Divry–Van Bogaert syndrome (see Chapters 12 and 15).

Rather superficial cutaneous desquamation, often termed physiological scaling of the newborn, occurs in up to 75% of normal neonates [5,15]. This usually first appears around the ankles on the first day of life, and is most commonly more or less confined to the hands and feet [5]. It may remain very localized or may gradually become more widespread, usually reaching its maximum extent and intensity by the eighth day. Although it has been reported that this type of desquamation is unusual in babies born earlier than the 39th week of gestation, and that it occurs with increasing frequency the greater the gestational age [15], this was not confirmed in a more recent study, in which it was found to occur with equal prevalence at all gestational ages [5]. It tends always to be more severe in neonates who are small-for-dates, whatever their gestational age. Physiological scaling may occasionally be fairly pronounced, not generally sufficiently so to lead to confusion with any of the more serious types of congenital ichthyosis, but milder varieties of ichthyosis, such as ichthyosis vulgaris, may be difficult to distinguish, and it should be borne in mind that X-linked hypohidrotic ectodermal dysplasia may present with scaling of the skin in the neonatal period [16].

One or two solitary blisters or erosions are occasionally present at birth on the fingers, lips or forearms, and are believed to be caused by vigorous sucking *in utero*; hence the term sucking blister is often applied. These heal rapidly without sequelae [17].

The scalp hair is shed synchronously during the fifth month of fetal life, and having regrown enters telogen in a wave from front to back, starting about 12 weeks before term. After shedding of the telogen hairs from the frontal and parietal areas, the roots again enter the anagen phase in a similar wave from front to back [18–20]. The roots in the occipital area do not enter telogen until term, and therefore rather conspicuous alopecia may appear at this site.

There appear to be two waves of hair loss and regrowth from front to back during early infancy, but by the end of the first year the typical mosaic pattern of hair growth is established [21]. In some babies, there is unusually synchronous hair loss during the neonatal period resulting in obvious diffuse alopecia (telogen effluvium of the newborn), but, by the end of the first 6 months of life, most babies have a full head of hair [22]. At this stage, the hairline often extends to the lateral ends of the eyebrows, but the terminal hairs comprising this extension gradually convert to vellus hairs during the remainder of the first year of life, causing the hairline to recede to its characteristic childhood position.

Sebaceous gland hyperplasia is a physiological event in the newborn, reflecting the influence of maternal androgens. It is visible to the naked eye in the great majority of infants as multiple, uniform, pinpoint yellowish papules that are most prominent on the nose, cheeks, upper lip and forehead, but may also be visible on the upper trunk, especially the areolae, the genitalia and the limbs. The phenomenon is associated in about 40% of infants with *milia*, which represent minute follicular epidermal cysts [23]. The number of milia present may vary from one or two to many hundreds. They comprise 1–3 mm, white, globular papules, which occur at the same sites. Rather larger and usually single milia, often termed pearls, are seen sometimes on the areolae, scrotum and labia majora.

Both the sebaceous gland hyperplasia and the milia tend to disappear spontaneously during the first weeks of life, though a few may persist longer. Milia which are exceptionally extensive or persistent, or whose distribution is atypical, may be features of the orofacial–digital syndrome type I, Marie–Unna type congenital hypotrichosis or the X-linked Bazex–Dupré–Christol syndrome, which features hypotrichosis and milia [24] (see Chapter 12).

The influence on the fetus of maternal and placental hormones gives rise to a group of phenomena, varying greatly in degree, sometimes described as 'miniature puberty'. In the newborn female, the genitalia appear succulent, and the size of the clitoris in particular may lead the inexperienced to suspect intersex. A mucoid vaginal discharge is common. Vaginal smears at this stage may be indistinguishable from those of pregnant women. A few days after birth, the hyperplastic vaginal epithelium desquamates to leave a more normal infantile mucosa; this desquamation may be manifest as a creamy white discharge. Frank withdrawal bleeding may occur from the uterus on the third of fourth day, usually lasting 2 or 3 days. The male genitalia appear similarly large and well-developed at birth.

Both sexes show hypertrophy of the mammary glands at birth. After 2 or 3 days the breasts may become engorged and lactation of so-called 'witch's milk' may occur. The swelling subsides during the second week and has usually become undetectable by the end of the fourth week. In some girls, however, it may be more persistent, and it is these girls in particular who are at risk of infection because of the presence of stagnant milk, leading to mastitis and abscess formation.

In about 8% of babies, the linea alba becomes pigmented, and this pigmentation may persist for 2 or 3 months. Mongolian spots occur in about 85% of oriental neonates [2,25], and the frequency in black babies is also high [26]. Mongolian spots are rare in white neonates, around 3% [26]. Exaggerated pigmentation of the scrotum occurs in about 30% of oriental neonates [25]. A rare type of congenital linear and/or reticulate pigmentation has been reported on the limbs and/or trunk of black neonates [27].

One or more 1–2-mm, yellowish white, keratinous cysts, known as *Epstein's pearls*, may be seen in the mouths of up to 85% of all neonates, along the alveolar ridges and/or in the midline at the junction of the hard and soft palate [5,28,29]. These generally disappear without treatment within a few weeks. Other common oral findings in the neonate [29] include rather succulent gums, analogous to the hypertrophic gingivitis often seen in pregnant women, a whitish hue to the oral mucosa (termed 'leukoedema', but probably synonymous with what other authors have called 'suckling pads' [30]), alveolar lymphangioma [31], ankyloglossia, commissural lip pits [32,33] and a median alveolar notch.

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The appearance of the preterm neonate

The skin of the preterm neonate tends to have a rather translucent, gelatinous quality, and the so-called 'miniature puberty' features are much less prominent.

Preterm infants are often covered in quite obvious lanugo hairs, which tend to be most dense on the face, limbs and trunk. This hair would normally be shed *in utero* about 1 month before term [1], to be replaced by a second coat of shorter lanugo, which is present at birth in full-term infants. Like the terminal scalp hair, this downy lanugo is shed during the first months of life and is itself replaced by vellus hair.

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Appearance of small-for-dates and postmature neonates

The small-for-dates or dysmature neonate presents a characteristic appearance due to relative prenatal malnutrition. The baby is small and, from the dermatological point of view, the most striking feature is the lack of subcutaneous fat, which causes the baby to look thin and wrinkled. Vernix is absent in the extremely immature infant, but may be profuse nearer to term. The skin and vernix are often stained yellowish green by meconium. After birth, the skin dries quickly and becomes 'crazed' with long transverse splits on the trunk. It then peels off to reveal more normal-appearing skin beneath. The fingernails are often long.

The postmature infant is longer, but of otherwise similar appearance to the small-for-dates neonate, having also experienced intrauterine malnutrition due to placental insufficiency. Vernix is often absent [1].

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Toxic erythema of the newborn

SYN. ERYTHEMA TOXICUM NEONATORUM

Terminology. The most widely used term for this condition is inappropriate in view of the complete absence of any evidence of a toxic cause.

Aetiology. The cause of toxic erythema of the newborn is unknown. It was at one time believed that the frequent finding of an associated blood eosinophilia implied an allergic origin, but there has never been any convincing support for the view that the condition is a manifestation of hypersensitivity to milk or drugs transmitted to the infant before birth via the placenta, or to vaginal secretions. Furthermore, the demonstration that tissue eosinophilia is a non-specific feature of inflammatory responses in neonates [1] adds little weight to such a view.

The intrafollicular location of mature pustules has led to the suggestion that the inflammatory response is elicited by some component of sebum [2].

Attempts to culture pathogenic bacteria from the lesions have always proved fruitless [3].

More recently, the suggestion has been made that toxic erythema of the newborn might represent a mild and self-limited acute graft-versus-host reaction due to maternal lymphocyte transfer to the neonate [4], but evidence for this is poor; in particular the histopathological features do not resemble those that have been demonstrated in acute graft-versus-host reactions in the skin.

Pathology [5,6]. Histologically, the macular erythema shows oedema in the upper dermis, associated with a sparse and largely perivascular inflammatory infiltrate comprising principally eosinophils. Papular lesions are characterized in addition by eosinophil infiltration of the outer root sheath of one or more hair follicles, above the point of entry of the sebaceous duct. Pustular lesions show intrafollicular accumulation of eosinophils immediately below the stratum corneum. Smears of the pustule contents demonstrate inflammatory cells, more than 90% of which are eosinophils [7,8].

There is an associated blood eosinophilia of up to 20% of the white cell count in around half the cases, and this is generally more marked when there is a prominent pustular element to the eruption [3,7].

Clinical features [3,7–11]. Up to 50% of full-term infants of all racial types will manifest some degree of toxic erythema during the first few days of life [9,12–15]. The incidence appears to decrease with both prematurity and smallness-for-dates [16]. In the majority of cases, the onset is during the first 48 h after birth, but it may occur at any time until about the fourth day. It is in rare instances present at birth [9,17,18].

Most commonly, the eruption initially takes the form of a blotchy, macular erythema, the number of individual lesions varying from one or two to several hundred. They are most profuse on the trunk, particularly the anterior trunk, but also commonly appear on the face and proximal parts of the limbs, especially the thighs. Lesions have been recorded, however, at almost any site except the palms and soles. In the mildest cases, these macules fade within a day. In more severe cases, urticarial papules arise within the erythematous areas, or, occasionally, independently of them (particularly on the back and buttocks).

These papules are, in about 10% of cases, surmounted by small pustules 1–2 mm in diameter.

Presentation with scrotal pustules present at birth has been reported more recently [18].

The infant appears well, and unperturbed by the eruption. Spontaneous recovery occurs rapidly, usually within 3 days, but recurrences are occasionally seen, and have been reported as late as the sixth week of life [19,20].

Diagnosis. Toxic erythema of the newborn has to be distinguished from several other disorders featuring pustular lesions during the neonatal period, particularly miliaria, transient neonatal pustular melanosis, incontinentia pigmenti, and, most importantly, herpes simplex virus (HSV) infection, varicella, impetigo neonatorum and *Malassezia furfur* pustulosis. Of these, perhaps pustular miliaria is the one most often confused clinically with toxic erythema. Toxic erythema can be rapidly distinguished from all of these by microscopic examination of a smear of pustule contents, stained with Giemsa, and by bacterial and viral culture.

Treatment. No treatment is required.

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Miliaria

Aetiology. Miliaria occurs when the flow of eccrine sweat is impeded by obstruction of the intraepidermal portion of the sweat duct. Its aetiology and pathogenesis are presumed to be similar at all ages and are considered in Chapter 45. Relative immaturity of the sweat duct may be an important predisposing factor in early infancy, as may a tendency for infants to be nursed in excessively warm and humid conditions.

Miliaria crystallina appears to reflect obstruction of the sweat duct within the stratum corneum itself. It is particularly common during the neonatal period, probably principally because of delayed patency of the sweat pore.

Miliaria rubra appears to be caused by sweat duct obstruction deeper within the epidermis, induced perhaps by increased activity of the intraductal microflora [1,2].

Pathology. Miliaria crystallina is characterized by the presence of intracorneal or subcorneal vesicles in communication with sweat ducts [3]. In miliaria rubra, focal areas of spongiosis and spongiotic vesicle formation are seen in close proximity to sweat ducts, which often contain an amorphous, periodic acid–Schiff (PAS) stain-positive plug [1,4].

Clinical features [5]. Miliaria crystallina presents as crops of clear, thin-walled, superficial vesicles 1–2 mm in diameter, without associated erythema (Fig. 14.1), resembling drops of water. These are exceedingly delicate, and generally rupture within 24 h, and are followed by branny desquamation. They arise most frequently during the first

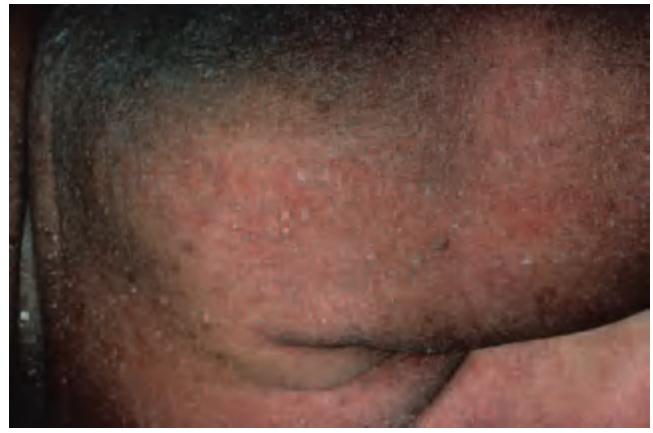

Fig. 14.1 Miliaria crystallina on the upper arm of a 7-day-old infant.

2 weeks of life, and are particularly likely to be seen on the forehead, scalp, neck and upper trunk. Though rare during the first 4 days, congenital cases have been reported [6,7].

Miliaria rubra ('prickly heat') comprises erythematous papules and papulovesicles about 1–4 mm in diameter, on a background of macular erythema. Sometimes, quite large, weal-like lesions occur. Frequently, some of the lesions are pustular (*miliaria pustulosa*), but this does not necessarily indicate secondary infection. Nevertheless, staphylococcal secondary infection of miliaria (periporitis) is not infrequent, and may lead to sweat gland abscesses.

Miliaria rubra is common and, although it may be seen throughout infancy, it probably occurs most frequently during the neonatal period. Crops of lesions arise fairly symmetrically, most often in flexural areas, especially around the neck and in the groins and axillae. The face, scalp and upper trunk are also frequently affected. It may also occur rather locally at sites that have been occluded, for example where there has been direct contact between skin and a plastic mattress cover or plastic pants. Where the eruption is profuse, the child may be restless and distressed. Each crop of lesions will subside within 2–3 days, but recurrences are common, unless the provocative environmental conditions are modified.

Recurrent bouts of miliaria pustulosa appear to be a rather specific finding in type 1 pseudoaldosteronism [8].

Diagnosis. Miliaria crystallina is distinguishable from viral infections of the skin by the lack of background erythema, and by the absence of inflammatory cells or giant keratinocytes on cytological examination of vesicle contents. When it occurs during the first few days of life, miliaria rubra is often confused with toxic erythema. However, miliaria rubra can generally be distinguished by its flexural predominance, by the frequent presence of vesicular lesions and by its tendency to recur. Where pustular lesions are seen in toxic erythema, a smear of their contents will reveal large numbers of eosinophils.

When pustular lesions are prominent in miliaria, there may be confusion with infantile acne or with folliculitis, but careful clinical examination of the individual lesions will show that they do not have a follicular distribution.

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Transient pustular melanosis

SYN. TRANSIENT NEONATAL PUSTULAR MELANOSIS

Terminology and aetiology. Despite having first been described more than 25 years ago [1], whether this is really an entity remains unresolved. Nothing is known of its aetiology other than that it would appear, like toxic erythema of the newborn, to be non-infectious. It was first reported in black Americans, and appears to be commoner in, but not confined to black neonates (4.4% in black US neonates against 0.6% in white US neonates) [1]. This probably reflects the fact that its diagnosis is currently based on the appearance of typical macular post-inflammatory pigmentation, as the name seems to require. It has been suggested that it is merely a variant of toxic erythema of the newborn [2].

Pathology [1]. Pustular lesions show intra- or subcorneal collections of neutrophils and a few eosinophils. The underlying dermis may show no abnormality, or a sparse perivascular and perifollicular inflammatory infiltrate, also mainly of neutrophils with a few eosinophils.

The pigmented macules demonstrate basal and suprabasal increase in pigmentation only, apparently without pigmentary incontinence.

Smears of pustular contents show predominantly neutrophils, and bacterial culture is negative.

Clinical features [1,3–7]. Lesions are almost invariably present at birth. The most characteristic component of the eruption is 1–3-mm flaccid, superficial, fragile pustules, with no surrounding erythema. These pustules may occur at any site, but favour the chin, neck, forehead, back and buttocks. Sites where they have ruptured are marked initially by a detachable brown crust, and subsequently by a small collarette of scale, which may surmount a pigmented macule. Sometimes, pigmented macules are already present at birth. The pigmented macules are a prominent element in black infants, and are seen more rarely in other races [5]. The pigmentation may persist for about 3 months. Affected infants are otherwise entirely well.

It has been suggested that this condition is responsible for the freckling or '*lentigines neonatorum*' that have been reported in some 15% of black neonates [8].

Diagnosis. It remains to be established whether this is really just an early-onset variant of toxic erythema of the newborn occurring in the dark-skinned. Stained smears and microbiological studies will distinguish staphylococcal and herpetic infections. The differential diagnosis of neonatal pustular eruptions is given in Table 14.1.

Table 14.1 Pustular eruptions in the neonate.

Infantile acne
Impetigo
Congenital syphilis
Neonatal listeriosis
Herpes simplex virus (HSV) infection
Congenital or neonatal candidiasis
Malassezia pustulosis
Scabies
Miliaria
Eosinophilic pustulosis
Toxic erythema of the newborn
Infantile acropustulosis
Transient neonatal pustulosis
Pustular psoriasis

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Infantile acropustulosis

Aetiology. Infantile acropustulosis is an uncommon disorder of unknown aetiology. It occurs in all races [1], though it was first described in black infants [2,3]. It has been suggested that eosinophilic pustular folliculitis and infantile acropustulosis may be different manifestations of the same disease [4,5]. It has also been suggested that, at least in some cases, infantile acropustulosis occurs following successful treatment of scabies [6–8]. Interestingly, it has been reported in a 2-month-old infant whose mother was treated for scabies 4 months previously [9]. It has also been reported in siblings [9], and in only one of a pair of identical twins [10].

Pathology [2,11–13]. Biopsies of fully developed pustules have revealed well-circumscribed subcorneal or intraepidermal aggregations of neutrophils, with a sparse perivascular lymphohistiocytic infiltrate in the underlying papillary dermis. Biopsy of pre-pustular lesions shows focal intraepidermal vesiculation [13,14] with keratinocyte necrosis. This intraepidermal vesicle is subsequently invaded by neutrophils and/or eosinophils. The pustule starts its life deep in the epidermis, but does not become clinically fully developed until it reaches a subcorneal location.

Direct and indirect immunofluorescence is negative in lesional, perilesional and normal skin [1,3,15].

Stained smears of pustule contents generally show a predominance of neutrophils, but there may be a preponderance of eosinophils early in the course of the disorder [3]. The pustules are sterile [2,11,16]. Peripheral blood eosinophilia has been reported [14,17,18], but is not invariable [9,13,17].

Clinical features [2,3,9,12,15,19,20]. Recurrent crops of intensely itchy, 1–4-mm vesicopustules appear principally on the soles and sides of the feet, and on the palms, but may also occur on the dorsa of the feet, hands and fingers, and on the ankles, wrists and forearms. Scattered lesions may also be seen on the face, scalp and trunk, but a predominantly acral distribution is characteristic. Mucosal lesions do not occur.

Individual lesions appear to start as tiny, red papules, which evolve into vesicles and then pustules over about 24 h. Excoriation results in erosions and then crusts. Healing is frequently succeeded by macular post-inflammatory hyperpigmentation.

Pruritus may be intense, with restlessness, loss of appetite and interference with sleep.

In the majority of cases, the onset is in the first year of life, particularly during the first 6 months [9]; lesions may be present at birth. Each crop lasts for 7–14 days. They tend to occur at intervals of 2–4 weeks in most cases, often being more frequent and more numerous in the summer months. The attacks occur with gradually diminishing numbers of lesions, and with decreasing frequency, until they cease altogether, usually within 2 years of the onset [8].

Treatment. The early use of fairly potent topical corticosteroids with [9] or without [12] occlusion appears to abort attacks.

The intense pruritus may be lessened by large doses of oral antihistamines [2].

Though rarely justified, dapsone is usually effective in controlling this condition in a dose of 1–2 mg/kg/day in two divided doses [3], and usually reduces pruritus within 24 h. Higher doses are occasionally required [17]. Too hasty withdrawal of treatment may provoke severe exacerbations [11].

Diagnosis. The predilection for the palms and soles and the recurrent attacks differentiate this disorder from most other pustular eruptions seen in the neonatal period, particularly toxic erythema, miliaria and transient pustular melanosis.

Persistent palmoplantar pustulosis may be similar histologically but characteristically has a much later onset, a more persistent course, and the skin surrounding the pustules is dusky red and glazed.

Subcorneal pustular dermatosis may also resemble infantile acropustulosis histologically, and has occasionally had its onset during the first 3 months of life [21]. It is, however, likely to be associated with fever and neutrophilia, and has a different distribution, favouring the proximal flexures, although lesions on the palms and soles have been described.

Scabies may initially be extremely difficult to exclude, and where there is any doubt a therapeutic trial of an appropriate acaricide is clearly justified. The persistence of acral pustulosis for many months in children aged less than 3 years, and previously treated for scabies, has been reported [22].

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Eosinophilic pustulosis

SYN. EOSINOPHILIC PUSTULAR FOLLICULITIS

Aetiology. This entity is now recognized as a characteristic skin disorder of infancy, with typical cases described from many different countries [1–5]. Its aetiology and its relationship to eosinophilic pustular folliculitis of adults [6] are unknown. It has been suggested that this condition and infantile acropustulosis may be different manifestations of a single disorder [5,7].

Pathology. Biopsy shows a dense perifollicular infiltrate of eosinophils, with some lymphocytes and histiocytes, in the mid- and upper dermis. The hair follicles themselves show spongiotic degeneration of the outer root sheath, and infiltration with eosinophils. The centre of the follicles is necrotic, and filled with eosinophils and eosinophilic debris. Smears of pustule contents show plentiful eosinophils. There is mild to moderate peripheral blood eosinophilia, and occasionally, neutrophilia.

Clinical features. The condition generally has its onset in infancy. Lesions occur predominantly in the scalp [2,4,5,7], comprising mildly pruritic, 1–3-mm-diameter pustules on an erythematous base, with prominent secondary crusting. However, pustules may also occur at almost any other site except the mucosae, occasionally even in areas lacking hair follicles [3]. Annular lesions resembling those seen in adults were reported in a 5 year old [8], but this is perhaps more likely to have been an early case of the adult form of eosinophilic pustular folliculitis. Patients are not systemically unwell.

A pattern of cyclical recurrences is characteristic, but the likely duration of the disease is unknown.

Diagnosis. Conditions that need to be considered in the differential diagnosis include infections, particularly impetigo and candidosis, and other non-infective pustuloses of infancy, particularly toxic erythema, infantile acropustulosis and transient neonatal pustulosis.

Infections are principally excluded by the sterile pustule contents, the absence of eosinophils in smears of pustule contents, and the lack of peripheral blood eosinophilia. While toxic erythema may initially be clinically and histologically similar, it does not show any predilection for the scalp, and lacks the cyclical recurrent course. Similarly, the pustular phase of transient neonatal pustulosis is confined to the neonatal period. Also, the pustules contain neutrophils rather than eosinophils. The lesions of infantile acropustulosis, while they do generally occur in recurring crops, tend to be larger and are located principally on acral sites including the palms and soles, rather than in the scalp.

Treatment. There is some evidence that higher-potency

topical corticosteroids and oral erythromycin may have some suppressive effect on the lesions seen in infants [3,4], but little treatment is required since the prognosis for spontaneous remission appears excellent.

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Congenital erosive and vesicular dermatosis healing with reticulated supple scarring

SYN. EXTENSIVE CONGENITAL EROSIONS AND VESICLES HEALING WITH RETICULATE SCARRING

This is a rare disorder of unknown aetiology [1–6]. There is no evidence of genetic transmission. It appears possible that the condition reflects an as yet unidentified intrauterine infection.

The majority of affected infants have been premature. Some have also had microcephaly and neurological problems including convulsions and developmental delay.

At birth, there are extensive superficial erosions, with scattered vesicles and bullae, affecting up to 75% of the body surface [1–6]. These heal fairly quickly within the first few weeks of life, leaving rather characteristic soft, reticulated scarring. The trunk and limbs tend to be more severely affected than the face and scalp. Following healing of the skin lesions, there may be residual loss of eccrine sweating in scarred areas, with the potential for hyperthermia under appropriate conditions, patchy alopecia, partial loss of eyelashes, and absence or hypoplasia of nails. Teeth have been normal. Mild localized recurrent vesiculation may occur [6].

Biopsies of vesicular areas have shown spongiosis or epidermal necrosis with dermal haemorrhage and inflammation [6]. In another report, an eroded area showed loss of the epidermis with a superficial and deep dermal inflammatory infiltrate comprising mostly neutrophils [4]. Scarred areas have shown an increased density of dermal collagen, and absence of eccrine sweat glands [1,5]. Direct immunofluorescence does not show any specific pattern of deposition of immunoglobulins, C3 or fibrin [4]. Electronmicroscopy and immunohistochemical mapping of perilesional skin have shown nothing to suggest that this is a variant of epidermolysis bullosa [5].

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'Cradle cap'

This term is applied, rather loosely, to almost any situation in which there is adherent scaling of the scalp during infancy. This type of scaling is very common, particularly on the vertex, during the first few weeks of life, and is generally believed to represent persisting vernix.

However, there is little doubt that such scaling may appear in early infancy in babies in whom the scalp was clear at birth [1]. The eyebrows are frequently affected in this acquired type of cradle cap, and lesions may also appear on the forehead and temples, the retro-auricular area and the folds of the neck. This rash is generally considered to be a manifestation of infantile seborrhoeic dermatitis.

If scaling or crusting is present during the neonatal period, the scalp should be regularly oiled with olive oil or arachis oil. In the more refractory case, Emulsifying Ointment BP, Aqueous Cream BP or any other water-dispersible emollient should be massaged into the scalp once or twice a day, left for several hours, and then rinsed out. Applications containing salicylic acid, and shampoos containing potentially toxic substances such as selenium sulphide should not be used on the scalp in neonates because of the dangers posed by their percutaneous absorption.

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Complications of prematurity

Anetoderma of prematurity [1]

A series of infants have recently been described in whom

nummular areas of cutaneous atrophy appeared on the trunk and/or proximal limbs within a few weeks or months of birth. All these babies had been born between the 24th and 29th weeks of gestation and in almost all cases the lesions had first appeared while the child was still in the neonatal intensive care unit. Histologically these lesions demonstrated reduction or absence of elastic tissue, consistent with anetoderma. An aetiological role for trauma resulting from care procedures cannot be ruled out.

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Complications of medical procedures on the fetus and neonate

Scarring following antenatal procedures

Amniocentesis comprises the insertion of a needle into the amniotic sac through the abdominal wall for the removal of amniotic fluid. Punctate scars and dimples may result from accidental puncture of the fetal skin during the procedure [1–4], although the frequency of such lesions can be greatly reduced by the routine use of ultrasound guidance. Generally, injuries are minor, but more substantial trauma can occur.

Other antenatal procedures on the fetus that may result in scarring include biopsies of skin, liver, tumours, aspiration of fluid collections, and a variety of therapeutic procedures, all of which are undertaken with ultrasound guidance.

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Intrauterine blood transfusion

Gangrene of the skin of the abdominal wall has been reported following intrauterine red cell transfusion for haemolytic disease of the fetus due to rhesus incompatibility [1].

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Scarring acquired due to procedures during delivery

Scalp electrodes are very widely employed to monitor fetal heart rate during labour. The most commonly used type of electrode is curved and is implanted by being 'screwed' into the scalp. Lacerations are not an uncommon sequela [1]. Although these generally heal rapidly, they may leave localized areas of permanent scarring in the scalp, which may later be confused with cutis aplasia. Cephalohaematoma has also been reported [2].

Scalp blood samples are also often taken to establish fetal acid-base status; these are taken via small incisions using a special lancet. Either type of injury can lead to abscesses in up to 4% of neonates [3], usually becoming evident by the third day of life. These are generally a minor problem [4], but osteomyelitis [5] and necrotizing fasciitis [6] may, however, occur. Infecting bacteria have included group A streptococci and *Neisseria gonorrhoeae* [7]. HSV infection may also occur at the site of electrode implantation, reflecting infection of the mother's genital tract [8]. Vesicles appear within 4–10 days of birth. Recognition of such lesions is important, as localized infection of this type has occasionally been complicated by meningoencephalitis [9,10] and by lethal dissemination [11].

Forceps delivery may occasionally result in local subcutaneous fat necrosis. Vacuum extractors (ventouse) may rarely cause permanent alopecia, most typically in a circle that clearly corresponds to the site of its application. Scalpel laceration during caesarean delivery may require suturing and will generally result in scarring.

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Complications of phototherapy

Phototherapy with blue light at 420–460 nm leads to the transcutaneous photo-oxidation of bilirubin, and has become firmly established as a safe and effective treatment for neonatal jaundice [1].

A number of minor cutaneous side effects have been described. Some babies develop a macular erythematous rash as the serum bilirubin level falls [2].

Darkening of treated areas of skin lasting for several months has been reported in racially black babies [3]. This effect may initially be due to the immediate pigment-darkening reaction, which is induced by visible as well as by long-wave UV radiation. However, the persistence of hyperpigmentation in these babies over several months implies that increased melanogenesis must also occur.

Unexplained UV burns have also been reported after phototherapy for neonatal jaundice [4].

Phototoxic reactions

Phototoxic reactions to a number of drugs given to the neonate, or injected into the amniotic cavity, may occur following phototherapy for neonatal jaundice. The best known of these drugs is furosemide (frusemide) [5].

Methylene blue is sometimes injected into the amniotic cavity to detect premature rupture of the fetal membranes at the end of pregnancy. Methylene blue is a photosensitizing compound, and the use of phototherapy for hyperbilirubinaemia in a neonate that has been exposed *in utero* can lead to erythema and blistering [6].

'Bronze baby' syndrome

This is a rare complication of neonatal phototherapy, in which a dark-grey-brown ('bronze') pigmentation of the skin, serum and urine follows phototherapy, and remains as the hyperbilirubinaemia fades [7,8]. Hepatic disease appears to be a prerequisite for the development of this complication, and is thought to cause abnormal accumulation of the responsible pigment. This pigment has not yet been precisely identified, but it has been suggested that it might be a photoisomer of bilirubin [9]. The abnormal hepatic function also leads to increased serum levels of porphyrin and copper, which in turn form copper–porphyrin complexes. Photodestruction of these complexes leads to the production of brown pigments, which might also be responsible for the 'bronze' colour [10]. A third suggestion has been that the pigment is biliverdin, which might accumulate as a consequence of reduced conversion of haem to bilirubin [11].

In making the diagnosis, other causes of similar pigmentation need to be considered, particularly central cyanosis secondary to congenital heart disease, the 'carbon baby' syndrome [12] and the 'grey baby' syndrome, due to chloramphenicol overdosage [13]. These can be ruled out, where appropriate, by skin biopsy, serum chloramphenicol level, blood gas analysis and serum spectophotometry [7].

The bronze pigmentation gradually fades after discontinuation of phototherapy, but death has been reported in several affected neonates, either from kernicterus or from extrahepatic biliary duct atresia [14].

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Bullous and purpuric eruptions resulting from transient porphyrinaemia

Bullous photosensitivity reactions may be seen in neonates with congenital erythropoietic porphyria, hepatoerythropoietic porphyria, erythropoietic protoporphyria and harderoporphyria [1,2].

It is clear that under certain, probably exceptional, circumstances, a bullous eruption closely resembling epidermolysis bullosa may develop following phototherapy in a neonate, due to transient porphyrinaemia [3]. The circumstances in which porphyrinaemia may occur in neonates who do not have inborn errors of porphyrin metabolism are not fully defined, but probably include prematurity, cholestasis, disturbed hepatocellular function and renal failure.

More recently, localized purpuric eruptions have been described at exposed sites in a number of neonates who had all been transfused prior to phototherapy; it was proposed that the cause may also have been transient porphyrinaemia [4,5].

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Umbilical artery catheterization

Umbilical artery catheters are often used in neonatal intensive care, for frequent blood sampling, for continuous Po_2 and blood pressure monitoring, for administration of fluids and drugs, and for exchange transfusions. Vascular complication may ensue, including aortic thrombosis, embolization and spasm. These may result in lower limb ischaemia, which may progress to gangrene or necrosis [1–7]. Analogous ischaemic changes may occur in the lower arm or hand following cannulation of the brachial and radial arteries, respectively.

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Transcutaneous oxygen monitoring

Transcutaneous oxygen monitoring is frequently used in neonatal intensive care. This uses an electrode applied to the skin and maintained at 44°C in order to increase cutaneous blood flow. This generally causes a superficial burn, which usually resolves within 60 h [1], but occasionally, after longer periods of monitoring, there may be a more severe burn [2], sometimes with vesiculation [3]; such lesions may result in permanent scarring [2]. Measures have been recommended to reduce the risk of these injuries [4], but the transcutaneous Po_2 monitor has now been largely superseded by pulse oximetry, which uses an unheated sensor with no risk of burning.

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Electrocardiographic electrodes [1]

Raised skin-coloured lesions approximately 5 mm in diameter on the forehead have been described at the age of 3 months following the use of electrocardiographic electrodes in intensive care monitoring of premature neonates. Biopsy demonstrated reduction of elastic fibres; hence the lesions were interpreted as an iatrogenic form of anetoderma, possibly provoked by hypoxia secondary to skin pressure.

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Transillumination blisters [1]

Transillumination is used in neonatal intensive care units as a way of diagnosing pneumothorax and for finding arteries and veins for blood sampling. Occasionally this procedure provokes discrete 2–4 mm blisters with necrotic bases in acral locations close to common venous access sites, such as the wrists and the lateral malleoli. The occurrence of such lesions should arouse suspicions that the transilluminitor unit may be faulty, or that the infrared filters might be missing or switched off.

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Cutaneous necrosis following extravasation of intravenous medications

Leakage of total parenteral nutrition and of a variety of medications have led to local skin and subcutaneous tissue necrosis in the neonate [1–4]. It appears that the risk is highest when intravenous cannulae are inserted in the lower limbs, particularly above the ankle. Severe lesions may lead to joint contractures requiring plastic surgical correction. Alopecia may result from extravation from cannulae placed in the scalp.

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Iatrogenic dystrophic calcification

Iatrogenic dystrophic cutaneous calcification has been reported in three situations:
1 on the heel due to heel pricks during neonatal care [1,2];
2 at the site of extravasation of calcium-containing solutions given intravenously or by intramuscular injection [3–5];
3 on the scalps of children who have undergone electroencephalography with calcium chloride-containing paste on abraded skin [6].

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Needle marks [1]

Children who have received neonatal intensive care will frequently have punctate white scars at sites of needle insertion. Individual lesions will generally be imperceptible, but groups of lesions at particular sites may be more apparent, resulting in curious speckled scarring.

REFERENCE

1 Cartlidge PH, Fox PE, Rutter N. The scars of newborn intensive care. *Early Hum Dev* 1990; **21**: 1–10.

Damage following use of chest drains for pneumothorax

These chest drains can cause substantial scarring [1] and permanent damage to the breast in females.

REFERENCE

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Cutaneous necrosis following chemical burns

Cutaneous necrosis has been reported following skin contact with a variety of antiseptics in premature neonates, reflecting the increased rate of percutaneous absorption that is a feature in this age group [1–5].

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Neonatal adnexal polyp

Solitary self-healing polypoid lesions have been observed in some 4% of neonates in a Japanese survey [1,2]; their occurrence in other racial groups has yet to be documented. These lesions are firm, pink, polypoid nodules, about 1 mm in diameter, usually found close and medial to one or other nipple. Histology shows a normal epidermis, a vascular dermis containing prominent hair follicles with vestigial sebaceous glands and well-developed eccrine glands. These lesions generally separate from the skin spontaneously after a few days.

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Disorders caused by transplacental transfer of maternal autoantibodies

Clinical manifestations in the neonate have now been reported in a number of maternal disorders that are believed to be induced by circulating autoantibodies. Of particular interest to the dermatologist are those reports concerning lupus erythematosus (LE) (see below), pemphigus vulgaris [1–5], pemphigus foliaceus [6–7], herpes gestationis [8] and aphthosis [9].

Because IgA, IgM and IgE antibodies do not cross the

placenta in significant amounts, this phenomenon is restricted to diseases caused by autoantibodies of IgG class. Where complement is also involved in pathogenesis, this must be provided by the fetus, as it does not pass across the placenta. Complement can be detected in the fetus from about the 11th week of gestation [9]. Maternal IgG is catabolized more or less completely within the first 3–6 months of life, and antibody-mediated transplacental diseases can be expected to remit spontaneously within this period.

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Neonatal lupus erythematosus

Definition. Neonatal LE is a rare syndrome comprising transient skin lesions resembling subacute cutaneous LE, and/or congenital heart block, occurring in the babies of mothers with clinical or subclinical autoimmune connective tissue disease, and associated with the transplacental passage of maternal autoantibodies to the ribonucleoproteins (RNPs), Ro-SSA, La-SSB, or U_1-RNP [1].

Aetiology. It is now accepted that this disease is provoked in the fetus or newborn infant by maternal IgG autoantibodies that have crossed the placenta [2,3]. In 95% of cases, these are of IgG1 class [4] and are directed against the Ro RNP antigen [5]. These antibodies are relatively prevalent in young women, and appear to be compatible with apparently normal health. For these reasons, neonatal LE is seen more commonly than neonatal pemphigus vulgaris or neonatal herpes gestationis. La, anti-native DNA, anticardiolipin or antinuclear antibodies, or rheumatoid factor, may be present in addition to Ro antibodies [6,7]. A small proportion of affected infants do not have detectable Ro antibodies but do have La, U_1-RNP (nRNP) antibodies [6–8]. Many affected infants fail to demonstrate a significant titre of circulating antinuclear antibodies, unless human tissue is used, when a speckled fluorescence pattern will be seen [9].

The presence of Ro and La antigens has been demonstrated in fetal skin and cardiac conducting tissue [10,11].

Up to 60% of the mothers of infants with neonatal LE have no clinical evidence of connective tissue disease at the time of the birth [3,7,12]. However, there is a substantial risk of subsequent development of symptoms of autoimmune connective tissue disease [13]. About 40% of the mothers do have signs or symptoms of systemic lupus erythematosus (SLE), subacute cutaneous LE or the sicca syndrome [14–17], although these may be minimal. More recently, it has been recognized that about 5% of women of child-bearing age who present with leukocytoclastic vasculitis will have Ro antibodies [18], and it is probable that about 5% of babies with neonatal LE have mothers with leukocytoclastic vasculitis [13,19].

Pathology. Skin biopsy specimens from infants with cutaneous lesions generally demonstrate the features of LE, i.e. epidermal atrophy, liquefaction degeneration of basal keratinocytes, colloid bodies and a perivascular and periappendageal lymphohistiocytic inflammatory infiltrate in the dermis [14,20,21].

Direct immunofluorescence is positive in about 50% of cases, showing dermal–epidermal junction and perivascular deposition of IgG, IgM and C3 [14,21].

Autoimmune haemolytic anaemia and thrombocytopenia are seen in a small proportion of affected infants [14].

Cardiac abnormalities occur in about 60% of infants with neonatal LE [1], although there appear to be some racial differences in this frequency, which is reported to be smaller, for example, in Japan [22]. Fibrosis of the conducting tissue of the heart commonly results in congenital heart block. It has recently been shown that anti-Ro antibodies can bind to cardiac conduction cells during mid- to late fetal development, leading to altered membrane repolarization and selective damage to the atrioventricular (AV) node [23]. Other developmental abnormalities of the heart may also occasionally occur, including subendocardial fibroelastosis and fibrinous pericarditis [24,25].

Asymptomatic central nervous system vasculopathy has been demonstrated in neonatal LE by ultrasound and colour Doppler flow imaging, but its longer term significance is unknown [26].

These antibodies disappear from the infant's serum within about 6 months, but are more persistent in the mother [14,21,27].

Clinical features [9,14–17,22,28–31]. Most infants with neonatal LE have either skin lesions or cardiac lesions; approximately 10% have both [13,32]. About 90% of infants with neonatal erythematosus have only skin lesions.

In about two-thirds of those infants who develop cutaneous lesions, these are already present at birth [15,30]. In

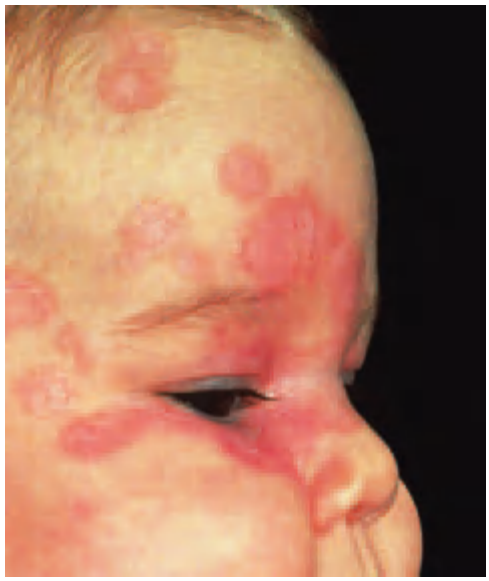

Fig. 14.2 Neonatal lupus erythematosus (LE): fading facial lesions in characteristic periorbital distribution, with residual atrophy, in a 4-month-old infant.

the remainder, the lesions appear during the first 2–3 months, although their appearance may be delayed as long as 5 months [13].

The skin lesions of neonatal LE generally take the form of well-defined areas of macular or slightly elevated erythema, frequently annular, occurring predominantly on the face, particularly the forehead, temples and upper cheeks, and on the scalp and neck (Fig. 14.2). A 'spectacle'-like distribution of lesions around the eyes is especially characteristic. The chest, back or limbs may also be affected.

Less commonly, lesions take the form of annular erythema without an epidermal component; this type of presentation has predominantly been reported in Japanese infants [22,27].

Subcutaneous lesions have also been described [33].

Occasionally, neonatal LE presents as extensive reticulate erythema with atrophy, closely resembling cutis marmorata telangiectatica congenita [34,35].

Depigmentation may be very prominent in racially pigmented infants [36].

Provocation or exacerbation of lesions by sun exposure has been reported in some cases.

Follicular plugging is not prominent, but scaling is a common early feature, and a degree of atrophy and/or telangiectasia are frequent long-term sequelae. Permanent hair loss may occur.

Lesions resembling morphoea have been reported [37].

In most cases, the skin lesions have resolved within the first year, but areas of atrophy and/or telangiectasia may be more persistent [38,39]. Long-standing depressions have followed subcutaneous lesions [33]. The most frequent sites for such lesions are the temples and scalp.

Systemic features are detectable in over half of all affected infants, of which cardiac involvement is the commonest, occurring in about 50% of cases. Cardiac involvement tends to affect a different group of infants, heart and skin abnormalities occurring together in only about 10% [9,13,32]. The reasons for this are unclear. Congenital heart block can be detected as early as the 18th week of gestation by ultrasound or electrocardiography [40]. The block is generally permanent, and is not associated with structural cardiac abnormalities such as septal defects. About a half of affected infants require pacemakers [29,40].

A smaller proportion of infants have combinations of hepatomegaly, splenomegaly, lymphadenopathy, autoimmune haemolytic anaemia, thrombocytopenia and pneumonitis, which are generally mild in degree and fairly transient.

Prognosis [41]. Infants with skin lesions alone, or with skin lesions and systemic features other than heart block, generally show little sign of residual disease after the age of 1 year. However, their long-term prognosis must remain slightly guarded in the light of reports of the later development by some of full-blown connective tissue disease [25,29,42–44]. Conduction defects of the heart tend to be permanent, and when severe are associated with a significant mortality [13,29,45].

The risk of recurrence in further pregnancies appears to about 25% [13,46]. This risk appears to be influenced by immunogenetic factors [47]. Spontaneous abortion and stillbirth do not appear to be more frequent in further pregnancies of mothers who have had a previous child with neonatal LE [13]. Mothers with Ro antibody may experience recurrent fetal loss if they do not have SLE, but do not appear to do so if they do have SLE [48].

Diagnosis [7]. The lesions of congenital rubella or cytomegalovirus infection may need to be considered, although these are of purplish colour and purpura is generally prominent. Congenital syphilis may also need to be excluded, but whereas mucosal, periorificial, and palmar and plantar lesions are common in congenital syphilis, these features are rare in neonatal LE. However, confusion may be caused by the false-positive antibody tests that are as much a feature of neonatal as of acquired LE.

Atrophy and telangiectasia of the cheeks is seen with photosensitivity in Bloom's syndrome, and without photosensitivity, in most cases, in the Rothmund–Thomson syndrome (see Chapter 12). In these disorders, skin lesions are not present at birth and generally appear later than in neonatal LE.

A skin biopsy will usually allow an accurate diagnosis of neonatal LE, particularly if combined with direct immunofluorescence studies, and tests for the appropriate circulating autoantibodies in both the mother and the child.

Treatment. The skin lesions of neonatal LE require no treatment, but sun protection is essential. Occasionally, thrombocytopenia, haemolytic anaemia or hepatitis may warrant systemic steroid therapy [49]. Up to 50% of infants with cardiac involvement will require a pacemaker [22].

The pregnancy of a woman who has Ro, La or U_1-RNP antibodies should be monitored to detect a slow fetal heart rate [50,51]. Treatment with high-dose systemic steroids may be indicated for fetal bradycardia where there are signs of heart failure [52].

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Neonatal pemphigus vulgaris

Pemphigus vulgaris is unusual in pregnancy, because it is largely a disease of an older age group and because affected individuals receiving systemic treatment rarely become pregnant. Nevertheless, several cases of trans-

placentally transmitted pemphigus vulgaris have been reported [1–6]. Not all mothers have had clinically apparent disease during pregnancy [7]; in other cases the disease has been mild [8].

Affected infants have had cutaneous and/or mucosal erosions or bullae. Several have been stillborn [1,6]. Direct immunofluorescence has been positive in skin biopsies from all affected infants, and circulating IgG pemphigus antibodies have been found in the majority.

No treatment is required; lesions have resolved spontaneously within about 3 weeks, and circulating IgG antibodies have become undetectable by the end of the second month of life.

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Transplacental pemphigoid (herpes) gestationis

Cutaneous lesions occur in about 10% of infants born to mother with pemphigoid gestationis, although maternal IgG antibasement-membrane autoantibody can be found in all infants of affected mothers [1,2]. The lesions may be present at birth or they may appear at any time up to the third day of life [3,4]. These lesions may vary from evanescent, non-specific, erythematous or urticarial papules to fully developed bullae [5,6]. Lesions in the infant may be extensive [7]. Spontaneous regression of lesions within 3 weeks is the rule. Direct immunofluorescence is normal by the end of the first month, and circulating IgG antibasement-membrane-zone antibody can no longer be found.

Earlier reports of increased fetal and infant morbidity and mortality when mothers have pemphigoid gestationis [8] have not been confirmed [9–11]. However, there does appear to be an increased risk of premature delivery when a mother has herpes gestationis [10,11]. The risk of adrenal insufficiency should be considered in neonates whose mothers have been treated with prednisolone for prolonged periods.

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Transplacental transfer of maternal malignant disease

Transplacental transfer of maternal malignant disease is fortunately extremely rare, despite the fact that malignancy occurs in 1 in 1000 pregnancies [1,2], and it is well established that maternal cells regularly reach the fetus [3].

The malignancy transferred in this way has been malignant melanoma in about 90% of cases, although this particular malignancy accounts for only about 8% of those occurring in pregnant women [4]. Malignant melanoma transmitted in this way may result in the appearance of nodular skin deposits in the neonate. Spontaneous regression of transplacentally transferred malignant melanoma has been reported [5,6].

Transplacental transmission of acute monocytic leukaemia [7] and of natural killer (NK) cell lymphoma [8] have also been reported.

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Disorders caused by transfer of toxic substances in maternal milk

When considering the cause of any rash in a young infant, the possibility that it reflects exposure of the mother to a toxic substance that has been transferred in her milk needs to be borne in mind. A good example is provided by two reports of bromoderma occurring in neonates whose mothers had taken bromide medicinally [1] or had been accidentally exposed in a photographic laboratory [2].

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'Collodion' baby

SYN. LAMELLAR DESQUAMATION/EXFOLIATION OF THE NEWBORN

Aetiology and nomenclature. This term describes a highly characteristic clinical entity. It precedes the development of one of a variety of ichthyoses, the commonest of which are the autosomal recessive ichthyoses termed lamellar ichthyosis and non-bullous ichthyosiform erythroderma [1–3] (see Chapter 34). The collodion baby phenotype has been reported in the rarer autosomal dominant form of lamellar ichthyosis [4] and a possibly autosomal dominant form of non-bullous ichthyosiform erythroderma [5]. It is also characteristic of the trichothiodystrophy-ichthyosis syndrome [6,7].

There are other ichthyoses in which an initial collodion baby phase has occasionally been reported. These include ichthyosis vulgaris [2], X-linked ichthyosis [8], Netherton's syndrome [9], neutral lipid storage disease [10] and the Sjögren–Larsson syndrome [2], but the great majority of neonates with these disorders do not demonstrate the collodion baby phenotype. A transient collodion membrane has also been reported in two neonates with Gaucher's disease [11,12].

In at least 10% of cases, the collodion baby phase is followed by a relatively mild ichthyosis of lamellar type; this may be so mild as to be considered more or less normal [2,3,13–19]. Autosomal recessive inheritance has been reported in this type of case [17], but it remains possible that these cases are genetically heterogeneous.

Pathology [1,2,20,21]. It was at one time popular to regard the collodion membrane as retained periderm (epitrichium) [22]. Histologically, however, the membrane is essentially orthokeratotic, rather than parakeratotic like the periderm [1,2,16,21], making this a highly improbable explanation. Apart from a compact, thickened orthokeratotic stratum corneum, the epidermis is fairly normal, similarly the dermis.

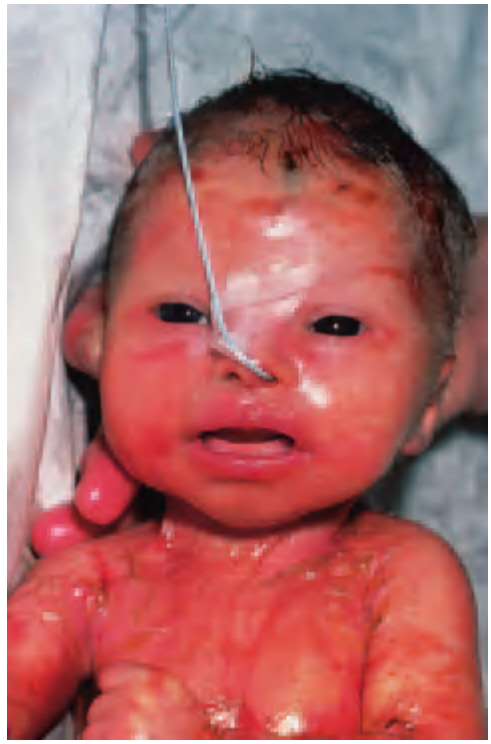

Fig. 14.3 Lamellar desquamation of the newborn in a 7-day-old infant. This child required peritoneal dialysis for acute renal failure secondary to inadequate hydration. A year later, the skin was normal apart from minimal fine scaling.

Although the histology of the skin is identical at birth whether the child later develops a severe ichthyosis or not, at about 15 days it may be possible to make a prediction on histological grounds [16], even though the clinical features are still indistinguishable.

Electron microscopy of the epidermis at 2 days in a baby whose skin later became clinically normal showed several distinctive features [14]. The upper two-thirds of the stratum corneum were of abnormal appearance; the corneocytes were convoluted and irregular in shape, and contained unusual, small, dense intracellular granules. There were large numbers of intercellular lamellar (Odland) bodies and exceptionally well-preserved desmosomes.

Clinical features [1–3,9,21,23,24]. The severely affected infant is bright red and encased in a taut, glistening, yellowish translucent covering resembling collodion (Fig. 14.3). The face is immobilized; tension on the skin results in ectropion, eversion of the lips (eclabion), producing a rather fish-like appearance of the mouth, and effacement of the nose and ears. The nostrils may be blocked. The skin over the fingers, hands, toes and feet may result in immobility and may interfere with blood flow, occasionally resulting in the loss of parts of digits.

Within hours, this membrane dries and cracks, and bleeding may occur along the resulting fissures. Within 1 or 2 days, it starts to peel off, either in extensive sheets or as large, light-brown scales, but may reform several times. The shedding will generally be more or less complete within 4 weeks. Subsequently, the typical features of one of several varieties of ichthyosis gradually emerge over a period of weeks or months.

During the first day or two, tightness of the skin on the thorax may interfere with respiration, and very occasionally, respiratory distress may be caused by nasal obstruction.

Diagnosis. The appearance of the collodion baby is unmistakable.

A degree of cracking and desquamation is a characteristic cutaneous finding in babies who are small for gestational age and/or post-term, presumably due to placental insufficiency, but this is unlikely to be mistaken for true lamellar desquamation of the newborn because of the lesser severity of the skin changes and the presence of other clinical features of these two states. Babies who are erythrodermic at birth, due, for example, to Netherton's syndrome, or to the Conradi–Hünermann syndrome, may be mistaken for collodion babies, but careful examination will reveal no collodion membrane.

The appearance of the neonate with harlequin ichthyosis (see below) has much in common with the collodion baby, the principal difference being the greater thickness of the stratum corneum, which typically encases the baby like a suit of armour. However, clinical differentiation may be less straightforward in milder cases.

Restrictive dermopathy also results in a neonate with tight and immobilizing skin, but in this condition, the skin appears thin and transparent, with prominent underlying blood vessels. The mouth is also open, but ectropion is not generally present. The skin does not dry out and come away. Death occurs rapidly as a consequence of respiratory failure.

Neonates with the lethal autosomal recessive Neu–Laxova syndrome [25] may have skin changes closely resembling a collodion membrane. The condition is characterized by intrauterine growth retardation, and central nervous system, skeletal and cranial abnormalities.

Boys with hypohidrotic ectodermal dysplasia may show lamellar scaling at birth, but it is unlikely that this would be mistaken for a collodion membrane.

Prognosis. The collodion baby is at risk, largely because of the consequences of loss of skin barrier function, resulting in:

- impaired temperature regulation;
- increased insensible water loss [26–28], which may lead to acute renal failure and/or permanent brain damage [29] if fluid replacement is neglected;
- septicaemia [27].

Respiration may become compromised as a result of intrapartum aspiration of squamous debris shed into the amniotic fluid [30]. Interestingly, this debris can be seen on fetal ultrasound, and in such cases, early delivery by caesarean section may be protective of life.

Immobility of the chest may also compromise respiratory function, and predispose to pneumonia.

In the short term, mortality from these causes is substantial.

The longer-term outlook depends on which type of ichthyosis develops, and it is important to be aware that there is no correlation between initial severity in a collodion baby and the gravity of the ichthyosis that follows. At present, only observation over a period of months will reveal the ultimate fate of the skin in collodion babies. It has however been suggested that a skin biopsy at about the 15th day may be helpful in this respect [16].

Treatment. The most important element in treatment is an awareness of the possible complications, as outlined above.

The baby should be nursed in an incubator in a high-humidity atmosphere, with careful monitoring of body temperature. Great attention needs to be given to fluid and electrolyte balance. In severe cases, fluid therapy should be given intravenously, but in less severe cases oral or nasogastric fluid supplementation will suffice. Peritoneal dialysis may be indicated if renal failure occurs.

Fluid loss can be reduced by frequent applications of lipid; a 50 : 50 mixture of white soft paraffin and liquid paraffin is ideal for this purpose. Frequent oiling of the skin increases mobility and comfort, accelerates healing of fissures and may reduce the risk of infection.

Prevention of infection is of the greatest importance in saving these babies. Great attention should be paid to this aspect of care. Skin punctures should be kept to a minimum, and vascular access should be avoided as far as possible.

Bands of tight skin constricting digits, hands or feet may occasionally require surgical division.

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Eczematous eruptions in the newborn

Eczematous eruptions are extremely common during the newborn period. Few are severe, and most are transient. However, in some babies they herald more chronic and possibly severe atopic dermatitis, and, in a few instances, they may provide an important clue to serious internal disease, as for example in the cases of zinc deficiency and the Wiskott–Aldrich syndrome (WAS). The following varieties of neonatal eczematous eruption will be considered here: contact dermatitis, particularly primary irritant napkin dermatitis and perianal dermatitis, intertrigo and infantile seborrhoeic dermatitis.

Contact dermatitis in the neonatal period

The skin of the newborn is particularly sensitive to irritants. Factors that contribute to the high incidence of primary irritant reactions in this age group include the widespread use of inappropriate toxic applications such as antiseptics, prolonged skin contact with urine and faeces, and the frequent presence of occlusive conditions. The commonest clinical patterns of primary irritant dermatitis seen in the newborn period are perianal dermatitis and napkin dermatitis. A non-allergic form of contact dermatitis to plastic identification bracelets has also been described in neonates [1]. The alcohol burn is a less common, but very important, form of acute irritant reaction.

True allergic contact dermatitis is exceedingly unusual in the neonatal period [2], partly because of the relative difficulty of sensitizing the skin for type IV hypersensitivity responses at this age [3,4] and partly because of the lack of appropriate antigen contact. Many authors have argued that reports of allergic contact dermatitis in neonates based on positive patch-test results require cautious interpretation, because the concentrations of allergens generally used for such tests may elicit irritant responses in small children [5–7], but relevant positive results have been described in early infancy to allergens such as nickel (from earrings), epoxy resin (from a plastic identification bracelet), and the components of various topical applications, particularly those used for the treatment of napkin dermatitis [7].

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Perianal dermatitis of the newborn

Aetiology. Perianal dermatitis has been reported to have an overall incidence of 5–20% [1]. The incidence is lower in breastfed infants than in those fed cow's milk formulae [2,3]. It has been suggested that this difference might be explained by the higher faecal pH of the formula-fed infants [3], but this has not been confirmed [4]. Although the precise cause of perianal dermatitis in the newborn remains unknown, it is assumed that it represents an irritant response to faecal constituents. It is likely that there is considerable variation in susceptibility.

Clinical features. In the great majority of cases, erythema of the perianal skin makes its initial appearance during

the first 8 days of life [2]. In the mildest cases, the erythema is confined to a zone some 2 cm in diameter around the anus, but commonly it extends to 4 cm or more. In the more severe forms, the affected skin may be oedematous and superficially eroded. Healing occurs spontaneously in 7–8 weeks. Although it usually occurs alone, perianal dermatitis may sometimes be associated with primary irritant napkin dermatitis or seborrhoeic dermatitis of infancy.

Diagnosis. The site and the early age of onset usually establish the diagnosis, but other dermatoses that appear in the napkin area need to be considered. The presence of pain and bleeding suggests a possible developmental defect of the anal papillae [5].

Treatment. Little treatment is usually needed, other than attention to hygiene. The affected area should be washed with water and a water-miscible emollient as soon as possible after defecation, and a protective lubricant such as White Soft Paraffin BP should be applied immediately afterwards.

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Primary irritant napkin dermatitis

SYN. DIAPER DERMATITIS

Terminology. The term napkin dermatitis implies an inflammatory eruption of the napkin area. Such an eruption may have many causes. The term is therefore best avoided except in this more general sense, and the term primary irritant napkin dermatitis should be preferred for the condition described here, even though its exact aetiology remains unestablished.

Aetiology [1–6]. It seems unlikely that every case of primary irritant napkin dermatitis has precisely the same combination of causes. It is, however, exceedingly rare in the absence of napkin wearing, and at least a degree of urinary or faecal incontinence. The following factors need to be considered in any discussion of the aetiology of primary irritant dermatitis.

Maceration by water. The stratum corneum is almost exclusively responsible for the water barrier function of the epidermis, containing cells that are continuously sloughed off and renewed in a cycle of 12–24 days [7]. The hydrophobic extracellular matrix acts as the water barrier, preventing water loss from the body, and the entry of water and other hydrophilic substances, while the hydrophilic cells of the stratum corneum ('corneocytes') provide mechanical protection from the external environment in the form of a waxy layer.

Excessive wetness has several effects on the stratum corneum. Firstly, it makes the skin surface more fragile, and therefore more sensitive to frictional damage [4,8]. Secondly, it interferes with the protective barrier function [8–10], allowing increased permeation of irritant substances into the sensitive living layers of the skin below the stratum corneum, and exposure of these layers to the drying effect of the air and to the entry of harmful microorganisms.

Prolonged occlusion of the skin can itself produce erythema, particularly if water is kept in contact with the skin surface [1], and it has been suggested that prolonged contact with water alone can provoke dermatitis [11].

Friction. It seems likely that friction between the skin and the fabric of the napkin will also be an important factor in most cases. This is supported by the frequent predilection of the eruption for sites where such friction would be maximal, i.e. the inner surfaces of the thighs, the convex surfaces of the genitalia, the buttocks and the waistline. Friction would be able to breach the stratum corneum in the presence of maceration.

Urine. Newborn babies pass urine more than 20 times in 24 h. This frequency reduces through infancy to an average of 7 times in 24 h at 12 months [12].

For many years it was believed that ammonia, produced by bacterial degradation of urea in the infants' urine, was the major cause of primary irritant napkin dermatitis [13,14]. It is now clear that this is not the case [4,15]. Neither the ammonia levels found in the first morning napkin nor the prevalence of urea-splitting microorganisms differ between infants with or without primary irritant napkin dermatitis [4]. The microorganisms isolated from affected infants are not able to release ammonia either faster or in greater quantity that those from unaffected infants [4]. It has been shown that urine containing various concentrations of ammonia does not cause significant erythema when applied under occlusion for 24 h to intact infants' skin, although it can do so when the skin has previously been abraded [4]. However, only about one in four of infants with primary irritant napkin dermatitis in this study had napkin ammonia levels in excess of the minimum concentration shown to cause such erythema. It appears, therefore, that the presence of ammonia is not mandatory, although it almost certainly will aggravate the eruption when the integrity of the skin is already compromised.

It has been suggested that urinary degradation products other than ammonia might also play a role. One study has shown that urine allowed to stand for 18 h at 37°C could induce dermatitis when applied to infants' skin, whereas fresh urine could not [16]. The effect was not related either to the pH or to the ammonia concentration, but the identity of the relevant irritant could not be established.

It is now clear that the role of urinary pH is critical. The higher the pH of the urine (i.e. the greater the alkalinity) the more liable an infant is to develop irritant napkin dermatitis. However, it seems that alkaline urine is not directly harmful; its harmful effect results from its interaction with faecal material in the napkin (see below).

In addition, urine appears to increase epidermal permeability more effectively than water alone [9].

Faeces. It has been known for many years that human faeces have an irritant effect on skin [17]. Infants' faeces contain substantial amounts of pancreatic protease and lipase, and similar enzymes are produced within the gut by a variety of bacteria [18,19]. These faecal enzymes appear to be important skin irritants [20,21]. The irritant effect of such enzymes may be enhanced by many factors, particularly impaired barrier function and high pH. One of the factors that have been shown to affect faecal pH is the infant's diet, a higher pH being found in the cow's milk formula-fed infant [22].

Ureases are produced by a variety of faecal bacteria [18], and have the effect of increasing pH when mixed with urine. Increased pH enhances the activity of faecal lipases and proteases [9]. This perhaps provides an explanation for the anecdotal observation that cow's milk formula-fed infants appear more liable to primary irritant napkin dermatitis than breastfed infants, as the faeces of the former group have been shown to be more heavily colonized by urease-producing bacteria [23].

A variety of other factors may lower the infant's threshold for development of irritant napkin dermatitis; or may worsen the eruption once it is established. These include:

Poor or misguided skin care. The use of liquid soap for washing [24] and of talcum powder remain surprisingly common; both will increase risk of an irritant dermatitis.

Microorganisms. Although it has often been claimed that bacterial infection plays an important role in the common primary irritant type of napkin dermatitis, quantitative studies have consistently shown that the bacterial flora isolated from such eruptions does not differ materially from that isolated from the same area of skin in normal infants [15,25,26]. Neither does the type of napkin appear to influence the bacterial flora [27].

On the other hand, the evidence for an aetiological role for *Candida albicans* seems somewhat stronger. This organism has been isolated from the affected area in many infants with the primary irritant type of napkin dermatitis, but only very infrequently from the same area in normal infants [15,26,28,29]. Furthermore, there appears to be a good correlation between the severity of primary irritant napkin dermatitis and the level of *C. albicans* in the faeces [3].

The question of a role for *C. albicans* is complicated by the issue of the relationship between primary irritant napkin dermatitis and the classical form of napkin candidiasis. It is possible that, in most cases, the latter is a complication of the former, and this view is supported by the fact that maceration of the skin is virtually a prerequisite for the establishment of *C. albicans* infections in human skin [30,31]. It is likely therefore that this organism will become established in the napkin area of infants who have primary irritant napkin dermatitis if it is present in the faeces.

Antibiotics. The use of broad-spectrum antibiotics in infants for conditions such as otitis media and respiratory tract infections has been shown to lead to an increased incidence of irritant napkin dermatitis [32]. This appears to parallel increased recovery of *C. albicans* from the rectum and skin in such infants.

Diarrhoea. The production of frequent liquid faeces is associated with shortened transit times, and such faeces are therefore likely to contain greater amounts of residual digestive enzymes.

Developmental anomalies of the urinary tract. Those anomalies that result in constant passage of urine will predispose to urinary tract infections.

In summary, the precise aetiology of primary irritant napkin dermatitis remains unestablished. Maceration and friction appear to be important in breaching the epidermal barrier. Faecal proteolytic and lipolytic enzymes appear able to act as irritants in skin whose barrier function is impaired, particularly if the ambient pH is high. The main factors in increasing the pH appear to be the action of faecal urease on urine, and the infant's diet. Secondary invasion by *C. albicans* appears to be a risk where this organism is present in faeces.

Pathology. The histological picture is generally that of primary irritant dermatitis with epidermal spongiosis and mild inflammatory changes in the dermis.

Clinical features [33,34]. Primary irritant napkin dermatitis is not often seen during the first 3 weeks of life. The onset is most often during the third to the 12th week, and the peak prevalence is seen between the seventh and 12th months [3,35]. Essentially the same condition has been reported in older children and adults who are incontinent of urine [36–38].

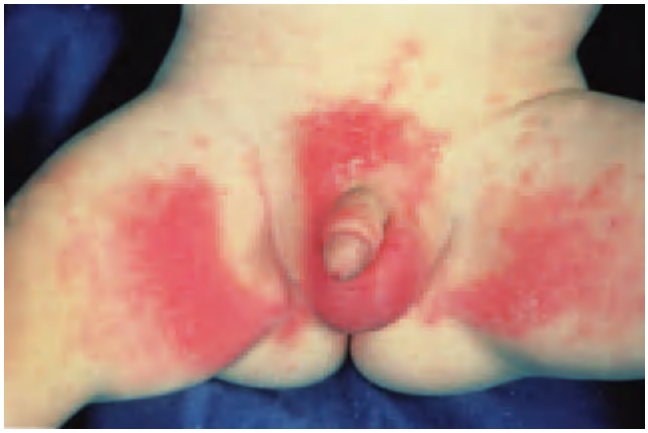

Fig. 14.4 Primary irritant napkin dermatitis, affecting the convexities predominantly with sparing of the groin creases.

The overall incidence of the condition is difficult to establish, and may now be less than in the past, due to a general change to disposable napkins, but there is evidence that some 50% of infants are affected to some degree at some stage [3]. Another index of the degree of the problem is provided by the fact that in one survey it accounted for some 20% of all skin consultations in children aged under 5 years in the UK [39]. Both sexes and all races appear to be equally affected.

The most common form of primary irritant napkin dermatitis comprises confluent erythema of the convex surfaces in closest contact with the napkin, i.e. the buttocks, the genitalia, the lower abdomen and pubic area, and the upper thighs. The deeper parts of the groin flexures are generally spared (Fig. 14.4).

In some infants, the eruption is more or less confined to the margins of the napkin area ('tidemark dermatitis') and may reflect either chafing against the edge of the napkin or prolonged skin contact with the edges of impervious napkin covers or pants.

Another distinctive pattern that has recently been described is one where the eruption is localized to the lateral parts of the upper thigh and buttock, most often unilaterally, but not infrequently bilaterally, in a position that corresponds to the areas where direct contact may occur with the bands that fasten the napkin [40,41]. It appears most often to be due to an irritant effect, but may also be a reflection of contact sensitization to rubber or glue chemicals [42].

Where the reaction is acute, the erythema may have a glazed appearance and be followed by peeling of the skin in sheets. A finer scaling is more commonly present in more long-standing cases. Post-inflammatory hypopigmentation may be a striking feature in racially pigmented infants.

Occasionally, an erosive form of primary irritant napkin dermatitis is seen, in which small vesicles and erosions may develop into rather characteristic, shallow, round ulcers with raised crater-like edges ('Jacquet's dermatitis').

In both sexes, involvement of the genitalia may lead to dysuria and occasionally, where the glans penis is severely affected, male infants may experience acute retention of urine [33].

Several fairly distinctive variants of primary irritant napkin dermatitis occur. When secondary invasion by *C. albicans* is present [15], the erythema may be more intense, and will no longer spare the deeper parts of the flexural folds. The margin tends to become more defined, scalloped with peripheral scaling. Within the marginal area small pustules are often visible, and these may also be seen scattered beyond the periphery of the erythema—so-called 'satellite' lesions. This clinical appearance is associated with faecal carriage of *C. albicans* [43].

In the second, less common variant, the erythematous areas are similarly well marginated but take on a markedly psoriasiform aspect with prominent scaling of a rather more adherent and micaceous type [39,44,45]. The onset of this eruption, commonly termed *napkin psoriasis*, may be quite sudden and its extension rapid. The relationship of this eruption to true psoriasis is discussed in Chapter 35.

A herpetiform presentation of primary irritant napkin dermatitis has occasionally been described [46]. This takes the form of an eruption of vesicles and pustules followed by shallow erosions, closely resembling herpes simplex clinically, but showing no evidence of this infection pathologically.

Rather rarely, one may see domed, reddish brown or purple nodules as an additional feature. These lesions, usually known as infantile gluteal granulomas, are discussed later in this chapter.

Not infrequently, primary irritant napkin dermatitis affects areas beyond the confines of the napkin area itself. This appears particularly likely where there has been prolonged contact between the skin, urine and an occlusive surface such as a plastic cot sheet. Thus, the lateral aspects of the thighs, the calves and the heels are especially commonly affected.

In other babies, rapid dissemination of the rash occurs without any clear explanation, most characteristically in the form of expanding nummular lesions on the trunk, and more confluent erythematosquamous plaques in the flexures of the axillae and neck. An 'id' reaction to *C. albicans* has been proposed as the explanation for some of these rashes, but without any convincing evidence being provided to support such a view [28,45,47]. Where a rash in the napkin area is the first manifestation of psoriasis, other lesions of psoriasis may eventually make their appearance elsewhere. Similarly, napkin dermatitis may be the first sign of atopic dermatitis (see Chapter 18), or of 'seborrhoeic dermatitis of infancy'.

In infants with racially pigmented skin, hypopigmentation may be very prominent, and is sometimes the

parents' principal anxiety. When there is an associated eczematous eruption on the face, this may similarly feature marked hypopigmentation, and this may be the presenting problem [48].

Prognosis. Primary irritant napkin dermatitis will almost always show some response to therapy, and, in the longer term, it will resolve when napkins are no longer worn. However, in some children the napkin area eruption is merely the first sign of a susceptibility to chronic skin disorders, particularly psoriasis and atopic dermatitis. Since atopic dermatitis often initially presents with a napkin dermatitis indistinguishable from simple primary irritant napkin dermatitis, one has to be cautious not to give too optimistic a prognosis to parents of any child with such a rash.

Differential diagnosis. A wide variety of skin disorders present with lesions in the napkin area during infancy.

A confluent glistening, sharply marginated erythematous rash with peripheral desquamation and/or pustulation, and usually with satellite pustules, is, together with oral candidiasis, the typical presentation of neonatal candidiasis, a superficial *Candida* infection transmitted to the baby during birth [49]. The rash normally appears during the second week of life, and is aetiologically distinct from napkin-area *Candida* infections secondary to primary irritant napkin dermatitis.

In the past, congenital syphilis was relatively common, and had to be considered seriously in any infant with a dermatosis in the napkin area. Congenital syphilis is now rare in many countries, but its continued existence must constantly be borne in mind. Reddish brown macules, sometimes slightly raised, arise principally on the extremities including the palms and soles, and on the face mainly around the mouth. The napkin area is also frequently affected. Bullous or erosive lesions may occur in the napkin area. Flexural condylomas, rhinitis, hepatosplenomegaly and low birth weight are regular features.

The important diagnosis of zinc deficiency must be considered in any infant with a napkin dermatitis which fails to respond to appropriate treatment. A history of prematurity should increase one's suspicion, and a normal plasma zinc level does not rule out the diagnosis. Infants with napkin eruptions caused by zinc deficiency usually have a concurrent facial dermatitis extending from the perioral area, an erosive paronychia and erosive lesions in the palmar creases of the hands.

Multiple carboxylase deficiency is a rare cause of rashes in the napkin area; however, the rash most characteristically starts on the face with a presentation resembling seborrhoeic dermatitis.

In infancy, one of the commonest presentations of Langerhans' cell histiocytosis (see Chapter 52) is intertrigo, which tends to be very persistent and to become eroded as the disease progresses. Although the intertriginous eruption of Langerhans' cell histiocytosis may appear very early, more often it does not do so until after the third month. Initially, the eruption comprises small, yellowish papules, which become confluent and subsequently may become ulcerated. The scalp is almost always concurrently affected, particularly the retro-auricular area.

Some diagnostic difficulty may be encountered by the occasional occurrence of dermatophyte infections in the napkin area [50–52]. It is important to bear in mind that the clinical appearances of such infections are likely to have been substantially modified by the application of topical corticosteroids.

Primary HSV infection of the genital area occurs from time to time in both boys and girls. The eruption is acute and accompanied by malaise and pyrexia.

Unusual infections causing eruptions in the napkin area should alert one to the possibility of primary or acquired immunodeficiency [53].

Treatment. Successful treatment of primary irritant napkin dermatitis depends on recognition of the relevant aetiological factors in the individual child, but can nevertheless generally follow a fairly standard pattern. The provision of topical medications without attention to such details as the frequency of napkin changes is often associated with therapeutic failure. The elements of successful treatment include the following:

Attention to the napkins

(a) *Disposable versus washable cloth napkins*. The use of good-quality disposable napkins, particularly those containing absorbent gelling materials ('super-absorbent' disposable napkins), is associated with a lower incidence and with lesser severity of napkin dermatitis compared with washable cloth napkins [3,54–56]. These gels are able to absorb about 80 times their own weight of water, and their use therefore results in reduced wetting, and, therefore, less maceration of the skin [57]. The use of such napkins is also associated with more normal skin pH values [54].

(b) *Continuous administration of emollient from certain disposable napkins*. Disposable napkins are now available in which the layer next to the skin (the 'topsheet') is impregnated with an emollient, usually predominantly white soft paraffin. The use of this type of napkin has been shown to reduce the severity of irritant napkin dermatitis [58].

(c) *Frequency of napkin changes*. The frequency of napkin changes is also important, but probably less so now, because the absorbency of disposable napkins has increased greatly over recent years. It remains important however to change napkins as soon as possible after defaecation.

(d) *Care of washable napkins*. The use of antiseptic solutions for the storage of cloth napkins prior to washing is more or less universal, and is safe as long as suitable agents are used and washing and rinsing procedures are adequate.

Poisoning of infants by antiseptics used in the laundering of napkins is well documented [59–61]. The quaternary ammonium compounds are now regarded as the best choice, of which benzalkonium chloride is perhaps the most widely employed. Antiseptics should never be used during the rinsing process.

Machine washing is generally preferable, as the cleaning and rinsing processes are reliable and thorough. A lower incidence of primary irritant napkin dermatitis has been demonstrated in babies whose napkins were laundered commercially rather than domestically [35]. 'Biological' detergents are best avoided, as are fabric 'conditioners' added during the rinsing. Tumble drying is preferable to air drying because it leaves the napkins softer, and therefore less liable to chafe.

Routine skin care in the napkin area. A routine of skin care should be instituted that will help prevent recurrence after the eruption has been successfully cleared. At each napkin change, a water-repellent emollient such as White Soft Paraffin BP, a half-and-half mixture of White Soft Paraffin BP and Liquid Paraffin BP, Zinc and Castor Oil Cream BP, or Bepanthen® [62] ointment should be applied.

When the napkin has been soiled, the area should be cleansed with water and a water-miscible emollient such as Aqueous Cream BP, and dried before applying a water-repellent emollient. Traditionally, cotton-wool balls have been used for this purpose. However, prewetted wipes are now available commercially which combine a very soft fabric with water, without the additives such as alcohol and fragrance that made such products undesirable in the past. It is very important that cleansing of the skin be undertaken as gently as possible, with the minimum of friction.

During remission, the baby should be bathed daily with a dispersible or semidispersible bath oil added to the water, and a water-miscible emollient should be used as a cleansing agent. While the eruption is under treatment, such baths should ideally be given twice a day.

The use of talcs and proprietary over-the-counter preparations containing potential irritants should be discouraged.

Specific therapy. Topical corticosteroids are helpful, and are indicated in all but the mildest cases. There is, however, virtually never any need to use applications containing anything more potent than 1% hydrocortisone. Such an application should be used twice a day after the bath, ideally in an ointment base.

It must be borne in mind that the rate of percutaneous absorption of corticosteroid from topical application in the napkin area will be considerably enhanced by the occlusive conditions found at this site. Fears that corticosteroid absorption might interfere with descent of the testes in male infants have not been confirmed in those of normal birth weight, but the possibility remains that such a problem could arise in low birth-weight babies [63].

As the eruption is often secondarily infected with *C. albicans*, the use of an ointment containing an anticandidal agent such as miconazole is justified and has been shown to be effective [64]. Systemic antibiotics are very rarely indicated, and there is no convincing evidence that oral nystatin has any additional therapeutic or prophylactic value when used in combination with a topical anticandidal agent [1,29,65].

In cases where flow of urine and especially of faeces over the skin is more or less continuous, topical sucralfate has been reported to provide a particularly effective barrier [37].

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Infantile gluteal granulomas

This term has been applied to a condition that arises as a complication of the primary irritant type of napkin dermatitis [1]. The apparent absence of any reports of the disorder before 1971, in contrast to the substantial number published throughout the world during the next decade, implied that this may have been a modern phenomenon, perhaps related to changes in the care of the napkin area in general, and the treatment of napkin dermatitis in particular. Conversely, a decrease in the number of case reports during the last decade may reflect a real improvement in these aspects of infant care.

In most, but certainly not all [2,3] of the reported cases, rather potent topical corticosteroids had been used, and the authors believed them to have been important precipitating factors [4–7]. *Candida albicans* has also been considered as an aetiological factor [6], but cannot be isolated from the napkin area in such infants any more often than in uncomplicated cases of napkin dermatitis [5]. Intracutaneous intradermal tests to *C. albicans* antigen have not shown evidence of either immediate or delayed hypersensitivity, and serum precipitins to *C. albicans* and *C. parapsilosis* have not been found [8]. A role has also been proposed for the use of occlusive pants, but these are now rather rarely used in the developed parts of the world. Starch particles were found within lesions in one case [9], but were sought and not identified in others [3].

Histologically, there is a dense granulomatous infiltrate occupying the full depth of the dermis, comprising lymphocytes, plasma cells, neutrophils, eosinophils and histiocytes [4,5,8,10].

The characteristic lesions most commonly make their appearance between the fourth and ninth months of life in a child with primary irritant napkin dermatitis. There is no correlation between the severity of the napkin dermatitis and the incidence of these lesions, and they frequently appear to arise at a time when the napkin dermatitis is improving. The lesions comprise one or several, rather

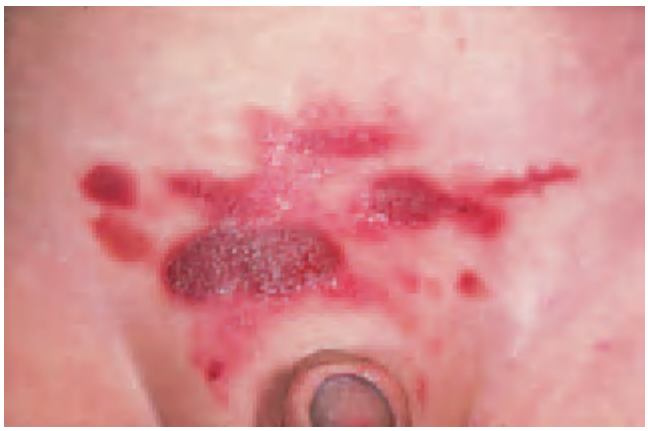

Fig. 14.5 Infantile gluteal granulomas in the pubic area of a 6-month-old infant.

uniform, livid purple nodules, which are usually oval in outline with their long axis parallel to the skin creases [5] and up to about 3 cm in length. They tend to occur on the convexities of the napkin area, not in the flexures themselves, and are definitely not confined to the gluteal region, as the name might be taken to imply (Fig. 14.5). They have occasionally also occurred at other sites in affected infants [5]. They persist for some weeks and appear to regress spontaneously, even if the use of potent corticosteroid applications is continued [11], and may leave atrophic scars [5]. Analogous lesions have been described in incontinent older patients [12,13].

These lesions require little treatment other than the removal of likely provocative factors, especially the withdrawal of topical corticosteroid therapy other than hydrocortisone alone, if this is required for the treatment of persisting napkin dermatitis, and the restriction to a minimum of the wearing of occlusive plastic pants. Napkin-area care should be as outlined above for primary irritant napkin dermatitis.

These lesions have a superficial resemblance clinically and histologically to Kaposi's sarcoma [10]. However, the latter more commonly arises on the extremities, even in infants [14], and histologically shows characteristic interweaving bands of spindle cells, at least in well-developed cases.

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Infantile 'seborrhoeic' dermatitis

Definition and nomenclature. The term infantile 'seborrhoeic' dermatitis is widely used to describe an allegedly distinctive eczematous or psoriasiform eruption seen in infants, having a predilection for the scalp and the proximal flexures, and a favourable prognosis compared with atopic dermatitis. The term nevertheless remains unsatisfactory, as the condition has no established relationship with seborrhoea or even with sebum; neither is there any convincing evidence that it is analogous to seborrhoeic dermatitis of adults. There must be some doubt whether the condition exists at all as a separate entity.

Aetiology. The authors regard the term *infantile seborrhoeic dermatitis* as a description of a somewhat distinctive but nevertheless highly variable clinical presentation rather than a single disease. It may be a presentation that can reflect a variety of different skin disorders, and that may therefore have a number of different causes. The term is used to describe cases that others would consider to be examples of cradle cap with intertriginous lesions, intertrigo, primary irritant napkin dermatitis with dissemination, atopic dermatitis, infantile psoriasis and multiple carboxylase deficiency, as well as rashes that may reflect primary immunodeficiency infants. Once all these have been excluded, how many cases of a genuinely distinct seborrhoeic dermatitis of infancy would remain is not clear. However, as there remains a considerable body of opinion that there is a true infantile seborrhoeic dermatitis, the condition is described in this chapter. It appears possible that disagreements on this subject might to some extent reflect regional variations in incidence, and possibly a dramatic fall in incidence in recent years.

The relationship between infantile seborrhoeic dermatitis and atopic dermatitis has been the subject of debate for many years. Some authorities have proposed that infantile seborrhoeic dermatitis is merely a characteristic pattern of atopic dermatitis and not a separate entity [1],

on the basis of the observation that apparently typical infantile seborrhoeic dermatitis not infrequently transforms into equally typical atopic dermatitis. The occurrence of such transformation is not disputed, only its frequency and interpretation. A prevalence of atopic dermatitis of 27.5% was reported in a group of children reviewed 5–13 years after a diagnosis of seborrhoeic dermatitis had been made in infancy [2]. In a more recent study [3], it was shown that 19% of a group of children, diagnosed as having seborrhoeic dermatitis of infancy about 12 years earlier, had atopic dermatitis on review, compared with a prevalence of 10% in a control group, and of 45% in a group of children diagnosed as having atopic dermatitis in infancy. Scientific resolution of this controversy is hampered by clinical overlap between the two conditions, at least in their earliest stages [4]. Furthermore, the incidence of atopic dermatitis is so high that a proportion of infants with infantile seborrhoeic dermatitis would in any case be expected to develop atopic dermatitis. Because the age of onset is similar, this would often occur before the seborrhoeic dermatitis had resolved. The most valid reasons for continuing to regard the two conditions as distinct entities are, firstly, a relative lack of association between infantile seborrhoeic dermatitis and atopic status in infancy [5] and, secondly, a better prospect of early resolution in infantile seborrhoeic dermatitis [4].

These problems are highlighted by the recent finding of a prevalence of psoriasis of about 27% in a group of children reviewed 2–13 years after a diagnosis of infantile seborrhoeic dermatitis had been made [6].

Controversy also surrounds the relationship between infantile seborrhoeic dermatitis and seborrhoeic dermatitis of adults. Sebum is no longer considered an important aetiological factor in the adult condition, although it is considered possible that seborrhoea plays a part in the seborrhoeic dermatitis seen in a relatively high proportion of patients with Parkinson's disease. As infants do secrete some sebum, at least in the first few months of life [7], an aetiological role for sebum in infantile seborrhoeic dermatitis is not entirely excluded and, it has been argued, without any scientific support, that the typical early resolution of the disorder is the direct result of decreasing levels of sebum production during the last 6 months of infancy. There is no evidence of an increased prevalence of seborrhoeic dermatitis in adult life among those who previously had a diagnosis of infantile seborrhoeic dermatitis.

A favoured view in the past was that infantile seborrhoeic dermatitis is an 'id' reaction to *C. albicans* skin and intestinal infection [8,9], but no convincing evidence has been put forward to support this hypothesis.

An aetiological role for *M. furfur* has been convincingly argued in adult seborrhoeic dermatitis [10], and is supported by the therapeutic benefit that follows therapy with ketoconazole [11]. It has been demonstrated that this organism can activate complement *in vitro* by the alternative pathway [12]. *Pityrosporum ovale* is part of the normal skin flora in adults, but is rare in prepubertal children; it is generally found in greatest density in the scalp and proximal flexures. The proportion of the normal scalp flora represented by *P. ovale* is increased in adults with seborrhoeic dermatitis [13], and the organism has been isolated with an increased frequency from several body sites in infants with infantile seborrhoeic dermatitis [14,15]. A possible aetiological role for this yeast in infantile seborrhoeic dermatitis is supported by reports of therapeutic response to topical ketoconazole [15,16].

In the past, there was a strong feeling that nutritional factors might be important in the aetiology of infantile seborrhoeic dermatitis, an impression that was strengthened by a report from Czechoslovakia of an increased incidence of the condition during the post-Second World War period of food shortage [17]. The appearance of an intertriginous dermatitis with some resemblance to infantile seborrhoeic dermatitis was described in infants fed a diet deficient in essential fatty acids [18], but evidence of essential fatty acid deficiency has not been demonstrated in infants with seborrhoeic dermatitis [19]. Data have been reported, however, that were interpreted as suggesting that affected children may have transiently impaired activity of the enzyme, δ-6-desaturase [20]. Seborrhoeic dermatitis has also been reported in breast-fed babies of malnourished mothers, in whom it improved when biotin injections were given to the mothers [21]. Dramatic responses have been described in infants with generalized seborrhoeic dermatitis who were themselves given oral or parenteral biotin [22,23]. In contrast, more recent controlled trials of biotin treatment provided no support for such claims [19,24], and biotin deficiency in infancy does not result in the clinical picture of seborrhoeic dermatitis [25,26].

Pathology. There have been very few studies of the histopathology of infantile seborrhoeic dermatitis. However, it seems clear that one finds patchy parakeratosis, with epidermal microvesicles and slight spongiosis, occasional lymphocytes, moderate acanthosis (often psoriasiform) and a poorly developed granular layer [27]. The dermis features a mild, patchy perivascular lymphocytic inflammatory infiltrate and prominent perivascular oedema. Direct immunofluorescence has been negative, and candidal antigen has not been identified.

Clinical features [4,28,29]. The eruption generally first appears between the second week of life and the sixth month, but perhaps most frequently between the third and eighth weeks. In some cases, it starts in the napkin area; in others, it starts on the face and scalp. Occasionally, the eruption first appears on the trunk outside the napkin area. Often, the rash occurs almost simultaneously on the

face, scalp and in the napkin area at its onset. It tends to spread fairly rapidly to involve the scalp, face, neck, napkin area and axillae. On the scalp, the vertex and frontal areas are the sites of predilection. On the face, the forehead, eyebrows, eyelids and nasolabial folds tend to be the worst affected areas. The eruption is often confluent around the neck and up the sides of the face to the temples, the area behind the ears tending to be the most severely affected. In the napkin area, the folds are confluently involved. On the trunk, the umbilical area is a favourite site.

The rash comprises well-defined areas of erythema and scaling with tiny vesicles. Papular and lichenified lesions are not seen. On the scalp and in the flexures, the eruption is confluent, but, elsewhere, the individual lesions usually start as small, round or oval areas, subsequently extending and coalescing to form patterns. The scales are rather adherent; they are yellow-brown in colour, large and greasy in the scalp, but smaller, whiter and drier in other areas.

Typically the infant is well, and pruritus appears to be relatively mild, in contrast to atopic dermatitis. As a consequence, feeding and sleep are generally undisturbed.

Differential diagnosis. The diagnostic features of seborrhoeic dermatitis are said to be its distribution in the scalp and proximal flexures, and the relative absence of pruritus, but these are not really sufficiently specific to define the disorder clinically.

Many of those diagnosed as having infantile seborrhoeic dermatitis could be given more satisfactory alternative diagnoses. These include cradle cap, intertrigo, disseminated primary irritant napkin dermatitis, atopic dermatitis, infantile psoriasis, zinc deficiency, multiple carboxylase deficiency and primary immunodeficiencies.

Perhaps the situation in which the diagnosis of infantile seborrhoeic dermatitis is most often incorrectly applied is that of disseminated primary irritant napkin dermatitis (see above). Some babies with typical primary irritant napkin dermatitis may experience progressive spread of the eruption beyond the confines of the napkin area. This generally only occurs when the napkin dermatitis is relatively intense. The pattern of dissemination in such cases may closely resemble the distribution of lesions regarded as characteristic for infantile seborrhoeic dermatitis.

It is likely that in a small proportion of cases, infantile seborrhoeic dermatitis is an early manifestation of psoriasis. There is certainly a suspicion that the dissemination of primary irritant napkin dermatitis is at least occasionally a reflection of underlying predisposition to psoriasis.

As discussed earlier in this chapter, there is a common, acquired type of cradle cap that is frequently associated with scaling lesions in the eyebrows, forehead and temples, and the retro-auricular area and neck, and occasionally with intertriginous lesions in the axillae and groins. This rash starts on the scalp and manifests relatively little inflammation. To some, this is a form of infantile seborrhoeic dermatitis; to others, it is a different entity.

Differentiation from atopic dermatitis may be particularly problematic, directly mirroring uncertainties about the existence of such an entity as infantile seborrhoeic dermatitis. There can be no doubt that rashes having the clinical characteristics of infantile seborrhoeic dermatitis may gradually transform into one that has the typical appearances of infantile atopic dermatitis, an observation that has led many to regard infantile seborrhoeic dermatitis as nothing more than a 'seborrhoeic pattern' of atopic dermatitis in infants [1]. The presence or absence of a family history of atopic disorders appears to be unhelpful in discrimination, as is the age of onset [4]. Pruritus is commoner and more severe in atopic dermatitis, but it should be borne in mind that pruritus may not in any case be evident in early infancy.

Langerhans' cell histiocytosis (see Chapter 52) may present with an eruption having features in common with infantile seborrhoeic dermatitis, particularly its distribution in the scalp, groins and axillae. However, careful examination will demonstrate that the eruption of Langerhans' cell histiocytosis comprises clusters of small, translucent, flesh-coloured papules, although these may become confluent at certain sites, particularly in the proximal flexures and in the retro-auricular area. There is often a petechial element in addition. Although the child may be pallid and unwell, this is not invariably the case. There may of course be other manifestations of the disease such as oral or anogenital lesions, soft masses in the scalp, or hepatosplenomegaly. Where there is any suspicion of Langerhans' cell histiocytosis, a skin biopsy should be undertaken.

Multiple carboxylase deficiency may present in infancy with a well-marginated erythematosquamous rash that starts in the scalp, on the eyebrows and at the eyelid margins, extending later to the perioral, perianal areas and to other flexural sites. There may be associated blepharitis, and keratoconjunctivitis causing photophobia. Vomiting is common. Neurological symptoms tend to be prominent, particularly convulsions, developmental delay, hypotonia and ataxia.

Certain primary immunodeficiency disorders may present with a progressive eczematous eruption having a predilection for the proximal flexures. Similar rashes may occur in secondary immunodeficiency disorders such as congenital human immunodeficiency virus (HIV) infection.

Prognosis. The outlook, even without treatment, is good, and clearance can be anticipated within a few weeks in the majority of cases. Relapses are unusual after clearance. Persistence suggests that the correct diagnosis is atopic eczema, psoriasis, zinc deficiency, Langerhans' cell histiocytosis or immunodeficiency.

Treatment. The treatment of this condition is similar to that of atopic dermatitis. Affected infants should be bathed at least once a day, and a dispersing bath oil may be added to the water. During the bath, affected areas should be cleaned with a water-dispersible emollient such as Ung. Emulsificans BP or Aqueous Cream BP. Soap should be avoided. After bathing, a topical anti-yeast agent should be given, because 2% ketoconazole cream has been shown to be effective in a high proportion of cases [16]. Treatment should be applied once or twice a day for 10–14 days. At other times during the day, a simple emollient cream or ointment should be applied, especially in the napkin area.

The scalp should be cleaned with 2% ketoconazole shampoo. Applications containing salicylic acid or corticosteroids should not be used, because of the very efficient absorption of these molecules at this site in infancy.

While it is reasonable to assess the nutritional value of the infant's diet, there is no evidence that either biotin or essential fatty acids are generally beneficial [19,24].

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Infantile psoriasis and napkin psoriasis

While it is uncommon for psoriasis to appear in infancy, this undoubtedly does happen [1–3], and there is some evidence suggesting the occasional occurrence of congenital psoriasis [1,4,5]. However, the term napkin psoriasis has been used rather loosely to describe what should probably more correctly have been called *psoriasiform napkin dermatitis* or *psoriasiform seborrhoeic dermatitis of infancy* [6–8]. In some infants with primary irritant napkin dermatitis and infantile seborrhoeic dermatitis, the eruption shows psoriasiform features clinically (Fig. 14.6) [9–12]; it has been demonstrated that these children have an increased risk of genuine psoriasis many years later [9,12–15].

True psoriasis occurs in infancy, most typically in the napkin area as an isomorphic (Koebner) response in a

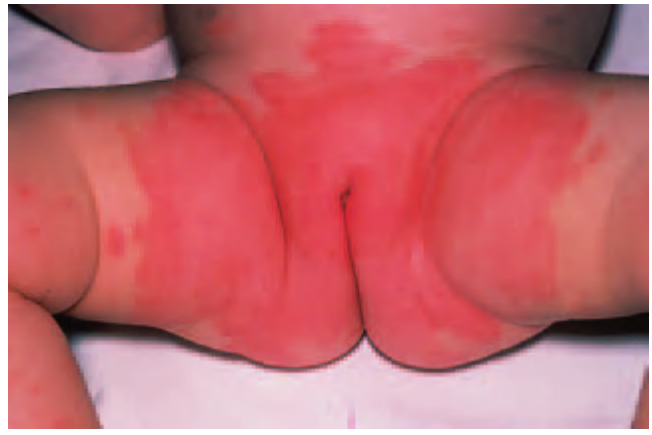

Fig. 14.6 Napkin psoriasis: confluent dry erythema with a sharp, scalloped margin in a 7-month-old infant.

genetically predisposed child with primary irritant napkin dermatitis [1]. While a fairly confident diagnosis of psoriasis can sometimes be made in such a case, it is more often appropriate to use the term 'psoriasiform' in this situation, as most infants with psoriasiform napkin dermatitis do not appear to go on to develop psoriasis [16]. Furthermore, it has been shown that the frequency of the three human leukocyte antigens (HLA), B13, B17 and BW37, is no different in infants with psoriasiform napkin dermatitis from their frequency in normal infants, whereas they are found with very significantly increased frequency in true psoriatics [17].

Psoriasiform napkin dermatitis has a mean onset at about 2 months, and generally lasts for 2–4 months [9,16]. The rash comprises psoriasiform plaques in the napkin area with smaller papular satellites of similar appearance. It frequently disseminates, to involve the trunk and limbs, where lesions will have the same morphology, and to the face and scalp, where affected areas tend to be more diffuse and covered with denser, adherent scale or crust. Frankly pustular lesions have been described in disseminated napkin psoriasis [18].

Generalized pustular psoriasis has also been described occasionally in infancy, including a case in which lytic bone lesions were present due to chronic recurrent multifocal osteomyelitis [19].

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Table 14.2 Differential diagnosis of the 'blueberry muffin' baby.

Dermal erythropoiesis
Congenital infections (rubella, cytomegalovirus, coxsackie B2, syphilis, toxoplasmosis)
Hereditary spherocytosis
Rhesus haemolytic anaemia
ABO blood group incompatibility
Twin–twin transfusion syndrome
Neoplastic infiltrates
Congenital leukaemia
Neuroblastoma
Congenital rhabdomyosarcoma
Other disorders
Neonatal lupus erythematosus (LE)

'Blueberry muffin' baby (dermal erythropoiesis)

Definition. This term has been used to describe a characteristic eruption in neonates, often present at birth, comprising widespread, purple, erythematous, oval or circular macules, papules and nodules reflecting dermal erythropoiesis.

Aetiology and pathology (Table 14.2). The 'blueberry muffin' type of lesion has been recorded in a number of congenital viral and bacterial infections, notably rubella [1–5], cytomegalovirus [1,6–9], coxsackie B2 infection, parvovirus B19 [10], and in congenital syphilis and toxoplasmosis [7,11]. These lesions have also been described in a variety of congenital haematological disorders, notably hereditary spherocytosis [12], rhesus incompatibility [13,14], ABO blood group incompatibility [6] and twin–twin transfusion syndrome [6,15]. Occasionally, clinically identical lesions have occurred in infants who appeared to have no underlying cause [6].

In the congenital infections and haematological disorders, the lesions have been shown histologically to comprise foci of dermal erythropoiesis [1,6,12,15,16]. The reticular dermis contains aggregates of nucleated and non-nucleated erythrocyte precursors, but generally no cells of myeloid or megakaryocytic type. It is possible that this process represents persistence and exaggeration of the dermal erythropoiesis that is a normal occurrence in early fetal development, but the reasons behind this persistence are unclear [8,12].

Clinical features. The skin lesions of dermal erythropoiesis are present at birth, comprising widespread or sometimes more local collections of macules and infiltrated domed papules up to about 1 cm in diameter, having a colour that is generally purple, but may vary from dark blue to magenta. There may be frank petechiae on the surface of some of the lesions. Favoured sites include the trunk, head and neck. The lesions generally fade into light-brown macules within a few weeks of birth.

Diagnosis. Clinically rather similar but more nodular lesions have occurred in a number of situations. Whether such lesions should be called 'blueberry muffin' lesions is debatable, as they do not show dermal erythropoiesis, but a variety of other histological appearances, in each case characteristic for their cause. Examples include congenital leukaemia [17–24], neonatal neuroblastoma [25,26], congenital rhabdomyosarcoma [27], congenital Langerhans' cell histiocytosis [28] and neonatal LE.

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Neonatal purpura fulminans

Definition. Neonatal purpura fulminans is a potentially lethal disorder characterized by progressive haemorrhagic necrosis of the skin associated with cutaneous vascular thrombosis. It is usually due to a genetically transmitted thrombophilic disorder.

Aetiology. In the older child, purpura fulminans is a highly characteristic feature of meningococcal septicaemia, where it results from acquired deficiency of protein C or S [1], and it may occur as a sequel to a number of other infections, including common infections such as streptococcal infections, varicella and measles [2].

However, the occurrence of purpura fulminans in the neonate is almost always a reflection of homozygous deficiency of protein C or, less frequently, of protein S [3,4]. Protein C resistance has also been reported, due to mutations in the factor V gene [5,6].

Clinical features. The skin lesions most characteristically appear within the first 12 h of life [5,7], but their initial development may occasionally be delayed until later in infancy [8]. They generally comprise more or less symmetrical and well-defined 'lakes' of confluent ecchymosis, without petechiae. The lesions occur most often on the limbs, particularly at sites of pressure, but may also appear on the trunk and on the face and scalp. The onset is sudden, and the lesions enlarge rapidly, with coalescence and the development of haemorrhagic bullae and central necrosis. There is surrounding erythema and the lesions are tender. The patient is frequently febrile. These infants are also at risk of thrombosis in the central nervous system, and in the retinal vessels [7,9–11]. There is a substantial danger of internal haemorrhage, shock and death.

Diagnosis. Disseminated intravascular coagulation can also occur as in association with severe bacterial infections in infants as well as in older children [12].

Treatment. Initially, fresh frozen plasma should be given with the minimum delay, in a dose of 10–15 ml/kg/12 h. If protein C deficiency is confirmed, onward therapy with protein C concentrate should continue until the skin lesions have healed [13]. Longer-term treatment is with oral anticoagulants. Liver transplantation has been undertaken successfully [14].

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Acute haemorrhagic oedema of childhood

SYN. FINKELSTEIN'S DISEASE

Definition. Acute haemorrhagic oedema of infancy is a distinctive type of leukocytoclastic vasculitis occurring in children under the age of 2 years. It was first described under this title by Finkelstein [1]. Clinically it is manifest by a combination of purpura, often in a cockade pattern, and an inflammatory oedema of the limbs and face, with a tendency to recurrence in the short term and subsequent spontaneous resolution [2].

Aetiology. The cause of infantile acute haemorrhagic oedema remains unknown, and there has been considerable debate about its relationship to Henoch–Schönlein purpura. Many regard it as an analogue of Henoch–Schönlein purpura, occurring in the very young, and this view is to some degree supported by a report of associated haematuria and proteinuria [3,4]. It is generally believed that infections, drugs and vaccines might all be precipitating factors in individual cases [2,5], and a recent case report provided evidence of provocation by a primary cytomegalovirus infection [6].

Pathology. Histopathology of the skin lesions has shown changes varying from a perivascular lymphocytic and histiocytic infiltrate with erythrocyte extravasation, to fully developed leukocytoclastic vasculitis with fibrinoid necrosis [4,7–9,10–12].

Direct immunofluorescence has generally demonstrated fibrin and C3 in and around dermal vessels [5]. IgM has been found in about three-quarters of cases and IgA in about one-quarter.

Haematological studies have invariably shown normal platelet counts and no abnormalities of coagulation. Serum complement levels have been normal.

Transient renal involvement may be revealed by the occurrence of microscopic haematuria and mild proteinuria [3,4].

Clinical features. The condition is seen almost exclusively in children between the ages of 4 months and 2 years. It is manifest by the sudden appearance of oedematous papules that feature petechial haemorrhage, and that extend to form ecchymotic plaques. These lesions most typically occur on the face, especially the cheeks, eyelids and ears, and the limbs, particularly the hands and feet. These plaques are usually of cockade (rosette) type, with scalloped margins, but occasionally small lesions join up to produce a more reticulate pattern. The lesions often follow immunizations or an upper respiratory tract infection (URTI). Accompanying oedema of the hands, feet or whole limbs is common.

Associated oedema of the penis and scrotum [3,13,14] or oral petechial lesions [13] have also been reported. Other occasional cutaneous findings have included ecchymotic [13] or necrotic lesions of the ear [9,11] and urticarial lesions [3,10,14].

In contrast to the rather dramatic cutaneous lesions, the patient generally remains well, apart from the frequent presence of pyrexia, which is usually mild. Visceral lesions are conspicuous by their general absence, although gastrointestinal complications have very occasionally been reported, including melaena [2] and lethal intussusception [9].

Differential diagnosis. Awareness of this disease should make diagnosis fairly straightforward. Meningococcal septicaemia will require consideration, but the well-defined symmetrical areas of confluent ecchymosis seen in this disorder are highly distinctive. Certain other disorders may produce annular lesions in infants, particularly urticaria and erythema multiforme, but these generally lack a haemorrhagic element and do not usually taken on a rosette configuration with scalloped margins. The same is true of the lesions of Sweet's syndrome, which may also occur occasionally in very young children [15,16]. Kawasaki disease characteristically causes oedematous induration of the hands and feet, and may result in a rash in which annular erythema may be a feature, but the skin lesions themselves are not as indurated, nor are

they purpuric. One of the most important differential diagnoses to consider in any disorder presenting with intracutaneous haemorrhage in the very young is non-accidental injury.

Prognosis. Recurring crops of lesions may occur, but spontaneous resolution normally follows within about 2 weeks. Recurrence must be rare, but has occasionally occurred [13]. No significant long-term sequelae have been reported.

Treatment. No specific therapy is required.

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Disorders of subcutaneous fat

Terminological confusion has bedevilled the literature on disorders of subcutaneous fat in the newborn. The four conditions described below are essentially separate entities, although not without some clinical and pathological overlap.

Cold panniculitis (see also Chapter 55)

Definition. Cold panniculitis is a distinctive form of panniculitis provoked directly by cold exposure, to which infants appear particularly predisposed.

Aetiology. The fat of the newborn appears to be more highly saturated than that of older children and adults, with the effect that it solidifies at a higher temperature [1,2]. The possible clinical relevance of this phenomenon was demonstrated by experiments in which young pigs were fed fats of various degrees of saturation, producing corresponding differences in the saturation of their own subcutaneous fat [3]. The subsequent application of ice to the skin induced panniculitis only in the pigs fed saturated fat.

Applying ice for 50 s causes panniculitis in all newborn infants, in only 40% of 6-month-olds and almost never in 9-month-olds [4].

Cold panniculitis in infancy has most often followed exposure of the cheeks to: (i) extremely cold air [5–7]; (ii) ice bags applied as a therapy for supraventricular tachycardia [8,9]; or (iii) lollipops [10–12].

Pathology [10,13]. An early feature in skin biopsies is a lymphohistiocytic infiltrate around blood vessels at the junction of the dermis and subcutaneous fat. After a few days, lipocyte rupture leads to the formation of cystic cavities surrounded by areas of marked infiltration by lymphocytes and histiocytes, with a few neutrophils and eosinophils.

Clinical features. Indurated, warm, red, subcutaneous plaques and nodules appear within hours or days of appropriate cold exposure.

The lesions have generally occurred on the cheeks in infants, although they may be seen elsewhere in older children and adults [13,14].

Prognosis and treatment. The induration resolves over a period of a week or so, often leaving some residual post-inflammatory hyperpigmentation. No treatment is required, although it is clearly advisable for the child to avoid further cold exposure of the type that precipitated the lesions.

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Neonatal cold injury

Definition. Neonatal cold injury is a disorder, now rare in developed countries, in which cold exposure of a small-for-dates neonate causes hypothermia associated with lethargy and generalized pitting oedema of the skin, clinically and pathologically distinct from sclerema neonatorum.

Aetiology [1–4]. Low environmental temperature has been the principal cause of virtually all reported cases of this disorder. Other factors that appear to have predisposed babies to this complication of cold exposure include intrauterine growth retardation, which results in a relatively thin panniculus, and tight wrappings, which would restrict muscular activity. Immaturity of either reflex shivering mechanisms or of protective vasomotor responses would also increase the risk. The condition seems to be much less common in the UK now than it was 40 years ago, probably because of improved heating in homes, very much reduced frequency of home delivery and abandonment of the previous habit of bathing babies at birth.

Pathology [5]. The panniculus is generally thin. Otherwise, there is little obvious abnormality apart from dilatation of dermal blood vessels. Profuse exudation of clear fluid from the cut surface at post-mortem suggests that the induration is due to oedema.

The dominant post-mortem finding in fatal cases has been massive pulmonary haemorrhage [2,4].

Clinical features [1–4]. The infant is usually a full-term neonate, born at home, but small for gestational age. In the great majority of cases, presentation is within the first 4 days of life, and usually during the first 24 h. The most striking features are intense erythema or cyanosis of the face and extremities, and firm, pitting oedema beginning at the extremities and spreading centrally, and becoming progressively more indurated in a proportion of cases. Petechiae have occasionally been observed.

The skin feels cold, and the baby is usually hypothermic. Associated non-cutaneous features of cold injury are generally present, and may occur in the absence of skin changes. These include immobility, drowsiness, poor feeding, vomiting, oliguria and gastrointestinal bleeding with vomiting of altered blood or melaena.

The condition appears to have been associated with a high mortality, around 25%.

Diagnosis. The main source of diagnostic confusion is with sclerema neonatorum. The generally healthy state of the infant before the onset of the cutaneous induration, its pitting nature, the history of cold exposure and a low rectal temperature all help to distinguish the two disorders. It is possible that the late non-pitting induration of the skin, which supervenes in some cases [2], may in fact be genuine sclerema.

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Subcutaneous fat necrosis of the newborn

Definition. Subcutaneous fat necrosis of the newborn is an uncommon and transient disorder of neonates in which focal areas of fat necrosis cause nodular skin lesions. This nodular necrosis of subcutaneous fat may occasionally be associated with hypercalcaemia.

Aetiology. Subcutaneous fat necrosis generally occurs in full-term or post-term infants of normal birth weight during the first 6 weeks of life. The precise cause is unestablished, but a variety of insults appear to have contributed in individual cases. These have included birth asphyxia [1–4], maternal pre-eclampsia [5,6], maternal diabetes [7], obstetric trauma [8–10] and hypothermia [11–13]. In many cases, there is no convincing history of any of these putative predisposing causes. It has been suggested that localized tissue hypoxia—albeit transient—may be the common link in every case [14]. This might explain the predominant localization of lesions to sites such as the shoulders and buttocks, where mechanical pressure might further compromise the circulation. However, intermittent reports of an analogous type of fat necrosis occurring in infants undergoing hypothermic

cardiac surgery implies that the common factor is perhaps more likely to be cold.

It has been suggested that another important predisposing factor for the development of subcutaneous fat necrosis might be a protease inhibitor deficiency, analogous to the α_1-antitrypsin deficiency seen in some patients with panniculitis [15]. Such a deficiency might allow trauma to trigger development of lesions, but perhaps it would be more likely that lesions developing in this way would show the pathological features of panniculitis rather than fat necrosis.

An interesting concept [13] is that subcutaneous fat necrosis of the newborn might be a disorder of brown fat, which is present in those areas most frequently affected [16].

The appearance of subcutaneous fat necrosis has been reported after intravenous prostaglandin E_1 (PGE_1) administration for congenital heart disease, and the suggestion was made that the PGE_1 may have been responsible [17].

A number of infants have now been reported in whom subcutaneous fat necrosis was associated with hypercalcaemia [18–26]. This complication probably occurs in around a quarter of all cases, and appears to occur more frequently in infants with more extensive disease, and almost exclusively when the trunk is affected [4].

The cause of the hypercalcaemia is unknown. Suggested mechanisms have been reviewed by Hicks *et al.* [27] and by Burden and Krafchik [4]. It currently appears most likely that it reflects increased calcium absorption due to extrarenal production of 1,25-dihydroxyvitamin D, which has been observed in other granulomatous disorders including sarcoidosis [4,19,28,29]. Elevated parathormone levels have been reported in one case [24], but post-mortem studies have not revealed any evidence of parathyroid hyperplasia. The finding of increased urinary excretion of PGE_1 led to the suggestion that increased bone calcium resorption might be responsible [25,30].

Pathology [3,31–33]. Biopsies of the affected subcutaneous tissue show patchy fat necrosis, with a granulomatous inflammatory reaction of foreign-body type, and fibrosis. Both the fat cells and the giant cells contain needle-shaped clefts, which may be radially arranged. Fibrotic obliteration of small arterioles has also been observed [34]. Calcium deposits are commonly found in the necrotic fat.

Ultrastructural examination has shown parallel aggregations of electron-lucent needle-shaped spaces within adipocytes [33].

Similar changes in visceral adipose tissue have been reported in post-mortem studies of affected infants [5,9]. Widespread calcium deposition in internal organs has also been shown in post-mortem specimens from hypercalcaemic cases [6,21] and nephrocalcinosis has been observed in such infants during life [23,35].

Transient thrombocytopenia has been reported during the period of initial development of the lesions, possibly due to sequestration of platelets [6,14,36].

Plasma lipid abnormalities have been reported in a neonate with subcutaneous fat necrosis, but their relevance was unclear [37].

Clinical features. Infants who develop subcutaneous fat necrosis are generally full-term or post-term neonates of normal weight. Nodular thickening of the subcutaneous tissues is usually first detected between the second and 21st days of life. Sometimes, the changes are present at birth, and, rarely, they may appear as late as the sixth week. The nodules tend to be symmetrically distributed, and show a predilection for buttocks, thighs, shoulders, back, cheeks and arms. Lesions may single or multiple, rounded or oval, and pea-sized or many centimetres in diameter. They are initially discrete, but may fuse to form large plaques. The overlying skin is often red or bluish red. The nodules feel rubbery or hard, and are not attached to the deeper structures. The lesions may be painful [38]. New nodules may continue to develop for a week or more.

In most cases, the child's health is not substantially impaired, and within a few months the nodules disappear. Where calcium deposition is marked, the lesions may take rather longer to resolve [39]. Usually no trace of the nodules remains, but there may be slight atrophy [12]. Rarely, the nodules may ulcerate, discharge their fatty contents and leave scars.

The condition has occasionally been fatal, particularly when visceral fat has been involved [5], or where there has been complicating hypercalcaemia [24].

Diagnosis. Neonates delivered by forceps may develop subcutaneous nodules where the forceps were applied, presumably as a result of traumatic fat necrosis.

Subcutaneous fat necrosis of the newborn was in the past frequently confused with sclerema neonatorum. Occasionally, the two conditions may occur simultaneously [40].

All infants who have experienced subcutaneous fat necrosis should have their serum calcium measured on presentation and a few weeks later. If hypercalcaemia is present, its cause requires thorough investigation to exclude disorders such as primary hyperparathyroidism and vitamin D intoxication.

Treatment. None is generally required.

Hypercalcaemia may warrant treatment by administration of furosemide, dietary restriction of calcium and vitamin D, and sometimes also by oral corticosteroid administration. There may be a role for biphosphonate administration in some cases [41].

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Subcutaneous fat necrosis following hypothermic cardiac surgery in infancy

There have been several reports of the occurrence of lesions analogous to those of subcutaneous fat necrosis of the newborn in children who have had cardiac surgery [1–5], and this may be a relatively frequent complication of such surgery. It appears likely that the principal provocative factor in these cases was the cutaneous application of ice to induce hypothermia, although trauma and/or hypoxia may have contributed. It is noteworthy that these children appear to have developed lesions of subcutaneous fat necrosis rather than cold panniculitis. The ages of the children at the time of surgery varied from 12 days to 20 months. Lesions appeared between 14 and 30 days later, principally at the sites subjected to the greatest cold exposure. Hypercalcaemia may occur [3]. The lesions resolve within a few weeks and no treatment is required.

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Sclerema neonatorum

Aetiology. Sclerema neonatorum is a very rare disorder that almost always appears during the first week of life,

although it has occasionally been recorded later in infants born preterm. It has generally been considered a non-specific sign of grave illness, and has been associated with a mortality up to 75% [1,2]. Prematurity and smallness-for-dates appear to be frequent predisposing factors [2]. It has been recorded as already present at birth in infants subjected to placental insufficiency [3]. The disorder does not seem to occur in otherwise healthy infants, and most characteristically develops during the course of one of a wide variety of severe illnesses, particularly serious infections, congenital heart disease and other major developmental defects [2]. A proportion of these infants has been hypothermic, and occasionally sclerema has been described as a complication of neonatal could injury [4]; nevertheless, cold does not appear to be an important aetiological factor in the majority of cases.

Lipolytic mechanisms are poorly developed in the newborn, particularly in those born preterm [5]. The maturation of these enzyme systems might be further compromised by major infection or hypoxia. It has been suggested that sclerema might reflect defective lipolysis within adipose tissue, which would result in failure of fat mobilization, and an impaired capacity to maintain body temperature. It has been reported that the ratio of saturated to unsaturated fatty acids is relatively high in the adipose tissue of all neonates, and that this ratio was even higher in an infant with sclerema [6,7]. This would lead to a raised melting point, and it is possible that the induration of subcutaneous fat, which is the major clinical feature of sclerema, might reflect its solidification due to a fall in the temperature of the adipose tissue during peripheral circulatory collapse [8].

Pathology [7–9]. Often, surprisingly little abnormality has been apparent histologically. However, in most cases the subcutaneous fat layer appears to be thickened, due to an increased size of the individual lipocytes and to an increased width of the intersecting bands of connective tissue, probably due to oedema. There is very little evidence of fat necrosis and, generally, only the slightest indication of inflammation. The most characteristic histological feature of sclerema neonatorum is the presence of radially arranged, needle-shaped clefts in adipocytes and, occasionally, in multinucleate giant cells, reflecting the presence of crystals prior to processing.

Clinical features [8,10]. The affected infant is generally severely ill at the time of onset of sclerema. Woody induration of the skin starts on the buttocks, thighs or calves and extends rapidly and symmetrically to involve almost the whole surface, with the exception of the palms, soles and genitalia. This skin is hard and cold to touch, and yellowish white in colour, often with purplish mottling. It will not pit with pressure. Mobility is limited, and as a result the face may take on a mask-like expression.

The prognosis is poor, and is largely determined by the nature of the underlying disease. In spite of advances in the treatment of many of the predisposing disorders, particularly sepsis, the mortality probably remains in excess of 50%. In infants who survive, the appearance of the skin returns to normal without long-term complications such as calcification.

Diagnosis. The main area of diagnostic confusion has been between sclerema and subcutaneous fat necrosis. It is now clear that the two disorders are distinct pathologically and clinically [10], although they can occur together on occasions [11]. Table 14.3 outlines their distinguishing features.

Scleroedema has been reported in an infant at 2 weeks of age, and was distinguished from sclerema principally on histological grounds [12]. Turner's syndrome is often recognizable at birth by the presence in a female of firm non-pitting lymphoedema of the dorsa of the hands and feet, associated with low birth weight and loose folds of skin around the neck. Where primary lymphoedema occurs in neonates, it will already be clinically evident at birth. The condition may be familial, and generally first affects the legs, particularly the lower legs. The presence of oedema at birth, and its very slow progression in an

Table 14.3 Distinctions between neonatal cold injury, sclerema and subcutaneous fat necrosis.

	Neonatal cold injury	Sclerema	Subcutaneous fat necrosis
Frequency	Previously common, now rare	Rare, usually seen in neonatal intensive care units	Uncommon
Patient	Full-term neonates often small-for-dates, born at home	Usually severely ill neonates, often preterm or small-for-dates or post-term	Healthy infants, usually full term
Onset	During the first week	Almost always during the first week	1–6 weeks
Sites	Extremities, spreading centrally	Lower limbs initially becoming generalized	Trunk, buttocks, thighs, arms, face
Appearance	Pitting oedema initially with erythema or cyanosis of face and extremities	Diffuse yellow-white woody induration with immobility of limbs	Firm reddish violet subcutaneous nodules
Histology	Thin panniculus	Subtle; thickened connective tissue trabeculae; radial needle-like clefts	Granulomatous inflammation and fat necrosis
Prognosis	Mortality around 25%	Poor, mortality greater than 50% in past	Generally excellent

otherwise healthy neonate, distinguish primary lymphoedema from sclerema.

Treatment. Treatment is primarily that of any underlying disease. Systemic corticosteroids are probably not effective [1], but there is evidence that repeated exchange transfusions may substantially reduce mortality [13,14].

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Infections

Although infectious diseases affecting the skin are described in detail elsewhere in this book, the clinical features of some of the more important infections affecting the skin during the neonatal period will be briefly considered here, because of their importance in the differential diagnosis of other dermatoses.

Viral infections

Neonatal herpes simplex

HSV infection in the newborn is generally a serious disease with a high mortality. The majority of such infections result from transmission of HSV of both types 1 and 2, by contact with an infected genital tract during delivery [1,2]. However, intrauterine HSV infection undoubtedly occurs occasionally [3], due either to transmission across the placenta [4], or to ascending infection related to prolonged rupture of the fetal membranes [5]. Infection may also occur postnatally by contact with non-genital sites, both maternal and non-maternal [6].

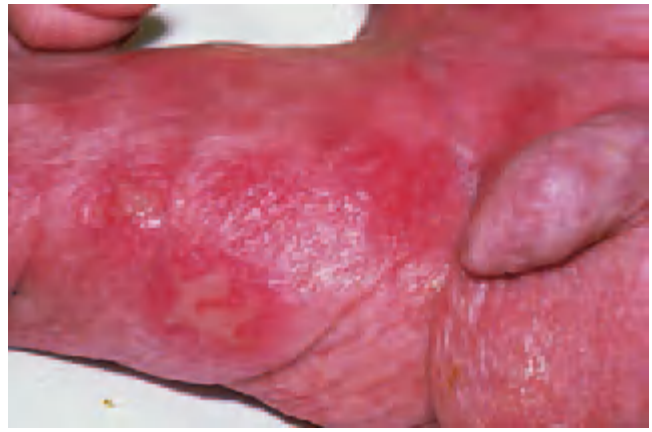

Fig. 14.7 Neonatal herpes simplex: congenital ulceration and scarring at 10 days. This infant responded rapidly to aciclovir therapy and is now entirely healthy apart from residual atrophy.

Over 70% of all infants with neonatal HSV have skin or mucosal lesions [7–9], but only in about 10% will the disease be confined to the skin. The skin lesions appear between day 2 and 20, unless intrauterine infection has occurred, in which case they will generally already be present at birth [3,10,11].

Isolated or grouped vesicles are the most common type of lesion, and the scalp and face are the most commonly affected sites, although lesions can occur at virtually any site (Fig. 14.7). Occasionally, the eruption may be generalized and bullous, and widespread erosions may occur without obvious vesicles or bullae, mimicking epidermolysis bullosa [11]. When infection is acquired during birth, the initial lesions have a predilection for the scalp in vertex presentations, and the perianal area in breech presentations [12]. Lesions may also be localized to areas of intrauterine or intrapartum skin damage [13], such as the area in which a fetal scalp electrode has been sited. Areas of cutaneous atrophy or scarring are not infrequent in the intrauterine form, and vesicular lesions may continue to appear within or at the periphery of these areas [3,14]. A zosteriform pattern has also been described [15], and, in some cases, localized or generalized non-vesicular erythematous macules. Congenital cutaneous calcification has been reported in a child with intrauterine HSV infection [16].

Oral lesions are also frequent, and take the form of erosions on the tongue, palate, gingivae and buccal mucosa.

A fatal outcome is unusual when infection is limited to the skin, mouth and eyes, but mortality and long-term damage are more likely when the central nervous system is involved or when infection is disseminated, even when appropriate antiviral therapy is given. Mortality is higher when infection is with HSV-2 [1].

Early recognition and adequate early treatment with aciclovir does appear to protect infants from dissemination of infection, where this is initially confined to the skin [13,14,17].

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Fetal varicella syndrome (FVS)

Approximately 85% of adults are seropositive for the varicella-zoster virus antibody. If a woman is seronegative, she may develop chickenpox during pregnancy; this occurs in up to 10 per 10 000 pregnancies [1,2]. The infection may be transmitted to the fetus, probably in about 25% of cases. Such transmission of varicella-zoster virus infection to the fetus is considered to be very rare in mothers who develop herpes zoster during pregnancy [3].

When a mother develops varicella between the seventh and 20th week of pregnancy, spontaneous abortion may follow, or the child may be born with a variety of abnormalities considered characteristic of FVS [4–6] (Table 14.4), and this appears to be most frequent when maternal infection has occurred between weeks 13 and 20 [3]. This syndrome was first described in 1947 [7]; many other cases have been reported since [8–12]. However, most children of such mothers are born with no detectable abnormality, despite laboratory confirmation of intrauterine infection [6]. FVS therefore appears to be a relatively rare complication of maternal varicella early in pregnancy, with a fetal risk of approximately 2% [1,3,6,13].

Table 14.4 Principal clinical features of the fetal varicella syndrome.

Low birth weight
Cutaneous lesions:
Localized absence of skin, usually on a limb
Scars, often of dermatomal outline
Papular lesions resembling connective tissue naevi
Hypoplasia of one or more limbs (usually the limb affected by localized absence of skin or scarring), and/or malformed digits
Ocular anomalies, including chorioretinitis, cataracts, microphthalmia, Horner's syndrome
Central nervous system abnormalities, including seizures, mental retardation, hydrocephalus, cortical atrophy, encephalitis, encephalomyelitis, dorsal radiculitis

Localized scarring, presumed to be the sequel to intrauterine ulceration, is the most common cutaneous feature of the FVS. The larger single lesions have characteristically occurred on a limb, and have frequently been associated with hypoplasia of that limb; these lesions have generally followed infections occurring in early pregnancy [4,13–16]. Their segmental outline may be a direct consequence of damage to the fetal nervous system [5,15], as the varicella-zoster virus is known to be strongly neurotropic, or to fetal herpes zoster [8]. The occurrence of larger numbers of smaller lesions appears to result in the main from varicella later in pregnancy; their antecedents seem likely to be vesicular lesions, essentially the same as those occurring in postnatal varicella. If fetal infection has occurred in the last trimester, these smaller skin lesions, reflecting fetal varicella, may still be ulcerated at birth [17].

Areas of congenital localized absence of skin, without associated limb hypoplasia or other neurological abnormalities, have been a less well recognized consequence of intrauterine varicella [18,19], and may reflect fetal herpes zoster later in gestation. Similar skin lesions have been reported in cases of intrauterine infection with human HSV [20].

Skin-coloured papular lesions have been described in children with FVS [21], which are likely to be a direct response to cutaneous injury by intrauterine chickenpox.

Herpes zoster occurring in early infancy is likely to indicate that the child has been infected with the varicella-zoster virus *in utero* [22,23].

Pregnant women who are not immune (on the basis of history, and, preferably, serologically), and who experience exposure to varicella-zoster, should be given varicella-zoster immune globulin (VZIG) [24]. Although this can prevent or modify clinical varicella if given up to 3 days after contact, there is no definite evidence that it prevents fetal infection or damage [3]. Giving VZIG to neonates of mothers who have chickenpox at the time of delivery does

not appear to reduce the incidence of clinical infection but may reduce its severity [25]. But, as the risk of fetal damage is small, termination of pregnancy is not indicated. Ultrasound examinations can be performed to detect some of the abnormalities that occur in the cardiovascular system [26], but several of the important ocular and neurological sequelae cannot be diagnosed in this way. Amniocentesis, fetal blood and chorionic villus sampling can be performed to isolate the virus or to detect specific IgM, but may fail to identify infection [23,27].

There are no reports that establish a role for aciclovir therapy in the prevention of FVS. Therefore, the decision whether to treat the mother should be based solely on the severity of her illness [24].

A potentially dangerous situation relates to maternal development of varicella in the 4 days either side of delivery [28]. In this case, neonatal varicella may also occur, but in the absence of the protection offered by the maternal immune system, mortality may be as high as 30%. Where maternal infection occurs at this time, VZIG is recommended for the newborn. If overt varicella develops in the child, intravenous aciclovir should be added to the VZIG [29].

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Congenital rubella

Rubella contracted by the fetus before the 20th week of gestation may result in disseminated infection, causing intrauterine growth retardation, microcephaly, microphthalmia and a wide variety of other abnormalities [1]. Cutaneous lesions are among the most prominent clinical features of congenital rubella [2–4]. The typical lesions are present at birth, or make their appearance during the first 48 h. They comprise discrete, rounded, red or purple infiltrated macules, 3–8 mm in diameter. Although such lesions may be seen at any site, they generally occur in largest numbers on the face, scalp, back of the neck and on the trunk. Occasionally, the lesions are slightly raised. They tend to fade over a period of weeks. These lesions have often been described as 'purpuric', and have generally been attributed to thrombocytopenia, which is another common feature of congenital rubella [3]. However, histological examination has shown them to comprise foci of dermal erythropoiesis [2,5,6]. Such lesions have frequently been described as 'blueberry muffin' lesions. Genuine thrombocytopenic purpura is probably rather uncommon.

Other reported skin manifestations of congenital rubella have included cutis marmorata, seborrhoea and hyperpigmentation of the forehead, cheeks and umbilical area [7], and discrete deep dimples over bony prominences, particularly the patellae [8].

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Human immunodeficiency virus (HIV) infections

HIV infection may be transmitted to the infant *in utero*, during delivery or through breast-feeding. Because most infections are probably transmitted around the time of birth, clinical manifestations are not commonly seen for the first few months, and some infected infants will remain asymptomatic for many years before manifestations first appear.

Dermatological manifestations are common in infant HIV infection [1,2].

Persistent mucocutaneous candidiasis is the commonest of all. In addition to infection of oral and napkin areas, there may be extensive cutaneous involvement. Dermatophyte fungal infections are also characteristic, and infection with more unusual fungi may occur, including *Aspergillus* [3]. Bacterial infections include unusually severe or recurring impetigo, folliculitis, cellulitis and abscesses. Problems with viruses include atypical chickenpox, herpes zoster, herpes simplex, and unusually severe molluscum and human papillomavirus infections. Norwegian scabies may present in infancy.

A wide variety of non-infectious manifestations of HIV infection may also occur. Perhaps the most characteristic in infancy is seborrhoeic dermatitis affecting face and scalp, often also proximal flexures, occasionally disseminating more widely. Drug eruptions are also rather frequent, especially with trimethoprim–sulfamethoxazole.

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Bacterial infections

Staphylococcus aureus infections

As in older children and adults, *S. aureus* causes a wide variety of cutaneous lesions in neonates.

Bullous impetigo

The neonate is peculiarly liable to the development of bullous impetigo, which is most often caused by phage group II strains of *S. aureus* [1]. The disorder in neonates differs in no significant way from that in older children and adults, although it was formerly distinguished by the rather confusing term, *pemphigus neonatorum*. Epidemics of bullous impetigo, in which some infants may develop staphylococcal scalded skin syndrome, have occurred in neonates due to transmission of infection in the nursery, principally via nursing or medical staff [2–4]. Although the infection is acquired in hospital following delivery, the lesions do not generally appear until the second week of life, when the child will now usually have left hospital.

The perineum, periumbilical area and the neck creases are predilection sites for the initial lesions. Rapidly enlarging bullae with thin, delicate walls and a narrow, red areola contain clear fluid at first, which may later become turbid or frankly purulent. The condition may remain localized or become widespread. Untreated generalized bullous impetigo in the neonate is associated with a significant mortality, and serious complications including lung abscess, staphylococcal pneumonia and osteomyelitis have been reported, even in cases treated with antibiotics [5,6].

The differential diagnosis of bullae and erosions in the neonate is illustrated in Table 14.5 [7–9].

Table 14.5 Differential diagnosis of bullae and/or erosions in the neonate.

More common disorders
Miliaria crystallina
Bullous impetigo
Thermal or chemical burns
Epidermolysis bullosa
Incontinentia pigmenti
Bullous ichthyosiform erythroderma
Mastocytosis
Rare disorders
Neonatal herpes simplex
Fetal varicella syndrome (FVS)
Herpes zoster
Congenital syphilis
Passively transferred
Pemphigus vulgaris
Herpes gestationis
Bullous pemphigoid [7]
Extensive congenital erosions and vesicles healing with reticulate scarring
Congenital erythropoietic porphyria
AEC syndrome
Sucking blisters
Congenital absence of skin
Porphyrias and transient porphyrinaemia [8]
Langerhans' cell histiocytosis [9]

Staphylococcal scalded skin syndrome

The staphylococcal scalded skin syndrome was first described in neonates by a German, Ritter von Rittershain [10]. It is caused by epidermolytic toxin A and/or B, which are elaborated by certain strains of *S. aureus*, most commonly of phage group II [1], particularly strains 71 and 55. These toxins reach the skin via the circulation from a distant focus of infection, usually in the umbilicus, breast, conjunctiva or the site of circumcision [11] or herniorrhaphy [12]. Transmission of the causative toxin through human milk has been reported [13].

The disorder is most often seen in young children, and particularly in neonates. The very much greater incidence of this condition in neonates is believed to reflect less efficient metabolism and excretion of the toxin [14]. Multiple cases can occur in a neonatal unit [15]. Cases occurring in later childhood tend to be associated with underlying disease, especially immunosuppression and renal failure [16].

It does not present at birth, although it may first appear within the first few hours thereafter [17]. The first sign of the disease is a faint, macular, orange-red, scarlatiniform eruption. The eruption generally becomes more extensive, and, over the next 24–48 h, turns to a more confluent, deep erythema with oedema. The surface then becomes wrinkled before starting to separate, leaving raw, red erosions. Sites of predilection for the development of erosions are the central part of the face, the axillae and the groins.

Extreme tenderness of the skin is an early feature, and may occur at a stage where cutaneous signs are not yet striking. The child is pyrexial and distressed. These features can lead to a suspicion that the child has arthritis or an acute abdomen. The presence of impetiginous crusting around the nose and mouth can be diagnostically helpful. Recovery is usually rapid, even without antibiotic therapy, although infants occasionally die in spite of such treatment [18]. Healing occurs without scarring.

The scalded appearance of the skin differentiates the disease from bullous impetigo, and the rapid onset with marked cutaneous tenderness distinguishes it from most of the other causes of erythroderma in infancy. The rarity of clinically apparent bullae and the confluent nature of the rash help differentiate it from those bullous disorders likely to be seen in young children.

The only real problem in differential diagnosis would be with toxic epidermal necrolysis, which, although clinically similar, has a worse prognosis. In the past, the staphylococcal scalded skin syndrome and toxic epidermal necrolysis were confused, but it is now clear that they are entirely distinct entities. Genuine toxic epidermal necrolysis does occur in young children but is relatively rare, and differs clinically by virtue of mucosal involvement. Wherever there is any doubt, the two conditions may be reliably distinguished by histology, as the level of skin separation is intraepidermal in the staphylococcal scalded skin syndrome and at the dermal–epidermal junction in toxic epidermal necrolysis. If the child's condition arouses anxiety, a frozen section will provide rapid differentiation [19].

Treatment is with either a penicillinase-resistant penicillin analogue, such as flucloxacillin or methicillin, or with an appropriate cephalosporin or sodium fusidate. If the attack is severe, the drug should initially be given intravenously. Systemic corticosteroids are contraindicated, on the basis of experimental [20] and clinical [21] evidence that they aggravate the disease. Appropriate compensation must be made for heat and fluid losses. Pain will also require treatment, and affected infants will generally be much more comfortable if the lesions are dressed rather than left open. In severe cases, it may occasionally be justifiable to ventilate the patient in order to obtain adequate relief of pain.

Periporitis staphylogenes and sweat gland abscesses

Periporitis staphylogenes is the term applied to pustular lesions appearing in neonatal skin as a result of secondary infection of miliaria by *S. aureus* [22–25]. Such lesions may progress to sweat gland abscesses, although it is not clear whether sweat gland abscesses are always a complication of miliaria. These disorders have in the past been incorrectly called 'folliculitis and furunculosis of the newborn'. Sweat gland abscesses are distinguished from furuncles clinically by a lack of any tendency to 'point', 'coldness' and absence of tenderness.

Periporitis must be distinguished from miliaria pustulosa, which is not an infective disorder, and from bacterial folliculitis, which in the neonate is usually caused by *S. aureus*. *Candida albicans* and *M. furfur* may also cause pustulosis in the neonate, and a number of non-infective conditions may cause confusion, such as eosinophilic pustulosis.

Mastitis and breast abscesses

Infection of the breast is common and is usually associated with *S. aureus*, but a variety of other bacteria may be responsible [26]. It is almost always unilateral; it occurs most commonly in the second or third week of life, more often in girls than boys, and only very rarely in the preterm infant. The affected breast is swollen, and often red and hot. Systemic toxicity is usually absent. Fluctuation implies abscess formation, which will require surgical drainage. The development of a breast abscess may lead to loss of breast tissue in the longer term [27].

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Omphalitis

The umbilical cord may become colonized by a variety of potentially pathogenic bacteria, and an equally wide variety of topical antiseptics and antibiotics have been used in an attempt to reduce this colonization. The use of hexachlorophane was popular until it became apparent that this could lead to serious neurotoxicity, particularly in the preterm infant [1]. The best substitute may be chlorhexidine, applied as a dusting powder rather than as an alcoholic solution [2].

Occasionally infection of the umbilical cord becomes disseminated, either by bloodstream invasion or by direct extension via the umbilical vessels to the peritoneal cavity. Tetanus, diphtheria and necrotizing fasciitis [3] may also occur as complications of umbilical infection. Such infections are still responsible for a high proportion of deaths in the neonatal period in developing countries.

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Preorbital and orbital cellulitis

Preorbital cellulitis is restricted to the part of the orbit anterior to the orbital septum and is manifest by eyelid swelling. Orbital cellulitis involves the structures deep to the septum and presents with painful proptosis, eyelid oedema and conjunctival erythema. A variety of bacteria can cause these infections, including *S. aureus*, group A and other streptococci.

Necrotizing fasciitis

This name is given to a distinctive form of cellulitis, in which infection tracks along the fascial planes, causing thrombosis of blood vessels running through the fascia with resulting necrosis of the skin, subcutaneous fat and even muscle [1,2]. In neonates, it may arise spontaneously, but more often is a complication of physical birth trauma, omphalitis [3], breast abscess, or iatrogenic skin wounds such as result from scalp electrodes [4] or circumcision [5]. The mother's genital tract is probably often the source of the infection [6].

Initially, the infant develops what appears to be straightforward cellulitis. However, the child becomes disproportionately toxic, and the area affected becomes indurated, discoloured and extends progressively [2,7]. The surface may show a peau d'orange appearance. Purpura and, occasionally bullae, may develop in the centre of the indurated area, often followed quite rapidly by frank necrosis. Destruction of superficial nerves results in local cutaneous anaesthesia. Gas and crepitation may be clinically apparent, or may be seen radiologically. Fever is not invariably present.

A wide variety of bacteria have been associated with necrotizing fasciitis, most commonly group A streptococci, but also group B streptococci, *S. aureus* and *Escherichia coli* [7–10]. In many cases, a synergistic infection by aerobic

and anaerobic organisms appears to be responsible. Occasionally, fungi have been responsible. Antibiotic therapy appears to be of limited value in this potentially lethal situation. The most important aspect of treatment is early surgical excision of necrotic tissue [3,10].

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Neonatal listeriosis

Listeriosis during the neonatal period is uncommon, but dangerous. The responsible organism, *Listeria monocytogenes*, may be transmitted to humans principally through contaminated foods [1]. In pregnancy, it causes a rather non-specific and generally mild, influenza-like illness in the mother [2], but it may lead to transplacental infection of the fetus. Maternal HIV infection may predispose to neonatal listeriosis [3].

Clinically, there are early-onset and late-onset forms of neonatal listeriosis [4]. The early-onset form results from the development of miliary granulomas following bloodborne dissemination of infection. Severely affected babies tend to be born prematurely, and there is a high mortality [5,6]. Post-mortem studies reveal miliary granulomas in many organs. A few infants will have analogous miliary skin lesions during life, manifest as scattered, discrete grey or white papules or pustules, about 1–2 mm in diameter, with a red margin [7,8], which will provide a source of organisms for culture [9]. The back appears to be the site of predilection for such lesions, which are also seen in the mouth and on the conjunctiva. Other cutaneous lesions have been described in such babies, including purpura and morbilliform rashes [3,5].

The late form of the disease is commoner, taking the form of meningitis, occurring a week or two after birth [10].

Diagnosis is by culturing the organism from a variety of sites, including cerebrospinal fluid, blood, urine and from biopsy material, including the skin. Treatment is most frequently with a combination of parenteral ampicillin and gentamicin or kanamycin [5], followed by a longer course of ampicillin or penicillin given alone.

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Pseudomonas aeruginosa infections

Ecthyma gangrenosum [1,2]

Pseudomonas aeruginosa is common in the hospital environment and infections are encouraged by the widespread use of broad-spectrum antibiotics. Most, but not all neonates who develop the skin lesions of ecthyma gangrenosum have *P. aeruginosa* septicaemia, usually in the context of predisposing factors that include prematurity, neutropenia and other immunodeficiencies, necrotizing enterocolitis and bowel surgery. Occasionally the lesions develop directly at the site of direct inoculation of the causative organism.

Histologically, the presence of vasculitis, due to bacterial infiltration of vessel walls, is characteristic [3], together with haemorrhage and necrosis; for this reason skin biopsy can be very helpful in diagnosis.

Clinically, lesions initially take the form of painful macular erythema or purple ecchymosis. The centre then generally develops either vesicles (or less commonly bullae) or pustules which rapidly ulcerate. One subsequently sees one or more ulcers with a depressed, necrotic, often black, crusted centre and a raised edge. The perioral and perianal areas may show grouped lesions.

This infection is potentially dangerous when it occurs in the setting of septicaemia. Appropriate parenterally administered combination antibiotic therapy will be required.

Noma neonatorum

Noma neonatorum is a gangrenous disorder of the nose,

lips, mouth, perianal area and, occasionally, the scrotum and eyelids, occurring in low birthweight and/or premature neonates, almost exclusively in underdeveloped parts of the world. It is frequently caused by *P. aeruginosa* and is almost invariably lethal in the absence of appropriate antibiotic treatment [4]. A similar condition may be seen in older children and adults in the context of immunodeficiency, most commonly in HIV infection [5].

Purpura fulminans

Although in the newborn this condition is most often a reflection of genetically transmitted thrombophilic disorder, it may be caused by acute infections, particularly with endotoxin-associated Gram-negative bacteria such as *Neisseria meningitidis* [6,7].

Congenital syphilis

Congenital syphilis is described in detail in Chapter 30, but its cutaneous manifestations in the neonate will be considered here briefly, because of their importance in differential diagnosis.

The skin is clinically affected in about 40% of neonates with congenital syphilis. In such cases, the skin is usually of normal appearance at birth, the initial lesions occurring between the second and eighth week, and occasionally later. Sites of predilection are the anogenital area, the face and the palms and soles. The lesions themselves are reddish brown in colour; they may be macular or papular, and tend to be larger and firmer than those seen in acquired secondary syphilis (Fig. 14.8). In about 3% of cases the lesions are bullous. Paronychia is commonly present. Small, round, moist, papular lesions, traditionally termed mucous patches, are frequently present in the mouth and on other mucosal surfaces. Condylomata lata may be present in the anogenital flexures or at other flexural sites, for example between the toes or in the angles of the mouth.

Birth weight is below 2500 g in approximately 50% of affected infants. Apart from the cutaneous features, the most frequent clinical manifestations of congenital syphilis in the newborn are hepatomegaly, splenomegaly, jaundice, pneumonia and rhinitis, often with a blood-stained discharge.

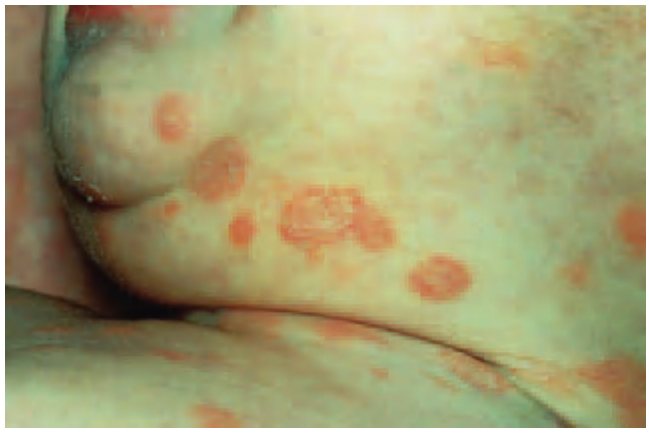

Fig. 14.8 Congenital syphilis: nummular erythematosquamous lesions in a 4-week-old infant.

Congenital tuberculosis

Tuberculosis in the newborn due to transmission of infection *in utero* is relatively rare. The lungs and/or liver tend to be the predominant sites of involvement, and skin manifestations are unusual. However, cutaneous lesions have occasionally occurred, in the form of small numbers of discrete, umbilicated, erythematous papules up to 4 mm in diameter [8].

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Fungal infections

Candida infections in the neonate

There are two distinct forms of candidiasis seen in the first weeks of life, which have been called *neonatal candidiasis*, which appears after birth, and *congenital candidiasis*, which is present at birth.

Neonatal candidiasis

This is a relatively common disorder that occurs in the early weeks after birth, in the form of oral candidiasis with or without candidiasis in the napkin area. The rash usually focused in the perianal area, and is a deep 'beefy' red colour, with a moist appearance, often with pustules at the periphery, which is often scalloped in outline. Just beyond the margin, in as yet unaffected skin, there may

be punctate erythematous lesions, sometimes pustular ('satellite' lesions).

It is assumed that the infection is acquired during delivery from the mother's genital tract, and it should be borne in mind that the frequency of vaginal candidiasis at the time of delivery is between 20% and 25% [1].

Occasionally, the rash may become more generalized. The occurrence of localized palmar pustules in an infant with neonatal oral candidiasis was believed to reflect the inoculation of *Candida* from the mouth into the skin as a result of sucking [2].

The most reliable treatment is generally a combination of a non-absorbed oral anticandidal agent, usually amphotericin drops or miconazole 2% oral gel, and a topical anticandidal agent such as ketoconazole 2% cream.

Congenital candidiasis

This is a rarer condition, seen at birth, which is generally believed to reflect maternal *Candida* chorioamnionitis resulting from ascending infection from the genital tract [3,4,5–9]. It appears that *Candida* is however able to find its way into the amniotic fluid without prior rupture of membranes [10]. Foreign bodies in the uterus or the cervix increase the risk, particularly intrauterine contraceptive devices [10,11]. There is no evidence that maternal antibiotic therapy or immunodeficiency in the infant play a role in predisposition [9,12].

An extensive eruption of scattered pinkish red macules and papules is present at birth or appears within a few hours. The lesions generally progress to a vesicular phase, and then either to a pustular or a bullous phase, over a period of 1–3 days. More or less any part of the skin surface may be affected, including the nails, palms and soles. In fact, palmar and plantar pustules are regarded as a hallmark of congenital cutaneous candidiasis. Isolated involvement of the nail plates has been described [13]. Oral involvement is usually absent, and the napkin area tends to be spared, at least initially.

Very-low-birth-weight infants may have a scalded appearance, and are particularly at risk of systemic infection.

When infection is confined to the skin, affected infants have generally been otherwise well, and the rash clears within a week with appropriate topical antifungal therapy, for example with topical ketoconazole. The rash clears with prominent post-inflammatory desquamation.

Skin and mucosal involvement may be complicated by systemic candidiasis, particularly in the premature [4,14]. The lungs may be affected [15]; hepatosplenomegaly and abnormal liver function have also been recorded [9]. Candidal meningitis is another potential complication [16]. Criteria have been proposed that indicate high risk of systemic involvement. Systemic antifungal therapy should be considered in at-risk infants [12]; amphotericin B is probably the drug of choice [11,14].

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Malassezia pustulosis

Colonization of the skin by *M. furfur* starts soon after birth and progresses until the age of about 3 months, probably reflecting the activity of the sebaceous glands during this period [1–3]. This yeast has been a cause of systemic infections in infants receiving intravenous lipids, and it is presumed that the source of organisms in such cases was the skin [4].

It is now believed that *M. furfur and M. sympodialis* may be a frequent cause of erythematous papulopustular eruptions occurring on the face and scalp in neonates, a condition now widely termed *neonatal cephalic pustulosis* [3,5–7], though not all neonates with this clinical presentation had detectable *Malassezia* in the lesions [8]. This type of rash was reported to have a frequency of 10% in neonates seen as outpatients in a paediatric dermatology department [7], with pustule contents showing *M. furfur* yeasts in over half of these, associated with a good therapeutic response to topical application of 2% ketoconazole cream for 15 days in almost every case. A frequency of 66% was reported in a recent study, with 62% being culture-positive for *Malassezia* [8].

There is reason to believe that some of the *Malassezia*-negative cases in these studies may have had genuine

neonatal acne, which is generally easily distinguished by the concurrent presence of comedones.

Certainly, *M. pustulosis* clearly needs to be considered in neonates presenting with pustular lesions on the face and/or in the scalp, in cases that might otherwise be diagnosed as eosinophilic pustulosis of the scalp, transient pustular melanosis, scabies, neonatal acne vulgaris, or cutaneous infections such as *S. aureus* or *C. albicans* [9].

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Primary immunodeficiency disorders

[A.R. Gennery & A.J. Cant, pp. 14.50–14.87]

Introduction

The immune system protects against a huge variety of infective agents, which bear a vast number of different surface proteins or antigens. To achieve this, a series of defence mechanisms have evolved, from simple mechanical barriers, through non-specific second-line defences which recognize certain proteins, to highly specific directed responses with 'memory' which are refined on repeated exposure and afford long-term protection. The interaction of man and microbe is an ongoing evolutionary struggle, each attempting to outwit the other, so that as existing systems become redundant, new defensive pathways evolve.

Increased understanding of immune mechanisms has given greater insight into the causes of primary and secondary immunodeficiency. Indeed, many aspects of immune function have been elucidated by the recognition of specific defects in individuals with immunodeficiency. It is therefore helpful to describe briefly the mechanisms of the immune response with examples of specific defects that result in primary or secondary immunodeficiency. Immunodeficiency states will then be reviewed in more detail, with particular reference to dermatological manifestations.

The importance of understanding the dermatological features of immunodeficiency within the context of specific immune defects cannot be overemphasized. Because many of the more severe primary defects of immunity have their initial clinical manifestations early in life, the dermatological features of these disorders will be considered in this chapter. The descriptions of cutaneous findings in the primary immunodeficiencies in the medical literature are often vague, probably reflecting the limited input from dermatologists both in the care of such patients, and the preparation of papers for publication.

The innate immune system

Physical barriers such as epithelial surfaces and mucous membranes employ many defences including hairs, cilia, and the secretion of sticky mucus, enzymes and acids, as well as antibiotics produced by commensal flora. The importance of these barriers is demonstrated by the greatly increased risk of sepsis that occurs when they are significantly breached such as occurs following severe burns, or in epidermolysis bullosa.

On breaching these barriers, and invading tissues, pathogens are confronted by the innate immune response, an early evolutionary adaptation. This response lacks immunological memory, so that its magnitude is the same no matter how many times the antigen is encountered. Pathogens are recognized by genetically pre-determined receptors which detect a limited range of highly conserved structures (known as *pathogen-associated molecular patterns*), such as bacterial lipopolysaccharide, mannan and peptidoglycan, which are present on many microorganisms but not on the host. Recognition of one of these pathogen-associated molecular patterns by complementary receptors on effector cells such as monocytes and macrophages causes immediate activation, accounting for the rapid response of the innate system.

Pattern-recognition receptors include:

- mannan-binding lectin, absence of which has been associated with a susceptibility to meningococcal infection;
- the macrophage scavenger receptor, which binds to bacterial cell walls and clears circulating bacteria;
- toll-like receptors, which induce release of chemical messengers such as cytokines and chemokines, which attract phagocytes, antigen-presenting cells (APCs) and lymphocytes to the area of infection.

Neutrophils are part of the innate response, endocytosing and killing invading pathogens. Macrophages and monocytes also endocytose pathogens, but in addition process antigen before presenting it to lymphocytes to initiate the adaptive response.

The innate system responds to activation of a limited number of receptors specific for conserved microbial structures, and also plays a pivotal role in activating the adaptive immune system, which responds only to antigen that has been presented by the innate system.

Soluble plasma proteins such as mannan-binding protein and complement play an important first-line role in innate defence once the epithelial surfaces are breached.

Complement is a series of plasma proteins that act in a cascading sequence to attack extracellular organisms. Direct activation by microorganisms proceeds through the alternative pathway and whilst the classical pathway acts in the same way, it requires activation by antibody. Coating by complement can kill pathogens directly, or can facilitate their removal by phagocytes, which bind complement to complement receptors.

Non-function or absence of components of the alternative pathway or terminal pathway lead to recurrent infection with extracellular pathogens, particularly *Neisseria* spp. Defects in the classical pathway, which plays a role in the clearance of immune complexes, lead to immune complex-mediated disease, chronic inflammation and SLE.

Neutrophil defects include severe congenital neutropenia (Kostmann's syndrome), associated with an absolute neutrophil count below 500 cells/mm^3, and cyclical neutropenia, in which neutropenia occurs at intervals of approximately 3 weeks. Patients with these conditions are at risk of bacterial and fungal infections. Once activated, neutrophils migrate from blood vessels to the site of infection.

In leukocyte adhesion deficiency (LAD), neutrophils lack integrin molecules, which are necessary for their adherence to blood vessel walls and for their subsequent migration between vascular endothelial cells to the site of infection. Affected patients can mobilize very large numbers of neutrophils, but these are unable to migrate into tissues. Patients present with delayed umbilical cord separation, rapidly enlarging and infected skin ulcers with no pus, and recurrent soft tissue, respiratory and gastrointestinal infection. Without bone marrow transplantation (BMT), the severe form of the disease is invariably fatal. To eliminate infection phagocytes must both ingest microorganisms and then kill them once ingested.

Intracellular killing is defective in chronic granulomatous disease (CGD) where patients cannot generate intracellular hydrogen peroxidase as the enzyme nicotinamide adenine dinucleotide (NADPH) oxidase is defective. Affected patients are susceptible to recurrent infections with catalase-positive bacteria and fungi, and suffer recurrent soft tissue, respiratory and gastrointestinal infection with tissue scarring due to granuloma formation.

Much of the immune response is mediated by soluble protein messengers called cytokines, which are secreted by the liver, vascular endothelium and white blood cells. Defects in cytokine signalling pathways may have serious consequences. Macrophages produce interleukin-12 (IL-12) in response to infection, leading to interferon-γ (IFN-γ) release by T lymphocytes and NK cells, which in turn activates hydrogen peroxide production by the macrophages. Defects in IL-12, IL-12 receptor chains and IFN-γ have been identified in patients with severe or recurrent atypical mycobacterial or bacille Calmette-Guérin (BCG) infection. Overproduction of cytokines due to genotypic polymorphisms can also lead to problems. Increased tumour necrosis factor-γ (TNF-γ) production gives increased protection to mycobacterial infection but leads to an overwhelming pro-inflammatory cascade and severe septic shock in meningococcal infection.

The adaptive immune system

T (thymus-derived) and B (bone marrow-derived) lymphocytes, which are responsible for the adaptive immune response, are generated in specialized lymphoid organs, namely the lymph nodes, spleen and mucosal-associated lymphoid tissue. Characteristics of the adaptive response include proliferation of antigen-specific T and B lymphocytes following activation by cells of the innate system. T lymphocytes act directly whilst B lymphocytes produce specific antibody. To respond to the vast number of possible antigens, B lymphocytes produce approximately 10^{16} different antibody variable regions, with a similar number of T-cell receptor (TCR) variable regions from fewer than 400 germ-line genes. This remarkable diversity means that there is a T or B cell with a receptor complement to every protein antigen that could be made. This variety is achieved by promiscuous recombination processes that cut, splice and modify variable region receptor genes. This randomly generated receptor diversity produces self-reactive lymphocytes as well as lymphocytes generated against specific microorganisms. Early lymphocyte development enables receptor rearrangement, but following expression of a mature receptor, continued survival is antigen-dependent, and self-reactive lymphocytes are usually eliminated.

B-lymphocyte development

The diverse repertoire of T- and B-cell receptors is generated by recombination of a small number of gene segments. B-lymphocyte receptors (BCRs) are membrane-bound immunoglobulin.

Immunoglobulins are comprised of two identical heavy (H) chains and two identical light (L) chains, held together by disulphide bonds. Immunoglobulins have two separate functions. The first is to bind to specific antigen through the variable (V) domain, and the second is to recruit other cells to the immunoglobulin-bound antigen to effect killing and destruction. This second function is mediated through the constant (C) domain. The constant region is invariable for each immunoglobulin class, although it has five main forms or isotopes which determine the immunoglobulin class (IgM, G, A, E, D). Small variations lead to four IgG and two IgA subclasses. Both heavy and light chains have C and V domains.

Variable domains are constructed from the recombination of gene segments from two or three 'families' of

genes. In L chains, a V (variable) segment is joined to a J (joining) segment. These are then joined to the light chain C domain. A similar process occurs in the heavy chain, but there are three different gene segments in the variable region, a V (variable) segment, a J (joining) segment and a D (diversity) segment, which join to the heavy chain C domain. There are a number of different gene segments in each 'family' and so diversity is generated by varying the combination in which the V (D) J segments are arranged. Further diversity is introduced by pairing different heavy and light chain variable regions, and by imprecise splicing and rejoining of different gene segments which give rise to different nucleotide sequences at the joining junction. These recombination events occur in the bone marrow. 'Fine tuning' of the response to produce antibody exactly complementary to antigen (somatic hypermutation) requires T-cell cooperation (see below). This unique and complex system is very prone to genetic faults which are not lethal *in utero*. Mutations in genes encoding B-cell heavy or light chains, or in the associated signalling molecules lead to absence of B cells and agammaglobulinaemia, as seen in X-linked agammaglobulinaemia (XLA; Bruton's disease), or to hypogammaglobulinaemia due to μ-chain deficiency. Defects in specific immunoglobulin heavy or light chain translation lead to individual class or subclass deficiency, although some humoral immunity is preserved.

T-lymphocyte development

TCR development is very similar to that of B cells, but occurs in a specialized microenvironment, the thymus. Precursor cells migrate to the thymus and undergo TCR chain rearrangements. The TCR consists of α/β or γ/δ heterodimers. Each α, β, γ, δ chain contains a variable and a constant domain. As in the BCR, the variable domains are constructed from gene segments from different V, (D) and J 'families'. TCR α and γ loci do not contain D segments. The BCR differs from the TCR in that TCRs only recognize antigen that is bound to an individual's own major histocompatibility complex (MHC) tissue type molecule expressed on the surface of their cells. Thus, during thymic development, T cells that recognize antigen/self MHC complex are positively selected (self MHC restricted) and survive, whereas those that recognize self-antigen/MHC complex are negatively selected (self-tolerance) and undergo apoptosis. Only about 2% of T-cell precursors entering the thymus pass this rigorous selection process and leave as mature, naïve T cells.

T and B cells use similar signalling and enzymatic processes to rearrange gene segments and construct antigen receptors. Some of the enzymes are the same as those used to repair damaged DNA. Many are critical to lymphocyte development, and lymphocytes cannot develop in their absence, which results in the various forms of severe combined immunodeficiency (SCID). For example, mutations of recombination-activating genes 1 and 2 (*RAG1* and *2*) results in T-negative, B-negative SCID.

The important role of the thymus is illustrated by the complete DiGeorge's syndrome, where congenital thymic absence leads to a SCID phenotype with absence of T cells. A number of signalling molecules and their receptors, particularly those for cytokines and their receptors, are also critical in lymphocyte development and survival. Thus, absence of the common cytokine receptor γ chain (which is integral to the IL-2, -4, -7, -9 and -15 receptors) leads to T-cell negative, B-cell positive, NK-cell negative SCID. Absence of Janus-associated kinase 3 (JAK3), a signalling molecule associated with the cytokine receptors, has the same consequence. Other defects can lead to dysregulation of thymic selection.

A cell that fails either negative or positive selection undergoes apoptosis. Defects in the apoptosis pathway, particularly the molecules Fas or Fas ligand, lead to the escape of autoreactive lymphocytes; this can result in autoantibody production and autoimmune disease.

Antigen presentation and lymphocyte interaction

Mature T and B lymphocytes circulate through the blood, lymphatics and tissues looking for the antigen which is specific for the particular receptor. Microorganisms are taken up by cells of the innate response, such as macrophages. They are broken down in lysosomes to small polypeptide fragments of 8–12 amino-acids long, combined with MHC class I or II molecules and presented at the cell surface as an antigen/MHC complex, with antigen bound within the groove of the MHC molecule. Defects in the MHC class II transcription molecules, or in the MHC class I transporter proteins (which transport antigen peptide to MHC class I molecules) occur, and although affected individuals have functionally normal lymphocytes, they suffer repeated life-threatening infections because antigen cannot be presented to their T- and B-lymphocyte receptors.

Most adaptive immune responses occur in lymphoid tissue, where lymphocytes and APCs (macrophages, dendritic cells) are concentrated. There are at most only a few hundred lymphocytes with a receptor complementary to a specific antigen. When a T lymphocyte interacts with a matching antigen/MHC complex (MHC class I with CD8 cytotoxic T cells, for intracellular organisms, MHC class II with CD4 helper T cells for extracellular organisms), a second signal is delivered from the APC to the T cell, via a B7 molecule on the APC interacting with a CD28 molecule on the T cell. The combination of these two signals (TCR/MHC-antigen and B7/CD28) activates the T cell causing repeated replication of T cells bearing the same antigen-specific receptor; a process called clonal expansion. Conversely, delivery of the first signal without

the second renders the T cell unable to respond to antigen, and this unresponsive state is known as T-cell anergy. Because only a few T lymphocytes have the receptor for the specific antigen, only a few are activated for that antigen. However, as each microorganism carries many antigens, infection will cause the proliferation and clonal expansion of many different T lymphocytes, leading to a polyclonal response.

As well as triggering clonal T-cell proliferation, an activated CD4 T cell can interact with a B cell carrying the BCR specific for the antigen, triggering clonal B-cell expansion. Initially the B cell responds by secreting IgM. In lymph node germinal centres, as the adaptive response matures, interactions between T cells via CD40 ligand (expressed on T cells) and CD40 expressed on B cells enables B cells to switch from making IgM to making IgA, IgG and IgE. This follows substitution of the appropriate C domain on the heavy and light chains, encoding for IgM, A, G or E respectively, a process known as isotype switching. Point mutations, deletions and insertions in the variable domain of the immunoglobulin molecule (somatic hypermutation) modify the immunoglobulin molecule further (the fourth method of creating antibody diversity). B cells making immunoglobulin that 'fits' the antigen most precisely are generated in great number (affinity maturation), whereas B cells that produce immunoglobulin of inferior 'fit' undergo apoptosis.

Once activated, these T cells and B cells are long lived, and act as memory cells. Thus, when the same antigen is encountered again, these cells react immediately, not requiring activation by the innate system. The immunoglobulin that is produced attaches to the microorganism via the antigen-binding region. The effector portion of the immunoglobulin attaches to immunoglobulin receptors on phagocytes and macrophages, facilitating phagocytosis, antigen processing and elimination.

Defects in these mechanisms illustrate their importance. In X-linked hyper-IgM syndrome, CD40 ligand is deficient, so B cells are unable to switch from making IgM to other immunoglobulin isotypes. T cells are also unable to interact with macrophages (which also express CD40), which are therefore unable to kill ingested intracellular pathogens such as *Pneumocystis carinii* and *Cryptosporidium parvum* resulting in opportunistic infections. An autosomal recessive form of hyper-IgM syndrome is due to mutations in the activation-induced cytidine deaminase gene, which encodes for a protein that is involved in the isotype switching and hypermutation processes.

Once switched on by antigen presentation, T cells develop in one of two different ways:

1 *Th1 cells* produce IL-2 and IFN-γ, whose main role is to stimulate macrophage function and cell-mediated immunity, but which also induces B lymphocytes to switch the class of antibody produced, particularly to IgG2.

2 *Th2 cells*, in contrast, predominantly produce IL-4 and IL-10, which promote antibody responses and class switching, particularly towards IgG1, IgG4 and IgE.

Allergic responses and responses to parasites are of Th2 type. Responses to an antigen may follow either a Th1 or Th2 route, depending on a complex set of circumstances. Once established, these responses are self-amplifying in that production of IFN-γ or IL-4 promotes Th1 and Th2 responses respectively, while inhibiting the other.

Over-activation of the antigen/TCR- or BCR-binding process can also cause disease. Bacterial toxins and some viruses act as 'superantigens', binding to the outside of the MHC molecule, and in particular to the outside of a V chain (one of the V segments of the β chain of the TCR), regardless of the antigenic specificity of the V domain of the β chain, or of the DJ segments of the V domain of the β chain. Thus, instead of activating say only 20 out of 10^{16} naïve T cells, a single superantigen is able to activate up to 20% of the T-cell pool. This leads to massive lymphocyte activation and cytokine release, and is the process that is responsible for the marked inflammation seen in superantigen-mediated diseases like toxic shock syndrome and Kawasaki disease.

The complex mammalian immune system has evolved a variety of mechanisms to counter invasion by microorganisms. Our understanding of its function has greatly increased by recognizing defects in 'knockout' laboratory animals, and in their human equivalent, individuals with congenital primary immunodeficiency. Elucidation of the molecular pathways has enhanced our understanding of the immune response, and identification and clarification of precise molecular mechanisms has led to advances in treatment of primary immunodeficiencies. Thus, X-linked hyper-IgM syndrome used to be considered an antibody deficiency, even though immunoglobulin replacement did not prevent liver disease secondary to *C. parvum* infection. Recognition that it is in fact a primary T-cell defect has led to BMT in selected patients. Identification of the genetic defect in X-linked SCID has lead to successful gene therapy for this condition.

The skin is a vital component of the innate immune system and the 'battleground' for many innate and adaptive immune responses to infection. It is not surprising, therefore, that skin sepsis and other dermatological manifestations are common features of primary immunodeficiency. Understanding the context of these responses ought to give a clearer view of these conditions and their treatment.

Immunodeficiency disorders: general principles

Classification and genetics

The risk of significant immunodeficiency (excluding selective IgA deficiency) has been estimated at 1 in 10 000. Table 14.6 shows an adapted version of the classification

Table 14.6 Combined immunodeficiencies. (Adapted from Rosen *et al.* [1].)

Immunodeficiency	Defect	Inheritance
CD40 ligand deficiency	CD40 ligand	XL
WAS	WASP	XL
XLP	SLAM-associated protein	XL
DiGeorge's anomaly	Developmental field defect chromosomal deletion (usually 22q11.2)	Sporadic (some AD)
Cartilage hair hypoplasia	*RMRP* gene	AR
Immunodeficiency with albinism:		
1. CHS	*LYST* gene	AR
2. Griscelli's syndrome	Myosin 5a gene	AR
Familial haemophagocytic lymphohistiocytosis	Perforin gene	AR
Ataxia–telangiectasia	*ATM* gene	AR
Nijmegen breakage syndrome	*NBS1* (nibrin) gene	AR
Ligase IV deficiency	DNA ligase IV	AR
Fanconi's anaemia	*FAND2* gene	AR
Ectodermal dysplasia—immunodeficiency	*NEMO* gene	AR

AD, autosomal dominant; AR, autosomal recessive; CHS, Chediak–Higashi syndrome; WAS, Wiskott–Aldrich syndrome; WASP, Wiskott–Aldrich syndrome protein; XL, X-linked; XLP, X-linked lymphoproliferative disease.

of primary disorders suggested by the World Health Organization working party on immunodeficiency [1].

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Diagnosis and investigation of immunodeficiency

A careful history and examination should precede laboratory tests, as the important clues obtained help determine which children should be investigated and which tests should be performed.

Most children present because of a problem with infection. An immunodeficient child is likely to have more infections, which take longer to resolve, or which follow an atypical course. Cutaneous infections in immunodeficient patients may be caused by microorganisms which are not usually pathogenic, or which follow a more severe course than in those with normal immunity. Such infections may not immediately suggest a primary immunodeficiency unless this diagnosis is actively considered.

When several members of the same family suffer from furuncles, nasal carriage of staphylococci and cross infection are more likely causes than immunodeficiency. Frequent upper URTIs alone in a young child are not indicative of an underlying immune defect unless associated with frequent bacterial infections. Clinical experience suggests that up to eight URTIs per year are normal in the pre-school years [1]. Infections with common organisms may run an atypical course (e.g. haemorrhagic chickenpox), or they may fail to respond to standard treatments, (e.g. a bacterial pneumonia which fails to respond to appropriate antibiotic therapy). Alternatively, infections may be caused by uncommon organisms which are in themselves highly suggestive of immunodeficiency, such as *P. carinii* pneumonia [2].

Failure to thrive is a common finding, and this may or may not be associated with diarrhoea due to chronic or recurrent infection or autoimmune enteropathy [3]. Evidence of end-organ damage, such as a cough productive of sputum, consistent with bronchiectasis, should also be sought. Allergic symptoms are common and may be unusually severe. Autoimmune and malignant diseases, though not common, have an increased incidence.

Delayed separation of the umbilical cord in the absence of local infection may suggest a neutrophil defect.

Taking a careful family history may indicate unusual or fatal infectious complications in siblings, suggestive of an autosomal recessive or X-linked pattern of inheritance. A history of consanguinity should be sought.

In some disorders, e.g. IgA deficiency, there may be a family history of collagen vascular or other immunopathological disease [4]. Older relatives who are carriers of an inherited immunodeficiency or who are affected by milder variants of primary immune defects may have autoimmune manifestations (e.g. mouth ulcers and SLE variant in CGD [5]), or have a history of malignant disease (lymphoma in X-linked lymphoproliferative disease (XLP) or Wiskott–Aldrich syndrome (WAS)).

Furuncular lesions or abscesses can be an overlooked manifestation of a primary immunodeficiency. They are most characteristically seen in neutrophil disorders such as CGD [6], Chediak–Higashi syndrome (CHS), LAD [7] and neutrophil-specific granule deficiency, but also in

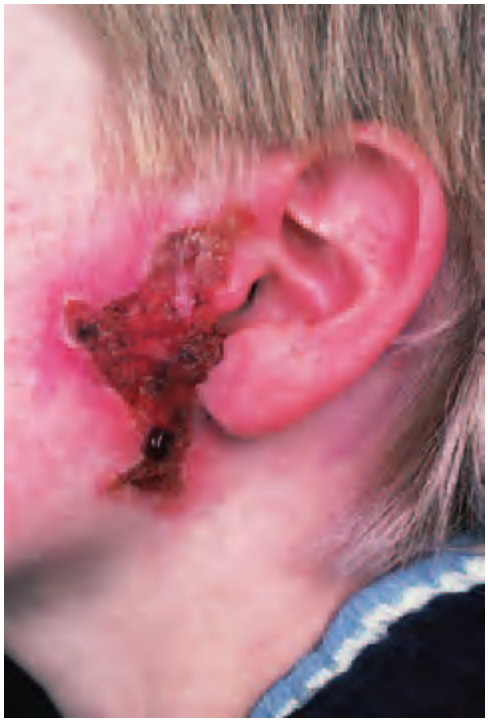

Fig. 14.9 Progressive cutaneous ulceration due to herpes simplex in a 9-year-old child with T-lymphocyte immunodeficiency.

hyper-IgE syndrome [8] and antibody deficiencies such as XLP, or in complement disorders. In these disorders it is, however, usual for infections of the skin to be accompanied by infection at other sites.

Cutaneous and mucosal ulceration are features of several immunodeficiency states and are the hallmark of LAD. Although infection is believed likely to be the cause of the ulceration, it can be difficult to identify the microorganisms responsible, and accumulation of neutrophils in small blood vessels to the point where blockage and tissue necrosis occurs probably plays a big part in their genesis. Such ulcers are a characteristic feature of disorders featuring neutropenia, including congenital neutropenia, cyclical neutropenia and CHS. Gradually extending cutaneous ulcers due to HSV (Fig. 14.9) are suggestive of T-lymphocyte defects, but have also been reported in XLA.

Unusually severe or extensive infections with HSV or varicella-zoster virus, including the haemorrhagic vesicles seen in haemorrhagic chickenpox, are characteristic of T-lymphocyte defects. Bullous impetigo with clear blisters may be a presentation of neutropenia. A vesicular presentation of the hyper-IgE syndrome in infancy has been described [9].

Ordinary viral warts are virtually never indicative of immunodeficiency. However, exceptionally rapid growth of warts, exceptionally large size or unusually extensive infections are suggestive of underlying defects of immunity (Fig. 14.10). Severe extensive persistent molluscum contagiosum is seen in similar disorders such as WAS, CD40 ligand deficiency and less well characterized combined immune deficiencies (Fig. 14.11).

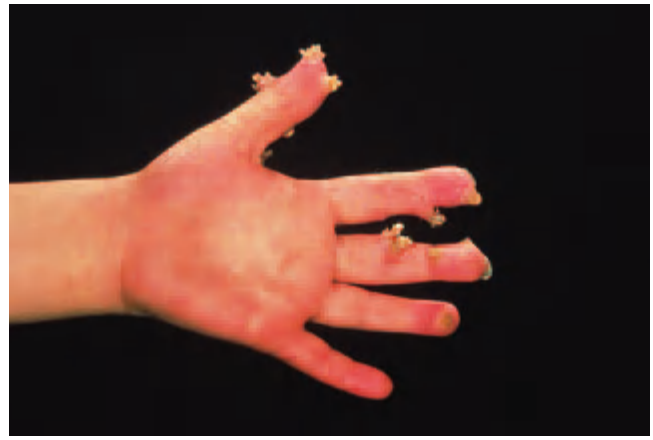

Fig. 14.10 Unusually large and rapidly proliferating viral warts in a child with combined immunodeficiency.

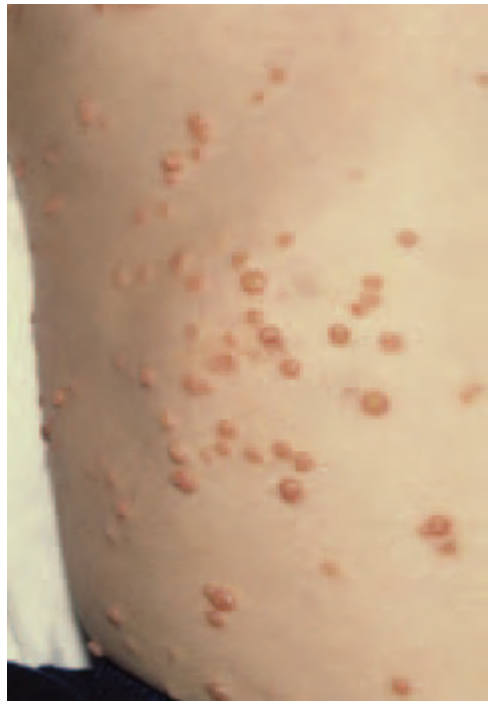

Fig. 14.11 Severe, extensive molluscum contagiosum in a child with Wiskott–Aldrich syndrome (WAS). (Reproduced with permission from the Audiovisual Centre, University of Newcastle, Newcastle, UK.)

Refractory mucosal and cutaneous *Candida* infections are a characteristic presenting sign of several immunodeficiency disorders, particularly SCID and severe T-lymphocyte defects. Surprisingly, systemic *Candida* infections are rather rare in these conditions. Persistent mucosal and cutaneous *Candida* infection, responding

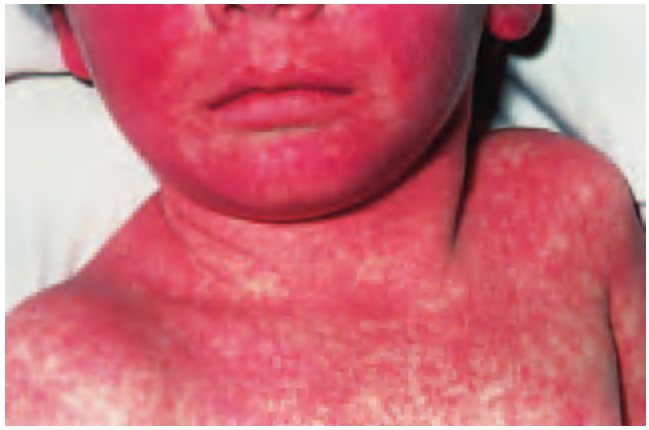

Fig. 14.12 Acute graft-versus-host disease (GvHD) following transfusion of non-irradiated blood in a child with severe combined immunodeficiency (SCID).

poorly to systemic treatment, suggests chronic mucocutaneous candidiasis (CMC).

Non-specific, non-infectious manifestations of immunodeficiency

Morbilliform eruptions are sometimes caused by viral infections, as in other children, but in SCID they are quite frequently manifestations of acute graft-versus-host reactions, due either to materno–fetal engraftment, or to the transfusion of non-irradiated blood products after birth (Fig. 14.12).

Petechiae due to thrombocytopenia are a highly characteristic feature of WAS and may also occur in Fanconi's anaemia, dyskeratosis congenita, Schwachman's syndrome and CHS.

A combination of early-onset erythroderma and failure to thrive in early infancy is highly suggestive of immunodeficiency, and often results from dysregulated activated T lymphocytes invading the skin. In some cases, these are maternally derived and represent true graft-versus-host disease (GvHD) [10]. In other cases, aberrant clones of the infant's own T lymphocytes cause a similar reaction, resulting in the condition known for many years as Omenn's syndrome, but now more precisely described as 'leaky' T-B-SCID.

If one considers atopic eczema to be an immunodeficiency disease, eczema would certainly be the commonest of all cutaneous manifestations of immunodeficiency. Eczema is also a characteristic cutaneous feature of certain well-established immunodeficiency disorders such as WAS, and has been recorded as occurring more frequently than one would expect in various other disorders, including selective IgA deficiency, selective IgM deficiency, ataxia–telangiectasia and combined immunodeficiency.

Patients with several different primary immunodeficiencies have featured indurated erythematous papules and plaques with central scaling, scarring, atrophy or ulceration, which have demonstrated caseating granulomas histologically. The conditions in which these have been reported include common variable immune deficiency (CVID) [11], XLA [12], ataxia–telangiectasia [13] and CGD [14].

As well as classical systemic and discoid LE, a syndrome resembling SLE from the cutaneous point of view but having only very mild non-cutaneous manifestations and either absent or very low-titre plasma antinuclear antibodies has been described in patients with a variety of complement deficiencies. In such patients, this syndrome can occasionally have its onset as early as the first year of life, and, because many of these patients are susceptible to certain infections, such as meningococcal meningitis, the association of a disorder resembling LE and recurrent infections of appropriate type is highly suggestive of a hereditary complement deficiency.

There is an increased incidence of SLE in patients with IgA deficiency, and skin lesions closely resembling discoid LE have occurred in female carriers of the gene for X-linked CGD.

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4 Cunningham Rundles C, Bodian C. Common variable immunodeficiency: clinical and immunological features of 248 patients. *Clin Immunol* 1999; **92**: 34–48.
5 Brandrup F, Koch C, Petri M *et al*. Discoid lupus erythematosus-like lesions and stomatitis in female carriers of X-linked chronic granulomatous disease. *Br J Dermatol* 1981; **104**: 495–505.
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12 Fleming MG, Gewurz AT, Pearson RW. Caseating granulomas in a patient with X-linked infantile hypogammaglobulinaemia. *J Am Acad Dermatol* 1991; **24**: 629–33.
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General examination

General physical examination should be directed towards potential sites of infection, including the throat, ears and sinuses, and examination of the oral cavity and nappy area for candidiasis. The presence or absence of lymphoid tissue should be noted, as should cutaneous problems consistent with defective immunity. In more severe antibody deficiency states such as XLA, there is a lack of tonsils and lymphoid tissues. Signs of end-organ damage from infections, such as clubbing and respiratory abnormalities, must be sought.

Some diseases may have specific physical signs, such as oculocutaneous albinism in CHS, typical facies and/or cleft palate in DiGeorge's syndrome, telangiectasia or neurological abnormalities in ataxia telangiectasia, and disproportionate short stature in some forms of combined immunodeficiency (see Immunodeficiency and short-limbed dwarfism below).

Radiological evaluation

Evidence of bony abnormalities may support a diagnosis of adenosine deaminase (ADA) deficiency [1], Schwachmann–Diamond syndrome [2] or other dysplasias associated with immune defects. Dilatation of the common bile duct may be suggestive of sclerosing cholangitis, associated with a number of combined immune deficiencies, especially X-linked hyper-IgM syndrome [3]. Careful review of chest X-rays may suggest bronchiectasis, and should prompt high-resolution computed tomography (CT) imaging. Although absence of a thymus on anterior posterior and lateral chest X-rays is consistent with a combined immune defect in infants and young children, thymic atrophy may also occur in response to stress (e.g. infection) and this finding is not diagnostic.

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Laboratory investigation

Two main questions need to be addressed, which children to investigate, and how extensively?

Investigation should be triggered by any of the following:

1 a family history consistent with immune deficiency;
2 a single infection with an unusual/opportunistic organism;
3 an usually severe single infection or one that runs an atypical course or occurs at an atypical age;
4 recurrent minor bacterial infections (e.g. otitis media more than two times per year despite appropriate Ear, Nose and Throat management, resulting in significant school absence);
5 more than one episode of serious bacterial infection [1].

Table 14.7 Examples of association between most likely type of immune defect and infecting organisms.

Candidate immune defect	Typical infecting organism
Antibody	*Streptococcus pneumoniae* *Haemophilus influenzae* *Giardia lamblia* *Mycoplasma* spp. Enteroviruses
Cell-mediated	*Salmonella* *Cryptosporidium* *G. lamblia* *Candida albicans* Herpesviruses (e.g. cytomegalovirus) Other viruses, e.g. measles Bacille Calmette-Guérin (BCG)
Neutrophil	*Staphylococcus* Gram-negative bacteria *C. albicans* *Aspergillus* spp. BCG
Type 1 cytokine defects	*Salmonella* Mycobacteria (typical and atypical) BCG
Monocyte	*C. albicans*
Natural killer cell	Herpesviruses
Complement	*Neisseria meningitidis* *S. pneumoniae* *H. influenzae*

Laboratory investigations can be directed to a certain extent by the organism causing infection (Table 14.7) and the age of the child.

Laboratory investigations range from those readily available in all centres, to highly specialized tests performed in research centres. Only a small proportion of children presenting with recurrent infections require complex investigation; most can be adequately investigated with a few relatively straightforward tests.

REFERENCE

1 Chapel HM. Consensus on diagnosis and management of primary antibody deficiency. *BMJ* 1994; **308**: 581–5.

Haematology

A full blood count and blood film examination can be very revealing.

Neutropenia is readily detected, and a bone marrow aspiration will distinguish failure of production from increased peripheral destruction. Bone marrow aspiration will also exclude a myelodysplastic or malignant process.

Neutrophilia in the absence of overt infection may be suggestive of a neutrophil adhesion defect or functional problem (e.g. CGD).

Lymphopenia, using appropriate age-related ranges, strongly suggests a combined immunodeficiency of primary or secondary aetiology [1], although SCID can occur in the presence of a normal lymphocyte count. Nucleated red cells in infants and abnormal leukocyte morphology in sick children may be detected as lymphocytes on the Coulter counter, and thus erroneously suggest a normal lymphocyte count. Abnormal leukocyte granules are seen in CHS, whilst a platelet volume is invariably low in WAS, making this the most rapid and reliable diagnostic pointer in this condition.

REFERENCE

1 Hague RA, Rassam S, Morgan G *et al*. Early diagnosis of severe combined immune deficiency syndrome. *Arch Dis Child* 1994; **70**: 260–3.

Tests of innate immunity

Complement

C3 and C4 are easily measured. However, null alleles for C4 are relatively common, so that the significance of an isolated low C4 in an individual with recurrent infections is less certain. Furthermore, normal levels of C3 and C4 do not exclude deficiencies of other complement components. It is therefore better to screen the whole complement system by assessing the functional integrity of the classical and alternative complement pathways, using assays which test the ability of patient serum to lyse sensitized red blood cells (CH50/100 and AP50 respectively). Deficiency in any one component will result in a failure of lysis. Low values may be seen in the presence of active infection, when complement components are being consumed, or if degradation of complement components has occurred because the sample was not separated and frozen within 2 h of venesection. However, if repeat testing shows a persistent abnormality, measurement of the levels of individual complement components should be performed until the defective component is identified.

Neutrophil function tests

Neutrophil function has three main components: chemically mediated movement towards microorganisms (chemotaxis), ingestion of microorganisms into a phagocytic vacuole (phagocytosis), and activation of the respiratory burst within the phagolysosome to produce free oxygen radicals that kill microorganisms.

Neutrophil function tests are fraught with technical pitfalls, as neutrophils rapidly activate upon venesection and also die quickly. Neutrophil chemotaxis testing is now recognized to be unreliable and only performed in a research setting.

Chemiluminescence measures all three phases of neutrophil activity, and such assays are now being superseded by flow cytometric assays (see below).

Nitroblue tetrazolium (NBT) is a yellow dye that is readily taken up by phagocytes and upon stimulation (e.g. with phorbol myristate acetate) is reduced to the purple dye formazan by the oxidative burst. Normally at least 95% of neutrophils should contain a purple deposit in stimulated cells. In CGD, less than 1% of neutrophils reduce NBT. Carrier mothers of the X-linked disease can also be detected by this method, as they show an intermediate level of NBT reduction (20–80%). In experienced hands, this is a rapid and sensitive test for CGD, but false normal results can be seen when the test is performed infrequently.

Flow cytometric assays of neutrophil function

Fluorescently labelled microorganisms can be used to assess the phagocytic ability of neutrophils, seeing what proportion of cells have ingested the labelled organisms. Comparison of phagocytosis using the patient's own serum with that using control serum gives a measure of the effectiveness of patients' antibody and complement systems to aid phagocytosis (opsonization).

Phagocytosis of organisms by neutrophils and monocytes normally leads to activation of the respiratory burst, and to the production of free oxygen radicals. If neutrophils take up dihydrorhodamine and, using a suitable stimulus, the dihydrorhodamine is reduced, it fluoresces within cells. This fluorescence can be assessed using a flow cytometer, absence of fluorescence indicating failure of the respiratory burst. This is the best test for identifying patients with CGD. It can also detect carriers for X-linked CGD, who exhibit a dual population of normal and abnormal cells. The test has the advantage that more laboratories are experienced in the interpretation of flow cytometric readouts than reading slide NBTs, so that false normal results are much less likely. It is, however, more sensitive than an NBT, so neutrophil function defects other than CGD may also be detected. Neutrophil killing defects may also occur in myeloperoxidase deficiency and in glucose-6-phosphate dehydrogenase deficiency, both of which can be assayed separately.

Adaptive immune system

Tests of humoral immunity

Immunoglobulins G, A and M are routinely measured by nephelometry which measures light scattering, the

amount of light scattered being proportional to the quantity of immunoglobulin within the sample. Results must be evaluated with reference to age-specific normal ranges, as production of all five classes of immunoglobulin is low at birth and gradually matures over the first 5 years of life [1]. Low levels of immunoglobulin can only be attributed to a production defect if gut or renal losses have been excluded, and if the serum albumin is within the normal range. Catabolic states, such as myotonic dystrophy, can also lower total immunoglobulin levels.

Immunoglobulin E is measured using a variety of techniques, including enzyme-linked immunosorbant assays (ELISAs), and automated solid-phase ELISAs.

Immunoglobulin G subclasses are commonly measured by nephelometry or radial immunodiffusion. Results should be compared with age-specific normal ranges, but the value of measuring IgG subclasses in children under 2 years of age, or if the total IgG is low, is debatable. Approximately 10% of the normal population have undetectable IgG4, and normal ranges should be adjusted to reflect this.

REFERENCE

1 Braun J, Steihm ER. The B-lymphocyte system. In: Stiehm RE, ed. *Immunological Disorders in Infants and Children*, 4th edn. Philadelphia: Saunders, 1996: 35–74.

Measures of in vivo antibody responses

The ability of the immune system to produce functional antibody is more important than the amount of circulating antibody. Functional tests of IgG production rely on measuring antibody titres to antigens to which the child is known to have been exposed, either naturally or by vaccination. Responses to protein antigens such as tetanus, diphtheria and the conjugated Hib vaccine are easily measured. However, although normal ranges for antibody titres exist, these are not well validated for antigens other than Hib, and may not be a true reflection of immunological memory. If antibody titres are low, booster vaccinations should be given to assess the memory response. The most reliable results are obtained when pre- and post-vaccination samples are assayed at the same time. In children over 2 years of age, administration of Pneumovax® (23 serovalent polysaccharide vaccine) is useful to assess the ability to respond to carbohydrate antigens. Loss of this response may be the first sign of an evolving immune deficiency in patients with CVID or WAS. Assessment of antibody responses to common respiratory viral pathogens and to varicella zoster may also provide useful additional information, although negative tests in the absence of microbiologically proven disease are difficult to interpret.

The optimal test of *in vivo* antibody production is assessment of IgM and IgG responses.

Cell-mediated immunity

Cell-mediated (T-lymphocyte) defects are usually accompanied by a degree of humoral immune deficiency, as T-lymphocyte help is crucial in making an antibody response with memory.

Quantification of cell numbers. Lymphocytes can be enumerated using flow cytometry, which detects the different light scatter properties of cells passed through a laser beam and enables populations of neutrophils, monocytes and lymphocytes to be differentiated. Lymphocytes can be characterized further by their cell surface markers, which are identified by specific monoclonal antibodies. The number of cells staining with a particular monoclonal antibody can be expressed either as a percentage of the lymphocyte pool, or as an absolute number. As with all immunological parameters, both proportions of different T lymphocytes and absolute numbers vary with age and reference should be made to published age-related normal ranges [1]. Approximately 60–80% of circulating lymphocytes are T lymphocytes, with 10–20% B lymphocytes and 5–15% NK cells.

REFERENCE

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Functional tests of cell-mediated immunity: in vitro lymphocyte proliferation assays. When lymphocytes encounter antigen *in vivo* they respond by upregulation of activation markers and proliferation, without which an effective immune response cannot occur. This can be mimicked *in vitro* by culturing lymphocytes with a non-specific stimulus such as plant lectins, using the incorporation of tritiated thymidine or a non-radioactive marker such as bromodeoxyuridine into the DNA of dividing cells as a surrogate measure of cell proliferation.

Definition of molecular defects

Protein assays

The genetic basis of an increasing number of immunodeficiencies is now well defined; many occur because a surface or cytoplasmic signalling protein is absent or defective. These abnormalities can be detected using a combination of western blotting and flow cytometry [1].

REFERENCE

1 Gilmour KC, Cranston T, Jones A *et al.* Diagnosis of X-linked lymphoproliferative disease by analysis of SLAM-associated protein expression. *Eur J Immunol* 2000; **30**: 1691–7.

Genetics

In the presence of an appropriate history or abnormal protein expression, molecular genetic analysis may be undertaken. Genes can be screened using single-stranded conformational polymorphism analysis, or by direct sequencing using automated sequences. It should be remembered however, that some polymorphisms within the human genome may have no clinical effects.

Once mutations have been defined, parents can be tested for carrier status. Carrier testing of siblings raises a number of ethical issues, and children should reach the age of informed consent before any tests are undertaken.

Antenatal diagnosis

Appropriate counselling by an individual conversant with the current prognosis of immunodeficiency states should be undertaken before antenatal diagnosis is undertaken. Due to the small risk of miscarriage, screening should only be offered to mothers when the parents would elect to terminate an affected pregnancy. Where the genetic defect is known, study of chorionic villus biopsy material can be performed in the first trimester. In other conditions, fetal blood sampling is performed at 18–20 weeks.

Disorders of cell-mediated immunity

Combined immunodeficiencies (severe combined immunodeficiency)

Failure to develop normal T lymphocytes, usually due to specific gene defects affecting early T-lymphocyte development or subsequent signalling pathways, leads to T-cell immunodeficiency, generally with concomitant humoral deficiency. In some combined immunodeficiencies, single gene defects affect both B- and T-lymphocyte development. The severity of the humoral deficiency varies from a subtle defect of specific antibody response to complete hypogammaglobulinaemia. Combined immunodeficiency results from a large number of disorders with X-linked or autosomal recessive inheritance [1]. The molecular basis of many, but not all, combined immunodeficiencies has now been elucidated (Tables 14.6, 14.8 & 14.9).

The most severe phenotype is SCID, and is associated with a profound T lymphopenia and panhypogammaglobulinaemia with early death from infection. Whilst the usual clinical features of this group of diseases are well characterized, atypical presentations and 'leaky' forms, with an attenuated phenotype, are increasingly recognized. Circulating T-lymphocyte numbers are usually low or absent but may be normal. In the classic SCID presentation, lymphocyte responses to mitogen are generally absent. Tests of antigen specific T-lymphocyte proliferation and antibody production are defective, and there will be cutaneous anergy. Patients usually have a limited diversity of T-lymphocyte receptors and immunoglobulin gene rearrangements.

Diagnosis may be more difficult in atypical patients. Identifying the molecular defect in specific patients with combined immunodeficiency or SCID is important for prognosis, treatment, genetic counselling and increasing our knowledge about these rare diseases.

General features of SCID

Although affected infants appear well at birth, they suffer persistent respiratory tract or gut infection and progressive failure to thrive from the first months of life [2]. Chronic diarrhoea and failure to thrive are due to persistent and sometimes multiple gastrointestinal viral infections, often with associated food intolerance.

Table 14.8 Defects of phagocytic function.

Immunodeficiency	Defect	Inheritance
XL CGD	Killing gp91^{phox}	XL
AR CGD	Killing defect p22^{phox}, p47^{phox}, p67^{phox}	AR
LAD type I	β integrin (CD18)	AR
LAD type II	CD15	AR
Neutrophil G6PD deficiency	Neutrophil G6PD	XL
Myeloperoxidase deficiency	Myeloperoxidase	AR
AR severe congenital neutropenia	Elastase	AR
XL severe congenital neutropenia	WAS activating mutation	XL
Mycobactericidal defect	IFN-γ receptor 1 deficiency	AR
	IFN-γ receptor 2 deficiency	AR
	IL-12 receptor deficiency	AR
	IL-12 deficiency	AR
	STAT1 deficiency	AR

AR, autosomal recessive; CGD, chronic granulomatous disease; IFN-γ, interferon-γ; IL-12, interleukin-12; LAD, leukocyte adhesion deficiency; WAS, Wiskott–Aldrich syndrome; XL, X-linked.

Table 14.9 Classification of severe combined immunodeficiency.

Syndrome	T lymphocytes	B lymphocytes	NK lymphocytes	Inheritance
Reticular dysgenesis	–	–	–	AR
ADA deficiency	–	–	–	AR
RAG1, *2* deficiency	–	–	+	AR
Artemis deficiency (RS)	–	–	+	AR
CgC deficiency	–	+	–	XL
JAK3 deficiency	–	+	–	AR
IL-7Ra deficiency	–	+	+	AR
ZAP-70 kinase deficiency	$CD4^+$	+	+	AR
MHC class II deficiency	$CD8^+$	+	+	AR
$p56I^{ck}$ deficiency	$CD8^+$	+	+	AR
IL-2/IL-15Rb	$CD8^+$	+	–	AR
Idiopathic CD4 lymphopenia	$CD8^+$	+	+	AR
CD45 deficiency	+	+	+	AR
WHN gene deficiency	+	+	+	AR
Omenn's syndrome	+	–	+	AR
Non-host T lymphocytes (MFE or transfusion GvHD)	+	+/–	+/–	

ADA, adenosine deaminase; AR, autosomal recessive; CgC, common interleukin-γ chain; GvHD, graft-versus-host disease; IL-2/IL-15Rb, interleukin-2/15 receptor b; IL-7Ra, interleukin-7 receptor a; JAK3, janus-associated kinase 3; MFE, materno–fetal engraftment; MHC class II, major histocompatibility complex class II; RAG, recombination activating genes; RS, radiosensitive; WHN, winged-helix-nude; XL, X-linked; ZAP-70, zeta-associated kinase-70.

Persistent respiratory tract infection with *respiratory syncitial virus* or parainfluenza viruses are common, with failure to clear virus being accompanied by persistent bronchiolitis-like signs. An insidiously progressive persistent respiratory infection with radiological evidence of interstitial pneumonitis should raise the suspicion of *P. carinii* infection, often a co-pathogen with respiratory viruses.

Other presentations include prolonged otitis media and invasive bacterial infections, particularly staphylococcal or *Pseudomonas* septicaemia and pneumonia, which may respond poorly to appropriate treatment.

Severe invasive fungal infection is rare, but often fatal. Persistent, treatment-resistant superficial candidiasis is the commonest dermatological feature. This may start in the napkin area, but will often extend rapidly to produce a picture resembling severe seborrhoeic dermatitis. Systemic *Candida* infections do not usually occur unless central venous lines are used.

Pyogenic cutaneous infection due to *S. aureus* or group A streptococci are not uncommon, and will often provoke lesions having a necrotic ecthymatous appearance. Resistance to appropriate antibiotic therapy should raise suspicion [3].

Occasionally babies present with disseminated BCG or vaccine strain poliomyelitis virus. Children presenting within the first 6 months or so of life are more likely to have SCID or a severe T-lymphocyte defect.

Non-infectious cutaneous manifestations of SCID may result from GvHD, caused by the inability to reject foreign lymphocytes acquired either from the mother *in utero* or from an unirradiated blood transfusion. Engraftment of transplacentally acquired maternal lymphocytes (materno–fetal GvHD (MFGvHD)) sometimes, but not always provokes the clinical signs of GvHD, typically with a mild reticular skin rash with or without slightly deranged liver function tests. Surprisingly, up to 50% of children with SCID have clinically silent MFGvHD [4]. In other cases GvHD will severe, even fatal, and in these cases the skin rash is more severe and lymphadenopathy and hepatosplenomegaly may be present. Such cases may be clinically indistinguishable from Omenn's syndrome (see below), but identification of maternal cells by karyotype or DNA fingerprinting will distinguish MFGvHD from Omenn's syndrome [5].

Investigations usually show a severe lymphopenia, with depletion of T lymphocytes; B lymphocytes and NK cells may be present or absent, depending on the genetic defect in the particular form of SCID. Some patients show unusual patterns of immature T-lymphocyte markers; in such cases maternal engraftment should be excluded. Mitogen responses, mixed lymphocyte reaction, *in vitro* antigen-specific responses and delayed hypersensitivity skin testing to common antigens are usually absent. Immunoglobulin G, A and M are low, but laboratory results may be misleading as residual maternal IgG may give a falsely reassuring result. Also, it can be difficult to distinguish IgA and IgM levels in SCID from the low levels seen in normal infants.

Isohaemagglutinins are a useful measure of IgM production. If SCID is suspected, lymphocyte phenotyping is more reliable than immunoglobulin estimation. Chest X-rays show an absent thymus with hyperinflation and/or interstitial pneumonia when respiratory infection is present.

Without treatment, most patients die from infection by 12 months of age. Currently, the only curative treatment is BMT [6,7], although clinical gene therapy trials for common γ chain deficiency are in progress [8]. Supportive interim treatments include antibiotic prophylaxis with co-trimoxazole as antipneumocystis treatment, antifungal prophylaxis and antibody replacement (intravenous immunoglobulin). Live vaccines should be avoided. The diagnosis of SCID is a paediatric emergency, and suspected cases should be urgently referred to a designated treatment centre for further assessment and treatment.

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Types of severe combined and combined immunodeficiencies

Severe combined immunodeficiency can be subdivided according to the presence or absence of T, B and NK cells, each phenotype being due to a number of distinct molecular defects.

T-negative, B-positive, NK-negative SCID is characterized by severe lymphopenia, absence of mature T and NK lymphocytes but normal numbers of circulating B lymphocytes.

The X-linked form is caused by a deficiency of the γ chain common to the IL-2, IL-4, IL-7, IL-9 and IL-15 receptors [1]. This is the easiest form of SCID to treat, and the first successful gene therapy was performed for this condition [2].

The autosomal recessive form is due to mutations in the gene encoding JAK3, a protein which binds to the common γ chain and through which signals are transduced following cytokine binding [3].

Another autosomal recessive form of SCID is characterized by a T-negative, B-positive, NK-positive phenotype, and is due to deficiency of the α chain of the IL-7 receptor [4].

Two forms of T- and B-negative, NK-positive SCID have been described, both with autosomal recessive inheritance. Phenotypically, they are identical, with absent T and B lymphocytes, but normal numbers of NK lymphocytes. The first form is due to a defect in the *RAG* genes which are necessary for the development of diverse T- and B-lymphocyte antigen receptors [5]. In the second form, cells cannot repair DNA normally following radiation damage and patients' fibroblasts show *in vitro* radiosensitivity. Recent studies have identified a defect in the *artemis* gene, which is necessary for rejoining DNA following TCR and BCR recombination [6]. Whilst treatable by bone marrow transplant (BMT), results are not as good as in the T-negative, B-positive form of SCID. 'Leaky' *RAG* defects have been shown in some patients with Omenn's syndrome.

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Omenn's syndrome

Omenn's syndrome is characterized by a generalized erythematous rash, often with scaling and erythroderma, lymphadenopathy, hepatosplenomegaly, increased serum IgE levels, with a marked eosinophilia and combined immunodeficiency [1]. The cutaneous abnormality is often the first sign of the disorder; a scaly erythematous rash appearing and evolving into a confluent erythema. The initial appearances may be papular, becoming confluent and the skin often becomes thickened with a 'leathery' consistency. Hair, including eyebrows, is often lost as the rash evolves (Fig. 14.13). The rash may be present at birth, or evolve over the first 2 weeks of life. Children usually present in early infancy, but atypical forms may present later in the first year of life. As well as the clinical features described, children suffer diarrhoea, failure to thrive and persistent infection. There are normally high numbers of activated oligoclonal poorly functional T lymphocytes of the Th2 phenotype, explaining the eosinophilia and exclusive IgE production [2]. B-lymphocyte numbers are low as are levels of immunoglobulin classes other than IgE. The syndrome has been called a 'leaky'

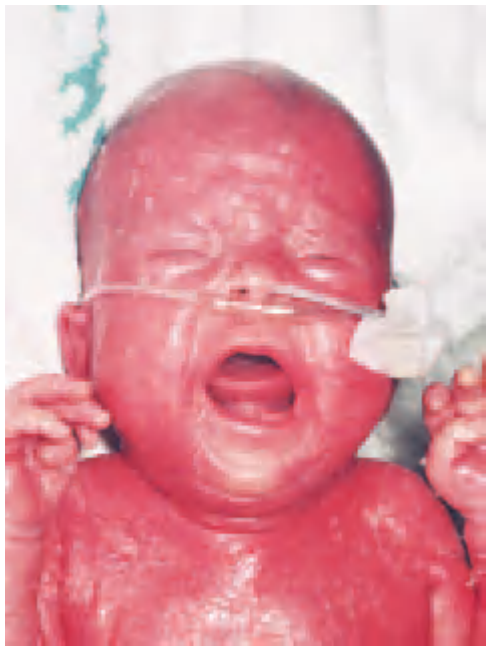

Fig. 14.13 Newborn infant with Omenn's syndrome due to a mutation in the *RAG1* gene. Note the confluent erythematous exfoliating, thickened rash with a 'leathery' consistency and loss of hair and eyebrows. (Reproduced with permission from the Audiovisual Centre, University of Newcastle, Newcastle, UK.)

form of SCID in that small numbers of very abnormal T lymphocytes 'leak' past the block in T-lymphocyte development [3]. The underlying defect, at least in some cases, is a mutation in the *RAG* genes [4]. In some families, one affected individual has presented with T-negative, B-negative, NK-positive SCID, whilst another has presented with Omenn's syndrome [5]. The clinical picture may resemble SCID with materno–fetal engraftment, when maternal T lymphocytes crossing the placenta cause a GvHD-like reaction in an immuno-incompetent patient. Molecular genetic studies to identify the origin of the T lymphocytes infiltrating the dermis will differentiate these two disorders [6]. Activated oligoclonal lymphocytes in skin seemingly provoke Langerhans' cells to migrate to lymph nodes, liver and spleen where lymphoid tissue architecture is severely disrupted. It has been suggested that IFN-γ may ameliorate the clinical symptoms, but BMT is the only curative treatment [7].

Histology of the skin shows a dense dermal perivascular lymphohistiocytic infiltrate, comprising activated T lymphocytes, with numerous eosinophils. S100-staining Langerhans' cells are usually absent, and there is no epidermotropism. Lymph node architecture is disordered, being replaced by a similar massive infiltrate of cells of S100-staining interdigitating reticulum cells with absence of germinal centres, absent B cells and a scarcity of T lymphocytes [8].

Omenn's syndrome has been reported in association with non-cartilage-hair short-limbed dwarfism [9] and DiGeorge's anomaly [10,11]. In the older literature this condition has been confused with Langerhans' cell histiocytosis (Letterer–Siwe disease). It is likely that several cases reported in the literature under other names were in fact examples of this disorder [12].

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Reticular dysgenesis

This rare form of SCID, inherited as an autosomal recessive trait, is characterized by defective lymphoid and myeloid differentiation. Bone marrow examination confirms the absence of myeloid precursors. Platelets and red cells are formed normally. There is some evidence that this is not a discrete entity, but due to other forms of SCID, and complicated by transplacental engraftment of maternal lymphocytes that cause severe bone marrow GvHD [1] and, in some affected infants, skin rashes. The absence of the non-specific cellular elements of the immune system makes the immune deficiency even more severe than in other forms of SCID. Clinical presentation often occurs earlier, as does the inevitable fatal outcome if immune reconstitution cannot be achieved.

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Lymphocyte metabolism defects

ADA deficiency [1] and purine nucleoside phosphorylase (PNP) deficiency [2] are both single gene defects inherited in an autosomal recessive manner. Both result in defective metabolism of DNA, allowing the accumulation of toxic purine metabolites that destroy immature lymphocytes.

ADA-deficient patients typically present earlier than other forms of SCID, with very low numbers of T, B and NK lymphocytes. Skeletal abnormalities (cupping deformities of the ends of the ribs, as well as abnormalities of the transverse vertebral processes and the scapulae) are reported in up to 50% of cases and can be correlated with histological changes [3]. Neuro-developmental problems may also occur in some patients [4]. Very rarely, partial forms of ADA deficiency occur, where some lymphocyte function is preserved. Interestingly, such patients have clinical features similar to those seen in hyper-IgE syndrome [5]. Treatment is by BMT [6] or by use of replacement polyethylene glycol-coupled ADA [7]. Gene therapy is being attempted in this condition [8].

PNP deficiency is initially less severe than ADA deficiency, and the onset of symptoms may be delayed for several years [9]. Most cases present in early childhood with recurrent and severe infections, particularly with viruses and fungi, accompanied by diarrhoea and failure to thrive. There is a marked tendency to autoimmune disease, especially haemolytic anaemia [10], which can progress to red cell aplasia, and also to GvHD following non-irradiated blood transfusion. Skeletal abnormalities do not occur, but neuro-developmental problems are found in over half of all patients, particularly spastic paresis, dysequilibrium and ataxia [10]. There may also be more general neuro-developmental and behavioural problems. In one series 20% of patients presented primarily with neurological disorder [11].

Laboratory tests show a progressive fall in T-lymphocyte numbers and function with time, poor *in vitro* mitogen responses and negative delayed hypersensitivity skin tests. Immunoglobulin levels and antibody responses are initially normal, but in the late stages, levels fall. Serum uric acid levels are very low. The diagnosis is confirmed by demonstrating absent PNP activity in red cells or fibroblasts, and deoxyinosine and deoxyguanosine in the urine.

The prognosis without corrective treatment is poor with most cases dying in early childhood. BMT is therefore indicated as early as possible.

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Other combined immunodeficiencies

Other rare immunodeficiencies have been described in only a few patients to date, with defects in other surface and signalling molecules such as ZAP 70 kinase. It is likely that these will become increasingly recognized as more laboratories are able to offer diagnostic testing.

Major histocompatibility complex antigen deficiency

Major histocompatibility complex class II

MHC class II antigens (HLA-DR, DP and DQ) are expressed on a limited repertoire of cells, and present antigen to $CD4^+$ T lymphocytes. With the help of an appropriate second signal, this activates T-helper lymphocytes specific for that antigen. Expression of MHC class II in the thymus is also essential for positive selection of $CD4^+$ T lymphocytes. Since HLA antigens are of vital importance for lymphocyte development and function, lack of MHC class II expression, previously described as a variant of the 'bare lymphocyte syndrome', results in a profound susceptibility to viral, bacterial, fungal and protozoal infections [1]. Lack of MHC class II expression results from defects in genes coding for regulatory factors that control transcriptional activation of MHC class II molecules [2].

The clinical picture resembles SCID, although sometimes infections develop slightly later. Intestinal and hepatic complications due to cryptosporidial infections are more common than in other immune defects. Neurological manifestations due to a range of viral infections are also well described. Coxsackievirus, adenovirus and poliovirus were the most frequently reported causes of meningoencephalitis [2].

The laboratory phenotype is very variable, but most patients will have a CD4 lymphopenia and hypogammaglobulinaemia, but lymphocyte proliferation responses are usually normal. The diagnosis can be confirmed flow cytometrically by showing absent or significantly reduced levels of class II molecules, e.g. DR, on cells that constitutively express class II (B lymphocytes and monocytes).

Affected children require initial treatment with replacement immunoglobulin, co-trimoxazole and antifungal prophylaxis. While BMT is the definitive treatment, it has to date had only limited success [3].

Major histocompatibility class I deficiency

Although described before MHC class II deficiency, SCID due to abnormal expression of the A, B and C components of the MHC class I complex is much less common. MHC class I is required for development of $CD8^+$ T lymphocytes, and affected children have low numbers of these cells. Mitogen responses are frequently normal [4]. MHC class I deficiency is due to mutations in the peptide transporter genes, which code for proteins that transport degraded protein antigen from the cytosol to the endoplasmic reticulum where they associate with MHC class I complex [5].

Clinically, this disease has a milder phenotype than MHC class II deficiency, with symptoms often not beginning until late childhood. Recurrent respiratory tract infections leading to bronchiectasis and sinus problems are common. Gastrointestinal disease is rare. The most striking clinical manifestation is necrotizing granulomatous skin lesions which are located on the extremities [6,7] and also in the mid-face [8]. The skin lesions begin as small pustules or subcutaneous nodules which slowly expand and ulcerate. The lesions are slow to heal, and usually leave hyperpigmented scars. Mid-face lesions can be particularly mutilating, and resemble midline granuloma. Diagnosis is confirmed by showing absent HLA class I expression in peripheral blood. Treatment is directed towards prevention/limitation of lung disease with judicious use of antibiotics (directed by sputum cultures), physiotherapy and bronchodilators as required. Prophylactic continuous antibiotics are of unproven benefit, but may be helpful. The majority of cases do not require replacement immunoglobulin therapy or BMT.

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Combined immunodeficiency forming part of other syndromes

DiGeorge's anomaly

This condition results from abnormal cephalic neural crest cell migration into the third and fourth pharyngeal arches in early embryological development. A microdeletion at chromosome 22q11.2 is present in 90% of cases; the remainder are associated with other chromosomal anomalies.

DiGeorge's syndrome belongs to a group of disorders which have been described as developmental field defects [1]. The syndrome is extremely heterogeneous with partial forms more common than the complete phenotype [2]. Whilst classically recognized by the triad of congenital heart defects, immunodeficiency secondary to thymic hypoplasia and hypocalcaemia secondary to parathyroid gland hypoplasia, an expanded phenotype is increasingly recognized, with dysmorphic facies (low-set, abnormally formed ears, hypertelorism and antimongoloid slant, micrognathia, short philtrum to the upper lip and high arched palate), palatal abnormalities (cleft palate, velopharyngeal insufficiency), autoimmune phenomena, learning difficulties (particularly speech delay), renal anomalies, neuropsychiatric disorders and short stature. Conotruncal heart defects are classically associated with the syndrome, but other defects are seen including tetralogy of Fallot, septal defects, pulmonary atresia and aberrant subclavian vessels. Some patients have normal hearts.

Severe T-lymphocyte immunodeficiency presenting with a SCID phenotype of profound lymphopenia and

poor lymphocyte proliferation is rare and accounts for less than 1.5% of cases [3]. Humoral immunodeficiency is more common than previously thought, presenting with recurrent sinopulmonary infection, which may improve with time [4]. Occasionally significant lung damage may occur due to repeated infection. Autoimmune features are increasingly recognized, including juvenile chronic arthritis and autoimmune cytopenias [5,6]. The long-term immunological outlook is not well defined, particularly in children with mild cardiac or palatal phenotypes. An Omenn's syndrome phenotype has been described in patients with DiGeorge's syndrome [7], and at least some of these have been secondary to engraftment of maternal T cells causing an MFGvHD [8].

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Wiskott–Aldrich syndrome

Immunodeficiency, thrombocytopenia, eczema and an increased risk of autoimmune disorders and malignancy characterize this X-linked recessive condition. The gene responsible for WAS codes for a novel 501 amino acid protein, the Wiskott–Aldrich syndrome protein (WASP) [1], which is only found in bone marrow derived cells, and is implicated in actin cytoskeleton polymerization [2]. Mutations in the same gene are found in patients with X-linked thrombocytopenia (XLT) [3] and, more recently, in X-linked severe congenital neutropenia [4]. Patients usually exhibit the classical triad of thrombocytopenia, recurrent infections and eczema (Fig. 14.14) but these vary in severity, and in some patients the eczema is surprisingly mild [5]. In general, it is indistinguishable from standard atopic eczema, apart from the presence of purpura and bleeding from excoriation in many patients. The condition usually presents in early life with bruising, petechiae and bleeding.

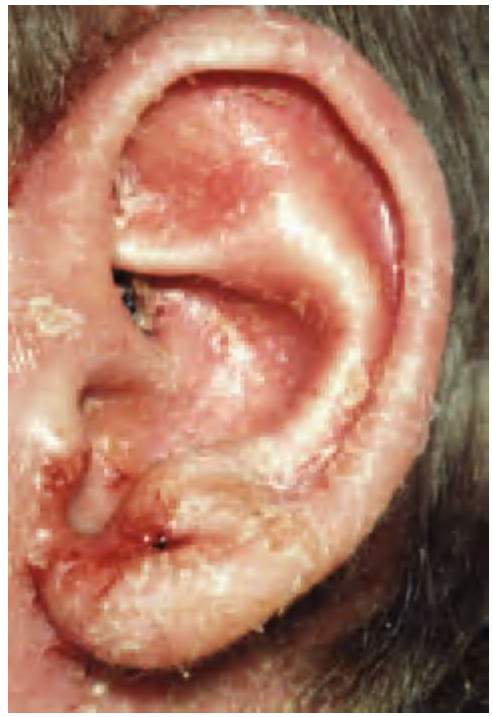

Fig. 14.14 Severe eczema in a patient with Wiskott–Aldrich syndrome (WAS). (Reproduced with permission from the Audiovisual Centre, University of Newcastle, Newcastle, UK.)

In XLT, thrombocytopenia with small platelet volume is the only symptom, perhaps with mild eczema. In WAS, bacterial and/or viral infections of the upper and lower respiratory tract are common [6] and opportunistic infection, such as *P. carinii* may occur. Herpesviruses, including HSV and varicella-zoster virus, are poorly handled and may cause severe and recurrent disease. Impetigo, cellulitis and skin abscesses are surprisingly common. Molluscum contagiosum and viral warts may be very extensive and, together with excessive bruising, help to clinically distinguish WAS from uncomplicated eczema. Indeed, very extensive molluscum contagiosum is quite characteristic of WAS (see Fig. 14.11). Infection exacerbates the bleeding tendency, and early death may result from bleeding. With increasing age, infective problems replace bleeding as the major cause of death [7]. Immunization with polysaccharide and typhoid vaccines is ineffective [8] and can cause severe, even fatal, reactions. The median survival is between 3–15 years.

Autoimmunity, particularly autoimmune haemolytic anaemia and vasculitis, and malignancy, particularly of the lymphoreticular system, become more common with increasing age [6] and in many cases are related to abnormal persistence of Epstein–Barr viral infection [9]. Scoring systems have been used to distinguish the milder phenotype of XLT from classical WAS. Heterozygous female carriers are clinically normal and demonstrate non-random X-inactivation in all haemopoietic cells.

Thrombocytopenia with an abnormally small mean platelet volume (mean platelet volume less than 5 fl) is pathognomonic [8]. The severity of immunodeficiency is variable, but affects cellular and humoral responses. T lymphopenia is progressive, with depressed responses to mitogens and antigens and delayed-type hypersensitivity skin test responses [6]. Serum immunoglobulins show a characteristic pattern with a very low IgM, normal IgG and raised IgA and IgE [8]. Antibody responses to tetanus, *Haemophilus influenzae* type B and *Pneumococcus* are often low, as are isohaemagglutinin titres. The direct Coombs' test is frequently positive, with or without a haemolytic anaemia. *In vivo* neutrophil and monocyte chemotaxis is impaired [8]. Electron microscopy shows greatly reduced numbers of microvilli on lymphocytes and platelets, due to failure of the normal binding of actin bundles which is critical to the organization of the cytoskeleton. Lymphoid and myeloid cell lines are all affected, so that phagocytes migrate poorly to sites of inflammation and do not put out normal filopodia, dendritic cells do not present antigen effectively, lymphocytes do not signal to each other normally and platelets form imperfectly from megakaryocytes [10].

The WASP has a number of unique domains, suggesting multiple functions, which may explain the complex phenotype of a single gene mutation. Missense mutations in exons 1–3 which lead to normal or truncated sized protein result in the milder phenotype of XLT, whereas most other mutations result in the classic WAS phenotype.

Acute bleeding episodes may be controlled by platelet transfusions (irradiated to prevent GvHD). Splenectomy and systemic steroids should be avoided if possible, as they will increase the risk of infection. Intravenous immunoglobulin, with or without prophylactic antibiotics, reduces bacterial sinopulmonary infections and in high dose may help treat autoimmune phenomena [11].

Despite these supportive measures, the prognosis is poor. Immunological and haematological reconstitution can be achieved by BMT, and despite a higher risk of Epstein–Barr virus (EBV)-driven lymphoproliferative disorders, 5-year survival is 87% after HLA-identical sibling donor BMT and 71% after unrelated-donor BMT. Results for unrelated-donor BMT after 5 years of age are much poorer [12].

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X-linked hyper-IgM syndrome (CD40 ligand deficiency)

X-linked hyper-IgM syndrome is a T-lymphocyte immunodeficiency caused by a defect in the gene encoding for the CD40 ligand glycopeptide (CD154), expressed on activated T lymphocytes [1,2]. CD40L binds to CD40, expressed on B lymphocytes and monocyte/macrophage-derived cells [3]. Lack of binding prevents immunoglobulin isotype switching from IgM to IgA, IgG and IgE as well as activation of Kupffer cells and pulmonary macrophages. Lack of IgA and IgG results in a similar clinical picture to XLA with sinopulmonary and invasive bacterial infection, but in contrast to XLA, opportunistic infections also occur. Failure of T lymphocytes to activate pulmonary macrophages results in *P. carinii* pneumonia, whilst ineffective Kupffer cell function allows repeated infections of bowel, pancreas and biliary tree with *C. parvum* and similar organisms. These infections lead to sclerosing cholangitis, cirrhosis, pancreatitis and hepatic malignancy in the second or third decades [4]. Neutropenia with oral ulceration is seen in as many as 66% of patients. Fatal cytomegalovirus infection or enteroviral meningoencephalitis can occur [5]. Autoimmune phenomena are relatively common, and include haemolytic anaemia, thrombocytopenia, hypothyroidism, arthritis and liver disorders [4]. Severe soft tissue infection due to *P. aeruginosa* may occur [6].

Laboratory findings include low or absent IgA and IgG with normal or raised levels of IgM [7]. Neutropenia may be present, but T- and B-lymphocyte numbers are normal.

Patients should receive co-trimoxazole prophylaxis for *P. carinii* and immunoglobulin replacement therapy. The neutropenia sometimes responds to granulocyte colony-stimulating factor (G-CSF) and intravenous immunoglobulin. All drinking water, including bottled water, should be boiled. Azithromycin prophylaxis may lessen the risks of *C. parvum* infection. Despite conventional treatment, many patients do not survive beyond the second decade

of life. A few patients demonstrate a CVID-like clinical course and no biliary or liver disease, often remaining relatively well into middle life. BMT is increasingly being recommended for this condition, and combined bone marrow and liver transplantation has been successful [8,9].

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Defects of lymphocyte apoptosis (autoimmune lymphoproliferative syndrome (ALPS))

Apoptosis, or programmed cell death, is important for regulating immune responses once an infection has been countered. Defects in this process lead to the autoimmune and lymphoproliferative features which characterize ALPS [1]. There are a number of pathways through which apoptosis can be induced [2]; one of the most important is initiated through the cell surface molecule termed Fas (CD95). Ligation of this molecule initiates a cascade of intracellular reactions that culminate in apoptosis, induced by proteolytic enzymes including caspases. Mutations in molecules in this cascade result in molecularly distinct, but clinically similar forms of ALPS.

Fas is expressed as a trimeric surface protein. Heterozygotes with a Fas mutation in one allele often develop the full clinical syndrome, as one abnormal protein chain is sufficient, by a dominant-negative effect, to significantly impair the trimer's function. Most of the cases are heterozygotes, though a few homozygous cases have also been reported.

Many present in early childhood, but adult presentation and asymptomatic cases may also occur. Haematological autoimmunity is most common [3], but any system can be involved. Chronic bullous dermatosis of childhood and localized purpura fulminans have been recorded in isolated cases. Other dermatological manifestations include vasculitis and urticaria [4].

Lymphoproliferation leads to massive asymmetric anterior cervical lymphadenopathy, with splenomegaly in nearly all cases, and hepatomegaly in some [3,4,5]. Malignant disease of the lymphoid system (both Hodgkin's and non-Hodgkin's) is reported with increased frequency, but has probably been over-diagnosed because the histological picture of proliferation resembles malignancy; clonality studies distinguish the two [6]. Affected individuals usually have high lymphocyte counts and normal or high immunoglobulin levels. Autoantibodies are usually present. The presence of circulating $CD3^+$ T lymphocytes expressing the α/β-receptor but not expressing CD4 or CD8 (the so-called double-negative T lymphocytes), and usually constituting between 5 and 20% of the total CD3 cell count, is a very important diagnostic clue.

Autoimmune phenomena usually respond to standard treatments, including corticosteroids and dapsone in the case of ALPS-associated chronic bullous dermatosis of childhood. Splenectomy should be avoided if possible, as severe infective complications may follow.

BMT has been successful in patients with homozygous Fas deficiency, but currently not enough is known of the long-term prognosis to justify elective BMT in (milder) heterozygous case, especially as some patients improve with age.

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X-linked lymphoproliferative disease

An X-linked immunodeficiency associated with fulminant fatal EBV-driven infectious mononucleosis was first recognized in the Duncan kindred [1]. There are three common clinical presentations: fulminant infectious mononucleosis (58%), dysgammaglobulinaemia, often evolving to CVID (31%), and EBV-driven B-lymphocyte lymphoma, usually extranodal, and affecting the gastrointestinal tract or central nervous system (20%). Less commonly, patients present with vasculitis, aplastic anaemia, haemophagocytic lymphohistiocytosis (HLH), pulmon-

ary lymphomatoid granulomatosis or vasculitis [2]. Few cases of XLP-associated vasculitis have been published. Polyarteritis nodosa-like vasculitis has been reported in one case [3]. Vasculitic changes in small- and medium-sized muscular arteries have also been reported [4].

The prognosis is poor, with a high risk of death during initial EBV infection, and no recorded survivors after 40 years of age [5]. Most patients are well until infected with EBV, although other viruses may act as triggers.

The gene responsible for the disease, on the X chromosome, codes for a small protein, SAP (signalling lymphocyte activation molecule (SLAM)-associated protein) which is expressed on the surface of T lymphocyte and is critical for T lymphocyte and NK cell control of EBV-infected B lymphocytes [6,7].

Confirmation of the diagnosis involves demonstrating EBV genome in blood by polymerase chain reaction (PCR), together with immune defects outlined above and an abnormal response to the EBV with absent antibody response to EB nuclear antigen (EBNA). SAP protein is absent or abnormally expressed in many cases, although a gene mutation is not apparent in up to 40% of patients. HLH episodes are treated with immunosuppression with cyclosporin, and intravenous immunoglobulin is beneficial, particularly when hypogammaglobulinaemia is present. BMT is the only curative treatment.

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Chronic mucocutaneous candidiasis

CMC is the name given to a group of disorders characterized by chronic infection of skin, nails and mucous membranes by *Candida* species, most commonly *C. albicans*. Recurrent and persistent candidiasis of the mouth, napkin area, skins and nails is the hallmark of this condition, but the severity varies considerably. Invasive disease almost never occurs. Failure of usually effective antifungal drugs to clear *Candida* distinguishes CMC from other conditions that predispose to candidiasis, such as secondary immunodeficiency, steroid treatment or systemic antibiotics.

Candidiasis is usually first noticed early in infancy. In severe cases, oesophageal involvement causes dysphagia, gastro-oesophageal reflux and failure to thrive, whilst skin lesions may be extremely disfiguring and distressing. As a patient becomes older, infections may become less severe.

In about half the patients, there is an associated endocrinopathy (with, in order of frequency, hypoparathyroidism, Addison's disease, pernicious anaemia, hypothyroidism and diabetes mellitus), which generally becomes apparent from the second decade onward.

Cases may be familial or sporadic with recessive or dominant patterns of inheritance. Nail dystrophy and dental enamel hypoplasia associated with autoimmune endocrinopathy, suggests that CMC is part of an autosomal recessive syndrome known as APECED (autoimmune polyendocrinopathy, candidiasis, ectodermal dystrophy) [1]. A minority of patients suffer from invasive bacterial sepsis, opportunistic infection, autoimmune haemolytic anaemia, malabsorption and chronic active hepatitis. Bronchiectasis and restrictive lung disease can occur [2].

The underlying defect is poorly defined, and immunological abnormalities are very variable. There may be diminished T-lymphocyte proliferation and cytokine production in response to *Candida* antigens, with impaired antibody production to polysaccharide antigens, and sometimes IgG2 subclass deficiency [3].

Treatment with azole antifungals, such as fluconazole, can be very effective, even in severe cases, but infection usually recurs after treatment has been discontinued. Continuous treatment may be necessary in severe cases.

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Immunodeficiency and short-limbed dwarfism

Cartilage hair hypoplasia, the best described of the osteochondrodysplasias, is inherited in an autosomal recessive manner. It is caused by mutations in the *RMRP* gene, which encodes endoribonuclease RNAse MRP [1]. Severe short-limbed short stature, with metaphyseal and spondyloepiphyseal dysplasia, is always present, and most patients have sparse light hair [2]. Severe anaemia and Hirschsprung's disease [3] are less common but

well-recognized associations, as are malignancies, notably lymphoma and skin carcinoma [4].

The immunodeficiency is surprisingly variable. Most have T lymphopenia, and impaired *in vitro* mitogen proliferative responses, but only half suffer recurrent infection [5]. However, some have IgA and/or IgG subclass deficiencies with frequent ear infections. Patients are excessively vulnerable to viral infections, particularly varicella-zoster virus, EBV and other human herpesvirus infections; the risk of infective death is 300 times greater than normal [2]. This condition should be considered in any child with severe chickenpox or herpes simplex infections who is short and has fine sparse hair.

Severely affected patients should be assessed for BMT, which has been successful in correcting the immunodeficiency.

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DNA repair defects and immunodeficiency

A huge number of genetically diverse lymphocytes, each bearing a unique receptor are needed for recognition of a wide array of foreign antigens. These are created by rearranging the variable (V), diversity (D) and joining (J) gene segments that code for T- or B-lymphocyte receptor genes (VDJ recombination). To do this, DNA double strand breaks are made between the gene segments, and are then rejoined after the segments have been re-arranged. This uses the DNA repair machinery found in all cells, which originally evolved to repair damage from UV light or toxic agents, but which the immune system has also exploited to generate the diversity of specific immune responses. Without fully effective DNA repair mechanism, cells with damaged DNA are more likely to apoptose or undergo malignant proliferation. Thus, individuals with defective DNA repair mechanisms have a predisposition to photosensitivity and skin abnormality, neurodegeneration, developmental anomalies and cancer as well as defective immunity [1]. As DNA repair mechanisms involve many control proteins, there is scope for many single gene defects causing distinct clinical entities. Only a few of these conditions are well understood, but several manifest both dermatological and immunological features. With the rapidly increasing understanding of their molecular basis, it is likely that these conditions will now be better delineated.

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Ataxia telangiectasia

This multisystem autosomal recessive disorder, the best known of the DNA repair disorders, is characterized by progressive cerebellar ataxia, oculocutaneous telangiectasia, variable immunodeficiency and an increased risk of lymphoid malignancy [1]. It is associated with chromosomal instability, and cellular radiosensitivity.

Diagnosis remains chiefly clinical, and depends on the age of presentation. In the absence of a family history, patients usually present with gait anomalies before telangiectasia becomes apparent. Ataxia and cerebellar signs are usually present by the second year of life. Neurological degeneration is progressive, resulting in severe disability by late childhood, although intellectual function is usually preserved. Telangiectases usually appear between 2 and 8 years of age, first on the bulbar conjunctivae but later elsewhere, particularly on the nose, the ears and in the antecubital and popliteal fossae. Other cutaneous manifestations include spotty hypo- or hyperpigmentation, cutaneous atrophy and atopic dermatitis [2–5]. Gonadal atrophy occurs in both sexes, and growth failure is also prominent in the later stages. Cellular and humoral immunodeficiency affects 60–80% of cases; low levels of IgA, IgG2 and poor antibody responses to viruses and *Pneumococcus* are seen most often [5].

Recurrent sinopulmonary infection is common, and may lead to bronchiectasis and clubbing, but clinical manifestations are extremely variable [6]. Lymphoreticular malignancies and, unusually for immunodeficiency, carcinomas, occur with increased frequency [7]. Radiosensitivity means that inadvertent treatment with radiotherapy is toxic and often lethal.

Irrespective of the development of malignancy, survival beyond early adult life is unusual.

Heterozygosity for the *AT* gene confers an increased risk of developing breast cancer [8].

A raised α-fetoprotein supports the diagnosis, as does increased chromosome breakage on exposure to ionizing radiation. The *ATM* gene has been located to chromosome 11q22.23 and codes for a phosphatidyl kinase, which is involved in meiotic recombination and cell cycle control [9]. This protein detects DNA damage and signals to proteins involved in DNA repair and cell cycle control [10]. Prophylactic antibiotics or intravenous immunoglobulin can reduce the morbidity of sinopulmonary infection in some patients.

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Nijmegen breakage syndrome

Other DNA repair defect disorders include Nijmegen breakage syndrome (NBS), an autosomal recessive disorder first described in the Dutch town of that name, and characterized by microcephaly with mild to moderate mental retardation, 'bird-like' facies, immunodeficiency, clinical radiation sensitivity and chromosomal instability. Bacterial sinopulmonary infection is common, as is hypogammaglobulinaemia and $CD4^+$ T lymphopenia with diminished T-lymphocyte proliferative responses. Absence of ataxia, together with normal α-fetoprotein levels distinguishes NBS from ataxia–telangiectasia.

Specific dermatological features include café-au-lait spots and vitiligo [1], as well as skin infections due to fungal and virus infections, particularly herpesviruses [2]. Sun sensitivity of the eyelids and cutaneous telangiectasia have been described [1].

Treatment with antibiotic prophylaxis or intravenous immunoglobulin may be helpful.

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Other disorders of DNA repair associated with immunodeficiency

Bloom's syndrome is a rare autosomal recessive disorder associated with increased sister chromatid exchange, severe growth failure, increased malignancy and immunodeficiency. Affected individuals are photosensitive and may develop telangiectases on the face, dorsa of the hands and forearms. Hypo- and hyperpigmented lesions may also develop.

Recurrent bacterial sinopulmonary infections associated with hypogammaglobulinaemia, most often low IgM, are the most common clinical manifestation of immunodeficiency, and may lead to bronchiectasis.

Bloom's protein, the gene for which is mutated in the disease, unwinds the DNA helix, but the exact mechanism by which this causes immunodeficiency is unclear [1].

DNA ligases are also involved in DNA repair. Defects in DNA ligases I and IV have been described in rare individuals with radiosensitive cell lines and combined immunodeficiencies. An immunodeficient individual with mutations in DNA ligase I had photosensitivity and developed venous dilatation on the skin, mainly on the limbs. Bulbar telangiectasia were also present [2]. Other individuals with microcephaly and immunodeficiency have mutations in the DNA ligase IV gene. Two individuals were described with skin photosensitivity and psoriasis, and a further patient developed multiple psoriasiform lesions [3].

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Fanconi's anaemia

Fanconi's anaemia is a chromosomal instability disorder characterized by developmental defects, progressive bone marrow failure and cancer susceptibility. Children with Fanconi's anaemia are generally small, and elfin like with a history of low birth weight. The central clinical manifestation of Fanconi's syndrome is progressive bone marrow failure during childhood and adolescence [1–3]. Easy bruising is generally the presenting symptom, and most often first becomes apparent between the ages of 4 and 10 years. In addition to thrombocytopenia, anaemia and leukopenia are usual, and the bone marrow is aplastic.

Cutaneous hyperpigmentation and skeletal anomalies are characteristic. Unfortunately, the dermatological findings are not well described, and there is considerable confusion with dyskeratosis congenita in the older literature. However, they comprise macular brownish pigmentation either resembling freckles and occurring mainly in sun-exposed areas or occurring more diffusely, in which case the abdomen, genital area and flexures appear to be predominantly affected [4]. Guttate macular

hypopigmentation is often also present in affected areas. Hypopigmentation and café-au-lait spots are reported. Persistent and exceptionally severe viral wart infection has been reported [4].

The principal skeletal abnormality is the absence or hypoplasia of at least one of the thumbs; hypoplasia or absence of the radius is also common. Structural renal abnormalities, endocrinopathies, genital hypoplasia, microcephaly and microphthalmia are other common features.

There is a high risk of leukaemia and other malignancies in these children [5], probably due to the structural instability of chromosomes observed in Fanconi's anaemia, which leads to a high frequency of chromosomal breaks and rearrangements [6]. Cultured cells are unusually sensitive to DNA cross-linking agents such as mitomycin C, but they are not sensitive to ionizing radiation, although cells from the Fanconi's D2 subgroup do show ionizing radiation sensitivity.

The disorder is transmitted as an autosomal recessive trait. Eight complementation groups (A–G) have been described [7] and six genes discovered. The Fanconi's proteins are involved in repair of DNA cross-linking damage and some interact with other DNA repair pathways. In particular, the Fanconi's D2 subgroup appears to interact with *ATM* and nibrin, mutated in ataxia–telangiectasia and NBS, respectively [8,9]. The induction of chromosomal breakage by the alkylating agent, diepoxybutane, can be used to detect heterozygotes and for prenatal diagnosis [10], although chorionic villus biopsy and genetic diagnosis is now possible if the specific gene defect within the family is known. There is a high incidence of diabetes [11] and of neoplastic disease [12] in heterozygotes.

The outlook for untreated patients with Fanconi's anaemia is poor, with death usually occurring within a few years of the first signs of marrow failure. Initially, bone marrow function can be stimulated with corticosteroids and with the androgenic steroid, oxymethalone. Bone marrow transplantation has been used successfully to treat patients, but care must be taken to avoid the use of alkylating agents in pretransplant conditioning [13].

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Other immunodeficiencies

A number of syndromes have been described which include primary immunodeficiency as part of the phenotype. In some, the syndrome is well described, and in a few the underlying molecular defect has recently been elucidated. Most lack clear definition.

Hoyeraal–Hreidarrson syndrome

This X-linked disorder is characterized by microcephaly, cerebellar hypoplasia, aplastic anaemia and growth retardation [1,2]. A progressive combined immunodeficiency, with hypogammaglobulinaemia and lymphopenia is a well-recognized association [3]. Mutations in the dyskeratosis congenita gene (*DKC1*) have been found and Hoyeraal–Hreidarsson syndrome probably represents a severe phenotype of dyskeratosis congenita [4]. Cutaneous manifestations include leukoplakia, oral and gastrointestinal ulceration, and reticulated hyperpigmentation, primarily in the regions of the neck, upper thorax and upper extremities [5]. Other cutaneous features include nail dystrophy, which begins with longitudinal striations, increasing brittleness, deformation, onychoclasis and nail loss. Palmar and plantar hyperhidrosis, blistering, hyperkeratosis, acrocyanosis and alopecia may also occur.

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Netherton's syndrome

This triad of generalized infantile erythroderma, diarrhoea and failure to thrive may be associated with a variable immunodeficiency including mild lymphopenia and polysaccharide antibody deficiency [1]. The clinical features are similar to those seen in Omenn's syndrome and SCID and materno–fetal engraftment, with erythroderma and ichthyosis characterized by abnormal cornification, dryness and fish-like scaling of the skin. Hair shaft abnormalities (trichorrhexis invaginata) are described which may not be seen until several months of age [2]. Distinguishing these entities is important as the other conditions are treated by BMT, whereas Netherton's syndrome is not. Hair shaft abnormalities are diagnostic (bamboo hairs). Squamous cell carcinoma has been described in Netherton's syndrome [3]. Mutations in the serine protease inhibitor gene *SPINK5* have been described [4].

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Anhydrotic ectodermal dysplasia, incontinentia pigmenti and defects in the *NEMO* gene

X-linked anhydrotic ectodermal dysplasia and immunodeficiency have been associated in an ill-defined manner for some time, but only recently has the pathology begun to be elucidated. Patients present with sparse scalp hair, conical teeth and absent sweat glands. Some suffer from recurrent sinopulmonary infection, often with encapsulated organisms, and have poor antibody responses to polysaccharide antigens, or frank hypogammaglobulinaemia [1]. Incontinentia pigmenti is a rare X-linked dominant condition characterized by developmental abnormalities in skin, hair, teeth and the central nervous system. Carrier mothers demonstrate well-recognized cutaneous features of Blashko's linear skin lesions occurring in four successive, sometimes overlapping stages: (i) erythema, vesicules, pustules; (ii) verrucous hyperkeratotic lesions; (iii) hyperpigmented whorls and streaks following lines of Blaschko; and (iv) pallor and scarring. In other respects, affected females are healthy. Previously affected males were all reported to die soon after birth, but some have now been described who survive albeit with a progressive combined immunodeficiency [2]. Recently, hypo-functional mutations in the *NEMO* gene encoding a protein required to activate the transcription factor NF-kB have been described in male patients with both X-linked anhydrotic ectodermal dysplasia and incontinentia pigmenti, suggesting that these conditions represent variants of the same disorder [3]. Such infants share many of the clinical features of ectodermal dysplasia, although they appear less severe than in children with 'classical' ectodermal dysplasia without immunodeficiency, and the majority of patients have normal or sparse scalp hair. Of 33 patients from 23 kindred reported to date, two unrelated children manifested a more severe phenotype with features including osteopetrosis and lymphoedema, so-called osteopetrosis lymphoedema ectodermal dysplasia immunodeficiency (OL-EDA-ID) [2–5]. Two related children from another kindred have been described with EDA-ID and increased bone density [6], suggesting that 'osteopetrosis' could be a variable clinical part of this syndrome. Only a few of the mothers of affected boys from EDA-ID kindreds showed variable features of EDA or incontinentia pigmenti (dry and/or hyperpigmented skin, hypodontia, conical teeth), as well as elevated IgA levels, whilst mothers of both children with OL-EDA-ID phenotype showed mild features of incontinentia pigmenti.

From early childhood affected boys suffer from unusually severe, life-threatening and recurrent bacterial infections of the lower respiratory tract, skin and soft tissues, bones, and gastrointestinal tract, including meningitis and septicaemia. Causative pathogens are most often Gram-positive bacteria (*Streptococcus pneumoniae*, *Staphylococcus aureus*), followed by Gram-negative bacteria (*Pseudomonas* spp., *H. influenzae*) and *Mycobacteria*. Interestingly, two children had *P. carinii* infection and another two had severe adenovirus and cytomegalovirus infections, suggesting a more profound combined T- and B-lymphopenia immunodeficiency. The two children with XL-OL-EDA-ID had a particularly severe phenotype as they acquired mycobacterium infections in the first year of life and died. A comprehensive description of the clinical features of children with XL-EDA-ID and XL-OL-EDA-ID is not available as yet, but an international survey has been undertaken.

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The immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome

The IPEX syndrome [1] is characterized by early-onset type I insulin-dependent diabetes mellitus, infantile ichthyosiform dermatitis, protracted diarrhoea and severe enteropathy and thyroiditis. Mutations in the *FOXP3* gene have recently been described in affected patients [2,3]. Insulin-dependent diabetes develops in early infancy. Atopic eczema and exfoliative dermatitis are the third most common presenting features after diabetes and enteropathy. Bruising may occur, leading to thrombocytopenia. BMT has been tried as a curative treatment [4].

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Immunodeficiency, centromeric instability and facial anomalies (ICF) syndrome

The ICF syndrome is an autosomal recessive disorder in which there are characteristic structural chromosomal abnormalities in chromosomes 1, 9 and 16 in lymphocytes. Other cells do not show these changes. Affected children develop severe recurrent infections and have immunoglobulin deficiency, often with agammaglobulinaemia, but with normal T- and B-lymphocyte numbers [1]. T-lymphocyte immunity is not normal and *P. carinii* infection, severe viral warts and cutaneous fungal infection are described. Facial dysmorphism is variable, but common features include low-set ears, hypertelorism, flat nasal bridge, epicanthic folds, tongue protrusion and micrognathia. Triangular facies are described. Mental retardation has been described, with speech delay being a common feature. This diagnosis should be considered in a child with very extensive warts or spreading cutaneous fungal infection (Fig. 14.15) and the characteristic facial features. The differential diagnosis is CVID. Mental retardation may occur but there is no increased risk of malignancy.

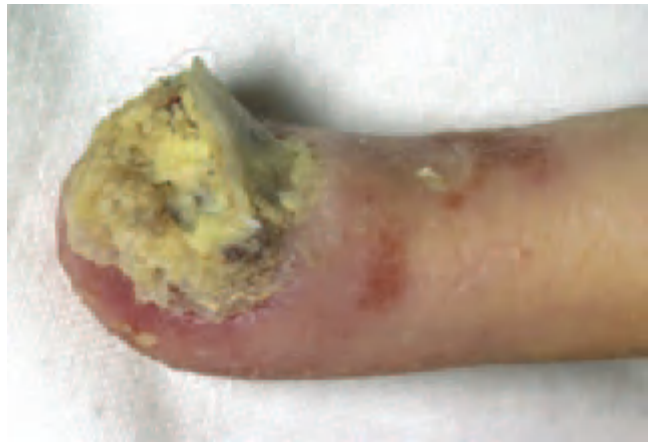

Fig. 14.15 Extensive chronic fungal infection of the nail bed in a patient with immunodeficiency, centromeric instability and facial anomalies (ICF) syndrome. (Reproduced with permission from the Audiovisual Centre, University of Newcastle, Newcastle, UK.)

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Defects of antibody production

X-linked agammaglobulinaemia (Bruton's disease)

First described by Bruton in 1952 [1], this X-linked intrinsic B-cell defect prevents B-lymphocyte development beyond the pre-B lymphocyte stage. It is caused by a defective gene that encodes a cytoplasmic enzyme, Bruton tyrosine kinase (btk) [2,3]. Classically affected boys produce no immunoglobulins and make no antibody responses but have normal cell-mediated immunity. Since the molecular basis has been defined milder phenotypes have been recognized where some antibody function is present [4]. Typically, recurrent pyogenic infections commence in the latter half of the first year of life, after maternal IgG levels have declined. The diagnosis is often made surprisingly late; in one series, the average age at diagnosis was 3 and a half years, and 2 years when there was a positive family history [5]. Sinopulmonary infections are most common, but pyoderma, gastroenteritis, arthritis, meningitis and osteomyelitis may be presenting features. Boils or impetigo are the most common dermatological features, frequently due to *S. aureus* or *Pseudomonas* (Fig. 14.16) and usually associated with neutropenia. Chronic ulcerative cutaneous HSV infection has been reported [6]. Asymptomatic papular lesions developed on the trunk and arms of a 34-year-old patient in which caseating granulomas were demonstrated on biopsy, but no infectious agent was identified [7]. Pyoderma gangrenosum may be a feature [8], and Stevens–Johnson syndrome [9], vitiligo

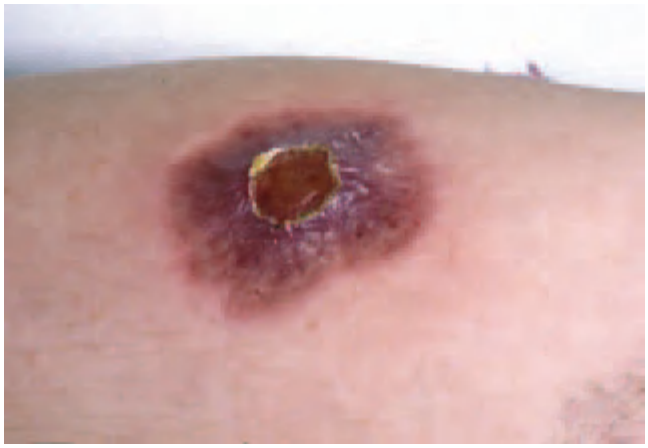

Fig. 14.16 Cellulitis due to *Pseudomonas aeruginosa* in a patient with X-linked agammaglobulinaemia (XLA). (Reproduced with permission from the Audiovisual Centre, University of Newcastle, Newcastle, UK.)

[9] and total alopecia areata [10] have also been described. Recovery from viral infections is normal with the notable exception of those caused by enteroviruses (especially echoviruses) [11], which can cause a chronic meningoencephalitis or dermatomyositis-like picture [12]. Non-purulent arthritis affecting predominantly large joints is occasionally seen, in some cases due to mycoplasma infection. Amyloidosis is an infrequent complication.

Usually there is absence or severe depletion of all serum immunoglobulin classes, and antibody responses to vaccines are absent. There are normal numbers of T lymphocytes but no B lymphocytes in peripheral blood, although pre-B lymphocytes (containing cytoplasmic μ chains) are found in bone marrow. Lymph nodes show absent follicles and germinal centre, and plasma cells cannot be demonstrated at any site. The diagnosis can be rapidly confirmed by demonstrating absence of the btk protein in cell lysates [13].

Immunoglobulin replacement therapy is the mainstay of treatment. Chronic lung damage and sinus disease may also progress on treatment, and for this reason vigorous and early antibiotic therapy should be used for respiratory tract infections. Since the introduction of intravenous immunoglobulin therapy, lung disease seems less common, and the patients developing progressive lung and sinus disease while on treatment appear to be those with damage sustained before immunoglobulin therapy was commenced [14], which emphasizes the importance of early diagnosis and treatment.

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Autosomal recessive forms of agammaglobulinaemia

When hypogammaglobulinaemia is found in a girl or a child with consanguineous patients, one of the recently recognized autosomal recessive genetic defects affecting B-lymphocyte differentiation should be considered. Mutations have been described so far in genes coding for: μ heavy chain [1], Ig α (part of the signal transduction complex of the B-lymphocyte-antigen receptor) [2], λ5 light chain [3] and B-lymphocyte linker protein (BLNK) [4]. These molecules are all required for early B-lymphocyte development from pro-B lymphocyte to pre-B lymphocyte stage. Unlike in XLA, pre-B lymphocytes are therefore not detectable in marrow samples. Other families have also been described in whom the molecular defect is yet to be identified. In all cases the defect is B lymphocyte specific. The number of cases described is too small to draw firm conclusions, but the clinical picture would seem to be similar to XLA, although patients with μ heavy chain deficiency may have more serious life-threatening infections than those with XLA with an earlier onset of symptoms [5]. Skin sepsis is described as a feature but less commonly than in XLA.

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Common variable immune deficiency

CVID is a poorly defined entity characterized by the presence of quantitative or qualitative hypogammaglobulinaemia. The incidence is described as between 1 : 10 000 and 1 : 50 000 of the population, and although the onset of symptoms typically occur in adolescence or early adult life, it is increasingly being diagnosed in childhood.

Selective IgA deficiency with or without IgG2 deficiency may be one end of the spectrum of this disease [1], and families are described where some members have CVID whilst others have selective IgA and/or IgG2 deficiency. Now that other immune deficiencies are being defined by their molecular defections, it has become apparent that at some patients with CVID have mild phenotypes of other immune deficiencies such as XLA, CD40 ligand deficiency or XLP [2,3]. Autoimmune diseases, such as rheumatoid arthritis, dermatomyositis and SLE [4,5] also have an increased incidence in these kindreds.

As with all patients with humoral immune defects, patients with often present with recurrent sinopulmonary and gastrointestinal infections. Other clinical manifestations in this disease exemplify the inherent immune deregulation, with an increased incidence of autoimmune disease, particularly autoimmune haemolytic anaemia, thrombocytopenia and neutropenia. Non-malignant granulomatous lymphadenopathy, hepatosplenomegaly and involvement of the gastrointestinal tract is a frequent finding in a subgroup of patients [6], and clinical differentiation from malignancy may be difficult, although histologically lesions resemble those seen in sarcoidosis. These granulomas are normally sensitive to steroid treatment. Patients with CVID also have a significantly increased risk of lymphoreticular and gastrointestinal malignancies [7,8]. Cutaneous manifestations are common and non-specific and include impetigo, boils, furuncles and cellulitis. Severe viral wart infection has been reported. Atopic eczema, vitiligo, alopecia areata and psoriasis have been described in CVID patients, and are probably more common than expected. Skin manifestations with other associated symptoms should raise suspicion of this diagnosis.

All patients have defective antibody function with hypogammaglobulinaemia, which varies from a failure to respond to vaccines to panhypogammaglobulinaemia. B-lymphocyte numbers are frequently normal, but a significant proportion of patients have T-lymphocyte abnormalities, in particular a reversed CD4/8 ratio and generalized lymphopenia. Mild phenotypes may require only prophylactic antibiotics. Significant degrees of hypogammaglobulinaemia should be treated with immunoglobulin replacement therapy. Granulomatous lesions and autoimmune phenomena may respond to treatment with steroids.

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IgA deficiency

Studies in healthy blood donors have shown that 1 in 600–700 white people have no demonstrable serum IgA, and whilst there is almost always concomitant lack of salivary IgA, many affected individuals are asymptomatic [1]. However there is increased incidence of IgA deficiency in populations of patients with chronic lung disease and autoimmune diseases [2,3], suggesting that it may be associated with disease, perhaps when there are other immunological abnormalities.

Recurrent upper respiratory tract and ear infections are the commonest symptoms in young children with IgA deficiency, and in the majority the frequency and severity of infections improves with age, regardless of the IgA level [4].

There is a strong correlation between autoimmune disease of all types and IgA deficiency [3], which appears independent of the infection suffered. It may be that abnormalities of antigen handling in the gut account for these autoimmune phenomena, and the increased incidence of gastrointestinal infection and coeliac disease seen in IgA deficiency, although the true incidence of these problems is not been well defined. Skin manifestations may be non-specific, and include atopic eczema, in association with sinopulmonary disease. Cutaneous features due to autoimmune disease including psoriasis, vitiligo and dermatomyositis have been reported [5].

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Other forms of antibody deficiency

Other forms of antibody deficiency are described (Table 14.10) but the cutaneous features are no different to those described above.

Disorders of phagocytic cells

Chronic granulomatous disease

CGD is an inherited defect of the phagocyte NADPH oxidase enzyme complex which generates superoxide and other reactive oxygen species that are toxic to organisms ingested into phagosomes. The gene defect for the most common form is found on the X chromosome, and codes for the major membrane component gp91^{phox}, and accounts for up to 60% of cases. Defects in the genes coding for the cytoplasmic components p67^{phox}, p47^{phox} and p22^{phox} are inherited in an autosomal recessive pattern [1].

The disease has protean clinical manifestations, but the hallmark is acute, and potentially fatal, bacterial or fungal infection [2]. The disease becomes apparent during the first 2 years of life in the great majority of cases [3], but the onset may occasionally be delayed into the second decade [4–6]. The earliest manifestations are often seen in the skin. Neonatal pustulosis is commonly the first sign of the disease. Subsequently, a rather non-specific, impetiginized periorificial rash is highly characteristic. This is most commonly seen around the nostrils, ears, mouth and eyes, and has sometimes been described as 'eczematous' or 'seborrhoeic'. Any area where the skin has been broken, by abrasion, for example, tends to become impetiginized or ecthymatous. Nodular lesions may follow, and these frequently break down to form necrotic ulcers.

Firm translucent papular lesions around the nose, eyes, lips and on the cheeks may mimic lupus vulgaris or sarcoidosis. A common manifestation is acute suppurative lymphadenitis in the neck, axilla or groin. Other frequent pyogenic infections include liver abscesses, osteomyelitis, arthritis, pneumonia, skin sepsis and perianal abscesses. Pathogens, such as *S. aureus*, *Burkholderia cepacia*, *Aspergillus* spp. and *Serratia marcescens*, are most commonly seen [7].

Subcutaneous nodules may develop at immunization sites, and these also tend in time to ulcerate. Poor healing of surgical wounds, and of these discharging nodular skin lesions, is highly characteristic. Perianal abscesses are a regular feature. Other frequent findings include chronic suppurative paronychia, folliculitis of the scalp and ulcerative stomatitis. Acute febrile neutrophilic dermatosis (Sweet's syndrome) have been rarely described [8], as has chronic bullous disease of childhood [9]. Fungal infection often causes pulmonary disease with pneumonia, lung abscess formation followed by empyema and spread across tissue planes into paraspinal tissue and vertebrae [10,11]. Discrete areas of persistent consolidation may be

Table 14.10 Classification of antibody deficiency.

Antibody deficiency	Gene defect	Inheritance
XLA (Bruton's disease)	btk	XL
XL hyper-IgM (see CD40L deficiency)		
Autosomal recessive hyper-IgM syndrome	AID	AR
	CD40	AR
	NEMO	XL
Autosomal recessive agammaglobulinaemia	μ chain	AR
	BLNK	AR
	λ5/14.1 gene	AR
	Igα (CD79a) gene	AR
Ig heavy-chain deletions	Chromosome 14q32 deletion	AR
Selective Ig deficiency:		
1. IgG subclass deficiency	Defect of isotype differentiation	Unknown
2. IgA deficiency	Terminal differentiation failure in IgA-positive B cells	Unknown
3. Polysaccharide antibody deficiency	Variable, described in some btk, *NEMO*, *DGA* patients	Unknown, specific diseases, XL
Common variable immunodeficiency	Unknown	Variable, may be AD, AR, XL
Transient hypogammaglobulinaemia of infancy	Unknown	Unknown

AD, autosomal dominant; AID, activation-induced cytidine deaminase; AR, autosomal recessive; XL, X-linked; XLA, X-linked agammaglobulinaemia.

seen radiologically and are often termed 'encapsulating pneumonia'; this sign is highly distinctive. Less specific reticulonodular shadowing and hilar lymphadenopathy are also frequent. Liver abscesses are rare in childhood, and when seen CGD should always be looked for [12,13].

The importance of non-infectious inflammatory complications is increasingly recognized. These include inflammatory bowel disease, which clinically and histologically can be indistinguishable from Crohn's disease, restrictive lung defects, genitourinary obstruction and cutaneous granulomas particularly at the vaccination sites. These non-infective manifestations sometimes respond well to corticosteroid treatment [14], but this may increase the risk of infectious complications.

Female carriers of X-linked CGD do not generally show increased susceptibility to infection. However, some carriers have experienced subcutaneous abscess, hidradenitis suppurativa and ulcerative stomatitis [15]. Carrier females are also prone to the development of erythematous macular, papular and urticarial skin lesions following light exposure, and to discoid LE or Jessner's lymphocytic infiltrate [7]. The carrier state for X-linked CGD should be considered in all women presenting with discoid LE, and appropriate attention should be paid to their family history. Identification of the carrier state offers such women the possibility of genetic counselling, and prenatal diagnosis of CGD in their sons.

Diagnosis is suggested by failure of reduction of nitrobluetetrazolium or dihydrorhodamine by neutrophils. X-linked carriers have both normal and abnormal neutrophils, and the presence of abnormal neutrophils may lead to abnormal clearance of cellular debris, which may in turn account for their excess risk of autoimmune disease.

Prophylactic antibiotics, in particular co-trimoxazole which is concentrated in neutrophils, has significantly reduced morbidity and mortality from bacterial infections in CGD [3]. Children should also be given antifungal prophylaxis; itraconazole is currently the best available agent, and this may help reduce the risk of fatal fungal disease in these patients [14].

Infections or unexplained fevers should be treated aggressively. IFN-γ is a useful adjunctive treatment in severe bacterial or fungal infections. Although used as prophylactic therapy in the US, in Europe it is mainly used for prophylaxis only after documented failure of oral antibacterial and antifungal agents [2]. White cell infusions may also be used as adjunctive therapy in severe infection. Registry data suggests that the outlook in early childhood has improved considerably in recent years, but considerable morbidity and mortality occurs, and consideration should be given to BMT when a suitable donor is available [7].

Survival is variable, but improving, with prophylactic administration of antibacterial and antifungal agents, but the risk of severe or fatal fungal infection resistant to antifungal prophylaxis remains. Increasingly, BMT is recommended, and even in those with active fungal infection, a good outcome can be achieved [16].

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Neutropenia

Neutropenia can result from reduced bone marrow production or increased peripheral destruction, which can be distinguished by bone marrow examination. Neutropenia most frequently follows decreased production induced by disease processes or drug treatments. Increased consumption may occur in autoimmune states, including those associated with immune deficiency. The degree of neutropenia will influence the clinical picture: neutrophil counts of less than 0.5×10^9/L carry a major risk of infection, whilst counts below 0.2×10^9/L are associated with a significant incidence of life-threatening sepsis.

Cyclical neutropenia

In cyclical neutropenia, decreases in haematopoiesis at

intervals of about 3 weeks (range 13–35 days) leads to neutropenia and susceptibility to infection. Patients are normally asymptomatic, but during the period of severe neutropenia, apthous ulcers, gingivitis, stomatitis and cellulitis may develop. Death from overwhelming infection occurs in a small proportion of patients. Symptoms resolve over 3–4 days as the neutrophil count rises. Thus, neutrophil counts taken after the onset of symptoms are usually normal, and to make the diagnosis neutrophil counts should be taken two or three times a week over a 4 or 5 week period. In some families, this is inherited in an autosomal dominant manner and mutations in the neutrophil elastase gene (*ELA2*) have been identified in patients with cyclical neutropenia [1].

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Severe congenital neutropenia

This was originally described by Kostmann in 1956 as an autosomal recessive disease [1]. Onset is within the first year of life, with recurrent and life-threatening infections. Symptoms include omphalitis, cellulitis, perirectal abscesses, peritonitis, stomatitis and meningitis. Examination of bone marrow shows an arrest at the promyelocyte to myelocyte maturation stage. Treatment with G-CSF results in increased counts and fewer infections in almost all patients with neutropenia not secondary to peripheral destruction. Concerns about the induction of leukaemias with the prolonged use of G-CSF have not been borne out, although pre-treatment and annual bone marrow aspirates are recommended to screen for the development of myeloid leukaemia [2]. BMT may be indicated in selected cases. A small number of patients with congenital neutropenia inherited in an X-linked manner have mutations that result in over-activity of WASP [3], whilst dysregulated expression of the guanosine triphosphatases (GTPases) RhoA and Rac2 has been described in families where inheritance is autosomal recessive [4].

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Shwachman–Diamond syndrome

This rare autosomal recessive disorder is characterized by exocrine pancreatic insufficiency, skeletal abnormalities characterized by metaphyseal chondrodysplasia, bone marrow dysfunction and recurrent infections [1]. Skin sepsis is a feature. Neutropenia occurs in all patients, whilst 10–25% of patients also have pancytopenia. There is an increased incidence of myeloid leukaemia inheritent to this condition. Cutaneous features are common, although not well documented. They may be due to pancreatic insufficiency with resultant malabsorption of fat-soluble vitamins, essential fatty acids and other nutrients. Patients may show xerosis and follicular keratosis. Facial skin in particular may be dry with associated perioral dermatitis. A widespread symmetrical eczematous rash has been reported, and with associated thrombocytopenic purpura, the diagnosis of WAS may be erroneously suggested. Palmoplantar hyperkeratosis and nail thickening may occur. A defect in the *SBDS* gene, a possible RNA-processing gene, has been described in these patients [2]. BMT has been successfully performed in this condition [3].

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Neutrophil-specific granule deficiency

This rare disorder is characterized by recurrent skin and lung infections with staphylococci and enteric bacteria [1]. Electron microscopy of patient neutrophils shows reduced or absent secondary granules; specific stains demonstrate lack of the secondary granule proteins such as lactoferrin and vitamin B_{12} binding protein. Proteins that reside in azurophilic (primary) granules, such as lysozyme and myeloperoxidase are present. Neutrophils also show abnormalities in migration and nuclear morphology. Mice lacking the transcription factor CCAAT/enhancer binding protein have a similar phenotype, and case reports of patients with mutations in this gene have now been published [2].

The clinical course of patients is variable. Treatment options include prompt institution of antibiotic therapy for infections and prophylactic antibiotic treatment. BMT should be considered in patients with a severe phenotype.

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Hyper-IgE syndrome

The hyper-IgE syndrome (previously Job's syndrome) is of special relevance to the dermatologist, as the initial presentation may be cutaneous. It is a complex disorder characterized by extreme elevation of the serum IgE level (usually in the range 2000–40 000 U/L), chronic dermatitis and repeated lung and skin infections [1]. The initial description was of severe recurrent staphylococcal skin abscesses in fair-skinned red-headed girls with eczema [2]. Both sexes and all races are affected equally.

In the literature, these patients are frequently described as having eczema, although authorities on the condition point out that this is different from typical atopic eczema [3]. Affected children develop a rather non-specific, excoriated, papular and pustular eruption in the first year of life, often within the first month, which favours the scalp, the scalp margins, the buttocks and the proximal flexures, such as the axillae, groins and neck [4,5]. The rash may appear as early as the first few days of life, at which stage it may be vesicular [6], but crusting becomes a prominent feature. Features of lichenification or scales are absent or mild in hyper-IgE.

There is almost invariably a long history of furunculosis and staphylococcal lung infections, abscesses and empyema. Many patients develop staphylococcal pneumatocoeles, which strongly suggest the diagnosis [7,8]. Although skin and lung infections predominate, infections of the ears, sinuses, joints and viscera are not uncommon. Skin abscesses tend to favour the scalp, face and neck and are sometimes cold (i.e. with little surrounding inflammation), but this is not always the case. Ulceration is frequently present. Lymphadenopathy may be complicated by the development of lymph node abscesses. *Staphylococcus aureus* is the predominant pathogen, but infection is also seen with *H. influenzae*, pneumococci, group A streptococci and *Candida*. Oral candidiasis and *Candida* nail infections are common [8]. Pneumatocoeles may provide the focus for the development of aspergillomas.

Non-immunological features of the condition which are variably present include abnormal, coarse facies with a wide nasal bridge and large head (Fig. 14.17); fragile bones leading to frequent fractures; joint laxity, a high incidence of scoliosis, and delayed resorption of primary dentition with consequent delayed eruption of secondary teeth [8]. While the immunological features can be explained as the consequence of a T-cell regulatory defect, the other features are not easily explained. Abnormal bone and connective tissue turnover as a consequence of abnormal cytokine profiles or a mesenchymal cell defect have been postulated to explain these disparate features

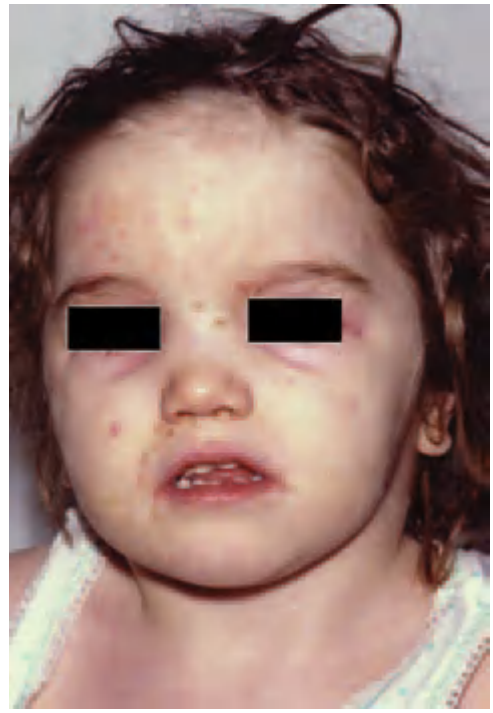

Fig. 14.17 A patient with hyper-IgE syndrome who presented with staphylococcal pneumatocoeles. Coarse facial features and an infected eczematous-like rash are demonstrated. (Reproduced with permission from the Audiovisual Centre, University of Newcastle, Newcastle, UK.)

[9]. The mode of inheritance is thought to be autosomal dominant with incomplete penetrance. The gene for the disorder has not been identified, but studies on familial cases have found linkage to the proximal part of chromosome 4q [10].

Peripheral blood eosinophilia may be marked, up to 50–60%. Serum IgE levels are consistently very high (more than 10 times the upper limit of normal), even in infancy, and most patients also have elevated IgD levels. Total IgE levels may fall in adults; however, IgG, IgA and IgM levels are usually unremarkable. In a significant proportion of patients, there is a failure of antibody response to polysaccharide antigens, which contributes to the susceptibility to infection [1,8]. In keeping with the great increase in circulating total IgE, patients show strongly positive immediate weal-and-flare responses on skin-prick testing with foods and commonly inhaled allergens, as well as bacterial and fungal antigens [11]. Circulating levels of IgG anti-IgE are also high, as they are in atopic eczema [12]. It is rather characteristic for patients to have excessive production of IgG specific for *S. aureus* [13].

Peripheral blood lymphocyte subsets are generally normal, and no consistent abnormality of T cells has yet been identified. Patients are not neutropenic and their neutrophils ingest and kill bacteria normally [14]. However, neutrophil chemotaxis is reduced but in rather an

inconsistent way, and it has been suggested that mononuclear cells from hyper-IgE patients produce a factor that is inhibitory to neutrophil chemotaxis [14,15]. There appears to be a defect in mononuclear cell response to IL-12, and a specific impairment of IFN-γ release following stimulation of lymphocytes with *S. aureus* in patients with hyper-IgE syndrome [16].

Hyper-IgE syndrome is not merely atopic eczema with predisposition to cutaneous staphylococcal infections but a very characteristic immunodeficiency disorder with specific diagnostic criteria, which include staphylococcal lung infections with an onset in infancy. However, individuals have been reported who appear to have a milder variant of the hyper-IgE syndrome, with a later onset, with typical cutaneous and immunological abnormalities but without lung involvement [3]. Nevertheless, it must be borne in mind when considering this diagnosis that the disorder does not feature atopic eczema but a recurrent pyodermatous eruption often associated with ulceration and/or lymph node abscesses. The serum IgE level alone does not allow clear differentiation between atopic eczema and the hyper-IgE syndrome, because it can be equally high in both disorders. A similar clinical picture has been described in older patients with partial ADA deficiency [17].

The mainstay of treatment is long-term anti-staphylococcal antibiotic prophylaxis, usually with flucloxacillin. Attention to skin hygiene is important, with judicial use of topical antimicrobials. *Candida* infections should be treated topically, or when refractory, with oral ketoconazole or fluconazole [18].

Histamine-2 receptor blockers such as cimetidine have been used, though their value is disputed. Interferon-γ treatment has been tried in a few patients, but although there was some lowering of the IgE levels, there was no clinical benefit [19]. Intravenous immunoglobulin therapy may be useful in those with a demonstrable antibody production deficit. Persistent pneumatocoeles should be excised. BMT failed to correct the disorder in the one patient in whom it has been reported as being attempted, despite successful engraftment of donor myeloid and lymphoid cells, an observation that suggests this disorder is not due to a haemopoietic stem cell defect [20].

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Leukocyte adhesion disorders

To counter infection in tissues, leukocytes egress from the circulation toward sites of inflammation. To do this, cells roll along the capillary endothelium, then adhere to endothelial cells, and finally pass between endothelial cells into tissues. A range of cell surface adhesion molecules are responsible for different stages of this process, as well as binding of different leukocytes to each other whilst immune responses occur. It is therefore not surprising that defects in the cell surface molecules responsible for the process result in life-threatening infection and dramatic cutaneous manifestations. In LAD type I, deficiency of the 95 kDa β chain (CD18), common to the β2 integrin family of cell surface adhesive molecules, leads to a profound immunodeficiency affecting the function of neutrophils, monocytes, T lymphocytes and NK cytotoxic cells [1,2]. Inheritance is autosomal recessive. Chemotaxis, adherence and phagocytosis are markedly depressed. Different mutations result in phenotypes of variable severity, and occasional patients express normal levels of CD18 but have a mutation affecting the function of the molecule. The β2 integrin family is also involved in the platelet function molecule Gp2b3a, and patients with a

combined leukocyte and platelet defect have been found [3]. The clinical picture is almost entirely explained by the way in which leukocytes are attracted to areas of infection and attach to the vessel walls at sites of inflammation in the usual way, but cannot pass out into the tissues. This leads to blockage of small vessels and rapidly expanding necrotic lesions without pus. Individuals with the most severe phenotype (less than 1% expression) present in the first weeks of life with delayed umbilical cord separation (the cord fails to shrink down and may not separate until 3–4 weeks of age), and omphalitis together with rapidly progressive erosive perianal ulcers. Delayed umbilical cord separation does not seem to occur in patients with some expression of the molecule (usually in the range 2–10% of normal expression). In all forms, there is excessive susceptibility to bacterial and fungal infections, with recurrent cellulitis and abscesses in the skin and other soft tissues. Deep-seated infections of bone, respiratory and gastrointestinal tracts are also seen. Gingivitis, ulcerative stomatitis and periodontitis are common and severe, leading to loss of teeth. Inflammatory lesions, particularly affecting the skin and resembling pyoderma gangrenosum, can occur in the partial forms of the deficiency, and may respond to steroids. Investigations almost invariably show a circulating neutrophilia (because of failure of the cells to migrate out of the circulation) and a profound neutrophil chemotactic defect. Diagnosis is confirmed by demonstrating the absence of the cell surface markers recognized by the anti-CD11/CD18 monoclonal antibodies. Treatment is with antibiotics in the first instance. Surgery should be avoided because of the poor healing. Neutrophil infusions appear helpful in the control of severe infections, but their use is limited by the production of alloantibodies to the transfused cells.

In the severe form, early death from infection is the rule unless a successful BMT can be performed. In the partial forms, supportive and expectant management is pursued in the first instance, but BMT may become necessary.

LAD type II is extremely rare and results from a defective fucose metabolism, whereby a failure to generate sialyl lewis X (CD15s) and other ligand molecules prevent the binding of selectin molecules. This results in a failure of the 'rolling' type weak adhesion of leukocytes to endothelium, which normally slows down the circulating leukocytes before β2 integrin binding can occur. There is a neutrophilia, and neutrophil chemotaxis and migration from the circulation is severely impaired. There is no deficiency in specific immune responses. As in LAD type I deficiency, patients have a neutrophilia and suffer repeated bacterial infections and periodontal disease. Delayed umbilical cord separation is however not seen; other features peculiar to LAD type II include mental retardation, short stature and the Bombay (hh) blood phenotype [4].

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Haemophagocytic lymphohistiocytosis (familial)

HLH is universally fatal without treatment. Patients present with high swinging fevers, hepatosplenomegaly, jaundice and erythematous rash, respiratory distress and pancytopenia; they appear septic, but blood cultures are usually sterile. Laboratory findings include an acute phase response, elevated ferritin and elevated fasting triglycerides with prolonged prothrombin time and reduced fibrinogen levels. Examination of bone marrow, cerebrospinal fluid, pleural effusions or ascitic fluid may demonstrate haemophagocytosis. This may be very difficult to find, and repeated sampling may be required. Haemophagocytosis may occur secondary to a number of infections, in particular viral infections, and careful exclusion of infections by serology/PCR methodology should be undertaken. Haemophagocytosis is also seen in a number of immunodeficient states, including Griscelli's syndrome, CHS and XLP. Diagnosis of familial HLH should be suspected in an infant with an appropriate clinical picture. Older children are more likely to have secondary HLH.

Twenty to thirty per cent of patients with familial HLH will have a mutation in the gene coding for perforin, which is normally found in the granules of NK and cytotoxic T lymphocytes. Perforin is important for cell lysis and apoptosis and so may be important for all cells that regulate immune responses with absence allowing dysregulated immune activation [1].

Treatment with a combination of chemotherapeutic agents, steroids and monoclonal antibodies that deplete lymphocytes may induce remission, but only BMT is curative.

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Chediak–Higashi syndrome

CHS is a rare autosomal recessive disease with partial

oculocutaneous albinism, recurrent bacterial infections with organisms such as *S. aureus*, streptococci and pneumococci, and approximately 85% of patients develop an accelerated lymphocyte and macrophage activation syndrome (similar to that seen in HLH and XLP), which untreated is usually fatal. Skin, hair and eyes are affected in most cases [1]. Recurrent skin infections are common, generally starting in early childhood [2]. Deficient cutaneous pigmentation may be obvious, but in some cases it is more subtle and only apparent if nipples and genitalia are carefully examined. The hair generally has a silver sheen and shows clumped pigment on microscopy. Photophobia and nystagmus are regular features due to ocular pigment dilution. Severe gingivitis and oral mucosal ulceration are well described [3].

Patients usually, but not invariably, enter an accelerated phase of the disease, with widespread infiltration with activated lymphocytes and macrophages resulting in rapid enlargement of liver, spleen and lymph nodes, together with jaundice, hepatic failure, respiratory distress, pancytopenia and bleeding, and so death usually occurs in the first decade; survival into the second and third decades has been recorded. Progressive neurological deterioration is common in patients who survive early childhood [4].

Characteristic giant lysosomal granules are seen in the cytoplasm of all cells containing these organelles, and are easily detected on a peripheral blood film. The gene for this disease codes for a regulator of lysosomal transport [5]; proteins normally transported through lysosomes enter these organelles but cannot exit, with subsequent lysosomal hypertrophy. In melanocytes this results in abnormal melanin transport and consequent albinism. Neutrophil lysosomes cannot degenerate and release bactericidal proteins into the phagosome, and so intracellular killing is defective. NK cell function is also defective as is monocyte function, probably because giant lysosomes interfere with the processing of MHC class II in endosomes, and thus antigen presentation is defective. The activation syndrome may result from failure to transport inhibitory molecules such as CTLA4 to the surface of leukocytes, with consequent failure of negative feedback mechanisms after T-lymphocyte and macrophage activation.

Prophylactic co-trimoxazole should be given to prevent bacterial infection. The accelerated phase cannot be predicted, and patients should be closely monitored, particularly if febrile. Symptoms, signs, laboratory and clinical findings, and diagnosis and treatment of the accelerated phase are as for HLH. The only definitive treatment is BMT. This should be considered early if there is a matched sibling donor. Although BMT prevents further episodes of macrophage activation it may not prevent later neurological deterioration.

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Griscelli's syndrome

This rare autosomal recessive disorder results in a partial albinism and a combined immunodeficiency [1]. Individuals with Griscelli's syndrome resemble those with CHS in that they have variable hypopigmentation of the skin and hair and recurrent pyogenic infections.

Skin colour seems to have been more or less unremarkable, without photosensitivity, in the few patients so far reported, but affected individuals are paler than their siblings [2] and the hair, including eyebrows and eyelashes, is silvery grey from early childhood.

Delayed type cutaneous hypersensitivity is absent, T-cell numbers may be reduced and NK cell function is impaired. Hypogammaglobulinaemia is often seen as a secondary phenomenon, although B-cell numbers are usually normal. In contrast to CHS, large lysozomal granules are not seen, and examination of hair by electron microscopy shows large clumps of pigment, with the accumulation of normal mature melanosomes in basal layer melanocytes in the epidermis. The liver, spleen and lymph nodes are infiltrated with histiocytic cells. Neurological abnormalities do not occur, but patients do develop an accelerated phase, which is fatal unless treated by BMT [3]. Two male siblings have been reported in whom immunodeficiency was combined with partial albinism, as in Griscelli's syndrome, but in which agenesis of the corpus callosum, cleft lip and palate and bilateral congenital cataracts were also features [4].

Two gene defects have been described in *MYO5A*, which codes for myosin 5a [5] and RAB27A [6].

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Defects in the IL-12-dependent IFN-γ pathway

Defects in the IL-12 dependent IFN-γ pathway have recently been described in patients affected by persistent, severe bone and soft tissue abscesses with discharging sinuses due to BCG or weakly pathogenic environmental non-tuberculous mycobacteria, which can be fatal [1]. There is also susceptibility to invasive non-typhi salmonella infections and severe viral infection, particularly due to herpesvirus. Oral ulceration and cutaneous vesicular eruptions have been described in those with viral infection [2]. Two patients with lesions mimicking those seen in Langerhans' cell histiocytosis, who were subsequently shown to have IFN-γ receptor deficiency, have been described. Osteolytic lesions were present in the skull and humerus, with granulomatous inflammation and central necrosis on biopsy [3], from which BCG was cultured. Infections result from a failure of upregulation of macrophage killing. The clinical picture depends on the precise molecular defect that is present. Defects have been described in a number of constituents of the IL-12/IFN-γ pathway, including complete or partial IFN-γ-R1 deficiency, IL-12p40 subunit deficiency and complete IL-12b1 deficiency. The outcome of patients with complete IFN-γ-R1 deficiency is poor, but BMT has been successfully attempted.

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Complement disorders

Complement deficiencies

Deficiencies of isolated complement components are rare, deficiency of C2 being the most frequent, and, with the exception of properdin and C1 esterase inhibitor deficiency, are generally transmitted in an autosomal recessive manner, severe disease occurring when both alleles are defective. However, heterozygosity results in approximately half the normal levels of the protein, which can sometimes be clinically important. A number of clinical patterns can occur depending upon which factor is deficient.

Deficiency of the early components of the classical complement activation pathway, i.e. C1, 4 and 2, tend to predispose to autoimmune disease, particularly SLE [1]. Photosensitivity and cutaneous manifestations of LE occur in association with mild non-cutaneous disease and absent or unimpressive plasma levels of antinuclear antibody.

Evidence, based on the finding that null alleles for a number of complement components (notably C2 and C4) occur with greater frequency in patients with autoimmune diseases such as SLE, suggests that heterozygosity for deficiency is also a risk factor. In general, the course of these diseases is similar to that in patients without complement deficiency. Partial deficiencies of certain complement components, particularly C2 and C4, is associated with an increased risk of certain diseases, notably SLE, discoid LE, juvenile rheumatoid arthritis, membranous glomerulonephritis and angio-oedema [2–4].

Recurrent pyogenic infections are a feature of complement deficiencies. Organisms such as streptococci and *H. influenzae* are the main problem, as opsonization/binding of antibody and complement to bacteria is critical for their elimination. C3 deficiency is the most severe. Deficiency of the classical pathway components C1q and C2 and of factor D in the alternative pathway also predisposes to infection; the first two also carry a predisposition to autoimmune phenomena. Deficiencies of the alternative pathway control proteins, factors H or I, lead to uncontrolled consumption of C3, resulting in increased susceptibility to pyogenic infections including meningococcal disease [5].

Deficiency of one of the later complement components, C5–C9 (leading to failure of membrane lysis), or of the control factor properdin (the only deficiency inherited in an X-linked manner) leads to a specific deficiency in handling *Neisseria* spp. (*N. meningitidis* and *N. gonorrhoeae*), but not to a generalized increase in susceptibility to pyogenic infections. There is a predominance of disease caused by rare serogroups of meningococci (W135, X, Y and Z) in these patients. In a Dutch study [6], complement deficiency (most commonly late components or properdin) was found in 33% of survivors of meningococcal disease due to rare serogroups compared to 2%, 0% and 7% in patients who suffered group A, B and C disease respectively. Recurrent attacks of meningococcal septicaemia/meningitis and severe invasive gonococcal disease are also associated with late complement deficiencies. C9 deficiency in Japan affects up to 0.1% of the population [5] but is less common in white people. Screening for deficiencies should be undertaken in patients and their immediate families where there has been recurrent meningococcal disease due to common serogroups or single episodes caused by a rare serogroup. In the UK, screening children with single episodes of meningococcal disease due to common serotypes is unlikely to reveal a

complement defect [7]. Where infections occur in children with deficiencies of the early complement components, these are predominantly caused by encapsulated bacteria, such as *Pneumococcus*.

Several proteins have been identified that have regulatory effects on the complement system. The existence of these activities has generally come to light through the profound clinical effects that may result from their deficiency. The best known of these deficiencies is that of C1 esterase inhibitor, which results in hereditary angio-oedema (see Chapter 47). Deficiency of factor 1, previously termed C3b inactivator, leads to unchecked cleavage of C3, and therefore to clinical manifestations closely resembling those seen in C3-deficient individuals [8,9]. In this condition, plasma infusions may provoke anaphylaxis, because the contained C3 is so rapidly cleaved to form the anaphylotoxin, C3a [10].

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C1q deficiency

A variety of clinical manifestations have been described in patients with C1q deficiency, including cutaneous vasculitis, SLE, membranous glomerulonephritis and problems with infections, particularly meningitis and septicaemia but also including stomatitis, pyoderma and persistent candidiasis of mouth and nails [1–5].

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C1r and C1s deficiencies

SLE, or a disorder clinically suggestive of SLE but lacking confirmatory serological findings, and/or membranous glomerulonephritis have similarly been reported in patients with deficiencies either of C1r [1] or C1s [2]. Infections have not been prominent, except in the case of an infant with C1r deficiency who had lung infections and hepatic abscesses [3].

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C4 deficiency

The majority of patients reported with C4 deficiency have been children or adolescents [1]. Their principal clinical abnormalities have comprised SLE, or a SLE-like syndrome, Henoch–Schönlein purpura or Sjögren's syndrome. Infections have only occasionally been a problem [2,3].

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C2 deficiency

This is the commonest complement deficiency. It has now been shown to be associated with a variety of diseases, but deficient individuals are often entirely healthy. Disorders occurring in C2-deficient patients have included SLE, discoid LE, membranous glomerulonephritis, Henoch–Schönlein purpura, rheumatoid arthritis, dermatomyositis, Crohn's disease and idiopathic thrombocytopenic purpura [1–5]. Serious bacterial infections may also occur, particularly pneumococcal, *H. influenzae* and meningococcal infections, in that order, although it is unclear why some patients are prone to such infections and others are not.

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C3 deficiency

C3 deficiency is the most serious of all the isolated complement deficiency states. Infections are the main hazard, particularly infections with organisms that require opsonization. Thus, meningococcal meningitis and pneumococcal pneumonia have been major problems [1]. The clinical picture is in many ways similar to that of hypogammaglobulinaemia. Transient maculopapular rashes have been reported to occur in association with infections; histologically these have shown the features of leukocytoclastic vasculitis [2]. Other manifestations such as SLE and membranous glomerulonephritis have also been reported [1].

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C5, C6, C7, C8 and C9 deficiency

Recurrent meningococcal meningitis and disseminated gonococcal infections have been the principal clinical consequence of deficiencies of all these complement components [1–3]. One patient has been reported in whom frequent cutaneous infections and subcutaneous abscesses were the presenting problem, as one would expect from the defective generation of C5a chemoattractant [4], but it is now clear that cutaneous infections are generally not a problem in these patients [5].

SLE, discoid LE, Sjögren's syndrome, rheumatoid arthritis and ankylosing spondylitis have also been associated with these deficiencies [1,4]. An affected 43-year-old woman has been reported in whom Raynaud's phenomenon, sclerodactyly and telangiectasia were associated with hereditary deficiency of C7 [6].

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Interaction of antibody and complement deficiencies

Deficiency of the early classical pathway complement components has been shown to be associated with poor antibody responses, presumably because the resulting poor opsonization leads to impaired antigen penetration. Later components are not implicated.

Alternative pathway opsonization is less efficient in the absence of specific antibody to bacterial surfaces. There is evidence that antibody may 'neutralize' surface molecules, such as sialic acid, which otherwise inhibit alternative pathway activation.

Deficiencies of C3 receptors

The distribution and function of cell surface receptors for C3b and its derivatives have been described above. Specific clinical syndromes have been attributed to deficiencies of some of these receptors. A dominantly inherited CR1 deficiency is associated with SLE and other immune complex disorders, presumably related to failure of the immune complex clearing function of this molecule.

Deficient expression of the CR3 receptor occurs as part of the LAD type I syndrome since it is a member of the β integrin family affected in this disorder, though what contribution this makes to the overall clinical picture in that condition is unclear.

Management of complement deficiencies

Apart from C1 esterase inhibitor, there are no specific replacement factor preparations. Fresh plasma infusions have been used prophylactically or can be reserved for the treatment of serious episodes of infection. Lifelong prophylactic penicillin and meningococcal vaccination are advised in those complement deficiencies resulting in susceptibility to neisserial infections. A polyvalent vaccine (A, C, W135 and Y) should be given. Prophylactic cotrimoxazole can be used in deficiencies which result in an increased susceptibility to a wider range of organisms. Clinical monitoring may allow earlier diagnosis and treatment of autoimmune disorders, should they emerge.

Chapter 15

Naevi and other Developmental Defects

D.J. Atherton & C. Moss

Definitions

Developmental defects are errors in morphogenesis arising during intrauterine life. Most are *congenital*, i.e. present at birth, and some are inherited. The term embraces *malformations*, *deformations* and *disruptions* [1,2]. There is clearly considerable overlap between these three categories.

A *malformation* is a primary anatomical defect resulting from abnormal development of an organ or tissue. It may be *isolated*, occurring in an otherwise normal child, or multiple, affecting several body systems. A *malformation syndrome* is the occurrence of multiple malformations in a recognizable pattern, frequently accompanied by mental retardation, e.g. Down's syndrome. A *malformation sequence* occurs when a primary malformation produces secondary defects, e.g. hydrocephalus secondary to spina bifida.

Deformation reflects abnormal intrauterine moulding by mechanical forces, e.g. positional deformation of the legs and feet in spina bifida. Severe oligohydramnios may result in a characteristic combination of congenital deformations referred to as Potter's syndrome, one cause of which is renal agenesis [3].

Disruption indicates intrauterine damage or destruction to a developed organ by agents such as infection, circulatory compromise or amniotic bands.

A *teratogen* (from the Greek, *teres*, a monster) is any extrinsic factor operative during fetal life that is capable of inducing developmental abnormalities.

Naevus is the Latin word for 'maternal impression' or 'birthmark' and indicates a circumscribed, non-neoplastic skin or mucosal lesion, usually present at or soon after birth, and fixed. The term should always be qualified according to the cell or tissue of origin, e.g. 'connective tissue naevus' and 'vascular naevus'. Confusingly, 'naevus', 'naevo-' and 'naevoid' are often used without qualification to imply melanocytic naevus. Thus 'naevus cell' means the cell type found in a melanocytic naevus, 'naevocytic naevus' means a melanocytic naevus, and 'naevoid basal cell carcinomas' look like melanocytic naevi.

The term 'naevus' is synonymous with *cutaneous hamartoma* (e.g. smooth muscle naevus/hamartoma), both comprising an abnormal mixture of a tissue's usual components (the word 'hamartoma' was coined by Albrecht from the Greek word *hamartia*, meaning 'to err' [4]).

Many, possibly all, naevi represent clones of genetically altered cells arising from mosaicism [5–9]. *Genetic mosaicism* (see also Chapter 12) denotes the presence of two or more genetically different cell populations in an individual derived from a single zygote. The differences can be between single genes, groups of genes or entire chromosomes. *Chimerism* denotes the presence of two or more genetically distinct cell populations in an individual derived from two different zygotes. Chimeras can result from the fusion of dizygotic twin embryos, or from the fertilization by two spermatozoa, and subsequent splitting, of an ovum containing a polar body. While mosaicism

generally involves an abnormal clone within a normal individual, chimaerism involves two different normal clones. Cutaneous anomalies due to mosaicism affect any skin cell type, but the cutaneous abnormalities observed in human chimeras are always pigmentary [10–12].

The word 'naevoid' is sometimes applied to mosaic forms of inherited skin conditions following Blaschko's lines, e.g. naevoid psoriasis.

The imprecise term *systematized*, applied to an extensive naevus, implies a linear, segmental or dermatomal distribution. The terms *segmental* and *zosteriform* should be confined to naevi following body segments and dermatomes respectively. In practice 'segmental' usually conceals ignorance about whether the pattern follows dermatomes or Blaschko's lines.

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Aetiology

Congenital malformations may be caused by environmental or genetic factors, or combinations of the two independently or interacting. Some abnormalities have different causes in different patients, e.g. aplasia cutis. It is important to recognize parents' tendencies to attribute neonatal defects to antenatal and perinatal events: the question 'What did you think might have caused this?' may reveal surprising and irrational concerns.

Environmental factors. Those provoking congenital malformations (teratogens) are listed below. In fact remarkably few cutaneous developmental defects have been attributed to teratogens: they include aplasia cutis congenita of the scalp due to methimazole and segmental aplasia cutis following first-trimester varicella.

1 *Intrauterine infections*: rubella [1–5], cytomegalovirus [6], toxoplasmosis [6] and herpes simplex virus [7], are well-known causes of non-cutaneous defects. First-trimester varicella can cause segmental aplasia cutis [7–9].

2 *Ionizing radiation* from X-rays, radiotherapy or accidental contamination [10,11].

3 *Drugs taken during pregnancy* [12–15], particularly cytotoxic and immunosuppressive agents, anticonvulsants, anticoagulants, androgens, lithium carbonate, thalidomide, vitamin A derivatives and methimazole [16] which can cause aplasia cutis congenita of the scalp.

4 *Alcohol* [17,18] *use during pregnancy* may result in a characteristic dysmorphic appearance (fetal alcohol syndrome) an occasional feature of which is neonatal hypertrichosis. Haemangiomas (mostly small, raised strawberry angiomas) were found in 12/41 (29%) infants with fetal alcohol syndrome [17].

5 *Trace metal excesses or deficiency during pregnancy*, particularly mercury exposure [19] and zinc deficiency [20].

6 *Exposure to other toxins during pregnancy*. Congenital polychlorinated biphenyl (PCB) poisoning occurred following exposure of mothers in two industrial accidents, in Japan and Taiwan, in which cooking oil was contaminated during its manufacture [21]. Affected babies had 'cola-coloured skin', with dark brown pigmentation of flexures, nails, mouth and sclerae that cleared in 2–5 months.

7 *Maternal diseases*, such as diabetes mellitus [22] and phenylketonuria [23].

8 *Paternal occupational exposure to toxins* can adversely affect the fetus either by direct effects on spermatozoa, or indirectly by maternal contamination. Paternal occupations that have been linked with birth defects include janitors, painters, printers, and occupations related to solvents or agriculture [24].

Genetic factors. Most developmental defects involving the skin probably have a genetic basis. The types of genetic abnormality, in descending order of size of the mutation, are summarized below:

1 *Chromosomal syndromes*: major abnormalities of chromosome number include trisomy 21 (Down's syndrome), and sex chromosome defects. Syndromes due to structural anomalies of chromosomes include Wolf–Hirschhorn syndrome, in which there is loss of the short arm of chromosome 4. Chromosomal syndromes involving an autosome are usually accompanied by mental retardation. Skin anomalies are unusual in this group, but include keratosis pilaris in Down's syndrome. Localized skin anomalies are even more unusual: an example is aplasia cutis in Wolf–Hirschhorn syndrome. Chromosomal anomalies may be inherited, or may arise after conception from chromosomal non-disjunction during mitosis, in which case they will be mosaic.

2 *Microdeletion syndromes*: submicroscopic deletion of contiguous genes can produce syndromes combining features caused by the individual genes. A dermatological example is X-linked ichthyosis with hypogonadotrophic hypogonadism, due to a microdeletion at Xp22 affecting both the steroid sulphatase and Kallmann's syndrome loci. Microdeletions are detected by fluorescence *in situ* hybridization (FISH).
3 *Mutations in specific genes*: this is the major cause of both inherited and mosaic syndromes and anomalies.

Genetic mechanisms in localized and isolated defects

Genetic skin disorders are usually generalized. The patchy and localized conditions that are the subject of this chapter can be produced and transmitted by the following genetic mechanisms:
1 Mutations in genes acting on morphogenesis may cause abnormal cell migration resulting in patchy defects. Examples include dominantly inherited scalp aplasia cutis, and white patches in autosomal dominant piebaldism.
2 Patchy skin manifestations in some generalized autosomal dominant and recessive disorders can be attributed to a genetic 'second hit' [25] (loss of heterozygosity), e.g. hamartomas in tuberous sclerosis, and the tumours of xeroderma pigmentosum.
3 Some localized anomalies represent a 'forme fruste' or minimal expression of a generalized disorder. For example, lower-lip sinuses, which most often occur alone, represent the minimal manifestation of an autosomal dominant gene, whose full expression results in Van der Woude's syndrome, with associated cleft lip and palate [26]. It is possible that isolated ash-leaf macules and café-au-lait macules have a similar significance.
4 Genetic mosaicism resulting from somatic mutation is probably the major cause of naevi and other localized skin defects [27–31]. The embryo is normal at conception, but at some point during early embryogenesis a mutation gives rise to a clone of cells in which the genetic change manifests as a localized cutaneous abnormality. Naevi caused by genetic mosaicism arising after conception are by definition not inherited from the parents. Occasional reports of familial clustering of mosaic conditions (such as epidermal naevus and segmental neurofibromatosis) may be attributable to inheritance of an unstable premutation. Happle has suggested two other mechanisms to explain familial clustering of mosaic conditions: 'paradominant inheritance' [32] in which a recessive gene is unmasked by loss of heterozygosity, and the silencing and activation of different genes by 'transposable elements' [33]. A particular risk of mosaic disorders is transmission of the generalized condition to the patient's offspring (e.g. generalized neurofibromatosis type 1 in offspring of patients with segmental neurofibromatosis). Some localized defects (e.g. Sturge–Weber syndrome) have been attributed to serious mutations compatible with survival only in the mosaic state, so that if the mutation were passed on it would cause miscarriage [34]: this has never been documented. Epidermal mosaicism is manifest as Blaschko's lines (see below).

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Classification of naevi

The classification of naevi is historical and not entirely logical. In general, naevi are classified according to the component cell, tissue or organ, and subdivided according to the macroscopic or histological nature of the abnormality (Table 15.1). The existing categories have stood the test of time, enabling dermatologists to distinguish naevi with different biological behaviour, and to advise patients

Table 15.1 Classification of naevi.

Epidermal naevi	Dermal and subcutaneous naevi
Keratinocyte naevi	*Connective tissue naevi*
Verrucous epidermal naevus	Collagen naevi
Epidermolytic verrucous epidermal naevus	Familial cutaneous collagenoma
Non-epidermolytic verrucous epidermal naevus	Eruptive collagenoma
Sebaceous naevi	Tuberous sclerosis
Naevus sebaceus	Other collagenomas
Follicular naevi	Elastic naevi
True hair-follicle naevus	Pseudoxanthoma elasticum
Comedo naevus	Perforating elastoma
'Acne-free' naevus	Juvenile elastoma and the Buschke–Ollendorff syndrome
Basaloid follicular hamartoma	Naevus anelasticans
Dilated pore naevus	Other elastomas
Hairy malformation of the palms and soles	Proteoglycan naevi
Apocrine naevi	Mucinous naevus
True apocrine naevus	*Smooth muscle naevi*
Naevus syringocystadenomatosus papilliferus	Congenital smooth muscle hamartoma
Eccrine naevi	Diffuse smooth muscle hamartoma
True eccrine naevus	Congenital leiomyoma
Eccrine angiomatous hamartoma	*Fat naevi*
Porokeratotic eccrine ostial and dermal duct naevus	Naevi lipomatodes cutaneous superficialis
Becker's naevus	Encephalocraniocutaneous lipomatosis
Inflammatory epidermal naevi	Congenital lipoma
ILVEN	Congenital lipomatosis
CHILD naevus	Neurolipomatosis
Other naevoid epidermal disorders	Congenital lipoma
Linear lichen planus	'Michelin tyre' baby
Naevoid psoriasis	*Vascular naevi*
Darier-like epidermal naevus	Haemangiomas
Hailey–Hailey-like epidermal naevus	Infantile haemangioma
Linear porokeratosis	Verrucous haemangioma
Atrophoderma of Moulin	Angioblastoma
'Blaschkitis'	Vascular malformations
Epidermal naevus syndrome	Capillary vascular malformations
	'Salmon' patch
	'Port-wine' stain
	Naevus anaemicus
	Naevus oligaemicus
	Mixed vascular malformations
	Cutis marmorata telangiectatica congenita
	Klippel–Trenaunay syndrome
	Venous malformations
	'Blue rubber bleb' naevus syndrome
	Maffucci's syndrome
	Zosteriform venous malformations
	Gorham's disease
	Other multiple vascular malformation syndromes
	Angiokeratoma

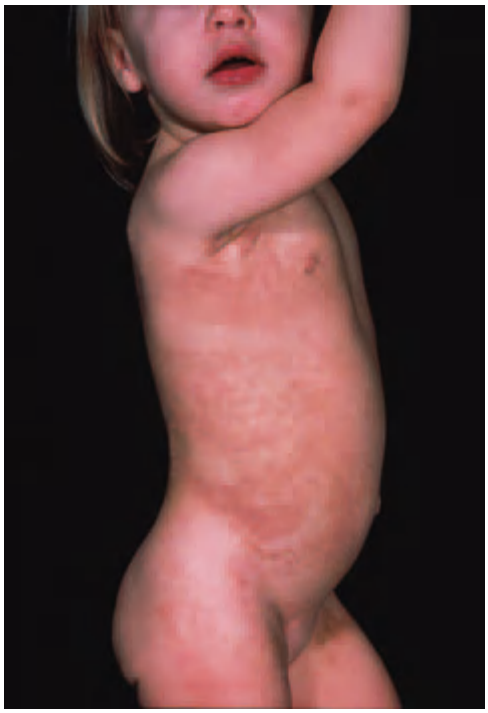

Fig. 15.1 Multiple verrucous epidermal naevi with the histological changes of epidermolytic hyperkeratosis.

accordingly. However, there are many areas of uncertainty, reflecting variability within and between lesions and patients. As we learn more about the molecular basis of naevi some of these uncertainties resolve. For example, we now know that epidermolytic and non-epidermolytic verrucous epidermal naevi are different entities, while Darier-like and acantholytic epidermal naevi are the same. The classification used here combines established clinical divisions with newer molecular definitions.

Blaschko's lines

Almost all epidermal naevi follow the pattern of lines painstakingly documented by Blaschko from drawings of epidermal naevi [1]. Blaschko's lines are characteristic of mosaic conditions of the epidermis and probably represent the routes of ectodermal cell migration from the neural crest [2,3]. On the trunk, these lines tend to take the form of transverse bands, differing from dermatomes in being more numerous, and in their S-shaped wave form on the lateral trunk (Fig. 15.1) and V-shape in the middle of the back. On the arms and legs, lesions follow lines roughly parallel with the axis of the limb. The lines spiral on the scalp, are vertical in the mid-face, and extend laterally from the angles of the mouth [4–6]. They never cross the anterior truncal midline, but run along it. Posteriorly, the 'Blaschko' midline is often shifted from the anatomical midline.

The shape and distribution of epidermal naevi probably reflect not only paths of cell migration but also the timing of mosaicism and cell type. Abnormal clones arising at the very early blastocyst stage will be widely distributed along the paths of migrating cells and appear linear, while those arising in the fully formed fetus are more likely to be single, small, round or oval lesions. Keratinocytes which migrate by directional proliferation produce linear lesions, whereas melanocytes which migrate singly more often form leaf-shaped (phylloid) or block-like lesions.

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Epidermal naevi

The term epidermal naevus is used for naevi composed of keratinocytes. Recently, the molecular causes of certain epidermal naevi have been elucidated, enabling us to differentiate between them. However, the older literature does not differentiate between, for example, epidermolytic and non-epidermolytic naevi, and therefore clinical descriptions must be read in this light.

Probably all epidermal naevi comprise an abnormal clone of cells, reflecting genetic mosaicism arising from somatic mutation (see above). The clinical implications of mosaicism are firstly that it is unlikely to recur in the same family, and secondly that there is a theoretical risk of the condition being passed on to the patient's offspring in a severe or even lethal generalized form. Curiously these predictions are not always borne out, as is discussed under the individual headings.

Verrucous epidermal naevus

SYN. NAEVUS VERRUCOSUS; NAEVUS UNIUS LATERIS

Definition. Verrucous epidermal naevi are congenital, non-inflammatory cutaneous hamartomas composed of keratinocytes. They are distinct from inflammatory, acantholytic and porokeratotic epidermal naevi, from sebaceous naevi, and from epidermal naevi derived from skin appendages. Their prevalence in adults is probably 0.1–0.5%, and they occur equally in males and females. They are divided into epidermolytic and non-epidermolytic types.

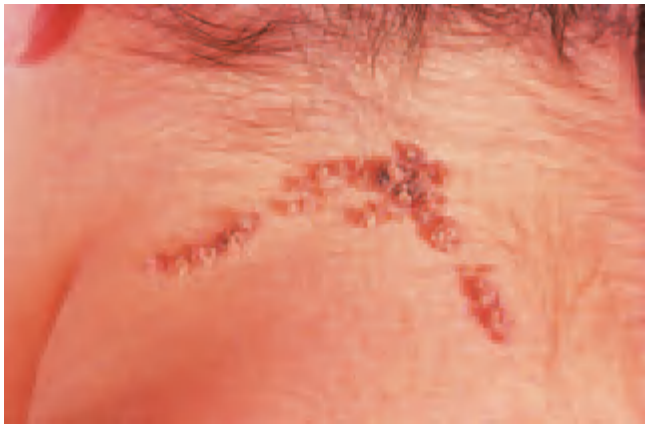

Fig. 15.2 Linear verrucous epidermal naevus on the neck.

Epidermolytic verrucous epidermal naevus

Aetiology. The histological similarity between epidermolytic verrucous epidermal naevi and autosomal dominant bullous ichthyosiform erythroderma (BIE) led to the idea that the former represents a clone of cells expressing a mutation in one of the BIE genes. This was confirmed by the finding of mutations in keratin 10 in such naevi but not in the adjacent normal skin [1,2] and more recently mosaicism for a keratin 1 mutation in a woman with verrucous epidermal naevi [3]. Such epidermal naevi are sporadic and cannot be passed on from parent to child. However a parent with an epidermolytic verrucous epidermal naevus is likely to have gonadal mosaicism as well as cutaneous mosaicism, and can therefore produce offspring with generalized BIE [2–4].

Pathology. Epidermolytic verrucous epidermal naevi show hyperkeratosis, acanthosis and papillomatosis with epidermolytic hyperkeratosis [1–5] identical to that seen in BIE. This comprises perinuclear vacuolization of the keratinocytes, associated with premature and excessive formation of irregular keratohyalin granules, indistinct cell borders and hyperkeratosis.

Clinical features [1–5]. By analogy with BIE, epidermolytic verrucous epidermal naevi at birth would be expected to be blistered, and only later to become verrucous. However there is no specific report of this. In young children they appear as slightly pigmented velvety or warty streaks or plaques. With age they darken and the surface becomes more warty (Fig. 15.2), sometimes with an erythematous base. They may be single or multiple, and size and site are variable. Flexural lesions may become macerated and foul smelling, which can cause the patient substantial social problems. Epidermolytic verrucous epidermal naevi are not associated with extracutaneous abnormalities (epidermal naevus syndrome: see below). This is because they are due to mutations in keratin genes which are expressed only in the skin. They probably do not have the malignant potential of sebaceous naevi [6].

Diagnosis. Epidermolytic and non-epidermolytic verrucous epidermal naevi are sometimes indistinguishable except on histology. Their lack of inflammation, presence at birth, warty, brown appearance and persistence distinguish them from most other types of epidermal naevus. They may be confused with linear viral warts, particularly filiform or digitate warts on the neck, scalp or body folds.

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Non-epidermolytic verrucous epidermal naevus

Aetiology. Non-epidermolytic verrucous epidermal naevi are probably heterogeneous, representing mosaicism for different, and as yet unidentified, mutations. Stosiek *et al*. [1] reported chromosomal mosaicism in two otherwise normal men with non-epidermolytic verrucous epidermal naevi. Several chromosomal abnormalities were found in the abnormal skin, with a breakpoint common to both patients at 1q23. This lies intriguingly close to a locus known as the epidermal differentiation complex, which includes a cluster of over 25 genes encoding structural components of the cornified envelope [2]. Other candidates for acanthosis nigricans-like epidermal naevi [3] include the fibroblast growth factor receptor (FGFR) genes [4]. A palmoplantar verrucous naevus has been reported which was due to mosaicism for a mutation in keratin 16, the gene responsible for pachyonychia congenita [5], but since hyperkeratosis in pachyonychia congenita is confined to the palms and soles, it is unlikely that verrucous epidermal naevi at other sites are caused by pachyonychia congenita gene mutations.

Pathology [6,7]. The most common histological pattern is sharply demarcated hyperkeratosis and acanthosis, often associated with papillomatosis, and occasionally by focal hypergranulosis and/or columns of parakeratosis. About 10% of lesions show a distinctive 'church-spire' pattern of acanthosis and hyperkeratosis, resembling acrokeratosis

verruciformis, and about 5% show features resembling seborrhoeic keratoses, i.e. hyperkeratosis, papillomatosis, acanthosis and horn pseudocysts, with a flat lower base. Rarely, they may show histological features more characteristic of common viral warts, acanthosis nigricans [3], or of the verrucous phase of incontinentia pigmenti [8].

Several other changes have been reported in verrucous epidermal naevi. Appendageal anomalies seen in early childhood include immature hair follicles, sebaceous, eccrine or apocrine glands. In later childhood and adult life, comedo-like dilated follicles, and sebaceous, eccrine and apocrine hyperplasia occur [9]. It is not at all clear to what extent these represent age- and site-related differences in the same disorder [9,10] or different naevi. The same difficulty applies to occasional reports of basal cell [11–13], squamous [13–18], verrucous [19] and adnexal carcinomas [20], and Bowen's disease [18], within epidermal naevi: usually they are those showing sebaceous or apocrine differentiation.

Clinical features. Verrucous epidermal naevi are usually present at birth but may appear or extend during childhood. A verrucous epidermal naevus in a 60-year-old woman reported to have developed only 5 years previously was highly atypical, with bilateral crusted, hyperkeratotic plaques on the head and upper trunk and histological signs of inflammation [21]. At birth they have a white, macerated appearance, but within a few days take the form of pink or slightly pigmented velvety streaks or plaques. Later, they darken and the surface becomes more warty (see Fig. 15.2), sometimes with an erythematous base. Their extent and distribution are highly variable, but sebaceous naevi are especially common on the face and scalp. They may extend on to an adjacent mucosal surface [22]. Nail ridging, splitting, discoloration or dystrophy may occur where the nail fold is involved. The lesions are as a rule asymptomatic, except, for example, when they impinge upon the nail fold, where they may cause recurrent paronychia, and may split or distort the nail plate. Flexural lesions may become macerated and foul smelling. Verrucous epidermal naevi have been associated with scalp woolly hair naevi [23], and in some cases the woolly hair directly overlies a verrucous epidermal naevus [24,25]. Tumours may develop within the naevi (see above). While most of the patients in whom this has occurred have been over 40 years of age, malignant tumours have been reported in patients as young as 17 years of age [14].

A wide variety of developmental anomalies may occur in association with verrucous epidermal naevi and are discussed in more detail in the section on epidermal naevus syndrome. They include localized anomalies such as megalopinna [26] and aplasia cutis of the scalp [27], and syndromes such as epidermal naevus syndrome, Proteus syndrome, McCune–Albright syndrome [28,29], Klippel–Trenaunay syndrome [30], and phakomatosis pigmentokeratotica. Tumour-induced rickets and osteomalacia sometimes accompany verrucous epidermal naevi [31].

Diagnosis. Epidermolytic and non-epidermolytic verrucous epidermal naevi must be distinguished histologically. Non-epidermolytic verrucous epidermal naevi can be differentiated clinically from other types of epidermal naevus as they are usually present at birth, asymptomatic, non-inflammatory and persistent. If the age of onset is uncertain they can be confused with viral warts. Historically verrucous epidermal naevi have been confused with a variety of epidermal naevi whose true identity has been recognized more recently, for example CHILD (*c*ongenital *h*emidysplasia with *i*chthyosiform naevus and *l*imb *d*efects) naevus.

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Management of epidermolytic and non-epidermolytic epidermal naevi

Reports of the responses of epidermal naevi to various therapies have rarely distinguished between the different histological types. Therefore both are considered together here.

Topical applications are rarely curative and therefore have a limited place in the treatment of verrucous epidermal naevi [1]. Preparations containing salicylic acid, lactic acid or retinoic acid [2] may decrease the keratotic element to some extent but require persistent application to maintain any improvement. Podophyllum may help [3] but its toxicity precludes its use in larger lesions [4]. Successful treatment with topical 5-fluorouracil and retinoic acid has been reported [5,6].

Cosmetically significant lesions may justify systemic retinoid therapy. Etretinate [7] and acitretin can produce worthwhile reduction of hyperkeratosis in epidermolytic lesions. Patients and carers must understand that retinoids are not curative and the condition will relapse if the treatment is stopped.

Even surgery is not curative unless underlying dermis is removed or destroyed at the same time as the epidermal component. Large lesions may require multistage, multimodality procedures, adapted according to anatomical site [8]. Skin-shaving procedures or dermabrasion thus tend to produce only temporary benefit. Cryotherapy is a simple alternative for smaller lesions. Problems with laser treatment include hypertrophic scarring, pigmentary changes and partial recurrence. However, improvments in laser technology are gradually overcoming these problems. The argon laser is helpful for softer, less hyperkeratotic lesions [9]. Continuous-wave carbon dioxide laser vaporization has been used successfully for extensive verrucous epidermal nevus [10], and pulsed carbon dioxide laser for thinner verrucous epidermal naevi [11]. Staged carbon dioxide laser treatment using different modalities for thick and thin lesions cleared an extensive verrucous epidermal naevus with no recurrence in 2 years of follow-up [10]. Newer erbium : yttrium aluminium garnet (Er : YAG) lasers with greater coagulative capacity can also be used with good effect [12]. The pulsed ruby laser may reduce and lighten dark-coloured epidermal naevi, but patients with a darker skin type risk post-irradiation depigmentation [13].

Patients with epidermolytic verrucous epidermal naevi are at risk of parenting a child with BIE. If the patient is a child the carers should probably be informed of this risk, and of the possibility of first-trimester antenatal diagnosis. Arrangements should be made to counsel the affected individual at a suitable age. Currently we lack data that allow quantification of the risk. Patients with non-epidermolytic epidermal naevi can be counselled that these are sporadic lesions and are not passed on as a generalized skin condition. It has been suggested that the generalized condition is lethal [14], and affected individuals survive only if they are 'rescued' by mosaicism.

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Sebaceous naevus

SYN. NAEVUS SEBACEUS OF JADASSOHN

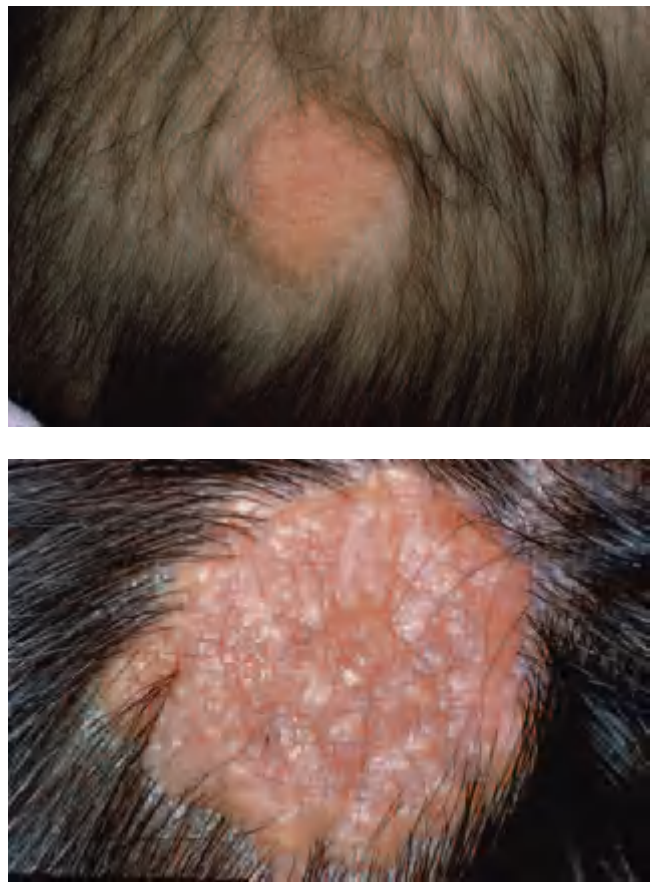
Definition and aetiology. Sebaceous naevi are epidermal hamartomas comprised predominantly of sebaceous

glands. The view that sebaceous naevi and verrucous epidermal naevi are variants of the same disorder, those on the head and neck being more sebaceous and those elsewhere more verrucous, is supported by the occurrence of both types in individuals and in the epidermal naevus syndrome [1–3].

Sebaceous naevi are usually sporadic, probably reflecting lethal genes rescued by mosaicism (see above). There have been occasional reports of familial cases [4,5] perhaps reflecting inheritance of an unstable premutation, but attributed by Happle and Konig to paradominant inheritance [6]. Because sebaceous naevi have a tendency to develop tumours, various tumour genes have been implicated in their aetiology. Constitutive activation of the patched-hedgehog signalling pathway (involved in Gorlin's syndrome and basal cell carcinomas) was suggested by Xin *et al.* [7] who found loss of heterozygosity at the *PTCH* locus 9q22.3 in sebaceous naevi. However, this finding was refuted by Takata *et al.* [8] who also found lack of expression of *Gli-1*, another gene in the patched-hedgehog signalling pathway expressed in basal cell carcinomas.

Pathology [9–11]. Before puberty, the sebaceous and apocrine glands in these lesions are sparse and underdeveloped, so that the lesions may be indistinguishable from verrucous epidermal naevi [10]. Cords and buds of poorly differented epithelial cells representing primordial pilosebaceous follicles are, however, a distinctive and diagnostic feature at this stage [9]. After puberty the characteristic mature sebaceous glands and associated papillomatous hyperplasia of the overlying epidermis are seen. Hair follicles are inconspicuous. Buds of undifferentiated epithelial cells resembling foci of basal cell carcinoma probably represent primordial hair follicles [11]. Merkel cells may be abundant [12]. Some lesions feature hypoplastic sebaceous glands, or sebaceous glands situated at an abnormally high level in the dermis. Ectopic apocrine glands are very commonly observed deep in the dermis beneath the sebaceous glands [9,11].

A variety of appendageal tumours may develop within sebaceous naevi [9,11,13–29]. The most commonly reported are syringocystadenoma papilliferum and trichoblastoma; less common tumours include nodular hidradenoma, apocrine cystadenoma, syringoma, infundibuloma and trichilemmoma. Locally invasive and malignant tumours include keratoacanthoma, proliferating trichilemmal cyst, and basal cell, sebaceous, apocrine, eccrine and squamous carcinomas. The true incidence of malignancy in sebaceous naevi is difficult to determine for several reasons, but mainly because different criteria were used to gather cases in each of the larger series. Furthermore basaloid proliferation has almost certainly been misinterpreted as basal cell carcinoma, the commonest malignancy reported in sebaceous naevi (see below). Takata *et al.* [8] found clear molecular differences between the basal cell carcinoma-like trichoblastomas arising in sebaceous naevi and true basal cell carcinomas.



(a) (b)

Fig. 15.3 Sebaceous naevus: (a) in a 6-month-old infant; (b) in an adult.

Clinical features. Sebaceous naevi occur in about 0.3% of all neonates [30,31]. They comprise circumscribed, slightly raised, pinkish, yellow, orange or tan plaques, with a smooth or somewhat velvety surface. Although usually congenital, they are occasionally first reported later in life [32]. The sex incidence is equal.

The lesions may be round, oval or linear, varying in length from under 1 to over 10 cm. Their shape may be determined by the stage at which they arise, early lesions conforming to embryonic epidermal migratory lines, while later lesions arising in a more fixed epidermis are round (see Blaschko's lines, above). They most commonly occur singly, but may be multiple and extensive, like verrucous epidermal naevi. Most occur on the head and neck, favouring the scalp, the areas around the ears, the temples, forehead and the central part of the face. They occasionally occur elsewhere [33]. Sebaceous naevi of the scalp are devoid of hair, and usually present with the complaint of a bald patch (Fig. 15.3).

Following birth, the lesions tend to become less prominent and then to remain unchanged until puberty, when they become thickened and more elevated. For this reason, many patients present at this stage. Gradually they become more nodular during adult life (see Fig. 15.3).

Development of an exophytic nodule on a naevus sebaceus usually represents a benign appendageal tumour or viral wart [26,27]. Rapid, circumscribed enlargement or ulceration should arouse suspicion of malignant transformation. This usually occurs in middle age, but can undoubtedly occur in adolescence, or even in childhood [13,34–37]. The lifetime risk of malignant transformation is probably less than 5%, but is difficult to establish with any precision because the major studies have varied considerably in methods of selection and in ages of the patients [9,11,15,27]. The most common malignancy is basal cell carcinoma, but the incidence of this tumour has been overestimated because of misinterpretation of trichoblastoma [26] and basaloid proliferation as basal cell carcinoma. Other malignant tumours reported include squamous, sebaceous and apocrine carcinomas. Despite occasionally aggressive histopathological features, most of these tumours are of low-grade malignancy. Nevertheless, local recurrence after excision, metastasis and a lethal outcome have all been reported [15,38].

Associated abnormalities occur in a small proportion of cases: these are considered under the heading of 'epidermal naevus syndrome'.

Diagnosis. Diagnosis is usually straightforward on clinical grounds alone. In early infancy, lesions in the scalp must be distinguished from aplasia cutis, which has a smoother papyraceous surface. Syringocystadenoma papilliferum may be very difficult to distinguish clinically, although the surface tends to be pink and nodular, rather than yellow and velvety. Early juvenile xanthogranulomas may be similar in their clinical appearance, although these generally develop rapidly into distinctive domed, papular or nodular lesions. Solitary mastocytomas may also be confused clinically during infancy, but histological examination will clearly identify all these disorders.

Very rarely, heterotopic brain tissue or an encephalocoele may result in a congenital bald patch overlying a subcutaneous nodule [39]. They may communicate with the brain so it is important to distinguish them from sebaceous naevus.

Treatment. Removal during childhood may be necessary for cosmetic reasons but is difficult to justify on grounds of risk of malignancy [26,27]. Excision of scalp lesions with primary closure gives an excellent cosmetic result, but larger lesions may require tissue expansion. Simple excision is generally adequate even in the presence of histological malignancy. Superficial removal by dermabrasion or carbon dioxide laser is likely to be followed by partial recurrence but may be helpful where excision is not feasible [40]. An extensive naevus sebaceus of face and scalp in a 38-year-old woman was cleared with 13 sessions of photodynamic therapy, with no recurrence 16 months later [41].

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Follicular naevi

True hair-follicle naevus [1–7]

SYN. CONGENITAL VELLUS HAMARTOMA

In the past, the lesions that are now more usually termed trichofolliculomas were often described as 'hair-follicle naevi' [1]. The term should be confined to a hamartoma comprising an excessive concentration of normal hair follicles. This rare tumour, sometimes also called *congenital vellus hamartoma*, generally takes the form of a small, skin-coloured papule on the face, usually present from birth. Histologically, the lesion contains numerous small but well-differentiated vellus hair follicles in the dermis, with a few sebaceous glands and eccrine sweat glands. Subepidermal calcified nodule of the ear has been reported in a child with hair follicle naevus [8]. The treatment of choice is simple excision.

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Comedo naevus

SYN. COMEDONE NAEVUS; NAEVUS COMEDONICUS; FOLLICULAR NAEVUS; ACNE NAEVUS

Definition. First described in 1895 [1], the comedo naevus is a linear lesion comprising numerous keratin-filled pits, sometimes with acneiform pustules.

Aetiology. This is probably a mixed group, reflecting mosaicism [2] for a variety of mutations that can predispose to acne. Acneiform naevi with predominantly inflammatory lesions may represent a clonal sensitivity to androgens [3–5]. The occasional histological finding of rudimentary hair follicles, sebaceous glands and trichilemmal cysts suggests a primary defect within the pilosebaceous gland. In naevi where comedones predominate, interfollicular histological changes typical of common verrucous epidermal naevi [6] or epidermolytic hyperkeratosis [7] suggest that follicular blockage is secondary to a keratinocyte defect. Comedo naevus on hair-bearing limbs contiguous with lesions involving eccrine ducts on the palms and soles, resembling *porokeratotic eccrine ostial and dermal duct naevus* [8–11], and glans penis [12], also supports a non-appendage-specific epidermal problem causing duct blockage. The suggestion that such lesions represent developmentally abnormal and ectopic pilosebaceous follicles [10] is less likely.

Munro and Wilkie hypothesized that mosaicism for a dominantly inherited disorder featuring severe acne might account for some acneiform naevi [13]. Apert's syndrome, characterized by acne, craniosynostosis and other bony defects, seemed a good candidate. This would explain the occasional association with skeletal abnormalities, as well as the linear distribution of acneiform lesions, and was confirmed by demonstrating an *FGFR2* mutation in lesional epidermis but not in adjacent normal skin [13]. Comedo naevi might also result from mosaicism for mutations, as yet unidentified, causing two other autosomal disorders featuring widespread comedones. The first of these is most commonly called *familial diffuse comedones* [14,15], but has been reported under the term 'nevus comedonicus' [16]. The comedo-like lesions appear progressively and in a diffuse bilateral distribution. Sporadic cases also occur [17]. In the second, called *familial dyskeratotic comedones*, the comedones are less extensive and demonstrate dyskeratosis histologically [18–20].

Pathology [9,21,22]. The characteristic histological feature of a comedo naevus is the deep, wide invagination of acanthotic epidermis, filled with concentric lamellae of keratin. These probably represent dilated hair follicles, as hair shafts are occasionally seen in the lower part of the invagination [6,22,23], and rudimentary sebaceous glands may open into them [22]. Arrector pili muscles are absent. The interfollicular epidermis may be histologically

normal, acanthotic and hyperkeratotic [6], or even epidermolytic [7,24,25]. Other reported histological associations have included trichilemmal cysts [26].

Clinical features [1–17,21–50]. This is a rare naevus: in their series of 235 epidermal naevi, Rogers found only four comedo naevi [2]. Acne naevus appears as a circumscribed asymmetrical area of skin demonstrating otherwise typical lesions of acne vulgaris in normal skin, or an area in which acne vulgaris is more severe. Comedo naevus comprises groups of pits filled with black keratinous plugs resembling blackheads with inflammatory acne lesions developing later. The intervening epidermis may appear normal, hyperkeratotic, or slightly hypo- or hyperpigmented [22,27]. Areas of more marked hypopigmentation have been reported by several authors [10,28]. There may be one or several lesions in a linear, unilateral [27,31–33] or, more rarely, bilateral distribution [23]. Lesions may be very extensive [28,33]. The commonest site is the face, followed by the neck, trunk and upper arm. Palms, soles and the glans penis, from which pilosebaceous follicles are normally absent, may occasionally be involved, usually in association with lesions in more characteristic sites, and often contiguous with them [8,9,12,28,34]. Curiously, the scalp is rarely affected [21,33,34].

Predominantly comedonal naevi are occasionally present at birth, but inflammatory acneiform naevi more often appear during childhood [2,30] or adolescence. They may be complicated by acneiform chronic inflammation, suppuration, fistula formation and hypertrophic scarring [6,27,30,33,35,36]. The development of multiple nodules within a comedo naevus may reflect the presence of associated trichilemmal cysts [26]. Benign or malignant tumours rarely complicate comedo naevi.

There have been occasional reports of associated developmental anomalies, including ipsilateral cataract [2,37], extensive naevus flammeus [38], transverse myelitis [39] and perforating elastoma [40]. While some of these are probably coincidental, skeletal malformations [28,39,41,42] may be manifestations of mosaicim for an *FGFR2* mutation, causing patchy manifestations of Apert's syndrome. The characteristic features of Apert's syndrome include craniosynostosis, mid-face hypoplasia, syndactyly and broad distal phalanx of thumb. The patient reported by Patrizi *et al.* [42] had a comedo naevus on the right cheek, syndactyly and a broad right thumb, and is very likely to have been mosaic for Apert's syndrome, although this was not investigated. Rogers' patient with extensive comedo naevus and syndactyly [2] may also have been mosaic for Apert's syndrome.

Diagnosis. Porokeratotic eccrine ostial and dermal duct naevus can be distinguished clinically by its occurrence on the palms and soles, and also histologically. Familial diffuse comedones and familial dyskeratotic comedones may be pathogenetically identical to comedo naevi (see above) but are symmetrical and widespread rather than linear. Atrophoderma vermiculata and keratosis pilaris atrophicans may show comedones, but can be distinguished from comedo naevus by their symmetry. The dilated pore naevus [43] can only be distinguished histologically. Comedones may occur in linear basal cell naevus. Comedo naevi have been reported as sequelae of lichen planus [44], herpes zoster [45], vaccination [46] and trauma [47], but the lesions described in these reports may simply represent an unusual pattern of scarring. Extensive comedones due to chloracne and sun damage are distinguishable from comedo naevus by their non-linearity.

Treatment. As with other epidermal naevi, surgical excision is more effective in the long term than superficial shaving or dermabrasion [27,48], but the latter can occasionally be useful cosmetically if the lesions are extensive [47], as can the regular use of a comedo extractor [27]. Both topical retinoic acid and 12% ammonium lactate may sometimes improve the appearance of lesions [36,49], and may help prevent secondary inflammation. Although oral isotretinoin has been reported to be ineffective [50,51], it is logical to treat extensive, inflamed acneiform naevi with anti-acne medication instead of, or in preparation for, surgical treatment.

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'Acne-free' naevus

A single case has been reported of an adolescent male with severe papulopustular acne vulgaris of the back, who had, within the affected area, four well-defined bilaterally symmetrical zones, which were completely free of acne [1]. Investigation revealed smaller sebaceous glands, reduced sebum excretion rate, decreased counts of *Propionibacterium acnes* in the pilosebaceous ducts and reduced conversion of testosterone to 5α-dihydrotestosterone in the 'acne-free' zones. This may be another type of 'functional' naevus, possibly due to abnormal end-organ androgen responsiveness, and could be regarded as the converse of the situation in acne naevi.

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Basaloid follicular hamartoma

SYN. LINEAR BASAL CELL NAEVUS; BASAL CELL NAEVUS WITH COMEDONES

Definition. A rare variety of epidermal naevus composed of multiple benign basal cell hamartomas.

Aetiology. Most cases probably represent mosaicism for autosomal dominant basaloid follicular hamartomas [1–3]. Those associated with skeletal malformations and palmar pits may reflect mosaicism for Gorlin's syndrome (linear basal cell naevus syndrome) [4].

Clinical features [5–17]. This benign, localized, usually linear naevus is generally present from birth and may be extensive. The lesion consists of numerous, translucent or brown, telangiectatic, hemispherical nodules up to about 0.5 cm in diameter, which occasionally demonstrate central ulceration, often associated with small areas of macular hypopigmentation. Some have the appearance of comedones, and other reported abnormalities in the affected area have included cysts, verrucous papules and stria-like areas of cutaneous atrophy. The face is a common site. Scalp lesions are usually associated with localized alopecia [11]. Normal hair growth on a scalp follicular hamartoma has been reported but the histology in that case was also atypical [15]. Malformations of the spine are rarely associated [7,8].

Pathology. Basaloid follicular hamartoma is characterized by anastomosing strands of well-differentiated basaloid or squamoid cells extending from the upper portions of follicles into a loose connective tissue stroma [15–17]. It can be distinguished from basal cell carcinoma by its low proliferative index (Ki-67 expression) and by circumferential expression of CD34 around the epithelial strands [17].

Differential diagnosis. Confusion may arise with other

adnexal tumours, particularly on the face. It must be differentiated from linear basal cell carcinomas.

Treatment. Treatment, if required, is usually surgical.

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Dilated pore naevus

While clinically indistinguishable from comedo naevus, histologically the dilated pore naevus shows aggregated dilated follicular cysts [1]. These cysts individually are indistinguishable from the dilated pore of Winer, a solitary lesion usually occurring on the face in middle-age. Steffen [2] has argued that the dilated pore of Winer is a primary neoplasm (infundibloma) rather than a cyst.

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Hairy malformation of the palms and soles

This rare disorder appears to be transmitted as an autosomal dominant trait. Asymptomatic areas of skin, having a somewhat altered texture and bearing hairs, are present bilaterally on the palms near the wrists, and on the medial aspect of the longitudinal arch of the feet [1,2]. Histologically, these show no abnormality other than the presence of hair follicles. A sporadic case has been reported in which the abnormality occurred on one palm only [3]. Differential diagnosis will include congenital melanocytic naevus and smooth muscle hamartoma.

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Apocrine naevi

True apocrine naevi

SYN. APOCRINE GLAND HAMARTOMA

True apocrine naevi are rare, although apocrine structures are frequently seen in sebaceous naevi [1] and are a component of the lesions known as naevus syringocystadenomatosus papilliferus. The clinical appearance is variable and includes solitary nodules on the scalp [2], and bilateral soft tumours in the axillae or upper chest [3–6]. In a patient with focal dermal hypoplasia, the lesions comprised multiple papules in the sternal area [7]. Histologically, true apocrine naevi comprise large numbers of mature apocrine glands extending from the upper dermis to the subcutaneous fat. Decapitation secretion and periodic acid–Schiff (PAS)-positive diastase-resistant granules in the luminal cells differentiate apocrine from eccrine gland differentiation [8]. There is only one report of malignant transformation: an apocrine gland carcinoma was excised within an area of skin histologically consistent with apocrine nevus, but a preceding clinical lesion was not described [9].

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Naevus syringocystadenomatosus papilliferus

SYN. SYRINGOCYSTADENOMA PAPILLIFERUM

Definition. Naevus syringocystadenomatosus papilliferus is a skin hamartoma with predominantly apocrine differentiation.

Aetiology. The histogenesis of these lesions is controversial. They show features of apocrine glands, or occasionally eccrine glands. However, associated hamartomatous malformations of hair follicles and sebaceous glands are common [1], and naevus syringocystadenomatosus papilliferus is a frequent component of sebaceous naevi [2]. Yamamoto *et al.* [3] postulated an origin in pluripotent cells on immunohistochemical and ultrastructural grounds. Boni *et al.* [4] showed mutations in *PTCH* or *P16* tumour suppressor genes in syringocystadenoma papilliferum.

Pathology. Histologically, a number of cystic invaginations extend downwards from a papillomatous epidermis. Numerous villous papillary projections extend into the lumen of the lower portion of these invaginations [1,2,5–9]. Both the invaginations and the papillary projections are lined by a glandular epithelium, comprising an inner cylindrical and an outer cuboidal layer; the latter occasionally demonstrating 'decapitation' secretion. Apocrine glands are prominent deep in the dermis below the invaginations, and the two can be shown by serial sectioning to be connected [9]. An inflammatory infiltrate is present, particularly in the stroma of the papillary projections, which typically is composed almost entirely of plasma cells. Secondary basal cell carcinoma has been reported in about one in 10 cases of this type [2].

Clinical features. These lesions occur either as a nodular plaque, a linear group of nodules, or as a solitary nodule [1,2,10,11]. The plaque and linear varieties are usually present at birth, or appear during infancy, while the less common solitary nodular form usually develops at puberty. The plaque form is most characteristically seen as a hairless area in the scalp, while the linear form is more often seen on the neck or face. These lesions will generally become more elevated and nodular, verrucous or crusted at puberty. Such lesions closely resemble sebaceous naevi. Close examination of a mature lesion demonstrates that it comprises clusters of generally pinkish brown nodules 2–10 mm in diameter, some of which have a central opening. The solitary nodular form predominates on the trunk, where it favours the shoulders, the axillae and genital areas. Occasionally it occurs on the limbs. Each nodule is up to 1 cm in diameter, domed, umbilicated or pedunculated, often having a friable or crusted surface. Several lesions may be scattered over an area.

Ulceration or rapid enlargement may indicate malignant transformation, usually a basal cell carcinoma [2], but occasionally a squamous carcinoma [12]. In the majority of such cases, there is a coexistent sebaceous naevus.

Naevi of this histological type may be associated with non-cutaneous abnormalities (see epidermal naevus syndrome).

Diagnosis. The plaque and linear forms on the head and neck may be difficult to distinguish clinically from the closely related and commoner sebaceous naevus, although syringocystadenoma papilliferum tends to be pinker and more nodular. The umbilication of individual nodules, particularly in the linear form, may cause some confusion with molluscum contagiosum [10].

Management. Because of the not infrequent development of secondary basal cell carcinoma, these lesions should be excised wherever possible. Pulsed carbon dioxide laser treatment of a surgically difficult lesion in and below the ear in a $2^1/_2$-week-old baby produced 'reasonable cosmesis' with minimal recurrence at 3 years [13].

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Eccrine naevi

Pure eccrine naevi

SYN. NAEVUS SUDORIFERUS; SUDORIFEROUS HAMARTOMA

Although an eccrine component is a not-infrequent feature of sebaceous naevus, purely eccrine naevi appear to be very rare, with fewer than 20 cases reported in the literature. The clinical appearance is variable. In one case a solitary pore that discharged a mucoid secretion showed histologically numerous coils, comprising both secretory and ductal elements, situated deeply in the dermis and leading to a central dilated pore on the surface [1]. A second comprised an otherwise unremarkable area of diffusely increased sweat production, with histologically prominent eccrine glands, which has been termed 'naevus sudoriferus' [2,3]. Other cases have taken the form of a small plaque [4], a congenital perianal skin tag [5], and grouped skin-coloured or brown papules, sometimes in a linear distribution [6].

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Eccrine angiomatous naevus

SYN. ECCRINE ANGIOMATOUS HAMARTOMA; SUDORIPAROUS ANGIOMA

Definition. Eccrine angiomatous naevus is a rare condition characterized histologically by numerous eccrine structures and capillary channels, most commonly found in acral skin where eccrine glands are numerous. The term covers a spectrum of lesions ranging from the predominantly angiomatous 'sudoriparous angioma' [1] up to the normally vascularized nevus sudoriferus.

Pathology. Histologically, lesions show nests of large, but otherwise normal eccrine glands [2], enmeshed in loose fibrous tissue, which contains numerous thin-walled blood vessels and lymphatics [3]. There may be a very intimate association between the glandular and vascular elements [4,5]. The overlying epidermis may be mildly acanthotic. Other components, particularly hair follicles, may also be closely associated with the eccrine angiomatous complexes [6,7]. Some have shown lipomatous involvement [8]. Immunohistochemical findings are similar to normal eccrine glands [8].

Clinical features [1–11]. These lesions are present at birth or arise during childhood in 77% of cases and affect both sexes equally [8,12]. They take the form of a nodule or plaque, often with a bluish colour and angiomatous appearance. Eighty per cent occur on the extremities [12], particularly the palm and sole, but also on other parts of the feet, on the face, neck and on the trunk. Occasionally, there are multiple lesions [1,12,13]. Most are painful on pressure [3,8,14]. Some demonstrate hypertrichosis and/or hyperhidrosis, but not all [15]. Generally, they enlarge very gradually; more rapid growth has been described during pregnancy and adolescence [16]. One atypical case presented at the age of 73 years, on the buttock, and was verrucous [17]. There have been no reported complications.

Treatment. Painful lesions may require removal, particularly those on the palm or sole; this has been successfully achieved by deep excision with full-thickness grafting [3], or by amputation [16]. Pulsed dye laser was helpful in only one of two patients [18].

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Porokeratotic eccrine ostial and dermal duct naevus

Definition. Porokeratotic eccrine ostial and dermal duct naevus (PEODDN) is a localized area of plugged pores usually on the palm or sole. It has been recognized only since 1980 [1], early cases having been reported as comedo naevus of the palm [2], or linear eccrine naevus with comedones [3]. Several cases have been reported since [4–15].

Aetiology. This is presumably a mosaic defect. As for comedo naevus, debate centres on whether the primary abnormality involves the epidermis or the appendage. Staining with carcinembryonic antigen (CEA) which labels the acrosyringium and dermal eccrine duct suggests that PEODDN represents an abnormally keratinizing epidermal invagination traversed by an acrosyringium-like duct, rather than a primary abnormality of the acrosyringium and dermal duct [11].

Pathology. Histologically, these lesions are characterized by dilated comedo-like epidermal invaginations filled with parakerotic plugs. The neighbouring epidermis demonstrates parakeratotic columns, which protrude above the rest of the stratum corneum. The granular layer is absent at the base of these columns, and in the lining of the comedo-like structures; keratinocytes with vacuolated cytoplasm and pyknotic nuclei may also be a feature. In the lower portion of the invaginations, intraepidermal eccrine ducts are generally visible, and there may be associated hyperplastic intradermal eccrine ducts with comma-shaped extensions.

Clinical features. The lesions are asymptomatic and are usually present from birth, although onset later in childhood is reported in 26% [12]. PEODDN resembles comedo naevus, comprising small keratotic papules, with a central plugged pit, in a linear distribution, usually on the palms and soles [13]. At other sites, the lesions tend to be more verrucous, resembling verrucous epidermal naevi, sometimes with filiform vegetations. PEODDN is occasionally quite extensive [1]. Involvement of all four limbs has been reported [10]. The lesions may be anhidrotic [1] or hyperhidrotic [2]. There are no known associated abnormalities.

Diagnosis. The entity described as *porokeratotic eccrine duct and hair follicle nevus* [16,17] is probably very closely related, the only real distinction being that hair follicles were affected as well as eccrine sweat ducts. Comedo naevi can be distinguished histologically, because they lack the characteristic intraepidermal and dermal eccrine ducts, and the parakeratotic columns. This disorder also appears to be distinct from *punctate porokeratosis* [18–20] in which multiple punctate seed-like keratoses and/or pits are present on the palms and soles, occasionally in a linear configuration, and sometimes associated with linear porokeratosis. Punctate porokeratosis does not resemble comedones, either clinically or histologically, and the cornoid lamellae are not obviously associated with eccrine duct ostia.

Treatment. As for other epidermal naevi, simple excision is usually the treatment of choice. An adult-onset lesion on the hand resistant to topical keratolytics and cryotherapy responded to four treatments with the carbon dioxide laser and remained clear 9 months later [14].

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Becker's naevus [1]

SYN. BECKER'S MELANOSIS; PIGMENTED HAIRY EPIDERMAL NAEVUS

Definition. An acquired and persistent asymmetrical area of skin pigmentation, sometimes showing evidence

of increased androgen sensitivity, and colocalizing with other developmental anomalies.

Aetiology. The sporadic occurrence and asymmetrical distribution of most Becker's naevi suggest cutaneous mosaicism. Indeed, chromosomal mosaicism was reported in one patient with Becker's naevus [2]. The lack of conformity to Blaschko's lines may be due to the relatively late occurrence of a causative mutation (see above). The mutant skin clone is presumably predisposed not only to pigmentation but also to androgen sensitivity, since Becker's naevus is prone to acne and hypertrichosis [3]. While most cases occur sporadically, Becker's naevus has been reported in siblings [4], father and son [5], and uncle and nephew [6]. As discussed above, familial occurrence of a mosaic disorder can be reconciled with mosaicism by mechanisms such as inheritance of an unstable premutation, paradominant inheritance [7] and chance. Colocalization with other developmental anomalies suggests a clonal defect in morphogenesis. Becker's naevus may be pathogenetically related to congenital smooth muscle hamartoma, which also shows hypertrichosis, hyperpigmentation and increased smooth muscle, albeit in different proportions [5].

Clinical features. Becker's naevus is a relatively common anomaly found in about 0.5% of young men, affecting most racial groups, and is about five times more frequent in males than females [8]. It may present in childhood, but is usually first noticed during adolescence, initially pale in colour and becoming more conspicuous after sun-exposure. The usual site is shoulder, anterior chest or scapular region, but lesions on face, neck and distal limbs have been reported [8,9]. It starts as an area of irregular macular pigmentation, which spreads to a diameter of several centimetres, new macules developing beyond the margin and fusing with it, giving a geographical contour. Later, thick, dark hairs may appear, on and around the lesion. The skin may thicken towards the centre of the lesion. Once present, Becker's naevi remain indefinitely.

Becker's naevus is more prone to acne vulgaris than the adjacent normal skin [3,10–12]. Tinea versicolor localized to a Becker's naevus has also been reported [13]. In one patient lichen planus was confined to a large Becker's naevus affecting the whole of one lower limb [14]. Other cutaneous anomalies may occur in the affected area, for example lymphangioma [15].

Although Becker's naevi generally occur without any associated pathology, several ipsilateral developmental abnormalities have been described, particularly breast hypoplasia [9,12,16–18] and supernumerary nipples [19], and also aplasia of the pectoralis major muscle [20] limb reduction [9], segmental odontomaxillary dysplasia [21] and lipoatrophy [17]. Spina bifida [16,22], scoliosis [20], pectus carinatum [16], congenital adrenal hyperplasia [2] and an accessory scrotum [23] have also been reported. The term *Becker's naevus syndrome* has been proposed to describe the association of a Becker's naevus with ipsilateral non-cutaneous abnormalities [18,24].

The possibility of an increased risk of malignant melanoma in patients with Becker's naevus was raised in a recent report [25].

Pathology. Histological changes may be subtle. Well-developed lesions show hyperkeratosis, acanthosis and papillomatosis, with hyperplasia of hair follicles and sebaceous glands. The basal and suprabasal keratinocytes are heavily pigmented, and melanocyte density is variably reported as increased [26] or normal [27], with a few melanophages in the upper dermis. There are no junctional or intradermal naevus cells. The dermis is thickened, and contains numerous, but often inconspicuous, bundles of smooth muscle fibres, unrelated to hair follicles or blood vessels [27]. Ultrastructurally there is evidence of enhanced melanin synthesis, with increased melanocyte activity and increased numbers of melanosome complexes in keratinocytes [28,29]. Giant melanosomes have been reported both in melanocytes and keratinocytes [30]. Increased numbers of androgen receptors [3] and androgen receptor messenger RNA (mRNA) [31] have been found in lesional skin.

Diagnosis. A well-developed Becker's naevus is unmistakeable. In early lesions, age of onset, geographical outline and site help to distinguish Becker's naevus from a café-au-lait macule and from linear and whorled naevoid hyperpigmentation. Whether *progressive cribriform and zosteriform hyperpigmentation* [32] should be regarded as a non-hypertrichotic variant of Becker's naevus is unclear.

Treatment. Benefit from the Q-switched ruby laser has been reported [33], but reactive patchy hyperpigmentation may recur [34]. In a 27-year-old man, three treatments with the 694-nm long-pulsed ruby laser decreased hair density as well as pigmentation, the improvement lasting for the 10 months of follow-up [35].

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Inflammatory epidermal naevi

Inflammatory linear verrucous epidermal naevus (ILVEN) and CHILD naevus present at or soon after birth and usually persist lifelong. They can thus be distinguished from naevoid variants of inflammatory dermatoses which occur later and often resolve, including linear lichen planus, naevoid psoriasis, lichen striatus and adult Blaschkitis. However all comprise hyperkeratotic lesions following Blaschko's lines, with histological evidence of inflammation. Probably all reflect genetic mosaicism, the former for potentially lethal dominant mutations rescued by mosaicism, and the latter for multifactorial dermatoses with an autosomal dominant component.

Inflammatory linear verrucous epidermal naevus

SYN. DERMATITIC EPIDERMAL NAEVUS

Definition. A pruritic, erythematous scaly lesion following Blaschko's lines [1].

Aetiology. ILVEN is probably due to mosaicism for a dominant mutation, as yet unidentified, which would be lethal if it affected all cells and is 'rescued' by mosaicism [2]. More recently Happle [3] has suggested that linear skin disorders such as ILVEN might reflect the action of a retroviral transposable element ('retrotransposon') that is partly expressed and partly silenced at an early developmental stage. ILVEN is usually sporadic, in keeping with both hypotheses, but there have been reports of familial cases, including two in which mother and daughter were affected [4,5] and one involving mother, two sons and (reportedly) maternal grandfather [6]. Two cases in patients positive for human immunodeficiency virus 1 (HIV-1) [7], suggested clonal dysregulation of growth triggered by infection. However, the histology of these two lesions resembled psoriasis, which is known to be associated with HIV infection. Absent involucrin expression in the parakeratotic epidermis has been reported, a finding that appears to distinguish ILVEN from psoriasis [8].

Pathology. The characteristic histology shows columns of hypergranulosis with orthokeratotic hyperkeratosis alternating with equally well-defined columns of agranulosis and parakeratotic hyperkeratosis [9,10]. Other cases simply show a rather psoriasiform chronic eczema. Spongiosis is occasionally seen. An associated upper dermal lymphohistiocytic inflammatory infiltrate is regularly present.

Clinical features. About 75% of ILVENs appear during the first 5 years of life, most often in the first 6 months, although later onset has been recorded [4,5,11–13]. They are characterized by pruritus, which may be intense. The lesions are linear, most commonly on a limb, and comprise eczematous or psoriasiform papules (Fig. 15.4). ILVEN can be of any length, occasionally extending the whole length of a limb. As with other epidermal naevi, nail dystrophy may occur when the nail fold is affected [14]. Occasionally ILVEN is bilateral and widespread [12,14–16]. Occasional reports of limb reduction anomalies associated with ILVEN on the adjacent skin have led to the

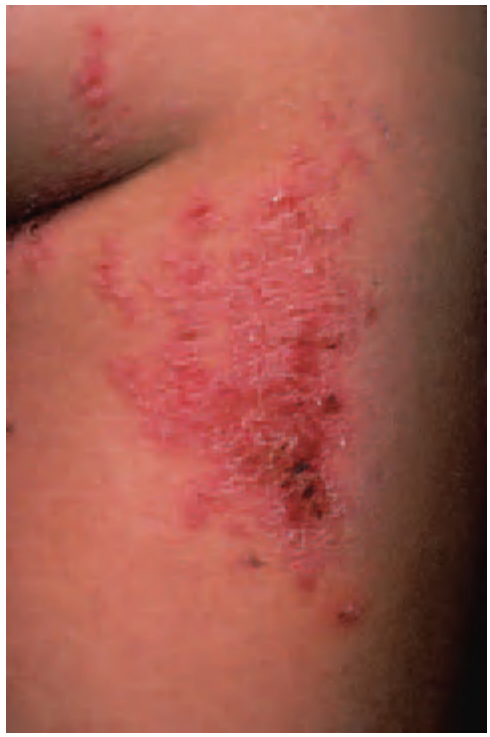

Fig. 15.4 Inflammatory linear verrucous epidermal naevus on the posterior thigh.

suggestion that ILVEN represents a limited form of CHILD naevus. Accordingly, it has been suggested that ILVEN and CHILD would more appropriately be named, respectively, PEN and PENCIL, indicating *p*soriasiform *e*pidermal *n*aevus with or without *c*ongenital *i*psilateral *l*imb defects [17]. A report of two girls with ILVEN and arthritis suggested a new association [18], but linear psoriasis with psoriatic arthropathy seems a more likely diagnosis for their symmetrical, distal, methotrexate-responsive arthritis, particularly since skin histology was not reported.

Although generally persistent and resistant to treatment, some lesions have been reported to resolve spontaneously [11].

Differential diagnosis. Earlier reports confused ILVEN with naevoid psoriasis, and with epidermal naevi in which psoriasis had developed as an isomorphic phenomenon [19–22]. Several patients have been reported in whom naevoid psoriasis and ILVEN both appeared to be present [23–25]. In one patient, transient inflammation of the ILVEN coinciding with an outbreak of guttate psoriasis probably reflected koebnerization of psoriasis by the ILVEN [25]. ILVEN can be distinguished from true naevoid psoriasis by pruritus and lack of response to antipsoriatic treatments [23,26]. Sodium dodecyl sulphate polyacrylamide gel electrophoresis (SDS-PAGE) has allowed the identification of stratum corneum fibrous polypeptide patterns that are distinct from that seen in psoriasis, but it is doubtful whether this will prove a useful test in normal clinical practice [27,28]. Lichen striatus is distinguished by its rapid development, generally after the first year of life, by its relative lack of pruritus, by its more lichenoid clinical and histological features, and, eventually, by its spontaneous involution. The distinction between CHILD syndrome and ILVEN is uncertain [29,30].

Treatment. ILVEN is notoriously resistant to treatment, although occasionally spontaneous resolution occurs. Potent topical corticosteroids applied under occlusion, or intralesional steroid injections, provide little more than temporary symptomatic relief [13]. Similarly, topical retinoids appear to provide no benefit [31]. Successful treatment with dithranol [23] has been reported. Calcipotriol or tacalcitol in some cases merely reduce the redness and itching, while in others have produced prolonged clearance [32–36]. Cryotherapy may be a reasonable approach, particularly for smaller lesions [37]. Surgical excision tends to be followed by rapid recurrence unless a generous depth of underlying dermis is removed [14,38]. Successful treatment has been reported with the flashlamp-pumped pulsed tunable dye laser [39]. ILVENs treated with the carbon dioxide resurfacing laser have remained clear for 2 years of follow-up [40,41], but this laser is less effective for ILVEN than for non-inflammatory verrucous epidermal naevi [41].

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The CHILD naevus

Definition. CHILD is an acronym for *c*ongenital *h*emidysplasia with *i*chthyosiform naevus and *l*imb *d*efects [1]. Internal organs are often hypoplastic on the affected side. The CHILD naevus is the characteristic skin lesion observed in this disorder.

Aetiology. CHILD syndrome is an X-linked dominant trait, with a strong female predominance and antenatal lethality in males. Survival of a karyotypically normal male can be attributed to a somatic mutation on the X chromosome [2]. It is usually sporadic but has been reported in a mother and daughter [3]. Initially it was thought to be allelic to X-linked dominant Conradi–Hünermann syndrome. Both conditions share the clinical features of linear scaling and asymmetric limb reductions. Both have shown peroxisomal deficiency in fibroblasts from involved areas of skin [4] and elevated plasma 8-dehydrocholesterol and 8(9)-cholestenol levels [5]. Grange *et al*. [5] indeed found, in a patient with CHILD syndrome, a nonsense mutation in the X-linked dominant Conradi–Hünermann syndrome gene, 3β-hydroxysteroid-δ8,δ7 isomerase, or emopamil binding protein (EBP). The EBP gene is located at Xp11.22–23. However, this finding has not been repeated, and Grange's patient may in fact have had the X-linked dominant Conradi–Hünermann syndrome, a diagnosis in keeping with her widespread punctate calcifications of bones and improvement in her ichthyosis. Simultaneously, Konig *et al*. [6] found, in both sporadic and familial patients with CHILD syndrome, mutations in *NSDHL* (NAD(P)H steroid dehydrogenase-like protein) gene at Xq28. *NSDHL* functions upstream of EBP in cholesterol biosynthesis. *NSDHL* mutations in mice produce the 'bare patches' and 'striated' phenotypes [7]. The extreme lateralization of CHILD syndrome contrasts with symmetry of X-linked dominant Conradi–Hünermann syndrome and has not yet been explained satisfactorily. CHILD syndrome might be an extreme form of ILVEN, an alternative name covering the whole spectrum being PEN or PENCIL [8]. This idea has been contested by Happle [9]. It could now be tested, knowing the defect in CHILD syndrome.

Pathology. Light microscopy [10] shows marked acanthosis, and areas of parakeratosis within a largely orthokeratotic epidermis. There is exocytosis of neutrophils, with focal collections resembling Munro microabscesses. The dermis contains a patchy lymphohistiocytic infiltrate. Some biopsies, particularly those taken from flexural sites, may show enlarged dermal papillae containing foamy lipid-laden histiocytes (verruciform xanthoma) [9,11–13]. Although verruciform xanthoma is very characteristic of CHILD naevi, it can also occasionally be seen in severe dystrophic epidermolysis bullosa and pemphigus vulgaris, and it may also be a feature of biopsies taken from the mouth, vulva or penis.

Ultrastructurally [10,12], many corneocytes contain lipid vacuoles. Vesicular structures are seen in the intercellular spaces of the epidermis, and become more numerous as

cornification progresses. Large intracytoplasmic vacuoles are seen within papillary dermal foamy cells.

Clinical features. Most affected individuals are female. CHILD naevi are generally present at birth, but occasionally first develop during the first few months of life or even later. Lesions may extend during life, and rarely partly disappear. The lesions are generally asymptomatic, comprising well-circumscribed areas of erythema covered in waxy scales, sometimes with a verrucous surface. There is a marked preference for flexural areas (*ptychotropism*) [14], where oozing vegetations may develop. Characteristically, lesions are confined or concentrated on one side of the body, with sharp midline demarcation. In more severe cases, one side of the body may be diffusely affected, generally but not always [15] with sparing of the face and the oral mucosa. In other patients, the distribution is more streaky, with lesions following Blaschko's lines, but not uncommonly both linear and diffuse unilateral patterns coexist in the same patient. Konig *et al.* [16] reported bilateral, almost symmetrical involvement in a woman with a novel missense mutation of *NSDHL*.

A wide variety of non-cutaneous anomalies have been reported in the CHILD syndrome [1,15,17,18]. Unilateral bone defects are particularly characteristic, and most likely to affect the long bones. The severity of limb lesions varies from hypoplasia of a few metacarpals or phalanges to complete absence of an entire limb. Hands or feet may be grossly deformed. Scoliosis may be present. In some cases, punctate epiphyseal calcifications have been shown radiologically in the first few months after birth; these disappear later.

Unilateral hypoplasia of the brain, cranial nerves or spinal cord may be present, with mental retardation, electroencephalogram (EEG) abnormalities and sensory defects.

Congenital cardiac defects may be present, and are perhaps the main cause of early death of children with the CHILD syndrome. Other anomalies of the kidneys, lungs and other internal organs have been described.

Diagnosis. Naevoid psoriasis, ILVEN and epidermal naevus syndrome can be confused with CHILD syndrome. Psoriasis is less persistent and does not show waxy scales clinically or verruciform xanthoma histologically. In contrast to CHILD naevi, ILVEN does not show flexural preference, and tends to be exclusively linear. The distinction from epidermal naevus syndrome is perhaps semantic. CHILD syndrome when first delineated had to be distinguished from epidermal naevus syndrome as it was then understood [19–21]. More recently, Happle has reclassified CHILD syndrome as an epidermal naevus syndrome [22].

Treatment. CHILD naevi appear to be highly refractory to all treatment, except occasionally oral retinoids [3].

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Other naevoid epidermal disorders

Several generalized dermatoses occasionally follow Blaschko's lines, probably reflecting a clonal 'susceptibility mutation'. Linear lichen planus, psoriasis, Darier's disease, Hailey–Hailey disease, porokeratosis, atrophoderma of Moulin, and 'adult Blaschkitis' or BLAISE (*B*laschko *l*inear *a*cquired *i*nflammatory *s*kin *e*ruption) are described

below. Linear lichen nitidis [1], lichen striatus (eczema) [2], segmental vitiligo [3] and linear morphoea [4] are discussed elsewhere in relation to the appropriate generalized disorder. The following have also been reported in a linear or naevoid distribution: linear lupus erythematosus [5], linear fixed drug eruption [6] and linear chronic graft-versus-host disease [7].

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Linear lichen planus

Some epidermal naevi show, in addition to histological features compatible with verrucous epidermal naevus, a lichenoid band-like lymphohistiocytic infiltrate at the dermal–epidermal junction, plus Civatte bodies and dermal melanophages [1]. Clinically such lesions resemble lichen planus except in their linear distribution. They can occur at any age and resolve leaving post-inflammatory pigmentation. If they exend to the end of a digit there may be associated nail dystrophy, and similarly there may be mucous membrane involvement [2]. Linear lichen planus is sometimes mutifocal [3] and in one female recurred three times after successive deliveries [4]. It seems likely that this entity represents lichen planus localized to Blaschko's lines by a clonal 'susceptibility mutation'.

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Naevoid psoriasis

Psoriasis rarely occurs in a 'naevoid' form, possibly reflecting mosaicism for a gene responsible for psoriasis [1]. The lesions present in the 6-year-old boy whose case was reported appeared clinically and histologically indistinguishable from ordinary psoriasis other than in their distribution. The lesions could be distinguished from invasion of a verrucous epidermal naevus by psoriasis as a result of the isomorphic phenomenon [2–5] and from dermatitic epidermal naevi, by their minimal pruritus and their therapeutic response to ultraviolet radiation. Further similar cases have been reported [6,7]. In one case, topical dithranol was therapeutically beneficial [8]; this patient appeared to have a small coexisting dermatitic epidermal naevus, which failed to respond to this treatment. Linear psoriasis is easily confused with ILVEN (see above).

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Linear Darier's disease

SYN. ACANTHOLYTIC DYSKERATOTIC EPIDERMAL NAEVUS

Several cases have been reported of acantholytic epidermal naevi comprising crusted keratotic papules, clinically and histologically resembling those seen in Darier's disease [1–8]. Such naevi appear relatively late, frequently after the age of 20 years [1], in individuals who lack a family history of Darier's disease. The lesions can extend over many years and are aggravated by UV exposure [1,3]. If the affected area includes the nails, typical nail changes of Darier's disease may occur [4], and if the hands are affected, pits and keratoses may be observed within the involved zone [4].

The suggestion that such naevi represent mosaicism for Darier's disease has now been confirmed by finding a mutation in the Darier's disease gene *ATP2A2* in the naevus, but not in unaffected skin [7].

Treatment is as for other linear epidermal naevi. It appears that topical retinoic acid may be useful [1], and it would be anticipated that oral acitretin might be of value where the distribution is extensive.

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Linear Hailey–Hailey disease

SYN. RELAPSING LINEAR ACANTHOLYTIC DERMATOSIS

A distinctive form of epidermal naevus has been reported, in which well-defined linear erythematous plaques demonstrate vesiculation, erosion and crusting, and the typical histological features of benign familial chronic pemphigus (Hailey–Hailey disease) [1,2]. This type of naevus appears to have an early onset, and a highly characteristic course, with periods of spontaneous improvement followed by relapse.

The suggestion that such naevi represent mosaicism for Hailey–Hailey disease can now be tested by seeking a mutation in the Hailey–Hailey disease gene *ATP2C1* [3] in the naevus but not in unaffected skin.

Curiously, the 5-year-old patient reported by Vakilzadeh [1] apparently inherited the condition from her mother and grandmother. In the older generations, the disease was manifest only in the perianal area. A possible explanation is that the Hailey–Hailey mutation was transmitted in the usual autosomal dominant manner, with limited flexural disease presenting in early adult life, while the child was mosaic for a loss-of-heterozygosity (Happle type 2 mosaicism [4]), and accordingly developed more severe and earlier onset disease in a linear distribution.

A single case of a distinctive type of keratinocyte naevus has been reported as 'naevus corniculatus' [5]. Clinically, the naevus featured filiform and horn-like keratoses, and giant comedones. Histologically, the lesion showed acantholytic changes more closely resembling those seen in Hailey–Hailey disease than in Darier's disease.

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Linear porokeratosis

Definition. This naevus, distributed along Blaschko's lines, is characterized by annular plaques clinically and histologically indistinguishable from the lesions of generalized porokeratosis [1].

Aetiology. Linear porokeratosis probably reflects mosaicism for a gene responsible for generalized porokeratosis. This idea is supported by the fact that the generalized forms of porokeratosis (porokeratosis of Mibelli, disseminated superficial actinic porokeratosis (DSAP), and porokeratosis plantaris palmaris et disseminata) can be inherited as autosomal dominant genes, whereas the linear variant usually occurs sporadically. The report of linear porokeratosis in monozygotic twins [2] can be reconciled with the idea of mosaicism by postulating that the somatic mutation in the porokeratosis gene occurred before the twinning division, so that the aberrant clone was present in both embryos. Reports of pre-existing linear porokeratosis in patients later developing DSAP [3–7], and the occasional occurrence of linear porokeratosis in the children or siblings of patients with DSAP [3,4,8] can be explained by loss of heterozygosity for this dominant gene, that is Happle type 2 mosaicim [9]. According to this hypothesis, an individual with inherited generalized porokeratosis undergoes a somatic mutation in the normal allele resulting in clonal loss of heterozygosity. The resultant line contrasts with the background skin because it has 'double the dose' of porokeratosis. Skin cancers in porokeratosis are particularly associated with the linear variant [10–12], in keeping with Happle's suggestion of loss of heterozygosity [9]. The role of *p53* is uncertain: overexpression of *p53* has been reported in linear porokeratosis [13,14] and in a superimposed squamous carcinoma, but not in the adjacent porokeratosis [12].

Generalized porokeratosis can be provoked by immune suppression [1]. Hunt *et al*. [15], however, reports exacerbations of linear porokeratosis during episodes of liver failure, and improvement following transplantation.

Clinical features. The lesions of linear porokeratosis comprise grouped hyperkeratotic plaques, each with a fine, rounded, annular rim and an atrophic centre. Lesions may be hyper- or hypopigmented and/or erythematous, and are disposed in an interrupted linear fashion along Blaschko's lines [16–23]. The lesions are often present at

birth, when they may be ulcerated [24]. Occasional spontaneous resolution has been described [25,26], but generally the lesions are lifelong, with increasing hyperkeratosis and a definite predisposition to skin cancer within the lesions [10].

Management. A variety of treatments have been used with variable success; of these the most consistently successful have been surgical excision [10,17,27] and ablation with the carbon dioxide laser [16]. Other helpful treatments have included cryotherapy [28], dermabrasion [27,29], oral retinoids [30,31], topical 5-fluorouracil [32], vitamin D analogues, urea [20] and dithranol [2]. In one case, etretinate worsened the porokeratosis [33].

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Linear atrophoderma of Moulin

In some patients, clearly demarcated cutaneous atrophy and pigmentation with minimal inflammation and sclerosis is distributed along Blaschko's lines [1]. This might represent a late 'burnt out' stage of linear morphoea, since some inflammatory cells are usually present.

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Adult Blaschkitis

SYN. BLASCHKO LINEAR ACQUIRED INFLAMMATORY SKIN ERUPTION; BLAISE

This remitting and relapsing eruption of itchy inflammatory vesicles and papules occurs usually on the trunk in adults [1]. The histology is more eczematous (spongiotic) than lichenoid. It would be difficult to distinguish from linear Grover's disease [2]. Taieb *et al*. [3] considered that 'adult Blaschkitis' represents an adult version of lichen striatus, and proposed the acronym BLAISE to cover both. BLAISE should perhaps be regarded as a description rather than a diagnosis, a useful category for many of the disorders in this section, pending more precise identification.

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The epidermal naevus syndromes

Non-epidermolytic epidermal naevi can be associated with a wide range of abnormalities in other systems (epidermolytic verrucous epidermal naevi are not, as the causative keratin gene mutations are expressed only in skin). Historically [1,2], the term 'epidermal naevus syndrome' referred to the association of sebaceous naevus with neurological, ocular and sometimes other abnormalities. Later, the term was extended to cover almost any multisystem disorder featuring sebaceous or verrucous epidermal naevus [3]. More recently, Happle has used the term 'the epidermal naevus syndromes' to include at least six separate disorders, namely: Schimmelpenning's syndrome, Proteus syndrome, comedo naevus syndrome, CHILD syndrome, Becker's naevus syndrome and phakomatosis pigmentokeratotica [4,5]. This has created two difficulties: firstly, most dermatologists would not regard Becker's naevus as an epidermal naevus; secondly, changing the meaning of 'epidermal naevus syndrome' leaves us without a name for the entity well established in the literature as 'epidermal naevus syndrome', none of the historical eponyms being satisfactory.

Therefore, this account maintains the original and well-established use of the term 'epidermal naevus syndrome' as 'the association of sebaceous and/or verrucous epidermal naevi with other developmental defects, particularly of the CNS, eye and skeleton'. It does not include syndromes where the naevus is not a sebaceous or verrucous epidermal naevus (e.g. Becker's naevus, CHILD naevus). Neither does it include those conditions which have been clearly defined in molecular terms (comedo naevus syndrome), or which feature epidermal naevi but are sufficiently distinctive to merit their own name (Proteus syndrome and phakomatosis pigmentokeratotica). It remains a heterogeneous group, within which further conditions will be defined in the future. Eventually, when all the different mutations responsible for epidermal naevus syndrome have been defined, the term will become redundant, but for the moment it remains useful.

Epidermal naevus syndrome

SYN. SEBACEOUS NAEVUS SYNDROME; SCHIMMELPENNING'S SYNDROME; FEUERSTEIN–MIMS SYNDROME; EPIDERMAL NAEVUS SYNDROME; ORGANOID NAEVUS SYNDROME; JADASSOHN'S NAEVUS PHAKOMATOSIS

Definition. Epidermal naevus syndrome describes the association of sebaceous and/or verrucous naevi with other developmental defects, particularly of the central nervous system (CNS), eye and skeleton, first reported by Feuerstein and Mims [1] and Schimmelpenning [2]. Other authors have used the term *Jadassohn's naevus phakomatosis* to describe this association [6]. Although early reports only included sebaceous naevi, the term is now used to include patients with verrucous naevi. The associations with both types of naevi are very similar, and some patients have both verrucous and sebaceous naevi, differentiation depending largely on the site, lesions on the head and neck being more often sebaceous [7].

Aetiology. Epidermal naevus syndrome is a sporadic disorder, probably reflecting genetic mosaicism for an autosomal dominant mutation which would be lethal if not 'rescued' by mosaicism [8]. To explain discordance in monozygotic twins, the mosaicism must have arisen after conception [9] and after the division into twin zygotes. The limited involvement (right eye and right side of the scalp only) in the affected twin [9] is also consistent with a relatively late mutation. Occasional occurrence in successive generations can be explained by inheritance of an unstable pre-mutation, or by loss of heterozygosity for a recessive mutation ('paradominant inheritance' [10]).

Clinical features. The cutaneous element of epidermal naevus syndrome can be sebaceous naevus, verrucous epidermal naevus [3,7,11–13] or syringocystadenoma papilliferum [14]. The naevus may grow abnormal hair, such as woolly hair [15], long, pale 'angora' type hair [16] or hair associated with follicular hyperkeratosis [17].

Additional cutaneous abnormalities seen in some patients include infantile haemangiomas, naevi flammei, hypochromic naevi, café-au-lait macules [18,19], congenital melanocytic naevi [19–21], Spitz naevi [22], follicular hyperkeratosis and dermatomegaly [11,13]. Ipsilateral facial lipoma with hemimegalencephaly has been reported in three cases of epidermal nevus syndrome [23].

Sometimes, the epidermal naevus involves the mucosae of the mouth, anus or genitalia [7,13,24,25]. Oral involvement may include dental enamel hypoplasia, malformations of the teeth and hypodontia [11,24] and maxillary giant cell granuloma [26].

Significant developmental anomalies occur in approximately 1.7% of all neonates [27] and 10% of children with epidermal naevi, the risk correlating poorly with number and extent of lesions. Skeletal deformities reported in the epidermal naevus syndrome include kyphosis, scoliosis, cystic and lytic changes, hypertrophy and atrophy, short limbs and syndactyly [7,11–13,28].

A similarly wide variety of neurological abnormalities have been identified in about 50% of patients with epidermal naevus syndrome [6,13,14,29–40]. Neurological abnormalities are much more frequent in patients who have sebaceous naevi on the head and neck [12,13,29,40], but the location of the skin lesions does not provide reliable prediction of the laterality of intracranial brain anomalies [41]. Seizures, especially infantile spasms, occur in some 50% of patients, many of whom have underlying structural abnormalities of the CNS [42]. Mental retarda-

tion also occurs in about 50% of cases; it varies in degree, but may be profound. Spastic hemiparesis affects about 20% of patients and may have its onset at any time from birth to adolescence; spastic tetraparesis has also been described. Conductive [43] and sensorineural deafness occur [11]. The commonest structural CNS abnormalities have been ipsilateral gyral malformations and complete or partial hemimegalencephaly [32,42,44–46], but others have included vascular malformations [31,35,47,48], hemiatrophy [34,37,49,50], posterior fossa abnormalities, lateral ventricle enlargement [34,51], porencephaly [52], agenesis of the corpus callosum [42] hamartoma [53] and intracranial or intraspinal lipomas [54]. Neuroimaging is surprisingly often normal, even in patients with clinical neurological abnomalities [40]. Cranial nerve palsies have also been described fairly commonly.

Some 35–70% of patients have ocular abnormalities [11,13,34,37,47–51,55–65], the commonest of which is involvement of the eyelid or conjunctiva by the epidermal naevus, sometimes causing trichiasis or interfering with lid closure. Other ocular problems have included colobomas of the eyelid, iris and retina, retinal dysplasia, conjuctival lipodermoids and choristomas. Cortical blindness, microphthalmia, macrophthalmia, anophthalmia, corneal opacities and cataracts have also been reported.

Many other non-cutaneous abnormalities have now been reported in association with epidermal naevi, including a variety of cardiac and genitourinary abnormalities [6,11,12], and endocrine disease [66,67], including inappropriate antidiuretic hormone (ADH) secretion [66] and precocious puberty [21,68,69]. In several patients, bone disease and/or muscle weakness has occurred secondary to vitamin D-resistant rickets [13,22,49,68,70–77]; some of these patients [22,74,76] have had radiolucent bone lesions, which were shown in one case to be angiomatous [76]. Debulking the epidermal naevi leads to biochemical improvement [68], suggesting that these epidermal naevi, or the associated intraosseous angiomatous tumours, secrete a substance that induces renal phosphate loss. A similar phenomenon occurs with a variety of benign mesenchymal tumours and occasionally with malignant tumours [78]. A strong candidate gene for 'phosphatonin', the postulated humoral factor responsible for tumour-induced rickets/osteomalacia, is fibroblast growth factor-23, localized to 12p13 [78]. One patient suffered both hypophosphataemic vitamin-D resistant rickets and precocious puberty [68]. An overlap has been suggested with the McCune–Albright syndrome [18], but radiologically the polyostotic fibrous dysplasia of the McCune–Albright syndrome is indistinguishable from the intraosseous angiomas reported with epidermal naevi [76].

Benign and malignant transformation may occur in these patients' epidermal naevi, exactly as it may when such naevi exist without associated abnormalities. However, insufficient attention has been drawn to the relatively high incidence of systemic malignancies that have arisen in patients with epidermal naevi, often at a very early age [13]. These have included nephroblastoma [13,28,36], salivary gland carcinomas [79], carcinoma of the oesophagus and stomach and breast [80], astrocytoma [81], glioma [82], mandibular ameloblastoma [25,83], transitional cell carcinoma of the bladder [84], rhabdomyosarcoma of the bladder [85] and intrathoracic teratoma [11].

Diagnosis. Epidermal naevus syndrome can be confused with the other epidermal naevus syndromes featuring verrucous epidermal naevi, such as Proteus syndrome, naevus comedonicus syndrome and phakomatosis pigmentokeratotica. CNS lipoma may lead to confusion with encephalocraniocutaneous lipomatosis [54].

Treatment. The management of a child with epidermal naevus requires careful clinical judgement. Most children with epidermal naevi are otherwise perfectly well and it is inappropriate to investigate a child who is thriving and developmentally normal. Parents can be informed of the 10% risk of associated abnormalities, but also reminded that most of these will be picked up on routine child health surveillance, such as problems with vision, hearing, growth and neurological development. There should be a low threshold for following up any reported problems, for example a disproportionate rise in head circumference, which may be the first sign of raised intracranial pressure. Children with epidermal naevus syndrome tend to have several associated abnormalities, so if a second developmental anomaly is detected it is appropriate to look for others. Reasonable non-invasive investigations would include ophthalmological assessment and cranial ultrasound. If the naevus is extensive, serum calcium and phosphate should be measured to exclude tumour-induced osteomalacia/rickets.

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Phakomatosis pigmentokeratotica

The concurrence of sebaceous or verrucous epidermal naevus with speckled lentiginous naevus has been called 'phacomatosis pigmentokeratotica' [1–3]. It could be argued that speckled lentiginous naevus is simply one of the many localized anomalies associated with verrucous and sebaceous epidermal naevi, and that there is no justification for separating this particular association from epidermal naevus syndrome. Multiple melanocytic naevi have frequently been reported in association with epidermal naevus syndrome (see above). Intriguingly, hypophospataemic rickets, which has been reported in several patients with multiple melanocytic naevi and widespread verrucous epidermal naevi, has occurred in phakomatosis pigmentokeratotica [2].

Happle and colleagues have argued not only that phakomatosus pigmentokeratotica is a distinct syndrome with its own spectrum of associated abnormalities, but further that the lentiginous element might occur without the verrucous element as the (so far unrecognized) 'speckled lentiginous naevus syndrome' [4]. Happle suggests that phakomatosis pigmentokeratotica represents twin-spotting [1,2,4].

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Dermal and subcutaneous naevi

Connective tissue naevi

Connective tissue naevi are circumscribed hamartomatous malformations of the dermal extracellular matrix, i.e. of collagen, elastic fibres or glycosaminoglycans [1,2]. They form a characteristic component of a number of well-defined inherited disorders, such as tuberous sclerosis and the Buschke–Ollendorff syndrome, but may also occur as isolated lesions without any identifiable genetic basis.

A wide variety of connective tissue naevi have now been described. The provisional classification in Table 15.2 is based on those proposed by Uitto *et al.* [1] and Pierard and Lapiere [2].

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Table 15.2 Classification of connective tissue naevi.

Naevi of reticular connective tissue
Collagen naevi
Familial cutaneous collagenoma
Eruptive collagenoma
Plantar cerebriform collagenoma
Shagreen patch (tuberous sclerosis)
Knuckle pads
Other collagenomas
Elastic naevi
Pseudoxanthoma elasticum
Perforating elastoma
Juvenile elastoma and the Buschke–Ollendorff syndrome
Naevus anelasticus
Other elastic naevi
Proteoglycan naevi
Mucinous naevus
Dermal nodules in Hunter's syndrome
Naevi of adventitial connective tissue
Fibrous papule of the face
Angiofibromas and subungual fibromas in tuberous sclerosis
Pearly papules of the penis
Perifollicular fibromas and trichodiscomas

Collagen naevi

Familial cutaneous collagenoma

Several families have been reported showing autosomal dominant inheritance of a condition termed *familial cutaneous collagenoma* [1–3]. Similar skin lesions have also been reported under this title in the absence of documented family involvement [4].

Affected individuals present with multiple, asymptomatic, indurated dermal nodules distributed symmetrically on the trunk and upper arms, but particularly on the upper two thirds of the back. Individual lesions vary in diameter from a few millimetres to a few centimetres. The condition generally first becomes manifest during adolescence, and an increased rate of appearance of new lesions has been noted during pregnancy.

Histologically, the nodules showed an accumulation in the dermis of dense, coarse collagen fibres, with an apparent reduction in the number of elastic fibres.

Cardiological abnormalities were reported in some of these patients, and the suggestion was made that these might be a reflection of fibrosis within the heart.

None of these patients have had osteopoikilosis, distinguishing this disorder from the Buschke–Ollendorff syndrome.

Eruptive collagenoma

Other cases have been reported in which cutaneous nodules, more or less indistinguishable from those seen in familial cutaneous collagenoma, have arisen in the absence of any family history. The term *eruptive collagenoma* has generally been applied to such cases, because of the abrupt development of these lesions [5–10]. The same term has been used, however, for cases which would seem, on clinical and histological grounds, to fall more correctly into the category of *lichen myxoedematosus* [11].

Plantar cerebriform collagenoma

This rare lesion, imaginatively termed 'paving-stone naevus' [12], comprises a flesh-coloured cerebriform mass on the sole of variable size. Although this condition may occur in isolation [13–15], it is probably more often a component of the Proteus syndrome, in which they would be associated with a variety of other anomalies including macrodactyly and hemihypertrophy [16–18].

Tuberous sclerosis

The shagreen patch is a mamillated plaque-type collagenoma occurring, most often in the lumbosacral area, as a common and highly characteristic component of tuberous sclerosis [19–21].

Other collagenomas

A variety of other clinical types of collagenous connective tissue naevus have been described [22–25]. Association with Down's syndrome [22] has been recorded. A large collagenoma resembling a shagreen patch has been reported in a patient with multiple fibrofolliculomas [26]. A family has been reported in which scalp lesions diagnosed histologically as collagenomas were associated with cardiomyopathy and hypogonadism [27].

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Elastic naevi

Juvenile elastoma and the Buschke–Ollendorff syndrome

SYN. DERMATOFIBROSIS LENTICULARIS DISSEMINATA

The association between connective tissue naevi of the skin and osteopoikilosis is now well recognized, and is generally known eponymously as the Buschke–Ollendorff syndrome [1,2].

The histological features of the skin lesions in such patients are highly characteristic [3,4]. While haematoxylin and eosin stained sections may fail to reveal any abnormality at all, those stained to demonstrate elastin will show thick, interlacing tracts of elastic fibres running between fairly normal collagen in the reticular dermis, an appearance to which the term juvenile elastoma has been applied. Ultrastructurally, the elastin comprises clumps, coated with fine fibrils, and the fibroblasts contain swollen endoplasmic reticulum containing abnormal fibrillar material [4–6].

Elevated elastin production [4] and elastin mRNA levels [7] have been demonstrated in cultured fibroblasts from individuals with the syndrome, suggesting a possible defect in pre-translational control of elastin production.

Two rather different clinical presentations have been described in the Buschke–Ollendorff syndrome. In some patients, there is a symmetrical eruption of uniform, small, asymptomatic lichenoid papules, sometimes reminiscent of pseudoxanthoma elasticum [5,8]; this type of eruption has been termed *dermatofibrosis lenticularis disseminata*. However, a second type of cutaneous presentation is more usual, comprising larger, yellowish nodules, often grouped and sometimes coalescing to form plaques [9–12] (Fig. 15.5). The distribution of these lesions is generally asymmetrical, and they may appear at any age, although most are present before puberty. Mixtures of these two types of lesions probably also occur. Although generally asymptomatic, occasional patients complain of pain, tenderness or pruritus in affected areas of the skin [12–14].

The second component of the Buschke–Ollendorff syndrome is a radiological abnormality termed *osteopoikilosis*, which comprises multiple, circumscribed, roundish or oval areas of increased opacity within bones, each usually measuring between 1 and 10 mm across [15] (Fig. 15.6). Such areas are found particularly frequently in the carpal and tarsal bones, in the phalanges, the epiphyses and metaphyses of the long bones and in the pelvis. They take several years to develop, but, after puberty, the appearances change very little. Histologically, these lesions are foci of tightly meshed bony trabeculae [16]. Osteopoikilosis has been identified in otherwise normal relatives of patients with the Buschke–Ollendorff syndrome; in such cases it presumably represents incomplete expression of the Buschke–Ollendorff gene. One imagines that, in at least some of these individuals, typical skin lesions will later make their appearance. Conversely, characteristic skin lesions have been reported in the absence of osteopoikilosis, even after puberty [10,17].

It is now clear that the Buschke–Ollendorf syndrome is transmitted as an autosomal dominant trait, albeit with

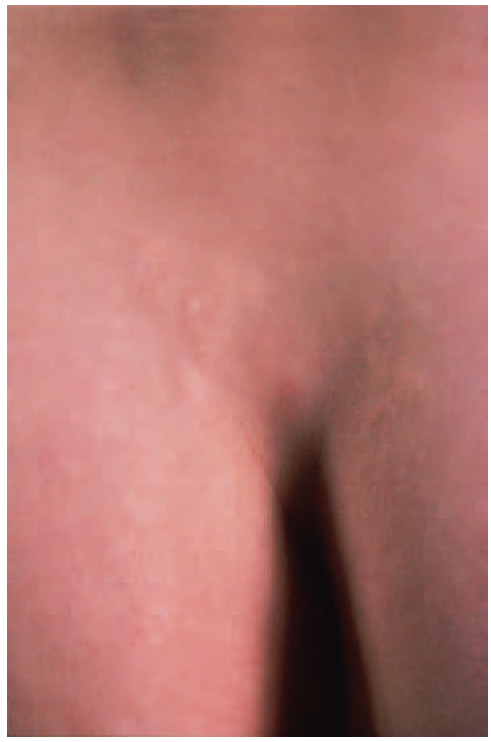

Fig. 15.5 Juvenile elastoma in the sacral area in the Buschke–Ollendorff syndrome.

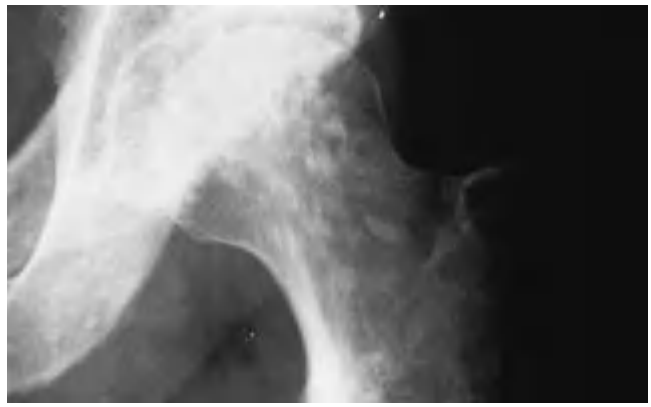

Fig. 15.6 Osteopoikilosis in the Bruschke–Ollendorff syndrome (X-ray of femoral head).

very variable expressivity. There is little evidence to suggest any overall increase in morbidity or mortality in this syndrome, although a number of possible associations have been reported. Otosclerosis has occurred in several cases; it seems likely that this association is a genuine one [18,19]. Muscle fibrosis or contractures have been reported in several cases [2,10,13,20] and are unlikely to be merely coincidental. Other possible associations have included spinal anomalies [18,21], short stature with or without precocious puberty [18,21] and peptic ulceration [13]. In one patient, the Buschke–Ollendorf syndrome was associated with protein C deficiency; it was suggested that this might reflect the fact that the genes for elastin and protein C are both located on chromosome 2q [22].

Papular elastorrhexis

Papular elastorrhexis is the name given in 1987 [23] to a distinctive condition that should probably be provisionally categorized as a type of elastic tissue naevus.

The clinical presentation [24,25] is with multiple small (1–3 mm) white papules, which are not follicular and are symmetrically distributed, predominantly on the trunk and, to a lesser extent on the limbs. The lesions tend to appear in the second decade of life. They show no tendency to group, or to merge into plaques. Biopsies consistently demonstrate diminution and fragmentation of dermal elastic fibres.

Although it has been suggested that it may be a variant of the Buschke–Ollendorff syndrome, cases so far reported have only once been familial [26], and in no case has osteopoikilosis or any other extracutaneous feature been associated.

Naevus anelasticans

Several authors have reported cases in whom groups of small, yellowish or pink, perifollicular papules were present on the trunk, sometimes resulting in a 'wrinkled' appearance of the skin [27–29]. Histologically, these lesions have demonstrated focal absence of elastic fibres. In the past, this condition was known inaccurately as *naevus elasticus of Lewandowsky* [28].

Other elastomas

Some cases reported under a variety of titles, including juvenile elastoma and naevus elasticus [29–31], may represent *formes frustres* of the Buschke–Ollendorf syndrome, but they may alternatively be genuinely unrelated forms of elastoma. An exophytic form has been reported [32].

A distinctive condition comprising bilateral, thickened and furrowed plaques on the cheeks with an increase in elastic tissue histologically has been described in two separate reports [33,34]. The patients were both young, and lacked any relevant family history. It is possible that sunlight played a role in the aetiology of these lesions.

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Differential diagnosis of connective tissue naevi

Several conditions need to be considered in the differential diagnosis of connective tissue naevi. Among these are congenital smooth muscle hamartoma, leiomyomas, naevus lipomatodes superficialis and neurofibromas.

Proteoglycan naevi

Mucinous naevus

SYN. NAEVUS MUCINOSUS; LINEAR CONNECTIVE TISSUE NAEVUS OF THE PROTEOGLYCAN TYPE

There have been a very small number of reports of lesions of this type in recent years [1,2], but it is likely that in the past such lesions were at least occasionally reported under the broader title of cutaneous mucinosis of infancy [3]. Histologically, these lesions are characterized by the presence of large amounts of proteoglycan in the superficial dermis, associated with variable overlying hyperkeratosis, acanthosis and elongation of rete ridges. Van Gieson staining shows a broad band in the upper third of the dermis in which elastic and collagen fibres are virtually absent, and alcian blue staining at pH 2.5 shows that there is accumulation of proteoglycan in this area, which disappears following pretreatment with hyaluronidase.

Clinically, the lesions comprise asymptomatic groups of flesh-coloured or slightly pigmented papules having a firm velvety surface and a tendency to coalesce to form plaques. They are generally linear in disposition. Lesions may be present from birth but may also develop some years later.

Clinically, the differential diagnosis includes epidermal naevi, connective tissue naevi of other types, the skin lesions of Hunter's syndrome (mucopolysaccharidosis type II) (see Chapter 57) [4] and naevus lipomatosus cutaneous superficialis. Histologically, one would need to consider papular mucinosis (lichen myxoedematosus), acral persistent papular mucinosis, self-healing juvenile cutaneous mucinosis, cutaneous focal mucinosis and papular mucinosis of infancy. At least some of the cases described as linear or localized papular mucinosis of infancy should probably be regarded as examples of mucinous naevus.

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Fibrous hamartoma of infancy

Histologically, fibrous hamartoma of infancy comprises a mixture of spindle cells forming fascicles, clumps of round cells resembling immature mesenchyme, and mature adipose tissue, located in the deeper part of the dermis and/or the subcutis [1].

It is a lesion that first appears during the first 2 years of life, but which can occasionally be present at birth [1,2]. It may be more common in boys [1,3]. It occurs most characteristically on the trunk, particularly in the axilla, and the upper limbs [2,3] but it may occur at almost any site, including the scrotum [4]. Lesions are almost always single. It generally takes the form of a slowly enlarging asymptomatic dermal nodule.

It can be cured by local excision.

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Muscle naevi

Congenital smooth muscle hamartoma

SYN. CONGENITAL ARRECTOR PILI HAMARTOMA

Definition. Congenital smooth muscle hamartoma is a malformation of pilar smooth muscle, first described by Sourreil *et al*. [1]. It is relatively common, occurring in about one in 3000 births [2]. Familial cases have recently been reported [3], but the great majority of cases occur in a sporadic fashion.

There appears to be a rare acquired type of smooth muscle proliferation that has occasionally been described under the title *smooth muscle hamartoma* [4] or *acquired smooth muscle hamartoma* [5,6]. It is distinct from the congenital smooth muscle hamartoma as described below.

Pathology. The histology shows well-defined bundles of smooth muscle fibres, which stain with Masson's trichrome [7–9]. The fibres themselves are generally long and straight, and extend in different directions. Each bundle is surrounded in turn by a clear space and by collagen. They

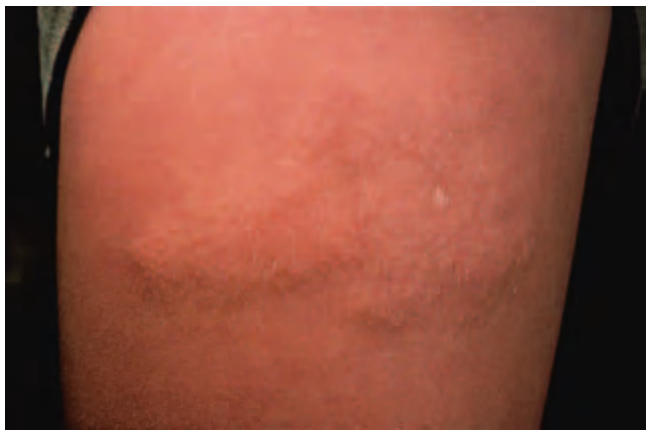

Fig. 15.7 Congenital smooth muscle hamartoma on the thigh.

are scattered over a wide area in the reticular dermis, and may extend into the subcutaneous fat. Sometimes, there is associated hyperkeratosis, papillomatosis and increased epidermal pigmentation [9]. Electron microscopy has shown characteristic wavy or whorled myofilaments within the smooth muscle cells, and axons, mostly unmyelinated, adjacent to the smooth muscle bundles [7,8,10,11].

Clinical features. Lesions are generally single and are initially noted at birth or during the first few weeks of life, most often on the trunk or proximal limbs.

Smooth muscle hamartoma presents as a variably indurated, asymptomatic plaque, with irregular poorly defined margins, 1–10 cm across (Fig. 15.7), often showing prominent follicular papulation [2,7–10,12–14]. Usually skin-coloured or faintly erythematous initially, subtle bluish brown pigmentation is a feature of the established lesion [15]. Firm stroking may provoke temporarily increased induration or piloerection, sometimes called the 'pseudo-Darier sign' [2,12,16]; this may diminish with age [17]. Occasionally, fasciculation has been reported [13,18]. In the majority of cases, there is a single plaque, but more extensively distributed multiple lesions have also been reported [3,16,19,20].

Linear variants of congenital smooth muscle hamartoma have been reported, either with an atrophic appearance [21], or with hyperpigmentated perifollicular papules [22].

The natural course of congenital smooth muscle hamartomas is not firmly established, but they probably persist indefinitely [10], perhaps with gradual slight diminution in induration and hypertrichosis [2]. No significant associated abnormalities have been reported.

Diagnosis. Differential diagnosis is from solitary mastocytomas, pilar leiomyomas and connective tissue naevi, which are not hypertrichotic, and from congenital melanocytic naevi [15], simple hypertrichotic naevi and Becker's naevi. The greatest confusion has been with Becker's naevi, which may feature smooth muscle bundles in the dermis [23]. Lesions described in the literature as '*congenital Becker's naevi*' have been congenital smooth muscle hamartomas [24,25], and the two conditions are generally distinguishable by their age of onset, and by their characteristic histological features [7,16].

Congenital plexiform neurofibromas are frequently hypertrichotic [26], but are generally softer than congenital smooth muscle hamartomas, and are of course histologically distinctive.

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Diffuse smooth muscle hamartoma

Several children have now been reported with an unusual diffuse type of smooth muscle hamartoma, presenting a unique clinical appearance [1–7]. Histology shows changes identical to the solitary type of congenital smooth muscle hamartomas, frequently associated with fragmented elastic fibres [7]. The baby is born with excess folds of rather firm skin on the limbs, particularly at the ankles and wrists, giving a 'Michelin baby' appearance. There is associated diffuse hypertrichosis, which may be especially marked at birth [1]. The palmar skin may have a rather cerebriform appearance [1]. One child also had cutaneous mastocytosis of urticaria pigmentosa type [8]. Another child had a paracentric inversion of chromosome 7q [9], suggesting that the gene responsible for the condition may be located on this chromosome. Personal experience with a case reported by one of us [1] suggests that the hypertrichosis and dermatomegaly will gradually diminish with time.

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Congenital leiomyoma

Cutaneous leiomyomas are only very rarely present at birth. However, a case has been reported recently of a neonate born with a pedunculated, firm, purple, spherical mass attached to the heel, which proved to be a pilar-type leiomyoma histologically [1].

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Striated muscle hamartoma

SYN. CONGENITAL RHABDOMYOMATOUS MESENCHYMAL HAMARTOMA; CONGENITAL MIDLINE HAMARTOMA

This entity has been recognized since 1986 [1]. A small number of cases have been reported since, occasionally under the title of *rhabdomyomatous mesenchymal hamartomas* or *congenital midline hamartoma* [2–7]. It has been suggested that it may be a first branchial arch anomaly.

Lesions are generally congenital and solitary. They occur at sites where striated muscle is found superficially. Most reported cases have occurred on the face, particularly on the chin [3,6,7], in a nostril [8] or on a lip [1], but others have been recorded on the anterior chest and in the perianal area [2]. They are usually soft and pedunculated or polypoid. Some may be elongated, and some have been branched.

Histologically these lesions show bundles of striated muscle fibres in the reticular dermis and the subcutis. They may also contain well-developed appendageal structures such as hair follicles, sebaceous glands, eccrine glands and ducts, nerve bundles and intradermal lobules of fat. It is the characteristic presence of these elements that is highlighted by the term rhabdomyomatous mesenchymal hamartoma [9].

Many of the cutaneous appendages that are a major cutaneous feature of *Delleman's syndrome* are striated muscle hamartomas, and any child in whom striated muscle hamartoma has been found should be examined carefully for other features of this syndrome [10]. Some cases of striated muscle hamartoma have occurred in association with a limited number of features that suggest the child may have had an incomplete form of Delleman's syndrome [11].

Striated muscle hamartomas need particularly to be distinguished from *fetal rhabdomyoma* and *neuromuscular hamartoma*. Fetal rhabdomyoma is a tumour of the subcutis that occurs in the neonate, and comprises a myxoid stroma containing undifferentiated mesenchymal cells with some that show differentiation towards embryonic skeleton [12]. Neuromuscular hamartoma, or a Triton tumour, occurs as a nodule in the subcutis comprising striated muscle mixed with nerves [13].

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Delleman's syndrome

This rare syndrome was first described in 1981, and is now reasonably well defined [1,2].

There has been no evidence of genetic transmission in any of the cases so far reported, and the syndrome may be a reflection of mosaicism for a lethal autosomal dominant gene [3].

The condition is characterized by orbital cysts, cutaneous appendages which are most frequently seen in the periorbital and postauricular areas, focal cutaneous hypoplasia, developmental delay, convulsions and skull defects. Most frequently, the disorder is unilateral, and in those cases in which it is bilateral there tends to be unilateral predominance. The cutaneous appendages, which may take on bizarre finger-like or tubular forms, are histologically indistinguishable from striated muscle hamartomas [4]. The severity of Delleman's syndrome may be more variable than is currently recognized, and it is possible that, in at least some cases, striated muscle hamartomas are its minimal expression. The focal cutaneous hypoplastic lesions may comprise cutis aplasia, areas of atrophy and distinctly punched-out defects.

Delleman's syndrome requires differentiation from focal dermal hypoplasia, encephalocraniocutaneous lipomatosis [5,6] and from Goldenhar's syndrome.

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Fat naevi

Naevus lipomatodes cutaneus superficialis

In this rare disorder, collections of mature lipocytes are situated ectopically within the dermis [1]. Associated histological abnormalities of the dermal connective tissue, blood vessels and epidermal appendages may also be seen within the lesions [2,3]. Electron microscopy has shown that the lipocytes are closely associated with capillaries, and it has been suggested that they may originate from pericytes, as in fetal lipogenesis [4].

Clinically, there are two principal presentations [3]. The first is the classic form, as originally described by Hoffman and Zurhelle [5], after whom these lesions are often eponymously known. In this type, a clustered group of soft, fleshy, skin-coloured or yellow nodules is found, most commonly on the lower trunk, especially on the back, buttocks or hips or abdomen, and on the upper posterior thighs [1,3,6–8]. Lesions have also been reported less frequently at other sites including the face [9] and scalp [10]. These nodules may be domed, sessile or pedunculated. Their surface is most often smooth, but can be wrinkled, cerebriform or they may have a peau d'orange texture. They are occasionally hairy [6], may contain comedo-like plugs [3,11] and have been associated with café-au-lait [12] or hypopigmented [13] macules. Although almost invariably asymptomatic, occasionally ulceration may occur [14]. They are generally present at birth, but may first appear during childhood or adolescence [6,15], and usually remain unchanged thereafter.

The second form comprises a solitary, domed or sessile papule, which develops in adult life, and has been reported at sites other than the lower trunk including the knee, axilla, arm, ear and scalp [3,16–19].

From a histological viewpoint, it should be borne in mind that similar dermal collections of adipose tissue may occur as a component of intradermal melanocytic naevi [3], and in the acquired lesion known as pedunculated lipofibroma [20]. Fat also tends to be found very superficially in the skin lesions of focal dermal hypoplasia, although clinically this condition is unlikely to be mistaken for naevus lipomatodes superficialis.

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Lipoblastomatosis

Lipoblastomatosis is a rare, benign tumour of embryonic adipose tissue that occurs principally in infancy and early childhood. Around 90% of cases present in the first 2 years of life, generally in infancy [1]. Occasionally these tumours are already present at birth [2,3]. There appears to be a male : female preponderance of about 3 : 1 [4].

Most lesions occur on the extremities [1]. The clinical appearance of these tumours is not consistent, though they generally take the form of flesh-coloured or reddish swellings or plaques that are generally asymptomatic unless they are locally compressing important structures. The diagnosis is based on histology. The tumour may or may not be encapsulated, and may be well-circumscribed or infiltrative [2]. Lobules of lipocytes and lipoblasts are mixed with spindle and stellate mesenchymal cells, separated by fibrous septa. Serial biopsies have demonstrated maturation of the immature lipoblasts into lipocytes [1,5]. There may be foci of extramedullary haematopoiesis and prominent capillaries [3,4]. There may be an Alcian blue-positive myxoid stroma, leading to possible confusion with myxoid liposarcoma, a tumour that is extremely rare in early childhood.

Magnetic resonance imaging (MRI) can be helpful in gauging the degree of infiltration of these tumours and the quality of the signals may provide diagnostic clues [6].

Both localized and diffuse variants of this condition are benign, and, while there may be infiltration of neighbouring tissues, metastasis has never been reported. Where feasible, surgical excision is the recommended form of treatment, though recurrence may occur if this is incomplete, particularly in the diffuse variant [1].

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Encephalocraniocutaneous lipomatosis

This neurocutaneous disorder has been recognized since 1970 [1]. To date, all reported cases have occurred sporadically, and both sexes have been affected [1–5]. Happle and Steijlen [6] have suggested that the disorder is due to a lethal autosomal mutation that can survive only in a mosaic state. Recently, a case has been reported in which a *de novo* mutation was demonstrated in the neurofibromatosis type 1 gene [7].

The principal cutaneous feature is multiple lipomatous hamartomas, which may be present from birth [4,5]. These comprise soft, skin-coloured or yellow, domed papules and nodules, which vary in diameter from a few millimetres to several centimetres. Most reported lesions have occurred on the head and neck, particularly in the scalp, where they may take the form of hairless plaques. Lesions have in most cases been unilateral, but bilateral lesions do occur. Histologically, most lesions demonstrate dermal fibrosis associated with increased amounts of subcutaneous fat, which extends into the reticular dermis, but some of the smaller papular lesions may show changes more closely resembling those seen in angiofibromas [5].

These cutaneous lesions are almost always accompanied by ocular anomalies, most often fleshy desmoid tumours [8], and a variable degree of mental retardation with or without convulsions. Intracerebral abnormalities also tend to be unilateral, on the same side as the cutaneous lesions; the most frequent finding is of unilateral cerebral atrophy with ventricular dilatation. Pathological studies in one case showed that lipomatous hamartomas were also present in the brain and leptomeninges [1].

Differential diagnosis will include focal dermal hypoplasia, oculo-auriculovertebral dysplasia (Goldenhar's

syndrome), oculocerebrocutaneous syndrome (Delleman's syndrome), Proteus syndrome and epidermal naevus syndrome.

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Congenital lipoma

Rarely, one may find rounded, soft, smooth, skin-coloured masses, histologically lipomatous, in the neonate.

The most characteristic and important site for such anomalies is the lumbosacral area, though analogous lesions may, more rarely, occur further up the midline of the back [1]. Lumbosacral lipomas tend to have extensions into the spinal canal which attach to the spinal cord [2–7]. These extensions will generally pass through bone defects in the spine, and lumbosacral lipomas are therefore markers of spinal dysraphism. One should consider this diagnosis in any child with a lumbosacral swelling with normal overlying skin, though a wide variety of other skin lesions may commonly be associated [8,9], particularly infantile haemangiomas [10–12], macular vascular stains [13] and localized hypertrichosis [14]. The swelling will often cause deviation of the upper end of the gluteal cleft.

Lumbosacral lipomas may show some characteristic histological features, including absence of a capsule, fibrous tissue scattered within the mass, and a variety of unusual ectopic neuroectodermal and mesodermal tissues [15].

The vulva appears to be another predilection site [16,17].

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Congenital lipomatosis

Congenital lipomatosis is a rare adipose tissue malformation in which accumulations of mature lipocytes are present in the subcutis and show a tendency to infiltrate adjacent tissues, particularly muscle [1,2]. The commonest site is the trunk, particularly the chest. The subcutaneous lesions form soft, usually mobile masses, which may be of substantial size. There may be underlying hypertrophy of bone and hemihypertrophy.

Although such lesions have been associated in some cases with haemangiomas and with macrodactyly, this disorder can be distinguished from both the Proteus and Bannayan–Riley–Ruvalcaba syndromes.

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Neurolipomatosis

SYN. NEURAL FIBROLIPOMA; FIBROLIPOMATOUS HAMARTOMA OF NERVE

This is a rare condition in which mature fat and fibrous tissue accumulate around peripheral nerves of an extremity [1]; the median nerve is most often affected. There is a sausage-shaped tumour in the skin without muscle infiltration.

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'Michelin tyre' baby

SYN. GENERALIZED FOLDED SKIN

Generalized folding of redundant skin results in an appearance that has fancifully been likened to the symbol of the French tyre manufacturer [1]. This rare cutaneous malformation was first reported in an otherwise normal baby girl in whom it had been present from birth [1]. The skin biopsy demonstrated diffuse lipomatous hypertrophy. A follow-up report recorded that the condition had gradually improved spontaneously [2,3]. Another baby girl has since been described in whom a more localized area of folded skin with similar histological features, was associated with microcephaly, mental retardation and deletion of the short arm of chromosome 11 [4,5].

There have been further reports of a similar folded 'Michelin tyre' appearance in otherwise healthy babies in whom the underlying lipomatous changes were histologically absent. Generalized smooth muscle hamartomatosis appears to be a cause in some cases, in which the redundant skin folds are associated with hypertrichosis. In another case, no histological abnormality whatsoever was identifiable, but a distinctive associated clinical feature was the presence of widespread stellate scarring [6]. Two further reports described the occurrence of folding of the skin in several family members, suggestive of autosomal dominant transmission [7,8].

Congenital generalized folding of the skin may also be a prominent feature of the Beare–Stevenson cutis gyrata syndrome [9]. However, most cases show more localized corrugation of the skin, particularly on the scalp, forehead, face and neck with furrowing of the palms and soles. In addition, patients show acanthosis nigricans, craniofacial anomalies, anogenital anomalies, skin tags and a prominent umbilical stump.

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Vascular naevi

A number of useful reviews of this subject have been published in recent years [1–6].

Classification. Abnormalities of cutaneous vascular development have been classified mainly on clinical grounds. A great number of alternative names are used to describe identifiable varieties. In practice, it is not uncommon for lesions of different types to coexist in the individual patient [7,8].

The broad classification in Table 15.3 [5] will be used in this chapter.

Table 15.3 Classification of vascular naevi. (Based on Requena and Sangueza [5].)

Vascular tumours of infancy and childhood
Infantile haemangioma
Congenital haemangioma
Miliary haemangiomatosis of infancy
Tufted angioma
Kaposiform haemangioendothelioma
Verrucous haemangioma
Haemangiopericytoma
Glomangioma
Vascular malformations
Low flow
Capillary
'Salmon' patch
'Port-wine' stain
Naevus anaemicus and naevus oligaemicus
Mixed vascular malformations
Reticulate vascular naevus
Klippel–Trenaunay syndrome
Venous malformations
Blue rubber bleb naevus syndrome
Maffucci's syndrome
Zosteriform venous malformations
Gorham's disease
Other multiple vascular malformation syndromes
Lymphatic malformations
Microcystic
Macrocystic
Rapid flow (arteriovenous malformations)
Angiokeratomas
Angiokeratoma circumscriptum
Angiokeratoma of Mibelli
Solitary papular angiokeratoma
Angiokeratoma of the scrotum and vulva

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Vascular tumours of infancy and childhood

Infantile haemangioma [1–3]

SYN. CAPILLARY HAEMANGIOMA; COMMON HAEMANGIOMA OF INFANCY

Definition. Infantile haemangiomas are benign developmental vascular tumours that appear during the first months of life, and which characteristically have an initial proliferative and a later involutional phase.

Nomenclature and classification. The nomenclature and classification of vascular developmental disorders has been the subject of great confusion. It is important to distinguish between genuinely angiomatous lesions, i.e. haemangiomas, and vascular malformations, although these may occasionally be difficult to differentiate on clinical grounds alone.

The term haemangioma designates a proliferative blood vessel tumour. As such tumours may occur in older children and adults, for example granuloma telangiectaticum and angiolymphoid hyperplasia with eosinophilia, the term 'infantile haemangioma' is preferable to describe the developmental type of haemangioma that arises in early infancy. This type of haemangioma has colourfully been called *strawberry naevus* or *strawberry haemangioma*, although in practice not all such lesions have a strawberry-like clinical appearance. The terms *capillary naevus* and *capillary haemangioma* have been used to describe infantile haemangiomas, but, although the description capillary haemangioma is perfectly correct and acceptable, the frequent and widespread misapplication of these terms to describe macular vascular stains of port-wine-stain type means that it is probably best to avoid their use altogether.

Infantile haemangiomas must be differentiated from other haemangiomas of infancy such as tufted angiomas, and from vascular malformations, whose clinical appearance may be similar in some cases, but whose aetiology, pathology and natural history are entirely different [4–6]. Lesions that were previously called *cavernous haemangiomas* were frequently not haemangiomas at all but vascular developmental malformations, and this term should probably therefore also be abandoned.

It is not uncommon for infants to develop more than a single infantile haemangioma, and most often the number of such lesions is fewer than 10. On the other hand, more rarely the situation arises in which an infant develops very large numbers of lesions, usually small (generally less than 1 cm) and numbering in the hundreds, an occurrence for which a wide variety of terms have been used, including *diffuse neonatal haemangiomatosis* [7], *disseminated haemangiomatosis* [8], *disseminated eruptive haemangiomas* [9] and *miliary haemangiomas* [10]. Whereas the term *multiple infantile haemangiomas* could reasonably be used to describe both the occurrence of small numbers of otherwise typical infantile haemangiomas and the presence of very large numbers of small lesions, the authors prefer to highlight the special problems that may arise in the latter situation by applying the term *miliary haemangiomatosis of infancy*. Cutaneous haemangiomas of this miliary type are particularly likely to be associated with systemic haemangiomas and an increased mortality, though in most cases complications due to systemic lesions do not occur. An attempt has been made to separate cases with systemic lesions from those without using the term *disseminated eruptive neonatal haemangiomatosis* for the former and the term *benign neonatal eruptive haemangiomatosis* [11] for the latter. A distinction of this type is highly artificial, as one cannot exclude the presence of systemic lesions without employing intensive investigation to do so, an approach that most clinicians would regard as unnecessary. The management of such cases requires a high level of awareness of the possible presence of visceral lesions, alertness for the development of symptoms resulting from such lesions, and limited investigations to identify cases at particular risk of high-output cardiac failure. Exclusion of visceral lesions in every case as a matter of routine is neither practical nor necessary.

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Aetiology. Infantile haemangiomas are benign proliferations of vascular elements. Familial transmission has been recorded exceptionally [1,2]; in the vast majority of cases, infantile haemangiomas occur sporadically.

While many of the cells appear to be endothelial in nature, forming readily visible blood vessels, a large population of cells is present in these lesions that have not been fully categorized. Because pericytes and dermal dendrocytes have been identified in infantile haemangiomas in addition to endothelial cells [3], it has been suggested that they are tumours of a primitive cell type capable of differentiating in all these directions [4].

It is generally agreed that vascularization of fetal skin begins during the third month of intrauterine life, but these vessels do not anastomose with the deeper vasculature until later in gestation [5]. It has been suggested that infantile haemangiomas arise where islands of embryonic cutaneous angioblastic tissue fail to establish normal contact with the rest of the developing vascular system [6]. It has also been suggested that there may be analogies with the retrolental fibrovascular proliferation seen in premature infants given oxygen therapy, and this concept receives some indirect support from the higher incidence of infantile haemangiomas in infants born prematurely [7,8].

Capillary endothelium has the capacity to develop new vessels under certain conditions [9]. In particular, this requires the presence of angiogenic factors [10], and it is possible that infantile haemangioma cells are able to secrete such a factor themselves, as has been shown to be the case in certain other types of tumour [11]. An imbalance has been demonstrated between expression of angiogenic and anti-angiogenic factors within infantile haemangiomas and adjacent normal tissue [12]. Certain other types of cell may play a 'helper' role in endothelial proliferation. The mast cell has been an important candidate for such a role [13,14]; the finding that mast cell numbers are high in proliferating haemangiomas is therefore of considerable interest [15].

It has also been proposed that endogenous steroid hormones may play a role in the growth of infantile haemangiomas. Both increased serum levels of 17β-oestradiol and increased numbers of tissue receptors for this hormone in proliferating infantile haemangiomas have been demonstrated [16].

Recently, it has been recognized that infantile haemangiomas are a common sequel to chorionic villous sampling; one study reported a 21% incidence, and in a third of the cases, the haemangiomas were multiple [17,18]. It would be anticipated that placental injury would lead to increased detachment of placental cells into the blood. Infantile haemangiomas might therefore result from embolization of fetal placental endothelial cells via the right-to-left shunts characteristic of the fetal circulation. This hypothesis is supported by the finding that infantile haemangiomas share immunoreactivity for tissue-specific markers with placental endothelium, in contrast with other vascular tumours and malformations [19].

Pathology [3,15,20–23]. In the earliest phase of growth of infantile haemangiomas, there is a solid mass of proliferating endothelial cells, with few if any lumina. The nuclei are not pleiomorphic, and only occasional mitoses are visible. Later in the proliferative phase, capillary-sized lumina are apparent, lined by plump endothelial cells. Reticulin staining confirms that each group of endothelial cells is surrounded by a limiting membrane of reticulin fibres. PAS staining shows a thickened basement membrane beneath the endothelial cells lining the lumina. Initially, these lumina are slit-like, but gradually they become more dilated. Mast cells are plentiful during the proliferative phase.

The onset of involution coincides with an increase in apoptosis [24]. As involution proceeds, the haemangioma becomes progressively more organized, with distinct lobules separated by fibrous septa containing the larger feeding and draining vessels. In children aged 2 years and older, the number of vascular channels decreases, and the diameter of the lumina increases with flattening of the endothelial lining, resulting in a 'cavernous' appearance, which must not be confused with the appearance of a venous malformation. There is a simultaneous progressive increase in intra- and interlobular connective tissue and fat.

Expression of a wide variety of cellular markers alters during the lifecycle of haemangiomas. Immunohistochemical studies have documented increased expression of basic fibroblast growth factor (BFGF) within proliferating infantile haemangiomas, and its excretion in increased quantities in the urine, which fall as involution progresses [25].

The endothelial cells comprising infantile haemangiomas show intense and persistent immunoreactivity for a number of tissue-specific markers termed FcγRII, Lewis Y antigen (LEY), merosin and GLUT1. This group of markers is highly characteristic of placental microvasculature [19]. However, infantile haemangiomas failed to show immunoreactivity for markers of placental trophoblasts [26].

The location of individual lesions varies. The most superficial are confined to the papillary and subpapillary dermis, while deep lesions may partly extend into the subcutis.

Ultrastructural studies show the proliferative phase lesion to comprise highly active endothelial cells, with multilaminated basement membrane [27]. Mast cell microvillous projections can be observed alongside the vessel walls, parallel to the basement membrane laminations [28]. During the involutional phase, there are signs of vessel degeneration.

Histology of the small multiple type of infantile haemangioma is essentially identical [29–31].

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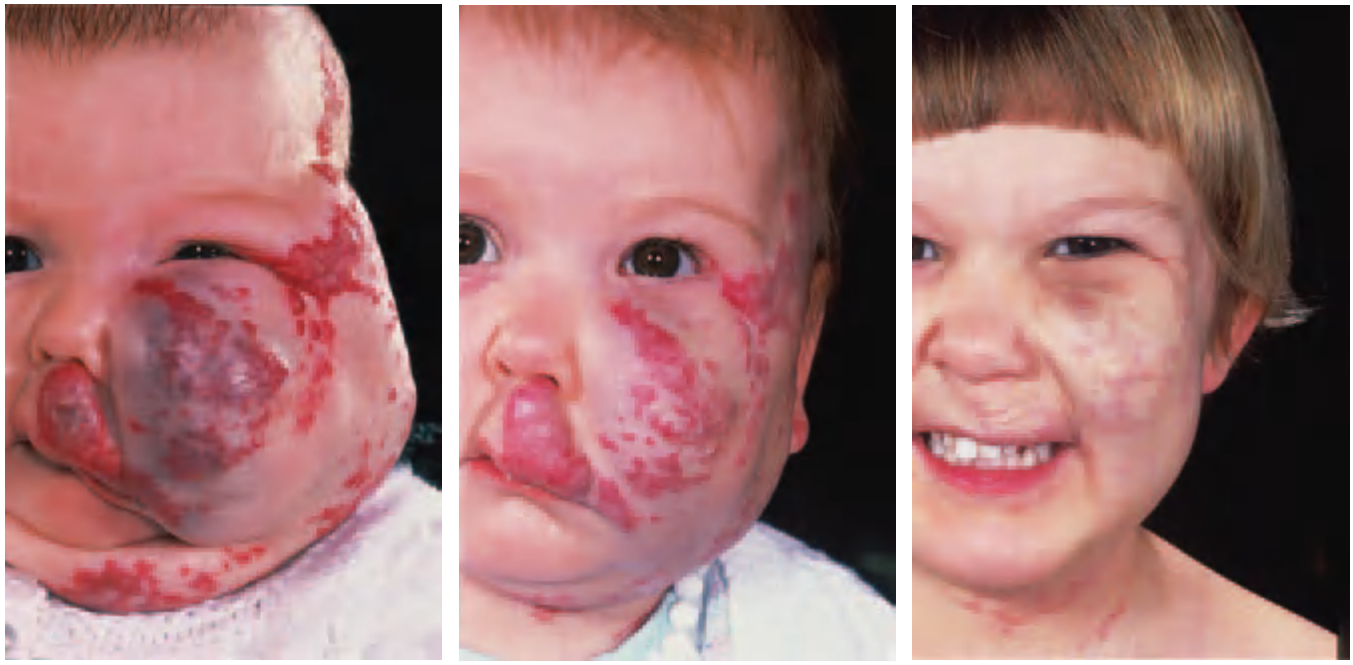
Clinical features [1–6]. Infantile haemangiomas are the commonest tumours of infancy, with a prevalence of about 1–3% after the first few days of life [7–10], and up to 12% by the end of the first year [3,11]. There is good evidence of a higher incidence in infants born prematurely, about 13% at 1 year for all preterm infants, increasing in inverse relationship to birth weight [12,13]. Thus, at 1 year, the prevalence in preterm babies with a birth weight below 1500 g is about 16%, and, in preterm babies with a birth weight below 1000 g about 23%. Conversely, the prevalence in preterm babies with a birth weight over 1500 g is no different from that of full-term babies [11–13]. In another recent study, the prevalence of infantile haemangiomas at 1 year in preterm infants was shown to be inversely related to gestational age at birth, being recorded as 8% for babies born after the 35th week, 11% for those born between the 30th and 35th weeks, and 19% for those born between the 25th and 29th weeks [14]. Superficial infantile haemangiomas, sometimes multiple, have also been reported to occur with increased frequency in the fetal alcohol syndrome [15]. Very occasionally, apparently typical infantile haemangiomas have appeared for the first time in adult life [16].

Infantile haemangiomas become apparent during the first month of life in about 90% of cases, and virtually 100% by the ninth month. Approximately 65% of infantile haemangiomas are superficial, 15% deep and 20% mixed. The term 'deep' is preferable to 'subcutaneous' as most of those infantile haemangiomas that are covered with normal epidermis are situated largely in the dermis rather than in the subcutis, although they may extend to this depth.

In the case of superficial infantile haemangiomas, an initial 'precursor' lesion is often visible on the first day of life. These precursor lesions may be quite subtle, and most characteristically take the form either of a macular area of hyperaemia resembling a salmon patch or a pale port-wine stain, or a macular area of pallor resembling a naevus anaemicus [17–20]. The latter, pallid type of precursor



(a) (b) (c)

Fig. 15.8 Large, mixed infantile haemangioma at: (a) 3 months; (b) 16 months; and (c) 3 years. A course of oral prednisolone was given at 3 months.

lesion area may contain grouped punctate telangiectases from the outset, or these may develop within a day or two. A group of small, closely packed angiomas usually then develops within the area, rapidly enlarging and coalescing until the lesion is mature. However, apparently typical precursor lesions occasionally fail to progress into infantile haemangiomas. In about 20% of cases, infantile haemangiomas are present at birth without a precursor lesion.

The superficial infantile haemangioma is most commonly known as a 'strawberry' naevus or 'strawberry' haemangioma, on account of its usual clinical appearance in the form of a sharply circumscribed oval or round, soft, domed swelling of intense scarlet-red colour. The surface may be smooth or lobulated. A thin plaque type is a distinctive variant of superficial haemangioma.

Infantile haemangiomas may occur at any site, but about 60% occur on the head and neck. Next in frequency are lesions on the trunk, about 25% of the total, where favoured sites are the perianal area in both sexes, and the vulva in girls.

In some 80% of cases, a single lesion only is present, but in the remaining 20% lesions are multiple; occasionally, very large numbers may occur (see miliary haemangiomatosis of infancy) [21–23]. Apart from the occasional lesion that is fully developed at birth (congenital infantile haemangiomas), infantile haemangiomas increase in size over a period that varies from about 3 to 18 months. However, the great majority will have reached their maximum size within 6–12 months of their first appearance. It is only exceptionally that lesions continue to enlarge beyond the first year of life [24,25]. The final diameter may vary from less than 1 to 25 cm or more. Very large congenital lesions can obstruct delivery if they are not previously detected.

There is frequently a deep element to superficial infantile haemangiomas of strawberry type, particularly when these are large; such lesions should be termed mixed infantile haemangiomas (Fig. 15.8). In other cases, the infantile haemangiomas are entirely, or more or less entirely deep. Exclusively deep infantile haemangiomas take the form of soft, warm, round bluish masses beneath normal skin, although there may be a few branching telangiectases or an area of vascular staining on the surface. Deep infantile haemangiomas often feel like a 'bag of worms', and a useful feature in their distinction from other tumours is that they can generally be compressed to about half their original size, quickly regaining their original dimensions on release of pressure. Similarly, they often become larger and darker when the child screams or cries. Only about 7% of infantile haemangiomas are exclusively of this deep type. Where the naevus is mixed, it may be principally deep or principally superficial. The superficial element usually emerges from the centre of the swelling, often in several places.

It is commonly stated that deep infantile haemangiomas are more likely than superficial infantile haemangiomas to have been present at birth, and that they are more likely to be of 'cavernous' type histologically. However, such statements result from the previously widespread tendency to confuse deep infantile haemangiomas

with venous vascular malformations, which are not angiomas at all and have an entirely different natural history.

Large superficial veins may be present in the skin at the periphery of larger infantile haemangiomas.

Virtually 100% of infantile haemangiomas undergo spontaneous regression, which is complete or almost complete in about 95% [5,9,26–29]. Although there is considerable variation in the rate of involution of individual lesions, there is no evidence to suggest that deep lesions generally involute more slowly than superficial ones. About 30% of infantile haemangiomas lesions will have resolved by the fourth birthday, about 50% by the fifth and 75% by the seventh. Age at first appearance does not appear to affect materially the likely speed of resolution. Smaller lesions probably resolve more rapidly. An early onset of resolution is generally associated with a more rapid disappearance and a superior cosmetic result. Conversely, a late start to resolution is generally associated with a higher chance of incomplete regression. Lesions that resolve completely have almost always started to regress by the age of 5 years. There is very little evidence to support the widely held theory that ulceration accelerates the initiation of resolution.

Resolution of superficial infantile haemangiomas is heralded by a softening of the lesion and by the appearance of focal areas of greyish opacification in the central part of the surface. These foci gradually become confluent and extend towards the periphery of the lesion. When resolution has ceased, the affected area may be perfectly normal, but commonly it shows subtle atrophy and telangiectasia. With larger superficial lesions and at certain sites, particularly the lips, eyelids and upper chest, a residual sac of redundant and slightly atrophic skin commonly remains. Areas of previous ulceration frequently leave yellowish scars. Lesions in the scalp usually resolve without permanent alopecia in the affected area, unless previous ulceration has occurred.

Infantile haemangiomas at certain sites appear to regress particularly slowly and generally incompletely. This is certainly true of lesions on the nose (sometimes termed the 'Cyrano' or 'Pinocchio' nose), the lips and the parotid area.

The engorged superficial veins that may be prominent around larger infantile haemangiomas also seem to disappear when resolution is complete.

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Diagnosis. There is rarely any difficulty making the diagnosis of infantile haemangioma, particularly in the case of the superficial type. The main problem has been to distinguish vascular malformations from deep or mixed deep and superficial haemangiomas of infancy. The literature contains many reports in which lesions called 'haemangioma', often 'cavernous' haemangioma, clearly relate to vascular malformations; these reports are frequently concerned with the failure of such lesions to resolve spontaneously, or the fact that they may enlarge, at puberty for example [1]. The principal features distinguishing vascular malformations are: (i) the history of a lesion present since birth; (ii) the lack of any tendency to spontaneous resolution, and (iii) the frequent presence in the area of the lesion of other elements such as port-wine staining,

eccrine angiomatous naevus and lymphangioma circumscriptum. Currently, ultrasound, computed tomography (CT) and MRI are of limited value in making the distinction, as both lesions tend to be reported as 'haemangioma'. However, the distinction is a very important one, and fundamental to the patient's correct management as it has such great effects on prognosis and therapy.

Several types of tumour occurring in infancy may present with cutaneous nodules resembling superficial, deep or mixed haemangiomas; these include congenital haemangioma, granuloma telangiectaticum [2], neuroblastoma [3,4], infantile myofibromatosis [5,6], rhabdoid sarcoma [7,8], fibrous hamartoma of infancy [9], fibrosarcoma [10], congenital leukaemia [11], haemangiopericytoma [12,13], rhabdomyosarcoma [14,15] and leiomyosarcoma [16].

Recent studies suggest that ultrasound can be useful in distinguishing infantile haemangiomas from other soft tissue tumours and from vascular malformations [17]. CT and MRI can also be useful in delineating the extent of an infantile haemangioma and in evaluating response to therapy [18,19].

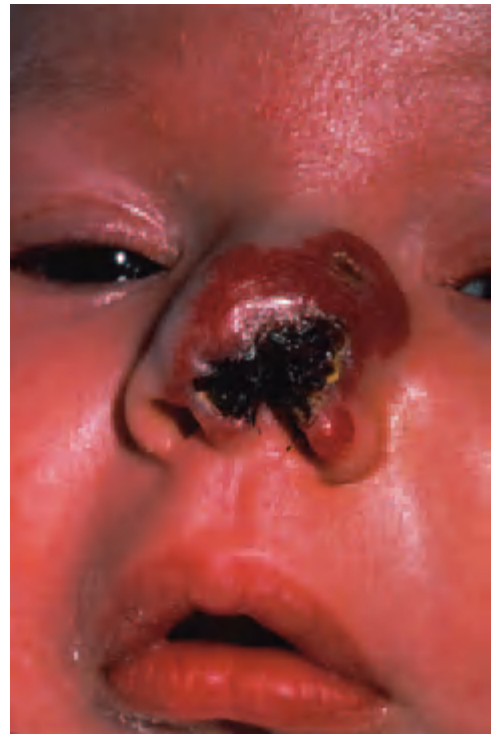

Fig. 15.9 Small ulcerated infantile haemangioma on the nose, which will result in substantial disfigurement.

Complications of infantile haemangioma

Ulceration and haemorrhage

Ulceration is a frequent complication of superficial infantile haemangiomas, and occurs almost exclusively during the proliferative phase. The commonest type of haemangioma to ulcerate is the plaque type [1]. Ulceration is commonest at sites which are vulnerable to trauma or maceration. It is for this reason that lesions in the anogenital area very commonly ulcerate, and this may result in dysuria or pain on defaecation. Other sites at which ulceration often occurs are the ears, nose and lips, where it may rapidly cause permanent loss of tissue, and mutilation (Fig. 15.9).

Bleeding is commonly the forerunner to ulceration, and may complicate it at any time. Such bleeding may be no more than a slow ooze, but it is occasionally brisk; it is however very uncommon for significant blood loss to occur. When bleeding has occurred, parents may become extremely anxious, fearing their child may exsanguinate when out of their sight, especially at night. Occasionally, an enuresis-warning blanket may provide reassurance in this situation [2]. Normally, compression will stop bleeding, but in an emergency, tissue adhesive sclerosis may be life saving [3].

Ulceration will almost certainly be followed by scarring.

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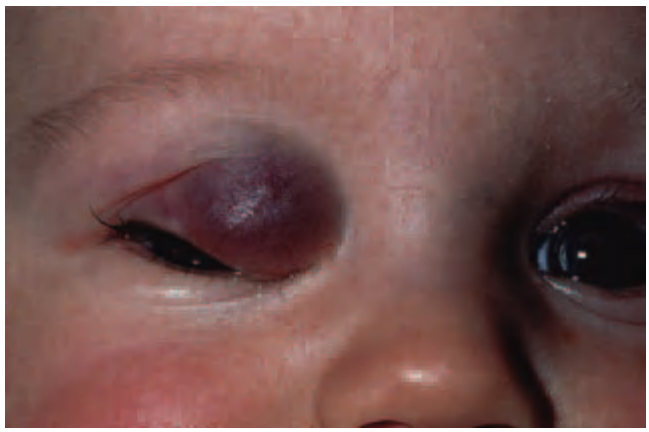

Fig. 15.10 Small upper eyelid infantile haemangioma obstructing the line of vision and indicating immediate intervention.

Infection

Secondary infection may occur in an ulcerated haemangioma, or following surgical intervention. Occasionally, this may lead to septicaemia, with a potentially disastrous outcome [4–6]. Group A streptococci appear to be particularly dangerous in this situation.

Malignant change

Although malignant change may be a complication of hepatic haemangiomas [7], it almost certainly never complicates cutaneous infantile haemangiomas. However, true malignant vascular tumours in infants might conceivably be initially mistaken for infantile haemangiomas, particularly when they have a deep location. Such tumours include malignant haemangioendotheliomas [8] and malignant haemangiopericytomas [9].

Heart failure

Shunting of large volumes of blood through a large infantile haemangioma may lead to high-output heart failure [10].

Systemic haemangiomas

Visceral haemangiomas may occur with or without coexistent cutaneous infantile haemangiomas [11]. They are most often, but not exclusively, encountered in association with miliary haemangiomatosis.

Impairment of vision [12–17]

Infantile haemangiomas involving the eyelids and/or the orbit can interfere with vision in several ways (Fig. 15.10).

Firstly, obstructive amblyopia may result if the lesion directly obscures the line of vision. Currently available data suggest that closure of the eye for only a few days during the first year can result in obstructive amblyopia, so that obstruction of the line of vision by an eyelid infantile haemangioma should be regarded as an emergency.

Secondly, lesions in the eyelid or orbit may lead to astigmatism, even when the line of vision is not obstructed, probably due to a direct pressure effect on the cornea, and this can lead to astigmatic amblyopia. Eyelid lesions able to cause astigmatism may be only a few millimetres in diameter. The only clue to orbital involvement, other than an eyelid haemangioma, is proptosis.

Very marked proptosis may lead to exposure keratitis.

Whatever form of treatment is selected for the haemangioma, referral to an ophthalmologist who is familiar with these issues will be indicated, and it will probably be necessary to patch the unaffected eye, in order to minimize amblyopia and strabismus.

Airway obstruction

It is important to consider the possibility that any infant with a cutaneous infantile haemangioma may have a concurrent subglottic haemangioma [18–20]. This is most likely if the cutaneous lesion is in the lower part of the face, or the neck [20,21]. There may be direct extension into the subglottic airway from these sites. Symptoms most characteristically first develop between weeks 6 and 12, with progressive stridor which is most marked during feeding or crying. Cough, hoarseness and cyanosis may also be present. Acute airway obstruction may occur suddenly during a period of rapid enlargement, or as a result of haemorrhage within the tumour, and it has been estimated that untreated subglottic haemangiomas are associated with a mortality approaching 50% [19].

Any suspicion of subglottic angioma is an indication for X-rays of the area, followed, if necessary, by direct laryngoscopy.

Involvement of the nose in the neonatal period may also obstruct respiration, as neonates normally will not breathe through the mouth. However, the obstruction generally occurs slowly enough to allow the infant to adapt, although inability to breathe through the nose is likely to interfere with sucking and therefore with nutrition.

Interference with feeding

Feeding difficulties may complicate haemangiomas on the lips, particularly if ulcerated, and those that restrict nasal breathing.

Obstruction of the external auditory canal

Infantile haemangiomas that encroach on the ear, particularly those in the parotid area, may obstruct the external auditory canal. Although this will interfere with hearing

in the short term, it will generally not affect the development of normal ear function in the longer term. Bilateral obstruction after the age of about 1 year would, however, be likely to interfere with normal speech development, but must be very rare.

Deformation of bone

Deformation of bone occasionally results from direct pressure of an infantile haemangioma, and this is particularly likely to happen in the calvarium, the orbit or the mandible [22]. Very rarely, large infantile haemangiomas of the face may provoke overgrowth of the facial skeleton or of the auricular cartilage [23].

Spinal dysraphism and anogenital anomalies

Infantile haemangiomas in the lumbosacral area may be associated with underlying spinal dysraphism, tethered spinal cord, sacral anomalies, lipomeningocoele, imperforate anus, and genital and renal anomalies [24–27]. MRI is indicated if there appears to be a risk of such an association, which appears to be highest when the haemangioma is of plaque type, when it crosses the midline and when there is an underlying swelling, which is likely to indicate an associated lipoma, the presence of which may be suggested by deviation of the upper end of the gluteal cleft.

*PHACES syndrome (**p**osterior fossa malformations, **h**aemangioma, **a**rterial anomalies, **c**ardiac anomalies and coarctation of the aorta, **e**ye abnormalities, **s**ternal cleft and/or supraumbilical raphe)*

An association between posterior fossa brain abnormalities and large facial infantile haemangiomas is now well recognized [24,28–33], and there is evidence that the association may occur more commonly in female infants [34]. The facial haemangiomas most characteristically take the form of extensive plaques, that appear to occupy one or more facial dermatomes, and they may initially be mistaken for port-wine stains. They may be either unilateral or bilateral. Ulceration is common. The commonest posterior fossa abnormality is the Dandy–Walker syndrome, but other abnormalities have included arachnoid cyst, cerebellar atrophy with enlarged cisterna magna and fourth ventricle, cerebellar atrophy with vermis agenesis, and agenesis of the corpus callosum. These posterior fossa abnormalities may be reflected clinically by macrocephaly, enlarging head circumference, hemiparesis, developmental delay, or may be found on imaging in the absence of symptoms. Ipsilateral intracranial haemangiomas may also occur; they are generally asymptomatic and appear to regress spontaneously in parallel with associated extracranial lesions [35].

Such structural brain abnormalities are the most common extracutaneous manifestation. Next in frequency are intracranial and neck arterial anomalies [36,37]. These anomalies are associated with a risk of aneurysms and cerebral infarction [38].

These patients may also have cardiac anomalies, particularly coarctation of the aorta [29], pharyngeal or laryngeal haemangioma, a wide variety of eye abnormalities, including glaucoma [39], and ventral developmental defects, most characteristically sternal clefting or a supraumbilical raphe [40–44]. Affected children may show only one extracutaneous component of this syndrome, or combinations of several.

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Congenital haemangiomas

It is now recognized that there is a distinctive type of haemangioma that is already fully developed at birth [1,2]. These tumours have been detected by ultrasound from the 12th week of gestation [1]. Pathologically they differ from other infantile haemangiomas by not expressing tissue-specific markers found in placental endothelium, in striking contrast to infantile haemangiomas [3].

Clinically, the feature that principally distinguishes them is their lack of a proliferative phase, and their tendency to involute very rapidly with the whole process generally being complete within the first year [1,3]. An occasional but highly characteristic finding has been the presence of hypertrichosis and/or milia-like lesions [2,4].

There is also a rare non-involuting type of congenital haemangioma [5]. These tumours have always been single, with an average diameter of 5 cm, enlarging in proportion to the child's growth. The overlying skin often shows coarse telangiectasia. The ideal treatment is excision.

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Miliary haemangiomatosis of infancy

Occasionally, infants are born with very large numbers, generally many hundreds of small infantile haemangiomas of 'strawberry' type, or develop these within the first few weeks of life [1,2]. In such cases, the cutaneous lesions are characteristically relatively small, generally between 2 mm and 2 cm in diameter. The lesions may bleed, and quite often at least some are pedunculated. This condition, which is perhaps best termed *miliary haemangiomatosis of infancy* (Fig. 15.11), should not be confused with the relatively common situation in which a child develops a number of otherwise standard infantile haemangiomas. In these cases, appropriately termed *multiple infantile haemangiomas*, the number of lesions present will rarely number more than 10, in great contrast to miliary haemangiomatosis of infancy, in which lesions will generally number several hundreds, often thousands.

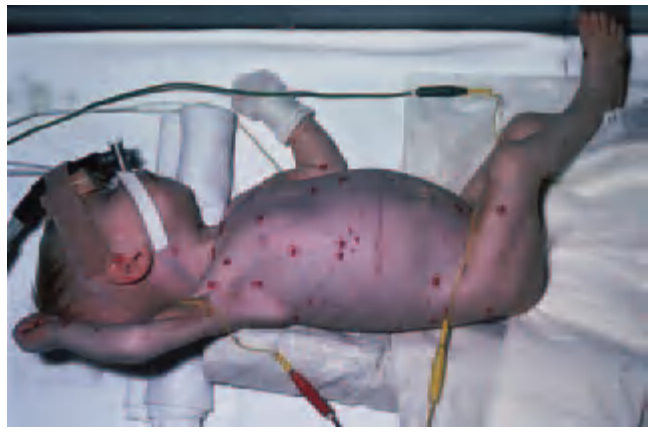

Fig. 15.11 Miliary haemangiomatosis causing cardiac failure in a 3-month-old infant.

Major complications may supervene, generally due to the presence of associated systemic haemangiomas, and these are responsible for a significant mortality, probably currently in the region of 25% [3,4]. The mean age of death in a large series was around 10 weeks [3]. The most serious of all complications is high-output cardiac failure, which is almost invariably due to shunting through one or more large hepatic angiomas [4–7], and which may be present at birth [8].

Apart from the liver, haemangiomas are also commonly present in the gastrointestinal tract, spleen, pancreas, salivary glands, adrenals, larynx, lungs, heart, skeletal muscle, kidneys, bladder, testes, thymus, thyroid, bone, meninges, brain and eyes [3,5,9–29].

Other potentially lethal complications include convulsions [12], intestinal haemorrhage [18] and obstructive liver disease [16,23].

The Kasabach–Merritt phenomenon has been reported frequently. However, while these cases may demonstrate low-grade thrombocytopenia, with platelet counts in excess of 50 000/mm^3 [3,11,12,30,31], the term Kasabach–Merritt syndrome is not warranted and the threat of severe coagulopathy is very low indeed.

In addition, individual haemangiomas may cause a wide variety of features due to local pressure. Convulsions and nerve palsies are particularly characteristic [32,33].

Intrauterine complications may occur, particularly hydrops fetalis and haemorrhage [8].

Certain investigations are therefore more or less mandatory in any infant with miliary haemangiomatosis, whether or not there is clinical evidence of systemic involvement. These include a full blood count including a platelet count, urinalysis to exclude bleeding, faecal occult blood testing, a chest X-ray to determine heart size and to seek lung lesions that might cause arteriovenous shunting, echocardiography to establish output status, and an abdominal ultrasound examination to examine the liver [34]. Where suspected on clinical grounds, lesions in other organs may be sought by appropriate investigations, including the use of technetium 99m-labelled red cells [6,35,36] and MRI.

The small haemangiomas that characterize miliary haemangiomatosis of infancy involute spontaneously, and typically do so more rapidly than in the case of standard infantile haemangiomas, the skin lesions often more or less disappearing by the age of 12 months [22].

Management is essentially as for single or multiple infantile haemangiomas. Treatment is not always indicated, and the need for intervention should be guided by careful evaluation of the risk of serious complications. It appears probable that prompt initiation of pharmacological treatment can reduce the risk of development of high-output cardiac failure where this is not yet established, and can be valuable when it is [6]. Where such complications are already present, systemic corticosteroid therapy is urgently indicated and the authors would recommend either pulsed intravenous methylprednisolone or prednisolone in a dose of 3–5 mg/kg/day, depending on the level of risk. If steroids are not rapidly effective, interferon-α (IFN-α) should be considered [7]. Anxieties have been raised concerning whether the combination of steroids and IFN-α is beneficial, and whether it might be associated with increased toxicity [37]. It is unclear therefore whether it is best to use the combination or to discontinue systemic steroid treatment when initiating IFN-α.

Where high-output failure is established and fails to respond to pharmacological therapy, selective arterial embolization of the responsible high-flow lesions in the liver will need to be considered urgently [7,38,39]. Resection may also be an option for single lesions [7].

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Treatment of infantile haemangiomas

In the absence of complications or substantial aesthetic handicap, the most appropriate management of infantile haemangiomas is generally expectant. No treatment is indicated where a good aesthetic outcome can be predicted with reasonable confidence, and where complications appear unlikely to supervene. It can be helpful to show parents serial photographs illustrating the spontaneous resolution that has been observed in other cases.

It is very important to be aware of the speed with which these lesions can enlarge during their initial phase of growth. The progress of lesions that are still increasing in size should therefore be supervised, especially where they occur at or close to the special sites mentioned above. The need for therapeutic intervention should be kept under review until the situation has stabilized.

Despite the good prognosis for spontaneous resolution of most infantile haemangiomas, there is no justification for therapeutic nihilism. The need for treatment of individual lesions should be carefully and sympathetically considered, and procrastination should be avoided because delay may severely reduce the opportunities for successful treatment. Even small lesions may result in major aesthetic handicap at certain sites, such as the tip of the nose, the lip or the forehead, and, while a good result may ultimately be anticipated following spontaneous resolution, sufficient psychological harm may have been done in the meantime to justify earlier therapeutic intervention.

Where infantile haemangiomas are causing or threatening tissue loss secondary to ulceration (e.g. on the nose or ears), where airway obstruction is threatened or feeding is impeded, where there is interference with important structures such as the eyelids, or where the aesthetic handicap is significant, immediate treatment should be contemplated.

Treatment options include: (i) systemic corticosteroids; (ii) intralesional corticosteroids; (iii) topical corticosteroids under occlusion; (iv) laser therapy; (v) compression; (vi) surgical excision; (vii) embolization; (viii) vincristine; (ix) cryotherapy; (x) IFN-α-2a; (xi) sclerosant injection; and (xii) radiotherapy. Each case requires careful assessment and observation, knowledge of the advantages and disadvantages of the available therapeutic options, and familiarity with the natural history of this tumour at various sites.

Systemic corticosteroids

Systemic corticosteroids are the treatment of choice in most situations in which therapy is indicated (see Fig. 15.8) [1]. However, it is important to be aware that they are only effective during the proliferative phase [2–7]. For this reason, there is some urgency in making the decision to start treatment. Oral corticosteroid therapy should therefore be initiated at the first sign that the patient is developing a significant eyelid lesion, cardiac failure or upper airway obstruction.

Prednisolone should be given in a daily dose of 3–4 mg/kg body weight for 4–8 weeks, followed by gradual reduction of the dose over a period of several weeks. Alternate daily dosage regimens tend to be ineffective if used from the start of treatment. If no response is seen after 3–4 weeks, prednisolone therapy should be abandoned. A good response can be anticipated in the great majority of cases if treatment is started sufficiently early at a dose no less than 3 mg/kg/day. Treatment should also be contemplated when the integrity of the nose, ears or lips is threatened. Rebound increase in size may occur if treatment is discontinued too soon in rapidly proliferative lesions. Since such lesions can generally be expected to continue to proliferate during the first 6 months of life, it is usually unwise to discontinue therapy altogether until the seventh month.

The mechanism by which corticosteroids prevent further growth and reduce the bulk of infantile haemangiomas remains unclear. It has been shown that corticosteroids are able to increase microvascular sensitivity to endogen-

ous vasoconstrictor substances [8], and this effect may impede endothelial proliferation. It is perhaps more likely that corticosteroids modify endothelial proliferation more directly. Corticosteroids have been demonstrated to have an inhibitory effect on angiogenesis in the presence of heparin and heparin fragments [9,10]. Corticosteroid molecules bind to steroid receptors within proliferating haemangiomas, and may thereby inhibit the binding of 17β-oestradiol; corticosteroid administration in this situation also appears to result in a reduction in the levels of circulating 17β-oestradiol [11].

Infants tolerate this type of therapy remarkably well, and it is very unusual for adverse effects to occur that will not reverse within months of discontinuing therapy [12,13].

Intralesional corticosteroids

Intralesional injection of corticosteroids may effect rapid shrinkage, and is a very popular treatment for lesions of the eyelids [14–18]. In general, two or three treatments are required at approximately 6-week intervals. The failure rate is around 30%. It is important to bear in mind that substantial quantities of corticosteroid are being injected and that significant adrenal suppression may occur [19]. Local complications are unusual [15], but have included subcutaneous fat atrophy and eyelid necrosis, orbital fat atrophy, eyelid depigmentation and localized dystrophic calcification [20–24]. Retrobulbar haemorrhage may occur [15], and there have been several reports of central retinal artery occlusion and blindness [25–28]. The incidence of complications, which include accidental injection of the eye itself and damage to the optic nerve, is higher when retrobulbar lesions are treated.

This treatment has been used successfully to arrest proliferation and to shrink infantile haemangiomas at other sites [29,30]. Superficial haemangiomas have shown the best response, though overall results have not been as good as for eyelid lesions. Complications have included cushingoid appearance, cutaneous atrophy and anaphylaxis [30].

Combination therapy with systemic and intralesionally injected corticosteroids has also been advocated [31].

Topical corticosteroids

It has been suggested that potent topical steroids, with or without occlusion, can be an effective treatment approach for small haemangiomas of infancy [32,33].

Interferon-α [34]

Recombinant IFN-α-2a was originally developed as an antiviral agent. During trials in patients with the acquired immune deficiency syndrome (AIDS), it was found that IFN-α-2a had an inhibitory effect on Kaposi's sarcoma. IFN-α appears to inhibit endothelial cell proliferation [35].

Experience in complicated cutaneous haemangiomas of infancy has suggested, but not firmly established, a useful effect for both IFN-α-2a [36–40] and IFN-α-2b [41,42]. It is extremely difficult to evaluate the results of such treatment in open studies in a disorder in which spontaneous resolution is the norm [43], and lack of benefit has been reported [44]. For the present, therefore, the true value of IFN-α remains unestablished. Its benefit appears more slowly than that of systemic corticosteroids and this is certainly a limiting factor when rapid shrinkage of a proliferating haemangioma is required. Treatment with IFN-α will generally need to be prolonged [45].

There are theoretical reasons to worry that combination of systemic corticosteroids and IFN-α may be contraindicated [46], though the possibility of syngergism has also been suggested [41].

The cost of treatment is very substantial.

Increased serum transaminase levels are almost invariable; increases up to five times the upper limit of normal are not a cause for withdrawal of therapy. Prolonged treatment carries a risk of thyroid dysfunction. Neurotoxicity, in the form of spastic diplegia, is now thought to occur in as many as 20% of infants treated with IFN-α-2a, possibly less with IFN-α-2b [47–49].

Vincristine

There have been reports indicating the potential value of vincristine given orally as a single weekly dose of 2 mg/m^2 of body surface area in the treatment of life-threatening haemangiomas [50,51].

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Laser therapy

The 585-nm flashlamp-pumped pulsed dye laser [1–5] has been used in an attempt to prevent enlargement of lesions at the macular or initial plaque stage during their early development. However, recent data suggest that it is unlikely to be effective [5–8].

The 585-nm flashlamp-pumped pulsed dye laser can be used to lighten any superficial haemangiomas and to flatten thin lesions (i.e. less than 4 mm), but flattening cannot be anticipated in thicker lesions [2] because the depth of penetration is limited to about 1 mm. This type of laser has been used to treat the very small haemangiomas that occur in miliary haemangiomatosis [9], but the excellent prognosis of this type of haemangioma would argue against such an intervention.

The flashlamp-pumped pulsed dye laser has proven valuable for reduction of pain and initiation of healing in ulcerated haemangiomas, where the ulceration has persisted despite good wound care techniques [10,11].

Excision using the carbon dioxide laser may be useful for the cosmetic therapy of lesions persisting into adult life, particularly lesions in the mouth, although a degree of scarring is inevitable [12–14].

Another laser that has been used for infantile haemangiomas is the neomydium : yttrium aluminium garnet (Nd : YAG) laser, which emits in the near infrared region and can produce photocoagulation to a depth of 1 cm [15]. Successful treatment of fully developed infantile haemangiomas has been reported, albeit with some post-treatment scarring, although this is probably less marked than with carbon dioxide laser excision [16,17]. In one report, treatment with this laser was followed by intralesional corticosteriod injection [18]. Improvements in the treatment of thick haemangiomas with the Nd : YAG laser may follow the introduction of special techniques such as skin surface cooling during irradiation or compression of

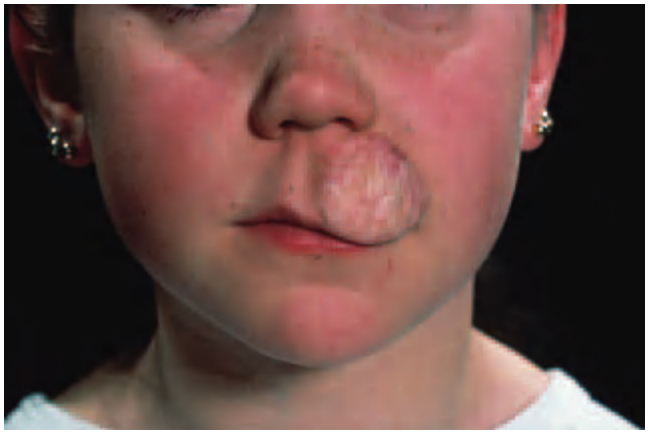

Fig. 15.12 Incompletely resolved infantile haemangioma in a 10-year-old, requiring surgical excision of residual sac.

lesions using cooled glass [19,20]. Intralesional radiation using light guides has also been described as having value in the shrinkage of large haemangiomas [21,22].

The development of the sapphire tip Nd : YAG laser scalpel permits excision with excellent haemostasis, and may prove a useful tool in the surgical treatment of infantile haemangiomas [23].

Compression

Another approach to the treatment of infantile haemangiomas that may be useful in individual cases is compression bandaging or intermittent pneumatic compression [24–30]. While it is not proven that this treatment can accelerate spontaneous resolution, compression bandaging can certainly provide temporary reduction of bulk that may allow a child with a giant infantile haemangioma on the trunk or a limb to wear normal clothes. Respiratory distress and/or cardiac failure are potential complications of overenthusiastic application of compression to large haemangiomas [31,32].

Surgical excision

Surgical excision is most often indicated for the redundant folds of atrophic skin that frequently persist after spontaneous involution of larger infantile haemangiomas (Fig. 15.12).

Surgical excision is also indicated in certain situations earlier in the evolution of infantile haemangiomas. This approach is particularly suitable for those lesions that are fairly spherical, particularly where these are of mixed type as this allows closure to be straightforward. Surgical excision should be considered for eyelid lesions, where it may sometimes be preferable to other techniques, similarly for disfiguring but small facial lesions, such as those that occur on the forehead [33].

A particular situation where surgery can be very successful is the nasal tip haemangioma [34–38], which can lead to significant cosmetic handicap, and which is notoriously reluctant to resolve spontaneously.

Extensive and complicated infantile haemangiomas affecting the head and neck may warrant surgical treatment in selected cases [39], and may be most appropriately treated by combining different treatment approaches [23].

Reconstructive surgery is indicated where tissue destruction has occurred during the proliferative phase of infantile haemangiomas. This is most commonly appropriate in relation to the face, when ulceration has led to the loss of parts of the nose, lips or ears.

Surgical excision may also be indicated for cosmetic reasons in lesions that prove unusually slow to regress or which fail to resolve completely. Sympathetic consideration is warranted for lesions on the face in school-age children, and occasionally in younger children, and the arguments for and against such intervention need to be carefully considered. A uniformly negative approach to treatment of infantile haemangiomas remains prevalent among dermatologists and paediatricians, and this may, in the authors' view, result in much unnecessary morbidity.

Embolization

Embolization techniques have been found to be useful in the treatment of hepatic haemangiomas, particularly in infants with high-output cardiac failure [40–42]. There has been considerable interest in the possible value of these techniques for the treatment of occasional complicated infantile haemangiomas in the skin, particularly those that threaten vision, for the relief of airway obstruction caused by oropharyngeal and subglottic haemangiomas [43,44], and for the treatment of high-output cardiac failure.

Cryotherapy

Excellent results have been claimed for cryotherapy in the treatment of superficial and deep infantile haemangiomas [45,46], although there is undoubtedly some risk of scarring [47].

Sclerosant injection

Where involution is incomplete and accurate serial measurements over a period of at least a year show no further involution, the injection of sclerosing solutions [48,49] may shrink deep infantile haemangiomas. The solutions preferred include sodium citrate 30%, mono-ethanolamine oleate 5%, glucose 30% and saturated saline. Using a small needle, 0.5–5.0 ml is injected at fortnightly or monthly intervals. Excellent results have been claimed.

Metallic magnesium is a powerful sclerosant, and its insertion into rapidly proliferating infantile haemangiomas has been reported to be an effective treatment approach [50,51].

Radiotherapy

Although radiotherapy is still sometimes employed [52], its use is difficult to justify in the case of cutaneous haemangiomas, though it may occasionally have a place in the therapy of certain systemic haemangiomas where these are causing problems, in bones, pituitary fossa or in the liver [41], for example, where other approaches have failed or are not feasible. The results of a controlled trial cast doubt on the effectiveness of radiotherapy for infantile haemangiomas [53]. Furthermore, there are a number of undesirable long-term sequelae. Such treatment carries the risk of carotid artery occlusion [54]. There is also a longer-term risk of disturbed bone growth and hypoplasia of soft tissues such as the breast [55,56] and larynx [57], and of cataract following therapy of eyelid lesions [58]. Although in one large survey, no evidence of an increased risk of malignancy was found [59], others have disagreed [60–62]; the CNS and thyroid gland appear particularly at risk in this respect [62]. In addition, there have been reports of development at the site of the irradiation of basal cell carcinomas [63], squamous carcinoma [64] or angiosarcoma [65,66], and in addition bone, thyroid, breast and soft tissue tumours [67–70].

Treatment of cardiac failure

Early therapy aimed at reduction of the shunt is essential, if life is to be saved once high-output cardiac failure becomes manifest, although medical treatment may occasionally be effective [71]. Systemic corticosteroids may lead to regression of hepatic haemangiomas and reversal of cardiac failure. If this approach fails, hepatic artery ligation [72–75], partial lobectomy [76] or transarterial embolization may be indicated [40,77,78].

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Other haemangiomas of infancy

Tufted angioma

SYN. ANGIOBLASTOMA [1–4]

This is a rare type of angioma, which is seen most often in prepubertal children of either sex. Most cases have had an onset during early childhood, and lesions probably most commonly are present at birth or appear in the early weeks of life. Acquired cases have also been described in adults [5–8]. The initial appearance of tufted angioma during pregnancy has been reported [9], as has the eruption of multiple lesions in an immunocompromised adult liver transplant recipient [10].

It is also now clear that this tumour and kaposiform haemangioendothelioma are together responsible for the great majority of cases of the Kasabach–Merritt syndrome [11,12]. Cases of the Kasabach–Merritt syndrome presenting to dermatologists will almost always be due to tufted angiomas.

Histologically, there is a lobular proliferation of plump, oval cells surrounding tiny slit-like lumina [3]. These blood vessels are tightly packed and organized in rounded tufts, scattered in the dermis, and often described as resembling cannon-balls. The tufts may occur deeply in the dermis, and into the subcutis [13,14]. Thin-walled lymphatic channels may be seen at the periphery of the cellular masses or throughout the dermis.

MRI has demonstrated extension into muscle and fascia [15].

Clinically, tufted angioma takes the form of a rather poorly delineated, pinkish macule that evolves into a deep-red or purplish, indurated plaque or nodule, up to 20 cm in diameter. The lesion may be a fully developed plaque or mass at birth. They need to be distinguished particularly from port-wine stains, morphoea, lipogranuloma,

connective tissue naevus, smooth muscle hamartoma, lymphoma and sarcoma. Most lesions are tender or painful, and fine lanugo hair and/or hyperhidrosis are often apparent over the surface of the lesion. The lesion may extend deeply through the subcutis, fascia and into muscle [1,15].

Most tufted angiomas expand slowly for a period of months or years, after which they stabilize. Although they probably mostly remain unchanged unless treated, on occasions they may slowly resolve spontaneously [6,16]. These tumours generally appear to behave in a benign fashion, but may progressively worsen in some cases [17].

Generally, excision has been performed, although incomplete excision may result in recurrence. Soft X-ray therapy has also been reported to be successful [18]. There has been a single report of successful treatment with the pulsed dye laser, although the depth of these lesions would suggest that this treatment would be unlikely to be helpful [19]. Potent topical corticosteroids have been reported to reduce pain [1]. Successful or partly successful use of IFN-α-2a has been reported [15,20,21], but not all lesions respond [22]. High-dose systemic corticosteroids may be beneficial [22], and perhaps this treatment or IFN-α-2a should be tried before proceeding to excision, particularly where lesions are extensive.

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Kaposiform haemangioendothelioma [1–3]

Kaposiform haemangioendothelioma is a rare vascular tumour occurring exclusively in childhood. It generally makes its appearance rather later than infantile haemangiomas, often months or years after birth, and is frequently a cause of the Kasabach–Merritt syndrome [2].

In the majority of cases, these tumours develop in the retroperitoneum, most often presenting around the age of 1 year [1,4]. Less commonly the presentation is cutaneous, either superficial or deep [1,5]. In the skin, kaposiform haemangioendothelioma tends to be a single lesion, which initially has the appearance of an innocuous vascular stain, but in other cases the lesion is subcutaneous and initially inapparent. After a variable interval, usually a few months, the lesion starts to grow rapidly to form a mass [6], which is generally complicated by development of the Kasabach–Merritt syndrome [5]. Congenital lesions have been reported occasionally [7]. Cases have also been reported in which there have been multiple cutaneous lesions [7].

Histologically, kaposiform haemangioendothelioma is composed of lobules or sheets of tightly packed spindled or more rounded endothelial cells and pericytes, with an infiltrative pattern in the dermis, subcutaneous fat and muscles. They contain few vascular lumina. Nuclear hyperchromasia and atypia are generally absent or minimal, and mitoses are rare [1]. As in tufted angioma, thin-walled bloodless vascular channels may be seen at the periphery of the cellular masses or throughout the dermis and subcutis; it is not clear whether these are an integral part of the tumour, or an associated lymphangiomatosis, or perhaps lymphatic hyperplasia secondary to obstruction of the lymphatics [1,2].

It is possible that tufted angioma and kaposiform haemangioendothelioma are the polar forms of a single pathological entity, and histological overlap has been observed [7].

Mortality in retroperitoneal kaposiform haemangioendothelioma appears to be high. These lesions are often large and frequently bleed locally. Skin lesions appear to have a much lower mortality [5]. Spontaneous regression of skin lesions has been reported, generally within the first 5 years of life [2].

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Kasabach–Merritt phenomenon [1]

SYN. KASABACH–MERRITT SYNDROME; HAEMANGIOMA–HAEMORRHAGE SYNDROME

Consumption coagulopathy is an uncommon but highly characteristic complication of haemangiomas in infancy (Fig. 15.13). It is now clear that this complication almost exclusively occurs in association with tufted angiomas and kaposiform haemangioendotheliomas, occasionally with congenital haemangiopericytoma, but rarely if ever in association with the common type of infantile haemangioma [2–4].

An analogous bleeding diathesis has also been described as a complication of glomangiomas [5], in association with Gorham's disease [6–8], the blue rubber bleb naevus syndrome [9] and of angiosarcoma, both in an infant [10] and in an elderly adult [11].

A low-grade consumption coagulopathy may occur on a life-long basis in association with extensive lymphatic and venous vascular malformations. However, this coagulopathy is characterized more by reduced levels of circulating fibrinogen and clotting factor, and by increased levels of fibrin degradation products, whilst platelet counts remain reasonably high, usually over 70 000/mm^3. Cases of this type have occasionally inappropriately been termed Kasabach–Merritt syndrome [12].

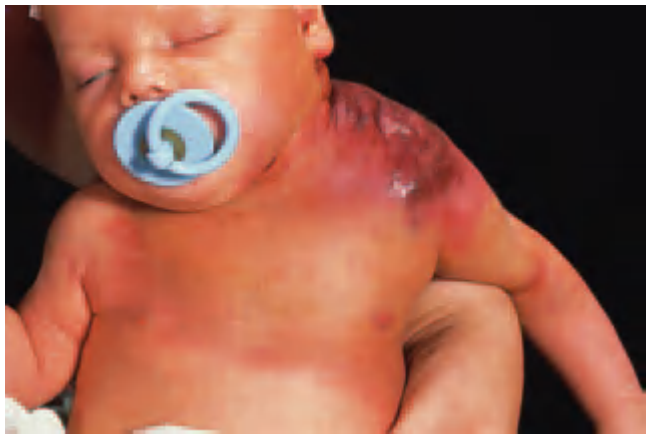

Fig. 15.13 Kasabach–Merritt phenomenon: a deep angioma which has rapidly increased in size and became indurated and tender, with extensive subcutaneous bleeding.

A degree of thrombocytopenia may also be noted in children with miliary infantile haemangiomas, although it is very rare for significant coagulation defects to supervene in such cases [13,14]. The term Kasabach–Merritt phenomenon is inappropriate for such cases.

Haemorrhage in the Kasabach–Merritt syndrome appears to be a consequence principally of platelet sequestration, with associated consumption of clotting factors, within the vascular bed of the angioma, which has been demonstrated using chromium-51 or indium-111-labelled platelets [15,16], and more recently by an immunochemical method using monoclonal antibody to CD61 (platelet glycoprotein IIIa) [17]. The platelet count is very often extremely low, frequently less than 10 000/mm^3. Activation of the fibrinolytic system leads to the development of a continuing consumption coagulopathy in which increased consumption of platelets and clotting factors is balanced by their increased production [18]. Activation of the fibrinolytic system in this situation can be detected by the appearance of fibrin degradation products in the circulation. Under certain circumstances, for example surgical procedures, it is possible for acute disseminated intravascular coagulopathy to supervene with disastrous results [19]. Microangiopathic haemolytic anaemia has also been described [20].

Angiomas leading to the Kasabach–Merritt phenomenon may be cutaneous [2], intrathoracic, most often mediastinal, abdominal, especially retroperitoneal or intrahepatic [21,22], pelvic [23] or skeletal [7,8,24].

Cases of Kasabach–Merritt phenomenon presenting to dermatologists will almost all be due to tufted angiomas. Most of these cutaneous tumours are present at birth or appear during a period of months thereafter [25]. They are usually single lesions, taking the form either of an infiltrated reddish-blue plaque or a less defined deeper bluish tumour. They most commonly occur on the trunk, neck and proximal parts of the limbs, particularly the thighs and shoulders. The onset of Kasabach–Merritt phenomenon is signalled by a sudden and rapid increase in volume of the tumour, by a change in colour to a deeper violet, by the appearance of ecchymosis, which generally extends some way beyond the margins of the tumour, and often by tenderness. The rapid expansion of the angioma may cause potentially lethal compression of neighbouring vital structures, particularly when the lesion is in the cervicofacial area. In some case, the coagulation defect may already be present at birth [26], and it will become apparent in most cases within the first year of life. Occasionally, the onset of the coagulopathy is more delayed.

As a result of the coagulopathy, internal bleeding may occur at a great variety of sites, and is associated with a significant mortality, which reaches 40% of cases in some reported series [27].

If there is any doubt about the location of the angioma responsible for the Kasabach–Merritt phenomenon, an indium-111-labelled platelet scan may be invaluable [28,29].

Spontaneous resolution of the coagulopathy can be anticipated within a period of 1–6 years, and a mean of around 3 years [2]. Whereas the coagulopathy resolves, the causative tumour generally remains [3]. Where the responsible tumour is close to a joint, there may be residual limitation of joint mobility; this appears to be particularly common at the shoulder.

The Kasabach–Merritt phenomenon remains potentially lethal, particularly where the causative tumour is internal or where a more superficial tumour behaves in a rapidly infiltrative manner. However, treatment may itself have fatal complications. Because spontaneous resolution of the coagulopathy can be anticipated in the majority of cases [30,31], treatment is only absolutely indicated when it is likely that the patient's life is threatened. The choice of treatment will be determined by several factors, particularly the severity of the coagulation defect, the site of the causative tumour, and the presence or absence of associated mechanical compression of neighbouring viscera. Treatment of the Kasabach–Merritt phenomenon is characterized by highly variable responsiveness, and considerable versatility may be required in order to obtain control of the coagulopathy. Frequently multiple therapies are needed.

Systemic corticosteroid administration has been reported to have a directly beneficial effect on the disturbed coagulation–fibrinolysis system [32], and has occasionally proved valuable in the Kasabach–Merritt phenomenon [7,30,32]. Initial dosage should be between 2 and 4 mg/kg/day of prednisolone. Intravenous pulse therapy may be useful as a short-term measure [33,34]. General experience has been that prednisolone therapy is disappointingly ineffective when the coagulopathy is severe [35–37].

Benefit has been reported for injections of IFN-α-2a [38–40]. However, because the benefit is slow, this method is generally unlikely to be appropriate for the management of acute profound coagulopathy, but be worth considering when the coagulopathy is of relatively low grade.

Improved haemostasis can be accomplished by the use of platelet transfusions [41], although the effect tends to be abbreviated by rapid consumption of the platelets and clotting factors. In some cases, the coagulopathy may be worsened [42]. The principal use of this approach is in the preparation of the patient for surgical procedures including embolization.

Inhibitors of platelet function appear to have a limited role [43,44], although this has been disputed by reports of successful use of ticlopidine combined with aspirin [45,46], and of pentoxifylline [47]. There have been reports suggesting a role for inhibitors of fibrinolysis [31,48,49]. The concept of antifibrinolytic therapy, with agents such as tranexamic acid [50] or epsilon–aminocaproic acid [29], is that local thrombosis will be encouraged within the angioma vascular bed, reducing blood flow. Cryoprecipitate may also be required as a source of fibrinogen [49]. Recently, successful control of the coagulopathy has been reported with antithrombin III administration [22].

Although the spleen is often enlarged, splenectomy appears to be not only dangerous but also ineffective.

Limited experience suggests that continuous bandaging or intermittent pneumatic compression may be an effective treatment in controlling coagulopathy in the event that the lesion is appropriately sited, which is the exception [19,51].

Embolization can be an exceedingly valuable treatment [21,33,52–55], and can result in rapid and permanent reversal of severe acute coagulopathy.

Vincristine has proven very effective in the Kasabach–Merritt phenomenon, perhaps because it becomes bound to platelets and is therefore released preferentially at sites of platelet sequestration [2,25]. The recommended dose is 1.0–1.5 mg/m^2/week by slow intravenous infusion for at least 7 weeks, then with decreasing frequency, depending on response. This treatment appears to have a rapidly beneficial effect on the coagulopathy, and generally can also be expected to lead to shrinkage of the causative tumour over a period of months [25]. Successful combination treatment including vincristine has also been reported [56].

Surgical extirpation of tumours causing the Kasabach–Merritt phenomenon has been achieved in a number of cases with rapid relief of the coagulation defect [22,35,43,57], so long as adequate intraoperative haemostasis can be achieved. In the absence of adequate control of bleeding, surgical intervention may be catastrophic, and for this reason should not be contemplated unless embolization has been considered. On the other hand, surgical treatment may be more useful in the post-acute situation where the coagulopathy is controlled but the residual tumour is painful.

Radiotherapy may be effective in improving the coagulation defect [58], although the benefit may be rather delayed. Despite the risk of long-term complications [59], this approach has its advocates [27,60,61], and requires consideration in particularly difficult cases, although generally embolization should be preferred.

In general terms, the management of patients with the Kasabach–Merritt phenomenon should be as conservative as possible. Serial clotting studies and platelet counts should be undertaken, and the levels of fibrinogen and fibrin degradation products should be monitored. Oral corticosteroid therapy should be initiated early, and the

lesion should be compressed where this is possible. If the situation deteriorates, the relative merits of embolization, surgery, radiotherapy and infusions of vincristine should be weighed up. Frequently, the appropriate management will involve multiple therapies, used simultaneously or sequentially [62]. The likelihood of eventual spontaneous recovery of normal haemostasis and eventual regression of the angioma should be borne in mind at all times. It appears that vincristine and IFN-α may induce more long-term benefit in terms of tumour shrinkage.

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Verrucous haemangioma [1–3]

This appears to be a distinctive entity. Although almost invariably present at birth, verrucous haemangiomas may appear later, even in adult life. Lesions are single or grouped, occurring on the legs in the great majority of cases. Small satellite lesions are commonly present. Sometimes lesions have a linear or serpiginous arrangement [1,4]. A variant has been described in which multiple lesions occurred in a more disseminated distribution, without evidence of systemic lesions [5]. Another variant has been termed digital verrucous fibroangioma [6].

They tend to start life as well-defined, dark-red, macular areas of vascular staining resembling port-wine stains, sometimes developing into soft, bluish red, vascular swellings. After a variable number of years, lesions start to take on their characteristic bluish black hue and an increasingly verrucous surface. Recurrent bleeding and infection often cause the patient to seek medical advice for the first time at this stage [7].

Histologically, verrucous haemangiomas are characterized by a hyperplastic epidermis showing orthohyperkeratosis, papillomatosis and irregular acanthosis with elongated rete pegs. The underlying dermis shows vascular spaces of variable size, which are congested with blood and which fill the rete pegs. There are lobules of capillaries in the subcutis interposed with fat cells and fibrous tissue [3,8]. The capillaries are lined by flat endothelium. The endothelium stains strongly with CD34, and the pericytes surrounding these vessels stain strongly with HHF-35 (anti-muscle specific actin).

Clinically, these lesions are frequently misdiagnosed, most commonly as infantile haemangioma or angiokeratoma, sometimes as lymphangioma circumscriptum or verrucous epidermal naevi.

They are best treated by excision [1,8,9]. Larger lesions will need grafting. There is a tendency for recurrence to occur unless excision is complete [3,7,10].

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Digital verrucous fibroangioma

This lesion is regarded as a variant of verrucous haemangioma, based on its histological features [1]. It is however sufficiently distinctive clinically to warrant separate description. Lesions are generally single, and present from birth. They take the form of asymptomatic, soft to firm, domed nodules on the dorsum of a finger. Initially they are skin-coloured; with time they darken to a purplish brown colour.

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Haemangiopericytoma

This vascular tumour is more fully considered in Chapter 53. However, it is a tumour that should be mentioned specifically in connection with infancy because about 3–5% of all haemangiopericytomas are congenital, with a pattern of behaviour that sets them apart from other haemangiopericytomas. In this subgroup, tumour growth may be very rapid and the histological features may suggest malignancy. Such tumours have mostly occurred subcutaneously on the head and neck, the trunk and limbs, and also internally. They generally have a dark red colour, suggesting a vascular origin. Despite the worrying

histological features, these tumours appear to be biologically benign; they may resolve spontaneously [1] or be cured by excision [2]. Local complications have included external haemorrhage. Recurrence may follow incomplete excision [3].

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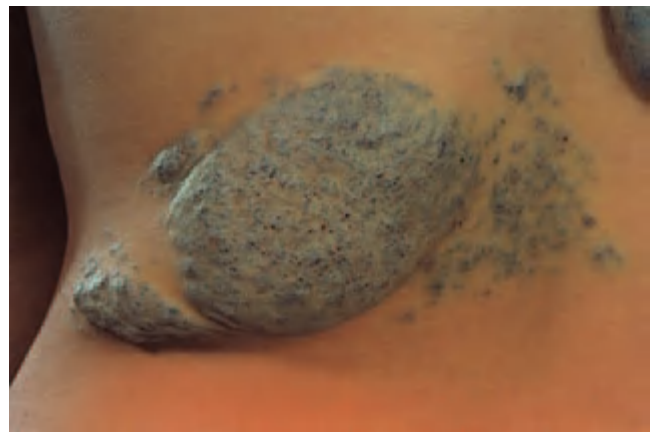

Fig. 15.14 Plaque-type glomangiomas on the back of a 14-year-old girl, which enlarged progressively.

Glomangiomas

SYN. MULTIPLE GLOMUS TUMOURS; GLOMANGIOMATOSIS

Although the commonest type of glomus tumour is the solitary form, which most frequently presents in young adult life, multiple forms are occasionally seen, predominantly in children, and these may cause substantial diagnostic difficulty.

Glomus cells are considered to be modified smooth muscle cells [1,2], which line the endothelial walls of structures known as *glomus bodies*. They are small cells which have eosinophilic cytoplasm and rounded, centrally placed nuclei [3]. They form structures termed glomus bodies which are found in the reticular dermis, and which are believed to function as temperature receptors. The solitary glomus tumour is an encapsulated proliferation of glomus cells lining small vascular lumina. In contrast, the childhood types are not encapsulated, and feature larger, more irregular vascular spaces, with fewer glomus cells; this type of lesion is considered hamartomatous and is now more usually termed *glomangioma*. Where a substantial proportion of the cells have the spindle appearance of conventional smooth muscle, the term *glomangiomyoma* has often been used [4].

Multiple glomus tumours generally have an earlier onset [2,5]. They are subdivided into three types:

1 disseminated multiple glomangiomas;
2 localized multiple glomangiomas;
3 plaque-like glomangiomas (glomangiomatosis).

Disseminated multiple glomangiomas. In the disseminated form, compressible red to blue papules or nodules, usually less than 1 cm in diameter, but occasionally larger, are widely distributed [6]. Their number is generally less than 10, but may occasionally be much greater [2,5]. Pain is less evident than it is in solitary glomus tumours [6].

Familial cases have been reported with what seems likely to be autosomal dominant transmission with variable penetrance and expression [2,4,7,8]. A mutation responsible for this condition has recently been identified and localized to chromosome 1p21–22 [9].

Localized multiple glomangiomas. The localized type of multiple glomangiomas features grouped blue nodules, which are usually limited to an area such as the hand or leg [3,10]. Mild pain may be present.

Congenital plaque-like glomangiomas. Plaque-like glomangiomas are extremely rare congenital lesions. They comprise numerous reddish blue compressible papules grouped in solitary or multiple plaques, each generally measuring between 10 and 20 cm across [11–14]. The lesions are soft, and the papules of which they are composed may be discreet or more confluent [15]. Such lesions may be painful. The centre of the plaque may be depressed [16]. The affected area may sag, and facial lesions may be very disfiguring [15]. Lesions affecting the lips tend to be spherical, soft, bright red nodules.

Some familial cases have been reported, suggesting an autosomal dominant transmission with variable expression [15,17,18].

Later onset has been described [19]. Partial involution has been described [20]. However, their normal behaviour is one of progressive growth with gradual enlargement of existing lesions and appearance of new lesions at previously unaffected sites (Fig. 15.14).

Deep infiltration into underlying muscles may occur [15].

Such lesions must be distinguished from tufted angioma, congenital plaque-like blue naevi [21], and from venous vascular malformations [11]. The latter distinction may be difficult, and can be simplified by the use of MRI [15].

Treatment has been disappointing, with poor response to pharmacological agents, to sclerotherapy and gradual recurrence after surgical resection [15].

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Vascular malformations

Vascular malformations are structural defects of vascular development. They can be subdivided into high- (arterial malformations and single arteriovenous fistulas) and low-flow types (capillary, venous and lymphatic malformations), although mixed anomalies are common (particularly capillary–venous, capillary–lymphatic and arteriovenous) [1–4].

Some types of vascular malformation are liable to be confused with infantile haemangiomas, particularly some types of venous and lymphatic malformation, and the term cavernous haemangioma has often been, and often still is, applied to lesions that are not haemangiomas at all, but one of a variety of vascular malformation. Although there may sometimes be a degree of clinical overlap, such vascular malformations can be distinguished pathologically by their lack of endothelial cell proliferation, and clinically by their presence at birth and their lack of any tendency to spontaneous resolution. They will generally grow in proportion to the child, although they may gradually increase in size, sometimes rapidly as a reflection of thrombosis, sepsis or trauma.

Under this heading we will consider those types of vascular malformations that are of most concern to the dermatologist.

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Capillary vascular malformations

SYN. TELANGIECTATIC NAEVI; VASCULAR STAINS

While this macular type of vascular anomaly has traditionally been separated into two principal types, the 'salmon patch' and the 'port-wine stain', the distinction is not always clear. Glabellar, forehead and upper eyelid salmon patches tend to fade very substantially, but similar lesions elsewhere, that are generally also called salmon patches, persist permanently. At several sites these lesions are called port-wine stains and salmon patches alternatively, for example those lesions on the upper lip or in the sacral area, and this can lead to substantial confusion. For this reason, there is a trend towards calling both types of lesion simply 'vascular stains'. In a recent review, the authors have called both types of lesion 'naevus flammeus', but have divided them into 'small' (salmon patch type) and 'large' (port-wine type) [1].

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Salmon patch

SYN. NAEVUS SIMPLEX; NAEVUS FLAMMEUS SIMPLEX; ERYTHEMA NUCHAE; UNNA'S NAEVUS; 'STORK BITE'; 'ANGEL'S KISS'

Salmon patches are extremely common anomalies, which have been observed in the neonatal period in about 20–60% of children of all races [1–13]. The apparently greater

incidence in white neonates reported in some studies may simply relate to the greater ease with which subtle salmon patches can be seen in white skin.

Like port-wine stains, these lesions have in the past been called *naevus flammeus*; this term is therefore best avoided. There is evidence of a definite genetic influence in their aetiology, and both nuchal and facial salmon patches seem to be inherited in an autosomal dominant manner [14–16].

Histologically, no abnormality may be apparent in infancy, but persisting nuchal lesions in adults show dilatation of subpapillary capillaries [17].

Clinically, the lesions take the form of irregular, dull, pinkish red, macular areas, often featuring fine, linear telangiectasia. The nape of the neck and the occiput are by far the most commonly affected sites, but facial lesions (on the glabella, forehead, upper eyelids, tip of the nose or philtrum) are also frequent, as are lesions elsewhere in the scalp [4,8,12,18,19]. Less frequently, there may be lesions at sites on the posterior trunk and, occasionally, the limbs. In a recent survey, nearly 1% of neonates were found to have a lesion in the sacral area [19]. Lesions are often present at more than one of these sites. However, where lesions occur at sites other than the back of the neck and the occiput, there will almost invariably be a lesion present at these sites in addition.

Lesions on the face fade rapidly, and most will have more or less disappeared within a year [4,11]. However, they may become transiently visible again during crying or exertion, particularly in the case of forehead lesions. Lesions at other sites tend to be much more persistent, and probably remain unchanged into adult life in most cases [11,20]. A reasonable working estimate of the frequency of persistent nuchal salmon patches in adults is in the region of 20–30%. Although such lesions are generally covered in hair and therefore inconspicuous, they appear to be a predilection site for other dermatoses, such as psoriasis and seborrhoeic dermatitis [21].

Sacral lesions are of significance as they may occasionally be associated with spinal dysraphism [19,22,23]. These may be single or grouped, single lesions frequently being of triangular or rhomboidal shape, generally not exceeding 4 cm in diameter [19,24]. The presence of such a lesion in a neonate only warrants anxiety if it is associated with a second abnormality, particularly a lipomatous swelling, or a haemangioma, pit, dimple, sinus, localized hypertrichosis, cutis aplasia or a congenital melanocytic naevus. In the absence of such a lesion, further investigation is probably unwarranted [25].

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Port-wine stain

SYN. NAEVUS FLAMMEUS

Definition. A port-wine stain is a vascular malformation of developmental origin characterized pathologically by ectasia of superficial dermal capillaries and clinically by persistent macular erythema.

Terminology. The port-wine stain is a less common but a more important lesion than the salmon patch. The term *naevus flammeus* has been applied to both, although most authorities would prefer to restrict its use to port-wine stains. In the past, port-wine stains have frequently been termed 'capillary haemangiomas', which they are not; unfortunately, this confusing practice still persists.

Aetiology and pathology. At birth, histological abnormalities are absent or minimal [1,2]. There is progressive

ectatic dilatation of mature dermal capillaries, which is initially most marked immediately below the epidermis [3]. The ectasia gradually involves increasingly deeply situated dermal blood vessels, although the number of affected vessels is always greatest in the upper dermis [1].

The endothelium is of normal appearance, and the total number of dermal blood vessels is probably not increased. It has been suggested that the lesion occurs as a result of a developmental weakness in the supporting elements of the blood vessel wall, although a recent study failed to demonstrate any gross quantitative or qualitative abnormality of distribution of immunofluorescent antibody-labelled type IV collagen, fibronectin or factor VIII [4].

The distribution of lesions on the face in areas roughly corresponding to those of sensory branches of the trigeminal nerve [5] has frequently been interpreted as suggesting that their pathogenesis may have a neurogenic basis, and in the past it was popular to ascribe them to neurological birth trauma [6]. It has now been demonstrated that the cutaneous superficial vascular plexus in port-wine stains has a greatly diminished density of perivascular nerves, suggesting that diminished neural influence on vascular tone may be the cause of port-wine stains [7–9].

Occasionally, lesions that appear to be identical to congenital port-wine stains have made their initial appearance later in childhood or in adult life [10–12], and may have followed trauma, possibly as a result of damage to the microvascular nerve supply.

Familial multiple telangiectatic naevi having the appearance of small port-wine stains have been reported on several occasions [13,14].

Clinical features. Port-wine stains are almost always present at birth, although they may initially be concealed by the normal hyperaemia of the neonatal skin. The reported incidence in the newborn has been from 0.1 to 2.0% [15–23]. They vary in colour from a fairly pale pink to a deep red or purple, and in size from a few millimetres to many centimetres in diameter. The face is the most frequently affected site, followed by the upper trunk, but lesions have occurred at almost any site including the mucosae. They are most often, but not invariably, unilateral with a fairly sharp midline cut-off. However, midline lesions are seen, and occasionally there is more or less symmetrical facial or limb involvement.

Port-wine stains are not infrequently associated with adjacent areas of naevus anaemicus [24,25], and it has been suggested that this phenomenon may be explained by somatic recombination [26].

Associated eye and brain abnormalities occur in 8–15% of patients with facial port-wine stains [5,27].

As a rule, the surface area affected remains unchanged relative to body size. On the face, the general rule is for port-wine stains to darken very slowly but progressively throughout life. At this site, it is also common for port-wine stains to become gradually raised and thickened, the thickening sometimes taking on a characteristic 'cobblestone' appearance [1,28]. Paradoxically, on the limbs and trunk, port-wine stains will often fade somewhat over the years.

A variety of venous and lymphatic abnormalities may be associated with port-wine stains [28,29], particularly when these occur on the limbs and trunk; such combinations are especially likely to occur in the Klippel–Trenaunay syndrome, but may also occur in the absence of limb hypertrophy.

Granuloma telangiectaticum is a relatively common complication of port-wine stains [30–33]. Other nodular angiomatous lesions may develop within or close to port-wine stains; a variety of histological appearances have been described in these lesions, including features of angiokeratoma, arteriovenous malformation and angiosarcoma [28,34,35].

Occasionally, the development of basal cell and/or squamous carcinomas has been reported as a long-term complication of port-wine stains, even in patients who had never been treated with radiotherapy [36–39].

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Ocular problems associated with facial port-wine stains. Vascular anomalies may occur in any part of the ocular circulation in patients with facial port-wine stains. Dilated conjunctival vessels are common, especially when the eyelids are affected [1,2]. An abnormal plexus of episcleral vessels is frequently present, but may be hidden from view by overlying fascia. It is this type of malformation that is believed to play an important role in the pathogenesis of the glaucoma seen in a substantial proportion of patients with facial port-wine stains. Tortuous retinal vessels are commonly present, occasionally associated with arteriovenous communications [3]. However, the most characteristic ocular vascular malformation in patients with facial port-wine stains is the choroidal angioma [1,4,5], which has a different appearance from isolated solitary choroidal angiomas. This lesion produces increased redness of the fundus on ophthalmoscopic examination, sometimes subtle; an appearance that has been termed 'tomato catsup' fundus [6]. Choroidal angiomas push the retina forward producing a refractive abnormality termed *hyperopia*. If unrecognized and uncorrected, this can interfere with visual development, and can therefore result in amblyopia [7]. Although initially the retina is unharmed by choroidal angiomas, degenerative changes develop after about 10–20 years, which may result in discomfort and permanent loss of vision in the affected eye [1,5].

Of all the ocular problems associated with facial port-wine stains, the most significant is glaucoma. This complication of facial port-wine stains is not sufficiently appreciated. It is particularly important that dermatologists and paediatricians should be aware that glaucoma is not confined to patients with the Sturge–Weber syndrome. Approximately 10% of all patients with facial port-wine stains in the region of the eye have evidence of leptomeningeal involvement. Of these, 30–60% have glaucoma, whereas glaucoma is found in about 10% of patients with a facial port-wine stain without leptomeningeal involvement [8,9].

The precise aetiology of glaucoma in this situation remains the subject of debate, but it seems likely that there are several contributory factors [10–14]. Choroidal angiomas may increase the production of aqueous fluid. Anatomical anomalies of the anterior chamber angle may impair aqueous drainage, which may be further impaired by raised episcleral venous pressure due to arteriovenous communications.

Glaucoma in association with facial port-wine stains is almost always unilateral. While it is widely recognized that glaucoma is unlikely unless the upper eyelid is affected by the port-wine stain, both upper and lower eyelids are affected in most cases [2,8,9,15]. Indeed, if the face is affected both below and above the eye, the chance of detecting glaucoma is about 30–45% [9,15]. Increased conjunctival vascularity does not appear to be predictive of glaucoma.

The glaucoma is detectable in infancy in about 40% of cases [16]. Its onset has two later peaks, between the ages of 5 and 9 years in another 20% of cases, and after the age of 20 years in another 20%. In the early-onset type, the eye is frequently enlarged and the cornea may appear cloudy, whereas, in the later-onset type, the eye tends to become elongated with increasing myopia. It is important to be aware that glaucoma of either type is initially asymptomatic but untreated will cause progressive damage to the optic nerve, resulting in visual field loss and, ultimately, blindness.

Patients at risk should be seen by an ophthalmologist in infancy and at regular intervals thereafter throughout life (Fig. 15.15) [16]. Treatment is initially by goniotomy, followed, if unsuccessful, by trabeculotomy, and ultimately by cyclocryotherapy in refractory cases [13,17]. Choroidal effusion or haemorrhage is a particular and threatening complication of surgery for glaucoma [18].

A small number of cases have been described under the title *orbitofacial angiomatosis*, in which a facial port-wine stain has been associated with an orbital vascular

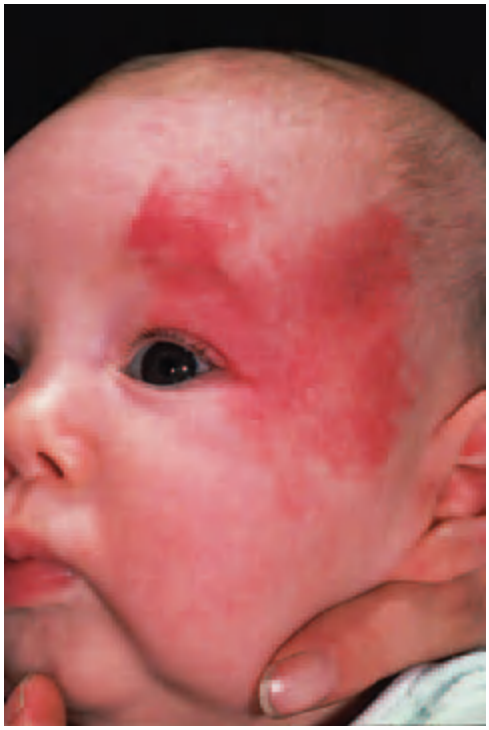

Fig. 15.15 Port-wine stain on the face of a 3-month-old child. Regular ophthalmological examination is imperative where a port-wine stain is close to the eye.

malformation causing proptosis, in addition to more common ocular complications such as glaucoma [19]. Whether this is a separate entity or not remains unclear, but it may be relevant that none of these patients had evidence of leptomeningeal angiomatosis.

Underlying soft-tissue swelling and/or bony overgrowth. Port-wine stains may be associated with angiomatous swelling and/or hypertrophy of underlying tissues at any site.

On the face, associated angiomatous swelling of the oral mucosa, lip, gingivae or eyelid is particularly characteristic.

On the limbs and trunk, soft-tissue swelling may occur with or without bony overgrowth.

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The Sturge–Weber syndrome

SYN. ENCEPHALOFACIAL ANGIOMATOSIS

This term is applied where a facial port-wine stain is associated with an ipsilateral leptomeningeal vascular malformation [1]. Ocular involvement is not a *sine qua non* for this diagnosis.

The syndrome is a developmental malformation of the vasculature of the leptomeninges and facial skin, often also of the eye. Convincing evidence of a genetic factor is lacking [2], but there are reports of its occurrence in monozygotic twins [3], and of facial port-wine stains in first-degree relatives [4].

The cutaneous lesion shows histological changes identical to those seen in other port-wine stains.

Neuropathological examination shows an increase in vascularity of the leptomeninges within the subarachnoid space, which most typically affects the posterior cerebral hemisphere, particularly the occipital lobe, but which may affect the entire hemisphere; these changes are generally unilateral, but bilateral in about 15% of cases [5]. The altered blood flow leads to stasis and ischaemia [6]. With time, there may be progressive gliosis, demyelination, calcification and cerebral atrophy [7]. The adjacent superficial cortical veins may be absent, and there may be associated enlargement of the deep venous system and choroids plexus on the same side.

Leptomeningeal melanocytosis has been an associated finding in several patients with Sturge–Weber syndrome [8–10].

The usual cutaneous finding is a unilateral port-wine stain, involving roughly the areas served by the ophthalmic and maxillary divisions of the trigeminal nerve

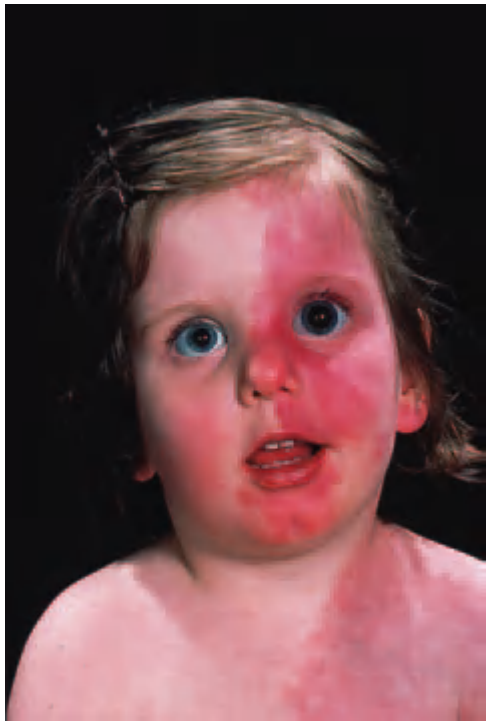

Fig. 15.16 Port-wine stains on the face and trunk in a 3-year-old with Sturge–Weber syndrome.

[11,12]. The lesion may be only a few centimetres across, but it tends to be extensive, involving much of one side of the face, scalp, neck and sometimes other parts of the body in addition (Fig. 15.16). It is virtually a rule that at least part of the port-wine stain extends to the forehead and upper eyelid [11]. In practice, either the whole upper lid or the root of the nose are affected in the great majority of cases [13]. The oral and nasal mucosae may be involved and the lips may be greatly swollen [1]. While usually predominantly unilateral, some extension over the midline is frequent. The facial port-wine stain is bilateral in around 50%, although not necessarily symmetrical [2,14]. Port-wine stains are present on limbs or trunk in addition to the face in about 40% of cases [15]. There is no correlation between the extent of the port-wine stain and either the extent of leptomeningeal vascular malformation or the degree of neurological impairment. In particular, bilateral facial port-wine stains do not seem particularly likely to predict bilateral leptomeningeal vascular malformation [16].

There are no reliable data to indicate what proportion of children with a port-wine stain involving the upper eyelid or forehead will never develop the CNS manifestations of the Sturge–Weber syndrome.

From the neurological and ophthalmological points of view, Sturge–Weber syndrome is a progressive disorder that varies greatly in severity. In most cases, neurological symptoms have their onset during the first 2 years of life [4,17], and their first appearance after the age of 6 years is unusual. Some patients with extensive leptomeningeal vascular malformation remain asymptomatic throughout life.

Epilepsy occurs in 75–90% of cases [2,4,14] most often starting between the second and seventh month of life, but very occasionally seizures have first occurred in adulthood. Early onset generally appears to predict a more severe course. The initial trigger for seizures is frequently fever. Initially, focal motor seizures are the most common type, but other types of seizures may occur, including infantile spasms, and tonic, atonic or myoclonic seizures. Seizures may be of generalized type from the beginning, or they may progress from focal to generalized as the child gets older. There may be long intervals between seizures. It is not uncommon for seizures to be followed by episodes of encephalopathy with altered consciousness and/or transient postictal hemiplegia and homonymous hemianopia. Later, more permanent hemiplegia may occur. Double hemiplegia reflects bilateral intracranial disease.

The onset of seizures is frequently associated with the development of a hemiplegia and a homonymous hemianopia. Once seizures have started, children with the Sturge–Weber syndrome often experience rapid, sometimes catastrophic neurological deterioration [4,14,18]. In contrast, patients who do not have seizures generally show no evidence of mental retardation [16].

The eye is involved in 50–60% of all cases [2,11,15,19,20].

The ocular abnormalities occurring in patients with the Sturge–Weber syndrome differ in no way from those found in patients with facial port-wine stains without leptomeningeal vascular malformation, although they do occur more frequently. Hemianopia or cortical blindness may also occur, and reflect damage to the occipital cortex.

The Sturge–Weber syndrome is not infrequently associated with the Klippel–Trenaunay syndrome [21,22]. The combination of Sturge–Weber syndrome and Wyburn–Mason syndrome has also been reported [23]. In other cases, Sturge–Weber syndrome has been associated with oculocutaneous melanosis [24–26], a combination which some authorities regard as a distinct entity, *phakomatosis pigmentovascularis* [27]. There have also been several reports of coincidental leptomeningeal [8–10] or neurocutaneous melanosis [28].

The EEG shows suppression of cortical activity over the affected area, which may or may not be associated with focal epileptiform spike discharges [29].

Cortical calcifications can generally be seen radiologically as sinuous, double-contoured lines running with the cortical convolutions on the affected side, but this change is generally absent in infancy and, in a proportion or cases, throughout life. However, intracranial calcification is generally visible by CT scanning, especially when enhanced by contrast injection, within the first few months of life

[30,31]. Both CT scanning, particularly with enhancement by contrast injection, and MRI are able to identify and localize the leptomeningeal vascular malformation [32,33]. Gadolinium-enhanced MRI scans are now considered to be the superior technique for the detection of the leptomeningeal vascular malformation, definition of its extent and of associated vascular anomalies, assessment of the degree of parenchymal atrophy and of ischaemic damage [7,34]. It is now widely recommended that all infants with a facial port-wine stain affecting the eyelid and/or forehead should have early gadolinium-enhanced MRI scans to establish whether leptomeningeal vascular malformation is present.

From time to time, the question arises whether the Sturge–Weber syndrome can be diagnosed without a facial port-wine stain. This is largely a matter of semantics [35]. Strictly, the presence of the cutaneous lesion is essential to make this diagnosis. However, there is no doubt that analogous unilateral leptomeningeal vascular malformation occurs without the typical skin or eye changes [16,17,36,37]. Patients affected in this way are otherwise no different from those who have facial port-wine stains, although the authors are not aware of any case reported in which unilateral congenital glaucoma was associated with ipsilateral leptomeningeal vascular malformation in the absence of a facial port-wine stain.

Control of seizures is essential to minimize brain damage; this relies on anticonvulsants in the first place, but neurosurgical intervention should be considered early when medical treatment does not secure adequate control; this may allow more normal developmental progress [38–41]. It has been suggested that anticonvulsant therapy is indicated prophylactically where the distribution of a facial port-wine stain suggests a high risk of Sturge–Weber syndrome [13], but the view in the UK is that the potential toxicity associated with such treatment contraindicates its routine use for prophylaxis. If early MRI scanning indicates leptomeningeal angiomatosis, careful follow-up is required to detect the onset of seizures, which should be treated as soon as possible to try to prevent neurological deterioration.

The eyes require regular examination by an ophthalmologist to detect the earliest changes of glaucoma.

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Phakomatosis pigmentovascularis. The word phakomatosis has come to imply simultaneous involvement by a developmental malformation syndrome of eye, skin and CNS. The rather clumsy term *phakomatosis pigmentovascularis* has been proposed for a syndrome combining vascular staining of port-wine stain type, oculocutaneous melanosis and CNS manifestations such as seizures and hemiplegia [1,2]. This disorder has also been reported under other titles, notably *Sturge–Weber syndrome with Klippel–Trenaunay syndrome, naevus of Ota and Ito* [3], *Sturge–Weber syndrome with oculocutaneous melanosis* [4,5] and '*oligosymptomatic form of Klippel–Trenaunay syndrome associated with giant nevus spilus*' [6].

This syndrome has much in common with the Sturge–Weber syndrome. However, it has been argued that it differs, firstly in the presence of widespread dermal, and usually scleral, melanocytosis, secondly in the generally more extensive port-wine staining, and thirdly in the presence of ultrastructural distinctions in the endothelial cell appearances [2].

It remains unclear whether there are yet good grounds for considering this disorder distinct from the Sturge–Weber syndrome. The situation has been complicated by the use of the term *phakomatosis pigmentovascularis* to describe a variety of other cases in which port-wine stains and pigmentary abnormalities of the skin were present. Cases showing such combinations of port-wine stains and cutaneous pigmentary abnormalities have been classified into several distinct subtypes, according to the skin lesions present [7]:

Type I: port-wine stain and linear epidermal naevus [1].
Type II: port-wine stain and dermal melanocytosis [3–5,7–10].
Type III: port-wine stain and naevus spilus [6,11–13]. Multiple granular cell tumours have been described in this subtype [11].
Type IV: port-wine stain, dermal melanocytosis and naevus spilus [7,14].

This classification includes cases in which there was evidence only of cutaneous disease, or of both cutaneous and extracutaneous disease; the subdivisions 'a' and 'b' have been used to denote, respectively, the absence or presence of extracutaneous involvement, particularly CNS, eye and skeletal abnormalities [15]. Many patients with intracranial involvement could be regarded as having Sturge–Weber syndrome [16]. This classification is perhaps too all-embracing, but it does serve to point out the wide variety of cases in which port-wine stains have been associated with congenital cutaneous pigmentary abnormalities.

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Spinal dysraphism. A port-wine stain over the lower spine may be a marker of spina bifida occulta [1,2], and may therefore be associated with neurological abnormalities secondary to malformations or tethering of the spinal cord. It is probable, however, that lumbosacral haemangiomas are a commoner cutaneous vascular marker of such problems [3–5]. Symptoms of neurogenic bladder dysfunction or lower limb weakness may be present. A careful history and neurological examination are indicated in children who have a midline port-wine stain in the lumbosacral area, and the need for spinal radiography should be considered.

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Cobb's syndrome (cutaneomeningospinal angiomatosis) [1–7]. This disorder comprises the very rare association of a port-wine stain in a segmental distribution and an arteriovenous malformation of the spinal cord within a segment or two of the involved dermatome. In practice, about 40% of patients with spinal arteriovenous malformations also have a port-wine stain, which is situated in the corresponding dermatome in about half of these [2]. There is no evidence of any genetic basis.

The port-wine stain may be rather faint [2], or, more rarely, may have a more verrucous appearance [8,9] in a segmental distribution on the trunk or limbs. This is associated with an arteriovenous malformation of the spinal cord, which generally will become symptomatic in childhood or adolescence, with fairly rapid onset of spastic paralysis of one or both lower limbs, and sensory loss below the level of the spinal lesion.

In many cases, the spinal vascular lesion is amenable to surgical treatment [10] and/or embolization [11].

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Hereditary neurocutaneous angioma. An apparently distinctive familial disorder was described under this name in 1979 [1]. The disorder was transmitted as an autosomal dominant trait. All the affected individuals had one or more port-wine stains, at almost any site, associated with localized vascular malformations within the CNS. These CNS vascular lesions showed a marked tendency to bleed, resulting in a variety of neurological manifestations, and a high morbidity and mortality.

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Treatment. Port-wine stains, particularly when they occur on the face, are liable to have a very profound effect on a child's psychological development and can cause substantial social disability [1–3]. Cosmetic camouflage has been used widely in an attempt to reduce their cosmetic impact, and, in the UK, a very satisfactory service is offered by the British Red Cross Society [4]. However, this approach appears to have limited appeal for patients in clinical practice.

Over the years, a great variety of treatments have been used to treat port-wine stains. These have included excision and grafting [5–7], tattooing [8–10], Grenz rays [11], thorium X [12], red phosphorus [13] and cryotherapy [14,15]. These techniques have largely proved unsatisfactory, and attention has more recently been focused on the therapeutic advances offered by infrared coagulation [16] and, more particularly, laser therapy [17].

The argon laser is capable of good results in treating port-wine stains [18–21]. However, initial optimism has been tempered by the occurrence of a variety of adverse effects, including hypopigmentation and scarring [22–25]. The incidence of these complications of argon laser therapy can be reduced by newer techniques, and this laser may continue to have a limited role in the treatment of port-wine stains, particularly dark or nodular lesions in adults. The argon laser has proved particularly unsuitable for the treatment of children because of the paler hue of their lesions, and the incidence of scarring in children is in the region of 40% [26].

Therapeutic results comparable to those achieved with the argon laser were reported with the much less costly, and simpler, non-laser infrared coagulator [16]. However, there is a substantial incidence of complications including hypertrophic scarring, post-inflammatory hyperpigmentation and atrophy. Although these make it a less satisfactory method for treating macular port-wine stains, it remains potentially valuable in the treatment of the more difficult nodular or plaque-like lesions [27].

Theoretically, the absorption spectrum of haemoglobin implies that yellow laser light at a wavelength of 577–578 nm should be optimal for the treatment of port-wine stains, rather than the blue-green argon light. These yellow wavelengths can currently be produced by three different laser systems: the argon-pumped tunable dye laser [28], the flashlamp-pulsed dye laser and the copper vapour laser [29]. Over recent years, the greatest interest

has focused on the flashlamp-pulsed dye laser. It is now clear that, in the hands of the skilled operator, this laser can substantially lighten the great majority of port-wine stains, particularly the lighter ones that are so common in children. Its wider availability over the past few years has revolutionized the treatment of facial port-wine stains [26,30–34]. In good hands, approximately 30% of patients with facial lesions will be discharged with complete or near-complete clearance, and over 60% will have a good or excellent result [35]. Adult patients tend to require more treatments than children [26,30–33]. Paler lesions tend to respond better than darker ones [33], and it has been recently demonstrated that this reflects a better response when the ectatic vessels are more superficial [36]. Location of the port-wine stain is also important in determining the likely response to treatment; lesions in the central area of the face (V2 distribution) and on the limbs often show a relatively poor response [37,38]. This appears to reflect the increased depth of the ecstatic vessels in these areas [39]. Smaller lesions tend to respond better than more extensive ones [40].

Results from the treatment of limb lesions have been relatively disappointing compared with those for facial lesions [33–35], and it has been found that distal limb lesions respond less well than more proximal lesions. However, there is some evidence that purple lesions may respond as well as lighter ones [35].

Unwanted effects of the flashlamp-pulsed dye laser include pain, bruising in almost every patient, oedema (70% of patients), occasional bullae (1%), crusting (25%), bleeding (12%), pyogenic granuloma (1%), transient hypopigmentation (1%) or hyperpigmentation (25%) [41,42]. Atrophic scarring occurs in 1–3% of cases [42,43], and hypertrophic scarring very rarely [42,44].

The treatment can be undertaken without general anaesthesia in adults. However, it does produce an unpleasant 'stinging' sensation and, for this reason, local anaesthesia is generally employed. In children, general anaesthesia should be used. To minimize the harmful effect of disfiguring facial port-wine stains on psychological development, it should be regarded as ideal to complete therapy before the age of about 5 years. Current pulsed dye laser equipment allows large areas to be treated much more rapidly than was the case in the past, but it remains the case that several treatments will be necessary to provide substantial improvements in most port-wine stains [26,30–32].

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Other syndromes featuring macular telangiectatic vascular naevi

While authors of reports of the following conditions frequently use the term haemangioma to describe vascular stains, it is often unclear whether these lesions are true port-wine stains or 'salmon patches'; this is why we have preferred to call these lesions vascular stains where there is doubt. Many authorities would prefer to regard midline lesions as more likely to be 'salmon patches' and lesions situated away from the midline as more likely to be 'port-wine stains'.

Proteus syndrome

Definition. This syndrome was only recognized as a distinct entity as recently as 1983 [1], but is now firmly established and of considerable importance to dermatologists. The name was coined after Proteus, the mythological Greek sea god who could change his shape at will, in order to stress the variable nature of the clinical manifestations and the rather haphazard nature of the growth abnormalities that characterize the condition [1].

The Proteus syndrome comprises an association of asymmetrical overgrowth of almost any part of the body, verrucous epidermal naevi, vascular malformations and lipoma-like subcutaneous hamartomas. A wide variety of other abnormalities have been described, but minimal clinical criteria for diagnosis have not yet been established.

It is now regarded as almost certain that Joseph Merrick, the 'Elephant Man', had the Proteus syndrome, not von Recklinghausen neurofibromatosis, as originally believed [2].

Aetiology. Both sexes are affected with equal frequency and severity. The available data suggest that the Proteus syndrome is not genetically transmitted, but that it should probably be regarded as a complex developmental abnormality. It has been hypothesized that it reflects mosaicism for a genetic mutation that would be lethal in a non-mosaic state [3,4].

Pathology. Little has been published on the histological features of the skin lesions observed in patients with the Proteus syndrome. Although the soft subcutaneous masses that are such a characteristic element in the clinical presentation have generally been described as lipomas, they appear more often to be complex hamartomatous malformations containing mixtures in varying proportion of vascular, lymphatic and adipose tissue [5–7]. The linear verrucous epidermal naevi show typical histological features of this condition [8], but hypopigmented examples may show large vacuoles and aggregations of ribosome-like particles at the melanocyte–keratinocyte interface [9]. Biopsies from the cerebriform plantar lesions show increased amounts of normal collagen and reduced density of elastic fibres compatible with a collagenoma [10,11], but in one case it was reported that light and electron microscopy showed elongated, fine, cytoplasmic projections from some basal cells into the dermal–epidermal junction [8].

Clinical features [5–8,11–15]. Some manifestation of the disorder is almost invariably present from birth. Although the presenting problem may be one of the cutaneous abnormalities, more often it is an overgrowth phenomenon that first causes anxiety.

The most characteristic forms of overgrowth are assymetrical hypertrophy of the face, of part or the whole of one or both limbs, the trunk, or any combination of these, including hemihypertrophy of one side of the body. Macrodactyly has been regarded as particularly characteristic, but should not be considered absolutely necessary to the diagnosis. The rugose or cerebriform overgrowth of the plantar and/or palmar soft tissues on a hypertrophied foot and/or hand seems to be highly distinctive. Macrocephaly and/or an excessive linear growth rate are also common findings.

Three main types of skin lesion may be seen, none of which is in itself entirely diagnostic; it is the characteristic combinations in which they occur that should lead to the correct diagnosis. They are (i) epidermal naevi, (ii) vascular malformations and (iii) soft subcutaneous masses. Some cutaneous abnormality is present in the great majority of patients.

The epidermal naevi are generally of linear verrucous type, but may have the clinical features of sebaceous naevi [7]. They may show hyperpigmentation and/or hypopigmentation [5,6,8,11,12].

The vascular lesions that are found in the majority of these patients include extensive port-wine stains, both macrocystic and microcystic lymphatic malformations, and complex combined vascular malformations of the leg identical to the Klippel–Trenaunay syndrome [16]. Varicosity of superficial veins is also often described, but prominence of veins may quite often reflect a degree of lipodystrophy.

Soft subcutaneous masses are extremely common, and highly characteristic.

Other skin findings have included café-au-lait macules and macular hypopigmentation, which may be of a linear or whorled type [5,12,13]. Several thickened hypopigmented areas were described in a case that otherwise had the hallmarks of the Proteus syndrome [17]; these lesions were interpreted histologically as connective tissue naevi. Venous varicosities are often a prominent feature [6,14,17].

Non-cutaneous findings have included skeletal abnormalities, such as exostoses, kyphosis, scoliosis and spinal canal stenosis leading to spinal cord compression, ocular abnormalities including congenital blindness, epibulbar tumours, enlargement of the eye, cataract and strabismus, misshapen teeth, hypodontia and hypoplastic enamel, myopathy, pelvic lipomatosis, amastia, goitre, testicular tumours, craniosynostosis and complex congenital heart defects [5,6,8,14,18]. Spinal abnormalities have been the cause of some of the most serious functional problems experienced by these patients [19]. The great majority of patients are of normal intelligence, and although mental retardation and convulsions have been reported, they are rare.

Macrodactyly, hemihypertrophy and the multiple exostoses tend to progress throughout childhood and thereafter to stabilize. Ultimately, the prognosis depends upon severity, which varies dramatically from case to case [9,14].

Diagnosis. For many years, patients with the Proteus syndrome were diagnosed as Klippel–Trenaunay syndrome, 'congenital hypertrophy' or epidermal naevus syndrome. The principal differential diagnoses are other overgrowth disorders, particularly the Klippel–Trenaunay syndrome, macrocephaly with cutis marmorata, midline facial telangiectatic naevus, and syndactyly, Bannayan–Riley–Ruvalcaba syndrome [20], the congenital lipomatosis, in which macrodactyly has been reported [21], partial lipodystrophy [6,22], Maffucci's syndrome and von Recklinghausen neurofibromatosis [2], but the clinical features of these disorders generally allow them to be distinguished.

Treatment. The aims of treatment are the minimization of disability. Substantial contributions can be made by plastic and orthopaedic surgeons, ophthalmologists, orthodontic specialists and by physiotherapists. It is, for example, possible to stop the overgrowth of elongated fingers or toes during childhood by the destruction of the growth plate. Lipomatous swellings can sometimes be reduced by liposuction. Sadly, despite treatment efforts, this disorder may be responsible for major degrees of deformity and disability.

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Cardiofaciocutaneous syndrome [1]

Vascular stains are a regular feature of this syndrome, a genetically determined disorder whose principal features include mental retardation, hypotonia, atrial septal defect,

pulmonary stenosis, eczema, hypotrichosis and a characteristic facial appearance [2]. It has been suggested that it may be a variant of Noonan's syndrome [3].

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Roberts' syndrome [1–6]

SYN. HYPOMELIA–HYPOTRICHOSIS–FACIAL HAEMANGIOMA SYNDROME; PSEUDOTHALIDOMIDE SYNDROME

This is an extremely rare but distinctive disorder, transmitted by an autosomal recessive gene, which is characterized by five principal clinical features:
1 a mid-facial vascular stain
2 cleft lip with or without cleft palate
3 sparse, silvery-blond hair
4 tetraphocomelia
5 marked growth retardation.
There is considerable variability in severity [6,7].

The vascular naevus extends in the midline of the face from the forehead on to the nose and philtrum. The facial appearance is rather characteristic, with hypertelorism, shallow orbits, prominent eyes with bluish scleras, thin nares, micrognathia and malformed ears with hypoplastic lobules.

Cells derived from most patients exhibit abnormal cytogenetic and cellular phenotypes that include the premature separation of para- and pericentromeric heterochromatin visible on C-banded metaphase chromosomes, a phenomenon referred to as heterochromatic splaying [8].

Severely affected individuals are often stillborn or die in early infancy.

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Thrombocytopenia–absent radii syndrome [1–5]

SYN. TAR SYNDROME; TETRAPHOCOMELIA–THROMBOCYTOPENIA SYNDROME

This disorder generally appears to be transmitted as an autosomal recessive trait, but parent-to-child transmission has been reported, also several cases in which an uncle or aunt and their niece or nephew have been affected, suggesting that the genetic situation may be more complex than it had appeared.

The principal findings are (i) congenital thrombocytopenia and (ii) absence or hypoplasia of the radius, which is usually bilateral.

Many patients also have vascular stains on the head and neck [1,3,4,5].

The thrombocytopenia may be very severe in infancy, with a mortality of about 40% from haemorrhage, but it generally improves considerably with time. The marrow shows absence or diminished numbers of megakaryocytes. Anaemia is also common.

Cow's milk allergic reactions seems to be unusually frequent in these infants, about 50% of whom have eosinophilia.

A single case report describes the failure of flashlamp-pumped pulsed dye laser to lighten the vascular naevus in this disorder, possibly because the platelet thrombi were not able to form in treated vessels [1].

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Wyburn–Mason syndrome [1,2]

SYN. BONNET–DECHAUME–BLANC SYNDROME

This is an extremely rare disorder, probably not genetically transmitted. There may be some overlap with the Sturge–Weber syndrome [3].

The principal features are:
1 a unilateral retinal arteriovenous malformation, which may also involve the optic nerve, orbit, optic chiasm and tract;

2 an ipsilateral aneurysmal arteriovenous malformation of the brain, usually in the mid-brain, associated with a variety of neurological findings that may have a sudden onset precipitated by intracranial haemorrhage;
3 ipsilateral cutaneous vascular abnormalities.

The visual tract abnormalities may occur in the absence of the other features, and the cerebral abnormalities may less often occur without visual tract involvement.

Cutaneous abnormalities are not always apparent, and are generally subtle, taking the form of rather faint ipsilateral vascular staining or telangiectasia in the region of the affected eye, sometimes featuring punctate telangiectases [4–6]. More rarely, a more substantial cutaneous vascular malformation may be present [5,7].

The occurrence of a basal cell carcinoma has been reported in a young man with this condition; whether the association was fortuitous is impossible to determine [8].

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Beckwith–Wiedemann syndrome [1–4]

SYN. EXOMPHALOS–MACROGLOSSIA–GIGANTISM SYNDROME

Although the majority of cases of this disorder have appeared to be sporadic, it is likely that this disorder is caused by an autosomal dominant gene with highly variable expression [5]. Genetic linkage studies have mapped the familial form to a specific region of chromosome 11, further supporting the underlying genetic aetiology of the Beckwith–Wiedemann syndrome [6]. Translocations and deletions of chromosome 11 have also been identified in some patients [7]. Prenatal diagnosis has been accomplished at 19 weeks gestation by ultrasound observation of abdominal enlargement and omphalocoele [8].

The major clinical feature of the syndrome is somatic and visceral overgrowth, resulting, most typically, in a baby that is large for gestational age with exomphalos, macroglossia and large kidneys. Hemihypertrophy occurs in approximately 13% of patients.

Vascular staining is present on the central forehead and upper eyelids in about 80% of cases, which often also extends to the nose and upper lip. It is reported that these naevi fade during the early years of life, sometimes becoming invisible later; this with their location suggests that they may behave more like salmon patches than classical port-wine stains. Linear indentations of the earlobe are also common and characteristic. These physical features are regularly associated with pancreatic hyperplasia, which may cause severe and refractory neonatal hypoglycaemia.

Hypoglycemia develops in the first few days of life in as many as one-third of affected infants, and it may result in neurological sequelae if it is not anticipated.

The ultimate prognosis of children who survive infancy is unknown. The excessive rate of growth appears to slow down, and the macroglossia, which initially may result in life-threatening respiratory obstruction, gradually becomes less prominent. There is an unexpectedly high incidence of a variety of malignancies, particularly Wilms' tumour, adrenal carcinoma, hepatoblastoma and rhabdomyosarcoma [9–11], and these tumours are commoner in those with hemihypertrophy.

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Other associations with vascular stains

Vascular stains occur in at least a half of all cases of the *Rubinstein–Taybi syndrome* and in a similar proportion of children with *trisomy 13* [1]; in both cases the forehead is the commonest site.

The commonest cutaneous abnormality in *trisomy 18* [2] is a reticulate vascular naevus, but lesions resembling

port-wine stains have also been recorded. Vascular stains have been reported in *short-arm 4 deletion syndrome* [3], in *XXYY syndrome* and other *Klinefelter* variants [4,5].

Mid-facial vascular stains also occur occasionally in the *amyoplasia congenita disruptive sequence* [6] and in the *lethal multiple pterygium syndrome* [7].

Coats' disease is primarily a disorder of the eye, with retinal telangiectasia leading to exudation and retinal detachment. Cutaneous telangiectasia has been reported in several cases, and a macular telangiectatic naevus of the cheek in a single case [8].

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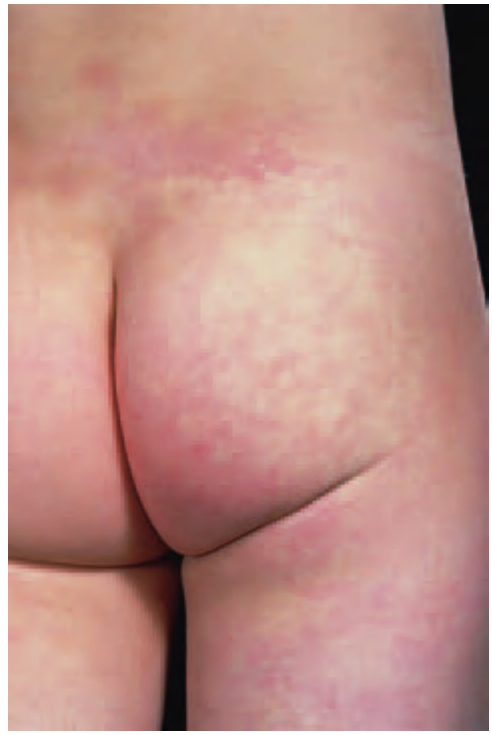

Fig. 15.17 Port-wine stain on the right buttock and leg, typically combined with areas of naevus anaemicus.

Naevus anaemicus

Definition. Naevus anaemicus is a congenital anomaly of the skin, characterized by macular areas of pallor having a normal texture and normal melanin pigmentation, due to reduced blood flow. Such lesions were first recorded by Vörner in 1906 [1].

Aetiology and pathology. The prevalence of naevus anaemicus is not known, but it is not rare [2]. It is more frequent in females [3].

This lesion is a pharmacological anomaly rather than an anatomical one. Examination by light and electron microscopy reveals no abnormality [4]. Physical stimuli such as rubbing, intralesional injection of bradykinin, acetylcholine, 5-hydroxytryptamine, nicotine or histamine all fail to produce the anticipated vasodilatation [3,4], but erythema does follow axillary sympathetic block [4]. It is now considered probable that naevus anaemicus reflects locally increased vascular reactivity to catecholamines [3,4], a conclusion supported by autograft exchange transplantation studies [5], and by the finding that the pallor can be overcome by local injection of the α-adrenergic blocker phentolamine [5,6].

Areas of naevus anaemicus, frequently extensive, are often seen in close association with vascular stains of port-wine stain type (Fig. 15.17) [2,7,8]. It has been suggested that this phenomenon may be explained by somatic recombination [9].

Lesions of naevus anaemicus occur with increased frequency in patients with neurofibromatosis [3,8,10,11].

Clinical features [3,10–12]. The naevus anaemicus is a circumscribed, rounded, oval or linear area of pallor, having a normal texture. Lesions may be single or multiple (Fig. 15.18). Small blotches may be irregularly grouped. The margins of the lesion or lesions are frequently ill-defined. Under diascopic pressure, the naevus becomes indistinguishable from the blanched surrounding skin. Rubbing the skin causes reactive hyperaemia in the surrounding normal skin, but no change within the lesion itself. There is no loss of melanin pigmentation in the affected area. It may occur on any part of the body, but is most commonly seen on the trunk. It may be present at birth, or may appear in early childhood. Later onset has been reported, but as the lesion may be inconspicuous the history may be unreliable. Naevus anaemicus persists unchanged throughout life.

Diagnosis. Diascopy provides the most reliable method to distinguish naevus anaemicus from other causes of circumscribed pallor such as hypochromic naevi and vitiligo. Wood's lamp examination does not accentuate the lesion.

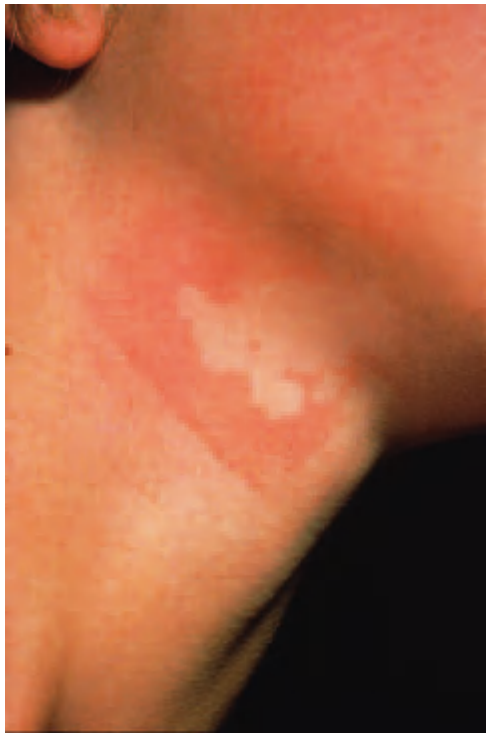

Fig. 15.18 Naevus anaemicus on the neck of a 12-year-old.

Treatment. Treatment is generally not required. Where there is a resulting cosmetic disability, the use of camouflage make-up is worth consideration.

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Naevus oligaemicus

A case has been reported of an adult in whom a persistent fixed area of cyanotic erythema had been present for many years on the trunk [1]. Histology was normal. Careful studies demonstrated decreased blood flow through the lesion. There was evidence that the cause was relative stasis in the superficial microvasculature secondary to increased vasoconstrictor tone in the deeper thermoregulatory vessels.

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Mixed vascular malformations

Cutis marmorata telangiectatica congenita

SYN. RETICULATE VASCULAR NAEVUS

Terminology. Though this disorder has most commonly been reported under the rather cumbersome term *cutis marmorata telangiectatica congenita* [1], it would in many ways be preferable to use a term such as *reticulate vascular naevus* [2]. This would have the additional advantage of emphasizing the distinction of the disorder from *cutis marmorata*, which is a cutaneous physiological response to cold.

Aetiology. This disorder is probably best considered as a combined capillary and venous vascular malformation. It is uncommon but not rare, occurring in about one in 3000 neonates [3].

Cutis marmorata telangiectatica congenita appears to be sporadic in the great majority of cases, but familial occurrence has occasionally been reported [4,5]. Taking into account the relatively high prevalence of associated problems in patients with the familial form [6,7], it has been suggested that it is the principal cutaneous manifestation of a syndrome inherited as an autosomal dominant trait but having highly variable expression [4]. It seems possible that the Adams–Oliver syndrome, believed to be transmitted as an autosomal dominant trait with variable penetrance and expression, may be a different manifestation of the same disorder [8].

Pathology [1,4,6,9]. The histopathology of this disorder remains ill-defined. Biopsies generally show dilated capillaries, capillary and venous lakes, and dilated veins throughout the dermis, and often also the subcutis. However, no abnormality has been apparent in some reported cases [10], implying that perhaps the problem is primarily functional rather than anatomical.

It was reported that the gestation of a fetus born with cutis marmorata telangiectatica congenita was associated with elevated maternal serum human chorionic gonadotrophin level and transitory fetal ascites [11].

Clinical features [6,12–14]. From birth there is reticulate

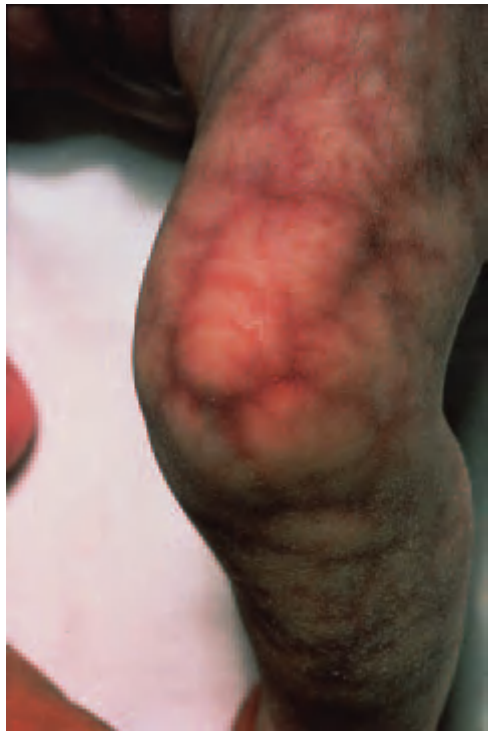

Fig. 15.19 Cutis marmorata telangiectatica congenita on the leg of an infant.

erythema of variable extent, producing a marbled effect (Fig. 15.19). The erythema varies in hue between patients and in different areas in the individual patient from a pale-red to a deep-purple colour. Telangiectasia is often visible within the hyperaemic areas and is sometimes prominent. The skin in these areas may be atrophic, and may be ulcerated at birth, resulting in linear or reticulate erosions [1,9,12–17]. The enclosed areas of skin may be of normal appearance or slightly erythematous.

Individual lesions sometimes measure only a few centimetres across. On other occasions, larger areas may be involved. Almost any area of the skin may be affected, but involvement of the limbs appears to be particularly common. The distribution may be segmental, and is generally asymmetrical if not strictly unilateral. Fairly sharp midline demarcation is common. In some cases, the condition has been very extensive, but it is very rarely generalized [18].

The face is often diffusely hyperaemic [19], and facial lesions may occur that are indistinguishable from typical port-wine stains [10,12,20,21]. Such patients are particularly at risk of congenital glaucoma [12,22,23], which may be bilateral if facial cutaneous involvement is diffuse [10,12]. In one of these cases, there was associated mental retardation, suggesting that the patient might have had Sturge–Weber syndrome [10]. Congenital glaucoma may also occur in the absence of a facial port-wine stain [12,22,24–26].

Underlying atrophy of the subcutaneous tissues appears to accompany the cutaneous lesions fairly regularly, resulting in associated facial hemiatrophy and reduced girth of affected limbs [6,14,26]. Reduced longitudinal limb growth has been reported [22], but is unusual. Hypoplasia of underlying bone has very occasionally been reported [27]. Hypertrophy of affected limbs rather than atrophy may rarely occur [6,13,20,21].

A wide variety of other congenital anomalies have been noted in reported cases. The frequency of these associated anomalies has varied from about 20% to 70% [7,12,18], but otherwise normal children with cutis marmorata telangiectatica congenita have almost certainly been relatively underreported. The most frequent have been transverse limb defects, cutis aplasia congenita, cleft palate and developmental delay. Cutis marmorata telangiectatica congenita has been reported in about 10% of cases of the Adams–Oliver syndrome [27,28]. Indeed, the clinical similarities between patients with cutis marmorata telangiectatica congenita and the Adams–Oliver syndrome are such that it has been suggested that they may be different expressions of the same disorder [8]. A family in whom congenital absence of the skin on the scalp was associated with cutis marmorata telangiectatica congenita may have had a limited expression of the Adams–Oliver syndrome [20].

More occasional associated abnormalities have included soft-tissue herniation [29], congenital generalized fibromatosis [26], macrocephaly [21,30], patent ductus arteriosus, scoliosis, spina bifida [13], double aortic arch [31], congenital retinal detachment [25], high myopia [32], congenital hypothyroidism [7], diabetes mellitus [33], chylothorax [27], neonatal ascites [11,33], renal artery stenosis [32], transient hepatic dysfunction [20,33,34] and dental anomalies [32].

The natural history of cutis marmorata telangiectatica congenita is usually one of gradual spontaneous improvement, although there may be some extension of the lesions during the first few days of life [7,9,13]. Ulcerations usually heal fairly rapidly. Generally the reticulate erythema fades, more rapidly in the first year, and slower thereafter. In patients with initially paler lesions, with limited telangiectasia and without ulceration, eventual complete disappearance is possible, but more prominent lesions will tend to be more persistent. Although even these will become less prominent over the years, a number of cases have been recorded where little significant improvement at all has occurred [4,7,15]. Limb circumference discrepancy becomes less prominent with time [14].

Diagnosis. Cutis marmorata telangiectatica congenita would appear to be a close relative of port-wine staining, clinically and pathologically, and vascular naevi of both types not infrequently occur together. The main differences are the better outlook for spontaneous improvement in cutis marmorata telangiectatica congenita, and their

more usual association with atrophy rather than hypertrophy of subcutaneous tissues. It is of particular importance to watch for development of glaucoma when the face is involved in either disorder.

There should be no confusion with cutis marmorata, a physiological cutaneous response to cold which is very prominent in the neonate, and which disappears with warming, also the more pronounced congenital livedo which may be seen in certain chromosomal and genetic disorders, most notably the de Lange syndrome, homocystinuria, the Divry–van Bogaert syndrome and trisomy 21.

It is important to be aware that congenital reticulate erythema with atrophy and telangiectasia may be a feature of neonatal lupus erythematosus [35,36]. The suspicion of neonatal lupus erythematosus should be greater where: (i) the head is affected; and (ii) the skin changes are bilaterally symmetrical. A clearly unilateral distribution would more or less rule out neonatal lupus erythematosus.

Treatment. Because of the natural tendency of these lesions to fade with time, active treatment should not be envisaged during the early years. Tunable dye laser therapy may help with persistent lesions, but it is often not very effective.

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Macrocephaly–cutis marmorata telangiectatica congenita

SYN. MACROCEPHALY WITH CUTIS MARMORATA; HAEMANGIOMA AND SYNDACTYLY SYNDROME; MACROCEPHALY, CUTIS MARMORATA, MIDLINE TELANGIECTATIC NAEVUS AND SYNDACTYLY SYNDROME

This distinctive overgrowth syndrome was first recognized in 1996 [1,2]. The syndrome comprises combinations of macrocephaly, cutis marmorata telangiectatica congenita, macular vascular stain (commonly and incorrectly referred to as 'haemangioma') on the upper lip and/or philtrum, syndactyly, high birth weight (above 75th centile), hemihypertrophy, regional overgrowth, developmental delay, hypotonia, joint laxity, hyperelastic skin,

thick subcutaneous tissue, short stature, hydrocephalus and, less commonly, hemimegalencephaly, internal arteriovenous malformations and postaxial polydactyly [2–5]. Macular vascular stains have also been reported with a smaller frequency at other sites in these patients, and may be extensive [4,6,7]. Occasional cases have featured subcutaneous vascular swellings, which have probably been venous vascular malformations [6,8]. Otherwise typical cases have been described in which cutis marmorata telangiectatica congenita has been absent [6,9,10]. Macular linear hyperpigmentation has also been described, suggesting that the condition reflects mosaicism [4,7].

While this syndrome is now regarded as a well-established entity, there is substantial clinical overlap with Proteus syndrome, with Klippel–Trenaunay syndrome and with a condition described as *slowly progressive macrocephaly with hamartomas* [11].

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Divry–van Bogaert syndrome [1–3]

SYN. CORTICO-MENINGEAL ANGIOMATOSIS

This extremely rare disorder appears to be transmitted as an autosomal recessive trait. The principal feature is diffuse non-calcifying leptomeningeal angiomatosis that is at least partly responsible for a variety of associated problems, which include epilepsy, visual field defects, progressive dementia and spastic paralysis. Congenital livedo has been a conspicuous feature in many patients. Affected individuals generally die during childhood.

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Klippel–Trenaunay syndrome

Nomenclature and aetiology. The association of a port-wine stain on a limb with soft-tissue swelling, with or without bony overgrowth, is generally termed Klippel–Trenaunay syndrome. As originally defined, the syndrome comprised the triad of a port-wine stain extending the full length of a limb, venous varicosities of the same limb, either congenital or of onset in infancy, and overgrowth of all the tissues of the affected limb, particularly bone [1]. Today, the term is generally used for any case where there is an association of port-wine staining and increased limb size, whether or not bony overgrowth is present and whether or not venous varicosities are apparent.

A few years after Klippel and Trenaunay's paper, Parkes Weber described a syndrome which he called 'haemangiectatic hypertrophy' [2,3]. Although limb swelling is a feature, the syndrome described by Parkes Weber is distinct, as it reflects the presence of arteriovenous anastomoses in the affected limb, rather than the predominantly venous malformations that underlie the Klippel–Trenaunay syndrome. Thus, the term Klippel–Trenaunay–Weber syndrome is inappropriate, and should not be used. In fact, both of the described syndromes are just a part of a wider spectrum of vascular anomalies of the limb that result in limb enlargement. The term, *haemangiectatic hypertrophy*, as coined by Parkes Weber, can be usefully employed to embrace all those conditions in which this association is seen. Cutaneous abnormalities will be present in only a proportion of such cases.

Classification of these disorders has proved exceedingly difficult, and no really adequate system of classification has as yet been devised. However, from the clinical point of view, it is convenient to separate these conditions into three broad groups [4].

1 Predominantly venous malformations. Most of these patients will have the features of the Klippel–Trenaunay syndrome.

2 Predominantly arteriovenous fistulae. This is the disorder described by Parkes Weber [2,3].

3 Predominantly mixed venous–lymphatic malformations.

It appears that genetic factors lead to an increased risk of the Klippel–Trenaunay syndrome, at least in some families [5–7], and it has been suggested that the disorder may

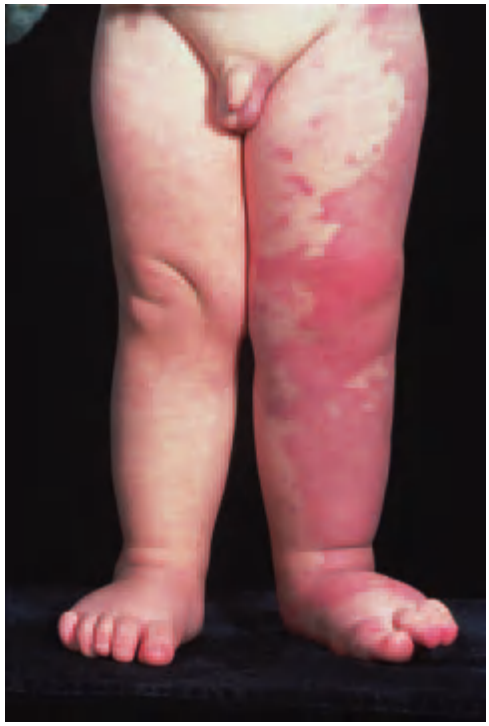

Fig. 15.20 Klippel–Trenaunay syndrome: port-wine stain with increased limb size.

reflect autosomal dominant inheritance with variable expression [7], or perhaps paradominant inheritance [8].

The aetiology of the Klippel–Trenaunay syndrome is unknown, but it has been suggested that it reflects defective remodelling of the fetal vascular tree during embryogenesis [9].

Clinical features. In cases demonstrating the classical Klippel–Trenaunay triad, the most characteristic cutaneous lesion, both clinically and histologically, is a vascular stain of port-wine stain type (Fig. 15.20) [4,10–17]. One or several vascular stains are almost invariably present at birth, but in some cases such lesions make their first appearance during early childhood. These lesions are extremely variable both in extent and in colour, which may range from pale pink to deep purple. Most often, these vascular naevi occur on the affected limb, but more distant lesions may be a feature, and several limbs and/or the trunk may be affected simultaneously. A tendency for the naevus to be patchy is frequently commented upon, as is its general tendency to stop abruptly in the midline. It has been noted that the hypertrophied limb is affected in virtually every case, with the vascular staining more or less confined to this limb in about 75% [10,18]. In about 20% of cases, the whole of the ipsilateral side of the body is affected [10,18], usually with the exception of the face, and in about 15% the contralateral limb is also affected. Patients with otherwise typical Klippel–Trenaunay syndrome may lack such skin lesions. In one report, the proportion of patients without vascular staining was as high as 68% [19].

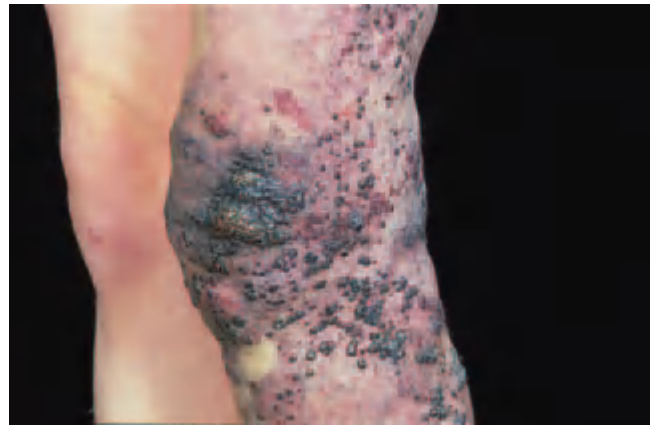

Fig. 15.21 Klippel–Trenaunay syndrome: port-wine stain on knee with numerous angiokeratomatous nodules.

It is not uncommon for other types of vascular malformation to be present (Fig. 15.21). Small angiokeratomas and lesions resembling granuloma telangiectaticum may occur as in other port-wine stains. Very occasionally, lesions of the type described as pseudo-Kaposi sarcoma or angiodermatitis have been reported in Klippel–Trenaunay syndrome [20]. These lesions have more often been reported in association with localized arteriovenous fistulae. It is in addition characteristic for other, often large or complex vascular malformations to coexist with the vascular staining. These quite often lie directly below areas of superficial vascular staining [18], and are likely to have been present since birth. Perhaps lymphangioma circumscriptum is the most typical of all, but lymphoedema is also common, and may be accompanied by recurrent bouts of cellulitis.

Very occasionally, patients have been prone to prolonged bleeding from telangiectatic areas of skin following trauma [21].

The legs are more often affected than arms. Many variations have been described, including facial involvement [22–24], often with features of the Sturge–Weber syndrome [23–25]. Hemihypertrophy may occur, in which the thorax is affected in addition to the arm and leg on the same side [15,26,27], as may bilateral involvement of two or all four limbs [27–30]. The affected part may be larger at birth or more rapid growth may only gradually become apparent. Increased length of limbs implies bony hypertrophy; increased girth implies soft-tissue overgrowth [10]. Rather rarely, there may be atrophy of the limb rather than hypertrophy [10,30,31]. Radiologically, the hypertrophic bone may show cortical thickening and osteoporosis may be a late feature [15,32].

Compensatory scoliosis is a complication of difference in leg length [10,33], and hip dislocation may occur [27].

Unilateral enlargement of the tongue has been described where the face is affected [26].

Venous varicosities of the affected limb are a frequent finding. Although these may appear early, more often they develop during later childhood or adolescence. The most common abnormality is a lateral venous anomaly [17]. Pain is a very common symptom [10]. About 25% of patients experience episodes of profound haemorrhage from ruptured varicosities [10], and about 5% have attacks of superficial thrombophlebitis.

Ulceration is said to be rare [11], but the real risk may have been underestimated [16,34]. The development of basal and squamous carcinomas has occasionally been reported [35], and is likely to be a greater risk in the presence of chronic ulceration [34].

There is a high rate of spontaneous deep-vein thrombosis and pulmonary embolism [10]. The deep venous system in the limb is frequently hypoplastic or absent [36,37].

Recurrent septicaemic episodes have complicated lower limb Klippel–Trenaunay syndrome [17].

Sympathetic overactivity in the affected limb may give rise to hyperhidrosis, which may be marked, or to vasoconstriction.

Entrapment syndromes, such as trigger finger and carpal tunnel syndrome, have been reported when the upper limb is affected, and are believed to be due to lymphatic obstruction [38].

Many associated developmental defects have been recorded. Occasional patients have had coincidental verrucous epidermal naevi [39,40]. Polydactyly, syndactyly and oligodactyly are relatively frequent [10,22,38]. Other associated abnormalities have included macrocephaly [24], blue naevi [23], pulmonary vein varicosities [41] and visceral venous malformations [10,29,42]. Lesions in the bladder causing haematuria appear to be present in as many as 5% of cases [10,29,42,43], and colonic and rectal lesions may be present in as many as 10% of patients [21,29,43], resulting in rectal bleeding and melaena.

Differential diagnosis. The principal problems in diagnosis are to differentiate between the Klippel–Trenaunay syndrome and (i) the Parkes Weber syndrome and (ii) the Proteus syndrome.

In the much rarer Parkes Weber syndrome, limb hypertrophy is caused by multiple arteriovenous fistulae. Vascular stains of port-wine-stain type may also occur, but appear to be less common and paler [13,17,44]. The affected limb is larger than the unaffected one, is warm and the superficial veins are conspicuous and may pulsate. A continuous bruit may be audible. Application of a tourniquet often results in slowing of the pulse (the Branham sign). The arm is more commonly affected than the leg [13,32]. The enlarged limb is not liable to be deformed, as is frequently the case in the Klippel–Trenaunay syndrome [12].

Confusion between the Klippel–Trenaunay and Proteus syndromes has been a major problem, and many cases of the Proteus syndrome were in the past reported under the title Klippel–Trenaunay syndrome. In the Proteus syndrome, limb hypertrophy and port-wine stains are associated with a variety of quite distinctive abnormalities, which serve to differentiate it clearly, at least in the majority of cases.

The syndrome of *diffuse phlebarteriectasis* appears to be an exceedingly rare but distinct condition in which the entire arterial and venous systems of a part or the whole of a limb is congenitally ectatic; bony hypertrophy may be a feature [32]. The existence of this syndrome has recently been questioned [17].

Patients with Maffucci's syndrome may have complex deep venous and lymphatic malformations in addition to the typical protuberant vascular swellings that may occur on the hands and feet in particular. In such cases, the clinical picture can resemble that of the Klippel–Trenaunay syndrome [17]. Other disorders featuring vascular malformations and overgrowth include the Bannayan–Riley–Ruvalcaba syndrome and the Beckwith–Weidemann syndrome.

Treatment. The majority of patients do well without treatment, or with elastic support alone [45]. Elastic support reduces symptoms of chronic venous insufficiency, decreases swelling caused by lymphatic stasis and protects the limb from minor external trauma that may provoke bleeding.

Few surgeons attempt more than ligation and stripping of superficial venous varicosities [10,45]. These procedures can relieve local symptoms, particularly pain. However, inadequate preoperative evaluation increases the risk of complications. In the 20% of patients with absence or hypoplasia of the deep venous system, this type of procedure is likely to make symptoms worse [13,32]. Both an MRI scan and contrast venography should be undertaken before any procedure on the superficial veins. Very occasionally, obstructions of the deep venous system can be relieved surgically with good results [19] and reconstructive procedures for deep-vein atresia or hypoplasia may occasionally be successful [45].

Gradual spontaneous fading of the naevus has been observed [10]. In selected cases, laser therapy may be appropriate on aesthetic grounds.

Patients with the Klippel–Trenaunay syndrome should probably be given thrombosis prophylaxis prior to any surgery because of the high rate of thromboembolic complications [10].

Bleeding from the lower gastrointestinal tract and the bladder may also require surgical treatment [43].

It is important to recognize the presence of any difference in leg length as this is likely to lead to scoliosis and early osteoarthrosis of knees and hips. During the early

years, the shoe on the shorter leg can be built up to compensate. Later, epiphyseal stapling (epiphysiodesis) or tibial osteotomy can be used to slow down growth in the longer leg. Amputation may be indicated if the enlarged limb, or part of it, is severely deformed [12,33,45].

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Venous malformations

Blue rubber bleb naevus syndrome

This is a rare disorder comprising multiple venous malformations of the skin, gastrointestinal tract and, frequently, other sites [1–3]. Most cases have been sporadic, but there has been good evidence for autosomal dominant inheritance in a number of families [4–6]. However, two of these families had a disorder that was clinically atypical, and, in another family, only males appeared to be affected [7].

Histologically, the skin lesions comprise large, blood-filled, vascular lumina in the dermis and subcutaneous fat. More superficially, these lumina are often lined only with endothelial cells, whereas deeper lumina have a better developed vessel wall with smooth muscle [4,8]. The vascular channels are separated from one another by strands of connective tissue. Gastrointestinal lesions are histologically similar, with the vascular channels observed in the lamina propria and submucosa.

The most characteristic cutaneous lesions are compressible, blue or purple, soft, rubbery nodules with a wrinkled surface, which have often been likened to nipples. They are generally small and present in limited numbers, but they have on occasion been as large as 5 cm in diameter.

They have occurred as solitary lesions, but, in other cases, have been extremely numerous [7–12]. They may occur virtually anywhere on the body surface, and on the mucosa of the lips, the mouth and the glans penis. They may lie fairly deeply in the skin so that only bluish discoloration is visible at the surface. It is characteristic for them to be spontaneously painful, particularly at night, although this feature may be absent before puberty and may never occur in some patients. They may also be tender. In some cases, the lesions have demonstrated increased sweating, and an intimate relationship between the angiomatous vessels and sweat glands has been described histologically [9]. They may be present at birth, but more often appear progressively during early childhood. Occasionally, the onset may be in adult life [5,13,14], although it is possible that not all such cases have been genuine examples of the blue rubber bleb naevus syndrome.

Analogous lesions also occur in the gastrointestinal tract at all levels, but particularly in the small intestine, where they frequently bleed [4,15–19]. Rather characteristic nodular, blue, vascular lesions may be clearly visible on and under the tongue [20]. The resulting anaemia may be profound. They may also be the cause of intussusception [21]. There appears to be no correlation between the number of skin and gastrointestinal lesions. Lesions may less commonly occur in a variety of other sites, where they may provoke a wide spectrum of symptoms [8,9,12,14,20,22–26]. Reported examples include the nasopharynx, lungs, heart, liver, spleen, CNS [26], eye [27], urinary tract [2], muscle and joints. A single case has been reported in whom blue rubber bleb naevi were associated with multiple enchondromas, as found in Maffucci's syndrome [28]. A number of musculoskeletal problems have occurred in affected individuals [23], including gigantism of an arm requiring amputation in infancy [8].

Early-onset chronic consumption coagulopathy may occur [29].

It may require judgement to decide how deeply to investigate cases where this diagnosis is suspected and where the patient is asymptomatic. Where anaemia is present, or where internal bleeding has occurred, appropriate investigations may include gastrointestinal tract and bladder endoscopy, and head and spinal MRI.

Once developed, the vascular malformations of the blue rubber bleb naevus syndrome remain unchanged for life, with no tendency to spontaneous regression.

Blue rubber bleb naevi need to be distinguished from multiple infantile haemangiomas. They may also occasionally be confused with eccrine angiomatous hamartomas, glomangiomas, Maffucci's syndrome and angiokeratoma corporis diffusum. It is possible that is some cases at least, lesions reported as blue rubber bleb naevi would now be reclassified as glomangiomas of the disseminated multiple type.

Treatment of the blue rubber bleb naevus syndrome largely comprises symptomatic treatment of its complications. If anaemia cannot be controlled by iron supplements or intermittent transfusion, resection of heavily involved lengths of bowel may be indicated. Endoscopic cauterization may also be effective. Amputation may be indicated for skeletal deformity [1]. Successful carbon dioxide laser treatment of the skin lesions has been reported [18].

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Maffucci's syndrome

SYN. DYSCHONDROPLASIA WITH HAEMANGIOMAS

Maffucci's syndrome comprises the association of cutaneous venous malformations with dyschondroplasia [1–8]. Familial occurrence does not appear to have been recorded.

Although few histological details have been published, it appears that the skin lesions comprise thick- and thin-walled dermal and subcutaneous vascular spaces, with a single endothelial lining. Although these lesions have frequently been called cavernous haemangiomas, they do not appear to be true haemangiomas but complex venous malformations.

Affected individuals are generally of normal appearance at birth, but multiple cutaneous vascular swellings generally start to appear in infancy. These lesions generally take the form of soft, bluish, occasionally tender subcutaneous protrusions. The skin lesions show no tendency to resolve, and grow proportionately with the child. Grotesque grape-like masses may develop on the hands and feet [6]. Cavernous lymphangiomas are also frequently seen [7], and may be the sole cutaneous manifestation [9].

Other cutaneous features reported have included pigmentary changes [1,3,5,10], particularly café-au-lait macules. Simultaneously with the appearance of the cutaneous vascular swellings, the patient develops hard nodules arising from the bones, especially those of the fingers and toes, and the metaphyses of the long bones of the arms and legs. Pathologically, these are enchondromas, which are radiologically translucent. These bone lesions may be unilateral or asymmetrical. The growth of affected bones is delayed and distorted due to interference with the epiphyseal cartilage, and slowly uniting pathological fractures are a common occurrence. Deformity may be gross, with hands and feet transformed into large and almost useless chondromatous masses [6].

A variety of other benign and malignant mesodermal tumours have been reported in Maffucci's syndrome, and the disease has a very high malignant potential [4]. The most common malignant tumour is the chondrosarcoma, which arises by malignant transformation in enchondromas, and probably occurs in some 15% of patients [4,11]. Other malignant mesodermal tumours have included fibrosarcoma [12], angiosarcoma [10], lymphangiosarcoma [13] and osteosarcoma [2]; various benign and malignant ovarian tumours have also been reported [4,10]. In addition, several non-mesodermal tumours have been described in these patients, including gliomas [3,4] and adenocarcinoma of the pancreas [12]. Multiple primary malignancies may occur [2,4,12].

Ollier's disease comprises dyschondroplasia without the cutaneous vascular malformations seen in Maffucci's syndrome; in other respects the two conditions are indistinguishable. Reports of internal vascular anomalies in Ollier's disease [14] add to the impression that the two conditions are extremely closely related.

A patient combining the features of Maffucci's syndrome and the blue rubber bleb naevus syndrome has been reported [15].

Clearly, these patients require careful follow-up, with a low threshold for obtaining radiological and histological examination of any lesions that enlarge rapidly or cause symptoms. Surgical excision of skin lesions may be justified to improve the patient's appearance. Radiotherapy is unhelpful.

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Unilateral dermatomal haemangiomatosis [1,2]

Cases have been described in which vascular tumours, histologically similar to those reported in the blue rubber bleb naevus syndrome, developed during the second decade in a unilateral grouping suggesting a dermatomal distribution. The lesions have taken the form of purplish

hemispherical nodules, which may be tender, up to 1.5 cm in diameter. There has been no evidence of any associated bony or systemic lesions, and the affected limb has been of normal size. The lesions have shown no tendency to resolve spontaneously.

These lesions have closely resembled those encountered in Maffucci's syndrome, but the associated bone lesions seen in this disorder have been conspicuously absent.

Dermatomal vascular abnormalities are also a feature of Cobb's syndrome and unilateral dermatomal superficial telangiectasia (unilateral naevoid telangiectasia).

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Gorham's disease [1–7]

SYN. HAEMANGIOMAS WITH OSTEOLYSIS; DISAPPEARING BONE DISEASE; OSTEOVASCULAR DYSPLASIA

In this condition, bone is replaced by vascular malformations comprising ectatic thin-walled sinusoidal blood vessels, and there may be associated cutaneous and soft-tissue vascular or lymphatic malformations. The osseous lesions cause osteolysis with fibrosis, and may lead to disappearance of entire bones. The skeletal lesions are usually unilateral and generally involve adjacent bones. There is a predilection for the bones of the shoulders and pelvic girdle [8].

Radiologically, there are lytic lesions of bone with little or no sclerosis. Associated coagulopathy has been described [9–11].

The condition appears to be self-limiting in many cases, but in some patients the disease may be aggressive and ultimately lethal [2,12].

Radiotherapy may be helpful, particularly for bone pain [1,6].

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Other multiple vascular malformation syndromes

Bannayan–Riley–Ruvalcaba syndrome [1–11]

SYN. BANNAYAN–ZONANA SYNDROME; RILEY–SMITH SYNDROME; RUVALCABA–MYHRE–SMITH SYNDROME

This term is now used to encompass the disorders previously described separately as the Bannayan–Zonana, Riley–Smith and Ruvalcaba–Myhre–Smith syndromes [3,12].

Clinical features include macrocephaly, multiple subcutaneous and visceral lipomas and vascular malformations, and skeletal abnormalities. The disorder is transmitted as an autosomal dominant trait with variable expression. Clinical similarities with Cowden's syndrome have been recognized for many years [2]. It is now known that mutations in the *PTEN* gene, a tumour-suppressor gene located at 10q23.3, underlie both conditions. Indeed, families have been reported in which individuals with Cowden's syndrome and the Bannayan–Zonana syndrome have both been present, with identical *PTEN* gene mutations in each, suggesting that these two syndromes represent different phenotypic expressions of one disease [13,14]. It now seems probable that patients with Bannayan–Zonana syndrome are at increased risk of malignancy, as are those with Cowden's syndrome [15].

The predominant cutaneous lesions are usually soft, deeply situated lipomatous swellings, but lesions resembling lymphangioma circumscriptum or angiokeratomas have also been described [7]. The trunk and proximal limbs appear to be sites of predilection for these lesions, some of which clearly reach a considerable size. They have shown no tendency to spontaneous resolution. Other skin lesions, in order of decreasing frequency, have included:

1 lentigines on the glans and shaft of the penis;
2 multiple facial papules, showing histological features of both trichilemmomas and viral warts [2];
3 acanthosis nigricans;
4 multiple achordons.

The macrocephaly is not associated with hydrocephalus, and many of the patients show hypotonia, delayed psycho-

motor development, variable degrees of mental retardation and/or seizures.

Intracranial vascular malformations [9] or arteriovenous malformations [16] have been reported. Patients with Bannayan–Zonana syndrome may occasionally have hamartomatous lesions producing cord compression or intracerebral haemorrhage [15]. Additional features have included hamartomatous intestinal polyposis and retinal abnormalities.

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Hereditary neurocutaneous vascular malformations [1–4]

SYN. HEREDITARY NEUROCUTANEOUS ANGIOMAS

Reports of this syndrome have been few in number, and it remains unclear whether it is a genuine entity. It appears to be transmitted by an autosomal dominant gene of highly variable expressivity. There are scattered cutaneous vascular anomalies, which are not well described, but are likely to be vascular malformations rather than haemangiomas. Some of the lesions in these families seem to have been macular [4], but others have been papular or nodular, occasionally large enough to warrant excision [2]. The importance of this disorder is the occurrence of intracranial arteriovenous malformations in several family members.

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Angiokeratomas

The term angiokeratoma is applied to a number of quite distinct conditions that share a clinical presentation with asymptomatic hyperkeratotic vascular skin lesions and a histological combination of superficial dermal vascular ectasia and hyperkeratosis. The following varieties are generally recognized:

1 angiokeratoma circumscriptum;
2 angiokeratoma of Mibelli;
3 solitary papular angiokeratoma;
4 angiokeratoma of the scrotum and vulva;
5 angiokeratoma corporis diffusum.

Of these, only angiokeratoma circumscriptum is present at birth. The angiokeratomas should be regarded as capillary vascular malformations rather than haemangiomas [1]. Individual patients may occasionally have lesions of more than one of these types [2].

Angiokeratotic lesions may be a feature of the Klippel–Trenaunay syndrome and of Cobb's syndrome. In an isolated case report, a boy was described in whom multiple, widely distributed angiokeratomas were associated with a connective tissue naevus on the foot and a venous vascular malformation of the ankle, with decreased size of the affected leg [3].

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Angiokeratoma circumscriptum

SYN. ANGIOKERATOMA CORPORIS CIRCUMSCRIPTUM NAEVIFORME

Aetiology and pathology [1–3]. Angiokeratoma circumscriptum is a vascular malformation of the vessels of the

papillary dermis. These vessels are ectatic histologically, and may be thrombosed. The overlying epidermis shows a variable degree of acanthosis, papillomatosis and compact hyperkeratosis. The elongated rete ridges may partially or completely envelop the dilated vessels. Transepidermal elimination of the dilated capillaries has been demonstrated [4,5]. Lesions in which deeper angiomatous elements have been reported were almost certainly verrucous haemangiomas.

Clinical features [1,5,6]. The condition is rare, and most characteristically takes the form of a fairly extensive hyperkeratotic vascular plaque, usually but not always present from birth. The lesions are typically situated unilaterally on a lower leg or foot, but can occur on thigh, buttock or occasionally elsewhere. They are deep red to blue–black in colour and tend to take on a streaky, banded or zosteriform configuration. The lesions become increasingly studded with warty keratotic papules or nodules, and they may bleed readily on trauma. There is no tendency to spontaneous improvement. Occasionally, they appear to extend during adolescence. Similar lesions have been a feature of the Klippel–Trenaunay syndrome [7], of other mixed vascular malformations [7,8] and of Cobb's syndrome [9].

Diagnosis. Angiokeratoma circumscriptum is distinguished from the other varieties of angiokeratoma principally by virtue of its very early onset and its clinical appearance as a plaque of aggregated papules. However, it may be virtually indistinguishable clinically from verrucous haemangioma; indeed, many of the lesions reported in the literature as angiokeratoma circumscriptum [10,11] were probably verrucous haemangiomas. The main distinction between these conditions is the presence of angiomatous capillary endothelial proliferation in the latter. Angiokeratoma circumscriptum may also be confused, both clinically and histologically, with lymphangioma circumscriptum; some lesions described in the literature as angiokeratoma circumscriptum have almost certainly been lymphangioma circumscriptum, for example several of those reported by Dammert [7]. When thrombosis occurs within the angiokeratoma, malignant melanoma may be mimicked clinically [3].

Angiokeratoma circumscriptum needs to be distinguished from acral pseudolymphomatous angiokeratoma of children, a distinctive entity that is a pseudolymphoma rather than an angiokeratoma [12].

Treatment. Small lesions may be treated by diathermy or by curettage and cautery, but larger lesions will require argon laser ablation [13,14] or surgical excision if treatment is contemplated.

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Angiokeratoma of Mibelli

Aetiology and pathology. There is a definite familial predisposition to angiokeratoma of Mibelli, and it is considered probable that this rare condition is transmitted as an autosomal dominant trait with highly variable penetrance [1–3]. Girls appear to be affected predominantly. The distribution and the regular association with acrocyanosis and chilblains appear to implicate cold injury as a provocative factor.

The histopathological features are essentially the same as those of angiokeratoma circumscriptum, i.e. marked ectasia of vessels within the papillary dermis, with associated acanthosis, papillomatosis and hyperkeratosis of the overlying epidermis [3,4]. Elongated rete ridges tend to encircle and enclose the vascular lacunae.

Clinical features [3,5–7]. The lesions commonly develop between the ages of 10 and 15 years, but both earlier and later onset has been recorded. A history of recurrent chilblains is usual, but not invariable. The earliest lesions are minute, bright-red macules, which slowly increase in size and become elevated, warty and darker in colour. Many attain a diameter of about 5 mm, but some may be larger. The dorsal and lateral aspects of fingers and toes are most often affected, but lesions also occur on the dorsa

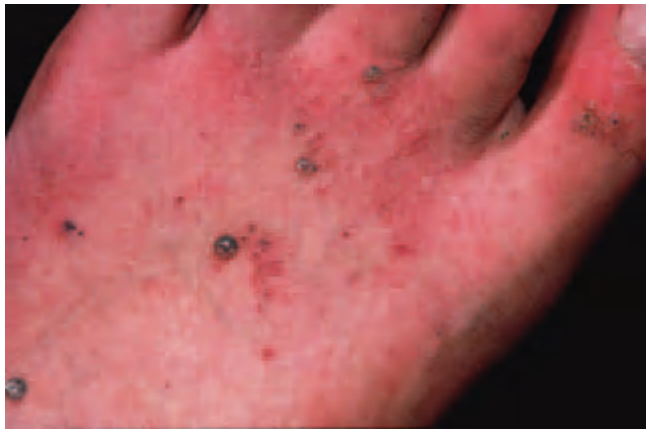

Fig. 15.22 Angiokeratoma of Mibelli in a 9-year-old child.

of hands and feet (Fig. 15.22) and occasionally on the knees and elbows. On the calves, lesions resembling erythema induratum may be present [2]. When climate and dress provide the right conditions, they may also develop on the buttocks. The lesions, which are often numerous, may be disfiguring but seldom cause symptoms; they have, however, been associated with ulceration of the fingertips [1,5]. There is little tendency to spontaneous resolution.

Treatment. The lesions can be treated, if desired, with liquid nitrogen, electrodesiccation, laser ablation or by local excision.

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Solitary papular angiokeratoma [1]

This entity has been convincingly distinguished from the other angiokeratomas, particularly from angiokeratoma circumscriptum [2]. Both solitary papular angiokeratoma and angiokeratoma of Mibelli are almost certainly acquired disorders, probably arising as a response to trauma and cold injury, respectively, rather than being developmental anomalies, but both are considered in this chapter because of the clinical and histopathological similarities with the other angiokeratomas.

Histologically, solitary papular angiokeratomas are more or less indistinguishable both from angiokeratoma circumscriptum and angiokeratoma of Mibelli. Solitary angiokeratomas differ clinically mainly by their much later appearance, usually between the age of 10 and 40 years, often with a history of preceding trauma. They occur in both sexes and at more or less any site, although the legs are the site of predilection. Although usually single, multiple lesions may occur. The patient often presents with a history of sudden enlargement, darkening or bleeding in a long-standing lesions, leading to suspicion of a malignant melanoma [2]. The lesions have the appearance of warty papules, generally between 2 and 10 mm in diameter, and dark red to blue-black in colour.

Solitary papular angiokeratomas are frequently mistaken clinically for viral warts, melanocytic naevi, or more importantly, malignant melanoma. They should be removed by local excision if there is any anxiety about the diagnosis.

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Angiokeratoma of the scrotum

SYN. ANGIOKERATOMA OF FORDYCE

Aetiology and pathology. The most common of the angiokeratomas, angiokeratoma of the scrotum, becomes more frequent with increasing age [1]. In a study in Japan, the prevalence was shown to increase from 0.6% in 16 year olds to 17% in those over 70 years of age [2]. It should probably be regarded as a degenerative disorder, and there is evidence that local venous hypertension plays a part in their development [1,3].

The histological features are similar to those observed in angiokeratoma of Mibelli and solitary papular angiokeratoma [4].

Clinical features [1,3,5,6]. Small, 1–4 mm, bright-red vascular papules may develop on the scrotum as early as late adolescence. With increasing age they become larger, darker and more numerous. Patients may occasionally complain of itching, soreness or bleeding [7]. Identical lesions may also occur on the glans or shaft of the penis, or even on the upper thighs and in the groins. Well-circumscribed, macular, telangiectatic lesions have been described on the oral mucosa in patients with angiokeratomas of the scrotum [8].

The diagnosis of angiokeratoma corporis diffusum

should be considered in any patient presenting with scrotal angiokeratomas.

Treatment. Liquid nitrogen cryotherapy, diathermy or laser ablation [9,10] can be used to treat symptomatic lesions. Evidence of associated disorders capable of increasing the scrotal venous pressure should be sought, particularly varicocoele, treatment of which may lead to regression of the angiokeratomas [3].

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Angiokeratoma of the vulva

Lesions entirely analogous to scrotal angiokeratomas may occur on the labia majora in older women [1,2].

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Other developmental defects

Complex defects of the first branchial arch

The complex disorders resulting from defective development of the first branchial arch [1] include the following of relevance to dermatologists:
1 mandibulofacial dysostosis (syn. Treacher Collins syndrome);
2 oculomandibulodyscephaly with hypotrichosis (syn. Hallermann–Streiff syndrome);
3 oculo-auriculovertebral dysplasia (syn. Goldenhar's syndrome) and hemifacial microsomia.
Defects in development of the other branchial arches do not result in cutaneous abnormalities, with the exception of thyroglossal cysts and fistulae, which are remnants of the thyroglossal duct, and branchial cysts and fistulae, which result from a failure to obliterate the cervical sinus.

Mandibulofacial dysostosis

SYN. TREACHER COLLINS SYNDROME; FRANCESCHETTI–KLEIN SYNDROME

Definition. An autosomal dominant disorder of craniofacial development resulting from defective development of the first branchial arch [1].

Aetiology. Treacher Collins syndrome is caused by mutations in the gene *TCOF1* at chromosomal locus 5q31.3 [2,3]. The gene product 'treacle' is a nucleolar trafficking protein, essential during craniofacial development, the mutational spectrum suggesting haplo-insufficiency during embryogenesis of the first and second branchial arches as the molecular mechanism [4]. Treacher Collins syndrome is a dominant trait, 60% of cases arising as new mutations [5]. Expression is highly variable with no apparent genotype–phenotype correlation, and in one study two of 28 families showed no mutation in *TCOF1* [6]. The abnormalities appear to result from arrested development of the first branchial arch at the 5–9-week stage. It will be of interest to dermatologists that the malformations observed in this disorder are similar to those produced in fetal mice by retinoids given at day 11.5 post-fertilization, corresponding to week 4 in humans [7,8]. Furthermore, Lungarotti *et al.* [9] described facial changes resembling mandibulofacial dysostosis in an infant whose mother took vitamin A during pregnancy. Mice deficient in endothelin-1 show strikingly similar craniofacial abnormalities to those seen in humans with the Treacher Collins syndrome [10].

Clinical features. The clinical presentation is highly variable with sometimes subtle manifestations. The facial anomalies are usually symmetrical and include antimongoloid slanting palpebral fissures, coloboma of the lower lid, absence of lower eyelid lashes, malformation of the pinnae with stenosis of the external auditory meati, micrognathia, hypoplastic zygomatic arches and extension of scalp hair on to the cheeks [2,3]. Blind fistulae and skin tags are sometimes present between the ear and the angle of the mouth. The mouth itself is unusually large, and the palate high and often cleft. Circumscribed scarring alopecia is an occasional finding. Most affected individuals are of normal intelligence but conductive-type deafness is a common problem.

Treatment. The facial appearance tends to improve as the child grows, and may be enhanced by surgery [1]. Early respiratory difficulties may develop as a result of a narrow airway, occasionally requiring tracheostomy [11]. Deafness requires early recognition and correction with hearing aids and, where possible, surgery.

Prenatal diagnosis by ultrasound may not be possible until the second trimester [12]. In some families a diagnosis can be made in the first trimester by linkage [13] or mutation [14] analysis. Ellis *et al*. [14] found mutations in *TCOF1* in 52 of 97 patients with Treacher Collins syndrome.

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Hallermann–Streiff syndrome

SYN. OCULOMANDIBULODYSCEPHALY WITH HYPOTRICHOSIS; DYSENCEPHALIC SYNDROME OF FRANÇOIS

Definition. A craniofacial dysostosis comprising skeletal, ophthalmological and cutaneous defects.

Aetiology. Hallermann–Streiff syndrome is usually sporadic. The data from familial cases has been variably interpreted as indicating an autosomal dominant gene, with most cases reflecting new mutations [1], or autosomal recessive inheritance [2].

Pathology. Histologically, the skin shows a rather loose-weave arrangement of dermal collagen and fragmented elastic fibres [3]. Scanning electron microscopy of hairs demonstrates circumferential grooving or absence of the cuticle [4].

Clinical features [3–8]. The head is short (brachycephalic), the mandible hypoplastic and the nose beaked, producing a characteristic bird-like appearance. Ocular abnormalities are a major problem, particularly bilateral microphthalmia and cataracts. The mouth is small with a high-arched palate. Teeth are often present at birth; partial anodontia, hypoplasia and malimplantation of the teeth are also common [7]. There is proportionate dwarfism, and psychomotor retardation in 15–31% [5].

Cutaneous abnormalities are a striking feature. The scalp hair may be normal at birth, but soon becomes diffusely sparse and brittle, with lack of hair particularly along the sides and back of the head. A highly characteristic finding is alopecia along the lines of the cranial sutures. The eyebrows, eyelashes, and pubic and axillary hair are also scanty. The skin of the face is atrophic, particularly in the central part of the face, and telangiectasia may be prominent. Vitiligo and livedo have been reported [8].

Diagnosis. This condition must be differentiated from progeria, in which atrophy of the skin is more generalized, and alopecia both more pronounced and more diffuse.

Treatment. Airway compromise can be life-threatening and requires early intervention [8]. Affected children require expert ophthalmological and dental care. Reconstructive procedures are dealt with later and sometimes a wig is helpful. Aesthetic surgery is difficult because the skin is generally thin and prone to scarring [8].

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Goldenhar syndrome and hemifacial microsomia

SYN. OCULO-AURICULOVERTEBRAL DYSPLASIA; FACIO-AURICULOVERTEBRAL SYNDROME; HEMIFACIAL MICROSOMIA

Definition. An association of defects arising in the first and second branchial arches.

Aetiology. Goldenhar syndrome is relatively common, with an incidence of about one in 5600 [1]. Genetic analysis has been hampered by phenotypic heterogeneity, particularly with regard to severity. The genetic data favours autosomal dominant inheritance although most cases are sporadic [2]. A minor related anomaly, such as pre-auricular skin tag, occurs in 8% of first-degree relatives [3]. Goldenhar syndrome appears to be the result of abnormal development of both the first and second branchial arches. Suggested causes include 'over-ripeness ovopathy' [4], haemorrhage involving the first and second branchial arches, and ectodermal non-disjunction and subsequent mesodermal tethering [5]. The last of these best explains the multisystem nature of this condition: involvement of the otic placode accounts for the ear anomaly and a similar process over the neuraxis explains the association with occult spinal dysraphism. Infants of diabetic mothers appear to be at increased risk [6]. Retinoic acid administered to rats on gestational days 10–12 produces similar anomalies [7].

Clinical features [3]. Much of the facial skeleton and musculature is hypoplastic. The pinna is small and deformed. Deafness may occur. Accessory auricles and pits are common, occurring along a line between the ear and the corner of the mouth. A low hairline on the forehead and temples has occasionally been reported. The facial, auricular and ocular abnormalities tend to be asymmetrical, occasionally more or less unilateral, when the term hemifacial microsomia is applied.

Ocular abnormalities are frequent and highly characteristic, particularly microphthalmia, upper eyelid coloboma, epibulbar dermoids and lipodermoids. Dermoids and lipodermoids present as yellow or white swellings at the limbus or corneal margin, dermoids usually in the lower outer quadrant and lipodermoids in the upper outer quadrant.

Vertebral anomalies are a constant feature, especially hypoplasia of vertebrae or hemivertebrae, most often in the cervical spine, and occult spinal dysraphism.

Diagnosis. There is phenotypic overlap with the oculocerebrocutaneous syndrome, in which ear anomalies are less common and focal skin defects more common than in Goldenhar anomaly [8].

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Pre-auricular cysts, tags and sinuses

SYN. EAR PITS AND TAGS; CONGENITAL AURICULAR FISTULAE

Aetiology. The auricle is formed by the fusion of six small tubercles, three from each of the first two branchial arches. Imperfect fusion leads to entrapment of the epithelium to form pre-auricular cysts, which connect with the skin via pre-auricular sinuses. Such cysts and sinuses may occur as an isolated autosomal dominant trait [1]. Pre-auricular pits and sinuses also occur in the first and second branchial arch syndromes discussed above, i.e. Treacher Collins syndrome, Goldenhar's syndrome and retinoic acid embryopathy. They are frequent also in the following syndromes: cat eye [2], cervico-oculo-acoustic, 3p-, 4p-, Kabuki's, Nager's acrofacial dysostosis, Peters'-plus, Townes–Brocks [3] and branchio-oto-renal (BOR). BOR syndrome can be caused by mutations in the *EYA1* gene [4]. Posterior ear pits occur in the Beckwith–Wiedemann syndrome [5].

Clinical features. Asymptomatic pre-auricular cysts and sinuses are very common (Fig. 15.23), occurring in 6.2 per 1000 live births in Israel [6], more often in black populations, and in 2.5% of the Chinese population [7]. These congenital, often bilateral, lesions may go unnoticed until infection develops, when they present as an acutely tender swelling anterior to the ear, with pus draining through a small opening just in front of the ascending limb of the helix. In most cases infection is recurrent, and an asymptomatic sinus is present on the other side. Very

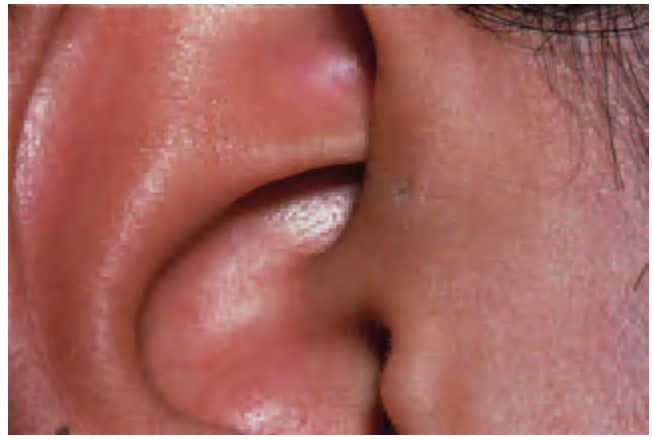

Fig. 15.23 Pre-auricular sinus.

occasionally, the patient may present with a granulomatous nodule at the mouth of the sinus.

Hearing impairment is found in 17% of neonates with isolated preauricular pits or tags [8]. Associated developmental anomalies of the branchial apparatus may coexist, particularly malformations of the auricle, accessory auricles, and branchial fistulae. CT scanning is more useful than MRI in the delineation of these anomalies [9]. Although preauricular sinuses coexist with renal anomalies in certain syndromes, e.g. the BOR syndrome [4,10], isolated pre-auricular tags or pits are not associated with renal anomalies [6,10].

Diagnosis. First branchial arch sinuses may discharge into the external auditory meatus (cervico-aural fistulae). Granulomatous lesions may be confused with lupus vulgaris [11].

Treatment. Hearing tests are indicated in neonates with isolated ear pits [8], but renal investigations are not [6]. Surgical excision is required when secondary infection has occurred, but should be delayed until the acute infection has been treated with systemic antibiotics. The lesion most typically comprises several cysts arranged along a longitudinal tract which blends with the periosteum of the auditory canal. Full visualization should be achieved before excision [12].

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Accessory tragus

SYN. ACCESSORY AURICLE; CARTILAGE NAEVUS

Aetiology [1]. The tragus (the prominence anterior to the external auditory meatus) is derived from the dorsal portion of the mandibular (first) branchial arch. During embryonic life, the first arches grow ventrally to join in the midline, and accessory tragi may be found anywhere along this migratory course, from tragus to sternoclavicular joint.

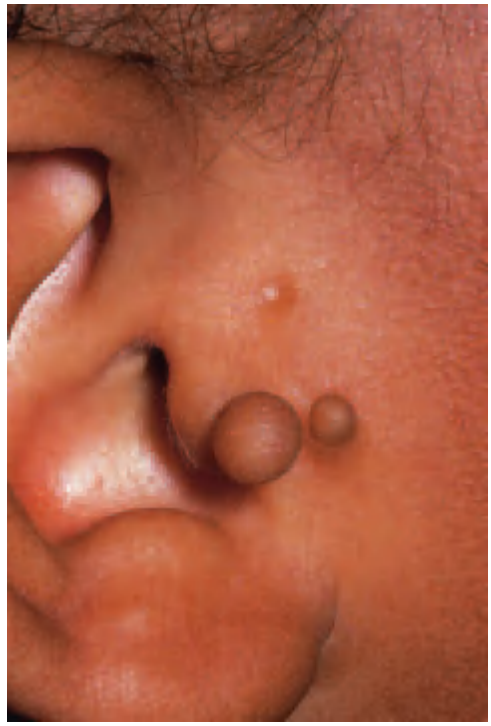

Fig. 15.24 Accessory tragi.

Pathology. Numerous tiny hair follicles and eccrine sweat glands are conspicuous in the dermal core of accessory tragi, which are covered by normal epidermis. There is a prominent connective tissue framework in the subcutaneous fat [2]. Cartilage is almost always present. They may be difficult to differentiate from hair follicle naevi [3].

Clinical features. Accessory tragi take the form of small, skin-coloured tags or nodules, arising on or near the tragus, along a line drawn between the tragus and the corner of the mouth, or on the neck (*cervical auricles* or *wattles*) along the anterior edge of the sternomastoid muscle [4]. Vellus hairs often protrude from the surface. They may be unilateral or bilateral, single or multiple (Fig. 15.24), and either soft or cartilaginous in consistency. Like preauricular cysts and sinuses, they most commonly occur as a solitary abnormality, present in about 1% of neonates [5], sometimes showing autosomal dominant inheritance [6]. They also occur with other malformations and syndromes of the first branchial arch, such as Treacher Collins, Goldenhar, Nager's acrofacial dysostosis [7], 4p- [8], oculocerebrocutaneous and Townes' syndromes [9,10].

Similar lesions have very occasionally been described at other sites on the face such as the glabella [11].

Treatment. Accessory tragi are best removed surgically, with careful dissection and excision of any associated cartilage that may extend more deeply [4,12].

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Cervical tab

SYN. CERVICAL AURICLE; WATTLE; CONGENITAL CARTILAGINOUS RESTS OF THE NECK [1–4]

Cervical tabs simply represent accessory tragi at the ventral end of the migratory path of the first branchial arch.

Histologically, they comprise lobules of mature cartilage embedded in dense collagen.

Clinically, cervical tabs take the form of an irregular, often pedunculated papule or nodule up to 15 mm in diameter, occurring on the neck along the line of the anterior border of the lower third of the sternomastoid muscle. They may be unilateral or bilateral, and are usually noted during infancy. Since these lesions are not associated with fistulous tracts or connections to deeper structures, excision is straightforward.

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Branchial cysts, sinuses and fistulae

A 35-day-old human embryo has four gill-like branchial clefts on the sides of the neck, separating the branchial arches. The first cleft persists as the external auditory meatus, the others normally disappear by fusion. Incomplete fusion results in sinuses, fistulae and cysts. Sinuses (blind tracts) and fistulae (patent tracts) which open on to the side of the neck are visible at birth, and may become more prominent later because of mucous secretion, inflammation, infection or granulation tissue at the external opening. Typical sites for cutaneous openings are the parotid area and below the angle of the mandible (first branchial cleft), and along the anterior border of the sternomastoid muscle (second branchial cleft). Cysts usually present in the second or third decade as a painful swelling due to inflammation or infection.

Branchial cyst

SYN. BRANCHIAL CLEFT CYST; LATERAL CERVICAL CYST; LYMPHOEPITHELIAL CYST

Aetiology. The precise origin of branchial cysts remains unclear. The second branchial arch extends caudally during early embryonic life to fuse with the fifth arch, thus enclosing the second, third and fourth arches and their respective clefts to form an ectodermal pocket, termed the cervical sinus [1]. Branchial cysts may represent unobliterated remnants of either this cervical sinus or of the unenclosed first branchial cleft [2–4]. A previously popular but now discounted theory is that branchial cysts arise from remnants of the thymopharyngeal tract, the original connection between the thymus and the third pharyngeal pouch, from which it takes it origin, as is the case with cervical thymic cysts [5]. Many authorities now prefer the view that they arise by cystic degeneration of remnants of parotid glandular epithelium trapped within cervical lymph nodes, a theory that better explains their late clinical appearance and the frequent presence of lymphoid tissue in the walls of branchial cysts [1,6]. However, the similarities between the lining epithelium of branchial cysts and the tonsillar crypt epithelium have recently been stressed [7], raising yet further possibilities in relation to the origin of these anomalies.

Although these defects most commonly occur sporadically, familial cases have occasionally been reported [8].

Pathology [1,7]. Branchial cysts are usually lined by stratified squamous, less commonly by respiratory-type ciliated, columnar epithelium. Beneath the epithelium one can usually observe abundant lymphoid tissue, often with germinal centres and subcapsular lymph sinuses.

Squamous carcinomas arise very occasionally in the epithelial lining of the cyst [9].

Clinical features [1,10]. Branchial cysts present at any age, but most commonly during the second and third decades. The usual complaint is of a painless, stable swelling in the neck. In some cases, the swelling is painful, usually because of secondary infection, and in others the swelling is only intermittently apparent. Pressure symptoms may occur. These cysts vary from less than 1 cm to about 10 cm in diameter and are usually unilateral. On palpation they are generally obviously cystic, but in other cases they may appear solid. Work's classification [4] differentiates the rare type I lesions which lie superior to the facial nerve and parallel to the ear canal, sometimes postauricular [11], from type II lesions which may be closely associated with the facial nerve and occur in the parotid area or upper third of the neck.

Diagnosis. In the differential diagnosis of swellings at this site, one has to consider causes of unilateral lymph-node enlargement, particularly malignant and tuberculous lymphadenopathy [12], parotid and thyroid tumours, thymopharyngeal cyst [5], thyroglossal cyst, dermoid cyst, teratoma, carotid body tumour, infantile haemangioma and neurofibroma. Cystic hygroma occurs in the posterior triangle of the neck, i.e. posterior to the sternomastoid muscle, and is usually apparent from birth or shortly afterwards.

Treatment. Otological and MRI examination are important to exclude associated anomalies [11]. Branchial cysts are removed surgically, with superficial parotidectomy and facial nerve dissection if necessary [3,13].

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Branchial sinuses and fistulae

SYN. CERVICAL SINUSES AND FISTULAE

Aetiology [1–3]. Branchial sinuses are believed to represent remnants of the branchial cleft depressions, particularly the second or cervical sinus. Familial occurrence has been recorded [4,5]. True branchial fistulae, opening into the pharynx, appear to be extremely rare, and must result from perforation of the second cleft membrane.

Pathology [3]. Branchial sinuses are lined by mucus-secreting columnar respiratory-type epithelium.

Clinical features [3]. Branchial sinuses are usually apparent from birth as pits or blind-ending tracts in the lower third of the neck, along the anterior border of the sternomastoid muscle. There is frequently a discharge, and infection may occur, although less frequently than in the case of branchial cysts. They are bilateral in about one-third of cases. A skin tag, sometimes containing cartilage, may mark the site of the opening. The tract itself may be palpable, running upwards in the neck from the cutaneous opening. Branchial fistulae share the same cutaneous distribution as branchial sinses, but open into either the pharynx or external auditory canal [6,7].

Branchial fistulae can occur as an isolated anomaly [7], but are also a characteristic component of the autosomal dominant BOR syndrome due to *EYA1* mutations, in which they are associated with pre-auricular pits, deafness and renal anomalies [8]. They also occur with pre-auricular pits, deafness, commissural lip pits and rib anomalies in the autosomal recessive branchio-oto-costal syndrome [9].

Treatment. Treatment is by surgical excision under general anaesthesia [10]. Injection of methylene blue into the cutaneous opening can be used to guide surgical removal [7]. Fistulae can be tackled by avulsion through the mouth using a varicose vein stripper [11].

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Midline cervical cleft [1–5]

Aetiology. This anomaly probably results from imperfect first or second branchial arch fusion in the midline.

Clinical features. This lesion takes the form of a vertically orientated atrophic area, several centimetres in length, and several millimetres in width, in the lower anterior midline of the neck. There may be associated skin tags and the upper end and a sinus tract at the caudal end. Fibrous bands may connect the lesion with the underlying platysma, causing contractures of the neck and lower jaw. Traction on the growing mandible may produce a bony spur. It may be associated with thyroglossal and other branchial cleft anomalies.

Treatment. Treatment is surgical, via a series of Z-plasty incisions, ideally in the first year of life. Deep fibrous remnants should also be removed.

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Thyroglossal cysts

Aetiology. Thyroglossal fistulae and cysts result from failure to obliterate the embryonic thyroglossal duct, and may occur anywhere along its length. Thyroglossal cyst is commoner in first-degree relatives of children with congenital hypothyroidism, segregation analysis supporting an autosomal dominant gene responsible for the different phenotypes [1].

Pathology. Thyroglossal cysts are lined by stratified squamous or mucus-secreting columnar epithelium.

Clinical features [2–5]. Thyroglossal cyst usually presents during the first 5 years of life but may not be diagnosed until adult life. It is the commonest cause of midline anterior neck swellings in children. It presents as a soft mass in the midline of the neck, 1–3 cm in diameter and close to the hyoid bone. It moves upwards on swallowing or on protrusion of the tongue. There may be an opening in the mouth at the foramen caecum, leading to fetor or an unpleasant taste. Occasionally, they drain externally, often as a result of previous surgical procedures. Recurrent infection may be a problem.

It is important to distinguish an ectopic thyroid from a thyroglossal cyst, because the former may be the patient's only functional thyroid tissue [6,7]. It is essential to undertake thyroid function tests and technetium-99m (^{99m}Tc) or iodine-123 (^{123}I) scintillation scanning to identify any possible ectopic thyroid tissue prior to surgical excision [8].

Malignant degeneration may occur in thyroglossal duct remnants, though generally this is associated with a good prognosis following excision [9].

Diagnosis. Enlarged lymph nodes and dermoid cysts are the main differential diagnosis [10]. Bronchogenic cysts may occur in the midline at the suprasternal notch, but are rare.

Treatment. Treatment is by dissection of the cyst and tract, and removal of the hyoid bone [10,11]. Ethanol sclerosis therapy has also been used [11].

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Other defects of relevance to dermatology

Bronchogenic cyst

SYN. PRESTERNAL CILIATED CYST

Aetiology. These anomalies usually occur in the chest or

mediastinum, but are very occasionally found in the skin [1–15]. They are assumed to develop from tracheal buds at the time of division of the foregut into its tracheal and oesophageal components. At this stage, the right and left mesenchymal bars of the sternum are still unfused. How such cysts come to occur in an extrathoracic location is difficult to explain. The characteristic suprasternal site may reflect pinching off of bronchogenic tissue by the closing sternal plates. The other locations may be reached by migration of this tissue [3]. Alternative explanations for bronchogenic cysts include lymphatic or haematogenous spread of respiratory tissue and *in situ* anomalous tissue differentiation (heteroplasia) [8].

Pathology. The cysts occur in the dermis or subcutis. The mucosal lining comprises lamina propria and a pseudostratified columnar ciliated epithelium with goblet cells. The cyst wall frequently contains smooth muscle and mucous glands. Lymphoid tissue is occasionally present, particularly when secondary infection has occurred. Cartilage is occasionally seen, in keeping with the bronchogenic origin of this lesion. There is no connection to underlying structures.

Clinical features. Bronchogenic cysts are solitary and four times more common in males [9]. They are apparent at birth or shortly afterwards, usually as a pinpoint orifice, or a soft, asymptomatic mobile nodule that very slowly increases in size and may eventually discharge mucoid fluid through a small fistula. Other morphologies include a papillomatous nodule [5] and an area with the appearance of aplasia cutis, and linear, erythematous pruritic hyperkeratotic papules resembling ILVEN [9]. Cutaneous bronchogenic cysts are characteristically located close to the suprasternal notch or over the manubrium sterni [11]. Occasionally, they occur in the shoulder and scapular area [10], or in the thyroid gland. Lesions have also been reported on the chin [12,13] and abdominal wall [14]. Malignant transformation occurs in non-cutaneous bronchogenic cysts [9] but has not been reported in cutaneous bronchogenic cysts [9,13]. Tanita *et al*. [15] reported a malignant melanoma arising in a bronchogenic cyst on the scapular area of a middle-aged Japanese man.

Diagnosis. Differential diagnosis includes branchial cysts, sinuses and fistulae [16], thyroglossal cysts [17], teratomas and heterotopic salivary gland tissue [18].

Treatment. Treatment comprises surgical excision, which is advisable in view of the possibility of later malignancy [15].

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Cutaneous associations with sternal clefts

Sternal clefts are rare congenital anomalies, which are, however, frequently associated with a variety of cutaneous abnormalities, including fistulae [1,2], an area of ulceration or scarring [3–5], supra-umbilical midline raphe [6] and facial haemangiomas. Congenital aortic aneurysm is one of the more serious extracutaneous associations. Recognized syndromes include the PHACE association [7] and the sternal malformation/vascular dysplasia association [8], which may overlap.

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Congenital inclusion dermoid cysts

Aetiology and nomenclature [1–4]. Most cutaneous dermoid cysts probably develop from epithelium trapped along lines of embryonic fusion. They should not be confused with benign cystic *teratomas*, which are also sometimes termed dermoids. They are usually sporadic but there are several reports of familial dermoid cysts of the nose, midline dermoids have occurred in a mother and daughter, and external angular dermoids have been reported in siblings [5].

Pathology [1]. These cysts are located in the subcutis; they are often adherent to periosteum, and may invade or erode underlying bone. The cysts are lined by keratinizing stratified squamous epithelium, complete with hair follicles, sebaceous and sweat glands. The lumen contains lipid, keratin and hair. There may be an associated sinus tract extending superficially or deeply or both.

Clinical features [1,3,5]. About 40% of dermoid cysts are present at birth, and about 70% by the age of 5 years. They typically appear as subcutaneous 'doughy' spherical nodules varying from around 0.5 to 6.0 cm in diameter, largely depending on site. Many have a sinus opening, from which hairs may project. They tend to present at different sites in children and in adults [6]. In children, they are most often seen on the head and neck [3,6]. Predilection sites are the outer third of the eyebrow, the so-called *external angle dermoid* [7], the midline of the nose, usually near the bridge (Fig. 15.25) [2,4,8,9], the scalp, the submental area, the anterior neck, the anterior chest wall and the occipital area [10]. In adults, they are most commonly seen in the genital and postanal areas [6].

Periorbital lesions may displace the eyelid. Recurrent infection may be a problem, and osteomyelitis and meningitis are occasional complications [8,10,11]. Pressure erosion of bone may also occur [12].

Diagnosis [13]. In the neck, the dermoid cyst is only slightly less common than the thyroglossal cyst and may be clinically indistinguishable. It must likewise be differentiated preoperatively from ectopic thyroid gland.

Cysts at the bridge of the nose must particularly be distinguished from nasal gliomas, which present at birth as firm, reddish tumours at the side of the bridge, and meningoencephalocoeles which may pulsate and may be associated with an underlying skull defect [14].

It is essential to use MRI scanning [13,15] and/or high-resolution ultrasound [16] to evaluate midline facial masses, and thyroid function tests and ^{99m}Tc or ^{123}I scintillation scanning to identify any possible ectopic thyroid tissue prior to surgical excision of neck lesions [17].

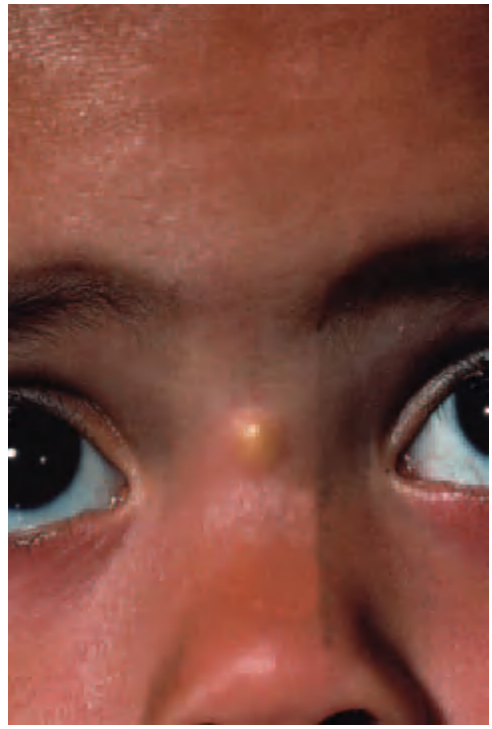

Fig. 15.25 Midline dermoid cyst on the bridge of the nose.

Treatment [2,3,7]. Surgical excision may be complicated by the presence of deep tracts adherent to underlying periosteum, or the septum in the case of nasal lesions. Failure to excise these tracts leads to recurrence, and treatment of these lesions is therefore best undertaken under general anaesthesia by a plastic surgeon.

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Nasal glioma

Nasal gliomas are rare childhood lesions [1–5], not true gliomas but rather encephalocoeles that have lost their intracranial connection. They comprise heterotopic neuroectoderm and probably develop from neuroectodermal tissue evaginated through the nasofrontal fontanelle, but subsequently not fully retracted by the dura, and amputated by closure of the craniofrontal sutures. Incomplete closure of these sutures may result in a stalk of fibroglial tissue attached to the neuroectodermal mass passing through the foramen caecum. Most are intranasal, but some appear externally.

Histology shows collections of astrocytes interspersed with dense connective tissue trabeculae, sometimes containing striated muscle fibres, within the dermis. In one case all three components of neural tissue were present, that is leptomeninges, glia and neurons, as well as sweat duct hyperplasia [5].

Nasal gliomas are generally present at birth, and thereafter grow in proportion to the child. They are asymptomatic and take the form of a firm, red or bluish, smooth, domed swelling to one side of the root of the nose. Unlike true encephalocoeles, they do not increase in size with the Valsalva manoeuvre. Intranasal gliomas take the form of a polypoid mass in the nose or pharynx, causing upper respiratory tract obstruction.

Differential diagnosis includes the true nasal encephalocoele and meningoencephalocoele [6], extracranial meningioma [7], other cutaneous neural heterotopias [8], congenital dermoid cyst, lacrimal duct cyst, neuroblastoma and rhabdomyosarcoma [9], but they are probably most often confused with infantile haemangioma [10,11].

Treatment is surgical. If preoperative imaging reveals an intracranial connection, collaboration is required between an ear, nose and throat surgeon and a neurosurgeon [4].

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Transverse nasal groove

The appearance of this lesion may be explained by differential growth of the alar and septal cartilages of the nose during childhood [1] or as a residual embryonic groove in the frontonasal cartilage [2]. It is probably not rare, but is seldom noticed. It is often hereditary [2], possibly determined by an autosomal dominant gene [3].

This is probably the same lesion that has been considered to be associated with allergic rhinitis, thought to be caused by repeated manipulation of the nose, and usually termed a 'nasal crease' [4]. No studies have been reported that seek to determine whether this lesion is in fact more frequent in children with allergic rhinitis.

A reddish pink, transverse streak or a shallow groove appears at the junction of the middle and lower thirds of the nose, generally at about the age of 10 years and most often in girls. It is obliterated spontaneously during early adult life. The presence of milia and comedones along this nasal groove has been described [2,5–8].

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Lip pits

There are three types of lip pits: commissural pits, sinuses of the upper lip and lower lip pits, also known as lip sinuses.

Commissural lip pits

These are the commonest type of lip pits, and are found in about 2% of neonates, the highest frequency being found in black neonates [1]. Pits are visible just within the oral cavity at the angle of the mouth. These pits are generally bilateral, and should be regarded as sinuses, ending blindly within a few millimetres of their openings. They probably arise as a result of locally incomplete fusion of the maxillary and mandibular prominences. Histologically, the sinuses comprise stratified squamous epithelium identical to that of the vermilion border. Ducts having a cuboidal epithelium have occasionally been noted to open into the main sinus lumen, but associated glands have not been identified. Commissural lip pits are frequently inherited as an autosomal dominant trait [2]. They may be associated with pre-auricular sinuses [3], and may rarely communicate with the parotid duct [4]. They have occasionally been reported in association with other defects particularly deafness, pre-auricular sinus, external ear anomaly [5–7], rib anomalies [8] and a variant of BOR syndrome without renal anomalies which mapped to 1q31 rather than to the established BOR gene (*EYA1*) locus at 8q13 [6,7,9]. Van der Woude's syndrome also features lip pits and maps to 1q31, but the two loci are distinct [9].

Sinuses of the upper lip

Congenital sinuses of the upper lip are extremely rare. One third are lateral, rarely symmetrical [10], while the rest occur in the midline above the vermilion border, between the philtrum and the frenulum [11–13]. The embryology of these sinuses is unclear. Lateral sinuses may represent a forme fruste of cleft lip due to failure of fusion of the maxillary processes, or aberrations in the normal mesodermal merging process [12]. However, cleft lip is more often lateral, whereas upper lip pit is more often medial [14]. The idea that upper lip sinuses arise from a burrowing process analogous to that which forms the nasal cavities [11] is supported by the facts that the upper lip and nasal cavities are formed at the same embryological stage, that both anterior nasal cavities and upper lip sinuses are lined by stratified squamous epithelium, and that the sinus never goes right through to the oral cavity [14].

Congenital midline sinus of the upper lip may present with recurrent swelling or cellulitis around the frenulum [14,15].

Occasionally, upper lip sinuses are associated with other developmental anomalies such as hypertelorism, nasal fistula and lip fistula [10,16,17].

Lower lip pits

SYN. CONGENITAL LIP SINUSES; CONGENITAL LIP FISTULAE

These take the form of bilateral openings in the vermilion border, at the peaks of the lower lip convexities, and may be associated with nipple-like protruberances [18]. Secretions may be expelled from these sinuses under the same conditions that stimulate secretion of saliva. Histologically, the pits are blind sinuses, about 2–15 mm in length, lined by stratified squamous epithelium identical to that of the lip [19]. At the blind end, mucous glands may be present.

Lower lip pits are a characteristic component of the Van der Woude syndrome, an autosomal dominant trait with very variable expression. When fully expressed, the syndrome comprises cleft lip, cleft palate and uvula, hypodontia and lower lip pits [20–24], but some patients and families have only lip pits [25]. Lower lip pits are also a characteristic feature of the popliteal pterygium syndrome, in which they are also associated with cleft lip and/or palate [26,27]. Van der Woude and popliteal pterygium syndromes share the facial phenotype and are in fact allelic variants, both caused by mutations in *IRF6* at 1q32 [28]. A variety of other anomalies have occasionally been reported in association with lower lip pits [29], including type I orofaciodigital syndrome [30].

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Rudimentary polydactyly [1,2]

The commonest form of supernumerary digit is postaxial polydactyly (PAP), in which the additional digit, which may be well-formed (PAP-A) or rudimentary (PAP-B), arises from the ulnar border of the hand, at or near the base of the fifth digit.

Postaxial polydactyly is ten times more common in black people than in white people: the US estimates of incidence are 1/3300–1/630 live births in white people and 1/300–1/100 in black people. It is transmitted as an autosomal dominant trait, possibly modified by a sex-linked recessive modifier gene [1]. The prevalence is 44% in the offspring of affected black fathers and 31% in the offspring of black mothers. In the offspring of non-black fathers and mothers it is 34% and 33% respectively [1]. PAP occurs in 75% of patients with trisomy 13 (particularly those involving q31–q34) [2] suggesting a locus on chromosome 13. PAP-A can be caused by mutations in the *GLI3* gene at 7p13 and possibly another gene at 7p15–q11 [2], and other loci have been identified on chromosome 13 and at 19p13.1–13.2 [3].

The condition is often bilateral. The rudimentary lesion is a small, skin-coloured, sometimes pedunculated nodule, which may contain cartilage or be capped by a vestigial nail. Sometimes the lesion is soft and globular, in other cases warty.

The presence of numerous nerve bundles is a histological feature [4], which may also be seen at sites from which supernumerary digits have been amputated spontaneously, or traumatically, in early life [5].

Solitary ectopic nails have been reported on the palmar aspect of fingers, usually the little finger. These have been regarded as a separate abnormality from supernumerary digits [6]. In adults, such lesions must be distinguished from acquired digital fibrokeratomas [7].

Supernumerary digits may be excised on cosmetic grounds.

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Supernumerary nipples

Supernunerary areolae and nipples are very common, occurring in about 6% of a German population [1]. There is some evidence that they are commoner in males than in females, and that they are commoner on the left side [1]. It is more frequent to have a supernumerary areola without a nipple, but supernumerary nipples do not occur without an areola. There appear to be a strong genetic predisposition, with the trait being transmitted on an autosomal dominant basis with incomplete penetrance. There is an unresolved debate as to whether there is [2–4], or is not [5,6], an association between supernumerary nipples and urinary tract malformations.

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Developmental anomalies of the umbilicus

Clinically significant developmental anomalies in the region of the umbilicus are rare but present important diagnostic problems for the dermatologist [1]. The commonest

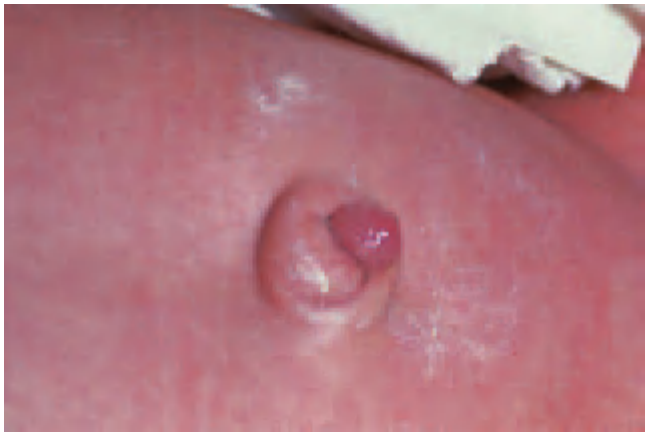

Fig. 15.26 Umbilical granuloma.

umbilical lesion in the neonate after detachment of the umbilical cord is umbilical granuloma (Fig. 15.26) [2,3], which has become less common since the routine application of talc to the umbilical stump was discontinued. A persistent umbilical lump or discharge requires investigation by ultrasonography or CT before considering surgical treatment [3,4].

Anomalies of the omphalomesenteric (vitelline) duct [3,5–8]

Very early in embryogenesis the omphalomesenteric (or vitelline) duct connects the yolk sac with the embryonic digestive tract via the umbilical cord. It is normally obliterated between the fourth and seventh weeks. Anomalies have been classified [7] as: (i) complete patency; (ii) partial patency (enteric, intermediate or peripheral); (iii) mucosal remnant at the umbilicus (umbilical polyp); or (iv) congenital band due to a fibrous remnant of either the vitelline duct or artery which can cause intestinal obstruction.

Completely patent omphalomesenteric duct [6,9,10]. Complete patency is clinically apparent soon after birth. The base of the cord separates to leave a sinus or a red nodule at the opening of an umbilical enteric fistula, the faecal discharge from which irritates the surrounding skin. Very rarely, ileum may prolapse through the fistula [6,11]. Treatment of these ducts requires excision of the umbilicus and tract.

Patency of the enteric portion of the duct [6]. Persisting patency of the proximal vitelline duct constitutes a Meckel's diverticulum. The duct may be patent throughout its length and closed peripherally only by skin or granulation tissue.

Patency of the mid-portion of the duct. A cyst along the course of a fibrosed vitelline cord presents as a periumbilical lump.

Patency of the peripheral portion of the duct [1,8,10,12]. This may present to dermatologists as a sinus 1.0–2.5 cm in depth intermittently discharging mucus, or a red, polypoid nodule (*umbilical polyp*) comprising ectopic gastrointestinal mucosa. Symptoms may be very slight, so that persistence of these lesions into adult life is not unusual. Occasionally the mucoid, serous or blood-stained discharge gives rise to troublesome dermatitis.

Omphalomesenteric umbilical polyp must be differentiated from umbilical granuloma (see above) and prolapsed urachal mucosa (see below). Fibrous umbilical polyp [13] presents in childhood, more commonly in boys, and is composed of fibrous tissue [13].

Treatment is by simple excision, having checked radiologically that there is no associated patent omphalomesenteric duct or urachus.

Anomalies of the urachus [4,5,14]

The elongation of the body stalk to form the umbilical cord obliterates the part of the allantoic cavity within it. The urachus is the residual intra-abdominal portion of the allantois, from the umbilicus to the vertex of the bladder. After birth it forms a fibrous cord, the median umbilical ligament. Persistence of epithelial remnants within the fibrous end is frequent. The urachus may remain patent throughout all or part of its length forming cysts, sinuses or fistulae leading from the umbilicus or bladder. Carcinoma may develop in a urachal remnant in adult life [15].

Complete patency of the urachus presents within days of birth by intermittent dribbling of urine from the umbilicus. The umbilicus may appear normal or the prolapsed distal portion of the urachal duct may form a globular nodule, covered partly by skin and partly by urachal epithelium. The surrounding skin may be irritated, but usually less severely than by a faecal fistula. The diagnosis may be confirmed radiologically. Surgical excision should be carried out as soon as possible, on account of the risk of urinary tract infection in the short term, and the risk of malignant change in adult life [15].

Partial patency of the urachus presents differently according to the site of the defect [4]. Peripheral patency (umbilical–urachal sinus) appears as a small opening or a granuloma-like lesion at the umbilicus. The lower portion of the urachus remains patent in about 33% of persons (vesico–urachal diverticulum). Urachal cysts may form at any point along the course of the urachus, and may communicate with the umbilicus, the bladder or with neither [16,17]. Unless they discharge their contents externally, they are seldom clinically evident unless large or infected. They present as tender midline swellings between the umbilicus and the symphysis pubis. If they communicated with the umbilicus, the discharged contents may consist of urine or mucus, pus or blood.

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Congenital sinuses and cysts of the genitoperineal raphe

SYN. MUCOUS CYSTS OF THE PENILE SKIN; PARAMEATAL CYSTS

Median raphe cyst of the penis takes the form of a translucent or blue cyst, a tender nodule or an indurated cord at any site along the ventral midline between the urethral meatus and the anus usually near the glans [1–9]. Several theories have been proposed to explain their occurrence [9]. They may result from incomplete ventral fusion of the urethral or genital folds. Alternatively they may represent ectopic periurethral glands of Littre (*mucoid cysts*) [8,10], or separated outgrowths of urethral endoderm (*urethroid cysts*) [11].

Median raphe cysts of the penis are usually lined by pseudostratified columnar epithelium, except in the distal portion of the raphe where they are lined by squamous epithelium. Ciliated epithelium, similar to that of a bronchogenic cyst, was reported in one case [12], but not in others [13]. Melanocytes have also been reported in the lining of multiple median raphe cysts in two unrelated Japanese boys [14]. Apocrine cystadenoma of the penis is sometimes considered to be the same as median raphe cyst, but can be distinguished by positive expression of human milk fat globulin 1, a marker for breast and apocrine tissue [15].

In most cases, median raphe cysts of the penis remain asymptomatic until after puberty [9], and present only when they become the site of staphylococcal or gonococcal infections [16]. However, they may present incidentally as an asymptomatic papule at any age, in some cases as late as the seventh decade [7,13]. Surgery is indicated where infection is not controllable by antibiotics.

Mucous cysts occasionally develop in the retrorectal space and are probably derived from hind-gut remnants. These may discharge via a sinus along the posterior part of the raphe.

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Anomalies of the anus

Anomalous anal papillae

Disturbance of the normal embryological development of the anus may rarely result in the appearance of one or more polypoid projections at the anus. These may be asymptomatic, but often become complicated by ulceration, faecal retention and constipation [1].

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Posterior midline cutaneous lesions associated with defects of the cranium, vertebrae and spinal cord

Aetiology. Failure of the caudal neuropore to close at the end of the fourth week of intrauterine life results in neural tube defects (*spinal dysraphism*), which may also involve tissues overlying the spinal cord, including the meninges, vertebral arch (*spina bifida*) and skin. Defective closure of the rostral neuropore, also during the fourth week, may result in analogous malformations in the occipital area.

Genetic factors are undoubtedly involved, and since the recurrence risk is less than 25%, a polygenic mechanism is likely. Spina bifida is commoner in infants of obese mothers, where obesity is defined as body mass index (BMI) > 29 kg/m^2 [1]. Environmental factors also play a part. Folic acid supplementation before and during pregnancy reduces the risk of open neural tube defects [2].

Classification. Neural tube defects can be classified according to whether they are open or closed, whether neural tissue protrudes externally, and whether their position is caudal or cranial.

Clinical features. An open defect of the caudal neural tube, with neural tissue widely exposed on the surface is termed a *myelomeningocoele*. This presents as a skin defect over the back, bordered laterally by the unfused dorsal portions of the vertebrae. The defect is generally covered by a transparent membrane, which initially leaks cerebrospinal fluid. It soon dries and ceases to leak, the fluid accumulation causing the membrane to bulge. Spinal cord function is variably impaired, and there may be associated defects of the brainstem and cerebellum, the *Arnold–Chiari malformation*, which result in hydrocephalus. *Meningocoeles* contain dura and arachnoid, but do not contain neural tissue. An open defect at the cranial end of the neural tube (*cranium bifidum*) may similarly be associated with protrusion of meninges (*meningocoele*) or brain tissue (*meningoencephalocoele* or *encephalocoele*).

Islands of ectopic neural tissue may persist externally as 'rests' overlying intact bone [3–5]. In the occipital and parietal areas of the scalp they are sometimes termed 'atretic' meningocoeles or meningoencephalocoeles [3] or 'meningiomas' [6]. Such lesions generally take the form of domed, hairless nodules with a collar of surrounding hypertrichosis (the 'hair collar' sign) [3,5,7,8], or sometimes just a tuft of hair [9], and are not necessarily confined to the midline. Ependymal rests may also be found in the sacrococcygeal area [10].

A *dorsal dermal sinus* is an open tract with no protrusion of neural or meningeal tissues. It appears as a deep dimple, the bottom of which cannot be seen. It may occur at any level from the occiput downwards, most commonly in the suboccipital and lumbosacral areas [11–15], only 1% and 10% occurring in the cervical and thoracic areas respectively [16]. The skin around the exit is often normal but may be dimpled, hairy or the site of a lipoma, abnormal pigmentation, port-wine stain or haemangioma [13,17]. Sometimes the cutaneous anomaly obscures the ostium of the sinus. In the occipital area, the exit site near the external protruberance of the occipital bone [15] is usually hidden by hair, which may be more luxuriant than elsewhere on the scalp. This insignificant dermatological anomaly is an important marker for serious associated complications including infection, underlying CNS anomaly and inclusion tumour [16]. Such sinuses are important as potential portals for the entry of infection into the subarachnoid space, leading to meningitis or a cerebellar abscess [18]. Spina bifida, spinal dysraphism or tethered cord may coexist with dorsal dermal sinus [16]. Congenital inclusion dermoid cysts are commonly associated [18] and may cause spinal cord compression [17,19].

In *spina bifida occulta* there is a defect in the vertebral arch, but the lesion is closed and not associated with protrusion of the spinal cord or meninges. The cord may be normal, malformed or hypoplastic, or it may be damaged by transfixation by a bony spicule or fibrous septum arising from a vertebra, usually in the lumbar spine (*diastematomyelia*). Occult spinal dysraphism may occur in as many as 20% of cases, but only a small percentage of these will have a significant associated neurological defect. While most common in the lumbosacral area, spina bifida occulta may occur at any level of the vertebral column [20]. Closed defects with overlying cutaneous malformations are of particular importance to dermatologists to whom they may present first [21]. In a series of 1449 healthy American neonates, 70 (4.8%) had dorsal cutaneous stigmata [22]. In 207 infants with midline dorsal cutaneous stigmata, there was associated occult spinal dysraphism in 16 (8%) diagnosed on ultrasonography [22]. In about 50% of cases of spina bifida occulta there is an overlying cutaneous abnormality [11,13,23–26]. Those reported include dermal dimple or sinus, lipoma [26,27], a tuft of long, soft, silky hair (often called a *faun-tail*) [28], pigmented macule, skin tag, tail-like protrusion [29], dermoid cyst, infantile haemangioma [30,31] macular vascular stain [32,33] and aplasia cutis congenita [34]. A *lipomyelomeningocoele* is a subcutaneous lipoma extending through the bony defect to the dura and attached to the cord. An association between cockade naevi at various body sites and spinal dysraphism has been suggested [35].

Even without any bony defect, a dorsal midline anomaly may overly a spinal abnormality, for example tethered cord with lumbosacral haemangioma, and vascular malformation of the spinal cord with an overlying port-wine stain (Cobb's syndrome).

A variety of other tumours and cysts, representing residual non-regressed distal cord and associated tissues, may occur in the retrorectal space, or subcutaneously over

the sacrum [36,37]. They include hamartomas [38], teratomas [39], lipomas [27], ependymomas [10,40] and vestigial tails largely composed of adipose tissue [41–44]. Non-neoplastic perirectal inflammatory conditions and giant cell tumours of the sacrum also occur. These may occasionally be associated with overlying cutaneous lesions such as skin tags and epidermal naevi [23].

The deep sacrococcygeal dimples and pits found in about 4% of all children are *formes frustes* of dorsal dermal sinuses, as probably also are *congenital pilonidal sinuses* [45,46]. In the absence of other cutaneous anomalies or neurological signs they require no investigation [22,47].

Diagnosis. The likelihood of a spinal defect underlying a posterior midline skin lesion depends firstly on age at presentation; a neurologically normal child or adult is unlikely to have a functionally significant spinal defect but might still have a sinus with risk of infection. Secondly it depends on the nature of the defect: simple postanal dimples are very common and usually uncomplicated; atypical dimples (> 5 mm diameter or > 2.5 cm from the anus), sinuses, masses, sacral hypertrichosis and multiple skin abnormalities are much less common, and warrant more intensive investigation [22,33,48]. Midline dorsal haemangioma, port-wine stain, and even sacral telangiectasia in an infant with an obvious naevus flammeus in the usual glabellar and occipital sites warrants investigation [33]. Ultrasound [49] or X-ray of the spine may be sufficient in the absence of a history of meningitis or neurological impairment. Ultrasound is most useful in neonates up to 3–4 months of age, before the posterior spinous elements ossify [49]. MRI is the investigation of choice for any suspicious lesions, allowing visualization of the tract and its termination as well as spinal anomalies and tumours compressing the cord [16,50].

Treatment. The treatment of large and open defects is beyond the scope of this book. Suspected dorsal dermal sinus should be investigated preoperatively with MRI to see whether it connects with the subarachnoid space [2]. Probing and sinography are inadvisable and may lead to meningitis. True sinuses are more likely above the lumbosacral area. Usually, no further action is required for asymptomatic lesions in the lumbosacral area noted in infancy if the plain spine X-ray is normal. However, any suggestion of neurological deficit should be investigated with a spinal MRI.

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Congenital absence of skin

SYN. APLASIA CUTIS CONGENITA

The term 'aplasia cutis congenita' implies a failure of skin development, while the broader term 'congenital absence of skin' includes situations where the skin developed but has subsequently been lost. The appearance at birth is extremely variable, in terms of site, extent, depth, and degree of healing and scarring, and there are probably several different causes [1,2]. From careful review of the literature, a number of distinctive clinical disorders have emerged, many of which are genetic [2,3]. Frieden's classification has proved helpful [2] and a modified version will be used here.

Few histological descriptions are available [1,4]. The epidermis is absent, and usually the dermis. Where the dermis remains, the connective tissue lacks appendages and elastic fibres. The subcutaneous fat may also be partly or wholly missing and there may be an underlying skull and dural defect [5,6]. Where re-epithelialization has occurred the epidermis is flat, characteristically lacking appendages [7,8]; hypertrophic scarring may also occur [9].

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Type 1: non-syndromic aplasia cutis congenita of the scalp

Non-syndromic aplasia cutis congenita of the scalp is the commonest pattern of congenital absence of skin. It sometimes shows autosomal dominant inheritance [1–8] with reports of concordant [9,10] and discordant [11] monozygotic twins. The usual position at or adjacent to the parietal hair whorl may be explained by this being the site of maximum scalp tension during the period of rapid brain growth from the 10th to the 18th week of gestation [7].

About 80% of all lesions of congenital absence of skin occur on the scalp [7,12–15]. Scalp lesions are single in about 70% of cases, double in about 20% and triple in about 5%. Lesions vary enormously in diameter (from 0.5 to over 10.0 cm), shape and depth. They may initially appear deeply ulcerated, superficially eroded, scarred or occasionally bullous [16], and sometimes heal with hypertrophic scarring [5,17]. A surrounding zone of hypertrichosis is frequently apparent, and it has been suggested that lesions demonstrating this feature are a *forme fruste* of a cranial closure defect [18]. The larger lesions are often the deeper ones, and may extend to the dura or even to the meninges [19–21]. Such deep lesions may be associated with haemorrhage, sagittal sinus thrombosis or meningitis [20,22–26]. Up to one-third of cases involve the underlying bone [6,9,21,27]. Locally dilated scalp veins reported in several cases [10,21,28,29] suggest that the scalp defect may result from a vascular developmental abnormality [29,30]. An isolated patch of congenital absence of scalp skin is often mistakenly attributed to birth trauma, particularly from fetal scalp electrodes [31].

Severe aplasia cutis congenita of the scalp regenerates spontaneously but has also been repaired with engineered skin [32] and bone grafts.

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Type 2: congenital absence of skin on the scalp with limb reduction abnormalities

SYN. ADAMS–OLIVER SYNDROME

Adams–Oliver syndrome is characterized by congenital midline scalp defects and asymmetrical distal limb reduction anomalies. It is an autosomal dominant trait with highly variable penetrance and expression [1–8]. Several isolated cases have been reported [7,9–13].

Typically, the skin lesions are solitary or multiple bald scars near the vertex. They vary in diameter, from about 0.5 to 10.0 cm, larger lesions being disproportionately common [1,2,5,14–16]. The lesions also vary considerably in depth, sometimes penetrating the skull to the dura. Dilated scalp veins [5,6,10] are frequently associated, and may be the sole abnormality [17]. Intellect is normal.

Hypoplastic or absent distal phalanges are the most common limb anomalies, but defects range from hypoplastic nails [7,8] to absent hands or lower legs [1,18]. The lower limbs are generally more severely affected than the upper limbs.

Persistent cutis marmorata is reported in about 12% of cases [3,6,7,9,14,17,19,20] and was the sole feature in an obligate gene carrier [4]. In another family, cutis marmorata and scalp aplasia cutis congenita without limb defects may represent a limited expression of the Adams–Oliver syndrome [21]. Congenital heart disease affects about 8% of cases [19].

Adams–Oliver syndrome must be differentiated from focal dermal hypoplasia, trisomy 13 and the amniotic band sequence. Congenital absence of skin with split hand deformities [7,22], and congenital absence of skin with postaxial polydactyly [23,24] probably represent distinct genetic disorders.

Spontaneous osseous regeneration has been reported in a patient with a large skull and scalp defect due to the Adams–Oliver syndrome [25].

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Type 3: congenital absence of skin on the scalp with epidermal naevi

Sebaceous naevi rarely occur in close proximity to areas of congenital absence of skin in the scalp [1–4]. Multiple areas of bullous congenital absence of skin have also been reported in a child with extensive unilateral verrucous epidermal naevi on the trunk and limbs [5].

Some of these cases have either had associated ophthalmological or neurological abnormalities identical to those seen in the epidermal naevus syndrome [2–4,6,7]. Happle and Konig [7] suggest that the co-occurrence of aplasia cutis congenita and nevus sebaceous is a twin spot phenomenon.

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Type 4: congenital absence of skin overlying developmental malformations

Congenital absence of skin may overlie herniations of neural tissue. In the occipital and parietal areas of the scalp, heterotopic neural and/or meningeal tissue appears as a domed, hairless nodule with a collar of surrounding hypertrichosis (the 'hair collar' sign) [1–5]. The surface of the lesion is typically translucent and 'membranous' [6]. The lesion may be flat or depressed rather than raised, and will not always be sited in the midline. There may be an associated port-wine stain [2].

The skin is also characteristically absent or hypoplastic over a number of other developmental malformations, including spinal dysraphism [7], omphalocoele, gastroschisis and sternal clefts [8–10].

Congenital absence of skin has also been reported over other cranial [11] and intracranial developmental anomalies including arteriovenous fistula [12], leptomeningeal angiomatosis [13], congenital midline porencephaly [14] and cranial stenosis [15].

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Type 5: congenital absence of skin associated with fetus papyraceus

Congenital absence of skin has been observed in a number of infants whose birth was accompanied by the delivery of a *fetus papyraceus*, that is a twin or triplet that had died *in utero* during the second trimester. [1–8]. In these cases, multiple, mostly symmetrical, linear or stellate areas of congenital absence of skin were present on the limbs and trunk (Fig. 15.27). Some also showed fibrous constriction bands on the limbs [1,3].

This type of congenital absence of skin may represent cutaneous infarction due to release of thromboplastin into

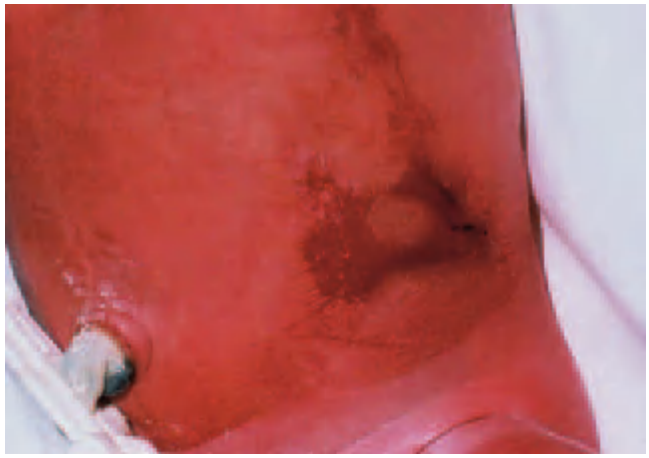

Fig. 15.27 Congenital absence of skin in an infant with a stillborn twin of fetus papyraceus type.

a shared placenta after an intrauterine death [9]. Symmetry of the skin lesions is hard to explain by this mechanism. Associated hyperechogenic areas diagnosed as haematomas in the liver of one patient were thought to support the idea of a vascular aetiology [7].

Similar skin lesions in one of surviving twins [10], and in singletons with no fetus papyraceus [11–16] might reflect *in utero* death of an unrecognized twin or triplet. In other similar cases without mention of a twin, placental infarction has occurred [17,18], or the placenta has been described as pale and large [18,19].

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Type 6: congenital absence of skin as a feature of epidermolysis bullosa

SYN. BART'S SYNDROME

Bart *et al*. [1] reported a dominantly inherited disorder in 26 members of a large kindred, characterized by congenital absence of skin on the lower legs, widespread blistering of skin and mucous membranes, and nail dystrophy. Further ultrastructural and genetic studies of this family confirmed dominant dystrophic epidermolysis bullosa due to a glycine substitution in type VII collagen [2,3]. The original idea that this pattern of absent skin at birth indicates a specific form of epidermolysis bullosa [1] has given way to the view that it is a non-specific feature of epidermolysis bullosa, particularly the junctional and dystrophic types. In at least one family with dominant dystrophic epidermolysis bullosa, some affected members had 'Bart's syndrome' while others did not [4]. This pattern of congenital absence of skin has occasionally been reported without epidermolysis bullosa being diagnosed [5], but it is highly likely that all such patients have epidermolysis bullosa [6,7], perhaps with skin fragility less apparent after birth than before.

The lesions appear as extensive, well-defined, glistening, red ulcerations on the dorsum and medial aspect of the foot, often extending up the shin. They may be unilateral or, less frequently, bilateral and probably result from rubbing one shin and foot with the other heel, perhaps in response to pruritus. The idea that the lesions are determined by Blaschko's lines [8] seems less likely.

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Type 7: congenital absence of skin caused by specific teratogens

Several cases have been reported of congenital absence of midline scalp skin in children whose mothers took methimazole or carbimazole for treatment of hyperthyroidism during pregnancy [1–6]. It is now regarded as highly likely that these drugs were responsible, although the risk appears to be low [6,7]. There have been isolated reports of scalp aplasia cutis congenita following first trimester intake of the prostaglandin misoprostol, and in one case benzodiazepines [8].

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Type 8: congenital absence of skin as a feature of intrauterine infections

Congenital absence of skin may occur in neonates with intrauterine herpes simplex infection [1–3], but is a more characteristic finding in intrauterine varicella-zoster virus (VZV) infection [4–7], where it may be associated with other features of the 'congenital varicella syndrome'. The cutaneous ulceration or scarring is unilateral and linear, usually occurring in a zosteriform distribution. Such lesions are most often a sequel to maternal chickenpox during the first trimester. Confirmation of the diagnosis rests on the persistence of VZV IgG antibodies beyond 7 months of age when maternal antibodies [8] should have disappeared. Maternal chickenpox in the last trimester may also result in congenital ulcerations in the neonate, usually multiple and no larger than about 1 cm in diameter [9].

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Type 9: congenital absence of skin as a feature of malformation syndromes

Congenital absence of the skin has been reported as a feature of several malformation syndromes, including the following.

Trisomy 13

SYN. PATAU'S SYNDROME

Congenital absence of skin in the parietal or occipital scalp is a regular feature of this chromosomal abnormality syndrome. Other characteristic findings include holoprosencephaly (a developmental anomaly of the forebrain), microphthalmia, iris colobomas, cleft lip and/or palate, polydactyly, narrow and excessively convex nails, and a port-wine stain on the forehead [1,2]. Infants with this syndrome rarely survive into the second year of life. Interestingly, patients with mosaic trisomy 13 may present as hypomelanosis of Ito with a rather characteristic 'phylloid' pattern of hypopigmentation [3], together with mental retardation and other features of trisomy 13 syndrome. Pigmentary reduction has not been reported in full-blown trisomy 13, but might not have been noticed in the presence of other serious defects.

Deletion of the short arm of chromosome 4 (the 4p- syndrome)

SYN. WOLF–HIRSCHHORN SYNDROME

Congenital absence of skin in the posterior midline scalp is also a frequent finding in this chromosomal abnormality syndrome [4,5]. Other typical features include ocular hypertelorism, a beaked or broad nose, microcephaly, low-set, simple ears and pre-auricular tags or pits. Affected individuals are profoundly mentally retarded and generally experience severe convulsions. Growth deficiency in weight relative to height is pronounced, and mortality in early childhood is high. Most patients have deletions involving large segments of 4p. Wolf–Hirschhorn syndrome is probably a contiguous gene syndrome, but exact genotype–phenotype correlations have not been established. A small critical region at 4p16.3 has been identified in a patient with growth retardation and minor facial features but no aplasia cutis [6].

Oculocerebrocutaneous syndrome

SYN. DELLEMAN–OORTHUYS SYNDROME

This distinctive malformation syndrome [7–14] occurs sporadically and in both sexes. The scattered, asymmetrical nature of the characteristic abnormalities suggests mosaicism for a mutant gene that would be lethal if the zygote were affected [15].

Typical non-cutaneous manifestations include orbital cysts, microphthalmia, eyelid colobomas, skull defects and cerebral malformations, particularly cystic spaces (porencephaly), and agenesis of the corpus callosum.

The cutaneous features comprise a highly characteristic combination of areas of cutis aplasia and skin tags. The skin tags may be up to about a centimetre in diameter and are usually on the face, around the eyes and the nose. Their histological features have not been reported. Well-defined areas of cutaneous hypoplasia occur mainly on the scalp, face, neck and lumbosacral area. Published details of these lesions are limited, but they are usually multiple, hypopigmented and sometimes appear 'punched-out' [14]. In one case, normal skin markings and lanugo hair within the lesions were regarded as evidence that these were not scars [14]. A ring of more profuse hair growth around scalp lesions has also been noted [10]. This syndrome overlaps with Goldenhar's syndrome (see above) [16].

Johanson–Blizzard syndrome

This rare autosomal recessive disorder is characterized by pre- and postnatal growth deficiency, microcephaly, variable intellectual impairment, deafness, thyroid dysfunction and rectourogenital abnormalities. Several features of ectodermal dysplasia make it of interest to dermatologists [17–21], including sparse hair with a marked frontal upsweep, absent eyebrows and eyelashes [20], hypodontia of both dentitions, peg-like deformity of remaining teeth [21] and hypoplastic nipples and areolae. Congenital absence of skin in the posterior midline scalp, and hypoplastic alae nasi also occur. Café-au-lait macules and dilated scalp veins may be observed.

Focal dermal hypoplasia syndrome

See Chapter 12.

*MIDAS syndrome (**m**icrophthalmia, **d**ermal **a**plasia, **s**clerocornea) (MLS syndrome [**m**icrophthalmia with **l**inear **s**kin defects])*

This syndrome was first described in 1990 [22]. A number of cases have been described since then [23–25]. This is an X-linked dominant condition, lethal in males, which is associated with heterozygous deletions on the X chromosome at Xp22.31. This region contains the gene *HCCS*, which encodes human holocytochrome *c*-type synthetase.

Girls with this syndrome have microphthalmia with linear skin defects of face and neck, sclerocornea, corpus callosum agenesis and other brain anomalies. The microphthalmia is usually but not invariably bilateral, as are the corneal opacities, though sclerocornea is not always present. The skin comprises erythematous atrophic lesions similar to those seen in focal dermal hypoplasia, but, in contrast to this condition, the skin lesions have in all cases so far been limited to the face, scalp, neck and upper trunk. They have also differed from those of focal dermal hypoplasia in not being accompanied by exophytic fatty protrusions. However, as in focal dermal hypoplasia, the lesions are asymmetrical and distributed in Blaschko's lines. Other, less regular manifestations have included congenital heart defects.

Focal facial dermal dysplasias

Symmetrical congenital atrophic lesions of the face resembling scars have been described under a number of different titles, including bitemporal aplasia cutis congenita, congenital ectodermal dysplasia of the face and hereditary symmetrical systemic aplastic naevi. The disorder may be isolated or associated with other facial anomalies. A review of published cases [26] suggested three distinct subgroups: (i) autosomal dominant focal facial dermal dysplasia without other facial anomalies; (ii) autosomal recessive focal facial dermal dysplasia without other facial anomalies; and (iii) focal facial dermal dysplasia with other facial anomalies (syn. Setleis' syndrome).

Autosomal dominant focal facial dermal dysplasia without other facial anomalies. A number of families have been reported in which the disorder is transmitted as an autosomal dominant trait [27–30]. The skin lesions appear to be the sole abnormality, and take the form of congenital, hairless, scarred areas on the face which are usually, but not always, oval in outline and symmetrical, and may be either hyper- or hypopigmented. These lesions may occur on the temple, or on the cheeks, where they tend to be disposed along a line that runs from the ear to the corners of the mouth. The size of the lesions is variable. There may be a surrounding rim of fine, lanugo-like hairs [31,32]. There may be a distinctly puckered appearance to the affected skin.

Histologically, there is atrophy of the dermis and subcutaneous fat, an absence of pilosebaceous follicles and eccrine glands but a normal epidermis. Striated muscle may be placed very close to the epidermis, and could be partly responsible for the occasionally reported puckering of the affected skin.

Autosomal recessive focal facial dermal dysplasia without other facial anomalies. Essentially identical skin lesions have been

reported in other families in which inheritance appeared to be of autosomal recessive type [26,28]. There have been reports of clinically indistinguishable but sporadic cases whose pattern of inheritance is uncertain [31,33].

Focal facial dermal dysplasia with other facial anomalies (Setleis' syndrome). Since the first report by Setleis *et al.* [34], several families have been reported in which children demonstrated a leonine, aged facies with absent or abnormal eyelashes and eyebrows, puckered periorbital skin, a rubbery feel to the nose and chin, and scar-like defects on each temple [35–39]. While most reported patients have been Puerto-Rican, other ethnic groups have been affected [39–41]. Both autosomal recessive [42] and autosomal dominant inheritance with variable penetrance and expressivity [38,40,43] have been reported.

Rare non-cutaneous manifestations include imperforate anus [39,44], megaureter [39], mental retardation [39] Fallot's tetralogy [34], iris coloboma, limb malformations and recurrent digital fibromas [44], and developmental delay [45].

Other disorders. Numerous other conditions have featured areas of absent skin at birth. Extensive symmetrical congenital erosions were reported in *congenital erosive and vesicular dermatosis healing with reticulate supple scarring* [46,47]. Aplasia cutis congenita can occur at any site in the amniotic band disruption sequence [48–50], and on the scalp in tricho-odonto-onychodermal ectodermal dysplasia [51]. Extensive congenital areas of absent skin resembling epidermolysis bullosa have been described in cases of ectodermal dysplasia with cleft lip and/or palate, in the EEC syndrome (*e*ctrodactyly, *e*ctodermal dysplasia, *c*lefting) [52], and in the AEC syndrome (*a*nkyloblepharon, *e*ctodermal defects, *c*left lip/palate) [53]. Areas of absent skin at birth have been recorded in a familial disorder featuring *lumpy scalp, odd ears and rudimentary nipples* [54]. Multiple scalp erosions at birth occurred in two phenotypic females with 46XY gonadal dysgenesis, associated with cleft lip and palate, ear deformity and pre-auricular pits [55].

Single families have been reported with conditions associated with congenital absence of skin. A disorder comprising congenital absence of skin, nipple and breast hypoplasia, nail dysplasia and delayed dental eruption has been described in a mother and her son [56]. Ear deformities and pre-auricular pits were also present in members of another family in association with unilateral facial paresis, dermal sinuses and congenital absence of skin [57]. Posterior midline scalp absence of skin and intestinal lymphangiectasia, leading to hypoproteinaemia and oedema, occurred in two siblings [58].

Single cases have been reported of a syndrome comprising bilateral scarring above the ears, linear submental scars, craniosynostosis, polydactyly, syndactyly, low-set, deformed ears, hypoplastic tibias and cardiac disease [59], and of a syndrome comprising extensive congenital erosions of the skin, anonychia and an atrophic lesion on the tongue [60]. Extensive aplasia cutis congenita occurred in a baby with an unbalanced translocation, being monosomic for distal 12q and trisomic for distal 1q [61]. In one fatal case with some features of very severe Johanson–Blizzard syndrome, almost complete congenital absence of skin was associated with absent ears, choanal atresia, syndactyly, imperforate anus, pulmonary hypoplasia and other anomalies [62].

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Differential diagnosis. In the neonatal period parents sometimes mistake congenital absence of skin for obstetric trauma due to forceps or scalp electrodes [1,2], a confusion which may have significant medicolegal repercussions [3]. Congenital absence of skin may also resemble Volkmann's ischaemic contracture [4].

During childhood, congenital absence of scalp skin may be confused with sebaceous naevus, traumatic scarring, cicatricial alopecia, the linear scarring alopecia seen in *en coup de sabre* morphoea and the alopecia along scalp suture lines characteristic of the Hallermann–Streiff syndrome.

Cases have been described of congenital bald patches in the scalp with histologically normal skin apart from absent appendages [5]. These 'aplastic naevi' might represent the minimal end of the spectrum of congenital absence of skin.

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Treatment. Most lesions will heal spontaneously from the margins, to leave a smooth, yellowish, hairless, papery scar. Underlying defects in the cranium generally resolve spontaneously during infancy [1–3]. Occasionally, hypertrophic scarring occurs [4], and linear lesions on the limbs may lead to joint contracture. In the vast majority of cases, the prognosis is excellent if attention is paid to the prevention of both secondary infection and further trauma.

Small lesions can be allowed to heal spontaneously, or treated by excision of the abnormal skin margins followed by primary closure [5]. Larger scalp defects are probably best treated by early grafting or flap rotation [6], as

delayed closure may be complicated by infection or haemorrhage from the sagittal sinus, which may be lethal [7–10]. Composite ('engineered') skin grafts have been used successfully, autologous fibroblasts being placed first, followed by keratinocytes a week later [11]. Bone grafts may be required to reconstruct large cranial defects [12,13]. However, some authors have recommended a conservative approach even for extensive lesions [2,14,15], with the opportunity for the scars of healed lesions to be excised later on if desired. Tissue expansion has proved very valuable for this type of procedure.

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Amniotic bands and adhesions

SYN. CONGENITAL RING CONSTRICTIONS; INTRAUTERINE AMPUTATION; ADAM COMPLEX SYNDROME (*A*MNIOTIC *D*EFORMITIES *A*DHESIONS *M*UTILATION); RAISED LIMB BANDS

Definition. These are circumferential bands, occurring at birth or soon after, usually on limbs, and occasionally associated with other anomalies, particularly distal limb reductions.

Aetiology. Spontaneous amniotic rupture results in the formation of tough amniotic bands, which may encircle developing limbs, resulting in annular constrictions, secondary syndactyly and intrauterine amputations [1] in about one in 10 000 neonates. Some amniotic bands may be related to adhesion of amnion to abnormal areas on the fetal surface, particularly craniofacial defects [1] and cleft lip [2]. Occasional reports of congenital bands with an intact amnion, and appearance after birth suggest a localized abnormality in limb development rather than external constriction [3]. Aetiology and classification of these disorders is confused [3,4]. Both ring constrictions [5] and congenital amputations [6] are occasionally familial.

Pathology. Biopsies of raised bands showed no specific abnormalities [3].

Clinical features [1,3,7–10]. The most characteristic appearance is ring constrictions of digits, limbs, neck or trunk. The groove is usually about 1–3 mm wide and 2–4 mm deep. Beyond the constriction, there is often lymphoedema. Raised, narrow, scar-like bands can coexist with the more typical grooves [3]. Distal limb deformities, such as syndactyly, polydactyly, talipes and distal limb reduction, not necessarily of the same limb, are also frequent, as is peripheral nerve palsy [11]. *In utero* amputation may also occur. Neonatal herpes simplex has been reported localized to an area of ulceration at the site of amniotic band compression [12].

Diagnosis. In the Michelin tyre baby syndrome there is abnormal limb enlargement with folds, rather than primary constrictions. Histology of the folds may show diffuse smooth muscle hamartoma or lipomatous naevus.

Treatment. Plastic surgery is indicated for residual constrictive grooves in a limb or digit, where there is interference with vascular or lymphatic circulation.

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Chapter 16

Pruritus

M.W. Greaves

Introduction and classification

Despite being the predominant symptom of skin disease and a frequent manifestation of systemic disease, pruritus (itching) has been largely neglected by investigators and consequently is poorly understood. The main difficulties have been lack of reproducible, standardized itch stimuli and a dearth of satisfactory methods for statistically analysable quantification. Itch can be defined subjectively as a poorly localized, non-adapting, usually unpleasant sensation which elicits a desire to scratch. Itch has recently been reclassified by Twycross *et al*. [1] as *pruritoceptive* (cutaneous, e.g. scabies), *neuropathic* (due to lesions of afferent pathways of the nervous system, e.g. peripheral neuritis, brain tumours), *neurogenic* (due to centrally acting mediators which do not damage the central nervous system, e.g. opioid peptides of cholestasis) and *psychogenic*.

Although itch and pain can readily be dissociated subjectively, they broadly share similar overall molecular mechanisms and neurophysiological pathways. However, new evidence indicates the existence of separate dedicated neurones for itch in both the peripheral and central pathways [2,3]. When itching is caused by a low-intensity mechanical stimulation involving weak activation of mechanoreceptors, the itch sensation is immediate, persists for no longer than the stimulus and is interpreted as a 'tickle'. In dry skin and skin of some atopics, mechanical stimulation may trigger a more persistent itching sensation (alloknesis) [4]. Prurigo is a term frequently incorrectly used to describe chronic itching of any cause. As originally defined by Hebra [5], prurigo denotes papules induced by scratching. On this basis, prurigo would include 'scratch prurigo', a rarely used synonym for symptomatic dermographism and, at the other end of the spectrum, chronic inflammatory and pigmented papules due to long-continued or repeated scratching (prurigo nodularis of Hyde) [6].

Itching as a symptom of skin disease is generally independent of external stimulation. The quality of itch varies greatly, ranging from burning, through pricking, to sensations of insects crawling over the skin. The psychophysiological basis of these differences remains unclear. Teleologically, itching, with resultant scratching, is of possible biological value in combating parasitic infestation. Although often publicly perceived as a trivial—even humorous—disability or even, with its associated scratching, as a pleasurable personal indulgence, it is more often socially disabling and a cause of serious impairment of quality of life. No effective and selective anti-itch drugs are available at the time of writing.

Measurement

There are no convincing animal models for pruritus. Methods used in humans include visual analogue scales (VAS) (statistical analysis is difficult) and recording of scratch movements [7] using fine glass electrodes

(microneurography) [8–10]. The 'Symtrack' computerized continuous itch-rating system, which is based on the VAS, or a variant of it, is the most widely used [11]. However, results obtained with a new method for quantifying scratching in which a piezoelectrical device is attached to the middle fingernail have been impressive [12].

Pathophysiology

Significant progress has recently been made in elucidating the neurophysiological pathways for itch. Although specialized nerve endings have been identified for a wide range of stimuli [13], no specific receptor has been identified for itch, and it is generally agreed that itch (and pain) are received by unspecialized free nerve endings [14] located close to the dermal–epidermal junction. Itch receptors are unmyelinated, confined to the skin and cornea, and are members of the polymodal nociceptor class. Recent immunohistochemical research utilizing protein gene product (PGP) 9.5 or neurone-specific enolase has supported, but not significantly extended, earlier light-microscope studies [15,16]. Itch-transmitting, polymodal, unmyelinated C fibres enter the dorsal horn of the grey matter of the spinal cord, synapse there with secondary neurones which cross over to the contralateral spinothalamic tract, and ascend to the thalamus. There, tertiary neurones relay itch to the level of conscious perception in the cerebral cortex.

That pain and itch are transmitted along the same nerve pathways was proposed by Rothman [17] and others and has been the prevailing view until recently. According to this interpretation, low-intensity stimulation of unmyelinated polymodal C fibres results in the sensation of itch, whereas high-intensity stimulation causes pain. However, a number of features of pain and itch argue against this interpretation. These include the difference in motor responses (itch induces scratching whereas pain evokes withdrawal); the differential effects of morphine, which relieves pain but makes itch worse; and the ability of itch and pain to be perceived independently at the same site. There is now convincing evidence that dedicated itch-transmitting neurones exist in both peripheral and central afferent pathways [2,3]. Microneurographic technology has enabled electrical recordings to be made from individual polymodal C fibres in peripheral cutaneous nerve fascicles. Stimulation of these neurones using histamine iontophoresis to cause itching has resulted in identification of a small (less than 5% of the total) subset of slowly conducting C fibres distinct from, and with a larger receptor field than, mechanosensitive polymodal neurones. Recently, the concept of dedicated itch neurones has been supported and extended by work demonstrating the presence of histamine-sensitive itch-specific secondary transmission neurones in the lateral spinothalamic tract of the cat [3]. That pruritus-specific C neurones are also temperature-sensitive is of clinical significance, since it offers an explanation for the everyday observation that itching is worse in a warm environment, e.g. in bed.

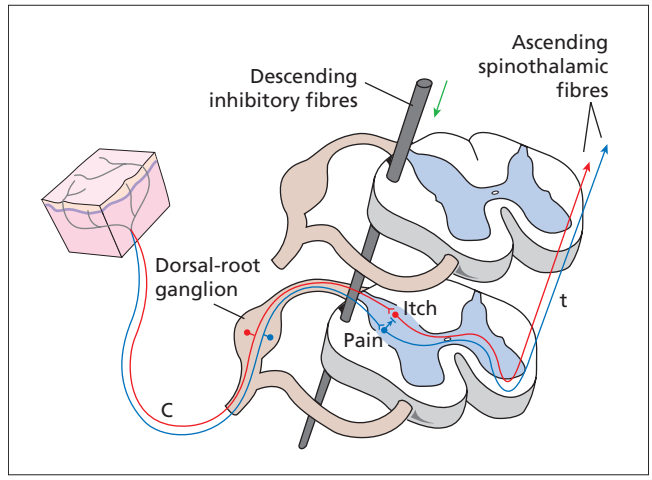

Fig. 16.1 Ascending and descending pathways modulating itch. C, unmyelinated slow-conducting C fibres; t, transmission neurone. (Reproduced with permission from Elsevier Science Ltd, *The Lancet* 2003; **361**: 690–4.)

Recent studies, using functional positron-emission tomography to measure changes in cerebral blood flow, suggest the involvement of the anterior cingulate cortex (Brodmann area 24) in the recognition of itch sensation at conscious levels [18], whilst the premotor cortical areas participate in intention to scratch. Ascending and descending pathways are represented in a simplified form in Fig. 16.1.

Central itch

Psychoneurophysiological aspects of itching are complex and poorly understood. They have led to the important concept of 'central itch', i.e. itching which is perceived as occurring in the skin, but which actually originates in the central nervous system due to dysfunctional processing of sensory information in the central pathways. Melzack and Wall [19] proposed the involvement of large, fast-conducting, myelinated sensory fibres in modulation of the discharge of the unmyelinated itch- or pain-transmitting fibres via the substantia gelatinosa ('gate' control of pain). According to this proposal, itch is due to a combination of peripheral excitation and central disinhibition. Scratching, by activating inhibitory fast-conducting myelinated fibres, closes the 'gate' by activation of suppressor neurones of the substantia gelatinosa and reduces the itch. Alloknesis (slight mechanical stimulation of skin causes intense itching) characteristically occurs in some patients with atopic eczema. It is thought to be due to excitation of central itch-transmission neurones due to reduced gating [4,19]. However, the recent suggestion that endogenous

opioid peptides of the central nervous system also play a crucial role in regulation of itch and pain traffic has complicated the picture. Opioid peptides have important peripheral actions, but also have an even more crucial central role. Morphine, administered spinally or epidurally, frequently causes intense itching [20–23], especially of the face, without visible inflammatory changes, and this symptom is rapidly relieved by intravenous naloxone or other opioid peptide μ-receptor antagonists [21,23]. Thus, the presence of opioid peptides and their μ-specific receptors, which modulate function of calcium channels specifically on unmyelinated C fibres in the central nervous system [24], provides a central itch- and pain-regulatory mechanism which is capable of therapeutic manipulation. Recent observations on the ability of serotonin (5-HT_3 receptor) antagonists to reduce itching, including that due to opioid peptide-induced pruritus, raise the possibility of an additional molecular mechanism to modulate itch centrally [25], and it is of interest that odansetron, a 5-HT_3 antagonist, has been reported to reduce morphine-induced pruritus [26]).

Peripheral mediators of itching in skin diseases

Itch can be evoked or augmented by a variety of stimuli, both physical and chemical (Table 16.1). That peripheral pharmacological mediators play a key role in the production of itching in inflammatory skin disease, originally proposed by Lewis as his 'H-substances', is supported by several lines of evidence. These include the ability of a wide range of naturally occurring pharmacological agents, including histamine and proteases, to reproduce the sensation of itch on injection into skin, the ability of antagonists of these agents to reduce itching and the regular experimental recovery of mediators known to be capable of causing or enhancing itching from inflamed pruritic skin. However, it must be appreciated that not all forms of itching involve release of peripheral mediators. Low-grade mechanical and electrical stimuli (Table 16.1) and the 'dry itch' of senescent skin may not involve peripheral mediators, although in these cases pruritus is likely to be peripheral rather than central. Nevertheless, it is a reasonable assumption that peripheral mediators cause itching in the majority of inflammatory dermatoses.

Table 16.1 Main classes (with examples) of externally applied factors which cause itching.

Physical
Light touch
Stroking
Vibration
Mild heat*
Electrical
Chemical
Acids
Alkalis
Other irritants
Pharmacological
Histamine
Histamine liberators
Morphine
Codeine
Compound 48/80
Serotonin (5-hydroxytryptamine)
Prostaglandins*
Platelet-activating factor
Kallikrein
Cytokines
Interleukin-2
Proteases
Trypsin
Papain
Mucunain
Tachykinins
Substance P
Calcitonin gene-related peptide
Opioid peptides
β-endorphin
Leu-enkephalin
Met-enkephalin

* Augmentation of itching.

Histamine and its receptors

Histamine causes severe itching if injected or iontophoresed into skin, or if it is applied to superficially abraded skin, although it produces pain if injected more deeply into skin [27]. At least three subclasses of histamine receptors are recognized. The recently described histamine H_3 subclass behave as autoreceptors, regulating release and biosynthesis of histamine in brain slices and certain other tissues, but they have yet to be positively identified in skin [28]. Both H_1 and H_2 receptors have been characterized in human skin using specific H_1- and H_2-receptor agonists and antagonists, and these studies have consistently implicated histamine H_1 but not H_2 receptors in histamine-induced itching [27]. Thus, there is no theoretical basis for use of H_2 antagonists (cimetidine, ranitidine) in the suppression of itching caused by histamine. A recently proposed fourth class of intracellular histamine receptors (H_{ic}) [29,30] may be involved in the ability of histamine to regulate cell proliferation and is not proposed to be involved in itching. Cutaneous responses to histamine may not be due solely to the direct actions of histamine. Recent work on the kinetics of the inflammatory responses of skin to histamine raises the possibility that some of these may be mediated indirectly by hitherto unrecognized substances whose release or formation is evoked by histamine [31]. The majority of histamine released in skin as a consequence of injury originates from the dermal mast cells. Evoked release of histamine and

other mast cell mediators is a consequence of an energy-dependent signal-transduction process. That alternative sources of histamine-evoked itching may exist in skin cannot be ruled out. A recent immunohistochemical study in rat skin [32] has clearly demonstrated immunoreactive histaminergic nerves, although this phenomenon has yet to be reported in human skin.

Histamine has been recovered directly from involved skin in a number of inflammatory dermatoses. In cold urticaria, release of histamine into the venous blood effluent from the cold-challenged limb consistently reflects the onset, development and regression of itching and other local changes occurring following cold exposure. Suppression of evoked histamine release by oral doxantrazole treatment also suppressed itching, but not wealing, in patients with cold urticaria [33]. Histamine has also been recovered from affected skin in ultraviolet-induced inflammation [34] and atopic eczema [35]. Further evidence of the involvement of histamine in inflammatory dermatoses derives from the well-known symptomatic relief obtained in many of these by systemic H_1 antihistamine treatment, although the sedative effect of the traditional H_1 antihistamines has been claimed to be at least as important as the antihistaminic action in atopic eczema [36].

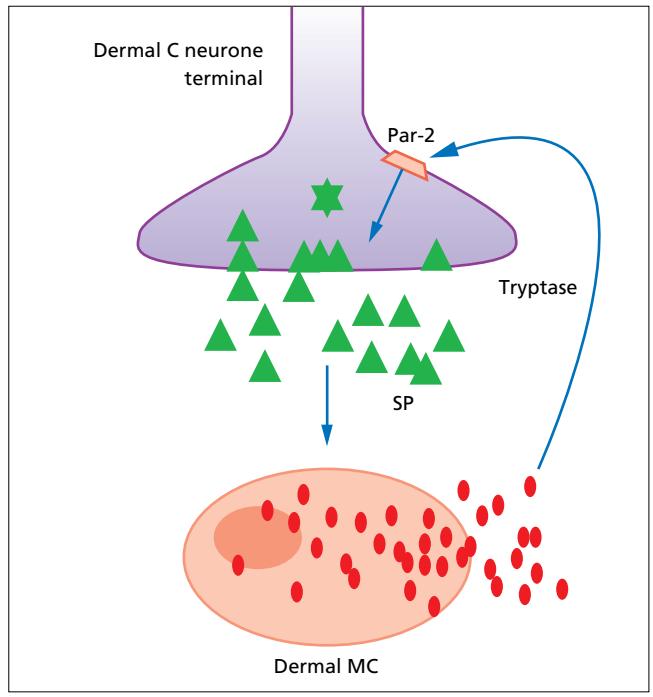

Fig. 16.2 Functional links between C neurone terminals and dermal mast cells: role of protein-activated receptor 2 (Par-2). SP, substance P; MC, mast cell.

Tachykinins

In view of their location in unmyelinated sensory nerve fibres in skin, neuropeptides are candidate mediators of itching in inflammatory dermatoses. Substance P, an 11-amino-acid neuropeptide, causes redness, wealing and itching [37,38]. Immunoreactive substance P is present in normal skin and in increased amounts in inflamed itchy skin [39]. To what extent substance P-induced itching is due to an indirect action via mast cell degranulation and histamine release is uncertain [37]. Of special interest is the fact that—unlike anti-IgE, compound 48/80 and other mast cell degranulators—substance P selectively and rapidly releases histamine but little or no prostaglandin D_2 or other cutaneous mast cell products from human isolated cutaneous mast cells *in vitro* [40]. Since the concentrations of substance P which degranulate mast cells tend to be unphysiologically high, it seems more likely that this neuropeptide has a priming function on histamine release evoked by other mast cell activators, including specific antigen–IgE interaction [41]. Recent work [42] has shed further light on links between dermal mast cells and afferent C neurones (Fig. 16.2). It has emerged that tryptase released by activated mast cells acts on a substrate called Par-2 (proteinase activated receptor 2) located in C neurone terminals. This results in release of vasoactive peptides including substance P. As already indicated, substance P can activate mast cells, thus closing the loop. Topical capsaicin application, which is known to deplete substance P from sensory nerve endings, abolishes pain and itch [43]. Substance P is colocalized with other neuropeptides, including calcitonin gene-related peptide (CGRP) and vasoactive intestinal peptide (VIP), in cutaneous human sensory nerve endings, but the involvement of CGRP and VIP in itch has not been fully explored. Substance P is synthesized in the dorsal root ganglion of nociceptor C fibres and transmitted peripherally in granules.

Opioid peptides

The opioid receptors consist of three classes: μ, δ and κ. The pruritic action of opoids is antagonized by naloxone and therefore belongs to the μ category.

The regulatory role of opioid peptides in the central nervous system has already been discussed above. Opioid peptides injected intradermally cause wealing and itching, probably at least partly through histamine release. However, more interestingly, low doses of opioid peptides, insufficient by themselves to cause itching, could strikingly enhance itching due to intradermal injection of histamine and this effect could not be antagonized by naloxone, indicating that this response does not involve μ-receptors [44,45]. Since the phenomenon also could not be inhibited by H_1 antihistamines or by prior depletion of cutaneous stores of histamine with compound 48/80 injections, or by indomethacin, it seems unlikely to be mediated by histamine release or prostaglandin synthesis [44]. Thus, opioid peptides may have an important peri-

pheral augmenting action on histamine itch, in addition to their pruritic central action. However, the former is not a class-specific action, since fentanyl and oxymorphone do not cause degranulation of human skin mast cells [46].

Other vasoactive peptide products of proteases

The use of the fine spicules of *Mucuna pruriens* (cowage) as probes enabled Shelley and Arthur [47] to carry out simple pathophysiological studies of itching in human volunteers, which led them to propose the involvement of peptide products of proteases as mediators of itching. The protease of cowage (mucunain) proved to be more active than histamine on a molar basis in inducing itching. However, no potent itch-producing peptide released by protease activity *in situ* has yet been recovered from human skin. The protease kallikrein is pruritogenic in human skin [48], but bradykinin produced by the action of kallikrein has little or no pruritic activity, although it causes pain [48]. Other proteases besides kallikrein cause itching, including chymotrypsin [49].

Cytokines

Cytokines are low-molecular-weight proteins produced by almost all eukaryotic cells, and they act on specific cell-surface receptors. They include the interleukins, chemokines, interferons and colony-stimulating factors. The first to be studied, interleukin-1 (IL-1), although powerfully pro-inflammatory in human skin [50], does not cause itching. Likewise, the chemokine IL-8, which causes leukocyte chemoattraction, causes no perceptible itch. Few others have been systematically studied from this standpoint. However, human recombinant IL-2 given intravenously to cancer patients for therapeutic reasons was noted regularly to cause intense itching, associated with redness and a blood eosinophilia [51]. Human recombinant IL-2 injected intradermally caused intense itching in skin of atopic and non-atopic human volunteers alike [52]. Since activated T lymphocytes, an important source of IL-2, are a feature of the dermal infiltrate of atopic dermatitis, a role for IL-2 in the characteristic itching of this disorder has been proposed. That ciclosporin (cyclosporin), a potent inhibitor of IL-2 production by T lymphocytes, causes relief of itching in atopic dermatitis lends further support to a proposed role for IL-2 in the itching of atopic dermatitis [53]. Leukocytes from atopic patients, but not those of control subjects, released increased amounts of IL-8 upon challenge by specific antigen, although this cytokine is not recognized as a direct cause of pruritus [54].

Prostaglandins and other eicosanoids

Increased cutaneous levels of arachidonate metabolites are found in a wide range of inflammatory skin diseases, including physical urticarias, ultraviolet inflammation, psoriasis and eczema [33,55]. The lipoxygenase metabolites most frequently identified in these conditions—leukotrienes B_4, C_4, D_4 and E_4, and 12- and 15-hydroxyeicosatetraenoic acid—cause little or no pruritus, despite being potent pro-inflammatory agents in human skin. Prostaglandin E also shows little or no pruritic activity in human skin, even when applied in a wide range of doses. However, it has the striking property of potentiating itching due to other mediators in concentrations which by themselves have no visible pro-inflammatory activity. By applying a range of concentrations of histamine to scarified human skin pretreated with doses of prostaglandin E_1 insufficient to cause visible reddening of the skin, it was possible to demonstrate a doubling of the sensitivity of the skin to histamine-induced itching [56]. Similar results were subsequently reported by others who have also shown potentiation by prostaglandin E_2 of itch due to other substances [57], and a study in which the H_1 antihistamine clemastine failed to antagonize the prostaglandin E enhancement of itching [58] suggests that this prostaglandin enhances itching due to other mediators. Increased skin concentrations of E prostaglandins have been reported in eczema and ultraviolet B inflammation, both of which are associated with pruritus [33]. Although aspirin, a prostaglandin synthetase inhibitor, has little or no effect as an anti-pruritic [59], non-steroid anti-inflammatory drugs have been demonstrated to reduce pruritus associated with morphine-induced spinal analgesia [60].

Factors modulating itching

Central mechanisms for regulation of itch traffic have already been referred to earlier. Psychological factors, including emotion, inattention and a variety of auditory, visual and other sensory inputs may act through these central pathways, resulting in modification of perception of itching. That warmth exacerbates itching is a familiar experience which has a physiological basis, conferring a rationale on cooling as a method of controlling itching. Cooling acts directly on sensory receptors, whereas heating stimuli appear to act centrally [61].

Scratching

Scratching is a reflex functioning at a spinal level, although modified greatly by higher centres. Scratching relieves itching for several minutes after scratching has ceased. Since the sensation of itching is reinforced by facilitating circuits in the relay synapses of the spinal cord, the prolonged scratch-induced relief could be due to temporary suppression of these circuits [19]. Stimulation of fast-conducting myelinated afferents inhibits these circuits via pre- and postsynaptic mechanisms. These afferents could

be activated by vibration, transepidermal electrical nerve stimulation (used therapeutically to allay itching) or more simply by scratching. Alternatively, scratching could simply damage sensory nerve endings, repair occupying several minutes. Why some itches evoke scratching and excoriation (as in scabies) whereas others prompt rubbing (as in lichen planus) is unknown. Scratching has been ingeniously utilized as an indirect, objective method of quantifying itch and as such has been utilized in the evaluation of treatment of itching [7,12].

Itching in non-inflamed skin

The molecular and physiological basis of pruritus associated with clinically normal skin in the absence of underlying systemic disease is in most instances uncertain, although clues are beginning to emerge. The problem of itch in ostensibly healthy skin is likely to become more pressing, with the increasing emergence of pruritus in senescent but visibly normal skin as a challenging therapeutic problem. Initially, careful examination of the skin must be made to exclude visible signs of skin disease. Patients with symptomatic dermographism who have the will to forbear scratching may have a normal-looking skin at the time of examination. It is also conceivable that localized or widespread itching without physical signs may be a manifestation of mild urticaria ('weal-less urticaria'). In such cases, levels of histamine and other mediators could be subthreshold with regard to vascular, but not sensory, effects. This phenomenon is recognized in aquagenic pruritus, contact urticaria, dermographic pruritus and cholinergic urticaria [62–65].

A detailed history is of paramount importance, including the quality, distribution and periodicity of itching. Itching, likened by the patient to insects crawling over the skin, is often psychoneurotic in origin—or occasionally due to insects actually crawling over the skin! Itch, which is migratory in timing and distribution, may be secondary to internal malignancy. Most patients with itching are especially uncomfortable in bed, probably because of warmth and little to distract their attention. Localized, fixed itching may be due to organic neurological disease—for example, in segmental neurofibromatosis [66].

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Itching in disease states

Chronic renal disease

Itching occurs in chronic, but not acute, renal failure. The majority of patients with chronic renal insufficiency experience pruritus at some stage in the progress of their disease, but it is severe in only a few. Estimates of the overall frequency of pruritus in patients with renal failure varies widely in different series, as does its relationship to haemodialysis, including maintenance dialysis. On maintenance dialysis, about 80% are affected [1,2], but it rarely improves with dialysis alone. Recent work suggests that patients dialysed using less permeable (cuprophane) membranes suffer pruritus more frequently than those using more permeable (polysulphone) membranes [3]. Although the skin of some patients may appear dry, frequently it is essentially normal in appearance. Itching may be persistent, extensive and intractable, but in other patients it may be transitory and localized [1,2]. Histologically, the clinically normal skin may show attenuation of sweat and sebaceous glands, and increased population densities of cutaneous mast cells have been described [4]. However, no correlation between mast cell population densities and pruritus has been established. There may be an angiopathy [5]. Abnormal sprouting of neurone-specific enolase-positive unmyelinated nerve fibres in skin of uraemic patients has also been reported [6]. Other suggested factors in the pathogenesis include raised serum parathyroid hormone levels due to secondary hyperparathyroidism [7], and it is of interest that parathormone is known to cause increased populations of tissue mast cells [8]. However, although parathyroidectomy has relieved pruritus in some patients [9], no convincing correlation between parathormone levels and pruritus has been demonstrated in renal failure patients [7]. Stahle-Backdahl has proposed a correlation between sequences in the mid-region of the parathyroid hormone, rather than the intact molecule [3]. Renal pruritus has been proposed to be related to aluminium overload during haemodialysis [10] (treatable by administration of desferrioxamine mesylate), but this has not been confirmed.

Pharmacological mediators have been proposed to be responsible for renal pruritus. Histamine is an improbable candidate, since treatment by antihistamines is ineffective. Skin biopsies from patients with chronic renal failure show increased numbers of intraepidermal $CD1^+$ T cells, raising the possibility that T-cell-derived cytokines could be implicated in pruritus [11,12]. Opioid peptides have also recently been implicated, elevated plasma met-enkephalin levels having been reported in haemodialysis patients [13], although a correlation has yet to be established [14]. The pathophysiology of uraemic itching has been usefully reviewed by Murphy and Carmichael [15].

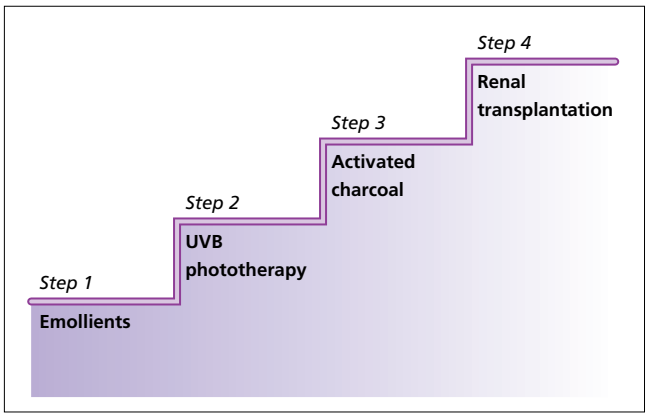

Fig. 16.3 Treatment ladder: pruritus of chronic renal failure.

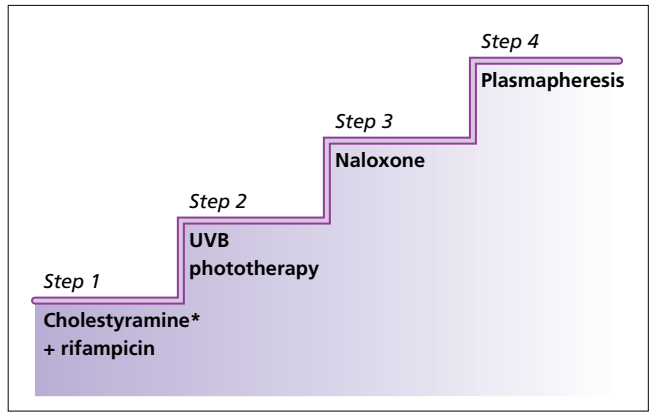

Fig. 16.4 Treatment ladder: pruritus of cholestasis. *Ineffective in total biliary obstruction.

The only treatment for renal pruritus (Fig. 16.3) which is reliably effective is renal transplantation. Parathyroidectomy may be followed by remission of pruritus in patients with secondary hyperparathyroidism [9]. Phototherapy with ultraviolet B (UVB) is frequently effective and may act systemically as well as locally [16]. That ultraviolet therapy depletes the vitamin A content of the skin has been proposed as a mode of action [17]. Only UVB phototherapy and possibly activated charcoal have an established track record for this indication [18,19]. Other treatments, including heparin, mexiletine, ion-exchange resin and intravenous lidocaine (lignocaine) have been advocated [16], but are of uncertain effectiveness and usually impractical to use. A 1996 report of a placebo-controlled trial of an orally administered opioid antagonist, naltrexone, attracted much attention, but the apparent effectiveness of this treatment remains to be independently confirmed [20]. Antihistamines and topical steroids are generally unhelpful in uraemic itching, but emollients may provide relief in those with a dry skin. Since itching may be restricted to certain areas, topical capsaicin 0.025% has been reported to be effective in localized uraemic pruritus [21]. In the longer term, only expansion of the renal transplant programme is likely to bring sustained relief to these greatly distressed patients.

Cholestasis

Pruritus, which may be generalized or localized, for example to the hands and feet, is a frequent and distressing symptom of cholestasis, and its molecular basis is still debated. Hepatitis C is an important cause of intense cholestatic pruritus, and should be considered as part of the work-up of patients with severe pruritus. Cholestatic pruritus is associated with elevated plasma levels of bile salts [22], but evidence of a direct correlation has been lacking. Measurements of skin-tissue levels of bile salts and their relationship to serum levels, and to intensity of itching, gave inconclusive results and the bile-salt levels did not differ from corresponding values in control subjects [23]. Bile salts applied to blister bases in human skin, although causing pruritus, do so at minimal effective concentrations far exceeding those achieved in cholestatic jaundice [24]. Analysis of individual bile acids in skin and serum, including quantitatively minor components of the bile-acid family, also failed to show a quantitative relationship with pruritus [23]. Lack of demonstrable quantitative relationships has not, however, discouraged a number of investigators from exploring methods for lowering serum and skin bile-salt levels in the management of itching due to cholestasis. For example, plasma perfusion through charcoal-coated glass beads was associated with a marked improvement in cholestatic pruritus, although a relationship between clinical response and fall in bile-salt level was not demonstrated. Similar results have been achieved with ion-exchange resins, including cholestyramine [25,26]. These reports raise the possibility that observed clinical improvements may be a consequence of removal of pruritogenic factors other than bile salts following such procedures.

Treatments for pruritus of cholestasis are summarized in Fig. 16.4. In a randomized cross-over trial comparing cholestyramine, terfenadine (a low-sedation H_1 antihistamine now withdrawn by the manufacturer owing to cardiac side effects) and chlorpheniramine with placebo in pruritus due to obstructive liver disease, only terfenadine and cholestyramine showed evidence of significant suppression of pruritus, but cholestyramine was associated with a high incidence of side effects [25]. Other methods advocated for the relief of itching of cholestasis include phenobarbital and rifampicin [27,28], plasmapheresis [29], phototherapy [26] and, more recently, ondansetron [30]. Effective treatments of hepatobiliary pruritus have recently been reviewed [31].

Earlier work highlighted the importance of dysregulation of central opioid peptides in patients with cholestatic pruritus [32]. The evidence can be summarized as follows.

Plasma levels of opioid peptides are elevated in human [32] and rat [33] cholestasis. Furthermore, plasma from patients suffering from pruritus of cholestasis induces facial scratching, reversed by naloxone, when injected into the medullary dorsal horn of the monkey [34]. Most importantly, carefully controlled trials established the effectiveness of systemic and oral opioid antagonists in the treatment of cholestatic pruritus [35,36]. Thus, the conclusion that opioid antagonists are of value in treatment of the pruritus of cholestasis is based upon evidence of increased opioidergic tone in chronic cholestasis patients, and the impressive response to naloxone (a specific opioid μ-receptor antagonist). This response can be associated with opioid withdrawal symptoms [35–37].

Apart from biliary disease, cholestatic pruritus may also occur in pregnancy [38] and premenstrually [39]. However, the role of opioid peptides in these contexts has yet to be established.

Iron deficiency

Iron deficiency has been implicated as a cause of intractable pruritus in the absence of visible skin disease, or even in the absence of anaemia [40]. Of special interest is a report by Salem *et al*. [41] of pruritus and severe iron deficiency in polycythaemia vera. In these patients, correction of iron deficiency apparently correlated with improvement in pruritus. However, a study of iatrogenic venesection-induced iron deficiency over a 60-month period revealed no instance of pruritus in 21 patients [42]. That patients with iron deficiency complain of troublesome pruritus is evident, but present data suggest that the itch is likely due to factors other than the iron deficiency itself.

Polycythaemia vera

As many as 50% of untreated patients with polycythaemia develop a severe, prickly and distressing discomfort within minutes of water contact, lasting 15–60 min [43]. As it frequently occurs after the patient emerges from bathing, it is often referred to as 'bath itch'. No visible changes are present in the skin, and the symptom may be associated with elevated serum and urinary histamine levels [43]. Platelet aggregation has been suggested as a possible mechanism and source of pruritogenic factors, including histamine [44]. Water-induced itching may precede development of polycythaemia vera by several years [45]. Bathing by regional sponging may mitigate the itch. Successful treatment of the underlying polycythaemia may not relieve the itching and although correction of venesection-induced iron deficiency may give relief, it may be at the expense of exacerbating the polycythaemia [41]. Antihistamines are generally ineffective. Psoralen ultraviolet A (PUVA) photo-chemotherapy, with 8-methoxypsoralen and UVA, has been successful in some patients [46]. One report cites the use of long-term treatment with interferon alfa-2b for severe pruritus of polycythaemia vera [47].

Spontaneous itching as a manifestation of endocrine and malignant disease

Thyrotoxicosis

Intractable itching, associated with a warm, moist skin, is a recognized accompaniment of thyrotoxicosis and may be the presenting symptom [48]. The cause is uncertain. Localized pruritus may result from mucocutaneous candidiasis. Cutaneous vasodilatation, a regular feature of the disease, leads to increased skin surface temperature, which lowers the itch threshold [49]. Myxoedema may also cause troublesome itching, but in this case the cause is usually excessive drying of the skin, which feels cool, and which responds to application of moisturizing creams.

Diabetes mellitus

Contrary to popular wisdom, generalized pruritus is not a manifestation of diabetic mellitus, the erroneous belief having originated from a 1927 report of a 3% prevalence in 500 patients [50], which coincides with the expected frequency in the general population. A more recent study [51] reported generalized pruritus in eight of 300 diabetic patients, which was not more common than in non-diabetic patients. However, intractable anogenital itching may occur due to mucocutaneous candidiasis. Localized pruritus of the scalp is also a recognized manifestation of diabetes and is usually resistant to antipruritic measures [52].

Pruritus and malignancy

The problem of pruritus as a manifestation of malignant diseases has been the subject of numerous publications reviewed by Lober [53] and Paul *et al*. [54]. Paul *et al*. followed up 125 patients with generalized pruritus for 6 years [54]. Of these, 66% still had pruritus at the end of the study. Although four proved to have a malignant condition at the onset of the study, only four others developed malignancy during the follow-up period. This is no different from the expected frequency in the general population. However, pruritus, often induced by contact with water, is a recognized presenting symptom of polycythaemia vera [45]. Pruritus is intense in Sézary syndrome, but the skin is inflamed in this malignancy. The practical issue of the extent to which patients with generalized pruritus in the presence of a normal skin should be investigated cannot be separated from economic considerations [55].

Aquagenic pruritus

This term was first used by Shelley [56] to describe what was considered to be a variant of aquagenic urticaria. Three cases of aquagenic pruritus were subsequently reported in detail and shown to be distinct from aquagenic urticaria [57]. The condition was subsequently extensively reviewed [58,59]. Typically, contact with water at any temperature leads to an intense pricking itch in the exposed skin, without visible change in the appearance of the skin. The same symptoms may be evoked by a sudden drop in temperature of the skin. The condition is very chronic and intractable, and sufferers frequently are wrongly considered to be psychoneurotic. The condition, which closely resembles the pruritus of polycythaemia vera, responds poorly to antihistamine treatment but may respond to UVB phototherapy or PUVA [46,60]. It may be a premonitory symptom of polycythaemia vera [45]. Other underlying causes recently reported include metastatic carcinoma of the cervix [61], hypereosinophilic syndrome [62], juvenile xanthogranuloma [63] and the myelodysplastic syndrome [64]. The molecular basis of the pruritus is uncertain. Investigation of affected skin has shown elevated histamine concentrations and increased cutaneous mast cell degranulation, and the serum histamine concentration has also been shown to be raised [43,57]. The lack of visible evidence of histamine release can be explained by its slow rate of release, leading to skin concentrations sufficient to cause itching but below the threshold for visible vascular changes. However, histamine is unlikely to be the sole mediator, since antihistamine treatment is generally ineffective, and there is also evidence of the involvement of acetylcholine, since topical hyoscine treatment rendered skin unresponsive to water contact [57]. Further evidence for acetylcholine as a mediator derives from a recent report of increased acetyl cholinesterase activity localized to nerve fibres investing eccrine sweat glands in patients with aquagenic pruritus [65]. There has also been a report of increased tissue fibrinolytic activity in affected skin of patients with aquagenic pruritus [66], which could be a response to increased local concentrations of histamine or acetylcholine.

Pruritus as a symptom of senescence

Persistent and widespread itching, often associated with extensive excoriation, is experienced by at least 50% of those in the seventh decade of life or beyond. Because of the gradually increasing proportion of elderly persons in the population, it is also a burgeoning problem. In women, the itching may be a manifestation of the postmenopausal syndrome. Pruritus of elderly people may be a symptom of subtle skin disease, a manifestation of underlying systemic disorder, including renal, hepatic or malignant disease, or it may be a skin manifestation of an adverse drug reaction. However, in most instances, itching is a result of excessive dryness (xerosis) of the skin. In a recent study of 149 elderly men and women, 39% had pruritus due to xerosis [67]. There is evidence of slow reduction of sebum production by skin in association with ageing, and its composition also alters [68,69]; however, this is not thought to be a major factor in xerosis of the elderly. Senescence in the skin is frequently associated with failure of the skin to retain water. The resulting dryness and fine cracking of the skin is associated with troublesome itching, which in most instances responds to emollient treatment. Water-induced itching in elderly people [59] is a variant of senescent pruritus, being particularly common in institutionalized elderly people who may be exposed to an overheated, dry environment, resulting in skin desiccation, and both it and the common spontaneous variety respond to emollient treatment. Analysis of senescent stratum corneum has shown a greatly reduced water content [70]. It is usually most expedient to prescribe several different emollients and encourage the patient to experiment with these, since it is not possible to predict with confidence individual responses. Soft white paraffin ointment is cheap, occlusive and has been shown to accelerate recovery of barrier function in damaged skin [71]. The patient must be encouraged to apply emollients at least four times daily and, if necessary, ambient temperature and humidity should be modified. Corticosteroids, antihistamines and cooling lotions are not indicated in itching due to xerosis.

Psychogenic pruritus

Itching, either localized or generalized, can be a skin manifestation of psychological disturbance. There are no satisfactory 'rule in, rule out' diagnostic paradigms; therefore, in practice the conclusion that local or generalized itch is psychogenic in origin is arrived at by a process of exclusion of cutaneous or systemic causes.

Perianal and, in women, vulval itching are the commonest manifestations of local psychogenic pruritus, although in these instances great care must be taken to rule out occult remediable causes, including threadworms (pinworms), dermatitis medicamentosa, diabetes-induced candidiasis and local inflammatory or neoplastic disease. Widespread psychogenic pruritus may result in extensive and disfiguring excoriations and even scarring to the extent of self-mutilation. Parasitophobia (delusions of parasitic infestation of the skin) is normally readily recognizable, because of the patient's description of the itch and even the presentation by the patient of particulate material considered by the sufferer to represent the supposed insects or their products. Of two recent patients of the author's, one brought along a small portable micro-

scope to aid viewing of the 'insects', and the other brought textbooks of dermatology and parasitology to the clinic to support her case! Although rarely successful, psychiatric advice should be sought, and antidepressant and anxiolytic drugs, including doxepin and hydroxyzine, should be tried. Treatment options for these patients have been well reviewed [72]. Pimozide (phenylbutylpiperidine), a phenothiazine, has been advocated for treatment of delusions of parasitosis [73]. It is also self-evident that patients experiencing severe persistent pruritus become secondarily depressed, and that this may itself lower the threshold for pruritus, thus completing a 'vicious circle' of itch, depression and more itch [74].

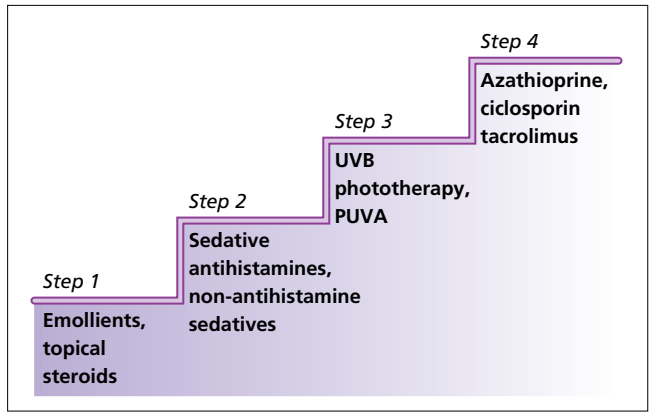

Fig. 16.5 Treatment ladder: pruritus of atopic eczema.

Postmenopausal pruritus

Persistent or episodic widespread itching is a frequent association with the postmenopausal syndrome. The itching characteristically evokes rubbing, rather than heavy excoriation, and is frequently associated with hot flushes. It is especially troublesome at night, and is usually associated with raised plasma levels of pituitary follicular and luteal stimulating hormones. These hormones are unlikely, however, to be the direct cause of the itching and associated flushing, which are probably attributable to local tissue mediators. Hormone-replacement therapy with ethinyl oestradiol is usually sufficient to control postmenopausal pruritus due to this cause [75], but since systemic oestrogen therapy can be hazardous, expert endocrinological advice should be sought. Localized genital pruritus may also be a postmenopausal manifestation of oestrogen deficiency and may be associated with mucocutaneous candidiasis. It should respond to corrective hormone therapy, combined if necessary with nystatin or other anti-*Candida* therapy.

Pruritus of atopic eczema

The itch of atopic dermatitis is aggravated by scratch damage, which causes enhanced inflammation (itch–scratch cycle). Itching is usually worse at night, and is aggravated by contact with wool, sweat, spicy foods and alcohol. Considerable sleep loss and incapacity ensues. No aspect of pruritus has provoked more debate than the pathophysiology of itching in atopic eczema and its management. Pruritus in atopic dermatitis involves pruritoceptive neurogenic and probably psychogenic mechanisms. Several studies, reviewed by Rajka [76], have reported an enhanced and abnormally prolonged response to application of pruritic pharmacological stimuli in unaffected skin in atopic patients. Studies of the itching response of atopic dermatitis patients to histamine iontophoresis suggest a decreased response of afferent cutaneous fibres to high doses, but an increased sensitivity to low concentrations—possibly because of increased permeability of clinically normal-looking skin of these atopic patients [77]. There is also an increased population density of sensory nerve fibres in the affected lichenified pruriginous skin [78], although this is probably non-specific. It is important to distinguish itching associated with inflammatory changes or chronic lichenification from that simply due to excessive drying of the skin in patients with atopic eczema, since emollients, which may be all that is required for the management of xerosis, will be inadequate where inflammatory changes are responsible for the itching. Recent dermal microdialysis studies have demonstrated the involvement of mast cell mediators other than histamine in lesional skin of atopic eczema patients [79]. In the latter situation, a combination of antihistamines with topical treatment may or may not be helpful, depending upon the importance of histamine as a pruritogen. Treatment approaches to itching in atopic eczema are summarized in Fig. 16.5. The role of sedative versus low-sedation antihistamines is controversial. On the basis of a comparison of itching in atopic eczema patients receiving successively terfenadine (now withdrawn by the manufacturers due to adverse cardiac side effects) or astemizole (low-sedation antihistamines), trimeprazine (sedative antihistamine) and nitrazepam (non-antihistamine sedative), one study [80] concluded that sedation was a required component of successful systemic treatment of itching in atopics, and that, moreover, itching in atopic eczema involved a central component. However, numbers of patients were small and subsequent studies have yielded conflicting results [81]. However, the itching of atopic eczema is multifactorial, being due to dryness, inflammation and probably to disturbed regulation of itch traffic in the central nervous system. In this context, alloknesis (itchy skin; see above) forms a major component of the itch suffered by the atopic eczema patient—explaining, for example, the paroxysms of itching experienced by patients in response to sudden

changes of temperature, humidity, undressing or dressing, etc. These multiple and distinct mechanisms may explain seemingly conflicting views on the nature and causation of pruritus in atopic eczema. Evening primrose oil, which contains essential fatty acids, including dihomo-γ-linolenic acid, has been proposed to be effective in relieving pruritus of atopic eczema [82], but other studies [83,84] have challenged this finding, and the use of this preparation in itching of atopic eczema is controversial. However, immunosuppressives—including systemic azathioprine and ciclosporin—are highly effective in relieving the itching (and other signs and symptoms) of chronic atopic eczema [85,86], probably due to an action on activated $CD4^+$ T-helper lymphocytes. Recently, a topical T-cell-suppressing immunosuppressant with an action closely resembling that of ciclosporin, called tacrolimus, which is highly effective in relieving the symptoms and signs of atopic eczema, including pruritus, has been introduced [87], but its long-term safety needs to be established, and it remains to be seen to what extent tacrolimus will form a practical replacement for topical steroids. Aspirin, contrary to reports in some textbooks, is ineffective in the suppression of itching in atopic eczema [88].

Acquired immune deficiency syndrome

Itching is an important symptom of acquired immune deficiency syndrome (AIDS) [89]. Whilst this may be associated with numerous causes, including cholestasis, seborrhoeic dermatitis, scabies or candidiasis (Table 16.2), it also occurs as a characteristic generalized papular and excoriated pigmented eruption resistant to topical steroid treatment. Histologically, affected skin shows follicular damage associated with an eosinophilic infiltrate [90]. Although the histological features are not dissimilar from those of Ofuji's eosinophilic pustular folliculitis, the clinical picture in the latter, which features polycyclic plaques, is different. Treatments reported to be effective include dapsone, pentoxifylline, UVB phototherapy and PUVA [91–93].

Table 16.2 Recognized causes of pruritus in HIV-positive patients.

Seborrhoeic dermatitis
Staphylococcal folliculitis
Scabies
Ringworm
Eosinophilic folliculitis
Insect bite reactions
Adverse drug reactions
Atopic dermatitis
Dry skin
Psoriasis
Reiter's syndrome
Photosensitivity
Systemic causes of pruritus (renal, hepatic, endocrine)

Important miscellaneous causes of intense itching

Hydroxyethyl starch-induced pruritus [94]

Hydroxyethyl starch (HES) is used widely as a plasma substitute, especially on the continent of Europe. It is also used to improve the function of the microcirculation. Generalized pruritus has been reported as a rare but well-recognized complication. It results from deposits of HES in the skin, and may be associated with erythema [94,95]. It is poorly responsive to antihistamines, but may respond to topical capsaicin [96].

Pemphigoid nodularis

Bullous pemphigoid can present with non-specific pruritus. There have also been reports from several centres [97–99] of patients presenting with a chronic prurigo nodularis-like eruption who subsequently proved—by histological examination, direct immunofluorescence and clinical follow-up—to have bullous pemphigoid; blisters eventually developed in most reported cases. It is important to carry out a skin biopsy for histological examination and direct immunofluorescence for immunoreactants on all patients with what appears to be prurigo nodularis.

Notalgia paraesthetica

This is a fairly common cause of localized persistent pruritus. Characteristically, patients complain of persistent burning pruritus localized to the mid-scapular area, but often extending from there to a more widespread distribution, including the scalp. Apart from mild lichenification and pigmentation with or without macular amyloidosis, there is usually little to see. Reports of increased cutaneous innervation are probably correct, but may represent a non-specific change [100]. Recent reports stress the importance of nerve root entrapment [101,102]. Capsaicin cream appears to be effective in some patients, and the current view is that it is a type of localized sensory neuropathy [103].

Brachioradial pruritus

This increasingly common sunlight-induced chronic pruritus is localized to the outer aspect of the elbow, and adjacent lower and upper arms [104]. The increased popularity of prolonged and frequent outdoor holidays in areas of high insolation amongst middle-aged and elderly fair-skinned people probably accounts for its increased frequency. A typical patient of the author's with this diagnosis had spent much of the year sailing and golfing in the Caribbean region. She responded to treatment with capsaicin cream [105]. However, it can be unresponsive to

treatment. Gabapentin has been reported to be effective in such cases [106]. Pruritus and prurigo due to chronic sun exposure may occasionally be much more widespread and has been termed 'solar pruritus'. They are probably identical to brachioradial pruritus [107].

Pruritus and anorexia nervosa

That generalized pruritus is one of several skin manifestations of anorexia nervosa is well recognized [108]. Itching is associated with low body weight and resolves with weight restoration. The itching is independent of underlying disease, including endocrine factors, renal or hepatic complications, or excessive washing. The skin may be excoriated and present a prurigo-like appearance. The itching could be central (neurogenic) in origin, but further evidence is awaited [109].

Investigation of generalized pruritus

History taking is important and can save time in the long run. The onset, quality, severity and timing of the itching should be established. The location and fixed or ephemeral nature of bouts of itching should be determined, together with relationship to activities, provoking factors, medications, recreational, social and ablutional habits. Use of a questionnaire, e.g. the Eppendorf Itch Questionnaire [110], enables elicitation of standardized historical information.

In the absence of obvious localizing symptoms or signs indicating systemic disease, it is essential to carry out a full physical examination, including rectal and pelvic examination. This should be followed by full blood counts, chest X-ray and thyroid, renal and liver-screening tests. Routine imaging investigations and endoscopy are probably not justified in the absence of localizing symptoms or signs, although examination of the stool for occult blood is a useful and cheap investigation. The possibility that persistent, generalized pruritus in the absence of skin signs can be an adverse reaction to a systemic drug should never be overlooked. All patients with generalized pruritus of unrecognized cause should be followed up regularly as long as the symptom persists.

Management of itching

Obviously, the most important step is to identify and treat the fundamental cause of the itch, whether it is primarily in the skin or of a systemic origin. At the same time, patients require symptomatic relief. Pruritus is temperature-dependent [49], and therefore wearing light clothes, keeping the bedroom cool, using light bedclothes and keeping the working environment as cool as possible are all helpful measures. A cool shower before retiring may allow sleep. Pruritus due to dry skin, especially prevalent in elderly people, may respond to emollients such as soft yellow paraffin and aqueous cream. Water-induced itching in elderly people, which is distinguished from aquagenic pruritus by the presence of clinical evidence of dry skin, is especially responsive to treatment by moisturizing preparations. H_1 antihistamines and topical corticosteroids should not be used in the absence of visible inflammatory changes in the skin. Topical antihistamines carry a small risk of contact sensitization, although the topical tricyclic compound 5% doxepin cream has been shown to be safe and effective for treatment of itch due to eczema [111]. However, it does cause sedation due to percutaneous absorption. Low-sedation antihistamines are of controversial value in the itch of atopic eczema, but are the treatment of choice for itching in patients with urticaria. There are no available effective and specific antipruritic drugs. Topical phenol and crotamiton [112], though widely used for this purpose, are of unproven value. A carefully controlled study suggests that topical 1% menthol in 90% ethanol is of significant value in the symptomatic relief of histamine-induced pruritus [113], probably due to activation of cold-sensitive Aδ nerve fibres. Capsaicin is being used topically with apparent success in several localized chronic pruritic disorders [114]. Systemic tricyclic antidepressants may be of help in some patients with intractable itching. Other suggested measures of uncertain efficacy include transcutaneous nerve stimulation [115] and acupuncture [116]. Use of opioid-receptor antagonists, including naloxone, shows early promise in the management of otherwise intractable pruritus [117]. Paroxetine, a selective serotonin reuptake inhibitor, may have a place in the treatment of intractable pruritus, including the pruritus of advanced cancer [118].

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Chapter 17

Eczema, Lichenification, Prurigo and Erythroderma

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Eczema

Definition. Eczema is an inflammatory skin reaction characterized histologically by spongiosis with varying degrees of acanthosis, and a superficial perivascular lymphohistiocytic infiltrate. The clinical features of eczema include itching, redness, scaling and clustered papulovesicles. A wide range of external and internal factors acting singly or in combination can induce the condition.

The terms 'dermatitis' and 'eczema' are nowadays generally regarded as synonymous, although some authors still use the term 'dermatitis' to include all types of cutaneous inflammation, so that all eczema is dermatitis, but not all dermatitis is eczema. The term 'dermatitis', however, should be used with care, as some patients regard it as implying an occupational cause. Unfortunately, there is still no international agreement on the use of these terms [1,2].

Ackerman [1] has argued that, as the term eczema cannot be defined in a way that meets with universal approval, it should be dropped from dermatological parlance, but there seems to be a consensus that the term still serves a useful purpose for the clinician.

Classification. Eczema accounts for a large proportion of all skin disease. The classification of the many clinical forms is difficult, not only because nomenclature is controversial [3], but also because in many cases the precise cause is unknown. Multiple factors may be implicated, and two or more forms of eczema may be present in the same patient simultaneously or consecutively. The classification shown in Table 17.1 divides eczema into two groups. The first, exogenous eczemas, are related to clearly defined external trigger factors, although inherited tendencies can also play a part. The term endogenous

Table 17.1 Classification of the principal forms of eczema.

Exogenous eczemas
Irritant dermatitis (Chapter 19)
Allergic contact dermatitis (Chapter 20)
Photoallergic contact dermatitis (Chapter 20)
Eczematous polymorphic light eruption (Chapter 24)
Infective dermatitis*
Dermatophytide*
Post-traumatic eczema*
Endogenous eczemas
Atopic dermatitis (Chapter 18)
Seborrhoeic dermatitis*
Asteatotic eczema*
Discoid eczema*
Exudative discoid and lichenoid dermatitis*
Chronic superficial scaly dermatitis*
Pityriasis alba*
Hand eczema*
Gravitational eczema*
Juvenile plantar dermatosis*
Metabolic eczema or eczema associated with systemic disease*
Eczematous drug eruptions*

* Discussed in this chapter.

eczema implies that the eczematous condition is not a result of exogenous or external environmental factors, but is mediated by processes originating within the body. In some conditions, however, there are both external and internal precipitating factors. Hand eczema, for example, even when primarily endogenous, is often aggravated by contact with irritants such as detergents or solvents. Discoid and asteatotic eczemas (both regarded as endogenous) can be adversely affected, if not caused, by excessive dehydration of the stratum corneum by low ambient humidity. There remain some cases of eczema that do not fit the described patterns [4]. However, it is convenient to continue to classify eczema as of endogenous or exogenous type. The classification includes the principal forms of eczema, although these conditions do not necessarily show the histological changes of eczema at all stages.

Some forms of eczema are altered by regional variations in structure and function of the skin, and these may modify its appearance in regions such as the hands (see p. 17.20) and the lower leg. Other forms occur only in special environments, in certain racial groups (see Chapter 69) or at certain ages (see below).

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Prevalence. There have been numerous studies of the prevalence of atopic dermatitis (see Chapter 18), but fewer in other types of eczema. An important survey of the prevalence of skin disease was carried out in the USA on a sample of over 20 000 people who were representative of the whole population, and who were examined meticulously by trained observers [1]. Nearly one-third had significant skin pathology. The prevalence of all forms of eczema was 18 per 1000, seven of whom had atopic dermatitis. Hand eczema, dyshidrotic eczema and nummular eczema each accounted for about 2 per 1000. In a recent population-based survey of public health issues in Stockholm, Sweden, a postal questionnaire was sent to 15 000 adult inhabitants. Fifteen per cent of respondents reported a history of childhood eczema. The 1-year prevalence of hand eczema was 8%, skin symptoms on the face occurred in 14% and allergy to nickel was reported in 15% of females [2]. Population-based studies of contact allergic dermatitis suggest 40% of subjects demonstrate at least one contact allergic reaction [3].

Consultations for eczema are common in primary care. Horn [4] recorded the details of 6819 dermatological consultations in a UK general practice of around 3000–4000 patients from 1958 to 1985. Eczema patients formed the largest group (19% of the consultations; see Table 17.2 for details).

Table 17.2 Incidence of various types of eczema seen in a single general practice over 27 years in Ipswich, UK. (From Horn [4].)

Eczema type	Incidence (%)
Hand eczema	15
Contact dermatitis	12
Seborrhoeic	11
Discoid	7
Lichen simplex	6
Atopic	5
Gravitational	4
Other (mainly unspecified)	40

In a general practice in Belfast, 8% of patients seen during an 8-week period had a dermatological condition. Dermatitis accounted for 25% of these, of which 63% were considered to be exogenous in origin [5].

In addition, many cases are referred to hospital, and in one series represented 17% of all new dermatological cases [6]. A national tertiary referral centre in Singapore has described the profile of eczema referred between 1989 and 1990 [7]; 25 448 new cases were analysed. These represented 34% of new cases seen at the centre. Sixty-seven per cent of eczema cases were classified as endogenous and 13.7% were contact dermatitis. Exfoliative dermatitis comprised 0.5% of all eczemas. The authors commented on the increase in the proportion of endogenous eczema seen in 1989–90 compared with that reported in 1973.

The uncertainty and variation in the nomenclature of endogenous eczema makes interpretation of statistics tentative. Atopic eczema is reasonably well defined, and there have been several recent studies suggesting an increased prevalence of atopic dermatitis (see Chapter 18), but prevalence of other forms of eczema may be decreasing [8].

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Eczema and age

Certain patterns of eczema can be seen more commonly in particular age groups. Most cases of eczema in infants and young children are atopic. In the HANES epidemiological survey in the USA [1], atopic dermatitis was by far the most common form found up to the age of 11 years; discoid and 'dyshidrotic' eczema were recorded, but were far less frequent. Perioral eczema or lick eczema around the mouth is common in children with atopic eczema (see Chapter 18), but it can also occur in non-atopic children. Hand eczema is common in atopic children, but uncommon in non-atopic children. Other specific patterns of eczematous change are almost restricted to children; for example, lichen striatus (see p. 17.43), juvenile plantar dermatosis (see p. 17.33), seborrhoeic dermatitis of infancy and napkin dermatitis (see Chapter 14).

Pompholyx and atopic eczema are less common in elderly people, but other forms of eczema assume greater importance. Discoid eczema occurs particularly in elderly males in winter, and asteatotic eczema of the legs is also common. In elderly factory workers, irritant hand eczema can be very troublesome, although contact dermatitis becomes less common with advancing age. The subject is discussed more fully in Chapter 70.

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Histopathology [1–4]. The histopathological features of eczema reflect a dynamic sequence of changes resulting from inflammation of the epidermis and the underlying dermal structures. These vary with the intensity and stage of the eczematous process, and are frequently modified by secondary events such as trauma and infection.

Spongiosis is an intercellular epidermal oedema that leads to stretching and eventual rupture of the intercellular attachments, with the formation of vesicles. The epidermal vesicles commonly occur in discrete foci, but on the palms and soles they tend to become large by coalescence. There is variable infiltration of the epidermis by lymphocytes. Increased epidermal mitotic activity leads to acanthosis, but if spongiosis is intense, disintegration of the suprapapillary epidermis may cause clefts to form, exposing the underlying dermis.

In the subacute stage, spongiosis diminishes, and increasing acanthosis is associated with formation of a parakeratotic horny layer. This often contains layers of coagulated plasma and pyknotic nuclei of inflammatory cells. Later, the rete ridges become elongated and broadened, and hyperkeratosis replaces parakeratosis. The changes are then those of lichenification.

Vascular dilatation in the dermis is marked in all stages. The papillary vessels are particularly involved, and in lichenification they may become tortuous. The infiltrate is predominantly lymphohistiocytic, although polymorphs and eosinophils may be present in very acute eczema, and eosinophils are particularly common in eczematous drug eruptions. In the presence of infection, polymorphs may invade the epidermis. In grossly lichenified eczema, prurigo and exfoliative dermatitis, the infiltrate is mixed, and may be so dense that it simulates a granuloma.

Secondary changes. The trauma of rubbing or scratching may cause superficial erosions, haemorrhage or subepidermal fibrinoid changes. Although some degree of lichenification is always present during a prolonged attack of eczema, it is particularly prominent in atopic dermatitis. At times, extreme hyperkeratosis and papillomatosis develop.

With secondary infection, the formation of follicular or subcorneal pustules can simulate the appearance of impetigo, although typical eczematous changes are still visible at the edges of the lesion. Other modifications of the histopathological pattern are mentioned below in relation to different clinical varieties of eczema.

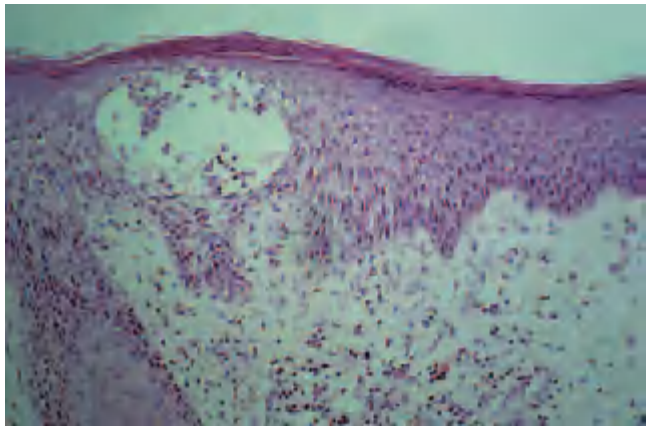
Differential diagnosis. Spongiosis and a dermal lymphohistiocytic infiltrate are always present at some stage in eczema, but the dynamic nature of the changes and their modification by secondary events may make histological diagnosis difficult. All the changes mentioned, with the exception of the spongiotic vesicle, may be found in burns or simple traumatic lesions of the skin.

The distinction between eczema and psoriasis can be especially difficult, particularly on the palms and soles. Seborrhoeic dermatitis (see p. 17.10) is particularly difficult to distinguish from psoriasis, but the finding of Munro's microabscesses is suggestive of the latter. It is generally true that cases that cause diagnostic difficulty clinically often have an equivocal histological appearance.

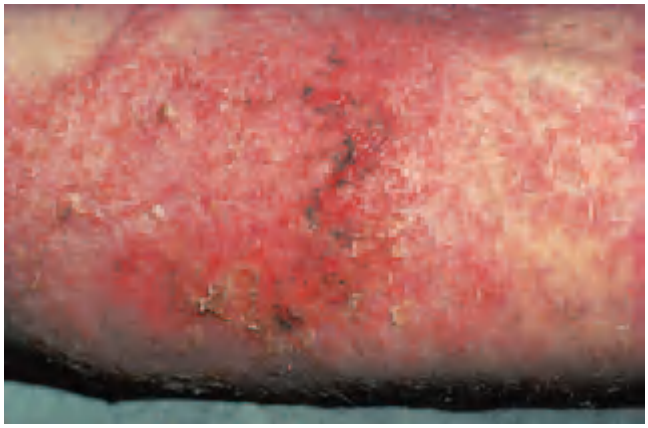
The histological features of pityriasis rosea are those of eczema, but the clinical features, particularly the distribution, are characteristic.

Changes in the various stages of eczema

1 *Acute* (Fig. 17.1). The histological picture is dominated by spongiosis and vesicle formation. The intercellular oedema may be diffuse, but more commonly occurs in discrete foci, and is most intense in the mid-epidermal region. Loosening and disruption of the individual Malpighian cells occur, and some intracellular vacuolation may be found, with displacement of the nucleus from the centre of the cell. Loose, shrunken epidermal cells may resemble histiocytes. Vesiculation occurs as a result of further fluid accumulation and detachment of cells. When



(a)



(b)

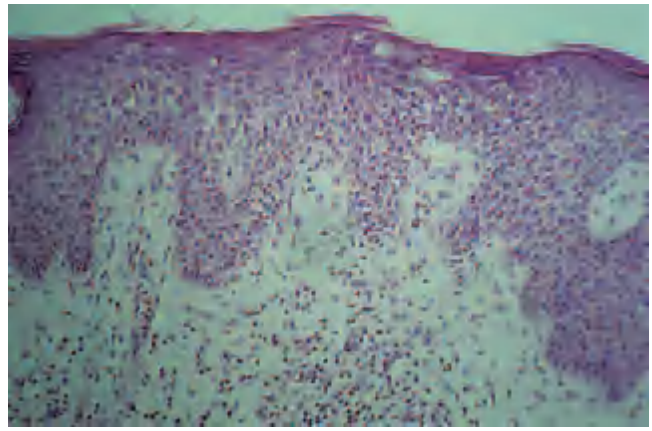
Fig. 17.1 (a) Acute vesicular eczema. The epidermis shows distinct vesicle formation. The vesicle contains serum, and a moderate number of inflammatory cells. H&E, × 100. (Courtesy of Dr M.G. Cook, Royal Surrey County Hospital, Guildford, Surrey, UK.) (b) Acute eczema of the arm, with redness, scaling and weeping.

this is intense, the appearances are those of reticular degeneration. The vesicles and the oedematous epidermis may be permeated by mononuclear cells, chiefly monocytes.

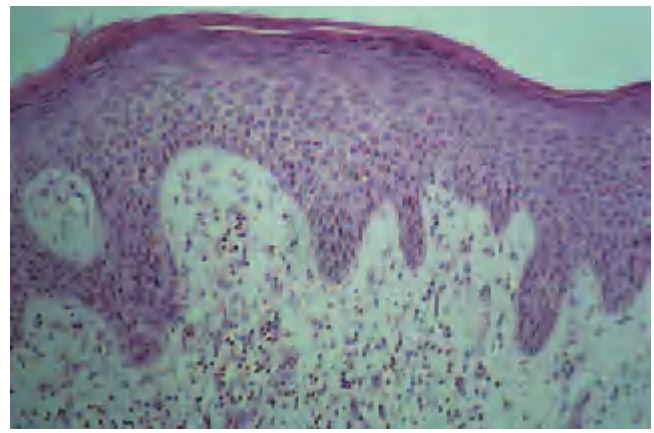
On the palms and soles, the resistance of the thick stratum corneum delays the rupture of the vesicles, which tend, in consequence, to become large and bullous by coalescence. In the weeping stage, thinning or destruction of the suprapapillary epidermis causes clefts, which may reach the underlying dermis.

2 *Subacute* (Fig. 17.2a). Spongiosis and vesiculation diminish and acanthosis increases. A parakeratotic stratum corneum forms, which contains coagulated plasma and the pyknotic nuclei of inflammatory cells. Later, the epidermal thickening becomes more marked, and the rete ridges more elongated and broadened. The appearances merge into those of lichenification.

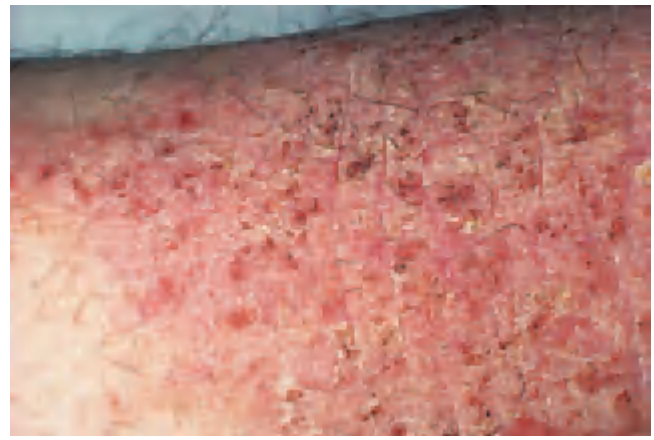
3 *Chronic* (Fig. 17.2b,c). Hyperkeratosis coexists with areas of parakeratosis. Spongiosis and vesiculation give rise to acanthosis. Cells no longer invade the epidermis, but dermal changes (see below) become more prominent.



(a)



(b)



(c)

Fig. 17.2 (a) Subacute eczema. There is irregular acanthosis and patchy spongiosis, with the formation of incipient microvesicles. A few lymphocytes are migrating up from the dermis into the epidermis. H&E, × 100. (Courtesy of Dr M.G. Cook, Guildford, Surrey, UK.) (b) Chronic lichenified eczema. There is compact hyperkeratosis, some patchy parakeratosis and irregular acanthosis. Mild spongiosis is seen throughout much of the epidermis, and there is a lymphocytic infiltrate in the upper dermis. H&E, × 100. (Courtesy of Dr M.G. Cook, Guildford, Surrey, UK.) (c) Chronic eczema of the arm.

4 *Recovery*. In uncomplicated eczema, where no secondary changes or fresh attacks occur, the changes gradually revert to normal. Infection, or the trauma of rubbing or scratching, obviously modify this process.

Pathogenesis. There has been considerable research on the pathogenesis of some types of eczema, particularly allergic contact dermatitis, primary irritant dermatitis and atopic dermatitis (see Chapter 18). A difficulty in the research has been distinguishing non-specific common pathways from specific mechanisms. The interaction of trigger factors, keratinocytes and T lymphocytes seems particularly important in most eczema types.

Allergic contact dermatitis represents a reproducible model of eczema development [5]. The condition is an immune reaction to small molecules (haptens). On first exposure to the hapten, Langerhans' cells and dermal dendritic cells bearing the antigen migrate to the regional lymph node and encounter naïve T cells. Interaction with the antigen-bearing dendritic cells causes T-lymphocyte differentiation into a variety of subtypes secreting different cytokine patterns (Th1 and Th2) and specialized $CD4^+$ T lymphocytes with regulatory functions to modulate allergic contact dermatitis. The T cells also acquire tissue-homing antigens such as cutaneous lymphocyte-associated antigen (CLA) along with receptors permitting adhesion to skin endothelium and response to cytokines promoting specific binding to keratinocytes.

On subsequent exposure to the contact allergen, $CD8^+$ T cells display a Th1 cytokine profile that is interferon-γ (IFN-γ) predominant. The hapten in the skin may be presented to the T cells by Langerhans' cells, keratinocytes or other T cells. T-cell activation ensues, with cytokine release and up-regulation of killer molecules such as perforin, granzyme-B and Fas ligand. IFN-γ promotes expression of major histocompatibility complex (MHC) class II, the intracellular adhesion molecule 1 (ICAM-1), and increases Fas expression on the keratinocytes. In addition, IFN-γ stimulates keratinocyte production of cytokines and chemokines that are responsible for the epidermal influx of lymphocytes. Chemokine release from infiltrating cells also modifies the reaction.

Epidermal damage and the characteristic feature of spongiosis seem to result from T-cell-mediated cytotoxicity, in particular Fas-induced keratinocyte apoptosis, which may be a final common pathway in many types of eczema [6].

Eczema may be provoked in a non-allergic manner, as in irritant contact dermatitis. The three predominant processes that occur in irritant dermatitis are disturbed barrier function, epidermal cell change, and release of inflammatory mediators and cytokines.

Certain irritants may provoke a chronic reaction in which an effect on epidermal cell turnover predominates, leading to lichenification, whereas in acute irritant reactions inflammatory mediator and cytokine release is similar to that seen in acute allergic contact dermatitis [7]. There is debate as to whether the cytokine profiles of the two reactions differ [7–9]. Indeed, it has been proposed that irritant reactions to haptens may be required to facilitate contact sensitization [10].

Following activation of the immune pathway by cytokine release, the accumulation of inflammatory cells progresses, leading to the morphological changes apparent histologically and clinically. In allergic contact dermatitis, the earliest changes seen by light microscopy occur some 3–6 h after the application of the allergen to the skin. Vasodilatation occurs, with extravasation of monocytes into the upper dermis [1]. After 8 h, the mononuclear cells enter the epidermis and spongiosis is seen, and by 72 h vesicles are present. The histological changes of primary irritant dermatitis are similar, but they appear to proceed more quickly, depending on the concentration of the irritant used. Both intracellular and intercellular oedema are visible throughout the epidermis at 3–6 h, and within 24 h there may be epidermal necrosis, with cellular vacuolation and nuclear pyknosis. In severe forms, the primary epidermal damage may progress to subepidermal blister formation.

Electron microscopy has shown that the earliest epidermal changes in allergic dermatitis start in the basal and Malpighian layers, where cytoplasmic vacuoles and dilated endoplasmic reticulum are seen. The keratinocytes then lose contact by breakage of their microvilli and retraction of desmosomes [11,12].

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Secondary dissemination

A very characteristic feature of eczema is its tendency to spread far from its point of origin [1]. This is especially likely when the primary site of the eczema is on the legs or the feet. The eczema may have been present for only a few days, or for many years, before dissemination occurs. The dissemination, which is often preceded by an exacerbation at the primary site, usually occurs explosively. The secondary eruption may at first consist of small oedematous papules, but these soon become obviously eczematous, and grouped papulovesicles may become confluent in small plaques. Occasionally, the lesions take the form of red macules, or weals. The distribution is usually symmetrical.

The course of the secondary eruption depends largely on the progress of the primary lesion. If the primary lesion remains acutely inflamed, the eruption increases in severity and may become generalized. If the patient is rested and the local lesion allowed to settle, the secondary eruption will subside, but will often recur very readily if the local lesion relapses. In a small proportion of patients, the generalized secondary eruption evolves into an erythroderma, which may become self-perpetuating.

Mechanisms of dissemination

There are four main mechanisms:
1 Spread by contact with an external allergen
2 Spread by ingestion or injection of an allergen
3 'Conditioned hyperirritability'
4 Bacterial hypersensitivity.

External contact

In many cases the extension is merely the result of continued contact of new areas of the skin with a specific external allergen. With increasing degrees of allergic sensitivity, minimal contact may provoke an eczematous response. The pattern of extension in such cases is asymmetrical and its progress is irregular. For example, a contact dermatitis of the lower leg induced by lanolin sensitivity may spread to the hand applying the offending ointment, whence, as a result of casual contact, it may appear on the face.

In chronic venous eczema of the lower leg without secondary dissemination, allergy to one or more topical medicaments can be demonstrated by patch testing in approximately 50% of cases. In chronic venous eczema with dissemination, however, positive patch tests to medicaments are demonstrated in over 90% of cases. It has been suggested that dissemination follows the percutaneous absorption of the medicament in such highly sensitized individuals.

Ingestion or injection

In other cases, an eruption originally induced by sensitivity to a topical allergen may relapse after ingestion or injection of the same chemical (e.g. a medication that can be used topically or systemically). The eruption tends to be widespread and more or less symmetrical, and is usually of sudden onset. Previously affected sites may be preferentially affected, and traumatized sites may also be involved. The diagnosis may be suspected in a widespread recurrent eczema that does not conform to the recognized pattern of endogenous eczema, yet cannot be related to external contact or to dissemination from a primary focus.

'Conditioned hyperirritability'

This term refers to the phenomenon whereby an area of inflamed skin on one part of the body results in a generalized hyperirritability of the skin at sites that are distant from the primary site of inflammation. There is considerable evidence that eczematous patients are more vulnerable to mild primary irritants than normal people, but the increased reactivity does not persist after the eczema subsides.

Conditioned hyperirritability seems to be associated with any focal inflammation of the skin, and it may explain some clinical phenomena such as the 'angry back' syndrome, in which a strongly positive patch-test response can increase the percentage of false-positive reactions on the back at the same time.

In the past, some clinicians have used the term 'autosensitization', for secondary dissemination of eczema when the cause of the dissemination is unknown [2]. Although it has long been suspected that autoallergy has a role in this dissemination, autoantibodies have been demonstrated convincingly in only a few cases [3]. Roper and Jones [4] reviewed the evidence, and concluded that autoantibodies are unlikely to play a significant part in the production of conditioned hyperirritability.

Circulating activated T lymphocytes are increased in number in autosensitization [5,6]. In addition, peripheral blood mononuclear cells show increased proliferation in the presence of an autologous skin homogenate compared with control subjects. This suggests that an abnormal cell-mediated immune response against autologous skin antigens could be occurring [7,8]. The role of cytokines in this phenomenon has yet to be elucidated, and the possibility of a non-immune process such as a neurological mechanism has not been completely excluded.

Bacterial hypersensitivity

Heavily infected eczema will sometimes disseminate in the absence of demonstrable allergic sensitivity to topical

medicaments. It is probable that allergy to bacteria or their products is sometimes a factor in the dissemination. The evaluation of patch tests or prick tests with bacterial filtrates is difficult, however, as some normal subjects and many with chronic localized eczemas give strongly positive reactions.

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Clinical features. Most of the exogenous types of eczema are discussed elsewhere (see Table 17.1). In view of the degree of overlap between infective eczema (generally regarded as exogenous) and seborrhoeic dermatitis (generally regarded as endogenous), infective eczema is discussed below with other types of endogenous eczema. Eczematous drug eruptions are also mentioned here, as there is an endogenous component, even though the drug is exogenous in origin. The most important example of endogenous eczema is atopic dermatitis. This is dealt with fully in Chapter 18. Other examples of endogenous eczema are discussed below.

Infective dermatitis

SYN. MICROBIAL ECZEMA

Definition. Infective eczema (Fig. 17.3) is eczema that is caused by microorganisms or their products, and which clears when the organisms are eradicated. This should be distinguished from infected eczema (Fig. 17.4) in which eczema resulting from some other cause is complicated by secondary bacterial or viral invasion of the broken skin. In practice, however, the two conditions can coexist, and the distinction can be difficult. Moreover, the bacterial flora of an eczematous lesion differs quantitatively from that of normal skin [1], and the demonstration that organisms are present does not establish that they are modifying the lesion. The distinction between colonization and infection can be very difficult, but the presence of an increased level of C-reactive protein in the blood may offer a useful clue [2].

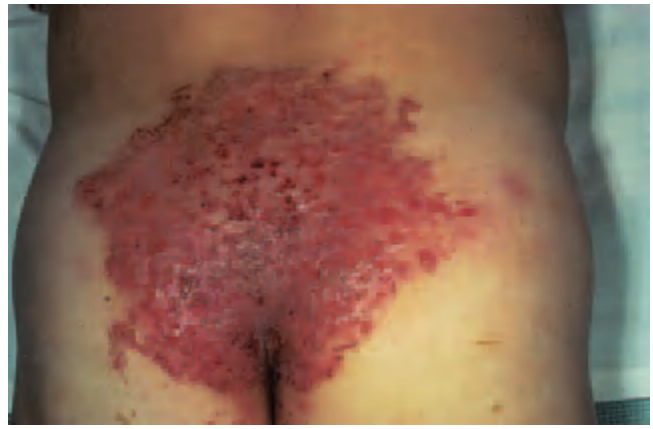

Fig. 17.3 Infective eczema in a non-atopic man. Histology of this localized rash showed eczema, and *Staphylococcus aureus* was repeatedly isolated. There was no response to topical steroid therapy, but the condition cleared rapidly with oral flucloxacillin.

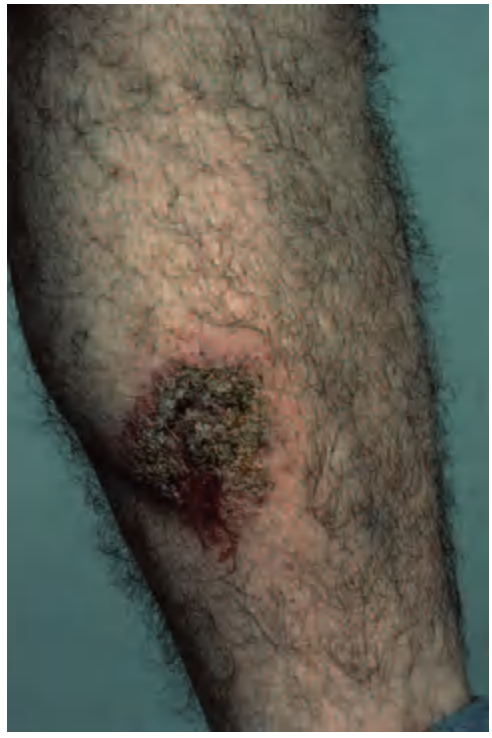

Fig. 17.4 Infected dermatitis. This man had a patch of discoid eczema that became secondarily infected with *Staphylococcus aureus*.

Infective dermatitis therefore is a controversial entity, and some dermatologists never make this diagnosis. Nevertheless, cases are seen occasionally in which bacterial or viral invasion of the skin seems to occur as the primary event, and is followed by secondary eczematization which can spread for some centimetres beyond the obvious infection. The patches of eczema that occasionally develop around lesions of molluscum contagiosum provide a good example (Fig. 17.5), because the pearly papules are

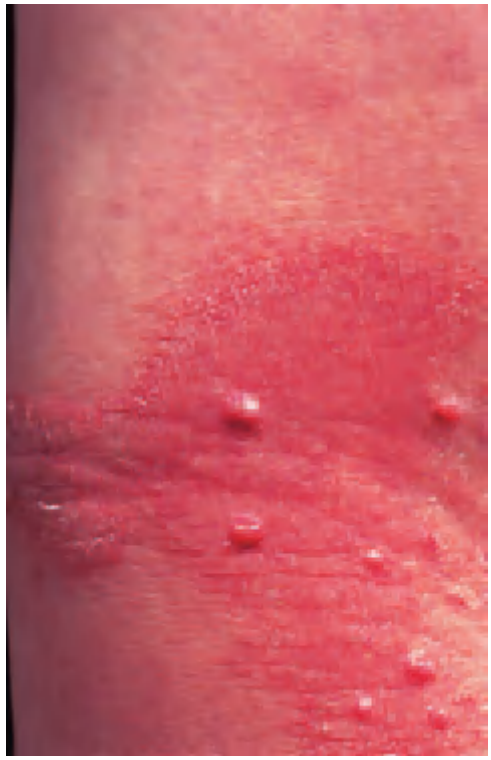

Fig. 17.5 An area of eczematization developing around lesions of molluscum contagiosum. The skin had previously appeared normal, and it returned to normal when the molluscum infection cleared. (Courtesy of Dr D.A. Burns, Leicester Royal Infirmary, Leicester, UK.)

the initiating event, and eczema can develop in the surrounding skin some days later, even when the lesions have not been scratched or traumatized. The eczema generally clears when the molluscum lesions subside. Similarly, one occasionally sees eczematous skin around infected wounds, and the eczema clears with antibiotic treatment alone.

Some experts would include seborrhoeic dermatitis as a form of infective dermatitis, on the grounds that the levels of *Malassezia* yeasts in the skin are increased, and the eczema may clear following anti-yeast therapy. However, the exact role of these yeasts in the pathogenesis of seborrhoeic dermatitis is still uncertain, and some authorities do not accept seborrhoeic dermatitis as infective.

Pityriasis rosea is not usually considered to be a form of eczema, although the histology may show spongiosis (see Chapter 25).

Pathology. The histological picture of infective eczema is in general that of subacute or chronic eczema, in which spongiosis is combined with acanthosis, hyperkeratosis and patchy parakeratosis. The dermis shows inflammatory changes, with polymorphonuclear and lymphocytic infiltration that invades the epidermis to a variable extent. In some stages, subcorneal pustulation may be conspicuous.

Pathogenesis. The mechanism by which microorganisms cause eczema is not understood. Bacterial antigens can promote a cytotoxic reaction in the skin, but such a reaction is perhaps more likely to aggravate or perpetuate than to initiate the eczematous process [3–6]. Bacterial superantigens such as staphylococcal protein A and enterotoxin B [7] may be profound immune stimulants and may aggravate atopic dermatitis (see Chapter 18). Bacterial antigens may play this part in a variety of syndromes, including discoid eczema, and not merely in infective dermatitis. Cultured staphylococci applied topically can also provoke an eczematous delayed hypersensitivity reaction [7,8].

The possibility that bacterial antigens from systemic foci of infection can cause eczema has not been fully established. It does seem to be accepted, however, that eczematous reactions can occur as an allergic reaction to a fungal infection elsewhere in the skin (see p. 17.9).

Clinical features. The distinction between infective and infected eczema can be difficult.

Infected eczema. Infected eczema shows erythema, exudation and crusting. The exudation may be profuse with crusting, or slight, with the accumulation of layers of somewhat greasy, moist scale, beneath which the surface is raw and red. The margin is characteristically sharply defined, and the horny layer often splits to form an encircling collarette. There may be small pustules in the advancing edge and, where a flexure is involved, it is often the site of a deep and persistent fissure.

Infective eczema. Infective eczema usually presents as an area of advancing erythema, sometimes with microvesicles. It is seen predominantly around discharging wounds or ulcers, or moist skin lesions of other types. Infective dermatitis is relatively common in patients with venous leg ulcers, but care must be taken to distinguish it from contact dermatitis caused by the application of topical medicaments.

Microbial eczema of the feet. This is a distinctive pattern of eczema that mainly affects the interdigital spaces on the dorsum of the medial toes. Staphylococci or streptococci can be cultured, and the lesions respond to antiseptic or antibiotic therapy [9]. This condition seems to occur particularly in patients with poor standards of hygiene, and it is favoured by hyperhidrosis and heavy footwear. In children, the condition must be distinguished from juvenile plantar dermatosis.

Tinea pedis. This may also become eczematous because of the overgrowth of Gram-negative organisms [10]. Infective dermatitis may also complicate chronic threadworm infestation, pediculosis or scabies. It is not always clear how much of the eczematous change is caused by repeated

scratching, how much is caused by secondary impetigo and how much, if any, is a direct response to the infestation.

Treatment. Factors predisposing to infection should be sought, and when possible eliminated. Although topical antibacterial agents are effective in mild forms of infective eczema resulting from bacteria, systemic antibiotics should not be withheld, especially in severe or widespread infections. In acute exudative lesions, potassium permanganate soaks are helpful for the first 2 or 3 days, in combination with a systemic antibiotic.

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Infective dermatitis of children associated with human T-cell leukaemia virus 1 (HTLV-1) infection

SYN. INFECTIVE DERMATITIS OF JAMAICAN CHILDREN

Sweet, in 1966 [1], used the term infective dermatitis to describe a pattern of dermatitis observed in Jamaican children. Subsequently, Walshe [2] documented the clinical features in 25 Jamaican children. They included severe exudative eczema with crusting involving the scalp, eyelid margins, perinasal skin, retro-auricular areas, axillae and groins. There was a generalized fine papular rash, a chronic nasal discharge, and positive cultures for *Staphylococcus aureus* or β-haemolytic streptococci from nose and/or skin. The rash responded to oral antibiotic therapy, but relapsed on its cessation.

LaGrenade *et al*. [3], in 1990, found HTLV-1 infection in all of 14 children with this pattern of dermatitis. A later case report identified one of the children originally described by Sweet and Walshe who, 17 years later, had developed adult T-cell leukaemia [4]. Some of these children may also go on to develop tropical spastic paraparesis [5]. This pattern of dermatitis may be an important early marker of HTLV-1 infection [6].

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Dermatophytide

Eczematous reactions can occur as an allergic response to a dermatophyte infection elsewhere on the skin (a dermatophytide) [1–3]. The following criteria must be fulfilled to confirm this diagnosis:

1 A proven focus of dermatophyte infection
2 A positive skin test to a group-specific trichophytin antigen
3 Absence of fungi in the dermatophytide lesions
4 Clearing of the dermatophytide after the fungus has been eradicated.

A dermatophytide is thus a secondary distant aseptic skin lesion, analogous to the cutaneous tuberculide of tuberculosis [1].

One study indicated that this condition is rare, as only 10 cases were confirmed in 1500 dermatophyte infections [2]. Other studies have suggested that dermatophytide may be more common. In one retrospective review of dermatophytide, 37 cases were seen in a dermatology department in a 2-year period. However, the patients were not skin tested to dermatophyte antigen [4].

Various clinical patterns of dermatophytide can occur. Eczematous vesicles on the hands or feet are the most common pattern. On the hands, the lesions occur symmetrically on the sides of the fingers, usually as a reaction to tinea pedis. An eczematous dermatophytide can also mimic pityriasis rosea [1].

Other dermatophytides have been described, often as single-case reports, including erysipelas-like dermatitis, erythema nodosum, erythema annulare centrifugum, urticaria and erythroderma.

A dermatophytide is probably more likely to develop with inflammatory dermatophytes, such as *Trichophyton mentagrophytes* of the zoophilic type [2].

A similar allergic reaction to a yeast infection may be termed a candidide (levuride). In this case the eczematous reaction may be localized to the hands or groin [1].

A dermatophytide can be mimicked by bacterial infection. In one study, *Staphylococcus aureus* and β-haemolytic streptococci were commonly isolated from lesions that were clinically thought to be examples of a dermatophytide [2].

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Post-traumatic eczema

There have been several case reports of dermatitis occurring in the saphenous vein graft donor site for coronary artery bypass surgery [1,2]. The rash is composed of reddish brown, slightly crusted and scaly patches, with occasional papulovesicles. Histology shows subacute spongiotic dermatitis. The condition responds to topical corticosteroids, but tends to relapse when the treatment is stopped.

Initially, postoperative venous stasis was suggested as the cause. Subsequently, two cases have been reported associated with sensory neuropathy in the distribution of the saphenous nerve [3]. The dermatitis was located in the same area. Otherwise, the cases were identical to those previously reported. The dermatitis and the sensory neuropathy resolved in tandem over a 2-year period.

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Seborrhoeic dermatitis

SYN. PITYROSPORAL DERMATITIS; DERMATITIS OF THE SEBACEOUS AREAS

Definition. This is a chronic dermatitis that is difficult to define exactly, but it has a distinctive morphology (red, sharply marginated lesions covered with greasy-looking scales) and a distinctive distribution in areas with a rich supply of sebaceous glands, namely the scalp, face and upper trunk. In some cases the flexures are also involved, but this is not an essential diagnostic criterion.

Dandruff (visible desquamation from the scalp surface) appears to be the precursor of seborrhoeic dermatitis, and this may gradually progress through redness, irritation and increasing scaling of the scalp to true seborrhoeic dermatitis.

Incidence. The prevalence of seborrhoeic dermatitis is approximately 1–3% in the general population of the USA, and 3–5% in young adults, although mild degrees of dandruff are much more common [1]. The figure is much higher, however, in patients with early human immunodeficiency virus (HIV) infection. Of 155 patients in the WR1A–2A stage of infection (with normal helper T-cell count and delayed hypersensitivity), 36% had seborrhoeic dermatitis [2].

Aetiology [3,4]. Yeast of the genus *Malassezia* is increased in the scaly epidermis of dandruff and seborrhoeic dermatitis [5,6]. Although it has been suggested that this is secondary to the increase in size of the habitat provided by the scaling [7], it is generally accepted that the presence of yeast of the genus *Malassezia* causes the condition [3,4,8].

The way in which *Malassezia* spp. induce inflammation and desquamation is not clear. Although patients with dandruff have high antibody titres to *Malassezia* compared with control subjects, and patients with seborrhoeic dermatitis have altered cell-mediated responses, the immunological reaction is variable [8–10]. Some of the histological features of seborrhoeic dermatitis can be reproduced by inoculating animal skin with killed yeasts [11], and the wide variety of cytokines expressed in the inflammation are similar to those in other yeast infections [12]. However, the principal evidence of a role for *Malassezia* spp. is the response of the condition to treatments that reduce the yeast numbers [4].

The sebaceous glands are active at birth, but when stimulation by maternal androgen ceases they become inactive for 9–12 years. This observation has been regarded as significant in relation to the age incidence of seborrhoeic dermatitis. The condition known as seborrhoeic dermatitis of infancy (see Chapter 14) is normally confined to the first months of life, but it is not established that it is the same condition as seborrhoeic dermatitis of adolescence and adult life. The latter is rare before puberty, and reaches its peak between 18 and 40 years of age; occasional cases are seen in old age. At all ages, seborrhoeic dermatitis is more common in males than in females.

Although maturation of the sebaceous glands may be a permissive factor for the development of seborrhoeic dermatitis, the role of seborrhoea in the pathogenesis of the condition is debatable. Many young adults with the condition appear to have a greasy skin, but when the sebum excretion rate from forehead skin was measured in patients with classical seborrhoeic dermatitis, it was normal in males and significantly reduced in females [13]. On the basis of this finding, it was suggested that 'dermatitis of the sebaceous areas' might be a more accurate term than 'seborrhoeic dermatitis'. Some clinicians believe that there is an increased prevalence of seborrhoeic dermatitis among patients with acne vulgaris and rosacea, but there are no data to support this.

Seborrhoeic dermatitis may also be a complication of parkinsonism, which is associated with seborrhoea. Treatment of parkinsonism with levodopa reduced sebum excretion when seborrhoea was initially present, but had no effect on the normal sebum excretion rate [14]. Treatment of parkinsonism with levodopa can also sometimes improve seborrhoeic dermatitis in these patients [15]. Seborrhoeic dermatitis has also been reported in a patient in whom unilateral seborrhoea and seborrhoeic dermatitis developed on the face after facial nerve paralysis [16], and also in patients with paralysis of the trunk [17]. The increase in the pool of sebum in immobile skin may be important in these cases, and in parkinsonism [18].

Qualitative abnormalities in the composition of sebum have not been demonstrated. Mild abnormalities in the surface lipids [19,20] could well result from the ineffective keratinization that is often demonstrable histologically.

The heightened susceptibility of the seborrhoeic skin to bacterial infection and to physical and chemical injury results in a high incidence of contact dermatitis and skin infection. Some authors confuse exogenous dermatitis in a seborrhoeic subject with the morphologically distinctive seborrhoeic dermatitis.

Seborrhoeic dermatitis is now established as a possible marker of early HIV infection [2,21], and exacerbations may be seen with progression of the HIV infection, presumably caused by the enhanced growth of yeasts secondary to immunosuppression [22]. It is also suggested that local cutaneous immunosuppression may increase the prevalence of seborrhoeic dermatitis [23].

It has also been claimed that seborrhoeic dermatitis is more common in a variety of general medical disorders, including myocardial ischaemia [24], malabsorption, epilepsy, obesity and alcoholism, especially alcoholic pancreatitis [25]. However, the evidence is far from convincing, and poor hygiene associated with hospitalization and severe illness may play a part in some of these cases.

Seborrhoeic dermatitis involving the usual sites on the face was observed to occur in 28 of 402 patients undergoing psoralen and UVA (PUVA) therapy for psoriasis, but not in 55 patients being treated with PUVA for other conditions [26]. Spongiosis was present in the three patients biopsied.

Pathology. The histology is not diagnostic, but generally shows features of both psoriasis and chronic dermatitis. Much of the stratum corneum is often lost in the process of fixation, and most of its cells are parakeratotic. There is slight to moderate acanthosis, with slight spongiosis. Spongiosis is the major feature which distinguishes it from psoriasis. The dermis shows a mild chronic inflammatory infiltrate.

It seems likely that the initial event is the 'squirting papilla' described by Pinkus and Mehregan [27]. Capillary dilatation in the papillae is followed by migration of inflammatory cells through the vessel walls and into the epidermis, where they incite spongiosis. This is similar to the burst of inflammation that sometimes occurs in psoriasis.

As the inflammation subsides there is an increase in production of keratinocytes. Epidermal proliferation, as measured by the mitotic and labelling indices, is increased, and desquamation is increased [28].

Ultrastructural studies show a closer resemblance to discoid eczema than to allergic or irritant contact dermatitis.

The histology of seborrhoeic dermatitis in patients with acquired immune deficiency syndrome (AIDS) tends to show more follicular involvement, and more plasma cells. Neutrophils and nuclear dust may be present focally among the epidermal parakeratotic cells [21]. *Malassezia* yeasts are prominent in the skin of AIDS patients with seborrhoeic dermatitis compared with seborrhoeic dermatitis patients without AIDS [29].

Table 17.3 Clinical patterns of seborrhoeic dermatitis.

Infantile (Chapter 14)
Scalp (cradle cap)
Trunk (including flexures and napkin area)
Leiner's disease
Non-familial
Familial C5 dysfunction
Adult
Scalp
Dandruff
Inflammatory—may extend onto non-hairy areas (e.g. postauricular)
Face (may include blepharitis and conjunctivitis)
Trunk
Petaloid
Pityriasiform
Flexural
Eczematous plaques
Follicular
Generalized (may be erythroderma)

Clinical features. Most forms of seborrhoeic dermatitis share certain distinctive characteristics. They commonly originate in hairy skin, and involve the scalp, face, presternal and interscapular regions, and the flexures. The lesions tend to be dull or yellowish red in colour and covered with greasy scales.

Morphological variants. There are several morphological variants of seborrhoeic dermatitis, which in the adult form occur in various combinations and degrees of severity (Table 17.3).

Scalp. Dandruff is usually the earliest manifestation of seborrhoeic dermatitis. At a later stage, perifollicular redness and scaling gradually extend to form sharply

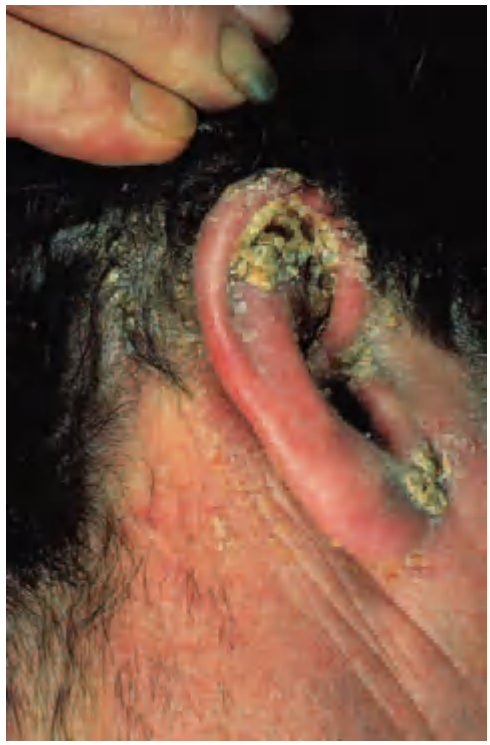


Fig. 17.6 This type of seborrhoeic dermatitis around the ears readily develops secondary bacterial infection.

marginated patches that may remain discrete, or coalesce to involve the greater part of the scalp and extend beyond the frontal hairline as the 'corona seborrhoeica'.

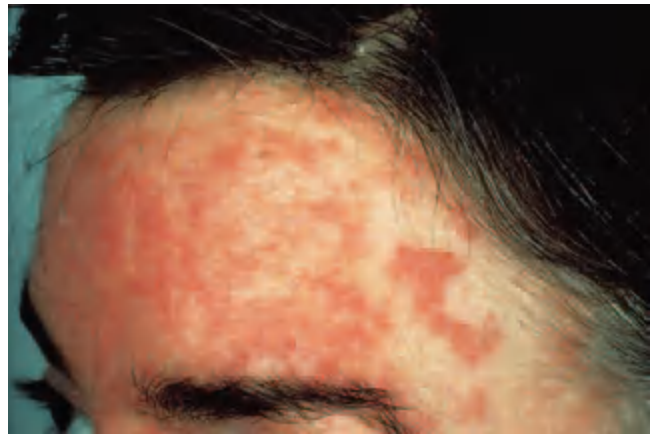
In chronic cases there may be some degree of hair loss, which is reversible when the inflammation is suppressed. It has not been established whether seborrhoeic dermatitis of the scalp accelerates the onset of male-pattern (androgenic) alopecia.

Behind the ears there may be redness and greasy scaling, and a crusted fissure often develops in the fold (Fig. 17.6). Adherent masses of sticky scale and crusts may extend into the adjacent scalp. Both sides of the pinna, the periauricular region and the sides of the neck may be involved. Otitis externa, irritable and intractable, may accompany seborrhoeic dermatitis in other sites, or may occur alone.

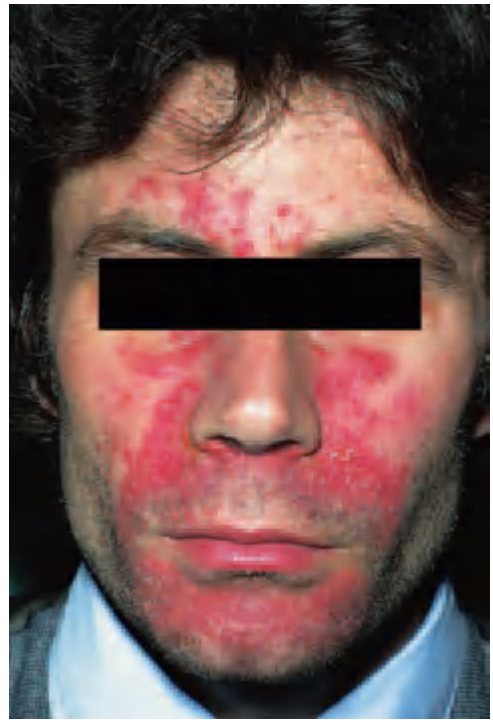
Face. On the face, seborrhoeic dermatitis characteristically involves the medial part of the eyebrows, the glabella and the nasolabial folds (Fig. 17.7). Areas of erythema and scaling occur, usually in association with involvement of the scalp.

Blepharitis is common. The margins of the lids are red and covered by small white scales. Yellow crusts may form, and separate to leave small ulcers, healing to form scars, with destruction of lash follicles.

Episodic variation in intensity is common, often being precipitated by tiredness or stress. Exposure to sunlight



(a)



(b)

Fig. 17.7 (a) Seborrhoeic dermatitis of the forehead. (b) Severe seborrhoeic dermatitis of the face with prominent involvement of the nasolabial groove.

produces a temporary exacerbation, followed by improvement as the tan develops.

A superficial form of seborrhoeic dermatitis of the chin is common in men in the early stages of growing a beard, but is cured when the beard is shaved off.

Young women sometimes have paranasal erythema associated with a tendency to flushing. It is not always clear whether this is rosacea or mild seborrhoeic dermatitis, but overtreatment with strong topical corticosteroids may convert this into perioral dermatitis.

Trunk. On the trunk, several forms of seborrhoeic dermatitis occur. Most common is the petaloid form (so-called

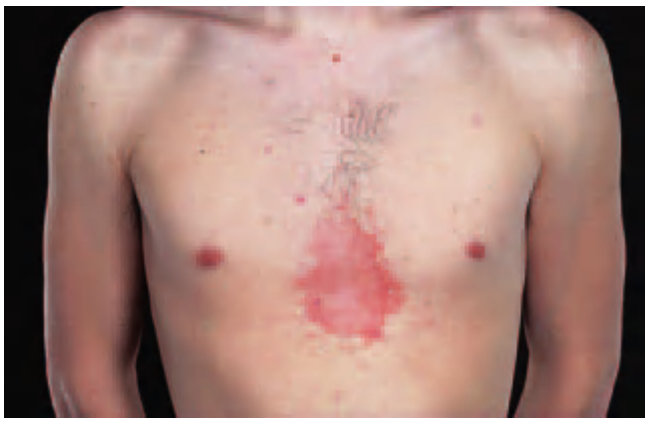


Fig. 17.8 Seborrhoeic dermatitis of the presternal region. (Courtesy of Dr D.A. Burns, Leicester Royal Infirmary, Leicester, UK.)

because the lesions are petal-shaped). This is often seen in men on the front of the chest and in the interscapular region (Fig. 17.8). The initial lesion is a small red-brown follicular papule, covered by a greasy scale. Some patients have a widespread eruption of lesions that do not progress beyond this stage. More often, extension and confluence of the follicular papules gives rise to a figured eruption, consisting of multiple circinate patches, with a fine branny scaling in their centres, and with dark-red papules with larger greasy scales at their margin.

A rarer form, involving the trunk and limbs, is the so-called pityriasiform type. This is a generalized erythematosquamous eruption, somewhat similar to, but more extensive than, pityriasis rosea. In particular it involves the neck up to the hair margin. It is not particularly pruritic, and it resolves spontaneously, although somewhat more slowly than does pityriasis rosea. In some patients the lesions may become psoriasiform.

Flexures. In the flexures, notably in the axillae (Fig. 17.9), the groins, the anogenital and submammary regions, and the umbilicus, seborrhoeic dermatitis presents as an intertrigo, with diffuse, sharply marginated erythema and greasy scaling. Crusted fissures develop in the folds, and with sweating, secondary infection and inappropriate treatment, a weeping dermatitis may extend far beyond them. The genitalia of both sexes may be involved, and the lesions show the usual range from minimal erythema and scaling to severe crusted dermatitis. In this site, and occasionally elsewhere, the chronic, thickened, dull-red scaly patches of the psoriasiform variety of seborrhoeic dermatitis may develop.

The severity and course of seborrhoeic eruptions are very variable. All show a tendency to chronicity and recurrence.

Severe and extensive forms may be complicated by eczematous reactions remote from the sites initially involved, especially by pompholyx and discoid eczema.

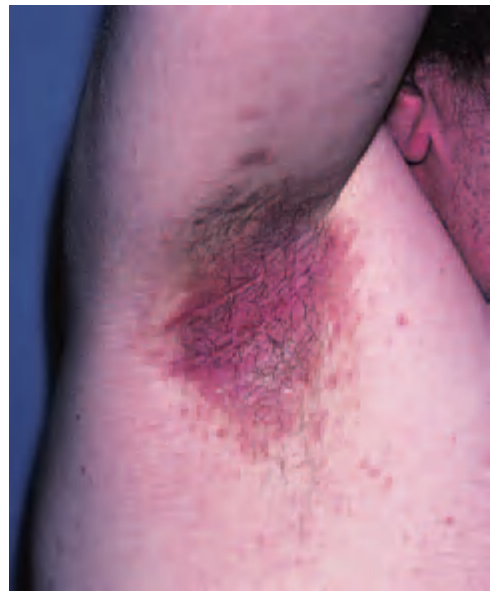


Fig. 17.9 Seborrhoeic dermatitis of the axilla; flexural areas often become secondarily infected. (Courtesy of Dr A. Marsden, St George's Hospital, London, UK.)

Such eruptions are discussed separately below. The pattern and course of the disease may also be modified by contact dermatitis and provoked by medicaments, by pyoderma or by an infective bacterial dermatitis. Occasionally, seborrhoeic dermatitis may become generalized, resulting in erythroderma.

Modifications in the clinical features and course may be seen when seborrhoeic dermatitis occurs in association with atopy, or with psoriasis, and in the latter case the diagnosis can be extremely difficult, because both the clinical and histological features can be equivocal. Some dermatologists use the term *sebopsoriasis* for this overlap condition.

Diagnosis (Fig. 17.10). In a classical case the diagnosis is easy, but in some cases the diagnosis can be difficult, partly because of the lack of well-defined diagnostic criteria. The diagnosis is often made too freely. Nowadays it is very important to consider the possibility of HIV infection in any patient with severe seborrhoeic dermatitis, particularly in a patient involved in high-risk activities.

The differential diagnosis covers an enormous range of conditions. Psoriasis, when confined to the scalp, may be confused with seborrhoeic dermatitis. The lesions are usually palpably thickened in psoriasis, and brighter pink in colour, with a silvery scale. The rest of the body must be examined, especially the nails, and there may be a family history of psoriasis.

Lichen simplex of the nape of the neck occurs in females, and can mimic seborrhoeic dermatitis. The thickened plaques in this condition are, however, intensely irritable.

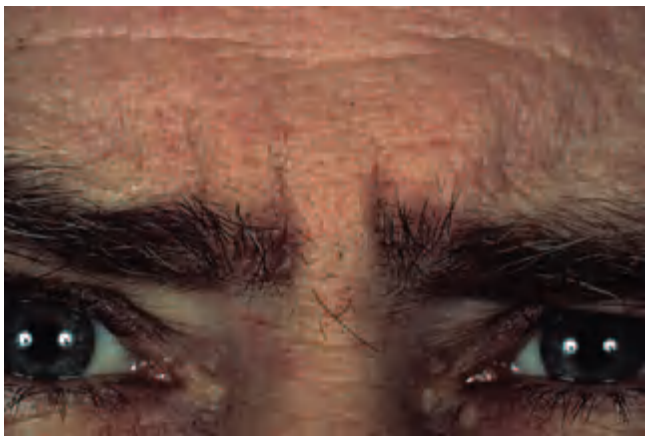


Fig. 17.10 Slight redness and scaling at the medial ends of the eyebrows may provide a diagnostic pointer to seborrhoeic dermatitis.

Infective dermatitis complicating pediculosis can also be confused with seborrhoeic dermatitis.

Contact allergy [30] and *Trichophyton tonsurans* infection [31] may mimic seborrhoeic dermatitis of the scalp.

Pityriasis rosea must be distinguished from the pityriasiform type of seborrhoeic dermatitis, in which the lesions are more widely distributed, and in which there is no herald patch. In the flexures, microscopic examination of scrapings from the advancing margin and examination under Wood's light will exclude ringworm infections, candidiasis and erythrasma. Acute flexural dermatitis may also suggest the possibility of allergic sensitization to a chemical in clothing, and patch tests may be needed. Moist crusting of the face or of the midline of the chest or back occurs in pemphigus erythematosus and in pemphigus foliaceus. Biopsy is required if these conditions are suspected. Axillary and sometimes interscapular crusting, tending to relapse in the warmer weather, occurs in benign familial pemphigus.

The brown scaly lesions of pityriasis versicolor are flatter, more extensive and less symmetrical than the lesions of petaloid seborrhoeic dermatitis of the trunk. Microscopy of scrapings quickly establishes the diagnosis.

Follicular seborrhoeic dermatitis of the trunk must be differentiated from Darier's disease, in which the papules are brown, greasy and dome-shaped, and tend to be clustered. Biopsy is diagnostic. Lesions resembling seborrhoeic dermatitis can occur in zinc deficiency and acrodermatitis enteropathica [32].

Drug eruptions, particularly those resulting from methyldopa, chlorpromazine or cimetidine may mimic seborrhoeic dermatitis.

Despite the non-specific nature of the histological appearances of seborrhoeic dermatitis, biopsy will often reliably differentiate it from many of the conditions with which it may be confused.

Treatment. It should be emphasized to the patient at the outset that, although seborrhoeic dermatitis can generally be suppressed, there is no permanent cure. The condition may require regular treatment for many years.

Dandruff is usually treated by the frequent and regular use of medicated shampoos which act against *Malassezia* yeasts, including selenium sulphide, ketoconazole [33] and various tar shampoos. One per cent terbinafine solution has also been shown to be effective [34]. Alcohol-based preparations and hair tonics should be avoided. For severe dandruff with persistent scaling or crusting, 5% salicyclic acid ointment may be useful. If secondary bacterial infection is present or suspected, oral erythromycin or flucloxacillin may be used.

Acute forms of seborrhoeic dermatitis on the face and trunk usually respond to mild steroid ointments. Hydrocortisone ointment (0.5%) is often effective, particularly if combined with sulphur (0.5%). Ketoconazole cream (2%) is possibly a more logical therapy, which has been shown to be equally effective [35–39]. In many situations, the acute inflammatory changes can be suppressed with mild topical corticosteroid creams or steroid and imidazole combination creams, which can then be changed to ketoconazole cream for long-term control. Topical metronidazole, ciclopiroxolamine and tacalcitol have also been reported to be helpful [40–42]. Frequent washing with soap and water is helpful, because removal of lipid removes the substrate for the yeasts.

For unresponsive cases, a course of UVB therapy may be helpful [43], or even a short course of oral ketoconazole (200 mg/day for 14 days). Oral itraconazole (100 mg/day for up to 21 days) is also effective, as is oral terbinafine [44]. Other topical preparations that have been shown to be effective include benzoyl peroxide [45] and 5% lithium succinate ointment [46].

Generalized seborrhoeic dermatitis usually responds to the medications listed above, but in recalcitrant cases systemic steroids may be required. Prednisolone 30 mg/day usually produces a rapid response. Isotretinoin may also be helpful [18].

Flexural seborrhoeic dermatitis is treated in the same way as intertrigo (see Chapter 68).

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Infantile seborrhoeic dermatitis

There is still some debate as to whether this condition occurs as a separate entity, or is merely a variant of atopic dermatitis (see Chapter 14 for discussion).

Malassezia folliculitis

SYN. SEBORRHOEIC FOLLICULITIS; PITYROSPORAL FOLLICULITIS

Definition. Folliculitis caused by *Malassezia* yeasts (e.g. *Malassezia furfur*). Although not an eczema, *Malassezia* folliculitis is included here because of its association with seborrhoeic dermatitis.

Aetiology. *Malassezia* yeasts can hydrolyse triglycerides into free fatty acids, and it has been postulated that an overgrowth of the yeast in a follicle produces folliculitis by a combination of fatty acid production and blockage of the follicular ostium by scale [1,2]. The ability of the yeasts to activate the alternative complement pathway may also be implicated in the inflammatory process.

Pathology. There is folliculitis, with a perifollicular mononuclear infiltrate, predominantly around the infundibular region of the follicle. Sparse *Malassezia* yeasts can be identified in the affected follicles, but mycelial forms are usually absent. *Malassezia* yeasts can also be identified in skin scrapings.

Clinical features [3,4]. The condition most commonly affects adult males, and is associated with a tendency to seborrhoeic dermatitis or severe dandruff. It has been reported in 12 of 42 patients with Down's syndrome [5]. The rash is dimorphic, with erythematous follicular papules and follicular pustules. Lesions occur mainly on

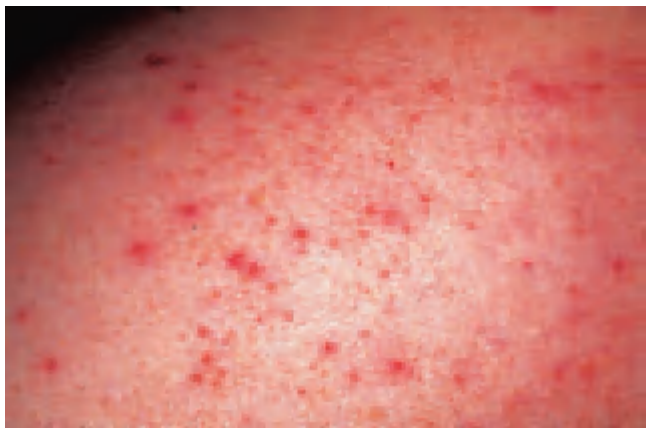

Fig. 17.11 *Malassezia* folliculitis. (Courtesy of Dr F.A. Ive, Dryburn Hospital, Durham, UK.)

the upper trunk and shoulders, and are usually pruritic (Fig. 17.11).

Differential diagnosis. Acne vulgaris may be distinguished by the presence of comedones, cysts and scars, which do not occur in *Malassezia* folliculitis. Similar lesions can occur in immunocompromised individuals such as those with AIDS and organ transplant recipients [6]. The condition should be considered in the differential diagnosis of steroid-induced folliculitis [7]. Transmission of the condition between individuals has been suggested [8].

Treatment. Patients should be advised to avoid occlusive clothing, and broad-spectrum antibiotic therapy should be stopped whenever possible. The condition responds well to 2% ketoconazole cream [9]. However, the eruption often relapses, and intermittent prophylactic treatment once or twice weekly may be indicated [10]. Systemic treatment with oral itraconazole may occasionally be helpful. In Down's syndrome patients the condition improved with oral itraconazole but relapsed when the medication was stopped [5].

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Asteatotic eczema

SYN. WINTER ECZEMA; ECZÉMA CRAQUELÉ

Definition. Eczema associated with a decrease in skin surface lipid. Senile eczema and asteatotic eczema are often regarded as synonymous, but it is not certain that all eczema without demonstrable cause, occurring in elderly people, is in fact of the asteatotic type.

Aetiology. Although the condition is thought to be caused by a decrease in skin surface lipid, the exact pathogenesis of the skin changes is obscure. The amino acid content of the skin is lower in the more severe cases [1]. A decrease in the keratohyaline-derived natural moisturizers may also be important [2].

Hyposteatosis occurs in many conditions of maldevelopment, malnutrition and atrophy of the skin, but does not necessarily lead to eczema. The part played by loss of fluid from the skin has been underrated in the past. The relationship between the transpiration rate and the lipid layer has been the subject of many studies [3]. Using excised skin it was shown that removal of lipid increased water loss 75-fold, and that this returned to normal when lipid was restored. The implications for treatment are obvious. At present the relevant factors in the production of asteatotic eczema can be considered to be a naturally 'dry' skin and a lifelong tendency to chapping; a further reduction in lipid with age, illness, malnutrition or hormonal decline; increased transpiration relative to the environmental water content; loss of integrity of the water reservoir of the horny layer; chapping and degreasing (and perhaps cell damage) by industrial or domestic cleansers or solvents; low environmental humidity and dry, cold winds increasing convection loss; or repeated minor trauma leading to inflammation and further disorganization of the surface aqueous–lipid balance. Percutaneous absorption through the degreased and damaged epidermis is increased, and contact irritants and sensitizers may further damage and irritate the skin.

A patient will often ascribe the onset to an event or change in life that is quite trivial, for example the installation of central heating or a particularly cold dry winter [4]. In industry, years of contact with degreasing agents may be tolerated until, usually in the 50–60 age group, some small additional hazard precipitates a disabling dermatitis.

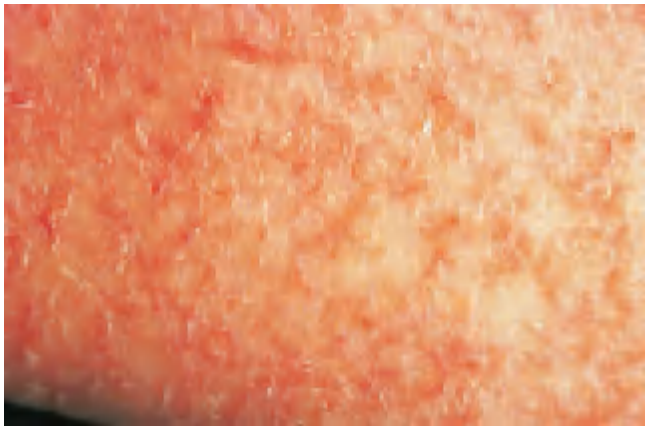

Fig. 17.12 Eczéma craquelé (winter eczema). (Courtesy of Dr W.A.D. Griffiths, St Thomas' Hospital, London, UK.)

Diuretics sometimes appear to be an important contributory factor in elderly people [5]. Asteatotic eczema may be a presenting sign of myxoedema [6]. It can also be caused by zinc deficiency [7]. Cimetidine has also been reported to cause asteatotic dermatitis [8], as have topical corticosteroids [9].

Histopathology. The features are those of a mild subacute eczema, with a varying amount of dermal infiltrate. When vesicular or nummular eczema supervenes, the changes are more marked, and are as seen in the latter disease.

Clinical features (Fig. 17.12). The condition occurs particularly on the legs, arms and hands. It tends to be more marked in the winter and in elderly people. The asteatotic skin is dry and slightly scaly. The surface of the backs of the hands is marked in a criss-cross fashion, as though the continuity and flexibility of the keratin had been disturbed. The finger pulps are dry and cracked, producing distorted prints and retaining a prolonged depression after pressure ('parchment pulps'). On the legs the pattern of superficial markings is more marked and deeper ('crazy-paving' pattern or eczéma craquelé). In some patients the fissures may become haemorrhagic. The borders of this irregular reticulation become erythematous and slightly raised, and frank eczematous changes finally develop. Similarly, on the hands, localized areas become 'chapped' or itchy, and eventually form eczematous patches.

The condition can remain in this state for months, relapsing each winter and clearing in the summer, but eventually becoming permanent. Scratching, rubbing or contact irritants and sensitizers cause further eczematous changes or spread; or a more diffuse vesiculosquamous eruption occurs.

Nummular eczema can also occur on this background, although the relationship between the two conditions is uncertain.

Irritation in this form of eczema is often intense, and worse with changes of temperature, particularly on undressing at night.

Treatment. The patient's immediate environment may need to be adjusted. Central heating should be humidified where possible, and abrupt temperature changes should be avoided. Wool is usually poorly tolerated and possibly damaging by irritation. Baths are best restricted and should not be hot. Bath oils or oatmeal packs are helpful. Emollients should be used after bathing or daily. Creams based on lanolin or mixtures of lanolin and paraffins are generally helpful.

Weak topical corticosteroids are often prescribed, and those contained in a urea base (see Chapter 75) are very appropriate in this situation as urea encourages hydration. Among the older remedies, ichthammol is of value.

This is one of the forms of eczema in which soaps and detergent cleansers can be seen by the physician and felt by the patient to be deleterious. Emulsifying Ointment BP (hydrophilic ointment) or oatmeal or bran can be substituted.

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Generalized eczéma craquelé

Extensive or generalized forms involving the trunk as well as the legs are rare but should raise the suspicion of malignancy. Cases have been reported in association with malignant lymphoma [1], angioimmunoblastic lymphadenopathy [2], anaplastic gastric adenocarcinoma [3] and spheroidal cell carcinoma of the breast [4].

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Discoid eczema

SYN. NUMMULAR ECZEMA

Definition. Discoid eczema is characterized by a single, non-specific morphological feature, namely circular or oval plaques of eczema with a clearly demarcated edge. It is to be distinguished from an irregular patchy form of eczema in which the lesions do not have recognizable clear margins. The condition is poorly defined, however, because many eczema patients have one or two circular or oval lesions and few patients with discoid eczema have only circular lesions [1,2].

Aetiology. In most cases the cause is unknown. Some authors have found a high incidence of atopy in their patients [3], but others have not [4], and the levels of IgE are within the normal range [5].

Many authors have stressed the role of infection [6,7]. As in other forms of eczema, heavy colonization of the lesions by staphylococci may increase their severity, even in the absence of clinical evidence of infection [6,7]. However, allergic sensitivity to staphylococci or micrococci may be responsible at least for secondary dissemination [8].

Local physical or chemical trauma plays a part in some cases, and discoid eczema sometimes develops at the site of an old injury or scar.

Specific allergy is uncommon, but may be overlooked in severe or persistent cases if patch tests are not performed [9].

Dry skin caused by low environmental humidity is sometimes associated with discoid eczema [2,10], particularly in the elderly [11]. An association between excessive alcohol intake and discoid eczema has been reported [12].

Discoid eczema has occurred rarely as a result of sensitivity to aloe [13], depilating creams [14], mercury [15] and in patients taking methyldopa [16] or gold [17].

Emotional stress may have a role in some cases, but it is unlikely to be the primary cause.

Discoid eczema is relatively rare in children [18].

Histopathology [19,20]. There is a subacute dermatitis indistinguishable from other forms of eczema, with spongiotic vesicles and a predominantly lymphohistiocytic infiltrate. Eosinophils may also be present in the upper dermis.

Electron microscopic studies have shown that the intense intercellular oedema leads to a reduction in the number of desmosomes between the cells of the basal layer, whereas those in the stratum spinosum are mostly preserved.

Clinical features. The diagnostic lesion of discoid eczema is a coin-shaped plaque of closely set, thin-walled vesicles on an erythematous base. This arises, quite rapidly, from the confluence of tiny papules and papulovesicles. These

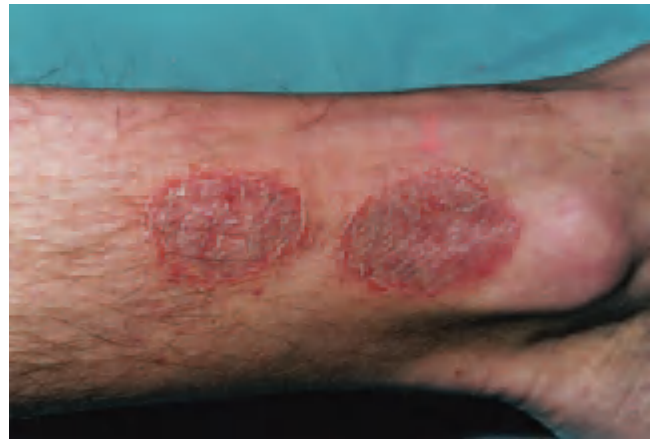

Fig. 17.13 Discoid eczema of the lower leg. (Courtesy of Dr W.A.D. Griffiths, Epsom Hospital, Surrey, UK.)

may occur, in the phase of very acute dissemination, as individual lesions on the trunk or limbs at the same time as localized plaques are being formed. In the acute phase the lesions are dull red, oozy, crusted and highly irritable (Fig. 17.13). They progress towards a less vesicular and more scaly stage, often with central clearing and peripheral extension, causing ring-shaped or annular lesions. As they fade, they leave dry scaly patches.

After any period between 10 days and several months, secondary lesions occur, often in a mirror-image configuration on the opposite side of the body. It is very characteristic of this disease that patches which have apparently become dormant may become active again, particularly if treatment is discontinued prematurely.

It may be convenient to recognize the following patterns:

1 Discoid eczema of the hands and forearms
2 Discoid eczema of the limbs and trunk
3 'Dry' discoid eczema.

Discoid eczema of the hands affects the dorsa of the hands or the backs or sides of individual fingers. It often develops as a single plaque, which may occur at the site of a burn or a local chemical or irritant reaction. Secondary lesions may occur on the hands, fingers or forearms, but generalized spread is uncommon. It is a not uncommon form of irritant occupational dermatitis, but may also occur in housewives or secretaries in whom the provoking factors are less clear. An atopic history appears to be more frequent in young women with discoid hand eczema than in other forms of the disease.

The more usual form of discoid eczema affects the limbs and trunk. It appears to be particularly prevalent among managerial or professional classes. It is also seen in elderly people, often with dry skin exacerbated by low humidity, central heating, car heating, etc.

The initial patch usually occurs on the lower leg, and secondary lesions spread to the other leg, the arms and often the trunk. In the course of their evolution, the lesions

Table 17.4 Diagnosis of some discoid lesions.

Disease	Distribution	Features	Histology	Course and evolution
Prelymphomatous eruption	Flank, trunk, proximal limbs	Angular, bizarre, infiltrated, itchy	Dermal primary	Persistent, may change to lymphoma
Chronic superficial dermatitis	Limbs more than trunk	Oval or round, no infiltration	Epidermal eczematous	Very chronic, benign, no fluctuations
Pityriasis alba	Face, proximal limbs	Depigmentation	Very mild eczema	Spontaneous remission after 1 or more years
Discoid (nummular) eczema	Limbs more than trunk	Oval or round, very itchy	Eczema, often intense changes	Variable, fluctuant or intermittent
Tinea corporis	Limbs or trunk	Oval or round, itchy Scraping produces scale for mycology	PAS stain shows fungus	Progresses and spreads steadily until treated

may become increasingly oedematous and crusted, possibly because of secondary infection. Extension then becomes rapid and, in severe cases, much of the trunk and limbs will be involved. Scattered papulovesicles may then be interspersed with large and small plaques.

All forms of discoid eczema are chronic, with partial remission during which plaques tend to clear in their centres. Most forms tend to relapse at long or short intervals, and most are worse during the colder months of the year. A review of 325 cases showed that most either cleared within a year or persisted for many years [21].

'Dry' discoid eczema is an uncommon variant, consisting of multiple dry, scaly, round or oval discs on the arms or legs, but also with scattered microvesicles on an erythematous base on the palms and soles [22]. Itching is minimal, in contrast with other forms of discoid eczema, and the condition persists for several years, with fluctuation or remission. It is notably resistant to treatment.

Diagnosis (Table 17.4). Discoid eczema may simulate ringworm, but even when the lesion of discoid eczema clears in the centre, the edge is broader, more vesicular and more vivid in colour than lesions caused by *Trichophyton* infection, where scaling of the edge is a more conspicuous feature. If there is any doubt, scrapings should be examined for the presence of mycelia.

Exogenous contact dermatitis should be suspected if the condition is unusually severe and persistent or if patches are few, asymmetrical or of unusual configuration. Irritants, and occasionally sensitizers, may provoke this discoid type of response; when the patient's occupation suggests this, patch tests should be carried out [9].

In psoriasis, the lesions are dry, the scaling is more prominent and the irritation milder.

The features of exudative discoid lichenoid dermatitis and chronic superficial scaly dermatitis are discussed below.

Treatment. Emollients and topical corticosteroids, perhaps with added clioquinol or antibiotic, are useful. In the early stages, a potent steroid may be needed, dilute forms often being relatively ineffective. Coal-tar pastes or ointments may be added in the less acute stages, and sometimes a combination of tar and dilute corticosteroids will be most effective for long-term management. Ambient conditions of low humidity should be corrected, and bath oils are soothing.

A course of a broad-spectrum systemic antibiotic such as oxytetracycline or erythromycin is often helpful in severe exudative cases. In severe cases, bed rest and removal from a stressful environment are advised, and oral steroids may occasionally be required.

General considerations such as the avoidance of irritants apply, as with other forms of eczema.

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Hand eczema

Hand eczema is such a common and distressing condition, and poses such difficult problems for the dermatologist, that it deserves separate consideration [1]. Up to 30% of occupational medical practice relates to hand eczema, with important issues regarding medical litigation, worker's compensation and disability. One-quarter of the patients referred to a specialized contact dermatitis clinic suffered from hand dermatitis [2].

Definition and nomenclature. The term hand eczema implies that the dermatitis is largely confined to the hands. If the eczema is widespread and the hands appear to be involved only coincidentally, it is preferable to speak of hand involvement.

Classification. No single classification of hand eczema is completely satisfactory. Although several different morphological forms exist as fairly consistent entities, some of these entities can have several different causes, and conversely a single cause can sometimes produce several different morphological patterns. This has led to considerable confusion in previous classifications.

An *aetiological classification* is shown in Table 17.5, and this may be useful to the clinician as a checklist in an individual case, although the list does not exhaust the aetiological possibilities. Other rare causes have been reported (e.g. gravitational eczema secondary to arteriovenous shunts in the forearm). There are probably other causative agents which have yet to be identified.

Most cases of hand eczema have a multifactorial aetiology. This not only makes treatment difficult, but it can also cause considerable problems in medicolegal cases (e.g. occupational dermatitis in which negligence is alleged against an employer).

Atopy, a naturally dry skin, a tendency to seborrhoeic dermatitis, a superadded contact allergic or irritant dermatitis, or even the effect of rubbing or scratching may all obscure or potentiate the original cause. Even the daily mild trauma of normal life and climatic influences may play some part [3], and litigation itself may cause an exacerbation of the condition. The role of stress in aggravating hand eczema is difficult to evaluate, and the disease itself is of course very stressful [4]. Many patients give a convincing account of exacerbations at times of acute anxiety, frustration or grief.

Table 17.5 Hand eczema: aetiological possibilities to be considered.

Exogenous
Contact irritants
Chemical (e.g. soap, detergents, solvents)
Physical (e.g. friction, minor trauma, cold dry air)
Contact allergens
Delayed hypersensitivity (type IV) (e.g. chromium, rubber)
Immediate hypersensitivity (type I) (e.g. seafood)
Ingested allergens (e.g. drugs, possibly nickel, chromium)
Infection (e.g. following bacterial infection of hand wounds)
Secondary dissemination (e.g. dermatophytide reaction to tinea pedis)
Endogenous
Idiopathic (e.g. discoid, hyperkeratotic palmar dermatitis)
Immunological or metabolic defect (e.g. atopic)
Psychosomatic: stress aggravates, but may not be causative
Dyshidrosis: increased sweating aggravates, but may not be causative

The role of hormonal factors is also difficult to assess. Occasionally, there is a history of premenstrual exacerbation or deterioration during pregnancy.

Exogenous causes. Contact irritants are the most common exogenous cause of hand eczema [5], but contact allergens such as chromium, epoxy glues and rubber are also important (see Chapter 20). All patterns of hand eczema are possible in contact allergy. Rubber dermatitis usually affects the dorsa of the hands (Fig. 17.14), but so can contact irritant and atopic dermatitis [6]. Certain occupations are particularly likely to provoke hand eczema. The problem of occupational eczema in hairdressers, fish industry workers, farmers, construction workers, dental and medical personnel, metal workers and caterers has provoked many studies to determine its prevalence and to develop programmes for prevention of hand dermatitis [7–9]. This topic is discussed in more detail in Chapters 19 and 20.

Mention must also be made of the possibility of type 1 allergic reactions to certain proteins. In mild cases they provoke a vesicular eczema of the fingers in certain individuals, particularly those who prepare seafood. In one Scandinavian study, no less than one-third of restaurant food handlers with hand dermatitis had such a contact urticaria [10]. Greater concern has arisen in recent years because of the increasing frequency of reactions to natural rubber latex protein found in latex gloves. The reactions range from contact urticaria to rhinitis, asthma and anaphylaxis [11]. Particular attention has been paid to hospital employees, and 7% of staff reported symptoms suggestive of latex sensitivity in a study conducted in the north-west of England [12].

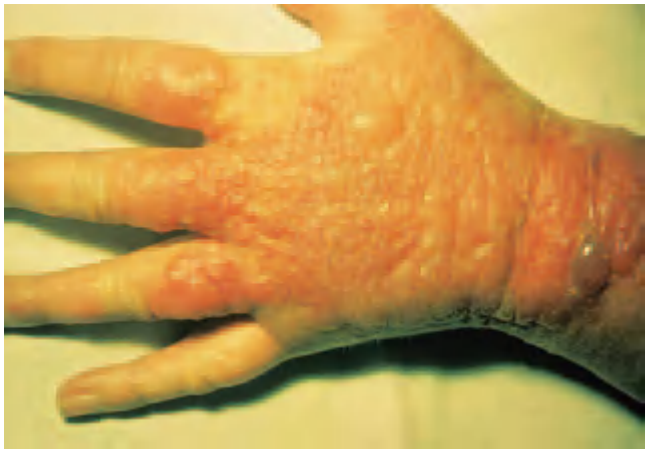

Fig. 17.14 Bullous eczema caused by contact allergy to rubber gloves.

Oral ingestion of allergens such as nickel, chromium or balsam of Peru is reported to provoke or aggravate hand eczema in sensitized individuals [13–17], although the subject remains controversial [18].

Endogenous causes. Twin studies suggest hereditary factors play a part in the development of hand eczema [19], with the atopic diathesis as the most common endogenous cause [20]. Hand eczema is more common in people with a previous history of atopic dermatitis elsewhere [21]. The most common site of atopic dermatitis in the adult is the hands, and in some patients the hands alone may be involved. Indeed, the atopic state may first become apparent by the development of hand eczema in an adolescent or young adult when they are exposed to school, hobby or occupational irritants. The eruption is often patchy and always very irritable, but there is no specific topographical pattern [22,23]. Lichenification may be evident at an early stage, and pompholyx may or may not be present. The atopic diathesis may also predispose to a discoid pattern of hand eczema in young adults. Atopic hand eczema probably has the worst prognosis of all types of hand eczema [5].

A morphological classification of hand eczema is often suggested. Although most cases are of a patchy vesiculosquamous nature without any special characteristics, about one-third of cases present particular patterns that deserve recognition (Table 17.6). The various patterns are discussed below. However, there are no hard and fast divisions; the morphology frequently changes in an individual case, so that the diagnosis may have to be revised.

Histopathology. In general, the differences between the various forms of hand eczema are clinical rather than histological, but the considerably thickened horny layer and the presence of numerous sweat glands modify the histological features of eczema on the hands.

Table 17.6 Morphological patterns of hand eczema.

Pompholyx
Recurrent focal palmar peeling
Hyperkeratotic palmar eczema
Ring eczema
'Wear and tear' dermatitis (dry palmar eczema)
Fingertip eczema
Apron eczema
Discoid eczema
Chronic acral dermatitis
'Gut' eczema
Other patterns (e.g. patchy vesiculosquamous)

Prevalence. Minor degrees of hand eczema are very common, and virtually everyone suffers from mild dryness and chapping at some time or another. The perception of whether these changes amount to hand dermatitis can influence the findings of epidemiological studies [24].

In most surveys, hand eczema is more common in females, in a ratio of approximately 2 : 1 [5], and in adolescents with hand eczema the prevalence increases in girls as they age whereas it decreases in boys [25]. Agrup [26] found that about 2% of people in one county in southern Sweden had active hand eczema, but only 25% of them had consulted their doctor about it in the previous year, and 25% had never sought medical advice. A study of prevalence in Sweden in 1984–8 by questionnaire of 16 584 individuals showed that 11% had suffered from hand eczema within the year, with a point prevalence of 5% [27].

In high-risk groups the figures are even higher. In Finland, 44% of 617 hospital personnel engaged in 'wet work' (e.g. nurses, cleaners, kitchen staff) had a past or present history of hand eczema, and 28% had at least two attacks [28]. This is confirmed by a study demonstrating significantly greater risk of hand dermatitis among hairdressers compared with office workers [29].

Eczema of the hands accounted for 34% of all cases of eczema seen in Singapore [30].

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Morphological types of hand eczema

Pompholyx

SYN. VESICULAR ECZEMA OF PALMS AND SOLES; DYSHIDROTIC ECZEMA

Definition and nomenclature. Pompholyx is a form of eczema of the palms and soles in which oedema fluid accumulates to form visible vesicles or bullae. Because of the thick epidermis in these sites, the blisters tend to become larger than in other body areas before they burst. When pompholyx occurs on the palms, it may be called cheiropompholyx, and when on the soles, podopompholyx. The alternative name, dyshidrotic eczema, refers to a supposed connection with sweat gland activity, as the condition is worse in hot weather. However, most authors feel that this term should be abandoned, as no causal relationship with the sweat glands or sweating has been demonstrated.

Incidence. Few figures are available, but pompholyx probably accounts for about 5–20% of all cases of hand eczema [1,2].

Aetiology. The cause remains obscure. In most cases no exogenous cause is found. Monozygotic twins have been affected simultaneously [3], suggesting that hereditary predisposition may be important, but in a study of nickel allergy in twins, only one pair out of 14 was concordant with pompholyx. In seven other pairs, pompholyx occurred only in the nickel-sensitive twin [4].

The role of the sweat glands has been disputed. Although the distribution of the lesions corresponds to that of emotionally activated palmoplantar sweating and the condition is worse in hot weather, hyperhidrosis is by no means a constant feature. Indeed, eczematous changes have been both induced and relieved by sympathectomy reducing hyperhidrosis [5,6]. A thorough examination of serial sections of pompholyx vesicles [7] showed that sweat ducts were often pushed aside by the tense vesicles or passed between them. The contents and pH of the vesicular fluid suggested that vesicles ruptured the sweat ducts rather than the reverse. In one study, biofeedback training aimed at reducing sweating produced slight improvement [8].

The role of atopy is also difficult to assess, partly because of the paucity of controlled studies [9]. In one study a family or personal history of atopy was obtained in 54 out of 131 patients with pompholyx [10]. Lodi *et al*. [11] found personal and family atopy in 50% of their patients with pompholyx compared with 12% of control patients, but other studies have found no correlation between atopy and pompholyx [12,13]. Schwanitz [9] reviewed the evidence relating to the causes of pompholyx in some detail, and concluded that atopy is probably the most important factor and the role of dyshidrosis has been overemphasized in the past.

Primary irritants can cause pompholyx; for example, in metal workers exposed to soluble oils [12].

Direct-contact allergens may sometimes evoke a palmar vesicular reaction instead of the more common dorsal pattern [14]. Responsible allergens include primin, isopropyl *para*-phenylenediamine, benzoisothiazolones and dichromates [15]. Perfumes, fragrances and balsam ingredients must also be considered as potential allergens [16]. Patch tests of nickel sulphate applied to the palms or fingers of nickel-sensitive subjects may produce a vesicular pompholyx-like reaction, but contact sensitivities found on patch testing may be secondary phenomena [17].

The role of ingested metals in provoking exacerbations of vesicular palmar hand eczema has been studied. Some authors [17–20] found that many nickel-sensitive patients have this pattern of hand eczema, and produced flares by giving oral nickel sulphate—although usually in doses far greater than the natural daily intake. Others have been unable to confirm this [21,22]. Chromium and cobalt allergy may also occasionally be implicated [16,23]. Oral neomycin provoked pompholyx in three of 10 neomycin-sensitive patients with leg ulcers [24].

Other haptens may give rise to pompholyx. These are difficult to detect, but a careful history, supplemented by 'feedback' tests, may occasionally pinpoint an offending allergen. Patch tests, although producing a low yield of positive results, should be performed in all cases of pompholyx.

Fungal infection elsewhere on the body, usually the feet, can provoke eczema of the palms. In the past this pompholyx *dermatophytide* [16] was diagnosed more frequently than it is now, and it has been regarded as a rare association in other studies [15,25]. The clinical picture is usually of a unilateral inflammatory fungal infection of the foot, followed by development of a bilateral vesiculobullous eruption on the palms. It is necessary to prove the presence of the fungus by examination of skin scrapings from the foot. Coexistence of pompholyx on the hands and feet is not uncommon, but in these cases involvement is bilateral and symmetrical.

Irritant or allergic dermatitis resulting from treatment of a fungal infection of the foot may also precipitate a palmar pompholyx. Primary allergic contact dermatitis of the feet (e.g. from rubber shoe chemicals) may induce a sympathetic palmar eruption.

The role of *bacterial foci* cannot be dismissed. Some reported cases may have been examples of a true pustular bacteride affecting the palms or soles.

The role of *stress* is, as usual, difficult to define. In some patients, recurrences can convincingly be related to stressful episodes, but in many others there is no such correlation. It has been suggested that patients with pompholyx are unduly susceptible to stress, but it should be remembered that pompholyx itself causes stress, particularly if there are financial problems because of loss of work.

Pompholyx may rarely follow a *drug eruption*. Aspirin ingestion, oral contraceptives and cigarette smoking also increase the risk of pompholyx [13].

Histopathology. The early features have not been sufficiently well studied. Fully formed lesions show the changes of acute eczema modified by the thick overlying epidermis. The subsequent course is that of a subsiding eczema, with hyperkeratosis and epidermal shedding.

Clinical features (Fig. 17.15). Pompholyx may occur at any age, but it is more common before the age of 40 years.

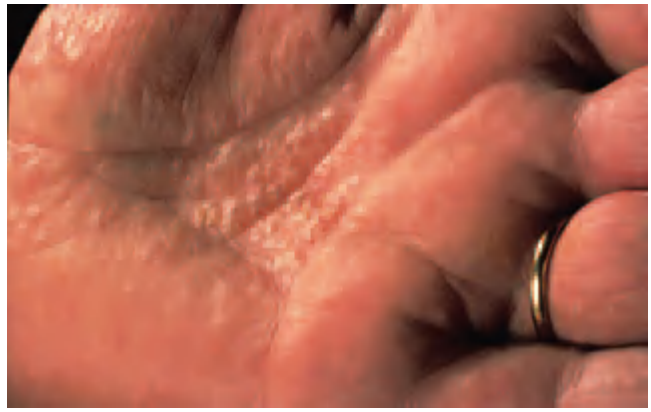

Fig. 17.15 Pompholyx, showing confluent vesicles of the palm.

Onset before 10 years is unusual. An attack of pompholyx is characterized by the sudden onset of crops of clear vesicles, which appear deeply seated and 'sago-like'. There is no erythema, but a sensation of heat and prickling of the palms may precede attacks. Vesicles may become confluent and present as large bullae, especially on the feet. Itching may be severe, preceding the eruption of vesicles. The attack subsides spontaneously, and resolution with desquamation occurs in 2–3 weeks in most cases, but recurrent attacks in this period may cause a wave-like continuation of symptoms in a minority of cases. In mild cases, only the sides of the fingers may be affected, but in a typical case the vesicles develop symmetrically on the palms and/or soles. Unilateral or asymmetrical patterns occur, but this should alert the dermatologist to look for contact causes of the eruption. In 80% of patients only the hands are involved. The hands and feet, and the feet alone each account for approximately 10% of patients. Secondary infection with pustule formation and lymphangitis is not uncommon, and may complicate each attack in certain patients. Rubbing and inappropriate treatment may produce secondary eczematous changes extending beyond the volar surfaces. After recurrent attacks spreading to the dorsa of the fingers, the nails may develop dystrophic changes, irregular transverse ridging and pitting, thickening and discoloration. Such changes can follow even mild attacks, and may be the patient's presenting complaint.

In cases in which no cause can be demonstrated (the majority) recurrences are usual. They may occur at intervals of 3 or 4 weeks for months or years, or at long irregular intervals. Pompholyx is more common in warm weather, and in some patients attacks occur annually each summer.

Diagnosis. There is some debate whether the term pompholyx should be reserved for typical cases in which the attacks resolve and recur. Chronic recurrent vesiculation without periods of remission may be termed chronic vesicular dermatitis.

A circumscribed and asymmetrical area of scaling and vesiculation of the palm or sole should suggest the possibility of dermatophytosis, and scrapings should be examined for fungus. If the erythema is limited to one or two interdigital clefts, is asymmetrical or involves the dorsal skin to any extent, the possibility of a contact dermatitis must be considered, and excluded by a careful history and by patch testing. In pustular psoriasis of the palms and soles there are usually no clear vesicles, although this is not invariably so [26]. The pustules are sterile on culture, and leave characteristic brown marks as they resolve. Occasionally, secondary bacterial infection of pompholyx may occur, with pustule formation, but in these cases the lesions tend to be painful, with surrounding erythema, and culture of the pus yields the causative organism. A pustular bacteride secondary to bacteria elsewhere in the body may also lead to confusion.

Repeated attacks of pompholyx may produce hyperkeratotic lesions that mimic psoriasis vulgaris.

Pemphigoid, linear IgA disease and pemphigoid gestationis occasionally present with blisters on the palms that mimic pompholyx [27,28].

Treatment. Any obvious cause of the eruption should be eliminated, but in most cases one will have to rely on non-specific measures. In the acute phase, rest and bland applications are indicated. Involvement of the feet may require the patient to be treated in bed. The hands or feet should be soaked three or four times a day in either Burow's solution (aluminium acetate 1%) or potassium permanganate solution (diluted 1 : 8000). Large bullae may be aspirated using a sterile syringe. Systemic antibiotics will be required if secondary bacterial infection develops. This is most likely to be staphylococcal, and flucloxacillin is usually effective.

As the eruption subsides the soaks should be discontinued, and zinc cream or oily calamine lotion can be substituted. Topical steroids are useful in the subacute and chronic phases. In a few severe cases, a course of oral steroids may be justified.

For chronic pompholyx that has entered the hyperkeratotic phase, tar preparations such as 2–5% crude coal tar may be used, or a steroid preparation may be combined with a coal tar solution. Low-dose methotrexate and radiation therapy have both been used with success in refractory cases [29,30].

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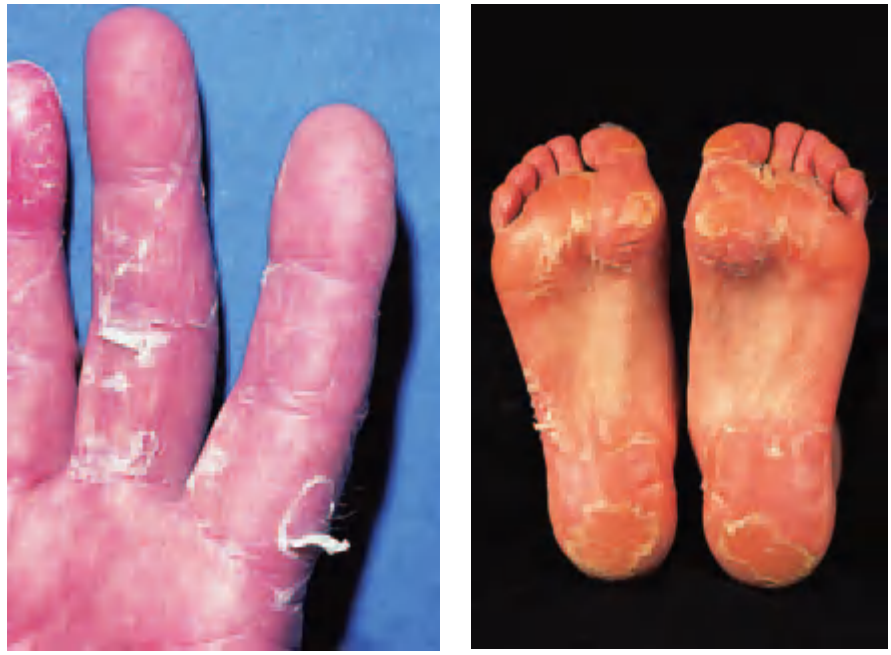
Recurrent focal palmar peeling

SYN. DESQUAMATION EN AIRES

In the past this condition was called keratolysis exfoliativa, but the term is best avoided because of confusion with another condition of the same name (see Chapter 34).

The condition is probably a mild form of pompholyx. During the summer months, small areas of superficial



(a) (b)

Fig. 17.16 Recurrent focal palmar peeling. Well-established lesions on: (a) hands (courtesy of Dr A. Marsden, St George's Hospital, London, UK); and (b) feet.

white desquamation develop on the sides of the fingers and on the palms or on the feet (Fig. 17.16). They appear abruptly, and expand before peeling off. There is little or no irritation, and vesicles as such are not seen. The condition is probably not rare, but because it is relatively asymptomatic it often does not reach the dermatologist. Some patients subsequently develop true pompholyx.

Hyperkeratotic palmar eczema

SYN. TYLOTIC ECZEMA

This condition is a distinct form of hand eczema which is characterized by highly irritable, scaly, fissured, hyperkeratotic patches on the palms and palmar surfaces of the fingers [1,2] (Fig. 17.17). It is a common condition, and 2–5% of all applications for permanent disability pensions in some western European countries are a result of hyperkeratotic hand eczema.

The aetiology is unknown. Patch tests are usually negative, and the incidence of atopy and psoriasis is no greater than in a normal control population. The distinction from localized psoriasis of the hands can, however, be very difficult. It is most frequent in men of middle age or over, and is extremely refractory to treatment, although PUVA may be helpful [3]. Steroid ointments, crude coal tar, salicylic acid and Grenz rays may be tried. A review of 32 patients re-examined 10 years after initial presentation showed that in 29 the condition had remained more or less unchanged [1,3]. Oral retinoid tablets such as etretinate may be helpful [4].

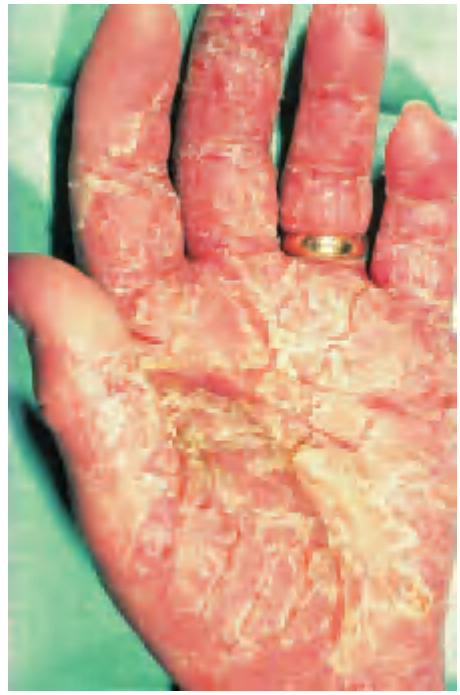


Fig. 17.17 Hyperkeratotic palmar eczema.

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Ring eczema

This characteristic pattern particularly affects young women, rarely men. The condition usually starts soon after marriage or childbirth. An irritable patch of eczema begins under a ring—usually a broad wedding ring—and typically spreads to involve the adjacent side of the middle finger and the adjacent area of the palm. It may remain confined to these sites, but is occasionally followed by the appearance of discoid patches elsewhere; or a more diffuse vesicular eczema may develop. Despite the clearly defined demarcation of the initial eruption, these patients cannot be shown to be sensitive to gold or copper although, curiously, nickel, cobalt and even chromium sensitivity are more commonly found on patch testing than might be expected; only rarely can 'white gold' alloys be implicated. Ring dermatitis has been described as the clinical presentation of fragrance sensitization [1]. Transference of the ring to the other hand is often rapidly followed by the appearance of eczema at the new site and, once affected, patients may aver that wearing of the ring for only a few minutes, even without washing, causes irritation. This type of hand eczema is probably caused primarily by concentrations of soap and detergent beneath rings (which may tighten on fingers immersed in hot water), but microtrauma, especially friction, may also have a role.

Very rarely, radioactive gold in a ring may cause radiation dermatitis, which mimics this type of wedding ring eczema [2].

'Wear and tear' dermatitis

SYN. ASTEATOTIC HAND ECZEMA; HOUSEWIVES' DERMATITIS; DRY PALMAR ECZEMA; DERMATITIS PALMARIS SICCA

This condition affects housewives and cleaners who frequently immerse their hands in water and detergents, and is presumably caused by a combination of asteatosis, exposure to mild irritants such as soap, and mild trauma (e.g. from wringing out dishcloths). The skin feels dry, it becomes criss-crossed with superficial cracks associated with a damaged horny layer, and it is unable to respond with its normal pliability to hand and finger movement (Fig. 17.18). These cracks often stand out white against an erythematous background. In addition to palmar involvement there may be dryness and chapping of the skin over the dorsa of the knuckle joints. The condition may also be associated with fingertip eczema (Fig. 17.19) or with ring dermatitis.

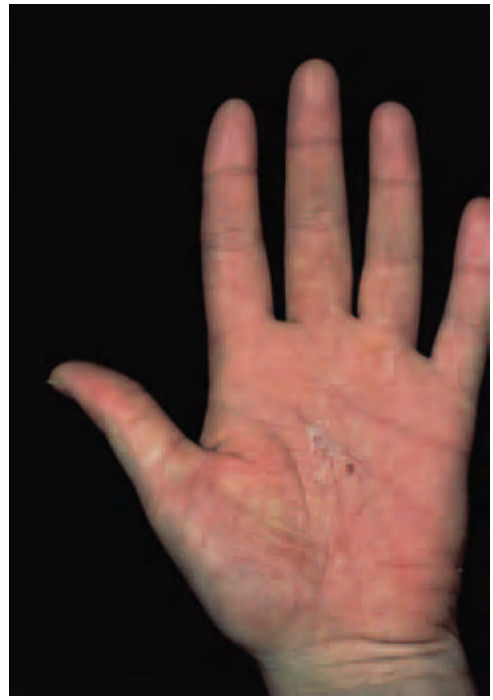

Fig. 17.18 Dry palmar eczema.

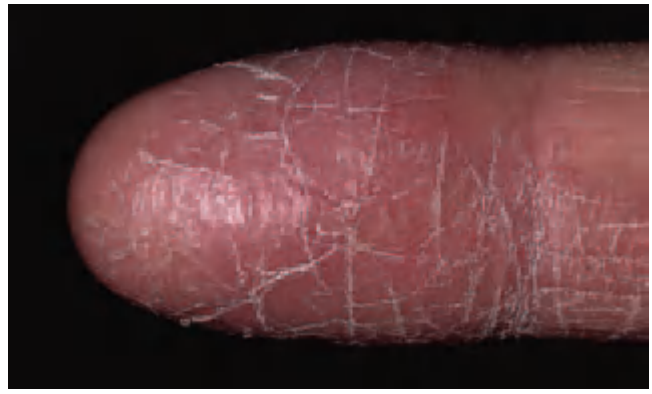

Fig. 17.19 Fingertip eczema in a patient with wear and tear dermatitis. (Courtesy of Dr D.A. Burns, Leicester Royal Infirmary, Leicester, UK.)

Some patients with juvenile plantar dermatosis also have hand involvement, and some patients have the distinctive palmar dermatitis alone. This is a dry, glazed, erythematous, fissured and only mildly pruritic condition, which has been called dermatitis palmaris sicca [3]. Exudation and weeping do not occur in this condition. There seems to be little or no clear morphological distinction between this condition and 'wear and tear' dermatitis.

Fingertip eczema

This condition also presents a very characteristic pattern, involving the palmar surface of the tips of some or all the

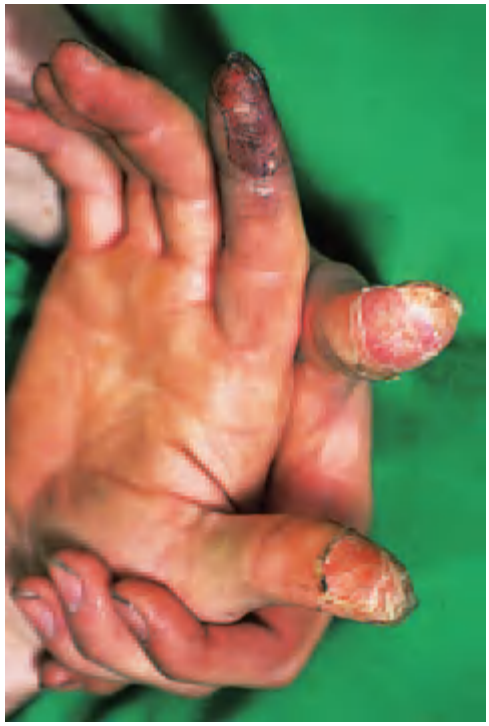

Fig. 17.20 Fingertip eczema resulting from allergy to plant bulbs. (Courtesy of Dr F.A. Ive, Dryburn Hospital, Durham, UK.)

fingers. The skin is dry, cracked and sometimes breaks down into painful fissures. Usually remaining localized, it may occasionally extend along the palmar surfaces of the fingers to merge with palmar eczema (Fig. 17.20).

Two patterns may be distinguished. The first and most common involves most or all of the fingers, mainly those of the dominant hand, and particularly the thumb and forefinger. The condition is usually worse in the winter and generally improves on holiday. Patch tests are negative or not relevant; it is a cumulative irritant dermatitis in which degreasing agents combine with trauma as causative factors. The second pattern involves preferentially the thumb, forefinger and third finger of one hand. This is usually occupational (whether in factory, market garden or house). It may be either irritant (e.g. in newspaper delivery employees) or allergic (e.g. to colophony in polish, or to tulip bulbs or stems [4,5]). The condition usually involves the dominant hand, but there may be allergy to onions, garlic and other kitchen products held in the serving hand. In these cases, patch testing (and 20-min contact tests) may be rewarding [6].

Apron eczema

This condition is a type of hand eczema that involves the proximal palmar aspect of two or more adjacent fingers and the contiguous palmar skin over the metacarpophalangeal joints, thus resembling an apron (Fig. 17.21). This

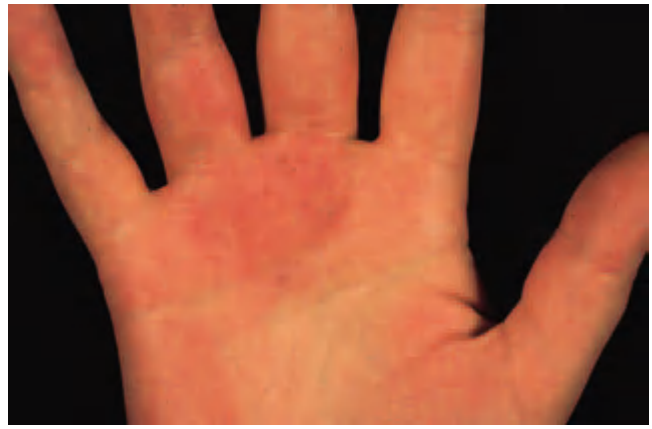

Fig. 17.21 'Apron' eczema, showing the characteristic distribution.

pattern of hand eczema is rarely caused by contact allergic dermatitis but may reflect the effect of irritants [7].

Discoid eczema

See page 17.18.

Chronic acral dermatitis

This is a distinctive syndrome affecting patients in middle age. A chronic hyperkeratotic papulovesicular eczema of the hands and feet, intensely pruritic, is associated with grossly elevated IgE levels in subjects with no personal or family history of atopy. The condition responds to oral corticosteroids, but the response to topical therapy is poor [8].

'Gut' eczema

SYN. SLAUGHTERHOUSE ECZEMA

Workers who eviscerate and clean pig carcasses are at risk of developing vesicular eczema, which starts in the finger webs and spreads to the sides of the fingers. This is a mild, self-limiting condition, which clears in a week or two, even if the patient remains at work, but it can recur at intervals. Workers in Danish bacon factories call this 'fat eczema', although there is little evidence that it is caused by fat and prick tests to pig fat extracts are negative [9]. The pathogenesis is unknown, but some slaughtermen have developed contact urticaria from exposure to animal blood [10].

Patchy vesiculosquamous eczema

There remains a large group of cases in which a mixture of irregular, patchy, vesiculosquamous lesions occur on both hands, usually asymmetrically. In contrast to the lesions of discoid hand eczema, the degree of activity and

distribution of the lesions vary, appearing now at one site, now at another. Nail changes are common if the nail folds are affected.

The above list by no means exhausts the possible morphological patterns of hand eczema. Some patients, for example, have dry, scaly eczema confined to a small area on the thenar or hypothenar eminence, and this is almost always endogenous. Others may have vesicular eczema confined to the edge of the hand in a very persistent form.

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Differential diagnosis. The diagnosis of hand eczema is usually self-evident, but the distinction from psoriasis can be very difficult. Most experienced dermatologists have seen cases they have confidently labelled as hand eczema, which have later developed typical psoriasis in other areas [1]. In some cases even biopsy does not allow a clear distinction to be made. In most cases of psoriasis on the hands, however, the silvery nature of the scale, involvement of the knuckles, sharply demarcated 'scalloped' edges to the erythema along the borders of the hands and fingers, and the relative absence of pruritus are helpful pointers. A family history of psoriasis and the presence of nail pits in the absence of nail fold lesions are also suggestive.

Tinea can also be missed, especially when it is extensive and irritable (Fig. 17.22), or secondarily infected. Unilateral scaling of the palm should always suggest a possible *Trichophyton* infection and a discoid plaque resulting from *T. verrucosum* is sometimes seen in farmers.

The special characteristics of palmar pustulosis are usually evident, and lichen planus (Fig. 17.23) and pityriasis rubra pilaris usually pose no difficulties.

It must be emphasized that the whole skin should be examined in any case of hand eczema in which the diagnosis is in doubt. There may, for example, be evidence of nickel allergy or tinea pedis, or small patches of psoriasis of which the patient is unaware.

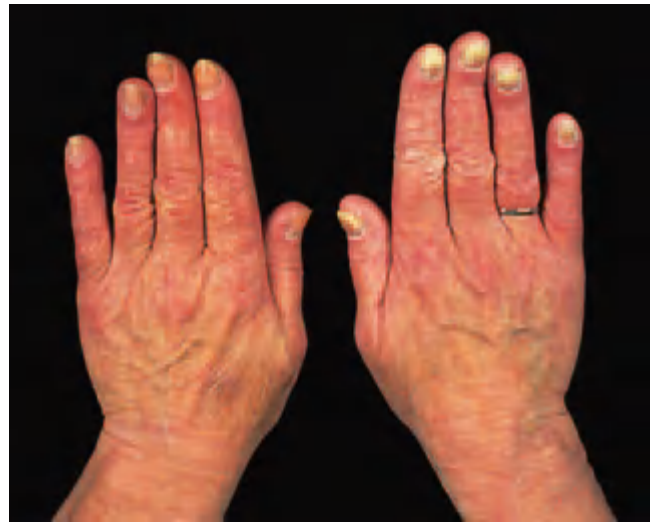

Fig. 17.22 *Trichophyton* infection of the hands, which had failed to respond to topical steroids. Note the nail involvement.

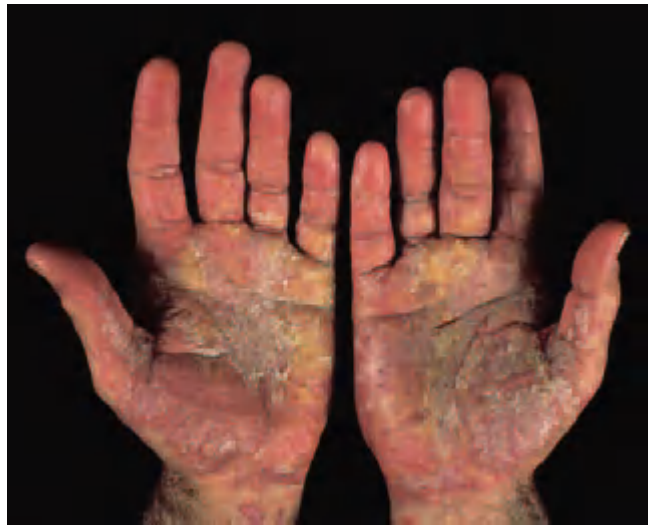

Fig. 17.23 Lichen planus mimicking hyperkeratotic hand eczema, but the margins are well demarcated, and the lesions on the left wrist are characteristic of lichen planus.

Prognosis. Unless a responsible allergen can be identified and removed, the prognosis of hand eczema is always uncertain. Some allergens such as nickel, rubber chemicals and fragrances are ubiquitous, however, and complete avoidance in the home environment is difficult to achieve [2–5]. In general, eczema on the dorsa of the hands clears more readily, and is less likely to recur than palmar eczema. Acute attacks of pompholyx will usually settle down and in one-third of the cases will not recur. In another third, recurrences will take place, and in the remainder the condition will pass into a chronic, possibly hyperkeratotic stage. Those forms of hand eczema that are caused in part or wholly by the effects of irritants carry a particularly poor prognosis unless these irritants can be

completely removed. Interdigital dermatitis has been shown to be a potential precursor of more severe hand dermatitis in hairdressers. Recognition of this sign by the patient may allow early intervention to prevent progression of the disease [6].

A prolonged period of rest for the skin is usually necessary for complete restoration of the protective function of the stratum corneum [7]. Patients who have suffered from severe hand eczema will often remain vulnerable to mild irritants for several months after the eczema has apparently cleared.

There are few figures available for assessing the prognosis of non-occupational hand eczema. Many patients learn to 'live with' their condition, and cease to attend doctors—a poor reflection of our capabilities in this field. The prognosis is worse in patients with atopic eczema [8,9].

In one study, one-quarter of patients were symptom-free, and a further half had improved after a follow-up period of 6–22 months [10]. In a longer follow-up of 213 cases, less than one-third had entered complete remission [11]. Change of occupation did not affect the prognosis.

The behaviour of hand eczema in pregnancy is variable.

Treatment. Treatment of acute hand eczema is as for pompholyx (see p. 17.22). For *chronic* eczema, particular attention must be paid to possible causative factors, and a full occupational and social history, with details of hobbies and spare time activities, is essential. Patients must be asked exactly what their job involves and how they protect their hands. Patch tests are advisable (see Chapter 20).

The same general principles of treatment apply as for chronic eczema on other parts of the body (see p. 17.39). The three most useful measures are:

1 Avoidance of irritants
2 Frequent application of emollients
3 Sparing use of topical steroids [12].

Avoidance of irritants. This is particularly difficult for patients with hand eczema, as irritants are so ubiquitous. Education of the patient to the possible dangers is of paramount importance, and printed advice sheets are useful, as patients often have a poor recollection of oral instructions. Examples of suitable instruction sheets have been provided by Epstein [12].

Cleanliness is important, but too much soap and water can be harmful. A wide variety of soap substitutes are now available. Older remedies such as a tablespoon of emulsifying ointment mixed in a cup of hot water are often helpful. Very brief exposure to soap followed by immediate application of a topical lipid is unlikely to be harmful, and may be beneficial by removing bacteria and debris [13].

Barrier creams are usually ineffective for hand eczema of occupational origin, although new products are frequently being reported as showing some promise [14,15]. In practice they may not be applied effectively [16] and the debate continues about their actual benefit [17]. Gloves usually provide the best protection, and time should be spent discussing with the patient the details of the material, size and weight of the gloves to be used, so that they can be tailored to the individual's particular need. Gloves with holes in them may be worse than no gloves at all, but gloves that are too thick may make it impossible to perform a particular task. It should also be remembered that some allergens such as acrylates and epoxy resins can penetrate vinyl or rubber gloves [18]. Rubber gloves generally give good protection for housework. In patients with rubber allergy, polyvinyl chloride household gloves should be worn instead. If sweating makes the condition worse, it may be helpful to wear cotton gloves beneath the protective gloves. Gloves should also be used for dry work, to prevent soiling and trauma, especially for gardening in cold dry air. Thin leather is usually better than cotton for this purpose.

Emollients. Emollients should be applied frequently as a thin smear rubbed gently into the skin, and several jars should be left at convenient locations such as near sinks, so that they are readily available. The choice of emollient will vary with the patient. Some people will benefit from a greasy preparation such as emulsifying ointment, and others will prefer a more cosmetically acceptable cream such as aqueous cream, which sinks into the skin more readily, and is less likely to stain. Numerous commercial preparations are now available. Patients should be warned that some topical preparations sold over the counter by pharmacists as antipruritics or emollients can contain irritants such as alcohol or propylene glycol, and they should use only what the dermatologist recommends.

Topical steroids. These are used in all but the mildest cases, but as always they should be used sparingly, and in the weakest potency that is effective. Hydrocortisone in a concentration of 1% is perfectly safe, but stronger steroids are often required and these can cause atrophy. Even though the palms are thick, the epidermis can be rendered thin and fragile by potent topical steroids. This is not a major problem in hyperkeratotic eczema, but in these cases steroids are relatively ineffective. If bacterial infection is present, a systemic antibiotic may be needed, and the use of a combined steroid–antiseptic or steroid–antibiotic preparation may help to lessen the risk of infection and improve the response. The risk of bacterial overgrowth resulting from steroids, however, is probably less than one might expect. It has been shown that a potent steroid used alone can reduce or even eliminate *Staphylococcus aureus* colonization in hand eczema [19].

In difficult, unresponsive cases the use of a potent steroid under occlusion may be considered. The steroid is

applied at bedtime, and polythene gloves are worn overnight, sealed at the wrist with sticky tape. This is an effective treatment, but it greatly increases the risk of atrophy and secondary bacterial infection, and should be discontinued as soon as the eczema shows satisfactory improvement.

If hand eczema does not respond to topical steroid therapy, the diagnosis should be reviewed, particularly with regard to the possibility of tinea. The patient should be quizzed again about exposure to irritants or allergens, and the possibility of sensitization to medicament bases or preservatives or even the corticosteroid itself should also be considered, with patch tests if necessary.

After improvement of the dermatitis with daily corticosteroid use, the intermittent use of a potent corticosteroid cream may safely prevent relapse [20].

Epstein [12] recommends intradermal injection of triamcinolone (10 mg/mL) into recalcitrant localized patches of hand eczema.

Other measures. Tar pastes are often useful for chronic unresponsive cases. Generally speaking, the messier preparations such as 5% crude coal tar tend to be more effective than the cosmetically more acceptable preparations.

Salicylic acid ointment is also sometimes helpful for hyperkeratosis and persistent scaling [21]. Various combinations of tar, steroids and salicylic acid may be tried, and Baden [22] has recommended the application of a keratolytic gel of salicylic acid and propylene glycol under occlusion for 2–4 h before the application of steroid ointments at night.

Oral PUVA chemotherapy and UVB therapy have proved useful for several types of hand eczema, including allergic contact dermatitis, dyshidrotic eczema and hyperkeratotic palmar eczema [3,23–29]. Topical PUVA soaks have also been shown to be effective and safe, although patient compliance is crucial to success [30]. A PUVA cream therapy may be more useful [31].

Radiotherapy is also effective for stubborn hand eczema. Grenz rays were widely used in the past, as these were thought to be safer than X-rays. Fairris *et al*. [32] have shown that superficial X-rays give a better result, and they advise that patients can safely receive three courses of 3 Gy of superficial X-ray therapy during a lifetime.

Etretinate is sometimes effective for hyperkeratotic eczema, but there is a high incidence of side effects [33]. Ciclosporin has been reported to be useful in recalcitrant cases of chronic vesicular hand eczema, and appears to be as effective as a potent topical corticosteroid, although side effects may be a concern [34,35]. Ranitidine was shown to have adjuvant benefits to topical steroid treatment of atopic hand dermatitis, without any side effects [36]. A pilot study of 9-*cis*-retinoic acid showed a good response to the drug in over half the cases [37].

Painful fissures of the fingertips are a therapeutic problem. The main requirement is to keep the keratin as pliable as possible by the use of greasy preparations, and it often helps to use polythene occlusion at night, with thin leather gloves during the day. Once formed, fissures are slow to heal, but they can sometimes be rendered painless by sealing them with a product such as compound benzoin tincture. Recurrent infection of fissured hand eczema can give rise to lymphoedema, and long-term low-dose antibiotic prophylaxis with penicillin may be required [38].

In indolent cases in which metal allergy of dietary origin is thought to be playing a part [39], the use of an oral chelating agent may be considered. Disulfiram 200 mg/day for 8 weeks produced good results in an open study, but this treatment carries a risk of liver dysfunction [40].

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Venous eczema

SYN. GRAVITATIONAL ECZEMA

Definition. Eczema secondary to venous hypertension.

Nomenclature. This condition is also called stasis eczema or varicose eczema. It is increased venous pressure rather than stasis that seems to be the prerequisite. Although it is often associated with varicose veins, these are not always present.

Pathogenesis [1–4]. The oxygen content in the femoral venous blood of the leg affected by venous hypertension is increased, and the venous blood in such limbs has a faster circulation time than normal [5,6]. These observations could be explained by the development of arteriovenous shunts in the affected areas, but the use of radioactively labelled macroaggregates or microspheres has failed to provide any evidence for such shunts.

An alternative explanation for these findings has been provided by Browse and Burnand [2], who suggested that the high ambulatory venous pressure within the calf muscle pump is transmitted to the capillary circulation in the skin and subcutaneous tissues of the calf. This distends the local capillary bed and widens the endothelial pores, thus allowing fibrinogen molecules to escape into the interstitial fluid, where they form a fibrin sheath around the capillaries. This layer of fibrin presumably forms a pericapillary barrier to the diffusion of oxygen and other nutrients that are essential for the normal vitality of the skin. The hypothesis that pericapillary fibrin impedes oxygen diffusion has been supported by a study using positron emission tomography [7].

It has also been suggested that cutaneous inflammation in venous hypertension may result from increased sequestration of white cells in the venules, with consequent release of proteolytic enzymes and free radicals which produce tissue damage [3]. In normal subjects, white cells are sequestered in the limb when venous pressure is elevated, and in patients with venous insufficiency the effect is enhanced, with increased endothelial contact and adhesion of white cells [8]. This effect may be related to an increase in expression of adhesion molecules ICAM-1 and VCAM-1 on the vascular endothelium in affected skin [9].

Clinical features. Venous eczema is an erythematous, scaly and often exudative eruption usually seen around the ankle and lower leg (Fig. 17.24). It often occurs as a late result of deep-vein thrombosis. On occasions, similar changes occur at other sites of venous hypertension such as the pendulous skin over an obese abdomen or in association with an arteriovenous fistula in the upper limb [10]. The eczema may develop suddenly or insidiously. The patients are usually middle-aged or elderly and most often female. The increased incidence in females is presumably a result of hormonal effects and the tendency for deep-vein thrombosis to occur during pregnancy.

The eczema is often accompanied by other manifestations of venous hypertension, including dilatation or varicosity of the superficial veins, oedema, purpura, haemosiderosis, ulceration or small patches of white atrophic telangiectatic scarring (atrophie blanche). These changes, which occur in various combinations, are discussed in more detail in Chapter 50. Leashes of dilated venules around the dorsum of the foot or the ankle are particularly common. There may be a subepidermal vascular proliferation producing purple papules around the ankle, which may resemble Kaposi's sarcoma [11]. Secondary patches of eczema may develop on the other leg, even when it is not affected by obvious venous insufficiency. Generalized secondary dissemination may occur and on occasions this can progress to erythroderma.

These changes are often modified by secondary contact dermatitis, infection and rubbing. Allergic contact

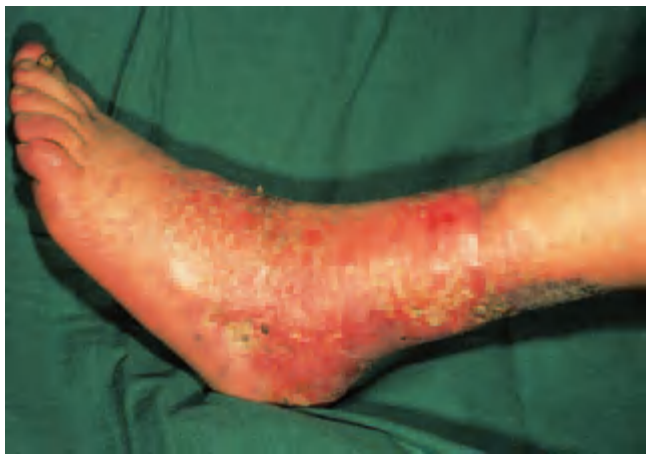

Fig. 17.24 Venous (gravitational) eczema.

dermatitis is a common complication of venous eczema, possibly because of the large numbers of antigen-presenting cells in the inflamed skin [12].

Differential diagnosis. Although most cases of eczema of the lower leg are secondary to venous hypertension, it must be remembered that many other types of eczema can affect this region, and in many cases there are multiple causative factors. In children or young adults, atopic dermatitis can manifest as lichenified patches around the ankle or behind the knees. Allergic contact dermatitis of the lower legs is usually caused by topical medicaments (Fig. 17.25). Patch testing is often indicated. An infected ulcer may be complicated by infective eczema spreading from the edge of the ulcer, and responding to appropriate antibiotic therapy (see p. 17.7). Discoid eczema is common on the lower leg, usually on the anterior or anterolateral aspect. Asteatotic eczema commonly affects the legs of elderly patients.

Although the exact cause of eczema on the lower legs can be difficult to elucidate, other conditions can usually be readily identified. Psoriasis may present as a single, irritable plaque on the leg, but is usually more scaly and clearly marginated. Hypertrophic lichen planus of the lower leg may occasionally be mistaken for eczema if there are no characteristic lesions elsewhere. Dermatophyte infection may present as diffuse erythema and scaling, and can be difficult to recognize, particularly if it has been treated with topical steroids. Profuse actinic keratoses may cause red, irritable patches on the lower legs in sunny climates. In the late stage of borreliosis the leg can feel heavy, with thick cyanotic itchy skin which may mimic the changes of venous hypertension [13].

Treatment. The underlying venous hypertension should be controlled. Obese patients should be urged to lose weight. Well-fitted support stockings or firm bandages can be helpful if worn regularly. The legs should be elevated when the patient is recumbent.

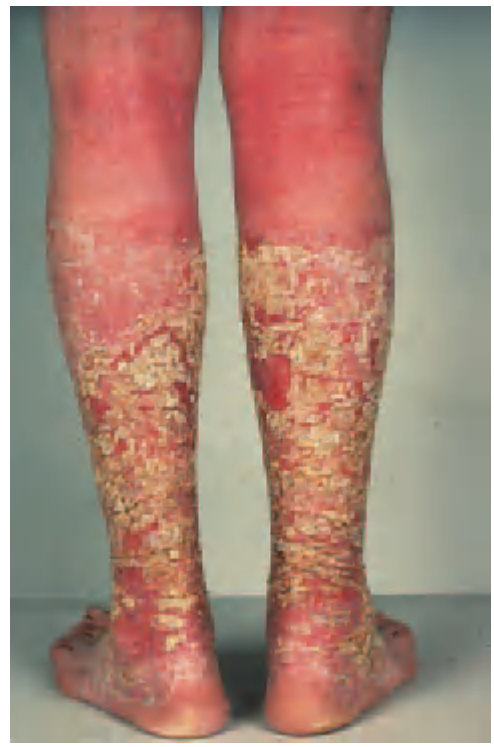

Fig. 17.25 Contact dermatitis of the lower legs caused by allergy to paste bandages.

Mild topical steroids may be used to relieve irritation, but the use of potent steroids should be limited to short periods of a few days as they may cause cutaneous atrophy and increase the risk of ulceration. Bacterial infection must be treated where appropriate, but the risk of sensitization to topical antibiotics and antiseptics should be borne in mind, and systemic antibiotics may be preferable. Bacteria cultured from a swab are not necessarily playing a pathogenic part. If trauma is thought to be playing a part, and the patient cannot resist scratching, a paste bandage may be helpful.

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Juvenile plantar dermatosis

SYN. FOREFOOT ECZEMA; PERIDIGITAL DERMATOSIS; DERMATITIS PLANTARIS SICCA; ATOPIC WINTER FEET

Definition. This condition is characterized by shiny dry fissured dermatitis of the plantar surface of the forefoot. It occurs mainly in children aged 3–14 years.

Nomenclature. The first record of this condition appeared in 1968, and since then it has been described under a variety of names depending on the author's beliefs concerning pathogenesis and the possible association with atopy. The name 'juvenile plantar dermatosis' has the merit of making no presumptions about cause.

Aetiology [1–4]. It is thought that changes in the composition of children's socks and shoes in the last 30 years or so may be responsible for the emergence of this disease. Biological materials such as cotton, wool and leather have gradually been replaced by various synthetic materials (nylon, plastics), and these are generally less porous than the natural materials they have replaced. This loss of permeability is enhanced by various repellent coatings designed to improve the durability of the shoe surface. The feet are thus subjected to hot humid conditions that encourage mild maceration, particularly in children who may wear trainer shoes throughout their waking hours. The maceration probably causes sweat retention and, although the exact mechanism is uncertain, this may aggravate the condition [3]. This is not the whole story, however, for occasional cases have occurred in children wearing open leather sandals and cotton socks. Many of the affected children are keen on sports, and this suggests that friction and enhanced sweating may be playing some part.

An association with atopy has been proposed but the evidence for this is not convincing. In a controlled study, a personal or family history of eczema or other atopic illness was not more common in cases than in controls [1].

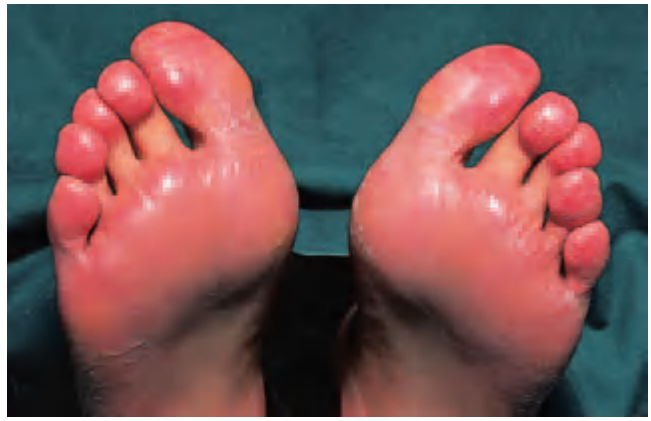

Fig. 17.26 Juvenile plantar dermatosis, showing the characteristic glazed appearance of the forefoot skin.

Juvenile plantar dermatosis has been seen in identical twins [5].

Pathology [2,6]. The histology shows a mild, non-specific eczema. Blockage of sweat ducts can sometimes be identified.

Clinical features. Few cases have been reported in adults or infants. There is a slight preponderance of male patients. The presenting features are redness and soreness on the plantar surface of the forefoot, which assumes a shiny, 'glazed' and cracked appearance (Fig. 17.26). The condition is most severe on the ball of the foot and toe pads, and tends to spare the non-weight-bearing instep. The toe clefts are normal, and this helps to distinguish the condition from tinea pedis. The symmetry of the lesions is a striking feature. Occasionally, the disease can affect the hands, resulting in sore, shiny, fissured palms or fingertips. This is more likely in atopic subjects [7].

Diagnosis. This is a clinical diagnosis, although skin scrapings to exclude fungus and patch tests to exclude footwear allergy may be helpful if there is any doubt. Consultation with the manufacturer of the shoes may help to identify potential allergens.

Treatment. Most cases will clear spontaneously during childhood or adolescence, but the condition may persist into adulthood [8]. Patients are usually advised to change from non-porous footwear to 100% cotton socks, and leather shoes or sandals, although the majority report that these changes in footwear do not help significantly [1,8–10].

In severe cases, with cracking and exudation, bed rest may be needed. A variety of topical preparations may help, including urea preparations, Lassar's paste, white soft paraffin or tar, but no single preparation is always effective [2,11,12].

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'Metabolic' eczema and eczema associated with systemic disease

Eczema associated with malabsorption

The possible interrelation of eczema and disordered intestinal absorption is not fully understood but it seems that widespread eczema can occasionally be either the cause or the result of intestinal malabsorption [1,2].

Severe inflammatory skin disease often seems to cause a degree of malabsorption—a condition known as dermatogenic enteropathy [1,3]. This is usually asymptomatic. The mechanism is not known, but the malabsorption improves rapidly as the skin is treated.

Many of the cases of eczema reportedly caused by malabsorption may, in reality, have been dermatitis herpetiformis, as they mostly predate the establishment of modern histological and immunological criteria for this disease [4,5]. However, the response of the eczema in some cases to correction of the serum calcium suggests that there may be other mechanisms involved [6]. A case of dermatitis associated with lactose intolerance and apparently improving in response to a lactose-free diet is also difficult to explain [7].

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Wiskott–Aldrich syndrome

This syndrome is fully described in Chapter 14.

Hypogammaglobulinaemia

A form of eczema, clinically very similar to atopic eczema, has been described in boys with hypogammaglobulinaemia [1,2].

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Hyper-IgE recurrent infection syndrome

SYN. JOB'S SYNDROME

This rare disorder is characterized by recurrent bacterial infections of the skin, nasal sinuses and respiratory tract, commencing in early childhood, in the presence of serum levels of IgE which are around 10 times greater than normal (more than 2000 i.u./mL). Chronic eczema, often impetiginized, is a common feature (see Chapter 14).

Pyoderma, folliculitis and atopy, with defective leukocyte and lymphocyte function

SYN. JUNG'S DISEASE

A familial immunodeficiency disease characterized by atopic dermatitis, recurrent and persistent pyoderma and folliculitis has been described in a father and son [1]. It was accompanied by abnormalities of lymphocyte function and defective leukocyte chemiluminescence responses, which were associated with defective intracellular killing of microbial organisms. The abnormalities of lymphocyte and leukocyte function and the clinical manifestations responded dramatically to treatment with the H_1 antagonist chlorphenamine (chlorpheniramine), suggesting that the underlying defect in this disease may be related to defective histamine metabolism or abnormal expression of histamine receptors on lymphocytes and leukocytes.

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Pellagra

Photosensitive dermatitis is a feature of pellagra. Hartnup disease, with massive aminoaciduria, may also be asso-

ciated with a pellagra-like rash after exposure to the sun, presumably because nicotinamide synthesis from tryptophan is decreased. A similar phenomenon can occur as part of the carcinoid syndrome.

Phenylketonuria

Eczema occurs in 25% of untreated patients with phenylketonuria in the early years of life. It responds to dietary treatment by exclusion of phenylalanine and recurs when the treatment is stopped [1–3].

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Eczematous drug eruptions

Eczematous drug reactions may be localized (e.g. resembling seborrhoeic or discoid eczema) or generalized. A carbamazepine reaction initially involving the flexures and resembling atopic dermatitis was reported recently [1]. Eczematous eruptions, including cheiropompholyx, may follow infusion of human immunoglobulin [2]. Severe reactions can rapidly progress to erythroderma.

Drug reactions are more fully described in Chapter 73.

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Exudative discoid and lichenoid chronic dermatosis [1]

SYN. SULZBERGER–GARBE DISEASE

Definition. This disease has no rigid criteria, but it is a widespread, extremely pruritic eruption, characterized by discoid, lichenoid and exudative phases, which either coexist or alternate rapidly with each other. After a chronic course of months or years, the condition ends in spontaneous cure. It occurs predominantly in adult male Jews, usually between the ages of 40 and 60 years. More than 100 cases have been reported [2], but some authors deny its existence as a distinct entity [3].

Aetiology. The cause is unknown.

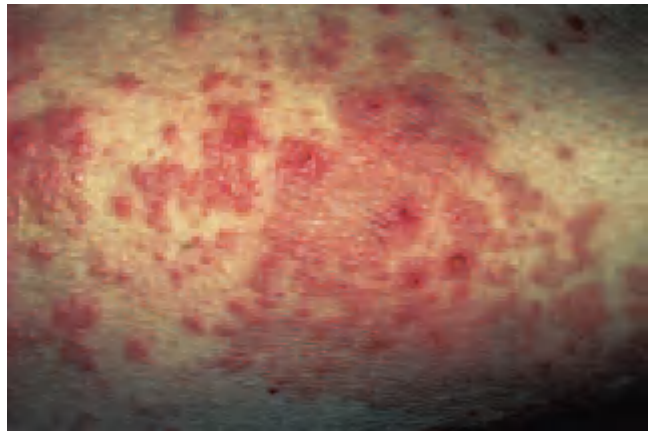

Fig. 17.27 Sulzberger–Garbe disease. (Courtesy of Dr A. Warin, Royal Devon and Exeter Hospital, Exeter, UK.)

Pathology. The histology is non-specific, and can mimic discoid eczema, allergic contact dermatitis or lichen simplex. There may be a characteristic swelling of the endothelial cells of the small vessels, which are surrounded by a 'cloudy' oedema. An infiltrate of mixed cells, including plasma cells and eosinophils, may form a mantle around the arterioles.

Clinical features. The eruption, which is exceedingly pruritic, has discoid, lichenoid and exudative phases, present together or alternately. The plaques are widely distributed (Fig. 17.27). In addition, there may be showers of round urticated lesions which appear as the discoid eczematous lesions wane.

Penile and scrotal lesions are common, and are almost pathognomonic. They are also the most persistent feature. Gynaecomastia is present in some patients [2], and blood eosinophilia is frequent.

Differential diagnosis. The differential diagnosis is wide, and includes mycosis fungoides, contact dermatitis, dermatitis herpetiformis, discoid eczema and lichen planus.

Treatment. Treatment is with systemic steroids, which may have to be continued until spontaneous resolution occurs. A rapid response to azathioprine was observed in two cases [4].

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Table 17.7 Features which distinguish between prelymphomatous (prereticulotic) eruption and persistent superficial scaly dermatitis.

Prelymphomatous eruption	Persistent superficial dermatitis
Bizarre or angulated shape	Regular, round or oval shape
Fine scale	Coarser scale
May be irritable	Little or no irritation
Progresses to cutaneous lymphoma	Does not become malignant
Histology	
Absence of epidermal eczema	May be eczematous changes
Dermal infiltrate	Little or no dermal infiltrate

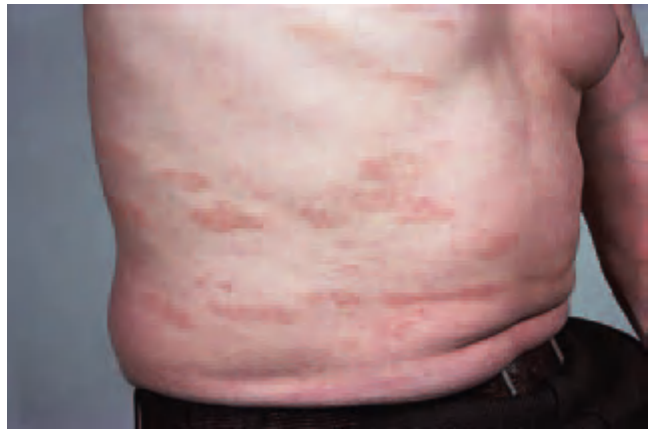

Fig. 17.28 Chronic superficial scaly dermatitis.

Chronic superficial scaly dermatitis

SYN. PERSISTENT SUPERFICIAL DERMATITIS; CHRONIC SUPERFICIAL DERMATITIS; SMALL PLAQUE PARAPSORIASIS; BENIGN FORM OF PARAPSORIASIS-EN-PLAQUES; DIGITATE DERMATOSIS; XANTHOERYTHRODERMIA PERSTANS OF RADCLIFFE-CROCKER

Definition. A chronic condition characterized by the presence of round or oval erythematous, slightly scaly patches on the limbs and trunk, which histologically show mild eczematous changes with little or no dermal infiltrate.

The condition is clinically benign by definition [1]. However, in some cases, clonality of the lymphocytic infiltrate can be demonstrated [2]—a feature suggesting that this may be regarded as an abortive form of cutaneous T-cell lymphoma [3]. Ackerman [4] has taken this argument further and expressed the view that even an abortive T-cell lymphoma is still a T-cell lymphoma so this condition is a clinical presentation of mycosis fungoides.

Nomenclature. This condition was formerly included with various potentially prelymphomatous eruptions under the general term of parapsoriasis [5–7]. The term chronic superficial scaly dermatitis was introduced by Calnan and Meara [1] to distinguish a subgroup of patients who did not progress to frank lymphoma, and the features that they used to distinguish this subgroup are shown in Table 17.7.

The nomenclature has been discussed in detail by Lambert and Everett [6].

Aetiology. The cause is unknown.

Pathology. The histology is not characteristic. It usually shows the changes of a very mild eczematous eruption, consisting of patchy parakeratosis, mild spongiosis and a slight, mainly perivascular infiltrate in the dermis, chiefly composed of lymphocytes [7].

Clinical features. The disease occurs in all races, although it is probably rare in dark-skinned people. Its geographical distribution varies considerably; for example, it is more common in the south than in the north of England, and appears to be uncommon in America. In most cases the onset is in middle life, and the disease persists indefinitely, with or without remission. It is much more common in men than in women.

The disease begins insidiously with one or more erythematous, slightly scaly patches. The legs, trunk and arms are most often affected (Fig. 17.28). It seldom involves the face, palms or soles. The patches are generally round or oval, but finger-like processes are also common, especially on the trunk, giving rise to the alternative name 'digitate dermatosis'. The patches are usually about 2.5 cm across, although much larger areas occur at times, especially on the legs. The colour is pink, brown or slightly yellow. The individual patches are often slightly wrinkled, resembling cigarette paper.

Symptoms are usually minimal, but some itching may occur. The patches are more prominent in winter than in summer, and may clear temporarily with natural or artificial sunlight. They will also clear for a time with suitable topical medications, but recur in the same—or adjacent—areas when treatment is stopped. After extending for a time, in most cases they then remain static and, with minor fluctuations, persist throughout life. In a few patients the condition clears permanently.

Some cases originally diagnosed as chronic superficial scaly dermatitis later develop reticulate pigmentation or atrophy, and these cases may then need to be reclassified as prelymphomatous poikiloderma.

Differential diagnosis. The main diagnostic problems are discoid eczema, eczematides, poikiloderma in its early phase and the early stages of the classical (Alibert) form of mycosis fungoides (Chapter 54 and Table 17.4).

The history, clinical appearance, response to treatment and histology will usually establish the diagnosis.

Treatment. Only symptomatic treatment is required to allay irritation. Mild steroid ointments are generally beneficial. Natural sunlight, broad-band UVB and PUVA can be helpful when required but relapse often occurs soon. Narrow-band UVB may also be effective in inducing remission, which can last from a few weeks to many months [8].

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Pityriasis alba

Definition. This is a pattern of dermatitis in which hypopigmentation is the most conspicuous feature. Some erythema and scaling usually precede the development of hypopigmentation but these are often relatively mild.

Aetiology. Pityriasis alba is sometimes a manifestation of atopic dermatitis but it is certainly not confined to atopic individuals.

Pathology. The histological changes are unimpressive—acanthosis and mild spongiosis, with moderate hyperkeratosis and patchy parakeratosis. There may be follicular plugging, spongiosis and sebaceous gland atrophy [1–4]. On electron microscopy there are reduced numbers of active melanocytes and a decrease in number and size of melanosomes in affected skin [3].

Clinical features [2,5,6]. Pityriasis alba occurs predominantly in children between the ages of 3 and 16 years. The sexes are equally susceptible. The individual lesion is a rounded, oval or irregular plaque, which is red, pink or skin-coloured and has fine lamellar or branny scaling. Initially, the erythema may be conspicuous and there may even be minimal serous crusting. Later, the erythema subsides completely, and at the stage at which the lesions are commonly seen by a physician they show only persistent fine scaling and hypopigmentation. It is this that commonly induces the patient to seek advice. The hypopigmentation is most conspicuous in pigmented skin, and in lighter skins may become more evident after sun-tanning (Fig. 17.29).

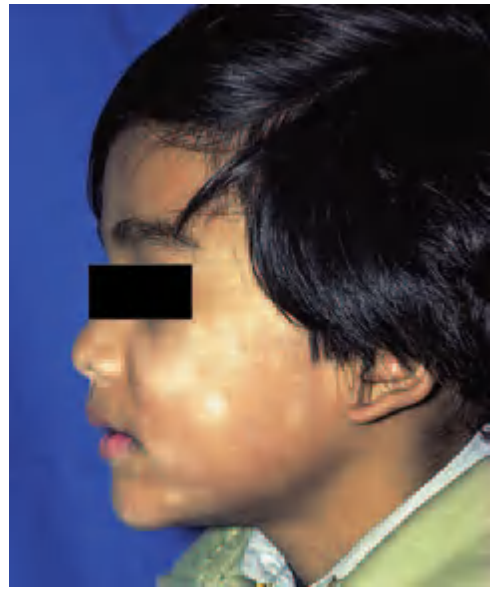

Fig. 17.29 Pityriasis alba: the failure of the affected patches to tan may first bring them to the patient's notice. (Courtesy of Dr A. Marsden, St George's Hospital, London, UK.)

There are usually several patches ranging from 0.5 to 2 cm in diameter, but they may be larger, especially on the trunk. In children, the lesions are often confined to the face, and are most common around the mouth, chin and cheeks. In 20% of affected children the neck, arms and shoulders are involved as well as the face. Less commonly, the face is spared and there are scattered lesions on the trunk and limbs.

The course is extremely variable. Most cases persist for some months, and some may still show hypopigmentation for a year or more after all scaling subsides. Recurrent crops of new lesions may develop at intervals. The average duration of the common facial form in childhood is a year or more.

Diagnosis. The age incidence, fine scaling and distribution of the lesions usually suggest the diagnosis. Conspicuous hypopigmentation may lead to a misdiagnosis of vitiligo. Discoid eczema in an atopic child is intensely pruritic, and the lesions are larger and more oedematous.

In older children and adults, the lesions on the trunk, during their early erythematous phase, may be mistaken for psoriasis but the distribution and the relatively mild scaling should exclude this diagnosis. Mycosis fungoides, although relatively rare, may present with lesions clinically resembling pityriasis alba [7]. This condition can

also be difficult to distinguish histologically, so follow-up and repeat biopsy are sometimes required.

Treatment. Response to treatment is often disappointing, mainly because the pigmentation takes a long time to recover. The scaling can be reduced by a bland emollient cream, and for chronic lesions on the trunk a mild tar paste may be helpful. Mild topical corticosteroids are helpful if inflammation persists. Topical tacrolimus and pimecrolimus are effective and well tolerated in facial atopic eczema and seem likely to prove helpful, if required, in pityriasis alba.

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Halo dermatitis

SYN. MEYERSON'S NAEVUS; MEYERSON PHENOMENON

Meyerson [1] described two patients with multiple pruritic, papulosquamous lesions surrounding melanocytic naevi (Fig. 17.30). More than 20 similar cases have since been described [2–4], mainly in young adults. Histology shows a benign naevus surrounded by a dermal lymphocytic and eosinophilic infiltrate, with overlying acanthosis, spongiosis and parakeratosis. One case developed during treatment with IFN-α2b in a patient with dysplastic naevus syndrome and Behçet's disease [5]. The condition usually resolves spontaneously within a few months, without involution of the naevus. It differs from Sutton's halo depigmentation, although the two conditions have been reported to coexist in the same patient and in one case progression to Sutton's naevus occurred [6]. Similar changes have been seen around seborrhoeic warts [7], and other elevated skin lesions [8], and termed the Meyerson phenomenon.

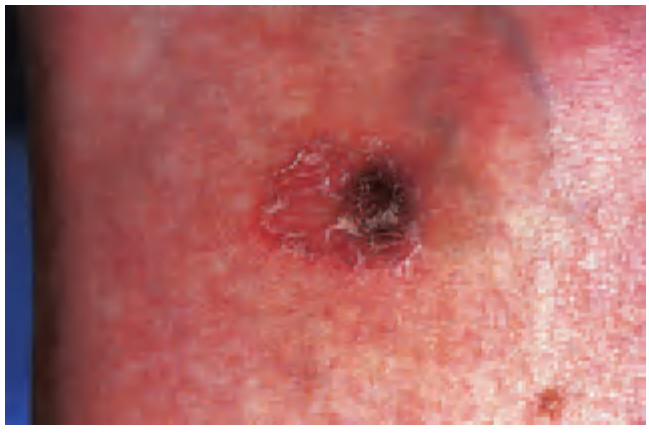

Fig. 17.30 Halo dermatitis: eczema around a mole. (Courtesy of Dr R.H. Champion, Addenbrooke's Hospital, Cambridge, UK.)

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Diagnostic tests for eczema

Most cases of eczema can be diagnosed clinically. It can sometimes be helpful to measure the total IgE level in order to determine whether an individual is atopic, particularly when the distribution of eczema is atypical and there is no background of other atopic illness. Secondary infection can be confirmed by taking swabs for culture and sensitivity to identify any bacterial resistance, such as methicillin-resistant staphylococci. When dermatophyte infection is suspected, scrapings should be taken for microscopy and culture. Microscopy can also be invaluable to confirm a diagnosis of scabies, which is easy to miss in a patient with pre-existing eczema. Biopsy can occasionally be helpful in confirming the eczematous nature of the eruption, and immunofluorescence can help identify less common conditions such as dermatitis herpetiformis or, in older patients, a non-bullous presentation of bullous pemphigoid.

Patch testing in eczema [1–3]

Routine use of patch testing is not indicated for typical presentations of endogenous eczema such as atopic dermatitis, pityriasis alba and seborrhoeic eczema. This investigation is much more important in atypical or asymmetrical eruptions and especially in dermatitis affecting the face, hands and feet [3].

Even in apparently endogenous eczema, the threshold for patch testing should be low. Sensitization commonly develops to topical medicaments, prescribed or self-administered, and this may exacerbate the eruption. Sometimes topical remedies are concealed or forgotten by the patient, or the reaction they cause is partially suppressed by the concomitant use of topical corticosteroids. Sometimes an unexpected positive test points to a 'hidden' or obscure cause (e.g. fragrances, preservatives, vehicles, epoxy or rubber chemicals). Such substances are commonly encountered in the environment and in topical medication.

When a strong suspicion of a contact allergic cause for the eczema exists, it may be important to test with other potential allergens in addition to the routine battery (e.g. household plants, material extracted from footwear, phosphorus sesquisulphide, acrylates). The observer must be wary of false-positive irritant reactions, especially in an 'excited' eczematous skin [4]. For this reason it is always wise to allow the acute phase of an eczema to subside before patch testing is carried out, or to repeat any positive tests when it has done so. If a contact urticaria is thought to be occurring, the patch tests should be read 1 h after application [5].

Even if a positive patch test is judged to be relevant (the patient comes into contact with that substance), it does not necessarily follow that the exclusion of that substance from the environment of the patient will result in a cure. The allergen may be only one of several contributory factors.

Although patch tests are designed to detect allergens, many substances give an irritant reaction when tested, and it is often difficult to be sure of the relevance of such a reaction to the patient's eczema. It must also be borne in mind that many topical medicaments can produce an irritant reaction (e.g. alcohol-based preparations and propylene glycol). The choice of concentration of test substance and suitable vehicle are vitally important (see also Chapter 20 for details of patch testing) [2].

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The management of eczema

A wide range of dermatoses are encompassed by the term eczema. Specific aspects of their treatment are described under their respective headings. Some fundamental principles of management shared by all eczematous dermatoses are described here.

Table 17.8 Indications for therapeutic agents in eczema.

Therapeutic agent	Acute	Subacute	Chronic
Rest, sedation	++	+	±
Wet dressings and soaks	++	±	–
Wet wrap bandaging	++	+	±
Paste bandages	±	+	++
Sedative antihistamines	++	++	+
Emollients	++	++	++
Corticosteroids, local	+	++	+
Pimecrolimus (topical)	+	++	++
Tacrolimus (topical)	+	++	++
Tar, ichthammol, etc.	±	+	++
Polythene occlusion	±	+	+
Intralesional steroids	–	±	+
Habit reversal therapy	–	±	+
X-ray therapy	–	–	±
Systemic corticosteroids	+	+	±
Ciclosporin	+	+	±
Azathioprine	–	+	+

In order to establish the underlying diagnosis, a careful history and examination are required. These will also help to identify additional aggravating factors (such as exposure to irritants) or complicating factors (such as infections or allergies to medications) that are playing a part in the pathogenesis. In order to optimize management, the dermatologist needs to be familiar with the patient's occupation, domestic circumstances and personality. It is also important to determine how the patient is affected by the disease. Which symptoms are most troublesome? How much embarrassment is experienced? Which aspects of the patient's work and social life are disrupted?

Previous treatment experience must be explored. It is necessary to assess how much time and effort a patient (or parent) is willing and able to devote to the care of their or their child's skin. An additional issue that must be addressed is the attitude of the patient to the risks and side effects associated with any treatment that may be required. A particularly common problem is an inappropriate level of anxiety about the use of topical corticosteroids. Only when all this information is available can the optimal treatment strategy be determined.

A considerable range of effective treatment modalities is available. These include conservative and extremely safe approaches such as rest and the application of emollients, and 'aggressive', more hazardous treatments such as phototherapy, systemic immunosuppressants or radiotherapy. Some frequently used treatments are listed in Table 17.8. When an extrinsic cause is identified or suspected this should be removed. In all cases, exposure to irritants should be carefully avoided and the skin should be protected using emollients and appropriate dressings.

Psychological support is an important aspect of management at all stages.

Acute eczema

Acute eruptions and exacerbations of eczema cause great alarm and anxiety, and the stress of the situation is usually aggravated by loss of sleep caused by intense pruritus and soreness. Patients should be reassured that the eruption will be brought under control. Adequate rest is essential, and on occasions this is best provided in a hospital bed. An affected leg should be elevated or well supported, and affected hands should be used as little as is practicable. In extremely acute hand eczema a sling is useful.

Highly oedematous, vesicular and exudative eruptions such as pompholyx benefit from soaks in an astringent such as a 1 : 10 000 solution of potassium permanganate. An alternative is Burow's solution BP, which contains the astringent aluminium acetate and is less messy than potassium permanganate. Liberal applications of aqueous cream and other bland emollients are soothing. Moderately potent or potent topical steroids are generally used, at least for a few days, to speed resolution of acute episodes. Topical immunomodulators such as tacrolimus and pimecrolimus seem likely to be beneficial in most forms of eczema and especially in atopic dermatitis [1]. Tacrolimus ointment 0.1% seems to be equivalent in potency to potent topical corticosteroids such as betamethasone valerate [2] and hydrocortisone butyrate [3]. When practical, tubular bandaging can be used to help keep topical medications in place. The wet wrapping technique, in which a layer of wet tubular bandage (e.g. Tubifast®) is covered with a dry layer, can be particularly useful. Hazards include a risk of hypothermia, although—in moderation—the cooling effect is highly beneficial. Emollients and other medications can be applied under the bandaging as required. Penetration of topical corticosteroids can be significantly increased by this form of occlusion, enhancing both beneficial and adverse effects. Mild or moderate potency corticosteroids should be used for the face and genital areas. Potent or very potent steroids are required, at least initially, for acute pompholyx on the hands or feet.

When secondary infection is present or staphylococcal contamination of the skin is thought to be an aggravating factor, oral antibiotics are often used. Topical preparations containing antibiotics or antiseptics in combination with steroids can also be helpful. These compound formulations should only be used when there is an indication for each constituent, in order to avoid unnecessary exposure to the risks of sensitization and emergence of bacterial resistance.

Excoriation can be reduced further by a sedative antihistamine such as hydroxyzine or alimemazine (trimeprazine), and additional hypnotics may be needed for a few days to ensure sleep.

Subacute eczema

If an acute eczema has failed to clear almost completely in 3–4 weeks, any perpetuating factors should be carefully sought. Has exposure to a sensitizing agent been overlooked? Has the patient become intolerant of the treatment prescribed? Has the treatment been effectively carried out?

Admission to hospital can often be helpful in these circumstances to ensure that the aetiological factors have been fully explored and that treatment will be regularly and effectively carried out. Rapid resolution usually follows admission and a period of rest. A prompt relapse on discharge may indicate photosensitivity or an allergic cause in the patient's home environment. Rapid deterioration after the arrival at the bedside of a generous bunch of flowers sometimes helps to establish the diagnosis of chrysanthemum sensitivity.

Paste bandages are of special value in occluding areas that are frequently excoriated, as in many lower leg eczemas. These must be applied skilfully to ensure that they are firm but not tight enough to cause discomfort or to restrict arterial or venous blood flow. Corticosteroids under polythene occlusion may be helpful at this stage, if only for a few days, to lessen itching. Topical immunomodulators such as tacrolimus and pimecrolimus are effective. Cleaning and bathing need not be routinely forbidden, and may be comforting, but long hot soaks and the use of soap should be discouraged. In some cases of asteatotic and discoid eczema, baths may be poorly tolerated and should be restricted. Liberal applications of emollients after bathing are helpful. Bath oils can be beneficial but are best avoided for elderly patients as they make the bath more slippery.

Chronic eczema

In chronic eczema, oedema, vesiculation and exudation give way to a more stable picture of erythema, scaling, excoriation and lichenification. Pruritus often remains troublesome, especially in atopic dermatitis. It is important to reconsider regularly whether complications such as sensitization to medicaments or superinfection are playing a part.

Emollients should be applied frequently. Soaps and other potential irritants, and sensitizers such as perfumes should be avoided. Mild, moderate or potent topical corticosteroids and topical immunomodulators are helpful [1–3]. In seborrhoeic dermatitis, and most cases of discoid eczema and atopic dermatitis, mild or moderate potency steroids are usually adequate. In severe atopic dermatitis and endogenous hand eczema, more potent steroids may be required. Long-term use of potent corticosteroids requires particular caution to minimize atrophy of the treated skin. For patients prone to frequent flares of eczema, a recently developed strategy that may prove

useful to limit steroid requirement is to induce remission with once or twice daily application of a potent topical steroid and then apply the steroid only for 2 days each week to maintain remission [4]. The use of topical immunomodulators such as tacrolimus and pimecrolimus provides a useful alternative, and these will also help in reducing cumulative exposure to steroids. This is particularly beneficial when prolonged treatment is required for eczema involving the face—a common situation in atopic dermatitis. Coal tar or shale tar (ichthammol), usually applied as creams containing tar extracts or bandages impregnated with tar paste, can be soothing and reduce pruritus. Occlusive dressings and bandages may be useful.

In the most severe cases, systemic steroids may be required. These act rapidly, improving symptoms within a day or two, but they should be discontinued as soon as possible. Alternatives to steroids include ciclosporin, which also acts rapidly [5], and azathioprine, which has a more gradual onset of action [6]. Cytotoxic immunosuppressants such as mycophenolate mofetil, methotrexate and cyclophosphamide have also occasionally been used. All these systemic modalities require careful monitoring. Various modalities of phototherapy have been successfully used in chronic eczema, especially in atopic dermatitis. These include UVB and, more recently, narrow-band UVB [7,8], PUVA [9] and UVA1 [10]. PUVA is also used for hand and foot eczema, often with topical application of 8-methoxypsoralen. However, phototherapy is potentially carcinogenic. In carefully selected cases of severe hand or foot eczema, superficial radiotherapy (Grenz rays) is effective. This is also potentially carcinogenic and is probably best reserved for older patients.

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Murray Williams' warts

Multiple seborrhoeic warts occurring in areas of resolved eczema have only occasionally been reported since the phenomenon was described by Williams in 1956 [1,2]. Multiple warts arise in the few months following resolution of the eczema and tend to gradually resolve by 5–6 months.

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Lichenification

Lichen simplex

SYN. CIRCUMSCRIBED NEURODERMATITIS

Definition. Lichenification is a pattern of cutaneous response to repeated rubbing or scratching. It is characterized histologically by acanthosis and hyperkeratosis, and clinically by a thickened appearance of the skin, with accentuation of the surface markings so that the affected skin surface resembles tree bark (Fig. 17.31). It is common in patients with atopic eczema, but may also be secondary to other irritant dermatoses.

The term *lichen simplex* is used where there is no known predisposing skin disorder, whereas if the excoriation is initiated by a pruritic dermatosis, the term *secondary lichenification* is applied. In some patients, the lichenification may become self-perpetuating after the initial dermatosis has subsided, and so the distinction between

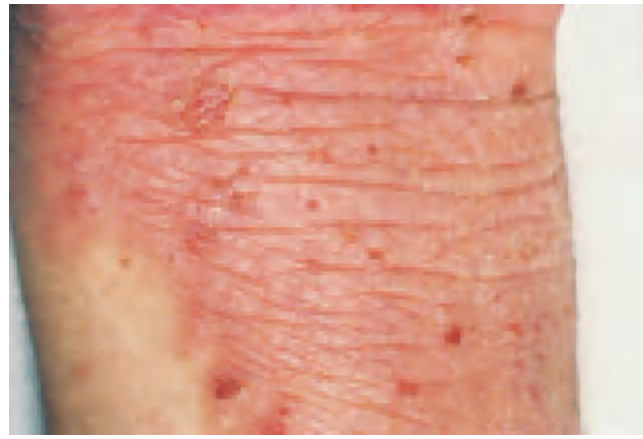

Fig. 17.31 Lichenification of the arm in a patient with atopic eczema.

primary and secondary lichenification is sometimes blurred.

Not all individuals are capable of developing lichenification. Patients with lichen simplex are more readily conditioned to scratch following an itch stimulus than control subjects [1]. Lichenification is a characteristic feature of the atopic state [2], but not all atopics lichenify, and lichenification is seen in many individuals who show no stigmata of atopy. There appears to be well-marked racial variation in the capacity of the skin to lichenify; the high incidence of lichenification in oriental people has often been emphasized.

In the predisposed subject, emotional tensions play an important part in favouring the development of lichenification and ensuring its perpetuation [3].

The borderline between lichenification and some prurigos is tenuous, both in nomenclature and in practice. Prurigo nodularis could also be called nodular lichenification.

Pathology [4,5]. The histological changes of lichenification vary with site and duration. Acanthosis and variable degrees of hyperkeratosis are usually observed. The rete ridges are lengthened. Spongiosis is sometimes present, and small areas of parakeratosis are occasionally seen. There is hyperplasia of all components of the epidermis [6]. The labelling index has been shown autoradiographically to be over 25%, but the transit time is longer than in psoriasis [7].

The dermis contains a chronic inflammatory infiltrate, and in very chronic lesions there may be some fibrosis. Silver impregnation techniques show proliferation of the Schwann cells, which may make up an appreciable proportion of the cellular infiltrate.

In very chronic lesions, especially in giant lichenification, the acanthosis and hyperkeratosis are gross, and the rete ridges are irregularly but strikingly elongated and widened.

Clinical features [5]. In all forms of lichenification, pruritus is the predominant symptom, and is often out of proportion to the extent of the objective changes. It may develop in paroxysms of great intensity. Scratching tends to give great satisfaction initially, but is then continued with violence until the skin is sore. There is then a refractory period of some hours until the itch recurs. During the early stages the skin is reddened and slightly oedematous, and the normal markings are exaggerated. The redness and oedema subside, and the central area becomes scaly, thickened and sometimes pigmented. Surrounding this central plaque is a zone of lichenoid papules, and beyond this an indefinite zone of slight thickening and pigmentation merges with normal skin. These features may be greatly modified by the site and duration of the lesion. In mild cases, follicular eczematous papules may be seen,

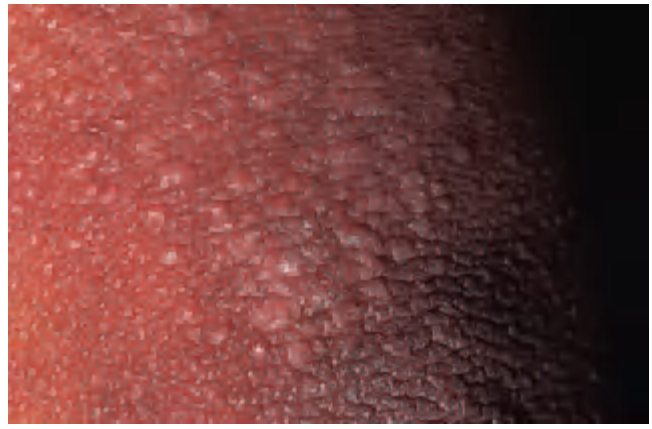

Fig. 17.32 Follicular papules of lichenification adjacent to the elbow.

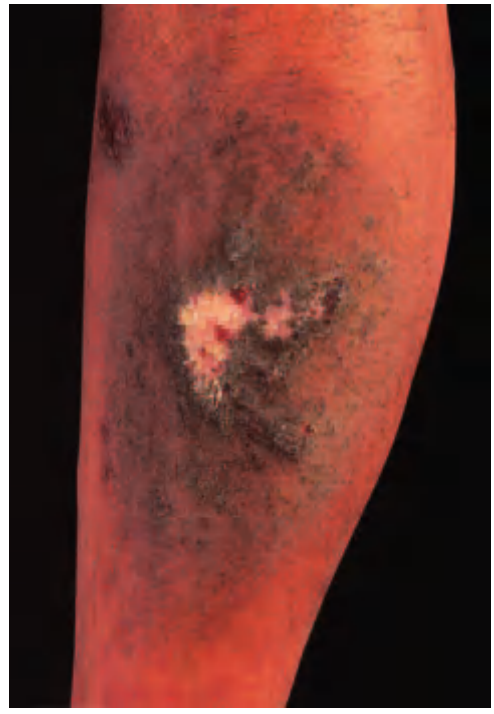

Fig. 17.33 Lichen simplex. (Courtesy of Dr D.A. Burns, Leicester Royal Infirmary, Leicester, UK.)

particularly on the forearms and elbow regions of children (Fig. 17.32).

Lichen simplex is uncommon in childhood. The peak incidence is between 30 and 50 years of age, but it is seen at any age from adolescence onwards. Women are affected more often than men. Single and multiple sites are involved with approximately equal frequency. Almost any area may be affected, but the most common sites are those that are conveniently reached. The usual sites are the nape of the neck, the lower legs (Fig. 17.33) and ankles, the sides of the neck, the scalp, the upper thighs, the vulva, pubis or scrotum, and the extensor forearms.

Lichen simplex of the nape of the neck, *lichen nuchae*, is almost confined to women. The plaque may be limited to a small area around the midline of the nape or may extend some distance into the scalp. Scaling is often profuse and psoriasiform, and episodes of secondary infection are frequent. The fold behind the ear may also be involved. Scaling, crusting and fissuring are more evident than the usual changes of lichenification. Other regions of the scalp are less often affected. The presenting manifestation is an area of scaling, with twisted broken hairs. The epidermal thickening may be great enough to form a nodule.

In other sites, the typical features of lichenification are usually retained, but if the subcutaneous tissues are lax, and excoriation continues for many years, solid tumour-like plaques may be formed, with a warty cribriform surface. This, the so-called *giant lichenification of Pautrier* [8], occurs mainly in the genitocrural region.

A localized patch of lichenification, *notalgia paraesthetica*, is described as a small patch of itchy lichenified skin most often observed at the inferior tip of the scapula.

The descriptive term *pebbly lichenification* has been applied to a distinctive clinical variant, consisting of discrete, smooth nodules, seen occasionally in atopic and seborrhoeic subjects, and in photodermatitis. Clinically it may simulate lichen planus.

A dermatomal pattern of lichen simplex chronicus has been described as the initial presentation of an intramedullary neoplasm with syringomyelia [9].

Secondary lichenification complicates persistent skin lesions of many types. It occurs on the lower leg in the presence of venous insufficiency, in atopic dermatitis, in asteatotic eczema, in low-grade chronic contact dermatitis and in some chronic infections with *Trichophyton rubrum*.

Diagnosis. The morphological diagnosis of lichenification is not usually difficult—lichen planus, lichen amyloidosus and psoriasis have to be excluded, and typical lesions should be sought in other sites. Sometimes, however, no conclusive diagnosis is possible on either clinical or histological grounds. A patient with psoriasis may occasionally develop lichen simplex that combines the histological features of both conditions.

Once the diagnosis of lichenification has been established, its causation must be carefully investigated. Symmetrical lesions in particular should suggest secondary lichenification of a contact dermatitis. More than one woman with formalin dermatitis of the base of the neck has been referred to a psychiatrist, when she should have been patch tested and advised merely to discard the offending article of clothing. Similarly, a chronic *T. rubrum* infection of the thighs or feet, with secondary lichenification, responds better to griseofulvin than to tranquillizers.

Treatment. If the lichenification is considered to be primary, a careful psychological history should be taken, and the patient given some assistance in reducing their tensions. The nature of lichen simplex and the need to break the scratching habit must be explained. Sedation is often needed, and sedative antihistamines may be helpful. A topical antibiotic may be prescribed for a few days if secondary infection is present. In most cases, a steroid cream is the treatment of choice.

On an arm or leg it is useful to apply an occlusive bandage that prevents scratching. For very chronic lesions the authors find tar paste medicated bandages very helpful. They should be renewed at intervals of 5–7 days. Self-adhesive steroid-impregnated tape (e.g. Haelan® tape) can often be effective. Alternatively, a potent steroid ointment under polythene occlusion, for short periods, may also be useful. Modest improvement has also been shown with 5% doxepin cream [10].

Circumscribed chronic lesions are often most effectively treated by dermal infiltration with triamcinolone (10 mg/mL).

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Lichen striatus

SYN. LINEAR LICHENOID DERMATOSIS

Definition and aetiology. Lichen striatus is a self-limiting, inflammatory, linear dermatitis of unknown origin. The factors determining the linear distribution are unknown, as none of the proposed embryological, neurological and vascular hypotheses is applicable to all cases. It has been suggested that the lesions develop in the lines of Blaschko [1], which are thought to be caused by a form of human 'mosaicism' in which different groups of cells behave differently for reasons that are not yet clear. In a series of 26 patients, 80% were atopic [2].

Pathology [3–5]. The histological appearances are variable, but may be distinctive. They often resemble lichen planus, with a band-like infiltrate in the dermis and overlying epidermal changes. The earliest change is intercellular oedema stretching the tonofilament–desmosome complexes and separating the epidermal cells. Like the spongiosis, acanthosis is variable in degree. Dyskeratotic keratinocytes, like the 'corps ronds' of Darier's disease, are seen in approximately 50% of cases. There is focal liquefactive degeneration of the basal layer. The dermis is oedematous, and the vessels and appendages are surrounded by an infiltrate of lymphocytes and histiocytes, which may be quite dense and extend deeply. Scattered cells often penetrate the epidermis.

Clinical features [2,6]. Over 50% of cases occur in children, usually between the ages of 5 and 15 years, but onset in early infancy and in old age has been reported. Females are affected two or three times as frequently as males. Small pink lichenoid papules, discrete at first but rapidly coalescing, appear suddenly and extend over the course of a week or more to form a dull red, slightly scaly linear band, usually 2 mm to 2 cm in width, and often irregular. Occasionally, the bands broaden into plaques, especially on the buttocks. The lesion may be only a few centimetres in length or may extend the entire length of the limb, and may be continuous or interrupted (Fig. 17.34). Parallel linear bands or zosteriform patterns have been recorded.

The initial lichenoid papules are pink and not violaceous, and show no umbilication or Wickham's striae. The papules may be hypopigmented in dark-skinned people.

The lesions occur most commonly on one arm or leg, or on the neck, but may develop on the trunk. The abdomen, buttocks and thighs may be involved in single extensive lesions, but multiple lesions are rare, and bilateral involvement is exceptional. Involvement of the nails may result in longitudinal ridging, splitting, onycholysis or nail loss [7,8].

There are usually no symptoms, but pruritus may occasionally occur. The course is variable. The lesion usually reaches its maximum extent within 2 or 3 weeks, but gradual extension can continue for several months. Spontaneous resolution can be expected within 3–6 months in most cases, but some lesions may persist for over a year. Resolution may be followed by temporary hypopigmentation.

Diagnosis. Epidermal naevi, linear or zosteriform, may first appear in childhood or later, and the inflammatory linear epidermal naevus (see Chapter 15) in particular has many clinical and histological features in common with lichen striatus, but the naevi persist indefinitely. Linear forms of lichen planus and psoriasis can usually be differentiated clinically, even in the absence of typical lesions in other sites, which should always be sought. Linear porokeratosis must also be considered [9]. Biopsy may be helpful.

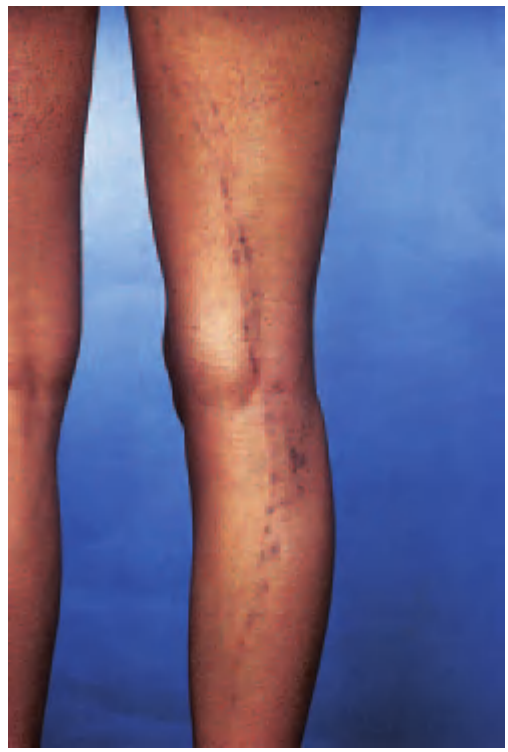

Fig. 17.34 Lichen striatus of the inner thigh in a girl aged 16 years. The histological changes were those of chronic eczema. (Courtesy of Dr R.A. Marsden, St George's Hospital, London, UK.)

Treatment. Usually none is necessary. In the unusual persistent case, infiltration with steroids may be effective. Nail involvement may respond to a potent steroid cream under occlusion.

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Prurigo

Definition. This term is best used to denote a group of skin

diseases characterized by intensely pruritic papules or nodules.

The definition has been the subject of much debate. Some authors have stressed the intense pruritus, others have emphasized visible excoriations, and yet others have suggested that there should be no identifiable local cause for the scratched lesions.

The term was originally introduced by Hebra [1] to denote papules induced by scratching. This definition allows the inclusion of entities such as the papular urticaria caused by insect bites, where dermographism may also be present. Many of the original cases of *Hebra's prurigo*, described in Vienna in the 19th century, were probably atopic patients in poor social conditions. Flea bites may well have played a part in producing the papular lesions.

The archaic term *Besnier's prurigo* has been applied to the chronic lichenified flexural form of atopic eczema.

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Nodular prurigo

SYN. HYDE'S PRURIGO

Definition. Nodular prurigo is characterized clinically by chronic, intensely itchy nodules and histologically by marked hyperkeratosis and acanthosis with downward projections of the epidermis. It is generally regarded as a variety of eczema. In many cases there is a history of atopic dermatitis or another form of eczema.

Aetiology [1]. The cause is unknown. Emotional stress seems to be a contributory factor in some cases and it can be difficult to determine whether this is the cause or a result of the prurigo. Approximately 65–80% of patients are atopic. In these patients, the age of onset may be earlier [2], even if no eczematous eruption is present. In 20% the condition starts after an insect bite [3].

Pathology [4,5]. The changes somewhat resemble those of lichen simplex, but the hyperkeratosis may be even greater, and the downward projections of the epidermis so marked as to suggest pseudoepitheliomatous hyperplasia (Fig. 17.35). The dermal infiltrate is dense, and there may be neural and vascular hyperplasia. These changes may arise, in part, as a non-specific reaction to repeated scratching [6]. In some cases the histology is that of chronic eczema. Mast cells are prominent, and there may be striking extracellular deposits of eosinophilic granule proteins such as major basic protein and eosinophil-derived neurotoxin [7], suggesting that mast cells and eosinophils may play a major part.

In the early literature, Pautrier described 'neuromas' in this condition, but these have not been seen in recent large series of patients [3,8]. However, there are increased numbers of calcitonin gene-related peptide and substance P immunoreactive nerve fibre bundles in the skin of the nodular lesions, and neuropeptides may play a part in causing the intense itching [9,10]. In 75% of cases an increase in the number of Merkel cells is also seen [11]. Such changes do not occur in the lesions of lichen simplex.

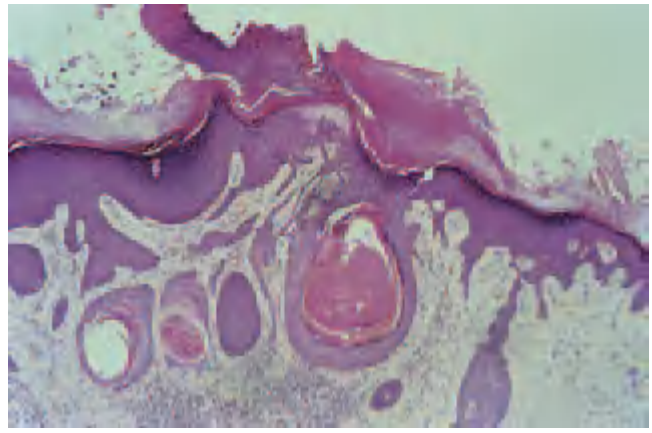

Fig. 17.35 Nodular prurigo. This shows gross accentuation of the changes found in lichenification. The epidermal downgrowth is pseudoepitheliomatous in extent. There is a mixed inflammatory cell infiltrate in the dermis and some sclerosis of the dermal collagen. H&E, × 40. (Courtesy of Dr M.G. Cook, Royal Surrey County Hospital, Guildford, Surrey, UK.)

Clinical features. Cases occur at all ages, but mainly from 20 to 60 years. Both sexes are equally affected. The individual lesions range from small papules to hard globular nodules, 1–3 cm in diameter, with a raised warty surface. The early lesion is red, and may show a variable urticarial component. Pigmentary changes are common. Crust and scale may cover recently excoriated lesions. The intervening skin often shows slight xeroderma, and there is often an irregular ring of hyperpigmentation immediately around the nodules. The number of lesions varies greatly and may be very large. The nodules may be arranged in groups. They usually develop initially on the distal parts of the limbs, and are worse on the extensor surfaces (Fig. 17.36). The trunk, face and even the palms can be affected.

The patient is tormented by crises of intense pruritus. New nodules develop from time to time, and existing nodules may remain pruritic indefinitely, although some may regress spontaneously to leave scars. The disease runs a very protracted course.

Diagnosis. The large, more-or-less symmetrical nodules, and the intense, often distressing pruritus are the key clinical features. These may also arise as a secondary event in a wide range of cutaneous and systemic diseases, which must be considered carefully before arriving at a diagnosis of idiopathic nodular prurigo.

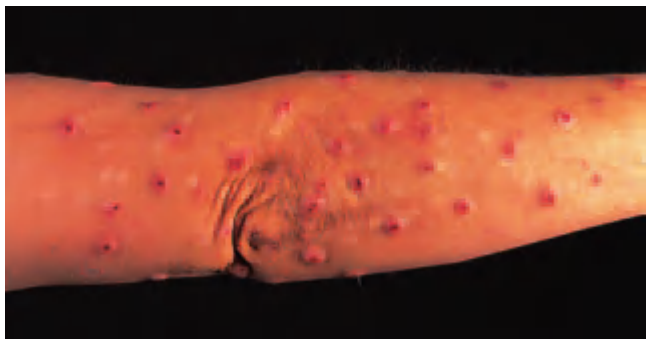

Fig. 17.36 Nodular prurigo of the arm. (Courtesy of Dr D.A. Burns, Leicester Royal Infirmary, Leicester, UK.)

Skin diseases that may mimic nodular prurigo include hypertrophic lichen planus, especially on the lower legs. The lesions are usually violaceous, and may be associated with more typical lichen planus lesions elsewhere. A variant of bullous pemphigoid called pemphigoid nodularis may present as nodular prurigo for some time before the typical urticated plaques and blisters supervene [12,13]. Immunofluorescence findings are those of pemphigoid, and the disease can be treated as pemphigoid with immunosuppressive therapy. Most cases occur in elderly women, but a juvenile form has been reported [14].

An unusual case of porokeratosis has been described in which some lesions, histologically demonstrating features of porokeratosis, clinically resembled prurigo nodules [15]. Cases are also described in association with oncocerciasis, leech bites, reactive perforating collagenosis and multiple granular cell tumours [1]. Allergic contact dermatitis may also result in a papulonodular eruption, and patch testing can sometimes be helpful [16].

Systemic causes of pruritus that can give rise to lesions resembling nodular prurigo include renal failure [17], liver disease [18], lymphoma [19] and HIV infection (see Chapter 26) [20]. Gluten-sensitive enteropathy has been found in some patients [21,22], but is not present in the majority [3,23].

Treatment. Measures used to reduce excoriation include cutting the nails very short, wearing gloves at night and occlusion of the involved regions of skin with bandages, dressings or steroid-impregnated tape. Sedative antihistamines are often used and are most helpful at night. Emollients may be helpful when xerosis is present. Topical steroids are not usually effective, but intralesional injection of triamcinolone can be beneficial. Topical capsaicin [24] has been used with success in some cases. Cryotherapy can be helpful but may result in pigmentary changes, especially in pigmented skin. Application of the sensitizer dinitrochlorobenzene (DNCB) improved nodular prurigo in one case [25].

Systemic agents, which can be highly effective, include thalidomide, although this is hazardous in fertile female patients because of teratogenicity. This drug can also induce a painful peripheral neuropathy [26,27]. Ciclosporin [28] and azathioprine [29] can also be highly effective, although the disease tends to relapse after the drugs are discontinued. Interestingly, ciclosporin also proved effective in a case associated with uraemia [30].

Nodular prurigo can respond well to PUVA, using local application of psoralen [31]. Oral PUVA is also used on occasions. A pleasing response has been reported to UVB [32], and narrow-band UVB may be effective alone and in combination with thalidomide [33].

Assessment of the patient's emotional state is desirable; antidepressants and tranquillizers can prove useful in selected cases [34].

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Chronic prurigo of adults

SYN. CHRONIC PAPULAR URTICARIA; SUBACUTE PRURIGO; PAPULAR DERMATITIS

These terms are used to denote pruritic papular eruptions, which often appear rather similar to nodular prurigo except that the lesions are smaller and less elevated. Chronic prurigo is regarded as eczematous in nature although, as in the case of nodular prurigo, a similar clinical picture can arise in patients with systemic causes of pruritus. Another similarity with nodular prurigo is the association with stress and other psychological factors in some cases. Neurotic excoriation has previously been included as synonymous with subacute prurigo (see below).

Biopsy shows a non-specific dermatitis.

Treatment is similar to that of nodular prurigo and tends to be difficult. Soothing topical applications such as crotamiton or 0.5% menthol in aqueous cream are often used. Some patients respond well to a course of UVB or PUVA [1].

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Prurigo pigmentosa [1–6]

Definition. Irritable red papules on the trunk and neck that fade to leave reticular hyperpigmentation.

Aetiology. The cause is unknown. Some cases have occurred in patients who were diabetic, dieting or anorexic, and it has been suggested that the associated metabolic changes, including ketosis, may have a role [7].

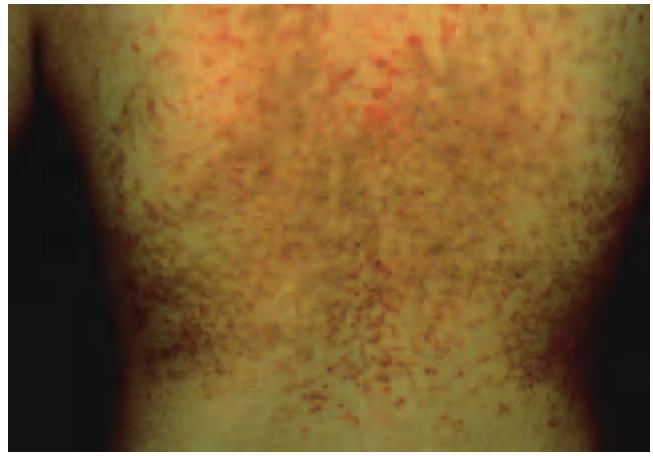

Fig. 17.37 Prurigo pigmentosa. (Courtesy of Dr M. Aso, Tottori University School of Medicine, Tottori, Japan.)

Pathology. The histology is non-specific, but often somewhat lichenoid. Immunofluorescence is negative. Occasional blood eosinophilia occurs.

Clinical features. The condition is rare in the Western world, but many cases have been described in Japan. The disorder is more common in adult females, with an onset in the spring and summer months. The characteristic lesions are found on the trunk and neck, and present as itchy red papules, sometimes with vesicles, which coalesce to produce a reticular pattern (Fig. 17.37). Later they are replaced by a reticular hyperpigmentation.

Diagnosis. This is based on the clinical and histological features. Patch testing may be helpful in excluding allergic contact dermatitis.

Treatment. Minocycline 200 mg/day appears to be the treatment of choice [1], as the pruritus and rash disappear within a week in most cases. About one-third of patients respond dramatically to dapsone. A prompt response to macrolide antibiotics has been reported [8]. Neither the rash nor the itching respond to oral antihistamines or topical steroids.

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Prurigo of pregnancy [1,2]

This is regarded as a specific dermatosis of pregnancy (see Chapter 70). It occurs in about 1 in 300 pregnancies. In some cases it appears to be a manifestation of atopy. Pruritic papules and nodules develop on the abdomen and/or limbs, usually at 25–30 weeks of gestation. These may persist for several weeks after delivery. Skin biopsy reveals non-specific epidermal thickening, parakeratosis and a lymphocytic infiltrate in the upper dermis. Immunofluorescence is negative. The itch is usually improved by potent topical steroids and sedative antihistamines. The condition is not associated with any risk to the pregnancy.

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Dermographic prurigo

This is a severe form of symptomatic dermographism in which urticarial weals and excoriations occur at sites of clothing pressure, especially around the edges of a brassiere or belt. There may eventually be some pigmentation.

Actinic prurigo

SYN. HUTCHINSON'S SUMMER PRURIGO

This is an uncommon photodermatosis (see Chapter 24).

Neurotic excoriation

This disorder, which predominantly affects middle-aged women who appear to be under emotional stress, has also been called subacute prurigo. This latter term is now more appropriately used synonymously with chronic prurigo of adults. It is not a satisfactory description of neurotic excoriation, as the lesions are excoriated erosions or ulcers rather than papules. This term should be reserved for cases where psychological factors are the primary cause of repeated excoriation. Neurotic excoriation is described further in Chapter 61.

Erythroderma

Definition. Erythroderma is the term applied to any inflammatory skin disease that affects more than 90% of the body surface. The term exfoliative dermatitis is used synonymously, although the degree of exfoliation is sometimes quite mild.

Table 17.9 Relative prevalence of erythroderma in adults.

Condition	Prevalence (%)
Hereditary disorders	
Ichthyosiform erythroderma	1.0
Pityriasis rubra pilaris	
Psoriasis	25.0
Eczema of various types	40.0
Drugs	
Especially organic arsenic, gold, mercury	10.0
Occasionally, penicillin, barbiturates, etc.	
Pemphigus foliaceus	0.5
Lymphoma and leukaemias	15.0
Other skin diseases	
Lichen planus	
Dermatophytosis	0.5
Crusted scabies	
Dermatomyositis	
Unknown	8.0

Incidence. A recent study from the Netherlands estimated the annual incidence at 0.9 per 100 000 population [1].

Aetiology [2–6]. The main causes of erythroderma in adults are listed in Table 17.9. The figures vary somewhat with the age of the population, and are based on several published studies. In younger people (e.g. military personnel) there will be a larger proportion resulting from drug allergies [6]. Drugs commonly causing erythroderma are listed in Chapter 73. In some communities the incidence of erythroderma may be higher because of self-medication and use of traditional remedies [7]. The use of herbal remedies such as St John's wort [8] may trigger this reaction.

The causes of erythroderma in the newborn are considered in Chapter 14. Other, rare causes of erythroderma include sarcoidosis [9], Hailey–Hailey disease [10], pemphigoid [11], toxic shock syndrome [12], lupus erythematosus [13], angioimmunoblastic lymphadenopathy [14] and dermatomyositis [15]. Graft-versus-host disease may progress to erythroderma in some cases. A related disorder was reported in Japan, where cases of fatal erythroderma occurred following major surgery. It was suggested that these cases were examples of post-transfusion graft-versus-host disease [16].

Erythroderma has rarely been reported with seroconversion following HIV infection [17]. In established AIDS, erythroderma can arise from a variety of causes. Some are examples of severe seborrhoeic dermatitis, others are associated with lymphoma, and some are of unknown cause [18]. However, it should be noted that $CD4^+$ T lymphocytopenia has been caused by erythroderma in the absence of HIV infection [19].

Males are affected between two and three times more frequently than females and, if the hereditary disorders and atopic dermatitis are excluded, most are over 45 years old.

Pathology. Histopathology can help identify the cause of erythroderma in up to 50% of cases, particularly if multiple skin biopsies are examined [20]. The histological appearances vary, depending upon the severity and duration of the inflammatory process. In the acute stage, spongiosis and parakeratosis are prominent, and a non-specific inflammatory infiltrate permeates, to a variable depth, a grossly oedematous dermis. In the chronic stage, acanthosis and elongation of the rete ridges become more prominent.

In erythroderma resulting from lymphoma, the infiltrate may become increasingly pleomorphic, and it may eventually acquire specific diagnostic features, such as a band-like lymphoid infiltrate at the dermal–epidermal junction, with atypical cerebriform mononuclear cells and Pautrier's microabscesses [21]. In other cases, however, it remains non-specific throughout its course, and the distinction can be difficult. Patients with Sézary syndrome often show some features of chronic dermatitis, and benign erythroderma may occasionally show some features suggestive of lymphoma.

Immunophenotyping of the lymphoid infiltrate may not solve the problem, as it generally shows features of mature T cells in both benign and malignant erythroderma [22].

In psoriasis, papillomatosis and clubbing of the papillary zones may be seen, and in pemphigus foliaceus, superficial acantholysis will be present. In ichthyosiform erythroderma and pityriasis rubra pilaris, repeated biopsies from carefully selected sites may reveal their characteristic features.

Clinical features. Erythroderma developing in primary eczema or associated with a lymphoma is often of sudden onset. Patchy erythema, which rapidly generalizes, may be accompanied by fever, shivering and malaise. Hypothermia may develop and a low-reading thermometer should be used to take the temperature.

The erythema extends rapidly and may be universal in 12–48 h. Scaling appears after 2–6 days, often first in the flexures, but it varies greatly in degree and character from case to case. The scales may be large, or fine and bran-like. At this stage the skin is bright red, hot and dry and palpably thickened. The intensity of the erythema may fluctuate over periods of a few days or even a few hours. Irritation is sometimes severe, but a sensation of tightness is more characteristic. Many patients complain of feeling cold, especially when the erythema is increasing.

When the erythroderma has been present for some weeks, the scalp and body hair may be shed and the nails become ridged and thickened, and may also be shed. The periorbital skin is inflamed and oedematous, resulting in ectropion, with consequent epiphora. In very chronic cases there may be pigmentary disturbances, especially in black people, in whom patchy or widespread loss of pigment is often seen.

The degree of enlargement of the lymph nodes in the absence of an underlying malignant lymphoma is variable. They are usually slightly or moderately enlarged and of rubbery consistency, but in some cases the enlargement may be gross. It is important that this dermatopathic lymphadenopathy is not mistaken for lymphoma. In difficult cases, lymph node biopsy may be advisable, but the pathologist must be told that the patient is erythrodermic for a reliable histological interpretation to be made.

The general picture is modified according to the nature of any underlying disease and the patient's age and general physical condition.

Eczemas. Generalization of an eczema occurs most frequently in the sixth and seventh decades when venous eczema is a common precedent. However, atopic erythroderma may occur at any age. Exacerbation of existing lesions usually precedes the generalization, which follows the usual pattern. Pruritus is often intense. Some elderly patients have increased serum IgE and lactic dehydrogenase levels, with eosinophilia [23].

Psoriasis. In generalized psoriasis, the clinical picture may also conform to the usual pattern, and when the exfoliative stage is fully developed the specific features of psoriasis are lost. In some cases, crops of miliary pustules may develop at intervals, and transition to generalized pustular psoriasis may occur, especially in cases treated with potent topical steroids or systemic steroids [24]. Emotional stress, intercurrent illness and phototherapy overdosage can also precipitate erythroderma.

Drugs. A wide range of drugs can cause erythroderma. Among the more commonly implicated are pyrazalone derivatives such as phenylbutazone, hydantoin derivatives, carbamazepine, cimetidine, gold salts and lithium [25]. The eruption may start as a generalized eczema, or scarlatiniform or morbilliform erythema, often accompanied by some irritation, which increases steadily in severity. Erythema may first appear in the flexures or over the whole skin (Fig. 17.38). This group has the best prognosis of all the causes of erythroderma [2,26], often resolving in 2–6 weeks [27].

Lymphoma, leukaemia and other malignancy. Cutaneous T-cell lymphoma is the most common malignancy to cause erythroderma, followed by Hodgkin's disease. Non-Hodgkin's lymphoma, leukaemias and myelodysplasia

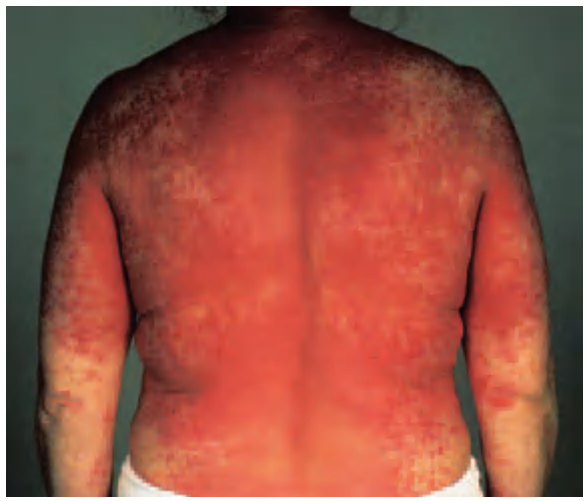

Fig. 17.38 Widespread drug rash. This will rapidly progress to erythroderma if the drug is continued.

have also been reported. Association with other internal malignancies has been observed less often [5].

The clinical picture follows the pattern already described, but the accentuation of certain features should arouse suspicion that a lymphoma is associated, even if repeated investigations over a period of months fail to provide convincing confirmatory evidence. In many such cases, the underlying disease will eventually be detected. Pruritus is often very severe. The erythroderma is universal, and the infiltration of the skin may be so severe that the patient's features are deformed. Rubbing and scratching may produce secondary lichenification. Enlargement of the lymph nodes may be considerable, even if they are histologically not involved by the lymphoma.

Biopsy of involved skin may show only non-specific features initially and may need to be repeated several times before infiltration with atypical lymphocytes becomes evident. The use of a skin biopsy for analysis of T-cell receptor genes to determine whether clonality is present in the infiltrate may prove to be a useful investigation in these circumstances [28,29]. Lymph node biopsy may be diagnostic of lymphoma but often shows only the features of dermatopathic lymphadenopathy. There may be hepatosplenomegaly. A differential white blood cell count should be performed and the blood examined for abnormal cells. Eosinophilia may suggest Hodgkin's disease. Atypical lymphocytes with cerebriform nuclei, *Sézary cells*, are often observed in erythroderma regardless of cause. When they constitute more than 20% of the circulating peripheral blood mononuclear cells they become diagnostic of the leukaemic variant of cutaneous T-cell lymphoma known as the Sézary syndrome. Large Sézary cells (15–20 μm in diameter) are diagnostic even in small numbers [30]. The demonstration of a clonal T-cell population in the peripheral blood by analysis of T-cell receptor genes, using polymerase chain reaction (PCR), appears to offer high diagnostic specificity for Sézary syndrome. The sensitivity also appears high but on occasions the test may need to be repeated if initial results are negative and this diagnosis is still suspected [30].

Pemphigus foliaceus. Moist, crusted lesions on the face and upper trunk often precede the development of the erythroderma. Scaling is conspicuous, moist and adherent. Crops of thin-walled bullae may erupt, especially on the limbs.

Ichthyosiform erythroderma. This condition is usually present from birth or early infancy.

Pityriasis rubra pilaris. The erythrodermic forms can begin in childhood or adult life. The presence of follicular horny plugs on the knees and elbows and on the backs of the fingers and toes is distinctive. In many cases, islands of normal skin persist in the erythrodermic regions, and horny plugs may be evident around their margins. These normal pale 'islands' are very suggestive of the diagnosis, and the skin on the palms and soles often has an orange discoloration.

Lichen planus. Erythrodermic lichen planus is very rare, but lichenoid reactions to gold, quinine and other drugs are not uncommon. As the initial erythema and oedema subside, individual violaceous papules may be revealed. The buccal mucous membrane may show typical lacy, bluish white streaks.

Dermatophytosis. Generalized erythroderma has very rarely resulted from chronic infection with organisms such as *Trichophyton violaceum*.

Norwegian scabies. The heavily crusted hands and feet, with thickened nails, so characteristic of Norwegian scabies, may occasionally be accompanied by generalized erythema and scaling. The condition is often mistaken for erythrodermic psoriasis. The occurrence of scabies in others in the same environment, or in the medical or nursing staff caring for the patient, will soon make the diagnosis clear.

Erythroderma of unknown origin. The percentage of cases in which no underlying disease is demonstrable diminishes with the thoroughness of investigation and the duration of observation, but in any series of cases it is rarely below 10% [3,4,27]. The cutaneous changes may precede any other evidence of a lymphoma by many months or years. If these cases are excluded, the hard core of chronic erythrodermas of unknown origin consists mainly of elderly men, in whom the condition runs a very long course with partial and temporary remissions. These have been

labelled the 'red-man syndrome'. It is characterized by marked palmoplantar keratoderma, dermatopathic lymphadenopathy and a raised serum IgE [23,31]. It is important to note that this condition is not established erythrodermic cutaneous T-cell lymphoma, which is occasionally referred to as 'l'homme rouge'.

The three most common causes of idiopathic protracted erythroderma are probably atopic dermatitis of the elderly, intake of drugs overlooked by the patient and prelymphomatous eruptions [3].

Secondary haemodynamic and metabolic disturbances. Chronic generalized erythroderma is associated with profound metabolic disturbances [11,32–34]. The blood flow through the skin is markedly increased, and this can result in high-output cardiac failure, especially in elderly patients [35,36]. The increased skin perfusion may lead to hypothermia [37]. When the body temperature is raised, heat loss is further increased. The regulation of temperature is grossly disturbed, and the patient behaves like a poikilothermic animal, tending to adopt the environmental temperature. The excessive loss of heat leads to compensatory hypermetabolism and a raised basal metabolic rate.

Fluid loss by transpiration is much increased and is roughly proportional to the basal metabolic rate. The loss of exfoliated scale may reach 9 g/m^2 of body surface or more each day [38].

Hypoalbuminaemia is common, and probably has several causes. Dilution by increased plasma volume may be one cause [39], but is likely to be less important than a lowered total albumin mass caused either by a decrease in synthesis or an increase in metabolism [40,41]. There is also an increased protein loss via scaling and exudation. Oedema is common. Occasionally, the increased capillary permeability is severe enough to justify plasma infusions as well as parenteral steroids.

Immune responses may become altered, reflected by an increase in gammaglobulins; occasional patients have been described with very high levels of serum IgE [42], and $CD4^+$ T lymphocytopenia may occur in the absence of HIV infection [19].

Elderly patients living alone may already be malnourished prior to developing erythroderma. Any exudative or extensive scaling condition will intensify this.

Prognosis and complications. Erythroderma is a serious condition in itself, quite apart from hazards associated with the underlying disease, and is sometimes fatal despite skilled management. It is particularly dangerous in elderly people. Reported death rates have varied from 18 to 64% [2,4,6], but with modern therapy the rate is probably lower.

The more common forms of erythroderma—eczematous, psoriatic or of unknown origin—may continue for months or years, and tend readily to relapse [24]. As the patients are often elderly, the prognosis must always be guarded. The metabolic disturbances involve a serious risk of hypothermia, cardiac decompensation, peripheral circulatory failure and thrombophlebitis. Cutaneous, subcutaneous and respiratory infections are common, and the majority of patients who die do so from pneumonia [24].

The treatment can also be hazardous, especially when systemic steroids and immunosuppressants are required.

Diagnosis. The recognition of erythroderma is easy, but the diagnosis of the underlying cause may be very difficult. The difficulty of exact classification of some of these cases is illustrated by the report of seven patients with erythroderma who were followed for 3–16 years before they developed the Sézary syndrome (cutaneous T-cell lymphoma). Four of these patients had multiple contact allergies or drug reactions, and one had severe atopic dermatitis [43].

The history is often helpful in identifying the hereditary disorders, drug reactions and psoriasis, but in some cases the erythroderma is of sudden onset and the history may not be helpful. Multiple biopsies are usually, but not invariably helpful [44], and the eczematous erythrodermas and those associated with lymphoma may not show any distinctive histological features.

Treatment. Treatment in hospital is advisable, because some patients can develop serious general medical problems. In these cases, the protein and electrolyte balance, circulatory status and body temperature require continual surveillance. The environmental temperature must be carefully regulated. Cooling and overheating must both be avoided by the use of extra blankets or fans, respectively.

Urea and electrolyte levels and fluid balance should be monitored. Adequate fluid intake must be maintained, but if there is oedema, diuretics and/or plasma infusion should be considered. Cardiac failure must be treated if it develops.

The possibility that the erythroderma is caused by a drug reaction should be considered in every case, and all non-essential drugs should be withdrawn.

The cutaneous inflammation should be treated in the first instance with soothing emollient creams, or a mild topical steroid. The majority of patients will improve over a week or two on this regimen, during which time the diagnosis of the underlying condition will probably be established.

If active topical medication is applied it must be remembered that the barrier function of erythrodermic skin is greatly reduced. This is potentially hazardous because topical application of medications such as salicylic acid, corticosteroids or vitamin D analogues will result in much higher systemic exposure than might be expected in other circumstances.

Many dermatologists prefer to avoid systemic steroids if possible, because of the dangers of fluid retention, secondary infection and diabetes, but in severe persistent cases they may become necessary. There is some evidence that the use of systemic steroids or potent topical steroids in psoriatic erythroderma can provoke the development of pustule formation [24]. In such cases, low-dose methotrexate, acitretin or ciclosporin [33] may be safer alternatives. Topical tar and UV therapy should also be avoided on erythrodermic psoriasis.

Antibiotics are required to control secondary infection. Heng [45] has suggested that colonization of the skin by *Staphylococcus aureus* may actually cause erythroderma, which will clear with appropriate antibiotic therapy.

The optimum treatment of erythrodermic cutaneous lymphoma is still debated. Options include systemic steroids, PUVA, total body electron beam irradiation, topical nitrogen mustard and systemic chemotherapy [46]. The use of methotrexate has appeared beneficial in a retrospective study of 29 patients [47]. However, diagnostic histology was only obtained in 13 of these cases so they may have been a somewhat heterogeneous group. Extracorporeal photopheresis has been advocated [48], but it is not yet clear whether this prolongs survival.

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Papuloerythroderma of Ofuji [1–5]

This distinctive pattern of erythroderma was described by Ofuji *et al*. in 1984 [1]. It differs from ordinary erythroderma in that papulation is prominent, it tends to spare the face and flexures, and it is consistently and often intensely pruritic.

It is not yet clear whether this represents a distinct disease or a reaction pattern. Although most cases have been seemingly idiopathic, several have been reported in association with other diseases.

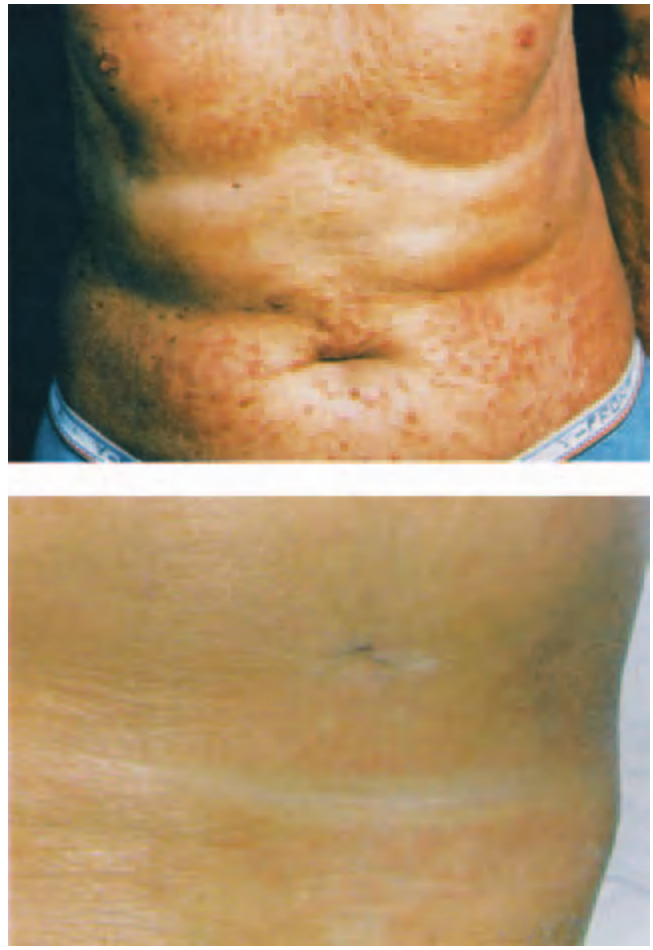
Pathology. Histological features are usually non-specific. In the epidermis there are variable, but most often mild degrees of acanthosis, spongiosis, hyperkeratosis and focal parakeratosis. There is marked lymphohistiocytic infiltration of the dermis, predominantly perivascular in distribution, with a variable and often conspicuous number of eosinophils. A mild degree of epidermotropism has occasionally been observed and, rarely, plasma cells and multinucleate giant cells. Immunofluorescence is negative.

Clinical features. Papuloerythroderma has been observed entirely in an elderly population with ages at diagnosis ranging from 57 to 100 years. Many cases occur in the eighth or ninth decades. Males are predominantly affected, the male : female ratio being estimated at 4.7 : 1 [2].

The erythroderma typically begins with an eruption of brownish red, flat-topped papules, which become confluent (Fig. 17.39a). The limbs and trunk are affected but the face and flexures, especially axillary and inguinal regions, tend to be spared. A characteristic and distinctive pattern of sparing of the abdominal flexures has been termed the 'deck chair sign' [3], indicating the similarity to the distribution of sunburn in one who has been sitting out in a deck chair for too long (Fig. 17.39b). The lesions sometimes develop along scratch marks. Pruritus is a consistent feature and ranges from moderate to extremely severe. Additional features often observed include hyperkeratosis and fissuring of the palms and soles and benign lymphadenopathy.

There is usually circulating eosinophilia and a raised IgE. There is often a mild degree of absolute or relative lymphocytopenia.

Reports of papuloerythroderma occurring in association with malignancies, which have included T-cell [4,5] and B-cell lymphomas [5], gastric [5], lung [5], colon [6] prostate [2] and hepatocellular carcinomas [7], would suggest that this eruption may sometimes occur as a paraneoplastic phenomenon. There are also several reports that papuloerythroderma may progress to mycosis fungoides [2,8,9], in one case 11 years after the onset of symptoms [10]. In some cases, papuloerythroderma therefore seems to be a presentation of cutaneous T-cell lymphoma. One case developed into psoriasis [2]. Papuloerythroderma has also been reported in association with HIV infection [11,12] and, in one case, biliary sepsis [13].



(a)

(b)

Fig. 17.39 Papuloerythroderma of Ofuji. (a) The papules. (b) The 'deck-chair' sign (sparing of the body folds). (Courtesy of Dr M.J. Tidman, Edinburgh Royal Infirmary, Edinburgh, UK.)

Treatment. Emollients, topical corticosteroids and antihistamines have produced a slow response in some cases. The condition can respond well to oral prednisolone, although high doses are sometimes required. PUVA, including bath PUVA, has proved effective in several reports. Azathioprine [14], ciclosporin [15] and etretinate [16] may be effective. In view of the possible associations with malignancy and HIV infection, and as some cases progress to cutaneous T-cell lymphoma, the use of retinoids or PUVA would seem preferable to immunosuppressant drugs. However, papuloerythroderma is sometimes very refractory to treatment. It typically persists for many years but some cases have remitted.

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Eosinophilic pustular folliculitis

The term eosinophilic pustular folliculitis has been used to describe several conditions characterized histologically by follicular and perifollicular inflammation containing numerous eosinophils. The original cases were described by Ofuji in immunocompetent Japanese patients [1]. Subsequently, the term was used for a rash with a different appearance in infants [2,3] and in immunocompromised patients on chemotherapy or with AIDS [4,5], or in patients who had received a bone marrow transplant [6]. These latter conditions are discussed elsewhere (see Chapters 26 and 59). Ofuji's variant is discussed here although its nosology is uncertain at present. Morphologically it is more like pustular psoriasis and subcorneal pustular dermatosis than eczema. The plaques in the Ofuji variant tend to be larger and more florid than the skin lesions in the immunocompromised patients.

Eosinophilic pustular folliculitis of Ofuji

Definition. This is an inflammatory disease characterized by the presence of plaques studded with numerous papules and sterile pustules in the seborrhoeic areas of the skin [1,7–10].

Aetiology. The cause is unknown.

Pathology. The inflammation is mainly centred on the hair follicles, which are infiltrated by eosinophils, with some neutrophils and mononuclear cells. There may be some degree of spongiosis and even destruction of the upper part of the follicle, to form a sterile eosinophilic pustule. The condition also affects the epidermis outside the follicles, where there is spongiosis and a tendency to form intraepidermal eosinophilic abscesses. There is a perivascular dermal infiltrate. Immunohistochemical analysis shows expression of adhesion molecules predominantly on follicular epithelium and perifollicular vascular endothelium. The authors suggested that these findings could explain the predominantly follicular distribution of the inflammation [11]. Chemotactic factors for eosinophils and neutrophils have been found in lesional stratum corneum extracts [12].

Clinical features. More than 90% of cases reported are from Japan and it is rare in other countries. Most non-Japanese patients have had the type associated with immunodeficiency or the infantile type, but some appear to have the Ofuji variant [10].

This disorder usually starts in adult life with pruritic circinate or serpiginous plaques, which are studded with follicular papules and pustules. There is a tendency to peripheral spread and central clearing. The lesions are located mainly on the face, trunk and extensor surfaces of the upper arms. Much less commonly, there is involvement of the palms and soles [13], and the term pustular folliculitis is then inappropriate. In severe cases, there may be scarring alopecia of the scalp [14]. There is a tendency for the disease to go into remission, followed by periodic exacerbations, which are accompanied by circulating leukocytosis and eosinophilia. When the inflamed plaques have reached a certain size, they tend to subside, leaving slight pigmentation.

Diagnosis. The condition can be confused clinically with other forms of folliculitis, follicular eczema, subcorneal pustular dermatosis or pustular psoriasis. The histology, however, is characteristic.

Treatment. The cases originally described by Ofuji [1] responded well to treatment with prednisolone, but this has not been true for all subsequent cases. Some patients have responded to dapsone [15], and others have responded to topical steroids, minocycline, oxyphenbutazone or IFN-γ [16]. In the AIDS-associated variant, some patients respond to permethrin cream [17] or oral itraconazole [18], but a few do not respond well to any treatment.

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Chapter 18

Atopic Dermatitis

P.S. Friedmann & C.A. Holden

Definition

Atopic dermatitis is a difficult condition to define, because it lacks a diagnostic test and shows variable clinical features. The following definition seems to be in accord with most consensus groups. Atopic dermatitis (which is synonymous with atopic eczema) is an itchy, chronic or chronically relapsing, inflammatory skin condition. The rash is characterized by itchy papules (occasionally vesicles in infants), which become excoriated and lichenified, and typically have a flexural distribution. The eruption is frequently associated with other atopic conditions in the individual or other family members [1–3].

Atopy

One of the difficulties in defining atopic dermatitis arises from the impreciseness of its association with atopy and the nature of atopy itself. The word 'atopy' was introduced by Coca [4] in 1923 as a convenient collective term for a group of diseases, chief among which are asthma and hay fever, which occur spontaneously in individuals who have a family history of susceptibility. Later [5], reagin (IgE) antibodies were detected in these individuals, and could be transferred to normal individuals by the Prausnitz–Küstner (PK) test. The atopic diseases were once considered to be peculiar to humans, but it is now recognized that several species are susceptible. Atopic dermatitis and disorders resulting from anaphylaxis, for example those resulting from insect stings and food allergies, were found to be associated with IgE antibodies and therefore grouped with the atopic diseases. Such grouping is not completely acceptable, as 20–40% of individuals with atopic dermatitis can have a normal total or specific IgE level [6], and it is rarely attributable to a specific allergic reaction; the IgE antibodies present in the blood often appear to be incidental to the condition.

Recently, it has been debated whether the group with dermatitis and normal IgE levels can be distinguished clinically, immunologically and prognostically [7]. This subgroup has been variably termed intrinsic, non-atopic infantile eczema or atopiform dermatitis [8].

Terminology

This debate has added to the already wide variety of historical names for the condition. Currently, 'atopic dermatitis' and 'atopic eczema' are the most widely used. 'Besnier's prurigo' was used in continental Europe. Previously used terms include 'disseminated neurodermatitis',

spätexudatives Ekzem and *prurigo diathésique*. We suggest maintaining the use of the term 'atopic dermatitis' until the clinical relevance of dividing the disease into subgroups is confirmed.

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Diagnostic criteria

Hanifin and Rajka [1] proposed major and minor diagnostic criteria based on their clinical experience. These criteria allow a uniformity of diagnosis for hospital-based and experimental studies but are not helpful for population-based studies [2]. The major criteria are found consistently in cases of atopic dermatitis, but the minor criteria are commonly found in control groups [3]. In addition, the criteria have not been validated against a physician's diagnosis or tested for repeatability.

In order to address these issues, Williams coordinated a UK working party to attempt to refine the criteria of Hanifin and Rajka into a repeatable and validated set of diagnostic criteria for atopic dermatitis [4–6] (Table 18.1).

These diagnostic guidelines appear to be valid for adults, children and non-white ethnic groups suffering from atopic dermatitis [6], and have been validated in a population setting [7]. They were primarily developed for epidemiological studies and, of necessity, exclude some signs that could be useful for diagnosis in individuals but are not common enough for use when assessing large populations.

More recently, other modifications of the diagnostic criteria have been proposed, but these have been less rigorously validated [8].

Table 18.1 The UK refinement of Hanifin and Rajka's diagnostic criteria for atopic dermatitis. (From Williams *et al*. [6].) Scabies should be excluded.

In order to qualify as a patient with atopic dermatitis with the UK diagnostic criteria, the child must have:
- An itchy skin condition (or parental report of scratching or rubbing in a child)

Plus three or more of the following:
1 Onset below age 2 years (not used if child is under 4 years)
2 History of skin crease involvement (including cheeks in children under 10 years)
3 History of a generally dry skin
4 Personal history of other atopic disease (or history of any atopic disease in a first-degree relative in children under 4 years)
5 Visible flexural dermatitis (or dermatitis of cheeks/forehead and outer limbs in children under 4 years)

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Prevalence

Although it is accepted that atopic dermatitis is a common disease, precise measurement of its frequency is difficult, because different methods of assessment have been used. For example, some studies have based information purely on questionnaire results without objective validation of the quality of responses. Other studies have used clinical examination by dermatologists to supplement and confirm data from interview and questionnaire. Detailed reviews of the prevalence studies are to be found in McNally and Phillips [1] and Williams [2]. The International Study of Asthma and Allergies in Childhood (ISAAC) used cross-sectional questionnaires to sample school children of 6–7 years and 13–14 years in 56 centres throughout the world. A history of an itchy relapsing rash affecting skin creases in the previous 12 months was a main outcome measure.

Overall, from the ISAAC study data and many other studies, a pattern emerges that atopic eczema is most prevalent in the most developed 'Westernized' countries, and least prevalent in the most non-Westernized and underdeveloped countries. Thus, in Norwegian children from 7 to 13 years of age, the cross-sectional prevalence was 19.7% [3]. In Danish children up to 7 years of age, the lifetime prevalence was 22.9%, whereas in Germany and Sweden 13.1% and 15.5%, respectively, were reported [4].

In England, the point prevalence in 3–11-year-old children was found to be 11.5–14% [5], and the 1-year period prevalence was reported as 11.5% [6]. In Japan, figures of 9.5% and 20% have been reported for elementary school children and 3-year-olds, respectively [7,8]. By contrast, in Tanzania, the point prevalence in 7–8 year olds was found to be only 0.7% [9].

Studies of migrants show some interesting patterns. There are reports comparing the frequencies of atopic eczema in particular ethnic/genetic groups in their homeland with those in their adopted new homeland. For example, children who migrated to New Zealand from Tokelau have a much greater prevalence of atopic eczema than those in their country of origin [10]. Immigrant populations appear to develop a prevalence of atopic eczema even greater than that of the indigenous population of their adopted homeland. Thus, black Afro-Caribbean children residing in London were shown to have twice the prevalence (16.3%) of atopic eczema of their Caucasian counterparts (8.7%) [5]. A study from Sweden showed that immigrant Turkish children had a significantly higher prevalence of atopic disease (32.4%) than Swedish children (6%) [11].

These observations clearly reflect the fact that environmental factors play a large part in determining the expression of atopic diseases. The tantalizing question is whether the Westernized countries have an environment that actively promotes the atopic phenotype, or whether the underdeveloped world has factors that actively suppress the expression of the atopic phenotype.

There is accumulating evidence that the prevalence of atopic diseases in general and atopic eczema in particular have been increasing over the last three or four decades. Among the epidemiological experts, there is concern that changing methods of assessment and methodological errors may have distorted the true picture [12]. However, a composite picture from many studies suggests that the cumulative incidence in children up to 7 years of age was less than 3% if they were born before 1960, 4–8% for those born between 1960 and 1970, and 8–12% for those born after 1970.

In the elegant twin studies by Schultz Larsen, the cumulative incidence was shown to rise progressively from about 3% for twins born between 1960 and 1964, to 12% for those born between 1975 and 1979 [13,14]. Selnes *et al*. surveyed large numbers of Norwegian children (7–13 years of age) in 1985 and 1995, and found the cumulative incidence of atopic eczema had risen from 13.2% to 19.7% over the intervening 10 years [3]. The reasons for this steady rise in the prevalence of atopic diseases is not clear, but there are a number of possible environmental candidates (see below).

The consequence of the rising prevalence of atopic eczema is a heavy burden on medical services and budgets. In Britain, it has been estimated that the annual cost of atopic dermatitis is about £465 million [15], and in the USA, insurance payouts to cover the costs of atopic eczema have been estimated at between $0.9 and $3.8 billion [16].

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Aetiology

Genetic factors

The importance of genetic factors in determining the expression of the atopic phenotype is reflected in data from twin studies. Thus, monozygotic twins have a concordance rate of 0.72, whereas dizygotic twins have a concordance rate of only 0.23 [1–3].

Recently, studies of genetic linkage have identified a number of genes related to the expression of different atopic syndromes, IgE levels, and cytokines relevant to the regulation of IgE levels. However, no gene of causal significance has yet been identified for atopic eczema. A gene predisposing to atopy, as defined by hyper-IgE responsiveness, was found on chromosome 11q13 [4,5], and it may encode the β chain of the high-affinity IgE receptor FCεR1β [6]. However, there appears to be no linkage of atopic eczema to this gene [7,8]. Genes on

chromosome 5q encoding the interleukin-4 (IL-4) gene cluster have been linked to atopic mucosal syndromes [9], but this linkage has also not been confirmed [10]. A gene at 16p11.2–12 encoding the α chain of the IL-4 receptor has been linked to atopy [11–13]. The gene encoding mast cell chymase has been linked to atopic eczema [14,15], but this association has not been confirmed [16]. Variants in the RANTES gene promoter-region have been reported to be associated with atopic eczema [17].

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Maternal factors and inheritance

There is accumulating evidence that atopic disorders are more frequently transmitted by mothers than by fathers. A number of population-based surveys have shown that the risk of children developing atopy is significantly greater with an atopic mother than with an atopic father [1,2]. Cord blood IgE is high in babies whose mothers are atopic or have high IgE, whereas paternal atopy or raised IgE were not associated with raised cord blood IgE.

Genes encoding IgE responsiveness, located on chromosome 11q13, are more frequently inherited from the maternal side [3,4]. Thus, of 203 sib pairs analysed, 62% shared the maternal allele and 38% did not. Of the alleles that were paternal, the proportion shared with the offspring was close to 50%.

Pregnancy/intrauterine factors

The question arises of how maternal factors can modify the expression of atopy. One possible mechanism is through so-called genetic imprinting—in which paternal genomic effects are suppressed. Another possible mechanism is intrauterine programming—a major factor of which is the balance between fetal nutrition and growth rate. A number of non-dermatological conditions are programmed in fetal life. For example, death rates from coronary heart disease fell progressively between those who were less than 5.5 lb (2.5 kg) at birth and those who were more than 9.5 lb (4.3 kg) [5]. For atopy, there is a positive correlation between increasing birth weight and prevalence of atopic eczema [6–8]. A third possible factor is the onset of immunological sensitization through intrauterine exposure to food and environmental allergens. Cord blood IgE levels and the presence of antigen-specific T lymphocytes in cord blood indicate that immune sensitization occurs in fetal life. The concentration of IgE in cord blood is a predictor for subsequent development of atopy [9]. Maternal exposure to a number of agents, including antigens, alcohol, cigarettes and other pollutants, has attracted attention, but none has emerged as a major regulatory factor.

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Environmental factors

The rate of increase in the prevalence of atopic eczema is too rapid to be accounted for by changes in population genetics. Therefore, environmental factors are the most likely modulating influences. The two principal aspects that have attracted attention are 'pollution' and microbes.

The fall of the Berlin Wall separating East and West Germany provided an opportunity to examine the role of industrial pollution by comparing the 'dirty' East with the 'clean' West. Cohorts of preschool children from comparable cities in the East (Halle) and West (Duisburg) and a rural area (Borken), were recruited in one study [1]. Questionnaires assessed the personal and family history of atopic disease, as well as many of the relevant factors such as socio-economic status. All of the children were examined by dermatologists. The levels of airborne pollutants were compared, and sulphur dioxide was fourfold higher in Halle, whereas dust and nitrogen oxides were comparable between the cities. The prevalence of atopic eczema was 17.5% in Halle, but only 5.7–7.3% in Duisburg. However, conflicting findings emerged in a study comparing the prevalence of atopic disease in Leipzig (East Germany) and Munich (West Germany). A slightly lower prevalence was observed in Leipzig compared with Munich [2]. The identification of relevant pollutants that might contribute to the expression of the atopic phenotype is still confused. Indoor pollution levels from cigarette smoke or nitrogen oxides in the gas exhaust from cookers and heaters are difficult to quantify.

Environmental microbes—the hygiene hypothesis [3,4]

Interaction with environmental microbes may be important in the causation of atopic eczema in a number of ways. Early-life exposure may condition the maturation of the immune system so that the apparent dysregulation associated with production of IgE antibody and formation of allergies does not occur. In individuals with the atopic phenotype, eczema may be induced or exacerbated by staphylococcal toxins or by the presence on the skin of *Malassezia* yeasts. The possible role of microbes in the early maturation of the immune system may be the major factor that could explain the differences between the Western world and the developing world regarding the incidence of atopy and allergic diseases. This idea was initially proposed as the 'hygiene hypothesis' [4]. Indirect support for this hypothesis derives from the observations that allergic sensitization is greatest in first-born and is less frequent in children from large families [4].

Many studies have examined the effects of particular organisms or routes of infection, and a preponderance of findings suggest that microbes entering via the faecal–oral route have a greater protective effect against the development of atopic allergic diseases than those entering via respiratory routes. Thus, early exposure to hepatitis A virus, *Helicobacter pylori* or *Toxoplasma gondii* is reported to reduce the risk of atopy by more than 60% [5]. By contrast, it seems that exposure to respiratory pathogens is not associated with this effect [5].

Significant differences have been observed in the prevalence of allergies between rural and urban areas within one country, which could also reflect different levels of exposure to microbes. Moreover, there are differences in the prevalence of allergic diseases among children living on farms and those living in the same rural environment, but not on farms [6–9]. This difference suggests that contact with livestock and poultry is a key factor, and although the levels of aeroallergens are likely to be higher in the farm environment, the levels of bacterial endotoxin are also much higher in the household dust from farms [8,10].

The potential importance of endotoxins lies in the powerful effects they can have in regulating the responses developed by the immune system (see below). The possibility that microbial endotoxins play a major role in driving the immune system towards 'productive'/protective responses and away from non-productive/nuisance responses associated with allergy, suggests that what matters is the total microbial burden to which the immature immune system is exposed, rather than particular infections. The effects of bacterial endotoxins on immune function will be discussed below in the section on immune dysregulation.

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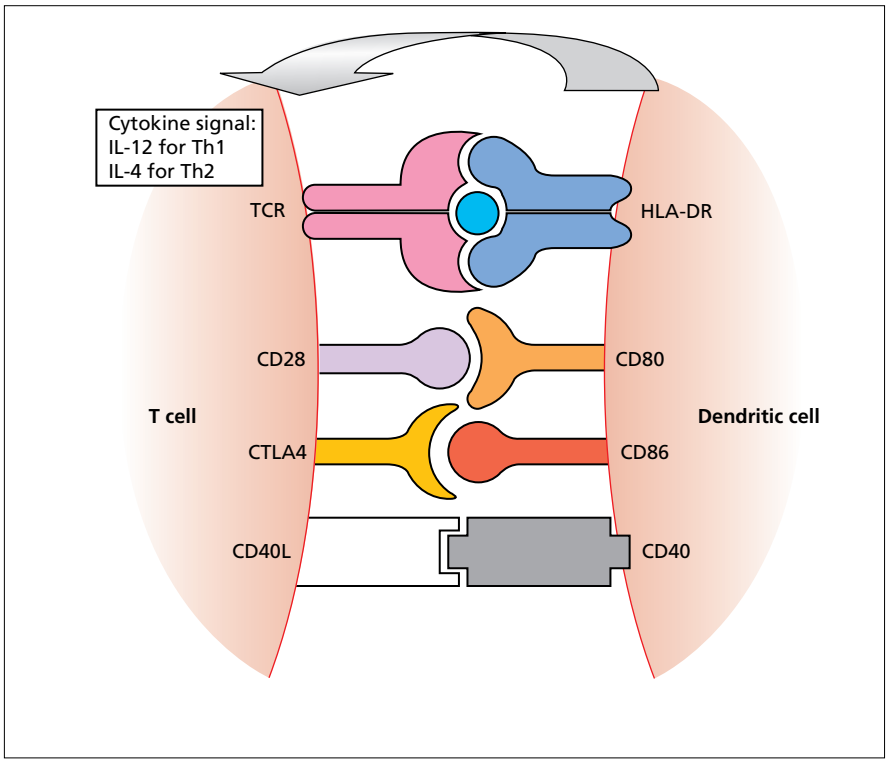

Fig. 18.1 Activation of naive T lymphocyte by interaction with dendritic antigen-presenting cell. Signal 1 comes from interaction of the T-cell receptor (TCR) with the complex of MHC class II and the antigenic peptide (blue circle) lying within its groove, on the surface of the dendritic cell. Signal 2 results from the interaction of co-stimulatory molecules (CD80, 86 and 40) on the dendritic cell with their counter receptors. CD28 is thought to give positive signals whereas CTLA-4 appears to give negative or inhibitory signals. Signal 3 is given by soluble cytokines including IL-1β and IL-12 which drive T-cell differentiation towards a Th1 phenotype, and IL-4 which favours differentiation towards the Th2 type.

Immune dysregulation

The defining characteristic of the atopic immune system is the capacity to generate IgE antibodies in response to allergens. The key disturbance to immune regulation that results in this IgE production appears to be the differentiation pathway followed by $CD4^+$ helper T lymphocytes. Naive precursor Th0 cells are induced to differentiate into Th2 cells, characterized by the production of interleukins (IL) -4, -5 and -13. Th2 cells 'help' or control the type of immunoglobulin (Ig) that B lymphocytes make, inducing synthesis of IgE.

Cellular mechanisms

The regulatory mechanisms that underlie the preferential development of Th2 cells appear to involve the interaction between dendritic antigen-presenting cells and $CD4^+$ helper T lymphocytes. The question arises of whether there is something different about the dendritic cells (DCs) of atopic individuals and the signals they give to T cells, or whether there is a defect in the T cells themselves.

Dendritic cells. Much work has gone into examining the mechanisms by which DCs regulate the differentiation of Th cells, and there is accumulating evidence that DCs may also subdivide into DC1, preferentially inducing Th1 cells, and DC2, inducing Th2 cells [1]. The critical stimulus, 'signal 1', is given during the presentation of antigenic peptides held in the groove of major histocompatibility complex (MHC) class II molecules (Fig. 18.1). Secondary signals ('signal 2') come via interactions of 'co-stimulatory' surface molecules such as CD80 and 86 on the DCs with their counter receptors CD28 and CTLA4 on the T cells. In murine systems, signalling via CD80 can preferentially induce Th1 differentiation, and CD86 can induce Th2 differentiation [2]. There is evidence that signalling through CD28 gives a positive activation signal, whereas signalling through CTLA4 may either give an inhibitory signal or activate T-regulatory cells which have inhibitory (suppressor) activities [3]. In addition, binding of CD40 ligand on T cells interacting with CD40 on the DC is one of the strongest signals for the T cell to produce interferon-γ (IFN-γ) and to differentiate towards a Th1 phenotype [4,5]. Cytokines released from the DCs give 'signal 3', which is also important in determining the final differentiation into Th1 or Th2 cells. IL-12 drives a Th1 response and IL-4 drives a Th2 response (Figs 18.1 & 18.2) [6–8].

There is little direct evidence that DC function is altered in atopic individuals. However, it has been observed that monocytes from atopic donors produce greater quantities of prostaglandin E_2 (PGE_2) and IL-10 than cells from non-atopic individuals [9,10]. PGE_2 can suppress production of IFN-γ, a cytokine which is not only produced by Th1 lymphocytes but which also favours the differentiation of naive Th0 cells towards the Th1 phenotype. Similarly, IL-10 is both a suppressive/regulatory cytokine and also drives Th0 cells towards a Th2 phenotype [11]. DCs from atopic individuals have yet to be shown to behave similarly.

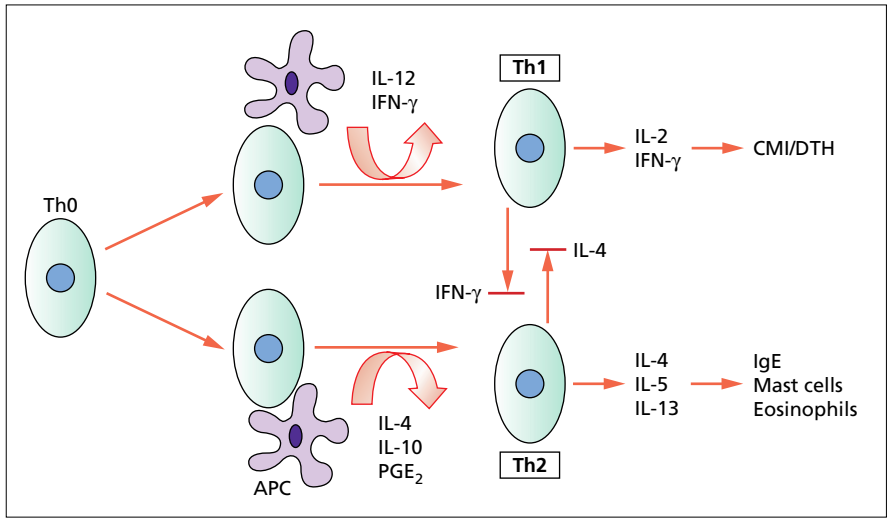

Fig. 18.2 Differentiation of helper T lymphocytes. Precursor Th0 cells have the potential to differentiate into either Th1 or Th2 type cells, depending upon the signals they receive during the interaction with dendritic antigen-presenting cells (APC) (see also Fig. 18.1). Depending upon the cell surface co-stimulatory molecule interactions and the presence of particular cytokines, the differentiation is directed. IL-12 is the critical determinant of Th1 generation, IL-4 and possibly IL-10 drive Th2 formation. Atopic monocytes (and hence possible dendritic cells) produce increased amounts of prostaglandin E_2 (PGE_2), which helps drive T-cell differentiation towards the Th2 phenotype.

A property of DCs in atopic individuals that has attracted much interest is the finding that they bear antigen-specific IgE on their surface [12,13]. The IgE is bound to the high-affinity receptor for IgE, FcεR1, normally found on mast cells and basophils [14–16]. There is controversy as to whether FcεR1 is expressed exclusively on DCs from people with atopic eczema, or whether it can be expressed in atopic individuals without eczema but with active 'allergic' disease such as asthma [16,17]. FcεR1 on DCs differs from that on mast cells and basophils in that it comprises the alpha and gamma chains, but lacks the beta chain [18]. This may alter its capacity either for expression on the cell surface or for activating intracellular signals [18]. FcεR1 is induced on DCs by IL-4 and possibly also by high levels of IgE. The surface-bound IgE on DCs has been shown *in vitro* to perform the function of 'antigen focusing' to allow DCs to present antigens to T cells much more efficiently. Thus, T cells can be activated to respond to one-hundredth to one-thousandth the amount of antigen [19]. However, it is not clear whether or how this is important in the pathogenesis of atopic eczema.

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T lymphocytes. The fetal immune system is normally weighted towards generating Th2 responses, which is necessary to reduce the chance of the fetus and mother reacting against each other with subsequent spontaneous abortion. This is reflected by production of low basal levels of IFN-γ. In the postnatal period, the immune system appears to 'mature', and production of IFN-γ increases. However, in infants destined to develop infantile atopic

eczema, the basal production of IFN-γ is particularly low [1]. This could reflect an intrinsic defect in T-cell function.

There is evidence that activation signalling in T cells may be different in atopic individuals (see below). Thus, constitutional over-activity of cyclic adenosine monophosphate (AMP) phosphodiesterase is associated with blunted or attenuated cAMP-mediated signalling. This has been shown to tie in with differentiation of atopic T cells towards a Th2 phenotype [2]. In addition, T cells from atopic donors respond to allergens such as Der p1 from dust mites with an increased production of Th2-type cytokines and IL-13 in particular [3]. This could be blocked with an inhibitor of adenylate cyclase—the kinase which transduces cAMP-induced signals to more downstream targets. Paradoxically, it is also blocked by rolipram, an inhibitor of type IV cAMP phosphodiesterase, which, by inhibiting breakdown of cAMP, augments intracellular cAMP levels and therefore has the exact opposite effect of inhibiting cAMP breakdown.

The reasons why the atopic immune system responds with ready generation of Th2 lymphocytes are not clear, but a hypothesis attracting much attention is the so-called 'hygiene hypothesis' (see above). This proposes that exposure in early life to microbes of various types, but especially those possessing lipopolysaccharide (LPS) endotoxin, such as *E. coli* and other enteropathogens, is critical in pushing immune responses towards a Th1 type. The LPS activates production of IL-12 by DCs, which promotes production of IFN-γ and hence can deviate T-cell activation induced by any other antigen present at the same time towards a Th1 response.

Apart from alterations in immune regulatory mechanisms, the allergens themselves seem to evoke different responses in atopic individuals. Thus, both atopic and non-atopic people make IgG antibodies against *Candida albicans*, whereas house-dust mite antigen Der p1 evokes IgE antibodies in atopics but IgG antibodies in non-atopics [4,5]. It has been suggested that this property is related to the natural function of many allergens as proteases.

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Immunoglobulins

IgE. The main immunoglobulin abnormality is increased production of IgE. This results in the presence of many antigen-specific IgE species to ingested or inhaled antigens and, frequently, an increase in total serum IgE. About 80% of patients with atopic dermatitis have increased amounts of total IgE. If dermatitis is the only clinical manifestation of atopy, the amounts of total IgE may be little above the normal range [1–3] and the patients show no anaphylactic sensitivity to environmental antigens [4,5]. However, even though total IgE levels may be normal, there are almost always specific IgEs directed at environmental aero- and/or food allergens. If there is concomitant asthma or allergic rhinitis, the concentrations of IgE may be very much above normal [2,3]. IgE also increases in amount with increasing severity and extent of the dermatitis, even without respiratory allergy, and patients with high levels are likely to have a poorer prognosis. The converse has also been demonstrated, in that persons who were free of classical signs of atopic dermatitis for a year had normal amounts of IgE, even if they had persistent or recurrent eczema of the hands, or discoid eczema [6].

The production of very large amounts of IgE equivalent to levels encountered in the hyper-IgE syndrome, may be induced by *Staphylococcus aureus* antigens [7]. Some staphylococcal exotoxins are superantigens [8], which activate a greater number of lymphocytes than those stimulated by specific antigen, resulting in a 'superstimulation' (Chapter 10). One manifestation is an excessive synthesis of IgE. Staphylococci colonize the skin of atopic dermatitis patients, and exotoxins with superantigen properties have been isolated from them [9,10]. One such exotoxin, the toxic shock syndrome toxin I, although inhibiting *in vitro* IgE synthesis by blood mononuclear cells at high concentration, was found to stimulate synthesis of IgE by the mononuclear cells of atopic dermatitis patients at low concentration. This pathway may have contributed to the increased IgE synthesis in this disorder [10].

IgE is involved in autoimmune reactivity in two ways. Firstly, it is an antigenic target for IgG anti-IgE antibodies, and secondly it can also be autoreactive, with specificity for self proteins. IgE occurs in serum in the form of immune complexes with IgG and C3, but the amounts of precipitable complexes are not related to the concentrations of serum IgE or to the severity of the skin condition [11,12]. As much as 32% of the serum IgE may be in the high-molecular-weight complexes [13], which should therefore influence the interpretation of serum IgE assays. IgE–anti-IgE complexes also occur, with antibody specificity to the CH_3 and the CH_4 IgE epitopes [12]. The ability of the free IgG anti-IgE antibodies to release histamine and other mediators from mast cells and basophils *in vitro*

varies. In some tests, no histamine was released [14,15], whereas in others histamine release occurred [16,17]. Similar autoantibody complexes occur in other atopic disorders.

Autoreactive IgE antibodies have been reported to be directed against self proteins, some of which may be skin-derived [18,19]. This autoreactivity probably develops secondary to the chronic exposure to skin-derived antigens. However, it is thought that once present, the autoreactivity may contribute to the chronicity and severity of the dermatitis.

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Other immunoglobulins. The amounts of IgG, IgA and IgM in atopic dermatitis are usually normal, but increases have been reported, particularly in severely affected persons. However, in patients with severe eczema complicated by cutaneous infection, an increase in IgG appears to be due to antibodies to bacteria. In other cases, the increase is due to antibodies to food antigens. Any change in total IgG is considered to be a secondary or unrelated phenomenon, and not contributory. Furthermore, *in vitro* synthesis of IgG by blood mononuclear leukocytes was less than in cells from normal persons, and attributed to decreased responsiveness of atopic B cells [1].

Although total IgG usually remains within normal limits, some patients show an increase in the subclass IgG4 [2,3]. However, because this subclass is quantitatively the smallest of the four subclasses, the increase in IgG4 is unlikely to make a significant difference to the total IgG. IgG4 antibodies were specific for β-lactoglobulin [4] and for egg [5]. No clinical relevance was found on comparison of the amounts of IgG4 antibody with those of IgE, or with skin-test results [5]. In children with eczema complicated by asthma, IgG4 was much increased, usually with increases in total IgE [6,7]. Those who had an increase only in IgE or IgG4 did not have eczema, but asthma alone [6]. There is no clear evidence that IgG4 is anaphylactic—i.e. mediating mast cell responses on challenge with antigens—or that it contributes to the clinical changes of atopic dermatitis. It may be protective, because it has been shown *in vitro* that IgG4 will impede sensitization of basophils by IgE [8]—a conclusion supported by the finding of increased amounts of IgG4 and relatively small amounts of IgE anti-ovalbumin in children with atopic dermatitis [9].

It has been proposed that atopic subjects have an IgA deficiency which permits excessive absorption of allergen through mucosae, resulting in increased production of IgE. A modification of this theory is that the IgA deficiency may be transient, occurring for a few months early in infancy, and that the increased allergen absorption primes the individual to excessive production of IgE later in life.

The contention that a transient IgA deficiency in infants, particularly those born of atopic parents, predisposes the infants to increased production of IgE antibodies and atopic eczema later in life, led to the proposition that the atopic state could be avoided if the infants were not exposed to potent allergens during the susceptible period. The most common allergens are foods, for example milk and eggs, and elimination of potent food allergens for the first 6 months of life in high-risk infants is reported to reduce the incidence of eczema. However, allergen avoidance by breastfeeding and soya preparations has not been associated consistently with a decreased incidence of atopy, although in these reports complete avoidance is not evidenced during the critical period. Likewise, allergen avoidance by the mother during pregnancy and during breastfeeding has led to modest or equivocal benefit.

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Pathogenesis of eczema—the role of allergy

There are many factors, including allergies, infections, emotional, climatic and other environmental influences that contribute to the causation of atopic dermatitis. In early life, atopic infants develop eczema as the first of the possible atopic syndromes, which include eczema, asthma and rhinitis. There is evidence that immune sensitization occurs to food-derived allergens as well as aeroallergens [1–3]. The infantile intestine shows increased permeability to macromolecules and this is greater in atopic infants. This may be due to inherent 'leakiness' and also, because of the transient deficiency of IgA, the IgA-mediated clearance mechanisms are less effective, allowing greater entry of food-derived macromolecules into the systemic circulation, where they may induce immunological sensitization. It is completely unclear why circulating T cells reactive with food antigens should home to the skin and generate an eczematous process rather than producing a gut-centred pathology. It may be hypothesized either that food-derived antigens somehow activate immature T cells to become skin-homing, or that skin-homing lymphocytes are stimulated as a result of their target antigens reaching the skin via the circulation. Perhaps because the epidermal permeability barrier is disrupted by the eczema, allowing penetration of environmental aeroallergens, during the first few years of life there is progressive development of immune reactivity to aeroallergens, reflected by the presence of specific IgE and T-cell responses [4].

The role of airborne environmental allergens both in the initial sensitization of atopic individuals and the subsequent elicitation of the clinical features is becoming clear. Environmental allergen levels are probably the major determinant of whether sensitization of genetically predisposed individuals occurs. Thus, children born just before the birch pollen season in Scandinavia have a higher risk of sensitization to birch pollen than those born after the season [5]. Babies born in autumn, when house-dust mite (HDM) numbers are highest, have a greater risk of sensitization by HDM [6], and avoidance of exposure to HDM and food allergens for the first year of life was associated with significant diminution in the proportions of clinically detectable eczema and asthma [7]. A recent Japanese study showed that if atopic babies (with detectable IgE antibodies to various foods but not HDM) were protected from contact with HDM by encasing their bedding in dust-proof bags, there was significantly less sensitization to HDM, reflected by IgE and prick test response [8]. However, it was not followed through to see whether there was a reduction in associated clinical problems. It has been proposed that the risk of becoming sensitized to HDM is greatly increased by exposure to dust containing 10 μg/g of Der p1, and that even 2 μg/g confers a significant risk [9]. It appears that, in some individuals, priming of immune responses to a range of allergens may happen during intrauterine development [10,11]. In others, the induction of sensitization appears to occur postnatally and during childhood. The sensitization is reflected by the presence of antigen-specific helper T lymphocytes and specific antibodies of IgE class.

The role of aeroallergens such as HDM in provoking or maintaining atopic dermatitis has been the subject of controversy and uncertainty. The presence of immune sensitization and allergic reactivity, reflected by the presence of positive responses to skin challenge administered in different ways, can be detected in the large majority of patients with atopic dermatitis. Prick testing with aeroallergens such as Der p1 or extracts of animal fur or pollens elicits a weal and flare response after 10–15 min. This is mediated by specific IgE antibodies on the surface of skin mast cells. When the IgE binds antigen, the mast cells are triggered to degranulate, releasing histamine and other mediators. Intradermal or epicutaneous patch challenge on tape-stripped skin elicits a triphasic allergic response [12,13] (Fig. 18.3). There is a 15-min immediate weal and flare due to histamine release from skin mast cells. There is a 'late-phase response' consisting of erythema and a deeper oedematous reaction between 6 and 24 h, and there is a delayed response at 48 h. After intradermal challenge, this is an erythematous papular reaction similar to a tuberculin test, but after patch challenge a classical eczematous reaction develops. The proportion of positive responses can be varied by more or less aggressive tape-stripping to disrupt the stratum corneum permeability barrier and by using higher concentrations of allergen [14]. This author (PSF) detected positive patch tests to HDM extract in up to 88% of adults and 60% of children older than 5 years. Others have used the so-called 'atopy

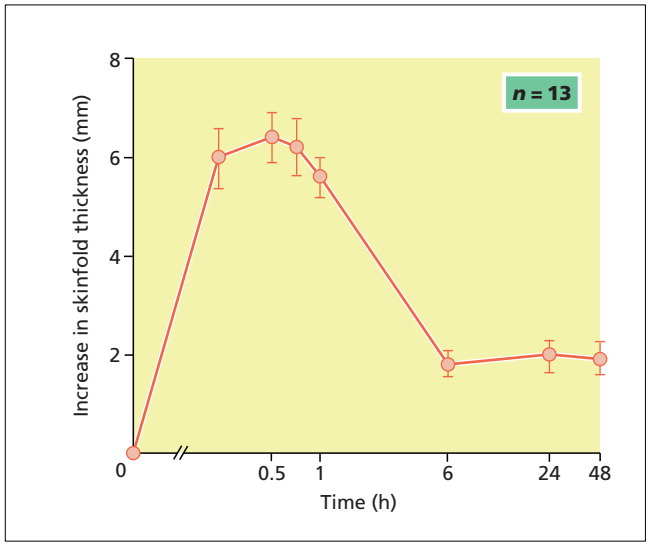

Fig. 18.3 Response elicited by intradermal inoculation of allergen (house-dust mite extract) in individuals with atopic dermatitis. A triphasic allergic response is seen, consisting of an immediate (15-min) weal and flare, a 6-h late-phase response and a 24–48-h delayed-type response. (Reproduced with permission from [12].)

patch test' without tape stripping and obtained positive responses to aeroallergens in about one-third of atopic eczema sufferers [15].

Patch test responses can be elicited in atopic eczema sufferers with a range of other allergens, including foods [16] and the ubiquitous skin surface *Malassezia* yeasts [17–19].

The eczematous response developing in allergen-induced patch test reactions has been used to model naturally occurring eczema for investigation of the role of T lymphocytes. From 8 h onwards, there is infiltration of $CD4^+$ T cells, 10–20% of which express $CD25^+$, the p55 chain of the IL-2 receptor, indicating that they have been activated through the T-cell receptor by contact with specific antigen. A number of workers have cloned the T cells in the first 12–24 h of such reactions and shown that they are predominantly of the Th2 type, producing IL-4 and IL-5 [20–22]. Also, up to 24 h after intradermal challenge with HDM, IL-4 and IL-5 production has been detected after amplification by polymerase chain reaction (PCR), but at later time points Th1 cells and their cytokines predominate [23–25]. In addition to the lymphocyte infiltration, there is heavy infiltration with eosinophils during the first 6–24 h of patch test challenge in atopic eczema sufferers.

The crucial question is whether allergic reactions induced by any allergen—aero or food—are of pathogenic importance in the causation of lesions of atopic eczema. The strongest evidence that this can be the case derives from studies of the effects of avoidance of house-dust allergens in the domestic environment. A placebo-controlled, double-blind study by Tan *et al*. [26] examined a combination of dust-mite eradication measures (sealed containment bags for the mattress, pillows and bedding top covers, a high-power vacuum cleaner and a spray containing agents to kill mites and denature their allergens). It was shown that highly significant reductions in Der p1 load in carpets and beds occurred. This was associated with great clinical benefits in both adults and children (over 6 years old) with severe atopic eczema. For unidentifiable reasons, these findings were not reproduced in a German study which used an essentially similar design [27].

The clinical relevance of allergy to *Malassezia* yeasts is indicated by studies showing that treatment with itraconazole to eradicate the yeast resulted in improvement of the eczema comparable with that obtained with betamethasone valerate [19]. Hence, there is some compelling evidence that allergic reactions to common allergens may play an important part in the pathogenesis of atopic eczema in many people. However, such reactions do not appear to account for the entire process, and the whole approach suffers from a lack of robustness in the tests to identify those individuals who would benefit from avoiding any particular allergen.

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Pharmacological and vascular abnormalities

The small blood vessels in atopic dermatitis show a tendency to vasoconstriction responses:

1 Pallor of the skin after stroking—white dermographism
2 Delayed blanch with acetylcholine
3 White reaction to nicotinic acid esters
4 Abnormal reactions to histamine in affected skin
5 Low finger temperature
6 Pronounced vasoconstriction on exposure to cold.

None of these findings is pathognomonic. The delayed blanch phenomenon with acetylcholine [1–3] and related drugs is characteristic for atopic dermatitis, and occurs less regularly with other atopic disorders. Whether these pharmacological changes in atopic dermatitis are secondary to cutaneous inflammation, or whether the deranged pharmacology and the immune abnormalities are both secondary to a common defect, is not known. However, these patterns in vascular responses led to the so-called β-adrenergic blockade theory proposed by Szentivanyi [4]. Although this theory no longer remains tenable, it has led to observations of abnormalities in a range of intracellular second messenger signalling pathways. In atopic individuals, attenuated cAMP signalling results from overactive cAMP-phosphodiesterase, which is associated with several of the phenotypic features. The principal observations summarized by Hanifin and Chan [5] follow from the well-known increased IgE synthesis that characterizes atopic individuals. *In vitro*, this appears linked to reduced IFN-γ production by mixed peripheral blood mononuclear cells (PBMCs) from patients with atopic dermatitis. However, atopic T cells actually show increased production of IFN-γ *in vitro*; hence, it was concluded that the monocytes produce an inhibitor of IFN-γ synthesis. Atopic PBMCs produce increased amounts of PGE_2 and it is the monocytes which are the source [6]. It was shown by Betz and Fox that PGE_2 inhibits IFN-γ production [7], and Chan *et al*. showed that inhibition of PGE_2 with indomethacin results in increased IFN-γ production by atopic PBMCs [6]. Atopic monocytes also produce increased amounts of IL-10, which also inhibits production of IFN-γ [8].

Hanifin had previously shown that PBMCs from atopic subjects have blunted cAMP responses to agents acting on adenylate cyclase such as histamine, isoprenaline or prostaglandins [9]. This was found to be a result of elevated cAMP-phosphodiesterase (PDE) activity [10], so the cAMP was hydrolysed more completely. These abnormalities were also present in people with respiratory atopic disease. Sawai *et al*. [11] showed that there was no correlation between cAMP-PDE activity and severity of eczema. The abnormality has also been shown to be present in cord blood from babies with atopic parents [12,13].

The elevated cAMP-PDE activity was shown to be located predominantly in monocytes [14]. Chan and colleagues went on to type the PDEs in atopic leukocytes [15]. They found that three isoforms were common to both monocytes and lymphocytes, and all were more active than in cells from non-atopics. However, the atopic monocytes had an additional isoform which was specific for cAMP and was calcium/calmodulin-dependent. Also, the PDE was more susceptible than control PDE to inhibition by Ro20-1724—an inhibitor of PDE type 4 [15,16]. It should be noted that Gantner *et al*. found no differences between PDE expression or activity in cells from healthy and atopic blood donors [17].

One aspect which makes interpretation of data about levels of PDE activity difficult is that PDE activity is subject to modulation by various factors. Thus, PDE activity is induced by stimuli which increase cAMP, such as long-term administration of β-adrenergic agonists. This has clouded the question of whether elevated PDE is found in atopic asthma, as most patients receive chronic therapy with these agents. In monocytes from healthy subjects PDE activity is increased by cytokines IL-4 and IFN-γ [18]. However, in monocytes from atopic dermatitis patients, IFN-γ at low concentrations was without effect and at higher concentrations it reduced PDE activity [18]. This difference may be because in atopic cells PDE activity is already maximally induced.

The PDEs form a family of at least seven groups [19]. The different types vary in their affinity for cAMP or cyclic guanosine monophasphate (cGMP), their susceptibility to

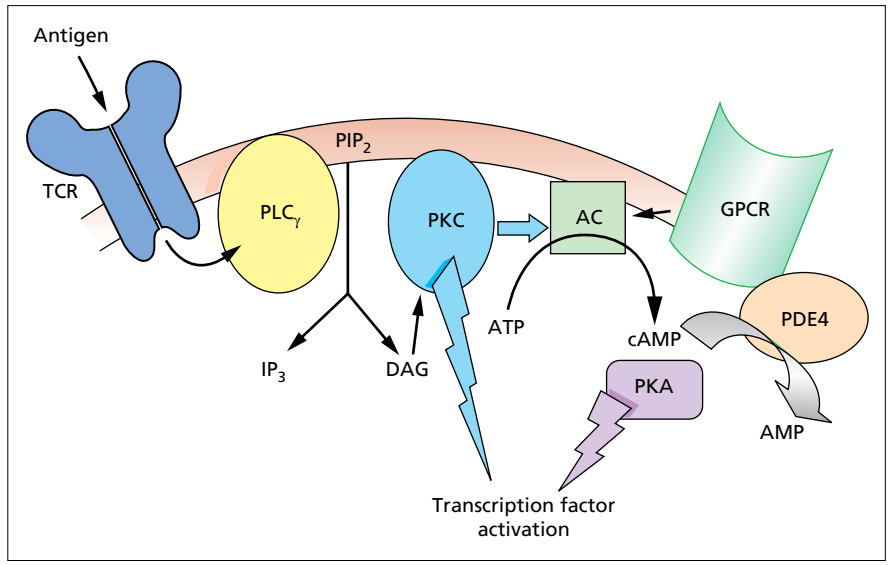

Fig. 18.4 Intracellular signalling that interacts with cAMP in T cells. The T-cell receptor (TCR) receives activating signals from the dendritic antigen-presenting cell. It activates phospholipase Cγ (PLCγ) which cleaves membrane phosphatidyl inositol bis-phosphate (PIP_2) to diacylglycerol (DAG) and inositol triphosphate (IP_3). The DAG activates protein kinase C (PKC), which activates a variety of targets, including transcription factors. It can also activate adenylate cyclase (AC), which generates cAMP. Membrane receptors that are coupled to G proteins (G protein-coupled receptors, GPCR) activated by their ligands signal via generation of cAMP which in turn activates protein kinase A (PKA). cAMP is degraded by the actions of cAMP phosphodiesterase type 4 (PDE 4), which is constitutively overactive in atopic cells. This attenuates or switches off cAMP signalling which may alter the balance of 'cross-talk' between different signalling pathways.

different inhibitors and, in some cases, in their cell/tissue distribution. Type 4 PDE (PDE 4) is cAMP-specific and was characterized by inhibition by rolipram and Ro20-1724. PDE type 4 is present in inflammatory cells—mast cells, eosinophils, monocytes, macrophages and lymphocytes.

Several activities of mononuclear cells are mediated via cAMP and can be reduced by inhibitors of PDE 4: increased PGE_2 production [8]; spontaneous IgE production by B cells [20] and release of histamine from basophils [8]; increased spontaneous production of IL-10 is reduced, as is the anti-CD3-induced increase in IL-4 production [8,21]; migration of eosinophils [22]; *in vitro* transmigration of lymphocytes, but not monocytes, through a monolayer of endothelial cells [23]; allergen-induced release of IL-5 [24].

cAMP is a second messenger that lies in the midst of a network of pathways (Fig. 18.4). Different signalling mechanisms are involved, depending on which cell surface receptors are activated. The T-cell receptor activates phospholipase Cγ, which in turn cleaves phosphatidyl inositol bis-phosphate to release diacylglycerol (DAG) and inositol tris-phosphate (IP_3). These moieties can both act as further signals in different directions; IP_3 activates release of calcium from intracellular stores, DAG activates protein kinase C (PKC). PKC can activate adenylate cyclase, generating cAMP which activates protein kinase A (PKA). The intensity of the effects of cAMP are blunted through the overactivity of PDE 4 (see above). The inositol pathway of peripheral blood mononuclear cells shows evidence of chronic activation and hyporesponsiveness to subsequent stimulation [25,26]. Apart from the clear evidence of the effects of the altered second messenger signalling in T lymphocyte differentiation towards a Th2 type (see above and [27]), the further importance of these processes in the wide range of vascular, neural and immune alterations in atopic eczema has yet to be elucidated.

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Neuropeptides

Neuropeptides mediate vasodilatation, oedema, itch and pain, the axon-reflex flare, sweat gland secretion, and have some, probably minor, ability to regulate T-cell activation [1]. Vasoactive and proinflammatory neuropeptides mediate tissue change and sensory stimuli in perturbed skin (Chapter 9). Theoretically, neuropeptides could have a significant role in many of the features of atopic dermatitis, including the vascular changes, the itch, the symptoms associated with sweating and the leukocyte infiltration. The neuropeptides which have been studied in the lesions are substance P (SP) and calcitonin gene-related peptide (CGRP), often present together in unmyelinated C sensory fibres, somatostatin (SOM), vasoactive intestinal polypeptide (VIP), which coexists with acetylcholine in postganglionic sympathetic fibres, and neuropeptide Y (NPY) in adrenergic fibres. Assays of skin extracts have shown greatly increased amounts of VIP in atopic lesions [2–4], and reduced amounts of SP [3,5], although SP has also been reported to be unchanged in comparison with normal controls in one study [2].

Immunohistochemical examination has revealed NPY-positive dendritic epidermal cells in lichenified atopic dermatitis lesions, but no somatostatin fibres. Healthy normal control skin showed the opposite—no NPY dendritic cells, but a normal network of somatostatin fibrils [6]. Elsewhere, it has been reported that NPY fibres (adrenergic) are fewer than normal, but CGRP and SP (sensory) fibres are increased in number [7].

The skin of atopic dermatitis patients shows altered reactivity to injections of neuropeptides. Intradermal injection of SP induces a weal and flare response—at low doses, this is the result of direct effects on vasculature, whereas at higher doses, SP induces degranulation of mast cells with histamine-mediated weal and flare. Contradictory findings have been reported regarding cutaneous responses to injection of SP in atopic individuals. Coulson and Holden [8] observed greater weal volumes in atopics than in non-atopics, with no difference in the area of flare. In another study, although injection of SP elicited weals of similar size, there was less flare in atopic dermatitis skin than in controls [9]. Injection of neuropeptides was also reported to induce less than normal weal and flare responses [10].

Apart from effects on vascular reactivity and pruritus, neuropeptides can play a part in recruitment of granulocytes by up-regulating expression of adhesion molecules, including VCAM-1 on endothelial cells [11]. They can also modulate lymphocyte function *in vitro*. Thus, SP augments production of IFN-γ and IL-4 by lymphocytes from atopic donors but has little effect on cells from non-atopic donors [1,12]. VIP had no effect on lymphocyte cytokine production [12]. Hence, neuropeptides may contribute to the complex mix of factors regulating lymphocytes in atopic dermatitis.

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Pruritus

The major symptom that accompanies the rash of atopic eczema is pruritus. The mediators and mechanisms responsible for this symptom are still totally obscure. Symptoms of itching are induced in patients with atopic eczema by stimuli that induce sweating, both thermal and emotional, as well as contact with fibres, especially wool. Clues regarding mediators come from the effects of therapeutic agents with defined mechanisms of action. Thus, despite the general presumption that mast cell degranulation via IgE-mediated allergen-specific mechanisms is important in atopic eczema, antihistamines generally have little effect on the pruritus of atopic eczema [1]. The older, sedating H_1 antagonists may improve the subjective comfort through sedation and deeper sleep. Ciclosporin (cyclosporin) causes very rapid cessation of the pruritus—which might indicate the involvement of T-lymphocyte products such as cytokines. However, ciclosporin has effects on cells other than lymphocytes, and may inhibit formation of prostaglandins [2]. As described above, responses to neuropeptides appear altered in atopic eczema. Neuropeptides such as SP, VIP, SoM and neurotensin provoke itch together with neurogenic inflammation in the form of erythema and weal and flare [3]. Capsaicin depletes nociceptive nerve endings of CGRP and SP and is reported to reduce pruritus in atopic eczema [4]. Acetylcholine (ACh), the archetypal neurotransmitter, activates both vasodilatation and sweating. ACh is also produced *in vitro* by keratinocytes [5]. ACh levels are raised in lesional skin of atopic eczema, and intradermal injection of ACh elicits pruritus rather than pain in patients with atopic eczema [6]. However, use of anticholinergic agents for treatment of the pruritus of atopic eczema has not become a useful therapeutic measure.

It has been suggested that opioids may play a part in the pruritus of atopic eczema; indirect evidence for this comes from the observation that opioid receptor antagonists such as naloxone or nalmefene can reduce pruritus [7]. However, others have failed to reproduce this observation [8].

Proteases, including tryptase and chymotryptase, are released by mast cells, and it has been proposed that they play a part in causing pruritus. Intradermal injection of mast cell tryptase elicits pruritus, erythema, leukocyte infiltration and oedema [9]. Proteases exert a range of effects through activation of protease-activated receptors (PARs), including PAR-2 in particular [10]. PAR-2 receptors are found on endothelial cells, sensory nerves and keratinocytes, and play a part in the inflammatory process resulting from mast cell degranulation. With greater availability of PAR-2 antagonists for use in clinical situations, it will be easier to assess the functional importance of these receptors.

There has been speculation that cytokines may contribute to the pruritus of atopic eczema. Cytokine-rich supernatants from mitogen-stimulated lymphocytes can induce pruritus when injected into atopic eczema sufferers but not healthy controls [11,12]. A wide range of cytokines are released in atopic eczema. They include IL-2, 4, 5, 6, 8, 10, 13, IFN-γ and tumour necrosis factor-α (TNF-α). Most of these have been injected into human skin without producing significant pruritus. The exception is IL-2 which can produce redness and itching when used in therapy of malignancy [13]. A possibility that has not been explored is that of synergism between some of the above mediators—say cytokines and neuropeptides.

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Sweating

Many patients are aware that sweating induces itching and aggravates their condition. This may reflect altered sensations associated with the neuropeptides released in the neurogenic control of sweat glands. Altered inflammatory responses to ACh are described above, and increased numbers of nerve fibres have been described around the sweat glands in atopic non-lesional skin compared with lesional and healthy control skin [1]. Sweating responses to neurogenic stimuli are altered in atopic eczema sufferers, although there is some lack of agreement between findings, and diverse methods have been used to quantify sweat production. Sweating in response to cholinergic stimulation was found to be reduced in volume by one group [2,3], but normal in volume, although of more prolonged duration, by another group [4]. A possible explanation for differences comes from the study of Eishi *et al*. [5], who measured both direct cholinergic effects on sweat glands and distant effects mediated via the axon reflex. They found that directly induced sweat production hardly differed from that in healthy controls, whereas axon reflex-induced sweating was of lower volume with a longer latency. In a study of the response to adrenergic stimulation, sweating was similar between atopic eczema patients and non-atopic controls at low concentrations of epinephrine (adrenaline), but at higher concentrations sweating in non-atopic individuals was increased, whereas in atopic eczema patients it was decreased [6]. Sweating in response to the thermal stress of sitting in a heated room was found to be reduced in atopic eczema patients [7]. However, there was no difference in sweating responses induced by hard cycling on a bicycle ergometer between atopic eczema sufferers and healthy controls [8].

Another way in which sweating may induce itching and aggravate the eczema is related to the observation that there seems to be an IgE-mediated allergic reactivity to components of sweat [9]. Thus, skin challenges with autologous sweat induced positive responses in 56 of 66 (84%) patients, compared with three of 27 (11%) healthy controls. Also, basophils were induced to release histamine in an IgE-dependent process [9]. The nature of the reaction-inducing substances is completely obscure.

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Psychological factors

It is a common clinical experience that patients with atopic dermatitis complain that their condition is exacerbated by episodes of psychological stress. This is also found in many inflammatory dermatological conditions. One demonstration that psychological stress modulates immune/inflammatory processes is by Buske-Kirschbaum *et al*. [1]. They showed that formal stressing of people who experience recurrent herpes simplex lesions could significantly increase the recurrence rate of cold sores, and there was also a rise in plasma levels of TNF-α. The role and mechanisms of psychosocial stress on the clinical course of atopic dermatitis still remain to be elucidated. When volunteers are subjected to formal stress tests in the form of public speaking and performance of mental arithmetic, a wide range of endocrinological changes occur. These include increased production of epinephrine, adrenocorticotrophic hormone (ACTH), corticotrophin-releasing factor (CRF) and cortisol, and reduced production of growth hormone, prolactin and progesterone [2]. The stress-induced rise in free cortisol is reportedly lower in patients with atopic dermatitis [3]. White blood cells and various cytokines also change in response to stress tests: increases in lymphocyte, monocyte, neutrophil and basophil numbers were seen 10 min after the stress provocation test, and were equal in atopic individuals and healthy controls [4]. Also, although IFN-γ increased and IL-4 decreased in both control and atopic groups, atopic individuals showed a significant increase in eosinophils and IgE in response to stress [4]. Fjellner *et al*. examined itch in response to intradermal inoculation of histamine, but found there was no demonstrable effect of stress [5].

Another humoral influence that appears to modulate atopic dermatitis is mediated by the sex steroids. One-third of 133 patients questioned claimed there was a significant premenstrual flare of atopic eczema [6]. Pregnancy exacerbated eczema in 52% of women, whereas it ameliorated eczema in 24% [6]. It has been proposed that a possible mechanism by which sex steroids alter susceptibility to inflammatory skin diseases is by modification of sensitivity to anti-inflammatory effects of glucocorticoids. In a comparison of differences in susceptibility between men and women, Rohleder *et al*. [7] stressed volunteers as

above; women were tested in the luteal phase of the menstrual cycle. Sensitivity to glucocorticoids was assessed *in vitro* by measurement of dexamethasone inhibition of LPS-stimulated production of IL-6 and TNF-α. Salivary cortisol levels increased equally between the sexes. However, in men, glucocorticoid sensitivity was markedly increased 1 h after stress, whereas it decreased significantly in women. Similarly, LPS-induced cytokine production decreased in response to stress in men, but increased in women. It is not clear whether this is the result of the increased cortisol production suppressing cytokine production in men or of a change in responsiveness to LPS itself. Hence, the premenstrual flares of atopic eczema could reflect the reduced sensitivity to the anti-inflammatory effects of endogenous cortisol.

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Pathology [1,2]

The histological changes are not specific, and are those of a subacute or chronic eczema. In infancy, early lesions show acanthosis and sometimes spongiosis, oedema of the dermis and infiltration with lymphocytes, histiocytes, plasma cells and eosinophils, sometimes in large numbers. In later age groups, the histology is that of lichenification, sometimes with more eosinophils in the dermis than are found in lichen simplex, and with an increase in the number of Langerhans' cells. Eosinophilia in tissues as well as in peripheral blood is found in many cases of atopic dermatitis, but is of no help in determining the role of allergy in producing the symptoms.

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Clinical features

Atopic dermatitis is an itchy, chronic, fluctuating disease that is slightly more common in boys than girls. The age of onset is between 2 and 6 months in the majority of cases, but it may start at any age, even before the age of 2 months in some cases.

The clinical features include:

1 Itching
2 Macular erythema, papules or papulovesicles
3 Eczematous areas with crusting.
4 Lichenification and excoriation
5 Dryness of the skin
6 Secondary infection.

The distribution of the eruption varies with age, as described below.

Infantile phase

The lesions most frequently start on the face (Fig. 18.5), but may occur anywhere on the skin surface. Often, the napkin area is relatively spared. When the child begins to crawl, the exposed surfaces, especially the extensor aspect

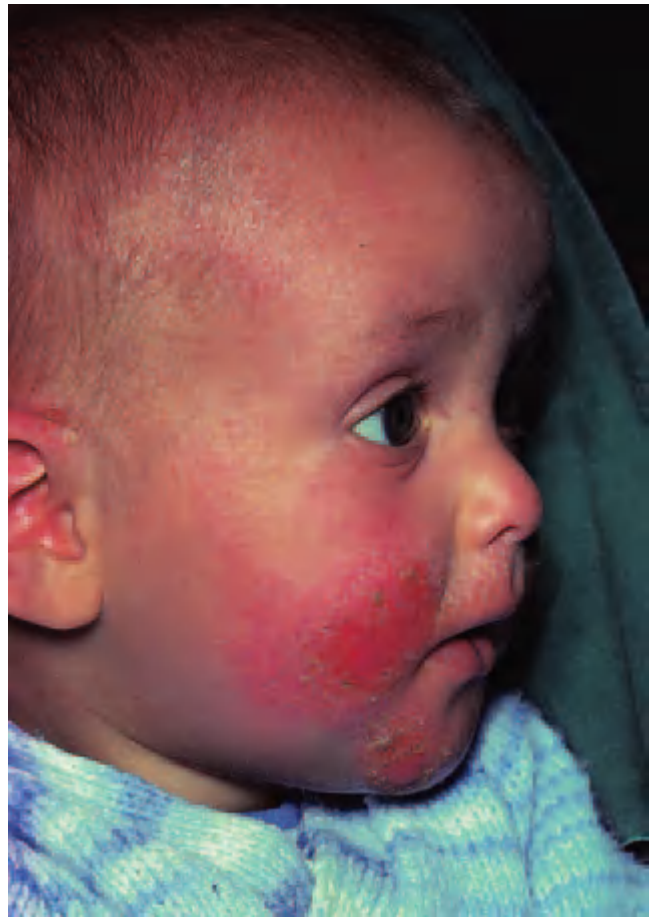

Fig. 18.5 Atopic dermatitis: infantile phase.

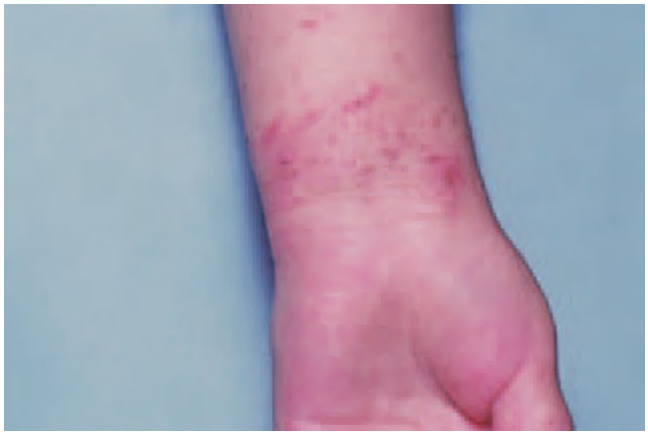

Fig. 18.6 Flexural atopic dermatitis of the wrist in a child.

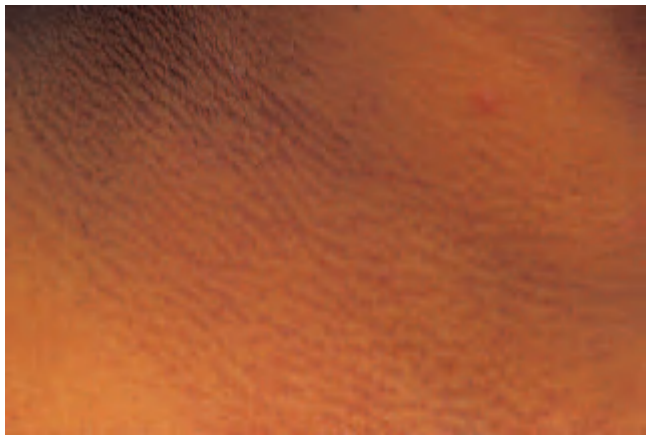

Fig. 18.7 Atopic 'dirty neck'. Reticulate pigmentation on the neck of a patient with long-standing atopic dermatitis.

of the knees, are most involved. The lesions consist of erythema and discrete or confluent oedematous papules. The papules are intensely itchy, and may become exudative and crusted as a result of rubbing. Secondary infection and lymphadenopathy are common. The disease runs a chronic, fluctuating course, varying with such factors as teething, respiratory infections, emotional upsets and climatic changes.

Childhood phase

From 18 to 24 months onwards, the sites most characteristically involved are the elbow and knee flexures, sides of the neck, wrists and ankles [1] (Fig. 18.6). The sides of the neck may show a striking reticulate pigmentation, sometimes referred to as 'atopic dirty neck' [2,3] (Fig. 18.7). The anatomical basis for this distribution is unknown. Sometimes only one site is involved. The erythematous and oedematous papules tend to be replaced by lichenification. Some patients with atopic dermatitis (Fig. 18.8) are apparently unable to lichenify, even after prolonged rubbing, and they may be very difficult to treat. Patients with an extensor distribution of eczema in later childhood are uncommon, and may take longer to remit. This distribution is said to be commoner in Asian or black children (Fig. 18.9), but frequently they show the typical distribution [4]. As well as the typical mixture of papules and lichenification, true eczematous lesions with vesiculation may occur, often in discoid patches. Involvement of the hands, often with exudative lesions, and sometimes with nail changes, is common (Figs 18.10 & 18.11). Acute generalized or localized vesiculation should always suggest the possibility of secondary bacterial or viral infection (p. 18.21).

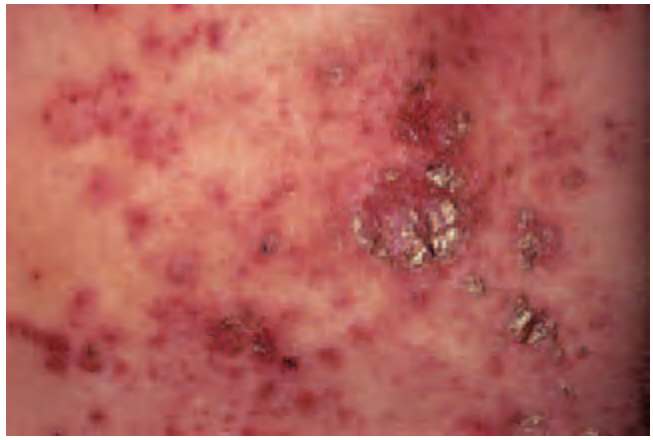

Fig. 18.8 Atopic dermatitis: erythema, papules, excoriations, crusting and secondary infection but, in this case, little lichenification.

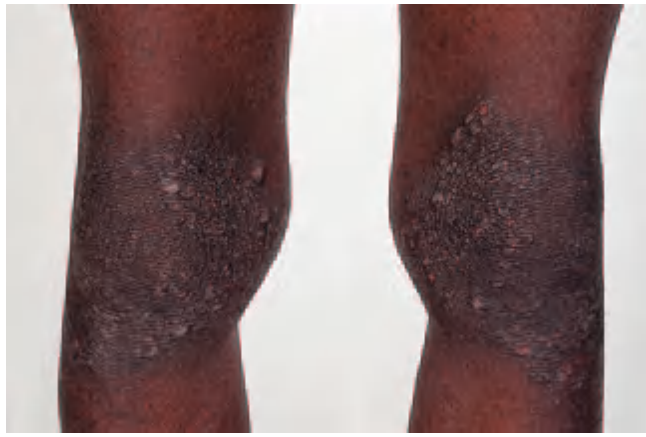

Fig. 18.9 Marked lichenification on the knees of an African child. The popliteal fossae were spared.

Adult phase (Fig. 18.12)

The picture is essentially similar to that in later childhood [5], with lichenification, especially of the flexures and hands. Localized patches of atopic dermatitis can occur on

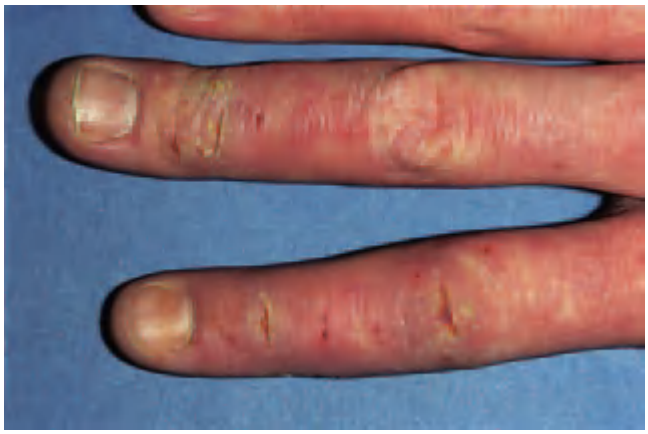

Fig. 18.10 Atopic eczema of the fingers of a child.

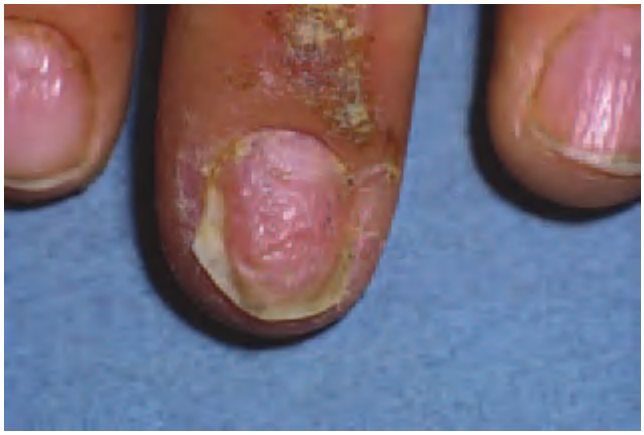

Fig. 18.11 Nail involvement in atopic dermatitis in childhood.

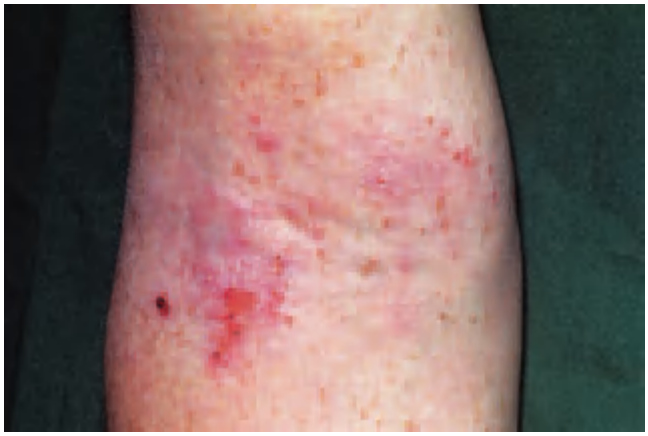

Fig. 18.12 Adult flexural dermatitis.

the nipples, especially in adolescent and young women. Involvement of the vermilion of the lips and the adjacent skin is commonly an atopic manifestation. Follicular lichenified papules are a frequent feature in black people and the Japanese. A distribution on the face, upper arms and back may correlate with areas of maximal thermal sweating or *Malassezia* sensitivity [6]. Photosensitivity is not uncommon, especially in adults with atopic dermatitis. The mechanisms involved are several and complex. Many such cases do not show sensitivity when tested with the monochromator. Rajka [7] has suggested that infrared and ultraviolet radiation may both contribute. Management of such cases requires a combination of approaches used for ordinary atopic dermatitis and for photosensitivity, neither alone sufficing.

Atopic hand eczema (see Chapter 17)

A patchy, somewhat vesicular and lichenified eczema is a common manifestation of atopic dermatitis in childhood. The nails are often involved, resulting in coarse pitting and ridging. The picture may closely resemble the discoid eczema of young adults, in whom it is not usually so apparently linked with an atopic predisposition. A more diffuse, chronic lichenified eczema of the hands is frequently found in cases of extensive atopic dermatitis which persist into adult life, and atopic dermatitis is frequently a contributory factor in many cases of what usually has to be called constitutional hand eczema [8]. A previous history of atopic dermatitis is also a significant factor in the development of occupational dermatitis [9]. Involvement of the feet is also common and almost half the patients with atopic hand eczema will have eczema on the feet [10].

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Associated disorders

Other manifestations of atopy (Fig. 18.13)

Allergic rhinitis (hay fever) and asthma are beyond the scope of this book. They occur in 30–50% of cases of atopic

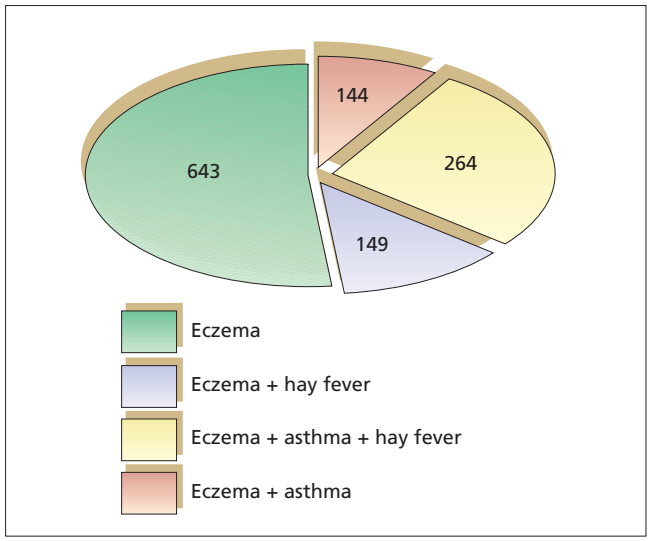

Fig. 18.13 The incidence of atopic respiratory symptoms in 1200 patients with atopic dermatitis. (From Rajka [2].)

eczema [1–3]. The age of onset is later than that of the eczema. Latent asthma may be detected by bronchial inhalation tests in a proportion of patients with atopic dermatitis without clinical asthma.

Dry skin

This is a common feature of atopic dermatitis and figures prominently in its management. It is likely that it occurs because of increased transepidermal water loss through an abnormal stratum corneum [4,5]. Recent studies have suggested that it may be a consequence of abnormal ceramide synthesis and have an important role in the development of inflammation. Ceramide-containing emollients may be helpful in managing the condition [6]. Ichthyosis vulgaris and keratosis pilaris may also be seen in association with the condition.

Other patterns of eczema

Infantile seborrhoeic dermatitis

This condition is discussed in Chapter 14. It normally starts earlier than atopic dermatitis, and it may be possible to distinguish between the two conditions clinically [7]. However, there are a number of children who present with what appears to be seborrhoeic dermatitis and then progress to typical atopic dermatitis [8].

Allergic contact dermatitis

It is clear that atopic dermatitis patients are at greater risk of developing irritant contact dermatitis than non-atopic patients [9]. However, there is a dispute about whether they are at greater risk of developing allergic contact dermatitis [10]. Nonetheless, patients can develop sensitivity to a variety of contact allergens such as topical medicaments, including topical corticosteroids [11,12]. Recently, the risk of protein contact sensitivity, such as that associated with latex in rubber gloves, has been highlighted [13,14].

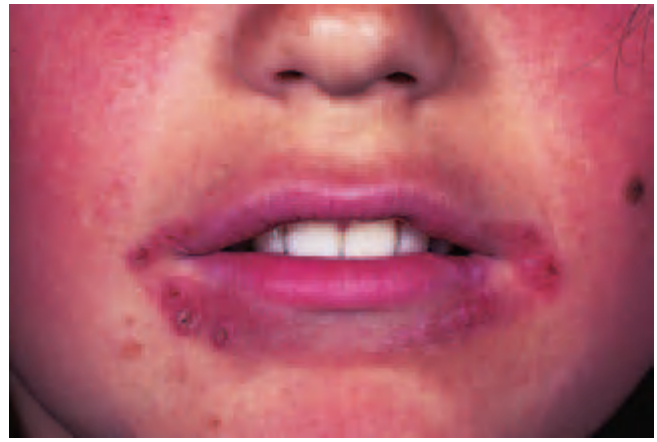

Fig. 18.14 Lip-lick cheilitis.

Lip-lick cheilitis

SYN. PERIORAL ECZEMA; 'LICK ECZEMA'

Moist or fissured eczema around the mouth is common in children with atopic dermatitis. It can also occur as a result of food allergy, and in children with no known atopy or allergy. Frequently spreading some distance around the mouth, it may become secondarily infected and crusted (Fig. 18.14). Its persistence, and perhaps its origin, is attributable to habits of lip licking, thumb sucking, dribbling or chapping. It is easily transformed into a true perioral dermatitis by the application of potent corticosteroids (Chapter 44). The regular application of 1% hydrocortisone ointment is usually most helpful. Contact sensitivity, for example to toothpaste ingredients, can occasionally be demonstrated.

Several other patterns of eczema are seen in individuals with atopy, but they are also seen in non-atopic individuals. These include eczema with a predominantly follicular accentuation, and discoid eczema. Certain well-defined conditions appear more common in atopic individuals; pityriasis alba and juvenile plantar dermatosis are discussed in Chapter 17. Nodular prurigo can quite frequently complicate the atopic diathesis (Chapter 17).

Infra-auricular dermatitis is quite frequently seen in atopic dermatitis patients, and infra-auricular fissures appear to be quite specific to atopic dermatitis [15].

Drug sensitivity

Drug reactions of the anaphylactic type are more common in atopic persons because of the increased propensity to

produce IgE after natural exposure to antigens. Anaphylactic reactions to injected antigens can occur in persons with no other atopic manifestations. Anaphylactic reactions to topically applied drugs have been reported [16]. Other types of drug reaction with different immunological mechanisms occur with equal frequency in atopic and non-atopic individuals.

Reactions to insect stings and bites

The frequency of reactions to insect stings is similar in non-atopic and atopic populations [17].

Food allergy

Abdominal symptoms due to food allergy are more frequent in patients with atopic disorders, but are not restricted to them. The role of food allergy in asthma and allergic rhinitis is probably minor. The role of food intolerance in the management of atopic dermatitis is discussed on p. 18.28.

Alopecia areata

There is a statistically significant association between alopecia areata and atopy.

Urticaria

The majority of cases of urticaria cannot be shown to be due to IgE or any other allergic sensitivity. Those cases in which an allergic basis is found occur more often in atopic individuals (Chapter 47). Contact urticaria—for example, on the hands—occurs not infrequently in atopic dermatitis, and may present as an acute exacerbation of the dermatitis [18]. It occurs particularly in food handlers and slaughterhouse workers [19], and more recently has been reported in health carers because of latex protein sensitivity [13].

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Complications

Impact on quality of life

Psychosocial aspects

Atopic dermatitis has a profound effect on many aspects of patients' lives and the lives of their families [1–4]. In children, one of the most disturbing impacts of the disease is on the sleep pattern. This can lead to behavioural difficulties in the most severely affected children [5,6]. The patient's dermatitis can also interfere with the functioning of the family [7]. Increasingly, a demonstration of improvement in the quality of life of patients forms part of the assessment of new therapies [8].

Growth delay

Growth delay can be associated with atopic dermatitis [9]. It used to be seen in severe cases before the advent of corticosteroid therapy, and can therefore be attributed to the disease. However, suspicion must also clearly rest on both oral and topical steroid therapy, which can cause growth stunting in any child on long-term therapy [10]. Prepubertal children with atopic dermatitis show features consistent with constitutional growth delay [11].

Bacterial infections

Secondary bacterial infection with staphylococci or streptococci is virtually an integral part of the clinical picture [12]. It contributes to many exacerbations of the disease, even without grossly visible purulent exudate. Widespread impetigo may sometimes closely mimic Kaposi's varicelliform eruption. Indeed, any acute vesicular eruption in an atopic should suggest the diagnosis of secondary bacterial or viral infection.

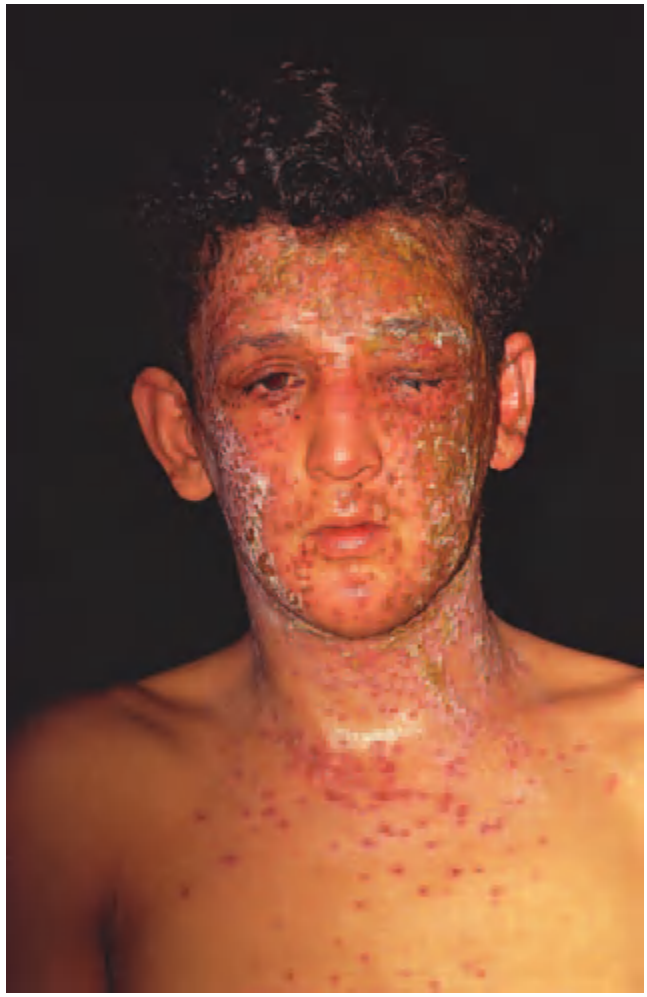

Fig. 18.15 Kaposi's varicelliform eruption: eczema herpeticum.

Viral infections

Patients with atopic dermatitis, both active and quiescent, are liable to develop acute generalized infections with herpes simplex (eczema herpeticum) and vaccinia (eczema vaccinatum) viruses, to produce the clinical picture of Kaposi's varicelliform eruption (Fig. 18.15) [13] (see Chapter 25). Such episodes may present as a severe systemic illness with high fever and a widespread eruption. However, there may be no systemic disturbance, and at times the eruption may be quite localized, often to areas of pre-existing atopic dermatitis. The individual lesions start as the characteristic viral papulovesicles, but not necessarily with a herpetiform grouping. There may then be rapid evolution to a state in which extensive purulent exudate masks the initial papulovesicles, or superficial scattered erosions may be the only clue to the cause of a rapid deterioration of the dermatitis. The differential diagnosis includes bacterial impetigo and chickenpox. Herpes zoster and chickenpox apparently behave as in normal persons.

There is a lack of agreement about whether viral warts are more prevalent in atopic dermatitis. An initial uncontrolled study suggested an increased frequency of viral wart infections [14], but a more recent epidemiological study cast doubt on this observation [15].

Similarly, the frequency of molluscum contagiosum in such patients is not clear. However, the clinical impression is that widespread molluscum contagiosum is more common in the atopic child.

An abnormal response to a Coxsackie infection in an atopic has been described [16]. Acquired immune deficiency syndrome (AIDS) may aggravate atopic dermatitis, and 'recall' atopic dermatitis has been described in AIDS patients [17]. A condition resembling atopic dermatitis has been seen in association with human T-lymphocyte virus type I (HTLV-I) infection (see Chapter 17) although this may be coincidental [18].

Sudden death

Sudden death was once reported to occur, especially in young infants with severe atopic dermatitis soon after admission to hospital [19]. However, it is now extremely uncommon.

Ocular abnormalities (see also Chapter 63)

A number of ocular changes can occur in atopic dermatitis [20]. The Dennie–Morgan fold is often present as a fold of skin under the lower eyelids [21]. However, this change is not specific to atopic dermatitis, and is commonly seen in non-atopic black children [22].

Conjunctival irritation is a common syndrome in atopic persons. As in hay fever, it may represent a true allergic reaction, or it may be due to a non-allergic irritability such as occurs in the nose or skin. Keratoconjunctivitis has been recorded [23].

Keratoconus [24,25], or conical cornea, is a rare condition. It may occur in the absence of any other disease or in association with atopic dermatitis. It is due to a degenerative change in the cornea, which is forced outwards by the intraocular pressure, to give rise to marked visual disturbances. Onset is in childhood, and after some years progress of the disease becomes arrested. Contact lenses may be helpful.

Cataract associated with atopic dermatitis (Fig. 18.16) has certain peculiarities which distinguish it from other types of cataract [24]. It occurs in up to 10% of the more severe adolescent and adult cases, but overall it is uncommon. It is associated with atopic dermatitis rather than with other atopic diseases. It may start in early childhood or up to the age of 30 years, but the peak incidence is between 15 and 25 years. It is almost always bilateral. The appearances on slit-lamp examination are characteristic, but not diagnostic. In the early stages, translucent glob-

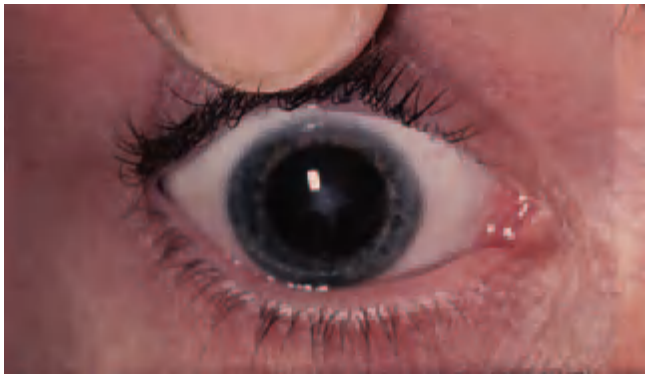

Fig. 18.16 Atopic cataract.

ules and small opacities appear at the pole in front of the posterior capsule and also in the anterior subcapsular zone. Progression may be slow, or alarmingly rapid over a few days, and seems to be related to severe facial involvement [26]. The final appearance may resemble a mature, cortical, senile cataract.

Atopic cataracts may resemble those induced by topical or systemic steroids. The potential for cataract formation is an important reason for examining the eyes of any patient with atopic dermatitis when psoralen and ultraviolet A (PUVA) therapy is being contemplated.

Retinal detachment has been reported, particularly in Japanese patients [27], and appears to be identical to the retinal detachment seen following trauma [28].

Miscellaneous

Cartilaginous pseudocyst of the external auricle may be more common in children with atopic dermatitis [29], as may olecranon and pretibial bursitis [30]. A case of Sézary syndrome has been described in a patient with severe atopic dermatitis [31].

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Natural history and prognosis [1–5]

Hospital-based studies suggest the age of onset is less than 6 months in 75% of cases and before the age of 5 years in 80–90%. However, community-ascertained cases may have a later age of onset than that reported in hospital-based studies [6]. The reported prognosis differs considerably according to how the cases are selected, the criteria for diagnosis, and many other variables. There is a general tendency towards spontaneous improvement throughout childhood and often some slight relapse during adolescence. Relatively few typical cases persist over the age of 30 years; perhaps half of all cases clear by the age of 13 years. The reported clearance rates range from 40% to 60% within 10–20 years [2,6]; 84% within 5–20 years [5]; and

50% at 10 years [3]. There is often a change in the distribution of the rash from the head and face to the flexural areas at around the age of 2 years (p. 18.18).

It is difficult to predict the prognosis in an individual case. It is worse if both parents are affected. The severity in infancy and the natural history in other members of the family serve as rather unreliable guides. The personality of the child and its parents, and environmental factors, are equally important [2,3]. The presence of a pronounced epidermal component adversely affects the prognosis; such cases are also more likely to develop ocular complications. Some 30–50% of cases of infantile eczema subsequently develop asthma or hay fever [7,8]. The atopic patient remains particularly at risk from occupational irritant hand dermatitis as an adult [9].

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Diagnosis

The diagnosis of atopic dermatitis is usually based on clinical criteria. The UK refinements of the Hanifin and Rajka's diagnostic criteria (see Table 18.1) appear to be valid for both adults and children of white and non-white groups. However, these criteria were developed primarily for epidemiological use and were considered less reliable in children under 1 year of age.

Differential diagnosis

In the individual patient, one must consider a number of other conditions. Scabies should always be excluded, and can cause confusion when superimposed on pre-existing atopic dermatitis. In the first few months of life, the differentiation of infantile seborrhoeic dermatitis from atopic dermatitis can be difficult [1], although with time the distinction becomes apparent. Immunodeficiency states should also be considered in infants in whom the disease is unusually severe, when there are recurrent systemic or ear infections, and if there is failure to thrive, malabsorption or petechiae. Recurrent infected eczema in Jamaican children may be associated with HTLV-I infection (Chapter 17).

In adults, flexural eczema may be a consequence of secondary dissemination of other types of eczema, for example in nickel allergy.

Genetic and metabolic disorders

An eruption resembling atopic dermatitis, with or without other atopic disorders, and sometimes with raised IgE levels, may be found in several syndromes:

1 Agammaglobulinaemia
2 Anhidrotic ectodermal defect
3 Ataxia–telangiectasia
4 Coeliac disease [2]
5 Cystic fibrosis heterozygote [3]
6 Experimental histidine depletion [4]
7 Hearing loss (genetic) [5]
8 Hurler's syndrome
9 Jung's disease (Chapter 17)
10 Nephrotic syndrome [6]
11 Netherton's syndrome (ichthyosis, bamboo hairs) [7]
12 Phenylketonuria
13 Wiskott–Aldrich syndrome (infections and thrombocytopenia).

A rash resembling atopic dermatitis is common in phenylketonuria, although disturbances in phenylalanine metabolism cannot be detected in ordinary atopic dermatitis.

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Hyper-IgE syndrome [1,2]

SYN. JOB'S SYNDROME; BUCKLEY'S SYNDROME

This is a syndrome which develops in infants or children. It resembles atopic dermatitis, but tends to involve particularly the scalp, axillae and groins. The associated features include persistent secondary bacterial infection, fluctuant cold abscesses, contact urticaria, bronchitis and more severe lung damage. The key laboratory finding is the great

elevation of serum IgE levels (greater than 2000 i.u./mL), often with some eosinophilia. Other immuno-globulins are often normal. Neutrophil chemotaxis is impaired.

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Hypereosinophilic syndrome [1,2]

Eosinophilia is a common feature of many diseases, including several skin diseases. However, the hypereosinophilic syndrome is a rare disorder, usually affecting middle-aged males, in which there is an intense blood eosinophilia in the absence of any of the usual causes. Only a few such cases can be attributed to an eosinophil leukaemia. The clinical manifestations appear to be attributable to the eosinophilia itself, and include cardiac involvement, and involvement of the nervous system, liver, lungs and gut. The skin changes include a non-specific, itchy, maculopapular eruption; urticaria or angio-oedema; an eruption resembling atopic dermatitis; or erythroderma [3,4]. Lymphomatoid papulosis [5] and aquagenic pruritus have also been associated. Distinguishing between atopic dermatitis and cases in which only the skin is involved may be difficult or even semantic. Treatment of cases with severe organ involvement is unsatisfactory, but has included the use of systemic steroids and cytotoxic drugs such as hydroxyurea.

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Pachydermatous eosinophilic dermatitis

Nir and Westfried described a generalized rash associated with marked blood and skin eosinophilia, and called it hypereosinophilic dermatitis [1]. More recently, a variant of this disorder has been described in three black South African teenage girls, and designated pachydermatous eosinophilic dermatitis [2]. This condition is thought to resemble severe atopic dermatitis or onchodermatitis. However, the three patients had peculiar hypertrophic genital lesions, peripheral blood eosinophilia and an eosinophil-rich lymphohistiocytic cutaneous infiltrate.

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Investigation

The diagnosis of atopic dermatitis is rarely aided by investigations. Estimation of total serum IgE, specific radioallergosorbent tests (RASTs) and prick tests usually serve only to confirm the atopic nature of the individual. It is possible that such confirmation may be of value occasionally in adult-onset dermatitis. However, one must remember that 20% of patients with atopic dermatitis have normal total IgE levels and negative RASTs, whereas 15% of apparently healthy individuals have a raised IgE [1].

The value of investigations in identifying trigger factors in atopic dermatitis is disputed. How helpful specific RASTs to foods or aeroallergens are for disease management is unclear [2–4], although it is suggested that if they are negative, allergy is unlikely [5]. It may be that skin prick test positivity to food allergens in young children with severe atopic dermatitis and a high serum IgE indicates a high risk of developing later allergic respiratory disease [6].

If one suspects immunodeficiency with atopic dermatitis, then the appropriate investigations should be performed—for example, immunoglobulin levels and subclasses, IgE levels, white-cell count, platelets, complement levels and function, and T, B and phagocyte cell numbers and functions. If clinically appropriate, one may also consider testing for HTLV-I and human immunodeficiency virus (HIV).

Bacteriology and virology swabs may be helpful in identifying causes for deterioration of atopic dermatitis. Although atopic dermatitis skin is often colonized by *Staphylococcus aureus*, bacterial culture can identify antibiotic resistance and detect β-haemolytic streptococci. Herpes simplex is usually readily cultured, but a Tzanck smear, an immunofluorescence slide test, or electron microscopy can also be helpful, and will provide more rapid confirmation of infection.

Patch testing may also help to identify a contact allergen responsible for deterioration of the skin condition, particularly in adults [7,8]. The 'atopy patch test' for aeroallergens [4] and foods [9] in atopic dermatitis, and the skin-application food test (SAFT) in the management of the IgE-mediated contact urticaria syndrome in children with atopic dermatitis [10], are recommended by some authorities.

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Treatment [1–3]

Atopic dermatitis is a chronic condition that is variable in severity and age of onset. Many current therapies are based on small studies or even anecdotal evidence. Nevertheless, treatment should be tailored to an individual's needs, bearing in mind age, sex, social conditions, sites of involvement and severity. A treatment strategy based on consistent advice and cooperation between health carers and the patient should be developed. It is clear that these aspirations are frequently not realized in practice [4–6]. However, recent years have seen the emergence of several new treatments that hold promise for the near future (see below).

First-line treatment

General advice

In order to develop a strategy the patient's specific requirements (in the discussion below the term patient refers either to the individual or the carers in the case of a baby or child) should be discussed and achievable aims agreed. These may include improvement in a range of factors such as decreasing itch, improving sleep, reducing absenteeism from school/work or improving family interactions.

It is the clinician's responsibility to determine a balance between effective control of the condition and improved quality of life, and safe long-term therapy. Education about atopic dermatitis by doctors, nurse specialists, self-help groups and national support groups, is very helpful in achieving these aims. As part of the discussion, patients should be taught current knowledge of the disease, the types of trigger factors, the treatment options and their likely benefits and risks. Demonstration of the use of topically applied medications, bandages or wet wraps, will improve compliance and disease control [7].

Reduction of trigger factors

Atopic dermatitis can be aggravated by a variety of trigger factors. These will vary between patients, and may differ at various times in an individual patient.

Most patients have dry skin, and soaps and detergents can irritate the dermatitis [8]. A dispersible cream can be used as a soap substitute to cleanse the skin. Simple measures such as turning down the central heating, not heating the bedroom, avoiding contact of wool with the skin and wearing cotton clothing, may make life more comfortable for the patient.

Formal dietary manipulation is really a second-line treatment, but if the patient clearly identifies aggravating foods then avoidance can be tried. Many patients have already started a restricted diet before seeing a doctor, so dietary assessment is important to confirm adequate nutrition. Airborne allergens are also aggravating factors, but formal manipulation of the environment is not required for most patients. Regular cleaning of the bedroom in particular, with hoovering and damp dusting, may be helpful. Animal dander can aggravate atopic dermatitis and contribute to HDM antigen levels, and so the keeping of household pets should be discouraged. Flares of the dermatitis may be associated with the introduction of a new trigger factor into the environment, or even a new environment, such as a change of childminder, and so the trigger factor history should be reviewed frequently.

Not only can stress aggravate atopic dermatitis, but the severely affected child is also a source of stress to the whole family [9,10]. The doctor's role in giving simple reassurance and listening to family problems should not be underestimated. Stress can respond to treatment, and the dermatitis can be improved by using a variety of cognitive behavioural techniques and group therapy [11].

Atopic dermatitis is not a contraindication to routine childhood vaccinations. Although egg protein is present in some vaccines the amount is so small that it should not be a problem in practice, unless the child has documented severe systemic reactions to egg protein. If in doubt, vaccination should be supervised in an environment where resuscitation equipment is available.

Parents should be advised about the risk of herpes simplex infection in a child with atopic dermatitis, and told to avoid contact of active cold sores with the child's skin.

Topical therapy

The principles of topical therapy are discussed in Chapter 75, and knowledge of such principles is essential for

effective management of atopic dermatitis. In general, in chronic lesions of atopic dermatitis ointments are to be preferred, particularly when lichenification is prominent. In certain individuals, ointments can cause irritation, and less oily preparations may be required. If lesions are exudative, then creams or lotions may be required for a short time until ointments become more appropriate.

Bathing and emollients

Bathing is soothing for the majority of patients, and is helpful as long as the skin is moisturized immediately afterwards. Foaming detergents and soaps should be avoided and a soap substitute used for cleansing [8]. Dispersible bath oils are helpful, but do not maintain skin hydration as long as emollients applied immediately after the bath. The regular use of emollients may even protect against inflammation provoked by irritants such as detergent [12] and increase the benefit obtained from topical corticosteroid therapy [13]. Indeed, ceramide-rich emollients may lead to improvements in childhood atopic dermatitis through a specific barrier repair mechanism [14]. In order to identify the emollient which best suits an individual, it may be useful to provide small quantities of several agents, so that they may choose which they prefer. Then a generous quantity should be prescribed to encourage frequent use throughout the day.

Topical corticosteroids

Topical steroids are the predominant treatment for the inflammation of atopic dermatitis, and if not abused are very safe. Anxiety among both the general public and family doctors about potential adverse effects of topical steroids has led to undertreatment of the skin in many sufferers [15].

The strength and mode of application of the topical steroids depends on the severity of the dermatitis, the sites to be treated and the age of the patient. Less potent topical steroids should be used on the eyelids, the face, the axillae, and the groins and inner thighs. Less potent topical steroids are also usually employed in children who are less than 1 year old, because systemic absorption occurs even with 1% hydrocortisone ointment.

A general principle is to use a topical steroid strong enough to settle severe dermatitis by twice-daily application for 3–7 days, and then to reduce either the frequency of application or the steroid potency for maintenance therapy. In adults, a sequence of a potent steroid followed by a moderately potent steroid would be appropriate, whereas in children moderately potent and mild topical steroids are preferable. A recent study has shown no differences in efficacy or side effects between pulsed potent corticosteroid creams and the continuous use of mild topical corticosteroids in patients with mild to moderate disease [16]. Once-daily treatment in the evening, with morning application of emollients, may be as effective as twice-daily corticosteroid treatment.

Corticosteroid resistant or infected or crusted dermatitis may respond better to steroid/antibiotic or steroid/antiseptic combinations. However, in young children there is some concern about the potential systemic toxicity of some antiseptics, such as clioquinol, if large surface areas are to be treated.

Monitoring corticosteroid use. Topical steroids can cause side effects if abused. Complications related to systemic absorption are rare. It is advisable to educate patients about the quantities to apply—for example, the fingertip unit [17]—and to ask them to estimate the quantity used per month. Height and weight should be monitored in young children if they have severe dermatitis requiring moderately potent or potent steroids. Local side effects, such as permanent telangiectasis on the cheeks in babies and striae of the breasts, abdomen and thighs in adolescents, may be minimized if appropriate steroid strengths are used. Particular care is required around the eyes, as glaucoma may be induced by topical steroids [18].

Ichthammol and tar

Preparations containing ichthammol and coal tar may be helpful as maintenance treatment in patients with lichenification. Generally, a 1–10% coal-tar solution in an appropriate cream or ointment is preferred to crude coal tar. Localized areas can be treated with bandages impregnated with these agents applied overnight.

Oral therapy

Antihistamines

Itch is the most difficult symptom of atopic dermatitis to treat, and currently there is no specific antipruritic treatment [19]. The use of anti-inflammatory preparations and emollients, and reduction of trigger factors, are still the first measures.

H_1-receptor antagonists are used predominantly for their sedative effect [20]. Agents such as promethazine or trimeprazine given 1 h before bedtime can be useful when there is severe nocturnal itching. However, they can cause drowsiness and lack of concentration the next morning. In infants, these preparations may occasionally cause paradoxical excitation. They are best used in short courses, for example 10–14 days, as tachyphylaxis can occur with prolonged use [21]. Most studies conclude that non-sedating antihistamines are of little value for the pruritus of atopic dermatitis [20], but in some cases with an allergic component—for example, contact urticaria—they may be of value [22].

Antibiotics

Exudation and pustule formation often implies staphylococcal infection of the skin, and oral antibiotics such as flucloxacillin or erythromycin are indicated. Colonization of the skin by these bacteria may exacerbate the dermatitis, and antibiotics may be helpful even if frank infection is not apparent. In patients with recurrent flares of atopic dermatitis associated with infection, long-term antibiotic treatment, topical steroid-antibiotic combination creams, and measures to reduce staphylococcal colonization of the nose and perineum should be considered [23].

Herpes simplex infection should be treated with oral aciclovir. If the patient is febrile or toxic, intravenous aciclovir should be used.

Second-line treatment

The majority of patients will respond to first-line treatment regimens. Patients who fail to respond should be reviewed to check compliance, to exclude antibiotic-resistant infection or herpes simplex infection, and to consider second-line treatment.

Intensive topical treatment

The strength of topical steroid treatment can be increased for a short period as an outpatient. If this is ineffective, inpatient treatment will often control severe exacerbations of dermatitis, and the skin frequently improves using the same treatment that was unsuccessful as an outpatient.

Wet-wrap technique

This can be a useful technique for the control of severe atopic dermatitis in younger children. Two layers of absorbent tubular bandage are applied to the skin. The inner layer is presoaked in warm water and the outer layer is dry. A generous quantity of a low-potency topical corticosteroid is applied to the skin before the dressings. The dressings can be used overnight or changed every 12 h. This regimen can be used in hospital or for short-term outpatient treatment. Close supervision should be maintained, because suppression of the hypothalamopituitary axis can occur when topical steroids are employed [24]. Regimens using emollient only under the wet dressings have become popular, but have not been subject to adequate clinical trial.

Immunomodulatory creams

In recent years, research has been undertaken on two non-steroidal anti-inflammatory topical compounds, tacrolimus (FK-506) [25] and pimecrolimus (ascomycin; SDZ ASM 981), and these are increasingly available for clinical use.

Tacrolimus ointment has been shown to be effective and safe during treatment of up to 1 year in adults (0.1% ointment) and children (0.03% ointment) [26,27]. It is indicated for moderate to severe atopic dermatitis that has failed to respond to conventional therapies and does not cause cutaneous atrophy [28].

Pimecrolimus 1% cream is a selective inhibitor of inflammatory cytokine release that has shown very promising results in the management of atopic dermatitis in adults and children as young as 3 months of age [29,30].

Studies comparing these preparations with potent topical corticosteroids with respect to both efficacy and safety are awaited eagerly.

Allergy management

Eighty per cent of patients with atopic dermatitis show IgE hyperreactivity to common allergens. Some authorities argue that the intrinsic type (with no demonstrable IgE hyperreactivity) is important to identify because it will never progress to allergic respiratory disease and such patients will not benefit from allergy management [31]. Although it is clear that reactivity can be demonstrated *in vivo* and *in vitro*, it is less clear how well such reactivity correlates with clinical improvement following allergen avoidance.

Foods

Dietary factors may aggravate the dermatitis of 15–35% [32] of children with atopic dermatitis, but in older children and adults this is far less common. Approaches to dietary management range from intensive investigation using double-blind food challenges [33] to empirical diets [34]. The clinical benefit of dietary management is still debated, because there are few controlled studies of its value [32]. Even so, because some children benefit who have failed to respond to simple general and topical therapy, there is much to be said for a 3–4-week trial period on a modified elimination diet. Increased suspicion may be caused by a history of urticarial reactions or gastrointestinal reactions to foods. A positive specific raised IgE, particularly the specific circulating titres (IgE cap), may have a predictive value in young children [35,36]. Commonly, dairy produce, beef, eggs, chicken, fish, wheat, citrus and berry fruits, food additives, chocolate and nuts may be excluded. Decreased itch and improvement of the dermatitis show the benefits of a relevant exclusion diet. It is important that the diet is appropriately supervised by a paediatric dietitian. If such measures do not reveal an obvious dietary culprit, a normal diet can be resumed, with the suspected foods reintroduced every 3–4 days.

It must be remembered that there have been occasional severe anaphylactic reactions when a food to which an atopic is very sensitive has been reintroduced [37]. Fre-

quently, in children, an inadequate, unbalanced diet is given before medical advice has been sought, and malnutrition may be present, usually because of cow's milk avoidance. It is important to thoroughly review the child's diet with the help of a dietitian in these circumstances. Extensively hydrolysed cow's milk formulates can be used as a cow's milk substitute, and recently an amino acid-based formula has been found to be an effective substitute in children with dermatitis [38].

Breastfeeding for at least 6 months in infants with atopic dermatitis is usually suggested [32]. However, the protective effect of breastfeeding against the development of atopic dermatitis remains controversial [39].

In older children and young adults, dietary management is rarely helpful [40], and screening tests are not helpful in this age group (roughly over 6 years) because of false-positive reactions. However, occasionally patients benefit from a diet free from food additives [41].

Inhalants

Although a variety of inhalants have been implicated in exacerbations of atopic dermatitis [42], HDM allergen appears to be the most important [43]. Clinical improvement in children's dermatitis has been noted following intensive eradication of mite allergens from the bedroom [44,45]. However, the benefit of HDM eradication on adults with atopic dermatitis is less convincing [46]. There is some suggestion that early avoidance of airborne allergens, along with common dietary allergens, may reduce the chances of later developing atopic conditions [47].

Contact allergy

Contact urticaria is usually quickly recognized from the history, and avoidance of the responsible foods is advised. Tests to identify such foods are not usually required (see investigations).

Delayed hypersensitivity to medicaments and fragrances may be responsible for treatment failure, particularly in adults with periorbital eczema [48], and patch tests are useful if this is suspected. However, because of irritancy, interpretation of patch tests can be difficult in atopics. It may be necessary to admit the patient to hospital to settle the eczema before performing patch tests. Contact allergy may be found in children, and this possibility must not be forgotten [49].

Third-line treatment

Phototherapy

Numerous types of phototherapy have undergone trials for the treatment of severe atopic dermatitis, and seem to be effective. These include UVB, narrow-band UVB, medium and high-dose UVA1 and PUVA [50–53]. Some studies suggest that air-conditioned treatment cabinets improve patients' tolerance of phototherapy [54]. A practical consideration is the relative timing of the use of phototherapy and immunosuppressant therapy, because of concerns about skin cancer development in later life.

Oral immunosuppressants

A number of systemic therapies are available for recalcitrant cases. Limited effectiveness or concerns over toxicity may restrict their long-term usefulness.

Low-dose ciclosporin therapy has been shown to be effective in the control of adult [55] and childhood atopic dermatitis [56,57]. Occasionally, permanent remission appears to be induced [58]. Renal toxicity, hypertension and the risk of skin cancer are limiting factors.

Oral corticosteroids have a limited but definite role in the management of severe exacerbations of atopic dermatitis, but long-term treatment often requires doses which may produce significant adverse effects.

Some authors claim that long-term azathioprine may be less toxic than other oral immunosuppressives, but the onset of its effect is slow [59,60].

Other therapies

Evening primrose oil is often recommended for patients with atopic dermatitis. A meta-analysis of placebo-controlled studies suggested a slight benefit [61], but this is strongly disputed [62].

Clinical trials of Chinese herbal medicines have been performed, and decoctions of a standard formulation appear to be helpful in adults and children [63,64]. Concern has been expressed about their potential for hepatotoxicity [65].

The value of oral sodium cromoglycate is still unclear, but high doses may be helpful in some patients [66]. Topical sodium cromoglycate solution has been helpful in children [67]. Several other drugs have been reported to be effective in atopic dermatitis, including IFN-γ [68], thymopentin [69], type 4 phosphodiesterase inhibitors [70], intravenous immunoglobulins [71], oral ketoconazole [72], mycophenolate mofetil [73,74], and montelukast [75]. Extracorporeal photopheresis has also been shown to be of benefit [76].

Desensitization and immunotherapy

Desensitization plays a very limited part in the management of patients with atopic dermatitis, even when an allergic factor has been firmly established clinically [77]. Trials of hyposensitization have shown variable results [78], but occasional cases of atopic dermatitis may benefit. A recent review of immunotherapy concluded that there

were encouraging results, but the studies were small in size and few in number. A new area of study which promises hope of controlling skin disease is sublingual immunotherapy [79]. Other approaches to alter the immune status of atopic dermatitis sufferers have included the use of intradermal injection of killed *Mycobacterium vaccae* suspensions [80] and probiotic suspensions added to milk formulas in infants [81].

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Disease prevention and occupational advice

There is conflicting evidence about whether maternal avoidance of milk, eggs and other dietary allergens during the last trimester of pregnancy and during lactation can reduce the incidence of atopic disorders [1,2]. The evidence that breastfeeding or diets to avoid potential allergens during the first 6 months of the infant's life will significantly protect against atopy or reduce its manifestations is also contradictory [1]. However, a cohort study of 1265 children followed for 10 years suggests that a diverse solid-food diet during the first 4 months of life roughly doubled the risk of developing atopic dermatitis [2]. It seems prudent to recommend breastfeeding children at special risk. There is interest in reducing exposure to dietary allergens, aeroallergens and irritants in children at high risk of developing atopic manifestations [3]. Some early evidence suggests that this approach may reduce the incidence of atopic manifestations [4].

Atopic dermatitis will often improve about the time of puberty. This is often the time when adolescents are deciding what occupation they should undertake. Exposure of the skin to irritant chemicals and physical trauma should be avoided as far as possible. Adolescents with atopic dermatitis would be well advised therefore to avoid occupations such as car mechanics, engineering, hairdressing or nursing.

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Chapter 19

Contact Dermatitis: Irritant

S.M. Wilkinson & M.H. Beck

Introduction

Irritant contact dermatitis in a broad sense represents the cutaneous response to the physical/toxic effects of a wide range of environmental exposures. A burn results when the effect on the skin is irreversible and necrosis occurs. Reversible cellular injury may cause contact urticaria or dermatitis dependent on the nature of the insult. Where there is no apparent cellular injury various sensory symptoms such as stinging, smarting and burning may occur. The following types of irritant contact reaction may be distinguished:

1 Burns
2 Irritant contact dermatitis:
(a) acute (toxic) irritant contact dermatitis
(b) cumulative irritant/insult contact dermatitis
3 Transient or immediate-type non-immune contact urticaria
4 Symptomatic (subjective) irritant responses
5 Other: pigmentary and granulomatous responses and those localized to appendageal structures (Table 19.1).

Allergic contact dermatitis and light-related skin reactions are covered in Chapters 20 and 24. Damage to the skin from physical and mechanical factors, thermal injury and ionizing radiation is discussed in Chapters 22 and 76. Pigmentary, follicular and granulomatous responses are covered in Chapters 58 and 69.

Table 19.1 Other irritant contact responses of the skin and their causes.

Folliculitis	Tar and oils, arsenic trioxide, fibreglass
Acne	Halogenated aromatic hydrocarbons
Miliaria	Aluminium chloride, occlusion
Pigmentary	
Hyperpigmentation	Phototoxic agents, metals (arsenic, silver, gold, mercury, bismuth)
Hypopigmentation	Substituted phenols & catechols
Granulomatous	Silica, talc, beryllium
Alopecia	Borax, chloroprene dimers

History

Contact dermatitis was first described to plants as long ago as 2000 BC, when an extract of the castor oil bean was rubbed into the scalp, as an irritant, to promote hair growth [1]. Whilst presumably recognized, there appears to be little subsequent documentation of irritant contact dermatitis other than in an occupational setting. For example, Agricola documented deep ulcers of the skin amongst metal workers in 1556. The apparent lack of interest may date back to ancient times and the Greek prejudice against manual labour, as a result of which in some cities it was illegal for a citizen to ply a manual trade. Consequently, medical works tended to concentrate on the afflictions of the citizen rather than of the work force. Increased awareness of occupational disease is noticeable from the 1700s and the Industrial Revolution. Ramazzini (1633–1714) described fissures on the hands of washerwomen and ulcers on the legs of salt miners. In England, during the 19th century, there was a revival of interest in occupational dermatoses, with Willan describing

dermatitis from shoemaker's wax and Bateman eruptions due to lime amongst builders [2,3].

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Epidemiology

Few population studies differentiate between irritant reactions and allergic contact dermatitis, and study populations are also often either selective or poorly defined. A questionnaire study of 20 000 persons in an industrial town in the south of Sweden [1] revealed a point prevalence of hand eczema of 5.4% (with a 1-year period prevalence of 11%). Females were twice as commonly affected as males, and in 35% of cases the hand eczema was thought to be irritant in nature. Atopic hand dermatitis accounted for 22% of cases, and allergic contact dermatitis only 19%. The most frequent sources of exposure were 'unspecified' chemicals, water, detergents, dust and dirt. Those involved in hairdressing, service work and medical and nursing occupations had the highest frequency of hand dermatitis. A retrospective study of hand eczema in Germany showed that 24% of those studied had an irritant pathoaetiology [2]. In one large study of adverse reactions to cosmetics [3], 16% were thought to be irritant in type.

'Sensitive skin' might be considered a marker of a form of skin irritancy. In a questionnaire-based study [4] of 3300 women and 500 men, 51.4% of women and 38.2% of men considered that they were susceptible. Fifty-seven per cent of women and 31.4% of men had had an adverse reaction to a personal care product during their lives. Amongst women, symptoms of subjective skin irritation (burning, stinging, etc.) occurred more frequently in those who considered they had a sensitive skin (53%) than in those who did not (17%). Dry skin and a predisposition to blushing/flushing were factors associated with a sensitive skin. An atopic background was a predictive factor for the presence of sensitive skin, as the incidence of atopy was higher among those with sensitive skin (49%) than among those in the non-sensitive group (27%). However, equal numbers of atopics and non-atopics constituted the sensitive skin group, indicating that other variables were involved. In North America, there has been shown to be no ethnic difference in the prevalence of sensitive skin, although there are racial differences in how it is perceived. Euro-Americans experience greater reactivity to wind and less to cosmetics; Afro-Americans have reduced reactivity to most environmental factors; Asians have greater reactivity to spices, change in temperature and wind, and itch more frequently; Hispanics react less to alcohol. Overall, however, there were more similarities than differences [5].

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Pathogenesis

The skin barrier

The skin provides the first and most important line of defence against exogenous noxious agents, and this is one of its primary physiological functions. This defence is far from perfect, as many substances penetrate readily into and through the epidermis, even when it is intact. The surface film is the first line of defence. It is composed of sebum emulsified with sweat and breakdown products from the horny layer [1]. The buffer capacity of the surface film varies considerably from one body region to another [2] but, in reality, it has a negligible influence on percutaneous absorption [3], stratum corneum hydration [4] and on the barrier function of the skin [5].

The principal epidermal barrier resides almost entirely in the stratum corneum [6]. This is normally renewed every 17–27 days [7,8], but barrier function can be restored in 2–5 days following stripping [9] or superficial injury. The stratum corneum appears to function as a homogeneous unit [6], the largest amount of penetrant always being found in the outermost layers. Damage to the stratum corneum is normally followed by an increase in percutaneous absorption and in transepidermal water loss, the increase in transepidermal water loss being proportional to the decrease in thickness of the horny layer [10].

For certain materials, there may be a second barrier at or near the dermal–epidermal junction or basement membrane [11] but, for most substances, the horny layer remains the principal barrier.

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The mechanism of action of irritants

An irritant is any agent, physical or chemical, which is capable of producing cellular perturbation if applied for sufficient time and in sufficient concentration. Immunological memory is not involved and dermatitis occurs without prior sensitization. Many chemicals penetrate the skin, and many substances will alter or damage skin cells. Dermatitis arises when the defence or repair capacity of the skin is exhausted, or when the penetration of chemicals excites an inflammatory response. Strong irritants will induce a clinical reaction in almost all individuals, whereas with less potent irritants the response may be physiological rather than apparent, dermatitis only developing in the most susceptible or in situations where there is repeated contact with irritants.

The relationship between physicochemical structure and cytotoxic activity remains to be fully elucidated, but it would appear that hydrophobicity (log P) and dissociation constant (pK_a) are among the factors which contribute to irritation potential [1,2] (Table 19.2). For sodium lauryl sulphate, concentration has been shown to be a more important determinant of subsequent dermatitis than exposure time [3]. The nature of the response is in part determined by the irritant [4].

In the laboratory, barrier disruption has been shown to induce interleukin-1α (IL-1α) release from a preformed pool in mouse epidermis [5] and upregulation of tumour necrosis factor (TNF)-α and granulocyte–macrophage colony-stimulating factor (GM-CSF). There is then a rise in Langerhans' cell-derived IL-1α stimulated by GM-CSF and IL-1α production [6]. Concurrently, the loss of the normal extracellular calcium gradient stimulates lamellar body secretion and barrier repair [6]. Oxidative stress also contributes to the development of inflammation with various irritants [7].

Detergents at lower levels of exposure predominantly affect the horny layer, causing dryness and scaling by destroying lysosomal enzymes in the horny layer [8], whereas at higher concentrations they will dissolve cell membranes and damage lysosomes [9]. With repeated exposure, there will be signs of chronic inflammation, with increased DNA synthesis, acanthosis and changes in cellular metabolism [8,10].

Detergents and other irritants such as croton oil and phenol esters are chemotactic for polymorphonuclear leukocytes at non-toxic concentrations [11], and may cause pustular reactions. Organic solvents such as methanol or chloroform will damage blood vessels causing hyperaemia [12], and dimethyl sulphoxide (DMSO) is a very effective degranulator of mast cells [13].

Irritants affect everyone, although individual susceptibility with regard to the development of dermatitis varies greatly. The body's immune response is important in generating dermatitis, and this has been shown in the attenuated response to irritants in CD4-deficient mice [14].

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Table 19.2 Factors influencing irritancy potential of substances on human skin.

Exogenous	Endogenous	Co-factors
Chemical characteristics	Individual susceptibility	Mechanical
Molecular structure	Atopy	Thermal
pH	Race/skin colour/phototype	Climatic
pK_a	Age	
Hydrophobicity (log P)	Hormonal	
Inherent toxicity	Barrier function	
Concentration/dose	Repair capacity	
Penetration characteristics	Eczema elsewhere	
Vehicle	Other skin diseases	
Solubility	Other unknown	
Duration of contact	Site of exposure	
Type of contact		

and expression of cytokines after application of 2 different irritants. *Contact Dermatitis* 1996; **35**: 355–60.
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Pathology

Whereas allergic contact dermatitis reactions are histologically almost always eczematous and rather monomorphic, those elicited by irritants show much greater pleomorphism. Histological changes vary according to the chemical nature and concentration of the irritant, the type and duration of exposure, the severity of the response and the time of sampling. Some irritant reactions may be histologically indistinguishable from allergic contact dermatitis, whereas others may possess morphological features characteristic of a certain type of chemical. More than one pattern of response may be induced by the same irritant.

Histology

Mild to moderate acute reactions to most irritants are characterized by spongiosis, intracytoplasmic vacuolation and nuclear pyknosis [1,2]. In general, spongiosis is less marked than that seen in allergic contact dermatitis, although more highly vesicular changes may be induced by such irritants as croton oil. With more severe irritation, necrolysis or cytolysis of epidermal cells occurs, leading to intra- or subepidermal vesicles and bullae. Such changes are seen particularly with cantharidin and trichloroethylene [3]. Parakeratosis is a common feature of acute reactions to one of the most widely studied irritants, sodium lauryl sulphate (SLS), possibly arising from enhanced keratinocyte proliferation [4] (Figs 19.1–19.4).

Electron microscopy has provided additional information on the nature of the cellular damage following acute exposure to various irritants. Ultrastructural changes include disruption of cell membranes and organelles, lipid accumulation, alterations in keratin filaments and modification of the stratum corneum [2,5–7].

Chronic or cumulative irritant contact dermatitis differs from acute reactions in that the histological picture is predominantly one of hyperkeratosis with areas of parakeratosis, moderate to marked acanthosis and elongation of rete ridges [8].

The role of Langerhans' ($CD1a^+$) cells in the induction and elicitation of allergic contact dermatitis is now well established, but it remains unclear whether these cells also actively respond to irritants. Studies of acute irritant contact dermatitis have demonstrated histological changes in Langerhans' cells, ranging from signs of cytotoxicity, such as reduced dendrite length, condensed nuclear chromatin and loss of integrity of organelles and membranes, to indications of cellular activation, including widened rough endoplasmic reticulum and increased numbers of Birbeck granules [9,10]. Epidermal density changes have also been described following the application of SLS, nonanoic acid, dithranol and croton oil [10–13].

Some indication that Langerhans' cells may have functional significance in irritant contact dermatitis has emerged recently from experiments by Brand and coworkers, in which increased numbers of Langerhans' cells were detected in regional draining lymph vessels, concomitant with increased lymph-cell antigen-presenting capacity [14,15].

Disruption and/or degeneration of collagen is commonly seen in irritant reactions, and oedema has been described by some investigators [16,17]. A number of irritants induce more specific changes in dermal cells, examples being DMSO, which acts as an effective mast cell degranulator, and organic solvents, which affect principally the vasculature, leading to capillary dilatation and hyperaemia.

Quantitatively and, to a limited extent, qualitatively, the cellular response to irritant-induced skin damage is dependent upon the nature and concentration of the irritant, the severity of the reaction, the time of sampling and the species under investigation. In mild to moderate reactions, the infiltrating cells are predominantly mononuclear, consisting mainly of helper–inducer T lymphocytes ($CD4^+$) with an accompanying admixture of suppressor/cytotoxic T cells ($CD8^+$), macrophages and $CD1a^+$ cells. B cells, natural killer (NK) cells and follicular dendritic cells are absent or rare [13,18–20]. Polymorphonuclear leukocytes, which play a significant role in guinea-pig responses, are generally only seen in substantial numbers in human reactions where there is severe epidermal damage with necrosis and the formation of subcorneal and intraepidermal bullae, or where infection has occurred.

The majority of the infiltrating inflammatory cells seen in irritant contact dermatitis reactions express human leukocyte antigen (HLA)-DR, with significant numbers of T lymphocytes also expressing the receptor for IL-2 (CD25) [20–22].

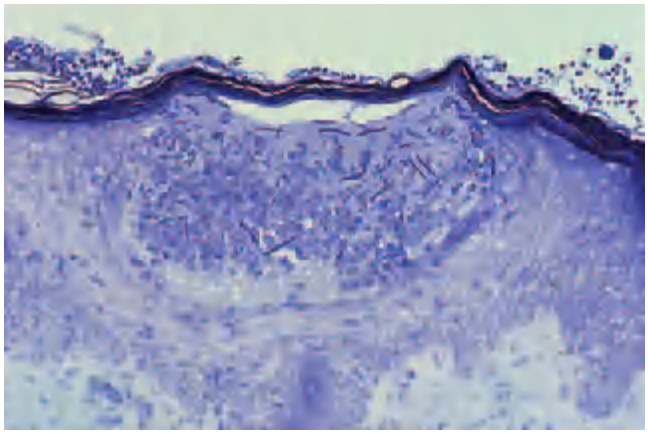

Fig. 19.1 Pustular reaction induced by 48-h patch testing with croton oil (0.08%). Toluidine blue stained, 1-µm resin section; original magnification × 200. (Courtesy of J.D. Wilkinson and C.M. Willis, Amersham General Hospital, Amersham, UK.)

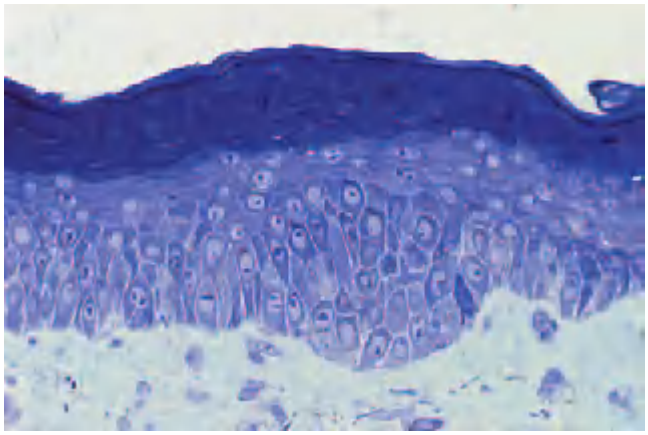

Fig. 19.2 Deeply stained parakeratotic layer induced in the epidermis by 48-h patch testing with sodium lauryl sulphate (5%). Such an appearance is characteristic of this irritant, and is probably related to increased epidermal cell division. Toluidine blue stained, 1-µm resin section; original magnification × 400. (Courtesy of J.D. Wilkinson and C.M. Willis, Amersham General Hospital, Amersham, UK.)

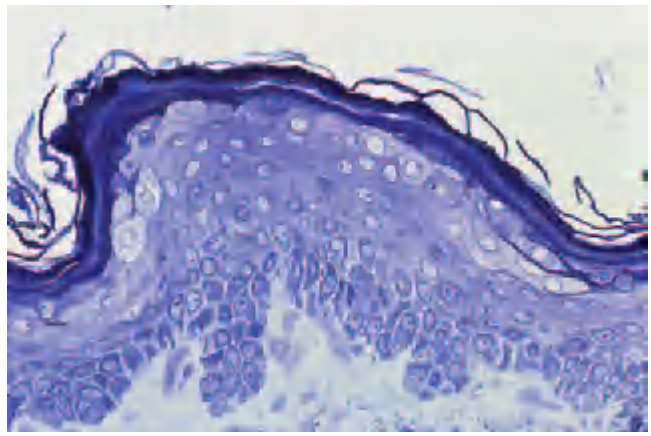

Fig. 19.3 Hydropic swelling of keratinocytes within the upper epidermis following 48-h patch testing with dithranol (0.02%). Toluidine blue stained, 1-µm resin section; original magnification × 400. (Courtesy of J.D. Wilkinson and C.M. Willis, Amersham General Hospital, Amersham, UK.)

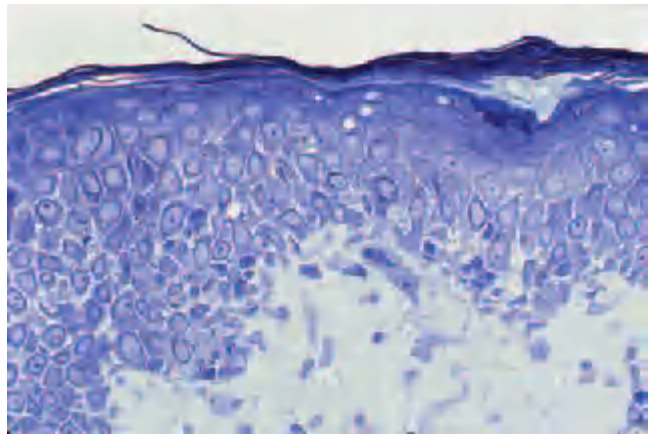

Fig. 19.4 Forty-eight-hour patch-test reaction to benzalkonium chloride (0.5%), exhibiting similar histopathological features (i.e. spongiosis and exocytosis) to those of allergic contact dermatitis. Toluidine blue stained, 1-µm resin section; original magnification × 400. (Courtesy of J.D. Wilkinson and C.M. Willis, Amersham General Hospital, Amersham, UK.)

Follicular pustules tend to develop, particularly in individuals with atopy, following exposure to such irritants as croton oil and metal salts. However, the presence of follicular spongiosis is said to be more typical of an allergic contact dermatitis [23].

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Immunopathology

Identification of the inflammatory mediators involved in irritant contact dermatitis is valuable both as a possible means to distinguish irritant from allergic reactions and as an indicator of potential therapeutic avenues. Substances derived from arachidonic acid, in particular leukotrienes and prostaglandins, are present in the reactions to at least some irritants [1,2], in particular elevated levels of prostaglandins E_1 and E_2, as well as 12-hydroxyeicosatetraenoic acid (12-HETE). The pattern of release is determined by the nature of the irritant [3]. Elevation of prostaglandins and leukotriene-B4 correlate with the degree of inflammation, which is not the case for IL-1α.

Cytokines are hormone-like secreted proteins that regulate the growth and differentiation of many cells, including those of the immune system. It is now widely recognized that keratinocytes produce a number of these cytokines and play an active role in the inflammatory process. Among the pro-inflammatory cytokines which have been found to be released from epidermal cells following exposure to some irritants are TNF-α, IL-1, IL-6 and IL-8 [2,4,5]. GM-CSF and T-cell-derived cytokines, including IL-2 and interferon-γ (IFN-γ), have also been observed, subsequent to irritant application or tape stripping. Cytokines exhibiting anti-inflammatory characteristics, such as IL-10, are likely to play an important role in the regulation of irritant reactions, but have, as yet, only been studied in the tape-stripping model of barrier function impairment [6].

Keratinocyte involvement in irritant contact dermatitis is not confined to the production and release of cytokines, but extends to the up-regulation and expression of immune-associated adhesion molecules, both in response to cytokine release and as a result of direct irritant induction. These molecules include intercellular adhesion molecule 1 (ICAM-1), which acts as ligand for the leukocyte function-associated antigen 1 (LFA-1) constitutively expressed by leukocytes [7,8], and certain integrins that are involved in a variety of cell–cell and cell–matrix adhesion interactions [9]. Expression of the class II major histocompatibility complex (MHC) molecule HLA-DR by keratinocytes has been described, but appears not to be a predominant feature of the majority of irritant reactions [8,10].

Activation of protein kinase C-mediated events, leading to cell proliferation and differentiation, has been shown [11,12].

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Differentiation from allergic contact dermatitis

With some irritants, the histopathological changes are obvious and sometimes even characteristic, whereas with others the epidermal and dermal appearances are indistinguishable from allergic contact dermatitis. In general, however, spongiosis is more marked in allergic reactions, whereas epidermal necrosis, acantholysis and pustulation are normally seen only with irritants.

Despite considerable effort, immunocytochemical analysis of the cellular infiltrate has so far failed to reveal any significant differential diagnostic features [1]. The problem is compounded by the fact that many allergens are also potentially irritant. Avnstorp *et al*. [2] found a histological diagnostic specificity of 87% and sensitivity of 81% for allergic reactions, with 100% specificity and 46% sensitivity for irritant reactions.

Early studies in man showed little evidence of differential cytokine release between allergic and irritant contact dermatitis, suggesting that, although their initiating events vary fundamentally, the cascade mechanisms responsible for the induction and release of regulatory mediators are similar [3,4]. Subsequently, quantitative differences have become apparent, with absent production of IL-4 in irritant compared with allergic dermatitis [5].

In mice, the chemokine IP-10, along with IL-1, was shown to be induced in allergic but not irritant contact dermatitis [6]. Subsequently, expression of IP-10 in man has been shown to mimic this pattern within the first 3 days, using SLS as the irritant. IP-9, IP-10 and Mig are all induced by IFN-γ and interact with the CXCR3 receptor that is almost exclusively expressed on activated T cells. Examination of the cellular infiltrate revealed that 50% of the T cells expressed CXCR3 in allergic compared with 30% in irritant contact dermatitis [7]. It was assumed that the differences reflected the presence of IFN-γ, which also mediates keratinocyte expression of ICAM-1 and HLA-DR. Other qualitative differences were noted, including increased expression of IL-8 in irritant contact dermatitis, which attracts neutrophils by binding to either CXCR1 or CXCR2 expressed on neutrophils.

Protective mechanisms have also been shown to be important in preventing the development of allergic contact dermatitis; specifically, glutathione and related thiols detoxify exogenous electrophilic compounds such as dinitrochlorobenzene [8].

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Predisposing factors (Table 19.2)

Individual

Age, skin colour, race, phenotype and presence of eczema elsewhere may all affect the skin's response to marginal irritants. There is also significant individual variation in the patch test result with the same irritant on retesting [1,2].

Genetic/racial background. Twin studies suggest that genetic factors may influence susceptibility to irritants [3]. A TNF-α gene polymorphism has recently been demonstrated as a marker for susceptibility to irritant contact dermatitis [4].

A high baseline transepidermal water loss (TEWL) value points to an increased susceptibility to irritants [5,6]. Those with fair (Celtic) skins are not only more susceptible to UVB, but may also be more sensitive to chemicals [7]. Traditionally, Afro-Caribbean, Asian or Hispanic skin was thought to be more resistant, but some studies measuring TEWL after SLS exposure have cast doubt on this [8]. However, black skin is thicker and more compact than white skin, and irritant responses relate both to mean corneocyte thickness and skin surface contour [9]. A comparison of matched Caucasian and Japanese women showed the Japanese to have a greater tendency to irritation [10].

Age. Although the skin of the very young is usually regarded as being more vulnerable, there is very little evidence to substantiate this, except perhaps in the neonate [11] or premature infant [12].

Older individuals react less strongly to some irritants [13]. There is often a reduced inflammatory response and TEWL is reduced, which may represent a reduced potential for percutaneous penetration [14]. This is true of repeated irritation as well as a single insult. Onset of the reaction and subsequent recovery are also delayed [15]. *In vitro*, keratinocytes from older individuals demonstrate comparatively reduced secretion of IL-1 in response to

SLS and, in an elderly age group, higher secretion in photo-aged skin than in intrinsically aged skin [16].

Sex. Women more frequently report skin disease than men, and epidemiological studies of hand eczema show that they are more often affected. This is particularly true of the younger age group, where many female-dominated occupations involve exposure to wet work. They do not appear to be any more susceptible to skin irritation than men and these differences presumably relate to differences in exposure between the sexes [17]. Female skin, however, may be more reactive in the premenstrual phase of the cycle [18]. In a large group of individuals, use of the 4-h patch test has shown men to be more sensitive than women [1].

Neurological factors. Experimentally, sleep deprivation and the stress of an interview, but not exercise, resulted in delayed barrier recovery following tape stripping. Simultaneous increases in plasma cortisol, noradrenaline, IL-1α, IL-10, TNF-α and NK cell number and activity were measured. Cytokine responses to the interview stress were inversely correlated with barrier function recovery [19].

Site. The effect of irritant contact varies from region to region on the body. This partially reflects differences in thickness or type of stratum corneum and density of transepidermal shunts (hair follicles, sweat ducts), as well as potential for occlusion by body folds. In addition, there are probably inherent differences in keratinization and in composition of the intercellular lipids, especially ceramides and glucosylceramides, which play an important part in the barrier function of the skin [20].

The skin of the face, the scrotum and back of the hands is more permeable than skin elsewhere [21], and therefore more vulnerable to the effects of irritants and, in the case of exposed skin, more prone to chapping. The skin of the palms and soles is, in comparison, so thick that it is almost impermeable to everything except water and caustics.

The structure and total lipid concentration of the stratum corneum have a significant effect on stratum corneum permeability [22], and may account for some of the site differences and also for some of the changes in barrier function following damage to the skin or associated with abnormal keratinization [23–25].

Fat-soluble chemicals can be absorbed through the sebaceous glands and epithelium of the follicular root sheath, and may cause both allergic and non-specific inflammation in the deeper parts of the skin, even when there is an undamaged horny layer. In general, however, except for ions and large polar molecules [26,27], the appendageal route is an insignificant one so far as the penetration of most irritants and allergens is concerned [28].

As a consequence of the above factors, the intensity of an irritant response varies according to body site with, for example, the strongest reactions to DMSO occurring on the face and upper back, and the weakest reactions on distal parts of the limbs. Barrier recovery also varies according to body site, with the face and back healing most rapidly [29].

Skin disease and atopy. Percutaneous absorption is facilitated by inflammatory changes in the epidermis [30]. Thus, an irritant contact dermatitis can promote penetration of allergens and, conversely, an allergic contact dermatitis can facilitate the penetration of irritants. Stripping of the skin by means of adhesive tape can significantly reduce barrier function [31] and, although the stripping leads to a burst of regenerative mitotic activity, it may take anything from 2 to 6 weeks for barrier function to be restored completely [32]. The presence of eczema or recently healed disease may predispose to further dermatitis [33].

Atopics, particularly those with atopic dermatitis or a past history of hand dermatitis, seem to have more easily irritated skins. In a study using serial dilutions of sodium lauryl sulphate, individuals with active and healed atopic dermatitis and with respiratory atopy alone had a lower threshold for irritation than normal controls [34]. This was most severe in those with current skin disease. Other studies do not show this predisposition, which may reflect patient selection and complexity of the processes involved [35].

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Environmental

Although toxic chemicals are the principal cause of irritant reactions, there are often significant contributory factors, including the potentiating effects of temperature, climate, occlusion and mechanical irritation.

The development of irritant dermatitis is partially temperature-dependent—higher temperature leads to a reduction in barrier function [1] and increases the penetration of SLS detergent through the skin [2]. Exposure to hot detergent appears to be more irritant than cold [3,4], and cement dermatitis often flares during the summer in hot, humid climates [5].

Low humidity. Low ambient humidity is the single most important factor with regard to the water content of the stratum corneum; a change to a low dew point can occur suddenly during winter, and can cause chapping even in normal persons [6]. Experimentally, low humidity has been shown to stimulate epidermal DNA synthesis and amplify the proliferative response to barrier disruption [7]. Susceptibility to SLS irritation is greatest during the winter in the Northern hemisphere [8] when stratum corneum hydration is reduced. Chapping, and atopic and hyperkeratotic forms of hand eczema, are often worse in temperate climates during the winter.

Low-humidity dermatosis has occurred in factories where the ambient humidity was too low [9]. Although the effects of temperature and humidity are to some degree interrelated, cold alone will reduce the water content and plasticity of the stratum corneum and lead to cracking. Simultaneous exposure to these and other factors may maintain a dermatosis or cause transition from simple chapping or low-humidity dermatoses to a more 'eczematous' dermatitis. In mice, epidermal IL-1 is constitutively expressed and released in greater amounts following tape stripping in a low humidity environment [10].

Occlusion. Occlusion promotes percutaneous absorption [11,12], and may facilitate skin irritation and enhance the effect of irritants to which an individual has already been exposed [13]. Water is imbibed by the keratin, which swells, producing wrinkling, as is seen after prolonged immersion in water. Increasing the water content of the stratum corneum by occlusion can enhance percutaneous absorption of certain substances many times [14]. It is of practical importance that rubber and plastic gloves, wristwatch straps, rings, waterproof adhesives, shoes, boots, clothes and the natural folds of the skin provide such occlusion. Soft paraffin by itself also has an occlusive effect [15].

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Chemical and physical

Different groups of chemicals show significant differences in absorption and diffusion characteristics [1,2]. Results obtained from hydrocortisone, for example, cannot be presumed to reflect the situation for water or other molecules [3].

The main barrier to water transport through the skin is attributed to stratum corneum lipids and to high-molecular-weight proteins of the corneocyte [4]. The stratum corneum, having a predominantly lipid intercellular composition, is more susceptible to lipid-soluble irritants [5], and modifying factors in respect of barrier function may be quite different for hydrophilic and hydrophobic substances [6,7]. When the lipids of the stratum corneum are removed by solvents, water transport rates through the skin increase [8]. Subsequent immersion in water for 2 min will remove as many of the water-soluble substances from the keratin layer as a 2-h immersion in water not preceded by defatting [9]. A detergent effects the combined removal of both lipids and water-holding substances and thus predisposes to chapping and dermatitis [10]. Combined exposure to both solvent and detergent has been shown to have an additive effect on inducing dermatitis [11].

Alkaline solutions have a deleterious action on the horny layer and promote percutaneous absorption. Cross-links in the keratin are broken, and water can penetrate into the fibrils and cause swelling of the horny layer. If reducing substances are present in alkaline solution the disulphide links are also broken, which leads to greater damage [12]. However, change in pH was found not to influence irritancy of alkaline detergents between pH 7.4 and 10.8 [13].

Physical injury often plays a role in dermatitis, e.g. rough sheets have produced facial dermatitis in neonates [14], and frictional factors were contributory in cases of hand dermatitis among post office workers [15]. Fibreglass [16,17] and rockwool [18] can also cause an irritant dermatitis which is aggravated by rubbing (see Chapter 21).

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Identifying irritants [1]

The need to reduce the use of animals for irritant testing has increased the amount of research directed towards the development of *in vitro* tests. None of these can as yet replace human or animal testing entirely, but they do allow a staged process of toxicological evaluation. Initially, this involves a literature search, and a search for any unpublished toxicological data. To this can be added an assessment based on chemical structure. Subsequently, *in vitro* testing methods can be used to assess both corrosion and irritation, although finally animal/human test methods may be needed to assess acute or cumulative irritant potential *in vivo*.

In vitro techniques used to assess for corrosion have gained governmental recognition and rely on viability assessments in skin culture models [1]. *In vitro* tests for irritation are varied and none is yet sufficiently well

validated for regulatory purposes. They include testing on the chorioallantoic membrane of hens' eggs, red blood cell assays and cytotoxicity testing on Balb/c 3T3 fibroblasts. The effects on cellular homeostasis and viability may be measured by uptake of neutral red, and changes in cellular protein levels by subsequent staining with Kenacid blue [2]. Dimethylthiazoldiphenyl tetrazolium bromide MTT assay, neutral red release assay [3] and release of pro-inflammatory mediators from cultured human keratinocytes [4], have all been proposed as possible models for the initial assessment of irritancy potential of surfactants and other chemicals. Correlation with *in vivo* tests is not absolute and results should always be interpreted critically as the epidermal barrier does not exist in cell culture models [5].

Most irritancy testing in animals and humans is done on a predictive basis, using a variety of techniques, such as the Draize test [6], the chamber-scarification test [7,8] and the 21-day repetitive insult test [9,10]. Strong irritants may cause dermatitis on first exposure, whereas weak irritants may only be detected by repeated application [9,10]. Internal standards are necessary to allow comparison with other established irritants [11].

The use of ethical tests in human volunteers is likely to prove the way forward where testing *in vivo* is considered essential. Closed 48-h patch tests on the intact skin of eczema-prone subjects may be used as a simple screen of irritancy for products intended for use on the skin. However, there are generally significant interindividual variations [12]. Recent protocols for human testing include 4-h irritant patch tests measured against standard internal controls [13].

Barrier function tests [14] and other bioengineering techniques [15,16] can be applied to increase panel sensitivity and reduce morbidity, as the differences in irritant potential can be detected earlier. A high baseline TEWL, for example, may act as a predictor for susceptibility to irritants [17]. Other techniques which have been used to try to identify hyper-reactors for inclusion in screening panels include ammonium hydroxide blistering [18], the SLS test [7], the chloroform pain threshold test [19] and the lactic acid stinging test [20]. Frequent or repeated use of a product, especially on those with hyperirritable skins or in those claiming an adverse reaction from a product, is another way to maximize the chance of reproducing a reaction in humans [21]. Comparative usage tests between similar products can be performed in the same way [22]. It is always important to bear in mind, however, that in an individual it is not possible to predict the strength of reaction to one irritant by knowing the strength of reaction to another [23].

However, not all irritant reactions are erythematous or impair barrier function. The immediate-type non-immunological contact reactions, and immediate and delayed symptomatic contact reactions encountered when applying some substances to the skin, produce principally subjective responses, such as stinging and smarting, and require a different approach [20] such as the lactic acid stinging test.

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Clinical features

Irritant contact reactions [1–3] are inflammatory reactions of the skin to an external agent or agents in which,

although inflammatory and immunological mediators may be activated, no memory T-cell function or antigen-specific immunoglobulins are involved.

Irritants produce a wide range of responses on the skin which are not necessarily eczematous. These may range from purely subjective sensations, such as stinging, smarting, burning, or sensations of dryness and tightness, through delayed stinging or transient urticarial reactions to more persistent irritant reactions or irritant contact dermatitis. Irritant contact dermatitis has a spectrum of clinical features, ranging from a little dryness, redness or chapping through various types of eczematous dermatitis to an acute caustic burn. Irritants may also penetrate skin via appendageal structures and cause folliculitis and other types of reaction (Table 19.1).

The same chemical may cause different irritant reactions depending on concentration; DMSO, for instance, is able to induce both conventional irritant dermatitis and immediate non-immunological contact urticarial reactions [4]. Reaction patterns vary between species, mast cells providing an important component of the cellular response in guinea pigs [5] but being generally less evident in humans [6]. The response may also vary according to site and mode of application [7], vehicle [8] and between individuals.

Although the nature, concentration and duration of contact with the irritant chemical are of primary importance, mechanical, thermal, climatic and constitutional factors are important modifying and/or enhancing factors in many irritant responses (Table 19.2).

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Chemical burns

A chemical burn (Fig. 19.5) results when there is irreversible cell damage, and necrosis occurs. There is usually rapid onset of painful erythema, often within minutes, at the site of exposure. This is followed by blistering and the development of necrotic ulcers. Weals may be seen as a result of toxic degranulation of mast cells. Symptoms

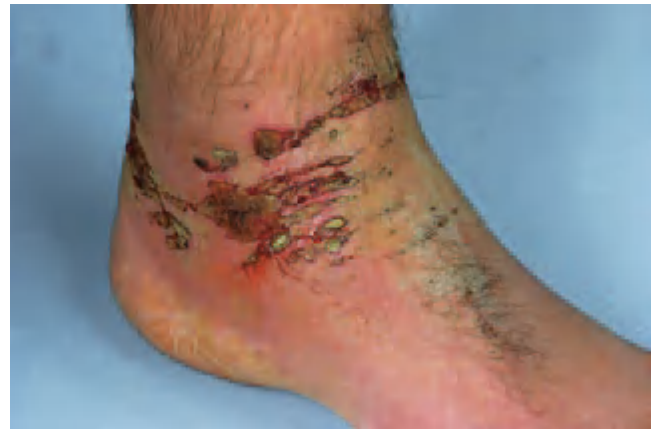

Fig. 19.5 Caustic 'burns' from wet cement. (Courtesy of J.D. Wilkinson and C.M. Willis, Amersham General Hospital, Amersham, UK.)

coincide with the exposure, but with some chemicals, including phenols and weak hydrofluoric acid, the onset may be delayed [1]. With ethylene oxide gas, used to sterilize medical instruments, textiles and plastic materials, the chemical can remain on items for several days if not allowed to evaporate. The possibility of exposure may therefore not be obvious. Damage continues to occur until all of the agent has chemically reacted or has been neutralized as a result of treatment.

Most acids (e.g. sulphuric, nitric, hydrochloric, chromic) coagulate skin proteins, and as a result form a barrier which impedes further penetration. Some acids can discolour (e.g. nitric acid turns the skin yellow). Ulceration of the skin and nasal passages 'chrome ulcers' used to occur, prior to modern safety precautions, in tanners, textile workers, smelters and electroplaters, due to corrosion by chromate fumes. Hydrofluoric acid [2] differs in that it causes a liquefactive necrosis, and penetration can continue for several days after exposure, even down to bone. Pain, which can last several days, is typical of burns due to hydrofluoric acid and other fluorides. It is related to the ability of the fluoride ion to bind calcium and disrupt neural function. If more than 1% of the body surface area is affected, systemic toxicity can develop.

Alkalis (e.g. sodium, calcium, potassium hydroxides; wet concrete [3]; sodium and potassium cyanides) degrade lipids, and saponification of the resulting fatty acids forms soaps which aid penetration deeper into the skin. As a consequence, damage is more severe than with most acids, and pain is also a feature. The dead skin turns brown and later black, usually without blistering, and forms a hard eschar.

Phenols [4] and unhardened phenolic resins penetrate the skin easily and rarely can cause nerve damage in the absence of visible skin change. Vasoconstriction may contribute to the necrosis that develops, and in the case of systemic absorption can lead to shock and renal damage.

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Irritant contact dermatitis

The clinical appearance of irritant dermatitis (eczema) is essentially no different from that due to other causes; allergic or endogenous. Diagnosis therefore is essentially clinical after exclusion of contact allergy.

Acute irritant contact dermatitis

Acute irritant contact dermatitis is often the result of a single overwhelming exposure to an irritant or caustic chemical (Fig. 19.6), or a series of brief chemical or physical contacts. This results in acute inflammation of the skin, and is usually associated with an immediate sensation of burning or stinging. Differentiation between an acute (toxic) contact dermatitis and a primary chemical burn is not always possible. The initial reaction is usually strictly limited to the site of application or contact, the concentration of the substance diffusing outside the area of contact almost immediately falling below the critical threshold necessary to provoke a reaction [1].

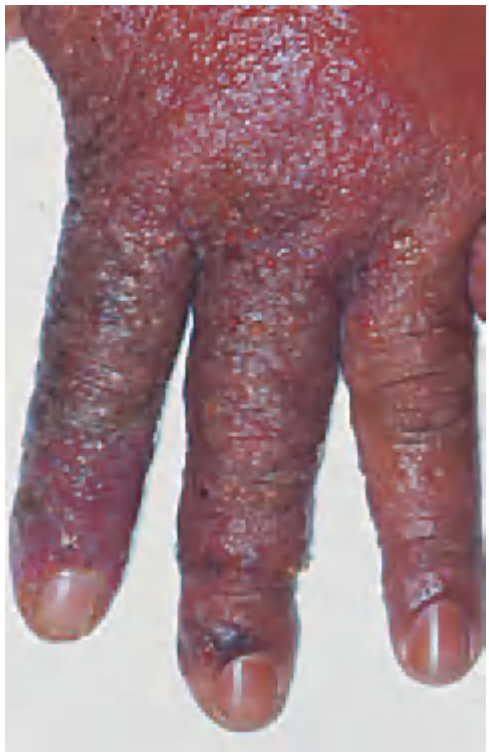

Fig. 19.6 Acute irritant contact dermatitis following immersion in concentrated bleach. (Courtesy of A. Yung, Leeds General Infirmary, Leeds, UK.)

Irritant effects may be considerably enhanced by occlusion, and care must always be taken to ensure that irritants do not penetrate gloves or protective clothing. Most cases of acute irritant dermatitis occur as a result of accidents at work. Some substances—for example, gentian violet [2] and dequalinium chloride—are toxic only under certain conditions, such as under occlusion, on mucosal surfaces, or when the stratum corneum barrier is breached.

The rapidity of an acute irritant response usually makes the cause obvious, especially with strong alkalis or acids, which will produce a toxic reaction within a few minutes. The duration of application necessary to provoke a reaction with less potent irritants will vary considerably. The clinical spectrum of acute irritant dermatitis may range from a mild irritant reaction with transient erythema or chapping to a much more florid dermatitis with oedema, inflammation, pain and vesiculation. In more severe cases there may be exudation, bullae formation and tissue necrosis indistinguishable from a chemical burn. Caustic burns from lime [3] or cement [4] may cause extensive tissue damage. In patients with accidental or sporadic exposure, the dermatitis usually heals quickly, unless there is skin necrosis. In mild cases, the skin may revert to normal within a few days, but in more severe cases several weeks may be required for complete resolution.

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Delayed irritancy

Delayed irritancy—or, rather, a delayed time course of irritation—has been reported in respect of several substances, including SLS [1], propylene glycol [2] and certain diacrylates [3]. This may sometimes cause problems in the interpretation of patch-test reactions because the inflammatory response occurs late (at 48 h), and may therefore simulate an allergic contact reaction.

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Cumulative irritant contact dermatitis [1]

SYN. CHRONIC IRRITANT DERMATITIS; 'WEAR AND TEAR DERMATITIS'; TRAUMITERATIVE DERMATITIS

This type of dermatitis develops as a result of a series of repeated and damaging insults to the skin. These insults may include both chemical irritants and a variety of harmful physical factors, such as friction, microtrauma, low humidity [2], the desiccant effects of powder [3], soil or water and temperature.

Once the stratum corneum barrier has been breached, a great number of normally innocuous substances can perpetuate an irritant contact dermatitis. Scratching, rubbing and even topical treatment may on occasions become causes of persistence. Chronic irritant dermatitis may therefore be due to the summation of various adverse factors, many of which would not in themselves be strong enough to cause irritant dermatitis but which, taken together, are enough to weaken the skin and lead to the development of cumulative irritant contact dermatitis [1]. These minor irritants may also act as perpetuating factors once the dermatitis has become established. Among this great variety of causative factors, there may be some which are overlooked by the patient because they do not appear to be related to the onset of the dermatitis (Figs 19.7–19.9).

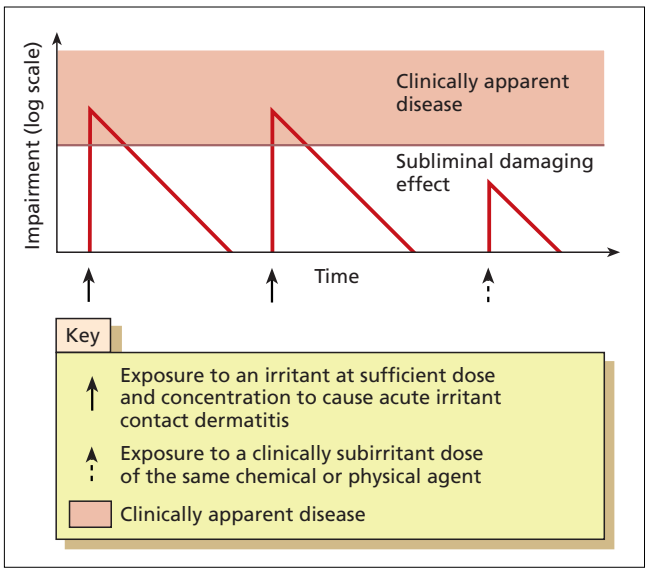

Fig. 19.7 Acute irritant contact dermatitis. The damaging effects on the skin of acute (non-cumulative) exposure to irritants. (From Malten [1].)

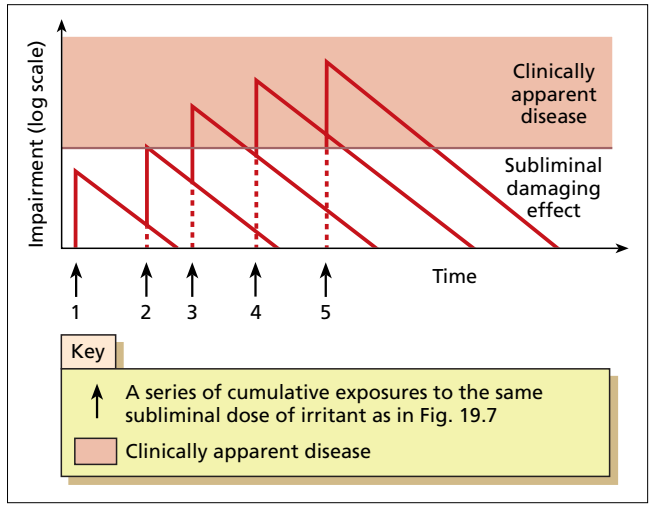

Fig. 19.8 Cumulative irritant contact dermatitis. The damaging effect on the skin of cumulative doses of a subliminal irritant. (From Malten [1].)

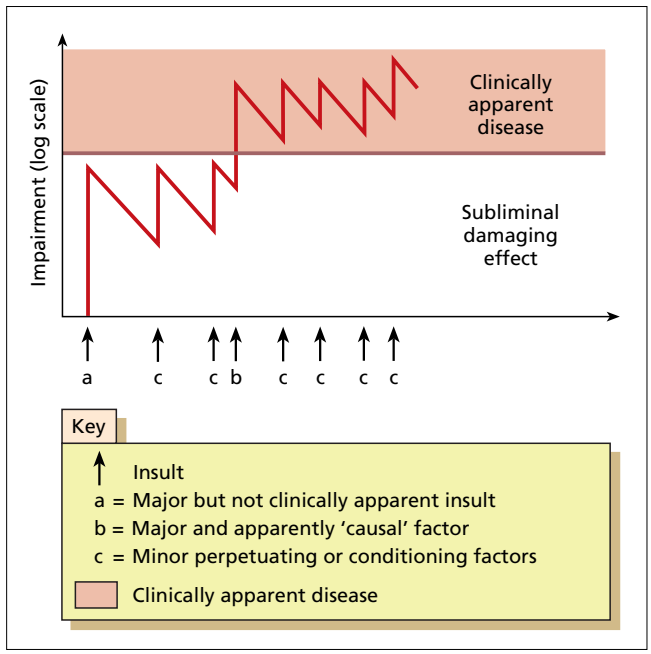

Fig. 19.9 Cumulative irritant contact dermatitis—mixed causation. (From Malten [1].)

Cumulative irritant dermatitis most commonly affects thin or exposed skin—for example, the dorsa of the hands, fingertips and the webs of the fingers (Figs 19.10 & 19.11), or the face and eyelids in those with cosmetic intolerance [4] or low-humidity dermatosis [2]. The face, eyes and upper respiratory tract are often affected by volatile types of irritant (Fig. 19.12) especially in those exposed industrially [5].

Irritant contact dermatitis often begins with a few localized patches of dry, slightly inflamed or chapped skin

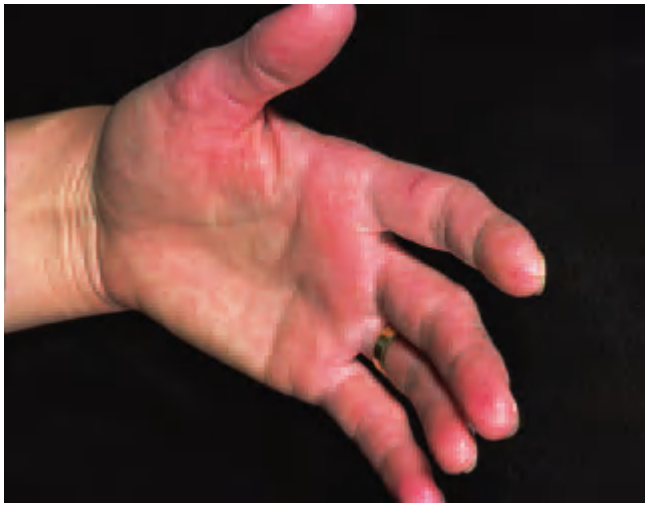

Fig. 19.10 Dry palmar or 'extended fingertip' dermatitis. Often associated with wet work. (Courtesy of J.D. Wilkinson and C.M. Willis, Amersham General Hospital, Amersham, UK.)

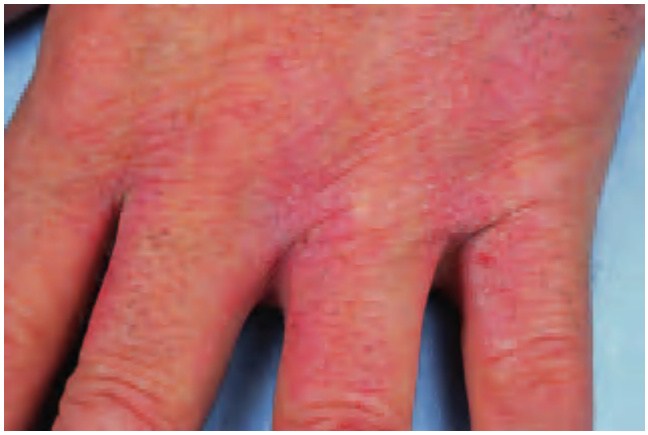

Fig. 19.11 An irritant pattern of 'finger web' eczema. (Courtesy of J.D. Wilkinson and C.M. Willis, Amersham General Hospital, Amersham, UK.)

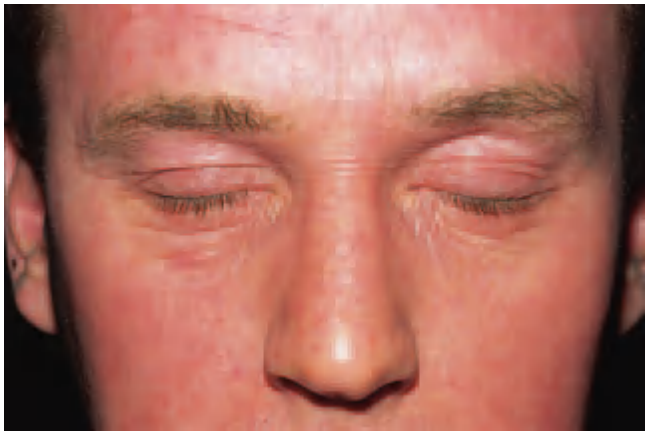

Fig. 19.12 Facial (eyelid) dermatitis from volatile irritant. (Courtesy of J.D. Wilkinson and C.M. Willis, Amersham General Hospital, Amersham, UK.)

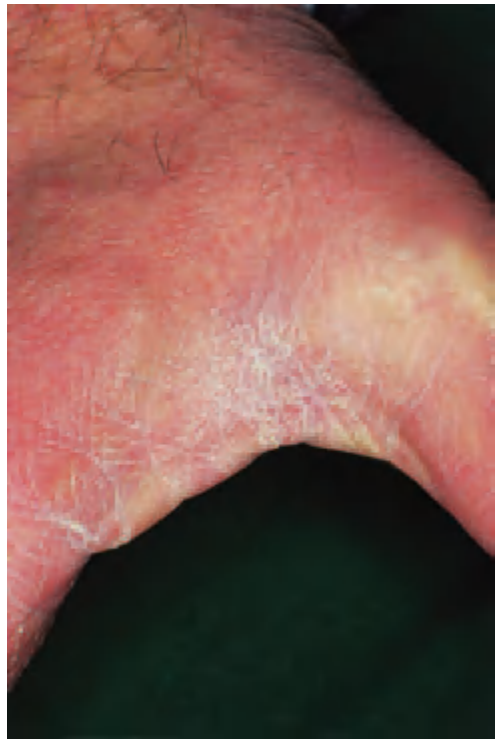

Fig. 19.13 Dry irritant reaction. (Courtesy of J.D. Wilkinson and C.M. Willis, Amersham General Hospital, Amersham, UK.)

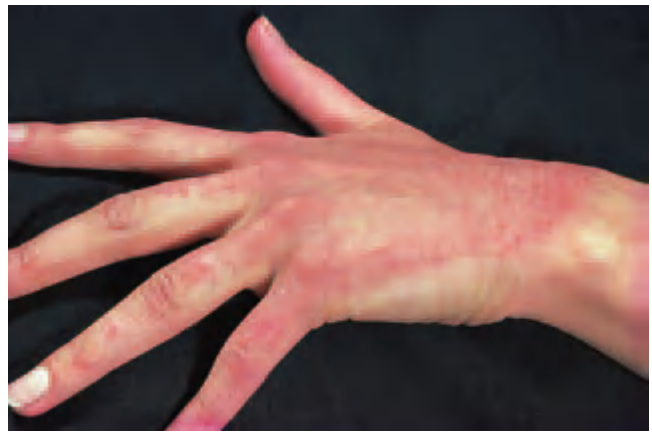

Fig. 19.14 Erythematous irritant reaction. (Courtesy of J.D. Wilkinson and C.M. Willis, Amersham General Hospital, Amersham, UK.)

(Figs 19.13 & 19.14), and the tendency to disseminate is normally less than with constitutional or contact allergic forms of eczema. Irritant contact dermatitis tends to be more static and monomorphic than other forms of eczema [1,6], but constitutional and allergic factors frequently coexist (Figs 19.15 & 19.16).

Occupations with a high incidence of cumulative insult dermatitis are listed in Table 19.3 (see also Chapter 21). Most workers, however, even those working in high-risk occupations, usually develop only minor degrees of

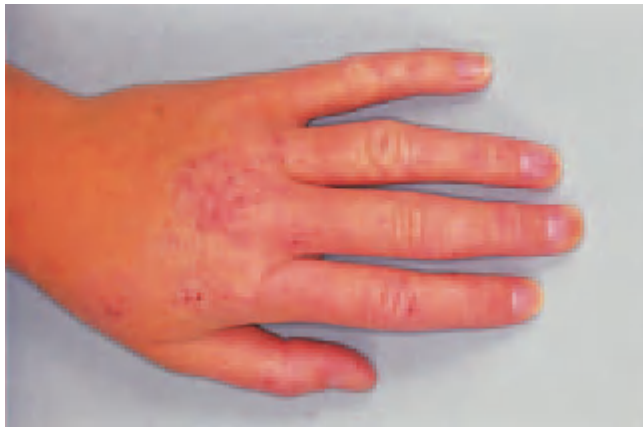

Fig. 19.15 A patchy 'discoid' eczema affecting the back of the hand in a hairdresser. Irritant, constitutional and allergic factors frequently coexist. (Courtesy of J.D. Wilkinson and C.M. Willis, Amersham General Hospital, Amersham, UK.)

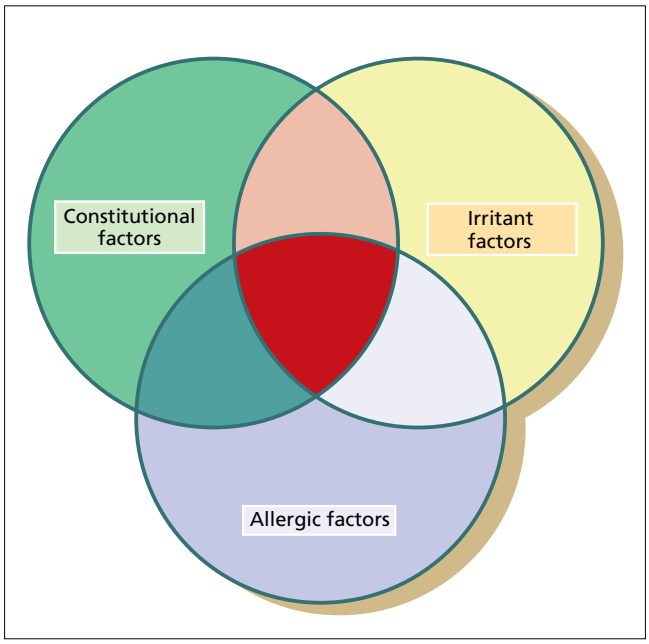

Fig. 19.16 A multifactorial view of dermatitis.

Table 19.3 Occupations associated with irritant contact dermatitis.

Hairdressing
Medical, dental, veterinary
Cleaning
Agriculture, horticulture, forestry
Food preparation and catering
Printing and painting
Metal work
Mechanical engineering
Construction
Fishing

Table 19.4 Common irritants.

Water and wet work: sweating under occlusion
Household cleaners: detergent, soap, shampoo, disinfectant
Industrial cleaning agents: including solvents and abrasives
Alkalis, including cement
Acids
Cutting oils
Organic solvents
Oxidizing agents, including sodium hypochlorite
Reducing agents, including phenols, hydrazine, aldehydes, thiophosphates
Certain plants, for example spurge, Boracinaceae, Ranunculaceae
Pesticides
Raw food, animal enzymes and secretions
Desiccant powders, dust, soil
Miscellaneous chemicals

dermatitis, and constitutional factors are therefore probably important in those who develop more severe forms of dermatitis. Nearly 80% of those with chronic disability dermatitis were found to be atopic in one survey [7]. Other factors are also important, such as additional exposure to irritants at home or in the pursuit of hobbies, for example car maintenance or gardening, accidental exposure to strong caustics or irritants, adverse climatic and environmental conditions, lack of attention to industrial hygiene and poor working technique. Excessive use of abrasive or solvent cleansers may be more damaging to the skin than some of the substances which they are designed to remove. Common irritants are listed in Table 19.4.

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Hand dermatitis

The pathogenesis of hand eczema is often complex. Constitutional, irritant and allergic factors frequently coexist. Although hand eczema is more common in women [1], this seems to be the result of increased irritant exposure rather than an inherent susceptibility [2]. Allergy can never be completely excluded, nor is any pattern of hand dermatitis pathognomonic for a single causation. In spite of this, there are certain types of hand dermatitis that are

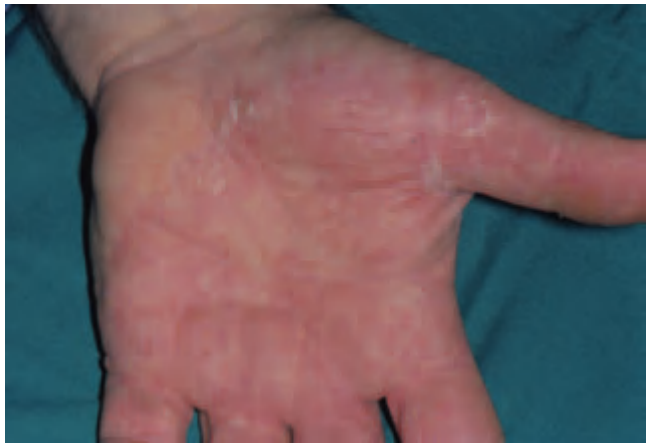

Fig. 19.17 A unilateral dry palm is characteristic of *Trichophyton rubrum* infection.

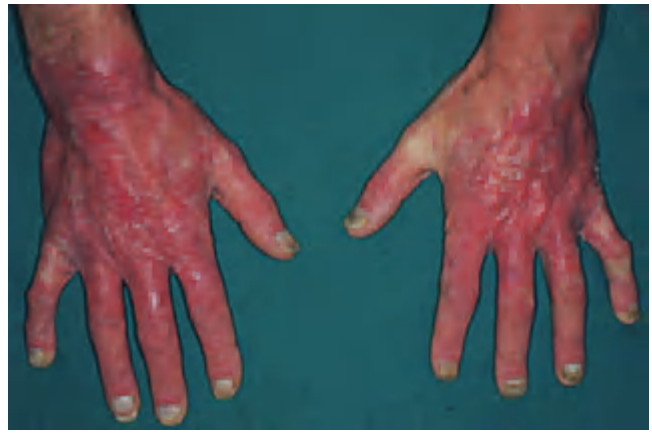

Fig. 19.18 Tinea incognito on the dorsum of the hand.

at least suggestive of irritant contact dermatitis. These include a patchy 'housewife'-type eczema affecting principally the dorsa, sides and webs of the fingers, or a 'ring' eczema—both are patterns associated with wet work and exposure to detergent. What may start as dryness can develop into patchy or diffuse erythema with scaling, fissuring and even vesiculation.

However, vesicles are less commonly seen in irritant than allergic or constitutional eczema, and the principal clinical features are usually dryness or chapping. The wrists and distal arms may also be affected. With increased mechanization in the house and more widespread use of protective gloves and hand creams, this pattern of hand eczema is less common than in the past.

Another common pattern of irritant hand eczema is the 'apron' or extended fingertip eczema, with dryness, redness and fissuring affecting principally the palmar aspects of fingers and distal palm. This pattern of dermatitis commonly occurs in those who frequently hold wet cloths containing detergent or household chemicals in the unprotected hand. Friction, irritants and repetitive wetting/desiccation all play a part. A similar pattern may be seen in occupations where employees are repeatedly exposed to solvents, friction or irritating food components. Discoid or nummular hand eczema is another rarer pattern of irritant contact dermatitis, affecting especially the dorsa of hands or fingers.

The differential diagnosis of hand dermatitis includes fungal infection, which simulates a unilateral palmar dermatitis (Fig. 19.17) and can resemble eczema on the dorsum of the hand (Fig. 19.18). Skin scrapings are important to exclude tinea as the cause of a hard to treat 'dermatitis'. Psoriasis frequently affects the palms, resulting in a hyperkeratotic appearance. This can be difficult to distinguish from dermatitis when there are no lesions elsewhere. Further, there may be a history of exacerbation when the disease leads to the Koebner phenomenon on the hands as a result of manual work. The presence of scaling erythema over the interphalangeal joints is often a helpful clue (Fig. 19.19) to the diagnosis. Scabies in the interdigital spaces can simulate an irritant dermatitis (Fig. 19.20).

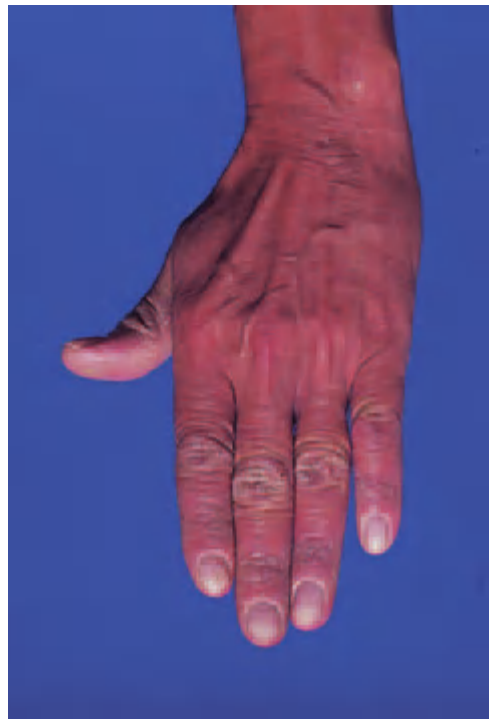

Fig. 19.19 Erythema and scale over the interphalangeal joints is a clue to the diagnosis of psoriasis.

Cosmetic dermatitis

Cosmetics, toiletries and skin-care products, including sunscreens, quite frequently cause adverse reactions [3]. In most cases, these are only mild or transient, and most consumers simply change to an alternative product. In a

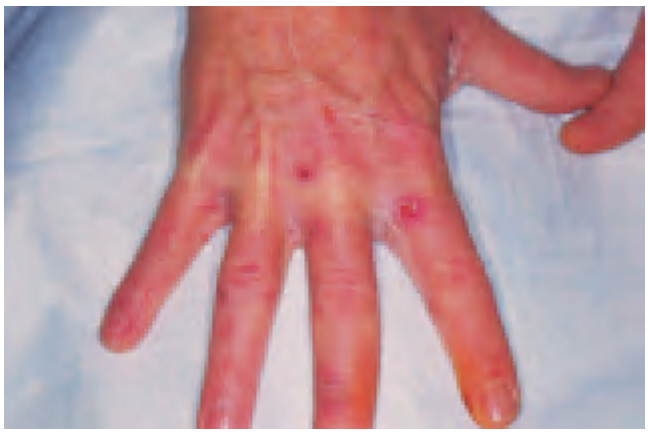

Fig. 19.20 Scabies affecting the finger web spaces. (Courtesy of A. Yung, Leeds General Infirmary, Leeds, UK.)

minority, reactions may be more severe, with redness, oedema, dryness and scaling. The eyelids are particularly susceptible to irritants [4], as are atopic individuals and those with very fair, rosaceous or seborrhoeic skins. It is of interest that irritant reactions are commoner in younger (premenopausal) women. Those using many products are at risk of 'cosmetic exhaustion', a form of cumulative cosmetic irritant contact dermatitis. Allergy is only excluded by comprehensive patch testing to both product and ingredients.

Volatile/airborne irritant contact dermatitis

Irritants, as well as allergens, may cause volatile contact dermatitis [5]. Volatile irritants are a not infrequent cause of eyelid dermatitis. In any exposed-site dermatitis, one should consider the possibility of irritant volatile fumes or airborne particles. The fumes can be from acids, alkalis, solvents, resins or any other irritant chemical, such as ammonia or formaldehyde. Irritant dusts include those of some (mostly tropical) woods, cement, fibreglass or rockwool, some metals and metal salts, and powdered chemicals.

Cheilitis

Cheilitis is a common problem, often of multifactorial aetiology. Atopic eczema frequently predisposes to its development [6]. The most common identifiable causes of cheilitis are irritant dermatitis, due to lip licking, cosmetics and medication, and allergic contact dermatitis, particularly from ricinoleic acid and the patient's own lip preparations [7].

Napkin (diaper), peristomal and perianal dermatitis

Irritant dermatitis will develop in situations of prolonged or too frequent contact with degraded urine or faeces/faecal residues [8]. Sweat, occlusion, irritant cleansers, secondary infection and secondary medicament allergy are all additional complicating factors. It occurs most frequently in the very young, or in the elderly in situations of urinary or faecal incontinence. Measures to improve continence in the elderly and sufficiently frequent changes of absorbent [9] napkins in infants are important, as are mild cleansers and protective pastes or silicone-based creams. Any dermatitis or secondary infection should be controlled with appropriate-strength topical steroids or steroid–antimicrobial combinations. In napkin dermatitis, secondary candidal infection is sufficiently common that routine treatment with an imidazole antifungal is of benefit [10].

A similar situation appertains to perianal dermatitis, where mucus or faecal leakage may occur in association with haemorrhoids and/or poor sphincter function. A bidet, or 'wet' cleansing routine using aqueous cream or equivalent, are of benefit.

With peristomal dermatitis, there is the additional complication of the need to maintain a protective seal between the stoma bag and skin. The use of corticosteroid-containing lotions, either aqueous or alcoholic, has been shown to be effective without interfering with stoma adhesion [11]. Dermatitis, as well as being caused by leakage, may also be due to continuous occlusion and repeated stripping of the skin. Where there is erosive disease, the use of topical sucralfate has been shown to promote healing in peristomal disease but not erosions from other causes [12]. The sucralfate acts as both a physical barrier and, it is suggested, by binding to basic fibroblast growth factor preventing its degradation, as a stimulus to healing.

Other sites

Irritant dermatitis at other sites occurs less frequently, but may develop on the feet from spillage under shoes or on the thigh from the habit of keeping an oily rag in a pocket.

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Phototoxicity [1]

A number of chemicals only cause irritation after absorption of photons; the photoactivated chemical has altered properties which are directly tissue damaging. They include psoralens, porphyrins, tetracyclines, non-steroidal anti-inflammatory drugs, phenothiazines and amiodarone. This is discussed in greater detail in Chapter 24.

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Mechanical irritation

In an experimental setting, distortion of the skin at the edge of adhesive tape (Fig. 19.21) has been shown to be directly related to the development of irritant dermatitis [1]. Koebnerization of eczema as both primary and secondary events following injury has been reported [2]. Friction is reported to cause nipple dermatitis in association with jogging [3] and ill-fitting bras [4]. Dermatitis has similarly been reported under other items of clothing at sites of friction. The presence of a rash, particularly in the summer months, suggested that damp clothing/skin

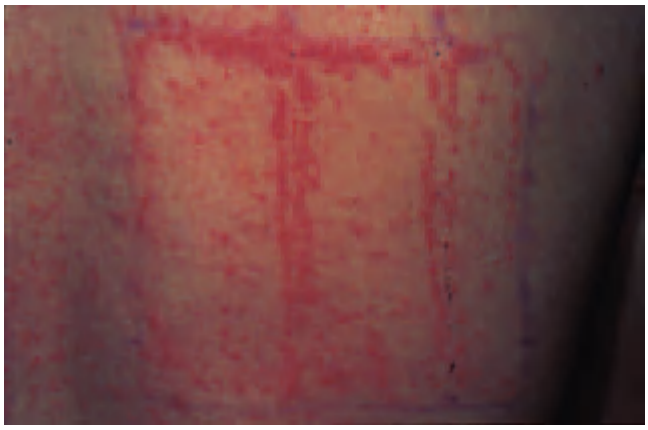

Fig. 19.21 Dermatitis developing at the edge of Scanpor tape after patch testing.

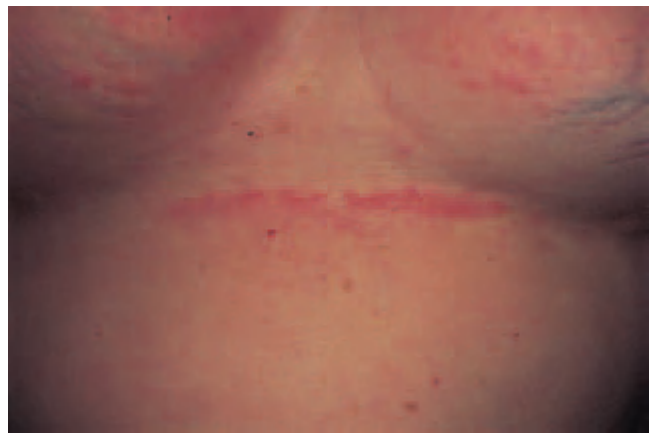

Fig. 19.22 In the same patient, frictional dermatitis under a bra strap (contact allergy excluded).

from sweating was implicated in the pathogenesis in 15 patients reported by Ramam *et al*. [5] (Fig. 19.22). Localized dermatitis from prosthetic limbs is also frequently trauma-induced [6]. In a retrospective review of physical irritant contact dermatitis [7], 35.3% of cases were induced by friction, 32.7% by drying and 11% by heat. The majority of cases had an occupational origin, with 36.3% of cases affecting the hands and 26.4% the face.

Fibreglass dermatitis [8] is usually irritant in nature, and is the result of skin injury by direct penetration of fibre particles. It is directly proportional to the diameter (greater than 3.5 μm) and inversely proportional to the length of the fibres. Pathologically, the changes are eczematous, with spongiosis. This is discussed in greater detail in Chapter 21.

Mechanical injury by plants is also common [9]. Most injuries to the skin by thorns or spines are purely mechanical. However, glandular hairs of some plant species inoculate pharmacologically active substances, and certain spines and thorns give rise to distinctive reactions, which suggest that the mechanical effects may be enhanced or modified by as yet unidentified toxic agents. The small bristles, or glochidia, of some species of cactus are retained in the skin and produce an eruption of very persistent, small, irritable papules. *Opuntia ficus-indica*, the Sabra, which is widely grown in the Mediterranean area, is a common offender, and the eruption has therefore been described as 'Sabra dermatitis' [10]. Similarly, trichomes of other plants have caused an irritating eruption of the interdigital spaces simulating eczema [11] or tinea. Barley awns cause an extensive papular dermatitis in farm workers. The sharp-tipped leaves of palms or yuccas and the thorns of roses may become deeply embedded in or near bones or in joints, especially in children's hands. They may then cause a chronic septic arthritis or intense periosteal reaction, which may mimic bone tumours [12]. Small thorns may induce foreign-body granulomas.

The common blackthorn, *Prunus spinosa* [13], is notorious among country dwellers for the chronicity of the granulomas it may cause. The persistent nodules are usually on the wrists and fingers.

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Non-immune contact urticaria

Immediate contact reactions may be either allergic or toxic. They are transient, developing within minutes, and fade quickly (usually within hours). They may appear on both normal and damaged/eczematous skin, and may present as only a transient symptomatic erythema or as a contact urticaria.

For some agents which cause immediate-type reactions, it is still unclear as to whether or not the mechanism is immunological. Non-immunological immediate contact reactions occur without prior sensitization. The reactions remain localized, and may present as a transient erythema or as an urticarial weal and flare, depending on concentration, area of contact, mode of exposure and agent involved [1,2]. Substances reported to cause non-immunological contact urticaria are listed in Table 19.5. The most potent of these, such as benzoic acid, sorbic acid, cinnamic acid, cinnamic aldehyde and nicotine acid esters, may induce a local reaction within 45 min in more than 50% of those tested. Reactions may occur at concentrations as low as 0.1% for benzoic acid, sorbic acid and sodium benzoate [3–5], and as low as 0.01% for cinnamic aldehyde. Reactions are not enhanced by occlusion, but may affect mucosal surfaces; low concentrations of cinnamic aldehyde are sometimes added to toothpaste and mouthwashes to impart a sensation of 'freshness'. Studies on an unselected population have shown that reactions to urticants are not predictable; an individual who reacted strongly to one urticant did not necessarily react to another. In addition, there was no significant correlation between age or sex and urticant response [6].

Table 19.5 Agents reported to cause non-immunological contact reactions. (From Lahti and Basketter [2].)

Animals	*Plants*
Arthropods	Nettles
Caterpillars	Seaweed
Coral	
Jellyfish	*Preservatives*
Moths	Benzoic acid
Sea anemones	Chlorocresol
	Formaldehyde
Foods	Sodium benzoate
Cayenne pepper	Sorbic acid
Fish	
Mustard	*Miscellaneous*
	Butyric acid
Fragrances and flavourings	Cobalt
Balsam of Peru	Dimethyl fumarate
Benzaldehyde	Histamine
Cinnamic acid	Pine oil
Cinnamic aldehyde	Pyridine carbo-aldehyde
Cinnamon oil	
Thyme	
Medicaments	
Alcohols	
Benzocaine	
Camphor	
Cantharidin	
Capsaicin	
Chloroform	
Dimethyl sulphoxide	
Friars' Balsam (Compound Benzoin Tincture)	

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Symptomatic (subjective) irritant responses

With some irritants there is little or nothing to see, but individuals complain of a subjective sensation of stinging, burning or smarting. These sensations most commonly affect the head and neck and may present as one form of cosmetic intolerance. With soaps and detergents, the perceived sensory symptoms correlate with and predict the development of clinical signs of irritant dermatitis [1].

Sensory symptoms are not limited to chemical exposure, the itch and prickle from woollen garments being well known amongst patients with atopic eczema. Experimental studies have shown this to be due to stimulation

of nerve fibres which transmit pain. It required a 100-mg force on the end of a 40-μm diameter textile fibre to trigger the nerve receptor. Thus, garments which induce the sensation will have protruding fibre ends that can withstand 100 mg pressure without buckling. Prickle was not experienced if the fabric was rubbed over the skin, if the skin was cold or if the area of contact was less than 1 cm^2. Moisture increased the severity of the sensation [2].

Immediate-type stinging

Some chemicals will cause painful sensations within seconds of contact [3]. These include acids, where the stinging may be a prodrome to the development of more severe cutaneous damage. Other chemicals, however, will cause stinging without any significant cutaneous damage. The best known of these are chloroform and methanol (1 : 1), and 95% ethanol. Responses vary according to site and individual susceptibility, and probably relate indirectly to stratum corneum thickness. The sensation abates quickly following removal of the irritant substance.

Delayed-type stinging

Delayed-type stinging [3] may occur following contact with a number of substances (Table 19.6). Typically, there is no immediate stinging, but discomfort develops within 1–2 min, reaches a maximum in 5–10 min, and fades slowly over the next half hour. The reaction normally only affects the face, especially in association with heat and humidity or sweating. The sensation is not alleviated by washing off the offending chemical. It is an idiosyncratic response, and only a proportion of the population will be affected.

The original cases occurred following use of a sunscreen containing amyldimethyl-*p*-aminobenzoate (ADP Padimate) [4]. Individuals can be screened to ascertain whether they are stingers or not by the application of 5% aqueous lactic acid to the nasolabial fold after induction of sweating. Among the substances able to induce this reaction are the sunscreen agent 2-ethoxyethyl-1-methoxy cinnamate, the insect repellent diethyltoluamide, several dermatological therapeutic agents and vehicles/solvents used in both cosmetics and medicaments. Preparations can now be screened for stinging potential by testing a predetermined panel of 'stingers and smarters'.

Little is known of the mechanisms involved in subjective irritant reactions. It is presumed that penetration of the irritant is primarily via sweat ducts and hair follicles, is not related to pH and that the reaction involves stimulation of sensory nerve endings. The reaction is substantially reduced in the absence of sweating. White people seem to be more sensitive than black people; atopics or those with easily irritated skins are also more susceptible [5,6]. Eyelid skin is especially vulnerable. It would appear that susceptible individuals have a lower skin capacitance and greater degree of skin reddening than normal controls. This was taken to indicate a tendency to barrier impairment and vascular hyperreactivity in affected individuals [7], although the sensation does not correlate with a predisposition to irritant dermatitis or non-immune contact urticaria [8].

Table 19.6 Substances known to cause delayed stinging or burning. (From Frosch [3].)

Weak
Aluminium chloride 30% aq.
Benzene 1% alc.
Phenol 1% alc.
Phosphoric acid 1% aq.
Resorcinol 5% aq.
Salicylic acid 5% alc.
Zirconium hydroxychloride 30% aq.
Moderate
Benzoyl peroxide 5% aq.
Dimethyl acetamide 100%
Dimethyl formamide 100%
Dimethyl sulphoxide 100%
Diethyl toluamide 50% alc.
Dimethyl phthalate 50% alc.
2-ethyl-1,3-hexanediol 50% alc.
Propylene glycol 100%
Propylene carbonate 100%
Propylene glycol diacetate 100%
Sodium carbonate 15% aq.
Trisodium phosphate 5% aq.
Severe
Amyldimethyl-*p*-aminobenzoic acid (Escalol 506) 5% alc.
2-ethoxyethyl-*p*-methoxy-cinnamate (Giv-Tan FR) 2% alc.
Hydrochloric acid 1.2% aq.
Lactic acid 5% aq.
Phosphoric acid 3.3% aq.
Sodium hydroxide 1.3% aq.

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Specific irritants

Substances which commonly cause irritant contact dermatitis are listed in Table 19.4. Certain, mostly 'wet', occupations, have an increased risk of irritant contact dermatitis; these are listed in Table 19.3.

Water [1]. Wet work occurs in a wide range of occupations. Water is hypotonic and acts as a cytotoxic agent on eroded skin. If the surface lipid layer has been removed previously by suitable solvents, including detergents, water may dissolve the hygroscopic substances needed to keep the skin pliable. Hard water is more irritant than soft [2]. Lime, magnesium and iron from hard water deposited in skin fissures may cause mechanical irritation. Irritation of the skin may arise from poorly controlled chlorination or bromination of swimming and spa pools [3,4].

Skin cleansers [5–8]. Soap, detergents and waterless cleansers containing organic solvents are the commonest irritants. They raise the pH and dissolve lipids. Added silica or sand tends to damage by mechanical abrasion. It is difficult to evaluate the role of soap in the causation of cumulative insult dermatitis and difficult to prove that it is, in fact, a perpetuating factor. In many occupations, for example the metal industries, the procedures used for hand cleansing may be more harmful to the skin than the work itself. Aromatics in the solvents in 'waterless cleansers' are particularly hazardous [9].

Detergents, surface-active agents, sulphonated oils, wetting agents, emulsifiers [6,10–12]. These are used for domestic and industrial cleaning, skin cleansing, and as wetting and emulsifying agents in many industries. Washing powders contain detergents, perborates, phosphates, optical bleaches and perfume. Some also have added soap and, to prevent precipitation of calcium soap, chelating agents. The irritant effect is different, being dependent on the chemistry of the detergent [13]. Most are alkaline, but even at neutral pH they remove the surface lipid film and the water-holding substances in the horny layer as well as the vital lipids from the semipermeable membrane of stratum corneum [14]. They denature protein and damage the cell membranes. Oxidation has been shown to increase the irritant potential of some surfactants [15]. Enzymes used in detergents may [16] or may not [17] act as irritants.

Preservatives. Most quaternary ammonium compounds have an irritant effect, particularly in superficial cracks in dry skin. Other preservatives, as well as being potentially allergenic, can be irritant [18].

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Alkalis. Alkaline solutions saponify the surface lipids and dissolve water-holding substances, break the cross-linkages of keratin and cause swelling of cells. Soap, soda, ammonia, potassium and sodium hydroxides, cement, chalk, sodium silicate, trisodium phosphate and amines (e.g. in epoxy hardeners or as an antistatic agent [1]) are the commonest irritants.

It should be noted that soda ash (anhydrous sodium carbonate) is three times stronger than washing soda. Stearyl amine is used as an emulsifier in mixtures of oil and gravel. Alkalis are used in many industries (dyeing, tanning, rubber, plastic, glass, etc.). Copying papers based on the diazo process are developed by ammonia gas, which sometimes causes irritant dermatitis of the face.

Acids. Acids are widely used in industry, for example chromic acid for rust-proofing iron and hydrofluoric acid [2] for glass etching, rust stain removal [3], and in the electronics [4] and petroleum industries. Sulphuric, hydrochloric and nitric acids are other common inorganic acids. Hydrochloric acid is used by masons for the cleaning of building stones, but sometimes also for cleaning their hands. Acetic [5] and oxalic acids are the most often used organic acids. Acid anhydrides such as phthalic anhydride

are stronger irritants than the corresponding acids. Weaker acids may be used as preservatives and have caused dermatitis due to their presence in animal feed [6].

Oils. The major offenders are metalworking fluids [7], which may be neat oils, oil-in-water emulsions ('soluble oils'), semisynthetic or synthetic, in roughly increasing order of irritancy [8]. The less viscous a neat oil, the more irritant it tends to be, although chlorination or sulphonation may make viscous oils more irritant. Oil acne/folliculitis is a localized form of irritancy (Chapter 21). In water-based metalworking fluids, the principal irritant is the emulsifier or wetting agent, although other factors, still poorly understood, may increase irritancy [9,10].

Organic solvents [11–13]. These include aliphatic petroleum solvents such as white spirit. Commonly, they contain 18–20% of aromatics [14]. Prime-grade kerosene contains about 2% of aromatics and is less irritant. The much more irritating diesel oil and fuel oil are used, for example, as solvents for oil in casting moulds [15].

Other organic solvents include the following: aromatic hydrocarbons such as benzene, toluene and aromatic petroleum solvents; chlorinated hydrocarbons such as trichloroethylene, perchloroethylene, methylene chloride and chlorobenzene; alcohols such as methanol, ethanol, isopropanol and propylene glycol; esters such as ethyl acetate; ketones such as acetone and methyl-ethylketone; ether alcohols such as ethylene glycol monomethylether; nitroparaffins such as nitroethane; turpentine; carbon disulphide.

Thinner is commonly a mixture of alcohols, ketones and esters, but sometimes also toluene, turpentine and dipentene (limonene). These are used in many industrial processes, including cleaning textiles and metals, the graphics industries, floor laying (where glue is used), wood-finishing, dyeing, painting, etc. They also act as solvents for many technical products, for example polishes and disinfectants. Sometimes, they are used as hand cleansers in dirty work, as in the rubber, plastics and metal industries. They remove the lipid film and water-holding substances, and damage cell membranes. Their irritating capacity depends on their chemical structure, and commonly the following range is valid:

aromatic > aliphatic > chlorinated > turpentine > alcohols > esters > ketones.

Oxidizing agents. Organic peroxides such as benzoyl peroxide and cyclohexanone peroxide are used in hardening polyester resins. Some are used in hair bleaching and some for bleaching textiles, oils and flour. They are strong cytotoxic agents and may cause unusual urticarial reactions [16].

Benzoyl peroxide and ammonium persulphate may be present in flour, and the cytotoxicity of persulphates may also cause irritation during their manufacture [17]. Sodium hypochlorite (bleach) is used, as well as for cleaning, by printers and dyers to remove staining from their hands. Its cytotoxicity makes its medical use in Dakin's solution (Eusol) unsuitable for clean wounds and ulcers [18].

Ethylene oxide is used as a sterilizing agent and may remain on instruments or rubber articles [19].

Reducing agents. Phenols [20], hydrazines, aldehydes [21], sulphureted hydrogen and thioglycolates are common in industry. Penta-, tetra- and trichlorophenols are used as wood preservatives [22]; thioglycolates for cold waving (Chapter 21). Thioglycolates break cross-linkages, including the strong disulphide bonds in keratin, in an alkaline environment. Keratin fibrils take up water, and percutaneous absorption is thereby increased.

Other organic and inorganic substances. Some other substances may also act as strong cytotoxic agents. Examples are as follows: formaldehyde, industrial processing of polyethylene with formation of acrolein [23], crotonaldehyde, thiomersal [24], allyl alcohol, cresol in pesticides (dog collars prepared with a flea repellant have caused irritant dermatitis) and halogenated acetophenones; alkyl bromides and chlorides in paint removers or fumigation [25]; bromine and chlorine derivatives in chemical synthesis; styrene; organic silicones can cause blepharitis; acrylic monomer, diallylglycol carbonate monomer [26] and epichlorohydrin in plastic processes; arsenic in wine culture [27]. Metal polishes, fertilizers and rust-preventive products often contain irritant agents [28]. Alkyl tin compounds are used as preservatives [29], and as antifoulants in marine paints [30]. Mercuric salts, cobalt, zinc chloride [31], etc., have an irritant effect.

Unsaturated aliphatic chains give compounds a more irritating effect—for example, allyl alcohol, diallylphthalate (in polyester resins), cinnamaldehyde compared with hydrocinnamaldehyde (in perfumes) and acrolein [23].

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Plants and woods [1–4]. Citrus peel, flower bulbs, garlic, flour, wood dust, spices, corn [5], onion, pineapple, pelargonium, iris, stinking mayweed, buttercup, daffodil [6] and the mustard family can act as irritants, and some can cause bullous reactions even without ultraviolet irradiation (Table 19.7). Spines can cause mechanical damage [7,8]. Thus, barley awns are sharp and may cause papular eruptions and severe pruritus all over the body.

Animal products. Vesicular or papular dermatitis may be caused by caterpillars [9], carpet beetles and moths.

Wet work with fish [10], shrimps, meat and herring in canning industries or restaurants may cause an irritant effect [11,12]. Herring brine contains trimethylamine. Separating the pancreas from the intestines involves contact with enzymes which can give rise to loosening of the nails in butchers. Irritation also arises from proteolytic enzymes in pineapple and papaya [13] and in baking [14].

Table 19.7 Irritating plants.

Ranunculaceae
Ranunculus (many species of buttercup)
Anemone
Clematis
Helleborus
Araceae
Dieffenbachia (ornamental plant in tropics and house plant in Europe)
Euphorbiaceae (spurge; the milky latex of many species is intensely irritating)
Hippomane manchinella (the manzanillo tree of the Caribbean contains a powerful irritant)
Cruciferae
Brassica nigra and other 'mustards'
Compositae
Achillea (milfoil and related species)
Anthemis (mayweeds)
Matricaria

Topical medicaments [15]. Tar, dithranol, potassium permanganate, gentian violet, mercury, hexachlorophane, etc. can, in susceptible persons, even in low concentrations, cause overtreatment dermatitis, which also occurs after prolonged use of wet dressings, particularly under occlusive bandaging. Occlusive transdermal drug delivery systems can also cause irritation [16].

Physical and mechanical factors. These include the following: heat, steam, cold, high or low humidity [17], electricity, sunlight, UV light and other rays; friction, pressure, trauma, rubbing, scratching and scrubbing; metal particles, metal dust, adhesive plaster, fibreglass and rockwool [18–20], textile particles, jute, wood dust, sand, asbestos, silica, cement [21], plaster, hot-metal particles from welding, and glass spicules [22].

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Investigations

Irritant contact dermatitis is essentially a clinical diagnosis based on knowledge of the nature and conditions of an individual's exposure in the context of their dermatitis. A complicating allergic contact dermatitis always needs to be excluded by patch testing but patch tests do not aid in the diagnosis. Investigations are most frequently used in the context of scientific studies but may also predict an individual's susceptibility. None can be reliably used clinically on a large scale.

Quantifying the irritant response

Although visual appraisal of skin erythema and surface changes is still widely used to assess irritant reactions, a number of non-invasive techniques have been developed in recent years which permit objective evaluation of key changes to the skin. The optimal method to be used varies with the nature of the irritant [1].

Erythema. Among the most overt clinical features of irritant reactions is erythema, which may be quantified using a number of different approaches. Laser Doppler flowmetry (LDF) provides a measure of superficial blood flow by transmitting monochromatic light from a helium–neon laser through optical fibres to the skin surface. The light is Doppler-shifted by moving blood cells in the upper dermis, remaining unchanged in the surrounding stationary tissue. By means of a differential signal detector and signal processing arrangement, the back-scattered or reflected light is interpreted. The final output, which is linearly related to the product of the number of blood cells and their average velocity in the measured volume, is expressed in relative and dimensionless units. Studies by a number of investigators have shown that LDF generally correlates well with visually assessed erythema, and is capable of discriminating between negative and weakly positive irritant reactions [2,3].

Alternative methods for objectively quantifying erythema rely upon the generalized increase in red blood cells resulting from both increased blood flow and blood vessel dilatation. Those which are based upon remittance spectroscopy emit red and green light from a tungsten halogen lamp or LED source. Oxyhaemoglobin in the blood vessels absorbs a proportion of the green light, and largely reflects the red light. Changes in the quantity of oxyhaemoglobin significantly alter the amount of green light absorbed, but have very little influence on the red light. An erythema index can therefore be calculated from the ratio between the reflected green and red light, such that the greater the erythema, the higher the value of the erythema index [4].

Erythema may also be quantified using tristimulus colorimeters, virtually all of which employ a system for colour definition known as the Commission Internationale de l'Eclairage (CIE) L*a*b* colour system. This provides a three-dimensional coordinate system where L* represents an axis for brightness, a* represents a green–red axis and b* represents a yellow–blue axis [5,6].

Transepidermal water loss. In addition to inducing erythema, irritants commonly affect barrier function, leading to alterations in TEWL. Measuring instruments employ open chambers, through which, when applied to the surface of the skin, water vapour evaporates, creating a water-pressure gradient from which the evaporative TEWL, expressed in $g/m^2/h$, is calculated [7]. Many variables influence TEWL measurements. Some relate to the environment and to instrument operation, necessitating a careful adherence to 'good laboratory practice', as outlined in a report from the Standardization Group of the European Society of Contact Dermatitis [8]. Others relate directly to the individual; age and anatomical site are among the most important variables. Measurements of TEWL have proved valuable in predicting susceptibility to skin irritation, assessing the protective effects of barrier creams, and evaluating the irritancy potential of different chemicals [9–12].

Hydration. Changes in the hydration state of the skin also commonly occur in irritant contact dermatitis, and, again, this parameter may be objectively measured. Several different devices are available, based on differing biophysical approaches. Using the principle of capacitance,

hydration of the stratum corneum can be measured to a depth of approximately 0.1 mm. In contrast, skin conductance has also been used as a measure of hydration. Studies suggest that capacitance may be more effective in the assessment of dry skin, whereas conductance is better suited for studies of water accumulation in the stratum corneum [13]. A third method uses the principle of impedance-based capacitance to assess hydration levels.

Skin thickness. Although not extensively applied, high-frequency ultrasound has also proved valuable for the assessment of another aspect of the irritant response, namely changes in skin thickness [14].

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Management

Chemical burns

Initial treatment of chemical burns [1] requires irrigation with large volumes of lukewarm water. Where the chemical is insoluble in water a soap solution may be used instead. High pressures should not be used, to avoid splashing other areas of the body or bystanders with the corrosive material. Whilst neutralizing solutions could represent an alternative treatment, an exothermic reaction might result in increased tissue damage and potential delay in treatment, and they are not generally recommended [2].

Nevertheless, for some chemicals specific antidotes can be used subsequently, e.g. 2.5% calcium gluconate gel for hydrofluoric acid. Application should be repeated 4-hourly and disappearance of pain is a sign of successful treatment [3]. If the pain fails to resolve infiltration or regional infusion have been used [4].

When there is a risk of toxicity from systemic absorption, as with chromic acid [5], early debridement of necrotic areas reduces blood levels, and consideration should be given to the use of dialysis to remove circulating chromium. Ulcerated areas should be managed with antibacterial creams to prevent secondary infection whilst re-epithelialization occurs. If there is a surrounding inflammatory reaction a moderately potent topical corticosteroid can be applied. Vapour permeable dressings are recommended in view of the role of TEWL in stimulating barrier repair [6].

Frequent review is required because the ulcers can progress over several days. Subsequent management with excision/debridement and/or grafting may speed the healing process. Where the ulcer extends into the dermis healing frequently results in a scar and pigmentary change is common. Several chemicals (e.g. hydrofluoric acid, phenolic compounds, chromic acid, gasoline) carry a significant risk of systemic toxicity even when cutaneous involvement is small (~1%). In these instances, regular monitoring of blood, liver and kidney function, with appropriate supportive treatment, is required [7].

When the chemical is a sensitizer, allergic contact dermatitis may subsequently occur on re-exposure to non-irritant concentrations, as burns and irritant dermatitis appear to promote sensitization [8–10].

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Irritant contact dermatitis

The successful management [1] of irritant contact dermatitis requires both prevention and subsequently treatment if dermatitis develops.

The most important aspect of treatment is avoidance of the cause (Table 19.8). In an occupational setting, automation of the production process may avoid exposure but can be expensive. A cost-effective compromise is the use of personal protective equipment and/or substitution of a chemical. It should be remembered that natural rubber latex gloves provide protection against water miscible substances but may be inappropriate for other exposures (Table 19.9). With organic solvents and chemicals the choice of glove material may vary [2]; advice may be found on the material safety data sheet.

Once present, dermatitis requires palliation of symptoms with topical steroids and emollients. The efficacy of topical corticosteroids in irritant contact dermatitis has been questioned [3,4] although another study has shown

Table 19.8 Advice to patients with hand eczema.

To speed healing and prevent your dermatitis from returning, you must now take great care of your hands and allow your skin to heal and recover its natural resilience/strength (this may take many months, even though the skin may look normal before then)

1 Use a hand cream many times a day so that the skin does not become dry
2 Use the steroid creams/ointments prescribed by the doctor
3 Washing hands. Use lukewarm water and soap substitute (e.g. aqueous cream). If soap is used, find a soap with no fragrance, tar or sulphur, use it sparingly, rinse thoroughly and then dry thoroughly (especially finger webs and wrists)
4 Avoid contact with detergents and other cleaning agents. Always dilute them according to manufacturers' instructions. Keep outside of container clean or you will contaminate your hands with the neat product
5 If gloves are worn, use plastic rather than rubber, preferably with a cotton lining
6 When washing up, use running water and a pot brush rather than a cloth
7 Washing machines and dishwashers are a great help, but avoid contact with detergent powder or liquid—use a measure with a handle
8 Avoid contact with shampoo. Either use plastic gloves or get someone else to wash your own and your children's hair
9 Do not apply hair products with bare hands, e.g. setting mousse/gel/lotions, colourants, creams, brilliantine. Some of these are irritant, but the friction of running hands through hair is considerable
10 Do not peel citrus fruits with bare hands, e.g. oranges, lemons, satsumas
11 Avoid contact with polish, e.g. metal, shoe, floor, car, furniture, window and wax polishes. NB: Spray polish carries a long way
12 Avoid contact with solvents, e.g. white spirit and brush cleaners, petrol, trichlorethylene, xylene, carbon tetrachloride, e.g. dry cleaning and stain-removal agents. Solvents pass through rubber gloves. Buy vinyl for these jobs
13 Wear gloves in cold weather
14 Water softeners are helpful, but too expensive unless you are not contemplating moving house for a long time. Try adding water softener, e.g. Calgon, to dish water, washing water, baths, etc.; less soap/detergent is then required
15 Individuals with hand eczema are at increased risk of contracting infection through damaged skin and should wear gloves when in contact with blood or potentially infectious biological secretions, e.g. when handling soiled linen, cleaning lavatories, etc.
16 If the skin becomes inflamed and throbs, it is likely to be infected. Visit your doctor, who may take a skin swab and prescribe antibiotic treatment
17 Patients with hand eczema should not be involved in commercial food preparation because the bacteria that cause infection may also cause food poisoning

Your hand eczema should improve if you follow all these suggestions. Once the skin appears to have healed, you should always continue to take care of your hands

Table 19.9 Recommended glove materials for chemical protection. (From Berardinelli [2].)

Glove materials	Nitrile	Butyl	Neoprene	Fluorocarbon	PVC	PVA	Notes
Aliphatic hydrocarbons	+			+		+*	Except cyclohexane*
Aromatic hydrocarbons	+			+		+*	Except ethylbenzene*
Halogenated hydrocarbons			+		+*		Except methyl chloride* & halothane*
Aldehydes, amines, amides	+*						Except butylamine* & triethylamine*
Esters			+*			+†	Except butylacrylate* & octylphthalate†
Alkalis		+		+		+	
Organic acids	+*	+	+†				Except acrylic*†, methacrylic*† & acetic* acids
Inorganic acids	+*		+†		+‡		Except chromic†, hydrofluoric*, nitric*‡ & sulphuric*‡ acids

PVA, polyvinyl alcohol; PVC, polyvinyl chloride.

benefit [5]. Retinoids and vitamin D analogues are not of any value [3].

Experimentally, an emollient alone has been shown to improve barrier repair [6,7]. The choice of emollient may be important. Studies have shown that barrier repair may be impaired or accelerated according to the constituents of a physiological lipid mixture [8]. It has been suggested that conditions in which the lamellar body secretory system is impaired or immature (radiation dermatitis, sunburn, irritant dermatitis due to some surfactants and retinoids, and premature infants of less than 33 weeks' gestation) should be treated with non-physiological lipids, e.g. petrolatum. Whereas most other causes of irritant dermatitis, where lipid metabolism has not been deranged (e.g. diaper dermatitis), should be treated with a mixture of cholesterol : ceramides : free fatty acids, in a 3 : 1 : 1 ratio, to achieve most rapid return to normal barrier function [9].

In severe cases, phototherapy or systemic drugs such as azathioprine and ciclosporin (cyclosporin) may be required. Where there is secondary infection, topical or systemic antimicrobial agents may be necessary.

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Non-immune contact urticaria

The mechanism of action of non-immunological contact reactions is not known, but is presumed to be via direct release of inflammatory mediators, including prostaglandins and leukotrienes [1]; the reaction is blocked by non-steroidal anti-inflammatory drugs and ultraviolet light, or by pretreatment with capsaicin, but not by antihistamines [2–4].

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Symptomatic irritant responses

Treatment is largely that of avoidance, although strontium salts have been shown to inhibit the sensation [1]. Currently this seems of little practical value.

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Prevention

Identification of the susceptible individual and appropriate career advice prior to employment may reduce an individual's risk of developing dermatitis. Skin irritation thresholds to SLS have been shown to correlate with the subsequent development of dermatitis in hairdressers [1]. Education of an individual or workforce is a prerequisite [2]. Whilst preventative measures may be available, individuals may not make use of them if they do not understand the rationale for so doing.

Mechanization

In general, increased use of mechanization for wet or irritant work, thus avoiding exposure, will help to reduce the incidence of irritant contact dermatitis.

Personal protective equipment

Prolonged use of gloves may increase TEWL [3,4], but in general their protective effects outweigh any potential to induce dermatitis. In a study of hairdressers, unprotected wet work for greater than 2 h per day was the most significant risk factor for the development of dermatitis [5].

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Topical preparations

Barrier creams are designed to reduce the penetration of hazardous materials into the skin. Some are specifically formulated for individual chemical exposure. It is said that water-in-oil emulsions protect against aqueous irritants and oil-in-water against lipophilic materials [1]. At best they have only a marginal effect [2,3], and inappropriate use may exacerbate dermatitis. Most claim to give 4 h protection, although others suggest applying 'as necessary'. They are, in general, more effective as a means of preventing excessive soiling of the hands, and therefore may help to avoid the need for strong cleaners which are often more damaging than agents causing the soiling. They may be effective against airborne irritants on the face [4]. The use of barrier creams should not be over promoted as this may engender a false sense of security rather than a reliance on more effective measures. If they are used, instruction in their application is essential if areas of skin are not to be missed [5].

Emollients or hand creams will help to prevent dryness or chapping of the skin, and may also help to prevent subsequent development of dermatitis [6–8]. They are promoted as after-work creams, and controlled trials have shown their effectiveness [9]. Conversely, prolonged use of emollient has been shown to increase susceptibility to irritant dermatitis [10] in an experimental setting. The relative risk/benefit may therefore depend on the circumstances of use.

Soaps and skin cleansers should have a reduced potential to cause irritation, and soap substitutes have been shown to be effective in preventing dermatitis [11].

Other practices associated with hand washing should also be critically evaluated. In medicine, the habit of using a brush when scrubbing for a surgical procedure has been shown to increase TEWL without any additional benefit in reducing bacterial contamination [12].

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Prognosis

Following experimental induction of contact dermatitis with 1% SLS, the response to further irritant exposure on previously irritated skin returned to normal after 4 weeks [1]. As the duration of the initial stimulus extends, recovery time is prolonged with the skin remaining abnormal 10 weeks following a 3-week induction [2].

Clinically, assessment of the prognosis of irritant contact dermatitis is mostly based on occupational studies in which exposure to irritants has been prolonged. In one study, only one-third had complete remission of their dermatitis [3]. Atopic individuals are known to have a worse prognosis [4,5]. A change of job may be helpful if undertaken early, but is of less benefit in those with established and chronic dermatitis [6]. Some individuals simply exchange one inappropriate job for another [7]. Delay in diagnosis and assessment worsens prognosis.

Although too frequent or too extreme exposure to irritants will normally lead to dermatitis [8], some workers exposed to irritants seem to develop hardening. Experimentally, following repetitive irritation with SLS for 3 weeks the skin returned to normal reactivity after 3 weeks, but subsequently became hyporesponsive up to 9 weeks following the initial insult [9].

The use of inappropriate cleansers [10] and lack of knowledge as to the cause of their dermatitis [11] will also affect a patient's overall prognosis and outcome.

Persistent postirritant dermatitis

Some hand eczemas which start as irritant or allergic contact dermatitis subsequently persist when the original cause has been eliminated. Whether, in these individuals,

there is some inherent constitutional factor which leads to persistence, or whether some eczemas simply become self-perpetuating, remains unclear. In the occupational setting this has been labelled 'persistent postoccupational dermatitis' [7], and affected 11% of individuals in the absence of any other contributory factor or known constitutional tendency. It seems probable that a similar situation would appertain following non-occupational exposures.

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Chapter 20

Contact Dermatitis: Allergic

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History [1]

The term 'allergie' was first coined by the scientist von Pirquet in 1906 [2]. The word was derived from the Greek *allos* and *ergon*, meaning other or different work [3]. However, idiosyncratic reactions to various substances had been recognized since the 17th century [2]. In 1829, Dakin observed the selectivity of *Rhus* dermatitis [4] and Fuchs suggested that 'dermatitis venenata' was an expression of constitutional idiosyncrasy in 1840 [5]. The word 'idiosyncrasy' was again applied by Neisser in his descriptions of iodoform dermatitis in 1884 [6].

Allergic sensitization of the skin was first proved experimentally by Bloch and Steiner-Woerlich using *Primula* extract on humans [7]. Thereafter research on the pathogenesis of allergic dermatitis has largely involved animal experiments using guinea pigs. Landsteiner and Jacobs [8] performed the basic experiment, which showed that a simple chemical capable of causing contact dermatitis must be combined with proteins in order to sensitize. Up to 1940 it was not known whether sensitization depended on a factor localized in the skin, but in 1942 Landsteiner and Chase [9] succeeded in transmitting sensitivity from one guinea pig to another by the use of a mainly mononuclear peritoneal exudate from sensitized guinea pigs. In the same year, Haxthausen's transplantation experiments [10] finally proved that allergy was due to a factor supplied to the skin from within.

Patch testing is the diagnostic tool for allergic dermatitis and it is Josef Jadassohn who is generally accepted as the founder of this technique in 1895 while working at Breslau University, publication taking place the following year [11]. Nevertheless, anecdotal observations of a similar nature had been made prior to this, usually by applying the suspected causative agent to intact skin [12]. By 1847 Stadeler had developed a rudimentary patch test using blotting paper to reproduce lesions provoked by *Anacardium occidentale* [13].

Bruno Bloch was a dermatological pioneer who was able to expand and enhance Jadassohn's technique while working in Basel in 1911, when he also produced a grading system for patch-test reactions [14]. He then moved to Zurich where he introduced the concept of a standard series of allergens [15]. He furthermore conceived important ideas about both cross-sensitization and systemic allergic contact dermatitis [1]. Marion Sulzberger had been an assistant to both Bloch and Jadassohn before returning to New York where he introduced the patch-test technique and was a strong advocate and promoter of its use in the New World. Another former assistant of Bloch's, Paul Bonnevie, Professor of Occupational Medicine in Copenhagen, expanded the standard series to what could be considered the prototype of our present-day series.

By the early 1960s, Scandinavian dermatologists were developing a standardized protocol for patch testing and their group was expanded to involve, initially, other European members before it finally evolved into the International Contact Dermatitis Research Group (ICDRG) [1]. Further national and international research groups have proliferated in the last 20 years, a fitting recognition of the significance of the findings and researches of these earlier pioneers.

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Epidemiology [1–3]

Prevalence and incidence (definition). Definition of these terms is important as they mean two different things. Prevalence relates to the number or proportion of individuals who are identified with the condition being studied (e.g. contact dermatitis, nickel allergy) at a given point in time, or over a certain period of time. Incidence relates to the number of new cases developing over a defined period of time and is expressed as number of cases per unit of time.

Methodologies

Epidemiological studies may be undertaken on the general population or on selected groups, for example those referred for patch testing or those with a specific occupation. Studies on the general population need to be large to gain useful information and are challenging to perform. For reasons of expediency, questionnaires have been used but when performed alone underestimate considerably those suffering from dermatitis [4,5]. Population assessments made on individuals attending a general practitioner or referred to a dermatologist may be unreliable, particularly in the UK where prompt access to a dermatologist is achieved only by the fortunate few. In a UK survey, only 21% of those with skin disease thought to justify medical care had seen their general practitioner about it in the previous 6 months [6]. In another large-scale study of a Swedish population of over 107 000, only 50% of the patients with dermatitis had seen a doctor within the previous year [4].

The reporting of contact dermatitis also varies according to the method of collection and the type of person collecting the data. Results from the UK EPIDERM occupational dermatoses surveillance study show how reports of occupational dermatoses differ according to whether the returns are made by dermatologists or by occupational health physicians [7] (Table 20.1). The differences probably reflect the different types of occupational population accessed by the two groups. Occupational physicians will relate to large industries and collective working groups, whereas dermatologists will mainly receive individual referrals, accounting for the comparatively high representation of, for example, hairdressers, florists and beauticians seen by them [7].

Table 20.1 Occupational skin disease: estimated rate per 100 000 workers reported to EPIDERM (Occupational Dermatoses Surveillance Scheme, University of Manchester) [7].

Dermatologists	
Hairdressers and barbers	116.3
Printers	85.8
Beauticians	76.8
Other chemical operatives	69.1
Window dressers, floral arrangers	68.1
Occupational physicians	
Other chemical operatives	183.8
Glass product and ceramic makers	101.2
Vehicle and metal assemblers	94.8
Engineering labourers	82.4
Machine tool operatives	67.9

Case definition

Dermatitis is commonly multifactorial. It is therefore difficult to analyse the relative prevalence of irritant versus allergic contact dermatitis as the two commonly coexist, and constitutional eczema may also be involved. Ideally, all those studied should be examined and those with dermatitis patch tested, but this is not always a practical proposition when large numbers of an unselected group are being assessed.

Apparent differences in overall sensitization frequencies may be due to differences in population structure, especially in relation to age and sex. This can be compensated for either by using standardized populations or by reporting results within specified age bands, and by reporting results for each sex separately [8].

However, in a particular clinic the incidence of allergic contact dermatitis is reflected not only by the sex and age of the patients but also by the industrial development in the area and the degree of interest dermatologists take in the various facets of contact dermatitis (e.g. occupational dermatitis, medicament allergy or leg ulcers). Furthermore, local prescribing habits can influence patch-test results [9]. It has been suggested that all comparative patch-test data should include an analysis of patient details, the MOAHL index [9,10], where M is percentage of males tested, O is percentage occupational, A is percentage of atopics, H is percentage of patients with hand eczema, and L is percentage of patients with leg ulcers or stasis eczema. The percentage of atopics is important, particularly in relation to irritant contact dermatitis [11]. Certain body sites, especially the lower legs in those with stasis eczema or leg ulcers [9] and the ears [12], eyelids [13] and perineum [14], have a particularly high level of allergic contact dermatitis from medicaments. Inclusion of a significant number of any such cases in a patch-test series will affect the overall sensitivity rates for various allergens [9]. Further enhancement to the index has been suggested by including the proportion of those with facial dermatitis and also those above the age of 40. The MOAHLFA index has been suggested (where F is face and A is age) [15].

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Prevalence [1]

General population studies

Contact dermatitis accounts for 4–7% of all dermatological consultations [2,3]. Skin disease, chiefly dermatitis [4,5], accounts for almost half of all reported cases of occupational disease [5,6]. Over 20% of females will suffer from hand eczema at some stage in their lives [7]. In one population study in southern Sweden, hand eczema was shown to affect 11.8% of the population aged 20–65 years over a 12-month period [8]. A recent follow-up study indicates that this frequency has dropped to 9.8% despite a rise in the level of childhood eczema [9].

A number of other studies on the prevalence of contact dermatitis in the unselected general population have been undertaken but those that include clinical assessments and patch tests are rare, making it more difficult to ascertain the prevalence of allergic contact dermatitis. Hellgren [10] studied the prevalence of skin diseases in certain Swedish counties and found that 4.8% of the population

were suffering from contact dermatitis diagnosed clinically at the time of examination. Similar figures have been obtained by Johnson *et al*. [11]. In another part of Sweden, the minimum prevalence of hand eczema was estimated by Agrup [12] who sent questionnaires to all persons aged over 10 years in a population of over 107 000; this was supplemented by examination, including patch tests, of those giving a positive reply. The prevalence was 1.7%, with one-third of these having a diagnosis of allergic contact dermatitis. In general, irritant dermatitis was more common than allergic contact dermatitis, but the latter had a worse prognosis. Clinical examination of a random sample of people living in the Netherlands found the prevalence of hand dermatitis to be 5.2% in men and 10.6% in women [13]. Among 1200 women seen during a compulsory health examination in a small Norwegian town, 13.2% of the housewives had some degree of dermatitis of the hands [14]. A questionnaire sent to more than 2500 women in Denmark revealed that over 20% had at some stage suffered from hand dermatitis [7]. Further studies in that country on an unselected population found that 15.2% of those sampled were allergic to a panel of 23 selected allergens [15]. Sensitivity to nickel was present in 6.7% of the population (11.1% women, 2.5% men). In Germany a similar study revealed higher figures, with frequency estimates of allergic sensitization being 28.0% for the overall population, including 11.4% for fragrance mix, 9.9% for nickel and 3.2% for thimerosal [16].

Selected population studies

Most other epidemiological studies have been based on patients already attending dermatology clinics, or have involved either specific occupational [17–19] or other population groups.

The selective nature of patients patch tested in dermatological clinics for investigation of contact allergy is not necessarily representative of the general population; nevertheless, the findings may reflect the relative frequency of the causes of allergic contact dermatitis in that population. Patch testing can be used to generate information on individuals, groups of patients and allergens, and also to assess risk factors in groups of workers [20] and particular subgroups of the population [21].

Dermatology patients

Among 43 000 Danish patients examined by patch tests during a period of 20 years, the percentage of patients with positive reactions to one or several of 23 standard test substances remained largely constant throughout [22]. Some allergens became rare, but this was balanced by an increase in other sensitizers. The prevalence of allergy to specific allergens in patch-tested patients is discussed later in the chapter. Only a few studies have explored the relationship between sensitization and the presence of dermatitis [7,23–26]. Variations in the reading or interpretation of patch-test results will affect the perceived prevalence of contact dermatitis [27].

In general, the commoner allergens are similar from one country to another, although there are differences in rank order [28–32]. The commonest allergens appear to be similar in Europe, the USA and Asia. Some environmental allergens are widely dispersed and the level of sensitivity remains fairly constant, but cosmetics and fragrance materials are becoming increasingly important sources of sensitivity [18–20]. Medicament allergens, such as benzocaine, neomycin and lanolin, are common in all countries [33–35]. However, there may be differences in prescribing habits even within the same country, which can be reflected by the pattern of medicament sensitization. Corticosteroid allergy has been shown to have a very different profile in Oxford compared with Manchester by virtue of differences in prescribing habits leading to greater usage of non-fluorinated corticosteroids in the latter catchment [36]. A similar discrepancy in corticosteroid allergy frequencies has been noted between Belgium and the Netherlands [37].

Young females tend to have more cosmetic and occupational sensitivities; in older people, many sensitivities will be of past relevance only, and there will be a higher prevalence of medicament sensitivity. Nickel sensitivity is common in women and, unless allowance is made for this, false occupational associations may be inferred. Allergens can come and go [38] and the prevalence of a sensitivity to an individual substance will depend on many variables, including the selection of individuals to be tested [39], exposure levels, fashion, environment, introduction of new materials and loss of others, maximum permitted concentrations and usage.

The incidence and prevalence of allergic reactions will therefore parallel the extent of such exposure, and occasionally this may lead to localized 'epidemics' of sensitivity to a particular allergen. One product, 'Eau de Javel', affected the whole pattern of sensitivity to chromate in France [40]. Photoallergy to chlorinated salicylanilides used in antibacterial soaps in the UK occurred as an epidemic in the 1960s [41], as did allergy to the preservative methylchloroisothiazolinone/methylisothiazolinone in cosmetics and medicated wipes in the Netherlands in the 1980s [42]. Cosmetic and preservative exposure varies from country to country and from region to region, according to the degree of usage [42]. This principle may extend to other allergenic sources, so there is a rationale for each centre and country developing its own epidemiological base.

Patterns also change with fashion, as shown by the virtual disappearance of suspender dermatitis from nickel, to be replaced by an increase in dermatitis from earrings, watches and jeans studs [43,44]. The sensitizers found

vary with the patients' social backgrounds, and they may change over the years.

Differences in environmental exposure influence the nature of sensitizers; for instance *Toxicodendron* spp. dermatitis is extremely common in the USA but virtually absent in Europe, whereas *Primula* dermatitis is well recognized in the UK but practically nonexistent in many other countries [45,46]. The introduction of new potential sensitizers will increase the incidence of contact dermatitis due to them in the exposed population; at the same time, allergens that were previously common may disappear. The sudden appearance of *Parthenium* dermatitis in some parts of India from a contaminated shipment of American wheat [47,48] serves as an example of the former, and the decline in sensitivity to turpentine [49] is an example of the latter.

Technological advances have led to new and more widespread exposures to allergens such as epoxy and acrylic resins in the occupational setting [50], although the potential for contact allergy may be reduced by improved personal protective equipment, better containment of sensitizing chemicals and allergen substitution. Similarly, in the domestic environment, phosphorus sesquisulphide allergy in the UK is disappearing because production of 'strike-anywhere' matches has diminished in this country.

Occupational studies

The incidence of occupational dermatitis in most western European countries is in the range of 0.5–1.9 cases per 1000 workers per year [51]; skin diseases account for 13–34% of all occupational diseases [6]. Risk factors are proportional to both constitutional susceptibility (atopy) and exposure [1]. Skin disease (contact dermatitis) is a significant occupational problem, accounting for 46–60% of days lost at work [6,11], with atopics [52–54] and those with nickel or chromate sensitivity [55] having a particularly poor prognosis.

Occupational disease surveillance and compensation registries identify occupations at high risk of dermatitis (see Table 20.1). Most are unable to distinguish between irritant and allergic dermatitis. Some countries have mandatory reporting. In the UK, EPIDERM is a scheme accepting reports made on a voluntary basis from dermatologists and occupational physicians [56]; in a recent study covering the years 1993–99, 52% of dermatitis cases reported by dermatologists and 30% of those reported by occupational physicians had allergic contact dermatitis as the primary cause or as a contributory factor [50]. The higher rate reported by dermatologists might be a reflection of their more frequent use of patch testing. The commonest allergens were rubber chemicals (including those in gloves), nickel and resins. The numbers and proportions of cases of contact dermatitis within occupations remained fairly constant over the 6-year reporting period, although nursing personnel showed an increase, perhaps as a result of increased exposure to agents required to reduce infectious disease transmission [50]. In northern Bavaria there is a mandatory reporting and follow-up investigation scheme [57]. In a recent survey of occupations at higher risk of dermatitis, positive patch tests of occupational and clinical relevance occurred in 52% of those with occupational skin disease, including 73% of construction workers, 72% of hairdressers and barbers, but only 20% of food industry workers [57].

Other occupational groups have a high prevalence of dermatitis [20,23,58]. Among bricklayers in Bergen [59] and building workers in Stockholm [60], 8% had dermatitis; among furniture-makers in Bergen, 12% had teak dermatitis [61]. The incidence, or number of new cases at a specified moment or during a period of time, is particularly high among apprentice hairdressers and nurses [62] compared with the normal population [63].

The pattern of employment has a significant effect on the incidence of skin disease [23], but most common allergens are widely dispersed and, except within small occupational groups, the pattern of sensitivity in a population mainly reflects environmental rather than occupational allergens [39]. Chromate, however, remains a predominantly occupational allergen [28]; the incidence of sensitivity in the normal population is reported to be low [64].

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Pathogenesis

The immunology of allergic contact dermatitis is discussed in detail in Chapter 10. There are two main processes [1]: (i) sensitization (induction, or afferent limb, of sensitivity); and (ii) elicitation (or efferent limb) of contact dermatitis.

Sensitization

Allergic contact dermatitis is due to delayed-type or cell-mediated immunity [2]. The induction of sensitivity is the primary event, which has to take place before clinical expression of dermatitis can occur. The main events are described below.

Binding of allergen to skin components. An allergen penetrating the skin associates with major histocompatibility complex (MHC) class II molecules [3] either directly or via antigen–peptide binding sites in the groove of the MHC class II molecule [4] on antigen-presenting cells (APCs). These MHC class II molecules are coded on the human leukocyte antigen (HLA)-D region genes, and are present on epidermal dendritic cells and Langerhans' cells. Epicutaneously applied allergen associates with these APCs within 6 h [5]. The 'danger model' proposed by Matzinger

[6] supposes that sensitization does not occur unless other co-stimulatory factors are also present and produced as a consequence of cell 'stress'. Interleukin-1β (IL-1β), tumour necrosis factor-α (TNF-α) and granulocyte–macrophage colony-stimulating factor (GM-CSF) are all required for the activation, maturation and migration of Langerhans' cells [7]. The danger hypothesis has been adapted to contact hypersensitivity, and evidence produced to support a role for irritant dermatitis in the generation of contact hypersensitivity [8]. In the absence of these co-factors it is assumed that tolerance would develop.

Recognition of 'complete' or conjugated antigen. Sensitization is possible only if the connection to the regional lymph nodes is intact [9]. The allergen-carrying Langerhans' cells travel via the afferent lymphatics to the paracortical areas of the regional lymph nodes, where they become apposed to T lymphocytes. The binding is assisted not only by physical factors—the ruffled membrane and dendritic nature of the Langerhans' cells and the intricate structure of the paracortical areas—but also by specialist cellular adhesion molecules (CAMs). These CAMs act at different loci to encourage binding. For example, leukocyte functional antigen-1 (LFA-1) on CD4 helper cells interacts with intercellular adhesion molecule-1 (ICAM-1) on Langerhans' cells, and CD2 on T cells binds to LFA-3 in plasma membranes on most nucleated cells [10]. With recognition of the antigen, many mediators or cytokines are released by this apposition, for example IL-1 by APCs and IL-2 by T lymphocytes [11].

Proliferation and dissemination of sensitized T lymphocytes. The cytokines cause blast formation [12] in the lymph node and the proliferation of antigen-specific cytotoxic $CD8^+$ (Tc1) and also $CD4^+$ (Th1) lymphocytes [13]. The type of T-cell response generated is dependent on the pathway by which the antigen is processed: small lipid-soluble molecules such as urushiol enter the cytoplasm and are presented on MHC class I as an endogenous antigen; polar haptens are more likely to be presented on MHC class II [14] as an exogenous antigen.

The T cells disseminate via the efferent lymphatics throughout the body and interact with Langerhans' cells and residual antigen in the skin [15]. Contact hypersensitivity is mediated through a subset of T cells that express cutaneous lymphocyte-associated antigen (CLA). Localization to areas of inflammation occurs via production of the chemokine CCL27 by basal keratinocytes, which binds to dermal glycoprotein; CLA-positive lymphocytes also express CCR10, the receptor for CCL27 [16]. The cytotoxic T cells induce keratinocyte death through release of Fas ligand and perforin-mediated pathways [17].

On first exposure to a strong sensitizer such as dinitrochlorobenzene (DNCB), most subjects develop a local reaction after 5–25 days. During this period, sensitization has been accomplished, and the residues of the allergen in the skin react with the newly formed sensitized T lymphocytes. Such a response has been termed a 'late' reaction. There is evidence to suggest that allergen-specific T lymphocytes may persist at the site of original contact for some months following an initial sensitization exposure [18], and this may explain the 'retest' or 'flare-up' reactions following re-exposure.

Elicitation

If a sensitized person is re-exposed to a specific allergen in sufficient concentration, the clinical reaction subsequently develops much more quickly, usually within 24–48 h; however, depending on the degree of sensitivity, penetration and other factors, this may vary from a few hours to many days. Antigen-presenting Langerhans' cells pass to the regional lymph nodes and bind with specific T lymphocytes [19]. They may also bind with the specific T lymphocytes present in the epidermis [20,21]. Furthermore, IL-1-secreting keratinocytes may acquire Ia/HLA-DR status and also present antigen to the specific T lymphocytes [22], augmenting the cascade of cytokine, immune cell and inflammatory response. This cascade is autoregulating, possibly mediated via $CD4^+$ Th2 cells [13].

A delayed reaction time (sometimes also referred to as a 'late' reaction) describes a delayed elicitation response following antigenic challenge in persons who are already sensitized. There has been confusion over the use of this term, as it has been used to describe not only reactions that have taken more than the usual 4 days to develop but also acute primary sensitization reactions which, in normal clinical practice, often present as more sudden and florid reactions around 21 days after challenge. A delayed reaction time is found with low degrees of sensitivity (when there are very few memory T cells), following exposures to small amounts of allergen (when it takes longer to augment the T-cell response) and in situations of delayed penetration of allergens (e.g. neomycin in petrolatum).

Historically, although it was known that idiosyncrasy was specifically directed against certain substances, in 1911 Bloch [23] showed that a sensitive person might react to substances of related chemical structure, a phenomenon later termed 'cross-sensitization'. Some sensitizers only provoke a reaction if activated by light, as found by Epstein in 1939 [24].

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Predisposing factors

Individual

Constitution. Sensitization presupposes individual susceptibility. This has been investigated using epidemiological, family and twin studies [1]. In humans, susceptibility does not seem to follow Mendelian inheritance and, in some cases, may occur by non-antigen-specific amplification of the immune response [2]. Nearly everyone can be sensitized with *Primula* extract, and most with 2,4-DNCB. However, experiments with the latter indicate that nearly all susceptible subjects will be sensitized after one or two applications of the allergen in a suitable concentration; repeated applications increase the number of persons sensitized only marginally [3]. Some individuals are thus resistant to sensitization. This resistance may have been acquired by repeated exposure to subsensitizing doses of the allergen [4].

The capacity for sensitization varies from person to person, but certain individuals are more prone to developing sensitivity to a particular substance, for example nickel [5]. The 'heritability' of nickel sensitivity has been calculated to be about 60% [5]. This may be a genetically determined trait but, if so, it is not known whether the property inherited is an increased capacity for conjugation to form an effective antigen, for sensitization or for facilitation of percutaneous absorption [6]. In guinea pigs, the capacity for sensitization, both in general and to particular substances, has been shown to be inherited [7–9]. In humans, such studies are less likely to be conclusive because of the difficulty in distinguishing between genetic and environmental factors. One experiment compared the susceptibility of parents and their children to contact sensitization with DNCB and *p*-nitrodimethylaniline. Children whose parents became sensitized were sensitized more commonly than were children whose parents were not sensitized [10]. However, another study failed to show any difference in capacity for sensitization to DNCB between monozygotic and dizygotic twins [11]. Studies of HLA types and blood groups have not proved very helpful to date [2,12–16]. A statistically significant increased proportion of rapid acetylators has been found in contact allergic patients [17]. The authors were unable to say whether this state was contributory or was a genetic marker for the ability to become sensitized.

Siblings and children of patients suffering from allergic contact dermatitis have an increased incidence of positive patch tests [18], and first-degree relatives of nickel-allergic subjects have increased prevalence of the same disorder [19].

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Sex [1]. Women have stronger cell-mediated immune responses than men [2] and yet, at least experimentally, women do not appear to be more susceptible to sensitization [3]. However, sensitization is accomplished more easily with some allergens, for example lanolin, fragrance and *p*-phenylenediamine, perhaps as a result of prior 'conditioning' exposure and subclinical sensitization [4]. In one study, women were found to have greater reactivity to DNCB than men [5] whereas, in another, men were more susceptible to DNCB sensitization than women [6]. The reason for the female preponderance in clinical patch-test studies is mainly explained by the large number of metal-sensitive females [7], which is largely the result of ear piercing [8] and the greater exposure to fragrances, cosmetics and hair dyes. It is of interest that nickel sensitivity seems to be less common in men even if they wear earrings [9].

Hormones. Hormones have some effect on contact dermatitis [10,11]. In one study [12], the response to DNCB was enhanced in women taking an oral contraceptive. Pregnancy and the use of gestagens may, unpredictably, either improve or aggravate contact dermatitis [13,14]. Contact dermatitis may flare premenstrually, and cutaneous reactivity to patch testing may vary according to the stage of the menstrual cycle [15]. No systematic studies on the capacity for sensitization in relation to the menstrual period have yet been performed.

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Race. Racial differences appear to exist, judging from experimental sensitization to poison ivy and DNCB, where Afro-Caribbeans are generally more resistant than white people [1,2], although weak reactions to the eliciting dose are difficult to discern on Afro-Caribbean skin [2]. Afro-Caribbeans are also generally more resistant to irritants. Although there are differences in prevalence of sensitization to individual allergens among racial groups, this is felt to be a reflection of exposure rather than predisposition [3,4].

Age. Age has little influence on capacity for sensitization [5]. Children are sensitized as easily as adults, and both infants and elderly people can be sensitized to poison ivy (*Toxicodendron* spp.). *Toxicodendron* dermatitis is very common in American children [6]. This suggests that the paucity of other types of contact dermatitis may be due to the simpler environment of childhood [7] and, being younger, they have had less time to develop sensitivities. Susceptibility to sensitization with DNCB declines after the age of 70 years but is otherwise constant [8]. However, the number of positive patch-test reactions tends to increase with age [9,10], due to the accumulation of allergies acquired over a lifetime, and occupational sensitization may occur only after decades of contact with a sensitizer [11]. Sensitivities may also fade with time [8,12], but this is probably due more to lack of exposure rather than age *per se*. However, the inflammatory response is diminished in elderly patients [13]. Young adults are more likely to have occupational or cosmetic allergies; elderly people are more liable to medicament and 'historic' sensitivities. Age is an important factor in any patch-test study [14].

Contact dermatitis in children [15]. This seems to be increasing [16], and either a child's environment is now less simple or dermatologists have been underestimating

the frequency of allergic contact dermatitis in children, possibly because of their reluctance to patch test younger children. There have now been several series of results of patch testing in children, summarized by Goossens *et al*. [15]. The increased prevalence of sensitivity in children is partly the result of increased exposure to nickel-containing objects and an earlier age of ear piercing [17]. Patch tests in unselected populations of healthy schoolchildren [18] and under-18s [19] found positive reactions in 13.3 and 20%, respectively.

The commonest allergens are nickel (especially in girls), fragrance, thimerosal, medicaments, rubber chemicals, chromate and resins in footwear [15]. Sensitivity to balsam of Peru has been reported to be common in young children [20,21], but this was before fragrance mix was a standard-series allergen. Reactions to thimerosal are also unexpectedly high in young people [22,23], although the relevance of these reactions remains obscure [24,25]. The increased level of reactivity to thimerosal has been blamed on vaccines and inoculations [26].

Small children pose practical problems with patch testing. There is a limited area to which a series of patch tests can be applied and they may become restless once the tests are applied, creating problems with adhesion. It is advised that more than one session of patch tests should be undertaken if necessary and a stronger adhesive used to keep the test units in place [27]. It has also been suggested that children are more susceptible to irritant patch-test reactions than adults [28]. This is not our experience, except for nickel and cobalt, and although positive patch-test reactions are less common than in adults, most reactions appear to be relevant apart from thimerosal. Lower concentrations for certain allergens have been suggested but most published reports have advocated no change. Although an abbreviated standard series based on previous published results has been suggested for children [29,30], we endeavour to perform a full adult standard series plus relevant extra tests wherever possible.

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Medication. Drug influences on skin-test reactivity have been reviewed by Schopf [1]. Antihistamines and sodium cromoglicate (disodium cromoglycate) appear to have little effect, whereas prednisolone (dose > 15 mg/day) [2] and potent topical steroids [3] both suppress allergic contact reactions. Similarly, other immunomodulators such as ciclosporin and azathioprine may reduce the intensity of allergic contact reactions. Aspirin will depress skin reactivity to trafuril [4]. Therapeutic UVB or psoralen UVA (PUVA) therapy may also temporarily reduce contact allergic reactions [5–7].

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Coincidental diseases. Patients with acute [1] or debilitating diseases such as cancer [2], Hodgkin's disease and mycosis fungoides [3] have impaired capacity for contact sensitization. This may also apply to patients who for other reasons have impaired T-lymphocyte function, for example patients with sarcoidosis [4], lepromatous leprosy [5] and parasitosis [6]. The relationship of allergic contact dermatitis to constitutional eczema and irritant contact dermatitis is discussed in the next section.

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Local (relationship of skin damage, irritancy and constitutional eczema to contact allergy). It is convenient to categorize eczemas as endogenous or exogenous, and the latter can be divided into contact irritant and allergic. It is common to see combinations of these disorders, particularly on the hands. Pre-existing or concomitant constitutional and/or irritant contact dermatitis damages the skin, affecting its barrier function and producing increased opportunities for allergen absorption and secondary sensitization.

It is known that hand eczema predisposes to nickel sensitivity and vice versa [1], and that the prevalence of chromate, cobalt and balsam sensitivity is increased in men with hand eczema [2]. The longer the duration of eczema, the greater the chance of sensitization. Occlusion greatly promotes percutaneous absorption and probably contributes to the extremely high incidence of medicament dermatitis in stasis eczema, otitis externa and perianal dermatitis [3–6], and is also a factor in dermatitis from shoes and rubber gloves.

The relationship of atopy, particularly atopic eczema, to predisposition to allergic contact dermatitis has prompted much debate. Atopics are known to exhibit down-regulation of Th1 cells [7,8], which should mean a decreased tendency to development of allergic contact dermatitis; indeed, patients with severe atopic dermatitis may have a diminished capacity for DNCB sensitization [9]. However, clinical studies are conflicting, some showing an increase in prevalence of contact allergy, especially to medicaments [10,11], others the same [12] and others a decrease [13–19]. In a study of 101 sets of twins, no correlation was found between positive patch tests and atopy [20], and the prevalence of allergic contact dermatitis in atopics was found to be similar to that in patients suffering from discoid or seborrhoeic eczema [12]. An increased level of nickel sensitization noted in one study [21] contrasts with another [22] where there was no increase. Confounding factors include the fact that in many cases of chronic atopic eczema there has been considerable exposure, both in extent and time, to medicaments and emollients applied to broken skin, which might explain the increased rate of allergy to medicament components noted in some studies. False-positive patch-test reactions to nickel, chromate and cobalt [23], and probably other marginally irritant allergens, are frequently seen in patients with atopic eczema and can be difficult to interpret. At this time no certain conclusion can be made about the relative risk of contact sensitization in atopic patients.

As sensitivity is more easily acquired if an allergen is applied to damaged skin, concomitant irritant contact dermatitis will promote sensitization and lower the threshold for elicitation of an allergic contact dermatitis in those exposed to associated allergens. In experimental sensitization, skin damage may be produced by previous application of sodium lauryl sulphate. The enhanced risk of sensitization may be due to: (i) increased absorption of allergen as a result of skin barrier disruption; (ii) priming of the immunological response with prior recruitment of immunocompetent cells, cytokines, etc.; or (iii) accumulation of mononuclear cells. Furthermore, by adapting Matzinger's 'danger model' concept for sensitization [24], it has been suggested that contact allergy can *only* develop in the presence of cytokine release from non-immune skin cells (principally keratinocytes) provoked by a coexisting irritant (often the same as the allergen) or trauma [25,26]. If there is no concomitant irritancy, then tolerance rather than allergy will follow.

In guinea pigs, sensitization is facilitated by acanthosis induced by detergents or paraffins, even in the absence of dermatitis [27–29]. Although the mechanism for this promotion of sensitization by acanthosis is unknown, it may be relevant to burns and other types of skin damage known to increase the chance of sensitization [30].

Once allergy is established, it seems reasonable to suppose that an allergen may be able to reactivate or maintain dermatitis in low concentration. However, even when

such exposure seems to have ceased, a hand eczema that started as a contact dermatitis may continue as an apparently 'constitutional' post-insult form of dermatitis [31].

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Environmental

By definition, the environment will influence exposure to potential allergens, which in turn will affect liability to contact allergy. For the individual, certain immediate environments, including those encountered in the home, at work and during spare-time activities, are particularly relevant. However, more general influences are important, including climatic, geographical, ecological, socioeconomic and cultural factors. Some of these may also affect the individual's response to allergen exposure. Climate, geography and ecology are often interrelated.

Climate. Climate, by virtue of varying UV exposure, heat and relative humidity, may play a part in liability to contact allergy. UVB exposure has been shown to diminish the skin's immune response to contact allergens [1–3]. Experimental sensitization with DNCB in humans is more easily achieved in winter than in summer [4], and elicitation of contact dermatitis is more difficult on sun-damaged skin [5]. UVA exposure, however, does not appear to have the same effect, and there is evidence that the reduction in immune responsiveness is transient, perhaps due to an adaptive mechanism preventing immunosuppression from ongoing UVA exposure [3]. UVB exposure from the sun may therefore temporarily reduce contact allergic reactions, although there is conflicting evidence about the effect of sunshine on patch-test reactions [6–9]. Conversely, chapping of the skin during winter predisposes to irritant contact dermatitis and also increases the incidence of false-positive patch-test reactions to substances such as formaldehyde [10], mercurials [11] and propylene glycol [12]. Warshaw and Hermann [13] found that positive reactions to propylene glycol were frequent in winter but not reproducible on re-examination in summer. Holland *et al*. [14] found many positive reactions in summer but far fewer during cooler weather in October. Occlusion and increased sweating may increase allergy from shoes and clothing. Kanan [15] also noted an increase in cement dermatitis in Kuwait during the summer months. Exposure to UV-absorbing chemical filters increases where there is a higher exposure to sunshine, with a consequent increase in contact and photocontact allergy from this source during the summer months, when photoallergy from other causes would also be anticipated to be more of a problem. These conflicting observations indicate that several factors must influence the seasonal liability to contact dermatitis.

Flora and fauna. Plant dermatitis commonly shows a distinct seasonal pattern, the allergenicity of some plants such as *Primula obconica* varying considerably with light and season [11]. Many allergenic plants, especially those belonging to the family Compositae, are destroyed by cold and frosty weather but return during the warmer

spring and summer months. Distribution of allergenic plant material will be facilitated by dry and windy climates. Similarly, geographical location is a very important influence. Exposure to *Toxicodendron* spp. is mainly confined to North America. Compositae allergy is seen in many parts of the world but the plants responsible vary: in the USA ragweed is the main cause, in Europe it is chrysanthemums and garden weeds, in India the weed *Parthenium*, and in Australia a number of wild Compositae found in the 'bush' [16]. Occupational contact allergy from plants is often seasonal, for instance in lichen pickers [17] and from plant and vegetable cultivation [18–20].

Fauna are not a major seasonal cause of contact allergy, although European fishermen are liable to contact dermatitis of exposed skin during the summer when handling nets containing marine organisms known as bryozoans [21]. The disorder is known as 'Dogger Bank Itch' in the UK. The allergen has been identified as the (2-hydroxyethyl)dimethylsulfoxonium ion [22].

Socio-economic and cultural. The relationship of contact dermatitis to socio-economic groups has not been studied in detail, but exposure to cheap (nickel-releasing) metals used as jewellery might be expected to be relatively increased in those with less disposable income. Similarly, the pattern of perfume and cosmetic use and exposure might vary according to social class.

Cultural factors are important and not always fully appreciated as a predisposing cause for contact allergy, particularly the use of sensitizing traditional herbal medicines and balms to treat skin disorders in the Middle and Far East [23–25]. Furthermore, ingested herbal folk remedies containing *Toxicodendron* have caused outbreaks of systemic allergic contact dermatitis in Korea [26].

Hair dyes are used much more commonly by men in the Middle East and the Indian subcontinent, including use on the beard [27,28]. Indian women may become sensitized to dyes and adhesives used in kumkum and bindi applied to the forehead [29,30]. Western culture, in contrast, is associated with higher cosmetic use and leisure pursuits, including lying in the sun and seaside holidays requiring the application of sunscreens.

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Chemical

Skin cells, especially their nucleic acids and proteins, are composed of molecules that contain nucleophilic atoms, i.e. negatively charged and electron rich. Most allergens (haptens) are 'simple' chemicals of low molecular weight (less than 500–1000 Da) that contain electrophilic atoms [1,2], i.e. positively charged and electron deficient. Interaction between these two types of atoms leads to strong

Hapten group	Example
1 Acids	Maleic acid
2 Aldehydes	Formaldehyde
3 Amines	Ethylenediamine, *p*-phenylenediamine
4 Diazo compounds	Bismark brown, Congo red
5 Esters	Benzocaine
6 Ethers	Benzyl ether
7 Epoxides	Epoxy resin
8 Halogenated compounds	Dinitrochlorobenzene, picryl chloride
9 Quinones	Primin, hydroquinone
10 Metals	Ni^{2+}, Co^{2+}, Cr^{3+}, Hg^{2+}, etc.
11 Unsaturated compounds	Δ^3-Carene (turpentine)

Table 20.2 Classification of haptens based on functional grouping. (From Dupuis & Benezra [4].)

covalent bonding to form a hapten–protein complex or 'complete antigen'. Metal and metal salts can bond to electron-rich atoms (ligands) by taking some of the electrons and forming coordinate bonds [3]. Dupuis and Benezra [4] have classified haptens into seven groups according to their chemical reactivity in relation to putative carrier proteins. Haptens can also be classified according to functional groups (Table 20.2).

Some molecules, although themselves not allergenic (pro-haptens), are converted into electrophilic molecules by the skin's detoxification processes, such as hydroxylation systems, monoamine oxidases and peroxidases. Peroxidases can convert electron-rich aromatic derivatives into electrophile quinones, for example poison ivy catechols are changed into highly reactive orthoquinones [5]. Hydrolysis can convert tuliposides into allergenic tulipalins [6]. Other pro-haptens can be transformed into haptens by the effect of atmospheric oxygen or UV irradiation [7]. Cutaneous enzymatic transformation of a chemical into many different metabolites, depending on the pathway taken, makes determination of the allergenicity of the original chemical more difficult. It also explains the difficulty in deciding if multiple sensitivities are cross-reactions or concomitant sensitization.

Enzymatic systems may also play a preventative role, as with glutathione in some drug-induced reactions [8].

Assessment of sensitization potential. The sensitization potential is the relative capacity of a given agent to induce sensitization in a group of humans or animals [9,10]. Both in guinea pigs and humans, an estimate of the sensitizing index requires patch-test exposures modified to increase the sensitizing impact. Such predictive patch tests are used to compare the sensitizing properties of new products or chemicals with those of known substances [11]. Many test procedures have been developed over the last 40 years to evaluate the sensitizing properties of new chemicals. Kligman and Basketter [12] have critically evaluated the various methods of predictive testing. Most previous methods could not reveal even potent sensitizers. Kligman and Epstein [13] have described a 'maximization test', based on the application of a high concentration of the chemical to be studied on a skin area previously irritated by sodium lauryl sulphate. This method was later modified by Marzulli and Maibach [14], who used repeated patch tests with high concentrations of the allergen to be studied. Jordan and King [15] have shown that some substances giving negative reactions in maximization tests in males sometimes sensitize females. This may reflect previous subliminal exposure to substances such as the ingredients of cosmetics [16].

Ethical considerations may prevent experimental sensitization in humans. The guinea-pig maximization test described by Magnusson and Kligman [17] gives results that compare favourably with predictive patch tests in humans. To enhance sensitization, the guinea-pig maximization test employs a combination of patch testing and intradermal injection of allergen in a simple solution of Freund's adjuvant. Other tests, such as the Buehler test [18] and the open epicutaneous test [19], use the epicutaneous route only, whereas the Draize test [20] and Freund's complete adjuvant test use a purely intradermal method of sensitization [21]. There is, however, no absolute conformity in the sensitizing potential of a substance in mouse, guinea pig and human.

The 6th Amendment of the EC Cosmetic Directive, which came into effect in January 1997, is committed to banning all animal testing [22]. The murine local lymph-node assay [23] uses a smaller number of animals, and the mouse ear swelling test [24] avoids post-mortem examination of tested animals. These newer methods are gaining regulatory acceptance [25].

The theoretical allergenicity of a compound may be studied by reference to databases [26] of cases of reported sensitivity and the results of previously performed guinea-pig maximization tests. By comparing the structure of known allergens with that of any new compound, its likely allergenicity can be assessed. Molecular modelling for sesquiterpene lactones [27] and primin [28] and relative alkylation index for sultones [29] are examples of how structure–activity relationships [30] can be used to assess allergenicity.

Sensitization risk. The risk of sensitization depends not only on the sensitization potential of the substance applied but also on its concentration per unit area of the skin [31], where the area of application is above 1 cm^2 [32], and individual susceptibility. With high concentrations of a strong allergen such as DNCB, individual susceptibility is of little importance; nearly everyone is capable of being sensitized.

In personal care products the concentration of any allergen is adjusted so that the risk of inducing sensitization is small, although there may still be sufficient to induce dermatitis in an individual already sensitized [33]. An approach to sensitization risk assessment for such products has been described [34]. This involves an assessment of both exposure, including knowledge of skin absorption, and sensitization potential, based on literature review and known structure–activity relationships. If *in vivo* testing is needed, various animal tests or human repeat-insult patch tests would then be performed. Legislative measures have been introduced in an attempt to reduce the prevalence of contact dermatitis [35].

Development of dermatitis. Some persons sensitive to a substance may tolerate normal contact with it, and are said to have a latent sensitivity. There is no immunological difference between latent and expressed sensitivity.

Whether sensitivity is manifest or latent is determined partly by the threshold of sensitivity, i.e. the lowest concentration of allergen giving a positive patch-test response. The dose at induction determines in part the strength of response at challenge, higher induction doses resulting in greater reactions at challenge [31]. Persons who are clinically sensitive to poison ivy invariably have a positive reaction to pentadecylcatechol (PDC) 1 : 10 000, but many who react only to 1 : 100 PDC are clinically immune [36,37]. Patch-test sensitivity and clinical sensitivity are not necessarily proportional. The threshold determined by patch tests depends on a number of technical factors, such as the base used and the region where the tests are applied. It also varies from time to time in the same person. The threshold may fall after repeated contact with an allergen, and positive test reactions in latent allergy may reveal candidates for future allergic contact dermatitis.

Patch testing with a new substance may reveal that some persons are already sensitive to it, either from contact with related substances or from exposure to the compound in other forms. Negative reactions in 200 persons do not exclude the possible occurrence of sensitivity in 1 of 38 consumers (99.5% level). This frequency would immediately preclude any practical use of the substance. It has been calculated that negative patch tests in 5300 subjects indicate that sensitivity would be liable to occur in less than 1 of 1000 consumers.

Immunological tolerance. The sensitization reaction induces effector T cells and suppressor T cells, the latter curtailing the immune response so that the epidermal reaction regresses and does not continue indefinitely [38]. Theoretically, therefore, preferential stimulation of suppressor cells could lead to antigen unresponsiveness [39]. This can be achieved by administering the allergen (in previously unsensitized individuals) by non-cutaneous routes, such as intravenously, orally or peritoneally [40–42], thereby bypassing epidermal Langerhans' cells. This tolerance is also achieved by applying the allergen to skin with no Langerhans' cells, for example mouse tails [43], or skin in which Langerhans' cells have been inhibited by UV radiation [44] or depleted by glucocorticoids [45].

Suppressor T cells, or their precursors, are sensitive to cytostatic drugs, so that administration of cyclophosphamide can reverse a tolerant state [46].

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Pathology

Biopsies are of limited help in contact dermatitis. Most types of eczema show identical pathological changes, and allergic and primary irritant contact dermatitis cannot be distinguished with certainty [1]. The role of basophils and mast cells remains controversial [2,3].

Ultramicroscopic examination suggests that Langerhans' cells play an important role in allergic contact dermatitis [4–6]. Recent studies on the histology, immunocytochemistry and electron microscopy of the early cellular events in patients with induced allergic and irritant responses are discussed in Chapter 19.

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Clinical features

Contact dermatitis can mimic or be associated with any type of eczematous eruption. The diagnosis is based on a careful history combined with a sound knowledge of common allergens and irritants in the environment.

History

A comprehensive history, to elicit potential allergens, is essential, and some knowledge of chemistry and industrial processes is of value. Sensitization and subsequent contact dermatitis may result from a single exposure to a strong allergen [1], although usually several or many exposures are necessary before sensitization and dermatitis occur.

Primary site. This must be ascertained by questioning the patient carefully. By definition, contact dermatitis must begin in sites where contact has taken place with the responsible agent(s), and the sites of origin are an important clue to the cause. Patients are frequently assessed at a stage when there has been worsening and secondary spread of the dermatitis, obscuring the original pattern.

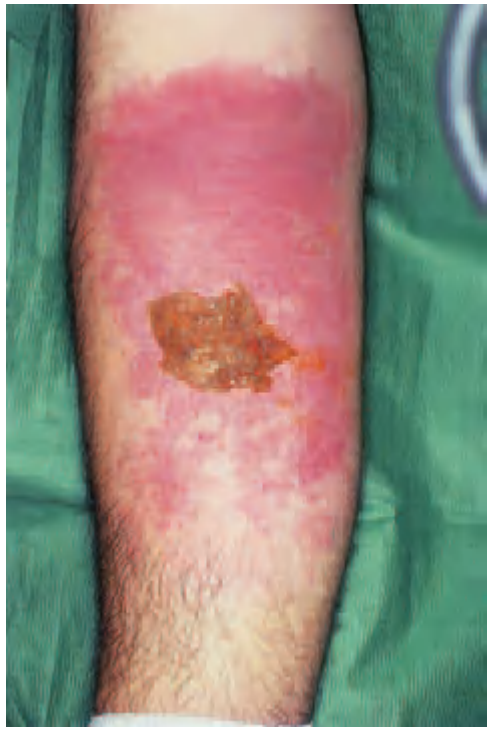

Fig. 20.1 Medicament contact dermatitis. (Courtesy of Dr J.D. Wilkinson, Amersham General Hospital, Amersham, UK.)

Duration and behaviour. Once the date of onset and the primary site(s) have been identified, it is necessary to establish the subsequent behaviour of the disorder. In particular, did the condition spread and if so where? Has the problem been persistent or intermittent? Repeated sudden exacerbations may point to an allergic contact dermatitis. Are there any obvious exacerbating factors?

Improvement of dermatitis during weekends or holidays favours an occupational origin. Relapse at weekends suggests a hobby or non-occupational allergen. Seasonal variation (worsening when light intensity is greatest) suggests a plant allergen, perhaps with photoaggravation, or photoallergy. Plant dermatitis may recur in atypical patterns. Dermatitis around a wound, especially leg ulcers, suggests sensitization to medicaments (Fig. 20.1) and exacerbations and recurrences induced by particular medicaments or cosmetics suggest contact allergy from these sources.

Previous history. A history of previous dermatitis may provide a clue to the origin of a relapse. For example, earring dermatitis may precede nickel dermatitis of the hands by several years. Previous dermatitis, especially if localized to the lower legs, may have been caused or complicated by repeated use of applications containing sensitizers, for example antibiotics, lanolin and preservatives in creams. It is useful to ask specifically about skin reactions to cheap metal, perfume and adhesive plasters.

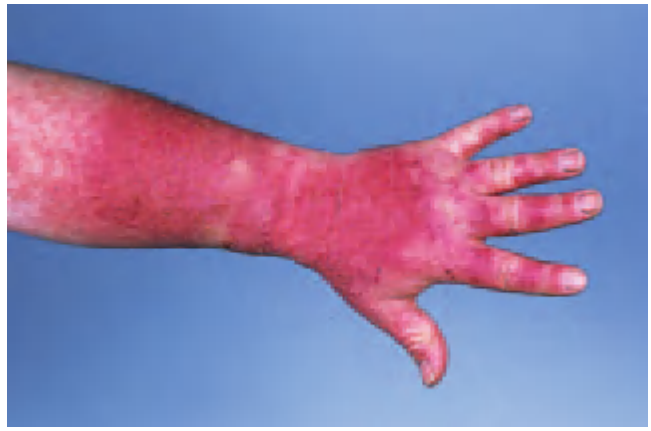

Fig. 20.2 Acute allergic contact dermatitis in a patient allergic to acrylates used in the printing industry. (Courtesy of Dr J.D. Wilkinson, Amersham General Hospital, Amersham, UK.)

A history of infantile or childhood flexural eczema, asthma, hay fever or conjunctivitis may point to an atopic diathesis. Atopic eczema predisposes to irritant dermatitis of the hands, and in such cases constitutional factors may be the major but not necessarily the sole cause [2].

Sources of allergy

A search for possible sources of allergic contact dermatitis should include a review of all the patient's activities but initially should concentrate on (i) occupation, past and present; (ii) hobbies; (iii) cosmetics, clothing and personal objects; (iv) home environment; and (v) current and previous topically applied medicaments both prescribed and 'over the counter'. Most patients believe that newly encountered items are the cause of dermatitis, whereas in fact those that have been in use for a long time are commonly responsible.

Occupational (Fig. 20.2). A precise history backed by a thorough knowledge of the materials handled at work, machinery operated and personal protection employed will be necessary when occupational dermatitis is suspected. However, no dermatologist can rely entirely on his or her knowledge of industrial processes, and a factory visit may be required to become familiar with the process described, especially if it is strange or new [3]. Health and safety data sheets must be examined as these may give the chemical names of materials used, as well as an indication of their irritancy or allergenicity. A telephone number or email address may be given for further enquiries, if required. The presence of other similar cases will alert one to an increased probability of occupational dermatitis. There are increasing reports of allergy to components of cleansers, creams and conditioners supplied at work, and workers must be asked about use of these [4].

Problems associated with housework should not be overlooked. The amount of housework performed and methods employed are extremely variable. The number of children and availability of labour-saving devices should be determined. Few volunteer information about domestic work outside their own home, and all must be directly questioned about it.

Patients who are unemployed may, in fact, be engaged in casual work, and even employed persons should be asked about second jobs.

Hobbies. Common sensitizers, well known as industrial allergens, are introduced into most homes for do-it-yourself work. Cement, glues, paint, wood and wood preservatives are handled by many householders. Another important source of hobby dermatitis is gardening. Other pursuits, such as car maintenance, sports, cookery and photography, should be considered.

Personal objects. These are items either worn or applied to the skin, and include textiles, footwear, protective clothing and gloves, jewellery, spectacles, hearing aids, medical appliances, cosmetics, toiletries, fragrances and medicaments. Untoward reactions to cosmetics, toiletries and topical applications are the commonest single reason for hospital referral with allergic contact dermatitis. The number of products used may be large, and some may be used only intermittently. Often, only prescribed therapies are declared and repeated specific enquiry must be made about over-the-counter preparations, including cosmetics used as moisturizers, herbal treatments and borrowed medicaments. Often patients will not mention 'hypoallergenic' products in the mistaken belief that they could not be responsible. Applied cosmetics may be removed by employing creams, lotions or wipes, the use of which may easily be overlooked. Patients should be specifically asked about the use of nail varnish, false nails and hair dyes. Skin cleansing and hair products, which are 'rinse off' as opposed to 'leave on', may also be responsible. Many patients have a poor recollection of products used, and most forget some items. They should be invited to bring all their topically applied items when they attend for patch testing.

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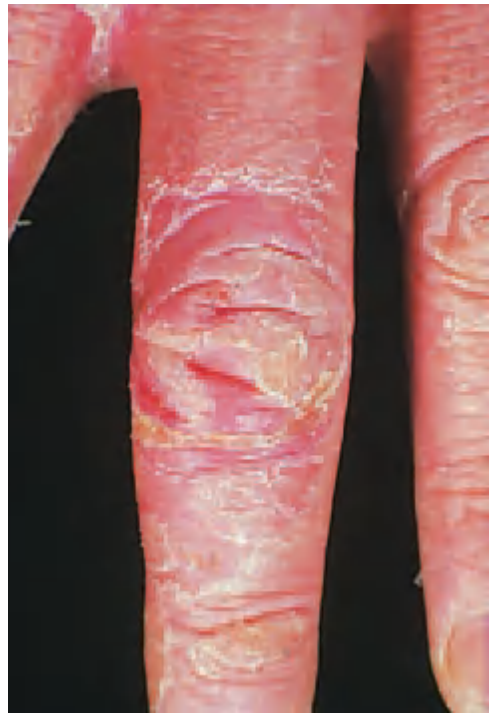

Fig. 20.3 Dry, scaling, thickened skin with fissuring due to chronic contact dermatitis.

Clinical examination

Eczematous responses (dermatitis)

The severity of the dermatitis is determined by the intensity of exposure and the level of sensitivity. The clinical picture is also to some extent dependent upon the site of dermatitis and on the causative agent. The distribution of the dermatitis may suggest a cause, for example that due to nickel or textiles.

The primary signs in contact dermatitis are erythema, swelling, papules and papulovesicles, which reflect the sequence of inflammatory changes in the dermis and the intracellular and intercellular oedema in the epidermis. In more acute and severe cases this spongiosis may progress to disruption of the intercellular bridges and the development of vesicles or blisters; if they burst, a weeping dermatitis results. The dominant symptom is itching.

If contact dermatitis persists, it may be due to continued or repeated exposure to the allergen or to secondary irritants or allergens. The skin becomes dry, scaly and thicker as a result of acanthosis, hyperkeratosis and oedema, and cellular infiltration in the dermis. Lichenification and fissuring may develop later (Fig. 20.3). These clinical features of chronic allergic contact dermatitis cannot always be distinguished from constitutional (Fig. 20.4) or irritant contact dermatitis, and the aetiology is indeed often mixed.

The distribution of the dermatitis is of diagnostic importance but its morphology is usually of no help in

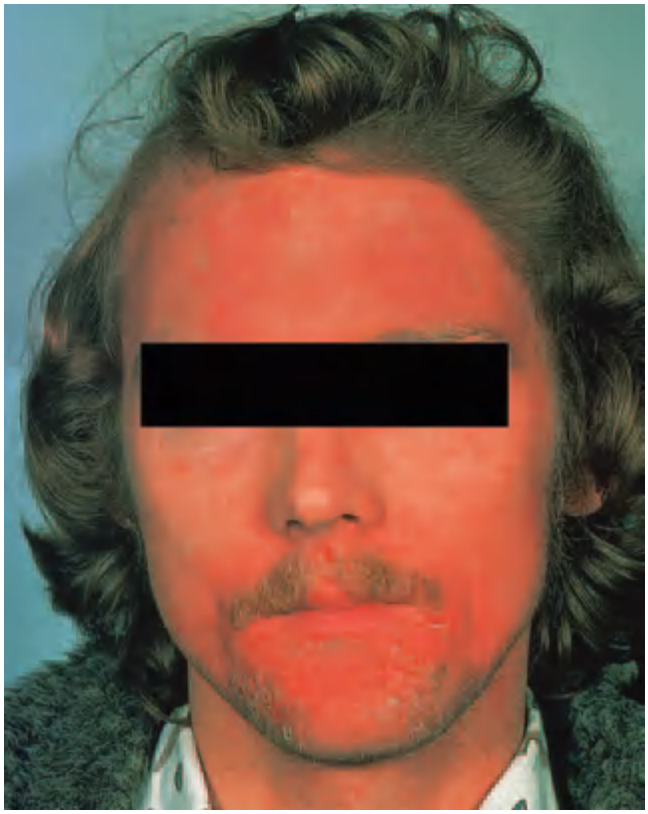

Fig. 20.4 A 'seborrhoeic dermatitis-like' pattern of allergic contact dermatitis due to phosphorus sesquisulphide ('strike anywhere' matches). (Courtesy of Dr J.D. Wilkinson, Amersham General Hospital, Amersham, UK.)

tracing the cause, with some exceptions, for example exceptionally strong allergens may provoke a bullous eruption even after brief contact.

Primary patterns [1]

Anatomical patterns of dermatitis often suggest a specific cause, but in other cases the pattern merely indicates a range of possible allergens, such as in shoe dermatitis.

Sometimes, the dermatitis is sharply limited to the usual site of contact, but because the area of contact with most objects varies, the distribution may be more erratic. Some allergens may be spread locally by the fingers or be carried to distant body regions. Even when there is no eruption on the hands, allergens on the fingertips may cause dermatitis elsewhere, for example the genital area, eyes, or face and neck.

Once the primary site has been established, questioning should focus on those allergens that are particularly frequent causes of dermatitis in that region.

Hands and arms [2–4]. Hand dermatitis is usually multifactorial [5]. About two-thirds of all cases of contact dermatitis involve the hands, which are the most important

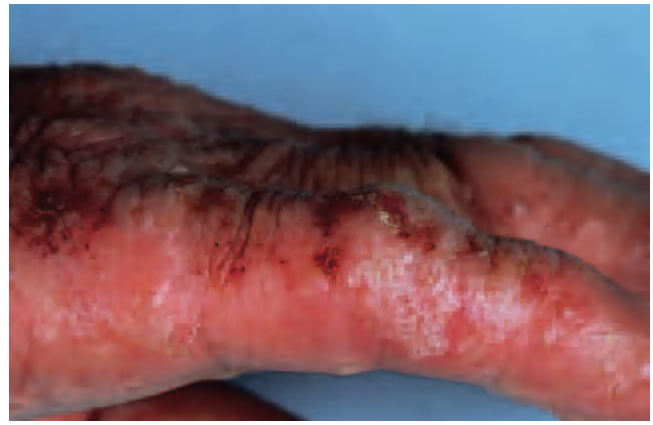

Fig. 20.5 Acute vesicular eczema in a patient allergic to 1,2-benzisothiazolin-3-one mimicking constitutional pompholyx. (Courtesy of Dr J.D. Wilkinson, Amersham General Hospital, Amersham, UK.)

site for both irritant and allergic contact dermatitis [1,2,6]. The hands are also a common site for constitutional patterns such as pompholyx, vesiculo-squamous and hyperkeratotic eczema. It may be difficult to differentiate between hyperkeratotic eczema and psoriasis [7]. Atopic eczema often affects the hands [8]. No pattern of hand eczema is characteristic of a particular aetiology, and allergic contact dermatitis may mimic constitutional patterns.

Housewives' dermatitis and most occupational dermatitis remain confined to the hands [9]. Although the majority of cases are of primary irritant nature, the yield of relevant positive reactions to patch tests is remarkably high [1,2]. Fortunately, many of the sensitizers found are included in the standard patch-test series, but obviously the selection of substances for further testing must be guided by history and occupation [10].

Unusual allergens may be traced by relating the shape and site of the eczematous patches to items handled. Rubber gloves may induce a clear pattern of dermatitis over the sites where they are worn.

Vesicular palmar contact dermatitis may mimic constitutional eczema and may also result from contact with or ingestion of an allergen to which the person is already sensitized. This has been shown to occur by oral challenge with nickel [11], chromate [12], balsams [13] and garlic [14]. Chromate in cement, *N*-isopropyl-*N*'-phenyl-*p*-phenylenediamine (IPPD) and 1,2-benzisothiazolin-3-one (Fig. 20.5) are three allergens particularly liable to induce a palmar pattern of allergic dermatitis. Discoid patterns of eczema are seen with chromate allergy.

Irritants affect mainly the dorsa of the hands, the webs, and the backs and sides of the fingers. Dermatitis caused by liquids often starts in the webs of the fingers, and extends to the front of the wrists and up the forearms. A recalcitrant type found in domestic workers begins under a ring and spreads to the neighbouring webs and adjacent

Fig. 20.6 Characteristic 'streaky' contact dermatitis on the wrists in a patient allergic to *Primula obconica*. (Courtesy of Dr J.D. Wilkinson, Amersham General Hospital, Amersham, UK.)

part of the palm. However, allergic contact dermatitis may also start under a ring [6].

Streaky dermatitis on the fingers, dorsa of the hands and forearms is mainly caused by plants (Fig. 20.6), and is allergic (e.g. *Primula obconica* and poison ivy), irritant (e.g. *Dieffenbachia* and spurge) or phototoxic (e.g. giant hogweed and rue).

Dermatitis of the hands in those involved with agriculture and food preparation may be associated with immediate-type hypersensitivity to animal and plant proteins [15,16]. Allergic contact dermatitis of the fingertips is seen with plant allergens such as tulipalins in horticulturists ('tulip fingers') [17]. Garlic allergy in chefs typically affects the non-dominant thumb, fore and middle fingers [18] (Fig. 20.7).

The arms are affected by the same allergens as the hands, but usually later. If protective gloves have been used at work, the forearms may be the major sites of occupational dermatitis (Fig. 20.8). Allergy to nickel, chromate and *p*-tertiary-butylphenol formaldehyde resin may develop at the wrists from sensitivity to the metal, leather and glue, respectively, in watchstraps containing these allergens. Dust (exotic woods, cement), nickel and textiles produce dermatitis in the elbow flexures, and this must be distinguished from atopic dermatitis.

Face [19,20]. Dermatitis of the face may occur alone or in association with hand eczema. Facial allergic contact dermatitis from fragrances, preservatives and other constituents of skin-care products and cosmetics, including

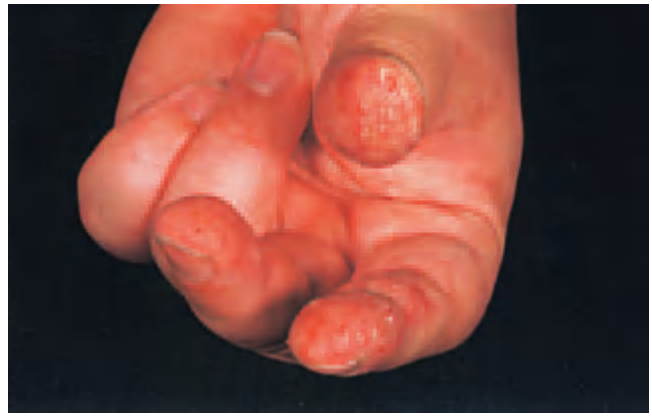

Fig. 20.7 Fingertip pattern of allergic contact dermatitis from garlic affecting the non-dominant thumb, forefinger and middle fingers.

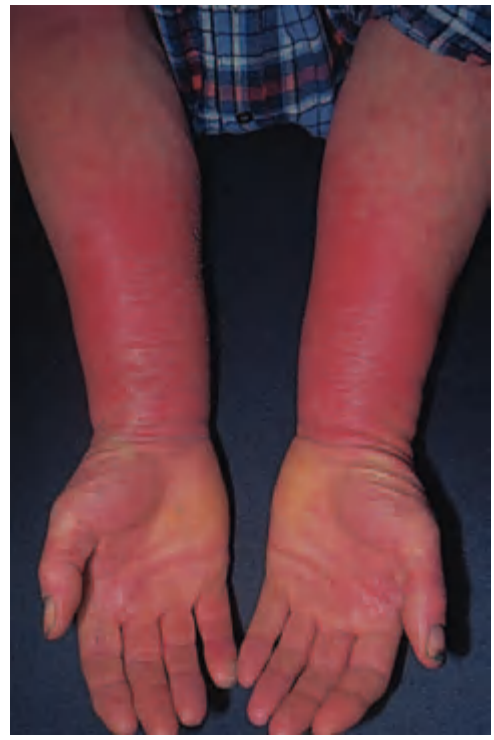

Fig. 20.8 Contact allergy to epoxy resin and hardener affecting unprotected forearms.

nail varnish, is common [21]. Nail varnish allergy often affects the face in well-localized patches, and may be associated with eyelid dermatitis and more extensive involvement of the neck, chest and even further afield [22]. The clinical presentation can even suggest artefact because the affected sites are so well demarcated [19,23]. A similar distribution may be seen from allergy to acrylic nails [24].

Allergy to rubber sponge cosmetic applicators has also been reported in this site [25]. Facial allergic contact dermatitis must be distinguished from intolerance, irritant contact dermatitis and constitutional eczemas, but it is sometimes multifactorial.

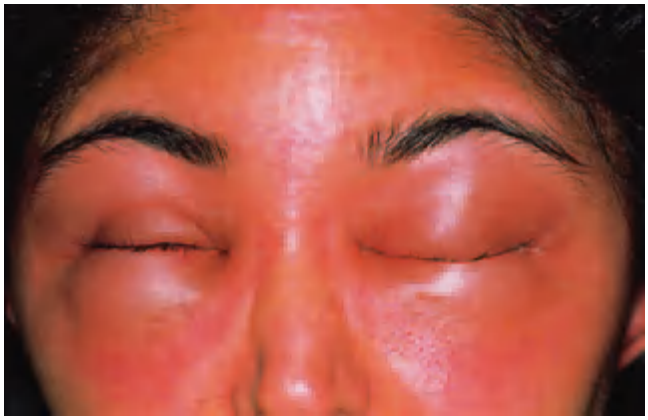

Fig. 20.9 Contact dermatitis presenting as acute oedema, as seen in patients sensitive to *Primula* and *p*-phenylenediamine-type hair dyes and in those with volatile patterns of contact dermatitis. (Courtesy of Dr J.D. Wilkinson, Amersham General Hospital, Amersham, UK.)

Dermatitis to a cosmetic may start with dryness, tightness and itching. Most women change to another brand at this stage and never reach the dermatologist. They are referred only if symptoms persist or are severe. Allergy cannot be totally ruled out unless all ingredients of all cosmetics have been tested individually at appropriate concentration and in a suitable vehicle. Ideally, the raw material should be the same as that used in the suspect product, because batch differences, source and purity may all be important. In practice, however, most cosmetics are initially tested 'as is'. A repeat open application test (ROAT) [26] or use test [27] may be performed to try to identify the offending cosmetic, although these will not necessarily differentiate between irritant and allergic reactions.

The forehead is affected by allergy to anything applied to the hair and also to chromate in leather hatbands. Spectacle frames containing nickel or plastics may cause dermatitis on areas of contact with the cheeks, nose, eyelids and ears [28–30].

The patterns of dermatitis caused by airborne or volatile allergens [31] and photosensitizers can often be distinguished by involvement of the eyelids in the former, and by triangles of relatively spared skin below the chin and behind and below the ear lobes in the latter.

Eyelids [32]. Allergens affecting the face may initially produce eyelid dermatitis, as the skin of the eyelids is thin, sensitive and may be contaminated by the fingers (e.g. nail varnish [33]), airborne droplets (e.g. fragrance sprays) or volatile substances (e.g. epoxy resin). Eye creams, eye shadows, mascara and eye make-up removers may be responsible, often for irritant dermatitis, but patch testing may reveal relevant allergens.

Some allergens provoke acute oedema (Fig. 20.9) and intense pruritus, but no manifest eczema followed by desquamation. *Primula obconica* and poison ivy [34] may cause such a reaction involving the eyelids, or a streaky pattern of dermatitis at contact sites, which may be haemorrhagic. Reactions to hair dyes and 'strike-anywhere' matches may also present in this way.

Dermatitis is frequently caused by remedies for ocular disorders [35]. Common sensitizers in eye drops and ointments are neomycin, framycetin, gentamicin, tobramycin, chloramphenicol, sulphonamides, local anaesthetics, antihistamines, β-blockers [36,37], anticholinergics [38] and sympathomimetics [39]. Eye drops and contact lens solutions contain preservatives (benzalkonium chloride, EDTA, mercurials), which may also sensitize [35].

Lips or perioral area [40]. Lipstick dermatitis is sometimes limited to the vermilion border, which appears dry, scaling or cracked; occasionally the perioral area is also affected. Eosin was a common sensitizer in lipsticks before 1960 [41] but since its allergenicity was found to be due to impurities there have been no further reports of adverse effects, and lipstick dermatitis is less common. Sensitivity has been reported to flavourings [42,43], shellac [44] and excipients, for example ricinoleic acid [40], castor oil [45], gallates [46,47] and UV filters [48] in lipsticks and lipsalves.

Allergy to toothpaste is a recognized cause of cheilitis and perioral eczema [40,49]. Flavours are the usual cause, such as cinnamic aldehyde [50,51], spearmint oil, peppermint oil, anethole and L-carvone [52].

Allergic reactions to dentures and fillings are considered in the section on mucous membranes (see p. 20.26). Angular cheilitis is usually due to badly fitting dentures, but cheilitis may exceptionally be caused by sensitizers habitually carried to the mouth, such as nail varnish or nickel-plated objects [53] (e.g. keys, pins or musical instruments).

Ears. External otitis has a complex aetiology (see Chapter 65) and usually runs a chronic relapsing course. Neurodermatitis (lichen simplex chronicus) is also common, and may be superimposed on seborrhoeic eczema.

Secondary medicament contact dermatitis, which is often unsuspected, is particularly common in the ear [54,55]. Dermatitis can also be both caused and maintained by habitual scratching with hairpins (nickel), matches (phosphorus sesquisulphide and chromate) [56] or fingertips (nail varnish, nickel, *Primula obconica*).

Dermatitis from hearing-aids occurs but is often a non-specific consequence of occlusion [57]. Hearing-aids may contain acrylates [58–60] and plasticizing and stabilizing chemicals [61]. Headsets may contain urea and phenol-formaldehyde resins, or rubber in earphones.

Spectacle-frame dermatitis may be of irritant origin, especially behind and over the ears. Metals, particularly nickel and palladium, may cause allergy, and some frames causing dermatitis have been wrongly described as being nickel-free or titanium [62–64]. Plastic components,

including epoxy resins [65], acrylates [66], plasticizers [61,67], UV inhibitors [68] and dyes [69,70], have been identified as the cause of the dermatitis. Earplugs for noise protection may contain antiseptics, dyes, rubber and plastic chemicals [71], and finishes including formaldehyde resins. Elastic on shower caps, and hair dyes, cause dermatitis in the retro-auricular area.

Earrings and clips commonly cause dermatitis on the ear lobes from the presence of nickel, and less commonly from gold [72]. Piercing of the ear lobe may be the sensitizing event in nickel dermatitis, leading to a chronic contact dermatitis [73,74].

Scalp. The scalp tends to be relatively spared from involvement by allergic contact dermatitis. Dermatitis caused by fragrances, biocides and amphoteric detergents in hair cosmetics is usually limited to the ears, neck and face, but may be preceded by persistent itching of the scalp. Permanent hair dye, *p*-phenylenediamine, and related semi-permanent dyes still remain an important source of dermatitis. Correctly used, permanent hair dyes are applied to the hair and not the scalp, followed by oxidation and rinsing. Bleaches contain ammonium persulphate, which may cause peculiar urticarial eruptions [75] as well as contact dermatitis. Glyceryl monothioglycolate, used for acid or cold perms, although a significant sensitizer in hairdressers, only occasionally causes problems in their clients [76]. Hair-styling products such as mousses, gels, waxes and holding sprays often contain fragrances and preservatives that may be allergenic, but they also contain conditioning quaternary ammonium compounds, which are often irritant. Medicated shampoos may contain tar extracts, zinc pyrithione or other agents, and many shampoos contain formaldehyde, formaldehyde releasers or isothiazolinones, added as preservatives. Cocamidopropylbetaine is also found in many shampoos. All these materials may potentially sensitize, although allergic subjects may tolerate them because of the short duration of contact, provided the hair is thoroughly rinsed after washing [27,77,78]. Scalp dermatitis from allergy to azo disperse dyes in a nylon wig has been reported [79].

Neck. Nickel from clasps of necklaces or zip fasteners produces a small area of dermatitis on the nape of the neck. Nail varnish (Fig. 20.10) or *Primula obconica* from fingertips may be the cause of a patchy allergic dermatitis sometimes simulating lichen simplex.

Textiles (finishes in collars, dyes) and necklaces (nickel, exotic wood) may cause a collar-like dermatitis, or eruptions on the sides of the neck. Dermatitis from airborne allergens and photosensitizers is sharply limited by the collar to the 'V' of the neck if blouses or open-necked shirts are worn.

Perfume may cause both allergic contact dermatitis and phototoxic dermatitis (Berloque dermatitis) on the neck, especially the sides. A characteristic pattern of photoallergic pigmentation was also seen in men photosensitized to musk ambrette [80].

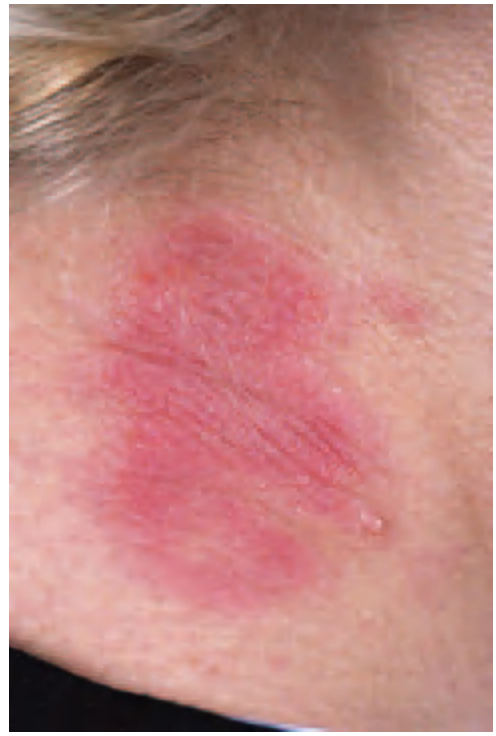

Fig. 20.10 A patch of 'lichen simplex-like' eczema on the nape of the neck associated with allergy to tosylamide formaldehyde resin (nail varnish). (Courtesy of Dr J.D. Wilkinson, Amersham General Hospital, Amersham, UK.)

Axillae. Many cases of dermatitis are irritant due to sweating, occlusion and the use of antiperspirants, which often contain aluminium salts to block the sweat glands. Allergic sensitivity may occur to fragrances used to mask the odour [81,82] and to antiseptics intended to reduce the bacterial flora [83,84]. The dermatitis produced by textiles tends to be periaxillary.

Trunk. The distribution of a clothing dermatitis may provide a clue to the responsible garment. In both sexes, nickel buttons and zip fasteners cause dermatitis localized to where they are worn, but a more widespread secondary spread eruption is often associated. Chromate sensitivity from leather and rubber allergy from elastic may present as truncal eczema [1]. Dermatitis from dresses, blouses and sweaters usually predominantly affects the neck and folds of the axilla, and spares areas of skin covered by undergarments. The allergens are usually textile dyes or finishes.

UV filters cause a diffuse allergic or photoallergic dermatitis. Outdoor workers sensitized to Compositae may have a diffuse dermatitis or dermatitis of an airborne pattern, which affects all the exposed areas, including the trunk if they remove their clothing to work. Detergents and fabric conditioners are commonly blamed for truncal

skin eruptions but objective confirmation is usually lacking. Perfume residues might possibly cause problems in fragrance-allergic individuals. Diffuse papular eczema may be a feature of medicament sensitivity with secondary spread.

Anogenital. The anogenital region is a common site for medicament sensitization [85,86]. There is often experimentation with a wide range of prescribed and over-the-counter medicaments for pruritus, skin eruptions and haemorrhoids, many of which contain sensitizers, most commonly perfume, local anaesthetics and balsam of Peru (*Myroxylon pereirae*). Other sensitizers prescribed by the medical profession include neomycin, hydroxyquinolines, ethylenediamine, corticosteroids and topical antifungals. Moist toilet tissues and wipes may contain unnecessarily high levels of preservative, which have been associated with an increased prevalence of allergic sensitivity [87,88]. Ectopic contact dermatitis from nail varnish may affect this site [89]. Nylon dyes, especially in tights, may also produce allergic contact dermatitis largely confined to this area.

Ingestion of contact allergens may cause pruritus ani particularly if they are excreted unchanged. Spices and medicaments may occasionally be suspected. Cashew nut oil in butter was found to induce perianal dermatitis in an individual allergic to the cross-sensitizing allergenic urushiol found in poison ivy [90].

Allergic contact dermatitis confined to the vulva is relatively less common [91]. Perfumes or antiseptics in soaps, sprays or sanitary pads [92] are said to be rare causes of genital dermatitis, although feminine hygiene sprays may cause both irritant and allergic reactions [93]. Medicaments used for vaginitis rarely provoke allergic reactions on the mucosa but sometimes produce a rash on the adjacent skin, and may cause connubial dermatitis in sexual partners. However, in one study of patients suffering from pruritus vulvae without associated inflammation, 49% had one or more relevant allergic reactions on patch testing, as did seven of 16 patients with lichen sclerosus. In over 50% of these patients, symptoms improved significantly or resolved when avoidance measures were taken [94]. Vulvodynia does not appear to be frequently associated with contact allergy [95].

Rubber accelerators in condoms can also be a cause of genital eczema or pruritus vulvae [96]. Genital dermatitis from transfer of material carried on the hands may occur in carpenters and cabinet-makers and those who work with resins.

Thighs. Dermatitis from nickel and rubber in suspenders is now rarely seen. Textile dermatitis starts at the edge of the underwear, and is usually more pronounced in the popliteal spaces or gluteal folds. Finishes in the material of the pockets or objects kept in the pockets (e.g. nickel coins or boxes of matches) may provoke a patch of dermatitis on the underlying skin (Fig. 20.11). Allergens may penetrate working clothes.

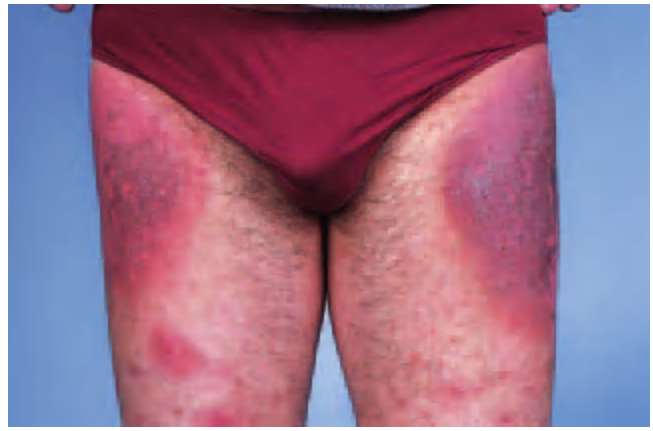

Fig. 20.11 Allergic contact dermatitis due to items kept in trouser pockets. (Courtesy of Dr J.D. Wilkinson, Amersham General Hospital, Amersham, UK.)

Lower legs. The lower leg is particularly prone to contact allergy. Allergic contact dermatitis from medicaments predominates, especially in those with varicose eczema and ulcers. The common allergens are topical antibiotics and components of creams and paste bandages, such as lanolin, cetearyl alcohol and parabens [97,98]. Allergy seems to occur readily to materials that are rarely problematic in other sites. Rubber allergy may be associated with compression bandaging and elastic hosiery. Allergy to colophony and derivatives may occur from dressing adhesives [99] and nylon dye allergy may be seen from hosiery.

Rubber boots provoke dermatitis either at their upper edge or on the calf in areas of greatest friction.

Feet. Dermatitis may result from shoes and stockings or remedies for 'athlete's foot', antiseptics and antiperspirants.

Generalized. Generalized erythroderma may be the result of a chronic contact dermatitis maintained by continued exposure to allergens in the environment, even in hospitals, for example contact with formaldehyde-disinfected mattresses or bed linen impregnated with topical medicaments. Patch testing is not possible until the skin has cleared.

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Exposed sites [1]

Contact dermatitis from dust, sprays, pollens or volatile chemicals is typically confined to the exposed surfaces of the hands, arms, face and neck. The first attack often originates from direct handling of an allergen, but recurrences may be seen despite avoidance of direct contact. There is great diversity in the nature of airborne reactions, which may be irritant, allergic, phototoxic, photoallergic and contact urticarial [1]. Some agents may cause more than one type of reaction. Hence, phosphorus sesquisulphide may cause both contact urticaria and allergic contact dermatitis [2]; *Parthenium* may cause both allergic and, rarely, photocontact dermatitis [3]; and formaldehyde can cause irritant and allergic dermatitis, and contact urticaria [1].

Lists of airborne allergens have been published and updated by Goossens *et al*. [1,4,5]. Plants, natural resins and woods are among the commoner causes of this distribution of contact allergy. In the USA, the oleoresins of ragweed commonly cause allergic contact dermatitis. A similar pattern is found in the UK during the summer months from other Compositae weeds [6,7] which, when they occur in other parts of the world, also cause an 'airborne' pattern of dermatitis [8,9]. In India, *Parthenium* has been associated with widespread epidemics of severe dermatitis and even deaths [10].

Dermatitis from wood dust is common in carpenters and cabinet-makers. It normally starts on the eyelids or the lower half of the face, and is often preceded by a period of itching. Swelling and redness spread to the neck, hands and forearms. By the time the patient attends for treatment, a diffuse dermatitis may have developed, distinctly limited at the margins of the sleeves and collar. Because of the accumulation of dust and sweat, the elbow flexures and the skin under a tight collar are often lichenified. Cabinet-makers frequently develop a genital dermatitis from accumulation of sawdust on the clothes during sawing and planing, and by hand contact. Swelling and redness of the eyelids may be the only signs of recurrence. Exotic woods are more likely to sensitize than fir or spruce, although the latter may cause dermatitis in patients sensitive to colophony [11], turpentine and *Myroxylon pereirae* (balsam of Peru). Dermatitis in woodworkers may additionally be caused by liverworts [12] and lichens on the bark of trees [13]. Colophony can also give an exposure pattern of dermatitis from its presence in solder fluxes, paper dust, polish and linoleum flooring [14,15].

Resin systems, particularly epoxy resins, including the more volatile amine hardeners, may induce an airborne pattern of allergy, especially in the occupational setting. Other causes of this pattern include perfumes, metals, many industrial and pharmaceutical chemicals, pesticides, fungicides, animal feed additives, textile dyes and matches [5]. Equivalent patterns of airborne dermatitis may be seen with type I allergens, such as house-dust mite antigens in atopics [16].

Photocontact allergy causes a similar distribution, and is discussed on p. 20.29.

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Mucous membranes

Application of DNCB to the oral mucosa may, in some cases, induce a low degree of contact sensitivity, but more often an immunological tolerance to later sensitization [1]. Similarly, prior exposure to nickel and chromate in orthodontic appliances seems to reduce the risk of later sensitization [2,3].

Contact inflammation of the mucous membranes is not common, and is often secondary to skin sensitization with the same substances. Reactions may be allergic or irritant in nature. Both immune and non-immune immediate-type contact urticarial reactions may occur.

The skin and mucous membranes differ in both anatomy and environment. In the mouth, except on the gums and hard palate, there is no horny layer with a barrier function and storage capacity. There is no lipid secretion but instead a continuous flow of saliva, which washes away foreign substances. Penetration of water-soluble substances is rapid. It is not known whether these differences are relevant to the paucity of allergic contact reactions in mucous membranes. The oral mucosa of sensitized animals has been shown to have an identical cellular phenotype and cytokine expression as the skin when challenged by the allergen [4].

Allergic reactions in the mouth show erythema and swelling but vesicles are rarely seen, except on the vermilion border. The symptoms are soreness and burning, and itching is uncommon. Eczematous reactions of the adjacent skin may occur, and these may be the only signs of an allergic contact dermatitis.

The burning mouth syndrome is an entity in which psychological factors are important. Sometimes, allergens such as metals, rubber, food additives and flavourings have been identified and the symptoms relieved by contact avoidance [5–7], but the return from investigations is often disappointing [8,9].

Orofacial granulomatosis has been associated with contact allergy to food additives and some of these individuals may obtain a favourable response, often only partial, to dietary elimination of the identified allergens [10].

Dentures are frequently incriminated as the cause of oral symptoms and lesions. Allergic reactions to denture materials have been found in some cases [11,12], due to traces of residual acrylic monomer following wearing of new dental appliances or following their repair with cold-curing resins. Most cases are caused by irritation from ill-fitting dentures. Candidal infection may also play a role [13], and is often present in angular cheilitis. Acrylate allergy has also been seen rarely after dental restorative work [14].

Mercury from amalgam fillings may cause local mucosal [15] or lichenoid [16–18] reactions; perioral dermatitis after dental filling may also occur, as may generalized skin eruptions [19]. Contact reactions have also been reported due to other metals [16–18,20], especially gold [16–18,21,22] used in dental restorative materials, and nickel and palladium in orthodontic appliances. There remains debate as to whether materials sensitize via the mucosal route [4,23] or whether there is only elicitation of pre-existing sensitivity (in those already sensitized) and the induction of tolerance (in those who have not already been sensitized) [3].

Toothpaste flavours can cause stomatitis, glossitis, gingivitis, cheilitis and perioral eczema [24].

The nasal mucosa may react to medications containing antibacterial agents and antihistamines. Corticosteroid allergy from nasal sprays has been reported, with one case of associated perforation of the nasal septum [25,26]. In the conjunctivae, various drugs are reported to have elicited allergic contact reactions, for example β-blocking compounds for the treatment of glaucoma [27], antibiotics, and preservatives in both drugs and contact lens solutions [28].

Genital mucous membranes may be affected by allergens causing dermatitis on the surrounding skin, particularly from medicaments [29,30].

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Secondary patterns

Contact dermatitis may start at one site, but commonly other sites are subsequently involved, and sometimes several regions simultaneously. By the time the patient has been sensitized, many body regions may have been in contact with the allergen, some indirectly by contamination from the fingertips. Heavily contaminated areas, or those that were exposed last, tend to be the ones to react first, other sites flaring later. This has been shown experimentally with poison ivy [1], and is an obvious clinical feature in *Primula obconica* dermatitis. Regions close to the primary site of allergic contact dermatitis are easily contaminated by the allergen.

Such a simple explanation cannot account for the frequent spread of dermatitis from feet to hands and vice versa. This occurs primarily in constitutional eczema but may occur in contact dermatitis. Sometimes, a common allergen is found that could explain occurrence at both sites, yet often it is a pattern of secondary spread. Epstein [2] suggested that skin protein might have a regional specificity, identical for fore and hind legs, i.e. 'four-hoof disease'; Parish *et al*. [3] suggested 'auto-allergy'. No precise explanation exists.

Because of the similarity to Darier's trichophytids and eczematids [4], dissemination to distant regions has been termed an 'id-like' spread. Local aggravation may precede secondary spread by several days.

The pattern of spread is largely determined by the primary site. Dermatitis of the hands commonly spreads to the arms and face; dermatitis of the feet tends to spread to the legs and hands.

Many patients with stasis dermatitis have secondary eruptions by the time they are seen by a dermatologist, and are referred because of the alarming dissemination. This may be due to an 'id' reaction or secondary contact dermatitis. Dissemination from leg eczema commonly involves the arms and shoulders in a patchy fashion before becoming generalized, often beginning with pruritus and sometimes progressing to generalized erythroderma. On the face, diffuse redness and oedema are common. Eyelid dermatitis or a diffuse dry dermatitis of seborrhoeic type may be seen.

Severe nickel allergy may induce extensive patchy eczema, which is slow to respond to treatment, and this will not settle unless strict nickel avoidance measures are undertaken.

Contact allergy to components of topical treatments presents special difficulties. The allergen may be an active ingredient or an excipient. If the dermatitis spreads further in spite of treatment, it may wrongly be assumed to be an endogenous eczema. In contact dermatitis caused by topical steroid preparations, the action of the steroid may partially suppress the local reaction. The sensitivity becomes clinically manifest only as 'failure to heal' of the

original eczema, or with the development of a secondary eruption.

Constant alertness is therefore a prerequisite for the diagnosis of allergic contact dermatitis in which dissemination is a dominant feature. Patch tests should be delayed until the acute eruption has settled.

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Systemically reactivated contact dermatitis [1]

Systemically reactivated allergic contact dermatitis, where ingestion or other systemic exposure to a contact allergen takes place in an already sensitized person, may result in a number of different patterns of skin eruption. The threshold of reaction varies in each individual case and depends on the dose given and the level of sensitivity. Reactions may occur not only after ingestion of the primary allergen but also after ingestion of secondary (closely related) allergens [2].

The most frequent types of reaction are focal flares of previous patch tests and sites of previous dermatitis [3], vesicular hand eczema, or much more widespread eczema and erythema, sometimes with additional urticarial features [4–7]. In severe cases vasculitis [8], erythema multiforme [9] and systemic upset may occur [1,10]. Involvement of the eyelids, body folds and buttocks induced by oral challenge with nickel in allergic subjects led to this particular reaction being labelled the 'baboon syndrome' [11]. This is often also the pattern seen in patients with a mercury exanthem [12]. In some patients following widespread reactions, and in others following attempts at 'desensitization', the level of patch-test reactivity appears to be reduced [10,13].

Probably all contact allergens can cause systemic reactions, provided the patient has a sufficient degree of pre-existing sensitivity and the dose administered is sufficiently large [14]. The causes are many, and include medicaments that may have been given not only by mouth but also parenterally, rectally, intravesically or as an inhalant. Dietary causes include metals, plants and spices.

Systemic contact dermatitis from medicaments has decreased as a result of reduced use of topical sensitizers such as the antibiotics streptomycin, sulphonamides and penicillin, and topical antihistamines such as promethazine. Nevertheless, exposure to other topical and systemic medicament sensitizers continues to give problems. Standard allergens responsible for these reactions include neomycin, quinolines [10], local anaesthetics [15], ethylenediamine and corticosteroids. In subjects with contact allergy to ethylenediamine, parenteral administration of aminophylline (which contains ethylenediamine) has resulted in widespread eczematous eruptions [16]. Ethylenediamine is structurally related to some antihistamines (e.g. hydroxyzine) and may therefore also trigger a systemic flare [2]. A positive patch test to tixocortol pivalate is an indication of hydrocortisone allergy. Systemic administration of hydrocortisone has induced recurrence and extension of dermatitis [17]. Furthermore, administration of parenteral adrenocorticotrophic hormone (ACTH), thereby raising endogenous hydrocortisone, has resulted in flares in hydrocortisone-allergic individuals [17]. Other systemic steroids have also induced systemic contact dermatitis [18,19]. Inhalation of budesonide has been associated with reactivation of positive patch tests, and continued exposure to budesonide from this source may therefore maintain dermatitis in sensitized subjects [20]. The reader should consult the more specialized literature for a full list of the many other medicament causes reported [21,22].

Persistence of dermatitis, especially vesicular hand eczema in metal-allergic subjects, has been blamed on dietary intake, particularly nickel [23]. Traces of metal dissolved by cooking acid or salty food in stainless steel may be of consequence in the persistence of dermatitis due to metals, such as chromium, nickel and cobalt [24–27]. However, the role of ingested or dietary nickel in hand dermatitis remains controversial [28–30], especially as a percentage of patch-test-negative patients also appear to have flares of vesicular hand eczema following oral metal challenge [31], and the challenge dosage has been artificially high. Nevertheless, dietary restriction of nickel helped about one-quarter of selected nickel-sensitive patients with resistant dermatitis [27].

Balsam of Peru [32], garlic, certain ingested food colours, preservatives and antioxidants have also been reported to cause flares of vesicular hand eczema [33,34].

Flares of dermatitis and perianal pruritus may occur in patients undergoing desensitization to *Toxicodendron* spp. [35], and systemic contact dermatitis may be induced following ingestion of cashew nuts, whose shells contain an oleoresin closely related to that of *Toxicodendron* spp. [36]. Similar problems may also occur after eating the fruit of the *Ginkgo* tree [37] and from other herbal medicines [38].

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Cutaneous reactions to implanted metals (see p. 20.44)

Photoallergic contact dermatitis [1]

Certain substances are transformed into irritants or sensitizers (photosensitizers) after irradiation with UV or short-wave visible radiation (280–600 nm). The wavelength required is usually, but not always, the same as the absorption spectrum of the substance [2].

The initial phase of all photoreactions is dependent upon absorption of photons by light-sensitive chemicals. Following absorption, a higher state of energy (excited state) is induced in the molecule (photoactivation). Some of the energy may be released as fluorescence, i.e. emission of radiation at a longer wavelength, but not all fluorescent substances are photosensitizers. Alternatively there may be phosphorescence, heat or other energy transfer to another molecule, or photochemical alteration of the molecule [3].

Photoactivation is a physical phenomenon and may occur *in vitro*. When it occurs *in vivo* the activation may have a phototoxic (non-immunological) or a photoallergic (immunological) action. The photoactivated molecules may be transformed into new substances capable of acting as irritants or haptens. Photoallergic reactions are based on immunological mechanisms, and can be provoked by UV radiation only in a small number of individuals who have been sensitized by previous exposure to the photosensitizer. The reaction to a photoallergen is based on the same immunological mechanism as contact allergic reactions. In guinea pigs the sensitivity can be transferred with mononuclear cells [4].

Newly formed haptens may, by virtue of the excited state and free-radical formation, be able to combine chemically with other substances, for example protein, to produce a full antigen. The basic mechanisms of photosensitization have been reviewed by Thune [5]. The photoallergen tribromosalicylanilide has been shown to change into dibromosalicylanilide and monobromosalicylanilide [6,7], and with sulphonamides it has been suggested that an oxidation product is formed [7–9]. Some photosensitizers may, in the presence of UV radiation, produce only short-lived reactive molecules [10].

Several photoallergic substances simultaneously produce phototoxic reactions when applied in high concentrations and with a sufficient amount and type of radiation. Thus, in an individual case, the two reactions may be clinically indistinguishable, although it is reported

that phototoxic and photoallergic reactions can sometimes be distinguished histologically [11].

The allergens

The first significant recognized problems from photoallergy were related to the use of chlorinated salicylanilides in germicidal soaps in the early 1960s, with many thousands being affected [12]. Regulatory elimination of these photoallergens resulted in the disappearance of the allergy, but some affected individuals became persistent light reactors [12]. By the mid-1980s the most important photoallergen was the fragrance musk ambrette whose use is now prohibited [13,14]. In the present era, UV-absorbing chemical filters are virtually the only substances causing clinical photoallergic problems in the UK [15,16]. Exposure to UV filters is becoming more common as a result of their increasing use not only in sun products but also in cosmetics, including hairsprays. Their presence in cosmetics may be not only to prolong shelf-life but also to support 'antiageing' claims for the products. These UV filters can also induce conventional contact allergy. Nevertheless, many photocontact allergens have been identified with varying degrees of confirmatory evidence, and these are summarized below.

1 UV filters, including *p*-aminobenzoic acid and its derivatives, cinnamates, benzophenones and dibenzoylmethanes [16–22]. Benzophenone 3 (oxybenzone) appears to be the most frequently identified photoallergen since the 1990s [16,18,20].

2 Perfumes: musk ambrette [23] and 6-methyl coumarin [24], although now prohibited in Europe and the USA, caused significant problems in the 1980s, but these products have now virtually disappeared.

3 Halogenated salicylanilides: tribromosalicylanilide and tetrachlorsalicylanilide, used as antibacterials in soaps and detergents, caused many outbreaks of photosensitive eczema in the 1960s [4,6,12,25]. Fentichlor (bis(2-hydroxy-5-chlorphenyl)sulphide and bromosalicylchloranilide) is used as a topical antifungal agent in Australia and is used domestically in Sweden. It is a known photosensitizer [26].

4 Topical non-steroidal anti-inflammatory agents [27,28], especially ketoprofen, which may cross-sensitize with the UV filter oxybenzone [29–31].

5 Phenothiazines (tranquillizers causing occupational dermatitis in hospital personnel, topical antihistamines, insecticides) [32,33].

6 Sulphonamides used for topical treatment [2,33].

7 Bithionol and hexachlorophene in toilet soaps, shampoos and deodorants [34,35].

8 *N*-Butyl-4-chlorsalicylamide (Jadit—antifungal) [9].

9 Eosin: used to be present in lipstick [36].

10 Quinines: hair tonic, quinidine, quindoxin and olaquindox used in animal feeds [37–43].

11 Thiourea (in design paper) [44,45].

Clinical features

Photoallergic reactions can resemble sunburn, but usually show the same spectrum of features seen with allergic contact dermatitis (see p. 20.18). The dermatitis is localized to exposed areas of the skin, usually with well-demarcated margins where the skin is covered by clothing, e.g. at the collar and 'V' of the neck, below the end of the sleeves and trouser leggings. The area below the chin is usually spared. The most distinctive sign is the exempt 'Wilkinson's triangle' behind the earlobe [6,12]. There may nevertheless be some spread to covered sites. Asymmetry may result from increased UV exposure to one side of the body, for example those who drive with the vehicle windows open.

Photoallergy to UV filters in cosmetics may be clinically identical to that seen from conventional allergy to cosmetics (see p. 20.56). It may be widespread when related to liberal use of sunscreen agents. Furthermore, it may simulate sunburn and other causes of photosensitivity.

Musk ambrette, used in men's aftershave lotions and colognes, was the cause of a distinctive patchy pattern of photosensitivity on the face [13,14,23].

In some individuals, photoallergic reactions may progress to produce a light sensitivity that may persist a long time after the elimination of the sensitizer. This is known as persistent light reaction [46]. The phenomenon has been reported with many different substances, including chlorpromazine [33], halogenated salicylanilides [12,26,47], musk ambrette [13,48], promethazine hydrochloride [49,50], ketoprofen [51], quindoxin [40] and olaquindox [41,42]. This chronic photosensitive dermatitis presents as chronic eczematous changes on light-exposed areas with or without spread elsewhere [52]; on monochromator testing, these patients have abnormal responses to UV radiation with a shift to UVB sensitivity [53].

Photoallergy may simulate other photosensitive dermatoses and airborne contact allergy, and vice versa. Furthermore, there may be a combination of these disorders in the same person. It is also important to recognize that photoallergy may sometimes fail to follow the typical pattern of sparing of light-protected sites, and airborne contact allergy may paradoxically induce the classical photosensitivity distribution. Combined airborne and photoaggravated contact allergy is seen particularly with Compositae [54] and lichens [55]. A similar pattern of dermatitis may also be seen in patients sensitive to Colophonium, pine and spruce. It is therefore important to identify every potential component of these clinical presentations by screening for contact allergy using patch tests (especially to plants), for photoallergy with photopatch tests, and also for photosensitivity using phototesting.

Patients with established photosensitivity who have a flare of their dermatitis may have reacted to an increase in light levels or re-exposure to their primary or a cross-

reacting allergen by airborne contact. Alternatively, they may have developed a secondary allergic or photoallergic contact sensitivity to their sunscreen [56] or to one of their other medicaments.

The disorder of chronic actinic dermatitis (see Chapter 24) [57] may be associated with contact allergy, particularly to Compositae. Often there are multiple contact allergies. Phototesting reveals abnormal results but photopatch tests to Compositae and other allergens are generally normal. Nevertheless, persistent light reactivity following photoallergy may progress to chronic actinic dermatitis.

The intensity of response to phototoxic and photoallergic agents depends upon a number of factors:

1 nature and concentration of the substance applied;
2 duration of exposure to the substance;
3 percutaneous absorption;
4 intensity and wavelength of the radiation;
5 duration of radiation exposure;
6 radiation absorption in the skin, depending on the thickness of stratum corneum as well as the amount and distribution of melanin;
7 extraneous matter and secretions on the skin;
8 humidity.

Avoidance

Photoallergy in the UK is now only likely to occur to UV filters or very rarely to imported perfumed materials containing musk ambrette, which should be easy to eliminate. Once photoallergy has been demonstrated to a UV filter, the patient should be informed of the INCI (International Nomenclature of Cosmetic Ingredients) name and synonyms of the material to which they are sensitive. UV filters relying totally on opaque/reflectant micronized titanium dioxide and zinc oxide will be free of chemical UV-filtering agents, and can be used for coexistent photodermatoses in those allergic to chemical UV filters.

Investigation

Investigation of photoallergy by photopatch tests is described on p. 20.109.

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Non-eczematous responses [1]

Well-recognized non-eczematous responses include contact urticaria, erythema multiforme-like, purpuric, lichen planus and lichenoid, lymphomatoid, pigmented, leukoderma, granulomatous, onycholysis and systemic.

Contact urticaria

Clinically this presents as an immediate wealing eruption at the site of contact, and may in some instances be associated with systemic features. The syndrome of contact urticaria is discussed in detail on p. 20.121.

Erythema multiforme-like reactions [2,3]

The characteristic presentation is that of a spreading eruption from the primary site, which may also involve distant sites. It has been called 'urticarial papular and plaque eruption' by Goh [4]. The rash has features of erythema multiforme, in that single lesions appear target-like, but the distribution is not necessarily acral as in classic erythema multiforme nor is the histology characteristic. There is sometimes a vasculitic purpuric element to the rash and, although the mechanism is unknown, it appears to represent an immune complex (type III) reaction as well as a delayed hypersensitivity (type IV) reaction. Many of these patients will give a very strong patch-test response to the causative allergen, often accompanied by a flare of their dermatosis.

It is often precipitated by strong allergens, such as quinones in exotic woods [2,5,6], and *Primula* [7,8]. Contact with other plant materials may cause this reaction, including poison ivy (*Toxicodendron* spp.) [9,10] and tea tree oil [11]. Ingestion of herbal remedies containing *Toxicodendron* [12] and sesquiterpene lactones [13] by sensitized persons has also induced erythema multiforme-like eruptions.

Topical medicaments, especially antimicrobials [3,14,15], corticosteroids [16–18] and anti-inflammatories [19–21], have all caused erythema multiforme-like eruptions. A nitroglycerin patch has also induced erythema multiforme at the applied site, with a secondary spread eruption [22]. Medicaments applied to mucosal surfaces may sensitize and may also be absorbed, causing systemic erythema multiforme-like reactions, for example sulphonamide in vaginal creams [23] and ocular preparations [24].

p-Phenylenediamine in hair dye [25] and temporary tattoos [26] and IPPD [27] in rubber and clothing dyes [28,29] are also recognized causes of this reaction pattern.

Purpuric reactions

Originally described from khaki uniforms [30], where the cause was not established, purpuric reactions are uncommon and have mostly been described recently from textile azo dyes [31–33] and also textile resins [31]. The presence of the rubber chemical IPPD in boots, diving suits, bandages and brassières is also reported as causing allergic contact purpura [34–38]. Purpuric reactions have also been described with allergy to diphenylthiourea in heat retainers [39], *p*-phenylenediamine in black hats [40] and as a secondary spread eruption from balsam of Peru [41].

Lichen planus and lichenoid reactions

These have been described following contact with colour developers used in the photographic industry [42,43]. The developers are *p*-phenylenediamine derivatives. New chemicals have been introduced to replace older more sensitizing ones, not always successfully.

p-Phenylenediamine-induced allergic lichenoid contact reactions from hair dye were recently reported from India [44]. We have also seen this pattern from hair dye in Asians in the UK. *Primula obconica* allergy has also produced a lichen planus-like eruption of the hands [45].

Lichen planus-like reactions of the buccal mucosa may represent allergy to metals [46–48] and other materials used in dental treatments [49,50]. Some patients have had improvement in their lichen planus following the removal of some or all of their fillings [51–54]. Oral lichen planus is more apparent where there is evidence of corrosion [55] and the aetiology of lichenoid lesions is likely to be multifactorial [53]. The histology may show features compatible with lichen planus or a non-specific chronic superficial perivascular dermatitis [1].

Lichenoid reactions to tattoo pigments are discussed in the section on granulomatous reactions below.

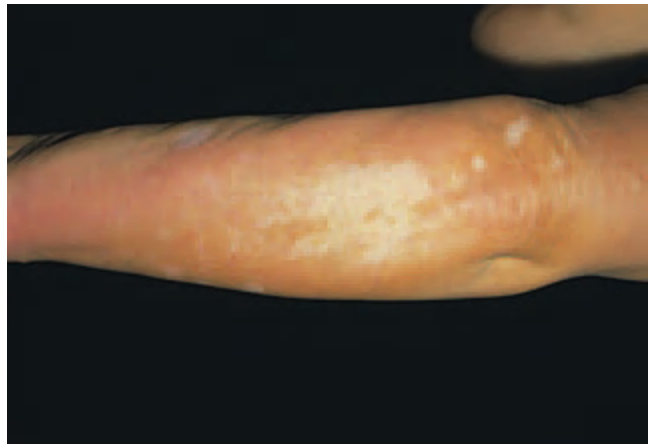

Fig. 20.12 Koebnerization of vitiligo as a result of previous *Primula obconica* allergy.

Lymphomatoid eruptions [56]

Occasionally, contact dermatitis presents with cutaneous lymphoma-like plaques and histopathology suggestive of mycosis fungoides [56]. These have been seen at the site of ear piercing in those sensitized to gold [57,58]. The reaction, however, tends to persist for months even when contact with metallic gold is avoided. The patch-test reaction to gold sodium thiosulphate in these patients is papular and very strongly positive. The histology of both the papular eruption and the patch-test reaction shows a dense T-cell infiltrate [59]. Other reported causes include matches [56], nickel [60,61], dental amalgam [62], medicament components [63,64] and isopropyl-diphenylenediamine [65].

Pigmented dermatitis [66]

Contact dermatitis may induce post-inflammatory hyperpigmentation, although distinctive patterns of pigmented dermatitis without a lichenoid appearance or histopathology are recognized. These patterns are much more commonly seen in the Far East. The first such cases of pigmented contact dermatitis in Europe were described by Osmundsen [67]. The hyperpigmentation occurred mainly on covered areas with or without dermatitis, and was traced to an optical whitener in washing powder, Tinopal CH 3566. Another outbreak was described by Ancona-Alayon *et al*. [68] in textile workers and was traced to contact with Naphthol AS, an azo-dye coupling agent. Cases also occurred on covered sites from garments in Japan [69], and this led to a systematic search for other causes of textile dermatitis. Chemicals implicated included the fungicide Biochek 60, an impurity of colour index blue CI Blue 19, and textile finishes [66].

Pigmented cosmetic dermatitis [70] is seen mainly in oriental women. Slight dermatitis may precede or coexist with the hyperpigmentation, which occurs mainly on the cheeks. The allergens associated with this have been found to be fragrances and pigments, especially D and C Red 31 and an impurity, and Yellow no. 11 in cosmetics and soaps [70,71]. Oral ingestion of flavourings allied to the fragrances, such as cinnamon, may cause not only a focal flare but also diffuse hyperpigmentation on the body [70].

Environmental agents, possibly pesticides and fungicides, have sometimes been thought to be a factor. In one study, a majority of pigmented dermatitis cases were found to have positive patch tests to chlorothalonil used as a fungicide in banana plantations. It is used in other parts of the world as a preservative of wood and paint [72].

Depigmented lesions [66]

Irritant and allergic contact dermatitis can induce hypopigmentation as a post-inflammatory effect or by koebnerization of vitiligo. This has to be distinguished from the direct melanocytotoxic effect of certain quinones and substituted phenols, which most commonly presents as an occupational vitiligo (Chapter 21). This effect occurs independently of their sensitizing potential.

A number of cases of persistent leukoderma following allergic contact dermatitis have been reported. In some it has been difficult to be certain whether the cause was post-inflammatory or melanocytotoxic. In particular, it is reported from *p*-phenylenediamine in hair dyes [73,74] and temporary tattoos [26,75], methacrylates [76], perfumes [77], *Alstroemeria* [78] and chloroxylenol [79]. *Primula* allergy has resulted in extension of pre-existing vitiligo in the sites affected by the dermatitis (Fig. 20.12). The allergic reaction to primin was followed by vitiligo at the positive patch-test sites [80].

Granulomatous reactions

Some topically applied metal salts produce non-allergic granulomatous skin reactions, for example zirconium in deodorants [81]. Granulomas occurring at the site of previous immunization with aluminium-adsorbed vaccines, or following the use of parenteral hyposensitization preparations, are often due to aluminium allergy [82–85]. Patch tests are positive either to aluminium chloride 2% aqueous or an empty Finn chamber [84]. Granulomatous reactions have also been found in association with allergy to gold in earrings [86].

Pigments in tattoos may cause allergic granulomatous and lichenoid reactions [1]. Metal salts are the usually identified culprits: mercury (red colour), chromium (green colour), cobalt (blue colour) and cadmium (yellow colour) [87]. However, in our experience most reactions are in the red areas, and patch testing with mercurials is negative, suggesting another cause. Unfortunately, tattooists are extremely secretive about the nature of the pigments they use.

Onycholysis

Onycholysis may be the only presenting feature in contact dermatitis to hairdressing chemicals. We have seen it as an isolated finding in nail varnish allergy, but more commonly it is found in women sensitized to multifunctional acrylates in false nails [88], when there may be concomitant dystrophy and persistent paraesthesiae [89].

Systemic non-eczematous

Extensive allergic contact dermatitis is not uncommonly associated with systemic upset from the metabolic effects of the disorder itself and secondary infection, particularly in those who are erythrodermic. Sultones occurring as impurities in lauryl ethyl sulphate have in the past caused several outbreaks of contact dermatitis characterized by intense oedema accompanied by general malaise [90,91].

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Differential diagnosis

It should always be remembered that allergic contact dermatitis can mimic or complicate other types of eczema and other dermatoses. Sensitization to topical applications may be a complication of almost any dermatosis that leads to specialist referral. The diagnostic problem differs according to the site of the dermatitis. Patch testing will often be required before confirming the cause in its entirety.

Head. Allergic and photoallergic conditions of the face must be distinguished from a number of disorders.

Atopic eczema may be confined to the face, especially around the eyes and particularly the medial aspects. A

previous or family history of infantile or childhood flexural eczema, asthma, allergic conjunctivitis, hay fever or immediate skin reactivity to animals and certain foods may point to the patient's atopic status. Associated flexural eczema, ichthyosis or xeroderma may be features. Multiple positive radioallergosorbent (RAST) or prick tests to common environmental allergens are used by some to confirm an atopic diathesis.

Seborrhoeic eczema, which commonly starts around the alae nasi, is usually accompanied by dandruff or seborrhoeic eczema in the scalp and eyebrows, and by blepharitis; involvement of the presternal region, the external auditory meatus and the retro-auricular areas is common. Older patients frequently develop a flexural pattern of seborrhoeic eczema.

Psoriasis is normally easy to distinguish as there is evidence elsewhere on the body, although psoriasis in and around the ears and scalp margins may mimic a dry scaly contact dermatitis.

Cellulitis and erysipelas may be difficult to distinguish from an acute allergic contact dermatitis, but a background of pyrexia and systemic symptoms is generally the rule.

Angio-oedema, especially of the eyelids, is notoriously difficult to differentiate from contact allergy. The swelling would be expected to resolve within 24–48 h. Patch tests are helpful in reaching a conclusion.

Dermatomyositis may initially appear identical to allergic contact dermatitis, and we have seen and patch tested such cases. The purple/mauve hue of the eyelids is a major clue, and the hands, fingers and nail folds must be carefully examined. The characteristic associated muscle pains and weakness may not always be present.

Herpes simplex may be simulated by *Primula obconica* dermatitis on the face and elsewhere [1]. Haemorrhage into the blisters seems more common with the allergy.

Photosensitivity, including reactions to ingested drugs, cannot always be distinguished from photoallergic contact dermatitis, and may also simulate contact dermatitis from airborne sensitizers.

Hands and arms. Allergic and irritant contact dermatitis, and constitutional eczemas, may only be distinguishable by a careful history and patch testing. They commonly coexist. Superimposed irritant contact dermatitis from home and work exposures is common.

Indicators of atopic eczema are discussed above. The eczema may be confined to the hands, especially in later life. A nummular pattern of eczema is commonly constitutional but may be a feature of irritant and allergic contact dermatitis, particularly from chromate in cement.

Recurrent vesicular eczema of the palms may indicate constitutional pompholyx, although contact allergy can produce an identical appearance. Some contact allergies, for example from IPPD [2] and 1,2-benzisothiazolin-3-one, seem to induce a palmar pattern of dermatitis preferentially. *Primula* allergy often induces a haemorrhagic vesicular dermatitis of the palmar surfaces and fingertips. The relationship of pompholyx to ingestion of contact allergens, especially nickel, by sensitized subjects is controversial [3–5]. There is evidence that oral intake of balsams and garlic can induce palmar vesicular eczema in patch-test-positive subjects [6,7]. Tinea pedis can induce palmar pompholyx as an id eruption. Papules and vesicles on the hands and fingers are a feature of scabies, and this disorder must always be excluded by a careful history and examination for diagnostic burrows. The condition is normally associated with a more generalized pruritus and rash.

Psoriasis of the palms and hyperkeratotic eczema are often confused. Differentiation is sometimes somewhat arbitrary. Often, hyperkeratotic plaques are localized at points of contact with tools for example, but not all frictional hyperkeratosis is necessarily an expression of psoriasis. The possibility of psoriasis koebnerizing into areas of contact dermatitis should not be forgotten.

Tinea manuum is classically unilateral or asymmetrical. An inflammatory edge may be seen extending on to the dorsum of the hand. Nail dystrophy may be an association. Unilateral and bilateral low-grade scaling of the palms should be scraped for mycology. These appearances may be complicated by a vesicular id eruption.

Lichen planus confined to the palm can be difficult to distinguish from a palmar dermatitis, but normally there are more typical changes elsewhere on the skin or in the mouth. Lichen planus-like contact reactions from colour developers may occur on the hands and forearms [8].

Porphyria cutanea tarda may simulate a bullous contact dermatitis such as plant dermatitis. The formation of bullae after minor trauma and the presence of white atrophic scars and milia suggest the diagnosis, which can be confirmed by porphyrin assays.

Flexures and anogenital region. Seborrhoeic eczema and psoriasis may preferentially involve the flexures and be difficult to distinguish from allergic contact dermatitis, but there is often evidence of these conditions elsewhere.

Tinea is usually asymmetrical or unilateral and has an inflammatory edge. Scrapings for mycology should be taken from inflammatory flexural rashes. The typical coral-pink fluorescence under Wood's light will help to distinguish erythrasma from other flexural rashes.

Legs and feet. Persistent varicose eczema is an indication for patch testing as it is often complicated by sensitivity to topical medicaments and dressings, including rubber in support bandages and stockings.

Vesicular and vesiculobullous areas may occur in tinea pedis, and mycological specimens should be taken if this is suspected. In common with the hands, scabies affecting

the feet may induce a papulovesicular eruption and must be considered in the differential diagnosis.

Trunk. Papular drug eruptions or scabies may sometimes be difficult to distinguish from nickel or textile dermatitis. Systemic diseases such as dermatomyositis and mycosis fungoides sometimes show eczematous features.

Exposed sites. Photosensitive dermatoses and drug eruptions must be distinguished from contact allergy to volatile and airborne materials. Although not always reliable, sparing in certain sites—behind the ears and under the chin—might indicate a photosensitive eruption. Nevertheless, some patients will require thorough investigation with phototesting, patch and photopatch testing before a diagnosis can be made.

Generalized. Erythroderma is rarely primarily due to contact allergy, and other causes such as drug eruptions, constitutional eczema and psoriasis should be considered; the possibility of secondary contact allergy from topical medicaments must not be forgotten. Skin biopsy may be helpful in such cases.

Scabies can easily be overlooked as a cause of a widespread pruritic rash, especially as skin lesions may look classically eczematous. Careful examination of the hands, feet and genitals for diagnostic lesions is required.

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Allergic contact dermatitis to specific allergens

Metals

Nickel [1–8]

Chemistry. In common with cobalt, but unlike chromium, the metal itself sensitizes and is, in practice, the most frequent source of sensitization [7]. Most salts, for example nickel chloride ($NiCl_2$) and nickel sulphate ($NiSO_4$), are readily soluble in water and sweat and have strong sensitizing properties. Some oxides (e.g. Ni_2O_3) and the hydroxide ($Ni(OH)_2$) can elicit contact dermatitis, but heated NiO does not. This compound is insoluble even in hydrochloric acid.

Table 20.3 European Union Nickel Directive (summary).

1 After piercing: posts, rings or other items used during the period of re-epithelialization shall not *contain* more than 0.05% nickel
2 Objects intended to be used in direct and prolonged contact with the skin shall not *release* more than 0.5 μg/cm^2/week of nickel. Examples include jewellery, watches, buttons and zips

Incidence and prevalence. Nickel is the most frequent contact allergen, and sensitivity is more common in women than in men [9]. The prevalence of nickel sensitivity recorded in a patch-test clinic is between 15 and 30%, and is influenced by the relative number of females tested [10–12]. Nickel is the most usual cause of contact dermatitis in women. All age groups are affected, but the prevalence of nickel sensitivity among females tends to rise from 10 years of age onwards [13]. The incidence of nickel dermatitis in Denmark varied with the total imports of nickel during and after the Second World War [14], which suggests that the level of sensitivity is determined by the total nickel exposure in the environment. In Denmark it was found that the prevalence of nickel dermatitis in the general population was 11.1% in women and 2.2% in men. Sensitization to nickel was found in 14.8% of those with pierced ears and 1.4% of those who had not had their ears pierced, confirming that ear piercing is a significant risk factor for the development of nickel sensitivity [15]. A previous study in Finland found the overall prevalence in the general population was 4.5%: 8% in women and 0.8% in men [16].

This female predominance is not universal. In Kuwait, nickel allergy was commoner in males [17], and in Nigeria [18] and Japan [19] the prevalence was similar in both sexes in patch-tested patients.

The prevalence may be higher in some occupational groups, for example hairdressers, in whom studies have shown that 27–38% are nickel allergic [20,21].

Legislation was introduced in Denmark in 1990 with the intention of controlling the use of nickel-releasing objects in contact with the skin. In 1994 the European Union passed regulations based on the Danish legislation (Table 20.3). These laws only relate to metallic items in prolonged and direct skin contact, for example jewellery, clothing items and spectacle frames. Other metallic materials with which there is relatively short-term contact (e.g. coins, keys and cutlery) have been excluded from the legislation. The level of allergy to nickel identified in under-18s attending for patch tests in Denmark has dropped considerably, from 24.8% in 1985–86 to 9.2% in 1997–98 [22].

Occurrence [23]. The commonest sources of metallic nickel are alloys and plated objects [24]. Sensitization is chiefly the result of frequent skin contact with corroded objects containing nickel [25]. A high rate of corrosion has been documented from nickel-plated items, nickel-iron, German silver, coin and several other alloys [25]. Chromium-plated metal is often first nickel-plated, and after long use the nickel may reach the surface, for example on water taps. Most stainless steels contain nickel but are incapable of releasing sufficient quantities to elicit contact dermatitis. Quantitative studies indicate that repeated exposure to occluded metal items releasing nickel at a rate greater than 0.5 μg/cm^2/week involves a significant risk of nickel sensitization [26,27], but thereafter very small amounts of nickel are sufficient to elicit dermatitis in sensitized persons.

Jewellery and metal components of clothing are the usual sources of nickel in prolonged contact with the skin. Transient but potentially frequent and repeated exposure may occur from handling coins, keys, scissors, knitting needles, thimbles, scouring pads and other metallic tools and utensils. Most silver coins, including the new 1 and 2 € coins, contain nickel and there is debate as to whether exposure might be a risk factor in those already sensitized to nickel [28–30]. Platers and some metal machinists are necessarily at risk of occupational nickel allergy [1]. Other sources include pigments in glass, pottery and enamel, electrocautery plates [31] and even soaps [32] and detergents [23]. Nickel has been identified in some eye shadows and mascaras [33,34].

Systemic exposure may take place from the diet. Certain foods and plants [35] contain much higher concentrations than others [36], as can particular sources of domestic water [37], and nickel may also be a contaminant in fertilizers [38] and fungicides. Stainless steel saucepans release negligible nickel, but cooking acid fruit in them, particularly when new, has the potential to contribute to dietary intake [39].

Systemic exposure from implanted metals is considered on p. 20.44.

Clinical features [40]. Classical nickel allergy is identified by patches of dermatitis at sites of contact with metal objects, most commonly the ears from earrings, the wrists from watches and bracelets, the neck from necklaces and their clasps, the central back and upper chest from bra components, the central abdomen from studs and zips in trousers, especially jeans (Fig. 20.13), and the dorsa of the feet from shoe buckles. Lesions on the upper cheeks and sides of the nose and face may relate to metal-framed spectacles. A discoid pattern around the lower trunk and thighs from metal studs in clothing is quite frequent, although the involvement of the thighs from metal suspenders has all but disappeared following the advent of tights (panty hose).

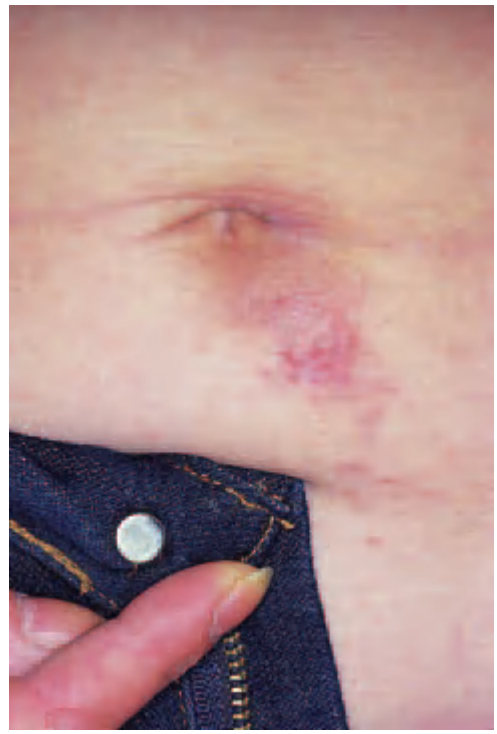

Fig. 20.13 Allergic contact dermatitis to nickel in metal studs on jeans. (Courtesy of Dr J.D. Wilkinson, Amersham General Hospital, Amersham, UK.)

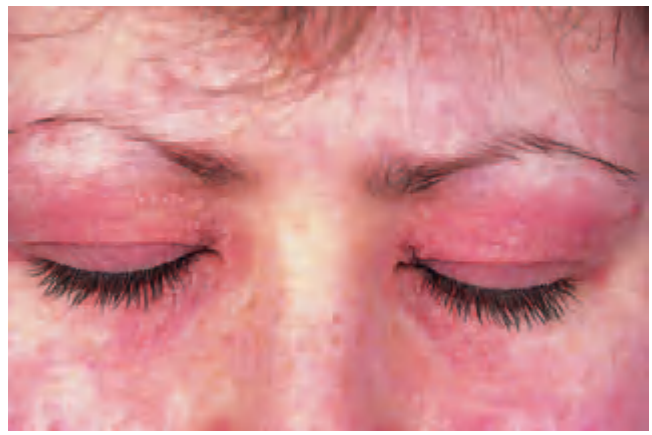

Fig. 20.14 Secondary eyelid dermatitis in a patient sensitive to nickel. (Courtesy of Dr J.D. Wilkinson, Amersham General Hospital, Amersham, UK.)

The eruption may be papular, nummular, diffuse or consist only of excoriated papules on almost normal-looking skin. Some patients are referred to dermatologists because of spread of dermatitis to distant regions. These secondary eruptions used to be a characteristic feature of nickel dermatitis [40,41], but now seem to be less common. The secondary rash normally starts shortly after, or at the same time as, the primary eruption. It affects the neck, face (especially the eyelids; Fig. 20.14), the elbow

flexures and the flexor surfaces of the arms; the anogenital area may also be affected, and the rash may be generalized. Flexural lesions may resemble textile dermatitis or atopic dermatitis.

The relationship between hand eczema and nickel sensitivity remains complex [42]; however, well-controlled statistical studies do support a connection between hand eczema and nickel allergy [43–45], and the nickel-sensitive woman does appear to have a predilection for hand eczema [42,46]. Hand eczema is often multifactorial, and is particularly common in women who have a heavy burden of housework or who are employed in other occupations that expose the skin regularly to trauma or wet work. There may be a vesicular palmar (dyshidrotic) pattern but other distributions occur without being diagnostic. Wet work, atopy and nickel sensitivity are associated with an increased risk of hand dermatitis [47], although atopy is probably the most important factor [48]. Analytical data demonstrate that consumer products such as personal care items, detergents and cleaning products do not contain sufficient nickel, cobalt or chromium to pose a risk to those who do wet work [23].

Sometimes, nickel allergy is directly of occupational origin, and in more than half of these cases it starts on the hands. It is normally associated with the metal and nickel-plating industries. The pattern of dermatitis on the hands is rarely diagnostic. Spread occurs to the elbow flexures, eyelids and face in the same manner as described above.

A recurrent vesicular palmar (dyshidrotic) pattern of eczema has been related to dietary intake of nickel. Ingestion of nickel sulphate caused a flare of vesicular hand eczema in nine of 12 patients studied by Christensen and Möller [49]. The significance of this has been disputed, as similar results have been demonstrated in non-sensitized patients and the challenge dose was artificially high [3,50–53].

Avoidance. Most people think of their environment in terms of objects rather than materials, and it is important to realize that they find it difficult to identify nickel, unless the possible causes of contact are specifically listed. The importance of minor items, such as eyelash curlers, zip fasteners and jeans studs, may not otherwise be appreciated. Many dermatologists provide all nickel-sensitive patients with a list of possible contact items. A dimethylglyoxime test kit (see p. 20.115) may also be of use in identifying nickel-containing objects among a patient's personal items, at work or in the home [25].

Nickel cannot be entirely avoided in daily life, but elimination of nickel from clothing and avoidance of nickel-containing jewellery may be sufficient to clear dermatitis. In our experience, initial compliance with avoidance advice is poor, particularly with clothing, and repeated explanations may be necessary. Waterproof tape and metal lacquer can be used to cover nickel-plated objects that cannot be replaced, although nickel can leach out if the contact site is sweaty and prone to friction. Contact may be difficult to avoid in certain occupations. Protection with rubber gloves may be insufficient, as nickel solutions may penetrate them [54]. Heavy-duty vinyl gloves have been suggested as an alternative.

It has been suggested that exposure of the oral mucosa to nickel (in the form of dental prosthetic devices) may protect against subsequent sensitization [55].

Prognosis. The prognosis of dermatitis from nickel in jewellery and clothing is excellent if further use of nickel-plated objects is avoided. Once the hands are involved, the eczema may remain chronic, persistent or intermittent. Ingestion of nickel is a possible cause of chronicity [56,57].

Specific therapies. Barrier creams and cleansers containing chelating agents may have potential, and a number have shown promise under experimental conditions [58–60]. Clioquinol is known to chelate nickel [61] and a topical clioquinol/steroid combination can be considered as a treatment.

Dietary reduction of nickel intake is recommended, by some, for those nickel-allergic subjects with recurrent palmar vesicular eczema. Knowledge of the nickel content of foods is at present imprecise, and the prescription of a low-nickel diet [62] is not always practical [52]. Nevertheless, there are strong advocates for this approach and a trial of dietary reduction may be worthwhile, although frequently disappointing in our hands.

Treatment with tetraethylthiuramdisulphide (disulfiram; Antabuse), which chelates nickel, has been reported as helpful, but has a significant prevalence of side effects [63]. Liver enzymes should be carefully monitored [64]. An alternative chelating agent, trientine, gave disappointing results in a small open trial [65].

Patch tests. Nickel sulphate 5% in petrolatum is used for patch tests. False-negative reactions are common with 2.5% nickel in petrolatum or 2% aqueous nickel [66]. False-negative reactions may also occur with 5% nickel sulphate in petrolatum because nickel ions penetrate the skin only very slowly [67]. Testing with nickel sulphate may produce irritant false-positive reactions with a deep erythema and pustulation, especially in atopics [68]. Some follicular reactions are irritant, but those with raised papules are often truly allergic in our experience. In cases of doubt, intracutaneous testing with 1 mol/L nickel sulphate in saline has been used to clarify the situation [69].

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Cobalt [1,2]

Chemistry. Cobalt metal and its oxides (e.g. Co_2O_3 and CoO) and salts (e.g. $CoCl_2$ and $CoSO_4$) are sensitizers. Also, heated CoO elicits positive patch-test reactions (unlike NiO).

Prevalence. Little is known of the prevalence of allergy in the general population but one study showed that 1.1% of an unselected Danish population of 567 individuals were patch-test positive [3]. Of patients with dermatitis 4.6–9% are patch-test positive, with females predominating [4].

Occurrence [1,5]. Metallic cobalt is present in 'hard metal' used for metal cutting and drilling [6,7]. It is used in magnets. It is always present as a contaminant in nickel [5]. It occurs in alloys, for example vitallium used in dentures and in nails for pinning fractures [8].

Cobalt oxides, present as traces in cement, are sensitizers [9]; however, isolated cobalt allergy from cement is much rarer than its occurrence in association with chromium allergy [10]. The cobalt content of cement is about the same as that of chromium [9].

Oxides are found in paints [1], glass, china, pottery [11], ceramics [12], enamel (blue), coloured crayons and animal feed additives [13], as well as in multivitamin pills, light-blue tattoos [14,15], soaps [16], cosmetic pigments, hair dye and detergents [17].

The salts are seldom used for plating, unlike nickel salts, although cobalt chloride has sensitized in a metal-etching solution [18].

Organic cobalt compounds (e.g. cobalt naphthenate, resinate and stearate) are used as driers in paints and varnishes, bonders of rubber to metal [19] and accelerators for unsaturated polyester resins [20,21]. They may also be present as additives in lubricating oils.

Clinical features. As cobalt is an invariable contaminant of nickel, the clinical features of cobalt allergy can be identical to those of nickel allergy. Cobalt sensitivity might explain why some women with dermatitis typical of nickel have a negative patch-test reaction to nickel. Furthermore, its presence in cement may induce a clinical pattern identical to allergy from chromate in this source. Isolated cobalt allergy is seen in hard-metal workers and in the pottery and glass industries, when it is usually associated with hand dermatitis [22]. Stomatitis has been reported from dentures [23]. Allergic granulomatous reactions to blue tattoo pigment are recognized, but are rare in our experience [14,15]. Animal feed may induce contact allergy [24], and photocontact dermatitis has been reported from this source, as well as from cement [25]. Vitamin B_{12} is a cobalt-containing compound and cheilitis has been reported from oral vitamin B_{12} ingestion [23], and dermatitis from its parenteral use [26]. It can sometimes be difficult to identify the source of allergy when there is an isolated positive cobalt patch test.

The relationship of cobalt allergy to metal implants is discussed on p. 20.44.

Avoidance. This will depend on identifying a relevant cause and eliminating contact. In those with a nickel allergic pattern, the advice is the same as for nickel-allergic subjects (see p. 20.39); similarly for those with cement allergy, the advice is the same as for chromate (see p. 20.43). Reduction of the dietary intake of cobalt (monitoring plasma vitamin B_{12} if prolonged) may benefit some cobalt-sensitive patients [27].

Prognosis. Concomitant cobalt and chromate sensitivity is associated with more troublesome dermatitis than that which occurs with chromate allergy alone [28]. Possibly the same applies to a combined nickel and cobalt sensitivity because of the increased number of contact sources, which may cause recurrence of the dermatitis.

Patch tests. Cobalt chloride 1% in petrolatum is reliable for testing [17]. False-positive, irritant, purpuric reactions are common, especially in atopics.

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Chromium [1–4]

Chemistry [5,6]. The metal itself, if not dissolved in oil [7] or acids or as a salt, seems to be non-sensitizing, unlike nickel and cobalt. This is probably due to the insoluble monomolecular layer of chromium (III) oxide (Cr_2O_3) on the surface [5].

Hexavalent chromium (occurring as an anion), for example in chromic acid or chromium (VI) trioxide (CrO_3) and in chromates and dichromates of potassium, sodium and ammonium, is the commonest sensitizer. It occurs in alkaline solution as chromate (K_2CrO_4) and in acid solution as dichromate ($K_2Cr_2O_7$). The less soluble lead chromate, barium chromate and zinc chromate ($ZnCrO_4$) are also allergenic [8].

The trivalent chromium compounds (occurring as cations), for example chromium trichloride ($CrCl_3$), are sensitizers [9] but, being less readily absorbed into the skin, they are of minor clinical importance [10,11].

Incidence and prevalence. In Europe, chromate was for many years a frequent cause of occupational allergic contact dermatitis and chronic incapacity [12–15]. The prevalence of sensitivity is commoner in men than in women and is higher in clinics where men with occupational dermatitis predominate. A study of construction workers attending occupational contact dermatitis clinics in Germany showed that potassium dichromate was the commonest allergen at 31.9% [16], whereas chromate sensitivity was found in less than 2% of patients attending the general patch-test clinic [17]. In some countries (including the UK) chromate sensitivity is less common [18].

In Scandinavian countries, the addition of ferrous sulphate to cement to convert the more sensitizing hexavalent chromate to the less sensitizing trivalent chromate (because it is less easily absorbed) appears to have decreased the risk of sensitization in construction workers [19–21], although other changes in cement manufacturing may also be contributing [22]. Chromate sensitivity in some European women was found to be related to chromate in household bleach [23,24], which was subsequently removed. The prevalence of chromate dermatitis seems to be decreasing since the introduction of these two measures, but the decrease may also be due to greater mechanization.

Occurrence [1,2,4,25]. The main source of hexavalent chromium is cement [19,26], although the amount varies widely [6,27–31]. Other important sources are antirust paints (lead chromate and zinc chromate) [8]. The dust liberated by drilling, cutting or sandpapering of metals painted with a primer containing chromate may cause contact dermatitis on the hands, arms and face. Further sources are plating salts [32], metal alloys, lithography/offset printing materials, anticorrosive oil, cutting oils [7,33], cooling water [34,35], foundry sand, polysulphide sealants [36], matches [37], photographic chemicals, chemicals for fat determination in milk [38], welding fumes [39,40], wood preservatives, wood ashes [41], wood pulp [42], mordant in wool dyeing, green baize, stains in glass, glazing enamels [43], catgut [44], violin strings [45], textiles [46], coating on zinc-galvanized iron sheets [33], glass polishing [47], flour [48], tyre-fitting solution [49], colour television manufacture [50], soaps [51] and detergents [52], and dental prostheses [53].

Among trivalent compounds, basic chromium sulphate used as a tanning agent for leather is the most important [10,54]. Chromium (III) salts [10] and oxides in tattoos [55] are less common sensitizers.

Clinical features. Acute weeping dermatitis is unusual, and more commonly there is a dry insidious eruption, which tends to fissure, particularly on the hands. Secondary lichenification is often a feature. There is frequently a concomitant irritant element with wet cement, which is

alkaline, hygroscopic and abrasive. Primary irritant dermatitis and discoid and atopic eczema may be mimicked, and a palmar distribution may be difficult to distinguish from chronic tinea manuum. Palmar vesicular eruptions have been blamed on traces of chromate in the diet [56]. Contact with leather footwear, gloves, belts and other clothing, or even handbags and purses, may produce dermatitis in those areas in contact with the material. Widespread eruptions may occur, with flexural accentuation and involvement of the ankles and dorsa of the feet from cement dust.

Prognosis. Chromate sensitivity tends to persist [57], and the prognosis of occupational dermatitis is poor as a result of its continuation and associated social and financial handicap [58,59]. Fewer than 20% of cases were clear of dermatitis when reviewed after 10 years [3]. In men, allergy to chromate carries a worse prognosis than does sensitization to other allergens [60]. Chronicity and frequent relapses are the rule; the latter are more frequent than in any other industrial dermatosis [12] and affected individuals have been labelled as 'chrome cripples'. Once established, hand dermatitis tends to continue, and superimposed shoe dermatitis may prevent any improvement unless chromate-free shoes can be acquired. Few of those affected give up their work despite the chronicity of the condition [13], and in one study only 8% of chromate-sensitized cement workers were clear of dermatitis 10–13 years after the initial eruption. Changing work to avoid contact with cement does not seem to improve the prognosis [59]. Many chromate-sensitized cement workers develop hardening and are able to continue at work, albeit with ongoing but manageable dermatitis. Positive patch tests have been reported in cement workers with no dermatitis [61]. Insufficient knowledge of the occurrence of chromate in the environment may account for the poor prognosis, and it is suggested that tiny amounts may maintain the dermatitis.

Avoidance. Avoidance of contact with sources of chromate, including leather footwear and gloves, will be necessary, although those cement workers with hardening can be encouraged to stay at their work bearing in mind the poor prognosis. Ferrous sulphate added to cement converts soluble hexavalent chromium to insoluble trivalent chromium, thus potentially preventing chromium sensitization by cement. Various reducing agents [62], chelating compounds and ion exchangers have been recommended as hand creams to prevent dermatitis in chromium-sensitive individuals [63,64] and these may have value, but long-term studies are lacking. It is not yet known whether reduction of the dietary intake of chromium might benefit chromium-sensitive patients [65]. Dapsone has been suggested as a treatment, but no controlled trial has been undertaken [66].

Patch tests. Sensitivity is demonstrated by a closed patch test with potassium dichromate 0.5% in petrolatum. At this concentration, weak irritant reactions are quite common especially in atopics, but lower concentrations will miss relevant positives [67]. Nevertheless, in the USA a concentration of 0.25% is recommended because of the potential for false-positive results. A compromise (0.375%) has been suggested, although there may still be a risk of false-positive and false-negative reactions [67]. Dilutions can be tested to assist in distinguishing allergic from irritant reactions.

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Implanted alloys [1,2]

Orthopaedic metallic prosthetic implants are made from a variety of metals, often alloys and especially stainless steel. Stainless steels contain up to 25% nickel, but for orthopaedic use generally contain 13–16% nickel and a minimum of 17% chromium [3]. However, nickel release from stainless steels, apart from those containing sulphur, is very low [4]. Nickel, cobalt and chromate may also be used in wrought and cast alloys. Vitallium, a cast cobalt/chromium alloy, and titanium may also be used for implants.

Orthopaedic implants may be static (e.g. plate and screws) or dynamic (e.g. artificial hips). There are two potential concerns in relation to metal allergy and these implants, namely allergic skin disorders and loosening. There is little doubt that static implants can be associated with localized eczema over the site of implantation and more extensive skin eruptions in sensitized subjects, sometimes only resolving after removal [5–7]. The delay between insertion of the prosthesis and onset of dermatitis may be days or years [1]. Similar eruptions were reported in the early days of hip replacements when metal heads articulated with metal cups [8,9]. Since plastic joint surfaces have been used, this problem seems to have largely disappeared, and retrospective and prospective studies of hip joint replacements in known metal-allergic subjects are reassuring [10–14].

There is evidence of increased metal sensitization associated with loosening and failure of joints, particularly when these joints involve metal–metal contact [8,9,15]. It is suggested that the increased allergy is caused by, rather than being responsible for, loosening [16,17].

Titanium allergy is virtually unknown, and thus titanium is an alternative for patients with extreme sensitivity to other metals. The patient may need to be appraised that the metal is not thought to be as long lasting as stainless steel.

Reactions have also been reported to sternotomy wires [18], shrapnel [19], mitral valve prostheses [20], dental prostheses [21], fillings [22], pacemakers [23], and infusion and acupuncture needles [24,25]. The contention that nickel allergy is associated with restenosis of coronary artery stents [26] is questionable at this time [27].

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Palladium [1]

Chemistry. Palladium is a relatively inexpensive metal of the platinum group of elements.

Prevalence. Of patients undergoing routine patch testing to palladium chloride, 3–8% were shown to be allergic [2]. Nearly always there is concomitant sensitivity to nickel, and guinea-pig experiments have suggested this may be a true cross-reaction [3]. There are, however, mixed views as to whether this association is concomitant sensitivity, cross-reactivity, or contamination of palladium chloride by nickel sulphate [4–6].

Occurrence. Palladium is increasingly used in dental alloys and prostheses. It can be used as a whitener in white gold. Occupationally, its main uses are in electrical components and as a catalyst.

Clinical features. The clinical relevance of a positive palladium chloride patch-test reaction is questionable in many instances, and may just be a reflection of nickel allergy. Stomatitis and lichen planus have nevertheless been related to palladium in dental materials [7–9]. Removal of prostheses or dental alloys containing palladium may need to be considered in these instances.

Patch tests. It is normally tested as palladium chloride 1% in petrolatum.

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Gold [1]

Chemistry. Metallic gold is soft, malleable and ductile. It is stable and resistant to corrosion. Its strength is increased when alloyed with other metals. Gold salts, such as gold trichloride and potassium dicyanoaurate, are recognized as sensitizing as well as irritant [2].

Occurrence. Metallic gold is mainly encountered in jewellery and dental materials. Gold salts are used in the plating, electronics, photographic, glass and porcelain industries [1].

Prevalence. Metallic gold has, until recently, been regarded as safe and very unlikely to sensitize. However, since gold sodium thiosulphate was introduced as a patch-test allergen to identify gold allergy there has been an upsurge in reports. When gold sodium thiosulphate was added to the standard patch-test series, positive reactions were obtained in 8.6% of a series of Swedish patients [3], with subsequent surveys of various selected subgroups ranging from 1 to 23% positivity [1]. There is a female predominance [4], and where a relevance has been found it has usually been in the context of jewellery or gold dental work [5–8]. However, the allergic mechanism behind the positive patch tests, and their relevance, have been questioned [5,9,10].

Clinical features. In our experience a relevance for a gold sodium thiosulphate positive patch test is found infrequently, and generally these patients can wear jewellery and have gold dental fillings without problems. Nevertheless, analysis of the involved anatomical sites has been undertaken by others who have found that involvement of fingers, ear lobes and eyes by dermatitis predominates [5]. A seborrhoeic eczema pattern has been described [11], as have persistent papules and nodules on the ear lobes, with lymphomatoid or granulomatous histology [12,13]. Reported oral manifestations of allergy have included erythema, burning mouth, erosions, ulceration and lichen planus-like lesions [8,14,15]. Most gold-allergic patients have gold dental work but the majority of them have no symptoms [3,5]. Sodium aurothiomalate injections for rheumatoid arthritis have induced systemic contact dermatitis and 'fever' in those previously sensitized to gold [16].

Acral dermatitis has been described from allergy to gold salts in the gilding industry [17].

Patch tests. Many gold salts have been used for patch testing, but most centres now use gold sodium thiosulphate 0.5% in petrolatum [18]. Late reactions are common and an additional 7-day or even 2- or 3-week reading has been advised [19]. The appearance of a positive patch test may be 'dermal', with erythema and oedema but no vesiculation, and persistent patch-test reactions are well recognized [19]. The controversy over the debatable relevance has led many to advise against routine standard-series screening for gold allergy [10].

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Mercury [1]

Chemistry. The metal and its inorganic salts, for example corrosive sublimate ($HgCl_2$), calomel (HgCl), fulminate ($Hg(CNO)_2$) and ammoniated mercury ($HgCl{\cdot}2NH_4Cl$), as well as organic compounds (e.g. mercurochrome, thimerosal and phenylmercuric salts; see p. 20.67), may all sensitize.

Occurrence. The metal is used in thermometers, instruments and amalgam (alloy of silver or copper and mercury) for filling teeth [2,3]. Mercury and inorganic mercurials may be used in disinfectants, fungicides, herbicides, insecticides, detonators, emulsion paints and jewellery, as well as in the production of caustic soda and chlorine. Ammoniated mercury has been used in the topical treatment of psoriasis, although concerns about toxicity have led to its withdrawal in the UK. Mercury and ammoniated mercury have been used in skin lightening creams [4]. Red mercuric sulphide (cinnabar, HgS) is used in red tattoos and in artists' paints; it may contain cadmium sulphide as an impurity and can thereby cause phototoxic reactions. Organic mercurials may be found in topical and parenteral medicaments (see p. 20.67).

Clinical features. The clinical features of mercury allergy can be divided into oral, contact dermatitis, systemic and granulomatous. Stomatitis has been described in patients already sensitized to mercury after amalgam fillings, and this settled when they were removed [5]. Reports of oral lichen planus in association with amalgam fillings are increasing [6,7]. A study consisting of 19 patients with lichen planus adjacent to amalgam fillings showed that 15 of these were allergic to mercury; 13 of these cleared on removal of the amalgam. This study also included 42 patients with oral lichen planus not anatomically related to fillings, 28 with other oral diseases and 46 with burning mouth syndrome. Only seven of these had a positive patch test to mercury [7]. Hypertrophic amalgam dermatitis simulating carcinoma of the tongue has been described in one patient [8].

Generalized exanthems and erythema multiforme have been reported from amalgam fillings and following the breakage of thermometers in the mouth and the use of an antiparasitic powder for the treatment of crab lice [9–11]. Recalcitrant eczemas in mercury-sensitized individuals are recorded as clearing after removal of mercury amalgam fillings [12], although most cases of systemic reactions from amalgam seem to develop a few hours after insertion and settle after 10–14 days [13]. In our view, malaise and general ill health are not related to allergy to mercury in amalgams.

Red mercuric sulphide (cinnabar) in a tattoo may induce granulomatous reactions in allergic subjects [14]. We have seen several granulomatous and lichenoid reactions confined to the red parts of tattoos, and none of the patients has been allergic to mercurials.

Patch tests. Mercury is normally tested at 0.5% in petrolatum, mercurochrome 2% in petrolatum or aqueous, mercuric chloride 0.1% in petrolatum and ammoniated mercury 2% in petrolatum. However, mercury compounds can be irritant, and aqueous solutions of mercury salts may react with aluminium in Finn chambers to cause false-positive reactions [15]. Patch testing with both mercury and ammoniated mercury is suggested if allergy is suspected [15].

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Aluminium

Occurrence and clinical features. Aluminium is widely used but contact allergy is very rare. Most reported cases are from aluminium-adsorbed vaccines and parenteral solutions, with granulomatous reactions at the injection site [1–4]. It is found in antiperspirants, and axillary dermatitis (usually irritant) may occur. Allergy in a child with chronic otitis externa treated with aluminium acetate eardrops has been seen [5].

Patch tests. As Finn chambers are aluminium, a positive patch test, often annular in configuration, may develop under every single test site in sensitized persons [6]. Patch testing is best undertaken with plastic chambers if this diagnosis is suspected. Pure aluminium metal or salts, for example aluminium acetate 10% aqueous or aluminium chloride 2% aqueous, can be used for testing.

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Other metals

Copper is a ubiquitous metal found especially in coinage, jewellery, pipes, electrical equipment and wiring. Its salts are used in insecticides, fungicides, wood preservatives, food processing, fertilizer and fur dyes. Contact allergy is

very rare. Dermatitis has been reported from copper intrauterine contraceptive devices and proven by patch testing and resolution of the dermatitis after removal [1,2].

Other metals used in dentistry may have the potential to cause contact allergy, including platinum, rhodium, indium and iridium [3–5].

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Fragrances, balsams, flavouring agents and spices [1–3]

Perfumes are blends of ingredients producing an odour intended to be aesthetically pleasant or to mask other less pleasant odours. The components are either of natural origin or produced synthetically. Natural sources include extracts from plants, trees, lichens and animals (e.g. musk, civet) [1]. Commercially available perfumes are mixtures of essential oils from these sources and synthetic compounds, with usually at least 10, and up to several hundred, ingredients [4]. The scent is determined by the mixture of volatile substances. 'Fixatives' are added to delay evaporation, influencing the quality and persistence of the perfume. Common 'fixatives' are balsams, benzyl benzoate, benzyl salicylate and synthetic musks.

Tree balsams contain many different fragrance and flavouring components. Balsam of Peru is one such material that has been studied in depth [5]. It comes from the Central American tree *Myroxylon pereirae*, and was widely used earlier this century for treating wounds and also scabies [5]. The composition is still not completely known, but the balsam does contain benzyl benzoate, benzyl cinnamate, cinnamic acid alcohol and aldehyde, benzoic acid, vanillin, farnesol and nerolidol [6]. It may cross-sensitize with resorcinol monobenzoate used in cellulose ester plastics [7]. Other related balsams include balsam of Tolu, balsam of spruce, gum benzoin and storax.

Flavours may similarly be of natural or synthetic origin. Examples of natural flavours include citrus fruit peel, peppermint oil, spearmint and vanilla. Natural spices include nutmeg, mustard, cinnamon, cloves and oil of juniper. In the modern food industry a large number of synthetic flavouring agents are used. As with perfumes, flavours may be complicated mixtures.

Prevalence. In general, as measured by the frequency of allergic reactions to the fragrance mix patch test in routinely patch-tested patients, fragrances are the second commonest allergen (after nickel) [2]. Studies with this patch-test allergen indicate that fragrance allergy affects in the region of 1% of the adult population [8], whereas children and adolescents have shown rates of 1.8% [9,10]. In those clinics investigating allergic contact dermatitis the rates have varied between 5.7 and 17.4%, with roughly 10% being an average for European investigation clinics [1]. Sex incidence has generally only shown a slight preponderance of females, and in some instances it has been equal [11–13]. There is evidence from some centres that perfume allergy, detected by fragrance mix, is increasing quite significantly [1].

The pattern of allergy is also changing. In one UK centre, although the level of fragrance mix allergy has remained stable, a significant reduction of cinnamic aldehyde and cinnamic alcohol allergy has occurred when components of the mix have been tested [12]. This is thought to reflect a decreasing concentration of these materials in cosmetics in the last 17 years.

Routine patch testing with balsam of Peru as a marker of allergy to perfume and certain flavours has shown a positive rate of allergy of around 4% [14]. It is thought to be a decreasingly relevant marker of perfume allergy [15].

Occurrence. Fragrances are ubiquitous. Perfumes, cosmetics, moisturizers, deodorants, aftershaves, soaps, bath additives, aromatherapy oils and toilet tissues and wipes are typical sources. Medicaments and work creams and cleansers often contain perfume. In the domestic environment cleansers, fabric conditioners and polishes may all be perfumed. At work some materials (e.g. coolant oils) may contain a masking perfume [16,17]. Limonene is used in industrial and histology solvents and degreasing agents. D-Limonene has been shown to act as an allergen when it becomes oxidized [18,19]. It may therefore only become allergenic with prolonged exposure to air.

Flavours and spices are to be found in foods, beverages, and dental products including toothpastes and lipsalves.

Clinical features. Analysis of common patterns of perfume dermatitis has shown a tendency to involve the hands, face and neck (Fig. 20.15) in women; hands, face and lower legs in men; and axillae in both sexes [20,21]. A streaky pattern may be observed. There is evidence that allergy to more than one perfume component may result in a synergistic effect [1].

Connubial allergy is well recognized [22], and allergy to lavender applied to a pillow has been described [23]. Many affected persons suspect their allergy, but a substantial number do not. Furthermore, those who are aware of their allergy may continue to suffer dermatitis by failing to take appropriate avoidance measures, for example by unwittingly applying perfumed medicaments

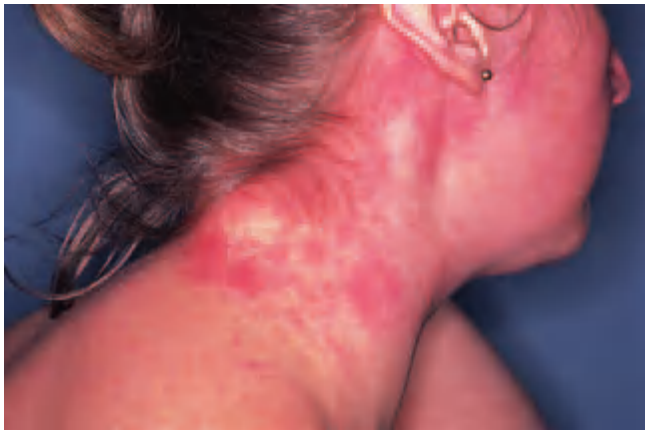

Fig. 20.15 An urticated contact dermatitis in a patient allergic to fragrance. (Courtesy of Dr J.D. Wilkinson, Amersham General Hospital, Amersham, UK.)

and cosmetics to their skin. Aromatherapists and their clients are liable to sensitization in sites where there is contact with the essential oils [24–27].

D-Limonene in its oxidized state may cause allergic occupational hand dermatitis [19], which can also develop in bakers and chefs as a result of contact with sensitizing flavouring agents [27,28]. Peeling of citrus fruit in the domestic environment may also induce an allergic hand dermatitis.

Cheilitis may be a reflection of allergy to flavouring agents in toothpastes [29–32], lipsalves [33,34], food and drink [35].

Balsam of Peru is still used as a medicament, particularly in haemorrhoid preparations, and allergy is therefore relevant to perianal problems. Sensitizing balsams are also used in medicaments and balms for wounds, sprains and joint pains, particularly in the Far East [36,37]. Tincture of benzoin is used in a similar way, and may also be used under orthopaedic plaster casts [38,39]. Vesicular hand dermatitis has been related to dietary intake of flavours related to balsam of Peru [40].

Musk ambrette is a synthetic perfume component responsible for photoallergy and although its use has been stopped in the western world, perfumed materials from other parts of the world might still contain it.

Avoidance. Perfumes are marketed as concentrated liquids, in more diluted form such as eau de toilette, or as sprays, and all should be avoided. Application of perfume to clothing may still cause problems in allergic subjects, who often believe they will only react if perfume is applied directly to the skin. Occasionally, affected subjects are able to use a specific perfume without any problem. Other perfumed skin products to be avoided include deodorants, aftershaves, talcum powders, soaps and bath additives.

The presence of perfume in a cosmetic or wet wipe will be denoted by the INCI term 'parfum' and the presence of balsam of Peru by the INCI term '*Myroxylon pereirae*'. Some cosmetics' labels may suggest they are fragrance-free, yet the products are found to contain perfume when the full ingredient label is studied, reinforcing the need to avoid unlabelled products. Some plant extracts may potentially be a hidden source of fragrance in cosmetics as the INCI nomenclature may use the plant's Linnaean name rather than the word parfum. Some extracts, however, may only contain traces of fragrance chemicals.

Surprisingly, some prescribable moisturizers, emollients, bath additives and corticosteroids, as well as over-the-counter medicaments, contain perfume. Allergic patients with ongoing problems should be counselled carefully about avoidance of these sources.

In the domestic situation, perfume-containing sprays such as air fresheners, insect repellants and hairsprays should be avoided, as should skin contact with perfumed household cleansing products and polishes. Unperfumed soaps or soap substitutes are required for washing the skin. The levels of perfume residues from washing powders and fabric conditioners for clothes are probably too low to cause clinical problems, but in those with a clothing pattern of eczema extra rinsing and avoidance of fabric conditioners can be considered.

In the occupational environment many cleansers, conditioning creams and barrier creams are perfumed, and similar avoidance measures are needed. Some work materials, including cutting oils and paints, may contain masking perfume and enquiries may be necessary to establish their components.

Dietary measures may be helpful in those with vesicular palmar eczema and balsam of Peru allergy, but the response can be disappointing [41–43].

Patch tests. The complexity of perfumes is such that there is not a perfect screening patch test for perfume allergy. Before 1977, the main recommended marker for perfume allergy was balsam of Peru, which is still advised. It is tested at 25% in petrolatum, but is thought to identify only 50% of perfume-allergic subjects [44]. Screening for perfume allergy was significantly advanced by the development of fragrance mix as a result of Larsen's studies [45,46]. He advised a mix of eight substances (Table 20.4). The original mix has been modified so that now each component is present at 1% concentration [47]. The mix contains an emulsifier, sorbitan sesquioleate at 5%, which is reported to have improved the return of identified perfume allergies [48,49]. Fragrance mix will identify approximately 75% of perfume-allergic subjects, although this figure is reported to increase to 90% if balsam of Peru is also tested [50,51].

An improved return may be achieved by testing with patients' own perfumed products [52]. In addition, there is

Table 20.4 Ingredients of fragrance mix* [45–49].

Substance	Concentration† (%)
Cinnamaldehyde	1
Cinnamyl alcohol	1
Eugenol	1
Amyl cinnamaldehyde	1
Hydroxycitronnellol	1
Geraniol	1
Isoeugenol	1
Oak moss absolute (*Evernia prunastri*)	1

* Fragrance mix allergens contain sorbitan sesquioleate (5% in petrolatum) as an emulsifier.
† All ingredients are diluted in petrolatum.

evidence from Europe that 4-(4-hydroxy-4-methylpentyl)-3-cyclohexine carboxyaldehyde (Lyral®) is a perfume sensitizer that might be missed with fragrance mix testing [50,53,54]. In a multicentre study, 2.7% of patients routinely tested were found to be allergic to it [50]. Other potentially missed perfume allergens include sandalwood, narcissus and ylang-ylang oil [51].

Fragrance mix may give false-positive irritant reactions, and testing the ingredients separately may help exclude these. However, when individual materials are mixed they may combine in such a way as to produce compound allergy, or other synergistic effect inducing a true allergic reaction, despite the components themselves being negative. The reverse situation (quenching), i.e. the mix is negative and one or more components positive, has been reported but also questioned [55]. Nevertheless, it is worthwhile testing with the breakdown in addition to the fragrance mix when perfume allergy is suspected.

An extended additional flavours series of patch tests can be developed for those with cheilitis or oral problems.

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Applied medicaments [1]

Prevalence and incidence. Of all allergic contact dermatitis, 30% is caused, or complicated, by sensitivity to medicaments [2,3]. The literature on contact dermatitis abounds with reports of reactions to medicaments, and it is not possible to review all of these. It is doubtful whether the incidence has changed significantly [4,5], although the incidence of sensitivity to a particular allergen varies from country to country [6–8] and from decade to decade, according to both local prescribing habits and the number of patients with leg ulcers and stasis eczema included in any series [3]. Cases are missed unless patch tests are routinely performed and if locally used medicaments are not included in a standard series. Meaningful sensitization indices for the various medicaments can be calculated only if prevalence of sensitivity is correlated with usage [3,9].

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Clinical features. Certain sites appear to be prone to the development of allergic contact dermatitis from medicaments. This is probably the result of frequent medicament usage at these sites, occlusive skin conditions and pre-existing skin damage. Sensitization to medicaments is particularly common in patients with leg ulcers or eczema of the lower legs (Fig. 20.16) [1], and is found in about half of those with chronic stasis eczema. Even weak allergens appear to sensitize if used on the lower leg. Contact dermatitis is also common in patients with chronic perianal inflammatory disorders (Fig. 20.17), pressure sores [2], chronic otitis externa [3] and in those who frequently use ocular medicaments [4].

However, dermatitis from applied medicaments can develop anywhere. Sometimes, the sensitivity is obvious but often is occult and easily overlooked, and it will then be detected only by patch testing. In burns, the damaged skin may be incapable of reaction, and dermatitis may be apparent only at the periphery of the burn site.

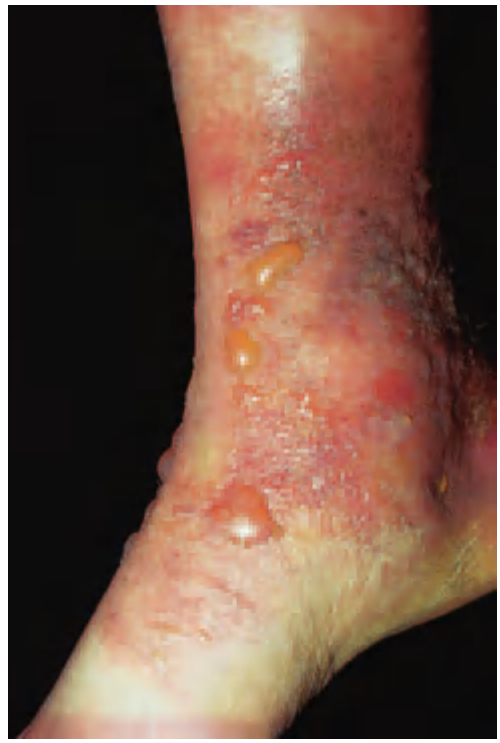

Fig. 20.16 Medicament allergic contact dermatitis superimposed on stasis eczema. Topical antibiotics/antibacterials, preservatives, lanolin and other constituents of the medicament base are often to blame. (Courtesy of Dr J.D. Wilkinson, Amersham General Hospital, Amersham, UK.)

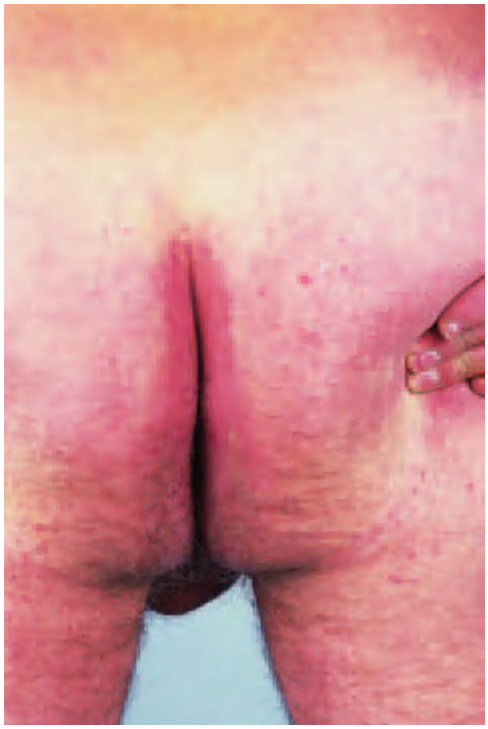

Fig. 20.17 Pruritus ani is often complicated by secondary contact dermatitis to local anaesthetics or other medicaments. (Courtesy of Dr J.D. Wilkinson, Amersham General Hospital, Amersham, UK.)

Sensitivity to a topically applied medicament may result in several types of reaction.

1 Local aggravation, with increased itching and redness.

2 Spread to other regions, in most cases preceded by local aggravation. This is especially common in patients with stasis eczema or leg ulcers.

3 A local reaction may not develop, and dissemination may be the only sign of sensitivity. This typically occurs with creams and ointments containing a potent steroid capable of suppressing the reaction locally, but not in other regions.

4 Sensitization can also manifest merely as failure to respond to treatment. The original condition may worsen or fail to improve, without there being any acute flares or spread to arouse suspicion. This is seen mainly when there is a low degree of sensitivity and low concentration of allergens, typically with parabens and lanolin, or where the contact allergen is a corticosteroid.

5 Persistent generalized erythroderma is a rare manifestation of allergic contact sensitization to medicaments.

6 Contact urticarial reactions have also been reported.

Systemic reactions. Patients sensitized by the topical use of a drug may develop systemic reactions if that drug, or one that is closely related, is then given systemically. A pattern of dermatitis with erythema of the buttocks and flexural involvement elsewhere has been termed the 'baboon syndrome' (see p. 20.28). Widespread dermatitis [5,6] or generalized exfoliative dermatitis [7] has been reported following challenge with a systemic drug to which the patient already has contact allergy.

Other patients may develop a systemic reaction after topical application of a medicament. Anaphylactic reactions have been reported, for example following the topical use of bacitracin [8], cephalosporins [9], rifamycin [10] and chlorhexidine [11]. Erythema multiforme-like reactions to topical medicaments have also been reported [12]. Some patients have positive patch-test reactions to a topically applied drug, having previously been sensitized by its systemic use [13].

Patients who have been sensitized by the topical use of promethazine hydrochloride may develop serious photosensitivity if the drug is given systemically. Care must always be taken in prescribing an antihistamine systemically if the patient is known to have been exposed to the same or a chemically similar drug topically. Patients who are known to be allergic to ethylenediamine should not be given promethazine hydrochloride, antazoline hydrochloride, piperazine or several other antihistamines [14].

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Avoidance and prognosis. Sensitization from a single constituent may lead to recurrent dermatitis due to its inclusion in several proprietary formulations. In only a few countries are the contents of a proprietary cream stated on the package or listed on the data sheet and, even then, the information is often insufficient, constituents sometimes

being given as trade names or only 'active' ingredients listed. In order to reduce the risk of relapse, the ingredients of all topical medicaments should be established. Ideally, all topical medicaments, whether prescribed or purchased without a prescription, would exhibit full ingredient labelling.

It is also necessary to consider cross-sensitivity to other, untested medicaments. This has received particular study in relation to contact sensitivity to the aminoglycoside group of antibiotics. A similar situation may develop in patients sensitive to the 'para' group of chemicals, with cross-sensitization between local anaesthetics, dyes, sulphonamides, UV filters, etc.

Patch tests. Patients with suspected contact dermatitis should be tested with all the medicaments they have applied. The information obtained in the history may be incomplete, and commonly used medicaments should also be routinely tested. It is often helpful to have a vehicle and medicament series, or several 'site' series with the ingredients of the most commonly used topical preparations in that geographical location. Testing to the medicament ('as is') may miss allergens, because they may be present in insufficient concentration. Where there is a high index of suspicion, the individual components should be obtained and appropriately diluted for patch testing.

It is important not to forget self-prescription of over-the-counter preparations. Popular habits of self-treatment vary from country to country and region to region. Knowledge of these habits is obtained by experience, but local pharmacists can often supply information. Certain remedies may be popular in one country but almost unknown in another. 'Natural' or herbal treatments are increasing in popularity. Some of these are irritant, and others, such as Chinese herbal remedies [1] and tea tree oil [2], contain allergens.

Various pharmaceutical developments have been associated with successive waves of dermatitis from applied medicaments; for example sulphonamides from 1945 to 1950, then antihistamine creams, and later neomycin and ethylenediamine [3]. Sensitivity to neomycin, gentamicin, lanolin, balsams, mercurials and preservatives is still common today. Newer sensitizers include the imidazoles, topical non-steroidal anti-inflammatory drugs (NSAIDs), transdermal delivery systems and topical steroids. Photosensitivity also occurs with some topical NSAIDs. Less common medicament allergens are listed in Table 20.5 [4–73].

Sensitivity may be confirmed in some patients exposed to drugs, particularly the penicillins, by *in vitro* lymphocyte transformation tests [74,75] and, for type I reactions, by specific RAST. Skin tests may also sometimes be positive in those who have had eczematous or urticarial reactions to ingested drugs [76,77]. Care must be taken in re-challenging anyone who has had a type I reaction because anaphylactic reactions may be induced. Guidelines for investigating potential drug reactions have been produced [78].

Medicament allergens included in the European Environmental and Contact Dermatitis Research Group (EECDRG) recommended European standard series include the following.

Neomycin 20% in petrolatum

Neomycin has two active components, neomycin B and neomycin C, which are stereoisomers [79]. It cross-reacts with other aminoglycoside antibiotics. The pattern of cross-sensitivity has been studied in guinea pigs [80]. Clinically, neomycin is known to cross-react frequently with kanamycin and framycetin (Soframycin), which would be anticipated with the latter as it consists almost entirely (99%) of neomycin B [81]. Cross-sensitivity also occurs to a varying degree with gentamicin and tobramycin [80]. Neomycin classically produces late reactions.

Clioquinol 3% in petrolatum

In areas where there is high use of chlorquinaldol the retention of the quinoline mix may be of value due to the lack of cross-reactions between it and clioquinol [82].

Benzocaine 5% in petrolatum

Experience suggests that, in the UK at least, the replacement of benzocaine with a mixture containing cinchocaine (dibucaine) 2.5% and amethocaine (tetracaine) 2.5% will double the yield of allergic positive reactions [83]. Local anaesthetics are either of the ester or amide type, and cross-reactions can occur within groups. Although cinchocaine is an aminoalkylamide and lidocaine (lignocaine) is an aminoacylamide [84], most individuals do not cross-react [83]. Ideally, any reaction to the mix should be followed up by testing to the constituents and to lidocaine [85]. Not all reactions to local anaesthetic are detected by the mix and patch tests should always be directed to the particular exposure of the patient [86].

Corticosteroids (tixocortol pivalate 0.1% in petrolatum and budesonide 0.01% in petrolatum) [87]

When testing with corticosteroids it is not unusual to see reflex vasodilatation following the steroid-induced vasoconstriction and this should not be interpreted as a positive reaction. Conversely, an annular response is frequently allergic, as a result of central suppression of the reaction by the corticosteroid.

A reaction to tixocortol pivalate almost invariably means that the patient is allergic to hydrocortisone. In the UK, a reaction to budesonide almost certainly represents a cross-reaction to another corticosteroid, most likely an

Table 20.5 Other medicament allergens.

Antiandrogens
Spironolactone [4,5]

Antiseptic agents
Benzoyl peroxide [5] used to treat acne, chloroacetamide [6], chlorocresol [7] and chloroxylenol. Less common sensitizers are benzalkonium chloride [8], nitrofurazones [9] in ear drops, benzyl alcohol [10], iodine [11], chlorhexidine [12], proflavine [13], resorcinol, glutaraldehyde as sterilizing agent [14], 4-aminoquinaldine [15] and isopropyl alcohol in medical skin wipes [16]

Antibiotics
Common sensitizers are the aminoglycosides, including framycetin [17], virginiamycin [18], sodium fusidate [19], minocycline [20] and chloramphenicol [21]. Less common are penicillins [22], metronidazole [23] and tetracyclines (e.g. as syrups), bacitracin [24] and clindamycin [5]. Streptomycin is a strong sensitizer but dermatitis is now rare because of more careful use

Antimycotic agents
Most antimycotics have sensitizing properties: tolnaftate [25], nystatin [26], amorolfine [27], undecylenic acid [28] and naftifine [29]. Imidazoles are rare but consistent sensitizers and cross-reactions are frequent [30–32]

Antiviral agents [33]
Aciclovir, interferons, amantadine [34], tromantadine, lamivudine, trifluridine and idoxuridine have all been reported as causing contact dermatitis

Antihistamines
The phenothiazines [35] are the strongest sensitizers, but all can sensitize when used topically [36], including doxepin [37]

Cytotoxic drugs
Topical mechlorethamine (nitrogen mustard), carmustine [38] and 5-fluorouracil [39], as well as intravesical mitomycin [40], can sensitize. Occupational contact dermatitis has been described from azathioprine [41] and diethyl-β-chloroethylamine [42], and occupational contact urticaria from cisplatin [43]

Non-steroidal anti-inflammatory drugs
The arylpropionic acid derivatives, such as ketoprofen, ibuprofen, ibuproxam and tiaprofenic acid, cause contact and photocontact dermatitis, with cross-reactivity, if used topically [44,45]. Topical benzydamine is also a contact and photocontact sensitizer [46] and phenylbutazone is a cause of erythema multiforme-like reaction [47]

Ophthalmic preparations [48,49]
Treatments for glaucoma, particularly β-blockers, including timolol and levobunolol, cause problems. Patch tests with the eye drops may give false-negative reactions. Preferably test with higher concentrations or enhance penetration [50]. Other glaucoma treatments reported as causing contact dermatitis include the parasympathomimetic pilocarpine and sympathomimetics apraclonidine and dipivefrine [51]. Sodium cromoglicate used for allergic conjunctivitis [52]. Mydriatics may also cause problems, especially phenylephrine [53], with which false-negative patch tests occur. Tropicamide contact dermatitis is also reported [54]

Otolaryngological preparations [55]
Antibiotics are frequent sensitizers, particularly neomycin and polymyxin. Some are peculiar to the ear, such as furaltadone [56]

Psoriasis drugs [57]
Reactions to both tars and dithranol have been reported (see also vitamins)

Traditional Chinese medicaments
Sensitization, as well as irritation, has been reported from Hong Kong, Japan and Singapore [58], as well as from China [59]

Transdermal therapeutic systems [60]
Sensitization has been reported to both active (clonidine [61], nicotine [62], nitroglycerin, oestradiol, norethisterone [63] and testosterone [64], scopolamine and pyridostigmine bromide [65]) and inactive (ethanol [66], methacrylates [67] and hydroxypropyl cellulose [68]) ingredients

Vitamins
Vitamins A, E [69] and K [70], the vitamin D_3 derivatives calcipotriol [71] and tacalcitol [72], and dexpanthenol [73] have all sensitized in topical medicaments

'ester' such as hydrocortisone 17-butyrate or an 'acetonide' such as triamcinolone acetonide. A reaction to either of these steroids in the standard series should prompt further testing to an extended steroid series, as 50% of tixocortol pivalate-positive and 90% of budesonide-positive individuals react to other corticosteroids [88]. Our experience suggests that although intradermal testing may have a role, testing other corticosteroids at 1% in ethanol is more sensitive. Together with knowledge of cross-reaction patterns [89], this helps in deciding what topical steroid to use as an alternative. Empirically, fluocinolone acetonide (Synalar) preparations react least frequently [90], and are available in a range of potencies. In view of the potential cross-reactivity between these two corticosteroids and prednisolone and its derivatives, it seems prudent to advise the use of either betamethasone or dexamethasone if a systemic steroid is needed, in order to reduce the risk of inducing a generalized dermatitis.

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Cosmetics [1–6]

Cosmetics have been defined as any preparation applied to the skin, mouth, hair or nails for the purpose of cleansing, enhancing appearance, giving a pleasant smell or providing protection [1]. There is consequently a considerable range of products that can be included within this definition, for example perfumes, deodorants, aftershaves, hairsprays, lipsticks, nail varnishes and extensions, moisturizers, emollients, cleansers, mascara, eye shadow, make-up, sunscreens, hair colours and styling agents, soaps, shampoos, shower gels, bath oils and toothpastes.

Good manufacturers aim to eliminate known sensitizers and irritants. However, because all cosmetics and toiletries have to be protected against bacteriological contamination and decomposition, and as most consumers require their cosmetics to have a pleasing smell, there are potentially sensitizing preservatives and fragrances in most cosmetic products. The substitution of one allergen by another may lead to the introduction of perhaps an even more sensitizing substance [7]. When entirely new products or ingredients are used on a large number of consumers, unexpected allergic or irritant reactions may occur, and it may be some time before the cause is identified.

The range of cosmetic allergens is potentially considerable. The more frequently detected allergens are discussed in the specific sections relating to perfumes (p. 20.48), preservatives (p. 20.59), *p*-phenylenediamine and related dyes (p. 20.71), UV filters (p. 20.73), and vehicles and excipients (p. 20.68).

Allergy to tosylamide formaldehyde resin in nail varnish has been shown to be relatively frequent in those who wear it, and to have important adverse consequences [8,9]. Allergy to acrylates used in artificial nail glues and sculptured nails can produce similar results [10–12].

There is an increasing vogue for including natural plant-based products in cosmetics, and these may be potentially allergenic [13–16].

Incidence and prevalence. Contact dermatitis to ingredients of cosmetics and toiletries is common in patients attending patch-test clinics; approximately 10% of patients investigated for contact dermatitis in a multicentre European study were allergic to cosmetic products [17]. The exact incidence and prevalence of sensitivity in the population is difficult to establish. In a UK study of 1022 persons, 8.3% had experienced some sort of adverse reaction to a cosmetic or toiletry in the preceding year; most reactions were irritant rather than allergic in nature [18]. In one American survey comprising 30 000 consumers, 700 reactions had occurred during 1 year [19]. Some reactions are transient, such as stinging and smarting [20], and contact urticarial [21]. Most people simply change brand and do not report adverse reactions to the manufacturer. It is nevertheless estimated that 1–3% of the population is allergic to a cosmetic or cosmetic ingredient [22], with a female predominance.

The commonest allergens are fragrances and preservatives [23,24]. Also of importance are *p*-phenylenediamine, UV filters, tosylamide formaldehyde resin in nail varnish, lanolin and derivatives and cocamidopropyl betaine, but there are potentially many others [1]. As many as 6.6% of women habitually wearing nail varnish are allergic to it, and 1.6% of patients routinely tested to the usual allergen, tosylamide formaldehyde resin, are patch-test positive [8,25].

Clinical features [1]. Cosmetic allergy is unsuspected in about half of those in whom it is subsequently diagnosed [23]. Apart from hair dye allergy, acute weeping and oedematous reactions are unusual. More commonly, there are erythematous scaling patches or a more diffuse erythema. Differentiation from atopic and seborrhoeic eczema and lupus erythematosus may be difficult, especially on the face.

Sites of involvement are very varied, and depend on the type of product containing the allergen(s) and where it has been applied. Patterns of perfume allergy are described on p. 20.48, and hair dye allergy on p. 20.72. The eyelids, face (Fig. 20.18) and neck (see Fig. 20.15) are sites commonly involved in cosmetic allergy, but hand involvement and more widespread dermatitis are seen. It is not always appreciated how often cosmetics, particularly moisturizers, are applied not only to dry skin but also to pre-existing eczemas, including constitutional forms. Flares may wrongly be blamed on the underlying disorder, and cosmetic allergy may go undetected unless appropriate patch testing is undertaken. In general, 'leave-on' products are more likely to sensitize than wash-off cosmetics, although dermatitis may be maintained from the latter source in allergic subjects [1].

Cheilitis is seen from lipstick, lipsalve and toothpaste allergy. Hair cosmetic allergy may cause a scalp margin pattern as well as periorbital swelling. A similar distribution is seen in hairdressers' clients allergic to permanent wave chemicals (usually glyceryl monothioglycolate) [26].

Nail varnish allergy is often ectopic, with patches and streaks on the face, neck (see Fig. 20.10) and behind the ears, and episodic periorbital swelling. The face and neck are involved in about 80% of cases, the eyes in about 50% and periungual dermatitis, although often absent or minimal, occurs in 60% [9]. The allergen is usually tosylamide formaldehyde resin, but allergy to other agents (e.g. dibutyl phthalate, methyl acrylate and nitrocellulose) has been described [27–29]. More widespread involvement of, for example, the chest and anogenital regions may be seen [9,30]. Onycholysis may occur [31], but this is more likely with allergy from acrylates in adhesives for false nails and from sculptured nails, which may also cause dystrophy and paronychia [10,32,33]. A similar, potentially widespread, ectopic pattern of contact allergy may occur from acrylate-based nail cosmetics [11]. The socio-economic and medical consequences of nail varnish allergy have been investigated and shown to be potentially severe, with sick leave, work loss and even hospitalization resulting [9].

Avoidance. Full ingredient labelling of cosmetics has made a major contribution to avoidance measures. It is important to give the patient the INCI name of the material to which they are allergic, as this is the nomenclature used on cosmetic ingredient labels in Europe. There is still potential for confusion, particularly for plants which, when used in cosmetics, are identified by their Latin name in the Linnaean system. Some plant extracts may potentially contain, or cross-react with, fragrances, and it may be difficult for the patient and the dermatologist to be absolutely sure if a product containing natural plant extracts is safe for fragrance-allergic subjects. Products not labelled should not be used. The reader is referred to the sections on individual cosmetic allergens for more details. It may be wisest to advise women who are allergic to tosylamide formaldehyde resin to stop wearing all nail varnishes, as some products claiming to be free of the resin have been shown to contain it [34].

An alphabetical list of INCI names has been published, and an up-to-date list can be obtained via the Internet on http://www.pharmacos.eudra.org/F3/inci/index.htm.

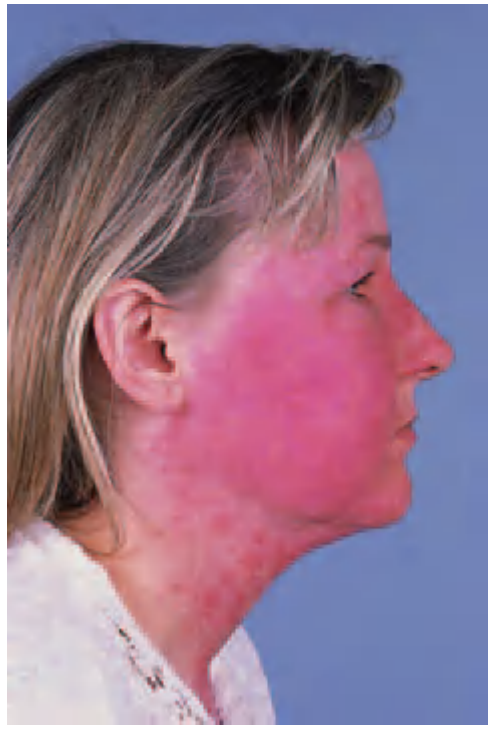

Fig. 20.18 Facial allergic contact dermatitis, often due to fragrance, preservatives or other ingredients of cosmetics. (Courtesy of Dr J.D. Wilkinson, Amersham General Hospital, Amersham, UK.)

Patch testing. The EEC-DRG standard series contains a number of cosmetic allergens, including fragrance mix, balsam of Peru (*Myroxylon pereirae*), parabens mix, quaternium-15, methylchloroisothiazolinone/methylisothiazolinone, formaldehyde, *p*-phenylenediamine and Colophonium (colophony). The British Contact Dermatitis Society (BCDS) include others in their recommended standard series: imidazolidinyl urea, diazolidinyl urea, methyldibromo glutaronitrile, chloroxylenol and 2-bromo-2-nitropropane-1,3-diol [35]. However, a wider screen of

allergens is advised when investigating cosmetic allergy; in particular, tosylamide formaldehyde resin (10% in petrolatum) and, if relevant, an acrylic nail chemical series when investigating facial and patchy disseminated eczemas and periungual problems. Patch testing with a series of UV filters is also advised. In addition, the main allergen suppliers have a range of other potential allergens, including more preservatives, antioxidants, surfactants, emulsifiers and other cosmetic excipients.

It is also most important to test all the cosmetics used by the patient. As a general rule, 'leave-on' products and perfumes can be tested 'as is' but, because of irritancy, soaps and shampoos should be diluted to 1% aqueous. There is still a risk of false-positive reactions and also, because of the dilution, false-negatives. We test toothpastes at 25% and hair dyes at 2%, both in petrolatum. Mascara and nail varnish are often irritant and should be applied to a chamber and left to evaporate before applying them as a patch test.

False-negative reactions and marginal irritant reactions are common when testing with cosmetics. Ideally, each component of a suspect cosmetic should be tested individually. Where there is high index of suspicion the individual components should be obtained. This is feasible if the manufacturer is willing to provide the raw ingredients. Each ingredient must be tested at an appropriate concentration in an appropriate vehicle. The test substance should also be of similar source/batch and purity to that contained in the product. Sometimes the allergy is to the substance itself, and sometimes to an impurity. The concentration necessary to test an individual substance is often greater than its concentration in the product. Manufacturers' patch-test kits, which contain ingredients at the concentration in which they are present in the product, are likely to be misleading and should not be used.

Testing with hair dyes is discussed on p. 20.72. The permanent wave chemical glyceryl monothioglycolate is tested at 1% in petrolatum.

Other tests. If cosmetic allergy is still suspected despite negative patch tests, the possibility of photoallergy should be considered and, if clinically indicated, photopatch tests should be undertaken.

ROATs (see p. 20.114) may also be worthwhile. Finally, after discussion with the patient, a usage test can be considered, with reintroduction of the suspected products, one at a time, and using each for up to 3 days.

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Table 20.6 Formaldehyde exposure.

Cosmetic preservatives	Cotton clothing (wash and wear, crease resistant)
Shampoos and soaps	Household cleaning products
Rayons	Polishes
Industrial biocides	Metalworking fluids
Orthopaedic casts	Wart treatment
Hyperhidrosis treatment	Antiperspirants
Embalming fluids and tissue fixatives	Preservatives
Renal dialysis	Colouring agents
Hardeners	Paints/lacquers
Glues	Water-resistant papers and tissues
Fibreboard/chipboard	Plywood
Tanning agents for leather	Photographic plates and solutions
Fumigators	Printing chemicals
Dry-cleaning materials	Disinfectants and deodorizers
Fertilizers	Insecticide (flypapers)
? Smoke from tobacco, coal and wood	

Antimicrobial agents and preservatives

Formaldehyde [1]

Chemistry [2]. Formaldehyde (HCHO) is a gas, and formalin is a solution of the gas in water (about 38%). Methylol groups can be combined with other compounds to form formaldehyde releasers, which are widely used as preservatives [3,4]. Formaldehyde may combine with other chemicals to produce resins, which may sensitize (see p. 20.86).

Prevalence. In individuals routinely patch tested for the investigation of contact dermatitis, the frequency of allergic positive reactions is generally 2–3%, although the North American Contact Dermatitis Group (NACDG) found 9.3% were positive between 1996 and 1998 [5–7].

Occurrence [2]. Formaldehyde is a ubiquitous allergen and Table 20.6 gives an idea of the wide variety of potential exposure that may occur. It can often be difficult to find a relevance for a positive patch test, but more commonly identified causes are cosmetic ingredients [1]. Shampoos may contain formaldehyde, although this is more likely to be of relevance in the context of hairdressers' hand dermatitis than in relation to transient use on the hair [8]. Some textile resins will release formaldehyde, and free formaldehyde may be found in treated cotton clothing and rayons (see p. 20.77). Cleaning products and polishes are considered to be an important source of exposure in the domestic environment [9]. Formaldehyde is used for the preservation of anatomical and pathological specimens, and those working with such specimens, for example histopathologists and embalmers [10], are at risk of allergy from free formaldehyde. It is used medically in renal dialysis [11] and may be found in orthopaedic casts [12]. It is also used as a treatment for warts and hyperhidrosis, especially of the feet, where powders containing paraformaldehyde may also be used. The very widely used surfactant sodium lauryl sulphate may be preserved with formaldehyde at a level of 0.1% [13,14]. It is used in detergents, shampoos, shower gels and bubble baths. Threshold concentrations for elicitation of contact dermatitis from formaldehyde are as low as 30 ppm in the axillae [15], and as low as 250 ppm under an occluded patch test [16].

In addition, formaldehyde-releasing chemicals must be considered, including certain preservatives and biocides widely used in industry (e.g. in cutting oils) and cosmetics (see below). Many of these releasers not only sensitize simultaneously with, but also independently of, formaldehyde [17–19].

Clinical features. The presenting dermatitis will depend on the source of contact, for instance a clothing pattern (see p. 20.78), a cosmetic pattern (see p. 20.57) or involvement of the hands in occupational dermatitis. Formaldehyde allergy is often only diagnosed retrospectively by finding a positive patch test, and relating this to the distribution of the problem by identifying formaldehyde or formaldehyde-releasing chemicals that come into contact with the affected site.

Avoidance. Avoidance may be difficult, bearing in mind the wide exposure possibilities, but it is important to recognize that avoidance steps are only required if the individual has skin problems that are relevant to the exposure. For those with a clothing pattern, avoidance advice is given on p. 20.79. If cosmetics and moisturizers come into contact with the affected sites, their ingredient labels should be carefully assessed in order that those containing not only formaldehyde but also the formaldehyde-releasing preservatives listed in Table 20.7 are avoided. It may also be necessary to contact manufacturers to enquire about the presence of formaldehyde in their products. The difficulties faced by patients in identifying formaldehyde in products is highlighted by the fact that in one study of sensitized persons with persistent dermatitis, all were still

Substance	Patch-test concentration
Quaternium-15	1% in petrolatum
Imidazolidinyl urea	2% in petrolatum (or 2% aqueous)
Diazolidinyl urea	2% in petrolatum (or 2% aqueous)
2-Bromo-2-nitropropane-1,3-diol	0.25% in petrolatum (or 0.5% in petrolatum)
DMDM hydantoin	2% aqueous

Table 20.7 Formaldehyde-releasing preservatives in cosmetics.

using at least one product containing formaldehyde. Only by detailed enquiries and access to product databases could the presence of formaldehyde be demonstrated [20].

A number of tests can be used to detect the presence of formaldehyde. The chromotropic test may give false-positive reactions and the alternative acetylacetone method may be more sensitive and specific (see p. 20.116). More recently, a closed container diffusion method for quantification of formaldehyde has been devised [21].

Prognosis. In a follow-up study of 57 patients with formaldehyde dermatitis, 29 (51%) still had frequent or persistent dermatitis several years later. Formaldehyde was identified in cosmetics, toiletries, household cleaners and other materials still being used by 38 of these patients. The authors concluded that patients who paid attention to their allergy had statistically significantly fewer eruptions than those who did not [22].

Patch tests. Patch testing is now recommended with formaldehyde 1% aqueous [23]. Previously, 2% aqueous was advised but false-positive reactions prompted a change in the recommended concentration, yet with the potential for the occasional false-negative reaction. It is a generally recommended standard allergen.

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Formaldehyde-releasing preservatives/biocides [1]

Quaternium-15

Quaternium-15 is also known as Dowicil 75, 100 or 200, chlorallyl methenamine chloride, *N*-(3-chlorallyl)-hexaminium chloride, and 1-(3-chlorallyl)-3,5,7-triaza-1-azoniondamantane. It is water soluble, odourless and colourless. Its broad antimicrobial activity is independent of the pH of the product [1].

Prevalence. Quaternium-15 can sensitize either independently or via formaldehyde release, or both [2–4]. The prevalence of positive patch tests in those attending for routine testing in North America is high, with 9.0% positive in a NACDG survey of 3436 patients [1]. Equivalent returns in Europe have generally shown lower levels, although the prevalence is dependent on the amount of usage in a given country. In the UK in 1986, 2.6% were positive, whereas there were no positives in a Dutch survey of the same year [2,5].

Occurrence. Quaternium-15 is found widely in cosmetic products and hand creams, including barrier and other creams used at work. It is found in a small number of medicaments in the UK [6].

Clinical features. These are discussed in the sections on allergy to cosmetics (p. 20.56) and medicaments (p. 20.51).

Avoidance. The INCI name is quaternium-15. Only ingredient-labelled cosmetics should be used, and any product shown to contain it should be avoided. Knowledge of synonyms is helpful, particularly as non-cosmetic products, including medicaments, may not adhere to INCI terminology.

Patch tests. For quaternium-15, 1% in petrolatum is the generally recommended concentration and vehicle. It is recommended as a standard allergen in Europe and North America.

Diazolidinyl urea

Diazolidinyl urea is also known as Germall II. It is a broad-spectrum biocide, soluble in water and effective at various pH levels [1].

Prevalence. Studies in the Netherlands on routinely patch-tested individuals showed that 0.6% of 2142 patients were patch-test positive [7], whereas in North America 3.7% were positive [1]. In one study 81% of those allergic to it were also allergic to formaldehyde [8].

Occurrence. Diazolidinyl urea has been used since 1982, predominantly in cosmetics, shampoos and creams, including barrier and other work creams.

Clinical features. These are discussed in the section on allergy to cosmetics (p. 20.56).

Avoidance. The INCI name is diazolidinyl urea. Only ingredient-labelled cosmetics and creams should be used, and any product shown to contain it should be avoided.

Patch tests. Patch testing at 1% and 2% aqueous has been advised [9], but it is generally supplied at 2% in petrolatum, which we have found satisfactory. Although not a frequent sensitizer in the UK, the BCDS has recommended its inclusion in the standard series [10].

Imidazolidinyl urea

Imidazolidinyl urea is also known as Germall 115. It has broad-spectrum antimicrobial activity and is colourless, water-soluble and not pH dependent. It acts synergistically with other preservatives and will kill *Pseudomonas aeruginosa* [1]. It releases only small amounts of formaldehyde, and may therefore possibly be less of a problem than other formaldehyde releasers for formaldehyde-sensitive subjects [11].

Prevalence. It is not a common allergen in most European studies, for example positive reactions occur in 0.7% of routinely patch-tested persons in Belgium [12] and the UK [2]. In North America the NACDG has reported a figure of 3.1% [13].

Occurrence. Imidazolidinyl urea is used in cosmetics, shampoos and hand creams, including barrier and other work creams. It is found in a cream containing the corticosteroid fluticasone, marketed in the UK as Cutivate®, where its presence is denoted by the word 'imidurea'.

Clinical features. These are discussed in the section on allergy to cosmetics (p. 20.56).

Avoidance. Imidazolidinyl urea is the INCI name. Only ingredient-labelled cosmetics should be used, and any product shown to contain it should be avoided. Cutivate® cream should also be avoided as a treatment.

Patch tests. Although patch testing with 2% aqueous has been advised [14], 2% in petrolatum is generally used. Its inclusion in the standard series is recommended by the BCDS in the UK [10].

2-Bromo-2-nitropropane-1,3-diol

2-Bromo-2-nitropropane-1,3-diol is also known as bronopol and BNPD. It has broad-spectrum antimicrobial activity and is particularly effective against *Pseudomonas aeruginosa*. It is soluble in water, alcohols, glycols and, to a lesser degree, oils [1].

Prevalence. The reported prevalence of positive reactions to 2-bromo-2-nitropropane-1,3-diol in routinely patch-tested individuals in North America in 1994–96 was 2.3% [13]. In the UK, 0.8% were positive in a 1986 study [2].

Occurrence. 2-Bromo-2-nitropropane-1,3-diol is present in a wide range of cosmetics, moisturizers, shampoos, medicaments and hand creams. It is used as a preservative when testing milk samples, and outbreaks of dermatitis have been reported from this source [15]. In the USA allergic problems have arisen from Eucerin cream [16] and in the UK from metronidazole gel used to treat rosacea [17].

Clinical features. These are discussed in the section on allergy to cosmetics (p. 20.56). In the occupational setting the usual site of involvement is the hands.

Avoidance. The INCI name is 2-bromo-2-nitropropane-1,3-diol. The simpler name of bronopol may be used in other products. Only ingredient-labelled cosmetics should be used, and any product shown to contain it should be avoided.

Patch tests. The two recommended concentrations are 0.5% and 0.25% in petrolatum; 0.5% may occasionally give false-positive reactions. It is recommended by the BCDS for the standard series in the UK [10].

DMDM hydantoin

DMDM hydantoin is also known as Glydant and is a colourless liquid that contains 0.5–2% free formaldehyde and over 17% combined formaldehyde [1].

Prevalence. In the Netherlands, 1.2% of patients routinely patch tested to DMDM hydantoin showed allergic reactions [5], and the NACDG reported up to 2.6% positivity [13]. Testing with formaldehyde demonstrated concomitant sensitivity in eight of 15 (57%) individuals [18].

Occurrence. DMDM hydantoin is used in a wide range of cosmetics. Surprisingly, there are no reports in the literature of allergy from this source [11], but we have seen occasional allergies relevant to cosmetics.

Clinical features. These are discussed in the section on allergy to cosmetics (p. 20.56).

Avoidance. DMDM hydantoin is the INCI name, and it can be identified in a product provided it is fully ingredient-labelled. There is evidence from ROATs that formaldehyde-allergic patients should avoid products containing DMDM hydantoin [18].

Patch tests. Patch tests have been undertaken at 1–3% aqueous and 1% in petrolatum. We have found 2% aqueous satisfactory.

Other biocides

The above formaldehyde releasers are encountered particularly in cosmetics, including shampoos and other hair-care products. A much broader series of formaldehyde releasers is to be found in materials such as industrial and household cleaning agents, colouring agents, paints and lacquers, polishes and metalworking fluids [19]. A knowledge of these is helpful, particularly when identifying ingredients in the aforementioned materials.

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Isothiazolinones [1]

Isothiazolinone preservative systems have effective broad-spectrum activity against both bacteria and fungi. A number of different formulations have been demonstrated to be sensitizing to the skin.

1 A mixture of 5-chloro-2-methyl-4-isothiazolin-3-one and 2-methyl-4-isothiazolin-3-one in a 3 : 1 ratio by weight. The INCI name is methylchloroisothiazolinone/methylisothiazolinone (MCI/MI). This mixture has various other names, including Kathon CG, Kathon WT, Euxyl K 100 and Acticide.

2 1,2-Benzisothiazolin-3-one (BIT), which is used under the commercial name Proxel in a range of biocides.

3 2-*n*-Octyl-4-isothiazolin-3-one, also known as Kathon 893, Kathon LP and Skane M-8.

There seems to be little in the way of cross-sensitization between these compounds [2]. A further isothiazolinone, 2-methyl-4,5-trimethylene-4-isothiazolin-3-one (MTI), has also sensitized but only in the laboratory setting [3].

Methylchloroisothiazolinone/methylisothiazolinone [4,5]

Prevalence. Since first marketed in 1980, there have been many reports of allergy, particularly from Europe, with a prevalence of positive reactions as high as 8.3% in routinely tested patients [6,7]. However, there has been considerable variability in the prevalence of allergy from country to country [7]. In the USA, rates of 2–3% have generally been the rule [7].

There has been much discussion about the reason for differing prevalence rates worldwide. It has been suggested that in some countries there has been lack of control over the amount of this biocide added to products that come in contact with the skin [7]. Furthermore, patch testing with concentrations as high as 300 ppm in some centres may have produced false-positive reactions, whereas other centres have tested with 100 ppm [7].

Levels below 15 ppm are felt unlikely to induce sensitization [8], and in those already sensitized this concentration has been shown to be insufficient to elicit a dermatitis in many instances [8,9]. A decrease in, and stabilization of, frequency of allergy is felt to reflect tighter regulation of concentrations used. The maximum allowable concentration in the European Union (EU) for both 'rinse-off' and 'leave-on' cosmetics is 15 ppm, with a lower recommended concentration of 7.5 ppm for 'leave-on' products in the USA [10].

Occurrence. MCI/MI is now mainly used in 'rinse-off' products, including liquid soaps and cleansers, shower gels, bubble baths and shampoos [9]. Nevertheless, some 'leave-on' cosmetics may contain it. It may be present in medicated wipes and moist toilet paper [11–13]. In 1990, a Danish study showed its presence in 48% of 'rinse-off' and 31% of 'leave-on' cosmetic products used there [14]. In 1988, 25% of all cosmetic products in the Netherlands were reported to contain it [4].

However, this biocide can be found in other situations, most notably soluble cutting oils, paints, glues, spin finishes, household cleansers, printing inks, latex emulsions, water cooling systems and as a slimicide in paper mills [1,15–25].

Clinical features. These are discussed in the section on allergy to cosmetics (p. 20.56). Shampoos do not usually cause problems from washing the hair but allergy may be associated with hairdressers' hand dermatitis. Hands are the usual sites for occupational allergic dermatitis, although an airborne pattern has been described [26]. A chemical burn from spillage of concentrated MCI/MI on to any part of the skin may be followed by a secondary delayed dermatitis from active sensitization [27].

A positive patch test to MCI/MI associated with perianal dermatitis suggests the possibility of moist toilet paper or wipes as a cause [11–13].

Patch tests. The recommended patch-test concentration and vehicle is now 100 ppm in water, as it has been suggested that 200–300 ppm might be associated with false-positive reactions and active sensitization [28]. However, there is also evidence that 200 ppm may identify sensitized subjects missed by the 100 ppm patch test [29,30]. MCI/MI is generally recommended as a standard allergen.

1,2-Benzisothiazolin-3-one

Occurrence. Sensitization normally occurs from manufacturing or handling the raw material, for example paint manufacture, water treatment or in the laboratory [31–33]. Painters and decorators may be exposed from not only paints but also wallpaper pastes [34,35]. Allergy has been reported in the pottery industry from its presence in mould-release agents. Other potential sources include soluble cutting oils, printing materials, water softener and air-freshener manufacture [1,36–40].

Clinical patterns. Classically, with hand dermatitis, a low-grade constitutional-looking palmar psoriasiform or pompholyx pattern occurs (see Fig. 20.5). In more severe cases an exposed-site pattern develops. Sensitized workers involved in manufacture may complain of a burning sensation of the eyes and face within the factory environment without there being observable dermatitis.

Patch tests. A number of patch-test concentrations in petrolatum have been suggested, varying from 0.05 to 1%. False-positive reactions have been reported with 0.1% in petrolatum [41], and as our experience is that false-positive reactions occur above 0.05% in petrolatum we advocate the use of this concentration.

2-n-*Octyl-4-isothiazolin-3-one*

Occurrence. 2-*n*-Octyl-4-isothiazolin-3-one may occur in leather, soluble cutting oils, paints and polishes, cleaning agents and wood preservatives [1].

Clinical features. Reports of contact allergy tend to be sporadic and anecdotal, and these include hand dermatitis associated with its presence in paints [35,42]. We have found a small number of positive reactions in individuals with possible shoe dermatitis, but of unproven relevance.

Patch tests. 2-*n*-Octyl-4-isothiazolin-3-one is usually patch tested at 0.1% in petrolatum.

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Parabens (hydroxybenzoates) [1–3]

Parabens are esters of *p*-hydroxybenzoic acid. The four main esters used are methyl-, ethyl-, propyl- and butylparaben (hydroxybenzoate). They may have a synergistic effect when used in combination. They are more active against Gram-positive than Gram-negative bacteria (including poor activity against *Pseudomonas*). They are also active against moulds and yeasts. They are stable, colourless, odourless and poorly soluble in water [1].

Prevalence. There is a relatively low prevalence of positive reactions in routinely patch-tested patients, and rates between 1 and 1.7% are typical [4–6].

Occurrence. Parabens are very widely used preservatives in topical and parenteral medicaments, paste bandages, cosmetics and foods [2,7].

Clinical features. The striking feature of allergy to parabens is its relative infrequency compared with the degree of usage and exposure in the general population [1,2]. Relevant allergies are mainly from sensitization to medicaments (including paste bandages) used on varicose ulcers and eczema [8,9], but contact allergy may be superimposed on other constitutional eczemas and it may occur on high-risk sites such as the anogenital region [10]. Relevant problems from parabens in cosmetics are rare

[1]. Interestingly, many individuals allergic to parabens in medicaments can use cosmetics containing them on normal skin without any problem, the so-called 'paraben paradox' [11]. However, there are exceptions, and sometimes cosmetics containing parabens have to be abandoned [10,12]. Flares from parabens in food have been reported in sensitized subjects, but a low-paraben diet did not help subsequently [13].

Avoidance. The INCI name for this group of preservatives ends in '-paraben' according to the ester used. In individuals in whom cosmetic allergy may be relevant, the full ingredient label must be examined in order that they may be avoided. Terminology for medicaments may be different, and the name may end in '-hydroxybenzoate'. Furthermore, the commercial names may sometimes be used, in particular Nipagin, Nipsasol and Nipabutyl, but there are many others. Only medicaments and paste bandages whose ingredients are known in full should be used, avoiding those containing parabens or agents whose names are synonyms of parabens. It is advisable to avoid all parabens even if only one or two are positive in breakdown testing.

Patch tests. Hydroxybenzoates are normally tested as a mix of the four esters, each at 4% in petrolatum. The mix is marginally irritant, and testing with each ester individually will help to confirm whether the patch-test reaction is truly allergic [2,4]. Often more than one ester will react, which may be a marker of both concomitant sensitization and cross-sensitization. Parabens mix 16% in petrolatum is generally advised for the standard series.

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Methyldibromo glutaronitrile [1]

Methyldibromo glutaronitrile (MDBGN), also known as dibromocyanobutane, is to be found in the preservative system Euxyl K 400 (also called Tektamer 38), which is a mix of MDBGN and phenoxyethanol in a ratio of 1 : 4. Euxyl K 400 is a broad-spectrum preservative with activity against fungi and bacteria. MDBGN is nearly always the allergen when sensitization to Euxyl K 400 occurs [2].

Prevalence. There is evidence that MDBGN is an emerging allergen in Europe and the USA [3–7]. Of particular significance are the findings of a multicentre European study monitoring rates of preservative allergy. The frequency of MDBGN allergy has risen from 0.7 to 3.5%, whereas the level of all other cosmetic preservative allergy has remained stable [6]. In one small US study involving 163 routinely patch-tested patients, 11.7% were allergic to MDBGN [4]. Rates for the NACDG have varied from 2.7 to 7.6% according to the test concentration used [7]. This has caused concern about the correct test concentration [2].

Occurrence [2,8]. MDBGN is widely used in cosmetics, sunscreens, shampoos, liquid soaps, and barrier and moisturizing creams used at work [9–13]. Other sources include moistened toilet tissues, ultrasound gel, adhesives, soluble cutting oils and latex paints [2,3,8,14–16]. The rising number of reports of allergy resulted in a proposal to restrict the use of this preservative to rinse-off products with a maximum concentration of 0.1% in Europe in 2002.

Clinical features. These are discussed in the section on allergy to cosmetics (p. 20.56). In the occupational setting the usual site of involvement is the hands. We have found a small number of subjects with unsuspected allergy who were clinically suspected of having occupational irritant hand dermatitis prior to patch testing. The source was their work cleansers and/or creams containing MDBGN, and following withdrawal of these the dermatitis resolved and they were able to continue in the same work [13].

Allergy to Euxyl K 400 in wipes and moistened toilet tissues is a potential cause of perianal dermatitis [3,14].

Avoidance. Methyldibromo glutaronitrile is the INCI name that should be sought on the full ingredient label. Many producers of work cleansers and creams now give a full ingredient list on the health and safety data sheet. Skin products whose ingredients are not known should not be used.

Other potentially allergenic sources may require specific enquiry as to the nature of the biocide/preservative used.

Patch tests. We prefer to test MDBGN at 0.3% in petrolatum, as we and others [6] have found it marginally irritant; 0.1% has been used as an alternative but may give false-negative reactions [17]. Euxyl K 400 is also available at 0.5% and 1% (containing 0.1% and 0.2% MDBGN) in petrolatum. A 2.5% concentration may increase the return, but with the risk of false-positive reactions [7]. It has been recommended for the BCDS standard series at a concentration of 0.3% [18].

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Chloroxylenol (parachlorometaxylenol, PCMX) [1]

Chloroxylenol is a halogenated aromatic compound used not only as a preservative but also as an active disinfectant. It is water and oil soluble and active against Gram-positive and Gram-negative bacteria [2].

Prevalence. Generally, reports of chloroxylenol allergy have been sporadic, with few large-scale studies. In one UK study 1.8% of 951 routinely tested persons were patch-test positive, with a high level of current or previous relevance [1]. A report from the USA documents seven patients sensitized by medicated Vaseline or electrocardiogram paste [3]. A more recent British study yielded a lower prevalence rate of 0.4% [4].

Occurrence. Chloroxylenol is a potential allergen for the UK as it is found in Dettol, a widely used household disinfectant. This may also be used in diluted form as a wound cleanser. However, it is important to know that Dettol is used in many ways that may not always be predictable. Some people use the product to 'decontaminate' themselves or their environment. It is not uncommon for them to add Dettol to bathwater, and if they have a skin disorder that they consider represents an infection, they may add extra in the hope of its eradication. Persons with perineal inflammatory disorders are particularly liable to do this. Some may apply it neat to their skin in the hope of eradicating a genuine or imagined infection; the residual smell may be a helpful diagnostic indicator of use. Clothes and bedding may be washed in Dettol and inadequately rinsed, and then worn or used.

Chloroxylenol may also be found in a number of over-the-counter pharmaceutical preparations for cuts, grazes and infections [1]. Other sources include foot and talcum powders, soaps and cleansers, work creams, coolant oils, electrocardiograph pastes and, rarely, cosmetics [3,5–8].

Clinical features. In many cases there is a localized skin eruption at the site where a product containing chloroxylenol has been applied, or allergy may present as an unexpected exacerbation of pre-existing dermatitis.

Hand dermatitis is a potential problem for cleaners coming in contact with disinfectants when their hands are unprotected, and allergy to chloroxylenol in other work materials (e.g. coolant oils) may give a similar distribution of rash.

More widespread eruptions may be associated with its use for washing and bathing (Fig. 20.19), and also when applied to clothing. Recently, widespread hypopigmentation following contact allergy to chloroxylenol added to bathwater has been reported [9].

Often, the source is only identified retrospectively after finding a positive patch test.

Avoidance. Chloroxylenol is the INCI name. Cosmetics and work creams that contain it can usually be identified from the full ingredient label or data sheet. Labels on medicated foot powders and talcs generally acknowledge it as

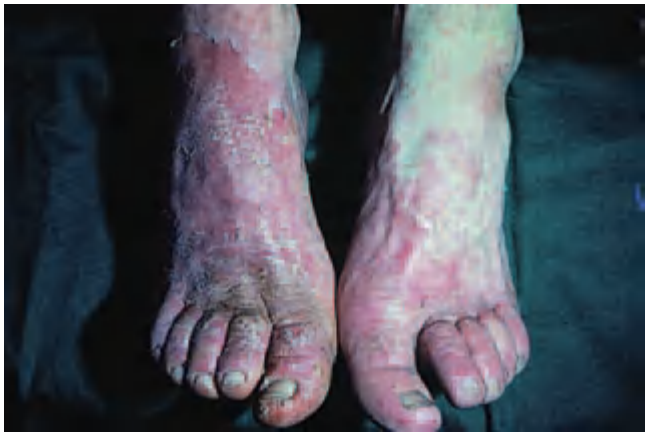

Fig. 20.19 Allergy to chloroxylenol from washing with Dettol. (Geoffrey Auckland collection, Hope Hospital, Manchester, UK.)

an ingredient, but specific enquiries may be necessary to establish its presence in some topical medicaments and disinfectants.

Patch tests. Chloroxylenol is generally patch tested at 1% in petrolatum. It may cross-sensitize with chlorocresol [10]. It has been recommended as a standard allergen for the UK [1,4].

Chlorocresol (parachlorometacresol, PCMC)

Chlorocresol is identical to chloroxylenol, except for the absence of a methyl group on the benzene ring [2]. It is active against Gram-positive and Gram-negative bacteria, and is water and oil soluble [2].

Prevalence. Chlorocresol is a rare allergen. Only 0.4% of routinely patch-tested patients in Manchester were allergic to it in a 1991 study [11]; more recently, a multicentre UK survey confirmed a continuing low rate of 0.6% [4].

Occurrence. The major source is corticosteroid creams [10,12,13]. In the past, aqueous cream BP was preserved with chlorocresol, but this is generally no longer the case. We have only seen it as a sensitizer from topical medicaments, although it may be used in hand cleaners, metalworking fluids and occasionally cosmetics [14,15].

Clinical features. These are discussed in the section on medicament allergy (p. 20.51).

Avoidance. It is helpful to give a sensitized patient a list of corticosteroid creams that indicates what they contain and which are free from chlorocresol. Moisturizers should not be used unless they are fully ingredient-labelled or known to be free from this preservative. The INCI name is chlorocresol.

Patch tests. The recommended test concentration and vehicle is 1% chlorocresol in petrolatum. Although contact allergy is rare, its use in many popular corticosteroid creams available in the UK has prompted the BCDS to recommend its inclusion in the standard series [16]. Cross-sensitivity with chloroxylenol is well recognized [10].

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Organic mercurials

Sensitizing compounds include phenylmercuric salts and thimerosal (thiomersal, merthiolate). Thimerosal is composed of an organic mercurial and thiosalicylate. Allergy may occur to one or the other moiety [1].

Occurrence. Organic mercurials are used as preservatives in vaccines [2–4] and antigen extracts [5], eye drops, contact lens solutions [6], and eye make-up and remover products [7]. Their use in all other cosmetics is banned by European legislation. Phenylmercuric salts have been used in contraceptive jelly, antifungal treatments, shoe linings and emulsion paints [8–10].

Prevalence. Positive reactions occur in 4–5% of individuals routinely patch tested with thimerosal; higher rates

have been reported in North America (10.9%) and Japan (9.5%) [10,11].

Clinical features. Allergy to organic mercurials in eye medicaments and contact lens preservatives will induce a localized dermatitis affecting the eyelids, with extension periorbitally. Palmar and fingertip dermatitis, isolated conjunctivitis, and even corneal neovascularization from contact lens solutions are described [12–14].

Many people have a positive patch test to thimerosal of no demonstrable relevance [15]. Sensitization is thought to develop from parenteral vaccinations and immunotherapeutic agents preserved with thimerosal [16–18]. Localized reactions from injections are rare but have been observed, with one case having a generalized dermatitis [19,20].

Allergy to the thiosalicylic acid component may be associated with photoallergy to piroxicam [21,22].

Patch tests. Phenylmercuric salts may be tested at 0.01% and 0.05% in petrolatum and water. Thimerosal is normally tested at 0.1% in petrolatum.

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Other preservatives/biocides

Many other antimicrobial agents have been used as preservatives and biocides, and reported to sensitize. These include chloracetamide, triclosan (Irgasan DP300), benzalkonium chloride, sorbic acid, benzyl alcohol, captan, chlorhexidine, ethylenediamine tetracetate (EDTA), dichlorophene, iodopropynyl butyl carbamate and many more [1,2]. Sources where antimicrobial protection is required are legion, but include particularly medicaments, cosmetics, cleansing agents, paints and soluble coolant oils. The possibility of allergy to this group of materials must always be considered as a cause of dermatitis.

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Vehicles and other cosmetic and medicament excipients

Lanolin [1]

Lanolin is a natural product obtained from sheep fleece. It is a complex and variable mixture composed of sterols, fatty alcohols, fatty acids and their esters. Wool wax alcohols (INCI name: lanolin alcohols) are obtained by hydrolysis of the oily wax fraction of the fleece. Although they are not all known, it is thought the allergens are mainly, if not all, in this fraction [2–5].

Attempts to reduce allergenicity include modification by acetylation, hydrogenation, ethylenation, transesterification and removal of the allergenic fractions by a purification process [1,2,5–8]. Allergenicity has been shown virtually to disappear by removing detergent residues and reducing the level of alcohols to below 3% (w/w) [9].

Prevalence. Prevalence of lanolin allergy in the general population is thought to extremely low [10]. Contact allergy is normally detected by patch testing with wool alcohols, and enhanced identification of allergic subjects

has been attempted by testing with a wider range of lanolin derivatives and lanolin itself. Most surveys of patients routinely patch tested to wool alcohols report positive reactions in 1.7–3.3% [11–13]. However, other studies, in which patch testing with lanolin derivatives including Amerchol L 101 (mineral oil and lanolin alcohol) was undertaken, have shown a much higher rate of positive reactions than those using wool alcohols alone [14,15].

The belief that lanolin is a frequent sensitizer has been questioned by Kligman [1,16,17], and there are grounds for this as experimental sensitization of animals and humans has not been achieved [16]. Furthermore, patch testing with wool alcohols at 30% in petrolatum (as generally recommended) and with Amerchol L 101, particularly if patch tested at 100%, may give false-positive results [11,17,18]. In addition, retesting showed that the allergy 'disappeared' in up to 40% of those originally considered to have positive reactions [8,18,19]. Nevertheless, there is good evidence of a high prevalence of allergy to lanolin in medicaments applied to varicose eczema [20,21]. The use of lanolin-containing medicaments on other chronic eczemas, particularly in elderly women, may be associated with the development of lanolin sensitivity [2,6]. However, usage on normal skin rarely seems to be associated with significant problems [22].

Occurrence. Lanolin is most commonly encountered in medicaments, emollients, bath additives and cosmetics. Other sources [1] include polishes, waxes, inks, adhesive tapes and bandages [23], anticorrosive coatings [24], sealants and cutting oil emulsions.

Clinical features. These are discussed in the sections on allergy to cosmetics (p. 20.56) and medicaments (p. 20.51).

Avoidance. Lanolin alcohols is the INCI name for lanolin, and its presence in cosmetics can be established by examining the full ingredient label. However, prescribed and over-the-counter medicaments are not always fully ingredient-labelled in the UK, and examination of the data sheet or contacting the manufacturer may be necessary to ascertain whether it is in a medicament. This also applies to other potential domestic and work exposures such as polishes, waxes, coatings and oils.

Patch tests. Many patients state that they are allergic to lanolin but patch testing does not substantiate this. Conversely, allergy may be unsuspected, particularly when there is an associated eczema being treated with a lanolin-containing medicament.

Standard testing with wool alcohols 30% in petrolatum is advised, but where medicament sensitivity is suspected or to be excluded, extra lanolin allergens should be tested. We use Amerchol L 101 50% in petrolatum and lanolin 'as is'. Weak positive reactions may be false positive, but can be exceedingly difficult to distinguish from weak allergic reactions.

Cetearyl alcohol

Cetearyl alcohol is the INCI name. It has emulsifying and stabilizing properties, and is also known as cetylstearyl alcohol and Lanette O. It is essentially a mixture of two long-chained stereoisomers, cetyl and stearyl alcohol. These alcohols are components of lanolin.

Prevalence. Reports of allergy are often anecdotal, although there is evidence of it being a significant allergen complicating varicose eczema and ulcers, with up to 16% positive reactions in patients with these conditions attending for patch testing [21,25,26].

Occurrence. Cetearyl alcohol is widely used in steroid creams, emollients and cosmetics. Sometimes only one of the stereoisomers is used. It is a component of emulsifying wax and therefore found in emulsifying ointment and aqueous cream BP.

Clinical features. These are discussed in the sections on allergy to cosmetics (p. 20.56) and medicaments (p. 20.51).

Avoidance. Cetearyl alcohol is the INCI name, but cosmetics labelled as containing cetyl or stearyl alcohol should also be avoided. Avoidance of medicaments, including emollients, is more difficult, as they are not always fully ingredient-labelled. Even when they are, they may not follow the rules for cosmetics. Emulsifying wax is an ingredient that may be listed without it being clear that the preparation contains cetearyl alcohol. The designations cetylstearyl alcohol or Lanette O may be used instead of the INCI name. It may be preferable to provide a sensitized individual with a list of products free of cetearyl alcohol.

Patch tests. Although it is an uncommon allergen, its ubiquitous presence in dermatological therapies means that identification of allergy is important. The BCDS has therefore recommended its inclusion in the standard series for the UK [27]. Patients suffering from varicose eczema should always be patch tested with it. It is normally tested at 20% in petrolatum.

Ethylenediamine dihydrochloride [28]

Ethylenediamine is a low-molecular-weight aliphatic amine. Some antihistamines are chemically related, which may be of significance to the sensitized patient.

Prevalence. Allergy to ethylenediamine is becoming less common, and sufficiently so for the EEC-DRG to

recommend omitting it from their recommended standard series [29,30]. In general, the prevalence of allergy reflects the amount of nystatin/neomycin sulphate/gramicidin/triamcinolone acetonide cream (see below) being used in the catchment area of those being tested, as this is the usual source of sensitization. This preparation has been reformulated in the USA, but the original formula may still occur in generic creams. It is still used and sensitizes sufficiently frequently in the UK for the BCDS to recommend the continued use of ethylenediamine in the standard series [27].

Occurrence. Ethylenediamine is used as a stabilizer in a combined preparation that contains nystatin, neomycin sulphate, gramicidin and triamcinolone acetonide, marketed in the UK as Tri-Adcortyl® cream and in the USA and other countries as Mycolog® cream. The equivalent ointment does not contain ethylenediamine. It is a component of parenteral aminophylline, which may also come in contact with the hands [31–33]. Other systemic and topical medicaments are also related to ethylenediamine, most notably hydroxyzine and probably cetirizine [34,35], as well as piperazines [36], which include the antihistamines meclozine and cyclizine [28]. Industrial exposure is potentially wide, as it and related amines are used as epoxy hardeners [37–39] and in coolant oil [40,41], wire-drawing lubricants [42,43], floor polish remover [44], antifreeze, synthetic waxes, anticorrosive paints and dye manufacture. It is used as a rubber stabilizer, but we have not seen sensitization occurring from rubber garments.

Clinical features. These are discussed in the sections on medicament (p. 20.51) and systemic contact allergy (p. 20.28).

Occupational patterns will depend on the source of the exposure, but the hands are the most likely site to be affected. In those sensitized to epoxy systems, there is often concomitant sensitization to epoxy resin, with an associated exposed-site pattern of dermatitis.

Avoidance. Avoidance of topical exposure to the creams containing nystatin, neomycin sulphate, gramicidin and triamcinolone acetonide is essential. It may also be necessary to avoid topical antihistamine creams and eye drops. Once sensitized, individuals may be at risk of systemic contact dermatitis. In the UK, avoidance of systemic hydroxyzine, piperazine and probably cetirizine is advisable [34,45–47]. Sensitized patients must also avoid parenteral aminophylline [48–50].

Avoidance of occupational exposure depends on identification of the source.

Patch tests. Ethylenediamine is tested at 1% in petrolatum. It is still recommended for standard testing in the UK because of the continued availability of Tri-Adcortyl® cream.

Other excipients

There is potential for virtually any vehicular component of a cosmetic or medicament to cause sensitization. If allergy is suspected, it may be necessary to widen the range of allergens tested. Examples include antioxidants (butylated hydroxyanisole, butylated hydroxytoluene, *t*-butylhydroquinone [51] and gallates [52–54]), surfactants (e.g. cocamidopropyl betaine, which may cause hand dermatitis in hairdressers from shampoos [55–57], and coconut diethanolamide [58–60]) and humectants (e.g. propylene glycol [61]). This list is by no means exhaustive but is a further indication of the range of possible excipient allergens in cosmetics and medicaments. Many such excipient allergens are available from the main allergen suppliers, suitably prepared for patch testing.

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p-Phenylenediamine and related dyes [1–3]

p-Phenylenediamine (PPD) and *p*-toluenediamine (PTD) are aniline derivatives, whose main use is for dyeing hair. These chemicals are colourless until oxidized by hydrogen peroxide in the presence of ammonia, and polymerized by a coupler, often in the presence of other intermediates, to produce a variety of shades of colour that stay fast within the hair shaft [2]. Once oxidized, PPD is said to be no longer allergenic, although some cases of allergy have been reported [3]. Semi-permanent hair dyeing may be undertaken with related dyes, for example *o*-nitro-*p*-phenylenediamine (ONPPD).

There is structural similarity to some azo dyes (e.g. *p*-aminoazobenzene). Many disperse dyes used to dye synthetic clothing and fibres are azo dyes [4]. It may be difficult to make these dyes fast to the fibres, thereby allowing sensitization of the skin to take place [5].

Prevalence. It was estimated in 1973 that 40% of women in the USA use hair colours [6]. Of those patch tested in the mid-1990s by the NACDG, 6.8% were allergic to PPD [7]. At the same time, 4.8% were allergic to PPD in Germany and Austria, where there was considerable geographical variation in frequency (2.8–7.1%) [8]. In a large Belgian study of over 5000 routinely tested patients, 7.2% were allergic to PPD, 1.6% were allergic to PTD and 1.8% were allergic to ONPPD [9]. PPD is the second most common allergen of relevance to hairdressers in Europe [10].

Generally, routine patch testing to azo dyes is not undertaken, although this has been advocated [11]. By routinely testing with four azo dyes, 4.8% of patients were found to have positive reactions and this increased to 5.8% when 12 further dyes were routinely tested [11]. PPD allergy is not a good marker for azo dye allergy as cross-sensitization occurs in only 20% of patients allergic to azo clothing dyes [11,12]. If textile allergy is suspected, a special series of clothing dyes, including azo dyes, is normally tested (see p. 20.79).

Occurrence. PPD and PTD are found in permanent hair dyes, and ONPPD in semi-permanent hair dyes whose colour will persist for 5–10 shampooings. In the EU, PPD is allowed in hair dyes up to a concentration of 6% free base [13]. PPD has been used to dye fur [14]. PPD may be mixed with henna and used on the skin as a temporary tattoo [15–19]. Application of these is particularly likely

during beach holidays. Allergy to PPD is reported from a violin chin-rest and cello bowstring stain [20,21].

PPD derivatives are used as rubber antioxidants, particularly in heavy-duty black rubbers. Although reported to be in photographic developers (including those for radiography), photocopiers, petrol, oils, greases and printing inks, sensitization is rare from these sources.

Azo dyes are mainly encountered as disperse dyes for synthetic clothing. Allergy to azo dyes in maggots used for fishing bait has been reported [22].

Clinical features. PPD and related hair dye allergy can result in extremely severe skin reactions. The scalp is often relatively spared, but severe oedema and weeping of the scalp margin, ears and eyes, with more extensive secondary-spread eruptions, may be seen. However, there can be lower grade reactions, usually around the scalp margin. The patient does not always recognize the relationship of the skin eruption to dyeing the hair. Oxidized hair dye is not thought to be allergenic [23]. Nevertheless, allergic contact dermatitis from partners' hair has been described [24–26], perhaps as a result of poor dyeing technique, which is more likely with self-application of the dye.

Lichen planus-like presentations of hair dye allergy have been reported from the Indian subcontinent, and we have seen similar patterns in Asian patients in the UK [27]. Furthermore, in our experience, hair dye allergy is relatively common in both sexes in this ethnic group. An equivalent overrepresentation has been identified in African-Americans [28].

Hairdressers may become sensitized by the dyeing process, resulting in hand dermatitis. A pre-existing irritant hand dermatitis may predispose to this. Styling of dyed hair should theoretically not present a problem in view of the reported non-allergenicity of the oxidized dye.

Reactions in temporary tattoos may be delayed for about 2 weeks while sensitization takes place, but the subsequent reaction can be severe and persistent. Erythema multiforme-like and lichenoid eruptions are described, and both post-inflammatory hypopigmentation and hyperpigmentation can be a feature [15–19,29].

Immediate-type hypersensitivity presenting as an urticarial reaction to PPD is also recognized [30,31] and contact anaphylaxis is described [32].

Clinical presentation of clothing dye allergy is described on p. 20.78.

Avoidance. Permanent hair dyes will be clearly marked 'contains phenylenediamines', and that patch testing is advised on each occasion prior to dyeing the hair. Open testing on retroauricular skin, with a 2-day reading, has been confirmed to be an accurate method of identifying sensitized persons [33], but this is rarely done by the individual or the hairdressing salon. Once PPD allergy is diagnosed, the hair should not be permanently dyed. Semi-permanent dyes might be tolerated, but in the region of 25% of PPD allergic subjects are likely to have problems due to cross-sensitivity [2]. An open patch test with these dyes is also advised before use. Other alternatives include henna and colour rinses with temporary (non-PPD related) dyes.

Disperse azo clothing dye avoidance is discussed on p. 20.79.

Cross-sensitivity. Molecules with a similar structure may cross-sensitize with PPD, for example benzocaine, procaine, sulphonamides, diaminodiphenylmethane, *para*-aminobenzoic acid (PABA) UV filters and certain azo dyes, and patients should be counselled about this possibility [2,3].

Patch tests. A significant drop in the frequency of positive allergic reactions was noted when PPD base 1% in petrolatum was changed to PPD dihydrochloride by the allergen suppliers, and relevant positive cases were missed [34]. PPD base is again the preferred standard test allergen. In some individuals close examination of the patch test site is required, as a positive reaction may be obscured by the black colour left by the patch test. Fierce '+++' reactions to PPD are seen on occasions. In those with a recent severe presumed hair dye allergic dermatitis, and particularly those with a temporary tattoo reaction, we would recommend an initial test concentration of 0.5% in petrolatum. Related hair dye chemicals are also usually tested at 1% in petrolatum.

Azo dyes will normally be incorporated into a larger series of allergens for the investigation of textile dermatitis (see p. 20.79). They are also tested at 1% in petrolatum.

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UV filters [1–3]

UV filters work by absorbing light chemically or by acting as a physical block. The latter agents are usually based on titanium or zinc oxide, which are not sensitizers. However, some chemical UV filters may be contact allergens, photocontact allergens or both. The main groups of light-absorbing chemicals are PABA and its derivatives, cinnamates and salicylates, which absorb predominantly UVB light; benzophenones, which also absorb some longer wavelength UVA light; and dibenzoylmethanes and camphor derivatives, which tend to absorb the longer wavelength UV light [2,3]. UV filters may be known by many synonyms; the INCI names are used here.

Prevalence. Ordinarily UV filters are not tested in the standard series, and aimed testing is generally the rule. However, many UV filters are included routinely in the photopatch-test series. The pattern of usage of UV filters varies and prevalence figures will reflect this.

Benzophenone 3 (oxybenzone) is the most frequently reported UV filter allergen [3–8]. Benzophenone 10 has also been identified as an allergen and photoallergen but is not commonly used in sunscreen manufacture [3,9].

Isopropyl dibenzoylmethane was a common photosensitizer in the past, and as a result has been withdrawn from the market [8,10]. Butyl methoxydibenzoylmethane is an occasional sensitizer and photosensitizer [3,6,9–12]. Allergy and photoallergy to PABA and derivatives are now less frequent, but these agents may still be found in cosmetics and sunscreens [6,13,14]. Cinnamates are commonly used as UVB filters and both allergy and photoallergy to them are seen occasionally [3–6,10]. A high prevalence of allergy to 4-methylbenzilidene camphor was noted in one survey, but other reports tend to be of single cases [10]. A small numbers of cases of phenylbenzimidazole sulphonic acid allergy and photoallergy have also been seen [3,6,10,15].

Occurrence. These chemicals are not confined to sunscreens. They may be added to cosmetics in small quantities to prevent photodegradation and also as an 'antiageing' agent. UV light absorbers may be added to plastics and spandex. Allergy from this source is unusual but has been reported, most notably from 2-(2-hydroxy-5-methylphenyl)-benzotriazole (Tinuvin P) [16,17].

Clinical features. Allergy and photoallergy from UV filters may coexist or occur separately. Clinical features are discussed under photocontact and also cosmetic allergy (see p. 20.56). It is important to appreciate that other photodermatoses can be complicated by photoallergy to UV filters being used to treat the disorder, and this may easily go unrecognized. The possibility of allergy and photoallergy to UV filters must be considered before individuals are diagnosed as having an idiopathic photodermatosis such as polymorphic light eruption.

Avoidance. Once allergy or photoallergy has been demonstrated, patients should be appraised of the need to avoid sunscreens and cosmetics containing the allergen, which will be identified by its INCI name. They should only use fully ingredient-labelled cosmetics (including hairsprays). In addition, a list of synonyms should be given to the patients as they may encounter sunscreens labelled differently in other countries.

Patch tests. UV filters are generally tested at 10% in petrolatum, although 5% has also been advocated. We believe that benzophenone 4 tested at 10% gives false-positive reactions and 5% may be a better test concentration. Sunscreens and cosmetics containing UV filters should also be patch tested, and if necessary photopatch tested at the same time.

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Rubber

Chemistry. Rubber was used by the native South Americans before the voyages of Columbus in 1492. For 200 years, Europeans tried to duplicate the water-resistant shoes, coats and capes but were unsuccessful. In 1791 the first commercial application of rubber began when an English manufacturer patented a method of waterproofing cloth by treating it with a solution of rubber in turpentine. Charles Macintosh, in 1823, established a plant in Glasgow for the manufacture of waterproof cloth and rainproof garments. Initially, the resulting products became brittle in cold weather and tacky and malodorous in summer. In 1839, the American Charles Goodyear discovered that heating rubber with sulphur removed the unfavourable properties, in a process termed vulcanization.

The term 'latex' defines an aqueous dispersion of a rubber. The rubber obtained from latex by drying or coagulation is called latex rubber. Natural latex is derived from the sap of the tree *Hevea brasiliensis*. During the world wars the availability of natural latex was limited and proved a stimulus to the development of various synthetic rubbers.

Rubber dermatitis is usually caused by accelerators, antioxidants and other chemicals used in its manufacture. More than 1000 substances are employed for these purposes [1,2].

Prevalence and incidence. The incidence of sensitivity is of the order of 5–10% of patients tested in most patch-test series [3]. Rubber dermatitis cannot always be suspected from the clinical appearance, and occurs with equal frequency in the two sexes [4]. However, the actual sensitizers differ, depending on exposure, the antioxidants in black rubber more frequently causing problems in men from occupational exposure.

Occurrence. Potential sources of exposure include the following.
1 Rubber industries and revulcanization shops: both non-vulcanized and vulcanized rubber-containing additives are sensitizers; in rubber-tyre factories, much dermatitis is irritant rather than allergic [5–7].
2 Other workplaces [7,8]: rubber gloves [9], other protection for hands and fingers, electric cords, tubes, handles (e.g. on hammers), packings, masks [10], rubber bands, etc.
3 Daily life [5]: shoes, gloves, clothing, condoms and many other articles.

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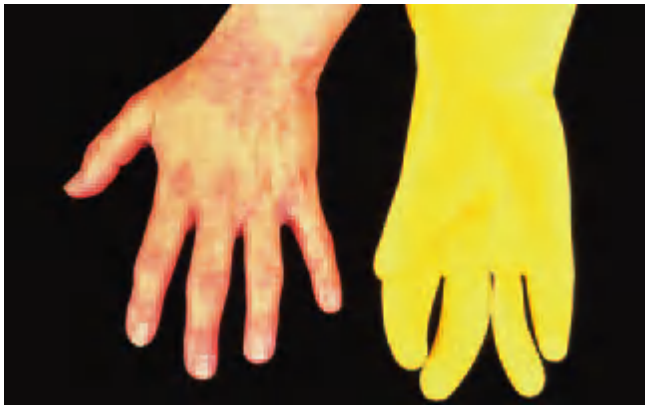

Fig. 20.20 Contact dermatitis from rubber gloves. (Courtesy of Dr J.D. Wilkinson, Amersham General Hospital, Amersham, UK.)

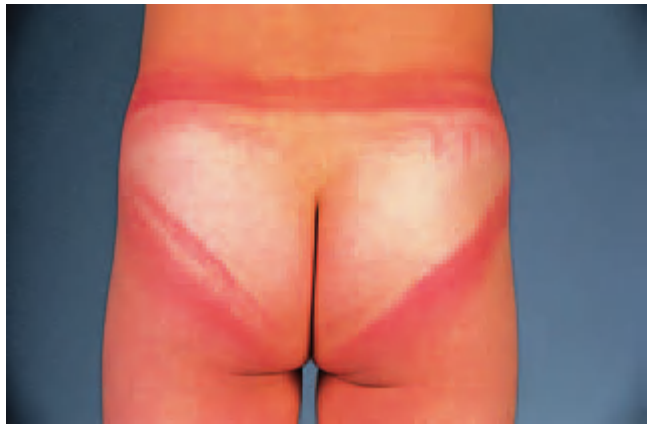

Fig. 20.21 Allergic contact dermatitis to elastic in clothing. (Courtesy of Dr J.D. Wilkinson, Amersham General Hospital, Amersham, UK.)

Clinical features. Rubber sensitivity may be the primary cause of a dermatitis or it may become superimposed on an existing dermatitis, as sometimes occurs following the use of rubber gloves [1] (Fig. 20.20). It is not always obvious [2], and many cases will be missed if patients are not routinely patch tested with a series of the more common rubber chemicals. A positive patch-test reaction to a rubber chemical is usually relevant.

Dermatitis from rubber gloves may be diffuse, but is more often localized to the dorsa of the hands, especially over the knuckles and the wrist, where a sharp proximal margin is often evident. The eyelids and face may also be involved from touching the face while wearing gloves. Dermatitis may be caused by objects touched only briefly during a daily routine. A digitate and patchy dermatitis has occurred in previously sensitized patients following examination with surgeons' gloves [3].

Shoe dermatitis occurs in both adults and children, and in the latter group needs to be differentiated from juvenile plantar dermatosis [4]. Rubber chemicals may occur in almost any part of the shoe, and a rubber adhesive is commonly used to glue parts together. The dermatitis may occur on the dorsum of the foot, soles or toes, usually with sparing of the web spaces and instep. A secondary dermatitis, especially of the hands, is not uncommon [5–7]. The outer soles rarely cause shoe dermatitis. Primary sensitization from all-rubber boots and rubber shoes is common, especially in agricultural workers [8].

Antioxidants related to PPD are used in car tyres and wear-resistant rubber products. They often impart a dark or black colour to the rubber materials vulcanized with them. Not all cases have an occupational origin. Black rubber flexes or cables, hoses, grips and even scuba masks [9] or squash balls may be responsible. The ensuing dermatitis may sometimes be purpuric [10], and an erythema multiforme-like presentation has also been reported [11].

In some cases, the site of dermatitis may provide a clue as, for instance, when the dermatitis is due to a rubber finger-stall used when counting money [12] or rubber bands under a wrist watch [13]. Rubber dermatitis may also occur at the site of contact with rubber in clothing (Fig. 20.21) or dressings, on the face from swimming goggles [14], between the thighs or on the abdomen from hot water bottles, and on the knees from kneeling mats. Genital dermatitis or pruritus vulvae may occur following the use of condoms [15,16] and diaphragms, and may also result from rubber catheters [17], when the dermatitis also spreads down the thighs. An apparent worsening of venous eczema may be related to allergy to rubber in elastic bandaging [18], and such patients are prone to develop a secondary generalized eczema. A generalized dermatitis may occur after sleeping on a rubber mattress or using rubber pillows, or the dermatitis may be predominantly on the side on which the patient sleeps.

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Avoidance and prognosis. Although it may be impossible to avoid contact with rubber entirely, many patients remain clear of dermatitis, and others may only have intermittent symptoms if they take simple precautions to avoid contact with rubber material. In many cases, hand eczema improves or clears if patients can be persuaded to change from rubber gloves to cotton-lined vinyl gloves.

Patch tests. Most rubbers contain up to 5% of potentially allergenic additives. Dermatitis from the smoked sheets of rubber used as raw material is rarely reported. The sensitizers in rubber change in accordance with industrial development, technical requirements and market prices. Unless the choice of substances kept for patch testing is constantly supplemented, rubber dermatitis will be missed. A list of potential sensitizers in rubber is shown in Table 20.8.

Most standard series contain rubber chemicals, both mixes and individual chemicals, as a screen for rubber-induced contact hypersensitivity. The mixes of rubber chemicals are useful because they allow allergy to be detected with fewer patch tests [1,2]. In order to avoid patch-test sensitization, the concentration of the individual chemicals must be reduced, and this involves the risk of false-negative reactions. This is especially so for mercaptobenzothiazole (MBT), and therefore MBT and MBT mix are usually both included in most patch-test series [3]. The concentrations of the individual chemicals in these mixes are therefore selected as a compromise. Too high a concentration will carry the risk of active sensitization, whereas too low a concentration of any of the individual ingredients may lead to false-negative reactions and missed sensitivities. PPD derivatives are sensitizing when tested at 2% in petrolatum, and should be tested at 0.25% and 0.1%. Simultaneous sensitivity to PPD and to the PPD derivatives in rubber is uncommon [4]. Carba mix and the diphenylguanidine in the carba mix often produce marginal irritant reactions. Although carba mix has been deleted from the European standard series, the predominant use of carbamates as accelerators in rubber gloves [5] argues for retention of the mix, as in the North American series, rather than relying on a cross-reaction with thiurams to detect the allergy.

Table 20.8 Common sensitizers in rubber.

Mercapto mix
Mercaptobenzothiazole (MBT)
Cyclohexylbenzothiazylsulphenamide (CBS)
Dibenzothiazyldisulphide (MBTS)
Morpholinylmercaptobenzothiazole
Patch-test concentration: 0.5% each = total 2% in petrolatum
Thiuram mix
Tetramethylthiuram disulphide (TMTD)
Tetramethylthiuram monosulphide (TMTM)
Tetraethylthiuram disulphide (TETD)
Dipentamethylenethiuram disulphide (PTD)
Patch-test concentration: 0.25% each = total 1% in petrolatum
Black rubber mix
Phenylcyclohexyl-*p*-phenylenediamine (CPPD)
Phenylisopropyl-*p*-phenylenediamine (IPPD) (identical to isopropylaminodiphenylamine)
Diphenyl-*p*-phenylenediamine (DPPD)
Patch-test concentration: 0.25% of CPPD and DPPD, 0.1% of IPPD = total 0.6% in petrolatum
Carba mix
1,3-Diphenylguanidine (DPG)
bis-(Diethyldithiocarbamato) zinc (ZDC)
bis-(Dibutyldithiocarbamato) zinc (ZBC)
Patch-test concentration: 1% each = total 3% in petrolatum

The mixtures mentioned are commercially available.

Where rubber allergy is suspected, additional testing with the ingredients of the mixes and additional rubber-related allergens may reveal what would otherwise have been a missed contact allergy [6,7]. Cyclohexylthiophthalimide, a common rubber antidegradant, frequently causes reactions but the relevance is often uncertain, particularly where there is no ingredient labelling [8,9]. Other allergens include trimene [10] and dithiodimorpholine [11]. It is also essential to test with a sample of the suspect rubber in case sensitization has occurred to a chemical not present in any standard or rubber series [12]. Delayed-type hypersensitivity reactions to natural rubber latex itself have been reported [13,14].

Synthetic rubbers such as styrene–butadiene, polybutadiene, polychloroprene (neoprene) and polyurethane (spandex) may contain similar accelerators and antioxidants, including thioureas [15]. Elastane (Lycra) does not contain rubber accelerators.

Sensitivity to a certain rubber chemical does not usually indicate any specific source. However, dihydroxydiphenyl is mainly present in dress shields and condoms [16]. Sensitivity to carbamates and thiurams suggests rubber gloves [17], mercapto compounds suggests shoes [18], and the PPD group is mainly associated with black rubber products such as tyres [19].

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Clothing [1–6]

Textile fibres may be natural, for example cotton, wool, silk, linen, rubber, or they may be synthetic, for example cellulose derivatives (rayon), polyamides such as nylon, polyesters, acrylics and elastomers [2,4]. Apart from rubber, they rarely sensitize in their own right.

Commoner allergens in clothing include nickel (p. 20.37), chromate (in leather and as a dyeing mordant) (p. 20.42), rubber (p. 20.74), textile dyes, formaldehyde (p. 20.59) and resins.

Disperse dyes are the class of dye most likely to sensitize, particularly as it is not possible to make them completely fast to the fibres [2]. They are principally anthroquinone and azo dyes. Disperse dyes may contain more than one fraction, as well as impurities, all of which can sensitize [7,8]. A mixture of several different dyes may be responsible for the final colour [1]. Fibre-reactive dyes are covalently bound to the fibre and unlikely to cause problems from clothing, but may sensitize those handling the dye powder [9–11]. Clothing dermatitis has also been reported from acid, basic, direct, vat and solvent dyes, as well as coupling agents [1].

Finishes are used on textiles to give 'body' to inexpensive materials, and provide crease-resistant and stain-repellent properties [12]. Urea and melamine formaldehyde resin finishes are now being superseded by others, such as dimethylolalkyl carbamate, dimethylolethylene urea, dihydroxydimethylethylene urea and other similar reactive cyclic urea resins [1,4]. These new resins may be less sensitizing, particularly as they release less formaldehyde and remain relatively fast.

Optical whiteners are frequently added to clothes, and although in the past they were associated with contact dermatitis, there are no recent reports of allergy [2]. Fire retardants in clothing have also been reported to cause sensitivity [13,14].

Incidence and prevalence. Since 1970, textile dermatitis has probably become rarer, mainly due to changed methods of production, although accurate information on the incidence and prevalence of clothing allergy is lacking. In those undergoing patch testing, the frequency of allergy to textile dyes has varied from 1.1 to 5.8% and for resins from 1.2 to 2.3%, either from formaldehyde or the resin or both [6].

Most, but not all, patients with formaldehyde textile resin dermatitis are also sensitive to formaldehyde [15,16]. Between 1950 and 1965, formaldehyde resins used for crease-resistant finishes caused numerous cases of textile dermatitis [17–19]. Recent surveys confirm that the most commonly identified azo disperse dye allergens are Disperse Blue 124 and the very closely related Disperse Blue 106, followed by Disperse Orange 3, Red 1, Yellow 3 and Red 17 [20–22]. In particular, Disperse Blue dyes 106 and 124 have been reported as causing frequent problems in Canada, especially from blue/black polyester or acetate garment liners [21]. The most frequently reported sensitizing anthroquinone dyes are Disperse Red 11, Blue 3 and Blue 35 [3,20].

Occurrence [1]. Disperse dyes are used to colour artificial fibres such as polyester, acetate, acrylic and nylon. Both azo and anthraquinone dyes may cause dermatitis from modern artificial fibres, and non-disperse azo dyes from natural fibres [23]. Rarely, other chemicals such as Naphthol AS (a coupling agent for cotton dyeing) may sensitize [24]. Textile resins are added to cotton and mixed cotton/polyester fibres as well as rayon and crease-resistant linen.

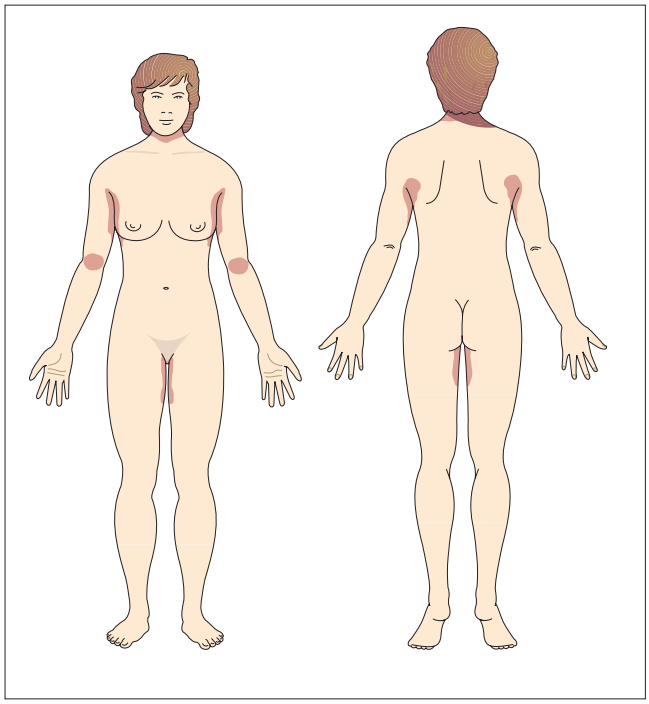

Fig. 20.22 Pattern of textile dermatitis.

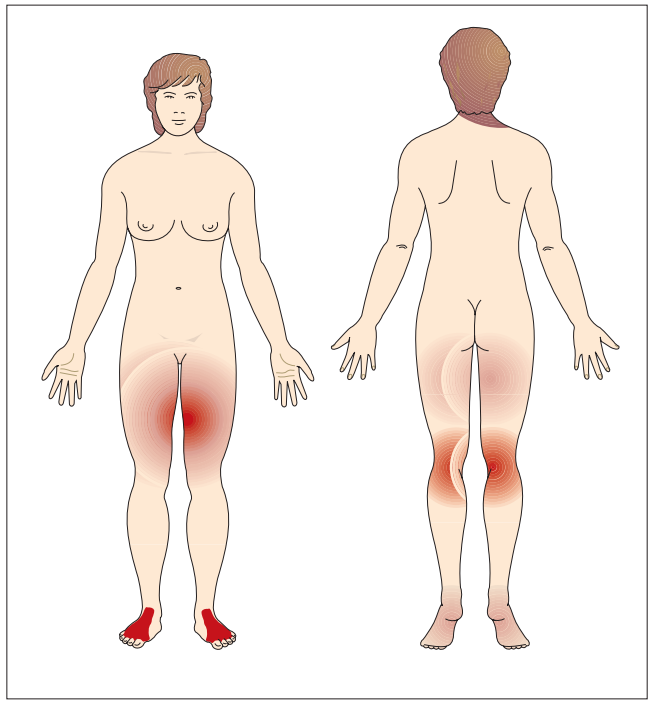

Fig. 20.24 Pattern of dermatitis from nylon stockings.

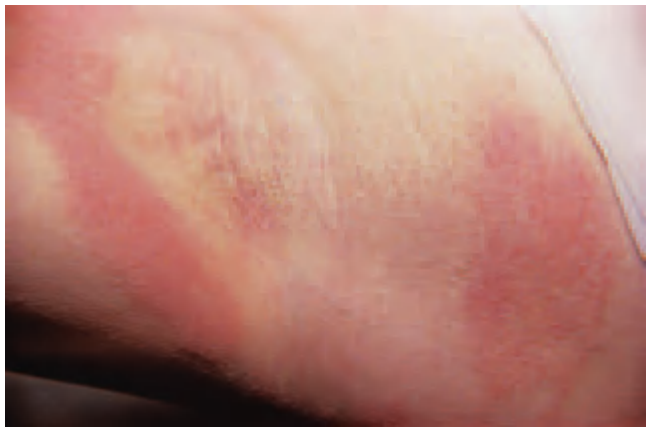

Fig. 20.23 Axillary dermatitis (sparing the axillary vault). The characteristic pattern of eczema seen in patients allergic to textile dyes and finishes. (Courtesy of Dr J.D. Wilkinson, Amersham General Hospital, Amersham, UK.)

Clinical features. The distribution of contact dermatitis, in areas of sweating and friction, is the same for dyes and finishes (Fig. 20.22). The eruption typically starts in the axillae, sparing the hairy part of the vault, and forms a crescentic patch on the anterior chest wall sharply limited by the underwear (Fig. 20.23). The anterior and posterior folds are also affected. The dermatitis is often sheeted, and the inner posterior thighs, popliteal fossae and lower leg may be involved when trousers or tights (panty hose) are the responsible garments. Allergy to dyes in socks, stockings and tights often starts on the dorsa of the feet, where they are occluded by footwear. The typical pattern for allergy to tights and stockings is shown in Fig. 20.24. Long sleeves cause eruptions in the elbow flexures, and collars provoke a rash around the neck. Later in the course of the disease, the chest and upper back may be involved, sparing areas protected by shoulder straps and underwear. In the flexures and round the neck the lesions are diffuse and oedematous; on the shoulders and chest they are usually papular. Papular dermatitis may cover the whole body, and eyelid dermatitis may rarely be a feature.

In the early 1970s permanent-press resins were also the source of an outbreak of follicular dermatitis due to a range of coloured Canadian perma-press sheets [12,25,26]. Patients developed a widespread itchy, follicular rash especially affecting the arms and legs, but also with eczema of the face and ears due to contact with pillowcases. Dyes have also been described as sensitizers in perma-press bed linen [27].

Some fabrics provoke a purpuric, sometimes lichenoid dermatitis in areas of contact, as seen with uniforms in the Second World War (khaki dermatitis) [28]. Textile dyes and resins will occasionally cause purpuric eruptions associated with contact allergy [29–32]. In the early 1970s a pigmented dermatitis was described that was caused by allergy to optical whiteners in detergents. It started on the inner aspects of the upper arms, from where it spread to the trunk, with indistinct coalescing macules as the major lesions [33]. In some cases, the dermatitis left persistent hyperpigmentation.

Patterns of allergy from nickel, chromate (in leather) and rubber are described in the sections discussing these allergens.

Avoidance [2,3]. Patients sensitive to formaldehyde or one of the formaldehyde resins should be advised to avoid treated fabrics, for example drip-dry, crease-resistant or durable-press cotton, cotton-mix and rayon clothes. Satisfactory alternatives include wool, silk and 100% nylon, polyester or acrylic fabric, as these rarely contain significant amounts of formaldehyde or formaldehyde resins. The washing of new clothes at least twice before wearing may also be useful as this will help to remove free formaldehyde [12].

A precise knowledge of the dye responsible for an individual's allergy is not helpful as cross-sensitivity is common and the finished colour is commonly a mix of several dyes. Strongly coloured synthetic clothing should be avoided, but lightly coloured garments may sometimes be tolerated. Pure natural fibres, such as cotton, wool, linen and silk of any colour, can generally be worn.

Patients with disperse dye stocking dermatitis can buy undyed nylon stockings and dye them by soaking in a potassium permanganate solution (0.3–0.6%) for 30–60 min. Stockings and tights (panty hose) without azo dyes may be commercially available, but manufacturers have to be contacted directly. Grey stockings and tights do not usually contain Disperse Yellow 3 or Orange 3. Lycra products are normally dyed with acid dyes rather than azo dyes.

The wearing of undergarments may protect the skin from allergy to outer clothing, although there is still the possibility that sweating could leach out allergens.

Patch tests. Patch testing with the suspected clothing can be undertaken, although there is a high risk of obtaining a false-negative reaction. Soaking 1 cm^2 of the fabric in water for 10 min before testing might increase the return, and extraction techniques have also been suggested [2,34,35].

Formaldehyde is a standard-series allergen. A PPD-positive patch test may alert one to clothing dye allergy, but it is an inadequate screen [3,21,23]. Standard-series screening with four textile disperse dye allergens has been advocated, and the possibility of using a textile dye mix explored, but further data are required [3,36–38]. The commercial allergen suppliers have developed screening series of clothing allergens and these will help detect most cases of textile allergy.

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Shoes [1–4]

The commoner identified allergens in shoes are rubber chemicals, chromate (in leather), nickel in buckles, and *p*-tertiary-butylphenol formaldehyde resin (PTBPFR) [4]. However, many others have been described, including vegetable tanning agents, dyes, colophony, leather preservatives and polyurethane components [1].

A typical shoe will be formed from an upper, a sole, an insole, and heel and toe counters to stiffen the shoe and give it shape. Adhesives may be required throughout the shoe.

Uppers tend to be leather, rubber or synthetic material. Leather is tanned, usually with chromate, but other tanning agents, including vegetable tans, formaldehyde and glutaraldehyde, may be used [1–3]. Formaldehyde is associated with the tanning of white or water-resistant leather and is tightly bound, making sensitization less likely [2]. After tanning, the leather may be oiled, dyed and finished. Biocides such as 2-*n*-octyl-4-isothiazolin-3-one may be added to the oils and finishes [3,5]. Uppers may be made from, or be lined with, dyed fabric. Polyurethane, rubber and neoprene foams are used in the uppers, particularly of sports footwear [1]. Neoprene is a synthetic rubber to which phenolic resins, most notably PTBPFR, thioureas, carbamates, and other accelerators and additives, may be added [1,2].

Shoe soles are made from similar materials and more solid forms of rubber. Insoles can also be made of a similar range of materials. Fibreboard is a composite of fibres, usually paper but occasionally wood or leather in a glue matrix, which may contain biocides [1]. This material is used for insoles.

Counters may be made from many different potentially allergenic materials, including natural rubber, formaldehyde resins, biocides and pine oil [1].

The main adhesives are hot melt, urethane, neoprene and natural rubber. Hot melt adhesives do not tend to cause allergy but the others may, particularly rubber accelerators and PTBPFR. Additives include isocyanates, epoxy resins and biocides. Tackifiers may contain formaldehyde resins and colophony [1].

Prevalence. The prevalence of shoe allergy has ranged between 3 and 11% in patients referred for routine patch testing [1,6–8]. A wide age range is seen, with young children prominently represented in many studies [9–14]. In one study on 55 patients the breakdown of the most frequent positive reactions was as follows: rubber 43.1%, chromate 23.6%, PTBPFR 20.0%, colophony 9.0% and PPD 3.6%. However, a further 14.5% reacted to pieces of their shoes but not to the shoe allergens tested. Most patients were noted to have hyperhidrosis and 43% were atopic. Follow-up (average 3 years) of 48 patients after they had employed a number of strategies to avoid contact with the allergens responsible for their dermatitis revealed that 87.5% were clear or significantly better, 10% the same and only one person was worse [4].

Clinical features. Sweating causes allergens in shoes to leach out and migrate, and as a result of this the pattern of dermatitis is often not distinctive. It may be patchy or superimposed on a pre-existing constitutional eczema. Nevertheless, in many instances the distribution will reflect whether the sensitizer is present in the upper or sole of the shoe.

Dermatitis from the upper commonly starts over the dorsal surface of the big toes and spreads to the dorsa of the feet and the other toes. Outbreaks of dermatitis from tanning agents (chromate and vegetable) and adhesives have often followed this pattern [15–17]. The interdigital spaces are normally spared. The heels may be involved, but less frequently than the toes. On the heels, patches of dermatitis may correspond to the heel-cap, and on the dorsum of the foot they may correspond to the tongue of the shoe. Adhesives and rubber components may cause localized areas of dermatitis limited to the toecap [11]. Nickel allergy from shoe buckles and eyelets may cause a localized dermatitis on the adjacent skin. Indian sandal dermatitis has a characteristic pattern, is often severe, and affects mainly the first toe web and adjacent toes and the dorsum of the foot [18].

Involvement of the sole usually affects only the weight-bearing areas—the instep is frequently spared. In sports shoes, the sole is usually moulded to fit into the instep and the dermatitis may affect the whole sole [19]. Sometimes, only the forefoot is involved [2] (Fig. 20.25), and in children the condition must be differentiated from juvenile plantar dermatosis by patch testing.

Surprisingly, not all cases are bilateral [6,10], but the great majority are. Patients with shoe dermatitis often have evidence of dermatitis elsewhere, especially on the hands [9].

Boots produce a pattern similar to shoe dermatitis, sometimes with an additional eruption on the calves. An eczematous and purpuric allergic contact dermatitis has been reported in a patient sensitive to thiourea and IPPD [20,21].

Allergy to socks and stockings, agents such as perfumed sprays, talcs and antifungal powders used in shoes, and medicaments applied to the skin may simulate footwear dermatitis [22,23].

Avoidance. Individuals who are allergic to leather tanning agents and additives can be advised to wear synthetic fabric or rubber footwear. Some specialized outlets sell 'vegetarian' shoes that should not be leather.

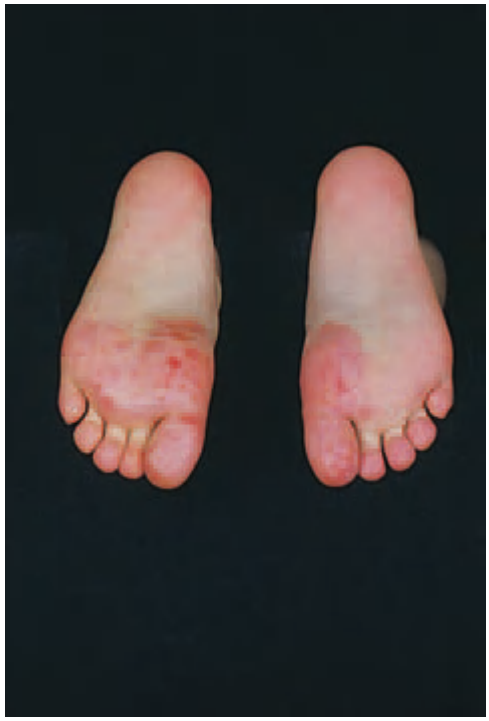

Fig. 20.25 Forefoot dermatitis from shoe allergy.

However, with other allergens avoidance is often difficult. Manufacturers and distributors will not generally guarantee their shoes are free of rubber chemicals and PTBPFR in adhesives, and may know even less about other sensitizers. Patients allergic to rubber, PTBPFR and colophony should consider all-leather stitched footwear with no insoles, or injection-moulded plastic shoes, moccasins or wooden shoes. Certain manufacturers will produce bespoke shoes free of the allergen(s) but these are expensive. Sometimes, orthotists advising hospital orthopaedic departments are helpful in making special shoes.

Those allergic to dyes will need to avoid dyed fabric and nylon-lined footwear, as well as coloured nylon socks and stockings. Old socks may act as a reservoir of allergen and should be discarded with the incriminated shoes, medicaments, etc. [24].

Hyperhidrosis is common in shoe dermatitis, and the dermatitis may be helped by treating the sweating with iontophoresis, or by other means, and by wearing cotton socks to absorb the sweat [2].

Patch tests. Many of the commoner shoe allergens are found in the standard series, including dichromate, certain rubber accelerators and antioxidants, PTBPFR, colophony and nickel. In addition, a special shoe series should be used, and Chemotechnique have such a series of commercially available allergens. More extensive series have been advocated as a screen, but even these may miss some shoe allergens, including biocides, vegetable tans, hydroquinone and polyurethane agents [1].

Investigation of possible shoe allergy can be frustrating, as even with special screening series 10–20% of shoe allergies have only been identified by testing with pieces of the shoe itself [2]. Ideally, pieces for patch testing should be taken from the parts of the shoe in contact with the dermatitic area. They should be thin and 1 cm^2 or larger [1]. Some have suggested testing the pieces under a special large Finn chamber, whereas others recommend occlusive tape [1,2]. Further suggestions have been to soak the pieces in water for 15 min before they are applied, and to leave the test pieces in place for 4–5 days [2,25]. False-positive reactions may be seen from pressure, particularly around the edge, and false-negative reactions are common. Furthermore, positive reactions may develop as a result of contamination by a non-shoe allergen, for example a medicament or perfume to which the patient is allergic [23].

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Resins and plastics

Resins are intermediate synthetic substances that are polymerized often using a hardener, plus other additives to produce a plastic end-product. Many low-molecular-weight materials including the monomers and oligomers used in resins are allergenic, but a fully polymerized resin should not be sensitizing. Many additives, fillers and hardeners also have allergenic potential. The systems most commonly associated with contact allergy include epoxy, acrylic and formaldehyde resins.

Epoxy resins [1,2]

In terms of usage, 75–90% of epoxy resins comprise diglycidyl ether of bisphenol A (DGEBA) [2]. They are reaction products of epichlorhydrin and bisphenol A. The monomer (molecular weight 340) is the main sensitizer, and oligomers with molecular weights above 900 do not sensitize [3,4]. Higher-molecular-weight resins may contain small amounts of the oligomers or monomer [5] but rarely sufficient for induction of sensitivity. However, they can elicit clinical and patch-test reactions in those already sensitized.

Non-DGEBA epoxy resins, such as cycloaliphatic epoxy resin, diglycidyl ether of bisphenol F (used in phenol epoxy novolac systems) and triglycidyl isocyanurate (TGIC), are also reported as sensitizers [6–12]. Sometimes, 'reactive diluents' in the resins used to reduce viscosity are responsible for their sensitizing capacity [13]. These diluents are usually glycidyl ethers or, occasionally, glycidyl esters and are thought to be present in over 50% of epoxy resin products [1,14]. Bisphenol A and epichlorhydrin themselves are seldom responsible for allergy from epoxy resins [15–17].

Resins containing latent hardeners are polymerized or cured by heat alone. Two-part resins require hardeners to be added immediately prior to their application. Some of these are cold-curing and some require heat to complete the polymerization. Hardeners are of many types: aliphatic amines, cycloaliphatic amines, aromatic amines, polyaminoamides, amidopolyamines, anhydrides, isocyanates, polyphenols and adducts. Formaldehyde resins may be used as hardeners [1,2].

The commonest sensitizers among the hardeners are amines, for example the aliphatic amines ethylenediamine, diethylenetetramine, triethylenetetramine, dipropylenetriamine and dimethylaminopropylamine [1]. Triethylenetetramine is a particularly strong sensitizer [18]. There are also sensitizing cycloaliphatic amines (e.g. isophoronediamine) and aromatic amines, such as diaminodiphenylmethane (methylene dianiline) and 2,4,6-tris-(dimethylaminomethyl)phenol [18–21].

Hardeners of the polyaminoamide type are much less likely to sensitize, and so are anhydrides (e.g. phthalic anhydride). They are used for thermal hardening. Adducts are non-sensitizing, providing they do not contain free amine.

Additives include colours, fillers, UV light absorbers, flame retardants and plasticizers.

Incidence and prevalence. Epoxy resin of the bisphenol A type is a standard allergen. However, figures for the prevalence of allergy in patch-tested patients with dermatitis will reflect the degree of occupational interest of a particular clinic, and also the local industry. Series of relatively unselected patch-tested patients have reported rates of 0.4–3% positive reactions, with a male preponderance [1]. However, higher rates (11.7–12.5%) are recorded for occupational referrals. Annually, approximately 1% of exposed workers are believed to develop an epoxy resin allergy [22,23].

Allergy to other components of epoxy systems is commonly concomitant with resin sensitization. Detailed analysis of 182 cases in Finland showed that 80% were allergic to DGEBA epoxy resins, 23% to polyamine hardeners, 16% to reactive diluents and 9% to non-DGEBA epoxy resins [1,24].

A high incidence of allergy among exposed individuals can occur in factory outbreaks, for example 56% in an aircraft construction factory, 45% in marble workers, 27% in ski-factory workers and 21% in paint factory workers [6,25–27].

Occurrence. The epoxy resins are among the most sensitizing substances that have been introduced to industrial work in recent years. Coatings, including paints, varnishes and metals account for roughly 45% of all epoxy resin use [2]. They are widely used in the construction industry, in cement to make it waterproof, and in floorings, grouts and filling materials, including those for marble and window frames. They are commonly used as binders and coatings for fibreglass and carbon fibre, for example in car body repairs and aircraft construction [1,2]. In the electronics industry they are used for insulation and in printed-circuit boards. They are efficient glues for metals, rubber, polyester resins and ceramics. Cardiac pacemakers [28] and hypodermic needles [29,30] may contain them. Dental personnel sensitized by epoxy acrylates in filling materials often also react to epoxy resin [14]. In the laboratory they have been found as sensitizers in microscopy immersion oil [31,32].

High-molecular-weight resins, which may contain residual low-molecular-weight resin [5], are used for

coating metal or wood [33]. Occasionally, uncured epoxy resins are used as stabilizers and plasticizers in, for example, polyvinyl chloride plastic. Thus, contact dermatitis may be elicited in consumers [34,35] as well as occupationally.

Non-DGEBA epoxy resins have found increasing use in electron microscopy, and in the aerospace and electronics industries [36]. TGIC is used, mainly as a hardener, in thermosetting one-component polyester powder paints [12,37–39].

Clinical features. Dermatitis is predominantly occupational. It usually affects the hands and arms (see Fig. 20.8), and often also the face and eyelids [40]. Facial and periorbital involvement may be indicators of associated or isolated allergy to the more volatile epoxy diluents and hardeners [40,41]. Partially cured epoxy resin dusts from sanding and drilling may induce dermatitis with a similar distribution.

Severe oedematous and weeping eruptions are not uncommon and widespread generalized eruptions can develop if exposure continues. Erythema multiforme-like reactions have also been described [42]. Other body sites, especially the genitals, may be affected following hand contact. Hand and fingertip dermatitis was a feature of window-frame restorers' dermatitis [21]. Localized dermatitis can sometimes be attributed to traces of free epoxy monomer found in a wide range of products, such as twist-off caps, coated door knobs, tool handles [34], microscopy immersion oil [31,32], stoma bags [35], clothing labels [43], portable infusion pumps [44], spectacle frames, plastic tubing in medical devices and gloves. A flare-up of hand eczema has been reported from an implanted epoxy resin-containing needle [29]. Children have been sensitized by a knee-patch adhesive in jeans [45].

Avoidance. Redeployment away from contact with epoxy resin is usually required for occupational dermatitis. Use of epoxy (usually two-part) adhesives and fillers in domestic and spare-time activities (e.g. car body repairs) should be avoided. Identification of epoxy chemicals in suspect materials by chromatography techniques may be helpful in confirming a suspected source of epoxy resin [46,47].

Prevention. Prevention of epoxy dermatitis is important, and includes education, instructions and warning notices for the workforce, stressing the need for 'good housekeeping'. High-molecular-weight epoxy resins and diluents are less sensitizing and, where possible and appropriate, are to be preferred. Aliphatic and aromatic amines may be replaced by polyaminoamides or amine-epoxy adducts [2]. If feasible, automation or a 'two in one' mixing package [48] is advised or, if not, mixing should be done in disposable containers.

Protective impermeable, preferably disposable, clothing and gloves should be worn [1]. Epoxy resin will nevertheless penetrate plastic and rubber gloves [49]. Heavy-duty vinyl gloves or multilayered gloves of folio type (4H-Glove; Safety 4, Denmark) provide the best protection [49,50].

Patch tests. Epoxy resin of the bisphenol A type is included in the standard series at 1% in petrolatum. Other components of epoxy resin systems are not, apart from ethylenediamine. Extra patch-test reagents, which incorporate the commoner amine hardeners and reactive diluents, are available from the commercial allergen suppliers, although these are not all-inclusive. Allergy to non-DGEBA epoxy resins and other components may still be missed unless the worker's own materials are tested [40].

A rough guide for patch-test concentrations (all in petrolatum) is 0.5% for non-DGEBA epoxy resins, 0.25% for reactive diluents and 1% for most polyamine hardeners, but a literature search should also be undertaken, and lower concentrations considered initially if in doubt.

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Acrylic resins [1]

Acrylic resins are formed from acrylic and methacrylic acids and their esters, and cyanoacrylic acid and its esters. These resins show a wide range of sensitizing potential [2] and a complex cross-reaction pattern [3,4]. Multifunctional acrylates [1,5–7], epoxy acrylates [8], acrylamides [9], acrylonitrile [10] and acrylated polyester [11] are other sensitizers. Polymerization may be induced by heat, by adding initiators, accelerators and catalysts, by tiny amounts of water, by anaerobic conditions and by exposure to UV and visible light or electron beams depending on the nature and function of the acrylate [1]. Sometimes, additives such as dimethyl-*p*-toluidine [12], benzoyl peroxide, hydroquinone [13], *p*-methoxyphenol [13], pyrogallol, resorcinol or pentaerythritol tetrakis 3-mercaptopropionate [9] may elicit contact dermatitis.

Prevalence. Acrylate allergy is not routinely sought and levels of allergy will reflect the referral pattern to a particular clinic. A recent UK study examined the records of approximately 14 000 unselected patients and identified 440 who had been tested for possible (meth)acrylate allergy: 67 had one or more positive reactions; 47 cases were occupational, with dental personnel and printers being the most frequent, followed by gas workers and gearbox fitters who were using sealants, and beauty therapists; and 16 cases were sensitized by wearing acrylic nail cosmetics [14]. Most other series have concentrated on occupational exposure. Dental personnel and printers are confirmed as occupational groups particularly at risk of sensitization [6,9,15–19].

Occurrence [1]. Monomeric acrylates and methacrylates may be used to produce transparent plastics, (e.g. Perspex), dentures, hearing aids, limb prostheses, spectacle frames, nail cosmetics and bone cement for orthopaedic surgery. Other commoner exposures include coatings, paints, inks and adhesives (including those for stick-on nails). UV-cured monomers are also encountered in coatings, printing plates, printing inks and dentistry.

Multifunctional acrylates, which have at least two reactive acrylic groupings, are also used in UV-cured resins, as well as printed circuit boards, artificial nails, adhesives, dental materials and anaerobic sealants used in screw-locks and gas pipes. Epoxy acrylates are used in dental restorative materials. Acrylamide and derivatives have sensitized in printing plates and paint manufacture [9].

Cyanoacrylates are known as 'superglues' and are used extensively to bond metal, glass, rubber, plastics and

textiles. They are also used by surgeons to bind tissues and seal wounds, and by dermatologists to treat painful fissures of the hands and feet. Sensitization to cyanoacrylates is rare, as a result of almost immediate polymerization [20], but it has been reported [21–23].

Clinical features. The commonest sites of occupational allergy are the fingertips and hands (see Fig. 20.2), but the face, arms and eyelids may also be involved. Workers with fingertip dermatitis should always be asked about contact with screwlocks and glues, as this is a typical distribution of allergic dermatitis from this source [24]. A similar distribution may be seen in dentists and dental technicians [25–27]. Localized dermatitis is seen from limb prostheses [28] and from the use of diathermy plates during surgery [29,30].

Dermatitis from artificial nails may be associated with painful onycholysis, nail dystrophy, periungual dermatitis, paraesthesiae, and an ectopic dermatitis of the face and neck and sometimes other parts of the body [31–34]. Paraesthesiae can persist for some months after patients stop wearing the nails [35,36].

Stomatitis has been blamed on incompletely cured acrylate in newly made or repaired dentures [37,38], and gingivo-stomatitis on acrylates in a temporary crown [39].

Avoidance. Once identified, avoidance should be possible by removal of the cause, redeployment, adequate protection or altered work practice. Acrylates penetrate latex and vinyl gloves [40–42].

The 4H multilayer folio glove (Safety 4, Denmark) [43] is the best protection, but may be impractical for some activities. In those with finger problems (especially dentists), it may be possible to remove the 4H glove fingers and wear these under another more pliable glove, although ideally dental personnel should use a no-touch technique [44]. Double gloving, polyethylene gloves and nitrile gloves are possible, but potentially less effective, alternatives.

Education, instructions on handling, printed warning notices and 'good housekeeping' are important preventative measures.

Patch tests. Chemotechnique allergens include three (meth)acrylate series: adhesive, nail and printing. In general, methacrylated monomers are tested at 2% in petrolatum and acrylated monomers at 0.1% in petrolatum. The lower 0.1% concentrations have reduced the incidence of the previously noted problem of active sensitization [45]. Cyanoacrylates are tested at 10% in petrolatum.

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Formaldehyde resins [1–3]

'Phenoplastics' are condensation products of formaldehyde and phenolic compounds, for example phenol, cresol, *p*-tertiary-butylphenol and resorcinol [1,2]. There are two main types of phenol formaldehyde resin (PFR): resol (phenol reacted with excess formaldehyde in alkaline conditions) and novolac (formaldehyde reacted with excess phenol in acid conditions) [1–3]. Fourteen different sensitizers have been isolated from PFRs [4]. The two types of PFR do not necessarily cross-sensitize and neither of them seems to cross-sensitize to any significant degree with PTBPFR [5,6].

'Amino-plastics' [1] are condensation products of formaldehyde or hexamethylenetetramine, and carbamide (= urea), thiourea, melamine, sulphonamide or anilide. They are often white or transparent. Formaldehyde, hexamethylenetetramine or low-molecular-weight condensation products can sensitize separately or simultaneously. Usually, sensitization occurs when the resins are handled in 'half-condensed' form.

Coexistent formaldehyde sensitivity is rare with PTBPFR and PFRs, but is quite common with urea and melamine formaldehyde resins [5–8].

Prevalence. Apart from allergy associated with clothing (p. 20.77), shoes (p. 20.80) and nail varnish (p. 20.56), formaldehyde resin allergy is uncommon. Many cases of PFR allergy are sporadic. Laminate manufacturers in Sweden were found to have a high frequency of allergy [9]. In a recent review, 17 cases of PFR allergy were seen in one clinic over a 15-year period. Commoner occupational associations were friction material (e.g. brake linings) production, work with fibreglass and contact with foundry sand [5]. Of routinely patch-tested patients, 0.3–2.6% are allergic to PTBPFR [10–12]. In many instances it is difficult to find a relevance for a positive patch test [13].

Occurrence. PFRs have electrical resistance and binding properties, resulting in their widespread use in electrical appliances, glues, laminated floorboards, plywood, fibreglass (including insulation), brake linings, clutch facings, grinding wheels, foundry sand moulds, abrasive cloths and papers, plastic moulds, telephones and steering wheels [1,2]. Finished plastics are often brown or black and of the Bakelite type. Cashew nut shell oil has been used to modify the PFRs incorporated into brake linings, and this has sensitized [14].

PTBPFR is used as an adhesive and is found in sealants and neoprene glues. Contact may occur directly following its use as a glue, particularly in shoemakers and cobblers [8,15,16], or when it is used to attach artificial nails [17], and indirectly from its use in shoes, watch straps and limb prostheses [13,18–20]. Other sources include furniture and upholstery glue [1] and marking pen ink [21].

Amino formaldehyde resins occur in textiles (p. 20.77) and in waterproof paper. They are also used for finishing parquet floors, for glueing wood, and in orthopaedic casts [7,22,23]. Tosylamide formaldehyde resin is extensively used in nail varnish. Formaldehyde, continuously liberated from formaldehyde resins in floors and walls, may elicit contact dermatitis in very sensitive people (p. 20.59).

Clinical features. Dermatitis from formaldehyde resins in clothing, shoes and nail varnish is discussed on pp. 20.77, 20.80 and 20.57, respectively. In most other cases of PTBPFR allergy, dermatitis is localized under leather watchstraps and limb prostheses, although the hands may be affected by contact with glues in the working and domestic environments.

Most cases of PFR allergy we have seen have had occupational dermatitis of the hands, with occasional manually transmitted spread to the face and genitals.

Patch tests. PTBPFR patch testing is discussed on p. 20.81 (shoes), amine formaldehyde resin on p. 20.79 (clothing) and tosylamide formaldehyde resin on p. 20.58 (cosmetics). PFRs are variable in composition and allergenicity [3]. There are a number of commercially available allergens: PFR-2 1% in petrolatum and monomethylol phenol 1% in petrolatum from Chemotechnique, and a novolac and resol resin each at 5% in petrolatum from TROLAB (Hermal). PFR-2 is the most successful in identification of allergic subjects [5,6]. However, testing with the patient's own resin at 1% and 5% in petrolatum, followed by testing controls if positive, is probably the most reliable method.

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Other plastics

Other plastics are rarely the cause of allergic contact dermatitis outside industry. Other resin systems, most notably unsaturated polyesters and their hardeners, and isocyanates in polyurethanes may sensitize [1–3]. The literature contains many case reports of allergens traced to specific products, for example spectacle frames. Additives in cellulose acetate spectacle frames have caused dermatitis [4–7]. Similar chemicals may be responsible for the sporadic cases of dermatitis from hearing-aids, ballpoint pens and other plastic items. Other plastic additives such as plasticizers, antioxidants, UV light absorbers, initiators, cross-linking agents, flame retardants and pigments may sometimes sensitize during the manufacturing process or during use [1].

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Plants [1–5]

Plant life is exceedingly diverse, with much geographical and seasonal variation, and consequently the range of reported allergens is huge, with considerable differences worldwide in the incidence and prevalence of allergy. The reader is therefore referred to the standard texts on this subject for in-depth analysis. We propose to concentrate only on those plant families frequently associated with contact allergy.

Incidence and prevalence. Accurate statistics for prevalence and incidence of plant allergy as a whole are not available. These parameters vary from country to country and depend on the local flora and the population's way of life. Numerous investigations have shown that 25–60% of North Americans are sensitive to poison ivy and other members of the Anacardiaceae family [6]. Occupational dermatitis to plants is common in gardeners, florists and undertakers [7,8], despite occasional grossly misleading impressions of its frequency—only two cases of tulip dermatitis could be traced in the files of the Leiden Hospital in the Netherlands [9] as it was an accepted occurrence and was therefore not reported.

It has been estimated that 5–10% of all cases of contact allergy seen in European dermatology clinics are caused by plants or their products [4]. Primin, found in *Primula obconica*, is recommended as a standard-series allergen in

Europe. Of 3075 patients patch tested in Denmark, positive reactions were recorded in 1.8%, about 95% of the positive reactors being female [10]; in the UK, positive reactions were recorded in 1% of 3462 patients routinely tested [11].

Sesquiterpene lactone mix in the standard series is used to identify Compositae allergy [12]. A multicentre European study showed varying frequencies of allergy in patch-tested patients, ranging from 0.1 to 2.7% according to the centre, with clinical relevance found in approximately three-quarters of cases [13]. In a large UK review of 7420 patients, 1.8% had positive reactions [14]. However, it has been suggested that the sesquiterpene lactone mix might only detect about one-third of those allergic to Compositae [15].

Anacardiaceae

Plants from this family have caused more contact allergy than all other plants combined [1]. Much of this sensitization relates to poison ivy, sumac and oak, which are species of *Toxicodendron* found extensively in North America. According to one source more than half the population of the USA are sensitive to poison ivy and its relatives [6]. The plants are generally found outdoors and recognized by their three-leafed configuration. Their diverse morphology and various habitats have been described by Guin *et al*. [16,17].

The main allergens found in the oleoresin (or urushiol) are derivatives of catechol, particularly pentadecylcatechols, phenol, resorcinol and salicylic acid [4]. Cross-reactions occur with cashew nut oil, which may be used industrially in resins, mucilages, printer's inks and electrical insulation [5]. Haitian voodoo dolls and swizzle sticks made from cashew nut shells have also sensitized [5]. Further cross-sensitivity is found with mangoes, gingko tree fruit, indelible laundry marking ink from the marking nut tree in India, furniture lacquer from the Japanese lacquer tree, *Lithraea* trees in South America, and plants and trees from the genus *Grevillea* found in Australia [4,5,18–22]. Localized outbreaks of dermatitis from contact with the Japanese lacquer tree have occurred in the UK [23,24].

Clinical features [5]. *Toxicodendron* spp. dermatitis occurs after contact with the sap of the plant. Classically the rash is streaky, with erythema, papules and vesiculo-bullous lesions on exposed sites. The hardened sap may leave a black spot on the skin in the areas of dermatitis and this may be helpful diagnostically [25]. Distant spread is common, particularly facial and genital involvement from contaminated hands. More profound erythema multiforme-like, exanthematous and urticarial eruptions, and even renal damage, may occur from systemic absorption [26]. Stomatitis and proctitis have occurred after chewing the leaves, and with hyposensitization [26]. Contamination of clothing, animals, garden tools, firewood, fishing rods and golf clubs may also act as sources of contact [5].

Phytophotodermatitis (Chapter 24) and *Primula* allergy have to be considered in the differential diagnosis.

Compositae

There are over 25 000 species of Compositae found throughout the world and more than 200 have been reported to cause allergic contact dermatitis [27]. They may be decorative plants (e.g. chrysanthemums, dahlias, sunflowers), weeds (e.g. ragweed, dandelion, tansy, marsh elder, feverfew, chamomile, yarrow, arnica, *Parthenium*) or foods (e.g. lettuce, endive, artichoke) [27].

The allergens are sesquiterpene lactones and more than 1350 have been described, including dehydrocostus lactone, alantolactone, costunolide and parthenolide [4,5,12,28]. In lettuce and chicory, lactucin and lactucopicrin have also been identified as sensitizers [29,30].

As might be expected, there is considerable but variable cross-reactivity among Compositae plants [31]. Cross-sensitivity with *Frullania* liverworts has been described [32–34]. Cross-sensitivity has also occurred with members of other plant families, most notably Lauraceae and Magnoliaceae [34–36].

Clinical features [37]. Six patterns of dermatitis are described, which are generally worse during the summer months in temperate climates.

1 *Pseudophotodermatitis*. Exposed sites are involved, including both eyelids, and photoprotected areas under the chin and behind the ears. In hot regions, during summer months, dry dead plant material contributes to the airborne pattern of dermatitis. In the USA many Compositae weeds, including ragweed (*Ambrosia* spp.), induce this pattern of dermatitis, almost exclusively in males [5,37]. A similar pattern is seen in Europe from Compositae flowers and weeds [28,38,39], in India from *Parthenium hysterophorus* (see below), and in Australia where it is known as bush dermatitis [40]. Chronic cases may produce a marked thickening of the facial skin—a leonine facies. Photosensitivity quite commonly coexists with Compositae allergy [41] (Fig. 20.26). In one UK study, 22% of the contact-allergic patients were also photosensitive [14]. True photoallergy to Compositae is, however, generally not a feature.

2 *Atopic eczema-like*. Compositae allergy may mimic late-onset atopic eczema, with a flexural accentuation of involvement, which may include the groins and genital area [42].

3 *Erythrodermatous exfoliative*. This pattern is classically seen from the weed *Parthenium hysterophorus*, which was

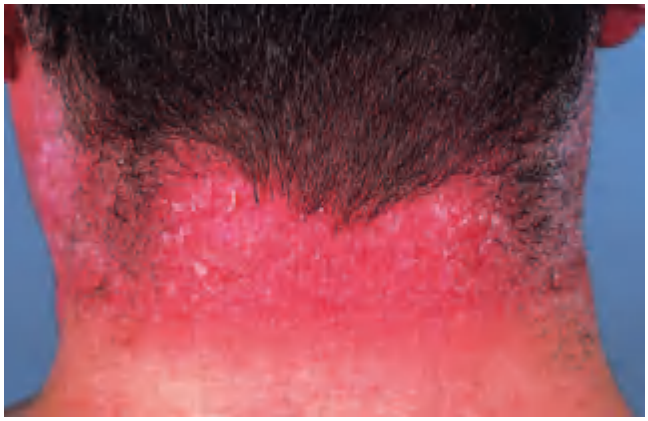

Fig. 20.26 Photosensitive eczema in a patient also allergic to Compositae (sesquiterpene lactones). A similar pattern may be seen in woodcutters sensitive to lichens, and in others with photosensitive eczema including photocontact allergy. (Courtesy of Dr J.D. Wilkinson, Amersham General Hospital, Amersham, UK.)

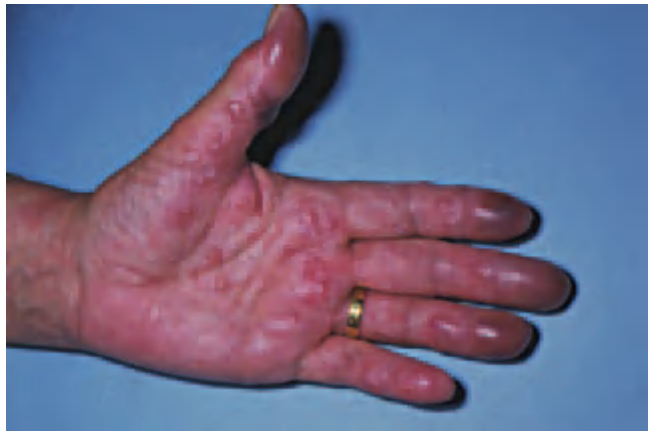

Fig. 20.27 Haemorrhagic blisters on the palm from *Primula* allergy.

transported to India in contaminated seed wheat [43]. Unfortunately, the weed has spread over much of the country, including urban areas [44]. It has become markedly allergenic in these environmental conditions, which also enhance the spread of dry plant dust and pollen. There is increased opportunity for skin exposure because many of the indigenous male population wear relatively scanty clothing. Severe incapacity and even fatalities have resulted from *Parthenium* dermatitis.

4 *Hand eczema* [12]. This pattern is seen particularly in gardeners after contact with weeds. A palmar distribution often predominates. Dermatitis of the hands is also associated with handling lettuce [45].

5 *Localized dermatitis*. Dermatitis may be confined to one or more localized areas [37], although this pattern is unusual in our experience.

6 *Oral*. Oral swelling and soreness after eating lettuce has been reported in sensitized persons [45].

Primulaceae

Primula obconica is the most important allergenic plant, although other *Primula* species may also cause allergic contact dermatitis [46]. *Primula obconica* is a decorative indoor plant. The major allergen is primin, a quinone found in the tiny breakable hairs on the leaves, stem and flowers of the plant [27]. Another potential allergen is miconidin [47].

Contact occurs particularly when dead leaves and plant heads are removed manually. Primin levels are at their highest between April and August [48]. The allergen content of the plant also varies with sun exposure, temperature and feeding [48]. The pattern of dermatitis is determined by both the allergen content of the plant and the patient's degree of sensitivity and exposure. Primin-free strains (*Primula obconica* 'Libre') have now been developed [49].

Clinical features. The classical appearance of *Primula* allergy is linear papulovesicles, oedema and blisters, which may be haemorrhagic, on the palms, dorsa of the hands and forearms (Figs 20.6 & 20.27). Transfer of the allergen via the fingers to the face, or more generally, is common. In some patients palpebral oedema is the presenting feature, but half of the cases have other patterns, and the diagnosis is easily missed unless the possibility of *Primula* dermatitis is kept in mind [11,50]. Misdiagnoses include constitutional pompholyx, urticaria or recurrent angio-oedema, and disseminated herpes simplex [51]. Erythema multiforme, a lichen planus-like eruption and toxic erythema as a result of *Primula* allergy can also cause diagnostic difficulty [52–54].

Alstroemeriaceae and Liliaceae

Alstroemeria (Peruvian lily) is a highly decorative plant commonly displayed as a spray with other flowers. The damaged plant's sap is allergenic to florists when the stems are wired and leaves stripped, in preparation for making the spray [55].

The allergen is tulipalin A, also known as α-methylene-γ-butyrolactone, released from the precursor tuliposide A [56]. This allergen is also found in tulips (especially the bulbs). Tulips are members of the Liliaceae family and dermatitis is a particular risk for bulb collectors, sorters and packers, as well as florists [57,58].

Clinical features. Dermatitis from tulip bulbs may cause a painful, dry, fissured and hyperkeratotic allergic dermatitis, at first underneath the free margins of the nails and then on the fingertip [59]. A similar pattern of dermatitis is

seen in florists sensitized to *Alstroemeria* [60], and it may be followed by depigmentation [61].

Alliaceae

Garlic and onion are both members of this family and may sensitize, but do not seem commonly to cross-sensitize mutually [62]. Diallyl disulphide is the major allergen in garlic [63]. The allergen(s) in onion has not been identified.

Clinical features. Classically there is fingertip involvement in those allergic to garlic (see Fig. 20.7) and onion. This may preferentially affect the non-dominant hand, as this is the one that holds the vegetable while it is being cut with an implement held by the dominant hand [64]. Systemic contact allergy, including pompholyx, caused by ingestion of garlic has been described [65,66].

Lichens and liverworts

Lichens consist of a fungus and an alga. They are found on trees, rocks, roofs and walls [4]. Oak moss (*Evernia prunastri*) is a perfume ingredient derived from lichens [67]. Allergenic components include atranornin, usnic acid and evernic acid [33,67]. Liverworts (*Frullania*) are small red/brown plants often growing with lichens and mosses. The allergens, in common with Compositae with which they commonly cross-react, are sesquiterpene lactones [32–34].

Clinical features. A pattern similar to pseudophotodermatitis from Compositae has been seen in woodcutters' dermatitis caused by sensitivity to lichens and liverworts [68,69]. Erythroderma may ensue in severe cases. Even walking through a forest may cause an exposed-site pattern of dermatitis in sensitized individuals [36].

Avoidance

Patients who know of their sensitivity may manage to avoid further contact if taught to recognize the plants to which they are allergic. This is fairly straightforward for *Primula obconica*, *Alstroemeria*, tulips, Alliaceae, lichens and liverworts. Tulipalin A, in tulips and *Alstroemeria*, penetrates vinyl gloves. Nitrile gloves are more satisfactory for handling bulbs and the plants [70]. Those sensitized to lichens may also be allergic to certain perfumes, particularly those containing oak moss (*Evernia prunastri*). Perfume avoidance advice (see p. 20.49) may also have to be followed.

The recognition of *Toxicodendron* spp. is particularly important. Although the classical three-lobed leaves are a helpful feature, clusters of five or more leaves can occur. As there is considerable regional variability in the morphology of these species [16,37], it is preferable that sensitized persons become familiar with the appearance of *Toxicodendron* spp. in their own region.

Toxicodendron oleoresin may remain under the fingernails and on the clothes, resulting in continuing problems [5]. Detergents, soap and water will inactivate the residual unreacted allergen. After exposure, thorough washing of the hands, fingers and the rest of the body should be carried out as soon as possible, ideally within 10 min. Clothes should be changed. Contaminated tools and clothing, including shoes, should be washed in detergent [5].

Specific creams, containing quaternium-18 bentonite and other barriers, have been developed and these may help prophylactically to a varying but incomplete extent [71,72]. Heavy-duty vinyl gloves afford better protection than rubber gloves [5].

Seasonal Compositae exposure may be difficult to avoid. Severe Compositae allergy may necessitate changing occupation (e.g. florists, gardeners) or avoiding pastimes such as flower arranging and gardening. It may be necessary to avoid handling lettuce, chicory, artichokes and endives in food preparation. Those with associated photosensitivity may have significant problems from this, especially over the summer months. A high protection broad-spectrum sunscreen is required for this subgroup. Where contact with *Toxicodendron* spp. and certain Compositae such as ragweed is unavoidable (e.g. outdoor workers), hyposensitization has been attempted, with limited success. There is a risk of unpleasant side effects, including extensive skin eruptions and perianal dermatitis [73–75]. This treatment does not have the approval of the Food and Drug Administration in the USA [5].

Patch tests

There are two plant allergens recommended for the standard series: primin is tested at 0.01% in petrolatum; sesquiterpene lactone mix contains alantolactone 0.033%, dehydrocostus lactone 0.033% and costunolide 0.033% emulsified with sorbitan sesquioleate [12].

Primin is the major allergen in *Primula obconica* but may fail to detect *Primula* allergy occasionally [76]. Other *Primula* species may contain this allergen [46,77].

Sesquiterpene lactone mix does not identify all persons with Compositae allergy [15,78–80]. An alternative screen consisting of a mix of arnica, yarrow, tansy, German chamomile and feverfew extracts has been developed [81]. In one study, it identified twice the number of sensitized persons detected by sesquiterpene lactone mix, and by testing with both allergens 76% of all allergic subjects were identified [82]. However, this Compositae mix gives frequent false-positive reactions and may be sensitizing [83–85]. A lower concentration than 6% has been suggested [85,86]. In the UK, dandelion allergy, in particular,

may be missed by the sesquiterpene lactone mix patch test [87].

Other commercially available plant allergens include a number of Compositae extracts, including dandelion. Diallyl disulphide, the main allergen in garlic, is tested at 1% in petrolatum, and α-methylene-γ-butyrolactone, the allergen in tulips and *Alstroemeria*, is tested at 0.01% in petrolatum. Lichen acid mix consists of atranornin, usnic acid and evernic acid, each at 0.1% in petrolatum.

Plant extracts, preferably of known concentration, can be used for patch testing. Dipping the plant in diethyl ether for 60–90 s, evaporating to dryness and resuspending in petrolatum (1–10%) is a suggested simple method, although there are many alternative approaches [4,5,88]. Patch testing for *Toxicodendron*, if considered necessary, can be undertaken by diluting the oleoresin 1 in 10 in acetone [5].

Patch testing with the plants themselves may be undertaken but carries the risk of false-positive irritant reactions and active sensitization. If multiple tests with plants and plant allergens are carried out, there is a possibility that many strong positives may occur leading to an 'angry back' and inducing false-positive reactions to other allergens. Ideally, before patch testing with a plant, it should be identified and if it is a known irritant then testing may not be advisable. A textbook on plant dermatitis is a useful reference source. Several parts of one plant may contain the same allergen, and if this is the case 1 cm^2 of leaf bruised gently with an orange stick is sufficient for patch testing. Sometimes, however, the allergen is concentrated in one organ of the plant (orange peel, cinnamon bark) or the concentration of the allergen varies from one part to another. When testing with unknown plants, several parts should be tested. For later botanical identification, half of the material should be kept in a refrigerator [1]. Any plant that has given positive allergic reactions should be properly identified by its Linnaean name.

In order to prevent registration of irritant tests, it is important to employ controls when testing with the plants and their extracts.

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Woods, colophony and turpentine [1–4]

Woods are normally of two types, hard and soft. The same woods may have many different names, and sometimes an incorrect name is mistakenly or deliberately applied [4,5]. The situation is complicated further by the occasional introduction of 'rogue' timbers into batches of hardwoods [5–7]. The commonest allergenic woods are listed in Table 20.9 [4].

Occupational allergic contact dermatitis is more frequently associated with hardwoods, and is more commonly seen among cabinet-makers, instrument makers, and so on. Some tropical hardwoods are especially allergenic. In many instances the precise allergens are not known, but some have been identified. Chemically, these include quinones (including dalbergiones and lapachol), phenols, terpenes, stilbenes and anthothecol [1–4]. Softwoods, apart from pines and other conifers, are not commonly associated with contact allergy [4]. Jelutong (*Dyera*

Table 20.9 Principal timbers causing dermatitis.* (From Hausen [4].)

Botanical name	Common name†	Origin	Uses
Apocynaceae			
Dyera costulata	Jelutong	SE Asia	Modelmaking Woodwork teaching
Boraginaceae			
Cordia goeldiana Huber	Freijo Frei jorge	Brazil	Boat building Furniture Interior construction Joinery
Cordia gerascanthus R. Br.	Canalete	Venezuela	Furniture Interior construction Joinery
Cordia millenii Baker	Cordia	W. Africa	Furniture Interior construction Joinery
Cordia platythyrsa Baker	Cordia	W. Africa	Furniture Interior construction Joinery
Cupressaceae			
Calocedrus decurrens (Torrey) Florin	Incense cedar	USA	Pencils Fence posts Furniture Interior construction
X Cupressocyparis leylandii	Leyland cypress	Temperate	Garden shrub Hedges
Thuja plicata Donn ex D. Don	Western red cedar Arbor vitae	USA	Construction Boat building
Ebenaceae			
Diospyros celebica Bakh.	Macassar	Indonesia	Cabinet and inlay work Musical instruments Rulers
Diospyros crassifolia Hiern	African ebony	Africa	Cabinet and inlay work Musical instruments
Diospyros ebenum Koenig	Ceylon ebony East Indian ebony	Sri Lanka, India, Indonesia	Cabinet and inlay work Musical instruments
Diospyros melanoxylon Roxb.	Coromandel	Sri Lanka, India, Indonesia	Cabinet and inlay work Musical instruments
Leguminosae			
Caesalpiniaceae			
Distemonanthus benthamianus Baillon	Ayan Movingui Nigerian satinwood	W. Africa	Coffins Furniture Floors Window frames
Mimosaceae			
Acacia melanoxylon R. Br.	Australian blackwood	W. Australia	Boat building Construction Furniture Musical instruments
Papilionaceae			
Bowdichia nitida Spruce ex Benth.	Sucupira	Brazil	Construction Floors Furniture
Brya ebenus	Cocus Jamaica ebony	W. Indies	Musical instruments Handles Plates
Dalbergia latifolia Roxb.	E. Indian rosewood Bombay blackwood Sissoo	India, Indonesia	Veneers Furniture Musical instruments Handles Wooden jewellery

(*continued p. 20.94*)

Table 20.9 (*cont'd*)

Botanical name	Common name†	Origin	Uses
Dalbergia melanoxylon Guillemin & Perrottet	African blackwood Grenadil	Africa	Musical instruments Handles
Dalbergia nigra All.	Brazilian rosewood Rio-Palisander Grenadilla Jacaranda	Brazil	Veneers Furniture Musical instruments Handles Wooden jewellery
Dalbergia retusa Hemsley	Cocobolo	Central America	Handles Scientific instruments Wooden jewellery
Machaerium scleroxylon Tul.	Pao ferro Santos palisander Caviuna vermelha	Brazil	Veneers Furniture Handles
Malvaceae (L.) Sol.			
Thespesia populnea (L.) Sol.	Milowood	USA	Carved utensils Bracelets Furniture
Meliaceae			
Khaya anthotheca C. DC	African mahogany Krala	W. Africa	Furniture
Khaya grandiflora DC	Big leaf mahogany	W. Africa	Furniture
Khaya ivorensis A. Chev.	Khaya mahogany	W. Africa	Furniture
Khaya senegalensis (Desr.) A. Juss.	Dry zone mahogany	W. Africa	Furniture
Moraceae			
Chlorophora excelsa Benth. & Hook.	Iroko Kambala African teak	W. Africa	Construction Shipbuilding Laboratory benches
Pinaceae			
Pinus spp.	Pine	Northern temperate	Construction Furniture General
Picea spp.	Spruce Fir	Northern temperate	Construction Furniture General
Proteaceae			
Grevillea robusta Cunn. ex R. Br.	Australian silky oak	Australia (planted elsewhere)	Floors Furniture Plywood Telegraph poles
Sterculiaceae			
Mansonia altissima A. Chev.	Mansonia African black walnut Bété	W. Africa	Furniture Walnut substitute
Verbenaceae			
Tectona grandis L.	Teak	India, SE Asia	Furniture Floors Construction Shipbuilding

* Lichens on the wood may also sensitize.
† There is no accepted international nomenclature.

costulata) is a South-East Asian tree whose timber has sensitized woodwork teachers [8].

Pine trees are the source of two significant allergenic materials, colophony and turpentine [4]. Turpentine is the balsam from species of *Pinus*. Oil of turpentine is the volatile oil distilled from this balsam. The term 'turpentine' is commonly used to designate oil of turpentine. Colophony is the non-volatile part of the balsam and is

known as gum rosin [9]. Swedish and Finnish turpentine is made in the processing of paper pulp from wood. Venice turpentine is the balsam from larch trees.

Colophony is also extracted as a distillate from pine tree stumps, when it is known as wood rosin, and as a by-product of pulping pine wood, when it is called tall oil rosin [9]. The chemical composition varies according to geographical source, production method and storage conditions. It is composed of approximately 90% resin acids and 10% neutral substances [10]. Auto-oxidation products of abietic and dehydroabietic acids, including peroxides, hydroperoxides, epoxides and ketones, have been proposed as allergens [11]. Colophony may be modified, thereby altering its allergenicity with the development of new allergens [12]. Maleopimaric acid and glyceryl monoabietate have been identified as allergens [13] in modified rosins [14]. Certain other resins are chemically related [15,16].

The major sensitizer in turpentine is hydroperoxide of Δ^3-carene [17], which is also an auto-oxidation product. Swedish and Finnish turpentine contains more of this substance than, for example, French and American turpentine. Limonene (D or L) and pinene (α or β) can also sensitize [18]. The term 'mineral turpentine' is used for the non-sensitizing, but irritant, white spirit, i.e. a petroleum product.

The sensitizer propolis used in bee glue is derived mainly from poplar resin. It may be found also in beeswax. The allergens include caffeates and benzyl isoferulate [19].

Lichens, liverworts and sensitizing plants may cause allergic sensitization by virtue of their coexistence with trees. Additives to wood such as varnishes, dyes, glues or preservatives may also sensitize at work.

Incidence and prevalence. The incidence and prevalence of occupational wood allergy are unknown. Colophony is a standard allergen, with a 2–6% prevalence of allergy in patch-tested populations [12].

Turpentine was removed from the ICDRG's recommended standard series because of infrequent allergy. It has been excluded from many industrial products, especially solvents, and replaced by petroleum products such as white spirit [20], although a high prevalence of sensitization continues to occur in Spain and Portugal [21,22]. Furthermore, there is now evidence of increasing sensitization to oil of turpentine, which will require further investigation [23].

In patch tests on 137 men and 2036 women, positive reactions to propolis occurred in 0.9 and 1.4% respectively [19].

Occurrence. Trees, wood and sawdusts are predictable sources. Colophony, however, is ubiquitous and not only found in pine and spruce trees and wood. The commoner sources of colophony and its modifications [10] are identified in Table 20.10, but this list is not all-inclusive. It is labelled in cosmetics by its INCI name Colophonium. Colophony derivatives (e.g. abietic acid, hydroabietic acid and hydraobietyl alcohol) may also be found in cosmetics.

Table 20.10 Sources of colophony.

Pine trees and wood	Spruce trees and wood
Rosin (grip/antislip materials)	Adhesive plasters and tapes
Adhesive dressings	Insulating and jointing tapes
Ostomy appliances	Dental dressings
Clear and brown soaps	Varnishes and coatings
Metalworking fluids (tall oils)	Solder flux
Glues, adhesives and sealants	Shoe adhesives and counters
Paper size	Flypaper
Shoe and floor polishes	Cosmetics (eye shadow, mascara)
Printing inks	Wood wool
Chewing gum	Linoleum
Balms and salves	Wart treatments

Turpentine is present in balsams and sawdust from pine and spruce. It was used as an industrial solvent but has now largely been replaced by petroleum derivatives and D-limonene [20]. It is still used by artists [20] and in ceramic decoration [24]. In certain producing countries such as Spain [21] and Portugal [22], turpentine is still more widely used than elsewhere, and it remains a common allergen there. In the USA it is still commonly used as a paint remover [25].

Propolis is encountered not only by beekeepers [26,27] but also in topically applied agents used in 'natural' products from health food stores and mainstream cosmetic outlets. Solid propolis can be chewed [28]. Increasing self-medication may mean increased contact allergy from this source. It may also be found in beeswax [27] used in cosmetics and topical medicaments [29].

Clinical features. Most cases of wood allergy present in the occupational setting and are related to contact with airborne sawdust. The pattern of dermatitis therefore affects the exposed sites, with the scalp of bald men being typically involved. Differentiation from a photosensitive eczema may be difficult, but light-protected sites (e.g. under the chin and behind the ears) are more likely to be equally affected in wood dermatitis. However, sawdust can gain access inside clothing to produce dermatitis predominating in the flexures. Genital involvement is a particular feature, in part from transfer of the allergen during urination [6]. Severe erythema multiforme-like eruptions have been described, particularly from *Machaerium scleroxylon* allergy [6,30,31].

Localized dermatitis may occur under exotic hardwoods, for example from a violin chin-rest, or wooden adornments and utensils [32–35].

Colophony allergy may present in many different ways because colophony is ubiquitous. Over 300 potential allergenic sources have been identified [25]. An exposed-site

pattern may be seen after machining pine and cutting down branches when gardening. Highly sensitive persons may suffer without having direct contact. Sensitivity to *X Cupressocyparis leylandii* trees has been associated with concomitant colophony allergy [36]. Allergy to colophony in solder fumes can give a similar distribution but dermatitis may be confined to the face [37,38]. Unsuspected sources for an exposed-site pattern have included linoleum flooring, paper dust and floor polish [39].

Facial and eye dermatitis can develop from contact with colophony-containing cosmetics, particularly mascara [39–42]. Reactions to sticky tapes and plasters, and colophony-containing medicaments, are often confined to the site of application. Adhesive plasters are often used to cover painful fissures on the hands and feet. These may have been caused by a pre-existing eczema or psoriasis, which may consequently be perpetuated or exacerbated by colophony allergy. Allergy to colophony derivatives (e.g. ester gum resin) used as adhesives for lower leg dressings may be confused with varicose eczema and secondary medicament sensitization [43,44]. A secondary-spread eruption may develop in such cases. A localized dermatitis may be induced by topical colophony-containing medicaments, including wart treatments [45–48].

Colophony may induce hand dermatitis due to contact with a diverse range of colophony-containing materials such as glues, polishes, paper, rosin, antislip powders, topical medicaments, waxes, and tall oils in metal machining coolants [10,12].

Perioral dermatitis and cheilitis have been related to colophony in chewing gum [48,49]. Dental materials, including floss, fluoride varnish, dressings and impression materials, may contain colophony, but rarely sensitize in the mouth [50–52]. A case of widespread dermatitis has been recorded after dental treatment in an allergic individual [53].

Colophony can also be present in adhesives in footwear [54,55]. It has also been incorporated, in modified form, in footwear in an impregnated cloth [56].

Turpentine allergy is usually associated with hand dermatitis or a localized pattern of dermatitis.

Allergy to propolis in medicaments is manifest at their sites of application. Allergy to chewed propolis may induce a perioral distribution of dermatitis [28].

Avoidance. Demonstration of allergy to a wood should be followed by anatomical confirmation of its botanical name and, ideally, by testing with the known allergen(s) for that wood [4]. Subsequent avoidance of the wood and related timbers may be necessary.

Detection of the origin of colophony allergy requires careful appraisal of potential sources. Use of traditional sticking plasters should be replaced by 'hypoallergenic' tapes. Insulating tapes may also contain colophony, as may certain adhesive leg ulcer dressings. Contact with pine and other coniferous trees, and probably *X Cupressocyparis leylandii*, should be avoided; in those with extreme sensitivity, felling and removing the offending trees may be necessary. Occupationally, it may be possible to change the allergenic product to an alternative.

Colophony and derivatives can be identified in fully ingredient-labelled cosmetics. The INCI term Colophonium is used. Derivatives that may be used in cosmetics include abietic acid, hydroabietic acid and hydroabietyl alcohol. Transparent colophony-containing soap should be avoided for washing. Wart paints incorporating collodion should also be avoided, along with colophony-containing topical medicaments and balms.

Colophony allergy from paper has been implicated in hand dermatitis, and the use of cotton gloves is suggested if this is a possibility [57].

However, the list of potential exposures is so extensive that it will often be a case of establishing whether any of the sources identified in Table 20.10 are relevant and tailoring avoidance advice accordingly. For a more comprehensive coverage of sources the reader is referred to *Fisher's Contact Dermatitis* [25].

Turpentine substitutes are now readily available for sensitized subjects. Propolis (and beeswax) found in topical applications can be avoided by using only fully ingredient-labelled cosmetics and medicaments.

Patch tests. Patch testing with freshly made, uncontaminated sawdust 10% in petrolatum is recommended but may carry the risk of false-positive and false-negative patch tests, and active sensitization [4]. Apparent allergic positive reactions should only be confirmed after testing on controls. It is advisable to ask the patient to bring a piece of unmachined wood at the same time as the sawdust. If a positive allergic reaction develops, the piece can be sent to a wood anatomist who will confirm the correct name for the wood. If the allergen for that wood is known, it is sometimes possible to patch test with it at the appropriate concentration. However, this may be difficult as most wood allergens are not commercially available.

Colophony is a standard allergen tested at 20% in petrolatum. A mixture of Chinese and Portuguese gum rosin is presently used in commercially available patch-test allergens [10]. As some modified colophony products may be allergenically different, they may also need to be tested separately [58].

Propolis is patch tested at 10% in petrolatum.

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Patch testing [1,2]

Background

The diagnosis of allergic contact dermatitis is made by patch testing and of photoallergic contact dermatitis by photopatch testing. The techniques have evolved into a generally standardized methodology worldwide, although there are some variations, particularly with regard to reading times, test units and photopatch-test protocols [1,3].

Patch testing relies on the observation that primed antigen-specific T lymphocytes will be present throughout the body [4], and hence allergen in the patch test can be applied to normal skin, usually on the upper back where the tests are least likely to be disturbed. Other sites may be considered when this is not practicable, for example when

Table 20.11 Indications for patch testing. (From Bhushan & Beck [6].)

1 Eczematous disorders where contact allergy is suspected or is to be excluded
2 Eczematous disorders failing to respond to treatment as expected
3 Chronic hand and foot eczema
4 Persistent or intermittent eczema of the face, eyelids, ears and perineum
5 Varicose eczema

there is pre-existing inflammation or other skin changes on the back.

The test relies on the allergen being absorbed in sufficient quantity to induce a reproducible inflammation of the skin at the site of application in sensitized subjects. A positive reaction to a correctly prepared and applied patch test confirms the person has an allergic contact sensitivity, although this does not necessarily mean that the substance is the cause of the presenting clinical dermatitis, and its relevance should always be carefully considered.

Indications

It is well established that aimed patch testing with a few suspected allergens is suboptimal. The reason is that even experienced dermatologists are poor predictors of the outcome of patch tests; 17% of patients with allergies were missed on a prepatch-test assessment in one large clinic [5]. This parallels our own experience, with 20% of allergic patients regarded as definitely not allergic prior to patch tests and, conversely, 16% of patients thought to have contact allergy who were negative when patch tested.

A recent audit of patch testing has suggested that the investigation is underused, and consequently important opportunities to improve or resolve potentially disabling and undiagnosed allergic contact dermatitis are lost [6]. Facilities should be available to patch test at least 142 per 100 000 population annually and the categories of patient listed in Table 20.11 should be patch tested where practicable [6]. Dermatology-specific quality of life has been shown to improve significantly more in those patients who are patch tested because of more accurate diagnosis and earlier intervention [7,8]. Furthermore, the investigation has been shown to be cost-effective and to reduce the cost of therapy in patients with severe allergic contact dermatitis [7,9].

Methods

The basis of testing is to elicit an immune response by challenging already sensitized persons to defined amounts of allergen and assessing the degree of response. The amount of allergen is defined by its concentration in the vehicle and the amount applied. By testing the same allergens in parallel, the technique has been confirmed to be generally reproducible [10,11].

Chambers or discs are used to ensure occluded contact with the skin [1]. The fixing tape should be non-occlusive, non-allergenic and non-irritant. If the adhesive tapes peel off, the test should be repeated. Ideally, patch testing should not be carried out in patients with active eczema because it may reduce the threshold of activity and cause non-specific reactions, although in practice this is commonly not possible. The procedure should be delayed until the test site has been clear of eczema for at least a fortnight. Patch testing should not be performed following sunbathing, and the patches should not be exposed to the sun or other sources of UV light [12]. This information should be given to the patients before they book their appointments. Corticosteroids and other immunosuppressive drugs should be stopped (if this is feasible) before patch testing as they may reduce or extinguish positive patch tests in sensitized subjects. Nevertheless, this is unlikely at doses below 15 mg prednisolone daily [13,14], and we have identified relevant positive patch tests in patients who could only be investigated while they were taking other immunomodulators.

We prefer not to patch test pregnant patients in case an adverse event is blamed on the test, although we are unaware of any proven problem. Young children, even infants, can be patch tested when indicated, but the number of allergens tested may have to be reduced because of lack of space [15].

Test materials

The allergens are obtainable from the following manufacturers: Hermal, D-21462 Reinbeck, Germany (email: Hermalinfo@hermal.de), who market TROLAB allergens; and Chemotechnique Diagnostics AB, PO Box 80, Edvard Ols väg 2, S-230 42 Tygelsjö, Sweden (email: info@chemotechnique.se); or from their local distributors.

The commonest system used to apply allergens is the Finn chamber (Epitest Ltd, Oy., Rannankoukku 22, FIN-04300 Tuusula, Finland) on Scanpor tape (Norgesplaster, Vennesia, Norway). These are also available from local distributors. The chambers are supplied in strips of five or 10 (two rows of five) and consist of small occlusive aluminium discs. They are mounted on non-occlusive tape with an acrylic-based adhesive backing that has been chosen for its hypoallergenicity.

Other systems consist of square plastic chambers (Van der Bend chambers), oval plastic chambers (Epicheck) and the older AL Test system (a filter paper disc mounted on aluminized paper), which is available in rolls of chambers and is mounted on acrylic-based adhesive tape.

There is now also a new prepackaged ready-to-use patch-test system, TRUE (thin layer rapid use epicutaneous) test, based on a dispersion of allergen in a

hydrophilic polymer [16], although this is presently only available as a standard series of 23 allergens. It was developed by Torkil Fischer and Pharmacia, and is marketed in the UK by ALK-Abelló (UK) Ltd and in the USA by Allerderm. This system has been tested in parallel with the established Finn chamber system and there was close correlation of results [17,18]. It is a consistent, convenient, portable method for those wishing to test only the standard series.

Reactions to the adhesive tape may occur, but they are normally irritant not allergic. To reduce the incidence of such reactions, the strips must be applied without tension, with the patient in a relaxed posture. Folliculitis may occur due to occlusion, particularly in those with a tendency to seborrhoeic eczema.

Patch-test vehicles

Few substances can be applied to the skin as they are. In order to avoid an irritant effect, they must be mixed or dissolved in a vehicle to achieve a suitable test concentration. The test substance should, if possible, be soluble in the vehicle. If a dispersion of allergen in petrolatum is used, contact with the skin depends on the size of the particles and on their solubility or dispersion in petrolatum. Uniform dispersion and particle size are important [19]. Many substances can also be dissolved in water, alcohol, acetone, methylethylketone (MEK) or olive oil, as appropriate. Irritant solvents such as chloroform and benzene must not be employed. False-positive or false-negative reactions may occur when inappropriate vehicles are used. In addition, the concentration of allergen tends to increase as the solvent evaporates. Petrolatum is generally more reliable, and has the added advantage of being occlusive, which helps to prevent oxidation and prolongs shelf-life. Allergic reactions to petrolatum itself are very rare [20]. In hot climates, petrolatum may not be ideal, as it melts too quickly between preparation and application of the patch test, and a series in modified Plastibase has been devised for the Indian Contact Dermatitis Group.

Patch-test concentrations

Choice of a suitable concentration is of fundamental importance. Excessive concentrations result in false-positive reactions, because of their irritant effect, and may even sensitize patients; insufficient concentrations produce false-negative results. The concentration of allergen routinely employed for patch tests may, under some conditions and in some individuals, give rise to false-negative or false-positive reactions. The choice of concentration is thus a compromise, but most have been chosen by long experience with commonly used allergens. The concentrations used for patch testing are usually much higher than those encountered during development of dermatitis. To demonstrate the existence of nickel dermatitis produced by the minute amounts dissolved from nickel-plated objects, a 5% concentration of nickel sulphate in petrolatum is necessary. Chromate 0.25–0.5% is required to prove sensitivity to cement containing 0.0005–0.002% of chromate. Neomycin should be tested at 20% despite only being at 0.5% concentration in many topical medicaments [21].

Lists of suitable concentrations and vehicles are provided in a number of texts listed on p. 20.108. Metal salts in particular are tested at the margins of irritancy and may give false-positive, irritant patch-test reactions, especially in atopic individuals [22,23]. Weak reactions may not therefore be allergic, and the patient should be retested at a different site and with serial dilutions. Other standard allergens such as fragrance mix [24], parabens mix and wool alcohols may also be marginally irritant. On rare occasions, active sensitization may still occur even at the concentrations recommended. Irritant reactions are rarer with other substances used in standard series. They are potentially much more common with materials brought to the clinic for testing. Many industrial or domestic chemicals would give irritant false-positive reactions if undiluted, and no chemical or substance should be applied to the skin until full details of its composition and potential irritancy or toxicity are known.

If work or other materials are brought, a number of factors should be considered before they are used for patch testing. Is it appropriate to test with the material? Some materials are strong irritants and not allergens (e.g. strong acids and alkalis), and others may be contaminated or of uncertain or mixed composition (e.g. dust or grime from a working environment). The product may be intrinsically dangerous (e.g. explosive or produces toxic fumes) and require special handling. Some patients bring foods in the mistaken belief that the test will diagnose ingested food allergy.

The precise nature of the material should be ascertained by questioning the patient and examining the product label. In the UK, employers are required by law to have Health and Safety data sheets for all materials handled at work. These provide key information and a contact point with the manufacturing company. They must be scrutinized carefully, particularly with regard to irritancy, allergenicity, stability and solubility of the product and its components. Named chemical substances may be recognized as irritants or allergens, and their concentrations documented. Substances can be checked for pH, and neutralized if necessary [25].

An initial patch-test concentration can often be selected either by reference to standard texts or by contacting the manufacturer for details of toxicological testing data. It is advisable to start low (0.01% or less), and increase the concentration gradually if there is doubt about the optimum level for testing. It may be advisable to perform open tests

before proceeding to closed patch tests because the effect of irritants is enhanced by occlusion [26]. Materials intended to be left on the skin, such as medicaments and cosmetics, can be tested 'as is', 'rinse-off' products at 5%, and soaps, shampoos and detergents at 1%. However, the dermatologist administering a patch test will need to refer to standard references for guidance on dilutions and vehicles when testing finished products or specific chemicals. These are discussed on p. 20.108.

If a positive reaction to an unknown substance occurs, it should not be immediately accepted as allergic. Volunteers, who are not suffering from dermatitis related to the same agent, should be tested at the same concentration and using the same methods. If any reaction occurs among 50 controls, the substance should be regarded as a primary irritant at that concentration, and subsequent tests should be performed with decreasing concentrations.

Patch-test dose

If petrolatum is used as the vehicle and disposable syringes are the containers, a length of 5 mm of test substance in vehicle will suffice. If the vehicle is a fluid, a digital pipette should be used to deliver 15 µL to a filter paper in the chamber. Dropper bottles supplied by the allergen manufacturers tend to overfill the chambers. A surplus should be avoided, as it may contaminate neighbouring test sites. With TRUE test, the patches are preprepared. The risk of patch-test sensitization increases with the concentration and amount of test substance applied.

Storage of allergens

'Shelf-life' is prolonged if test substances not in daily use are stored in the dark in a refrigerator at 4°C. Many substances are unstable if exposed to light. Commercially available allergens are labelled with an expiry date.

Storage in small jars has the drawbacks of oxidation, drying and evaporation of volatile test substances [27]. Rubber pipette caps contaminate the solutions and may cause false-positive reactions in persons sensitive to rubber. Homogeneity of patch-test allergens may be lost, especially in hot climates, unless they are kept refrigerated [28].

Test site

Most dermatologists prefer to apply patch tests to the back [29]. The region used for testing is important with regard to the results of the investigation: both allergic and irritant reactions are most easily provoked on the upper back [30] (Table 20.12). Reactions on the lateral aspect of the upper arm are stronger than on the medial aspect. Sites other than the back and lateral aspect of the upper arm are generally less suitable as test areas, but when necessary we have used the abdomen or even the thighs rather than abandoning the investigation.

Table 20.12 Reactivity of various test sites. (From Magnusson & Hersle [30].)

	Type of reaction	
Test site	Irritant (%)	Allergic (%)
Upper back	100	100
Lower back	50	95
Upper arm	52	72
Forearm	38	74
Thigh	36	50

Marking

Test sites must be marked with indelible ink or stratum corneum stains (or fluorescent markers on dark skins). Marking materials can be obtained from allergen suppliers. It is necessary to repeat marking before removal of the patches, because their positions cannot be distinguished once the pressure effects have subsided. The patient should be instructed not to bathe or shower for the duration of the tests, and to avoid exercise or other activity likely to dislodge the patches.

Exposure time

The mere touch of a *Primula* leaf may provoke a subsequent bullous response in a sensitive person, but with some materials (e.g. textiles) even 5 days of occlusive patch tests may lead to false-negative reactions. Well-established allergens, however, are conventionally tested in such concentrations that a 48-h exposure under an occlusive patch will generally allow penetration of an amount sufficient to provoke a reaction. With low sensitivity, low concentration of allergen or poor absorption of a particular agent, there may be a long period of latency. The ideal regimen is a 48-h application time, with readings taken 1 h after removal and again 48 h later, i.e. at 2 days and 4 days [31], preferably with the same observer performing each reading. Others have suggested that a 3-day second reading is better [32]. A single 2-day reading is not advised as it may lead to the labelling of some marginal irritants as allergens, and positive reactions to more poorly absorbed allergens may be missed [31,33]. Variations to this schedule are made for expediency, to fit in with clinic times, and for the convenience of patients travelling long distances. If only one patch-test reading is possible, a 4-day reading has been recommended [34,35] although, according to some authors, a single 4-day reading is also associated with the risk of missing some significant positive reactions [36]. A third reading at 5–7 days seems to identify a small proportion of additional

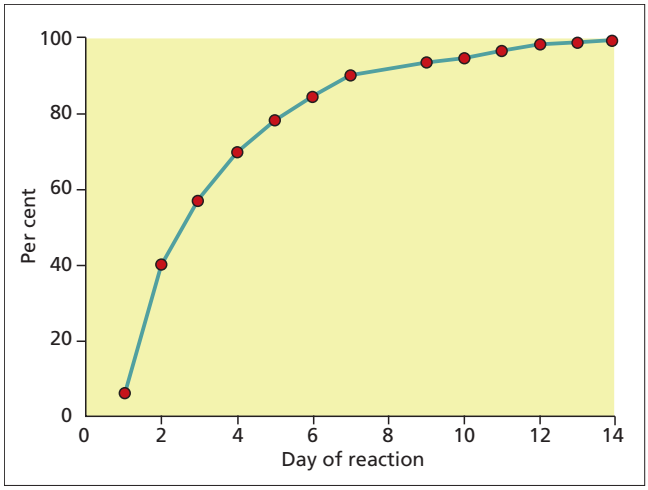

Fig. 20.28 Patch tests with neomycin 20% in petrolatum: positive reaction times after application.

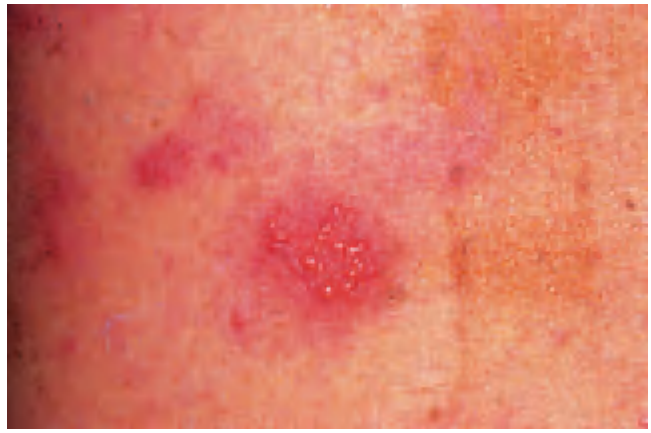

Fig. 20.29 A positive allergic (++) patch-test response in a patient sensitive to neomycin. (Courtesy of Dr J.D. Wilkinson, Amersham General Hospital, Amersham, UK.)

relevant positive allergies where sensitivity is weak or partially 'forgotten', or where there is poor absorption of the allergen [32,35,37,38]. Neomycin (Fig. 20.28) and corticosteroids are particularly liable to give late reactions.

Immediately after removal of the patch tests, there may be erythema from the stripping action of the tape, especially in dermographic subjects, and this must be allowed to settle. Furthermore, some reactions may take up to 1 h to develop once the pressure of the strips has been released and the infiltration allowed to swell the dermis.

Readings and interpretation

It is important that patch-test readings are scored according to the reactions seen and not according to the interpretation placed on the reaction by the reader. As the strength of a reaction is not always reproducible, an over-detailed quantification should be avoided. The scoring system devised by the ICDRG in 1970 is shown in Table 20.13 [39].

There are drawbacks to the ICDRG system in that it confuses morphology with interpretation. The ideal system is to record what is seen at 2 and 4 days, and then to decide if this represents an allergic or irritant response. This is done by assessing morphology and skin type, combined with knowledge and experience of the substance and the patient's history. Patch-test results should be recorded objectively, and the interpretation of the results should be recorded separately. In this way raw data remain available for re-examination.

Once they have developed, positive allergic reactions often persist for several days. The strength of the reaction depends on barrier function, the presence or absence of sweating, the atmospheric humidity, test material, technique and the reactivity of the individual.

Strong reactions of an allergic nature are erythematous and infiltrated, commonly with minute papules or vesicles (Fig. 20.29), which in severe reactions coalesce into bullae. The infiltration causes a thickening in the dermis, which is palpable and can be distinguished from surface changes in the epidermis. The reaction may extend beyond the margins of the patch, and there is often some itching. Nevertheless, sometimes true allergic reactions can be weaker than this, making interpretation more difficult.

In most instances there is little difficulty for the experienced clinician in identifying true positive allergic patch-test reactions. Nevertheless, there are occasions when distinguishing an allergic from a false-positive non-allergic irritant reaction can be difficult or even impossible. There may be clues—no infiltration, lack of itching, deep redness or a brown hue, and sharp delineation corresponding to the margins of the patch test (particularly around the edge with solid materials)—these all point to an irritant reaction. Some irritants provoke a 'soap effect', with a well-localized, glistening, finely wrinkled surface. Patch tests with nickel may cause pustular reactions that are often false positive (Fig. 20.30), although some progress to more typical allergic reactions. Cobalt also

Table 20.13 Recording of patch-test reactions according to the International Contact Dermatitis Research Group. (From Wilkinson *et al*. [39].)

–	Negative
?+	Doubtful reaction; faint erythema only
+	Weak positive reaction; palpable erythema, infiltration, possibly papules
++	Strong positive reaction; erythema, infiltration, papules, vesicles
+++	Extreme positive reaction; intense erythema and infiltration and coalescing vesicles
IR	Irritant reaction of different types
NT	Not tested

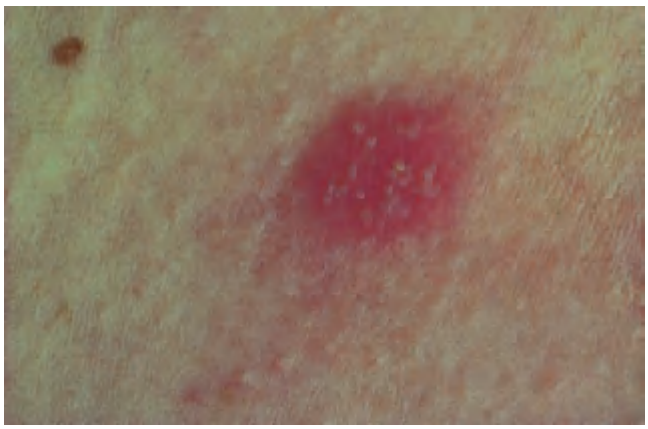

Fig. 20.30 Pustular patch-test reactions to metals are common in atopics and are often irritant in type.

produces a distinctive false-positive purpuric reaction. In our experience these tend to occur much more in atopic individuals, and need to be distinguished from allergic follicular reactions consisting of papules without pustules or purpura.

Patch tests positive at 2 days and negative at 3–4 days may be irritant. False-positive irritant reactions are liable to induce stronger reactions at 2 days than at 4 days, the so-called crescendo–decrescendo effect. However, this is not always the case and the reverse can happen in our experience. Difficulties in evaluation are particularly common with substances brought in by the patient for testing. It may be necessary to apply several concentrations at the first visit; controls should be performed with any substances giving positive reactions.

There is no substitute for a thorough knowledge and experience of the allergens used for patch testing. Even some standard allergens may be liable to induce weak false-positive reactions (e.g. metal salts, fragrance mix, parabens mix, wool alcohols and carba mix). Repeat patch testing may be helpful, especially with a breakdown of the mixes.

Non-invasive measurement techniques [40]

There are several non-invasive techniques that can be used to quantify and delineate the effects of patch tests, including measurements of changes in skin surface, epidermal hydration and water barrier function, and parameters of inflammation [40]. At present, these are more useful to the investigator than to the clinician [41]. They include replica techniques [42], transepidermal water loss [43], skin reflectance [44], laser Doppler flowmetry [45,46], thermography [47] and high-frequency ultrasound [48]. Attempts have been made to use some of these techniques to differentiate irritant from allergic patch-test reactions [49] but they have not superseded the combination of human brain, eye and hand in the assessments of patch tests.

Relevance of patch tests

It is important to try to relate the actual episode of dermatitis, with regard to both site and timing, to a history of exposure to the putative allergen. A positive reaction to a patch test commonly proves the cause of a dermatitis, i.e. the reaction is relevant. Other reactions may relate to previous attacks of dermatitis and are thus of past relevance. Some sensitivities cannot be interpreted within the limits of the knowledge available. Such unexplained positive reactions are quite common. However, many previous positive formaldehyde reactions were unexplained until it eventually became apparent that they indicated possible textile dermatitis. A similar situation occurred with balsam of Peru (*Myroxylon pereirae*) before its many associated allergens were recognized. Overall, approximately 75% of '++' and '+++' patch-test reactions are of current or past relevance. The relevance of '+' reactions is less certain [18].

A person may react to a patch test but still tolerate contact with the allergen. Dermatitis from face creams is uncommon in patients with dermatitis of the legs related to parabens sensitivity, known as the paraben paradox [50]. Clinically, latent sensitivity to occupational contactants is common in healthy workers who have never suffered any skin disease [51]. In a patient with dermatitis, a positive patch test must never be disregarded. If found in a healthy person, it may indicate a future risk of contact allergic dermatitis from that particular allergen.

Sources of error

False-positive reactions (Table 20.14). Irritant reactions occur if a chemical is tested at excessive concentration. Incorrectly interpreted false-positive reactions may lead to the wrong conclusions about the cause of a dermatitis, and this may result in inappropriate career or medicolegal advice. Recent or active dermatitis in the test area lowers the threshold for irritant reactions, as does dermatitis in other areas [52], and non-specific reactions can occur.

Table 20.14 Causes of false-positive reactions.

Excessive concentration
Impure substance (contaminants)
Irritant vehicle
Excess allergen applied
Uneven dispersion
Current or recent dermatitis at patch-test site
Current dermatitis at distant sites
Pressure effect of hard materials
Adhesive tape reactions
'Angry back' reaction causing intensification of weak irritants
Artefact

Table 20.15 Causes of false-negative reactions.

Insufficient concentration
Insufficient amount applied
Poor adhesion of patches
Patches applied at wrong site
Inappropriate vehicle
Readings performed too early
Substance degraded
Pretreatment of patch-test site with topical corticosteroids
UV irradiation of patch-test site
Systemic treatment with immunosuppressants

Secondary non-specific reactions close to genuine positive ones have been termed 'angry back' [53] or the 'excited skin syndrome' [54], and this may be an important cause of false-positive patch-test reactions. The phenomenon has been extensively investigated by Bruynzeel [55]. However, multiple positive reactions to nickel did not cause 'angry back' in a study by Andersen *et al*. [56].

If there is any doubt, the patch tests should be repeated some weeks later, preferably with individual agents and at various dilutions, as false-positive irritant reactions tend to stop abruptly below a certain concentration whereas allergic responses tend to persist, albeit proportionally weaker, at lower concentrations. Testing the same substance on a panel of controls, using the ROAT on the elbow flexure [57] or usage tests, may help to differentiate allergic from irritant responses. Controls should be tested at the lowest concentration of a positive test to avoid interpreting a false-positive irritant reaction as allergic.

False-negative reactions (Table 20.15). Sometimes a patch test fails to provoke a positive reaction in a person who is sensitive to the substance tested. The dermatitis therefore persists because of continued exposure to the allergen. The most common cause of false-negative reactions is insufficient penetration through the skin.

A low degree of sensitivity or poor penetration sometimes results in a long period of latency before a positive reaction develops, so that up to 7.5% of allergic positive patch tests do not become apparent until after 4 days, and may go unnoticed unless read 7–14 days after application [35]. This particularly applies to neomycin [21] and corticosteroids [58].

The apparent discrepancy between the concentration of allergen needed to elicit clinical dermatitis and the occasional failure of a patch test to elicit a reaction can be explained by many factors. In particular, a single exposure on normal skin is probably not representative of the accumulation of the allergen during repeated exposure conditions and chronic usage on already primed skin.

False-negative reactions are common when testing with textiles, cosmetics, medicaments, leather and rubber, as some ingredients are present in very low concentrations. False-negative reactions also occur when allergens are present in irritant products. Because of irritancy, a product may have to be diluted to such an extent before it can be safely tested that the allergen is present in insufficient concentration to elicit a response. Such products include cutting oils and washing materials. Sensitivity to finished products and topically applied preparations is best confirmed and revealed by testing with the individual components.

An allergy may be missed on patch testing if the test material has been wrongly diluted in a material in which it is immiscible or insoluble. Furthermore, an incorrect diluent may change the allergen into another substance altogether [59]. Partition coefficients are also important, because oil/water solubility may be a significant factor in skin penetration and allergenic potential.

Local treatment with topical corticosteroids [60], and systemic treatment with immunomodulators including ciclosporin, azathioprine and corticosteroids such as prednisolone (at a dose above 15–20 mg/day), may diminish or abolish reactions [13], as does prior sunbathing [12]. Negative reactions, in spite of clinical sensitivity, also occur in photocontact dermatitis if appropriate allergens are not photopatch tested.

Compound allergy [61,62]. Compound allergy occurs when a positive allergic patch-test reaction is seen to a finished product but tests with the ingredients are negative. Hence, the product and the constituents should be patch tested when allergy is suspected. This was a concept first proposed by Calnan [63] and considered in depth by Dooms-Goossens in her thesis [61].

New compounds may be formed within a product, and their presence can be confirmed by the finding of incongruous peaks on spectrometry. This was elegantly demonstrated in Hirudoid cream, where a new allergen was formed as a reaction product of two preservatives in the medicament [64]. The additive effect of multiple weak sensitizers [65], or the additive effect of weak allergens and irritants, should be considered [66]. Commonly, the reaction to the finished product is irritant [67]. A product's irritancy is not merely the sum of the irritancy of the ingredients, but an expression of the hydrophilic–hydrophobic balance of its ingredients. This can change with varying manufacturing techniques, for example changing the temperature or manipulating the proportion of one of the ingredients.

There are several possible alternative explanations. A constituent allergen may be an undeclared ingredient or there may be batch/source differences between the original compound and the subsequently provided components. The allergen may be in the container, for example a rubber stopper, and not in the product. The allergen may not have been tested in the correct vehicle or at the correct concentration, and testing it in its own base may reveal the allergy [61].

Quenching [68]. Theoretically, just as there may be potentiation of allergic and irritant responses, so a combination of chemicals may lead to a quenching effect [69]. This phenomenon has been investigated mostly in fragrance material aldehydes. It might be explained by the combined compounds changing available bonding sites for class II molecules or forming a compound that does not follow the same detoxification pathway. However, some authors have been unable to demonstrate any physicochemical interaction [70], and it remains questionable whether the phenomenon really exists [68].

Other observed quenching effects may be due to one of the compounds having anti-inflammatory properties [71,72], such as triclosan having a 'quenching' effect on nickel allergic contact dermatitis.

Other factors. The interpretation of patch-test reactions can be affected by the presence or absence of impurities or degradation products [73], hidden additives [74], batch differences [75] and the fact that some chemicals may undergo reactive metabolic changes in the skin. Natural products vary according to source [76,77], season [78] and method of extraction [79]. Storage or 'ageing' of a product may also affect its allergenicity [80] and irritancy [81]; D-limonene has been shown to be allergenic only in its old and oxidized state [82]. Patients should therefore always be tested with their own product. Season may also influence patch-test results, but whether this is due to UV radiation suppression of test reactions in summer or an enhancement of irritant-type reactions in winter remains uncertain [83,84].

Errors may occur in the registration of the relative sites of the tests. It is therefore advisable to repeat the test if in doubt.

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Selection of test substances [1]

The decision about what to test is dependent on a sound knowledge of the common sensitizers, in conjunction with a thorough history of exposure. Fortunately, a high proportion of cases of contact dermatitis are caused by sensitivity to a small number of contactants, although there are potentially thousands. In relatively few cases of contact dermatitis are the clinical appearances and history so typical that an allergen can be incriminated readily [2,3].

It is therefore essential to test with a standard series of common contact allergens. Many investigation clinics have extra allergens and some of these may be grouped into additional special test series (e.g. for certain occupations or affected sites). Furthermore, it may be necessary to test with materials encountered in patients' working and domestic environments, and with any medicaments and cosmetics applied to affected areas.

Standard series [4]

The principle of screening all patients with a series of allergens commonly encountered in their environment is now well established. Aimed patch testing is ill-advised. The decision as to what should be in the standard series has now generally devolved from the ICDRG to other national and international groups. The standard series recommended by the EEC-DRG contains 25 allergens [5,6]. The BCDS has recently advised 35 allergens for their standard series [7]. Table 20.16 shows the standard series recommended in various parts of the world [5–9]. As some allergens disappear from a given environment and others attain significance, it is important that a standard series evolves. In the past, several common sources of contact dermatitis were overlooked until they were included in a standard series. Nowadays, fragrance materials are familiar contact allergens but were virtually unknown

Table 20.16 Comparative lists of allergens in four different standard series.

	EEC-DRG*	BCDS†¶	NACDG‡	JSCD§
Potassium dichromate	0.5	0.5	0.25	0.5
Neomycin sulphate	20	20	20	20 (fradiomycin)
Thiuram mix	1	1	1	1.25
p-Phenylenediamine (PPD) base	1	1	1	1
Cobalt chloride ($CoCl_2 \cdot 6H_2O$)	1	1	1	1
Benzocaine	5	—	5	—
Formaldehyde	1 (aq.)	1 (aq.)	1 (aq.)	1 (aq.)
Colophony (Colophonium)	20	20	20	20 (rosin)
Clioquinol	5	—	—	—
Balsam of Peru (*Myroxylon pereirae*)	25	25	25	25
N-isopropyl-*N*′-phenyl-*p*-phenylenediamine	0.1	0.1	—	—
Wool (lanolin) alcohols	30	30	30	30
Mercapto mix	2	2	1	2
Epoxy resin	1	1	1	1
Parabens mix	16	16	12	16
p-Tertiary-butylphenol formaldehyde resin	1	1	1	1
Fragrance mix	8	8	8	8
Quaternium-15	1	1	2	—
Nickel sulphate ($NiSO_4 \cdot 6H_2O$)	5	5	2.5	2.5
Methylchloroisothiazolinone/methylisothiazolinone	0.01 (aq.)	0.01 (aq.)	0.01 and 0.01 (aq.)	0.01 (aq.)
Mercaptobenzothiazole	2	2	1	—
Primin	0.01	0.01	—	0.01
Sesquiterpene lactone mix	0.1	0.1	0.1	—
Tixocortol pivalate	0.1	0.1	1	—
Budesonide	0.01	0.1	0.1	—
Quinoline mix	—	6	—	—
Imidazolidinyl urea	—	2	2 (aq.)	—
Diazolidinyl urea	—	2	1	—
2-Bromo-2-nitropropane-1,3-diol	—	0.5	0.5	—
Chloroxylenol	—	1	1	—
Carba mix	—	3	3	—
Ethylenediamine dihydrochloride	—	1	1	1
Caine mix	—	10	—	7
Cetearyl alcohol	—	20	—	—
Fusidic acid	—	2	—	—
Chlorocresol	—	1	—	—
Methyldibromo glutaronitrile	—	0.3	—	—
Methyldibromo glutaronitrile/phenoxyethanol	—	—	2.5	—
Methyldibromo glutaronitrile/phenoxyethanol	—	—	0.4	—
Thimerosal	—	—	0.1	0.1
Sodium gold thiosulphate	—	—	0.5	—
Bacitracin	—	—	20	—
Ethyleneurea melamine formaldehyde resin	—	—	5	—
Propylene glycol	—	—	30 (aq.)	—
Cinnamic aldehyde (Cinnamal)	—	—	1	—
Amidoamine	—	—	0.1 (aq.)	—
DMDM hydantoin	—	—	1 and 1 (aq.)	—
Glyceryl thioglycolate	—	—	1	—
Glutaraldehyde	—	—	1	—
Ethyl acrylate	—	—	0.1	—
Tosylamide formaldehyde resin	—	—	10	—
Mixed thioureas	—	—	1	—
Benzophenone 3	—	—	3	—
Iodopropynyl butylcarbamate	—	—	0.1	—
PPD/black rubber mix	—	—	—	0.6
Bisphenol A	—	—	—	1
Dithiocarbamate mix	—	—	—	2
Urushiol	—	—	—	0.002
Ammoniated mercuric chloride	—	—	—	1
Petrolatum	—	—	—	‘as is’

Concentrations are quoted as percentages in petrolatum except where otherwise stated; aq, aqueous.

* European standard series as recommended by the European Environmental and Contact Dermatitis Research Group 1995 and 2000 [5,6].

† British Contact Dermatitis Society recommended standard series [7].

‡ North American standard series according to the North American Contact Dermatitis Group [8].

§ Japanese standard series according to the Japanese Society for Contact Dermatitis [9].

Table 20.17 Comparative results of patch-test series (expressed as percentage positive).

	UK (BCDS) [7] 2000	Germany [12] 1993–99	USA [8] 1998–2000	Japan [9] 1994
Metals				
Nickel sulphate	18.6	15.7	16.2	13.5
Cobalt chloride	5.8	4.9	7.6	17.3
Potassium dichromate	2.1	3.9	5.8	9.2
Rubber chemicals				
Thiuram mix	3.5	2.4	4.7	2.6
Carba mix	1.6	NT	4.8	0.5
Mercapto mix	1.1	0.7	1.3	0.6
IPPD/black rubber mix	0.4	0.8	1.0	1.2
Pharmaceuticals				
Caine mix	1.5	NT	NT	1.8
Benzocaine	NT	1.5	1.7	NT
Neomycin sulphate	2.9	2.5	11.5	4.0
Quinoline mix	0.7	NT	NT	NT
Ethylenediamine dihydrochloride	1.3	NT	2.5	0.3
Parabens	1.1	1.5	1.0	1.8
Chlorocresol	0.6	NT	NT	NT
Wool alcohols	3.3	4.0	2.4	2.8
Cosmetic ingredients				
Balsam of Peru (*Myroxylon pereirae*)	6.7	8.2	12.3	5.2
Fragrance mix	10.7	11.7	10.9	5.8
Formaldehyde	2.1	1.9	9.2	1.2
Quaternium-15	1.3	NT	9.2	NT
Methylchloroisothiazolinone/methylisothiazolinone	2.4	2.4	2.7	1.3
Plants				
Sesquiterpene lactone mix	1.1	NT	0.9	NT
Primin	0.6	NT	NT	0.7
Miscellaneous				
p-Tertiary-butylphenol formaldehyde resin	1.0	1.1	1.6	1.7
Epoxy resin	1.2	1.2	2.7	NT
Colophony	5.2	3.9	2.5	2.3
p-Phenylenediamine	3.0	4.2	4.9	6.1

IPPD, *N*-isopropyl-*N*′-phenyl-*p*-phenylenediamine; NT, not tested.

30 years ago [10]. Conversely, others (e.g. wood tars and turpentine) were removed from the standard series some years ago.

Newer standard allergens recommended for Europe include markers for corticosteroid allergy [6] (tixocortol pivalate and budesonide) and Compositae plant allergy (sesquiterpene lactone mix) [5]. The European standard series identified 75–80% of all allergies diagnosed in one multicentre study [11].

In some studies, as many as half of the relevant positive reactions were unexpected. Obviously, if patch testing is carried out for very wide indications, the percentage of negative reactions will increase, but at the same time unexpected positive reactions will correct misdiagnoses of constitutional or irritant dermatitis.

The selection of substances for a standard patch-test series must be based on local experience, but several substances are universally recognized allergens. Unless a permanent record is kept, a number of substances will continue to be included despite a low yield of positive reactions. In general, a substance should be included in the standard battery if it gives positive reactions in more than 1% of those tested, or if without it a significant number of unsuspected allergic reactions would be missed. This is true of ubiquitous allergens such as rubber chemicals, nickel and chromate, fragrance materials and common therapeutic and cosmetic allergens such as lanolin, neomycin and preservatives. However, less common allergens may be included if they are potentially easily overlooked and important. Such commonly unsuspected but infrequent standard allergens include primin and IPPD. The results of testing to a standard series of allergens vary from one part of a country to another, and from one country to another (Table 20.17) [7–9,12]. In most countries, additions to the international standards are required. In order to reduce the number of tests, defined groups of substances can be made up as ‘mixes’.

Additional series

There are many situations in which additional series of allergens are useful [1,13], for example in the investigation of dermatitis occurring in certain sites liable to medicament allergy (eyes, ears, perineum and venous ulcers/eczema) or sensitization from components of shoes or clothing. Some occupational groups, for example hairdressers, florists, dentists and metal machinists, are exposed at work to a variety of potential allergens not found in the standard series. Others may handle a specific group of allergenic chemicals, for example epoxy or acrylic resins. The main patch-test allergen producers now market extra series, although these may have to be further adapted to local habits or occupational exposures. Allergens provided by commercial allergen manufacturers tend to be of pharmaceutical grade, and may be negative when the actual sensitizer is an impurity in a commercial-grade product.

Other materials

Commercially produced patch-test allergens, either singly or in small numbers, may be applied where relevant. Patients may bring a wide variety of materials of their own from home or work for testing and, as mentioned previously, these must be thoroughly assessed and diluted appropriately before being tested.

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Concentrations and vehicles for patch testing

Recommended patch-test concentrations and vehicles for many different materials, including specific chemicals, chemical groups and substances, and finished products, have been collated in a number of standard contact dermatitis references as outlined below. Most (but not necessarily all) of these lists are reliable, in that the stated concentrations do not usually give an irritant effect. Before patch testing with any unfamiliar material, the appropriate vehicle and concentration should be sought from one or more of these databases.

1 General [1–5]
2 Selective:
  (a) Occupational [6,7]
  (b) Clothing and footwear [8]
  (c) Cosmetics [8,9]
  (d) Medicaments [8,9]
  (e) Woods [10]
  (f) Plants [11–13].

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Table 20.18 Photopatch-test protocols. (From British Photodermatology Group [1].)

	Day				
	0	1	2	3	4
Protocol 1	Phototest Apply allergens	Read phototest results Remove patches and irradiate allergens		Read results	
Protocol 2	Apply allergens		Remove patches, read results and irradiate allergens		Read results
Protocol 3	Apply allergens	Phototest	Read phototest results. Remove patches, read results and irradiate allergens		Read results

Photopatch testing [1]

Indications

The main clinical indication for photopatch tests is in the investigation of patients with eczematous eruptions predominantly affecting light-exposed sites, and from whom a history of worsening following sun exposure is obtained. Some patients have coexisting photosensitive disorders, causing practical problems in performing and interpreting the investigation.

Method

A British Photodermatology Group (BPG) workshop has achieved a consensus on the protocol for photopatch testing in the UK and Ireland [1], but the technique may vary slightly in other parts of the world. The BPG states that photopatch testing is an evolving technique with a need for further research.

A UVA source is required, which in most centres will be the UVA lamps used for PUVA therapy [1], commonly a hand/foot treatment unit. In photobiology centres, the more sophisticated irradiation monochromator may be used as an alternative. Other UVA sources include UVA blacklights, and filtered metal halide and xenon arc lamps [1]. In all cases irradiance should be measured with a calibrated UVA meter. The energy source must be monitored regularly, as the tubes deteriorate with time [2].

Historically, administered dosages of UVA to the photopatch-test site have generally ranged from 5 to 10 J/cm^2. However, the higher doses have the disadvantage of being more likely to induce false-positive phototoxic responses without increased detection of photoallergic subjects [3–5], and therefore a dose of 5 J/cm^2 is recommended. Modification of the dose may be necessary in UVA-photosensitive individuals, in which case 50% of the UVA minimal erythema dose is suggested. However, UVA phototesting to establish the minimal erythema dose is not always feasible or practicable, but is nevertheless advised before photopatch testing known photosensitive individuals.

Application of the allergens is performed in an identical fashion to conventional patch tests, except that they must be applied in duplicate—one set is irradiated and the other (the control) is not. Usually, the two sets of tests are applied on either side of the vertebral column at the same level. It is suggested that the patient's back is positioned 15 cm from the front panel of the lamps [1]. Steps must be taken to avoid any incidental irradiation by natural light of both the irradiated and the control set of allergens. The control site and the rest of the skin must be covered with opaque material during irradiation of the photopatch-test site. Three protocols have been used and these are described in Table 20.18. There is no evidence that any of these is superior to the others, although a recent study has failed to show an improved return with UVB irradiation or with a 7-day reading [6].

Test materials

A positive reaction on the irradiated side only is an indication of photoallergy. There are occasional difficulties distinguishing a false-positive phototoxic reaction from photoallergy but this is less likely with a dose of 5 J/cm^2. Readings are scored identically to conventional patch tests but the positive symbol is preceded by the prefix Ph, for example Ph++ is a strong positive photoallergic reaction. If the same allergen provokes an equally strong reaction on both sides, it is an indication of contact allergy alone; if it is significantly stronger on the irradiated side, then combined allergy and photocontact allergy may be occurring [7]. Doubtful and slight amplification of photoallergic reactions may be the result of phototoxicity.

The principle of a standard series also applies to photopatch tests. Having considered the available evidence, the BPG recommended just six compounds for a standard photopatch-test series, five UV filters and musk ambrette. The latter, although no longer incorporated into perfumed materials in the western world, was felt to be relevant to

Table 20.19 Photopatch-test standard series. (From British Photodermatology Group [1].)

Substance*	Concentration (%) in petrolatum
p-Aminobenzoic acid (PABA)	10.0
Octyl dimethyl PABA	10.0
Octyl methoxycinnamate	10.0
Benzophenone 3	10.0
Butyl methoxydibenzoylmethane	10.0
Musk ambrette†	5.0

* A more extensive series of UV filters and photosensitizers may now be appropriate for some centres.
† Musk ambrette is no longer thought to be a significant problem.

imported fragranced materials. This series is listed in Table 20.19. However, for some centres a more extensive series of UV filters and other photoallergens may be advisable according to the potential exposures in different populations [8].

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Complications of patch and photopatch tests (Table 20.20)

Generally, the risks of patch testing when it is performed correctly are minimal, but there are a number of potential complications outlined below.

Positive reactions may spread locally and cause a flare of contact dermatitis at the original site or more generally. The long strips of adhesive semi-occlusive tape, which preclude bathing for several days, may lead to eczema, itching or folliculitis, especially with high temperature and humidity. In warm weather there may be leakage of the test materials on to clothing and patients should be advised to wear an old shirt or blouse during the test. Irritants at excessive concentrations may induce caustic burns and scarring, and even a strong allergic reaction might leave a scar on extremely rare occasions. Secondary infection of a positive reaction is virtually never a problem.

Table 20.20 Potential complications of patch testing.

Pruritus
Folliculitis
Leakage of materials on to clothing, especially dyes
Localized flare of dermatitis
Flare of dermatitis at previous contact sites
Generalized flare of dermatitis
Irritant reactions from patients' own inappropriately diluted products
Active sensitization
Pigmentation or depigmentation
Scarring
Anaphylaxis (very rare)

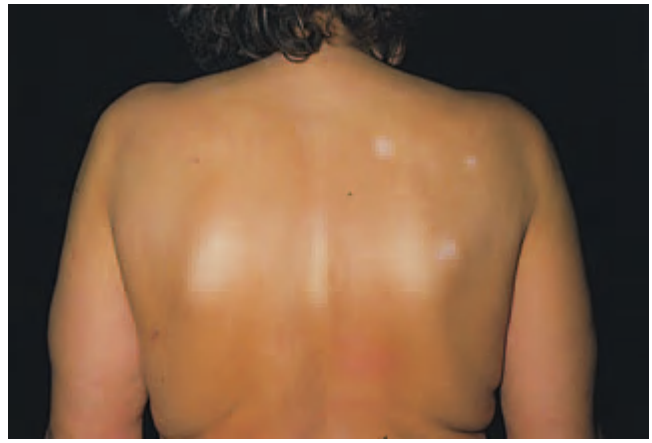

Fig. 20.31 Persistent hypopigmentation after patch tests.

Short-term post-inflammatory hypopigmentation does occur occasionally in positive patch tests, but more permanent hypopigmentation may develop from patch testing some quinones, phenols and dental acrylics, as well as by koebnerization of vitiligo (Fig. 20.31) [1–3]. Post-inflammatory hyperpigmentation may also develop, although this is usually temporary. Phototoxic substances may cause pigmentation if exposed to UV light, for example at photopatch tests or from natural sunlight [4].

Short-lived, non-immunological, urticarial reactions are common, particularly from cinnamates and sorbic acid. More importantly, anaphylactic reactions are a potential risk when patch testing with some materials, especially rubber latex [5] and penicillin [6]. A history of immediate hypersensitivity to rubber should be sought before patch testing with latex.

Active sensitization

Patch testing involves a small risk of sensitization. A reaction appearing 7 or more days after the application

may indicate either delayed expression of a pre-existing sensitivity or sensitization from the patch test. However, some late reactions, occurring up to 14 days after application of patch tests, are weak sensitivities from poorly penetrating allergens. Active sensitization usually presents as a strong positive patch test occurring at around 3 weeks [7]. Few clinics observe their patients long enough to note such reactions, but patients report them. The true incidence of sensitization is therefore difficult to establish, because even re-examination of a random sample of the patients tested [8] cannot differentiate between those sensitized by patch testing and those whose pre-existing subliminal sensitivity has been boosted by further exposure from patch testing. Patch-test sensitization from most routinely tested substances is very uncommon, and occurs more frequently when new substances are being investigated to ascertain the correct patch-test concentration [9]. Sensitization is also more common when testing with unrefined wood or plant extracts or with material provided by the patient.

Testing itself may cause a reawakening of sensitivity. However, the practical consequences of this are uncertain. Patients who can be resensitized by patch tests must also be easily resensitized by contact with the allergen under everyday conditions.

Such induced sensitivity tends to fade relatively quickly, and the patient's clinical course does not appear to be adversely affected. These rare adverse events are usually of no long-term consequence and must be balanced against the benefits of finding one or more relevant allergens.

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Multiple patch-test reactions [1–6]

The finding of multiple positive patch tests is common, and it is important to consider the reasons for this so that the correct advice can be given to the patient. The main explanations are:

1 non-specific hyperreactivity;
2 multiple primary hypersensitivities;
3 cross-reactions (true and false).

Non-specific hyperreactivity [7,8]

Ideally, patch tests should be applied at a concentration that always identifies the allergen and never induces false-positive reactions. Unfortunately, some allergens have to be applied at a concentration that is marginally irritant in some subjects in order that allergic positive reactions are not missed. The threshold at which a false-positive irritant reaction develops differs from individual to individual and may even be variable in the same subject [9]. During active dermatitis, uninvolved skin, even at distant body sites, exhibits increased susceptibility to irritant reactions [7]. This 'status eczematicus' [2,7] may lead to false-positive patch-test results. It has become a well-established tenet that 'eczema creates eczema' [8], and that a strongly positive patch-test reaction [10] or four positive patch tests [11] may induce other non-specific false-positive patch-test reactions. When this affects adjacent patch-test sites it is often referred to as 'spillover' [12], 'excited skin' [13] or 'angry back' [6,7,10,14]. Rietschel [15] has proposed that 'stochastic resonance' may be involved. This suggests that there is signal amplification of immune-mediated events by neurological influence. False-positive reactions occur more readily with marginally irritant chemicals, and the incidence has been variously assessed as 8.6% [16] to 63.5% [10,14,17–20]. In view of this, it has been proposed that repeat patch tests should be undertaken in all individuals with three or more strong positive allergic reactions, with exclusion of the strongest reactants. However, other studies [21,22] have not found evidence to support a concept of non-specific hypersensitivity.

The occurrence of weak false-positive patch-test reactions can be reduced by delaying patch testing until all active eczema has settled [16]. As skin hyperirritability may persist for some weeks or months, even when a dermatitis has resolved [14,23,24], this is often impractical.

Multiple primary hypersensitivities

Multiple primary specific (or concomitant) sensitivities to substances that are unrelated chemically are frequent among patients with contact dermatitis. Among 5000 Scandinavian patients, they occurred in 20% of all persons tested. The reason why some patients develop multiple sensitivities and others do not is not clear. Patients with a long history of dermatitis are those most likely to accumulate several primary sensitivities, because of the opportunities to encounter new allergens under conditions favourable for sensitization [25]. Patients with leg ulcers [12,26] are especially prone to developing multiple allergies, as are patients with chronic actinic dermatitis [27].

One sensitivity may predispose to the acquisition of another, and there may be a genetic or constitutional predisposition to acquire sensitivities [19,28]. In one study of patients with leg ulcers, although multiple sensitivities occurred more commonly than might be predicted from their individual prevalence, it was suggested that this reflected duration of exposure rather than the theory of systemic ampliative allergy [12].

Sensitization is facilitated if an allergen is applied on injured (e.g. eczematous) skin [29], and such local factors may be sufficient to explain the frequency of sensitivity to topical medicaments and simultaneous sensitivity to several constituents. In dermatitis from applied medicaments, concomitant sensitivity to both an antibiotic and a component of the vehicle is quite common.

Different materials may contain more than one allergenic substance, and exposure therefore occurs simultaneously. In rubber dermatitis, sensitivity to unrelated vulcanizing agents is not unusual. Cobalt and nickel are difficult to separate, and thus cobalt commonly contains traces of nickel, and nickel traces of cobalt. Sensitivity may be caused by either or both. Patients sensitive only to cobalt often have dermatitis from nickel-plated objects and give positive reactions to patch tests with nickel of commercial quality [30]. Combined cobalt and chromate allergy is common among cement workers. However, closeness in the periodic table is a hypothesis put forward to explain the finding of palladium sensitivity in a high proportion of individuals with a strong positive reaction to nickel [31].

In dermatitis of the feet, concomitant sensitivity to chromate, rubber and dyes in shoes or stockings presents a particularly difficult clinical problem; one allergen may be primarily responsible but others are important in maintaining the eczematous state. The inflammatory response to allergens has been shown to be additive [32], as has the response to an allergen and an irritant [33].

Cross-reactions [4]

Cross-sensitization is defined as the phenomenon where sensitization engendered by one compound, the primary allergen, extends to one or more other compounds, the secondary allergens, as a result of structural similarity. The proposal is that the primary and secondary allergens are so closely related that sensitized T cells are unable to distinguish between them, and therefore react as if the compounds were identical. However, as we now assume that T-cell sensitivity is specific then the basis of the conclusions in many of the older publications [3,34,35] may be in doubt [1,36]. Contaminants may cause 'false' cross-sensitivity, and one substance may contain traces of another. In studies of cross-sensitivity, absolutely pure test substances must be used. Few investigations in the past have fulfilled these requirements and most should be repeated using modern methods of separation. Enantiospecificity or stereospecificity may lead to cross-reactivity with some isomers and not others [36]. Examples include usnic acid, 4-methoxydalbergiones and frullanolides. A computerized resource has been used for the systematic evaluation of structure–activity relationships [37].

However, poor solubility and other physical factors may prevent demonstration of cross-sensitization between substances with structural formulae which, to a dermatologist, might suggest a chemical similarity. Patients sensitive to both isoeugenol and cinnamic acid never react to ferulic acid, which might seem to be a hybrid of the two. The side-chain of isoeugenol is lipophilic and the phenolic ring hydrophilic; the side-chain of cinnamic acid is hydrophilic and the benzene ring lipophilic. Ferulic acid, with hydrophilic groups both in the ring and the side-chain, cannot imitate either of them if, somewhere in the development of the reaction, a distribution on a lipid–water interface is involved [25]. Similar physical properties are assumed to determine the nature of the secondary allergens in *Toxicodendron* spp. sensitization [38,39].

In simultaneous sensitivity to natural products such as perfumes, balsams and wood tars, it is impossible to decide whether reactions to several of the substances may be due to related or identical chemicals. Cinnamic aldehydes, for example, may occur in them all. The same applies to plants such as Compositae and *Frullania*, and to patients sensitive to *Toxicodendron* spp.

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Other tests

Occlusive patch testing has stood the test of time. Although it is an artificial procedure, it has not been superseded. Nevertheless, alternatives continue to be sought and some of these may be useful adjunctive investigations.

Open tests

Patch testing is usually performed with the test site occluded, in order to increase percutaneous absorption. This is an artificial procedure, and clinical exposure might be more closely simulated by simple application of the sensitizer to uninvolved skin. However, few allergens provoke a dermatitis with a single exposure on normal skin. It is seen in *Primula* dermatitis, some patients having positive, even bullous, reactions to an open patch test to the leaf [1]. In most cases of clinical contact dermatitis, however, the allergen gradually accumulates in the epidermis, and irritants and mechanical injury promote its absorption. These conditions are not readily reproduced in a test procedure.

In highly sensitive individuals, allergens with good penetration can produce positive reactions in an open test, although the concentrations used for testing must be much higher than those used in a closed test. Thus, potassium dichromate 5% in water and nickel chloride 10–20% in alcohol [2] provoke a positive reaction in many chromate- or nickel-sensitive persons. Positive reactions often develop in a few hours [2].

The technique is simple [3]: the liquid test substance is dropped on an area of skin measuring about 1 cm in diameter and the solution is allowed to dry. The time for reading and the characteristics of the reaction are the same as for closed patch testing. The reaction can be followed from the start and may develop sooner than with a closed patch-test reaction [2]. It is often weaker, and a positive reaction, especially in the initial phase, may consist of isolated papules only.

One area where open testing has been widely used and advocated is prior to dyeing hair. Application of the dye to the retro-auricular area and examination of the site 2 days later has now been confirmed as an accurate method of detecting sensitized subjects [4]. However, hairdressers and individual users tend to do this only once and not each time the hair is tinted, and often they mistakenly undertake a 30-min reading. They may therefore miss the allergy if it develops subsequently.

With irritants, the reactions are also usually fewer and weaker in open than in closed patch testing because of reduced absorption [5]. Open tests are therefore sometimes used as a preliminary screening procedure with less well-known substances to reduce the risk of severe reactions. However, experience with open tests is limited and the risk of sensitization cannot always be estimated.

Usage tests

In cases of doubt, when either a closed patch test or open test is negative yet the history suggests a contact dermatitis, the patient can be asked to use the preparation again. This is especially helpful with cosmetic and clothing

dermatitis. Because it reproduces all the other factors associated with the original dermatitis, for example sweating, friction and application of allergen on damaged or presensitized skin, it is sometimes positive when conventional patch tests fail to reveal a sensitivity. However, it is not always possible to differentiate between an allergic and a non-specific or irritant response. With cosmetic preparations or medicaments, a repeat 'dab' test may be performed on previously affected skin.

Repeat open application tests [6]

In this test, substances are applied twice daily for 7 days and sometimes beyond, or until an eczematous reaction develops. The most appropriate site is the upper arm or flexor surface of the forearm, as patients can perform the test and observe any developing reaction. They should be told to discontinue the application if eczema occurs. An area of at least 5 cm^2 should be employed. The test may be used to determine the relevance of doubtful positive patch-test reactions to preparations in which the putative allergen is present in a low concentration, although false-negative results may occur [7]. It may also establish the clinical relevance of such products and confirm the source of the allergy [8–11]. A scale for recording ROAT reactions has been proposed and advocated [12].

Intradermal tests

Intracutaneous tests, as used in tuberculin sensitivity, have also been performed with simple chemicals, although mainly for investigative purposes. Within 1 day erythema and swelling appear at the site of injection. Later, usually after 2–4 days, papules or vesicles may develop. Sometimes, a flare may be seen shortly after the injection, and this lasts a few hours [13]. Over the next few days, erythema and infiltration are sometimes seen along the lymphatics leading from the test site.

Technical pitfalls with intracutaneous testing are numerous, as is known from extensive studies with tuberculin [14]. Too deep an injection will result in negative reactions. An immediate reaction, which is not a rarity with metal salts, may result in dilution and removal of the test substance. The concentrations employed should be at least 10–100 times lower than those used for epicutaneous testing [15,16]. In cases of extreme sensitivity, the concentration may need to be 1000–10 000 times lower.

The technique has proved reliable for nickel [2] and may identify corticosteroid allergy in patients with false-negative patch tests [17,18].

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In vitro tests [1]

The principle of diagnosing contact allergy by *in vitro* testing is attractive, although the use of peripheral blood as a routine investigation for contact dermatitis may not be viable, not only from the budgetary point of view but also for logistical and practical reasons [2]. Nevertheless, attempts continue to be made to achieve this, albeit with single or small numbers of allergens. A number of different techniques have been tried and these are described below.

As yet, none of these tests is a substitute for the *in vivo* system of the challenge patch test. However, they may be helpful in elucidation of the immune cascade as they are based on measurements of products from T-cell activation. What is needed is a system to detect the presence of specific memory helper T-cell subsets within the skin or circulation.

Migration inhibition test

Migration inhibition factor is a soluble factor released by sensitized lymphocytes following stimulation. It inhibits the migration of monocytes and macrophages but not

polymorphonuclear leukocytes [3]. A direct and indirect assay is performed and the results expressed as a migration index. The test has been employed in nickel and chromate allergy, but is not completely reliable as there is overlap between sensitized and non-sensitized patients. Interference may be caused by a cytotoxic action of the allergens, and concentrations have to be optimum at just below non-toxic levels. The investigation was not reliable as an investigation for medicament contact allergy [4] but a capillary tube assay has been demonstrated to be of practical clinical value for diagnosing chromium allergy [5]. The method needs further investigation and refinement [6,7].

Lymphocyte transformation tests

Antigens are able to induce specific transformation of lymphocytes to large lymphoblasts, culminating in mitosis [8]. Most work has been carried out on nickel allergy [9,10], although there are conflicting accounts of the optimum stimulatory concentration of nickel and the method of preparation of cells following culture for radioactive thymidine uptake assays. Nickel may induce non-specific transformation in non-allergic subjects [11], but several groups of investigators have reported a significant difference between lymphocyte transformation in nickel-sensitive patients and controls [9,10,12,13]. Other standard-series allergens investigated, with potentially promising results, include chromate, PPD, neomycin sulphate and thiuram [14,15]. On the other hand, tests with a range of medicament allergens failed to reach statistical significance [4]. This investigation may be useful for investigating cross-reactivity patterns [16], although considerably more work is required before it can be regarded as a routine diagnostic test.

Leukocyte procoagulant activity

When stimulated by an antigen, leukocytes produce a significant level of procoagulant that activates the extrinsic cascade of blood clotting. The production of fibrin may explain the inhibition of macrophage migration. The activity is measured as a ratio of the clotting time of plasma incubated with cells, with and without antigen. It has been used in nickel-sensitive patients [17], when the procoagulant activity increased as the stimulatory nickel concentration increased. Interferon-γ (immune interferon; previously called macrophage activity factor) has modulatory effects on immune function, which are important in the transfer of antigenic information to T lymphocytes. It also has antiviral potential. It is employed in an assay to measure activity after incubating lymphocyte suspensions from hypersensitive patients, or controls, with the antigen. Conflicting results have been reported.

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Spot tests [1]

Two spot tests are of particular practical value in the patch-test clinic as the materials are easy to handle and store.

Dimethylglyoxime test for nickel [1–3]

Dimethylglyoxime 1% (alcoholic solution) and ammonium hydroxide (aqueous solution) are stored in separate bottles. A few drops of each are put in separate clean white saucers, a cotton bud is then dipped in each of these and rubbed on the surface of the test object. A pink coloration on the cotton bud denotes the presence of nickel (Fig. 20.32). This test is accurate to 10 ppm of nickel, but the immune system may be able to detect lower levels

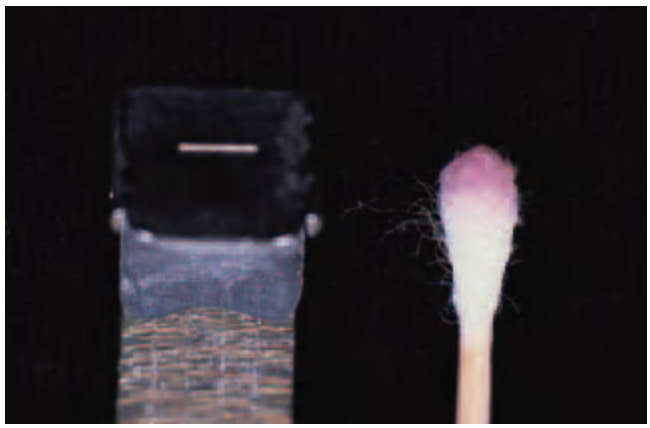

Fig. 20.32 Dimethylglyoxime test: a pink colour is detected when metals release a significant amount of nickel. (Courtesy of Dr J.D. Wilkinson, Amersham General Hospital, Amersham, UK.)

than this. It is a very useful test, and patients can be given kits to test items in the home and at work.

Acetylacetone method for formaldehyde [4]

The reagent is prepared by dissolving 15 g of ammonium acetate, 0.2 mL of acetylacetone and 0.3 mL of glacial acetic acid in 100 mL of distilled water. It can then be stored in a refrigerator. A sample (1 mL or 1 mg) of the product to be tested is put in a disposable glass test tube and 2.5 mL of the reagent is added. The mixture is shaken and stoppered and then placed in a water bath at 60°C for 10 min. A yellow colour is produced in the presence of formaldehyde, due to the formation of 3,5-diacetyl-1,4-dihydrolutidine. The alternative chromotropic acid method is less specific.

Other analyses

There are other spot tests for chromate [1] and epoxy resin [5] but these are not simple to perform during a clinic. More sophisticated tests such as chromatography, spectrophotometry, mass spectrometry and nuclear magnetic resonance spectroscopy require specialized equipment and expertise.

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Prevention [1]

Many statutory bodies have a role in the prevention of contact dermatitis, including medical personnel, legislative bodies, central and local government, corporate industry, the media, surveillance and consumer bodies, and patient support groups. Principles of prevention can be related to two categories, individual and collective, and further divided into primary, secondary and tertiary. Primary prevention focuses on the induction of contact sensitization and control of exposure. Secondary prevention relates to elicitation, and tertiary to measures for established and continuing dermatitis. Some of the more important elements of prevention are discussed below; the reader is referred to Lachapelle's overview for more detailed coverage [1].

Allergen containment and replacement [2]

Potent allergens encountered in industry can be kept in closed systems, thereby avoiding the potential for direct skin contact [3]. In other instances products can be kept in special containers, which allow a no-touch technique when using the contents [4,5]. Replacement and elimination of potential allergenic hazards can be helpful in both the domestic and working environments, for example perfume-free cosmetics and medicaments, non-latex gloves, high-molecular-weight epoxy resins [6], and white spirit instead of turpentine.

Legal and other regulatory measures [7]

Regulatory measures can influence the incidence of dermatitis [8,9]. They may be legally or voluntarily enforced. The EU has passed a number of directives relating to contact dermatitis, particularly in relation to nickel and cosmetics.

As most consumers are primarily sensitized to nickel either following ear piercing [10] or by prolonged close contact with nickel-releasing alloys, it was proposed that such items should not release more than 0.5 μg/cm^2/week of nickel [11,12]. Ten per cent of the female population of Europe and the USA are sensitive to nickel [13], and this has significant implications with regard to hand eczema [14–16] and employment [17]; hence, nickel sensitivity is an issue where legal restraints could prove effective in improving the health of the population. Following the lead of Denmark and Sweden, the Nickel Directive was introduced with the aim of primary and secondary prevention of the presently high levels of nickel allergy in the EU [7]. The recommendations are summarized in Table 20.3. A Danish follow-up study comparing 1985–86 with 1997–98 patterns of nickel sensitization has already shown a decrease in allergy from 24.8% to 9.2% in the

tested populations aged 0–18 [9]. A debate continues over the wisdom of allowing certain recently introduced Euro coins to contain nickel [18–20].

The Cosmetics Directive lists materials allowed, not allowed and restricted. For instance, the preservative MCI/MI is not permitted above 15 ppm [7]. Enforced ingredient labelling on the packaging of cosmetics, which is also a requirement in the USA, has been a major factor in enabling avoidance of cosmetic allergens by sensitized customers [21]. Concern continues over the lack of labelling of components of fragrances, which are identified by the term 'parfum'. Natural ingredients, including plant extracts, must be denoted by their Linnaean name, which may confuse some individuals who are allergic to plant-derived components of cosmetics, including some perfumes.

The Directives on Dangerous Substances and Dangerous Preparations list 360 skin sensitizers and their concentration limits (e.g. formaldehyde 0.2%, acrylates 0.5–2%). A chemical product containing a classified skin sensitizer above 1% concentration must be labelled with the risk phrase 'R43—may cause sensitization by skin contact' [7]. For many substances 1% is above the level of sensitization and elicitation of contact dermatitis. The usefulness of labelling in this unselective quantitative way has been questioned [22].

Dermatitis accounts for a significant proportion of occupational disease [23]. Allergy to chromate in cement is a significant problem in the construction industry [24]. For over 10 years some Scandinavian countries have restricted hexavalent chromium in cement to below 2 ppm [7], which is achieved by adding ferrous sulphate. There is already evidence in these countries of a reduced prevalence of chromate allergy and hand dermatitis [8], which can be a cause of significant persistent disability [24].

Some legislation may apply only to one or a few countries. For instance, the use of PPD in hair dyes is forbidden in some countries and controlled in many others, bithionol in toiletries is forbidden in the USA, and dibromosalicylanilide in Germany. Formaldehyde in clothing is limited in Finland [7]. Prohibition of persulphate improvers in flour in Denmark (1938) and Germany (1956) led to a striking decline in bakers' dermatitis in both countries [25]. In Germany, the use of turpentine for paint is strictly limited [26,27].

In the UK, the assessment and monitoring of hazards and risks at work has improved following the introduction of Control of Substances Hazardous to Health (COSHH) legislation, but attention to dermatitis checks and risks is still suboptimal [28]. In addition, the HSE have a statutory right to investigate skin problems at work through the employment and medical advisory service (EMAS), provided they are reported [29].

Corporate responsibility

Although legal measures can influence the incidence of dermatitis, few have been introduced. In many instances governments will not intervene with legislation, relying on self-regulation, and this includes the cosmetic and pharmaceutical industries. The withdrawal of musk ambrette is an example of cosmetic industry self-regulation.

Manufacturers of all goods should ensure that their products are safe to use. Dermatologists and consumers have a role in reporting adverse events to the manufacturers, who should respond to any concerns. Surveillance systems, particularly of occupational dermatitis [30–32], and rapid computerized analysis of epidemiological information, with feedback to interested parties, can provide early warning of new allergens and sources of work-related dermatoses [33–35].

Risk assessments should be undertaken before a new product is placed on the market, including its potential for allergenicity. A product must be clearly labelled to ensure that it is handled safely.

Work

The preventative aspects of occupational contact dermatitis are discussed in detail in Chapter 21.

Domestic

The availability of modern domestic equipment should significantly reduce skin contact with irritants and potential sensitizers in the home; however, housewives are still one of the greatest 'at-risk' groups as far as the development of hand dermatitis is concerned. Cotton-lined gloves should be worn when the hands are in contact with irritants, including food, cleaning agents and polishes. Plastic gloves are less allergenic than rubber but are less pliable and malleable.

Education

Education of the community and workforces through the media, courses, lectures and wall charts in public places (including medical waiting areas) and at work will help to promote awareness of the problem of contact dermatitis. Patient support groups have played an increasing role in education of the public as well as those suffering from dermatitis.

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Management [1,2]

Avoidance advice

A diagnosis of allergic contact dermatitis is reached on the basis of a detailed history and examination followed by patch tests, with an assessment of the relevance of any positive reactions. Once a diagnosis has been made, possible sources of exposure to the causative allergen(s) should be identified, and avoidance advice given. The first principle of management is to give advice on avoidance tailored to an individual. Examples of specific avoidance measures include plastic instead of rubber gloves, cosmetics and medicaments free of an identified allergen, and clothing free of nickel-containing studs, zips, etc. More general written information on the allergen sources may be helpful, but may also be confusing if many are not relevant to that person. In some instances, particularly of work-related problems, appropriate protective clothing or changes in handling technique may be advised. Materials used for protection, especially gloves, should not allow penetration of the allergen responsible for the dermatitis.

Ideally, the result of this advice will be resolution of dermatitis, but this does not always occur, and other factors, such as the possible contribution of irritant or constitutional eczemas to persistence of the problem, should be considered and discussed with the patient. Reassessment and reinforcement of avoidance measures is often required, sometimes repeatedly, in order that patients are fully aware of what action they should take. In some patients continued exposure is unavoidable but can be reduced to a sufficient degree to keep the dermatitis at an acceptable level. It is advisable to stress that allergy does not disappear when the dermatitis clears but that the risk of relapse after further contact with the allergen persists throughout life.

Active treatment

The mainstay of treatment of allergic contact dermatitis is avoidance of the causative factor(s), although topical corticosteroids will be required in most instances to control the disorder. The manner in which they are used will vary, and optimum regimens have yet to be established [3]. In acute, severe, localized allergic contact dermatitis a potent topical corticosteroid should be used. In more chronic or widespread contact allergies the potency may need to be reduced, and for long-term use in certain sites

(face, genitals and flexures) mild topical corticosteroids are indicated. On the palms and soles, the longer-term intermittent use of a potent corticosteroid preparation is usually beneficial and well tolerated [4].

General principles of eczema treatment should be followed, with regular and liberal use of hydrating emollients [5,6] and soap substitutes. Fissures of the fingers, palms and soles can be covered with hypoallergenic tape. Alternatively, zinc and salicylic acid paste BPC twice daily may be helpful, and cyanoacrylates (superglues) have been used with benefit by some dermatologists [2].

For acute weeping forms of allergic contact dermatitis, wet dressings with saline, aluminium acetate or silver nitrate (0.5%; stains black) may be of benefit. Potassium permanganate 1 in 8000 in warm water is helpful when used four times a day as a soak for vesiculobullous eruptions of the palms and soles. Brown staining of the skin and nails is a problem, and the treatment should be stopped when the affected areas become dry.

New topical ascomycin derivatives [7,8], which act as immunomodulating agents, are now being introduced for the treatment of atopic eczema, and there is also evidence of their benefit in allergic contact dermatitis in animal studies [7–9]. Topical tacrolimus was introduced in the UK in 2002 and is expected to be followed by pimecrolimus. These agents are considerably more expensive than topical corticosteroids.

Secondary infection will require antibiotics, and a sedative antihistamine is indicated for pruritus, particularly at night. In severe or widespread eruptions, systemic steroids may be necessary [10].

Recalcitrant disabling cases may require consideration of immunosuppressive therapy such as azathioprine [11–13] and ciclosporin. Assessment of thiopurine methyltransferase levels should be performed before undertaking treatment with azathioprine [14]. The investigation will identify a subset of patients potentially at high risk of myelotoxicity from this treatment. There is evidence in animals that ciclosporin [15] suppresses allergic contact dermatitis, but most reported clinical studies have been undertaken on chronic hand eczemas of mixed aetiology [16–18].

It has been reported that certain patterns, especially vesicular palmar eczema, have benefited from dietary avoidance or reduction in intake of allergen, most notably nickel and balsams, in sensitized subjects [19–23]. The effects of a low-nickel diet have been disappointing in our hands; nevertheless, there are strong advocates of these measures. Dietary chelation of nickel has also been attempted [24,25], but is not widely used in practice because of side effects [24].

Dietary manoeuvres have also been reported to be helpful for cheilitis and oral symptoms, particularly in those with positive patch tests to balsam of Peru, cinnamates, eugenol, colophony, flavours and antioxidants [26–30], although the relationship between 'burning mouth' and contact allergy is questionable [31,32].

Superficial X-rays and Grenz rays, which have been shown to suppress experimental contact dermatitis [33], can be safely used for localized dermatitis, although facilities for this treatment are gradually dwindling in the UK [34–36]. Phototherapy, both PUVA and UVB, is helpful in some subjects [37–39], including Compositae-allergic individuals with photosensitivity [40].

The use of barrier creams as preventatives in already sensitized persons is generally unsatisfactory. However, there is documented evidence of the value of products containing quaternium-18 bentonite in the prevention of *Toxicodendron* spp. dermatitis [2,41]. Other barrier creams containing active agents (e.g. chelating agents) against specific allergens may have future potential [42–44]. In one study clioquinol was the most effective agent at preventing nickel dermatitis [43].

Hyposensitization [45]

Many attempts have been made to down-regulate the immune response to allergens in an already sensitized individual. This has proved difficult to realize in practice. The degree of hyposensitization achieved by oral doses of allergens is limited and transient, for example DNCB and chromate in guinea pigs [46,47], and poison ivy in humans [48]. Although it has been attempted for *Toxicodendron* spp. allergy [49–51], oral hyposensitization is not routinely recommended [2,52]. Some success has nevertheless been claimed in India for hyposensitization against *Parthenium hysterophorus* [53].

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Prognosis

The prognosis of allergic contact dermatitis depends on its cause and the feasibility of avoiding repeated or continued exposure to the causative allergen. Associated irritant dermatitis and constitutional factors are also important. Most studies suggest age of onset is not important prognostically for occupational dermatitis [1–3], although a recent UK study showed that older atopic individuals are less likely to improve, and those with allergic contact dermatitis are more likely to have time off work [4].

The prognosis is relatively poor for those allergic to nickel [5] and chromate [1,6,7], probably as a result of their ubiquity in the environment, even though most chromate studies have involved those with occupational dermatitis, which is a selective group. It has been suggested that dietary nickel [8] and chromate [9] exposure might be responsible for the chronicity, but this is disputed [10]. There is a better outlook for those allergic to materials that are easy to identify and avoid, and often the dermatitis will resolve within a few weeks if conscientious avoidance measures are taken. This was exemplified by a European joint study where the sources of contact with allergens could be traced in only 35% of those who reacted to colophony but in 85% of those sensitive to tetramethylthiuram disulphide. The reason for the limited success with colophony was probably lack of knowledge of the sources of this sensitizer [11]. It is also clear from a number of studies that poor compliance and understanding results in a higher rate of ongoing exposure to the

causative allergen, and is associated with a worse prognosis [12–14].

As the skin integrity is compromised, there are enhanced opportunities for new sensitivities to medicaments or other substances to develop during the course of dermatitis. Sensitivity to rubber gloves may complicate pre-existing dermatitis of the hands. Such allergies are revealed only by repeat patch tests. During a long course of relapsing dermatitis, sensitivity to various allergens may accumulate, and this increases the risk of recurrence or persistence [15].

Contact dermatitis of the hands is often of mixed origin, with alternating or simultaneous exposure to allergens and irritants. In a study of the prevalence of dermatitis of the hands, half the patients had suffered from their dermatitis for more than 5 years. When 408 of them were followed up after 6–22 months, one-quarter had healed completely, half had improved and one-quarter were unchanged or worse. There was no difference in prognosis between irritant and allergic dermatitis [16]. A change of occupation does not necessarily alter the prognosis of occupational hand dermatitis [6,10,17–21].

Once acquired, contact sensitivity tends to persist [22]. The degree of sensitivity may decline unless boosted by repeated exposure, but with a high initial level of sensitivity it often remains demonstrable even several years later [23]. Sensitivity to ubiquitous allergens, such as nickel and chromate [24], and to strong allergens, such as primin and PPD [25], is reported to persist, whereas sensitivity to other weaker and avoidable allergens may disappear. Patterns of cross-sensitization tend to persist [26]. New sensitivities to additional allergens may be acquired subsequently.

Relapse or chronicity is due not only to unavoidable or unrecognized re-exposure to allergens and irritants but also to other contributory mechanisms [27,28].

1 The barrier function of the skin is impaired for months after an attack of dermatitis. Recovery is prevented by exposure to allergens or irritants in concentrations that might well be tolerated by normal skin.

2 Inappropriate treatment, including the overzealous use of cleansers and antiseptics, and the use of sensitizing popular or herbal remedies may also prolong the course of dermatitis.

3 Ingestion of allergens.

4 Secondary infection, especially with dermatitis of the hands. Microbial allergy may also be a factor in some eczemas [11].

5 Contact sensitivity has been thought in some cases to involve sensitization to the protein moiety ('protigen') of the hapten–protein conjugate. On this assumption, autosensitization might account for chronicity.

6 Stress is common in chronic dermatitis and may be both a consequence of and a trigger for eczema.

7 Constitutional factors predispose to chronicity.

8 There appears to be an 'inherent tendency' in almost any eczema to become continuous and chronic, but the factors causing this are unknown [28].

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Immune contact urticaria

Contact urticaria may be non-immune or immune due to IgE antibodies against protein peptides. Immune contact

urticaria is commoner in, but not exclusive to, atopic individuals [1,2].

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Pathogenesis

The pathogenesis of urticaria is discussed in more detail in Chapter 47. In a previously sensitized individual, the protein allergens react with IgE molecules on mast-cell membranes, releasing vasoactive substances, including histamine.

It has been reported that patients with atopic dermatitis and raised IgE levels have IgE on the surface of Langerhans' cells. This does not occur in atopic individuals with normal IgE levels or non-atopic controls [1,2]. This may explain why patients with atopic dermatitis have delayed hypersensitivity on patch testing to aeroallergens and develop a vesicular response to handling food proteins (protein contact dermatitis).

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Clinical features

The symptoms usually occur within 1 h and fade by 3 h. The spectrum of associated symptoms is wide. Local symptoms are itching and burning, with the development of erythema and the characteristic weal and flare reaction. Early symptoms are commonly missed by physicians although well recognized by patients.

Exposure to allergens in those who are highly sensitized, topically or via the oral or respiratory route, may result in widespread urticaria [1] and swelling of mucous membranes, resulting in conjunctivitis, rhinitis, oropharyngeal swelling, bronchoconstriction and anaphylaxis.

Contact urticaria to foodstuffs

The commonest causes of contact urticaria are foodstuffs, which can provoke orolaryngeal symptoms from ingestion or hand symptoms in food handlers [2], such as fish processors [3] and slaughterhouse workers [2]. The diverse range of compounds includes fruit and vegetables [4], potato [5], eggs [6], fish [7], some medicaments [8,9], teak [10], *Myroxylon pereirae* [11], silk [12], animal saliva [13] and dander [14], and human sweat and semen [15]. In Scandinavia there is a strong association between the incidence of birch-pollen allergy and contact urticaria to fruit and vegetables, which is due to the presence of similar peptides [16]. Birch pollen is a common aeroallergen in Scandinavia, whereas in the UK the commonest aeroallergens are house-dust mite antigen and grass pollen, which may explain why there are fewer reports of contact urticaria in food handlers in the UK. If contact urticaria is confirmed there are recognized cross-reactions between various foodstuffs [17] (Table 20.21).

Contact urticaria to natural rubber latex [18]

Allergy to natural rubber latex was first recognized in 1979 by Nutter [19]. It has become a major health-care issue. The allergens are present in the water-soluble protein moiety of the sap collected from the rubber-bearing tree *Hevea braziliensis*, harvested mainly in Malaya and South-East Asia. The problem has been associated primarily with dipped rubber items [20–23], i.e. those made by dipping a mould or former into a latex solution, such as gloves, condoms, balloons, dummies and teats, catheters and medical tubing. These items are vulcanized at a lower temperature than solid rubber products such as tyres, seals and gaskets.

Since the advent of acquired immune deficiency syndrome (AIDS) and the huge increase in the use of latex examination gloves among health-care personnel, the production of inexpensive disposable natural rubber latex gloves has escalated. During the production process, the natural rubber latex is not left to stand in holding tanks as long, the process has been shortened by lower vulcanization temperatures and there is less thorough washing of the final product [24]. All these measures have led to an increase in the protein content of the gloves and this, coupled with their increasing use, has resulted

Table 20.21 Cross-reactions between foods causing contact urticaria. (From Sicherer [17].)

Food type	Risk (%)	Cross-reaction
Fish, e.g. salmon	5	Other fish, e.g. swordfish, sole
Grain, e.g. wheat	20	Other grains, e.g. barley, rye
Peach	55	Other Rosaceae fruit, e.g. apple, pear, cherry, plum
Melon (cantaloupe)	92	Watermelon, banana, avocado
Fruit (kiwi, avocado, banana)	11	Latex

in an increase in the incidence of allergy to natural rubber latex.

Natural rubber latex allergens are adsorbed on the maize starch powder on latex rubber gloves, and are released into the air when packets are opened or gloves are pulled out of multipack boxes. The allergens contaminate the air, and in operating theatres with recirculated air systems they can be spread to the whole theatre suite and cause unsuspected problems [25]. The use of powder-free gloves prevents contamination of the environment and the development of symptoms in already sensitized individuals [26].

Anaphylaxis can occur in any sensitized patients, and seems to be particularly prevalent when challenge is via mucosal surfaces, as in dental and vaginal examinations, intraperitoneal operations [27], catheter changing (especially in spina bifida patients who have frequent surgery and catheter changes [28]) and barium enemas [29].

The allergenic proteins are multiple. Many of the allergenic peptides in natural rubber latex cross-react with those found in other plants, such as banana [30], lychees [31], chestnuts [32] and avocado, and patients allergic to latex may exhibit sensitivity to such foods [33]. It is possible that some patients were first sensitized by the fruits and have a secondary allergy to latex.

Protein contact dermatitis [34,35]

Patients who have repeated exposure of the hands, especially the fingertips, to contact urticants, such as food proteins, may develop a vesicular eruption or protein contact dermatitis. Characteristically, the condition involves skin sites that have been affected previously by dermatitis. Damaged skin probably facilitates penetration of the allergens, and inflammatory cells already present in the dermis may explain the accelerated clinical response [36]. Many patients have no other signs of atopy. Protein dermatitis is common in dairy workers and veterinarians [37,38], slaughterhouse workers [39], chefs and sandwich makers [40], who become sensitized to the proteins they touch during work. A similar situation has also been reported with latex, both with and without contact urticaria [41,42].

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Investigations

Testing is usually performed by a scratch patch test (or a prick test) to the food in question. A small piece of the substance is applied on a closed patch test to an area of skin. The skin may be lightly scarified with a needle or degreased with 96% alcohol [1]. After 20 min the area is examined for erythema or weal and flare. Sometimes, the patient will state that the symptoms are being reproduced well before the end of the test time. Occasionally, there is no reaction on normal skin and the substance has to be applied to previously affected skin, for example the fingertips. Skin testing should be performed with appropriate positive and negative controls. With an unknown allergen, exposure should be graded with initially an application test (open and subsequently occluded) followed by a prick test and, if appropriate, an intradermal test. Although commercial allergen extracts are available, it should be remembered that unless standardized they may not contain the relevant protein allergens, and the gold standard should always be test and challenge with a sample of fresh material. Skin tests should only be performed where resuscitation facilities are available.

If the patient has experienced an anaphylactic reaction and a specific IgE test is available, the blood test may confirm the diagnosis and thus avoid the risk of anaphylaxis as a result of skin tests.

In the case of latex, the specific IgE test is not sensitive and a negative test does not exclude the diagnosis. Although skin tests with glove extracts have been recommended, many gloves now contain low levels of latex protein and prick testing with home-made extracts frequently gives false-negative results. Prick test solutions for latex are commercially available, some of which claim greater than 98% sensitivity and 100% specificity. The final arbiter is a usage test in which a patient wears the suspect glove on a moistened hand and any reaction is observed.

Localized symptomatic dermographism is a common cause of urticaria to gloves in the absence of latex allergy [2]; contact urticaria to rubber chemicals is extremely rare [3].

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Management

Management is by means of avoidance or the use of appropriate personal protective equipment, as desensitization for the majority of allergens concerned is not available. Avoidance measures are required for latex articles, especially rubber gloves, condoms, balloons, pacifiers, catheters and other medical tubing. Treatment of the acute episode includes the use of systemic antihistamines and epinephrine (adrenaline), depending on the severity of the attack.

In the case of latex, the use of a 'medic-alert' type bracelet will warn health-care workers should a patient be taken to casualty unconscious. The management of the latex-sensitized individual in the hospital environment can be a particular problem due to the widespread use of natural rubber latex products. Most hospitals are now aware of the problem and maintain a latex-free environment to treat such individuals. Examinations and interventional surgical and radiographic procedures should not be undertaken with latex gloves or equipment.

A change to low-protein gloves has been associated with a reduction in the prevalence of latex contact urticaria among health-care workers [1].

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Chapter 21

Occupational Dermatoses

J.S.C. English

Eczematous dermatoses

The occupational aspects of dermatology have attracted increasing attention [1–13]. This has been reflected in the establishment in some countries of special departments of occupational dermatology [3,6]. Full-time and part-time appointments in occupational dermatology now exist in many countries [3]. Occupational dermatoses are common enough and sufficiently disabling to demand a wide knowledge from dermatologists of the noxious agents in various occupations, as well as an understanding of the workings of compensation systems.

Epidemiology

In many countries, loss of income due to occupational illness is compensated more fully than economic hardship from other diseases. Because of the public expenditure involved, governmental and legal definitions of an occupational dermatosis do not always agree with medical concepts.

A medical definition adopted by the Committee on Occupational Dermatoses of the American Medical Association (1939) was: 'An occupational dermatosis is a pathological condition of the skin for which occupational exposure can be shown to be a major causal or contributory factor.' This definition, although comprehensive, does not address the question of attributability to occupation rigorously enough for all purposes. Many dermatologists prefer to limit their concept of occupational dermatoses to 'a skin disease which would not have occurred if the patient had not been doing the work of that occupation' [4].

In practice, lack of knowledge and of diagnostic tests often makes the diagnosis of occupational dermatoses very difficult [4]. Evidence in favour of an occupational origin is [14–17]:

1 Occupational contact with an agent known to have caused similar skin changes in other individuals.
2 Occurrence of similar dermatoses in fellow workers or within the same occupation.
3 Correct time relationship between exposure and dermatitis.
4 Type and site of lesions consistent with information of exposure, and similar to other cases.
5 Attacks of dermatitis appearing after exposure, followed by improvement or clearing after exposure ceases.
6 History and examination corroborated by patch (or sometimes skin prick) test results.

The legal definitions of occupational dermatosis vary considerably from one country to another [18]. In the UK, the majority of occupational dermatoses are defined by Prescribed Disease D5 of the Department of Social Security as 'non-infective dermatitis of external origin (including chrome ulceration of the skin but excluding dermatitis due to ionizing particles or electromagnetic radiations other than radiant heat)'. The disadvantage of this type of definition is that it may exclude certain newly recognized occupational dermatoses, so that these require their own additional definitions. This was necessary in the UK in the case of occupationally acquired hypomelanosis (Prescribed Disease C25) (Chapter 39).

In the assessment of individual cases, the legal attitude revolves around whether the patient could reasonably have been expected to contract the disease if he or she had not been engaged in that particular occupation and type of work [19,20]. In the UK, the compensation that may be obtainable through a legal action is of a higher order of magnitude than that provided by the state system. Patients therefore will frequently seek both forms of compensation. In other European countries, the equivalent regulations vary [18]. Most include infections such as ringworm. Some traditionally reserve compensation for conditions and causative agents specifically listed. This practice is gradually being abandoned because in a period of rapid industrial progress, any list of substances proves too restrictive. In some countries, only some employees are covered by the compensation laws, and self-employed persons are excluded. In spite of its frequency and chronicity, housewives' dermatitis receives no legal compensation.

Outside the workplace, the worker is exposed to the same risk of contact dermatitis as anyone else in the community. Contact dermatitis is therefore not necessarily of occupational origin. Dermatologists demur at the popular terminological identification of 'dermatitis' with 'occupational dermatitis'. A dermatitis that primarily originates from occupational exposure is influenced by many other factors. A number of problems cause legal dispute:

1 Constitutional factors [21]. Most manufacturing processes cause dermatitis in certain workers only. If others similarly exposed remain healthy, those whose skin breaks down must have a lower resistance. Such a lowered resistance to contact irritants may be present in patients with previous atopic dermatitis [22] or in those with dry, seborrhoeic or fair skin [21]. Accordingly, any occupational contact dermatitis presupposes a certain constitutional predisposition and usually only occurs in a minority of the workforce. This has to be taken into account in deciding whether, in an attack of dermatitis, an occupational trauma is sufficient to be considered as a major causal factor or only as a contributory factor. A young person with previous atopic dermatitis may do office work with impunity, but if apprenticed as a hairdresser is likely to develop dermatitis. Similarly, a young atopic person runs a great risk of dermatitis if working in a coal mine [23]. It may be beyond dispute that dermatitis would not have developed in occupations suitable for the particular person, but medical and legal opinions are still divided over the justification of compensation to young people with constitutional eczema and occupational dermatitis. Similar constitutional factors may be implicated in the middle-aged group, but as they cannot yet be identified they do not disqualify.

2 Sensitization to medicaments prescribed or self-prescribed for occupational dermatitis inevitably occurs in some cases. This complication must be regarded as a sequel of disease, just as is secondary infection. Problems arise from late relapses due to repeated contact with the same medicaments.

3 Sensitization in private life, with relapse of dermatitis from occupational exposure (e.g. dermatitis of the hands from contact with nickel in patients sensitized by nickel in jewellery [17]; formaldehyde dermatitis in patients sensitized by textiles).

4 Primary occupational dermatitis, with chronicity maintained by private activity [24]. For example, to relieve the strain of inactivity, some workers resort to do-it-yourself work during sick leave (perhaps involving exposure to cement, paint, solvents, etc.), and housework is unavoidable.

5 The contributions of factors broadly grouped under the term 'stress' cannot be dismissed, but are usually difficult to assess [25]. It is accepted by many dermatologists that episodes of stress may be an aggravating factor in both irritant and allergic contact dermatitis and may even contribute to their initial onset.

Table 21.1 Occupations with the highest risk (rate/100 000 employed/year)–using labour force survey data as the denominator and cases of contact dermatitis reported to the UK EPIDERM survey as the numerator.

Occupation	Rate/100 000/year
Hairdressers	120
Printers	71
Machine tool operators	56
Chemical, gas and petroleum plant operatives	45
Car assemblers	35
Machine tool setters	34

Incidence

Most available incidence statistics are unsuitable for comparison. Some do not distinguish between occupational accidents and illnesses; others fail to separate dermatitis from other skin conditions. Few give information on short periods of absence from work or on dermatitis without disability, and most are based on compensation paid. However, the ongoing UK EPIDERM and the BKH-S surveillance schemes are addressing the epidemiology of occupational contact skin reactions [26,27]. Dermatitis was the predominant cutaneous reaction (79%), compared to urticaria (3.5%), infective conditions (2.5%) and neoplasia (12.8%) [26]. Recent findings show that skin diseases rank second (29%) to musculoskeletal conditions (57%) as causes of occupational disease [26]. The frequency of work-related skin reactions has been looked at in various occupational groups (Table 21.1).

The introduction of new chemicals may have increased the incidence of industrial dermatitis, but such a trend is counteracted by preventive and educational measures. The total number affected has increased, as the number of persons employed in industry has risen.

In a population sample from an industrial city, the overall 1-year period prevalence of hand eczema was 11.8% [28]. Hand eczema was significantly more common among those reporting potentially harmful skin exposures, cleaners for example having a corresponding prevalence rate of 21.3%.

In a joint European study of consecutive clinic patients with dermatitis, 30% of the men and 12% of the women had occupational dermatitis [29].

Of all occupational diseases, dermatoses comprise from 20 to 70% in different countries, and of the dermatoses between 20 and 90% are contact dermatitis. The relative proportions are determined by the extent and type of industrialization in an area, and certainly also by the skill and interest of dermatologists in contact dermatitis [29].

Age

Occupational dermatitis may occur at any age. The average age of onset varies from one occupation to another [7]. In some studies [30], two peaks appear, one at each end of working life. The young age group includes many patients with irritant and atopic dermatitis of the hands. Others find that the risk increases progressively with age [31].

Occupations

Certain industries and occupational groups contribute the majority of cases: in England and West Germany hairdressers [26,27] and in Italy bricklayers [32]. Agriculture, manufacturing and construction consistently head the list in the USA [33,34]. If the number of persons exposed is taken into account, certain subgroups or departments of large industries have a particularly high risk of dermatitis [12]. A high chromate content in local cement may place building workers at the top of the list. Among 1071 building workers, 6% had occupational cement dermatitis and half of them were sensitized to chromium [35].

Certain high-risk groups may not be identified because the number employed is low. Thus, tilers were found to have a much higher risk than bricklayers when the number of cases seen was correlated with the number employed. Self-employed persons are rarely compensated and are therefore not registered. A high risk of dermatitis among veterinary surgeons thus escaped notice. The most common occupational contact dermatitis is probably housewives' dermatitis. In a Swedish public health examination, this affected approximately 1% of adult women. Thirty-eight per cent of these had allergic contact dermatitis [36].

Period of exposure

Bakers get their dermatitis early, bricklayers later in life [7]. In one study, chromate in primers caused dermatitis after an average exposure of 5–7 months [37]. Hairdressers generally develop dermatitis early in their career [7], but the number who leave hairdressing before the age of 30 years is considerable and many leave for reasons other than dermatitis [38].

No comprehensive statistics have analysed the sum total of factors determining occupational risks. Wagner and Wezel [39] have suggested an approach. They base their calculations of occupational risk on three factors:

1 The number of cases related to the number employed.
2 The average age of onset of occupational dermatitis.
3 The average period of work before onset.

Ideally, the number employed should be divided into age groups. All three factors vary independently. Many workers start a job late in life (e.g. unskilled labour in manufacturing industries) and develop their dermatitis rapidly. Others get their dermatitis after decades of work.

Clinical features

Occupational contact dermatitis has the same morphology as any other contact dermatitis, i.e. cumulative irritant, allergic and photocontact dermatitis. The regional distribution, however, differs considerably because occupational contact dermatitis is mainly on exposed parts. The hands are affected, alone or together with other sites, in 80–90% of all cases of occupational contact dermatitis [29]. Irritant contact dermatitis started under finger rings in 12% of women and 2% of men [40]. The arms are also involved, especially if not covered by sleeves. Dusts and vapours affect the face and neck. Cement workers and miners often have dermatitis on the lower legs and feet. Those wearing rubber boots may have dermatitis from footwear.

Irritants and sensitizers

The most important irritants and sensitizers encountered in different occupations are detailed at the end of this chapter. The relative importance of occupational noxious agents varies considerably in different reports. Irritants such as detergents, alkalis and organic solvents head the list [39]. Schwartz *et al*. [41], in an extensive investigation, found petroleum products and alkalis to be the most important. The incidence of dermatitis from synthetic resins, such as epoxies and acrylates, has become increasingly frequent in the last few decades. In most reports, cumulative irritant dermatitis is more common than the allergic type. Most authorities agree that the most common sensitizer is chromium. Because a cumulative irritant contact dermatitis increases the penetration of allergens, it may predispose to the development of a superimposed allergic contact dermatitis. Likewise, an allergic contact dermatitis may render the skin more vulnerable to attack by irritants.

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Diagnosis

The diagnostic approach to a suspected occupational dermatosis needs to be systematic. Most diagnostic difficulties arise from eczematous dermatoses [1]. Great care must be taken in the accurate distinction between contact dermatitis and endogenous eczema, and between irritant and allergic contact dermatitis. Skill is needed, not only in dermatology, but also in taking an occupational history [2,3], and in obtaining as detailed a picture as possible of what the patient actually does at work [4].

The clinical distinction on the hands, forearms or face between endogenous eczema, irritant contact dermatitis and allergic contact dermatitis is beset with pitfalls. Differences in distribution and morphology are useful guides, but dangerous to rely on uncritically. There is a tendency for irritant contact dermatitis to affect the dorsa of the hands (Fig. 21.1) and fingers (Fig. 21.2) and the finger webs, rather than the palms, and to be relatively devoid of vesicles. There is a tendency for vesicular eczema of the palms and sides of the fingers to be endogenous. However, certain irritants and allergens (Fig. 21.3) can produce a highly vesicular eczema of the palmar aspects of the hands and fingers, and both allergic contact dermatitis and endogenous eczema frequently involve the dorsal aspects of the hands, fingers and webs. Discs of eczema on the dorsa of the hands and forearms are frequently endogenous, but allergic contact dermatitis from chromium and cumulative irritant contact dermatitis can present in a very similar distribution (Fig. 21.1). Gross eyelid swelling usually indicates allergic contact dermatitis, but degrees of eyelid swelling can occur in both irritant contact dermatitis and endogenous eczema.

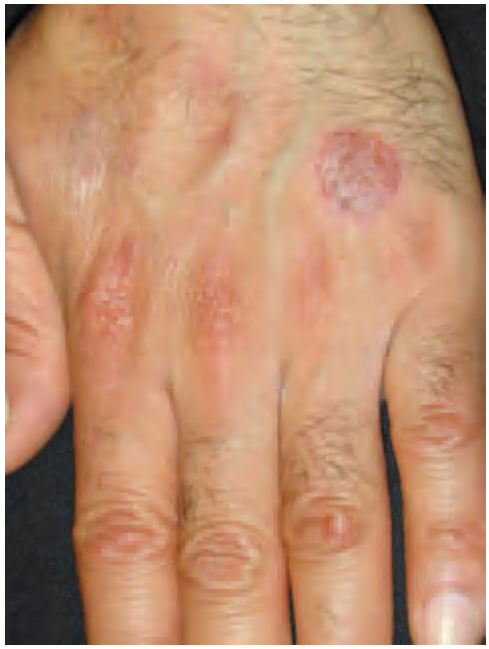

Fig. 21.1 Discoid pattern of irritant contact dermatitis from soluble oil.

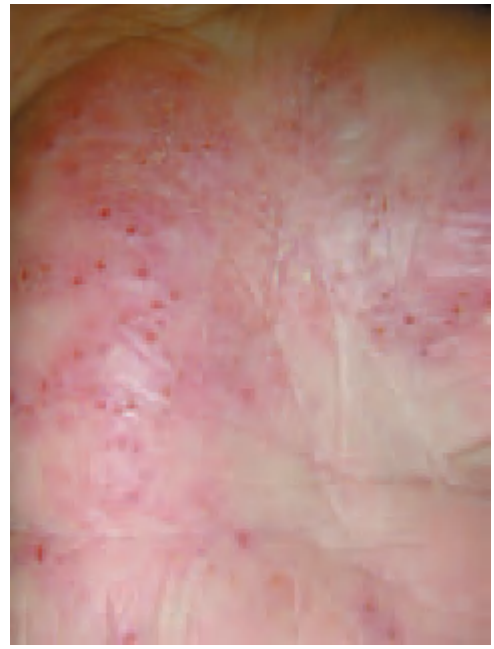

Fig. 21.3 Allergic contact dermatitis from Compositae plants in a florist.

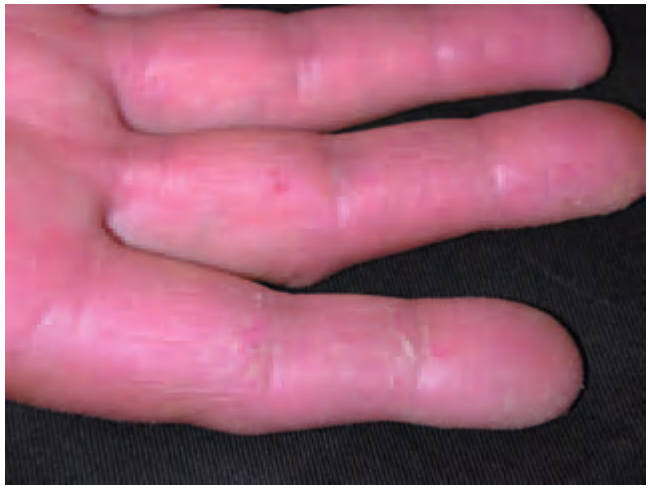

Fig. 21.2 Irritant contact dermatitis of the fingers in a printer.

It is difficult to overemphasize the importance of a sound working knowledge of occupational irritants, as well as allergens, and of patch testing, in overcoming these difficulties in clinical differentiation. It should be appreciated that hand eczemas, in particular, are often the joint outcome of endogenous, irritant, allergic and even general climatic factors, and may be partly occupational as well as wholly occupational or non-occupational. In identifying the primary and/or major cause of a contact dermatitis, antecedent and aggravating causes should not be neglected. Diagnosis of secondary bacterial infection in occupational contact dermatitis, for example, may allow significant improvement to be obtained with antibiotic therapy.

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Occupational contact urticaria [1,2]

High-molecular-weight antigens such as proteins may induce specific immunoglobulin E (IgE) antibody production [3]. Many of these antigens can penetrate only thin skin or a defective skin surface. If the antigen and specific IgE antibodies bind to Fc receptors on the mast cells, these will release histamine and other mediators. The typical clinical picture is an urticarial reaction with erythema and oedema [1,2]. Contact urticaria can frequently be an occupational dermatosis [4,5]; immediate hypersensitivity to natural rubber latex in rubber gloves is an obvious example [6].

Veterinarians exposed to amniotic fluid, and kitchen staff who have contact with uncooked food items, may develop protein contact dermatitis, a variant of contact urticaria [7].

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Occupational irritant contact dermatitis [1–9]

Dermatitis from the type of metalworking fluid or coolant most commonly known in the UK as 'soluble oil' is a prime example of occupational contact dermatitis that is usually primarily, and frequently totally, of cumulative irritant (Chapter 19) rather than allergic causation [9–14]. Soluble oils are oil-in-water emulsions used to cool and lubricate metalworking and certain other industrial manufacturing operations [15]. Synthetic coolants are aqueous chemical solutions and can have similar effects on the skin. Both types of product contain numerous additives, some of which are potential sensitizers (especially biocides [16,17]), but it is the substantial content of surface-active agents as emulsifiers or wetting agents in coolants that appears to underlie their potential for skin irritation [15,18]. Synthetic coolants also contain traces of nitrosamines, formed by triethanolamine or diethanolamine reacting with nitrites. Although currently under evaluation as carcinogens, there is no evidence that nitrosamines in coolants are irritant or sensitizing to the skin.

Soluble oil dermatitis is typical of occupational irritant contact dermatitis in that it is cumulative and has a multifactorial aetiology [11,12]. The degree of skin contact [19], individual susceptibility, machine type and control method [20], and biocide additions [21] are all important factors, in addition to the specification and condition of the metalworking fluid itself. Clinically, the dorsa of the hands, finger webs, wrists and forearms are predominantly affected [22] and the dermatitis can have a patchy distribution that mimics nummular eczema [12] (Fig. 21.1). This is also true of several other forms of occupational contact dermatitis, including cement dermatitis [23] and dermatitis from machine oil in hosiery workers [24]. There are two reports [25,26] of soluble oil dermatitis presenting as 'dyshidrotic' eczema; a similar pattern has been described from mechanical irritancy [27]. The prognosis is highly variable but may eventually be good even without a change of work [28].

Irritant contact dermatitis provoked by soluble oils and synthetic coolants is to be distinguished from oil acne, discussed later in relation to neat (or insoluble) non-aqueous cutting oils.

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Occupational physical irritant contact dermatitis [1,2]

The skin can react in a variety of ways to excessive friction and microtrauma. The reaction depends upon constitutional factors, such as a tendency to develop psoriasis, or the type of trauma. Various types of reactions can occur: calluses, fissuring, lichenification, blistering, Koebner phenomena aggravating psoriasis and granulomas.

Fibreglass dermatitis is a well-known example of a physical irritant contact dermatitis and was first described in 1942 [3]. It consists of sharp glass spicules which are capable of penetrating the superficial part of the horny layer of the skin to cause immediate skin irritation. The acute irritation reaction results in a pruriginous dermatitis; as clothing may trap the fibreglass, this may occur on covered parts of the body.

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Occupational allergic contact dermatitis [1–4]

Although probably less common than occupational irritant contact dermatitis, occupational allergic contact dermatitis still tends to be underdiagnosed [5]. Better history taking [3], more extensive patch testing, workplace visiting and greater use of chemical investigations [3] significantly increase the proportion of patients found to have contact sensitization relevant to their occupation. Allergic contact dermatitis also frequently complicates irritant contact dermatitis in occupational cases. A prime example of occupational allergic contact dermatitis is that from chromium [6,7] (Chapter 20).

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Investigations

Skin prick test/RAST

Although testing for immediate hypersensitivity is not always a part of assessment of contact dermatitis, it can be important, particularly in the situation of hand dermatitis when type 1 hypersensitivity to natural rubber latex (NRL) is suspected [1]. The two tests in common use are the skin prick test and the radioallergosorbent test (RAST). The glove usage or challenge test requires a highly allergenic brand of glove and is potentially dangerous—emergency treatment facilities for the management of anaphylaxis are needed [2]. Skin prick testing involves an intradermal puncture through a drop of allergen or glove. A positive reaction consists of an urticarial weal, which is usually apparent after 15 min although it may take as long as 45 min to develop. A positive control test of histamine should also be performed to exclude a false-negative reaction due to oral antihistamine ingestion. A negative control prick test with saline should be also be performed to check if the patient is dermographic. There are occasional reports of anaphylaxis following prick testing with NRL extract [3]. With the advent of standardized commercially available NRL extracts, this risk is probably greatly reduced. Some clinicians may prefer to perform a RAST for NRL allergy, as they may not have adequate facilities or training to deal with anaphylaxis, however, the sensitivity and specificity may be less for RAST compared with prick testing. Skin prick and use tests are also useful when investigating protein contact dermatitis in occupations at risk, such as chefs or veterinarians [4].

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Patch testing [1–5]

Four general problems of patch testing (Chapter 20) are particularly relevant in suspected occupational dermatitis:
1 False-positive reactions
2 False-negative reactions
3 Unexplained positive reactions
4 Missed allergens

False-positive reactions are commonly obtained if industrial chemicals are applied as patch tests undiluted [3]. Such reactions can be shown to be false-positive irritant

reactions if testing in control subjects also demonstrates positive reactions; applying serial dilutions of the chemical to the original patient will often demonstrate an abrupt loss of the reaction. The uncritical use of undiluted chemical samples as patch tests also increases the risk of active sensitization and other complications of patch testing (Chapter 20). When testing an unknown substance, a preliminary open test is often advisable [4].

False-negative reactions can also be obtained with samples acquired from the patient's workplace. This is because the concentration of an allergen in a sample—for example, rubber—may be too low to elicit a positive patch test reaction. This problem also arises when allergens are found in irritant products such as cutting fluids, solvents and soaps. Dilution of these to avoid a false-positive reaction from the irritancy of the sample may overdilute an allergen initially present in only low concentration (Chapter 20).

Unexplained positive reactions found on standard patch testing in suspected occupational cases should always be pursued for explanation [4,6]. This is particularly so when the allergens concerned are known to have a multiplicity of industrial uses, such as chromate, cobalt and colophony. A factory visit can be invaluable in the detection of previously unsuspected sources of allergens [7–9].

Missed allergens. When clinical assessment points strongly towards an occupational allergic contact dermatitis, the occurrence of negative patch test results should always raise the possibility of the responsible allergen having been omitted from testing [5,6]. Another major function of a factory visit is to detect such missed allergens.

Routine pre-employment testing with potential sensitizers to be used in the future job should not be carried out [4].

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Chemical investigations

There is an array of qualitative chemical spot tests [1,2], of which four are likely to be of particular use in the investigation of occupational cases. These are the dimethylgloxime test for nickel [3], the diphenylcarbazide test for chromium [1], the lutidine test for formaldehyde [4] and the filter-paper test for epoxy resin [5]. These are all tests which can be carried out simply and reliably with minimum time and bench space.

Quantitative microanalysis of allergens and physicochemical techniques for the isolation of allergens [6] are likely to be beyond the scope of most dermatologists outside special departments, although they may be available within neighbouring departments. Thin-layer chromatography does, however, offer opportunities for relatively simple separation and identification, such as the detection of the sensitizing low-molecular-weight oligomers of epoxy resin [2,5].

Liquid and gas chromatography, which may be linked to mass spectrometry, colorimetric spectrophotometry, and atomic absorption and emission spectrophotometry all play important parts in current investigations [2].

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Factory visiting

The diagnostic advantage to the dermatologist of seeing the way in which a patient carries out the work cannot be overestimated. Some general guidance is available [1–5], but it is the experience of making such visits that is the best instructor. The main types of information that are worth establishing during such visits, and recording subsequently, are as follows.

1 *Organizational*. Name, address (including postcode) and telephone number of workplace; names and status of all medical, nursing, employer and employee representatives met.

2 *Demographic*. Numbers employed overall and in patient's work area; current expansion, contraction, turnover; shift system and pay scheme.

3 *Technological*. Broad concept of production as a whole; detailed understanding of work carried out by patient and in patient's work area, including all potential irritants and allergens observed and their degree and extent of skin contact; names and addresses of suppliers of materials requiring further identification.

4 *Preventive*. Broad impression of working conditions (space, lighting, ventilation); more detailed review of protective installations, protective clothing, skin-care products and education; assessment of actual uptake and practical effectiveness of preventive methods.
5 *Miscellaneous*. Industrial relations, psychological, sociological or economic factors, any similar problem in sister factory, etc.
6 *Clinical*. Skin complaints in employees other than the patient, their clinical assessment, subdivision into occupational and non-occupational (often provisional).
7 *Epidemiological*. Prevalence of skin complaints as a proportion of the total exposed, estimate of prevalence of occupational dermatoses.
8 *Aetiological*. Opinions of others, with attribution as to source and estimate of reliability; own opinion, with grounds for it (may be inconclusive).
9 *Operational*. Summary of findings; recommendations for future investigation, management and review; follow-up.

Factory (or other workplace) visits can provide many major benefits [4].
1 Detection of relevance of previously unexplained positive standard patch test reactions.
2 Detection of missed allergen.
3 Substantiation of diagnosis of irritant contact dermatitis.
4 Diagnosis of mild or unfamiliar occupational dermatoses by their occurrence in several members of a workforce.
5 Substantiation that various non-occupational skin conditions have been grouped together as a pseudo-occupational dermatosis [6], and why.
6 Recognition of phenomenon of visible dermatoses, whether occupational or not, causing anxiety and subconsciously imitative symptoms in fellow employees [7].
7 Initiation of research on new occupational dermatoses.
8 Incidental effects, including improved dermatologist–occupational physician [8] and dermatologist–patient relationships.
9 Progressive increase in dermatologist's overall knowledge of the working contactants of his or her patients.

A second-best alternative that can still provide useful information if a factory visit is impossible is to communicate with medical, nursing, employer or employee representatives by letter or telephone.

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Prognosis [1] (Chapters 19 and 20)

The most important aspect of prognosis in occupational dermatoses is that neither irritant or allergic contact dermatitis may be as beneficially affected by change of work as some believe [1–4]. This has a profound influence on the management of the established case [5], as well as underlining the importance of primary prevention.

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Prevention [1–4] (Chapters 19 and 20)

Secondary preventive measures can reduce the risk of dermatitis in an established case, although success can be obtained only by close collaboration between the management of the factory and the dermatologist. Changes in the process, when practicable, are always likely to be more successful than personal protection [5]. Some preventive measures that are desirable from a dermatological point of view may be unsafe or impractical in an industrial environment. The wearing of gloves is often ruled out because of these strictures [6].

Materials selected for protective clothing may in practice allow many contactants to penetrate. Various sources provide practical guidance as to the choice of protective material [2,7–11]. There are now multilayered materials that show much greater resistance to allergens such as methyl methacrylate [12] and irritants such as organic solvents [7]. Even when protective clothing is practicable and competent to protect, the way in which it is taken off and put on again may lead to contamination of inside surfaces. Because occlusion increases penetration, wearing a glove that has been contaminated on the inside can be more harmful than wearing no glove at all [4]. Correct procedures must therefore be instituted and maintained.

Automated processes are often far from free of skin contact. Fregert [13] has listed many possible sources of skin contamination. Service engineers are particularly at risk [14].

Table 21.2 Basic workplace skin-care principles.

Luke-warm water for washing
Use correct gloves before exposure for the shortest time
Remove rings
Cotton liners underneath protective gloves
Avoid disinfectant hand cleansers
Apply emollient hand creams
Protect hands at home
Workforce education

Allergen replacement [1,14,15] is a useful concept. Extreme care must be taken to ensure as far as possible that the replacement is genuinely safer in all respects.

Some skin-care creams ('barrier' and moisturizing creams) have been demonstrated by various test methods [2,16–19] to have a protective effect against certain irritants. Their effectiveness in actual use remains less securely established [2]. Topical binding agents may have a role in the prevention of nickel dermatitis [20].

The basic principle of prevention of occupational contact dermatitis continues to be that of reduction of contact, or preferably avoidance. If chemicals remain on the skin for 24 h instead of 8 h, sensitization and irritation occur more readily [4]. Evidence-based skin care recommendations have been published [21] (summarized in Table 21.2). If improvements are made to the working conditions by intensified preventative measures, then this is likely to lead to a reduction in cases of occupational contact dermatitis [22].

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Management of the established case [1,2]

As most workers naturally prefer to continue their work, a detailed analysis of causative factors is required. Minor changes of procedure may be helpful once guided by a precise diagnosis. A change of job may be considered in first-year apprentices, in those with uncomplicated allergic contact dermatitis from readily avoidable substances or in atopics who have unavoidable contact with irritants. This should only be decided after full dermatological investigation. In the majority of cases, continuation in the same occupation should be made possible [1,3–5].

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Assessment of dermatitic potential

The potential of chemicals to act as contact irritants [1,2], contact allergens [3–7], photoirritants [8] and photoallergens [7,9,10] can be assessed by test methods in laboratory animals and, to a lesser extent, in human volunteer subjects. These methods assess potential; they do not in themselves predict the incidence of dermatitis. Actual risk depends not only on dermatitic potential but also on

other factors, the most important of which concern the conditions of exposure (concentration, frequency and duration) and the normality of skin. Also useful is background knowledge of the structure–activity relationships of chemical groups [11].

Modifications of widely accepted test procedures such as the guinea-pig maximization test [6] tend to occur with experience of their use [12–14], and sufficiently different tests have been developed to justify separate names [7,15–17]. Standardization of test procedures greatly reduces inter- and intralaboratory variation in results—but as this is never likely to cease to be a problem to some degree [18], the development of new tests that may offer greater ease of standardization (and economy) continues [19]. The use of mouse models for the prediction of sensitizing potential is now well established [20,21].

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Alkali tests

The usefulness of alkali resistance and alkali neutralization tests as predictors of susceptibility to irritants remains controversial. Neither test is sufficiently simple and reliable to achieve widespread clinical use [1–3], and their diagnostic value has been overestimated.

More sophisticated tests with panels of irritants have been used to identify a 14% proportion of the general population with 'hyperirritable skin' [1]. Susceptibility to one irritant, however, does not necessarily imply susceptibility to another irritant in the same individual [1,4].

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Transepidermal water loss

Measurement of the baseline transepidermal water loss (TEWL) may be a useful indicator of reactivity to irritants, although there is variation between studies [1].

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Measurement of skin contamination

Methods of quantifying the degree of skin contamination by substances include skin wiping [1], skin rinsing [2], exposure pads [3,4], and the use of natural fluorescence (oils and tars) [5] or fluorescent tracers [6].

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Non-eczematous occupational dermatoses

These constitute an important minority of occupational dermatoses. Particularly significant examples also described in other chapters are acquired hypomelanosis (see p. 21.15 in this chapter, and Chapter 39), scleroderma (Chapter 56) and carcinoma (Chapter 36). Many other dermatoses can be occupational, including some skin diseases caused by arthropods (Chapter 33), *Candida* paronychia (Chapter 31), onycholysis (Chapter 62) and exogenous pigmentations such as argyria (Chapter 39).

Chemical burns

Many chemicals used in industry and the home are capable not only of causing burns, but also of being absorbed and causing toxic effects leading to acute yellow atrophy of the liver or renal failure. Burns from acids and alkalis may cause acidosis or alkalosis, both requiring treatment.

Certain chemicals cause chemical burns, the first perceptible or visible changes of which can be delayed for several hours. Examples of these are mustard gas, podophyllin, dithranol, hydrofluoric acid, propane sultone, ethylene oxide and epichlorohydrin [1].

The primary—and essential—treatment of all chemical burns is copious washing (except for metallic potassium and sodium, which ignite in water). Specific remedies are available for only a few chemicals. Buffered phosphate solution, when readily available, is useful for acid and alkali burns, but is only practicable in large units likely to deal with more than the occasional case.

The depth of necrosis depends on the concentration, duration of contact and time before treatment is instituted.

Acids and alkalis

Sulphuric acid and potassium or sodium [2] hydroxide are the most common agents. Strong acids are hygroscopic and cause coagulative necrosis and discoloration of the tissues. Alkalis form proteinates and saponify fats. Copious washing may have to be continued for a long time. Sodium bicarbonate solution can be used for acid burns and vinegar and ammonium chloride for alkalis.

Cement (lime) [3–6]

Wet cement under occlusion (e.g. due to kneeling in cement, or contamination inside boots) can cause delayed full-skin-thickness burns. Soiled clothing should be removed immediately and the injury bathed copiously with water or, if available, phosphate buffer; excision and grafting of necrotic areas is frequently required [4].

Chromic acid [7]

This produces skin ulceration and necrosis. It may be absorbed and cause renal failure. Deeper burns may require excision and grafting. Superinfection with *Streptococcus pyogenes* may be a missed cause of delayed healing.

Phosphorus

This ignites on exposure to air. Burns should be kept moist until all particles are removed. Dry dressings should not be used. Small residual particles can be detected by phosphorescence in a dark room. Severe metabolic changes may occur, and patients who have suffered phosphorus burns should be carefully monitored. Copper sulphate solutions (in small amounts) have been advocated [8].

Hydrofluoric acid (HF) [9–12]

One of the strongest acids known, it is widely used in industry and research. It is ionized in solution and penetrates deeply. Burns are characterized by intense pain (often delayed) and deep tissue necrosis, which progresses for several days. Skin contact must be dealt with instantly with copious washing with water for at least 10–15 min. Repeated application of 2.5% calcium gluconate gel is then usually adequate for minor exposure of the skin to less than 20% HF. If this fails to reduce the pain within 30 min–1 h, repeated infiltration with 5–10% calcium gluconate (0.5 mL/cm^2 burned surface area) should be considered [10]. Regional intra-arterial calcium gluconate [10] or chloride [13] infusion also has its expert advocates, but hypercalcaemia is a significant risk. Surgical debridement may be required later, as in all chemical burns. Earlier surgical intervention has been successful in severe burns [14].

Phenol [15]

This is rapidly absorbed through the intact skin. Local necrosis is proportionate to concentration and small amounts of water or alcohol may increase the absorption. Toxic effects are numerous. 'Deluge' washing with large amounts of water or swabbing with polyethylene glycol [15] should be employed.

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Acne of external chemical origin

SYN. ACNE VENENATA

Aetiology. A variety of chemicals possess, to some degree, the capacity to induce acne by external contact [1]. Many are occupational hazards, but some may be encountered in the home. The occupational chloracnes are of outstanding medical importance, for their development provides a valuable indicator of exposure to a toxic hazard. Many of the substances inducing chloracne are also hepatotoxic.

Halogenated aromatic hydrocarbons [2–7] are the most potent acnegenic agents. The chloronaphthalenes, chlorobiphenyls [8] and chlorobiphenyl oxides are used as dielectrics in conductors and insulators. Exposure occurs in those manufacturing these substances or making or handling cables [9,10]. A naphthalene wax used to 'feather proof' a counterpane caused acne on the face and arms of a child [11]. These substances will induce acne at any site [12] and at any age, usually after 1 or 2 months' exposure. The chlorophenols are used as insecticides, fungicides, herbicides and wood preservatives [13]. Their capacity to cause chloracne depends on the degree to which they are contaminated with chlorinated dioxins and the precise chemical structure of the latter, for example 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) (Fig. 21.4) is the most powerful chloracnegenic agent known [14–18].

Similarly, the toxicity of the polychlorinated biphenyls (PCBs) is largely due to contamination with polychlorinated dibenzofurans (PCDFs). Chloracne has been caused by a weedkiller containing 2,4-dichlorophenoxyacetic acid and 2,4,5-trichlorophenoxyacetic acid [19], by sodium tetrachlorophenate used as a wood preservative [2], by the herbicide 2,6-dichlorobenzonitrile [20], by a trifluoromethylpyrazole derivative being developed as an antirheumatic drug [21] and by an intermediate product found in the manufacture of tetrachloroazobenzene [4].

As a consequence of industrial or other accidents, large numbers of individuals may be heavily exposed to such

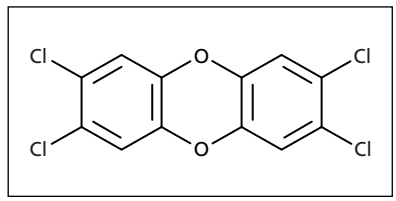

Fig. 21.4 2,3,7,8-tetrachlorodibenzo-*p*-dioxin—a halogenated aromatic compound—is highly toxic and causes chloracne.

chemicals [22]. In such circumstances, TCDD caused serious systemic symptoms and severe chloracne [23]. After another industrial accident the same chemical caused chloracne in members of the families of affected workers [24]. TCDD-induced chloracne, mainly in children, cleared well within a decade, and systemic effects were absent, following the more recent Seveso accident [25].

The induction of chloracne by the ingestion of PCBs has occurred in two large epidemics caused by the contamination of cooking oil [2,26]: the chloracnegen was shown to have caused transplacental, as well as direct, toxicity [27]. Polybrominated biphenyls became widely distributed in the state of Michigan, following a labelling error that resulted in their introduction into cattle feed [22].

Neat (insoluble) cutting oils, which are impure paraffin–oil mixtures, are the commonest chemical cause of acne, because they are so widely used in the engineering industry, but their acnegenic capacity is inconstant and not necessarily high. Men are more readily affected than women, and those with acne vulgaris are particularly susceptible. The use of moulding oil in the manufacture of precast concrete can cause oil acne [28]. Brilliantines containing impure paraffins may have a similar effect [29]. Comedones and cysts behind the ears have been attributed to paraffin products in shaving soap inadequately rinsed from this region [30].

Crude petroleum is acnegenic in oilfield and refinery workers [7]. Diesel oil can cause acne in motor mechanics [31].

Heavy coal-tar distillates, especially pitch and creosote, are also to some extent acnegenic. Conduit makers and road workers are affected. Under experimental conditions the lesions induced by crude coal tar are more inflammatory in white people than in black people [32].

Cosmetics [33]. Mild comedo acne with occasional papulopustules occurs in one-third of adult women in the USA. Of 25 facial cosmetic creams tested in rabbits, 50% were comedogenic; so were lanolin, petrolatum and some vegetable oils [34]. Pomades had an even more marked effect in black Americans [29]. Also acnegenic were indigenous vegetable oils in India [35]. The salts of fatty acids in conventional soaps are comedogenic if used excessively [36]. Fatty acid esters, especially isopropyl linoleate, acetylated lanolin alcohol, grape seed and sweet almond oils, have

Clinical features	Acne vulgaris	Halogen acne
Usual age	Teenage	Any
Comedones	Present	> 3 (if absent not chloracne)
Straw-coloured cysts	Rare	Pathognomonic
Temporal comedones	Rare	Diagnostic
Inflammatory papules and cysts	≥ 3	Present
Retroauricular involvement	Uncommon	Common
Nose involvement	Often spared	Often spared
Associated systemic findings	Rare	Common

Table 21.3 Clinical features of acne vulgaris vs. halogen acne.

been found to be particularly comedogenic in rabbits [37].

Asbestos. A large percentage of workers in a hardboard factory in Germany developed acne which was attributed to asbestos [38].

Topical corticosteroids. The continued application of topical corticosteroids under occlusive dressings may also induce comedo formation. It does not occur under the age of 10 years and is difficult to induce experimentally in subjects over 50 years of age [39].

Psoralen and UVA therapy. A predominantly perioral acne can appear during psoralen and UVA (PUVA) therapy [1].

Pathology [40]. In chloracne, squamous cell proliferation occurs in sebaceous gland acini and acanthosis in the upper part of the external root sheath. The wall of the comedo is at first acanthotic and tortuous, but later becomes thin.

Clinical features [3] (Table 21.3). Chloracne, or more correctly halogen acne, may be differentiated from chemical acne of other origins. The eruption involves the face predominantly, even if the chemical has been ingested. The nose tends to be spared, and skin of the malar regions, the angles of the jaw and behind the ears is often most severely affected. The typical lesions are small, skin-coloured cysts, 1 mm to 1 cm in diameter, associated with numerous comedones (Fig. 21.5). There may be some itching. If exposure to the causative agent ceases, the lesions very slowly resolve, leaving some scarring. Asymmetrical lesions in any region of the body may be seen when unusual sites are in direct contact with the acnegenic agent. When the poison has been ingested, constitutional symptoms are frequently present; hypertrophy of Meibomian glands of the eyelids, a predominantly sensory peripheral neuropathy, and patchy pigmentation of skin, nails and gums have been reported [26]. In acne caused by pitch or tar, comedones of the malar region predominate and there are few or no cysts. There may be a folliculitis of thighs and forearms. There is often some melanosis of exposed skin. Although it is doubtful that acne vulgaris predisposes to chloracne, its victims are more susceptible to oil acne. A highly inflammatory folliculitis of the forearms and thighs, with many comedones, is associated with aggravation of existing acne. Comedones induced by brilliantines or pomades [29] occur mainly around the frontal hair line.

Fig. 21.5 Chloracne. Profuse open comedones in malar crescent.

Diagnosis (Table 21.4). Acne in the 'wrong' sites and at the 'wrong' age, or with a predominance of comedones, should initiate an enquiry into possible external chemical factors. Mechanical trauma alone can aggravate or even induce acne in predisposed subjects [41], and its possible role as a contributory factor should always be taken into account.

Treatment. Even treatment with isotretinoin [21] or acitretin [19] may fail to prevent chloracne from persisting for many years, despite avoidance of further contact.

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Table 21.4 Differential diagnosis of various forms of occupational acne.

	Aetiology	Location	Lesion
Chloracne	Halogenated aromatics	Malar, retroauricular, mandibular	Comedones, straw-coloured cysts (0.1–1.0 cm)
Oil folliculitis	Oil	Arms, thighs, buttocks	Erythematous, papules, pustules
Pitch acne	Tar/pitch	Exposed facial areas, especially malar	Open comedones
Tropical acne	Heat/humidity	Back, neck, buttocks, proximal extremities	Nodules, cysts

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Chemical depigmentation [1,2]

Definition. Occupational leukoderma is defined as pigmentation or hypopigmentation of the skin due to industrial exposure to a chemical or chemicals known to have a destructive effect on epidermal melanocytes [1].

Aetiology. Certain chemicals, particularly the substituted phenols, are destructive to functional melanocytes [2]. Many of these compounds cause permanent depigmentation of the skin, resembling vitiligo. The most commonly implicated chemicals are *para*-tertiary butyl phenol, *para*-tertiary butyl catechol, monobenzyl ether of hydroquinone (Fig. 21.6), hydroquinone and related compounds [1,2]. A list of chemicals known to cause occupational leukoderma is shown in Table 21.5.

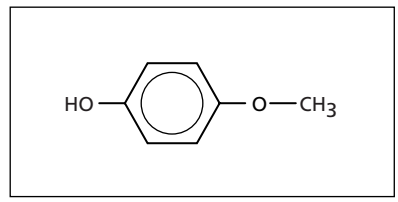

Fig. 21.6 Monomethylether of hydroquinone (4-hydroxyanisole or 4-methoxyphenol) is an intermediate in the manufacture of several chemicals.

Table 21.5 Chemicals capable of causing occupational leukoderma.

Hydroquinone
Monobenzylether of hydroquinone
Monoethylether of hydroquinone (*p*-ethoxyphenol)
Monomethylether of hydroquinone (*p*-methoxyphenol)
p-Cresol
p-Isopropylcatechol
p-Methylcatechol
p-Nonylphenol
p-Octylphenol
p-Phenylphenol
p-*tert*-Amylphenol
p-tertiary-Butylcatechol
p-tertiary-Butylphenol
N,*N*′,*N*″-Triethylenethiophosphoramide (thio-TEPA)
Mercaptoamines, e.g. *N*-2-mercaptoethyl-dimethylamine hydrochloride (MEDA)
Physostigmine

Table 21.6 Occupations with potential exposure to depigmenting chemicals.

Insecticides, paints, plastics and rubber
Lubricating and motor oils
Photographic chemicals
Antimicrobials and disinfectants
Detergents and deodorants
Inks

Diagnosis. The diagnosis of occupational vitiligo should be suspected if a worker who potentially has been exposed to depigmenting chemicals develops leukoderma on the dorsal aspects of the hands or in a more widespread distribution [3]. There should be particular suspicion if more than one worker is involved. The chemicals to which the worker is exposed should be identified and investigation made to see if it or they are known to cause depigmentation. Some occupations known to be at risk of exposure to depigmenting chemicals are shown in Table 21.6.

Treatment. There is no specific treatment for occupational vitiligo. Removal of the offending chemical may result in partial repigmentation, but this process may take years and may not occur at all. Treatment should be aimed at preventing further exposure. Camouflage cosmetics may be used and the depigmented skin protected from ultraviolet irradiation by sunscreens.

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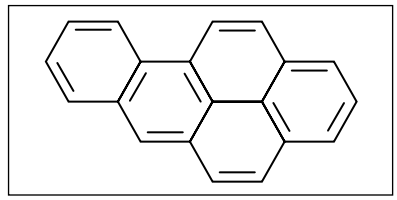

Fig. 21.7 Benzo[*a*]pyrene.

Occupationally induced skin tumours

Occupational skin cancers are rare and mainly of historical importance, apart from obvious examples such as epitheliomas developing in outdoor workers; however, some occupational exposures will predispose patients to develop skin tumours.

Historical review [1–4]

In 1775, the first cancer of any type to be linked with occupational exposure was scrotal squamous carcinomas in British chimney sweeps, reported by Percivall Pott [1]. In the rest of Europe, the disease was unknown because of wearing protective clothing and the reduced carcinogenicity of wood soot as opposed to coal predominantly burnt in Britain. Soot formed by burning wood has much lower levels of the polycyclic hydrocarbon, benzo[*a*]pyrene (Fig. 21.7), implicated in the aetiology of skin cancer compared to coal soot. Skin cancer was still reported in chimney sweeps in Britain in the 1950s. By 1945 in Britain, almost 50% of industrial skin cancer was attributable to exposure to pitch and tar in occupations such as mule spinners, jute workers and the engineering industry [2].

Definition. Occupational skin cancers are defined as those in which a person's occupation has played a major role in the aetiology of the tumour. Currently, multiple aetiological factors are thought to contribute to the development of skin cancer. In the past, however, there have been several virtual epidemics of skin cancer which were traceable to occupational exposures. The major occupational carcinogens recognized were polycyclic hydrocarbons, ionizing radiation and arsenic. Ultraviolet radiation is now the most important carcinogen in the aetiology of occupational skin cancer.

Aetiology and occupations (Tables 21.7 & 21.8). Polycyclic hydrocarbons are produced by incomplete combustion and distillation of coal, natural gas and oil shale. These chemicals are contained in tar, fuel oils, lubricating oils and greases, oil shale and bitumen.

Diagnosis. The diagnosis of skin cancer is similar to that of non-occupational skin cancers. Generally, the exposed

Table 21.7 Causative agents in occupational skin cancer.

Polycyclic hydrocarbons
Soot
Tar
Pitch
Mineral oil
Shale oil
Crude paraffin
Asphalt
Ionizing radiation
Arsenic
Ultraviolet light

Table 21.8 Occupations with potential exposure to causative agents in occupational skin cancer.

Causative agent	Occupation
Polycyclic hydrocarbons	Tar distilling Coal gas manufacturing Briquettes manufacturing Shale oil workers Refinery workers
Ultraviolet light	Outdoor workers Welders Laser exposure Printers
Ionizing radiation	Nuclear power plant workers X-ray technicians Uranium mining

sites are involved. Previously, the scrotum was involved frequently, because of continuous exposure to carcinogens and the increased likelihood of skin absorption in that site. There may be coexisting signs of exposure prior to or in addition to evidence of skin cancer. These may include oil folliculitis and hyperkeratoses, described in people working with mineral oil, and pitch or tar warts. Oil hyperkeratoses were described as being flat, white, circular, hyperkeratotic smooth plaques, small in diameter and often clustered. In addition, there were verrucose pigmented round or oval irregular raised warts. Tar warts were pigmented small papules, which were often seen around the face on the eyes, eyelids, cheek, forearms and back of the hands.

Management. Prevention of the development of skin cancers is most important. In the workplace, it is important to consider substitution of carcinogens where possible; an example is the declining exposure to polycyclic hydrocarbons in recent decades. Protection of the skin, with either protective clothing or with engineering control such as machine guarding, is important. Daily washing is essential. Since most of the skin cancers are associated with a very long latency period, it is important to have continued surveillance of older or retired workers. Finally, the skin cancers need to be treated as appropriate.

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Scleroderma and related diseases [1–4]

Scleroderma and related diseases are dealt with elsewhere, but a summary is shown in Table 21.9.

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Table 21.9 Scleroderma-like diseases related to occupational and environmental factors.

Inducing factors	Symptoms or disease
Occupational agents	
Vinyl chloride	Raynaud's phenomenon, sclerodactyly, acro-osteolysis, hepatic fibrosis, angiosarcoma, plaque-like fibrotic cutaneous lesions, leukocytopenia and thrombocytopenia
Organic solvents	Skin fibrosis, irritant dermatitis, hepatitis, neurological symptoms
bis(4-amino-3-methylcyclohexyl) methane (used in epoxy production)	Skin sclerosis, erythema, fatigue, myalgia, arthralgia
Quartz (silicon dioxide, SiO_2)	Systemic sclerosis
Iatrogenic agents	
Bleomycin	Pulmonary fibrosis, scleroderma-like lesions
Pentazocine	Pigmentary changes, panniculitis, ulcerations and sclerotic fibrosis on injection sites
L-tryptophan	Sclerodermatous induration, peripheral eosinophilia, myalgia, arthralgia
Silicon	Systemic sclerosis, Sjögren's syndrome, arthritis
Other substances	
Toxic oil syndrome	Scleroderma-like changes, neuromuscular atrophy, hypertension, sicca syndrome

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Vibration white finger [1] (see also Chapter 22)

Definition. Vibration white finger (VWF) consists of the episodic appearance of white-finger skin patches (Raynaud's phenomenon [2]) in response to environmental cold and is accompanied by secondary loss of sensation caused by vascular ischaemia. It can be part of, but is not synonymous with, the hand–arm vibration syndrome [1].

Aetiology. The pathogenesis of VWF is poorly understood. Chronic vibration exposure may damage endothelial vasoregulatory mechanisms by disturbing the endothelial-derived relaxing factor-mediated vasodilatory function [3].

Clinical features. Operatives using vibrating tools, such as lumberjacks, coal miners and road and construction workers, are at risk of developing VWF. Affected individuals develop symptoms of Raynaud's phenomenon on exposure to cold or vibration, usually after many years of working with vibrating tools [1].

Diagnosis. The diagnosis is usually made by history alone; ice provocation tests are not always reliable in precipitating attacks of VWF [1].

Prevention. With widespread knowledge of the cause of VWF, controls over duration of use of relevant machinery and improved personal protective equipment has led to a reduction in the incidence of VWF [1].

Treatment. The treatment of VWF is the same as for Raynaud's phenomenon. It is generally believed that symptoms of VWF regress some time after cessation of exposure [1].

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Medicolegal aspects of occupational dermatoses [1–4]

A report on a patient seen for compensation purposes should be prepared with much thought and care. Medical terms not of common currency should be explained as they occur. The following items of information should always be considered for inclusion:

1 Sources of information other than the patient (previous case notes; previous medical reports; workplace inspections).
2 Family history of atopy or any other allergies or skin disorders.
3 Previous personal history of atopy or any other allergies or skin disorders.
4 Previous occupations. Job titles, employers, types of contact, dates.
5 Present occupation. Job title, employer's name and full address, dates.
6 Time in contact with suspected causal factors. May be shorter (or longer) than time in present occupation.
7 Description of the working process. In sufficient detail to give accurate assessment of degree of skin contact, as well as the range of skin contactants.
8 Other cases of dermatitis, and standard of hygiene at the place of work. Types of skin cleanser, skin creams and protective clothing used at work.
9 Time and site of initial skin complaints. Previous injury at the initial site.
10 Progress, with approximate dates of gradual or sudden aggravation or improvement, and the influence of weekends, holidays, sickness absence.
11 Degree of incapacity during period of illness. Dates of absence from work. Level of earnings: previously, during illness, at present.
12 Changes in occupation since onset of skin complaint. Job titles, dates, details of changes in skin contactants.
13 Medical advice sought, treatment obtained and its effectiveness.
14 Clinical findings. Present state (have the lesions been suppressed by topical steroids?).
15 Special investigations; patch tests, prick or scratch tests, open tests, repeated open application tests (positive and negative tests, times of readings, vehicles, concentrations, application method, site). Exposure tests. Mycological/bacteriological examination.
16 Intercurrent diseases (fever, light eruptions, mycotic infection).
17 Diagnosis. With the Woolf reforms in the UK, it is necessary to give the full range of the opinions, including the reasons for the opinion given [5].
18 Common knowledge of risk at the occupation in question. Whether the employer could reasonably have been expected to have foreseen any risk to the skin.
19 Conclusions (in terms understandable to non-medical readers):

(a) Probable connection between occupational activity and the present pathological condition; balanced against predisposing factors and contributory factors in spare time.

(b) Possibility of continuing in previous occupation. If change of work is required, what are the chances of rehabilitation?
(c) Probable medical prognosis (state of the dermatitis), probable social prognosis (capacity for work).

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Specific occupational hazards [1–4]

The following is offered as an *aide-mémoire*. Many causes of contact urticaria [4] have also been described as causing protein contact dermatitis.

Agriculture [5–15]

Irritants. Artificial fertilizers, disinfectants and cleansers for milking utensils, petrol, diesel oil.

Sensitizers. Rubber (boots, gloves, milking machines), cement, local remedies for veterinary use, wood preservatives, plants, pesticides, antibiotics in animal feeds, penicillin for mastitis, nickel and cobalt in fertilizers, cobalt and vitamin K_3 in animal feeds, ethoxyquin (preservative) in feed, quinoxaline and derivatives (growth factor), dinitolmide (anticoccidiosis), phenothiazine sedatives, soil disinfectants.

Contact urticaria. Animal hair and dander.

Artists [16,17]

Irritants. Solvents, clay, plaster.

Sensitizers. Turpentine, cobalt–nickel pigments and chromium pigments, azo and phthalocyanine dyes, colophony, epoxy, acrylic and formaldehyde resins.

Automobile and aerospace industries [18–20]

Irritants. Solvents, oils, cutting oils, paints, glass fibre, carbon fibre, hand cleansers.

Sensitizers. Chromate (primers, anticorrosives, oils and cutting oils), nickel, beryllium, cobalt, rubber, epoxy and acrylic resins, dipentene in thinners.

Baking and pastry making [21–25]

Irritants. Flour, detergents.

Sensitizers. Citrus fruits, flour improvers, thiamine, spices (cinnamon, cardamom), essential oils, azo dyes, fat preservatives (lauryl gallate), sodium carboxymethyl cellulose.

Contact urticaria. Flour, spices, essential oils, α-amylase.

Bartenders [26–28]

Irritants. Detergents, citrus fruits.

Sensitizers. Flavouring agents, citrus fruits, antibacterials in detergents, nickel.

Bathing attendants [29,30]

Irritants. Detergents, free or combined chlorine/bromine.

Sensitizers. Antimicrobial agents, sodium hypochlorite, formaldehyde, essential oils.

Contact urticaria. Sodium hypochlorite.

Bookbinders [31,32]

Irritants. Glues, solvents, paper.

Sensitizers. Glues, formaldehyde, plastic monomers, size (colophony, maleopimaric acid).

Building trade [33–36]

Irritants. Cement, chalk, fly ash, hydrochloric and hydrofluoric acids, glass wool, wood preservatives (also phototoxic), organic tin compounds.

Sensitizers. Cement and fly ash (chromate, cobalt), rubber and leather gloves, additives in shale oils, glues (phenol- or urea-formaldehyde resins), wood preservatives, teak, glass wool impregnated with phenol-formaldehyde resin, epoxy resin, polyurethanes, rubber strip seals, jointing materials.

Butchers [24,37–40]

Irritants. Detergents, meat, entrails.

Sensitizers. Nickel, colophony (sawdust), antiseptics, hardwood knife handles, meat.

Contact urticaria. Meat, blood.

Canning industry

Irritants. Brine, syrup, prawns and shrimps.

Sensitizers. Asparagus, carrots, preservatives (hexamethylenetetramine in fish canning), rubber gloves.

Contact urticaria. Fruit, vegetables, prawns, shrimps.

Carpenters, cabinet makers [41–45]

Irritants. French polish, solvents, glues, cleansers, wood preservatives (also phototoxic), glass fibre.

Sensitizers. Exotic woods (teak, mahogany, rosewood, etc.), glues, polishes, turpentine, nickel, rubber (handles), plastics, colophony, and epoxy, acrylic, formaldehyde and isocyanate resins.

Chemical and pharmaceutical industry [46–50]

Irritants and sensitizers are numerous and specific for each workplace. Halogenated chemical intermediates are frequent sensitizers.

Cleaning work [51,52]

Irritants. Detergents, solvents.

Sensitizers. Rubber gloves, nickel, formaldehyde, perfumes.

Contact urticaria. Rubber gloves, perfumes, alcohols.

Coal miners [53–56]

Irritants. Stone dust, coal dust, oil, grease, hydraulic fluid, wood preservatives, cement, powdered limestone and anhydrous calcium sulphate.

Sensitizers. Rubber (boots), face masks, explosives, chromate and cobalt in cement.

Cooks, catering industry [2,24,57–61]

Irritants. Detergents, dressings, vinegar, fish, meat, fruit and vegetable juices.

Sensitizers. Fruit and vegetables (onions, garlic, lemons, lettuce, artichokes), hardwood knife handles, spices, formaldehyde, rubber gloves.

Contact urticaria. Meat, fish, fruit, vegetables.

Dentists and dental technicians [51,62–64]

Irritants. Soap, detergents, plaster of Paris, acrylic monomer, fluxes.

Sensitizers. Local anaesthetics (tetracaine, procaine), mercury, rubber, UV-curing acrylates, aromatic epoxy acrylates, aliphatic acrylates, melamine-formaldehyde resin, BAC-esterchloride, disinfectants and sterilants (formaldehyde, glutaraldehyde, eugenol), nickel, epoxy resin (filling), periodontal dressing (balsam of Peru, colophony, eugenol), catalysts (methyl-*p*-toluenesulphonate and methyl-1,4-dichlorbenzenesulphonate) in impression and sealant materials.

Contact urticaria. Saliva, rubber gloves.

Dyers [3,34,65–68]

Irritants. Solvents, oxidizing and reducing agents, hypochlorite, hair removers.

Sensitizers. Dyes, chromate, formaldehyde.

Electricians [1,69]

Irritants. Soldering flux.

Sensitizers. Soldering flux, insulating tape (rubber, colophony, tar), rubber, nickel, bitumen, epoxy resins, glues (phenol-formaldehyde), polyurethanes.

Electronics industry [70–72]

Irritants. Soldering flux, organic solvents, HF, fibreglass, antistatic agents.

Allergens. Soldering flux, chromate, cobalt, nickel, epoxy resins, anaerobic acrylic sealants.

Contact urticaria. Soldering flux.

Enamel workers [73]

Irritants. Enamel powder.

Sensitizers. Chromate, nickel, cobalt.

Fishing [57,74–78]

Irritants. Wet work, friction, oils, petrol, redfeed from mackerel, fish juice (polypeptides).

Sensitizers. Tars, organic dyes in nets, rubber boots, rubber gloves, marine organisms (Dogger Bank itch) and plants.

Contact urticaria. Fish, marine organisms and plants.

Floor layers [1,79]

Irritants. Solvents, detergents, cement (can be ulcerative).

Sensitizers. Chromate (cement), epoxy resin, glues (phenol- and urea-formaldehyde), exotic woods, acrylates, varnish (urea-formaldehyde), polyurethanes.

Florists, gardeners, plant growers [80–84]

Irritants. Manure, bulbs, fertilizers, pesticides.

Sensitizers. Plants (*Primula obconica*, chrysanthemum, Asteraceae (Compositae), weeds, tulips, narcissus, daffodils, alstroemeria), formaldehyde, pesticides, lichens.

Food industry [24,25,57,59,61]

Irritants. Detergents, vegetables.

Sensitizers. Rubber gloves, spices, vegetables, fruits, preservatives.

Contact urticaria. Vegetables, fruits, meats, fish.

Foundry work [1,34,85]

Irritants. Oils, phenol-formaldehyde resins.

Sensitizers. Phenol- and urea-formaldehyde resins, furan and epoxy resins, chromate (cement, gloves, bricks).

Glaziers [1]

Sensitizers. Rubber, epoxy resin, hardwoods.

Hairdressers and barbers [2,51,86–90]

Irritants. Shampoos, soaps, permanent-wave liquids, bleaching agents.

Sensitizers. Hair dyes, rubber, nickel, perfumes, lanolin, thioglycolates, cocamidopropylbetaine.

Contact urticaria. Ammonium persulphate, henna, rubber gloves.

Histology technicians [1,91,92]

Irritants. Solvents, formaldehyde.

Sensitizers. Formaldehyde, glutaraldehyde, organic dyes, epoxy resin, acrylates, D-limonene.

Hospital workers [51,52,93–96]

Irritants. Disinfectants, quaternary ammonium compounds, hand creams, soaps, detergents.

Sensitizers. Rubber gloves, formaldehyde, chloroxylenol, penicillin, cephalosporins, streptomycin, neomycin, piperazine, phenothiazines, hand creams, nickel, glutaraldehyde, acrylic monomer, nitrogen mustard, local anaesthetics, propacetamol.

Contact urticaria. Rubber gloves, cisplatin.

Housework [59,61,97]

Irritants. Detergents, solvents, polishes, wet work, vegetables.

Sensitizers. Rubber (gloves), nickel, chromate, flowers and plants, hand creams and lotions, handles of knives and irons, oranges, balsams, spices, pyrethrum.

Contact urticaria. Vegetables, fruits, meats, fish, spices, rubber gloves.

Jewellers [1,98,99]

Irritants. Solvents, fluxes.

Sensitizers. Nickel, epoxy resins, enamels (chromate, nickel, cobalt), precious metals.

Masons [33,100]

Irritants. Cement, chalk, bricks, acids.

Sensitizers. Chromate and cobalt in cement, rubber and leather gloves, epoxy resin, hardwoods.

Mechanics [1,18,101,102]

Irritants. Solvents, detergents, degreasers, lubricants, oils, cooling system fluids, battery acid, soldering flux.

Sensitizers. Rubber, chromate, nickel, epoxy resin, polyester resin, D-limonene.

Metal workers [1,34,103,104]

Irritants. Cutting and drilling oils, hand cleansers, solvents.

Sensitizers. Nickel, chromate (antirust agents and dyes, welding fumes), cobalt, colophony (tall oil), antibacterial agents and antioxidants in cutting oils, and chromate, cobalt and nickel in used cutting oils.

Office workers [1,105–109]

Irritants. Photocopy paper, fibreglass, indoor climate.

Sensitizers. Rubber (erasing rubber, mats, cords, finger stalls), nickel (clips, scissors, typewriters), copying papers, glue, felt-tip pen dyes.

Painters and handymen [1,99,110–113]

Irritants. Solvents, turpentine, thinner, emulsion paints, wallpaper adhesive, organic tin compounds.

Sensitizers. Turpentine, dipentene, D-limonene, cobalt (dyes, driers), chromate (green, yellow), polyurethane, epoxy and acrylic resins, triglycidyl isocyanurate, glues (urea- and phenol-formaldehyde), varnish (colophony, urea-formaldehyde), preservatives in water-based paints and glues (methylol-chloroacetamide, chloroacetamide), polyester paint pigments.

Performing artists [114–117]

Irritants. Mechanical, sweating.

Sensitizers. Cosmetics, colophony, nickel, hardwoods.

Photography [1,118,119]

Irritants. Alkalis, reducing and oxidizing agents, solvents.

Sensitizers. Metol (*p*-aminophenol), colour developers (azo compounds), chromate, formaldehyde, PBA-1.

Plastics industry [120,121]

Irritants. Solvents, styrene, oxidizing agents, acids.

Sensitizers. Low-molecular-weight raw materials, hardeners, additives, dyes, styrene.

Plating–electroplating (and electroforming) [1,34,122–126]

Irritants. Metal cleaners, alkalis, acids, detergents, heat, dust from metal blasting.

Sensitizers. Nickel, chromate, cobalt, mercury, gold, rhodium, rubber gloves.

Plumbers [1,127,128]

Irritants. Oils, soldering flux, hand cleansers.

Sensitizers. Rubber (gloves, packing, hoses), nickel, chromate (cement, antirust paint), epoxy resin, hydrazine, epichloro-hydrin (solvent cement).

Printers [1,34,129,130]

Irritants. Solvents, acrylates in radiation-curing printing inks and lacquers.

Sensitizers. Nickel, chromate, cobalt, formaldehyde, isothiazolinones, colophony, paper finishes, glues, turpentine, azo dyes, acrylates, etc., in radiation-curing printing inks, lacquers and printing plates, rubber gloves.

Radio and television repair [1,34]

Irritants. Soldering flux, solvents.

Sensitizers. Soldering flux (hydrazine, colophony), epoxy resin, nickel, chromate.

Restaurant personnel [59,61]

Irritants. Detergents, vegetables, citrus fruits, shrimps, herring.

Sensitizers. Nickel, spices, vegetables, hardwoods (knife handles).

Contact urticaria. Vegetables, fruits, meats, fish.

Road workers [1]

Irritants. Sand–oil mix, asphalt (phototoxic), hand cleansers.

Sensitizers. Cement, gloves (leather, rubber), epoxy resin, tar, chromate in antirust paint.

Rubber workers [131–134]

Irritants. Talc, zinc stearate, solvents.

Sensitizers. Rubber chemicals, organic dyes, tars, colophony, chromate, cobalt, phenol-formaldehyde resin.

Sheet metal workers [34,135,136]

Irritants. Solvents, paints.

Sensitizers. Chromium in paints and on zinc-galvanized sheets, glues.

Shoemakers [1,137–139]

Irritants. Solvents.

Sensitizers. Glues (PTBPF resin), leather (formaldehyde, chloroacetamide, chromate, dyes), turpentine, rubber, colophony, bisphenol A.

Shop assistants [140]

Irritants. Detergents, vegetables, fruit, meats, fish.

Sensitizers. Nickel, colophony (price labels).

Contact urticaria. Vegetables, fruits.

Tanners [1,34,141–143]

Irritants. Acids, alkalis, reducing and oxidizing agents.

Sensitizers. Chromate, formaldehyde, glutaraldehyde, vegetable tanning agents, finishes, anti-mildew agents, dyes, resins.

Contact urticaria. Formaldehyde.

Textile workers [1,67,142,144,145]

Irritants. Solvents, bleaching agents, fibres, formaldehyde.

Sensitizers. Finishes (formaldehyde resins), dyes, mordants, caprolactam, nickel, diazo paper.

Contact urticaria. Formaldehyde.

Veterinarians [51,146–149]

Irritants. Hypochlorite, quaternary ammonium compounds, cresol, rectal and vaginal examinations of cattle.

Sensitizers. Rubber gloves, antibiotics (penicillin, streptomycin, neomycin, tylosin tartrate, virginiamycin), antimycotic agents, mercaptobenzothiazole (MBT) in medicaments, glutaraldehyde, preservatives in rectal lubricants.

Contact urticaria. Animal hair and dander, obstetric fluids, animal tissues, rubber gloves.

Welders [1,34]

Irritants. Oil.

Sensitizers. Chromium (welding fumes, gloves), nickel, cobalt.

Woodworkers [42,43,150–153]

Irritants. Woods, wood preservatives, solvents, detergents, fibreboard (urea-formaldehyde resin).

Sensitizers. Woods, wood preservatives, colophony, turpentine, balsams, tars, lacquers, glues (urea, phenol- and PTBP-formaldehyde resins), *Frullania*, lichens.

Contact urticaria. Woods.

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Chapter 22

Mechanical and Thermal Injury

C.T.C. Kennedy & D.A.R. Burd

[C.T.C. Kennedy, pp. 22.1–22.66]

The skin is constantly subjected to both internal and external mechanical forces, so that for experimental purposes it may be impossible to determine what constitutes the normal resting state. These forces are likely to be as important in the maintenance of the structural integrity of the connective tissues of the skin [1,2] as they are with bone, which becomes demineralized during the protracted absence of normal gravitational force during space travel [3]. In contrast to events in the whole organism, isolated human dermal fibroblasts in culture make more collagen when subjected to reduced gravity [4]. Many normal biochemical functions of the skin are dependent on appropriate mechanical forces, and when these become excessive, as in lymphoedema, protease inhibitors are released with many deleterious consequences [5].

Healthy skin is well adapted to resist the adverse effects of a wide range of mechanical injuries [6]. These include friction, pressure, contusion, laceration, suction and vibration. The clinical consequence of injury will depend on characteristics of the noxious stimulus, such as its intensity and duration. Factors related to the skin also influence the response; thus, the same degree of friction may produce a blister in one person but no visible change in another. Time is required for adaptive responses, such as callus formation and lichenification, to occur.

Determinants of the response to injury

It is likely that racial and genetic factors have a major role in determining the responses to mechanical forces. At extremes of age, the skin has a reduced ability to withstand shear and other forces. Body site can determine how the skin responds, for example friction blisters do not occur on loose skin. The presence and degree of subcutaneous fat will influence the effect of pressure on the skin.

The physiological status of the skin that is being subjected to injury can have a major effect; for example, a moderate degree of sweating hydrates the stratum corneum and increases the coefficient of friction, whereas higher levels of sweating sufficient to produce free fluid on the surface markedly reduce the coefficient of friction. Environmental temperature is also important, as is humidity, the stratum corneum becoming brittle and inelastic when humidity is reduced. The withdrawal response to noxious stimuli is impaired by neurological disorders, such as syringomyelia, and as a result burns and other injuries are common in patients with neurological deficits. Some systemic diseases can result in a qualitatively different response to injury, for example the dermopathy of diabetes, and debilitating disease will increase susceptibility to pressure. The defective organization of the dermal–epidermal junction or of the superficial dermis seen in the mechanobullous disorders predisposes to blister formation with trivial trauma, and individuals with disorders of the connective tissue, such as Ehlers–Danlos syndrome and Marfan's syndrome, show abnormal fragility to mechanical injury. Some drugs, notably corticosteroids and d-penicillamine, can modify the structural integrity of the skin. Occasionally, structural changes in the skin protect patients from mechanical injury. In amyotrophic lateral sclerosis, pressure ulcers occur less than in comparably bedridden patients, probably because of more dense packing of collagen fibrils [7]. Finally, there seem to be reproducible differences in response between individuals that are poorly understood.

The discussion of mechanical and thermal injury to the skin in this chapter is limited to those effects that may concern the dermatologist. Some conditions are discussed elsewhere; for example, self-inflicted trauma (see Chapter 61) and the effects of cold (see Chapter 23). The therapeutic uses of pressure applied to the skin for venous hypertension (see Chapter 50), lymphoedema (see Chapter 51) and hypertrophic scars (see Chapter 46) are discussed in other chapters.

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Isomorphic (Koebner) response

Definition. The development of lesions in previously normal skin that has been subjected to trauma [1,2]. The response should be reproducible and not limited to one type of trauma. The term Koebner response is best not used when a dermatosis occurs resulting from the spread of an infective agent (e.g. molluscum contagiosum or warts); for this phenomenon, the term *pseudo-Koebner* could be used. In the 'reverse' Koebner response, trauma to a lesion results in it resolving.

It differs from the *isotopic response* [3,4], in which a dermatosis occurs at the site of a previous healed and unrelated dermatosis; this is not within the scope of this chapter.

History. Koebner originally described the localization of psoriasis to skin injured by a wide range of stimuli [1] but the term has been used for a similar phenomenon in other diseases [2].

Aetiology. Many forms of physical trauma, including friction, pressure, incision and laceration, skin grafting, bites, vaccination skin tests, burns, freezing, and ultraviolet (UV) and ionizing radiation have been implicated; in addition, many infections of the skin and dermatoses have been associated with the Koebner response.

Pathogenesis. Underlying mechanisms have been most intensively studied in psoriasis (Fig. 22.1) [5] in which it seems that the epidermis and dermis both contribute [6], but epidermal damage is probably a critical event [7]. There is an increased influx of CD4 lymphocytes [8] and local production of cytokines and adhesion molecules are likely to be important. Little is known about the pathogenesis in other conditions in which the Koebner phenomenon occurs.

Clinical features. A dermatosis develops at a site of trauma. In psoriasis, the Koebner response occurs in about 20% of patients, but reported series vary widely [5]; the latency is about 10–14 days, and a Koebner response is more likely to occur when the disease is active. As well as in psoriasis [9], the Koebner response is often seen in lichen planus [2] and vitiligo [10–13]. It has been well

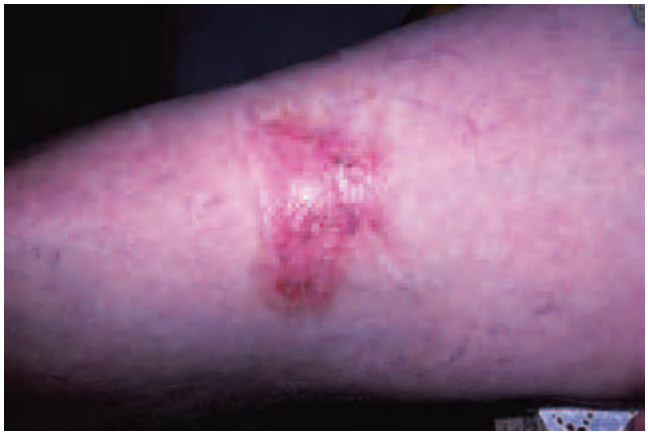

Fig. 22.1 Histologically proven psoriasis appearing in a split-skin donor site. (Courtesy of Southmead Hospital, Bristol, UK.)

Table 22.1 Diseases showing the Koebner response.

Carcinomas	Fisher *et al*. [14]
Darier's disease	Penrod *et al*. [15]
Erythema multiforme	Huff and Weston [16]
Hailey–Hailey disease	Morales *et al*. [17]
Leukaemia	Koizumi *et al*. [18]
Lichen planus	(Chapter 42)
Lichen sclerosus	Todd *et al*. [19]
Scleromyxoedema	Durani *et al*. [23]
Multicentric reticulohistiocytosis	Aldridge *et al*. [26]
Necrobiosis lipoidica	Gebauer & Armstrong [21]
Perforating collagenosis and folliculitis	Jelinek [22]
Psoriasis	Farber *et al*. [9]
Myxoedema, pretibial	Missner *et al*. [20]
Vasculitis	Green & Narajan [24]
Vitiligo	Sweet [10]
Xanthoma	Miwa & Kanzaki [25]

recorded in many other diseases, some of which are shown in Table 22.1 [14–26].

It is controversial whether it is appropriate to use the term Koebner phenomenon for the pustular response to injury in Behçet's disease and pyoderma gangrenosum; this is usually termed pathergy (see Chapter 49). Kaposi's sarcoma is still sometimes included, although some cases could be an example of pseudo-Koebner response caused by Kaposi's sarcoma-related herpesvirus [27] and others are examples of the isotopic response [28].

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Nikolsky sign

This well-known effect of shearing trauma was originally described as evoking lesions of pemphigus foliaceus but may be positive in other bullous diseases (see Chapter 41).

Utilization of mechanical stimuli [1]

Selective use may be made of mechanical stimuli to confirm the diagnosis or to allow for biopsy of early lesions in conditions in which dynamic changes and secondary effects occur rapidly. Simple frictional trauma, such as that caused by twisting a rubber-tipped pencil on the skin, can be used to facilitate accurate diagnosis of mechanobullous diseases.

The Nikolsky and Koebner phenomena may be used to study the early changes in diseases in which they are characteristic and can be of value in the diagnosis of pemphigus when patients are already on treatment and immunofluorescent techniques are not available [2]. The pustular reaction to skin puncture (including venesection) is evidence of an active stage of Behçet's syndrome. Suction [3,4] evokes bullous diseases and may produce petechiae in scurvy, etc. It has also been used to study vasculitis [5,6].

Firm stroking of the skin may elicit purpura in amyloidosis, is routinely used to diagnose dermographism, and has also been used to study the early lesions of vasculitis [7] and to confirm a diagnosis of delayed pressure urticaria [8].

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Biomechanical considerations [1–3]

Resistance to various mechanical stimuli, both external and arising within the body, is a fundamental property of the skin. External forces include friction, stretching, compression, vibration and penetration. The major mechanical properties of skin are stiffness (resistance to change of shape), elasticity (ability to recover the initial shape after deformation) and viscoelasticity (see below). Quantification of the behaviour of skin subjected to mechanical forces is complicated by many factors. The skin is composed of not one but multiple and interrelated functional components, and its behaviour is subject to the confounding effects of physiological phenomena, such as the previous experience of the tissue, nutritional status, sweating and sebum excretion. Other variables of practical relevance [4] are related to body site, age, sex and disease—not only cutaneous disease but also systemic (e.g. diabetes). In addition, the mechanical properties of the skin may be profoundly influenced by environmental factors such as UV and heat radiation.

The generation of mechanical forces within the skin and subcutis has long been of interest to surgeons, with early contributions by Langer on the oval shapes produced when round punctures are made in the skin, and the recognition of relaxed skin tension lines [5]. The mechanical qualities of skin, especially creep, are critical to understanding expansion techniques used in dermatological surgery [6]. The effects of mechanical forces have also been studied extensively in relation to wound healing and the consequences of excess fluid in tissues [7].

In vitro studies have shown that application of mechanical stress results in increased DNA synthesis [8], production of collagen and proteoglycans [9], non-collagenous proteins [10] and cytoskeleton formation. Application of mechanical force intermittently results in more cellular activity than a constant force [11]. Wounds that heal under some stress have greater strength than those where there is no stress [12].

The importance of weight bearing on bones for their normal structural integrity was recognized long ago, and the stress imposed by gravitational forces is also important for the maintenance of dermal constituents [13].

A quantitative analysis of mechanical properties of skin and subjacent tissues must begin from engineering principles [1,14]. Most studies involve the measurement over time of deformation produced by a given constant force. The force is standardized as force per unit area or 'stress'. Stresses perpendicular to the surface are termed normal, whereas those in other directions are termed shearing stresses. The change in dimensions may be expressed as 'strain' and is the ratio between the deformation and the original length. Many elastic materials show a linear relationship between stress and strain, for example:

Stress = Young's modulus × strain.

Similarly, linear viscous liquids obey Newton's law in which stress is directly proportional to the rate of strain but independent of the strain itself. Many biological materials combine the characteristics of elastic solids and viscous liquids and are termed viscoelastic. Skin, in common with other viscoelastic materials, has non-linear stress–strain properties and has time-dependent behaviour even with low loads [15]. The best known of these are the properties of hysteresis (in which the stress–strain relationships are different between loading and unloading), stress relaxation (the stress resulting from a constant strain decreases with time) and 'creep' (increasing strain or length of the material when a constant stress is maintained). These time-dependent properties are thought in part to be a function of the ground substance. Furthermore, skin shows anisotropic properties; there is a systematic and regular directional variation in its mechanical and viscoelastic properties. The elastic component is broadly analogous to a linear spring and the viscous component to a dashpot shock absorber.

Much of the earlier work on the mechanical properties of the skin was carried out on tissues or their components (collagen, elastin, etc.) *in vitro* [1,16–18]. Strength-related values such as breaking strain, time-dependent creep and non-time-dependent parameters, such as elasticity and viscosity, have been measured, but these studies can be unhelpful in predicting the behaviour of whole skin *in vivo*.

The principal source of mechanical strength in the skin and subcutis is the reticular dermis; the papillary and periadnexal dermis (often known as adventitial dermis) and the connective tissue running between fat lobules to deeper structures have somewhat similar and lesser capacity to resist deformation [19], and it is likely that the epidermal components are only relevant in resisting relatively minor forces [2]. At a molecular level, it is the properties of collagen, usually of types I and III and its relationship with elastic fibres and ground substance, that determine the mechanical responses of skin.

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Mechanical properties of the skin

Methods of evaluation [1–3]

Many methods have been used to derive information about mechanical properties of the skin. Most methods measure properties of the dermis, although some give information predominantly about the stratum corneum [4,5], and all have limitations.

1 Tensile tests, in which the skin is extended by applying a force parallel to the surface [6–16]
2 Torsional tests, in which force is used to rotate a disc glued to the skin [3,17–22]
3 Vertical traction [4,23–25]
4 Indentation [5,24–29]
5 Suction within a cup pressed on the skin [30–37]
6 Vibration, for example using the hammer of a ballistometer [38–41]
7 Elastic wave propagation [42]
8 Hardness, using a durometer [43,44].

Because of problems with standardization of methods, results are usually not comparable between investigators. Details of methodology, such as the area of skin subjected to suction, are of great importance in understanding which zone of the skin is being evaluated. Results should always be standardized for skin thickness [45,46]. One of the few studies that has directly compared different methods concluded that the suction cup device mainly measures elasticity whereas the ballistometer predominantly measures stiffness [47].

Some of the measurements that can be derived from *in vivo* methods such as torsion [45] and suction [46] can be expressed as ratios, obviating the dependence on skin thickness, and give useful information about the elastic and viscoelastic properties of skin (Fig. 22.2). Despite their shortcomings, the various methods used have led to a general understanding of the mechanical properties of the skin, and quantification of some of these properties has proved useful in the recognition of pathological changes in connective tissues before they have become clinically apparent [1].

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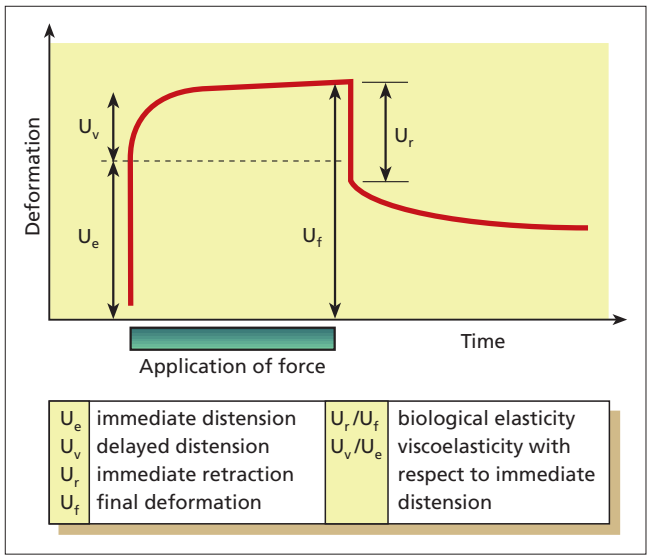

Fig. 22.2 Deformation of skin by an applied force showing how elastic and viscoelastic properties can be deduced from ratios of measurements.

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Determinants

Stratum corneum

The main function of the stratum corneum is to provide a limited barrier across which exchanges occur with the

environment. *In vivo* it is criss-crossed by a series of depressions outlining polygonal zones. This pattern is anisotropic and related to the anisotropy of the underlying dermis. When subjected to stretch it is only slightly extensible [1], deformation occurring by flattening out or redistribution of these depressions [2]. These changes cause secondary alterations in shape of the cells in the Malpighian layer and the underlying papillary dermis [2]. The elastic modulus of the individual corneocyte is far higher than of the complete stratum corneum, suggesting that the biomechanical properties of the latter are largely a function of the substances binding the cells to each other [3,4].

The extensibility of the stratum corneum is greatly influenced by the relative humidity and its state of hydration [4–9].

Frictional contact with the stratum corneum is an essential prerequisite for tactile sensation and many physical activities. It is also a cause of a variety of acute and chronic injuries to the skin. The stratum corneum behaves as a viscoelastic membrane when subjected to frictional force. The major component producing friction is a tendency to adhesion at the surface. In general, frictional resistance increases with the state of hydration, although free water or sebum on the surface reduces resistance. The contribution of the stratum corneum towards skin biomechanics can be seen in studies evaluating the effect of moisturizers and emollients. Extensibility and creep were both rapidly increased by water and paraffin oil, and glycerine more slowly; water only had a very short-term effect [10]. Chemical modification of stratum corneum proteins (e.g. by glutaraldehyde) can also reduce frictional resistance [11].

Basement-membrane region

This has been evaluated mainly by suction devices, which can split the skin in this region. It is likely that the basement-membrane region has a relatively minor role in the overall mechanical integrity of the skin [12], although abnormalities of structural components such as laminin 5 in the lamina lucida cause marked weakening of the skin in some types of junctional epidermolysis bullosa.

Dermis

The dermal collagen bundles are an intermeshing network of undulating fibres (see Chapter 3). Although electron-microscopic studies show the bundles running in all directions, in the reticular dermis the predominant direction is parallel with the skin surface, and in the adventitial dermis and subcutis the alignment is perpendicular to the surface. The initial response to deformation is a straightening of the collagen bundles and realignment of the straightened fibres in the direction of the applied force; beyond this, extension may occur through slip between fibrils, a process opposed by the closely associated glycosaminoglycans (see Chapter 3). Elastic fibres are responsible for returning the collagen to its predeformation state, particularly with low levels of load [13]. Elastin is the only mammalian protein with truly elastic properties. The interdependence of elastic tissue and collagen has been demonstrated in experiments using selective removal [14].

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Physiological variation

Age

From about the age of 35 years in women and 45 years in men, the thickness of skin decreases with ageing on light-protected sites and the dermal–epidermal junction becomes flatter [1–4]. Many studies, using a variety of techniques, have evaluated the skin at different ages (reviewed in [5]). Although there are some conflicting results, overall there is agreement that there is a decrease in elastic properties with age. It seems likely that there is increasing resistance by the dermis to traction parallel to the skin surface, at least until the age of 60 years, but vertical resistances at the dermal–epidermal junction and within the dermis and subcutis progressively fall. Using a

device for propagation of low amplitude shear disturbances it has been shown that there is a progressive increase in viscosity of the skin with age [6].

Sex

Again, no clear answer emerges as to whether there is a difference between sexes, except for skin thickness after menopause. Some methods have shown that female skin is more extensible [7–9], although others have failed to confirm this [1,10,11]. The increase in extensibility from hydration of the stratum corneum may be greater in women than men [12]. Hormone replacement therapy appears to alleviate increased slackness of the skin associated with the menopause [13].

Body site

There are great differences between body sites, mainly because of differences in skin thickness [3,14]. When this is corrected for, skin distensibility and elasticity are lower in the acral areas than centrally, and are subject to diurnal variation, with elasticity increasing in the evening [15]. These properties contribute resistance to gravitational oedema formation, and are diminished in the elderly.

Using a small suction device, the ratio between viscous deformation and elastic deformation and the biological elasticity (i.e. the ratio between immediate recovery and total deformation) was lower in vulva than in forearm skin [16].

Light exposure

Chronic sun exposure produces a decrease in extensibility, elastic recovery and elastic modulus. The higher the melanin content, the lower the differences between sun-exposed compared with sun-protected sites [17]. Sun-exposed facial dermis has both increased thickness and decreased parameters of elasticity [18].

Pathological variation

Various *in vivo* techniques have been used to measure mechanical properties of the skin in disease states over a period of time. In some situations, the abnormalities have predated the clinical changes. Such measurements clearly have application for monitoring therapy [19]. Examples include scleroderma [20–23] and its treatment by d-penicillamine [24,25]; the decreased distensibility but unaltered elasticity of scleroderma of Buschke [26,27]; the consequences of corticosteroid atrophy [28,29]; the waxy skin of diabetics [30]; reduced extensibility (photosclerosis) resulting from psoralen and UVA (PUVA) therapy [31–33]; an acute increase in elasticity during radiotherapy [34] and the gravitational syndrome [35]. In lymphoedema there is reduced viscoelasticity [36]. Chronic haemodialysis produces some impairment of the viscous properties similar to those of ageing [37]. Useful correlations have emerged between biomechanical and genetic differences in diseases of connective tissue such as pseudoxanthoma elasticum [38] and Ehlers–Danlos syndrome [39–41]. Smoking can cause facial wrinkling [42] but the biomechanical correlates have not been defined.

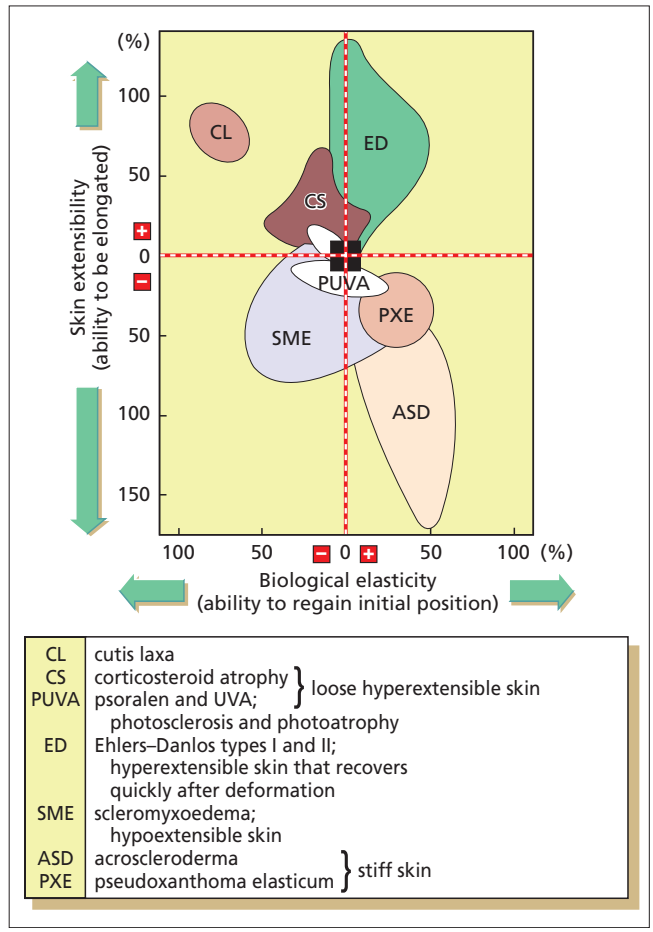

Fig. 22.3 Rheological properties of some conditions affecting the dermis. Each area represents data from several patients. (From Piérard *et al*. [33].)

Piérard *et al*. [31] have studied the ability of skin to be elongated (skin extensibility) and its capacity to regain the initial position after deformation (biological elasticity) in a number of disease states: their findings are used in Fig. 22.3 to illustrate the principles outlined in this section.

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Effects of friction

Friction is defined as the resistance that any body meets in moving over another. Humans cannot function without friction between themselves and the environment, although even mild degrees of friction can cause distress, as in the unpleasant sensation that wool can induce for an atopic subject. Excessive frictional forces will cause injury, which may be acute, occurring in seconds or minutes, or chronic as a result of repeated, lesser degrees of friction. The response of the skin will depend on the magnitude and duration of the frictional force applied and properties of the skin itself. Abrasions and friction blisters are examples of acute frictional trauma, but blisters can only form if the stratum corneum is tough and thick enough to form a blister roof. Friction blisters are therefore difficult to produce except on the palms and soles [1]. The chronic effects of friction are dependent on adaptive responses, in particular a steady rate of increase in epidermal turnover, and perhaps the laying down of thickened, vertically orientated collagen bundles in the papillary dermis, as seen in lichenification. The best defined clinical consequences of chronic frictional injury are calluses and corns, but various forms of dermatitis are perpetuated and perhaps initiated by friction (see below).

The scientific study of friction-induced injury has largely been directed towards understanding friction blister formation. The laws of static friction state that frictional resistance is: (i) directly proportional to load; and (ii) independent of the area of contact between the surfaces [2]. The ratio between the force necessary to move one surface over the other and the load between the two surfaces is thus a constant, called the coefficient of friction. The static coefficient of friction is the force required to start one object in motion past another and the dynamic coefficient is the force required to sustain the motion of

one object past another. Because of its viscoelastic properties, skin deviates from Amonton's laws. Several different techniques have been used to measure friction [1–12]. Coefficients of static and dynamic friction have been determined for a number of materials in contact with human skin, with and without lubricants, but there is great individual variation [1,2,13,14]. Of the various anatomical sites measured, the palm of the hand has the highest coefficient of friction [15]. A number of machines to simulate repetitive rubbing have been devised, but there is no entirely satisfactory model for chronic frictional injury [6].

Physiological changes, such as the degree of hydration, have a large effect—very dry or wet skin having a much lower frictional resistance than moderately hydrated skin [16] for most sites but not for the dorsal forearm or lower back [17]. Skin surface lipids have relatively little effect [18]. Petrolatum initially decreases the coefficient of friction because of its lubricating property but then increases it because of its occluding effect on skin, causing increased hydration [14]. Age and sex have no significant effect on frictional properties of the skin, but body site is important; the forehead and behind the ear have the highest dynamic coefficient of friction and the abdomen the lowest [17]. The rough skin in atopics has a lower coefficient of friction than normal [10].

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Callosities, corns and calluses

Definition [1]. A callosity is a plaque of hyperkeratosis caused by repeated friction and/or pressure. A corn is a sharply demarcated callosity occurring over a bony prominence, usually on the hand or foot, and is painful. A soft corn occurs between the toes. Podiatrists often refer to a corn as a heloma (Greek *helus*, a stone wedge). A callus is a broad-based diffuse area of hyperkeratosis of *relatively* even thickness, usually under the metatarsal heads.

Aetiology. Calluses (Fig. 22.4) and corns on the feet are usually the result of deformity, sometimes associated with dynamic changes in the function of the foot, and are often made worse or even caused by unsuitable footwear [2]. Perhaps the most extreme example of footwear causing gross abnormalities is the Chinese foot-binding syndrome, although some Western shoe fashions, such as 'winkle-pickers' and high-heeled shoes, can be similarly damaging albeit on a lesser scale [3]. Various intrinsic abnormalities of the foot predispose to callosities. These include bony prominences, a prominent condylar projection or malunion of a fracture. In some rheumatic diseases

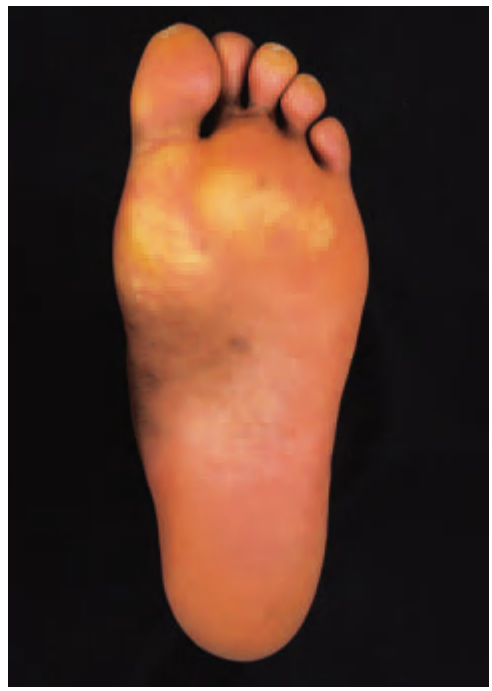

Fig. 22.4 Calluses of the forefoot.

(e.g. rheumatoid arthritis) there are distinctive patterns of callosity formation which can be predicted from the joints involved [4]. Diabetic subjects, especially those with neuropathy, are prone to callus formation, and high pressure is strongly associated with ulceration [5]. Faulty foot mechanics can occur when there is a toe deformity (claw, hammer, mallet), a short first metatarsal or hallux rigidus. The dermatologist should be aware of the effects of deformity throughout the foot. In the hindfoot, a varus or valgus position of the heel as an anatomical abnormality will lead to a failure of the foot to absorb loads applied to it during the stance phase of gait. The net result is that excessive loads are applied to the plantar skin, leading to callosities. The pattern of these changes can be very distinctive. With the hindfoot anomaly, there is often an associated forefoot deformity with excessive pronation or supination of the metatarsals, hallux valgus and fixed deformities of the lesser toes. Calluses on the edges of the weight-bearing area of the sole are often caused by shoes that are too loose.

The biomechanics of the foot that lead to callosities have been investigated in detail [6–8]. A variety of measuring devices are available to document the abnormal forces and assist design of appropriate orthoses [9].

On the dorsum of the foot, factors provoking callosities include footwear and a habit of sitting with the foot tucked under the body [10,11], with or without a prominent underlying talus.

The soft corn usually occurs when tight shoes press the condyle of a metatarsal or phalanx against the base of a phalanx on the adjacent toe.

On the hand and at other sites, callosities generally reflect repeated frictional injury which will be apparent from the history.

An inherited disposition to callosities has been described, with an autosomal dominant inheritance [12,13].

Pathology. In a callus, there is epidermal hyperplasia. The stratum corneum is thickened and compact, sometimes with parakeratosis over the dermal papillae, and there may be expansion of the granular layer. The underlying dermis may show an increase in dermal collagen and fibrosis around neurovascular bundles.

A corn differs in that there is a thick parakeratotic plug set in a cup-shaped depression of the epidermis, usually with loss of the granular cell layer.

Clinical features. These are as follows.

Feet [1,5,10–12]. On the plantar surface, the most common site for corns and callosities is over the metatarsal heads (Fig. 22.4), although the sides of the arches and heel can be involved. A callus is an ill-defined area of waxy, often yellowish thickening over which the dermatoglyphic markings may become indistinct. A corn is smaller, usually very painful, and may have a glassy centre. Corns can occur within an area of callus. On the dorsum of the foot, corns and calluses are particularly found over the interphalangeal joints and tips of the toes. A distinctive variety of callus occurs over the talus, anteromedial to the lateral malleolus [12].

In the autosomal dominant 'hereditary callosities', blisters occur at the periphery of hyperkeratotic skin [12]. This is distinct from epidermolysis bullosa, epidermolytic hyperkeratosis and blistering sometimes associated with palmoplantar keratodermas (see Chapter 34).

The soft corn is usually between the fourth and fifth toes, is typically very painful and exhibits hyperkeratosis that becomes white from maceration. A small sinus may be present, and secondary bacterial infection can then present as cellulitis.

Hands. Callosities on the hands most commonly occur as distinctive occupational stigmata in many trades and professions [14,15]. Areas of thickening most commonly occur on the palmar surface and over the metacarpophalangeal joints. The site of the callosity may be highly specific [16]. They are rarely complained of, as was shown in a survey of solid-waste handlers in whom there was a 75% prevalence of palmar calluses [17]. Unless they become fissured or infected, they should be considered as an adaptation rather than a disability.

The habit of biting or chewing the side or knuckle of the finger is not uncommon in children ('gnaw warts'). Larger callosities are sometimes seen in the mentally retarded.

Callosities on the hands caused by frictional injury against the teeth have been described in patients with bulimia nervosa as a result of repeated manual stimulation of the gag reflex [18,19]. A distinctive hyperkeratosis on the side of the thumb can occur with use of a cigarette lighter [20].

Prayer nodules [21–23]. These are seen on the forehead of Shi'ite Muslims from repeatedly touching the forehead on a prayer stone. They may also occur on the knees and ankles from the squatting position adopted by worshippers. A similar pattern has been described on the ankles from sitting cross-legged [10].

Callosities from clothing and appliances. Trusses, especially if ill-fitting, may cause circumscribed patches of hyperkeratosis and pigmentation. Pressure from calipers or reinforced shoes may cause calluses in the disabled. The effects of friction and pressure on the amputee are discussed on p. 22.29.

Diagnosis. Corns on the feet can be difficult to distinguish from viral warts, particularly when the latter have a zone of reactive hyperkeratosis around them. Corns are generally more painful when pressed vertical to the skin

surface, whereas warts are more tender when squeezed laterally between the finger and thumb. Paring down a wart usually reveals the circumscribed abnormal surface markings. Granuloma annulare occasionally resembles callosity, but can be distinguished by biopsy. Various forms of keratoderma can resemble callosities, but do not occur selectively over sites of excessive compression.

Management. The major difficulties with diagnosis lie with foot callosities. The patient's footwear and any orthoses, the gait and the alignment of the feet should all be examined. Palpation may reveal abnormal bony prominences. There may be a past history of surgery. Radiography can be helpful. Pressure studies (pedobarographs) can be helpful in evaluating foot biomechanics (reviewed in [9,24]).

The aims of treatment are to:

1 Provide symptomatic relief
2 Determine the source of abnormal mechanical stress
3 Relieve the cause by conservative means
4 Consider surgery if these fail.

Relief of symptoms caused by corns and calluses can usually be achieved by careful and regular paring. Regular paring reduces the pressure induced by corns [25]. The initial procedure is often best done with a scalpel and subsequent treatment with an abrasive device. For soft corns, the use of a toe separator (felt, foam or silicone) can provide rapid relief. Salicylic acid (10–20%) keratolytic preparations can be of some help, but care is needed to avoid irritancy.

The role of the patient's shoes in producing callosities should be carefully assessed, and appropriate corrective steps taken. Extra width may be needed, especially with the toebox. A softer upper may be needed. With marginal calluses, the shoe is likely to be too loose. The shoe may need to be adapted to receive an orthosis—a cushioning device designed to redistribute the mechanical forces causing the callosity. Examples are the metatarsal pad for localized plantar callus, and a medial wedge for the cavovarus foot. Customized shoe inlays can be moved from shoe to shoe. Another useful orthosis is the silicone sleeve that can be used on deformed toes that have corns on them.

Sometimes, conservative measures are insufficient or fail. Surgical correction of toe deformities and resection of prominent condyles causing soft corns can be rewarding. Surgery for other bony causes should only be undertaken after careful study of radiographs and pedobarographs by an orthopaedic surgeon with expertise in the field [26,27]; results can be encouraging [28,29], but can also be disappointing [30].

The principles outlined above can be applied to symptomatic callosities elsewhere, for example at sites of abnormal pressure from a limb prosthesis. Occasionally, excision is justified on cosmetic grounds, for example for athlete's nodules [31].

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Friction blisters

For friction blisters to occur, the stratum corneum must be strong enough not to be rubbed away. Usually, friction

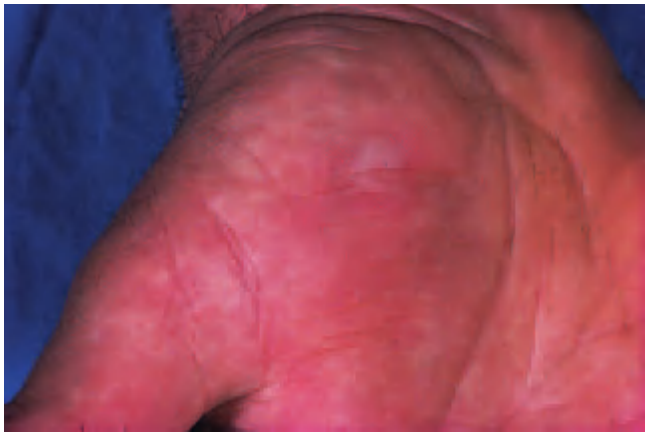

Fig. 22.5 Friction blister on the palm mimicking a target lesion of erythema multiforme. This patient had generalized pruritus caused by biliary cirrhosis, and he repeatedly rubbed his thenar eminence on his skin to relieve the itch.

blisters do not form on lax or thin skin but are common on the palm (Fig. 22.5), sole, heel or dorsum of the fingers. Frictional force and the number of times an object moves across the skin determine the likelihood of blister development; the greater the force, the fewer the number of cycles of movement needed.

Pathology [1]. The blister usually forms in the spinous layer, just beneath the stratum granulosum. The keratinocytes in the base of the blister show variable oedema and perhaps degenerative changes. Mitotic activity commences in the base within 30 h [2].

Clinical features. These are usually self-evident and seldom present diagnostic problems when the cause is known. However, a patient may seek advice when a bulla appears unexpectedly or under inappropriate circumstances. It then becomes important for the dermatologist to consider whether the trauma was merely a localizing factor in a hitherto undiagnosed congenital or acquired disease (Fig. 22.5). As well as blister formation, there may be other consequences of the inciting trauma such as callus formation, petechiae, etc.

Prognosis. Uncomplicated blisters heal rapidly.

Diagnosis. A careful history of appropriate frictional trauma will usually enable the diagnosis to be made. There are often specific aspects of the circumstances in which blisters occur that are relevant to occupational causes [3] and other situations such as sporting activities. Trauma may induce lesions in both acquired and hereditary epidermolysis bullosa. Skin fragility can occasionally be a presenting feature of systemic amyloidosis, and the blisters seen in patients comatose from neurological lesions or drug overdose can clinically resemble those caused by friction; however, they differ histologically. Occasionally, bullous insect-bite reactions and other bullous diseases can be confused with friction blisters.

Management. Preventive measures include antiperspirants [4]; some case studies have shown that these may reduce blistering in epidermolysis bullosa simplex (Weber–Cockayne) [5] and in pachyonychia congenita [6]. Although most controlled trials have not shown convincing evidence of benefit [7,8], 20% aluminium chloride hexahydrate in anhydrous ethyl alcohol used for 3 days before hiking can reduce blistering [9]; but such preparations may cause irritant dermatitis. Foot powders with the aim of absorbing moisture are another traditional approach [10], but again controlled trials show lack of efficacy [11–13].

By contrast, certain types of synthetic insole can absorb frictional force and reduce blistering, for example Spenco, a closed-cell neoprene material [14,15], and the polyurethane product Poron [16]. Acrylic socks [17] and the use of a thin polyester sock under a thick, dense outer sock [18] can reduce blistering. It is likely that subthreshold exposure of the feet to friction reduces the likelihood of blistering [19].

When blistering has occurred, drainage so as to allow the roof to adhere to the base provides relief of symptoms and optimizes healing [20]. If the blister has burst and the roof has torn away, the wound should be treated with a non-adherent dressing and protective padding. Hydrocolloid dressings have been used with success [21,22].

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Friction and dermatitis

The inflammatory changes that characterize eczematous dermatitis have been reported as a result of friction, and there are a number of eczematous conditions in which mild repetitive frictional injury has an important initiating, localizing or perpetuating role [1]. The importance of friction was recognized long ago [2], but has often been underestimated since. An experimental model has been devised [3].

Friction as a direct cause

Physical irritant contact dermatitis accounted for just over 1% of all patients attending a large contact dermatitis clinic in London, and of these about one-third were attributable to friction; low humidity was a common accompanying factor, especially for office workers [4].

Menné and Hjorth [5] described two workers repeatedly handling NCR (No Carbon Required) paper and a third whose contact was with bus tickets, who developed scaling, vesicles and occasional pustules on the areas of maximal contact; patch tests were negative. Three cases of nipple dermatitis were attributed to friction from poorly fitting brassieres [6].

Friction treatment for acne can lead to dermatitis [7].

Airbag dermatitis [8]

Although dermatitis was not proven in the histological sense, a symptomatic red rash has been described from injury from deployment of the airbag in automobiles. It is possible that talc used in the packaging plays a part as well as frictional injury. The bizarre shapes produced by the impact of the airbag can give the appearance of dermatitis artefacta [9].

Juvenile plantar dermatosis [10]

In this distinctive condition, there is a glazed, erythematous, hyperkeratotic and often fissured change on the contact areas of the anterior third of the plantar aspect of the feet (see Chapter 17).

Friction from footwear and barefoot sporting activities may be important causes, but are clearly not the only factors involved. In some series, there is a pronounced worsening in winter [11,12], whereas in others there is exacerbation in summer [13–15]. Certain types of occlusive footwear, such as the trainer shoe and rubber boots, often combined with relatively non-absorbent synthetic fibre socks, have been thought to contribute [15,16] and in some cases this may explain the seasonal effect. However, in a controlled study, children without juvenile plantar dermatosis had a similar use of trainer-type shoes as those with the disorder [17]. Up to 10% of cases have relevant contact allergy to shoe materials [10,17,18] and are clinically indistinguishable from the majority of cases, which are not caused by an allergic reaction.

Atopic dermatitis

Friction is probably one of many factors that account for the localization of atopic dermatitis, for example on the backs of the thighs in school children [19] and on the feet.

An eruption of follicular papules on the chin brought about by repeated contact with the knee has been described in Japanese children. It can resemble naevus sebaceous [20].

Contact dermatitis

Frictional injury presumably enhances percutaneous penetration of irritants and allergens. In the clinical setting, friction has been shown to have an adjuvant role in irritant dermatitis to soaps and detergents [21,22] and to cement [23], and is probably important in many other circumstances.

The induction of contact allergy is also more likely when there is concurrent mechanical trauma. In a series of 8230 patients patch tested for eczematous disorders, those who had sustained cuts, abrasions and other mechanical injuries had a much higher incidence of positive results than other groups [34]. In a number of industries, friction has been regarded as contributory to the high rate of allergic as well as irritant reactions, for example cobalt allergy in hard-metal workers [25].

Friction and nummular dermatitis

Patients sometimes attribute localization of nummular (discoid) dermatitis to repeated mild chronic frictional injury. An unusual example has been described as

shower-jet dermatitis, in which eczematous lesions were localized to an area on the front of the chest subjected to a high-pressure jet for 10–15 min/day [26].

Hyperkeratotic palmar and plantar dermatitis

Hyperkeratotic palmar dermatitis (see Chapter 17) has been described mainly in middle-aged or elderly men, and less commonly in women [27]. It may be difficult to distinguish from psoriasis, and some authors dispute its existence [28]. Chronic mechanical trauma and friction from hard manual work has been thought to be a contributory factor in some cases [1,27].

Frictional dermatitis of children

Although first described in 1956 [29], the exact status of this condition remains obscure and its prevalence undetermined. In a more recent series of cases, nearly half were atopic [30].

Aetiology. Friction from surfaces such as sand and rough carpets [31] and activities such as tobogganing [32] have been held responsible. Other authors have attributed the condition to sunlight [33] and similar cases have been described in which neither friction nor sunlight were considered to have a role [30].

Pathology. The histology shows mild non-specific changes with acanthosis, hyperkeratosis, small foci of spongiosis and a lymphohistiocytic infiltrate in the upper dermis [30].

Clinical features. An eruption of pinhead-sized pale or white papules or warty lesions occurs on the elbows, knees or backs of the hands, spreading to the adjacent areas, in children and occasionally in adolescence. Pruritus is mild. The condition may be more common in spring and summer.

Prognosis. The condition often recurs during childhood. Long-term studies have not been performed.

Treatment. A mild topical steroid or tar ointment is usually helpful.

Frictional sweat dermatitis

A spongiotic dermatitis occurring beneath undergarments during the hottest months of the year has been described from New Delhi and attributed to friction, heat and contact with sweat [34].

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Friction and other dermatoses

Frictional trauma can localize skin diseases by means of the Koebner phenomenon (p. 22.2).

Psoriasis on the palms can be difficult to distinguish from hyperkeratotic eczema, and may be localized by

repetitive exposure to friction. A relationship to occupation is not always obvious [1].

Mechanical forces, including friction, are aetiological factors in acne mechanica (Chapter 43) and in dermographism and deep pressure urticaria (see Chapter 47).

Hyperpigmentation following repetitive rubbing occurs in predisposed, usually dark-skinned individuals and has been termed frictional melanosis. It is often localized over bony prominences of the trunk and limbs [2,3]. Frictional melanosis may occur *de novo*, or may accompany or follow dermatitis [4]. A distinctive rippled pattern, which overlaps with macular amyloidosis, has been described following the use of vigorous washing practices [5,6]. In some of these subjects, superficial amyloid deposits have been found on biopsy.

Pachydermodactyly, a distinctive digital fibromatosis (see Chapter 46), has been attributed to repetitive mechanical trauma such as repeated clasping of the hands and rubbing of crossed fingers [7]. Diffuse swelling of the digits, involving dermis as well as epidermis, clearly differs from calluses, knuckle pads, etc.

Bos and de Koning [8] described a distinctive frictional dermatosis on the upper gluteal region of elderly people, characterized by skin colour or slightly red patches with a rough surface and hyperkeratotic ridges running parallel to the natal cleft. These lesions occur particularly in those who spend most of the day sitting, and superficial ulceration may be a complication. Skin biopsies showed hyperkeratosis, psoriasiform hyperplasia, 'meandering' superficial vessels and some degenerative changes in the connective tissue.

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Black heel and palm

SYN. TALON NOIR; CALCANEAL PETECHIAE

Definition. Pigmentation of the heel (or palm) secondary to extravasation of red blood cells.

Aetiology. The condition results from shear–stress rupture of the papillary capillaries, for example during violent sport, particularly where repeated jumping and sudden stopping or twisting of the heel occurs. Similar circumstances explain the occurrence on the palm.

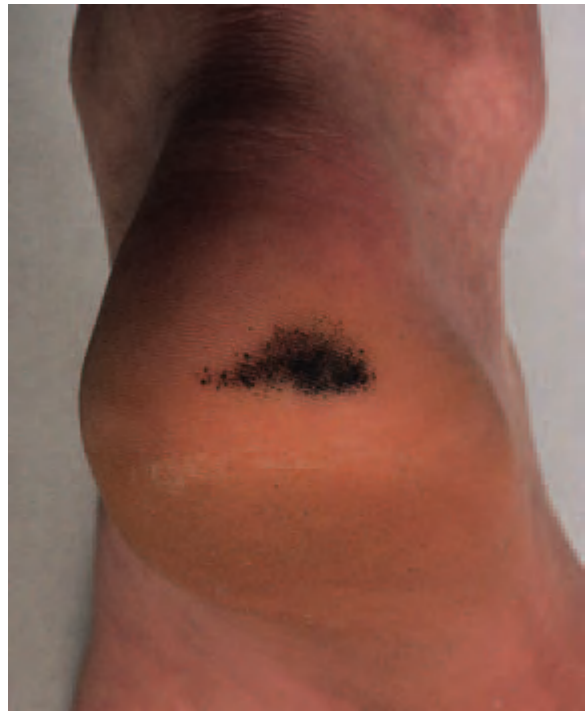

Fig. 22.6 Black heel. Stippled pigmentation within the stratum corneum.

Pathology. Extravasated erythrocytes may be found in the dermal papillae [1], but often the histological changes are limited to the stratum corneum, where amorphous yellow–brown material may be found in rounded collections having undergone transepidermal elimination. This material is often negative with Perls' stain (which stains haemosiderin) but gives a positive benzidine reaction, showing that it is derived from haemoglobin [2,3].

Clinical features. Closely aggregated groups of bluish black specks occur suddenly at the back or side of the heel (Fig. 22.6), just above the hyperkeratotic edge of the foot. The metatarsal area has, rarely, been involved. The lesion may resemble a tattoo [4] or even a melanoma [2,5].

Either sex may be affected [2], but the condition is virtually confined to athletic adolescents [6]. Football, basketball, lacrosse and, less often, tennis and squash players are mainly affected. The condition can occur on the hands of weightlifters [7].

Diagnosis. When there is a history of sudden appearance of the pigmented lesions at a typical site, diagnosis is rarely in doubt. Viral wart can also produce a black stippled

appearance because of extravasation of red cells, but the skin surface is generally abnormal. Occasionally, melanoma or atypical melanocytic hyperplasia [8] will need to be excluded. With black heel, the patient and physician can usually be reassured by carefully paring the affected area, thereby completely removing the abnormality. By epiluminescence microscopy, black heel has highly specific features [9].

Treatment. The condition is usually asymptomatic, and its importance lies in its resemblance to malignant melanoma. When in doubt as to the diagnosis, carefully paring away the stratum corneum is generally sufficient to remove the pigment.

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Pressure ulcer

SYN. DECUBITUS ULCER; BEDSORE; PRESSURE SORE

Definition. A localized area of necrosis caused by ischaemia, resulting from compression of soft tissue between a bony prominence and an external surface. Although formerly terms such as bedsore and decubitus ulcer (from the Latin 'to lie down') have been used, pressure ulcers can occur from prolonged pressure in any situation.

Epidemiology. The composition of populations studied for estimates of incidence and prevalence vary greatly, and even the definition of pressure ulcer (in particular whether erythema without ulceration is included), but nevertheless it is clear from the data that some groups are especially prone. Among hospital in-patients the prevalence varies between 3 and 14% [1–3].

The incidence for acquisiton of pressure ulcers in a UK district hospital was 4–10%, depending on case mix [4], and overall was about 10% in a US teaching hospital [5]. The elderly are especially susceptible [5,6] and the risk rises still further in some disease groups, for example those with fractured neck of femur in whom 66% developed pressure ulcers in one series [7]. The circumstances before, during and after major surgery are all important contributory factors to pressure ulcer formation [8]. The prevalence is usually higher in spinal injuries units than in general hospitals, despite optimal preventive measures being utilized. Others at particular risk include those in wheelchairs [9].

Many pressure ulcers develop at the patient's home and in nursing homes, with similar or higher prevalence and incidence figures to those derived from hospital-based studies [1,10,11]. At least in the hospital setting, various measures introduced during the 1990s appear to have reduced the prevalence of pressure ulcers [12–14].

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Pathogenesis and pathophysiology

Although protracted pressure is a necessary component, there are usually additional factors that contribute to the occurrence of ischaemic injury.

Pressure. Compression of, or repeated trauma to, tissue over a bony prominence is usually a key factor in causation of a pressure ulcer. Kosiak showed a parabolic relationship between pressure and time, indicating that higher pressures require a shorter time period to cause ulceration than lower pressures [1–3]. Tissue damage is thought to occur when pressures over 9.3 kPa are sustained for more than 2–3 h. This is readily achieved when lying on a standard hospital mattress. Fat and muscle are more susceptible to pressure than skin and may show evidence of damage earlier [4,5].

Some areas of the body are more susceptible than others to the effects of pressure, notably the sacrum [6] and the heel [7].

Shearing forces. Shearing forces are exerted on a patient who is lying supine when the head of the bed is raised. The skin tends to adhere to the bedclothes, and the force exerted by gravity stretches and thus damages blood vessels, most markedly in the fat and fascia [8]. Shear can significantly decrease the amount of pressure needed to occlude blood flow [9]. Elderly patients develop higher shearing forces while sitting, further disposing them to pressure ulcers [10].

Friction. Friction to the skin can reduce the amount of pressure required to produce an ulcer [11], compromise skin barrier function and sometimes produce blisters. This easily occurs when patients are dragged across bed sheets rather than being lifted.

Increased temperature and moisture. Increased heat when patients are in bed or on cushions exacerbates the effects of ischaemia. Maceration of the skin, whether from increased sweating or resulting from contamination by urine, faeces, wound drainage, etc., is an important contributory factor by increasing frictional resistance and by rendering skin more susceptible to infection.

Microvascular damage. An early feature in the evolution of a pressure sore is endothelial cell damage. This is associated with accumulation of fibrin, both within and outside capillaries, venules and arterioles. Endothelial cell shedding is associated with deposition of microthrombi of fibrin, platelets and red cells, blocking the vessels [12]. There is defective fibrinolysis in and around pressure ulcers [13], which may well contribute to their very slow rate of healing compared with ulcers that are histologically similar but of different aetiology. Lymphatic drainage is also disrupted and this is likely to be a contributory factor [14].

Neural dysfunction. Spinal cord injury confers an increased susceptibility to pressure ulceration. This is in part caused by sensory and motor deficit and disuse atrophy, but other factors have been recognized. Following damage to the upper spinal cord, there is a large and immediate increase in the degradation of collagen in both skin and bone [15]. As a measure of defective collagen synthesis, it has been shown that the cross-linking enzyme lysyl hydroxylase is reduced in activity in the insensitive compared with the sensitive skin in paraplegics [16]. Spinal cord injury, particularly above the T6 level, is associated with a progressive decrease in α-adrenergic receptors after the injury and is therefore liable to impair autonomic control of the cutaneous vasculature [17]. Observations on patients with amyotrophic lateral sclerosis, a condition associated with not developing pressure ulcers, suggest a role for ciliary neurotrophic factor [18] as well as for alterations in connective tissue discussed earlier (p. 22.2).

Systemic factors. A number of factors relating to ageing changes in skin render elderly patients more susceptible to pressure ulceration. These include reduction of dermal–epidermal interface area, loss of subcutaneous tissue, diminished pain perception, reduction in skin vascularity, slower wound healing and reduced tissue elasticity. It is notable that a much lower external skin pressure was sufficient to stop the skin blood flow in the sacral area of elderly patients compared with younger volunteers [19].

The risk for pressure ulcers is increased by any circumstance that impairs the patient's mobility. Most severe illnesses can lower the degree and duration of pressure required to cause necrosis [20]. Malnutrition enhances the development of pressure ulcers [21]. Prolonged pyrexia, hypermetabolic states, hypoalbuminaemia and cancer have a similar effect [22]. Hypotension has been recognized as a risk factor in a controlled study [23], and significant arterial disease is also important. Patients undergoing procedures that involve extracorporeal circulation are notably at risk, whatever their age; pressure ulcers in such patients may occur at atypical sites, such as on the occiput of the scalp. Conditions that elevate whole-blood viscosity, uraemia, vitamin deficiency and uncontrolled diabetes are contributory factors in some cases. Even an otherwise healthy individual may develop a pressure sore if subjected to prolonged immobility, for example during operations or simply from sitting still for many hours.

Infection. There is a significantly greater likelihood of finding *Pseudomonas aeruginosa*, *Providencia* species and anaerobes in enlarging ulcers compared with those that are healing. It is likely that bacterial colonization of pressure ulcers can have an important perpetuating role [24].

In summary, the main clinical factors responsible for pressure necrosis are as follows:

1 Prolonged immobility and recumbency:
   (a) paraplegia
   (b) arthritis
   (c) severe physical disease
   (d) apathy
   (e) operation and post-operative states
   (f) plaster casts
   (g) intensive care

2 Loss or dulling of sensory stimuli:
   (a) coma, neurological diseases (especially multiple sclerosis)
   (b) drug-induced sleep

3 Vascular disease:
   (a) arteriosclerosis.

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Risk factors [1]

Immobilization. Any circumstance that results in prolonged immobilization increases the risk for pressure ulceration. Examples include coma, debilitation, neurological and rheumatological illnesses, lying on a trolley in an accident department, a lengthy operation, post-surgical and other high dependency and critical care situations. Uncontrolled pain is an easily neglected reason for immobility.

Reduced oxygen profusion. Hypotension [2], whether caused by cardiac failure or drugs, anaemia, blood dyscrasias, arterial insufficiency and situations producing interstitial oedema such as nephrotic syndrome, can all increase the likelihood of pressure-induced ischaemia or may delay healing. Extracorporeal circulation is an important risk factor [3].

Malnutrition. Several studies have demonstrated a correlation between inadequate nutrition and pressure ulcers [4–8]. Postulated mechanisms include reduction of subcutaneous fat and delayed wound healing. Nutritional status can be gauged from the serum albumin, total lymphocyte count and body weight, provided there are no other reasons for these parameters being abnormal.

Age. Old age is associated with an increased risk, but it is unclear whether this is an independent variable. Neonates may also be at increased risk.

Other risk factors. Some surveys have suggested that diabetes mellitus, cancer, sepsis, prolonged pyrexia, prior corticosteroid therapy, dehydration and lifestyle parameters such as smoking and excessive alcohol intake are additional systemic risk factors.

Within the context of surgery, warming blankets have been identified as a risk factor [9].

Compression stockings to prevent venous thrombosis [10] and compression bandaging for venous leg ulceration can contribute to pressure ulcers [11].

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Pathology. The most complete study of the histopathology of pressure ulcer and its antecedents in humans is given by Witkowski and Parish [1]. In the earliest clinically recognizable stage of blanchable erythema, there is dilatation of superficial dermal venules and papillary capillaries with a mild perivascular inflammatory infiltrate

and degenerative changes in occasional sweat coils and ducts. At the stage of non-blanchable erythema, there is marked red cell engorgement of superficial vessels, platelet thrombi in many of them, and extravasation of red cells. More eccrine units are degenerate and there is evident fat necrosis. Before ulceration occurs, various additional changes are recognized, including epidermal atrophy, subepidermal blister formation, tissue eosinophilia and necrosis of hair follicles. Some other studies have emphasized the presence of intra- and extravascular fibrin [2,3]. In early ulceration, there is loss of the epidermis, and at the stage of a black eschar there is full-thickness destruction of the skin. The antecedent for black eschar formation was not seen in the biopsies studied, but was presumed to be vascular disruption at a deeper plane. In a chronic ulcer, there was fibrosis with isolated collections of capillaries and no residual appendages.

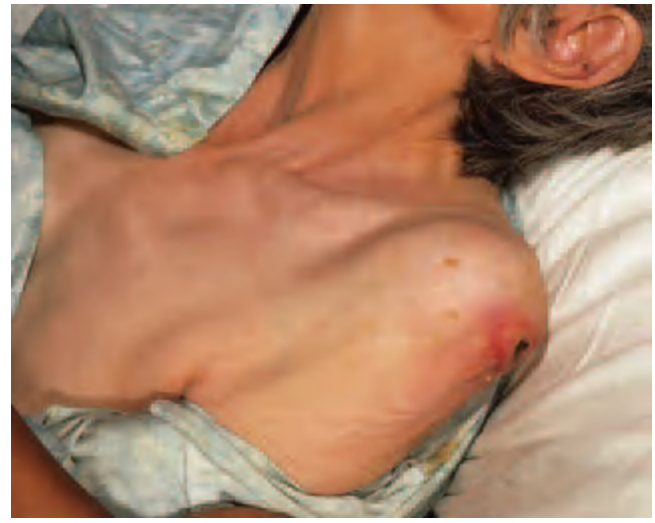

Fig. 22.7 A grade 2 (Shea classification) pressure ulcer over the shoulder in an elderly bedridden female with rheumatoid arthritis. Note that there is also chondrodermatitis of the antihelix, indicative of pressure on the ear.

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Clinical features and classification. Most pressure ulcers develop over bony prominences on the lower part of the body: 65% in the pelvic area (the sacral bone, ischial tuberosities and greater trochanters); and 30% on the lower limbs, usually the heels and lateral malleoli. On the upper part of the body the more common sites are the shoulder and elbow (Fig. 22.7).

Pressure-induced injury varies in appearance from blanchable erythema to necrosis of all tissues down to and including bone and joints. Assessment of erythema can be difficult in darkly pigmented skin and there may be extensive injury beneath eschar formation.

Based on clinicopathological correlations, clinical features have been classified to several somewhat different grading systems, three of which are contrasted in Table 22.2. The Shea classification [1] has been widely used, so is described here. In grade 1 there is erythema, sometimes accompanied by induration, warmth and pain. The erythema is reversible when pressure is relieved. Repeated pressure may result in brownish discoloration caused by extravasation of red blood cells and deposition of haemosiderin. Grade 2 is represented by blister formation and/or minor ulceration. In grade 3, there is a deeper degree of damage, involving the subcutaneous tissues, often producing a thick black eschar. Removal of this necrotic tissue may reveal tendons, ligaments and muscle. Grade 4 is represented by the appearance of deep fistulae, usually a consequence of progression to osteomyelitis. Grade 5 describes an ischaemic necrosis of subcutaneous fat, with or without deeper structures, with no or negligible skin ulceration. As skin is more resistant to ischaemia than the underlying fat and muscle, the subcutaneous

Table 22.2 Comparison of pressure ulcer classifications.

Shea [1]	Yarkony *et al*. [2]	National Pressure Ulcer Advisory Panel [3–5]
1 Limited to epidermis, exposing dermis; includes a red area	**1** Red area: (a) present longer than 30 min but less than 24 h (b) present longer than 24 h	**1** Non-blanchable erythema of intact skin
2 Full-thickness ulceration of dermis to junction with subcutaneous fat	**2** Epidermis and/or dermis ulcerated with no subcutaneous fat observed	**2** Loss of epidermis ± dermis
3 Fat obliterated, limited by the deep fascia; undermining of skin	**3** Subcutaneous fat observed, no muscle observed	**3** Ulceration into subcutaneous fat
4 Bone at the base of the ulceration	**4** Muscle/fascia observed, no bone	**4** Muscle/bone/joint exposed
5 Closed, large cavity communicating through a small sinus	**5** Bone observed but no involvement of joint space	
	6 Involvement of a joint space	

damage usually far exceeds the impression given by the surface changes. Deep sores typically have overhanging edges. With chronicity, calcification may occur.

The classification system of Yarkony *et al*. [2] has rather greater interrater reliability, and the National Pressure Ulcer Advisory Panel's system [3–5] is simple to use, but as none of the systems is universally accepted this can make comparison of studies difficult.

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Complications

Infections. Colonization of pressure ulcers with one or more of a wide range of aerobic and anaerobic bacteria is very common, but wound healing is not necessarily impaired [1]. Extension of necrosis, bacteraemia and septicaemia can occur when there is invasion of adjacent healthy tissue. There may be obvious physical signs to indicate true infection, such as erythema, warmth, tenderness and increased purulent discharge. However, these signs may not occur in the debilitated; such so-called inapparent infection [2] may be difficult to distinguish from colonization. When taking a swab, surface contamination (pus, etc.) should be removed with a non-bacteriostatic liquid such as normal saline, and tissue fluid should be sampled; needle aspiration or even biopsy material are better for obtaining relevant microbiology [3]. In practice, inapparent infection may only be surmised when an ulcer does not heal despite pressure relief, correction of nutritional needs, etc. An empirical course of antibiotic therapy may be justified in such circumstances [4].

Osteomyelitis. This is more likely in the non-healing ulcer, and can be difficult to diagnose. All imaging techniques have shortcomings. A bone scan is usually abnormal and, if so, bone biopsy and culture will enable the appropriate antibiotic therapy to be determined [5].

Sinus tracts. These can extend deep into joint spaces, causing osteomyelitis, septic arthritis and, occasionally, communicate with viscera. A sinogram will assist surgical management [6].

Squamous carcinoma. Although rare, squamous carcinoma can arise in long-standing pressure ulcers. Such lesions have a high risk for metastasis [7].

Other complications. These include endocarditis, meningitis, amyloidosis and myiasis.

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Prevention. Individuals likely to develop pressure ulcers can often be predicted and preventive measures are both cost-effective and avoid unnecessary patient suffering.

Recognition of the at-risk patient. A number of risk scales have been devised so that nursing staff and other carers can maximize their application of preventive measures. These risk scales vary in complexity, and consequently in the ease with which they can be used. The best known are those of Norton *et al*. [1] and Braden and Bergstrom [2,3] (Tables 22.3 & 22.4). With the Norton scale, a score of 14 or below indicates risk; with the Braden scale, 12 or less indicates high risk, 13–15 moderate risk and 16–17 mild risk.

Institutions should try to select the most appropriate at-risk scale for their needs [4,5].

Table 22.3 Norton scale.

Physical condition	Mental condition	Activity	Mobility	Incontinent
Good 4	Alert 4	Ambulant 4	Full 4	Not 4
Fair 3	Apathetic 3	Work/help 3	Slightly limited 3	Occasionally 3
Poor 2	Confused 2	Chairbound 2	Very limited 2	Usually/urine 2
Very bad 1	Stupor 1	Stupor 1	Immobile 1	Doubly 1
Name	Date			*Total score*

From [1].

Table 22.4 Braden scale for predicting pressure sore risk.

Patient's name _____ Evaluator's name _____ Date of assessment _____

SENSORY PERCEPTION (Ability to respond meaningfully to pressure-related discomfort)				Score
1 Completely limited Unresponsive to painful stimuli (does not moan, flinch, grasp) due to unconsciousness or sedation. *OR* Limited ability to feel pain over most of body surface.	**2** Very limited Responds only to painful stimuli. Cannot communicate discomfort except by moaning or restlessness. *OR* Has a sensory impairment that limits the ability to feel pain or discomfort over half the body.	**3** Slightly limited Responds to verbal commands, but can't always communicate discomfort or need to be turned. *OR* Has some sensory impairment that limits ability to feel pain or discomfort in 1 or 2 extremities.	**4** No impairment Responds to verbal commands. Has no sensory deficit that would limit ability to feel or voice pain or discomfort.	
ACTIVITY (Degree of physical activity)				
1 Bedfast Confined to bed.	**2** Chairfast Severely limited or non-existent ability to walk. Cannot bear own weight and/or must be helped into chair or wheelchair.	**3** Walks occasionally Walks sometimes but for very short distances, with or without assistance. Spends most of each shift in bed or chair.	**4** Walks often Walks outside the room at least once every 2 h during waking hours.	
MOBILITY (Ability to change and control body position)				
1 Completely immobile Does not make even slight changes in body or extremity position without assistance.	**2** Very limited Makes occasional slight changes in body or extremity position but cannot make frequent or significant changes independently.	**3** Slightly limited Makes frequent though slight changes in body or extremity position independently.	**4** No limitations Makes major and frequent changes in position with no assistance.	
MOISTURE (Degree to which skin is exposed to moisture)				
1 Constantly moist Skin is kept moist almost constantly by perspiration, urine, etc. Dampness is found every time the patient is moved or turned.	**2** Very moist Skin is often, but not always moist. Linen must be changed at least once a shift.	**3** Occasionally moist Skin is sometimes moist, requiring an extra linen change about once a day.	**4** Rarely moist Skin is usually dry, linen needs changing at routine intervals.	
NUTRITION (Usual food intake pattern)				
1 Very poor Never eats a complete meal. Rarely eats more than a third of any food offered. Eats 2 servings or less of protein (meat or dairy products) per day. Takes fluids poorly. Does not take a dietary supplement.	**2** Probably inadequate Rarely eats a complete meal and generally eats only about half of any food offered. Protein intake includes only 3 servings a day. Will occasionally take a dietary supplement. *OR* Receives less than optimum amount of liquid diet or tube feeding.	**3** Adequate Eats more than half of most meals. Eats 4 servings of protein each day. Will sometimes refuse a meal, but usually takes a supplement if offered. *OR* Is on a tube feeding or TPN regimen that probably meets most nutritional needs.	**4** Excellent Eats most of every meal. Never refuses a meal. Usually eats 4 or more servings of meat and dairy products. Sometimes eats between meals. Does not require supplementation.	
FRICTION AND SHEAR				
1 Problem Requires moderate to maximum assistance in moving. Complete lifting without sliding against sheets is impossible. Often slides down in bed or chair requiring repositioning with maximum assistance. Spasticity, agitation or contractions lead to almost constant friction.	**2** Potential problem Moves feebly or needs minimum assistance. During a move, skin probably slides to some extent against sheets, chair, restraints or other devices. Usually maintains relatively good position in chair or bed, but occasionally slides down.	**3** No apparent problem Moves in bed and in chair independently and has sufficient muscle strength to sit up completely during move. Maintains good position in bed or chair at all times.		Total score ☐

General nursing measures. Standard nursing practices to prevent pressure ulcer formation in those most at risk include:

- A skin inspection at least once daily, especially over bony prominences.
- Prevention of moisture accummulation from incontinence, wound drainage, etc. (e.g. by absorptive pads).
- Avoidance of friction and shear by lifting rather than dragging the patient, ensuring that the bed is kept free of food particles, etc.
- Avoidance of elevation of the head of the bed by greater than 30° as shearing forces increase beyond this angle.
- Pressure relief by turning the patient at least every 2 h. Patients should be turned successively from the back to the right side, then to the left side; when on the side, the patient should be positioned at an angle to avoid pressure on the trochanter and lateral malleolus.
- Soft pillows or foam wedges should be used to prevent sites such as the knees and ankles from direct contact with each other; the heels should be suspended away from contact with the bed (e.g. by pillows under the lower leg).
- Ensure that there is a shift of weight every 20–30 min for those in wheelchairs, to relieve pressure on the ischial tuberosities.

Specialized beds, mattresses and cushions. All at-risk patients being nursed in beds should have a pressure-relieving mattress in addition to frequent repositioning [6]. The support system can be subdivided as either static or dynamic in type. The former mould around the patient and distribute weight over a greater area. They are foam, water, gel or air-filled and may be suitable for patients who can assume a variety of positions. It is important that the material is not completely compressed. Dynamic systems (e.g. air-fluidized and low air-loss beds) change their support characteristics in a cyclical fashion and can successfully relieve pressure for patients unsuitable for a static system. They are generally more expensive.

There has been a systematic review of the randomized controlled trials evaluating most of the support systems currently available in the UK [7]. Although there are significant shortcomings in the trials evaluated, some valuable conclusions emerged. There is a useful reduction in incidence and severity of pressure ulcers when simple static supports (e.g. the foam type) are used, compared with standard hospital mattresses. There is no clear difference when the various types of static support are compared. Pressure-relieving overlays on the operating table are also of proven value and should be used more often than they are. Low air-loss beds are probably more effective in prevention than foam mattresses, but are much more expensive. For treatment, the air-fluidized type of support may improve healing rates.

Wheelchair cushions are rarely adequate for the job required of them, in that over 50% of the body weight is being supported on 8% of the sitting area, at or near the ischial tuberosities. However, air-filled cushions have been shown to be of value [8]. The most effective way of protecting the heel is to elevate it completely from the bed [9].

General medical measures. Any medical condition adding to the tally of risk factors (e.g. diabetes mellitus, cardiac failure or anaemia) should be controlled. Nutritional status should be assessed and appropriate measures taken if necessary.

Measures for patients with neurological disease. Spasticity should be relieved if possible by use of muscle relaxants, nerve block or surgery. In paraplegic patients, functional electrical stimulation has been shown to help, possibly by inducing shape changes in the buttocks and improving blood flow [10–12].

Overview—assessment and prevention. Those closely involved with the care of patients liable to pressure ulcer will find the assessments of available literature by the UK National Institute for Clinical Excellence (NICE) [13] and by the Royal College of Nursing [14] useful.

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Management. The principles outlined above for prevention apply to management of the ulcer. Once the early reversible signs of pressure-induced injury are evident, action should be prompt.

Relief of pressure. The imperative consideration is the removal of the pressure. This must continue throughout the treatment of any pressure sore; all other forms of treatment are of secondary importance. Nursing in a prone position may be required and is acceptable for all patients except, perhaps, quadriplegics. The 90° lateral position must be avoided, as it frequently causes pressure sores over the greater trochanters and malleoli. Special nursing skills are required in positioning pillows to protect the knees and iliac spine. Pressure-relieving mattresses, beds and cushions are discussed above. If healing does not occur with use of a static device, a dynamic support system may prove more effective.

General treatment. It is essential to treat the whole patient. Pressure sores can be extremely painful and adequate analgesia is essential. Nutrition should receive special attention and a positive nitrogen balance should be achieved. For those with poor appetite, or unable to take sufficient solid food by mouth, frequent sip feeds of protein supplement or, occasionally, nasogastric tubal feeding may be required. Anaemia, zinc and ascorbic acid deficiency must be corrected. Blood transfusions may be required. Any serious underlying disease should be assessed and treated appropriately. The blood urea and serum albumin should be checked regularly. Whenever possible, the advice of a geriatrician conversant with the problem of pressure sores should be sought if early measures do not bring about restitution. The special problems of the paraplegic patient are not considered in detail here; these require the attention of a spinal physician or surgeon. Just as electrical stimulation may have a role in prevention, it may also assist healing in spinal cord-injured patients, although randomized control trials are needed.

Wound care. It is important to assess the nature and progress of a pressure ulcer, so there should be regular inspections—at a minimum weekly, with well-documented observations including a tracing and/or photographs. Signs of infection, sinus tract formation, offensive discharge, new necrotic tissue, undermining, etc. may determine the need for a change in management.

Irrigation with normal saline is generally sufficient to keep the ulcer clean [1]. Although it is desirable to minimize growth of bacteria, the many antiseptics and antibiotics used on pressure ulcers are mostly of unproven benefit; some can cause local and systemic toxicity, select resistant bacteria and/or result in contact allergic dermatitis. If used at all, a topical antimicrobial should not be applied for more than 2 weeks at a time.

When pressure is relieved, in many cases the necrotic tissue will separate naturally in 1–2 weeks but if there is eschar this is best removed by scalpel or scissors. If the patient cannot tolerate this, an enzyme preparation may be used (usually containing streptokinase, streptodornase, deoxyribonuclease, trypsin, papain, fibrinolysin and collagenase in various combinations), but these are of unproven value, can cause contact allergy and should not be used if there are exposed tendons.

Wounds generally heal best when moist. The choice of dressing for a pressure ulcer will be dictated in part by the stage. Thus, a superficial stage 2 ulcer will usually heal beneath a transparent semipermeable membrane such as Opsite®. For deeper ulcers with some necrotic debris, the choice is usually between a hydrocolloid, a hydrogel or an alginate. Hydrocolloids may be more effective at assisting autodébridement [2], but should not be used if muscle, tendon or bone are exposed and may be associated with overgranulation. Hydrogels are soothing to skin but are not adherent and dessicate easily. Alginates are useful in cavities and have a high absorption capacity. Dextranomer paste is also useful in reducing discharge [3].

Surgery. With some deep ulcers (e.g. when there is necrosis of bone) operative surgical débridement will be needed. Where spontaneous healing is not apparent within a reasonable period, surgical intervention may be necessary, provided circumstances are such that the ulcer is not likely to recur after surgery and that the patient's medical and nutritional status have been optimized. Most deep ulcers require radical excision and appropriate flap repair. Even when musculocutaneous flaps are used, recurrence is a significant problem [4,5]. Whenever possible, the flap should be sensate [6,7]. Tissue expansion may have a role in the surgical treatment of pressure ulcers [8,9]. Recurrence rates after surgery tend to be high [10].

When appropriate, vascular reconstructive surgery can improve wound healing.

Other measures

Electrical stimulation. The use of direct current has been shown to improve the healing of pressure ulcers [11]; possible mechanisms include an effect on wound repair processes and reduction of the bacterial population [12].

Hyperbaric oxygen. There are anecdotal reports of this modality being used as an adjunct to healing pressure ulcers [13,14].

Growth factors. Several growth factors have been evaluated for their effect on chronic wounds, but few have been assessed adequately. A placebo-controlled trial has shown that platelet-derived growth factor reduced ulcer volume [15], but its place is yet to be established. Anecdotal

reports such as the use of nerve growth factor [16] require further evaluation.

Vacuum-assisted closure. The application of negative pressure may facilitate healing of pressure ulcers [17–19].

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Effects of suction

Localized suction to the skin usually produces either blisters, which can rupture to form erosions, or purpura. Early work evaluated the inverse relationship between the degree of negative pressure and time taken for blistering to occur [1,2] and demonstrated that the time taken to blister could be shortened if the temperature at the suction site was raised to 40°C [3]. Suction blisters are often used in experimental dermatology (e.g. to yield fluids for analysis of inflammatory mediators) and to generate pieces of epidermis for grafting as used in the treatment of vitiligo [4]. Blisters induced by suction are subepidermal in type, in contrast to friction blisters, which develop within the epidermis. The dermal papillae are usually well preserved, producing the effect known as festooning [5]. When the force of suction is sufficient to produce purpura, this may either take the form of petechiae or, if the injury is over a larger surface area, an ecchymosis will result. At the outset, such lesions are red, but they then undergo the usual changes associated with extravasation of red cells into the skin, producing purplish and then yellow staining.

Neonatal suction blisters

These present as one or a small number of blisters or erosions, typically on the fingers, lips or forearms. They heal quickly after birth [6]. (For further discussion see Chapter 14.)

Therapeutic cupping

This is a widespread folk medicine practice, particularly in Oriental countries [7] and in some parts of eastern Europe, although it has been used in the West and may increase because of migration of populations [8,9]. Cupping is performed on patients with various diseases, particularly febrile illnesses, by warming the edge of a cup and applying it to the patient's back. Suction is produced when the cup cools. The visible effect is a round area of ecchymosis often with petechiae at the border (Fig. 22.8). Cupping is often combined with acupuncture, and a number of complications have been associated (e.g. panniculitis) [10]. The skin changes caused by cupping can simulate child abuse [11,12].

Suction purpura in children

Vacuum extraction to assist in parturition can cause a characteristic rounded purpuric lesion on the forehead of the infant. Ecchymoses have been induced by suction cups attached to babies' rattles [13]. The habit of sucking on a cup and aspirating the air trapped within it can produce a distinctive zone of petechiae on a child's chin [14]. As a habit or neurotic activity, children sometimes suck on their arms, and this can produce small areas of purpura, typically arranged in lines [14]. The sucker-shaped rubber ends on toy arrows have also been recorded as producing purpura by a suction effect [14]. Distinctive rounded purpuric lesions on the forehead (purpura cyclops) from the rubber suckers on their children's toys can occur on fathers—the 'sucker-daddy' syndrome [15,16].

Penile suction injuries

Penile injuries resulting from sexual experimentation may be bizarre. Vacuum cleaner injuries can cause ecchymosis

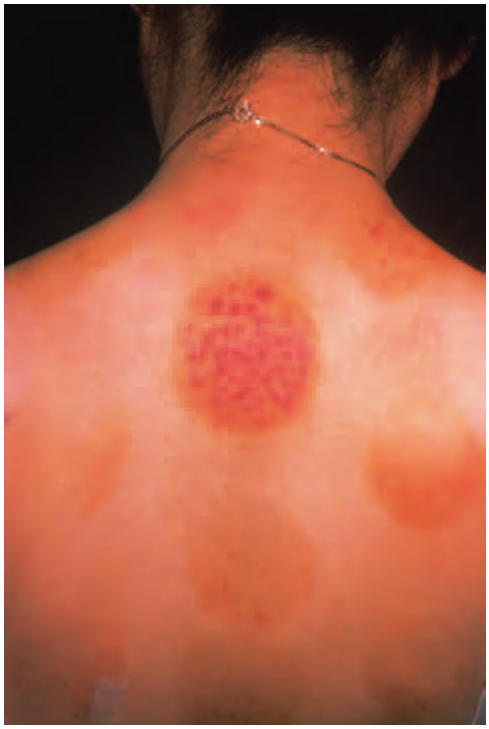

Fig. 22.8 Purpura caused by therapeutic cupping. (Courtesy of Dr M. Rustin, Royal Free Hospital, London, UK, and the Editor of the *British Medical Journal*.)

if the suction is mild, and extensive lacerations when severe [17].

Other examples of suction purpura

Other recorded examples include the so-called 'love bite', a consequence of sucking while kissing; the use of suction devices on electrocardiograph leads; and gas masks, for example used during the Gulf War [14]; suction from cup-shaped indentations on a bath mat [18] and from getting stuck in the bath [19].

Suction pads

Hyperkeratotic lesions on the thumbs of a child attributed to repetitive suction have been described, but chewing was also taking place and may have been a contributory factor [20].

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Miscellaneous reactions to mechanical trauma

Coin-rubbing injuries

Coin rubbing or *kua'sha* originated in China and has spread to many other countries in South East Asia. It is often known by the Portugese term *cao gio*. As a form of folk medicine, it is used to treat many complaints. The coin (usually copper or silver), or sometimes a silver spoon or other object, is dipped in wine, water or an aromatic oil and then scraped over the skin surface until a visible change—redness or purpura—is observed. The technique is often accompanied by pinch-pulling (*t'i-sha* or various synonyms) in which the index and middle fingers are used to pluck the skin. Common sites include the intercostal spaces, bridge of the nose, the space between the eyebrows, the occipital depression over the neck, either side of the larynx, and the elbow and knee flexures.

Clinical features. There are symmetrical bands and ovoid patterns of bruising. Occasionally, the lesions can be misinterpreted as representing foul play [1].

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Reactions to musical instruments

These have been reviewed by type of instrument [1,2], and by type of causative injury [3,4]. Mechanical injuries can

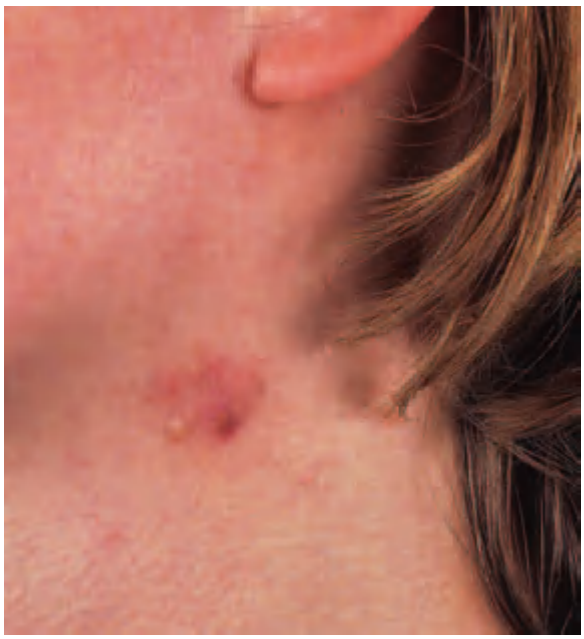

Fig. 22.9 'Fiddler's neck'. Lichenification and cysts on the neck of a violinist. (Courtesy of Dr R.D.G. Peachey, Bristol Royal Infirmary, Bristol, UK.)

be acute (e.g. friction, blisters and erosions) but are more commonly chronic resulting from repetitive friction and/or pressure between the musician and the instrument, in some situations aggravated by sweating, faulty techniques or excessive hours of playing. Not only the skin but also bony and soft tissues can be affected, and in younger wind instrument players there can be permanent distortion of dentition and palatal morphology. Trauma to fingers can also quite often damage nails and associated tissues. Contact allergies in musicians are usually to rosin (various string instruments), exotic woods (e.g. used for chin rests), nickel, cane reeds (saxophones and clarinets) or to propolis (violin varnish) [3].

Violin and viola players may develop 'fiddler's neck' [5], characterized by localized plaques of lichenification, often with hyperpigmentation, erythema, inflammatory papules and pustules and sometimes cysts. Marked oedema may be associated in some cases [6]. The condition occurs at the site where the chin rest of the instrument presses against the skin over the angle of the jaw (Fig. 22.9). The mode of grip on the instrument and the fitting of the chin rest are likely causative factors and a soft cloth may ameliorate a poor fit in the short term [7]. Violinists are also subject to developing thickened pads over the interphalangeal joints (Garrod's pads or fiddler's fingers). These are areas of thickening over the dorsal aspect of the left second and third proximal interphalangeal joints. They may result from the intermittent relaxation and contraction of the extensor tendon over an interphalangeal joint that is held in extreme flexion [8]. Thrombosis of the axillary and subclavian veins has occurred from pressure from a viola [9]. Pizzicato paronychia is another hazard for string players.

Finger callosities occur on the pulps of the fingers of many musical instrument players. A typical example is 'harpist's fingers', which usually show paronychia and calluses on the sides and tips of the fingers, often together with onycholysis and subungual haemorrhage [10].

Piano paronychia is associated with long hours of piano playing, and nails can be loosened by repetitive glissando (gliding of fingers over the keys).

'Guitar nipple' is usually found in young girls and presents as an inflamed cystic swelling at the base of the nipple [11]. Deep-vein thrombosis has been described in guitarists as a result of a combination of flexion of the left leg with pressure from the belly of the guitar on the medial aspect of the thigh [12]. Acro-osteolysis has been described in the digits of the left hand, the only symptom being tenderness in relation to pressure on the nails [13].

Cellists can develop a lesion known as 'cellist's chest' [14] from pressure, producing erythema, oedema and pigmentation over the sternal area. There may be changes similar to those of 'fiddler's neck'. 'Cellist's knee' and even 'cello scrotum' have been described, although the validity of the latter has been questioned [15].

'Clarinettist's cheilitis' [16,17] is an eczematous condition, not caused by contact allergy, that affects the middle of the lower lip (see Chapter 66).

'Flautist's chin' [18] is probably similar to fiddler's neck.

Wind instrument players can develop permanent laxity of the cheeks, and forceful blowing of the trumpet can rupture the orbicularis oris (Satchmo's syndrome) [19].

'Drummer's digit' is an erosion or blister on the left ring finger [20].

Black dermographism of the lip has been described in a flute player using a lotion containing zinc oxide, titanium dioxide, iron oxides and talc [21] (for further details on black dermographism see p. 22.84).

Treatment. Modification of technique can usually result in resolution of trauma-related problems in musicians. Callosities can be helped by keratolytics and a pumice.

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Hypothenar hammer syndrome

This condition is brought about by the effects on the ulnar artery and associated soft tissues of repetitive trauma to the hypothenar eminence [1]. It is typically associated with actions that use the hand to hammer, push or squeeze. It is mainly found among individuals in certain craft occupations, such as mechanics and carpenters, but can also occur as a sporting injury (e.g. in golf and badminton) [2] and may present in those using a vibrating tool [3].

The proposed pathogenesis is that the superficial palmar branch of the ulnar artery is compressed against the hook of the hamate and this can lead to stenosis, occlusion or aneurysm, with thrombosis or emboli ensuing. Although the condition typically presents unilaterally, the presence of bilateral abnormalities when patients are investigated suggests that there is an underlying predisposition [4].

Among manual workers, most patients are middle-aged men and present with pain or paraesthesia and variable degrees of ischaemic change including blackened eschar formation on the ends of the second, third, fourth or fifth digits of the dominant hand. There may be surrounding hyperkeratotic changes [5]. Fingers affected by the underlying vascular pathology are cooler, and may show other signs of chronic ischaemia. Allen's test is often positive. Some patients have comorbidity factors such as smoking and cold exposure.

The condition is often misdiagnosed as collagen vascular disease, or some other vaso-occlusive disorder.

Investigations should include arteriography, which can demonstrate stenosis, occlusion, aneurysm, etc. and provide essential information for vascular surgical repair. Magnetic resonance angiography is proving to be a highly informative minimally invasive method of evaluation [6].

Management includes counselling to avoid repetitive trauma, minimize exposure to the cold and stop smoking. Aspirin and calcium-channel blockers may be helpful. Vascular surgical expertise will generally be required for thrombolytic measures or resection of the abnormal vasculature and appropriate reconstruction.

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Achenbach's syndrome

This disorder is characterized by sudden painful blue discoloration and swelling of a finger or fingers (or sometimes the palm of the hand), often after physical effort of gripping or twisting. It is probably caused by rupture of a small vein. Its importance is that it may be confused with Raynaud's phenomenon (discussed further in Chapter 23).

Trauma and subcutaneous fat

Acute panniculitis is considered in detail in Chapter 55. It should be noted here that mechanical injury to the subcutaneous fat, especially on the lower legs, can be a primary cause of fat injury, although more often it is a localizing factor [1,2]. It is often followed by atrophic changes.

Semicircular lipoatrophy

This distinctive condition, also known as lipoatrophia semicircularis, is characterized by one or more partial horizontal band-like depressions, usually on the anterolateral thigh or thighs. It mainly occurs in women. Since the initial report [3], relatively few cases have been reported, but it is asymptomatic so may be underreported; several authors have commented that it may well not be rare [4].

Repetitive mild trauma has been suggested as causative in most cases. In one series, seven women of different heights and body mass index working in the same office all developed the condition at the same vertical distance from the floor, corresponding to the height of the edge of their desks; pressure against this edge was postulated to have caused the semicircular lipoatrophy [5].

When a cause is identified and remedial action taken, spontaneous resolution generally occurs [5], in most cases after 9 months to 4 years.

Semicircular lipoatrophy is considered further in Chapter 55.

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Computer palms and mouse fingers

It has long been recognized that manual occupations can leave characteristic changes on the skin, some of which are discussed elsewhere in this chapter.

Computer palms

Two cases of a distinctive non-blanchable erythema with telangiectasia on the ulnar side of the palms has been described in two healthy computer programmers who had spent 10 or more hours a day, 7 days a week, leaning forward and thereby putting pressure on the hands [1]. The authors speculated that there were similar causative factors to those producing pressure ulcers (pressure, shear, moisture and friction).

The differential diagnosis includes liver disease, connective tissue disease, exposure to chemotherapeutic agents, internal neoplasia and erythema ab igne.

Mouse fingers

A single case has been described of erythema, scaling and peeling of the thumb and fifth finger tip of the right hand, attributed to friction, pressure and sheer exerted on these digits while holding a computer mouse for long periods at a time [2].

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Dermatological problems of the amputee [1–3]

Skin problems arising from amputation are seen much more on the weight-bearing lower limb than the upper limb. The main factors are pressure, shear friction and overhydration of the stratum corneum. Lesions that might be trivial elsewhere on the skin, such as minor calluses or fissures, can have a major impact when they occur on a weight-bearing amputation stump. Factors relating to the stump, the prosthesis and other systemic or cutaneous disease all contribute to the likelihood of dermatological complications.

Ideally, the skin on the stump should be well vascularized, freely mobile and with no redundant folds, tension or adhesions to the bone. Scars should be away from weight-bearing areas and bony prominences. The muscles should be fixed so that movements are balanced and no muscle groups are left free to undergo atrophy. Sockets should be designed to provide a close but comfortable fit, with weight-bearing areas designed onto the inner wall and outer rim, and the greatest pressure should be exerted onto those regions most able to receive it. These ideal circumstances may be impossible to achieve, for example after a traumatic amputation the stump may be too short, and often in cases of vascular disease there is reduced blood supply.

Above-knee amputation prostheses are of two basic types: the conventional prosthesis, which is suspended from a belt; and the suction-socket type, which is held in place by negative pressure and therefore must be a very accurate fit to the stump. Because of the dearth of soft tissues, the prostheses for below-knee stumps are usually suspended, although recently suction-socket types have begun to appear. Nowadays there is usually a socket liner made of silicone gel between the stump and the socket, and this is tethered to the socket by a quick-release shuttle lock [4]. The silicone gel roll-on liner is advantageous for some amputees but creates additional problems for others, notably skin problems resulting from heat retention and friction injury from the edge of the liner [5,6]. Dermatological problems in the first weeks after an amputation are unusual; if they occur, they are usually the consequence of secondary infection of the wound or of reaction to topical medicaments.

Management of the conditions that present in the amputee requires a multidisciplinary approach [2,7].

Common mechanical injuries

Constant rubbing over pressure points readily produces a burning sensation, associated initially with erythema and desquamation. If there are folds in the stump skin, intertrigo can occur, particularly in hot humid weather. With chronicity, painful fissures and secondary eczematization can occur. Friction blisters and erosions usually occur around the brim of the socket and the distal end of amputation stumps. On below-knee stumps, the pretibial area is also a common site for friction blisters. Friction-related injuries, including blistering, can be a problem with the cut edge of silicone gel sleeves. Erosions can progress to ulceration (Fig. 22.10), especially when there is underlying arterial insufficiency, oedema, scars adherent to bone or neurological impairment. Sometimes, quite

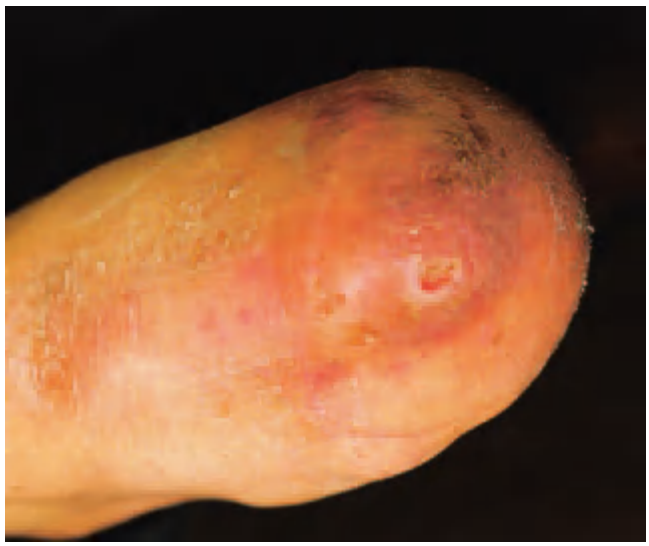

Fig. 22.10 Pressure-induced lichenification, inflammation and ulceration on an amputation stump. (Courtesy of Dr N. Purry, Disablement Services, Southmead Hospital, Bristol, UK.)

soon after the prosthesis has been fitted, there is some reduction in size of the stump, such that the limb wedges into the prosthesis. This can cause oedema and also ulceration.

Skin thickening can also occur in response to injury. Lichenification, often with hyperpigmentation [8] may be seen, sometimes as part of an eczematous response. Callosities and corns may occur at focal pressure points, especially in below-knee amputees. The 'lenticular button' hyperkeratosis [9] is often painful. Pressure and friction can induce follicular hyperkeratoses [10], sometimes containing entrapped hairs, which can then develop into sterile abscesses. Acne mechanica has been described, responding to isotretinoin [11]. Trauma to the stump can occasionally produce purpura.

Treatment. It is important to recognize injuries resulting from mechanical factors, as they are likely to require adjustments to the prosthesis.

Epidermoid cysts

These are common, usually occurring a few months or more after the prosthesis has been in use. In one series of 67 amputees with epidermoid cysts, the cysts interfered with the wearing of a prosthesis in 23 [12]. Predisposing factors include the previous occurrence of acne, hairy skin and a poor prosthetic fit so as to cause a roll of flesh above the socket brim. Common sites are the adductor, ischial, inguinal and popliteal areas. It seems likely that the cysts originate from shearing forces invaginating fragments of the epidermis into the dermis. Cysts can rupture to produce granulomatous inflammation and discharging sinuses.

Treatment. Adjustment of the prosthesis is necessary, but is sometimes not sufficient to cure the difficult problem of cyst formation. This may require incision and drainage, or excision. It is often necessary for the patient to do without the prosthesis if such measures are undertaken. For the inflammation associated with rupture of the cysts, intralesional steroid may be helpful. If there is true secondary infection, this will require appropriate treatment.

Circulatory disorders

Both venous and lymphatic return are readily impaired by unsatisfactory pressure gradients and inadequate muscle activity in the amputation stump, and these problems are aggravated if there was a pre-existing venous disorder in the limb. The clinical features are oedema, often accompanied by eczema, and sometimes with purpura leading to haemosiderin staining. Stump oedema is very common and can occur even without circulatory insufficiency. Obesity, lack of exercise and poor fit are among the most common contributory factors. As well as correcting underlying causes, application of a graduated pressure bandage at night is useful, and counter-pressure can be produced by modifications to the prosthesis.

A distinctive verrucous hyperplasia can occur with the combination of venous impairment and poor fit [13] and is associated with below-knee amputation [14]. Kaposi-like acroangiodermatitis can present as bluish plaques [15,16].

Treatment. It is important to exclude abnormal pressure or lack of support as a cause of oedema, and to make appropriate adjustments. The garment worn over the prosthesis can provide some useful support, as can wind-on elasticated bandaging when the prosthesis is not in use.

Other problems

Infection. Bacterial colonization and both primary and secondary infections are more common on amputation stumps than on normal skin, probably because of the increased humidity and tendency to frictional injury of the stratum corneum. Folliculitis is one of the more common problems that occur with the silicone gel socket liner. Antiseptic cleansers, such as chlorhexidine, have an important role in prevention.

Miliaria. In warm weather, miliaria of the stump is often seen. The papules, papulovesicles or pustules may cause no symptoms, but can be intensely irritating. Problems resulting from heat retention with silicone gel socket liners can sometimes be relieved by careful, more frequent washing [6].

Contact dermatitis. This can be caused by a metal, plastic or leather component of the prosthesis, or to medicaments, talcs, oils, etc., and may be overlooked or may be falsely attributed to infection or friction. In a cross-sectional study of 210 amputees, 71 had a related skin disorder and, of these, 12 had relevant patch-test reactions [3]. Patch tests [17,18] should include azo dyes, methacrylates and acrylates, epoxy resins, polyester resin, chrome, nickel, paraphenylenediamine (PPD), *para*-tertiary butylphenol, formaldehyde resin, *para*-tertiary butyl catechol and when suction-socket prostheses are used, appropriate rubber additives and neoprene [3,17–20].

Bullous pemphigoid. This has been reported localized to the amputation stump [21,22].

Neoplasms. Most tumours occurring in stump skin are coincidental or related to the disease necessitating the amputation. A traumatic neuroma can result from amputation, usually appearing on the end of a nerve that has been cut and, when painful, excision may be needed. Squamous carcinoma can rarely arise from a persistent stump ulcer [23] or from verrucous hyperplasia [24].

Incidental reactions

Dermatoses localized by trauma (Koebner response; p. 22.2) are liable to occur on the amputation stump, especially psoriasis or lichen planus. Troublesome psoriasis has also been noted on the palms through the use of crutches as a result of amputation. Patients with atopic dermatitis often have exacerbations on prosthesis-bearing stumps because of the effects of increased temperature, humidity, friction and, perhaps, oedema and bacterial infection. Mechanical forces and increased hydration in amputees can localize acne vulgaris and can aggravate hidradenitis suppurativa. Particularly when sympathy or compensation are sought, the amputation stump may become the site for dermatitis artefacta.

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Spectacle-frame acanthoma

This is the preferred term for a condition initially described as *granuloma fissuratum of the ear* [1] and also known as *acanthoma fissuratum*.

Factors that contribute to the pathogenesis include the weight of the spectacles, minor derangement in local anatomy and maceration.

Histology shows acanthosis and hyperkeratosis of the epidermis, with a central depression and occasionally ulceration. In the dermis, there is often hyalinization of the collagen and a mild mixed inflammatory infiltrate [2]. Granulomatous change is not usually present.

The typical lesion occurs behind the ear or on the side of the nose [3–5] as a soft flesh-coloured papule, nodule or plaque, often with a groove at the site where there is contact with the spectacle frame (Fig. 22.11). In a review of 27 published cases, males predominated [2]. Cases with bilateral involvement are uncommon [6].

Spectacle-frame acanthoma usually resolves after a few weeks or months if the patient discontinues wearing spectacles or changes are made to obviate the mechanical trauma.

The main importance of the condition is that it can mimic basal cell carcinoma, which can also be bilateral behind the ears. If necessary, the condition can be treated by surgical excision, electrosurgery and curettage, or intralesional corticosteroids.

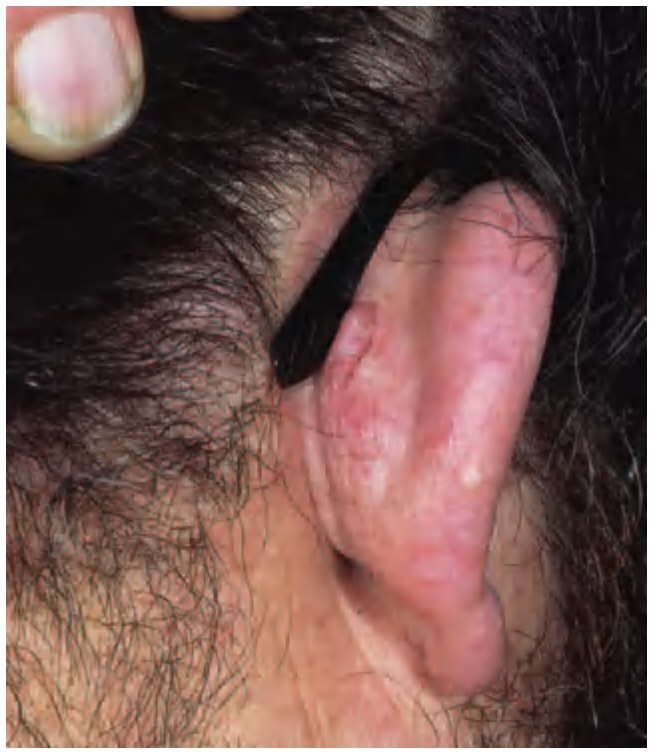

Fig. 22.11 Acanthoma fissuratum. A soft plaque, which may mimic basal cell carcinoma, caused by pressure and friction from the spectacle frame.

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Acne mechanica [1]

Pressure of tight clothing or friction, often with heat and increased humidity causing maceration, may exacerbate acne vulgaris or cause its appearance in unusual sites in susceptible subjects. Right-handed students may have predominantly left-handed facial acne from pressure of the left hand. High-necked jerseys, shoulder pads, seat backs in trucks or even adhesive plasters may produce the required mechanical stress. Some athletes are prone to this condition [2]. Acne mechanica has also been described in other circumstances (e.g. on the backs of young patients lying in hospital beds for several weeks, and on the face following jaw splinting [3] and with the use of orthopaedic crutches [4]). The resultant acne can be severe (e.g. acne conglobata occurred on the buttocks in a transatlantic rower) [5].

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Traumatic effects of sports [1]

Skin conditions related to sport include mechanical injuries and other direct consequences of the sporting activity, conditions initiated by the environment and infections [1,2]. While the professional sportsperson and trainer may be well aware of these, the amateur may not recognize any connection and even the dermatologist may at times be puzzled. Some of the clinical entities are highly characteristic [3]. The skin adapts to training, developing a higher degree of 'elastic efficiency', but this requires time and continuity in the chosen sport. Many traumatic effects occur in the 'weekend jogger' or the summer holiday activist. The wheelchair athlete is particularly prone to blisters and pressure injury [4,5].

Many conditions affecting those engaged in sports are an indirect consequence of trauma. These include infections commonly transmitted by contact [6,7], such as herpes simplex [8], molluscum contagiosum [9] and tinea corporis [10,11]. Other infections that appear to be more common include viral warts [12], impetigo and furunculosis [13]. The sport of mud-wrestling has been associated with Gram-negative folliculitis [14]. Tinea pedis, often in a mixed infection with Gram-negative bacteria, is a common problem particularly in those using swimming pools. Otitis externa is also an important problem for the swimmer (see Chapter 65). Trauma to nails and trauma-related paronychia is considered in Chapter 62. The sports enthusiast is often at significant risk from sunburn or cold injury. In hot conditions, miliaria and hyperhidrosis can be problems. There are many circumstances in which contact dermatitis can occur; from sports equipment [3], environmental allergens, etc. Sporting activities can exacerbate pre-existing skin disease, such as atopic dermatitis, psoriasis, acne and other skin diseases. The spectrum of sports-related skin disorders also includes the consequences of anabolic steroid misuse, the physical urticarias, exercise-induced anaphylaxis [15] and leukocytoclastic vasculitis [16].

Blisters

These usually result from violent or unaccustomed local-

ized friction, and are most common on weight-bearing surfaces; in the wheelchair athlete, this includes the back [5]. Heat and humidity favours the development of blisters. Preventive measures and the management of friction blisters are discussed above (p. 22.13).

Haemorrhagic effects

Calcaneal petechiae ('black heel') [17] is described above (p. 22.16). It is particularly common after sports where there are sudden stops such as basketball. A similar condition, 'black palm', can occur in weightlifters [18] and is occasionally seen in golf and tennis players. Petechiae around the ankle in a long-distance runner have been described [19]. Annular purpura can occur when the skin is struck by a table tennis ball ('ping-pong patch') [20]. Annular purpura of a different type has been described in association with step aerobics; annular purpuric lesions developed on the legs [21]. Subungual haematoma, sometimes preceded by erythema, oedema and a throbbing pain, is common among racket-sport enthusiasts ('tennis toe') [22] and runners ('jogger's toe') [23]. Splinter haemorrhages have been seen in golfers [24]. Tennis toe most often affects the first or second toe, whichever is the longer, and the symptoms and signs may mimic a fracture. Jogger's toe tends to involve the third, fourth or fifth toe. Hyperpigmentation resulting from small ecchymoses of the skin on either side of the upper portion of the gluteal cleft is a distinctive finding in long-distance runners, and has been called 'runner's rump'. It is caused by contact between the buttocks while running [1].

Abrasions

These are common in many sports but are particularly associated with contact with wrestling mats [25,26] and artificial turf, which can also produce 'turf toe' (see below). Abrasions from use of skateboards are also common [27].

Acute inflammation

'Turf toe', a painful condition in which there is oedema and erythema over the dorsal aspect of the great toe with acute tendonitis of the flexor and extensor tendons, frequently occurs in athletes playing on artificial turf [28,29]. 'Jogger's nipples' was described in women who run without brassieres [30], but also occurs in men who wear shirts consisting of coarse fibres. It may be more prevalent when ambient conditions are cool, making the nipples erect, and when the skin is moist from sweating, increasing frictional resistance. A similar condition can be seen in competitive cyclists, but it has been suggested that the injury is thermal rather than the result of friction [31].

Corns and calluses

Many sporting activities result in calluses and corns. Some special examples include 'pulling boat hands' [32] in which there is an additional effect of cold injury, and 'rower's rump' [33]. When calluses or corns are a problem on the feet in runners, it is important to consider basic biomechanical principles of the foot, which may require specialist orthopaedic intervention.

Athlete's nodules

An entity sometimes known as surfer's or athlete's nodules can present on the anterior tibial prominence [34], dorsa of the feet or knuckles [35]. These asymptomatic nodules show dermal fibrosis as well as epidermal hyperplasia. A similar ovoid, largely dermal nodule occurring in the sacrococcygeal area of Japanese students has been attributed to pressure from the bicycle saddle over a distinctive abnormally posteriorly projecting sacrum [36,37].

Other frictional effects

Acne mechanica is common in many participants in sports [38] and may precede acne keloidalis nuchae in football players [39].

'Swimmer's shoulder' is a transient erythematous plaque caused by friction from an unshaven face during freestyle swimming [40].

Intertrigo of the groins is a frequent problem in the heavily muscled athlete. 'Judo jogger's itch' [41] occurred while jogging following vigorous judo but may be a manifestation of a dry skin subjected to abnormal physical and climatic trauma. A distinctive eruption of symmetrical erythematous linear plaques on the palms has been described in children, resulting from grabbing the floor and walls of the pool while swimming underwater [42].

'Mogul skier's palm' consists of hypothenar ecchymoses from repetitive planting of ski poles [43]. 'Hooking thumb' is unique to competitive weightlifters and consists of abrasions, haematomas and calluses on the distal third of the thumb [44].

Miscellaneous

Striae distensae have been associated with weightlifting [45,46]. The areas of skin most frequently involved are the anterior shoulders, lower back and thighs. Painful piezogenic pedal papules have also been ascribed to sporting activities [47]. 'Bicyclist's vulva' is a unilateral lymphoedema resulting from repeated chafing and folliculitis; investigations showed previously unrecognized abdominopelvic lymphatic abnormalities [48].

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Skin signs of torture

Definition. In its Tokyo declaration, the World Medical Association in 1975 defined torture thus: 'Deliberate, systematic or wanton infliction of physical or mental suffering by one or more persons acting alone or on the orders of any authority, to force another person to yield information, to make a confession, or for any other reason'.

Prevalence. Amnesty International has listed 144 countries known for some form of human rights violation [1].

Clinical features. Dermatologists may be involved in caring for victims of torture immediately after it has been inflicted, but are far more likely to see individuals as patients or for legal purposes when the acute injury has settled and the signs are those of previous tissue damage [2,3]. The immediate signs of torture (e.g. abrasions, skin defects and haematomas) are dealt with in depth by Rasmussen [4].

It is important to recognize that, in some societies, the torturer takes great effort to minimize or avoid visible external signs from the injuries inflicted. Another characteristic is that beneath the normal or near-normal skin, there may be long-term or permanent injury (e.g. fractured bones, fibrosis of muscles, damage to nerves and tendons).

Examination of the victim of torture should take account of the potential legal implications as well as the emotional welfare of the victim [5]. The wider aspects of the psychological consequences for the victim, and aspects of rehabilitation, should also be considered by the physician caring for the victim of torture [6].

Specific injuries

Acute injuries in the form of bruising, oedema, abrasions and lacerations may be evident from their pattern as being consistent with some form of assault. As with child abuse, the weapon may have left a distinctive imprint, such as petechial haemorrhages produced by a hand, or parallel lines from a truncheon or stick. Usually, the dermatologist will be presented with scars, and it is important that a careful history is taken to support the diagnosis. There are a number of close mimics of the sequelae of torture.

Beating or whipping

These often produce parallel or criss-cross lines on the back or buttocks. Over bony points the residual marks tend to be circular. If the victim has been able to use his or her arms to protect the face, scars may be found on the backs of the forearms and hands rather than the face.

Beating on the soles of the feet

SYN. FALANGA; BASTINADO

This form of torture is used throughout the Middle East, in India and Sri Lanka. As well as damage to the skin and soft tissues, falanga can produce alterations in the plantar aponeurosis, tendons and joints in the feet. Immediately after the beating has been carried out, there is gross swelling and exquisite pain on walking. Late falanga symptoms include pain in the legs and feet, which tends to increase during the day and with exercise. The springiness of the subcutaneous tissue of the forefoot area and heels can be permanently damaged, producing so-called 'smashed' balls of the feet [7,8]. The loss of elastic resistance in the soft tissue of the balls of the feet is best tested when the patient is standing. Not all observers of falanga victims have found these characteristic changes [5]. Magnetic resonance imaging shows a distinctive thickening of the plantar aponeurosis in most cases [9].

The after-effects of falanga can be greatly helped by appropriate physiotherapy and supportive footwear.

Kicks

Injury from kicking tends to produce more or less circular scars over areas where there is bone close to the skin such as the patellae, shins and ankles.

Electrical burns

Electrical burns rarely leave permanent scars, but there may be fine, white, linear or puckered circular scars or groups of red punctate marks. If electricity is passed through clips applied to the skin, there is a greater likelihood of scarring. If seen early after electrical torture, there may be brown scales at the site of application of electrodes [4]; there are vesicular changes in the nuclei of cells in the epidermis, vessel walls and sweat glands [10], and a distinctive pattern of calcification is seen [11]. These changes can be helpful in distinguishing electrical and thermal injury. Scars may be grouped around a target area such as the nipples, lips, ear lobes or helices [12]. In a type of electrical torture known as Picona, an electrically charged needle is used repeatedly on a sensitive site, and may leave clusters of scars [13,14]. Scars on the genitalia, a frequent site of electrical torture, are rare because the skin of the penis or vulva does not scar easily. The pubic skin nearby, however, is very easily scarred.

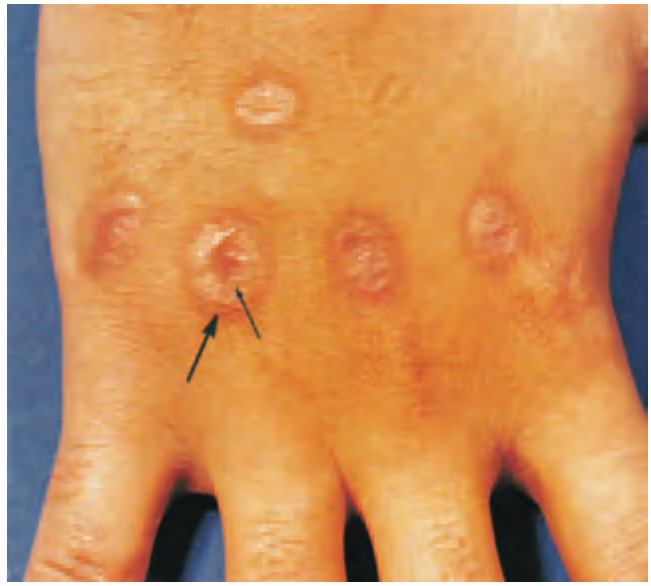

Fig. 22.12 Torture. Circular lesions on the dorsum of the left hand presenting a thin, atrophic and wrinkled centre (thin arrow) and a narrow hyperpigmented zone in the periphery (thick arrow). (Courtesy of Amnesty International.)

Cigarette burns

Burns from cigarettes or heated circular instruments tend to be distinctive (Fig. 22.12). Brief contact with a cigarette tends to leave little scarring, but if there has been prolonged contact, there may be a deep puckered circular scar with a thin silvery surface. Deliberately inflicted cigarette burns are often applied to a part of the body that is readily accessible to the interrogator, for example the front of the thigh, or back of the forearm or hand, if the victim was seated. Such injuries are often inflicted in a regular pattern.

Stab wounds

Stabbing with a knife usually leaves a regular 1–2 cm linear scar. A bayonet, however, has one sharp edge and one blunt one and this may leave a teardrop-shaped scar. If a metal implement sharpened to a point is used to prod the victim it leaves a circular scar somewhat like a deep cigarette burn.

Inflicted injury to finger- and toenails

Finger- and toenails may be crushed or removed, or implements pushed beneath them. The end result is usually thickening and distortion of nail growth, but this can be difficult to distinguish from other forms of trauma.

Mimics of torture

Scars may have an innocent origin, for example from accidents, sporting injuries, etc. These are often on the most exposed parts of the body. Common dermatoses, such as acne and insect bites, particularly if the latter are infected, can leave prominent scarring. Tribal markings and traditional healing practices, involving injuries inflicted by knives, burning, etc., can be problematic in differential diagnosis. Scars from such practices are often parallel and in groups. Some Islamic fundamental sects ritually flog themselves with whips or chains and this can also result in parallel linear scarring. Vaccination may be a cause of prominent scarring, but the site is usually characteristic. Occasionally, operation scars can cause confusion.

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Skin signs of child abuse

Child abuse is usually a clandestine activity denied by the perpetrator. The diagnosis can be very difficult to establish and may require the analytical observational skills of a dermatologist. There is often a differential diagnosis—physical abuse, accidental injury and various naturally occurring conditions can closely resemble one another and may coexist. Four circumstances may arouse suspicion of child abuse: suggestive physical findings, the past and present medical history, behavioural abnormalities exhibited by the child and the psychosocial conditions that are unearthed during the consultation. Suspected child abuse is best managed by a team including a paediatrician and social worker, following a framework of guidelines. Over the past two decades several reviews have detailed the features that should be understood by the dermatologist [1–7].

Definition. Child abuse is treatment of a child by an adult in a way that is unacceptable in a given culture at a given time [8]. Commonly, there is subdivision into four categories:

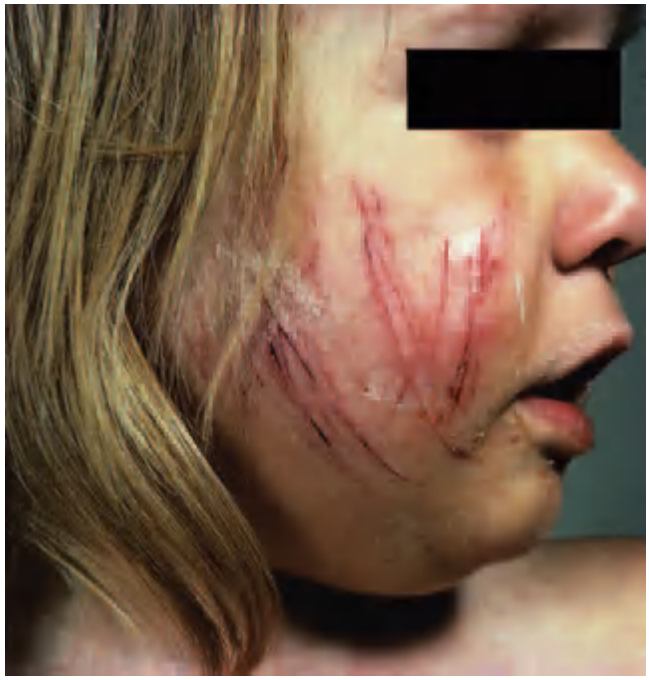
1 *Physical abuse* (syn. non-accidental injury): bodily injury is deliberately inflicted or the child is forced to engage in a harmful activity
2 *Sexual abuse*: inappropriate exposure to sexual acts or materials
3 *Emotional abuse*: coercive, demeaning or overly distant behaviour so as to interfere with normal psychological or social development
4 *Neglect*: the failure to provide the basic needs of life [9].

There are many difficulties with these definitions. For example, physicians (and others) do not agree among themselves as to what constitutes an 'acceptable' level of physical punishment for a child [10]. Society itself may have a high level of violence, and may tolerate widespread use of corporal punishment in its schools [11]. It can be difficult to categorize physical damage caused by healing practices used by some cultures and faiths, for example coin-rubbing (p. 22.26) and moxibustion, although members of satanic cults who subject children to physical and sexual abuse are generally regarded as transgressing the law.

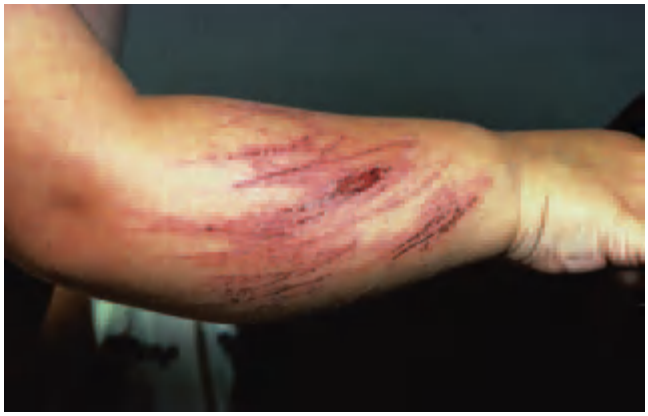
Epidemiology. In the USA, a national survey indicated a prevalence of 16 in 1000 for child abuse [12]. The actual prevalence may be much higher—in the UK, 4% of children up to the age of 12 years are brought to the notice of professional agencies because of suspicions about possible abuse, and approximately 1 in 1000 children under 4 years suffer severe physical abuse [8]. In the USA, at least 4000 children die each year as a result of child abuse and neglect [13]; Meadow gives an estimate of 1 in 10 000 for the UK [8]. There is evidence that child abuse is becoming more common [8,11]. Although child sexual abuse occurs across the social strata, physical abuse and neglect are correlated with poverty [13].

Most child abuse is perpetrated by a family member, usually a parent or a cohabitant, for example the mother's boyfriend. Abuse is about 20 times more likely if one of the parents was abused as a child. Young parents seem more prone to abusing than older ones.

The different forms of child abuse may be concurrent, so the dermatologist must be vigilant to examine for forms of injury beyond that presenting in the skin (e.g. fractures, ruptured viscera, brain damage) and to evaluate for emotional abuse and neglect.



(a)



(b)

Fig. 22.13 Non-accidental injury. Scratches inflicted by the child's mother. (Courtesy of Dr B.K. Sandhu, Bristol Royal Children's Hospital, Bristol, UK.)

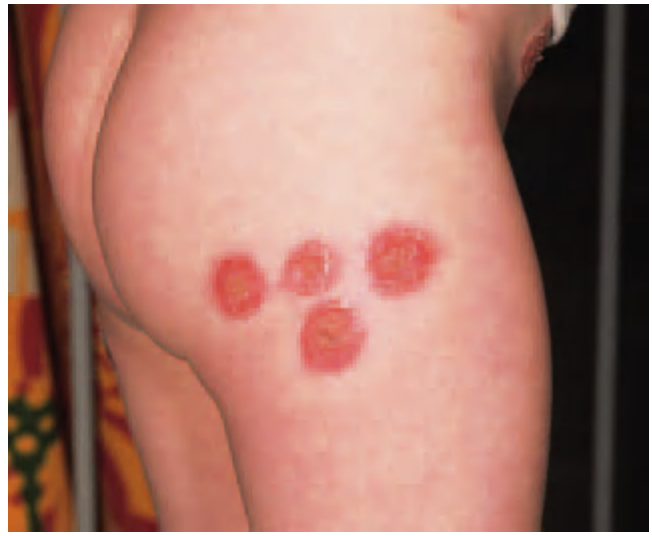


Fig. 22.14 Non-accidental injury. Superficial burns.

Physical abuse

Clinical features. The many manifestations of deliberate harm to children are illustrated in great depth in the monograph by Hobbs and Wynne [6]. The most common lesions that may present to a dermatologist are bruises and abrasions, followed by lacerations, scratches (Fig. 22.13), soft-tissue swellings, strap marks, haematomas, burns and bites [11]. Bites can be recognized as human by measuring the intercanine distance (greater than 3 cm implicates a perpetrator with secondary dentition) and recording the pattern of the puncture marks. Cigarette burns can often be suspected when there are one or multiple rounded crater-like ulcers or erosions. Acutely, there may be singed vellus hairs. Immersion burns tend to be sharply demarcated and uniform in degree [14] and there are often no splash marks (for further discussion of deliberately inflicted burns see p. 22.83). Needle injuries are a rare cause [15].

In general, one or more of several clues may point towards physical abuse:

1 Unconvincing delay in seeking medical help. With genuine injury there is a speedy request for help in most cases.

2 Details of the history appear implausible, change over time and/or are inconsistent with the developmental capabilities of the child.

3 Lack of concern by the person bringing the child.

4 Abnormal reactions, for example hostility to medical staff.

5 Abnormal demeanour by the child.

6 Disclosure by the child that the injury was inflicted.

7 Lesions have a shape or pattern recognizable as being caused by the means that inflicted them. Examples include bruises in the shape of a hand or pressure from fingers, linear lesions from being struck by a cord or coat hanger, the imprint from the buckle of a belt, and burns from metal utensils such as spoons (Fig. 22.14).

8 Location of lesions. Bruises from accidental trauma are usually over the bony prominences [16], such as knees, forearms, elbows, shins and forehead. Those resulting from abuse are often on the soft parts of the thighs, abdomen, buttocks, cheeks, neck and anogenital regions. Bruising in the mouth, and tears of the frenulum of the tongue, should arouse suspicion.

9 Multiple injuries over many body sites in different stages of healing.

10 The presence of other signs that suggest physical abuse. These may include bilateral periorbital ecchymoses,

retinal haemorrhages, rib fractures and traumatic hair loss. The latter may be suspected when the scalp is bruised or tender.

Management. It is essential that the child is examined in a comfortable supportive environment and that meticulous details are recorded in any case of suspected child abuse. It is important that the examination includes the mouth and anogenital areas. It is often necessary for permission to be granted. If possible, photographs should be taken. There is usually a statutory procedure to be followed when child abuse is suspected, which will necessitate the involvement of those with expertise in paediatric examination and assessment of the social setting of the child.

When bruising is present, the colour and location of each lesion should be documented. Bruises can be aged according to colour: red, 0–1 day; blue/purple, 1–4 days; green/yellow, 5–7 days; yellow/brown, 8–10 days; cleared 1–3 weeks [17], although more recent work has cast doubt on the reliability of these conclusions [18–20].

Investigations may be needed. When bruising is present, it is prudent to request a full blood count and clotting screen. Swabs should be taken from fresh bite marks. If there are reasons to suspect bony injury, a skeletal survey may be appropriate, as may an abdominal ultrasound for evaluation of the viscera.

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Differential diagnosis. As well as being called on to recognize the varied physical signs of deliberate damage to the skin, the dermatologist may have to diagnose a wide variety of simulants of inflicted injury. These include purpuric and vascular disorders, some other causes of hyperpigmentation, blisters that can mimic burns and unusual scars. Establishing the dermatological diagnosis will require a full and careful history with all appropriate investigations. Animal bites can usually be distinguished by the narrower punctures and different spacings. Some examples of physical and sexual child abuse are summarized in Table 22.5 [1–34].

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Table 22.5 Some dermatological mimics of physical abuse.

Mimics of bruising caused by physical abuse
Purpura, vascular and pigmentary problems
Disorders of coagulation [1,2]
Valsalva petechiae (vomiting and coughing) [3]
Sports injuries
Vasculitis [4]
Acute haemorrhagic oedema [5,6]
Erythema multiforme [7]
Perniosis [8]
Vascular malformations [9]
Haematoma from hair combing [10]
Ehlers–Danlos syndrome [11]
Topical steroid misuse
Incontinentia pigmenti [12]
Phytophoto dermatitis [13,14]
Medication-induced hyperpigmentation (e.g. fixed drug eruption)
Maculae cerulae (pediculosis) [15]
Coin rubbing (*cao gio*) [16] and spooning [17]
Cupping [18]
Hair-thread tourniquet syndrome [19]
Mongolian spots [20]
Urticaria pigmentosa [21]
Subcutaneous fat necrosis
Morphoea
Neuroblastoma [22]
Ink or dye stains [23]
Mimics of burns caused by physical abuse
'Therapeutic' burn [24]
Moxibustion [25]
Car seat burns [26]
Impetigo [27]
Immunobullous diseases
Photodermatoses, phytophotodermatitis
Enuresis blanket [28]
Chemicals [29]
Mimics of scarring caused by physical abuse
Ehlers–Danlos syndrome [30]
Striae [31–33]
Miscellaneous disorders that have mimicked physical abuse
Congenital indifference to pain [34]
Angio-oedema [1]

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Sexual abuse

Sexual abuse has been defined as: 'Each and every sexual act that injures the self-determination of any person, who has either not reached a certain age, or who stands in a particular relation to the perpetrator, or who is unable to defend him/herself as a result of their physical or mental condition' [1]. It may occasionally have to be considered when there are physical signs suggestive of acute injury to the vulva, penis, anus and oral cavity in adults with learning difficulties, but the dermatologist is much more likely to see cases suspected of child abuse.

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Child sexual abuse

Child sexual abuse has been defined as: 'Any use of children for the sexual gratification of adults' [1]. The dermatological features have been reviewed [2,3] and are illustrated extensively in Hobbs and Wynne's monograph [4].

Acutely, child sexual abuse presents with one or more of four types of complaint:

1 Symptoms caused by local trauma or infection, such as perineal soreness, bleeding, vaginal discharge and anal pain
2 Those caused by emotional effects of the abuse (e.g. enuresis, encopresis and anorexia)
3 Sexualized conduct
4 Sexually transmitted disease.

When a child presents with perianal warts or molluscum contagiosum, the possibility of sexual abuse will need to be considered even though there may be an innocent explanation.

As with the examination for physical abuse, it is important that the conditions for the examination are conducive and that appropriately skilled personnel are involved [1,5]. For anal and genital examination, colposcopy is very useful [4]. An assessment of the vulva should include the size, shape and any irregularities of the hymenal orifice, especially tears, and whether there are any swellings within the hymenal membrane; any erythema, swelling or bruising of the labia; and any vaginal discharge. Digital penetration tends to produce tears anteriorly, whereas penile penetration is associated with tears of the posterior fourchette. The examiner should be aware of normal variants of paediatric genital anatomy [4,6]. Bruises or scratching in areas adjacent to the anogenital region should raise suspicion. Perianal signs that may cause concern include multiple fissures, swelling or thickening, and

purpura. It is important to examine the mouth for signs of oral sex (e.g. palatal petechiae). There are specialized techniques for detection of semen [7].

With the exception of finding semen, lubricants or hairs, or genital infection with *Neisseria gonorrhoeae*, it can be impossible to prove sexual abuse on the basis of physical signs and investigations alone. Nevertheless, appropriate swabs should be taken to culture the full range of sexually transmitted pathogens and other likely infective agents.

For most cases where there is some suspicion (e.g. from sexually precocious conduct by the child), evident emotional disturbance or a disclosure of sexual abuse, it is essential for the dermatologist to involve the appropriate paediatrician and support team. The dermatologist should be aware that child sexual abuse often has long-term psychological consequences that can underlie dermatitis artefacta, 'neurotic excoriations', various manifestations of body dysmorphic disorder, compulsive washing practices and vulvodynia [8]. If previous child sexual abuse is recognized as a causative factor, psychotherapy can prove helpful.

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Differential diagnosis. Almost any condition that can cause inflammation or bruising in the anogenital region may cause concern if there are social or other circumstances pointing towards sexual abuse, as may infection that is not inevitably sexually transmitted. Accidental trauma can also present difficulties [1]. Probably the most common dermatosis mistaken for child sexual abuse is lichen sclerosus, especially when there is subepidermal haemorrhage or when fissures are present [2,3]. If necessary, a biopsy can confirm the diagnosis. The dermatologist should, however, be aware that lichen sclerosus and sexual abuse are not mutually exclusive, not uncommonly coexist, and it has been suggested that trauma is a contributory factor in the aetiology [4].

As with physical abuse, other causes of bruising may need to be considered. These include idiopathic thrombocytopenic purpura, other bleeding diatheses and Ehlers–Danlos syndrome [5]. Haemolytic uraemia syndrome has presented with rectal bleeding thought to be caused by sexual abuse [6]. Conditions that mimic bruising include Mongolian spot, phytophoto-dermatitis (e.g. from prior handling of psoralen-containing plants or innocent transfer of lime juice onto the buttocks and thighs followed by sun exposure) [7,8] and dyes on the skin from clothing. Bleeding from vulvar haemangioma has been mistaken for sexual abuse [9], as have various congenital anomalies of the genitalia, such as hymenal tags and clefts [10]. Urethral disorders, particularly those that bleed, have led to suspicion of abuse (e.g. caruncle [5] and urethral prolapse [11]). Many blistering disorders have been mistaken for child sexual abuse (e.g. vulvar pemphigoid) [12] and chronic bullous disease of childhood [13].

Perianal Crohn's disease [14], abscesses and fistulae may resemble the fissures and scarring that can occur from anal abuse. Strangulation of the penis or clitoris is usually accidental [15–17].

The reliability of anal dilatation as a sign of abuse has been questioned [18,19]. However, gross examples are more likely to be significant. It is worth noting therefore that severe constipation [20] and neurological disorders [21] can cause marked anal dilatation. Accidental trauma (e.g. from the crossbar of a bicycle) can cause contusion of the external genitalia, including the clitoris and anterior parts of the labia, but is not likely to damage the hymen; in contrast, penetrative vulval abuse tends to damage the posterior parts of the vulva [15,16,22].

Much trauma is done by the act of female circumcision, which may not be admitted. Infectious diseases that may be wrongly attributed to sexual abuse include yaws, in which syphilis serology will be positive [23], and streptococcal infection of the anus, vagina, urethra and penis.

Some infections that can be sexually transmitted, but are not necessarily so, include herpesvirus type 2, anogenital warts (even the human papillomavirus types most associated with the genital tract) [24] and molluscum contagiosum.

Occasionally, common dermatoses that produce erythema, such as irritant dermatitis, seborrhoeic dermatitis, atopic dermatitis, napkin dermatitis, psoriasis, candidal infection or threadworm infestation, may require correct diagnosis in the context of suspicion of abuse.

Some of the conditions discussed above are included in Table 22.5.

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Traumatic lesions during intensive care

The complex technology now involved in intensive care includes a number of invasive procedures and other devices that can cause cutaneous lesions [1–3], and for convenience these are summarized here. Continuous arterial catheterization may lead to bruising, haematomas and even local or peripheral skin necrosis [4–6]. Other sites of necrosis may be caused by pressure of headbands or other attachments. Phlebitis may occur from infection or irritant intravenous agents. Blisters can arise resulting from heat generated beneath oxygen transducers, perhaps more so in children than in adults [7]. When conducting gel is smeared across the chest wall, electrical burns can result from arcing between the paddle electrodes used for defibrillation or cardioversion; in most centres this is avoided nowadays by using prepackaged conducting gel pads [7]. Erythema ab igne has been described following malfunction of an adjustable temperature blanket [8]. Even though preventive measures are widely used, pressure ulcers do occur (p. 22.17).

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Cutaneous injuries in the newborn

In the neonatal period, iatrogenic injury can be caused by trauma before, during or after delivery [1]. The skin of the newborn, especially if premature, is especially vulnerable to various noxious insults. Examples of prenatal injury include amniocentesis or fetal skin biopsy, leaving a dimpled scar. Common intrapartum injuries include that caused by the heart-monitoring scalp electrode, laceration from episiotomy or amniotomy, ecchymosis and variable oedema from vacuum extraction or delayed delivery. Post-natal mechanical trauma can be caused by the identification tag, blood sampling by heel prick, intravenous cannulae, and pressure from the prone position to the nose, toes and knees. Heating pads and monitoring devices can cause second- or even third-degree burns.

Neonatal injuries are considered further in Chapter 14.

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Penile injuries

A variety of constrictive bands at the base of the penis are used by some individuals to increase sexual gratification. Sometimes these can become incarcerated and cause secondary ischaemic injury [1].

Human hair accidentally wrapped round the penis has caused penile oedema [2].

Petechiae may result from squeezing the glans to prevent premature ejaculation [3]. Zip-fastener tears are less common than previously, possibly because of the popularity of Y-front briefs. Lesions resulting from sexual experimentation may be bizarre. Vacuum cleaners can cause various injuries to the skin and urethra [4,5] and a meatal stricture may result.

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Signs of emotional abuse and neglect

Neglect may be evident from malnutrition, an uncared-for dirty appearance, exaggerations of common dermatoses or lack of appropriate immunizations for the child's age [1]. Some examples of burn and scald are a result of neglect rather than deliberate physical abuse [2]. Both physical neglect and 'emotional abuse' can result in failure to thrive with depressed gain in height and weight. Cold swollen blue or red hands and feet have been described in cases of emotional neglect [3,4]. Some would consider the failure to administer treatments (e.g. to a child with eczema) as a form of child abuse.

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Munchausen syndrome by proxy

This term is used to denote the situation in which the parent or caretaker falsely attributes symptoms in order to gain medical care or some other benefit. Such behaviour can result in multiple unnecessary surgical interventions [1].

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Foreign bodies

Definition. Some extraneous materials (e.g. silica and zirconium) incite a characteristic pattern of granulomatous reaction in which a distinctive type of multinucleate giant cell, the foreign-body giant cell, is prominent. The term foreign-body reaction is used for this tissue response but may also be used for other patterns of pathological response to extraneous materials that become deposited in the skin or deeper tissues, usually as a result of direct penetration of the skin by the material itself, during surgery or by injection. Epidermis, hair and nail can induce a 'foreign-body' response if implanted in or beneath the dermis. Cutaneous reactions to medicaments introduced at a distant site (e.g. the pigmentation caused by minocycline) and some local adverse reactions to drugs are considered in Chapter 73.

Aetiology. Some examples of the types of foreign body and routes of entry are shown in Table 22.6 [1–48].

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Table 22.6 Foreign bodies: their source and investigation.

Source	Material	References	Pathological features
Traumatic	Metals		H, EDXA as appropriate, e.g. Hg
	Glass		P, EDXA (Si)
	Graphite, e.g. carbon fibre	Young *et al*. [1]	P, characteristic heat resistance up to 600°C
	Thorns, wood splinters	Mehregan & Faghri [2]	
	Other vegetation	Hirsh & Johnson [3]	P, H&E; rectangular cell walls
	Cactus spines	Winer & Zeilenga [4]	PAS + (may be concurrent) bacterial and/or fungal infection [7]
		Snyder & Schwartz [5]	
		Lindsey & Lindsey [6]	
		Connor & Gibson [8]	
	Sea-urchin spines	Kinmont [9]	
	Arthropod mouth parts	Allen [10]	
	Grease gun injury	Schon *et al*. [11]	H&E; extensive necrosis and thrombosis
	Blast injury	Mesquita-Guimaraes *et al*. [12]	EDXA (Si)
		Hanke [13]	
	Amalgam tattoo	Hatch [14]	EDXA (usually Hg, Ag, Sn)
		Hartman *et al*. [15]	
	Synthetics:		
	Plastics	Cortez Pimentel [16]	
	Fibres	Centeno *et al*. [17]	P, H, FTIRM
	Epidermis	Stein [18]	
	Hair	Hogan [19]	P, H&E appearance
	Nail	Brown *et al*. [20]	
Occupational	Beryllium	Jones Williams [21]	EELS
	Silica	Mowry *et al*. [22]	P, EDXA (Si)
	Hair	Hogan [19]	P, H&E appearance
	Fibreglass	See p. 22.49	P
Cosmetic	Tattoos	See p. 22.50	H&E appearance, EDXA (appropriate elements)
	Silicone	Travis *et al*. [23]	
	Collagen	Swanson *et al*. [24]	IRS or EDXA (Si), H&E; vacuoles
		Kligman *et al*. [25]	Immunoperoxidase using antibovine type I collagen antibody
		Morgan [26]	
	Paraffins	Oertel & Johnson [27]	
	Vegetable oils	Alagaratnam & Ong [28]	H&E; 'Swiss cheese' cavities
		Nakamura *et al*. [29]	FDMS
	Zirconium	Hirsh & Johnson [30]	EDXA (Zr)
Surgically implanted	Suture materials	Postlethwaite *et al*. [31]	P, H&E
	Talc	Terzakis *et al*. [32]	P, EDXA
	Starch	Lennard [33]	P, PAS + crystals with Maltese cross appearance on polaroscopy
	Absorbable gelatin	Jaworsky [34]	
Injected drugs	Insulin	Jordaan & Sandler [35]	H&E appearance of acellular sponge material
	Vaccines	Slater *et al*. [36]	
		Garcia-Patos *et al*. [37]	EDXA (Zn)
		Morgan [38]	EDXA (Al)
	Calcium salts		H, EDXA (Ca)
	Intralesional corticosteroid	Goldman [39]	
		Weedon *et al*. [40]	H&E; granular, amorphous, acellular material
		Bhawan [41]	
		Morgan [38]	
	Polyvinylpyrrolidone	Kossard *et al*. [42]	
		Morgan *et al*. [43]	
	Vitamin K	Texier [44]	
Self-inflicted	Narcotic and analgesic abuse, e.g. pentazocine (Fig. 22.16), meperidine	Padilla [45]	H&E (P if talc from tablets is used); thrombosis and fibrosis
		Posner & Guill [46]	
	Talc in fillers used by intravenous drug abusers	Hirsch [47]	EDXA
	Dermatitis artefacta using injections of faeces, milk, etc.	Sullivan [48]	H&E; necrosis, abscesses

Key to techniques: EDXA, electron dispersive X-ray analysis; EELS, electron energy loss spectroscopy; FDMS, field desorption mass spectroscopy; FTIRM, Fourier transform infrared microscopy; H, histochemical reaction available; H&E, haematoxylin and eosin; IRS, infrared spectrophotometry; LAMMA, laser microprobe mass analysis; P, birefringence by polarization microscopy; PAS, periodic acid–Schiff stain.

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Pathogenesis. The biological response to a foreign body will depend on its composition, how it enters the body, the body site, the quantity of material and its physical form. In some instances (e.g. mercury and some animal and vegetable matter), a toxic or allergic reaction can occur as well as a later foreign-body reaction. Some reactions are complicated by infection, especially traumatic inoculation of wooden splinters and vegetation spines, which can introduce sporotrichosis and deep mycotic organisms as well as more common pyogenic infections. Infection may also localize to sites of inert foreign bodies during bacteraemia [1].

Pathology. When material has penetrated the skin there is usually a phase of acute inflammation in response to the injury. This may be necrotizing if there is significant trauma, toxin release or bacterial infection. Persistence of foreign material results in accumulation of monocytes, evolution of these into tissue macrophages, epithelioid histiocytes and giant cells (Langhans' and foreign-body type) and a fibroblastic reaction with laying down of new connective tissue around the area of foreign-body deposition.

Penetration injury can also result in implantation cysts mixed with granulomatous response.

Polarizable foreign bodies can be seen in biopsies of otherwise typical sarcoidosis, and if adequate criteria are met for a diagnosis of sarcoidosis, such foreign body material does not alter the diagnosis [2].

Clinical features. The clinical presentation will depend on the mode of entry and nature of the foreign body, the tissue response to it and whether there is associated infection. In some instances, there may be characteristic toxic effects (e.g. absorption of mercury from a broken thermometer) [3]; pharmacological effects (e.g. resulting from alkaloids in blackthorn) [4]; or allergic responses (e.g. to oils and resins in some woods).

Retained foreign bodies are commonly associated with bacterial infection, which tends to be resistant to antibiotic therapy. Vegetative foreign bodies may be associated with fungal infection. Soft-tissue infections may manifest as cellulitis, an abscess or a draining sinus. A wound that fails to heal or continues to cause pain with movement may conceal a foreign body, as can the persistence of a purulent discharge.

Many types of foreign body elicit a granulomatous response, seen clinically as erythematous brown or purple papules, nodules or plaques. The lesions often become harder over time because of fibrosis. Some materials result in discharge even when there is no infection (e.g. paraffins and other oils).

The implanted material may produce pigmentary change (e.g. carbon and metals result in a tattoo-like, black or bluish-black colour). Occasionally melanoma is simulated.

Clinical presentation can be modified by epidermal cyst formation, resulting from pieces of epidermis being carried in by a penetrating foreign body. It is important to recognize that even small external signs of entry of a foreign body can denote significant damage to deeper structures, such as tendons, joints and bones. This is especially true of high-pressure injection (grease, paint, water and some firearm injuries).

Diagnosis. Lacerations should be carefully examined for foreign bodies, using instruments rather than the gloved finger if there might be a sharp object in the wound. Palpation of a mass may justify extending the wound so as to explore it adequately.

When there is strong suspicion that all or part of a foreign body is in or beneath the skin, imaging techniques should be considered.

Plain radiography. A plain X-ray will often detect a foreign body, but visualization depends on the object's density, configuration, size and orientation. Metal, bone, teeth, pencil graphite, some plastics, glass and gravel are radio-opaque but may not be visible if located over a radiologically dense background such as bone. Some materials that are less dense than tissue can be seen as filling defects (e.g. white pine) [5], but very often organic foreign bodies are not visible on plain radiographs, especially 48 h or more after entry [6]. Plain films, using multiple projections, can enhance localization.

Ultrasonography. Ultrasound imaging is often helpful for vegetative foreign bodies that are not visible on plain X-ray, but there are a number of pitfalls in interpretation, especially in the hand [7,8]. Wooden splinters can be obscured by surrounding granulomatous tissue [9], and old scar tissue, small bones, fresh bleeding and sutures can produce false-positive reactions [10].

Computed tomography. Computed tomography (CT) scanning, which can visualize wooden material, has the advantage of producing images in multiple planes, which can aid localization and can relate a foreign body accurately to nearby structures. However, there is a greater radiation dose than plain radiography, so CT is best avoided as a screening procedure.

Magnetic resonance imaging. Magnetic resonance imaging (MRI) is comparable to CT for materials of similar density to soft tissue (Fig. 22.15) and may be superior for the detection of plastics [11], but must not be used for metal fragments. Gravel produces a severe artefact.

Histopathological techniques [12]. For foreign bodies below the limits of detectability by imaging techniques, it may be possible to make a diagnosis on material taken at biopsy by microscopic or ultrastructural techniques.

Some foreign materials have a distinctive microscopic structure, for example the regular arrays of plant cells in some vegetative material, such as wooden splinters and thorns. The presence of particulate material in phagocytic cells can often be seen on routine haematoxylin and eosin-stained sections. The periodic acid–Schiff (PAS) stain often shows up splinters, talc, starch and fungi. Dark-field illumination can help visualize some metallic materials. Polarization microscopy can demonstrate silica, talc, suture material, wood and plant matter [13]. In suitably processed material, the elements present can be ascertained by electron dispersive X-ray analysis (EDXA) and for lower-molecular-weight substances electron energy loss spectroscopy (EELS) may be appropriate [14].

The application of different methods is indicated in Table 22.6.

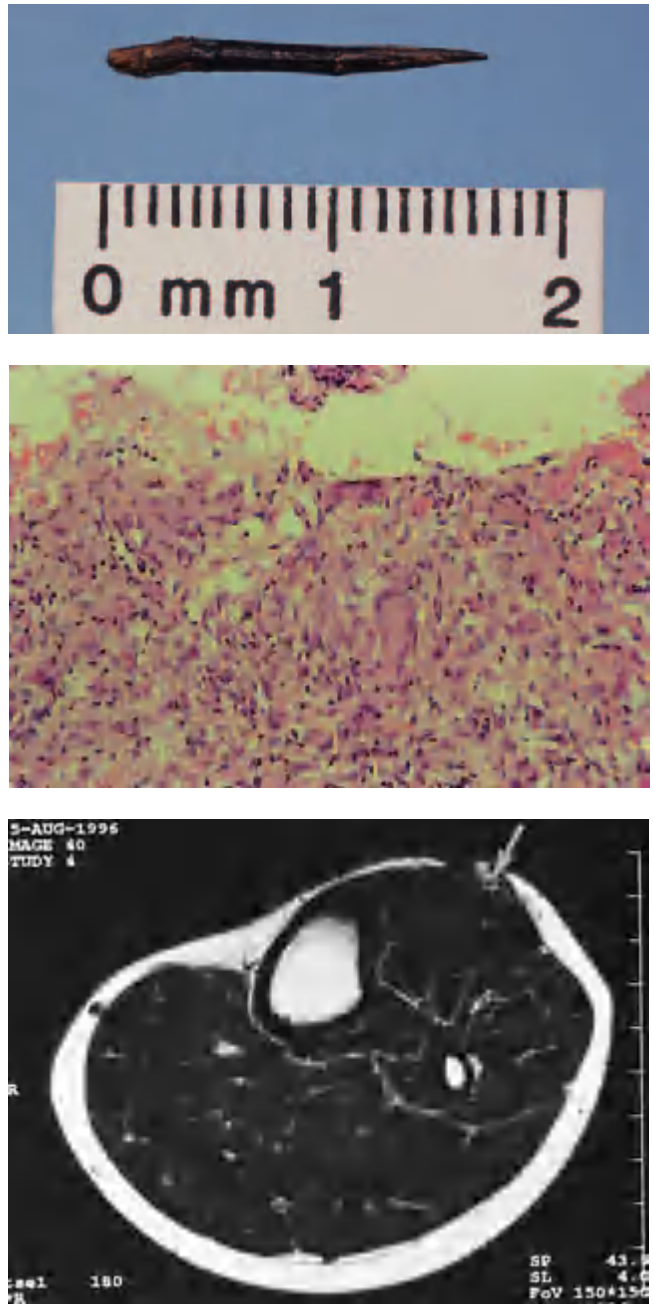

Fig. 22.15 Foreign-body reaction caused by deeply embedded thorn. The patient presented with a chronic leg ulcer. (a) Thorn that eventually emerged spontaneously. (b) Mixed inflammatory and granulomatous reaction from the ulcer bed. (c) Magnetic resonance imaging scan showing sinus tract containing the thorn (in cross-section, at tip of arrow).

Treatment [15]. It can be a difficult judgement as to whether or not to remove a foreign body. Some indications for removal of a foreign body are shown in Table 22.7. Non-reactivity, small size and inaccessibility may weigh in favour of leaving a foreign body. Vegetable material is often best removed. All wounds should be clean and tetanus immunization provided if necessary.

Table 22.7 Indications for removal of a foreign body. (Adapted from Lammers and Magill [15].)

Reactivity of the material (e.g. thorns, spines, clothing)
Heavy bacterial contamination (e.g. teeth, soil)
Toxicity (e.g. spines with venom, heavy metals)
Proximity to tendons, vessels, nerves or fractured bone
Impairment of mechanical function (e.g. abnormal gait from foreign body in foot)
Intra-articular location
Potential for migration towards an important anatomical structure
Intravascular location
Persistent pain
Established infection or inflammation
Allergic reaction
Cosmetic or psychological considerations

The best approach to remove a foreign body will depend on the size, location and nature of the material, and length of time it has been there. A simple method for locating a radio-opaque foreign body is to insert two or three needles of different sizes angled at 90° to each other. Using radiographs in multiple projections, ultrasound or CT, the needle closest to the foreign body is identified, and tissue dissected along its path [16]. It may be possible to pull out the foreign body intact, or slide out a long pointed object along the axis it entered. Material likely to be dealt with by the dermatologist may often be excised as a block of tissue.

After removal, the wound should be irrigated and débrided if necessary. If the foreign body was radio-opaque, and there is any doubt about completeness of removal, a post-operative film can be carried out.

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Some distinctive foreign-body reactions

Paraffinoma

SYN. SCLEROSING LIPOGRANULOMA

Some vegetable oils containing triglyceride can be digested by lipases, but others, and mineral oils, greases and wax, cannot be broken down, and elicit a foreign-body reaction. Most instances of paraffinoma nowadays are caused by misguided attempts at tissue augmentation, often self-administered. The male genitalia is the most common site [1]; other sites include the male breast [2], gluteal regions and extremities. Paraffin gauze that was used to pack the nasal passages and sinuses has caused chronic inflammatory paraffinoma of the periorbital tissues [3,4].

The pathology of paraffinoma shows rounded clear spaces of varying sizes surrounded by fibrous tissue and a mixed inflammatory reaction, including foamy macrophages and multinucleated giant cells—the 'Swiss cheese' appearance.

Treatment is by excision.

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Polyvinyl pyrrolidone

This hydrophilic polymer, formerly used as a plasma expander, is still used as a slow-release agent in a few injectable medications. Occasionally, it can produce a soft-tissue mass, often after a long latent period [1]. The material appears as a distinctive blue-grey deposit in macrophages with little or no inflammation or fibrosis. By Congo red, polyvinyl pyrrolidone (PVP) stains a cherry-red colour [2].

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Hydroxyethyl starch pruritus

Hydroxyethyl starch (HES) is a plasma expander. It is widely used in intensive care units, and to improve the microcirculation in some otological and peripheral vascular diseases. Pruritus is a well-recognized complication, with a frequency of more than 30% in some European retrospective series [1,2] and 13% in a UK questionnaire survery [3]—although in a large prospective study the incidence was only 1% [4]. HES is deposited in the skin.

The pruritus usually begins between a few days and several months (typically within a few weeks) after the infusion. It is usually generalized, although can be localized (e.g. to the trunk or anogenital regions). Bouts of itching can be triggered by friction, bathing in warm water and physical exertions. HES pruritus is often severe and can last years. Usually there are no visible signs, but a single case has been described of diffuse erythematous skin infiltration [5].

HES is degraded in the plasma, taken up by histiocytes in many tissues including skin, and cleared through the kidneys. In the skin, HES accumulates in vacuoles within macrophages, which if abundant can resemble a storage disorder [5]. The vacuoles may also be seen in endothelial cells and basal epithelial cells. The identity of HES can be confirmed using specific immunostaining [6]. Only in patients who develop pruritus, the characteristic vacuoles are also seen in the various components of peripheral nerve cells, and resolution of itching is associated with eventual loss of the vacuoles [7].

It is not clear why only some patients given HES develop pruritus. In several series there is a threshold cumulative dose of approximately 200 g, although there is no close relationship to the volume given [3]. Patients with otological disease may be more susceptible than other groups [4]. Tissue storage is greater in those who develop pruritus [8].

The mechanism for pruritus is uncertain, although direct stimulation of cutaneous nerves by the deposits of HES has been proposed [9].

Treatment is unsatisfactory. The pruritus is unresponsive to oral antihistamines, topical or systemic corticosteroids and phototherapy, although topical capsaicin has some therapeutic value [9]. In most cases the pruritus resolves after 6–18 months.

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Sclerodermiform reaction to vitamin K

The intramuscular injection of preparations of vitamin K has been followed by an erythematous plaque in the lumbosacral area, which takes on a dusky colour and becomes infiltrated and itchy after 10–15 days. After some months, it resembles a patch of scleroderma, ivory-white in colour with a surrounding lilac ring. Confluence of plaques in the trochanteric and lumbosacral area produces the so-called 'cowboy's belt' appearance, complete with holsters. All the nine cases studied by Texier [1] had received other vitamins, liver extract or iron injections and no case resulted from vitamin K alone, but this ingredient was a common factor. Occasional cases have been described subsequently [2]. A case resembling eosinophilic fasciitis has also been described [3].

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Pentazocine ulcers (Fig. 22.16)

A distinctive woody induration with overlying ulceration is characteristic of repeated intramuscular or subcutaneous use of the analgesic pentazocine (Table 22.6). Such reactions are usually found in narcotic abusers.

Immunization granulomas

Temporary nodule formation at the site of immunization procedures may occur and usually subsides quickly. A more persistent granulomatous reaction resulting from the aluminium hydroxide component has been described [1] and may have an allergic basis in some cases [2,3]. This reaction has been found after administration of tetanus–diphtheria–pertussis [2,3], influenza [4] or hepatitis B [5] vaccines and after desensitization therapy with allergen extracts. A pure histiocytic foreign-body reaction is often

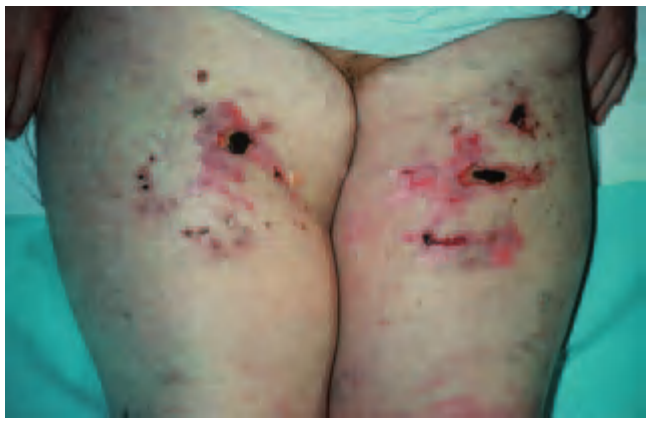

Fig. 22.16 Pentazocine ulcers.

observed in early lesions, whereas a delayed hypersensitivity granulomatous reaction is seen in older lesions. Although patch tests may be positive to aluminium [2], there is no relationship between patch-test results and the histopathological pattern [6]. X-ray microanalysis has shown the presence of abundant aluminium in the histiocytes [7]. In a series of 21 cases followed for up to 8 years, five cleared, improvement occurred in 11 and five were unchanged [3]. Patients known to have such reactions should in future receive non-adsorbed vaccines or toxoids [8].

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Angiolymphoid hyperplasia with eosinophilia
(see Chapter 53)

This has also been associated with tetanus toxoid inoculation [1].

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Zinc-induced insulin granuloma

A distinctive granulomatous response to zinc-insulin has been described [1] in which there is an acute neutrophilic response before granuloma formation. Other cutaneous and subcutaneous adverse effects of insulin preparations are discussed in Chapter 73. Use of a non-zinc insulin usually results in resolution.

REFERENCE

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Intralesional corticosteroids

Occasionally, deposits of injected insoluble corticosteroids have been associated with a granulomatous response [1,2] and in one instance a reaction resembling rheumatoid nodule has been described [2]. Other adverse effects of intralesional corticosteroids are discussed in Chapter 46.

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Silicone

Silicone (polydimethyl siloxane) is used medically in three forms: liquid for soft-tissue augmentation; bag-gel implants for augmentation mammoplasty; and as a solid elastomer in joint prostheses. In tissues, it has a characteristic of tending to migrate both locally and via lymphatics. Many of the reported adverse effects are likely to have been a result of adulterants, although even medical grade silicone can produce a granulomatous reaction [1,2]. The possible role of silicones in the aetiology of scleroderma and other connective tissue diseases is discussed in Chapter 56.

When silicone bag-gel material ruptures, it can migrate along fascial planes and gravitate into the skin, producing indurated inflammatory subcutaneous masses [3].

Following liquid or gel silicone injections, the histological appearance is of varying sized vacuoles similar to paraffinoma, but with less fibrosis and usually an absence of granulomatous response if medical grade silicone was used [4]. Sometimes, however, granulomatous reactions do occur [5].

Recently, cases have been described of multiple silicone-containing granulomas at the site of entry of acupuncture needles that had been coated in silicone oil [6,7].

If adulterants are present, a more inflammatory reaction is described. Particles of rubbery silicone elastomer

can elicit a vigorous foreign-body granulomatous response.

The Si–C chemical bond, characteristic of silicone and not found in nature, can be detected by infrared spectroscopy, and silicon can be demonstrated by EDXA.

Silicone reactions can only be eliminated by appropriate surgery, although amelioration of the inflammatory response by treatment with minocycline has been reported [8].

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Collagen implants

Injectable collagen for tissue augmentation has traditionally been of bovine origin; it is produced by selective hydrolysis of telopeptide regions, and is mainly type 1 collagen. A more durable form is cross-linked with glutaraldehyde (Zyplast®). Although bovine collagen implant is non-toxic and in general produces little irritation, transient erythema lasting 2–4 days is very common following its use. Before substantive treatment using this material is undertaken, patients receive a skin test. Of those who do not react to the test site, 1–3% will subsequently develop induration, which may progress to nodule formation. These nodules may last several months [1]. The glutaraldehyde cross-linked material is associated with fewer reactions [2]. Rarer reactions include intermittent swelling at the same site, which can last up to 3 years, sterile abscesses [3] and local necrosis [3,4].

When deposited in the dermis, bovine collagen implant appears microscopically as an amorphous eosinophilic material, less birefringent than normal collagen. When hypersensitivity reactions occur, there is a diffuse granulomatous reaction in the early stages [4] and later the response tends to be a palisaded granuloma, with an admixture of lymphocytes, plasma cells, eosinophils and neutrophils [5]. This can produce a superficial similarity to necrobiotic granulomas such as granuloma annulare. Special stains can be useful, for example colloidal iron, which stains the bovine collagen a strong magenta colour compared with the pink of normal collagen [1,6].

In most instances, bovine collagen injection reactions can be treated symptomatically or left to involute.

Although reactions to human-derived collagen implants are less likely they have been reported [7].

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Fibreglass dermatitis

Reactions to glass fibre are usually caused by physical injury, although allergic contact dermatitis resulting from residual epoxy resin on the fibres has been described [1]. The fibres that cause reactions are generally greater than 4 μm in diameter [2].

Pruritus is very common and may occur with or without skin lesions, which, if present, usually consist of transient erythematous papules that are often follicular. The forearms, hands, face, neck and flexural folds are common sites. Covered sites can be affected because the fibres can penetrate clothing. Fair-skinned blue-eyed individuals seem to be more susceptible [3]. The fibres only penetrate the more superficial epidermis, yet the histopathological changes include subcorneal pustules, spongiosis and a mixed upper dermal infiltrate [4]. The mechanisms underlying these changes remain speculative. Glass fibres are often difficult to see in biopsy specimens but can be recovered by Scotch tape stripping and this may be of use in diagnosis [5].

With prolonged exposure, a form of hardening can occur, with the pruritus, but not the visible signs of dermatitis, reducing in intensity [3].

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Complications of tattoos

The term tattoo, derived from the Tahitian *tatau* [1], has been used for both the deliberate introduction of permanent colours into the skin through punctures, and for accidental entry of pigmented material [2]. The latter is common after abrasion injuries, for instance in cyclists and coal miners. Cases have been described of tattooing from close exposure to black gunpowder, as used in replica firearms [3]. Accidental tattooing from Monsel's solution or ferric chloride [4,5] provides rare iatrogenic causes. Tattooing can occur from contact with jewellery (e.g. earrings) [6].

Complications of decorative tattoos are relatively rare in Western countries. More sophisticated techniques have lowered although not abolished the risk of transmission of syphilis, tuberculosis and hepatitis [7–9], molluscum contagiosum [10] and viral warts [11]. Pyogenic infection is uncommon. An acute inflammatory reaction may last for days or weeks but is of no serious import. The complications of tattoos can have forensic implications [9].

The most commonly used pigments are carmine, indigo, vermilion, India ink, chrome green, cobalt blue, cinnabar (red), cadmium sulphide (yellow) and manganese (purple). Hypersensitivity reactions [12–14] are most commonly seen to cinnabar (mercuric sulphide), but are also seen with cobalt, chrome and manganese [15] and aluminium (purple) [16]. A photosensitivity reaction to cadmium yellow occurs occasionally [17]. When photosensitive reactions to red tattoos are investigated, the cause is sometimes a cadmium salt [18]. New non-metallic dyes are now being used increasingly and may produce reactions. The compound responsible can sometimes be identified by nuclear magnetic resonance and mass spectroscopy. Even carbon, long thought to be inert, may be capable of eliciting a granulomatous response [19].

Permanent pigmentation of the eyebrow area by injections of a ferrous oxide preparation has become popular since its introduction in 1984 [20] and a granulomatous dermatitis has been described [21]. A similar reaction has been recognized resulting from chromium salts [22] and mixed pigments [23].

Histological findings may resemble contact dermatitis with or without a granulomatous infiltrate, lichen planus or 'pseudolymphoma' [24,25]. B-cell lymphoma has been recorded as evolving from a tattoo-induced pseudolymphoma [26]. Perforating granuloma annulare can follow tattooing [27].

A sarcoidal reaction occasionally occurs. This is often non-specific, although it may obviously be a manifestation of sarcoidosis in some patients [28,29] and has been associated with uveitis as an isolated finding [30,31].

Psoriasis and lichen planus may occur in tattoos as examples of the Koebner phenomenon in patients with the active disease.

Traumatic tattooing (e.g. from an explosion) is amenable to laser treatment (e.g. with the erbium-YAG) [32].

The treatment of decorative tattoos is discussed in Chapters 77 and 78.

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Hair as a foreign body

Fragments of hair may penetrate the skin and cause a variety of reactions, according to the site and depth of penetration, ranging from slight erythema to the formation of abscesses and sinuses. Chronic reactions take the form of foreign-body granulomas, which may present as subcutaneous nodules or with hypertrophy of the overlying epidermis. The clinical syndromes encountered are very diverse and their cause is often unsuspected.

Barbers' hair sinus

Interdigital sinuses are common in men's barbers, presumably because of the short sharp hair fragments generated from cutting men's hair [1,2]. They also occur in female hairdressers [3] and those who cut animal hair [1]. The sinuses usually affect the first or third left or second right finger web. The lesions—tender nodules with a central sinus or intermittently discharging papules—are relatively inconspicuous and are often disregarded. Hair can also cause inflammation when implanted into the finger pulp [4] and beneath fingernails [5], probably when there is an abnormality of the nail or a pre-existing dermatosis [6].

Hair sinuses of the feet

Hair fragments may penetrate the skin of the feet. Long curved hairs embedded in the toes or ankles have been recorded in ladies' hairdressers; one case resembled larva migrans [7]. Deeper penetration may provoke tender nodules or abscesses.

A distinctive syndrome, seldom recognized, may follow the penetration by a hair of the toe-cleft skin, usually the fourth. The patient complains of pain and tenderness, which is usually attributed to other causes. There is oedema of the dorsum of the foot above the involved cleft. A pinhole sinus is found beneath the accumulated interdigital debris. Surgical excision may be necessary. The hair-thread tourniquet syndrome may also involve the feet (see below).

Milker's sinuses

Milker's sinuses are now uncommon but are more disabling. Fragments of cow hair may penetrate deeply, involving even the tendon sheaths. Secondary infection often follows, sometimes by dermatophytes [8]. Most lesions involve the second or third web of the right hand, forming tender nodules and discharging sinuses [9]. Recurrent episodes of cellulitis follow. Spontaneous cure may eventually take place, but may be so long delayed that surgical intervention is advisable.

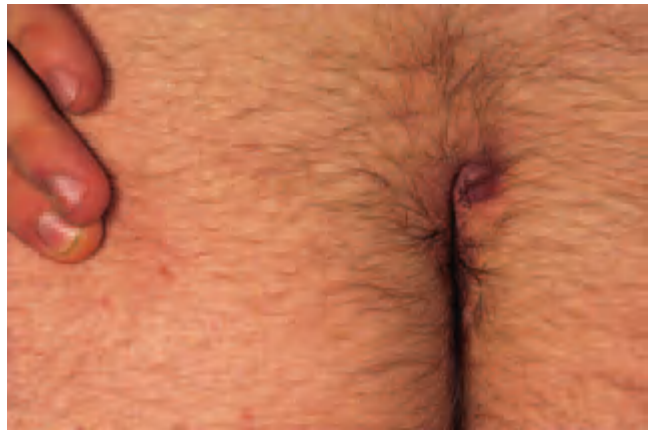

Fig. 22.17 Pilonidal sinus.

Anogenital pilonidal sinus

Anogenital pilonidal sinus is discussed more fully in Chapter 68. Some cases are of developmental origin but many follow the penetration of the skin by hair(s) by the root-end, through the action of the cuticular cells. The sinus itself does not have hair follicles. The penetrating hair(s) may cause a foreign-body giant cell reaction, sometimes with secondary bacterial infection, which can cause a sudden onset of pilonidal abscess. In addition to the primary track resulting from the initiating hair(s), there may be secondary tracks opening from the cavity. Presentation is usually as a midline opening or series of openings in the natal cleft about 5 cm from the anus. Pilonidal disease usually starts at the onset of puberty. Males are affected much more commonly than females, but three cases have been described in young women under the title of 'jazz-ballet bottom', in which secondarily infected natal cleft abscesses were associated with the presence of hair shafts [10]. Frictional trauma from the dancer's movement of the sacrococcygeal region against the floor was thought to have driven the hair into the skin.

Half of affected patients present as emergencies with an acute pilonidal abscess; the remainder have chronic fluctuating discomfort associated with a foul-smelling discharge from one or more sinus openings [11]. Examination reveals the characteristic opening in the natal cleft (Fig. 22.17) through which a tuft of hair is often seen emerging.

There is no uniform approach to management. A small sinus can sometimes be treated by removal of the hairs and regular shaving of the surrounding skin. A phenol injection technique has been used, either alone, with curettage or combined with excision [11]. Most patients are treated either by excision and primary closure, or by laying open and healing by secondary intention or repair with skin flaps. Primary closure or flap repair produces more rapid healing and shorter time off work [12,13];

wound breakdown after suturing may be lessened by prophylactic use of clindamycin [14]. Modifications of direct closure can be used to flatten the natal cleft and thereby reduce the risk of recurrence [15], but there may be greater morbidity if such techniques fail [11].

A pilonidal abscess is probably best treated by incision, drainage, curettage of hair and granulation tissue, and leaving open for secondary intention healing.

Squamous cell carcinoma has been described as a rare complication of pilonidal sinus [16,17].

Miscellaneous hair-filled sinuses

The penis can occasionally be the site for a pilonidal sinus-like lesion [18]. Pain, tenderness and discharge in the umbilicus has been associated with the presence of hair, perhaps in association with a hirsute abdomen and poor umbilical hygiene [19]. A hair sinus originating on the chin has resulted in loss of a tooth resulting from penetration of the sinus through into the incisor tooth socket [20]. Trauma was reported to account for a hair sinus over the mandible [21]. Hair sinuses of the areola of the breast [22–24] are discussed further in Chapter 67.

Hair-thread tourniquet syndrome

A foreign-body reaction to hair and hair-like fibres has been described following the encirclement of fingers, toes and the penis, usually as an accidental event [25] but also as an instance of child abuse. The affected area presents as a dusky swelling, sometimes with focal discharge, and the hair may be completely buried and only evident after surgery [26]. Removal of the constricting fibre is usually sufficient [25,27].

Pseudofolliculitis barbae

This foreign-body reaction to the ingrowth of obliquely cut, often tightly curled hair causes an eruption of erythematous papules in the beard area [28,29]. It is especially common in dark-skinned races. Stretching of the skin and shaving against the 'lie' of the hair increases the tendency. The pubic hair has also been involved. A similar condition has been described in Iraqi women who pluck the hairs of their legs, leaving some broken stumps which curl back into the follicle [30]; 'pseudofolliculitis vibrissae' [31] represents a variant caused by close cutting of nasal hairs, that may be confused with perforating folliculitis of the nose.

Preventive measures include discontinuing shaving, use of a clipper to maintain a beard hair length of 1 mm, and use of specialized single blade razors and depilatories.

Treatment is generally unsatisfactory; many symptomatic remedies have been reported (e.g. topical retinoids, α-hydroxyacids and antibiotics) but laser hair removal techniques may offer the best approach thus far [29,32].

Complications of artificial hair implantation

Although the use of synthetic fibres implanted in the scalp has been known for many years to produce severe foreign-body reactions [33–35], baldness sufferers continue to undergo implantation procedures with synthetic materials. Although some fibres, such as polyester, have been promoted as less liable to produce reactions [36], chronic purulent foreign-body reactions remain a typical consequence [37,38].

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Other penetrating injuries

Reactions to ornamental metal piercing [1]

Piercing of body parts with metal ornaments is a tradition in many societies, and may have originated in the Hindu religion. Piercing of sites in addition to the earlobe have become increasingly fashionable in Western societies over the past three decades.

Non-traditional facial sites include high ear piercing and nose boring, in which cartilage is penetrated, and piercing of the eyebrow, lip, cheek and tongue. The navel (periumbilical skin) and nipple are common sites on the trunk. A variety of genital piercings are encountered, some specific to particular cultures, for example the 'Prince Albert' or 'dressing ring' which penetrates the urethra and was said to be used to secure the penis inside tight fitting trousers in Victorian times [1]. The use of non-traditional body piercings extends far beyond the young, adventurous and sado-masochistic [2].

In general, complications are frequent [3] but, unless serious, do not come to the attention of specialists. They include redness and swelling, exudation, minor infection, bleeding and, less often, cyst formation, significant tears and scars. Allergic contact dermatitis, usually to nickel, is also common.

Much of the data on complications from piercing in relation to ears is discussed in Chapter 65. Serious infections can occur, for example a tongue piercing leading to intraoral cellulitis requiring associated ventilation and surgical intervention [4], endocarditis was reported from a nose piercing [5] and a breast abscess from a nipple ring [6]. There is increased risk for local infection if the ring is placed through tissue with potentially pathogenic resident flora (e.g. eczematous skin) and for cardiac complications if there is a pre-existing cardiac susceptibility [7]. As with ear piercings, lack of attention to sterility can lead to transmission of viral infections such as hepatitis and human immunodeficiency virus (HIV) [8].

Unlike ear piercing, nose boring does not seem to be particularly associated with hypertrophic scar or keloid formation but is often followed by a self-limiting type of pyogenic granuloma-like capillary proliferation [9]. The nose piercing clasp can become embedded in a mass of granulation tissue, necessitating surgical intervention [10].

Significant trauma is particularly a feature of body piercing through genitalia (e.g. urethral rupture after insertion of a Prince Albert ring) [11].

It is sometimes necessary to remove a body piercing, for example because of infection, local tissue damage or the need for a radiological investigation. Removal depends on the design of the piercing. There are three basic designs: the barbell stud in which a straight bar has a threaded ball on each end; the labret stud in which the threaded ball is on one end only, and the captive bead ring, which consists of a bead held 'captive' by tension from both sides of an incomplete ring. Removal is usually straightforward once the design is appreciated [12].

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Titanium implants

Bone-anchored skin-penetrating titanium implants are now a well-established method for securing auricular and other facial prostheses and hearing aids. There can be secondary infection with *Staphylococcus aureus* [1] and occasionally untreated reactions at the skin interface can lead to loss of osteo-integration [2]. Although most patients have no adverse cutaneous reaction to this procedure, inflammation does occur in about 10% [3]. Even in clinically normal skin around such implants, there is an increase in B lymphocytes, presumably because of the

breach of skin barrier function by virtue of the passage through it of the titanium to the bone beneath [4], and the cellular components for a T-cell-mediated hypersensitivity response may be present to the same degree as happens with stainless steel implants, even though a clinically evident allergic event does not take place [5].

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Skin lesions in drug addicts [1,2]

The skin in an injecting drug addict can manifest lesions as a direct result of injection into veins or arteries, from subcutaneous deposition of the drug, and as a consequence of dissemination of the drug or contaminants in the injection fluid. Skin changes have also been described when addictive drugs have been taken by routes other than an injection. The skin manifestations of alcohol abuse [3] are outside the remit of this chapter.

The drug addict will seldom disclose his or her addiction during a routine examination for a skin disease. In view of their increasing incidence, the dermatologist should be aware of the nature of the more commonly found stigmata of addiction. Puncture scars in a linear distribution over a vein (or running parallel on each side of it) were seen in all of 54 addicts examined [4]. An extraordinary number of veins may be used—often those on the hands or fingers and even the dorsal vein of the penis [5]. The granulation tissue of chronic ulcers may be used when no more veins are available [6].

Serious infection is the most common manifestation of drug abuse. Abscesses, ulcerating nodules [7] or necrotizing lesions [8] occurring in unusual sites, particularly a painless ulcer on the dorsal penile shaft [9], should arouse suspicion; a past history of similar abscesses even more so (although these patients are likely to be unreliable witnesses). Abscesses caused by the drugs themselves or resulting from infection are more common when drugs are injected subcutaneously or intramuscularly (often called 'skin popping'), and the damage to deeper structures can be severe [10,11]. Ulcers can be very slow to heal [12]. Potentially fatal necrotizing soft-tissue infections can present like simple abscesses in illicit drug users [13]. The use of a cocaine and heroin mixture (colloquially known as 'speedball') is a risk factor for abscess formation, probably by the enhanced vasoconstrictive effect [14]. Wound botulism in the USA is now almost always caused by skin popping of black tar heroin [15,16] and is also seen in Europe [17]; even anthrax has occurred [18]. In the injecting addict, HIV infection is a risk factor for both abscesses and endocarditis [19].

Injections of the analgesic drug pentazocine may cause marked ulceration, sclerosis and hyperpigmentation (Fig. 22.16). Panniculitis is also a feature. Seventeen cases, of whom six were physicians, were recorded at the Mayo Clinic in 11 years. Psychiatric illness was almost always present and a personal family history of diabetes was common [20]. Two patients have been described who developed a systemic disease with pulmonary granulomatosis secondary to pentazocine abuse [21]. Benzodiazepine by injection can also cause skin necrosis with scarring [22].

A syndrome brought about by systemic candidiasis, presenting with purulent nodules in the scalp and follicular pustules in other hair-bearing areas, tenderness over various bones and cartilages and distinctive eye lesions, has been described in intravenous heroin addicts [23]. This unusual candidal infection has been attributed to the use of lemon juice as a solvent for the drug [24–26] and has also occurred with buprenorphine dissolved in juice from a 'plastic lemon' [27]. The skin itself may, however, be the source of *Candida albicans*, the profuse sweating associated with heroin usage and drug-related immunosuppression contributing to the follicular localization of the skin lesions and the pattern of dissemination that occurs [28]. The condition is typically seen in users of brown heroin [29], although it has been described in an white heroin addict in whom the *Candida* was thought to originate in the mouth [30].

Post-inflammatory pigmentation is a very common feature in intravenous drug abusers. More specific 'soot tattooing' may occur from flamed needles [31]. Other signs include thrombosis of, or bruising over veins; local urticaria from leakage of heroin or methadone; painful necrotic ulceration from barbiturates; and, rarely, keloids. Thrombosed subcutaneous veins can be felt as fibrous cords, and oedema is a common occurrence when most of the vessels in an extremity have been damaged. Circular scars are characteristic of skin popping.

Leukocytoclastic vasculitis occurring in one extremity has been described as a complication of intravenous drug abuse and was probably a result of intra-arterial injection [32].

Systemic amyloidosis is emerging as a serious complication of heroin abuse [33–35].

Free-base cocaine ('crack') by inhalation has been associated with acrocyanosis, severe necrotizing livedo

reticularis and muscle infarction [36–38]. The vasoconstrictive effects of cocaine have been implicated as a cause of scleroderma in a man addicted to the drug for 9 years [38], and a localizing factor for vasculitic lesions [39].

Itching at the site of the injection or in the centre of the face is a common initial effect of heroin, but passes off after 2–3 weeks on the drug. Paraesthesiae from cocaine or methyl amphetamine may lead to excoriation and scarring. Such findings would be significant in a young patient in whom scabies has been excluded. Piloerection is a well-known feature of the opiate abstinence syndrome.

Decorative and sometimes cryptically informative tattoos are sometimes found over injection sites in intravenous drug abusers [2].

In South Africa, a distinctive brown staining of the palmar surface of the first web space is associated with smoking cannabis by means of a broken-off bottle neck [40].

The anabolic and androgenic steroids are liable to abuse in athletes and bodybuilders, and should be considered in cases of seborrhoea, acne, hirsutism and striae distensae when appropriate [41].

A papular and pustular facial eruption has been attributed to *N*-methyl-3,4-methylenedioxyamphetamine (MDMA)—'ecstasy pimples' [42].

Frostbite has been described with recreational use of nitrous oxide [43].

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Skin hazards of swimming and diving

The increasing popularity of aquatic leisure activities has brought into prominence a wide variety of water-related dermatoses [1,2] (Table 22.8). Amateurs in underwater swimming and scuba diving are not always conversant with the hazards, particularly if these activities are carried out in unaccustomed waters on holiday.

Table 22.8 Some water-related dermatoses.

General
Sunburn
Cold urticaria
Aquagenic pruritus
Dry skin (swimmer's xerosis)
Swimmer's ear (external otitis)
Contact reactions
Bathing costumes
Wet suits
Snorkel masks, goggles, etc.
Fresh water
Swimming pools
Fungal infection, verrucae
Chlorine and bromine irritation
Chapping in atopics
Aquagenic acne
Green and blond discoloration of hair
Swimming pool granuloma
Jacuzzi/hot tubs
Pseudomonas folliculitis
Sauna
Miliaria
Tinea versicolor
Rivers, lakes
Cercarial itch
Trench foot
Streams
Onchocerciasis
Showers
Aquagenic pruritus
Sea water
Immersion syndrome
Algae dermatitis
Jellyfish and other venomous stings
'Sea-bather's eruption'
Coral abrasions and sea-urchin injuries
Surfer's nodules
Deep-sea diving
Otitis externa
Intertrigo
Staphylococcal infections
Scalds, flash burns
Abrasions from wetsuit folds
Pruritus, erythema (decompression)
Tropical (e.g. sponge divers)
Venomous bites and stings
Coral, sea urchin injuries

General hazards

The hazards of UV radiation associated with swimming and aquatic sports are discussed in Chapter 24. People falling from boats into very cold water can die within minutes unless specially protected from heat loss. Prolonged immersion in warmer sea water can cause electrolyte imbalance by percutaneous absorption (immersion imbalance). Dry skin after swimming ('swimmer's xerosis') may in part be brought about by an osmotic gradient; other factors include dilution of sebum and use of soap afterwards [1]. The relationship of external otitis ('swimmer's ear') to water sports is discussed in Chapter 65. Cold urticaria and aquagenic urticaria and pruritus are discussed in Chapter 47.

Bacterial contamination from sewage disposal accounts for many cases of gastrointestinal disorders in swimmers using coastal resorts, even in the UK [3], and in those bathing in recreational rivers [4]. Skin infections resulting from faecal organisms may also be more common in contaminated rivers [3], and skin irritation can occur from toxins released by blue–green algae in inland waters [3]. 'Bikini bottom' is a nodular folliculitis of the inferior buttocks, probably caused more by poral occlusion from not changing out of a damp swimming costume than by specific pathogens [5].

Allergic contact dermatitis can occur, for example to bathing costume elastic or dyes, goggles, snorkel masks or mouthpieces [6]. Rarely, toxic leukoderma from use of goggles has been reported [7].

Traumatic conditions include 'surfer's knees', waterslap injuries on the anterior thighs of speed swimmers, rope burns on the extremities of water skiers [8], 'purpura gogglorum' caused by the effects of pressure and suction [9] and 'swimmer's shoulder'—an erythematous rough plaque caused by friction from the unshaven chin while swimming freestyle [10].

Swimming pools and whirlpools [11,12]

Chlorine causes irritation in subjects with dry skin or atopic dermatitis. Contact urticaria from exposure to chlorinated pool water has also been described [13]. 'Aquagenic acne' is attributed to rebound hyperactivity of the sebaceous glands, an irritating effect of chlorine on pilosebaceous duct orifices and poral obstruction by overhydration [1]. A bromochlorine pool antiseptic (1-bromo-3-chloro-5-dimethyl-hydantoin) resulted in several outbreaks of pruritus and irritant dermatitis [14]. Chemical conjunctivitis may occur if the subject swims with the eyes open. The use of communal changing room facilities may increase the risk of spread of verrucae and tinea pedis. *Mycobacterium marinum* infections are discussed in Chapter 28. The bleaching effect of chlorine may lighten the colour of hair if bathing and sun exposure are excessive. In competitive swimmers even black hair can become golden; mechanisms involved include damage to the cuticle, entry of hypochlorous acid and resultant damage to melanosomes [15]. Green tinting of hair may occur in blondes from frequent swimming in pools, probably because of exposure to copper-based algicides. Regular shampooing and 3% hydrogen peroxide lotion may decrease this effect [16,17].

Pseudomonas folliculitis

Pseudomonas aeruginosa has been associated with outbreaks of folliculitis, mainly in those using whirlpools (jacuzzis)

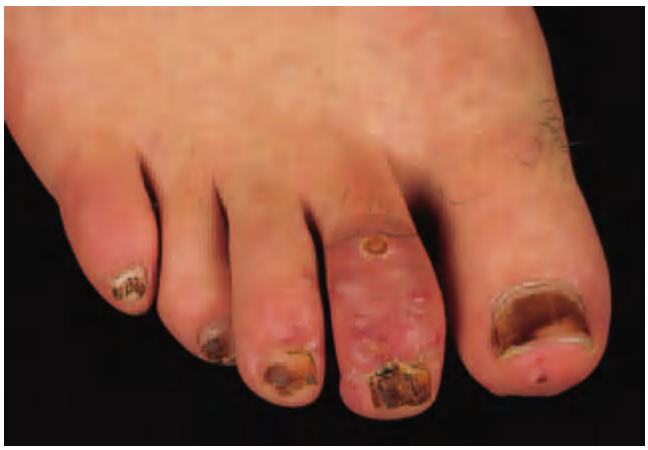

Fig. 22.18 Sea-urchin granulomas. The nail discoloration is caused by potassium permanganate. (Courtesy of Bristol Royal Infirmary, Bristol, UK.)

and hot tubs, although in some cases the source has been indoor swimming pools [18–20]. *Pseudomonas aeruginosa* is able to withstand relatively high temperatures and high chlorine levels. The organism colonizes the overhydrated stratum corneum of the follicular ostia. Symptoms usually appear 8–48 h after exposure, quite often with multiple members of a family being affected [21]. The rash is usually itchy and polymorphous, with erythematous macules, papules, vesicles and pustules. The areas most affected tend to be those covered by the bathing suit. The head and neck are rarely affected. There may be associated conjunctivitis, pharyngitis and, occasionally, swollen and painful breasts, abdominal symptoms and lymphadenopathy. 'Hot-tub dermatitis' is discussed further in Chapter 27. Acute external otitis, also usually caused by *Pseudomonas* infection, may occur concurrently.

Treatment is symptomatic. The problem usually clears spontaneously over 7–10 days.

Outdoor swimming

Sea bathing

Many hazards ranging from the trivial to the fatal can occur in seabathers [6]. These include the distinctive stings and other lesions inflicted by members of the phylum *Cnidaria*, which includes jellyfish, sea anemones, corals and hydroids [22]; 'seabather's eruption'; irritant and toxic contact reactions to seaweed, bryozoa (e.g. Dogger Bank itch), sponges, bristle worms, sea cucumbers and some fishes; physical injury from the scales of elasmobranch fish, such as dog fish and skate, lacerations from coral; suction injury by some ray fish; puncture wounds from sea urchins (Fig. 22.18) and some molluscs; and octopus bites and fish stings [23]. These aquatic injuries are all considered in detail in Chapter 33.

Two distinct pruritic papular dermatoses are associated with microscopic cercarial larvae in contaminated water, namely swimmer's itch, discussed here, and seabather's eruption (see Chapter 33).

Swimmer's itch [2,24–26]

This is an allergic response to the larvae of animal schistosomes for which humans are not the primary host. The biology is discussed further in Chapter 33. Swimmer's itch occurs at 12–24 h after exposure to the larvae of animal schistosomes, usually in fresh water, although less often in salt water. Outbreaks are more common in the summer.

The initial symptom may be a prickling sensation soon after leaving the water, corresponding to when the larvae penetrate the skin, and can last an hour or so. Erythematous macules appear 10–15 min after penetration, mainly on areas not protected by the swimming costume. If the individual is not sensitized to the cercariae, symptoms and signs subside in less then 12 h. In the sensitized, lesions evolve over 10–20 h into intensely itchy papules, which can coalesce into plaques. Itching and the papular eruption can last 1–2 weeks. In severe cases, usually those repeatedly exposed to cercariae, lesions may evolve into vesicles and pustules, and systemic symptoms such as headache and fever can occur.

The epidermis shows spongiosis with collections of neutrophils and eosinophils. Occasionally, biopsies taken within 48 h of the exposure may show cercariae in the outer epidermis [26,27].

Seabather's eruption, caused by cnidarians (see Chapter 33) may be similar, with pruritic papular lesions, but tends to maximally affect the skin covered by the swimsuit and only occurs in salt water. Other possibilities may include arthropod bites of various types and seaweed dermatitis.

Covering the skin, for example with a wetsuit, may be protective. Vigorous towelling down after swimming is said to reduce cercarial penetration. Topical steroid creams, and topical antipruritics such as 0.5% menthol or calamine lotion, may improve the pruritus.

Professional deep-sea diving [28]

A considerable experience has accumulated over the past two to three decades as a result of marine oil drilling, where divers may spend up to 90 days at considerable depths. They are exposed to high temperature and sometimes humidity exceeding 90%, conditions that favour *Pseudomonas* external otitis [29]. This may be preventable by good prophylactic hygiene and by the use of aluminium acetate eardrops. Staphylococcal infections of the skin may become troublesome within diving suits and are less amenable to antibiotic therapy than usual (perhaps because of the high temperature and humidity). Scalds may occur from overheating of the diving suit and flash burns from welding procedures are an occasional hazard.

Skin squeezing at the folds of the suits may cause linear abrasions. During decompression, the diver may suffer from pruritus and erythema: a more severe lymphoedematous peau d'orange occasionally occurs. Furthermore, if the diver is underwater for a long time, the equivalent of a 'napkin eruption' can develop from micturition within the clothing.

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Vibration

Vibration is defined as a repetitive movement about a point of equilibrium. Transmission of vibration energy to the skin has been associated with a number of chronic biological consequences, the best defined of which is the hand–arm vibration syndrome (HAVS) (see below and Table 22.9). It is also recognized that vibration can induce localized hyperhidrosis, callus formation, vibratory angio-oedema and a condition characterized by pain, swelling and erythrocyanosis [1]. Vibration may be a contributory factor to the hypothenar hammer syndrome (p. 22.28). Potentially beneficial effects have been ascribed to short-term exposure to vibration, such as elevation of skin temperature and increased lymphatic clearance [2]. The monographs by Griffin [3] and Pelmear *et al*. [4] deal comprehensively with the study of vibration and its medical consequences.

Hand–arm vibration syndrome

SYN. VIBRATION WHITE FINGER; VIBRATION SYNDROME

The term 'vibration white finger' has long been used for Raynaud's phenomenon resulting from the use of hand-held vibratory tools. Recognition that there are also neurological and musculoskeletal consequences of vibration exposure in the exposed limb led to the now-preferred

Table 22.9 Vibration injury: Stockholm Workshop Scales.

	Stages	Grade	Description
Vascular component	0V		No attacks
	1V	Mild	Occasional attacks affecting only the tips of one or more fingers
	2V	Moderate	Occasional attacks affecting distal or middle (rarely also proximal) phalanges of one or more fingers
	3V	Severe	Frequent attacks affecting all phalanges of most fingers
	4V	Very severe	As in stage 3, with trophic changes in the fingertips
Sensorineural component	0 SN		Vibration-exposed but no symptoms
	1 SN		Intermittent numbness with or without tingling
	2 SN		Intermittent or persistent numbness, reduced to sensory perception
	3 SN		Intermittent or persistent numbness, reduced tactile descrimination and/or manipulative dexterity

term HAVS [5–8]. Because there is an associated generalized disorder of the autonomic nervous system, the terms vibration syndrome [9] and vibration disease [10,11] are also used. Vibration-related changes can also occur in the feet [12].

Aetiology. Almost any vibratory source within the range 4–5000 Hz can produce HAVS if sufficiently intense. The time of exposure may be as little as 1 month to more than 30 years. There are numerous variables that determine whether or not the condition occurs [13]. Some relate to the equipment, some to the environment and others to the individual [14]. Thus, low ambient temperature, lower frequencies of vibration, firm gripping of the equipment, smoking [15,16] and stress are risk factors. Existing vascular disease and vasoconstrictive medications may be risk factors in some cases [17]. HAVS tends not to occur in hot climates.

The most common tools causing HAVS are percussive metal-working machines, such as rivetting and fettling tools, drills, impact wrenches, jack hammers, road-breaking tools and chainsaws. In many other occupations there is some risk, albeit less well studied [18]. In high-risk occupations, the incidence and prevalence can be 90% or more [10,19]. The condition has even been described in a teenager making prolonged use of a hand-held vibrating computer game [20].

Prevalence. In the UK approximately 500 000 workers are exposed to vibration and of these about 20 000 suffer moderate to severe HAVS [7].

Pathophysiology and pathology. There are vascular and neurological changes. There may also be changes in connective tissues and in the blood, the latter probably occurring secondary to endothelial damage.

The initial events are not well understood [21]. The following documented changes are likely to be important: mechanoreceptor nerve endings and non-medullated fibres become damaged [22], there is a more generalized loss of neuronal activity than in primary Raynaud's phenomenon [23] and there is selective damage to α_1-adrenergic receptors in vessels causing an excessive vasoconstrictor response from the predominant α_2-receptors [15,24,25]. Other structural changes noted include loss of myelin, increased numbers of Schwann cells and fibrosis [26].

Vascular lumina are reduced, probably by both internal thickening and smooth muscle hypertrophy [22,27–29]. There is an increase in fibrous tissue within and around blood vessels [30] and arterial thrombosis can occur [31]. Soluble intercellular adhesion molecule 1 (ICAM-1) levels are increased, as in scleroderma, suggesting that neutrophils may adhere and contribute to the microvascular damage [32]. Whole-blood viscosity may be elevated [33], although the importance of this is uncertain.

A generalized abnormality in the autonomic nervous system [34] may cause orthostatic hypotension [35], vasoconstriction of limbs not directly exposed to vibration [36] and an impairment of hearing, possibly caused by ischaemia in the inner ear [37]. A site of putative damage in the central nervous system has been suggested [38].

As well as damage to nerves, there is evidence of damage to muscles, especially the intrinsic muscles of the hand [39].

Bone cysts have been described in HAVS but may be a coincidental finding and not purely a result of vibration injury [40].

Clinical features. There are three possible major components to the HAVS: circulatory, neural and musculoskeletal [41].

After a highly variable latent period, the initial symptom is usually tingling and/or numbness in one finger. This often occurs directly after using the vibrating tool and also at night. This sensory change is followed by episodes of blanching, initially of the tip of the finger most exposed to the vibration source, with progression towards the base, and then increasing numbers of digits are affected. The thumb below the tip is usually spared. The pattern of digits affected reflects the subject's grip on the tool. Attacks are usually precipitated by cold and sometimes damp conditions, most common early in the morning and during rest periods rather than work. The attacks may last 15–120 min followed by painful reactive hyperaemia. With progression of the disease there is reduction in touch sensation, and difficulty doing fine manual work. Muscle fatigue and weakness are common, probably because of incomplete muscle contraction.

Late in the disease, attacks of pallor wane but there is persistent dusky cyanosis, swelling and stiffness of the digits and focal areas of necrosis of the fingertips. When the latent period is short, the symptoms and signs of HAVS tend to be more severe and more rapidly progressive.

The toes can be affected, either directly (e.g. from exposure to a vibrating platform) or by reflex sympathetic spasm.

Other changes attributed to vibration injury include carpal tunnel syndrome [42,43]. Although this may be more a result of mechanical and ischaemic factors [44], noise-induced hearing loss is exacerbated by the effects of the autonomic nervous system [45,46].

Patients with HAVS should be staged as part of the assessment of their disability, for each hand separately. The Stockholm Workshop Scales [5,47] are most widely used (Table 22.9).

Diagnostic tests. The diagnosis of HAVS is based on a history of vibration exposure before the onset of symptoms, and exclusion of other causes of Raynaud's phenomenon, such as primary Raynaud's disease, thoracic

outlet syndrome, syringomyelia, spinal cord compression, collagen vascular disease, peripheral vascular disease and vasoconstrictive drugs [6,48,49].

A variety of tests have been used in diagnosis and assessment of vascular, neurological and musculoskeletal abnormalities [49,50]. For the purposes of assessing a claim for an industrial injury compensation, certain tests may be regarded as the most reliable [51]. Thus, in the UK the following are recommended: finger systolic blood pressure following cooling, to assess vascular abnormalities; either vibrometry or aesthesiometry, for neurological dysfunction; and grip strength [52,53]. These tests are likely to be available only in centres specializing in evaluation of HAVS.

Even with a battery of tests it may be difficult to determine which patients will benefit from carpal tunnel release [54].

Prognosis. Early stages of HAVS are reversible, but advanced stages in patients over 45 years are irreversible and may progress despite withdrawal from vibration [2,55]. If measures are taken early in the course of disease, improvement is possible [56].

Treatment. It is important to maintain central body temperature and to avoid allowing the hands to become cold. Mittens are preferable to gloves. Smoking should be strongly discouraged. If possible, further vibration exposure should be avoided; if this is not feasible, frequent work breaks should be allowed.

Calcium-channel antagonists such as nifedipine can help the vascular symptoms. Other drugs that may be useful include α-adrenoreceptor antagonists such as thymoxamine and some prostanoids. Other remedies used in Raynaud's syndrome are given in Chapter 56. Sympathectomy is not generally effective.

Prevention. Because the more advanced stages of HAVS are irreversible, preventive measures and surveillance of at-risk workers are widely regarded as essential. Various steps can be taken to reduce exposure, for example automation [57], shorter shifts, antivibration gloves and pads on the tools. Much effort has been made to redesign equipment so as to reduce vibration [58,59] and the need for excessive grip strength. Workers should be informed of the hazards of their occupation, and should wear warm antivibratory gloves, avoid smoking and undergo regular medical surveillance. It is best for those at risk to avoid medications that can cause vasoconstriction (e.g. β-blockers).

Current industry standards in the USA and Europe are reviewed [60].

Other vasomotor symptoms

A condition in which pain, swelling and erythrocyanosis is induced by high-speed electrical tools (frequency 166–833 Hz) was described many years ago [1]; this syndrome is not provoked by exposure to cold.

Vibratory angio-oedema

Unlike the other dermatological phenomena induced by vibration, vibratory angio-oedema tends to occur at low frequencies (approximately 10 Hz) [61], such as are produced by handling a power lawnmower, or by rubbing or towelling the skin. The condition may be quite common among mountain bikers [62]. Vibratory angio-oedema is considered in more detail in Chapter 47, together with other physical urticarias.

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Reactions to internal mechanical stress

Tissue expansion [1]

Skin and subcutaneous tissues clearly expand during pregnancy and morbid obesity. The recognition that skin can be expanded artificially by certain African tribal customs involving the upper lip and ear led surgeons to develop methods of tissue expansion [2–5].

The standard method is to carry out the expansion over a 2–8-week period by inflating sacs inserted beneath the skin. Other techniques include external traction systems [6,7] and intraoperative techniques to produce expansion rapidly [8–11].

The response of skin and soft tissue to progressive expansion has mainly been studied in relation to progressively inflated silicone implants [12]. The main changes [13] are seen in the dermis, where there is reduction in thickness. The rate of thinning is maximal in the first few weeks of expansion and then decreases because of compensatory mechanisms. Within a few days of implantation, a dense fibrous capsule forms around the expander. The number of fibroblasts and their metabolic activity increase, and there is also evidence for increased metabolic activity in the myofibroblasts [14]. Collagen fibres are morphologically normal, but elastic fibres become thickened and appear more compact [14]. The epidermis

undergoes increased mitotic activity and maintains its thickness [4,15]. The appendages become separated with expansion of skin but probably are otherwise normal. There is a proliferation of blood vessels, particularly at the junction between the expansion chamber and the tissue around it. This increased vascularity is clearly of value when expanded skin is used in plastic surgical manoeuvres [16]. At a molecular level, various cellular mechanisms seem to be involved, including the cytoskeleton, extracellular matrix and several interrelated signal transduction pathways, with protein kinase C having a central role [17].

In intraoperative tissue expansion, the skin is stretched beyond its inherent extensibility by a device, usually for 30 min, allowing direct closure under much reduced tension. In such rapidly expanded skin, the collagen fibres become aligned in the direction of the stretching force, and elongated; the epidermal thickness remains unaltered [18].

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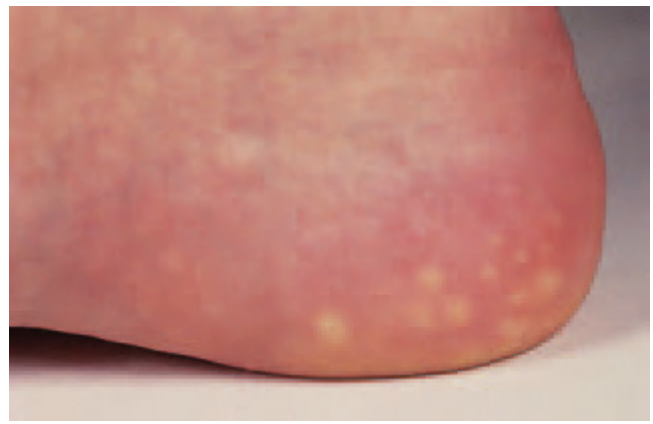

Fig. 22.19 Piezogenic pedal papules.

Piezogenic pedal papules

This rather cumbersome title, derived from 'piesis' (pressure), has been given to soft skin-coloured papules and nodules that appear on the side of the heel, usually the medial aspect (Fig. 22.19), when the subject is standing, and disappear when weight is taken off the foot [1]. Observation of healthy subjects has shown that such papules are common, although painless and indeed often unnoticed [2–6]. The frequency of the condition makes it difficult to assess the assertion that piezogenic pedal papules can be familial [7] and also that there is an increased frequency in Ehlers–Danlos syndrome [8]. In a population study there was no association with hypermobile joints [5].

Pain on standing is usually the reason for presentation, although some patients do express curiosity about the papules even when they are symptomless.

Similar papules have also been noticed on the lateral edge of the hand [9] and wrist [10].

Pathogenesis. Painless papules consist of normal fat tissue [3], but when pain occurs it has been attributed to herniation of the fat into the dermis with a resultant reduction in dermal thickness [9,11]. Postulated reasons for this pain include a defect in septation of the adipose tissue [11] and ischaemia resulting from extrusion of fat within its vascular supply and associated nerves [12].

Treatment. When piezogenic pedal papules of the feet are painful, improvement of the symptom can sometimes be achieved by avoidance of prolonged standing and, when relevant, loss of weight. Compression hosiery [13] and electro-acupuncture [14] have been reported to relieve symptoms. Supportive rubber footpads and heel cups can also be helpful. If conservative measures fail, small excisions of the papules can be curative [15].

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Muscle herniation of the lower legs [1,2]

Small asymptomatic herniations of the tibialis anticus are probably common in those whose legs are exposed to continual muscle stress. Discomfort occasionally prompts referral [2]. They are usually easily distinguished from varicosities.

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Mechanical trauma and skin neoplasia

Patients often describe an injury preceding the appearance of a cutaneous malignancy. However, the role of trauma in such cases is complicated by fallibility of the memory and uncertainty of the nature of the skin prior to the injury. Also, in many instances the injury is multifactorial, possibly involving a foreign body, heat, a chemical carcinogen such as tar or soot, as well as mechanical trauma [1,2].

When a single episode of mechanical injury to normal skin has been followed by carcinoma, the wound has often healed slowly, broken down repeatedly or failed to heal, and the neoplasm is nearly always a basal cell carcinoma [3–6]. On circumstantial evidence, basal cell carcinoma of the sole has been attributed to trauma in some cases [7].

Occasional instances of squamous carcinoma have been reported [8,9] but these have not followed simple mechanical trauma and have been complicated by other factors, such as foreign material left in the skin. Bowen's disease has been reported arising in a scar [10]. Basal cell carcinoma and squamous cell carcinoma have been recorded at sites of vaccination to smallpox [11–15], tattoos [16,17] and bacillus Calmette–Guérin (BCG) immunization [18]. Basal cell carcinoma has been reported at a skin graft recipient site [19]. The role of trauma in the genesis of malignant melanoma has been considered, but there is no strong supportive evidence [20,21]. Occasional instances of melanoma have been recorded in relation to immunization sites [22,23] as have sarcomas [24,25]. Lymphoma has rarely been associated with preceding trauma [26].

The development of a malignant neoplasm can be divided into at least three stages: initiation, promotion and progression. Environmental factors may be relevant for any of these stages [27]. Using a mouse model in which the initiator was the chemical carcinogen dimethylbenzanthracene, it has been shown that repeated abrasion is an effective promoter of both papillomas and carcinomas of the skin [28,29]. It has not proved possible to initiate carcinogenesis with surgically induced ulceration [30].

In the clinical context, however, the role of repeated mechanical trauma in the genesis of skin malignancy remains speculative [31]. For medicolegal purposes, the association of trauma with ensuing skin cancer should fulfil criteria that were laid down long ago, but remain valid [32]: authenticity and sufficient severity of the injury, previous integrity of the wounded part, tumour originating within the boundaries of the injury, histological variety of cancer compatible with an origin from local tissue, and a latent period.

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Effects of heat and infrared radiation

The physical and biochemical effects of infrared (IR) radiation, comprising approximately 40% of solar irradiation, have been relatively neglected [1], but are the subject of a comprehensive review [2].

IR is the segment of the electromagnetic spectrum that extends between red visible light and microwaves and radiowaves. The wavelengths range from 0.75 µm (750 nm) to 100 µm. As with UV radiation, there is an arbitrary subdivision into near IR (0.75–3 µm), middle IR (3–30 µm) and far IR (30–100 µm). Energy is inversely proportional to wavelength, therefore most biological effects are seen at shorter wavelengths. IR causes molecular vibration, the most obvious effect of which is to raise temperature. Radiation from 0.75 to 0.8 µm can cause photochemical reactions. Some wavelengths of IR are strongly absorbed by water—both in the atmosphere and in the hydrated stratum corneum. Transmitted IR can penetrate up to 30 mm [3]. The major sources of IR radiation are the sun and IR lamps.

Most experimental work into the effects of IR radiation on skin have used sources that emit UV and/or visible radiation as well, and the data are conflicting.

Experimental effects

Acute effects

IR alone produces erythema, which disappears by 6 h [4]. Histological studies have shown vasodilatation and mast cell degranulation [5]. The mediators have been studied in suction blisters and are essentially similar to those found in UVB erythema: free arachidonic acid, prostaglandins PGD_2, PGE_2, PGF_2 and 6 oxo-$PGF_{1\alpha}$. The free arachidonic acid level is still high after 72 h [6]. Epidermal proliferation is reduced by IR and does not become normal until after 7 days [7].

Prior heating with IR reduces the phototoxic response to methoxypsoralen and UVA [8]. The interaction between UV and IR radiation has been evaluated but with conflicting results [8–10] and further studies are needed.

Chronic effects

In a mouse model, over a 45-week period, the histological effects of radiation were studied, using a visible plus IR source—alone, in combination with UVA and UVB, and with UV followed by IR [11]. There was deposition of fibres with the staining properties of elastin in animals receiving only visible plus IR radiation, and an augmentation of the elastosis was attributable to UV. As with clinical solar elastosis, there was also an increase in ground substance.

Carcinogenesis

IR radiation can coagulate protein and nucleic acid and is synergistic with UV radiation in denaturing DNA. The production of UVB-induced cyclobutane dimers is temperature dependent [12], therefore this tumour-initiating event is likely to be augmented by IR. DNA repair after UV- and X-ray-induced damage is slower at 41–43°C than at 37°C, as occurs with heating resulting from IR [13]. It has been shown that mice heated to 35–38°C had a shorter latent period for UVR-induced tumours than controls [14,15]. Heat, wind and humidity have been shown to enhance UV carcinogenesis [16].

Erythema ab igne

Definition. A characteristic reticular telangiectatic and pigmented dermatosis, resulting from repeated or prolonged exposure to IR radiation, insufficient to produce a burn. It most commonly affects the legs of women.

Aetiology. The condition, once common in the UK, has become rare since the introduction of central heating, although it is still sometimes seen in rural areas among elderly people who stand or sit closely over fires, or who are habituated to the use of hot water bottles. It may be a valuable sign of hypothyroidism. A resurgence of the condition in the USA affects not only the elderly but also impecunious students [1], because of the high cost of central heating.

Sources other than domestic heating may be responsible for erythema ab igne at other body sites. Examples include the repeated application of hot water bottles or heated pads for chronic backache, recliner chairs with built-in heaters [17], occupations such as foundrymen and bakers, and the various customs of carrying heated coals (see below). It has been reported as a useful marker of chronic pancreatitis because local heat relieves the abdominal pain [18] but also occurs when heat is applied for other real and imagined pains [19]. The car heater may be a cause [20]. In mentally disturbed patients with thermophilia, bizarre areas of erythema ab igne are sometimes encountered.

Histopathology [21–23]. In the early stages, epidermal atrophy, dermal pigmentation and vasodilatation are evident. Basophilic degeneration of the connective tissue, focal hyperkeratosis and epithelial cellular atypia occur later, closely resembling the changes induced by actinic damage [24]. Electron microscopy shows similar changes in the elastic fibres as found in chronic sun exposure [25]. There can be loss of type IV collagen from the basement membrane zone [26]. Keratoses and eventually squamous cell carcinomas may form (see below).

Clinical features. Any surface of the body is susceptible [27] and the condition can occur at all ages including children [28]. Following a single exposure to IR radiation of a subthreshold intensity, a mild and transient reticular erythema occurs. Further or repeated exposure causes a more marked erythema with noticeable hyperpigmentation and, sometimes, superficial epidermal atrophy. Subepidermal blistering [29] can occur in the affected skin (Fig. 22.20). The cumulative effects of small and repeated thermal exposures often clear during the summer months but involution gradually becomes less complete. The changes caused by repeated and prolonged exposure to IR radiation eventually resemble those of poikiloderma, with reticulate telangiectasia, atrophy, melanosis and diffuse hyperkeratosis.

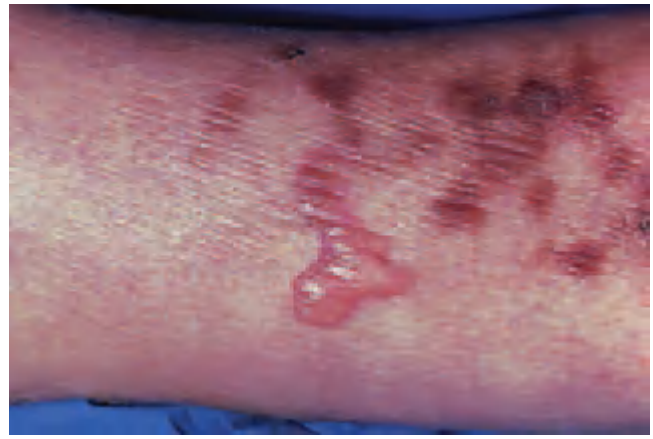

Fig. 22.20 Erythema ab igne with subepidermal bulla formation.

The distribution of the dermatosis depends not only on the direction of the incident radiation, but also on the contour of the skin and the interposition of clothing. When erythema ab igne results from sitting in front of the fire, people may sit sideways, causing the outer aspect of one leg and the inner aspect of the other to be particularly affected. Others habitually sit directly in front, and a strictly symmetrical eruption is seen. In severely affected individuals the reticular pattern is lost, a wide area of skin becoming pigmented and atrophic, with only the periphery showing the characteristic pattern.

An unusual variant has been described in elderly immobile females with lymphoedema in which there are reticulate ridges of tissue that can be compressed [30].

Rarely, lichen planus, psoriasis or chilblain lupus may appear as a Koebner phenomenon in the affected area.

Diagnosis. Although diagnosis is usually straightforward, there may be confusion with livedo reticularis, in which changes are strictly symmetrical and telangiectatic rather than pigmented. When large vessels are involved, nodules and ulcers may coexist with livedo reticularis, a triad diagnostic of a severe vasculitis (see Chapter 49).

Management. Hypothyroidism should be excluded. In elderly women living alone, erythema ab igne may be a sign of hypothermia. The help of ancillary social services may be needed. Advice should be given on clothing and efforts made to improve the microvascular circulation. 5-fluorouracil cream has been used to eliminate the dyskeratotic keratinocytes [31].

Heat-associated carcinomas

Squamous carcinomas of the skin occurring in areas of

heat damage have been known from ancient times, often regarded as exotic curios and their significance has been overlooked [32]. They include the Kang cancer of northern China [33] and Japan [34] from sleeping on beds of hot bricks, the Kangri cancer of Kashmir [35,36] from wearing pots of hot coals and the Kairo cancer of Japan caused by carrying metallic benzene-burning flasks—all devices to counteract cold. 'Turf' cancer of the legs of rural Irish women has been associated with standing for long periods of time over peat fires [37]. Simultaneous occurrence of Merkel cell carcinoma with squamous carcinoma has been recorded [38,39]. Basal cell carcinomas and actinic keratoses have been reported at a site on the cheeks of those wearing rimless glasses, where the temperature is higher than the surrounding skin because of focusing of the sun's rays [40,41].

Skin cancer following burns is discussed on p. 22.82.

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Burns

[D.A.R. Burd, pp. 22.66–22.84]

A burn is an injury caused by a pathological flux of energy within a tissue resulting in a disruption of functional integrity [1]. The source of the energy may be thermal, chemical, electrical or radiation. The spectrum of burn injury is the greatest of any form of trauma, ranging from an inconsequential superficial burn to the fatal destruction of the entire body surface, depending on the severity of the burn. What is remarkable is that with the advances in the understanding of the pathophysiology of the burn injury and the more aggressive approach to management, the prospect of surviving a complex major burn is better now than ever before.

Burns may be of industrial, domestic or environmental origin. In developed countries where there is a strict adherence to health and safety issues, the incidence of industrial burns has shown a gratifying decrease [2,3]. There have also been changes in the pattern of domestic injuries. Major flame burns from house fires have

decreased but there are still a large number of scalds in the second year of life when children are developing independent mobility but have not yet learnt fear. The true incidence of burns in any population is difficult to determine because of the wide spectrum of the injury. Serious burns will be treated in specialist units. In the UK, there are 5000–6000 admissions to such units annually. An equal number of patients are seen and treated as outpatients in specialist clinics, and for each such patient approximately a further five are treated in accident and emergency departments without referral to a specialist clinic. An additional unknown number of burns are self-treated in the general population or treated in general practice.

Pathophysiology. The pathophysiological reaction to a burn injury is complex and varies with the cause. In thermal injuries, the changes in the burn wound are mainly caused by the direct effects of heat but superimposed on these are changes associated with an acute inflammatory process. It is these latter changes that account for the widespread and devastating effects of major burns on the entire range of homoeostatic functions of the body.

The initial local response to a sudden increase in body surface temperature is the dilatation of blood vessels in an attempt to dissipate heat. A further increase in tissue temperature triggers an inflammatory response, mediated by peptides and low-molecular-weight substances that regulate the cellular function and microenvironment of the tissues. The key cells in the post-burn inflammatory response are the polymorphonuclear leukocyte, mast cell and endothelial cells. These, together with platelets, are the prime components responsible for the mediation, progression and resolution of the inflammatory response. A very simplified account of this process is given here, more detailed accounts are given elsewhere [4,5]. Activation of complement and coagulation cascades with the release of histamine from mast cells results in a short phase of vasodilatation and plasma protein leakage from post-capillary venules, resulting in local oedema formation. Intracellular proteases released as a result of cell damage activate kallikrein, which is responsible for transforming kininogen to kinin. Kinins have several effects, including vasodilatation, pain stimulation and leukocyte migration. A delayed phase of leukocyte and platelet margination then results in the release of prostaglandins, prostacyclins, thromboxanes, leukotrienes and lipoxins, which is accompanied by a substantial increase in microvascular permeability and changes in vasomotor control. The prolonged post-traumatic phase of vasodilatation and anti-platelet aggregation is regulated through endothelial cells via two different mediators: prostaglandin I_2 (PGI_2) and nitric oxide. Hypercoagulability of the lymph and the plasma has been observed 2–3 h after injury and correlates with the finding of increased levels of kinins in lymph.

Disseminated intravascular coagulation may also accompany a severe burn. As the tissues are infiltrated by leukocytes, the efficient elimination and destruction of injured tissue is effected. Neurotransmitters are also involved, especially substance P, which evokes vasodilatation and plasma protein leakage, and calcitonin gene-related peptide, which is a potent vasodilator.

Histopathology [6,7]**.** An accurate determination of the depth of injury is an important consideration when formulating a management plan for a burn patient. Theoretically, wound biopsy with histopathological examination would seem to be a very precise method for achieving this determination. Clinically, however, it is necessary to accept that burn wounds are rarely homogenous in nature and partial thickness burns may well be of mixed depth. Biopsies will leave permanent scars in partial thickness wounds; they are also expensive and time-consuming to process. In addition, the burn wound is a dynamic entity and it may take up to a week for a stable state to be achieved. Nevertheless, histological studies of the response of the skin to graded burn injuries have contributed to the knowledge of the mechanism of bullae formation.

In the most superficial injuries, only the upper epidermis shows changes. Nuclei appear either pyknotic and possess a perinuclear halo or, with greater damage, stain only faintly eosinophilic or not at all. In superficial partial thickness burns, subepidermal blisters are often seen. There is necrosis of the epidermis together with the coagulation of collagen in the papillary dermis. As the burn becomes progressively deeper, a good indicator of the depth of irreversible damage to the collagen is apparent in the appendageal structures where there is generally a fairly sharp demarcation between heat-coagulated and relatively normal epithelium. With full thickness burns there will be complete dermal necrosis with loss of all appendageal structures, and coagulation necrosis may extend into the subcutaneous fat and underlying muscles.

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Clinical aspects

The rationalization of the care of burns patients requires effective prehospital management, transportation and

assessment, and triage in a hospital emergency department. The importance of education and communication at this level cannot be overestimated. Subsequent, safe transfer of a stable patient to a specialized burns unit initiates the next phase of treatment. Several texts give excellent comprehensive accounts of total burn care [1,2]. The account that follows is an overview of the immediate assessment and management of a burn, and is aimed at the non-burns specialist who may be faced with the emergency care and short-term treatment of such patients.

First aid and prehospital management

Stop the burning process

The patient must be removed from the source of injury and the ongoing damage halted. Obviously care must be taken to ensure that rescuers and helpers do not themselves become injured but this can and does happen. This is a particular problem with electrical and chemical injuries. Patients sustaining chemical injuries should have clothing removed as quickly as possible and copious irrigation with water is the key to first aid. In chemical burns, the tissue damage is very much a function of the concentration of the agent and the duration of exposure, therefore in the otherwise fit patient, copious irrigation at the scene of the accident is preferable rather than immediate transfer to an emergency centre. It is essential to be aware of the possible dangers of handling contaminated clothing; and appropriate protective clothing, including gloves and eye protection, should be available for the emergency services.

With electrical injuries, the source of electrical current should be identified and switched off, if possible, and the victim moved from the source of the current using non-conductive materials.

In flame burns, the first priority is to extinguish the source of the burn, which can be accomplished by rolling the patient on the ground, by application of a smothering blanket or coat or by the use of water or extinguishing foams. The next priority, as with scald burns, is to promote cooling. This is best performed with water or water-soaked towels. Early cooling can reduce the depth of the burn and reduce pain, but caution must be exercised as a significant drop in body temperature can result in hypothermia.

Primary survey

The primary survey is the rapid assessment of the patient to ensure immediate survival. Attention is focused on airway, breathing, circulation and cervical spine immobilization. The most immediate threat is to the airway. This is always a problem when there has been significant smoke inhalation, but also when there have been burns of the face or neck. Upper airway oedema can develop rapidly, compromising the patency of the airway. Oxygen 100% should be available and administered. The patency of the airway should be assured using customary techniques. The neck is extended and, if the victim is unconscious and the tongue appears to be obstructing the airway, an oropharyngeal airway should be inserted. If upper airway obstruction appears to be developing, for example if there is severe and progressive hoarseness after severe smoke inhalation, the insertion of an endotracheal tube may be necessary. It should be noted, however, that it is rare for oedema to develop in under 30–40 min from the time of removal from the fire. It is far better for correct placement of an oro-endotracheal tube to be performed by an anaesthetist in controlled circumstances than for the blind nasal intubation by an inexperienced paramedic or emergency physician.

It is important to establish that there is a pulse. In a large burn, this may be more meaningful than blood pressure measurement in establishing that there is a circulation.

Sometimes, the incident that has resulted in the burn may have caused other injuries, for example in automobile accidents, explosions and house fires. In these situations, it is very important to be aware of the possibility of spinal cord injury. Cervical spine immobilization must be accomplished using an appropriate cervical collar until the patient can be appropriately evaluated.

Secondary assessment

The secondary assessment involves a thorough head to toe examination of the patient. A rapid check is made of the patient's head, neck, thorax, abdomen, upper and lower limbs to ensure that no other life-threatening injuries are present and that, if they are, the appropriate measures may be taken. It is also appropriate at this time to ascertain, if possible, any relevant past medical history, medications or allergies and to establish the mechanism and time of injury.

It may be appropriate to establish an intravenous line but it must be recognized that in a major burn access is going to be a significant problem and it is essential not to damage possible sites for cannulation. If it is possible to get a patient to hospital within 60 min of injury, an intravenous line is not essential and may be deferred.

With regard to the burn wound, the patient should be wrapped in clean dressings. Sterility is not important. No topical antimicrobial dressings should be applied. The priority is to transport the patient to hospital, and unnecessary delay should be avoided. Covering the wound may diminish the pain, and small aliquots of intravenous analgesia may be given.

During the process of transport, the receiving accident department should be notified of the incoming patient and the severity of the problem so that appropriate receiving

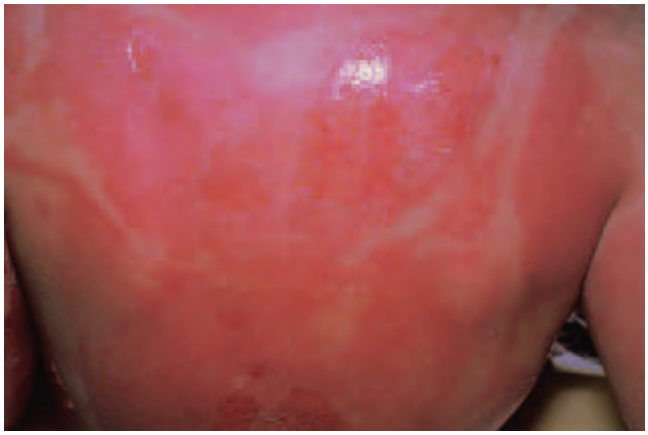


Fig. 22.21 A superficial partial thickness burn in a young girl who fell into a bath of hot water. Clothing marks are visible. The burns were completely healed by 5 days.

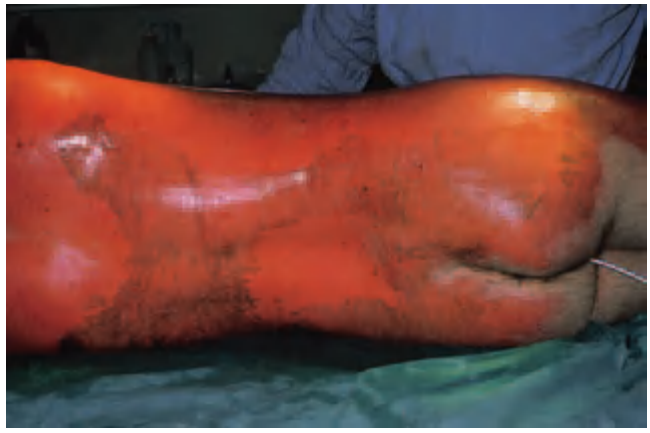


Fig. 22.22 A deep partial thickness burn of the back sustained in an explosion. The scorched skin has been débrided. The burns healed within 3 weeks with conservative therapy.

staff and facilities can be mobilized. The determination of the severity of the injury is, however, particularly difficult for those who do not have regular experience of assessing burns patients.

Important information includes:

1 Age
2 Sex
3 Type of injury
4 Brief details of incident
5 Time of injury
6 Extent of injury
7 Associated injuries
8 General status of patient.

Assessment in the hospital accident department

The assessment of the patient in the accident department is essentially the same as for any trauma patient, with treatment priorities based on the stability of the vital signs and the mechanism of injury [3]. The logical sequence of treatment priorities can be quickly established using the same overview as briefly described in the prehospital treatment. Two unique aspects of burns are critical determinants of severity: the depth of the burn and the area of the burn.

Depth of burn [4]

Burns can be simply classified as being partial (Figs 22.21 & 22.22) or full thickness (Fig. 22.23); partial thickness burns are then subdivided into superficial partial thickness and deep partial thickness (Fig. 22.24). This classification is very important in subsequent decisions regarding surgical management of the burn, but in the initial assessment other factors will determine the more immediate aspects of treatment, including whether to refer the patient to a specialized burns centre. It is possible to make an estimate of the depth of the burn from the clinical appearance (Table 22.10).

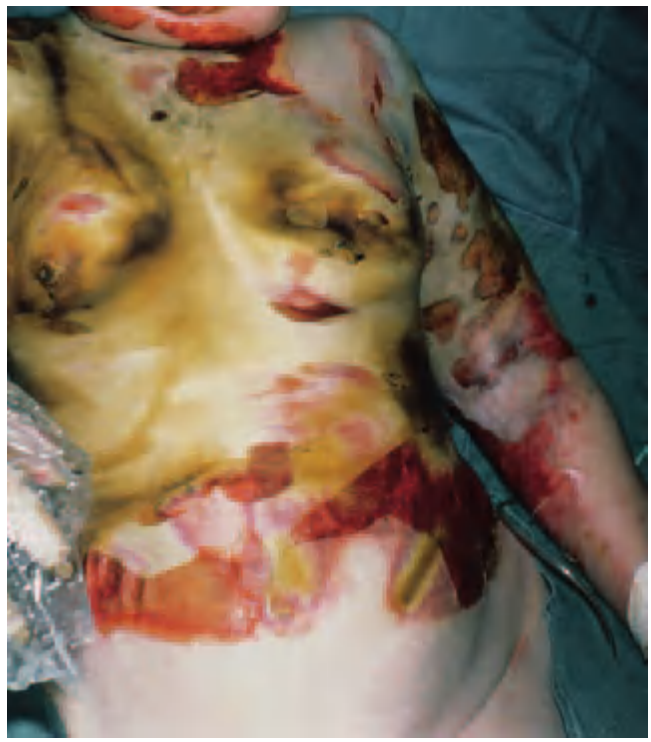


Fig. 22.23 A full thickness fatal burn in an elderly woman whose nightdress caught fire on a gas cooker.

Area of burn

The assessment of area of the burn is important as it directly affects the fluid resuscitation of the patient together with the disposition of the patient. Various methods are available to determine the percentage of the body surface that is burnt. The simplest method is the

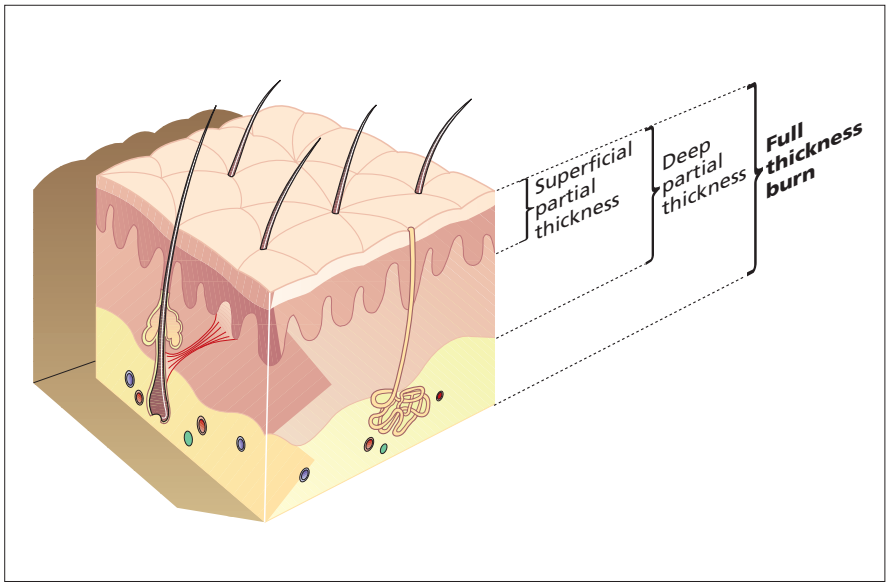


Fig. 22.24 Burns are classified according to their thickness.

Table 22.10 Clinical features of partial and full thickness burns.

Depth	Colour	Blisters	Capillary refill	Sensation
Superficial partial thickness	Pink	±	Present	Painful
Deep partial thickness	Red/pale	±	No	±
Full thickness	White	No	No	No

'Rule of Nines', which divides the body surface into areas of 9% or multiples of 9% (Fig. 22.25).

In the infant or child, a more accurate assessment can be made using the Lund and Browder chart, which takes into account the relative changes in proportions of head and legs in the growing child (Fig. 22.26).

A further guide to estimating the area of the burn is to realize that the closed palm of the patient is equal to approximately 1% of the body surface. This can be useful for assessing the total area of scattered burns. It is important not to include simple erythema in the estimation of the burn injury. Erythema is a reversible hyperaemia, which is not associated with tissue damage. As such it will not give rise to the pathophysiological changes that occur with tissue destruction, which may require intravenous fluid replacement.

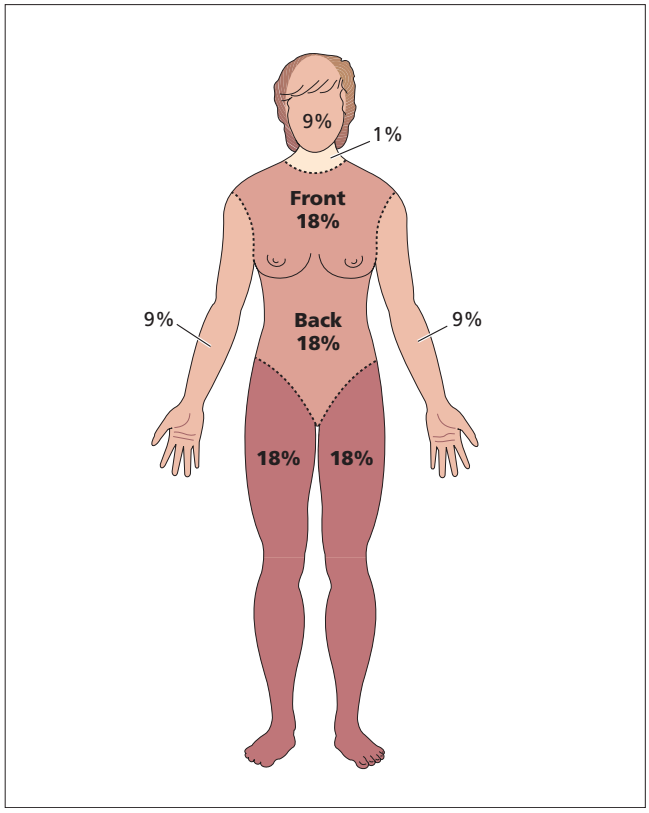
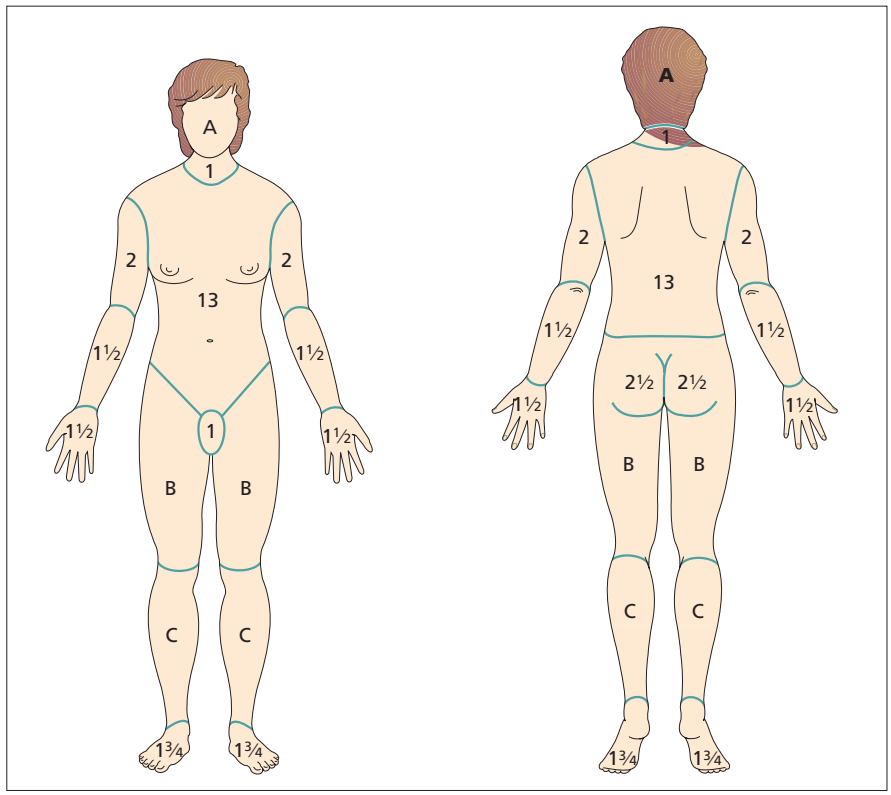


Fig. 22.25 The Rule of Nines.

Fluid resuscitation

The hypovolaemic shock that follows burn injury is caused by a shift of fluid from the vascular to the extravascular compartment. The more extensive the burn, the more extensive the shift of fluid. This fluid shift is a progressive phenomenon, which is maximal within hours of the burn and can persist for several days after the burn. As a simple guide, all patients who have burns in excess of 10% body surface area (BSA) should be commenced on



	Relative percentage of body surface area affected by growth					
Area	**Age 0**	**1**	**5**	**10**	**15**	**Adult**
A = ½ of Head	9½	8½	6½	5½	4½	3½
B = ½ of one Thigh	2¾	3¼	4	4½	4½	4¾
C = ½ of one Leg	2½	2½	2¾	3	3¼	3½

Fig. 22.26 Lund and Browder chart.

intravenous resuscitation. Intravenous fluid resuscitation is also indicated for all patients with inhalation injury and other associated injuries. A minimum of two large-bore intravenous cannulae should be inserted, preferably through unburned tissue. After insertion, blood should be taken for blood grouping and cross-matching, and baseline laboratory studies that include a complete blood count, serum electrolytes, glucose, blood urea nitrogen and creatinine. As soon as feasible, the patient should be weighed, as resuscitation formulae are based on a combination of body weight and area of burn.

The intravenous fluid infusion has to be regulated to give in the first 24 h:

- *Adults*: 2–4 mL Hartmann's solution/kg body weight/% BSA burn
- *Children*: 3–4 mL Hartmann's solution/kg body weight/% BSA burn

The intravenous fluid rate is adjusted to give half of the estimated volume in the first 8 h post-burn. The remaining half of the estimated resuscitation volume should be administered over the subsequent 16 h of the first day post-burn.

In children, there should be an additional element given for maintenance fluids because of the increased evaporative fluid losses. Maintenance requirements for the first 24 h are 1000 mL for the first year of life, plus 100 mL for each subsequent year of life up to 5 years of age. A 5-year-old child would thus require the following maintenance fluids in the first 24 h:

$$1000\ \text{mL} + (4 \times 100) = 1400\ \text{mL}.$$

The formula is only a guide, and clinical and laboratory monitoring are essential to tailor the fluid requirements to the individual patient.

The goal of resuscitation is to maintain vital organ function while avoiding the complications of inadequate or excessive fluid infusion. Excessive volumes of intravenous fluid can increase tissue oedema formation and compromise tissue oxygenation. This is particularly a problem with pulmonary and/or cerebral oedema. Inadequate

fluid resuscitation can cause diminished perfusion of the renal and mesenteric vascular beds, which can lead to organ failure [5].

Urine output

Urine output is the single best indicator of fluid resuscitation in the uncomplicated burn. Accurate measurement of urinary output requires the insertion of an indwelling Foley catheter. Acceptable hydration is indicated by a urine output of more than 0.5 mL/kg/h in an adult and 1.0 mL/kg/h in a child. In the initial stage of resuscitation, diuretics are not usually indicated. Patients with high-voltage electrical injuries or crush injuries may have myoglobin and/or haemoglobin in the urine. This predisposes to renal tubular obstruction. In this situation, an osmotic diuresis should be promoted by giving intravenous mannitol 1 g/kg (20% solution), and urinary alkalinization should be considered. The urine can be alkalinized using isotonic sodium bicarbonate intravenously at a rate sufficient to maintain urinary pH > 6.5 without the plasma pH exceeding 7.45. The urine pH should be monitored 4-hourly, and acid–base balance and serum electrolytes 6-hourly. This is continued until the myoglobinuria and/or haemoglobinuria disappears.

Gastrointestinal tract decompression

In the immediate and early stages of management of the major burn, it is important to be aware that the patient may require surgery and general anaesthesia. The patient should be given nil by mouth until seen and assessed by a burns physician. It is appropriate to insert a nasogastric tube. This can decompress the stomach, which may become distended from the combination of the stress response to trauma together with diminished peristalsis in the gastrointestinal tract associated with use of narcotic analgesia.

Immediate wound care

Very little needs to be done to the burn wound itself prior to assessment by the burns physician. Frequent reassessment is necessary to look for harmful effects of the wound on ventilatory and circulatory function with a view to undertaking escharotomies to relieve the splinting effect of the wound.

The patient must be kept warm and dry. It is essential to prevent the traumatized patient from becoming hypothermic, and wet dressings should be avoided on the burns. Appropriate dressings will depend upon local conditions and duration of transport. Clean surgical drapes can be used to cover the patient. Clingfilm can be used if there is no danger of hyperthermia; in cold climates 'space blankets' may be useful.

Pain relief

There are two aspects to the pain experienced by the burn victim: one is the physical pain from the injury, but another major component is the psychological trauma that the victim suffers. Morphine is indicated for both pain relief and as a powerful anxiolytic. It should be given only by the intravenous route, as changes in peripheral perfusion make the subcutaneous or intramuscular route unpredictable. In adults, a dosage of 1–4 mg i.v. every 2–4 h is indicated for severe pain. For children, the dosage of morphine should be modified according to the weight of the child, using 0.2 mg/kg i.v. in the first instance, and subsequently titrating the dose according to the response.

Additional medication

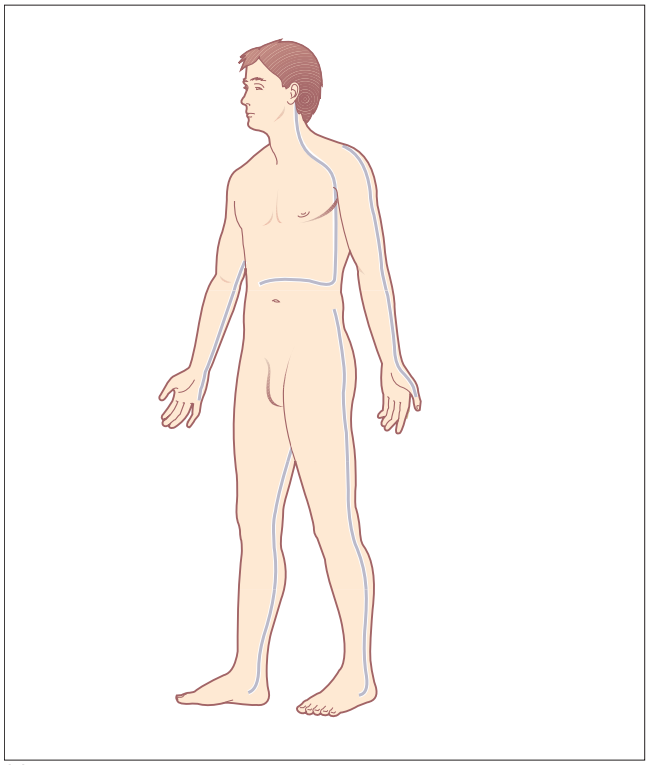
The need for tetanus prophylaxis is based on the patient's immunization status and the nature of the wound. All patients with burns in excess of 10% BSA should receive 0.5 mL tetanus toxoid. If prior immunization is unclear or unknown, 250 units of tetanus immunoglobulin are also given.

Escharotomy

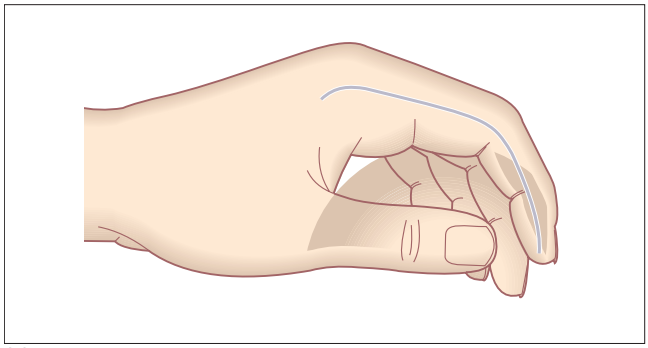
When there has been a circumferential deep dermal or full thickness burn affecting the limbs or the chest or neck, the skin will lose its normal plasticity. On the trunk, this may cause sufficient rigidity of the chest wall to compromise respiratory excursions and ventilatory function. When it occurs in a limb, oedema forming within the inelastic envelope will result in an increase in pressure within the limb, which may be sufficient to compromise the arterial inflow. Peripheral pulses and capillary refilling should be checked regularly, and if there is concern that perfusion of the limb is failing, escharotomies should be considered. Escharotomies are preferably made with electrocautery using mid-axial incisions in the limbs (Fig. 22.27). These incisions are made through the eschar and into the level of the superficial fascia of the limb. The wounds so made will gape open (Fig. 22.28) and the adequacy of the procedure can be assessed by the return of peripheral pulses and capillary refilling. It must be emphasized that escharotomies are not without morbidity, and care must be taken to avoid damage to underlying nerves. Escharotomies should ideally be undertaken under anaesthetic within an operating room environment.

Triage

When the burn patient has been evaluated and stabilized, a decision has to made about further treatment. There are recognized criteria for those burns that should be referred to a specialized burns unit (Table 22.11). Local conditions



(a)



(b)

Fig. 22.27 Escharotomy lines.

may dictate modifications to this list, but if there is any doubt about a patient's suitability of transfer, there should be direct consultation with the burns unit physician.

Transfer of the patient

The decision to transfer a patient becomes more difficult when there are associated injuries. The treatment of these may take precedence over the treatment of the burn, for example an intra-abdominal injury, major long-bone fracture, open-chest injury or intracranial bleed. A senior clinician should be involved in the referring hospital and a decision should be made jointly with a senior specialist in the burns unit. Once a decision has been made to transfer a patient to the burns unit, it is essential that he or she is properly stabilized before transfer. Essential prerequisites are listed in Table 22.12.

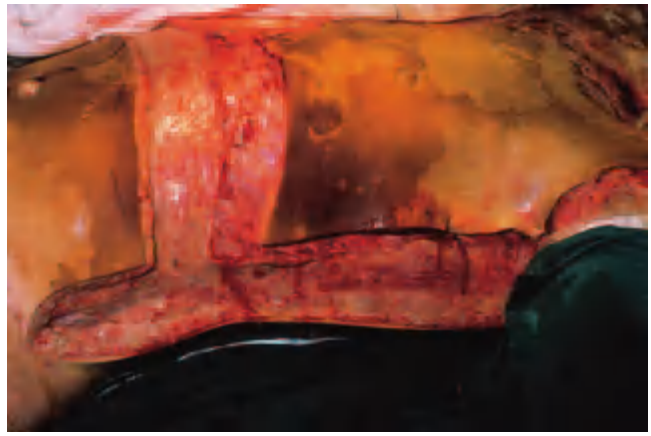


Fig. 22.28 An escharotomy performed transversely across the lower chest and in the mid-axillary line for a full thickness burn of the trunk. Note that this is purely an incision of the skin and subcutaneous tissue, and no tissue has been excised. The massive gaping results entirely from swelling of the incised burnt tissues and the escharotomy allows the chest to expand.

Table 22.11 Criteria for referral to a burn centre.

Burns greater than 10% BSA
Burns that involve and threaten functional or cosmetic impairment of the face, hands, feet, genitalia, perineum and major joints
Full thickness burns greater than 5% BSA
Electrical burns
Chemical burns
Burns associated with inhalational injury
Circumferential burns of limbs or chest
Burns at the extremes of age (children and elderly)
Burn injury in patients with pre-existing medical disorders which could complicate management, prolong recovery, or affect mortality
Any burn patient with concomitant trauma

BSA, body surface area.

Table 22.12 Essential measures to be performed before transfer to a specialist burns unit.

1 Respiratory support
• 100% oxygen with or without intubation
2 Circulatory support
• Intravenous access + infusion + urethral catheter
3 Gastrointestinal decompression
4 Wound care
5 Pain medication
6 Tetanus immunization

Documentation

It is essential to include all available information about the nature of the injury as well as the physical findings and

extent of the burns. In addition, there should be a clear flow chart documenting resuscitation measures, drugs given and blood results. Doctor-to-doctor contact is essential to ensure the safe transfer of the patient. This is particularly the case where a patient has been intubated in the referring hospital. The communication should be a two-way process, and the burns unit should inform the referring hospital of the outcome of treatment of the burn patient, not only as a matter of professional courtesy but also from the point of view of continuing medical education.

Overview of continued fluid resuscitation

In most situations, the continued resuscitation of the burns patient will take place in a specialized centre. There will be occasions, however, as a result of associated injuries or problems with transport, where a non-burns specialist may have to supervise the management of the patient through the critical period of fluid resuscitation.

The patient who has been managed in the orderly manner as described above is in the best condition to move into the next critical phase of proper fluid management. Mortality in the first 24–48 h post-burn has decreased considerably with increasing understanding of the massive fluid shifts from the intravascular to the extravascular (intracellular and interstitial) spaces that occur during the burns shock phase. The primary goal of fluid therapy is to replace the fluid sequestered as a result of the thermal injury. It is obvious from the many formulae that have been proposed over the years that there is no universally accepted burns resuscitation formula. It must be emphasized that whatever formula is used, it is only a guideline and the actual amounts of fluid given should be varied according to clinical response.

In principle, the least amount of fluid should be given to maintain adequate organ perfusion, and the infused fluid must contain sodium to replace the extracellular salt lost into the burned tissue and into the cell. In the past, there has been great debate over the relative merits of crystalloid versus colloid resuscitation regimens. In the absence of convincing clinical evidence to support either, the burns physician should take into account local practices, availability and cost of solutions, and should develop a protocol that can be safely and effectively adhered to but that will provide the flexibility to take into account individual patient requirements.

In this overview, the fluid to be infused in the first 24 h is derived from a consensus formula recommended by the Advanced Burn Life Support Course in the USA and the Emergency Management of Severe Burns Course from Australia and New Zealand. The figures are based on the Parkland formula.

However, it must be recognized that plasma proteins are extremely important in the circulation, as they generate the inward oncotic force that counteracts the outward capillary hydrostatic force. It has been demonstrated experimentally that restoration and maintenance of plasma protein concentrations are not effective until 8 h post-burn, at which time normal levels can be maintained with infusion. With this in mind, it is recommended that colloid should be introduced into the resuscitation regimen once the initial phase of massive fluid shift has begun to stabilize [5]. While this may occur as early as 12 h post-burn, a consensus recommendation is to introduce the colloid in the second 24 h using 0.3–0.5 mL of colloid/kg body weight/% BSA burned. The colloid should be 5% normal serum albumin (50 g/L).

Monitoring response to resuscitation

There is no single parameter of perfusion in the burn patient that can be considered to be a completely reliable indicator of tissue oxygenation. Therefore, a combination of observations should be made. As the severity of the burn increases so does the need for more complex and invasive monitoring [6].

Continuous monitoring

Cardiac monitoring. Arrhythmias are not worrying in the young patient so long as oxygenation is adequate, but are a major concern in the patient over 45 years of age in whom they may be the first indicator of hypoxia or of electrolyte and acid–base abnormalities.

Arterial blood pressure *per se* is an insensitive measure of volume status because of the increased sympathetic tone in the early stage of resuscitation. However, a minimal level of perfusion pressure must be maintained and therefore blood-pressure monitoring must be established. An arterial line may be required if the patient is haemodynamically unstable and if frequent blood gases are required.

Pulse oximetry can provide continuous information on the oxygen-haemoglobin saturation and is non-invasive.

Body temperature. The core and peripheral temperature should be recorded. The burn patient is very prone to hypothermia with the infusion of cool fluids, and it must be recognized that thermoregulation is abnormal in burns. The damage to the skin interferes with normal mechanisms of heat conservation and dissipation; in children, there is also a disturbance of hypothalamic control. This has two important consequences:

1 Pyrexia in children in the first 36 h post-burn is most probably not related to infection

2 Core–peripheral temperature gradients become unreliable indicators of haemodynamic status.

Fig. 22.29 Total burning of the legs in a patient who fell asleep smoking and woke up with the bed on fire. Skin, fat, muscle, tendon and bone were all burnt.

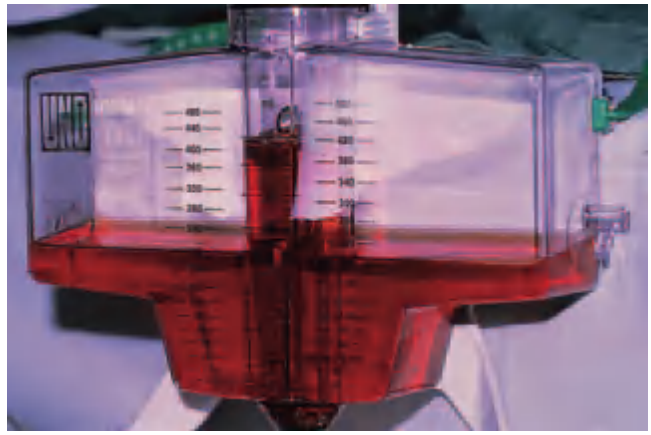


Fig. 22.30 The urine in the same patient showing the bright-red colour of myoglobinuria.

Fluid balance. During the first 24 h post-burn, in the absence of an abnormal solute load (e.g. glucose, mannitol or alcohol, which may falsely increase urine output in the presence of hypoperfusion), urine output should reflect the glomerular filtration rate and therefore renal perfusion. A urine output of 0.5–1.0 mL/kg/h normally reflects adequate renal blood flow. The rate of fluid administration should be increased if urine output is below 0.5 mL/kg/h but this should not be too rapid as boluses will cause marked transient increases in venous pressure and thus will significantly increase oedema. A urine output of more than 1.0 mL/kg/h usually means too much fluid is being given, with the possibility of excess oedema formation. Myoglobinuria will cause red discoloration of the urine (Figs 22.29 & 22.30).

Monitoring central venous pressure (CVP) or pulmonary artery wedge pressure may be necessary. In the early stage of resuscitation of a patient with a large burn, the CVP is usually low, in the region of 0–5 cmH_2O even with adequate fluid resuscitation, but can be used to follow trends. The majority of young patients, even with massive burns, do not require pulmonary artery wedge pressure monitoring for initial resuscitation, and the morbidity associated with pulmonary artery lines may outweigh the benefits. As with the CVP, the pulmonary artery wedge is usually normal to low (6–10 mmHg) after a burn even when adequate perfusion is present. Hypoperfusion is almost always caused by hypovolaemia.

The interpretation of the values obtained by this level of intensive monitoring is the domain of the intensive care specialist. In patients with severe burns, unlike other forms of trauma, the ideal values for more complex cardiorespiratory variables such as measurements of oxygen delivery and consumption are at present unknown, and aggressive attempts to optimize microcirculatory blood flow by the use of volume loading, inotropes or vasodilators may be inappropriate [7]. This is because generation of high intravascular pressures in the presence of a generalized capillary leak may only serve to increase the rate of fluid loss and to exacerbate the oedema-related complications of increased tissue pressure and decreased tissue oxygen tension.

Intermittent monitoring

Haemoglobin and haematocrit. Baseline values are useful but thereafter changes in values may not accurately reflect changes in blood volume because of the selective loss of plasma from the blood. Haemoconcentration invariably occurs after large burns, and normalization of blood volume will take some 24–48 h. Blood loss during this time can be underestimated, for example from escharotomies, internal bleeding or associated with fractures, because the rate of plasma loss may exceed the rate of whole-blood loss resulting in a normal haematocrit despite severe volume depletion.

Electrolytes. As the initial losses are primarily from plasma, the sodium, chloride and potassium values remain relatively constant despite hypovolaemia and vary mainly as a result of the type of resuscitation fluid used. Osmotic hyponatraemia occurs in the presence of a solute such as glucose or mannitol to which cells, including osmoreceptors, are incompletely permeable (solutes to which cells are readily permeable such as ethanol or urea do not exert the osmotic effect to expand extracellular volume and lower the plasma sodium concentration).

Water intoxication occurs when sodium losses are replaced by hypo-osmolar solution or if hyponatraemia is corrected too rapidly.

The term *sick-cell syndrome* is used by some to describe clinical states of hyponatraemia associated with profound systemic disease such as renal and hepatic failure. It is

also described in burns where it is thought to result from hypovolaemia, infection, anaemia or undernutrition. Dysfunction of the cellular sodium-potassium adenosine triphosphatase pump is thought to be the cause. If other causes of hyponatraemia have been excluded, this diagnosis should be considered if there is reversal of the sodium : potassium ratio (normally > 1) to < 1. Treatment is directed at the primary cause [8].

Elevated potassium levels occur if there is marked haemolysis or rhabodomyolysis, or if renal disease is present. It is important to note, however, that potassium-sparing drugs have prolonged effects, and that actual hyperkalaemia may occur in the absence of significant renal dysfunction. Emergency management should be given if serum potassium exceeds 7.0 mmol/L, or if there is widening of the QRS complexes, heart block or dysrhythmia.

Creatinine and blood urea nitrogen. It is useful to establish baseline values to rule out intrinsic renal disease. Thereafter, changing figures indicate trends in resuscitation.

Coagulation screen. Initial values of prothrombin time, partial thromboplastin time and platelet count are useful in the resuscitation phase to establish baseline values. It is not common to replace clotting factors and platelets during the first 36 h, although this may become a critical issue in the later stages of burn management.

Chest X-ray. If the patient is ventilated, a daily chest X-ray should be obtained. The development of pulmonary problems following smoke inhalation is a progressive phenomenon and requires intensive and specialized care.

Burn wound management [9]

The management of the burn wound is in a continuous state of evolution and is not without controversy. The principle is to achieve healing as quickly as possible with the minimum of scarring. One of the problems concerning burn wound management relates to the phenomenon alluded to earlier, the 'burns spectrum'. There are two critical aspects that determine the severity of burn injury: the depth of the burn and its extent.

The vast majority of burns are small and superficial and may be self-treated, or treated in emergency rooms or by general practitioners. These burns are best treated by deroofing blisters, gentle cleansing with saline and the application of a non-adherent dressing overlain with an absorbent layer.

When the depth of burn is greater, the role for conservative treatment becomes more controversial. Surgery is definitely indicated for full thickness burns unless there are overriding clinical considerations to the contrary.

The major controversy surrounds the management of the deep partial thickness burn [10]. These burns can and will heal if allowed to do so in an environment that protects the wound from infection. Healing can take several weeks, however, and there is a high incidence of hypertrophic scarring in deep partial thickness burns that have been allowed to heal spontaneously. The decision will depend on the experience of the burn surgeon because there have been no extensive randomized controlled trials to indicate the 'best' approach. The controversy is of particular relevance to the vast majority of children's burns, which are scalds, and which are often of 'indeterminate' depth. Some burn surgeons advocate waiting until the depth of burn declares itself at approximately 48 h; if it is assessed that the burn will not heal within 7–10 days, the patient will be taken to the operating room and the dead tissue tangentially excised until there is a wound bed of viable tissue on which a split-thickness autograft can be placed. The arguments for this approach include rapid wound closure with less likelihood of infection, shorter hospital stay and improved cosmetic result. This approach will mean that certain patients might have unnecessary surgery, with the risks of general anaesthesia and an additional wound at the donor site. Other surgeons advocate waiting for 10–14 days before making the assessment, and then grafting only those areas that look unlikely to heal by 3 weeks. This approach reduces the likelihood of unnecessary or extensive surgery, but does require a longer time to complete healing with an increased time of exposure to the risk of infection and a greater chance of hypertrophic scarring.

A third approach, which is particularly suitable for children in whom scalds predominate, is to perform an examination under anaesthetic at 3–5 days post-burn. At this stage the depth of burn is assessed clinically by assessing turgor in the tissues, as well as the presence or absence of blanching or 'fixed' staining of the burned skin. Even in the presence of fixed staining, indicating a deeper dermal burn, if there is absence of maceration of the wound, a biological dressing can be applied after thorough cleansing. Figure 22.31 shows the progression of healing after the application of glycerolized human cadaver skin [11]. While the surgical management of the burn wound is not within the remit of the dermatologist, advice may be sought regarding management of the burn wound in the acute stage. It is very important that the preferences of the local specialist centre are known as the application of different dressing materials may radically alter the appearance of the burn wound and thus affect the surgical decision-making process.

The critical determinant regarding whether to treat surgically or conservatively is the depth of burn. While there have been many attempts to develop techniques to achieve this objectively, the most common and practical clinical approach remains the assessment by an

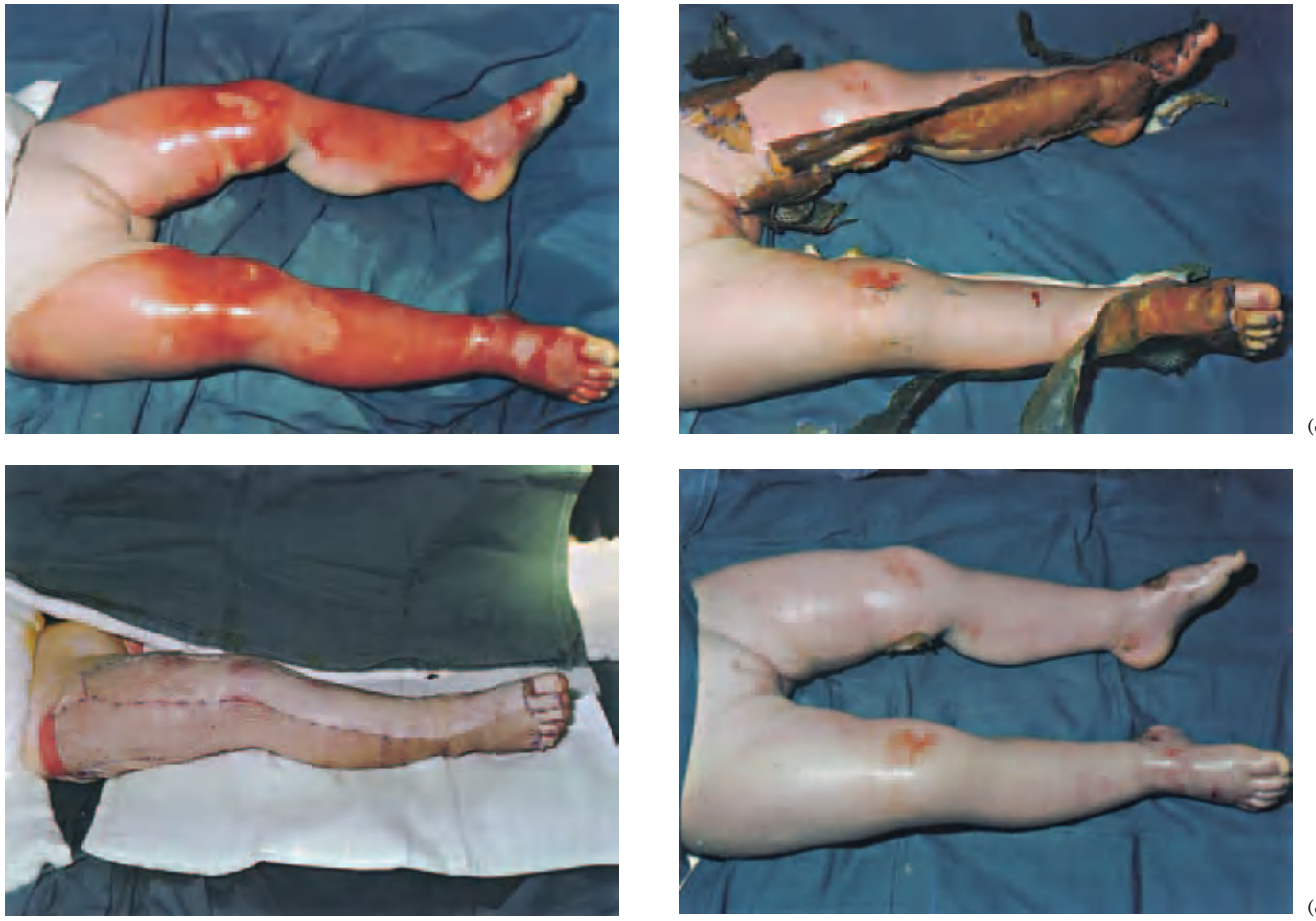


Fig. 22.31 (a) An 11-month-old child with a deep dermal scald exhibiting fixed staining in the wound; (b) covered with closed meshed glycerolized human allograft; (c) 2 weeks later the allograft is dry and spontaneously separating; (d) allogenic skin all removed, healed burn that did not develop hypertrophy. (Reprinted from [11], © 2002, with permission from Elsevier Science.)

experienced burn surgeon who will use visual and tactile cues. Such clinical subjective assessment is only 70–80% accurate as compared to the use of laser Doppler imaging [12,13]; although this technique remains in the research domain at present, its incorporation into routine clinical practice would give a more predictable outcome to the management of the burn wound.

Use of topical antimicrobial treatment, as with dressings, should not interfere with the wound appearance, and has to be balanced with the very real risks of infection developing within the burn wound. Early colonization of the burn wound is likely to be associated with Gram-positive cocci. Patterns of microbial activity vary between units and within time; *Streptococcus pyogenes* group A used to be regarded as the most serious pathogen but there is now far more concern about staphylococcal toxaemia, particularly in children with small burns [14,15]. For this reason, certain centres in the UK advocate using mupirocin as a topical agent on burns in children when the total burn surface area (TBSA) is less than 10%. This is covered with a dressing that combines a non-adherent layer and an absorbent layer, which will not affect the appearance of the burn wound. For more extensive burns where early surgery may be considered, dressing with paraffin gauze and dressing gauze soaked with povidine-iodine will not affect the appearance of the burn.

Where early surgery is not the practice or is not indicated for some other reason, topical antibacterial creams are commonly used. Silver sulfadiazine 1% cream, with or without chlorhexidine, is active against Gram-negative bacteria, including *Pseudomonas* spp. Typically, the cream is spread liberally on to dressings and applied to large areas. There is now also increasing use of silver sulfadiazine cream with cerium nitrate [16,17]. The advantage of this combined preparation concerns the effect on the burn wound. Topical creams produce a macerated wound that renders surgery less precise. The combination of silver sulfadiazine and cerium nitrate produce a calcium-rich layer on the surface of the dermal burns. The resultant

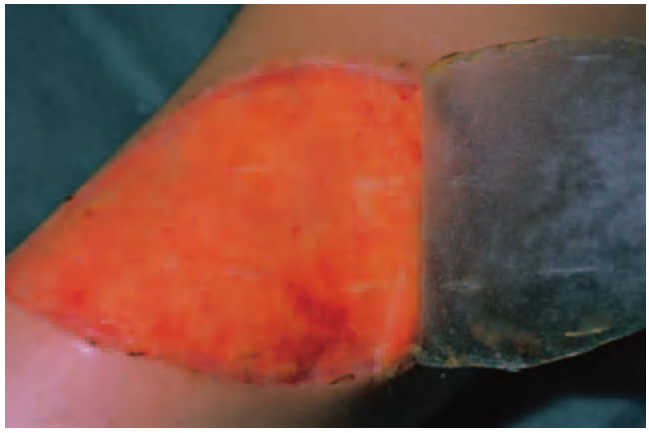


Fig. 22.32 A full thickness skin defect that has been treated with Integra® for 3 weeks. The outer silicone layer is here being removed. New dermis has been formed, and is now ready for a thin graft.

Fig. 22.33 Six years after applying Integra® to resurface a full thickness burn on the left hand the skin shows multiple fine wrinkles. The patient was aged 19 years.

shell-like layer acts as a bacterial barrier and, coupled with a dry wound, minimizes infection. This combined preparation is also associated with a lesser infiltration of polymorphonuclear neutrophils (PMN) into the burn wound. This may account for the drier nature of the burn eschar as opposed to the macerated wound associated with silver sulfadiazine, where PMN infiltration is prevalent.

While formulations containing silver remain the most widely used topical antimicrobials in burns care, the delivery of silver continues to be the focus for new developments. Sustained release of silver from dressing materials has distinct advantages over the cream formulations and will become more a feature of topical burns wound care in the next decade [18].

Surgical intervention

Surgery essentially involves removing the irreversibly damaged burned tissue and closing the wound. Surgery can involve tangential shaving of partial thickness burns or excision of full thickness burns. The surgeon now has an increasing number of options for closing the burn wound. When the wound is small, an autograft is the method of choice. The larger the burn area, the smaller the available donor sites for obtaining autografts. It is in these larger burns that great advances in terms of survival have been made with the trend towards early surgery and burn wound closure. Wound closure has been achieved using a wide range of materials including human allografts, fresh, frozen and glycerolized porcine xenografts, *in vitro* cultured keratinocytes used as both allo- and autografts, together with a variety of synthetic materials used as temporary dressings. Continuing interest is focused on burn wound closure using a dermal regeneration template, Integra® [19–21]. This synthetic bilaminate membrane is manufactured using biological raw materials (Fig. 22.32). The dermal analogue is an open lattice of fibres made of bovine collagen covalently linked to chondroitin-5-sulphate. The temporary outer layer, the epidermal analogue, is medical grade silicon, which is subsequently replaced with an ultrathin epidermal autograft. The collagen-GAG dermal analogue has a three-dimensional architecture similar to that of normal dermis and completely biodegrades after 30 days. It thus serves as a scaffold for the ingrowth of fibroblasts and endothelial cells, facilitating the formation of a neodermis. This functions like a human dermis in terms of biomechanical performance and response to growth. Six-year follow-up of Integra® used in reconstruction after burn scar revision does show the phenomenon of 'premature aging' in some cases (Fig. 22.33) and the search for new biomaterials continues [22–25].

General care

Small and minor burns require little care other than the specific treatment of the burn wound. Larger burns, however, require more specialized and extensive care. After the period of fluid resuscitation and early stabilization, with or without surgery, there will be a prolonged period of treatment and rehabilitation, which can be physically and psychologically demanding [26,27]. Constant attention must be paid in the earlier phases to reducing the risks of infection; early feeding with high-protein high-calorie diets with added vitamin and minerals is important to counteract the hypercatabolic response to the burn injury. While there have been considerable improvements in survival, major burns are still associated with a significant mortality and morbidity. It is important to balance encouragement and hope for recovery with realism that survival is not always certain and recovery is a long process. It must also be appreciated, particularly in children, that the magnitude of the physical trauma is mirrored by

the magnitude of the psychological trauma to the parents and relatives. Great sensitivity is required by those caring for these patients, and professional counselling should be available for the relatives.

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Cutaneous sequelae of burns

Superficial partial thickness burns will heal without scarring, although there may be some loss of pigment, which is usually temporary. Deeper burns are associated with scarring and there is a high incidence of hypertrophic scarring, especially in the deeper partial thickness burns that have been allowed to heal conservatively (Fig. 22.34). Hypertrophic scars go through a phase of many months when they can be intensely pruritic and this can be a significant problem for children. Pressure garments (Fig. 22.35) and silicone gel and elastomers are used in the management of hypertrophic scars [1]. Occasionally, the scarring can result in functional problems that require surgical intervention (Fig. 22.36). Aesthetic problems related to scarring and contracture with deformity also require combined approaches of splinting and surgical intervention, which may need to be repeated over a considerable period of time. Late neoplastic change in burn scars is discussed below.

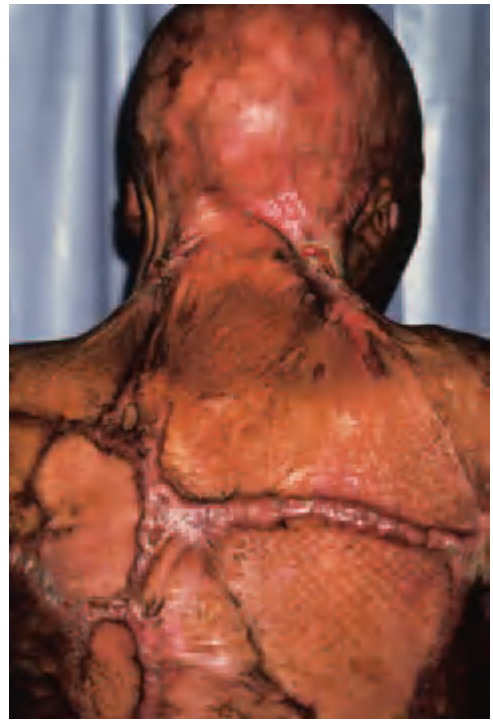

Fig. 22.34 Hypertrophic scarring in a burn in a dark-skinned person. Areas on the back were grafted and the burn scars between the grafts became hypertrophic.

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Electrical burns

These occur from environmental, domestic and industrial sources and present a unique form of trauma, which may affect multiple organ systems and present challenging problems for clinical management. Electrical burns are arbitrarily classified as high- or low-tension injuries, with

Fig. 22.35 Commercially available pressure garments made by Biersdorf.

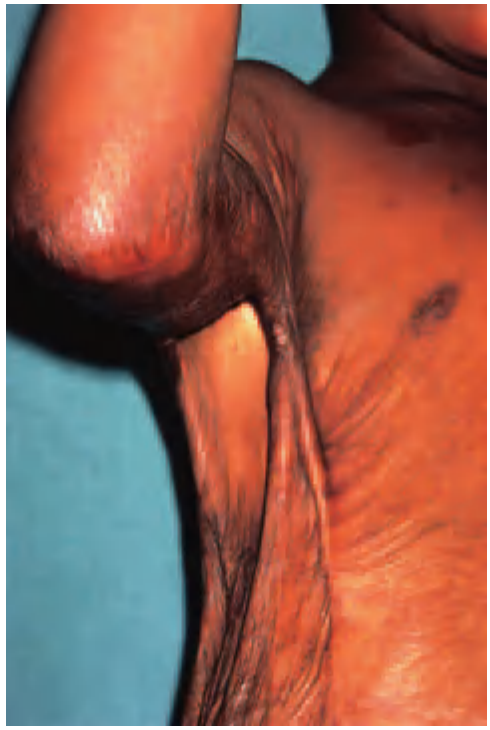

Fig. 22.36 Contracture of the shoulder resulting from scarring of the axilla.

low-tension burns being less than 1000 V and high-tension burns greater than 1000 V. Electrical injuries account for approximately 3% of burn patients admitted to specialized centres, and the majority come from contact with the domestic 240 V alternating current at 50 Hz single phase. Other sources of current are the high-voltage power lines that pose a threat not only to workers but to sports enthusiasts involved in pursuits such as fishing, hang-gliding, parachuting and kite flying [1,2]. Other injuries are associated with electrification in rail transport, both the overhead lines and the 'third' rail. Finally, car batteries cause a significant number of injuries to car mechanics (usually in amateurs).

The pathophysiology of the electrical injury is complex [3] and not completely understood. Historically, the mechanism was thought to be heat, as the passage of electric current through a solid conductor results in the conversion of electric energy to heat (the joule effect). However, it is probable that significant damage is also produced directly by the effect of the electric current inducing cell membrane breakdown, a phenomenon called electroporation. Clinically, the severity of injury relates to the voltage, the thickness and wetness of the skin and the duration of contact. The location of the entry and exit points determine the areas that will have been potentially damaged. High-voltage injuries may result in extensive muscle damage with subsequent risk of renal failure. All organs between the entry and exit points are liable to injury, and cardiac standstill can occur.

Electrical burns show distinct histological features. The nuclei of the basal cells, and sometimes of the more superficial epidermal cells, appear stretched vertically. There may be dermal–epidermal separation, with elongated degenerated cytoplasmic processes from the basal cells protruding into this space.

Management of the patient with electrical injury involves general supportive treatment as well as specific wound treatment [4]. If there are electrocardiogram (ECG) abnormalities then continuous cardiac monitoring is necessary together with pharmacological treatment of any dysrhythmia. Fluid resuscitation may be indicated. It must be appreciated that the extent of the injury is often 'hidden' with deep muscle damage. Because of this, fluid requirements may considerably exceed those predicted by the cutaneous burn alone. A particular concern is myoglobinuria with the risk of renal failure, in which case a brisk urine output should be encouraged with the use of mannitol (see above).

Historically, the teaching on wound management was that there was delayed muscle necrosis and therefore that early wound débridement and wound closure was contraindicated. Current thinking is that débridement of obviously necrotic tissue should be performed as early as possible, preferably soon after admission at the same time as escharotomies, fasciotomies and nerve decompression

are undertaken [5]. Wound closure should, however, be delayed for a short period to allow progressive tissue damage to declare itself [6]. This damage is thought to result from the effects of the electroporation. The tissue damage resulting from this would be recognized several days after injury when arachadonic acid metabolites have caused microvascular ischaemic cell death.

Lightning burns are not infrequent and can produce a variety of injuries. Characteristically, there are arborescent lesions (Lichtenberg figures), which are erythematous, mottled or charred, and small linear burns at the site of metal objects held in the hands or in clothing pockets. However, the skin lesions are overshadowed by the general effects of respiratory arrest, gastric dilatation, ileus, cerebral oedema and fractures.

Electrical flash burns can occur with both low- and high-tension injuries. These involve the exposed areas, typically hands and face. Superficial flash burns can be treated conservatively but deeper ones will require surgery in specialist units. Extensive flash burns will require intravenous fluid resuscitation.

Miscellaneous electrical burns

There are a number of electrical burns that can give rise to medicolegal issues because they can mimic torture or child abuse. For example, burns that were actually caused by a defective enuresis alarm system were similar to cigarette burns, which, because of their shape and multiplicity, were thought unlikely to have been caused accidentally (Fig. 22.37).

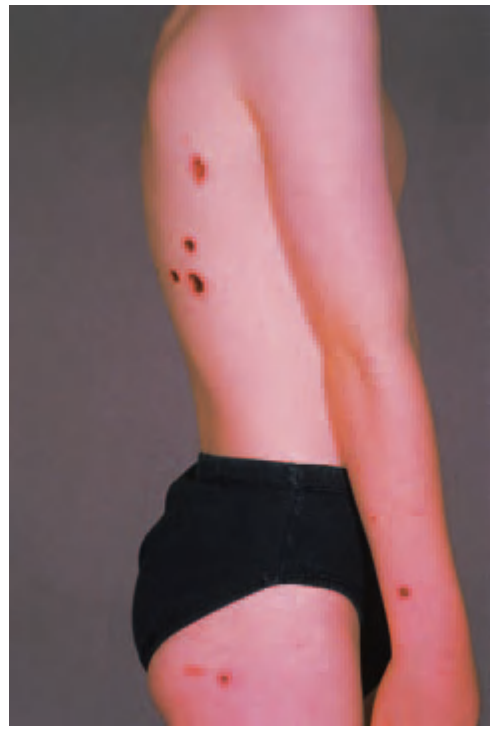

Fig. 22.37 These lesions raised the suspicion of child abuse because they were initially thought to be caused by multiple cigarette burns but in fact they were caused by repeated accidental burns from an enuresis alarm.

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Laser burns [1,2]

When laser energy is absorbed by skin, it is converted into heat. The principal chromophores are melanin and haemoglobin. The effects on the skin are determined by a number of variables, such as wavelength of the laser emission, power, duration of exposure, direction of the beam and skin colour. The carbon dioxide laser produces non-specific destruction, often vaporizing the skin with a narrow zone of coagulative necrosis adjacent to the healthy tissues. In contrast, the wavelength of the tuneable dye laser can be chosen for maximal absorption by one component of the skin, and with very brief duration pulses the damage can be restricted. Laser light of 577 nm, delivered in impulses of nanoseconds' duration, is used to treat port-wine stains without scarring. Histologically, damage is limited to the superficial dermal vessels. When thermal damage is more extensive, hypertrophic scarring can occur; this is a more significant risk with the argon laser.

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Microwave radiation burns [1]

Microwave radiation is non-ionizing high-frequency short-wavelength radiation, which generates heat by its effects on water molecules. Accidental exposure to microwave radiation has caused burns sufficient to result in amputation [2]. Lesser injuries have been followed by paraesthesia. Two cases of children deliberately injured

by microwave ovens have been described in which the injuries were sharply demarcated [3]. Subsequent studies of the effects of microwave radiation on piglet skin and the underlying tissues indicated that, when sufficient microwave energy was given to burn the skin and muscles or viscera, there was relatively little injury to the subcutaneous fat [4]. This sparing of the fat appears to be a unique property of the microwave burn.

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Burns and skin neoplasia

Malignant transformation in burn scars was described by Marjolin in 1828. Clinical features to suggest the development of malignancy include induration and persistence of ulceration after a burn; the appearance of an elevated border at the edge of a post-burn ulcer; breakdown of a burn scar with an indurated base; and nodule formation within a burn scar.

Most malignancies arising in burns scars derive from epithelial keratinocytes, although malignant melanoma, sarcoma and schwannoma have also been described [1–5]. The frequency with which burn scars develop a neoplasm is unknown, but in a previous generation it was estimated that approximately 2% of squamous carcinoma and 0.5% of basal cell carcinomas arose in burn scars. Most carcinomas that develop in burns scars are squamous in type [6,7]. Neoplastic change is more likely when there is delayed healing or repeated ulceration (Fig. 22.38), and the incidence of carcinoma is reduced if such wounds are grafted at an early stage [8]. Burn scar carcinoma is most common in the lower limb and in limb flexures. Most squamous carcinomas occur after a long latent period, sometimes several decades, although it is shorter in the elderly. Uncommonly, a carcinoma may arise within weeks or months of a burn: this short latent period neoplasm is more commonly basal than squamous cell in type. Metastasis to regional nodes is much more common in the squamous carcinomas arising in burn scars than those associated with actinic damage. It occurred in 16 of 44 cases, of whom 15 died [9]. Metastases occurred in 20% in one series [8] and 36% of another [10]. The prognosis is worse for lower limb lesions [9].

Basal cell carcinomas occurring in burns scars are more common on the head and neck, in actinically damaged skin and in older patients [8]. Carcinoma following exposure to hot metal fragments, as occurs in welders, is more likely to be basal than squamous cell type [11].

It is not known how burns result in carcinogenesis. When the latent period is short, and a neoplasm develops in sun-damaged skin, it is likely that the burn is acting as a promoter. When the latent period is long, other mechanisms are more likely. Burning itself may act as an initiator of carcinogenesis [12]. When the burn results in chronic ulceration or repeated cycles of healing and ulceration, this in itself may act as a promoter. Because squamous carcinoma can occur even when the damaged area is grafted, the carcinogenic stimulus may arise in the dermis in some situations. It is also possible that locally impaired immune function contributes to the development of malignancy.

For medicolegal purposes, the criteria established long ago [13] for associating a carcinoma with a previous burn are still valid.

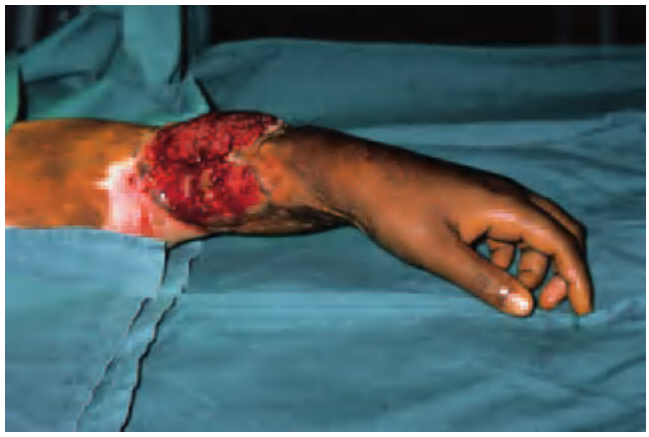

Fig. 22.38 Chronic ulceration of a burn scar with malignant degeneration (Marjolin's ulcer). (Courtesy of Dr L. Sacks, Frenchay Hospital, Bristol, UK.)

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Abuse by burning

Regrettably, human beings sometimes cause serious injury to others, including members of their family circle and especially those who are helpless, such as young children or elderly parents. Abuse may be willful and malicious but in many cases it is caused by thoughtless neglect. The problem of deliberate injury to children by burning has been identified for over 20 years [1,2]. Similar aggressive acts towards dependent elderly are not widely recognized but it is highly probable that there is a much higher frequency of this type of injury than is reported in the literature [3,4] and that, as with child abuse, the more burn-care professionals become sensitive to the possibility of abuse of the elderly, then the more the observed incidence will rise. Burning has been the mechanism of abuse in about 10% of cases of child abuse. The incidence of abuse associated with childhood burns varies considerably from 1% to 25% of burn admissions to specialized centres.

It can be very difficult to diagnose a non-accidental injury but there are a few features that should give cause for concern (see also p. 22.36):

1 A child is brought for treatment by an unrelated adult
2 There is an unexplained delay in seeking treatment
3 The parents seem to be responding inappropriately to the injured child (e.g. they are inattentive or unconcerned)
4 Blame for the injury is placed on another person (usually not present)
5 The injury is not consistent with the history.

Inflicted burns can have characteristic patterns of injury (Fig. 22.39) [5]. The majority of non-accidental burns in children are scalds; these may be spill injuries or immersion burns. Immersion burns are very rare as accidental injuries in children under 1 year of age. Suspicious features are burns of glove and stocking distribution or the classical 'doughnut' of spared skin on the buttock on a child who has been forced to sit in a bath of hot water. Flame burns are less common. Contact burns may occur with the placing of a child against a hot object or by branding the child with cigarettes or a domestic iron.

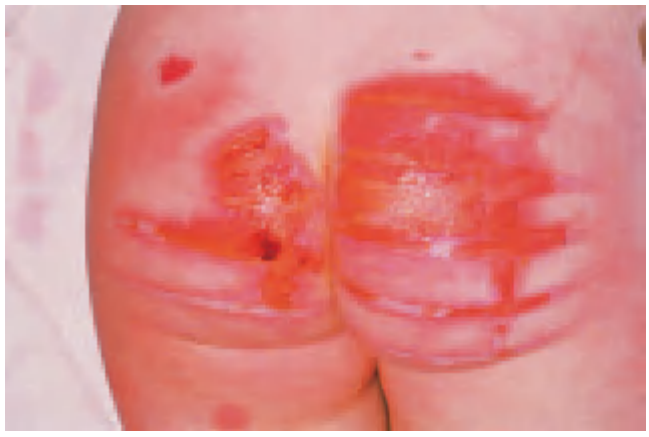

Fig. 22.39 This pattern of a heating grill on the buttocks of a child was a result of child abuse.

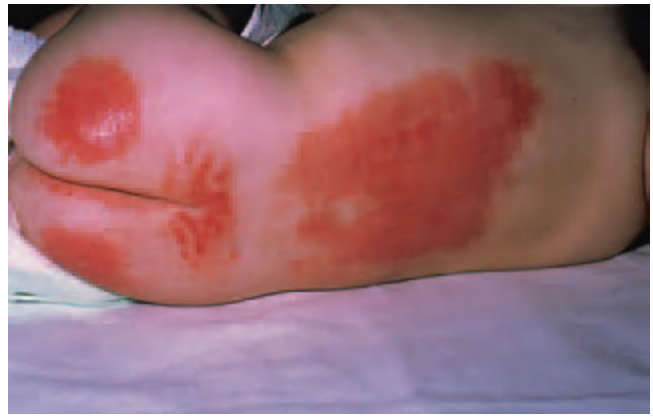

Fig. 22.40 This child with 'staphylococcal scalded skin syndrome' and no history of burns was originally admitted to a burns unit as a case of suspected child abuse.

While the diagnosis of child abuse is very important, the misdiagnosis of abuse can be a tragedy that can destroy family groups. It is very important therefore to be aware of injuries that may simulate abuse. Cutaneous infections can mimic deliberate injury, for example impetigo, severe napkin rash and scalded skin syndrome (Fig. 22.40). Hypersensitivity can sometimes be mistaken for intentional burns. Photodermatitis can be caused when substances in certain fruits come into contact with skin exposed to sunlight. A pattern of erythema and blistering can develop that simulates a splash burn. Without a history of injury, abuse may be suspected. Cigarette burns can be accidental but multiple cigarette burns are pathognomonic for child abuse.

The patterns of abuse of the elderly are less well documented, but the author has knowledge of cases of immersion of physically dependent elderly people in hot baths resulting in burns. While this may not come into the category of malicious abuse, it is indicative of negligence on the part of the carer. Another distressing injury comes from contact burns against hot water pipes or radiators. These can be sustained by elderly people collapsing in the night and not being able to move away from the source of heat. There may be no conscious abuse but the exposure of at-risk individuals to preventable environmental hazards, together with the lack of supervision, may constitute negligence. While there is legislation that protects children (e.g. fireguards are a legal requirement when there are children under a specified age in a room), the same degree

of legislation does not yet apply to dependent elderly people. This situation will probably change, particularly as the at-risk elderly population increases.

Abuse by burning is a very disturbing and emotive injury. It is essential that, while a high index of suspicion should be maintained with burns patients at the extremes of age, these suspicions should be thoroughly and sensitively pursued. Multidisciplinary teams should be established to undertake this investigation. Experienced and trained professionals will then have to confront the suspected abuser if appropriate.

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Miscellaneous reactions

[C.T.C. Kennedy, pp. 22.84–22.85]

Blackening of the skin by metals

SYN. BLACK DERMOGRAPHISM

The black discoloration produced when the skin is stroked against certain metals is called black dermographism [1]. Unlike other forms of dermographism it has a purely physical, not a physiological basis. It is caused by the abrasive effect of powders on the skin, which rub against a relatively soft metal, generating particles that are so small that they absorb but cannot reflect light [2]. Any powder harder than a metal in contact with it can abrade the metal and produce skin blackening. Calamine lotion (zinc and ferric oxide), face powders (zinc oxide, titanium dioxide and ferric oxide) and some dentifrices containing pumice readily produced the phenomenon from gold, silver or platinum jewellery. In some individuals who exhibit black dermographism, the powder originates from the workplace.

Pure gold (24 carat) does not seem to have the property of skin blackening, possibly because the surface has more plasticity and deforms rather than fragments when friction is applied [3].

In addition to the presence of powders on the skin, factors that increase the likelihood of blackening include dryness and roughness of the skin, and amino acids in sweat (especially those containing sulphur, which can produce black complexes with gold). Sodium chloride (e.g. from sweat and sea water), which may promote corrosion, and tarnishing of the base metal in gold alloys can both contribute to the phenomenon.

Black dermographism can mask a contact allergic dermatitis to gold [4].

Blackening of the skin can be treated by simply washing with soap and water, and it can be prevented if the skin that will be in contact with the metal is carefully cleansed free of powder.

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Rusting

Certain individuals have the ability to corrode metal. This comes to light in apprentices in the precision engineering industry and makes them unable to pursue their career. Such individuals are known as 'rusters' [1].

Rusters tend to have hyperhidrosis [2] and the mechanism of the electrolytic corrosion has been investigated in detail [1]. 'Rusters' have an increased secretion of salt in their sweat [3].

The composition of the steel being handled is important; with increasing amounts of copper, the phenomenon is less likely to occur [2].

Treatment is difficult. Measures to reduce hyperhidrosis such as aluminium chloride hexahydrate under occlusion may help, as can hand washing and protective gloves [2].

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Finger wrinkling

Early and excessive wrinkling of the skin of the fingers after immersion in hot water was thought to be a useful sign of cystic fibrosis [1,2] or a test of sympathetic nerve function [3,4], but false-positive results limit its value, and nearly one-third of normal subjects showed no wrinkling at all [5]. The factors influencing wrinkling include hydration of keratin and patency of sweat pores [6,7].

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Carbon monoxide poisoning [1]

Symptoms and signs become increasingly apparent with circulating levels of carboxyhaemoglobin above 30%, and coma, convulsions and cardiorespiratory arrest are likely to occur with concentrations of 60% or more.

A burning sensation may be the earliest symptom in mild cases [2]. The distinctive vivid erythematous or oedematous plaques may appear, especially at pressure sites, within hours after carbon monoxide poisoning [3] but this often-quoted 'cherry red' change only occurs in about 1% of cases of carbon monoxide poisoning [4].

Vesicles and bullae may develop, often in a geographical pattern [5,6]. The lesions simulate those seen in barbiturate poisoning or after cerebral vascular accidents or drug-induced coma.

Histologically, the bullae show epidermal necrosis, intraepidermal vesiculation and necrosis of the secreting portions of the sweat glands [3,5]. Spontaneous resolution occurs, in those who survive, in about 15 days [3,7]. Pressure and hypoxia are probably the main factors in the pathogenesis.

Complications include haemolytic anaemia, renal insufficiency from rhabdomyositis, and peripheral neuropathies.

Treatment. This is with 100% oxygen, administered by a tightly fitted face mask or, if necessary, endotracheal intubation and mechanical ventilation. General supportive measures may also be required.

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Chapter 23

Reactions to Cold

P.M. Dowd

Introduction

The stimulus of an adverse environment, if not too extreme, is one of the factors which encouraged humans and other animals towards civilization. Humans and animals have adapted to cold by several mechanisms [1–4]. They include tolerance of changes in body temperature, increased production of heat and increased insulation. In humans, increased insulation is achieved by an increase in fat, vascular changes and especially by social changes related to housing and clothing.

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Physiological reactions to cold [1–9]

The cutaneous changes induced by cold depend on many variables other than the actual temperature achieved and the duration of chilling. These include the rate of chilling and the rate of rewarming. These variables are of importance when considering clinical damage caused by accidental exposure to cold as well as when cold injury is deliberately inflicted therapeutically (see Chapter 77). Extreme cold, sufficient to freeze tissues, causes gross damage to cells. There is disorganization of the macromolecular structure, perhaps due to the formation of ice crystals outside or inside the cell, leading to hypertonicity and denaturation of protein. Lesser degrees of cold also cause pronounced changes in normal physiology. All enzymes and vital processes are depressed by lowering the temperature, but to a differing extent. Some of the most obvious effects are those on the vascular system. Exposure to cold causes constriction of the arterioles and veins by a direct mechanism mediated, at least in part, via endothelial synthesis of the vasoconstrictor peptide endothelin-1 (ET-1). There is also a reflex increase in sympathetic tone arising from cold receptors in the skin and, moreover, if the blood temperature falls, from the heat-regulating centre in the hypothalamus. The direct effect of cold on the veins tends to be greater than on the arteries, and both rewarming and local metabolites have a greater dilator effect on the arterial side, so that resumption of arterial flow after exposure to cold tends to lead to oedema [5].

Moderate exposure of fingers to cold leads to the 'hunting reaction' of Lewis [10]. Normally, cold-induced vasoconstriction is a protective device to prevent loss of heat from the body. With more severe exposure to cold, this may jeopardize the integrity of the skin tissues. A local vasodilatation mediated by the sensorimotor peptidergic nervous system then comes into play, and there is a resultant phasic increase and decrease in blood flow through the cutaneous microvasculature [10].

An important effect of cold is to increase the viscosity of blood. This plays a part in some abnormal reactions to cold. Other physiological effects of cold include changes in platelet adhesiveness, diminished conduction velocity in cutaneous nerves and slowing of the dissociation of oxyhaemoglobin to haemoglobin.

The interplay of these numerous factors with the general depression of metabolism determines the varied colours which may occur in normal or pathological skin in response to cold.

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Diseases caused or aggravated by cold

The severity of cold injury to the skin depends on several factors, not solely the absolute ambient temperature and duration of exposure to cold, which determine the type of cold injury sustained by all normal individuals on adverse exposure to cold. Perhaps the greatest variable determining the cutaneous manifestations of cold exposure is the individual's susceptibility to cold injury. Individuals who have an endogenous susceptibility to cold suffer clinical cold-related disorders on exposure to modest degrees of cold that would be tolerated without ill effect by other normal individuals. Hence, diseases caused or clinically revealed as a result of cold injury to skin are perhaps best divided into two groups: (i) diseases of cold exposure, and (ii) diseases of abnormal susceptibility to cold (Table 23.1).

Table 23.1 Diseases caused or aggravated by cold.

Diseases of cold exposure
Frostbite
Trench foot
Diseases of abnormal susceptibility to cold
Raynaud's phenomenon
Livedo reticularis
Cryoglobulinaemia
Cold agglutinins
Cold haemolysis
Cold urticaria
Perniosis
Acrocyanosis
Erythrocyanosis
Cold erythema
Cold panniculitis
Neonatal cold injury
Prurigo hiemalis

Diseases of cold exposure

Frostbite

Aetiology and pathology. Frostbite is the result of acute freezing of the tissues on exposure to extreme degrees of cold. Exposure of only a few seconds' duration may be sufficient to cause it. Factors which increase the rate of loss of heat from the skin, for example contact with good conductors such as metals, result in greater severity of injury for the same duration of exposure. Traditionally it has been accepted that wind chill increases the severity of frostbite, but a recent survey in Antarctica demonstrated that although the frequency of frostbite tended to follow the frequency of wind-chill values, except at higher wind-chill values, neither temperature nor wind chill was found to significantly influence the severity of frostbite. Prior cold injury was shown to be significantly associated with further cold injury [1].

The pathological changes are dependent upon the duration and severity of the exposure to cold, and vary from mild perivascular inflammatory changes to severe bulla formation and tissue necrosis extending as far as bone. The acute response to cold leads to actual freezing of, and ice crystal formation in, the affected part, with destruction of superficial tissues in milder cases and of deeper tissue, including larger blood vessels, nerves and bone, in the most severe cases.

The diagnosis is made on the history and clinical appearances and the exclusion of other causes of cold-related erythema, blister formation and gangrene [2].

Clinical features. The parts of the body that can be least protected from cold are affected—toes, feet, fingers, ears, nose and cheeks (Fig. 23.1). After the initial pain or feeling of burning on exposure, the affected part becomes pain-free and the sensation of cold in the affected part disappears. The affected zone of skin becomes waxy and white, and these appearances persist until the time of thawing. Depending on the severity of the cold exposure, muscles and nerves may be damaged, leading to paralysis, and arteries and subcutaneous tissue and even bone may be injured [3].

The extent and severity of tissue damage become really apparent on rewarming. Erythema, mild pain and soreness, lasting for a few hours, may be the only sequelae in mild cases. Blistering and destruction of the epidermis, dermis and deeper tissues occur in more severely affected individuals, and gangrene may then ensue [3].

Damage to the nerves and blood vessels may result in persistent paraesthesiae, abnormal sensitivity to cold and compromised nutrition to the tissues, even where loss of tissue does not occur. Hyperhidrosis may also occur. These effects, which are considered to result from damage causing functional abnormality of the sympathetic and

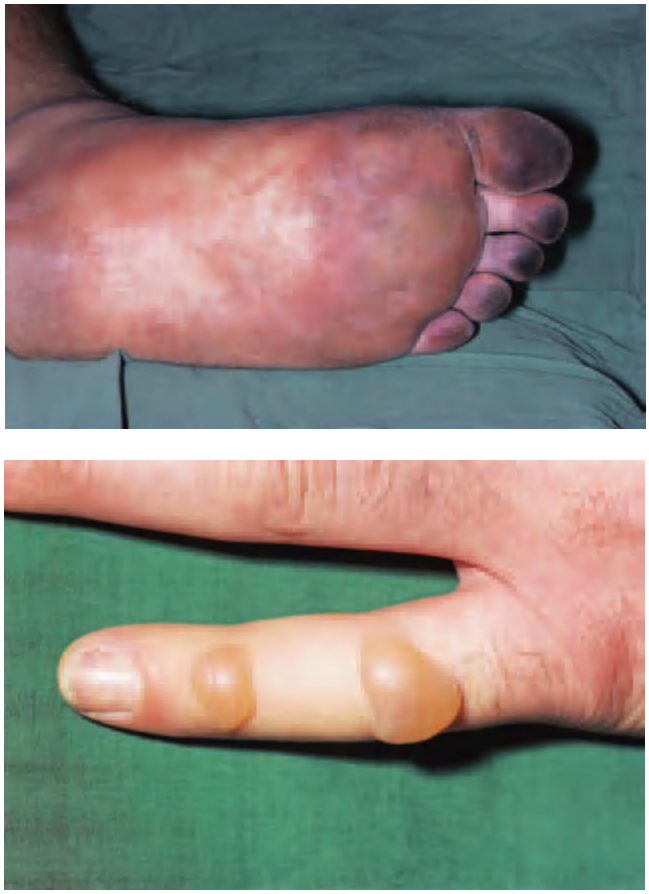

Fig. 23.1 (a,b) Frostbite.

non-adrenergic non-cholinergic nervous systems, may last for months or even years. Squamous cell carcinoma in the resultant scars may occur many years after the injury [4].

Treatment. Rapid rewarming by immersion in water at 40–42°C for 20 min is now recommended, in the light of experimental and clinical studies [5,6]. Exposure to higher temperatures is contraindicated. Treatment of frostbite in field conditions must invariably be on an ad hoc basis, and it cannot be too strongly stressed that further trauma must be avoided. In particular, rubbing the affected part with snow, a technique which has enjoyed some popularity in the mistaken belief that it hastens rewarming, is absolutely contraindicated as it has adverse effects of considerable magnitude. The prompt and early administration of heparin, and also infusion of low-molecular-weight dextran, appear to have proved beneficial [5,7].

Sympathectomy has little or no effect in the early stages. It used to be considered helpful in the later stages but now the indications for this operation are rarely encountered. Vasodilator and thrombolytic agents may be useful as adjuvant therapy, but randomized multicentre trials are still required to prove their efficacy [8,9].

Surgical removal of gangrenous tissue should be delayed for weeks or even months to allow tissue regeneration after maximum vasodilator therapy.

Trench foot

SYN. IMMERSION FOOT

Aetiology and pathology. Trench foot and immersion foot are now regarded as more or less identical processes [5]. Prolonged exposure to cold, usually above freezing, accompanied by damp and windy conditions, together with prolonged immobility and dependency of the limbs, results in the production of this clinical picture, either by tissue damage involving vessels or occlusion of vessels and resultant tissue damage. Smoking and vascular disease are considered to contribute to the severity of the tissue damage [10].

The pathological changes are those of dependent oedema and stasis, with perivascular inflammation, or in more severe cases actual occlusion of vessels and ischaemic necrosis of tissues. Both myelinated and unmyelinated nerve fibres are damaged, resulting in a decreased density of terminal cutaneous nerve fibres within the plantar skin [11].

The diagnosis is based upon the history and the clinical findings of cold, anaesthetic limbs and possibly limited superficial gangrene. The differential diagnosis includes other causes of arterial occlusion [12].

Clinical features. The limb feels cold, and is anaesthetic. On rewarming, it initially becomes oedematous. The ability to sweat is lost, and anaesthesia persists. Subsequently, hyperaemia and painful paraesthesiae occur. In severe cases, limited superficial gangrene may occur, but this is not severe enough to necessitate extensive surgery. Cold sensitivity, vasomotor instability and hyperhidrosis may persist for many months. This syndrome is now being seen with increasing frequency among the homeless population [13].

Treatment. The best approach is prevention, but once the condition has occurred bedrest, analgesics and antibiotics should be given initially. Adjuvant vasodilator therapy is still of unproven long-term benefit.

Conservative surgical excision of non-repairable tissue together with appropriate plastic reconstruction may be necessary, but this should not be undertaken until medical measures have had a chance to exert maximum effect over several weeks.

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Diseases of abnormal sensitivity to cold

Perniosis

SYN. CHILBLAINS

Aetiology and pathology. Chilblains are localized, usually tender, inflammatory, erythematous, often itchy lesions, which may blister or ulcerate. They occur as an abnormal reaction to a cold ambient temperature [1]. Why cold causes chilblains in some individuals and not in others is uncertain. A genetic factor is often apparent in perniosis, several generations not infrequently being affected, and the lesions are often superimposed on a background of acrocyanosis and/or erythrocyanosis. Other factors include nutrition, focal sepsis, hormonal changes and systemic disease, especially dysproteinaemias, myelodysplastic disease and anorexia [1–3]. Pregnancy may have a beneficial effect on chilblains [4].

In contrast with normal individuals, in whom moderate cold exposure induces cutaneous vasoconstriction succeeded by vasodilatation in an attempt to maintain reperfusion, a persistent cold-induced constriction of the large cutaneous arterioles and persistent dilatation of the smaller, more superficial vessels occurs in individuals who are afflicted by perniosis.

Histologically, classical acral lesions exhibit intense oedema of the papillary dermis, a marked perivascular mononuclear cell infiltrate in the upper dermis sparing the oedematous papillary dermis, and oedema and vacuolation of thickened blood vessel walls ('fluffy oedema') [5]. The dermal infiltrate characteristically shows peri-eccrine as well as angiocentric concentration [6,7]. Epidermal changes in chilblains consist mainly of necrotic keratinocytes and spongiosis. Immunohistochemically, the dermal infiltrate is composed of a majority of T cells with macrophages and a few B lymphocytes [6,7]. The term 'superficial perniosis' distinguishes this group of clinical and histological changes as a discrete entity.

In contrast with acral perniosis, the majority of lesions from thigh perniosis exhibit a histological pattern referred to as 'deep perniosis' [5]. They are characterized by an intense mononuclear cell perivascular infiltrate extending throughout the dermis and into the subcutaneous fat, with 'fluffy oedema' of blood vessel walls. Dermal oedema is not a persistent feature. A minority of thigh perniosis lesions have a mixture of superficial and deep patterns of perniosis. No pathophysiological mechanism has been proposed for these histologically different patterns. It is possible that thigh perniosis is due to a combination of external cooling and insulation from internal warming, whereas acral perniosis involves only outside cooling, as there is little or no adipose tissue at acral sites.

There does not appear to be a primary neurological deficit in idiopathic acral perniosis [8]: immunohistochemical staining of the cutaneous nerves by the panneuronal marker PGP 9.5 and of the peptidergic nerves with antibodies to calcitonin gene-related peptide (CGRP), substance P, neuropeptide Y and vasoactive intestinal peptide is not qualitatively or quantitatively different from normal controls matched for site, age and sex. However, in the affected skin of patients with acral perniosis and acrocyanosis associated with a past history of very low body weight, immunohistochemistry revealed a great increase in nerve bundles in the papillary dermis, some with an abnormal morphology. A generalized increase in CGRP-, substance P-, neuropeptide Y- and vasoactive intestinal peptide-containing fibres was also demonstrated in this group of patients by immunohistochemistry [8]. The pathophysiological significance of these findings in the different groups of patients with perniosis remains to be elucidated, but does indicate that at least in uncomplicated acral perniosis the primary pathophysiology does not reside, at least structurally, in the nerves supplying the cutaneous microvasculature, and that idiopathic perniosis is probably primarily a disease of the microvasculature. Further evidence in support of this comes from the hyporesponsiveness of the microvasculature to a variety of vasoactive agents injected intradermally [9]. The abnormal nerve bundles in perniosis associated with low body weight may develop as a compensatory mechanism in response to loss of insulating fat, although the pathophysiological mechanism resulting in the increase in nerve bundles is, as yet, not understood.

The diagnosis is based on the history and clinical picture. Histological confirmation may be obtained, and can be useful in the differential diagnosis. Perniosis must be distinguished from acrocyanosis, chilblain lupus erythematosus and cryofibrinogenaemia. If blistering is present, bullous lupus erythematosus should also be excluded. In the presence of ulceration, organic peripheral vascular insufficiency should also be included in the differential diagnosis.

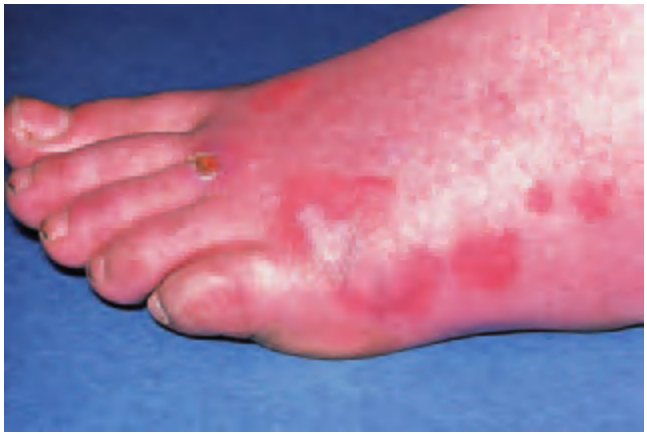

Fig. 23.2 Chilblains.

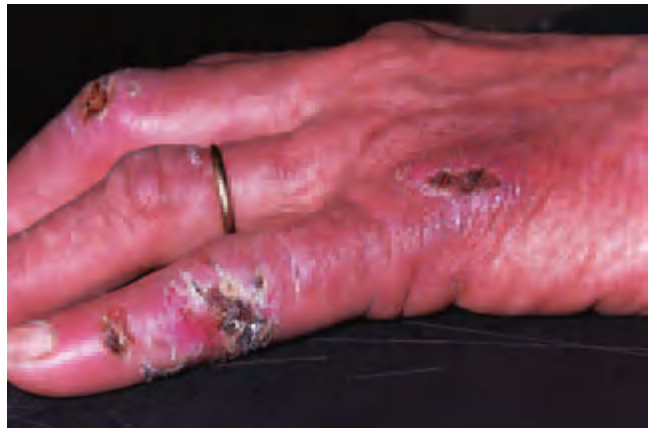

Fig. 23.3 Ulcerated chilblains associated with senile arterial disease.

Clinical features. The onset of perniosis is in the autumn or early winter, when humidity is high. Individual lesions are tender, pruritic, red or purple lesions, which may blister or ulcerate. They occur especially on the fingers and toes (Fig. 23.2), heels, lower legs, thighs, nose and ears. Individual lesions usually run a self-limiting course over about 3 weeks. The condition in severely affected individuals may persist throughout the winter, and may be unremitting even in the summer months.

Chilblains occur frequently in children in northern Europe, but can develop at any age. They are more rarely seen in North America, except in northern New England, British Columbia and northern California (P.M. Dowd, personal communications), than in north-western Europe, probably because of warmer living and working conditions and the more prolific use of clothing with a high insulation factor. In childhood perniosis in North America, a high incidence of cryoglobulins and cold agglutinins was found [10].

A particular type of perniosis occurs in young, mainly female patients who are horse-riding enthusiasts and wear tight-fitting breeches [11]. This type of perniosis is also encountered in North America, and may also occur after wading across mountain rivers [12]. Infiltrated erythrocyanotic plaques are distributed symmetrically on the outer aspects of obese thighs; occasionally there is ulceration and follicular plugging. High titres of cold agglutinins may occur in equestrian perniosis [13].

A subgroup of patients with acral perniosis, often with acrocyanosis, have had anorexia nervosa or bulimia and have often indulged in a sustained vigorous exercise programme in order to maintain a low body weight. The perniosis and acrocyanosis may persist for many years after a return to an acceptable body weight and the resumption of regular menstruation [14,15].

Other variants of chilblains. In the presence of arterial disease, systemic disease or prolonged exposure to cold or friction, irreversible changes of fibrosis, hyperkeratosis and lymphoedema may occur, and the lesions persist for many weeks or even months. Senile chilblains are an example (Fig. 23.3).

There are less common forms of chilblains. Papular perniosis may closely mimic erythema multiforme [2]. The lesions appear in crops and favour the sides of the fingers, often superimposed on a background of acrocyanosis. They may last for many days. The histology shows subcutaneous oedema, but not the changes of erythema multiforme. Some such cases may later develop more typical recurrent erythema multiforme [5].

Pustular chilblains have also been called 'acrodermatitis pustulosa hiemalis' [1] and have to be distinguished from tuberculides. Chilblains are sometimes annular. Perniotic lesions, sometimes with necrosis, on the fingers, toes, nose and ears may occur in elderly men in association with monocytic leukaemia [3].

Chilblains have to be distinguished from chilblain lupus erythematosus (see Chapter 56) and, especially on the nose, from the variant of sarcoidosis called lupus pernio (see Chapter 58).

Treatment. The importance of, and the benefit which can be obtained from, the prophylactic wearing of warm clothing and living in warm housing conditions should not be underestimated [16]. Recently, the vasodilator calcium channel blocker nifedipine has been demonstrated to be an effective therapy and prophylaxis for acral idiopathic perniosis [17,18]. It is also effective in acral perniosis associated with low body weight. The author finds the calcium channel blocker diltiazem also effective, but to a lesser degree than nifedipine (P.M. Dowd, unpublished observations). It is, however, also less prone to undesirable adverse effects than nifedipine. Tamoxifen, and the vasolidator nicotinic acid derivatives and minoxidil topically applied are also effective in some patients (P.M. Dowd, unpublished observations), and are alternatives to

systemic therapy with nifedipine in those individuals who find the adverse effects of this drug intolerable. UV radiation has been a time-honoured remedy [19], and has been used in prophylaxis, but a more recent study of its efficacy concluded that phototherapy was of no value in the prophylaxis of chilblains [20].

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Acrocyanosis

Aetiology and pathology. Acrocyanosis is a persistent cyanotic or erythrocyanotic discoloration of the skin, usually with a mottled pattern. It chiefly affects the hands; less commonly the feet and face are also involved. It may be idiopathic or secondary, occurring in association with a number of diseases and after drug administration (Table 23.2).

The peripheral arterioles are said to react unduly to the cold, and the smaller vessels, especially those of the subpapillary venous plexus, are dilated. The mechanism resulting in the changes is not understood, but has been said to involve the veins [1]. Changes in blood viscosity have been reported [2]. As in cases of uncomplicated perniosis, no neuronal deficit can be demonstrated by conventional light microscopy and immunohistochemistry of the neuronal supply to the cutaneous vasculature, including that of the vasoactive peptidergic nerves [3], indicating a primary vascular pathology.

Table 23.2 Aetiology of acrocyanosis.

Idiopathic
Secondary
Autoimmune
Connective tissue disorders
Primary and secondary antiphospholipid antibody syndrome
Neoplastic
Benign and malignant paraproteinaemias
Paraneoplastic syndrome
Cold agglutinin disease
Cryoglobulinaemia
Eating disorders
Anorexia nervosa
Bulimia nervosa
Orthostatic disorders
Chronic orthostatic intolerance
Postural orthostatic tachycardia syndrome of adolescents
Adolescent chronic fatigue syndrome
Neurological disorders
Brachial plexus neuropathy
Chronic arsenic poisoning
Drugs
Butyl nitrate
Interferon-α (2a)
Metabolic diseases
Fucidosis
Ethyl-malonic aciduria
Psychiatric
Mental retardation
Schizophrenia
Essential thrombocythaemia

In acrocyanosis and oedema of the lower limbs accompanied by light-headedness and fatigue, and occurring within 10 min of assuming upright posture (postural orthostatic tachycardia syndrome), blunted arterial vasoconstriction in the presence of normal venous compliance produces massive redistribution of blood within the peripheral venous capacitance beds [4].

Clinical features. In idiopathic acrocyanosis, the changes may be transient after cold exposure, but frequently persist during the winter and even throughout the summer months. The face may be involved as well as the hands. There is often a family history, indicating a genetic basis for this condition. The disorder usually starts in adolescence and persists into adult life. In some individuals it spontaneously remits. Large-vessel disorders are not usually associated with this disease except when it begins much later in life. Perniosis, erythrocyanosis and livedo reticularis may occur simultaneously with acrocyanosis.

The diagnosis is based on the clinical finding of persistent cyanotic discoloration in the presence of normal

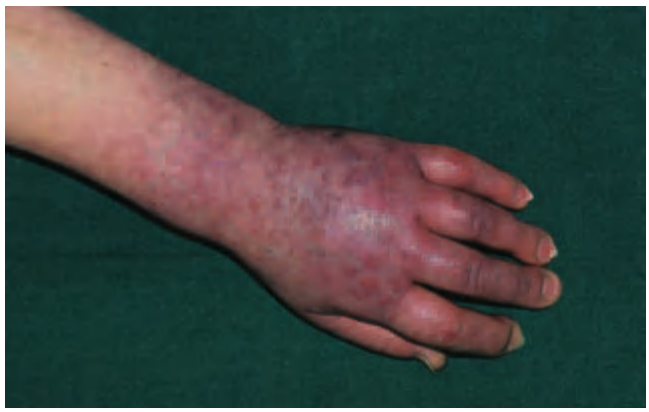

Fig. 23.4 Acrocyanosis/erythrocyanosis due to neurotic immobility.

peripheral pulses and absence of venous occlusion. Acrocyanosis must be distinguished from severe Raynaud's phenomenon and perniosis. In cases developing for the first time in adult life, a secondary cause should be sought.

Acrocyanosis in mentally retarded and schizophrenic patients is said to be due to immobility, but the real reason why the incidence of acrocyanosis is increased in these disorders is unknown (Fig. 23.4).

Treatment. There is no medical cure for this condition. Synthetic vasodilator therapy, including the calcium channel blocking agents nifedipine and diltiazem that are effective in episodic peripheral vascular insufficiency and perniosis, is not usually effective [5], although topically applied nicotinic acid derivatives and minoxidil can be beneficial (P.M. Dowd, unpublished observations).

In acrocyanosis secondary to drugs, marked improvement follows cessation of drug administration. Therapy of associated diseases may result in clinical improvement in acrocyanosis but this is by no means a universal occurrence.

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Erythrocyanosis [1]

Aetiology and pathology. Erythrocyanosis is persistent dusky erythema, and often deep cyanosis, occurring usually over areas with a thick layer of subcutaneous fat, such as the thighs and lower legs, and less commonly the buttocks and forearms. It is exacerbated in the winter months. It is thought that the thick layer of subcutaneous fat insulates the cutaneous vessels from the warmth of the underlying blood supply and renders them susceptible to the effects of environmental cold exposure, but the precise aetiology is unknown.

Areas of erythrocyanotic skin may be preferentially affected by diseases that characteristically involve areas of slow circulation, including tuberculosis, leprosy, sarcoidosis and lupus erythematosus.

Clinical features. Erythrocyanosis may occur together with or independently from acrocyanosis. Dusky, frequently deeply red–purple discoloration of the skin occurs most commonly on the lower legs in adolescent girls, and on the thighs and buttocks of obese prepubescent boys. Very occasionally, it can occur on the forearms of infants and on the thighs and lower legs of middle-aged women. It may be accompanied by ulceration, erythema, and also keratosis pilaris and more diffuse desquamation. Nodular lesions resembling chilblains or Bazin's disease may occur after acute cold exposure, and oedema and fibrosis may occur as late manifestations.

The diagnosis is based on the clinical picture, in the absence of any history of localized cold exposure. The differential diagnosis includes deep perniosis, superficial thrombophlebitis, Bazin's disease (erythema induratum) and varicose eczema, depending on the anatomical site.

The disease may persist indefinitely and be accompanied by progressive thickening and fibrosis. Fortunately, spontaneous improvement can occur in adolescent patients, usually after a few years.

Treatment. Warm clothing, exercise, weight reduction and elastic support hose may all be helpful. Systemic vasodilators are largely ineffective, and local vasodilators of limited value. UV light, previously regarded as beneficial, has not, in the author's clinical experience, been of any value.

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Livedo reticularis

SYN. LIVEDO RACEMOSA; LIVEDO ANNULARIS; INFLAMMATIO CUTIS RACEMOSA; ASPHYXIA RETICULARIS MULTIPLEX; DERMATOPATHIA PIGMENTOSA RETICULARIS

Definition. Livedo reticularis is a mottled cyanotic discoloration of the skin, with a characteristic network pattern, which is accentuated by cold.

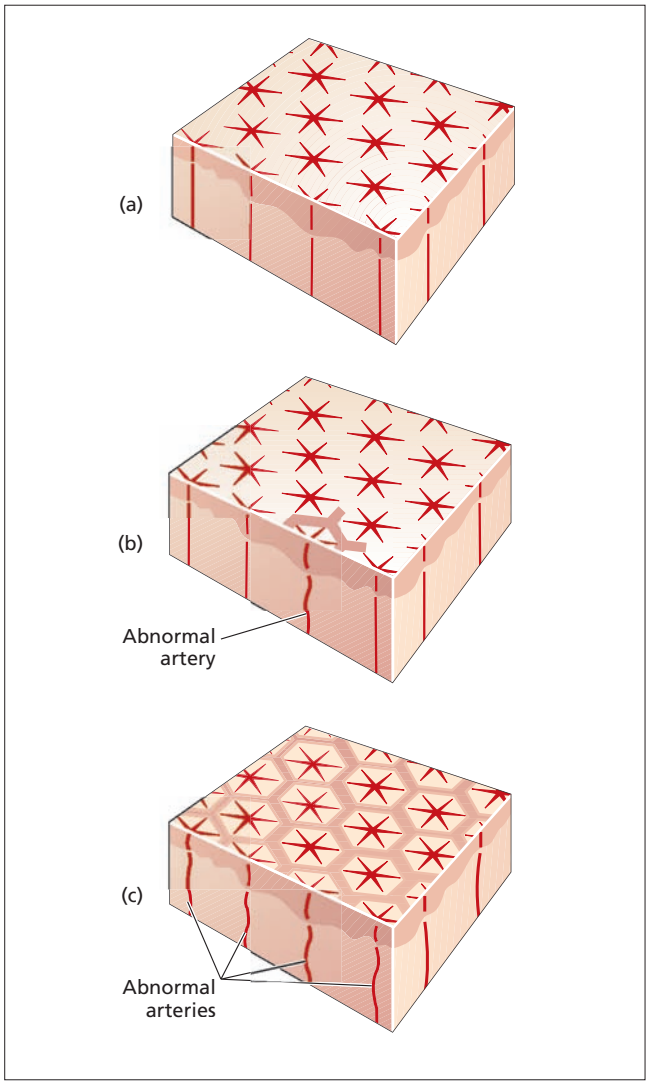


Fig. 23.5 Diagrammatic representation of (a) normal vasculature; (b) livedo racemosa due to patchy arterial pathology; (c) livedo reticularis due to diffuse arterial pathology.

Aetiology and pathology. Unna [1] postulated that the blood supply of the normal skin is arranged in cones, their bases 1–4 cm across on the surface of the skin, and each supplied by an arteriole. Such an arrangement may be presumed to exist. The mottling of livedo reticularis follows this pattern, the abnormal dark area of the network corresponding to the areas of anastomosis between two cones where the blood supply is relatively diminished (Fig. 23.5).

Livedo reticularis may be physiological, idiopathic or secondary to intravascular obstruction or vessel wall disease (Table 23.3).

The aetiology of the physiological and idiopathic varieties of this disease is unknown, but the histological changes of endarteritis are found in the small arterioles and venules of livedo reticularis of any degree of severity.

Table 23.3 Classification of livedo reticularis.

1 Physiological livedo reticularis
Cutis marmorata

2 Idiopathic or primary livedo reticularis
Congenital
Cutis marmorata telangiectatica congenita

Acquired idiopathic
Uncomplicated
With winter ulceration
With summer ulceration
With systemic vascular involvement

3 Secondary livedo reticularis
Intravascular obstruction
Stasis
- Paralysis
- Cardiac failure
- Amantadine therapy

Occlusive disease
- Emboli [2,3]
- Oxalosis (primary hyperoxaluria) [4,5]
- Compressed air
- Bismuth, pentazocine, non-steroidal anti-inflammatory drugs, minocycline [6]

Thrombocythaemia [7,8] (see Fig. 23.9)
Cryoglobulins
Cold agglutinins

Vessel wall disease
Arteriosclerosis
Arteritis
- Polyarteritis nodosa
- Systemic lupus erythematosus
- Rheumatoid arthritis
- Dermatomyositis
- Lymphoma
- Pancreatitis

Infections
- Tuberculosis
- Syphilis
- Hepatitis C
- Brucellosis
- *Coxiella burnetii*

Hyperparathyroidism and hypercalcaemia [9]
- Calciphylaxis [10] (see Fig. 23.10)

The colour changes of livedo reticularis are believed to be due to the dilatation of, and stagnation of blood within, the capillaries and minute vessels in areas of anastomosis between two cones of vessels, each supplied by an arteriole —it is at this anastomotic point that the blood supply is relatively diminished and hence particularly vulnerable to a variety of adverse intravascular and vessel wall events.

The inherent pattern of livedo reticularis may be brought about by two quite separate mechanisms.

1 A change in the wall or within the lumen of the vessels. Although the visible changes are due to superficial small-vessel dilatation, the basic pathology affects the larger arterioles.

2 Some other pathological process that selectively picks out the area of slightly diminished vitality.

Clinical features. The diverse causes of livedo reticularis are reflected in localized and more diffuse visible changes in the skin of varying degrees of severity. The mottled cyanotic discoloration of livedo reticularis most commonly occurs on the legs, but the arms and trunk may also be affected. Tingling and numbness of the skin commonly occur on exposure to cold, which also intensifies the severity of the cyanotic discoloration. Diffuse arterial disease and viscosity changes give rise to diffuse mottling of the skin; patchy arterial disease to patchy mottling. Sometimes, this mottling takes the form of a complete network; sometimes, apparently a branching configuration (livedo racemosa). Dilatation of the small vessels is usually the only visible change, although there may be slight oedema.

Ulceration, starting in the dark area, occurs in some cases. Pigmentary change, scaling, etc. strongly suggest that external heat is concerned or that there is some other dermatosis localized to the dark areas. Cold will intensify the cyanosis whatever its cause. The changes are initially reversible if the cause can be removed, or on warming, but after a time the vessels become permanently dilated and telangiectatic.

Physiological livedo reticularis

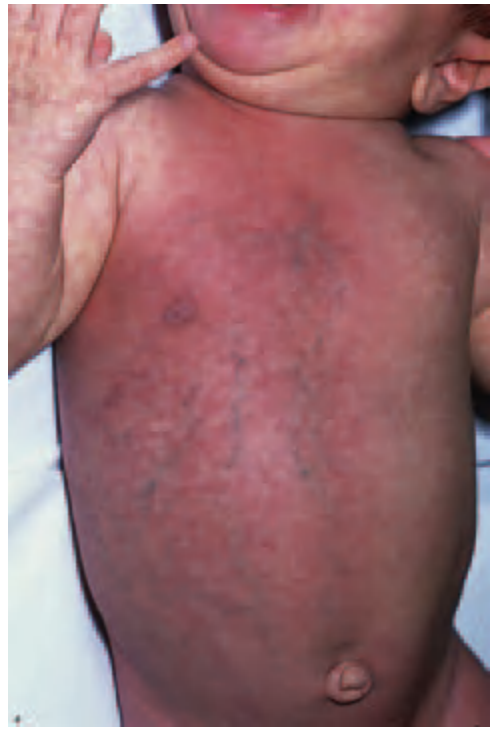
SYN. CUTIS MARMORATA

This physiological, mottled, cyanotic, transient reaction to cold may be seen in up to 50% of normal children and in some adults. The mottling is diffuse, mild and usually symptomless. It is more prominent in association with a wide variety of systemic diseases leading to debility, or any disorder which causes stasis of blood within vessels, for example paralysis. It is accentuated in several disorders in the neonate. Chilblains, acrocyanosis and erythrocyanosis may be associated. The diagnostic dividing line between this condition and idiopathic livedo reticularis can be fine, and the two conditions may represent a spectrum of disease.

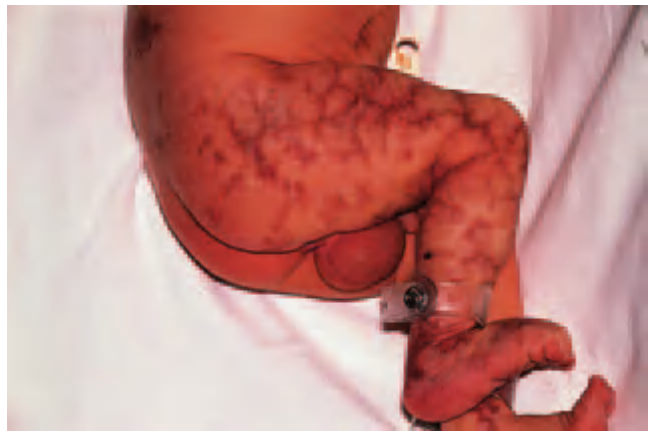
Congenital livedo reticularis

SYN. CUTIS MARMORATA TELANGIECTATICA CONGENITA

This is a rare developmental defect of the skin, which is present at birth [11–13]. It is usually asymmetrical and severe; atrophy of the skin may coexist (Fig. 23.6). Commonly, it is not associated with any other disorder, but occasionally a variety of other congenital lesions may be associated. Rarely, it may be familial. No treatment is effective, but the condition usually improves spontaneously with age.



(a)



(b)

Fig. 23.6 (a) Cutis marmorata telangiectatica congenita. (Courtesy of West Suffolk Hospital, UK.) (b) Cutis marmorata telangiectatica congenita. (Courtesy of Dr F.A. Ive, Dryburn Hospital, Durham, UK.)

Acquired idiopathic livedo reticularis

This occurs predominantly in young adult and middle-aged females. Mild degrees appear to be common and harmless, and merge with physiological cutis marmorata. In the more severe cases it is associated with ulceration, usually in winter, although sudden ulceration in summer can occur (Fig. 23.7). The mottling usually has its onset in the third or fourth decade, and is at first transient on exposure to cold; subsequently, permanent discoloration can occur. Tingling and numbness of the skin, and sometimes oedema, may be present. The disease may be progressive or remain stationary. Its aetiology is unknown.

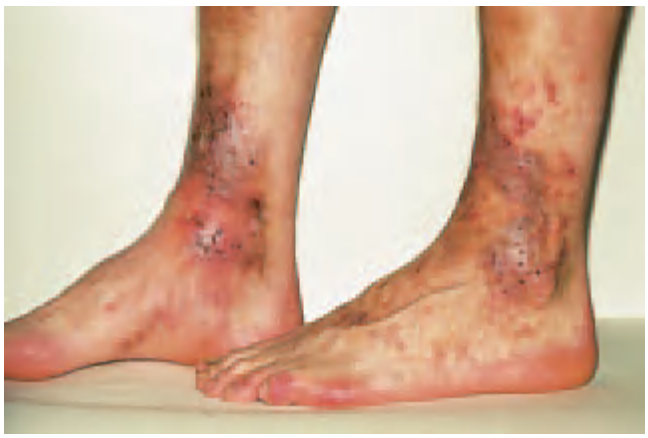


Fig. 23.7 Idiopathic livedo reticularis with summer ulceration.

The diagnosis is based upon the presence of the persistent cyanotic discoloration of the skin in a characteristic network pattern. The differential diagnosis includes erythema ab igne, capillary naevi and angioma serpiginosum, and rarely drug rashes occurring in a livedo pattern. Underlying causes and associated diseases (Table 23.3) must be excluded before making a diagnosis of idiopathic livedo reticularis.

Livedo reticularis occurs in 20–25% of migraine sufferers and in this subset stroke is more frequent, raising the possibility that livedo reticularis can be used as a clinical marker to identify those migraine sufferers with an increased risk of stroke [14].

Idiopathic livedo reticularis with systemic involvement

SYN. SNEDDON'S SYNDROME

In a rare group of apparently idiopathic livedo reticularis, which should now be regarded as a separate pathological entity [15–19], widespread and severe patchy livedo reticularis (syn. livedo racemosa) is associated with arterial disease in peripheral, cerebral, coronary and sometimes renal vessels (Fig. 23.8). There is a progressively worsening course over several years, with intermittent cerebral and other vascular occlusive episodes, and a poor prognosis [19]. Histologically, the arteries show an endarteritis obliterans.

In about 40% of patients with Sneddon's syndrome (SNS), anticardiolipin or antiphospholipid (APL) antibodies are found in the circulation. This group are diagnosed as having the APS or lupus anticoagulant syndrome [20–22]. Approximately 35% of APS patients have systemic lupus erythematosus (SLE). The fishnet of the livedo is larger in APL-negative patients and these do not develop thrombocytopenia. Seizures and clinically audible mitral valve regurgitation are more frequently encountered in APL-positive patients. Patients with primary APS and SNS do not differ from those with livedo reticularis, ischaemic cerebral events and APS within SLE. Whether SNS covers a continuum of diverse clinicobiological entities ranging from APL-negative to SLE-related cases with primary APS–SNS in the middle, or whether SNS should be regarded as a nearly similar clinical expression of two distinct disorders remains a subject for debate and investigation [23–25]. Recent studies suggest specificity of APL antibodies for different phospholipid-binding plasma proteins, including β_2-glycoprotein 1, prothrombin, protein C and protein S [26].

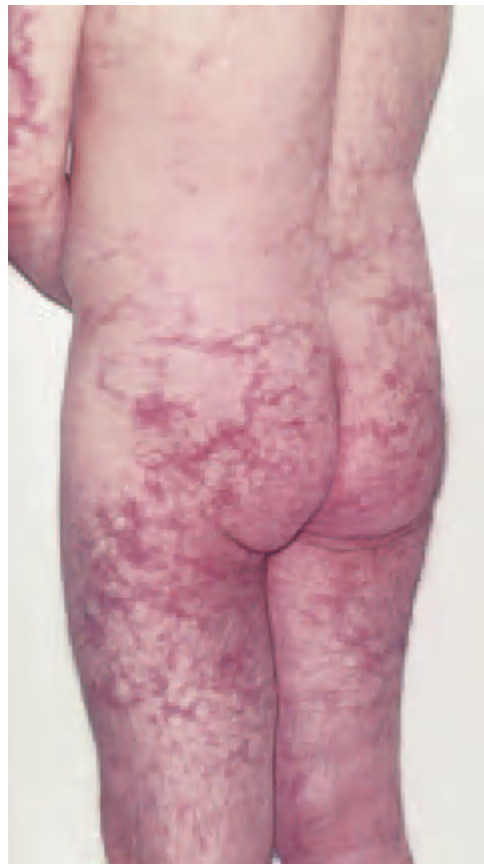


Fig. 23.8 Idiopathic livedo reticularis with systemic involvement (Sneddon's syndrome). Male aged 45 years; 10 years' progressive livedo with coronary, renal and eventually fatal cerebrovascular disease.

Treatment. Uncomplicated idiopathic livedo reticularis does not require active therapy other than the prophylactic measure of protection from cold by warm clothing and avoidance of cold exposure. Severe cases, including those with ulceration, may be helped by prolonged anticoagulant and antithrombotic therapy [22]. Corticosteroids are disappointing, although azathioprine has been successfully used [27]. Sympathectomy is not beneficial. Prostacyclin can be very valuable in the management of the ulceration (P.M. Dowd, unpublished observations). Corticosteroids and antithrombotic therapy have been

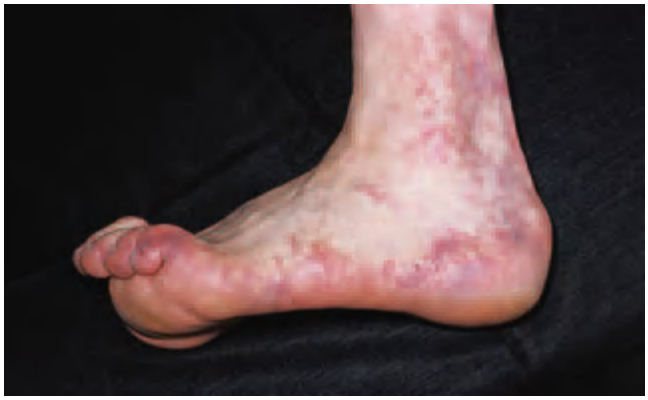


Fig. 23.9 Patchy livedo reticularis due to idiopathic thrombocythaemia.

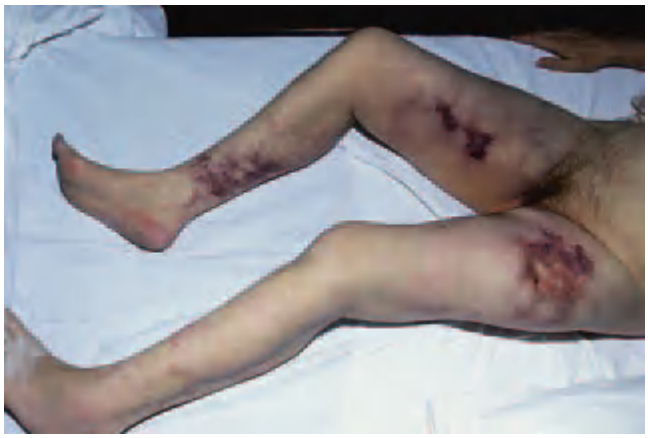


Fig. 23.10 Patchy livedo reticularis due to calcification of blood vessels secondary to chronic renal failure. A fatal *Pseudomonas* septicaemia followed skin ulceration. (Courtesy of West Suffolk Hospital, UK.)

recommended in the management of the APL syndrome, but not usually until the advent of a thrombotic episode [22]. Whether these drugs should be given prophylactically in this condition is still a matter of debate.

Secondary livedo reticularis

Secondary livedo reticularis, of which there are many causes (Table 23.3), tends not to be widespread or symmetrical but patchy and asymmetrical, reflecting patchy arterial change (Figs 23.9 & 23.10). Full investigation is required to exclude polyarteritis nodosa, and the estimation of antineutrophil cytoplasmic antibodies (ANCA) is now mandatory. Patchy livedo, sometimes with ulceration, occurs in the syndrome of benign cutaneous polyarteritis nodosa [28,29]. This is not associated with the severe systemic involvement of polyarteritis nodosa. The other causes of secondary livedo reticularis should be systematically sought.

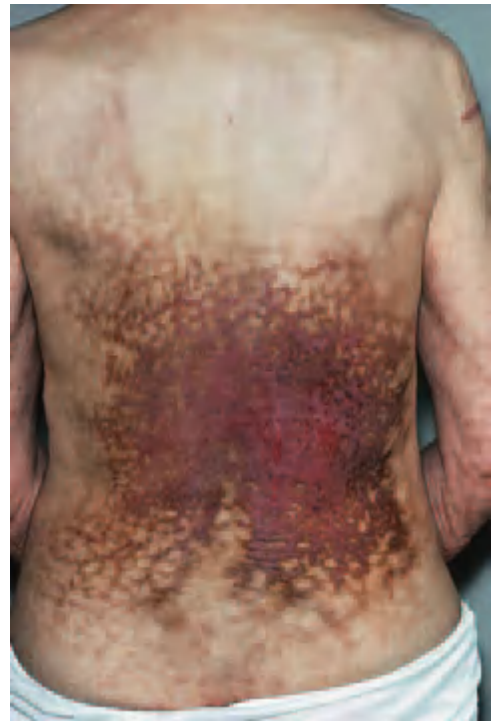


Fig. 23.11 Erythema ab igne. A local burn which also accentuates the livedo pattern.

Treatment. The treatment of secondary livedo reticularis is that of the underlying condition.

Eruptions localized in livedo pattern

A wide variety of eruptions, which can at times demonstrate the Koebner phenomenon, may selectively involve the outer zones of the livedo network. This does not necessarily indicate any significant vascular abnormality in the skin. Psoriasis, lichen planus, discoid and systemic lupus erythematosus, tuberculides, secondary syphilis and drug eruptions may all occur in this pattern. Vascular naevi of the port-wine type may be reticulate; it is necessary to exclude a deep-seated change involving the larger vessels, but often the process seems to be quite superficial.

Erythema ab igne (see Chapter 22)

This is due to the prolonged effect of heat on the skin and is, in effect, a low-grade burn selectively involving the more vulnerable areas at the periphery of the livedo network. Commonest sites are the legs just below the knee, but a variety of different, sometimes quite bizarre, patterns occur when heat is applied to the skin either for warmth, relief of pain or at work [30] (Fig. 23.11). The earliest change is erythema, which may be associated with quite marked inflammatory changes and be followed by pigmentation. Bulla formation sometimes occurs. The

pigmentary changes may persist for many months or even years. Squamous carcinomas and other malignancies have been recorded in very chronic cases.

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Raynaud's phenomenon

Definition. Raynaud's phenomenon is defined as episodic digital ischaemia occurring in response to cold or emotional stimuli. It is characterized by sequential colour changes (white, blue and red). Pallor is essential for the diagnosis. However, in severe recalcitrant Raynaud's phenomenon, with attacks of long duration occurring in association with connective tissue diseases, the initial pallor may be short-lived and succeeded by prolonged cyanosis, with or without discrete foci of tissue necrosis. Raynaud's phenomenon may be primary, or secondary to other causes. In recent years there has been a vogue, chiefly in the non-dermatological literature, to refer to Raynaud's phenomenon as Raynaud's syndrome. The two terms are often now used synonymously. Primary Raynaud's phenomenon is idiopathic, and occurs as an isolated innocuous disorder. This type of Raynaud's phenomenon is also called Raynaud's disease. Secondary Raynaud's phenomenon occurs in association with identifiable underlying diseases, or is either environmentally or drug induced.

Aetiology and pathology. The sequential changes of pallor, cyanosis and rubor were first described and delineated by Maurice Raynaud in 1862 [1]. In 1900, Jonathan Hutchinson [2] had realized that there were several causes of the clinical phenomenon, and by 1926 Allen and Brown [3] had established clinical criteria to delineate innocent Raynaud's phenomenon from Raynaud's phenomenon associated with underlying diseases. The modified criteria of Allen and Brown [3] still provide a sound clinical basis for differentiating primary from secondary Raynaud's phenomenon. The advent of immunological tests for the connective tissue diseases has enabled further refinement of the criteria for the diagnosis of primary Raynaud's phenomenon (Table 23.4).

Table 23.4 Criteria for the diagnosis of primary Raynaud's phenomenon.

Intermittent attacks of discoloration of extremities
Absence of evidence of organic peripheral arterial occlusion
Symmetrical or bilateral distribution
Exclusion of any disease, occupation, trauma or drug ingestion that could give rise to vasospastic abnormalities
Absence of immunological abnormalities
Female sex, age under 25 years
History of cold intolerance since childhood
Normal nail fold capillaries

Raynaud's phenomenon other than of occupational origin is more common in women. The prevalence is variously quoted as 5–30%: the marked statistical disparity appears to be due to the size and origin of the populations studied and the clinical diagnostic criteria used by the researchers, particularly with regard to colour changes. Rigorous investigation to differentiate primary from secondary Raynaud's phenomenon in general practice is probably not cost-effective. Application of the criteria listed in Table 23.4 is sufficient in most cases to make the differentiation. Female patients with age of onset over 25 years, no pre-existing cold intolerance even of mild degree, no occupational, traumatic or drug-related aetiological factors, and no history of a low body weight should be regarded as being at high risk of developing connective tissue disease and merit rigorous investigation, including screening for the presence of antinuclear, anti-Scl 70 and anticentromere antibodies. The presence of abnormal capillaries on nail fold microscopy, or structural defects on angiography (now, however, rarely indicated), is incompatible with a diagnosis of primary Raynaud's phenomenon, and merits a search for an underlying cause. Cutaneous nail fold blood vessels may be abnormal clinically and on microscopy in the connective tissue diseases. Lewis and Pickering [4] found atherosclerotic changes in the digital arteries of patients who had underlying disease but not in patients with primary Raynaud's phenomenon. Digital arteries in post-mortem biopsies from patients who had died of systemic sclerosis exhibited severe intimal hyperplasia, consisting predominantly of deposits of collagen. This was sometimes accompanied by luminal narrowing and thrombosis. Diminution in the number of blood vessels, fibrosis and replacement of the dermis with collagen have also been demonstrated in systemic sclerosis. In addition, digital vasculitis has been reported in some patients with connective tissue diseases. Electron microscopy of finger-pulp biopsies from patients with a variety of underlying causes of Raynaud's phenomenon showed luminal narrowing associated with endothelial cell swelling and thickening of the basement membrane in the dermal capillaries [5]. The basement membranes of unmyelinated nerves were similarly affected, and there was marked degeneration of myelinated nerves. In nail fold biopsy specimens there was a decreased number of cutaneous nerve bundles and deposition of globular eosinophilic PAS (periodic acid–Schiff)-positive material in systemic sclerosis and mixed connective tissue disease [6]. The causes of Raynaud's phenomenon are listed in Table 23.5.

By immunohistochemistry, it has now been shown that patients with primary Raynaud's phenomenon and Raynaud's phenomenon secondary to systemic sclerosis and vibration white finger have a deficiency of sensorimotor CGRP-containing vasodilator neurones [7–9]. This is reflected in a decreased ability of these patients to produce a neurogenically mediated flare upon intradermal injection of ET-1 (intradermal injection of ET-1 induces pallor, i.e. vasoconstriction, immediately around the injection site and this is surrounded by an area of spreading flare, i.e. neurogenic vasodilatation).

In patients with vibration white finger there is a more profound neuronal loss than in primary or secondary Raynaud's phenomenon (systemic sclerosis), and this loss

Table 23.5 Causes of Raynaud's phenomenon.

Primary Raynaud's phenomenon (Raynaud's disease)
Secondary Raynaud's phenomenon
Trauma or vibration
Reflex sympathetic dystrophy
Vibration exposure
Arteriovenous fistula
Hypothenar hammer syndrome (ulnar artery thrombosis)
Intra-arterial drug administration
Connective tissue disease and vasculitis
Systemic sclerosis
Systemic lupus erythematosus
Rheumatoid arthritis
Sjögren's syndrome
Mixed connective tissue disease
Dermatomyositis
Temporal arteritis
Hepatitis B antigen vasculitis
Obstructive arterial disease
Atherosclerosis
Thromboangiitis obliterans (Buerger's disease)
Hypothenar hammer syndrome (ulnar artery thrombosis)
Neurological disease
Thoracic outlet syndrome (cervical rib)
Carpal tunnel syndrome
Hypothenar hammer syndrome
Reflex sympathetic dystrophy
Haematological disease
Cryoglobulinaemia
Cold agglutinins
Paroxysmal haemoglobinuria
Waldenström's macroglobulinaemia
Drugs and toxins
Ergot
β-Blockers
Methysergide
Bleomycin
Amfetamines (amphetamines)
Imipramine
Bromocriptine
Clonidine
Ciclosporin (cyclosporin)
Oral contraceptives
Vinyl chloride
Nitroglycerin withdrawal
Heavy metals
Miscellaneous
Paraneoplastic syndrome
Chronic renal failure
Primary pulmonary hypertension
Hypothyroidism
Anorexia nervosa

is not confined to CGRP-containing nerves [9]. *In vivo* pharmacological studies in these patients have demonstrated decreased flare responses to intradermal injections of both ET-1 and histamine, findings consistent with the more widespread neuronal loss demonstrated by immunohistochemistry [10]. Immunostaining for ET-1 and endothelial nitric oxide synthase in the cutaneous blood vessels has not revealed any significant differences from normal in any of these patient groups. However, in patients with Raynaud's phenomenon, circulating ET-1 levels are elevated independently of vasospastic attacks, and are further increased in these patients and in patients with vibration white finger following cold challenge. The raised levels of ET-1 could be explained by the consideration that ET-1 is the product of a 'stressed' endothelium [11,12]. Raised circulating levels of von Willebrand factor protein (vWF, factor VIII-related antigen) have also been reported in patients with Raynaud's phenomenon, pointing to the 'stress' effect of cold on endothelium. The deficit of CGRP-containing vasodilator nerves means that the cold-induced vasoconstriction mediated by the direct action of ET-1 on the blood vessels is unopposed. Current evidence indicates that the CGRP-containing sensorimotor nerve fibres are concerned with cold nociception, controlling both reflex local (through antidromic release of peptides from perivascular fibres) and systemic (through their central sensory connections and projections) neurovascular responses. The precise quantitative contributions of the peptidergic and autonomic nervous systems to the production of the clinical features of Raynaud's phenomenon awaits further elucidation [10].

Previously, attention has also been focused on the blood. Changes have been found in circulating catecholamines [13], red cell deformability [14], blood viscosity, platelet aggregation and fibrinolysis [15]. These abnormal findings are chiefly encountered in patients with Raynaud's phenomenon secondary to connective tissue disease, and their relevance to the aetiopathology of Raynaud's phenomenon is uncertain.

Clinical features. Raynaud's disease (or Raynaud's phenomenon without apparent cause) is much commoner in women, in the proportion of at least 5 : 1. The age of onset is usually under 40 years, but it may occur over this age. The age and sex distribution of secondary cases is that of the underlying disease, and is not therefore so restricted to the female sex. Raynaud's disease affects the hands and, less often, the feet; changes elsewhere are exceptional, although the tongue can be involved [16], and primary pulmonary hypertension has been reported.

A typical attack consists of sudden pallor of one or more digits, followed after a few minutes by cyanosis or sometimes by erythema. In Raynaud's disease the condition is usually symmetrical and affects several digits. In Raynaud's phenomenon secondary to other vascular disease, only one or more digits may be involved, and asymmetry is not unusual. Such asymmetry can occur in primary Raynaud's disease. Attacks are usually precipitated by cold, either local or of the whole body, by pressure or by psychological stimuli. They may be very mild, and occur infrequently or many times each day. In severe cases, almost invariably of the secondary type of Raynaud's phenomenon, secondary changes may occur in the skin. These include telangiectases of the nail fold, thinning and ridging of the nail, and atrophy or sclerosis of the fingers (sclerodactyly). Gangrene is extremely rare in true Raynaud's disease, but not uncommon in the presence of organic arterial diseases or systemic sclerosis. The disease runs a variable course. In Raynaud's phenomenon secondary to vascular disease, the prognosis is that of the underlying disease, and extensive destruction of the digits may occur. In Raynaud's disease, the prognosis is good in 80% of cases, but progressive disability occurs in the remainder.

Diagnosis. The diagnosis of Raynaud's phenomenon can usually be made with ease on the basis of the history. Acrocyanosis is distinguished by the absence of the characteristic paroxysmal pallor.

Establishing the cause of Raynaud's phenomenon is less easy, but application of the modified criteria of Allen and Brown provides a good basis for the diagnosis of primary Raynaud's phenomenon. The history should exclude those cases due to vibration [17] and heavy metal or ergot intoxication. Buerger's disease and other organic arterial diseases are very rare causes of Raynaud's phenomenon. The secondary cases tend to show asymmetrical changes of later onset. In difficult cases, prolonged observation and arteriography may be needed. Neurovascular disorders around the thoracic outlet must be excluded in atypical cases and where asymmetry occurs. Such disorders require full neurological examination, observation of the effect on the pulse of movement at the shoulder girdle, and radiological investigation. However, the thoracic outlet syndrome and cervical rib are rare causes of Raynaud's phenomenon. An underlying neoplasm must be sought in any case with sudden onset in adult life, especially in men, and if gangrene supervenes [18].

The distinction between Raynaud's disease and the early onset of systemic sclerosis is sometimes difficult. Sclerodactyly may occur secondarily to vascular disease in the absence of systemic sclerosis, and histology does not distinguish between them. Raynaud's phenomenon is frequently the presenting symptom of systemic sclerosis, but if there are no other signs within 2 years of onset, systemic sclerosis is less likely to develop [19], although it is possible [20]. The presence of circulating autoantibodies (antinuclear, anticentromere and anti-Scl 70 antibodies) should be regarded as indicating the presence of a connective tissue disease until proven otherwise. Radiology of the oesophagus may provide evidence of systemic

sclerosis, in the form of aperistalsis. However, this may also occur in uncomplicated Raynaud's disease or in Raynaud's phenomenon secondary to lupus erythematosus, mixed connective tissue disease or dermatomyositis, in which Raynaud's phenomenon may be the presenting symptom. A search for cryoglobulins and cold agglutinins should be made (see below).

Treatment. Patients with primary Raynaud's phenomenon often respond to conservative measures, including the wearing of woollen gloves and sheepskin mittens (two layers are recommended rather than one), and avoidance of draughts and exposure to cold, wet and windy ambient climatic conditions. Battery-powered, electrically operated gloves are available but tend to be cumbersome. Smoking should be prohibited. When these measures are ineffective, the medications of choice are the calcium channel blockers nifedipine [21] (10–80 mg slow-release orally daily) or diltiazem (60–120 mg orally three times daily). When the adverse effects of these drugs are intolerable, topical vasodilators, such as 1–2% hexyl nicotinate [22] in aqueous cream, may be beneficial.

Therapy of more severe cases is far from satisfactory, although a large number of treatments have been used successfully in some cases. Conventional vasodilators are often tried. However, calcium channel blockers, such as nifedipine and diltiazem, are more satisfactory. The topical vasodilators glyceryl trinitrate [23] and hexyl nicotinate [22] have been used. Other drugs have included methyldopa [24], the serotonin antagonist ketanserin [25], fibrinolysis enhancement therapy with stanozolol [26] and even griseofulvin [27]. Oral administration or infusions of reserpine have been used for some years [28], and also low-molecular-weight dextran [29]. More recently, these have been superseded by infusions of prostaglandin E_1 [30,31], prostacyclin [32,33] and CGRP [34], or plasma exchange [35]. Fluoxetine may be useful in some patients [36].

Sympathectomy provides only moderate benefit in cases severe enough to warrant it, and only in those in which organic arterial disease or scleroderma can be excluded and in which changes secondary to long-standing spasm have not occurred. Cases with a pronounced neurogenic factor are helped, but the improvement is only temporary. Thoracoscopic sympathectomy has given encouraging results in a small series [37].

Treatment of secondary Raynaud's phenomenon is that of the underlying disease whenever possible.

The most important aspect of the management of occupationally induced Raynaud's phenomenon, such as vibration white finger, is prevention by reducing occupational exposure to vibration. In a small study to assess the efficacy of calcium channel blockers in the treatment of vibration white finger, patients who were treated with diltiazem for 18 months showed significant improvement in both vascular and neurological symptoms, and in objective *in vivo* pharmacological tests [38].

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Cryoglobulinaemia [1–7]

Cryoglobulins are globulins precipitated from plasma or serum on cooling. Single-component cryoglobulins are composed of an immunoglobulin (IgG, IgM, IgA), and may be associated with myeloma, macroglobulinaemia and lymphoma, or occur as a primary or idiopathic form.

Mixed cryoglobulins are immune complexes of an IgG immunoglobulin with an antiglobulin, usually IgM, less often IgA or IgG. Small amounts may be found in normal persons and in many different diseases, sometimes only temporarily. These include the following.

1 Infections
  (a) Glandular fever
  (b) Hepatitis B
  (c) Syphilis
  (d) Borreliosis
  (e) Subacute bacterial endocarditis
  (f) Leprosy
  (g) Kala-azar
  (h) Hepatitis C
  (i) Human immunodeficiency virus (HIV)-1 infection
2 Autoimmune diseases
  (a) SLE
  (b) Rheumatoid arthritis
  (c) Sjögren's syndrome
  (d) Vasculitis
3 Lymphoproliferative diseases
  (a) Myeloma
  (b) Lymphoma
  (c) Macroglobulinaemia
4 Liver disease
5 Sarcoidosis.

Mixed cryoglobulins are found not infrequently in patients with vasculitis and in some patients with chronic urticaria; in such patients there is little indication that the cryoglobulins are responsible for the lesions (although they may activate complement), and aggravation by cold is usually not apparent [3].

Demonstration is relatively simple. Venous blood is drawn into a warm syringe and allowed to clot at 37°C. The serum (or plasma if cryofibrinogen is suspected) is cooled to 4–5°C and any precipitate noted. This should redissolve on warming. Rheumatoid factor is usually positive. More elaborate methods are required for quantitative studies and to determine the nature of the protein.

The amounts of cryoglobulin reported to cause symptoms are very variable: less than 25 mg/dL may rarely be associated with symptoms; much higher levels may be symptomless. Levels as high as 80 g/L have been recorded. Symptoms are most easily explained in terms of intravascular precipitation of cryoglobulins. They include purpura on exposed parts after cooling, patchy livedo reticularis, cold urticaria, Raynaud's phenomenon and atypical ulceration of the legs, even resembling a dermatitis artefacta. Haemorrhages from the nose, eyes and retinal vessels are not uncommon. Systemic symptoms include those of the underlying disease. Glomerulonephritis, arthralgia and fatigue are among the many manifestations. A search for all the known causes of cryoglobulinaemia is indicated, together with characterization of the nature of the cryoglobulin, before regarding the disease as primary or idiopathic. Treatment is unsatisfactory where the cause cannot be removed. Anticoagulants and corticosteroids have provided symptomatic relief in some cases. Plasmapheresis may be helpful.

Cryofibrinogenaemia [8,9]

Cryofibrinogenaemia occurs in a variety of different diseases, but has not often been associated with cold sensitivity. In idiopathic cryofibrinogenaemia, vascular lesions, purpura and even frank gangrene may occur. The cold-precipitated protein is found in plasma but not in serum.

Cold agglutinins [5,10]

Cold agglutinins are found in low titres in 95% of normal persons. They are increased in many diseases: virus infections, especially viral pneumonia and glandular fever; trypanosomiasis; lymphomas; disseminated lupus erythematosus; and haemolytic anaemias. They may also be elevated in the absence of any other disease. Abnormal titres range from 1 : 128 to 1 : 168 million. Symptoms, which most frequently occur in elderly people, include Raynaud's phenomenon, acrocyanosis and even gangrene. Cold urticaria is not usually part of the syndrome. Treatment is not satisfactory. Corticosteroids and anticoagulants have been reported as helping a proportion of cases.

Cold haemolysins [5,11]

SYN. PAROXYSMAL COLD HAEMOGLOBINURIA

Haemolysis after exposure to cold is typically associated with syphilis. However, cold haemolysis may occur in the absence of syphilis and may even be associated with a false-positive Wassermann reaction. Symptoms occur on rewarming, and include haemoglobinuria, fever and general systemic symptoms. Cold urticaria and Raynaud's phenomenon may also occur, and be the presenting symptoms. Antisyphilitic treatment helps some cases where syphilis is the cause, although the haemolysin itself usually persists. Treatment in other cases is unsatisfactory.

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Cold urticaria

This disease is described in Chapter 47.

Cold erythema

This is one of the rarest of the diseases of hypersensitivity to the cold. Areas of erythema and pain occur after cold exposure. The lesions are transient, with a time course very similar to that of primary acquired cold urticarias. Cold erythema is considered to be a disorder related to cold urticaria but characterized only by erythema rather than erythema and wealing [1].

Treatment. The rarity of this condition has precluded controlled studies of potentially novel therapies, and prophylaxis remains the mainstay of therapy.

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Other syndromes caused by cold

Neonatal cold injury

SYN. SCLEREMA NEONATORUM

This condition is discussed in Chapter 14.

Cold panniculitis

SYN. ADIPONECROSIS E FRIGORE

This term may be loosely used to describe a variety of clinical syndromes, notably perniosis. It has also been applied in a much stricter sense to a rare panniculitis with a much more clear-cut and reproducible reaction to cold exposure [1]. Firm plaques of fat necrosis on the chubby cheeks of young children have been described after exposure to cold. The lesions cleared up spontaneously without scarring [2].

Hypothermia

This may cause changes in the subcutaneous tissues (see Chapter 55) or may be induced by extensive inflammatory skin conditions (see Chapter 17).

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Chapter 24

Cutaneous Photobiology

J.L.M. Hawk, A.R. Young & J. Ferguson

Basic principles of cutaneous photobiology

[A.R. Young, pp. 24.1–24.10]

Definition. Photobiology is the study of the effects of UV and visible radiation on living matter. Cutaneous (dermatological) photobiology is concerned with those effects on skin.

Ultraviolet radiation (UVR), its production and measurement

The nature of UVR [1]

UV and visible radiation, which comprises a very small part of the electromagnetic radiation spectrum (Fig. 24.1), is energy released during the transition of a molecular electron from a higher energy outer molecular orbital to a less energetic inner one. Each such emission, known as a photon, is a discrete oscillating electromagnetic pulse of energy E (joules, J), wavelength λ (nanometres, nm, 10^{-9} m) and velocity through space c (3×10^8 m/s), such that $E = hc/\lambda$, where $h = 6.63 \times 10^{-34}$ J/s (Planck's constant) (Fig. 24.2). Thus, a 300-nm photon has energy 6.63×10^{-19} J, where 1 J is defined as the work required to accelerate 1 kg over 1 m in 1 s to a velocity of 1 m/s in a frictionless environment. Repeated molecular emissions from a point source lead to multiple spherical radiation wavefronts, each of total energy equal to the sum of the individual photon energies, but diverging with gradually diminishing intensity per unit surface area. The amount of such energy incident on a surface is known as the radiant exposure, exposure dose or fluence (J/m^2, formerly mJ/cm^2), and the rate of incidence as the irradiance, dose rate or intensity (W/m^2, formerly mW/cm^2), where 1 W = 1 Watt = 1 J/s.

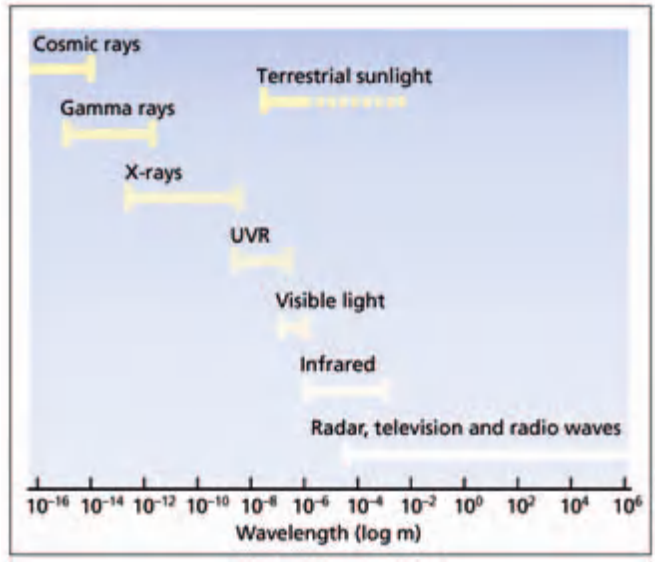

Fig. 24.1 The electromagnetic spectrum.

The UVR spectrum, 100–400 nm, comprises three wavebands: UVC (100–280, commonly but less precisely, 200–290 nm), UVB (280–315 nm, 290–320 nm) and UVA (315–400 nm or 320–400 nm); visible light is 400–700 nm.

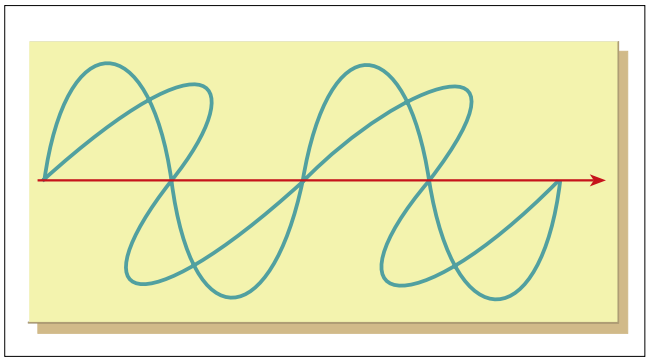

Fig. 24.2 Schematic representation of electromagnetic wave.

UVA has recently been subdivided into UVA-I (340–400 nm) and UVA-II (320–340 nm) because, biologically speaking, the effects of UVA-II are more like those of UVB.

Sources of UVR [2–4] (Fig. 24.3)

UVR is emitted spontaneously in large amounts by the sun and other stars. Terrestrial sunlight, modified by the Earth's atmosphere, contains both UVB and UVA. At noon, when the sun is high in the sky, the UVB content is approximately 5% and UVA accounts for the remaining 95%. However, when the sun is lower, early or late in the day, the UVA content is even higher. UVR is also produced by artificial sources, the most common in dermatological photobiology being gas discharge lamps, glass or quartz columns containing molecules of mercury vapour or xenon gas; these are excited to emit UVR by constant collisions with electrons passed through them between electrodes. The simplest are low-pressure mercury arc lamps emitting 254 nm UVC radiation, which are useful in limited fashion for research and germicidal purposes. Alternatively, alkaline earth phosphor coatings may convert these into reliable broad-spectrum UVB or UVA fluorescent tubes, commonly used for phototherapy or basic cutaneous phototesting.

More compact and of higher output, however, are medium-pressure mercury lamps, which emit a discrete spectrum of wavelengths ranging from the UVC to the infrared; but these require cumbersome power supplies and are relatively inefficient. Hence, they are now rarely used except for occasional localized UVB phototherapy (Alpine and Hanovia sunlamps), contact UVB and UVC phototherapy (Kromayer lamp) and fluorescence diagnosis (Wood's lamp).

The powerful high-pressure xenon arc lamp, although also bulky, when appropriately filtered has a smooth, broad, approximately solar-simulating emission throughout the whole UVR, visible and infrared wavebands, and is thus increasingly used in solar simulators for clinical investigation and research. Outside photobiology, fluorescent visible tubes, regularly used for room lighting, emit moderate amounts of UVA but minimal UVB, whereas incandescent tungsten light bulbs produce only trivial quantities of each, apart from the brighter quartz halogen type, which can produce considerably more.

Optical components for the modification of UVR [5]

The intensity, spectral content and direction of propagation of a UVR beam may be modified for photobiological purposes by systems of lenses, mirrors, filters and radiation-dispersing elements. The most complex of these, used particularly for precise cutaneous phototesting, is the irradiation monochromator, comprising a high-pressure xenon arc source, radiation focusing lens or

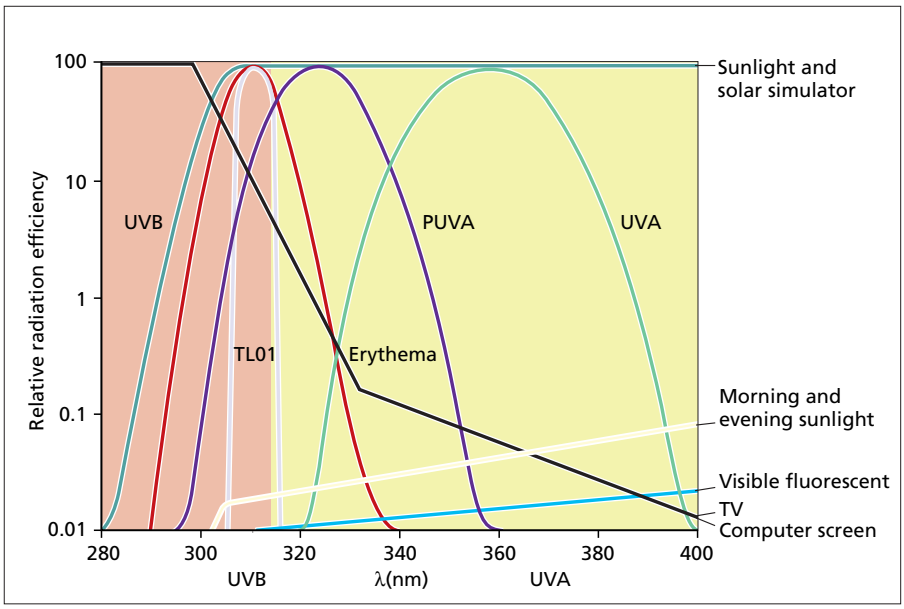

Fig. 24.3 Approximate emission spectra of typical sources encountered in dermatological photobiology and elsewhere, with action spectrum for human cutaneous erythema for comparison.

mirror, entrance aperture, collimating mirror, dispersing prism or grating, telescope mirror and exit aperture, from which emerges a selected narrow adjustable radiation waveband onto the skin.

Dosimetry (radiometry) of UVR [6,7]

For measurement purposes, radiation energy from a particular spectral region of interest, such as that for erythema or photochemotherapy with psoralen and UVA (PUVA) for treatment of psoriasis, is converted into electrical energy for meter readout. The total irradiance over such a waveband is assessed by means of an instrument known as a radiometer, made up of a radiation filter, input optics and a detector, whereas that at specific wavelengths, known as the spectral irradiance, is measured with the much more complex spectroradiometer, which includes a monochromator instead of a filter; the radiation dose is then calculated as the product of the measured irradiance and the exposure time in seconds. Spectroradiometric measurements are necessary to characterize emission spectra used for research purposes. These instruments have a dynamic range over several orders of magnitude, which can identify 'contaminating' radiation (e.g. UVB in a supposedly UVA source) that may be biologically important. There are a number of different types of radiation detector—four employed in dermatological photobiology are the variable spectral response photomultiplier tube, the vacuum phototube and the solid-state photodiode (all converting photon energy directly into electrical energy), and the uniformly responsive thermopile (which transforms it into heat first). Photomultiplier tubes are very sensitive but fragile, and therefore useful in spectroradiometers for accurate work, whereas the less responsive vacuum phototubes and solid-state photodiodes are more robust, small and suitable for rapid portable radiometry, for example of phototherapy equipment; thermopiles, on the other hand, which are also small and robust but have flat spectral responses, are best for the quick accurate measurement of monochromatic irradiances, or of serial broad-band irradiances of fixed spectral content.

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UVR interactions with matter

General [1–5]

Radiation incident on a surface is either reflected, or transmitted and scattered within the medium beneath, particularly at short wavelengths, by collision with the contained particles. It then eventually exits, unless it first collides with and is absorbed by an appropriately structured molecular moiety, known as a chromophore (Fig. 24.4). Any of a broad range of contiguous wavelengths, each representing equivalent photon energies, the so-called absorption spectrum, may be absorbed, with slightly differing probabilities (Fig. 24.5), leading to electronic excitation to an outer, higher energy molecular orbital (Fig. 24.6), enabling chemical reactions to occur and leading to possible clinical consequences such as skin sunburning, photoageing or cancer. More usually, however, the electron rapidly returns to its resting state, accompanied by harmless, longer wavelength radiation re-emission.

UVR interaction with atmosphere [6,7]

Solar radiation incident upon the Earth's atmospheric envelope is either reflected, or transmitted and attenuated, principally by gas molecule and water droplet scattering at wavelengths above 330 nm, by stratospheric ozone absorption between 200 and 330 nm, and by oxygen absorption below 200 nm. Extraterrestrial sunlight intensity is thereby reduced to about 1350–900 W/m^2 at the Earth's surface, comprising around 450 W/m^2 for visible

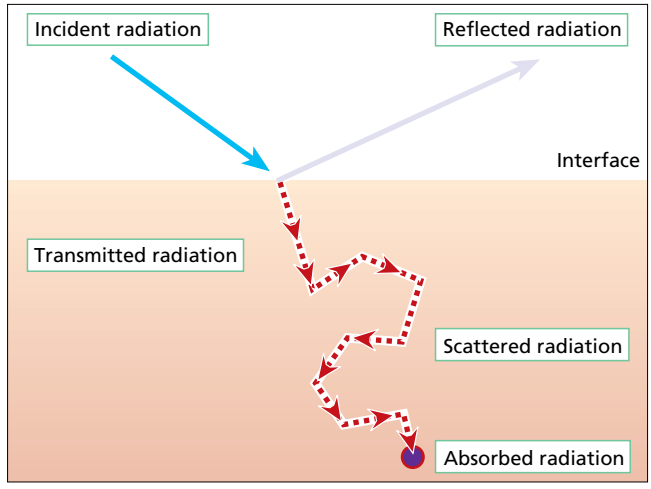

Fig. 24.4 Interaction of UV radiation (UVR) with physical matter.

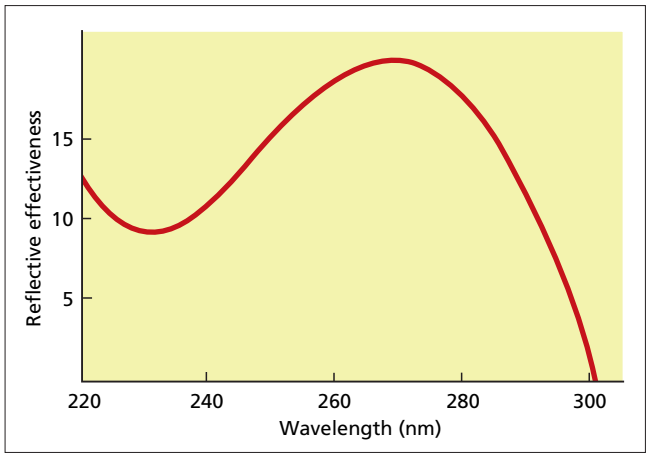

Fig. 24.5 Typical appearance of wavelength probability curve for excitation of orbiting electron to outer electronic orbital (absorption spectrum).

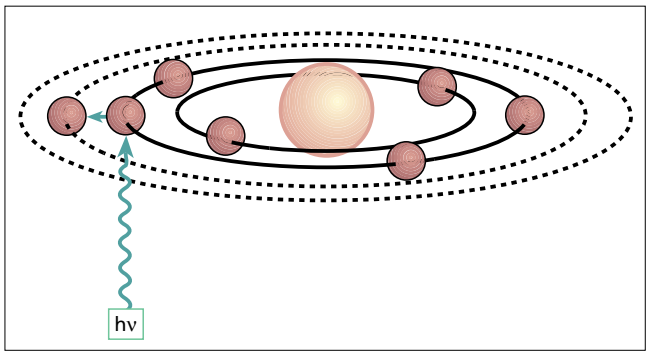

Fig. 24.6 Schematic representation of photon absorption, leading to excitation of orbiting electron to outer electronic orbital.

light, up to about 40–50 W/m^2 for UVA and 2 W/m^2 for UVB, and the remainder for infrared.

UVR interaction with sunscreens [8–10]

Sunscreens are topical preparations that attenuate UVR intensity by reflecting or absorbing it, or both. Reflectant sunscreens remit both UVB and UVA from a film of inert mineral oxide particles, usually zinc oxide or titanium dioxide in a suitable vehicle, whereas absorbent products absorb it into specific chemicals and re-emit it as harmless quantities of visible light or heat; combination preparations are a mixture of the two.

UVR interaction with skin [1–3,11–14]

Approximately 5% of the UVR incident on skin is diffusely reflected, the remainder being transmitted, scattered and absorbed, or passed out of the medium (Fig. 24.4) [2,8]. Thus, transmitted radiation below approximately 300 nm is largely attenuated within the epidermis by chromophores such as urocanic acid, DNA, RNA, tryptophan, tyrosine and melanin, whereas dermal DNA, RNA and the amino acids in elastin and collagen presumably absorb any radiation that passes through the epidermis. At approximately 300 nm and above, UVR is more readily transmitted to the dermis, after initial variable absorption by epidermal chromophores, followed by reflection back from dermal collagen bundles to the environment; in addition, minor absorption by intravascular haemoglobin, tissue bilirubin and β-carotene in fat is possible.

DNA is almost certainly the most important skin chromophore, UVR-induced lesions potentially severely inhibiting cellular metabolism or leading to mutation or cell death by apoptosis or necrosis. DNA photoproducts include cyclobutane pyrimidine dimers (CPD), pyrimidine (6–4) pyrimidone and Dewar photoproducts, DNA hydration products, DNA–protein and DNA–DNA cross-links, and thymine glycols, all of which are largely but not necessarily completely repaired by specific enzymatic processes. DNA photolesions in the epidermis, such as CPD, can be readily detected *in vivo* after suberythemal and erythemal UVR exposures.

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Environmental exposure to UVR [1–3]

The sun is the principal source of environmental UVR. Recently, the standard erythema dose (SED) has been advocated as the best means of quantifying UVR exposure. A SED is equivalent to an erythemally effective exposure of 100 J/m^2 and is independent of individual sensitivity to UVR and the specific UVR spectrum. An exposure of 2–4 SEDs would be expected to produce a mild sunburn on previously unexposed skin. Indoor workers in northern Europe receive about 200 SEDs/year, which is approximately 5% of the total available ambient radiation. Of this annual dose, 50% is received in just 33 days of the year. Outdoor workers would be exposed to 400–600 SEDs/year. Children spend more time out of doors and it is estimated that those in the UK receive an annual dose of about 300 SEDs. Behaviour is a major determinant of UVR exposure such that it is possible for children in the UK to have higher solar exposure levels than in Queensland, Australia [3]. Various studies have shown that approximately 10% of the UK population has had UVR exposure from sunbeds and other tanning devices. Other artificial sources may also be important; some indoor workers are significantly irradiated by, for example, arc welding devices and hospital phototherapy equipment. Office workers and home dwellers may be at risk from low-intensity UVR from fluorescent or, more importantly, quartz halogen lamps used for indoor lighting.

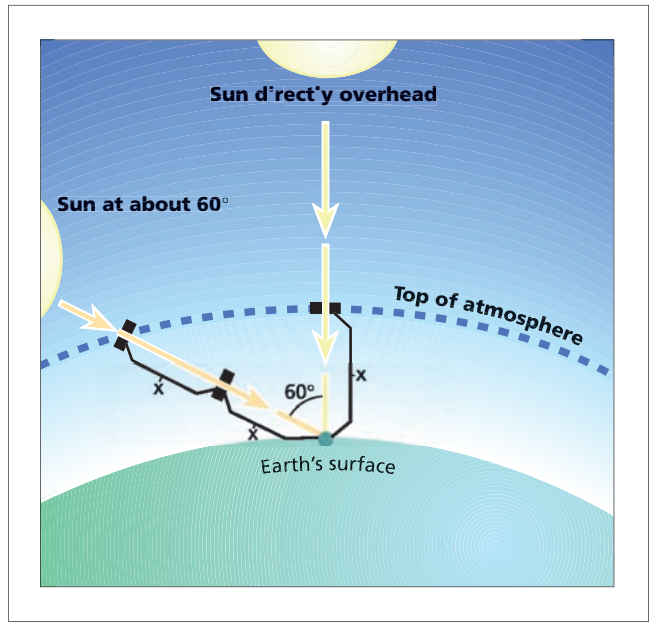

Fig. 24.7 UVR path lengths for differing solar elevations.

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Prophylactic measures to minimize human cutaneous UVR exposure [1]

Restriction of skin exposure to direct sunlight is advisable when UVR intensity is high, such as following short atmospheric radiation transit at times around the solar zenith, particularly at high altitudes, low latitudes and in summer (Fig. 24.7); furthermore, because much of this UVR is incident from areas of blue sky as a result of normal atmospheric molecular and aerosol scattering, exposure to sky light should also be minimized at such times. Finally, as UVR intensity is increased by reflection from snow by up to 85%, sand by 25% and rippling water by perhaps 5%, but decreased by only 20–90% by cloud cover and 60% for every 50 cm travelled through water, extra care should also be taken when these factors apply, particularly in alpine areas or near the sea. Radiation intensity is not, however, significantly altered by any accompanying heat, cold, wind or visible light.

Clothing consisting of close-weave, loose-fitting material covering as much of the skin as fashionably acceptable is further invaluable protection against UVR exposure and if opaque to visible light is generally protective against UVR as well; in particular, broad-brimmed headwear is useful for the face and scalp.

In addition to these measures, the regular adequate prophylactic application of high-protection, absorbent, reflectant or combination sunscreens is helpful in minimizing the short- and possibly long-term effects of cutaneous UVR exposure [2–8]. Absorbent products have traditionally been the most popular; they act well against UVB and are also cosmetically satisfactory, although cutaneous irritation and contact or photocontact dermatitis are possible hazards [3,4]. For the UVA-induced photodermatoses and very photosensitive normal subjects, however, the relatively inert, mineral oxide-containing reflectant preparations, although less cosmetically appealing, have been preferred, as they are less irritating and less liable to cause contact sensitivity, as well as being very effective against both UVB and UVA. Recently, new, increasingly effective UVA absorbers such as the dibenzoylmethanes and terephthalylidene dicamphor sulphonic acid have significantly improved absorbent screen efficacy [9], and micronized reflectant particles, although recently giving rise to temporary minor concerns about possible photodegradation and cutaneous absorption, have increased reflectant preparation acceptability, thus improving choice. Combination preparations have also become more common, and appear to

provide optimal cover in all circumstances except severe UVA photosensitivity.

The efficacy of a sunscreen is determined by its ability to afford protection against erythema, which is primarily caused by solar UVB but with some contribution (15–20%) by UVA. The measure of protection, assessed under controlled laboratory conditions, is known as the sun protection factor (SPF) [3,4] and is the multiple by which UVR exposure may be increased, after sunscreen application, before burning begins. One requirement of SPF assessment is the application of 2 mg/cm^2 skin. However, several studies have shown that people typically apply less than half this concentration and so will receive a much lower level of protection than indicated by the SPF on the label [2]. Attempts have also been made formally to assess UVA protection alone, as these wavelengths are important at high doses and in many photodermatoses, but no internationally agreed method has yet been found [3]; however, many UK sunscreens display a rough guide [10], denoted as an approximate proportion of the protection offered against UVB. High SPF (15–25) products providing substantial UVA protection are suitable for all purposes, particularly the photodermatoses, but many have a mild propensity to induce contact sensitization and appear white on the skin [3,4], so that lower levels of protection (10–15) may sometimes be more satisfactory for normal, particularly darker, skins and moderate exposures. Sunscreen resistance to removal by water, known as 'substantivity', may also be quantified in terms of its rate of loss of efficacy on submerged skin [3]. Highly substantive preparations are clearly preferable in circumstances where they may be washed or rubbed off.

In the UK, certain highly protective sunscreens may be prescribed as so-called 'borderline substances' for the treatment of abnormal photosensitivity, the exact choice depending on the circumstances in which the preparation is to be used (Table 24.1).

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Systemic effects of UVR exposure in humans

Solar radiation is essential for life and the provision of human well-being, offering warmth, illumination and nourishment from plant photosynthesis. However, the UV component of such radiation does not appear necessary. Thus, various past claims of reduced minor illness and improved work rates following UVR exposure have not been substantiated [1–3] and, although UVR exposure is known to induce some systemic change, for example increasing circulating vitamin D concentration [4] and modifying blood immunological function [5], the widely claimed mood-enhancing and health-giving properties of sunlight [6], if they exist at all, seem more likely to be mediated through visible irradiation effects on the eye.

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Normal cutaneous effects of UVR exposure

Early effects

Inflammation

UVR absorption by skin chromophores leads to widespread epidermal and dermal cellular damage, which is associated with inflammation [1]. DNA is probably the primary molecular target of injury [2], as a result of both direct UVB absorption and also secondary UVA-induced photosensitization reactions. Nuclear transcription factors and cytokine production are also induced at this stage [3,4], very likely by the same DNA damage [5], leading to increased production of serum and epidermal interleukins [3], with consequent cellular adhesion molecule activation [6], mild neutrophil and moderate mononuclear cell infiltration [7], and the release of various inflammatory mediators, such as prostaglandin E_2 and nitric oxide

Table 24.1 Sunscreens currently available in the UK for prescription as borderline substances; note, however, that formulations may be regularly altered.

Sunscreen*	Active ingredients	Spectral efficacy
Delph Lotion SPF15	Ethylhexyl *p*-methoxycinnamate 7.5% Oxybenzone 3.0% Titanium dioxide 0.6%	Moderate UVB, moderate UVA
Delph Lotion SPF20	Ethylhexyl *p*-methoxycinnamate 7.5% Oxybenzone 3.0% Titanium dioxide 1.6%	Moderate UVB, moderate UVA
Delph Lotion SPF25	Ethylhexyl *p*-methoxycinnamate 3.5% Oxybenzone 1.3% Avobenzone 4.0% Titanium dioxide 2.1%	Good UVB, good UVA
Delph Lotion SPF30	Ethylhexyl *p*-methoxycinnamate 4.8% Oxybenzone 1.5% Avobenzone 4.0% Titanium dioxide 2.5%	Good UVB, good UVA
E45 Sun Block lotion SPF25	Zinc oxide 13.9% Titanium dioxide 3.6%	Good UVB, good UVA
E45 Sun Block lotion SPF50	Zinc oxide 16.0% Titanium dioxide 6.4%	Very good UVB, very good UVA
RoC Total Sunblock cream SPF25	Octyl methoxycinnamate 7.5% Butyl methoxydibenzoylmethane 2.0% Titanium dioxide 5.5%	Good UVB, good UVA
SpectraBan Alcoholic solution SPF25	Octyldimethyl *p*-aminobenzoic acid 3.2% *p*-aminobenzoic acid 5.0%	Good UVB, minimal UVA
SpectraBan Ultra lotion SPF28	Butyl methoxydibenzoylmethane 2% Oxybenzone 3% Octyldimethyl *p*-aminobenzoic acid 8% Titanium dioxide 2.0%	Good UVB, good UVA
Sunsense Ultra lotion SPF60	Octyl methoxycinnamate 7.5% Oxybenzone 3.0% Titanium dioxide 3.0%	Very good UVB, good UVA
Uvistat Cream SPF20	Ethylhexyl *p*-methoxycinnamate 7.0% Butyl methoxydibenzoylmethane 4% Titanium dioxide 4.5%	Good UVB, good UVA
Uvistat Cream SPF30	Ethylhexyl *p*-methoxycinnamate 7.5% Butyl methoxydibenzoylmethane 4% Titanium dioxide 6.5%	Good UVB, very good UVA

* Trade names.

[8]. Clinically, erythema, pain, warmth and, in severe cases, swelling and loss of function, develop over hours to days. These changes are accompanied histologically by epidermal spongiosis and, except after UVA, the formation of sunburn cells (apoptotic cells) [9], along with dermal vasodilatation, oedema and neutrophil and mononuclear cell infiltration [7]. UVR wavelengths around 300 nm are the most DNA damaging and erythemogenic [2]. The lowest dose to induce erythema is known as the minimal erythema dose (MED), and is around 500 J/m^2 for the UVC–UVB boundary (280 nm), 250 J/m^2 for UVB (300 nm) and 320 kJ/m^2 for UVA (360 nm) (Fig. 24.8).

Avoidance of sunburn requires restriction of UVR exposure, covering up with appropriate clothing and the use of high-SPF sunscreens. If burning occurs in spite of these precautions, treatment is largely symptomatic, and involves the administration of oral fluids, particularly in severe cases, the application of soothing topical emollient creams or evaporating lotions and, more actively, the use of topical or oral non-steroidal (or perhaps occasionally steroidal) anti-inflammatory agents from the earliest onset of symptoms. On rare occasions, sunburning may be severe or life-threatening and then requires treatment as for thermal burns.

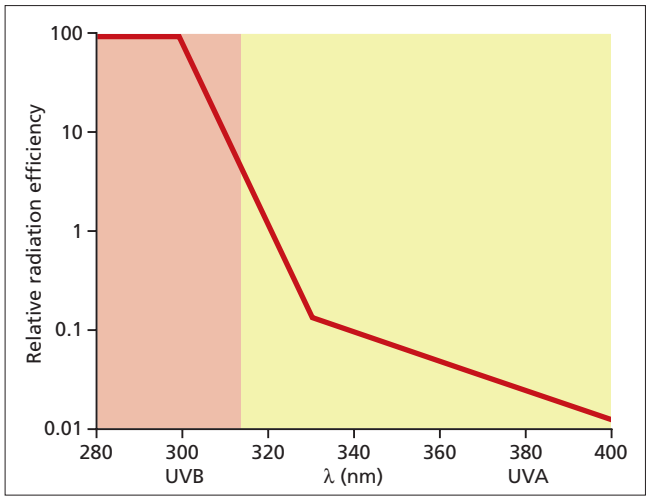

Fig. 24.8 Action spectrum for induction of erythema in human skin.

Tanning

Immediate

Immediate, often greyish, tanning of irradiated skin, lasting for a minute or so up to hours, may occur within seconds of exposure to 20–120 kJ/m^2 of UVA, and perhaps also short-wavelength visible radiation, particularly in more pigmented subjects. This probably results from photo-oxidative darkening and cellular redistribution of epidermal melanocytic melanin, although sunburning sensitivity is not apparently decreased by this response; however, supranuclear melanin caps present in strategically important basal layer cells may protect vulnerable genetic sites.

Delayed

Delayed (facultative) tanning of irradiated skin, persisting for weeks to months, gradually appears over hours to days after cutaneous exposure to around 400 J/m^2 of broad-band UVB (somewhat greater than the MED, particularly in fair-skinned subjects), 150–200 kJ/m^2 of broad-band UVA (somewhat less than the MED) or 100 J/m^2 of UVC (about equal to the MED). The mechanism of such tanning is uncertain, but tyrosinase activation by nucleotide residues from sites of UVR-induced melanocytic DNA damage appears likely to initiate the process [10], thus leading to new melanin production and its transfer from melanocyte dendrites to adjacent keratinocytes. Melanocyte size, dendritic arborization and enzyme activity are also increased during this process and, in addition, quiescent melanocytes are activated and new melanocytes recruited by cell division. Sunburning sensitivity in white subjects is thereby moderately decreased by about two- to fourfold [11].

Hyperplasia

Skin hyperplasia persisting for a month or two develops over hours to days following UVB or UVC (but generally not UVA) exposure, and results from a marked increase in cell mitosis, DNA, RNA and protein synthesis rates, after some hours of early inactivity. The stimulus for this is unknown but, as for tanning, may conceivably be UVR-induced cellular DNA damage. The epidermis and dermis, particularly the inert stratum corneum, thicken as a result by up to two to four times, thereby apparently giving some protection against subsequent UVR-induced inflammation, an effect that combines with and may perhaps supersede the concomitant protection from tanning, particularly in fair-skinned races.

Immunological changes

The skin is a major immunological organ in which the dendritic Langerhans' cells in the epidermis normally present antigens to naïve T cells. It is now well established that UVR has profound effects on skin immunity that are mediated by alterations to the antigen-presenting capacity of Langerhans' cells and the stimulation of abnormal antigen presentation by CD11b macrophages [12]. These alterations are the result of UVR-induced changes to the chemical microenvironment of the skin, in particular the cytokine profile [4].

UVR has been shown to inhibit the induction and elicitation phases of the contact hypersensitivity response in mice and in humans. Mouse studies have shown that UVR-induced immunosuppression has a major role in skin cancer and susceptibility to infectious agents, and a similar role is suspected in humans. Recent studies have shown that a single suberythemal exposure of solar simulated radiation (SSR) suppresses the induction phase of the contact hypersensitivity response in sun-sensitive skin types I/II (Table 24.2). An erythemal exposure was necessary to give a comparable level of immunosuppression in sun-tolerant skin types III/IV and this difference may be a factor in the differing susceptibilities of skin types I/II and III/IV to skin cancer [13]. The most likely chromophores for the immunomodulatory effects of UVR are DNA and stratum corneum-bound urocanic acid which undergoes a *trans* to *cis* isomerization in the presence of UVR. The ability of sunscreens to prevent UVR-induced immunosuppression is a controversial issue that is in the process of being resolved [14].

Vitamin D synthesis

UVB irradiation, most efficiently in moderate doses, rapidly converts epidermal 7-dehydrocholesterol into previtamin D_3, which is then isomerized over several days to vitamin D_3, and transported by plasma vitamin D-binding protein into the circulation [15].

Table 24.2 Acute and long-term characteristics of different skin phototypes.

Skin type	Susceptibility to sunburn	Constitutive skin colour	Facultative tanning ability	Susceptibility to skin cancer
I	High	White	Very poor	High
II	High	White	Poor	High
III	Moderate	White	Good	Moderate
IV	Low	Olive	Very good	Low
V	Very low	Brown	Very good	Very low
VI	Very low	Black	Very good	Very low

Photo-onycholysis

A few subjects develop recurrent, probably UVA-induced, photo-onycholysis of nails exposed to strong sunlight, conceivably from photosensitization by endogenous photoactive cutaneous substances such as porphyrin in the presence of high-intensity UVA exposure, a process probably similar to those operating in drug- or porphyria-associated photo-onycholysis [16].

Late effects

Pseudoporphyria

Regular skin exposure to the predominantly UVA radiation from sunbeds, or perhaps also to strong sunlight during the use of high-protection UVB sunscreens, may lead over weeks or months to largely reversible cutaneous blistering and fragility, as well as to superficial atrophic scarring, as occurs in the hepatic porphyrias, particularly in fair-skinned subjects [17]. This may conceivably be the result of photosensitization by endogenous photoactive cutaneous substances such as porphyrin in the presence of high-intensity UVA exposure, a process probably similar to those operating in drug-associated pseudoporphyria and the hepatic porphyrias.

Photoageing

Skin photoageing is the gradual deterioration of cutaneous structure and function following long-term recurrent exposure to sunlight or artificial UVR sources. These events are superimposed on intrinsic chronological skin ageing [18]. The epidermis and dermis are both affected, probably principally by UVB, but the dermis may be affected to some extent by UVA. Cutaneous fine and coarse wrinkling, dryness, coarseness, telangiectasia, yellowness, mottled pigmentation, laxity, loss of tensile strength and comedones are characteristic. Histologically, there is a mild inflammatory infiltrate and profuse upper dermal accumulation of a form of amorphous degenerate elastic tissue, known as elastosis. *In vivo* studies provide evidence for an important role for UVR-induced matrix metalloproteinases, which degrade collagen, the major structural protein of the dermis [19]. Restriction of UVR exposure and the use of high-SPF broad-spectrum sunscreens may slow progression of this process [18], and long-term use of the topical retinoid all-*trans* retinoic acid [18,19], and to a lesser extent of α-hydroxyacid preparations, may improve any changes already present.

Photocarcinogenesis

Human epidemiological and animal studies strongly suggest that chronic cutaneous UVB and, to a lesser extent, UVA exposure are responsible for the induction of most non-melanoma skin cancers, and probably of melanomas as well, although it has been suggested that UVA may play a relatively more important part in the latter [20]. A number of UVR-induced cutaneous events appear to be important, including the mutation of the *p53* tumour suppressor gene [21], and possible alterations in immune surveillance (as apparently occur in exaggerated fashion in the skin cancer-prone disorder xeroderma pigmentosum), appear aetiologically important. Restriction of UVR exposure, the use of appropriate clothing and the application of high-SPF sunscreens prevent actinic keratoses [22] although, overall, the evidence that sunscreen use prevents skin cancer is not impressive [23,24], perhaps because of less than assiduous use or excessive UVR exposure. In addition, long-term topical use of the retinoid tretinoin may perhaps very slowly improve actinic keratoses, and topical 5-fluorouracil cream and liquid nitrogen cryotherapy are very effective in the rapid treatment of these lesions. However, for fully developed skin cancers treatment with surgery or radiotherapy is required (see Chapters 76–78).

Skin phototypes

An individual's genetically determined cutaneous sunburning and tanning tendency following UVR exposure may be roughly graded by self-assessed skin phototype (Table 24.2) [25,26]. This assists in the determination of safe but effective regimens for phototherapy and photochemotherapy, as well as an individual's susceptibility to sunburn and skin cancer, and thus the degree of photoprotection required. In general, MED increases with skin type, but there is considerable overlap between skin types, such that a skin type I may have the same MED as a skin

type IV [27]. Thus, although broadly useful, skin type assessment is only a guide.

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Abnormal cutaneous effects of UVR exposure: the photodermatoses

Acquired disorders with a probable immunological basis (Table 24.3)

Polymorphic light eruption

[J.L.M. Hawk, pp. 24.10–24.14]

Definition. Polymorphic light eruption (PLE) is a common intermittent sunlight or artificial UVR-induced eruption, particularly of temperate regions, affecting subjects of any race within hours or rarely days of exposure. The rash is non-scarring, itchy, erythematous and usually papular, although it is sometimes plaque-like, vesicular, bullous or mixed. It usually affects exposed skin, but may occur on covered areas, and lasts for days to a week or two after exposure has ceased. It is most common in young women, is often worse in spring, and is probably a delayed-type hypersensitivity reaction against endogenous cutaneous photoantigen as a result of a genetically determined reduction in UVR-induced cutaneous immunosuppression.

Aetiology. The eruption of PLE is induced by UVR [1], and perhaps also rarely by visible irradiation [2], whether from sunlight or artificial sources, including sunbeds [3]. However, bright summer sunlight in temperate climates is generally the trigger. Artificial induction is difficult, although not infrequently achievable through solar-simulated exposures [4,5]. The evoking action spectra have not been precisely determined, apparently varying between patients, but typical lesions have followed broadband UVB [6–8], UVA [9,10] and, very rarely, visible [2] irradiation. Monochromatic induction is more difficult, but lower than normal MEDs or abnormal papular responses occur in rather more than half of exposed patients [1], and evaluation of the literature suggests around one-quarter of patients overall may be sensitive to just UVB, one-quarter to both UVB and UVA, and half to just UVA.

PLE appears to have a largely genetic basis, affecting the families of patients some three times more commonly than the general population, and both of some 70% of identical but only 30% of non-identical twins [11]. As only up to approximately 20% of the population express the disorder, however, environmental factors [11] and penetrance of the affected allele [12] are also apparently important.

It was long thought that PLE was a delayed-type hypersensitivity (DTH) reaction against UVR-induced cutaneous antigen. Sequential skin biopsies following

Table 24.3 Distinguishing features of some acquired photodermatoses.

Disease	Clinical features	Specific investigations (in all cases estimation of circulating antinuclear antibodies and extractable nuclear antigen and screening for blood, urine and stool porphyrins is advisable)	Differential diagnosis	Treatment (in all cases restriction of UVR exposure, wearing of protective clothing and use of high-protection broad-spectrum sunscreens is advisable)
Polymorphic light eruption	Very common, affects mostly young women in temperate climates. Intermittent, summer sun-induced, non-scarring, erythematous, itchy, symmetrical, papular eruption of usually only some exposed areas. Onset in hours, resolution in days. Examination in remission normal	History most important in diagnosis. Histology useful in uncertain cases. Direct immunofluorescence negative. Solar or solar-simulated irradiation may induce rash. Broad-band UVB and UVA, or monochromatic, irradiation tests may also help, but only sometimes abnormal. Lupus must be excluded by serology	Persistent lymphocytic infiltrations, e.g. Jessner's; solar urticaria; lupus erythematosus and other light-exacerbated dermatoses; erythropoietic protoporphyria	Prophylactic, low-dose broad- or narrow-band UVB or PUVA; short-course, topical, oral or injected steroids; ciclosporin or azathioprine in intractable disease
Actinic prurigo	Rare, affects mostly girls and adult females, may persist indefinitely. Chronic UVR-induced, papular or nodular eruption, itchy, symmetrical, excoriated, most severe on exposed areas; fades towards covered sites, may affect buttocks a little. Worse in summer, may flare after sun exposure. Superficial scarring of face possible. PLE may accompany. Probable persistent variant of PLE	Clinical features most important. Broad-band UVB and UVA, or monochromatic, irradiation tests sometimes abnormal. HLA tissue typing for DRBI *04(07) helpful if positive	PLE; nodular prurigo; atopic prurigo; insect bites; atopic eczema; scabies; erythropoietic protoporphyria	Topical steroids or occasionally intermittent oral steroids and emollients; low-dose UVB or PUVA; intermittent oral thalidomide, with care to avoid pregnancy and peripheral neuropathy, in severe, unresponsive cases
Hydroa vacciniforme	Very rare. Affects mostly children, often remits in adolescence. Intermittent, summer sun-induced, painful, scattered or confluent, symmetrical, vesicular eruption of some or all exposed areas. Onset in hours, crusting in days, disfiguring pock scars in weeks	Clinical features most important. Histology usually characteristic. Solar simulated, broad-band UVB or especially UVA irradiation may induce rash, monochromatic irradiation a UVA erythema. Viral and porphyrin studies negative	Xeroderma pigmentosum; erythropoietic protoporphyria; PLE; actinic prurigo; herpes simplex	Largely intractable; high-protection, broad-spectrum sunscreens most often useful; prophylactic, low-dose UVB or PUVA may help; hydroxychloroquine reported effective, but questionable
Solar urticaria	Rare. Affects all ages, both sexes. Intermittent, UVR- or visible light-induced, non-scarring, wealing eruption of some or usually all exposed areas. Onset in 5–10 min, resolution in 1–2 h. Often perennial. Very rarely associated with lupus erythematosus, drug or chemical use, erythropoietic protoporphyria. Examination in remission normal	Clinical features important. Broad-band UVB, UVA or visible, or monochromatic, irradiation usually elicits rash, defines action spectrum	PLE; drug- or chemical-induced photosensitivity; erythropoietic protoporphyria; other urticarias	High-dose, non-sedating antihistamines; prophylactic PUVA; induction of tolerance by recurrent exposure to action spectrum wavelengths; plasmapheresis
Chronic actinic dermatitis	Rare. Affects mostly elderly men, often outdoor enthusiasts. Chronic, UVR- and sometimes also visible light-induced, itchy, excoriated, lichenified or pseudolymphomatous, eczematous eruption, especially of exposed areas, sometimes generalized. Worse in summer, may flare after sun exposure. Allergic, especially airborne, contact dermatitis and endogenous eczema may coexist	Broad-band UVB, UVA or visible, or monochromatic, irradiation elicits eruption, defines action spectrum, necessary for diagnosis. Histology often characteristic. Patch and photopatch tests frequently positive to exacerbating allergens. $CD4^+$: $CD8^+$ T-cell ratio reduced in skin and circulating blood, particularly in florid cases	Atopic eczema; seborrhoeic eczema; other forms of endogenous eczema; allergic, especially airborne, contact dermatitis; cutaneous T-cell lymphoma; other forms of erythroderma	Topical steroids and emollients; high-protection, broad-spectrum, non-irritating sunscreens; intermittent oral steroids; intermittent immunosuppressive therapy with azathioprine, ciclosporin or mycophenolate; PUVA may also help

PLE, polymorphic light eruption; PUVA, psoralen and UVA.

low-dose solar-simulated irradiation then supported this experimentally by demonstrating a perivascular infiltrate with a predominance of $CD4^+$ T cells in lesions up to 72 h post-induction, and in later lesions an infiltrate dominated by $CD8^+$ cells [4]. This clearly differs from the immunosuppressive response seen in normal subjects [13], as does the associated release of interleukin-6 (IL-6), IL-8 and possibly IL-1 [14], rather than the IL-10 and tumour necrosis factor-α (TNF-α) of unaffected individuals [14]. Further, the characteristic adhesion molecule activation patterns for E-selectin, vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) [15] further support a DTH response [16], and the stimulation of autologous peripheral blood lymphocytes *in vitro* by UVR-irradiated PLE but not normal keratinocytes [17], through presumed UVR-induced antigen production in the former, provides even more supportive evidence.

The genetic abnormality in PLE leading to apparently enhanced UVR-induced cutaneous antigen recognition may well be a reduced capacity for normal UVR-induced cutaneous immunosuppression [18]. This suggestion is supported by the finding of increased patient susceptibility to dinitrochlorobenzene skin sensitization following solar-simulated irradiation, compared with normal controls [18]. Further, specific features permitting this abnormality may well include a marked Langerhans' cell resistance to depletion by even very intense UVR exposure [19], and a conceivably reduced capacity to handle free radical insult through genetically determined glutathione depletion [20].

Cutaneous UVR molecular absorbers initiating the PLE rash have not yet been identified, but may at least sometimes be a variety of heat-shock protein found in PLE-affected, but not unaffected or UVB-irradiated normal skin [21]. Perhaps more likely, however, is that a variety of absorbers may be responsible, possibly by becoming antigenic themselves or leading to putative antigen production through secondary free radical activity [20].

Pathology [22]. There is variable epidermal spongiosis and dermal, perivascular, predominantly mononuclear cell infiltration with oedema, often extending to the deeper dermis in more long-standing lesions. The cells are generally T lymphocytes, but eosinophils and neutrophils may also be present.

Clinical features (Fig. 24.9) [1]. PLE is most common in temperate regions, affecting up to 20% of subjects in such areas [23–25], particularly women under 30 years of age. Far fewer suffer in tropical regions [24,26], although all ethnic groups appear susceptible, and dark skin does not apparently confer significant protection. Familial occurrence is also common [11,25]. PLE attacks are most common in spring and summer following sun exposure, the first episode sometimes occurring after solar overexposure, and then often diminishing gradually in severity or ceasing as summer progresses. Reflected solar UVR from snow in winter and sunbed radiation [3] may also provoke outbreaks. Several minutes' to hours' irradiation is generally needed for rash induction, sometimes days, particularly after periods of sunlight abstinence. Pruritus almost always occurs, often within minutes, and a rash within minutes to hours. The rash lasts hours, days, or rarely weeks, particularly if exposure continues. It may be localized or widespread. Variable areas of exposed or lightly clad skin may be affected, generally symmetrically but often patchily. The eruption distribution in any patient is generally characteristic, although sometimes varying with time or exposure intensity. Typically affected sites are the bridge of nose, malar areas of cheeks, front of chin, sides and back of neck, upper chest, dorsa of hands, dorsolateral aspects of arms, fronts and backs of legs, and dorsa of feet. Lesions vary greatly both between and within patients, but are generally itchy, clustered, erythematous or skin-coloured, large or small papules, sometimes coalescing into smooth or irregularly surfaced confluent plaques. Vesicles, papulovesicles and, rarely, bullae, or generalized oedematous swelling, the last especially affecting the face, may also occur. Rarely, there may be pruritus alone [27], but erythema alone, with or without itch, is extremely rare. Mild papular PLE sparing the face is sometimes known as benign summer light eruption

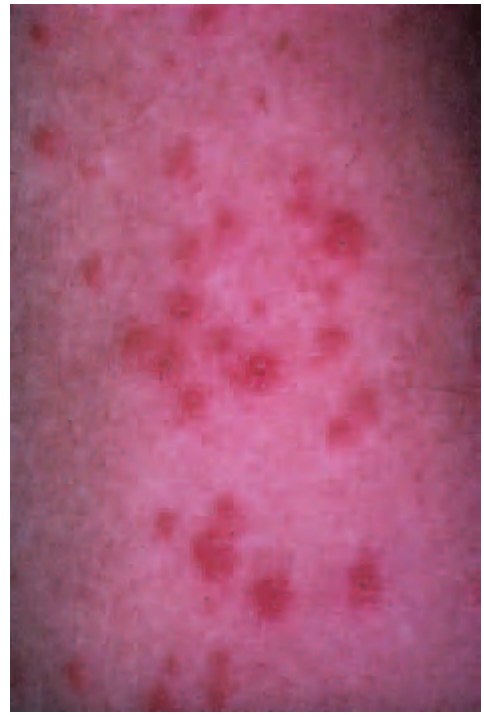

Fig. 24.9 Polymorphic light eruption, showing variably sized, erythematous papules.

in continental Europe [28], and that of the light-exposed helices of boys' ears, which is often vesicular and was initially reported as a springtime epidemic, is sometimes called juvenile spring eruption [29–31]. Systemic malaise, chills, headache, fever and nausea may rarely accompany PLE. The condition may persist indefinitely, but often gradually improves, and occasionally remits [32].

Diagnosis. This is suggested by the history, clinical findings, absent circulating antinuclear antibodies and extractable nuclear antigen, and normal blood, urinary and stool porphyrin concentrations. In doubtful cases, lesional histology may be helpful but not diagnostic; immunofluorescence findings are negative. If uncertainty persists, skin irradiation monochromator testing may demonstrate reduced minimal erythemal or abnormal papular responses, and broad-spectrum testing, or solar exposure if available, may elicit the eruption itself. Solar urticaria is differentiated from PLE by its rapid (5–10 min) onset delay after exposure, short (1–2 h) total time course, and different lesional morphology; from erythropoietic protoporphyria by its painful nature, usual lack of rash and raised red blood cell protoporphyrin concentration; from light-exacerbated atopic eczema by its eczematous clinical and histological features; from lupus erythematosus (LE), which may also precede or coexist with PLE [33,34], by its characteristic circulating and cutaneous immunological abnormalities; and from erythema multiforme by its clinical features, distinctive histology and not infrequent association with a precipitating agent.

Treatment. Mild PLE may be managed by the restriction of UVR exposure, covering up with appropriate protective clothing, and the application of high-protection broad-spectrum sunscreens [35], although these last agents may perhaps exacerbate the condition on occasion by transmitting the often inducing UVA but not the relatively immunosuppressive UVB wavelengths [13]. In more severely and frequently affected patients, prophylactic broad- or more reliably narrow-band UVB phototherapy, or the slightly more efficient but less convenient PUVA, is regularly helpful for many months [36,37], almost certainly through immunosuppressive activity [13,38]; follow-up courses annually are then usually necessary for at least some years [39]. Suitable protocols include administering approximately 30–70% of the predetermined broad- or narrow-band UVB MED with subsequent increments of approximately 10–40% two to three times weekly for 4–6 weeks, or UVA 0.5 J/cm^2 and psoralen 0.6 mg/kg with increments of approximately 10–40% twice weekly for a month; for treatment-induced PLE flares, oral steroids may be given as below.

Oral antimalarial therapy has long been advocated for prophylactic use, but probably provides at best mild protection [40,41], and beta-carotene probably less or none [40]. More recently, oral omega-3 fatty acids have been reported as moderately helpful [42]. For occasional PLE attacks, however, or if rash develops in spite of the above measures, brief oral steroid courses, perhaps prednisolone 25–30 mg at earliest disease onset and then each morning until clear, are almost always effective [43]. Steroid by injection is probably similarly useful, but topically less so. Oral azathioprine [44] or ciclosporin [45] may also rarely be required for unremitting disabling disease.

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Actinic prurigo

[J.L.M. Hawk, pp. 24.14–24.16]

Definition. Actinic prurigo (AP) is a rare, sunlight-induced, papular or nodular, extremely itchy and therefore usually excoriated eruption of light-exposed and, to a lesser extent, covered skin, sometimes associated also with acute PLE-like attacks. It is usually worse in summer. It may begin at any age and often persists indefinitely. A similar condition, also called hereditary or familial polymorphous light eruption, may afflict North, Central and South Americans of native or mixed extraction. AP is probably a persistent variant of PLE, but is usually clinically distinct.

Aetiology. A causal role for UVR in AP is suggested by the condition's usually greater severity in summer along with abnormal monochromatic skin responses in about two-thirds of exposed patients [1–3], perhaps about half to UVB alone, and half to both UVB and UVA; a few are sensitive to just UVA, the rest normal. Broad-spectrum responses have not been formally reported, but solar-simulated irradiation appears on occasion to induce an acute PLE-like eruption that can progress to the AP rash. Further, the regular association of AP with PLE in patient or family [4], and the fact that some AP patients later develop PLE or vice versa [3], again suggests a relationship between the two conditions. In addition, the perivascular mononuclear cell infiltrate of early AP, not yet immunohistochemically characterized, resembles that of PLE [5,6], and the reported possible AP erythemal enhancement by the topical prostaglandin inhibitor indometacin [7] further supports an immunological basis for the disease [8]. AP may thus be a persistent PLE variant, and very likely a DTH response against endogenous cutaneous photoantigen. Hereditary factors appear predominant in determining the AP phenotype. Over 80% of white British patients demonstrate human leukocyte antigen (HLA) type DRB1*04 (DR4), which is present in only 30% of normal and PLE subjects, and 60% have the rare subtype DRB1*0407 [3,9], which is relatively common in native Americans [10]. This feature may very likely be the determinant transforming PLE into AP, a contention further supported by the fact that some genetic AP patients have clinical PLE but atypical lesional persistence [3]. The cutaneous UVR molecular absorbers initiating the AP eruption have not been identified, but may well be as postulated for PLE.

Pathology [5,6,11]. There is early variable epidermal acanthosis and spongiosis along with dermal perivascular mononuclear cell infiltration and oedema, as may also occur in PLE. Later, however, non-specific excoriations, increasing acanthosis, variable lichenification and an increasingly heavy mononuclear cell infiltrate tend to supervene. Rarely, a more bizarre picture reminiscent of cutaneous T-cell lymphoma may be present.

Clinical features (Fig. 24.10) [1,2,12]. AP may begin at any age in children or adults (most commonly female) and persist indefinitely [13]. A family history of AP, or more often PLE, is common [4], but personal and family atopy, previously considered a likely AP association, is probably no more frequent than in normal subjects. The eruption is seasonal, if often not clearly related to specific sun exposure, and generally worse in summer; rarely, however, it

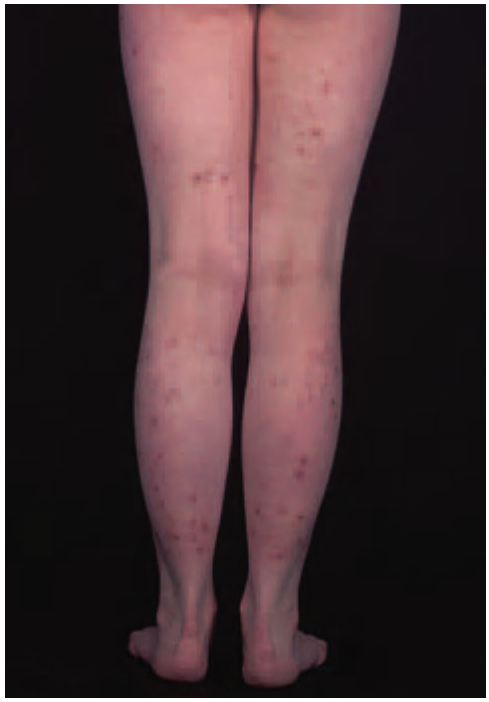

Fig. 24.10 Actinic prurigo, showing excoriated papules, more profuse distally.

may be more severe in both spring and autumn, or winter. The condition generally demonstrates very pruritic erythematous papules or nodules early on, and later these are often excoriated, crusted or scabbed, sometimes with eczematization or lichenification. The face and distal limbs are most affected, whereas the proximal limbs and the forehead under the fringe are relatively spared. The rash generally gradually fades towards more frequently covered sites, but even the sacral area and buttocks may be involved in severe cases. The limbs may also demonstrate hypo- or hyperpigmented healing lesions or flat white scars, and the face minute linear or pitted scars. Cheilitis and conjunctivitis may also occasionally be present, particularly in native American patients [14,15]. Attacks of an eruption indistinguishable from PLE may also sometimes occur, at times fading thereafter into AP.

Diagnosis. This is suggested mainly by a carefully taken history supported by appropriate examination findings, along with absent circulating antinuclear antibodies and extractable nuclear antigen, and blood, urine and stool porphyrins. In doubtful cases, early lesional histology may also help; immunofluorescence findings are nonspecific. If there is continuing diagnostic difficulty, irradiation monochromator skin testing may confirm light sensitivity in up to two-thirds of patients, and broad-spectrum irradiation may sometimes induce an acute PLE-like rash. HLA typing is diagnostically supportive if HLA-DRB1*04 (DR4) is demonstrated, much more so if there is the rare DRB1*0407 subtype [3,9]. Atopic eczema, particularly light-exacerbated, may be distinguished by its history, appearance and distribution; insect bites by their shorter time course and often asymmetrical distribution; scabies by its lack of seasonality and presence of the mite; prurigo nodularis by its lack of seasonality, usual adult onset and generally more widespread lesions; and erythropoietic protoporphyria by its abnormal red blood cell protoporphyrin concentration. Nevertheless, AP diagnosis may often remain uncertain in the early stages, and depends on disease evolution for confirmation.

Treatment. Mild AP may be managed by the restriction of sun exposure, use of appropriate protective clothing, regular application of high-protection broad-spectrum sunscreens and topical steroids and emollients. As in PLE [16], sunscreens may perhaps, on occasion, exacerbate the disorder by permitting inducing UVA but not immunosuppressive UVB transmission. Poorly responsive patients may sometimes do well with occasional oral steroid courses for flares [13]. For more persistent disease, however, prophylactic low-dose broad- or narrow-band UVB phototherapy or PUVA, given as for PLE, may be helpful [13,17,18], the latter preferably in bath form in children, and perhaps best after initial rash clearance with steroids or as below. Resistant cases, however, usually require oral thalidomide 50–100 mg nightly until clearance, adjusted thereafter to as low a dose as possible [13,19], although a high risk of teratogenicity and moderate risk of peripheral neuropathy necessitate extreme care in its use; 3–6-monthly nerve conduction studies generally preempt the latter [20]. Conjunctival manifestations may respond to topical ciclosporin [21], and preliminary work suggests topical tacrolimus or pimecrolimus may inhibit early skin lesions; severe disease in patients unsuitable for thalidomide may perhaps respond instead to oral ciclosporin or other immunosuppressive agent, an approach, nevertheless, not yet apparently reported.

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Hydroa vacciniforme

[J. Ferguson, pp. 24.16–24.17]

Definition. Hydroa vacciniforme (HV) is a rare acquired photodermatosis, usually with onset in childhood, and characterized by vesicle, crust and scar formation that follow exposure to sunlight.

Aetiology. The origin of this condition is unknown. Spring and summer exposure, particularly to UVA wavelengths [1], appears responsible. Recently, an association between HV and latent Epstein–Barr virus (EBV) infection has been proposed [2].

Pathology. Acute lesion histology is non-specific, showing a reticulate keratinocyte degeneration with spongiosis and a perivascular mononuclear cell infiltrate. Lesion biopsy days later shows ulceration, necrosis and capillary oedema followed by scarring [3]. Although monochromator testing is usually within normal limits, repetitive high-dose skin irradiation with a UVA source can induce papulovesicles [4] (Fig. 24.11).

Clinical features. Although the incidence is unknown, HV is a rare, usually sporadic, but occasionally familial [5] condition occurring equally in both sexes [6]. Presentation is usually during the first decade, but there is a late-onset variety [7]. Twelve to 24 h after exposure to direct or window glass-transmitted sunlight, pruritic, sometimes haemorrhagic vesicles and papules arise on an erythematous background, typically affecting the cheeks, ears, nose and hands (Fig. 24.12). As the lesions resolve, they enter a dry crusting phase followed by permanent scars, which can be disfiguring [8] (Fig. 24.13). In some children, acute episodes are accompanied by systemic malaise [3]. Rarely, eye involvement may take the form of anterior uveitis with corneal clouding and visual impairment [9]. HV-like lesions have been reported in association with T-cell lymphoma, and as EBV has been shown to be associated

Fig. 24.11 Papulovesicles following 10 J/cm^{-2} three times daily to mid-upper back skin.

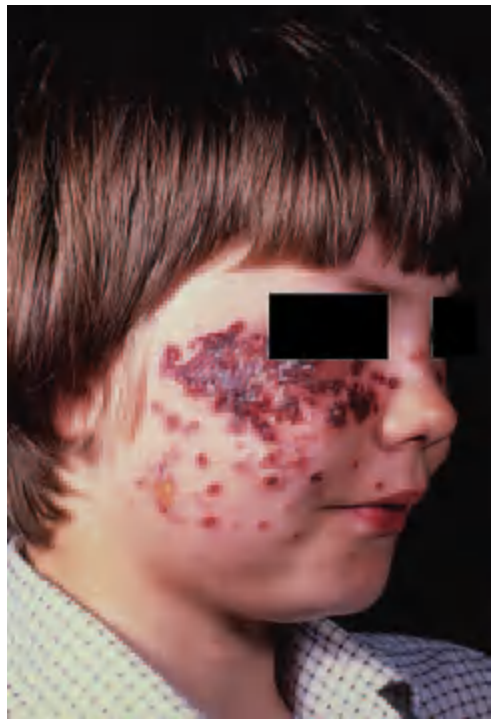

Fig. 24.12 Hydroa vacciniforme, showing vesiculation and crusting. (Courtesy of Dr M. Price, Brighton General Hospital, Brighton, UK.)

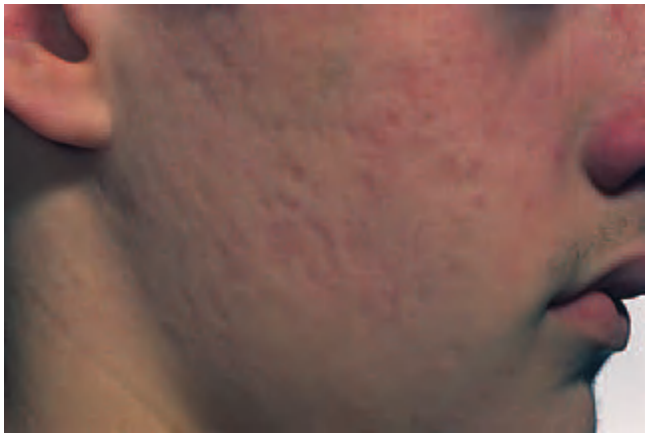

Fig. 24.13 Post-hydroa vacciniforme scarring.

with T-cell lymphoma there is interest in the relationship between EBV, HV and lymphoma [10].

In most cases, HV resolves spontaneously by adulthood, with a typical disease duration of 9 years [6]. In a few cases, disease activity persists undiminished, even into middle age [11].

Treatment. Photoprotection with appropriate clothing and a broad-spectrum sunscreen form the standard approach. If there is no response to photoprotection, springtime prophylactic therapy using broad-band UVB, narrow-band UVB or PUVA can be beneficial [6,12,13]. Although some anecdotal evidence exists to support the use of beta-carotene/canthaxanthin [14], azathioprine and antimalarial therapy, their true benefit is uncertain. Prophylactic fish oil may also be of help, although poor tolerance limits its use [15].

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Chronic actinic dermatitis

SYN. PHOTOSENSITIVITY DERMATITIS AND ACTINIC RETICULOID (PD/AR) SYNDROME

[J.L.M. Hawk, pp. 24.17–24.19]

Definition. Chronic actinic dermatitis (CAD) is a rare UVR- and rarely visible light-induced eczema of the exposed and, to a lesser extent, covered skin. There is often an associated, frequently airborne, contact dermatitis. It most commonly affects older men, but sometimes occurs in younger individuals with atopic eczema or human immunodeficiency virus (HIV)-infected patients. It is usually persistent, may be incapacitating, and is generally worse in summer. It may represent a contact dermatitis-like DTH reaction against endogenous photoinduced allergen.

Aetiology. CAD is an eczematous eruption clinically [1] and histologically [2], and is reproducible at all skin sites, in the absence of exogenous photosensitizer, by UVB, UVB and UVA, or rarely UVB, UVA and short visible irradiation [3]; UVA alone may also occasionally be responsible. Broad-spectrum and monochromatic exposures appear similarly effective, frequently at considerably lower than minimal sunburning doses. Furthermore, the often pseudolymphomatous clinical and histological appearances of severe forms of the condition [4,5], and the dermal infiltrate containing a predominance of CD8$^+$ T cells [5], resemble persistent allergic contact dermatitis [6,7], suggesting that CAD is similar, but by inference a response directed against cutaneous photoinduced endogenous antigen. This may presumably be the result of either direct UVR molecular absorption and change, or endogenous secondary photosensitization [8], a suggestion supported by the fact that albumin, for example, may become antigenic *in vitro* through photo-oxidation of its component histidine [9]. In addition, CAD often occurs in association with pre-existing widespread, often airborne, contact dermatitis to exogenous sensitizer or photosensitizer [10–13], or perhaps occasionally drug-induced photosensitivity [14]. Such reactions arguably enhance cutaneous immune function sufficiently during light exposure to enable putative endogenous photoantigen recognition. Alternatively, or in addition, chronic photodamage may conceivably impair UVR-induced cutaneous

immunosuppression such that endogenous UVR-induced skin photoantigen is more easily recognized, as apparently also occurs genetically in PLE [15]. Elderly outdoor workers or leisure enthusiasts [16] are most often affected, and their photo-aged skin may engender slower putative antigen removal, as well as easier associated contact allergen penetration, such that immune antigen recognition is further facilitated. Finally, CAD may occasionally develop in patients with long-standing PLE or endogenous eczema, and also in previously normal skin. As the disorder gradually develops [12], so too do the characteristic irradiation abnormalities of CAD. UVR molecular absorbers initiating the CAD rash have not been definitively identified, but DNA, RNA or a similar or related molecule may conceivably be involved in at least some instances; the CAD action spectrum in one patient series resembled that for sunburn inflammation [17], for which DNA is now considered a prime target [18].

Pathology [3,19]. There is epidermal spongiosis and acanthosis, sometimes with hyperplasia. A mononuclear cell infiltrate, predominantly perivascular and frequently dense, is present in the dermis. These cells sometimes have large hyperchromatic convoluted nuclei or show mitotic figures. In addition, there may be macrophages, eosinophils and plasma cells. In florid cases the appearances may be indistinguishable from those of cutaneous T-cell lymphoma.

Clinical features (Fig. 24.14) [3,20]. CAD occurs most commonly in temperate climates, and affects mostly elderly men of any race. Familial incidence does not occur. The condition may develop in previously normal skin, or following endogenous eczema, photo-allergic or allergic contact dermatitis, perhaps oral drug photosensitivity, occasionally PLE or, rarely, HIV infection [20]. In addition, allergic contact sensitivity to ubiquitous, often airborne, substances such as plant antigens, fragrances and topical medications often coexists. The eruption generally worsens in summer or after sun exposure, a relationship not always recognized by the patient, especially as marked or continuing irradiation may sometimes temporarily improve it. It is eczematous, patchy or confluent, markedly itchy, often lichenified, and in severe cases there are scattered or widespread, erythematous, shiny, infiltrated, pseudolymphomatous papules or plaques arising on a background of erythema, eczema or normal skin [7]. Exposed sites are predominantly affected, particularly the face, scalp, back and sides of neck, upper chest and dorsal aspects of forearms and hands. There are often sharp demarcations at lines of clothing, and sparing of skin creases, upper eyelids, finger webs and areas under the ear lobes, and sometimes too of geographically shaped, variable sites on the face or elsewhere. In addition, palmar and plantar eczema is not uncommon, eyebrow and scalp hair may be stubbly or lost, and erythroderma may occasionally supervene.

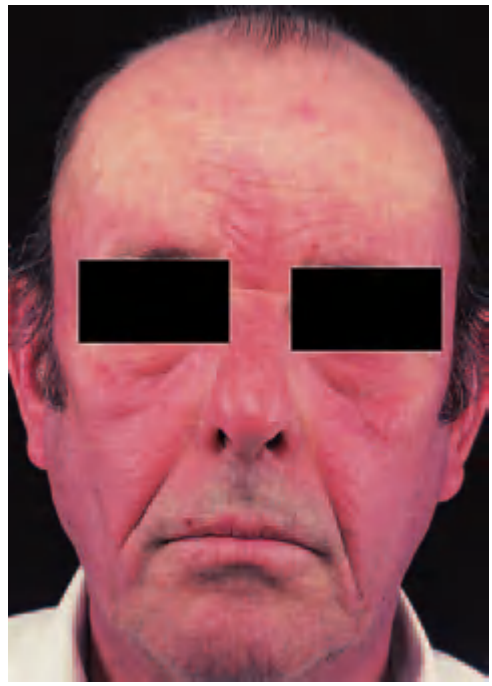

Fig. 24.14 Chronic actinic dermatitis, showing pseudolymphomatous infiltration of the face but sparing of the scalp.

Once established, CAD tends to persist over many years before not infrequent gradual resolution [21]. Malignant lymphomatous transformation has also been claimed [3], conceivably following chronic antigenic stimulation in long-standing untreated CAD, but this seems extraordinarily rare [21]. However, it does seem possible that very occasional malignant lymphomas may be markedly light-sensitive of themselves [22]. Pseudolymphomatous CAD induced by combined UVB, UVA and, occasionally, visible wavelengths has been known as 'actinic reticuloid' [4], eczematous CAD induced by UVB and UVA as 'photosensitivity dermatitis' [1], and by UVB alone as 'photosensitivity dermatitis' or 'photosensitive eczema' [23]. CAD arising in association with photoallergic contact dermatitis has also been known as 'persistent light reaction'.

Diagnosis. This is suggested by the typical clinical findings in conjunction with absent antinuclear antibodies and extractable nuclear antigen, and normal blood, urine and stool porphyrin concentrations. In addition, there are abnormal erythematous or eczematous responses on clinically normal skin to broad-band or monochromatic irradiation, generally at doses much lower than the normal sunburning MED. The provoking wavelengths are UVB in virtually all patients, UVA also in most, and visible light in addition in some. A small proportion, however, appear to react to UVA alone, although drug photosensitivity

must be carefully excluded in such instances. In cases of uncertainty, the histological findings, sometimes florid in severe cases, are generally helpful in confirming an eczematous response. Other eczemas of light-exposed areas, even those exacerbated by UVR exposure, are generally distinguished by their normal cutaneous irradiation responses, along with other evidence of the underlying disorder. In drug or chemical photosensitivity, there is often clear evidence of exposure to an inducing substance, and the eruption is generally not eczematous, unless the agent is topical and the rash therefore usually localized; in addition, cutaneous irradiation testing is usually normal or positive only to the UVA wavelengths. In cutaneous T-cell lymphoma, also reported as occasionally photosensitive, the clinical picture, histology and T-cell receptor gene rearrangement studies are generally definitive. Any light sensitivity and irradiation test abnormalities, usually principally in the UVA range, are also generally mild [24], except possibly in very occasional, markedly photosensitive cases [22]. Erythrodermic CAD must be distinguished from other erythrodermas, if necessary by irradiation skin testing after the eruption has resolved in a darkened room. Significant circulating Sézary cell numbers may also occur in such cases [25], but with a $CD4^+$: $CD8^+$ ratio generally much lower than in the malignant Sézary syndrome [26].

Treatment. It is essential to minimize exposure to UVR and, if necessary, visible light, even from fluorescent room lighting. Relevant contact allergens should also be avoided. However, computer and television screens are safe. Appropriate clothing cover and the use of non-irritating broad-spectrum high-protection sunscreens of low allergenic potential are also often helpful. However, these measures are rarely effective alone, and topical or intermittent oral steroid therapy are usually also necessary. For resistant disease, prolonged very low-dose PUVA or perhaps narrow-band UVB phototherapy may be needed in addition, or oral immunosuppressive therapy [27,28], as phototherapy is often poorly tolerated, especially initially, except under high-dose systemic and topical steroid cover. Thus, ciclosporin 3.5–5 mg/kg is usually effective within weeks [29], or azathioprine 1.0–2.5 mg/kg [30] or mycophenolate mofetil 25–40 mg/kg. In addition, topical tacrolimus has recently been reported as helpful [31].

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Solar urticaria
[J. Ferguson, pp. 24.20–24.21]

Solar urticaria (SU) may be primary (idiopathic) or secondary to porphyrias, phototoxic drugs and chemicals. Idiopathic SU is an uncommon wealing disorder induced by UVB, UVA and visible wavelengths.

Aetiology. SU is considered to be an allergic type 1 hypersensitivity response [1] mediated by histamine [2,3] and other agents. Some patients have a circulating factor (putative photoallergen), which has been reported to passively transfer the disease to normal individuals. Isolation of the transfer factor suggests it behaves like a globulin and has a molecular weight in the range of 25–1000 kDa. Provocation wavelengths, which vary between patients, may change during the disease course [4], and this suggests a range of photoallergens activated by UVB, UVA and visible light, separately or in combination. The finding of SU provoked by visible light should raise the possibility of a porphyria. In some cases, augmentation [5] by a different part of the spectrum is seen [6]; in others, visible wavelengths can inhibit provocation of urticaria [7]. The explanation of these phenomena is unknown.

Phototesting using monochromator or broad-band sources reveals immediate urticaria with a 24-h delayed erythema component. Knowledge of the wavelength dependency is important for management. If the condition is severe and unresponsive to treatment, intradermal testing with irradiated autologous serum and/or plasma may help indicate whether there might be a beneficial response to plasmapheresis. Where secondary SU is suspected, a careful drug history and tests to exclude porphyria are required.

Pathology. The histopathology of SU in provoked lesions shows at 5 min and 2 h a predominantly perivascular neutrophilic and eosinophilic infiltrate, with dermal oedema separating the collagen bundles. At 24 h, mononuclear cells predominate. In some, features of a vasculitis are seen [8–10].

Clinical features (Fig. 24.15) [11–14]. The incidence of idiopathic SU is unknown. It occurs in both sexes, with a slight female preponderance. It occurs at any age, but has a peak onset between 20 and 30 years [15]. It affects all races, although whether equally is unknown. Typically, the onset of disease is sudden, with most patients aware of tingling of sunlight-exposed skin, erythema and flare within minutes of visible radiation exposure. As with other urticarias, the symptoms and signs subside within a few hours, although rarely they may persist for 24 h [16], and they may be localized to fixed sites [17]. A minority of patients may only describe symptomatic erythema [18], with urticaria only evident on high irradiation dose testing. Sensitivity to the provoking wavelengths varies between patients, some requiring as little as 2–3 min of light exposure whereas others require an hour or more. When the condition is severe, it can pose great problems for the patient, particularly if visible wavelengths are involved, and if unresponsive to treatment it may induce a hermit-like existence.

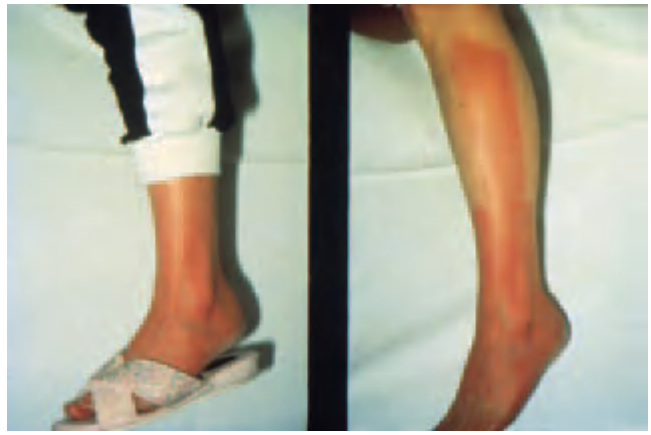

Fig. 24.15 Solar urticaria provoked by window glass-transmitted sunlight. The white tracksuit stripe has failed to prevent visible wavelength penetration.

The weal (and often the flare) reaction is typically confined to sunlight-exposed skin with a cut-off at the edges of clothing. Occasionally, patients may experience erythema, weal and flare under thin light-coloured clothing that allows the penetration of visible wavelengths. Lesions typically fade over the following hour or two, leaving an erythema that may persist for 24 h or more, and representing a delayed component. Following each episode, the skin may be refractory to further provocation for a number of hours. If the skin reaction is severe and extensive it may be associated with nausea, bronchospasm, light-headedness and syncope [19].

Idiopathic SU resolves spontaneously in approximately 50% of cases within 5 years [15]. The disease severity may run a fluctuating course, with periods of improvement and remission.

Treatment [20]. Although some mildly affected patients only require simple light-avoidance measures, which include advice on use of dark clothing and a broad-spectrum sun barrier, others may require regular antihistamines taken early in the morning prior to sunlight exposure. Approximately one-third respond completely to non-sedative H_1 blockade [21], with a further one-third having partial relief. The addition of an H_2 antagonist may provide further benefit [22]. It is curious that the response to antihistamine [21] may be drug- and dose-dependent.

Successful desensitization with photochemotherapy (PUVA) [23], UVA [24] and UVB (TL-01) [25,26] has been

reported, although benefit may be short-lived. Limited treatment to normally photoexposed sites can be combined with antihistamines, and should be preceded by a minimal urticarial dose (MUD) determination.

In the severely affected patient who is unresponsive to standard therapy, plasmapheresis should be considered, particularly if the intradermal test is positive [27,28], and this can be combined with PUVA [29]. Some, but not all, have had lasting benefit from this approach. Alternatively, ciclosporin [30] or intravenous immunoglobulin [31] may be of value. Other treatments that have been reported, but which probably are not of benefit, include beta-carotene [32] and antimalarials [33].

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DNA repair-defective diseases (see Chapter 12)

Drug- and chemical-induced photosensitivity: exogenous [1,2]

[J. Ferguson, pp. 24.21–24.23]

Abnormal skin reactions to sunlight and artificial sources of UV and visible radiation induced by photosensitizing drugs and other chemicals are often labelled as exaggerated sunburn and therefore underdiagnosed. Such reactions are subdivided, according to route of administration, into systemic and topical.

Aetiology. Most photosensitivity reactions involve oxygen in a variety of ways to produce toxic photosensitizer and substrate radicals.

Most systemic photosensitizers are phototoxic (non-immunologically mediated) in mechanism. The subcellular targets vary for each drug and photoactive metabolite, and the resulting clinical spectrum of reactions may mislead the unwary. For the drug prescribing pattern in the UK and Europe, the agents most commonly responsible for photosensitivity are listed in Table 24.4 [3]. Although phototoxicity is said to occur in any individual providing there is enough phototoxin and appropriate irradiation, there is an idiosyncratic variant in which a few individuals taking the drug develop the problem whereas the great majority are unaffected. This unexplained phenomenon may account for the frequent sporadic reports of reactions attributed to a surprisingly large range of drugs. Other less common mechanisms include drug-induced lupus, pellagra and photoallergy [4]. Photoallergy is usually associated with topical exposure to agents such as non-steroidal anti-inflammatory drugs (NSAIDs), fragrances and sunscreens. Topical phototoxicity has been reported with dyestuffs and psoralen-containing plants (phytophotodermatitis). Contact with the sap of members of the Umbelliferae and Rutaceae plant families followed by sunlight exposure will produce typical clinical features

Table 24.4 A general classification of photosensitizers.

Exogenous
Drugs: antibiotics; major tranquillizers; antidepressants; anti-inflammatories; diuretics; antiarrhythmics/antihypertensives
Plant materials: psoralens
Dyestuffs: methylene blue, toluidine blue xanthenes, fluorescein, eosin, anthraquinones
Polycyclic hydrocarbons: pitch, coal tars, anthracene, acridine, fluoranthrene
Perfumes and cosmetics: musk ambrette, 6-methylcoumarin
Sunscreens: benzophenones, dibenzoylmethanes, cinnamates, PABA* esters
Miscellaneous: fabric whiteners; quinoxaline-*N*-dioxide
Endogenous
Porphyrins

* Para-aminobenzoic acid.

of linear blistering and late onset pigmentation as seen in the phytophotodermatitis termed 'strimmer's dermatitis'. Our knowledge of photoactive drugs is obtained from anecdotal case reports, post-marketing surveillance and, more recently, controlled trials required by regulatory authorities.

Clinical features. Acute phototoxic reactions to drugs and chemicals can present with an immediate burning sensation in light-exposed sites, accompanied by erythema and, on some occasions, urticaria. Usually, these agents (Table 24.5) also produce a delayed erythema component, which may blister. Some follow the sunburn time-course, with painful erythema and blistering at 24–48 h, whereas the newest reported group, the calcium-channel antagonists, produce an exposed-site telangiectasia following years of therapy. Psoralens, whether by the topical or oral route, produce erythema delayed by 72–96 h. Pseudoporphyria, which clinically mimics porphyria cutanea tarda or variegate porphyria, is caused by a group of agents that damage the dermal–epidermal junction, probably by recurrent low-grade phototoxicity. Porphyrin levels are normal. Most photoactive drugs are UVA-dependent. With some, such as quinine and thiazides, responsible wavelengths extend into the UVB and visible regions, and the most recent intravenous anticancer photodynamic therapy agents (Photofrin and Foscan) have a UVA and visible wavelength dependency.

Post-phototoxic pigmentation, which can persist for years, is a particular feature of amiodarone, chlorpromazine and tetracyclines. With photomutagenic psoralens, multiple phototoxic episodes can result in skin malignancy [5]. Persistent photosensitivity (persistent light reactor) is a rare and little studied complication.

Topical drug usage varies between countries. Photoallergic dermatitis caused by NSAIDs, although rare in the UK, is much more common in Spain and Portugal. Drug-induced LE, although uncommon, can occur. Major topical photoallergens are listed in Table 24.6.

Pellagra rarely can be precipitated by isoniazid, phenytoin and other drugs.

Prognosis. The duration of photosensitivity after stopping a photoactive drug also varies. With most psoralens it is a matter of hours, whereas photosensitivity resulting from fluoroquinolones lasts 2–3 days. It may last for up to a year with amiodarone, thiazides and quinine, and the postphototoxic pigmentation can last even longer.

Investigation. Suspected drug-induced photosensitivity is best investigated with phototesting 'on' and after a

Table 24.5 Major patterns of cutaneous phototoxicity.

Skin reactions	Photosensitizers or diseases
Prickling or burning during exposure; immediate erythema; oedema/urticaria with higher doses; sometimes delayed erythema/hyperpigmentation	Coal tar; pitch; anthraquinone-based dyestuffs; amiodarone; chlorpromazine; erythropoeitic protoporphyria; Photofrin; Foscan
Exaggerated sunburn	Chlorothiazides; quinine; demethylchlortetracycline
Telangiectasia and angiomas	Calcium-channel antagonists
Late-onset erythema; blisters with slightly higher doses; low exposures—hyperpigmentation only	Psoralens; phytophotodermatitis
Increased skin fragility giving blisters with trauma	Nalidixic acid, furosemide, tetracycline, NSAIDs, amiodarone

Table 24.6 Major reported topical photoallergens.

Sulfonamides/sulfonylureas	Sulfanilamide; tolbutamide; chlorpropamide
Phenothiazines	Promethazine; chlorpromazine
Furocoumarins	5- and 8-methoxypsoralen
Fragrances	6-methylcoumarin; musk ambrette
Sunscreens	Benzophenones; PABA esters; dibenzoylmethanes; cinnamates
NSAIDs	Piroxicam; ibuprofen; naproxen

period 'off' the drug. Clinical and phototest improvement support the diagnosis. If drug-induced lupus is suspected, lupus serology and histology will help establish that diagnosis. Photopatch testing for photoallergy should be conducted when a topical photosensitizer is suspected.

Treatment. The simplest and most effective measure is to replace the offending drug with a non-phototoxic alternative. Although this is usually straightforward, with some, such as amiodarone, it may not be possible. Reduction in drug dosage and use of an appropriate broad-spectrum sunblock and, on occasions, UVB or PUVA desensitization may be required.

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Drug- and chemical-induced photosensitivity: endogenous—the cutaneous porphyrias

(see Chapter 57)

Dermatoses exacerbated by UVR

[J.L.M. Hawk]

Certain dermatoses not initiated by UVR exposure may be exacerbated by it (Table 24.7) [1,2]. Immunological events associated with their underlying pathogeneses are perhaps modified in some cases, and pre-existing inflammation exacerbated in others. Precise mechanisms, however, have only rarely been addressed [1]. The underlying disease may on occasion be significantly worsened, even if only mild to begin with, and this is particularly the case in seborrhoeic [2] or atopic eczema, which in some countries represent a relatively high proportion of all photodermatoses [3]. More usually, however, the disorder may be unaffected or more likely improved by irradiation. If light exacerbation does occur, the eruption most commonly develops or worsens at all exposed sites, less often only at those typical of the disorder. Treatment is by restriction of UVR exposure, use of appropriate clothing cover, application of high-protection sunscreens and assiduous therapy of the underlying disorder, even if mild [1,2]. The last measure alone can frequently result in resolution of the light sensitivity [2]. If such measures are insufficient, courses of low-dose UVB or PUVA therapy (as for PLE) may be carefully tried in conditions that usually respond to such treatment—for example, seborrhoeic or atopic eczema and psoriasis—but not in disorders such as cutaneous LE or dermatomyositis, in which the aggravation of systemic features is a potential severe hazard.

Table 24.7 Dermatoses sometimes aggravated by sunlight exposure.

Acne
Atopic eczema
Bullous pemphigoid
Carcinoid syndrome
Cutaneous T-cell lymphoma
Dermatomyositis
Disseminated superficial actinic porokeratosis
Erythema multiforme
Familial benign chronic pemphigus (Hailey–Hailey disease)
Granuloma annulare
Hartnup syndrome
Herpes simplex
Keratosis follicularis (Darier's disease)
Lichen planus
Lymphocytic infiltrate of Jessner
Lupus erythematosus
Pellagra
Pemphigus
Pemphigus foliaceus (erythematosus)
Pityriasis rubra pilaris
Psoriasis
Reticular erythematous mucinosis (REM) syndrome
Rosacea
Seborrhoeic eczema
Smith–Lemli–Opitz syndrome
Transient acantholytic dermatosis (Grover's disease)
Viral infections

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Clinical evaluation of the patient with suspected cutaneous photosensitivity

[J.L.M. Hawk, pp. 24.23–24.24]

Patients with photosensitivity usually present with intermittent or persistent abnormalities of light-exposed areas, or rarely with generalized erythroderma. Those with inter-mittent problems are more likely to attribute the eruption to sunlight. If they do not, as is often the case in individuals with a persistent abnormality or erythroderma, careful history taking is essential, first to identify light as the likely cause, and then to determine the probable specific diagnosis. Patient details generally relevant for this process are age at disease onset, gender, family history, prior sunlight sensitivity, occupation, leisure activities and systemic or topical substance use, and

information on the eruption required includes its seasonal behaviour, exposure duration for elicitation, latent interval between exposure and onset, duration, occurrence through window glass or clothing, associated systemic symptoms, patient-described morphology and distribution. Thus, young women most commonly suffer PLE, women or girls AP, children of either sex HV, xeroderma pigmentosum (XP) or erythropoietic protoporphyria (EPP), and elderly men or individuals with atopic eczema CAD. A family history of photosensitivity is often present in PLE, AP, XP and the porphyrias. CAD is more usual in outdoor leisure enthusiasts exposed simultaneously to sunlight and airborne contact allergens. Disease deterioration despite sunscreen use suggests possible sunscreen contact dermatitis, although this may also occur not infrequently in PLE. Development of an eruption within minutes with resolution in approximately an hour suggests SU or photosensitivity to drugs such as amiodarone, and occurrence within 20 min to several hours with resolution over days suggests PLE, HV, EPP, XP, subacute cutaneous lupus, other light-exacerbated dermatoses, or other drug photosensitivity such as thiazide diuretics. Systemic malaise occasionally occurs in PLE, HV, SU or cutaneous lupus. Reactions through window glass or clothing suggest a disease action spectrum including the UVA wavelengths, which is possible in most photodermatoses except normal sunburn and XP.

The morphology of lesions described by PLE patients is of variable-sized, raised, itchy, red or skin-coloured, often clustered, spots or blisters, affecting exposed areas, and in HV, blistering with scarring is reported. SU features raised itchy weals. In EPP and amiodarone drug photosensitivity, a severe burning sensation without visible signs is usual, although with prolonged exposure, firm, colourless or pink diffuse swelling, rarely with scattered blisters, may occur in the former. In most other drug-induced photosensitivity and some cases of XP, exaggerated sunburning responses are described, often peaking in XP later than normal at 2–3 days. In light-exacerbated dermatoses, the morphology reported generally suggests the underlying disorder; in subacute cutaneous LE, however, concomitant PLE is also rarely possible [1,2].

Any eruption generally affects some, rarely all of the forehead, nose, upper cheeks, point of chin, ear rims, back and sides of neck, upper chest, dorsa of hands and feet, and limb extensor surfaces; covered sites may also be affected to a lesser extent. However, the light-protected hair fringe area, upper eyelids, finger webs, skin creases and sites beneath the nose, lower lip, chin and earlobes are often spared, except potentially with concomitant airborne contact dermatitis. Persistent excoriated papules are suggestive of AP, an eczematous eruption suggests CAD, especially with associated airborne allergen exposure, or light-exacerbated atopic or seborrhoeic eczema, and skin fragility, blistering and superficial scarring a hepatic porphyria or pseudoporphyria, particularly following drug, excessive alcohol or frequent sunbed exposure. Light-associated erythroderma suggests CAD.

Following such assessment, a specific diagnosis is generally already strongly suspected, but absolute certainty usually requires at least some further investigation, as described below.

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Further investigation of the patient with cutaneous photosensitivity

[J. Ferguson]

Patients suspected of photosensitivity should have their antinuclear factor and extractable nuclear antigen (anti-SSA [Ro] and -SSB [La]) assessed. When appropriate, the cutaneous porphyrias can be excluded by spectrofluorimetry and, if necessary, by quantitative assessment of blood, urine and stool porphyrins. Histological examination of lesional or provoked skin lesions may be helpful, but is rarely diagnostic.

After taking a standard photodermatology history, investigation is to some extent disease-specific. Photobiology units often use a structured investigational referral form identifying phototest procedures such as monochromator, solar simulator and broad-spectrum larger area provocation testing [1]. As with all optical test equipment, quality control with calibrated metering and spectroradiometry is essential. Use of such devices is followed by immediate and delayed readings, and abnormality is detected by comparison with normal data. Provocation testing of larger skin areas is particularly useful in PLE and AP.

If the morphology is eczematous and an exogenous chemical is suspected, patch and photopatch testing will help identify the responsible allergen or photoallergen. Recently, photopatch testing has been standardized within the UK [2], where the most common photoallergens are the organic sunscreens. In the genophotodermatoses, assessment of DNA repair, DNA and RNA synthesis rates, cell survival post-UVA irradiation, sister chromatid exchange frequencies and, more recently, cell mutation studies, may establish the diagnosis.

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Chapter 25

Virus Infections

J.C. Sterling

Introduction

A virus particle, or virion, consists of a length of nucleic acid, either RNA or DNA, within a protein shell, the capsid. The genetic information is sufficient to encode proteins involved in viral replication and production of the protective coat, but requires host cell ribosomes for translation. This absolute dependence on the host is the distinguishing feature of viruses.

A simple classification of viruses that cause illness in humans and their relationship to the skin is given in Table 25.1. This classification is followed throughout the chapter. Other viral-associated skin diseases, including Gianotti–Crosti syndrome and pityriasis rosea, a condition of unknown but possible viral aetiology, are also discussed.

General pathology of viral infections

Pathogenesis of viral disease

For a virus to produce infection, it must gain entry into a susceptible cell within an appropriate host. Many viruses, particularly those producing systemic infection, enter the body via mucous membranes after inhalation, ingestion or contact. The skin can act as a portal of entry, although this usually depends on some breach of the barrier function of the integument, for instance a scratch or fissure or by direct inoculation. Attachment to the cell surface by means of a receptor is followed by entry of the virion into the cell, by pinocytosis or phagocytosis. Viruses differ in the range and type of cells which they can infect; host specificity and tissue tropism are hallmarks of viral infections. For example, poliovirus can infect neurones and is called a neurotropic virus, while human papillomaviruses have a tropism for epithelial cells. A cell in which a particular virus can replicate is described as permissive for that virus. After entry into the cell, pre-existing cell enzymes

Table 25.1 A classification of human viruses.

Nucleic acid	Family	Size (nm)	Viruses	Skin changes	Main associated disease
DNA-ds	Poxviridae	200 × 300	*Ortho*	+	Generalized vesicular eruption
			Variola	+	
			Monkeypox	+	Localized vesicular eruption
			Vaccinia	+	
			Cowpox	+	
		150 × 200	*Para*		Localized benign cutaneous tumours
			Orf	+	
			Pseudocowpox	+	
			Yatapox	+	Localized benign cutaneous tumours
			Molluscipox	+	Generalized benign cutaneous tumours
	Herpesviridae	180–250 enveloped (100 naked)	α Herpes simplex	+	Vesicles/encephalitis
			α Varicella	+	Chickenpox/shingles
			β Cytomegalovirus	+	Congenital/in immunocompromised
			γ Epstein–Barr	+	Infectious mononucleosis
			β Human herpesvirus 6	+	Roseola infantum/exanthem subitum
			β Human herpesvirus 7	+	Macular eruption
			γ Human herpesvirus 8	+	Kaposi's sarcoma
			α B virus (monkey)	+	Encephalomyelitis
	Adenoviridae	70 naked	Subgenera A–F	–	Respiratory tract infection Conjunctivitis Haemorrhagic cystitis Gastroenteritis
	Papovaviridae	44 naked	Polyomavirus	–	Ureteric obstruction
			BK		
			JC	–	PMLE
	Papillomaviridae	50 naked	Human papillomavirus (> 77 types)	+	Warts, CIN, cervical cancer
DNA-ds*	Hepadnaviridae	42 naked	Hepatitis B	+	Hepatitis
DNA-ss	Parvoviridae	22 naked	Human parvovirus (B19)	+	Erythema infectiosum/aplastic crisis
RNA-ss(+)	Retroviridae	100 enveloped	Oncoviruses	+	T-cell leukaemia
			HTLV-1, HTLV-2		Tropical spastic paraparesis
			Lentiviruses	+	AIDS
			HIV-1, HIV-2, HIV-0		
	Coronaviridae	80–150 enveloped	Coronavirus	–	URTI
	Togaviridae	42 enveloped	Rubella	+	German measles, arthralgia
			Alphaviruses	+	Rash, arthralgia
			Ross River	±	Encephalitis
			Sinbis		
			EEE, WEE, VEE		
	Flaviviridae	42 enveloped	Hepatitis C	–	Hepatitis
			Dengue	+	Febrile illness
			Japanese encephalitis	–	Encephalitis
			Yellow fever	–	Hepatitis
			Tick-borne encephalitis	–	Encephalitis
	Caliciviridae	38 naked	Calicivirus (Norwalk)	–	Gastroenteritis
			Hepatitis E	–	Hepatitis

(*continued*)

Table 25.1 (*cont'd*)

Nucleic acid	Family	Size (nm)	Viruses	Skin changes	Main associated disease
	Picornaviridae	27 naked	Rhinovirus	–	URTI
			Foot and mouth (cattle)	+	
			Enterovirus		
			Polio	–	Polio
			Coxsackie A	+	Meningitis/herpangina
			Coxsackie B	+	Meningitis, Bornholm
			Echovirus	+	Meningitis
			Hepatitis A	(–)	Infectious hepatitis
RNA-ss(–)	Rhabdoviridae	70 × 180 enveloped	Rabies Lyssa	–	Rabies
			Vesicular stomatitis virus	+	Flu-like illness
	Filoviridae	Filamentous	See Table 25.4		
	Paramyxoviridae	150 × 300 enveloped	Measles	+	Measles
			Mumps	–	Mumps
			Parainfluenza	–	RTI
			Respiratory syncytial virus	(+)	RTI
8 segments	Orthomyxoviridae	> 100 enveloped	Influenza A, B, C	–	Flu
2 segments	Arenaviridae	100 × 300 enveloped	Lymphocytic choriomeningitis (and see Table 25.4)	–	Meningitis
3 segments	Bunyaviridae	100 enveloped	See Table 25.4		
RNA-ds 11 segments	Reoviridae	70 naked	Rotavirus	–	Gastroenteritis

ds, double stranded; ss, single stranded; ss(+), single stranded (plus strand); ss(–), single stranded (minus strand); ds*, incomplete ds; +, skin changes frequent; (+), skin changes less frequent; (–), skin changes rarely reported; –, skin changes not recognized; CIN, cervical intraepithelial neoplasia; PMLE, progressive multifocal leukoencephalopathy; RTI, respiratory tract infection; URTI, upper respiratory tract infection.

remove or damage the capsid sufficiently for the nucleic acid to emerge.

The next stage depends on the nature of the virus. In relatively simple ones, like enteroviruses, the RNA acts as a messenger, is infectious on its own and is immediately translatable by host ribosomes into viral proteins. More complex RNA viruses, such as influenza, have non-infectious RNA, sometimes called 'negative-strand' RNA, which has to be transcribed into messenger RNA (mRNA) by a polymerase enzyme carried in the virus itself. RNA tumour viruses contain a 'reverse transcriptase' enzyme which synthesizes DNA from the viral RNA template. DNA viruses are generally more complex and are able to transcribe mRNA from their DNA using either cell polymerase (e.g. adenoviruses) or viral polymerase (e.g. vaccinia). At the same time, replication of the viral nucleic acid also occurs.

A variety of proteins—regulatory, enzymic and structural—are produced and these, together with the products of cell damage, probably contribute to the local and general response to the infection. The time required for new virus production in acute infections is measured in hours and the number of new virions in thousands per cell. Newly produced virions can invade adjacent cells or be carried via the bloodstream and so the infection spreads. During this process the cell itself may be destroyed by a *lytic infection* (e.g. enterovirus and herpes simplex) or damaged transiently (e.g. myxovirus). With time, an immune response develops against the virus particles and processed viral proteins, which can lead to containment and clearance of the infection.

Not all virus infections end in this fashion. Some viruses infect cells that apparently remain normal and may multiply while virus replication continues within, i.e. *persistent infection*. When persistently infected cells produce no infectious virus because the replication cycle is arrested, the virus is said to be *latent*. From time to time, a latent virus can become active—*reactivation*—new virions are produced and other cells are infected. This process can result in clinical signs and symptoms as in the case of cold

sores (reactivated herpes simplex) and shingles (reactivated varicella-zoster). Other viruses cause cell proliferation, for example poxviruses and human papillomaviruses. Viruses can also be implicated in the process of carcinogenesis as in the development of cervical cancer and hepatoma.

Exanthems of viral infections

Widespread exanthems may be a manifestation of viral infections that cause a viraemia. An attempt to explain the different types of viral exanthem (Table 25.2) can be made by tracing the sequence of events which follows the arrival of blood-borne virus particles in the skin, where they lodge in dermal capillary loops. Some microorganisms (e.g. some togaviruses, poxviruses and rickettsiae) can replicate in capillary endothelium, causing damage directly or by a type 3 (Arthus) reaction that results in infarcts and haemorrhages. The great majority of viruses, however, act as inert foreign particles, reacting with circulating antibodies and sensitized lymphocytes to produce inflammation. Circulating immune complexes of antibody and viral antigens also localize in dermal blood vessels and are responsible for the rashes in many virus infections, for example human parvovirus. The complex cascade of inflammation in the dermis results in erythematous macules and papules.

In the case of most RNA viruses there is no replication, these are the only reactions and the intruding particle is removed (e.g. echoviruses, coxsackie A, most togaviruses and rubella). A few RNA viruses are, on occasion, able to enter actively metabolizing epidermal cells and replicate for a limited time, with cytolysis and production of a vesicular lesion (e.g. the vesicular exanthem of coxsackie A and some rarer vesicular exanthems).

Replicative ability in epidermal cells is mainly a feature of the DNA viruses, which may explain why this group contains those viruses capable of replication after direct inoculation of the epidermis. Vesicles and pustules result from viral replication in the epidermis, where the focal necrosis is followed by an immune response and

Table 25.2 Viral exanthems.

Type of rash	Pathogen associated
Macular	Rubella Echovirus (esp. 2, 4, 6, 9, 11, 16, 18) Coxsackie A (esp. 4, 5, 6, 9, 16) and B (esp. 5) EBV (infectious mononucleosis) Human herpesvirus 6 (roseola) Human herpesvirus 7
Maculopapular	Togavirus Echovirus (esp. 6, 9) Measles Human parvovirus (B19) (erythema infectiosum)
Maculopapular–vesicular	Coxsackie A (occasional 5, 9, 10, 16) Echovirus (occasional 4, 9, 11) Marburg
Maculopapular–petechial	Togavirus (esp. Chikungunya) and bunyavirus haemorrhagic fevers (including Lassa)
Urticarial	Coxsackie A9 (occasional) Hepatitis B (occasional)
Vesicular	Herpes simplex virus Hand, foot and mouth disease (Coxsackie 16, 5) Vesicular stomatitis virus
Vesiculopapular	Varicella-zoster
Papulovesiculopustular	Vaccinia Variola Cowpox
Papulovesicular	Orf Milker's nodule
Papular	Molluscum contagiosum Warts Gianotti–Crosti

The type of rash given is the most common clinical association but it may in some patients overlap with the next category.
EBV, Epstein–Barr virus.

infiltration with leukocytes. Vesicular lesions are caused by poxviruses, herpes simplex, varicella-zoster and some coxsackievirus infections. The cell proliferation caused by human papillomaviruses and molluscum results in localized tumours.

The antibody production that produces local inflammatory lesions may serve to prevent further dispersal of infection by the bloodstream. However, the cell-mediated immune response is probably the major local inflammatory factor, the means of containment and healing of the infection. When it is not competent, as in immunosuppression or immunodeficiency, there may be serious spread of the lesions, as seen in vaccinia and varicella. The factors which influence the areas of distribution of the rash and the sequence of affected regions are imperfectly understood [1]. Where there is an area of capillary trauma, caused for example by intermittent pressure or a pre-existing area of inflammation, viruses will localize, but the caudal progression in rubella and the centripetal distribution in varicella are unexplained.

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Laboratory diagnosis [1–6]

The extent to which laboratory procedures are helpful depends on the nature of the infection and locally available resources. The general condition of the patient should always be considered and it is stressed that in early pregnancy any rash should be investigated to establish the possible risk to the fetus from rubella, parvovirus or other congenital infections. A considerable expansion of technical methods is taking place and clinicians are urged to discuss current local facilities with their microbiologists.

Some rapid methods are now feasible, using fluorescence microscopy, electron microscopy and immunological techniques, so that laboratory confirmation for such diverse conditions as orf and hepatitis B is possible on the day of receipt of specimens. Tissue culture can give an answer in 24 h in herpes simplex. At the other end of the time scale, especially where animal inoculations are required, a diagnosis may take weeks. When a particular infection is suspected, guidance on the most useful laboratory tests can be obtained from the section on diagnosis given for each infection. Broadly, the following groups of tests are available.

1 Virus isolation, usually done in cell cultures but occasionally in fertile eggs or laboratory animals.
2 Examination of histological specimens for features typical of a virus infection, for example inclusion bodies, koilocytes.
3 Visualization of virus by electron microscopy.
4 Detection of viral antigens by immunological techniques, for example fluorescent antibodies, radioimmunoassays.
5 Detection of viral nucleic acid by molecular techniques such as hybridization or polymerase chain reaction (PCR).
6 Serological tests to detect seroconversion, rising antibody titres or specific antibodies, for example IgM, low-avidity IgG.

Specimens for virus isolation are most likely to be positive if taken early in the illness. After the onset, the amount of live virus declines, especially when accessible to circulating antibody.

Specimens should be sent to the laboratory with the minimum of delay. Throat swabs should mop up the maximum nasopharyngeal material and the broken-off swab head should be immersed in a virus-transport medium, kept cool if in transit for more than 1 h.

Cerebrospinal fluid should be transported rapidly, preferably chilled.

Vesicle fluid is best collected in a glass capillary, which can have one end sealed but not so as to heat the fluid. An alternative is to use a sterile disposable hypodermic needle and transport it in its plastic container. A swab of vesicle fluid transported as for a throat swab is also valuable. Small biopsies from proliferative skin lesions are best transported in medium. Crusts are sent dry in a sterile bottle.

Urine is of limited value; as a special transport medium may be needed, arrangements should be made with the laboratory. Faeces should be sent as a few grams in a sterile container.

The fraction of blood—white cells, plasma or serum—most suitable for PCR varies according to the viral nucleic acid to be detected. Blood for togavirus isolation must be chilled and reach the laboratory quickly. It is best processed without delay or rapidly frozen below −40°C because of inactivation of virus by antibody.

If smallpox, Lassa fever, Marburg disease or haemorrhagic fevers are suspected, consult both the laboratory director and the local community physician before any specimens are taken.

Serological tests

Two specimens of clotted blood (5–10 mL each) should always be taken to achieve an unequivocal diagnosis in infections for which serology is available. The first must be taken as soon after the onset of symptoms as possible in order to have serum before appreciable antibody production has taken place. The second should be taken after a considered interval, depending on the type of infection. In general, 10 days is optimal, but when the antibody response immediately follows the rash as in rubella, 5 days may suffice, provided the first blood was taken on the day of eruption of the rash.

It is a long-established convention that a fourfold or greater rise in titre between acute and convalescent sera is

diagnostic. Because of technical variations it is customary to titrate both sera in parallel so that comparison of titres is accurate. Interpretation has to take into account possible anamnestic rises caused by organisms with some antigenic similarity.

Examination of a single serum may provide strong presumptive evidence of infection when it demonstrates a high relevant antibody titre, but this can be quite misleading at times as the particular antibody level may antedate the infection under consideration. The demonstration of specific IgM or IgA antibody in a single acute serum is also of diagnostic value in rubella and other infections. Unfortunately, in human immunodeficiency virus (HIV) infections and many immunodeficient or immunosuppressed people, serological responses to infection are unpredictable and cannot be relied upon for diagnosis.

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Poxviruses

The poxviruses are the largest animal viruses and are just visible by light microscopy. They are complex double-stranded DNA viruses that replicate in the cytoplasm where they produce eosinophilic inclusion bodies (*Guanieri bodies*). They are generally resistant to physical damage; some, for example variola, have remarkable resistance to drying and can remain viable for months in crusts. Spread is mainly by direct-contact inoculation, with droplet spread in some, for example variola, which can produce respiratory tract lesions. Some grow readily in eggs and tissue culture, others not at all.

The human is host for four genera.

1 Orthopoxvirus: variola (smallpox), vaccinia, monkeypox and cowpox, which are ovoid, 300 × 250 nm.
2 Parapoxvirus: orf and milker's nodule viruses, which are cylindrical, 260 × 160 nm.
3 Molluscipoxvirus: molluscum contagiosum, intermediate in structure, 275 × 200 nm.
4 Yatapoxvirus: tanapox virus.

Smallpox

Smallpox infection is now eliminated from the world and routine vaccination against it has been abandoned. Eradication of smallpox was accepted at the 23rd World Health Assembly in May 1980. A review of this historic development is provided elsewhere [1]. The last case of smallpox in the UK occurred in Birmingham in 1978 as a result of a laboratory accident. The last case in an endemic area was in October 1977 in Somalia.

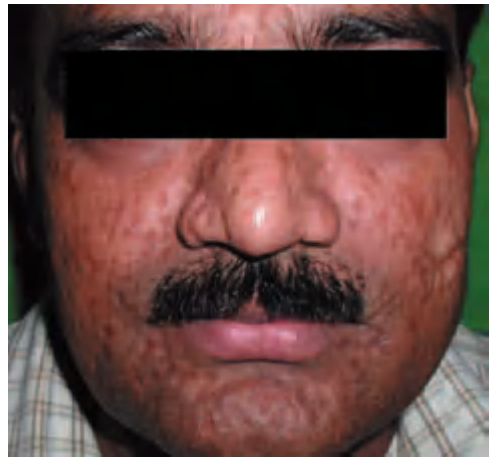

Fig. 25.1 Scarring of face following smallpox infection. (Courtesy of Dr S.B. Verma, Baroda Skin Clinic, Baroda, India.)

The recent global terrorism has reawakened concerns that the virus could be released as a biological weapon. This has led to a rapid increase in the number of medical and military personnel receiving vaccinia vaccination and an awareness of the clinical features of smallpox infection.

Clinical features [2,3]. After an incubation period of 10–14 days, a high fever with malaise, headache and backache are the first symptoms of smallpox. Within 1–3 days a macular eruption develops, which evolves over about 3 days into a rash of tense vesicles and then pustules. The eruption usually starts on the face and spreads caudally, usually affecting the extremities more than the trunk. The palms and soles are frequently affected. Lesions within an area are at the same stage. After about a week, the lesions dry, scab over and finally heal. There is frequently skin scarring following recovery, which can be marked and is still recognized in areas of the world where the infection was last evident (Fig. 25.1).

The severity of smallpox is variable. Over one-third have severe disease and mortality is between 25 and 40% of those affected.

Diagnosis. The most likely differential diagnoses are chickenpox and Kaposi's varicelliform eruption. Laboratory identification of smallpox from blister fluid is made only by designated laboratories. The virus is recognizable as an orthopoxvirus by electron microscopy and can be definitively identified by PCR amplification.

Treatment. There is no specific antiviral agent of proven efficacy for smallpox. Treatment is supportive. Strict isolation procedures must be observed and contacts of any infected individual traced as quickly as possible.

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Vaccinia

Vaccinia virus, a distinct entity now named poxvirus officinalis, is unique in that it does not occur naturally but is the first stable virus to have resulted directly from human activity in the serial propagation of viruses for human inoculation. Antigenically it closely resembles variola and is invaluable for vaccination against smallpox; culturally it resembles cowpox. It could be a mutant of either, but as adaptation of variola to growth on calf skin has not succeeded, opinion in general favours a mutant of cowpox. Buffalopox is considered to be a strain of vaccinia virus that has spread to these animals by farmers and has since evolved, necessitating classification as a subspecies. It is found in buffalo herds in certain areas in India and may cause bullous or crusted lesions in buffalo farmers [1]. Several severe infections have been reported from India in people handling buffaloes.

Vaccinia virus can potentially be used as a carrier of genes for protective antigens of other pathogenic microorganisms (recombinant vaccinia viruses), and it is used in some specialized laboratory research. It is recommended that vaccination should cease except for investigators at special risk [2]. Vaccination of military and some medical personnel continues because variola could be used in biological warfare. It is worth remembering that vaccination is not without risk. Reported complications of vaccination characterized by abnormal skin lesions are described below.

1 Generalized vaccinia (Fig. 25.2): after 6–9 days a generalized rash develops as a result of the brief viraemia following successful vaccination. Recovery is the rule.

2 Accidental infection: the result of autoinoculation from the site of vaccination to another part of the body (e.g. eye), or inoculation of another person.

3 Eczema vaccinatum: this occurs in people with atopic eczema or a history of past eczema. Lesions occur on eczematous areas of skin about 5 days after exposure to the virus. Apparently healthy skin may also be involved. The condition is associated with high fever, lymphadenopathy and about 5% mortality rate.

4 Progressive vaccinia: the lesion at the site of vaccination fails to heal in immunodeficient people. Instead it enlarges progressively. Secondary lesions develop and they also enlarge. Without antiviral treatment there is usually a fatal outcome. The incidence of progressive vaccinia was about one per million vaccinations in 1968 in the USA [3].

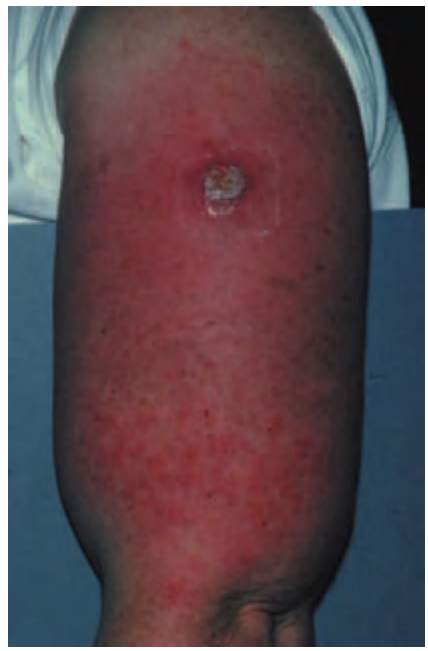

Fig. 25.2 Vaccinia: vaccination site with generalized spread. (Courtesy of Addenbrooke's Hospital, Cambridge, UK.)

5 Encephalomyelitis can also rarely complicate vaccination.

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Monkeypox

Human monkeypox is an emerging viral infection in tropical Central Africa. Apart from variola, it is the only other member of the Orthopoxvirus genus to cause significant infection in humans. Monkeypox in humans was not recognized until 1970 and since then cases have been described in the tropical rainforest areas of Central and West African countries, mainly the Democratic Republic of Congo.

The animal reservoir of the virus is not yet known but is not thought to be a monkey. The disease in monkeys is similar to that in humans but subclinical infection is more common. There is, however, a 3–4% mortality rate in monkeys, depending on the species infected. A variety of African rodents, especially squirrels, are found to harbour the virus. In a recent outbreak of 81 cases in the southern

USA it was thought that small rodents transported from Ghana were the source of the infection [1].

Clinical features. The majority of cases occur in children under 10 years old, and the case fatality rate in African cases is of the order of 17%. The infection is clinically indistinguishable from smallpox, although there is a more marked lymphadenopathy [2]. At the onset of the disease, there is general malaise with fever, upper respiratory tract symptoms and a rapidly spreading pustular eruption mainly on the limbs and head. There is frequently lymphadenopathy. The rash is generally monomorphic, with individual lesions evolving together over the course of a few days from pustules to scabs. It can be confused with chickenpox.

Human-to-human spread in close contacts may occur, and the disease in such secondary cases is often milder [3]. Vaccination with vaccinia gives partial protection against monkeypox.

Diagnosis. The electron microscopic appearance of the virus is similar to variola and vaccinia. Cultural characteristics of monkeypox not shared with variola are good growth in RK13 cells and the development of pocks on the chorioallantoic membrane of fertile eggs at 39°C. PCR can distinguish monkeypox DNA from other orthopoxviruses.

Treatment. Supportive treatment is usually all that is necessary. It has been suggested that cidofovir would be a useful treatment [4].

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Cowpox

Aetiology. Since before Jenner used cowpox virus inoculation in the 18th century to protect against smallpox infection, it has been accepted that cowpox is primarily a disease of cattle, yet despite the name it appears that cattle are only infected by chance, as are the cat and human. Evidence is increasing that a small wild rodent (possibly a vole or wood mouse) is the natural host [1]. Most recognized infections in the UK now are in feral or domestic cats [2] and there is a seasonal increase in the late summer and autumn. Humans usually acquire cowpox from cats by implantation of virus into broken skin [3].

Cowpox appears to occur only in Europe [2], Russia or Mediterranean Asia, where human infection is uncommon and usually sporadic.

Pathology [4]. The histological appearance is very similar to vaccinia but epithelial necrosis is less rapid and there is more inflammation, erythema and haemorrhage. Hypertrophy and proliferation are seen in the basal layer of the epidermis and there are large cytoplasmic inclusions in the lower epidermal cells.

Clinical features [4,5]. After an incubation period of 5–7 days (range 2–14 days) a papule appears and rapidly becomes vesicular. This passes through a haemorrhagic stage before becoming pustular and then ulcerating during the second week. This crusts over with a hard black eschar 1–3 cm in diameter. The pustule, which is often umbilicated, is surrounded by a zone of erythema and oedema. Lymphangitis and lymphadenitis are usual, and fever, myalgia and constitutional symptoms are frequent. Healing takes place in 3 or 4 weeks. Post-vaccinial encephalitis is a rare complication [6]. The lesions, which are usually on exposed skin of the hands, arms or face, are often multiple, and may spread centrally from the periphery [7]. Conjunctivitis has also been reported [3].

Widespread cowpox infection mimicking eczema herpeticum has been reported in a patient with atopic eczema [8] and may rarely be fatal [9]. An extensive but self-limiting eruption of probable cowpox occurred in the previously healthy anogenital skin of a woman with Darier's disease [10].

Diagnosis. A history of contact with cats or cows is suggestive but half the cases will have no such history [4]. Milker's nodules and orf should be excluded. Primary tuberculosis, foreign-body granuloma, anthrax and sporotrichosis should not cause difficulty.

Rapid diagnosis of a poxvirus can be made by electron microscopy of a scraping or crust. Should this prove negative, growth in tissue culture or on the egg chorioallantoic membrane, where characteristic haemorrhagic pocks develop, is advised because a negative result may be due to the small amount of virus in clinical samples. Diagnosis of the virus type can be made by analysis of PCR-amplified DNA [5].

Treatment. None is required, other than control of secondary infection should this develop. In immunocompomised individuals, post-exposure immune globulin may be considered but is not readily available.

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Orf

SYN. ECTHYMA CONTAGIOSUM; CONTAGIOUS PUSTULAR DERMATITIS

Aetiology. Orf is caused by a parapoxvirus. The characteristic woven appearance of the virus is seen with negative staining on electron microscopy (Fig. 25.3). The disease is widespread in sheep and goats. It affects mainly young lambs, who contract the infection from one another, or possibly from persistence of the virus in pasturelands. Human lesions are caused by direct inoculation of infected material and are not uncommon among shepherds, veterinary surgeons and farmers who bottle-feed lambs. A child has been infected by falling in a contaminated pasture [1]. Butchers, meat handlers and housewives are sometimes infected from carcasses, especially sheep heads [2]. Two small outbreaks in Turkey were due to close contact with infected sacrificial animals [3]. One attack normally confers immunity, and human-to-human spread has not been recorded. Vaccination with vaccinia does not give protective immunity against orf.

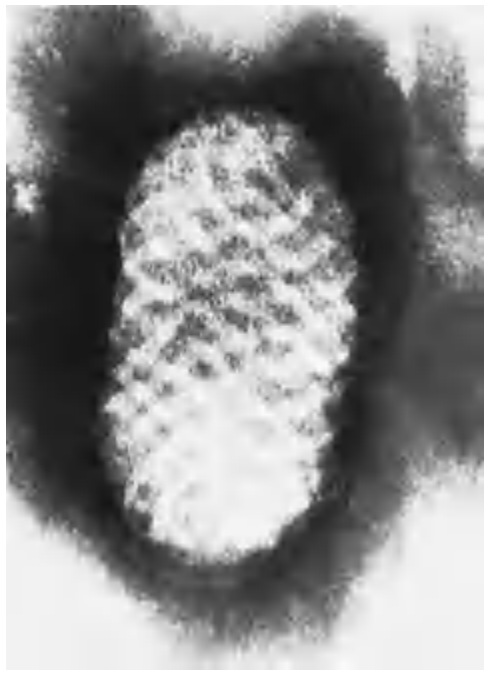

Fig. 25.3 Orf virus: phosphotungstate preparation, × 230 000. (Courtesy of Dr J. Nagington, Cambridge, UK.)

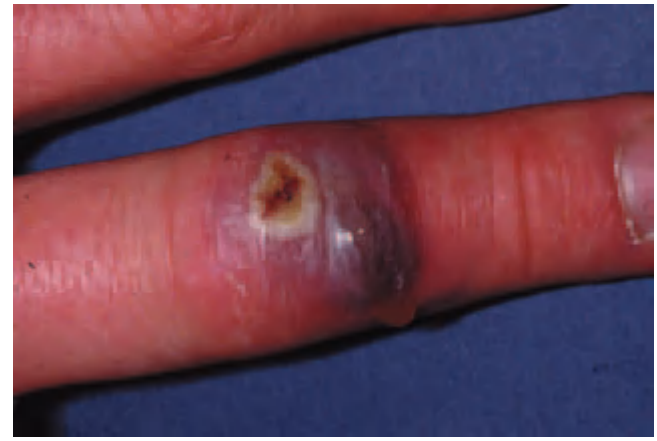

Fig. 25.4 Orf. (Courtesy of Addenbrooke's Hospital, Cambridge, UK.)

Orf is common among sheep handlers [4], and is readily recognized by them and their local physicians so that secondary referral is infrequent.

Similar parapoxvirus lesions in humans have followed contact with infected reindeer and musk ox calves [5].

Pathology [6–8]. The epidermal cells show gross intercellular and intracellular oedema, vacuolization and ballooning degeneration. A dense cellular infiltrate in the dermis consists in the centre mainly of histiocytes and macrophages and peripherally of lymphocytes and plasma cells. There are very few polymorphonuclear leukocytes. Throughout the lesion there is an increased number of small blood vessels, many of which show swelling and proliferation of endothelial cells. Ultrastructural studies show viral particles only in the cytoplasm of degenerating epidermal cells [9].

Clinical features [2,4,7,10,11]. After an incubation period of 5 or 6 days, a small, firm, red or reddish-blue papule enlarges to form a flat-topped haemorrhagic pustule or bulla (Fig. 25.4), often crusted in its umbilicated centre. In the fully developed lesion, which is usually 2 or 3 cm in diameter but may be as large as 5 cm, the central crust is surrounded by a rather characteristic greyish-white or violaceous ring, which is in turn encircled by a zone of erythema. It is sometimes irritable during the early stages and is often tender. The lesions are solitary or few in number and are common on the fingers, hands or forearms, but may be on the face. Lymphangitis and regional adenitis are not uncommon but are slight and there may be mild fever and malaise. Spontaneous recovery, usually without scarring, occurs in 3–6 weeks. Second attacks are quite common.

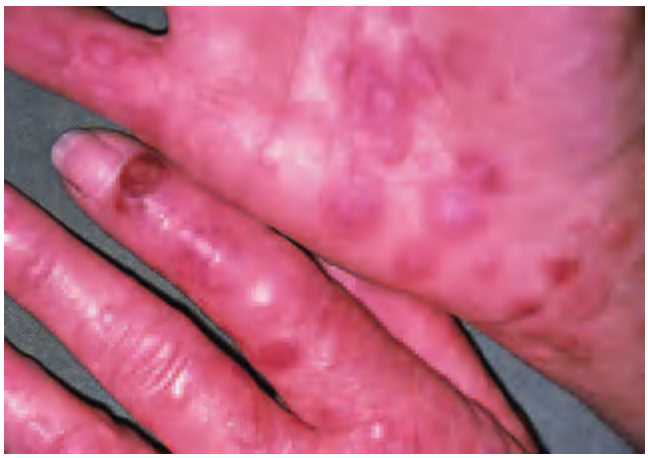

Fig. 25.5 Orf with erythema multiforme. The orf lesion on the dorsum of the forefinger has been present for 14 days, the secondary erythema multiforme for 4 days. (Courtesy of Dr A.S. Highet, York District Hospital, York, UK.)

Large fungating lesions are occasionally reported, and may resemble large pyogenic granulomas or malignant tumours. One such patient was immunosuppressed during treatment for lymphoma [12] and the lesion was refractory to treatment; another had chronic lymphatic leukaemia but appeared to be in remission at the time of the orf infection [13]. A similar lesion developed in the facial abrasions of a frictional 'rope burn' in an otherwise healthy boy [14]. A 16-month-old girl with widespread atopic dermatitis developed a pyogenic granuloma-like lesion with satellites [15].

Rare, widespread, papulovesicular or bullous lesions, which resolve after a few weeks, suggest the possibility of viraemic dissemination [16,17].

Erythema multiforme occasionally develops, typically 10–14 days after the onset of orf (Fig. 25.5), and less distinctive 'toxic erythemas' are also seen.

Diagnosis. The diagnosis is easy if the possibility of orf is suspected. Confirmation is best made by electron microscopy of the crust or a small biopsy [18]. Vesicle fluid should not be used as it contains very little virus and is usually negative. Growth of the virus in tissue culture is slow and inconstant. Serological tests are not available routinely, but a detectable antibody response does occur [19]. Molecular viral DNA analysis by PCR is possible but not routine [20].

Treatment. Any secondary infection should be treated while spontaneous recovery is awaited. Large exophytic lesions can be treated surgically [13,14] or with cryotherapy, although recurrence may occur in the immunosuppressed [21]. The use of 40% idoxuridine has been claimed to shorten the duration of the lesions [13,22], but its effect has not been rigorously assessed. The antiviral agent cidofovir has recently been reported to induce regression [23].

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Milker's nodule

SYN. PSEUDOCOWPOX; PARAVACCINIA

Aetiology. Milker's nodule virus is a parapoxvirus with the same cylindrical morphology as orf virus. In the UK it produces mild infections of the teats of cows, i.e. 'ring sores', and ulcers in the mouths of calves. Bovine papular stomatitis virus affects the same sites in cattle in Europe and North America, sometimes without obvious lesions and sometimes with greater severity. The two viruses are variants. Both can produce lesions on the hands of milkers or veterinarians who examine the mouths of animals [1,2]. Human infection is accidental and human-to-human spread does not appear to have been recorded. The

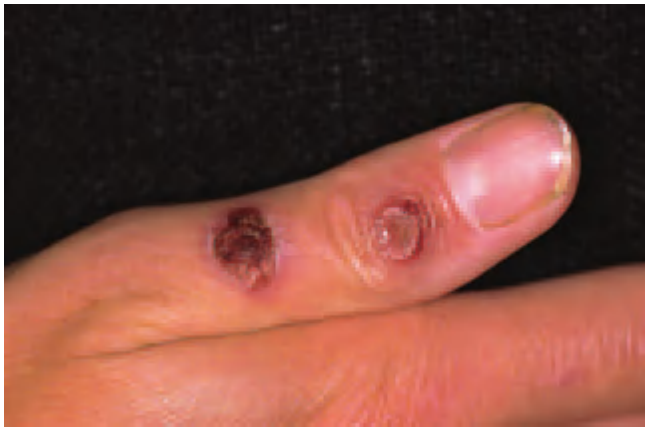

Fig. 25.6 Pseudocowpox. (Courtesy of Dr J.B. Kurtz, Oxford, UK.)

infection may be transmitted by contaminated fomites in burns [3] or scalds [4].

Pathology [5,6]. Histologically there is multilocular vesicle formation in the acanthotic epidermis. Parakeratosis is often conspicuous. Cytoplasmic, or more rarely intranuclear, inclusions may be detectable. There is a granulomatous reaction in the upper dermis.

Clinical features [6–9] (Fig. 25.6). After an incubation period, which is usually about 5 days but may be as long as 2 weeks, flat red papules are formed. Within a week they appear as reddish-blue, firm, slightly tender nodules. The tense and shining epidermis becomes opaque and grey and forms a small crust over the depressed centre of the nodule. A zone of erythema usually surrounds the nodules. Many cases develop lymphangitis but there are rarely any constitutional symptoms, and resolution without scarring takes 4–6 weeks. Between two and five nodules are usually present, but they may be solitary or more numerous. They commonly occur on the hands, particularly the fingers, but are occasionally seen on the face.

One or two weeks after the appearance of the nodules some patients develop a papular or papulovesicular eruption on the hands, forearms and arms, and sometimes on the legs and neck [10]. It fades in 1 or 2 weeks.

Diagnosis. The nodules may be very vascular, and have been confused with pyogenic granulomas. Differential diagnosis from orf on morphological grounds is not possible. The history is more helpful.

Isolation of the virus is slow and unreliable. Electron microscopy of biopsy fragments of the scab is most useful if facilities are available.

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Tanapox

This is an acute febrile illness associated with a localized nodular skin lesion. It is caused by tanapox virus, classified as a yatapoxvirus.

The infection was first seen as epidemics in 1957 and 1962 around the Tana River in Kenya. It has subsequently been seen in the Congo again in close proximity to the river Congo and is probably more widely distributed in tropical Africa. The virus is known to affect monkeys and humans, but its natural reservoir and mode of spread are not known. It may be acquired by inoculation through abraded skin or via mosquitoes.

Clinical features. There is mild pre-eruptive fever accompanied by headache and backache. The lesion begins as erythema surrounding a central thickening, which slowly develops as a nodule to reach a maximum diameter of 15 mm by the end of the second week. Local lymph nodes are enlarged and tender. The nodule ulcerates in the third week and is followed by gradual healing, leaving a scar after about 6 weeks. Occasionally there is more than one lesion, the maximum recorded being 10 [1] and they are usually on the limbs.

Diagnosis. The slow evolution and lack of a pustular stage are characteristic of tanapox infections. The diagnosis can be confirmed by electron microscopy, which shows enveloped poxviruses. The virus does not grow on the chick chorioallantoic membrane but some strains will give a typical appearance in tissue culture.

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Molluscum contagiosum [1,2]

Aetiology. Molluscum contagiosum virus (MCV) causes characteristic skin nodules, and is largely if not exclusively

a human disease. It is classified within the Poxviridae in a specific genus, Molluscipox, and has features intermediate between the orthopox and parapox groups. It cannot be grown in tissue culture or eggs and although not readily transmissible to laboratory animals, has recently been shown to produce typical changes on human skin cultured on immuno-incompetent mice [3]. Two types have been identified, MCV-1 and MCV-2, distinguished by restriction endonuclease analysis or PCR [4,5]. Type 1 causes the majority of infections (76–97%), but there is no relationship between virus type and lesional morphology or anatomical distribution [6,7].

Epidemiology. The virus occurs throughout the world. The disease is common, although its incidence in most areas is not reliably known. Infection follows contact with infected persons or contaminated objects, but the importance of epidermal injury is unknown.

The disease is rare under the age of 1 year, perhaps due to maternally transmitted immunity and a long incubation period [8]. Otherwise the incidence seems to reflect exposure to others. In hot countries where children are lightly dressed and in close contact with one another and where personal hygiene may be poor, spread within households is not uncommon: the age of peak incidence is reported as 2–3 years in Fiji [8], and 1–4 years in the Congo (Zaire) [9]. In New Guinea the annual attack rate for children under 10 years of age has been reported to be 6% [10]. In cooler climates, however, spread within households is rare and infection is more common at a later age.

Use of swimming pools has been correlated with childhood infections, with a peak incidence at age 10–12 years in Scotland [8] and 8 years in Japan [11]. In these and other studies, boys were affected more often than girls, perhaps due to more frequent use of swimming pools and communal bathing facilities and participation in contact sports. A later incidence peak in young adults is attributable to sexual transmission. Infection of children through sexual abuse is presumably possible [12]. However, to a greater extent than warts, molluscum contagiosum is seen quite commonly on the genital, perineal and surrounding skin of children, and abuse should not be regarded as likely unless there are other suspicious features.

There is a clinical impression that molluscum contagiosum is commoner in patients with atopic eczema, and occasional reports describe widespread infections, possibly based on impaired immunity [13,14]. Topical steroids and, more recently, other topical immunomodulatory therapy have been suspected as a contributing factor in patients with eczema and in other patients [15].

Unusually widespread lesions have been reported in patients with sarcoidosis [16], those taking immunosuppressive therapy [17–20] or those with HIV disease (see Chapter 26), suggesting that cell-mediated immunity is significant in control and elimination of the infection.

Pathogenesis and pathology [21–24]. The pathogenesis of the lesions is uncertain. The virus seems first to enter the basal keratinocytes, causing an increase in cell turnover that extends into the suprabasal layer. In the prickle cell layer, mitosis declines as viral DNA synthesis increases. The cellular proliferation produces lobulated epidermal growths that compress the papillae until they appear as fibrous septa between the lobules, which are pear-shaped with the apex upwards. The basal layer remains intact. Cells at the core of the lesion show the greatest distortion and are ultimately destroyed, and appear as large hyaline bodies (molluscum bodies) some 25 μm in diameter, containing cytoplasmic masses of virus material [25]. These bodies are present in large numbers in the cavity, which appears near the surface at the centre of the fully developed lesion. Inflammatory changes in the dermis are absent or slight [26], but in lesions of long duration there may be a chronic granulomatous infiltrate. It has been suggested that the inflammatory reaction may be induced by the discharge into the dermis of the contents of a papule [27].

Specific antibodies have been found in 60–80% of patients with molluscum contagiosum and, perhaps due to unrecognized infection, in about 5–15% of controls [28,29], but a role for humoral immunity in regression of lesions has not been established. Genes encoding proteins with immune-evasion properties have been identified within the MCV genome [30].

Clinical features (Fig. 25.7). The incubation period is variously estimated at 14 days to 6 months. The individual lesion is a shiny, pearly white, hemispherical, umbilicated papule which may show a central pore. It may be identified with a hand lens when less than 1 mm in diameter. Enlarging slowly it may reach a diameter of 5–10 mm in 6–12 weeks. Rarely, and usually when one or very few are present, a lesion may become considerably larger. Plaques composed of many small lesions ('agminate' form) occur rarely [31]. Lesions frequently spread and the number of lesions ultimately present is sometimes very large. After trauma, or spontaneously after several months, inflammatory changes result in suppuration, crusting and eventual destruction of the lesion. There is healing without scarring, but occasionally, especially at sites with more subcutaneous fat, depressed scars may remain [32] (Fig. 25.7b).

The duration of both the individual lesion and the attack is very variable and although most cases are self-limiting within 6–9 months, some persist for 3 or 4 years. Follow-up studies in children in Fiji [33] confirmed these figures but showed that individual lesions were unlikely to persist for more than 2 months. However, solitary lesions may persist for up to 5 years [34]. Temporary remissions of up to 2 months may occur.

The distribution of the lesions is influenced by the mode of infection, and by the type of clothing worn, and hence

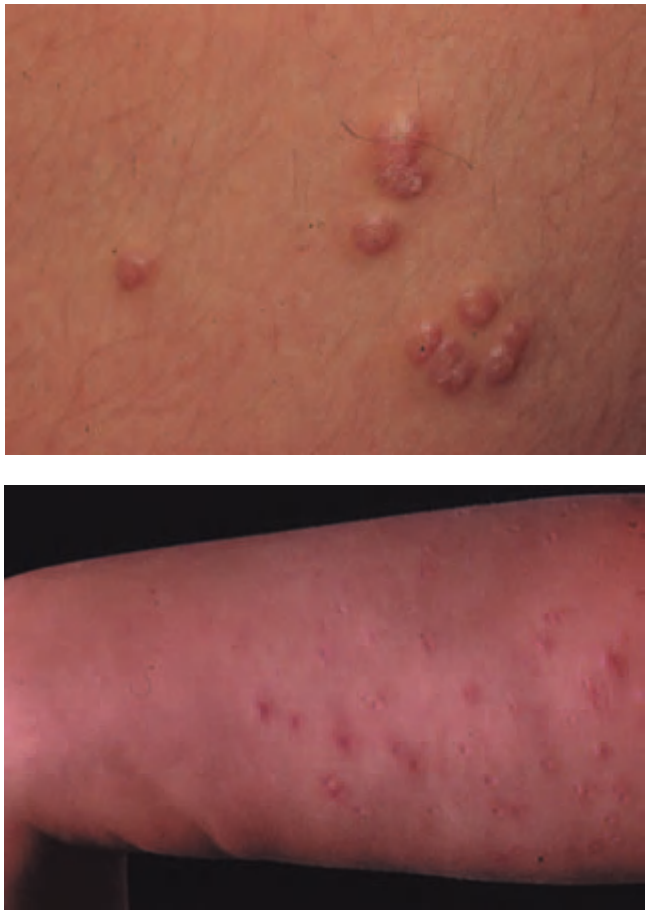

Fig. 25.7 Molluscum contagiosum: (a) typical umbilicated lesions; (b) depressed scars following infection. (Courtesy of Addenbrooke's Hospital, Cambridge, UK.)

by the climate. In temperate regions they are commonly seen on the neck or the trunk, particularly around the axillae, except in sexually transmitted infection, when the anogenital region is usually involved. In children in the tropics lesions are more common on the limbs. The widespread and refractory mollusca of HIV disease occur especially on the face [35]. In otherwise healthy subjects occasional facial lesions are seen, particularly on the eyelids. Molluscum may affect the scalp, and has occurred on the lips [36], tongue and buccal mucous membrane, and indeed on any part of the body surface, including the soles where the appearance is atypical [37]. Molluscum has occurred in scars [38] and in tattoos, apparently transmitted in the pigment [39].

In at least 10% of cases, particularly in atopic subjects, a patchy eczema, often very irritable, develops around one or more of the lesions a month or more after their onset [40] and erythema annulare centrifugum has also been reported [41]. Chronic conjunctivitis and superficial punctate keratitis may similarly complicate lesions on or near the eyelids [42]. The delayed papular response observed in some of the subjects of unsuccessful inoculation experiments [43] is probably a comparable hypersensitivity to the virus. The eczema and the conjunctivitis subside spontaneously when the lesion is removed.

Follicular molluscum contagiosum in four adults produced atypical, less protuberant pale papules [44]. Squeezing of comedo-like follicular lesions in a 9-year-old boy led to large abscesses that were attributed to the dispersion of virus into the dermis [45].

Diagnosis. The diagnosis of molluscum contagiosum is usually obvious when multiple lesions are present, and the identity of an indeterminate suppurating lesion is revealed by other, often very small, lesions at an earlier stage of their evolution. Rapid freezing with ethyl chloride or liquid nitrogen may accentuate their distinctive umbilication. Direct microscopical examination of unstained or stained expressed core or a curetted lesion crushed on a slide can establish the diagnosis [46]. The solitary molluscum may resemble pyogenic granuloma, keratoacanthoma or epithelioma and may be difficult to identify. The diagnosis is often not made until the lesion is examined histologically, but it can be carried out rapidly by electron microscopy [47]. Molecular analysis of DNA from specimens confirms molluscum contagiosum using hybridization or PCR techniques [4,5]. In HIV disease, molluscum contagiosum may resemble cutaneous cryptococcosis (see Chapter 26).

Treatment [48]. To avoid spread of infection, patients should be advised to avoid swimming pools, communal baths, contact sports, shared towels, etc. until clear.

In many instances, therapy is not necessary and natural resolution can be awaited. If this is slow, lesions are symptomatic or associated eczema is troublesome, treatment may be desirable. The choice of treatment will depend on the age of the patient and the number and position of the lesions. Destruction of lesions or production of an inflammatory response can hasten clearance.

Cryotherapy is effective, but needs to be repeated at 3–4 weekly intervals. Curettage and diathermy are appropriate for large lesions, especially when histology is required. Other simple mechanical methods, like expression of the contents of the papule by squeezing it with forceps held parallel to the skin surface, superficial curettage or shaving off the lesions with a sharpened wooden spatula, may each suffice. In children, however, prior application of local anaesthetic cream for an hour under plastic film occlusion may permit treatment to be performed painlessly in most cases [49]. Destruction by laser may also be considered [50], although, as with some of the other methods of surgical removal, scarring may result [51].

Topical preparations can be used to produce an inflammatory response. Liquified phenol applied precisely to lesions will certainly result in inflammation but is painful. Dilution of the phenol to 10 or 20% will be better tolerated

and hardly less efficaceous. Cantharidin, also used to produce a local irritant inflammation, has been used extensively in North America with success [52]. Topical wart paints of 15–20% salicylic acid in collodion or acrylate base applied carefully to lesions once or twice weekly will also speed clearance. The combination of salicylic acid plaster with povidone-iodine has been reported to be more effective than either alone [53].

The antiviral agent cidofovir has been shown to effectively resolve molluscum lesions [54] and has been used topically as a 1–3% ointment or cream or intravenously. It should be considered for treating extensive lesions in, for example, immuno-incompetent patients where eradication has proved difficult with standard treatment regimens or in immunosuppressed patients.

Local immune stimulation with imiquimod cream has produced clearance in both immunocompetent and immunosuppressed children and adults. Treatment regimens have used various application protocols, from one to three times daily for 3–7 days per week for 4–16 weeks, resulting in clearance in about 80% of patients [55,56]. The immunomodulatory effects of cimetidine may be able to induce remission of molluscum contagiosum. A 2-month course of oral cimetidine at a dose of 40 mg/kg daily was associated with clearance of lesions in 10 of 13 children [57].

Other possible topical preparations include tretinoin [58], potassium hydroxide solution [59], nitric oxide cream [60], silver nitrate paste [61] and podophyllotoxin cream [62].

The eczema that can arise in association with molluscum lesions is best treated without topical steroids or other topical cytokine inhibitors.

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Herpesviruses

The herpesvirus group consists of relatively large DNA viruses. Their replication is intranuclear and produces typical intranuclear inclusions detectable in stained preparations. They are subgrouped according to genome similarities into the α, β and γ herpesviruses.

The eight human members of the group are herpesvirus hominis (herpes simplex virus, HSV) types 1 and 2 (α), herpesvirus varicellae (varicella-zoster virus, β), human cytomegalovirus (β), Epstein–Barr virus (γ), human herpesvirus 6 (β), human herpesvirus 7 (β) and human herpesvirus 8 (γ).

A feature of infection by members of the herpesvirus group is the absence of virus elimination following clinical recovery. Virus persists throughout the person's life as a latent infection in the cells for which the strain is specific. Under certain conditions, especially immune suppression, the virus may become reactivated and produce an acute infective episode with cellular damage.

Herpes simplex

Aetiology [1–6]. Herpes simplex, caused by HSV, is one of the commonest infections of humans worldwide. There are two major antigenic types: type 1, which is classically associated with facial infections; and type 2, which is typically genital, although there is considerable overlap in disease manifestations.

Both HSV-1 and HSV-2 persist in sensory nerve ganglia after primary infection. The virus produces no viral proteins while latent and can therefore remain undetected by host defence mechanisms. From this condition of latency, the virus may travel peripherally along the nerve fibre and, if it replicates in the skin or mucous membrane, may cause recurrent disease. The virus can be shed in saliva and genital secretions from asymptomatic individuals, especially in the months following the first episode of disease, although the amount shed from active lesions is 100–1000 times greater.

Spread is by direct contact with, or droplets from, infected secretions. Primary type 1 infections occur mainly in infants and young children, when they are usually minimal and often subclinical. Primary infections may rarely produce a painful vesicular stomatitis. In crowded areas of the developing world, up to 100% of children have antibody by the age of 5 years, but in higher socioeconomic groups the incidence is lower, for example less than half of university entrants in the UK have been infected. Type 2 infections occur mainly after puberty and are often transmitted sexually. About one-third of young adults are seropositive for type 2 and this rises to half the population by later life. The primary HSV-2 infection is more commonly symptomatic. In one sample of women, overall transmission rates between couples, from infected to uninfected partner, averaged 4–30% annually [7]. Transmission was most frequent during periods of asymptomatic shedding, which ranged from 0.5 to 4% of days sampled. The apparent increase over the last few decades in the proportion of genital infections involving HSV-1, about 20–40% in some recent studies, may be attributable to orogenital contact. Four of six children with genital herpes (three with HSV-1 and one with HSV-2) were identified as having been sexually abused [8].

Trauma facilitates transfer of the virus to fully keratinized skin. The virus can be inoculated into any body site to cause a new infection, whether or not there has been previous infection with either type. The source may be endogenous (autoinoculation), for example to the finger especially in nail-biters or thumb-suckers. Examples of exogenous inoculation are lesions of the hand in health care workers (Fig. 25.8) and others [9,10], facial lesions contracted during contact sports, and infection of a breast-feeding mother's nipples from the infected mouth of her baby [11].

Following primary infection, humoral and cell-mediated immune responses take place, the latter probably being

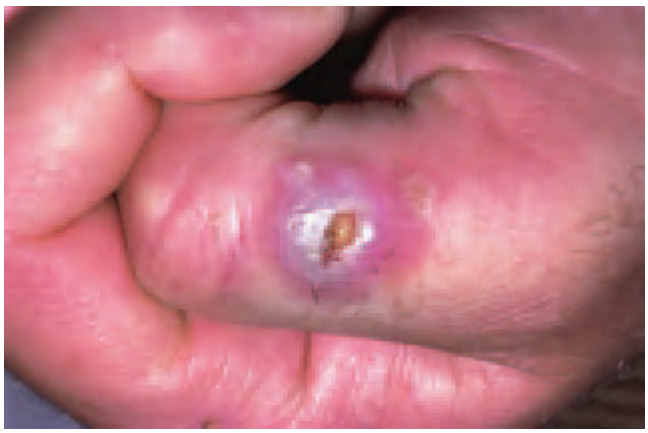

Fig. 25.8 Herpes simplex: inoculation lesion on thumb of dermatologist. (Courtesy of Dr A.S. Highet, York District Hospital, York, UK.)

more important [12]. They do not fully protect against reinfection or recurrent disease. The acquisition of HSV at a new site in a patient previously infected at a different site is referred to as a non-primary, first-episode infection. Initial (non-primary) genital herpes tends to be less severe in patients who have had previous oral infection. Where immunity is deficient (either congenitally or due to disease or drugs), both primary and recurrent herpetic infections may be increased in incidence and severity, and may run a prolonged and atypical course. Examples include patients immunosuppressed following organ or marrow transplantation, patients receiving cytotoxic therapy for malignancy [13] including cutaneous T-cell lymphoma [14–16], and patients with HIV infection and acquired immune deficiency syndrome (AIDS) (see Chapter 26).

Immunological abnormalities, in addition to possible local cutaneous factors, may explain the increased incidence in atopic eczema of recurrent herpes simplex [17] and the evolution in some individuals of erythema multiforme, as well as the occasional more severe infections [12,18,19], including eczema herpeticum.

Maternal primary genital infection at the time of birth, before the maternal immune response has taken place, is transmitted to the infant in about 50% of cases and the neonatal infection may be severe and fatal. Primary infection earlier in the third trimester may cause fetal growth retardation and prematurity. However, serious morbidity is rare if non-primary, first-episode or recurrent genital infection occurs during pregnancy or at delivery, presumably because the fetus in these situations is protected by maternal antibody [20–22].

In the otherwise healthy patient, herpetic recurrences are associated with temporary depression of cell-mediated immunity [22]. Peripheral trauma, including sunburn, may also stimulate reactivation of the virus.

Herpes simplex may occur in certain bullous disorders, complicating the oral presentation of pemphigus [23,24], infecting the erosions of familial benign chronic pemphigus [25], and occurring as severe infections in patients receiving immunosuppressive treatment for pemphigus [26]. It has also complicated pyoderma gangrenosum in a case of chronic lymphatic leukaemia [27].

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Pathology. In the cutaneous lesions, the cytoplasm of the infected epithelial cells becomes oedematous and the cells swell, producing the so-called 'ballooning degeneration'. Thick-walled vesicles are formed by the combination of intracellular and intercellular oedema. The dermis, and later the epidermis, are infiltrated with polymorphonuclear leukocytes. Specific changes occur in the cell nuclei and different stages in the process of the development of the intranuclear inclusions can usually be seen in a single section. In addition, giant cells containing two to 15 or more nuclei are almost invariably present in cutaneous and corneal epithelium. The cytological changes are essentially the same in all organs and foci of necrosis surrounded by a zone of inflammation are characteristically found in brain and liver when these organs are involved [1].

Viral particles can be identified ultrastructurally, mainly in the cell nucleus, and with detailed examination HSV-1 and HSV-2 can be distinguished [2].

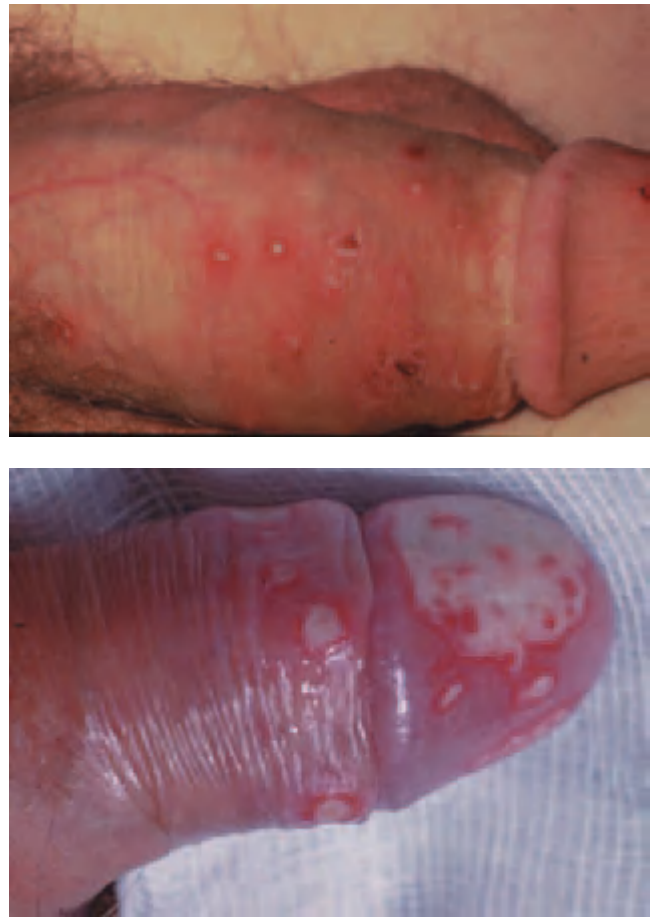
Clinical features [3–7]

Primary infection. Primary infection occurs in a previously seronegative individual and is often subclinical. When clinical lesions develop, the severity is generally greater than in recurrences. Genital primary disease is more commonly symptomatic than oral.

Herpetic gingivostomatitis. This is the most common clinical manifestation of primary infection by HSV-1, although the sites infected by the two HSV types are not mutually exclusive. Most cases occur in children between 1 and 5 years of age. After an incubation period of approximately 5 days, the stomatitis begins with fever, which may be high, malaise, restlessness and excessive dribbling. Drinking and eating are very painful and the breath is foul. The gums are swollen, inflamed and bleed easily. Vesicles presenting as white plaques are present on the tongue, pharynx, palate and buccal mucous membranes. The plaques develop into ulcers with a yellowish pseudomembrane. The regional lymph nodes are enlarged and tender. The fever subsides after 3–5 days and recovery is usually complete in 2 weeks.

In differential diagnosis, streptococcal infections, diphtheria, thrush, aphthosis, coxsackievirus infections including herpangina, Behçet's syndrome and Stevens–Johnson syndrome must be considered.

Herpes genitalis. Infection in the genital area is usually sexually transmitted. HSV-2 is the most common type in this area, although there is an increasing frequency of HSV-1 herpes genitalis [8]. Penile ulceration from herpetic infection (Fig. 25.9) is the most frequent type of genital ulceration seen in genitourinary medical clinics in the UK. The ulcers, which may be preceded by a general malaise, are most frequent on the glans, prepuce and shaft of the penis. They are sore or painful and last for 2–3 weeks if untreated. In male homosexuals, herpes simplex is common in the perianal area and may extend into the rectum. In HIV-infected individuals, ulceration may become chronic.



(a) (b)

Fig. 25.9 Herpes genitalis: (a) scattered lesions on penile shaft; (b) confluent lesions resulting in large erosions. (Courtesy of Addenbrooke's Hospital, Cambridge, UK.)

In the female, similar lesions occur on the external genitalia and mucosae of the vulva, vagina and cervix. Pain and dysuria are common. Infection of the cervix may progress to a severe ulcerative cervicitis.

Recurrences may be rare, but two-thirds of those affected have recurrences two to six times per year. Where a person has had past HSV-1 infection, this is likely to decrease the severity of a primary HSV-2 infection, shortening the clinical course and reducing systemic symptoms.

Keratoconjunctivitis. Primary herpes infection of the eye causes a severe and often purulent conjunctivitis with opacity and superficial ulceration of the cornea. The eyelids are grossly oedematous and there may be vesicles on the surrounding skin. The pre-auricular gland is enlarged and tender.

Inoculation herpes simplex [9] (see Fig. 25.8). Direct inoculation of the virus into an abrasion or into normal skin gives rise to indurated papules, large bullae or irregularly scattered vesicles after an incubation period of 5–7 days. The regional nodes are enlarged but fever and constitutional symptoms are usually mild. Inoculation of the fingertips results in a 'herpetic whitlow' [10], in which painful deep vesicles coalesce to produce a honeycombed appearance or a large bulla. The condition is easily confused with pyogenic infections. Recurrences of herpetic whitlow may arise; the majority are reported to be due to HSV-2 and occur in women with recurrent genital herpes [11].

Multiple crops of vesicles and pustules on plaques or erythema and oedema on the face, scalp and upper trunk, simulating impetigo and lasting some 10–12 days have occurred in wrestlers. On the face of the adult male the appearance of herpes may be deceptive; it may take the form of a folliculitis, but satellite umbilicated vesicles soon suggest the correct diagnosis [12]. Facial contact during rugby is another recognized means of acquiring HSV infection [13], commonly called 'scrumpox'.

Complications. Eczema herpeticum is discussed on p. 25.35 and in Chapter 18. Pharyngitis may accompany primary orofacial herpes, but also occurs in 10% of primary and 1% of recurrent episodes of genital herpes.

Headache and meningism affected 36% of women and 11% of men in a series of 268 patients with primary genital herpes simplex [3]. All recovered fully. In such patients, HSV DNA can be found by PCR in the cerebrospinal fluid.

Radiculoneuropathy is seen occasionally in primary anogenital infection in women, and especially in perianal disease in homosexual men [3,7,14]. There may be sacral paraesthesia, urinary retention, constipation and, in men, impotence. Recovery takes a few days to a few weeks.

Disseminated or systemic infection may occur in the immunodeficient and in those neonates not protected by maternally acquired antibody, but rarely in otherwise healthy patients. Systemic infection may develop with or without widespread cutaneous lesions. At any age, encephalitis, untreated, has a high mortality and a high incidence of disability in survivors [15,16]; in neonates HSV-2 gave a worse prognosis than HSV-1, even with antiviral therapy [17]. HSV hepatitis is rare in adults; when severe, it is often fatal [18,19], but mild disturbances of liver function are not uncommon [20]. Lower respiratory tract infection has occurred in immunosuppressed, burned or intubated patients [21], and in neonates [22].

Monoarticular arthritis complicated a case of widespread herpes simplex [23].

Recurrent infection. After the first infection, whether symptomatic or inapparent, there may be no further clinical manifestations throughout life. Recurrences arise in 30–50% of cases of oral herpes, but are more frequent after genital herpes infection, developing in 95% of individuals with HSV-2 compared with 50% of those with HSV-1 infection [6,24].

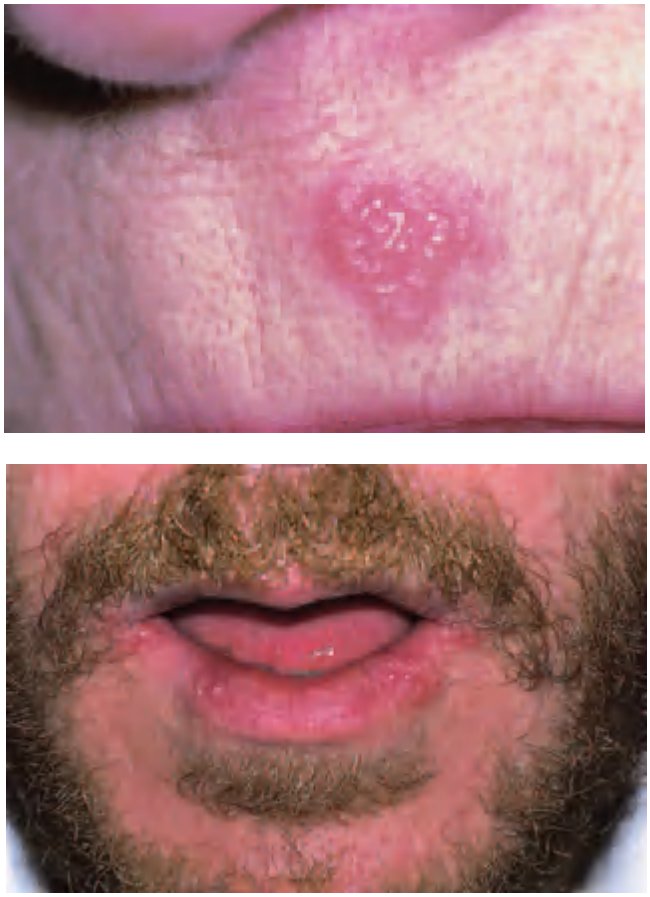
Recurrences may be triggered by minor trauma; other infections including febrile illnesses but also trivial, non-febrile, upper respiratory tract infections; ultraviolet radiation [25]; trigeminal neuralgia and especially after intracranial operations for that disease [26]; other neural surgery [27]; dental surgery [28]; or dermabrasion [29]. Some women have more recurrences in the premenstrual period. Emotional stress is blamed in some cases [30], possibly related to the effect on immune function [31]. However, in many cases no reason for the eruption is evident.

Recurrent infections differ from primary infections in the smaller size of the vesicles and their close grouping, and in the usual absence of constitutional symptoms. In the immunocompetent, they do not as a rule affect the buccal mucosa, although inapparent oral shedding occurs in about 12% of the UK population.

Itching or burning precedes by an hour or two the development of small, closely grouped vesicles on an inflamed base. They usually become pustular and crusted before healing in 7–10 days without scarring. The eruption may be painful just at the onset or pain may last for a few days. They occur most frequently on the face, particularly around the mouth (Fig. 25.10), but can be situated anywhere on the body. Larger vesicles are not uncommon, especially in children. Recurrences tend to be in the same region but not always on the identical site. Although the vesicles usually form an irregular cluster, they may be arranged in a line or in zosteriform distribution, particularly in the lower thoracic or lumbar region [32,33]. In such cases there may be considerable deep pain and regional lymphadenopathy. Fever, pain and lymphangitis may also be associated with herpes of the hand or forearm. Recurrent herpetic lesions are most commonly vesicular and ulcerative, but occasionally they are atypical with the appearance, for example, of folliculitis, candidal fissures or minor 'frictional ulcers'. Laboratory confirmation is needed for the accurate diagnosis of atypical lesions.

Herpes genitalis. Recurrences are fairly common, with clusters of small vesicles that produce non-indurated ulcers on the glans or shaft of the penis (see Fig. 26.9). They are of shorter duration than the initial infection. Similar lesions may occur on the labia, vagina or cervix and can cause distressingly painful symptoms. In other individuals the lesions can be unnoticed.

Subclinical viral shedding. Asymptomatic shedding of HSV-2 is more frequent than of HSV-1 and correlates with the frequency of symptomatic recurrences. In the first year following acquisition of HSV-2, asymptomatic shedding is more common than in subsequent years.



(a)

(b)

Fig. 25.10 Herpes labialis: (a) typical recurrent lesion on upper lip; (b) more widespread recurrent lesions following streptococcal pyoderma with lymphangitis. (Courtesy of Dr A.S. Highet, York District Hospital, York, UK.)

Complications. Constitutional symptoms rarely occur with recurrent herpes of the face or lips, although fever and an organic psychosis accompanied each attack in one child [34]. Cranial nerve palsies may occur [35], sometimes with each eruption [36]. Rarely neuralgic pain may precede each recurrence of herpes by 1 or 2 days, a syndrome often associated with the name of Maurice [37]. An association with cluster headaches has also been reported [38].

Eczema herpeticum (see p. 25.35 and Chapter 18) can be associated with recurrent as well as primary HSV. In the immunocompromised, persistent ulcerative or verruciform lesions may occur (see Chapter 26).

If recurrent herpes simplex involves the eye, keratoconjunctivitis, dendritic ulcers, disciform or hypopyon keratitis and iridocyclitis may occur. An ophthalmological opinion should be sought.

Lymphoedema has followed recurrent attacks on a limb, but probably only in the presence of developmental lymphatic hypoplasia [39]. Secondary leukoderma may develop in pigmented skin, and accompanying granulomatous changes have been recorded [40].

1 *Inoculation herpes*. This may recur with or without further exposure to infection. Recurrent crops of grouped vesicles have been reported from birth, continuing throughout infancy, without systemic involvement [41].
2 *Erythema multiforme* [42,43]. In 65% of patients with recurrent erythema multiforme there is a history of herpes labialis, usually preceding the erythema multiforme by several days to 2 weeks, but occasionally seeming to coincide with it. Although virus cannot be seen by electron microscopy or isolated, HSV antigen gB has been detected around keratinocytes in the epidermis in erythema multiforme skin lesions [44], and HSV DNA has been demonstrated by PCR in lesions, probably in the epidermis [45,46]. This evidence is not confined to cases with clinically apparent preceding herpetic lesions. All of 15 patients with recurrent post-herpetic erythema multiforme expressed the human leukocyte antigen (HLA) DQw3 [47]. Treatment of HSV-associated recurrent erythema multiforme, if started by the patient in the prodrome stage (with a 5-day course of aciclovir), will often prevent development of erythema multiforme. If this is not effective and attacks are frequent, a 6-month course of prophylactic aciclovir should be tried even in patients in whom HSV is not obviously a precipitating factor. Dapsone or azathioprine may be effective in cases resistant to aciclovir or not associated with HSV [48].
3 *Bell's palsy*. The suggestion that Bell's palsy is due to reactivation of HSV has been strengthened by the detection of the HSV-1 genome in facial nerve endoneurial fluid and posterior auricular muscle in patients with this condition. The use of an appropriate antiviral should therefore be considered in the early management of Bell's palsy [49].
4 *Recurrent lymphocytic meningitis*. A benign form of aseptic meningitis that lasts 3–14 days and may recur at intervals of months or years is associated with HSV [50]. In a study of cerebrospinal fluid from 13 patients, 12 had HSV-2 antibodies (of whom 10 also had HSV DNA detectable by PCR), while one had both HSV-1 DNA and antibodies. Among 27 people who had primary HSV-2 meningitis, five had recurrence of symptoms [51]. Prophylactic or pre-eruptive aciclovir has been reported to prevent recurrences [52].
5 *Encephalitis*. This severe disease can occur after the virus has established latent infection. Rapid diagnosis [53] and treatment are essential to minimize the mortality and morbidity of the condition.

Diagnosis. Diagnosis of infection by culture of the virus from vesicle fluid usually requires only 1–5 days. Primary infections can be distinguished by seroconversion or a rise in antibody titre. Recurrences tend to produce little change in antibody titre; measurement of antibody is therefore not helpful in the diagnosis of recurrent HSV. For a more rapid diagnosis, viral antigen may be detectable by immunofluorescence in scrapings from lesions

[54] or the virus seen by electron microscopy in vesicle fluid. The detection of HSV DNA in the cerebrospinal fluid by PCR has become the diagnostic method of choice for herpes encephalitis and aseptic meningitis and can also be used to identify the virus and the type at other sites [55].

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Treatment [1,2]. Mild uncomplicated eruptions of herpes simplex require no treatment. The use of a topical antiseptic agent on affected skin may help to reduce the risk of

secondary bacterial infection. In severe primary infection or troublesome recurrent disease, antiviral therapy should be instigated.

Aciclovir (acyclovir). After triple phosphorylation, this drug is incorporated into DNA where it interferes with the action of DNA polymerase and acts as a chain terminator. The first phosphorylation step is catalysed by a specific viral thymidine kinase so that the effect of the drug is confined to virus-infected cells. Aciclovir is of proven clinical value against herpes simplex and varicella-zoster viruses, although the latter is somewhat less sensitive.

Valaciclovir and famciclovir are chemically related to aciclovir and have the same mechanism of action. They are precursor drugs; valaciclovir is converted to aciclovir and famciclovir is converted to penciclovir. They are absorbed from an oral dose better than aciclovir and have improved bioavailability.

Primary infection. Aciclovir systemically is the treatment of choice for severe or potentially severe primary herpes simplex infection, but there is no effect on establishment of virus latency and rates of recurrence after therapy. Treatment should be started as soon as possible. The usual dose is 5 mg/kg i.v. 8-hourly, though twice that dose has been used for neonatal herpes [3] and encephalitis [4]. As the drug is excreted via the kidneys the dose must be scaled down in renal failure. Transient rises in blood urea and creatinine may occur with bolus injections; slow infusion over 1 h in an adequately hydrated patient is recommended. The usual oral dose is 200 mg five times daily, although 800 mg twice daily has been used with success [5]. The drug is given for 5 or more days.

Recurrent infection. Recurrent herpes labialis may need no treatment if attacks are mild or infrequent [6]. Oral aciclovir started as soon as possible after onset of symptoms can shorten the duration and decrease the intensity of an episode [7]. If recurrences are frequent, long-term prophylactic aciclovir at a dose of 200–400 mg twice daily for 4–6 months may increase the time between episodes [8,9].

In the immunocompromised patient, mucocutaneous herpes simplex responds well to intravenous aciclovir [10,11]. After exposure, the infection can be prevented by intravenous [12] or oral [13] aciclovir, which should be started several days before the anticipated immunosuppression and continued throughout the period of greatest risk. Longer-term prophylaxis where indicated is also effective [14].

Prophylaxis against reactivation or spread of HSV may be useful before cosmetic laser treatment of the face, as widespread herpes has been reported following such procedures [15].

Aciclovir is effective in eczema herpeticum [16,17] and neonatal herpes [3] and reduces the mortality and morbidity of herpes simplex encephalitis [4].

Initial eruptions of genital herpes [18] improve significantly with oral aciclovir [19,20] but recurrent infections respond less well [21]. However, treatment of the more severe recurrences may be worthwhile; in such cases it is important to minimize delay before starting treatment, and patients should have a supply of tablets to be started on their own initiative [5]. Frequent recurrences, and also any associated erythema multiforme [22], can be suppressed by long-term treatment [23,24], although cessation of therapy, even after several years, may allow resumption of recurrences [25]. Prophylactic doses vary between 200 and 1000 mg daily; a typical regimen is 400 mg twice daily, gradually reduced to find the minimum effective dose for the individual patient. Valaciclovir 250 mg twice daily or 1 g once daily [26] or famciclovir 125 mg three times daily or 250 mg twice daily [27] are also effective in suppression of recurrent episodes.

Topical aciclovir is of established value for herpetic keratitis. In the treatment of recurrent eruptions of herpes labialis [28], and of first-episode and recurrent herpes genitalis [29], improvement has been demonstrated [30] but seems less impressive than that obtained by oral administration and in some studies has been ineffective [31]. Similarly, there is no strong evidence that topical aciclovir influences the disease course in recurrent cutaneous herpes simplex. Topical penciclovir compares favourably with aciclovir [32], and reduces the duration of pain and the eruption in comparison with placebo [33].

Resistance of herpes simplex to aciclovir has not emerged as a significant problem in immunocompetent patients [34]. However, in the immunocompromised, resistant strains that cause intractable lesions have emerged following long-term or frequently repeated treatment. Resistance is usually due to a change in, or loss of, viral thymidine kinase [35] or more rarely to alteration of viral DNA polymerase [36]. The former strains may respond to antivirals that have a different mode of action (e.g. phosphonoformate, also known as foscarnet, or cidofovir; see below).

The risk to the infant from primary herpetic vulvovaginitis in the mother at the time of delivery is so great that caesarean section is indicated [37], and prophylactic aciclovir should be considered for the neonate [3].

Other treatments. In the treatment of severe herpes simplex infection resistant to aciclovir, systemic phosphonoformate (foscarnet) may be considered [38]. An alternative antiviral is cidofovir, which acts by blocking DNA replication. This can be administered systemically but is also active topically. A small number of individuals with severe HSV infection resistant to conventional treatment have responded to cidofovir [39].

Enhancement of the immune response to HSV could reduce recurrences. Vaccines against the virus are under development but not yet in clinical use. Topical imiquimod and resiquimod, which cause local release of cytokines and enhancement of antigen presentation, have shown some promise in treatment of recurrent genital herpes [40].

Zinc ions inhibit the activity of HSV-specific DNA polymerase. A 10-min application of zinc sulphate 0.025–0.05% in water to the expected site of the herpes, repeated two to four times per month, has been reported to prevent recurrent eruptions and previously associated erythema multiforme [41], although a small controlled trial of the same regimen could not confirm this effect [42]. Topical zinc sulphate in a gel formulation has also been reported to be of benefit in episodes of reactivated infection [43].

Recurrences of herpes labialis may be prevented or reduced in intensity by the use of a topical sunscreen [44].

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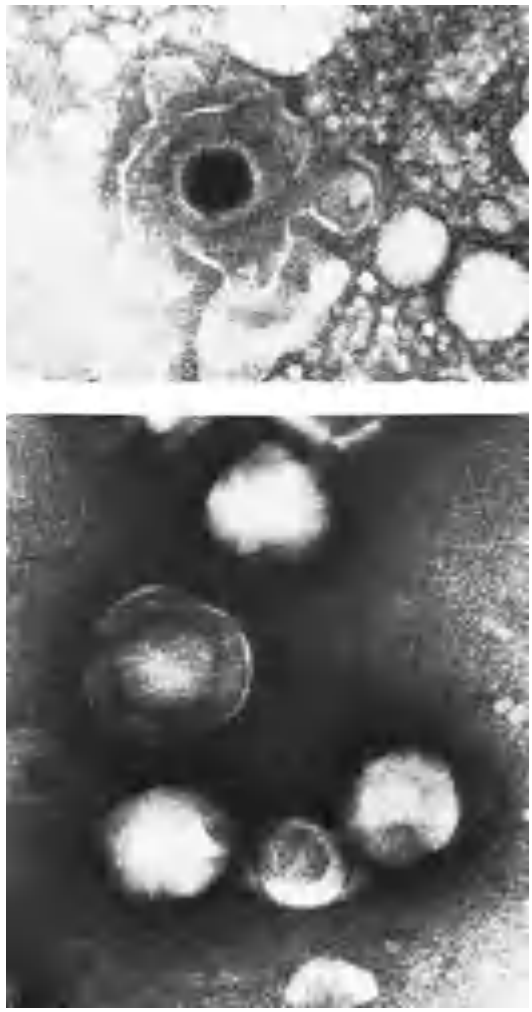
Varicella (chickenpox) and zoster (shingles)

Aetiology [1]. Varicella and zoster are caused by the same virus, herpesvirus varicellae, sometimes referred to as varicella-zoster virus (VZV) (Fig. 25.11). Varicella is the primary infection with a viraemic stage, after which the



(a)

(b)

Fig. 25.11 Herpesvirus varicellae. Phosphotungstate preparations from vesicle fluid: (a) the dark centre is due to penetration of the capsid by phosphotungstate (× 72 000); (b) the envelope encloses the nucleocapsid and obscures detail (× 116 250). (Courtesy of Dr J. Nagington, Cambridge, UK.)

virus persists in nerve ganglion cells, usually sensory. Zoster is the result of reactivation of this residual latent virus.

Varicella occurs throughout the world and is transmitted by droplet infection from the nasopharynx. Patients are infectious to others from about 2 days before to 5 days after the onset of the rash. Vesicle fluid contains a large amount of virus, but its importance in transmission is not known. Dry scabs are not infectious. In cities, epidemics occur at irregular intervals, with the highest incidence in children aged 2–10 years. Subclinical infections may occur.

Zoster (from the Greek word meaning a girdle, a reference to its segmental distribution) is a sporadic affliction of individuals. The average annual incidence in the UK has been estimated at 3.4 per 1000 [2]. It is uncommon in childhood and the incidence increases with age. The sexes are equally affected. Zoster patients are infectious, from virus in the lesions and, in some instances, the nasopharynx. In susceptible contacts of zoster, chickenpox can occur.

Varicella confers lasting immunity and second attacks are uncommon, especially in immunologically healthy subjects, but clinical reinfection with a mild varicella-like illness occurs occasionally [3].

In varicella, IgG, IgM and IgA antibodies appear 2–5 days after the onset of the rash, and their levels peak during the second and third weeks. Thereafter, the titres gradually fall although IgG persists at low levels. If zoster occurs later, the levels of IgG antibody increase rapidly and become much greater than during the primary infection. Antibodies seem to have an incomplete protective effect; maternal or administered antibody reduces the severity of infection but does not prevent it.

Cell-mediated immunity is more important. If the primary infection occurs when cell-mediated immunity is impaired, as in organ-transplant patients, varicella may be severe and occasionally fatal. In patients with impaired immunity, both the incidence and severity of zoster are increased, and it is frequently complicated by disseminated cutaneous disease and systemic involvement, usually pneumonia, hepatitis or encephalitis. This is seen in malignancy, especially lymphomas, so that the incidence of zoster in Hodgkin's disease has been estimated to be 9%; of 221 patients in the USA with cutaneous T-cell lymphoma [4], 10% developed zoster. Also at risk are patients receiving cytotoxic or immunosuppressive therapy, especially the more profound suppression required for bone marrow transplantation; in one series of over 1300 marrow recipients, 30% of those surviving 1 year developed zoster [5]. In patients infected with HIV, zoster is 10 times more common than in the normal population and may become disseminated and chronic (see Chapter 26).

Maternal varicella in the first 20 weeks of pregnancy is associated with an approximate 2% risk of fetal damage, including central nervous system and ocular defects, and limb hypoplasia; neonatal death has been reported [6]. Maternal zoster in pregnancy is not associated with intrauterine infection [7,8]. Zoster in infancy has followed maternal varicella, the baby's primary infection having occurred *in utero* [9–11]. If the mother has varicella within 4 days before to 2 days after term, the neonate would have no maternal antibody and is at risk of severe varicella, with a mortality rate of up to 30% in the absence of treatment [12,13].

Varicella may be more severe at sites of cutaneous inflammation [14]. The factors determining the site of an eruption of zoster are often not clear, but it may be precipitated by pressure from neoplastic deposits on the nerve roots; by radiotherapy, usually at the level of the affected nerve root [15]; by spinal [16] and other surgery; and by other, often trivial, traumas [17,18].

Frontal sinusitis preceded 16% of all cases of ophthalmic zoster [18].

Occasional clusters of cases of shingles are reported, and it is suggested that, uncommonly, exposure to exogenous VZV may trigger reactivation of latent virus [19]. A possible mechanism is blocking of cell-mediated defences by specific antibody whose level rises following subclinical reinfection [20].

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Pathology [1]. Following an initial period of replication in the oropharynx, a viraemia causes widespread dissemination. In varicella, cells of the Malpighian layer of the skin show ballooning of their cytoplasm due to intracellular oedema, and distinctive nuclear changes comprising eosinophilic inclusions and marginated chromatin. Some nuclei develop additional nuclear membranes that divide the nucleus into small compartments. The multinucleate giant cells, with up to 15 nuclei, are a characteristic feature of infections with VZV and HSV, and are produced mainly by cell fusion [2]. Intracellular oedema combined with intercellular oedema forms the vesicle, the roof of which consists of the upper Malpighian and horny layers. A mild inflammatory reaction in the dermis later extends to the epidermis and the proportion of polymorphonuclear cells increases with ulceration.

In fatal cases of varicella [3] essentially similar cytological changes with areas of focal necrosis are found in the liver, kidney and other organs. The lungs show interstitial pneumonia with focal consolidation and haemorrhage.

In zoster, as well as skin lesions, there are inflammatory changes in the posterior nerve roots and ganglia and sometimes these involve the anterior horn. Virus particles have been seen in ganglion cells and Schwann cells in the affected nerve bundles [4]. More extensive changes are sometimes reported: leptomeningitis, encephalitis with local demyelination [5], and myelitis. Disseminated lesions in other organs may occur as in varicella.

Zoster can cause some destruction of nerve fibres in the middle and lower dermis, detectable with silver-impregnation techniques [6]. Partial denervation may persist for over a year and characteristically does so in patients with post-herpetic neuralgia [7]. Corresponding fibres in the spinal cord degenerate and there may be scarring in the region of the ganglion.

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Clinical features

Varicella (Fig. 25.12). The incubation period is usually 14–17 days (range 9–23 days). After a day or two of fever and malaise, often slight or absent in children, an inconstant and fleeting scarlatiniform or morbilliform erythema is followed by the development of papules which very rapidly become tense, clear, unilocular vesicles. Within a few hours the contents become turbid and the pustules are surrounded by red areolae. In 2–4 days a dry crust forms and soon separates, to leave a shallow pink depression which, in the absence of secondary infection, heals without scarring. The vesicles appear in three to five crops over 2–4 days. They are most numerous on the trunk, then on the face and scalp and on the limbs. Their distribution is centripetal, and on the limbs the eruption is more profuse on thighs and upper arms than on lower legs and forearms. A characteristic feature is the presence of lesions at different stages in each site. The total number of lesions is very variable: they may be few or profuse. The distribu-

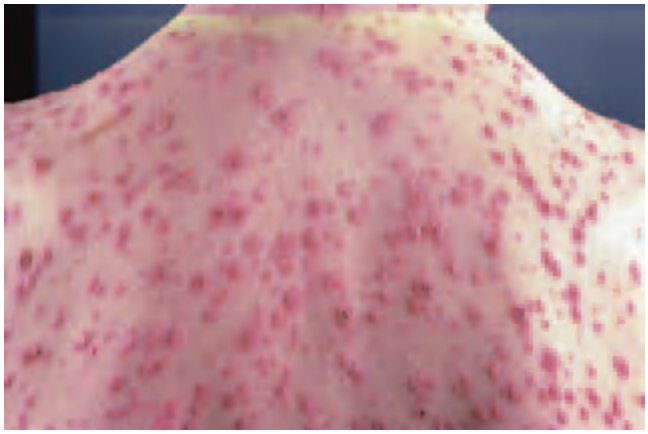

Fig. 25.12 Varicella. (Courtesy of York District Hospital, York, UK.)

tion may be modified by pre-existing inflammatory changes, at the sites of which lesions may appear in increased density [1]. The vesicles in such areas tend to be at the same stage and are often small, but may occasionally be bullous [2]. In exceptional cases of normal distribution the lesions are larger and umbilicated or varioloid. Vesicles are common in the mouth, especially on the palate, and are occasionally seen on other mucous membranes, including the conjunctiva. On the anal mucosa they may be followed by painful ulcers.

Fever is variable in severity and duration and roughly parallels the extent of the eruption. It may be trivial or may reach 40 or 41°C for 4 or 5 days. Constitutional symptoms tend to be proportionate to the fever. In some patients pruritus is troublesome. Haemorrhagic varicella, in which a very extensive eruption of haemorrhagic vesicles is accompanied by high fever and severe constitutional symptoms, is rare in the previously healthy patient. It is relatively more common in some tropical regions in which malnutrition may be a factor, but most cases now seen in temperate regions occur in immunocompromised patients.

The fetal and neonatal consequences of varicella in pregnancy are discussed on p. 25.23.

Complications. These are rare in otherwise healthy children, are less infrequent in neonates and adults and are common in the immunosuppressed. Relatively short courses of oral steroid treatment in children and adults may permit the development of severe and potentially fatal chickenpox [3].

Encephalitis [4] in the otherwise healthy patient occurs in less than 1 per 1000 cases and complete recovery occurs in 80%. Other neurological complications are very rare. The other main systemic complications are varicella pneumonia and hepatitis. Varicella pneumonitis is more likely to occur in adults and is 15 times more common in smokers than in non-smokers [5].

Secondary infection is seldom a serious problem in temperate climates, but under tropical conditions may be severe [6] and may be complicated by septicaemia. Cutaneous gangrene ('varicella gangrenosa') may follow secondary infection, but rarely extensive local gangrene may occur in the absence of bacterial involvement, and sometimes during a mild attack of varicella [7]. The mechanism is unknown.

Thrombocytopenic purpura, beginning on the fifth to tenth day and usually recovering spontaneously after 3 or 4 months, occasionally follows otherwise benign varicella.

Rhabdomyolysis has been reported in association with varicella [8]. Viral arthritis during varicella has been reported, although bacterial arthritis also occurs [9]. Reye's syndrome has been associated with preceding varicella [10].

Stevens–Johnson syndrome occurring as a consequence of varicella infection has been reported [11], and should be considered if bullae develop in addition to the typical vesicles of chickenpox. Treatment with systemic corticosteroids, in addition to aciclovir, may be necessary. Erythema multiforme has been reported immediately prior to the eruption of chickenpox or zoster [12].

Varicella in immunocompromised people may be severe and progressive, with a mortality of 7–10%. Features associated with a progressive varicella include haemorrhagic varicella, pneumonitis, hepatitis and encephalitis; chronic varicella is associated with hyperkeratotic lesions and acute retinal necrosis syndrome. Repeated attacks of varicella have also been observed.

Zoster. The first manifestation of zoster is usually pain, which may be severe and may be accompanied by fever, headache, malaise and tenderness localized to areas of one or more dorsal roots. The pain may be sharply localized to the same area, but may be more diffuse. The time between the start of the pain and the onset of the eruption averages 1.4 days in trigeminal zoster and 3.2 days in thoracic disease. Closely grouped red papules, rapidly becoming vesicular and then pustular, develop in a continuous or interrupted band in the area of one, occasionally two and, rarely, more contiguous dermatomes. Mucous membranes within the affected dermatomes are also involved. New vesicles continue to appear for several days. Often in children, and occasionally in adults, the eruption is the first indication of the attack. The lymph nodes draining the affected area are enlarged and tender. The pain and the constitutional symptoms subside gradually as the eruption disappears. In uncomplicated cases recovery is complete in 2–3 weeks in children and young adults, and 3–4 weeks in older patients.

Occasionally, the pain is not followed by the eruption ('zoster sine eruptione') [13].

The thoracic (53%), cervical (usually C2,3,4, 20%), trigeminal including ophthalmic (15%), and lumbosacral

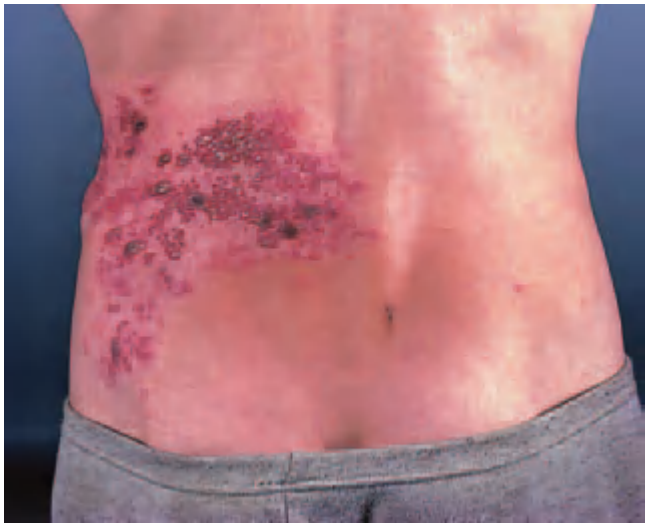

Fig. 25.13 Zoster of trunk. (Courtesy of York District Hospital, York, UK.)

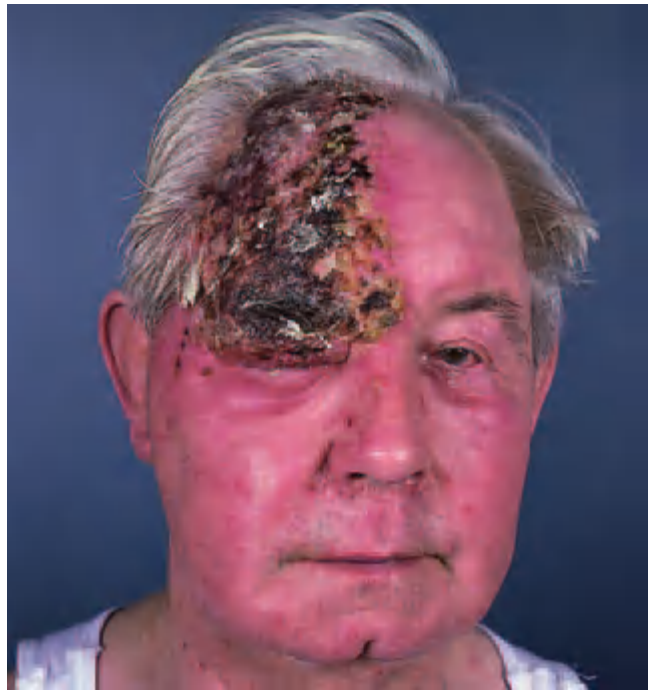

Fig. 25.14 Ophthalmic zoster. (Courtesy of York District Hospital, York, UK.)

(11%) (Fig. 25.13) dermatomes are most commonly involved at all ages, but the relative frequency of ophthalmic zoster increases in old age. Rarely, the eruption may be bilateral.

In some 16% of patients with zoster, vesicles develop beyond the dermatome involved within a few days of the local eruption. This is more common in the elderly but in most cases only a few lesions appear and the course of the zoster is unchanged. In patients with lymphomas or who are otherwise immunocompromised, generalized varicella ('disseminated zoster') develops and may be haemorrhagic. Rarely in such cases the zoster may successively involve further dermatomes. Systemic involvement may follow and can be fatal [14].

In the elderly and undernourished the local eruption often becomes necrotic, and healing, which may require many weeks, may be followed by severe scarring. In the otherwise healthy child, zoster usually runs a benign course.

In immunosuppressed individuals, especially due to HIV infection, zoster may run a protracted course, with a small number of lesions developing into verrucous or crusted nodules (see Chapter 26).

Variations in the zoster syndrome depend on which dorsal root is involved, on the intensity of its involvement and on the extension of the inflammatory changes into the motor root and anterior horn cells. Visceral involvement may be responsible for abdominal pain, pleural pain or temporary electrocardiographic abnormalities with or without precordial pain [15,16].

Motor involvement [17]. This occurs overall in 5% of cases and is commoner in older patients and those with malignancy, and in cranial compared with spinal nerve involvement. The motor weakness usually follows the pain and the eruption, by a few days to a few weeks, but occasionally precedes or accompanies them. The affected segment is usually but not always the same. Complete recovery is expected in 55% and significant improvement in a further 30%. Facial palsy in herpes zoster oticus is discussed below. In ophthalmic zoster, ocular palsies occur in 13% and facial palsies in 7% [18]. An abdominal hernia followed zoster involving the thoracic 10th and 11th motor roots [19]. Zoster of the anogenital area may be associated with disturbances of defecation or urination [20–22].

Trigeminal nerve zoster. In ophthalmic nerve zoster (Fig. 25.14) [23], the eye is affected in two-thirds of cases, especially when vesicles on the side of the nose indicate involvement of the nasociliary nerve (Hutchinson's sign). Ocular complications include uveitis, keratitis, conjunctivitis, conjunctival oedema (chemosis), ocular muscle palsies, proptosis, scleritis (which may be acute or delayed for 2–3 months), retinal vascular occlusion, and ulceration, scarring and even necrosis of the lid. Involvement of the ciliary ganglia may give rise to Argyll Robertson pupil.

Zoster of the maxillary division of the trigeminal nerve produces vesicles on the uvula and tonsillar area, while with involvement of the mandibular division, the vesicles appear on the anterior part of the tongue, floor of the mouth and buccal mucous membrane. In orofacial zoster, toothache may be the presenting symptom [24].

Herpes zoster oticus. The facial nerve, mainly a motor nerve, has vestigial sensory fibres supplying the external ear (including pinna and meatus) and the tonsillar fossa and adjacent soft palate. Classical sensory nerve zoster in these fibres causes pain and vesicles in part or all of that distribution, though the skin involvement may be minimal and limited to the external auditory meatus. To what extent other neural elements are actually infected is debated, but swelling of the infected sensory fibres in their course through the confined spaces of the facial canal and the internal auditory meatus, leading to compression of adjacent neural structures, explains the commonly associated features [25–27]. Thus, pressure on the facial nerve motor fibres adds facial palsy, which with the ear pain and associated vesicles completes the classic triad of Ramsay Hunt syndrome; compression of the vestibulocochlear nerve may cause sensorineural hearing loss, dizziness and vertigo; and involvement of the nervus intermedius or its geniculate ganglion would impair taste sensation from the anterior two-thirds of the tongue and alter lacrimation.

Herpes zoster oticus accounts for about 10% of cases of facial palsy. The paralysis is usually complete and full recovery occurs in only about 20% of untreated cases.

Post-herpetic neuralgia [28]. The commonest and most intractable sequel of zoster is post-herpetic neuralgia, generally defined as persistence or recurrence of pain more than a month after the onset of zoster, but better considered after 3 months. It is unusual in childhood and increases in incidence and severity with age. It occurs in about 30% of patients over 40 years of age and is most frequent when the trigeminal nerve is involved. It is more likely to develop if there was dermatomal pain prior to the eruption, if the acute pain of zoster was severe and if the zoster rash was prolonged. The pain has two main forms, a continuous burning pain with hyperaesthesia and a spasmodic shooting type, although a pruritic 'crawling' paraesthesia may also occur. Allodynia, pain caused by normally innocuous stimuli, is often the most distressing symptom and occurs in 90% of people with post-herpetic neuralgia. The neuralgia varies in intensity from inconvenient to profoundly disabling.

Other complications

1 Scar sarcoid [29] and other granulomas [30] have been reported in healed zoster scars.

2 Bacterial infection of damaged skin.

3 Encephalitis or meningoencephalitis. This is more common in the elderly, the immunosuppressed and in association with disseminated zoster.

4 Acute retinal necrosis syndrome. This rare complication follows an attack of shingles affecting the ophthalmic nerve or an unrelated dermatome [31].

5 Guillain–Barré syndrome and transverse myelitis have also been noted occasionally following zoster.

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Diagnosis. The distinctive features of varicella are the centripetal distribution, the polymorphism in each affected site and the rapid progression of the individual lesion from

vesicle to crust. Typical zoster presents few difficulties once the eruption has developed and can be confused only with zosteriform herpes simplex (see p. 25.18). This diagnosis should be excluded virologically in apparently recurrent zoster.

The virus is readily identified by electron microscopy of vesicle fluid and can be grown in tissue culture but this takes longer and is less reliable than for HSV. Detection of VZV antigen by direct fluorescent antibody staining of a smear or of VZV DNA by PCR in a scraping from the base of a vesicle offers an alternative method. Titration of complement-fixing antibody in acute and convalescent sera may be a useful test in atypical infections. PCR analysis permits detection of VZV and is particularly useful in patients with suspected encephalomyelitis, in whom examination of the cerebrospinal fluid can lead to rapid diagnosis.

Prevention of varicella

This can be by pre-exposure, post-exposure and antiviral prophylaxis.

Pre-exposure prophylaxis. A live attenuated vaccine is effective in preventing varicella in healthy children [1] and in children with leukaemia in remission; in the latter patients, vaccination reduces the incidence and severity of varicella [2] but does not affect the incidence of zoster [3]. Two doses of vaccine, 3 months apart, result in approximately 90% seroconversion and 75% of responding recipients continue to have detectable antibody for up to 10 years [4].

Post-exposure prophylaxis. Specific zoster immune globulin (ZIG) administered within 10 days of contact reduces the severity of varicella but does not prevent it [5,6]. It should be given to neonates whose mothers develop varicella within the period from 7 days before to 7 days after delivery [7]. Some advocate additional prophylactic intravenous aciclovir, for the mother before delivery [8] and the baby after delivery [9–11]. ZIG is indicated for immunocompromised children and adults, for example organ-transplant recipients and patients who have taken oral steroids for at least 14 days within the previous 3 months who have not had previous chickenpox, if exposed to varicella or zoster [12]. It should also be given to exposed non-immune pregnant women not only to reduce the severity of chickenpox but also to reduce the risk of fetal transmission in those women who develop disease despite ZIG prophylaxis [13].

Vaccination in later life, when immunity against VZV is waning, may help to reduce the occurrence or severity of zoster.

Antiviral prophylaxis. In the immunocompetent person, aciclovir given from about 9 days after exposure for 1 week appears to be effective in aborting or reducing the severity of chickenpox and allows immunity to develop. In the immunocompromised, such prophylaxis only delays the onset of the disease. Prophylaxis with aciclovir has also been effective in preventing zoster in the early months following bone marrow transplantation [14].

Treatment [15,16]. Varicella in the otherwise healthy child requires only symptomatic treatment [16]. Some advocate the use of aciclovir in childhood chickenpox to reduce the severity and duration of the eruption [17]. Rest and analgesics are sufficient for mild attacks of zoster. Soothing antiseptic applications may be helpful and secondary bacterial infection will require antibiotics.

An antiviral [18] is indicated for varicella in adults and for severe varicella or zoster infections at any age in the immunocompromised. Treatment should be started as early as possible, preferably within the first 1 or 2 days. The virus is less sensitive to aciclovir *in vitro* than HSV and higher doses are usually recommended, typically 10 mg/kg or 500 mg/m^2 i.v. 8-hourly. Courses of 5, 7 and 10 days have been used and some advocate a change from intravenous to oral drug after 48 h. In general practice, zoster is often treated with aciclovir 800 mg five times a day for 7–10 days [19] or with valaciclovir 1 g or famciclovir 250 or 500 mg three times a day for 7 days. Such treatment prevents progression of the eruption, reduces the systemic complications of varicella and zoster, lessens zoster pain during treatment and can reduce the risk of development of post-herpetic neuralgia [20]. In patients over 50 years old, famciclovir (500–750 mg three times a day for 7 days) started within 72 h of the onset of shingles has also been shown to decrease the duration of post-herpetic neuralgia by approximately 2 months (2.6 times faster resolution than in the placebo group) [21].

If the first division of the trigeminal nerve is involved, there is a risk of damage to the eye, and antiviral therapy and ophthalmological advice are indicated.

Studies of the benefits of corticosteroid therapy together with aciclovir in the treatment of shingles have given conflicting results. One study in immunologically normal patients found that, in conjunction with aciclovir, prednisolone 40 mg daily tailed off over the following 3 weeks hastened the return to normal activity, better sleep and reduced the time analgesia was required [22]. Another study [23] concluded that the addition of prednisolone conferred only a slight benefit on the rate of healing and reduction of acute pain but at the expense of an increase in adverse effects. Without antiviral cover, serious dissemination of infection due to systemic steroids is a risk.

In the treatment of herpes zoster oticus (Ramsay Hunt syndrome), steroid therapy is better established, probably because of the central importance of inflammatory swelling in its pathogenesis. The prognosis is improved by prednisone 60 mg daily for 2 weeks tailed off over the third week [24], or by aciclovir 10 mg/kg i.v. 8-hourly for

7 days [25]. A combination of the two drugs may give better results [26].

For post-herpetic neuralgia the use of opiates should be avoided if possible. A tricyclic antidepressant such as amitriptyline [27] or nortriptyline (or clomipramine or doxepin) is useful, especially for hyperaesthesia and constant burning pain, an effect independent of any antidepressant activity. For best results, it should be given early in a dose of 25 mg daily and continued for 3–6 months. These adrenergically active antidepressants may be most effective if antiviral treatment is given during the acute attack of shingles [28]. For stabbing pain, sodium valproate (or another anticonvulsant such as clonazepam or carbamazepine) is of value. Especially in the elderly, doses should be initially low and increased every few days as required. Gabapentin is a useful analgesic for the pain. The application of aspirin (a suspension of two tablets crushed in 15–30 mL chloroform) has been reported to give substantial relief within half an hour [29]. Topical capsaicin 0.025%, a substance P depleter, may relieve pain in some patients, though its usefulness in some is limited by a burning sensation following application [30].

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Cytomegalovirus

Aetiology and epidemiology. Cytomegalovirus (CMV) infections are common throughout the world and are usually inapparent. Primary infection is followed by lifelong carriage of the virus with intermittent shedding in various secretions. This may be increased by physiological stimuli such as pregnancy, and by immune suppression due to disease or therapy as in AIDS and transplant recipients respectively.

Depending on socio-economic conditions, between 40 and 100% of adults in a community are infected as shown by the prevalence of antibodies against CMV. There are several ways of transmitting CMV, which are to some extent age dependent. Intrauterine transmission occurs in 0.1–1.0% of births. Perinatal and neonatal infections arise as a result of exposure to infectious cervical secretions in the birth canal or from infected breast milk. Pre-school children may acquire CMV from oral secretions or urine of other infected infants. At an older age, sexual transmission is important. Blood transfusion is also a source of CMV, the virus being associated mainly with neutrophils. CMV may be transmitted in transplanted organs from CMV-seropositive donors.

Clinical features [1,2]

Congenital CMV infection. In its most severe form, hepatosplenomegaly, jaundice and purpura are present. Most cases die within 2 months and survivors usually have severe neurological damage. There may be erythropoietic

tissue in the dermis derived from undifferentiated dermal mesenchyme; this presents as purple or red papules or nodules lasting 4–6 weeks ('blueberry muffin' lesions). Vesicles very rarely occur in congenital CMV disease [3]. In a case of acute graft-versus-host disease in a young infant, CMV was suspected as the cause of the underlying immunodeficiency [4]. About 15% of congenitally infected infants will have long-term neurological sequelae, especially deafness.

CMV mononucleosis. In the otherwise healthy child or adult there is usually no clinical disturbance. When symptoms do appear they resemble infectious mononucleosis, with fever and lymphocytosis, although lymphadenopathy and splenomegaly are not usually striking. In up to one-third of cases, there is a follicular, maculopapular [5] or rubelliform eruption, often affecting the legs and lasting up to 2 days. Urticaria may occur [6]. As in Epstein–Barr virus infectious mononucleosis, ampicillin commonly triggers a widespread eruption. Lymphocytic vasculitis manifesting as papules and plaques in a partly annular configuration, with livedo reticularis, has been described in a 7-year-old girl with CMV mononucleosis [7]. Guillain–Barré syndrome is a not uncommon complication of CMV mononucleosis.

Other dermatological features in childhood. CMV was suggested as the precipitating factor in a case of scleroedema in a young infant [8], and may be one of several viral infections that can cause Gianotti–Crosti syndrome [9,10] (see p. 25.78). CMV may also play an aetiological role in an acral eruption termed the papular purpuric gloves-and-socks syndrome [11].

CMV in the immunosuppressed [12]. CMV infection in the immunocompromised can be severe and even fatal, with pneumonitis, hepatitis, gastrointestinal ulceration, retinitis and superinfection with other opportunistic pathogens. Neurological complications include encephalitis, myelitis and especially myeloradiculitis when the peripheral nerve roots are infiltrated with lymphocytes in AIDS [13].

Skin lesions may occur in disseminated CMV infection, a characteristic histological feature of which is the presence of cytomegalic cells in vascular endothelium. This may progress in some cases to vasculitis. The dermatological features include a widespread eruption that may become papular and purpuric, with vesiculobullous or pustular lesions and indurated pigmented nodules or plaques. Sharply demarcated ulceration may occur, mostly around the genitalia, perineum, buttocks and thighs. In AIDS, keratotic skin lesions [14] and severe oral [15] and skin ulceration [16] have been reported.

Following a course of antiviral treatment of CMV in immunosuppressed or immunocompromised people, relapsing infection and progression of organ involvement may occur.

Diagnosis. Classically the infection is diagnosed histologically by finding typical intranuclear inclusions surrounded by a clear halo in enlarged cells. This method is relatively insensitive, but with the addition of immunohistochemistry, cytomegalic inclusions are more readily demonstrable. Virus isolation from throat washings, urine, bronchoalveolar lavage fluid, blood or biopsy material is carried out in human embryo fibroblast cells, but it takes 5–28 days to produce a cytopathic effect seen as 'owl eye' nuclear inclusions. This can be accelerated by looking for CMV early antigen (pp65) after 24–48 h culture [17]. Rapid methods with greater sensitivity include direct detection of CMV antigenaemia and PCR. Primary infection can be diagnosed serologically by the appearance of CMV IgM and IgG antibodies. Congenital CMV can only be diagnosed confidently by virus isolation or the presence of CMV IgM antibody within 3 weeks of birth.

Treatment. Most CMV infections do not require specific therapy, but in life-threatening situations or when CMV retinitis threatens sight, two antiviral agents—ganciclovir and foscarnet—have been used with some success.

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Epstein–Barr virus

Epstein–Barr virus (EBV) selectively infects B lymphocytes and occasionally certain squamous epithelial cells. This tropism depends on the expression on the cell surface of the CD21 molecule (the receptor for complement C3d), to which the virus must bind before gaining entry to the cell [1].

Primary infection is often asymptomatic but may be symptomatic and present as infectious mononucleosis. Following infection, the virus persists for life in a latent state in long-lived resting B cells, of which 0.1–5 are infected per millilitre of blood. Under certain conditions, these cells are activated when a range of viral and cellular proteins are expressed. In those EBV-infected B cells that undergo terminal differentiation or apoptosis, viral replication occurs and the cells die. No latent infection takes place in epithelial cells, although persistent infection with viral shedding may occur. In the oropharynx, liberation of virus into the saliva from localized differentiated B cells explains the spread of infection between individuals.

EBV is associated with nasopharyngeal carcinoma and with various B-lymphoproliferative lesions.

1 B-cell tumours, histologically characterized as large cell lymphomas, occur in immunocompromised people and especially immunosuppressed transplant recipients.

2 EBV-associated post-transplant lymphoproliferative disease occurs in 0.5–1.5% of the recipients of solid organs. Primary EBV infection is an important risk factor that explains the three- to four-fold increased frequency of post-transplant lymphoproliferative disease in the paediatric transplant population. Unchecked B-cell proliferation may cause a glandular fever-like illness or progress to polyclonal and monoclonal lymphomas.

3 Burkitt's lymphoma, found in equatorial Africa and New Guinea.

4 A rare X-linked recessive lymphoproliferative syndrome.

5 Both large cell lymphomas, which are frequently cerebral, and Burkitt's lymphoma are seen in patients with HIV.

Epidemiology. In all populations, the great majority of people are infected with EBV by middle age; infection, once acquired, is lifelong. In early childhood the virus is probably spread by contact with saliva on fingers or fomites, and in economically disadvantaged societies most infection is acquired at this stage. In more developed communities, early childhood infection is less frequent (e.g. about 40% of college entrants in the USA have been infected) and primary infection occurs most commonly in early adult life, when kissing is the usual route of infection, though occasional droplet spread may occur. Most primary infection, especially in childhood, is asymptomatic or mild, but when it is delayed to adolescence or adulthood, clinical illness is more frequent, i.e. infectious mononucleosis [2].

Infectious mononucleosis

SYN. GLANDULAR FEVER

Infectious mononucleosis is characterized by fever, sore throat with exudative pharyngotonsillitis and lymphadenopathy. Enlargement of the spleen has been recorded in about half of those acutely infected. There is a lymphocytosis with at least 10% atypical cells, and usually some abnormalities in liver function tests indicating hepatocellular damage, which results in jaundice in about 4% of those infected. Petechiae at the junction of the hard and soft palate are a distinctive feature of the disease and usually appear on the second or third day of fever.

An exanthem occurs in about 10% of cases, usually between the fourth and sixth days. Most common is a macular or maculopapular eruption of trunk or upper arms, involving face and forearms in some cases and thighs and legs occasionally. Morbilliform and scarlatiniform eruptions are sometimes seen. Acute urticaria is a presenting manifestation in some cases [3]. The lesions fade after a few days. If ampicillin is taken during the course of the illness, an extensive maculopapular or morbilliform eruption develops in over 90% of cases, 7–10 days after the start of treatment. A similar effect is occasionally seen with penicillin and tetracyclines.

Cold agglutinins are common in infectious mononucleosis, usually without clinical manifestations, but they might explain occasional cases of transient cold urticaria [4]; one case had, in addition, cutis marmorata and ulcerating bullae [5].

Thrombocytopenic purpura is common but platelet counts below $1000/mm^3$ are fortunately rare. Splenic rupture and encephalitis are life-threatening complications.

Diagnosis. Diagnosis can be made by examination of a blood film for abnormal lymphocytes. Tests for heterophile antibodies that agglutinate sheep or horse red blood cells and which can be adsorbed with ox red blood cells but not by a guinea-pig kidney suspension become positive in 90% of patients after 1–2 weeks. This (the Paul–Bunnell) test occasionally gives false positives and is less reliable in childhood. During the infection, antibody to EBV viral capsid antigen is produced: IgM class antibody persists for a few months and IgG antibody for life. Virus isolation is a specialized technique not performed by most diagnostic laboratories.

Other cutaneous manifestations of EBV

Oral hairy leukoplakia. This is an AIDS-associated lesion presenting as white plaques on the sides of the tongue (see Chapter 26). EBV replicates in maturing epithelial cells

but is not present in basal and parabasal keratinocytes. Oral hairy leukoplakia is also reported to occur in patients receiving immunosuppressive therapy [6–10] and occasionally in immunocompetent individuals [11,12].

Gianotti–Crosti syndrome (see p. 25.78). EBV has been reported in association with this eruption, which is believed to be a reaction to viral infection in childhood [13,14].

Lipschütz ulcers. Painful genital ulceration occurring in adolescents without venereal infection [15] can be due to primary EBV infection [16]. The sloughy ulcers are often multiple and develop in association with malaise, fever and inguinal lymphadenopathy. They heal spontaneously but somewhat slowly.

Kikuchi's histiocytic necrotizing lymphadenitis. This may occur in association with EBV infection.

Subcutaneous NK-cell ($CD56^+$) lymphoma. Presenting initially as a panniculitis, this has been reported to contain EBV DNA [17].

Hydroa vacciniforme-like lesions. These have been reported as a presentation of cutaneous angiocentric T-cell lymphoma with EBV present in the lymphoid cells of the lesions [18].

Other associations. There are reports of cases of EBV infection associated with a variety of reactive dermatoses: erythema multiforme [19], erythema nodosum [20], erythema annulare centrifugum [21], acute pityriasis lichenoides [22], and a predominantly facial eruption resembling inflammatory granuloma annulare [23].

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Human herpesvirus 6 [1]

Human herpesvirus 6 (HHV-6) was originally isolated in 1986 from peripheral blood leukocytes (B cells) of patients with HIV infection or lymphoproliferative disorders [2]. In culture, infected cells (B and especially T cells) are large and refractile and frequently contain intranuclear and/or intracytoplasmic inclusions. The virus is serologically and genomically distinct from other human herpesviruses, although it is closest to CMV and its genome has some regions that cross-hybridize with CMV under stringent conditions. There are two distinct groups: group A and group B. Although there is a high degree of antigen cross-reactivity between group A and group B strains, only HHV-6 B strains appear to be associated with human disease.

This virus causes roseola infantum (exanthem subitum), the most common exanthematic fever in children under the age of 2 years, with a peak incidence between 6 and 9 months, reported to account for 24% of acute febrile illness presenting at a paediatric emergency department [3]. In the acute stage of the disease there is HHV-6 viraemia, which is followed by the appearance of antibodies to the virus [4]. Seroprevalence studies have shown that by the age of 1 year, 75% of infants have antibodies to HHV-6 [5] and 90% of adults are seropositive [5]. Subclinical infection is common and it is estimated that only about one-third develop clinical disease. After the initial infection, the virus persists and can be detected in saliva

from a high percentage of healthy subjects, the likely mode of spread [6].

Clinical features

Roseola infantum (exanthem subitum) [7,8]. The incubation period is 10–15 days. Fever, sometimes ranging between 39.5 and 40°C, begins abruptly, persists for 3–5 days and is usually accompanied by few or no symptoms. Irritability, inflamed tympanic membranes and, occasionally, periorbital oedema and haematuria are early manifestations. As the temperature falls, an eruption of discrete rose-pink maculopapules develops on the neck and trunk; it may later spread to the arms, face and legs. The lesions may rarely become vesicular [9]. After 1 or 2 days the rash fades, leaving no scaling or pigmentation. The patient's cervical and occipital lymph nodes are usually enlarged.

Febrile convulsions are not uncommon, occurring in 13% in one series [2]. HHV-6 DNA has been demonstrated in the cerebrospinal fluid of children with primary HHV-6 infection and also at times of recurrent seizures following exanthem subitum [10], which suggests that HHV-6 is a direct cause of the associated encephalitides. Fatal encephalitis is rare but has been reported in primary infection [11]. Other complications reported are fatal hepatitis and haemophagocytic syndrome [12]. During the first 2 days there may be leukocytosis but as the rash develops, leukopenia with a relative lymphopenia is usual.

The eruption of primary HHV-6 infection is almost restricted to the first 3 years of life. If primary infection occurs in adults, there may be a mononucleosis-like illness, with variable fever or rash and with mainly cervical lymphadenopathy that may persist for up to 3 months, or an acute but self-limiting hepatitis [13–15].

Reactivation of HHV-6. In immunosuppression, latent HHV-6 may reactivate and cause a variety of symptoms [16]. Fever, rash, hepatitis and pneumonitis are recognized.

Other manifestations. HHV-6 infection has been associated with multiple sclerosis, Guillain–Barré syndrome, chronic fatigue syndrome, lymphoproliferative disorders, pityriasis rosea and Kikuchi–Hashimoto disease, although the importance of the associations are not clear.

Diagnosis. The lack of symptoms during the febrile phase and the appearance of the eruption as the fever subsides should suggest the diagnosis, although clinical confusion with rubella or measles is not uncommon [17] and the picture of roseola infantum can also be caused by HHV-7 infection. Confirmation is by demonstrating seroconversion or rise in antibody titre to HHV-6, typically by indirect immunofluorescence using cells infected with HHV-6 as antigen. IgM antibody is usually present 5–7 days after the rash, maximal 2 weeks after infection and persisting for about 2 months. Virus isolation requires specialized techniques not available in most diagnostic laboratories. Molecular detection of viral RNA by reverse transcriptase (RT)-PCR or DNA by PCR is possible but may need to be qualitative to distinguish primary from latent infection. HHV-6 DNA has been detected by PCR in peripheral blood mononuclear cells during the acute illness and was still positive in 78% of samples taken within 2 months and in 66% of samples taken 2 months to 2 years after the primary infection [2].

Treatment. Only symptomatic measures are usually required. Antiviral therapy with ganciclovir, cidofovir or foscarnet would be appropriate in individuals with severe disease.

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Human herpesvirus 7

Frenkel *et al*. [1] isolated a new herpesvirus from human $CD4^+$ T lymphocytes in 1990. Now named HHV-7, this virus is distinct from, but related to, HHV-6. The virus has been subsequently isolated from the peripheral blood of healthy people and a patient with chronic fatigue

syndrome. It has been found to be very prevalent, infecting children at a similar age to HHV-6 [2]. At present it is not known if HHV-7 is specifically related to any disease but, like HHV-6, it has been reported in illness with clinical features of exanthem subitum (roseola infantum) [3–5]. HHV-7 viral DNA has been detected in the blood and lesional skin of patients with pityriasis rosea, sometimes together with HHV-6, although the pathogenetic relationship is debated (see p. 25.79).

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Human herpesvirus 8

SYN. KAPOSI'S SARCOMA-ASSOCIATED HERPESVIRUS

Epidemiological evidence suggests that Kaposi's sarcoma (see Chapter 26) is caused by an infectious agent. In 1994, Chang *et al*. [1], using molecular techniques, identified two novel DNA fragments in AIDS-associated Kaposi's sarcoma tissue. This DNA had partial homology to two γ herpesviruses, herpesvirus saimiri and EBV. Subsequently, this new lymphotropic human herpesvirus has also been found in association with classic Kaposi's sarcoma in immunocompetent people [2]. Kaposi's sarcoma-associated herpesvirus (KSHV) DNA has been detected in 95% of Kaposi's sarcoma lesions and is present in the monocytes, endothelial cells and spindle cells. The same DNA sequences have been found in AIDS-related lymphomas of the body cavity [3] and in Castleman's disease [4]. The association between Kaposi's sarcoma and HHV-8 is strengthened by the observation that most AIDS patients with Kaposi's sarcoma develop antibodies against KSHV-related nuclear antigens 6–75 months before the sarcoma appears [5]. The mechanism by which KSHV produces tumours is different to most other malignancies. Many of the proteins expressed by the virus influence cell proliferation, angiogenesis and apoptosis and down-regulate local immunity. Early lesions of Kaposi's sarcoma are polyclonal [6], although clonal growth may develop as a late event.

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Herpes B virus

Herpes B virus, or cercopithecine herpesvirus 1, is a benign enzootic infection of Asiatic monkeys (the *Macaca* genus), and readily spreads among other monkeys in captivity. The virus remains latent in infected monkeys and may reactivate spontaneously or at times of stress. The virus is highly pathogenic to humans, in whom it typically causes fatal encephalitis. However, the frequency of mild or asymptomatic infection is not known. Human infections have occurred in attendants and research workers, most frequently following monkey bites, but occasionally in those who have handled monkeys or monkey tissues and have not been bitten. Guidelines to prevent B virus infections in monkey handlers have been published [1]. Person-to-person transmission is rare [2].

Clinical features [1,3]. In humans, lesions resembling herpes simplex develop after 5–21 days at the site of the bite or scratch. There may be symptoms of tingling, itching, numbness or pain before the vesicular eruption appears. The eruption may remain localized or show some extension, with regional lymphangitis and lymphadenopathy. Fever, malaise, headache and abdominal pain indicate a systemic illness. Encephalitis, usually fatal, develops after 10–35 days in a high proportion of cases.

Diagnosis. There is usually a history of contact with monkeys or monkey tissue. Culture of the virus from vesicle fluid or brain biopsy material will confirm the diagnosis but must be performed in a specialized laboratory. Specific primers for PCR are available for the direct detection of B virus DNA. Serological tests of paired samples can also be helpful.

Treatment. Monkey-inflicted wounds should be vigorously cleaned with soap and water, followed by iodine or alcohol. An acute serum sample should be collected. Aciclovir has been successful in the treatment of experimental B virus infections [4]. Two people, treated early in the course of their infection with aciclovir, developed only a mild illness from which they recovered, although two others, treated late, died [2]. Valaciclovir orally is now the

recommended treatment given as soon as possible following exposure. The dose is 1 g three times a day for 14 days. Intravenous ganciclovir is more potent than aciclovir *in vitro* [5] and has also been used clinically.

If symptoms of B virus disease develop, treatment is with aciclovir 12.5–15 mg/kg i.v. three times daily or ganciclovir 5 mg/kg i.v. twice daily; if there are signs of encephalitis, ganciclovir is the treatment of choice.

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Kaposi's varicelliform eruption including eczema herpeticum

Aetiology. Kaposi's varicelliform eruption refers to a widespread cutaneous infection with a virus that normally causes localized or mild vesicular eruptions, occurring in a patient with pre-existing skin disease. The great majority of such cases are infections with HSV-1, for which the term *eczema herpeticum* is now preferred, especially for the more localized infections. The more general eponymous title may be used to encompass similar widespread infections with other viruses, including coxsackie A16 [1] and vaccinia [2] (eczema vaccinatum), rarely seen now that smallpox vaccination is limited to selected groups. Atopic eczema is by far the commonest predisposing condition, although the term 'eczema herpeticum' has not been restricted to cases with a background of eczema. Other susceptible dermatoses include Darier's disease [3,4], pemphigus foliaceus [5,6], benign familial pemphigus [6], ichthyosis vulgaris [7], including a case complicated by allergic contact dermatitis [8], congenital ichthyosiform erythroderma [9], mycosis fungoides [10], Sézary syndrome [11] and other inflammatory dermatoses [12]. Extensive spread of herpetic infection has followed trauma or cosmetic procedures to the face such as burns [13], dermabrasion [14] and laser therapy [15].

Most herpes simplex infections in patients with atopic eczema are not unusually severe or widespread, although an increased frequency of recurrent cold sores has been reported [16]. In 179 consecutive children with severe atopic eczema, eczema herpeticum was diagnosed in 10 and was judged severe in six [17]. Less severe, localized eczema herpeticum is not rare among patients with atopic eczema [18,19].

Of eczema herpeticum cases, the majority are primary infections. There may be a history of herpes simplex infections in family members or other close contacts. However, in one study of 75 cases, 20% followed ordinary recurrent herpes labialis, so that eczema herpeticum may result from endogenous recurrent infection [18]. Eczema herpeticum may be worse in patients with severe, especially erythrodermic, atopic eczema [19] but frequently occurs in mild or quiescent cases [17,18]. Recurrences of eczema herpeticum were noted in five of 10 [17] and eight of 75 [18] cases.

Cases are seen at all ages, most commonly in the second and third decades [18]. In localized cases, local spread seems likely, but widespread dissemination is haematogenous.

Patients who develop eczema herpeticum usually have intact cell-mediated immunity to HSV and have antibodies against the virus [20]. There are reports of eczema herpeticum developing in patients without HSV-specific cell-mediated immunity and one child with severe recurrences of eczema herpeticum had IgG2 deficiency [18]. Whether other immunological abnormalities are involved is unknown. An association with systemic [18] or topical steroid treatment has not been consistently found [17]; whether heavy steroid use predisposes to herpetic infection or simply reflects the severity of the eczema is not known. Other topical and systemic immunosuppression has also been associated with eczema herpeticum, namely topical tacrolimus [21].

Clinical features [1,17,22,23] (Fig. 25.15). In severe cases, after an incubation period of about 10 days (range 5–19 days), vesicles that rapidly become pustular erupt in massive crops. They may be confined to abnormal skin but are often widely disseminated and may generalize, simulating smallpox [2]. They may be haemorrhagic and the face may become grossly oedematous. New crops of vesicles may appear for 5–7 days. Fever, which may be high, commonly develops 2 or 3 days after the onset of the eruption and constitutional symptoms may be severe. The regional lymph nodes are enlarged. The fever subsides after 4 or 5 days and the pustules become crusted and slowly heal, leaving little permanent scarring. Rarely, there may be progression to potentially fatal systemic infection [18,24].

In localized infections, the diagnosis may be confused by secondary bacterial infection, but typical vesicles or subsequent erosions, generally confined to eczematous areas, should be sought, especially if there is a poor response to antibacterial therapy [3]. Low-grade fever and lymphadenopathy are common. These milder infections are usually self-limiting [19].

Recurrences of eczema herpeticum may commonly be milder than the initial episode, but are sometimes of comparable severity [17].

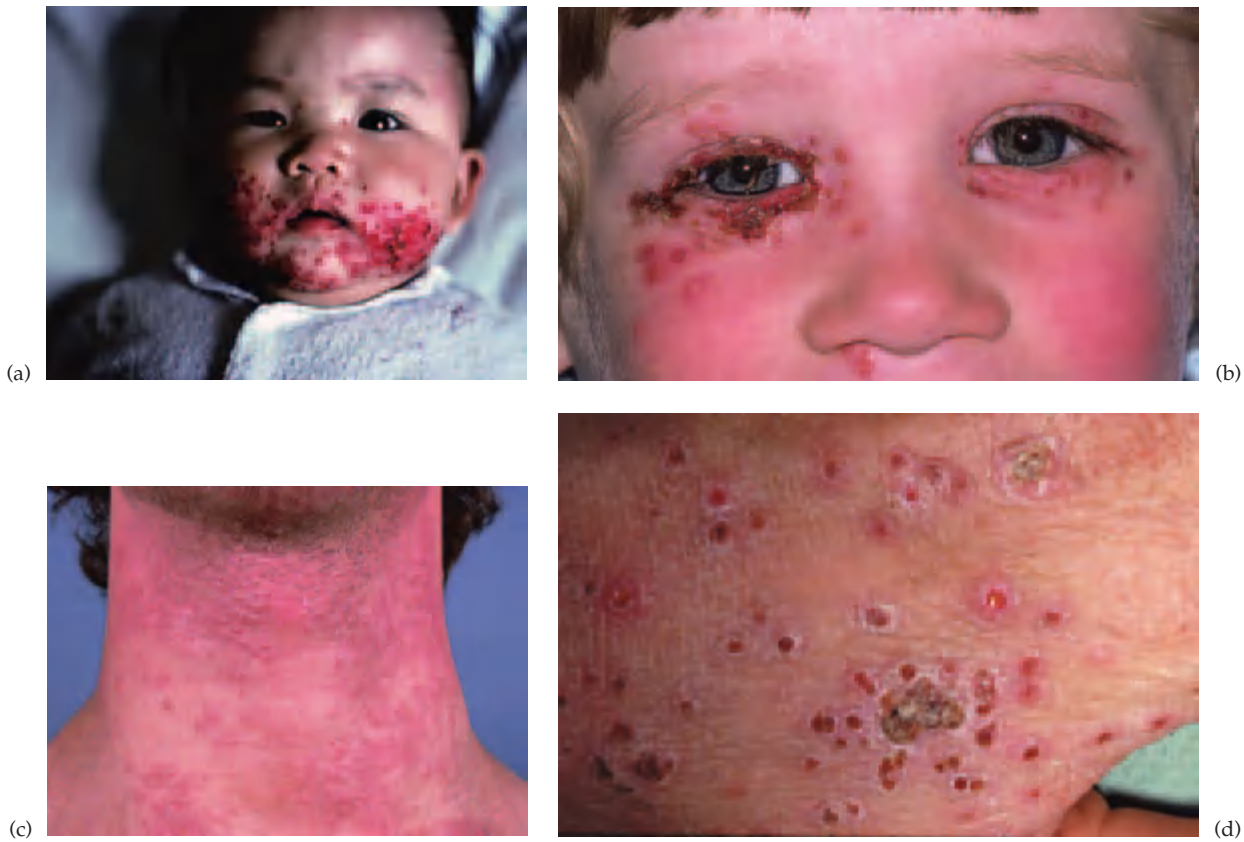

Fig. 25.15 Eczema herpeticum: (a) perioral; (b) periocular; (c) front of neck of 20-year-old man; (d) resolving lesions. (c, Courtesy of York District Hospital, York, UK; d, courtesy of Addenbrooke's Hospital, Cambridge, UK.)

Treatment and prevention. Awareness of the possibility of widespread herpetic infection should be encouraged in atopic eczema patients or their parents. Patients with atopic eczema, especially those with a history of eczema herpeticum, should avoid close contact with relatives and friends with active herpes simplex.

Severe cases should receive intravenous aciclovir [25,26] as early as possible. Less ill patients respond well to oral aciclovir [27,28] or one of the newer antiherpes agents.

Bacterial infection and the underlying eczema or other dermatosis should be treated in the usual way, except that if aciclovir is being withheld, more cautious use of steroid therapy may be advisable until the viral lesions have healed.

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Human papillomaviruses

Papillomaviruses are small (50–55 nm diameter) DNA viruses that infect squamous epithelia, causing cell proliferation. The commonest effect of human papillomavirus (HPV) infection is the development of warts (verrucae). These virus-induced tumours are pleomorphic and can affect a wide variety of sites, principally skin of extremities, genital skin and mucosa, larynx and oral mucosa. The virus infects the basal layer of the epithelium, possibly the stem cells, but viral replication takes place only in fully differentiated keratinocytes, i.e. cells of the upper stratum spinosum and stratum granulosum. The viral DNA is functionally divided into early (E) and late (L) regions; the early genes are responsible for DNA replication, transcriptional regulation and transformation while the late genes code for the structural proteins of the viral capsid. Expression of the late genes depends on differentiation of the host cell. Propagation of papillomaviruses in tissue culture *in vitro* is therefore extremely demanding, as it is difficult to mimic all the necessary requirements for completion of the virus life cycle [1,2].

HPVs form a large group of closely related viruses that can be distinguished on the basis of their DNA. Originally, types were distinguished by DNA homology in liquid hybridization under defined conditions [3]. The ease of PCR and DNA sequencing now permits a different definition of typing: a distinct genotype has greater than 10% difference in nucleotide homology within the *L1* gene compared with other papillomavirus types [4]. If the homology is greater than 90%, the strain is regarded as of that subtype. The number of HPV types is continuously increasing. To date, about 80 types have been cloned and fully characterized. However, new methods of HPV detection have revealed a large number of potential new types, which are yet to be completely evaluated.

The main clinical associations of the different HPV types are shown in Table 25.3. All papillomavirus types have a tropism for stratified squamous epithelial cells, but they vary in their specificity for different anatomical sites [8]. For example, HPV-1 replicates in heavily keratinized skin of palms and soles, whereas HPV-16 has a preference for genital areas and HPV-11 replicates in genital and laryngeal epithelium.

Papillomas caused by HPVs are initially benign. In these lesions, viral genomes replicate as extrachromosomal episomes. A small percentage can progress to dysplasia or neoplasia. This occurs only with certain so-called 'high-risk' or 'cancer-associated' types of HPV, and under certain genetic and environmental circumstances, some of which are incompletely understood. In the majority of malignantly transformed cells (i.e. those affected by high-risk genital HPVs), the viral DNA is integrated into the cellular chromosomes, usually with the loss of large sections of the viral genome. Viral replication does not occur, but the viral regulatory genes *E6* and *E7* are always retained. The oncogenic potential of the high-risk HPV types depends on the expression of these early genes, whose products play a role in cell transformation and immortalization: the E6 protein inactivates the cellular tumour-suppressor protein p53 and the E7 protein inhibits the cellular pRb protein, which normally functions as a negative regulator of the cell cycle.

The clinically evident infections due to HPVs are described on subsequent pages, although there is also evidence that after initial infection, HPV may persist in a latent form and may be subsequently reactivated.

Subclinical and latent HPV infection. Evidence is accumulating, mainly from studies of genital skin and mucosa, for subclinical and latent HPV infection. It has been estimated that up to 70% of genital HPV infections may be subclinical, i.e. unnoticed by the patient but detectable by full clinical examination, histology, cytology or molecular analysis. In a latent infection, there may be no morphological changes but the viral DNA is present.

Of 545 students attending an annual gynaecological examination in an American university, 1% were aware that they had signs of genital warts, but a further 16% had evidence of HPV infection from colposcopy, cytology or detection of HPV antigen or HPV DNA assessed by hybridization [9]. Among female adolescents in an urban population, 24% had clinical, cytological or DNA evidence of HPV infection, although of these, infection was clinically evident in only 15% [10]. Of over 9000 women routinely screened by cervical cytology in Germany, 2.1% had simple HPV infection (koilocytosis) and 3.7% had signs of dysplasia or neoplasia; of the other (cytologically normal) cases, HPV DNA was detected by hybridization in 9% [11]. The same method demonstrated HPV DNA (including type 16) in penile smears from apparently healthy men [12], in neonatal foreskins obtained at routine

Table 25.3 The main clinical lesions caused by different human papillomavirus (HPV) types. (Data from Cobb [5], de Villiers [6] and Meyers *et al*. [7].)

HPV type	Associated clinical conditions
1	Deep plantar and palmar warts
2	Common warts, filiform warts, plantar warts, mosaic plantar warts
3	Plane warts
4	Common warts, plantar warts
5	EV, SCC in EV
6	Anogenital warts, laryngeal papillomas
7	Butchers' warts
8	EV, SCC in EV
9	EV
10	Plane warts
11	Anogenital warts, laryngeal papillomas
12	EV
13	Focal epithelial hyperplasia
14	EV, SCC in EV
15	EV
16	Anogenital warts; CIN, VIN, PIN; cervical carcinoma
17	EV
18	Genital warts, CIN, cervical carcinoma
19	EV
20	EV, SCC in EV
21–25	EV
26	Cutaneous lesions in immunosuppressed, rarely genital lesions
27	Common warts (rare)
28	Flat and common warts in normal and immunosuppressed
29	Cutaneous warts (rare)
30	Anogenital lesions, laryngeal carcinoma
31	Anogenital warts, CIN, cervical carcinoma
32	Focal epithelial hyperplasia, oral papillomas
33	CIN, VIN, cervical cancer
34	Orogenital warts
35	Anogenital warts, CIN, cervical cancer
36–38	EV
39	Anogenital warts, CIN, cervical cancer
40	Anogenital warts, CIN, VIN, PIN
41	Plane warts, SCC skin
42, 43	Anogenital warts
44	Orogenital warts
45	Anogenital warts, CIN, cervical cancer
46	Reclassified as HPV-20b
47	EV, SCC in EV
48	Cutaneous warts (rare)
49	EV
50	EV
51	Anogenital warts
52, 53	Anogenital warts, CIN, cervical cancer
54	Anogenital warts, Buschke–Löwenstein tumour (rare)
55	Orogenital warts
56	Anogenital warts, CIN, cervical cancer
57	Orogenital warts, skin lesions in immunosuppressed
58	Anogenital warts, CIN, cervical cancer
59	Orogenital warts
60	Plantar epidermoid cysts
61, 62	VIN
63	Cutaneous warts (rare), multiple punctate keratoses of foot
64	Orogenital warts, VIN
65	Pigmented plane warts
66–68	Anogenital warts, CIN, cervical cancer
69	CIN
70	Anogenital warts
72	Cervical lesions
73	Anogenital warts
75–77	Skin lesions in immunosuppressed

CIN, cervical intraepithelial neoplasia; EV, epidermodysplasia verruciformis; PIN, penile intraepithelial neoplasia; SCC, squamous cell carcinoma; VIN, vulval intraepithelial neoplasia.

circumcision [13] and in the majority of a series of Panamanian prostitutes [14].

The highly sensitive PCR has revealed apparently very high rates of HPV cervical infection in the general population [11]. In both the Panamanian [14] and Taiwanese [15] studies, when individual women were assessed serially, results were not always consistently either positive or negative, suggesting either an uneven distribution of HPV in affected epithelium or intermittent reactivation of HPV.

Diagnosis. Clinical diagnosis of warts is often sufficient, but atypical, subclinical or dysplastic lesions may need laboratory confirmation of HPV infection. Methods available include:

1 histology;
2 detection of virus particles by electron microscopy—this method would not be helpful for those types of wart which have few virus particles, for example genital warts;
3 immunohistochemistry or immunocytochemistry using type-common or type-specific antibodies;
4 DNA hybridization on tissue extracts or *in situ*;
5 PCR.

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Warts

HPVs can infect and cause disease at any site in stratified squamous epithelium, either keratinizing (skin) or non-keratinizing (mucosa). The clinical problems encountered with such infections can be broadly divided into cutaneous warts, genital warts, oral warts and laryngeal warts.

Epidemiology. Warts occur at any age, but are unusual in infancy and early childhood. The incidence increases during the school years to reach a peak in adolescence and early adulthood [1–3], then declines rapidly through the twenties and more gradually thereafter. In various studies, it has been estimated that 3–20% of school-age children have warts. Of 1000 children under 16 with warts referred to hospital clinics in Cambridge, UK in the 1950s, 70% had common warts, 24% plantar warts, 3.5% plane warts, 2.0% filiform warts and 0.5% anogenital warts [4].

In countries with highly developed medical services, referral rates of warts to dermatology clinics have greatly increased in the last 50 years; however, for common and plantar warts, there are insufficient data to assess whether this reflects a true increase in incidence rather than increased demand for treatment. Over the same time frame, there has been a steady increase in the incidence of anogenital warts (condylomata acuminata) [5]. A study in the UK in 1994 estimated the incidence in young adults aged 16–24 to be 500 per 100 000, with an overall population incidence of 300 per 100 000 [6]. A large study in Rochester, Minnesota, in the 1980s [7] recorded an annual incidence of 106.5 per 100 000, or about 0.1% (0.5% in young adults). This latter study found an adjusted male/female incidence ratio of 1 : 1.4 for anogenital warts, with median ages of 22 for women and 26 for men.

An increase in the incidence of anogenital warts in childhood has also been claimed [8], although numbers of reported cases are small and the purported increase has not been substantiated by epidemiological data; in particular, the Rochester study showed no such trend between 1950 and 1978 [7].

Incubation period. The time of acquisition of the infection can seldom be ascertained for common and plantar warts, but the incubation period has been estimated to range between a few weeks and more than a year [9], and experimental infections have taken as long as 20 months to produce clinical warts [10].

A prospective study of sexual contacts of patients with genital warts indicated an incubation period of 3 weeks to 8 months (average 2.8 months) [11]. It is believed that perinatally acquired HPV infection may not manifest as genital warts for up to 2 years [12]. Only 57% of cases of laryngeal papilloma in children are diagnosed by 2 years of age [13].

Infectivity. Two-thirds of 97 sexual contacts of patients with genital warts themselves developed lesions within 9 months; infectivity seemed highest early in the course of the disease [11]. Studies of male sexual contacts of women with genital HPV disease have shown that use of the hand lens or colposcope on penile skin treated with 3% acetic acid (as in standard gynaecological colposcopy), with biopsy in cases of doubt, can reveal previously unsuspected (subclinical) HPV lesions. The percentage of male contacts ultimately diagnosed as infected was given as 69% [14] and 88% [15]. Thus, it should probably be assumed that any sexual contact of a patient with genital warts is likely also to be infected.

There is no reliable information on the infectivity of common and plantar warts, but experience suggests that it is substantially less. The infectivity of maternal genital HPV as regards laryngeal papilloma in the child seems low; of 51 cases of pregnancy in women with genital warts in the Rochester study, no cases of childhood laryngeal papilloma were seen [7]. The risk of transmission from mother to child with subsequent development of disease in the child has been estimated to be between 1 in 80 and 1 in 1500 [16].

Modes of transmission. Warts are spread by direct or indirect contact. Impairment of the epithelial barrier function, by trauma (including mild abrasions), maceration or both, greatly predisposes to inoculation of virus, and is generally assumed to be required for infection at least in fully keratinized skin [9], as in the following examples.

1 Plantar warts are commonly acquired from swimming pool or shower-room floors, whose rough surfaces abrade moistened keratin from infected feet and help to inoculate virus into the softened skin of others.

2 Common hand warts may spread widely round the nails in those who bite their nails or periungual skin, over habitually sucked fingers in young children, and to the lips and surrounding skin in both cases.

3 Shaving may spread wart infection over the beard area.

4 Occupational handlers of meat, fish and poultry have high incidences of hand warts, attributed to cutaneous injury and prolonged contact with wet flesh and water.

5 Genital warts have a high infectivity. The thinner mucosal surface is presumably more susceptible to inoculation of virus than is thicker keratinized skin; in addition, lesions were noted to be commonest in sites subject to greatest coital friction in both sexes [11].

Iatrogenic transmission. Because of the long incubation period, iatrogenic spread would be difficult to establish and seems not to have been reported, though the possibility exists. HPV DNA has been detected on instruments used for the examination of women with clinical or subclinical HPV infection [17,18]. The virus was still detectable after rinsing in aqueous chlorhexidine and therefore heat sterilization is recommended. HPV DNA was found in the smoke plume from warts treated with laser or electrocautery [19]. The common practice of dipping cotton-wool swabs for a series of patients into the same flask of liquid nitrogen could transfer herpes simplex virus (used as a model, and by implication HPV) between patients [20].

Transmission of anogenital warts in adults. HPV transmission has been most closely studied in the case of anogenital warts. The fact that Oriel's study [11] of 332 patients took place in venereology clinics may involve some selection bias, but his conclusion is generally accepted that anogenital warts in adults are usually but not always transmitted sexually. He observed prospectively 97 people who had had intercourse with patients known to have anogenital warts; 64% developed lesions within 9 months. There are also epidemiological parallels between anogenital warts and other sexually transmitted diseases.

Perianal warts may accompany genital warts, presumably often due to local spread of infection in both sexes, but especially in women. In Oriel's venereologically based study [21], 60 of 72 men and four of eight women, with exclusively perianal warts, reported anal coitus within the preceding year. However, it was not suggested that this was the only possible route. A Danish study of surgical treatment in patients with perianal warts found that 58% of the men were homosexual and 33% of the women regularly practised anal intercourse, but numbers were small and patients with exclusively perianal lesions were not differentiated, genital warts being associated in 38% [22].

Occasional non-sexual acquisition of anogenital warts in adults is assumed to be possible. HPV-1 and HPV-2 may occur in genital warts [23,24]. Warts on the penile shaft in three men in Oriel's series [11] were clinically and histologically similar to common warts which they had in other sites. The sensitivity of PCR analysis has shown that HPV DNA may be present on underwear and the fingers of patients with genital warts [25,26], suggesting that transmission could occur by a number of routes.

Transmission of anogenital warts in children [8,12,27]. Anogenital warts are uncommon in children, although their occurrence frequently stimulates discussion of the possibility of sexual transmission. With the lack of large-scale prospective studies, the possibility of bias in referral or in reporting should be considered, and there remains insufficient information to offer a reliable estimate of the relative frequency of sexual abuse in such cases.

Infection from the mother's genital tract at delivery [28–30] is regarded as a frequent source of childhood anogenital warts, probably including those presenting up to 2 years of age. Genital papillomaviruses transmitted from mother to baby at birth may persist in childhood [31,32] as shown by the retention of the DNA and/or a

humoral response against the viral proteins. Postnatally, transmission from adults with genital warts may occur non-sexually [33], such as by sharing a bath with an infected adult. A review of reports published between 1976 and 1983 [34] found that, of the total of 21 cases, the probable route of infection was believed to be sexual in 11, prepartum or intrapartum in three, and unknown in seven. Studies involving HPV typing of childhood anogenital warts have produced somewhat varying conclusions. Rock *et al*. [29] found genital HPV types (6, 6/11 or 16) in all of five cases and suspected sexual abuse in three. Benton *et al*. [35] found types 6/11 and/or 16/18 in six of 10 cases, and none was positive for HPV-1, HPV-2 or HPV-4; one or both parents of seven of the 10 cases had genital warts, but sexual abuse was considered unlikely in all cases. Venning *et al*. [36] typed nine of 11 cases; three had HPV-2, one HPV-3, two HPV-6, one HPV-11 and two were negative. Of the 11 children, five had coexisting extragenital warts and one of these had HPV-2 in both sites, supporting the possibility of autoinoculation from common warts. The clinical types included classical condyloma acuminatum, fleshly pedunculated lesions, verucca vulgaris and plane warts, but morphology did not correlate fully with HPV type.

Thus, on present incomplete information, both sexual and non-sexual routes are significant in transmission of childhood anogenital warts. The long and variable incubation period, the possibility of latent or subclinical infection in the source and the problems in eliciting an accurate account of sexual contact from the child and of confirming it from the perpetrator all make it difficult to decide which applies in an individual case. Absence of other physical evidence of molestation, location of the warts on fully keratinized skin as opposed to genital or anal mucosa, a clinical resemblance to common warts and young age of the child, perhaps up to 1–2 years at the onset of the warts, would tend to support non-sexual transmission. Where sexual abuse is suspected, the case should be referred to a child-abuse specialist. In addition, HPV typing, if available, may be forensically useful; the same type in child and in suspected abuser would be consistent with, but not proof of, sexual transmission, while different types would be strong evidence against the possibility.

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Pathology. The characteristic histological feature of viral warts is vacuolation in cells in and below the granular layer, often with basophilic inclusion bodies composed of viral particles, and eosinophilic inclusions representing abnormal keratohyaline granules. This cytopathic effect may show detailed features typical of the HPV type involved [1,2] and is almost always accompanied by epidermal acanthosis and often papillomatosis.

Common and plantar warts. These are characterized by hyperplasia of all layers of the epidermis. There is gross hyperkeratosis with areas of parakeratosis especially in plantar warts, and both Malpighian and granular layers are conspicuously thickened. Elongated and flattened dermal papillae are bent inwards towards the centre of the wart. The granular layer may be disordered and vacuolated cells are carried up with the parakeratotic stratum corneum.

Plane warts [3]. The hyperkeratosis is of a loose lamellar type and there is acanthosis without papillomatosis. Vacuolated epidermal cells are more numerous and some are very large.

Genital warts. Genital warts show extreme acanthosis and papillomatosis, although the horny layer is parakeratotic and not much thickened. There may be many vacuolated cells in the upper Malpighian layer, but they may be limited in distribution and not found in all sections. The epidermal processes are wide and rounded, with a well-defined lower border. The connective tissue is frequently very oedematous and the capillaries tortuous and increased. Benign giant condylomas may be difficult to differentiate from malignant condylomas [4]. In the latter the processes are narrower, multiple and often irregular, and mitoses are frequent. Repeated biopsies from a giant condyloma may fail to reveal the malignancy established by its subsequent course [5].

The histology and cytology of cervical epithelium with regard to HPV infection, dysplasia and neoplasia have been widely discussed in the literature and different classifications have developed.

Immunity to HPV [1–3]. The relative sequestration of the virus in the upper reaches of the epidermis, the difficulty of finding control subjects who have never been infected and the large number of HPV types have delayed research and our understanding of the immune mechanisms in relation to this virus. Recently, however, the ability to clone the viral genes and to produce recombinant capsid proteins and early (E) gene peptides has led to many advances. For example, beagle dogs immunized with virus-like particles of major capsid protein of the canine oral papillomavirus developed neutralizing antibodies and were completely protected from developing mucosal papillomas [4]. Also, cell-mediated immune responses have been produced in mice by injecting an HPV-16 E7 peptide. This protected them against subsequent challenge with HPV-16 transformed tumour cells which would otherwise have caused a lethal tumour [5]. These and other studies have led to the development of both prophylactic and therapeutic vaccines. The recent report of 100% protection afforded by vaccination with HPV-16 virus-like particles is dramatic evidence that protective immunity against HPV disease may be possible in the future [6].

HPV lesions are under immunological surveillance. A humoral immune response is mounted against papillomavirus products [7], but the importance of this in modulation of the disease process or prevention against reinfection is yet to be determined. Cell-mediated immunity appears to be the principal mechanism for the rejection of warts. Warts can disappear when the immune response is stimulated. In contrast, in persistent disorders of cell-mediated immunity, the prevalence and severity of warts and the incidence of HPV-related malignancy are increased. In addition, the histological changes in regressing warts are consistent with cell-mediated attack; a study of resolving plane warts showed lymphocytic and phagocytic infiltrates including helper and suppressor T cells, Langerhans' cells and satellite-cell necrosis [8]. A more detailed dissection of the immunological events occurring in resolving genital warts has shown that the lymphocytic infiltrate comprises predominantly $CD8^+$ cells [9].

The apparent failure of the immune system in otherwise healthy individuals to clear warts for months or years remains incompletely understood. A subdued local immune response is suggested by the observations that Langerhans' cell numbers are reduced within warts [10] and ICAM-1 expression is reduced in the proliferating epidermis [11]. In non-regressing warts, T lymphocytes are rare within the epidermal compartment, although they are relatively plentiful in the dermis beneath warts. Some early studies of non-specific measures of lymphocyte function in otherwise healthy patients with warts showed reductions compared with controls, the significance of which was uncertain. In patients who harbour high-risk genital HPVs with the development of cancer, it is possible that the immune system may be unable to

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target certain HPV proteins, possibly due to the development of tolerance. The initial success of the virus in establishing infection may depend in part on avoidance of detection by the innate immune response and certain immunomodulatory effects of the viral proteins. These are as yet not fully characterized but involve altered regulation of interferon-response gene effects.

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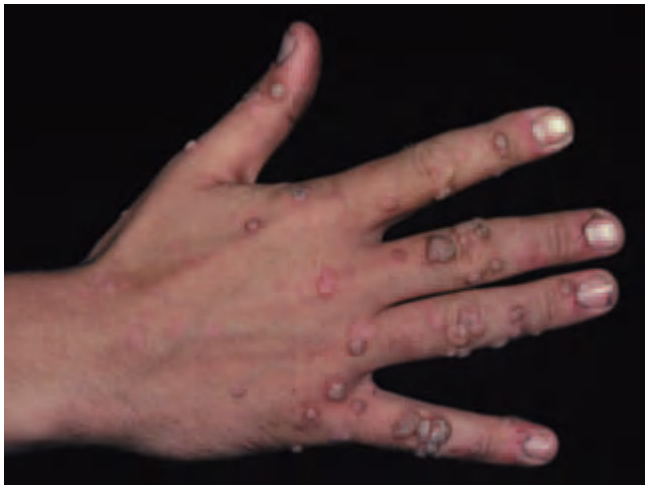
Clinical features

Common warts (Fig. 25.16). Common warts (excluding plantar warts) are due mainly to HPV-2, but also to the closely related HPV-57 and to HPV-1 and HPV-4. Firm papules with a rough horny surface, they range in size from less than 1 mm to over 1 cm in diameter, and by confluence can form large masses. They are most commonly situated on the dorsa of the hands and fingers and, in children under 12 years of age, on the knees, but may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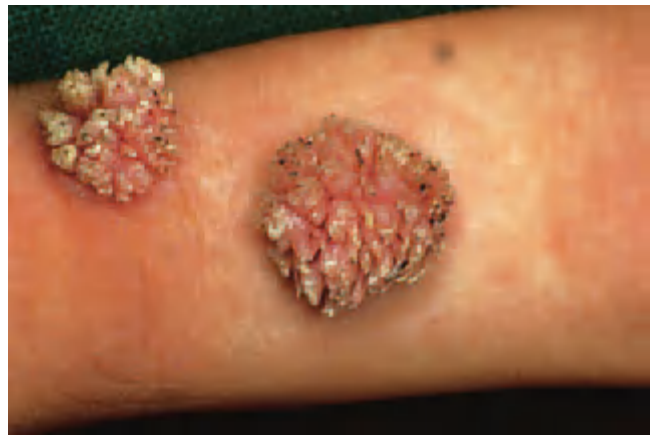
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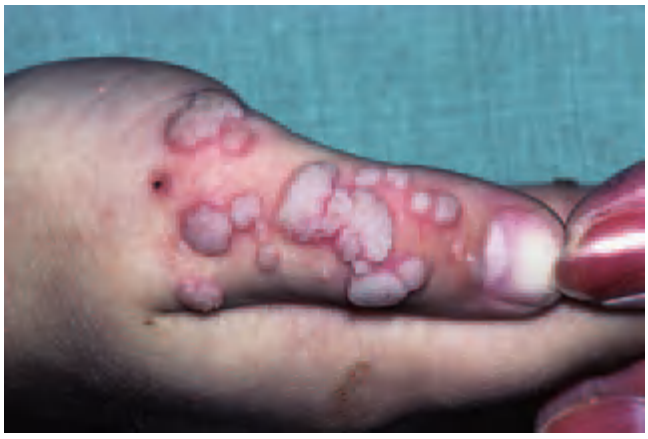
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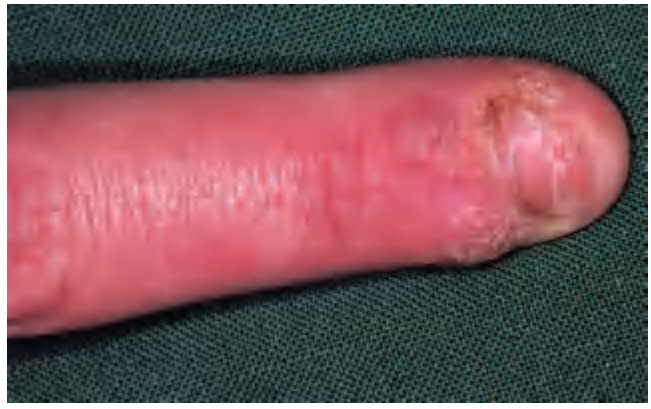
(d)

Fig. 25.16 Common warts: (a) hand; (b) dorsum of finger; (c) warts on thumb spread by thumb-sucking; (d) periungual warts in a nail-biter. (a, Courtesy of Addenbrooke's Hospital, Cambridge, UK; b,c, courtesy of Dr A.S. Highet, York District Hospital, York, UK; d, courtesy of York District Hospital, York, UK.)

occur anywhere on the skin. A single wart may persist unchanged for months or years, or large numbers may develop rapidly or after an interval. New warts may form at sites of trauma, although this Koebner isomorphic phenomenon is usually less marked than in plane warts. However, multiple warts around the nail folds are often seen in nail-biters.

Common warts are usually symptomless, but may be tender on the palmar aspects of the fingers, when fissured or when growing beneath the nail plate. Warts around the nail folds or beneath the nail may disturb nail growth, and warts on the eyelids may be associated with conjunctivitis or keratitis. Common warts account for only 1 or 2% of warts on or around the genitalia; in the male they are almost always confined to the shaft of the penis. They often retain their usual morphological characteristics with dry hyperkeratosis and frequently do not resemble soft acuminate (genital) warts.

It is impossible to offer a reliable prognosis in the individual patient. About 65% of warts disappear spontaneously within 2 years [1–3] and tend to do so earlier in boys [2]. Neither the patient's age nor the number of warts present influences the course. Regression of common warts is asymptomatic and occurs gradually over several weeks, usually without blackening [3,4].

Malignant change in common warts is extremely rare but has been reported.

Plantar warts [5]. Plantar warts involve HPV-1, HPV-2, HPV-4 or HPV-57. The deep 'myrmecia' form is due to HPV-1. Smaller lesions may contain HPV-2, HPV-4 or HPV-57, while mosaic warts are commonly caused by HPV-2.

A plantar wart at first appears as a small, shining, 'sago-grain' papule but soon assumes the typical appearance of a sharply defined rounded lesion, with a rough keratotic surface surrounded by a smooth collar of thickened horn. If the surface is gently pared with a scalpel, the abrupt separation between the wart tissue and the protective horny ring becomes more obvious, as the epithelial ridges of the plantar skin are not continued over the surface of the wart. If the paring is continued, small bleeding points, the tips of the elongated dermal papillae, are evident.

Most plantar warts are beneath pressure points, the heel or the metatarsal heads. In older girls and women they occur predominantly beneath the forefoot and toes. Individuals may be affected by single or numerous lesions. Sometimes, a cluster of small satellite warts, the smallest of pinhead size, having at first an almost vesicular appearance, may develop around a large wart. Mosaic warts are so described from the appearance presented by a plaque of closely grouped warts (Fig. 25.17). The angular outlines of the tightly compressed individual warts are seen when the surface is pared. Groups of warts on the plantar aspect of the heel may in fact be connected under the surface [6].

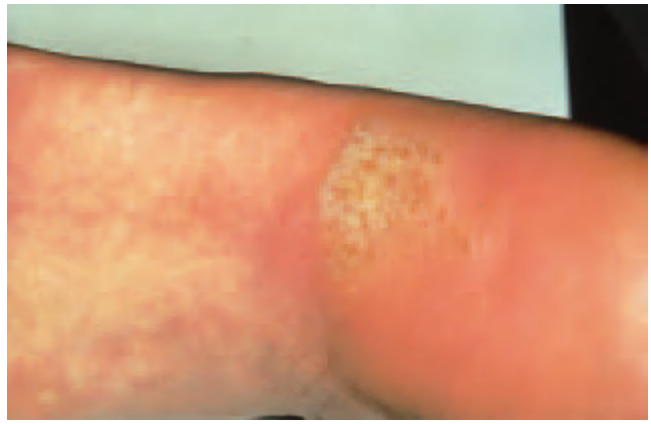

Fig. 25.17 Mosaic plantar wart. (Courtesy of Addenbrooke's Hospital, Cambridge, UK.)

Pain is a common but variable symptom. It may be severe and disabling but may be absent, and many warts are discovered only on routine inspection. Mosaic warts are often painless.

The duration of plantar warts is very variable. Spontaneous regression occurs sooner in children than in adults and is delayed if hyperhidrosis or orthopaedic defects are present. In children before puberty the average duration is probably less than a year and some 30–50% disappear spontaneously over a 6-month period of observation. In older children and adults a longer duration is not uncommon and persistence for several years is not exceptional. The number of warts present does not influence the prognosis, although mosaic warts tend to be persistent. Regression is occasionally clinically inflammatory, and often culminates in blackening from thrombosed blood before the lesion separates [3], but in many cases simply takes the form of apparent drying and gradual separation.

Plantar warts are often confused with callosities or corns, with which they may indeed be associated. Callosities have a uniformly smooth surface across which the epidermal ridges continue without interruption. In cases of doubt the horny layer should be gently pared. Corns occur on pressure points on the toes, soles or interdigital skin.

Plantar warts may rarely be confused with the discrete horny papules of punctate keratoderma of genetic origin (see Chapter 34), which develop during childhood or early adult life, are irregularly scattered over the palms and soles, and are often largest in pressure areas.

Plane warts (flat warts) (Fig. 25.18). Plane warts, due mainly to HPV-3 and HPV-10, are smooth, flat or slightly elevated and are usually skin-coloured or greyish-yellow but may be pigmented. They are round or polygonal in shape and vary in size from 1 to 5 mm or more in diameter. The face and the dorsa of the hands and the shins are the sites of

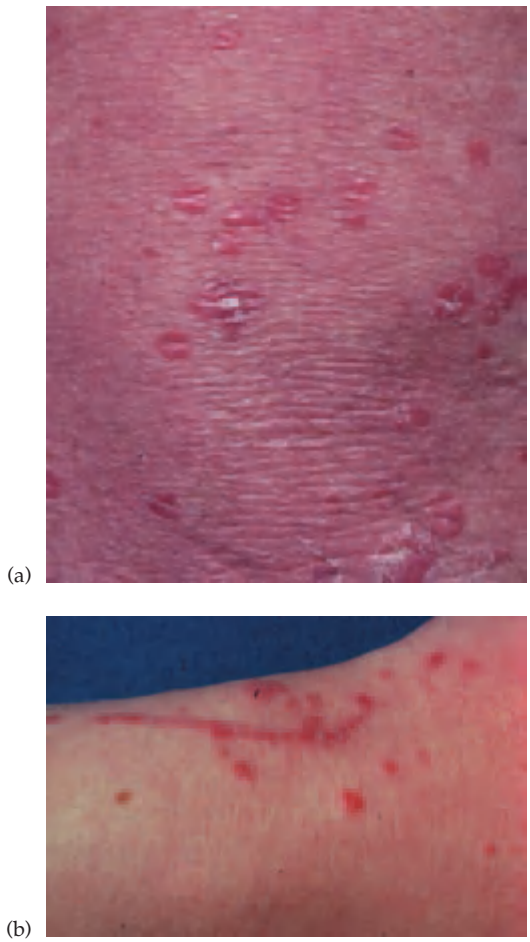

Fig. 25.18 Plane warts: (a) warts on knee; (b) warts on arm with spread into a scratch. (Courtesy of Addenbrooke's Hospital, Cambridge, UK.)

predilection and the number present ranges from two or three to many hundreds. Contiguous warts may coalesce and a linear arrangement in scratch marks is a characteristic feature (Fig. 25.18b). Although all warts present are usually of the same type, a few common warts may be associated, especially on the dorsa of the hands. Laryngeal papillomas have sometimes been associated with plane warts on the face.

Regression of plane warts is usually heralded by inflammation in the lesions, causing itch, erythema and swelling, such that previously unnoticed warts may become evident. Depigmented haloes may appear around the lesions. Resolution is usually complete within a month, and appears to be HPV-type specific as it generally occurs in all plane warts at all body sites, though not in any coexisting warts of other types [7,8].

In differential diagnosis, lichen planus causes most difficulty. It is relatively less common in children, favours the flexor aspects of the forearms, is unusual on the face and is often itchy. The mucous membranes may be

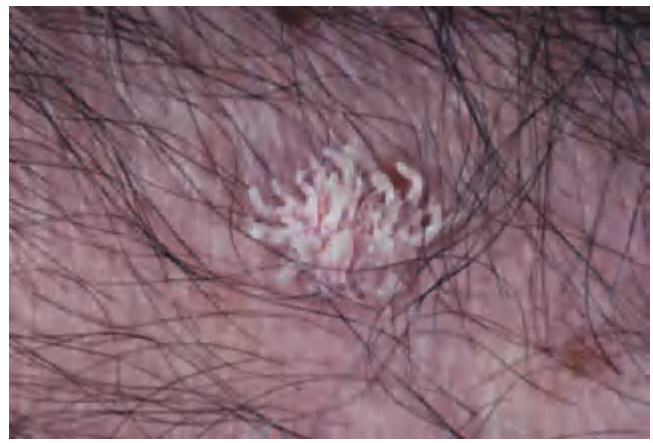

Fig. 25.19 Filiform wart on forearm. (Courtesy of Addenbrooke's Hospital, Cambridge, UK.)

involved. The flat polygonal papules are lilac-pink and smooth and may show Wickham's striae. In contrast, the surface of plane warts has a stippled appearance under the hand lens.

In acrokeratosis verruciformis, numerous warty papules are symmetrically distributed on the dorsa of the hands.

Filiform and digitate warts (Fig. 25.19). Filiform and digitate warts occur commonly in the male, on the face and neck, and are irregularly distributed and often clustered. Digitate warts, often in small groups, also occur on the scalp in both sexes, where they are occasionally confused with epidermal naevi. Isolated warts on the limbs often assume a filiform shape.

Anogenital warts (Figs 25.20 & 25.21). The term 'condyloma acuminatum' (*condyloma*, knuckle; *acuminatum*, pointed; plural condylomata acuminata) was originally used to emphasize the difference between anogenital warts, which are usually protuberant, and the flatter syphilitic lesions called condylomata lata. It became an accepted term, mostly in the American literature, for viral anogenital warts. With developments in the understanding of HPV disease, it is clear that the term is used variously to denote (i) the classical protuberant type of anogenital wart only; (ii) all clinically identifiable HPV disease of the anogenital region, including flat warts on the external genitalia and cervical 'flat condylomas'; and (iii) all clinical lesions due to the HPV types usually associated with genital warts, including those in extragenital sites, for example the mouth.

Anogenital warts are common, with an estimated 1.3 million new cases per year in the USA. They are often asymptomatic, but may cause discomfort, discharge or bleeding. The typical anogenital wart is soft, pink, elongated and sometimes filiform or pedunculated. The lesions are usually multiple especially on moist surfaces, and

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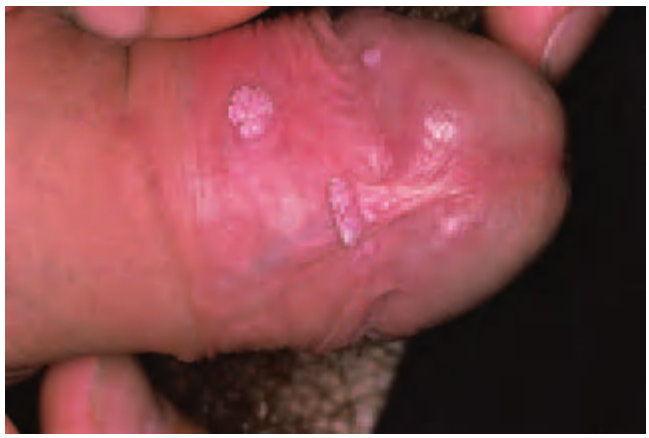

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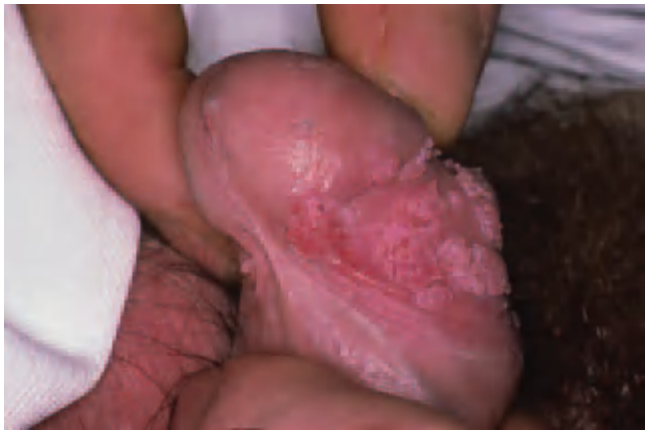

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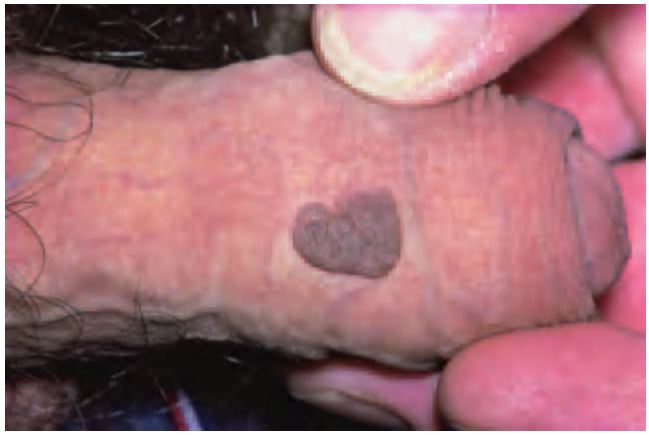

Fig. 25.20 Penile warts: (a,b) classical condylomata acuminata; (c) this pigmented lesion was confirmed histologically to be a viral wart. (Courtesy of York District Hospital, York, UK.)

their growth can be enhanced during pregnancy [9] or in the presence of other local infections [10,11]. Large malodorous masses may form on vulvar and perianal skin. This classical 'acuminate' (sometimes called papillomatous or hyperplastic) form constitutes about two-thirds of anogenital warts. The commonest sites, the area of frenulum, corona and glans in men, and the posterior fourchette in women, correspond to the likely sites of greatest coital friction [9]. Most other lesions are flat, though more conspicuous than plane warts elsewhere, and some of these, generally on non-mucosal surfaces such as the penile shaft, pubic skin, perianal skin and groins, may be sufficiently pigmented to resemble seborrhoeic keratoses. Both acuminate and flat types may coexist. Occasionally only lesions resembling common warts are seen, in men usually on the penile shaft, and these may be the result of contact with common warts elsewhere on the patient or on the sexual partner [9,12].

In children, warts in the anogenital area are often more hyperkeratotic than in adults and may be caused by HPV types associated with cutaneous disease as well as by HPV-6 and HPV-11 (see p. 25.40).

The duration of anogenital warts varies from a few weeks to many years. Recurrences can be expected in about 25% of cases, the interval varying from 2 months to 23 years [13]. HPV DNA has been demonstrated in clinically and histologically normal skin adjacent to warts and intraepithelial neoplasia, and this latency correlated well with recurrence after clinical cure [14].

Of 59 examples of the classical acuminate form, 75% contained HPV-6 and 25% HPV-11. These virus types were also found in flat lesions of low epidermal atypia, but clinically indistinguishable flat lesions containing HPV-16 showed severe epidermal atypia (anogenital intraepithelial neoplasia, Bowenoid papulosis) [12].

Patients with genital warts frequently have other genital infections. These are mainly minor conditions such as candidiasis, trichomoniasis and non-specific genital infection with occasional major venereal infections (syphilis or gonorrhoea) [15,16], although in some series based in venereology departments the incidence of these associated infections has been as high as 10–20% [9,10].

Vulval papillomatosis, with a diffuse velvety or granular appearance, has been associated with HPV infection [17], although more recent studies have refuted a causal link [18,19].

The development of large protuberant masses, induration, pain or serosanguineous discharge should arouse suspicion of malignant change (including Buschke–Löwenstein tumour), requiring prompt excision or biopsy.

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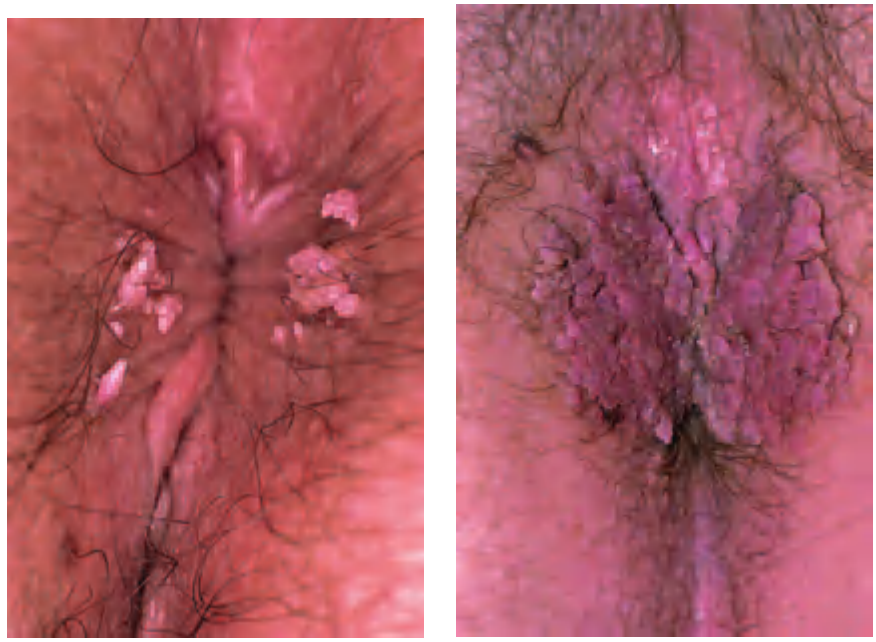

(a) (b)

Fig. 25.21 (a,b) Perianal warts. (Courtesy of York District Hospital, York, UK.)

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Human papillomavirus and warts in special situations

Butcher's warts. Occupational handlers of meat, poultry or fish have a high incidence of warts on skin that is in prolonged contact with animal flesh, usually the hands. Among 1480 New York meat-trade workers, 23% of those directly handling meat had warts compared with 10% of those employed in other tasks [1]. In a Polish study, warts affected 49% of slaughterhouse workers who had direct contact with flesh, but only 9% of those working in a slaughterhouse automated so that little handling of meat took place [2].

These lesions affect the hands, are often larger than common warts and recur after successful treatment in 50% of cases. HPV-2 (the cause of common warts) is frequently found in butcher's warts, but HPV-7 is present in up to one-third of lesions [2–4]. Of 11 fish handlers with hand warts [5], HPV-7 occurred in seven and multiple types in four. HPV-7 initially seemed specific to meat handlers, although there is no evidence that it is an animal papillomavirus which has crossed the species barrier. It has, however, been reported occasionally in warts of non-meat handlers [4,6], and in facial and oral warts of patients with HIV disease [7].

Epidermoid plantar cysts. Epidermoid cysts of weight-bearing areas of the sole have been found to contain papillomavirus (HPV-60 and in one case HPV-57) in several Japanese patients [8,9]. The cysts, which may arise by implantation, show histological features of HPV infection in the stratifying squamous wall. The upper epidermal cells produce large cytoplasmic granules and abundant viral particles.

Pigmented warts. Warts with pigmentation have been reported mainly on palms and soles in Japanese patients [10]. Melanosomes are increased within the lesions, which are associated with HPV-65 (64%), HPV-4 (23%) and HPV-60 (13%).

Respiratory papillomatosis [11,12]. This condition is most commonly due to HPV-11 but is also associated with other common genital types, HPV-6, HPV-16 and HPV-18. Childhood cases are believed to result from maternal infection, probably at birth during vaginal delivery. Latent virus in the laryngeal mucosa [13] presumably explains recurrences after successful treatment, and might explain adult-onset cases, although some of these might be due to sexual transmission [14,15].

Oral warts and HPV [16]. Oral warts, including some which appear to have been sexually transmitted [17], usually contain HPV-6 or HPV-11 [18]. HPV-13 and HPV-32 seem to be almost specific for lesions of the rare, benign, familial disorder focal epithelial hyperplasia (Heck's disease) [19]. HPV-16 has been detected in over 80% of cases of oral leukoplakia, and in some cases of oral squamous carcinoma.

Conjunctival papillomas and HPV. HPV antigen is frequently identified in conjunctival papillomas [20]. Two childhood cases, presenting at about 1 year of age, had genital HPV types suggesting intrapartum infection [21,22].

Nasal inverting papillomas. HPV-11 and HPV-57 have been detected in nasal inverting papilloma and in an inverting papilloma of the maxillary sinus [23–25].

Psoriasis. The use of sensitive PCR amplification has revealed HPV sequences in patients with psoriasis and it is speculated that the virus may have a role in the disease process. DNA of the epidermodysplasia verruciformis HPV types has been demonstrated in over 80% of psoriatic skin lesions compared with nearer 20% of normal skin of non-psoriatic individuals [26,27].

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Treatment [1,2]. The routine treatment of every wart is unnecessary and undesirable. Before specific treatment is given, it is helpful to explain to the patient or parent that warts can be expected to resolve spontaneously without trace, and that the common, more radical measures, such as cryotherapy or cautery, have their disadvantages. Patients may need encouragement to persevere with long-term daily use of the simpler preparations. Whatever method is used there will be failures and recurrences. The best clinical guide to cure is the restoration of normal epidermal texture including the epidermal ridge pattern where appropriate.

Advice on simple measures to limit the spread of the infection will be appreciated. Plantar warts should be covered with adequate plaster strapping or the foot with close-fitting rubber 'verruca socks'; pool-side sandals should be worn at swimming pools or communal baths or showers. The spread of periungual and perioral warts is often due to biting of nails or periungual skin, and this practice must be strongly discouraged if attempted treatment is to be worthwhile; the use of adhesive strapping

after the application of a 'wart paint' helps to break the habit. In addition, simple domestic hygiene, such as cleaning of baths after use and avoidance of shared towels, may be advised.

Below are additional points regarding anogenital warts.
1 The full extent of subclinical and latent genital HPV infection in both sexes is not yet clear. It is generally assumed that treatment of clinical lesions, and probably also subclinical infection, reduces infectivity, although the extent to which this may be confounded by latent virus is unknown. Considering the high sexual infectivity of anogenital warts and the high incidence of latent genital HPV, it may be prudent to assume that the sexual partner is very likely to be infected and that virus is likely to persist, perhaps indefinitely, even after clinical cure. It is usual to advise abstention from intercourse or use of condoms until visible lesions are clear or, some suggest, for 6 months or more thereafter [3]. However, it might be supposed, in stable relationships, that infection of the partner will already have taken place, and it is not known whether the patient can ever be deemed free of infectivity.
2 Occasionally, vulvar warts may be so large in pregnancy as to obstruct vaginal delivery and require caesarean section.
3 The main long-term concern is the risk of cervical dysplasia and neoplasia, so that cervical smear examinations, perhaps at annual intervals, should be advised both for female patients with anogenital warts and for female partners of male patients. This would be especially important if an HPV type known to be associated with neoplasia has been identified. Viral typing can be done by PCR or DNA hybridization techniques on cervical smears or brushings.
4 In children with anogenital warts, consideration should be given to the possibility of sexual transmission and the advisability of referral to a child abuse specialist.

The most commonly used treatments for warts involve destruction of the area of epidermis infected with the virus. Such treatments may involve application of topical preparations or surgical approaches. Other therapies aimed at modifying the growth of the epidermis or stimulating an immune response require either a topical or a systemic approach. Where treatment trials have been placebo-controlled, a 30% response rate is generally observed for placebo treatment.

Salicylic acid. The keratolytic effect of salicylic acid helps to reduce the thickness of warts and may stimulate an inflammatory response. A preparation containing 12–26% salicylic acid, possibly with additional lactic acid, in a quick-drying collodion or acrylate base, is the treatment of first choice for common and plantar warts. Daily use in a comparative study for 3 months achieved cure rates of 67% for hand warts, 84% for simple plantar warts and 45% for mosaic plantar warts, comparing favourably with other methods including liquid nitrogen [4]. A review of six placebo-controlled trials confirmed this impression, with 75% cured compared with 48% of placebo-treated patients [2]. Removal of surface keratin and the remnants of the previous application by gentle use of a pumice stone, emery board or foot file is a helpful preliminary in all warts and essential in very hyperkeratotic plantar warts. However, overenthusiastic abrasion is a common, if understandable, mistake that may enhance spread of the virus by inoculation into adjacent skin. It is conceivable that abrasion of warts may help to stimulate an immune response [5]. Accurate application of a salicyclic acid preparation, avoiding normal skin, may require a fine applicator such as a sharpened matchstick or a cocktail stick, and will minimize subsequent local discomfort. After drying, a whitish deposit remains. Penetration into thick keratin, as on the sole, is enhanced by adhesive plaster occlusion, which promotes maceration of the keratin layer and a reduction in barrier function. Occlusion can improve the response rate for treatment with salicylic acid [6].

These preparations are not suitable for anogenital warts. They can be particularly irritant on facial skin, though especially careful application or the use of weaker formulations, such as 4% salicylic acid in flexible collodion, may be successful.

Collodion contains colophony, which may cause allergic contact dermatitis. Long-standing warts have been observed to disappear if the patient perseveres with this inadvertent immunotherapy, but the discomfort is usually too great for this approach to be regularly useful.

Adhesive plaster containing 40% salicylic acid is useful for plantar warts. It is applied daily, cut to the shape of the wart or group of warts and held in place by plain adhesive plaster. The regular use of salicylic acid preparations on warts may need to be continued for at least 3 months and often longer.

Glutaraldehyde. The virucidal properties of glutaraldehyde can be used in wart treatment. Proprietary preparations contain 10% glutaraldehyde in aqueous ethanol [4] or in a gel formulation. Treated skin hardens and is coloured brown, which limits acceptability on the hands, but the fact that glutaraldehyde dries into the skin without a surface deposit (which may be rubbed off) makes it a useful application for warts on the feet. A preparation of 20% glutaraldehyde in aqueous solution produced a 72% cure rate for a variety of different cutaneous warts in 25 individuals [7]. Allergic contact dermatitis to the glutaraldehyde occurs occasionally and cutaneous necrosis is a rare complication of the strong solution.

Podophyllin and podophyllotoxin. Podophyllin is a plant-derived resin containing several cytotoxic compounds in unpredictable ratios. The most active of these is podophyllotoxin. Both the crude resin and purified podophyllotoxin are used in the treatment of anogenital warts, as

they are more effective on mucosal than keratinized surfaces. They act as antimitotics, disrupting the formation of the spindle on which chromosomes align at mitosis.

Purified podophyllotoxin 0.5% in ethanol applied twice daily for 3 days, extending treatment to 4 or 5 days if necessary and if tolerated, gives better results than podophyllin, with cure rates between 60 and 70% [8,9]. The same routine may be repeated after a week's break if lesions persist. Once-daily treatment is less effective. For both penile and vulval warts, self-application of podophyllotoxin in either solution or cream formulation can be performed by the patient and can give a higher remission rate than the use of podophyllin [10,11].

Podophyllin resin is not used so commonly now, but treatment should be under professional supervision. A solution of 10–25% in compound tincture of benzoin is applied accurately to the area and then allowed to dry for a few minutes. The resin should be thoroughly washed off after 4 h, though the time can be cautiously increased if the treatment is well tolerated. Applications are repeated weekly or more often. Of over 100 men treated weekly for 6 weeks, 22% were clear 6 weeks later and a 10% solution was as effective as a 25% solution [12].

Podophyllin should not be used on exceptionally large or bleeding areas, where its application has been followed by intrauterine death [13], vomiting, diarrhoea, liver damage, renal damage, coma, peripheral neuropathy [14], bone marrow suppression [15] and death [16], due to presumed systemic absorption. Oral ingestion has similar effects and can be fatal [17,18]. In animal studies, podophyllin is abortifacient but not teratogenic [19]. However, though its use in the usual small quantities appears safe, it is generally regarded as contraindicated in pregnancy [19]. The side-effect profile of podophyllotoxin appears to be safer, although the usual precautions for its use should be observed.

Some local irritation is expected especially with podophyllin and is usually greatest 1 or 2 days after application. Histologically, epidermal intracellular and intercellular oedema, mitoses and necrosis are seen, but no signs suggesting carcinogenicity [20].

Podophyllin and podophyllotoxin are generally ineffective if simply applied to warts of other types, due to the lack of penetration of the keratin layer. However, they can be used with caution under occlusion. A technique has been described for plantar warts [21] in which the keratin is pared down well and 25% podophyllin (in soft paraffin, liquid paraffin or a mixture of the two) is applied and occluded by plain adhesive plaster. The dressing is removed after a week, and the process repeated if the wart persists. Although success was achieved, acute pain can occur with intense local inflammation.

Formalin. Soaks or compresses of 2–3% formalin in water (formalin is about 37% formaldehyde in water) may be effective for plantar warts [22], but is time-consuming and difficult to limit to affected skin. The affected area must be soaked in the solution for 15–20 min daily, using soft paraffin as a barrier application to protect more sensitive skin. The formalin is virucidal but also dries and hardens the skin, facilitating paring. A comparative study of formalin soaks with either water soaks or oral saccharose showed no difference in clearance [23].

Topical 5-fluorouracil. A 5% solution of 5-fluorouracil (5-FU) carefully applied daily under occlusion for a month is more effective than placebo [24], but if used periungually may cause onycholysis. A paint containing 5% 5-FU and 10% salicylic acid cleared 50% of hand warts in poultry workers, compared with 4% with the salicylic acid alone [25]. An ointment containing 5% 5-FU was effective for plane warts, although its value was limited by a high incidence of hyperpigmentation as well as erythema and erosion [26]. Application of a solution containing 0.5% 5-FU, 10% salicylic acid and 8% dimethylsulfoxide three times daily for 5 days immediately followed by curettage was successful in six patients with widespread warts [27]. A newer formulation of 5-FU may soon permit slow-release of the compound within warts following intralesional injection.

Caustics. Monochloracetic acid, trichloracetic acid, silver nitrate [28] and other highly irritant chemicals can be used with effect but may cause painful reactions. In treatment of genital warts, cryotherapy is slightly more effective than trichloracetic acid alone [29].

Retinoic acid. This may be applied topically in plane warts, although the best results are claimed for higher than usual concentrations and irritation is common [30]. Of 25 children with plane warts treated with 0.05% tretinoin cream, 85% cleared their warts compared with 32% of controls [31].

Photodynamic therapy. Systemic or topical aminolaevulinic acid can be taken up by dividing cells, metabolized to protoporphyrin and then photoactivated to produce a damaging effect on the cell. The use of this method to treat common warts has so far been limited but has shown some useful effect in hand and foot warts [32] and also in laryngeal papillomatosis [33].

Surgical methods. Excision is usually to be avoided since scarring is inevitable and recurrences of the wart in the scar are frequent. However, good results have been obtained by snipping out perianal warts after subcutaneous injection of 1 in 300 000 epinephrine (adrenaline) in physiological saline under general or local anaesthesia [34]. Curettage can also be effective as treatment for filiform warts.

Curettage and cautery/electrocoagulation, usually in combination, may be used for painful or resistant warts, but carry a risk of scarring. Topical application of eutectic mixture of local anaesthetics (EMLA cream) to the vulva for 10 min numbed the area in over 90% of cases [35]; otherwise, and for keratinized skin, local anaesthetic injection or even general anaesthesia would be required.

A technique of blunt dissection has been advocated for plantar warts [36].

Cryotherapy. Liquid nitrogen is commonly used in hospital practice. Sophisticated instruments are available for producing a thin stream of the liquid to be directed at the lesion, but very satisfactory results are obtained by application of a cotton bud dipped in the fluid. This is made by twirling loose wisps of cotton wool by hand around one end of an orange stick; proprietary buds are too small and too tightly packed. This simple method can be surprisingly versatile: the rate of discharge of the fluid onto the skin is affected by the overall size of the bud, the amount of fluid with which it is charged, the size of the end (a fine point can be fashioned for treating very small warts), the angle at which it is held (holding away from the vertical lessens the discharge rate) and the tightness of packing of the cotton wool, which may be increased temporarily by local pressure.

Any thick keratin should be pared off. This will improve the cure rate in plantar warts [37]. Mucosal surfaces should be dry to avoid the formation of surface ice, which sticks to the bud. The end of the bud should not overhang the wart surface. In standard treatment, the application is continued until a rim of iced tissue (easily seen as a white discoloration) about 1 mm in width develops in the normal skin surrounding the wart. This may stimulate the development of an immune response [38]. After thawing, a second freeze cycle will improve the cure rate in plantar warts, although the benefit is less marked in hand warts [39].

The response to treatment with cryotherapy is comparable to that achieved with salicylic acid [4,40]. Treatment repeated every 3 weeks gives a 30–70% cure rate for hand warts after 3 months [2,4,41]. More frequent treatments may improve responses [41] but will induce more pain, and longer intervals are less effective [4]. If this fails or when a wart is particularly painful or deep, or both, as may occur over a bony prominence on the foot, more prolonged application, typically up to 30 s, perhaps repeated after thawing, may be used to achieve a greater destructive effect at the cost of significantly greater blistering and pain. For such treatment, local or even general [42] anaesthesia may be considered. The common practice of dipping cotton buds for different patients into a common flask containing the liquid nitrogen may carry a risk of cross-infection (see p. 25.40).

Carbon dioxide snow can be used similarly, but the temperature is higher than that of liquid nitrogen and freezing takes about three times as long. The snow is made by allowing the gas to expand rapidly, as by discharging it into a chamois leather bag tied over the gas cylinder outlet. It can be kept in a vacuum flask for several hours. 'Pencils' of the snow can be made by packing it into hollow metal cylinders. Alternatively, the snow can be mixed with acetone to form a slush that can be applied with a cotton bud.

The main disadvantage of freezing is pain. This is unpredictable and surprisingly variable between patients, but in some cases, especially with longer freezing times, it may be severe and persist for many hours or even a few days. Oral aspirin and strong topical steroids may help. Swelling of the treated area and the surrounding skin begins within minutes, and where tissues are lax as in the periorbital area it may be dramatic. A blister, sometimes haemorrhagic, may ensue within a day or two but is not a prerequisite for resolution of the wart, and usually follows overtreatment. After the usual short freezing times, the reaction will be likely to have resolved within 2–3 weeks. Scarring is unlikely with freezing times under 30 s. Occasionally, damage to underlying tissues may result, for example to a tendon [43] or the nail matrix, and excessive freezing times should be avoided over nerves, for example on the sides of the fingers. Depigmentation may occur, and can be a significant cosmetic disadvantage in patients with darkly pigmented skin.

Laser. The carbon dioxide laser has been used to treat a variety of different forms of wart, both cutaneous and mucosal [44,45]. It can be effective in eradicating some difficult warts, such as periungual and subungual warts, which have been unresponsive to other treatments. Clearance at 12 months of up to 70% of individual warts is reported [46]. However, as a destructive method, carbon dioxide laser therapy can cause significant post-operative pain, scarring and temporary loss of function [47].

The pulsed dye laser produces less scarring and has been used to treat warts with varying degrees of success [48–50], with one study suggesting clearance in 48% of patients [51].

Infrared coagulator. As another destructive method, the infrared coagulator can be used to treat warts. The reported cure rate in a series of 44 warts was 70% [52], which compares favourably with cryotherapy.

Contact sensitization. Dinitrochlorobenzene has been used to elicit a repeated contact sensitivity reaction at the site of warts and to induce clearance [53,54]. It may not be of great advantage in treating plane warts [55]. There have been several open studies of contact sensitization with diphenylcyclopropenone (diphencyprone, DPC) using different protocols [56]. Cure rates of 44–88% of patients were obtained at the end of treatment [57,58]. Itching at

treatment sites was generally tolerated, but some patients developed dermatitis in other areas. Regression in plantar warts as well as common warts may be induced [59]. The use of squaric acid dibutylester as a contact allergen in such regimens may be equally efficacious and better tolerated [60].

Interferon [61]. Different interferons (IFNs) have been administered by different routes to patients with refractory warts in various sites. These studies are seldom directly comparable and the use of IFNs in warts is still experimental.

For the most part, IFN use has been disappointing. The majority of studies have involved patients with refractory genital warts. Of 28 patients given intramuscular recombinant human IFN-γ, two were cleared and 13 improved, although the treatment appeared to potentiate the response to subsequent cryotherapy [62]. In a larger multicentre trial, 172 patients received systemic IFN-α or placebo, but there was no difference in response between the groups [63].

IFN has been used as adjuvant therapy, together with surgery, cryotherapy or topical measures. No augmentation of clearance of HPV infection was observed by the addition of IFN-α therapy to caustic application or surgery [64], podophyllin [65] or laser ablation [66]. Used with cryotherapy, IFN-β and IFN-γ reduced the rate of acquisition of new lesions [67] but none of the IFNs when combined with cryotherapy produced any improvement in clearance rate compared with cryotherapy alone [67,68].

The most encouraging report is of complete clearance of injected warts in 11 of 12 patients with recalcitrant common and plantar warts treated with human IFN-α [69]. Cutaneous warts on the palms and soles may also be treated with intralesional IFN, using a needleless injector [70].

No lasting effect was observed in the treatment of recurrent respiratory papillomatosis with intramuscular human IFN-α [71].

Imiquimod. Topical immunomodulation is a promising new treatment for warts. Imiquimod as a 5% cream is currently licensed for treatment of genital warts [72]. Used three times a week for 16 weeks, the clearance rate is 65% with a 20% recurrence rate. Cutaneous warts have also responded to imiquimod treatment [73,74], although poor penetration through the keratinized surface may necessitate combination with occlusion, salicylic acid or more frequent application to achieve useful results.

Cimetidine. In adults, the use of cimetidine in wart treatment has given conflicting results. In an open study of 18 patients treated with 30–40 mg/kg daily for 3 months, two-thirds demonstrated complete resolution of their warts without recurrence after 1 year [75]; however, in a placebo-controlled trial of 54 patients, no significant benefit of cimeditine therapy was observed, with approximately one-third responding in both treatment and placebo groups [76]. Cimetidine has also been used in a small number of children to treat common warts [77] and plane warts following failed treatment with contact sensitization [78] and showed a potentially useful response.

Retinoids. Etretinate orally has been helpful in cases of extensive and hyperkeratotic warts in immunosuppressed patients, one with sarcoidosis [79] and one with chronic lymphatic leukaemia [80]. The bulk of the lesions was greatly reduced, but the warts were not eradicated and relapsed when the drug was reduced or stopped.

Hyperkeratotic warts in otherwise healthy patients may occasionally show a similar response during etretinate therapy [81,82]. This effect may be temporarily useful, perhaps in relieving pain or disability due to exceptionally hyperkeratotic warts, or in facilitating the use of other treatments.

Intralesional bleomycin. Doses of this cytotoxic agent are measured in units or milligrams; 1 mg contains 1500–2000 units. Protocols vary, but typically bleomycin sulphate 0.25–1 mg/mL is injected up to three times to a maximum total dose of 4 mg [83]; or 1000 units/mL to two injections and a maximum total dose of 2000 units [84,85]. A lower concentration of 500 units/mL seemed as effective [86]. Injections are into the wart itself, confirmed by observing blanching in the lesion, the volume per injected lesion ranging between 0.2 and 1.0 mL. Injections are very painful and preceding or concurrent local anaesthesia should be considered, especially for sensitive sites such as fingers and soles [87]. A haemorrhagic eschar develops 2–3 weeks later; it is pared down if it has not detached spontaneously. These studies reported wart cure rates for previously refractory warts of between 30 and 100% [86,88]; in addition, warts which do not clear commonly improve or become painless.

Used in this way, there has been no evidence of systemic toxicity. Local complications include nail loss [89] or nail dystrophy [90] following periungual injections, Raynaud's phenomenon in treated fingers and local urticaria [89]. The risk of systemic absorption is a contraindication for intralesional bleomycin in pregnancy [86].

Hayes and O'Keefe [86] give useful guidance on method and contraindications. Implantation of the bleomycin from a surface application using a bifurcated needle [91] or a sterile lancet [92] may be better tolerated.

Local heat. Repeated raising of the temperature of wart-affected skin to a maximally tolerated level of about 50°C is reported to induce wart clearance [93]. The Nd:YAG laser can be used to produce a similar effect [94].

Psychological methods. Most studies claiming that warts can be effectively treated by suggestion or 'magic' were inadequately controlled for spontaneous regression [95]. Formal hypnosis, however, has been reported to clear warts on only the suggested (the more severely affected) side in nine of 10 patients who achieved a satisfactory depth of hypnosis, the other side of the body acting as an internal control [96]. Children appear to have a higher rate of success than adults [97]. Persistent refractory warts disappeared following hypnosis in an uncontrolled study of three immunodeficient children [98].

Radiotherapy. The use of radiotherapy for warts should never be employed routinely as the first line of attack; moreover, the efficacy of safe doses is questionable [99]. A follow-up of 100 patients showed serious post-irradiation damage in 7% and slight radiodermatitis in 31% [100]. If used at all it should be reserved for selected cases and administered only by an experienced dermatologist or radiotherapist who is fully aware of the potential hazards. The correctness of the diagnosis must, of course, be beyond doubt.

Antiviral therapy. The large number of treatments listed above indicate the lack of an ideal method for eliminating warts. The antiviral cidofovir, a purine nucleotide analogue of cytosine, applied topically as a 1% gel or by intralesional injection (2.5 mg/mL) is extremely effective. Plantar, anogenital and laryngeal warts [101] resolve completely. Grade III cervical, vulval and penile intraepithelial neoplasia also respond to this drug.

Therapeutic vaccination. Although not yet available as a treatment modality for HPV disease, animal models to test the most effective approach to vaccination are available. In addition, clinical trials of therapeutic vaccination for cervical carcinoma, cervical intraepithelial neoplasia, genital warts, laryngeal papillomatosis and cutaneous warts are in progress. Recent reports of the use of intralesional *Candida* antigen to produce a local hypersensitivity reaction suggest that this approach could be effective wart treatment in recalcitrant cases [102].

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HPV-associated epidermal dysplasia and neoplasia

HPVs have been associated with several different dysplastic or malignant conditions. An aetiological association between infection with high-risk HPVs and the development of cervical carcinoma is now recognized, but the precise role of HPV infection in other genital malignancies, cutaneous squamous cell carcinoma and a variety of other tumours is yet to be clarified. Only the relationship between genital and cutaneous malignancy and HPV infection is discussed in detail, although there are reported associations of HPV or warts with some other premalignant and malignant conditions.

1 Oral leukoplakia and carcinoma: HPV-16 and others [1].

2 Conjunctival and corneal dysplasia and neoplasia: HPV-16 [2].

3 Carcinoma of nasal cavities, oesophagus and larynx: mostly HPV-11 and HPV-16 [3] and also HPV-57b [4].

4 Carcinoma of lung [5,6], including a patient with laryngeal papillomatosis [7].

5 Basal cell carcinoma in immunosuppression: HPV-2 [8] and epidermodysplasia verruciformis-associated types (see p. 25.59).

6 Keratoacanthoma: HPV-25 [9] and HPV-16 [10], although absence of HPVs is also reported [11].

7 Adenocarcinoma of the cervix: HPV-18 is more commonly associated than HPV-16 [12].

Cervical intraepithelial neoplasia and invasive carcinoma [13]

These conditions are epidemiologically associated with sexual activity, including multiplicity of partners and a history of sexually transmitted diseases, in both the female patient and her male partner(s). Cervical intraepithelial neoplasia (CIN) is often associated with a personal history of overt genital warts [14], and with previous penile warts [15,16] or penile intraepithelial neoplasia [17] in the partner.

HPV is commonly detected in dysplastic cervical lesions and is found in 90–100% of cervical cancers [12,18]. Types 16 and 18 are the most commonly associated HPVs, accounting for 70–80% of HPV-positive lesions, although approximately 30 different HPV types can infect the cervix. In carcinoma cells, HPV DNA is integrated into the host cell genome, in contrast to its extrachromosomal location in benign and premalignant lesions [19].

Antibody to HPV-16 capsid antigens is present in about 75 or 50% of women with HPV-16-positive CIN or invasive carcinoma, respectively [20,21]. HPV-16 antibody may also predate the development of cervical disease as shown in a Finnish study where 18 000 blood donors were followed for up to 23 years after giving a baseline blood sample. Antibody was detected in 24% of those who subsequently developed cervical carcinoma compared with only 2% of the matched controls, a risk ratio of 12.5 [22]. Although the most important risk factor, HPV infection by itself does not appear to cause cancer; additional environmental co-factors are required [23].

However, HPV-16 can also be detected by sensitive PCR in a proportion, variously reported to be 5–80%, of cytologically normal cervices [24,25]. This association is highest in young, sexually active women, and one European study showed that only 5% of women aged 35–55 years carried the virus latently in the cervix [26]. In a study of over 200 cervical smears, HPV-16 DNA was found using a hybridization technique in 47% of patients with high-grade intraepithelial lesions (CIN-III) or invasive carcinoma [27]. The finding of a high-risk HPV type in the cervix increases the likelihood of progression of the disease [28].

The management of subclinical HPV infection, cervical dysplasia and neoplasia is beyond the scope of this book; however, the possible risk of the eventual development of these conditions when anogenital warts are diagnosed in either sex will affect the management of the wart patient.

Vulval intraepithelial neoplasia, penile intraepithelial neoplasia and Bowenoid papulosis [29] (Fig. 25.22)

Full-thickness epidermal dysplasia of the vulva or penis is now classified as grade III vulval intraepithelial neoplasia (VIN) or penile intraepithelial neoplasia (PIN) [30], although the term 'Bowenoid papulosis' is still used by many dermatologists. VIN-III and PIN-III are strongly associated with HPV-16 [31,32]. Small papules, usually multiple and sometimes pigmented, present on cutaneous and mucosal surfaces of the anogenital region in both

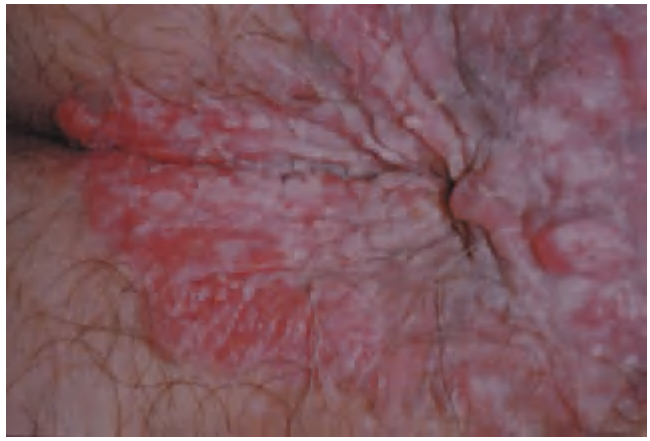

Fig. 25.22 Perianal intraepithelial neoplasia, grade III. (Courtesy of Addenbrooke's Hospital, Cambridge, UK.)

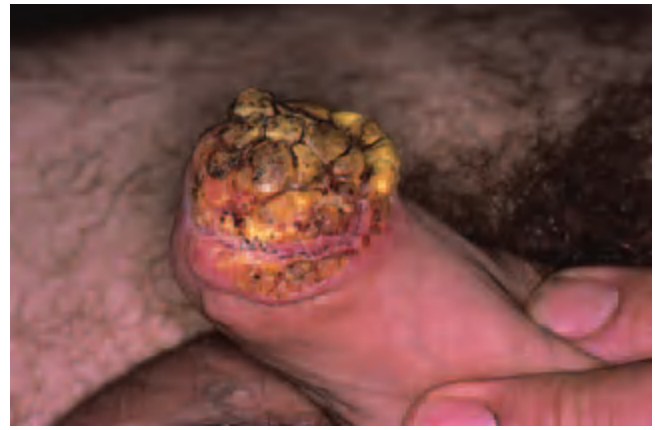

Fig. 25.23 Buschke–Löwenstein tumour. (Courtesy of Dr A.S. Highet, York District Hospital, York, UK.)

sexes, often resembling simple warts, seborrhoeic keratoses or cellular melanocytic naevi. There may be areas of erythematous thickening or small erosions or ulcers. There is often a history of preceding genital warts and the disease is more common in smokers. It usually affects young to middle-aged adults, but no age is exempt. Low-grade and some high-grade lesions resolve spontaneously. For many years, progression to carcinoma has been considered rare, occurring in less than 5% [33], but a recent study of affected individuals in New Zealand has suggested that, untreated, VIN-III may carry a high risk of progression to invasion [34]. Analyses of carcinomas of the vulva, penis and anus have confirmed that many harbour high-risk HPVs, especially type 16 [17,35–38].

Conditions clinically similar to genital intraepithelial neoplasia include Bowen's disease and erythroplasia of Queyrat, which, in contrast, affect the middle-aged and elderly, present as one or a few larger flat plaques, show more advanced dysplasia and carry a significant risk of invasive malignancy.

Persistent and refractory cases of VIN-III and PIN-III may have underlying immune deficiency and may develop malignancy at other sites. Four such (HIV-negative) men had T-helper-cell depletion, anergy or both, and one developed squamous carcinoma of the tongue, which, like his Bowenoid papulosis, contained HPV-16 [39].

Treatment. Extensive surgery is generally not indicated and to remove all infected tissue could be mutilating. Simple excision of small areas, cryotherapy, carbon dioxide laser and diathermy can help to contain the disease. Good results without scarring have been reported for the Nd:YAG laser [40]. Oral retinoid therapy may be effective [41]. More recent studies with the antiviral cidofovir [42], the topical immunomodulator imiquimod [43] and therapeutic vaccination [44] offer hope of disease control.

Buschke–Löwenstein tumour (Fig. 25.23)
SYN. GIANT CONDYLOMA; VERRUCOUS CARCINOMA

This lesion enlarges from a pre-existing benign anogenital wart. It harbours HPV-6 or HPV-11 [45], which is often mutated. It is locally invasive on a broad front, but is well differentiated and rarely metastasizes. Clinically and histologically it resembles verrucous carcinoma, and some authorities classify it as such [46]. Treatment is usually surgical, although aggressive cryotherapy [47], bleomycin [48] and recombinant IFN-α-2a [49] and systemic retinoid [50] have also been used. Radiotherapy should be avoided as it may precipitate transformation to an anaplastic carcinoma.

Cutaneous squamous cell carcinoma without immunosuppression

The high- and low-risk HPV types that cause genital disease are also reported in certain extragenital warts and carcinomas. Although such cases are more common among the immunosuppressed, immunocompetent individuals may also be affected. A child with atopy and sickle-cell disease was found to have HPV-6 in pigmented warty lesions on the limbs [51]. Squamous cell carcinoma of the fingertip and nail bed has been associated with HPV-16 [52,53]. Cutaneous intraepithelial carcinoma of the skin (Bowen's disease) has been found occasionally to harbour HPV-2 [54], HPV-16 [55] and HPV-34 [56].

Malignant change may rarely develop in apparently normal warts, usually when very long-standing. A facial wart in an elderly man became invasive [57]. Plantar warts that have developed into carcinoma cuniculatum may develop from pre-existing plantar warts [58] and such lesions can be found to contain HPV sequences [59].

Ionizing radiation may act as a co-factor for malignant change in warts [60]. Widespread actinic keratoses and

cutaneous squamous cell carcinomas arising after arsenic treatment or PUVA photochemotherapy may also be associated with HPV infection [61,62]. With the advent of more sensitive PCR methods for detection of HPV DNA, the viral genome has been found in approximately 25–50% of keratoses and non-melanoma skin cancers of immunocompetent individuals [63]. It is DNA of the epidermodysplasia verruciformis-associated types that is present in these lesions. The viral DNA is not exclusive to dysplasia—it can also be found in normal skin and hair follicles in 45% of people tested [64]. The molecular role of the virus in the development of skin cancers is a subject of intense debate [65].

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Epidermodysplasia verruciformis

Epidermodysplasia verruciformis (EV) is an inherited disorder in which there is widespread and persistent infection with HPV, giving rise to a characteristic combination of plane warts, pityriasis versicolor-like lesions and reddish plaques. Malignant change is very common but metastasis is rare.

Aetiology. Susceptibility to the virus is inherited, usually autosomal recessive, although autosomal dominant [1] and probable X-linked dominant [2] patterns have been reported. Two loci on chromosomes 17q25 and 2p21–p24 are associated with the disease within some studied families. Impairment of cell-mediated immunity, notably T-helper-cell number and function, is commonly but not invariably found, although EV patients are not unusually susceptible to other infections. These changes are similar to, but more pronounced than, those seen in ordinary wart patients, and may be secondary to the infection rather than a primary abnormality predisposing to it. The increased natural killer cell activity in EV patients infected with oncogenic HPV types is interpreted as an appropriate response [3].

There is no impairment of DNA repair [4] and no association with HLA-A or HLA-B antigens [5].

There are at least 20 HPVs characteristic of EV, including types 5, 8, 9, 12, 14, 15, 17, 19–25, 28, 29, 36–38, 47, 49 and 50. In addition, HPV-3 and HPV-10, which cause ordinary plane warts, are found in EV. There may be more than one HPV type in the same patient [6,7].

Pathology [1,8]. The histological picture is similar in the different clinical types of lesion. As in ordinary plane warts, hyperkeratosis and acanthosis are present. However, vacuolation in the keratinocytes is more extensive, and may affect the upper half to three-quarters of the Malpighian layer. Viral particles can be identified ultrastructurally not only in the Malpighian cells but also in basal cells and, perhaps due to apoptosis, below the basal lamina. There is a gradual progression towards dysplasia.

Clinical features [1,9–13]. Lesions on the face and neck are generally indistinguishable from plane warts, but on the trunk and limbs they tend to be larger and of two main types. Scaly macular lesions closely resemble pityriasis versicolor, showing depigmentation or varying degrees of brown pigmentation. Thicker plaques are dull pink to violet in colour and may resemble seborrhoeic keratoses.

There is a tendency for HPV-3 and HPV-10 to be found in plane warts in EV, as in other patients, but the correlation between HPV type and lesional appearance is not close [10], except that HPV-5 and HPV-8 are the main types associated with malignancy [6,7], with HPV-14, HPV-17, HPV-20 and HPV-47 occasionally involved [14].

Irregular confluence of neighbouring lesions to form lines or large plaques is often seen. Typical common warts are often present, especially on the sides of the fingers and on the palms and soles, and small warts on the vermilion border of the lips or in the urethra have occasionally been noted.

The warts usually develop rapidly in childhood but may first appear at any age. They are most numerous on the face and neck and dorsa of the hands and feet, and may be restricted to these sites, but there are often scattered lesions elsewhere and warts may be generalized over the entire body surface. Cases have been reported in which all the warts were larger and hypertrophic [15]. EV is remarkably persistent and may remain unchanged for decades. However, slow spontaneous regression following two pregnancies has been reported in a single case [16].

A family with probable X-linked dominant inheritance also had dystrophy of fingernails and toenails [2]. There

has been a report of a patient with EV who had palmar pits in addition to the more typical signs [17].

Dysplastic and malignant changes occur most often on exposed skin, commonly as actinic keratoses and Bowen's disease, suggesting that UV radiation is an important factor. Squamous cell carcinoma has ultimately developed in one or more lesions in about 20–30% of reported cases, even before the age of 20 and when the lesions have been present for under 10 years. However, metastasis is rare.

Diagnosis. Acrokeratosis verruciformis (see Chapter 34) is superficially very similar. Flat warty papules on the dorsa of hands and feet and on knees and elbows are present from infancy. The palms are diffusely thickened and show small keratoses and punctiform breaks in the papillary ridges. Histologically there is no vacuolation.

Similar cases that appear to be based on acquired immune deficiency, such as lepromatous leprosy [18] and treated Hodgkin's disease [19], might more appropriately be labelled generalized verrucosis.

In lichen planus (see Chapter 42) the papules, which are usually pruritic, are pink or lilac in colour and distinctive mucosal lesions are often present. The histology is diagnostic.

Treatment. Patients should be observed for the development of carcinomas and premalignant lesions, which should be excised or locally ablated. Avoidance of excessive sun exposure, with diligent use of effective sunscreen, should be advised.

The role of etretinate in EV is not clear. Substantial clinical improvement is often achieved at a typical starting dose of 1 mg/kg daily, but signs of viral infection persist histologically. The effect is dose dependent and relapse occurs if the drug is stopped. Some cases respond poorly [20]. Whether dysplastic or malignant change is prevented by etretinate is not yet known [1].

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HPV in immunosuppression

Warts and HPV in immune deficiency

Chronic immune deficiency, especially of cell-mediated function, predisposes to clinically evident warts, perhaps by allowing the development of lesions from previously latent virus. The warts may be so widespread that they constitute generalized verrucosis or resemble EV.

This is seen especially in the long-term immunosuppression of organ transplantation. Of 120 renal transplant recipients, 15% had warts 1 year post transplant [1], but this can rise to 90% at the end of the fifth year [2]. Of 47 children with renal transplants, 18 (38%) had warts, some of unusual severity and, except for the mildest cases, refractory to standard methods of treatment [3]. In renal transplant recipients, HPV-2 and HPV-4 warts are the most frequent. Long-term immunosuppressed individuals may develop lesions very like those in EV, with small erythematous non-warty plaques and squamous cell carcinomas especially on sun-exposed areas. Viral analysis from flaking, keratotic or invasive lesions has shown heterogeneity of HPV types [1,4–6], including those associated with EV. Recent techniques using degenerate primers in PCR have shown that many more, some as yet incompletely characterized, HPV types may be present in dysplastic or malignant lesions of transplant recipients [7,8] and also in clinically normal skin and hair follicles [9,10]. The incidence of CIN is also increased [11].

The prevalence of warts is not increased by short-term immunosuppression given to bone marrow transplant recipients [12].

HIV infection and AIDS (see Chapter 26)

The incidence of warts is reported to be between 5 and 27% in HIV infection. Common and plantar warts are probably somewhat increased in frequency and severity but are not a major problem in most patients. There is an increased incidence of facial and intraoral warts, many of which contain HPV-7, the 'butcher's wart' virus [13]. Perianal warts, especially in homosexual men, may be florid and refractory to treatment. Malignant change including CIN is increased in incidence [14,15]. Patients with HIV infection may also develop an EV-like syndrome, with widespread plane warts, keratoses and development of cutaneous malignancy [13].

Other causes of immunodeficiency

The incidence of warts is increased in patients with Hodgkin's disease and, to a lesser extent, in those with other malignant lymphomas and chronic lymphatic leukaemia [16]. Of a series of patients with systemic lupus erythematosus (SLE), 45% had warts compared with 12% among controls [17]. Chronic extensive plane warts were reported in a woman with immune deficiency secondary to intestinal lymphangiectasia [18]. EV-like conditions have been associated with treated Hodgkin's disease [19] and with lepromatous leprosy [20].

Primary immune deficiencies, mostly involving cell-mediated immunity, may be accompanied by widespread warts, for example ataxia-telangiectasia [21], Fanconi's anaemia [22] and Wiskott–Aldrich syndrome [23].

The association of warts of palms and soles, seborrhoeic keratoses of the trunk and Bowen's disease of the face in two brothers, who also had congenital dislocation of the hips and kyphoscoliosis, has been labelled Bittner's syndrome [24]. The patients had low IgA levels and a poor cell-mediated response.

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Hepatitis viruses

Hepatitis B

Aetiology and pathology [1,2]. Hepatitis B virus (HBV) is transmitted mainly percutaneously or sexually in Western developed countries like the USA and the UK, while in areas of high prevalence, for example the Far East and sub-Saharan Africa, perinatal transmission from the mother or horizontal spread from other children predominates.

In acute infection, three types of particle are seen in the serum by electron microscopy: 42-nm-diameter virions consisting of the viral DNA in the core (HBc) surrounded by surface antigen (HBsAg), and 20-nm round and tubular structures which are excess HBsAg. There are highly sensitive techniques for the detection of HBsAg and of antibodies to HBs and HBc. HBeAg is a soluble protein, part of the core (HBc) antigen, and its presence parallels that of complete virions and HBV DNA in the blood, providing an assessment of infectivity.

During the incubation period of 6 weeks to 6 months, antigenaemia can occur more than 4 weeks before symptoms; however, about two-thirds of those infected have an asymptomatic or unrecognized infection. In some people, early antibody is produced and becomes complexed with

this antigen, resulting in a serum sickness-like illness that precedes hepatitis.

After acute hepatitis in otherwise normal people, antigenaemia persists in about 5% of cases, who are called carriers; the carrier state is defined as the presence of HBsAg positivity for more than 6 months. In general, when HBeAg has disappeared and anti-HBe is present in a carrier, the infectivity is low. Most carriers have become infected in the neonatal period or are immunocompromised and do not give a history of hepatitis or suggestive symptoms.

Dermatological manifestations [1,3–5]. Apart from Gianotti–Crosti syndrome, the dermatological features of HBV infection are mostly believed to be associated with immune complex formation [6].

Serum sickness syndrome. This occurs in 20–30% of cases usually as a prodrome 1–6 weeks before the onset of clinical hepatitis, though occasionally coinciding with it, and sometimes without clinically evident liver disease. Urticaria and angio-oedema are common, and when histology has been performed it has confirmed the expected vasculitic basis [4]. More advanced vasculitis may manifest as petechiae, palpable purpura and erythema multiforme-like lesions. Macular, maculopapular and lichenoid eruptions and erythema nodosum [7] may occur. Arthralgia or arthritis, and headache [8] are commonly associated.

Polyarteritis nodosa. Urticaria, purpura and multiform exanthems occur in about one-quarter of cases of polyarteritis nodosa. HbsAg has been detected in 8 to over 50% of patients with polyarteritis nodosa [9,10]. In one study, when HBsAg disappeared and anti-HBs appeared in two patients, both had a dramatic clinical improvement. This suggests an immune-complex mechanism for the pathogenesis of hepatitis B-associated polyarteritis nodosa. Polyarteritis nodosa associated with hepatitis B infection has also cleared following treatment with lamivudine [11].

Prophylaxis. Active immunization is achieved by a course of three doses of recombinant surface-antigen vaccine. In many countries, universal immunization is given to infants with the added long-term goal of eradicating the disease. In other countries, a policy of selective immunization of high-risk groups has been followed [12]. The efficacy for young adults is about 90%, but decreases with age and in immunocompromised people. Response to the vaccine should be checked 2–3 months after the third dose of vaccine by testing for anti-HBs antibody. Responders retain long-lived immunological memory that effectively sustains immunity even when the level of antibody declines.

Passive immunization with high-titre anti-HBs human immunoglobulin is used (in conjunction with vaccine) for newborn babies of highly infectious (HBeAg positive) HBV-carrier mothers and for unimmunized people or in those who have failed to respond to the vaccine after accidental exposure (e.g. needlestick injuries).

Erythema nodosum, generalized granuloma annulare, thrombocytopenic purpura and Reiter's syndrome have followed hepatitis B vaccination [13–16].

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Hepatitis C

Aetiology. Hepatitis C virus (HCV), previously called non-A, non-B hepatitis virus, is a member of the Flaviviridae. It is found throughout the world, although the prevalence of seropositivity varies between 1 and 10% depending on the region. It is spread parenterally by blood and blood products, by needle sharing and perinatally from infected mothers to their babies in 1–10% of cases. Sexual transmission is at a low rate.

The virus replicates in hepatocytes and blood mononuclear cells. Most acute infections are subclinical, but in 75% of individuals infection leads to a chronic hepatitis, which in some cases can progress to cirrhosis and occasionally development of hepatoma. Improved awareness

of HCV has led to a decrease in acute infection but, as yet, no change in chronic infection.

Cutaneous manifestations [1,2]. The immune response to the virus affects the degree and form of liver damage and may also contribute to extrahepatic effects.

Vasculitis. Cryoglobulins are commonly found in patients with HCV infection but only some develop clinical mixed cryoglobulinaemia, which presents as asystemic vasculitis, with symptoms of fatigue and arthralgia with hepatosplenomegaly and palpable purpura particularly of the lower legs. The effects are due to the precipitation of immune complexes of HCV virions or proteins with IgG and IgM. The skin lesions show the classic histological features of a leukocytoclastic vasculitis. Of patients with mixed cryoglobulinaemia, up to 80% are HCV positive.

Porphyria cutanea tarda. Liver disease is a well-recognized association of porphyria cutanea tarda, but the detection of antibodies to HCV in some non-familial cases has renewed the search for a possible aetiological link. Of sporadic cases of porphyria cutanea tarda in southern Europe, approximately 80% were seropositive for HCV [3–5], although the prevalence appears to be nearer 10% in northern Europe [5] and intermediate in North America.

HCV infection has also been reported in association with lichen planus [6], Sjögren's syndrome [7], urticaria [8], erythema multiforme [9], erythema nodosum [10], pruritus [11], prurigo nodularis [12], cutaneous polyarteritis nodosa [13], pyoderma gangrenosum [14], disseminated superficial actinic porokeratosis [15], generalized granuloma annulare [16] and necrolytic acral erythema [17], although the causality of these links is not yet certain.

Treatment. Supportive measures can help to minimize hepatitis-induced, immune-mediated effects on different organs. IFN-α (given as a dose of 3 million units regularly three times weekly for 6 months) produces a good initial response in mixed cryoglobulinaemia [18], but relapse is common and only 10–30% will achieve a satisfactory long-term response. The combination of interferon with ribavirin produces a better (30–50%) viral clearance rate for chronic HCV infection.

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Parvoviruses

Human parvovirus B19 [1,2]

Aetiology. Parvovirus B19 is the only parvovirus of known pathogenicity to humans (Fig. 25.24). It is the cause of erythema infectiosum (fifth disease) [3].

The virus was detected first in serum in 1975 [4]. The name B19 comes from the serum panel (B), sample number (19) in which the virus was discovered. Subsequently B19 has been found to be a cause of aplastic anaemia [3,5].

Small outbreaks of fifth disease usually occur in the spring. The distribution is worldwide, with most cases being seen in children aged between 2 and 10 years. The incubation period from infection to viraemia is 6 days. The viraemia peaks at 8–9 days and at day 10 there is an almost complete loss of bone marrow erythroid precursors. The rash of erythema infectiosum appears about day 15, as the marrow recovers and IgM antibody becomes detectable. Spread occurs by droplets from the nasopharynx, with secondary attack rates of about 50% in susceptible household contacts. One infection gives lifelong immunity. In a group of 5–9 year olds in the USA, 21% had evidence of past infection. Between 20 and 50% of infections are asymptomatic, and in the UK 60% of adults are seropositive.

Pathogenesis. The major target for parvovirus B19 is the bone marrow erythroid progenitor cell. This viral tropism is mediated through the erythrocyte P antigen (globoside) and the rare person who lacks this antigen is not susceptible to B19 infection [6]. The virus is cytotoxic for these

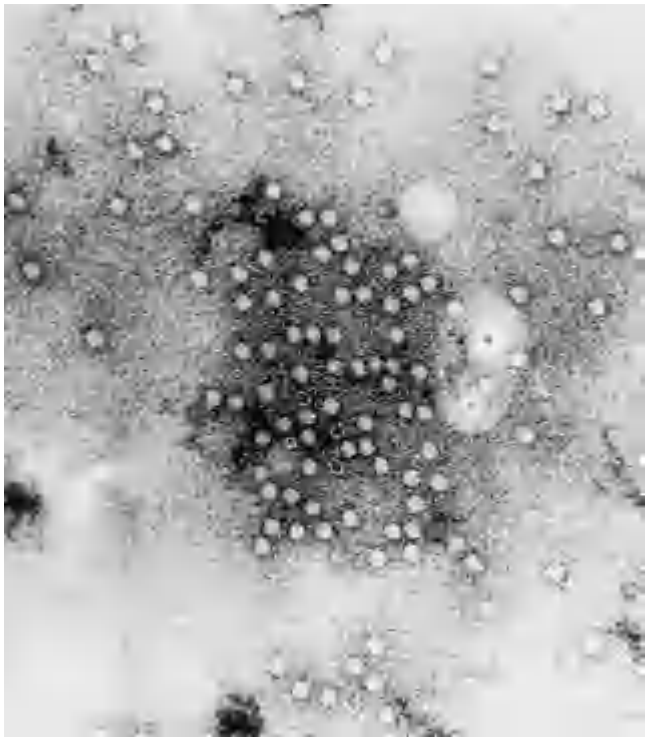

Fig. 25.24 Human parvovirus (B19) in serum of patient with aplastic crisis. Negatively stained electron micrograph, × 200 000. (Courtesy of Mr T.W. Lee, John Radcliffe Hospital, Oxford, UK.)

cells, which causes inhibition of red cell production. The bone marrow shows erythroid hypoplasia and occasional giant pronormoblasts. The exanthem and polyarthralgia are the result of antibody–antigen immune complexes and occur as bone marrow recovery is underway. Persistent infection causing severe chronic anaemia has been reported in people with congenital or acquired immune deficiency [7,8].

Infection in the pregnant woman has a transplacental transmission rate of about 33%. This may cause spontaneous abortion in the first trimester, and fetal hydrops in the second trimester [9]. Intrauterine death occurs in about 10% of B19 infections in pregnancy, although infants who survive have no evidence of congenital infection. The interval between maternal infection and fetal death is often 4–5 weeks, but may be up to 11 weeks.

Clinical features

Erythema infectiosum (fifth disease) [3,10–12]. The exanthem commonly develops suddenly without prodromal symptoms, although there may be mild malaise, myalgia or fever. Rose-red papules on the cheeks rapidly coalesce to form a hot turgid erythema, almost erysipeloid, giving a 'slapped cheek' appearance. There is often perioral pallor. During the next 2–4 days maculopapules appear on the proximal extremities and extend distally to the hands and feet and proximally to the trunk, often forming a lace-like pattern. The palms and soles may be involved and acral lesions may be petechial. Rarely lesions may be vesicular or pustular. There may be dark-red macules on the buccal and genital mucous membranes. The eruption usually fades in 6–10 days, but evanescent recurrences on previously affected sites may continue for up to 2 weeks [10,13].

In adults, polyarthralgia is often the predominant symptom of infection [14], and when the exanthem does occur the features of facial erythema are usually less marked than in children.

While the arthropathy usually resolves in a few weeks, joint symptoms persist for more than 2 months in 10% of infected women. In some cases, the combination of parvovirus infection with rash and arthritis is accompanied by other features diagnostic of connective tissue disease, such as SLE or rheumatoid arthritis [15,16].

During the early stages there is leukocytosis with relative lymphopenia: later an eosinophilia of up to 36% may be accompanied by a lymphocytosis.

Other manifestations. Systemic vasculitis in the form of polyarteritis nodosa, Wegener's granulomatosis and arterial occlusion have been reported in association with parvovirus B19 infection [17–19]. Urticaria and angio-oedema have also been reported. The papular pruritic gloves and socks syndrome is associated most commonly with parvovirus B19 infection.

Diagnosis. In the acute aplastic phase, virus can be detected in the serum by electron microscopy or PCR amplification of viral DNA. By the time the rash appears, the virus is rapidly disappearing from the blood and the diagnosis is made by finding specific IgM antibody to human parvovirus. This antibody is present for up to 2–3 months following the acute infection. Because clinically the picture can mimic rubella, it is of utmost importance to obtain laboratory diagnosis, especially of infections during pregnancy.

The exanthem shows a perivascular mononuclear cell infiltrate with a focal interface dermatitis [16].

Treatment. Erythema infectiosum is itself harmless and no treatment is required. Chronic B19 infection causing red cell aplasia should be treated with intravenous immunoglobulin infusions. Treatment may result in a cure, but if a relapse occurs a further course may be required some months later. Intravenous immunoglobulins may also be of benefit in B19-associated polyarteritis nodosum [19].

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Retroviruses

Human T-lymphotropic virus

Human T-lymphotropic virus (HTLV)-1 and HTLV-2 belong to the deltaretroviruses or oncovirus group of the Retroviridae. HTLV-1 was first isolated in 1980 [1] and was associated with an aggressive form of adult T-cell leukaemia (ATL) that had been described in Japan [2]. This disease is also referred to as adult T-cell leukaemia–lymphoma (ATLL) because it usually begins as a lymphoma that progresses to a late leukaemia phase. It is widespread and endemic in south-west Japan, the Caribbean, sub-Saharan Africa and in south-east USA. Subsequently HTLV-1 has been associated with a chronic neurological disease, tropical spastic paraparesis (TSP) [3]. It is not known what determines the form of disease the infection can take. HTLV-1 nucleic acid has also been found in the skin and mononuclear cells of patients with cutaneous T-cell lymphoma and a pathogenetic role for the virus in this disease has been proposed. HTLV-2 has been isolated from patients with a T-cell variant of hairy cell leukaemia [4,5] but has not yet been conclusively linked to any human disease. HTLV-2 is endemic in intravenous drug abusers throughout the Western hemisphere and has also been found in some native American tribes.

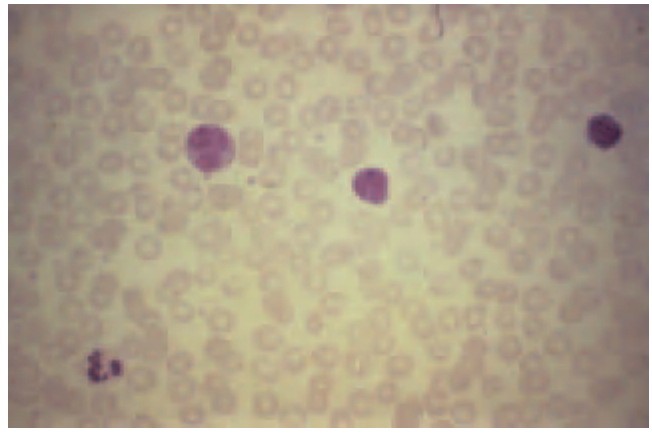
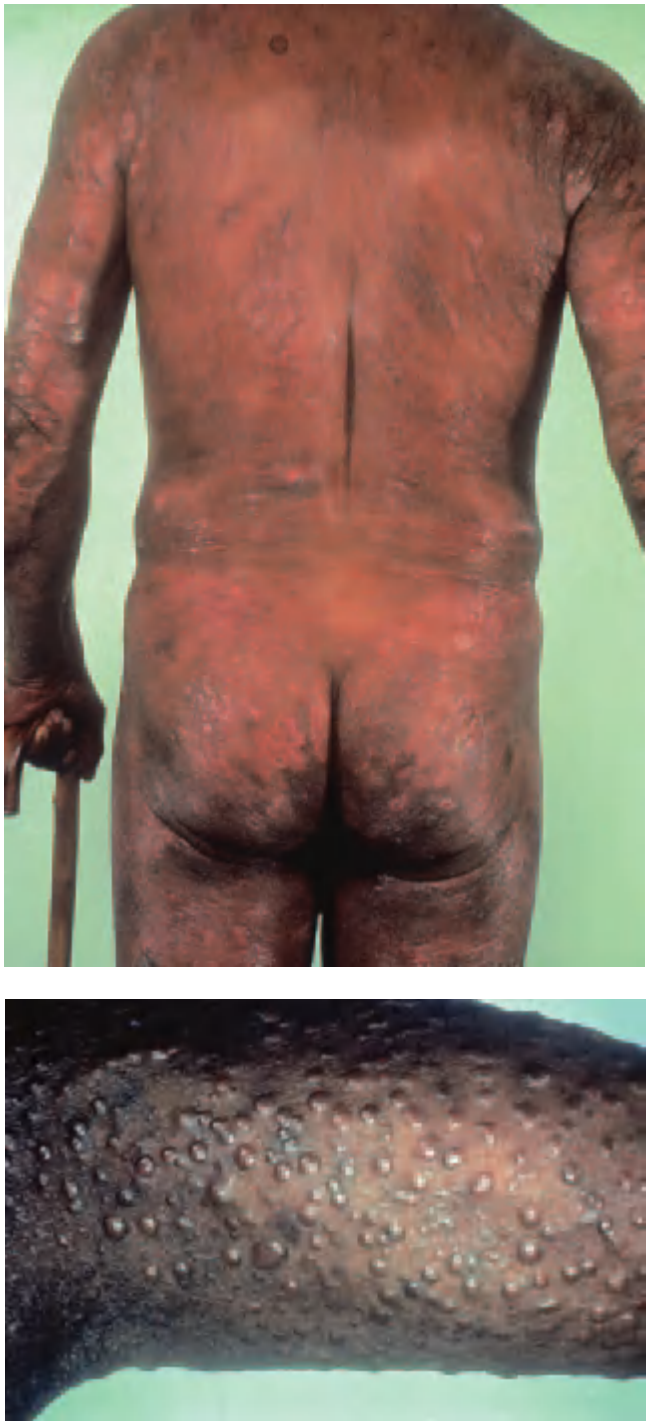


Fig. 25.25 HTLV-1 infection: 'flower cells' in peripheral blood. (Courtesy of Dr S. Whittaker, St John's Institute, London, UK.)

HTLV-1 infects $CD4^+$ T lymphocytes. After entering the cell the virus makes a DNA copy of its genome, using virally encoded reverse transcriptase. This integrates randomly into the cell genome. The pro-viral DNA produces proteins that regulate not only viral but also cellular promoters in adjacent genes and at a distance (a *trans*-activation mechanism). However, the role of these HTLV-1 gene products in transformation of the cell is still uncertain [6].

Only about one in 80 of those infected will develop ATLL. The leukaemic cells in ATLL represent a monoclonal expansion of cells, each of which carries one or occasionally more copies of the pro-viral DNA. These cells ('flower cells') (Fig. 25.25) are pleomorphic and display characteristically lobulated nuclei. Leukaemic cells can infiltrate the dermis or subcutaneous tissue to cause nodular cutaneous lesions that may appear many years before ATLL, as long as 21 years in one case report [7]. In endemic areas the prevalence of infection as manifested by antibody to HTLV-1 can be as high as 10–15%, and in the families of patients with ATLL this can rise to 30–40%. In non-endemic areas, HTLV-1 antibody prevalence rates are much lower. The major route of transmission of HTLV-1 is from infected mother to child via breast milk, with a 25% chance of the baby becoming infected. Horizontal spread is by sexual transmission (mainly from male to female) and by blood (leukocyte transfer is necessary). The incubation period for ATLL has been calculated to be 15–20 years or more but is considerably shorter for TSP—6 months to 3 years has been recorded following blood transfusion. The lifetime risk of developing ATLL, if infected with HTLV-1, is 2–5% and of developing TSP is about 0.25%.

Clinical features. Four clinical subtypes of ATLL have been defined: smouldering, chronic, acute and lymphomatous [8]. Typically, these subtypes appear in sequence in a



(a)

(b)

Fig. 25.26 Adult T-cell leukaemia/lymphoma: (a) widespread plaques; (b) papular lesions. (Courtesy of Dr S. Whittaker, St John's Institute, London, UK.)

patient. The principal features of infection are lymphadenopathy, hepatosplenomegaly, hypercalcaemia and skin lesions. ATLL has a rapid progressive course with a mean survival time of less than 1 year. The skin manifestations [9–11] (Fig. 25.26) include:

1 erythematous papules, plaques and nodules due to dermal aggregates of malignant lymphoid cells;
2 hyperpigmented rash on the face that may spread to trunk, arms and legs;
3 exfoliative dermatitis on the palms (in Afro-Caribbeans);
4 chronic infective eczema on the face without preceding atopic eczema.

T-cell leukaemia/lymphoma in a child with associated HTLV-1 infection has also been reported [12]. In this case, the disease appeared to be less aggressive than in most adult cases.

HTLV-1 infection has also been associated in rare cases with an inflammatory myopathy, which may show features suggestive of dermatomyositis [13]. However, it responds poorly, if at all, to systemic corticosteroids or other immunosuppressive drugs.

Diagnosis. HTLV-1 infection is confirmed by detecting antibodies to the virus in a serum sample. Cultivation and detection of the virus is only available in specialist laboratories. ATLL is diagnosed by the presence in circulating blood of pleomorphic leukaemic cells that express the surface markers of activated mature helper T cells ($CD2^+$, $CD4^+$, $CD7^-$, $CD8^-$) and have lobulated nuclei.

Biopsy of abnormal skin shows a heavy dermal infiltrate, often with a mixed population of cells in which lymphocytes predominate. There may be prominent atypical morphology of cells and epidermotropism. The lymphoma is most commonly classified as a pleomorphic lymphoma but cases of angiocentric lymphoma [14] and $CD30^+$ large cell lymphoma [15,16] have been reported.

Hypercalcaemia is a common and characteristic finding and erosions in the bones are frequently seen on X-ray [17]. The differential diagnosis includes Sézary syndrome and mycosis fungoides, although the latter may itself be associated with HTLV-1 [18,19].

Treatment. Combination therapy with zidovudine and IFN-α has successfully induced complete or partial remission [20]. Maintenance therapy may be needed to prolong remission and chemotherapy has been given for unresponsive relapses, although the latter therapy has been disappointing. Recurrent superficial fungal infection of the skin and other opportunistic infections are common in ATLL. They should be actively diagnosed and managed with appropriate therapy.

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Viral insect-borne and haemorrhagic fevers

These conditions are conveniently grouped together and are classified as shown in Table 25.4. The epidemiology has been reviewed [1].

Thrombocytopenia is present in all viral haemorrhagic fevers and reduced levels of coagulation factors in many. Additional mechanisms that may apply in some cases are platelet dysfunction, disseminated intravascular coagulation, circulating anticoagulants and vascular injury [2].

Rubella belongs to the Rubivirus genus of the family Togaviridae but is neither insect-borne nor haemorrhagic, and is discussed separately on p. 25.70.

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Togaviruses

The viruses of this genus are mostly mosquito-borne and include the equine encephalitis viruses and many others of limited geographical distribution causing febrile illness in humans and ungulates (Table 25.4). In the majority there is no exanthem (e.g. Venezuelan equine encephalomyelitis [1]), but Sindbis [2,3], Chikungunya [4] and O'Nyong-Nyong [5] in East, Central and South Africa are all acute febrile illnesses with severe joint pains and a maculopapular rash. In Australia and the Pacific islands, epidemic polyarthritis is associated commonly with Ross River and Barmah Forest viruses [6]. A disease with exanthem and arthralgia seen in Sweden in the 1960s (Ockelbo disease) and in Finland in 1974 (Pogosta disease) was found to be serologically related to Sindbis [7].

Ross River virus

Ross River virus infection is caused by a togavirus, spread to humans by a variety of mosquito species, and is common in Australia and Fiji, accounting for the majority of cases of epidemic polyarthritis [8]. Illness is characterized by polyarthritis and rash. After an incubation period of 3–21 days (mean 9 days) a mild fever with headache and tender and painful muscles occurs; 95% of patients develop polyarthritis commonly of ankles, knees, fingers and wrists. A non-itching maculopapular rash appears on limbs and trunk in 50–60% of those affected; it may begin several days before to 11 days after the arthritis and lasts 2–7 days. Many infections are symptomless but rarely a severe meningoencephalitis has been seen. The most common group affected are 30–40 year olds and illness is rare under 10 years of age.

Chronic arthritis and tiredness often persists for several months with acute exacerbation and relapses, and recovery can only be assessed after 1 month without symptoms. Full recovery is expected within 6 months and is followed by lasting immunity.

This infection must be distinguished from acute rubella and in its chronic form from rheumatoid arthritis. In the acute phase, virus can be isolated from the blood by intracerebral inoculation of suckling mice or more quickly by molecular identification of viral RNA [9]. The presence of IgM antibodies or a rising antibody titre to Ross River virus is also diagnostic.

Barmah Forest virus

This virus, another togavirus, has been reported in Australia to cause an illness similar to Ross River virus [10]. A rash occurs in 70–90% of those infected and is associated with polyarthralgia and lethargy. These togavirus infections are indistinguishable clinically but can be differentiated by the virus-specific IgM response and rise

Table 25.4 Viral insect-borne and haemorrhagic fevers.

Family	Virus	Distribution	Vector	Rash	Incubation (days)
Togaviridae	Sindbis	Africa Europe USSR	Mosquito	+	3–12
	Chikungunya	Africa India SE Asia	Mosquito	+	3–12
	O'Nyong-Nyong	Africa	Mosquito	+	3–12
	Ross River	Australia	Mosquito	+	3–21
	Barmah Forest	Australia	Mosquito	+	3–21
	Eastern, western and Venezuelan equine encephalitis	C., N. and S. America	Mosquito	–	5–15
Flaviviridae	Yellow fever	Central Africa C. and S. America	Mosquito	–	3–6
	Dengue*	India SE Asia West Indies Central Africa	Mosquito	+	3–15
	West Nile	Africa India Israel	Mosquito	+	1–6
	Murray Valley	Australia	Mosquito	–	5–15
	Kunjin	Australia	Mosquito	+	8–10
	Japanese encephalitis	E. Asia	Mosquito	–	5–15
	Tick-borne encephalitis	C. Europe	Tick	–	7–14
	Omsk*	Central USSR	Tick/rodent	–	3–8
	Kyasanur Forest*	India	Tick	–	3–8
Arenaviridae	Lassa fever*	West Africa	Rodent	+	7–14
	Junin*	Argentina	Rodent	+	7–14
	Machupo*	Bolivia	Rodent	+	7–14
Filoviridae	Marburg*	Africa	?	+	3–10
	Ebola*	Zaire, Sudan	?	+	3–10
Bunyaviridae	Bwamba	Africa	Mosquito	+	3–12
	Rift Valley*	Africa Infected animals	Mosquito	+	2–6
	Crimea/Congo*	S. USSR Africa Middle East	Tick	+	2–9
	Hantavirus (HFRS)*	Korea USSR, Europe N. America	Rodent	+	14–21

* Virus infections associated with haemorrhage.

in IgG in an enzyme-linked immunosorbent assay (ELISA).

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Flaviviruses

This family contains the largest group of antigenically related types of both mosquito- and tick-borne viruses.

The majority of the diseases concerned, including the tick-borne encephalitides complex, have no cutaneous manifestations. HCV does not cause haemorrhagic fever.

Yellow fever

Yellow fever is a disease that primarily affects the liver and causes abnormal liver function. Jaundice, severe leukopenia and thrombocytopenia develop. As a result of the latter, bleeding may occur.

The live attenuated vaccine contains the 17D strain grown in chick embryos. It should be given to all visitors to areas where yellow fever is endemic. It is also used to halt an epidemic along with control measures to eradicate the mosquito vectors.

Dengue [1,2]

Dengue is perhaps the most important mosquito-borne (mainly *Aedes aegypti*) virus disease in humans, affecting 50 million people annually worldwide. Since the 1980s, this disease has been widespread in Africa, Central and South America and Oceania, as well as in South-East Asia, where annual epidemics are common. Travellers to these areas are not uncommonly affected. The virus causes a range of infections: asymptomatic; a febrile illness; and a haemorrhagic fever associated with a 1–10% mortality. Symptoms, especially if severe, are more common in secondary infections. There are four antigenically distinct dengue viruses (serotypes 1–4) and infection is followed by lifelong immunity to the infection serotype. The usual form after primary infection in childhood is asymptomatic. Dengue fever starts after an incubation period of 2–14 days as a fever (frequently biphasic) with nausea, vomiting, headache, joint and bone pain, severe backache and often a rash. The rash, maculopapular or scarlatiniform, appears on the third to fourth day of the fever. It may start on the legs and spread caudally or on the chest and trunk and spread to the face, arms and legs [3]. The rash fades as the fever subsides (day 7) but can be followed by petechiae on the arms and legs. In dark-skinned people the rash is frequently not visible.

Confirmation of dengue infection is obtained by culture or detection of the virus in blood by PCR in the acute phase or by serological studies on acute and convalescent sera.

Dengue haemorrhagic fever

This form of the infection occurs in areas where dengue is hyperepidemic and there is co-circulation of multiple serotypes of the virus. This is because people who have been infected with one serotype and are subsequently infected with a different serotype are at greater risk of developing dengue haemorrhagic fever. HLA type can also influence susceptibility and resistance to haemorrhagic fever. Typically, dengue haemorrhagic fever occurs in children. The acute fever is accompanied by a haemorrhagic diathesis, which is manifest as petechiae and can be demonstrated by a positive tourniquet test. There may be bleeding from the nose or gums.

After 2–7 days there is a fall in body temperature and shock ensues, at which stage the patient may die. Vascular permeability increases leading to plasma loss, some of which collects as effusions in the pleural and abdominal cavities.

Certain clinical diagnosis from other arbovirus infections, such as West Nile fever and Chikungunya, may not be possible. The diagnosis must be guided by knowledge of the infections locally endemic.

Measles and other exanthems may obviously require exclusion.

Treatment. Only symptomatic measures are available.

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Other viral haemorrhagic fevers

These belong to the families Arenaviridae, Filoviridae and Bunyaviridae. Infections are accompanied by disordered haemostasis. This may be marked, with profuse bleeding, although non-haemorrhagic disease also occurs. Viral haemorrhagic fevers are endemic in many countries, particularly in the tropics. They may be caused by a variety of viruses (Table 25.4). Most are zoonotic infections, humans being an accidental host, although person-to-person transmission also occurs. Nosocomial infections have been reported as have outbreaks of Ebola in rural African hospitals.

Diagnosis. Diagnosis cannot be made by clinical features alone. As these infections may closely resemble typhoid fever and malaria, it is important to exclude these treatable conditions. Laboratory diagnosis by virus isolation or demonstration of virus-specific antibodies must only be carried out at the highest level of biological containment (class 4). Suspected cases of viral haemorrhagic fever must therefore be discussed with the microbiologist before any material is taken for laboratory testing.

Arenaviridae

There are two groups of arenaviruses that cause severe viral haemorrhagic fever in humans: Lassa and the Tacar-

ibe complex viruses [1]. Another arenavirus, lymphocytic choriomeningitis virus, causes meningoencephalitis not viral haemorrhagic fever. These arenaviruses are endemic in rodents.

Lassa fever [2]

The natural host is the multimammate rat, *Mastomys natalensis*, a common rodent in West African villages [3]. Transmission to humans produces short-lived outbreaks with secondary infections by person-to-person spread in households and hospital staff but few tertiary infections, presumably because of a rapid decline in infectivity with human passage. Transmission by sexual intercourse with an infected person has also been recorded. This disease was first recognized in humans in 1969 in West Africa. Serological surveys in Guinea and Senegal have shown that up to 50% of the population of some villages have had past infection.

Clinical features [4,5]. The incubation period of Lassa fever is 7–18 days. Fever, malaise, headache and non-productive cough herald the onset of disease. There is joint and lumbar pain in over 50% of patients. A painful sore throat, often with exudate, develops in most cases by the fifth day. High fever and severe prostration follow. Diarrhoea, renal damage with proteinuria, central nervous system involvement with confusion, coma and convulsions, and respiratory complications may all occur in the first week of illness.

Conjunctivitis is common. Apart from one 2-month-old child with a morbilliform rash [3], exanthems have not been a feature. A petechial rash occurred in two of 23 cases in an outbreak in Nigeria [6]. Bleeding is rare but indicates a poor prognosis. The overall mortality rate is 2–4% but rises in hospitalized patients to 10–20%. Lassa fever in the third trimester of pregnancy is associated with a mortality rate of more than 30%. In survivors, about one-quarter develop deafness in one or both ears, which may be permanent or slowly resolve.

Treatment [7]. Ribavirin (tribavirin), a guanosine analogue, is an effective antiviral drug in Lassa fever, especially if given within 6 days of the onset of illness [8]. In a therapeutic trial the mortality rate in severely ill patients, treated early, was reduced from 61 to 5%. Intravenous ribavirin is given as a 2-g loading dose followed by 1 g 6-hourly for 4 days and then 0.5 g 6-hourly for 6 days.

Prevention. Post-exposure prophylaxis with oral ribavirin is recommended for persons known to have been exposed to Lassa virus. Early diagnosis of the infection by RT-PCR amplification of the viral RNA in serum samples can identify those infected and help to prevent spread.

Argentinian, Bolivian and Venezuelan haemorrhagic fevers [9,10]

Argentinian, Bolivian and Venezuelan haemorrhagic fevers are caused, respectively, by Junin virus (natural host *Calomys musculinus*), Machupo virus (natural host *Calomys callosus*) and Guanarito virus (natural host *Sigmodon alstoni*). These viruses are grouped together as the Tacaribe complex viruses and the diseases they cause are clinically alike. The 7–10-day incubation is followed by a high fever, malaise and myalgia, erythema of the face, neck and thorax, a pharyngeal exanthem and petechiae. Epistaxis and haematemesis may also occur in the first week of the illness. Shock ensues in over half the patients. These infections are associated with about a 15% mortality rate.

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Filoviridae

Marburg and Ebola disease

Aetiology. The disease was first observed in Marburg [1] and Frankfurt [2] in Germany and in Yugoslavia in 1967 when 30 infections, seven of which were fatal, followed the importation of a consignment of African green monkeys (*Cercopithecus aethiops*) from Uganda [3]. Three further cases of Marburg disease occurred in Johannesburg in 1975 in travellers from Zimbabwe [4], and a third outbreak occurred in Kenya in 1980 [5]. Serological surveys have shown evidence of infection of both monkeys and humans in Uganda and Kenya [2].

In 1976 a similar outbreak of several hundred cases occurred in northern Zaire and the Sudan, caused by the closely related but antigenically distinct Ebola virus [6]. More recently Ebola virus has been isolated from *Cynomolgus* monkeys imported from the Philippines to the USA [7] and was associated with four subclinical

but well-documented infections of humans. In 1995, an outbreak took place in Kikwit and the surrounding region of Zaire [8]. At least 296 people developed haemorrhagic fever due to Ebola virus. One-third of the cases were in health care workers, and the overall mortality rate was 79%. The natural reservoirs of these viruses remain unknown.

Person-to-person spread occurs, probably through direct contact with blood-stained body fluids, re-use of unsterile medical equipment and needlestick injuries. Aerosol spread has not been described. Body fluids may remain infectious for as long as 80 days.

Clinical features [9]. These are similar for both Marburg and Ebola diseases. The incubation period is usually 1–2 weeks followed by the sudden onset of headache and high fever and myalgia, especially lumbosacral. Diarrhoea and dehydration, hepatitis, haemorrhages and renal damage occur with many other changes due to the pantropic nature of the infection. Bleeding, commonly gastrointestinal and mucosal, begins about the fifth day of illness.

The acute febrile stage lasts about 2 weeks and death may occur as early as the eighth or as late as the 17th day. A measles-like rash develops, more obvious on white skins, between the third and fifth day. It is mainly on the buttocks, trunk and outer aspects of upper arms. Initially erythematous macules occur around the hair follicles; these progress to maculopapular lesions next day and become confluent. An enanthem may be present as a dark-red palatal discoloration and vesicles may occur on the soft palate at the time of or just before the exanthem. Severe cases have a diffuse livid erythema over the face, trunk and limbs. After about the 16th day, desquamation occurs in survivors.

Death is usually preceded by severe blood loss and shock. The mortality rate is 30–50%. Virus excretion continues for days to weeks in survivors.

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Bunyaviridae

Crimean Congo haemorrhagic fever, Rift Valley fever and the febrile illness associated with Oropouche viruses are all caused by arthropod-borne members of the Bunyaviridae (Table 25.4). Infections with these viruses cause a serious influenza-like illness with hepatitis and haemorrhagic signs, which often progress to a fatal shock syndrome. In their more severe forms, these infections may be associated with petechial rashes (oral and on the upper body), mucosal bleeding, ecchymoses and uncontrollable haemorrhage.

The hantaviruses have a rodent reservoir and are transmitted directly from animal to human. Two types of infection are associated with the hantaviruses.

1 Haemorrhagic fever with renal syndrome [1], in its milder form, causes nephropathia endemica. Most infections are subclinical, but the classical illness presents abruptly as a flu-like illness followed by a hypotensive phase on day 5 and an oliguric phase on day 9. Petechial bleeding and substantial haemorrhage is recorded in less than 10% of cases. Mortality varies with the infecting strain from less than 1 to 10% and occurs typically in the oliguric phase. Recovery is accompanied by a diuresis in the third week of the illness.

2 Hantavirus pulmonary syndrome [2,3] was first recognized in 1993 in New Mexico and adjoining states, where the deer mouse, *Peromyscus maniculatus*, is the reservoir for the causative pulmonary syndrome hantavirus. This illness has a sudden onset, with fever, cough, myalgia and headache. Pulmonary oedema and respiratory failure (adult respiratory distress syndrome) rapidly ensue and are associated with a high mortality rate.

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Rubella

Aetiology. Rubella virus is the only member of the Rubivirus genus of the Togaviridae. Unlike other togaviruses it does not require an insect vector to spread.

The disease occurs throughout the world and is endemic in large cities. Epidemics occur at irregular intervals, usually during the spring, and affect mainly older children and young adults. Transmission is by droplets from the nasopharynx and infectivity is greatest at the end of the incubation period and falls rapidly during the 4 days after the appearance of the rash. No distinctive pathological changes have been described.

Clinical features. After an incubation period of about 18 days (range 14–21 days) the rash appears without prodromes in the child but after a brief prodromal illness lasting 1–5 days in adolescents and adults, consisting of fever up to 39°C, headache and malaise, sore throat without coryza and suffusion of the conjunctivae with a gritty sensation. The symptoms subside as the rash develops [1].

An enanthem, Forschheimer's sign [2], is present in up to 20% of patients during the prodromal period or on the first day of the rash. Dull-red macules or petechiae are confined to the soft palate. Enlargement of lymph glands begins 5–7 days before the rash appears whether or not there are prodromal symptoms, and reaches its maximum on the first or second day of the rash. The enlargement is generalized but characteristically involves the suboccipital, post-auricular and cervical glands. However, these glands are not invariably affected and their involvement is not pathognomonic of rubella. The tenderness of the glands subsides after a day or two but palpable enlargement may continue for several weeks.

The rash appears first on the face and spreads rapidly downwards to the trunk and limbs. It consists of pink macules, at first discrete but soon becoming confluent on the face as a diffuse erythema. During the second day the face begins to clear and the macules on the trunk show some coalescence, those on the limbs remaining discrete. By the third day the trunk has cleared and by the fourth the eruption on the limbs has also faded. Recent epidemiological surveys show that the rash may be absent in some 40% of cases.

The blood count may be normal, or there may be a leukopenia with an inconstant increase in plasma cells.

Complications. These are few in childhood. In older children and adults arthritis is not uncommon and affects some 30% of females and 5% of males [3]. The clinical picture is variable. Either the small joints of the hands and feet or the knees, elbows and shoulders may develop pain and swelling associated with a return of fever as the rash is fading. The arthritis usually resolves within a month.

Rarely, purpura (thrombocytopenic or non-thrombocytopenic) occurs as a complication of rubella. An association between rubella infection and the development of the haemophagocytic syndrome has been noted in an adult [4]. Very rarely, encephalitis is reported.

Rubella in pregnancy. The prenatal damage produced by rubella in early pregnancy was first noted by Gregg in Australia in 1941 [5]. The overall risk of fetal damage now appears to be about 90% for primary maternal infection during the first 11 weeks [6]. Infection at this stage usually results in multiple defects. Between weeks 12 and 16 the risk of a rubella defect is about 25% and is principally that of deafness. Thereafter, although fetal infection occurs it does not result in damage. The number of women of child-bearing age at risk of primary rubella in the UK is now probably less than 10%. Although of considerably less risk, maternal reinfection, both symptomatic and asymptomatic, can be followed by intrauterine infection and malformation of the fetus.

Heart and eye damage is most frequent in embryos infected under 6 weeks; deafness and mental deficiency occur in embryos of all ages up to about 16 weeks. Mental retardation and microcephaly may not be apparent until a year or more after prenatal infection [7]. During the neonatal period congenital rubella may give rise to a number of manifestations that are self-limiting in those infants who survive [8,9]. The most frequent is thrombocytopenic purpura, which tends to clear after a few weeks. Other features are bone lesions, which may simulate congenital syphilis, and skin changes of jaundice. One child was reported to have a widespread eruption of pigmented macules and erythematous papules and plaques [10].

Prophylaxis. Active immunization by inoculation with live attenuated rubella virus is employed in many countries. It was introduced in the UK in 1970. It is now routinely offered to infants aged 1–2 years old, together with measles and mumps vaccine (MMR vaccine). A preschool booster of MMR is also recommended. If they are found to be susceptible, rubella vaccine is also given to selected groups of women who require protection, such as nursing staff and teachers [11].

Pregnancy is a contraindication to vaccine and should be avoided for 4 weeks after its administration. There have, however, been no reports of damage to the fetus following inadvertent vaccination of pregnant women [12]. Vaccinated females apparently do not infect their contacts [13]. Arthralgia is common in adult women 2–4 weeks after vaccination and in children a rubelliform rash may occur.

Diagnosis. In view of the fetal hazard it is unwise to rely on the clinical features for the diagnosis of rubelliform rashes. In the typical infection the morphology of the pink macules and their coalescence to a diffuse erythema on the face and trunk is suggestive, as are the presence of enlarged suboccipital glands and the sequence of onset and fading of the rash on the face, trunk and limbs, although these features can also be produced by enterovirus and human parvovirus infections.

Laboratory investigations must be carried out to confirm a diagnosis in pregnancy or immunosuppression. Serology remains the appropriate technique and the first clotted blood should be taken as soon as possible after the rash is noted. A second blood sample is required 7–10 days later and the haemagglutination inhibition test [14] provides a clear answer in most instances. When the patient does not present sufficiently early, the presence of specific IgM antibody is also diagnostic of a recent

infection. In pregnant contacts the presence of antibody within 14 days of contact is indicative of immunity from previous infection. In neonates the presence of IgM and continued antibody production are indicative of congenital infection.

Treatment. There is no specific treatment.

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Picornaviruses

This group includes: (i) the enteroviruses (poliomyelitis, coxsackieviruses and echoviruses); (ii) the rhinoviruses, generally associated with the common cold but now also including foot and mouth virus; and (iii) hepatitis A.

The enteroviruses are widely distributed and comprise well over 70 antigenic types. They replicate in the alimentary tract so that spread is by droplets from the nasopharynx and by faecal contamination. Epidemics are common especially in the warmer months of the year and affect mainly children. Infection is transient without long-term persistence (but see echoviruses). The illnesses are generally mild and often subclinical, but can vary through exanthemic fevers to myocarditis and paralytic poliomyelitis. Poliomyelitis has no exanthem.

Coxsackieviruses

Coxsackieviruses are divided into two groups, A and B. There are 24 group A serotypes and six group B serotypes. Both are commonly found in the faeces of children in the absence of disease. Both may produce a febrile exanthematic illness, respiratory infections, aseptic meningitis and encephalitis.

Diagnosis. Infection can be confirmed by isolation of the virus from stool, vesicle fluid or nasopharynx in tissue culture or better in newborn mice, since only a few coxsackie A strains grow in tissue culture. Isolation from faeces alone may be misleading in the diagnosis of the disease, owing to the frequency of asymptomatic infection. Serology is of limited value. The enteroviral genome can be detected and typed in appropriate specimens by RT-PCR.

Coxsackie A strains cause herpangina and hand, foot and mouth disease. Group B coxsackieviruses are especially associated with epidemic pleurodynia (Bornholm disease), epidemic myalgia, myocarditis and pericarditis. A causal association between coxsackie B and juvenile dermatomyositis has been suggested [1]. As with other enteroviruses, the clinical syndrome produced by any one strain is very variable.

Herpangina

Aetiology. Herpangina is a specific infection caused by group A coxsackieviruses of types 2, 3, 4, 5, 6, 8 and 10 and group B type 3. It occurs throughout the world, affecting mainly children aged 1–7 years, but it is not uncommon in adults. Epidemics and sporadic cases are most frequent in the summer and autumn. Herpangina is often noted in cases with predominant features of hand, foot and mouth disease, as in the 1999/2000 epidemic in the Far East.

Clinical features. Fever of sudden onset, ranging from 38.5 to 40°C, is commonly the first manifestation of the disease and continues for 4 or 5 days. It is accompanied, or soon followed, by sore throat and dysphagia and occasionally by vomiting and abdominal pain. Up to 15 or 20 minute vesicles, 1–2 mm in diameter, with a vivid red areola, develop on the pharynx, tonsils, the pillars of the fauces, the uvula and soft palate. They erode to leave ulcers, which enlarge for 2 or 3 days and heal in 4 or 5 days. Complete recovery in 5–7 days is invariable.

Diagnosis. See above. The clinical differential diagnosis is discussed in Chapter 66.

Treatment. Symptomatic measures alone are usually adequate. Allopurinol mouthwashes have been reported to be of help [2].

Hand, foot and mouth disease

Aetiology and pathology. The characteristic but somewhat variable syndrome described as hand, foot and

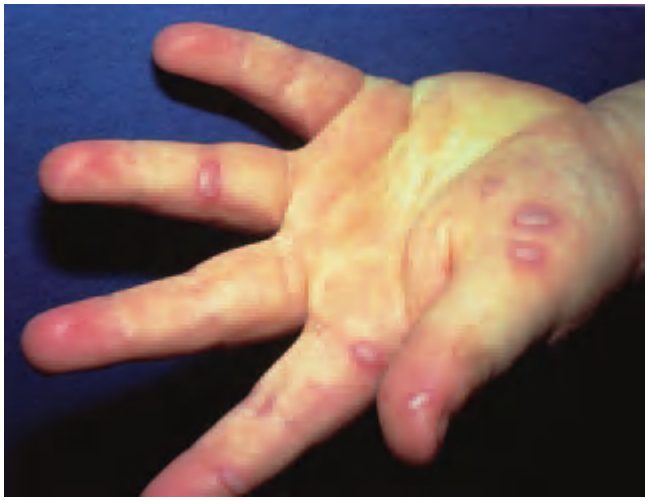

Fig. 25.27 Hand, foot and mouth disease. (Courtesy of Addenbrooke's Hospital, Cambridge, UK.)

mouth disease by Alsop [3] was first noted in Toronto in 1957 [4]. It has occurred in epidemic form in many parts of the world, and has usually been associated with human enterovirus A species, especially coxsackie A16, with outbreaks also caused by A5 [5,6], A10 [7] and other types such as human enterovirus 71. Most cases are in young children during the autumn months, although outbreaks have occurred in communities of adults [8].

Histology is not usually performed but shows spongiosis, intraepidermal splits progressing to vesicle formation, mononuclear cells entering the epidermis, and necrosis of individual keratinocytes. Electron microscopy shows viral particles in addition [9].

Clinical features [3,5,6,8–11]. The disease is usually mild, has an incubation period of 5–7 days and lasts about 7 days. The presenting feature in adults is usually a painful stomatitis, but in children this may be mild. The oral vesicles, which rapidly ulcerate, resemble those of herpangina but are rather larger and fewer in number and are irregularly distributed over the palate, buccal mucous membrane, gums and tongue. Fever is usually slight and of short duration. Skin lesions are inconstant, but when present may be characteristic, and in children may dominate the clinical picture. These lesions are small vesicles up to 5 mm in diameter, thin-walled, pearly grey, with a narrow red areola, oval or linear rather than rounded (Fig. 25.27). They are most common on the hands, usually occurring on the sides or dorsa of fingers and toes, especially around the nails, and around the margins of the heels, but may be seen in the finger flexures and on the palms and soles. They are often few in number, although there may be 50 or more, and they fade over 2 or 3 days. In some cases, especially in infants, there is a more extensive exanthem, papular or vesicular, favouring the buttocks, but sometimes generalized. Relapses are rare and a chronic intermittent course is exceptional. In an atopic infant the generalized vesicles resembled Kaposi's varicelliform eruption [12].

Other features. Complications of hand, foot and mouth disease include hyperglycaemia, encephalitis, meningitis, pulmonary oedema, myocarditis, paralysis and Guillain–Barré syndrome.

Diagnosis. See Chapter 66.

Other exanthematic coxsackievirus syndromes

Rashes have been reported in a proportion of cases in outbreaks of other coxsackievirus syndromes.

A vesicular stomatitis involving the anterior portions of the oral cavity and the lips, associated with erythema multiforme, was caused by coxsackie B5 [13], which can also give a morbilliform exanthem [14]. Coxsackie A4 has caused a widespread vesicular eruption lasting for up to 2 weeks [11]. The exanthem in these and other coxsackievirus infections presents few features that are sufficiently constant to suggest the diagnosis, although the association with oral lesions should arouse suspicion.

A Gianotti–Crosti-like eruption was associated with coxsackie A16 infection in a 2-year-old boy [15]. Congenital coxsackie B3 infection has been described in a child with florid papulovesicles with nodules and ulceration, plus associated pneumonia, carditis and hepatitis [16].

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Echoviruses

The echo (*e*nteric-*c*ytopathic-*h*uman-*o*rphan) viruses were so called because they occur in the human intestinal tract, are cytopathic in tissue culture and were believed not to cause disease in humans. Many of the 34 distinct serological types are now known to cause a wide variety of syndromes, including encephalitis, aseptic meningitis, exanthematic fever and diarrhoea and vomiting. Typically, annual summer/autumn epidemics occur in which one or more serotypes predominate.

Rashes have been noted in association with at least half of the echovirus types, and are more likely to occur in children than adults. Macular, maculopapular, vesicular and petechial eruptions, and tonsillar and buccal exanthems may occur. The erythematous eruptions commonly affect the face and trunk. Close correlation between the morphology of the rash and the virus type is not seen, but the following associations have been reported.

1 Echovirus 9: rubelliform or morbilliform eruptions [1–3].
2 Echovirus 16: the 'Boston eruption', large pink macules on face and trunk, occasionally widespread including palms and soles, following a brief febrile illness in children or adults [4].
3 Echovirus 2: rubelliform rash [5].
4 Echoviruses 11 and 19: petechial rash [6].
5 Echoviruses 6, 11 and 25: maculopapular rashes [7,8].
6 Echoviruses 23 and 32: telangiectatic macular lesions [9].
7 Echovirus 19: punctate macular rash in infants [10].
8 Echovirus 11: vesicular eruptions [11,12].

Diagnosis. Echovirus and rubella infections are often present simultaneously in a community, and the eruptions they produce may be indistinguishable. It is therefore essential for any woman developing a rash in the early stages of pregnancy to be investigated for both enterovirus and rubella infection by isolation of virus in tissue culture from throat swab and secretions, faeces or cerebrospinal fluid for the former and by serological tests for the latter.

Chronic echovirus infection

In hypogammaglobulinaemia, a condition of chronic enteroviral infection has been reported [13]. This causes a progressive encephalitis that is fatal within about 4 years. A dermatomyositis-like syndrome may occur in the early stages in some of these patients. It is associated with mild non-pitting oedema of the lower legs and a transient erythematous rash.

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Foot and mouth disease [1–3]

Aetiology and pathology. This common and serious epidemic viral disease of farm animals in Europe, Asia and Africa very rarely infects humans. Some cases reported under this diagnosis, but not confirmed by complement fixation or animal inoculation, may have been vesicular stomatitis or hand, foot and mouth disease. True foot and mouth disease has occurred in both adults and children in direct contact with infected stock. Type O virus has been isolated from some human cases. Loculated vesicles are formed in the deeper layers of the epithelium of mucous membranes and intranuclear inclusions are present in neighbouring cells.

Clinical features. The incubation period ranges from 2 to 18 days. Malaise, headache and fever, with burning of the oral mucous membranes, are followed after 2 or 3 days by vesicles of the buccal mucous membrane, tongue and lips, and on the palms, soles and interdigital skin. The vesicles are followed by ragged ulcers and may be accompanied by pain and oedema. Sometimes only the mouth or the hands are involved. The disease tends to be more severe in infants and children than in adults, but it is usually mild, the temperature falling after a few days and the lesions healing within a week.

Diagnosis. The other mucocutaneous syndromes must be excluded (see Chapter 66). The diagnosis is confirmed by isolation of the virus from the vesicles or by detection of

antigen from the vesicles or antibody in the serum by ELISA. The viral nucleic acid may be detected by RT-PCR in problematic cases.

Treatment. Only symptomatic measures are available.

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Hepatitis A

The hepatitis A virus constitutes a unique genus in the Picornaviridae family. The virus is very stable in the environment and is spread by the faeco-oral route, by ingestion of contaminated food and water or through close person-to-person contact. In developing countries where hepatitis A is highly endemic, almost all the population has been infected and is immune by age 10 years. Developed countries with good water and sewage systems have very low rates of hepatitis A infection; consequently travellers from these countries to areas of high endemicity are at risk of infection.

Clinical features. The average incubation period is 30 days. Most people suffer a prodrome of a flu-like illness, anorexia and arthralgia in the week preceding the jaundice. Occasionally, in about 10% of cases, there is a transient eruption [1], usually maculopapular, petechial or urticarial. One patient has had a morbilliform eruption with predominance in sun-exposed sites [2]. During the prodrome and the early icteric phase, the patient excretes virus in the faeces and is infectious, although only a transient viraemia occurs. Jaundice develops in 65% of toddlers and about 90% of adults. Mortality in the over-50 age group is quoted as 2% [3].

Occasional reports of a vasulitic eruption with relapsing or persistent hepatitis A infection have been attributed to cryoglobulinaemia [4].

Diagnosis. Hepatitis A must be distinguished from other causes of jaundice. The diagnosis is confirmed by detecting hepatitis A IgM antibody. The presence of IgG antibody indicates past infection (or immunization) and gives protection.

Treatment. Symptomatic measures are usually sufficient. The infection is of a few weeks duration and no chronic carrier state exists. Alcohol should be avoided during the convalescent period. Patients with fulminant hepatitis should be referred to a specialized liver unit.

Prevention. Active immunization with inactivated vaccine or short-lived passive protection using human immunoglobulin are both available for susceptible contacts and travellers.

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Vesicular stomatitis virus

Aetiology and pathology. Vesicular stomatitis is a specific virus infection of horses and cattle in the Americas, Asia and Africa. It is generally mild but can mimic foot and mouth disease. It is occasionally transmitted to humans by direct or indirect contact. As the name implies the virus can cause vesicles; these are intraepithelial. Intranuclear inclusions are present in infected cells.

Clinical features [1]. The incubation period is 2 days, after which there is fever with myalgia and malaise. This is occasionally followed by mild stomatitis with vesicles on the gums and buccal and pharyngeal mucosa, and lymphadenitis. Some patients develop vesicles of the fingers. Recovery takes about a week.

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Myxoviruses and related RNA viruses

Two families are distinguishable, the Orthomyxoviridae, consisting of influenza viruses A, B and C, and the Paramyxoviridae, which comprises three genera:
1 Paramyxovirus, containing the parainfluenza virus and mumps;
2 Morbillivirus, in which the human representative is measles; and
3 Pneumovirus, which contains respiratory syncytial virus (RSV).

Cutaneous manifestations are not usually produced except in measles and occasionally in RSV infections.

Measles [1]

SYN. MORBILLI

Aetiology and pathology. Measles infection is transmitted

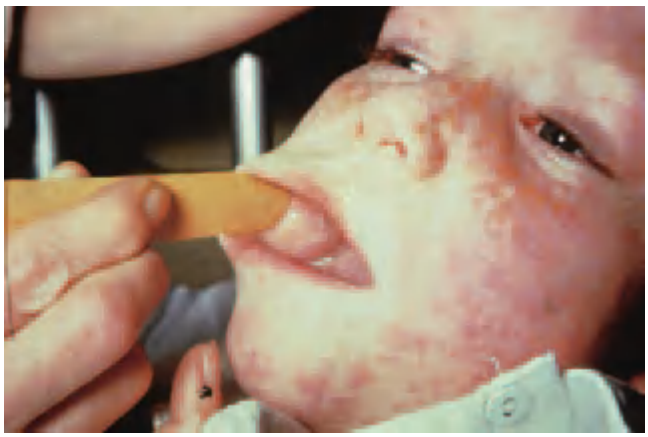

Fig. 25.28 Koplik's spots on buccal mucosa in measles. (Courtesy of Dr J. Kurtz, Oxford, UK.)

from human to human via the upper respiratory tract where initial replication occurs before wide dissemination throughout the body.

The cellular receptors for the virus are the CD46 and CD150 (signalling lymphocyte activation molecule, SLAM) molecules. During the prodromal period of establishment of infection in the reticuloendothelial system, there is lymphoid hyperplasia with formation of fused multinucleate giant cells. The prodromal rash [2] appears to be the result of viraemia with lodgement of antigen and virus in the capillaries. Cells in Koplik's spots also contain viral nucleocapsids. The conspicuous macular eruption on the fourth day is the result of the cell-mediated immune response against this material. If the response is defective as in leukaemia, especially when cytotoxic drugs are used, there may be no rash and progressive viral replication leads to giant cell pneumonia or a fatal encephalopathy [3].

Shortly after the rash appears, measles virus causes a transient depression of T-cell-mediated immune responses, which are an important feature of the infection [4]. This was observed by Von Pirquet [5] as a fading in sensitivity to tuberculin, and this anergy persists for 1–2 months. It is generally considered a mechanism that increases susceptibility to tuberculosis and may permit the invasion of the brain by measles virus, which later produces subacute sclerosing panencephalitis. Lifelong immunity follows natural measles infection.

Clinical features. After an incubation period of about 10 days, the prodromal symptoms of fever, malaise and upper respiratory catarrh begin acutely. The conjunctivae are injected and there may be photophobia. From the second day, Koplik's spots (bluish white spots with bright-red areolae) are usually present on the buccal mucous membrane opposite the premolar teeth (Fig. 25.28). Fever, catarrh and cough increase for 3–5 days. The exanthem characteristically develops on the fourth day on the forehead and behind the ears, and spreads within 24 h to the rest of the face, the trunk and the limbs. The rash is at first macular but soon forms dull red papules that tend to coalesce in irregularly concentric patterns but may be more diffusely confluent. From the 6th to the 10th day the rash fades, to leave some brownish staining and fine desquamation. In very severe forms it may be haemorrhagic.

An extensive bullous eruption may develop during the acute stage of measles. In some cases this eruption has the features of Stevens–Johnson syndrome [6], but in others it resembles epidermal necrolysis. It is possible that in some suspected cases drugs were responsible, but in others the eruption appears to have been directly related to the virus infection. It is sometimes inappropriately referred to as 'measles pemphigoid'.

Complications are more common in young children, the malnourished and the chronically ill. Bronchopneumonia, enteritis and otitis media are less frequent now as effective antibiotics are available. The most serious complication is encephalitis, which occurs in 1 in 2000 cases.

Diagnosis. The features of other infective exanthems are considered in this chapter. Drug eruptions should not cause confusion because the upper respiratory catarrh and conjunctival suffusion are absent. Specific measles antibodies are usually detectable 3 or 4 days after the appearance of the rash, and maximum titres are reached 2–4 weeks later. Virus isolation is not easy but viral antigen can be detected by immunofluorescence in cell smears prepared from nasopharyngeal aspirates taken early during the illness and in skin biopsy of the exanthem [7]. Molecular diagnosis of measles is possible [8] but not yet routine.

Treatment. The patient should be confined to bed and given symptomatic treatment. Children with measles, especially in areas of high mortality, should be given vitamin A (two doses of 200 000 units). Antibiotics may be required to control secondary bacterial complications. Passive protection is possible using normal human immunoglobulin given within 5 days of exposure, which prevents or attenuates the infection in contacts and is reserved for those children at special risk. Active immunization with the live attenuated vaccine has reduced the incidence of measles infections but a mild illness with a rash is common during the 3 weeks following the vaccine [8].

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Respiratory syncytial virus

Aetiology and pathology. The virus is pleomorphic, a little smaller than measles, and derives its name from the multinucleate syncytia produced when grown in tissue-culture cells. There are two distinct subgroups, A and B, which differ most in their surface glycoprotein G. There appears to be no difference in severity between group A and B infections but group A viruses are more frequently detected [1]. RSV causes annual epidemics during the winter months or in the rainy season in the tropics. Most people have been infected by age 1 or 2 years and suffer repeated infections throughout life.

Clinical features. Infection occurs after an incubation period of 4–5 days. The virus is especially associated with bronchiolitis in babies. Bronchitis and pneumonia occur in a proportion of infections. In older children and adults, upper respiratory symptoms occur that are indistinguishable from a common cold. Again in old age, RSV pneumonia is not uncommon and in bone marrow transplant recipients is associated with a high rate of mortality [2]. A transient, fine, pink, macular rash on the face and trunk has been observed in a few instances in children, but is of no diagnostic significance. Occasionally it is more extensive and involves the arms, shoulders, chest, back and buttocks [3]. The diagnosis is achieved rapidly by examination of nasopharyngeal exudate cells for the presence of viral antigen [4]; growth in tissue culture takes longer and serology may be of occasional value.

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Other cutaneous problems associated with viral infections

Several cutaneous syndromes are associated with viral infections or other triggering factors.

Papular–purpuric gloves and socks syndrome

An acute acral dermatosis, occurring predominantly in adults, was first described in 1990 [1]. The hands, wrists, feet and ankles are intensely pruritic and are affected with erythema and papular oedema. There may also be associated purpura and rarely petechiae. The cutaneous features are frequently accompanied by oral inflammation and ulceration. Malaise and fever can follow a few days after the onset of the eruption but the condition settles within 2 weeks. In many cases, no specific cause can be identified [2] but parvovirus B19 infection has been suggested to act as a trigger for the syndrome [3] and measles, hepatitis B and CMV infections have been reported in association [4–6].

TORCH syndrome

The term 'TORCH syndrome' was originally used to encompass congenital infection caused by ***To****xoplasma gondii*, **r**ubella, **c**ytomegalovirus or **h**erpes simplex types 1 and 2 in which the clinical presentation was somewhat similar. In practice, there are some distinctions between the manifestations of the various infections, although all may cause cutaneous and disseminated abnormalities. Skin abnormalities of jaundice, purpura and petechiae are most common. Vesicles and mucosal ulceration may occur with herpes infection. Since the acronym has been used, several other congenital infections are recognized to be of importance and the concept of TORCH is now of limited value [7].

Kikuchi–Fujimoto disease [8]

SYN. KIKUCHI'S DISEASE; HISTIOCYTIC NECROTIZING LYMPHADENITIS

The clinicopathological entity consists of painful lymphadenitis affecting mainly the cervical nodes associated with fever, malaise and upper respiratory tract symptoms. Occasionally symptoms may be severe enough to mimic a malignant lymphoma. Cutaneous involvement, especially overlying affected lymph nodes, may be present in 30% of cases. Erythematous indurated plaques but also macules and papules may be seen. Viral infections reported in association include EBV, parvovirus B19, HSV and HHV-6 [9], although not all investigators have confirmed these findings [10].

Erythema nodosum

Septal panniculitis presenting as erythema nodosum, most commonly on the shins, is associated with a variety of conditions (see Chapter 49). Viral infections implicated as possible precipitants include milker's nodule, infectious mononucleosis, HBV and HCV.

Erythema multiforme

Erythema multiforme may be precipitated by several different viral infections. HSV is the most commonly associated virus, but VZV, infectious mononucleosis, mumps, polio, orf, milker's nodule, HIV, HBV and HCV [11] may all need to be considered as trigger factors.

Polyarteritis nodosa

Inflammation of medium-sized vessels presenting with only cutaneous lesions or with systemic effects has been associated with infection with HBV and HCV (see pp. 25.60–25.62).

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Gianotti–Crosti syndrome

SYN. PAPULAR ACRODERMATITIS OF CHILDHOOD

Aetiology. Gianotti–Crosti syndrome is a characteristic cutaneous response to viral infection [1,2]. The majority of the earlier reported cases had HBV infection, and indeed Gianotti concluded in 1979 [3] that the eruption was exclusively associated with that virus, and he distinguished the condition from other 'papulovesicular acro-located syndromes' that were clinically similar but not associated with HBV. Other authors have found the distinction between the eruptions less convincing [4] and have suggested that they should all be included within the Gianotti–Crosti syndrome, so that HBV infection is not a requirement for the diagnosis [2,5]. On this basis, several other viruses have been associated; the most common of these is EBV [2,6,7], including a case with primary infection with both HBV and EBV [8]. Infrequently reported, and of less certain significance, are coxsackie A16 [9], coxsackie B4 and B5 [7], echovirus 7 [10], echovirus 9 [11], poliovirus [12], CMV [7], RSV [12], parainfluenza virus [2], hepatitis A [13], parvovirus B19 [14] and HIV [15]. Occasional cases following immunization, for example diphtheria, pertussis and influenza [7,16], are of uncertain significance. A preceding upper respiratory tract infection was found to be common in patients or family members [2]. In a minority of cases, no evidence of viral infection can be found.

The syndrome mainly affects children between the ages of 6 months and 12 years, though occasional adult cases have occurred [3]. Small epidemics or clustering of cases is often observed.

Pathology [2,17]. The skin lesions show slight or moderate acanthosis and hyperkeratosis. In the oedematous upper dermis an infiltrate of lymphocytes and histiocytes surrounds dilated capillaries. The lymph nodes show a diffuse reticulum cell hyperplasia, often of severe degree. When histology of bone marrow or liver is indicated, they show what appears to be a generalized, low-grade, inflammatory reaction of the entire reticuloendothelial system.

Clinical features [2,3,18]. Over the course of 3 or 4 days a profuse eruption of dull, red, flat-topped papules develops first on the thighs and buttocks (Fig. 25.29), then on the extensor aspects of the arms, and finally on the face. The distribution is often asymmetrical. The fleeting appearance of a few lesions on the trunk is occasionally noted. The individual papules are 5–10 mm in diameter, and their characteristic deep-red colour may later be modified by purpuric staining, especially on the legs. Itch is said not to be a feature of the HBV cases, but may occur in those due to other viruses. The eruption fades in 2–8 weeks with mild desquamation. Recurrence is unlikely but has been reported [19].

Generalized lymphadenopathy, mostly axillary and inguinal, is common but not invariable, and persists for months after the rash. Constitutional symptoms are not usually marked, although there may be mild fever and lassitude. The changes in the peripheral blood are inconstant: there may be a leukopenia or a slight leukocytosis with 2–15% of monocytes; the erythrocyte sedimentation rate is not raised.

In the HBV cases, liver involvement appears to be invariable, usually mild and anicteric, but occasionally there is jaundice, and histological recovery may take between 6 months and 4 years. Rarely there is persistent hepatitis. Hepatomegaly and liver function abnormalities each occasionally occur in HBsAg-negative cases [2].

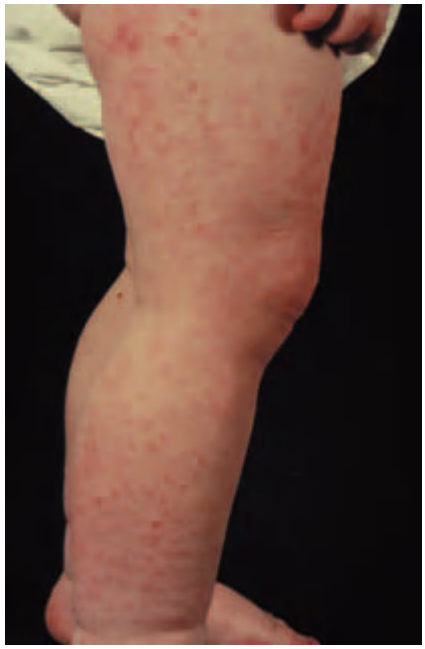

Fig. 25.29 Gianotti–Crosti syndrome: papular eruption on leg. (Courtesy of Dr N.P. Burrows, Addenbrooke's Hospital, Cambridge, UK.)

In some otherwise typical cases the exanthem is absent or minimal.

Diagnosis. The skin lesions are sufficiently distinctive in morphology, distribution and duration. It may in selected cases be worth examining clotted blood for hepatitis B antigen and assessing liver function.

Treatment. There is no specific treatment. Emollients and topical steroids may help to relieve pruritus.

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Pityriasis rosea

Definition. Pityriasis rosea is an acute self-limiting disease, probably infective in origin, affecting mainly children and young adults, and characterized by a distinctive skin eruption and minimal constitutional symptoms.

Aetiology [1–4]. Pityriasis rosea is relatively common throughout the world. In temperate regions, it is more frequent during the winter months. In tropical areas, there may also be some seasonal variation. Changes in incidence from year to year, though not great, may be statistically significant [3].

A large series of 249 cases in Minnesota [2] showed a female/male ratio of 1.5 : 1, although previous large studies in Sweden [1] and England [5] showed equal susceptibility of the sexes.

Most cases of pityriasis rosea occur between the ages of 10 and 35 years and it is uncommon in early childhood or old age, although it has occurred in infants and in the ninth decade. Susceptibility to the disease appears not to be influenced by race or other genetic factors. Earlier suggestions of an association with atopy [1] were not confirmed in the Minnesota study [6].

The cause of pityriasis rosea is uncertain, but many epidemiological and clinical features suggest that an infective agent may be implicated.

True epidemics have not been reported, and the possibility that recent clinical experience of the disease might increase the tendency to diagnose subsequent cases could lead to erroneous impressions of contagiousness. However, reported epidemiological evidence for (admittedly low) infectivity includes occasional family or household outbreaks, seasonal and year-to-year fluctuations [1,3,5,7], statistical evidence for clustering in space and time [8], and a higher incidence among dermatologists than among ear, nose and throat surgeons and pre-specialization dermatologists [9]. The natural history of the disease, i.e. a

primary lesion that could correspond to the site of inoculation, a disseminated secondary eruption after an interval, a self-limiting course and the infrequency of second attacks, shows features paralleled by many diseases of proven infective origin. Occasional mild constitutional symptoms are reported and might support an infective cause, but were found to be no more frequent in 108 patients with pityriasis rosea than in the same number of controls [1]. Exacerbations accompanying oral steroid therapy were noted in a small series [10] and pityriasis rosea-like eruptions have been reported after bone marrow transplantation [11], although several aetiological effects could be implicated in such a situation.

The search for a microorganism continues. Earlier suspicions about fungi, streptococci, spirochaetes [7] and *Legionella* [12] have not been confirmed, and most speculation now centres on a viral aetiology. Attempts to culture virus from affected skin have been fruitless [13,14]. Virus-like particles were detected ultrastructurally many years ago [15,16] and more recently herpes virus-like particles have been found in 71% of pityriasis rosea lesions [17]. Involvement of two herpesviruses, HHV-6 and HHV-7, has been suggested as a cause for the eruption. The viral DNA is reported to be present in peripheral blood mononuclear cells and lesional and unaffected skin of the majority (80–100%) of individuals with acute pityriasis rosea. HHV-7 is detected slightly more frequently than HHV-6, but often both viruses are found [18,19]. However, evidence for the presence and activity of HHV-6 or HHV-7 is also found in a proportion (10–44%) of unaffected individuals, suggesting that if there is a causal relationship, infection with the viruses does not always lead to disease. Not all groups working in this field have confirmed the presence of these viruses in patients with pityriasis rosea [20,21] or found a weaker association [22].

There are several reports associating pityriasis rosea-like eruptions with drugs. The rashes caused by arsenic, bismuth, gold and methopromazine seem more likely to have been atypical lichenoid reactions [1]. Other drugs implicated include metronidazole [23], barbiturates, clonidine, captopril [24] and ketotifen [25]. In some reports the resemblance of the eruption to pityriasis rosea has not been close, and in others coincidence might explain the association. Thus, while some drug eruptions may somewhat resemble the condition, there is no convincing evidence that typical pityriasis rosea can be caused by drugs.

Pathology [14,26–28]. The herald patch and the secondary lesions are similar histologically. The changes are not diagnostic.

In the epidermis, spongiosis, vesicles and patchy parakeratosis are common. The upper dermis shows oedema and a mononuclear cell infiltrate from which there is exocytosis into the epidermis, where these cells may form pustules, mainly subcorneal. The infiltrate comprises mainly helper T lymphocytes but also Langerhans' cells, and HLA-DR antigens are expressed on the keratinocyte surface. Occasional dyskeratotic keratinocytes are seen, sometimes adjacent to a Langerhans' cell. These findings suggest a cell-mediated immune reaction in the epidermis [28].

Clinical features [1,4,7] (Fig. 25.30). The eruption of pityriasis rosea follows a distinctive and remarkably constant pattern and course in some 80% of cases. Prodromal symptoms are usually absent and the vague complaints of headache and slight malaise elicited by direct questioning may not be more frequent than in healthy control subjects. The first manifestation of the disease is usually the appearance of the herald patch, which is larger and more conspicuous than the lesions of the later eruption and is usually situated on the thigh or upper arm, the trunk or the neck; rarely it may be on the face, scalp or the penis. It is a sharply defined, bright-red, round or oval plaque, soon covered by fine scale. It rapidly reaches its maximum size, usually 2–5 cm in diameter but occasionally much larger. Rarely, there may be more than one herald patch. After an interval, which is usually between 5 and 15 days but may be as short as a few hours or as long as 2 months, the general eruption begins to appear in crops at 2–3 day intervals over a week or 10 days. Less often, new lesions continue to develop for several weeks. In its classical form the eruption consists of discrete medallions often oval in outline and dull pink in colour covered by fine, dry, silvery-grey scales. The centre tends to clear and assumes a wrinkled atrophic appearance and a tawny colour, with a marginal collarette of scale attached peripherally, with the free edge of the scale internally. The long axes of the lesions characteristically follow the lines of cleavage parallel to the ribs in a Christmas-tree pattern on the upper chest and back. The medallions are commonly associated with pink macules of varying size and the eruption may be exclusively macular.

The lesions are usually said to be confined to the trunk, the base of the neck and the upper third of the arms and legs. These sites are certainly most consistently and severely affected but involvement of the face and scalp is quite common, especially in children, and in one large series of cases lesions were found on the forearms and lower legs in about 12% and 6%, respectively. Lesions on the palms are exceptional but can occur. There may be discrete, scaly, red patches, diffuse redness and scaling or scattered small vesicles. Involvement of the oral mucous membrane is also unusual but is probably often overlooked. Either ill-defined red patches, with some desquamation or with punctate haemorrhages, or bullae may be observed. Oral lesions are not infrequently present [29] and, exceptionally, there may be lesions on the vulva.

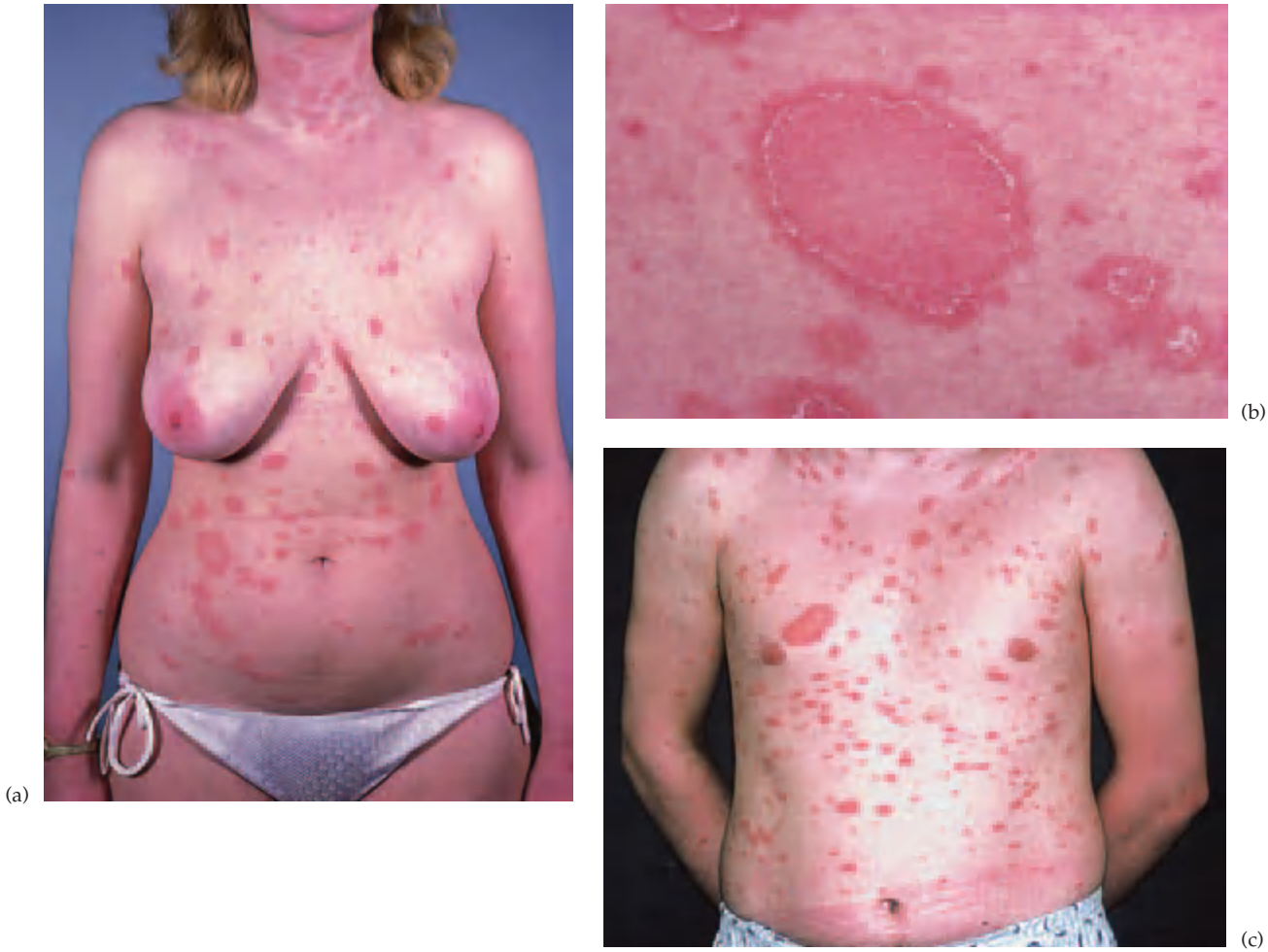

Fig. 25.30 Pityriasis rosea: (a) with herald patch on right of abdomen, shown in close-up in (b); (c) with herald patch on right of chest. (a,b, Courtesy of York District Hospital, York, UK; c, courtesy of Dr A.S. Highet, York District Hospital, York, UK.)

Subjective symptoms are usually absent but there may be slight or moderate pruritus, particularly as a result of injudicious attempts at treatment. Occasionally, slight fever, malaise and enlargement of lymphatic glands, generalized or confined to the cervical glands, may be present; exceptionally, more severe constitutional symptoms have been recorded, although their extreme rarity suggests that they may have been fortuitously associated and may not be a manifestation of the disease.

The skin lesions commonly fade after 3–6 weeks, but some clear in 1 or 2 weeks and a few persist for as long as 2 months. A longer duration, except in the localized forms considered below, is very unusual. There may be temporary hyperpigmentation or hypopigmentation, but usually the lesions vanish without trace.

Second attacks of pityriasis rosea occur in about 2% of cases [1] after an interval of a few months or many years, but this may be an underestimate [3]. Rarely, partial or complete relapse of a fading eruption may be seen.

Pityriasis rosea may be atypical in the appearance or distribution of the lesions or in its course [30,31]. The herald patch is absent or undetected in about 20% of cases. The 'secondary' eruption varies greatly in extent. It may be almost generalized or may be limited to a few lesions, often around the herald patch. At times the eruption is confined to a single region, or may be maximal on the extremities almost sparing the trunk. Unilateral pityriasis has been reported [32]. Especially in children, the lesions may be predominantly papular or urticarial in the early stages, but they are soon surmounted by an inconspicuous ring of fine scales. Acute purpuric lesions have occasionally been reported [33]. Papulovesicular, vesicular and even pustular forms also occur, and erythema multiforme-like lesions formed part of the eruption in one child [34]. In a variant of the papular form more common in Africans than Europeans, small lichenoid papules are thickly set in the edges of the lesions [7].

In pityriasis circinata et marginata of Vidal [35], sometimes regarded as a special form and seen mainly in

adults, the lesions are few and large, and are often localized to one region of the body, especially the axillae or groins. They tend to become confluent and may persist for several months. Rarely, this form may follow a typical generalized pityriasis rosea, but it usually occurs alone.

Diagnosis. In the typical fully developed case the diagnosis usually presents little difficulty as the distribution, morphology and absence of constitutional symptoms are sufficiently distinctive. Some patterns of drug eruption may have to be excluded. An acute onset without a herald patch, pruritus and a tendency for the lesions to become lichenoid in appearance are suggestive features. A progressive, irritable, atypical pityriasiform eruption in a patient taking a drug known to provoke reactions of this nature can be tentatively accepted, in the absence of any method of laboratory confirmation.

Seborrhoeic dermatitis may be pityriasiform. There is no herald patch, the lesions often develop slowly and are most numerous on the upper trunk near the midline, on the neck and in the scalp, and they are duller in colour with thicker and more greasy scales. Small, scaly, follicular papules may also be present. The eruption is persistent if untreated.

Secondary syphilis is the classical trap but the resemblance is not very close. The genital and oral mucosae should be examined. There is no herald patch and the lesions are roseolar or maculopapular.

The acute urticarial forms in childhood can sometimes not be identified with complete certainty on first examination unless a herald patch can be discovered. Re-examination after 2 days enables a confident diagnosis to be confirmed.

Guttate psoriasis and pityriasis lichenoides may sometimes need exclusion. In both, the lesions are papular and persistent. In psoriasis they are surmounted by silvery scales. In pityriasis lichenoides they are polymorphic, some showing haemorrhagic crusting and some adherent scales.

The hypopigmented patches with dry branny scales of pityriasis alba are most frequent on the face, and are seen mainly in young children.

The herald patch and the localized forms such as pityriasis circinata are easily, and in practice frequently, confused with ringworm. The lesions of ringworm are red and oedematous and may show marginal vesiculation. In case of doubt scrapings from the edge of the lesions should be examined microscopically for mycelium.

Treatment. The common asymptomatic and self-limiting cases require no treatment [36]. Oral erythromycin given at a dose of 200 mg four times a day has been shown in one study to hasten the clearance of the lesions when compared with placebo [37]. If itch is troublesome or the appearance distressing, a topical steroid, usually of moderate strength, or UVB irradiation [38] can be helpful.

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Chapter 26

AIDS and the Skin

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Introduction

It is now 20 years since acquired immune deficiency syndrome (AIDS) was first recognized as a novel disease. Within 2 years of defining AIDS as a distinctive syndrome in 1981, the human immunodeficiency virus (HIV) was identified as the causative agent. HIV infection is acquired sexually, from blood or blood products, or vertically from an infected mother during pregnancy, birth or breastfeeding. The virus infects immunocompetent cells including CD4 T cells and macrophages. It creates variable patterns of disease in individuals, groups and races but all are characterized by evolving, sometimes fulminant immunodysfunction (AIDS) affecting many systems of the body.

Dermatological involvement in AIDS has been appreciated since the disease was first recognized as a cryptic acquired immune deficiency illness in homosexual men and before the causative virus was identified. Mucocutaneous involvement establishes criteria for diagnosis and staging; the prognostic significance of some complications, for example pruritic papular eruption/eosinophilic folliculitis, hairy leukoplakia and Kaposi's sarcoma (KS), was well recognized before specific treatments were introduced. The proportion of patients with skin complications and the number of these manifestations in any one patient increase as HIV progresses and AIDS develops. The incidence and severity of several common cutaneous diseases (such as mollusca, herpes simplex, seborrhoeic dermatitis) are increased in patients with HIV and this correlates in many instances with the absolute numbers of CD4 T-helper cells. The effect HIV infection may have on some dermatological conditions such as psoriasis and atopic dermatitis is less clear-cut. Since the recognition of AIDS there have been many case reports of rarer dermatoses in HIV-positive patients where an association is speculative. HIV has been demonstrated in the dermis of infected individuals and may be present in Langerhans' cells. Different cytokine expression patterns distinguish different cutaneous manifestations. The advent of highly active antiretroviral therapy (HAART) has been largely beneficial to patients with HIV-associated skin disease, but novel side effects of these drugs (such as lipodystrophy) have emerged and the skin can be affected by the immune reconstitution syndrome.

The dermatological complications of HIV and AIDS may be distressing to patients and difficult for dermatologists to diagnose and manage. However, they are of further interest in that the 'experiment of nature' sheds light on both the immunopathological natural history of HIV infection and the aetiology of common and rarer dermatoses that happen to be found with a higher incidence in HIV-infected than non-HIV-infected patients. Their occurrence emphasizes the importance of the skin as a dynamic immunological organ.

HIV infection

Epidemiological trends

AIDS was first described as a distinct clinical entity in 1981 [1]. HIV.1 infection now represents a global pandemic and in the past 20 years there have been an estimated 21.8 million AIDS deaths worldwide. Of AIDS cases, 95% occur in non-industrialized countries, 75% in sub-Saharan Africa; 36.1 million people are currently believed to be living with HIV infection [2].

Global trends in the HIV pandemic are shown in Table 26.1. These data are sourced from UNAIDS [2] who take estimates available from published studies and combine them with unpublished data, collected as part of AIDS control programmes in many countries, to provide national estimates of prevalence and deaths.

Table 26.1 Global trends in the HIV pandemic. (From UNAIDS [2].)

Region	Epidemic started	Adults and children living with HIV/AIDS	Adult prevalence rate* (%)	HIV-positive adults who are women (%)	Main mode of transmission for adults living with HIV/AIDS
Sub-Saharan Africa	Late 1970s, early 1980s	25.3 million	8.8	55	Heterosexual
North Africa and Middle East	Late 1980s	400 000	0.2	40	Heterosexual, IDU
South and South-East Asia	Late 1980s	5.8 million	0.56	35	Heterosexual, IDU
East Asia and Pacific	Late 1980s	640 000	0.07	13	IDU, heterosexual, MSM
Latin America	Late 1970s, early 1980s	1.4 million	0.5	25	MSM, IDU, heterosexual
Caribbean	Late 1970s, early 1980s	390 000	2.3	35	Heterosexual, MSM
Eastern Europe and Central Asia	Early 1990s	700 000	0.35	25	IDU
Western Europe	Late 1970s, early 1980s	540 000	0.24	25	MSM, IDU
North America	Late 1970s, early 1980s	920 000	0.6	20	MSM, IDU, heterosexual
Australia and New Zealand	Late 1970s, early 1980s	15 000	0.13	10	MSM
Total/mean		**36.1 million**	**1.1**	**47**	

IDU, transmission through injecting drug use; MSM, sexual transmission among men who have sex with men.
* The proportion of adults (15–49 years of age) living with HIV / AIDS in 2000.

In the UK, an average of more than 2500 HIV infections was reported each year between 1991 and 1997 [3]; 66% of these were from London. During this time 57% of infections were in homosexual men, 29% were as a result of heterosexual sex, and intravenous drug use accounted for 7%, except in Scotland, where it accounted for 20% of infections. During this time less than 1% of HIV infections diagnosed were attributed to blood, tissue or blood-factor treatment, and almost all of these infections were acquired before the widespread introduction of screening of donors.

Molecular epidemiology

One of the major characteristics of HIVs is their extremely high genetic variability. This extensive heterogeneity is a result of the high error rate of reverse transcriptase [4] and the extremely fast turnover of virions in HIV-infected individuals [5,6]. In addition, the reverse transcriptase enzyme is highly recombinogenic [7], so that radically different genomic combinations may be generated in individuals infected by genetically diverse viruses. Recombination requires the simultaneous infection of a cell with two different pro-viruses, allowing the encapsidation of one RNA transcript from each pro-virus into the heterozygous virion. After the subsequent infection of a new cell, the reverse transcriptase, moving back and forth between the two RNA templates, generates a newly synthesized retroviral DNA sequence that is a recombinant between the two parental genomes [7–9]. It is now well established that recombination events between different subtypes or clades of HIV are relatively common, and may result in circulating recombinant forms (CRFs) of HIV. Members of one distinct CRF should resemble each other over the entire genome, with similar break-points reflecting similar ancestry from the same recombination event(s).

Two main types of HIV infect humans: HIV.1 and HIV.2. Worldwide, HIV.1 is by far the commonest cause of AIDS. HIV.2, which differs in a number of its regulatory genes and is found predominantly in West Africa, apparently causes immune deficiency and AIDS more slowly than HIV.1, and is less infectious with lower rates of either sexual or mother-to-child transmission.

Phylogenetic analyses of many samples of HIV.1, isolated from diverse geographical origins, have revealed that they can be divided into *groups*, *subtypes* (or *clades*), *sub-subtypes* and *CRFs* [10–13]. Groups are the distinctive HIV.1 lineages: M (major), N (new) and O (outlier). The vast majority of HIV.1 strains found worldwide and responsible for the pandemic belong to the M lineage. Group O is endemic in Cameroon and neighbouring countries, and group N has only very recently been identified in West Central Africa.

Within group M there are further genetic subtypes or clades which are approximately equidistantly related to each other and represent a homogeneous group not resembling any other subtype across their entire genome. There are presently nine subtypes of HIV.1 identified: A–

Table 26.2 Clades of HIV.

Clade	Estimated incidence 2000 (%)	Primary geographical distribution
A	27	East, West and Central Africa, Eastern Europe
B	12.3	USA, UK, Australia
C	47.2	South Africa, India, China
D	5.3	East Africa
A/E	3.2	South-East Asia
F, G, H, J, K	5.0	Central Africa, Caribbean, Latin America

D, F–H, J and K. All known representatives of what was initially described as subtype E appear in fact to be recombinants of subtypes A and E and are now designated CRF01-AE. Within some subtypes further phylogenetic structure can be identified, for example subtype or clade F is divided into two sub-subtypes or subclades F1 and F2. It is also clear that clades B and D might be better considered as subclades of a single subtype, but for historical reasons it is difficult to change these descriptions [14].

Different subtypes of HIV.1 are predominantly found at different geographical locations, although in no country of the world is a single subtype circulating alone. The contribution of the different clades to the worldwide pandemic has been calculated [15–17] (Table 26.2).

Virology

HIV is a single-stranded RNA virus. The structure of the virus is complex, with three major structural genes: *gag* (coding for nuclear proteins), *pol* (coding for reverse transcriptase) and *env* (coding for the envelope). The rate of transcription of the genome is controlled by a number of regulatory genes including *rev*, *tat* and *nef*, and there are a number of other small accessory genes important for infection (*vif*, *vpu*, *vpr*).

The virus gains access to the cells by docking the envelope protein on the CD4 receptor and on co-receptors (primarily CCR5 on monocytes/macrophages, and CXCR4 on T cells). The process of fusion and inward passage of the genetic material of the virus is accomplished by the transmembrane envelope protein gp41 coming into contact with the cell surface. Components of the *gag* protein have an important chaperone function within the cell and allow reverse transcription to occur and the circular DNA product to be transported to the nucleus of the cell. There, a virally encoded enzyme, integrase, cleaves the circular DNA and inserts it into the host DNA, repairing the insertion sites. Pro-viral DNA may remain integrated for a substantial period of time before viral transcriptional events are triggered when the cell becomes activated. Initial transcriptional products are the regulatory proteins *rev*, *tat* and *nef*. The *tat* protein increases viral transcription, and *rev* acts in cis to enhance replication by interacting with *rev* regulatory elements within the viral genome; *nef* has a number of putative functions, one of which may be to reduce the amount of major histocompatibility complex (MHC) class I antigen on the cell surface and thus impede recognition of the infected cell by cytotoxic T cells (see below). The *vpr* gene is involved in nuclear transport and may down-regulate cellular apoptosis. The *vpu* gene may down-regulate the amount of CD4 receptor protein being produced in the endoplasmic reticulum. Viral products of transcription are then transported to the cytoplasm, where the nuclear capsid proteins may again have an important chaperone function. Viral proteins are produced as a long polyprotein that is split into active proteins by the virally encoded protease enzyme. Viral RNA and viral proteins are then assembled around the nuclear capsid antigen, and when the virus is fully assembled it buds from the cell surface.

It is now realized that enormous amounts of viral RNA are continually released into the plasma ($> 10^8$ viral particles per day) in untreated HIV-infected patients [5,6].

Immunology

The immune system is capable of mounting very strong attacks on invading pathogens and in many cases is able to eliminate them completely. Unfortunately this does not seem to be the case with HIV infection, except perhaps in a very few individuals in whom exposure to the virus has resulted in specific cellular immune responses to the virus, but who have neither seroconverted nor become productively infected [18]. Although often strong and apparently useful anti-HIV responses are induced in HIV-infected individuals, these do not seem to have the capability of clearing viral infection; however, in some individuals immune responses apparently play a role in allowing the host to coexist with the virus without progression to disease (long-term non-progressor patients; see 'Natural history' below and [19]).

Primary infection with HIV results in natural or innate immune responses that are mobilized within hours of infection and include inflammation, non-specific activation of macrophages, natural killer cells and complement, and release of cytokines.

After antigenic stimulation, acquired immune responses are primed. These responses emerge at the same time as

clearance of viraemia and rebound of CD4 T cells is seen. These HIV-specific responses are outlined below.

Specific humoral or antibody responses [20]: neutralizing antibodies to the envelope proteins of the virus and other non-neutralizing antibodies to internal viral proteins such as *gag*. Specific secretory IgA mucosal antibodies are also produced. Neutralizing antibodies are usually measurable by 12 weeks after infection.

Specific cellular (T-lymphocyte) responses [21]. $CD8^+$ T lymphocytes or cytotoxic T cells (CTL) form a primary component of the critical cellular immune response induced by HIV infection. CTL are differentiated from existing CTL precursors, and express T-cell receptor molecules capable of recognizing specific viral epitopes presented in the context of human leukocyte antigen (HLA) or MHC molecules at the surface of infected target cells. Mature CTLs are functional 5–10 days after antigenic stimulation, recognizing, binding and then lysing the infected target cell. Virus-specific CTLs evolve faster than antibody responses and are often induced before seroconversion and before viral RNA has reached peak titres. Thus $CD8^+$ CTLs are temporally associated with the fall in viraemia during acute infection, and there is good evidence that CTLs play a major role in the control of HIV infection at this time and later in HIV disease. Evidence for strong $CD8^+$ antiviral pressure can be appreciated by the number and variety of strategies which viruses have evolved to avoid apoptosis and CTL recognition, thus prolonging the life of the virally infected cell and enabling viral replication and dissemination [22]. In addition to the lysis of infected cells, CD8 T cells can reduce viral replication by the production of soluble factors. These factors are not antigen specific but their production requires specific T-cell activation. Anti-HIV effects have been found for interferon (IFN)-γ, interleukin (IL)-10, IL-13, IL-16 and the C-C chemokines MIP-1α, MIP-1β and RANTES. Such soluble factors may also have profound effects on other opportunistic infections including those affecting the skin.

$CD4^+$ T-cell responses induced by HIV infection provide help to both HIV-specific CTLs and B cells. CD4 T-helper cells recognize antigen in the context of HLA class II molecules on the surface of antigen-presenting cells such as dendritic cells. CD4 responses to a variety of HIV proteins (including *env*, *gag* and *nef*) have been demonstrated in early disease, but immunological abnormalities in T-helper function occur very early in HIV infection, even before CD4 T-cell numbers diminish. Reduced proliferative capacity and diminished IL-2 production in response to stimulation by exogenous antigens (including those from HIV and other pathogens) is one of the hallmarks of HIV disease.

On recognition of their specific antigen, naive CD4 T cells differentiate from a common (Th0) precursor into T-helper (Th)1 cells, which differentially secrete IL-2, IFN-γ, transforming growth factor-β and IL-12 and can activate macrophages and 'help' CTLs, or into Th2 cells, which secrete IL-4, IL-5, IL-6 and IL-10 that can activate B cells to proliferate and differentiate into antibody-producing plasma cells.

Central to the cellular immune response is the dendritic cell, which is the most potent antigen-presenting cell. However, such cells on mucosal surfaces (Langerhans' cells) may be some of the first targets in transmission: as well as transporting viral antigens across mucosal barriers and presenting them to CD4 cells, dendritic cells may themselves become infected with HIV, and their function compromised.

It should be noted that the immunosuppressive nature of HIV infection, where CD4 T cells are infected and destroyed, may have a profound effect on immune responses to other pathogens, many of which result in dermatological disease and are described later in this chapter. It is interesting to observe that HAART, which has a profound effect on HIV replication and enables some CD4 T-cell reconstitution, may also result in the re-emergence of useful opportunistic infection-specific cellular immune responses. Unfortunately, for reasons which are not well understood, HIV-specific responses are often not reconstituted. However, many AIDS-defining opportunistic infections, including diseases of the skin, may be resolved or avoided, and consequently HAART has had a profound effect on morbidity and mortality in HIV disease.

AIDS case surveillance definition

The case definition of AIDS in adults is shown in Table 26.3 [23]. The indicator conditions used in the case definition of AIDS in adults are shown in Table 26.4. The rank order of AIDS diagnoses reported to the Centers for Disease Control (USA) in 1996 is shown in Table 26.5.

Changes in the natural history of HIV which have followed the introduction of HAART in the mid-1990s include a sharp reduction in the frequency of KS and a decrease in *Pneumocystis carinii* pneumonia, reflecting the impact of prophylaxis and possible reconstitution of immune responses specific for opportunistic pathogens. The median CD4 T-cell count at the time of an AIDS-defining complication in those parts of the world where HAART is available is now 67×10^6/L. However, it should be remembered that, at present, such efficacious therapy is not available to more than 90% of persons infected with HIV.

It should also be noted that the AIDS case definition in children may be different from that in adults [24]. Furthermore, in contrast to the surveillance definitions described in Table 26.3, in clinical care HIV disease should be viewed as a continuum, rather than just the presence

Table 26.3 Case definition of AIDS in adults.

	Clinical category		
CD4 T-cell count	A: asymptomatic persistent generalized lymphadenopathy or acute HIV infection	B: symptomatic* (not A or C)	C: AIDS indicator condition (see Table 26.4)
1) > 500 × 10^6/L (> 29%)	A1	B1	C1†
2) 200–499 × 10^6/L (14–28%)	A2	B2	C2†
3) < 200 × 10^6/L (< 14%)	A3†	B3†	C3†

* Symptomatic conditions not included in category C that may be attributed to HIV infection or indicative of a defect in cell-mediated immunity, or may be considered to have a clinical course or management that is complicated by HIV infection. Examples include, but are not limited to, bacillary angiomatosis; thrush; vulvovaginal candidosis that is persistent, frequent or poorly responsive to therapy; cervical dysplasia (moderate or severe); cervical carcinoma *in situ*; constitutional symptoms, such as fever (> 38.5°C) or diarrhoea > 1 month; oral hairy leukoplakia; herpes zoster involving two episodes or more than one dermatome; idiopathic thrombocytopenic purpura; listeriosis; pelvic inflammatory disease; and peripheral neuropathy.
† All patients in categories A3, B3, C1, C2 and C3 are considered to have AIDS based on the AIDS indicator conditions and/or a CD4 T-cell count of < 200 × 10^6/L.

Table 26.4 Indicator conditions in the case definition of AIDS in adults.

Candidosis of oesophagus, trachea, bronchi or lungs
Cervical cancer, invasive*
Coccidioidomycosis, extrapulmonary*
Cryptococcosis, extrapulmonary
Cryptosporidiosis with diarrhoea for > 1 month
Cytomegalovirus of any organ other than liver, spleen or lymph nodes
Herpes simplex with mucocutaneous ulcer for > 1 month or bronchitis, pneumonitis oesophagitis
Histoplasmosis, extrapulmonary*
HIV-associated dementia: disabling cognitive and/or motor dysfunction interfering with occupation or activities of daily living
HIV-associated wasting:* involuntary weight loss of > 10% of baseline plus chronic diarrhoea (more than two loose stools per day for > 30 days) or chronic weakness and documented enigmatic fever for > 30 days
Isosporosis with diarrhoea for > 1 month*
Kaposi's sarcoma in patient younger than 60 years (or older than 60*)
Lymphoma of brain in patient younger than 60 years (or older than 60*)
Lymphoma, non-Hodgkin's of B-cell or unknown immunological phenotype and histology showing small non-cleaved lymphoma or immunoblastic sarcoma
Mycobacterium avium or *M. kansasii*, disseminated
Mycobacterium tuberculosis, disseminated*
Mycobacterium tuberculosis, pulmonary*
Nocardiosis*
Pneumocystis carinii pneumonia
Pneumonia, recurrent (bacterial)*
Progressive multifocal leukoencephalopathy
Salmonella septicaemia (non-typhoid), recurrent*
Strongyloidosis, extraintestinal
Toxoplasmosis of internal organ

* Requires positive HIV serology.

Table 26.5 Rank order of AIDS diagnoses reported to the Centers for Disease Control (USA) in 1996.

Pneumocystis carinii pneumonia	20%
Wasting	14%
Cytomegalovirus disease	6%
Kaposi's sarcoma	6%
Tuberculosis	5%
Disseminated *Mycobacterium avium–intracellulare* infection	4%
Chronic herpes simplex	4%
Recurrent bacterial pneumonia	4%
HIV-associated dementia	4%
Toxoplasmosis	3%

or absence of AIDS. This continuum includes primary infection, symptomatic infection, early symptomatic state (previously known as AIDS-related complex), late symptomatic disease and advanced disease.

Natural history

Prospective epidemiological studies in HIV-infected but untreated individuals with known dates of seroconversion have allowed us to quantify many aspects of the natural history of HIV disease, and have shown that the course of HIV infection may vary considerably in different individuals. Thus, although some individuals develop AIDS within 2–3 years and are termed 'rapid progressors', others remain free from AIDS for more than 10–15 years and are termed 'long-term non-progressors' or 'long-term survivors'. In the absence of treatment, the average time from seroconversion to the development of AIDS is 8–11.6 years, with a median time of approximately 10 years. Interestingly this median survival time is the same in the USA as it is in Uganda [25]. It should be noted that most existing data were obtained before the availability (in the West) of antiretroviral drugs and prophylaxis for *Pneumocystiis carinii* pneumonia. Clearly such drug treatment, when available, has a profound and beneficial effect on the natural history of HIV disease.

Certain clinical and laboratory factors are known to influence and help predict the rate of disease progression to AIDS in the HIV-infected individual. Rates of progression

appear similar by gender, race and risk category after adjustment for access to health care. The predictors for progression to AIDS may be summarized as follows.

- *Transmission risk group*. Time from HIV seroconversion to AIDS is approximately 7 years in transfusion recipients, 10 years for haemophiliacs, 10 years for intravenous drug users and 10–12 years for homosexual men.
- *Age at onset of infection*. It has been reported that for patients aged 16–24 years at time of HIV acquisition the median time from seroconversion to AIDS is 15 years, whereas for those aged over 35 at seroconversion it is 6 years.
- *Clinical indicators*. Patients with symptomatic primary HIV infection progress more rapidly than those with asymptomatic seroconversion. Other clinical markers of progression include the development of oral thrush, oral hairy leukoplakia, herpes zoster, constitutional symptoms and weight loss.
- *CD4 T-cell count*. CD4 T-cell counts and their decline over time are very important predictors of disease progression. On average the CD4 T-cell count decreases by $40–80 \times 10^6$/L annually; an acceleration in CD4 T-cell decline heralds progression of disease. A CD4 T-cell count of $< 200 \times 10^6$/L is diagnostic of AIDS, and the median survival time in an untreated patient with a CD4 T-cell count of $< 200 \times 10^6$/L is 38–40 months. The average CD4 T-cell count for the most common AIDS-defining conditions is in the range of $20–100 \times 10^6$/L.
- *Viral load*. Plasma HIV RNA viral load correlates well with the extent of viral replication in an infected individual. Progressively increasing HIV RNA concentrations can signal the development of advancing immunodeficiency. A single measurement of plasma RNA viral load early in infection is a powerful predictor of the subsequent risk of progression to AIDS and death. The combined measurement of CD4 T-cell count and viral load is an extremely accurate method for assessing the prognosis of infected patients.

Other factors that may be predictive of HIV disease progression have not been well defined. Thus co-infection with other pathogens such as cytomegalovirus (CMV), Epstein–Barr virus, hepatitis B or malaria has not been shown conclusively to accelerate disease progression. Although the genetic background of the patient may have relevance, very few genetic markers of progression have been defined. The size and route of the initial inoculum of virus may have an important role to play, as may the pathogenicity, virulence, attenuation state or genotype of the infecting virus.

HIV treatment

Antiretroviral treatment of HIV began in the mid-1980s with the nucleoside analogue zidovudine (azidothymidine) and the demonstration that this was better than placebo in the treatment of symptomatic disease. However, the treatment of HIV infection was revolutionized in developed countries as a result of the introduction of HAART. This has reduced short-term mortality and markedly increased quality of life by preventing opportunistic diseases [26]. HAART has developed as a result of controlled trials showing that dual nucleoside analogue therapy improves survival compared with zidovudine monotherapy [27], and that three-drug therapy consisting of two nucleoside analogues and a protease inhibitor is superior to two drugs [28].

One of the causes of drug failure is the development of viral mutations displaying reduced sensitivity to drugs. Such mutations may arise either because of selection of mutants already existing in the viral swarm or the *de novo* generation of new mutations as a result of selective pressure by the drugs. Avoidance of the development of drug resistance requires drugs to be used in combination, making selection or generation of new resistant mutations more difficult, and by the use of potent therapy, which suppresses viral replication as completely as possible.

The dramatic improvements in survival with the use of HAART coincided with the development of two potent classes of drugs. Following incorporation of viral DNA into the host genome, viral progeny are produced as a result of the transcription of this DNA, which accompanies cell activation. This produces polyproteins, which to be effective have to be digested by a virally coded protease. A variety of inhibitors of this protease are now available to clinicians and all are extremely potent.

The other potent class of compounds are the non-nucleoside reverse transcriptase inhibitors (NNRTIs). As described previously, the virus encodes for a unique enzyme, reverse transcriptase, that is responsible for converting viral RNA into a DNA copy, which is then incorporated in the host genome. The originally introduced therapies for HIV were all nucleoside analogues, which act as chain terminators of the growing DNA chain. Reverse transcriptase can also be inhibited very potently by a variety of chemicals that act in a pocket of the reverse transcriptase closely adjacent to the catalytic site. The potency of these drugs was only appreciated when they were given to individuals who had not previously received treatment, accompanied by nucleoside analogues [29]. This combination inhibits viral replication sufficiently completely to prevent selection of viral mutants with resistance to the NNRTI class [30].

The original hypothesis for optimum treatment of HIV infection was 'hit hard and hit early' [31], i.e. to use potent regimens and to use them early in the disease course with the hope of completely eradicating evidence of infection within a finite period. Unfortunately, as our understanding of the pathogenesis of HIV infection has improved, this hypothesis has turned out to be unrealistic, perhaps most importantly because HIV is also incorporated into

Table 26.6 Nucleoside analogue reverse transcriptase inhibitors. (After Moyle & Gazzard [38]; Ward *et al*. [39].)

Drug	Side effects
Zidovudine (AZT/ZDV)	Nausea, bone marrow suppression, myopathy
Zalcitabine (ddC)	Peripheral neuropathy
Didanosine (ddI)	Nausea, bloating, diarrhoea, pancreatitis, peripheral neuropathy, gynaecomastia, gout
Stavudine (d4T)	Peripheral neuropathy, gynaecomastia
Lamivudine (3TC)	Nausea, bone marrow suppression, peripheral neuropathy
Abacavir, tenofovir (nucleotide)	Nausea, diarrhoea

Table 26.7 Non-nucleoside reverse transcriptase inhibitors. (After Moyle & Gazzard [40].)

Drug	Side effects
Nevirapine	Clinical and biochemical hepatitis
Delavirdine	Biochemical hepatitis
Efavirenz	Insomnia, nightmares

Table 26.8 Protease inhibitors. (After Moyle & Gazzard [41].)

Drug	Side effects
Amprenavir	Nausea, diarrhoea,
Indinavir	Nausea, nephrolithiasis, haematuria, hyperbilirubinaemia, porphyria, hyperaesthesia
Nelfinavir	Diarrhoea
Ritonavir	Nausea, vomiting, dysgeusia, biochemical hepatitis, hyperaesthesia
Saquinavir, lopinavir	Nausea, diarrhoea

long-lived cells which generally divide very occasionally [32]. It is only during the process of cellular replication that anti-HIV drugs are active, and therefore the early hopes of eradication within a 3–4 year period have not been realized, and it is likely that present treatment will be required lifelong to continually suppress viral replication. Early treatment was also advocated because it was assumed that HIV caused irreversible deletions in the immune repertoire and so if treatment was started late patients would remain susceptible to opportunistic infections. Fortunately this has been shown not to be the case. Even individuals treated in late disease show considerable reconstitution of the immune repertoire [33,34].

Perhaps the most important practical reason for renewed caution about the timing of initiating antiretroviral therapy has been the emergence of a variety of drug toxicities that were unsuspected at the time the drugs were originally licensed. For the nucleoside analogue class this includes mitochondrial toxicity and hyperlactataemia [35], and for the protease inhibitors a variety of abnormalities of lipid metabolism.

However, the greatest problem to a more complete understanding of these syndromes is that, of necessity, most of the present studies are cross-sectional and represent the end result of processes which have been present in the patient for some years. New drugs are being developed in the presently available classes, i.e. nucleoside analogues, NNRTIs and protease inhibitors. The main objective of such new drugs is to improve adherence to treatment by enhancing the convenience of the regimen or to diminish side effects. Thus a new protease inhibitor, atazanavir, appears to be free of blood lipid abnormalities in controlled trials [36], but whether this will translate into freedom from the lipid redistribution syndrome remains to be determined. Classes of drugs that attack new targets within the replication cycle of HIV are also being developed; the most advanced of these are those which inhibit the process of fusion. This is an important example of where an understanding of the detailed mechanisms involved in viral fusion have led to the development of new drugs. The most advanced of these is Roche T20; this drug inhibits the contraction of the helical coils associated with gp41, which normally contract and bring the surface of the envelope protein of the virus (gp120) into close contact with the cell surface. The disadvantage of this drug is that it has to be given by subcutaneous injection once or twice a day, and it is therefore unlikely that this drug will be tolerated in the long term for naive patients. Its chief benefit is likely to be in patients who are failing other therapies. Also in the process of development is a variety of small molecules that are orally bioavailable and which may inhibit the interaction between HIV and the second receptor on the host cell surface, i.e. CCR5 or CXCR4. Such drugs have been shown to produce viral load reductions in phase I studies by inhibiting the CCR5 receptor, although the drug AM3100, which inhibits CXCR4, has not shown equivalent benefit [37]. At an even earlier stage of development are products that inhibit the interaction between the CD4 receptor and the conserved portion of gp120. These molecules are highly potent *in vitro*; some HIV strains are relatively resistant to its action. However, in the future it is hoped that a variety of fusion inhibitors may act synergistically, thereby allowing some of the older drugs with an important side effect profile to be used less often.

Those drugs in current usage are listed by class in Tables 26.6–26.8. The principal non-dermatological side

effects are included. Lipid abnormalities and lipodystrophy are discussed on p. 26.20. Mucocutaneous side effects are detailed on pp. 26.19 and 26.20, and in Table 26.18. Dermatologists should be aware of the risks of drug interactions in treating patients with HIV on HAART, particularly because of the metabolism of protease inhibitors by the cytochrome P-450 system in the liver.

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Dermatological manifestations of HIV infection

Skin disease may provide the first suspicion of the diagnosis of HIV infection, cause significant morbidity as the disease progresses and point to a diagnosis with important systemic implications. The number of mucocutaneous diseases, like the CD4 T-cell count, is a prognostic indicator of the development of AIDS and overall survival [1]. Some skin problems are less consequential than other manifestations of HIV infection but many are very distressing to patients and some potentially very serious or fatal. Although some situations are clinically straightforward and readily amenable to satisfactory intervention, all of the dermatological complications of HIV infection can be a challenge to diagnose and manage. They may present with unusual symptoms and signs, coexist with other pathologies, be altered by treatment and drug reactions are common [2–5].

In general, HIV dermatology presents four broad challenges to the dermatologist. Firstly, there is the

opportunity to make the initial diagnosis of HIV in patients with a seroconversion illness or with subtle or florid manifestations of one or other dermatoses associated with underlying HIV infection. Next, there is differentiating whether a skin problem is caused by HIV infection or by HIV therapy. Thirdly, the dermatologist's therapeutic imagination and experience is occasionally tested. Lastly, there are the implications of HIV-associated skin disorders for the better understanding of the skin in health and disease: the virus has been demonstrated in the cutis of infected individuals; cutaneous dendritic cells and Langerhans' cells may be the main targets in acute HIV infection [6] and the cause of skin disease in chronic infection; different cytokine expression patterns distinguish different cutaneous manifestations [7,8]; and involvement of cutaneous nerves may contribute to the pathogenesis of HIV-related dermatoses [9].

Until recently, suspecting, or failing to suspect, that a patient presenting with a common dermatosis known to be associated with HIV infection might be HIV positive has not been so important. Indeed, in the past the patient's best psychological and fiscal interests might have been better served by relative ignorance. However, the benefits of earlier diagnosis that have ensued from HAART place a greater onus on the dermatologist than hitherto to discuss HIV risk with patients presenting with skin diseases known to be associated with HIV and to recommend assessment, counselling and testing if the overall clinical situation dictates it. A high index of suspicion is essential, especially in assessing high-risk patients. The commoner scenario is the evaluation of the patient already known to have HIV infection who presents with dermatological symptoms and whose physician is concerned that the skin condition is a complication of HIV or its treatment.

Classical clinical dermatological history-taking and examination is the beginning of the diagnostic endeavour. Some dermatoses can be diagnosed confidently on clinical grounds, but experience has shown that it is easy to be misled. Immunopathophysiological and neurovascular mechanisms in the skin determine the symptomatic and morphological presentation of all skin diseases, so it is not surprising that 'things look different' in HIV-infected patients. Several cutaneous conditions may coincide sometimes within a single lesion. The commonest dermatological conditions associated with HIV infection are listed in Table 26.9.

Investigations are frequently necessary. Skin scrapings may be examined microscopically in the clinic (after clearing with potassium hydroxide) for the presence of fungal hyphae or spores. Swabs for bacteria and viruses and scrapings for fungi may be taken for laboratory microscopic examination and culture. Skin biopsy is often undertaken. The operator and assistants should wear gloves, gowns and eyeglasses. Representative samples of lesional skin should be carefully selected for histopathology and culture for fungi and acid-fast bacilli. Many laboratories decline to perform direct immunofluorescence. It is the responsibility of clinicians to take due care in the collection and submission of all pathological material for investigations so that no hazard is created for themselves, staff or other patients.

Table 26.9 Common dermatological conditions in HIV infection. (After Bunker & Staughton [5].)

Pruritus/xerosis/ichthyosis
Eosinophilic folliculitis
Pruritic papular eruption
Seborrhoeic dermatitis
Psoriasis
Folliculitis
Drug eruptions
Herpes simplex
Herpes zoster
Viral warts
Mollusca
Tinea (including onychomycosis)
Scabies
Basal cell carcinoma
Squamous cell carcinoma

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Acute primary HIV infection/seroconversion

Acute primary HIV infection may be clinically silent but up to 90% of patients develop a non-specific symptomatic illness 1–6 weeks after exposure that lasts a few days to several months but usually less than a fortnight [1]. Symptoms and signs are often those of a non-specific viral infection, like infectious mononucleosis with lassitude, fever, arthralgia, myalgia and lymphadenopathy. Weight loss, nausea, vomiting and diarrhoea are common. Headache and photophobia may signify aseptic meningitis and cognitive dysfunction encephalitis, although other recognized

Table 26.10 Clinical manifestations of primary HIV infection. (From Hawkins [2].)

Clinical manifestation	Frequency (%)	Mean duration (days)
Fever (> 38°C)	77	17
Fatigue	66	24
Erythematous maculopapular rash	56	15
Myalgia	55	18
Headache	51	26
Pharyngitis	44	12
Cervical lymphadenopathy	39	15
Arthralgia	31	23
Oral ulcer	29	13
Odynophagia	28	16
Axillary lymphadenopathy	24	164
Weight loss	24	29
Nausea	24	18
Diarrhoea	23	13
Night sweats	22	15
Cough	22	18
Anorexia	21	15
Inguinal lymphadenopathy	20	9
Abdominal pain	19	15
Oral candidosis	17	10
Vomiting	12	10
Photophobia	12	11
Sore eyes	12	13
Genital ulcer	7	14
Tonsillitis	7	13
Depression	6	23
Dizziness	6	11

neurological presentations include Bell's palsy, brachial neuritis, radiculopathy, peripheral neuropathy and Guillain–Barré syndrome. Table 26.10 lists the frequency and duration of the principal clinical manifestations of primary HIV infection [2].

The principal dermatological manifestations of seroconversion are given in Table 26.11 [3]. A rash is found in up to 75% of people with symptomatic seroconversion. A symmetrical maculopapular erythematous exanthem, notably of face, palms and soles, occurs. Pale pink macules and perifollicular erythematous papules have been described. Occasionally there may be urticarial or vesicular lesions, and alopecia. The histology is characterized by a perivascular lymphocytic infiltrate with or without epidermal changes, ranging from vacuolar change and spongiosis to epidermal necrosis [4]. Painful oral ulceration, genital ulceration, erythema multiforme and Stevens–Johnson syndrome may occur [5–8]. Acute erosive genitocrural intertrigo has been described [9]. If the CD4 count falls precipitously, oral candidosis can develop. The exanthem may represent infection of cutaneous Langerhans' cells and the orogenital lesions sites of viral inoculation [10].

Thus primary infection, including non-specific dermatological reaction patterns, may go unnoticed, unreported or undiagnosed. And because the dermatological and

Table 26.11 Dermatological manifestations of HIV seroconversion. (After Bunker & Staughton [3].)

Exanthema
Enanthema
Urticaria
Toxic erythema
Erythema multiforme
Oropharyngeal candidosis
Acute genitocrural intertrigo
Oral ulceration
Genital ulceration

Table 26.12 Differential diagnosis of primary HIV infection. (After Bunker & Staughton [3].)

Toxic erythema (and its differential diagnosis, drugs, infections, connective tissue disease)
Urticaria (and its differential diagnosis, drugs, infections, connective tissue disease, neoplasia)
Erythema multiforme (and its differential diagnosis)
Orogenital ulceration (and its differential diagnosis, drugs, infections, connective tissue disease, immunobullous disease, Behçet's syndrome, Stevens–Johnson syndrome)
Pityriasis rosea
Guttate psoriasis
Reiter's syndrome
Still's disease
Infections
Epstein–Barr virus
Cytomegalovirus
Parvovirus B19
Herpes simplex virus
Human T-lymphotropic virus type 1 and 2
Hepatitis A, B and C
Gonococcaemia
Syphilis
Rheumatic fever
Toxoplasmosis
Drug reactions

other manifestations of seroconversion are non-specific, there is a differential diagnosis (Table 26.12). Syphilis was the great imitator: perhaps now it is HIV [11]. It must also be appreciated that two (or more) illnesses may coexist.

The more severe and numerous the manifestations, and the more prolonged the duration, the more likely a more rapid progression of HIV disease in that individual (Table 26.13) [12–14].

Precise diagnosis and exclusion of other causes can be complicated in the acute stage by interpretation of bacteriological and virological results (e.g. serological diagnosis of syphilis). There may be lymphopenia (usually a modest fall in CD4 count, mild rise in CD8 and inverted CD4/CD8 ratio) and thrombocytopenia and a biochemical hepatitis or cholestatic biochemical profile. A skin biopsy may not be helpful showing non-specific histology; spongiosis, apoptosis, interface dermatitis and mild perivascular chronic inflammatory infiltrate. Seroconversion illness is

Table 26.13 Useful prognostic indicators around primary infection. (From Hawkins [14].)

Clinical (soon after initial infection)	Laboratory (3–4 months after infection)
Presence of symptoms	CD4 T-cell count
Duration of symptoms (> 14 days)	Quantitative viral load (HIV RNA measurement)
Number of symptoms (more than three symptoms)	Polymerase chain reaction
	b-DNA
Candidosis	β_2-Microglobulin
Acquisition of HIV from an individual with advanced HIV disease	
Neurological involvement	

b-DNA, branched chain DNA.

Table 26.14 Diagnosis of primary HIV infection. (From Hawkins [2].)

Essential assays
Enzyme-linked immunosorbent assay (ELISA)
Western blot (should also be able to detect HIV. 2 infection)
HIV. 1 p24 antigen testing
HIV DNA or RNA polymerase chain reaction (PCR)
Supplementary tests after inconclusive ELISA results
HIV DNA or RNA PCR if not previously performed
HIV RNA quantification (especially if antiretroviral therapy is being contemplated)
T-cell subset enumeration
Exclusion of other viral illnesses (e.g. cytomegalovirus, Epstein–Barr virus)

diagnosed by positive plasma HIV polymerase chain reaction (PCR) alongside negative or equivocal HIV antibody tests (Table 26.14) [2].

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Established HIV infection

Pruritus, xerosis, ichthyosis

These are common in HIV and can be variably symptomatic [1]. HIV belongs in the differential diagnosis of generalized pruritus (see Chapter 16) [2]. Patients must be evaluated carefully for other pruritic dermatoses (e.g. scabies, atopic dermatitis, papular eruption of HIV and eosinophilic folliculitis) and the other medical causes of generalized pruritus (e.g. hepatic and renal disease). Excoriations, eczematization and impetiginization can complicate scratching. IgE estimation and skin swabs, scrapings and biopsy may be helpful. Treatment follows conventional lines and includes phototherapy [1,3–5]. The mechanism is uncertain but cutaneous peptidergic neuronal loss has been demonstrated [6]. Severe intractable pruritus with eosinophilia may indicate a subset of HIV-infected patients with hyperactivation of humoral immunity and augmented viral load [7]. Pruritus and xerosis are also side effects of protease inhibitors (see Chapter 16) [8].

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Table 26.15 Inflammatory dermatoses rarely associated with HIV. (Modified from Bunker [7]; Bunker & Staughton [8]; Penneys [9]; Duvic [10]; Cockerell [11,12]; Cowley & Staughton [13]; Aftergut & Cockerell [14]; Rico *et al*. [15].)

- Erythroderma [1]
- Photosensitivity [16–19]
- Kwashiorkor [20]
- Allergic contact dermatitis [21–23]
- Chronic actinic dermatitis [24]
- Prurigo nodularis [25,26]
- Urticarias [27]
- Persistent insect bite reaction
- Hyperimmunoglobulin E syndrome [28]
- Hypereosinophilic syndrome [29–31]
- Granuloma annulare
- Papuloerythroderma [32]
- Pityriasis rubra pilaris [33]
- Lichen spinulosus [34]
- Pityriasis lichenoides [21,35]
- Pityriasis rosea, particularly if persistent [36]
- Erythema dyschromicum perstans/ashy dermatosis of Ramirez [37]
- Acne vulgaris and variants [38,39]
- Perforating folliculitis [40]
- Hidradenitis suppurativa [2]
- Neutrophilic eccrine hidradenitis [41]
- Lichenoid granulomatous papular dermatosis
- Cutaneous malakoplakia [42]
- Lichen amyloid [43,44]
- Varicose ulceration [45]
- Acrocyanosis ± cryoglobulinaemia, *Pneumocystis carinii* septicaemia [46]
- Perniosis [47]
- Erythema nodosum [48,49]
- Vasculitis [50,51]
  - Erythema elevatum diutinum [52–54]
  - Polyarteritis nodosa [55,56]
  - Parvovirus B19 [57,58]
  - Kawasaki-like syndrome [59]
  - Red finger syndrome [60–63]
  - Livedo reticularis/Raynaud's phenomenon/cryoglobulinaemia/hepatitis C [64]
  - Degos' disease [65]
  - Behçet's disease [66]
  - Pyoderma gangrenosum [67,68]
  - Sweet's neutrophilic dermatosis [69]
  - Atypical neutrophilic dermatoses [70]
- Anetoderma [71,72]
- Transient acantholytic dermatosis/Grover's disease [73]
- Autoimmune bullous diseases
  - Bullous pemphigoid [74,75]
  - Cicatricial pemphigoid [76]
  - Pemphigus [74,77–79]
  - Dermatitis herpetiformis [80,81]
- Acrodermatitis enteropathica [82,83]
- Eccrine squamous syringometaplasia (± cytomegalovirus) [84,85]
- Cutaneous mucinoses [86]
  - Reticular erythematous mucinosis [87]
  - Lichen myxoedematosus/papular mucinosis [88–90]
  - Eccrine ductal mucinosis and follicular mucinosis (with scabies) [85]
  - Scleroedema [86]
- Atypical cutaneous lymphoproliferative disorder [91,92]

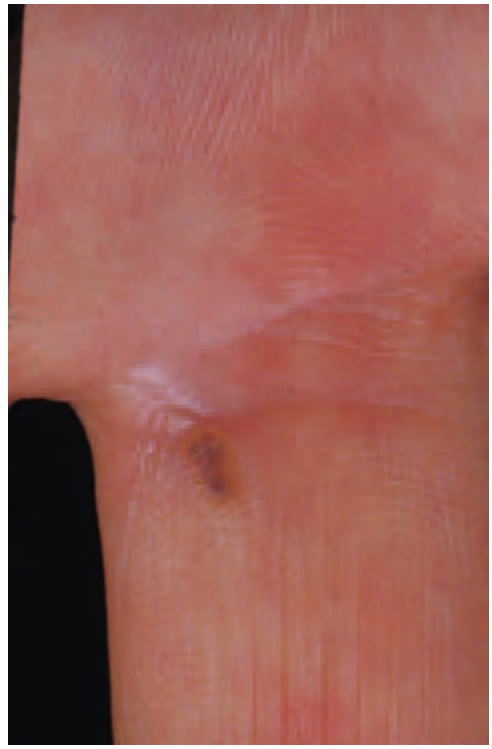

Fig. 26.1 Thrombocytopenic purpura: purpuric macule on the finger. (Courtesy of Dr C.B. Bunker and Medical Illustration UK Ltd, Chelsea and Westminster Hospital, London, UK.)

Inflammatory dermatoses

The commonest of the inflammatory dermatoses associated with HIV infection (see Table 26.9) are discussed below. Table 26.15 lists rarer inflammatory dermatoses that have been observed in the context of HIV infection.

Erythroderma may have several causes and the same differential diagnostic approach employed in general dermatology is recommended: in a young black patient, erythroderma may be a marker for HIV infection [1].

Proctitis, piles, perianal ulceration, abscess, fissure and fistula are prevalent in homosexual men and HIV infection [2–4] and are discussed in Chapter 68.

Thrombocytopenic purpura may present to a dermatologist: it can be mistaken for KS (Fig. 26.1) [5,6].

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Seborrhoeic dermatitis

Only 1–3% of the general population have seborrhoeic dermatitis compared with 20–85% of patients with HIV. Seborrhoeic dermatitis is more common in seropositive homosexual men than seronegative homosexuals, and among infected patients it is commoner and has an earlier onset in homosexuals and bisexuals compared with intravenous drug users [1]. Although found in seropositive individuals who are otherwise well, its severity is increased at CD4 T-cell counts below 100×10^6/L. This phenomenon is not adequately explained. The consensus is that classical seborrhoeic dermatitis represents an aberrant cutaneous reaction to commensal *Malassezia* yeast species. Probably the cutaneous immune dysfunction caused by HIV alters the host–organism relationship. The severity of seborrhoeic dermatitis may be related to yeast density or yeast strain [2,3]. There is a correlation between the numbers of yeast cells intimately associated with keratinocytes and the clinical severity of seborrhoeic dermatitis in patients with AIDS [4]. Patients taking ketoconazole have a lower prevalence of seborrhoeic dermatitis [5]. Also, imidazole treatment elicits clinical improvement, with a concomitant decrease in the numbers of *Malassezia* organisms per keratinocyte [6]. Abnormalities of skin surface lipids are not associated with the development of seborrhoeic dermatitis but are associated with HIV infection itself [7]. Seborrhoeic dermatitis has been related to low plasma zinc levels but this may not be significant [8]. Neuroendocrine and sebotropic factors are influenced by HIV infection and seborrhoeic dermatitis and neurological disease may coexist in some patients. Seborrhoeic dermatitis is essentially a hyperproliferative dermatosis and keratinocyte stimulation may result from HIV infection because of either monocyte-derived lymphokines or a direct effect of the virus itself [9].

Itchy scaly patches are found at the classical sites (Fig. 26.2) and elsewhere. There may be folliculitis. Erythroderma has been reported [10]. An association of erythroderma, xerosis and seborrhoeic dermatitis with the development of dementia and spinal cord disease has been noted [9]. Extensive refractory seborrhoeic dermatitis appears to occur in particular conjunction with pulmonary tuberculosis and AIDS in Zambia [11].

The differential diagnosis includes other causes of erythroderma, eczema, psoriasis and dermatophytosis. Scrapings can be examined for fungi to exclude tinea, and *Malassezia* sp. may be seen in large numbers. Biopsy may show hyperkeratosis, acanthosis, spongiosis, spotty ker-

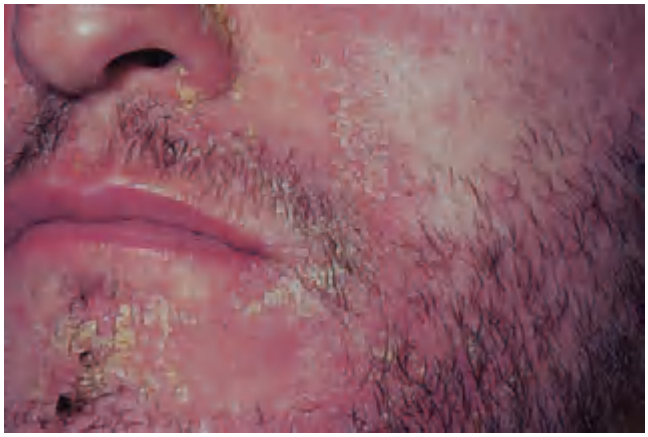

Fig. 26.2 Seborrhoeic dermatitis on the face. (Courtesy of Dr C.B. Bunker and Medical Illustration UK Ltd, Chelsea and Westminster Hospital, London, UK.)

atinocyte necrosis, leukocytosis and subcorneal neutrophil infiltration. A deeper lymphocytic infiltration of sebaceous glands and a more perivascular neutrophilic (with occasional leukocytoclasis) and plasma cell infiltrate is seen in HIV compared with classical seborrhoeic dermatitis [9,12]. The histology may be very similar to psoriasis.

Management follows conventional lines: emollients, topical steroids and antifungals and oral imidazoles. Although clinical improvement of seborrhoeic dermatitis is often reported after immune reconstitution with HAART, Schaub *et al*. [1] have opined that antiretroviral treatment does not influence the prevalence, onset or disease-free survival times.

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Atopic dermatitis

Atopic dermatitis or an atopic dermatitis-like condition appears to be common in children with HIV [1], although it should be borne in mind that atopy is common anyway. In adults there have been reports of patients whose atopic eczema recurred or worsened during the course of HIV infection [2,3] and hyper-IgE syndrome has also been described [4]. Others believe atopic dermatitis is not affected by HIV [5,6]. A decreased frequency of atopic diseases, fewer positive radioallergosorbent tests and lower average levels of IgE in HIV-positive compared with HIV-negative homosexual individuals has been found [7], as has dysregulation of IgE synthesis [8]. Fungal allergen-specific IgE responses may contribute to the pathogenesis of eczematous skin disease in HIV-infected individuals [9].

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Psoriasis

Psoriasis is prevalent (2%) in the general population and can worsen or appear for the first time (often very severely) in HIV infection [1,2] but may regress preterminally [3]. It may (5%) [4] or may not (1%) [5] be more prevalent in the HIV-infected population. HIV-associated psoriasis provides some insights into the pathogenesis of psoriasis. Most patients with HIV-associated psoriasis are positive for HLA-Cw0602 as are all HIV-negative patients with streptococcal-associated guttate psoriasis [6,7]. There

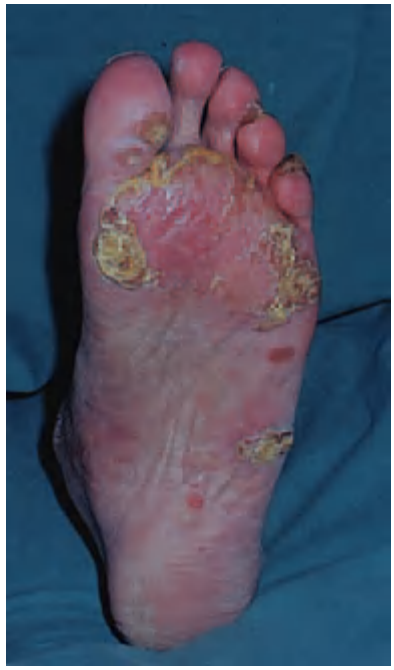

Fig. 26.3 Severe plantar psoriasis in HIV infection. (Courtesy of Dr C.B. Bunker and Medical Illustration UK Ltd, Chelsea and Westminster Hospital, London, UK.)

are decreased numbers of epidermal Langerhans' cells in the skin of HIV-infected individuals, as there may be, contentiously, in psoriasis [8–11]. Langerhans' cells are infected by HIV and either the viral burden or HIV gene products may alter the antigen-presenting function of the cell. HIV gene products may have a role in the pathogenesis of proliferative epidermal disorders: transgenic mice that express some HIV genes in skin develop a diffuse psoriasiform epidermal hyperplasia [12]. There may be a selective defect in soluble antigen recognition by CD4 T lymphocytes, and numbers of CD8 T lymphocytes increase until just before death. Polyclonal B-cell activation, increased numbers of γδ T lymphocytes, decreased natural killer cell function and defective reticuloendothelial cell function have all been reported.

The classical clinical presentations of psoriasis are detailed in Chapter 35. Psoriasis in HIV-infected patients may be florid, severe and atypical (Fig. 26.3). Reiter's syndrome (arthritis, urethritis and conjunctivitis), within the same clinical continuum as psoriasis in genetically predisposed individuals, occurs in HIV, sometimes very severely [13,14].

The differential diagnosis of psoriasis includes seborrhoeic dermatitis, atopic dermatitis, dermatophytosis, drug eruption and mycosis fungoides. A psoriasiform eruption with the histological features of verruciform xanthoma has been described [15]. Investigations include mycology and skin biopsy.

Conventional treatment options for psoriasis serve most patients well. Moderate to severe psoriasis (with or without arthritis) should be regarded as an indication for HAART. There is no evidence that the theoretical risks and complications of phototherapy are *clinically* deleterious to individual patients [16–19]. T-cell numbers are unaffected and the *gag* p24 antigen and HIV RNA levels may or may not increase [17,20]. Overriding the theoretical concerns about immunosuppression and photocarcinogenesis is the clinical need to relieve the morbidity of the severe, atypical, refractory psoriasis often seen in HIV [5]. PUVA may be superior to UVB therapy [21].

Ciclosporin [22] and methotrexate have caused serious complications in HIV-infected patients, such as leukopenia and fulminant KS [23]. The synthetic retinoid etretinate and its successor acitretin have been most useful therapies for severe Reiter's syndrome and psoriasis in HIV infection, often alongside phototherapy [1,13,14,24]. Treatment with zidovudine improves psoriasis [1]; specific constituents of HAART regimens (e.g. zalcitabine and ritonavir) appear to do likewise, with comcomitant improvement of the clinical condition and virological status of the patient [25,26]. Etanercept has been used with good effect in HIV-related psoriasis and arthritis in one patient but had to be discontinued because of frequent infectious complications [27]. Claims have been made for the efficacy of cimetidine [28]. Serendipitous success due to carbamazepine has been witnessed [29].

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Eosinophilic folliculitis

Eosinophilic folliculitis is an HIV-specific disorder [1,2] related to Ofuji's disease (see Chapter 17). Originally thought to be an *early* sign of HIV infection, it occurs at CD4 T-cell counts of $250–300 \times 10^6$/L and therefore identifies patients at immediate risk of developing opportunistic infections. It may be part of the same spectrum as papular pruritic eruption of HIV and this complicates interpretation of published studies. The cause is unknown but Th2 cytokines (IL-4, IL-5), RANTES and eotaxin are increased in lesional skin [3]; foscarnet has been implicated in the development of eosinophilic folliculitis [4].

Eosinophilic folliculitis presents as a centripetal (face and trunk) eruption of pruritic, erythematous, perifollicular papules and pustules (Fig. 26.4). Patients with eosinophilic folliculitis may be subclinically photosensitive [5]. It mimics staphylococcal or *Pityrosporum* folliculitis and acne vulgaris, with which it can coexist. Histology is characteristic, with degranulating eosinophils and mast cells in a perifollicular distribution. There may be a peripheral eosinophilia and elevated levels of IgE. Swabs are negative: the lesions are sterile. Treatment can be problematic but the disease has virtually disappeared in the developed world in recent years with the introduction of HAART, although exacerbations have been reported [6]. Phototherapy is the most successful treatment modality but other treatments that have been tried include topical sodium cromoglicate (disodium cromoglycate), potent topical steroids, oral antibiotics (erythromycin, tetracyclines, co-trimoxazole), oral antihistamines such as astemizole and cetirizine, oral dapsone and oral isotretinoin [7–10]. Eosinophilic folliculitis may be an indication for HAART.

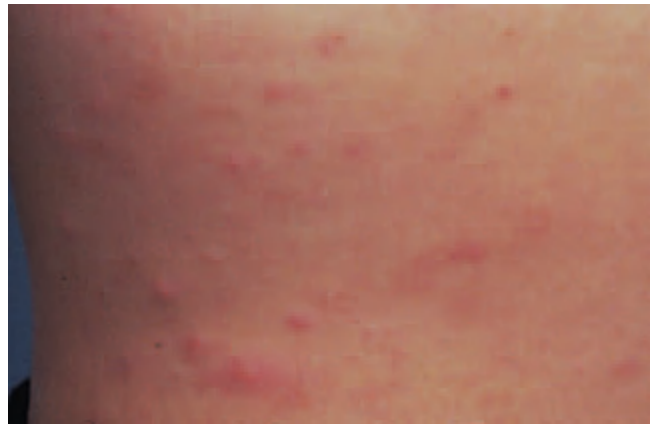

Fig. 26.4 Eosinophilic folliculitis: excoriated papules on the trunk. (Courtesy of Dr C.B. Bunker and Medical Illustration UK Ltd, Chelsea and Westminster Hospital, London, UK.)

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Pruritic papular eruption

Pruritic papular eruption (PPE) is a common cutaneous manifestation of HIV, the prevalence varying between 10 and 45% depending on geographical area [1,2]. It has some interesting similarities with the papular eruption of pregnancy (see Chapter 70). Insect bite hypersensitivity, as in papular urticaria (see Chapter 33), is a speculative pathomechanism [3]. For example, Palungwachira *et al*. [4] suggest that the fact that PPE is the commonest HIV-associated dermatosis in Thailand might be due to the prevalence of mosquitoes. Of patients with PPE, 75% have circulating bullous pemphigoid autoantibodies and up to 30% meet the diagnostic criteria for bullous pemphigoid on histology, Western blotting, immunofluorescence and immunoelectron microscopy [5]. PPE is a sign of an advanced degree of immunosuppression, occurring at CD4 T-cell counts below $100–200 \times 10^6$/L [2,6], and may often be the first sign of HIV. Conversely, it has been suggested that it most frequently complicates established HIV infection. PPE presents as excoriated, erythematous, urticarial papules associated with eosinophilia and elevated IgE. The differential diagnosis includes papular urticaria and eosinophilic folliculitis: it is possible that eosinophilic folliculitis and PPE are part of the same spectrum of disease and this can cause confusion in interpreting the literature. Both are idiopathic. However, the cytokine pattern of PPE differs from that of eosinophilic folliculitis [7,8]. The treatment of PPE is similar to that of eosinophilic folliculitis, with phototherapy the linchpin; thalidomide and pentoxifylline (oxpentifylline) have been claimed to be efficacious [9,10].

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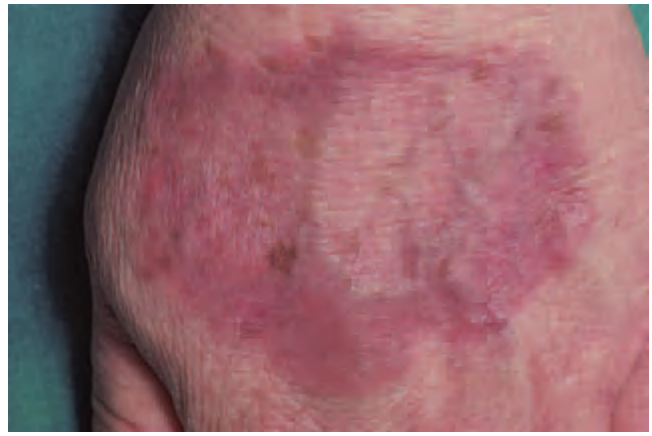

Fig. 26.5 Granuloma annulare on the left hand. (Courtesy of Dr C.B. Bunker and Media Resources UCL, London, UK.)

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Granuloma annulare

Localized, generalized and atypical forms of granuloma annulare (see Chapter 57) occur in HIV infection [1,2] (Fig. 26.5). Violaceous lesions may mimic KS and a perforating variant has been described [3]. Some cases have been associated with zalcitabine treatment [4]. Cultures are negative [2].

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Porphyria cutanea tarda

Porphyria cutanea tarda (see Chapter 57) is polyfactorial in HIV [1]. Familial influences, viral hepatitis B and C (e.g. in haemophiliacs), alcohol and sunlight may be involved. *N*-acetylcysteine has been used for treatment [2].

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Table 26.16 Side effects of drugs in patients with HIV/AIDS. (After Bunker & Staughton [10].)

Morbilliform toxic erythema
Erythema multiforme, Stevens–Johnson syndrome, toxic epidermal necrolysis, hypersensitivity syndrome (see Table 26.17)
Erythroderma
Anaphylaxis, urticaria, angio-oedema
Xerosis, cheilitis
Lichenoid reactions
Psoriasis
Photodermatitis
Purpura
Orogenital ulceration
Neutrophilic eccrine hidradenitis: zidovudine (AZT)
Vasculitis
Fixed drug eruptions
Pentamidine: also causes ulcers at the site of injection
Foscarnet: penile ulceration
Saquinavir
Palmar/plantar keratoderma: glucan
Flagellate erythema: bleomycin
DRESS syndrome: nevirapine
Eosinophilic folliculitis: foscarnet
Porphyria: indinavir
Granuloma annulare: zalcitabine (ddC)
Lipodystrophy
Gynaecomastia: stavudine (d4T), didanosine (ddI), indinavir
Panniculitis: ritonavir, nelfinavir
Acrocyanosis: butylnitrite

DRESS, drug rash with eosinophilia and systemic symptoms.

Table 26.17 Causes of hypersensitivity syndrome, erythema multiforme, Stevens–Johnson syndrome and toxic epidermal necrolysis in patients with HIV/AIDS. (After Coopman & Stern [1]; Bunker & Staughton [10]; Rustin *et al*. [11]; Penneys [12]; Vidal *et al*. [13]; Rzany *et al*. [14].)

Co-trimoxazole (sulfamethoxazole–trimethoprim)
Pyrimethamine
Sulfadoxine
Sulfadiazine
Thioacetazone (thiacetazone)
Streptomycin
Phenytoin
Probenecid
Griseofulvin
Fluconazole
Vancomycin
Nevirapine
Indinavir
Efavirenz
Abacavir

Drug reactions

Drug reactions (see Chapter 73) are commonly encountered in HIV infection [1–4]. Of patients with *Pneumocystis carinii* pneumonia treated with co-trimoxazole (sulfamethoxazole–trimethoprim), 60% experience fever, nausea, vomiting and a rash [5]. Amoxicillin (amoxycillin)–clavulanate causes a skin eruption in about half of HIV-infected patients who receive the drug compared with more than 90% of patients with acute lymphoblastic leukaemia or infectious mononucleosis and 3–10% of the general population [6]. Dapsone, pentamidine and antituberculous chemotherapy, especially with rifampicin, thioacetazone (thiacetazone) and ethambutol, pose particular risks [7,8]. Probenecid (given to reduce the nephrotoxicity of cidofovir) can cause a hypersensitivity reaction [9].

The types of drug eruptions that have been encountered in HIV infection and AIDS are summarized in Table 26.16. A morbilliform toxic erythema is the usual drug reaction seen (with fever, arthralgia, abnormal liver function tests and eosinophilia) but erythema multiforme, Stevens–Johnson syndrome or toxic epidermal necrolysis/Lyell's syndrome [1,10–14] (Table 26.17), erythroderma [8], vasculitis, fixed drug eruptions, cutaneous photosensitivity, photocutaneous drug eruptions, and skin sensitivity to radiotherapy have all been experienced [2,15,16]. Glucan has been implicated in causing palmar/plantar keratoderma [17]. The striking flagellate erythema due to bleomycin has been observed [18,19], but this is relatively common in general oncological practice. Pustular psoriasiform reactions to pegylated doxorubicin (used for KS) have been seen [20]. Fixed drug eruptions have been reported with pentamidine, which can also cause ulcers at the site of injection [12,21], and foscarnet, which causes penile ulceration [22]. Interferons may precipitate ulceration at injection sites [23]. Hydroxyurea can result in mucocutaneous hyperpigmentation (and melanonychia; see later) [24]. Butylnitrite may produce acrocyanosis [25].

The cutaneous side effects of the antiretroviral drugs are listed in Table 26.18 [10,26]. The side effects of anti-HIV drugs on the oropharynx, hair and nails are discussed below (see also Tables 26.22 & 26.23). Zidovudine (AZT) can cause skin, mucosal and nail discoloration, vasculitis, insect bite hypersensitivity and possibly neutrophilic eccrine hidradenitis [26–28]. Patients with black skin have a tendency to develop progressive but reversible proximal melanonychia and also mucocutaneous hyperpigmentation during zidovudine (AZT) therapy. Some patients on zidovudine (AZT) have developed polymyositis [29] and vasculitis [30].

Exanthems, erythema multiforme, Stevens–Johnson syndrome and toxic epidermal necrolysis can be complications of the components of HAART [31–34]. As in other causes of toxic epidermal necrolysis, intravenous gammaglobulin may be an effective treatment [35]. An exanthematous pustulosis has been described [36]. Nelfinavir can cause urticaria [37]. Xerosis and cheilitis are common with protease inhibitors [38]. A syndrome of drug rash with eosinophilia and systemic symptoms (DRESS) has been reported with nevirapine [39] and erythroderma, abdominal pain and renal failure with indinavir [40]. An anaphylactoid reaction and allergic contact dermatitis to

Table 26.18 Cutaneous side effects of antiretroviral drugs. (After Bunker & Staughton [10]; Ward *et al*. [26].)

Nucleoside reverse transcriptase inhibitors	
Zidovudine (AZT)	Insect bite reaction Discoloration of the skin (also mucosa and nails) especially in dark-skinned individuals) Polymyositis Vasculitis
Didanosine (ddI)	Vasculitis Stevens–Johnson syndrome Ofuji's papuloerythroderma
Lamivudine (3TC)	Vasculitis Anaphylaxis, urticaria and angio-oedema Allergic contact dermatitis
Zalcitabine (ddC)	Granuloma annulare
Stavudine (d4T)	Lipodystrophy
Non-nucleoside reverse transcriptase inhibitors	
Nevirapine	Stevens–Johnson syndrome/toxic epidermal necrolysis Lipodystrophy
Efavirenz	Photosensitivity Stevens–Johnson syndrome/toxic epidermal necrolysis Gynaecomastia Vasculitis
Protease inhibitors	
Ritonavir	Toxic erythema Haematoma IgA-mediated hypersensitivity Panniculitis Paraesthesia Bullae
Indinavir	Toxic epidermal necrolysis Erythroderma Paronychia/pyogenic granuloma Striae Paraesthesia
Saquinavir	Photosensitivity Fixed drug eruption
Nelfinavir	Urticaria Panniculitis
All protease inhibitors	Lipodystrophy Toxic pustoloderma Pruritus and xerosis Panniculitis Tendon xanthomas Hypersensitivity syndrome

lamivudine have been described [41,42]. Ritonavir can cause an IgA-mediated hypersensitivity syndrome and haematoma formation [26]. Didanosine (ddI) has been associated with papuloerythroderma of Ofuji [26]. Some cases of granuloma annulare have been blamed on zalcitabine (ddC). Fixed drug eruption has been reported with saquinavir [40]. Photosensitivity and photoallergic dermatitis have been documented with saquinavir and efavirenz [43–45]. Gynaecomastia has complicated stavudine (d4T) and didanosine (ddI) treatment [46]. Indinavir has precipitated acute porphyria [47]. Panniculitis has been blamed on ritonavir and nelfinavir [48]. Painful perioral and peripheral paraesthesiae and bullae have been associated with ritonavir and peripheral paraesthesia with indinavir [33].

The mechanisms of common drug reactions are not clearly known but correspond to classical immunopathological models. In HIV, acute or reactivated Epstein–Barr virus, CMV or other viruses, polyclonal B-cell activation, hypereosinophilia, hypergammaglobulinaemia, immune complex formation, and the generation of autoantibodies and autoreactive T-cell clones may interact with drug or tissue complexes. Also, the pattern of immune dysregulation (decreased Th1 cytokines; increased Th2 cytokines; increased IgE, IgA and eosinophils) predisposes to drug hypersensitivity. For example, co-trimoxazole exacerbates this hypersensitivity by decreasing Th1 responses; macrolides increase Th1 responses [49,50].

It is common experience that adverse reactions to co-trimoxazole may disappear with continued therapy and that some patients will tolerate rechallenge with amoxicillin–clavulanate. *N*-acetylcysteine pretreatment may prevent co-trimoxazole hypersensitivity [51]. Prednisolone does not prevent nevirapine-induced cutaneous hypersensitivity [52]. Tolerance has been induced for nevirapine and nelfinavir [53]. Drug hypersensitivity can also disappear at very low CD4 T-cell counts ($< 20 \times 10^6$/L) and before death occurs. Therefore, a prior drug reaction does not constitute an *absolute* contraindication to continued or further treatment with a particular drug.

The ability of all protease inhibitors and some nucleoside reverse transcriptase inhibitors, especially stavudine (d4T), to cause lipodystrophy is a matter of both intense clinical frustration (because the appearances are distressing and stigmatizing to patients) and mechanistic fascination. Fat loss from the periphery, with fat accumulation in the abdominal and dorsocervical (buffalo hump) and mammary regions, is accompanied by hyperlipidaemia, insulin resistance and lactic acidaemia. Mitochondrial toxicity is one proposed mechanism. There is concern about accelerated atherosclerosis and cardiovascular disease [54–57]. Benign symmetrical lipomatosis [58], striae [59] and tendon xanthomas [60] have been reported.

Of equal interest to dermatologists are the retinoid-like effects of the protease inhibitors, particularly indinavir—paronychia, periungual pyogenic granuloma-like lesions, xerosis and cheilitis, and curly hair. The mechanism is uncertain [61–64] but experience shows that isotretinoin can be used safely and effectively alongside protease inhibitors. Concomitant administration has paradoxically resulted in *lower* plasma retinoid levels [65].

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Infections

Cutaneous bacterial infection in HIV-infected patients poses the risk of bacteraemia and septicaemia or may signify systemic infection. Central lines, concomitant chemotherapy, intravenous drug use and the presence of other skin diseases present additional risks [1]. The clinician must be alert to the dermatological signs of systemic bacterial infection, such as splinter haemorrhages and acral papulonecrotic lesions. A high index of suspicion and a low threshold for performing microbiological investigations and skin biopsies (including Gram stain and special stains and cultures) should be inculcated to allow precise diagnosis and specific treatment. Systemic antibiotics should be chosen on the basis of the clinical situation and sensitivities, when they become known. Abscesses should be treated by surgical drainage but also biopsied and cultured: cutaneous malacoplakia has been encountered [2].

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Bacterial infections

The differential diagnosis of folliculitis is a common challenge in the patient with HIV. Clinical differentiation between staphylococcal folliculitis, malassezial folliculitis, dermatophyte folliculitis, eosinophilic folliculitis and, very rarely, micrococcus folliculitis and herpes simplex and zoster viral folliculitis may be impossible and they may coexist [1–4]. Cryptococcosis has presented as a corporeal pseudofolliculitis [5]. On the face, demodicidosis and acne vulgaris are other possibilities. A facial folliculitis due to *Clostridium perfringens* has been observed [6]. Intertriginous staphylococcal folliculitis may mimic candidosis.

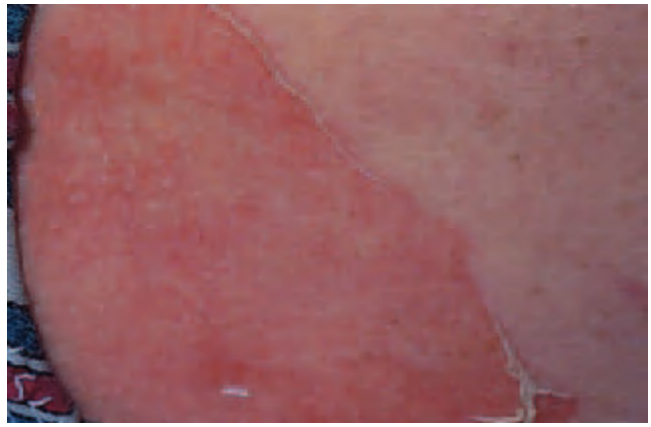

Fig. 26.6 Staphylococcal scalded skin syndrome: staphylococcal pneumonia in HIV-positive intravenous drug addict. (Courtesy of Dr C.B. Bunker and Medical Illustration UK Ltd, Chelsea and Westminster Hospital, London, UK.)

Secondary staphylococcal infection of the skin may be a commonplace complication of many of the inflammatory dermatoses discussed above. Methicillin-resistant *Staphylococcus aureus* (MRSA) may present particular problems, although MRSA carriage does not seem to be an appreciable problem in HIV-positive outpatients [7–10].

Other staphylococcal infections found in HIV include *bullous impetigo* [11], *ecthyma* and *staphylococcal scalded skin syndrome* (Fig. 26.6) [12–14]. Subcutaneous abscesses due to staphylococci may complicate injection or intravenous-line sites. Sometimes uncommon organisms are isolated. Severe streptococcal cellulitis (erysipelas) with lymphadenitis has been reported [15].

Pseudomonas aeruginosa is an important potential cutaneous pathogen in HIV infection and AIDS. *Ecthyma gangrenosum* and *panniculitis* [16–19] may be pointers to *Pseudomonas* septicaemia.

Fournier's gangrene is a hazard with a high mortality in AIDS and may complicate chemotherapy [20].

Bacillary angiomatosis, originally entitled 'epithelioid (haem)angiomatosisis', is caused by the Gram-negative cat-scratch disease organism *Bartonella* (previously *Rochalimaea*) *henselae* affecting the skin [1,21]. When it was first encountered, clinicians were intrigued by the similarity of bacillary angiomatosis to the cutaneous stigmata of chronic infection with *Bartonella bacilliformis*, the 'forma mular of verruga peruana'. These lesions may occur in the chronic phase of Oroya fever and are clinically and histologically very similar to those of bacillary angiomatosis. The abnormal vascular spaces, lined with proliferating endothelium, contain *B. bacilliformis*. Bacillary angiomatosis presents with purple, papular and nodular vascular lesions resembling KS (Fig. 26.7). Patients with bacillary angiomatosis do not appear to have an overt acute febrile haemolytic illness. Diagnosis is made by biopsy. Histologically, bacillary angiomatosis is distinguished from

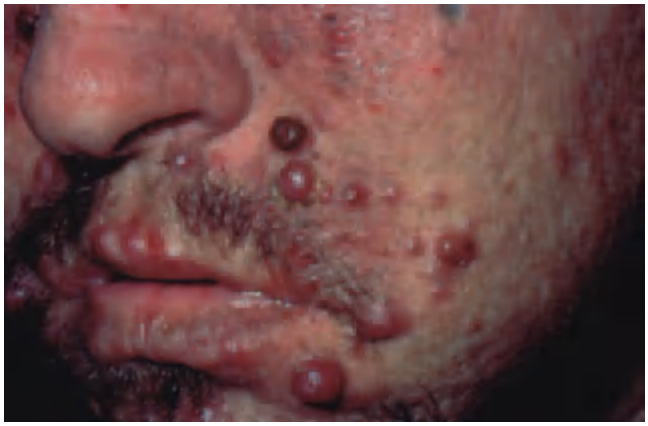

Fig. 26.7 Bacillary angiomatosis: purple nodules on the face. (Courtesy of Dr C.B. Bunker and Medical Illustration UK Ltd, Chelsea and Westminster Hospital, London, UK.)

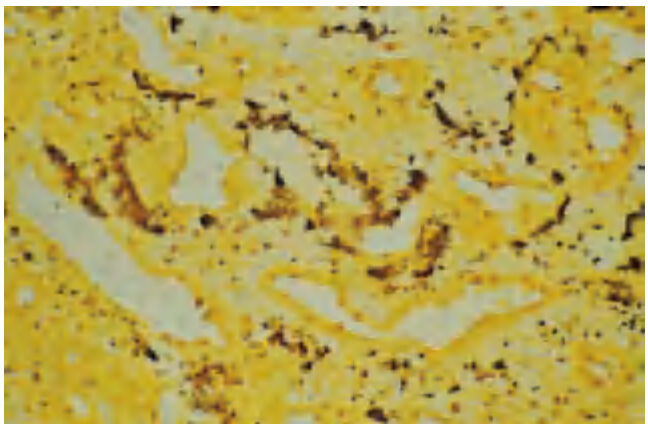

Fig. 26.8 Bacillary angiomatosis: Warthin–Starry silver staining of *Bartonella bacilliformis* and proliferative vascular channels. (Courtesy of Dr N. Francis, Imperial College School of Medicine, London, UK.)

KS by being a vascular proliferation where the abnormal endothelial cells are epithelioid rather than spindled and by having a prominent neutrophilic infiltrate. The organisms can be demonstrated by Warthin–Starry silver staining (Fig. 26.8), immunoperoxidase staining of lesional tissue (where the bacilli are found within the abnormally proliferative cutaneous vasculature) or electron microscopy. Bacillary angiomatosis responds to oral erythromycin in most patients; isoniazid, rifampicin, ethambutol or clofazimine, either in addition to or instead of erythromycin, have also been used.

Syphilis (see Chapter 30) may present differently in HIV infection [22]. This may confound the clinical recognition of the classical dermatological manifestations of primary chancre, the papulosquamous eruption of secondary syphilis and gumma [23]. The interpretation of serological tests can be complicated. Dermatologists should regard all genital, perianal and oral ulceration and any papulosquamous eruption with great suspicion and handle them with circumspection [24]. Rarer manifestations of syphilis not previously encountered by this generation of physicians, such as keratoderma and lues maligna (necrotic red nodules), have been reported [25].

Similar problems with *yaws* [26] and *leprosy* [27,28] have not been extensively encountered. *Lyme borreliosis* pseudolymphoma [29] and a persistent erythema chronicum migrans (with meningoradiculitis) have occurred [30].

Reinfection with, or reactivation of, *Mycobacterium tuberculosis* seems to occur early in HIV infection and extrapulmonary, including cutaneous, tuberculosis (see Chapter 28) is common [31] and becoming commoner [32]. The clinical presentation is diverse, including scrofula [33], scattered violaceous papules [34], acute miliary tuberculosis of the skin [35,36], keratotic papules, nodules and palmar/plantar keratoderma [37] and tuberculides [38]. Tuberculous lymphadenitis has been said to be a characteristic manifestation in HIV and in intravenous drug users co-infected with tuberculosis [39]. Management of co-infection (about one-third of the estimated 30–40 million people infected with HIV) poses particular challenges and is a specialist field [40].

Atypical mycobacterial skin disease in patients infected with HIV is usually due to *Mycobacterium avium–intracellulare*. This occcurs as part of a disseminated infection in up to one-third of patients [41] at CD4 T-cell counts below 50×10^6/L (rare below 200×10^6/L). Lesions described include violaceous papules, nodules and ulcers [42]. Skin disease has also been reported with *M. kansasii* [34], *M. haemophilum* [43,44], *M. fortuitum* [45] and *M. marinum* [46]. In these instances the eruption has probably occurred after primary infection of the skin by the organism but a fatal case of disseminated *M. marinum* has occurred [47]. Sporotrichoid spread (see Chapter 28) can involve an affected limb emanating from a distal primary site [48]. Concomitant *M. tuberculosis*, *M. avium–intracellulare* and CMV has been seen [49]. *M. avium* complex has been isolated from an HIV-positive woman with erythema multiforme [50].

The diagnosis of mycobacterial infection can be problematic because characteristic histopathological features such as caseating granuloma may be absent due to diminished cell-mediated immunity [51]. All biopsies where tuberculosis and/or atypical mycobacterial infection are suspected should be stained for acid-fast bacilli (which may be very numerous because of diminished cell-mediated immunity) and a separate portion sent for mycobacterial culture.

Prophylaxis and treatment of tuberculosis and atypical mycobacterial disease depends on the clinical scenario (including CD4 count) and the results of microbiological investigations (including sensitivity testing) and is an expert area. HAART and specific conventional antituberculous drugs are used. Atypical mycobacterial infection is treated with a macrolide and ethambutol.

Other bacterial infections. Extragenital donovanosis [52], an unusual presentation of chancroid [53], a paranasal ulcer due to *Chryseomonas luteola* [54] and a disseminated papular eruption caused by *Serratia marcescens* have been described.

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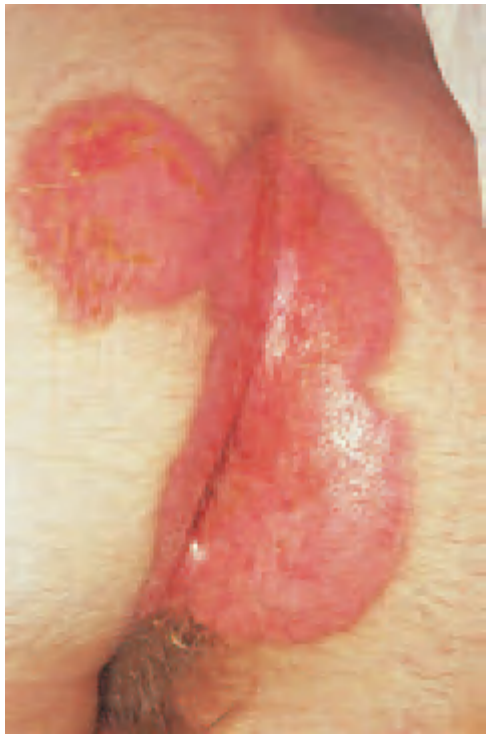

Fig. 26.9 Chronic perianal ulceration in herpes simplex infection before highly active antiretroviral therapy.

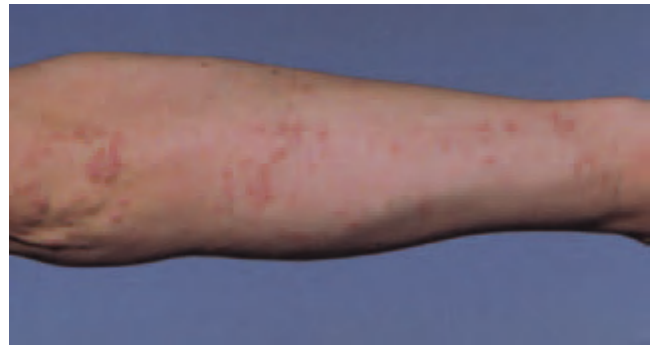

Fig. 26.10 Chronic verrucous herpes zoster. (Courtesy of Dr C.B. Bunker and Medical Illustration UK Ltd, Chelsea and Westminster Hospital, London, UK.)

Viral infections

Herpes simplex. Severe chronic ulcerative perianal disease (Fig. 26.9) caused by herpes simplex virus (HSV)-2 (human herpesvirus 2, HHV-2) was one of the first features of AIDS to be reported [1]. HSV-1 and HSV-2 infections are extremely common during the course of HIV illness [2,3]. Although anogenital involvement is frequent, any site can be affected with acute lesions that are vesicobullous but which become chronic, eroded and crusted, vegetative, or ulcerating; HSV infection may not be self-limiting as it is in normal individuals. Persistent necrotic digits [4] and perioral ulceration may occur. A facial folliculitis (sycosis) has been reported [5]. Secondary bacterial infection is probably universal. Concomitant infection of the skin with CMV has been seen [6]. Resolution can occur with specific treatment for HSV and general HIV treatment. However, herpetic lesions recur: the impact of HAART has been to improve this situation, although Fox *et al*. [7] have reported persistent erosive and verrucous anogenital disease with erosion and ulceration in several heterosexual Ugandan men despite HAART and multiple systemic and topical treatments, possibly representing an immune recovery/reconstitution/restoration phenomenon (immune restoration disease) (see Fig. 26.28).

Diagnosis depends on clinical suspicion supported by electron microscopy of fresh lesional fluid, DNA hybridization, immunofluorescence and viral culture; additionally, acute and convalescent sera may be examined for HSV antibodies (IgM and IgG). A skin biopsy may show typical cytopathic signs and positive immunostaining for HSV. In the USA, the Tzanck test is popular for rapid identification of multinucleate giant cells, which are not pathognomonic because they are seen also in varicella, herpes zoster and pemphigus [8,9].

The treatment of HSV infection in HIV requires the systemic deployment of specific antiviral drugs (of which aciclovir is the prototype), including prophylactically [2]. The approach should be aggressive because HSV activates HIV replication [10]. Topical and systemic treatments for secondary bacterial infection are often necessary. HSV mutants (i.e. those with mutant or absent viral thymidine kinase) are responsible for HSV resistance, although progressive HSV-2 infection has been reported despite aciclovir therapy and demonstrable sensitivity of isolates to aciclovir. Intravenous vidarabine has been effective in aciclovir-resistant herpes simplex, but foscarnet (trisodium phosphoformate), which is a direct inhibitor of HSV DNA polymerase, is better for severe HSV-2. Famciclovir [11] and valaciclovir are alternatives to aciclovir. Cidofovir is a DNA polymerase inhibitor used in CMV infection, but is also effective against HSV.

Varicella-zoster virus. Reactivation of varicella-zoster virus (HHV-3; see Chapter 25) frequently accompanies HIV infection and can be severe [2,12]. Recurrences of HHV-3 do occur in HIV-negative people and in up to 20% of HIV-negative immunocompromised patients. The frequency of recurrence in HIV-positive individuals is unknown. It is controversial whether all patients presenting with dermatomal HHV-3 should be counselled about HIV testing but it is regarded as a predictor of HIV infection in African patients [13]. Reactivation of HHV-3 is the commonest cutaneous manifestation of immune restoration disease [14].

The distribution of the eruption is characteristically dermatomal but differentiation from herpes simplex may

not always be clinically certain. Ophthalmic zoster may be complicated by conjunctivitis or optic neuritis, so ophthalmological input is advised. The involvement of sacral nerves may cause acute retention of urine, haemorrhagic cystitis and constipation. Other manifestations include motor zoster, zoster encephalomyelitis and purpura fulminans.

A non-bullous folliculitis has been described [5]. A chronic verrucous dermatomal form can occur (Fig. 26.10). An atypical, sometimes protracted, disseminated HHV-3 eruption of sparse but ecthymatous necrotic lesions is occasionally seen, but there is usually a concomitant dermatomal recurrence. The differential diagnosis includes *Pseudomonas* ecthyma gangrenosum and disseminated infection with atypical mycobacteria, fungi, vaccinia or HSV. Central nervous system and pulmonary involvement should be suspected. The clinical diagnosis is supported by virological methods and occasionally by biopsy.

An important component of management is the treatment of pain. Potent analgesia may be supplemented by carbamazepine and doxepin. Intractable post-herpetic neuralgia may require specialized pain control. A topical or systemic antibiotic is often needed for secondary infection. Oral prednisolone is given by some. Systemic parenteral therapy with aciclovir is indicated in HIV-associated herpes zoster especially when sight, sphincteric function and facial expression are threatened and where pulmonary or neurological involvement is suspected. Disseminated HHV-3 infection can be severe with a poor prognosis. Intravenous high-dose aciclovir is the treatment of choice. Intercurrent intramuscular HHV-3 immunoglobulin has been used to prevent recurrences and may be used intravenously if aciclovir fails. Emerging aciclovir resistance may become a problem but vidarabine and recombinant IFN-α are possible alternatives [15]. Vaccination may boost immunity and varicella immune globulin can prevent or modify the clinical illness [12].

Cytomegalovirus. Reactivation of CMV in HIV infection occurs with a CD4 count below 50×10^6/L. Despite the frequency of ocular (blindness), gastrointestinal (dysphagia, diarrhoea), neurological (encephalopathy) and adrenal (postural hypotension) disease, skin involvement with CMV is relatively uncommon in HIV but when CMV affects the skin the mortality is about 85% in 6 months [16]. It is possible that cutaneous involvement goes unnoticed and hence is underdiagnosed. Purpura, papules, nodules, verrucous plaques and ulcers (Fig. 26.11), and nodular prurigo (Fig. 26.12) have been described [17]. The differential diagnosis of these clinical possibilities is broad. HSV and CMV skin involvement may be seen concurrently [9] and concomitant CMV, *M. tuberculosis* and *M. avium–intracellulare* has been documented [18].

CMV infection should be suspected histologically if dermal capillary neoangiogenesis, fibrinoid thrombi, necrotic endothelial cells, epidermal hyperplasia, acantholysis and keratinocyte degeneration are seen. Keratinocytes and endothelial cells contain characteristic CMV inclusions. Syringosquamous metaplasia has been observed [19,20]. Immunohistochemistry, *in situ* hybridization and electron microscopy may be employed. Skin biopsy material can be cultured with human fibroblasts to demonstrate the cytopathic effect; the demonstration of CMV viraemia can be similarly achieved by the co-culturing of a patient's leukocytes [21]. Serological testing may be difficult to interpret.

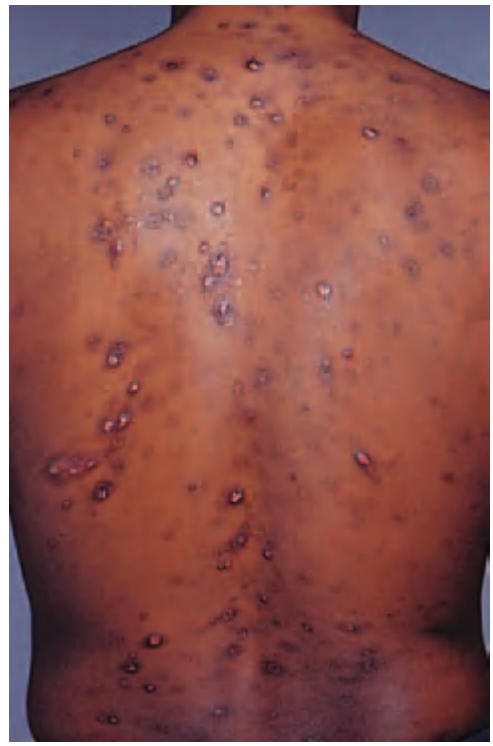

Fig. 26.11 Cytomegalovirus infection: nodular prurigo-like eruption on the back. (Courtesy of Dr C.B. Bunker and Medical Illustration UK Ltd, Chelsea and Westminster Hospital, London, UK.)

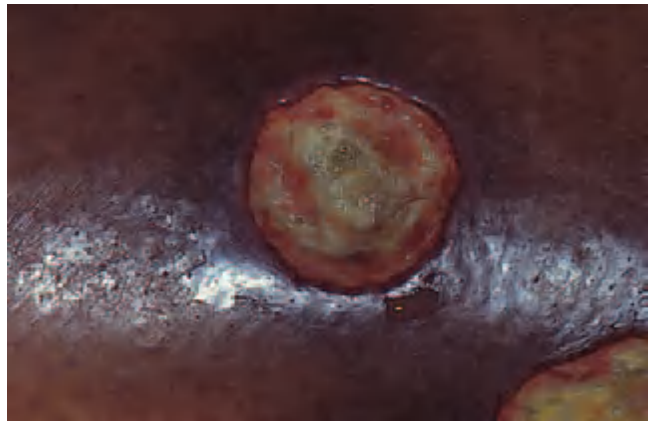

Fig. 26.12 Cytomegalovirus vasculitis: leg ulcers. (Courtesy of Dr C.B. Bunker and Medical Illustration UK Ltd, Chelsea and Westminster Hospital, London, UK.)

Treatment and prophylaxis centres on immunoreconstitution with HAART, although a severe cutaneous ulcerative eruption (see Fig. 26.29) has been reported after the initiation of HAART and possibly represents immune restoration disease [22]. Intravenous foscarnet, ganciclovir and cidofovir are specific treatments [23]. Mutations in the viral kinase allow the development of drug resistance. Other drugs are under evaluation.

Human papillomavirus. Human papillomavirus (HPV) infection of the skin is discussed in Chapter 25. Warts are found in about 5–30% of patients with HIV [2,24,25]. Anogenital warts (condylomata acuminata) may be a non-specific and insensitive marker for HIV infection. HPV-6 and HPV-11 (not associated with malignant potential) have been identified as the types most frequently found [26]. Anogenital HPV infection is a risk factor for anogenital cancer particularly of the anus (and cervix) yet it is rare for condylomas to contain HPV-16, which has a well-documented association with anal carcinoma. Homosexual men have a higher incidence of both perianal warts and *in situ* and invasive anal carcinoma. Yet Reynaud-Mendel *et al*. [27] have found that genital warts are more frequent in seropositive intravenous drug users. HIV infection may alter and worsen the expression and consequences of anogenital HPV infection [28,29]; HPV-16 and other oncogenic types have been found in carcinoma *in situ*, and high-grade dysplasia has been found in genital warts from HIV-positive individuals [30,31]. Overall, the risk of progression of anal intraepithelial neoplasia associated with anal HPV wart infection to invasive squamous carcinoma is low [32], although HPV infection is thought to be linked to the incidence and aggressiveness of anal carcinoma in AIDS. The same is probably true of penile cancer. Invasive cervical cancer is not more common but does behave more aggressively and is an AIDS-defining diagnosis.

The clinical diagnosis of warts is straightforward when classical sites are involved with lesions of typical morphology. In patients with HIV, warts may be extensive (Fig. 26.13), numerous, exuberant and admixed with other pathologies (e.g. mollusca). HPV may be found in, and presumably contributes to the causation of, Bowen's disease, erythroplasia of Queyrat and Bowenoid papulosis (clinically like viral warts, often pigmented, with the histology of Bowen's disease/squamous carcinoma *in situ*), and invasive penile, anal and cervical cancer. A pattern resembling the rare inherited condition epidermodysplasia verruciformis can occur (Fig. 26.14), presenting in some patients as a pityriasis versicolor-like eruption [33–36].

CD4 T-cell estimation and HIV testing should be considered in any patient with atypical clinical presentations of viral warts. Occasionally, a skin biopsy may be necessary particularly if *in situ* or invasive squamous malignancy is suspected. Conventional treatments may fail. Topical imiquimod and cidofovir have been used [37,38]. HAART can lead to regression of warts [39,40], but some patients have been seen whose warts persist or return after many years remission and this seems to be related to low nadir or mean CD4 counts [41].

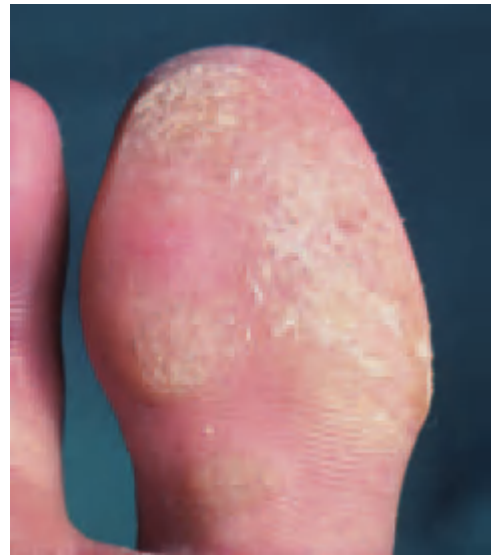

Fig. 26.13 Human papillomavirus infection: myrmecia on the great toe. (Courtesy of Dr C.B. Bunker and Media Resources UCL, London, UK.)

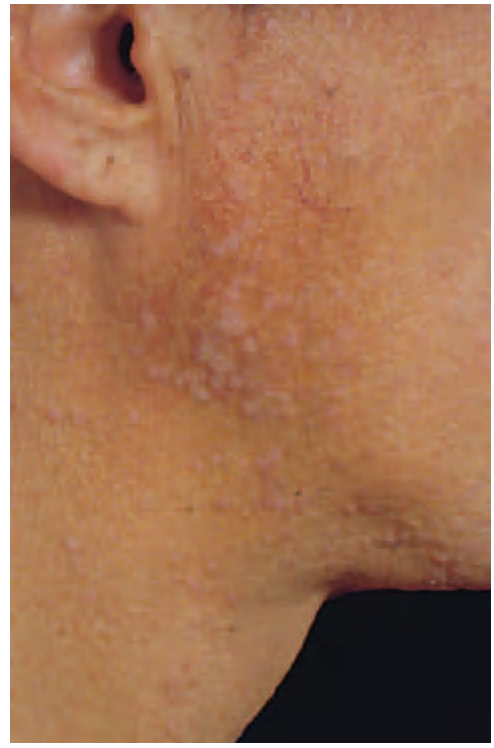

Fig. 26.14 Epidermodysplasia verruciformis in human papillomavirus infection: discrete and confluent warty papules on the right cheek and neck. (Courtesy of Dr C.B. Bunker and Imperial College School of Medicine, London, UK.)

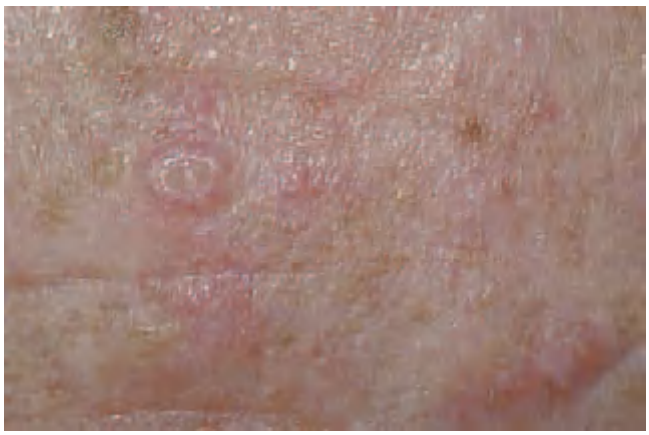

Fig. 26.15 Atypical mollusca: flesh-coloured papules and nodules on the forehead. (Courtesy of Dr C.B. Bunker and Media Resources UCL, London, UK.)

Molluscum contagiosum. Molluscum contagiosum is caused by infection with molluscipoxvirus (see Chapter 25) and frequently affects the skin of patients with HIV [42], homosexual seropositive patients more than intravenous drug users [27]. There may be several or many papular or larger nodular lesions, particularly on the face and neck. Often, in the context of HIV infection, the lesions do not manifest pathognomonic classical morphology (Fig. 26.15) and are not typically domed in shape and lack the characteristic central umbilication or delling [43]. A cheek abscess has been described [44]. The differential diagnosis includes sebaceous hyperplasia, syringoma, warts, cryptococcosis and histoplasmosis, and even basal cell carcinoma. These entities can all concur and be found in the same clinical lesion. Molluscum is diagnosed with the greatest confidence by skin biopsy because the morphology in the HIV-positive patient may not be pathognomonic. The classical histological features (see Chapter 25) are usually present [9].

Molluscum varies widely in its response to conventional treatment [2] but the introduction of HAART can be very effective [39]. Topical imiquimod may also be effective. Systemic and topical cidofovir may be effective for severe recalcitrant molluscum [38,45]. Electron-beam treatment has been employed [46].

Other viral infections. Parvovirus B19 can cause cutaneous vasculitis [47] and a persistent papular–purpuric gloves and socks syndrome with anaemia [48].

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Fungal infections

Candidosis. Oral candidosis has classically been associated with immunosuppressive states and was one of the first features to be recognized in the early days of the HIV epidemic before the syndrome was clearly defined and the causative agent identified [1]. Oesophageal candidosis is an AIDS-defining diagnosis. It is commoner in homosexual seropositive patients than intravenous drug users [2]. Treatment is with ketoconazole or fluconazole. Resistance can occur. Long-term prophylaxis with azoles is avoided. Oral candidosis predicts AIDS in a median of 2 years so is an indication for institution of prophylaxis for *Pneumocystis carinii* and HAART.

Candida is also responsible for paronychia, onychodystrophy, angular cheilitis and intertriginous candidosis [3,4]. Practically all people with HIV infection will have *Candida* as a pathogen at some stage in their disease [5].

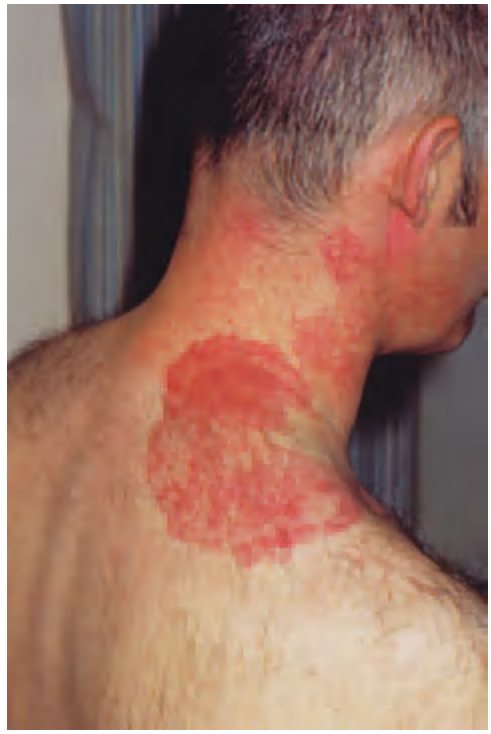

Fig. 26.16 Tinea corporis and faciei. (Courtesy of Dr C.B. Bunker and Medical Illustration UK Ltd, Chelsea and Westminster Hospital, London, UK.)

Dermatophytosis. Generally, dermatophytes are only occasionally responsible for cutaneous infection in immunocompromised patients [6], but the situation is subtly different in HIV infection [7]. Homosexual men are very likely to have a superficial fungal infection regardless of their HIV status. For example, in Sweden, Torssander *et al*. [8] showed that 37% of seropositive homosexual men had mycologically proven toe cleft dermatophytosis, usually *Trichophyton rubrum*, compared with about 30% of seronegative homosexual men and about 9% of heterosexual men. Clinical findings, for example interdigital scaling, similar to those of tinea pedis are very common in men. Dermatophytes can be isolated from normal toe clefts in about 7% of homosexual men (regardless of HIV status) but not from clinically normal toe clefts in heterosexual men. Tinea incognito secondary to chronic potent topical steroid misuse for another dermatosis may develop, as sometimes seen in lupus erythematosus. Widespread dermatophytosis is not common in HIV/AIDS: Torssander *et al*. found dermatophytes only in the groins, toe clefts and toe nails. However, folliculitis and extensive and deep dermatophytosis (Fig. 26.16), including Majocci's granuloma and deep abscess, can occur [7,9].

Onychomycosis is very common in HIV and AIDS. *Trichophyton rubrum* is the commonest pathogen [10]. Psoriasis and the yellow nail syndrome should be

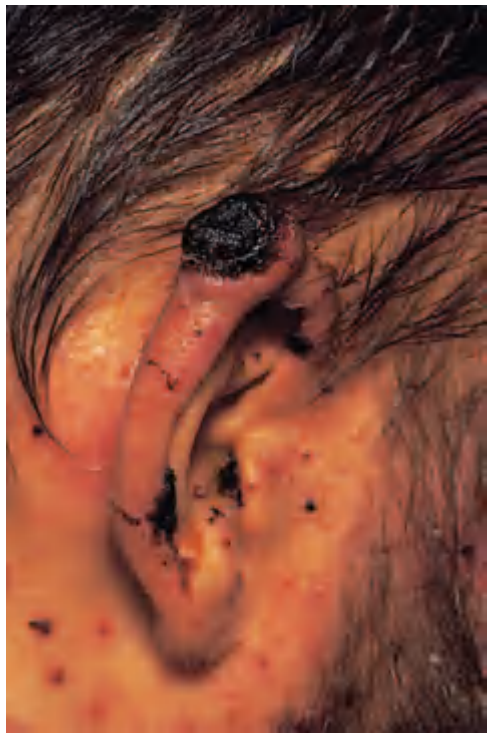

Fig. 26.17 Cryptococcosis: necrotizing papules and nodules on the right ear and neck. (Courtesy of Dr C.B. Bunker and Medical Illustration UK Ltd, Chelsea and Westminster Hospital, London, UK.)

considered in the differential diagnosis of nail discoloration and dystrophy. Mycological confirmation should be obtained. Improvement of onychomycosis with HAART in the absence of specific antifungal treatment has been observed [11].

Esoteric superficial fungal infections have been reported. A patient presented with 'dirty' brown spots on the scrotum from which were co-cultured the dematiaceous fungi *Bipolaris* and *Curvularia* [12].

Dermatophyte infection is treated with conventional topical and systemic therapy (see Chapter 31) depending on clinical assessment and the results of mycology. Oral terbinafine is safe and efficacious [13].

Cryptococcosis. *Cryptococcus neoformans* infection affects 5–10% of patients with AIDS in the UK and USA and 30–40% in Africa. Brain, lung and skin are sites of predilection. Up to 20% of patients with disseminated disease may have skin involvement. In HIV/AIDS cryptococcal skin involvement should be suspected when papulonodular necrotizing skin lesions with central umbilication, like molluscum contagiosum (Figs 26.17 & 26.18), are encountered in the context of neurological or pulmonary disease. Herpetiform lesions, violaceous lichenoid lesions, an acneiform papulopustular and nodular eruption on the chin, rhinophyma, a warty tumour on the foot, a pseudofolliculitis and *Cryptococcus* admixed with, and mimicking, KS have also been described [14–16].

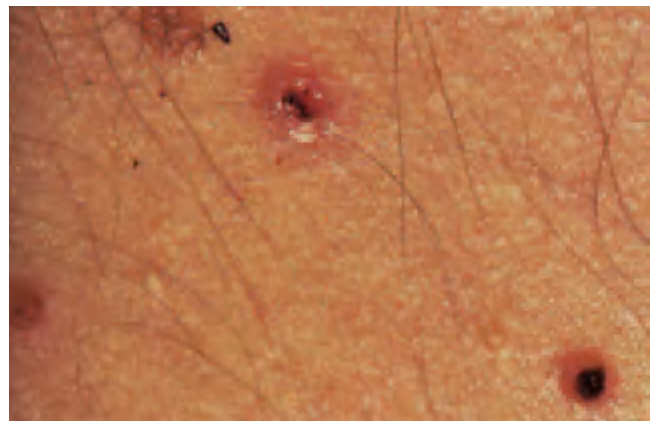

Fig. 26.18 Cryptococcosis: necrotizing papules. (Courtesy of Dr C.B. Bunker and Medical Illustration UK Ltd, Chelsea and Westminster Hospital, London, UK.)

Systemic diagnosis is by serology, blood culture, urine culture and lumbar puncture (including serology, culture and India-ink staining). Cutaneous diagnosis is by skin biopsy with special stains for the cryptococcal capsule (e.g. mucicarmine) and culture, or Tzanck preparation [17].

Treatment aims to eradicate the disease in the immunocompetent patient and to control symptoms in the patient with advanced HIV disease. Intravenous liposomal amphotericin and oral fluconazole are the mainstays of treatment. Primary and secondary prophylaxis is with oral fluconazole. Cryptococcal meningitis has a poor prognosis even with treatment.

Histoplasmosis. Infection with histoplasmosis is an AIDS-defining illness. It is very rare in the UK, although commoner where histoplasmosis is endemic so a travel history is important. In endemic areas 20–50% of patients with AIDS will develop histoplasmosis at CD4 counts below 200×10^6/L. The systemic presentation can mimic tuberculosis. There is fever, lymphadenopathy, hepatosplenomegaly, lung disease and pancytopenia. Disseminated histoplasmosis may produce skin involvement in 10% of patients. An exanthem, lesions resembling molluscum contagiosum, lesions admixed with KS, acneiform folliculitis, psoriasiform eruptions, depressed pits on the palms and soles, and oral involvement have been described [7,18–21].

Systemic diagnosis is by chest X-ray, Wright's staining of a blood film (demonstrating intracellular fungi), blood cultures, and lymph node, liver or skin biopsy or Tzank cytology [17,22] and culture. *Histoplasma capsulatum* can be demonstrated by Gomori methenamine silver stain of a skin biopsy section.

Treatment is with itraconazole or amphotericin with long-term itraconazole secondary prophylaxis because relapse is so common.

Other fungal infections. Coccidioidomycosis is endemic in south-west USA: extrapulmonary disease is an AIDS-defining diagnosis but skin lesions seem rare [7]. Numerous ulcers have been attributed to cutaneous sporotrichosis [5]. Paracoccidioidomycosis [23], blastomycosis [24], nocardiasis [25,26], primary cutaneous aspergillosis [27,28] and penicilliosis (especially in northern Thailand) [29,30] have all been reported to cause skin lesions in HIV/AIDS.

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Protozoal infections

Pneumocystis carinii pneumonia is common in HIV infection but disseminated disease and cutaneous involvement is rare [1,2]. Two patients have been described with mass lesions in the external auditory canal. Spread from middle ear infection (itself due to retrograde spread from the pharynx via the eustachian tube) was the probable mechanism. Lesions masquerading as KS have been described [3].

Disseminated amoebiasis may rarely cause skin involvement and the dermatological manifestation may lead to diagnosis of the systemic illness. A solitary papule of the thigh, a soleus muscle abscess and cutaneous ulceration have been described [4–6]. Genital ulceration due to amoebiasis should lead to the suspicion of underlying HIV infection [7].

Cryptosporidiosis and microsporidiosis can cause skin lesions [8,9]. Endemic protozoal diseases such as leishmaniasis [10–12] may behave differently in the HIV-infected patient and also mimic or complicate KS and dermatofibroma: cutaneous nodules and ulcers, digital necrosis, linear brown macules of the digits and palms, ulceration of the tongue, a tattoo reaction and cutaneous hyperpigmentation and post kala-azar dermal leishmaniasis have been described [13–18]. Reactivation of American trypanosomiasis (Chagas' disease) in AIDs may manifest with skin lesions [19].

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Scabies

Scabies (see Chapter 33) occurs frequently in HIV-infected patients [1,2] and may have unusual clinical features (Fig. 26.19) when it arises in the context of HIV infection, for example the skin of the head and neck is often involved, which is highly unusual in non-HIV-infected adults. It is important to have a high index of suspicion. Scabies has been endemic in the HIV population in London and there are occasional epidemic outbreaks on HIV wards, in hospices and in the community. Transmission is by sexual intercourse, nursing, comforting and massage. Norwegian/crusted scabies [3] is highly contagious and its diagnosis should arouse suspicion of underlying HIV infection (AIDS 2002). Crusted scabies in HIV infection may be localized to the soles [4]. Eccrine ductal and follicular mucinosis have been found on histology [5]. Treatment follows conventional lines but eradication may be difficult. Topical sulphur and oral ivermectin can be useful [6,7].

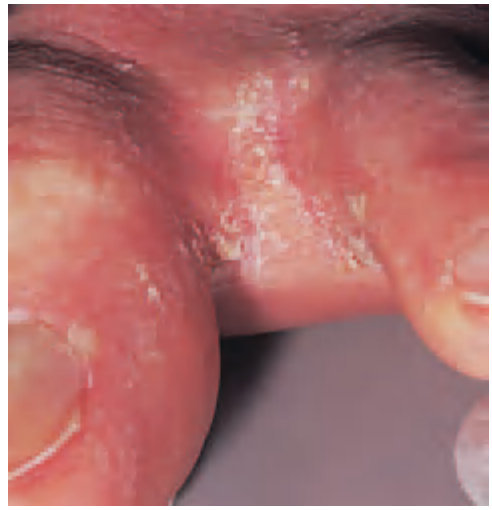

Fig. 26.19 Norwegian scabies: interdigital scale.

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Miscellaneous

Demodex (see Chapter 33) can cause dermatological morbidity in HIV-infected patients. A pruritic papulonodular eruption on the face and neck that responded to acaricide treatment has been attributed to *Demodex* [1], as has a rosaceal eruption [2] and an ivory white, poorly defined, indurated plaque on the temple [3].

Cutaneous larva migrans has presented with fever in an HIV-infected individual after commencement of treatment with zidovudine (AZT) and didanosine (ddI) [4].

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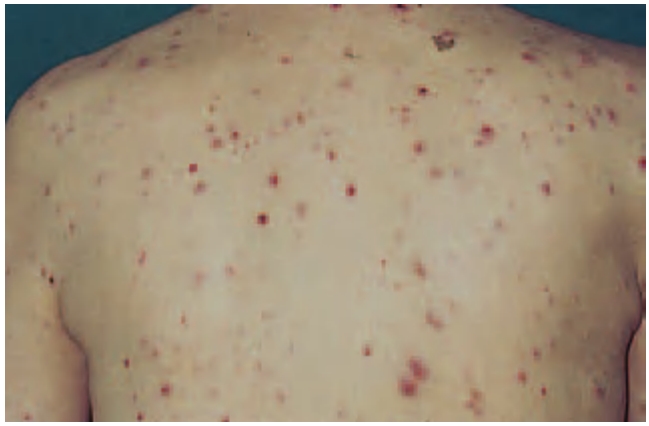

Fig. 26.20 Kaposi's sarcoma: multiple purple nodules and plaques on the back. (Courtesy of Dr C.B. Bunker and Medical Illustration UK Ltd, Chelsea and Westminster Hospital, London, UK.)

Table 26.19 Differential diagnosis of Kaposi's sarcoma. (After Bunker & Staughton [10].)

Naevus
Histiocytoma
Cryptococcosis
Histoplasmosis
Leishmaniasis
Pneumocystis
Dermatophystis
Angioma
Bacillary angiomatosis
Pyogenic granuloma
Melanoma

Neoplasms

Kaposi's sarcoma (see Chapter 53)

Classical sporadic KS, African endemic KS, Greek (Peloponnesian) endemic KS, iatrogenic immunosuppression-associated KS and AIDS-related KS are recognized [1,2]. KS has been encountered in HIV-negative homosexual men [3]. The prevalence of KS in patients infected with HIV has declined throughout the epidemic. It has been shown that KS is caused by HHV-8, which may be transmitted sexually, probably more by the faeco-oral route or the ejaculate than by blood, in HIV-positive homosexual men [4,5]. However, KS is also seen in non-homosexuals and in children arising from other routes of transmission, for example saliva [6,7].

HIV/AIDS-related KS may be a disseminated disease with gastrointestinal and pulmonary involvement. Cutaneous KS is multicentric and often involves the face, oral mucosa, palate (see Fig. 26.26) and genitalia. Lesions may be multiple, follow skin creases and may be grouped or linear and koebnerize (Fig. 26.20). Lymphoedema may eventuate [8]. The classical lesion in HIV is a purple patch, plaque or nodule, which may ulcerate; phimosis may occur [9]. There may be diagnostic difficulty with morphologically banal lesions in at-risk or worried individuals and the importance of index of suspicion and skin biopsy must be stressed. The common differential diagnosis (Table 26.19) [10] includes naevi, histiocytoma and lymphangioma [11], although cryptococcosis [12,13], histoplasmosis [14], leishmaniasis [15,16], lesions due to *Pneumocystis* [17], and dermatophytosis [18] may also mimic and/or complicate KS. Pyogenic granuloma and bacillary angiomatosis masquerading as KS are important to consider and confirm or exclude.

The differential diagnosis of oral lesions is discussed below and includes the other causes of mouth ulcers and tumours, *Candida*, lichen planus, drug eruption and angina bullosa haemorrhagica. The differential diagnosis of genital lesions includes psoriasis, lichen planus, lichen sclerosus, fixed drug eruption, Zoon's balanitis and erythroplasia of Queyrat.

Diagnosis is either clinical or clinicopathological. The histological features of KS are well described [19] and consist of dilated, irregularly shaped, vascular structures that are typically slit-like in a fully developed nodular lesion. The differential diagnosis may be clarified by immunohistochemical techniques that identify endothelial cells (immunostaining for factor VIII-related antigen and *Ulex europaeus* lectin), which have been thought to be the cell of origin of KS. Staging of KS takes into account tumour bulk, systemic illness and immunosuppression (Table 26.20) [20].

Systemic and local treatment of KS is summarized in Table 26.21. HAART itself can be very effective [21,22]. Radiotherapy can cause significant sequelae, for example radiodermatitis, in survivors.

Table 26.20 Modified AIDS Clinical Trials Group staging of Kaposi's sarcoma (1997). (From Bower & Portsmouth [20].)

Condition	Good risk (all the following) T0 I0	Poor risk (any of the following) T1 I1
Tumour (T)	Confined to skin, lymph nodes or minimal oral disease	Tumour-associated oedema or ulceration Extensive oral Kaposi's sarcoma Gastrointestinal Kaposi's sarcoma Kaposi's sarcoma in other non-nodal viscera
Immune status (I)	CD4 count > 150 cells/μL	CD4 count < 150 cells/μL

Table 26.21 Treatment for Kaposi's sarcoma. (After Bunker & Staughton [10]; Bower & Portsmouth [20].)

Local treatment
Cryotherapy
Radiotherapy
Topical retinoids: alitretinoin [23]
Topical antivirals: cidofovir, docosanol [24]
Intralesional, e.g. TNF-α, IFN-α, vinca alkaloids
Surgery, e.g. curettage, cautery, infrared coagulation [25]
Laser
Photodynamic therapy
Cosmetic camouflage
Systemic treatment
Highly active antiretroviral therapy (HAART)
Isotretinoin (cidofovir)
Aggressive chemotherapy, e.g. daunorubicin, doxorubicin, bleomycin, paclitaxel [26], vincristine, etoposide
Human chorionic gonadotrophin [27]
Interleukin-4 [28]

IFN, interferon; TNF, tumour necrosis factor.

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Melanoma and non-melanoma skin cancer

It is evident that there is an increased incidence of non-melanoma skin cancer (basal cell carcinoma [1], squamous cell carcinoma [2,3]) and melanoma (Fig. 26.21) [4–13] in people with HIV infection, particularly in association with actinic damage. Actinic keratoses are very common. Squamous cell carcinoma may be multifocal, aggressive and present atypically (Figs 26.22 & 26.23) [14]. Basal cell carcinoma may be multiple and of the infundibulocystic [15] or micronodular neurotropic [16] variants, and even metastatic [17]. Porokeratosis is associated with immunosuppression, sun damage and HIV [18]. Anogenital

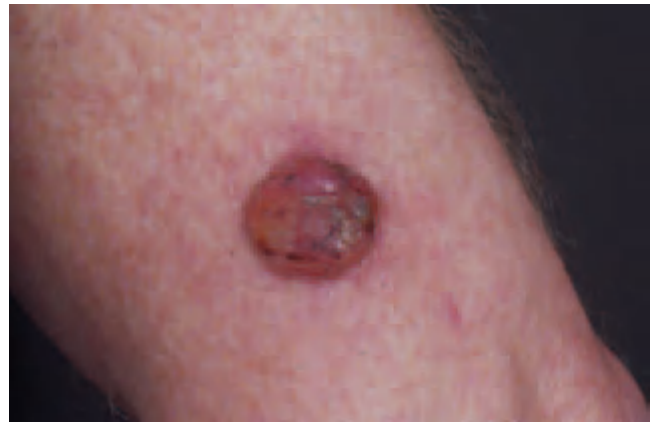

Fig. 26.21 Melanoma: rapidly growing (2/12) amelanotic nodule on the left arm. Breslow thickness > 10 mm. (Courtesy of Dr C.B. Bunker and Medical Illustration UK Ltd, Chelsea and Westminster Hospital, London, UK.)

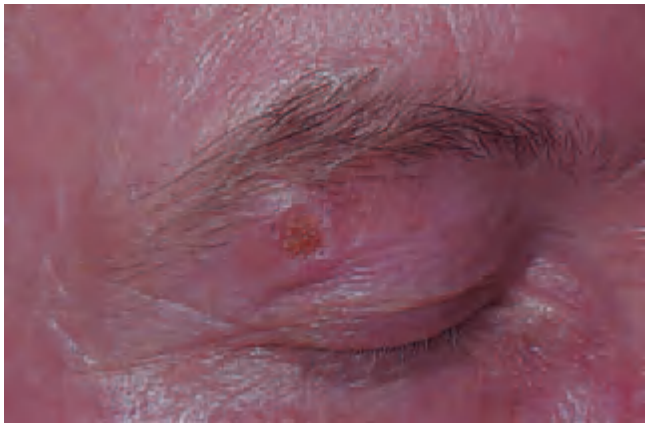

Fig. 26.22 Squamous carcinoma: ulcerated nodule on the right upper eyelid. (Courtesy of Dr C.B. Bunker and Medical Illustration UK Ltd, Chelsea and Westminster Hospital, London, UK.)

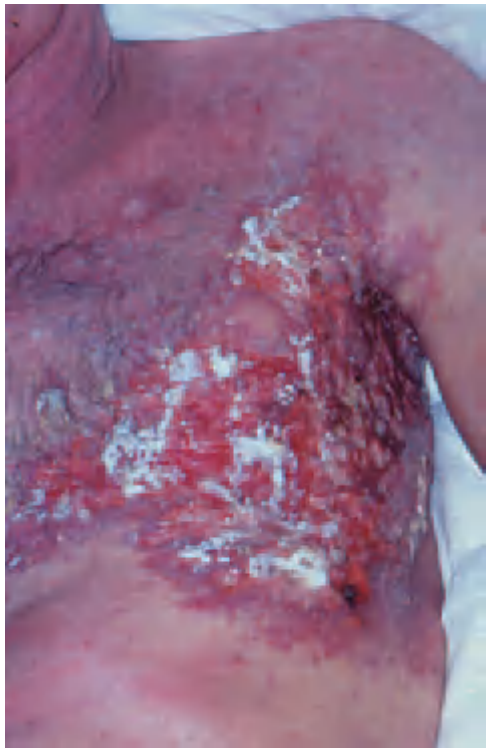

Fig. 26.23 Metastatic squamous carcinoma: zosteriform ulceration on the left axilla and chest. (Courtesy of Dr C.B. Bunker and Imperial College School of Medicine, London, UK.)

squamous cancer and precancer and its relationship to HPV and HIV are discussed in Chapter 68 [19–22].

Patients receiving HAART and therefore surviving HIV longer, even indefinitely, need to have careful dermatological evaluation and follow-up, including of the anogenital skin and mucosa. They should be warned about the possible synergistic risk of the sun and HIV. All new or changing skin lesions should be evaluated assiduously, with a low threshold for biopsy.

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Other tumours

The appearance of eruptive naevi, which presented in crops as the patients became more symptomatic from HIV infection, has been reported. These patients did not have the full-blown atypical naevus syndrome, although biopsy showed dysplastic features [1].

Other benign and malignant skin neoplasms have been reported in association with HIV, including: dermatofibrosarcoma protuberans [2]; sebaceous carcinoma [3];

Merkel cell carcinoma [4]; metastatic tufted angioma [5]; histiocytoma (solitary and multiple and eruptive forms) [6,7], including one case where the histiocytoma was parasitized by leishmaniasis [8]; pilomatrixoma (in association with myotonic dystrophy) [9]; leiomyoma [10]; xanthoma [11], including normolipaemic xanthomas [12,13].

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Lymphoma

A spectrum of involvement of the skin with lymphoma is seen in HIV/AIDS [1]. Non-Hodgkin's B-cell lymphoma, common in HIV [2], can cause skin lesions [3,4]. The relationship of Hodgkin's disease to HIV is still controversial [3,5]: several hundred cases have been reported. HIV-associated Hodgkin's disease differs from non-HIV-associated disease by manifesting 'B' symptoms more commonly, a more advanced stage at presentation, extranodal disease, a higher incidence of Epstein–Barr virus in affected tissue, predominant mixed cellularity and lymphocyte-depleted histologies, a less complete response rate, a higher relapse relate and a significantly shortened median survival [5]. It can present as a panniculitis [6].

Cutaneous T-cell lymphoma (mycosis fungoides and Sézary syndrome) may be associated with HIV/AIDS [7]. Atypical cutaneous lymphoproliferative disorder, which has been called 'pseudo-Sézary' or 'cutaneous T-cell lymphoma simulant' is a rare reactive inflammatory condition that rarely progresses to frank lymphoma [8]. Castleman's disease has been seen [5,9]. Multiple myeloma has presented in the skin with primary cutaneous plasmacytomas [10].

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Hair and nails

The abnormalities of hair and nails found in HIV infection are listed in Table 26.22 [1–4]. A striking case of kwashiorkor has been documented [5].

Acquired trichomegaly of the eyelashes may be an early marker of HIV infection [6]. Alopecia areata (Fig. 26.24) and alopecia universalis are reported associations [7]. Hair loss has been reported with indinavir, lamivudine and stavudine [8–11]. Colebunders and Vandenbruaene [9] have described curly hair (with lipodystrophy) during HAART.

Cribier *et al*. [2] reported that nearly 70% of HIV-infected individuals have nail changes. Onychomycosis is usually due to *T. rubrum* or unusual *Candida* species [2]. Some African patients with the yellow nail syndrome [12] have AIDS *and* tuberculous pleural effusion or pneumonia: the yellow nail syndrome is a recognized association of chronic pulmonary disease (see Chapter 62). Paronychia and ingrown toenail are particular complications of indinavir and probably not lamivudine, as has been suggested [13]. Blue nails are a sign of HIV infection [14].

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Table 26.22 Abnormalities of the hair and nails in HIV infection. (After Prose *et al*. [1]; Cribier *et al*. [2]; Bunker & Staughton [3]; Ward *et al*. [4].)

Hair
Patchy and generalized alopecia
Hypertrichosis of the eyelashes
Eyelash trichomegaly
Hypertrichosis including of the eyelashes: zidovudine (AZT)
Alopecia: indinavir, lamivudine (3TC), stavudine (d4T), didanosine (ddI)
Alopecia universalis: HAART
Curly hair: HAART
Nails
Clubbing
Half and half nails
Transverse (Beau's lines) and longitudinal ridging
Loss of the lunula
Leukonychia
Onycholysis and onychoschizia
Periungual erythema [15]
Longitudinal melanonychia
Blue nails [14]
Onychomycosis
Longitudinal melanonychia: zidovudine [16]
Melanonychia: hydroxyurea [17,18]
Paronychia/pyogenic granuloma: zidovudine (AZT), lamivudine (disputed)
Ingrown toenail and paronychia/pyogenic granuloma: indinavir

HAART, highly active antiretroviral therapy.

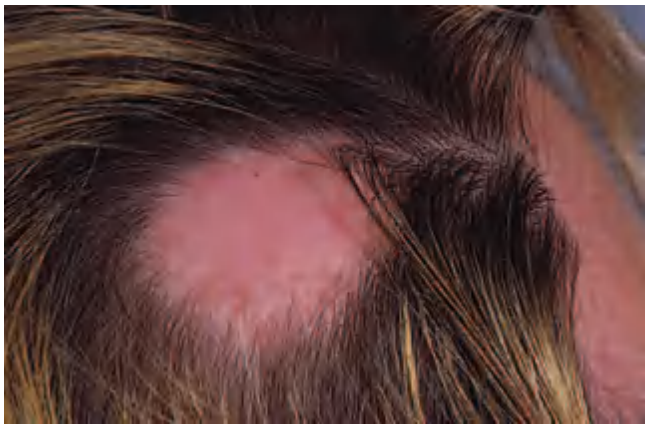

Fig. 26.24 Alopecia areata. (Courtesy of Dr C.B. Bunker and Medical Illustration UK Ltd, Chelsea and Westminster Hospital, London, UK.)

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Oropharynx

Many oral manifestations have been reported in acute HIV infection and seroconversion [1]. Transient intraoral redness, erosions and ulcers and candidosis are all described. Xerostomia is common. Salivary gland swelling is frequently seen in children but less so in adults infected with HIV [2].

Distressing mouth ulceration occurs frequently in established HIV. The differential diagnosis includes malignancy (KS and lymphoma), HSV, CMV, fungal infections, Behçet's disease, zalcitabine- and didanosine-induced ulceration, and idiopathic aphthous ulceration. Thalidomide has proved useful for the last of these [3] at a dose of 100 mg nightly for 2 weeks followed by maintenance therapy of 100 mg every 5 days, with monitoring to avoid peripheral neuropathy [4].

Oral candidosis is common in HIV-positive individuals and almost universal in AIDS. The extent and persistence of the disease are responsible for much morbidity in patients with HIV and AIDS. Sometimes the entire oropharynx, larynx and oesophagus may be involved but mild forms with just angular cheilitis and/or focal red or white patches on the oral mucosa, palate or tongue are seen [1,5].

Severe periodontal disease is also not unusual [1]. Gangrenous stomatitis, due to opportunistic anaerobic organisms and *Candida*, *Pseudomonas* and staphylococci, causes severely symptomatic perioral ulceration complicated by pain, bleeding and inability to feed [6].

Hairy leukoplakia is a new clinical entity that has emerged during the HIV epidemic and is probably associated with Epstein–Barr virus infection. It is particularly important because it is an early specific sign of HIV

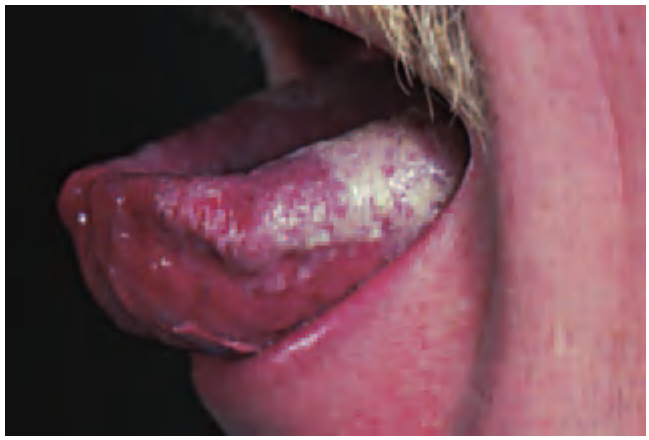

Fig. 26.25 Hairy leukoplakia. (Courtesy of Dr C.B. Bunker and Media Resources UCL, Trust, London, UK.)

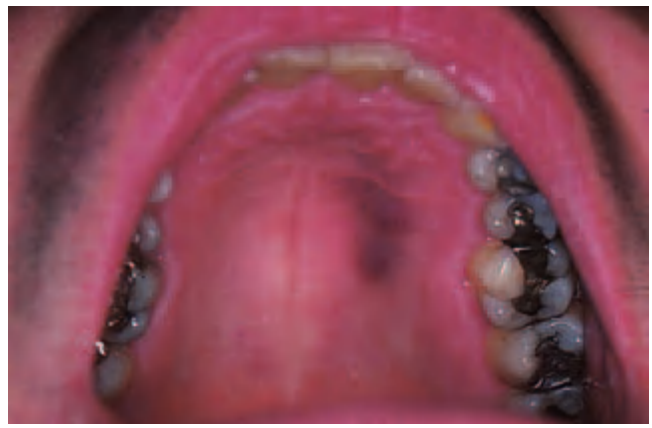

Fig. 26.26 Purple nodules on the palate in a patient with Kaposi's sarcoma. (Courtesy of Dr C.B. Bunker and Media Resources UCL, London, UK.)

infection, with the sinister implication that 75% of patients develop AIDS within 2–3 years. It is usually asymptomatic, although patients have often noticed the appearance of a roughened patch along the lateral margin of the tongue (Fig. 26.25). To the patient it may feel rough and to the physician it may look craggy but it is not truly 'hairy'. Other intraoral sites have been reported. The differential diagnosis includes trauma, *Candida*, leukoplakia, lichen planus and white-sponge naevus. Hairy leukoplakia has not yet been shown to involve other mucosal or extramucosal sites. White-sponge naevus may be familial and may occur on the tongue. Biopsy may be necessary. Hairy leukoplakia is now known to occur in other immuncompromised people and has even been reported in healthy individuals [1]. Treatment is with oral aciclovir [7].

HSV infection is common in and around the mouth. Painful red eroded lesions are characteristic and the extent and chronicity or frequent recurrences cause much debility. Just over 1% of HIV-infected individuals have oral HPV infection [2]. CMV may present similarly.

KS occurs frequently in the mouth, often the palate. It appears as red patches, plaques or nodules (Fig. 26.26). The early red lesions may be mistaken for HSV or *Candida*. The differential diagnosis also includes the other causes of mouth ulcers and tumours, lichen planus, drug eruptions and angina bullosa haemorrhagica (see Chapter 66).

Other problems that can affect the oral cavity include petechiae from thrombocytopenia [2], disseminated histoplasmosis [8,9], sporotrichosis [10], paracoccidioidomycosis [11], hyperpigmentation and oral labial melanotic macules [2,12] (Fig. 26.27), warts and warty carcinoma due to HPV [13], lymphoma, and the side effects of radiotherapy and drugs (Fig. 26.27, Table 26.23) [2,14,15]: foscarnet, IFN and zalcitabine are particular causes of mouth ulceration.

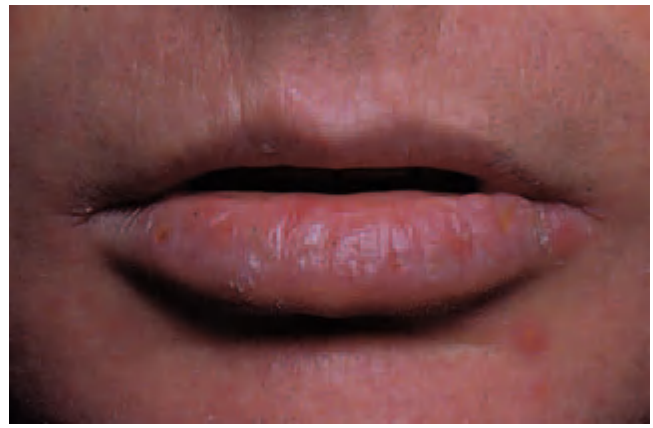

Fig. 26.27 Cheilitis caused by indinavir. (Courtesy of Dr C.B. Bunker and Imperial College School of Medicine, London, UK.)

Table 26.23 Oral side effects of drugs and radiotherapy given for HIV infection.

Hydroxyurea	Oral pigmentation
Foscarnet	Oral ulceration
Interferon	Oral ulceration
Zidovudine (AZT)	Oral pigmentation
Zalcitabine (ddC)	Oral ulceration
Didanosine (ddI)	Dysgeusia, xerostomia
Protease inhibitors	Cheilitis (Fig. 26.27)
Amprenavir	Dysgeusia, perioral paraesthesia
Ritonavir	Dysgeusia, perioral paraesthesia

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Women and children

Women and children represent the fastest growing subpopulation of HIV-infected patients in the developed world. There are few significant differences in dermatological morbidity between HIV-infected men and women save that women have less KS and hairy leukoplakia and possibly onychomycosis and that mollusca may appear earlier in women [1].

There are some important differences in children compared with adults. Vertical transmission from an infected mother is the usual mode of infection. There exists a challenging and broad differential diagnosis of immunosuppression in children (Table 26.24) [2]; all of these conditions may have cutaneous manifestations.

Dermatological disease is common in children with AIDS [3–5]. An eruption resembling seborrhoeic dermatitis has been described. Atopic eczema is found in increased frequency but unclassified eczematous eruptions are also seen. Widespread nappy dermatitis can occur. The pruritic papular eruption is common and, as in adults, so are drug eruptions.

Table 26.24 Differential diagnosis of childhood immunosuppression.

DiGeorge's syndrome
Ataxia-telangiectasia
Wiskott–Aldrich syndrome
Agammaglobulinaemias
T-cell and B-cell immunodeficiencies
Malnutrition
Malignancy
Congenital infections
Iatrogenic immunosuppression
Graft-versus-host disease

About half of children with advanced HIV disease can be expected to suffer a serious bacterial infection and 20% of these involve the skin. The commonest organism is *Staphylococcus aureus* and the usual clinical patterns are of cellulitis, impetigo, folliculitis and abscess formation; a persistent staphylococcal folliculitis may also be seen. The most common fungal infection is candidosis, 75% of 36 children in one study. Dermatophyte infection is frequently encountered (tinea capitis, tinea corporis and onychomycosis). HSV infection of the skin and mucosae is common and may be very serious and chronic; likewise disseminated zoster infection. Persistent verrucous varicella in a 3-year-old girl has been described as the first manifestation of HIV infection [6]. In HIV infection, molluscum lesions have a predilection for the face rather than the trunk. Perianal warts have been reported and it is likely that persistent HPV infection at other sites will become more widely seen, although digital warts and verrucae are a common if not universal experience in childhood.

KS is rare (about 5%) and often affects other organs, with sparing of the skin. Non-Hodgkin's and other lymphomas with cutaneous involvement are even rarer.

There have been reports of skin changes compatible with pellagra, scurvy and acquired zinc deficiency (acrodermatitis enteropathica), the latter attributed to malabsorption associated with chronic infectious diarrhoea caused by opportunistic organisms [7].

Non-specific findings in paediatric HIV practice include exanthematous rashes and cutis marmorata or livedo appearance [8], cold urticaria and idiopathic urticaria, long eyelashes requiring frequent trimming, patchy alopecia (common), erythema dyschromicum perstans (ashy dermatosis) and pyoderma gangrenosum [9]. Children infected with HIV are at risk of child abuse [5].

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Haemophiliacs

Atopic eczema, seborrhoeic dermatitis, candidosis, dermatophyte infection and folliculitis occur with increased prevalence in HIV-positive compared with HIV-negative haemophiliacs. These conditions may develop earlier in infected haemophiliacs than in homosexuals [1,2].

Intravenous drug users

Drug abusers often have severe ecthyma and abscesses complicating injection sites but there is often concomitant malnutrition and liver disease [3]. Oral candidosis and seborrhoeic dermatitis are the most common skin problems; KS and oral hairy leukoplakia are rare [4]. Reynaud-Mendel *et al*. [5] found that genital warts were commoner in HIV-infected intravenous drug users than in male homosexuals.

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Immune restoration disease

Patients with AIDS starting treatment with HAART and undergoing immune reconstitution can suffer exacerbations of immune or inflammatory disease such as progressive multifocal leukoencephalopathy, uveitis or vitreitis in CMV retinitis, sarcoidosis, hepatitis C reactivation and lymphadenitis in tuberculosis and *M. avium–intracellulare* infection [1–5]. Of dermatological import are chronic oroanogenital herpes simplex (Fig. 26.28) [6], reactivation of herpes zoster [2,5], cutaneous warts [7], acute multifocal cutaneous ulceration due to CMV (Fig. 26.29) [8], mycobacterial disease [9], post-kala-azar dermal leishmaniasis [10], eosinophilic folliculitis [2], 'immune recovery folliculitis' (possibly re-emergent hypersensitivity to *Demodex* and *Malassezia* [11]) and alopecia universalis associated with Graves' disease [12], all of which have been reported in the context of relatively successful treatment of HIV/AIDS by HAART.

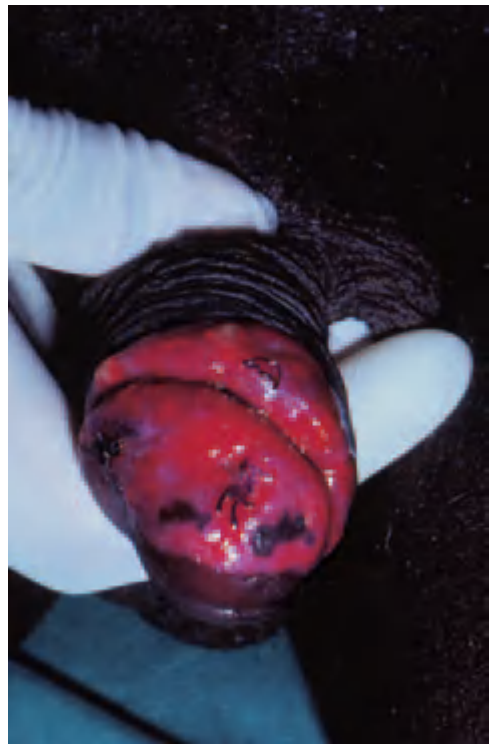

Fig. 26.28 Herpes simplex immune restoration disease: chronic erosions on the penis. (Courtesy of Dr C.B. Bunker and Medical Illustration UK Ltd, Chelsea and Westminster Hospital, London, UK.)

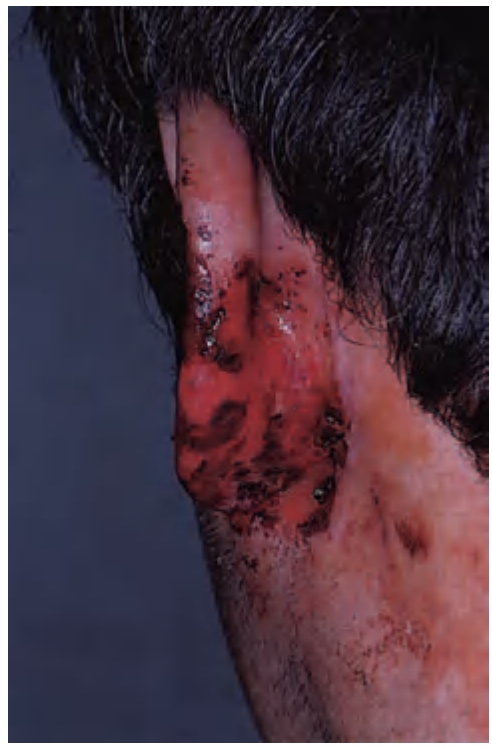

Fig. 26.29 Cytomegalovirus immune restoration disease: necrotizing impetiginized ulcer on the left ear. (Courtesy of Dr C.B. Bunker and Imperial College School of Medicine, London, UK.)

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Chapter 27

Bacterial Infections

R.J. Hay & B.M. Adriaans

Introduction

The normal human skin is colonized by huge numbers of bacteria that live harmlessly as commensals on its surface and within its follicles. At times, overgrowth of some of these resident organisms may cause minor disease of the skin or its appendages. On other occasions, bacteria not normally found there may colonize the epidermis and lead rapidly to disease. Apart from the arrival of these frankly pathogenic organisms, a wide range of bacteria land more or less fortuitously on the skin, and linger briefly in small numbers before disappearing, unable to multiply and thrive in this relatively inhospitable environment. Bacteriological sampling will reveal the presence of these otherwise unsuspected 'transients' [1]. Organisms not normally considered as resident members of the skin flora may sometimes colonize and become established in modest numbers for relatively long periods. Bacteria of this intermediate category have been labelled temporary residents [1]. Furthermore, certain sites such as the skin of the face may be repeatedly contaminated from the nostrils or mouth by *Staphylococcus aureus* or β-haemolytic streptococci, giving the false impression that these organisms are members of the normal facial flora. As they do not reside and replicate there, they are, as far as the face is concerned, transients.

When the skin is inflamed or otherwise abnormal, it is often difficult to determine whether an organism isolated from its surface is causing or contributing to the observed pathology [2,3]. Bacteriology reports must be interpreted with caution in the light of the known capabilities of the organism isolated. If the skin is damaged or the immune status of the subject impaired, bacteria usually regarded as non-pathogenic on the body surface may assume the role of opportunist pathogens. The number of organisms in the inoculum is of considerable importance. Within a given species there are also strain differences in virulence. Some strains have a particular tendency to cause disease, perhaps due to greater adherence to epithelial cells, perhaps because of differences in enzyme production. The underlying mechanisms are not fully understood, but the principle is well recognized.

From the point of view of host defence, there are three aspects to be considered: first, the nature and health of the epithelial surface including its ability to replicate and produce secretions; second, the interactions between commensal organisms of the normal flora and the potential parasite; third, the cellular and humoral factors acting

within the body—both classical immune mechanisms and non-specific mechanisms.

Even on the skin, the most accessible of sites, the complexities of host–parasite relationships remain incompletely understood. Detailed quantitative studies of pathogens and commensals, and investigations of epidermal replication and of the immune capabilities of the host, are becoming feasible in a research setting. The lessons they teach must be used to interpret the problems found in daily clinical practice, where such sophisticated methods are generally unavailable.

There is now a considerable literature on the microbiology of human skin of which these references are some of the most important texts [4–6]. For general microbiology and infectious disease Mandell *et al*. [7] and Collier and Balors [8] are recommended.

Normal flora of the skin

Methods of sampling

Numerous methods have been used to sample the normal or commensal flora of the skin, as no one method is satisfactory for all sites or for all aspects of the work [9]. Simple qualitative studies, especially when large numbers of subjects must be sampled, are usually performed by swabbing. This should be done in a standardized manner. The number of organisms is increased by the duration of rubbing, pressure exerted and moistening the swab. Semi-quantitative data and some information as to the spatial distribution of bacteria are provided by sticky tape sampling, roll tubes or replica plating. The best quantitative estimates of the total bacterial flora are determined by applying an open-ended cylinder of known cross-sectional area to the skin, introducing a small, known volume of suitable liquid vehicle (phosphate buffer plus Triton X-100) and scrubbing the surface of the skin to free the organisms. This method is useful for studying changes in the number of organisms under different environmental conditions in small numbers of subjects, but it is very time consuming and gives a poor yield of the intrafollicular anaerobes. Full-thickness skin-biopsy material should in theory provide the best sample, but in practice it is not easy to handle and this method is of course traumatic to the subject [4].

The disposal of organisms can be studied quantitatively by air sampling techniques using either settle plates or an impaction sampler while the subject performs a specified activity, for example undressing in a small room [10].

The media used for isolation clearly influence the results of sampling. Noble, although recognizing the special value of selective media, recommends in general the use of ordinary blood or serum agar for aerobic organisms and solid Brewer's thioglycolate medium without indicator but with 1% Tween 80 for *Propionibacterium acnes* [1].

The normal flora

The concept of a stable normal resident flora composed of large numbers of organisms belonging to relatively few species is well established [5]. There are some variations from subject to subject and perhaps in a given subject with time. A few geographical differences have also been noted [9].

Temporary resident bacteria may confuse the picture, being less easy to distinguish from stable commensal organisms than obvious transients. These problems are discussed at length by Noble [1]. It is possible, however, to describe a basic pattern of colonization of healthy human skin from which some variations may be observed. In simple terms, dry skin supports a low level of colonization, while moist areas and those well supplied with sebaceous glands are heavily populated. Most organisms reside on the surface of the stratum corneum in the crevices between squames in the rather loose outermost layers. These surface dwellers are not evenly distributed but are aggregated into microcolonies of varying sizes comprising perhaps 50 or several hundred cells. Some may be larger still. The hair follicles are inhabited by anaerobes (*Propionibacterium* spp.) in their deeper parts and nearer the surface aerobic cocci in addition to *Pityrosporum* spp. of yeasts. There are, however, no bacterial inhabitants of sweat ducts or glands, eccrine or apocrine.

The resident aerobic flora consists of Gram-positive cocci of *Staphylococcus* spp., *Micrococcus* spp. and a variety of Gram-positive rods, the coryneforms or diphtheroids. These coryneform organisms are mainly *Corynebacterium* spp. but some have recently been recognized as *Brevibacterium* spp. The only significant Gram-negative residents are *Acinetobacter* spp., previously known as *Mima* and *Herellea*.

Propionibacteria are regularly found in the follicles in adult skin and are the main anaerobic residents. The species *Peptococcus saccharolyticus* (Micrococcaceae) is now thought to be an anaerobic *Staphylococcus* and is a member of the normal flora in about 20% of subjects. Streptococci are notable by their absence, although they may frequently be found as transients (from the mouth) on perioral skin, or other sites prior to the onset of impetigo [11].

Most cutaneous microbiologists have now accepted that the Kloos and Schleifer [12] scheme for classifying staphylococci and micrococci (Micrococcaceae) is more meaningful, at least from an ecological standpoint, than the much used Baird–Parker system [1]. Kloos and Schleifer separate *Staphylococcus* spp. and *Micrococcus* spp. on the basis of several tests. For example, *Staphylococcus* spp. are able to produce acid aerobically from glycerol in the presence of erythromycin (0.4 μg/mL), and they are sensitive to lysostaphin and nitrofuran at defined concentrations, whereas *Micrococcus* spp. are not. Separation of

the two genera by these criteria is supported by molecular genetic techniques.

Within the genus *Staphylococcus*, 10 different species have regularly been isolated from normal skin. The coagulase-positive species *S. aureus*, however, should not be considered as a resident on healthy skin in most subjects, although it is frequently found in the anterior nares. It occurs there as a resident in about one-third of most populations and is carried on perineal skin in perhaps 20%. Healthy axillary skin, and toe clefts in shoe-wearing populations, may also harbour it in a smaller percentage of subjects. On damaged skin, for example in eczema or psoriasis, *S. aureus* may be found, sometimes widely over the skin surface.

Of the coagulase-negative resident *Staphylococcus* spp., *S. hominis* and *S. epidermidis* (moist sites) are the most important numerically, but *S. capitis*, *S. cohnii*, *S. haemolyticus*, *S. saprophyticus* and *S. warneri* have also been isolated from many subjects. Interestingly, *S. xylosus* has also been found to be fairly common on North American skins but does not seem to be a cutaneous resident in the UK. *S. simulans* is another recognized but uncommon cutaneous *Staphylococcus* on both sides of the Atlantic.

Organisms of the genus *Micrococcus* are less numerous than *Staphylococcus* spp. on healthy skin but are relatively more important on sparsely populated dry sites and in childhood. *Micrococcus luteus* and *M. varians* appear to be the dominant species but *M. kristinae* and *M. sedentarius* are accepted as residents and *M. lylae* may have significance in infancy [1].

Coryneforms

The coryneform (or diphtheroid) organisms are aerobic, Gram-positive pleomorphic rods. The coryneform bacteria are difficult to separate by conventional taxonomic methods, and chemotaxonomic methods, such as identification of specific protein patterns on gel electrophoresis and restriction fragment length polymorphism (RFLP) analysis, are time consuming and unsuitable for routine use. A recently proposed scheme in which the aerobic coryneforms are divided into four *Corynebacterium* spp. complexes, *C. bovis*, *C. minutissimum*, *C. xerosus* and *C. hofmani*, with *Brevibacterium epidermis* and an apparently aerobic *Propionibacterium* spp. making up a total of six groups, has the obvious value of simplicity, which all its predecessors lacked [1]. It is notable, however, that a trichomycosis axillaris associated group is not defined, and it is not clear whether the strains included in the *C. minutissimum* complex are closely associated with clinical erythrasma. *Brevibacterium* spp. are clearly separable from the genus *Corynebacterium* by cell-wall composition studies, nutritional requirements and by the production of methane thiol. These relatively recently recognized organisms have now been established as normal inhabitants of the skin (at least in a sizeable minority of subjects) and are particularly associated with (but not confined to) moist sites. They are related to *Brevibacterium* spp. isolated from dairy products, and by the production of methane thiol are the probable cause of the cheesy odour of sweaty feet [13].

A further group of coryneforms, implicated as copathogens in the superficial fungal infection of hair shafts, white piedra, has been identified as *Brevibacterium mcbrellneri* [14].

Three species of Propionibacteria, which are anaerobic, Gram-positive, rod-shaped organisms, are now generally acknowledged as members of the resident flora in adults. *Propionibacterium acnes* and *P. granulosum* are widespread but particularly associated with follicles that have large sebaceous glands over the face and upper trunk. They have both been associated with acne lesions in which their role is a matter of considerable interest. The third species, *P. avidum*, is found in moist sites, particularly the axillae and groins. Its pathogenic potential on the skin is unclear.

Quantitative studies

The population of Micrococcaceae on the skin has been estimated as 600/cm^2 for the hand, 60/cm^2 for the forearm, 300/cm^2 for the scapular region and 500 000–1000 000/cm^2 in the axilla [1]. Total anaerobic organisms, i.e. including diphtheroids as well, were reported by Williamson as averaging 1.46×10^6/cm^2 for the scalp and 2.41×10^6/cm^2 for the axilla [15]. Figures for the forehead were 200 000/cm^2, whilst for the forearms there were two populations of normal subjects, one tending to have high counts, with an average of 4500 organisms/cm^2 and one with low counts with just over 100/cm^2. For the back, the average for the whole group was a little over 300/cm^2. Anaerobic organisms are most numerous in those regions with large follicles—face, chest and back—and reports suggest numbers from 50 000 up to several million/cm^2 [16]. The follicular location of many of these organisms makes their estimation technically difficult, but Puhvel *et al*. [17], using microdissection techniques, have found the mean anaerobic count to be 3.8×10^4 per follicle. The number of organisms on a particular subject's skin varies little with time. There is, however, considerable variation within the population. Some individuals habitually carry high, and others very low, numbers of bacteria, but this distribution does follow a 'log normal' curve.

Modifying factors

The influence of various factors on the microbial population has been investigated by using a quantitative sampling technique. Abstinence from washing does not increase the count. Taking a shower probably produces a brief temporary reduction in the bacterial flora, but because it leads to the break-up of the microcolonies on

the skin and a more even distribution of bacteria, it may actually cause increased dissemination of bacteria for an hour or two afterwards [1]. Season has little effect apparently, but in one investigation an increase in the number of organisms was reported with increase in external temperature and humidity, but not when either of these factors operated alone [3].

The effects of increased hydration have been studied by covering the skin with plastic film [2]. The total flora increases greatly; in the early stages, coagulase-negative staphylococci and micrococci predominate, but later lipophilic coryneforms become numerous and micrococci diminish in importance. Gram-negative rods increase steadily with time. In jungle conditions, *Pseudomonas aeruginosa* is commonly isolated from moist areas, and in neonates nursed in high-humidity atmospheres, colonization and infection with *P. aeruginosa* occur with increased frequency [18].

Age, sex and race differences

The human skin becomes colonized from birth. In infants the bacterial flora is somewhat unstable and varied, being more likely to include, probably as temporary residents, streptococci and spore-forming bacilli [19]. *Micrococcus* spp. appear to be more prominent than on the adult skin, but *Propionibacterium* spp. require the increased skin lipid levels of puberty before becoming established, and are present at very low levels, if at all, before the onset of puberty. In elderly subjects, streptococci make an appearance as residents, and in this age group enteric organisms are found more often, particularly in moist sites. There is evidence that males carry higher numbers of bacteria, at least of aerobic organisms, than females [1], a fact which probably accounts for the observation that men are more likely to be disseminators of *Staphylococcus aureus*, if they are perineal carriers, than are women [20]. The subject of dispersal, of considerable importance in surgery, has been extensively reviewed by Noble [21].

Racial differences have been demonstrated in the nasal carriage of *S. aureus* in children—white individuals (at 41% positive) being more likely than black individuals (at 30%) to carry this organism [22], but comparative data on the densities of the bacterial populations of the main groups of resident organisms are lacking.

Other influences

Changes in normal flora, including an increase in the number of subjects carrying Gram-negative organisms, may occur in seriously ill patients, apparently to an extent that cannot be accounted for by the treatment they are receiving [23].

Antiseptics applied to the skin, as in the preparation of operation sites, generally remove the transient flora and reduce the resident organisms [4]. The application of agents that specifically inhibit Gram-positive cocci is generally followed by an increase in the population of Gram-negative rods [9]. Carriage of *Staphylococcus aureus* may also be affected by cold weather, duration of hospital stay or needle injection [24].

The role of the normal flora

The normal flora of the skin appears to have several functions, of which the most important is probably defence against bacterial infection through bacterial interference. It is almost certainly responsible for the production of free fatty acids from skin lipids. There is now considerable evidence that *Propionibacterium acnes* and the Gram-positive cocci are capable of hydrolysing lipids of sebum to produce free fatty acids [25]. It seems likely from their localization, and from evidence comparing the effects of systemic tetracycline administration with topical neomycin application, that *P. acnes* deep in the follicles actually undertakes most of this hydrolysis [26].

Apocrine sweat is sterile and odourless when secreted. The odour develops due to bacterial action, mainly attributable to aerobic corynebacteria. Deodorants are effective largely through their antibacterial activity [27].

The flora of specialized areas

Certain areas of skin have specific floras, which differ quantitatively or qualitatively from the general picture outlined above, and are therefore worthy of special consideration.

The nasal vestibule

The common organisms found on swabbing are coagulase-negative staphylococci, micrococci and coryneforms. *Staphylococcus aureus* is present as a resident in about 35% of healthy subjects [1]. *Streptococcus pyogenes* is not rare. The percentage incidence varies greatly with different populations but, as nasal carriers sometimes disseminate large numbers of organisms, their detection and treatment are most important in the control of streptococcal infections.

External auditory meatus

In addition to coagulase-negative staphylococci and coryneforms, *Proteus* spp., *Escherichia coli, Neisseria catarrhalis* and *N. flora* have been isolated in small but significant numbers from normal ears.

Axilla

This site supports a very high level of bacterial colonization, mostly staphylococci, micrococci and coryneforms.

Some individuals have a mainly coccal flora; in others aerobic coryneforms predominate. *Propionibacterium acnes* is usually present and *P. avidum* is often found, as are *Acinetobacter* spp.

Toe clefts

In shoe wearers, the fourth toe cleft is often hyperhydrated and the skin macerated. Such conditions sustain an extraordinarily large number of bacteria, mainly the common organisms of the general resident flora, but Gram-negative organisms are also found in this site. The toe web is an important site for *Brevibacterium* spp., and not surprisingly *Acinetobacter* spp. are often isolated, as are *Alkaligenes* spp. In the elderly and in tropical climates, coliforms and other organisms of the intestinal flora may be present [28].

The vulva

Organisms regularly isolated from this area include the expected coagulase-negative staphylococci, micrococci and coryneforms, with coliforms and enterococci occurring frequently as residents and as transients from faecal sources. Group B streptococci may be cultured from this site, usually in small numbers.

The perineum and groin

Coagulase-negative staphylococci, micrococci and a variety of aerobic coryneforms are usually present. Gram-negative organisms of the intestinal flora rapidly disappear after faecal contamination, but *Acinetobacter* spp. are resident in about 15% of subjects.

Umbilicus

The umbilicus of the newborn is frequently colonized by *Staphylococcus aureus* shortly after birth. The incidence varies greatly, but for infants born in hospital it is probably not very different from the nasal colonization rate.

The umbilicus of the newborn may also be colonized by *Streptococcus pyogenes*, and look normal. The organisms can readily spread from infant to infant in a hospital nursery. Searches for the source of staphylococcal and streptococcal infection in a maternity unit should always include umbilical swabs from the babies.

Adherence

The ability of bacteria to stick to the skin surface, the process of adherence, is still not well understood. On wet surfaces, the hydrophobic nature of many bacterial walls promotes close apposition between the bacterium and human cells. In addition, there are smaller elements of the outer surface, adhesins, which also promote adhesion [29].

These are usually specific and interact with the host cell via a receptor site. Examples of bacterial adhesins include lipoteichoic acid [30] found in both staphylococci and streptococci; in the latter this is located in fine cell-wall projections or fibrillae. Similar filamentous structures, fimbriae or pili, occur in many Gram-negative bacteria. Adhesins not only allow the organisms to remain on the epithelial surface, they may also regulate the relationship between different bacteria, such as the composition of microcolonies, via the interaction of complex excreted material covering the bacterial surface. The secretion of extracellular material, such as slime, allows bacteria to adhere to foreign surfaces as well as stratum corneum [31]. Where this involves suture materials or plastics such as percutaneous cannulae, heavy colonization may then be followed by invasion resulting in abscess formation or septicaemia.

The skin and defence

The skin provides a dry, mechanical barrier from which contaminating organisms are constantly being removed by desquamation. Investigators have spread organisms on the skin surface, studied their disappearance and attempted to elucidate the factors concerned.

The early theories that the acid pH of most of the skin surface was an important defence mechanism against bacteria have now been completely rejected [1]. Desiccation appears to account for the difference in the rate at which implanted bacteria disappeared from acid and alkaline areas, the alkaline areas being more moist.

Ricketts *et al*. [32] investigated the survival of several bacteria species on the forearm skin under plastic films of two kinds, one permeable to water vapour and one not. The plastic films were held by a frame of adhesive tape, so that the inoculated area could be sampled at intervals up to 7 days. By studying the survival of bacteria on the dry and on the moist areas thus produced, these workers concluded that a chemical mechanism was largely responsible for the destruction of *Streptococcus pyogenes*, whereas drying was responsible for the destruction of *Escherichia coli* and *Pseudomonas aeruginosa*. Both factors appeared to contribute to the elimination of *Staphylococcus aureus*. They then investigated the nature of the chemical mechanism and concluded that unsaturated fatty acids, particularly oleic acid, were the active agents. These may be produced on the skin surface as a result of the splitting of esters in the sebum by the commensal flora (Chapter 43).

Lacey has confirmed that extraction of the fatty acids from the skin diminishes resistance to colonization by staphylococci, and that fatty acids may be neutralized to some extent by binding with neomycin [33].

The phenomenon of bacterial interference is sufficiently closely related to skin defence to be mentioned here. Colonization of some sites by one strain of staphylococci interferes with the subsequent colonization by a different strain. Shinefield *et al*. [34] deliberately colonized the noses and umbilical stumps of newborn infants against infection and disease caused by epidemic strains of *S. aureus*, and obtained most encouraging results. A similar method has been used in an attempt to prevent recurrent attacks of boils, but the technique has not found general acceptance, largely because the avirulence of the inoculated strain cannot be guaranteed. Competition for available nutrients is thought to explain this phenomenon.

Selwyn has drawn attention to the importance of antibiotic production by normal skin bacteria [35]. It seems that more than 20% of normal subjects carry some skin bacteria that produce antibiotics capable of inhibiting other microorganisms. On nearly one in 10 of normal human skins, these antibiotic producers actually predominate, in which case they appear to be helpful in protecting against staphylococcal wound infection after surgery.

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Gram-positive bacteria

Staphylococcus aureus

Staphylococcus aureus, distinguished from other staphylococci by a positive test for coagulase, is among the most important causes of skin infections and of serious, and sometimes fatal, systemic disease. Many of the conditions of modern life have tipped the precarious balance between commensalism and parasitism in its favour. Crowded cities and hospitalization of the sick provide increased opportunities for dissemination of the organism, and the wide use of antibiotics results in selective survival of resistant strains [1].

Carriage

The frequency with which *S. aureus* can be isolated from the skin has been extensively studied by many different techniques. If a sufficient number of sites are sampled frequently enough, the carrier rate may approach 100%, especially if enrichment culture techniques are used. With conventional techniques and random sampling, approximate rates for the resident carriage sites of *S. aureus* are: anterior nares 35%, perineum 20%, axillae 5–10% and toe webs 5–10% [2]. Resident carriage on other, dry, healthy skin surfaces is believed not to occur, but contamination from carriage sites is common, notably of the hands from the nose. In the same person, different phage types may colonize different areas.

Nasal carriage has been studied in most detail. Serial examinations suggest that some 20% of individuals are persistent nasal carriers, 60% are intermittent carriers and 20% are resistant to nasal colonization [3].

Genetic factors, perhaps involving bacterial adherence [4] and immune responses, are suggested by higher nasal carriage rates in white people than in black people [5], by studies of families and twins [6], by higher-than-normal rates in patients with phenylketonuria [7], by increased adherence in atopic eczema [8] and by an association of nasal carriage with human leukocyte antigen (HLA)-DR3 [9].

In those susceptible to nasal colonization, the overall rate depends on the extent to which the many transient carriers acquire the organism by contact with persistent carriers. This at least partly underlies the increase in carriage rates following hospital admission [2], higher rates in urban than in rural areas [10] and variation in carriage rates with age.

The neonatal nose and umbilical stump [11] tend to be rapidly colonized by *S. aureus*, perhaps partly because colonization by saprophytic cocci has not yet taken place. The nasal carriage rates are rather higher (e.g. 72%) [12] in infants born in hospital and lower in those receiving antiseptics on the umbilicus. The hospital-born baby may transmit infection to other family members [13]. The nasal carriage rate falls to a minimum of 10–15% at the age of 1 year and rises again to reach adult levels by the age of 5 years [12].

Within the nasal passage, the anterior nares are the most readily colonized parts and are the site usually sampled. However, carriage of *S. aureus* on the mucosal surfaces of the turbinates is common, and recolonization by these organisms may partly explain the difficulty of eradicating nasal *S. aureus* by topical application [2].

High rates of nasal carriage in atopic eczema (79%) [14] may partly derive from the heavy load of *S. aureus* on the skin, but increased adhesion of the organism to nasal mucosal cells may be relevant [8].

In patients on ambulatory peritoneal dialysis, those carrying *S. aureus* in the nose are much more likely to get infection of the exit site, which is usually with the same bacterial strain [15].

Suppression of carriage of S. aureus. Carriage of *S. aureus* is physiological and is not in itself an indication for treatment. Reasonable indications include prophylaxis in those whose occupations would render staphylococcal dispersal a significant hazard to others, such as operating theatre and neonatal nursery staff, and confirmed carriers among patients suffering frequent recurrences of staphylococcal infection and their household contacts [16].

Permanent eradication of carriage of *S. aureus* is not possible, but temporary elimination or a substantial reduction in numbers may be of significant clinical benefit. If the organism is cleared, eventual recolonization is to be expected, as was confirmed in a study of an isolated and well-motivated group of 28 men in an Antarctic base [17].

Minimum efforts to reduce carriage are regular, long-term application of chlorhexidine cream to the appropriate sites (anterior nares, perineum or axillae) and use of an antiseptic, typically chlorhexidine or povidone iodine, in a detergent base for daily bathing or showering including hair washing [18]. Oral or topical antibiotics may contribute to elimination of the organism, but in general recolonization occurs soon after the treatment is stopped [19], with two main exceptions. Intranasal mupirocin eliminated nasal *S. aureus* after a 5-day course in all patients treated, and 50% remained free of the organism after 5 months [20]. Oral rifampicin, 600 mg daily for 7–10 days cleared the organism for 3 months in 80% of cases [21]. Good results also were obtained with long-term, low-dose clindamycin, 150 mg daily for 3 months [22].

Bacterial interference. Nasal inoculation of *S. aureus* strain 502A, of relatively low virulence, has been advocated as an artificial method of achieving bacterial interference against more virulent strains. In a study of families with recurrent furunculosis, colonization with strain 502A persisted for 6 months in 83% of treated patients and the infections became much less frequent [23]. However, strain 502A may cause occasionally severe infections, including a case of fatal septicaemia [24], and its use cannot be generally recommended [25,26].

Colonization of diseased skin by *S. aureus*

Moist lesions and those in which the integrity of the epidermal barrier is disrupted are readily colonized by *S. aureus*. Loss of a physical barrier against invasion is one factor, but the reported inactivation by serum of the inhibitory effect on *S. aureus* of linolenic acid [27] is of interest.

In atopic eczema high numbers of *S. aureus* are present. The organism can be isolated from 91% of chronic plaques and 100% of acute exudative lesions [28] and from uninvolved skin in 76% of patients [13]. Numbers of *S. aureus* correlate with the severity of the eczema [29]. Adherence of *S. aureus* to nasal mucosal and skin epithelial cells [8], including specifically corneocytes [30], is increased in atopic eczema. Patients taking retinoids may develop mucocutaneous side effects, such as cheilitis and blepharo-conjunctivitis. These are often associated with *S. aureus* infection.

Biologically active substances produced by *S. aureus* [26,31]

Staphylococcus aureus can produce several toxins, some of which contribute to invasion and survival of the organism in the tissues.

More specific in the dermatological context are the exfoliative toxins (epidermolytic toxins ET-A and ET-B) responsible for the generalized staphylococcal scalded skin syndrome (SSSS) (Chapter 14) and bullous impetigo. The superantigen toxic shock syndrome toxin 1 (TSST-1), and probably other toxins, are involved in toxic shock syndrome. Staphylococcal scarlatina is thought to be mediated by staphylococcal erythrogenic toxin or other byproducts of the organism [32]. Superantigens from *S. aureus* may also affect the evolution of atopic dermatitis.

Staphylococcal cell-wall products (teichoic acid, peptidoglycan and protein A), exert many effects on the host immune system [33,34]. Protein A may be involved in adherence of the bacterium to the host cell [30], and it can bind to the Fc portion of IgG in addition to the specific Fab fragment of IgE [35,36].

Table 27.1 Involvement of *Staphylococcus aureus* in cutaneous disease.

Direct infection of skin and adjacent tissues
Impetigo
Ecthyma
Folliculitis
Furunculosis
Carbuncle
Sycosis
Occasionally in cellulitis
Others
Secondary infection
Eczema, infestations, ulcers, etc.
Cutaneous disease due to effect of bacterial toxin
Staphylococcal scalded skin syndrome
Toxic shock syndrome
Staphylococcal scarlatina

Resistance to staphylococcal infection [26]

The main host defence against invading staphylococci is ingestion and killing by phagocytes. Antibodies to various *S. aureus* antigens are universally found, but appear to make a relatively small contribution to host defences and are of limited diagnostic and prognostic value [37]. Cell-mediated responses to *S. aureus* occur but their role in immunity is uncertain.

Resistance to staphylococcal infection is reduced in patients with poorly controlled diabetes [38], renal insufficiency, haematological malignancies, nutritional deficiency or alcoholism, and in those receiving corticosteroid or cytotoxic therapy.

In acquired immune deficiency syndrome (AIDS), staphylococcal bacteraemia may occur [39], and angular stomatitis and facial impetigo and folliculitis are common (Chapter 26).

The increased incidence of *S. aureus* infections in patients on retinoids may be partly due to increased adherence to epithelial cells [40].

Pure deficiency of cell-mediated immunity appears not to predispose to staphylococcal cutaneous infection. Immunoglobulin deficiency, including selective IgM deficiency [41], may contribute to staphylococcal skin infection, as may certain deficiencies of the complement system (Chapter 59).

In the Chediak–Higashi syndrome (Chapter 39) and chronic granulomatous disease (Chapter 59), deficiencies of granulocyte function underlie a strong predisposition to staphylococcal and other infections. An isolated deficiency of neutrophil killing function in two siblings responded to ascorbic acid [42]. Cyclical neutropaenia has also been associated with recurrent infected eczema [43].

In Job's syndrome (Chapters 14 and 17), hyper-IgE syndrome and Buckley's syndrome [44] an increased incidence of severe staphylococcal infection is associated with eczema, markedly raised serum levels of IgE and defective neutrophil chemotaxis [45]. Staphylococcal and other infections are associated with eczema in the Wiskott–Aldrich syndrome (Chapter 14), in which a number of immunological abnormalities occur inconstantly, including hyper-IgE. Recurrent pyoderma and folliculitis with atopic eczema were associated with deficiencies in both lymphocyte and granulocyte function in a boy and his father. The clinical and immunological abnormalities responded to conventional (H_1) antihistamine treatment [46].

Cutaneous staphylococcal infection

The main skin diseases due to *S. aureus* are listed in Table 27.1.

Staphylococci cause infections by direct invasion of the skin, or by the release of toxins which may affect the skin or other organs.

Staphylococcus aureus and eczema. Staphylococcus aureus is very frequently isolated, often in heavy growth, from lesions of eczema, especially of atopic type. The extent to which the bacteria may play a pathogenic role in the eczema has been controversial, and may be difficult to assess in the individual case.

In true infective eczema, bacteria, including *S. aureus*, are regarded as the primary stimulus for an eczematous response, although the mechanisms are uncertain (Chapter 17).

Cytotoxic antibody and IgE reactions against bacterial (including *S. aureus*) antigens may be important in atopic and discoid eczema (Chapters 17 and 18) [47].

Staphylococcus aureus was isolated from 14 of 20 children with infantile seborrhoeic dermatitis, but its pathogenicity was uncertain [48].

Secondary colonization and infection have been studied most in atopic eczema; there is a high rate of staphylococcal carriage in this condition. When overt signs of infection

[49] are present, a pathogenic role is generally accepted. There is also evidence that high bacterial density (over $10^6/cm^2$) on lesions, short of overt signs of clinical infection, significantly aggravates the eczema [28]. The staphylococci may produce exotoxins with superantigenic properties, which may cause T-cell activation, cytokine release and mast cell degranulation [50].

The significance is still uncertain of reports in atopic eczema of impaired neutrophil chemotaxis [49], specific antistaphylococcal IgE [36], altered reactivity to protein A [51] and increased [52] or decreased [53] cell-mediated responses to staphylococcal extracts or antigens [34].

When bacteria are regarded as significant in a case of eczema, combined steroid and antibacterial therapy is appropriate [54,55].

Antibiotic resistance. The application of antibiotics to the skin with its large potential culture area and its resident flora may increase the likelihood of the development or the transfer of antibiotic resistance [56]. Of special importance is gentamicin resistance, which can be transferred between strains of *S. aureus*, and also between coagulase-negative staphylococci and *S. aureus* [56].

Gentamicin should not be used as a first-line topical antibiotic. Topical fusidic acid and mupirocin are associated with a low incidence of resistance when used to treat acute infections in the community setting. With prolonged use, the incidence of resistance increases. Fusidic acid resistance has been reported from a dermatology unit following cross-infection by a single strain [57].

During the past few decades, epidemics of methicillin-resistant *S. aureus* (MRSA) infection have increased in frequency throughout the world. Many hospitals have had to institute control measures to contain the spread of the infection [58]. Unfortunately, MRSA carriage may persist for years, and increases the risk of spread if patients who are carriers are readmitted to hospital [59]. Although the glycopeptides (vancomycin and teicoplanin) have been the agents of choice, some strains of MRSA are also now becoming resistant to these agents. Alternative therapies now include quinupritin/dalfopristin, a semi-synthetic streptogramin, and linezolid, an oxazolidinone antibacterial agent [60]. However, resistant enterococci have emerged already, and linezolid should only be used when other antibiotics have failed or are inappropriate because of bacterial resistance.

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Coagulase-negative staphylococci

These organisms are members of the normal skin flora and contribute to resistance against colonization by pathogenic bacteria [1].

Staphylococcus epidermidis [2–4] is the main pathogen of the group. In the otherwise healthy patient it is probably an occasional cause of minor skin infections including superficial folliculitis, although its significance in an individual case may be difficult to judge. Secondary infection of pre-existing dermatoses, such as eczema, seems not to occur. *Staphylococcus epidermidis* may cause infections in wounds and especially around implanted surgical devices. The ability to adhere to foreign bodies and produce extracellular slime during the course of colonization is thought to be important for pathogenicity [5]. As implantations become more frequent, these infections have increased and are recognized as a cause of major internal infections including endocarditis and septicaemia, especially in patients with immune deficiencies. A case of cellulitis in a woman with acute myelocytic leukaemia was reported [6], and the organism has been associated with vasculitis in a patient on cytotoxic therapy for ovarian carcinoma [7]. A single isolate of *S. epidermidis* from blood culture could be due to contamination, but if found repeatedly it may be regarded as probably significant. *S. saprophyticus* is a recognized cause of urinary tract infection, especially in young women [8].

Multiple antibiotic resistance is common and may be transferred to *S. aureus*.

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Streptococci

The streptococci are Gram-positive catalase-negative cocci characteristically arranged in chains. They are nearly all facultative anaerobes, i.e. they can grow aerobically or anaerobically [1,2].

Lancefield group antigens are the usual basis for routine classification of streptococci. There are at least 18 (A–R). The system covers not only the β-haemolytic streptococci, to which it was originally applied, but also some α-haemolytic and non-haemolytic (γ-haemolytic) organisms.

The involvement of streptococci in skin disease is summarized in Table 27.2.

Table 27.2 Involvement of streptococci (mostly group A) in cutaneous disease.

Direct infections of skin or subcutaneous tissue
Impetigo
Ecthyma
Erysipelas
Cellulitis
Vulvovaginitis
Perianal infection
Streptococcal ulcers
Blistering distal dactylitis
Necrotizing fasciitis
Others
Secondary infection
Eczema, infestations, ulcers, etc.
Tissue damage from circulating toxin
Scarlet fever
Toxic shock-like syndrome
Skin lesions attributed to allergic hypersensitivity to streptococcal antigens
Erythema nodosum (Chapter 49)
Vasculitis (Chapter 49)
Skin disease provoked or influenced by streptococcal infection (mechanism uncertain)
Psoriasis, especially guttate forms (Chapter 35)

Streptococcus pyogenes

The major streptococcal pathogens in humans belong to group A, collectively referred to as *Streptococcus pyogenes*. These may be subdivided according to M and T surface-protein antigens. The M proteins protect the organism against phagocytosis, affect adherence to different epithelial tissues and contribute to virulence. Lipoteichoic acid, expressed on the surface of group A streptococci, is involved in adhesion of the organism and extracellular products, including streptolysin O, hyaluronidase and pyrogenic exotoxins, and contribute to the virulence of the organism.

Carriage. Streptococcus pyogenes is carried in the throat by about 10% of the normal population and in the anterior nares less frequently. Natural antibiotic production by some other members of the throat flora may contribute to resistance to colonization by *S. pyogenes* [3], but carriage is often not eradicated by therapeutic antibiotics. Carriage rates are higher after clinical infection. However, in persistent throat carriers, the streptococci tend to lose their M proteins and consequently their virulence [4].

The normal skin does not provide a favourable habitat for *S. pyogenes*, perhaps due partly to a bactericidal effect of skin lipids [5], and transient skin carriage is found in only 0.5–1.0% of individuals [6]. However, the duration of survival of streptococci on the normal skin of patients with infections, and on the hands and arms of those handling such patients, may be sufficient to allow their dispersal by this route.

Asymptomatic anal carriage is an occasional source of significant infection in contacts [7].

Streptococci colonize damaged skin, although less readily than staphylococci. They can frequently be isolated from eczematous and other moist lesions, although the borderline between colonization and infection is often difficult to define.

Strains in skin and throat [8]. *Streptococcus pyogenes* can be divided broadly into 'throat' and 'skin' serotypes. Stronger adherence of the former to mucosal cells and of the latter to skin cells, and better survival of the latter in oleic acid and in nutritionally poorer media, may be relevant [9]. Throat strains survive poorly on skin and are infrequently found on the healthy skin even of patients with streptococcal throat infection. The strains isolated from normal skin are usually those common in streptococcal pyoderma: in a study of endemic disease [10], colonization of normal skin preceded the development of lesions in a majority of patients. Small numbers of skin strains may colonize the throat or the nose, but no streptococcal respiratory disease occurred among 1300 cases of streptococcal pyoderma in a military establishment [11].

Initiation and complications of infection. On experimental application under occlusion to intact normal skin, several strains of *S. pyogenes* failed to cause disease and indeed rapidly died; localized superficial infection occurred only if the skin had been scarified [12].

It is widely assumed that skin damage, albeit minor, is necessary for the development of naturally occurring streptococcal pyoderma.

Rheumatic fever is a complication of *S. pyogenes* pharyngitis, but occurs after pyoderma rarely if at all. The serotype of the organism does not appear to be relevant [5].

Acute glomerulonephritis follows both throat and skin infections with certain 'nephritogenic' serotypes of *S. pyogenes*. There are reports of glomerulonephritis infrequently following throat infections but apparently not skin infection with group C and group G streptococci [13–15].

Erythema nodosum and psoriasis are known to follow a streptococcal throat infection.

Scleredema of Bushke has also been linked with streptococcal infection of the throat.

Management of carriage and control of epidemics. The mere presence of *S. pyogenes* in an asymptomatic subject is not in itself an indication for attempts to eradicate it. Furthermore, such attempts are often unsuccessful [16].

Different approaches may be considered: surveillance of contacts of infected patients for clinical signs of infection;

instruction in hygiene and use of antiseptics; bacteriological investigation for carriage of the organism in patients and asymptomatic contacts with a view to antibiotic treatment of positive cases; and routine penicillin administration to those at risk without prior bacteriological investigation. Factors affecting the policy in individual cases include the extent of the outbreak, the closeness of contact, a special risk of infectivity by virtue of occupation [11], and the actual or expected risk of nephritis (and, for throat infections, rheumatic fever) [17,18]. Residents in nursing homes may be at risk of infections with *S. pyogenes* because of the propensity of the organism to cause disease in the elderly, and the ability of the organism to spread from person to person [19].

Other streptococci

Group C [20] streptococci are relatively frequently found colonizing diseased skin, but they are occasional causes of impetigo, erysipelas and cellulitis. Group G streptococci [21] colonize the pharynx, intestine, vagina or skin and may be implicated in the aetiology of cellulitis or erysipelas in patients with vascular disease or those who have undergone cardiac surgery and venous ligation [22].

Group B streptococci frequently colonize the anorectum (probably its natural habitat) [7,23,24] and, secondarily, the vagina. It is a major cause of severe infections, especially in neonates [24]. Group B streptococci may be associated with invasive disease in adults, particularly in patients with chronic disease.

In the skin, it appears to have a causal role in bacterial intertrigo, and may rarely cause erysipelas, cellulitis, necrotizing fasciitis and blistering distal dactylitis. Group F streptococci may be important secondary pathogens in suppurative hidradenitis.

Group D streptococci (enterococci) are usually harmless, but have uncommonly been implicated in cellulitis and necrotizing fasciitis. These organisms only cause infection in previously damaged tissues. More recently, the enterococci have been given genus status distinct from streptococci since they differ from streptococci in many respects [25].

Lancefield group L streptococci have been reported to cause skin sepsis in two meat handlers [26], and a facial abscess [27].

Of the α-haemolytic streptococci, *Streptococcus viridans* is commonly transferred to the skin of the face and hands from its normal habitat in the mouth; it seems to have little cutaneous significance.

Non-haemolytic streptococci are occasionally found as transients on the skin, but are feebly pathogenic under normal conditions.

Of the microaerophilic and the true anaerobic streptococci, some species can colonize wounds and are important in progressive bacterial synergistic gangrene and in some cases of necrotizing fasciitis [28].

Streptococcal serology [16,29]

Type-specific antibodies to the M proteins of group A streptococci persist for a few months or a year or two and protect against reinfection by the specific strain only.

The antistreptolysin-O (ASO) titre is an indicator of previous infection by streptococci of groups A, C or G. The upper limit of normal is 200 U/mL and highest titres range from 2000 to 3000 U/mL. In streptococcal skin infection; however, the ASO response is weak and an unreliable guide to diagnosis.

Similarly, antibody to nicotinamide adenine dinucleotidase (NADase) may indicate group A, C or G infection but is unreliable in skin infection.

Antibodies to deoxyribonuclease (DNase) B [30] and to hyaluronidase are more regularly raised in streptococcal skin disease. DNase B antibodies are probably specific for group A streptococci. One hyaluronidase antibody is specific for group A, and another for groups C and G jointly [29]. Susceptibility of neonates to group B streptococcal infection is related to the level of capsular-type-specific antibodies in the maternal serum [24].

In some countries where streptococcal infection is common, the ASO titre may be persistently elevated, so that raised titres may not be indicative of recent infection. More specific investigations may thus be required.

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Impetigo

Definition. Impetigo is a contagious superficial pyogenic infection of the skin. Two main clinical forms are recognized: non-bullous impetigo (or impetigo contagiosa of Tilbury Fox) and bullous impetigo. Bullous impetigo is accepted as a staphylococcal disease, although streptococcal bullous impetigo has been reported [1]. The non-bullous form may be caused by *Staphylococcus aureus*, by streptococci, or by both organisms together.

Bacteriology [2,3]. Non-bullous impetigo may be caused by both *S. aureus* and streptococci, but there has been controversy as to the relative importance of the two genera. This may partly depend on geographical variations, the streptococcal form being more prevalent in warmer climates. Some confusion may have been semantic, as some authors use the term pyoderma to apply to the streptococcal disease reflecting the clinical differences between the two forms, and others regard pyoderma and impetigo as synonymous. *Staphylococcus aureus* may be a secondary invader in streptococcal impetigo and in some such cases, depending on bacteriological techniques, it may be the predominant or the only isolate, and the evidence for streptococcal involvement may rest on serology [4].

Detailed studies of endemic pyoderma among children in the Red Lake Indian Reservation in northern Minnesota [5] detected both *S. aureus* and streptococci, each alone in a sizeable minority, but both together in 58% of cultures. Early lesions were more often purely streptococcal; in cases with both types the streptococci lasted longer, and the strain of *Staphylococcus* changed more often than that of the *Streptococcus*. The authors concluded that, in many of the mixed-culture cases, the disease was primarily streptococcal with *S. aureus* a secondary colonizer.

Recent publications suggest that the staphylococci may be the predominant infectious agent in most areas [6].

The preponderance of group II phage types seen in bullous impetigo seems also to apply to the non-bullous staphylococcal disease [3]. In streptococcal impetigo (streptococcal pyoderma) Lancefield group A is by far the commonest, but there are occasional infections with group G and group C organisms [5,7].

Bullous impetigo is a superficial cutaneous infection with *S. aureus*. The organism can generally be cultured from blister fluid. Injections of bacterial isolates from affected patients into newborn mice result in a generalized SSSS [8]. Epidermolytic toxin has been recovered from the blister fluid of some cases [9] and is accepted as the basis for the bulla formation. The toxin is produced commonly but not exclusively by staphylococci of phage group II. The localization of the epidermal splitting in bullous impetigo compared with the widespread involvement in the generalized form is probably related to local production of the toxin, whereas in SSSS the toxin is disseminated haematogenously [10].

Epidemiology. Pure staphylococcal non-bullous impetigo [3,6,11] is relatively frequent throughout the world, and large outbreaks often occur. It is commoner than the streptococcal disease in temperate climates. In warmer and more humid areas, for example the southern USA, the streptococcal form predominates and is endemic. The peak seasonal incidence is in late summer. Preschool and young school age children are most often affected. In adults, males predominate and large outbreaks may be troublesome in barracks and similar communities [12]. Although over-crowding, poor hygiene and existing skin disease, especially scabies, predispose to infection, many cases occur in previously healthy subjects with good living standards.

Streptococci isolated from fomites outside epidemics are frequently non-infective [13], but in epidemics, frequently handled materials like gymnasium equipment and room dust may be important in transmitting disease [12]. Biting insects may transfer the disease, but in addition small non-biting flies of the genus *Hippelates* can contribute to the rapid spread of the streptococcal infection in tropical and subtropical regions [14].

Bullous impetigo is usually sporadic, but clusters of cases may occur in families and other groups, and larger outbreaks are occasionally seen in institutions [15]. It is most

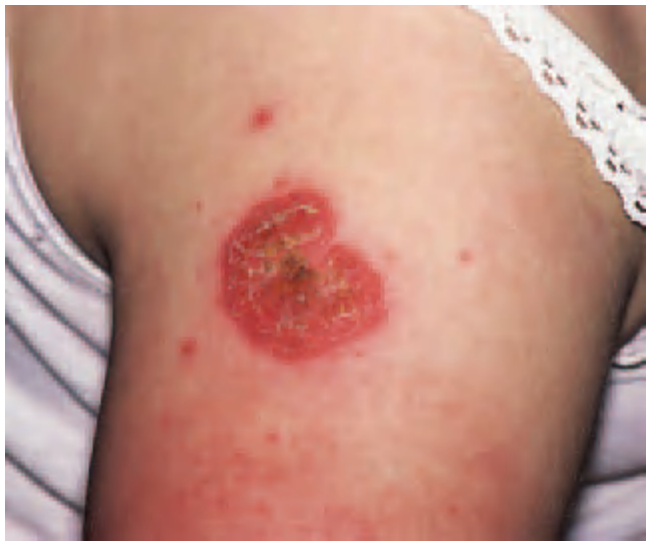

Fig. 27.1 Staphylococcal impetigo. (Courtesy of Dr A.S. Highet, York District Hospital, York, UK.)

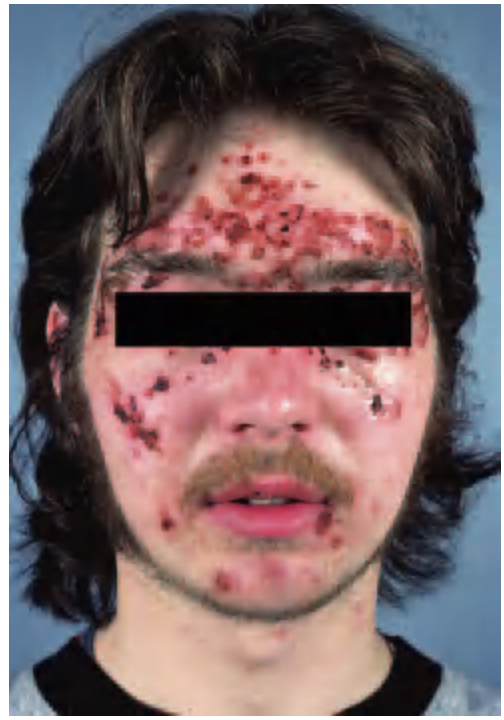

Fig. 27.2 Streptococcal (group A) pyoderma. (Courtesy of York District Hospital, York, UK.)

frequent in the summer months. Bullous impetigo occurs at all ages. It is said to be commoner in childhood but adult cases are probably under-reported [16]. In the newborn, bullous impetigo may be especially widespread and was formerly called pemphigus neonatorum (Chapter 14).

Minor abrasions and other skin lesions may predispose to infection if the patient or a contact carries an appropriate strain of staphylococcus [17]. An increased incidence in hospital workers has been noted [18].

Pathology. In *bullous impetigo*, the epidermis splits just below the stratum granulosum forming large blisters. Neutrophils migrate through the spongiotic epidermis into the blister cavity, which may also contain cocci. Occasional acantholytic cells may be seen, perhaps due to the action of neutrophils. The upper dermis contains an inflammatory infiltrate of neutrophils and lymphocytes. Cases with positive pemphigus-like antibodies on direct or indirect immunofluorescence have been reported [19–21].

The histology is similar for *non-bullous impetigo* except that blister formation is slight and transient.

Clinical features [6]. In *non-bullous impetigo*, the initial lesion is a very thin-walled vesicle on an erythematous base. The vesicle ruptures so rapidly that it is seldom seen as such. The exuding serum dries to form yellowish brown crusts. (Fig. 27.1) which are usually thicker and 'dirtier' in the streptococcal form (Fig. 27.2). Gradual irregular peripheral extension occurs without central healing, and multiple lesions, which are usually present, may coalesce. The crusts eventually dry and separate to leave erythema, which fades without scarring. In severe cases, there may be regional adenitis with fever and other constitutional symptoms. The face, especially around the nose and mouth, and the limbs are the sites most commonly affected, but involvement of the scalp is frequent in tinea capitis, and lesions may occur anywhere on the body, especially in children with atopic dermatitis or scabies. Involvement of the mucous membranes is rare. There is a tendency to spontaneous cure in 2–3 weeks but a prolonged course is common, particularly in the presence of underlying parasitic infestations or eczema, or in hot and humid climates. In heavily pigmented skin, the lesions may be followed by temporary hypopigmentation or hyperpigmentation.

In *bullous impetigo*, the bullae are less rapidly ruptured and become much larger; a diameter of 1–2 cm is common but they may be of very considerable size, and persist for 2 or 3 days. The contents are at first clear, later cloudy. After rupture thin, flat, brownish crusts are formed. Central healing and peripheral extension may give rise to circinate lesions (Fig. 27.3). Although the face is often affected, the lesions may occur anywhere, and may be widely and irregularly distributed, often favouring the sites of existing skin disease, especially miliaria or trivial injuries such as insect bites. The buccal mucous membrane may be involved. Commonly, rather few lesions are present, but the picture is very variable. Regional adenitis is rare.

Complications [22]. Infective complications are uncommon in the absence of systemic disease or malnutrition,

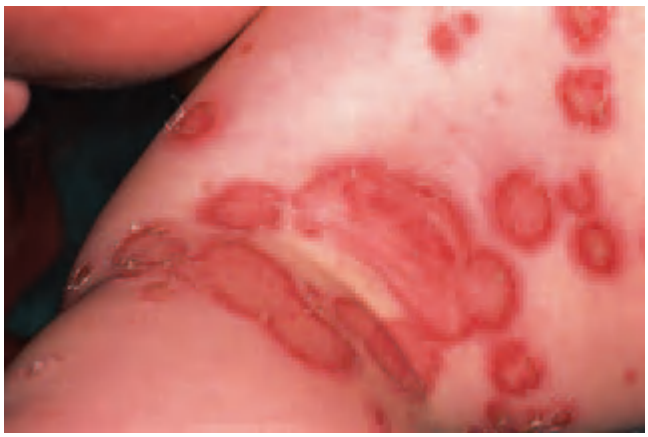

Fig. 27.3 Bullous impetigo after disruption of bullae.

although deeper infections like cellulitis occasionally occur with the streptococcal disease.

Streptococcal impetigo accounts for the majority of cases of post-streptococcal acute glomerulonephritis (AGN) [11,23]. The incidence of AGN in different series of patients with streptococcal impetigo depends on the nephritogenic potential of the infecting strain. Some never cause nephritis [12], but 25% of patients with pyoderma due to *S. pyogenes*, type M-49 are affected. The overall incidence of post-streptococcal AGN has declined in recent decades. The latent period for development of nephritis after streptococcal pyoderma is 18–21 days, compared with about 10 days for throat infection, raising the unproven possibility that early treatment of skin infection might offer a better chance of preventing the renal disease.

Scarlet fever, urticaria and erythema multiforme may follow streptococcal impetigo [22].

Rheumatic fever is not a complication of streptococcal impetigo [11,24].

Treatment. In mild and localized infection, a topical antibiotic alone may suffice. Topical mupirocin is an effective antibiotic with a low incidence of adverse effects and, in localized disease, may equal oral erythromycin [25]. Fusidic acid is also effective against both organisms, but in order to reduce the likelihood of the development of resistance because of its value in systemic infection, it may be prudent to restrict its use as first-line topical therapy to the community if suitable alternatives are available. Topical neomycin is effective in staphylococcal infections, but less active against streptococci; bacitracin has activity against both, and the two drugs are often used in combination.

If the infection is widespread or severe, or is accompanied by lymphadenopathy, or if there is reason to suspect a nephritogenic *Streptococcus*, an oral antibiotic such as flucloxacillin or erythromycin is indicated [6]. Local patterns of resistance need to be considered, as resistance of *S. aureus* to penicillin, erythromycin and to tetracycline is now common even in developing countries. The addition of a topical antibiotic or antiseptic is likely to hasten the response and help to limit the spread of infection.

Antiseptics are less effective than appropriate antibiotics but are a useful adjunct to systemic treatment, and are a rational sole therapy for impetigo where antibiotics are unavailable. Either chlorhexidine or povidone–iodine would be suitable.

Removal of infected crusts is bacteriologically and cosmetically helpful. Frequent application of an ointment, preferably containing an antibacterial agent, and washing with soap and water are as effective as messier regimens.

In developing countries where impetigo is endemic among children, measures to reduce the transmission frequency of infections should be adopted. These include installing indoor water supplies, distributing medical resources more efficiently, educating the population on health matters and instituting treatment early in the course of the disease. Emphasis should be placed on the identification of predisposing factors such as insect bites, pediculosis, scabies and minor trauma.

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Ecthyma

Definition. Ecthyma is a pyogenic infection of the skin characterized by the formation of adherent crusts, beneath which ulceration occurs.

Aetiology. The bacteriological status of ecthyma is essentially similar to that of impetigo. It was formerly regarded as a streptococcal infection, since many cases yield a pure culture of *Streptococcus pyogenes*. From others both streptococci and staphylococci are isolated, and from some staphylococci only. Group A streptococci were grown from all of 66 cases, and coagulase-positive staphylococci from 85% of these [1]. It may prove to be a synergistic infection. In Europe, most cases occur in children, but in the tropics, where the disease is very much more common, it may occur at any age. Poor hygiene and malnutrition are predisposing factors, and minor injuries or other skin conditions, particularly scabies, may determine the site of the lesions. Several of these predisposing factors, may coexist in drug addicts.

Clinical features. Small bullae or pustules on an erythematous base are soon surmounted by a hard crust of dried exudate (Fig. 27.4), which increases in size by peripheral accretion. The base may become indurated and a red oedematous areola is often present. The crust is removed with difficulty, to reveal a purulent irregular ulcer. Healing occurs after a few weeks, with scarring. The lesions are usually few but new lesions may develop by autoinoculation over a long period. The buttocks, thighs and legs are most commonly affected.

Treatment. Improved hygiene and nutrition, and the treatment of scabies and any other underlying disease, are important. The antibiotic chosen should be active against both *Streptococcus pyogenes* and *Staphylococcus aureus*.

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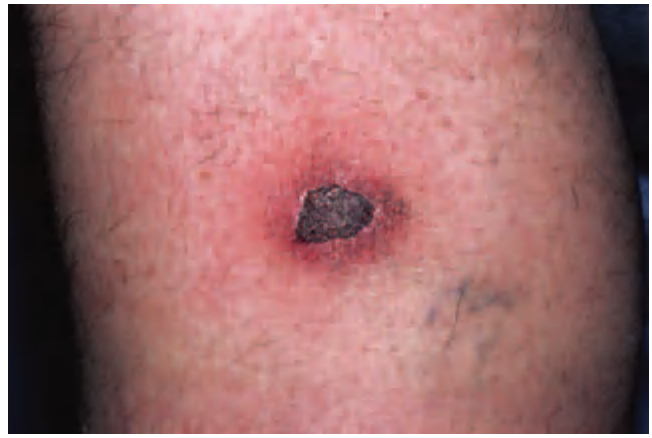


Fig. 27.4 Ecthyma. (Courtesy of Dr A.S. Highet, York District Hospital, York, UK.)

Cellulitis and erysipelas

Definition. Cellulitis is strictly an acute, subacute or chronic inflammation of loose connective tissue, but the term has been applied mainly to inflammation of subcutaneous tissue in which an infective, generally bacterial, cause is proven or assumed. Erysipelas is a bacterial infection of the dermis and upper subcutaneous tissue; its hallmark is a well-defined, raised edge reflecting the more superficial (dermal) involvement. However, cellulitis may extend superficially and erysipelas deeply so that in many cases the two processes coexist and it is impossible to make a meaningful distinction. Current usage tends to regard erysipelas as a form of cellulitis rather than a distinct entity, so that the definition of cellulitis would include inflammation of dermal as well as subcutaneous tissue. The closely similar bacteriology of the two conditions [1,2], and the demonstration of streptococcal antigens in both dermis and subcutis in both conditions [1], support this view. However, the two terms are still sometimes used in the traditional sense, especially when their typical distinctive features are being contrasted. Erysipelas is classically a facial infection, but, as defined above, it is not confined to the face, and the authors do not support the definition [3] of erysipelas as simply cellulitis of the face.

Bacteriology. Bacteria are present in affected tissue in small numbers, and attempts to culture them, from biopsy material, from swabs of biopsy sites, from needle aspiration of saline-injected tissue, and even from fluid from blisters or erosions when present, are often unsuccessful. Blood cultures and swabs from possible entry sites, for example wounds or inflammatory lesions, generally situated distally to the infection, occasionally yield presumably relevant organisms. Cultures of biopsy specimens, needle aspirates and probable sites of entry in 50 patients

with cellulitis gave a positive result in only 26% [4]. Streptococcal serology may be helpful retrospectively [2], and immunofluorescence may identify streptococcal group antigens in biopsy specimens [1].

These studies confirm the traditional view that cellulitis and erysipelas in the immunologically normal patient are predominantly streptococcal diseases, usually involving group A organisms, but they have also demonstrated streptococci of other Lancefield groups, especially G but also C and B, in both conditions. Group B infections are seen especially under the age of 3 months [5,6]. In adults, group B streptococci may cause pelvic erysipelas especially after surgery [7]. In cellulitis (as opposed to erysipelas), *Staphylococcus aureus* is occasionally implicated alone or together with a *Streptococcus*. There is a suspicion [2] that a primary pathogenic role should not be accepted for it in all cases, as in that study all cases treated with benzyl-penicillin improved rapidly even when *Staph. aureus* was detected; however, detailed accounts of bacterial sensitivities and individual responses to treatment were not given. *Staphylococcus aureus* is occasionally isolated from lesions of erysipelas. However, in three cases out of 27 in which it was the sole isolate, there was serological evidence of streptococcal infection [1]; and another two cases responded slowly to penicillinase-sensitive penicillins in keeping with a streptococcal cause [8]. *Staphylococcus aureus* should be regarded as an occasional cause of cellulitis, but rarely if at all of classical erysipelas. *Haemophilus influenzae* type b is an important cause of facial cellulitis in young children, especially up to the age of 2 years [9–11], but rarely causes cellulitis in adults [12].

In cellulitis in a setting of venous or lymphatic compromise, including limbs on which saphenous venectomy has been performed, non-group-A streptococci, especially group G, predominate [13].

Other bacteria. A variety of other bacteria are occasionally implicated in cellulitis and erysipelas, usually in specific situations of exposure or in immunocompromised patients.

Thus, while the bacteriology of periorbital cellulitis is similar to that in other sites, orbital cellulitis that usually results from sinusitis involves the major sinus pathogens, i.e. *Strep. pneumoniae*, other streptococci, *Staph. aureus*, *H. influenzae* and penicillin-sensitive anaerobes [2]. Cellulitis due to *Aeromonas hydrophila* can complicate injuries contaminated by water (usually fresh) or soil [14]. A case of cellulitis due to the marine organism *Vibrio alginolyticus* has been recorded [15]. Cellulitis is part of the spectrum of infection due to *Pasteurella multocida* inoculated by animal bites [16].

Erysipelas-like infections and cellulitis due to *Strep. pneumoniae* [17,18], *Pseudomonas aeruginosa* [19] and *Campylobacter jejuni* [20] have been reported, mostly in the immunocompromised. In such patients, *P. aeruginosa* may cause gangrenous cellulitis and ecthyma gangrenosum [21,22]; and cellulitis may be caused by *Acinetobacter calcoaceticus* [23] and *Staph. epidermidis* [24]. A case of *Bacteroides fragilis* cellulitis responding to metronidazole has been reported [25]. *Yersinia enterocolitica*, an intestinal pathogen, may also cause cellulitis [26].

Clinical features (Fig. 27.5). Erythema, heat, swelling and pain or tenderness are constant features. In erysipelas, the edge of the lesion is well-demarcated and raised, but in cellulitis it is diffuse, although cases showing both types of edge or an intermediate picture are not uncommon. In erysipelas, blistering is common, and there may be superficial haemorrhage into the blisters or in intact skin, especially in elderly people. Severe cellulitis may show bullae and can progress to dermal necrosis (Fig. 27.6), and uncommonly to fasciitis or myositis. Lymphangitis and lymphadenopathy are frequent. Except in mild cases, there is constitutional upset with fever and malaise. Classical erysipelas starts abruptly and systemic symptoms may be acute and severe, but the response to treatment is more rapid.

The leg is the commonest site, and here there is usually a wound, even if superficial, an ulcer or an inflammatory lesion, including interdigital fungal or bacterial infection, which can be identified as a possible portal of entry. The next most frequent site for classical streptococcal erysipelas is the face, where a traumatic entry site is less commonly seen and where bilateral infection occasionally occurs.

Without effective treatment, complications are common —fasciitis, myositis, subcutaneous abscesses, septicaemia and, in some streptococcal cases, nephritis—and the more severe infections may be fatal, especially in infants and in the debilitated or immunosuppressed.

Childhood facial cellulitis due to *H. influenzae* type b is typically unilateral and often associated with ipsilateral otitis media, the presumed source in those cases. The patient presents with systemic illness and the affected cheek or periorbital tissue shows induration and discoloration, occasionally pink, but characteristically purplish blue. A similar violaceous colour may occur in childhood periorbital and buccal pneumococcal cellulitis [27].

Otherwise, periorbital cellulitis follows trauma to the eyelids or local skin sepsis and is usually streptococcal, occasionally staphylococcal. If the infection is behind the orbital septum, in the deeper orbital tissues, the term orbital cellulitis applies, and it is commonly a sequel to sinusitis, although it is to be distinguished from the periorbital oedema which may also accompany sinus infection. In addition to cutaneous signs, proptosis, ophthalmoplegia and loss of visual acuity may occur. Periorbital and orbital cellulitis may be complicated by cavernous sinus thrombosis, orbital, subperiosteal or cerebral abscess formation, or meningitis [11,28].

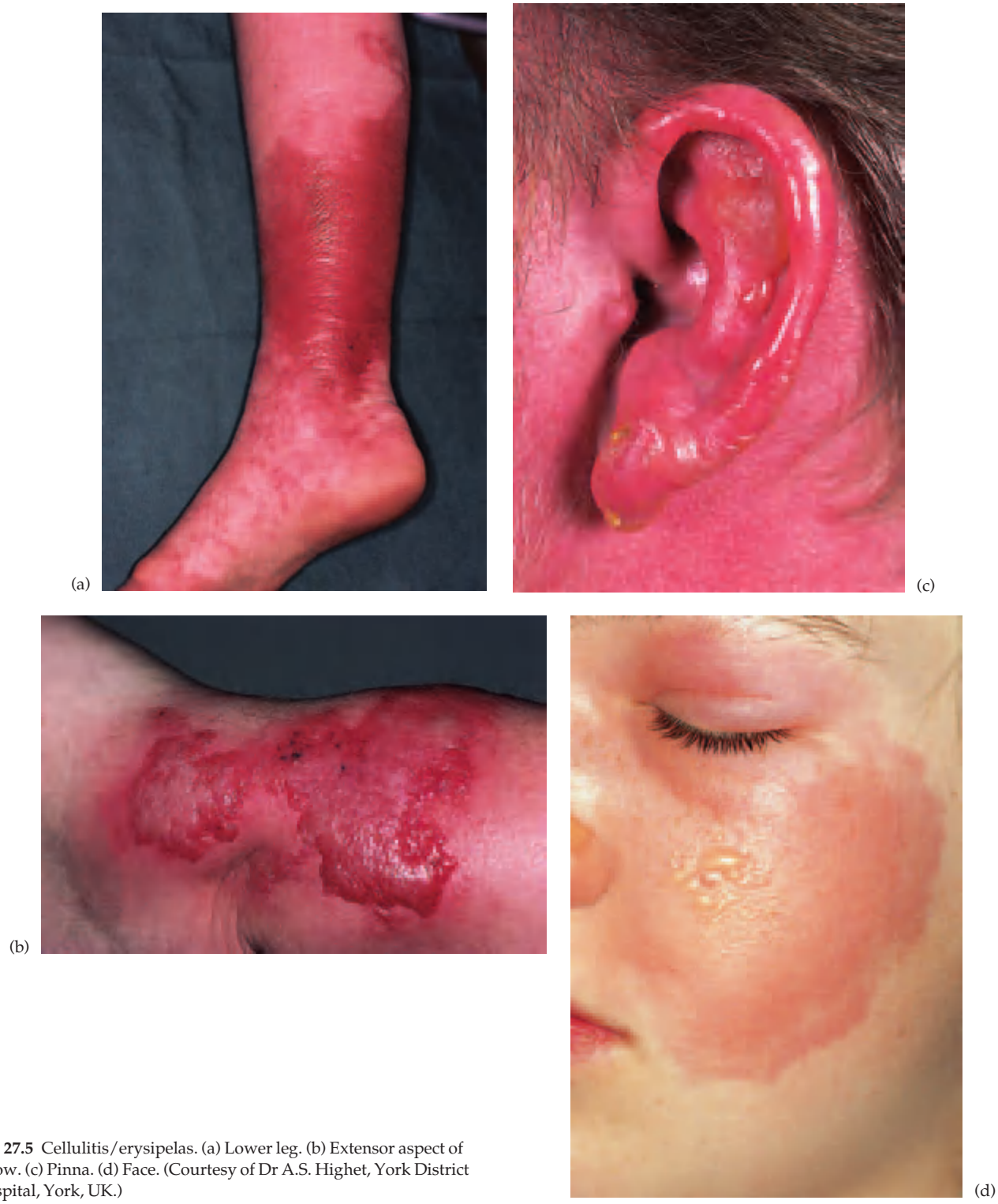


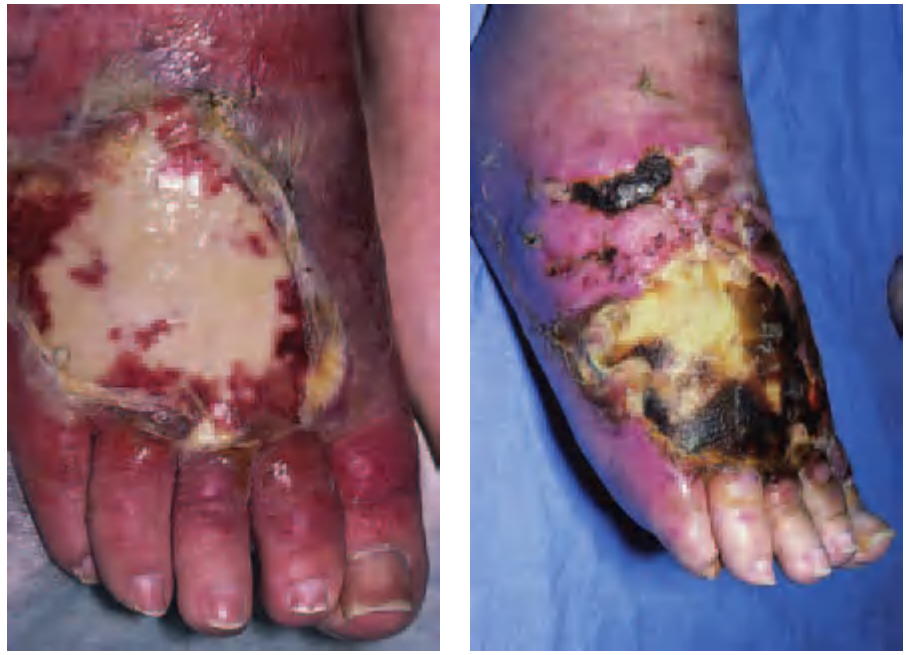
Fig. 27.5 Cellulitis/erysipelas. (a) Lower leg. (b) Extensor aspect of elbow. (c) Pinna. (d) Face. (Courtesy of Dr A.S. Highet, York District Hospital, York, UK.)

Severe myocardial depression has been reported in a previously healthy young woman with streptococcal cellulitis [29].

Cellulitis of the tongue in neutropenic patients may cause upper airway obstruction [30].

In the immunodeficient, the presentation may be atypical, as in two cases of erysipelas without erythema [31], and previous antibiotic treatment may modify the clinical appearances in the otherwise healthy patient.

Recurrent streptococcal cellulitis (or erysipelas) is attributed to lymphatic damage, which, although sometimes initially clinically inapparent, predisposes to further



(a) (b)

Fig. 27.6 (a) Cellulitis with early dermal necrosis. (b) The same foot after 11 days; the dermis is forming a black eschar, which eventually sloughed off; the resulting ulcer healed rapidly. (Courtesy of York District Hospital, York, UK.)

infection and further lymphatic impairment manifesting as lymphoedema (Fig. 27.7). Venous insufficiency often predisposes to recurrent erysipelas of the leg [32].

Perianal streptococcal infection is discussed in Chapter 68.

Diagnosis. Specimens for bacteriological examination should be taken from vesicle fluid or eroded or ulcerated surfaces, in addition to blood cultures. Exudative, fissured or traumatized sites distal or adjacent to limb infections may yield relevant organisms. Surface swabs from intact skin are unlikely to be helpful, but in the case of facial infections the pathogen should be sought in nose, throat, conjunctiva and sinuses. Aspiration of tissue fluid, alone or following subcutaneous infiltration of saline, occasionally results in a positive culture, but is not routinely recommended. Skin biopsy is often similarly disappointing. Identification of soluble streptococcal antigens is more effective [1]. If either of these invasive techniques is considered, care should be taken not to penetrate the fascia. However, as discussed earlier, even a combination of such techniques commonly fails to yield the pathogen, and the possibility of contamination must be remembered [1,2,4].

Serological studies may provide evidence of streptococcal, and less commonly staphylococcal, infection. An initial high titre may be regarded as suggestive, especially in a patient presenting several days or more after the onset, but paired sera from days 1 and 14 would be more reliable in retrospective diagnosis. Early use of antibiotics may, however, limit the antibody response. The antibodies and their significance are discussed below.

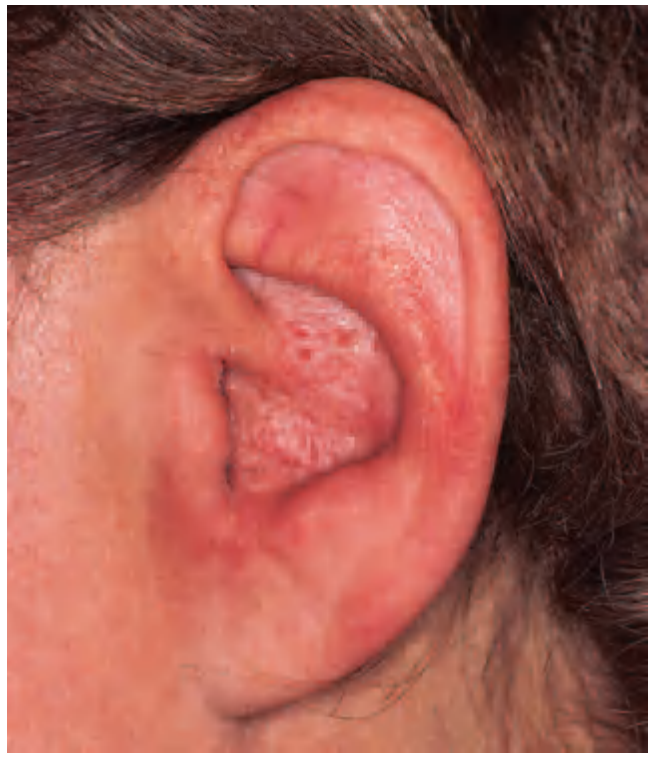


Fig. 27.7 Post-streptococcal lymphoedema of pinna; this patient had frequent recurrences of cellulitis requiring long-term penicillin. (Courtesy of Dr A.S. Highet, York District Hospital, York, UK.)

In differentiating cellulitis of the leg from deep-vein thrombosis, phlebography, plethysmography and Doppler ultrasound examination may be helpful. The protein concentration in 0.3–0.5 mL of oedema fluid aspirated from

swollen subcutaneous tissue provides a rapid and inexpensive alternative; in deep-vein thrombosis the average concentration was 5.5 g/L while in cellulitis it was 19.8 g/L; a level over 10 g/L was found only in cellulitis [33].

Fungi may cause cellulitis in the immunocompromised [34].

A cluster of cases closely resembling cellulitis, but bacteriologically negative and unresponsive to antibiotics, was attributed to insect bites, plant toxins or an unidentified virus [35].

Treatment. A clinical assessment as to the likely pathogen(s), as discussed earlier, should guide the initial choice of treatment. Appropriate antibiotic(s) should be given in full dosage, by the intramuscular or intravenous route in the more severe cases that are associated with septicaemia, arthritis or suspected fasciitis, although oral treatment may suffice for the milder infections. In all cases, initial treatment should cover streptococci and, for facial infections in young children, *H. influenzae*. For presumed streptococcal infections, penicillin is the treatment of choice, given as benzylpenicillin 600–1200 mg i.v. 6-hourly in the more severe cases. Treatment should be continued for at least 10 days. A macrolide antibiotic or clindamycin are alternatives [36]. Anticoagulant therapy should be considered if there is associated thrombophlebitis. A wider range of organisms should be considered in patients with deficient immunity, in the special situations discussed earlier and in those not responding to initial treatment.

In recurrent cases, long-term penicillin, 500–2000 mg daily can prevent attacks. Vigorous treatment of any local skin damage is important to prevent recurrent disease. In patients allergic to penicillin, an alternative drug, such as clindamycin or erythromycin, should be taken. Some patients may require lifelong prophylaxis [37].

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Inflammatory diseases of hair follicles

Staphylococcus aureus, coagulase-negative staphylococci and physical or chemical irritation are common causes of superficial folliculitis. The deeper forms of staphylococcal folliculitis, furuncles and carbuncles are discussed separately.

Other microbial causes of folliculitis are considered elsewhere: *Pseudomonas aeruginosa* later in this chapter; Gram-negative folliculitis developing in antibiotic-treated acne in Chapter 43; *Pityrosporum* yeasts in Chapter 31; and dermatophytes in Chapter 31. Patients with human

immunodeficiency virus (HIV) disease may have 'itchy folliculitis' of uncertain cause (Chapter 26).

Pseudofolliculitis due to ingrowing hairs is discussed below and in Chapter 22.

There are, however, a number of inflammatory diseases involving the hair follicle whose aetiology is complex or uncertain; although the role of bacterial infection may be partial, secondary, unknown or absent, these disorders are included in this chapter for convenience: sycosis barbae, folliculitis cheloidalis, acne necrotica, perforating folliculitis, trunk folliculitis, actinic folliculitis, disseminate and recurrent infundibulofolliculitis, eosinophilic pustular folliculitis, suppurative hidradenitis and perifolliculitis capitis. Folliculitis decalvans is considered in Chapter 63.

Superficial folliculitis

Subacute or chronic folliculitis, in which the inflammatory changes are confined to the ostium or extend only slightly below it, and which heals without scar formation, is an extremely common condition, but is usually of such little clinical importance that it has not been thoroughly investigated.

Superficial folliculitis is not always primarily or exclusively infective in origin. Physical or chemical injury to the skin may be associated with a folliculitis, the pustules of which may be sterile or may contain coagulase-negative staphylococci. Occupational contact with mineral oils or therapeutic or occupational exposure to tar products very typically produce such lesions, which in the case of oil folliculitis are associated with conspicuous oil plugging of many follicles. Other chemical irritants can cause folliculitis, which may be the only visible change, or may accompany an eczematous reaction. Beneath adhesive plasters or adhesive dressings, a sterile folliculitis is common. Following epilation, a traumatic folliculitis may develop [1].

Occasional isolated lesions are also frequent on the neck and beard, and heal so rapidly, that they are commonly ignored. Also frequent, but more persistent, are papules or pustules on the thighs and buttocks of adolescent and young adult males, and occasionally females, especially those with acne. They are usually too few and small to have attracted the patient's attention. On culture, the pustules may be sterile, but coagulase-negative staphylococci are sometimes isolated. Clinically, the lesions present as small, follicular papules or pinhead pustules. They are rarely painful. Sometimes, small crusts cover a red, pouting, follicular orifice.

Staphylococcus aureus superficial folliculitis (follicular impetigo of Bockhart) is an infection of the follicular ostium with *S. aureus*. Use of topical steroids, especially of the stronger grades, is a predisposing factor. Otherwise, it is commonest in childhood, and occurs mainly in the scalp or scalp margins or on the limbs. The individual lesion is a domed, yellow pustule, sometimes with a narrow, red areola. The pustules develop in crops and may heal within 7–10 days, but sometimes become chronic. In older children and adults, the infection may extend more deeply in some follicles as furuncles or as sycosis. In some cases, recurrent or chronic staphylococcal folliculitis may merge imperceptibly with folliculitis decalvans and related processes (Chapter 63). However, acute staphylococcal folliculitis is common and the many clinical variants of cicatrizing folliculitis are rare.

Chronic folliculitis of the legs [2,3] has been described mainly in young adult males in India. The profuse eruption of superficial and deep follicular pustules on the thighs and lower legs persisted for many years and was resistant to treatment. *Staphylococcus aureus* was regularly isolated. No systemic abnormality could be detected other than hypergammaglobulinaemia. The pustular dermatitis atrophicans of the legs [4], described as accounting for 0.5% of skin disease in Lagos in West Africa, appears to be a similar condition. It occurs predominantly in males and affects symmetrically the anterior tibial surfaces of the legs, sometimes involving thighs and forearms. Miliary pustules are followed by atrophic scars.

Diagnosis. Follicular pustules are readily confused by the inexperienced with the non-follicular lesions of pustular miliaria, which should be considered when a widespread papulopustular eruption develops in hot and humid conditions, on previously normal skin, or studding an existing inflammatory dermatitis. Follicular pustules are also a feature of subcorneal pustular dermatosis, in which they are grouped around the margins of plaques of erythema and scaling (Chapter 41).

Follicular pustules may occur in ringworm. The more-or-less simultaneous development of pustules on a circumscribed, red and oedematous or scaling plaque should arouse suspicion.

Treatment. Superficial folliculitis of external chemical or physical origin will settle if the irritant is removed.

Mild staphylococcal folliculitis is often self-limiting, or may respond to cleansing or topical antiseptics. In more severe cases, antibiotics, topical or systemic, may be required. If the infection is persistent or recurrent, the usual sites of staphylococcal carriage should be sought in the patient and his or her contacts.

Daily application of 6.25% aluminium chloride hexahydrate in completely anhydrous ethyl alcohol was reported to be very effective treatment for chronic folliculitis of unspecified type, except for scalp lesions [5].

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Pseudofolliculitis

SYN. PILI INCARNATI

Aetiology [1]. Inflammation results from penetration into the skin of sharp tips of shaved hairs. If shaven too long, or if it escapes shaving for a few days, the hair may curve backwards after emerging from the follicle to penetrate the adjacent skin [2]; conversely, if cut very short so that it retracts into the follicle, it may directly penetrate the follicle wall [3].

Curly hair is more liable to both of these aberrations so that the condition is very common and more severe in black people [2]. Skin folds or irregularities due to scarring may allow ingrowth of straight hairs. Any shaved surface in either sex [4], may be affected, but the male beard area is naturally the most common. Plucking may cause pseudofolliculitis [5,6]. There is evidence of genetic predisposition [7].

Coagulase-negative staphylococci may sometimes be grown from the lesions but the condition is not primarily infective.

Clinical features (Fig. 27.8). The patient complains of minor discomfort and cosmetic embarrassment from papules and pustules on shaven skin. In the beard area, the skin of the neck and over the jaw is most commonly affected, although in black people lesions on the cheeks are also frequent. The papules may be large in black individuals: scarring, keloid formation and hyperpigmentation may ensue. It is generally possible to identify some penetrating hairs but they may not be visible in all cases.

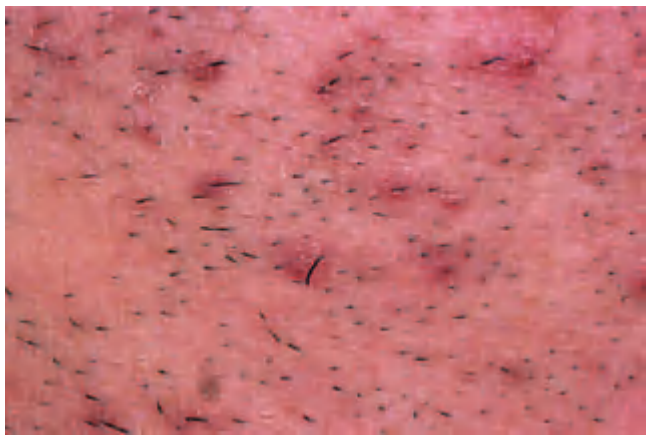

Fig. 27.8 Pseudofolliculitis.

Pseudofolliculitis of the scalp was reported in four brothers who were black and whose father had shaved their scalps [8]. Cut nasal hairs may ingrow similarly [9].

Treatment [1,10]. The only certain cure is to stop shaving for a minimum of 4–6 weeks, but resumption of shaving will lead to relapse. Lifting out of re-entrant hairs with a needle is helpful but tedious: brushing with an abrasive sponge or toothbrush is less effective but quicker. Hair should be left about 1 mm long. This may be achieved by adjustment of individual shaving technique, or by specially designed razors [11] or electric clippers. Plucking should be avoided. Some relief is possible with topical steroid–antimicrobial combinations combined with intensive use of emollients.

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Furuncle

SYN. BOIL

Definition. A furuncle is an acute, usually necrotic, infection of a hair follicle with *Staphylococcus aureus*.

Aetiology. Furuncles are relatively uncommon in early childhood in temperate climates except in atopic subjects, but increase rapidly in frequency with the approach of puberty, and in adolescence and early adult life are a common disability [1]. In adolescence, boys are affected more than girls and the peak incidence parallels that of acne vulgaris. In the UK, furunculosis occurs mostly during the early winter months [2]. As with other superficial staphylococcal infections, the factors responsible for the outbreak and its persistence are unknown. There is seldom any evidence of impairment of the immune response. Reports on the possibility of impairment of neutrophil function are conflicting [3,4]. The infecting strain

of *Staphylococcus* is usually also present in the nares or the perineum [5], which may imply that the repeated and heavy inoculation that occurs in the chronic carrier may be a necessary condition for the development of furunculosis. The surface defence mechanism, and hence the normal balance of microflora, may be disturbed in favour of the staphylococci, which may be carried for some months in the neighbourhood of recently healed lesions. From the sites of carriage, the infection is disseminated by the fingers and by clothing. Mechanical damage to the skin, even the friction of collars and belts, may determine the distribution of the lesions. Malnutrition is an important predisposing factor in some countries. Diabetes is widely believed to predispose to furunculosis, although the published evidence does not uniformly confirm this [6]. Furunculosis is common in patients infected with HIV (Chapter 26). Hyper-IgE syndrome is also a predisposing factor [7]. However, in a high proportion of cases in healthy young adults, no convincing predisposing factor can be incriminated.

Epidemics of furunculosis attributable to specific strains of staphylococci have occurred, and in such cases the attacks are often severe but short, and obvious predisposing factors are usually absent. From the very common, milder, persistent and recurrent cases a wide variety of strains common to many types of staphylococcal infection may be grown, and predisposing factors must be assumed to be of relatively greater significance, although their nature is often difficult to establish. The observation of families over a period of years showed that the same phage type may be responsible for irregular episodes of infection between long intervals of clinical quiescence [1].

Pathology. A furuncle is an abscess of a hair follicle, usually of vellus type. The perifollicular abscess is followed by necrosis with destruction of the follicle.

Clinical features. A furuncle first presents as a small, follicular, inflammatory nodule, soon becoming pustular and then necrotic, and healing after discharge of a necrotic core to leave a violaceous macule and, ultimately, a permanent scar. The rate of development varies greatly, and necrosis may occur within 2 days or only after 2 or 3 weeks. Tenderness is invariable, and in the more acute and larger lesions there may be throbbing pain. Lesions in the nose or external ear canal can cause very severe pain. The lesions may be single or multiple, and tend to appear in crops. Occasionally, there may be fever and mild constitutional symptoms. Pyaemia and septicaemia are favoured by malnutrition. On the upper lip and cheek, cavernous sinus thrombosis is a rare and dangerous complication.

The sites commonly involved are the face and neck, the arms, wrists and fingers, the buttocks and the anogenital region.

Attacks may consist of a single crop, or of multiple crops, at irregular intervals with or without periods of freedom. The prognosis cannot be reliably determined during a first attack. In some individuals, crops continue to develop for many months, or even years.

In HIV disease, furuncles may coalesce into violaceous plaques [8] (Chapter 26).

Diagnosis. Other pustular lesions must be differentiated. Furuncles are deep-seated nodules, in contrast to the lesions of superficial staphylococcal folliculitis. The vesicopustules of disseminated herpes simplex are umbilicated and appear simultaneously in large numbers on sites of active or healed eczema (Chapter 18).

The pustules of acne are but one type of lesion in a polymorphic syndrome. They are associated with papules and comedones, and are usually confined to the face and trunk. Pustules can also occur in halogen eruptions (Chapter 73), usually symmetrical and of rapid onset. Nodules and abscesses occur mainly in the axillae and perineum in hidradenitis. Single or few, large, suppurating nodules on exposed skin raise the possibility of myiasis.

Prognosis. The course of the untreated disease is infinitely variable [1] and the prognosis cannot be reliably determined during a first episode. Some patients suffer only one attack while others continue to develop recurrences over months or years, with or without periods of freedom.

Treatment. Each episode may need to be treated systemically with flucloxacillin or another penicillinase-resistant antibiotic. A topical antibacterial agent reduces contamination of the surrounding skin. Occlusive dressings should be avoided.

In recurrent disease [9], further lesions develop after the end of each course of antibiotic. It may be prudent in these cases to exclude diabetes and other possible underlying conditions. Nasal and perineal carriage of *S. aureus* in the patient and other household members should be sought; the management of carriers is discussed earlier in this chapter. Low-dose clindamycin may be helpful [10].

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Carbuncle

Nomenclature. In French, Spanish and some other Latin languages, 'anthrax' is the term commonly applied to a carbuncle, whilst 'charbon' (French), or a similar related word, describes infection with *Bacillus anthracis*.

Aetiology. A carbuncle is a deep infection of a group of contiguous follicles with *Staphylococcus aureus*, accompanied by intense inflammatory changes in the surrounding and underlying connective tissues, including the subcutaneous fat. Carbuncles occur predominantly in men, and usually in middle or old age. They may be seen in the apparently healthy but are more common in the presence of diabetes, malnutrition, cardiac failure, drug addiction or severe generalized dermatoses, such as exfoliative dermatitis or pemphigus, and during prolonged steroid therapy.

Clinical features. The term carbuncle is derived from the Latin word for a small, fiery coal, and describes the painful, hard, red lump that is the initial stage of the infection. It is at first smooth, dome-shaped and acutely tender. It increases in size for a few days, to reach a diameter of 3–10 cm or occasionally more. Suppuration begins after some 5–7 days, and pus is discharged from the multiple follicular orifices. Necrosis of the intervening skin leaves a yellow slough surmounting a crateriform nodule. In some cases, the necrosis develops more acutely without a preliminary follicular discharge, and the entire central core of the lesion is shed, to leave a deep ulcer with a purulent floor.

Most lesions are on the back of the neck, the shoulders or the hips and thighs and, although usually solitary, they may be multiple or associated with one or more furuncles.

Constitutional symptoms may accompany, or even precede by some hours, the development of the carbuncle. Fever may be high, and malaise and prostration may be extreme if the carbuncle is large or the patient's general condition poor.

In favourable cases, healing slowly takes place to leave a scar. In the frail and ill, death may occur from toxaemia or from metastatic infection.

Diagnosis. Anthrax presents the only important problem. In the typical case, the haemorrhagic crust and the vesicular margin are quite unlike a carbuncle, but sometimes certain clinical differentiation is difficult. A swab must be taken, but treatment should not be postponed until bacteriological confirmation is available.

Treatment. Flucloxacillin or another penicillinase-resistant antibiotic should be given. Diabetes and other possible underlying conditions should be sought.

Sycosis

Definition and nomenclature. Sycosis is a subacute or chronic pyogenic infection involving the whole depth of the follicle. If the follicles are destroyed with clinically evident scarring, the term lupoid sycosis, or its cumbersome synonym ulerythema sycosiforme, is applied. Folliculitis decalvans (Chapter 63) is essentially the same process involving the scalp. Many sites may be involved in the same individual.

Aetiology. Sycosis occurs only in males after puberty, and commonly involves the follicles of the beard. Most cases begin in the third or fourth decade, but we have seen a severe infection in a boy aged 14 years. The infecting organism is *Staphylococcus aureus*, the same phage type of which can often be isolated from the nose [1], but unknown constitutional factors must be accorded the major role in determining susceptibility, for the staphylococci do not normally penetrate more deeply than the follicular ostia. Many patients are seborrhoeic, with a greasy complexion and chronic blepharitis. Clerical and other indoor workers are affected more often than those who work in the open air.

Pathology. The affected follicle is packed with polymorphonuclear leukocytes, which infiltrate its wall. Around the follicle there is a chronic granulomatous infiltrate in which lymphocytes, plasma cells, histiocytes and foreign-body giant cells are conspicuous. The sebaceous gland, or the whole follicle, may be destroyed and replaced by scar tissue.

Clinical features [2]. The essential lesion is an oedematous, red, follicular papule or pustule centred on a hair. The individual papules remain discrete, but if neighbouring follicles are involved the perifollicular oedema may coalesce, to produce the raised plaques studded with pustules, which suggested the appearance of a ripe fig to the ancient author who coined the term sycosis. In the common subacute forms, the lesions may be scattered irregularly over the beard, or grouped especially on the upper lip and below the angles of the jaw. Attacks of varying duration occur at irregular intervals over months or years. In more chronic forms, the lesions are typically clustered into plaques, especially on the upper lip and

chin, and may persist for very long periods—nearly 20 years in one case [3]. There is often some crusting and scaling, but the hairs are retained and there is no evident scarring.

In lupoid sycosis, the follicles are destroyed by scarring, and active papules and pustules fringe the advancing margin around a pink atrophic scar. Granulomatous inflammatory changes may give the papules a lupoid appearance. The process usually begins in front of one ear or under the chin and extends irregularly in any direction. The scalp may be extensively involved. Rarely, a similar process affects axillary and pubic hair, or the lower legs, thighs and arms. Lupoid sycosis tends to persist indefinitely, although the rate of extension may vary from time to time.

Diagnosis. The most frequent misdiagnosis is certainly the pseudofolliculitis caused by ingrowing hairs. The papules and pustules are irregularly scattered over the sides of the neck and the angles of the jaw and are not grouped but may lie in skinfolds.

Mycotic sycosis, a kerion of the beard (Chapter 31), usually occurs on the chin or cheeks. The oedematous plaque of grouped pustules of acute onset is easily recognized. The diagnosis is suggested by the patient's contact with cattle, and confirmed by mycological examination.

Lupoid sycosis rarely simulates lupus vulgaris. The presence of pustules establishes the diagnosis. Biopsy can be undertaken if doubt remains. The scarring of lupoid sycosis may have medicolegal implications if the patient falsely attributes it to the use of radiotherapy during its early stages.

Treatment. The subacute forms are relatively easily controlled by antibiotic ointments, but tend to relapse when the application is stopped. If a nasal swab indicates a chronic carrier state, the antibiotic should also be applied to the nasal vestibules.

The chronic forms respond less readily to antibiotics, although the response may sometimes be enhanced by using a steroid–antibiotic combination. The application must often be continued indefinitely and potential sensitizers, such as neomycin, should therefore be avoided. In resistant cases a 10- to 14-day course of a systemic antibiotic deserves a trial. Any chronic nasopharyngeal sepsis should be treated.

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Folliculitis keloidalis

SYN. ACNE KELOID

Aetiology. Folliculitis keloidalis is a chronic inflammatory process involving the hair follicles of the nape of the neck and leading to hypertrophic scarring in papules and plaques. It occurs only in males after puberty and is most frequent between the ages of 14 and 25 years, especially in black males. Many patients have, or have had, significant acne, and a patient with previous hidradenitis has been reported [1]. No specific organism can be isolated, although *Staphylococcus aureus* is often isolated [2]. Although friction from the collar is often incriminated, the evidence is unconvincing [2]. The location on skin which is often closely shaven, and the observation of foreign-body granulomas surrounding fragments of hair, has led to the suggestion that the process begins with penetration of cut hair into the skin, as in pseudofolliculitis [3]. However, Brauner of the US Army [4] had no experience of the condition despite the persistence of close-shaven hairstyles among soldiers, and he pointed out that the ingrowing of hair could well be secondary to the scarring. Whether the initial event is pseudofolliculitis, bacterial folliculitis or some other process, there is significant individual predisposition especially as regards the severity of the scarring process.

Associated keloids in other sites seem not to have been reported, and the process is regarded as hypertrophic scarring rather than true keloid [1].

Pathology. The most frequent histological finding is dense hypertrophic scar tissue and a patchy perivascular infiltrate of plasma cells, which can simulate syphilis. Serial sections may reveal evidence of folliculitis or a foreign-body reaction to hair and follicular remnants.

Clinical features. Follicular papules or pustules, often in irregularly linear groups, develop on the nape of the neck just below the hair line. Less often, they extend upwards into the scalp. The early inflammatory stage may be inconspicuous, and the patient may first be aware of the hard, keloidal papules that follow the folliculitis. The papules may remain discrete, or may fuse into horizontal bands or irregular plaques. In other cases, the inflammatory changes are persistent and troublesome, with undermined abscesses and discharging sinuses.

The condition is extremely chronic and new lesions may continue to form at intervals for years.

Treatment. Bacterial infection should be treated if present, and antiseptics may help to reduce further or secondary infection. Avoidance of closely shaven hair on the back of the scalp may be advised. Intralesional steroids may reduce scarring and inflammation. Oral steroids prescribed for another condition helped, but long-term treatment is

unlikely to be justified [1]. In general, medical treatment is disappointing, and in troublesome cases the affected area may be excised and grafted, excised and allowed to heal by secondary intention, or treated with a carbon dioxide laser [5] and again allowed to heal by secondary intention. Surgery followed by radiotherapy has also been advocated previously.

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Acne necrotica (varioliformis)

Nomenclature. There are few clinical syndromes with a more confused nomenclature. The term acne necrotica has included a chronic follicular necrotizing process, which evolves into small, round scars, affecting mainly areas close to scalp margins (acne necrotica varioliformis); this is the entity discussed here. Also included has been a milder disease occurring throughout the scalp without significant scarring (acne necrotica miliaris). The relationship between the two is still uncertain, but we regard the latter as possibly synonymous with *Propionibacterium acnes* folliculitis of the scalp [1,2], which is considered below.

Aetiology. Acne necrotica varioliformis is much less common than acne necrotica miliaris. It occurs slightly more frequently in men than in women, and is usually seen between the ages of 30 and 50 years, but never before puberty.

The lesion is essentially a folliculitis, but the cause is uncertain. The most widely suggested pathogens have been *Staphylococcus aureus* and *P. acnes*, but neither is universally accepted, and whichever (if any) microorganism(s) may be involved, it is the follicular and perifollicular necrosis, presumably mediated by host response mechanisms, which characterizes the condition.

Staphylococcus aureus is often isolated from surface swabs, but the lesions are very frequently crusted or excoriated, so that the *Staphylococcus* may be a surface contaminant or secondary pathogen, and this finding may not reflect a primary pathogenetic role [3]; in addition, treatment appropriate for staphylococcal infection is usually disappointing.

Emotional disturbance has been a frequent finding in some studies [3,4]; it has been suggested that repeated excoriation of lesions of a primary folliculitis leads to more destructive changes [3]. Histologically, however, acne necrotica varioliformis can be distinguished from excoriations as well as from pyogenic infections [5].

A response to tetracyclines is in keeping with a primary role for *P. acnes* [5,6], as in acne necrotica miliaris, but the greater severity of the varioliformis type suggests a qualitative difference in host response.

Pathology [5]. Early lesions show a lymphocytic folliculitis with extensive individual cell necrosis of keratinocytes in the external root sheath and the surrounding epidermis, and marked subepidermal oedema. Later, the follicle and adjacent epidermis and dermis show confluent necrosis.

Clinical features. The typical lesion of acne necrotica is a red papule 2–5 mm in diameter, often umbilicated and rapidly transformed by necrosis into an adherent haemorrhagic crust, which separates after 3 or 4 weeks to leave a permanent scar, which may be varioliform. Some burning or pruritus may precede or accompany the development of new lesions, but subjective symptoms are seldom severe. The lesions are usually few in number at any one time, but exceptionally may develop in large crops. The most frequent sites are the temples and the anterior margin of the scalp. In some patients, the greater part of the hair line may be involved, but lesions more than a centimetre or two within the scalp are unusual. Much less commonly affected are the midline chest and back, and the cheeks and nose. On the nose, the lesions may be exceptionally large and destructive. In many patients they remain confined to the same region in successive attacks, for example, the temples. In some patients in whom two or three lesions develop at long intervals, acne necrotica is of little significance, but in others in whom recurrences are frequent and the lesions more numerous they may ultimately produce disfiguring scarring.

Diagnosis. Both the distribution and the relatively short course, rarely exceeding 6 weeks, of the individual lesions should differentiate the papulonecrotic tuberculides (Chapter 28). In tertiary syphilis, the lesions are larger, grouped and asymmetrical, and not pruritic. In acne necrotica miliaris (described as *P. acnes* folliculitis below) the lesions are typically distributed throughout the scalp, and are smaller, usually more numerous, non-scarring and more itchy.

Treatment. If *S. aureus* is isolated, a course of an appropriate antibiotic should be given, and an antiseptic shampoo may be advised. Otherwise, and if there is no response or only transient improvement, prolonged courses of an oral antibiotic as for acne, for example a tetracycline, should be given. Topical clindamycin in addition has been

recommended [3]. Excoriation should be discouraged, and any significant emotional disorder managed appropriately. Doxepin has been suggested for both its psychotropic and antipruritic effects [3]. Isotretinoin has been successful in some difficult cases [7].

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Perforating folliculitis

This largely asymptomatic eruption of chronic follicular papules occurs mainly on the limbs of young adults. Histologically, the follicles are dilated and plugged with keratin. The follicular epithelium shows one or more perforations into the dermis. Hair is frequently seen close to the epithelial perforations and sometimes within the dermis, as if the inflammatory changes were a reaction to mechanical damage by the hair. Of 25 patients in the original report [1], one was diabetic, but none of the others had systemic disease.

A similar process, less regularly involving hair follicles, and with frequently superimposed nodular prurigo, is associated with renal disease and diabetes (separately or together) [2–4]. Recent studies have included such cases under the more general title of acquired perforating dermatosis [5,6].

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Trunk folliculitis

The authors have seen several cases of a papular and pustular folliculitic eruption on the trunk of young and middle-aged adults. Lesions number a few dozen, widely scattered over the upper trunk unlike *Malassezia* folliculitis, and miconazole–hydrocortisone cream is ineffective. Routine bacteriology is negative, and comedones and facial acne are absent. There is no improvement on tetracyclines, erythromycin or trimethoprim–sulfamethoxazole in short or long courses. The response to UVB therapy is good, but the condition tends to relapse within a month of stopping and repeated courses or maintenance treatment are required.

Actinic folliculitis

Actinic folliculitis has been described in young to middle-aged adults of both sexes, and occurs repeatedly within 24 h of sun exposure. One description is of numerous superficial follicular pustules on the upper trunk and upper outer arms, with a burning sensation at the onset, resolving within 10 days [1,2]. Another report describes itchy pustules and papules on the lower face resolving within 4 days [3]. The mechanism is unknown. Sunscreens give partial protection at best. Standard acne therapy is ineffective, but the two facial cases responded to isotretinoin [3].

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Disseminate and recurrent infundibulofolliculitis

This uncommon condition affects mainly black people [1], but has been reported in white people [2,3]. Beginning in childhood or in adult life, there is a widespread eruption of follicular papules on the trunk and limbs sparing the flexures (Fig. 27.9). Itch is often but not always present. Occasionally pustules develop. The course is chronic or recurrent. No infective agent has been isolated. Histologically, inflammatory changes are confined to the infundibular portion of the follicles. Apart from oral vitamin A, which seemed beneficial in some cases [3], no effective treatment has been reported.

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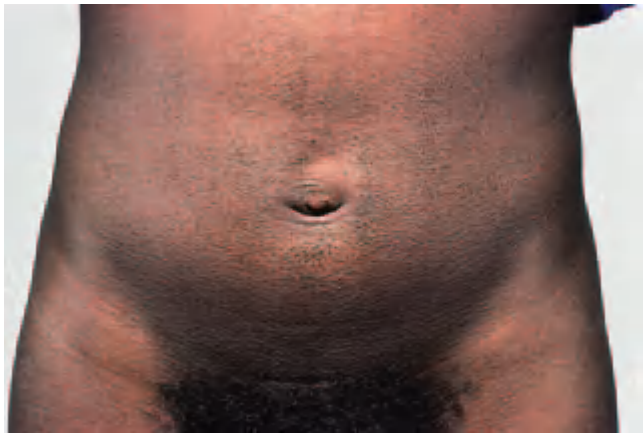

Fig. 27.9 Disseminate and recurrent infundibulofolliculitis. (Courtesy of Dr W.A.D. Griffiths, St John's Institute of Dermatology, London, UK.)

Eosinophilic pustular folliculitis

SYN. OFUJI'S DISEASE

Aetiology [1,2]. Eosinophilic pustular folliculitis has been reported mostly from Japan. Small numbers of cases in Europe and the USA have included patients of oriental extraction, but also some white people. The male/female ratio is about 5 : 1. The peak age incidence is the third decade, but cases have occurred in all age groups.

The pustules are sterile and the cause is unknown. An association with past or present acne has been noted, and the affected areas are usually those with high sebaceous activity. Eosinophil chemotactic factors have been detected in skin of normal subjects and it has been suggested that they may serve to localize excessive circulating eosinophils [3]. An abnormal response to saprophytic organisms has been suggested, but there is little supporting evidence.

Pathology. The follicle, heavily infiltrated with eosinophils, is necrotic with degeneration of the outer root sheath. The blood eosinophil count is raised.

Clinical features. The face is the commonest site, and is the site of onset in most cases. The trunk and the upper outer arms are frequently involved, legs and scalp occasionally. Widespread involvement has occurred [4]. In about 20%, there are pustules of palms or soles, simulating palmoplantar pustulosis.

Groups of papulopustules extend peripherally with central clearing, sometimes forming by confluence annular lesions or plaques, typically 3–5 cm in diameter, before subsiding to leave slight pigmentation. Lakes of pus and erosions are sometimes seen. Itch is frequent but not invariable. Patients are systemically well. The overall course is chronic, with new crops of lesions repeatedly reappearing in affected areas, although a few cases have entered spontaneous remission.

One otherwise well patient developed pyoderma gangrenosum with a fatal outcome [5].

Cases of eosinophilic pustular folliculitis have been reported in patients with AIDS [6] (Chapter 26).

Treatment. No treatment has been consistently effective. Systemic corticosteroids are usually but not always helpful, and topical steroids are sometimes partially effective. Dapsone works well in some cases and may be the drug of first choice [2,7,8]. Other reported therapies include non-steroidal anti-inflammatory drugs, for example indometacin [9], minocycline and colchicine [1]. UVB therapy was helpful in six AIDS-associated cases [10]; maintenance treatment was required.

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Eosinophilic pustulosis

Eosinophilic pustular folliculitis of the scalp was first reported by Lucky *et al*. [1]. The lesions that develop in infancy or childhood are characterized by recurrent crops of itchy, sterile pustules, which recur over several months or years. The sterile pustules develop on the scalp predominantly, but lesions may occur at other sites. Children may develop axillary, inguinal or cervical lymphadenopathy [2].

Histologically, the lesions demonstrate a heavy eosinophilic infiltrate in the dermis. Bacteriology is usually negative. The condition is self-limiting, but as recurrent lesions are common, dapsone may be helpful.

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Fig. 27.10 Perifolliculitis capitis. (Courtesy of St John's Institute of Dermatology, London, UK.)

Perifolliculitis capitis (abscedens et suffodiens)

SYN. DISSECTING CELLULITIS OF THE SCALP

Definition. Perifolliculitis capitis is a rare, chronic, suppurative disease of the scalp.

Aetiology. It occurs predominantly between the ages of 18 and 40 and almost exclusively in men, and is more common in black than white men. It usually occurs alone, although often in acne subjects, but is occasionally associated with acne conglobata and suppurative hidradenitis, leading to suggestions that these three conditions may have a similar basic pathogenesis in follicular occlusion. It has been regarded as infective in origin, but the evidence is inconclusive, and the response to antibiotics is usually disappointing. The suggestion that it is a granulomatous response to keratin requires confirmation: keratin may be found in the dermis as a result of destruction of the follicle by other mechanisms.

Pathology [1,2]. An intense folliculitis and perifolliculitis destroys the follicles, and a chronic inflammatory infiltrate with clumps of foreign-body giant cells extends widely in the dermis. In some areas, the inflammatory changes are more acute and polymorphonuclear leukocytes predominate. The epidermis is atrophic.

Clinical features [1,3] (Fig. 27.10). The earliest lesions are firm, tender nodules, usually developing in close groups at short intervals. The hairs overlying the nodules are soon shed or are easily extracted and the follicular openings discharge pus. Nodules may coalesce to form roughly cerebriform ridges, devoid of hair on their summits, but still hairy in the clefts that separate them. Eventually, the nodules may cover the greater part of the scalp and may persist for years, before eventually healing to leave irregular scarring, which may be keloidal. Fatal squamous carcinoma has been reported [4].

Diagnosis. The diagnosis is not usually difficult. Very extensive infection with ringworm of animal origin may produce a massive kerion of the scalp, but the short history and the morphology of the lesions should suggest the diagnosis, which must be confirmed mycologically.

Treatment. Bacterial pathogens should be sought and treated, but cultures are often negative and antibiotics often disappointing, including long-term regimens as in acne. Anecdotal reports of substantial but temporary improvement has been reported with isotretinoin. One patient improved on 1.0 mg reducing to 0.5 mg/kg/day for 16 weeks, with partial regrowth of hair, but relapsed if the dose was reduced further [5]. Another healed completely with full regrowth after a course of 0.5 mg/kg/day but relapsed 3 months after stopping treatment; a further successful 12-week course of 1 mg/kg/day did not delay the second relapse [6].

Zinc sulphate 400 mg three times a day for 12 weeks, followed by half that dose for 10 weeks, resulted in complete healing with satisfactory hair regrowth in one patient with no relapse within 5 years [7]. Combined therapy with fusidic acid (both topical and systemic), and oral zinc also proved helpful especially when zinc was continued over 6 months [8].

Oral prednisolone 60 mg daily, initially in combination with antibiotics, produced rapid improvement in one woman. The dose was gradually reduced to a maintenance level of 5 mg on alternate days and healing was complete with full regrowth of hair [9].

The carbon dioxide laser has been reported to be successful [10]. In recalcitrant cases, widespread excision and grafting may be considered [11,12]. There are no comparative trials of any of these treatments.

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Toxin-mediated staphylococcal disease

Staphylococcal scalded skin syndrome

Definition. SSSS is an exfoliative dermatosis in which most of the body surface becomes erythematous and the necrotic superficial epidermis strips off. The syndrome was first described in children, but adults may be affected. Factors such as renal failure, malignancy, immunosuppression or alcohol abuse predispose adults to the disease [1]. Outbreaks of SSSS in nurseries have been reported [2].

Aetiology. The epidermal changes are produced by the exfoliative (or epidermolytic) toxins of the staphylococci. The majority of strains responsible are phage group II, but other phage groups have been described [3]. A mouse model of the disease confirms that the disease is caused by the exfoliative toxins [4]. In adults, blood cultures are often positive for the staphylococci, whereas this is rarely the case in children.

Clinical features [1]. The initial event is usually a localized staphylococcal infection. This may be in the skin or at a distant or 'occult' site. A few days later, patients develop fever, irritability and skin tenderness. A widespread erythematous eruption follows, which progresses rapidly to blister formation. The tender skin becomes gathered into folds and, as it shrinks, leaves raw areas which are extremely painful. The condition usually heals within 7–14 days. Swabs and cultures of blister fluids do not usually grow the staphylococci, as the blisters are toxin mediated. The toxins are disseminated haematogenously. The staphylococci may be isolated from the original septic site.

Pathology. Histologically, there is splitting of the epidermis between the granular and spinous layers. A few lymphocytes surround the superficial blood vessels. The disease is caused by one or more epidermolytic toxins elaborated by some strains of *Staphylococcus aureus*. Two of the toxins (A and B) have been shown, by immunofluorescence, to bind to keratohyalin granules [5]. Immunological methods to detect and identify the causative toxins have been described [6].

The same toxins are involved in bullous impetigo, which may be regarded as a localized form of SSSS. Toxin A is chromosomally encoded whereas toxin B is plasmid derived [7]. There is some evidence that the toxins are proteases [8].

Management. The prognosis is good in children and, if antibiotics are administered early, the mortality rate is low. Children usually recover within 7 days. In adults, the overall mortality rate seems to be higher. Those patients without underlying disease recover more rapidly. Parenteral antibiotics such as methicillin, flucloxacillin, a cephosporin or erythromycin are required.

'Scalded skin syndrome' has been used as a synonym for toxic epidermal necrolysis (TEN). However, it is now clear that cell necrosis does not occur in the staphylococcal disease, and it is widely accepted that the term 'staphylococcal TEN' is inappropriate. Where there is doubt about the diagnosis, a frozen section of peeled skin will confirm the split in the granular layer in SSSS. Alternatively, a Tzanck preparation from a freshly denuded area may be helpful. In SSSS, there are a number of epithelial cells with large nuclei but no inflammatory cells, whereas in TEN there are only a few rounded epithelial cells but many inflammatory cells.

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Toxic shock syndrome

Definition. Fever, a rash followed in 1–3 weeks by desquamation, circulatory shock and multisystem disease characterize this syndrome, which is mediated by one or more toxins elaborated by *Staphylococcus aureus*.

Aetiology. Nearly all cases have been infected or colonized by *S. aureus*. Staphylococcal infection of any severity, at any site, at any age and in either sex may cause toxic shock syndrome [1]. However, in most of the early cases the organism was isolated from the vagina of menstruating women using tampons in the USA; in these cases, symptomatic vaginitis was common but not invariable. It seemed likely that staphylococci, perhaps introduced by hand or from perineal skin, found appropriate conditions for growth in the medium of the menstrual blood, facilitated in some way by superabsorbent tampons. Avoidance of these tampons was followed by a dramatic fall in the incidence, so that after 1985 the majority of US cases were non-menstrual [2].

TSST-1, previously identified as staphylococcal enterotoxin F or as pyrogenic exotoxin C [3], is produced by 80–90% of *S. aureus* isolates from affected cases, and is believed to be the main bacterial mediator of the disease. Other toxins, including staphylococcal enterotoxins A–D and H have also been implicated in the pathogenesis of some cases [4].

A similar disease has been associated with severe infections with *Streptococcus pyogenes* [5], and may be mediated by re-emergent scarlet fever toxin A [6].

Clinical features [7–9]. The onset is acute with fever and rash. Vomiting and diarrhoea are common early features, and involvement of muscle, liver, kidneys and central nervous system may follow. Circulatory shock may be severe and the mortality rate is about 7%.

The rash may be the presenting feature or may develop within the first day. A widespread macular erythema, sometimes faint, and clearing within 3 days, is commonest, but scarlatiniform and papulopustular eruptions are also described. Oedema of hands and feet may be marked. There is generalized mucous membrane erythema, especially intense in the conjunctiva, under which there may be haemorrhage. Oral, oesophageal, vaginal and bladder mucosae may ulcerate. Occasionally, vesicles and bullae may form. Towards the end of the second week, the majority of patients develop a widespread, itchy, maculopapular, sometimes urticarial, rash, which is thought not to be drug induced in most cases. Thrombocytopenia may cause purpura. Desquamation is highly characteristic. It occurs 10–21 days after the onset, and may be confined to the fingertips, may affect all the palmar and plantar skin or may be generalized. Reversible patchy alopecia or telogen effluvium, and transverse ridging and partial loss of nails are later non-specific findings.

Pathology. There are no specific histological features. A perivascular mononuclear cell infiltrate and papillary oedema may occur in the dermis. In cases with blister formation the split is subepidermal [8].

Diagnosis. The diagnosis is primarily clinical, supported by the confirmation, in the great majority of cases, of staphylococcal infection. Fever, rash and later desquamation, are required for the diagnosis; shock is a marked feature in the fully developed disease, but postural dizziness may suffice for the diagnosis in mild cases.

Septic shock and other infections should be excluded by appropriate investigations. Some reported adult cases of Kawasaki disease may have had toxic shock syndrome. The diseases have features in common, but Kawasaki disease can usually be differentiated by prolonged fever, cardiac involvement, generalized lymphadenopathy and absence of peripheral shock. Reports of staphylococcal scarlatina may represent milder cases of toxic shock syndrome. Ehrlichosis may present with a life-threatening illness similar to toxic shock syndrome [10]. *Clostridium sordellii* infection may be associated with toxic shock syndrome and a high mortality rate. The disease resembles the staphylococcal syndrome except that there is no associated rash; it may follow postpartum infections [11].

Treatment [2]. Appropriate systemic antibiotic therapy should be given. Intensive general supportive measures are essential.

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Recalcitrant, erythematous, desquamating (RED) disorder

Definition [1]. Primarily associated with AIDS, this disorder shows some similarity with toxic shock syndrome. Fever, hypotension and a macular eruption characterize the disorder.

Aetiology. *Staphylococcus aureus* has been isolated from most patients with RED disorder. The staphylococci often produce TSST-1. Group A streptococci have also been cultured.

Clinical features [1,2]. RED disorder has a rather prolonged course with a mean duration of 50 days. This is unlike toxic shock syndrome, which has an abrupt onset and evolves more rapidly. RED is a multisystem disease associated with fever, hypotension, diffuse macular erythema, ocular and mucosal injection and delayed acral desquamation. Patients often have underlying medical conditions, which may result in higher mortality rates from the condition.

Treatment. Antibiotics, hydration and supportive care are required, particularly as the underlying medical condition may require treatment as well.

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Toxin-mediated erythema

Definition [1]. First described in 1996, this condition is characterized by a diffuse macular erythema in the perineal area. This develops abruptly and lasts for a few days. There may be associated pharyngitis, a strawberry tongue and acral erythema. Recurrent episodes are common.

Aetiology. The disease is thought to be caused by the toxins produced by either *Staphylococcus aureus* or *Streptococcus pyogenes*. The organism has been cultured from the pharynx.

Clinical features. Patients develop macular erythema in the perineal area. This usually follows an episode of pharyngitis. Episodes are recurrent and may be associated with hypotension, fever and mucosal oedema.

Treatment. Treatment with oral antibiotics is helpful.

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Other staphylococcal and streptococcal infections (see also Table 27.1)

Periporitis staphylogenes [1] is secondary infection with *Staphylococcus aureus* of miliaria of the newborn. It is an infection of sweat glands and should not be confused with folliculitis or furunculosis, which are rare in neonates. Pustular miliaria itself is sterile.

Staphylococcal blepharitis [2] commonly presents with hard scales on the lid margins ('squamous' type). If thicker crusts form around the lashes, their removal may leave ulceration of the follicle ('ulcerative' type). Conjunctivitis is nearly always associated.

A sporotrichoid distribution of infected nodules was reported in two cases [3], one involving *S. aureus* alone and the other a combined infection with *Streptococcus pyogenes*.

Staphylococcal fissure of the lower lip [4], may be caused by *S. aureus*, where there is persistent fissuring at or close to the midline of the lower lip. The fissures may start in cold weather but persist for many months despite the use of emollients. Traditional signs of infection are absent, presumably because any exudate is promptly licked away. There is a rapid response to a topical antibiotic.

Acute paronychia (Chapter 62) is commonly due to *S. aureus*.

Staphylococcal scarlatina is a scarlatiniform rash, clinically indistinguishable from streptococcal scarlet fever, but without the accompanying exudative tonsillitis, which may complicate staphylococcal infection, beginning 1–9 days after the initial symptoms [5–11]. Negative Schultz–Charlton tests with streptococcal scarlet fever antitoxin suggest that the staphylococcal and streptococcal toxins are antigenically distinct [6,10].

Some of the reported cases were hypotensive and the similarity to milder forms of toxic shock syndrome has been noted [12–14], although it would be premature to regard the two conditions as pathogenetically identical. There is insufficient evidence for the proposed inclusion [15] of staphylococcal scarlatina within SSSS.

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Streptococcal vulvovaginitis

Streptococcus pyogenes accounts for 10% of cases of vulvovaginitis in prepubertal girls [1]. Perianal infection

occasionally coexists. The child complains of genital soreness or irritation and the skin is acutely erythematous. There may be purulent discharge or dysuria. Other bacterial causes, including *Neisseria gonorrhoeae*, cannot be distinguished clinically. The infection responds to oral penicillin or erythromycin.

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Perianal streptococcal infection

The term 'cellulitis' [1,2] seems inappropriate for this superficial infection that lacks fever and other systemic symptoms, although surface swabs yield group A streptococci in all cases.

Most patients are children aged 1–10 years, but occasional adult cases are seen. Some, but not all, patients were found to harbour *Streptococcus pyogenes* in the throat, usually of the same strain, and sometimes there is a recent history of pharyngitis in a family member. In some reported cases, there had been symptoms for many weeks or months suggesting that chronic infection may occur. Perianal soreness or irritation, pain on defaecation and sometimes secondary faecal retention are typical presenting symptoms. The affected skin is bright red, swollen and may be fissured. A purulent discharge with balanoposthitis may occur. Guttate psoriasis and, in girls, vulvovaginitis are occasionally associated.

The condition responds to an oral antibiotic. Penicillin is often successful, but recurrences in some patients respond to erythromycin and topical mupirocin [3]. A 2-week course is recommended [2].

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Streptococcal ulcers

Acute ulcers, often on the legs and feet, are one of the more frequent forms of streptococcal pyoderma under humid tropical conditions [1]. Chronic ulcers of streptococcal origin may follow insect bites or abrasions, and are not uncommon [2]. Serpiginous in outline with an undermined edge and an uneven, roughly granular floor, they may persist for many months but heal rapidly with antibiotic treatment.

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Blistering distal dactylitis

This is nearly always a group A streptococcal infection in children or teenagers [1,2], but group B organisms are occasionally involved [3], and a group B infection in a diabetic adult has been described [4]. A large blister containing thin, seropurulent fluid forms on the distal phalanx, usually of a finger, and typically on the palmar pad (Fig. 27.11), although it may extend to the nail folds, and more proximal involvement of the palmar skin is sometimes seen [3]. An upper respiratory tract infection is sometimes present. One recurrent case occurred beside an ingrowing toe nail [5]. The organism is cultured from blister fluid and responds to oral antibiotic treatment.

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Streptococcal intertrigo [1]

Intertrigo of simple mechanical origin or associated with other dermatoses is readily colonized by many organisms. Haemolytic streptococci may become established and

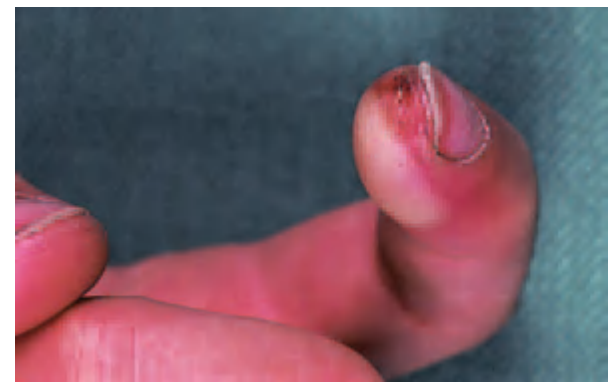

Fig. 27.11 Blistering distal dactylitis. (Courtesy of York District Hospital, York, UK.)

may give rise to crusting and fissuring in the depth of the affected flexure. Such fissuring is a characteristic feature of infective eczematoid dermatitis behind the ears, and may complicate intertrigo in any site.

The fissure may be healed with appropriate antibiotics, but recurrence is frequent unless the predisposing factors can be effectively eliminated.

Sporotrichoid nodular lesions yielded both *Staphylococcus aureus* and *Streptococcus pyogenes* in one case, and *S. aureus* only in another [2].

A woman with streptococcal septicaemia developed TEN for which no other cause was found [3].

Streptococcal throat infection was suggested as a cause of acute urticaria in children [4].

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Toxin-mediated streptococcal disease

Scarlet fever

SYN. SCARLATINA

Aetiology [1–4]. Scarlet fever is an acute infection caused by strains of *Streptococcus pyogenes* producing pyrogenic exotoxin (erythrogenic toxin, erythrotoxin), of which there are three antigenically unrelated types, A, B and C. All three are capable of producing scarlet fever. Toxin production appears to depend on the presence of a temperate bacteriophage and is exclusive to group A streptococci, a single strain of which may produce none, one, two or all three toxins [5]. In the 1970s and 1980s, type B was the most frequent toxin in the USA, Germany and England, and type C was also seen; type A is believed to have been responsible for the severe disease seen several decades ago. Whether an infected individual develops scarlet fever or a septic streptococcal illness, such as tonsillitis or cellulitis, depends on the level of antitoxic immunity, normally acquired by previous exposure.

The disease occurs throughout the world but the full syndrome is uncommon in the tropics, where surveys suggest that subclinical infections must be frequent [6]. Scarlet fever is endemic in large towns but the incidence varies greatly from year to year. The incidence in the Oxford (UK) region at a time of greater frequency of the disease was 0.30 confirmed, and 1.25 suspected, cases per 1000 per year [7]. In the last few decades, scarlet fever has been less severe than in the late 19th and early 20th centuries, perhaps because of the virtual disappearance of type A toxin [8].

The upper respiratory tract is the usual portal of entry and, although infection of surgical and other wounds may sometimes be responsible, most reports of this association have not included bacteriological examination of the throat. Droplet infection is commonest but the disease may be spread by fomites or by milk. Most cases occur between the ages of 1 and 10 years, and infections are rare in infancy and old age.

Pathology. The erythrogenic toxin is responsible for cutaneous vasodilatation, which may be associated with oedema and a perivascular cellular infiltrate. The toxin may also produce a degenerative myocarditis. The bacterial component of the syndrome consists of septic lesions in many organs, with abscess formation. Glomerulonephritis depends on an immunological mechanism.

An attack with a rash confers permanent specific antitoxic immunity. The toxin produced by other strains is not neutralized, hence second attacks, although rare, can occur. Bacterial immunity is temporary and there is therefore no permanent protection against the septic manifestation of infection by the same or related strains of *Streptococcus*.

Clinical features [9]. After an incubation period, which is usually 2–5 days, fever, anorexia and vomiting usher in the infection. If the throat is the portal of entry, there is an acute follicular or membranous tonsillitis, with painful lymphadenopathy. If the infection has entered a wound, there may be increased tenderness and some serous discharge.

The rash, which appears on the second day, first on the upper trunk, is a finely punctate erythema which has been likened to 'sunburn with goosepimples'. It generalizes within a few hours or over 3 or 4 days. Transverse red streaks in the skin folds due to capillary fragility are known as Pastia's lines. The face is flushed but rarely shows punctate erythema, and relative pallor around the mouth is characteristic. The lower legs are involved last and least. After 7–10 days the rash is succeeded by desquamation, branny in most areas but in large, lamellar scales on palms and soles.

The oral mucous membranes are bright red and there may be deeper red puncta on the palate. The tongue is at first heavily coated, but by the second or third day scattered, swollen, red papillae give the 'white strawberry tongue' appearance. As the epithelium is shed, the tongue becomes smooth and dark red ('red strawberry tongue') before returning to normal.

Fever usually settles in 7–10 days. The typical course of the mild or moderate case may be modified if either the toxic or septic manifestations are severe.

In the severe toxic form the eruption is very intense and may be purpuric. Fever is high and the patient is delirious or comatose. Myocarditis is often present.

In the septic forms, the local pharyngeal lesions are severe and there may be extensive oedema. Otitis media and peritonsillar abscesses are frequent. The rash may be slight.

Complications are caused either by the toxin, or by bacterial invasion of tissues by local extension or by haematogenous dissemination, or by a probably allergic reaction. Of the toxic manifestations, myocarditis is the most important. The suppurative complications include arthritis, meningitis and osteomyelitis. Rheumatic fever and glomerulonephritis are presumed to be allergic in origin.

The prognosis is now good and the mortality of treated cases is under 1%.

Second attacks are more frequent in patients in whom early antibiotic control of the initial attack has impaired the immune response [10].

Diagnosis. The classical form of the disease associated with tonsillitis is unlikely to be misdiagnosed if it is considered. The diagnosis may be supported by culture of a haemolytic *Streptococcus*, a rising ASO titre and blanching of the rash around the point of injection of antitoxin: the Schultz–Charlton test. The peripheral blood usually shows polymorphonuclear leukocytosis.

Rubella, the early stage of smallpox and some drug reactions can simulate scarlet fever. The lack of pharyngeal lesions and the distribution of the exanthem will usually enable the diagnosis to be established. Rarely, staphylococcal infections are accompanied by a scarlatiniform erythema.

In the so-called recurrent scarlatiniform erythema, repeated attacks of a somewhat similar rash, followed by exfoliation, occur without discoverable cause.

Treatment. Penicillin should be given in full dosage for 10 days as soon as the diagnosis is suspected. The management of the complications lies beyond the scope of this book, but the possibility of myocardial or renal damage should always be borne in mind and careful and prolonged supervision is obligatory.

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Streptococcal toxic shock syndrome

Definition. Fever, myalgia and flu-like symptoms are followed by pain in an extremity or in the abdomen. A rash followed by desquamation, circulatory shock and multisystem disease characterize the streptococcal toxic shock syndrome (STSS).

Aetiology. This disorder has been associated with the recent re-emergence of invasive group A streptococcal infections. Group A streptococci, producing streptococcal pyrogenic exotoxin-A, are usually cultured from the blood, although other streptococci have been isolated too. Several streptococcal toxins are likely to be responsible for this condition, although the exact pathogenic mechanisms are currently still unknown.

Clinical features [1,2]. The disease may occur in immunocompetent children or adults.

The disease is similar to staphylococcal toxic shock syndrome, although there may be some differences. Cases of STSS are associated with severe invasive group A streptococcal disease, whereas staphylococcal toxic shock syndrome may be associated with either severe or trivial infection. Surgical wounds, throat infections, vaginal infections postpartum or soft-tissue infections due to group A streptococci, may be followed by the STSS. The disease is associated with a higher mortality rate than staphylococcal toxic shock syndrome. Complications include myositis, endophthalmitis, peritonitis and renal failure [3].

Diagnosis. Blood cultures are frequently positive, and swabs from the site of clinical infection almost always yield group A streptococcal M types 1, 3, 12 and 28. The streptococcal pyrogenic exotoxins A and B are produced in the majority of these cases.

Treatment. Penicillin, erythromycin or clindamycin would be the treatment of choice for most soft-tissue infections caused by group A streptococci. Where necrotizing fasciitis or myositis have developed, debridement, fasciotomy or amputation may be required. Intravenous gammaglobulin may be helpful to neutralize the toxin [4].

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Coryneform bacteria

The term coryneform bacteria is currently used to describe Gram-positive, non-sporing, rod-shaped organisms commonly referred to as diphtheroids [1,2]. This heterogeneous group has a wide distribution in nature and is of considerable importance to the dermatologist. It embraces *Corynebacterium diphtheriae*, the cutaneous aerobic coryneforms, *Corynebacterium* and *Brevibacterium* spp., as well as the anaerobic *Propionibacterium* spp. Two animal species that may cause human diseases, *Listeria monocytogenes* and *Erysipelothrix insidiosa*, may be included in this group (Table 27.3).

Aerobic coryneforms of the resident normal flora

Many different strains of aerobic coryneform bacteria may be isolated from the normal human skin. Their classification remains unsatisfactory, but recent attempts to divide them into a mere six species complex on the basis of obligate lipophilicity, glucose fermentation, tyrosine clearance and nitrate reduction are encouraging to the non-specialist [1]. Apart from *Corynebacterium* spp., it is now clear that *Brevibacterium* spp., non-lipophilic coryneform organisms, can be isolated regularly from most human skin, especially the toe clefts [2]. It is generally accepted that trichomycosis axillaris and erythrasma are caused by an overgrowth of resident coryneforms, and there are grounds for suggesting that the organism involved in pitted keratolysis is also a resident coryneform. In trichomycosis, a variety of different strains of aerobic coryneforms have been implicated, not a single species (*C. tenuis*) as originally thought. In erythrasma, the term *C. minutissimum* is still used, but it is probably wise to recognize that this label implies a species complex of fluorescent aerobic coryneforms capable of initiating, alone or with others, the characteristic scaling and pigmentary changes of that condition.

Table 27.3 Coryneform bacteria.

Human commensals or pathogens	
Aerobic	
Corynebacterium diphtheriae	Primarily throat
C. haemolyticum	
C. pyogenes	
C. xerosis	
C. hofmannii	Primarily skin
C. minutissimum	
Brevibacterium epidermis	
Anaerobic	
Propionibacterium acnes	
P. granulosum	Primarily follicular
P. avidum	
Pathogens of other vertebrates sometimes infecting humans	
Listeria monocytogenes	
Erysipelothrix rusiopathiae	

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Diphtheria

Aetiology. In temperate regions, and probably also in urban areas in the tropics, *Corynebacterium diphtheriae* is isolated predominantly from the nose and throat of healthy carriers who have recovered from an attack of faucial diphtheria. In some tropical rural areas, the organism is found only rarely in the nose and throat, but is present in 30–60% of skin lesions of various types—impetigo, yaws, infected abrasions—in the indigenous population [1].

However, generally the rates of infection are considerably less in individuals receiving adequate courses of immunization, and where infections occur they are usually less severe in these groups than in the non-immunized [2]. It is likely that widespread immunization programmes have been in part responsible for the decreased incidence of diphtheria, even though the numbers of new cases of infection were falling before the introduction of toxoid. One interesting observation is that isolates of *C. diphtheriae* from immunized subjects are less likely to be toxogenic than those from the non-immunized.

The diphtheria toxin consists of two fragments: the A polypeptide, which is the active segment, and the B fragment, which binds to cell-surface receptors. The A segment inactivates transfer RNA translocase, preventing protein synthesis.

Strains of *C. diphtheriae* differ in toxigenicity, and those isolated from chronic skin lesions often produce little toxin. All strains are lysogenic for temperate phages: strains which lose their phage lose their ability to produce toxin.

The association of *C. diphtheriae* with yaws in the Pacific area is statistically significant, and suggests that the lesions produced by the spirochaete may provide particularly suitable conditions for colonization by diphtheria.

Cutaneous diphtheria is rarely reported in temperate climates, but the diagnosis is easily overlooked [3]. An outbreak occurred in Vancouver, Canada, in all numbering

44 cases. Another report from northern Canada has stressed the persistence of diphtheria in spite of high immunization rates, and the more frequent isolation of *C. diphtheriae* from Native Americans, than from Eskimos or white people [4]. In the tropics, especially where hygienic standards are low, the infection is more readily established in pre-existing skin lesions, and in the southern USA cutaneous infections have been shown to be significant in the epidemiology of diphtheria, particularly in poor communities [5,6].

Pathology. Colonization of skin lesions by a strain of low virulence may not modify their morphology or produce any remote toxic effects. Such strains may provide a sufficiently strong antigenic stimulus for immunity to develop.

A toxigenic strain induces local necrotic changes and systemic effects.

Clinical features [3,4]. The typical early lesion is a superficial ulcer, rounded, oval or irregularly linear, with a clearly defined, overhanging edge. Exudate from the ulcer floor tends to form a tough grey or brownish grey adherent membrane. Later, the ulcer may deepen and its edge become rolled, raised and avascular. There may be moderate enlargement of the regional lymph nodes. In temperate climates, the lesions occur most commonly at the umbilicus, behind the ears, in the genitocrural flexures, in a toe cleft or in a finger or toe, where a whitlow may be simulated. They may, however, develop in any pre-existing skin lesion, and in the tropics commonly complicate such conditions as impetigo, scabies or desert sores. Cutaneous diphtheria may persist for 6–12 weeks, healing with scar formation.

In many cases, the lesions are less distinctive and may simulate impetigo or ecthyma. A rare clinical form has been described in children with eczema: varicelliform vesicles or pustules are succeeded by diphtheritic ulcers. For this reason the role of *C. diphtheriae* in the pathogenesis of skin lesions has been questioned, particularly as other potentially pathogenic bacteria, such as staphylococci and streptococci, may be present [3].

Systemic manifestations are characteristically absent or mild in cutaneous diphtheria but are occasionally severe, especially in infants. In all forms, neurological complications, on which the retrospective diagnosis of diphtheria is sometimes based, occur in some 30% of cases and myocarditis in 5–10%.

Faucial diphtheria may be associated with adherent haemorrhagic crusts around the nose and mouth.

Diagnosis. The diagnosis may be suspected in persistent ulcers with an adherent membrane, but must be confirmed bacteriologically. The organisms are easily seen on a Gram stain. Swabs should be taken for culture and toxin assessment.

Treatment. Specific antitoxin should be administered as soon as the diagnosis is suspected: 20 000–50 000 U i.m. should be given. Penicillin or erythromycin should also be prescribed. The subsequent management will depend on whether there is neurological or cardiac involvement, and will be facilitated if the toxigenicity of the infecting strain can be established.

Erythromycin is probably the most effective compound for eradicating skin carriage.

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Corynebacterium haemolyticum infection

This organism has been reported as a cause of throat infections associated with a maculopapular rash. Patients usually presented with sore throats, mild to moderate in severity with little malaise or fever, and approximately half developed a maculopapular rash [1,2].

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Corynebacterium pyogenes infection

Corynebacterium pyogenes has been connected with outbreaks of skin ulceration in Thailand [1]. The clinical appearances of the lesions closely resemble those seen with other forms of pyoderma including tropical ulcers. Spread by flies in the area has been suggested. The pathogenetic mechanism by which these organisms produce skin necrosis has yet to be established.

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Erythrasma

Definition. Erythrasma is a mild, chronic, localized superficial infection of the skin caused by a group of closely related aerobic coryneform bacteria, usually known as *Corynebacterium minutissimum*.

Aetiology. For over a century, erythrasma was thought to be due to an actinomycete, for which the name *Nocardia minutissima* was proposed. It is now recognized that the Gram-positive rods and filaments always found in the scales of erythrasma are coryneforms. The name *C. minutissimum* has been given to the organisms isolated, but possibly more than one species may be involved [1,2]. The epidemiology of erythrasma has not been fully elucidated. There seems to be little doubt that the organisms responsible are frequently members of the normal flora, at least in the toe clefts, and that some shift in the host–parasite relationship results in the development of classical erythrasma. A warm, humid climate is a predisposing factor.

Clinical infection may occur at any age but is more common among adults than children. In institutions, the incidence may increase steadily with age [3]. Among normal populations, mild toe-cleft scaling with pink fluorescence is common. Clinically important infections of the groins are much less frequent and those of the axilla are uncommoner still. Within closed communities, the condition is likely to be more prevalent: in one hospital for the mentally subnormal, the incidence in the toe clefts was 30%, in the groins 18% and in the axillae 4% [4]. The incidence of erythrasma has been reviewed by Noble [3].

A variety of erythrasma that affects the axillae, inframammary folds and large areas of the trunk, as well as the groins, is particularly common in obese, middle-aged black women. Diabetes was found to coexist in eight of 13 patients with lesion of this type [5].

Clinical features [6] (Fig. 27.12). Erythrasma, as detected by Wood's light examination, involves the toe clefts more frequently than any other site. As clinically manifest lesions it occurs most commonly in the groins, axillae and the intergluteal and submammary flexures. In the groins it affects the area of one or both thighs in contact with the scrotum. Lesions on the glans penis and beneath the prepuce have rarely been reported [7] but have probably seldom been sought. The patches are of irregular shape and sharply marginated, at first red, but later becoming brown. New lesions are smooth, but older lesions tend to be finely creased or obviously scaly. In the generalized form, the sharply marginated, reddish brown plaques may cover extensive areas of the trunk and limbs.

In temperate climates most lesions are symptomless, but in the tropics particularly, irritation of lesions in the groins may lead to scratching and lichenification. Involvement of the perianal skin may present as pruritus ani, of which erythrasma is an uncommon cause.

Toe-cleft infections are often asymptomatic; the scaling, fissuring and maceration that may be present are not necessarily caused by the corynebacteria. Rarely *C. minutissimum* has been associated with systemic disease, such as recurrent abscesses or endocarditis.

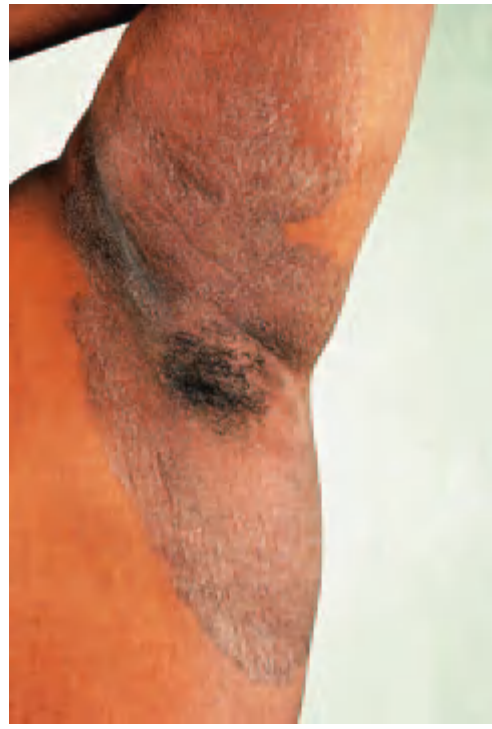

Fig. 27.12 Erythrasma. (Courtesy of St John's Institute of Dermatology, London, UK.)

Fluorescence under Wood's light. Coral-red fluorescence with Wood's light is attributable to coproporphyrin III and strongly suggests erythrasma, although it does not necessarily indicate active infection. The persistence of fluorescence after eradication of the coryneforms may depend on the thickness of the horny layer for it is common at the margins of the toe webs [3].

Pink fluorescence is also demonstrable in some necrotic tumours and on the normal tongue where it is not apparently caused by coryneforms. It is seen in the follicular openings of the normal skin of the face and the upper trunk, where corynebacteria or propionibacteria are the likely cause. In the groins and axillae, acanthosis nigricans may fluoresce a brilliant pink colour, presumably due to heavy colonization with fluorescent coryneforms, although other bacteria may show pink fluorescence.

Differential diagnosis. Pityriasis versicolor (Chapter 31) is most commonly confused with erythrasma, but it occurs predominantly on the upper trunk, and the individual lesions are small and are not erythematous. On the thighs, groins and pubic area, tinea cruris may be simulated, but the relative lack of inflammation, complete absence of vesiculation and absence of satellite lesions point against tinea. It is difficult to differentiate erythrasma of the toe clefts from tinea pedis or *Candida* infection, but, as in all varieties of erythrasma, the presence of coral-red fluorescence under Wood's light is diagnostic. Since many

patients have both tinea pedis and erythrasma, mycological examination of scales is important.

Prognosis. Without treatment the condition tends to persist indefinitely, although there may be spontaneous fluctuations in severity.

Laboratory identification. Scrapings from the affected skin may show bacteria and fine filaments if stained with Gram or Giemsa or even with simple potassium hydroxide clearance. Culture on Tissue Culture Medium 199 (without antibiotics) with 20% calf serum and 2% agar yields colonies that fluoresce coral red under Wood's light after 18–36 h. *Corynebacterium minutissimum* may resemble *C. jeikeium* but the latter does not grow on triple sugar iron agar, whereas the former does. Cultural confirmation is not normally necessary if the clinical appearance is typical and Wood's lamp examination of the patient is positive [2].

Treatment. Erythrasma responds well to most topically applied azole antifungal agents, such as clotrimazole and miconazole [5]. The duration of therapy varies, but 2 weeks is usually sufficient. For more extensive lesions, erythromycin is probably the most effective approach. Alternatives include topical fucidin and oral tetracycline. Relapse is a problem in some patients. In these cases the usual approach adopted is to give long-term antiseptic soaps, such as povidone–iodine, and to use drying agents, such as powders, in the affected areas.

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Trichomycosis axillaris

SYN. TRICHOMYCOSIS NODOSA

Definition and aetiology. This is a superficial infection of axillary and pubic hairs with the formation of adherent granular nodules—yellow, black or red—on the hair shaft. The misleading term 'trichomycosis' is retained in the absence of a generally agreed alternative, although it has been clear for many years that the causative agent is not a fungus [1]. Studies using transmission and scanning electron microscopy [2] have shown that the concretions consist almost exclusively of tightly packed bacteria. They grow within and between the cuticular cells and may invade the cortex [2]. Cultural studies have shown a variety of different biochemical types of aerobic *Corynebacteria* to be involved and not a single species, *C. tenuis*, as was at one time believed. These biotypes probably reflect the range of resident coryneform types in the normal axilla. It has been shown that the changes in chemical environment of these organisms may induce pigment production, perhaps explaining the different colours of the nodules, which are not attributable to different bacterial strains [3].

Clinical features. Trichomycosis occurs in both temperate and tropical climates and is not limited by race or sex. It is usually asymptomatic and the patient is often unaware of its presence. Yellow, black or red concretions are present on the hair shaft and these may be hard, or soft and nodular, or more diffuse. In the nodular varieties, the hair may be brittle and easily broken [2]. The underlying skin is normal. The axillary sweat may be yellow, black or red according to the colour of the concretions, and the clothing may be stained. The yellow type is the most common and the black the rarest. The few figures available on the prevalence of trichomycosis show it to be common.

Axillary infection was present in 27% of adult male students in one UK survey, and in 42% of male patients but only 7% of women patients in a hospital for the mentally subnormal [4]. This sex difference is largely explained by absence of axillary hair in the women. Pubic infection is less common but should not be forgotten [5].

Differential diagnosis. Pediculosis pubis, which may affect axillary as well as pubic hair, and piedra should be considered. Examination under Wood's light is helpful. Microscopical confirmation of the diagnosis is desirable.

Laboratory identification. Potassium hydroxide mounts show the bacteria as narrow bacillary organisms in the yellow or red concretions. They are Gram-positive. For culture, the hairs must be surface sterilized, and this may be satisfactorily done by immersion in 70% alcohol. Incubation at 37°C in blood agar is recommended.

Treatment. Clipping the affected hairs and the application of an antimicrobial ointment such as benzoic acid compound ointment or 1% aqueous formalin are effective. However, the use of an effective antiperspirant such as anhydrous aluminium chloride is a rapid means of therapy.

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Pitted keratolysis

SYN. KERATOLYSIS PLANTARE SULCATUM

Definition and aetiology. A superficial infection of the skin apparently caused by a species of *Corynebacterium* and producing circular erosions on the soles [1]. Filamentous and coccoid microorganisms were originally observed in skin scrapings and the organism was named *Actinomyces keratolytica*. Other reports tended to incriminate a species of *Streptomyces*, but a species of *Corynebacterium* has also been isolated, and recent work suggests that either a *Streptomyces* or a *Corynebacterium* or both, and possibly other organisms too, invade keratin softened by sweat [1,2]. The problem is, however, not fully resolved: an actinomycete identified by histological appearances as *Dermatophilus congolensis* was present in some cases [3].

Histology. Filamentous microorganisms may be seen in abundance in the most superficial parts of the stratum corneum [4].

Laboratory identification. The organisms are not always easy to find in potassium hydroxide mounts but are more easily detected in Gram-stained scrapings. Culture on brain–heart infusion agar, incubated at 37°C in a mixture of pure nitrogen containing 5–10% carbon dioxide, gives minute, irregular, colourless colonies within 3–5 days [5].

Clinical features (Fig. 27.13). There are numerous superficial erosions of the horny layer of the soles and the undersurfaces of the toes. All parts of both soles may be affected. Conspicuous, discrete, shallow, circular lesions with a punched-out appearance coalesce in places to produce irregular erosions. There is occasionally green or brown discoloration of the horny layer. Hyperhidrosis is often associated, sometimes with maceration and a foul odour. Soaking the feet in water for 15 min causes swelling of the horny layer and accentuates the lesions. Irritation is minimal and in most cases patients are unaware of the condition. Under battle conditions, soreness and pain have been reported in severe cases [1,6].

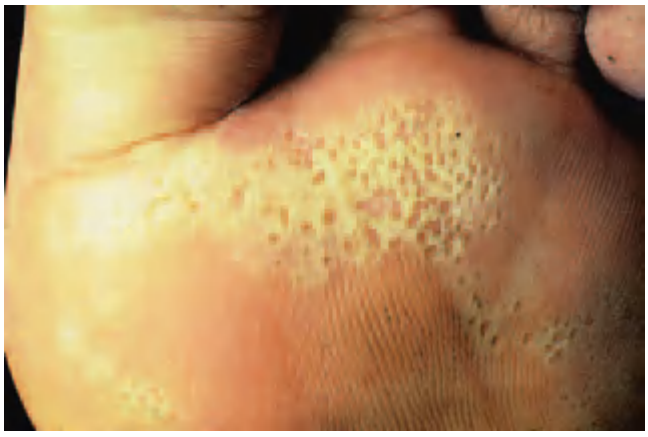

Fig. 27.13 Pitted keratolysis. (Courtesy of St John's Institute of Dermatology, London, UK.)

Similar changes affecting the palms have been described on rare occasions in the Far East, UK and southern USA.

Differential diagnosis. The lesions are easily recognizable, but simple hyperhidrosis, erythrasma and tinea pedis have to be considered.

Treatment. Treatment of hyperhidrosis (Chapter 45) slowly brings the condition under control, but a more rapid response may be obtained with fucidin ointment. Other topical antibiotics and imidazoles such as clotrimazole are reputed to be effective [1].

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Propionibacteria

Definition. Propionibacteria are anaerobic coryneforms of the resident normal flora. These Gram-positive, pleomorphic bacilli are found in large numbers and are widely distributed over the whole skin. Though formerly all termed *Corynebacterium acnes*, it is now recognized that they are more properly classified as propionibacteria and may be divided into three species. *Propionibacterium acnes* and *P. granulosum* are found predominantly in the pilosebaceous follicles of those sites where sebum is plentiful, and *P. avidum* is mainly isolated from moist intertriginous zones [1].

From its location, it is unlikely that *P. avidum* has any part in the causation of acne. *Propionibacterium acnes* and *P. granulosum* may well have a key role, but on present evidence it is difficult to be dogmatic on this point or to blame one species more than the other. The importance of *P. acnes* and *P. granulosum* in acne is considered in Chapter 43.

In addition to its association with acne, *P. acnes* has been isolated from cases of endocarditis and meningitis associated with the presence of ventriculoatrial or ventriculoperitoneal shunts. It has also been proposed as a cause of indolent folliculitis [2].

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Anthrax

Aetiology [1]. Anthrax is a specific infection with *Bacillus anthracis*, a Gram-positive, aerobic, encapsulated organism, which can survive as spores for over 20 years in soil. It is primarily an infection of herbivorous animals, but occasional outbreaks occur in other species. Animals are infected by ingesting the spores. Animal infections, and hence human infections, are still a serious problem in Africa (e.g. Zimbabwe and Chad), Pakistan, India, Iran, the Middle East and parts of Russia. Only occasional cases are seen in other areas. However, sporadic cases are easily overlooked as the diagnosis is not considered. In the endemic areas, humans are infected directly from animals or animal products, and male adults are most at risk, but in some rural communities children minding cattle may be infected.

Anthrax most often follows occupational exposure during care of livestock or the handling of products. In western Europe, most cases of anthrax formerly occurred among workers in the wool, hair or bristle industries, or those handling animal materials imported from India, Pakistan or Africa. In many countries, stricter codes of practice for hygiene in the work place has been followed by a decline even in sporadic infections. Unsterilized imported bone meal, or sacks contaminated with it, remains a potential hazard, although warning labels on this product appear to be effective in reducing the danger still further.

Human resistance to infection is normally high. Cutaneous inoculation is favoured by minor trauma or pre-existing skin lesions, and pulmonary and intestinal forms result from the inhalation or ingestion of spores.

Pathology. The anthrax bacillus induces an inflammatory tissue response in which haemorrhage and necrosis are associated with a gelatinous oedema, which contains much bacterial capsular material. The bacillus is present in large numbers in the skin lesions, and in the blood in systemic infections. The virulence factors are encoded on two plasmids—one inhibits phagocytosis of vegetative forms and the other carries the genes for synthesizing the exotoxins. These exotoxins (oedema toxin, lethal toxin and protective antigen) account for the pathology [2].

Clinical features [1]. The lesion of cutaneous anthrax, the malignant pustule, commonly occurs on exposed skin, especially the face, neck, hands or arms, and is usually single but may be multiple. Between 1 and 5 days after infection an irritable papule develops at the site of inoculation. A bulla on a red oedematous base soon follows. The bulla ruptures and forms a haemorrhagic crust around which is a zone of oedema and erythema in which there may be several small vesicles. The surrounding tissues are oedematous, and although the regional lymphatic glands may be tender, their involvement is slight in relation to the severity of the lesion and lymphangitis is unusual. In some cases, particularly when the face is involved, the oedema may be extreme and the localized pustule inconspicuous or absent. The clinical picture is very variable and purely or predominantly bullous lesions have been reported.

Constitutional symptoms may begin 3 or 4 days after the onset of the pustule. In severe untreated cases, malaise, high fever, toxaemia and prostration may be followed by delirium, collapse and death. In most cases, general symptoms are mild and healing occurs in 2–3 weeks.

The mortality of untreated cutaneous anthrax is between 5 and 20%. Severe oedema or toxaemia are of poor prognostic significance. With early and adequate antibiotic treatment, all cases are curable.

Other forms of anthrax include respiratory and gastrointestinal varieties. In the respiratory type, a mild primary illness is followed in 2–4 days by respiratory distress. The gastrointestinal type may cause haematemesis and diarrhoea with abdominal pain. Oesophageal involvement may also give rise to massive swelling of the neck. During 2001, several cases of confirmed anthrax infection occurred in the USA after about 20 years absence. None of these followed conventional exposure and were thought to result from bioterrorism [3]. There were several fatal cases.

Diagnosis. Staphylococcal infection, vaccinia, cat scratch disease (formerly named para-anthrax), North American blastomycosis and sporotrichosis may need exclusion. In the authors' experience, both staphylococcal infections and cowpox can simulate anthrax very closely. Both may show the central black haemorrhagic crust and the zone of oedema and erythema. The history, rapid course, clinical appearance and lack of lymphangitis should suggest the diagnosis, which must be confirmed by bacteriological examination. A Gram stain of the fluid from a cutaneous lesion may show the bacilli. Blood cultures confirm systemic infections. Smears should be chemically fixed as the spores may survive the standard fixation with a flame. A serological test is also available, although antibody levels in this disease are often very low [1].

Treatment [1,4]. For cutaneous anthrax, oral ciprofloxacin, doxycycline or amoxicillin may suffice for 7–10 days.

Where biological warfare is suspected treatment should continue for 60 days. For systemic disease, treatment should not be withheld until bacteriological confirmation has been obtained. Penicillin G should be given i.v. for 7–10 days, in a dose of 4 million units 6-hourly for the first 3–4 days. Tetracycline or erythromycin can be given in the presence of allergy to penicillin or in the very rare cases in which the bacillus is resistant to penicillin. If the patient is already severely toxic when treatment is started, intravenous fluids and corticosteroids are advisable. Where biological warfare is suspected, ciprofloxacin is the drug of choice at a dose of 400 mg every 12 h for up to 60 days. Penicillin may be added if meningitis is suspected.

Vaccination gives some protection [5] and should be offered to those who are exposed in the course of their occupations, but prevention should be directed primarily at control of the disease in animals and disinfection of animal products.

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Other *Bacillus* spp.

Rarely, other species of the genus *Bacillus* may cause deep subcutaneous infections resembling necrotizing fasciitis [1]. *Bacillus cereus* and *B. subtilis* may cause a variety of different infections of the eye ranging from conjunctivitis to panophthalmitis.

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Listeriosis

Aetiology [1–3]. Listeriosis is an infection caused by *Listeria monocytogenes*, a Gram-positive microaerophilic, motile bacillus easily confused with coryneform organisms. It can survive low temperatures and will grow at 4°C.

The organism is found in water and soil, and has been isolated from sewage sludge and inferior silage. It infects animals, farm, wild and laboratory, worldwide. Direct infection from cattle and sheep is a hazard to veterinary surgeons [4] and farmers, but food, especially milk, cheese and poultry, is the main source of human disease [5]. Transplacental and birth canal infections are a well-recognized hazard to the fetus and neonate [6]. Infection of a baby from the mother's milk has been reported [7]. Otherwise, direct transfer from human to human does not seem to occur. However, *L. monocytogenes* may be carried asymptomatically in the human gut as well as in the cervix and vagina, at least for short periods, so the potential for transfer of infection does exist.

Clinical features [8–11]. Most adult infections are now thought to be subclinical, but a mild febrile illness with gastrointestinal symptoms and loin pain may occur. More serious infections with a meningitic or glandular fever-like illness are well known, and in immunocompromised patients meningitis or pneumonia may dominate the picture. Cutaneous lesions are uncommon in these cases, but when present are purpuric. During pregnancy, an indeterminate febrile illness, not necessarily severe, may arouse no suspicions but the infant may be stillborn or premature, and may develop a combination of respiratory and gastrointestinal symptoms with granulomas of the posterior pharynx, generalized erythema and dark-red or bluish papules, especially on the trunk and legs [12]. Meningitis and septicaemia may be seen later in the neonatal period [6].

In veterinary surgeons, a mild, predominantly cutaneous form of the disease may occur 1–3 days after contact with an infected animal [4]. Fever and malaise are followed after a day or so by an eruption of discrete, dull-red papules, some of which later show central pustulation. In serious adult infections, in the immunocompromised patient and in the neonate, the prognosis is poor without treatment, at least 60% of cases being fatal [6].

Diagnosis. As there are no specific clinical features, the diagnosis will be missed unless it is borne in mind in unexplained fevers, glandular fever-like illness and meningitis. In those at risk through occupation, or predisposing states, the diagnosis is established by blood culture and, if a high index of suspicion towards diphtheroids is maintained, through isolation from other sites. Cold enrichment may help. Unfortunately, serology is unreliable [3].

Treatment. The drug of choice is ampicillin, but the organism is also susceptible to penicillin, erythromycin and tetracycline. Gentamicin may advantageously be used with ampicillin or penicillin, as synergism occurs.

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Erysipeloid

Aetiology [1,2]. Erysipeloid is an acute, rarely chronic, infection with *Erysipelothrix rusiopathiae* (formerly known as *E. insidiosa*). This organism is widespread in nature as a commensal or pathogen in a wide variety of animal species; it can survive in soil, although its survival time in this environment is unknown. It colonizes a wide variety of animals worldwide, including mammals, birds, fish and shellfish, and causes disease in many of these, especially in pigs. Human infection is contracted by direct contact, occasionally from living animals, but more commonly from carcasses, so that erysipeloid usually affects slaughtermen, butchers, cooks, fishermen, farmers and veterinary surgeons. Scratches or pricks with fish, rabbit or chicken bones are sources of infection in housewives [3]. The existence of L forms might explain the occasional chronic or recurrent infections [1]. The organism, *E. rusiopathiae*, produces a neuraminidase and a hyaluronidase, both of which are believed to be virulence determinants.

Pathology [1]. Cultures of biopsy material from the advancing edge of recent lesions occasionally yield the organism, but are commonly negative. Histology shows epidermal spongiosis or vesiculation, dermal oedema, lymphangitis, capillary engorgement and infiltration with neutrophils and eosinophils. Organisms have only rarely been detected by light microscopy. However, electron microscopy has demonstrated cell-wall-deficient bacteria (L forms), which may explain the difficulty of demonstrating the bacteria by conventional methods.

Clinical features [1,2]. Three clinical syndromes have been distinguished in humans: localized cutaneous, which is much the most common (erysipeloid of Rosenbach), generalized cutaneous and systemic, in which skin lesions may occur.

Most human infections are localized and self-limiting. About 3 days after inoculation, a hot violaceous and tender erythema develops around the inoculation site and extends centrifugally, but irregularly, with a sharp and sometimes gyrate border, which may be vesicular. Most lesions are on the hand, fingers or forearms, but any exposed area may be involved. Fever and mild constitutional symptoms such as arthralgia are present in only some 10% of cases. Extension continues for 3 or 4 days, rarely for as long as a week, but the area eventually involved is seldom more than 10 cm in diameter. Without treatment, healing normally occurs spontaneously in 2 weeks without desquamation or suppuration.

Widespread skin lesions are rare, described as violaceous, with a variable, pink advancing border and with central resolution. There may be systemic symptoms, but blood cultures are negative. This form is also usually self-limiting, but runs a more protracted course with the possibility of recurrences.

The commonest manifestation of the rare systemic *E. rusiopathiae* infection is endocarditis, but joint, bone, brain and pleural involvement have been described. Patients are ill, lose weight and may show localized cutaneous swellings with central necrosis, or scattered perifollicular papules. Blood cultures are usually positive with appropriate techniques.

Diagnosis [2]. The diagnosis of the cutaneous disease is mainly clinical. Compared with erysipelas/cellulitis, erysipeloid usually lacks constitutional symptoms and lymphangitis, the lesions are more purplish, and local joint involvement is more common. Diagnosis is by culture of aspirated material or biopsy specimen. The organism is a non-motile, non-sporulating Gram-positive bacillus.

Treatment [1]. The usual choice is penicillin, given parenterally in severe infections. Ciprofloxacin or erythromycin are alternatives. Tetracyclines are often satisfactory, but the sensitivity of the organism is variable.

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Gas gangrene

Aetiology. Gas gangrene designates a clinical syndrome caused by the infection of wounds with various species of *Clostridium*, alone or in combination with anaerobic streptococci, and often with aerobic organisms such as *Proteus*. The most important *Clostridia* spp. are *C. perfringens*

(formerly *C. welchii*), *C. oedematicus*, *C. septicum* and *C. histolyticum*, but other species may play a minor role [1].

The clostridia are anaerobic, Gram-positive, spore-forming bacilli, widely distributed in the soil and in the gastrointestinal tracts of humans and other mammals. *C. perfringens* can be isolated from the skin of the thighs, groins and buttocks of many healthy persons [1]. A high proportion of war wounds are contaminated by clostridial spores, but clinical infection usually develops only in the presence of severely damaged anoxic muscle. The incubation period varies from 12 h to 5 or 6 days, according to the species predominantly involved.

Gas gangrene used to be an infection of the greatest importance in war time; better management of casualties has reduced its incidence enormously. It is an uncommon but well-documented complication of civilian trauma and of orthopaedic surgery, particularly above-knee amputations in ischaemic limbs. In these latter patients, the organism usually originates in the patient's own bowel [1,2].

Clinical features. Deep and dirty wounds in the muscular regions of the body are most susceptible. However, abdominal and intrauterine infections also occur. The affected area becomes painful and swollen and there is increasing serous discharge from the wound. Toxaemia is severe; tachycardia and prostration develop rapidly and the patient is pale and apprehensive but often not febrile [1,3]. The oedema around the wound continues to spread and is associated first with brownish staining and mottling, then with bullae and later with the formation of black sloughs. Crepitation from gas in the tissues is classical but inconstant. There are usually severe systemic symptoms including tachycardia, irritability and hypotension.

Diagnosis. The diagnosis must be made promptly on clinical grounds supported in due course by bacterial examination of the ooze from lesions, which contains large numbers of typical Gram-positive bacterial rods. Necrotizing fasciitis, Meleney's synergistic gangrene and anaerobic streptococcal infection should be considered.

Treatment. The immediate surgical debridement of all damaged tissue is essential. Penicillin in high dosage (10–20 million units) is the usual treatment [4], although there are reports of penicillin resistance among *Clostridium* spp. Alternatives include chloramphenicol, metronidazole and imipenem [5].

The role of hyperbaric oxygen remains controversial because of the lack of controlled studies, and unless readily available may lead to delays in essential surgery [6]. There are, however, experimental data indicating that it reduces the mortality rates.

Suppurative myositis may also be caused by *Clostridium* spp. This complication is seen most often in intravenous drug abusers. However, there is less toxaemia than with gas gangrene [7].

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Gram-negative bacteria

Meningococcal infection

Aetiology [1,2]. *Neisseria meningitidis* is a Gram-negative coccus. It can be divided into different serotypes on the basis of capsular polysaccharides, types A, B and C being the most important. All types are pathogenic. This bacterium colonizes the human upper respiratory tract, and is transmitted by droplet from patients or healthy carriers. It may cause localized infections, such as conjunctivitis and otitis media, or severe and potentially fatal disease with septicaemia and often meningitis. The factors determining whether the organism is a mere colonizer or causes mild or severe disease in the individual case are not understood. Severe disease affects mainly children under the age of 10 years, but epidemics in adults may occur, for instance in institutions such as military barracks.

Bacteraemia is believed to be the primary event in all forms of the infection, and to be the route by which the organism reaches the meninges.

Pathology. The early petechial skin lesions result from the presence of the organisms in capilliary endothelium accompanied by disseminated intravascular coagulation, with necrosis of the vessel wall or thrombosis [1]. The skin lesions occurring late in the course of acute infections or in chronic infections show a vasculitis thought to be produced by soluble antigen–antibody complexes [3].

Clinical features. Acute meningococcal septicaemia and meningitis may present as a fulminating illness, and the rash may be a very useful clue to early diagnosis. The incidence of rash is estimated at between 40 and 90%, perhaps depending on the thoroughness with which lesions in the more sparsely affected cases are sought [1]. Early skin lesions are not always haemorrhagic, and may take

the form of discrete pink macules or papules a few millimetres in diameter on any part of the body, including palms and soles [4]. Purpura follows in many cases. Transient erythematous, morbilliform or urticarial eruptions are occasionally seen.

A purpuric eruption is characteristic, and occurs mainly on trunk and limbs. The petechiae are usually small and scanty, but vary in size and number. In severe cases, larger purpuric lesions may occur including extensive ecchymoses and necrotic ulceration, particularly in dependent areas and under pressure sites, and are associated with a high mortality [5].

Vasculitis may occur during the acute illness, beginning 5–9 days after the onset, even if adequate antibiotic treatment has been given. Nodules or bullae may be sparse and confined to the limbs, or may be more numerous and widespread; the lesions may ulcerate [6]. Arteritis and episcleritis may be associated. Similar vasculitic lesions occur in chronic septicaemic infection [7], in which milder maculopapular eruptions are also seen.

Diagnosis. The diagnosis is confirmed by isolation of *N. meningitidis* from blood or cerebrospinal fluid.

Treatment and prophylaxis [1,8]. Intravenous benzylpenicillin in high doses is the treatment of choice [9]. Chloramphenicol and cefotaxime are suitable alternatives.

Rifampicin for 2 days is recommended as prophylaxis for close family contacts, but does not eliminate the need for close clinical surveillance [8].

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Gonococcal infection

Aetiology and pathology [1,2]. *Neisseria gonorrhoeae* is a Gram-negative, aerobic diplococcus. It causes gonorrhoea, one of the commonest and most important sexually transmitted diseases. The incidence in industrialized countries fell after the high levels of World War II, and rose during the 'sexual revolution' of the 1960s and 1970s. There were an estimated 2 million cases in the USA in 1983. The incidence is high among homosexual men. Prostitutes are an important source of the infection, especially in developing countries [2].

The incubation period is 2–5 days (1–14 days). Genital infection affects primarily the urethra in both sexes, but may spread especially in the female to para-urethral glands and cervix, and more deeply (pelvic inflammatory disease) to endometrium, fallopian tubes and peritoneum. Local spread may involve the skin. Anorectal and oropharyngeal infections may follow relevant sexual contact. Most cases of childhood gonorrhoea are sexually transmitted [3], although accidental inoculation may account for some cases. If a mother has genital infection at the time of delivery, gonococcal ophthalmia may occur in the neonate. In the adult, the conjunctivae may be infected by autoinoculation from the genitalia [4]. Primary cutaneous infection is discussed below. Asymptomatic infection of genitalia, pharynx and rectum is common.

Disseminated gonococcal infection, which may include cutaneous lesions, occurs in about 1–3% of cases, and usually involves strains that are resistant to the killing effect of host serum, but very sensitive to penicillin [5]. Histologically, the metastatic lesions show haemorrhage, thrombosis and vasculitis [6]. Diplococci may be detectable in the vessel wall and in the surrounding inflammatory infiltrate. Immunofluorescence may identify gonococcal antigen where Gram stain and culture are negative [7–9].

Clinical features. Gonococcal infection may be cutaneous, oral or disseminated and there may be local complications.

Primary cutaneous infection. Areas contaminated by the urethral, vaginal or rectal discharge may show multiple erosions, 0.5–2.0 cm in diameter, sharply marginated, rounded or oval but often ragged, with a light-red surface and a vivid, non-indurated areola. The erosions heal when the discharge ceases. Very rarely, there may be discrete pustules of the coronal sulcus. A gonococcal ulcer of the penis in a patient without urethritis is unusual [10] as is a chancriform primary infection of the female thigh [11].

Pustular primary lesions have been described on fingers, but in each case the skin had been injured prior to exposure [12,13]. Similarly, minor trauma from fetal monitoring electrodes is likely to have facilitated scalp infection with *N. gonorrhoeae* in offspring of infected mothers [4,14].

Primary oral infection [15]. Direct oral infection may occur alone or in association with genital infection. The clinical picture may be that of acute or chronic tonsillitis, or of gingivitis. Asymptomatic pharyngeal colonization is a well-recognized occasional finding, which responds poorly to antibiotic treatment but seems to clear spontaneously

within weeks. It does not apparently lead to mouth-to-mouth infection [16].

Local complications. Infection of Tyson's glands causes the development of firm, tender nodules on one or both sides of the fraenum. Ecthymatous lesions of the supra-pubic region have been reported in association with urethritis [17]. Infection of the median raphe of the penis presents as an indurated, red and sometimes tender ridge on the surface of the penis. Dorsal lymphangitis may lead to oedema of the penis. Infections of Littré's glands may be followed by abscess formation. An indurated nodule along the course of the urethra may discharge externally.

Infection of Bartholin's glands is the only local complication in the female which involves the skin. An acutely tender abscess up to 10 cm in diameter distends the labium (Chapter 68).

Disseminated gonococcal infection [2,5,9,18]. The usual features are pain and swelling in or around one or several joints, fever and chills, and skin lesions, although none of these is invariable. Mucosal infection is often asymptomatic, but a positive culture is usually obtained from the site of primary infection. The joint disease may be tenosynovitis, when blood cultures are commonly positive, but synovial fluid cultures negative; or suppurative arthritis, usually without skin lesions, in which synovial fluid cultures are often positive but blood cultures are negative. Fever is intermittent and may be high. The skin lesions, to which some authors apply the term septic gonococcal dermatitis [9], occur early in one or more crops, usually three or four, each of which consists of relatively few lesions, usually less than 20, scattered over the limbs. Initially there may be macules, papules or small vesicles with a red halo, but they soon develop into pustules or bullae, which may become haemorrhagic or necrotic. They heal after a few days and may leave small, superficial scars. Gonococci are only rarely cultured from the skin lesions. Erythema nodosum, erythema multiforme and urticaria have been described.

In the rare acute septicaemic forms, the patient is gravely ill, with high fever, and meningitis or endocarditis may occur. Skin lesions may be of the type described, but often take the form of non-specific transient erythema or purpura.

Diagnosis. In bacteraemic and septicaemic forms, certain clinical diagnosis is usually impossible. There is not always a history of genital infection. Genital foci should be sought and should be cultured repeatedly. The haemorrhagic vesicles are distinctive but not pathognomonic: they may also occur in septicaemia caused by the related *N. meningitidis* and *Acinetobacter* spp. and less often by other organisms. They may simulate *Varicella*, but they spare the scalp.

Gram stain and culture of exudate or secretion remain the essential methods. In the disseminated form, repeated blood cultures and culture of aspirated fluid from affected joints are required.

Other methods including immunological and molecular biological techniques are not universally applicable or available.

Treatment [19]. Effective drugs recorded in the past include certain penicillins, i.e. intramuscular aqueous procaine benzylpenicillin (procaine penicillin), or oral ampicillin or amoxicillin, all with oral probenecid; intravenous benzylpenicillin; ceftriaxone; cefoxitin; tetracycline; doxycycline; spectinomycin; and erythromycin. The choice of drug and regimen depended on the clinical condition, bacterial sensitivities, anticipated patient compliance, drug allergies and the coexistence of other suspected or confirmed diseases such as syphilis and chlamydial infection. However the more recent recommended single-dose regimens for gonorrhoea include ceftriaxone, cefixime, ciprofloxacin, ofloxacin, azithromycin or doxycycline [20].

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Acinetobacter infection

The Gram-negative organisms *Mima* and *Herellea* are now renamed *Acinetobacter*. *Mima polymorpha* has become *Acinetobacter calcoaceticus* var. *Lwoffi* and *Herellea vaginicola* is *Acinetobacter calcoaceticus* var. *anitratus*. These closely related *Acinetobacter* organisms are found as members of the resident skin flora in the axilla and groin in about 20% of normal subjects and may occur in the toe webs and on drier sites [1–3]. They have been isolated from skin pustules and from cellulitis [4,5], but their main importance lies in their role as uncommon but undoubted opportunistic pathogens. *Acinetobacter* spp. have been found to cause septicaemia, meningitis, osteomyelitis, synovitis, burn sepsis and wound infections. In the very young and the very old particularly, the source of infection may be exogenous, but endogenous infection clearly occurs, and indwelling intravenous catheters are likely routes in septicaemia. Reports of summer peaks of infection due particularly to *A. calcoaceticus* var. *anitratus* suggest that increased sweating leading to higher carriage levels may be important [6].

The role of these organisms in primary skin infections is unclear, but as cutaneous bacteria capable of causing nosocomial infections and exhibiting multiresistance, *Acinetobacter* demand attention.

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Moraxella infection

These organisms were previously grouped with *Mima* and *Herellea* spp. (now *Acinetobacter* spp.). They are now regarded as distinct. *Moraxella osloensis* has been reported as a cause of gonococcaemia-like systemic infection with skin lesions [1], and arthritis with skin lesions has been attributed to another *Moraxella* spp. [2]. These cases apart, *Moraxella* are more closely associated with conjunctival inflammation than cutaneous colonization or disease [3].

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Chancroid

SYN. SOFT SORE; CHANCRE MOU

Definition. Chancroid is a venereal disease caused by *Haemophilus ducreyi*, a Gram-negative bacillus, forming short chains.

Aetiology. The disease is prevalent in Africa, the Far East and Central and South America in communities with low hygienic standards [1]. Although previously rare in western Europe and the North American continent, it has in recent years become much more common, for example in France, Holland, Greenland and North America [2,3]. It is, however, difficult to be certain of the true incidence of this disease, as isolation of *H. ducreyi* from classical cases often failed in the past. In many studies therefore there is no bacteriological confirmation of the diagnosis. There is general agreement that clinical infection is reported very much more commonly in men than women, but the existence of an asymptomatic carrier state is not proven [4]. Chancroid may affect prostitutes.

Pathology. There is a non-specific inflammatory infiltrate. Involvement of the walls of small blood vessels in the region leads to ulceration.

Clinical features [5–7]. After an incubation period of 5–8 days, ranging from 1 to several weeks, a small, red papule develops and rapidly becomes pustular and then ulcerated. The ulcer, usually rounded or oval, has a ragged, undermined edge, surrounded by a red, very vascular, areola. It is tender and sometimes painful, but not indurated, enlarges slowly and often gives rise to satellite ulcers; two to five in a cluster are quite often present. Multiple ulcers are commoner in women than men.

In the male, the prepuce, the balanopreputial fold or the shaft of the penis and in the female, the labia majora, the posterior commissure and the perianal region are the commonest sites of infection. Extragenital lesions, although rare, do occur.

The course is variable. Without treatment, the lesion may rarely disappear spontaneously in a few days. Usually it persists for some weeks and may be complicated by severe phimosis and even by gangrene, or by destructive ulceration from secondary fusospirochaetal infection. In about 50% of cases, even if the initial lesion has been transient, inguinal adenitis develops about a week after the appearance of the ulcer. The glands on one or both

sides are enlarged and tender and may suppurate leading to chronic draining lesions.

Diagnosis. The chancre of syphilis is indurated and painless, and develops after a longer incubation period, but clinical differentiation is not always easy, and mixed infections can occur. Herpes simplex may also coexist in genital lesions with *H. ducreyi* [8].

Haemophilus ducreyi may be identified in the form of chains of coccobacilli in smears from the ulcer, or preferably of pus from a bubo. Ideally it should be cultured on one of the modern selective media at 33°C in an atmosphere of high humidity [9]. Even if the organism is present, dark-ground examination for *Treponema pallidum* and serological tests for syphilis should be undertaken.

Treatment [10–12]. The main treatment for chancroid is erythromycin given over at least 7 days. Resistance to sulphonamides, tetracyclines and trimethoprim has been reported in several countries. Ceftriaxone or azithromycin are alternatives given as a single dose.

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Salmonella infection

Aetiology. The *Salmonella* spp. are Gram-negative, motile bacilli, which are widely distributed parasites of mammals and birds. Some species, notably *S. typhi* and *S. paratyphi*, are primarily human pathogens; others are primarily pathogenic for other animals, but may infect humans. A third group is pathogenic only in animals other than humans. All are transmitted by contaminated food or water, with a portal of entry in the gastrointestinal tract.

The exanthematic cutaneous manifestations accompany active infection but metastatic abscesses may occur in carriers during periods of lowered resistance.

Veterinary surgeons handling infected cattle may develop skin lesions due to *S. dublin*. *S. typhimurium*, *S. abortus equi* and *S. saint-paul* have produced a similar clinical problem.

Clinical features [1–3]. Exanthematic eruptions are seen most frequently in untreated infections with *S. typhi*, and occur in about 50% of cases. The classical rose spots are crops of pink papules about 5 mm in diameter, each lasting for 3–5 days, and continuing to appear at irregular intervals from the end of the first week for 10–14 days. They are most numerous on the abdomen, chest and back. Exceptionally, vesicular or haemorrhagic rashes may be seen.

In infections with *S. paratyphi* B the eruption occurs less frequently but may be more extensive, involving the face and limbs as well as the trunk.

In *S. typhi*, *S. paratyphi* C and other *Salmonella* infections, for example *S. rostock*, single or multiple metastatic cutaneous and subcutaneous abscesses may develop [4,5].

Infections contracted by direct inoculation present as inflammatory nodules with central pustulation. In veterinary surgeons, forearm lesions may be small, inconspicuous papules or pustules, but larger painful nodules also occur. Malaise and fever are typically absent and spontaneous resolution within a few days is usual.

An ulcerative vulvitis or vulvovaginitis may rarely be the presenting symptom of *Salmonella* infection [1].

Diagnosis. The diagnosis of systemic infections must be established by culture from faeces or blood, or occasionally from the skin lesions, and confirmed by a rising antibody titre. The organism may be isolated directly from lesions contracted by inoculation. In such cases, the antibody titre does not rise.

Treatment [6]. Chloramphenicol remains an effective treatment for many systemic infections, but ampicillin, cotrimoxazole, cefotaxime and ciprofloxacin are also useful drugs for treating carrier states and cases of chloramphenicol resistance. Unfortunately, these are becoming increasingly common and in many cases it is advisable to use a quinolone such as ciprofloxacin or ofloxacin.

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Pseudomonas infection

Aetiology and pathology [1–3]. *Pseudomonas aeruginosa* (*P. pyocyanea*; *Bacillus pyocyaneus*) is an aerobic, Gram-negative rod, which occurs only as a transient member of the skin flora, mainly in the anogenital region, axillae and external ear, and is normally kept in check by the dominant Gram-positive cocci. It occurs in soil and water and is present in the intestine of a small percentage of adults and a high proportion of infants. It readily colonizes burns, ulcers or other moist skin lesions, and frequently contaminates bedpans, urine bottles, polythene sheeting and the hands of nurses in wards in which such patients are treated. It is mainly a nosocomial pathogen. Jars of ointment may also be contaminated [4]. Systemic infections are seen frequently, largely as a result of medical practices, such as the increased use of antibiotics in a variety of patients and high-humidity environments in nursing the newborn [3]. There is some evidence that the numbers of cases may be declining slightly, but this infection is still common. In older children and adults, clinical infections occur mainly in patients with debilitating diseases. *Pseudomonas* infections are frequent in intensive therapy units, in neutropenic patients and as causes of nosocomial pneumonia.

However, the repeated application of bactericidal agents effective against the Gram-positive flora, or prolonged maceration as in the syndrome of tropical immersion foot, favours the establishment of *Pseudomonas* even in previously healthy adults [1], and clinical infections eventually develop in a large proportion.

Experimental superhydration of the skin for 7 days with water-soaked cotton pads produced a vesiculopustular rash from which *Pseudomonas* was isolated [5]. Epidemic outbreaks of a follicular rash in areas of skin covered by swimsuits have affected users of overcrowded, heated swimming pools.

Under experimental conditions, *Pseudomonas* is pathogenic only in massive dosage or in damaged tissue, a pattern of behaviour that parallels that observed in humans. *Pseudomonas* appears to play a part in modifying and perpetuating some paronychial infections [6]. It is commonly isolated from chronic leg ulcers and from many other persistently moist lesions, including chronic external otitis, and, although its presence may be clinically apparent, it is uncertain to what extent it is pathogenic under these conditions. It is believed to be capable of maintaining the inflammatory changes after other organisms have been eliminated.

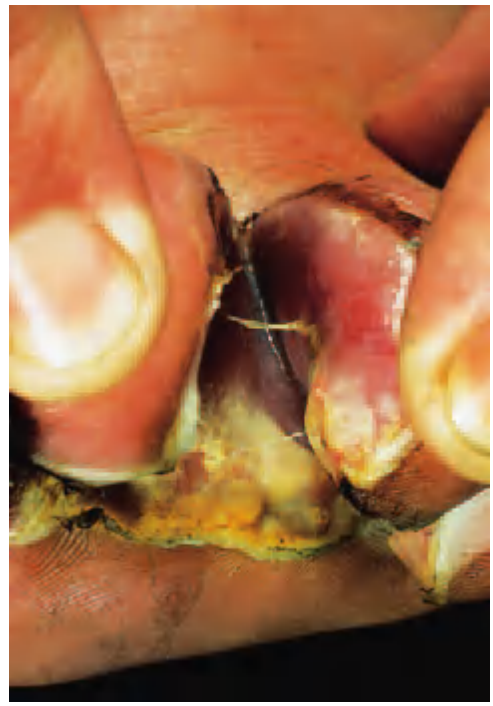

Fig. 27.14 *Pseudomonas* infection of the foot. (Courtesy of St John's Institute of Dermatology, London, UK.)

Typical strains produce two pigments, the blue-green pyocyanin, a phenazine derivative, and a greenish yellow pyoverdin.

Other species of *Pseudomonas* are sometimes of clinical significance. *P. cepacia* has caused lesions of the toe webs in troops training in swamp conditions [7]. The same species caused endocarditis and gangrenous ecthyma in a heroin addict [8]. This organism has now been transferred to another genus, *Burkholderia cepacia*.

Clinical features [9,10]. The commonest local infection in infancy is periumbilical, with a foul-smelling, bluish green discharge and spreading erythema. In some cases, usually under conditions of high humidity, widely scattered pustules may break down to form necrotic ulcers. Perionychial pustules may be accompanied by green discoloration of the nails. Involvement of the lips and cheeks may be followed by progressive gangrene. Sometimes, in the severely ill or in compromised neutropenic patients, primary cutaneous invasion with extensive necrosis may develop around a local erosion [11].

Inhibition of the Gram-positive flora or dermatophytes by maceration or antibiotics allows the development of a distinctive *Pseudomonas* infection of the toe webs [1] (Fig. 27.14), also called tropical immersion foot, characterized by sharply demarcated maceration, sometimes tinged with green, and showing green fluorescence under Wood's light. The sodden plaque tends to break down and secondary invasion by *Candida* may follow [7].

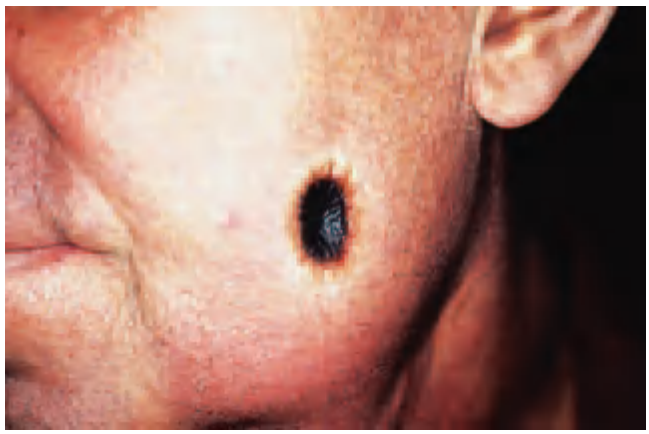

Fig. 27.15 Ecthyma gangrenosum. (Courtesy of Dr G. Scott, University College Hospital, London, UK.)

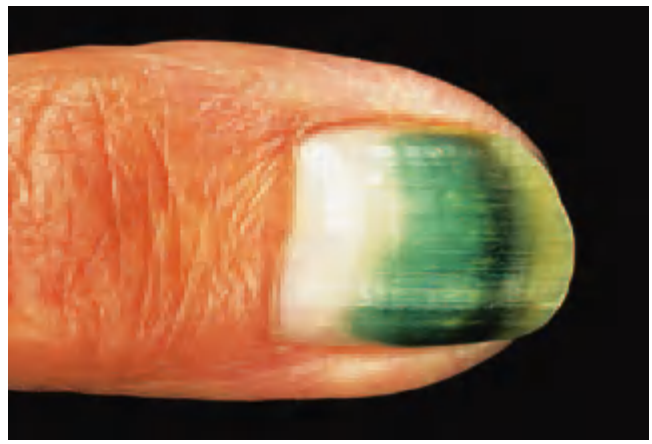

Fig. 27.16 *Pseudomonas* infection of the nail. (Courtesy of St John's Institute of Dermatology, London, UK.)

Pseudomonas can also invade superficial wounds, particularly burns [12]. This complication still carries a high mortality as large quantities of these organisms may thrive in burn eschar, and secondary septicaemia may result. Secondarily infected burns show discoloration of the slough with extensive surrounding oedema. Fever and shock may supervene.

Gram-negative folliculitis seen in swimming pool users is now a well-documented entity [13,14]. It may include macular, papular or pustular lesions. Some are urticarial, suggesting insect bites. Any part of the body that has been immersed may be affected but often the worst areas are those in contact with bathing costumes. In most cases, the rash settles spontaneously within 7–10 days in the absence of re-exposure. Hot tubs and whirlpools have also been associated, although changes to their outflow drainage has reduced this hazard. *Pseudomonas*, usually of serotype II, may be cultured from the skin and the infected water.

Pseudomonas septicaemia most commonly occurs in the severely compromised host [15]. Usually there are no skin lesions, but in a minority of patients the skin is affected and in a variety of ways. There may be non-specific erythema, which can be tender or spontaneously painful [16], purpura, or a cellulitis-like picture. Bullae may form, particularly in moist areas, such as the axillae, perineum and the buttocks. These may rapidly rupture to give necrotic ulcers—ecthyma gangrenosum (Fig. 27.15).

In elderly diabetics and neutropenic patients, the *Pseudomonas* is sometimes associated with a serious necrotic infection of the external ear known as malignant external otitis [17]. *Pseudomonas* spp. have also been implicated in severe exacerbations of acne vulgaris [18]. The presence of *Pseudomonas* spp. beneath nails with onycholysis gives rise to characteristic green discoloration (Fig. 27.16).

The prognosis of systemic infections is always grave, even with early treatment. Local infections in infants or patients with debilitating illnesses should be regarded as potentially dangerous, for systemic extension occurs readily. The invasion of damaged skin in the otherwise normal subject may be difficult to control permanently until the lesions are healed, but has no serious significance.

Diagnosis. Bacteriological confirmation of the diagnosis is readily obtained by cultures from the skin lesions or blood. The significance of the isolation of *Pseudomonas* from non-specific lesions must be carefully evaluated on the clinical findings.

Treatment. Superficial lesions respond best if drying out is possible. One per cent acetic acid compresses, potassium permanganate soaks and silver sulfadiazine cream may be of value, but topical antibiotics (e.g. polymyxin) are generally disappointing.

In the case of burns, extensive debridement followed by topical applications of silver sulfadiazine therapy is useful, although in some cases carbenicillin can also be used. In every case where antibiotics are contemplated it is important to base therapy on the results of *in vitro* sensitivity tests.

In septicaemia or where a severely compromised patient has superficial infection, systemic therapy using intravenous antibiotics should be started promptly under a bacteriologist's guidance. Ciprofloxacin, gentamicin, piperacillin, azlocillin, tobramycin and amikacin as well as ceftazidime may be used in appropriate combinations [19].

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Melioidosis

Definition and aetiology [1,2]. *Pseudomonas pseudomallei*, the causative organism, is a saprophytic bacterium, which may be isolated from soil and water in low-lying rice-growing regions of the Far East, particularly northern Thailand. It also occurs in Central and South America, Australia, the West Indies and Madagascar [3]. Although wild and domestic animals may become infected, it is no longer thought that animals form an important natural reservoir of infection. Transmission in humans is thought to follow environmental contamination of a minor injury. In humans, *P. pseudomallei* typically causes a severe glanders-like illness, which may be fatal, but serological evidence and retrospective enquiries suggest that mild febrile illnesses and subclinical infections occur in human subjects and probably in animals [1]. Other rare modes of transmission include inhalation or ingestion; the incubation period is very variable.

Clinical features [2,4]. The disease may run an acute, subacute or chronic course. The acute form with fever, prostration, gastroenteritis and pneumonia may be fatal within 2–4 days, but acute pulmonary infection due to *P. pseudomallei* is the commonest clinical manifestation of the illness. Septicaemia may complicate pneumonitis or appear without localizing signs elsewhere.

Many cases are subacute and last from one to many weeks. If the initial lesion is cutaneous, local abscess formation is rapidly followed by lymphangitis, lymphadenitis and septicaemia; characteristically multiple abscesses develop, subcutaneously, or in muscles, lung, liver and spleen. After infection by inhalation, pneumonic symptoms precede the septicaemic stage. In many cases, however, the clinical picture is variable, with unexplained fever and disseminated pyogenic lesions.

Chronic forms also occur: pulmonary symptoms and metastatic abscesses are most commonly seen, and in one such patient an associated severe urticaria cleared after treatment with tetracycline. Rarely, the infection remains limited to skin and regional lymph nodes, without systemic symptoms.

Diagnosis. The acute pneumonic and septicaemic forms can simulate tuberculosis, typhoid or staphylococcal infections. The diagnosis is established by isolating the organism or by detecting a rising antibody titre.

Treatment. A combination of high doses of tetracyclines and sulphonamides, supplemented by chloramphenicol in serious cases, should be continued until lesions have resolved. Alternatives include imipenem, piperacillin and cefotaxime. Abscesses require surgical drainage once antibiotic treatment is established. Resistance to some antibiotics including co-trimoxazole has been reported in some endemic areas [5], and where possible antibiotic sensitivities should be determined [6].

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Glanders

SYN. FARCY; EQUINA

Definition [1,2]. Glanders is a specific infection of horses and donkeys by *Pseudomonas mallei*.

Aetiology. It is now extremely rare worldwide. No accurate figures for the present world incidence are available but the disease is still endemic in horses in parts of Asia

and South America. Humans are infected by direct contact with horses, the bacillus usually gaining entry through an abrasion or through the conjuctiva or nasal mucous membrane. Very rarely there may be no discernable portal of entry.

Pathology. *Pseudomonas mallei* gives rise to a local adenitis, followed by necrosis and abscess formation. The infection spreads by the regional lymphatics and by metastasis.

Clinical features [2]. Glanders may be an intensely acute, rapidly fatal disease or may run a chronic relapsing course over months or years. After an incubation period varying from a few days to 2 or 3 weeks, malaise, headache and fever accompany the development at the site of inoculation of an area of cellulitis, which soon breaks down to form an irregular ulcer with an offensive, haemorrhagic, purulent discharge. If the primary site is cutaneous, the regional lymphatics become swollen and tender, and dull-red nodules along their course break down to form abscesses and sinuses. If the nasal or oral mucous membrane is the site of inoculation, there is extensive necrosis and destruction of the septum and palate. After a variable interval—a few days or many weeks—metastatic lesions begin to appear: grouped, dull-red papules, pustules or bullae, especially over the joints and face, are followed by ulcers that enlarge and coalesce. Deep subcutaneous abscesses with multiple sinuses may also occur. The symptoms that accompany septicaemia are, as expected, rigors, headache and confusion. Chest X-ray appearances range from acute abscess formation to lobar infiltration.

At this stage of dissemination meningitis, pneumonia and polyarthritis may also develop.

Although some cases survive for long periods with intermittent bacteraemia with severe constitutional symptoms and metastatic manifestations, others are rapidly fatal and in general the mortality without treatment is very high.

Diagnosis. The different clinical variants may simulate sporotrichosis, acute pyogenic infections or gangrenous pyoderma. The diagnosis may be suspected on the history of contact with horses, in which, however, the infection may sometimes be clinically inapparent, but must be confirmed by isolation of the organisms and by serological tests.

Treatment [2,3]. There are few reports on the response of glanders to the newer antibiotics, but it responds to sulphonamides. It would seem advisable to combine sulphonamides with other antibiotics, perhaps tetracycline or chloramphenicol as is recommended in melioidosis. Alternatives which show potential promise in melioidosis are co-trimoxazole, ceftazidime and imipenem, although the latter has not been fully assessed in either condition.

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Stenotrophomonas maltophilia infections [1]

Stenotrophomonas maltophilia, previously classified as a *Pseudomonas* spp., is the rare cause of opportunistic infection seen in intensive care settings or in neutropenic patients. It can cause pneumonia or septicaemia. However, in addition it can cause cellulitis, particularly around catheter insertion sites. It can also be isolated from wound infections. Sometimes the cutaneous lesions are nodular and accompany septicaemia.

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Rhinoscleroma

SYN. SCLEROMA

Definition. Rhinoscleroma is a chronic, slowly progressive, potentially fatal, infectious and mildly contagious disease caused by the bacterium *Klebsiella rhinoscleromatis* (or *Klebsiella pneumoniae rhinoscleromatis*) that affects the upper and lower airways. It is originally localized in the nasal fossae, and invades the upper respiratory tract and lacrimal apparatus, where it produces an infiltrating granuloma with a marked tendency to sclerosis and subsequent obstruction. It is a condition difficult to cure.

Incidence [1]. The disease occurs sporadically almost all over the world and is endemic but rare in certain countries including Central, East and West Africa, and Central and South America and the USA. The disease is acquired by direct or indirect contact with the nasal exudate of an infected person. The infection occurs in both sexes at any age, but it is more frequent between the ages of 20 and 40 years. It is more common in rural areas where social and hygienic standards are low.

Aetiology [1]. Rhinoscleroma is caused by *K. rhinoscleromatis*. This bacillus measures about 3 μm in length. It appears isolated, in pairs, or even in short chains, and is encapsulated, non-motile and Gram-negative.

Koch's postulates were not fulfilled until 1961, when Steffen and Smith [2] injected the bacillus into the nasal cavity and intracranially in mice and produced a

pneumonia that in some cases became chronic and granulomatous.

Pathophysiology [3]. The disease probably begins at the junction between the stratified squamous epithelium of the vestibule and the respiratory epithelium of the nose. Most investigators agree that the mucopolysaccharide in the capsule of the bacterium may be responsible for most of the damage.

Histopathology [1]. The histopathological picture is pathognomonic. A dense infiltrate is observed consisting mainly of plasma cells and two types of highly characteristic cells, the association of which allows this process to be distinguished from other granulomas. These cells are the Mikulicz cell and the Russell body. The Mikulicz cell is a large, round, vacuolated histiocyte measuring 100–200 μm in diameter. With Giemsa or Gram staining, numerous bacilli (A granules) or amorphous clusters of mucopolysaccharide (B granules) can be observed within the cytoplasm.

The Russell body or colloid body, measuring 20–40 μm, is a structure in the cytoplasm of the plasma cells, elliptical in shape, homogeneous, and extremely eosinophilic, and as such stains bright red.

Polymorphonuclear leukocytes actively phagocytose the bacilli as they enter the nasal mucosa. These cells then degenerate, either disintegrating or being engulfed by histiocytes and Mikulicz cells present in the stroma. These findings suggest that, while inside the Mikulicz cells, the bacilli are protected from therapeutic products in the blood, and hence there is a need for long-term therapy to be active against the bacteria when they are released [4]. Scar formation may be prominent.

Clinical features [1,5]. The first manifestations are usually nasopharyngeal. Since the disease runs a very slow progressive course and the lesions are indolent, the patient tends to seek medical advice only when it has been present for several years, as general health is not impaired.

The disease progresses through three overlapping stages:

Exudative (catarrhal), rhinitic or atrophic stage. This begins with symptoms of a common cold. There is headache and difficulty in breathing, a foetid, purulent rhinorrhea of long duration (weeks or months), with scabs, dryness of the throat and occasional epistaxis (Table 27.4). Hypertrophy of the mucous membrane can be observed, especially on the septum.

Proliferative or granulomatous stage. First, there is the infiltrative period. As the symptoms of coryza begin to subside, infiltration and obstruction of the lower portion of the nasal fossae occur, with an exuberant, friable granulation tissue, crusting and induration, which later extends to the pharynx and larynx. At this time a change in the modulation and tone of the voice (hoarseness) is produced. Anaesthesia of the soft palate is frequent.

Table 27.4 Frequency of initial symptoms of rhinoscleroma, determined by review of literature.

Symptom	Frequency (%)
Nasal obstruction	94
Nasal deformity	32
Hoarseness	12
Epistaxis	11
Upper lip swelling	10
Sore throat	6
Epiphora	4

Table 27.5 Approximate frequency of sites involved in rhinoscleroma, determined by review of literature. (From Miller *et al*. [6].)

Site	Frequency (%)
Nose	95
Palate	31
Pharynx	18
Larynx	14
Upper lip	12
Paranasal sinuses	4
Lacrimal sac	4
Trachea	2
Orbit	1

Later on, the nodular period supervenes. From the initial localization in the septum, the disease may spread forward to invade the nasal lobule and the upper lip. Backward extension may produce laryngeal and tracheal involvement, obstruction of the respiratory tract (Table 27.5), loss of the senses of smell and taste, epistaxis and epiphora (affecting the lacrimal apparatus). Bony destruction and cervical node involvement can occur. Breathing becomes difficult and painful, and tracheotomy is sometimes necessary.

Fibrotic (sclerotic) stage. Clinical improvement occurs. The previously inflamed tissue is replaced by dense collagen. The healing process (spontaneous or after therapy) leads to anatomical distortion and stenosis of the structures affected during the proliferative stage [7].

Radiographic findings. These include non-specific paranasal sinus opacification, nasal turbinate atrophy, nasal mass with bone destruction, transglottic narrowing, vocal cord thickening, and discrete subglottic narrowing, which can be shown using plain radiography and computed tomography [8].

Laboratory findings [1]. The identification of the bacterium is not easy, and is based on its biochemical activity, which distinguishes it from other *Klebsiella* spp. However, *K. rhinoscleromatis* has a unique antigenic marker, 02K3, with 0 representing the smooth somatic antigen and K the capsular antigen. This antigenic marker allows immunological identification using the peroxidase–antiperoxidase immune complex method. Serological reactions, such as the complement-fixation test, agglutination test and intracutaneous test, are of doubtful value.

Diagnosis. The diagnosis is based on:
1 the clinical features—especially when the lesions are advanced or pronounced;
2 the characteristic histopathological picture;
3 the finding of Frisch bacilli, adequately identified bacteriologically;
4 complement-fixation tests, which give inconsistent results.

Differential diagnosis. Rhinoscleroma must be differentiated from other diseases involving the nasal fossae and upper respiratory tract. At the early stages, chronic bacterial rhinosinusitis and atrophic rhinitis should be considered. At the late stages, the following enter the differential diagnosis: mucocutaneous or American leishmaniasis, which is highly destructive but not as proliferative or obstructive as scleroma, and paracoccidioidomycosis, which affects especially the mucous membranes of the mouth and is accompanied by marked adenopathy and granulomatous lesions that bleed easily ('blackberry' stomatitis). Rhinosporidiosis presents with polyps in the form of soft masses with minute white spots that represent sporangia. Lethal midline (facial) granuloma, Wegener's granulomatosis and malignant epithelial tumours and sarcomas can be differentiated by their rapid evolution. Other diseases that must be considered are: tertiary syphilis with bone involvement, sarcoidosis, nasal tuberculosis, which produces atresia rather than destruction by proliferation, yaws, with its destructive form called gangosa and its proliferative osseous form called goundou, leprosy, lymphomas and nasal polyps.

Prognosis. This is essentially a chronic disease with a slowly progressive course. Relapses are frequent after apparent bacteriological cure. Involvement of trachea or bronchi inevitably worsens the prognosis. The disease is rarely associated with AIDS [9].

Treatment [10,11]. *Klebsiella rhinoscleromatis* may be sensitive to several antibiotics, including trimethoprim–sulfamethoxazole, streptomycin, tetracycline, chlortetracycline, triacetyl-oleandomycin, kanamycin, gentamicin, cephaloridine and rifampicin. It is advisable to determine the antibiotic sensitivity of each strain and to continue the treatment until bacteriological cure is obtained.

Tetracycline is one of the drugs of choice for long-term treatment, at a dose of 2 g/day, given in divided doses for 6 months, followed by 1 g/day for a similar period of time. In case of recurrence, cephalexin, at similar doses and duration, should be tried [6]. Ciprofloxacin, 250–500 mg twice a day with meticulous nasal lavage with saline twice a day for 4 weeks, has recently been advocated [12]. The local treatment of rhinoscleroma with nasal packs of a 2% aqueous solution of acriflavine (a mixture of 2,8-diamino-acridine and 2,8 diamino-10-methylacridinium chloride), continued for 8 weeks, has been reported as effective [11]. Trimethoprim–sulfamethoxazole, 160–800 mg twice a day (based always on *in vitro* sensitivity studies), and betamethasone sodium phosphate, 4 mg i.m. every 3 weeks for 6 months, have been used.

During the healing process, scarring affects the upper respiratory tract, the nose, pharynx and larynx [9]. In this inactive fibrotic stage, surgical treatment may be required to correct severe structural and functional abnormalities, such as the narrowing of the nasal vestibule, nasopharyngeal stenosis and laryngeal web formation [6]. Nasal endoscopic techniques and the carbon dioxide laser have been used for the treatment of the obstructive scars [9].

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Tularaemia

Aetiology and pathology [1,2]. Tularaemia results from systemic infection with the Gram-negative bacteria, *Francisella tularensis*. Wild rodent or other small animal populations are probably the main reservoir of infection, which is transmitted to humans by the bites of ticks, usually species of *Dermacentor*, or of other arthropods, or by direct contact with infected rodents [2]. The epidemiological

pattern is extremely variable and infected food and water have sometimes been responsible for outbreaks in schools or camps. Most cases are sporadic. The disease is endemic in the northern hemisphere, including the USA and many parts of Europe apart from the UK. Sportsmen and women and campers are most exposed to infection, but cases have occurred in laboratory workers and in housewives.

Francisella tularensis is a pleomorphic, non-motile, Gram-negative coccobacillus, which produces a powerful endotoxin. It is a facultative intracellular parasite. Histologically, the rather variable tissue reaction consists largely of reticuloendothelial cells and monocytes with focal necrosis.

Clinical features [3,4]. The incubation period varies from 1 to 10 days. The clinical manifestations depend on the portal of entry: skin, eye, or respiratory or gastrointestinal tracts. Most sporadic cases are of the ulceroglandular, glandular or oculoglandular type. An ulcerated nodule at the point of inoculation is associated with enlargement and tenderness, and later with breakdown of the regional lymph nodes [3]. Systemic symptoms and toxaemia may be severe, but are often moderate, although pneumonia may occur. The typhoidal and pulmonary forms, which present with severe generalized or respiratory symptoms, respectively, run a more fulminating course.

During the toxaemic stage of all forms, cutaneous lesions may develop: a generalized eruption, maculopapular, or resembling erythema multiforme or profuse crops of nodules, usually on the limbs, may occur [3,5]. Nodular lesions resembling erythema nodosum have also been described.

Untreated, the course may be prolonged; the mortality of the typhoidal and pulmonary forms exceeds 30%, and that of the oculoglandular form is about 5%.

Diagnosis. The organism may be cultured from the primary lesion, the lymph nodes or gastric or pharyngeal washings. Specific agglutinins appear in the serum after about 10 days and increase in titre for some 4 weeks. Cross-agglutination with the *Brucella* antigen is a possible source of error. An enzyme-linked immunosorbent assay (ELISA) is available in some laboratories.

In differential diagnosis, cat scratch disease and sporotrichosis must be excluded, as must melioidosis and glanders.

Treatment [6]. Streptomycin 12-hourly i.m. in high doses (30–40 mg/kg body weight/day) for 3 days followed by half dosage for 3 days more, is recommended. Kanamycin and gentamicin are potentially useful alternatives [7]. Tetracycline controls symptoms but does not eradicate the organisms, and so relapses are frequent.

A live attenuated vaccine against tularaemia is available in some centres but it is usually restricted to laboratory workers at risk [8].

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Pasteurella infection

Pasteurella multocida infection

Aetiology [1]. *Pasteurella multocida* is a small, Gram-negative bacillus widely distributed as a member of the normal flora of the respiratory tract or intestines of many domestic and wild animals, in which it may cause haemorrhagic septicaemia if the resistance of the host is low. The organism does not normally occur in humans, but may be demonstrable in the sputum of patients with bronchiectasis. Most human infections follow bites by cats, dogs or other animals, and scratch injuries (usually from cats) may also become infected.

Clinical features and diagnosis [1–3] (Fig. 27.17). Most lesions are on the hands, arms or lower legs. The clinical picture is influenced by the extent and depth of the bite. Redness and swelling around the wound may spread rapidly over a wide area and may break down to discharge greyish yellow haemorrhagic pus through one or more sinuses. In other cases, the inflammatory changes, often associated with great tenderness, remain localized to the edges of the wound. If the bite is deep, there may be osteomyelitis or synovitis. About 15% of patients, particularly those patients with internal disease affecting the abdominal cavity or lung, have no history of exposure to animals.

The diagnosis will be suggested by the history and is confirmed by the isolation of the slow-growing Gram-negative bacillus.

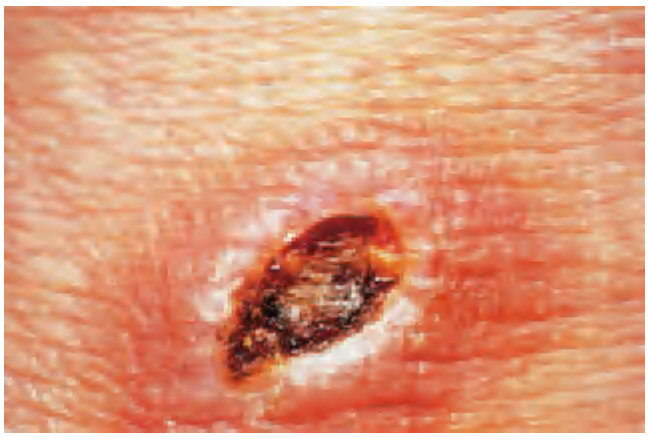

Fig. 27.17 *Pasteurella multocida* infection. (Courtesy of St John's Institute of Dermatology, London, UK.)

Treatment. The infection responds to penicillin, ampicillin and tetracyclines.

Other *Pasteurella* spp.

Other rare causes of animal-bite infections are other *Pasteurella* spp., such as *P. haemolytica*, *pneumotropica* and *ureae*. Their clinical manifestations are similar to those produced by *P. multocida* [4].

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Plague and *Yersinia* infections

Aetiology and distribution. *Yersinia pestis* [1], the cause of plague, is a small, Gram-negative, non-sporing and non-motile bacillus. With Giemsa it shows characteristic bipolar staining. It is a zoonotic infection that affects a wide variety of rodents, but particularly the urban and domestic rats, *Rattus rattus* and *R. norvegicus*, and is conveyed from them to humans by the bites of fleas (patient-to-patient transfer rarely occurs in pneumonic plague), or humans may be infected after contact with contaminated material. Plague is endemic in parts of India and the Far East, and in Madagascar and Southern and Central Africa [2,3]. Sporadic outbreaks occur in North Africa and the Middle East and there are foci of infection in the USA [4]. Occasional cases are recognized elsewhere in travellers from the endemic areas. The incubation period is 3 or 4 days, but it may occasionally be over 7 days. Following inoculation of the organism by a flea bite, the regional lymph node becomes swollen (the classic bubo of bubonic plague), and systemic spread, typically with a severe febrile illness, develops, frequently leading to death within days. Lung involvement occurs in some cases, with sputum that is highly infectious. If *Y. pestis* is inhaled, it is likely to lead to primary pulmonary infection (pneumonic plague), which is almost invariably fatal within 3 or 4 days.

In plague epidemics, mild bubonic infections with no systemic spread and truly subclinical infections both occur. Conversely, a patient may rapidly die of flea-transmitted plague without ever developing a bubo. In some instances, cerebral symptoms may be severe.

Clinical (cutaneous) features [2,5]. Although typically there is no distinct lesion at the site of the initial flea bite, an erythematous plaque may appear, become bullous and then crusted like an anthrax lesion. Such primary cutaneous lesions may occur in 10% of patients. The bubo arises in the regional lymph nodes several days later. The bubo is a swollen lymph node that becomes acutely painful. During the bacteraemic phase, a macular, erythematous or petechial rash may develop, sometimes frankly purpuric (the black death). Necrotic lesions that closely resemble ecthyma gangrenosum may develop [5]. These are the result of vasculitis and occlusion of vessels with fibrin thrombi.

In a few cases, umbilicated vesicles or pustules are seen particularly over the trunk [3]. This atypical eruption has been a notable feature of certain epidemics and is generally associated with a high mortality. If bubos are excluded, cutaneous lesions probably occur in about 10% of cases in most epidemics.

Diagnosis. Despite the short incubation period, air travel may carry infected individuals to any part of the world. Even in endemic areas, sporadic cases are often misdiagnosed. The adenitis is the most characteristic feature. Aspiration of a bubo and direct examination of smears and culture confirm the diagnosis. The culture of blood and sputum should also be undertaken.

Treatment [6]. Streptomycin, tetracycline and chloramphenicol are all effective and are preferable to the traditional sulphonamides for pneumonic cases.

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Yersinia enterocolitica infection

Yersinia enterocolitica is an important cause of a syndrome in which diarrhoea and pain similar to appendicitis occurs. In some reported cases there is polyarthritis, and a high proportion of patients, 30% in some series, also have erythema nodosum. Lesions appear from 2 to 20 days after the onset of abdominal symptoms [1].

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Brucellosis

Aetiology and pathology. Brucellosis is a widespread infection of cattle and sheep, goats and pigs with *Brucella abortus*, *B. melitensis* and *B. suis*, respectively. Humans are infected by the ingestion of contaminated milk or milk products, or by direct contact with infected animals. The incidence is therefore highest in veterinary surgeons and farmers.

The organism—a Gram-negative, aerobic coccobacillus—colonizes the cells of the reticuloendothelial system and induces a granulomatous tissue response.

The histological changes in the skin lesions [1] are usually not distinctive, but there may be intense inflammatory changes around vessels showing gross intimal proliferation, and granuloma formation may occur.

Clinical features [2,3]. After an incubation period, which is usually between 5 and 30 days but may be longer, headache, backache and general malaise accompany the onset of an intermittent fever. Other symptoms, gastrointestinal or nervous, are variable. The lymph nodes and spleen are enlarged in about 50% of cases and the liver in about 25%. Skin lesions develop in about 10% but are not pathognomonic. Morbilliform, scarlatiniform and roseolar exanthems are described. Less often there may be papular, bullous or haemorrhagic lesions. Erythema multiforme-like nodules of the legs have also been reported [4,5].

The course of brucellosis is variable. The illness usually lasts for 3 or 4 months, but both acute fulminating and extremely chronic forms occur. In the latter there may be persistent infection of bone, gall bladder or other organs.

Contact brucellosis [3]. Veterinary surgeons, and others who are in frequent contact with infected animals, may develop a high degree of allergic sensitivity to *Brucella* antigens. Contact with the secretion of an infected animal, usually during delivery, gives rise to pruritus, erythema and wealing within a short time of contact, often followed within 48 h by a profuse eruption of fine follicular papules, many of which become vesicular or pustular, and heal in 10–14 days to leave small scars. Secondary eruptions of erythema multiforme type may develop remotely from the sites of contact.

The contamination of abrasions by *B. suis* may cause indolent ulcers [6].

Diagnosis. Systemic brucellosis can be reliably diagnosed by laboratory investigation only. There is usually no leukocytosis but there may be a relative lymphocytosis. Specific agglutinins in a titre over 1 : 100 must be regarded as suspicious and over 1 : 300 as diagnostic. Positive blood cultures can sometimes be obtained.

Treatment. The recommended course of treatment for brucellosis now includes doxycycline and rifampicin, both of which should be given for at least 6 weeks. Shorter periods of therapy are frequently followed by relapse. Co-trimoxazole is an alternative drug. However, both this and single drug regimens, such as tetracycline or streptomycin, are reported to have a 10–40% relapse rate [7]. An alternative combination regimen is streptomycin and tetracycline, and the use of oxytetracycline plus gentamicin for an initial period of 5 days has been successful in children over the age of 8 years. Other drugs such as ciprofloxacin are active *in vitro* against *Brucella* spp., but their clinical role has not been fully evaluated [8].

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Infections due to *Bartonella* spp.

There has been a certain amount of taxonomic change about the position of species of the genus *Bartonella*, which were formerly classified as members of a distinct genus,

Rochalimea. Originally classified as Rickettsiae, they are now regarded as bacteria more closely related to *Brucella* than to other genera [1]. The human diseases associated with these organisms are trench fever due to *B. quintana*, bacillary angiomatosis (*B. henselae*, *B. quintana*) cat scratch disease (*B. henselae*) and Oroya fever (*B. bacilliformis*). Other newly decribed *Bartonella* spp. such as *B. elizabethae* have rarely been associated with human disease, for example bacteraemia.

Trench fever

Trench fever is caused by *Bartonella quintana*, which is transmitted to humans by the body louse [2]. It has been diagnosed in many different countries, usually under conditions where there have been very poor levels of hygiene. There is no known animal reservoir and it appears to be spread from person to person. After an incubation period of 5–38 days, there is a recurrent febrile illness. Most cases have a widespread maculopapular eruption, most prominent on the trunk, which fluctuates with the fever. The illness is usually mild with spontaneous recovery.

Cat scratch disease

This is a syndrome characterized by the development of peripheral lymphadenopathy after a cat scratch or bite. The causative agent is *Bartonella (Rochalimea) henselae* [3,4]. Patients with the syndrome usually have antibodies to this organism, which has also been isolated from lymph nodes. The same organism also causes a chronic form of bacteraemia in cats without any apparent ill effects.

Epidemiology [5,6]. The disease is worldwide and is most common in autumn and winter. It affects all ages, but mostly children and teenagers; 87% of 1200 cases were aged 18 years or under [6]. There is a history of cat contact, not necessarily prolonged or close, and of a local wound. In many cases it is believed that the cat is the source of the organism and the wound is the portal of entry. A scratch by a cat fulfils both requirements and is the commonest mode of infection. In a study of 1200 cases, it was found that while a bite or scratch from another animal may provide a route for infection, a feline source could nearly always be identified [6]. The cat is usually young but not ill. In only 3.5% of families was more than one member affected, and epidemics did not occur.

The diagnosis may easily be missed in mild cases, and subclinical infection may be frequent if skin-test surveys are valid, which give a 4% positive result in the general population, 18% in the families of patients and 23% in veterinary surgeons.

Pathology [6,7]. Both the primary lesions and the regional lymph nodes show characteristic, although non-specific, changes. In the early stages, there is focal reticulum-cell hyperplasia, which forms granulomas of sarcoid type. Later, there are microabscesses surrounded by a palisade of epithelioid cells and occasionally Langhans' giant cells.

The earlier a lymph node is biopsied, the greater the numbers of bacilli visible with the Warthin–Starry silver stain; they are usually undetectable by the time suppuration has occurred.

Clinical features [5,6]. Three to 5 days after the inoculating event, a papule (occasionally a group of papules) may form which progresses through vesicular and crusting stages in 2 or 3 days, and may ulcerate. This lesion may be inconspicuous, or may take several weeks to regress and then often leaves a superficial scar. Its identification is of diagnostic importance, and by diligent searching including examination of the scalp, ears and fingers, the inflammatory lesion or a residual scar can be found in over 90% of cases. About half are on the hands and arms and one-quarter on the head and neck.

Constitutional symptoms are usually mild, but fever is present in 60% of cases, persisting for a few days or 1 or 2 weeks. Illness lasting more than 2 weeks is uncommon [8].

Lymphadenopathy is present in all cases, and usually develops within 1 or 2 weeks of the initial papule, although it may not be noticed until later. The affected node is in the drainage path of the primary lesion but there is no lymphangitis. It is solitary in 85% of patients; two or three are seen occasionally. Uncommonly, bilateral lymphadenopathy is seen, but this can be explained by separate inoculations or a single one close to the midline. The glands are painful and tender and occasionally progress to suppuration and discharge before regressing in a period of weeks or months; persistent enlargement is uncommon. Recurrent lymphadenopathy is exceptional [8].

Primary inoculation of the eye, which does not require injury, causes a granulation, usually painless, and usually on the palpebral conjunctiva, followed by enlargement of the preauricular gland, constituting one of the forms of Parinaud's oculoglandular syndrome [9].

Unusual cutaneous manifestations include a maculopapular rash, urticaria, thrombocytopenic purpura, erythema nodosum, erythema multiforme and erythema marginatum; they appear to be more common among patients with severe or systemic disease [8].

Rarely, there may be systemic involvement [6,8,10] with arthritis, osteolytic lesions, intra-abdominal or intrathoracic lymphadenopathy, encephalopathy [11], myelitis [12], radiculitis, cerebral arteritis [13], pneumonia, pleurisy or granulomatous infection of liver [14] or spleen.

In the uncomplicated case, there may be a polymorphonuclear leukocytosis and a slight elevation of the sedimentation rate.

Cat scratch disease, even when accompanied by the more severe complications, is benign and self-limiting.

Diagnosis. Unilateral lymphadenitis is the usual presenting feature. A history of a cat scratch days or weeks previously resulting in a granulomatous nodule distal to the gland would immediately confirm the diagnosis, and the importance of actively seeking these two features has been emphasized [6]. If they are lacking, the clinical diagnosis is made by exclusion.

Primary tuberculosis, other mycobacterial infections, lymphogranuloma, pyogenic adenitis and sporotrichosis must be considered, and in the absence of a visible inoculation lesion, lymphoma or sarcoidosis must also be excluded.

Histochemical demonstration of the bacilli in the inoculation lesion or, more commonly by the time of presentation, in the lymph node, would confirm the diagnosis. However, the organisms are increasingly difficult to detect as the disease progresses. Otherwise, histology is not specific, and biopsy is not routinely recommended. Skin testing with cat scratch disease antigen made from pus from affected lymph nodes has its advocates [6] but is not generally advised.

Treatment [6]. Antibiotics are not effective, despite the fact that they are used with success in bacillary angiomatosis. Fluctuant glands may be aspirated, but should not be incised as chronic drainage may occur. Excision of lymph nodes is not justified therapeutically, although it may occasionally be indicated for histology.

Bacillary angiomatosis

Aetiology. Bacillary angiomatosis is an uncommon disease found in AIDS patients and occasionally other patients with severe immunosuppression [15]. It is characterized by the development of friable angiomatous papules and nodules. Two *Bartonella* spp. have been associated with this infection: *B. henselae* and *B. quintana* [16]. The appearance of these lesions follows a septicemia, which is usually mild and often passes unnoticed.

The disease has been described mostly from the USA although it is also seen in Europe. The infection is sporadic and there is not necessarily a history of exposure to cats or of skin injury. There are no known differences between infections caused by the two species of *Bartonella*.

Clinical manifestations. The lesions of bacillary angiomatosis are very variable [17]. They may be solitary or appear in crops. They may be small papules of dermal nodules. The more superficial lesions closely resemble pyogenic granulomas. They can involve any site including mucosal surfaces. Local lymphadenopathy is common. Very extensive lesions may cover parts of the face or trunk.

There is lobular proliferation of small blood vessels that contain swollen endothelial cells. These contain granular material, which consists of clumps of bacteria seen with the Warthin–Starry stain.

Complications include bacillary peliosis, where cyst-like inflammatory structures may develop in internal organs such as the liver. Again the endothelial cells lining these spaces contain large numbers of organisms.

Diagnosis. The diagnosis is made by the appearances of the typical lesions and the presence of large clusters of bacteria on Warthin–Starry staining. Cultures are not usually taken as they are technically difficult to process. However, polymerase chain reaction (PCR) is now increasingly used [18]. Lesions have to be distinguished from those of pyogenic granulomas, molluscum contagiosum, Kaposi's sarcoma and deep fungal infections disseminated to skin. They are also very similar to those of verruca peruana.

Treatment. There are no controlled studies of treatment of this condition, but doxycycline or erythromycin are usually given. It may be necessary to use long periods of treatment for 8 weeks or longer. Relapses are common.

Oroya fever and verruga peruana

SYN. CARRION'S DISEASE

Definition [19]. Oroya fever is an infectious disease transmitted by *Phlebotomus* spp. and caused by the small, rod-shaped organism *Bartonella bacilliformis*.

Aetiology. It is endemic in parts of Peru, and epidemics have occurred in neighbouring Latin American countries. In the endemic areas, most individuals are infected in childhood and acquire a permanent immunity.

Clinical features [20]. The incubation period is usually about 3 weeks but ranges from 2 to 6 weeks. Two forms of infection are recognized: Oroya fever and verruga peruana; these are now known to represent two stages of infection. In the first stage (Oroya fever) there is a sudden onset of pyrexia accompanied by a rapidly progressive haemolytic anaemia. Hepatosplenomegaly and generalized lymphadenopathy occur and a petechial or ecchymotic rash may develop. The mortality is high and many cases are accompanied by *Salmonella* septicaemia.

Verruga peruana may develop without previous Oroya fever, or may follow it weeks or months later. The eruption is composed of erythematous papules, which appear in crops and often become nodular or pedunculated. Some lesions become very large, others may be haemangiomatous or haemorrhagic. They are most numerous on the face, neck and limbs but may also involve mucous membranes. Mild constitutional symptoms and fever coexist in this form of infection, which may settle spontaneously. Lesions may persist for months or years. One

characteristic is that they may be present in different stages of evolution in the same patient [21].

Diagnosis. The diagnosis should be considered only if the patient has visited the endemic areas. Verruga peruana must be distinguished from yaws, acquired haemangiomas and Kaposi's sarcoma.

The biopsy appearances of verruca peruana show lesions containing numerous small blood vessels with endothelial proliferation. There is a variable infiltrate of chronic inflammatory cells and lesions heal with fibrosis [22].

In Oroya fever, the organism can be seen in blood films or isolated in blood cultures. Blood cultures are also positive during the active phase of the benign form, and in skin biopsies *B. bacilliformis* can be seen in the cytoplasm of endothelial cells.

Treatment. In Oroya fever, chloramphenicol 2 g/day for a week is the treatment of choice because of the frequent coexisting *Salmonella* infection, but *B. bacilliformis* itself responds to penicillin, tetracyclines and streptomycin. In verruca peruana, response to antibiotics is unsatisfactory; most lesions evolve and eventually settle uninfluenced by treatment.

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Ehrlichiosis

Ehrlichia spp. are small, Gram-negative bacteria. They form clusters of intracellular inclusion bodies known as morulae. Formerly associated predominantly with veterinary infection, a human form of the disease has been recognized more recently as a tick-borne zoonosis. A number of different species have been recognized in humans, although *E. chaffeensis* and *E. sennetsu* are most commonly involved. Most cases have been described from the USA [1], although patients with this infection have been recognized in Europe. In the USA, the distribution of the dog tick, *Dermacentor variabilis* and the Lone Star tick, *Amblyomma americanum*, coincide with the distribution of human cases. The main target cell for these bacteria are macrophages.

The median incubation period is 7 days and patients generally present with fever, malaise, headache and myalgia. Over 30% of patients have a diffuse maculopapular rash and in some this becomes petechial [2].

Leukopenia and thrombocytopenia may develop. *Ehrlichia sennetsu* infections that occur rarely in the Far East are similar in presentation, although rashes are uncommon [3].

The diagnosis is difficult as cultural techniques are complicated and a serological assay using immunofluorescence is employed instead. The clinical history is also important. It is important to distinguish erhlichosis from Rocky mountain spotted fever in which more patients develop a rash.

Treatment depends on the use of tetracycline or doxycycline.

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Other Gram-negative bacilli

On occasions, other Gram-negative bacteria have been associated with skin disease. *Actinobacillus actinomycetemcomitans* is frequently isolated from lesions of actinomycosis along with the usual *Actinomycete* cause, giving rise to the view that it is involved in the pathogenesis of this condition [1].

The aeromonads may occasionally cause cellulitis. These bacteria are inhabitants of water and cause infections in fish and reptiles. Cellulitis or necrotizing fasciitis caused by *Aeromonas* spp. is rare, but may follow contamination of a wound in contact with fresh water [2]. It may also occur in immunocompromised patients. *Aeromonas hydrophila* is sensitive to co-trimoxazole and chloramphenicol, but usually resistant to ampicillin and other penicillins. Cellulitis can spread rapidly and may involve muscle tissue or periosteum unless treated promptly [3].

Members of the bacterial group known as dysgonic fermenters (DF), such as DF-2, may also cause severe skin lesions. These organisms are Gram-negative rods that grow poorly on most cultural media. They are thought to be zoonotic in origin, and have been isolated from the oral cavity of dogs. DF-2 causes infections in patients who have undergone splenectomy or have other predisposing conditions, where it causes an acute septicaemic illness. More indolent infections including cellulitis are seen in otherwise healthy patients [4]. However, septicaemia may also develop in this group. Eugonic fermenters (EF agents) have also been isolated from dog bites.

Eikenella corrodens, an anaerobic, Gram-negative bacillus, may cause abscesses of the skin in intravenous drug abusers. It has also been isolated from wounds caused by human bites [5].

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Vibrio vulnificus infections

Certain non-cholera vibrios have been found to cause severe cellulitis. *Vibrio vulnificus* is the best known of these organisms. It is found in warm sea-water areas such as around the gulf of Mexico, South America, Asia and Australia and may invade via the gastrointestinal tract, for instance, after eating raw oysters, or contaminate superficial wounds [1,2]. In predisposed patients, such as those with diabetes or chronic liver disease, and occasionally in the otherwise healthy, it may cause a septicaemic illness of rapid onset. A characteristic is the appearance, in almost two-thirds of patients, of erythema and haemorrhagic bullae or vesicles which progress to ulceration. Systemic signs include hypotension and rigors leading to multiorgan failure. The infection is often rapidly progressive and fatal. Alternatively, it may cause cellulitis, necrotizing fasciitis and ulceration after infection of a skin wound, which may then progress to septicaemia [3]. Direct Gram stains of smears will show curved Gram-negative bacilli. The main treatment is large doses of ceftazidime, ciprofloxacin or tetracycline and surgical debridement where necessary.

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Anaerobic bacteria

Anaerobic bacteria are organisms that cannot grow on a solid surface in the presence of oxygen. They can be divided into those that are strict anaerobes, such as *Treponema* spp., and the moderate anaerobes such as *Bacteroides fragilis*. They include both Gram-positive (e.g. *Propionibacterium* spp.) and -negative (e.g. *Bacteroides* spp.) organisms and certain spiral bacteria. Most of the bacteria considered in this section are Gram-negative.

The family Bacteroidaceae consists of Gram-negative, rod-shaped bacilli with rounded or pointed ends. Some are fusiform. They are non-motile, do not form spores and are strict anaerobes [1]. Within the family are four genera: *Bacteroides*, *Prevotella*, *Porphyromonas* and *Fusobacterium*. These include the *Bacteroides fragilis* group, many of which are gastrointestinal tract commensals. The *Prevotella* spp. includes the organisms formerly known as *B. melanogenicus* and *B. oralis*, now *P. melanogenica* and *P. oralis*, respectively. The different genera can be classified according to nutritional requirements, pigmentation and morphology. Classification within the genus, *Fusobacterium* spindle-shaped bacilli, is unsatisfactory and, although a few species have been clearly defined, many isolates of commensal fusiform bacteria from animals and humans cannot be reliably identified as named species. *Fusobacterium necrophorum*, the cause of calf diphtheria and a variety of human infections, and *F. nucleatum*, a member of the

normal flora of the human mouth with a pathogenic capacity, are well-characterized exceptions. A newly described species, *F. ulcerans*, has been isolated exclusively from tropical ulcers and contaminated mud from endemic areas.

Leptotrichia buccalis is the single species recognized in the *Leptotrichia* genus. It is a long, rod-shaped organism with pointed ends, not truly spindle-shaped, and sometimes forming lengths of separate filaments. *Leptotrichia buccalis* is possibly synonymous with Vincent's fusiform organism, and therefore should not be labelled a *Fusobacterium* spp. It is an oral commensal in humans.

Bacteroides spp. are now recognized as common causes of Gram-negative bacteraemia and of abscesses. They are occasionally important in suppurative hidradenitis and in infected pilar cysts. Their role in decubitus ulcers is unclear but their frequent presence is not in doubt. Mixed infections are characteristic of this group of bacteria. In diabetic ulcers, in particular, *Bacteroides* spp. may be isolated and appear to be contributing to the clinical condition [2].

Prevotella infections dominate in intraoral infections including piorrhoea and Ludwig's angina. In many cases they may act in concert with other bacteria.

Fusobacterium organisms, although a well-known cause of infections in animals, are less often isolated today from human pathological material. In the past, *F. necrophorum* was regarded as an uncommon but important human pathogen among those in contact with animals. The term necrobacillosis was applied to such infections, characterized as they were by necrosis and abscess formation. *Fusobacterium nucleatum* can be found in severe intraoral infections.

In common with many anaerobic bacteria, fusibacteria appear to synergize with other organisms, including spiral bacteria, to produce disease. They have been implicated in the pathogenesis of cancrum oris (noma) as well as tropical ulcer (*F. ulcerans*), where the production of butyric acid by these organisms contributes to tissue necrosis.

Clinical manifestations. This group of organisms are important causes of a variety of infections from sinusitis and oral abscesses to endocarditis. *Bacteroides*, *Prevotella* and *Porphyromonas* spp. may also cause abscesses below the waist area. They have also been associated with other severe cutaneous infections such as necrotizing subcutaneous infection (see below).

Treatment. Treatment of anaerobic Gram-negative infections is largely empirical, and testing the organisms for sensitivity is difficult. The choice of drugs includes metronidazole, clindamycin, imipenem and amoxicillin–clavanulate. However, advice should be sought before selecting therapy.

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Tropical ulcer

SYN. TROPICAL PHAGEDENIC ULCER; TROPICAL PHAGEDENA

Aetiology. Tropical ulcer is a synergistic bacterial infection that follows invasion of the skin by at least two organisms, one of which is a *Fusobacterium* spp., usually *F. ulcerans*; the others include spirochaetes or other anaerobic bacteria [1,2]. It occurs very commonly throughout the hot and humid tropical regions, in some of which, for example northern Papua New Guinea [3], it is the commonest skin disease. It has acquired in different parts of the world numerous local names, but there are few minor differences in its clinical features and course.

There is no clear evidence that host-predisposing factors play a part in the pathogenesis of this condition. Previously, malnutrition was thought to be critical to the development of tropical ulcers, but it is likely that social factors such as overcrowding are equally important. Recent studies have not shown a correlation between nutritional indices and the development of tropical ulcer [4], although the possible role of deficiencies in micronutrients is unknown. Zinc therapy, however, does not appear to hasten healing of lesions [5].

There is now considerable evidence to suggest that this disease is an infection [6]. The condition has been shown to be transmissible by inoculation of material from affected patients [7]. Recently, the appearance of early ulcers and preulcerative papules has been correlated with the isolation of *F. ulcerans*, a fusobacterial species unique to tropical ulcers [1]. Other anaerobes are also sometimes isolated, and a consistent feature is the presence of spiral bacteria, which have not been isolated in culture but which have the ultrastructural features of *Treponema* spp. In late-stage ulcers, other bacteria including many aerobes such as *Staphylococcus aureus* can be found in tropical ulcers. *Fusobacterium ulcerans* causes destruction of tissue-culture cells and can synergize with other bacteria to cause destructive skin lesions in experimentally infected animals [1]. It is likely therefore that the infection is a synergistic anaerobic infection confined to parts of the humid tropics. While the reservoir of *F. ulcerans* is not known, it has been isolated from mud and stagnant water in endemic areas [8].

Clinical features (Fig. 27.18). Most tropical ulcers develop at a site of potential trauma, a scratch, cut or insect bite,

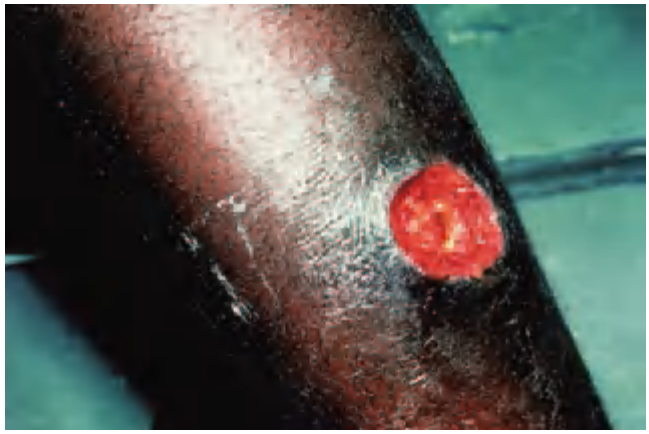

Fig. 27.18 Tropical ulcer. (Courtesy of St John's Institute of Dermatology, London, UK.)

and are therefore commonest on the lower legs and on the unshod foot. They are not unusual on the arms, and may occur anywhere. Ulcers developing in skin that was apparently previously healthy begin as a small papule or bulla, which may be haemorrhagic, and which soon breaks down rapidly to form a sharply defined ulcer, with a slightly indurated edge that may be undermined. An important feature is the rapid breakdown of the preulcerative papule to form a tropical ulcer [8].

The floor is covered by a foul-smelling, greyish, purulent slough. Pain is usual, and there may be fever and constitutional symptoms. There is usually no regional adenitis. If the lesion is treated promptly, even with careful dressing, the spread is limited to a lesion 2–4 cm in diameter, which heals slowly. In about 4–15% of cases, depending to some extent on the availability of primary health care, chronic ulcers may form and may involve deep structures such as tendons and periosteum [8]. Squamous epithelioma develops after 10 years or more in some such cases.

Diagnosis. While pleomorphic fusiform and spiral bacteria are important pathogenic organisms, their presence or absence is not diagnostic and their isolation in culture impracticable. The mainstays of diagnosis are the rapid onset of lesions, their clinical appearance and the clustering of cases in the locality. In endemic areas, the main differential diagnosis is between yaws, leishmaniasis, ecthyma and mycobacterial ulcers. Sores due to infected skin lesions are more indolent and smaller in size.

Treatment. Rest, elevation of the limb and adequate diet are of great importance. Any underlying chronic disease should be treated. During the early stages of the disease, penicillin or metronidazole are recommended, combined with bland local applications, and a plaster boot may be helpful in allowing early ambulation when infection has been controlled.

Early grafting has been very successful in the rapid treatment of tropical ulcers, but it is dependent on the availability of the necessary expertise and patient compliance [3].

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Granuloma inguinale

SYN. GRANULOMA VENEREUM; DONOVANOSIS; ULCERATING GRANULOMA OF THE PUDENDA

Definition. Terminological confusion with the chlamydial disease lymphogranuloma inguinale must be avoided. Granuloma inguinale is a chronic granulomatous infection of the genitalia and surrounding skin caused by *Calymmatobacterium granulomatis*, formerly known as *Donovania granulomatis*. This organism has not been isolated in pure culture and therefore its taxonomic status is uncertain.

Aetiology [1]. Granuloma inguinale is widespread in the tropics and subtropics, but in most areas is relatively uncommon. It is mainly seen in Africa, South America, the Caribbean and New Guinea. Cases are rare outside these areas. In some countries, males are more frequently affected than females, but in others, such as Brazil, the disease is commoner in women. Venereal transmission, although almost certain, is not entirely proven, and infectivity is undoubtedly low. Most patients are young adults, and homosexual men are said to be more frequently infected, suggesting perhaps that the gastrointestinal tract is the natural habitat of this organism.

Calymmatobacterium granulomatis is a small, pleomorphic, non-motile, Gram-negative bacillus showing bipolar staining. It is fastidious and must be isolated on the yolk sac of the chick embryo, although it may subsequently be grown on media containing egg yolk. In tissue scrapings stained by Wright's method, *C. granulomatis* may be seen within characteristic large mononuclear cells as Donovan

bodies. *Calymmatobacterium granulomatis* cross-reacts serologically with *Klebsiella rhinoscleromatis*.

Pathology. The histological changes are not specific. In the inflammatory reaction that infiltrates the cutis and subcutis, plasma cells and polymorphonuclear leukocytes predominate. There are also some lymphocytes and large mononuclear cells containing Donovan bodies [2]. In chronic lesions, fibrosis and epithelial hyperplasia are also present to a variable degree.

Clinical features [3,4]. The incubation period, which is not always easy to determine, is probably 9–50 days. The earliest lesion is a firm papule or nodule, which breaks down to form an ulcer with a sharply defined, overhanging edge. The ulcer is not painful and there is no adenitis.

The lesion subsequently evolves in a variety of ways, dependent on the balance between healing and destruction and the degree of epithelial hyperplasia.

Deep and rapidly extending ulceration is seen mainly in women. Serpiginous extension with or without vegetative epithelial changes occurs in the groins and other flexures.

The initial lesion is usually on the pubis, the genitalia, the perineum, the groins or the perianal region. While clinically it may appear that the lymph nodes in the groins are enlarged; this is usually caused by a subcutaneous granuloma, which may subsequently undergo necrosis. Rectal lesions have also been described.

In 3–6% of cases [5], the lesion is extragenital, occurring especially on the face, where it favours the nose and lips, but it sometimes occurs on the limbs.

Healing may occur at any stage, or slow or rapid extension may continue intermittently and irregularly for years. Secondary infection may be severe and may lead to adenitis. Temporary remissions may be followed by recrudescences, which may occur in healed scars. When the lesions are extensive, cachexia may, after a long course of many years, predispose to death from intercurrent infection.

In some patients, usually women, metastatic involvement of liver, spleen and bones may occur.

Diagnosis. In the early lesions, syphilis must be excluded by dark-ground examination and serology, and at all stages the possibility of associated syphilitic infection must be remembered.

Smears should be taken and searched for Donovan bodies. It is convenient to take the smear from part of a biopsy from the edge of the lesion, the remainder of the specimen being examined histologically. This organism cannot be cultured.

Treatment [6]. The tetracyclines, erythromycin, streptomycin, azithromycin, gentamicin and chloramphenicol are all effective. Tetracycline must be given in a dose of 500 mg four times a day for 10–20 days. Minocycline or doxycycline may also be used. Resistance of the organism to tetracycline, although previously unknown, was reported in a single case in 1973. The most effective of the current drugs is probably azithromycin, which has the added advantage of being active against other sexually transmitted bacteria such as *Treponema pallidum* and *Haemophilus ducreyi* [7].

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Spirochaetes and spiral bacteria

Spirochaetes are long, flexible, spiral organisms, motile but without external flagella. Many exist in nature in aquatic habitats [1,2]. Three genera include important human pathogens and commensals: *Treponema*, *Borrelia* and *Leptospira*. *Treponema pallidum* causes syphilis; *T. pertenue* causes yaws; *T. carateum* causes pinta (Chapter 30). *Borrelia recurrentis* causes louse-borne relapsing fever; *B. duttoni* and other species cause tick-borne relapsing fever; *B. burgdorferi* is the name for the *Ixodes dammini*-associated spirochaete, the cause of Lyme arthritis with associated erythema chronicum migrans. *Leptospira interrogans* complex causes leptospirosis including Weil's disease. Commensal spirochaetes occur in the mouth (*T. microdentium* and *T. macrodentium*) and around the genitalia (*T. refringens*), as well as in the intestine. They appear to have no pathogenic potential but they are important as they may be confused with *T. pallidum*, from which they differ morphologically.

Spirillium minor, the cause of one form of rat-bite fever, is a spiral bacterium which is short, rigid and has bipolar flagella.

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Relapsing fever

Aetiology. There are two forms of this disease: louse-borne or epidemic relapsing fever due to *Borrelia recurrentis*, for which the human body louse is the vector, and tick-borne endemic relapsing fever caused by various species of *Borrelia*, for example, *B. duttoni* and *B. hermsi*. The louse-borne epidemic form is found in Ethiopia, the Sudan, other parts of Africa and the Far East, while the milder sporadic tick-borne cases occur worldwide [1,2].

Clinical features [1,3]. The very variable symptom complex develops after an incubation period of about a week. High fever, headache, myalgia, vomiting and respiratory symptoms usher in the acute attack. Jaundice and hepatosplenomegaly with liver tenderness are common, and a petechial or purpuric rash, predominantly on the trunk, is found in up to 60% of patients. A remission occurs after a few days, to be followed by a relapse, and this pattern may continue for weeks. The cutaneous eruption does not, however, recur after the initial episode.

Diagnosis. Diagnosis is best confirmed by demonstration of the spirochaete in blood films using stained preparation or dark-ground illumination.

Treatment. The usual treatment is either tetracycline or erythromycin. Penicillin is an alternative. In the case of louse-borne infections, this is given as a single dose, for example, 0.5 g tetracycline [4]. Because treatment failures are more frequent in the tick-borne group, the course of therapy is usually prolonged, for instance, by giving 6-hourly treatment for up to 10 days. A severe reaction similar to the Jarisch–Herxheimer reaction is very common at the outset of treatment, particularly in louse-borne relapsing fever treated with penicillin [5].

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Borrelia burgdorferi and Lyme disease

Definition. *Borrelia burgdorferi* is a spirochaete transmitted to humans by tick bites. The resulting clinical conditions are encompassed in the term Lyme disease (or Lyme borreliosis), named after the town of Lyme in Connecticut, USA, where the disease was first recognized in 1977. The characteristic eruption, erythema chronicum migrans (ECM), at the site of inoculation, is a common early manifestation, and dissemination of the infection may cause disease of the nervous system, heart and joints, in addition to other dermatoses. Differences in the disease spectrum in different geographical areas have been noted, and may be due to variation within the bacterial species [1] or to differences in diagnostic criteria and treatment practices [2].

Aetiology [1]. The principal vector of *B. burgdorferi* infection is the *Ixodes* tick, different species of which predominate in different parts of the world, their distribution corresponding to that of Lyme disease. Patients usually live close to, or have visited, woodland areas, where small mammals are necessary hosts for immature stages in the life cycle of the tick. Adult ticks may infest larger mammals, especially deer.

Lyme disease has been reported in most parts of the world but especially in the USA, where it is the commonest vector-borne infection, and in Europe, particularly in Scandinavia and central Europe. All ages and both sexes are affected. High rates of infection have occurred in areas in which the tick had recently become established in high numbers [3]. In contrast, 10 of 40 agricultural workers, with long-standing high exposure to tick bites, had positive *B. burgdorferi* serology, but Lyme disease was infrequent and mild in this group, a possible interpretation being that frequent tick bites may confer a degree of immunity [4].

Infection may occur at any time of year. Young nymphal ticks feed in early summer, when there is a marked peak in incidence of acquisition of human Lyme disease. The smaller autumn peak noted in some studies is associated with bites from adult ticks [3,5]. Deer, in particular, appear to harbour the infection in endemic areas.

After *B. burgdorferi* infection, specific antibodies are produced, but if the patient is treated early in the course of the disease, antibodies may disappear within a period of months and reinfection may occur.

Clinical features [1,6–9]. Of patients ultimately diagnosed as having Lyme disease, about 50% recall a tick bite; a bite by the autumn and winter feeding adult tick is more likely to be noticed than a bite by the summer feeding nymphs. About 90% develop ECM at the site of inoculation (Fig. 27.19). The eruption appears 1–36 (average 9) days after the bite, and is due to local spread of the spirochaete, usually in a ring formation enlarging at a rate of several centimetres per week. In some cases the erythema is intense, in others barely detectable; it

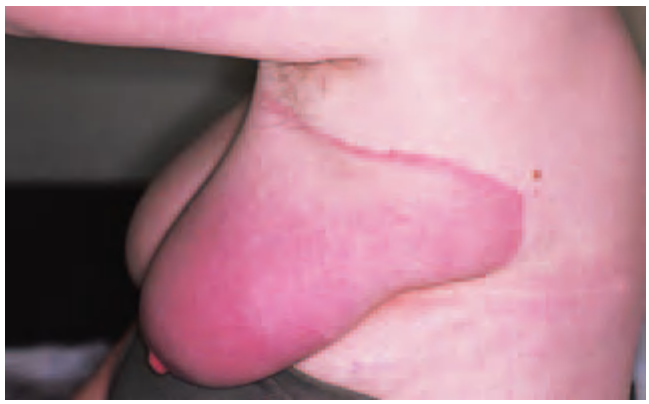

Fig. 27.19 Erythema chronicum migrans (ECM). (Courtesy of Dr A.S. Highet, York District Hospital, York, UK.)

may be entirely flat or show elevation at the centre, the periphery or both. Slight scaling is occasionally seen. Older areas of residual erythema may become dusky blue. There may be a zone of clearing behind the advancing ring producing a target-like morphology. Moderate burning or itching occurs in one-third of cases. If untreated, the lesion fades, usually within a few weeks, but the duration may vary between 1 day and 14 months. Regional lymphadenopathy and mild constitutional symptoms may occur.

Dissemination of the infection may occur within days or weeks of inoculation. Spirochaetes have been detected in affected organs, although immunological processes may also contribute. Of the over 5000 cases reported to the US Centers for Disease Control between 1983 and 1986 [5], 57% had arthritis; 18% had neural involvement, characteristically meningitis, cranial nerve palsies and peripheral radiculoneuritis; and 10% had heart disease including myocarditis, pericarditis and conduction defects. In a European series, neurological disease was prominent, but arthritis and carditis are not commonly diagnosed [6,10]. Migratory joint pains, myositis, conjunctivitis, hepatitis, generalized lymphadenopathy and splenomegaly may occur.

Two cases of fatal intrauterine infection have followed first-trimester maternal infection. In a prospective study of 19 women infected in various stages of pregnancy, there was an adverse fetal outcome in five, including one intrauterine death, but without proof of cause [11].

Other cutaneous manifestations. With dissemination of the infection, secondary lesions of ECM are seen in about 10% of patients, and are typically smaller and less migratory than the original lesion. Malar erythema in febrile cases, and a diffuse maculopapular rash, may occur. Localized urticaria, generalized urticaria, urticarial vasculitis [12] and septal panniculitis have been reported.

Lymphadenosis benigna cutis, or solitary lymphocytoma, developing near the site of the original ECM and occasionally coexisting with it, has been reported from Sweden [13]. The lesion is seen mainly on the ears or on the breast areola. *Borrelia burgdorferi* serology is usually positive, spirochaetes can be demonstrated in affected tissue, and the lesion subsides within 5 weeks of antibiotic therapy.

Acrodermatitis chronica atrophicans (ACA) (Chapter 46) is a late cutaneous manifestation of *B. burgdorferi* infection seen mainly in northern, central and eastern Europe, although a case has been reported from England [14]. The eruption develops 1 or more years after the original infection. Typical sites are hands, feet, knees and elbows. The lesion begins as an erythematous plaque, which slowly enlarges and gradually becomes violaceous and atrophic. Spirochaetes have occasionally been cultured, but *B. burgdorferi* serology is strongly positive in all cases. Lesions respond to appropriate antibiotic therapy.

Evidence for an aetiological role for *B. burgdorferi* in morphoea and lichen sclerosus has come mainly from Austria and Germany, and comprises clinical associations of these conditions with ACA and with neural disease consistent with neuroborreliosis [15]; positive *B. burgdorferi* serology in some patients with morphoea [15,16]; and histological identification of spirochaetes in biopsy material [15] and their culture from it [16,17]. However, other studies using more specific serological methods in the UK [18] and Denmark [19] have not confirmed the association.

Histology. A superficial and deep perivascular and interstitial lymphohistiocytic infiltrate containing plasma cells is characteristic of ECM [8,20]. The Warthin–Starry stain identified spirochaetes in 40% of cases [7].

In ACA, plasma cells are prominent within the lymphohistiocytic infiltrate; the epidermis is atrophic and there may be liquefaction degeneration of the basal layer and telangiectasia of the papillary dermis. Spirochaetes may be identified by the Warthin–Starry stain [14,21].

Diagnosis. In the differential diagnosis of ECM, other forms of insect- or spider-bite reactions, cellulitis and drug eruptions may be considered. Erythema multiforme may resemble multiple ECM, but in the latter, palms, soles and mucous membranes are spared [7].

Confirmation of *B. burgdorferi* infection is mainly by serology, although this is often negative in the first few weeks after inoculation. The main tests available are an ELISA, an indirect immunofluorescence test and a Western blot. The latter is particularly useful for screening negative sera or those showing indeterminate results. The incidence of false-positive results may decline with the advent of increasingly specific methods [1,22,23]. False-negative tests may be due to sequestration of antibody in immune complexes [24]. The detection of intrathecal

antibody is useful in the diagnosis of Lyme neuroborreliosis [23]. PCR is increasingly being used and provides a rapid diagnostic test [25].

Treatment [1,26–28]. Patients with solitary lesions of ECM, and no more than regional lymphadenopathy and minor constitutional symptoms, i.e. those in whom there is no evidence of bacterial dissemination, respond well to oral antibiotic treatment, and the incidence of serious sequelae is reduced [26]. Amoxicillin 500–1000 mg three times a day (perhaps with probenecid), or doxycycline 100 mg two or three times a day, is recommended. A 3-week course is suggested and, because of the possible severe sequelae, early treatment is advised. Cefuroxime and erythromycin are alternatives, although the latter is less active against *B. burgdorferi in vivo*.

After dissemination has occurred, the results of even intensive therapy are less impressive; whether this is due to incomplete eradication of the organism or to an immunological pathogenesis is not known. Mild systemic disease may be treated as above, but the more severe cases require intravenous treatment. Ceftriaxone 2 g daily i.v. for 2 weeks seems best, but there is still a 15% failure rate. Benzylpenicillin 24 mU daily for 2–3 weeks is also useful and chloramphenicol is a possible alternative.

Prophylactic treatment following tick bites in endemic areas may be considered, but careful inspection of the skin after walking in endemic areas and removal of ticks may be more useful.

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Leptospirosis (including Weil's disease and canicola fever)

Leptospirosis is an infection caused by organisms of the *Leptospira interrogans* complex [1,2]. These leptospires are commonly carried by rodents, particularly rats, but also pigs, dogs, cattle and wild animals, such as hedgehogs and moles. Rodents especially may excrete the organism in urine persistently after recovering from infection. Human infections occur mainly in sewer workers and in those handling animals but are occasionally seen in those swimming or fishing in contaminated water. The portal of entry is usually the gastrointestinal tract but may be a cut or abrasion.

After an incubation period of 1–2 weeks, an acute febrile illness begins abruptly. The most distinctive features are muscular pains and tenderness, and intense conjunctival infection. Headache and respiratory symptoms are frequent. In some forms—Weil's disease, for example—jaundice and purpura are associated [3]. In others, such as the leptospiral form of pretibial fever and canicola fever, there is a blotchy erythema most constant on the legs. In many forms, there is a polymorphonuclear leukocytosis of the peripheral blood.

In Weil's disease, the mortality may reach 10%, but in the other forms spontaneous recovery occurs after about a week.

The diagnosis must be established by specific agglutinin reactions.

Treatment with large doses of penicillin [4] (or tetracycline if renal function is satisfactory) is recommended but must be given early. Haemodialysis or peritoneal dialysis may be required. In less severe cases oral ampicillin, doxycycline or amoxicillin can be given.

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Rat-bite fevers

Spirillum minor rat-bite fever

SYN. SODOKU

This form of rat-bite fever is caused by a spiral flagellate organism *Spirillum minor*, and is usually transmitted by the actual bite of a rat. It is rare, with most cases being reported in Japan. It may cause disease in animal technicians bitten during the course of their work [1].

Ten or more days after the bite, the wound shows persistent inflammation and an eschar may form. A fever develops accompanied by malaise and regional lymphadenopathy [2]. A macular or maculopapular rash may become widespread, extending from the original lesion. A recurrent course with remissions and relapses accompanied by increasingly severe local inflammation and a generalized cutaneous eruption is characteristic. Arthritis, however, is rare in this type of rat-bite fever.

Sodoku may be differentiated from streptobacillary fever by finding the spiral organism in exudate or blood. Animal inoculation—intraperitoneally into mice or guinea pigs—is necessary as culture on artificial media cannot be achieved.

Untreated, most patients with *S. minor* infections recover without complication, but penicillin in low dose is rapidly effective and streptomycin or tetracycline are useful alternatives.

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Streptobacillary rat-bite fever and Haverhill fever

Streptobacillus moniliformis is a natural inhabitant of the nasopharynx of rats and is the cause of the commoner and more severe form of rat-bite fever. When infection with this organism occurs in the absence of a rat bite, the term Haverhill fever is often used in recognition of an epidemic in Haverhill, Massachusetts, USA, when raw milk was thought to be the source of infection. The organism is a pleomorphic facultative anaerobic bacillus, sometimes showing beaded swellings.

When a rat bite is the origin of infection with this bacillus, the incubation period is short: 2–9 days. There is no sign of inflammation at the site of injury but (in most patients) a macular or petechial rash develops and involves the extremities, particularly the palms and soles [1]. There is characteristically a high fever and arthralgia of large joints [2]. Other manifestations of this infection include endocarditis and, particularly in children, diarrhoea [1]. The clinical picture is similar if not identical in Haverhill fever in which papules, vesicles, pustules and crusted lesions have been described along with late-onset pharyngitis.

The diagnosis is confirmed by blood culture. Without treatment, most cases eventually settle, but chronic arthritis and complications such as abscesses, pneumonia and endocarditis have been recorded. Penicillin is the drug of choice continued for at least a week with high-dose therapy in patients with complications; streptomycin and the tetracyclines are alternatives.

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Legionellosis

Legionellosis is an acute respiratory infection caused by a variety of different species of the genus *Legionella*, of which *L. pneumophila* accounts for over 90% of cases [1]. One of the major features of the infection is the clustering of cases, often associated with exposure to organisms in the environment such as water-cooling systems, showers and humidifiers. The disease may present with a flu-like illness without pneumonia (Pontiac fever) or with pneumonia. In the latter a variety of different rashes from maculopapular eruptions to pretibial erythema have been described. These exanthems are not diagnostic [2].

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Botryomycosis

SYN. ACTINOPHYTOSIS; BACTERIAL PSEUDOMYCOSIS

Definition and aetiology [1,2]. Botryomycosis is a chronic granulomatous reaction to bacterial infection, containing granules resembling the sulphur granules of actinomycosis. Most cases are caused by *Staphylococcus aureus*, but from some a pure culture of *Pseudomonas* [3] has been obtained. Botryomycosis may develop in the skin or elsewhere and a variety of underlying predisposing factors have been described.

Very extensive skin forms have been described, for instance in association with diabetes [4]. In AIDS, different forms have been reported, ranging from disseminated cutaneous papules [5] to extensive perianal sinus formation [6]. In addition, botryomycosis has been recorded in a patient with follicular mucinosis [7].

A history of injury is common in skin cases, and the literature relating to experimental models as well as some early case reports stresses the importance of a foreign body as well as infection [1]. The size of bacterial inoculation may be crucial—a delicate balance between host and pathogen has been regarded as significant [8].

Pathology [2,9]. The granules contain masses of bacteria. The surrounding tissue reaction is not distinctive: histiocytes, plasma cells, lymphocytes and foreign-body giant cells predominate.

Clinical features [1,10–12]. The resemblance to actinomycosis is also evident clinically. Most lesions are on the limbs, but other sites including the perianal region and the face have been affected. In the primary cutaneous form, single or multiple abscesses of skin and subcutaneous tissues break down to discharge serous fluid through multiple sinuses, and heal after a course of many months to leave atrophic scars. The general condition may remain good. Patients may present with a smaller painful papule without sinus formation.

The pulmonary form may reach the skin and present as irregular masses with multiple sinuses.

Diagnosis. The key to the diagnosis is the presence of a small cluster of microorganisms on biopsy. This cluster resembles the grain of a mycetoma or sulphur granule of actinomycosis. Gram stains are often ineffective in distinguishing the morphology of the organisms, but the methenamine silver stain often works well with bacteria and their shape can be distinguished. The organisms should be identified by culture.

Treatment. Treatment depends on the nature of the organism and, where appropriate, antibacterial sensitivities should be determined. For *S. aureus* infections, flucloxacillin or erythromycin are usual. Sometimes an alternative approach such as flucloxacillin and fusidic acid can be used for very extensive lesions. The response is often determined by the presence or absence of underlying predisposing disease.

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Necrotizing subcutaneous infections

There is a group of infections in which the principal focus of disease lies within soft tissues of the deep dermis, adipose tissue and subcutaneous fascia, where the hallmark of infection is extensive necrosis accompanying cellulitis [1,2]. The affected patient is usually severely ill and toxic, and there is a mortality of over 45% reported in some series [3]. The extent of infection is clearly variable with, in some cases, pathology restricted to a zone bound by fascia while in others infection extends to involve muscle and deep vessels. The bacteria isolated from patients with these conditions have varied between different studies, and in some cases adequate bacteriological data are notably absent. This has complicated the clinical classification of these infections, as it has not been possible to validate the causative organisms. However, it has been suggested [4] that there are at least two distinct groups of infections—those caused by β-haemolytic, usually group A, streptococci and others that depend on an infection with multiple organisms, one of which is usually an anaerobe. The presence of a streptococcal aetiology is often difficult to establish with certainty and infections without a proven cause may show striking increases in antistreptococcal antibody titres, suggesting that this may

have been the original or a contributory cause [5]. The pathogenesis of the mixed bacterial infections is not well understood. Other variations include the presence or absence of muscle involvement.

While it is difficult to provide accurate data on the incidence of this infection, figures from Canada suggest that the annual incidence of necrotizing fasciitis is 1/200 000 with a 25% mortality [6].

While a complete and taxonomically valid list is difficult to compile, these infections include the following proposed types.

1 Clostridial cellulitis (gangrene).
2 Necrotizing cellulitis or fasciitis due to
  (a) streptococci, or
  (b) other bacteria.
3 Progressive bacterial synergistic gangrene.
4 Gangrenous cellulitis due to other pathogens such as *Pseudomonas* spp. or zygomycete fungi (mucormycosis). These are mainly seen in the immunocompromised patient.

To complicate the issue, eponymous titles have been used, and Meleney's name has been associated both with streptococcal necrotizing cellulitis [7] and with progressive bacterial synergistic gangrene [8]. Likewise, Fournier's gangrene, which describes a specific cellulitic necrotizing process affecting the lower anterior abdominal wall and the scrotal fascia, probably includes at least two aetiologically different conditions, but in this specific site [9].

The clinical hallmark of all these infections is the appearance of necrosis in addition to cellulitis, which is often accompanied by a rapid course and considerable toxaemia. In practice, the main features of these infections are difficult to separate on clinical grounds, although there are some variations due to site of infection, and it is possible that they are part of a continuum of disease from cellulitis to myonecrosis. Death is a frequent outcome in such cases. Predisposing factors include trauma, infection, diabetes mellitus and previous surgery.

Necrotizing fasciitis, including streptococcal necrotizing cellulitis, may follow entry of group A streptococci, *Staphylococcus aureus*, *Aeromonas hydrophila*, *Vibrio vulnificus* (see above) or a mixture of other bacteria, including at least one anaerobic organism, into the skin, most commonly on the head and neck or the limbs [3]. While the portal of entry is thought to be a cut or even a surgical wound, it may be difficult to pinpoint the site of entry. Patients usually present with a hot, tender area of swelling, which is erythematous, occasionally dusky [10]. Bullae and necrosis of underlying tissue may intervene and the overlying skin may become anaesthetic. Unfortunately, the onset may be indolent, giving rise to a false sense of lack of urgency [11]. Swabs from the skin surface are usually negative.

The most important step in diagnosis and management is surgical exploration in which subcutaneous tissues down to the fascia are found to be necrotic and may contain chains of Gram-positive bacilli. The skin appears to be undermined. Occasionally, group A streptococci, rarely groups B, C or D can be isolated, or serological evidence of streptococcal infection found. In other patients, a wide range of different aerobic and anaerobic bacteria are cultured. This should not, however, delay therapy, which consists of surgical debridement of the infected tissue and the immediate surrounding area. The overlying skin is usually surgically removed, although in some cases this has been laid back as a flap once the necrotic tissue has been removed. Treatment with intravenous penicillin G in high doses is recommended; metronidazole may also be used in addition. However, if antibiotics are given without surgical intervention, therapy is rarely successful. Heparinization should be used to control disseminated intravascular coagulation.

Progressive synergistic gangrene is usually seen in association with abdominal or other surgery, where there is contamination of the wound by leakage of bowel contents [12]. It may occur without apparent injury to the skin surface [13]. The organisms vary but microaerophilic streptococci, *Bacteroides* spp. or other anaerobes as well as Gram-negative bacteria are found. The wound becomes extended with surrounding necrosis and oedema, and the patient becomes toxic and unwell. The extending infection may affect muscle. Rapid deterioration of the patient's clinical state occurs with dehiscence of the surgical wound and toxaemia. Once again it is difficult to diagnose bacteriologically, and although careful culture with appropriate swabs being taken for anaerobes should be carried out, waiting for the results should not hinder start of therapy. The presence of gas in the tissue may suggest the diagnosis, but its absence does not exclude this infection. Computed tomography is a more precise method of demonstrating gas in tissues than X-ray [14].

The wound has to be explored surgically and necrotic tissue removed. The patient should receive penicillin in high dosage and a second drug should be added depending on the sensitivity of organisms isolated, but once again surgery is the most important aspect of therapy. The response rates are not high. There is no clear clinical difference between this disease and necrotizing fasciitis as long as a streptococcal aetiology is considered.

Pyoderma gangrenosum (Chapter 49) can easily resemble this disorder and indeed may sometimes be localized around a surgical wound.

Fournier's gangrene occurs where there is infection around the lower abdominal fascial plane in men, with tracking of the infection into the scrotum [8]. It may be caused by group A streptococci or multiple organisms, although it is commoner with the latter. The management is identical to that used for these infections in other sites.

It is important to consider other potential causes of acute necrosis and toxaemia, particularly in the neutropenic patient, where cellulitis associated with single, such

as *Pseudomonas*, or multiple organisms can occur. The zygomycete fungal infection, mucormycosis, should also be considered and impression smears taken from the wound edges or biopsy material may be helpful in excluding this possibility.

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Mycoplasma infections

Mycoplasmas, formerly known as pleuropneumonia-like organisms, are the smallest free-living organisms. They lack a rigid cell wall but can grow, although slowly, on artificial media. There are about a dozen species known to be associated with humans [1,2]. Some, for example *Mycoplasma orale* and *M. salivarium*, are commensals in the mouth; others such as *M. hominis* and *Ureaplasma urealyticum*, are found in the healthy genital tract and may, at least in the case of *U. urealyticum*, be a cause of urethritis, as may *M. genitalium*. *Mycoplasma incognitus*, a variety of *M. fermentans*, is associated with lesions in patients with AIDS as well as other immunocompromised patients.

Mycoplasma pneumoniae is a well-recognized cause of pneumonia and minor upper respiratory tract infections, particularly in young people [3]. This organism has also been associated with meningoencephalitis, polyarthritis and other syndromes [4], such as severe erythema multiforme (Stevens–Johnson syndrome) [5,6]. The commoner minor form of erythema multiforme in patients without clinical evidence of lower respiratory tract infection is in a relatively small proportion of cases also causally related to *M. pneumoniae* infection, as established by a rising titre of complement-fixing antibody and the isolation of the organism from the skin lesions. Raynaud's phenomenon has also been reported in patients with *M. pneumoniae* infection.

In outbreaks of upper respiratory infection by *M. pneumoniae*, about one-third of patients developed rashes of various types [7,8].

Diagnosis. Cold agglutinins are produced in the majority of patients. In addition, complement-fixing antibodies can also be demonstrated. The agglutinins are raised early in the infection, whereas it may be several days before raised complement-fixing antibody titres can be demonstrated. Culture is time consuming. There is a new DNA probe assay, which is currently under investigation [9].

Treatment. Tetracycline and derivatives are effective in *M. pneumoniae* infections; an alternative is erythromycin. There is no evidence that the use of antibiotics triggers the appearance of skin rashes.

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Chlamydiae [1,2]

Chlamydiae are obligate intracellular parasites, but in their infectious form they have a cell wall, contain both DNA and RNA, replicate by fission, and are susceptible to broad-spectrum antibiotics, notably tetracyclines; they are therefore classed with the bacteria. There is a single genus with two subgroups or species.

Chlamydia trachomatis or subgroup A is classified into 15 serotypes with different pathogenic properties: Types A, Ba, B and C cause trachoma, an endemic ocular infection in many developing countries, frequently leading to blindness; types D to K, which are sexually transmitted, most commonly cause urethritis, but also deeper

infections such as cervicitis, endometritis and salpingitis [3]. Eye infection may result from contact with infected genital secretions. There is evidence for a role in post-urethritic reactive arthritis including Reiter's syndrome (Chapter 35) [4].

Types L1, L2 and L3 infect predominantly lymphatic tissue and cause the sexually transmitted disease lymphogranuloma venereum.

Chlamydia psittaci or subgroup B is endemic in many species of birds and occasionally causes an interstitial pneumonitis in humans known as psittacosis or ornithosis.

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Lymphogranuloma venereum

SYN. LYMPHOGRANULOMA INGUINALE; NICHOLAS FAVRE DISEASE; CLIMATIC BUBO

Note: This disease should not be confused with granuloma inguinale (granuloma venereum, donovanosis) caused by *Calymmatobacterium granulomatis* (see above).

Aetiology [1–3]. Lymphogranuloma venereum is caused by *Chlamydia trachomatis* types L1, L2 and L3. The organism is difficult to isolate and the diagnosis mainly depends on the serological response. Since the complement-fixation test is based on a group antigen, it is necessary to interpret with caution early records or prevalence based on this test because the respiratory and genital chlamydia cause cross-reactivity.

The human is the only natural host. Infection declined in the UK and Scandinavia without specific attempts at eradication. Most infections are sexually transmitted and the disease is common in tropical countries.

Pathology [1,4–6]. The lymphogranulomatous chancre usually shows no specific changes, but the necrotic area may be surrounded by epithelioid cells and a zone of granulation tissue rich in plasma cells.

The lymph nodes first show scattered foci of epithelioid cells, with occasional giant cells. These foci enlarge irregularly and undergo necrosis to form the stellate abscesses characteristic of the disease. The abscesses, which contain polymorphonuclear leukocytes and macrophages, are surrounded by epithelioid cells and chronic granulomatous tissue with numerous plasma cells.

In the later stages, very extensive fibrosis and large areas of coagulation necrosis are usual.

Clinical features [1,3,4,7]. After an incubation period of about 10 days (5–21 days) a small papulovesicle develops on the external genitalia, or occasionally elsewhere. The chancre is inconspicuous, heals rapidly and is often unnoticed. After an interval that is usually between 1 and 4 weeks, but may be longer, the regional lymph nodes enlarge—'climatic bubo'. The subsequent course of the disease depends on which glands are involved and on the extent and severity of the constitutional disturbance. Some cases resolve spontaneously within a few months, but in the majority chronic symptoms persist, often with irregular acute episodes.

The inguinal syndrome is the most frequent manifestation in men. Inguinal adenitis is unilateral in 60% of cases. Lymphatic glands are at first hard and tender, but soon become matted together and within a week or two develop small areas of fluctuation, some of which break through the reddish purple overlying skin to form chronic sinuses. The groin fold frequently divides the glands characteristically into upper and lower groups—the sign of the groove. Palpable enlargement of the iliac glands often develops and may be considerable. Suppuration does not occur and spontaneous resolution ultimately takes place.

The rectal syndrome occurs mainly in women, in whom the primary lesion is often in the vagina. The pelvic glands are involved and periproctitis and proctitis are followed by a rectal stricture usually between 5 and 10 cm from the anal margin, around which fistulae frequently develop. Carcinoma is not uncommon later.

The genital syndromes occur in both sexes. Most characteristic is genital lymphoedema, which may develop a few weeks or many years after infection and gives rise to elephantiasis. The association of elephantiasis of the vulva with scarring and fistulae of the buttocks and thighs is known as esthiomene. Occasionally, small abscesses develop along the course of the superficial lymphatics draining the primary lesion and break down to form ulcers.

Urethral lesions may cause strictures and fistulae, and lymphoedema may produce a 'saxophone penis'. Extragenital primary lesions have produced a wide variety of syndromes.

Constitutional symptoms often accompany the glandular enlargement but vary greatly in severity. Fever is usually slight, but general malaise is frequent and many patients complain of joint pain and stiffness. The spleen and liver may be enlarged. Rarely, there may be encephalitis.

Erythema nodosum occurs in about 10% of females and 2% of males, usually in the bubo stage but sometimes later.

Light sensitivity is common in white patients and develops in 30% of women and 12% of men in the subacute stage and in about 50% of chronic cases. It is first apparent about 10 weeks after infection and may persist as

long as the disease remains active. Papular, urticarial or plaque-like lesions are confined to light-exposed skin and may be associated with restlessness and headache.

Occasionally, erythema multiforme and exanthemata of various types may occur during periods of activity.

Prognosis. The untreated disease usually runs an average course of 6–8 weeks and may then resolve completely. Many cases are left with the sequelae of lymphatic obstruction and some show periodic recrudescences of activity for many years. The disease is not transmitted transplacentally in humans [8].

Diagnosis. Fluctuant or discharging, painful and often unilateral adenitis, with or without a history of a primary lesion, is most likely to be confused with cat scratch disease, pyogenic infection and tuberculosis. The adenitis of infectious mononucleosis, syphilis, granuloma inguinale, Hodgkin's disease or leukaemia is less acute and usually not painful.

A suspected diagnosis should be confirmed serologically by demonstration of a rise in chlamydia group-specific, complement-fixing antibody, although this is not always conclusive because the production of antibody may be reduced by antibiotic therapy. A fluorescence antibody test is more specific [9].

Culture is not practical. Biopsy of a lymph node or a smear of the bubo pus may be helpful.

In general, the results of laboratory investigations must be assessed with caution.

Treatment. Lymphogranuloma is best treated with chlortetracycline 500 mg four times a day for 14 days. Where there may be infection by *Haemophilus ducreyi*, it is preferable to give erythromycin or doxycycline instead. This infection also responds to a single dose of azithromycin.

Early cases will usually show a response in 7–10 days, but some early, and most late, cases will require prolonged or repeated courses.

Fluctuant buboes may require aspiration to prevent spontaneous rupture, the needle being passed inferiorly from above through normal skin to reduce the risk of sinus formation [1]. Surgical incision and excision of buboes should be avoided. Other complications will often require surgical treatment.

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Psittacosis

SYN. ORNITHOSIS

Nomenclature. The name 'psittacosis' was introduced because human infections were acquired from parrots (psittacines). Subsequently, many non-psittacine birds, for example domestic and sea birds, were found to carry the infection and 'ornithosis' was introduced as a more general term. The terms are now used synonymously.

Aetiology. The disease is endemic not only in the parrot family, but also in over 120 species of birds, including pigeons, domestic fowl, ducks and finches, all of which have caused human infection; transmission occurs from inhalation of infected dust from excreta of sick or latently infected birds.

However, in many cases no bird source can be identified. Human-to-human spread by infected respiratory tract droplets is known to occur and may be commoner than previously recognized [1–3].

Clinical features [2,4,5]. The incubation period is about 2 weeks. The manifestations are very variable. There may be severe pneumonia, with cyanosis and collapse, myocardial involvement, jaundice, encephalitic symptoms and death, but many cases present only the symptoms of a mild respiratory infection without special characteristics. There may be headache and sore throat at the onset, and cough after a few days, with complete recovery during the second week. Even milder attacks are probably frequent.

Exanthemas occur occasionally, including a morbilliform eruption, and in severe cases lesions resembling the rose spots of typhoid, although sometimes of a darker hue. Erythema nodosum was noted in five of 150 cases [3] and may occur irrespective of the severity of the primary illness. Of six cases of psittacosis with erythema nodosum, two also had erythema multiforme [4]. Disseminated intravascular coagulation has been reported [5].

Diagnosis [3]. The diagnosis is based on the demonstration of complement-fixing antibody, appearing about 10 days from the onset and often present as soon as the

diagnosis is suspected, so that examination of a single serum may be helpful. Confirmation by a rise in titre may require a further 10 days, as antibody production is slow and reduced by antibiotic therapy.

The antibody is group-specific but this is not a practical limitation since the diseases caused by *Chlamydia trachomatis* are quite different.

Treatment. Tetracyclines are the drugs of choice and early administration can be life-saving. A dose of 500 mg four to six times a day should produce a response in about 48 h and should be continued for 10 days. Erythromycin is recommended for children [2].

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Rickettsial infections

Rickettsiae are regarded as small bacteria, and most are obligate intracellular parasites. They are spread by the bites of blood-sucking arthropods and cause widespread infection in endothelial cells, which may result in vascular infarcts, extravascular fluid loss and disseminated intravascular coagulation. Rickettsiae can be classed into five main groups on clinical and serological grounds (Table 27.6) [1]. Q fever has no exanthem and is not considered further.

Epidemic typhus [1]

Aetiology and pathology. Epidemic typhus is caused by *Rickettsia prowazeki* and is transmitted by the human body louse. It occurs throughout the world but epidemics are mainly associated with the displacement of populations by war or natural disasters. Humans are the only reservoir of infection.

The essential pathological lesion is produced by the multiplication of rickettsiae in the endothelial cells of small blood vessels, leading to obstruction, thrombosis, haemorrhage and perivascular inflammatory infiltration. The lesions are widely distributed but are often numerous in the skin, brain and heart.

Clinical features. After an incubation period of 7–14 days the abrupt onset of fever, headache and malaise ushers in the illness, which at first has no distinctive features. The symptoms increase in severity for several days. Between the fourth and seventh day a rash develops in over 80% of cases. It consists of crops of pink macules about 5 mm in diameter, which appear first on the sides of the trunk and spread centrifugally, but spare the palms and soles, and spare the face, which is usually flushed with intensely injected conjunctivae. During the second week, the rash becomes deeper red and often frankly purpuric, and in severe cases may be confluent.

The other clinical manifestations and the outcome depend on the degree of involvement of the myocardium and the central nervous system. Gangrene of fingers, toes, genitalia or nose may result from vascular obstruction. Untreated, up to 40% of cases are fatal, but serious sequelae are unusual in those who recover. Death, or recovery, occurs between the second and third weeks.

Brill–Zinsser disease [1]

SYN. SPORADIC TYPHUS

This is the recrudescence of epidemic typhus, sometimes after many years, in individuals who have previously recovered from an attack. The clinical features are those of the primary attack, but often milder and less often with a rash.

Table 27.6 Rickettsial infections.

Group	Disease	Rickettsia	Vector	Distribution
A. Typhus	Epidemic typhus and Brill–Zinsser's disease	*Rickettsia prowazecki*	Louse	Worldwide
	Endemic murine typhus	*R. mooseri*	Rat flea	Central and South America, Malaya
B. Spotted fever	Rocky Mountain spotted fever	*R. rickettsi*	Tick	North and South America
	Tick typhus			
	(a) African	*R. conori*	Tick	Mediterranean, Africa
	(b) Siberian	*R. siberica*	Tick	Russia, Central Asia
	(c) Queensland	*R. australis*	Tick	Australia
	Rickettsialpox	*R. akari*	Mouse mite	North America, Russia, Africa
C. Scrub typhus	Tropical typhus or Japanese river typhus	*R. tsutsugamushi*	Mite	South-East Asia
D. Q fever	—	*Coxiella burneti*	—	Worldwide (except Scandinavia)
E. Trench fever		*Rochalimaea quintana*	Body louse	Europe, Africa, North America

Murine typhus [1]

SYN. ENDEMIC TYPHUS

Aetiology and pathology. Murine typhus is caused by *Rickettsia mooseri* and is spread to humans from the rodent reservoir by the rat flea, *Xenopsylla cheopsis*. The infection occurs throughout the world, but the incidence is highest in Central and South America. The pathological changes are similar to those of epidemic typhus.

Clinical features. The clinical features parallel those of epidemic typhus, but are very much milder. The rash is sparse and seldom haemorrhagic, and gangrene and other complications are rare. Recovery occurs during the second week in all but 1 or 2% of cases.

The spotted fever group

The infections in this group (Table 27.6) are spread by ticks or mites. Similar infections caused by distinct species occur in the tropical and subtropical regions of all continents. The incidence of this group of infections increased during the 1970s and 1980s [2,3].

Rocky Mountain spotted fever [1,4–6]

Aetiology and pathology. This is the most virulent of the rickettsial infections. The organism *Rickettsia rickettsii* is transmitted by the bite of various species of the tick, *Dermacentor*. It occurs in the Rocky Mountain areas of North America, in Maryland, Virginia and North Carolina, and in Mexico, Colombia and Brazil. Widespread inflammatory and destructive changes are produced in the small blood vessels, especially in the skin and central nervous system.

Clinical features. Five to 7 (range 3–12) days after the tick bite, a short period of malaise and headache is followed by fever, which sometimes rises to 39–40°C. After 3 or 4 days a maculopapular eruption appears on the wrists and ankles and soon spreads centrally to limbs, trunk and face. The palms and soles are usually involved. Except in the mildest cases, the rash becomes haemorrhagic, and in the most severe may be confluent. Acral gangrene may occur. In favourable cases, the high, irregular fever subsides during the third week, but without treatment the mortality exceeds 20%.

Tick typhus [1]

SYN. MEDITERRANEAN FEVER; FIEVRE BOUTONNEUSE; KENYA TICK TYPHUS; AFRICAN AND INDIAN TICK TYPHUS

Aetiology. Tick typhus is caused by *Rickettsia conori*, which is transmitted by the bites of a variety of ixodid ticks. It is endemic in the countries of the Mediterranean littoral and in many parts of Africa and India. This diagnosis is often not considered in returning travellers who fail to associate the characteristic black eschar at the site of the bite with the febrile exanthem for which they seek treatment [7]. The pathological changes follow the usual rickettsial pattern (see Epidemic typhus above).

Clinical features. After an incubation period, which is usually between 5 and 7 days, the onset of fever is accompanied by headache, malaise, joint and stomach pains and, sometimes, mental confusion. Fever of 39–40°C lasts for 7–14 days. In some 80% of cases the onset of fever coincides with the development of a small ulcer—the tache noire—at the site of the tick bite. The ulcer, which is 2–5 mm in diameter has a black necrotic centre and a red areola. The regional lymph nodes are enlarged and tender. Three or four days later, a pink, maculopapular eruption develops first on the forearms and then rapidly generalizes, involving the face, palms and soles. It increases in density for a few days and in severe cases may be haemorrhagic. The rash fades slowly after the fever subsides. Apart from weakness and lassitude, convalescence is uneventful and recovery is usual, except in the severe forms in frail or elderly people.

Leukocytoclastic vasculitis has been reported in occasional cases of *R. conori* infection [8].

Other forms of tick typhus

Other tick-borne rickettsial infections have been reported from many parts of the world, and the number of distinct infections recognized increases each year as more refined serological techniques are developed and are more widely applied.

The clinical syndromes, while showing variations in the extent of the eruption and the severity of the constitutional symptoms, all follow the same general pattern: a primary lesion, the eschar, develops at the site of the bite together with fever and influenza-like symptoms. A few days later a generalized maculopapular eruption develops and may become haemorrhagic.

Rickettsialpox [1,9]

Aetiology. *Rickettsia akari* is a parasite of the house mouse, which is transmitted to humans by the mite, *Allodermanyssus sanguineus*. It was first identified in 1946, in New York but cases have since been reported from other areas of the USA, from Central Africa and from Russia. Because the reservoir and the vector are widely distributed, the disease may be worldwide.

Pathology. Vacuolar degeneration in the basal layer results in blurring of the dermal–epidermal junction and

vesiculation best regarded as subepidermal, although regenerating epidermis may give an impression of intraepidermal separation. The superficial and middle dermal layers contain a neutrophilic and mononuclear cell infiltrate, but light and electron microscopy fail to demonstrate the organisms.

Clinical features. After an incubation period of 7–14 days, a papule appears at the site of the mite's bite, enlarges, becomes vesicular and dries to form a crust. The regional lymph nodes are enlarged. The patient often fails to notice the lesion. A few days later, influenza-like constitutional symptoms develop and persist for 4 or 5 days. Their onset is accompanied, or soon followed, by a generalized eruption of papules surmounted by small vesicles, which crust and heal in a few days. The distribution and extent of the eruption are very variable. The illness is usually mild and recovery is complete.

Many cases are probably diagnosed as atypical varicella, but the lesions of rickettsialpox are papules surmounted by vesicles, their distribution is irregular and there is usually, but not invariably, a discoverable primary lesion.

Scrub typhus [1]

Aetiology. The infective agent of scrub typhus, *Rickettsia tsutsugamushi*, is conveyed to humans from its natural rodent reservoir by the bites of the mites, *Trombicula akamushi* and *T. deliensis*, and probably by related species. The disease is widely distributed throughout the Far East and the South-West Pacific, and was a serious source of morbidity in troops in World War II.

The pathological changes are a focal vasculitis, involving the skin, lungs, heart, brain and kidneys.

Clinical features. After an incubation period of about 10 days (6–21 days) an acute fever with headache and conjunctivitis accompanies the development of the primary lesion, which is more frequently seen in white people than in Asian people. The primary lesion, or eschar, is a firm papule up to 1 mm in diameter surmounted by a vesicle, which dries to form a black crust. The regional lymph nodes are enlarged and tender. After about a week, a generalized macular or maculopapular eruption develops and may fade rapidly or persist for 7–10 days.

The clinical picture varies with the virulence of the strain. Pneumonitis and myocarditis are frequent and without treatment the mortality in some outbreaks reaches 60%. In favourable cases, the fever subsides and recovery occurs during the second or third week.

Diagnosis of rickettsial infections [1,5]

Various serological techniques and other methods are available, but are generally of retrospective value, and treatment should be started on the basis of a clinical diagnosis.

Treatment of rickettsial infections

Tetracyclines are the drugs of choice and treatment should be started as soon as the clinical diagnosis is made. The drug is given in full dose as a standard course, except that epidemic typhus and scrub typhus respond to a single 200-mg dose of doxycycline (100 mg for children) [1]. Chloramphenicol is also effective and has been recommended for Rocky Mountain spotted fever in pregnant women and children aged 8 years and under [10]. General supportive measures are necessary in severe cases.

With louse-borne disease (epidemic typhus, trench fever), isolation and effective delousing are necessary to control the spread of infection.

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Actinomycete infections

The actinomycetes are higher bacteria whose members cause two uncommon but important human infections: actinomycosis and nocardiosis. They show a number of unusual characteristics. *Actinomyces* spp. usually form large granules *in vivo* and *Nocardia* spp. are partially acid fast. Both form branching filaments *in vitro* and *in vivo*.

Actinomycosis

Definition. A chronic, spreading suppurative and granulomatous disease caused primarily by *Actinomyces israelii*: draining sinuses are formed through which the characteristic sulphur granules are discharged [1].

Aetiology. Actinomycetes are bacteria producing filamentous branching hyphae. Most of the pathogenic actinomycetes occur in nature and belong to the soil saprophytic flora. Pathogenic anaerobic actinomycetes are normal inhabitants of the human mouth, and actinomycosis is therefore acquired endogenously. In some respects, actinomycosis and mycetoma are similar. Actinomycosis differs from mycetoma in being caused by endogenous and anaerobic agents, and in having no tendency to be confined to the extremities.

Actinomycosis is caused by the invasion of the tissues by *A. israelii*, the most ubiquitous of the pathogenic actinomycetes [2]. *Actinomyces bovis*, which is isolated usually from cattle but rarely from humans, closely resembles *A. israelii*, and is considered to be identical by some authorities. Recent studies using serological and biochemical procedures have not resolved this controversy. *Actinomyces naeslundii*, *Arachnia propionica* and *Bifidobacterium eriksonii*, all inhabitants of the mouth, are rare causes of human disease [3,4]. *Actinomyces israelii* occurs in the normal mouth, and the higher incidence of the disease in rural tropical areas and in agricultural workers is difficult to explain. It has been suggested that it is more likely to affect people who live in remote areas, partly because of poor dental hygiene, and secondly because of poorer access to antibiotics to which the organisms are extremely sensitive. Trauma is thought to provide the portal of entry, and it is commonly found that actinomycosis of the jaw develops after dental extractions, pyogenic abscesses, etc. The disease is worldwide in its distribution but is seldom common. It can occur at any age, including infancy, but is rare under the age of 10 years. Although adult males are more commonly affected than females, the sex incidence is equal in childhood. Full-blown actinomycosis is also rare now in most countries where dental care is readily available. It is possible that it may cause minor dental infections, which are treated with antibiotics before major pathology can develop or a definitive diagnosis be established.

Histology [3]. The usual appearance is that of a suppurating fibrotic inflammatory process. Small abscesses and pus-filled sinus tracts are formed. Blood spread to distant organs is unusual. In the tissues, the organism forms granular colonies from which radiate delicate mycelial filaments, some of which bear club-shaped processes (ray fungus). Surrounding the colonies a chronic neutrophil and lymphocytic infiltrate extends towards the skin, irrespective of where the primary lesion is, and this readily breaks down to form multiple fistulae from which pus containing the granules may be discharged. These so-called sulphur granules are lobulated masses of intertwining filaments. Lesions of actinomycosis almost always contain other bacteria besides *Actinomyces*, and it is thought that some of these associated organisms have a synergistic role in the development of the infection.

Clinical features. Actinomycosis can affect all organs and tissues of the body [3]. Apart from the very common minor infections of the lacrimal apparatus, five main clinical types can be recognized, depending on the primary site of infection; namely, cervicofacial (lumpy jaw), thoracic, abdominal, primary cutaneous and pelvic. In a large series, published long before pelvic infections were recognized, 56.7% of cases were in the cervicofacial area, 22.3% in the lungs and 15% in the abdomen.

Cervicofacial actinomycosis [5]. This presents as a dull-red, indurated nodule on the cheek or submaxillary region. Multiple sinuses, puckered scarring and the formation of new nodules produce an uneven, lumpy surface. The sinuses may close temporarily and later reopen or they may be replaced by other sinuses. The characteristic sulphur granules may be found in the discharging pus. The primary lesion is usually in the mandible or maxilla, and probably arises as a direct extension from a periodontal abscess formed in turn as the result of carious teeth, dental extraction or trauma to the jaw. Maxillary lesions may extend to the orbit, bones of the skull and brain. Lesions may also extend from the tonsillar crypts to the mandible. Involvement of bone occurs early, usually before sinuses are formed. Periostitis is followed by osteomyelitis with cystic spaces within the bone. The induration felt in the skin is very hard (board-like). This is the least uncommon type and is the type most often seen by dentists.

Thoracic actinomycosis. The thoracic type of actinomycosis may simulate active tubercolosis with cough, haemoptysis, night sweats and weight loss. There are no cutaneous changes unless the thoracic wall is secondarily involved. The lung may be affected as the result of aspiration of *Actinomyces* from the mouth. It is doubtful whether the normal lung can be infected, and most cases are thought to result from secondary infection of a lung abscess, tuberculosis, lung cancer, bronchiectasis, etc. Once again the organism tends to extend outwards from the lung to the skin through the thoracic wall, perhaps with osteomyelitis of the ribs and eventually with multiple draining sinuses [4].

Abdominal actinomycosis [3]. It usually begins in the appendix or caecum and is manifest either as appendicitis or a slow-growing mass with constitutional disturbance. It is thought that the organisms reach the gastrointestinal tract from the mouth and tonsils. Extension to the liver with resulting jaundice is frequent. Likewise, extension to the ovaries, kidneys, bladder or spine may occur. The organism may extend into the abdominal wall with the resultant sinus tracts appearing on the skin surface. Blood spread to distant organs occurs but is very rare.

Primary cutaneous actinomycosis. This is very uncommon

and usually occurs on the exposed skin. Subcutaneous nodules extend slowly and break down to form sinuses [6] and the regional lymph nodes may be affected. This is thought to follow a similar pathogenetic mechanism to mycetoma, through implantation.

Pelvic actinomycosis. Recognized as a distinct form of the disease is pelvic actinomycosis, associated with the use of intrauterine contraceptive devices [7]. The skin is not affected in pelvic actinomycosis, but many patients with other forms of actinomycosis do have involvement of the skin causing tumour-like lesions.

Prognosis. The prognosis of any variety of actinomycosis without treatment is generally poor but the cervicofacial and cutaneous varieties may remain localized for long periods.

Differential diagnosis. Actinomycosis has a fairly typical appearance, but as the disease is rare the diagnosis may not be suspected. The condition resembles other chronic inflammatory diseases, such as tuberculosis, syphilitic gummata, appendicitis, osteomyelitis and liver abscess, and also lung and intestinal cancer. The diagnosis is established by identifying the granules in the pus and on histological examination. Diagnosis should be confirmed by culture.

Laboratory identification. Attempts should be made to detect the characteristic sulphur granules, which provide a strong presumptive diagnosis of actinomycosis. They can generally be seen macroscopically as yellow granules up to 1–2 mm in diameter, often adherent to gauze dressings. When crushed and examined microscopically, narrow bacillary forms and elongate hyphae with occasional branching may be found. Cultures of *A. israelii* appear after anaerobic incubation at 37°C for 2–4 days on enriched media (brain–heart infusion glucose agar) as white, glistening, nodular colonies with somewhat irregular margins. Colonies of *A. bovis* are smooth, convex and shiny with clear margins.

Treatment. Actinomycosis is a chronic disease producing a marked fibrotic reaction, and it is difficult to obtain effective drug levels where required, so that a quick response to treatment should not be expected [8]. *Actinomyces israelli* is sensitive to those antibiotics that are effective in the treatment of Gram-positive bacterial infections. It is sensitive to sulphonamides, streptomycin, penicillin, chloramphenicol, chlortetracycline, oxytetracycline, tetracycline, rifampicin and erythromycin, but high doses of long-term penicillin is the therapy of choice. In severe cases, 10–12 million units of penicillin a day are administered i.v. for 12 h daily for 30–45 days. This is followed by wide surgical excision of the infected tissue and then 2–5 million units of penicillin given i.m. daily for 12–18 months, or 5 million units of penicillin V given by mouth. In an average case, daily i.m. penicillin in doses of 1–6 million units for periods of 6–8 months have been employed.

Large-scale trials are not possible with this disease, but alternatives to penicillin include tetracycline derivatives, erythromycin, chloramphenicol [8] and, more recently, imipenem [9]. Erythromycin is the most active antimicrobial *in vitro* [10].

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Nocardiosis

Definition. An acute-to-chronic suppurative disease caused by the aerobic actinomycete *Nocardia*. The primary infection is usually pulmonary, but there may be haematogenous spread to other organs. The central nervous system is frequently attacked. Primary cutaneous nocardiosis as well as mycetoma due to *Nocardia* spp. are both well described.

Aetiology. Nocardiosis is caused by the bacteria *N. asteroides*, *N. brasiliensis* and *N. otitidis caviarum* [1]. Like many of the fungi causing systemic mycoses, pathogenic strains of *N. asteroides* have been isolated from soil. There is general agreement that infection is therefore exogenous, for example by inhalation of contaminated dust. The frequency of mild subclinical nocardiosis is unknown, but since the organism is known to cause fatal infections in humans, the demonstration of *N. asteroides* in sputum or other materials should therefore not be disregarded. Although uncommon, the disease is no longer a rarity, as improved technique has led to the recognition of more examples of this infection. In one review, 179 cases were recorded [2].

In addition, *Nocardia* spp. can cause localized skin infections presumably after implantation. *Nocardia asteroides*,

in particular, may cause a localized abscess without dissemination—primary cutaneous nocardiosis. *Nocardia brasiliensis*, and less commonly other species, is also a common cause of actinomycetoma following entry via a wound. *Nocardia* is an opportunistic pathogen and is often found in people with progressive chronic disease or with some defect in immune response, including AIDS, and in solid organ transplant recipients. It has also been reported with Cushing's syndrome, diabetes and following the use of corticosteroids in the treatment of various diseases. Nosocomial outbreaks of nocardiosis associated with contamination of ventilation systems have been described [3].

Clinical features. In systemic nocardiosis, the clinical picture may closely simulate pulmonary or meningeal tuberculosis. Pulmonary involvement, with cough, dyspnoea, haemoptysis and fever, occurs in 75% of cases [4,5]. Involvement of the brain or meninges is present in 30% of cases, and of the skin in 30%. Infection of the skin and subcutaneous tissue produces multiple abscesses, which may involve muscles and bones [6]. The prognosis without treatment is poor.

A lymphangitic form with multiple suppurative nodules and a primary chancriform syndrome [7], which usually presents with a localized cold abscess, have been described.

Actinomycetoma due to *Nocardia* spp. is described elsewhere (Chapter 31).

Differential diagnosis. Nocardiosis should be considered in obscure pulmonary and meningeal syndromes and in chronic suppurative disease of skin and bones.

Laboratory diagnosis. Pus or sputum smears are examined after staining by Gram, methenamine silver and acid-fast techniques for the narrow (less than 1 μm) branching hyphae, which are only partially acid fast. Cultures can be obtained on Sabouraud's glucose agar and on other isolation media from which antibacterial antibiotics are withheld. Colonies are compact, folded and glabrous, ranging from cream to red.

Treatment. The treatment most widely used is co-trimoxazole, although sulphonamides are also active [8–10]. Alternatives that have been reported to be effective include ampicillin, minocycline, amikacin and, more recently, imipenem. There is also difficulty in correlating the results of *in vitro* assessments of sensitivity with clinical responses [9]. In most cases it is still preferable to initiate therapy with co-trimoxazole and modify this later in the light of the clinical response.

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Dermatoses possibly attributable to bacteria

There are many distinctive clinical syndromes in the causation of which bacteria appear to play a principal or secondary role, but in which the lesions cannot be correlated with the known pathogenetic activities of the species isolated. An abnormal response of the tissues of the host has therefore to be postulated.

In some such syndromes, allergic hypersensitivity to the infecting organisms or their products has been demonstrated, and in others it is believed to be an important factor in determining the altered response to the bacteria.

The clinical features of many infections are modified by defects, inherited or acquired, in the host's capacity to produce a normal antibody and leukocytic response. Chronic granulomatous disease of childhood, for example, results from the failure of leukocytes to destroy certain species of ingested bacteria.

Chancriform pyoderma

This uncommon condition occurs more often in children than in adults. Cases have been reported from Europe and from North and Latin America [1]. The aetiology is uncertain, but a necrotizing reaction to a strain of *Staphylococcus aureus*, inoculated by minor trauma, has been suspected. The lesion, which is usually solitary, is often situated around the eyelids or near the mouth, or occasionally on the genitalia [1,2]. A sharply marginated ulcer, sometimes exceeding 1 cm in diameter, with an indurated base and a bright-red areola, enlarges slowly for a few days. The regional lymph nodes are enlarged and tender. Without treatment the ulcer may persist for several weeks before healing to leave a superficial scar. Treatment with antibiotics shortens the duration but the response in our experience is not dramatic.

The importance of the lesions lies in the possibilities for diagnostic confusion. Epithelioma, syphilis, primary

tuberculosis, accidental vaccination, swimming-pool granuloma, leishmaniasis and dequalinium necrosis must be excluded.

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Dermatitis vegetans

SYN. PYODERMA VEGETANS

Definition and nomenclature. Dermatitis or pyoderma vegetans is a condition of uncertain aetiology characterized by the development of epithelial hyperplasia and chronic granulomatous changes [1]. Crusting, sinus tract formation and ulceration may all occur in this disease. Dermatitis vegetans is thus difficult to define and almost certainly the name has been used to describe a number of differing skin rashes, such as blastomycosis-like pyoderma [2] and possibly superficial granulomatous pyoderma [3]. As the aetiology of the disease is unknown, it is not known whether these share a common pathogenesis.

Aetiology. Dermatitis vegetans may develop in any site, but the flexures are often involved. Commonly, either *Staphylococcus aureus* or group A streptococci are isolated from lesions but, as the rash does not usually respond to antibiotics alone, the role of these bacteria in the pathogenesis of the condition is unclear. The disease has been described in patients with a variety of underlying conditions, such as ulcerative colitis [1], alcoholism, lymphoma [4] and in association with a primary immunodeficiency state that responded to treatment with transfer factor [5]. For this reason it has been suggested that it is a response to heavy bacterial colonization or epidermal invasion in a patient with defective immunity [6]. The pustule-fringed variety called pyodermite vegetante of Hallopeau has been described in association with ulcerative colitis.

Pathology. The main hallmarks of the histological response are the appearance of chronic granulation responses and epithelial hyperplasia. Eosinophils are often present in the infiltrate, particularly in pyodermite vegetante. In some ways, it is the absence of other diagnostic features that supports the diagnosis of pyoderma vegetans.

Clinical features [4,5,7]. In some cases, encrusted and hyperplastic plaques appear on the skin surface. These may break down and weep and there is often central clearing. Where a prominent edge with crust formation is seen, the lesions may mimic blastomycosis. Alternatively, there may be ulceration, the condition resembling a form of pyoderma gangrenosum. In pyodermite vegetante, crusted, red plaques containing pustules have been described in multiple sites from the flexures to the scalp. Oral involvement may also occur with white plaques and pustules. Lesions may heal spontaneously but generally this is a chronic disease.

Diagnosis. This is difficult and largely depends on the exclusion of other conditions, such as specific infections, iododerma, pyoderma gangrenosum and pemphigus vegetans.

Management. It is important to exclude underlying disease such as ulcerative colitis, lymphoma or leukaemia. In doubt, repeat biopsies from the skin lesion may be necessary. There is usually a poor response to antibiotics alone, and the widespread application of antiseptics, although the latter may help to dry lesions. In some cases, topical corticosteroids appear to produce some response.

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Dermatitis gangrenosa infantum

The aetiology of this rare condition is unknown. It is mainly reported to occur within the first 2 years of life. The infant presents with multiple necrotic ulcers on the skin surface. While these may arise *de novo*, they often appear on a pre-existing skin rash such as varicella or severe seborrhoeic dermatitis. The affected child is usually acutely ill with a high pyrexia and rapid deterioration follows [1], often ending in death. The histology of the few reported cases shows an acute necrotic reaction involving dermis and epidermis similar to that seen in pyoderma gangrenosum. While it is possible that, in some cases, this may be a form of infantile pyoderma gangrenosum, secondary complications, such as septicaemia, dominate the clinical picture. *Staphylococcus aureus* may be isolated from cutaneous ulcers, but it is not clear whether this is a secondary event.

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Kawasaki disease

SYN. MUCOCUTANEOUS LYMPH-NODE SYNDROME

This condition is a disease usually seen in children, often affecting those under 2 years of age [1]. It presents with fever and a generalized exanthem with lymphadenitis. Complications include myocarditis and arthritis. The aetiology is unknown, although recent evidence would support a role for bacterial superantigens as possible trigger factors.

Aetiology. The disease was first described by Kawasaki in 1967 from Japan, and since then other cases have been recorded from a wide variety of different countries [1]. The condition does not appear to show a significant geographical variation in distribution. It is also more common than originally thought, with over 3000 cases occurring annually in the USA [2]. Males are more commonly affected, and the condition is also seen more often in siblings than in the general population, suggesting the possibility of transmission; however, epidemics of the disease have not been recorded [3].

Various hypotheses have been advanced to account for its symptoms. Initially, these included a rickettsial illness, as small inclusion bodies had been found in vascular endothelium. Some epidemiological evidence suggested that exposure to house-dust mite was a potential risk factor—with the possibility of transmission of an infection through contact with mites. There were also antibodies to a canine rickettsia in some patients' sera.

There has been recent evidence, however, that certain subsets of T lymphocytes ($V\beta2^+$ and $V\beta8^+$) are stimulated, suggesting activation by superantigens [4]. Superantigen (e.g. toxic shock antigens) producing strains of both *Staphylococcus aureus* and *Streptococcus pyogenes* have been isolated from the majority of patients with Kawasaki disease [5]. It has been suggested that these cause disease through widescale activation of immune mechanisms, with cytokine release bringing other cell types, including vascular endothelium, into an uncontrolled immunological reaction. This hypothesis has to be confirmed.

The major complication, the development of small aneurysms of the coronary arteries, is secondary to a vasculitis centreing on these vessels with subsequent damage to the elastic layer [6].

Clinical features. The disease occurs in childhood, often before the age of 2 years, although cases are rarely seen in adults [1,2,7,8]. The onset is acute, with a high fever, which lasts for at least 5–7 days. The mucosae and conjunctivae are injected. In the mouth, the lips are dry and fissured, the tongue appears red with prominent papillae (strawberry tongue), and the throat is injected. After 3–4 days, there is a widespread exanthem on the limbs and trunk, although it becomes localized over the distal extremities, hands and feet [9]. The area affected on the limbs becomes oedematous, and this is followed by scaling over the area previously affected, usually starting with the digits and in the periungual area. In other cases, the rash is morbilliform or erythema multiforme-like.

There is accompanying cervical lymphadenitis in many patients, although it is not always present, and may only involve a single node. Fever resolves after 1–2 weeks, but conjunctival infection and lassitude may persist. In about one-quarter of cases there is accompanying myocarditis, which may be followed by symptomatic coronary artery disease and in 1–2% by myocardial infarction. Myocarditis presents with arrhthymia or tachycardia; pericarditis and valve incompetence may also occur. Coronary disease occurs secondary to aneurysms of the coronary arteries, which may thrombose. However, these also regress over a couple of years in most patients.

Other complications include arthralgia, arthritis, severe erythema multiforme, iritis, proteinuria, hepatitis and aseptic meningitis.

Diagnosis. Abnormalities on investigation include leukocytosis and thrombocytosis with a raised erythrocyte sedimentation rate. The raised platelet count is most often seen in the post-acute phase. There is no specific diagnostic test for this syndrome.

While this condition may resemble a number of virus-associated exanthems, the presence of the typical rash and accompanying myocarditis are characteristic.

Treatment. Intravenous gammaglobulin in high dosage (2 g/kg in a single infusion over 10 h) is very helpful, and reduces the overall mortality and complications of the disease, including the risk of coronary aneurysms [10]. The treatment appears to work rapidly with resolution of fever. Aspirin is also helpful in reducing the risk of platelet aggregation, and is used short term in most patients and long term if there is evidence of coronary aneurysms.

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Suppurative hidradenitis

SYN. APOCRINITIS; HIDRADENITIS SUPPURATIVA

Definition. Suppurative hidradenitis is a chronic relapsing inflammatory disease originating in apocrine gland follicles, which may become chronic and often indolent due to subcutaneous extension with induration, scarring, destruction of skin appendages and sinus formation.

Aetiology. Hidradenitis begins after puberty, when the apocrine glands are fully developed. Most sizeable studies show a preponderance of females, for example 62 of 95 [1]; 40 of 62 [2]; 19 of 32 [3]; and 22 of 24 [4]; but the reason for this is not known. Onset after the age of 40 years is uncommon, although chronic recurrent disease may occasionally persist into the seventh decade. The size and density of apocrine glands are the same in patients as in normal adults [5].

Many apocrine glands do not open directly to the skin surface, but into the upper portion of the pilosebaceous duct above the sebaceous gland. Comedones are not normally present in apocrine gland-bearing skin, but are generally seen in or around affected skin in hidradenitis patients. Comedonal occlusion of the 'apocrine gland follicle' unit therefore obstructs the outflow of the apocrine gland in addition to that of the sebaceous gland, and is believed to be the initiating event in hidradenitis. The association of suppurative hidradenitis with severe or conglobate acne and with perifolliculitis capitis (the 'follicular occlusion triad', or tetrad if pilonidal sinus is included) is impressive in a few cases [6], but is not seen in the majority of hidradenitis patients. In a series of 70 women with hidradenitis, acne was not more frequent than in controls [7]. In a genetic study involving 62 patients, eight had acne conglobata, and five of these were from one family [2]. In most cases therefore the aberrant and characteristic occlusive process is limited to apocrine sites. Whether the earliest inflammatory changes in the occluded gland and its associated follicle are based on pyogenic bacterial infection, or more closely resemble the acne process, is not known. After that, bacterial infection seems to be important in the extension of the disease and probably in the destructive scarring, and once the sinuses have formed, secondary bacterial infection is readily understandable. Considering the volume and purulence of the discharge in some cases, the frequent negative results on routine bacteriological examination are striking, but with attention to laboratory technique, a higher yield of potential pathogens can be obtained. In one study of 32 patients with inguinal perineal hidradenitis, the majority had pathogenic bacteria at some stage in their course; from correlation with disease activity, and the generally partial but occasionally impressive responses to antibiotic treatment, there was evidence that certain bacteria contributed to the disease process [3]. These included *Staphylococcus aureus*, anaerobic streptococci and, notably, the microaerophilic organisms *Streptococcus milleri* (Lancefield group F), a recognized cause of purulent disease and abscesses [8,9]. Micro-aerophilic streptococci had been identified in six of the 13 cases studied in detail by Brunsting in 1939 [10]. Cases with *Bacteroides* spp. responding to appropriate treatment have been reported [11]. In other studies including stated or probable cases of hidradenitis, *S. aureus*, anaerobic streptococci and *Bacteroides* spp. were cultured [12,13], although not all cases yielded pathogenic bacteria.

As the apocrine gland extends well below the dermis into the less supportive subcutaneous tissue, the suppuration readily breaks through the gland and extends under the skin. The subsequent scarring process is poorly understood, but the resultant induration, tissue distortion, obliteration of appendages and the formation of partly epithelialized sinuses are hallmarks of the fully developed disease process.

There is evidence for hormonal effects in hidradenitis, apart from the necessity for pubertal development of the apocrine glands [14]. Improvement during and relapse after pregnancy, and premenstrual and menstrual exacerbation, are commonly noted by women patients, suggesting that low levels of oestrogen predispose to disease activity. Seven women developed hidradenitis while they were taking oral contraceptives, generally those with androgenic progestogens and a low oestrogen/progestogen ratio [15]. Androgen levels were on average increased compared with controls, but were normal in many individual patients [16]. In that study, hirsutism was commoner than expected, but there is no evidence of systemic virilization [7]. End-organ sensitivity may be the main mechanism for the effects of androgens in hidradenitis [14], but it is not known whether this applies to the sebaceous gland or the apocrine gland or both. Hidradenitis and acne were presenting features of acromegaly in two men [17].

Various immune defects presumably predispose to the infective element of the disease in individual cases [18–20]. Seven of 27 patients with hidradenitis had a marked reduction in T lymphocytes and a higher frequency of HLA-A1 and -B8 [21]. However, immunity in most patients appears to be intact [22].

Two of 27 cases were diabetic and a further four had impaired glucose tolerance [22]. There is no evidence to incriminate shaving, chemical depilation, deodorants or talcum powder [23]. A genetic study of 26 probands

eliciting a total of 62 cases found that 48 belonged to 11 families with patterns in keeping with autosomal dominant inheritance [2]; a reluctance to admit to the disease was noted and the authors suspected under-reporting. Of 70 women with hidradenitis, 18 had a family history of the disease [7].

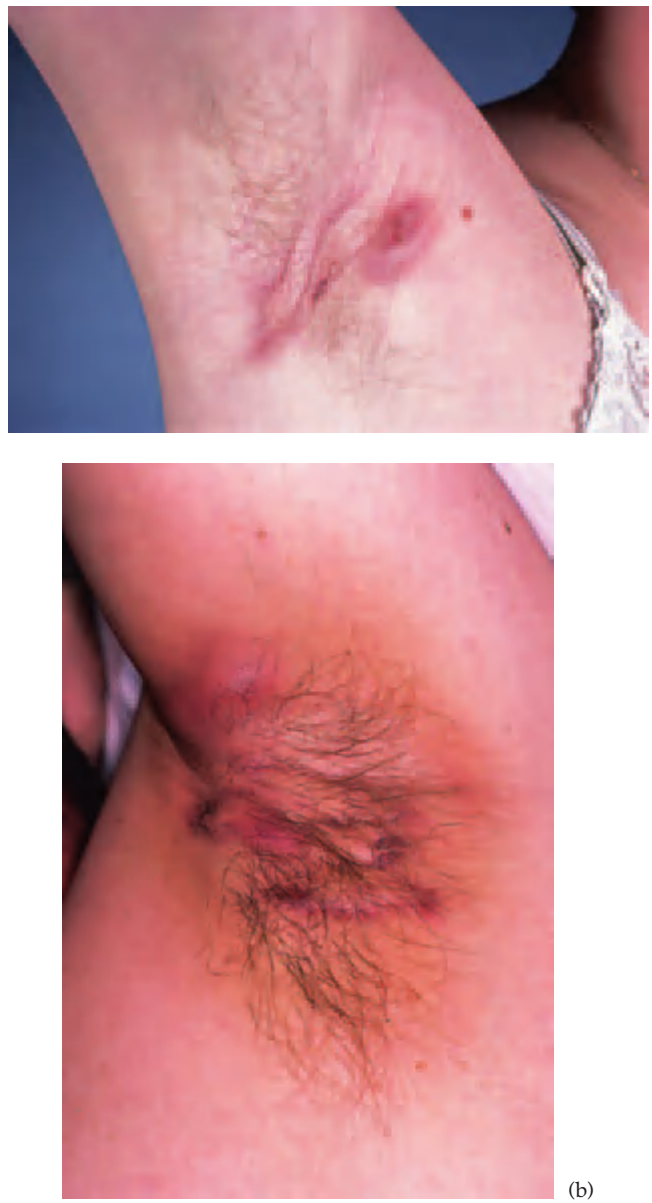
Pathology. In the predestructive stages, keratin plugs are seen in the apocrine gland follicles, along with inflammatory changes within and around the apocrine glands, the ducts of which may be distended with leukocytes. There is some evidence that occlusion of abnormal hair follicles may play an important part in the initiation of these lesions [24]. Groups of cocci may be seen within the glands and in the dermis. Later, the suppuration extends into the adjacent and subcutaneous tissues, where there may be a chronic inflammatory cell infiltrate involving histiocytes and giant cells related to remnants of glandular epithelium and keratinous debris. Amid dense fibrosis, there are sinus tracks lined partly by granulation tissue and partly by squamous epithelium. Skin appendages are obliterated by scarring [10,25].

Clinical features [10,26]. Suppurative hidradenitis occurs in skin containing apocrine glands. The axillae (Fig. 27.20) and the perineal region (including genital, pubic, inguinal (Fig. 27.21), and perianal areas, buttocks and upper thighs) are therefore the main sites, the more severe disease usually occurring in the latter. The disease may also affect the female breast, the neck, the posterior aspect of the ears and the adjacent scalp, and the back. Onset and resolution of active inflammation often occur independently in the different areas.

Comedones, often polyporous, are usually present in or beside affected skin. Pruritus and vague discomfort may precede the development of one or more small, firm, subcutaneous nodules with pain and tenderness, and for weeks or months there may be no clinically obvious suppuration except that small pustules may surmount the nodules. If subcutaneous extension occurs it leads to indurated plaques, or, in lax, flexural skin as in the axillae and groins, to thick linear bands. Inflammatory nodules often rupture externally, giving rise to chronic sinuses with intermittent or persistent discharge of fluid consisting of serous exudate, blood and pus in varying proportions. Ulceration sometimes occurs and burrowing abscesses may perforate neighbouring structures.

The severity and the course are variable but persistence for many years with partial remissions and acute relapses is common. Episodes of acute cellulitis are sometimes a feature accompanied by fever and toxicity.

Complications. The formation of fistulae to urethra, bladder, rectum or peritoneum has occurred rarely [6,27]. Sequelae of chronic inflammation include secondary anaemia [28], hypoproteinaemia, amyloidosis, renal disease [29], interstitial keratitis [30], and peripheral and axial arthropathy [31]. Squamous carcinoma, sometimes metastatic, is an occasional complication in long-standing cases, which has occurred mainly in perineal disease [32,33]. Chronic malaise and depression are understandably present in many severe cases.



(a) (b)

Figs 27.20 (a,b) Axillary suppurative hidradenitis. (Courtesy of York District Hospital, York, UK.)

Diagnosis. Possible misdiagnoses are numerous, and vary with the stage and site. Axillary and inguinal lesions that have ulcerated may be confused with scrofuloderma. Inguinal lesions may simulate actinomycosis, granuloma inguinale or lymphogranuloma venereum. When only

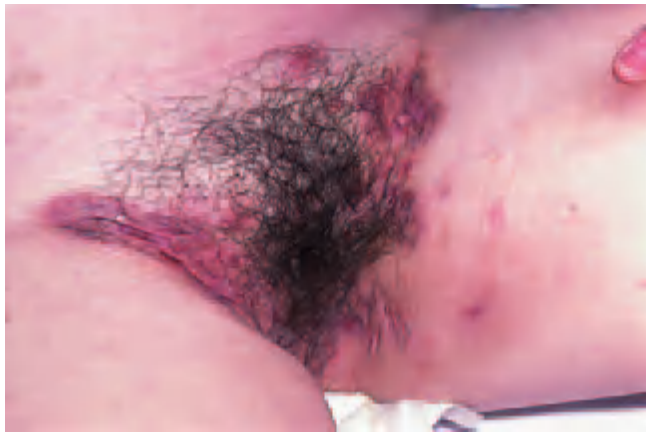


Fig. 27.21 Inguinal suppurative hidradenitis. (Courtesy of York District Hospital, York, UK.)

one of a few nodules and sinuses are present in the anogenital region, pilonidal sinus, sigmoidal diverticulitis and Crohn's disease must be excluded.

In atypical cases, the diagnosis may be difficult. The characteristic comedones should be sought and the non-specific histological changes may be negatively useful.

Treatment. Improvement in local hygiene, including weight reduction in the obese and the use of antiseptic–detergent agents for washing, is advisable.

Acute episodes and relapses should be treated as bacterial infections. Repeated specimens, and active collaboration with the microbiologist, are essential. Plausible pathogens should be treated with full doses of appropriate antibiotics, probably for 2 weeks in most cases [3]. Penicillins seem often to be disappointing, perhaps due to inadequate penetration into scarred and sequestered lesions. Erythromycin, combined with metronidazole if tolerated, may be a suitable initial choice pending the results of bacteriological examination. Clindamycin [11] and minocycline are each useful in some cases. The response to this bacteriological approach is variable; a few patients achieve lasting remission, but in most the improvement is partial and reinfection is common.

Long-term antibiotics, usually tetracyclines or erythromycin, in an acne-type regimen are useful in some patients. As in acne, efficacy may eventually be lost, but may be restored after a short break, for example 1 month [34]. Topical clindamycin appeared useful in a double-blind trial [35].

The anti-inflammatory effects of systemic corticosteroids may be useful in acute exacerbations, for example prednisolone 60 mg daily [36], and lower maintenance doses may give some degree of long-term control.

The choice of oral contraceptive for women with hidradenitis should probably be made from preparations with a high oestrogen/progestogen ratio, and possibly also with low androgenicity in the progestogen [16]. An oral contraceptive containing 50 mg ethinyloestradiol was shown to be useful in some cases as the sole therapy apart from topical antiseptic [37]; a regimen with the same oestrogen combined with cyproterone acetate 50 mg was no more effective, but in another study, cyproterone acetate 100 mg was superior to 50 mg [38].

Retinoids appear useful in some cases. Isotretinoin in a dose of about 1 mg/kg/day for 4 months was accompanied by improvement in four out of eight patients [39], but others have not seen a response [40,41]. Isotretinoin does not affect the size of apocrine glands [42]. Etretinate (or acitretin) may be more useful at least in some cases: a woman who had failed to respond to isotretinoin 2 mg/kg daily, improved on acitretin 0.5 mg/kg daily for 6 months; a relapse after 11 months responded to a further course [43]. The drug's effects on inflammation and on epithelial differentiation may be relevant. Lithium may trigger hidradenitis suppurativa [44].

Surgery should be considered in refractory cases. Relatively minor techniques include exteriorization, curettage and electrocoagulation of sinus tracts [45], and simple excision of troublesome areas with direct closure or grafting. However, severe disease unresponsive to medical treatment is best treated by deep and wide excision of the whole of the disease-bearing skin along with a margin of at least 1.5 cm, following which silastic foam dressings to permit eventual spontaneous healing are an alternative to grafting [46]. Following this method, recurrence rates were lower for axillary and perianal lesions than for anterior perineal disease, although results in all these groups were generally satisfactory; however, the outcome for inframammary hidradenitis was disappointing [1].

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Chapter 28

Mycobacterial Infections

V.M. Yates & G.A.W. Rook

Introduction

The genus *Mycobacterium* contains more than 80 species, most of which are harmless environmental saprophytes. A few species are important pathogens of humans and other vertebrates. The most important obligate human pathogens are *Mycobacterium tuberculosis* and *M. leprae*, but others such as *M. avium* and *M. ulcerans* are also significant. Disease-causing mycobacteria other than *M. tuberculosis* have been variously known as atypical, environmental or opportunistic mycobacteria, but are perhaps now best referred to as non-tuberculous mycobacteria [1].

Tuberculosis (TB) is likely to be as old as the human race. The DNA of *M. tuberculosis* has been detected in a Peruvian mummy, indicating that the disease crossed the Atlantic well in advance of Columbus [2], and it has recently been demonstrated in a skeleton from 300 BC. Tuberculosis has become a global emergency, and there are now more cases than ever before. The situation is aggravated by synergy with human immunodeficiency virus (HIV) [3], the breakdown of health care systems and the inexorable rise in multidrug-resistant (MDR) tuberculosis [4].

This chapter will deal first with the general properties and characteristics of the mycobacteria, before moving on to discuss tuberculosis and then infections with other mycobacteria. Leprosy is considered separately in Chapter 29.

Characteristics of the mycobacteria

The term 'mycobacterium' was given in 1896 to a large group of bacteria producing mould-like pellicles when grown on liquid media. All are slender, non-motile, aerobic, non-sporing rods with a waxy coating that makes them resistant to most stains. Once stained, however, they are not easily decolorized (acid-fast).

The genus can be subdivided into two subgenera, known as the fast (or rapid) growers [5] and the slow growers (which include most of the pathogens). The techniques of biochemistry and molecular biology have made the early classification of Runyon [6] obsolete for the modern mycobacteriology laboratory, since it has no true taxonomic validity [7]. Nevertheless, it is still useful for the classification of those species that may cause human disease. Runyon grouped mycobacteria by their ability to produce a yellow pigment in the dark or only in the light, and by their rate of growth (Table 28.1). This approach is being superseded because the entire sequence of the genome of *M. tuberculosis* is now known [9], and several other species of mycobacterium are also being sequenced [10].

The cell wall of the mycobacteria, which is responsible for their acid-fast staining properties, has a complex structure. The typical peptidoglycan backbone of a Gram-positive bacterial cell abuts onto a typical phospholipid plasma membrane. Outside the peptidoglycan layer, and covalently bonded to it, there is a branched polymer arabinogalactan. Onto this are attached the long chain (C60–C86) fatty acids termed mycolic acids. Numerous other lipids and glycolipids are non-covalently inserted into this lipophilic outer layer. Lipoarabinomannan (LAM, a phosphatidylinositol mannoside) is inserted into the plasma membrane and reaches out through the layers of the wall to the exterior [11].

Table 28.1 Mycobacteria of dermatological interest. (Adapted from Grange *et al*. [8].)

A *Slow growers*	
I Photochromogens	*M. marinum*, *M. kansasii*
II Scotochromogens	*M. scrofulaceum*
	M. szulgai
III Non-chromogens	*M. tuberculosis*
	M. avium
	M. ulcerans
B *Rapid growers*	
IV	*M. smegmatis*
	M. fortuitum
	M. chelonae/abscessus
C *Non-culturable*	*M. leprae*

Epidemiology

The re-emergence of *M. tuberculosis*

Tuberculosis is an ancient disease, but in Europe it was industrialization and urbanization which provoked a sharp rise in its incidence. From the mid-1700s for about a century, a pandemic of tuberculosis swept Europe. By 1800, a quarter of all deaths were caused by it [12]. Migration spread the disease to the Americas, where rates in the former Europeans peaked 50–80 years later, and to South Asia, and Central Africa, where the incidence peaked 100 years later [13]. Nevertheless, right up until the mid-20th century, the disease was being newly introduced into previously uninfected populations—for example, the Inuit of north Canada and the highland natives of Papua New Guinea [14]. In the indigenous population of western Europe, tuberculosis rates declined from 1800 [13].

The organism responsible for tuberculosis was identified over 100 years ago; diagnostic skin tests were developed about 100 years ago; a tuberculosis vaccine has been in use for over 60 years, and chemotherapy for over 30 years. It is one of the anomalies of modern health care that, despite the availability of effective treatments and a trend of decline over the last few decades, tuberculosis is now becoming more common and represents a huge international health problem [15]. The World Health Organization (WHO) has calculated that the global incidence of tuberculosis will rise from about 7.5 million cases in 1990 to about 12 million in 2005 [16]. Increases are due to the arrival of immigrants from countries with a high prevalence of tuberculosis [17], to epidemics in certain communities [18], to co-infection with HIV [3], and to wars and the breakdown of health care systems and economies. It is estimated that one-third of the world's population (i.e. 1.86 billion) is infected (though mostly without any apparent disease) [19]. There are 7.96 million (95% CI, 6.3–11.1 million) new cases per year and 1.8 million deaths (95% CI, 1.4–2.8 million) [19]. The case fatality is 23% overall, but more than 50% in some African countries.

Notification rates for tuberculosis were declining in most developed countries until the mid-1980s, but between 1988 and 1992, tuberculosis notification rates increased by 12% in England and Wales in the poorest 30% of the population [20]. In England and Wales, the incidence of tuberculosis in the white population is about 4.6 per 100 000 per year [16]. This represents 37% of cases. Among immigrants from the Indian subcontinent, the annual incidence is 120 per 100 000 overall (38% of cases). The incidence in the black/African population was the highest (210 per 100 000; 13% of cases). More than 50% of all cases were born overseas, and the incidence during the first 3 years after entry to the UK is as high as 400/100 000 [17]. An estimated 3.3% of all adults with tuberculosis in the UK were co-infected with HIV, so HIV co-infection has had a relatively small impact [17].

In the USA, HIV infection is undoubtedly the most important cause of the increase in tuberculosis, a breakdown in control programmes being a contributing factor [21]. In the USA, the incidence of tuberculosis in inner cities has risen to 150 per 100 000, and MDR has become a problem [4,22]; although the overall frequency of MDR in new, previously untreated, cases is about 1%, it is much higher in some countries (see also p. 28.26). Poverty, unemployment and homelessness all increase the risk of tuberculosis and of drug resistance, because of the difficulties of management in these circumstances [21,23].

The global impact of HIV on the incidence of tuberculosis

It is estimated that 4 million people are co-infected with HIV and with *M. tuberculosis*, and that three-quarters of these live in sub-Saharan Africa [24]. It is estimated that 50% of HIV-infected individuals in the developing world are co-infected with tuberculosis [25]. The risk of active tuberculosis in people infected with HIV and *M. tuberculosis* is 3–8% per year, with a lifetime risk of 50% or more [26]. The WHO estimates that there will be a fivefold increase in HIV-associated tuberculosis deaths over the next 10 years [27].

The epidemiology of non-tuberculous mycobacterial infections

In addition to the recent rise in incidence of *M. tuberculosis* infection, there has been a relative increase in infections caused by other mycobacteria which are widespread in nature. They are found in soil, animal and human faeces, vegetation, and water in lakes, rivers, swimming pools and aquaria [1]. They are essentially environmental saprophytes and can elicit an immune response in humans without causing overt infection. Skin tests using tuberculins prepared from different non-tuberculous mycobacteria have been used to estimate the frequency of such covert

infections in various populations [28,29]. The results have been hard to interpret, as different species share many antigens and may cross-react, but it is clear that reaction rates are high in many populations, especially in country areas in comparison with cities.

Because these organisms are of relatively low pathogenicity, some host impairment is generally needed for the development of disease. The lungs, bones, joints and—less frequently—the skin are the chief target organs, but the clinical manifestations are as variable as those of tuberculosis itself. A mycobacterial cause should always be suspected for lesions developing at the site of trauma if these follow a chronic course despite antibiotic therapy.

The passage of infection from person to person is exceedingly rare with the opportunistic mycobacteria; it follows from this that established control methods, known to be effective in tuberculosis, have no effect upon the incidence of opportunistic mycobacterial infections [30].

In addition, the isolation of such organisms does not necessarily imply that they are causing disease [30]. Of the 105 strains of mycobacteria isolated from house dust in Queensland, Australia, for example, only 56% were potentially pathogenic; *M. fortuitum* was isolated 11 times [31]. On the other hand, in a series extending over 10 years, non-tuberculous mycobacteria were the cause of skin disease in seven patients in whom the diagnosis had not been made clinically [32].

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Immunology of tuberculosis

The three major paradoxes

Three factors in the immunology of tuberculosis remain poorly explained, as discussed below. These are the latent state, the balance between protection and immunopathology after previous exposure, and failure to eliminate persistent mycobacteria.

Following infection, only 5–10% of individuals develop progressive disease, but some bacteria remain viable in the tissues of the subclinically infected individuals. When tissues from healthy individuals living in TB-endemic

countries are examined by *in situ* polymerase chain reaction (PCR), DNA from *M. tuberculosis* can be detected not only in macrophages, but also in cells such as fibroblasts and type II pneumocytes, located in lung tissue devoid of lymphocyte infiltration [1]. Neutralization of tumour necrosis factor-α (TNF-α) for the treatment of rheumatoid arthritis can lead to reactivation and progressive disease [2], and so can extreme stress, living in war zones and immunosuppression. Clearly, we need to understand more about the nature and significance of the latent state.

About 5–10% of exposed individuals manifest disease. Such overtly diseased individuals usually develop a powerful necrotizing skin-test responsiveness to the antigens of *M. tuberculosis*, and this immunopathological reaction is also likely to account for much of the lung damage. Robert Koch in the 1890s observed that killed bacteria or culture supernatant injected into the skin of tuberculous guinea pigs would evoke necrosis both at the injection site and in existing tuberculous lesions —the 'Koch phenomenon' [3]. At first, he mistakenly believed this phenomenon to represent a protective mechanism. However, attempts to treat the human disease by provoking the Koch phenomenon were often fatal, because necrosis was induced in pre-existing lesions, whether in the lung or spine [4]. Subsequent studies in the 1940s proved that guinea pigs that had been immunized so that they developed the Koch phenomenon before challenge with living bacteria were in fact more susceptible than animals that had not been immunized at all [5]. The same is true in humans. Protection correlates with small tuberculin reactions such as those seen in recipients of bacille Calmette–Guérin (BCG) vaccine, rather than with large necrotizing reactions [6]. A crucial question is therefore the difference between protection and immunopathology.

The inefficiency of this immunopathological response as a microbicidal mechanism has a second important consequence. When patients with tuberculosis are treated with the conventional antibiotics and chemotherapeutic agents, most of the organisms are killed rapidly by the drugs. However, there are 'persisters' (which may be biologically distinct from the latent bacteria discussed above) that are not eliminated by the drugs or by the immune response. The failure of the immune response to eliminate persisters, even when virtually all bacteria have been killed by drugs, is attributable to the fact that the immunopathological response does not quickly revert to the non-necrotic protective mechanism characteristic of the responses in successfully BCG-vaccinated individuals. Therefore treatment must continue for at least 6 months, or relapse will occur [7]. A research priority is the development of immunotherapy that will 'turn off' the Koch phenomenon, and boost protective mechanisms, and so allow shorter treatment regimens.

Protective immunity to *M. tuberculosis*

The cell wall of the mycobacterium is resistant to damage mediated by antibody and complement, and immunity depends on the presence of an intact T-lymphocyte response. Experiments in mice using gene knockout and neutralizing antibodies have shown that immunity is mediated by Th1 lymphocytes that recognize antigens from *M. tuberculosis* and as a result secrete cytokines including interleukin-2 (IL-2) and interferon-γ (IFN-γ). These cells activate macrophages and enhance formation of cytotoxic T cells, which are effector systems involved in killing of the mycobacteria [8–11].

Definitive evidence that the type 1 response is also crucial for immunity to tuberculosis in man has come from the study of children with genetic defects of the type 1 cytokine system. Vaccination with BCG, an avirulent derivative of the organism responsible for bovine tuberculosis, occasionally causes disseminated infection. The IFN-γR1 gene in such a child had a single nucleotide deletion that resulted in the creation of a premature stop codon near the N terminus [12]. A different defect in the IFN-γ receptor was identified in another study of four children with disseminated *M. fortuitum*, *M. avium* (two strains) and *M. chelonei* [13]. IL-12 receptor deficiency has also been found in otherwise healthy individuals with mycobacterial infections [14].

Despite this understanding, the precise effector mechanisms that kill *M. tuberculosis* remain controversial. There may be several pathways, some involving activation of macrophages by IFN-γ and TNF-α [15], others involving killing of the infected macrophage by cytotoxic $CD8^+$ T cells (or γ/δ T cells), with simultaneous killing of the contained bacteria [16–18], and some involving death of the bacteria during certain types of apoptosis of the infected cells [19,20]. It has proved extremely difficult to demonstrate convincing killing of *M. tuberculosis* by human peripheral blood or lung lavage cells *in vitro.*

The issue is further complicated by the multitude of T lymphocyte types, in addition to conventional $CD4^+$ and $CD8^+$ cells, that recognize components of *M. tuberculosis*. In humans and other large long-lived animals, there are several types of T cell—including αβ T lymphocytes negative for both CD4 and CD8 molecules (so-called double-negative T cells), γδ T cells and certain $CD4^+$, $CD8^+$, $CD8\alpha/\alpha^+$ cells and natural killer (NK) lymphocytes—that recognize mycobacterial LAM, mycolic acids or isoprenoid glycolipids, presented by the major histocompatibility complex (MHC) class 1-like molecules of the CD1 family [21,22]. It is fascinating that the different forms of CD-1 'survey' different intracellular compartments, and so will encounter products of *M. tuberculosis* in different ways [23]. Nevertheless, the role of these cells is unclear, partly because the appropriate forms of CD1 are not present in the mouse, in which most experiments are performed.

A dominant theme in other domains of immunology is the regulatory T cell ('T_{reg}'), though these cells have received little attention in the context of tuberculosis. T_{reg} cells characteristically release IL-10 and transforming growth factor-β (TGF-β), and suppress inflammation in models of allergy, inflammatory bowel disease and autoimmunity [24]. It has been claimed that T cells cloned from the bronchoalveolar lavage of human patients with tuberculosis make both IFN-γ and IL-10, and so may be a form of T_{reg} [25]. At least one mycobacterial species has been formally proven to evoke regulatory T cells, so inappropriate or premature activation of T_{reg} is clearly a possible mechanism of failure of the immune response, and failure to eliminate persisting bacteria [26].

The role TNF-α in tuberculosis

TNF-α is crucial for protection in the early stages of tuberculosis in the mouse [27], but becomes toxic in the later stages [28]. Proof of the protective role of TNF-α in man is available only in relation to latent tuberculosis. An antibody that neutralizes TNF-α has been achieving some success as a treatment for rheumatoid arthritis, but a clear consequence in some individuals is the reactivation of latent tuberculosis [2]. As in mice, the role of TNF-α in late progressive disease changes, and it becomes toxic [29]. This may be related to the mechanism of the immunopathology as discussed in the next section.

Immunopathology

At present, the only viable hypothesis is that the immunopathology is related to a switch towards expression of Th2 cytokines such as IL-4. Since IgE is IL-4-dependent, the discovery some years ago that tuberculosis patients have specific IgE antibody that binds to *M. tuberculosis* should have made this clear [30]. Recent work has proved that IL-4 and IL-13 production are increased in human pulmonary tuberculosis, and correlate with cavitation and with the immunopathological features [31–35]. It was particularly $CD8^+$ cells secreting IL-4 (or more probably IL-4δ2; see below) that correlated with cavitation in van Crevel's work [33]. It was also shown by quantitative reverse transcriptase polymerase chain reaction (RT-PCR) that the IL-4 mRNA copy number correlated significantly with serum IgE, serum soluble CD30 and extent of cavitation [31,32]. Similarly, IL-4 expression can be detected in many lesions from severe tissue-damaging tuberculosis by *in situ* hybridization [36].

Not only are expression levels markedly increased in fresh unstimulated blood cells from tuberculosis patients [31], but T cells from tuberculosis patients cloned in response to *M. tuberculosis in vitro* release IL-4 when driven by TB antigen [34]; however, the cytokine profile secreted returns to Th1 after successful treatment [34]. This, together with the presence of *M. tuberculosis*-specific IgE [30], indicates that the increased IL-4 secretion is a true result of a response to TB antigens. Similarly, there is accelerated disease in mice with pre-existing Th2 responses to the 'common' antigens shared with environmental saprophytic mycobacteria [37], to protein antigens of *M. tuberculosis* [38], or even to a single 16 amino acid epitope from ovalbumin expressed within the strain of recombinant *M. tuberculosis* used for challenge [39].

Interestingly, the IL-4 response in human tuberculosis differs from the Th2 response that accompanies allergic disorders, in that it involves both IL-4 and the splice variant of IL-4, IL-4δ2 [32]. In contrast, in allergic disorders there is a disproportionate rise in expression of IL-4 itself [40]. Moreover, in tuberculosis the IL-4 response occurs in the presence of a much larger Th1 response than is the case in allergic diseases.

As IL-4 expression increases, so TNF-α becomes more toxic [28,37], as is also seen in models of schistosomiasis [41] and *Trichinella spiralis* [42]. As mentioned earlier, this increasing toxicity of TNF-α is also seen in the human disease [29].

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The tuberculin test

The tuberculin test depends upon delayed-type hypersensitivity to mycobacterial antigens, mediated by lymphocytes, following an intradermal injection of purified protein derivative (PPD). PPD is stable but not particularly specific, so a positive test can result from clinical or subclinical infection, from BCG vaccination or from contact with environmental mycobacteria. More species-specific 'new tuberculins' are available [1], prepared by the ultrasonic disruption of other mycobacteria—these include, for example, burulin, prepared from *M. ulcerans* [2]. These may be of particular value in difficult cases in which mycobacteria other than *M. tuberculosis* may be involved. Reactions to environmental non-tuberculous mycobacteria explain the high proportion of non-specific reactions to tuberculin in certain areas such as south-eastern USA.

Tuberculin sensitivity appears within a few weeks of the onset of an infection with *M. tuberculosis*, and is usually lifelong. In any community, the number who react strongly to tuberculin relates to the prevalence of active tuberculosis. It does not necessarily imply immunity to tuberculosis. Indeed, the risk of developing clinical tuberculosis in tuberculin-positive children is roughly proportional to the strength of their tuberculin reaction [3], and protection consistently correlates with small non-necrotizing responses, while large necrotic responses indicate either susceptibility or actual disease [4]. Presumably this represents the switch from a protective Th1 response to the immunopathological Koch phenomenon discussed earlier.

Weaker reactions do not correlate with the amount of active tuberculosis in a community. Some, as mentioned earlier, are due to infection with other mycobacteria, and others are due to the waning of reactivity under various influences, including ageing. Reversion after a primary infection occasionally occurs in children, and the maintenance of reactivity may depend on continuing exposure to environmental mycobacteria. Eskimos, for example, who live in an almost mycobacterium-free environment, do not always remain tuberculin-positive after the use of BCG, but may still be protected by it. The significance of a positive tuberculin test, therefore, depends partly upon the origin of the patient.

In addition, misleading negative reactions occur in anergic patients, who are usually those who are very ill (for instance, with miliary tuberculosis), or whose delayed

hypersensitivity reactions are non-specifically reduced by other diseases, e.g. an acute viral infection, sarcoidosis, malnutrition or malignant disease (particularly lymphoma). Similarly, tuberculin reactions can be altered by immunosuppressive drugs, including corticosteroids, and by calciferol therapy.

The Mantoux test

PPD is injected intradermally into the volar aspect of the forearm using a 27-gauge needle. This test has the advantage of allowing different or serial strengths of tuberculin to be delivered to the dermis. The test is read at 48–72 h, and the diameter of the area of induration (in millimetres), not the area of erythema, is recorded (although some authors feel that persistent erythema may be important [5]). Five or 10 tuberculin units (TU) may be used initially unless active tuberculosis is suspected, in which case a dose as low as 1 TU may be selected. Serial testing might start with 1 TU, which can be followed by 10 TU and 100 TU if negative. Using 5 TU, induration of more than 10 mm is strongly suggestive of a past or present tuberculous infection.

The Heaf test

This is performed with a spring-loaded instrument, which causes six short needles to penetrate through a solution of PPD or old tuberculin to a depth of 1.2 mm. Heaf testing is reliable and the equivalent of 100 TU by standard testing [6]. Four to six papules constitute a grade I reaction; a continuous circle of induration grade II; a plaque of 12 mm grade III; and a grade III reaction with added vesication or ulceration is termed grade IV. Grade III or IV reactions suggest past or present tuberculous infection. Grades I and II may be due to other mycobacteria or past BCG vaccination.

Diagnosis of mycobacterial infections

Some mycobacterial infections may be suspected from their clinical features, geographical location, or the interests or occupation of the patient. For example, *M. marinum* infections are seen in tropical aquarium owners or dolphin trainers. Others such as *M. ulcerans* may not be recognized so easily. Any obscure granulomatous or ulcerative lesion of the skin should pave the way for a laboratory diagnosis. This may well take several weeks in the case of 'slow growers', and treatment may have to be initiated on the basis of clinical probabilities. The histology, if granulomatous, as with *M. marinum* infections, will be helpful. Sections should always be stained for acid-fast bacteria. Impression smears or curettage samples may provide a more rapid answer, as in *M. ulcerans* infections. The techniques of molecular biology are now making it possible to identify different species rapidly by using nucleic acid probes to recognize specific DNA or RNA base sequences. These newer diagnostic methods have been reviewed [7,8], and their utility in the real world of clinical diagnostic medicine has been critically considered [9].

Co-infection with *M. tuberculosis* and HIV

The risk of active tuberculosis in people infected with HIV and *M. tuberculosis* is 3–8% per year, with a lifetime risk of 50% or more [10]. It is estimated that 50% of HIV-infected individuals in the developing world are co-infected with mycobacteria [11]. Two-thirds of the isolates are organisms of the *M. avium* complex, and 10% are *M. tuberculosis*. The two other organisms most commonly isolated are *M. kansasii* and *M. scrofulaceum*, but more unusual species such as *M. terrae* or *M. xenopi* are also reported [12–14].

Roughly 5% of patients with acquired immune deficiency syndrome (AIDS) develop disseminated mycobacterial infections which cause their death. Their tuberculosis seems usually to be the reactivation of a latent infection, and is often extrapulmonary. In HIV-infected patients, the clinical and radiographic appearance of pulmonary tuberculosis is often atypical, and extrapulmonary involvement, including involvement of the skin, is frequent [15]. For example, acute miliary tuberculosis of the skin and scrofuloderma may be seen [15,16]. With non-tuberculous mycobacteria, the portal of entry is often intestinal, perhaps via contaminated drinking water, and the symptoms may include chronic diarrhoea.

The question has been raised of chemoprophylaxis with antituberculous drugs in patients with HIV and coexisting *M. tuberculosis* infection, to prevent reactivation of latent tuberculosis [17]. Prophylaxis with isoniazid, in a 12-month study in Haiti, reduced the incidence of tuberculosis from 10.0 to 1.7 per 100 person-years, and delayed the progression of HIV disease [18,19]. Single-drug prophylaxis does not increase drug resistance in the community unless used in patients with active disease, and so screening for this has to be carried out if prophylaxis is being considered [18]. The cost of prophylaxis in developing countries has been assessed as favourable when compared with a course of standard antituberculous therapy.

The increased risk of problems with BCG vaccination [20], and recommendations covering this, are discussed in the section on BCG vaccination below.

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Tuberculosis

Introduction

In western Europe, tuberculosis of the skin had become relatively uncommon as the incidence of all forms of tuberculosis fell up to the late 1980s [1]. Since then, numbers of notified cases of tuberculosis have risen, especially in urban areas and in minority ethnic groups, notably those of the Indian subcontinent and black African origin and where there is HIV co-infection [2]. In one UK district, cutaneous tuberculosis made up 4.4% of all cases of tuberculosis notified between 1981 and 1995 [3]. In India in the 1950s and 1960s, cutaneous tuberculosis affected 2% of all skin outpatients. By the 1980s, this had fallen to 0.15% [4] and in two recent series this had fallen to 0.1% [5,6]. A current problem is that atypical and even standard presentations may be overlooked through lack of familiarity with them.

Natural history

M. tuberculosis and *M. bovis* are pathogenic to humans. *M. bovis* is also found in a wide range of animal species. The majority of human disease is due to *M. tuberculosis*, *M. bovis* being found in only 1–1.5% of isolates [7]. Transmission of infection within and between species is mainly by inhalation of airborne droplet nuclei particles containing *M. tuberculosis* complex, resulting in pulmonary infection. *M. bovis* may also penetrate the gastrointestinal mucosa and lymphatic tissue of the oropharynx when ingested in milk. Direct inoculation of the skin by *M. tuberculosis* complex also occurs. Survival of *Mycobacterium* species in aerosols generated from human saliva is usually less than an hour, indicating that close and prolonged contact is required for transmission of infection [8]. Studies of contact tracing have shown that 1% of close contacts are affected [9].

Spread takes place rapidly via the lymphatics to the lymph nodes draining the area of infection, and then further spread occurs via the bloodstream. In persons with intact cell-mediated immunity, activated T cells and macrophages form granulomas that limit spread of the organism. The granuloma that forms at the site of pulmonary infection constitutes the Ghon focus, and this, together with the enlarged hilar nodes, is termed the primary complex. The tuberculin test becomes positive after 3–8 weeks; this may be accompanied by fever or erythema nodosum, which is therefore a sign of a recent primary infection.

The subsequent course varies, depending on factors of virulence, resistance and the immunological responses described earlier. Often the organisms fail to thrive and the disease is arrested; less often, it progresses. Sometimes organisms may lie dormant after a primary infection, only to reactivate later, causing a recrudescence of the primary infection.

In the lung, the Ghon focus may be absorbed, become fibrotic and calcified, or may break down, liquefy and discharge bacilli into the lung. On the skin, the primary focus is a tuberculous chancre (p. 28.11). If the contiguous regional lymph nodes break down, scrofuloderma occurs (p. 28.13).

To the epidemiologist, 'primary' tuberculosis means any lesions developing within 5 years of the original infection [10], while later lesions are considered as 'secondary'. There must always be difficulty in determining whether post-primary lesions are due to the reactivation of existing disease, for example as in patients with AIDS, or due to reinfection, particularly since BCG protection diminishes with time.

Exogenous reinfection is probably rare, but does occur [11], and the reactions seen in a host already sensitized by a previous infection differ from those of the unsensitized. A primary infection in the skin, for example, will be manifest as a cutaneous chancre whereas inoculation into a previously sensitized host may lead to tuberculosis verrucosa cutis (p. 28.12).

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Histopathology [1]

Early non-specific inflammatory changes give rise after 3–6 weeks to a characteristic tubercle. At this stage, tubercle bacilli are rarely found, although inoculation cultures may be positive. The fully formed tubercle consists of a focus of epithelioid cells containing a variable, but usually sparse, number of Langhans' giant cells and a surrounding infiltrate of mononuclear cells. The centre of the tubercle undergoes caseation necrosis and sometimes calcifies. Endovascular or perivascular changes in the vicinity of the tubercle become more marked as necrosis proceeds, and are accompanied by a cellular reaction leading to fibrosis.

Such granulomas vary greatly in appearance, depending on the predominance of one or other of the elements mentioned. These variations and their correlation with the clinical types of cutaneous tuberculosis are described later. In general terms, the presence of bacilli is a sign of immunological poverty in the host. Typical or less well-developed tuberculoid granulomas occur in many conditions other than tuberculosis (see below).

Development of the granuloma

Histochemical studies have shown that the mononuclear cells of a tubercle are blood-derived monocytes with a high content of lysosomal enzymes. They develop into macrophages which then give rise to epithelioid cells, some fusing into multinucleated giant cells [2]. Caseation necrosis is due to the death and degeneration of these epithelioid cells.

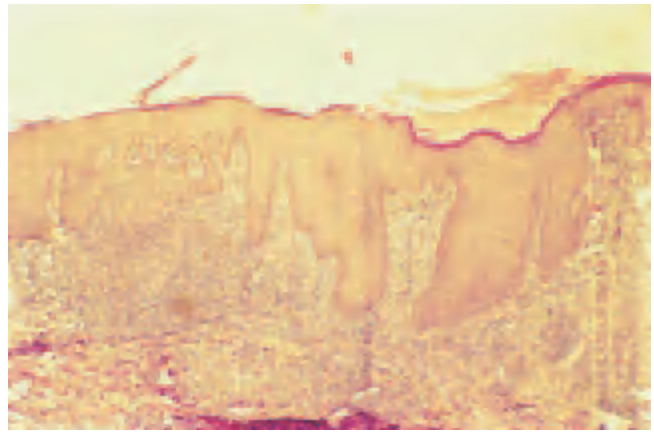

Fig. 28.1 Warty tuberculosis. The epidermis shows marked acanthosis, while the superficial dermis contains a mixed infiltrate of neutrophils and lymphocytes, deep to which there are granulomas. (Courtesy of Dr T.J. Stephenson, Royal Hallamshire Hospital, Sheffield, UK.)

Specific changes

Differences in the histopathological appearances depend on the balance between infection and immunological response. In the tuberculous chancre (p. 28.11), an acute necrotic neutrophilic reaction changes to a mononuclear infiltrate and, after 3–6 weeks, into typical tubercles in which the bacilli may no longer easily be seen. In *miliary* and *orificial* forms, the typical tubercle does not form or is imperfect or necrotic [3]. Bacilli are normally numerous, except in the milder neonatal form of miliary tuberculosis [4].

In *scrofuloderma*, the skin is destroyed by non-specific abscess formation and ulceration. Tubercle formation and caseation necrosis occur at the periphery, and bacilli can, with diligence, be found. In warty tuberculosis, the classical hallmarks are often missing, but there is marked hyperkeratosis, acanthosis and papillomatosis (which may be pseudoepitheliomatous) and an intense dermal infiltrate of neutrophils, lymphocytes and some giant cells (Figs 28.1 & 28.2). Bacilli are rarely demonstrable; typical tubercles are uncommon, and caseation is rare.

The appearances in *lupus vulgaris* (Fig. 28.3) are variable and may give rise to diagnostic difficulty. The typical changes are those of well-marked tubercle formation with epithelioid nodules embedded in sheets of lymphocytes. Occasionally, the epidermal changes resemble those of warty tuberculosis. Caseation is usually sparse or even absent, and the amount of lymphocytic infiltrate is variable. Bacilli are seldom demonstrated, although guinea-pig inoculation may be positive. As the lesions heal, increasing fibrosis strangles the remaining small foci of tubercle bacilli or epithelioid cells, which slowly become absorbed by the reparative process. Squamous and basal cell epithelioma may arise in long-standing lesions.

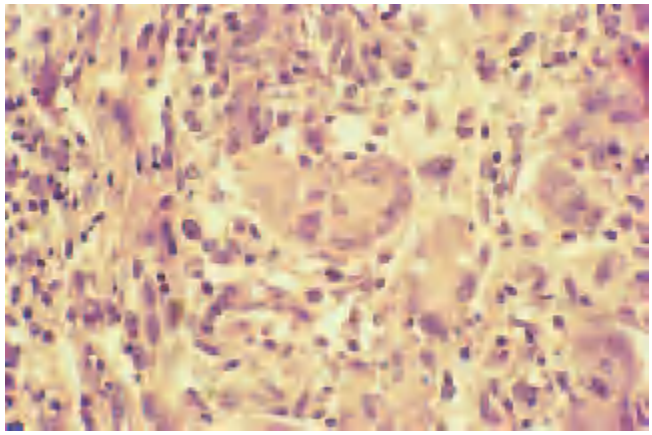

Fig. 28.2 The deep dermis in warty tuberculosis. The infiltrate consists of numerous histiocytes and epithelioid granulomas with prominent Langhans' giant cells (centre), characterized by a horseshoe-shaped configuration of nuclei. (Courtesy of Dr T.J. Stephenson, Royal Hallamshire Hospital, Sheffield, UK.)

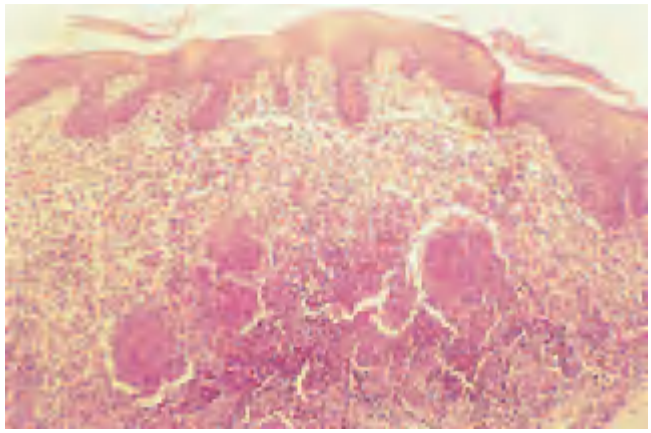

Fig. 28.3 Lupus vulgaris. The epidermis is mildly hyperplastic, while the mid-dermis contains a focus of caseous necrosis surrounded by well-formed epithelioid granulomas containing Langhans' giant cells. (Courtesy of Dr T.J. Stephenson, Royal Hallamshire Hospital, Sheffield, UK.)

Differential diagnosis

The histological signature of the tubercle bacillus is susceptible to forgery. The typical features are characteristic, but the variations invite confusion with many other diseases, especially if caseation necrosis is absent or the subject's immunity is poor.

It is impossible to differentiate the lesions of other mycobacterial infections except by successful culture at 25–30°C. In sarcoidosis, all the features except caseation necrosis may be present, and differentiation from lupus vulgaris may be impossible, although the epithelioid cell foci tend to be more scattered and well defined, and are surrounded by relatively fewer lymphocytes and by reticulin. In tuberculoid leprosy, a neural and perineural involvement is the only distinguishing feature. In leishmaniasis, one must rely on finding the causative organism; similarly with blastomycosis and chromoblastomycosis. Tertiary syphilis shows more pronounced vascular changes and a plasma cell infiltrate.

A non-specific tuberculoid infiltrate, with irregular groups of epithelioid cells in an inflammatory infiltrate but without the formation of typical tubercles—as seen, for example, in rosacea or panniculitis—may also cause confusion.

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Tuberculosis of the skin

M. tuberculosis can induce a spectrum of cutaneous changes dependent on the route of infection and the immunological state of the host. Primary infection of the skin produces a tuberculous chancre in the non-immune host, whereas the so-called 'prosector's wart', or tuberculosis verrucosa cutis, occurs in primary infection in the immune host. Post-primary skin lesions such as lupus vulgaris, where single or multiple chronic skin lesions occur, are much more common manifestations of skin tuberculosis. Scrofuloderma results from contiguous involvement of the skin overlying tuberculosis in a deeper structure. This is most commonly lymphadenitis, bone or joint disease, or epididymitis. Metastatic tuberculous abscess can occur due to haematogenous spread from a primary focus. This usually occurs when host resistance is suppressed, can be part of miliary tuberculosis and results in single or multiple lesions. Orificial, perioral or perianal tuberculosis can occur following ingested mycobacteria from either swallowed respiratory secretions or milk contaminated with *M. bovis*.

Most of the tuberculides—once attributed to cutaneous immunological reactions to tuberculosis elsewhere in the body in an immune host—are now known to be true forms of cutaneous tuberculosis, following identification of *M. tuberculosis*-complex DNA in the skin lesions [1]. There are three main forms: micropapular, e.g. lichen scrofulosorum; papular, e.g. papulonecrotic tuberculide; and nodular, e.g. erythema induratum of Bazin.

The incidence of the different forms of cutaneous tuberculosis varies globally. Scrofuloderma was the commonest form in the most recent UK series [2], whereas lupus vulgaris occurred most commonly in a study from South Africa [3]. Reviews from Hong Kong have shown a

Table 28.2 Classification of cutaneous tuberculosis. (Modified from Beyt *et al*. [7].)

I *Inoculation* tuberculosis (exogenous source)	Tuberculosis chancre Warty tuberculosis (verruca cutis) Lupus vulgaris (some)
II *Secondary* tuberculosis (endogenous source)	
A Contiguous spread	Scrofuloderma
B Auto-inoculation	Orificial tuberculosis
III *Haematogenous* tuberculosis	Acute miliary tuberculosis Lupus vulgaris (some) Tuberculous gumma
IV *Eruptive* tuberculosis (the tuberculides)	
(i) Micropapular	Lichen scrofulosorum
(ii) Papular	Papular or papulonecrotic tuberculide
(iii) Nodular	Erythema induratum (Bazin), nodular tuberculide

change in the commonest form of skin tuberculosis in recent years from tuberculosis verrucosa cutis in 1968 [4] to erythema induratum in 1995 [5]. In India, scrofuloderma was the most frequently found form in childhood, whereas lupus vulgaris was the commonest form in adults [6].

Classification

No entirely satisfactory classification exists, reflecting the difficulty in classifying a disease whose diverse manifestations are dependent on so many factors, such as the host's cell-mediated immunity and route of infection. Darier separated proven tuberculosis lesions from the remainder. This led, inevitably, to a number of conditions being accepted as 'tuberculides' on circumstantial evidence. Confusion between true tuberculosis and a less specific 'tuberculoid' histology compounded the difficulty until the advent of effective antituberculosis drugs. Then the lack of response of many of the so-called tuberculides, and their tendency to resolve spontaneously, led to a more critical evaluation of their aetiology. With the advent of new methods to detect *M. tuberculosis*-complex DNA, the picture has become much clearer. The classification adopted here [7] (Table 28.2) has the merit of extreme simplicity, since it does not attempt to introduce immunological considerations.

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Primary inoculation tuberculosis

SYN. TUBERCULOUS CHANCRE

Definition. A tuberculous chancre is the result of the inoculation of *M. tuberculosis* into the skin of an individual without natural or artificially acquired immunity to this organism.

Pathogenesis. The bacillus enters the skin through abrasions and minor injuries, usually on the face or limbs and commonly in children. Tuberculous chancres have followed ritual circumcision [1], infections with inadequately sterilized syringes [2], wounds [3], operations [4], ear-piercing, mouth-to-mouth artificial respiration [5] and tattooing [6]. In regions where tuberculosis is prevalent in the community, lesions may occur anywhere on the body from contact with sputum or following insect bites [7] or pyococcal infections of the skin. Sexual transmission has been reported [8,9].

Incidence. This is now a very uncommon primary presentation of tuberculosis, and a rare form of skin tuberculosis [10], except in Asia.

Histopathology. The early changes are those of acute neutrophilic inflammation with necrosis. Numerous bacilli are present. After 3–6 weeks, the infiltrate becomes more granulomatous and caseation appears, coinciding with the disappearance of the bacilli.

Clinical features. The earliest lesion may be a nondescript, brownish papule or nodule, or a ragged ulcer with an undermined edge and a granular haemorrhagic base. In time, the edge becomes firmer, and a thin adherent crust develops. When obvious trauma is absent, the initial lesion is often small, with a central silvery scale, and may show 'apple-jelly' nodules on diascopy. The lesions may be seen on the face [11]. Apparent healing may conceal active infection below the surface or be accompanied by regional lymphadenopathy. Occasionally, lupoid nodules occur around the healed ulcer or deeper infection simulates scrofuloderma. Lesions closely simulating paronychia have been described [12].

Mucosal lesions. Conjunctival lesions cause oedema and irritation [13]. Ulceration and oedema of the lids, with preauricular lymphadenitis, has been described [14]. Oral lesions are uncommon [5], but painless lesions, often

misdiagnosed, may form in a tooth socket or on the gums.

Diagnosis. Any painless unilateral, localized glandular swelling, especially in a child, should arouse suspicion; careful examination may reveal a small scar or a lupoid patch. Before adenitis occurs, the diagnosis can be confirmed by microscopy and culture. If acid-fast bacilli are seen, antituberculosis therapy should be started without waiting for further proof. At this stage, the lesion may be confused with tularaemia, sporotrichosis or actinomycosis [15]. Cat scratch fever (see Chapter 27) and especially *M. marinum* infections (p. 28.28) closely resemble primary tuberculosis, but are distinguished by their distribution or course, and cultural characteristics. The correct diagnosis is most likely to be overlooked in the anal and genital areas [1], particularly in children.

Course. The chancre will heal slowly, taking many months, but rarely may proceed to lupus vulgaris. Occasionally, fever is marked at the onset; more often, it is slight. Erythema nodosum developed in four out of 40 patients in one series [13].

The enlarged draining lymph nodes usually subside slowly, often calcifying; less often, cold abscesses and sinuses develop. Rarely, miliary tuberculosis supervenes.

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Warty tuberculosis [1]

SYN. TUBERCULOSIS VERRUCOSA CUTIS

Definition. An indolent, warty, plaque-like form of tuberculosis occurring as a result of the inoculation of organisms into the skin of a previously infected patient who usually has a moderate or high degree of immunity. It was the predominant form of tuberculosis in the Chinese in Hong Kong in the 1960s [2].

Pathogenesis. Lesions arise in three ways. The first is by accidental superinfection from extraneous sources: physicians, pathologists and post-mortem attendants are traditionally at risk (thus, 'anatomist's warts', 'prosector's warts', 'verruca necrogenica') [3].

The second is by autoinoculation with sputum in a patient with active tuberculosis. Finally, children and young adults, already infected and having some degree of immunity, may become infected from sputum by sitting or playing where the organism is present [4,5].

Histopathology. There is a striking pseudoepitheliomatous hyperplasia with superficial abscess formation. The intense, mixed infiltrate may show only sparse tuberculosis foci. Bacilli are seen only occasionally.

Clinical features. Lesions occur on those areas exposed to trauma and to infected sputum or other tuberculous material. In Europe, the lesions are most likely to occur on the hands, but in Asia the knees, ankles and buttocks are mainly involved [5,6].

The lesion starts as a small, symptomless, indurated, warty papule with a slight inflammatory areola. By gradual extension, a verrucose plaque is formed. Irregular extension at the edges leads to a serpiginous outline with finger-like projections. The centre may involute, leaving a white atrophic scar, or the whole lesion may form a massive, infiltrated papillomatous excrescence (Fig. 28.4). The colour is purplish, red, or brown. The consistency is generally firm, but there may be areas of relative softening. Pus may sometimes be expressed from these soft areas or from fissures. The lesions may resemble lupus vulgaris [7], but the sites are different. At times, the appearance is psoriasiform (Fig. 28.5) or keloidal. Occasionally, exudative and crusted features are predominant. Perianal lesions from intestinal tuberculosis may be mimicked. Tuberculous lymphadenitis can occur, but is rare [8]. More commonly, lymphadenitis is due to secondary pyococcal infection.

Anomalous forms. Deeply destructive papillomatous and sclerotic forms may cause deformity of the limbs. A generalized form, associated with papulonecrotic and lupoid lesions [9], occurs in patients with active disease, but is best regarded as a haematogenous form with a variable

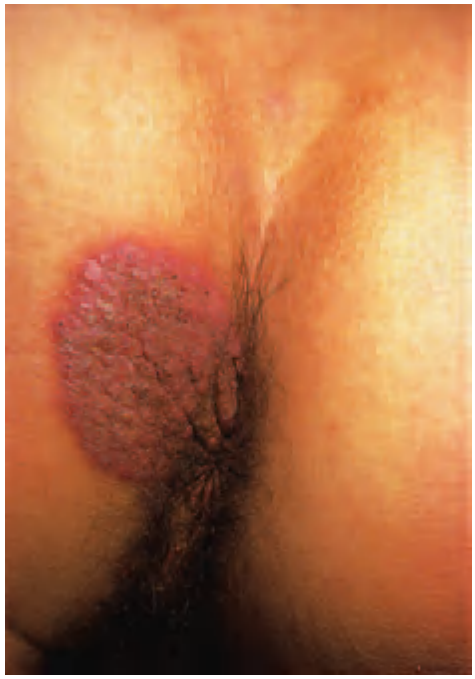

Fig. 28.4 Warty tuberculosis of the perianal skin.

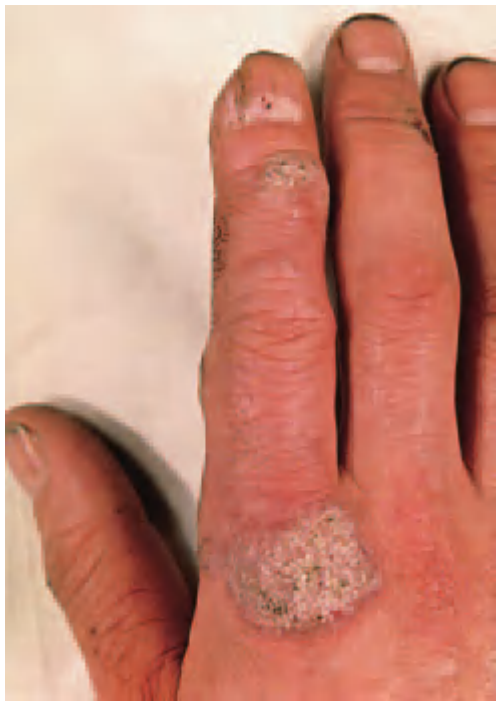

Fig. 28.5 Warty tuberculosis of the hand.

tissue response. An exuberant granulomatous form was described in the Chinese in Hong Kong [5] and is also seen in other Eastern races [6]. Tumour-like forms can occur [10].

Differential diagnosis. Subungual and digital lesions must be distinguished from warts, and those on the hands from keratoses. Blastomycosis, chromoblastomycosis and actinomycosis may simulate exuberant forms, and crusted lesions may resemble leishmaniasis. Tertiary syphilis may be confused when the central scarring is surrounded by a serpiginous edge. Hypertrophic lichen planus and lichenification occasionally cause difficulty, but lesions of these disorders are multiple or itchy. Lupus vulgaris is not usually hyperkeratotic and shows apple-jelly nodules on diascopy (Chapter 5).

The lesions caused by non-tuberculous mycobacteria can usually only be distinguished by microbiological culture. *M. marinum* poses particular difficulties (p. 28.28). Pyoderma due to other organisms may simulate this condition; the histology differs only by the absence of tuberculoid foci.

Course. The condition responds to antituberculosis treatment; without it, extension is usually extremely slow and lesions may remain virtually inactive for months or years [11]. Spontaneous remission may occur and usually results in atrophic scars. Active disease of other organs should be looked for, as bone, glandular or pulmonary tuberculosis may coexist [5].

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Secondary tuberculosis

Scrofuloderma

SYN. TUBERCULOSIS COLLIQUATIVA CUTIS

Definition and pathogenesis. Scrofuloderma results from the involvement and breakdown of the skin overlying a contiguous tuberculosis focus. This is usually a lymph gland, an infected bone or joint, or a lacrimal gland or duct (Figs 28.6 & 28.7) [1]. In a report which included details of 23 patients with scrofuloderma [2], the condition

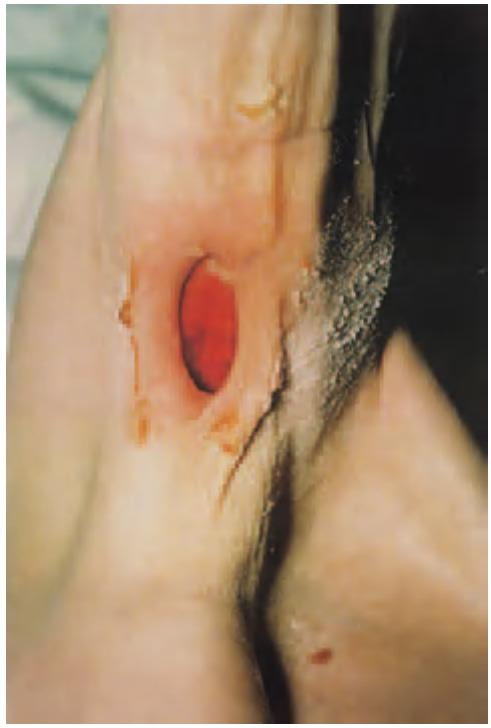

Fig. 28.6 Scrofuloderma associated with tuberculosis of the axillary glands occurring in a 74-year-old Caucasian man prior to antituberculous therapy. (Courtesy of the Editor of the *British Journal of Dermatology*.)

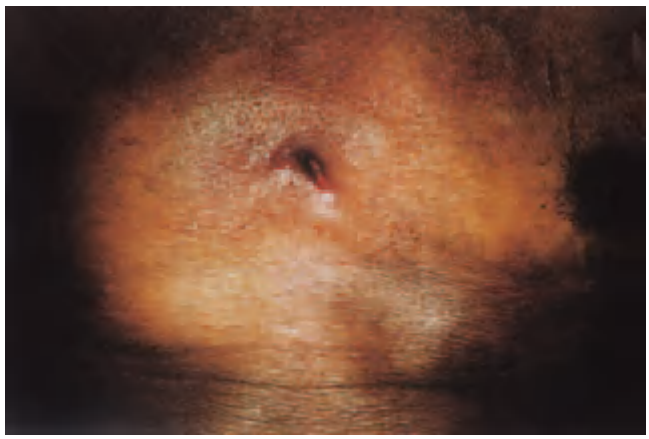

Fig. 28.7 Scrofuloderma associated with sternal tuberculosis occurring in a 62-year-old Pakistani man. (Courtesy of the Editor of the *British Journal of Dermatology*.)

occurred most commonly after cervical gland infection, less often with axillary, inguinal, epitrochlear and retroauricular gland infection, and in only two patients after infection of the tibia and fibula. The face and neck were again the most frequently affected sites for lesions in another series of 27 patients [3]. It was the commonest form of cutaneous tuberculosis in childhood in a recent large series from India [4] and in another series of adults from the UK [5].

Histopathology. There is usually an ulcerated dermal abscess with an ill-defined histiocytic component. Marked caseation necrosis, in which there are usually numerous bacteria, is seen in the deeper structures. Tubercle bacilli can usually be easily isolated from the pus.

Clinical features. A bluish-red nodule overlying the infected gland or joint breaks down to form undermined ulceration with granulating tissue at the base. Numerous fistulae may intercommunicate beneath ridges of a bluish skin. Progression and scarring produce irregular adherent masses, densely fibrous in places and fluctuant or discharging in others. Excessive granulation tissue may give rise to fungating tumours. After healing, characteristic puckered scarring marks the site of the infection. Sweet's disease has been described in association with scrofuloderma [6].

Diagnosis. The nature of the underlying lesion is usually evident. The diagnosis is confirmed bacteriologically. *M. intracellulare* lymphadenitis and the more benign *M. scrofulaceum* need to be excluded by culture.

Course. Spontaneous healing can occur, but the course is very protracted and leaves typical cord-like scars.

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Orificial tuberculosis

SYN. TUBERCULOSIS CUTIS ORIFICIALIS; ACUTE TUBERCULOUS ULCER

Definition. Tuberculous infection of the mucosa or the skin adjoining orifices in a patient with advanced internal tuberculosis. It is now very rare. It occurs particularly in those with pulmonary, intestinal or anogenital disease [1]. Most of those affected are males.

Pathogenesis. This is normally a form of autoinoculation tuberculosis, although extraneous sources are occasionally responsible [1]. The lesions occur where there is

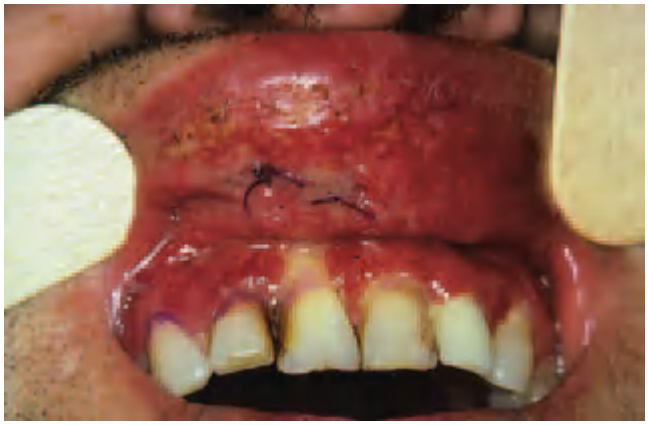

Fig. 28.8 Periorificial tuberculosis. Crusty erosions are evident on the gingival surface and mucosal surface of the lip. (Courtesy of Dr F. Nachbar, Ludwig Maximilian University, Munich, Germany, and the Editor of the *British Journal of Dermatology*.)

advanced pulmonary, intestinal or genitourinary disease from which large numbers of mycobacteria are shed and inoculated into the mucous membranes of orifices. In general, local trauma determines the site of the lesions.

Histopathology. The histopathological changes are variable and are often of non-specific inflammatory type, but tubercle bacilli are usually present.

Clinical features. The affected patient is usually a severely ill adult with advanced visceral tuberculosis who may have impaired cell-mediated immunity. Lesions occur most commonly in the mouth (Fig. 28.8). In a series of 42 patients with orofacial disease, 69% had oral ulceration, 21% had bone involvement and 14% salivary gland and/or lymph-node involvement [2]. A tooth socket may be involved after dental extraction. Other sites include the genitalia [3], around the anus in those with intestinal tuberculosis, and other locations adjacent to an orifice draining an active tuberculous infection.

Small oedematous red nodules rapidly break down to form painful shallow ulcers with undermined bluish edges. The ulcers seldom exceed 2 cm in diameter and show no tendency to heal spontaneously.

Diagnosis. Pain is the cardinal feature. There is usually evidence of disease elsewhere; 79% of one series had associated pulmonary disease [2]. The diagnosis is confirmed bacteriologically. Polymerase chain amplification of mycobacterium-specific gene segment has been demonstrated and may speed up diagnosis [4]. The tuberculin test is variable; in the later stages at least, the patient is often anergic.

Treatment. The source of the local infection must be traced and antituberculosis therapy instituted.

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Haematogenous tuberculosis

Miliary tuberculosis

Definition and pathogenesis. Miliary tuberculosis of the skin occurs in association with generalized miliary tuberculosis and is due to haematogenous dissemination of mycobacteria into the skin. It is rare and usually affects young children or immunosuppressed patients such as those with concurrent HIV infection [1] or following viral infections such as measles [2].

Clinical features. The skin manifestations are often deceptive—profuse crops of minute bluish papules, vesicles, pustules or haemorrhagic lesions in a patient who is obviously ill. The vesicles may become necrotic to form small ulcers [3]. Erythematous nodules have been described [4]. The underlying disease may not be manifest, and the diagnosis is sometimes only made by the biopsy of a skin lesion showing acid-fast bacilli [5].

A search should be made for evidence of internal tuberculous infection [6].

Diagnosis. The development of an unusual exanthematic rash in an ill person with known tuberculosis or tuberculous contacts suggests the diagnosis, which should be confirmed by biopsy. Antituberculosis therapy should be started immediately if there is a strong suspicion. The tuberculin test is negative.

Course. The prognosis is poor, but response to treatment is possible.

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Lupus vulgaris

Definition. A chronic progressive post-primary form of cutaneous tuberculosis occurring in a person with a moderate or high degree of immunity. The characteristic lesion is a plaque, composed of soft, reddish-brown papules, said by some on diascopy to resemble apple jelly. The edges of the lesion gradually extend in some areas and heal with scarring in others, sometimes causing considerable tissue destruction over many years.

Incidence. In recently published series from India and South Africa, lupus vulgaris was the most commonly found form of cutaneous tuberculosis in adults [1,2] and the second most prevalent after scrofuloderma in a series from the UK [3]. The condition appears to be more common in women than men.

Pathogenesis. Lupus vulgaris originates from an underlying focus of tuberculosis, typically in a bone, joint or lymph node, and arises by either contiguous extension of the disease from underlying affected tissue or by haematogenous or lymphatic spread. Sometimes the underlying focus is not clinically apparent, and in such cases reactivation of a latent cutaneous focus secondary to previous silent bacteraemia is postulated [4]. It can also arise after exogenous inoculation or as a complication of BCG vaccination [5].

Lupus vulgaris is typically a paucibacillary form of cutaneous tuberculosis, which often makes successful culture difficult. In one series, bacilli were cultured from only 6% of nearly 4000 patients [6]. Concomitant diagnosis by both culture and detection of mycobacterial DNA using PCR has been reported and may be useful where small numbers of mycobacteria are present [7].

Histopathology. The histological features are variable. Normally, tubercles with scanty or absent central caseation, surrounded by epithelioid histiocytes and multinucleate giant cells, are present in the superficial dermis. Peripheral lymphocytes are often prominent. Occasionally, tubercle bacilli may be numerous [8]; more often, they are hard to demonstrate. The epidermis may be ulcerated with an associated mixed inflammatory infiltrate, atrophic or acanthotic. If the acanthosis is severe, giving rise to pseudo-epitheliomatous hyperplasia, differentiation from squamous cell carcinoma may be a problem [9].

Clinical features. Lupus vulgaris commonly appears in normal skin as a solitary lesion, although it can arise at the site of a primary inoculation, in the scar of scrofuloderma or at the site of a BCG vaccination [5]. In Europe, over 80% of lesions are on the head and neck, particularly around the nose [6,10]. Next in frequency are the arms and legs, but involvement of the trunk is uncommon. In India, the face is affected less often and the buttocks and trunk more frequently [11].

The initial lesion is a small, reddish-brown, flat plaque of soft, almost gelatinous, consistency. On diascopy, the diagnostic apple-jelly nodules may be demonstrated. The lesion gradually becomes elevated, infiltrated and brown and grows by slow peripheral extension to become gyrate or discoid in shape with areas of atrophy. There is usually only a single focus, except in disseminated forms which usually occur in association with active pulmonary tuberculosis [12]. Sporotrichoid-like spread has also been reported [13].

The many clinical forms fall into five general patterns, depending on the local tissue response to the infection, but atypical forms are becoming more common.

1 *Plaque form* (Fig. 28.9). Flat plaques with irregular or serpiginous edge. The surface of the lesion may be smooth or covered with psoriasiform scale. Large plaques may show irregular areas of scarring with islands of active lupus tissue. The edge often becomes thickened and hyperkeratotic.

2 *Ulcerative and mutilating forms* (Fig. 28.10). Scarring and ulceration predominate. Crusts form over areas of necrosis. The deep tissues and cartilage are invaded and contractures and deformities occur. In milder forms, keratotic plugs overlying pinpoint ulcers are associated with slow scar formation.

3 *Vegetating form* (Fig. 28.11). This is characterized by marked infiltration, ulceration and necrosis with minimal scarring. Mucous membranes are invaded and cartilage is slowly destroyed. When the nasal or auricular cartilage is involved, extensive destruction and disfigurement ensue.

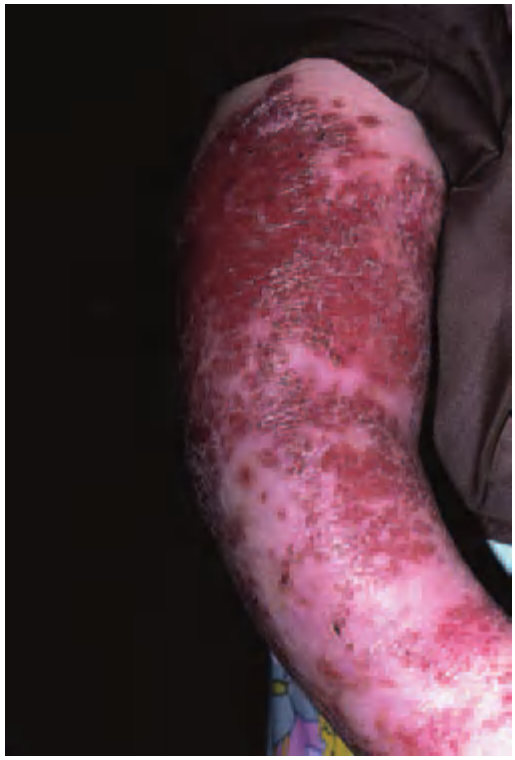
4 *Tumour-like forms* (Fig. 28.12). The hypertrophic form presents either as soft tumour-like nodules or as epithelial hyperplasia with the production of hyperkeratotic masses. In the 'myxomatous' form, huge soft tumours occur predominantly on the ear lobes, which become grossly enlarged. Lymphoedema and vascular dilatation are sometimes marked.

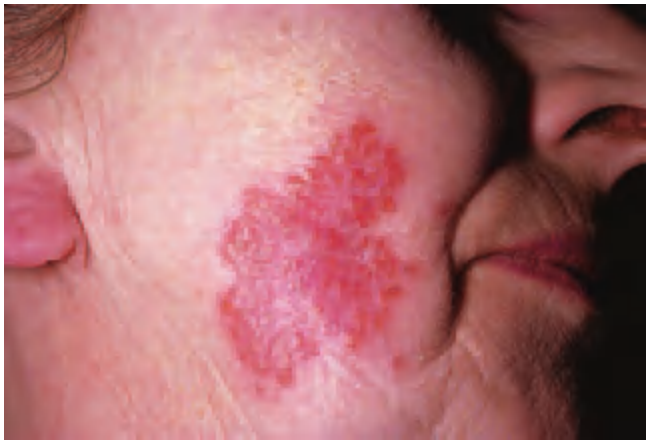
5 *Papular and nodular forms*. Multiple lesions occur in disseminated lupus—true 'miliary lupus'.

Mucosal involvement. The nasal, buccal or conjunctival mucosa may become involved, either primarily by a papule, nodule or ulcer, or by spread from a contiguous skin lesion. Nasal lesions start as nodules, which bleed easily and then ulcerate, leading sometimes to cartilage destruction. A dry rhinitis may be an early symptom. Granulating, vegetating or ulcerating lesions of the buccal mucosa, palate, gingiva or oropharynx may occur by direct extension or by lymphatic spread from nasal lesions. These can produce stenosis of the larynx and scarring deformities of the soft palate.

Prognosis and complications. Despite long periods of indolence, the natural course of an untreated lesion is

(a)





(b)

Fig. 28.9 (a) A huge plaque of lupus vulgaris on the right arm. (b) Lupus vulgaris of the right cheek. (Courtesy of Professor J.A.A. Hunter, Royal Infirmary, Edinburgh, UK.)

inexorably progressive. Scarring, contractures and tissue destruction are prominent features. The scars are usually thin, white and smooth, but are unstable and may break down or become keloidal. Active lupus vulgaris frequently reappears in scar tissue. Contraction may lead to ectropion or microstomia, which may require plastic surgery.

Squamous cell and, less commonly, basal cell carcinomas, or sarcomas, may occur insidiously in up to 8% of patients [14,15] and may be confused with renewed activity of the lupus itself (Figs 28.13 & 28.14). A plasmacytoid lymphoma developed in a patient with evidence of impaired immunity [16]. A previously well-controlled

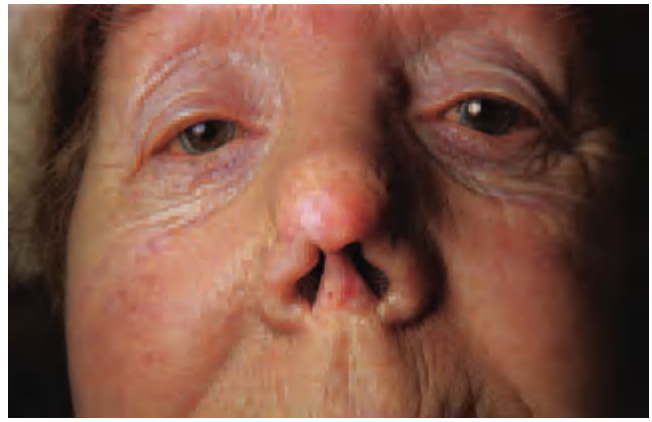


Fig. 28.10 Nasal deformity as a late sequela of lupus vulgaris.

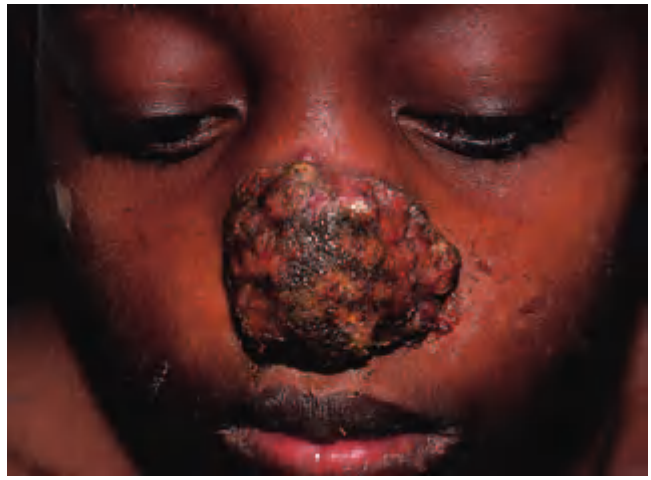


Fig. 28.11 Vegetating lupus vulgaris on the nose. (Courtesy of Dr J.E. Bothwell, Barnsley District General Hospital, Barnsley, UK.)

case became fulminant when the patient developed Hodgkin's disease [17].

Diagnosis. Because of its rarity in the UK, the index of suspicion may be low [18]. The well-established plaque with central scarring presents few difficulties, but in the early stage lupus may easily be confused with lymphocytoma, Spitz naevus or lupus erythematosus. In older patients, syphilis must be excluded. The histological features and culture results will differentiate lupus vulgaris from the deep mycoses, which may closely resemble the vegetating and crusted type. The lupoid form of leishmaniasis may be impossible to distinguish clinically. On the face, lupus may be mistaken for rosacea [18] or for a port-wine stain [19], and on an extremity for other mycobacterial infections.

Leprosy and sarcoidosis, however, are the chief causes of diagnostic difficulty. The nodules of leprosy are firmer, and other signs are present. The nodules of sarcoidosis resemble grains of sand rather than 'apple jelly': this

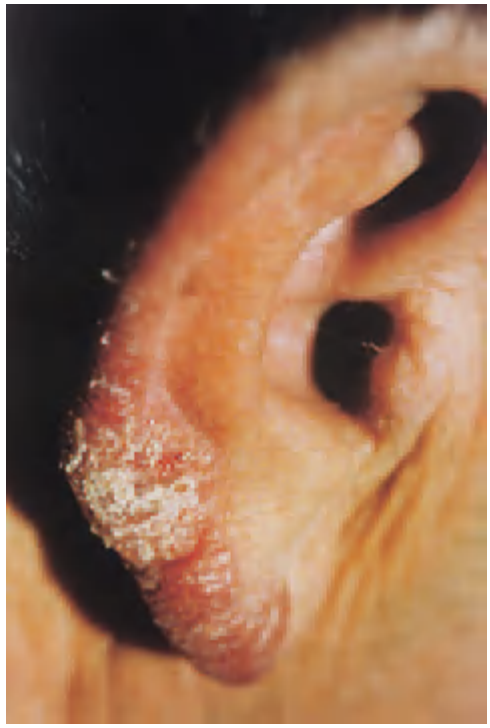


Fig. 28.12 Hypertrophic form of lupus vulgaris on the ear lobe. (Courtesy of the Editor of the *British Journal of Dermatology*.)

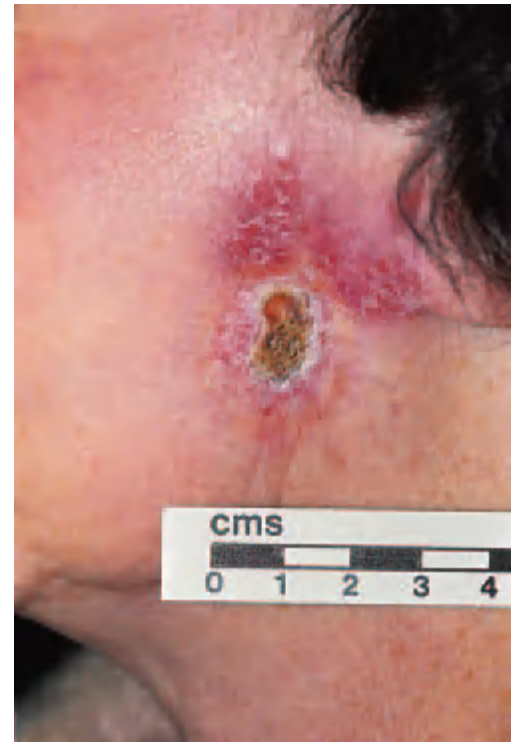


Fig. 28.14 A basal cell carcinoma arising in an old area of lupus vulgaris.

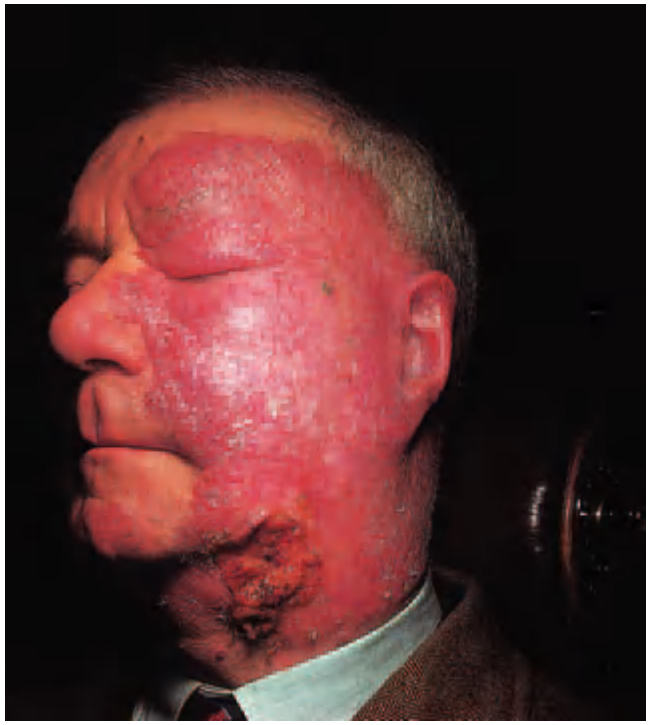


Fig. 28.13 Squamous cell carcinoma of the neck in a patient with lupus vulgaris of many years' duration.

applies to the feel on probing rather than to the colour, which is often greyish.

Lupus vulgaris may resemble psoriasis, but is more infiltrated and usually solitary; Bowen's disease can resemble both. Lupus vulgaris of the perianal area mimicking lichen simplex chronicus has also been reported [20]. Warty tuberculosis usually affects the hand and is more scaly and verrucous than lupus; the histological features are different. Wegener's granulomatosis may be mimicked by rapidly extending granulomatous lesions. It is important that biopsies are deep enough to be representative [18].

Treatment. Standard antituberculosis therapy should be given. Isoniazid has in the past been used as monotherapy, but this practice is strongly discouraged, as up to 26% of patients have clinical evidence of tuberculosis at other sites [1].

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Metastatic tuberculous abscess

SYN. TUBERCULOUS GUMMA

Definition. This form of tuberculosis is the result of haematogenous dissemination from a primary focus during periods of lowered resistance, resulting in single or multiple lesions. It is seen particularly in malnourished children or in patients who are immunosuppressed, and has been noted after local trauma [1] and in association with underlying lymphoma [2].

Histopathology. The features are those of tuberculous granulation tissue, with necrosis and abscess formation. Tubercle bacilli can usually be isolated from the pus.

Clinical features. A tuberculous gumma presents either as a firm subcutaneous nodule or as a fluctuant abscess. The extremities are more often affected than the trunk. The overlying skin may break down to form an undermined ulcer, often with sinuses [2]. Lesions may be multiple. Unusual and transitional forms may occur [3]. Rarely, multiple abscesses have been noted during treatment of miliary tuberculosis [4]. Lesions causing carpal tunnel syndrome have been well documented [5].

Diagnosis. The diagnosis is confirmed by culture.

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Unusual forms of cutaneous tuberculosis

Unusual forms of cutaneous tuberculosis are well recognized. Some of these have already been mentioned as anomalous forms of the various clinical entities. There remain a number of reported cases that are difficult to fit into any one category. They often resemble lupus vulgaris in histology and morphology, though not in site or behaviour [1,2]. Some of the bizarre manifestations seen in the past were assumed to be due to double infections, poor natural immunity or other coexistent disease as modifying factors.

Gangrenous or vegetating forms with underlying lung or glandular disease have been reported [3]. Patients with coexisting HIV infection may have atypical and widespread skin lesions [4]. Correct diagnosis requires a high index of suspicion and biopsy and culture of any unusual skin lesions. Tuberculous cellulitis-like lesions have been reported in a patient who was diabetic and taking oral corticosteroids [5]. Sehgal *et al*. reported patients with multifocal guttate tuberculosis verrucosa cutis and necklace lupus vulgaris [6].

Suspicion of a tuberculous aetiology should be aroused by painless abscess formation, indolent ulcers with bluish undermined edges, or by nodular, plaque-like or necrotic lesions that defy easy classification. It is not enough to demonstrate acid-fast bacilli—culture or PCR is necessary to confirm the species of mycobacterium. A therapeutic trial may be necessary and desirable, while awaiting laboratory results.

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Congenital tuberculosis [1–3]

This is now exceedingly rare. The skin manifestations may be discrete, erythematous lesions, with a central necrotic dell, occurring in infants with a febrile systematic illness.

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Malignant disease and cutaneous tuberculosis

Malignant disease may complicate or be associated with tuberculosis of the skin. Squamous cell and basal cell carcinomas may arise in areas of long-standing lupus vulgaris. They may only be detected when one area of the lesion fails to respond to treatment [1,2]. A plasmacytolymphoma has also been reported [3]. A pre-existing, well-controlled case of lupus vulgaris became fulminant with the onset of the lymphoma [4]. Erythema gyratum repens, usually seen in association with an internal malignancy, has been reported with pulmonary tuberculosis [5].

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The tuberculides

Definitions. The concept of tuberculides was introduced by Darier in 1896. In contrast to true skin tuberculosis, tuberculides were explained as a hypersensitivity reaction to *M. tuberculosis* or its products in a patient with significant immunity. The main features of tuberculides are a positive tuberculin test, evidence of manifest or past tuberculosis and a positive response to antituberculous therapy. There is virtually always absence of bacilli in skin biopsy specimens and culture, although PCR has detected mycobacterial DNA in some forms. Several conditions once thought to represent tuberculides are now classified as variants of rosacea.

True tuberculides can be grouped as follows:

- Micropapular: lichen scrofulosorum
- Papular: papulonecrotic tuberculide
- Nodular: erythema induratum of Bazin: nodular tuberculide.

Aetiology. The pathogenesis of the tuberculides is poorly understood. All tuberculides are thought to be due to haematogenous spread of bacilli in a person with a moderate or high degree of immunity against *M. tuberculosis*. However, it is not usually possible to detect the tubercle bacilli in tuberculides, either because they are present in a fragmented form or because they have been destroyed at the site of the tuberculides by immunological mechanisms [1]. Mycobacterial DNA has been detected in significant numbers of the papular and nodular forms of tuberculide [2–4], but not as yet in the micropapular form, lichen scrofulosorum [1]. It has therefore been suggested [3] that the papular and nodular forms of tuberculide should be regarded as forms of true post-primary tuberculosis.

Fluctuations in the immunological state of the patient may determine the development and features of the eruption. The onset of lichen scrofulosorum has been noted to occur after the initiation of antituberculous treatment and probable shift in the cell-mediated immune status of the patients [1]. Papulonecrotic tuberculide developed in a patient with HIV infection after an increase in the CD4 T-lymphocyte count occurred following the addition of a second antiretroviral drug [5].

In a large study from Hong Kong, in which 150 patients with cutaneous tuberculide were identified, erythema induratum was by far the commonest tuberculide identified (93.3%), followed by papulonecrotic tuberculide (4.7%), then lichen scrofulosorum (2.0%).

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Lichen scrofulosorum

Definition. Lichen scrofulosorum was first described by Hebra in 1868 and is a lichenoid eruption of minute papules occurring in children and adolescents with tuberculosis. It is usually associated with a strongly positive tuberculin reaction.

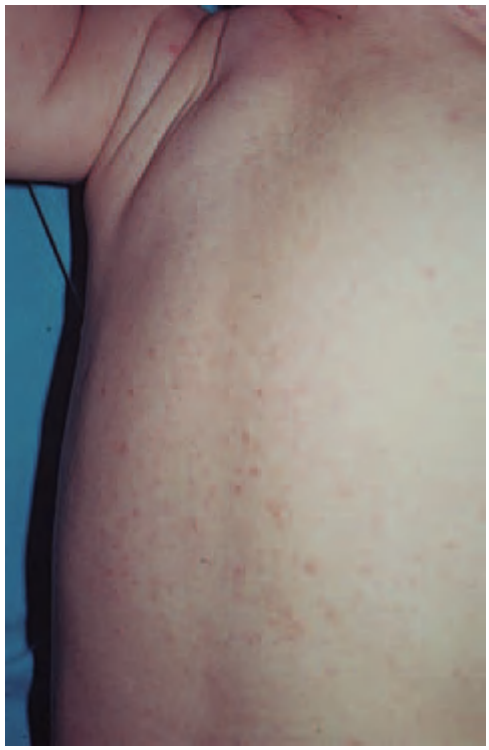

Fig. 28.15 Lichen scrofulosorum of the trunk. (Courtesy of Dr Antonio Torrelo, Hospital del Niño Jesus, Madrid, Spain.)

Pathogenesis. Previously a common tuberculide, it is now rarely seen in Europe, except among immigrants. It occurs mainly in association with tuberculous lymph nodes [1] and foci in bone [2,3]. More recently, it has been reported with pulmonary tuberculosis and generalized lymphadenopathy [4–6] and in association with *M. avium* infection [7]. It is thought to result from haematological spread. Its onset in some patients may be linked to an up-regulation of their immune system [4]. It has also been reported after BCG vaccination [8]. It has not been reported in association with miliary or meningeal tuberculosis, where the host's immune response is usually poor. Other forms of cutaneous tuberculosis such as lupus vulgaris, tuberculous gumma and tuberculosis verrucosa cutis may coexist [5].

Histopathology. Superficial dermal granulomas surround hair follicles and sweat ducts, and may occupy several dermal papillae. Epithelioid cells, lymphocytes and occasional giant cells are seen. Usually there is no caseation. Mycobacteria are not seen in the sections and cannot be cultured from biopsy material. Mycobacterial DNA has so far not been detected by the PCR, as it has in the other forms of cutaneous tuberculides [1].

Clinical features (Fig. 28.15). The eruption consists of symptomless, 0.5–3.0 mm, closely grouped lichenoid papules. The lesions are usually skin-coloured, but may be yellowish or reddish-brown. They are often perifollicular and appear in groups or in an annular arrangement. The papules may have an adherent crust or small pustule. They are mainly found on the abdomen, chest and back, and proximal limbs.

Diagnosis. Differential diagnosis includes all asymptomatic follicular lesions, where the lesions demonstrate a tendency to group together. These include lichen nitidus, in which the lesions are more shiny and tend to be peripheral; keratosis spinulosa, in which the lesions have spiny projections over lichenoid papules; keratosis pilaris, where the lesions are non-inflammatory and usually on the upper thighs and arms; and papular or lichenoid sarcoidosis, secondary syphilis and drug eruptions. The tuberculin reaction is normally positive, but was negative in one patient with AIDS [9].

Treatment. With specific antituberculous therapy, the lesions usually clear within 4–8 weeks without scarring [5].

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Papulonecrotic tuberculide

Definition. An eruption of necrotizing papules mainly affecting the extensor aspects of the extremities and occurring in symmetrical crops. Individual lesions heal with varioliform scarring [1].

Pathogenesis. An associated focus of tuberculosis can be demonstrated in many patients. This ranged from 38% to 75% of patients in three different studies [2–4]. The rapid response to antituberculous therapy usually leaves no doubt of the aetiology when a tuberculous focus cannot be found. In a series of 91 patients, papulonecrotic tuberculide evolved into lupus vulgaris in four patients [2]. Papular tuberculide has also been described after BCG vaccination [5,6], indicating possible haematogenous

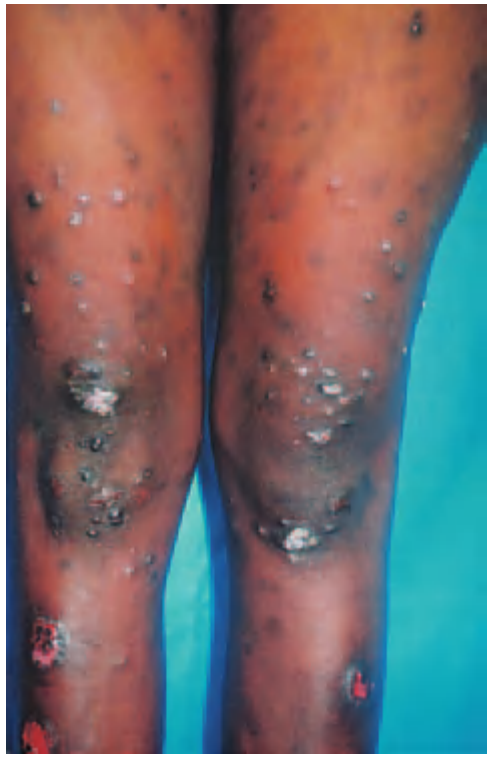

Fig. 28.16 Papulonecrotic tuberculide of the legs. (Courtesy of Professor Jamila Aboobaker, University of Natal, Durban, South Africa.)

bacterial spread as a cause of this tuberculide. Mycobacteria are rarely demonstrated in skin lesions, although they were found in two of the patients who had associated lupus vulgaris in the series discussed above [2], and *M. tuberculosis* DNA has been demonstrated in skin lesions using PCR [7]. Papulonecrotic tuberculide has occurred with *M. avium* complex in a patient with AIDS [8]. The tuberculin test is normally positive, often with a severe, and even necrotic, reaction appearing within 8–12 h.

Histopathology [4]. In fully developed lesions, a large central zone of coagulation necrosis is surrounded by inflammation extending from the superficial to the deep dermis, and sometimes into the subcutaneous tissues. A histiocytic palisade, similar to that of granuloma annulare, is seen around larger lesions. The involvement of adjacent small vessels is striking, ranging from a mild lymphocytic vasculitis to fibrinoid necrosis and thrombotic occlusion.

Clinical features (Fig. 28.16). The eruption consists of recurring crops of symmetrical, hard, dusky-red papules. These crust or ulcerate, leaving pigmented, sometimes atrophic, varioliform scars over the course of a few weeks. Lesions are usually asymptomatic. New crops may continue over months or years. In some cases showers of rapidly healing lesions occur, in others a chronic open ulcer may last for some months [3]. Phlyctenular conjunctivitis may be present.

Young adults are predominantly affected, but papulonecrotic tuberculide has also been seen in infants and young children. Two-thirds of a large South African series were under 30 years of age [2]. The legs, knees, elbows, hands and feet are the sites of predilection, but the ears, face, buttocks and penis—sometimes alone [9,10]—may be involved. Perniotic areas may be favoured. A transition to [2] and coexistence with lupus vulgaris [11] has been described and also an association with erythema induratum [12,13].

Diagnosis. Differential diagnosis includes pityriasis lichenoides, where the lesions may be more widespread and affect the palms and soles; leukocytoclastic vasculitis, whose lesions are more pleomorphic; and nodular prurigo. Biopsy and tuberculin testing should be carried out in all cases; a therapeutic trial of specific antituberculous therapy is usually decisive in doubtful cases.

Treatment. Full specific antituberculous therapy should be given.

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The nodular tuberculides

Erythema induratum of Bazin [1], in which the main pathology is in the subcutaneous fat, is accepted as a true

nodular tuberculide. There have been recent proposals to separate out a nodular form where there is no ulceration and in which the pathology is at the junction of the dermis and subcutaneous fat; the term 'nodular tuberculide' has been proposed for this pattern [2]. Erythema nodosum, panniculitis and, rarely, nodular vasculitis may also be evoked by tuberculosis, though other causes are more common.

Erythema induratum [1]. This was first described by Bazin in 1861 as a condition occurring 'on the legs of female laundresses and in young and plump well nourished women with the typical phenotype of those with the scrofula'. The lesions are characterized by recurrent nodular and ulcerative lesions and occur secondary to tuberculosis elsewhere in the body. Lesions are usually localized to the lower legs, but can affect other areas. In most published series, the disease has occurred at least four times more commonly in women than men [3].

Pathogenesis. Past or active foci of tuberculosis are usually present and the tuberculin test is positive. *M. tuberculosis* is seldom recovered from the lesions, but mycobacterial DNA can be found in up to 77% of skin biopsy specimens [4]. It has been suggested that purified protein derivative-specific T cells capable of producing IFN-γ may be involved in the formation of erythema induratum as a type of delayed hypersensitivity response to mycobacterial antigens at the site of skin lesions [5].

Histopathology. The features are those of either focal or diffuse, lobular or septolobular, granulomatous panniculitis in association with neutrophilic vasculitis of either large or small blood vessels. There are areas of coagulative and caseation necrosis and, usually poorly developed, granulomas although mixed, pallisading and lipophilic granulomas can occur [6,7].

Clinical features (Fig. 28.17). An indolent eruption of ill-defined nodules, usually affecting the backs of the lower legs of young or middle-aged women. However, lesions may affect other body areas, such as the upper limbs, thighs, buttocks and trunk [6]. Follicular perniosis may be present. Lesions may ulcerate, and this may be precipitated by cold weather. The ulcers are ragged, irregular and shallow, with a bluish edge. Resolution may be slow, even with adequate therapy [8], if there are associated erythrocyanotic features.

Erythema induratum is rare in the UK, accounting for five out of 47 cases of cutaneous tuberculosis in a recent series, all of whom were from the Indian subcontinent [9]. It is now the commonest form of cutaneous tuberculosis found in Hong Kong [3]. It is associated with nasopharyngeal, renal and endometrial tuberculosis [10,11], and a search should be made for active tuberculosis elsewhere.

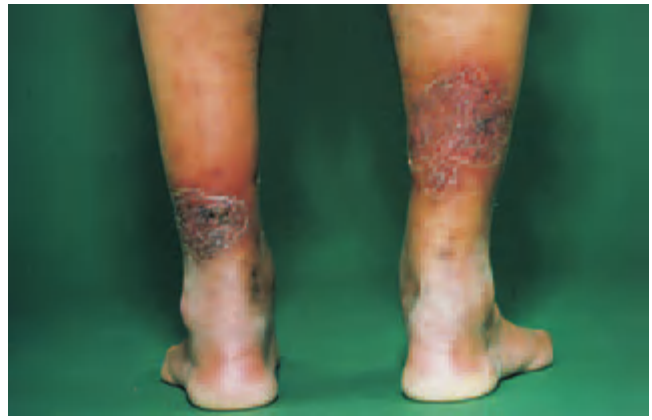

Fig. 28.17 Erythema induratum of the legs.

Treatment. Full specific antituberculous therapy should be given. There is no place for monotherapy as has been recommended in the past [12], as drug resistance is likely to develop, which means effectively that no treatment is being given.

Nodular tuberculide. Jordaan *et al*. [2] have documented four female patients with dull red or bluish-red non-tender, non-ulcerating, nodules 1 cm or slightly larger in size, located on the lower legs. Pathological changes of granulomatous vasculitis were situated at the junction of the deep dermis and adjacent subcutaneous fat. The Mantoux test was strongly positive in all patients, and associated pulmonary tuberculosis was present in two. All lesions cleared promptly with full antituberculous therapy. They argue that there is a case for a tuberculide where the pathological process occurs neither in the superficial dermis, as in papulonecrotic tuberculide, nor in the subcutaneous fat as in erythema induratum, but rather at the junction of the dermis and subcutaneous fat.

Erythema nodosum. This is fully discussed in Chapter 49. Tuberculosis is now a rare cause in western Europe and the USA, but a more frequent one in countries where the disease is still common. A tuberculous cause should always be considered in children. It occurred in nine out of 113 children with non-respiratory tuberculosis reported in the UK in 1978–79 [13].

Nodular vasculitis. This is fully discussed in Chapter 49. There is an obvious overlap with erythema induratum, though the lesions do not usually ulcerate. Women are most frequently affected, and the lesions are usually dusky, tender and persistent. Tuberculosis has caused some cases seen in the past in the UK [14]. Most authors would now accept those of tuberculous origin to be categorized as erythema induratum and to be separate from those of non-tuberculous origin. An exhaustive search for underlying tuberculosis should be made before

commencing oral steroids or other immunosuppressive agents [15].

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Prognosis

Now revolutionized by modern therapy, the prognosis depends largely on early and accurate diagnosis. When tuberculosis has become generalized or has affected the meninges, the prognosis must be doubtful. The mortality in patients with dual tuberculosis/HIV infection is higher than in HIV-negative patients [1,2]. In infants and young children, tuberculosis is always a serious disease.

Tuberculosis confined to the skin usually responds well to multiple therapy, although the acute disseminated and orificial forms may respond less readily.

Diagnosis

Several circumstances may suggest the diagnosis of cutaneous tuberculosis, but the only absolute criteria are a positive culture of *M. tuberculosis* from the lesion or successful guinea-pig inoculation, or mycobacterial DNA identification by PCR (see below). Inoculations are rarely performed now, as equally reliable results can be obtained with multiple cultures. Rapid culture diagnosis, within 2–6 days, can be achieved with the Bactec system [3].

Other indications toward the diagnosis, which are by themselves unreliable, include the following:

1 The presence of active proven tuberculosis elsewhere in the body.
2 The presence of acid-fast bacilli in the lesion itself—this will also be seen in infections with other mycobacteria.
3 The histopathology.
4 A positive reaction to tuberculin.
5 The clinical history and physical signs.
6 The effect of specific therapy.

The difficulties in separating tuberculosis from a 'tuberculoid reaction' (p. 28.10), leprosy (Chapter 29), leishmaniasis (Chapter 32), deep mycoses (Chapter 31), infections with non-tuberculous mycobacteria (p. 28.28), syphilis (Chapter 30) and sarcoidosis (Chapter 58), are dealt with elsewhere.

Polymerase chain reaction

The *in vitro* amplification of specific DNA sequences using the PCR has become a valuable tool in the rapid detection of slow-growing organisms such as *M. tuberculosis*. Several systems have been reported for the molecular detection of mycobacterial DNA using different parts of the mycobacterial genome to generate highly sensitive and specific probes [4–6]. Some assay systems have amplified the insertion sequence IS6110 because of the repetitive nature of this element in the *M. tuberculosis* genome [7]. As few as two colony-forming units of *M. tuberculosis* cells, or as little as 15 fg of DNA, can be detected [8]. Using the PCR technique, mycobacterial DNA has been demonstrated in all the different histopathological variants of cutaneous tuberculosis and in two of the tuberculides (papulonecrotic tuberculide and erythema induratum) [8–12]. The technique reduces the time required for diagnosis in those cutaneous lesions where bacteria can be cultured easily, and may be particularly useful in paucibacillary lesions such as lupus vulgaris. The technique can be used in a variety of pathological specimens, including archival formalin-fixed tissue sections. A generic criticism of this technique lies in its sensitivity; tissue samples containing bacterial DNA may be positive because of bacteraemia and not necessarily because the organism is involved in the pathogenesis of the tissue lesion [11].

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Treatment

General measures

In the UK, all patients with tuberculosis must be notified, as this is a statutory requirement [1] and initiates contact tracing if appropriate [2]. Attention to the patient as a whole is an essential part of the proper management of any cutaneous tuberculous lesion and involves a careful search for an underlying focus of disease and coexistent infections. Because of the rising incidence of drug-resistant tuberculosis, it is vital to confirm the diagnosis bacteriologically whenever possible and to obtain drug susceptibilities [3]. Tuberculosis, pulmonary or extrapulmonary, is an AIDS-defining illness. HIV testing, with informed consent and counselling, should be considered if a risk assessment shows the patient to be from an area or background with increased risk of HIV co-infection. If pulmonary, osseous, lymph-node or renal tuberculosis is found, a combined approach with other specialists is essential, as therapy will depend upon the organs involved, the extent of the lesions and the patient's immunity.

Drug therapy

The Joint Tuberculosis Committee (JTC) 1998 guidelines [4] recommend that the treatment of all patients should be supervised by physicians with full training in the management of tuberculosis and with direct working access to tuberculosis nurse specialists or health visitors. In most cases, this will be the respiratory physician of the hospital or district.

Patient non-compliance is currently the most important factor limiting successful treatment. Directly observed therapy (DOT), where the ingestion of every drug dose is witnessed, has shown improved cure rates in a number of countries [5,6] and is recommended for patients who are unlikely to comply. These include patients who are homeless, alcoholics or drug abusers, drifters, seriously mentally ill, patients with multiple drug resistances and those with a previous history of non-compliance with antituberculous medication [7]. DOT should be considered for new immigrants/refugees. DOT can be daily, but an intermittent regimen is often more convenient.

Standard drug regimens

Controlled trials have defined a number of highly effective short-course regimens, and the basic mechanisms of action of the key antituberculous drugs are now better understood [8]. Isoniazid is the most effective bactericidal drug, followed by rifampicin. Rifampicin and pyrazinamide are the most important sterilizing drugs and act by killing different populations of semi-dormant organisms or persisters. Isoniazid and rifampicin are the most effective drugs at preventing the emergence of resistance to other drugs. Streptomycin and ethambutol are weaker, but nevertheless effective, drugs.

Six-month regimens, including four drugs in the initial 2-month phase (rifampicin, isoniazid, pyrazinamide plus streptomycin or ethambutol), followed by rifampicin and isoniazid in the 4-month continuation phase, are highly effective in patients with fully sensitive organisms [9]. Combination tablets should be used whenever possible to aid compliance and to prevent monotherapy.

Drugs in present use [4]. A standard 6-month regimen for adults is now recommended by the British and American Thoracic Societies. It includes four drugs (doses for adults only are given here):

1 Isoniazid (300 mg daily) for the full 6 months
2 Rifampicin (450 mg daily for those weighing less than 50 kg and 600 mg daily above this weight) for the full 6 months
3 Pyrazinamide for the first 2 months (1.5 g daily for those weighing less than 50 kg; 2.0 g daily for those weighing over 50 kg)
4 Ethambutol for the first 2 months (dosage 15 mg/kg body weight daily).

All drugs are taken on an empty stomach once daily.

Isoniazid remains the standard drug, given in all regimens because of its efficacy, cheapness and low toxicity. Its commonest side effects are peripheral neuropathy (most common in elderly people), which can be countered by giving pyridoxine (10 mg daily) prophylactically from the start of treatment, and hepatitis in adults over 35 years of age.

During the first 2 months of *rifampicin* treatment, elevated serum transaminases are common, but therapy can usually be continued, though occasionally more severe liver damage necessitates a change of treatment. Urine,

sweat and tears may be coloured orange. The induction of liver enzymes by rifampicin may reduce the effectiveness of oral contraceptives.

Pyrazinamide causes hepatitis in 1%, arthritis and the precipitation of gout and cutaneous hypersensitivity in 3.5%. The side effects of *ethambutol* include visual disturbances and rarely a retrobulbar neuritis, which is reversible if detected early so that the ethambutol can be stopped. Patients should be warned of this risk and advised to stop the drug if visual symptoms develop. Visual acuity using a Snellen chart should be carried out before treatment starts. The drug is best avoided in young children and in those with renal impairment. Vertigo and tinnitus may limit the use of *streptomycin* in patients over the age of 40 years, and in those with impaired renal function.

In summary, all antituberculous drugs may cause adverse reactions; in one study, reactions occurred in 10% of patients treated. Reactions were significantly more common in those not receiving standard antituberculosis chemotherapy [10].

HIV disease. In HIV-infected patients, there have been no controlled trials of sufficient power to detect differences in efficacy between regimens. A small clinical study suggests that standard regimens, particularly if supervised properly, are as effective in HIV-positive as in HIV-negative patients [11], hence the JTC recommends the same 6-month regimen [4]. The response rate is the same as for non-HIV-infected patients, but there are higher drug reaction rates and higher reinfection rates.

Multidrug resistance. This is defined as resistance to rifampicin and isoniazid with or without resistance to other antituberculous drugs, and is now a worldwide problem. A recent global assessment of resistance [12] showed a median prevalence of 1%, but higher rates were observed in Estonia (14%), Henan province in China (10.8%), Latvia (9%), the Russian *oblasts* of Ivano (9%) and Tomsk (6.5%), Iran (5%) and Zhejiang province in China (4.5%). The situation is getting worse, and the prevalence of MDR is even higher amongst patients with previously treated tuberculosis; in such individuals, the prevalence of MDR can be as high as 34% (Henan province), 25% (Tamil Nadu, India) or 48.2% (Iran). The numbers affected are much higher in developing countries that do not have resources for effective treatment. Increasing rates of MDR tuberculosis in HIV-infected individuals have been reported mainly in the USA [13]. Treatment of such patients is complex and should only be carried out by experienced physicians in hospitals with appropriate isolation facilities and in consultation with appropriate mycobacterial reference laboratories [4]. Currently, only rifampicin resistance can be routinely detected by molecular probes on microscopy-positive or culture-positive tissue. No other drug resistance can be routinely checked without susceptibility tests.

Modification for dermatological practice. Yates and Ormerod have shown that the standard 6-month regimen is effective in treating cutaneous tuberculosis [14]. In their series of patients, over 50% had coexisting disease elsewhere, all had a good clinical response, and there were no relapses following treatment. Historically, some forms of skin tuberculosis have been treated by isoniazid alone [15]. This is no longer appropriate, as drug resistance is likely to develop with monotherapy—and if drug resistance to isoniazid is already present, it means, in effect, that no therapy is being given.

The excision of small lesions of lupus vulgaris or warty tuberculosis, if diagnosed early, may be effective. Surgery may be helpful in scrofuloderma, sometimes shortening the time needed for chemotherapy. Plastic surgery may help the disfigurement left by treated lupus vulgaris.

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BCG vaccination [1]

BCG vaccines owe their origin to the *in vitro* attenuation by Calmette and Guérin, between 1906 and 1919,

of a strain of *M. bovis* [2]. Evidence of the efficacy of BCG vaccination derives from studies in infants [3] and schoolchildren. There are few data in adults to suggest that BCG vaccination offers protection if given over the age of 16 years [4,5], although absence of evidence does not necessarily mean absence of effect. In the UK, BCG vaccinations appear to reduce the incidence of childhood tuberculosis by 75% or more [6]. BCG vaccination protects the host by blocking the secondary haematogenous spread of the pathogen, limiting the primary infection to subclinical proportions [7]. In a recent report from northern India of childhood cutaneous tuberculosis, BCG vaccination appeared to protect against disseminated disease [8].

The protective effect of BCG in children is likely to last at least 15 years [9]. In the UK, it is still the policy–particularly in light of the rise in tuberculous notifications since 1987—that BCG is routinely offered in schools to all children aged 10–14 years [10,11] and to certain groups at higher risk of exposure to tuberculosis. These include infants and children of immigrants from countries with a high prevalence of tuberculosis [3], and children born to adults born in the UK but from ethnic groups originating in high-prevalence countries, children with a family history of tuberculosis, and tuberculin-negative travellers to areas of high prevalence. It should also be offered to tuberculin-negative health workers and to staff working in hostels for AIDS patients and the homeless.

Because of the risk of generalized BCG infection, BCG vaccination should not be given to individuals known to be HIV-infected in the UK [12].

Complications

After BCG vaccination, a local reaction usually occurs 2–6 weeks later as a small papule that may slowly enlarge and discharge purulent material to leave a shallow ulcer. Tuberculin conversion normally takes place within 12 weeks.

Complications are rare in relation to the number of vaccinations carried out. Excluding abnormal BCG primary complexes, all reported localized or generalized reactions among nearly 1500 million persons vaccinated between 1948 and 1974 made up less than two per million [13]. Of these, keloids, rashes and ocular manifestations accounted for 1.35 per million and 'tuberculosis-like' lesions for 0.16 per million.

Non-specific reactions to BCG include urticaria and erythema multiforme [14]. Unusual reactions have also occurred, such as generalized maculopapular or purpuric eruptions associated with arthralgia and abdominal pain or myalgia, usually after repeated vaccination [15,16]. Extensive or protracted ulceration sometimes occurs.

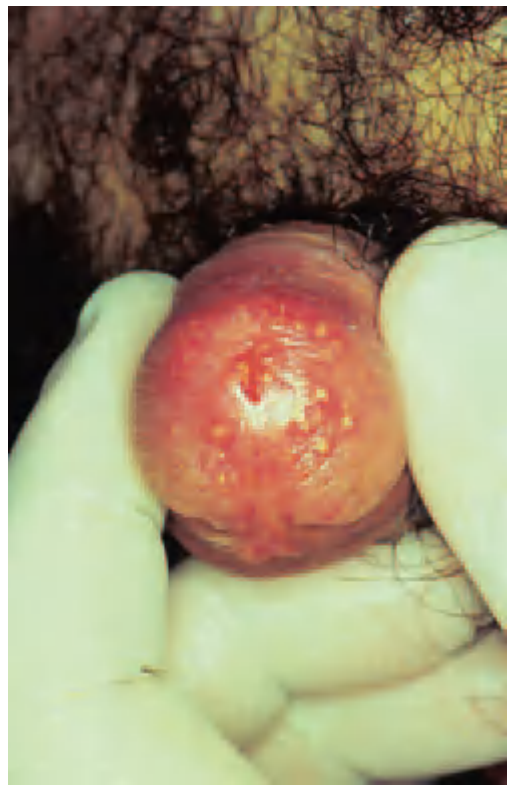

Fig. 28.18 *Mycobacterium bovis*–bacillus Calmette–Guérin infection of the glans penis, showing an infiltrated red plaque containing small, deep-seated, yellow papules. (Courtesy of Dr M. Ribera, Hospital Universitari Germans, Universitat Autònoma de Barcelona, Badalona, Spain, and the Editor of the *British Journal of Dermatology*.)

Specific complications include tuberculous processes caused by the BCG organism. Lupus vulgaris may develop at the vaccination site, usually a few months after vaccination, but cases have been reported as long as 3 years after vaccination [17,18]. This can be a recurrent problem [19] and is more likely to occur after multiple vaccinations [20]. Lichen scrofulosorum and papulonecrotic tuberculides have both followed vaccination [15]. Other reports have included the development of basal cell carcinomas in a BCG scar [21], and disseminated cutaneous granulomas in infants with immunodeficiency syndromes [22].

Therapeutic use

BCG is used as immunotherapy in the management of superficial and *in situ* transitional cell carcinoma of the bladder. The BCG vaccine is usually instilled into the bladder on a monthly basis. Primary infection of the glans penis by *M. bovis*–BCG has been described (Fig. 28.18) after intravesical BCG treatment [23]. Distant cutaneous granulomas have been described after BCG immunotherapy for malignant melanoma [24].

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Non-tuberculous (atypical) mycobacteria

The non-tuberculous mycobacteria are *Mycobacterium* species different from *M. tuberculosis*. In the late 1950s and 1960s, these organisms were referred to as 'atypical', as they were thought to be unusual *M. tuberculosis* strains [1]. Non-tuberculous bacteria occur much more frequently in immunocompromised hosts, and with the advent of the AIDS epidemic their clinical importance has increased. This has led to recent major advances in our understanding of their biology, epidemiology and clinical presentations. Pulmonary disease remains the commonest clinical presentation following infection with this group of organisms. The commonest non-tuberculous mycobacteria that cause cutaneous infection are members of the *Mycobacterium fortuitum* complex (*M. fortuitum*, *M. peregrinum*, *M. chelonae*, *M. abscessus* and *M. mucogenicum*), *M. marinum* and *M. ulcerans*. In immunocompetent patients, cutaneous infection is usually related to trauma, and skin lesions tend to be localized. Immunocompromised hosts show a tendency to develop widespread or disseminated lesions [2].

M. marinum [3–4]

SYN. SWIMMING POOL GRANULOMA; FISH-TANK GRANULOMA

M. marinum (formally *M. balnei* and *M. platypoecilus*) was first isolated in 1926 by Aronson from saltwater fish carcasses in the Philadelphia aquarium [5]. In 1942, Baker and Hagan showed that the bacteria caused tuberculosis in freshwater platy fish and named the organism *M. platypoecilus*. The first report of human disease appeared in 1951 [6], when the organism was found to be the cause of granulomatous skin lesions in those using a contaminated swimming pool in Sweden and was named *M. balnei*. Subsequently, *M. balnei* and *M. platypoecilus* were shown to be the same organism, and they are now called *M. marinum*. In the late 1950s, *M. marinum* was found to be the cause of infections acquired from aquaria in humans [8].

Aetiology. The natural habitat of *M. marinum* is water, particularly enclosures of water that are not often replenished, such as swimming pools and aquaria [8]. Its distribution is worldwide, but the organism is especially prevalent in heated water in temperate climates and in the sea, natural pools, rivers and on beaches. Its vectors include fresh- or salt-water fish, snails, shellfish, dolphins and water fleas [4]. It can also be isolated from cracks in masonry, mud and from water even where chlorination appears to be sufficient [9].

On immunodiffusion analysis, the organism can be shown to possess antigens characteristic of the slow-growing mycobacteria [10], though its growth is more rapid than that of most members in that group. It will grow on ordinary laboratory media in 7–10 days if cultured at 30–33°C; significant inhibition of growth occurs at 37°C.

M. marinum is probably only pathogenic on abraded skin, although a history of trauma cannot always be elicited [11].

Fig. 28.19 Fish infected with *Mycobacterium marinum*. (Courtesy of Professor J.A.A. Hunter, Royal Infirmary, Edinburgh, UK.)

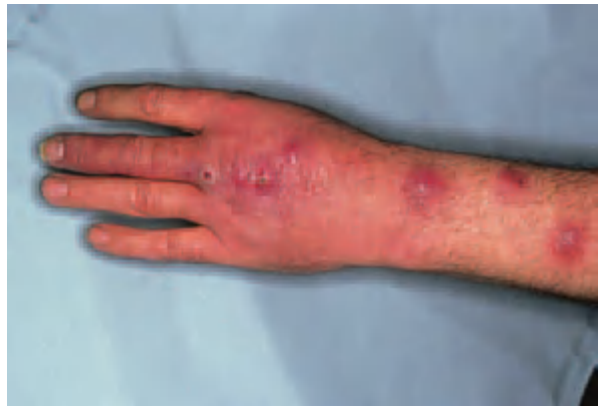

Fig. 28.20 *Mycobacterium marinum* infection showing sporotrichoid spread from the hand to the forearm in an aquarist. (Courtesy of Dr I.H. Coulson, Burnley General Hospital, Burnley, UK.)

Epidemiology. Occupational or recreational exposure to salt or fresh water occurs in the majority of cases. Most of the early proven cases of *M. marinum* infections were described in individuals frequenting swimming pools [12]. The first two cases of 'swimming-pool granuloma' in the UK were reported from Yorkshire in 1964 [13]. In one outbreak, over 300 cases were traced [14]. Similar outbreaks have occurred in Wales [15], France [16] and Germany [17]. The infection has also been contracted in natural bathing pools by the Dead Sea [18] and in the sea in the USA [19].

In many recent cases, the source of infection has been tropical fish tanks [20]. In a national survey of 63 culture-confirmed cases occurring in France between 1996 and 1998, inoculation related to fish tank exposure was documented in 84% of cases [21]. Fish tuberculosis is a chronic infection that causes wasting of the fish, but may take up to 12 months to cause death (Fig. 28.19). Most infections are acquired while cleaning out the tanks. *M. marinum* survives readily in water and can be cultured from dead fish, the sides of tanks, and sand and water samples [22]. One child developed the infection indirectly after bathing in the bath in which his father had recently cleaned a tropical fish tank [23].

Pathology. Lesions may show non-specific inflammation in the first few months, while older lesions show well-formed tuberculoid granulomas [24], with fibrinoid masses rather than caseation. Langhans' giant cells are not always present. Intracellular acid-fast bacilli—longer and broader than tubercle bacilli—are detectable in only approximately 10% of cases [11].

Clinical features. Skin lesions develop after an average incubation period of 2–3 weeks following inoculation of the organisms onto abraded skin. Occasionally, the incubation period can be as long as 9 months [25], leading to delays in diagnosis, as important clinical clues in the patient's history may be overlooked. The initial lesion is either a solitary nodule or pustule that may break down to form an ulcer or abscess, or remain as a verrucous plaque. Lesions are often multiple, and in the sporotrichoid form, which occurs in approximately 20% of cases [26], nodules may extend along the line of lymphatic vessels (Fig. 28.20). The regional lymph glands may be enlarged, but never break down. Deeper infections occurred in 29% of patients in one series [21] and resulted from direct extension of the cutaneous infection. Tenosynovitis, osteomyelitis and septic arthritis can occur [27]. Immunocompromised patients may develop disseminated lesions [28,29].

Lesions are most common on the elbows, knees and feet of swimmers, and on the dominant hand and fingers of fish fanciers. The inhibition of *M. marinum* growth at 37°C accounts for its ability to infect the cooler body extremities whilst rarely spreading systemically.

The infection probably resolves spontaneously in some cases, although complete resolution may take up to 2 years [20].

Diagnosis. As with all mycobacterial disease, the diagnosis requires a high index of suspicion. A history of contact with water, fish tanks, aquaria etc., combined with granulomatous histology, is suggestive of the diagnosis. A positive culture can be obtained in some 70–80% of cases if the organism is grown between 30 and 33°C. It is important to alert the microbiologist to the suspicion of *M. marinum* infection so that specimens are cultured in the appropriate manner. Cultures should be observed for 6 weeks, but generally colonies will be seen in 10–28 days [25]. Species-specific monoclonal antibody against 56-kDa *M. marinum* antigens may have potential use in rapid culture identification [30]. *M. marinum* infection has also been identified using PCR-reverse cross blot hybridization assay with species-specific gene probes [31]. This may

lead to more rapid diagnosis, but cultures will still be necessary to assess antibiotic sensitivities of different strains.

Cultures are of particular value in exclusion of leishmaniasis and sporotrichosis in endemic areas, as well as to identify other atypical mycobacterial infections such as *M. kansasii*, *M. chelonei* and *M. gordonae*, all of which may spread in a sporotrichoid manner. Skin tests using antigens specific to *M. marinum* are of little value [3].

Treatment. Optimal treatment of *M. marinum* infection has not yet been established, and most studies reflect the personal experiences and preferences of individual authors. Antibiotics that have been used include a combination of sulfamethoxazole and trimethoprim [31], the cyclins, particularly minocycline and doxycycline [33], rifampicin plus ethambutol [20,34] and clarithromycin, levofloxacin or amikacin [25]. Cures and failures have been described with all of these drugs. The optimal length of treatment is not certain, but the mean in the most recent study was 14 weeks, with the duration being significantly longer in those patients with infection involving deeper structures [25]. Surgical debridement of lesions is somewhat controversial, but may be useful when deeper structures are involved [35].

One recent study has attempted to draw recommendations for standardized treatments by looking at treatment outcomes [25], and there are also some potentially helpful *in vitro* studies of antibiotic susceptibility patterns for *M. marinum* [36,37]. Rifampicin and rifabutin were found to be the most active drugs in these studies. The mean inhibitory concentrations of minocycline, doxycycline, clarithromycin, amikacin, sparfloxacin, moxifloxacin and sulfamethoxazole were also acceptable. Minocycline consistently had a twofold higher activity than doxycycline, and the cyclines have been shown to give a high percentage cure rate *in vivo*, especially for superficial lesions [25]. Mean inhibitory concentrations were above concentration break points for ethambutol, ciprofloxacin, ofloxacin and levofloxacin and trimethoprim [36], making *in vivo* efficacy less probable. This correlates with results from one study [25] in which treatment failures were reported in half of the patients treated with these antibiotics. The place of the newer fluoroquinolone sparfloxacin still needs to be evaluated clinically. *In vivo* tests of the new glycycline, GAR936, showed similar activity to that of the parent minocycline compound [37].

The public health authorities should be notified when a public source of infection is identified, and other cases should be looked for. Maximum chlorination of swimming pools is effective [16].

Fish fanciers are seldom aware of the risk of mycobacterial infection from their hobby. Simple preventative measures, such as the use of gloves or covering of cuts and grazes should be recommended to fish handlers [22].

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M. kansasii

M. kansasii is a slow-growing photochromogenic bacterium of Runyon Group I that grows optimally at 37°C. Water supplies, swimming pools and sewerage are usual habitats. It is found worldwide, but is particularly prevalent in temperate zones such as the USA, the UK, northern France and Belgium. Classically, *M. kansasii* infection produces a granulomatous pulmonary infection in middle-aged men with underlying lung disease [1]. It may also cause superficial cervical lymphadenopathy in young children [2], meningitis, tendonitis, synovitis, arthritis, osteomyelitis or carpal tunnel syndrome. It most commonly affects persons exposed to contaminated water, particularly after local trauma. There is no evidence of person-to-person spread. First reports of the organism as a cutaneous pathogen were not until 1965 [3], and it remains rare, with only 45 cases reported in the literature in a review in 2001 [4]. In 72% of those cases, an immunological disorder resulting from chemotherapy, autoimmune disease [5], AIDS [6], renal or cardiac transplantation [7] or other predisposing factors was noted [8]. Most patients who present with very localized primary cutaneous infection are immunocompetent, whereas the majority of persons with disseminated skin lesions or pulmonary infection are immunocompromised [1].

As a primary cutaneous disease, *M. kansasii* produces a variety of lesions, usually confined to a distal extremity. Sporotrichoid nodules [9], verrucous papules, papulopustules with necrotic centres, erythematous plaques, cellulitis [10], rhinophyma [11], single and multiple abscesses have all been reported. Papulonecrotic tuberculide skin lesions have been reported in one patient [12].

Skin lesions associated with disseminated *M. kansasii* have increased since the onset of the AIDS epidemic, and *M. kansasii* is the second most frequent cause of disseminated mycobacteriosis in AIDS patients after *M. avium* complex [13]. Disseminated visceral infection can be life-threatening.

The choice of treatment should be determined by *in vitro* sensitivity. Current recommended guidelines for treatment of *M. kansasii* extrapulmonary disease are rifampicin and ethambutol for 9 months, with continuation of therapy for a total of 15–24 months in those patients who are immunocompromised. The addition of prothionamide and streptomycin and/or a macrolide should be considered if the condition is not responding [14].

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M. ulcerans

SYN. NUMEROUS LOCAL NAMES, INCLUDING BURULI ULCER (UGANDA)

Aetiology. *Mycobacterium ulcerans* is a slow-growing mycobacterium that classically infects the skin and subcutaneous tissue, giving rise to large, indolent, necrotizing ulcers. It grows optimally on routine mycobacteriological media at 32°C. Large ulcers, almost certainly caused by *M. ulcerans*, were first described by Cook in Uganda in 1897 [1]; however, the aetiological agent was not isolated and characterized until 1948 in Australia by MacCallum [2]. In the 1960s, the disease was noted to be endemic in refugee camps in Buruli, an area near the river Nile in Uganda. The disease has since become known as Buruli ulcer and has now been reported in at least 32 countries worldwide. It is the third most common mycobacterial disease in immunocompetent people, after tuberculosis and leprosy. It is prevalent in riverine and swamp areas of

the tropical zone in Africa, Asia, South America and a few scattered foci in Australia. Its emergence in West African countries over the past decade has been dramatic [3], and the socio-economic burden of Buruli ulcer for afflicted populations is formidable [4].

Epidemiology and transmission. The mode of transmission is unknown, but infection is probably acquired from mycobacteria present in soil, shallow water, certain vegetation or from insects living in or near water [5]. Infection probably results from small, penetrating injuries, which allow transmission of the bacterium to the subcutaneous fat [6]. Children outnumber adults in most reported series, and this fact may explain why many affected individuals have no record of previous injury. PCR-based assays to detect *M. ulcerans* have been developed [7] and have identified *M. ulcerans* in an irrigation system on a golf course on Phillip Island, Australia, and in samples from a swamp which drained onto the golf course [8]. Reduction in new cases of Buruli ulcer followed drainage of the swamp and restriction of irrigation. *M. ulcerans* has recently been isolated from the salivary glands of aquatic insects in the Daola region of the Ivory Coast, where Buruli ulcer is endemic [9]. Infections have also been recorded in koalas and opossum in Australia where the disease is enzootic [10]. Person-to-person transmission has only rarely been documented [11]. HIV infection does not seem to predispose to *M. ulcerans* infection or to render infection more aggressive [12].

Pathogenesis and pathology [13]. There is a latent period of 2 months or more before an infection becomes overt. After inoculation into the skin, *M. ulcerans* proliferates and elaborates toxins that lead to tissue necrosis. One of the toxins has been identified as mycolactone, a polyketone toxin [14], and phospholipase C has also been implicated [15]. The earliest change is an acute necrosis of dermal and subcutaneous tissue; characteristically, there is an extensive involvement of the subcutaneous fat as a septate panniculitis. The fat becomes necrotic and may calcify. Mycobacteria can be found, in spherical clumps, outside cells, in the layer of exudate on the ulcer floor, and in the fatty septa; some organisms show signs of degeneration and lose their usual rod-like shape. Necrosis of the dermis extends laterally, leading to the characteristic undermining of the ulcer edge. The organism selectively destroys those tissues within its own viable temperature range [16]; muscle is usually spared, perhaps because of its higher temperature. In the deeper dermis, a leukocytoclastic vasculitis is seen, affecting small and medium-sized vessels. After some months, healing starts and is accompanied by a lymphocytic or granulomatous reaction. The skin test to burulin—a 'new tuberculin' prepared from cultures of ultrasonically disrupted *M. ulcerans*—is positive. Fibrosis and scarring complete the sequence.

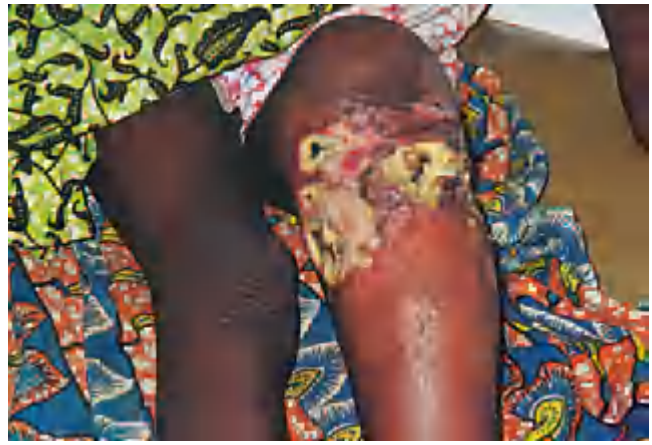

Fig. 28.21 *Mycobacterium ulcerans* in an 8-year-old child. (Courtesy of Professor Françoise Portaels, Institute of Tropical Medicine, Antwerp, Belgium.)

Clinical features [17]. About 70% of patients are children below 15 years of age. The initial lesion is a small, firm, mobile, subcutaneous nodule, usually on an arm or leg, which may be pruritic. Intradermal papules have been observed in some Australian cases. Well-demarcated painless plaques can also occur. Some cases do not progress further, but usually a nodule will break down to form a shallow necrotic ulcer, which extends rapidly and irregularly, with deeply undermined edges (Fig. 28.21) An ulcer may reach a diameter of several centimetres over the course of a few weeks. The floor of the ulcer is formed of necrotic fat, and there may be a clear mucoid discharge. Ulcers are usually single, though satellites may develop. Large lesions may be surrounded by extensive induration. There is little or no constitutional disturbance even with severe local disease. Rarely, the onset is a diffuse cellulitis-like infiltration, with massive oedema.

The course is variable, but usually prolonged. Healing may occur after 6–9 months, but small intractable lesions may persist longer. An ulcer may grow to more than 25 cm in diameter. Necrosis may extend to muscle or bone. The fibrosis and calcification, which accompany healing, may lead to contractures and severe deformity.

Unfortunately, because the ulcers are painless and victims often live in remote areas, most patients do not receive medical attention until the damage is extensive. A review of 102 patients in Ghana indicated that the average length of hospital stay was more than 100 days; the infection led to 10 amputations, 12 joint contractures and two deaths from tetanus and sepsis in these patients [4].

Diagnosis. In endemic areas, suspicion should allow an early diagnosis to be made. However, sporadic or anomalous cases, presenting when the patient has left the area [18], may be confused with tuberculosis, a deep fungal infection or cellulitis. Bacteriological examination of

smears, or of curettage or biopsy specimens, will reveal clumps of acid-fast organisms, which can be cultured at 32°C, although this may take 6–8 weeks. Identification using PCR methods is now feasible [7].

Treatment. As primary antibiotic therapy has been found to be ineffective, possibly because of low drug levels in necrotic tissue, lesions should be treated by surgical excision, followed by grafting if required [3]. Local recurrence is as high as 16% [19]. This is thought to be due to the fact that the margins of lesions are often difficult to define and residual organisms continue to proliferate. Antimicrobials may have a role in prevention of recurrences and metastatic infection, but this has yet to be established [20]. Several drugs, including clarithromycin [21], rifampicin, ciprofloxacin and sparfloxacin [20], have shown good *in vitro* activity against *M. ulcerans*. BCG vaccination for tuberculosis appears to have a partial cross-protective effect against *M. ulcerans* [3]. The protective effect of a DNA vaccine encoding antigen 85A from *M. bovis* BCG has also recently been demonstrated in *M. ulcerans*-infected mice [22].

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Other slow growers

M. scrofulaceum, *M. szulgai* and *M. avium* are of dermatological interest.

M. scrofulaceum

Historically, *M. scrofulaceum* has been associated with cervical adenitis in young children, but in recent years, the frequency of cervical lymphadenitis caused by *M. scrofulaceum* has declined and there are now more cases caused by *M. avium* complex [1]. Submandibular and submaxillary nodes are usually involved, and the disease is often unilateral with few constitutional symptoms and can resolve spontaneously. Skin abscesses due to M. *scrofulaceum* infection have been reported [2] and also chronic ulcerative and nodular skin lesions and pulmonary infection in a patient with AIDS [3]. Surgical treatment of infected lymph nodes is the treatment of choice. For more widespread disease, regimens similar to those used for treatment of *M. avium* complex have been recommended, as isolates of *M. scrofulaceum* have been shown to have similar antibiotic susceptibility patterns [4].

M. szulgai

M. szulgai was first described in 1972 [5] and has a worldwide distribution. Infection is principally pulmonary, but infections have also involved bursae, tendon sheaths, bones, lymph nodes and skin. Skin lesions include diffuse cellulitis, nodules and sinuses [6], and multiple inflammatory skin lesions [7]. Intralesional or systemic steroids were found to be a risk factor for development of skin lesions in two-thirds of patients in one reported series [8]. Isoniazid, rifampicin, ethambutol and streptomycin have been used for treatment of *M. szulgai* infection [8].

M. avium complex

Incidence. Disseminated infections with *M. avium–intracellulare* were rare before the emergence of the AIDS epidemic, but their incidence is now rising sharply [9,10], and organisms of the *M. avium–intracellulare* complex are now one of the commonest causes of opportunistic infection in patients with AIDS [11].

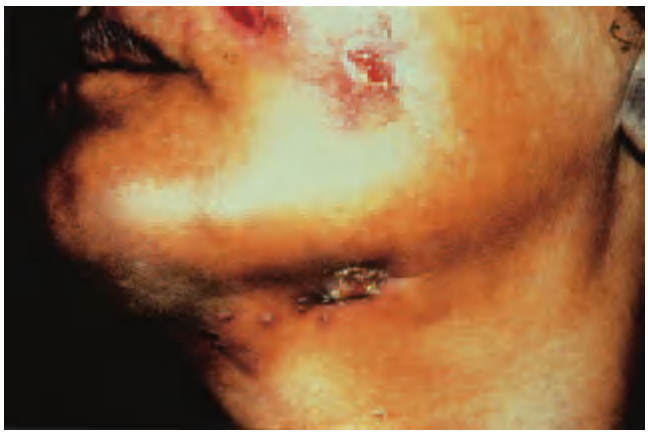

Fig. 28.22 *Mycobacterium avium* complex infection of the left cheek and submandibular area, showing sinuses and resembling lupus vulgaris. (Courtesy of Dr P. Kullavanijaya, Institute of Dermatology, Bangkok, Thailand, and the Editor of the *British Journal of Dermatology*.)

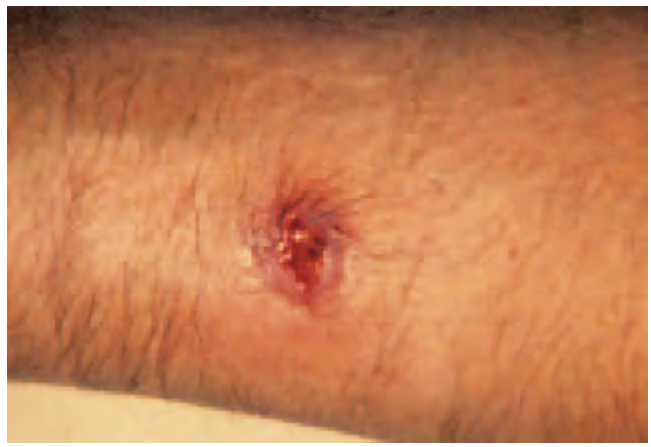

Fig. 28.23 *Mycobacterium avium* complex infection presenting as an erythematous nodule with central ulceration on the extensor aspect of the forearm in an immunosuppressed patient with systemic lupus erythematosus. (Courtesy of Dr H. Kakinuma, Surugadai Nihon University Hospital, Chiyoda, Tokyo, Japan, and the Editor of the *British Journal of Dermatology*.)

Pathogenesis. The *M. avium* complex comprises *M. avium* and *M. intracellulare*; these are closely related organisms that cannot be differentiated by standard laboratory methods [12], although the separate genomes can be distinguished by PCR-aided DNA–DNA hybridization [13]. They are slow-growing organisms with optimal growth at 37°C and are ubiquitous saprophytes, found in tap water, soil, dairy products, animals and house dust [14]. Both the respiratory and gastrointestinal tracts serve as portals of entry for systemic infection, and as many as 30% of normal human faecal samples yield isolates of *M. avium* complex [15]. Skin involvement secondary to disseminated disease is uncommon and primary skin infection is rare [16].

Clinical features. Chronic pulmonary infection is the most common form of human disease, with lesions similar to tuberculosis. In immunocompetent hosts, infection usually occurs in patients with predisposing lung conditions, which include pneumoconiosis, silicosis and cystic fibrosis, and the prognosis is strongly influenced by the associated disease [14]. Osteomyelitis [17] and granulomatous tenosynovitis [18] have both been reported, and *M. avium* complex is now the commonest cause of cervical lymphadenitis in children [1,19]. Involvement of the skin is uncommon (Fig. 28.22), but can occur following traumatic skin inoculation in cervical lymphadenitis—with sinus formation giving lesions indistinguishable from tuberculous scrofuloderma—and in immunocompromised hosts, in whom *M. avium* may disseminate from primary visceral lesions. Skin lesions are of variable appearance and include multiple ulcers [20], nodules [21], ulcerated nodules (Fig. 28.23), abscesses [22], painless nodules and plaques resembling lepromatous leprosy [23] or lupus vulgaris [24], and also lesions resembling prurigo nodularis [25]. Lichen scrofulosorum has also been reported with *M. avium* infection [26].

In HIV-infected patients, the most common manifestation of *M. avium* complex infection is mycobacteraemia, but skin lesions may provide a clue to the presence of disseminated *M. avium* complex infection. Infection tends to occur late in HIV disease and most frequently in patients whose $CD4^+$ cell counts have fallen below 50 cells/mm^3 [14]. The incidence of disseminated and cutaneous lesions is decreasing in most centres because of the use of highly active antiretroviral therapy (HAART), which restores some immune competence, and the use of prophylactic antimycobacterial drugs [27]. On starting HAART, some patients may experience *M. avium* immune restoration disease due to restoration of delayed hypersensitivity responses to mycobacterial antigens. Symptoms include fever, lymphadenitis and cutaneous lesions [28].

A review of the published cases of disseminated infection in patients without AIDS emphasizes the frequent association with haematological malignancies (particularly hairy cell leukaemia), connective tissue disease and corticosteroid or cytotoxic therapy [29,30].

Diagnosis. The diagnosis may be made by blood culture, or by the culture of *M. avium–intracellulare* complex from bone marrow or liver biopsy. In patients with cutaneous lesions, culture of skin biopsy specimens or aspirated seropurulent fluid may give positive results [21]. Tissue staining for acid-fast bacilli is often negative. Histology shows non-caseating granulomas, and sometimes acid-fast bacilli within giant cells or extracellularly.

Treatment. Treatment of *M. avium* complex was unsatisfactory due to frequent MDR, but the introduction of the newer macrolides clarithromycin and azithromycin, and of rifabutin, has greatly improved treatment outcomes. These agents are, however, associated with many adverse effects and potential drug–drug interactions, particularly in those patients who are on antiretroviral therapy. Clarithromycin and azithromycin must be administered in combination with other agents such as ethambutol to prevent emergence of macrolide resistance [31]. Ciprofloxacin has also been used in some treatment regimens [32]. It is recommended that patients with lymphadenitis are treated surgically with complete excision of the nodes [33]. Surgical excision has also been used in some patients with localized skin lesions [21]. In immunocompetent patients with extrapulmonary disease, chemotherapy should probably be continued for 18–24 months. In patients with HIV disease, treatment should be lifelong unless there is confidence that the immune system has been restored by HAART [33]. Azithromycin appears to be protective against disseminated *M. avium* complex in those patients unresponsive or non-adherent to HAART, but does not appear to prevent the development of immune restoration disease [34].

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Rapidly growing mycobacteria [1]

The species of rapidly growing mycobacteria capable of producing disease in humans are the *Mycobacterium fortuitum* group, the *M. chelonae/abscessus* group, and the *M. smegmatis* group. The *M. fortuitum* group includes *M. fortuitum* and *M. peregrinum* and the taxon known as the 'unnamed third biovariant complex'. *M. chelonae* and *M. abscessus* along with the newly recognized *M. immunogenum* are members of the group known collectively as the *M. chelonae/abscessus* group. The *M. smegmatis* group contains *M. smegmatis* and two newly described species, *M. goodii* and *M. wolinskyi* [2]. They cause skin, soft tissue, bone and pulmonary infection, as well as disseminated disease.

M. fortuitum complex, *M. chelonae*/*M. abscessus* and *M. smegmatis* group

These organisms are widely distributed in the environment in soil and water and may also be commensal organisms of human skin. They are extremely hardy; members of the *M. fortuitum* group and *M. smegmatis* group can grow at 45°C, and the *M. chelonae/abscessus* group and *M. mucogenicum* resist the activity of organomercurials, chlorine, 2% concentrations of formaldehyde and other commonly used disinfectants [3]. These organisms are commonly isolated from municipal tap water [4]. *M. chelonae* was found as a contaminant in a gentian violet solution [5] and *M. abscessus* has been isolated from contaminated lidocaine (Xylocaine) [6] and histamine solutions [7]. Pseudo-outbreaks have most commonly related to contaminated bronchoscopes and endoscopic cleaning machines, and to contaminated hospital water supplies [3].

Clinical cutaneous disease with these pathogens seems to follow two patterns. In the immunocompetent host, a traumatic injury is followed by the development of localized abscess formation [8]. In the immunocompromised individual, there may be no history of trauma and patients present with disseminated disease, with multiple subcutaneous nodular lesions, positive blood cultures, cervical lymphadenitis, keratitis and occasionally endocarditis [9]. Conditions associated with disseminated infection include organ transplantation, rheumatoid arthritis, renal failure and autoimmune disorders. Disease due to *M. chelonae* is strongly associated with concomitant corticosteroid therapy [10].

The *M. fortuitum* group accounts for 60% of community-acquired localized cutaneous infection caused by the rapidly growing mycobacteria, but is a rare cause of pulmonary disease. This group is also responsible for the majority of health care-associated (nosocomial) cases of post-surgical wound infections and catheter infections [1]. *M. fortuitum* infection of the sternum has been reported after open-heart surgery [11], as a cause of peritonitis in patients receiving continuous ambulatory peritoneal dialysis [12] and after localized microinjections (mesotherapy) for pain control [13]. A patient with lupus vulgaris-like lesions has also recently been described [14].

The *M. chelonae/abscessus* group (Fig. 28.24) is responsible for approximately 95% of disseminated cutaneous infections caused by the rapidly growing mycobacteria [1] and also causes chronic lung disease. Post-injection abscesses are probably the commonest skin lesions caused by *M. abscessus*. An outbreak in 12 patients at an ear, nose and throat (ENT) clinic in 1969 was due to contaminated histamine injections [7]. An alternative medicine practitioner infected a total of 232 patients with contaminated lidocaine injections [6]. Haemodialysis is also a risk factor [15]. A survey across the USA found that non-tuberculous mycobacteria were recovered from 83% of water supplies to dialysis units [4]. Two employees at a hot spring bath in Korea developed sporotrichoid lesions due to *M. abscessus* and were assumed to have been contaminated from the bath water [16].

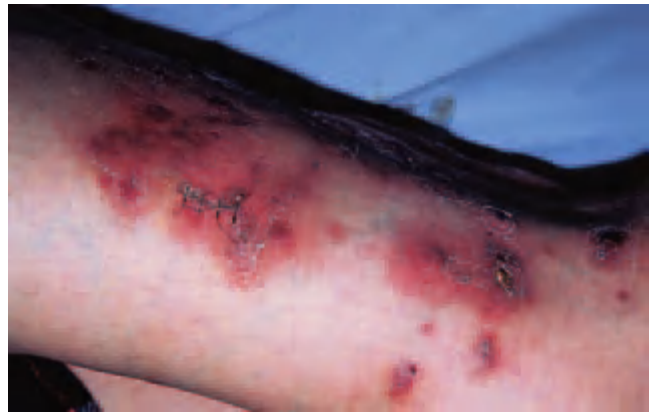

Fig. 28.24 *Mycobacterium abscessus* infection causing abscesses. (Courtesy of Dr A.G. Smith, North Staffordshire Hospital, Stoke-on-Trent, UK, and the Editor of the *British Journal of Dermatology*.)

M. chelonae causes community-acquired disease—for example, post-traumatic skin or soft-tissue infection, bone infection and disseminated cutaneous infection; and sporadic nosocomial infections—for example, after surgery, after injections and related to catheter use [17]. Implanted porcine heart valves themselves may be contaminated with *M. chelonae* [18]. Disseminated erythematous subcutaneous nodules are the commonest manifestation, most commonly seen on the distal parts of the limbs (Fig. 28.25), or in a sporotrichoid pattern [19]. Localized cellulitis, subcutaneous abscesses and osteomyelitis (usually following skin injury), are also seen. Sixty-two per cent of patients infected with *M. chelonae* in one series were receiving corticosteroids and 72% were immunosuppressed [10]. Infection has also been reported after acupuncture [20]. Disseminated disease is rare and HIV infection does not seem to carry a risk for *M. chelonae* infection.

Infections involving the *M. smegmatis* group have included cellulitis, localized abscesses and osteomyelitis after trauma [21]. No cases of disseminated cutaneous infection have been reported to date. Sporadic cases of catheter sepsis and infection after plastic surgery have also been noted [1].

Pathology. Abscess formation in the dermis and subcutis is the rule, but tuberculoid granulomas with or without necrosis may occur.

Diagnosis. These infections are easily missed or attributed to foreign bodies, deep mycoses or osteitis. They should be considered in the differential diagnosis of chronic relapsing nodules and abscesses in immunocompromised

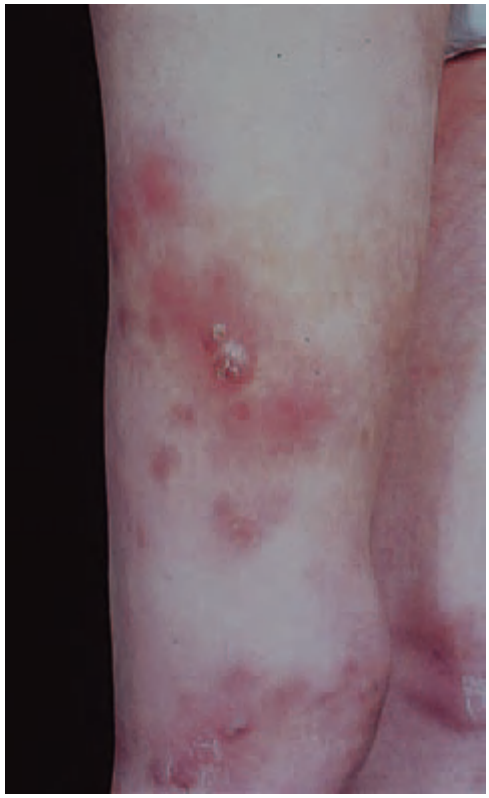

Fig. 28.25 *Mycobacterium chelonae* infection of the lower limb. (Courtesy of Dr R.D. Ead, Hope Hospital, Manchester, UK.)

individuals. Diagnosis is usually made by the culture of biopsy material, and in the case of abscesses a biopsy from the wall is more likely to yield the organism than is aspirated pus. They all have the distinctive ability to produce visible colonies between 5 and 7 days at temperatures ranging between 22°C and 45°C, but some strains may fail to grow at 37°C. Their identification is possible by differences in culture requirements, biochemical tests and DNA homology. Clinically, the lesions are not specific to the species involved in the infection [22].

Treatment [1]. In contrast to treatment for most slowly growing mycobacteria, antimicrobial therapy for rapidly growing mycobacteria is determined by the extent of the disease. Single-drug therapy is usually sufficient for localized or minor disease, with minimal risk of developing mutational drug resistance. In contrast, disseminated cutaneous disease and pulmonary disease require multiple antimicrobials. Newer drugs such as linezolid, an oxazolidinone, and the 8-methoxyfluoroquinolones gatifloxacin and moxifloxacin offer great promise compared to injectable medicines, but clinical experience is limited.

The *M. fortuitum* group is much less drug-resistant than the *M. chelonae/abscessus* group and strains are usually susceptible to amikacin, ciprofloxacin, sulfonamides, cefoxitin and imipenem. The presence of tetracycline-resistant genetic determinants in approximately 50% of members of the *M. fortuitum* group precludes the use of tetracyclines including doxycycline. Approximately 80% of isolates are sensitive to clarithromycin.

The treatment of localized infections due to the *M. chelonae/abscessus* group is with clarithromycin. Azithromycin appears also to work well, but there is less clinical experience with this drug. Acquired resistance to the macrolides has not been seen with localized infections, but it is suggested that more severe infections are treated for the first 2 weeks with an additional injectable agent. For extensive extrapulmonary disease or for disseminated infections involving *M. chelonae*, the injectable agents tobramycin plus imipenem have been used for 2–6 weeks in combination with clarithromycin. For serious disease with *M. abscessus*, amikacin plus cefoxitin or imipenem is used for 2–6 weeks in combination with clarithromycin. *M. abscessus* lung disease is still generally incurable with available therapeutic agents.

The *M. smegmatis* group is uniformly sensitive to sulfonamides, doxycycline, imipenem and amikacin.

Surgical debridement may be a useful adjunct to treatment in some patients. It is not certain how long chemotherapy should be continued for these infections, as there is no evidence from controlled clinical trails. If the response to initial treatment is anything less than optimal, then prolonged chemotherapy for up to 2 years would seem sensible.

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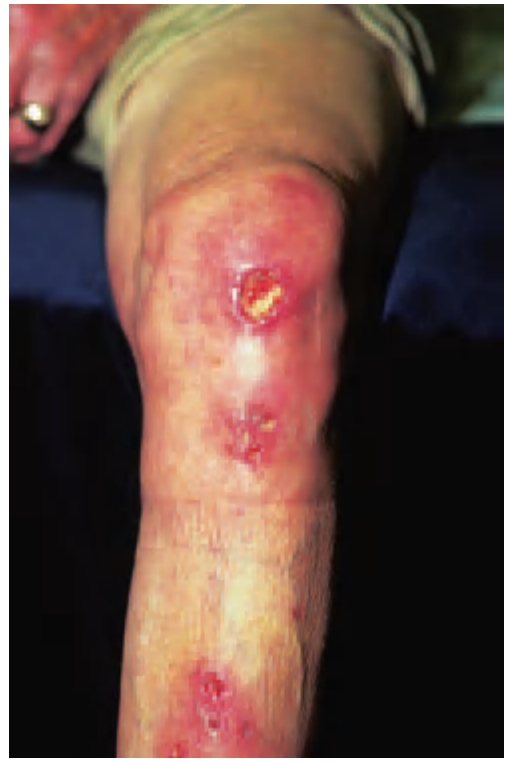

Fig. 28.26 *Mycobacterium haemophilum* infection producing ulcerated nodules on the left knee and shin, with a non-ulcerated nodule on the medial aspect of the knee. (Courtesy of Dr J.C. Murray, Duke University Medical Center, Durham, NC, USA, and the Editor of the *British Journal of Dermatology*.)

M. haemophilum

This mycobacterium is an increasingly recognized pathogen in immunocompromised patients, including those with HIV infection, following organ transplantation, and in patients with haematological malignancies or with chronic conditions requiring prolonged immunosuppressive therapy. It causes cutaneous, synovial and, less frequently, pulmonary infections [1]. It has also been isolated from otherwise healthy children with lymphadenitis.

M. haemophilum causes multiple tender cutaneous nodules, often violaceous, which may develop into abscesses or ulcers (Fig. 28.26), and occasionally may present as annular plaques [2] or panniculitis. Lesions typically occur on the extremities and are often situated over joints. This may reflect low optimal temperature growth requirements and a predilection to grow on the cooler areas of the body. Systemic features such as weight loss, tenosynovitis, joint effusions, osteomyelitis or respiratory tract symptoms may coexist.

M. haemophilum may be cultured from the skin or other tissues or secretions, but has unique growth requirements and therefore may be relatively under-recognized and under-reported. It grows optimally at 30°C to 32°C and the growth media must contain iron.

Histologically, suppurative granulomas containing acid-fast bacilli are usually seen, but occasionally granulomas may be poorly formed and have varying amounts of necrosis [3].

Treatment is difficult. Lesions may persist despite therapy or relapse after treatment is stopped. Improvement of immunological status is the basis for successful treatment. There are no current recommended guidelines for treatment. A three-drug regimen containing clarithromycin, rifabutin and ciprofloxacin has been recommended [1,4]. In ill patients, the addition of amikacin and doxycycline is suggested [1]. In common with the response to treatment for some of the rapidly growing bacteria, an immune reconstitution syndrome may occur on starting treatment.

Other mycobacteria

The use of molecular testing has brought about the recognition of multiple newly characterized mycobacterial species that were previously unrecognized by standard techniques [5]. Some are non-pathogenic, but it is likely that the majority will cause clinical disease. There is also evidence that previously seldom-encountered mycobacteria are being increasingly recognized as causing human disease. These include *M. malmoense*, which was recently shown to be the cause of disseminated cutaneous infection in an immunocompetent patient [6]; *M. xenopi*, which was reported to cause lupus vulgaris-like skin lesions [7] and disseminated cutaneous lesions in immunosuppressed patients [8]; and *M. genavense*.

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Chapter 29

Leprosy

D.N.J. Lockwood

Synonyms

Hansen's disease, hanseniasis and elephantiasis graecorum, and names in local languages in endemic areas.

Definition

A chronic granulomatous disease caused by *Mycobacterium leprae*, principally affecting peripheral nerves and skin.

History

Endemic in India and the Far East since ancient times, leprosy was imported into Europe in the 4th century BC, perhaps by the troops of Alexander the Great. The European epidemic peaked in the 13th century, then slowly died out [1]. French settlers took leprosy to Canada and black slaves took it to America. It is not known how the disease reached the Australian aborigines. Even after the discovery of the agent, *M. leprae*, by Armauer Hansen in Norway in 1873 (the first bacillus to be associated with a human disease), the infectious nature of leprosy was not readily accepted [2]. The slow spread of the disease and its familial association suggested that it was inherited. This belief, and the fear of the deformities that leprosy may cause, have contributed to the stigma and ostracization that still characterize attitudes towards leprosy. Stigma remains a major obstacle to leprosy control, despite advances in bacteriology, chemotherapy and epidemiology.

Aetiology

Mycobacterium leprae has never been grown *in vitro*. Limited growth has been achieved in the mouse footpad [3], and more widespread growth and disease in immunosuppressed and nude mice [4] and the nine-banded armadillo [5]. The latter has provided mycobacteria for genetic and biochemical analysis and the production of trial vaccines. A primate model of leprosy has been established in three species of monkey [6]. *Mycobacterium leprae* grows at 30–33°C, with a doubling time of 12 days. It is a remarkably hardy organism, remaining viable in the environment for up to 10 days [6]. The sequence of the *M. leprae* genome was published in 2001. *Mycobacterium leprae* has a 3.27-Mb genome that displays extreme reductive evolution [7]. Less than half the genome contains functional genes: many pseudogenes are present. One hundred and sixty-five genes are unique to *M. leprae*, and functions can be attributed to 29 of them. Comparison of biosynthetic pathways with *M. tuberculosis* shows that for lipolysis *M. leprae* has only two genes (*M. tuberculosis* has 22). *Mycobacterium leprae* has lost many genes for carbon catabolism, and many carbon sources (e.g. acetate and galactose) are unavailable to it. *Mycobacterium leprae* growth may be restricted to a few carbon sources on which it can maintain a balanced carbon metabolism. It has also lost anaerobic and micro aerophilic electron transfer systems. *Mycobacterium leprae* has many genes for haem and iron based proteins, but it is severely limited in its iron uptake capacity, since it has lost the ability to produce iron scavenging sideropores [8]. Restriction

fragment length polymorphism (RFLP) analysis [9] suggested that *Mycobacterium leprae* was a single species, but recent work based on amino acid sequencing of *M. leprae* proteins suggests that there are subtle strain differences, and this may enable new studies on transmission [10].

Mycobacterium leprae has a complex antigenic cell wall composed of lipids, carbohydrates and proteins. The organism also synthesizes a species-specific lipid, phenolic glycolipid (PGL) [11]. Several polymerase chain reaction (PCR) probes (18 kDa, 36 kDa, 65 kDa and ribosomal RNA sequences) have been developed for the detection of *M. leprae* DNA in tissues from leprosy patients [12]. Although these are specific, they are not yet sensitive enough to be useful in diagnosing patients whose skin is bacteriologically negative on conventional staining. The molecular basis for rifampicin resistance has been elucidated and it is now possible, using a polymerase chain reaction-single strand polymorphism (PCR-SSC) technique, to identify rifampicin resistant isolates within hours [13].

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Geographical distribution

About 4 million people have, or are disabled by, leprosy. The apparent fall in registered patients from 12 million in 1988 to 0.82 million on treatment in 1999 hides an intriguing picture. Prevalence has fallen due to a combination of effective antibiotic therapy and a change in case definition. Incidence, however, remains stable at around 800 000 new cases annually, with high rates of childhood cases [1]. Intensive leprosy elimination campaigns held in 1998 and 1999 detected large numbers of new cases. A week-long campaign in Nepal found 11 696 new cases; this doubled the national case load.

India dominates the global picture with 70% of the world's leprosy cases; 86% of leprosy patients reside in six countries (India, Brazil, Indonesia, Myanmar, Madagascar and Nepal). Leprosy has not always been a tropical disease; it was endemic in Norway until the early twentieth century. Nearly all the new cases now seen in Europe and North America acquired their infection abroad [2].

Leprosy is a chronic disease with a long incubation period. An average incubation time of 2–5 years has been calculated for tuberculoid cases, and 8–12 years for lepromatous cases. American servicemen who developed leprosy after serving in the tropics presented up to 20 years after their presumed exposure [3].

Although leprosy is rarely a primary cause of death, patients have a standardized death rate at least twice that of the general population due to the indirect secondary effects of the disease [4]. It is estimated that 1 million disability adjusted life years (DALY) are lost globally each year due to leprosy, with 6.3 years of healthy life being lost per patient.

Age, sex, household contact and bacille Calmette-Guérin (BCG) vaccination are important determinants of leprosy risk: leprosy incidence reaches a peak at the ages of 10–14 years [5]. An excess of male cases has regularly been found, although this may be due to women being reluctant to present to health workers with skin lesions [6]. Clustering of cases is well recognized, particularly in low endemic areas [7]. Although poor nutritional status was thought to predispose to leprosy, no good evidence substantiates this. Improved socio-economic conditions, extended schooling and good housing reduce the risk of leprosy [8]. There are weak human leukocyte antigen (HLA) associations with leprosy; HLA-DR2 and HLA-DR3 occur at a higher frequency in tuberculoid (TT) patients than in lepromatous (LL) or borderline lepromatous (BL) patients in at least two populations [9], whereas HLA-DQ1 is associated with susceptibility to BL/LL leprosy in three different countries [10]. In South India an association has been found between paucibacillary leprosy and a locus on chromosome 10p13 [11].

Studies from Malawi [12], Uganda [13], Mali and south India [14] have not shown human immunodeficiency virus (HIV) infection to be a risk factor for leprosy. HIV/leprosy co-infected patients have typical skin lesions and leprosy histology, and granuloma formation even with low circulating CD4 counts [15].

Subclinical infection with *M. leprae* is probably common, but the development of established disease is rare. There is no reliable test for determining whether a person has encountered *M. leprae* and mounted a protective immune response. In contacts of leprosy patients, there is

frequently evidence of specific sensitization to *M. leprae* using markers of infection such as serum antibody levels, *in vitro* lymphocyte transformation tests (LTTs) and skin-test responses to soluble *M. leprae* antigen [16]. Contacts of an untreated elderly man with borderline lepromatous leprosy in a British residential home showed that 23/30 and 25/30 had positive Mitsuda skin test and positive LTT responses, respectively, to *M. leprae* sonicate, but only two contacts had positive antibody (IgM PGL) responses [17]. Self-healing often occurs in early monomacular tuberculoid cases [18]. Leprosy is probably analogous to tuberculosis, in which only 10% of infections manifest as clinical disease [19].

Nasal discharges from untreated lepromatous leprosy patients, who are often undiagnosed for several years, are the main source of infection in the community [20]. In Indonesia and Ethiopia, *M. leprae* DNA has been detected in nasal swabs in up to 5% of the population [21]. Infection probably also occurs through the nose. *Mycobacterium leprae* is inhaled, multiplies on the inferior turbinates and has a brief bacteraemic phase before binding to Schwann cells and macrophages.

The skin is unimportant in leprosy transmission. Bacilli are not excreted by the skin and are rarely found in the epidermis. The only evidence of bacilli entering via the skin comes from case reports of direct inoculation. Leprosy has been transmitted to nude mice through pricks from infected cactus thorns [22]. There is no evidence that biting arthropods transmit leprosy. It is surprising that, in contrast to tuberculosis, there are few documented cases of leprosy occurring in both the medical and non-medical attendants of leprosy patients.

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Pathogenesis of leprosy [1]

The pathogenesis and thus the clinical features reflect four principle causes of tissue damage (Fig. 29.1):

1 The degree to which cell-mediated immunity (CMI) is expressed [2]. Lepromatous leprosy represents a failure of CMI specifically towards *M. leprae* with resultant bacillary multiplication, spread and accumulation of antigen in infected tissues. The absence of activated lymphocytes and macrophages means that nerve damage is slow and gradual in onset. In tuberculoid leprosy, CMI is strongly expressed, so that the infection is restricted to one or a few skin sites and peripheral nerves. Lymphocytic infiltration rapidly causes nerve damage. Between those two polar forms lies the borderline forms of disease, with the extent of disease reflecting the balance between CMI and bacillary load.

2 The extent of bacillary spread and multiplication. In lepromatous leprosy, haematogenous spread of bacilli occurs [3] to cool, superficial sites, including eyes, upper respiratory mucosa, testes, small muscles and bones of hands, feet and face, as well as peripheral nerves and skin. In tuberculoid leprosy, bacillary multiplication is restricted to a few sites and bacilli are not readily found.

3 The appearance of tissue-damaging immunological complications: lepra reactions [4]. Borderline patients (borderline tuberculoid, BT; borderline, BB; borderline lepromatous, BL) are immunologically unstable and at risk of developing immune-mediated reactions. Type 1 (reversal) reactions are delayed hypersensitivity reactions caused by increased recognition of *M. leprae* antigens in skin and nerve sites. Type 2 reactions, erythema nodosum leprosum (ENL), are due in part to immune complex deposition and occur in BL and LL patients who produce antibodies and have a large antigen load.

4 The development of nerve damage and its complications. Nerve damage occurs in two settings, in skin lesions

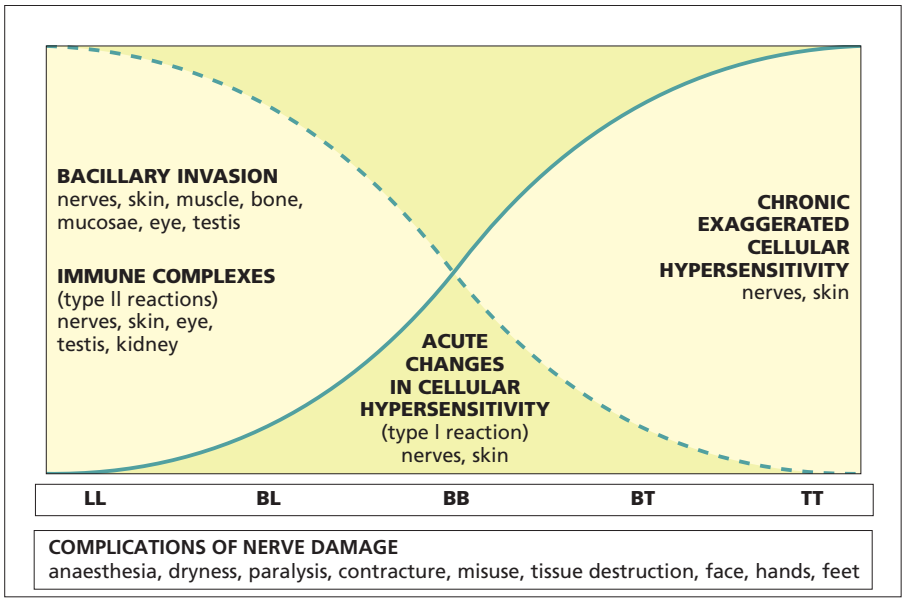

Fig. 29.1 Mechanisms of damage in leprosy, and tissues affected. Mechanisms under the broken line are characteristic of disease near the lepromatous end of the spectrum, those under the solid line of the tuberculoid end. They overlap in the centre where, in addition, instability predisposes to type 1 reactions.

and in peripheral nerve trunks. In skin lesions, the small dermal sensory and autonomic nerve fibres supplying dermal and subcutaneous structures are damaged, causing local sensory loss and loss of sweating within the area of the skin lesion [5]. Peripheral nerve trunks are vulnerable at sites where they are superficial or are in fibro-osseous tunnels. At these points, a small increase in nerve diameter leads to raised intraneural pressure, with consequent neural compression and ischaemia. Damage to peripheral nerve trunks produces characteristic signs, with dermatomal sensory loss and dysfunction of muscles supplied by that peripheral nerve. Physiological evidence of central and peripheral autonomic nerve involvement has also been reported [6,7].

Nerve damage leads to anaesthesia, muscular weakness and contracture, and autonomic dysfunction. These permit trauma, bruising, burns, cuts and, especially, tissue necrosis from prolonged, inappropriate or repetitive trauma, which in turn lead to ulceration, secondary cellulitis and osteomyelitis and loss of tissue, so that deformity is added to disability.

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Histology [1]

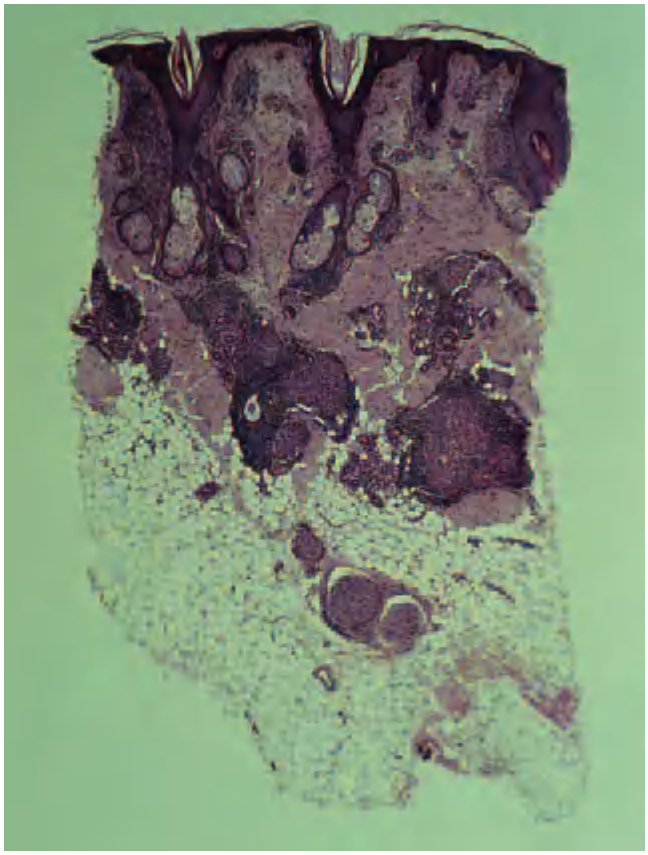
Mycobacterium leprae has a predilection for neural tissue, and the first evidence of infection is often found in the peripheral nervous system. Patients with early leprosy of both tuberculoid [2,3] and lepromatous types have abnormalities in nerve conduction studies and a histological picture of small fibre loss, with segmental demyelination and remyelination [4]. Bacilli probably enter nerves via endoneural blood vessels [5], the target cell being the Schwann cell. In the dermis, the type and degree of cellular infiltrate reflects the degree of CMI. The classification of Ridley and Jopling [6] describes five groups on the immunological spectrum, which are designated tuberculoid (TT), borderline tuberculoid (BT), borderline (BB), borderline lepromatous (BL) and lepromatous (LL). In this classification, epithelioid cells and lymphocytes at the tuberculoid end of the spectrum give place to macrophages, which appear increasingly foamy as the lepromatous pole is reached.

Tuberculoid leprosy

Tuberculoid granulomas collect in foci surrounding neurovascular elements (Fig. 29.2). The granuloma invades the papillary zone and may even erode the epidermis, but acid-fast bacilli (AFB) are not seen. Cutaneous nerves that are not completely destroyed appear greatly swollen by epithelioid cell granulomas and surrounded by a zone of lymphocytes; occasionally there may be caseation within the nerve.

Lepromatous leprosy

Histological examination of skin lesions (H & E) shows



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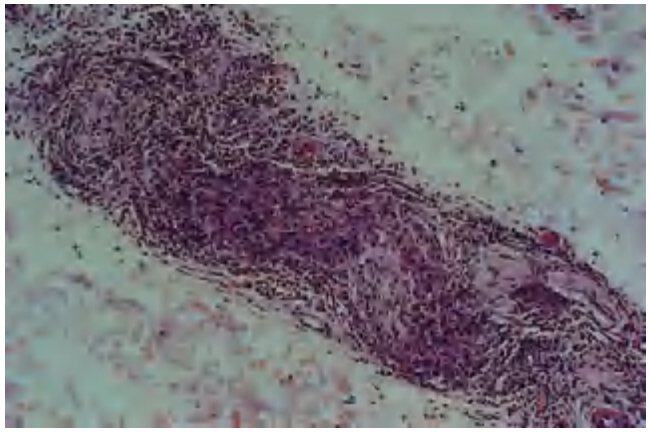
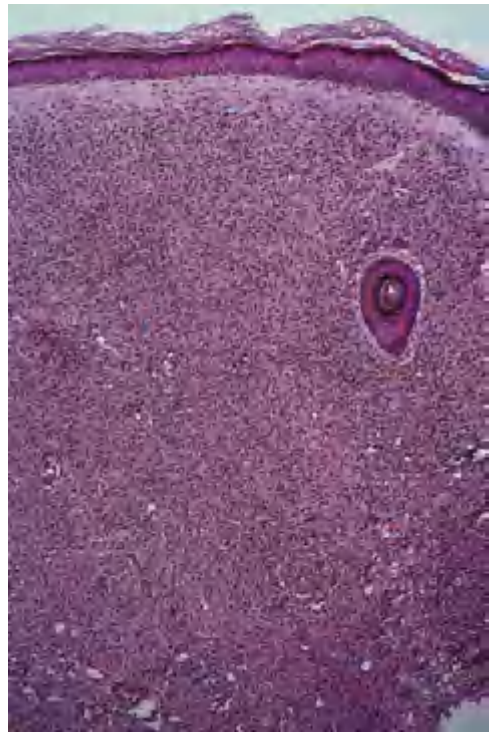


(b)

Fig. 29.2 (a) Low-power view (H&E) showing tuberculoid granulomas around nerve and skin appendages in mid-dermis and a swollen, deep dermal nerve. There is no epidermal erosion. Around the granulomas there is a dense lymphocytic infiltrate. (b) A different case. Medium-power view (H&E) of a deep nerve in tuberculoid leprosy showing granulomatous disruption of the nerve with surrounding lymphocytic infiltrate. (Courtesy of Professor S. Lucas, United Medical and Dental Schools of Guy's and St Thomas' Hospitals, London, UK.)



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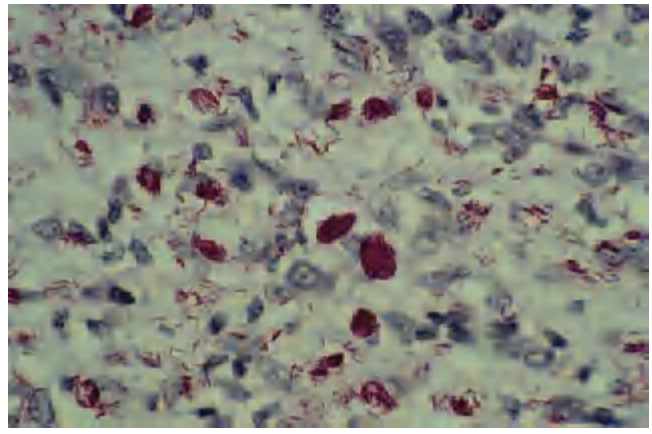


(b)

Fig. 29.3 (a) Lepromatous leprosy. Medium-power view (H&E) showing thin epidermis, a clear subepidermal zone and dense, uniform macrophage infiltrate in the dermis. Towards the bottom of the photograph there is an 'onion skin' perineurial lamination. (b) High-power view, Wade–Fite stain showing single and clustered acid-fast bacilli (AFB), part solid, part fragmented; bacillary index (BI) = 5. (Courtesy of Professor S. Lucas, United Medical and Dental Schools of Guy's and St Thomas' Hospitals, London, UK.)

thinning of epidermis and flattening of rete ridges (Fig. 29.3). The papillary layer of the dermis appears as a clear band, whilst deeper in the dermis lies the typical diffuse leproma consisting of foamy macrophages, with the addition of a few lymphocytes and plasma cells. The dermis contains enormous numbers of AFB, singly or in clumps (globi). With treatment, the leproma shows increased foamy change, vacuolates and breaks up into discrete foci with fibrocytes at the periphery. These foci shrink as treatment is continued and bacilli become fragmented and granular. In lepromatous neuropathy, there is quiet asymptomatic bacillation of Schwann cells leading to foamy degeneration of these cells. Demyelination,

damage and destruction of the axis cylinder are prominent features and later Wallerian degeneration occurs [7]. Despite the large numbers of organisms in the nerve there is only a small inflammatory response; ultimately the nerve fibroses and is hyalinized [8].

Borderline leprosy

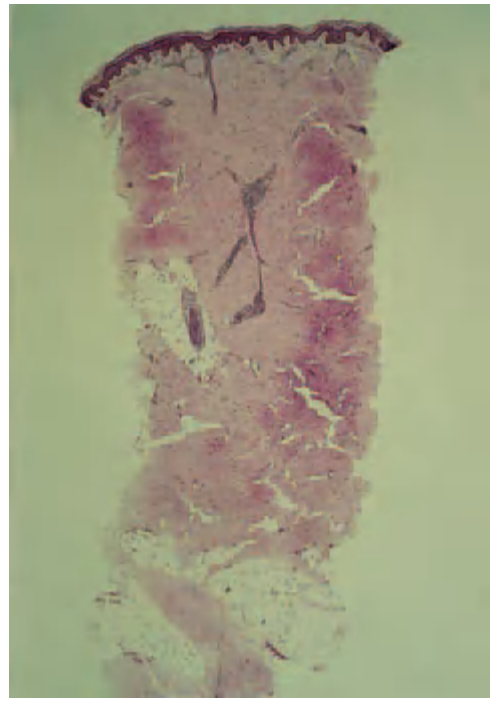
In BT leprosy, the epithelioid cell granuloma is more diffuse than in TT with a free, but narrow, papillary zone. Giant cells tend to be foreign body rather than Langhans in type, and dermal nerves are moderately swollen by cellular infiltrate, or may show only Schwann cell proliferation. AFB are usually absent or scanty. In mid-BB, there is diffuse epithelioid cell granuloma with very scanty lymphocytes and no giant cells; the papillary zone is clear, nerves are slightly swollen by cellular infiltrate, and AFB are present in moderate numbers. In BL leprosy, macrophages may show slight foamy change. Lymphocytes are present in dense clumps or are widely distributed in parts of the granuloma; a few epithelioid cells may be seen occasionally. The formation of small granulomas is characteristic of borderline leprosy and granulomatous regions may abut strands of normal looking but heavily bacillated Schwann cells [9]. Nerve damage in borderline leprosy results from a combination of lepromatous bacillation and a tuberculoid tissue damaging response producing widespread nerve damage. Acute neuritis damage occurs particularly during reversal reactions: oedema of the epithelioid cell granuloma compresses the remaining Schwann cells causing rapid functional loss in an already compromised nerve. In ENL nerve damage occurs more slowly and is probably due to inflammation associated with ENL nodule formation in nerve trunks.

Indeterminate leprosy

This early and transitory stage of leprosy occurs in those whose immunological state has not yet been determined, and histologically there is a scattered non-specific histiocytic and lymphocytic infiltration with some concentration around skin appendages (Fig. 29.4). Rarely, a single bacillus will be found within a dermal nerve. The indeterminate phase may last for months or years before resolving or giving way to one of the determinate types of leprosy described above.

Reactions

Type 1 reactions are characterized by an increase in lymphocytes within lesions, severe oedema with disruption of the granuloma, and giant cell formation [10]. In type 2 (ENL) reactions polymorphs infiltrate the granuloma and there is vasculitis and macrophage degeneration together with breakdown of foam cells (Fig. 29.5).



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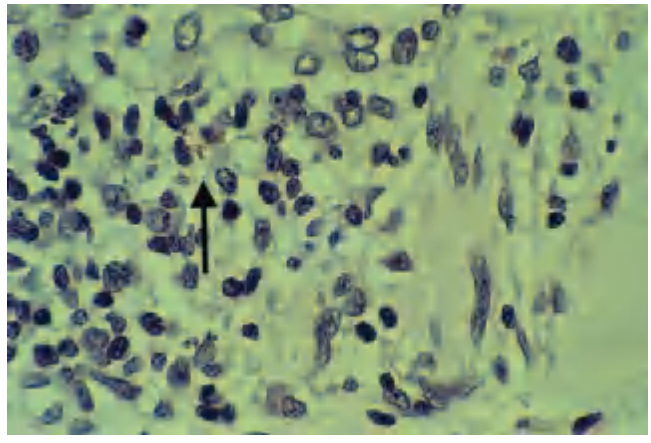

(b)

Fig. 29.4 (a) Indeterminate leprosy. Low-power view (H&E) showing minimal perineurovascular inflammation in the mid-dermis. (b) High-power view, Wade–Fite stain showing one acid-fast bacillus in a Schwann cell. (Courtesy of Professor S. Lucas, United Medical and Dental Schools of Guy's and St Thomas' Hospitals, London, UK.)

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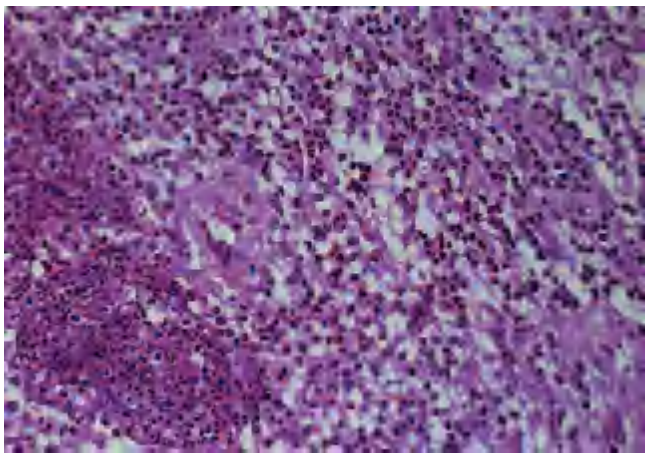

Fig. 29.5 Erythema nodosum leprosum (ENL). Medium-power view (H&E) showing foamy macrophages with infiltrating polymorphs. There is also a swollen small artery in the centre of the photograph. (Courtesy of Professor S. Lucas, United Medical and Dental Schools of Guy's and St Thomas' Hospitals, London, UK.)

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Immunology [1]

The immune response to *M. leprae* determines not only whether disease will develop, but also which type of leprosy. Both T cells and macrophages play important roles in the processing, recognition and response to *M. leprae* antigens. The T-cell response to mycobacteria results in activation and proliferation of α/β CD4 T cells with release of interleukin-2 (IL-2). This cytokine amplifies the local response through recruitment and activation of T cells. In addition, IL-2 stimulates the expansion of α/β CD8 T cells and antigen non-specific natural killer cells in the lesion. All three types of cell can produce interferon-γ (IFN-γ), the major cytokine responsible for activating bactericidal mechanisms within the parasitized macrophage [2].

In tuberculoid leprosy, there is good evidence of a strong CMI response. Tests of T-cell function such as LTTs show that tuberculoid leprosy patients respond to *M. leprae* antigens as in whole *M. leprae*, separated *M. leprae* antigens [3] and cloned antigens (18 kDa and 65 kDa) [4,5]. Skin tests with lepromin, a heat-killed *M. leprae* sonicate preparation, are strongly positive in these patients. Staining of skin biopsies from tuberculoid lesions with T-cell markers show highly organized granulomas composed predominantly of CD4 cells and macrophages, with a peripheral mantle of suppressor/cytotoxic CD8 cells [6]. This strong CMI response has been misdirected at some stage, and the end result is a late strong cell-mediated response that clears antigen at the expense of local tissue destruction.

Lepromatous leprosy patients are unable to mount a CMI response to *M. leprae*, with a failure of the T-cell response, and lymphocytes from LL patients respond poorly in LTT to whole *M. leprae* and cloned antigens. Similarly, LL patients fail to mount a skin test response to intradermal challenge with lepromin. The anergy of the lepromatous patient is striking because it is specific for the leprosy mycobacterium. Lepromatous patients can respond to antigens of other mycobacteria such as *M. tuberculosis*, both in *in vitro* and in skin tests [7,8]. Identification of cell types in LL granulomas shows them to be a disorganized mixture of macrophages and T cells, mainly CD8 cells [9].

Both T-cell and macrophage dysfunction occur in lepromatous patients. The T-cell failure may be due to clonal anergy or active suppression [3]. Defects in cytokine production have been demonstrated in lepromatous patients; addition of IL-2 to T-cell culture media restored the proliferative response to *M. leprae* [10] in lepromatous patients, and intralesional injections of recombinant IL-2 reconstituted the local immune response with elimination of *M. leprae* from macrophages [11]. Macrophage defects described in LL disease include defective antigen presentation and recognition, defective IL-1 production, a failure of macrophages to kill *M. leprae* and a macrophage suppression of the T-cell response [2].

Studies of circulating cytokines in leprosy patients, and cytokine production in skin lesions, show that tuberculoid patients have a Th1 type response to *M. leprae* with predominant IL-2 and IFN-γ production, whilst lepromatous patients have a response characterized by Th2 type cytokines.

The inflammation seen in type 1 reactions is due to T-cell activity, with enhanced T-cell proliferation towards *M. leprae* antigens, increased numbers of $CD4^+$ and IL-2 producing cells in granulomas, and local production of cytokines such as IFN-γ [12] and tumour necrosis factor-α (TNF-α) [13]. Type 1 reactions are associated with an over-production of Th1-type cytokines [14]. ENL has classically been regarded as an immune complex disorder. This is supported by the presence of immunoglobulin and complement in the lesions and circulating immune complexes [15]. There is also evidence of enhanced T-cell activity during ENL episodes, with increased numbers of CD8 cells [16], increased circulating IL-2 receptors [17] and high levels of circulating TNF-α [18] in acute episodes. Despite increased immune activity during ENL

episodes, lepromatous patients revert to a state of immunological unresponsiveness after an episode.

Serology

Specific anti-*M. leprae* antibodies are produced against lipoarabinomannan (LAM), PGL and the protein antigens of *M. leprae*. No single antigen has been identified for use in a serological test to confirm disease and detect early subclinical infection. For all three types of antigen, multibacillary patients produce antibodies prolifically, while paucibacillary patients show a variable, often undetectable, response. The evaluation of PGL serology in extensive field studies shows that more than 90% of untreated multibacillary patients have positive serology in comparison with 40–50% of paucibacillary patients and 5–10% of healthy controls [19].

Lepromatous patients produce a range of autoantibodies, both organ-specific (directed against thyroid, nerve, testis and gastric mucosa), and non-specific, such as rheumatoid factors, anti-DNA, cryoglobulins and cardiolipin.

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Clinical features of leprosy [1]

Early lesions and presenting symptoms

The commonest early lesion is an area of numbness on the skin, or a visible skin lesion. The classic early skin lesion, especially in surveys, is that of indeterminate leprosy, which is most commonly found on the face, extensor surface of the limbs, buttocks or trunk (Fig. 29.6) [2]. Scalp, axillae, groins and lumbar skin tend to be spared. Indeterminate lesions consist of one or more slightly hypopigmented or erythematous macules, a few centimetres in diameter, with poorly defined margins. Hair growth and nerve function are unimpaired. A biopsy may show the perineurovascular infiltrate, and only a prolonged search will reveal scanty acid-fast organisms. Alternatively, the initial skin lesion has features of one of the established forms of the disease.

Patients frequently present with signs of nerve damage [3]: weakness or anaesthesia due to a peripheral nerve lesion, or a blister, burn or ulcer [4] in an anaesthetic hand or foot. Borderline patients may present in reaction with nerve pain, sudden palsy, multiple new skin lesions, pain in the eye, or a systemic febrile illness [5,6].

Features of established leprosy

Careful attention to the eight different clinical aspects of leprosy listed in Table 29.1 will enable accurate recognition

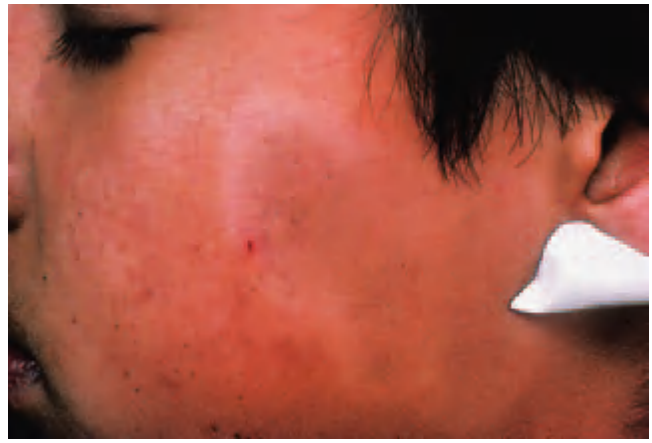

Fig. 29.6 Indeterminate leprosy. Face of a Nepali child showing vague hypopigmented patch with some central healing. Note the mark of a recent slit-skin smear.

Table 29.1 Characteristics of lesions of polar leprosy.

	Tuberculoid	Lepromatous
Number of lesions	1–10	Hundreds, confluent
Distribution	Asymmetrical, anywhere	Symmetrical, avoiding 'spared' areas
Definition and clarity	Defined, edge, markedly hypopigmented	Vague edge, slight hypopigmentation
Anaesthesia	Early, marked, defined, localized to skin lesions or major peripheral nerve	Late, initially slight, ill-defined, but extensive, over 'cool' areas of body
Autonomic loss	Early in skin and nerve lesions	Late, extensive as for anaesthesia
Nerve enlargement	Marked, in a few nerves	Slight but widespread
Mucosal and systemic	Absent	Common, severe during type 2 reactions
Number of *Mycobacterium leprae*	Not detectable	Numerous in all affected tissues

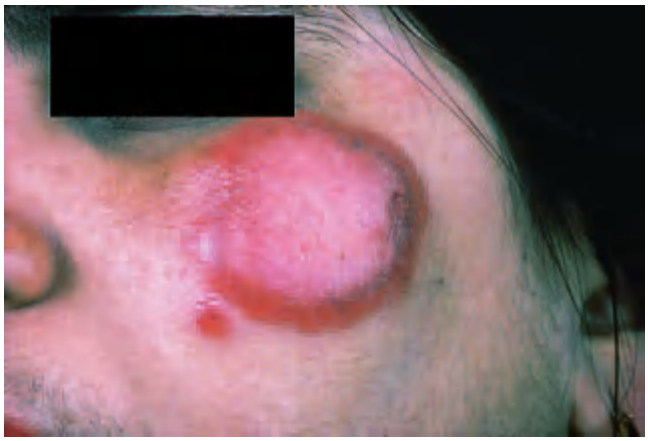

Fig. 29.7 Tuberculoid leprosy (TT). Face of Pakistani lady showing erythematous plaque with a well-defined active edge, and a small satellite lesion. On the face, such lesions may not be anaesthetic.

and classification, which are prerequisites to correct treatment and accurate prognosis.

Tuberculoid leprosy

Only nerves and skin show clinical evidence of disease; lesions are few, often solitary. The condition may be purely neural, with pain and swelling of the affected nerve followed by anaesthesia and/or muscle weakness and wasting. Alternatively, a skin lesion appears with or without evidence of nerve involvement. The typical lesion is a plaque that is conspicuous, erythematous, copper coloured or purple, with raised and clear-cut edges sloping towards a flattened and hypopigmented centre (Figs 29.7 & 29.8). Dark skins may not show the erythema. The surface is dry, hairless and insensitive, and sometimes scaly. Sensory impairment may be difficult to demonstrate on the face because of the generous supply of sensory nerve endings. If the examiner runs a finger around the lesion, just beyond the outer edge, a thickened sensory nerve may be palpated or a thickened nerve trunk may be felt in the vicinity, e.g. a thickened ulnar nerve if the lesion is on the arm. Less commonly the lesion is a macule, erythematous in light skins and hypopigmented (never depigmented) in dark skins (Fig. 29.9). Such macules have a dry, hairless and insensitive surface.

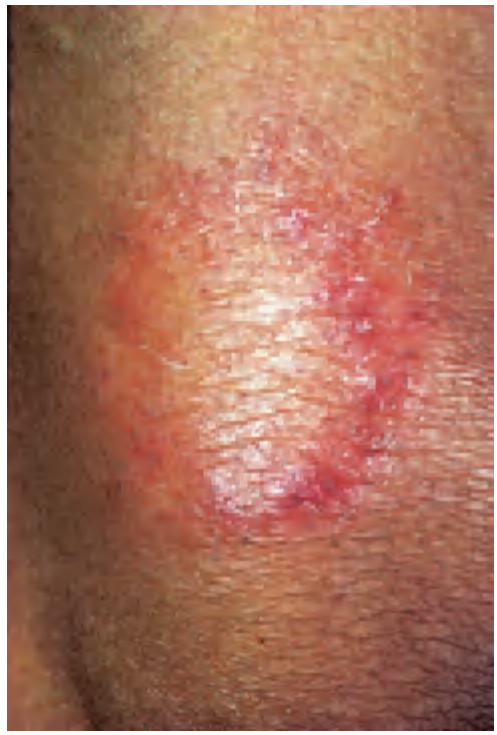

Fig. 29.8 Tuberculoid or borderline tuberculoid (TT/BT) leprosy. Upper arm of Indian man, showing typical dry, hairless, hypopigmented plaque with scaly, erythematous edge. Such lesions are usually anaesthetic.

Lepromatous leprosy

The first clinical manifestations are usually dermal (because early nerve involvement is usually asymptomatic), but they may go unnoticed by the patient, who often complains of other early symptoms; these include nasal symptoms of stuffiness, discharge and epistaxis [7], and oedema of legs and ankles due to increased capillary stasis and permeability. Dermal signs comprise

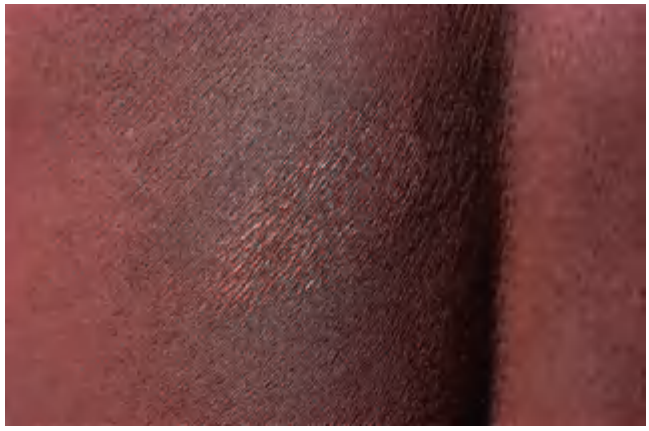

Fig. 29.9 Tuberculoid or borderline tuberculoid (BT/TT) leprosy. Back of a Nigerian child showing well-defined hypopigmented macule with altered skin texture. The lesion was anaesthetic.

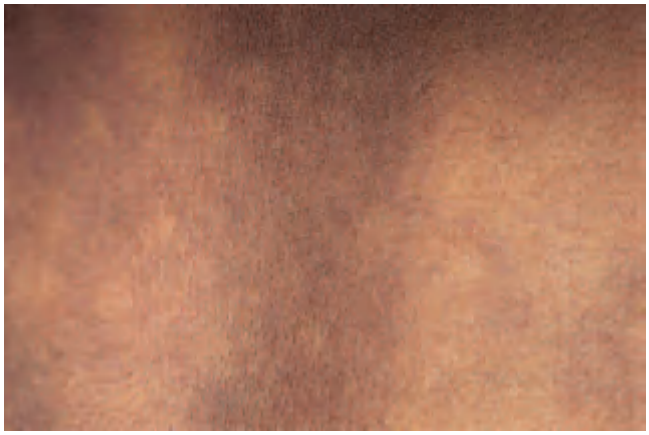

Fig. 29.10 Lepromatous leprosy (borderline lepromatous/lepromatous; BL/LL). Back of a Bangladeshi boy showing numerous, often confluent hypopigmented macules, with relative sparing of the midline.

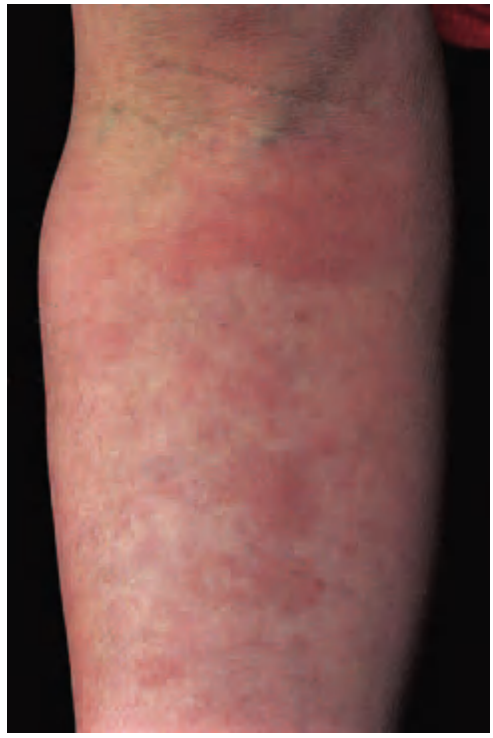

Fig. 29.11 Lepromatous leprosy (LL). Forearm of an English man showing erythematous macules and infiltration, which characterize a relapse of dapsone-resistant lepromatous leprosy.

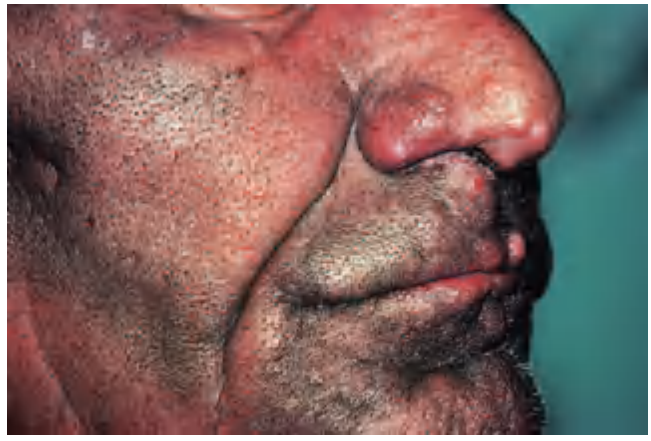

Fig. 29.12 Lepromatous leprosy (LL). Face of an Anglo-Indian man showing diffuse infiltration of the skin and appearance of nodules on nose and lip.

macules, diffuse papules, infiltration or nodules, or all four. Macules are small, multiple, erythematous or faintly hypopigmented, with vague edges and shiny surface (Fig. 29.10). Papules and nodules usually have normal skin colour but sometimes are erythematous (Fig. 29.11), with a bilaterally symmetrical distribution on face, arms, legs and buttocks, but may be anywhere apart from hairy scalp, axillae, groins and perineum (regions of skin with the highest temperature). Hair growth and sensation are not initially impaired over the lesions. In polar LL, diffuse infiltration and gradual thickening of the dermis may precede nodulation by months or years (Fig. 29.12). Lesions of oral mucosa occur as papules on lips and nodules on palate (which may perforate), uvula, tongue and gums (Fig. 29.13). The nasal mucosa is hyperaemic or ulcerated and bleeds easily; epistaxis is common (Fig. 29.14).

The longest peripheral sensory nerve fibres are first affected, causing numbness and anaesthesia on the dorsal surfaces of hands and feet, and later on extensor surfaces of arms and legs, and finally over the trunk. Infiltration of corneal nerves causes anaesthesia, which predisposes to injury, infection and blindness if there is also lagophthalmos due to damage to the facial nerve. The hands and feet swell and may become oedematous. Radiographs may show osteoporosis in the phalanges, small osteolytic cysts and often hairline or compression fractures. The fingers

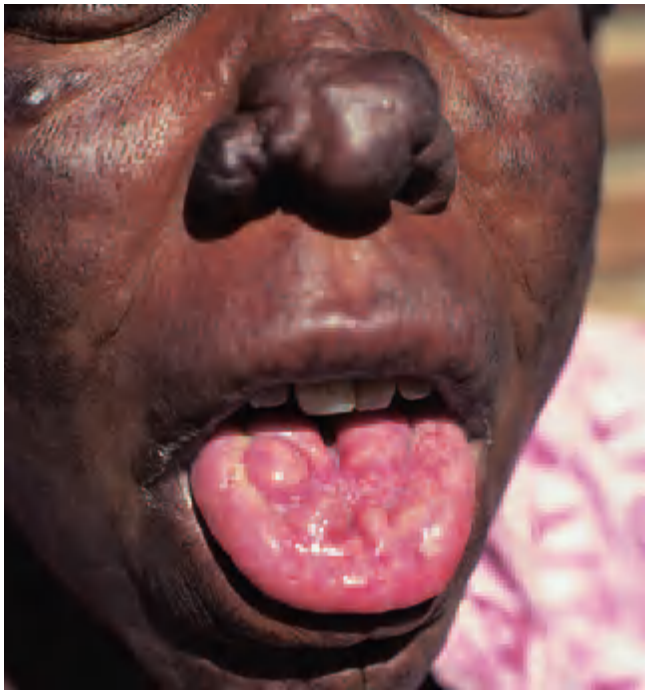

Fig. 29.13 Lepromatous leprosy (LL). Face of an Ethiopian child showing typical pattern of late lepromatous infiltration. Note the collapsed nasal bridge and the infiltration of the tongue.

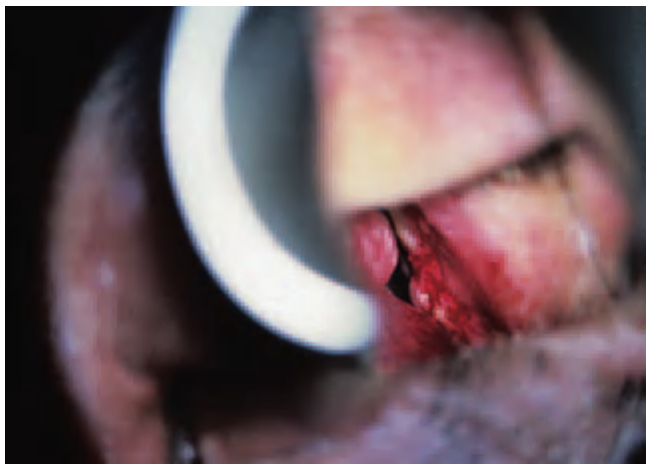

Fig. 29.14 Lepromatous leprosy (LL). Examination via a nasal speculum shows a pale septal nodule and bleeding. Such lesions in untreated lepromatous patients constitute a major source of infection.

may become crooked or short (Fig. 29.15). Nails are thin and brittle.

If the patient remains untreated the lines of the forehead become deeper as the skin thickens (leonine facies), eyebrows and eyelashes become thinned or lost (madarosis), ear lobes are thickened, the nose becomes misshapen, and may collapse due to septal perforation and loss of the anterior nasal spine, the voice becomes hoarse and the

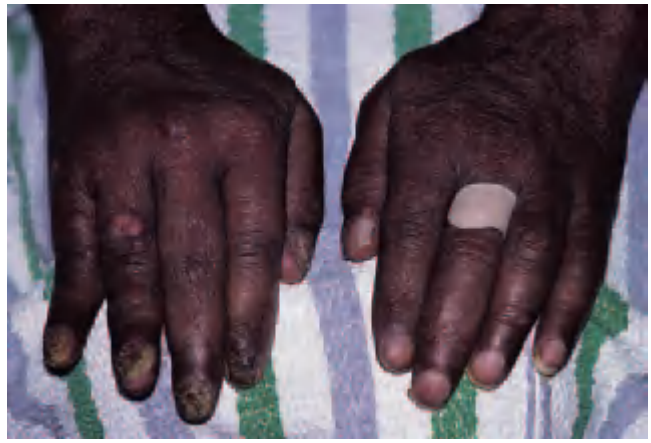

Fig. 29.15 Lepromatous leprosy (LL). Hands of an Indian man, showing swollen fingers due to leprous dactylitis and one crooked finger due to a pathological fracture. Note also the lepromatous nodules. The nail dystrophy is due to a dermatophyte infection.

upper incisor teeth loosen or fall out [8]. The skin of the legs becomes ichthyotic and thickened, ulcers may form on the legs when nodules break down, and a slow fibrosis of peripheral nerves results in nerve thickening and bilateral 'glove and stocking' anaesthesia. Sensation of palms and soles is retained until late in the disease. Leprous deposits in the eyes cause keratitis, iridocyclitis and iris atrophy. Testicular atrophy causes sterility, impotence and gynaecomastia.

One particular variety of lepromatous leprosy requires special mention, namely, the pure diffuse type described by Lucio and Alvarado in Mexico in 1852. The patients first notice impairment of sensation in hands and feet, and this is followed by gradual loss of eyebrows, eyelashes and body hair. At the same time, the skin of the whole body becomes diffusely thickened, rendering it stiff and smooth as in scleroderma. There may be alopecia, nasal and laryngeal involvement, and widespread small telangiectases, but cutaneous nodules and plaques do not develop. The eyes have a shining appearance [9].

Histoid lesions are distinctive round, regular, cutaneous nodules that stand out on normal skin. They are characteristic of relapse after treatment [10].

Borderline leprosy

Skin lesions are intermediate in number between those of the two polar types already described, depending on the position of the patient on the borderline spectrum, and are distributed asymmetrically. They may take the form of macules, plaques, annular lesions or bizarre-shaped bands. Plaques with a 'punched-out' appearance are characteristic of the middle of the spectrum (Fig. 29.16). Towards the tuberculoid end of the spectrum, lesions are fewer and drier (Figs 29.17 & 29.18), have more hair loss

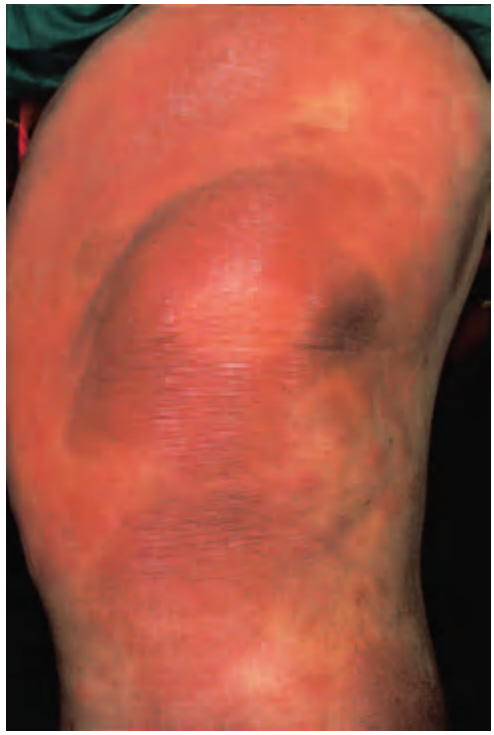

Fig. 29.16 Borderline (BB) leprosy. Knee of Saudi-Arabian woman, showing classical annular lesions with well-defined centres (?healing of old borderline tuberculoid, BT) contrasting with spreading erythematous infiltration. Slit-skin smears show acid-fast bacilli (AFB).

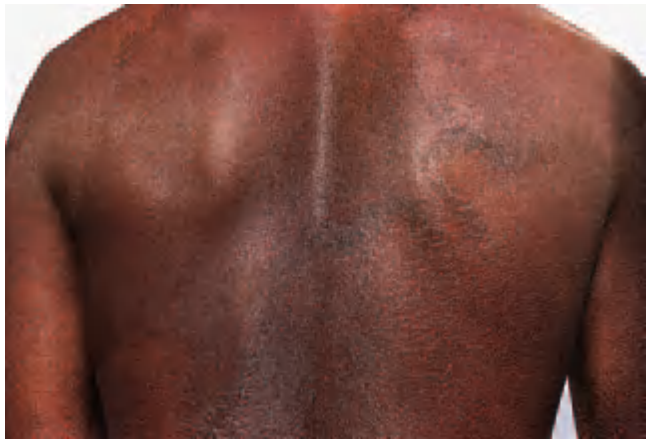

Fig. 29.17 Borderline tuberculoid leprosy. Back of Nigerian man showing large, well-defined, scaly macules with some marginal elevation. Extensive disease, such as this, may seriously impair sweating and heat control.

and anhidrosis, are more insensitive, and have fewer bacilli in smears and biopsies, and vice versa towards the lepromatous pole. One or more nerves are likely to be thickened and non-functioning (Fig. 29.19). Neural symptoms may precede the appearance of skin lesions by as much as 8 years [11]. When borderline leprosy

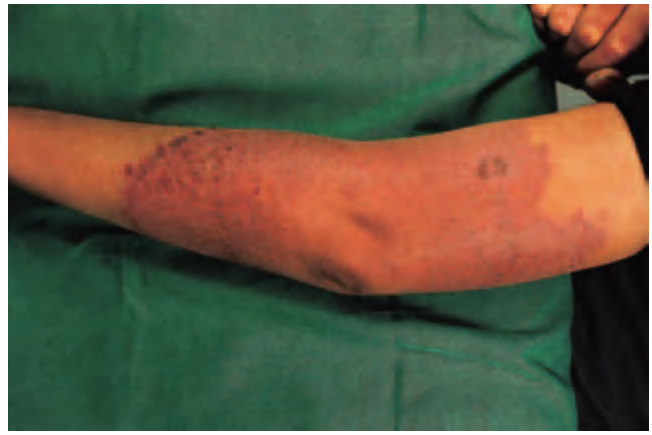

Fig. 29.18 Borderline tuberculoid leprosy. Arm of an Indian woman. A large, scaly macule is developing secondary ichthyotic change.

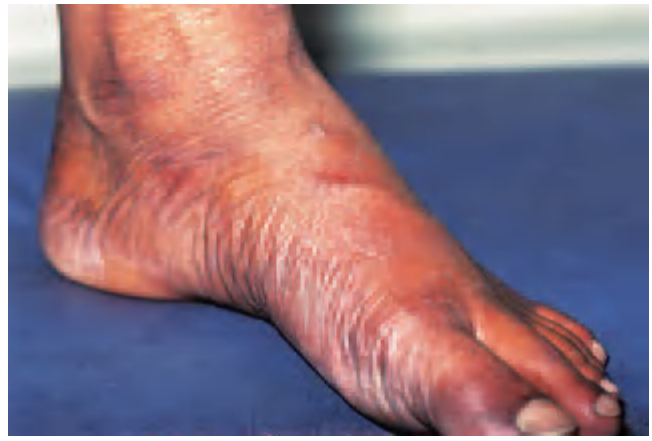

Fig. 29.19 Borderline leprosy (BL). Foot of a Bangladeshi child showing enlargement of posterior tibial and anterior tibial nerves.

downgrades to lepromatous, the resulting subpolar lepromatous leprosy (LLs) can be differentiated from polar lepromatous (LLp) because, in addition to typical lepromatous skin lesions, there are several asymmetrical thickened nerves and one or more typical borderline skin lesions. Damage to structures other than skin and nerves will not be manifest clinically in borderline leprosy, even though bacilli may be present in other tissue. Borderline leprosy is the commonest type of disease encountered, with BT predominating in Africa and BL in Asia. Borderline disease is unstable and 'down-grades' towards lepromatous, especially if untreated, or 'upgrades' towards tuberculoid. The clinical change lags behind the immunological and histological changes (Fig. 29.20).

Pure neuritic leprosy

Pure neuritic leprosy presents with asymmetrical involvement of peripheral nerve trunks and no visible skin

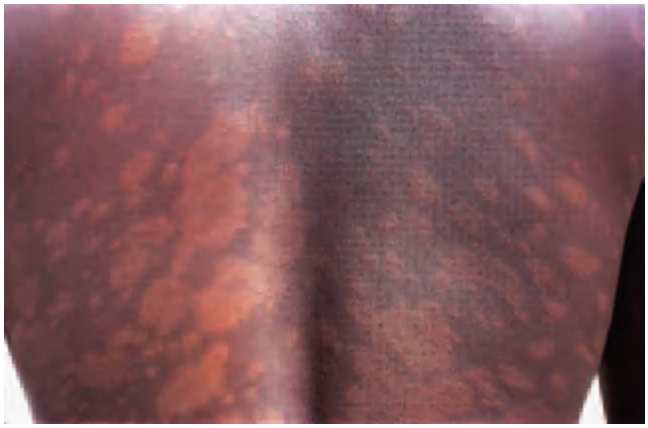

Fig. 29.20 Borderline leprosy (BL). Borderline tuberculoid (BT) down-grading to BL. Back of a Nigerian woman, showing typical well-defined hypopigmented macules of BT leprosy and many small lesions, some of which are papular. Slit-skin smears showed acid-fast bacilli (AFB).

lesions; on histology of a cutaneous nerve biopsy, all types of leprosy are seen [12]. It is seen most frequently, but not exclusively, in India and Nepal where it accounts for 5–10% patients [4,13].

Reactions

Type 1 reactions occur in borderline disease and are characterized by acute neuritis and/or acutely inflamed skin lesions [14]. Nerves often become tender with loss of sensory and motor functions. Existing skin lesions become erythematous or oedematous and may desquamate or rarely ulcerate. New lesions may appear (Fig. 29.21). Occasionally, oedema of face, hands or feet is the presenting symptom, but constitutional symptoms are unusual. Although type 1 reactions can occur spontaneously, the commonest time is after starting treatment and during the puerperium [15].

Type 2 (ENL) reactions occur in patients with multibacillary disease (LL and BL). They may occur spontaneously (roseolar leprosy) or whilst on treatment. During the dapsone monotherapy era, an estimated 50% of LL patients experienced ENL reactions; with the newer drug regimes containing clofazimine, this proportion has fallen to about 15%. Attacks are often acute at first, but may be prolonged or recurrent over several years and eventually quiet but insidious, especially in the eye. ENL manifests most commonly as painful red nodules on the face and extensor surfaces of limbs. The lesions may be superficial or deep, with suppuration (Fig. 29.22), ulceration (Fig. 29.23) or brawny induration when chronic [5]. Acute lesions crop and desquamate, fading over several days (Fig. 29.23). ENL is a systemic disorder producing fever and malaise and may be accompanied by uveitis, dactylitis, arthritis, neuritis, lymphadenitis, myositis and orchitis [16]. Peripheral nerve neuritis and uveitis with its complications of synechiae, cataract and glaucoma are the most serious complication of ENL.

The Lucio reaction only occurs in patients with Lucio leprosy [16]. It is due to infarction consequent upon deep cutaneous vasculitis, and causing the appearance of irregularly shaped erythematous patches which become dark and heal, or form bullae and necrose, leaving deep

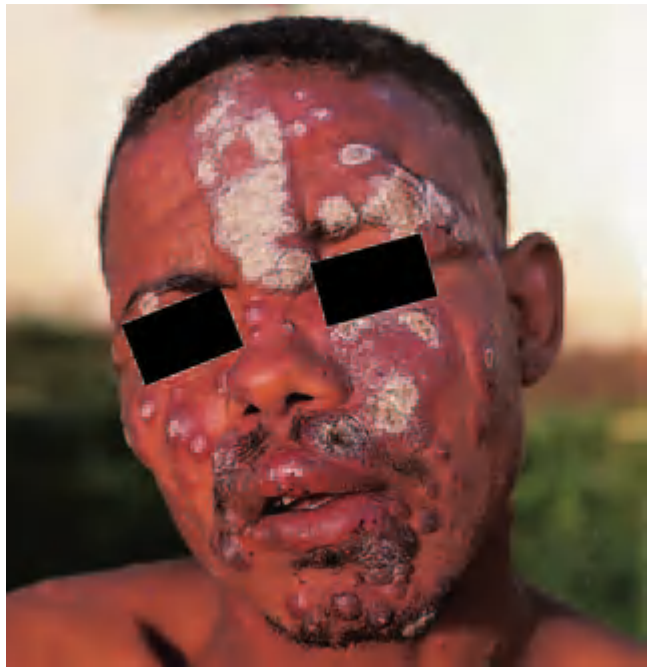

Fig. 29.21 Type 1 reaction: borderline leprosy in an Ethiopian man. Existing lesions become acutely inflamed, scale and threaten ulceration. Many small, new lesions have appeared. The histology shows a borderline tuberculoid (BT) pattern.

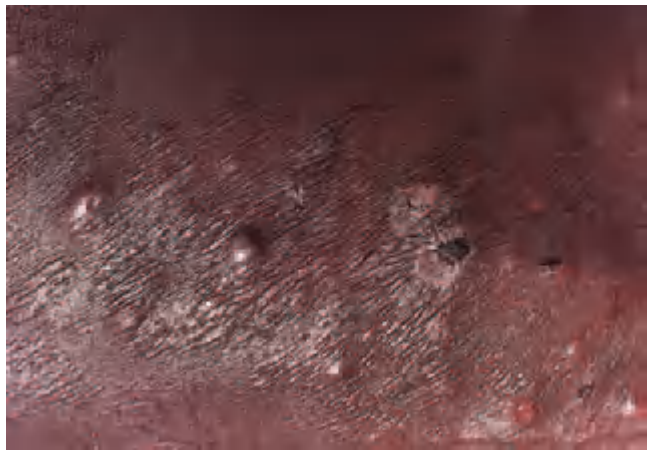

Fig. 29.22 Type 2 reaction in lepromatous leprosy in a Nigerian man: erythema nodosum leprosum (ENL). Several of the reaction nodules have broken down, releasing pus.

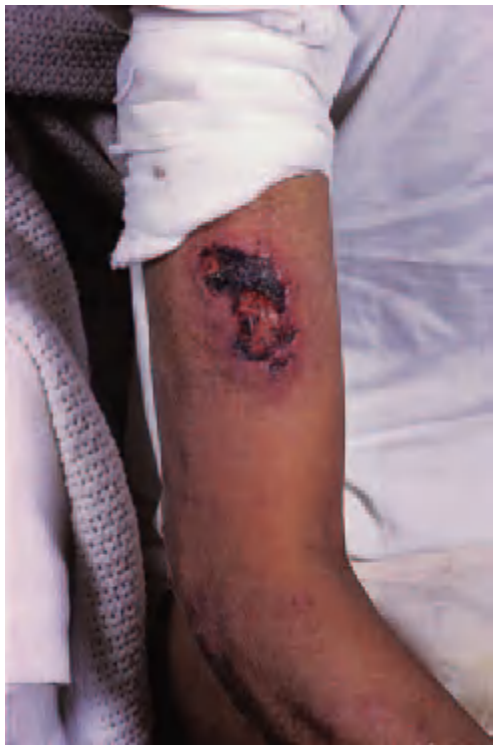

Fig. 29.23 Type 2 reaction in lepromatous leprosy in a Bangladeshi man, showing severe necrosis and ulceration. Erythema nodosum leprosum (ENL) tends to be more severe in Asian than in African people.

painful ulcers that are slow to heal (Fig. 29.24). The systemic upset is severe and can be fatal.

Nerve damage [17]

Of the three physiological functions of nerves, the sensory component is commonly the first and most severely affected, but occasionally there is a pure motor lesion. Autonomic dysfunction is always present in severe nerve damage [18]. In skin lesions this is associated with loss of hair growth, and of sebaceous and sweat secretion, and poor pigment formation. In a limb it causes capillary stasis, cyanosis and dryness, which predispose to fissuring. Two large cohort studies with systematic nerve examination at entry showed that the posterior tibial nerve is the most frequently affected nerve, followed by ulnar, median, lateral popliteal and facial [19,20]. Ulnar and median nerve lesions are usually low, causing small muscle but not deep flexor weakness, and anaesthesia of the two halves of the hand. Isolated median nerve lesions are unusual. Common peroneal nerve lesions cause difficulty in dorsiflexion and eversion of the foot and anaesthesia of the outer border of the foot, a combination which predisposes to traumatic damage and plantar ulceration (Fig. 29.25). Posterior tibial nerve damage is serious

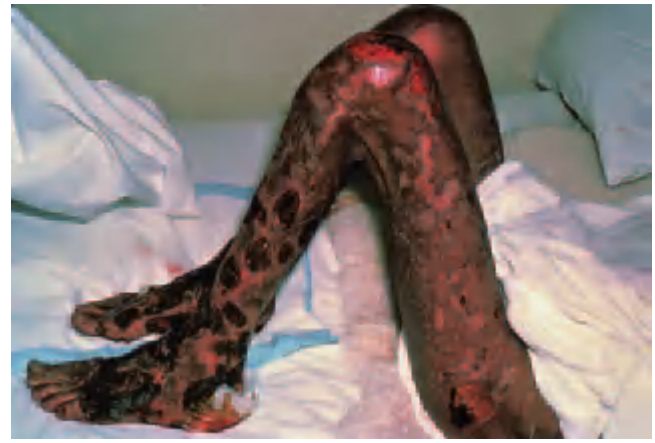

Fig. 29.24 Lucio phenomenon in a Mexican man. The severe recurrent ulceration due to deep subcutaneous vasculitis may be fatal. (Courtesy of Dr J. Keystone, The Toronto Hospital, Toronto, Canada.)

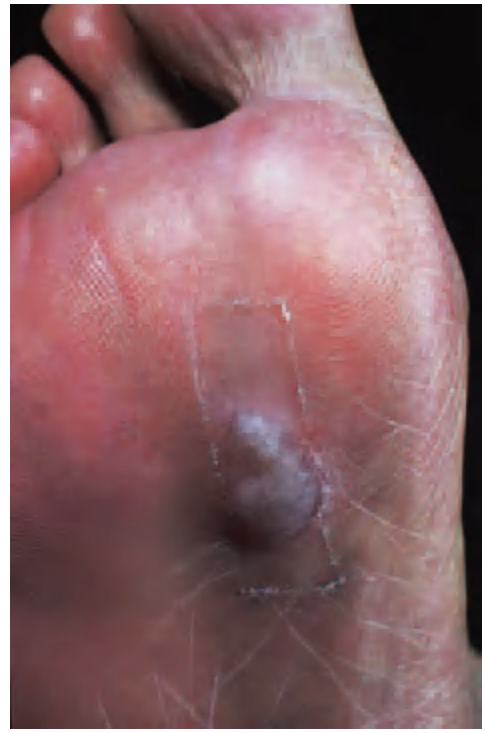

Fig. 29.25 Necrosis blister in an anaesthetic foot. Necrotic material has tracked to soft skin from the site of trauma, beneath the metatarsal heads.

because it causes paralysis and contracture of the small muscles of the foot and anaesthesia of the sole.

Eye involvement in leprosy

Blindness due to leprosy is a devastating complication, especially for a patient with anaesthetic hands and feet. Eye damage results from both nerve damage and bacil-

lary invasion, and a recent cohort study found that 2.8% of multibacillary patients were blind at diagnosis, and a further 11% patients had potentially blinding ocular pathology [21]. Lagophthalmos results from paresis of the orbicularis oculi due to involvement of the zygomatic and temporal branches of the facial (VIIth) nerve. Facial lesions cause a 10-fold increase in the risk of facial nerve damage [22]. In lepromatous disease, lagophthalmos occurs later and is usually bilateral. Damage to the ophthalmic branch of the trigeminal (Vth) nerve causes anaesthesia of the cornea and conjunctiva, which results in drying of the cornea, a reduction in blinking, and leaves the cornea at risk of minor trauma and ulceration. Bacillary invasion of the iris and ciliary body makes them extremely susceptible to reactions.

Prognosis

Antibacterial treatment for leprosy is highly effective, with low relapse rates, but needs to be taken over many months. Left untreated, borderline patients will downgrade towards the lepromatous end of the spectrum, and lepromatous patients will suffer the numerous consequences of bacillary invasion. Borderline patients are at risk of developing type 1 reactions, which may result in devastating nerve damage. BL patients may suffer either type of reaction. Many patients present with established nerve damage which cannot be reversed. Treatment of the neuritis is currently unsatisfactory, and some patients with active neuritis will develop permanent nerve damage despite treatment with corticosteroids. It is not possible to predict which patients will develop reactions or nerve damage. Nerve damage and its complications may be severely disabling, especially when all four limbs and both eyes are affected. Women are at risk of reactions during the puerperium [23].

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Diagnosis [1]

The diagnosis is usually made clinically on the basis of two out of three characteristic findings, or by the demonstration of AFB in slit-skin smears, or by histology typical of leprosy: The cardinal signs are:

1 anaesthesia of a skin lesion, or in the distribution of a peripheral nerve, or over dorsal surfaces of hands and feet;

2 thickened nerves, especially at the sites of predilection;

3 typical skin lesions.

The AFB load of a patient is determined by modified Ziehl–Neelson staining of slit-skin smears. Suspect lesions, and sites commonly affected in lepromatous leprosy, should be sampled (forehead, earlobes, chin, extensor surface of the forearm, buttocks and trunk). The density of bacilli is expressed using a logarithmic scale, extending from very few AFB to many per high power field. The number of AFB per field is scored according to a logarithmic scale. A mean score, the bacterial index (BI), is derived by adding the scores from each site and dividing by the number of sites sampled [2]. In untreated lepromatous leprosy, the BI is 5+ or 6+. The BI falls to zero in TT disease. Slit-skin smears only detect bacilli present at a concentration greater than 10^4/g tissue, and so cannot be

used as a test of microbiological cure. With treatment, bacilli disappear from BB lesions in a few months and from BL lesions in a year or two. It may take 6–10 years for the last bacillary remnants to disappear from the skin in LL.

Slit-skin smears [3]

The lesion is cleaned with ether or alcohol, and a fold is gripped firmly between thumb and forefinger to render it blood free. An incision 5 mm long and 3 mm deep is made with a small-bladed scalpel (size 15 Bard Parker blade); the blade is turned at right angles to the cut, and without relaxing finger pressure, the wound is scraped several times in one direction. Fluid and pulp from the dermis, collected on one side of the blade, are gently smeared on to a glass slide. A bloody smear is useless. The smear is then fixed over a flame and stained.

Skin biopsy [4]

The incision should be made down to subcutaneous fat, so that the whole depth of the dermis is included, otherwise leprous changes in the deeper layers of the dermis will be missed. The best fixative is 40% formaldehyde 10 mL; mercuric chloride 2 g; glacial acetic acid 3 mL; and distilled water to 100 mL. After 2.0–2.5 h, the specimen should be transferred to 10 mL of 70% alcohol, in which it can remain indefinitely.

Nerve biopsy

In pure neural leprosy a nerve biopsy is necessary to establish the diagnosis. A purely sensory thickened peripheral nerve should be sampled, e.g. radial cutaneous at the wrist, superficial peroneal in front of the ankle or sural nerve at the ankle.

Lepromin test

Lepromin is a crude, semi-standardized preparation of heat killed bacilli from a lepromatous nodule or infected armadillo liver. The lepromin test is a non-specific test of occasional value in classifying a case of leprosy. It is strongly positive in TT, weakly positive in BT, negative in BB, BL and LL, and unpredictable in indeterminate leprosy. Lepromin, 0.1 mL, is injected intradermally, and the reaction is read at 48 h (Fernandez reaction) or 3–4 weeks (Mitsuda reaction). The Fernandez response indicates delayed hypersensitivity to the soluble components of Lepromin. The Mitsuda reaction is a granulomatous response to particulate antigenic material. Neither test is diagnostic, since both may be positive in people with no evidence of leprosy.

Differential diagnosis

Leprosy tends to be over-diagnosed in endemic countries and under-diagnosed in non-endemic countries. Of new patients seen 1995–9 at the Hospital for Tropical Diseases, London, diagnosis had been delayed in over 80% of cases [5]. Patients had been misdiagnosed by dermatologists, neurologists, orthopaedic surgeons and rheumatologists. A common problem was failure to consider leprosy as a cause of peripheral neuropathy in patients from leprosy endemic countries. These delays had serious consequences for patients, with over half of them having nerve damage and disability. In any population it is also important for the doctor to know the normal range of skin colour and texture, the common endemic skin diseases, such as onchocerciasis, that may coexist with leprosy and the common medical and artefactual practices that may cause lesions resembling those of leprosy.

Macular lesions

Birthmarks are abnormally pigmented but otherwise physiologically normal. Vitiligo lesions are depigmented; leprosy lesions are never completely depigmented. Hypopigmented lesions of eczema, especially of pityriasis alba in children, are difficult to distinguish from lepromatous macules, but their surface is often scaly and smears do not contain AFB. Pityriasis versicolor is not always scaly, but central distribution on the trunk, and the presence of minute distinct macules, are contrary to the characteristics of lepromatous macules. Lesions of tinea corporis itch and may have a vesicular edge, characteristically absent in tuberculoid patches, and scrapings usually show the fungus.

Plaques and annular lesions

In addition to ringworm (above), granuloma multiforme, sarcoidosis and cutaneous tuberculosis may resemble tuberculoid leprosy, having a similar immunological basis and often indistinguishable histological pattern. However, the lesions are not anaesthetic. Peripheral nerves may occasionally be enlarged in sarcoidosis [6].

Nodules

Cutaneous leishmaniasis causes nodules, but they usually crust and ulcerate after some weeks or months, and are seldom as numerous as those of lepromatous leprosy. Slit-skin smears, appropriately stained, reveal leishmania, and the leishmanin test is positive. Lesions of the rare diffuse cutaneous leishmaniasis may be confusing, until slit-skin smears have been examined [7]. Post-kala-azar dermal leishmaniasis in India and East Africa has a similar distribution and appearance to the skin lesions of lepromatous leprosy [8].

Table 29.2 World Health Organization (WHO) multidrug therapy regimen.

	Drug treatment			
Type of leprosy	Monthly supervised	Daily self-administered	Duration of treatment	Duration of follow-up
Paucibacillary	Rifampicin 600 mg	Dapsone 100 mg	6 months	2 years
Multibacillary	Rifampicin 600 mg Clofazimine 300 mg	Clofazimine 50 mg Dapsone 100 mg	24 months	5 years

Nerves

Peripheral nerve thickening is rarely seen except in leprosy. Hereditary sensory motor neuropathy type III is associated with palpable peripheral nerve hypertrophy. Amyloidosis, which can also complicate leprosy, causes thickening of peripheral nerves. Peroneal muscular atrophy (Charcot–Marie–Tooth disease) is an inherited neuropathy that causes distal atrophy and weakness. Nerve biopsy is characteristic. The causes of other polyneuropathies such as acquired immune deficiency syndrome (AIDS), diabetes, alcoholism, vasclitides and heavy metal poisoning should all be considered where appropriate [9].

Likewise, there are many causes of eye disease in endemic countries which may cause signs that in isolation mimic leprosy, especially trachoma, in which trichiasis and entropion follow scarring of the lids, and onchocerciasis, which causes uveitis and its complications.

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Treatment

There are five main principles of treatment:

1 Stop the infection with chemotherapy.
2 Treat reactions and reduce the risk of nerve damage.
3 Educate the patient to cope with existing nerve damage, in particular anaesthesia.
4 Treat the complications of nerve damage.
5 Rehabilitate the patient socially and psychologically.

These objectives can only be achieved with the patient's co-operation and confidence. In endemic countries, and in the patient's own town or village setting, this may be done through the leprosy outpatient clinic. In countries where leprosy is uncommon, or when the clinical or social situation is complicated, it is often best to admit the patient for a careful assessment and classification of the disease, to record accurately the degree of nerve and eye involvement and damage, assess disability and to start patient education and treatment.

Chemotherapy

All leprosy patients should be given an appropriate multidrug combination. The effectiveness of dapsone against *M. leprae* was discovered in the late 1940s, and it was used widely as a single agent. This lead to the widespread development of dapsone resistance, initially presenting as disease relapse 15 years after treatment with dapsone monotherapy, but then also as primary dapsone resistance in untreated patients [1]. In response to the failure of dapsone monotherapy, the World Health Organization (WHO) proposed a multidrug regime (MDT) for the treatment of leprosy [2]. In a multibacillary patient, there are three distinguishable types of bacilli: fully drug-sensitive bacteria, drug-resistant mutants and a small population of 'persisters', dormant non-multiplying bacilli. Treatment with a multidrug regime should eliminate nearly all organisms. The first-line antileprosy drugs are rifampicin, dapsone and clofazimine. Table 29.2 gives the details of drug dosages, duration of treatment and length of follow-up.

Rifampicin is a potent bactericidal for *M. leprae*. Four days after a single 600-mg dose, bacilli from a previously untreated multibacillary patient are no longer viable [3]. It acts by inhibiting DNA-dependent RNA polymerase, thereby interfering with bacterial RNA synthesis. Rifampicin is well absorbed orally. Hepatotoxicity may occur with a mild transient elevation of hepatic transaminases, but this is rare at the dosage and intervals recommended for leprosy, and is not an indication for stopping treatment. Because *M. leprae* resistance to rifampicin can develop as a one-step process, rifampicin should always be given in combination with other antileprotics [4].

Dapsone (DDS, 4,4-diaminodiphenylsulphone) acts by blocking folic acid synthesis. It is only weakly bactericidal. Oral absorption is good and it has a long half-life, averaging 28 h. Dapsone, in the doses recommended for leprosy, commonly causes mild haemolysis, and rarely anaemia or psychosis. Glucose-6-phosphate dehydrogenase deficiency seldom causes a problem and is not routinely looked for. The 'DDS syndrome', which is occasionally seen in leprosy, starts 6 weeks after commencing DDS and manifests as exfoliative dermatitis associated with lymphadenopathy, hepatosplenomegaly, fever and hepatitis, and may be fatal [5]. Agranulocytosis, hepatitis and cholestatic jaundice occur rarely with DDS therapy.

Clofazimine is a brick red, fat-soluble crystalline dye. The mechanism of its weakly bactericidal action against *M. leprae* is not known. It has an anti-inflammatory effect, which is useful in the management of ENL reactions. High drug concentrations are found in the intestinal mucosa, mesenteric lymph nodes and body fat. The most noticeable side effect is skin discoloration, ranging from red to purple-black, the degree of discoloration depending on the dose and amount of leprous infiltration. The pigmentation usually fades within 6–12 months of stopping clofazimine, although traces of discoloration may remain for up to 4 years. Urine, sputum and sweat may become pink. Clofazimine also produces a characteristic icthyosis on the shins and forearms. Gastrointestinal side effects, ranging from mild cramps to diarrhoea and weight loss, may occur as a result of clofazimine crystal deposition in the wall of the small bowel.

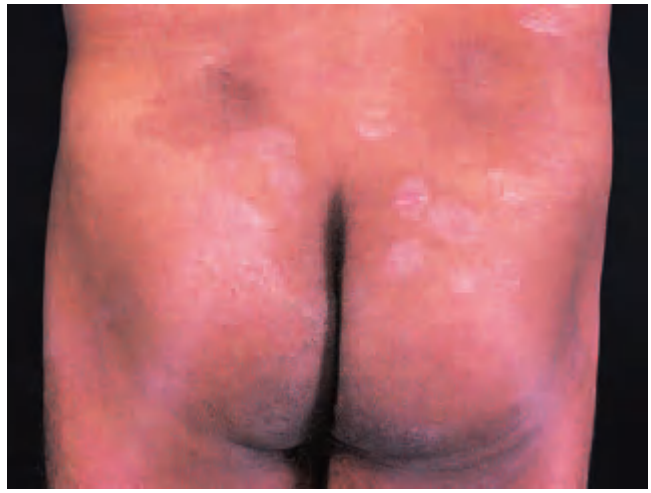

Fig. 29.26 Borderline leprosy (BL). Borderline leprosy up-grading to borderline tuberculoid (BT). Buttocks of an Indian man who 'relapsed' 3 years after completing multidrug therapy for BL leprosy. The lesions here are typical hypopigmented, erythematous, scaly, plaques of BT leprosy in reaction. No acid-fast bacilli (AFB) were seen on slit-skin smears. In this situation, the distinction between (bacterial) relapse and simple reversal reaction may be impossible.

Relapse

Relapsed multibacillary patients are also retreated with triple therapy regardless of any change in classification [6].

The distinction between relapse and reaction may be difficult (Fig. 29.26). Therefore, paucibacillary patients require 2 years, and multibacillary patients at least 5 years, monitoring after treatment. Patients can be discharged if there is no evidence of activity or reaction, but should be advised to return if new symptoms develop, especially in hands, feet or eyes. Patients with reactions or physical or psychological complications may need much longer care.

Published clinical outcomes for patients treated with the paucibacillary regimen show that 2–44% of patients had clinically active skin lesions at the end of treatment [7]. Nerve impairment occurred *de novo* in 2.5% of patients, and visible disabilities increased from 4% at enrolment to 7% at 8–10 years follow-up. Relapse rates are low, ranging from 0% in Ethiopia [8] to 2.5% over 4 years in Malawi [9]. For patients treated with the multibacillary regime for 24 months, one study in Thailand found that 29% of lesions were still active after 3 years and that visible disabilities increased from 5% at enrolment to 13% at 8–10 years follow-up [10]. Relapse rates have been reported from six observational studies varying from zero in China and Ethiopia to 2.04/100 person years in India. Data from West Africa [11] and India [12] shows that patients with a high initial bacterial load (BI > 4+) treated with 2 years of rifampicin, clofazimine and dapsone had a relapse rate of 8/100 person years, whereas patients treated to smear negativity had a relapse rate of 2/100 person years. These patients may form a subgroup who need treating to skin-smear negativity [13]. Susceptibility testing of *M. leprae* strains from relapsed multibacillary patients have shown them to remain drug sensitive.

Several new drugs bactericidal for *M. leprae* have been identified: fluoroquinolones, minocycline and clarithromycin. The fluoroquinolones pefloxacin and ofloxacin have a remarkable degree of bactericidal activity, with 22 daily doses killing 99.99% of viable *M. leprae* present in multibacillary cases at the start of treatment [14]. Multicentre trials of daily rifampin/ofloxacin are being conducted by the WHO and these may lead to a shortening in the duration of MDT. Daily minocycline (100 mg) treatment of multibacillary patients for 3 months resulted in killing of all viable *M. leprae* organisms [15]. Clarithromycin, given in 500-mg daily doses to multibacillary patients, has a similar bactericidal effect [16]. Antagonism between these new drugs has not been demonstrated [17]. Ofloxacin, minocycline and clarithromycin are established second-line drugs, and may replace dapsone and clofazimine. Minocycline may also cause hyperpigmentation of skin lesions, and so may not be an appropriate

substitute for clofazimine if pigmentation is to be avoided [18].

A single-dose triple-drug combination (rifampicin, ofloxacin and minocycline) has been tested in India for patients with single skin lesions; 47% of patients were completely cured 18 months after treatment. Although the study had major flaws, and single-dose treatment is less effective than the conventional 6-month treatment for paucibacillary leprosy, it is an operationally attractive field regimen and has been recommended for use by the WHO [19].

The recommended length of treatment for multibacillary patients has dropped from 24 months to 12 months. There was no controlled trial data to guide this decision, but the classification of multibacillary patients had been widened, so some patients who would previously have received paucibacillary treatment from 6 months are now receiving multibacillary treatment for 12 months. New proposals include testing a common 6-month regimen of dapsone, clofazimine and rifampicin for all patients [20]. This would simplify leprosy treatment but would give 60% of patients a third drug that they do not need, and under-treat patients with a high bacterial load [21].

Reactions and neuritis [22]

Nerve damage occurs before diagnosis, during and after multidrug treatment. It may occur during a reaction or without overt signs of nerve inflammation (silent neuropathy). In field cohort studies 16–56% of newly diagnosed patients have nerve damage [23]. In a Bangladeshi study 25% of multibacillary patients developed nerve damage during treatment [24]. Analysis from a large cohort study in Ethiopia showed that standardized nerve function testing was needed monthly to detect new nerve damage early [25].

Patients frequently seek medical advice for their leprosy only when a reversal reaction develops in a previously quiescent skin lesion, or when they develop pain, weakness or numbness. Awareness of the early symptoms of reversal reactions by both patient and physician is important, because if left untreated severe nerve damage may occur. The peak time for reversal reactions is in the first 6 months of treatment [26], so it is important to warn patients about reactions. The sudden development of reactional lesions soon after starting treatment is distressing and undermines confidence.

The treatment of reactions is aimed at controlling acute inflammation, easing pain, reversing nerve and eye damage and reassuring the patient. Multidrug therapy should be continued. Neuritis (nerve tenderness, new anaesthesia and/or motor loss) or moderately inflamed skin lesions should be treated with corticosteroids. Standardized courses of prednisolone have been used, starting at 40–60 mg daily, reducing by 5 mg every 2–4 weeks [27]. Patients with BT reactions commonly need 2–4 months of steroids, while BL reactions may need 6 months. A recent Indian study compared different starting doses (60 vs. 30 mg) and durations (12 vs. 20 weeks) and showed that the longer durations gave the best outcomes. A study looking at cytokine profiles in reactional patients showed that, even after 6 months of steroid treatment, some patients still had high levels of pro-inflammmatory cytokines in their skin lesions [28]. In another approach, the prevention of reactions has been explored. In one study, multibacillary patients were randomized to either prednisolone 20 mg daily or placebo for the first 3 months of their multidrug therapy. Reactional episodes were significantly lower in the prednisolone-treated group at 4 months, but the protective effect was lost by 12 months. These studies all demonstrate that reactions are difficult to prevent and to switch off once established. Other established immunosuppressants may have a role in treating reactions; in a pilot study in Nepal, patients had equivalent outcomes whether treated with an azathioprine/prednisolone combination or prednisolone alone [29]. Ciclosporin (cyclosporin) has also been used in reactions, and again is effective in skin and nerve inflammation, but patients relapse when treatment is stopped (Marlowe SN, Knuutilla FH, Bizuneh E *et al*., Verbal communication, 16th International Leprosy Congress, Brazil.).

This is a difficult condition to treat, and frequently requires therapy with high-dose steroids (80-mg daily, tapered down rapidly) or thalidomide. Since ENL frequently recurs, steroid dependency can easily develop. Thalidomide (400 mg daily) is superior to steroids in controlling ENL, and is the drug of choice for young men with severe ENL [30]. Women with severe ENL may benefit from thalidomide treatment. This is a difficult decision for the woman and her physician, and needs careful discussion of the benefits and risks (phocomelia when thalidomide is taken in the first trimester). Women should use double contraception and report immediately if menstruation is delayed. Unfortunately, the problems with thalidomide mean that it is unavailable in several leprosy endemic countries despite its undoubted value. Clofazimine has a useful anti-inflammatory effect in ENL and can be used at 300 mg/day for several months. Low-grade chronic ENL, with iritis or neuritis, will require long-term suppression, preferably with thalidomide or clofazimine. Acute iridocyclitis is treated with 4-hourly instillation of 1% hydrocortisone eye drops and 1% atropine drops twice daily.

Education of the patient

Educating a leprosy patient about their disease is the key to successful management. The patient needs to be reassured that within a few days of chemotherapy they will not be infectious and can lead a normal social life.

A clear explanation of the disease and refutation of myths about leprosy will help the patient come to terms with their diagnosis and may well improve compliance. It is important to emphasize that gross deformities are not the inevitable end point of disease, and that care and awareness of their limbs is as important as chemotherapy. Anxieties about transmission and reactions, as well as issues about compliance, should be addressed.

Complications of nerve damage [31,32]

The complications of nerve damage, which are the major causes of disability and deformity in leprosy, are preventable by early diagnosis, correct treatment and education of the patient. Monitoring sensation and muscle power in patient's hands, feet and eyes should be part of the routine follow-up, so that new nerve damage is detected early.

Dry skin should be treated by soaking in water, followed by rubbing with emulsifying ointment or petrolatum. Callus should be rubbed down with pumice or an abrasive nylon pad, and fissures need to be covered to allow them to heal.

The morbidity and disability associated with leprosy is secondary to nerve damage. A major goal in prevention of disability is to create patient self-awareness, so that damage is minimized. The patient with an anaesthetic hand or foot needs to understand the importance of daily self-care, especially protection when doing potentially dangerous tasks, and inspection for trauma. It is helpful to identify for each patient potentially dangerous situations, such as cooking, car repairs or smoking. Soaking dry hands and feet followed by rubbing with oil keeps the skin moist and supple.

An anaesthetic foot needs the protection of an appropriate shoe. For anaesthesia alone, a well-fitting 'trainer' with firm soles and shock-absorbing inners will provide adequate protection. Once there is deformity, such as clawing, shoes must be made specially to ensure protection of pressure points and even weight distribution.

The patient should be taught to question the cause of an injury so that the risk can in the future be avoided. Plantar ulceration occurs secondary to increased pressure over bony prominences. Ulceration is treated by rest. Unlike ulcers in diabetic or ischaemic feet, ulcers in leprosy heal if they are protected from weight-bearing. No weight-bearing is permitted until the ulcer has healed. Appropriate footwear should be provided to prevent recurrence.

Weakness or paralysis

These require physiotherapy, with the objective of permitting the return of function while preventing the formation of contracture. Patients with contractures are taught exercises to prevent fixation. Contractures of hands and feet, foot drop, lagophthalmos, entropion and ectropion are amenable to surgery.

Social, psychological and vocational rehabilitation

The social and cultural background of the patient determines the nature of many of the problems that may be encountered. The patient may have difficulty in coming to terms with leprosy. The community may reject the patient. Education, gainful employment, confidence from family, friends and doctor, and plastic surgery to correct stigmatizing deformity, all have a role to play.

Prevention and control

The current strategy of leprosy control in endemic countries through vertical programmes providing case detection, treatment with WHO MDT and contact examination, and supported by case finding campaigns, especially in schools, has been very successful. Effective treatment is not merely restricted to chemotherapy but also involves good case management with effective monitoring and supervision. An important secondary role of leprosy control programmes is the prevention of disabilities.

Vaccines against leprosy

The substantial cross-reactivity between BCG and *M. leprae* has been exploited in attempts to develop a vaccine against leprosy. Trials of BCG as a vaccine against leprosy in Uganda, New Guinea, Burma and South India showed it to confer statistically significant but variable protection, ranging from 80% in Uganda to 20% in Burma [33]. In Northern Malawi, BCG gives 50% protection against leprosy but no significant protection against tuberculosis [34]. A case–control study in Venezuela showed BCG vaccination to give 56% protection to the household contacts of leprosy patients [35]. The variability and unpredictability of BCG has lead to various attempts to improve its protective efficacy. Combining BCG and killed *M. leprae* is one approach, but in both a large population-based trial in Malawi [36] and in an immunoprophylactic trial in Venezuela [37] there was no advantage with BCG plus *M. leprae* over BCG alone. Possibly the variable protection induced by BCG is due to early contact with environmental mycobacteria priming the immune system and conferring protective immunity against *M. leprae*. Vaccination with BCG after contact with environmental mycobacteria will then contribute little towards inducing improved immunity against *M. leprae* [38].

The WHO declared that 'the elimination of leprosy as a public health problem' should be achieved by the year 2000 [39]. Whilst this has not been possible for all areas,

major progress has been made. Leprosy is unlikely to be eradicated until there is considerable improvement in general health, wealth, living conditions and education.

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Chapter 30

The Treponematoses

The late R.S. Morton, G.R. Kinghorn & F. Kerdel-Vegas

Syphilis

General features

Definition. An infectious disease caused by *Treponema pallidum*. The systemic nature of the disease, in which there are florid clinical manifestations interspersed with periods of asymptomatic latency, is also characterized by transmission to offspring and chronic late disease in 25% of those who are untreated.

The name of the disease was drawn from a poem *Syphilis sive morbus gallicus*, written by Fracastoro of Verona in 1530, in which the mythical swineherd Syphilis refused to make sacrifices to Apollo and was smitten as a result.

Medicosocial background. Syphilis, 'the great imitator', is among the most fascinating of skin diseases. It may present to the dermatologist as a sexually acquired, contagious disease or as a congenitally acquired infection. When sexually acquired, it commonly coexists with at least one other sexually transmitted infection (STI).

The prevalence of syphilis in a community is determined by the socio-economic structure of the country concerned, and how that structure functions [1]. Humans and their social, economic and medical environment are in constant interaction. Changing attitudes determine changes in behaviour patterns and as these become integrated norms, so they become the custom. Thus, although syphilis is endemic worldwide, its steady decline over the last 400 years has been punctuated by epidemic peaks associated with unstable social conditions or upheavals. These changes include mass migrations and wars, as well as growing prosperity and economic reversals precipitating real or relative poverty.

The high incidence of syphilis in the Second World War peaked as thousands of demobilized men and women returned home to resettle. The period of relative socio-economic stability of the early 1950s saw a decline in all STIs, including syphilis. Its recrudescence, albeit modest compared with other sexual infections, began in the late 1950s [2–6]. It has been a variable manifestation. As in the 16th and 18th centuries in Europe and America, respectively, growing prosperity in the 1960s was not only associated with much scientific invention and technological innovation, but with the human's revolt against society's restraints and constraints—political, religious, social and sexual. A wide variety of changes thus determine the variations in incidence. At one extreme is the country recently freed from colonial domination, where health and social services have declined and disintegrated, and at the other is the country recently freed from written or unwritten laws controlling censorship, abortion and sexual activity.

In each case, socio-economic change disturbs some people's stability and sense of security, and exposes social and individual ineptitudes. West African countries lose control of yaws and it becomes common and disregarded.

In the UK and the USA, tens of thousands of young people manifest unprecedented high levels of medicosocial pathology in the form of self-poisoning episodes, premarital conception, sexual infection, and alcohol and drug abuse.

Unlike some STIs, the increase in the incidence of syphilis has been modest. The reasons are many and varied. For example, syphilis is not as infectious as some other STIs, and the infected are readily rendered non-infectious by even short courses of antibiotics given for a wide variety of infections—not least two common STIs, gonorrhoea and non-specific genital infection. In 1973, Felton [7] estimated that, in the UK, for every case of early syphilis diagnosed another remained undetected.

Population growth since the 1950s with a growing proportion of young people in many societies, like increasing population movement, has increased incidence rates more directly.

The extent to which available statistics reflect the incidence of syphilis depends on case-finding efforts, variation in notification practices and social factors that may limit increase or reduce the interaction between infected individuals and health services [8]. Comparison of one country with another is therefore essentially meaningless.

Incidence. The World Health Organization (WHO) estimates that the annual global incidence of syphilis is approximately 12.2 million cases, most of which occur in developing countries, where the disease has remained a prominent cause of genital ulcer disease in heterosexual men and women, of stillbirth, and of neonatal morbidity and mortality. The prevalence of pregnant seropositive women is 0.1–0.6% in developed countries, but it may exceed 10% in many developing countries. In some parts of Southern Africa, seroconversion during pregnancy has been reported to occur in more than 2% of women [9]. The growth of penicillin and other antimicrobial resistance amongst gonococci, for example in South-East Asia but increasingly also in Western Europe, and the use of drugs that are less treponemicidal may open the way for a greater prevalence of syphilis [10,11].

In North America and the developed countries of Northern Europe, syphilis had become predominantly a disease of homosexual men by the 1970s. There were renewed outbreaks of heterosexual and congenital syphilis in North America during the late 1980s in the wake of the human immunodeficiency virus (HIV) epidemic [12]. This resurgence was mainly observed in commercial sex workers, in whom it was often associated with selling sex for drugs (especially crack cocaine), and in other persons of lower socio-economic status. In 1994, there were 20 627 reported cases of primary and secondary syphilis in the USA (8.1 cases per 100 000 people, the rate being 60 times higher in non-Hispanic black people than in white people) compared with 304 cases in England (fewer than 0.6 cases per 100 000 people) [13]. Subsequently, incident syphilis cases have declined to less than four cases per 100 000 and syphilis has again been targeted for national elimination [14].

Eastern Europe experienced a 50-fold increase in reported syphilis cases between 1990 and 1997, with similar increases in the Ukraine, some central Asian countries and the Baltic States. Neighbouring Scandinavian countries have witnessed an increase in imported cases [15,16].

Although the overall incidence of syphilis in the UK was only 0.3 cases per 100 000 people in 1998, there have since been outbreaks in several cities where there was previously a low prevalence [17,18]. The outbreaks have been characterized by rapid increases in sexual networks with high rates of partner change; travel or migration links with high incidence areas; and an increasing predominance of homosexual transmission with a high proportion of HIV co-infection among incident cases. A similar trend in the increasing numbers of men who have sex with men engaging in unsafe sexual practises and who acquire syphilis and other bacterial STIs has also been observed in North America and elsewhere in Western Europe [19,20].

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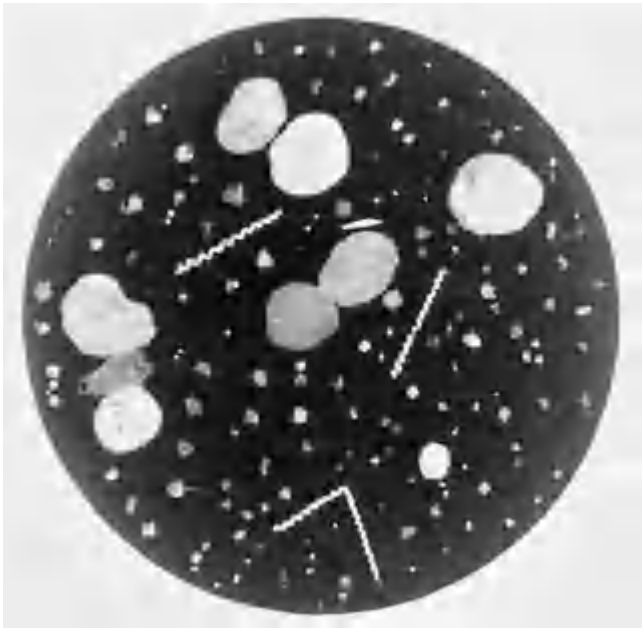

Fig. 30.1 *Treponema pallidum* showing regular spirals and marked angling.

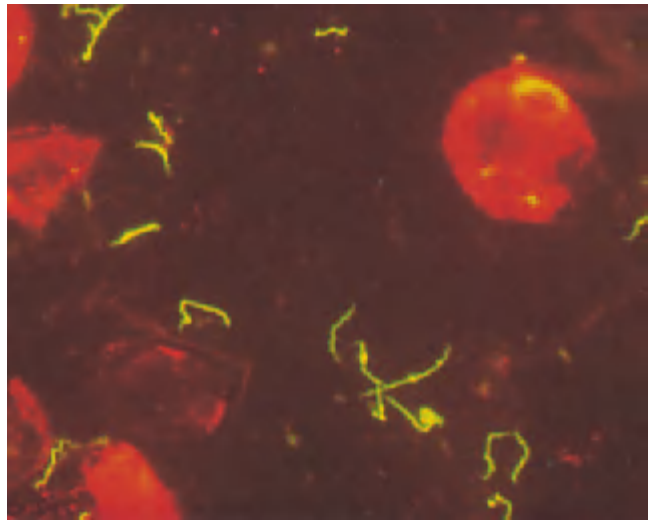

Fig. 30.2 Fluorescein-stained treponemes.

Causative organism

The causative spirochaete of syphilis, *Treponema pallidum* ssp. *pallidum*, was discovered by Schaudinn and Hoffmann in 1905 and originally was called *Spirochaeta pallidum*.

Treponema pallidum cannot be grown in the laboratory on any biochemical medium. Not all animals are susceptible to it. The rabbit, although liable to be a victim of a treponeme peculiarly its own, is commonly used in laboratory studies and as a source of *T. pallidum* used in diagnostic tests. *Treponema pallidum* cannot be differentiated from those treponemes involved in other forms of treponematosis, nor from Nichol's strain, which was isolated in 1912 from the brain of a patient and kept alive by passage through many generations of rabbits. Another experimental treponeme, the Reiter strain, is said to have been isolated in 1922. In contrast with the Nichol's strain, it is avirulent and can be cultivated on a relatively simple medium. Freeze-dried extracts were used for many years in the Reiter protein complement fixation test.

Morphology. In daily practice, *T. pallidum* is demonstrated by dark-field microscopy. It appears as a pale, white, fine, corkscrew organism with close and very regular coils (Fig. 30.1). Its length varies from 6 to 15 µm and its coils from 0.09 to 0.18 µm. There are between eight and 20 coils. As a practical guide, to help differentiate the organism from others like it, there are about seven to eight coils per diameter of a red blood corpuscle. It contains a periplasmic flagellum and is actively motile. The movements of the *T. pallidum* are pathognomonic. It rotates around its long axis and thus appears to quiver and screw slowly backwards and forwards; it shows a highly typical angling movement, forming both acute and obtuse angles. It shows both grace and elegance and these help to distinguish it from other genital or oral spirochaetal organisms. Treponemes can also be demonstrated by the direct fluorescent-antibody method [1,2], and by rapid immunofluorescent staining (RIS) of smears from lesions [3] (Fig. 30.2).

Of the several spirochaetes found in the genital area and requiring differentiation from *T. pallidum*, the most important are *Borrelia refringens* and *B. balanitidis*. Both are thicker than *T. pallidum* and have fewer and irregular coils. In addition, they move with more fidgety, snake and eel-like movements. *Borrelia gracilis* is finer than *T. pallidum*, with closer coils and a lack of typical movements. It can be found at the gum margins between teeth.

Microbiology. The organism is microaerophilic and has evolved to become a highly invasive and persistent pathogen with little toxigenic activity and an inability to survive outside the mammalian host. It has extreme nutritional requirements due to deficiencies in biosynthetic pathways, and has a narrow equilibrium between oxygen dependence and toxicity. It cannot be cultured on artificial media but it can be propagated in organ culture, such as rabbit testis. It has a slow growth rate, optimal at 33–35°C, with a doubling time of 30–36 h. The organism is similar to and shares extensive DNA homology with three other pathogenic treponemes, which cause yaws, bejel and pinta.

Analysis of the genome, which is contained on a single circular chromosome with 1 138 006 base pairs, shows that the organism lacks lipopolysaccharide and lipid biosynthesis mechanisms, as well as many metabolic pathways, including for the tricarboxylic acid cycle, components of oxidative phosphorylation, and for most

amino acids and vitamins. It requires D-glucose, maltose, and mannose but cannot utilize other sugars [4]. It is able to use exogenously supplied amino acids and is dependent upon serum components such as fatty acids.

Treponema pallidum initiates an inflammatory response at the site of inoculation and is disseminated during the primary infection. The organism has a surface-associated hyaluronidase enzyme, which may play a role in this process. Phagocytosis by cytokine-activated macrophages, as part of a predominant T-helper (Th1)-type early response, aids bacterial clearance and resolution of the primary lesion [5]. Virulent organisms promote adhesion of lymphocytes and monocytes to human vascular cells, and this is important in immunopathogenesis [6]. As with other organisms that cause chronic disease, *T. pallidum* has evolved mechanisms for evading immune responses. A Th1–Th2 switch occurs with macrophage suppression caused by prostaglandin E_2 down-regulation; however, the molecular mechanisms remain poorly understood [7]. Depressed cell-mediated responses occur during the later stages of syphilis, and a lowered $CD4^+$ lymphocyte count has been reported [8].

Pathogenesis. Relatively few genes are involved in pathogenesis. It has been postulated that the immunoevasiveness of *T. pallidum* is the result of the organism's unusual molecular architecture. The outer membrane lacks lipopolysaccharide and contains few poorly immunogenic transmembrane proteins; the highly immunogenic proteins are lipoproteins anchored predominantly to the periplasmic leaflet of the cytoplasmic membrane [9].

The dominant immunogen is a 47-kDa membrane lipoprotein, which can induce synthesis of tumour necrosis factor-α. Immunoblotting has also shown IgG responses to an antigen of 65 kDa that is shared with non-pathogenic treponemes and antigens of 44.5, 17.0 and 15.5 kDa that are specific for *T. pallidum*.

Natural history

Stages. The clinical presentation of syphilis is extremely diverse and may occur decades after initial infection. Syphilis, if untreated, may pass through four stages: primary, secondary, latent and late. The first two stages are contagious. They seldom last more than 2 years and do not exceed 4 years. Latency may last from 5 to 50 years. Only 25–30% of patients present with late, chronic, crippling or killing manifestations. The frequency of these late manifestations continues to decline, and in many countries they are now rare.

Incubation period. The incubation period of syphilis is generally given as 9–90 days, and varies inversely with the size of the spirochaete inoculum. Typically, most genital primary sores appear 3 weeks after exposure. Enlarged glands appear in one groin after a further week and can usually be detected in both groins 5 weeks after infection. Reactive reaginic serological tests are detectable at 5.5–6.0 weeks; the macular rash at 8 weeks; papular lesions at 3 months and condylomas at 6 months.

Course of untreated syphilis. Several investigations have helped to elucidate the natural history of untreated syphilis, for example the Oslo study of untreated syphilis [10] and the Tuskegee study [11]. Regarding the first of these, Caesar Boeck believed that *no* treatment was better than using mercury. He therefore kept some 2000 infectious syphilitics in hospital for 1–12 months (average 3–6 months), i.e. until all traces of their infection had gone. Gjestland [10] made a follow-up study of 1147 patients and summarized the findings as follows:

- 24% developed mucocutaneous relapses;
- 11% died of syphilis;
- 16% developed benign late manifestations, usually cutaneous nodules or gummata;
- 10% developed cardiovascular syphilitic lesions;
- 6% developed neurosyphilis.

It would appear therefore that long before the arsenicals and penicillin were introduced, at least 60% of people with syphilis lived and died without developing serious symptoms of their infections.

Histopathology

The fundamental pathological changes in syphilis are the same in early and late disease. They occur in and around blood vessels in the form of a perivascular infiltration of lymphocytes and plasma cells, accompanied by intimal proliferation in both arteries and veins (endarteritis obliterans).

In early lesions, perivascular infiltration by lymphocytes and plasma cells is accompanied by intimal proliferation in arteries and veins. This leads to ischaemia and ulceration. Organisms are most numerous in the walls of capillaries and lymphatic vessels. They can be demonstrated by Levaditi's silver stain or by the fluorescent antibody technique [12]. The papular skin lesions of secondary syphilis also show endothelial swelling in dermal vessels.

In late lesions, the characteristic lesion of mucocutanous surfaces is the syphilitic gumma. Granulation tissue forms with histiocytes, fibroblasts and epithelioid cells. Endarteritis obliterans and necrotic areas are pronounced. Gummata most often originate in subcutaneous tissues and spread in all directions. Spirochaetes are not readily demonstrable in these lesions.

Heubner's arteritis occurs in cardiovascular and meningovascular syphilis. It is characterized by lymphocytic and plasma cell infiltration of the vasa vasorum and adventitia of large and medium-sized vessels. Occlusion

of the vasa vasorum results in medial necrosis and fibroblast proliferation. There is associated subintimal proliferation, which leads to luminal occlusion and thrombosis.

Some manifestations of syphilis (e.g. neuropathy) are immune-complex mediated.

Transmission. Transmission occurs almost exclusively during sexual intercourse, including by oro-genital contact [13]. *Treponema pallidum* is very sensitive to drying and heat, and also to soap and weak disinfectants. It can probably penetrate intact skin and mucous membrane but more readily enters the body through microscopic or visible breaks in the epidermis. Treponemataemia is established even before the appearance of the primary lesion. Syphilis therefore can be transmitted by blood transfusion. In deep inoculation, as by accidental puncture with a needle or in transfusion, no primary lesion appears. This is called syphilis d'emblee.

Congenital syphilis is acquired by placental transmission of infection from the mother. The longer the mother has had syphilis, the less likely she is to transmit it.

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Acquired syphilis

Primary syphilis (Figs 30.3–30.7)

The primary chancre appears at the site of initial treponemal invasion of the dermis. Initial lesions are papular but rapidly ulcerate. It may occur on any skin or mucous membrane surface and is usually situated on the external genitalia.

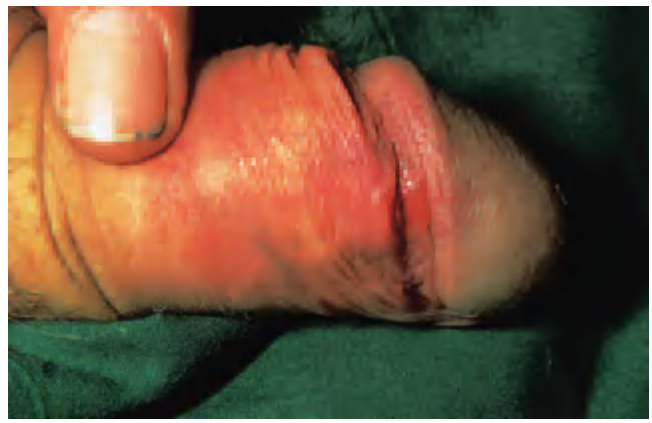

Fig. 30.3 Small but well-circumscribed primary syphilis. (All sores in the coronal sulcus are indurated.) Serology was negative.

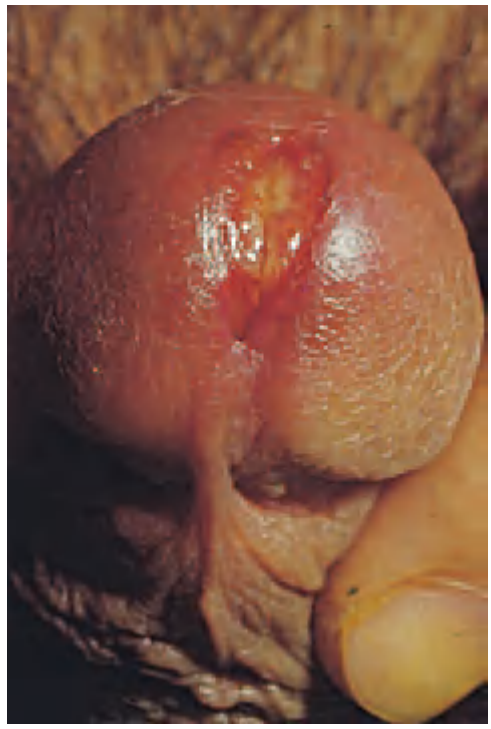

Fig. 30.4 Primary syphilis: meatal chancre.

The typical primary sore appears as a regularly edged, regularly based, hard and button-like ulceration measuring up to a centimetre in diameter. Unless secondarily infected, primary sores are not painful. The ulcer is often surrounded by a narrow, red border, 1–2 mm wide. This marks the limits of the inflammatory reaction and is most productive of *T. pallidum*. The lesion may be crusted due to drying of serous exudate. The induration of the ulcer is probably the best-known characteristic but it should be

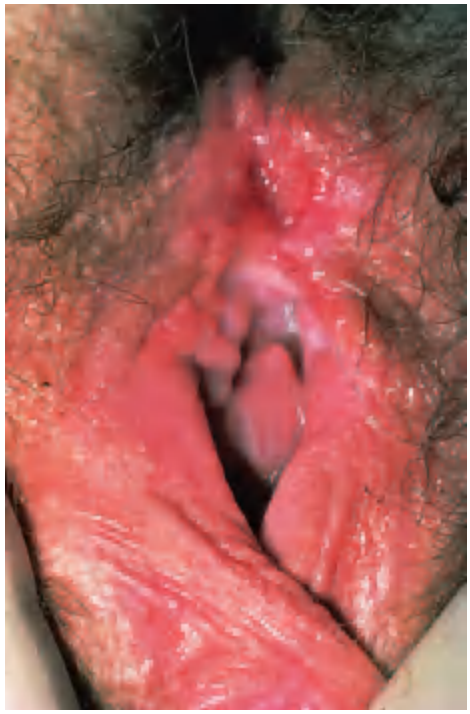

Fig. 30.5 Healing primary chancre of 3 weeks duration. It was accompanied by bilateral adenitis. Dark-field and serological tests were positive.

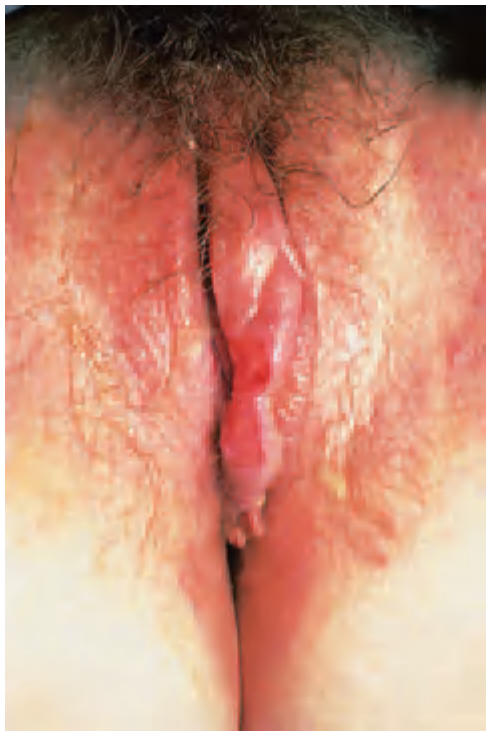

Fig. 30.6 Slightly indurated primary chancre of 2 days duration. It was neither painful nor tender. It points to the need for a high index of suspicion concerning all genital lesions. Dark-field microscopy prevents diagnostic error and embarrassment.

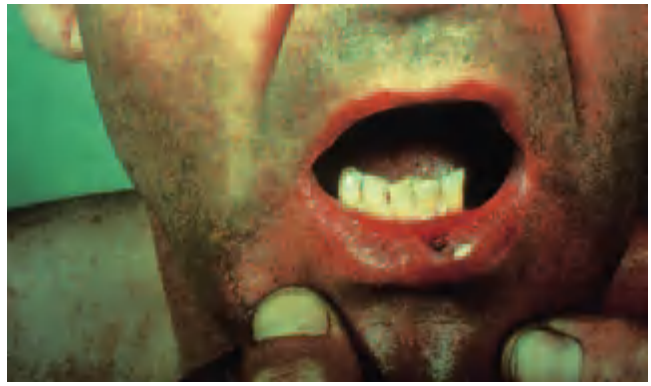

Fig. 30.7 Extragenital chancre of the lip. (Courtesy of Dr P. Taylor, Bristol Royal Infirmary, Bristol, UK.)

remembered that all lesions in the coronal sulcus of the penis are indurated. 'Kissing' ulcers, sometimes hourglass in shape, are not uncommon. Atypical lesions are common and around half lack one or more of the classical features. If the infection is inoculated into pre-existing lesions such as anal fissure, genital herpes or balanitis, the chancre may assume the shape of these conditions. In most cases, there is only a single chancre. Multiple chancres may appear simultaneously or within a few days of each other. Without treatment, the chancre persists for a period that can vary considerably, but seldom if ever exceeds 3 months. As a rule, it heals spontaneously in 3–8 weeks. In about one-third of cases, it leaves a regularly edged, slightly depressed, thin, depigmented, atrophic scar.

The appearance of the genital and perianal chancre is followed by swelling of the inguinal lymph nodes, usually one side and then the other. Maxillary and submental lymph nodes enlarge when infection is in or around the oral cavity. Wherever they appear, the enlarged glands are discrete, rubbery and free from fixation to skin or underlying tissues.

Sites. In men, the chancre most usually occurs on the glans penis, near the frenum or on the underside of the prepuce. Less commonly, the primary lesion appears on the shaft of the penis. If near the hilt, it may be called a 'condom chancre'. Less common sites are the pubic region or the external urinary meatus where it may masquerade as non-specific urethritis with scanty serous discharge. Lesions are often surrounded by oedema. Subprepucial lesions may be accompanied by some degree of acquired phimosis and it is in such cases particularly that lymphangitis dorsalis penis occurs; it is felt as an indolent 'string', some 2 mm in diameter.

In homosexually acquired syphilis, the anus and rectum may be sites of primary infection. Anal lesions may present as an indurated fissure difficult to distinguish from an ordinary fissure of the anal ring. Pain may be a feature as may itch and bleeding, especially after

defaecation. Like genital primary lesions, extragenital sores are accompanied by regional adenitis.

In women, most cases of early syphilis have reached the secondary stage when diagnosed [1]. A chancre is less frequently demonstrated, partly because the primary lesion may be on or in the cervix. The most common sites for a vulvar chancre are the labia minora or majora, around the urethral orifice, on the clitoris or quite commonly on the posterior commissure where it may masquerade as an indurated irregular fissure. Surrounding vulval oedema is common. Chancre very rarely occurs on the vaginal wall.

Extragenital chancres may be found on the lips as a result of kissing, cunnilingus or fellatio (Fig. 30.7). The indurated ulcer may be surrounded by oedema. Chancres of tongue and tonsil and primary lesions of the fingers, acquired occupationally or in sexual foreplay, also occur. Other extragenital chancres may follow from nibbling or biting the nipple, the ear, neck or arm.

Differential diagnosis. A wide variety of diseases can affect the genitals and must be considered. Genital herpes and balanoposthitis have typical clinical features, although they may occur with a chancre. Secondarily infected traumatic sores may look like chancres. Chancroid should be considered, and not only in subtropical areas of the world. Sporadic epidemic outbreaks of clinically modified chancroid have been reported in the UK, Canada and Kenya. Improved techniques for culture of *Haemophilus ducreyi* have been widely sought in several countries. The organism appears to be more common as a secondary invader than previously believed. Carrier states in both men and women are described. In general, the lesions described are rarely of the destructive and painful type previously believed to be classical [2].

As in chancroid, so in lymphogranuloma venereum, 'inflammatory bubo' may resemble the unilateral and bilateral adenitis of early syphilis. Unlike syphilis, the glands are usually matted, adherent to the inflamed skin and show a tendency to central fluctuation.

Excoriated secondary syphilitic papules in women can be confused with multiple small chancres. *Chancre redux* is a recurrence of the primary sore at its original site [3]. Tertiary syphilis, tuberculous ulceration, cancer or precancerous dermatoses such as erythroplasia of Queyrat and Bowen's disease, can occasionally cause difficulty. The papules of scabies on the glans or on the shaft of the penis may arouse strong suspicions. Any lesion at the site of a healed primary has been labelled pseudochancre redux [3,4].

On the cervix, a chancre may easily be taken for an 'erosion' or a cancer [5], especially when suspected syphilis is not the reason for examination.

With a chancre on the lip, the most important differential diagnosis is facial herpes simplex. Apart from the appearance, the recurrent nature of herpes is helpful.

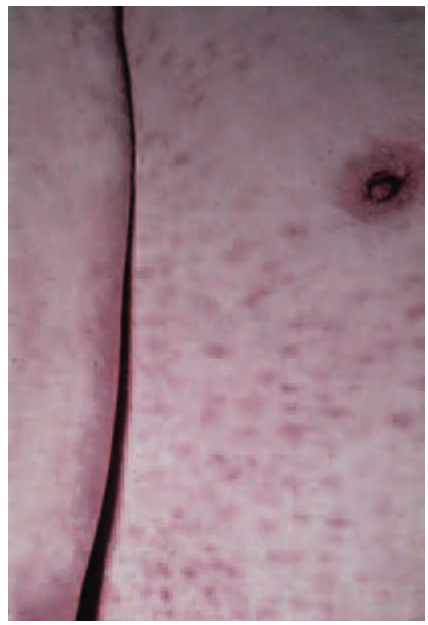

Fig. 30.8 Secondary syphilis. Like the macular rashes of other infections, it is not associated with the presence locally of the causative organism. It also appears at a recognized time after exposure, in this infection, 8 weeks after exposure. It is most readily seen, following the lines of cleavage of the skin of the trunk, in daylight.

Secondarily infected traumatic lesions with oedema may closely resemble a chancre, as may cancer of the lip. Traumatic ulcers of the tongue can sometimes be infiltrated. Behçet's syndrome with both oral and vulvar lesions may present a problem. Tonsillar chancres may be mistaken for tonsillitis, glandular fever or Vincent's angina. When the accompanying angular or submental adenopathy is painless, syphilis should be seriously considered.

A long-standing whitlow or paronychia ought to lead to examination for both herpes virus and *T. pallidum*. Where epitrochlear or axillary adenitis is painless, serological tests for syphilis are indicated.

In 'modern' societies, all oral and rectal lesions should give rise to suspicion of possible syphilis. Anal fissures and anal warts, 'haemorrhoids', anal discharge and irritation or a finding of some form of sexually transmitted proctitis, for example due to gonorrhoea, herpesvirus or *Chlamydia trachomatis*, should alert the physician to the possibility of concomitant syphilis. In the rectum, a chancre may be mistaken for a cancer.

Secondary syphilis (Figs 30.8–30.19)

Secondary syphilis is the stage when generalized manifestations occur on the skin and mucous membranes. Serological tests are always positive in immunocompetent persons. Rashes in secondary syphilis have three common features:

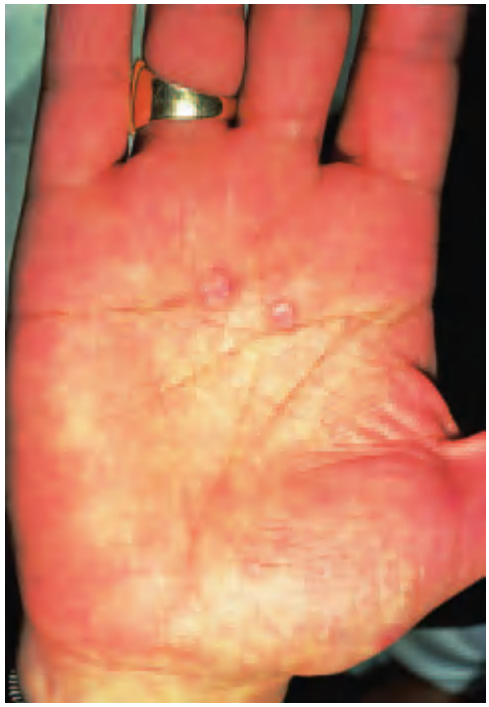

Fig. 30.9 Papulosquamous secondary syphilis involving the palm. (Courtesy of Dr P. Taylor, Bristol Royal Infirmary, Bristol, UK.)

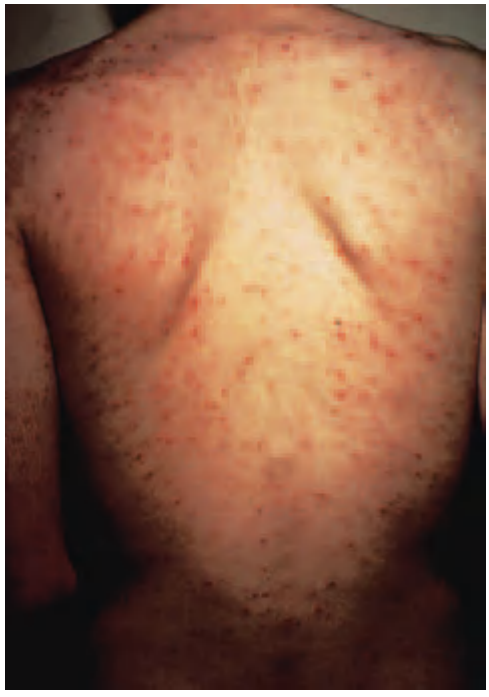

Fig. 30.10 Typical coppery red papules in secondary syphilis.

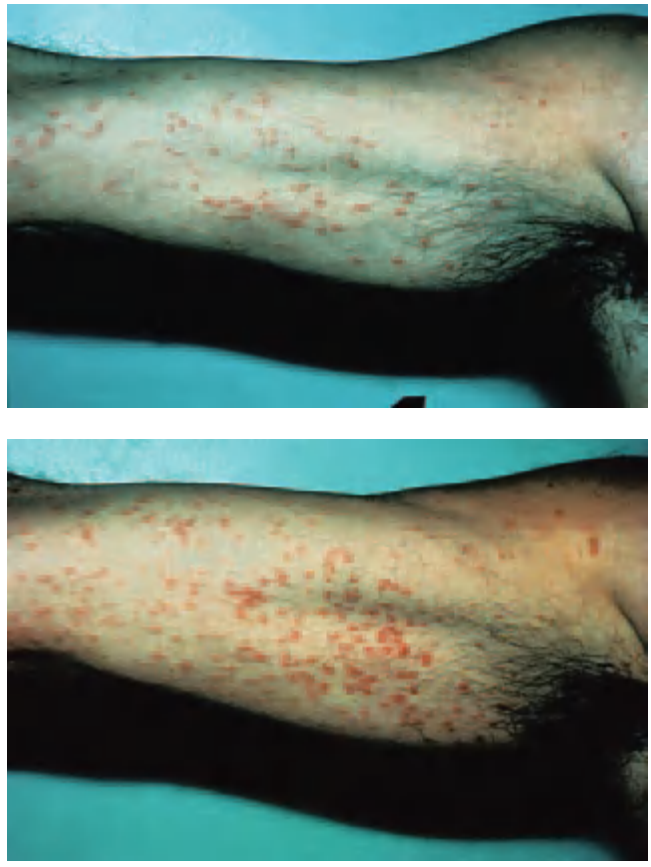

Fig. 30.11 Symmetrically distributed, coppery red and non-itchy rash typical of secondary syphilis. The only suggestion of syphilis in the partner was a history of laryngitis 5 months earlier. Her serological tests were strongly positive.

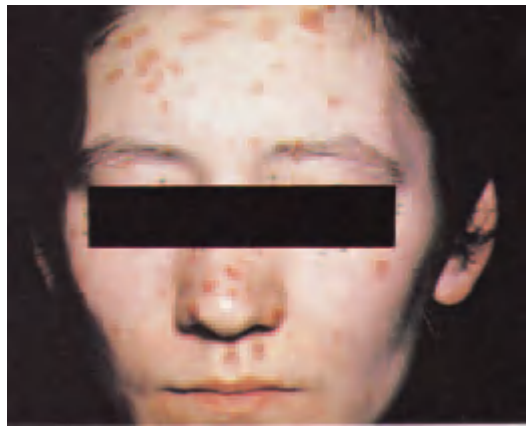

Fig. 30.12 Secondary syphilis imitating seborrhoeic dermatitis. Note the coppery red corona veneris.

1 they do not itch;
2 they are coppery red;
3 the lesions are symmetrically distributed.

The manifestations of generalized treponemal dissemination first appear at around 8 weeks. Constitutional symptoms consist of fever, headache, and bone and joint pains that are more pronounced at night. There is wide diversity in physical features.

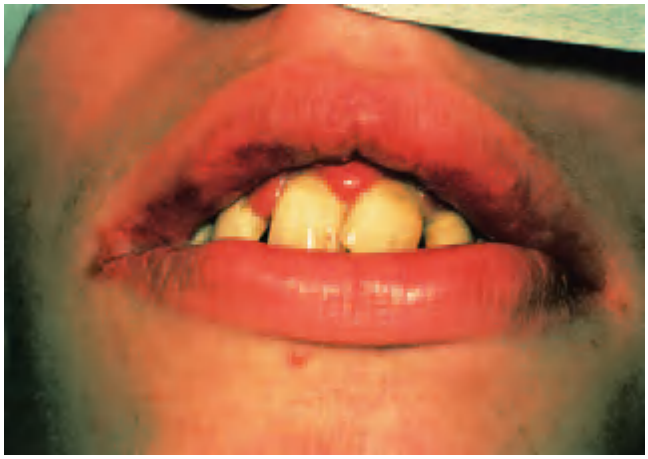

Fig. 30.13 Secondary syphilis presenting as 'split' papules at the angles of the mouth.

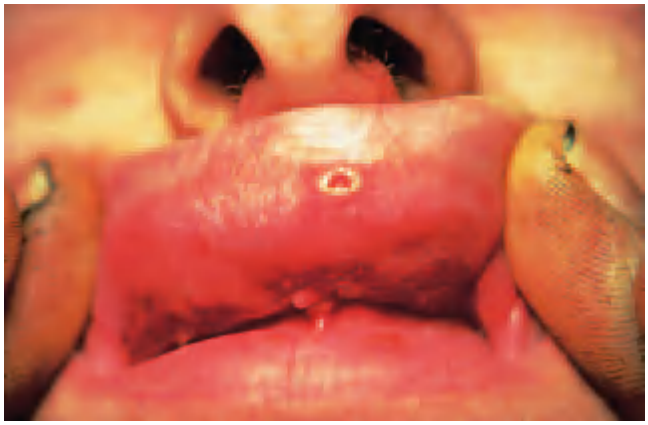

Fig. 30.14 Secondary syphilis. This eroded papule was the only lesion. Similar solitary lesions, demonstrating *Treponema pallidum*, are occasionally found just inside the anus in asymptomatic contacts.

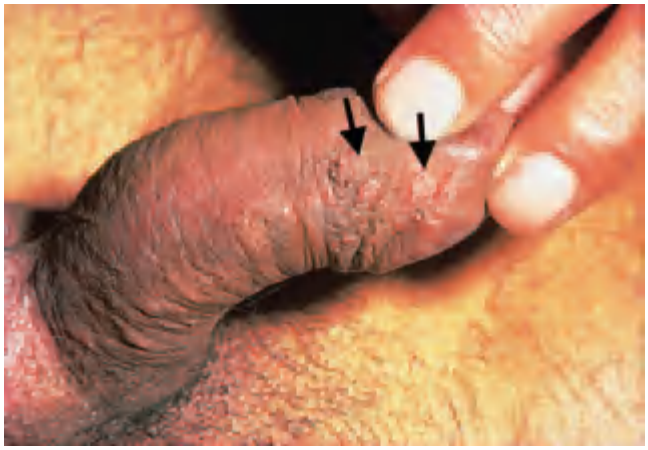

Fig. 30.15 Papules. These were the only evidence of reinfection in the regular consort of a pregnant women referred from an antenatal clinic with strongly positive serological tests for syphilis. She was an undeclared regular consort when the man was originally treated for primary syphilis, 18 months earlier.

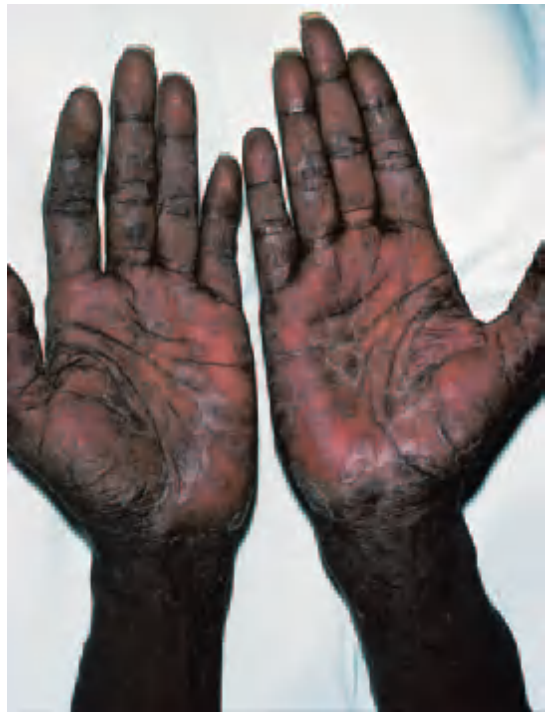

Fig. 30.16 Psoriasiform papules in secondary syphilis. Such lesions, sometimes shiny when squames are shed, of palms and soles are most commonly found in people of African origin.

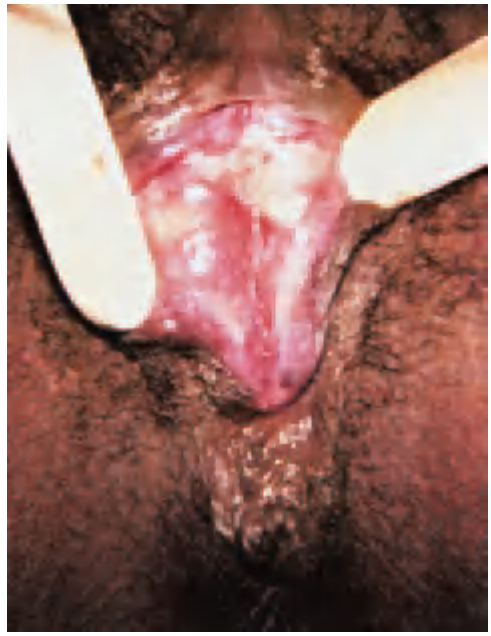

Fig. 30.17 Mucous patches around vaginal introitus.

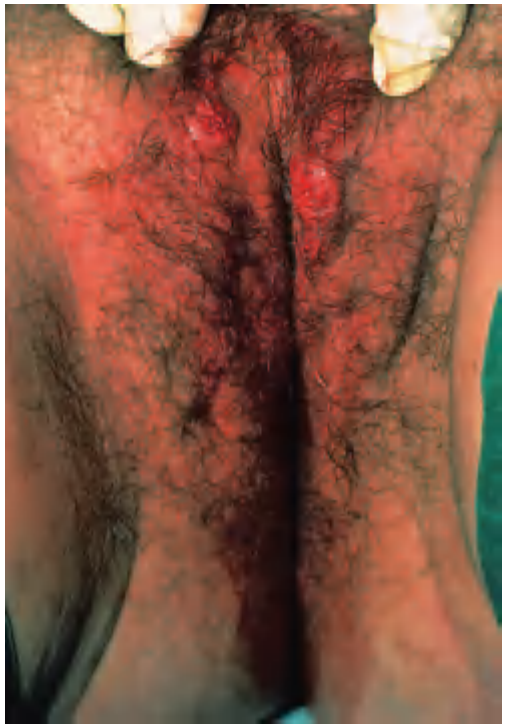

Fig. 30.18 Here the lesions are more exuberant. The sodden surface epithelium has been shed to reveal lesions describable as 'moist papules'.

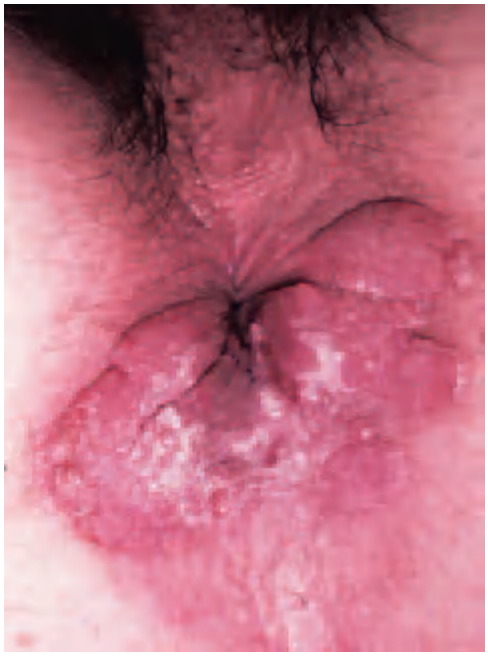

Fig. 30.19 When large opposing papules coalesce, as in the perianal region, the surface epithelium becomes sodden. Such lesions are called condylomata lata. *Treponema pallidum* organisms abound in them. They rarely appear in infections of less than 6 months duration.

Rashes are the commonest feature. They are initially macular and become papular by 3 months.

Macular syphilide (roseolar rash). This is the earliest generalized syphilide. It appears as symmetrical, coppery red, round and oval spots of no substance. On the back, the lesions clearly follow the lines of cleavage of the skin. The patients should be examined in daylight, as it is easy to overlook an early or fading rash. The roseolar spots do not scale or itch and, being in some patients sparse and evanescent, may pass unnoticed. Roseola is easily overlooked and seldom diagnosed in patients with deeply pigmented skin. When a roseola is fading, it sometimes leaves a pattern of depigmented spots on a hyperpigmented background. Such a *leukoderma syphiliticum* is most commonly located on the back or sides of the neck and was formerly known as 'the necklace of Venus'.

Papular syphilide. The papule is the basic lesion of secondary syphilis. Individual papules seldom exceed 0.5 cm in diameter. Its particular form of presentation can vary widely depending on the nature and colour of the patient's skin, the site affected and the climate, hygiene and clothing. Papular rashes may recur and be punctuated by spells of apparent latency. More usually, early papular rashes are in fact maculopapular and they have an even and generalized distribution all over the body. However, a purely coppery red papular rash, widely and symmetrically distributed, may also be seen.

The typical papule is firm and round, although the largest may be oval. Early papules tend to be shiny, but gradually a thin layer of scale forms and is quickly shed. This is the typical papulosquamous syphilide. Older lesions tend to be more pigmented. In the late phases of a papular syphilide, nummular lesions, 1–3 cm in diameter and covered by massive layers of scales, may closely resemble psoriasis. Because the underlying lesions are exuding serum, the scales are easily removed. Psoriasiform papules of the palms and soles are especially common in black people, as are annular and circinate papular rashes. Such rashes may resemble granuloma annulare, annular sarcoid or scaly varieties of tinea.

On macerated skin surfaces and mucous membranes, eroded weeping papules with a tendency to hypertrophy often appear. On the genitals, for example, at the penoscrotal junction, there may be small, eroded papules flush with the skin or hypertrophic, coalesced papules (condylomata lata). Such lesions more commonly occur around the anus and the vulva. In men, the papules frequently occupy the entire surface of the glans penis, the coronal sulcus and the inner aspect of the prepuce. Partial or complete acquired phimosis is not infrequent in such cases. The free margin of the prepuce may be a circle of tender fissured ('split') papules. In women, in the axillae and beneath the breasts, small, superficial, eroded, lentil-sized

(about 0.3 cm) papules are sometimes seen, but more typical are hypertrophic papules, which may affect the adjacent mucous membrane. In the last stages of pregnancy, hypertrophic, coalesced, sodden-surfaced papules may be very pronounced. Later, the papules are more irregularly distributed but show a predilection for certain sites, such as the corners of the mouth, angles of the nose, the palms and soles and body folds such as beneath the breasts or in the axillae. The face is often affected, particularly if the patient has greasy skin. The seborrhoeic areas involved are the same as those in acne vulgaris and seborrhoeic dermatitis. Sometimes, the papules form a line along the hair margin, the *corona veneris*.

Hyperkeratotic lesions of the palms and soles may flake, peel and fissure. Hypertrophic papules between the toes may resemble severe tinea pedis.

Micropapular and miliary eruptions. These are especially seen late in the second stage, i.e. about a year or more after infection. Characteristics of such a lichenoid syphilide include small conical or spinular elements, which tend to be arranged in groups of varying size over the body. A *corymbose syphilide* is one with a large central papule surrounded by small satellite papules.

Pustular ulcerative syphilide. These, which characterized the 16th-century epidemic, are now all but unknown. Lesions that most nearly resemble this nowadays are the crusted papules of the scalp, where brushing and combing tears papules, which ooze serum and which may become secondarily infected. Such lesions, unlike other syphilides, may leave scars. Atypical facial plaques or ulcerated nodules (lues maligna) are more common with coexisting HIV infection [6].

Syphilitic alopecia. Patchy hair loss is characteristic of syphilis. The hair falls leaving small, scattered, irregularly thinned, 'moth-eaten' patches of semi-baldness. The eyebrows and beard may be affected [7,8]. Syphilitic alopecia may be accompanied by a more generalized diffuse alopecia associated with generalized infection and anaemia.

Nails. Syphilitic paronychia with secondary onychia is sometimes seen in the secondary stage. It has no special characteristics.

Lesions of the mucous membranes. On the mucous membranes, the basic papular eruptions are less distinctive, but they tend to be symmetrically distributed (Fig. 30.17). As the surface epithelium dies, it turns grey and forms round or oval mucous patches on the palate or inner aspects of the lips and cheeks. These mucous patches may coalesce to form 'snail-track' ulcers. Ulceration is not common. Sharply defined, round or oval lesions devoid of dead epithelium may appear on the tongue and may be associated with flattened papillae. Bilateral syphilitic tonsillitis may coexist, as may syphilitic laryngitis associated with eroded papules and hoarseness.

Generalized lymphadenopathy. Occurs in 50% of secondary syphilis cases. As in the localized lymphadenopathy of primary infection, the nodes are painless, discrete, mobile, rubbery and vary in size from about 0.5–2.0 cm.

Neurological involvement. During the secondary stage, the central nervous system (CNS) may be invaded. Abnormalities in the cerebrospinal fluid (CSF), such as raised cell count and increased protein, can be found in at least 15% of cases. Less often, serological tests are positive in the CSF. The patient may complain of headache only. Occasionally, meningitis may present as paralysis of one or more cranial nerves. Meningomyelitis with paraplegia and double incontinence is rare.

Other systemic features of secondary syphilis include panuveitis [9], periostitis and joint effusions, glomerulonephritis, hepatitis, gastritis and myocarditis.

The lesions of secondary syphilis resolve spontaneously in a variable time period, and most patients enter the latency stage within the first year of infection. In some, especially the immunocompromised, primary or secondary lesions may recur.

Differential diagnosis. The skin manifestations of secondary syphilis are so variable that it must be considered in the diagnosis of all dermatoses that are in any way atypical. Some of these dermatoses have already been mentioned.

With the macular rash, drug eruptions must first be considered. The history, itching and lack of adenopathy aid differentiation. Measles and rubella may cause difficulty, but it is pityriasis rosea that is most often called into question. The presence of a herald patch and the collarette of scales distinguish this condition from macular syphilis.

With papular eruptions, many diseases can cause difficulty in diagnosis, and it has to be remembered that people with seborrhoeic dermatitis or psoriasis can also have syphilis. Lichen planus with its shiny, angled, violaceous lesions, should seldom cause difficulty. Acne vulgaris and seborrhoeic dermatitis may confuse the unwary, as may impetigo and, occasionally, leprosy or tuberculosis if the face is affected. In the anogenital region, condylomata lata have been diagnosed as haemorrhoids and as condylomata acuminata. Balanitis circinata, hyperkeratotic lesions of Reiter's disease and genital herpes may also lead to misdiagnosis.

The micropapular varieties of syphilis can be confused with keratosis pilaris, lichen scrofulosorum, trichophytide and lichen planopilaris. Eruptions of palms and soles may bear a striking resemblance to psoriasis and scaling mycoses.

With oral lesions, the question of aphthae has first to be considered. The painful nature of the lesions contrasts with syphilis and the aphthous lesions are markedly areolated [10]. Tonsillitis or tonsillar papules with lymphadenopathy may make differential diagnosis from infectious mononucleosis a difficult clinical problem. An accompanying morbilliform rash, perhaps precipitated by administration of ampicillin, may add to the confusion, especially as the condition is sometimes accompanied by false-positive serological tests for syphilis.

Latent syphilis

In latent syphilis there are no clinical stigmata of active disease, although disease remains detectable by positive serological tests. In early latency, within 2 years of infection, vertical transmission of infection may still occur, but sexual transmission is less likely in the absence of mucocutaneous lesions. The late manifestations of syphilis subsequently arise, often decades later, in about 25% of those who have latent syphilis.

To establish a diagnosis of latent syphilis, strict criteria are called for. Clinical evidence of active, early, late or congenital syphilis must be absent; the CSF must be normal and a chest X-ray (preferably posteroanterior and left oblique, to view the aorta at a right angle) must also be normal. Positive (reactive) serological tests for syphilis must be confirmed by examination of a second specimen.

The differential diagnosis may be from biological false-positive (BFP) reactions or from other treponematoses, particularly yaws in immigrants to Westernized countries. The presence of a scar of a primary chancre or leukoderma syphiliticum at the back of the neck may be helpful. Yaws is usually acquired by children living in poor rural conditions in the tropics. Presenting in adulthood with positive serological tests for syphilis, they may give a history of yaws or chronic sores or bone pains, or they may know of the disease in their family, school or parish. Some have clinical or radiological evidence of old periostitis in their long bones [11]. Much the same may apply to bejel [12].

Great care is called for in assessing immigrant patients. For example, in the UK, one would hesitate to diagnose old yaws in a West Indian immigrant under the age of 40 years. The WHO declared Jamaica free of yaws in 1950, and it has remained free of the disease. On the other hand, yaws has been recrudescing in West African countries for more than 20 years, and the differentiation of latent syphilis from old yaws in immigrants from that part of the world may now present problems.

Tertiary syphilis

After a period of latency of up to 20 years, manifestations of late syphilis can occur. However, screening for syphilis of 'captive' groups, for example blood donors and pregnant women, has contributed greatly to the prevention of late syphilis. In addition, since the commencement of the antibiotic era, many latent and asymptomatic late syphilitics have happened to receive penicillin or other treponemicidal antibiotics in circumstances unconnected with syphilis ('happenstance antibiotic therapy'). Such inadvertent therapy has also contributed to the decline of late syphilis, so that it is becoming rare in many parts of the Western world including the UK and the USA.

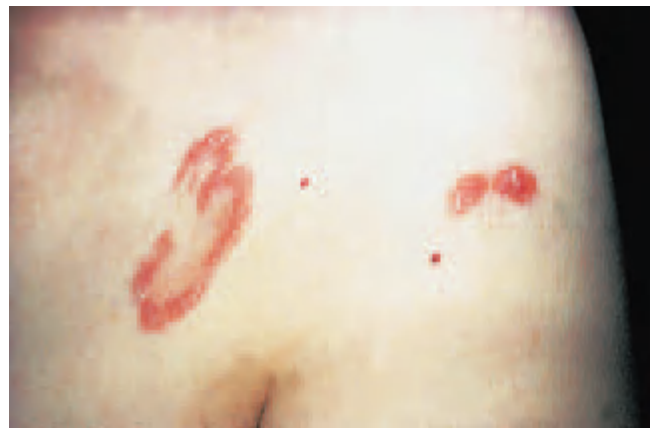

Fig. 30.20 Late syphilis. Coalescing circinate papular lesions. Note the typical coppery red colour. *Treponema pallidum* organisms are not found in such lesions. The clinical diagnosis is confirmed serologically.

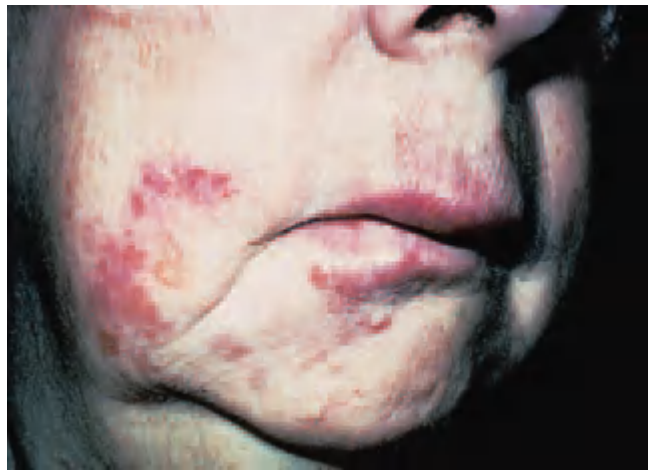

Fig. 30.21 Late syphilis. Nodulocutaneous syphilide in a 62-year-old woman with positive serology. The lesions healed completely within 3 weeks of starting treatment with penicillin.

Late skin syphilis appears in two types: the superficial or nodular syphilide and a deeper gummatous syphilide. Transitional forms also occur.

Nodular or tubercular syphilide (Figs 30.20 & 30.21). The lesions are protruding, firm, coppery red nodules (larger than 0.5 cm diameter). On dependent limbs, they may be cyanotic. The nodules appear in groups with a tendency to a circinate arrangement, i.e. forming interwoven circles

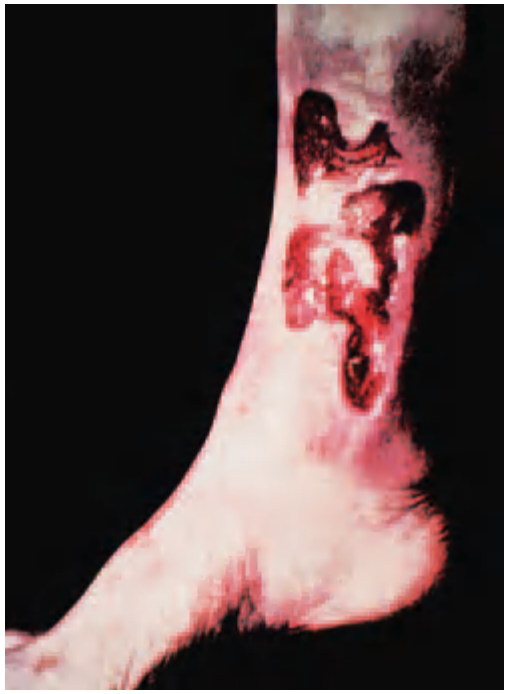

Fig. 30.22 A gumma is a syphilitic swelling with a tendency to ulcerate. The ulcers tend to be 'punched out' in the case of skin gummata.

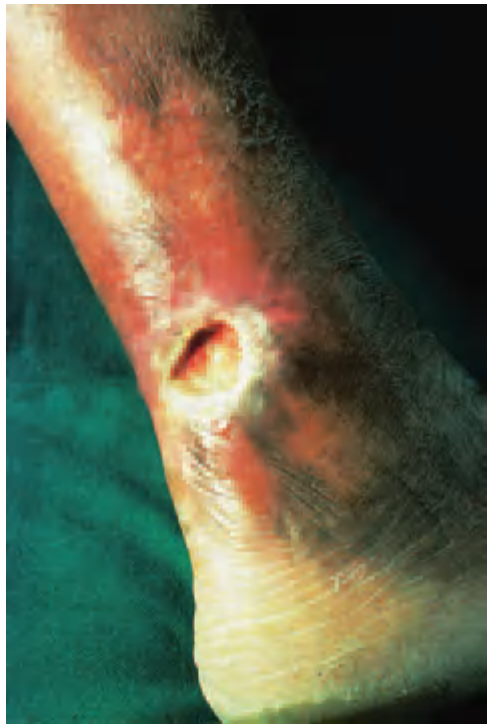

Fig. 30.23 Healing gumma. Delay in diagnosis is suggested by widespread pigmentation and scarring. Response to treatment was slow and the final scarring led to permanent oedema of the foot, sometimes called 'paradoxical healing'.

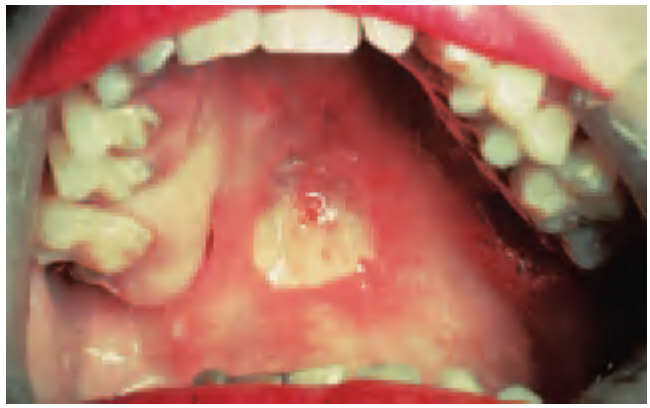

Fig. 30.24 Gumma of the palate. This is a favoured site for such lesions in both acquired and congenital syphilis.

and part of circles. As the disease heals centrally, it extends peripherally. The spread does not take place equally in all directions, so that the outline may be horseshoe shaped, tongued, kidney shaped or serpiginous. Some nodular eruptions resemble granuloma annulare or annular forms of sarcoid. Their histology resembles secondary syphilis. In other cases, the abundance of waxy scales gives the eruption a psoriasiform appearance. Most frequently, serpiginous nodulo-ulcerative eruptions are covered by massive crusts. Even the smallest ulcers have a punched-out appearance.

Lesions of nodular syphilis can appear anywhere on the body, but favour the extensor surfaces of the arms, the back and the face. They are symptomless. Where they have spread extensively, smooth, soft, finely wrinkled ('cigarette paper') central scarring is a feature. In their early stages, these scars may be pink, but after a year or two they are white. Nodular syphilis spreads slowly but more rapidly than lupus, producing a lesion of similar size in months rather than years.

Gummata (Figs 30.22–30.24). The characteristic lesions of tertiary syphilis appear 3–10 years after infection and consist of granulomas or gummata. The granulomas appear as cutaneous plaques or nodules of irregular shape and outline and are often single lesions on the arms, back and face. They have a tendency for central necrosis and ulceration and for peripheral healing with tissue-paper scarring. They most often originate in the subcutis, growing in all directions, i.e. into the dermis and epidermis as well as the deeper tissues. Gummata, which start in bone or muscle, also tend to ulcerate the skin, and their true origin may be difficult to determine. Gummatous changes sometimes take place more superficially with scattered small ulcerations along the margins. This form is difficult to differentiate from a nodular syphilide.

Gummata are usually painless even when they ulcerate. Their central necrotic tissue may turn into a slimy, stringy mass, and it is this that gives rise to the name 'gumma'. Multiple gummata tend to coalesce, the bridges of skin between them gradually undergoing necrosis. Such

ulcerations offer a wide variety of scalloped and geometrical patterns. A 'punched out' appearance is characteristic.

Gummata vary in size from 2 to 10 cm. They favour the scalp, face, sternoclavicular areas of the chest and lateral calf.

Late mucous membrane lesions. Gummata not infrequently attack the palate, both the hard and the soft, with tissue destruction that may lead to loss of the uvula and scarring or perforation of the hard palate. In cases of congenital syphilis, destruction of the nasal septum may also occur producing saddle-nose deformity. They may also cause painless testicular swelling, mimicking a tumour; portal hypertension and portosystemic anastomoses; and diffuse interstitial glossitis. Late syphilis of the tongue may present with localized or diffuse changes, i.e. the solitary gumma or diffuse gummatous infiltration. The latter often passes through a stage of chronic interstitial glossitis with fissuring and, later, obvious leukoplakia with patchy necrosis, sometimes associated with trauma from the teeth. In other cases, changes are more superficial, with red, smooth, glazed areas and loss of papillae. Although sometimes painless, these changes may be accompanied by discomfort on eating hot or acid foods. All the forms of tongue involvement described are recognized as precancerous, so that even after adequate antisyphilitic treatment, regular observation of the patient is an essential element of sound management.

Differential diagnosis. Skin reactions to bromides and iodides commonly deceived the physician in the past. On the face, lupus vulgaris, epithelioma and Bowen's disease can cause diagnostic difficulties. Midline granuloma, sycosis barbae, infiltrated forms of rosacea and lupus erythematosus have all been confused with late syphilis. On the trunk and limbs, it can resemble circinate psoriasis, leukaemic infiltrations and mycosis fungoides. On the legs, gummatous ulceration can look very like a venous ulcer. Bazin's disease may also be simulated.

The changes in the tongue should not be confused with the congenital deformity of scrotal tongue, when the tongue remains quite soft. Where leukoplakia is associated with interstitial glossitis or fibrotic nodules, biopsy is necessary to exclude carcinoma.

The serious forms of neurosyphilis such as tabes dorsalis and general paralysis, and cardiovascular syphilis, although detectable earlier, may take 20 or more years to become clinically evident.

Cardiovascular syphilis

The typical lesion of cardiovascular syphilis is aortitis affecting the ascending aorta and appearing 10–30 years after infection. The aortitis may be asymptomatic and detected as dilatation of the ascending aorta on chest X-ray, often accompanied by linear calcification of the aortic wall, or it may lead to stretching and incompetence of the aortic valve, left ventricular failure or aneurysm formation. Aneurysms may be associated with a variety of syndromes caused by pressure on adjacent structures in the mediastinum, and they may cause sudden death from rupture. Other symptoms include angina pectoris from associated coronary ostial stenosis. Cardiovascular syphilis is more commonly associated with neurosyphilis than with gummatous disease.

Neurosyphilis

Neurosyphilis is characterized by a number of heterogeneous syndromes [13,14]. The differential diagnosis of neurosyphilis covers the whole spectrum of neurological and psychiatric conditions. The onset can occur weeks or decades after treponemal dissemination.

Asymptomatic neurosyphilis. This precedes the development of clinically apparent disease and accounts for one-third of all neurosyphilis. It occurs in 10% of those with latent disease and has a peak incidence at 12–18 months after infection. It reverts spontaneously in 70% of patients.

Meningeal neurosyphilis. This usually has its onset during secondary disease and is characterized by symptoms of headache, confusion, nausea and vomiting, neck stiffness and photophobia. There may be focal seizures, aphasia, delirium and papilloedema. Cranial nerve palsies cause unilateral or bilateral facial weakness and sensorineural deafness [15].

Meningovascular syphilis. This occurs most frequently between 4 and 7 years after infection. The clinical features of hemiparesis, seizures and aphasia reflect multiple areas of infarction from diffuse arteritis.

Gummatous neurosyphilis. This results in features typical of a space-occupying lesion.

Parenchymatous syphilis. This appears later and has become rare in its classic forms in the antibiotic era. The peak incidence of general paralysis from parenchymatous disease of the brain used to be 10–20 years after infection. The onset is insidious with subtle deterioration in cognitive function and psychiatric symptoms that mimic those of other mental disorders. As the disease progresses neurological signs develop, including pupillary abnormalities, hypotonia of the face and limbs, intention tremors and hyper-reflexia.

Tabetic neurosyphilis. This was the most common form of neurosyphilis in the preantibiotic era, with an onset 15–25 years after primary infection. The most characteristic symptom is of lightning pains—sudden paroxysms of lancinating pain affecting the lower limbs. Other early

symptoms include paraesthesiae, progressive ataxia, and bowel and bladder dysfunction.

Syphilis and HIV infection

There is epidemiological synergy between HIV and other STIs [16]. Syphilis increases the risk of HIV acquisition and onward transmission. Infection with HIV may alter the natural history of syphilis.

In most patients with early HIV infection, the clinical features, serological test results and response to treatment are similar to those in non-HIV-infected persons. With advancing immunosuppression, all of these may be significantly altered. Lues maligna, neurological and ocular involvement [17–20] have been reported more commonly.

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Congenital syphilis

Despite the fact that congenital syphilis can be prevented by detection and treatment of infected expectant mothers, it still occurs with distressing frequency in many parts of the world. This is in spite of the long-established cost-effectiveness of public health measures [1], and repeated reminders [2,3] showing that it is not enough to establish control and prevention of syphilis, but to ensure, year in year out, that both are maintained. Only a few countries, the UK included, have achieved and maintained single figures for incidence of early congenital syphilis over more than a decade [1–3]. The need for antenatal testing and treatment is greater in the multiparous than the primiparous. A woman in the early contagious stage will almost certainly infect her unborn child by haematogenous spread of treponemes to and through the placenta. The chances of the fetus being infected in the latent or late stages depends largely on the duration of the expectant mother's infection, and it may be overall as high as 60%. Whether syphilis in the fetus occurs as a first-trimester infection with *T. pallidum* is still debated [4].

The fetus may be overwhelmed by an infection, which is usually more massive than occurs in acquired syphilis. Abortion, stillbirth or early neonatal death are common outcomes. When infections occur late in pregnancy, or are milder, the child is born alive but prematurely. Some children are born apparently healthy and signs may be delayed for days, weeks or months. Children without early signs of congenital syphilis or with unrecognized signs may develop overt symptoms and signs in their teens. The division between early and late congenital syphilis is usually placed at the end of the second year of life.

Incidence. The incidence of congenital syphilis varies from one country to another, and probably depends more on the prevalence of early acquired infection in a country than the quality of the antenatal care [5,6]. In most of the Westernized world it is now rarely seen.

In the UK, the number of cases of congenital syphilis in children under 2 years of age declined from 17 in 1995 to 2 in 1999. The corresponding numbers of cases of congenital syphilis in those aged 2 years or more were, respectively, 27 and 21 [7,8].

The annual incidence of congenital syphilis in infants aged less than 1 year in the USA increased from 3.0 per 100 000 live births in 1980 to a peak of 107.3 per 100 000 live births in 1990. The very large increase in reported cases has been artificially elevated by the introduction of a new reporting system [9–11], which takes account of epidemiological factors, especially maternal treatment status, in addition to cases showing characteristic clinical stigmata. The annual incidence has since declined to 30.4 per 100 000 live births in 1996.

The clinical description of congenital syphilis includes:

1 early congenital syphilis;
2 late congenital syphilis;
3 the stigmata, including scars and deformities that are the consequences of early and later congenital syphilis.

Early congenital syphilis

Many infants with congenital syphilis are asymptomatic at birth. The placenta may show proliferative vascular changes and there may be acute inflammation of the umbilical cord (funisitis) [12]. Early congenital syphilis is manifest as rhinitis with serosanguinous nasal discharge, vesiculobullous eruptions of the skin and oral mucous patches. Skin lesions on the lips, nostrils and anus heal with radiating scars (rhagades). In addition, there are often bone abnormalities, characterized by diaphyseal periostitis, osteochondritis and a positive Wimberger's sign, which may present with limb pseudoparesis. Other features include chorioretinitis, visceral lesions causing pneumonia alba, hepatosplenomegaly associated with jaundice and the nephrotic syndrome.

Mucous membranes. Syphilitic rhinitis, generally described as 'snuffles', is the most important and frequent sign. It is manifest as a profuse, serous nasal discharge in which *T. pallidum* can readily be demonstrated. The inflammatory process can lead to severe nasal cartilage and bone destruction.

The skin. The rash resembles the acquired papular rash in being coppery red. Individual lesions may be relatively large. They are chiefly found on the extremities, especially the palms and soles, which may show a homogeneous, shiny, coppery red infiltration. Lesions on the face may present as deeply fissured ('split') papules at the angles of the mouth or lateral to the external nares. The eruptions often become papulosquamous and anal condylomas may be present. Paronychia is said to be typical. *Treponema pallidum* can be demonstrated in serum from any of these lesions.

'*Pemphigus syphiliticus*' occurs in some babies. The bullae most commonly occur on the red infiltrated palms and soles described in the previous section. Their serous contents contain abundant active treponemes. The bullae of staphylococcal impetigo (pemphigus neonatorum) erupt on normal skin. Other bullous diseases in neonates are described elsewhere (Chapter 40).

A napkin dermatitis is sometimes mistaken for syphilis. The syphilitic papules are generally less 'hypertrophic' and the appearance less eczematous than in napkin dermatitis.

Other features. Osteochondritis is an early and common sign. In a 1985 study in Zambia, X-ray changes were found in 95% of 202 cases less than 6 months of age [13]. Osteochondritis occurs at the end of long bones, particularly the lower end of the tibia and fibula. The zone between the bone and the cartilage becomes broad and irregular. It shows as a very tender, painful swelling and may lead to Parrot's pseudoparalysis. Even without treatment, it tends, like other signs, to disappear within the first year of life. It may be confused with rickets or trauma from physical abuse.

Later, there may be periosteal changes or, more rarely, a characteristic osteomyelitis syphilitica in one or more phalanges *(syphilitic dactylitis)*.

Hepatosplenomegaly and splenomegaly, sometimes with jaundice, are common, as is anaemia. Thrombocytopenia has been demonstrated [14]. Meningitis and meningoencephalitis with convulsions have been described, with bulging of the fontanelle, neck stiffness and, later, hydrocephalus and severe intellectual impairment. Choroiditis may occur, but anterior uveitis is rare.

Late congenital syphilis

In late congenital syphilis (presenting after 2 years of age) there may be a variety of skeletal developmental defects and a characteristic facies. Dental abnormalities occur. Other features include hydrocephalus and mental retardation, as well as other typical lesions of gummata and neurosyphilis.

The common problem is to differentiate latent or late acquired syphilis from late congenital syphilis. In some patients, the situation is further complicated by the possibility of non-venereal treponematoses. The results of serological tests for syphilis (STS), both reaginic and specific, are of marginal help at best. One must rely on a thorough history, including antibiotic history, and clinical examination to establish a diagnosis of late congenital syphilis. The examination of the mother and siblings, often essential, may have to be augmented by the examination of a spouse and children.

Late congenital syphilitic eruptions of skin and mucous membranes are essentially like those of late acquired syphilis, for example nodular syphilides, gummata and periostitis. Signs characteristic of congenital syphilis alone must therefore be sought. They are of great diagnostic importance as they generally appear in children from 5 to 16 years of age.

Interstitial keratitis. This is the commonest and most serious late lesion [15]. It is rare before 6 years of age and over 40 years of age [16]. Both eyes are usually affected and recurrences are recognized. Attacks may have a 3-month course. There is spotty or diffuse clouding of the cornea, with pronounced ciliary and pericorneal injection. 'Brush-like' vessels are seen penetrating from the sclera into the deeper layers of the cornea. This vascularization is best seen with a slit lamp [17]. Vision is soon affected, and photophobia and pain are marked features. Iridocyclitis and choroidoretinitis may coexist. The condition is not directly influenced by antisyphilitic treatment. Patients must be referred to an ophthalmologist. Corticosteroid eye drops or subconjunctival injections are indicated, and may well

have to continue for 3 months or longer to prevent relapse of this 'allergic' phenomenon [18]. Corticosteroid therapy, if well supervised, almost certainly eliminates the danger of blindness.

Clutton's joints. This is a painless synovitis affecting the knees. Apart from increased joint space there are no radiological findings. The condition resolves spontaneously over several months. It is uninfluenced by antisyphilitic treatment [19].

Bone involvement. Periostitis of the long bones is common, particularly of the tibiae, which may become thickened and bent anteroposteriorly ('sabre tibiae'). Exostosis and eburnation may occur. Rarely, there may be changes in the inner ends of the clavicles or localized destruction of the outer table of the skull. Gumma of the palate is common, with residual perforation of the hard palate. A similar condition of the vomer is well recognized.

Eighth-nerve deafness (neurolabyrinthitis). This is a characteristic and moderately common complication. It is eventually bilateral in most cases. It may follow interstitial keratitis after some years. Tinnitus and vertigo are common prodromal symptoms and may continue and accompany the increasing perceptive deafness. The condition is uninfluenced by antisyphilitic treatment. Corticosteroid treatment has a variable beneficial effect in a modest majority of cases [20].

Cardiovascular syphilis. If it occurs at all, it is extremely rare [21,22].

Neurosyphilis. Cerebrospinal changes are not rare. Juvenile general paralysis may start between 6 and 21 years of age. Tabes is less frequent.

Third-generation congenital syphilis. The possibility of third-generation congenital syphilis is very small.

Stigmata

Lasting changes in the shape of scars and defects caused by congenital infection have diagnostic importance in distinguishing it from acquired syphilis.

The teeth. One of the most common and characteristic stigmas is deformity of the upper, central incisor teeth [23]. These so-called '*Hutchinson's teeth*' are due to defective development of permanent teeth buds, and are often associated with abnormalities in the development of the upper jaw (Figs 30.25–30.27). The incisors are conical or barrel shaped, with a degree of notching at the free edge. They may be well separated and converge or diverge. Some are described as 'screwdriver teeth'. Rarely, other incisors may

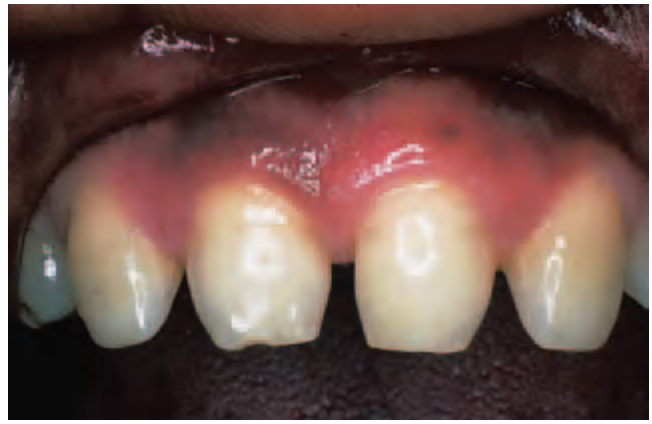

Fig. 30.25 Late congenital syphilis. The upper central incisors may be peg- or barrel-shaped. They are called 'Hutchinson's teeth'.

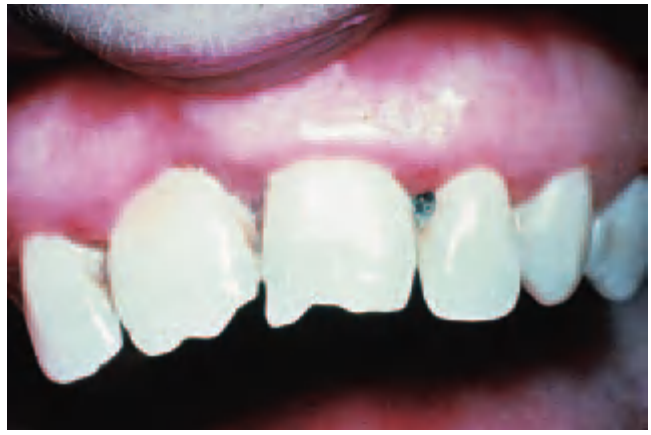

Fig. 30.26 Hutchinson's teeth are commonly notched at the free margin.

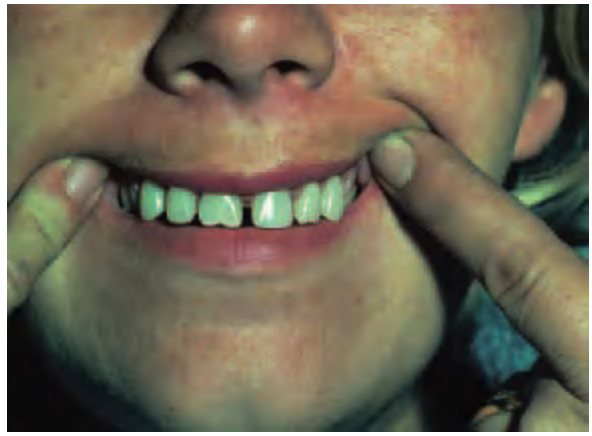

Fig. 30.27 This 32-year-old woman, referred with positive serology from an antenatal clinic, had insisted on an impression of her teeth being taken before extraction. She had been wearing artificial Hutchinson's incisors for 2 years.

Table 30.1 Features of congenital syphilis. (Modified from Parish [24].)

	Early	Late
Birthweight	Low birthweight: may be < 2500 g	
Mucocutaneous	Snuffles	Rhagades
	Maculopapular rash	Gummata
	Pustules	Palatal perforation
	Mucous patches	
	Condylomata lata	
	Vesiculobullous lesions	
	Rhagades	
	Desquamation	
	Alopecia	
Dental		Hutchinson's teeth
		Mulberry molars
Laryngeal	Hoarse cry	
Ocular	Chorioretinitis	Interstitial keratitis
	Uveitis	Uveitis
	Glaucoma	Glaucoma
Gastrointestinal	Hepatosplenomegaly	
	Pancreatitis	
	Enteritis	
Renal	Nephritis	
	Oedema and ascitis	
Lymphatics	Lymphadenopathy	
Haematological	Thrombocytopenia	
	Anaemia	
	Disseminated intravascular coagulation	
Central nervous system	Aseptic meningitis	Mental delay
	Chronic meningovascular syphilis	8th-nerve deafness
	Cranial nerve palsies	Convulsive disorders
	Hydrocephalus	Paresis and paralysis
		Tabes dorsalis
Skeletal	Periostitis	Periostitis causing frontal and parietal bossing
	Osteochondritis causing pseudoparalysis	Sabre tibiae, scaphoid scapula
	Osteitis	Thickening of medial part of clavicle
		Short maxilla and protuberant mandible
		Saddle nose
		Clutton's joints

show damage, or the teeth are irregularly spaced. Another deformity, not so characteristic, is the 'mulberry molar'—usually the first molar—which has a flat, occlusive surface with only poorly enamelled rudiments of the usual cusps.

Interstitial keratitis, Hutchinson's teeth and eighth-nerve deafness form '*Hutchinson's triad*'. Other stigmata are rhagades at the corner of the mouth, broad-based, saddleback nose, 'dish face', Parrot's nodes on the skull, the 'pepper-and-salt' fundus, due to scarred choroiditis, and optic atrophy.

The features of congenital syphilis are summarized in Table 30.1 [24].

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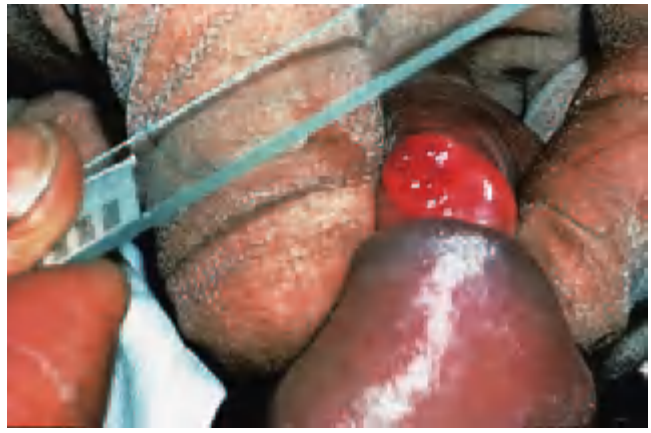

Fig. 30.28 Typical solitary, regularly edged, regularly based and indurated primary sore or chancre. Cleaned with saline and firmly rubbed with dry gauze it oozes serum. In view of endarteritis, bleeding is nearly absent. A specimen is being taken for dark-field microscopy.

Tests for syphilis

Dark-field microscopy

Treponema pallidum can be identified from lesions of primary, secondary or early congenital syphilis by dark-field microscopy. In primary syphilis, it makes the diagnosis possible before measurable antibodies appear. In secondary syphilis, it provides immediate confirmation of a clinical diagnosis. The organism has a characteristic morphology and motility, with a sinusoidal profile and a wavelength and amplitude of 1.1 and 0.4 μm, respectively [1].

The sore should be thoroughly cleaned with saline washes and/or saline compresses. A course of oral sulphonamides may be initiated. Where lesions are dry and crusted, it is necessary to scrape with a Volkmann's spoon or open scarifier. Suspected secondary lesions almost always require scarifying, and patience is needed if *T. pallidum* is to be demonstrated. Time must be allowed for red cells to settle so that clear serum can be obtained for microscopy (Fig. 30.28).

If the lesion is syphilitic, bleeding will not be marked. After scraping, some 5 min should be allowed for red cells to settle. The serum can then be collected and examined. Special care is indicated when assessing treponemes found in serum from oral lesions. If a suspected primary lesion has been treated with antiseptic or antibiotic remedies or if there is a marked secondary infection of the sore, the examination may not be successful. Repeat testing on two or more consecutive days is advised.

In all highly suspect genital and/or oral lesions where it proves impossible to demonstrate *T. pallidum*, lymph-node puncture material, mixed with injected sterile saline (0.5 mL), should be examined. Any treponeme found will always be *T. pallidum*.

In women, some 25% of the primary sores occur on or in the uterine cervix. A primary sore may be obvious on examination. In other cases, the cervix is oedematous, enlarged and pale. The suspicion that there is a primary lesion in the cervical canal can be confirmed by dark-field microscopy of material obtained 'blindly' from the cervical canal by a platinum loop. *Treponema pallidum* has also been demonstrated in material from the apparently healthy cervical canal of named contacts of early syphilis.

The organism can also be identified by direct immunofluorescent antibody testing where no facilities for dark field microscopy exist.

In biopsy specimens from late syphilis, or in atypical early lesions, it may be possible to identify the organism by silver stains such as Warthin–Starry preparations or by direct immunofluorescent antibody testing.

Molecular amplification tests

Polymerase chain reaction (PCR) diagnosis has been based upon primers and probes prepared from the 47-kDa gene. After a 40-cycle series of denaturing, annealing and extension, the PCR products can be visualized by electrophoresis or Southern blot hybridization with a ^{32}P-labelled probe and then autoradiography. This technique should be of greatest value in detecting the low numbers of treponemal products in neurosyphilis; it should also be useful in congenital syphilis, in which the interpretation of serological test results may be difficult. Molecular amplification tests have also been successfully used in multiplex systems to investigate the aetiology of genital ulcers.

RNA amplification is more sensitive than PCR, and positive results are indicative of living organisms. The reverse-transcriptase PCR uses the 16 S ribosomal RNA of *T. pallidum* as the template.

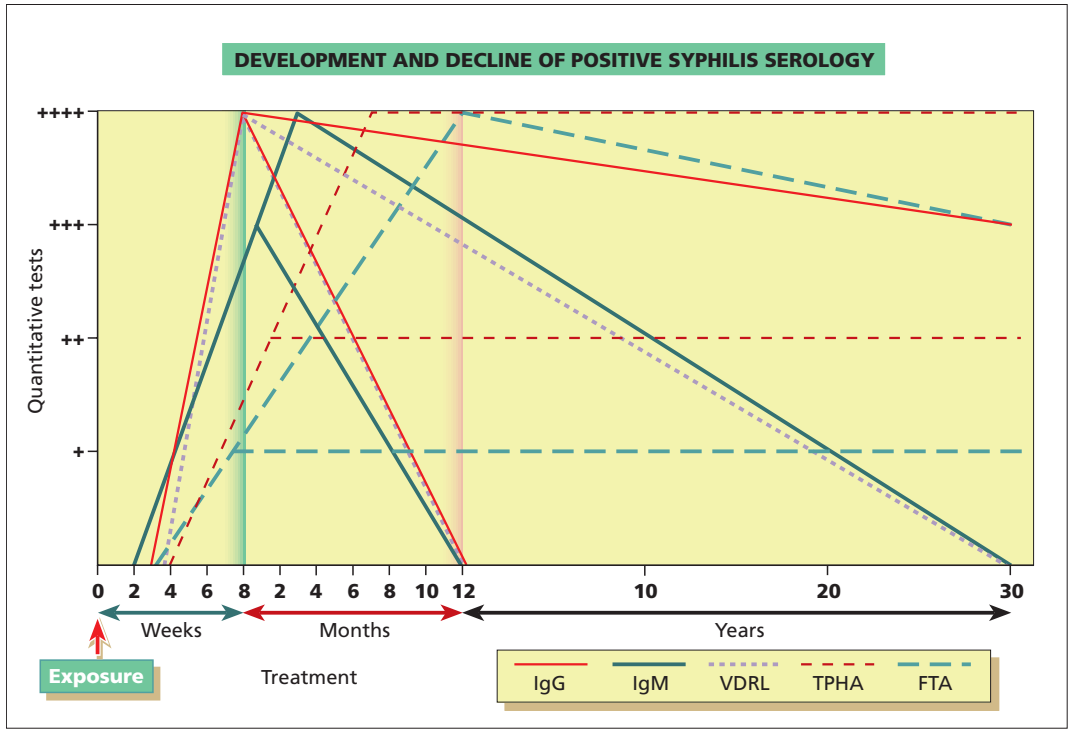

Fig. 30.29 Serological responses in syphilis as prompted by early infection, time and treatment.

Recently, molecular diagnosis on lymph node biopsy specimens has been described [2].

Serological tests (Fig. 30.29)

The STS and serological tests for other treponematoses can be divided into reaginic or non-treponemal tests, and specific or treponemal tests. The antibodies detected by the treponemal tests may be further divided into those generated by specific antigens, present only in pathogenic treponemes, and those shared with non-pathogenic treponemes (group antibodies). This distinction has significance in so far as different types of antibody may influence results of several serological tests. The immune responses in all the treponematoses appear to be the same, and there is no test that will differentiate one treponematosis from another.

Standard non-treponemal tests. The non-treponemal tests detect IgM and IgG antibodies to lipoidal material released from damaged host cells and to lipoidal-like antigens of *T. pallidum*. There are four tests available that use the venereal disease research laboratory (VDRL) antigen (consisting of cardiolipin, cholesterol and lecithin) as the principal component. These tests are quantitative and are useful in assessing response to treatment. Reactivity to these tests does not develop until 1–4 weeks after the chancre appears in primary syphilis. Titres are highest in secondary syphilis. The prozone phenomenon occurs in 2% of sera; undiluted sera give negative results because of antibody excess, the presence of blocking antibodies, or both. The titre slowly declines after the 1- to 4-week period following the appearance of the chancre, and it may spontaneously become negative in some cases of late latent syphilis and neurosyphilis.

The VDRL slide test is widely used and requires the microscopic demonstration of antigen–antibody flocculations in heat-inactivated serum.

The unheated serum reagin (USR) test is similar to the VDRL test but does not require preheated serum, because the antigen has been stabilized.

The rapid plasma reagin (RPR) test and toluidine red unheated serum test (TRUST) use either charcoal or red paint pigment added to the USR reagent to enhance visualization of the antigen–antibody flocculations. The flocculations are visible macroscopically. This test can be performed in consulting rooms, clinics and laboratories where facilities, experience and personnel are limited.

Treponemal antigen tests. Specific treponemal antibody tests are used for confirmatory testing. They detect antibodies to antigenic determinants of treponemes. They are qualitative procedures and are not helpful in assessing treatment responses; once positive, they tend to remain positive for life, irrespective of treatment. They are used to differentiate true-positives from false-positives in the standard non-treponemal antibody tests.

The hunt for a test giving 100% sensitivity and specificity has gone through several stages. In 1949, Nelson and Mayer [3] proved that serum from syphilitic patients contains an antibody, which in the presence of complement inhibits the normal movements of virulent *T. pallidum* (specific treponemal immobilizing antibody). For this test—the *T. pallidum* immobilization (TPI) test—virulent *T. pallidum* (the Nichol's strain) is obtained from rabbits. The reaction of the treponemes in the presence of the patient's serum is observed by dark-field microscopy. If 50% or more of the treponemes are immobilized, the test is reported as positive: if less than 20%, it is negative. In 99% of cases, the result is very clear-cut and certainly very specific, probably nearly 100% [4,5]. The test is time consuming and therefore expensive.

The TPI becomes positive a few days to a week later than the reagin tests, i.e. later in the primary stage. In the late stage it is almost always positive, although a negative result may occur. The great importance of the TPI has been its specificity, making it possible to distinguish BFP reaginic reactions from genuine positives.

With early treatment of syphilis, the TPI may become negative. However, if the disease has been untreated for more than 5–6 months, the reaction is likely to remain positive for the rest of the patient's life, despite any later treatment. The TPI became a 'gold standard'.

The fluorescent treponemal antibody absorption (FTA-ABS) test [6–8] and the FTA-ABS double-staining (FTA-ABS DS) test are both indirect immunofluorescent tests. The double stain test employs a fluorochrome-labelled counterstain for *T. pallidum* and an antihuman IgG conjugate labelled with tetra-methyl rhodamine isothiocyanate to detect antibody in patient serum. False-positive results may occur in about 1% of sera; possible causes include technical error, Lyme borreliosis, pregnancy, genital herpes, alcoholic cirrhosis and connective tissue diseases such as systemic lupus erythematosus and scleroderma.

The *Treponema pallidum* haemagglutination assay (TPHA) was first described by Rathlev in 1967 [9]. A microtechnique has since gained popularity. In all forms, the TPHA is simple to perform and results are readily reproducible [10]. The test is very sensitive and specific [11,12]. The microhaemagglutination assay for antibodies to *T. pallidum* (MHA-TP) detects passive haemagglutination of erythrocytes sensitized with ultrasonicated Nichol's strain *T. pallidum*. In many laboratories, the TPHA has been replaced by the similar *T. pallidum* particle agglutination (TPPA) test that uses gelatin particles rather than erythrocytes as the carrier. It is more sensitive than the FTA-ABS.

Treponemal enzyme immunoassay (EIA) commercial tests were initially designed as confirmatory tests for syphilis [13]. Serum is added to microwells coated with a treponemal antigen. After incubation, an enzyme-labelled antihuman immunoglobulin conjugate and enzyme substrate are added to detect antigen–antibody reaction. The test can be modified to detect specific IgM antibody.

Western blot. Treponema pallidum Western blot is available in some research laboratories and has similar sensitivity and specificity to the FTA-ABS test [14]. The presence of antibodies to the immunodeterminants with molecular weights of 15.5, 17.5, 44.5 and 47 kDa appears to be diagnostic for acquired syphilis. When an IgM-specific conjugate is used, the test has value in the diagnosis of congenital syphilis.

Guidelines for serological screening

There are many commercial tests in any given format whose performance characteristics vary. Recent studies suggest that a treponemal EIA used as a single test is an appropriate alternative to the combined VDRL/RPR and TPHA screen. It has a higher specificity than the FTA-ABS. The test also has advantages of automated or semi-automated processing and objective reading of results, and can be interfaced with laboratory computer systems to allow electronic laboratory report generation.

Screening can be performed by either EIA or the combined VDRL/TPHA. Positive results are confirmed with a treponemal test of a different type. It is essential to confirm the presumptive serological diagnosis of syphilis on a second patient specimen.

Biological false-positive reactions

All the tests in use can produce BFP results. Reagins can be found in the blood of most normal people, and it is possible to make tests for reagins so sensitive that a high percentage of positives can be demonstrated. Some apparently healthy persons produce reagins in excess. They are classified as BFP reactors. Biological false-positive reactions may be acute or chronic, i.e. they last less than or more than 6 months. The same occurs in association with acute and chronic diseases. Persistently low-titre positive reagin tests with repeatedly negative treponemal tests are the rule in acute BFP reactions. They rarely last more than 3 months. Strongly positive reactions are more common in chronic BFP reactors.

Among the commonest associations with acute BFP reactions are the following: malaria, leprosy (especially the lepromatous form) [15,16], typhus, respiratory tract infection (especially viral pneumonia), infectious mononucleosis, active pulmonary tuberculosis, hepatitis, subacute bacterial endocarditis, measles, chickenpox, filariasis, trypanosomiasis, leptospirosis and relapsing fever. Biological false-positive reactions are also reported in connection with pregnancy [17] and narcotic addiction.

Chronic BFP reactions are associated with 'collagen', autoimmune diseases and dysgammaglobulinaemia.

Chronic BFP reactions may exist for some time and herald the onset of 'collagen' disease by some years; for example, systemic lupus erythematosus (especially in rhesus-negative women), polyarteritis nodosa and rheumatoid arthritis [18,19].

Not all authors agree that the VDRL is the most likely test to be associated with BFP reactions. One study, which concentrated on the phenomenon associated with dermatological diseases, found that the FTA and FTA-ABS tests most often produced BFP reactions [20]. In some elderly persons, BFP reactions with FTA-ABS are associated with connective tissue diseases and, in addition, in healthy people with the prescence of 'rheumatoid factor'; but ageing itself may be responsible [21–23].

A completely new cause of false-positive FTA-ABS was described in 1986 by Hunter *et al*. [24] at the Centers for Disease Control and Prevention (CDC) in Atlanta, USA. They investigated patients with Lyme disease and compared their serological findings with specimens from patients with syphilis. Cross-reactivity with the causative spirochaete of Lyme disease could be absorbed out with *T. phagedenis* (Reiter's strain).

Examination of CSF

Indications for examination of CSF in syphilis include:

- neurological, ophthalmic, or auditory symptoms and signs;
- other clinical evidence of active infection—aortitis, gumma, iritis;
- treatment failure;
- HIV infection;
- serum non-treponemal titre of more than 32 if duration of syphilis is over 1 year; and
- non-penicillin-based treatment regimen planned.

Many syphilologists consider an examination of CSF unnecessary in the second stage, but prefer to examine it before discharging the patient as cured, after 1–2 years post-treatment follow-up. In untreated asymptomatic syphilis, a CSF examination should always be done. A normal CSF is by definition an essential prerequisite for a diagnosis of latent syphilis.

The typical CSF findings of neurosyphilis consist of:

- moderate mononuclear pleiocytosis (10–400 cells/mL),
- elevated total protein (0.46–2.0 g/L), and
- positive CSF VDRL.

The CSF VDRL is highly specific and false-positive results are rare in the absence of blood contamination. A negative CSF VDRL does not exclude neurosyphilis, although non-treponemal serological tests usually remain positive in both serum and CSF in such cases.

Reactivity to tests using treponemal antigens, particularly to the FTA-ABS test and/or TPHA test, may be caused by transudation of *T. pallidum*-specific IgG from the serum of patients with adequately treated disease, and therefore is not necessarily a sign of active CNS involvement. On the other hand, non-reactivity of the CSF to these assays in all probability excludes the diagnosis of neurosyphilis.

Evaluation of neonates for congenital syphilis

It is recommended that the following investigations be carried out in the children born to seropositive mothers if there has been no documented treatment completion at least 4 weeks before delivery, or if a non-penicillin regimen was administered, or if relapse or reinfection is suspected:

- examination for stigmata of congenital syphilis;
- X-ray long bones for evidence of periostitis; and
- CSF examination.

Infection of the neonate is also suggested if the serum non-treponemal antibody titre is four or more times more than the mother's, or if specific IgM treponemal antibody tests are positive. Passively transferred maternal IgG antibody can persist in the infant's serum for up to 12 months [25].

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Management of syphilis

Overview (Table 30.2)

Current treatment regimens are based on over 50 years' clinical experience with penicillin, expert opinion and open clinical studies rather than on randomized clinical trials [1–4]. Many antibiotics, with the notable exceptions of the aminoglycosides and sulphonamides, have some treponemicidal activity, and their administration for other conditions may abort or modify the natural history of syphilis [5].

Parenteral penicillin G is the preferred drug at all stages of syphilis; the preparations used, the dosage and the duration of treatment depend on the clinical stage and disease manifestations. Penicillin remains not only the most effective treponemicide, but it is easy to administer, has few side effects and is relatively inexpensive. Results continue to be excellent in all forms and stages of treponemal disease, and there are no signs that *T. pallidum* has developed resistance to this antibiotic. Injectable penicillins are generally preferred to oral preparations, because of problems of patient compliance and uncertain absorption from the gastrointestinal tract.

Adequate treatment requires the maintenance of serum concentrations in excess of 0.03 U/mL for at least 10 days. A 600 000 U i.m. single dose of aqueous procaine benzylpenicillin (procaine penicillin) gives an effective serum concentration for at least 24 h; in comparison, 2 400 000 U i.m. single dose of benzathine penicillin G maintains effective levels for about 2 weeks. As this preparation may cause pain on injection, 1.2 mU are usually given in the upper and outer quadrant of each buttock.

Treatment of late syphilis theoretically may require a longer duration of therapy because organisms are dividing more slowly; however, the validity of this concept has not been addressed. The penetration of aqueous procaine benzylpenicillin into the CSF (as into the aqueous humour) is poor; that of erythromycin is poorer and that of benzathine penicillin, poorest of the three [6–8]. For treatment of neurosyphilis, high dosages of crystalline benzylpenicillin G plus probenicid should be considered. Desensitization of penicillin-allergic patients is recommended.

In patients who are hypersensitive to penicillin, regimens based on tetracycline, doxycycline, erythromycin, ceftriaxone and chloramphenicol have all been successfully used to treat syphilis; however, success is less assured than with penicillin. Azithromycin, given in dosages of 500 mg daily for 7 days, has recently been successful but experience is limited.

All patients with syphilis should be offered screening for other STIs and HIV. Serological testing for HIV should be repeated after 3 months in those persons presenting with primary syphilis who initially test negative.

Pregnant women. Only penicillin-based regimens have documented efficacy and desensitization should be considered in those who are allergic. Those women who have had documented treatment for syphilis in the past do not need retreatment in the current or subsequent pregnancies so long as there is no clinical evidence of syphilis, and the VDRL or RPR titre is negative.

First-line treatment is with procaine benzylpenicillin G. Benzathine penicillin regimens are generally not recommended. Alternative drug therapies include erythromycin or azithromycin.

Treatment of syphilis in HIV seropositive individuals. It is recommended that a CSF examination be performed in all patients with syphilis who are HIV seropositive, and that a penicillin-based regimen appropriate for neurosyphilis, regardless of the stage of infection, is administered. As *T. pallidum* can persist in the CNS in spite of adequate antibiotic treatment, some clinicians have recommended that chronic maintenance treatment be administered after initial formal treatment. Erythromycin has been reported to be ineffective. Close follow-up is essential, and CSF examination may be repeated after 6 months.

Treatment of congenital syphilis. The optimal treatment of congenital syphilis is unknown. Regimens that have been recommended for early congenital syphilis are aqueous crystalline penicillin G 100 000–150 000 U/kg/day i.v. given as 50 000 U/kg every 12 h for the first 7 days of life and every 8 h thereafter for a total of 10 days. An alternative is procaine benzylpenicillin G 50 000 U/kg/dose i.m. daily for 10 days for infants with normal CSF findings; intravenous benzathine penicillin 50 000 U/kg/dose i.m. in a single dosage has also been successful. In children who are identified as having reactive serological tests for syphilis after the neonatal period, maternal serology and records should be reviewed to assess whether the child has congenital or acquired syphilis. Any child at risk for congenital syphilis should be fully evaluated and tested for HIV infection. The recommended regimen is aqueous crystalline penicillin G 200 000–300 000 U/kg/

Table 30.2 Treatment of syphilis.

	First-line therapies	Dose	Penicillin allergies	Dose
Early syphilis	Aqueous procaine benzylpenicillin	600 000–900 000 U i.m. daily for 10 days	Doxycycline	100 mg p.o. twice daily for 14 days
	or	*or*	*or*	
	Benzathine penicillin	2.4 MU i.m. in single dosage	Erythromycin	500 mg p.o. four times daily for 14 days
			or	
			Azithromycin	500 mg p.o. daily for 14 days
			or	
			Oxytetracyline	500 mg p.o. four times daily for 14 days
			or	
			Ceftriaxone	500 mg i.m. or i.v. daily for 10 days
Late syphilis	Aqueous procaine benzylpenicillin	600 000–900 000 U i.m. daily for 15–21 days	Doxycycline	100 mg p.o. twice daily for 28 days
	or		*or*	
	Benzathine penicillin	2.4 MU i.m. weekly for 3 weeks	Oxytetracyline	500 mg p.o. four times daily for 14 days
	or			
	Amoxicillin	2 g p.o. three times daily for 28 days		
	plus			
	Probenecid	500 mg p.o. four times daily for 28 days		
Neurosyphilis	Benzylpenicillin G	1.8–2.4 g daily for 21 days (given as 0.3–0.4 g i.v. every 4 h)	Consider penicillin desensitization	
	or		*or*	
	Aqueous procaine benzylpenicillin	2.4 MU i.m. daily for 21 days	Ceftriaxone	2 g i.m. or i.v. daily for 10–14 days
	plus			
	Probenecid	500 mg p.o. four times daily for 28 days		
	or		*or*	
	Amoxicillin	2 g p.o. three times daily for 28 days	Doxycycline	200 mg p.o. twice daily for 28 days
	plus			
	Probenecid	500 mg p.o. four times daily for 28 days		

i.m., intramuscular; i.v., intravenous; p.o. *per os* (oral administration).

day i.v. administered as 50 000 U/kg every 4–6 h for 10 days.

In children with late congenital syphilis presenting after 2 years of age, regimens should be the same as those recommended for late acquired disease.

Penicillin reactions

Accidental deaths following treatment are very rare and mainly due to anaphylactic shock reactions to penicillin. In addition to early and late allergic reactions and the Jarisch–Herxheimer reaction, *Hoigne reactions* (acute psychotic symptoms due to procaine in procaine benzylpenicillin) are recognized.

If penicillin is used in patients with a history of allergy, it is advisable to keep the patient under observation for 15–20 min after the injection. An emergency kit should always be available. Many physicians use an alternative antibiotic rather than risk a reaction.

Jarisch–Herxheimer reaction. The Jarisch–Herxheimer reaction is an acute febrile reaction that occurs in many patients within 24 h of commencing treatment. It is mediated by cytokines. Headache, myalgia, bone pains and an exacerbation of skin lesions may accompany the fever. It must be differentiated from penicillin allergy. Patients should be advised that it might occur. Symptoms may be controlled by antipyretics. The fever (38–40°C) rarely persists more than 8 h.

In pregnant women the reaction may induce early labour or cause fetal distress. In late neurosyphilis and cardiovascular syphilis, the Jarisch–Herxheimer reaction can be more serious and may be associated with life-threatening sequelae. Many clinicians advocate a short course of corticosteroids to lessen its effects in these patients; one such regimen is to prescribe prednisolone 30–60 mg p.o. daily for 3 days, beginning syphilis treatment on the third day, and then tailing off the corticosteroid course by reducing the daily dosage by 10 mg each day during the succeeding week.

Follow-up

Follow-up for clinical and serological assessment should be done at 3, 6 and 12 months after the completion of treatment in early syphilis. Recurrence is due more often to reinfection than to relapse.

Reinfections are more likely during the first year after penicillin therapy. Non-treponemal antibody test titres correlate with disease activity and will usually become negative with time after successful treatment. In some patients, who are described as being 'reagin-fast', low titre positivity in these tests may persist for life. Apart from up to 25% of patients treated during the primary phase, the treponemal antibody tests will continue to remain positive after successful treatment.

In late latent or tertiary benign syphilis, a 2-year follow-up is adequate. Quantitative non-treponemal serological testing is repeated at 3 and 6 months, and each 6 months thereafter. Follow-up of cardiovascular and clinical neurosyphilis should be for life.

Treatment failure is suggested by a fourfold increase in titres, less than a fourfold decrease in pretreatment titres within 12–24 months and development of symptoms or signs attributable to syphilis. All treatment failures require CSF examination. In cases of serological or clinical relapse, retreatment with double doses is recommended.

In latent syphilis, a 2-year follow-up is adequate. The same applies to late benign syphilis. In neurosyphilis, it is usual to repeat the CSF examination every 6 months until the cell count has become normal. There is a slower response of the CSF VDRL and total protein. Retreatment should be considered if the cell count shows an inadequate response or if all of these parameters have not returned to normal by 2 years. In cases of serological or clinical relapse, retreatment with double penicillin doses is recommended. Patients treated for neurological or cardiovascular syphilis should be followed up for many years.

Management of sexual contacts

It is recommended that attempts be made to identify, trace and offer further investigation to at-risk sexual contacts. In early syphilis, these are those contacts occurring within 3 months plus the duration of symptoms for primary syphilis, within 6 months plus the duration of symptoms for secondary syphilis and within 1 year for early latent disease. All long-term partners of patients with late syphilis should be offered investigation.

Many clinicians recommend presumptive treatment of all sexual contacts within the 90-day period preceding patient presentation of early syphilis if serological test results are not immediately available and if follow-up cannot be assured.

Prognosis

Cure rates with initial treatment of early syphilis are better than 95%. The long-term outcome of adequately treated cases is excellent. In late syphilis, infection can usually be arrested although some treponemes may persist in less accessible sites (e.g. the eye and nervous system). As long as immune function is normal, this rarely has clinical sequelae. The outlook for HIV-positive and other immunocompromised patients appears to be less assured; however, long-term studies in these patients are needed.

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Syphilis control

The risk factors for acquisition of syphilis mirror those of other STIs and primary prevention depends on similar methods, such as reducing the number of sexual partners and consistent use of condoms. Community outreach activities should target education at persons at high risk. Single-dose treatment with intramuscular benzathine penicillin G and oral azithromycin have been employed as treatment for incubating syphilis [1]. Administration of treponemicidal antibiotics to treat other STIs, such as gonorrhoea and chancroid, may also abort incubating concurrent syphilis. The development of a vaccine against syphilis has long been inhibited by the inability to grow the organism on artificial media, although the recent sequencing of the *T. pallidum* genome should advance new research efforts.

Secondary prevention by early diagnosis, treatment, partner notification [2], education and counselling remain the mainstay of prevention efforts [2,3]. Access to prompt and appropriate services for infected persons are essential. In many developed countries, clinic-based specialist services have long been established. In developing countries, the WHO has recommended that STI management be integrated into basic health care and reproductive health services [4–6].

Serological screening for syphilis remains a cost-effective measure for control. Congenital syphilis may be prevented by maternal screening and treatment during early pregnancy. In Europe, screening remains a routine part of antenatal care, usually at about 12 weeks' gestation. In developing countries, where congenital syphilis is more common, the disease occurs when there has been no maternal screening, when no treatment has been administered in response to positive tests, or when primary infection occurs later in pregnancy. Repeat screening during the final trimester or at delivery is advocated in high prevalence regions [7].

Compared with other STIs, the control of syphilis is relatively easy. It is favoured by a combination of factors:
1 low cost and ready availability of screening test;
2 effective, simple and inexpensive therapy;
3 a long incubation period with a relatively low transmission rate;
4 self-limiting symptomatic periods with long asymptomatic periods of presumably low infectivity.

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Non-venereal treponematoses

Although the endemic treponematoses were eradicated from large parts of the world during the mass treatment campaigns organized by WHO and the United Nations Children's Fund (UNICEF) in the two decades that followed the Second World War, the progress made has not been sustained, and there is evidence of a resurgence in some countries. It is estimated that there are 2.5 million cases worldwide, most of which remain unreported. There is a very patchy geographical distribution, which is strongly influenced by both climatic and socio-economic conditions.

The endemic treponematoses consist of three diseases —endemic syphilis, yaws and pinta.

Characteristics

The causative organisms cannot be distinguished serologically or morphologically. Minor genetic differences have been reported in the causative organism of pinta, *Treponema carateum*, which can only be propagated in primates and is considered to be a separate species. The causative organisms of venereal syphilis, yaws and endemic syphilis are so similar that they are considered as

subspecies of *Treponema pallidum*. These organisms can also be propagated in rodent species. No specific antigenic differences have been demonstrated. Differences have been demonstrated in the *tp15* gene that permits rapid differentiation of pallidum strains from non-pallidum strains by restriction fragment length polymorphism. Further differences have been shown in the *gpd* and *tp92* genes. None of the genetic differences described to date can differentiate non-pallidum subspecies from each other [1].

These diseases have comparable natural histories and principally affect children under the age of 15 years, especially those in the most underprivileged and remote rural communities isolated from organized health and social services [2,3].

Transmission is by direct skin-to-skin contact and is assisted by breaks in the skin, especially in hot and humid conditions, where clothing is scanty. Mouth-to-mouth transmission may also be important in endemic syphilis. Sexual transmission does not play a role and congenital infection does not appear to occur.

The histopathological patterns of disease are similar and only vary in degree and range of tissues affected.

Protective immunity is induced by infection and is subspecies specific. The level of cross-protection is roughly proportional to severity of clinical disease induced by the initial infection.

Like syphilis, they have early (which includes primary and secondary lesions) and late stages of the disease. Lesions of the early stage are generally regarded as infectious or potentially infectious. This lasts for up to 5 years, with periods of latency between symptomatic episodes. All have a relapsing clinical course and prominent cutaneous manifestations. In yaws and endemic syphilis mucous membranes and bones are also infected. Late lesions affecting the cardiovascular and nervous systems are generally considered not to occur.

These infections are usually diagnosed by their typical clinical features, supported by the microscopic identification of their causative treponemes from the serous exudate of cutaneous and mucosal lesions, and serological testing.

Treatment is similar. Long-acting penicillin preparations such as benzathine penicillin G are administered to affected individuals, family members and other contacts. Tetracycline and erythromycin can be used as alternatives. Lesions usually heal within 2 weeks, but healing may be slower in pinta. Response to treatment can be assessed by changes in quantitative serological tests; however, the specific treponemal tests will usually remain positive for life.

So far, there have been no reports of the effect of HIV infection upon these conditions, probably because of the contrasting locations in which STIs and the non-venereal treponematoses are prevalent.

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Endemic syphilis

SYN. BEJEL; FIRJAL; LOATH

Definition. Endemic syphilis is an infectious, contagious, chronic, relapsing, non-venereally transmitted disease caused by *T. pallidum* ssp. *endemicum*. It is a disease of hot and temperate climates characterized by latency interrupted by early infectious lesions and, after several years, by late destructive lesions of the skin and bones.

History. Endemic syphilis was previously seen in Northern European populations where it was known as the *sibbens* in Scotland, *radesgye* in Scandinavian countries and *skerlievo* in the Balkans. It also occurred in Russia and Mongolia. In the Near East and Eastern Mediterranean it is known as *bejel* and in Southern Africa as *njovera* or *dichuchwa*. Social and economic improvements in many of these areas made endemic syphilis a receding disease long before the availability of modern antibiotic treatment.

Aetiology. The causative organism is morphologically identical to other subspecies of *Treponema pallidum*.

Epidemiology. The disease is still encountered in dry desert regions and among children living in rural areas with primitive and unhygienic conditions. It occurs predominately among Sahel peoples of sub-Saharan Africa and nomads of Saudi Arabia. Transmission occurs by direct skin contact, kissing and perhaps by sharing of contaminated drinking cups or household utensils.

Histopathology. This does not show significant differences from that found in venereal syphilis.

Clinical features. The incubation period is usually around 3 weeks if a primary lesion is seen. These most often occur in the mouth and on the lips, and may also be found on the nipples of breastfeeding women.

More often, the disease presents after 3 months in the secondary stage with features that are similar to those of venereal syphilis. Characteristic lesions include mucous patches on the lips and oral mucosa. They may also affect the tongue, pharynx and vocal cords where they cause syphilitic laryngitis. Split papules and angular stomatitis are also seen. A generalized rash, condylomata lata affecting the intertriginous areas and generalized lymphadenopathy also occur. Painful periostitis of the long

bones, with symptoms worse at night, may affect the legs or hands. Untreated, crops of secondary lesions last for 6–9 months, and may recur after an apparent period of latency.

The late stages of endemic syphilis are characterized by gummata of the nasopharynx, which may cause gangosa, and destructive lesions of skin and bone. The development of sabre tibiae and of juxta-articular nodules resembles late yaws. Neurological and cardiac involvement does not occur, but ocular disease including optic atrophy, chorioretinitis and uveitis has been reported.

Attenuated endemic syphilis with reduced severity and numbers of lesions in the secondary and tertiary stages has been reported, in which the most frequent finding was of painful legs caused by osteoperiostitis.

Diagnosis. This is based on clinical features, microscopic identification of the causative treponemes and positive serological tests for syphilis.

Differential diagnosis. This is similar to that of venereal syphilis.

Treatment. The treatment is similar to that of other non-venereal treponematoses. Active infections in adults, as well as non-infectious cases, should be given 2.4 mU i.m. benzathine penicillin in a single injection. The WHO recommends treating all cases and contacts over 10 years of age with 1 200 000 U of benzathine penicillin, and half that amount for children and contacts aged less than 10 years. Tetracycline and erythromycin are the antibiotics of choice in cases of penicillin allergy.

Yaws

SYN. FRAMBOESIA (GERMAN AND DUTCH); PIAN (FRENCH); BUBA (SPANISH); BOUBA (PORTUGUESE); PARANGI (SINHALESE)

[F. Kerdel-Vegas, pp. 30.28–30.34]

Definition. Yaws is an infectious, contagious, chronic, relapsing, non-venereally transmitted disease caused by *T. pallidum* ssp. *pertenue*. It is a disease of tropical rural populations, in areas with high levels of humidity and rainfall, characterized by latency interrupted by early infectious lesions and, after several years, by late destructive lesions of the skin and bones, where the condition is limited. It is a crippling disease; in the late stages it can be very destructive.

History. Bone lesions with probable yaws have been traced to AD 854 on the Mariana Islands in the west Pacific. The disease made its entry to the New World with the black slaves introduced first in the Caribbean islands and then in the mainland of the Americas from the 16th century onwards; ever since it has remained mainly restricted to this population of African origin, especially on the coastline.

The causal organism was discovered by Aldo Castellani in 1906 in Sri Lanka, who described the condition as:

> A horrible disease in which the whole body is covered with red fungating excrescences the size of a cherry and with a granular, raspberry-like surface. The eruption disappears after a few months, but the infection remains dormant, and years later enormous ulcers develop and the bones are affected. The disease is not hereditary and a mother whose whole body is covered with horrible sores will give birth to a perfectly healthy and smooth-skinned baby [1].

Beginning in the 1920s, arsphenamine, neoarsphenamine and bismuth were used successfully in the treatment of yaws, until the efficacy of penicillin was demonstrated by Guimaraes in Brazil and by Findley and coworkers in the Gold Coast in 1943.

The eradication campaigns organized by the WHO and UNICEF in many endemic areas, from 1954 to 1963, surveyed 350 million persons, of whom 42 million received penicillin. The great success of these campaigns explains the lack of interest in a disease considered nearly extinct, but since 1967 there is evidence that yaws is returning in several countries from which it had disappeared.

Incidence. As shown in the map (Fig. 30.30), yaws is found in the Caribbean, Central and South America, throughout tropical Africa, the Far East, northern Australia and the tropical Pacific islands.

Clinically, it is very similar to the other forms of non-venereal syphilis known as bejel (Near East), njovera (Zimbabwe), skerlievo in the Balkans (Bosnia), dichuchwa (Botswana) and siti (Gambia); thus, in general, it can be said that yaws and/or other non-venereal treponematoses are endemic in the whole tropical belt between the tropics of Cancer and Capricorn.

Yaws used to be one of the commonest tropical diseases of the skin [2]. Over 40 years ago (1959), the WHO estimated that yaws affected more than 50 million people in the warm regions of the world, and its largest reservoir is found in Central Africa. Since that time, there have been intensive campaigns designed to eradicate the disease, but there are still 100 million people susceptible to yaws living in endemic areas where little has yet been done. In mass treatment campaigns against endemic treponematoses (mostly yaws) in 46 countries, about 160 million persons were examined during initial treatment surveys; another 400 million re-examinations were carried out during subsequent resurveys, and an estimated 50 million cases and contacts were treated [3]. The WHO and UNICEF-assisted mass campaigns against the endemic treponematoses (yaws, endemic syphilis and pinta) still remain important success stories in the history of medicine [4]. Resurgences of yaws have been reported from

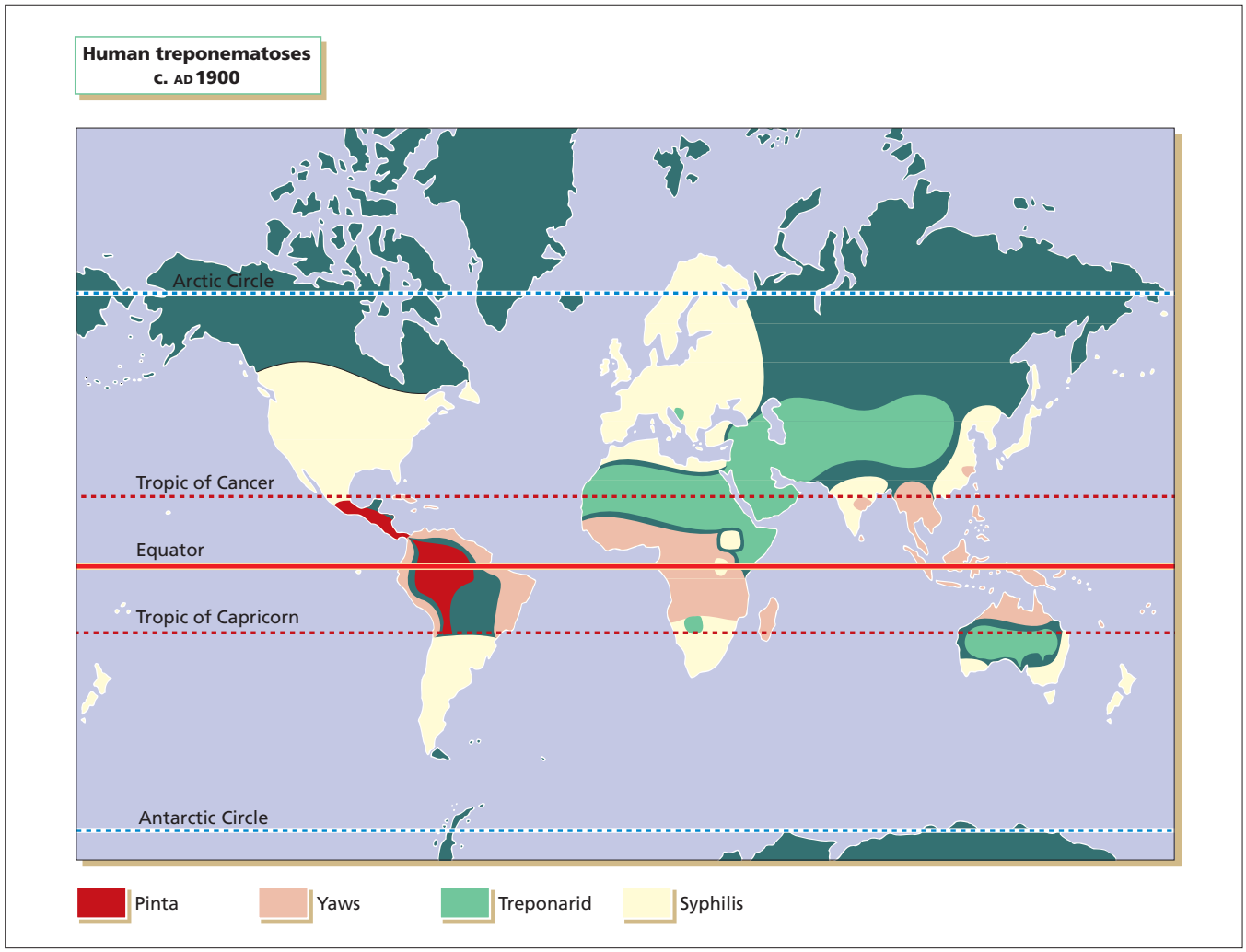

Fig. 30.30 World distribution of the treponematoses.

Karkar Island (on the northern coast of Papua New Guinea), Indonesia, the Solomon Islands, Burundi, Rwanda, Zaire and Ghana. In several African countries, including Ghana, Benin, Togo and the Central African Republic, the situation resembles the precampaign times; in others, such as Nigeria, the Ivory Coast and Mali, increasing seroreactivity has been reported [4].

It is a disease of rural areas, where living conditions are poor. It is said that yaws begins where highways end. Transmission is favoured by overcrowded conditions, where abrasions or other open lesions on the skin are common, and where little protective clothing is worn [4]. A hot or warm climate along with high humidity (over 100 cm of rainfall) lasting for more than 6 months, together with poor socio-economic conditions are requirements for the development of yaws [5]. Mutilating skin lesions due to yaws in the late stage result in severe disability but can be prevented if the disease is detected and properly treated at an early stage.

Aetiology. The aetiological agent is the *T. p. pertenue*, a rigid spirochaete that is 8 µm long and 0.2 µm wide, and has about eight to 16 regular spirals. It divides about every 30–33 h. All the treponemes causing chronic granulomatous diseases are morphologically and serologically indistinguishable; classification into species was based on clinical and epidemiological considerations. They have now all been reclassified as subspecies of *T. pallidum* [6], although clinically the diseases can be differentiated adequately. No serological differentiation between syphilis, yaws, endemic syphilis (bejel) and pinta can be made on the basis of routine laboratory tests. In 1989, Noordhoek *et al.* [7] reported that *T. p. pertenue* differs from *T. p. pallidum* by a single nucleotide. The only molecular difference so far detected between these two subspecies is in one amino-acid residue at position 40, in the subunits of the 190-kDa multimeric proteins TpF1 and TyF1. A difference in the flanking region of a lipoprotein gene has been reported, and this 'genetic signature' can differentiate the several subspecies [8].

Epidemiology. Although the identity of yaws and syphilis is still under discussion, there are important clinical and epidemiological differences between these conditions and it is therefore justifiable to consider them as two separate processes. Yaws is neither venereal nor congenital. It occurs predominantly in childhood—75% of new cases arise in persons under the age of 15 years [9]—and does not affect the CNS or cardiovascular system during its tertiary stage. The primary lesions in yaws are generally extragenital and indistinguishable in appearance from secondary lesions. Yaws is a disease particularly of warm climates and rural environments, whereas syphilis is predominantly an urban disease. It is rightly said that civilization and syphilis go together. Yaws is more frequent in men than in women, and predominantly affects the indigenous population.

The spirochaetes probably cannot enter intact skin, so that several factors are necessary for infection to occur. There must firstly be an individual with an open lesion and an exudate rich in treponemes (as in primary and secondary lesions) and, second, an uninfected person with skin excoriations, abrasions, wounds or bites to provide a portal of entry for the spirochaetes. In addition, there must be contact between these two individuals directly, or through contaminated fomites. The disease is usually acquired by direct personal contact. Mechanical transmission by the *Hippelates* fly has been established but perhaps does not account for a statistically appreciable proportion of cases. New cases appear more frequently during the rainy season.

It has been observed in some African nations from which yaws has been eradicated after a mass treatment campaign that venereal syphilis has risen sharply, suggesting a decline of herd immunity against yaws and, secondarily, to syphilis.

Histopathology. Cutaneous invasion is the most striking feature of the disease, and large numbers of treponemes are found in the epidermis at affected sites.

The epidermotropism of *T. p. pertenue*, compared with the mesodermotropism of *T. p. pallidum*, has been well established [10].

In the primary lesion, considerable acanthosis and papillomatosis are observed. The epidermis is oedematous, and shows a marked degree of neutrophil exocytosis, giving rise to intraepidermal microabscesses. The dermis displays a fairly dense infiltrate consisting chiefly of plasma cells, but neutrophils, eosinophils, lymphocytes, histiocytes and fibroblasts are also present. The blood vessels do not show endothelial proliferation, in contrast with syphilis.

The secondary lesions show similar histological changes to the primary lesions, and in fact closely resemble condylomata lata, from which they differ in that the dermal infiltrate is diffuse rather than essentially perivascular.

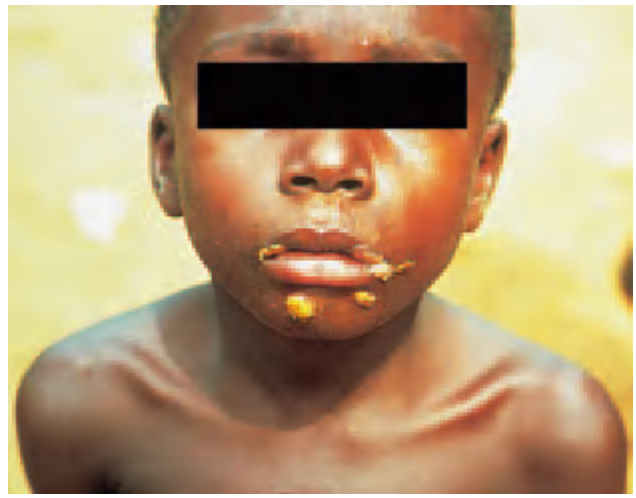

Fig. 30.31 Primary lesions of yaws.

The late lesions are ulcerated, and are very similar to those of tertiary cutaneous syphilis. Despite this clinical similarity, vascular changes are either discrete or non-existent. Keratotic lesions of the palms and soles show no distinctive characteristics. Hyperkeratosis with parakeratosis and acanthosis, and a moderate dermal infiltrate, are seen. It is said that *T. p. pertenue*, as well as *T. p. carateum*, is epidermotropic, contrasting markedly with *T. p. pallidum*, which is mesodermotropic.

Clinical features. As is the case with the other treponematoses, yaws has three distinguishable stages [11], although, as in pinta, they do not display the typical features seen in syphilis. The incubation period varies from 2 weeks to 6 months, although the former is more usual.

Primary stage. This stage is known by the names of protopianoma, buba madre, mamanpian (mother yaw), etc. It is characterized by the appearance, anywhere in the skin where the treponeme enters, of an erythematous infiltrated papule, which later ulcerates and is covered by a yellowish crust formed by the exudate. It grows by peripheral extension or by confluence with small satellite lesions. There is no itching or pain or other subjective symptom. Progressive growth gives rise to a large, raised rounded or oval ulcer, papillomatous or vegetative, bearing some resemblance to a raspberry (Figs 30.31 & 30.32) (the reason why Dutch and German authors originally called the disease framboesia), which bleeds easily but is almost painless. It is covered by serous fluid swarming with the easily identifiable treponemes. It may be accompanied by general symptoms such as fever, joint pains and constitutional disturbance, but these can be overlooked or may be absent. Other manifestations are regional adenopathy, adenitis without periadenitis and large, firm glands that are non-adherent and painless, and do not

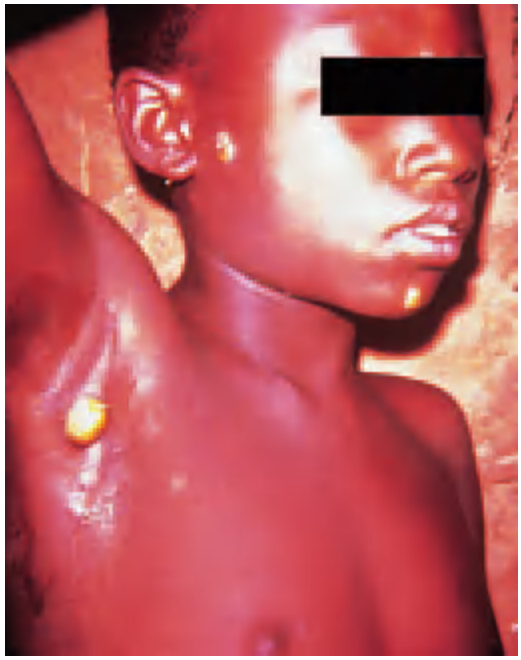

Fig. 30.32 Predilection of primary lesions for warm and moist areas.

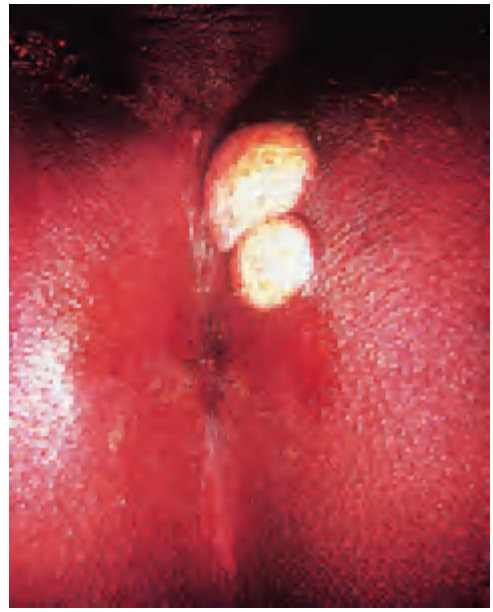

Fig. 30.33 Perianal yaws lesions.

tend to form abscesses. It is estimated that 'decapitated' yaws occurs in about 10% of cases; the mother yaw is not observed and the disease passes directly to its secondary stage.

The mother yaw persists for 2–6 months and heals spontaneously, leaving a large, atrophic and depressed scar, with an achromic or hypopigmented centre sometimes surrounded by a darker halo. Lesions may occasionally persist considerably longer, probably as a result of secondary pyogenic infection.

Secondary stage. After the primary lesion heals, or concurrently between the second and fourth month after the onset of the disease, or sometimes later, the secondary stage sets in, characterized by the appearance of small papules, which rapidly become raised, ulcerated and covered with yellow crusts. These exudative papillomas may resemble ripe raspberries and closely resemble the mother yaw except in size and number. They are termed daughter yaws, pianomas or framboesiomas, and are widely distributed, but are most often seen around the body orifices: mouth, nose, penis, anus and vulva (Fig. 30.33). Two clinical varieties are described: one very large, closely resembling the mother yaw, and the other very small, and known as the 'miniature yaw'. At times, peripheral extension of the framboesioma produces 'circinate yaws' (Fig. 30.34). When the lesions occur on palms and soles, they do not ulcerate but produce hyperkeratotic plaques called foot yaws ('crabs', or 'crab yaws'). When they arise in the periungual region, they produce deformities of the nail fold called pianic onychia.

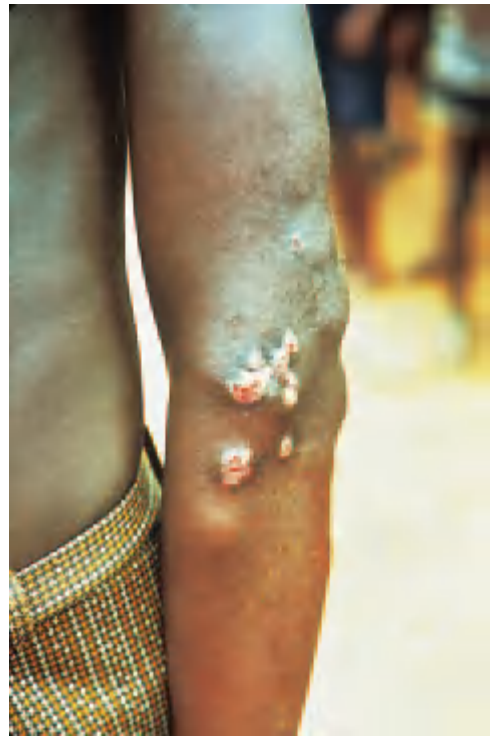

Fig. 30.34 Secondary yaws. Note also the premature subcutaneous gummatous lesions.

The lesions of secondary yaws do not directly involve the mucosa, and the occasional invasion of body cavities is the result of the extension of contiguous framboesiomas. In general, these ulcerative lesions do not develop simultaneously but rather in successive crops of a few lesions. After a variable period of 6 months to 3 years, they

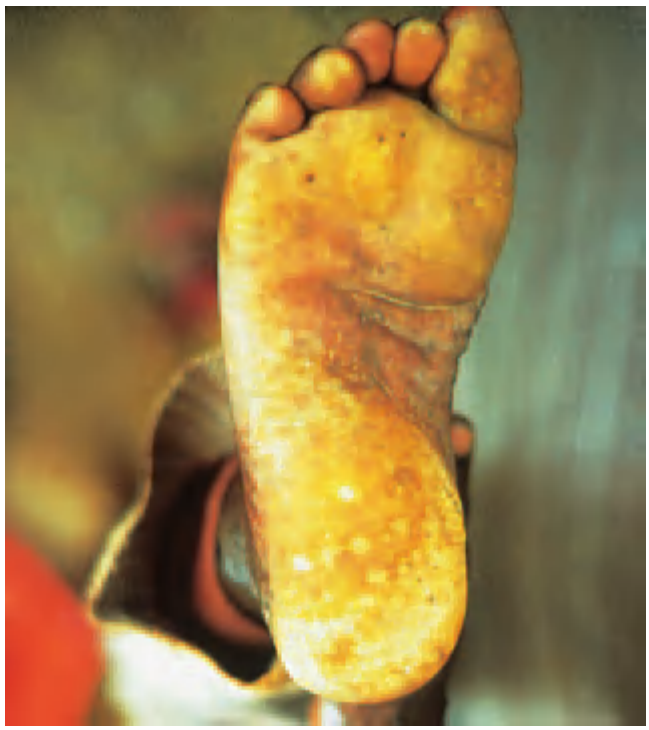

Fig. 30.35 Crab yaws, i.e. the painful fissures of yaws that typically incapacitate adult breadwinners.

Fig. 30.36 Periostitis in yaws may affect the outer table of the skull or the inner ends of the clavicles, but most commonly the long bones. This degree of bowing due to tibial periostitis is markedly severe.

involute, sometimes leaving scars but more frequently only hyperpigmented macules, which disappear completely after some months.

Sometimes, the secondary stage consists only of lenticular, hypochromic macules, which are believed to represent an 'ide' reaction, and are called 'bubides', 'framboesides', or 'pianides' ('yaws of the seven layers'). General symptoms that may precede this eruption include headache, fever, pain in the bones and joints, and generalized adenopathy of the syphilitic type, illustrating the importance of treponemal septicaemia.

After 3–4 years, the disease enters a chronic late phase, or tertiary stage.

Tertiary stage. The late manifestations of yaws affect the skin as well as the bones. The tertiary stage is characterized by ulcerated cutaneous lesions, nodular and tuberous lesions, keratoderma of palms and soles, juxtaarticular nodes, gangosa, lesions of the joints and bones, and goundou [12].

The most frequent sequelae of the disease are keratoderma and hyperkeratoses of palms and soles. These lesions can sometimes appear as raised, rounded nodules, which exfoliate from the trauma of walking, making the patient transfer his or her weight to unaffected areas, causing some degree of disability—'crab yaws' (Fig. 30.35). Also observed are hyperkeratotic plaques without nodules, which can present with fissures oozing serous fluid. Minute craters surrounded by hyperkeratotic papules, similar to keratoderma punctatum and also observed in syphilis, are sometimes seen; they are not painful and are known as 'hormiguillo'.

Periostitis and osteitis are important features of the disease. They are localized mainly in long bones (tibia, forearm), the metatarsals and metacarpals, where there is thickening of the periosteum and a reaction of the underlying bone, which gives rise to pianic osteoperiostitis. The condition is painful; in the tibia, the deformity can involve the entire anterior border of the bone, so that it closely resembles the sabre tibia of congenital syphilis (Fig. 30.36).

Gummatous lesions. In the limbs, particularly in the legs, the formation of subcutaneous nodules occurs. These are small at first, but slowly enlarge. They are hard, mobile and painless, but later tend to soften; the overlying skin ulcerates, allowing thick pus to escape. These are the 'gummatous framboesides'. Healing eventually takes place, to leave atrophic and pigmented scars. Juxtaarticular nodes, described by Jeanselme and Lutz, also appear.

Inflammation of the synovia and tendinous synovitis. Inflammation of the synovia can be observed in the knee, the

Fig. 30.37 Yaws may be intraoral and intranasal with septal and bone destruction.

ankle and the elbow. The entire joint appears encased in a gelatinous mass. These lesions are painful, and can cause severe disability. True synovial cysts also develop along the course of the tendons; they are painless, elastic and mobile, and must not be confused with ganglions.

Gangosa or deforming rhinopharyngitis. Gangosa is a hideous mutilation of the central part of the face (Fig. 30.37), which begins at the base of the nasal fossae or at the septum and, destroying the mucosa and cartilaginous and osseous structures of the septum, the palate and the posterior aspect of the pharynx, produces a cavity at the bottom of which the ethmoid mass can be seen.

The disease should be considered in any patient with an idiopathic septal perforation or nasal deformity (American leishmaniasis also produces these lesions) [13].

Goundou. This term is applied to the exostoses of the nasal bones and neighbouring osseous structures that appear in children who have suffered from secondary pyogenic infection.

Another manifestation of the late stage is so-called rheumatic yaws, producing pain in the joints but no gross objective changes.

Neurological and ophthalmological involvement have been debated, as some reports suggest that disc atrophy, optic atrophy and myeloneuropathies can be part of this disease [14].

Attenuation. Attenuated disease has been described in Surinam, South-East Asia and the Solomon Islands. This type of yaws has been seen during the last decade and is not the classical textbook yaws described above, with profuse collections of abundant, large elevated papillomatous lesions. Instead, a receding, attenuated yaws, characterized by scanty, less florid lesions is seen [15].

Laboratory findings. *Treponema pallidum* spp. *pertenue* is easily isolated from primary and secondary lesions, and can be identified by dark-ground examination or with silver stains. This treponeme can be inoculated into monkeys, rabbits and hamsters. The serological reactions for syphilis are positive in both non-treponemal and specific treponemal antibody tests.

Diagnosis. The country of origin (epidemiologically suspected diagnosis) and the clinical manifestations suggest a tentative clinical diagnosis, to be confirmed by the laboratory tests mentioned above.

Differential diagnosis. Framboesiomas must be differentiated from framboesiform syphilides, framboesoid leishmaniasis and paracoccidiodomycosis. Pianides or bubides may resemble pityriasis rosea, pityriasis versicolor or psoriasis. Syphilis produces keratoderma and infiltrative, ulcerative lesions indistinguishable from those seen in the later stages of yaws [16].

Treatment. Active infections, as well as non-infectious cases, should be given 2.4 mU i.m. benzathine penicillin in a single injection. The WHO recommends treating all cases and contacts over 10 years of age with 1 200 000 U of benzathine benzylpenicillin, and half that amount for children and contacts aged less than 10 years.

When the prevalence of cases with active lesions is above 10% of the population examined, penicillin should be administered to the whole community. When the prevalence is between 5% and 10%, penicillin should be administered to patients, contacts and children of less than 5 years of age. If the prevalence is less than 5%, the treatment should be limited to active cases and their contacts in the same household. Tetracycline or erythromycin, 500 mg p.o. four times daily, is the recommended treatment for patients allergic to penicillin.

Control and prophylaxis. It is very unlikely than non-venereal treponematoses can ever be eradicated (in contrast to the experience with smallpox) due to the fact that patients with these diseases do not develop lifelong immunity and remain contagious for prolonged periods of time. It is also unlikely that an effective vaccine can be developed, again due to the fact that the infection does not confer prolonged immunity [17]. The widespread use of soap has been mentioned as one of the reasons connected with the decline of the disease [1].

As spread of the disease is favoured by poor hygiene and overcrowding, the elimination of these factors will lower its incidence. Contact with patients with ulcerative lesions should be avoided. The use of insecticides reduces

the risk of transmission by a vector. Mass treatment with penicillin has given satisfactory results in extensive areas throughout the world.

Yaws control programmes have produced large yaws-free areas by carefully planned and executed campaigns, but the need for active surveillance, as the only way to prevent reintroduction or resurgence of the disease, has been painfully demonstrated in the recent past.

According to the WHO there were 460 000 new cases of endemic treponematoses in 1997 and, even when they remain very sensitive to penicillin, resistance to the antibiotic is always a possibility (plasmid DNA in *Treponema pallidum* is known) and penicillin treatment failures in Papua New Guinea and Ecuador have been reported [9].

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Pinta

SYN. CARATE; CUTE; MAL DEL PINTO; MORADO; AZUL

[F. Kerdel-Vegas, pp. 30.34–30.36]

The term carate, of Carib origin, has priority over the others because it was used by native Americans before the discovery of America. In Mexico, the term used is pinta, meaning spotted (from the Spanish verb 'pintar', to paint); in Cuba, mal del pinto is employed; in Venezuela and Colombia, carate and cute; in Guatemala and Nicaragua, morado; and in Peru and Chile, azul (the two last terms meaning 'the bluish ones') [1].

Definition. Pinta is a chronic, non-venereal, infectious treponematosis caused by *T. p. carateum*, which affects only the skin, producing dyschromic eruptions and hyperkeratoses.

History. Pinta is an autochthonous disease of the American continent, originally reported by Gonzalo de Ovieto y Valdez and Hernán Cortés between 1505 and 1516 as a cutaneous manifestation common among the Carib and Aztec native Americans. Menk, González-Herrejón and Pallares found that the Wassermann reaction was positive in a high percentage of pinta patients. Alfonso-Armenteros, Grau-Triana and León y Blanco discovered the specific causative agent. León y Blanco autoinoculated himself with the disease and described its early lesions [2].

Incidence. Pinta is endemic only in the Americas; conditions that resemble pinta reported from the Pacific area are probably 'pintoid' yaws. Pinta is occasionally found in Central and South America, including Mexico, Venezuela, Colombia, Ecuador, Peru and Brazil. The incidence is lower in Guatemala, British Honduras, El Salvador, Honduras, Nicaragua, Haiti, Santo Domingo, Costa Rica, Panama and Bolivia. In other Caribbean islands (Cuba, Puerto Rico, Guadaloupe, Virgin Islands) and in the Guianas, it occurs only sporadically. The infection was supposed to be extinct in Brazil until 1975, when 20 new cases of pinta were found amongst the Tucuna native American tribe; later on several foci were detected in the area of the western Amazon, and 265 additional cases were diagnosed [3]. In Venezuela, pinta was found to be affecting the whole of a small community of Cuiva native Americans in the south-western part of the country.

There is no predilection for either sex. Exposed regions of the body are the most frequently affected during the early stages. Pinta appears more frequently at low altitudes in warm climates and is observed predominantly in persons who live in primitive, unhygienic conditions, as applies to certain native American communities. Generally, the condition is acquired during childhood by direct skin or mucous membrane contact; venereal transmission does not occur, as lesions of the genitalia are unusual. It is known that *T. p. carateum* penetrates cutaneous abrasions. Transmission by insects, as occurs with yaws, is possible but has never been proved. The large majority of patients acquire the condition during childhood.

Aetiology. The causative agent is *T. p. carateum*, morphologically indistinguishable from the treponemes causing syphilis, yaws and endemic syphilis (bejel). On the basis

of DNA homology studies, the treponemes causing venereal syphilis, endemic syphilis, yaws and pinta have been reclassified as subspecies of *T. pallidum*. However, despite limited reports of experimental infection in the chimpanzee, no animal model has been developed for *T. p. carateum* infection; consequently, *T. p. carateum* is the least studied of the pathogenic treponemes, and may yet be considered a separate species [4]. Experimental inoculation in humans reproduces the clinical manifestations of the disease, and apparently gives a degree of immunity to inoculation with *T. pallidum* and *T. p. pertenue*.

Experimental inoculation of human volunteers has been carried out by depositing lymph obtained from active pinta lesions on superficial scratches on the skin or by injection of the material intradermally [5]. The period of incubation varies from 6 days to 4 months, with a mean of 8–10 days. The initial lesion is a pink papule with moderate infiltration; it grows slowly, forming a plaque of about 7 cm after 9 months. After 2 months, the patches become erythematous and hypochromic, sometimes with grey or pale-blue pigmentation in the pigmented skin of native Americans. Some degree of scaliness is frequent in all lesions.

The experiments of Medina [6] demonstrated that the 'pintosos', with natural or experimental lesions, cannot be infected by artificial inoculation with *T. p. pertenue*, and that it is very difficult to infect them with *T. p. pallidum*. On the other hand, yaws and syphilis patients during any stage of their evolution are easily infected with *T. p. carateum*.

It has been reported that in the Purú–Purú native American tribe of the Amazon basin, a tribal religious ritual of whipping, in alternating sessions, by affected adults and unaffected youths is performed in order to transmit the disease [1].

Histopathology. The treponemes are located chiefly in the Malpighian cells, especially in limited areas of acanthosis in the epidermis. The treponemes can be visualized in the epidermis, sometimes in large numbers, by means of silver staining methods or immunofluorescence techniques [7]. The primary lesion shows migration of lymphocytes through an oedematous, slightly acanthotic epidermis. The basal layer shows loss of melanin and liquefaction degeneration. Numerous melanophages are found in the upper dermis, indicating that even in the initial phase the mechanism of normal pigmentation is grossly disturbed. In the dermis, in addition to melanophages, a moderately dense infiltrate of plasma cells, lymphocytes and some histiocytes and neutrophils can be seen.

In the secondary stage, the same changes are observed, but they may be pronounced, and large numbers of treponemes can be demonstrated.

In the tertiary stage, the clinically hyperpigmented area shows atrophy of the epidermis and absence of melanin in the basal layer. The dermis contains accumulations of melanophages with a moderate lymphocytic infiltrate. At this stage, there are still an appreciable number of treponemes among the epidermal cells. Hypochromic or achromic lesions show atrophy of the epidermis, and a complete absence of melanin, inflammatory infiltration and treponemes. This type of lesion represents the final or residual stage of the disease. However, recent achromic lesions can still reveal a discrete inflammatory infiltrate in the dermis and treponemes in the epidermis [8].

Clinical features. Infection occurs through skin or mucous membrane contact, generally before adolescence, and is manifested as early (active) disease followed by latent (inactive) infection; a course characteristic of all the treponematoses. Usually, the evolution of the disease is divided into three stages:

1 initial lesions;
2 generalized cutaneous phase;
3 late phase.

It is characteristic of pinta that these three stages are not clearly defined and frequently overlap [6].

Initial lesions. Multiple erythematous lesions, usually localized on exposed areas of the body, sometimes macular, sometimes slightly infiltrated, grow by peripheral extension, or by the development of satellite lesions at their edges, with a marked tendency to become confluent and form larger lesions.

Generalized cutaneous phase. After a lapse of months or even years, when the primary lesions can still be observed or when these have resolved spontaneously, the secondary lesions, called 'pintides', appear. Clinically there are three varieties: hypochromic, pigmentary and erythematosquamous. Usually, there are extensive lesions showing mottled pigmentation, and often the second and third stages occur simultaneously. The lesions always retain their tendency to merge together, producing progressive atrophy of the skin with a tendency to hypochromia and achromia, thus leading to the late phase.

The late phase [9]. This takes from 2 to 5 years to develop and has the following characteristics:

1 *Pigmentation* is irregular, with a range of different shades according to the site of deposition of melanin in the dermis; the colour may be greyish, steel, ashy or bluish. In general, the pigmentary changes present a spotted and highly characteristic appearance.
2 *Achromia* may occur in any part of the body, but more frequently in sites close to bony protuberances, such as elbows, knees, ankles, wrists and backs of hands.
3 *Hyperkeratoses* are found on the legs, forearms, elbows, knees and ankles; the skin becomes thick and often scaly; they may also appear on palms and soles.

4 *Atrophy* is the final stage, and a consequence of the previous ones. It is localized mainly in the neighbourhood of the larger joints, and is accompanied not only by thinning of the skin, wrinkling and dryness but also by loss of sweating and sebaceous secretions [3].
5 *Adenopathy*. Generalized adenopathy accompanies the last two stages of the disease, involving mainly the epitrochlear, cervical and inguinal nodes. It is difficult to demonstrate treponemes in these glands.
There are no systemic symptoms and the CNS and cardiovascular systems are not involved.

Laboratory findings. Confirmation of a diagnosis of pinta is made by isolating *T. p. carateum* in the lymph taken from primary, secondary or tertiary lesions (except in old achromic areas) and observing them under dark-ground illumination or phase-contrast microscopy. Antigenic cross-reactivity has been observed among the pathogenic treponemes; infection with any of them will induce reactivity in both non-treponemal and treponemal tests for syphilis. Non-specific and specific serological reactions for syphilis are positive, although it takes over 2 months from the beginning of the condition before they become positive. Eosinophilia has been described as a frequent feature of this disease.

Diagnosis. Dyschromia, hypopigmentation with hyperpigmented spots giving a characteristic mottled aspect, together with the country of origin of the patient, prompt one to suspect the presence of the disease and to initiate the necessary laboratory procedures to establish the diagnosis, which must be based on the finding of the treponeme.

Differential diagnosis. Erythema dyschromicum perstans, originally denominated 'pintoide' by Venezuelan authors because of its similarity to pinta and also known as 'dermatosis cenicienta' ('ash-coloured dermatosis') in Central America, is obviously the dermatosis that clinically resembles pinta most closely. Other hypochromic processes such as pityriasis alba, atrophic lichen planus, tuberculoid leprosy, various leukodermas and vitiligo must be considered in the differential diagnosis of the late phase. The initial lesions can be confused with plaques of tinea corporis, psoriasis, lichen planus pigmentosus, frictional dermatitis, lupus erythematosus, pellagra, melasma, tinea versicolor and eczema. The other two treponematoses, yaws and syphilis, must also be considered.

Course. The disease runs a progressive course, with increasingly widespread involvement of the skin. Medina [6] demonstrated, however, by means of experimental inoculations, that the disease could remain localized for many years. Visceral complications of any type are not recorded. This disease is confined exclusively to the skin and even lesions of the nail apparatus are infrequent.

Treatment. Benzathine penicillin should be given in total doses of 2 400 000 U i.m. for patients aged over 10 years, and 600 000 U i.m. for patients (and contacts) aged under 10 years, by a single injection [10]. Tetracycline and erythromycin are the antibiotics of choice in cases of penicillin allergy.

Prognosis. In the primary and secondary stages, and even in the early tertiary stage, there is total restoration of pigment, and the skin returns to normal. However, the lesions of the late stage, such as achromic and atrophic areas, will persist. As far as the general health of the patient is concerned, the prognosis is always good.

Prophylaxis. The disease can be eradicated by means of comprehensive penicillin treatment of infected patients, which so far has been restricted to the endemic zones previously mentioned.

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Tribute

The late Dr Robbie Morton was a major figure in UK venereology for over 50 years. His career spanned the early days of antibiotic treatment during the Second World War, when syphilis was common, through to the present revolution in genomic medicine. He remained a very active author and research collaborator until his death on 4 May 2002.

Chapter 31

Mycology

R.J. Hay & M.K. Moore

Introduction

Every dermatologist should be familiar not only with the common superficial mycoses but also with the cutaneous manifestations of subcutaneous and systemic infections. With increasing numbers of people taking advantage of the ease of worldwide travel, mycoses that were previously regarded as geographically limited can now be seen in any part of the world. Furthermore, in recent years the number of fungi recognized as human pathogens has risen, caused partly by an increasing population of debilitated and immunocompromised patients. Fungi that were considered as non-pathogenic are now being recovered as opportunistic invaders. The identification of the majority of pathogenic fungi still relies largely on the direct observation of their morphology rather than comparison of DNA patterns, and this requires a knowledge of some of the fundamental features of fungal classification and structure. Over the last 20 years, a precise and complex terminology has been developed to describe the characteristic features that may be observed [1–4] and an outline knowledge of this is essential in order to appreciate the often subtle differences that distinguish fungal pathogens.

Fungi are ubiquitous, capable of colonizing almost any environment, and generally play an invaluable part in the decomposition and recycling of organic matter. Although they were once believed to be descended from plants, it was recognized over 20 years ago that they represented a distinct kingdom, and that certain features of their biochemistry, such as the pathway of lysine synthesis, were quite different from those found in bacteria and plants. With the use of molecular techniques, it is now recognized that the organisms originally included in this kingdom of Fungi contained at least three phylogenetically distinct groups, and some phyla have now been reclassified in the kingdoms Protozoa and Chromista. Almost all the fungi previously regarded as human pathogens, however, remain in the reclassified Fungi [5]. They have probably evolved from protozoan ancestors, and the kingdom Fungi is now believed to have originated before the separation of Animalia and Plantae. All fungi are heterotrophic and must exist as saprophytes or parasites. However, relatively few of the estimated quarter of a million species are pathogens of humans or other warm-blooded animals. The vast majority exist purely as saprophytes or plant parasites and, even among the few that do cause human disease, many have a well-established saprophytic or plant parasitic life cycle in which human infection has no role.

Members of the kingdom Fungi show all the typical eukaryotic features, such as the organization of genetic material into chromosomes enclosed within a membrane-bound

nucleus, mitochondria and ribosomes. Unlike animal cells, however, their cells are enclosed by a rigid cell wall containing varying amounts of chitin, a polymer of *N*-acetyl glucosamine, and β-glucans. The wall also contains mannans, glycoproteins and enzymes, some of which are secreted into the surrounding environment and break down complex organic compounds prior to their absorption. Fungi have an absorptive mode of nutrition. Within the cell wall, the cytoplasm is bounded by a plasma membrane in which the predominant sterol is not cholesterol, as in humans, but ergosterol.

The fungi may be broadly divided into two basic forms: moulds and yeasts. Moulds are made up of long multinucleate filaments called hyphae (singular hypha), which are either largely coenocytic (see Fig. 31.56) or divided into a series of cells by regular cross walls or septa (singular septum) (see Fig. 31.17a). Hyphae grow continuously at the apical tip, where the cell wall is constantly plasticized and new material added. This is the most metabolically active area of the cytoplasm. Further back, the cells may become vacuolated, and often the cytoplasm is reduced to a thin layer lining the cell membrane. Hyphae branch regularly, the branches diverging away from the parent hypha to utilize the environment to the maximum extent. Typically, the longest cell is at the apex of the hypha. The cytoplasm streams continuously, and the majority of septa contain pores that allow the movement of cytoplasm and even of organelles from one cell to another. An aggregation of hyphae is termed a mycelium, and the whole mass of the fungus is the thallus. Growth of a mould on solid media results in a circular colony, and in liquid media the mould forms a ball. Moulds produce cottony or velvety colonies in culture, and even large structures such as mushrooms are simply made up of a mass of hyphae.

In the yeasts, the main phase of the life cycle is unicellular, made up of ovoid to globose cells which usually reproduce by budding (see Fig. 31.43) or, more rarely, by fission. After budding, when the daughter cell separates from the parent, a distinct bud scar is left behind. In addition, however, some pathogens can also form filaments that may be true hyphae, similar to those of moulds or pseudohyphae which develop when two cells fail to separate after budding, and simply elongate and lie end to end forming a chain. Pseudohyphae may be distinguished from true hyphae by the characteristic constrictions that may be seen at the points where two cells meet (see Fig. 31.43), and the shortness of the apical cell. Yeasts produce soft, pasty or mucoid colonies.

Some fungi can completely switch their form of growth depending on the environmental conditions. These are termed thermally and nutritionally dimorphic fungi, and include several of the major respiratory pathogens such as *Histoplasma capsulatum* and *Coccidioides immitis*. When cultured at room temperature, these fungi are typical moulds, yet in human tissues or on special media at 37°C they convert into yeasts or other non-filamentous forms.

Fungi reproduce both sexually and asexually, sometimes simultaneously. The sexual phase is termed the teleomorph and the asexual phase the anamorph; when both are present the growth is termed the holomorph. Much confusion has arisen because at the moment it is quite legitimate to give the sexual and asexual stages of growth completely different names. Thus, the dermatophyte *Trichophyton mentagrophytes* was originally described and named in the asexual phase in 1896. When a sexual phase was discovered in 1967, it was called *Arthroderma benhamiae*. Currently, both names are correct and their usage is simply determined by the phase isolated. If both sexual and asexual forms are present simultaneously, the sexual name has precedence. In the laboratory, sexual phases of pathogens are rarely seen, as the majority of fungi are heterothallic, which means that sexual reproduction requires the presence of two or sometimes four different mating types. Relatively few fungi can reproduce sexually by the mating of hyphae from a single mycelium, a condition termed homothallic.

In an attempt to reflect true phylogenetic relationships, the formal classification of fungi is based upon the features of the sexual phase of growth. This involves the fusion of two nuclei followed by meiotic division. Unlike higher plants and animals, many of the fungi are haploid for the major part of the life cycle, the diploid phase being relatively short lived. Three groups of sexually reproducing fungi, *Zygomycota*, *Ascomycota* and *Basidiomycota*, contain human pathogens (Table 31.1). A fourth, completely artificial group, the *Deuteromycota* or Fungi Imperfecti, was originally created to include those fungi with no known sexual phase, and the asexual phases of the *Ascomycota* and *Basidiomycota*. With the more sophisticated techniques available today, such as ultrastructural data on septa and molecular sequencing, these asexual 'mitosporic' species can now be placed within the recognized sexual groups, and it is possible that at some time in the future the artificial form-phylum *Deuteromycota* will disappear from the literature.

The *Zygomycota* are all moulds, and reproduce sexually by the formation of thick-walled zygospores following the fusion of two outgrowths arising from the hyphae. The hyphae of the *Zygomycota* are very characteristic, being both extremely wide and often sparsely septate. The septa that are formed usually cut off sporing structures and old parts of the mycelium, and are complete, so that damage to any part of the hypha will result in the death of the whole aseptate length. Branching in this group is typically at right angles. Asexual reproduction is usually by means of sporangiospores formed by the cleavage of cytoplasm within a sporangium. This is a sac-like structure, which is supported by a specialized hypha, the sporangiophore (Fig. 31.1a).

Table 31.1 Classification of fungi.

Phylum	Growth form	Hyphae (if present)	Sexual propagules	Asexual propagules
Zygomycota	Moulds	Broad Few septa	Zygospores	Sporangiospores
Ascomycota	Moulds Yeasts	Narrow Regular septa	Ascospores	Conidia*
Basidiomycota	Moulds Yeasts	Narrow Regular septa Clamp connections	Basidiospores	Conidia*
Deuteromycota	Moulds Yeasts	Narrow Regular septa	None	Conidia

* The asexual conidia of the *Ascomycota* and *Basidiomycota* are classified in the *Deuteromycota*.

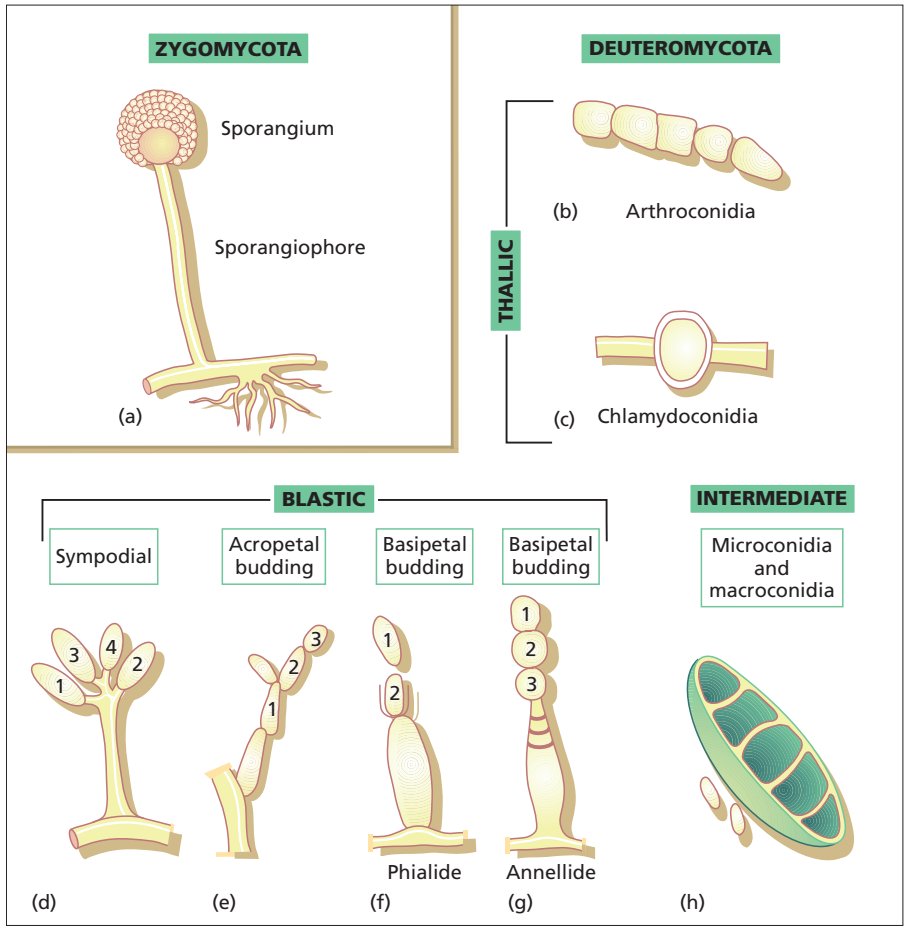

Fig. 31.1 Asexual reproduction in fungi. *Zygomycota*. The most characteristic form of asexual reproduction is the production of sporangia and sporangiospores (a). *Deuteromycota*. Asexual conidia may be formed by two main processes: thallic conidiation results in the production of arthroconidia (b) and chlamydoconidia (c). Blastic conidiation may take several forms, including sympodial conidiogenous cells (d), acropetal budding (e) and basipetal budding from phialides (f) or annellides (g). The conidia of the dermatophytes do not fit in with this thallic–blastic division, but show features of both. They are also examples of fungi that produce two kinds of conidia simultaneously, which differ in size. These are termed microconidia and macroconidia (h).

The *Ascomycota* contains both moulds and yeasts. Sexual reproduction is by the production of ascospores, formed within a sac-like ascus. These asci may themselves be contained within a specialized fruiting body or ascoma, which may be large enough to be visible to the naked eye. The hyphae of the *Ascomycota* have a lamellate cell wall, with a thin electron-dense outer layer and a thicker electron-transparent inner layer. The hyphae are narrow and regularly septate, but passage of cytoplasm and even nuclei from one cell to the next is made possible by the presence of a pore in the centre of each septum. When hyphae are damaged, however, this septal pore quickly becomes plugged by structures termed Woronin bodies, limiting the damage to those particular cells that were injured. A few of the *Ascomycota* have multiple pores in their septa.

In the *Basidiomycota*, sexual reproduction is by the production of basidiospores formed externally on sterigmata protruding from a club-shaped basidium. Many of this group produce the complex structures we know as mushrooms and toadstools, with gills, covered by basidia, raised above the ground to aid in airborne dispersal of the spores. Others, such as the rusts, smuts and basidiomycetous yeasts, are microscopic. The cell walls of the

Basidiomycota are lamellate and electron dense. When present, the hyphae are narrow and septate. The septal pore structure in this group is more complex and characteristic, and usually comprises a lip-like extension termed a dolipore, which may be surrounded by perforated membranes called parenthosomes. These allow passage of cytoplasm, but not nuclei, from one cell to the next. In the *Ascomycota* and the *Basidiomycota*, after fusion of hyphal initials of opposite mating type, subsequent fusion of the two nuclei may be delayed, so that for part of the life cycle these cells contain two nuclei of opposite mating type, a state termed dikaryotic. For this reason, some workers combine these two groups into the *Dikaryomycota*. It is characteristic of the *Basidiomycota* that when a dikaryotic hyphal cell divides, a hook-like structure known as a clamp connection is formed between the two resulting cells as a way of allowing one daughter nucleus of each type to migrate into each cell.

The form-phylum *Deuteromycota* was artificially constructed, as the phylogenetic relationships of many of the asexual fungi contained within it could not at that time be fully determined. The asexual propagules of all the fungi classified in this group were called conidia. Three main divisions were recognized in the *Deuteromycota* and are current in the literature: *Blastomycetes*, which are yeasts reproducing by budding; *Hyphomycetes*, which are moulds bearing the conidia exposed unprotected on the hyphae; and *Coelomycetes*, where the conidiogenous cells that produce the conidia are enclosed in a specialized protective fruiting structure, either a flask-shaped pycnidium or a saucer-shaped acervulus. The majority of fungi isolated in the laboratory are *Hyphomycetes*, and this group may be further subdivided according to colour into fungi that have dark hyphae—dematiaceous fungi—and those that are pale or brightly coloured—moniliaceous fungi. An amazing variety of conidia are formed by these fungi, and their laboratory identification still relies almost entirely on the study of the method of conidial formation or ontogeny and conidial morphology.

Two main methods of conidial production are seen in the *Hyphomycetes*: thallic and blastic (Fig. 31.1). In thallic conidiation, a whole cell or section of a hypha is transformed into the conidium. The most common examples of this are arthroconidia (Fig. 31.1b), when a hypha produces a series of septa, forming a chain of cells that separate at maturity, and chlamydoconidia, which are formed when a single cell becomes thick walled and acts as a storage and survival cell but does not disarticulate at maturity (Fig. 31.1c).

In blastic conidiation, the conidium is formed by 'blowing out' or budding from only a small weakened area of the cell wall of the conidiogenous cell. If both the outer and the inner cell wall are blown out to form the conidial wall the budding is termed holoblastic. If the first conidium ruptures the outer cell wall, and only the inner cell wall is blown out as the conidial wall, the budding is termed enteroblastic. An enormous range of blastic conidia are produced, but certain basic patterns of conidial development may be recognized. Holoblastic conidia include solitary conidia, which may simply be produced by the blowing out of a small part of the hyphal wall, to form a lateral or terminal conidium. In other fungi, more specialized conidiogenous cells are found, and these may produce a succession of holoblastic conidia. Examples of this include those fungi with sympodial conidiogenous cells (Fig. 31.1d), where after the first conidium has been formed, the conidiogenous cell continues to grow and produces a second conidium slightly ahead of and to one side of the base of the first conidium. It then repeats the process, forming a third conidium slightly ahead of and to the opposite side of the second conidium. This eventually results in a zig-zag appearance, with conidia coming off alternately on each side of the fertile cell. Such conidiogenous cells are very characteristic and are termed geniculate.

Many of the fungi with sympodial conidiation have multicellular conidia, either with transverse septa—phragmoconidia—or with both transverse and vertical septa—dictyoconidia.

Chains of holoblastic conidia may be formed by acropetal budding (Fig. 31.1e), where, after the cell has budded, the cells remain attached and a further conidium is produced by the budding of the daughter cell. This continues building up a chain of cells with the youngest at the tip of the chain. The chains may branch.

Enteroblastic chains of conidia with the youngest cell at the bottom of the chain are termed basipetal, and are formed by the repeated blowing out of the inner layer of the cell wall of specialized structures termed phialides and annellides. Phialides are often flask shaped, and may have a pronounced collarette—a flaring ring of wall material surrounding the apex of the cell. The phialoconidia are formed by repeated budding at exactly the same point at the tip of phialide, which does not increase in length during this process (Fig. 31.1f). In contrast, as a series of annelloconidia is formed, the cell apex proliferates slightly as each conidium is produced, leaving a series of ring-like scars at the tip of the cell, and the annellide becomes progressively narrower and longer (Fig. 31.1g). Conidia produced by phialides and annellides may aggregate to form balls rather than chains.

A number of pathogens produce conidia that are not strictly thallic or blastic, and which show a particular method of separation from the hypha. A specialized cell at the base of the conidium breaks, leaving a frill of wall material at the base of the conidium. These conidia are termed aleurioconidia.

Another feature that is seen in several fungal pathogens is polymorphism—the simultaneous production of more than one form of conidium. For instance, in the case of the

dermatophytes two types of conidia are formed, which differ greatly in size; in such instances, the larger conidium is termed a macroconidium and the smaller a microconidium (Fig. 31.1h).

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Nomenclature. Nomenclature is the system whereby the correct names are applied to specific organisms, and is a necessary adjunct to any system of classification. In mycology, as in other sciences, the lack of a uniform approach towards the recognition and description of new species of fungi led to the accumulation of a bewildering number and variety of names in the literature. As an example, *Candida albicans* has been described and redescribed many times since its original description in 1850. A classic taxonomical work [1] lists no fewer than 110 species in 22 genera for this fungus. The need to provide a single name for a single species becomes obvious, particularly when so many synonyms have been proposed for one and the same organism. In order to provide some conformity and stability to the naming of fungi (separate consideration is given to bacterial and zoological nomenclature), a series of principles, rules and recommendations have been incorporated into an internationally recognized code, whose authoritative guidance has done much to bring order to a state of confusion.

As well as confusion in specific names, disease names have also given rise to controversy. As an increasing number of fungi have been shown to be capable of causing infection, particularly as opportunists in only a limited number of recorded cases, the habit of using the generic name of the fungus to produce a new disease name has become increasingly unwieldy, particularly when fungi are so frequently re-examined and often renamed. Well-established disease names have been retained, but where a new pathogen or pathology is involved the International Society of Human and Animal Mycology [2] recommends that individual mycoses should be named as often as possible in the form 'pathology A caused by pathogen B'. Thus, the use of such terms as fusariosis and trichosporonosis is best discouraged, and replaced by use of 'eumycetoma caused by *Fusarium* species' or 'disseminated mycosis caused by *Trichosporon* species'.

Disease names used throughout this text are based on lists published independently by the Council for the International Organization of the Medical Sciences (CIOMS) [3] and the International Society for Human and Animal Mycology [2].

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Superficial and cutaneous mycoses

During the last decade, there has been an increasing tendency on the part of mycologists to separate the infections that affect hairs, skin and nails alone into two rather artificial groups: the superficial mycoses, which include diseases that generally do not provoke a significant histopathological inflammatory response in the host; and the cutaneous mycoses, where, although the fungus is confined to the non-living layers of the stratum corneum, pathological changes do occur in the host tissue. Among the superficial infections are pityriasis versicolor, tinea nigra, and black and white piedra.

The cutaneous infections include dermatophytosis, candidosis and a range of non-dermatophyte infections of the skin and nails, such as dermatomycoses caused by *Scytalidium* species and onychomycosis caused by other non-dermatophyte moulds. Some of the fungi causing these infections are present in the environment, but others, such as *Candida albicans* and *Malassezia* spp., have an intimate association with humans and are part of the normal flora of the gut and skin, respectively. Only a few, such as the anthropophilic dermatophytes, have evolved to the point where they have become almost completely reliant on the human host for survival.

Laboratory methods

The laboratory diagnosis of superficial and cutaneous mycoses relies first on the direct microscopical observation of the pathogen in samples from the affected area. This is usually followed by culture and the specific identification of the fungus. For the laboratory to provide the optimum performance, the quantity and the quality of the material examined is critical.

Collection of material

Skin

Disposable scalpel blades of the solid type held vertically to the skin are used to obtain scrapings. Alternatively, heat-sterilized blunt banana-shaped scalpels, which are

available from chiropody firms, may be used. Cleaning of the skin with alcohol may be useful if the patient has applied ointment or powder, but is not usually necessary. If the lesion has a definite edge, the material should be taken from the active margin, otherwise a general scraping is adequate. In cases of partially treated pityriasis versicolor, when very little scaling is present, it is possible to take a sample by pressing a strip of sticky tape (Sellotape®) on to the lesion and then on to a drop of mounting fluid on a slide and use this for the direct examination. The method is less suitable for direct examination of samples from the cutaneous mycoses [1]. If it is difficult to obtain sufficient material for culture in cases of dermatophytosis, transport swabs are a good back-up as is usual with candidosis. When blisters are present, a pair of fine scissors may be used to cut off a blister roof for microscopical examination and culture; such samples are often packed with hyphae.

The scrapings should be collected and transported in folded paper, which keeps the specimen dry, thus preventing contamination. Plastic containers are unsuitable, as the skin adheres to the sides and is difficult to remove. The use of glass slides, which then have to be transported to the laboratory, is hazardous as they are frequently broken. Squares of brightly coloured paper are ideal; these may then be carefully folded and secured by a paper clip. The details of the patient, exact site of the lesion and time of sampling should then be clearly written on the outside of the sample. Specially designed commercial transport packs for hair, skin and nail samples are available from several sources. Dermatophytes in skin scrapings may remain viable for months, and yeasts for several weeks.

Hairs

Hairs to be examined for the presence of black or white piedra may be simply cut off at skin level. If dermatophytosis is suspected, the hairs should be removed with the roots intact; cut hairs are unsuitable. In many instances, the affected hairs may be recognized because they are dull and broken but, if not, the fact that they slip out easily with fine forceps may also help in selecting the right material. This is particularly useful in examining scalp or beard kerions caused by *Trichophyton verrucosum*, where relatively little fungus may provoke a severe reaction, and it may be necessary to test many hairs before an infected hair is found. In those instances where the hairs break off very short, as in black-dot infections, a scalp scraping will yield the best material, with the infected roots appearing as tiny stumps among the skin scales. It should be noted that, in cases of steroid-treated tinea corporis or tinea incognito, the examination of vellus hairs may be the easiest method of diagnosis as, although fungi such as *T. rubrum* rarely invade the hair shaft, they may colonize the hair follicle. In addition to collecting scales and hairs, brush samples are an excellent method for the culture of scalp infections, and may also be useful in testing suspected animal sources of infection [2–4]. A sterile plastic scalp massager or disposable toothbrush is brushed firmly through the hair at least 10 times, and is then pressed against the culture medium in a 90-mm Petri dish. This simple technique is an extremely sensitive culture method, and is invaluable when screening large numbers of children. Several hundred children may be examined in a day by performing a Wood's light examination and taking a brush sample from each child, which can then be taken back to the laboratory for culture. Cultures from infected children produce a fungal colony from many of the inoculation points; contacts of infected children usually yield only a few colonies. In cases of kerion, when brush sampling may be unsuitable and painful, a transport swab wiped over the lesion will usually pick up enough conidia to give a positive culture.

Wood's light examination. The discovery by Margarot and Deveze [5] in 1925 that hair infected by certain dermatophytes produced a characteristic fluorescence in ultraviolet (UV) light filtered by Wood's glass was an important advance in medical mycology. Wood's glass, which consists of barium silicate containing about 9% nickel oxide, transmits rays of wavelength above 365 nm. Most sources of UV light are suitable. The nature and source of the fluorescent substances in infected hairs are not fully understood. The hair remains fluorescent after the fungus has ceased to be viable, and the fluorescent material can be extracted from the hair in hot water [6,7] or in a cold solution of sodium bromide [5]. The colour of the fluorescence is influenced by the pH of the solution [8]. Because fungi growing in culture or on hair *in vitro* do not fluoresce in this way, the phenomenon must be attributed to some substance produced by the interaction of the fungus and the growing hair. Its chemical nature has not been defined, and the suggestion that it may be a pteridine has been challenged [7–10].

Only some of the dermatophytes capable of invading hair will induce fluorescence, but these include members of the genus *Microsporum* (e.g. *M. audouinii* and *M. canis*), which are common in a number of densely populated parts of the world. Hairs infected by these species produce a brilliant green fluorescence, easily recognized in a darkened room. Only the fully invaded portions of the shaft develop this property. In recent infections or at the spreading margin of early lesions, the fluorescent part of the hair may not yet have emerged from the follicle, and can be detected only after the hair is plucked. Among other *Microsporum* species and variants, only *M. canis* var. *distortum* and *M. ferrugineum* regularly induce fluorescence, and *M. gypseum* and *M. nanum* occasionally do so. *Trichophyton schoenleinii* causes a paler green fluorescence of infected hair. In favus, the fluorescent hairs tend to be

long, in contrast to the short broken stumps characteristic of *Microsporum* infections.

In areas where *Microsporum* infections are prevalent, the Wood's light is an essential tool in the diagnosis and treatment of the individual patient, and in the control of epidemics. The lamp is easily transportable and can be taken to schools or institutions for the rapid examination of contacts. The most common sources of error are the bluish or purplish fluorescence produced by ointments containing petrolatum, scales, serum, exudates, an insufficiently darkened room, light reflected from the examiner's white coat and the failure to remember that not all fungi cause fluorescence. Correctly performed and interpreted, the test is virtually specific, but the absence of fluorescence in infections with *M. audouinii* and *M. canis* has been reported [11]. The lamp can be used in the detection of subclinical infection, and to assess response to treatment or spontaneous cure. The Wood's lamp is also of value in the diagnosis of pityriasis versicolor, where the scales fluoresce yellow in some cases. A similar yellow fluorescence, presumably because of the presence of yeasts of *Malassezia* species, may be seen in some cases of severe dandruff, in cradle cap in infants and in the follicular orifices of the face and upper trunk in normal subjects.

Nail

The diagnosis of onychomycosis is complicated by the fact that the isolation of the pathogen in culture from nail material is more difficult to achieve than for skin and hair samples. In the majority of nail infections, the material for examination is taken from the distal end of the nail, despite the fact that the infection is advancing proximally. The hyphae at the distal end of the nail are less likely to be viable [12]. Unfortunately, it is usually not practicable to take deep samples from the proximal advancing edge with minimum discomfort to the patient. The full thickness of the nail should be sampled, as most infections start in the hyponychium. Debris from under the nail is a fruitful source of material, which may be scraped out using the flat end of a dental probe. Superficial scrapings are inadequate, except in cases of superficial white onychomycosis or proximal subungual onychomycosis.

In cases of paronychia, the nail fold may be moistened with saline using a wet swab, and the flat end of a dental probe may be gently pushed into the fold to withdraw material for direct examination and culture. After this, a swab should also be taken for culture.

As the isolation of fungi from nail material is difficult, samples should also be taken from any skin lesions that may be present, as these are very likely to be invaded by the same pathogen as the nail, and cultures are more likely to be positive. It is essential when submitting nail material to the laboratory to specify whether the sample is a fingernail or toenail, as some pathogens are more prevalent in one than the other.

Mucous membranes

The mouth or vagina may be sampled using a blunt scalpel or by using swabs. If the specimen is not to be examined immediately, swabs with transport medium are preferable, as yeasts rapidly die in dry conditions. However, delays in processing of transport medium swabs will allow multiplication of yeasts in the samples.

Ear

Scrapings from the external ear canal may be supplemented with swab samples.

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Direct examination

For routine examination, specimens are usually mounted in 10–30% potassium hydroxide; the higher the percentage, the faster the specimen will clear. For skin scrapings, warming gently over the pilot light of a bunsen burner will speed up the process, but boiling should be avoided, if possible, as this tends to encourage the formation of artefacts, which may confuse the inexperienced observer. It is impossible to soften skin samples too much, for the thinner the specimen, the easier it will be to observe the fungal elements. Excess potash will etch microscope lenses, so it must be removed using small squares of filter paper, and the cover slip can be pressed down gently, using a needle, to flatten the specimen. A few minutes

spent carefully preparing the specimen in this way are well spent. Nail specimens take longer to clear, but if small pieces and debris are taken, they will usually soften within 10 min. In those instances where the nails do not soften satisfactorily, the slide may be put in a 37°C incubator for 1 h, and the material can then be flattened. In contrast to skin and nail samples, infected hairs are very delicate, and if heated or left in mounting fluid for more than a few minutes tend to disintegrate, obscuring the characteristic arrangement of the arthroconidia. They should therefore be examined as soon as possible after mounting. If examining specimens using bright-field illumination, the lighting is critical; overillumination, particularly when scanning the slide under low power (× 10), will render the fungal elements invisible. The light should therefore be low initially and then raised when the presence of fungus is confirmed by examination with a higher power lens (× 20 or × 40). An alternative clearing agent, which does not require warming of the specimen, is 10% sodium sulphide solution [1,2].

With experience, bright-field examination of specimens cleared in this way is quick and relatively straightforward. However, several authors have recommended a variety of techniques to make observation of the fungal elements easier. Phase-contrast and dark-field microscopy can produce good results [3], but do require that the specimen be really thin, and thus may need a longer period of softening of the material than bright-field microscopy. The addition of 35% dimethylsulfoxide to the potash may speed up softening, but overdigestion is then a problem, and the specimens should be examined within 1–2 h. Dimethylacetamide or dimethylformamide have been suggested as alternatives [4]. Several stains such as Congo red, methylene blue and cotton blue have been recommended to enhance the contrast between fungus and skin, but again these require a fully softened specimen. One stain that has been extremely useful is Parker's stain, made by the mixing of equal volumes of potassium hydroxide and Parker's blue–black Quinck permanent fountain pen ink [5]. Unfortunately, the manufacturers have now changed the formulation of the ink and the new product no longer stains hyphae; when current stocks are finished this stain will become unavailable.

Fluorescence microscopy using either acridine orange [6] or a fluorescent brightener such as Calcofluor white or Blankophor [1,2], which specifically stain polysaccharides in the fungal cell wall, is becoming increasingly popular. A comparative study of different methods used in direct examination [2] concluded that most of the recommended staining procedures for direct microscopic examination were no better than the classic potassium hydroxide method, but that if a fluorescence microscope is available, the use of fluorescent brighteners does give superior results. A more recent study [1] concluded that fluorescence microscopy using Blancophor P flussig in sodium sulphide solution was quicker, and produced significantly fewer direct microscopy negative samples, which subsequently yielded fungus on culture, than bright-field microscopy using sodium sulphide solution alone. In the authors' experience the fluorescent technique is superior to bright-field microscopy and strongly recommended, particularly for nail samples.

Whatever method is used, the ability to find fungi on direct examination of samples is largely a matter of practice. The beginner may well be confused initially by the common artefacts that may be present, such as mosaic fungus—cholesterol-forming polygonal deposits around cells—air bubbles, fibres and crystals, but with practice it becomes progressively easier to find the fungi and distinguish the various infections.

It must be noted that some workers advocate the histopathological processing of nail material and staining with a fungus-specific stain such as periodic acid–Schiff (PAS) as a routine measure [7]. It has been suggested that this not only confirms that the nail plate is actually invaded, but also reduces the number of false-negative direct reports, where fungus is cultured from a microscopically negative nail. However, the facilities for histopathological processing may not be available in a small laboratory.

Culture (Table 31.2)

For some of the superficial mycoses, the appearance of the fungal elements observed on direct examination is so characteristic that culture is not strictly necessary for diagnosis of the infection. This is certainly true of pityriasis versicolor and, to a lesser degree, black piedra, white piedra and tinea nigra. For otomycosis, in contrast, culture is essential, as the range of organisms that can cause infection is enormous, and the specific identification of the pathogen will have a profound effect on the therapy selected. Similarly, differences in the response of the different pathogenic yeasts to some of the newer antifungals, such as fluconazole, necessitates identification down to species level, at least in patients on long-term treatment. The situation with dermatophyte infections is rather different because, although on direct examination of skin and nail samples the different species are indistinguishable, generally all the dermatophyte species have been believed to respond similarly to the major systemic and topical antifungals available, and treatment has been initiated on the basis of the direct examination. However, this may not be true with some of the more recent antifungals developed. In addition, culture will provide valuable information on the possible source of infection and the likelihood of spread of the disease. Culture of specimens with negative direct microscopical results is also desirable, as it will allow the detection of the small percentage of cases where prolonged therapy, or a very inflammatory

Table 31.2 Cultural conditions for isolation of superficial and cutaneous pathogens.

Disease	Causative organisms	Media		Antibiotics		Temperature		Maximum length incubation (days)
		GP	MEA	Cyc	Chlor	26–28°	37°	
Black piedra	*Piedrai hortae*	+	+	+	+	+		28
White piedra	*Trichosporon* spp.	+	+	–	+	+		14
Tinea nigra	*Phaeoannellomyces werneckii*	+	+	–	+	+		21
Dermatophytosis	*Trichophyton* spp. *Microsporum* spp. *Epidermophyton* spp.	+	+	+	+	+		21–28
Dermatomycoses caused by *Scytalidium* spp.	*Scytalidium dimidiatum* *Scytalidium hyalinum*	+		–	+	+		21
Onychomycosis caused by non-dermatophyte moulds	*Scopulariopsis* spp *Acremonium* spp. *Fusarium* spp., etc.	+	+	–	+	+		21
Candidosis	*Candida* spp.	+	+	–	+	+	+	7
Otomycosis	*Aspergillus* spp. *Candida* spp., etc.	+	+	–	+	+	+	21

Chlor, chloramphenicol 0.05 g/L; Cyc, cycloheximide 0.4 g/L; GP, glucose–peptone agar; MEA, malt extract agar; + recommended; – not recommended.

host reaction, may make the microscopical detection of the fungus in the skin difficult. The non-dermatophytic moulds capable of infecting skin or nail, such as *Scytalidium* species and *Scopulariopsis brevicaulis*, can be diagnosed on the basis of direct microscopy, but this requires considerable expertise, and in addition mixed infections with dermatophytes do occur, so that it is advisable to always perform cultures in these cases.

Fungi grow readily on simple media containing glucose and preferably an organic nitrogen source; they are not particularly fastidious. The primary culture medium used therefore is largely a matter of personal choice. Many laboratories will select a simple glucose/peptone agar, either with 4% sugar, 1% peptone and an acid pH (Sabouraud's dextrose agar) or with 2% sugar, 1% peptone and a neutral pH (Emmon's modification). Antibacterial antibiotics such as gentamycin (0.0025%) and/or chloramphenicol (0.005%) may be added to reduce contamination and, if a dermatophyte infection has been diagnosed, the addition of cycloheximide at 0.04% will inhibit the growth of non-dermatophyte moulds. This antibiotic must be excluded, however, if infection by a non-dermatophyte mould such as *Scytalidium* or candidosis is suspected as, although *C. albicans* is not affected, many of the less common species of *Candida* found, particularly in nail and mucous membrane sites, will be inhibited. For sites where non-dermatophyte moulds such as *Scytalidium dimidiatum* may be significant —palms, soles, toe webs and nails—duplicate cultures with and without cycloheximide are recommended. Sabouraud's dextrose agar is available from a number of different commercial sources. It should be noted, however, that variations in the different makes, particularly the type of peptone included, will affect the overall morphology of the isolates, and cause differences in pigmentation and texture of the fungal colonies, particularly of dermatophytes. It is easiest therefore to become familiar with the morphology of these pathogens on one brand only. One should also note carefully which formulations have cycloheximide and/or chloramphenicol already incorporated (e.g. Mycosel and Mycobiotic agars) and which require their addition. Another medium that is frequently used for primary culture is 3–4% malt extract agar, which is also commercially available.

As incubation is much longer than for bacterial cultures, the medium should be poured relatively thickly to prevent drying out; 30 mL/90-mm Petri dish is adequate. The majority of laboratories now perform their cultures in disposable plastic Petri dishes, but if screw-capped glass bottles or tubes are used, the tops must be left slightly loose to provide adequate aeration. For moulds, the temperature of incubation should be 26–28°C and cultures should be held for a maximum of 3–4 weeks. For *Candida* species, the temperature of incubation should be 37°C, and plates may be discarded after 1 week. As some *Trichosporon* species will not grow at 37°C, incubation should be at 26–28°C for up to 2 weeks.

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Identification of isolates

Yeasts

The identification of yeasts requires morphological data together with physiological and biochemical investigations. Examination of the yeast colony should include colour and texture. Microscopic features of note may include the size and shape of the budding cells (blastoconidia), and the presence of pseudohyphae, true hyphae, capsules, arthroconidia and ascospores. In the case of *C. albicans*, the formation of terminal vesicles (chlamydospores) on cornmeal or rice agar supplemented with Tween 80, or the production of germ tubes after incubation in serum at 37°C for 2–3 h, allows specific identification. For speciation of other pathogenic yeasts, physiological tests must be performed. An increasing number of commercially produced yeast identification kits are available and widely used, including the API 20C (bioMerieux) and the Auxacolor (Sanofi Diagnostic Pasteur). Primary isolation media that allow the specific identification of certain species to be made by the production of a characteristic colour are also now available. On Albicans ID medium (bioMerieux), *C. albicans* colonies develop a blue colour; on Chromagar (Becton & Dickinson) *C. tropicalis*, *C. krusei* and *C. albicans* produce blue, pink and green coloured colonies, respectively. These media facilitate the detection of mixed infections, which has become increasingly important because of the relative insensitivity of certain *Candida* species to some of the currently available antifungal drugs.

Moulds

The identification of moulds relies almost entirely on examination of the colonial and microscopical morphology. Examination of the fungal colonies should include noting the colour of the surface and reverse of the culture, and the presence of any pigment diffusing into the medium. The texture of the surface of the colony is also important, and terms such as downy, powdery, granular and glabrous are widely used (see Glossary, p. 31.101). Hyphae that project above the surface of the agar—aerial hyphae—and growth completely submerged in the medium may also be characteristic. Folding may take very characteristic forms, either radial, circular or cerebriform (see Glossary, p. 30.101).

Microscopic features to note include the shape and size of the conidia, their colour, septation and the presence of wall thickenings or other ornamentation. The arrangement of the conidia on the conidiogenous cell and the type of conidiation is of critical importance. Such microscopic features may be observed using a needle mount, a sticky tape strip or a slide culture. The simplest method is a needle mount, when a portion of the growth is removed with a stiff wire needle, and teased out in a drop of a suitable stain, such as lactophenol cotton blue. A cover slip is applied and the sample examined microscopically. The disadvantage of this method is that, as it entails relatively rough handling of the material, it is inevitable that many of the conidia will become detached from the hyphae. A method that will retain more of the conidia in position is to apply a piece of sticky tape, sticky surface down, onto the surface of the colony, and then mount this in a drop of stain and examine the preparation directly through the back of the tape. The sticky tape strip is extremely useful for the examination of colonies with many conidia. The most successful but time-consuming method for examining the details of conidial structure and formation, however, is the slide culture [1]. In this method, the fungus is inoculated onto the four sides of a square of agar, sandwiched between a glass slide and cover slip, and maintained in a sterile Petri dish with a moist atmosphere. The fungus grows out from the agar block directly onto the glass of the cover slip and slide, which may be used to prepare two undisturbed mounts of the growing fungus. When sealed with nail polish, these form permanent preparations.

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Pityriasis versicolor

SYN. TINEA VERSICOLOR; DERMATOMYCOSIS FURFURACEA; TINEA FLAVEA; LIVER SPOTS; CHROMOPHYTOSIS

Definition. A mild chronic infection of the skin caused by *Malassezia* yeasts, and characterized by discrete or concrescent, scaly, discolored or depigmented areas mainly on the upper trunk.

Aetiology. The normal flora of the skin includes a number of morphologically distinct lipophilic yeasts. It was thought that a single polymorphic yeast, *Pityrosporum ovale*, or two species, *P. ovale* and *P. orbiculare*, were present, but it is now recognized that this genus name was invalid, and these yeasts were reclassified in the genus

Malassezia as a single species, *M. furfur*. However, genetic analysis has now demonstrated that the situation is far more complex, and at least seven separate species of lipophilic yeasts exist on the human skin. These comprise *M. sympodialis*, *M. globosa*, *M. restricta*, *M. slooffiae*, *M. furfur*, *M. obtusa* [1] and the recently described *M. dermatis* [2] and are all lipid dependent. One lipophilic but not totally lipid-dependent species, *M. pachydermatis*, is more often found on animal skin. The isolates previously known as *M. furfur* therefore probably include a complex of species. Colonization by these species is especially dense in the scalp, the upper trunk and flexures. Various studies have examined the distribution of the different species in normal skin from various sites and in lesional skin in various *Malassezia*-associated dermatoses. Some have included direct microscopical observation or counting of yeasts, some rely on cultures alone. However, as different workers have used different sampling techniques, few of them quantitative, and different culture media, the studies are not directly comparable. The current consensus from these studies is that *M. globosa* is the species most frequently associated with pityriasis versicolor and *M. sympodialis* is that found most commonly on normal skin [3]. Microscopy of the scales of pityriasis versicolor nearly always reveals thick-walled spherical yeast forms budding from a narrow base—compatible with *M. globosa*—and coarse septate mycelium often broken up into short filaments. In some instances, however, more commonly in tropical zones [4–6], mycelium is observed together with oval yeasts budding from a broad base, a morphology more suggestive of *M. furfur* or *M. obtusa* [3]. Initially it was found impossible to demonstrate the mycelial phase of *Malassezia* species *in vitro*, but in 1977 Dorn and Roehnert [7] achieved this using a glycine-containing medium.

Pityriasis versicolor in most cases represents a shift in the relationship between a human and his or her resident yeast flora. Factors contributing to the change are probably multiple. It is known that some *Malassezia* species more readily become mycelial, and have perhaps a slightly greater pathogenic potential. A positive family history among blood relations is found more often than chance would suggest in pityriasis versicolor, but whether this is caused by a genetically determined host-susceptibility factor, or the greater opportunity for heavy colonization by *Malassezia* species, is at present undetermined. Conjugal cases also occur, and it is possible that in some instances infection does not arise from the individual's own autochthonous flora but by transmission from another individual [8]. The relationships between different *Malassezia* species causing pityriasis versicolor and other skin diseases are partly understood. *M. globosa* is associated in particular with pityriasis versicolor, whereas a number of different *Malassezia* species are isolated from seborrhoeic dermatitis [3]. Most attention has been devoted to environmental factors and individual host susceptibility. The sexes are probably equally prone to this condition, but there are certainly differences in susceptibility at different ages [9,10]. In temperate zones, the condition is rare in childhood but becomes more common in the late teens with a peak in the early twenties. Infections in old age are rare. In tropical climates, the condition is more common than in temperate zones, and as many as 40% of some populations may be affected [11]. Although no reliable figures are available for colder climates, the prevalence is almost certainly less than 1%. In temperate zones, among patients who can give a reliable history, the onset is more often in the warmer months of the year [10]. Pityriasis versicolor has been claimed to be more common in various disease states, but only in Cushing's syndrome, spontaneous and iatrogenic [12], and possibly in malnutrition are these suggestions reliably supported by evidence. Pregnancy and oral contraceptives may have some influence in increasing susceptibility, but again firm data are lacking. Pityriasis versicolor does not appear to be more common in acquired immune deficiency syndrome (AIDS) patients [13]. There have been many attempts to explain susceptibility in terms of physical and biochemical abnormalities, but a variety of differing and conflicting results leaves the problem unresolved. Application of oils to the skin may increase susceptibility but is not proven.

There is ample evidence of an antibody response to *Malassezia* species in subjects without pityriasis versicolor. There have been many studies on humoral response to *Malassezia* species in patients with pityriasis versicolor and controls but, prior to the recognition of the new species, antigens used were probably made from a number of different species, making the often conflicting results difficult to interpret. Similarly, studies of cell-mediated responses have also produced conflicting results with a wide range of antigens [14]. One interesting new approach has been to use mycelial-phase antigens and this has shown significantly greater lymphocyte transformation responses in pityriasis versicolor patients compared to controls [15]. The initial views that patients with pityriasis versicolor have a cell-mediated deficiency specific to *Malassezia* species or depletion of specifically reactive T cells from the blood [16,17] have been questioned. The extensive review of the immunology of diseases associated with *Malassezia* species is recommended to those interested in these aspects [18]. T-cell inhibition by a lipid component of the *Malassezia* cell wall has recently been reported [17].

Malassezia species do not attack the hair shaft, nails or mucous membranes, but recently pulmonary infections in infants on long-term intravenous lipid therapy have been attributed to *Malassezia*.

Histology and pathogenesis. In those patients who do produce a cellular response, hyperkeratosis, parakeratosis

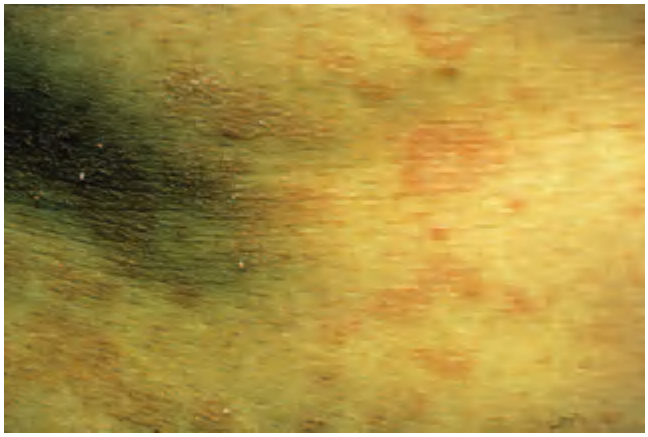

Fig. 31.2 Pityriasis versicolor.

and slight acanthosis, with a mild inflammatory infiltrate in the upper dermis, are the characteristic histological changes. Immunophenotyping of the infiltrates revealed a dominance of memory T cells, an accumulation of macrophages and a lack of B cells [19]. A marked accumulation of Langerhans' cells in the epidermis, reduced expression of cellular activation markers and the presence of suppressor T cells were also demonstrated. The infecting organism is usually present in the upper layers of the stratum corneum, and on electron microscopy may be seen to invade not only between but within the keratinized cells. Corneocyte counts have demonstrated an increased cell turnover in affected skin. Depigmentation has been explained on the basis of dicarboxylic acids produced by *Malassezia* species (e.g. azaleic acid) causing competitive inhibition of tyrosinase and perhaps a direct cytotoxic effect on hyperactive melanocytes [20]. However, these acids had no effect on normal melanocytes in tissue culture. The explanation for the hyperpigmentation seen in fair-skinned subjects remains obscure, although electron microscopy reveals abnormally large melanosomes in hyperpigmented lesions, and smaller-than-normal melanosomes in hypopigmented ones [21,22]. It has also been noted that total epidermal pigmentation is reduced in hypopigmented lesions, and a thicker keratin layer in hyperpigmented lesions may be significant [23].

Clinical features [3,8]. The patient usually complains only of a patchy and varying change of skin colour, but mild irritation is sometimes noticed. The primary lesion is a sharply demarcated macule, sometimes slightly erythematous, but characterized essentially by fine branny scaling (Fig. 31.2). Typically, the eruption shows large confluent areas, scattered oval patches and outlying macules. Where scaling is minimal, it may be emphasized by firm scraping or stretching of the skin, but a sticky tape strip is a better alternative. The site most commonly affected is the upper trunk, but there is often spread to the upper arms, the neck and the abdomen. Lesions in the axillae and groins, and on the thighs and genitalia occur, and extension down the forearms on to the backs of the hands, and into the popliteal fossae is by no means rare. Facial and scalp involvement are well recognized in the tropics, and occasional cases in which only these areas are affected are seen. Palmar lesions have been reported from the tropics, and rarely occur in temperate zones. A few unusual cases have been described where the disorder appears to have been localized by occlusion or pressure, as under the straps of a rucksack or in the groins under a 'T' bandage.

The term versicolor is particularly apt. The colour of the scales may vary from pale ochre to medium brown. In the untanned white skin, the affected areas are darker than normal, but they fail to respond to light exposure; in the suntanned subject, the abnormal skin is commonly paler, as it usually is in black people. The terms pityriasis versicolor alba or achromia parasitica are sometimes used in such cases. In ordinary cases that settle spontaneously or as a result of treatment, the residual depigmentation may remain for many months without any scaling. Under the Wood's lamp, the scaly lesions may show pale yellow fluorescence, and unsuspected macular lesions more widely scattered are often revealed by this technique.

Differential diagnosis. Vitiligo and chloasma are normally distinguishable by their complete absence of scaling. Seborrhoeic dermatitis, pityriasis rosea, secondary syphilis, pinta and tinea corporis show more inflammatory change than pityriasis versicolor, and none of these ever has the even branny scale of the latter condition. Erythrasma may closely mimic pityriasis versicolor with pigmentary change and scaling, but satellite lesions are less common, and pink fluorescence under the Wood's lamp is often present. Erythrasma and pityriasis versicolor may occasionally coexist, sometimes confusingly.

Laboratory diagnosis. The finding on direct examination of coarse mycelium, fragmented to short filaments 2–5 μm wide and up to 25 μm long, together with spherical thick-walled yeasts 2–8 μm in diameter confirms the presence of infection (Fig. 31.3). Occasionally, oval yeasts may be seen. However, it is the mycelium that is the diagnostic feature, and sometimes this predominates to the extent that there are few yeast forms. As they are members of the normal flora, isolation of *Malassezia* species from scrapings is of no diagnostic value, and is not normally undertaken by diagnostic laboratories.

Treatment. There are a number of different methods of treatment [3]. The topical azole antifungals work well in pityriasis versicolor, and there is no significant difference in results achieved by different compounds [24]. The usual time to recovery is 2–3 weeks. However, there is

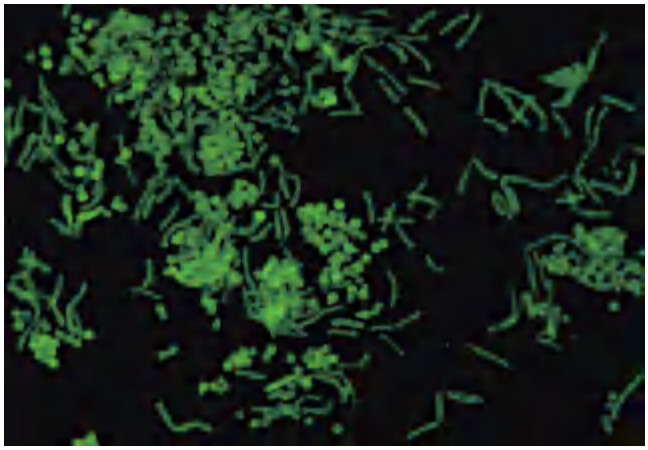

Fig. 31.3 Pityriasis versicolor. Skin scales mounted in KOH and calcofluor white, ultraviolet (UV) illumination. The hyphae diagnostic of the condition have taken up the stain immediately. *Malassezia* yeasts are also present. (Courtesy of the Department of Medical Mycology, St John's Institute of Dermatology, King's College London, London, UK.)

increasing evidence that shorter application periods using appropriate formulations such as lotions may work after only one or two applications. As has been shown with oral itraconazole, the organisms die rapidly after exposure to azoles, but in view of the thickened *Malassezia* cell wall are not rapidly cleared from the epidermis, giving the false impression of a persistent infection [25,26]. Terbinafine 1% cream is also effective in pityriasis versicolor. The main problem with the use of topical antifungals is the difficulty of applying creams to such a wide body surface area. A possible solution to this is provided by the development of a shampoo version of ketoconazole, and although it has not been fully evaluated in pityriasis versicolor, two or three applications of the shampoo appear to clear most infections.

A second cheaper approach is the application of 2.5% selenium sulphide in a detergent base (Selsun® shampoo). It is applied to all the affected areas and left overnight. The liquid is pinkish yellow and is best applied at bedtime and should be washed off the next morning. Estimates vary as to the most appropriate length of treatment, and in many cases it is necessary to apply the material regularly (e.g. every other night over 2 weeks). In some patients, however, one or two applications may be sufficient. The principal advantages of selenium sulphide are its low cost and the convenience of application. On the other hand, it is irritant if inadvertently applied to the face or genitalia, necessitating care in its application. It also stains clothes and bedding. Alternatives include 20% sodium hyposulphite solution, and 50 : 50 propylene glycol in water. The latter has also been used intermittently as long-term suppressive therapy to prevent relapse [27].

Both oral ketoconazole and itraconazole are also very effective in cases of pityriasis versicolor. The dose of ketoconazole recommended varies, but some patients respond to a single 400-mg dose; others may require longer periods of treatment [28,29]. While opinions differ as to the appropriate place for oral therapy, the authors usually reserve oral itraconazole for recalcitrant cases. Itraconazole is active against pityriasis versicolor in a total dosage of 800–1000 mg [9,26], usually given over 5 days.

Relapse is unfortunately very common, whatever the primary treatment; in all but the most resistant cases it is probably simplest to re-treat each episode rather than resort to long-term suppressive therapy. Patients should be warned that repigmentation may take several months, as otherwise they will often report treatment failure, even when the organisms have been destroyed, simply because the hypopigmentation persists.

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Other cutaneous disorders associated with *Malassezia* yeasts

Lipophilic yeasts of the genus *Malassezia* are part of the normal skin flora, and therefore any evidence that they are either directly or indirectly implicated in the pathogenesis of skin disease is often difficult to assess.

For many years, it has been known that *Malassezia* yeasts are found in large quantities in the scales of seborrhoeic dermatitis both on the scalp and elsewhere. This has been attributed largely to hyperproliferation of the epidermis, the assumption being that the organisms were merely colonizing this particular site. The same was thought to be the case with skin-surface bacteria [1]. However, it has become apparent that most patients with seborrhoeic dermatitis or scaling of the scalp (dandruff) clear on treatment with azole antifungal agents coincidentally with the disappearance of the yeasts, and that if they relapse after therapy this occurs when the organisms reappear [2,3]. The circumstantial evidence therefore that the two events are causally related is very strong. In animals, it is possible to induce skin scaling that bears some resemblance to seborrhoeic dermatitis after the application of *Malassezia* yeasts [4]. Some but not all authors have reported that patients with seborrhoeic dermatitis have significantly raised levels of antibody to these organisms [5], but do not appear to develop contact sensitization to antigenic extracts. One further intriguing piece of evidence is that seborrhoeic dermatitis is one of the earliest and most consistent abnormalities seen in patients with AIDS not on antiretrovirals [6,7]. Yet, as with seborrhoeic dermatitis in non-AIDS patients, there is no consistent correlation between colonization and primary disease, although numbers of yeasts are higher in those with low CD4 counts. All these observations reinforce the view that adult-type seborrhoeic dermatitis is directly related to *Malassezia* yeasts but not to a single species. The relationship between infant seborrhoeic dermatitis and these organisms is less well established. The mechanisms by which they induce skin changes are not known, and the possibilities of direct lipase activity [8] or antibody-mediated epidermal damage [5] have both been considered. It is also apparent that a small percentage of patients with typical seborrhoeic dermatitis do not respond to azole antifungals, and the exact mode of pathogenesis is not clear. However, it is possible that a number of different stimuli can trigger this common condition of which the most common is *Malassezia*.

A further observation is that certain patients with eczema affecting the head and neck may also respond to topically applied azole antifungals, and also show immediate-type hypersensitivity to extracts of *Malassezia* [9]. Patients have usually had childhood atopic disease or are atopic on family history, and the condition is most often seen in young women.

The second condition associated with *Malassezia* yeasts is a form of folliculitis on the back and upper trunk. *Malassezia* folliculitis is a clinically distinct condition most often seen in teenagers or young adult males [10,11]. Lesions are itchy papules and pustules, which are often diffusely scattered on the shoulders and back. The itching and distribution distinguish them from acne vulgaris. Patients often report the development of lesions following a holiday in the sun. The condition responds well to oral itraconazole or ketoconazole shampoo. Biopsies taken from typical cases show clusters of yeasts within follicles surrounded by inflammatory cells, which are distinguishable from the colonization of follicular openings that can be seen in normal individuals. The exact pathogenesis of this condition is once again unknown, but treatment with appropriate antifungals is highly effective. *Malassezia* yeasts have also been associated with other skin conditions such as confluent and reticulate papillomatosis [12–14]. However, their presence in this condition is not invariable, and their removal with antifungals not necessarily followed by significant changes in the skin lesions. In addition, some patients respond to minocycline. Finally, there is a variant of psoriasis that has been termed 'sebopsoriasis' where, it is speculated, lipophilic yeasts may have a pathogenic role [15]. While clinically this condition shows some features of both psoriasis and seborrhoeic dermatitis, it still needs to be defined more clearly before it is possible to ascribe a role to the yeast flora.

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Tinea nigra

SYN. TINEA NIGRA PALMARIS; KERATOMYCOSIS NIGRICANS PALMARIS; PITYRIASIS NIGRA

Definition. Tinea nigra is an asymptomatic superficial fungal infection generally affecting the skin of the palms and characterized by deeply pigmented macular non-scaly patches.

Aetiology. Tinea nigra is generally caused by *Phaeoannellomyces werneckii* (syn. *Exophiala werneckii, Hortaea werneckii*) [1]. A different organism, *Stenella araguata* has been isolated from some cases diagnosed in Venezuela [2]. The disease occurs sporadically in many parts of the world, including the Americas and the Caribbean, South Africa, Australia, Europe and the Far East. It can easily be reproduced experimentally by scarifying the skin and applying a pure culture of *P. werneckii* under a bandage. The incubation period in separate studies was reported to be 10–15 days and 7 weeks, respectively.

Histology. There is thickening of the stratum corneum in which hyphae are present. Inflammatory reaction in the dermis is minimal.

Clinical features [3]. The lesions are asymptomatic, macular, sharply defined and not scaly. The most distinctive feature is the brown or black colour resembling a silver nitrate stain. The palms are most commonly affected [4,5] in cases reported in the western hemisphere, but other areas of the body such as the soles and, more rarely, neck and trunk have been recorded, particularly in Asia. By uneven rate of spread or coalescence of lesions, irregular outlines are produced. Spontaneous clearance is very unusual.

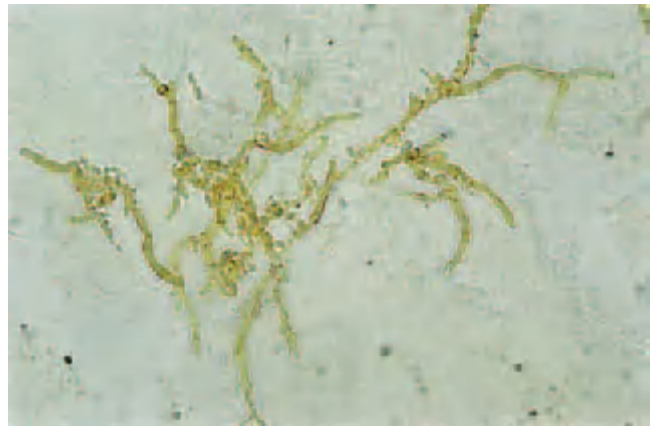

Fig. 31.4 Tinea nigra. Skin scales mounted in 30% potassium hydroxide, bright field. The natural brown colour of the septate hyphae is apparent. (Courtesy of the Department of Medical Mycology, King's College London, St John's Institute of Dermatology, London, UK.)

Differential diagnosis. The black colour and the absence of scaling differentiate the condition from pityriasis versicolor. The pigmented lesions of Addison's disease, syphilis, pinta and junctional naevi of the palm may have to be differentiated, and mycological examination of scales is usually required.

Laboratory diagnosis. Microscopy of infected epidermal scales in potassium hydroxide mounts reveals brown branched closely septate hyphae up to 5 μm in diameter, and elongated budding cells (Fig. 31.4).

Phaeoannellomyces werneckii. Colony: cultures on glucose peptone agar may be relatively slow growing, and initially yield a dirty white to grey moist yeast-like colony, which darkens to black, and over the course of several days becomes more filamentous and velvety. Microscopy: examination of young cultures reveals annellidic yeast-like budding cells, which are often uniseptate, the septum being dark in mature cells. The conidia are initially hyaline but become brown on maturity. Hyphae in older cultures produce intercalary and lateral conidiogenous cells, which are annellidic or sympodial.

Treatment. Topical azole creams such as econazole and ketoconazole [6] are effective. The condition also responds to the topical application of fungicidal preparations such as Benzoic Acid Ointment Compound BPC. Tiabendazole 2% in 90% dimethylsulfoxide once a day for 14 days gives good results, as does the ordinary commercially available 10% tiabendazole suspension.

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Black piedra

SYN. TINEA NODOSA; TRICHOMYCOSIS NODULARIS

Definition. A fungal infection confined to hair shafts and resulting in the formation of hard dark superficial nodules thereon.

Aetiology. Black piedra is caused by the fungus *Piedraia hortae*. It occurs in humid wet tropical regions [1] in the Americas and in South-East Asia, and affects monkeys as well as humans [2]. The infection was thought to be more common in males than females, but a study among the Zoro indians of Brazil [3] showed no significant difference between the sexes. The same study showed a prevalence of infection of 57% in subjects over the age of 11 years.

Clinical features. Black piedra is characterized by the presence of firmly adherent black gritty hard nodules on the hairs of the scalp, or less frequently of the beard, moustache or pubic area. The nodules vary in size from microscopic to 1 mm or more in diameter, and their thickness often tapers, either from one end to the other or from the middle to the edge. They are usually multiple, and oval or elongate in shape. Subcuticular fungal growth may rupture the cuticle, and the fungus may then grow on the outside of the cuticle, completely surrounding the hair shaft. Because the fungus grows into the hair shaft, the hair may fracture easily. Untreated, the infection may last for months or years.

Histology. In histological section or in potassium hydroxide mounts, the nodules are observed to be made up of closely packed brown hyphae held in a mass by a viscous or cement-like substance (Fig. 31.5). At the edges of the nodule, regularly aligned hyphal strands and arthroconidia, 4–8 µm in diameter, can be seen, while in the thicker parts club-shaped asci containing eight elongated ascospores may be formed. The ascospores have a polar filament at each end, and can be observed by crushing or sectioning the nodule. *Piedraia hortae* is almost unique among the human pathogenic fungi in producing sexual spores in its parasitic phase.

Fig. 31.5 Black piedra. Hairs mounted in 30% KOH, bright field. The dark nodules are formed of dematiaceous hyphae cemented together to form a hard mass. (Courtesy of the Department of Medical Mycology, King's College London, St John's Institute of Dermatology, London, UK.)

Laboratory diagnosis. The direct examination is so characteristic that culture is not absolutely necessary. If culture is performed, it should be noted that the fungus is not inhibited by cycloheximide.

Piedraia hortae. Colony: the culture is slow growing, compact, domed and black. Microscopy: brown thick-walled septate hyphae and chlamydoconidia are present. Asci and ascospores may be present in the thicker portion of the colony [4], but are not formed by every isolate.

Treatment. Shaving or cutting the hair effects a cure. To prevent recurrence, antifungal preparations such as Benzoic Acid Ointment Compound BPC or a 1 : 2000 solution of mercury perchloride may be applied to the hair after shampooing. The first case treated with terbinafine has been reported [5].

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White piedra

SYN. TRICHOSPOROSIS NODOSA

Definition. A fungal infection confined to hair shafts and resulting in the formation of soft, white, grey or brown superficial nodules.

Aetiology. Until 1994, the aetiological agent of white piedra was considered to be the basidiomycetous yeast *Trichosporon beigelii*, but genetic analysis has now determined that this name covered a complex of different species [1], and the agent of capital white piedra is now considered to be *T. ovoides* and those reported from crural white piedra include *T. inkin*, *T. asahii* and *T. mucoides*. The infection occurs in South America, Africa, central and eastern Europe, and Japan [2,3]. The horse and certain species of monkey may be affected. The cases occasionally observed in temperate countries have usually been in visitors from the tropics, but cases have occurred in both Europe and the USA in individuals who have never left these regions [4]. A study in equatorial Africa demonstrated a prevalence of 18% among inguinal specimens from 449 female subjects [2].

Clinical features. White piedra is characterized by the presence of soft white or light brown nodules. The infection is more common on the hairs of the beard, moustache and genital areas than the scalp [5,6]. The fungus grows both within and outside the hair shaft, and the hair shaft may be weakened and break off. The nodules are transparent, easily detached from the hair and vary in size from microscopic to 1 mm in diameter. The underlying skin is not affected and there is no fluorescence under Wood's light.

There have been some new findings relevant to the pathogenesis of this condition. First, there is evidence that some cases may be sexually transmitted [7]. In addition, it has been postulated that the bacteria known to accompany the concretions of the fungi on hair, now identified as a new species of *Brevibacterium*, *B. mcbrellneri* [8], may have a synergistic role in the infection [9]. The strong proteolytic activity of the bacterium may facilitate hair shaft invasion by both yeast and bacterium, while fungal byproducts may stimulate bacterial growth. There is an increased carriage rate of perianal '*T. beigelii*' reported in human immunodeficiency virus (HIV)-positive individuals, suggesting that this region may provide a reservoir for carriage. Interestingly, there does not appear to be an increased incidence of hair shaft infection in these patients.

Histology. The nodules of white piedra are in the form of a sheath, which may extend around the hair shaft. There may be extensive growth within the hair, giving rise to the characteristic nodular swellings on the hair shaft. The hyphae segment into arthroconidia 2–4 μm in diameter, and budding blastoconidia may also be seen (Fig. 31.6).

Differential diagnosis. The presence of pruritus and the distinctive shape of egg cases of pediculi should serve to distinguish pediculosis from piedra, but microscopical examination is desirable.

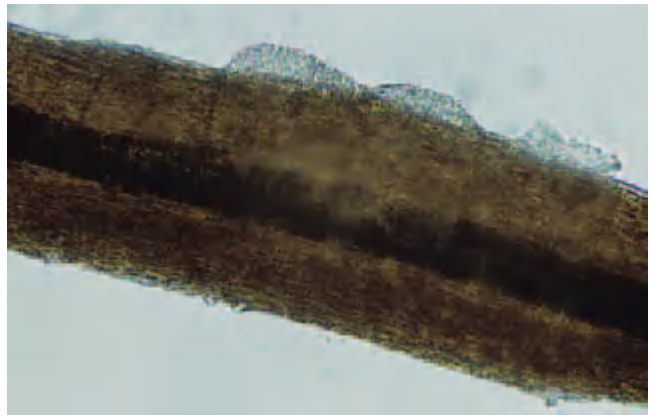

Fig. 31.6 White piedra. Hair mounted in KOH, bright field. The gelatinous nodules formed by various *Trichosporon* species surround the hair. (Courtesy of the Department of Medical Mycology, King's College London, St John's Institute of Dermatology, London, UK.)

Laboratory diagnosis. Most *Trichosporon* species are inhibited by cycloheximide, so this antibiotic should be excluded from the culture medium. As a few isolates fail to grow at 37°C, it is also advisable to incubate at 28–30°C.

Trichosporon species. Colony: the colonies of *Trichosporon* species develop rapidly and are soft, creamy and wrinkled, and sometimes mucoid [10]. Microscopy: the genus *Trichosporon* is characterized by the presence of hyphae, arthroconidia and budding cells. These are best observed with a deep cut streak on a cornmeal or rice agar supplemented with Tween 80. Physiological tests: the species recently recognized using genetic analyses can be identified in the routine laboratory using their morphological characteristics, together with carbohydrate assimilation patterns determined by the commercial API 32C system (bioMerieux), failure or ability to grow at 37°C and relative sensitivity to cycloheximide [1].

Treatment. As with black piedra, shaving or cutting the hair may effect a cure. Responses to concentrated topical antifungals, azoles and allyamines have been reported but are unpredictable.

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Otomycosis

SYN. MYCOTIC OTITIS EXTERNA

Definition and clinical features. A chronic inflammatory condition of the external auditory canal caused by fungal infection (external otitis in general, including the differential diagnosis and the management, is considered in Chapter 65). In some patients with external otitis, fungi may be isolated from swabs or scrapings, and indeed material taken from the normal external ear may on occasions yield a variety of moulds [1]. Such isolates are more common in tropical regions. Very occasionally in external otitis, the fungus isolated appears to be playing a pathogenic part, perhaps even a primary one. The species most commonly accepted as a pathogen in this situation is *Aspergillus niger*. Other species implicated as pathogens include *A. fumigatus* and other *Aspergillus* species [2,3], *Scedosporium apiospermum*, numerous other moulds and *Candida* species.

The inflamed, itchy and sometimes painful external canal usually discharges a little serous fluid. In advanced cases of true mycotic otitis, an overgrowth of fungal hyphae may produce a mass of white material suggesting damp cotton wool, lodged in the external canal. Where *A. niger* is the causative organism, the mat of fungus is often covered by black fruiting heads [4]. In severely immunocompromised patients, the external auditory meatus can be extensively eroded by fungal invasion to produce a necrotic form of otitis externa [5]. This form may spread to involve other sites including the middle ear and the mastoids. The pinna may be the site of several mycotic diseases including chromomycosis [6], sporotrichosis [7] and tinea [4], but such infections usually spare the external auditory meatus.

Laboratory diagnosis. A light growth of a mould from a swab taken from the ear is of little significance. *Rhizopus*, *Absidia*, *Mucor* or *Penicillium*, or indeed *Aspergillus* species, in small amounts mean little. Nor should any great weight be given to a light growth of *Candida*, although this organism can cause external otitis. The criteria for accepting the fungus as having an aetiological role are the absence of any significant bacterial pathogens and the presence of large masses of fungi, such as may sometimes be seen on examination of the patient. If there is a considerable amount of fungal material in specimens taken for direct examination, this may be adequate evidence.

Aspergillus niger. Colony: growing rapidly, the colony initially has a white or cream surface, which becomes black as the conidia are produced. The reverse remains pale cream to celadon green. Microscopy: the conidiophores arise at right angles to the supporting hyphae, and have a swollen globose vesicle at their tip, which is completely covered by a layer of supporting cells or metulae. These metulae support a layer of phialides, which produce chains of dark brown, rough-walled phialoconidia. The bottom end of the conidiophore ends in a foot cell inserted in the supporting hypha.

Treatment [4,8,9]. Careful toilet, with removal of debris and fungal material from the ears, is of paramount importance. Various local applications have been suggested. One routine consists of applying 2% thymol in 70% alcohol during cleansing, followed by 50% metacresyl acetate or olive oil on a pledget of cotton wool left for 24 h. Clotrimazole lotion has been employed with success in both *Aspergillus* and *Candida* infections. Bifonazole lotion and cream were effective in the majority of 35 patients included in a long-term study attempting to correlate the bacterial and fungal flora in patients with symptomatic otomycosis [9]. Oral itraconazole has been used in the aggressive invasive form of otitis externa.

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Miscellaneous superficial fungal infections caused by saprophytic moulds

The normal skin, especially the scalp and toe clefts, is commonly contaminated with spores or even short lengths of mycelium of saprophytic species. Where the fungal mycelium is pigmented or where distinctive spores are concerned, they may be recognized in direct examination of skin scrapings. If cycloheximide-free media are used, they may be readily cultured. Usually, such species are present in small amounts, and may without difficulty be dismissed as contaminants that have impacted on the skin, in the same way as the pollen grains occasionally observed. From time to time, however, reports appear in

the dermatological literature of cases in which species such as those of *Aspergillus* [1] appear to colonize damaged tissues, become firmly established and perhaps cause secondary tissue destruction. Most authors wisely counsel caution before accepting any sort of pathogenic role for the moulds in these cases.

Laboratory diagnosis and management. In situations like these, it is important to take repeated scrapings, to use cycloheximide-free media in culture and then to weigh the facts carefully before assuming that the organism is anything more than a contaminant. In many cases, simple correction of local precipitating factors, such as maceration or occlusive dressings, may be all that is needed.

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Dermatophytosis

Introduction

Dermatophytes are related fungi [1,2] capable of causing skin changes of the type known as ringworm or dermatophytosis. Thus defined, the ringworm species are all moulds belonging to three asexual genera: *Microsporum*, *Trichophyton* and *Epidermophyton*. Forty years ago, the sexual state of dermatophytes was unknown, and this phase of the life cycle has still not been found for many of the common species. However, in those species where the sexual state has been identified, all the organisms are classified in the single genus *Arthroderma* in the phylum Ascomycota [3]. A list of synonyms of sexual and asexual names is included for reference (Table 31.3). However, as sexual states are not routinely seen in the diagnostic laboratory, the asexual anamorph names will be used throughout this section.

In addition to the recognized pathogens, a number of fungi have been discovered that are keratinophilic and that are clearly close relatives of the ringworm fungi—indeed, some are even classified in the same three anamorph genera—but that are soil dwellers and non-pathogenic. Although some authors include these fungi within the dermatophytes, in the authors' opinion they are better classified in the broader group of keratinophilic fungi, retaining the term dermatophyte for those species that can act as true cutaneous pathogens.

Table 31.3 Asexual–sexual connections of dermatophytes.

Asexual state	Sexual state
Microsporum canis	*Arthroderma otae*
Microsporum fulvum	*Arthroderma fulvum*
Microsporum gypseum	*Arthroderma incurvatum*
Microsporum gypseum	*Arthroderma gypseum*
Microsporum nanum	*Arthroderma obtusum*
Microsporum persicolor	*Arthroderma persicolor*
Trichophyton mentagrophytes	*Arthroderma benhamiae*
Trichophyton mentagrophytes	*Arthroderma vanbreuseghemii*
Trichophyton simii	*Arthroderma simii*

The three asexual dermatophyte genera are distinguished by the morphology of the large multicellular macroconidia that are produced [4]. In the genus *Microsporum*, the macroconidia are rough, usually thick walled and range from fusiform to obovate in shape with 1–12 or more septa. Those of *Trichophyton* species are thin walled, smooth and may be cylindrical, fusiform or clavate in shape, with up to 12 transverse septa. In *Epidermophyton*, the macroconidium is clavate, broadened and rounded at its distal pole, thin walled and has up to five septa; the conidia are smooth when first formed, but as the colony ages discrete wall thickenings may be observed.

Apart from the mycological classification of dermatophytes, it has been traditional for clinical and epidemiological reasons to group dermatophytes that infect humans according to their ecological niche: geophilic species originating in the soil (Table 31.4), zoophilic species having animal origins (Table 31.4) and anthropophilic species, which are largely restricted to human skin (Table 31.5). However, these three groups are not always sharply demarcated. Species that are clearly geophilic may contaminate or infect the coats of animals, especially small rodents, and may thus infect humans through an intermediate animal host. Similarly, animal species may shed infective material on to the soil and, although incapable of multiplying there, fungal elements may survive long enough to be isolated in a soil survey [5]. In the case of species affecting farm animals, their environment, cow sheds and fences may be contaminated by shed keratinocytes or hair containing fungal spores, just as the floors around swimming baths and the air of hospital clinics may be contaminated by anthropophilic species [5].

The distribution of the zoophilic species reflects that of the major animal hosts. Those geographically limited include *Microsporum canis* var. *distortum*, *M. persicolor*, *Trichophyton mentagrophytes* var. *erinacei* and *T. simii* (Table 31.4). Many of the anthropophilic species are also geographically limited and the classic endemic distributions are indicated in Table 31.5. However, to some degree these must reflect the distribution of diagnostic facilities, and data for some areas are slight or outdated. Also, the anthropophilic dermatophytes are spread by population movements. For example, species classically thought of as African, such as *T. soudanense*, have been isolated in the USA and Europe with some regularity. The European infections have not been among immigrants from the endemic areas alone, but also in children born in Europe of African immigrants and, more rarely, among the

Table 31.4 Geophilic and zoophilic dermatophytes.

	Geographical distribution	Major host
Geophilic species		
*Microsporum gypseum**	Worldwide	
Microsporum praecox	USA, western Europe	
Zoophilic species		
Microsporum canis var. *canis*	Worldwide	Cat, dog
var. *distortum*	New Zealand, USA	Cat, dog
Microsporum equinum	Worldwide	Horse
Microsporum gallinae	Worldwide	Fowl
Microsporum nanum	Worldwide	Pigs
Microsporum persicolor	Americas, Europe	Voles
Trichophyton equinum	Worldwide	Horse
Trichophyton mentagrophytes		
var. *mentagrophytes*	Worldwide	Rodents
var. *erinacei*	Europe, New Zealand	Hedgehogs
var. *quinckeanum*	Worldwide	Mice
Trichophyton simii	India	Monkey
Trichophyton verrucosum	Worldwide	Cattle

* This asexual species is a complex of three sexual species.

Table 31.5 Anthropophilic dermatophytes.

Species	Geographical distribution
Epidermophyton floccosum	Worldwide
Microsporum audouinii	Worldwide
var. *rivalieri*	Africa
var. *langeronii*	Africa
Microsporum ferrugineum	Far East, eastern Europe, Africa
Trichophyton concentricum	Pacific, South-East Asia, Latin America
Trichophyton gourvilii	Central Africa
Trichophyton mentagrophytes var. *interdigitale*	Worldwide
Trichophyton megninii	Mediterranean
Trichophyton rubrum	Worldwide
Trichophyton schoenleinii	Worldwide
Trichophyton soudanense	Subsaharan Africa
Trichophyton tonsurans	Worldwide
Trichophyton violaceum	North Africa, India, Middle East
Trichophyton yaoundei	Central Africa

endemic European population. Some of the species that have been regarded as cosmopolitan, including *M. audouinii* and *T. schoenleinii*, are currently rarely isolated in the USA and many parts of western Europe, although in some areas, particularly parts of Africa, they remain endemic.

It must also be appreciated that these distributions are not static, and the range of species in some areas may change dramatically and quickly. For instance, in one central London laboratory during the period between 1980 and 1990, the most common isolate from tinea capitis was the zoophilic organism *M. canis*. In contrast, during 2000 and 2001 *T. tonsurans*, a species that was rarely seen in the 1980s, was responsible for 87% of scalp infections (M.K. Moore, St John's Institute of Dermatology, London, unpublished data). A resurgence of infection by other anthropophilic species, such as *T. soudanense* and *M. audouinii*, has also been noted in London during the period between 1993 and 2002 (M.K. Moore, St John's Institute of Dermatology, London, unpublished data).

From the evolutionary point of view, it is likely that the anthropophilic species represent the end of a line, starting with non-pathogenic keratinophilic soil species, existing as saprophytes on keratinous debris, passing through the geophilic dermatophytes and the zoophilic species. The increased specialization that this evolutionary trend implies seems to be accompanied by a progressive loss of the sexual state and a reduction in the production of conidia, particularly macroconidia, and a loss of certain mating types [6–8]. Virtually all the non-pathogenic keratinophilic species and geophilic dermatophytes have demonstrable sexual states, as do a few of the zoophilic group, particularly those infecting animals living in

burrows or dens and thus soil-associated. However, dermatophytes that infect larger animals, such as *T. verrucosum* from cattle, *T. equinum* from horses and the anthropophilic dermatophytes, have as yet no known sexual state. It has been suggested that this transition from sexual to asexual life cycles had led to an unprecedented level of adaptive radiation among the anthropophilic dermatophytes, resulting in a large number of species and variants. Other factors that may have contributed to the adaptive radiation on humans include the separation of the human skin into distinct areas differing in the distribution of sebaceous glands and hairs, resulting in a marked affinity for particular body sites among the anthropophiles, which is not seen in zoophiles.

Characteristically, zoophilic species tend to produce highly inflammatory reactions in humans and this may lead to a spontaneous cure. Anthropophilic species produce mild but chronic lesions. There are many exceptions to this useful generalization, and the degree of inflammatory response depends in part on the site of infection—large follicles of scalp and beard are associated with an intense reaction—and the immune status of the host [9].

An important characteristic of the dermatophytes as parasites is their restriction to dead keratinized tissue. Although the inflammatory responses of ringworm infection involve the dermis and the Malpighian stratum of the epidermis, the fungus itself is found growing only within the stratum corneum of the epidermis, within and around the fully keratinized hair shaft, and in the nail plate and keratinized nail bed. Within these keratinized tissues, the fungus exists only as mycelium and arthroconidia. In this parasitic phase of fungal growth, there are no micro- or macroconidia and no specialized vegetative structures, such as spiral or pectinate hyphae. For these reasons, precise identification of the species of an infecting dermatophyte is generally impossible on direct microscopy of skin or nail.

In dermatophyte infections involving hair, the fungus invades the follicle from the adjacent stratum corneum and follows one of several precise patterns of growth. In the case of *M. canis* and *M. audouinii*, for example, the fungus penetrates the keratinized hair at about mid-follicular level, having grown down on the hair surface [10]. It then grows downwards within the hair towards the bulb, until the zone of incomplete keratinization is reached. Growth is then arrested, or rather slowed and resisted. An equilibrium is established, the fungal mycelium invading new, fully keratinized hair shaft at the same rate as it is formed, but never growing down into the incompletely keratinized tissue. Further up the shaft, hyphae from the existing mycelium grow outwards from inside the hair and proliferate on its surface. These secondary extrapilary hyphae are tortuous; they fragment into small arthroconidia, which rapidly round up to become spherical structures, and are seen as a packed mosaic of spores coating the surface of the hair. This is the small-spored ectothrix type of hair invasion.

Other species of dermatophytes show different patterns of hair invasion. *T. verrucosum* and *T. mentagrophytes* var. *mentagrophytes*, like the *Microsporum* species, show arthroconidia on the surface of the hair and hyphae within it, but these conidia are larger and are arranged in straight chains. This is known as large-spored ectothrix hair invasion. *T. tonsurans* and *T. violaceum*, among others, produce an endothrix type of hair invasion, with the hyphae inside the hair fragmenting completely into a mass of relatively large arthroconidia, which are retained entirely within the hair shaft. *T. schoenleinii*, the cause of favus, is different again. The hyphae within the hair are fewer in number than in other endothrix infections and do not break up into a mass of arthroconidia but run intact through the hair, forming tunnels within its structure. When mounted in potassium hydroxide, these tunnels around the hyphae, initially filled with air, form the characteristic air spaces seen. While in favus the infected hair commonly grows to normal lengths, in endothrix infections where arthroconidia are formed the hair, being most severely damaged, breaks at the skin surface. In small-spored ectothrix infections the shaft tends to fracture a few millimetres above the surface.

All these parasitic patterns are very different from the mode of growth of dermatophytes on hair *in vitro* [11]. If plucked hair is inoculated with any of the *T. mentagrophytes* varieties, for example, frond-like fungal hyphae develop on the surface and lift the cuticle cells. Conical pits are then formed perpendicular to the surface of the hair as penetration of the keratinized hair cortex occurs. Intrapilary growth follows along the hair shaft in both directions, and micro- and macroconidia may be produced. There are no linear chains of arthroconidia on the surface. Moreover, if a hair, parasitized *in vivo*, is plucked, and then cultured *in vitro*, the specialized growth pattern initially established will cease and the saprophytic phase, with the development of micro- and macroconidia, will rapidly follow.

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Pathogenesis of infection

Invasion of the epidermis by dermatophytes follows a common pattern starting with adherence between arthroconidia and keratinocytes, followed by penetration through and between cells and the development of a host response.

Adherence

On the stratum corneum, the first phase of dermatophyte invasion involves the adherence of infectious arthroconidia to keratinocytes. *In vitro*, this process is completed after about 2 h of contact, at which stage germination and penetration of the keratinocyte occurs [1]. Different dermatophytes show similar kinetics, which are also unaffected by the source of the keratinocytes. The germination of arthroconidia and hyphal prolongation which follows adherence proceeds radially, and *in vitro* there is evidence of indentation of keratinocytes beneath the growing hyphae, possibly resulting from enzymic action [2].

Penetration

It is widely accepted that dermatophytes are keratinophilic. Evidence for this ranges from the success of hair-baiting techniques for isolating the fungi from the soil, to the ability of many dermatophytes to invade hair and nail *in vitro*, and the presence of evidence of damage around penetrating hyphae in nail, suggesting digestion of keratin. However, many workers have been unable to demonstrate enzymes produced by dermatophytes with keratin-specific proteinase activity [3]. *In vitro*, non-keratin substances extracted from keratinized tissues will support growth of dermatophytes much better than the keratin, which remains after extraction [4]. Dermatophytes produce a variety of proteolytic enzymes, which range in size from 40 to over 200 kDa [5]. There is evidence in *T. mentagrophytes* that both a cell-free and a membrane-bound keratinase are present [6]. One group of workers has demonstrated that keratinase activity from certain dermatophytes is inducible by low-molecular-weight peptides released from the epidermis by the action of other fungal proteinases [7]. From this it can be seen that the precise part that keratin-specific enzymes play in fungal invasion of the stratum corneum is not entirely clear, and that other proteinases and even mechanical forces caused by hyphal growth may have a role. Clinically, there appears to be a certain amount of heterogeneity in substrate preference as, while all dermatophyte species invade the stratum corneum of the skin, different species vary widely in their capacity to invade hair and nail. *T. rubrum* rarely invades hair but frequently invades nail; *Epidermophyton floccosum* never invades hair and only occasionally nail. In addition, other factors, such as those concerned with host resistance (e.g. serum) have a role in limiting the ability of dermatophytes to penetrate further than the stratum corneum [8].

Host resistance and immunology

Defence against the fungi causing ringworm depends on both innate and acquired immune mechanisms [9], the latter requiring the intervention of immunological memory [10]. Serum factors appear to be able to inhibit the growth of dermatophytes *in vitro* and on cultured explants of skin. It is not entirely clear what is responsible for this, but unsaturated transferrin is one candidate, which inhibits the growth of dermatophytes by binding to the hyphae [11]. Its mode of action appears to be independent of iron-binding capacity. In experimental infections of skin grafted on to *nu/nu* mice, there is evidence of increased turnover of epidermis, which occurs in the absence of effective T-lymphocyte-mediated defence [12]. A further, potentially important mode of defence is provided by the presence of fatty acids from sebaceous glands, which inhibit dermatophyte growth *in vitro*. This activity appears to reside in saturated fatty acids with chain lengths of 7, 9, 11 and 13 carbon residues. It has been postulated that their presence on the skin in postpubertal children may account for the spontaneous resolution of tinea capitis after this age, and the rarity of new infections in adults. Undecenoic acid derivatives are a practical example where fatty acids have been used for the treatment of dermatophytosis. Whatever the influence of these factors, it is clear that in experimentally infected mice the initial inflammatory changes occur as early in the process as 4 h after infection. This suggests that endogenous mechanisms may attract leukocytes [13], and the role of inflammatory mediators, such as the eicosanoids, in this respect needs to be investigated.

It has also been found that dermatophytes are chemotactic and that they can activate the alternative pathway of complement activation. This has been demonstrated for *T. rubrum*, *T. mentagrophytes* [13] and fungi causing endothrix scalp infections, such as *T. violaceum*. The production of cytokines, such as interleukin-1 (IL-1), by keratinocytes has not been investigated in the mobilization of neutrophil defences. It has been shown that neutrophils, and to a lesser extent monocytes, can kill dermatophyte conidia [14]. This activity depends both on intra- and extracellular mechanisms, and the generation of the respiratory burst is an important stage in this process [15]. Dermatophytes produce catalase and superoxide dismu-

tase, which may act as defences against the phagocyte myeloperoxidase system.

By contrast, there is little evidence that antibodies to dermatophytes are protective. Patients with widespread infections, such as tinea imbricata, may have high antibody titres [16]. The presence of elevated IgE in particular is associated with chronicity (see below) [17]. Transfer of specific serum containing a high titre of antibody to irradiated mice does not confer immunity on recipients. It is still premature to rule out a role for antibody, as dermatophytes show some cytological changes when grown in the presence of specific antibody *in vitro*. However, there is strong evidence that the development of cellular immunity via sensitized T lymphocytes is a key factor in immunological defence. Lymphocytes bearing T-helper phenotypic markers are responsible for transferring immunity to infection to naïve recipient mice [18]. In humans, the appearance of inflammation in ringworm correlates with the development of delayed-type skin reactivity to trichophytin [19–21] and cytokines such as interferon-γ. Chronic infections are associated with poor T-lymphocyte-mediated response to specific fungal antigens, suggesting that depression of responses is responsible for the poor clinical response [19,22]. Langerhans' cells can act as antigen-presenting cells for dermatophyte antigens [23].

The reason for failure of immunity in persistent infections, and its relationship with chronicity, are still not well understood. There is an association between the presence of atopy and chronic dermatophytosis, with a high proportion of those with persistent disease having atopy (usually asthma or hay fever) as well as immediate-type hypersensitivity and raised IgE levels [19,22]. It has been suggested that modulation of T-lymphocyte activity either locally or systemically may be responsible. Possible mechanisms include activation of a type 2 helper T (Th2) lymphocyte pathway, which might explain the spectrum of antibody responses. It has also been found that dermatophyte antigens, including those that contain mannose residues, can reversibly suppress lymphocyte proliferation, but not the expression of human leukocyte antigen (HLA)-DR [24]. Patients with persistent infection have detectable levels of circulating antigen [25]. Both are possible factors in the regulation of immunity in dermatophytosis.

Patients with dermatophytosis are usually otherwise healthy. However, altered or chronic infections have been noted in a number of patient groups, such as those with chronic mucocutaneous candidosis, AIDS [26] and patients on corticosteroid therapy or with endogenous Cushing's syndrome. In addition to these, there is the raised incidence of atopy in those with chronic infection, suggesting that host factors may well determine the clinical course. However, this is not the only factor, and it has been found that where there is ample facility for the spread of infection (e.g. among coalminers), the incidence of atopy is no different to that seen in uninfected co-workers [27].

Other factors affecting infection

Age, sex, genetic and racial factors

The known differences in the incidence of ringworm infection between the age groups and sexes seem, in general, to reflect differing rates of exposure and of sebum production, differing clothing and fluctuations of immunity with old age. What little evidence there is does not support the suggestion that susceptibility to ringworm infection is linked to any of the ABO blood groups. There may be racial differences of susceptibility, but they are not clearly established [28]. In tinea imbricata, a genetic susceptibility factor inherited as an autosomal recessive has been suggested [29]. It has also been suggested that a genetically determined factor(s) may be wholly or partly responsible for family clusters of cases of infection [30]. The definitive proof awaits the demonstration of appropriate genetic abnormalities by linkage studies.

Endocrine and metabolic factors

There is no reliable evidence that diabetic patients are especially susceptible to dermatophyte infection [31], even though diabetes may affect the course of established infections; for example, diabetic patients with tinea pedis are more likely to develop onychomycosis. In malnutrition and in Cushing's syndrome, the apparently diminished resistance to infection may well have followed depressed cellular immunity.

Temperature and microenvironment

With the exception of *T. verrucosum*, dermatophytes grow poorly at 37°C. This factor alone may be responsible for the lack of deeper penetration of the epidermis and dermis. Raised carbon dioxide tension is known to facilitate arthroconidial formation, and may also aid either adhesion or penetration [32]. Moisture is also important for germination of arthroconidia on keratinocytes.

Competing organisms and co-pathogens

The ability of certain dermatophyte species to produce penicillin-like antibiotics may allow these fungi to regulate the bacterial flora [33]. Although there is some competitive interaction [34], *Staphylococcus aureus* may occasionally act as a co-pathogen, increasing the degree of inflammation in dermatophyte infections [34].

Histopathology

The clinical appearances of the various forms of ringworm infection are the result of the combination of direct damage to the keratinized tissues by the fungus (this

applies mainly in hair and nail infections), and of the inflammatory host response. The latter varies widely. At one extreme there is the simple hyperkeratosis seen, for instance, in dry-type *T. rubrum* infections; at the other is the pustular, highly inflammatory kerion seen most frequently in zoophilic infections, such as those caused by *T. verrucosum*. This subject has been extensively reviewed [35]. *T. rubrum*, for instance, may provoke the epidermal changes seen in chronic dermatitis with hyperkeratosis, patchy parakeratosis, hyper- or hypogranulosis, spongiosis, mononuclear invasion, and mild or moderate acanthosis. The accompanying dermal infiltrate of lymphocytes and histiocytes is largely perivascular. The picture may be more inflammatory with superficial crusting, and the more acute inflammatory changes in the epidermis may at times become vesicular, to the extent of mimicking acute contact dermatitis. Other changes described include an erythema multiforme-like process with subepidermal bullae [35], and dermal blood-vessel changes of an allergic angiitis, accompanied by an infiltrate of lymphocytes, histiocytes, neutrophils and eosinophils. Another further histological pattern is a granuloma faciale type of reaction, in which the epidermis and the upper dermis are substantially normal, but the mid-dermis has an infiltrate of neutrophils, eosinophils, lymphocytes, histiocytes and plasma cells in close proximity to dilated blood vessels.

Pustular reactions may be subcorneal or follicular. The folliculitis and perifolliculitis are normally associated with fungal remnants in the follicles. Inflammatory changes range from spongiosis of the outer root sheath, to deep perifollicular granulomatous inflammation showing areas of necrosis and foreign-body giant cells, perhaps induced by fragments of hair exuded from disrupted follicles. In cases of kerion, the histology is that of a combined subacute dermatitis and a marked folliculitis, with disrupted follicles and a diffuse granulomatous inflammatory response with many foreign-body giant cells, blood-vessel changes and fibrosis [35].

In classical annular ringworm, the rim of the lesion is marked by clear inflammatory changes including a perivascular infiltrate of lymphocytes. By contrast, in the central zone inflammation is usually less, possibly following elimination of the fungus in the stratum corneum. For reasons that are not entirely clear but that may depend on the persistence of immunological surveillance [10], previously infected skin remains free of fungal hyphae compared with uninfected, and fungal growth proceeds centrifugally. The epidermal turnover rate is normal within the ring, but more than four times as rapid in the zone where inflammation is maximal. Central clearance is often partial and, in tinea imbricata caused by *T. concentricum*, successive waves of fungal growth occur in skin previously cleared of infection, but overall mycelial expansion is centrifugal.

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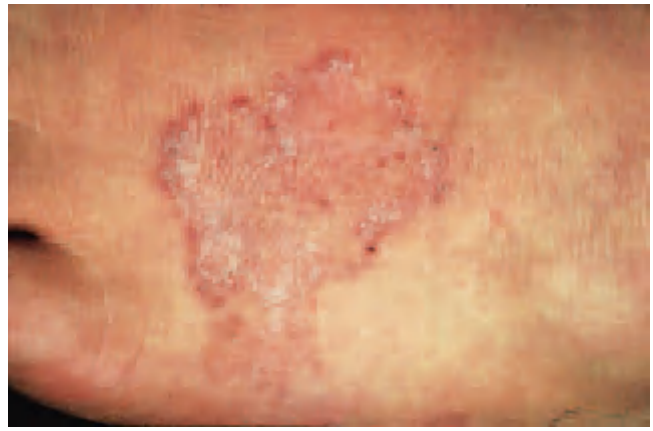

Fig. 31.7 Tinea circinata: ringworm.

Clinical forms of ringworm infection

The clinical features of dermatophyte infections result from a combination of keratin destruction and an inflammatory host response. The wide variation in clinical presentation depends upon the species and probably the strain of the fungus concerned, upon the size of the inoculum, upon the site of the body infected and upon the immune status of the host. In the following sections, the traditional division of ringworm into different syndromes according to the site of the body infected is followed because it is of considerable merit in terms of diagnosis and management.

Tinea corporis

SYN. RINGWORM OF THE BODY; TINEA CIRCINATA

Definition. Ringworm of the glabrous skin. The clinical manifestations result from invasion and proliferation of the causal fungi in the stratum corneum. Terminal hair in the affected parts may be invaded. By definition, it includes lesions of the trunk and limbs, excluding ringworm of specialized sites such as the scalp, feet and groins, which are considered below.

Species concerned. All known dermatophytes can produce lesions of the glabrous skin. A comprehensive list of causal species thus corresponds to a complete list of dermatophytes. For any part of the world, the causes of tinea corporis can be assessed by reference to the prevailing dermatophyte flora in the region [1–3]. Some species have predilections for particular parts of the body; for example, *M. audouinii*, classically a cause of tinea capitis, and *T. rubrum*, which usually causes tinea pedis, but these can and on many occasions do cause tinea corporis [4,5].

Pathogenesis. Natural infection is acquired by the deposition of viable arthrospores or hyphae on the surface of the susceptible individual. The source of infection is usually an active lesion on an animal or on another human, although fomite transmission is known to occur, and infection from soil is a well-established if unusual occurrence. In young children infected with *T. rubrum* and *E. floccosum*, half of the infections may come from their parents. In geriatric wards, epidemics may occur [1]. Spread from existing localized infection (e.g. feet, groins, scalp and nails) is not uncommon. Invasion of the skin at the site of infection is followed by centrifugal spread through the horny layer of the epidermis. After this period of establishment (incubation), which lasts 1–3 weeks, the tissue responses to infection become evident. The characteristic annular appearance of many ringworm infections results from the elimination of the fungus from the centre of the lesion, and the subsequent resolution of the inflammatory host response at that site. This area usually becomes resistant to reinfection, although a second wave of centrifugal spread from the original site may occur with the formation of concentric erythematous inflammatory rings. However, many lesions lack any tendency to central clearing. The natural history is very variable. Some inflammatory cases of animal infection resolve spontaneously in a few months, while a typical case of *T. rubrum* tinea corporis may persist for years.

Clinical features. The site of infection is typically on exposed skin, unless the infection represents an extension from a pre-existing infection. In such cases, infection may spread from the scalp, down the neck on to the upper trunk, or from the groins on to the buttocks and lower trunk. Characteristic lesions are circular, usually sharply marginated with a raised edge (Fig. 31.7). Single lesions occur, or there may be multiple plaques. The latter may remain discrete or become confluent. This clinical pattern is often modified in patients with defects in cellular immune responses [6]. The degree of inflammation is very variable. This feature depends not only on the species of the fungus and the immune status of the host, but it is also very roughly proportional to the extent of follicular invasion; thus, tinea corporis is generally less inflammatory

than tinea capitis or tinea barbae. In inflammatory lesions, pustules or vesicles may dominate and even in quiet infections close observation may reveal one or two small pustules. Rarely, frank bullae have been reported as an extreme expression of inflammatory change. In quieter infections, scaling is a common but not constant finding. Central resolution, which, as has already been stated, is a common but not invariable feature of tinea corporis, is perhaps more frequent in inflammatory lesions, but it is by no means confined to them. The process is often incomplete, and the central skin may show postinflammatory pigmentation, a change of texture or residual erythematous dermal nodules.

Special forms and species variations. Lesions of the glabrous skin caused by *M. canis* are not rare. They are as common in adults as in children, and are characteristically annular. *M. audouinii* produces short-lived lesions of tinea corporis in perhaps one-third of cases of scalp infection [7]. *T. equinum* from horses also gives plaques of tinea corporis but, although this may be a fairly common infection among those who work with these animals, the lack of a severe inflammatory response and a tendency to early spontaneous regression explain its rarity in patients attending skin clinics. *T. verrucosum* from cattle, *T. mentagrophytes* var. *erinacei* from hedgehogs, *T. mentagrophytes* var. *mentagrophytes* from small rodents in general and *M. persicolor* from voles are all likely to cause inflammatory lesions of exposed skin. Although classically a cause of kerion, *T. verrucosum* can lead to extensive annular lesions of the upper trunk, especially in children [8]. These often start around the neck.

The ubiquitous anthropophilic species *T. rubrum* may invade the buttocks and lower back, as well as more distant sites of the trunk as an extension from tinea cruris. Similar patterns are seen occasionally with *E. floccosum* and *T. megninii*. In infants, ringworm is rare, but the moist conditions of the napkin area may predispose to *E. floccosum* or *T. rubrum* infections [1].

Tinea corporis resulting from *T. rubrum* is often particularly extensive, and the inflammatory margin difficult to distinguish [9]. On the legs and usually extending from the feet, *T. rubrum* may cause typical lesions with raised margins, but rather psoriasiform lichenified plaques without central clearing may also occur, and a variety of vasculitis-like lesions are recognized. The perifollicular granulomatous papules of the Majocchi type are classical (Fig. 31.8) [10,11], but erythema induratum-like plaques sometimes occur with an almost haemorrhagic appearance.

Tinea imbricata (Tokelau) [12] resulting from *T. concentricum*, an anthropophilic dermatophyte found in southern Asia, the islands of the South Pacific and in Guatemala, southern Mexico and Brazil, causes a distinctive infection. It seems to affect mainly the native peoples

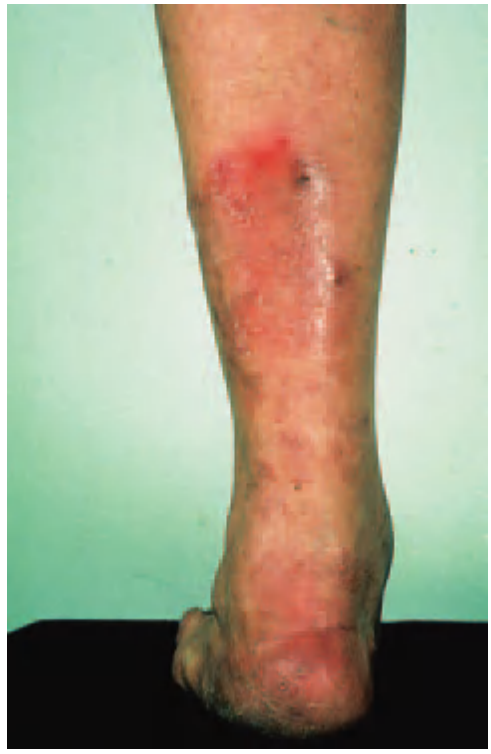

Fig. 31.8 Nodular folliculitis caused by *Trichophyton rubrum*.

of these areas, and although susceptibility may be inherited as an autosomal recessive character [13], it occurs in both sexes and at all ages. Occasional cases may be seen elsewhere in travellers from these regions [14]. The infection begins as a scaling ring; centrifugal spread follows, but within the area of central clearing a second wave of scaling soon arises. The process is repeated to give numerous concentric rings (Fig. 31.9) and, as the natural history is normally extremely prolonged, the whole body may become affected. Pruritus is intense and may lead to lichenification. Hypopigmentation may accompany the lesions [15].

Atypical deep forms of tinea corporis occur. There are some reports of extensive and persistent cases of tinea corporis, in which dermal or subcutaneous involvement has been a feature [16,17]. Occasionally, a specific defect of immune function has been detected, such as a missing plasma factor. In other patients, depression of cellular immune responses is associated with the presence of a serum factor, possibly circulating antigen or immune complexes [6,18]. Such cases may present with dermal nodules, abscesses or draining sinuses [19]. A few particularly bizarre dermatophyte infections with invasion of bone, central nervous system and lymph nodes have been reported [16,20], but no satisfactory explanation for the highly unusual behaviour of otherwise superficial pathogens is as yet forthcoming.

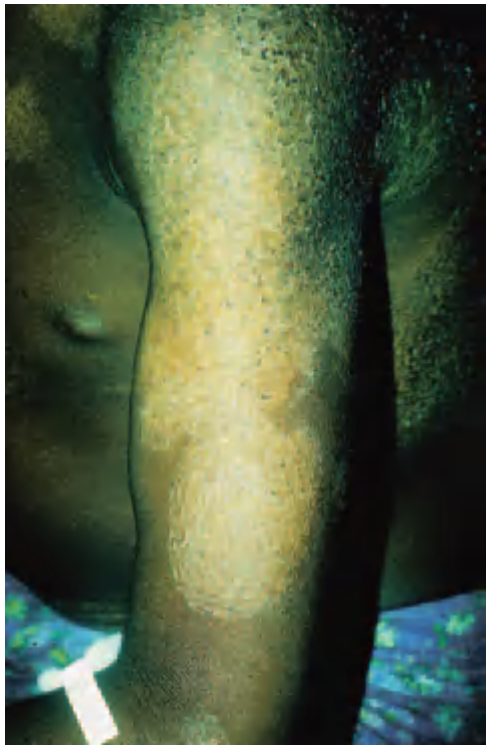

Fig. 31.9 Tinea imbricata affecting the upper arm.

Differential diagnosis. Although tinea corporis can masquerade as any of a vast number of skin diseases, in practice the diagnosis is usually straightforward.

The characteristic lesions seen with infection resulting from *M. canis* are easily diagnosed, but atypical infections caused by the more exotic fungi and by *T. rubrum* can, on occasions, cause great difficulty. Indeed, the possibility that any red scaly rash on the body is a fungus infection should be considered, because the lesions produced by fungi are so curiously variable. Seborrhoeic dermatitis often causes difficulty, but the condition is symmetrical and there is often associated seborrhoeic dermatitis of the scalp and perhaps intertrigo in the body folds. Psoriasis can lead to confusion in those cases in which the distribution is not quite typical. Its presence on the knees, elbows and scalp, and associated psoriasis of the nails, particularly if pitting is present, is helpful. Patches of impetigo are often confused, particularly when of the circinate type. The finding of staphylococci on a skin swab does not, of course, exclude tinea. Lichenification of a patch of tinea (e.g. of the leg) can mimic lichen simplex very closely. Nummular eczema is a common source of error. The plaques of papulovesicles tend to occur symmetrically on the limbs. Pityriasis rosea is also symmetrical and characteristically confined to the trunk and proximal parts of the limbs, but the herald patch, if seen, is almost impossible to differentiate from ringworm without microscopic examination of scales. Candidosis, tertiary syphilis and pityriasis versicolor should be excluded.

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Tinea capitis

SYN. RINGWORM OF THE SCALP; TINEA TONSURANS

Definition. Ringworm of the scalp in which the essential feature is invasion of hair shafts by a dermatophyte fungus. Ringworm of the beard area, although essentially similar, is discussed separately. Tinea capitis is predominantly an infection of children, although adult cases are seen particularly with *T. tonsurans* infections. Tinea capitis may also be seen in adults with AIDS.

Species concerned. Most species of dermatophyte are capable of invading hair but some species (e.g. *M. audouinii*, *T. schoenleinii* and *T. violaceum*) have a distinct predilection for the hair shaft. *E. floccosum*, *T. concentricum* and *T. mentagrophytes* var. *interdigitale* are exceptional in apparently never causing tinea capitis. All dermatophytes causing scalp ringworm can invade glabrous skin and

many attack nails as well. Those species of dermatophyte fungi most likely to be causing tinea capitis vary from country to country and from region to region [1–5]. Moreover, in any given location, the species may change with time, particularly as new organisms are introduced by immigration [6,7]. It is of interest that in tinea capitis anthropophilic species predominate.

The principal feature of tinea capitis in recent years has been the rise of *M. canis* as the dominant organism in infections in some parts of Europe [4], and the spread of *T. tonsurans* in urban communities in the USA [3]. A similar rise in the prevalence of *T. tonsurans* has recently been recorded in urban areas of the UK [8,9] and in some other European countries.

Pathogenesis. The principles of hair invasion and the distinctions between *in vitro* and *in vivo* activity have been already outlined. The spores of ringworm fungi causing tinea capitis can be demonstrated in the air in close proximity to patients with the condition. It is highly likely that scalp hair acts as a trapping device, and it is known that contamination of hair without demonstrable clinical findings may occur among classmates of children with tinea capitis [10,11]. From the classical experimental work of Kligman [12,13] on *M. audouinii*, it is clear that if actual hair infection is to occur, invasion of the stratum corneum of the scalp skin must first develop. Trauma assists inoculation, which is followed, after approximately 3 weeks, by clinical evidence of hair shaft infection. Spread to other follicles proceeds, then for a period of variable duration the infection persists but does not spread further. Finally, there is a period of regression with or without an inflammatory phase.

There are several distinct types of hair invasion that are worthy of note.

Microsporum type. This may be a small-spored ectothrix caused by *M. audouinii*, *M. audouinii* var. *rivalieri*, *M. canis*, *M. canis* var. *distortum*, *M. equinum* or *M. ferrugineum*. In this type, the hair shaft is invaded in mid-follicle. The intrapilary hyphae continue to grow inwards towards the bulb of the hair. Secondary extrapilary hyphae burst out and grow in a tortuous manner over the surface of the hair shaft, which is growing outwards continuously. These secondary extrapilary hyphae segment to produce a mass of small arthroconidia (2–3 μm diameter), each one of which becomes rounded off and eventually spherical. The size of these conidia is such that they cannot easily be distinguished as separate structures under the low power of the microscope. Fluorescence under the Wood's lamp is characteristically present in this type of hair invasion.

A similar type of hair invasion occurs with other *Microsporum* species (e.g. *M. gypseum*, *M. fulvum*, *M. nanum* and *M. vanbreuseghemii*). The spores, although similarly arranged, are larger, in this case about 5–8 μm. Fluorescence has been reported in some cases.

Trichophyton types. These may be large-spored ectothrix (in chains) caused by *T. verrucosum*, *T. mentagrophytes* var. *mentagrophytes*, *T. mentagrophytes* var. *erinacei*, *T. megninii* or *T. rubrum* (rarely). The arthroconidia are spherical, arranged in straight chains and again confined to the external surface of the hair shaft. They apparently arise from straight primary extrapilary hyphae, rather than from the hyphae inside the hair. Although size varies with species, up to 10 μm in the case of *T. verrucosum*, they are all larger than those seen in small-spored ectothrix *Microsporum* infection, and individually distinctly visible under the low power of the microscope. There is no fluorescence.

The endothrix type may be caused by *T. tonsurans*, *T. soudanense*, *T. violaceum*, *T. yaoundei*, *T. gourvilii* or *T. rubrum* (rare). Intrapilary hyphae fragment into arthroconidia up to 8 μm in diameter, which are entirely contained within and completely fill the hair shaft. Hair thus affected is especially fragile, and breaks off close to the scalp surface. This type is non-fluorescent.

The favic type is caused by *T. schoenleinii*. Broad, regularly septate hyphae and air spaces are seen in the hair shaft, but disarticulated arthroconidia are absent. The affected hair is less damaged than in other types, and may continue to grow to considerable lengths. Greenish grey fluorescence is present [14]. Air spaces are characteristic and fungal hyphae form clusters in the vicinity of hair follicles.

Clinical features. The clinical appearance of ringworm of the scalp is most variable, depending on the type of hair invasion, the level of host resistance and the degree of inflammatory host response [15,16]. The appearance therefore may vary from a few dull grey, broken-off hairs with a little scaling, detectable only on careful inspection, to a severe painful inflammatory mass covering most of the scalp. Itching is variable. In all types, the cardinal features are partial hair loss with inflammation of some degree (Fig. 31.10). It is useful to recognize several basic clinical pictures, as described below.

Small-spored ectothrix type. In *M. audouinii* [1] and *M. ferrugineum* infections, the basic lesions are patches of partial alopecia, often circular in shape, but showing numerous broken-off hairs, dull grey from their coating of arthrospores. Inflammation is minimal, but fine scaling is characteristic, usually with a fairly sharp margin. There may be several or many such patches arranged more or less randomly. In *M. canis* and in the much rarer *M. canis* var. *distortum* infections, the picture is similar but there is typically more inflammatory change. In infections caused by all these species, green fluorescence under the Wood's

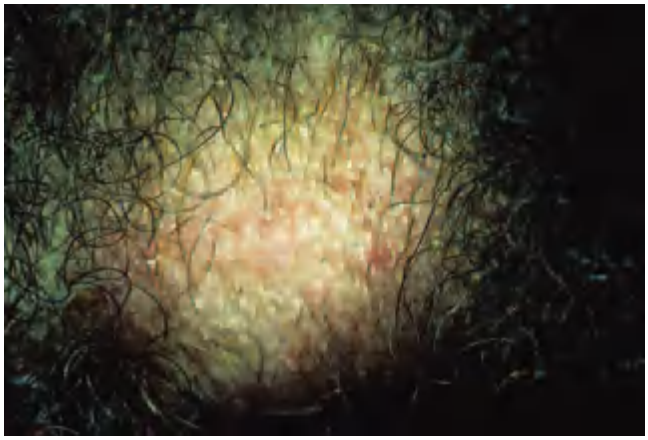

Fig. 31.10 Tinea capitis caused by *Microsporum canis*.

lamp is usual, but occasional non-fluorescent cases have been reported, and may not be rare with *M. ferrugineum* (perhaps as many as 10%) [17]. Children are affected much more frequently than adults, although the occasional case of tinea capitis in older patients must not be forgotten [18,19]. The attack rate for epidemic infections caused by anthropophilic species may be as high as 30%, within a school class for example, but it is commonly lower than that [20]. In the past, infection rates of both *M. audouinii* and *M. canis* have been higher in boys than girls [1], often at least twice as high.

Kerion. The most severe pattern of reaction is known as a kerion. It is a painful inflammatory mass in which such hairs as remain are loose. Follicles may be seen discharging pus, there may be sinus formation, and on rare occasions mycetoma-like grains may be found [21]. Thick crusting with matting of adjacent hairs is common. The area affected may be limited, but multiple plaques are not rare, and occasionally a large confluent lesion may involve much of the scalp. Lymphadenopathy is frequent. Although this violent reaction is usually caused by one of the zoophilic species, typically *T. verrucosum* or *T. mentagrophytes* var. *mentagrophytes*, occasionally a geophilic organism will be isolated, and anthropophilic infections that have been smouldering quietly for weeks may suddenly become inflammatory and develop into kerions if a high degree of hypersensitivity develops [22]. The possibility that a bacterial co-pathogen may be playing some part should not be ignored, and in this type of case a swab sent to the bacterial laboratory is a useful procedure in addition to the plucking of hairs for mycology. Generally, however, pustule formation represents an inflammatory response to the fungus itself [23].

Agminate folliculitis, a somewhat less severe inflammatory ringworm of the scalp consisting of sharply defined, dull red plaques studded with follicular pustules, is also seen in zoophilic infections.

Endothrix infections. In *T. tonsurans* [20,24,25] and *T. violaceum* [25,26] infections, a relatively non-inflammatory type of patchy baldness occurs. Formation of black dots (swollen hair shafts) as the affected hair breaks at the surface of the scalp is classical in this condition, but such findings may be inconspicuous [27]. The patches, which are usually multiple, may show minimal scaling, sometimes mimicking discoid lupus erythematosus, sometimes seborrhoeic dermatitis [28,29]. They are commonly angular in outline rather than round. Other forms include the diffuse and patchy alopecia, even with involvement of single isolated hair shafts and without scales. A low-grade folliculitis is often seen, while sometimes a frank kerion may develop. The three African species, *T. soudanense*, *T. yaoundei* and *T. gourvilii*, induce very similar lesions, in which the inflammatory reaction is usually mild but occasionally violent. Approximately 2 or 3% of patients have some nail involvement [30,31] or lesions on the face.

Favus. Infection with *T. schoenleinii* is seen sporadically in a variety of countries, such as South Africa [32], Ethiopia, where it is still endemic, as well as the Middle East, Pakistan, USA, Canada, the UK and Australia. The classical picture of tinea capitis caused by this organism is characterized by the presence of yellowish cup-shaped crusts known as scutula [33]. Each scutulum develops round a hair, which pierces it centrally. Adjacent crusts enlarge to become confluent and form a mass of yellow crusting. Many patients may show less distinctive changes, in early cases perhaps amounting to no more than perifollicular redness and some matting of the hair. Extensive patchy hair loss with cicatricial alopecia and atrophy among patches of normal hair may be found in long-standing cases, where much of the hair loss is irreversible. In such patients, the glabrous skin is commonly affected by the development of similar yellowish crusts. Although the initial infection is probably a childhood event in nearly all cases, it shows little if any tendency to clear spontaneously at puberty, particularly in women. Families with several generations affected are well recognized [14].

Differential diagnosis. The differential diagnosis of tinea capitis includes all conditions capable of causing patchy baldness with inflammatory changes of the scalp. Alopecia areata may show erythema and, although of itself it is not a scaly condition, it may coexist with seborrhoeic dermatitis. Such cases can be confusing, although careful examination usually shows that the scaling and the hair loss are not co-extensive. Exclamation-mark hairs must be distinguished from broken hairs of tinea capitis. Traumatic alopecia from hairdressing procedures and trichotillomania may also be confused [34]. Seborrhoeic dermatitis is usually more diffuse than tinea capitis, but in tinea amiantacea the changes are often localized. In this

condition, the scaling is adherent to the hair, but breakage of the hair shaft does not normally occur. In psoriasis, hair loss is found only occasionally, and again broken-off hairs are not usually present.

In impetigo, which may be secondary to pediculosis of the scalp, loosening of the hair is not normally present, but matting and crusting may cause confusion with inflammatory ringworm. A carbuncle of the scalp is much more acutely painful, and shedding of loosened hairs much less evident than in kerion. Discoid lupus erythematosus, lichen planus and other causes of cicatricial alopecia may sometimes have to be considered.

Control [35,36]. It is of considerable importance with scalp ringworm to discover the species involved. Clearly, some information may be obtained from the clinical picture, the presence or absence of fluorescence, etc., but culture is required for this to be firmly established. Where animal species are concerned, the source should be proved mycologically; it is not always the expected one. The course of action to be taken clearly depends upon the situation and the value placed upon the animal. A small much-loved domestic pet can often be treated successfully and economically with griseofulvin. Cattle ringworm in calves will normally settle spontaneously. A group of highly infected laboratory mice should probably be destroyed.

With anthropophilic infections, careful investigation of the outbreak or epidemic is recommended, and exclusion of children from school is not recommended [37]. It may also be resented by the parents and lead to non-compliance with treatment. With zoophilic infections such as *M. canis* ringworm, children can normally be allowed to remain at school as infectivity from human to human is small. The main treatments in all these conditions are terbinafine or griseofulvin. Topical therapy has little place, although it is sensible to remove matted crusts and to follow a routine of frequent shampooing.

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Tinea barbae

SYN. RINGWORM OF THE BEARD

Definition. Ringworm of the beard and moustache areas of the face with invasion of coarse hairs. It is thus a disease of the adult male. Tinea of the chin and upper lip in females and children are considered as tinea faciei (ringworm of the glabrous skin of the face).

Species concerned. The animal species *T. verrucosum* and *T. mentagrophytes* var. *mentagrophytes* are responsible for

the great majority of cases [1]. *M. canis* is an uncommon cause (eyelashes may be affected in some cases) as is *T. mentagrophytes* var. *erinacei*. The anthropophilic species, *T. violaceum*, *T. schoenleinii*, *T. megninii* and *T. rubrum* [2] are recognized as occasional causes.

Pathogenesis. Although tinea barbae has attracted fewer investigations than tinea capitis, all the available clinical evidence points to a similar pathogenesis. Infections with *T. verrucosum* and *T. mentagrophytes* var. *mentagrophytes* lead to large-spored ectothrix invasion with the spores in chains. The other less commonly involved species produce their own characteristic type of hair invasion.

Clinical features. The affected men are commonly farm workers in cases caused by the two main species, *T. mentagrophytes* var. *mentagrophytes* and *T. verrucosum*. The clinical picture in these is that of a highly inflammatory pustular folliculitis, often showing all the features of a kerion. Hairs of the beard or moustache regions are surrounded by red inflammatory papules or pustules, usually with exudation or crusting. Many hairs within the affected areas are loose and easily removed with the forceps without causing pain. These inflammatory lesions, although tending eventually to settle spontaneously, often persist for some months. A little irritation is commonly present, and at times pain, but this latter symptom is less marked than might be expected from the clinical signs. Some infections are less severe and consist of dry circular reddish scaly lesions enclosing lustreless hair stumps which are either broken off close to the surface of the skin or plug the follicles.

Differential diagnosis. The classical, highly inflammatory lesions are distinguished from boils by their relative lack of pain. Loosened hairs, although present in some bacterial infections, are rarely as obvious as they are in tinea barbae. The quieter cases of tinea must be distinguished from bacterial folliculitis, acne, rosacea and pseudofolliculitis. The presence of *Staphylococcus aureus* on a swab taken from lesions in this area does not exclude ringworm, as bacterial colonization or frank co-infection may occur in tinea barbae. Unfortunately, mycological cultures are often negative.

Control. Cases of tinea barbae are likely to continue to occur sporadically until more satisfactory means of controlling ringworm in cattle are found. Early diagnosis and prompt treatment of the individual patient and the encouragement of high standards of hygiene in the livestock industry are as much as can be expected in the present state of knowledge. A vaccine against *T. verrucosum* in cattle has resulted in a reduced incidence of infection, not only in cows but also among their human contacts in some countries in eastern Europe [3].

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Tinea faciei

SYN. RINGWORM OF THE FACE; TINEA FACIALE

Definition. Infection of the glabrous skin of the face with a dermatophyte fungus (the moustache and beard areas of the adult male are excluded).

Species concerned. *T. mentagrophytes* var. *mentagrophytes* and *T. rubrum* predominate but *M. audouinii* and *M. canis* are also common causes worldwide. *T. concentricum* frequently spreads to the face in cases of tinea imbricata and, as with tinea corporis, all dermatophytes must be considered potentially capable of producing this condition.

Pathogenesis. Facial skin may be infected either by direct inoculation of a dermatophyte fungus from an external source (e.g. *T. mentagrophytes* var. *mentagrophytes* from an infected pet mouse) or there may be secondary spread from pre-existing tinea of another body site. The latter pattern is likely to occur with *T. rubrum* as well as with *T. concentricum* infections.

Clinical features. The prime reason for separating tinea faciei from tinea corporis in this account is to draw attention to the frequency of misdiagnosis in facial ringworm [1]. The clinical features vary considerably, but complaints of itching, burning and exacerbation after sun exposure are common. The last mentioned symptom is a frequent source of diagnostic error [2]. There will often be a history of exposure to animals. Erythema is usual, but scaling is present in fewer than two-thirds of cases. A substantial proportion of patients do show annular or circinate lesions, and induration with a raised margin is present in about half (Fig. 31.11). Simple papular lesions, and in some cases completely flat patches of erythema, also occur. A few vesicles or pustules may be found, but these are rarely conspicuous. The application of topical steroids may be expected to modify the appearance still further, and in the authors' experience this complication is as frequent among patients with tinea faciei as it is in those with tinea cruris.

Differential diagnosis. Because of light sensitivity, the frequent absence of scaling and the somewhat nondescript appearance, this condition may be confused with discoid lupus erythematosus (DLE) [1] and polymorphic light eruption. Moreover, tinea faciei coexisting with DLE has

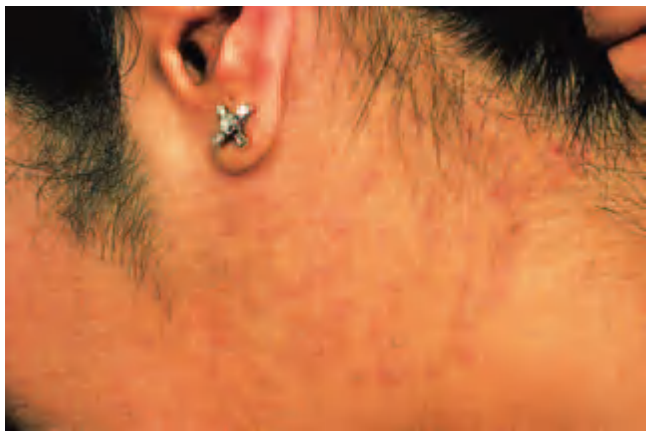

Fig. 31.11 Tinea faciei caused by *Trichophyton rubrum*.

been described [3]. Bowenoid solar keratoses, psoriasis, impetigo, rosacea, seborrhoeic dermatitis [4] and benign lymphocytic infiltrates must also be considered. Reluctance to biopsy the face adds to the problem, but if the possibility of tinea faciei is remembered, careful examination and scrapings taken from the skin surface, even if this is not obviously scaly, should enable a diagnosis to be made. General examination of the skin, particularly the scalp, should not be forgotten. If topical steroids have been applied, a cessation of the therapy may be followed a few days later by a great increase in scaling and by appearances much more readily diagnosable.

Control. Pets and laboratory animals may require treatment or elimination according to their value. It is customary to give short-term oral antifungal treatment, but the authors have seen minimal lesions respond well to topical imidazoles. Long-standing steroid-modified cases, especially those resulting from *T. rubrum*, may require prolonged oral antifungal therapy.

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Tinea pedis

SYN. FOOT RINGWORM; ATHLETE'S FOOT

Definition. Infection of the feet or toes with a dermatophyte fungus. The term athlete's foot is used by some to imply any form of toe cleft intertrigo. In this account, we therefore prefer the terms tinea pedis or foot ringworm, which clearly exclude infections caused by bacteria, *Candida* and non-dermatophyte moulds.

Species concerned. Three anthropophilic species, *T. rubrum*, *T. mentagrophytes* var. *interdigitale* and *E. floccosum*, are together responsible for the vast majority of cases of foot ringworm throughout the world. Double infections with any two of these species occur and, for precision, especially in clinical surveys, it is useful to adopt a standard terminology to describe them. Combined infections are those in which different species are present in the same lesion. Concurrent infections are those in which different species are found in different lesions at the same time, and consecutive infections are those in which the same patient has a different organism at the single site on different occasions. Other species, including zoophilic ones, occur occasionally as a cause of tinea pedis. In countries where *T. violaceum* is common, foot involvement with this anthropophilic species is sometimes seen and may be very intractable [1]. The relative numerical importance of the three main species of dermatophyte can be discovered from the extensive published data on foot ringworm seen in dermatological clinics throughout the world. Although minor variations are frequent, an average clinic sample would be: *T. rubrum* infections, 60%; *T. mentagrophytes* var. *interdigitale* infections, 25%; *E. floccosum* infections, less than 10%; mixed infections, 5%. The prevalence of *T. rubrum* infections has been growing over several decades [2]. Prior to 1970, in surveys of populations consisting of subjects in institutions, coal mines [3] or swimming baths [4], the relative frequency of infections with *T. mentagrophytes* var. *interdigitale* was higher than those caused by *T. rubrum*. *T. mentagrophytes* var. *interdigitale* would outnumber *T. rubrum* by as much as eight to one [5,6]. Since 1980, surveys in industry have indicated that this pattern is changing, with over 60% of isolates being *T. rubrum*. A high proportion of patients also have Gram-negative bacterial infection of the web spaces [7,8].

Pathogenesis. Tinea pedis is the most common form of dermatophyte infection in the UK and North America [9], and probably throughout the developed world. Occlusion of toe clefts through wearing shoes predisposes to this condition, which is in most cases initially a lateral web space infection. The condition is more common in adults than children, but may begin to occur in young children aged 6 or more. The mean age of onset was 15 years in one survey [10]. Overall prevalence within the community and including all age groups is not reliably known, but extrapolation from the most useful surveys [4,10] suggests that in the developed world at any one time as many as 10% of the total population may be expected to have dermatophyte infections of the toe clefts. Adult males probably have about a 20% chance of developing tinea pedis, while among women only 5% are likely to become chronically infected. Living in an institution, especially where washing facilities are shared, is likely to increase the chances of infection [10,11]. Prevalence figures as high

as 80% have been reported among German miners, and in some wards of a long-stay hospital more than two-thirds of the patients were infected [11]. Nevertheless, tinea pedis may be equally well transmitted within the family bathroom [12]. Among dermatological outpatients with *T. rubrum* infections there is a significant excess of atopics [13], but in a study of coalminers with recurrent *T. rubrum* tinea pedis this was not so [14], suggesting perhaps that reinfection from the environment is important in their case.

Experimental evidence [15] suggests the importance of maceration in dermatophyte infections of the toe clefts. These moist conditions probably favour growth of the fungus directly, and damage the stratum corneum at the same time. A simultaneous increase in the bacterial flora is likely and may also play a part. There is growing evidence that during some symptomatic episodes in chronic tinea pedis, resident bacteria, such as large-colony coryneforms, may be acting as important co-pathogens, but whether or not they assist in initiating new infections remains, so far, unknown [16].

Although dermatophytes are occasionally isolated from clinically normal toe clefts, and a contrary situation exists in which mildly abnormal toe clefts yield no dermatophytes, it is now generally held that where dermatophytes are present (in perhaps 10% of the population) they do cause abnormalities, and are not in the true sense members of the normal skin flora. The sex differences in the level of tinea pedis may be partly explained by different exposure to the causal fungi. In this context, in one survey the level of infection among men who attended swimming baths was higher than those that did not. In contrast, surveys at a swimming bath showed that the level of infection among girl swimmers was only one-quarter of that among boy swimmers [4]. However, further enquiry showed that the girls swam much less than the boys, so that there was, even in this instance, a true difference in exposure, although both groups went swimming. The sex difference in choice of footwear—men generally wearing more occlusive and heavier footwear throughout the year than women—is probably important and this correlates well with the known rarity of interdigital tinea pedis among those who habitually go barefoot [17].

Clinical features. The most common form of tinea pedis is an intertriginous dermatitis characterized by peeling, maceration and fissuring affecting the lateral toe clefts, and sometimes spreading to involve the undersurface of the toes. This picture may be produced by any of the three species. Itching is a common complaint in warm weather. The condition is highly persistent. In *T. rubrum* infections, a squamous hyperkeratotic variety, which is particularly chronic and resistant to treatment and which affects the soles, heels and sides of the feet, is often found. The affected areas are pink and covered with fine silvery white scales. If the foot is extensively involved, the term 'moccasin foot' or dry-type infection are sometimes applied (Fig. 31.12). The dorsal surfaces of the toes and feet are not often affected (Fig. 31.13), but associated nail infection is very common. If there is hyperhidrosis, the symptoms are more severe. This hyperhidrosis seems on occasions to be secondary to the presence of fungi, because it may improve if the fungus is successfully treated. As well as itching of the feet, the patient may also complain of their smell, and secondary bacterial infection, with fissuring in the toe clefts, may aggravate symptoms [16].

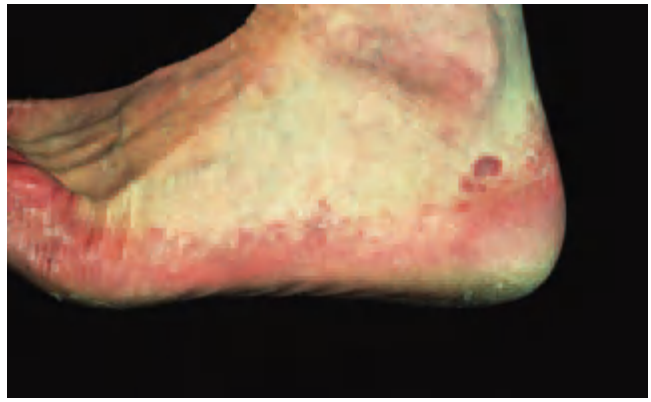

Fig. 31.12 Dry-type *Trichophyton rubrum* infection.

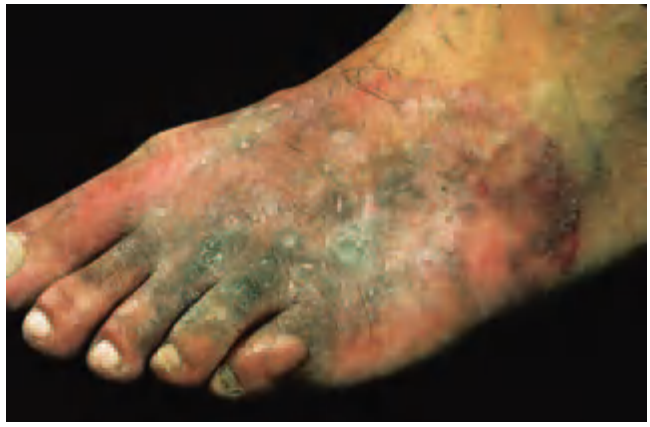

Fig. 31.13 Tinea pedis spreading to the dorsum of the foot.

The changes produced by *T. mentagrophytes* var. *interdigitale* vary from mild insignificant scaling in the toe clefts to severe acute inflammatory reactions affecting all parts of the feet [18]. A vesiculobullous reaction is more likely to be caused by this species than to any other fungus (Fig. 31.14). The reaction may occasionally extend over the whole sole. It may be preceded for months or years by maceration or fissuring in the toe clefts. Vesicles may become pustules, and when they rupture they tend to leave collarettes of scaling with the intervening skin normal, or showing various degrees of scaling and inflammation. This variety of ringworm frequently goes on to

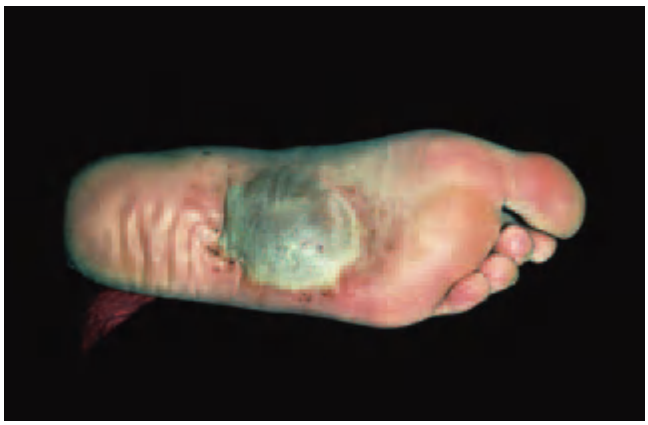

Fig. 31.14 *Trichophyton mentagrophytes* var. *interdigitale* infection: bullous lesion on the sole.

apparent spontaneous cure, but tends to recur in warm weather; indeed, under hot humid conditions the inflammatory reaction may be extremely incapacitating. There is very often associated hyperhidrosis.

Apart from mild toe cleft intertrigo, *E. floccosum* may produce on occasions a vesicular infection of the sole similar to that typically produced by *T. mentagrophytes* var. *interdigitale*, or a dry hyperkeratotic condition resembling infections caused by *T. rubrum*. With *Epidermophyton* infections, there is significantly less toenail involvement than with *T. rubrum* or *T. mentagrophytes* var. *interdigitale*, but chronicity of the skin infection may be just as troublesome.

When the lesions on the feet are acutely vesicular, irrespective of the fungus responsible, a vesicular allergic reaction (ide) may develop on the uninfected hands. This clinical picture, which closely simulates pompholyx, was vastly overdiagnosed in the past but is now known to be quite uncommon, and an ide reaction of this type should not be considered unless the primary foot condition is acutely inflammatory.

Differential diagnosis. Where changes are largely restricted to the toe cleft, erythrasma, which is usually asymptomatic and rarely causes fissures, and candidosis, which is characterized by a build-up of rather more white macerated skin, must both be considered. Other bacterial infections with staphylococci or streptococci or Gram-negative organisms, including *Acinetobacter* species, can produce inflammation and often odour. Any of these organisms may coexist with tinea pedis, contributing to a greater or lesser extent to the abnormalities seen. Apart from swabs and scrapings for bacteria and ringworm organisms, the Wood's lamp, which may show pink fluorescence for erythrasma and a greenish blue for *Pseudomonas* infections, may be useful.

Soft corns or callosities, sometimes with sinus formation, are common in the lateral toe clefts, especially in women. Younger children do not commonly suffer from foot ringworm but frequently have eczema of the foot such as juvenile plantar dermatosis. Where the sole of the foot is affected without obvious involvement of the toe cleft, a diagnosis of pustular psoriasis must be considered. The latter condition more commonly affects the heels than does tinea, but this is not a reliable criterion. Psoriasis, pityriasis rubra pilaris, Reiter's syndrome, contact dermatitis from nylon dyes or shoe materials, and tylosis may all need to be excluded. Scrapings by which a positive diagnosis of tinea pedis may be established should always be taken, and they may need to be repeated if an initial negative result is incompatible with the clinical features.

Control. Clearly, if infected individuals avoided exposing others to their infection by not walking on the floors of communal changing rooms and by avoiding swimming baths, the level of infection in the community would fall. Because such large numbers of people are involved, many of whom are completely asymptomatic, this is usually not feasible. Moreover, eradication of these fungi from the toe clefts is often a long and tedious process, and elimination of the organism may never be achieved. Among industrial workers using communal showers, it is virtually impossible to avoid continual exposure to infection. There are two simple measures that do seem fruitful. Frequent hosing of the floors of shower rooms and the sides of swimming baths does reduce the prevalence of dermatophytes on these surfaces, and probably would lead to a reduction of infection in time. This should certainly be encouraged. Satisfactory antifungal powder is readily available, and encouragement of its use has been demonstrated to be effective in the long-term reduction of tinea pedis at one swimming bath.

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Tinea manuum

SYN. RINGWORM OF THE HAND

Definition. Any species of dermatophyte may affect the skin of the hand. Infections of the dorsal surface present no specific features and are considered as ringworm of the glabrous skin under tinea corporis. This section is therefore concerned with ringworm of palmar skin and with infections beginning under rings.

Species concerned. For the most part, the organisms concerned are the three anthropophilic species involved in tinea pedis. *T. rubrum* is, among cases coming to the skin clinics, the most common cause by far. In the authors' experience, *E. floccosum* and *T. mentagrophytes* var. *interdigitale* are involved in a small minority of cases.

The anthropophilic species *T. violaceum* may also produce this clinical picture and animal species may occasionally infect the palmar skin. *T. mentagrophytes* var. *erinacei* from contact with hedgehogs has been notable in this regard.

Pathogenesis. In most cases, apart from animal infections, there is pre-existing foot infection with or without toenail involvement. A special mention should be made of ringworm beginning under rings, wrist watches, and where anatomical deformities or occupational usage predispose to maceration between the fingers. Here, there may be a particular susceptibility to *T. mentagrophytes* var. *interdigitale* infections, and in such cases infection may occur without obvious foot involvement [1]. Poor peripheral circulation and palmar keratoderma are other possible predisposing factors [2].

Clinical features. *T. rubrum* infection may take several different clinical forms. Hyperkeratosis of the palms and fingers affecting the skin diffusely is the most common variety, and is unilateral in about half of cases. The accentuation of the flexural creases is a characteristic feature. Other clinical variants include crescentic exfoliating scales, circumscribed vesicular patches, discrete red papular and follicular scaly patches, and erythematous scaly sheets on the dorsal surface of the hand. The latter forms are more likely to be zoophilic infections.

Differential diagnosis. Dermatophyte infections of the palm are often quiet and chronic, commonly passing unnoticed or misdiagnosed. Contact dermatitis, especially the primary irritant variety, psoriasis, pityriasis rubra pilaris, constitutional eczemas, keratoderma, syphilis and post-streptococcal peeling must all be considered. In ring infections and web space cases with anatomical deformity, candidosis and bacterial intertrigo should be excluded.

Unilateral scaling should always alert the clinician to the necessity of taking scrapings. Nail changes may help: pitting suggests psoriasis, but subungual hyperkeratosis if present should always be scraped. If the palmar infection spreads to the dorsal surface, a more classical picture of tinea circinata may be seen, although this happens relatively infrequently. Tinea manuum, like tinea cruris and tinea faciei, is sometimes modified by inappropriate treatment with topical steroids leading to further diagnostic difficulties.

Control. The prevalence of tinea manuum is directly related to the level of tinea pedis in the population. Prompt treatment of tinea pedis and the use of separate towels are sensible measures that can be recommended, but it is likely that tinea manuum will continue to occur sporadically and a greater awareness of this condition, so that it may be recognized promptly, is of prime importance.

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Tinea cruris

SYN. RINGWORM OF THE GROIN; DHOBIE ITCH; ECZEMA MARGINATUM

Definition. Infection of the groins by a species of dermatophyte.

Species concerned. The causal species are those implicated in foot ringworm but in different proportions. *T. rubrum* is the main cause [1]; *T. mentagrophytes* var. *interdigitale* and *E. floccosum* also account for some cases.

Pathogenesis. Ringworm of the groins is a common condition throughout the world, and is probably more prevalent in tropical zones and particularly among migrants from temperate countries. The warm humid conditions in this site seem important [2]. This condition has always been much more common in men than in women [3].

Apart from the numerous cases of autoinfection from the foot to the groin [4], the sharing of towels and sports

clothing is undoubtedly important [5]. In cases thus contracted, the toe clefts may be normal.

Clinical features. Whatever the causal species, itching is a predominant feature. The lesions in the early stages are erythematous plaques, curved with sharp margins extending from the groin down the thighs. Scaling is variable, and occasionally may mask the inflammatory changes. Vesiculation is rare, but dermal nodules forming beading along the edge are commonly found in older lesions. One or two minute pustules are often detected if sought with care. Some central clearance is usually present, but is often incomplete with nodules scattered throughout the affected area.

Satellite lesions, if present, are few in number and relatively large. Spread to the scrotum is common, but scaling is minimal and inflammation inconspicuous against a background that is normally rugose and erythematous [6]. *E. floccosum* infections are clinically indistinguishable from *T. rubrum* infections, but are often not associated with tinea pedis. *T. rubrum* cases are classically chronic and sometimes more nodular. The rarer *T. mentagrophytes* var. *interdigitale* infections may be vesicular and inflammatory. Extension of infection from the groins to other sites is common, in *T. rubrum* classically to the buttocks, the lower back and the abdomen. The penis is occasionally affected.

Differential diagnosis. Candidosis, which is more common in women, does not have a distinct raised margin. White pustules are often found, satellite lesions are numerous and small, and the frayed peeling edge that occurs as the tiny pustules rupture is characteristic. Pityriasis versicolor may be localized to the groin but is usually non-inflammatory and asymptomatic, as is erythrasma. Central clearing is rarely found in either of these infections.

Intertrigo with heavy bacterial colonization is common in the obese subject of either sex. It may show a sharp margin, but this edge is usually a simple curve where the opposed skin surfaces meet. In many cases, extension upwards from the groin is as prominent as that down the thigh, a feature usually absent in tinea cruris. The central skin is often macerated and the submammary, periumbilical and axillary skin may also be affected, resembling flexural seborrhoeic dermatitis. However, this feature is not a completely reliable distinguishing criterion, as *E. floccosum* in particular may involve the axillae and the submammary areas. Psoriasis and mycosis fungoides may occasionally mimic tinea cruris, but characteristic lesions in other sites can usually be found. In atopic eczema there may be lichenification, but these changes usually extend up towards the hip. Contact dermatitis from clothing or deodorants may confuse, and Hailey–Hailey disease and flexural Darier's disease require consideration.

Topical steroids lead to suppression of the physical signs of tinea cruris.

Control. Greater control of foot ringworm might lead to fewer cases of tinea cruris. A person suffering from tinea pedis or cruris should not lend towels to others, even if they have been laundered. In the tropics, sensible clothing and prompt treatment of tinea pedis are probably of considerable importance. Topical therapy is often sufficient to control early cases, but long-established *T. rubrum* infection will require terbinafine or itraconazole.

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Onychomycosis caused by dermatophytes

SYN. RINGWORM OF THE NAILS; TINEA UNGUIUM

Definition. Invasion of the nail plates by species of dermatophytes. A different category of onychomycosis is associated with certain other species of filamentous fungi that are frequently found in dystrophic nails; these are considered separately [1,2].

Species concerned. The principal dermatophytes concerned are: (i) with associated foot and hand infections—*T. rubrum*, *T. mentagrophytes* var. *interdigitale* and *E. floccosum*; (ii) with associated scalp infections—*T. tonsurans*, *T. violaceum* and *T. soudanensei.*

Pathogenesis. Ringworm of the nails occurs in all parts of the world, and almost all dermatophytes have been reported to infect nails at one time or another [3]. Although nail infections may be the only manifestation of fungus disease in a patient, in the great majority of cases they are associated with tinea pedis or tinea manuum, and the three dermatophytes most commonly implicated are therefore *T. rubrum*, *T. mentagrophytes* var. *interdigitale* and, rarely, *E. floccosum* [4–6].

T. soudanense has been reported as a cause of onychomycosis, and other dermatophytes usually encountered as a cause of tinea capitis, such as *T. tonsurans* and *T. violaceum*, not infrequently infect fingernails. In regions or populations where tinea pedis is uncommon and tinea capitis caused by these fungi is frequent, they are likely to predominate as a cause of onychomycosis.

It is likely that *T. rubrum* and *T. mentagrophytes* var. *interdigitale* both invade the nail plate with relative ease [3]. *T. rubrum* predominates in fingernail infections, owing no doubt to the prevalence of that species in tinea manuum. It is also the main cause of infection of the toenails. *T. mentagrophytes* var. *interdigitale* is a less common cause, and often only affects the great toenail. Invasion of the nail plate usually occurs either from the lateral nail fold or from the free edge and, as Alkiewicz [7] has shown, an elaborate network of channels and lacunae is formed, leading to opacity and eventually destruction and crumbling of the nail plate. Subungual hyperkeratosis, sometimes difficult to distinguish from softening of the nail plate proper, frequently occurs, but the mechanism of its production is obscure. As might be expected from the age distribution of tinea pedis, onychomycosis is largely a disease of adults [8], but children, especially those in institutions and in households where the adults are infected with *T. rubrum*, may be infected from time to time. A poor peripheral circulation is frequently blamed for resistance to treatment [9]. It may also be a factor in susceptibility. Nails that have been traumatized and nails of elderly people, where the linear growth is slow, are both unduly susceptible to infection.

Clinical features [2]. Four distinct patterns of tinea unguium have been described.

Distal and lateral subungual onychomycosis. Distal and lateral subungual onychomycosis (DLSO) is the most common pattern of infection, and usually presents as a streak or a patch of discoloration, white or yellow at the free edge of the nail plate, often near the lateral nail fold. The initial invasion of the hyponychium shows through a relatively normal dorsal nail plate. It commonly spreads towards the base of the nail and may occasionally become darker brown or black (Fig. 31.15). The nail plate becomes obviously thickened, and may crack as it is lifted up by the accumulation of soft subungual hyperkeratosis. A later phase of invasion may lead to massive destruction of the nail plate (total dystrophic onychomycosis; TDO). Although commonly starting with a single affected nail, other digits later become invaded. The variation in the severity of damage is sometimes marked, so that minor changes, a little discoloration or just fraying of the nails, may be all that is seen. Indeed, nail clippings may reveal fungus mycelium in nails that appear completely normal [10].

Superficial white onychomycosis. Superficial white onychomycosis (SWO) is a less common presentation and can produce a distinct form of nail invasion in which the dorsal surface of the nail plate is eroded in well-circumscribed powdery white patches, often away from the free edge [11]. It is distinguishable from other causes of leukonychia by the powdery nature of the white material, which can easily be scraped away. The whole surface of the nail plate may be thus affected, and occasionally this picture may also coexist with deep invasion of the nail plate of the ordinary type starting at the free edge. Although more common with *T. mentagrophytes* var. *interdigitale*, it can occasionally be seen in *T. rubrum* infections and also occurs with certain non-dermatophytes. Toenails are usually affected, but in AIDS patients SWO of both toe- and fingernails has been reported [12]. In AIDS patients, superficial infection may coexist with proximal nail plate invasion (see below).

Fig. 31.15 Onychomycosis caused by *Trichophyton rubrum.*

Proximal subungual onychomycosis. This is a pattern that was very uncommon, but in the last 10 years has become particularly associated with AIDS patients. Rapid invasion of the nail plate from the posterior nail fold may develop to produce a white nail with only marginal increase in thickness [12]. The most common cause is currently *T. rubrum*, although in the past more unusual species such as *T. megninii* were associated with this picture.

Endonyx onychomycosis. This is seen with infection caused by dermatophytes that cause endothrix scalp infections, notably *T. soudanense*. The nail plate is scarred with pits and lamellar splits. The invasion occurs from the top surface, but penetrates deeply into the nail plate.

On occasions, patients with onycholysis alone may have positive cultures of dermatophytes, suggesting that carriage of dermatophytes without invasion is possible [13].

Differential diagnosis. The destructive changes of the nail plate and nail bed produced by dermatophytes can be mimicked closely by psoriasis. Fine pitting of the dorsal nail plate is never produced by fungal infections and strongly suggests psoriasis, as does the oil-drop sign away from the free edge. The irregularly buckled nail of eczema

and the ridged or dysplastic nail of lichen planus must be distinguished. Paronychia, caused either by bacteria or by *Candida*, usually affects the nail plate proximally and laterally, while the free edge is often spared, at least initially. Conversely, swelling of the nail fold is rare in dermatophyte infections, and purulent discharge is never a feature of uncomplicated tinea unguium. Onycholysis and other nail dystrophies must be considered. Ringworm of the nails is rarely symmetrical, and it is common to find the nails of only one hand affected. The skin of the feet and of the palms should always be examined carefully. Nail clippings or scrapings are essential, and direct microscopy should be carried out with great care, as culture often fails with nail plate material [10,14]. For this reason, it is wise to sample any obvious skin lesions present, as these are usually infected with the same organism and will be more likely to yield a positive culture [15]. It must be remembered that double pathologies do occur and a nail, dystrophic from some other cause, may become invaded by a dermatophyte fungus. This is not uncommon with onychogryphosis.

Control. Proper early treatment of tinea pedis and manuum would almost certainly reduce the prevalence of tinea unguium.

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Steroid-modified tinea

SYN. TINEA INCOGNITO

Definition. Ringworm infections modified by corticosteroids, systemic or topical, prescribed for some pre-existing pathology or given mistakenly for the treatment of misdiagnosed tinea.

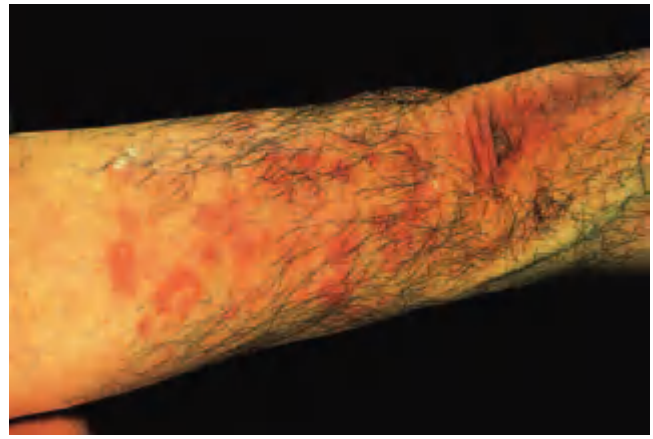

Fig. 31.16 Tinea corporis in a patient on systemic corticosteroids.

Pathogenesis and clinical features [1–3]. Normally, the clinical diagnosis of tinea depends heavily on the inflammatory changes involved. This inflammatory response may be almost totally suppressed by corticosteroids, systemic or topical. At the same time, it is probable that the resistance to infection mediated by the immune response, especially the cell-mediated response, is diminished by corticosteroids. In this situation, the patient suffers doubly: the infection is less likely to be diagnosed, and the patient has been rendered more susceptible to that infection.

With patients on systemic steroids (perhaps treated with additional immunosuppressive agents or irradiation [4]), the degree of modification is often minor, but even in these cases it may be sufficient to mislead (Fig. 31.16), especially on the face. With topical steroids, the degree of modification can be profound. The usual sites where this problem occurs are the groins, lower legs, face and hands, but tinea circinata elsewhere may be steroid treated.

The history is characteristic. The patient is often satisfied initially with the treatment. Itching is controlled and the inflammatory signs settle. He or she stops applying the cream, the eruption relapses, with varying rapidity. Further applications bring renewed relief and the cycles are repeated. In the groins, the patient may develop few persistent nodules, which become unsuppressible by the steroid preparation.

Typically, the raised margin is diminished. Scaling is lost and the inflammation is reduced to a few nondescript nodules. Often, a bruise-like brownish discoloration is seen, especially in the groins. On the face, the picture may be modified by a superimposed perioral dermatitis with papules and tiny pustules. Steroid-modified eyelid infection may closely resemble a sty. With chronic use, atrophy, telangiectasia and, in the groins and axillae, striae are likely to be observed. In some cases, concentric rings of erythema are seen among the atrophy and telangiectasia. Presumably, these represent waves of fungal growth. The eruption remains localized but, especially in

E. floccosum infections, it spreads more widely than one would expect in the unmodified case. Accumulation of fungal hyphae may lead to cross-infection, as has been reported with steroid-modified *T. violaceum* infection in a dermatology ward [1]. Strong fluorinated steroids seem most likely to produce this syndrome, but even 1% hydrocortisone cream can, on occasions, modify tinea to a confusing extent.

Diagnosis. The differential diagnosis of other steroid-modified infections in the groin, particularly candidosis, must be considered, and these may be indistinguishable without cessation of therapy and mycological investigations. A ready awareness that the face, groins and the hands are sites of diagnostic error is important in alerting the physician, and the history is usually extremely suggestive. Scrapings may be difficult to obtain in a patient who is currently applying a steroid cream, but if he or she stops it for a few days an upsurge of inflammation with marked scaling often occurs, making clinical diagnosis easier and facilitating the taking of scrapings. In such samples, fungal mycelium is usually abundant but scrapings taken while steroids are still being applied may show very few fungal elements, unless a fluorescent whitener is used [5].

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Dermatophytide reactions

SYN. MICROSPORIDE; TRICHOPHYTIDE OR EPIDERMOPHYTIDE (ACCORDING TO GENUS)

Definition. A non-infective cutaneous eruption representing an allergic response to a distant focus of dermatophyte infection.

Pathogenesis and criteria. Jadassohn in 1918 first described a dermatophytide reaction in a patient with a kerion. Since then a great many cutaneous eruptions have been labelled unconvincingly as dermatophytides. It is now clear [1] that the essential criteria required for the diagnosis of an ide reaction to a dermatophyte infection are:

1 Proven dermatophyte infection, which usually becomes highly inflamed before the appearance of the secondary rash.

2 A distant eruption, which is demonstrably free of ringworm fungus.

3 Spontaneous disappearance of the rash when the ringworm infection settles, with or without treatment.

Even with these criteria, ide reactions may be overdiagnosed. An additional criterion has been recommended; the morphology of the ide eruption should match one of the well-recognized types.

Clinical features. The focus of infection is often a kerion, for instance caused by *T. verrucosum*, but the species is not important as long as it provokes inflammation. Highly inflammatory tinea pedis may be insufficient. The main ide reactions are well established.

1 A widespread eruption of small follicular papules grouped or diffusely scattered. The eruption is symmetrical, usually pronounced on the trunk, but in severe cases extending down limbs, even at times covering the face. Sometimes the follicular papules are topped by horny spines. The common cause of this type of ide reaction is a scalp ringworm kerion, typically caused by *T. verrucosum*. On occasions, *T. tonsurans* and *M. audouinii* may be responsible, when they produce inflamed ringworm. Treatment of the original ringworm lesion may play a part in initiating the process.

2 A pompholyx-like ide affecting the web spaces and palmar surfaces of the fingers, the palms and sometimes the dorsal surfaces of the hands. This eruption is characteristically associated with an acutely inflammatory tinea pedis, which may have arisen spontaneously or as a result of inappropriate treatment. The palmar and web space skin may be covered with papules or vesicles. On occasions, bullae or pustules may occur. Clinically, this is indistinguishable from a constitutional eczema of the pompholyx variety, and the diagnosis of a dermatophytide in this clinical situation demands rigorous application of the criteria outlined above. In the past, failure to adhere to these criteria has led to inordinate overdiagnosis of this uncommon syndrome.

Of the many other suggested morphologies for ide reactions, erythema nodosum seems most acceptable [2]. There are a few published accounts of this, and the authors are aware of other cases that fit the above criteria.

It is possible that erythema multiforme, erythema annulare and urticaria may, on occasions, be manifestations of an allergic reaction to the ringworm infection, but such instances must be extremely rare and the clinician is cautioned to apply critical judgement vigorously before accepting new examples of such associations in his or her own practice, or indeed in new published accounts.

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Laboratory diagnosis

The isolation and identification of dermatophytes is a relatively simple process and needs only basic laboratory facilities. The features of the most common species will therefore be outlined and illustrated grown on 2% glucose, 1% mycological peptone (Oxoid) agar supplemented with 0.04% cycloheximide and 0.005% chloramphenicol at 26°C. Illustrations of the more unusual species are beyond the scope of this chapter and the reader is referred to more specialized texts [1–3].

All the dermatophyte species appear identical in skin and nail samples. Septate hyphae are observed, which may branch without constriction at the branching point and which display an even diameter along their length (Fig. 31.17a). In some specimens, the hyphae fragment into arthroconidia, which disarticulate when mature, and may then round up and increase notably in size (Fig. 31.17b). These germinate to produce true hyphae. Hair invasion results in four distinct patterns: small-spored ectothrix, large-spored ectothrix, arthrosporic endothrix and favus endothrix (Fig. 31.17c–f) and these are readily distinguishable by the arrangement and the size of the fungal elements. When trying to determine whether infection is endothrix or ectothrix, it is useful to note that the pigment in the hair clearly delineates the edge of the hair shaft, and can be used as a marker to judge whether the fungus is entirely confined within the hair, or has formed an ectothrix sheath of arthroconidia on the surface.

Most isolates can be identified directly from the primary culture, but if sporulation is poor, a number of media may be used to encourage the production of conidia, including potato dextrose agar and lactritmel agar [4]. A few simple physiological tests, such as growth on polished rice grains, the production of urease, the ability to penetrate human hair *in vitro* and specific vitamin requirements, may be used to confirm the identification of certain species (Table 31.6).

In recent years there have been numerous molecular studies of dermatophyte taxonomy. As a result various changes have been recommended to the nomenclature and separation of the classically recognized species. These include the merging of some anthropophilic and zoophilic species (e.g. *T. equinum* and *T. tonsurans*) and of some morphologically very distinct species, such as *T. soudanense* and *T. violaceum* [1]. In the authors' opinion, although these results may show taxonomic relationships among this still evolving and comparatively young group of fungi, they are not helpful and would probably be epidemiologically confusing in clinical diagnosis. The changes have certainly not been universally accepted and in this text the classic species are retained. In cases where cultures are completely atypical morphologically, however, molecular methods such as polymerase chain reaction patterns and ribosomal DNA analysis will allow species identification. Whether the cost can be justified in all but the most exceptional cases is questionable.

Genus Microsporum

When present, macroconidia are species specific; their production is enhanced by subculture on to lactritmel agar. Microconidia are similar in most species, clavate to elongate and borne along the sides of the hyphae, and thus not useful in species identification. The presence of specialized hyphae, such as racquet hyphae, where the cells are swollen at one end, and pectinate hyphae, which bear unilateral flattened comb-like protrusions, may be helpful.

Table 31.6 Physiological tests used in the identification of dermatophytes.

Production of urease Filter-sterilized urea agar base (Difco) is mixed with sterile molten agar and allowed to set. The medium is then inoculated with the test organism. After incubation at 26°C for 7 days, if urea is degraded the colour turns from yellow to magenta red
Penetration of human hair in vitro Sterile human hair is suspended in sterile distilled water supplemented with yeast extract. The test organism is inoculated onto the hairs. After 2 weeks' incubation at 26°C, hairs are mounted to look for wedge-shaped penetrations perpendicular to the hair axis
Vitamin tests Trichophyton agars 1–7 (Difco) are used to determine vitamin requirements. Agar 1 is a casein-based, vitamin-free control; agar 2 is supplemented with inositol; agar 3 with thiamine and inositol; and agar 4 with thiamine alone. Agar 5 contains nicotinic acid. Agar 6 is an ammonium nitrate vitamin-free control for Agar 7, which is supplemented with histidine. Small, agar-free inocula are transferred from Sabouraud's agar plates and incubated for 2–3 weeks at 26°C
Growth on rice grains Ordinary white rice is covered with distilled water and autoclaved. The test organisms are then inoculated straight onto the surface, and growth is assessed after 2–3 weeks' incubation at 26°C
Growth on 1% peptone agar On this sugar-free medium *Microsporum persicolor* will produce a pink surface colour, in contrast to *Trichophyton mentagrophytes* var. *mentagrophytes*, which remains white

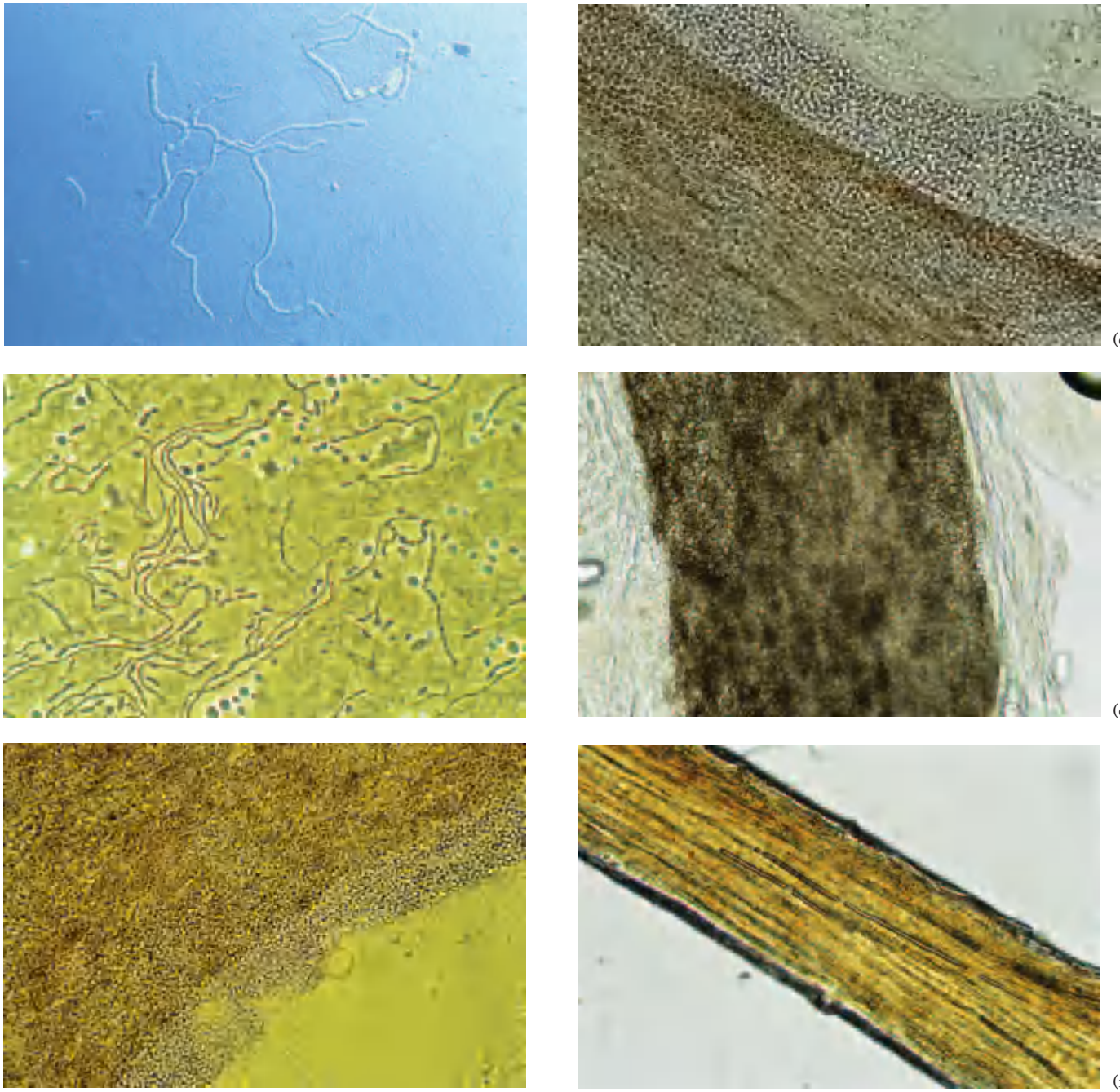
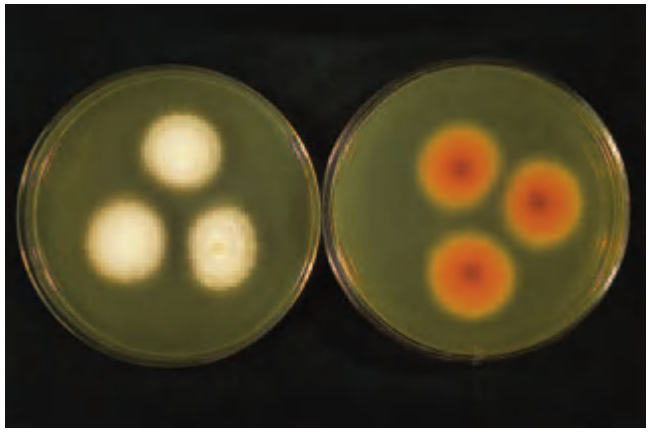


Fig. 31.17 Dermatophytosis. (a) Skin scales mounted in 30% KOH, Nomarski illumination. The hyphae are very even in diameter and regularly septate. (b) Skin scales mounted in 30% KOH, phase contrast. The hyphae are fragmenting to form arthroconidia, which may increase notably in size and round up as they mature. (c) Small-spored ectothrix hair invasion, 30% KOH bright field. The brown pigment delimits the edge of the hair, and the sheath of small arthroconidia that has formed on the surface of the hair is clearly visible. (d) Large-spored ectothrix hair invasion, 30% KOH, bright field. The sheath surrounding the hair is formed of arthroconidia, which are significantly larger than those seen in small-spored ectothrix infections. (e) Endothrix hair invasion, 30% KOH, bright field. The fungus inside the hair has broken up into a mass of large arthroconidia. These are retained entirely within the hair shaft. (f) Favus hair. The fungus is entirely confined within the hair shaft but does not fragment into arthroconidia. When first immersed in KOH, air is trapped around the hyphae forming the characteristic, long air spaces. These rapidly fill in with KOH, when the hyphae themselves become visible. (Courtesy of the Department of Medical Mycology, King's College London, St John's Institute of Dermatology, London, UK.)

(a)



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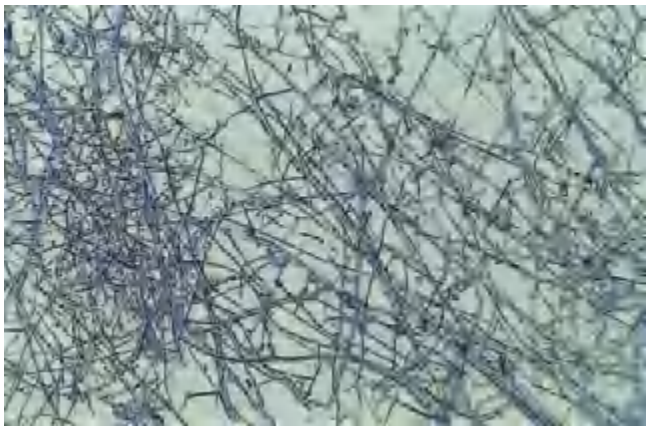


(c)

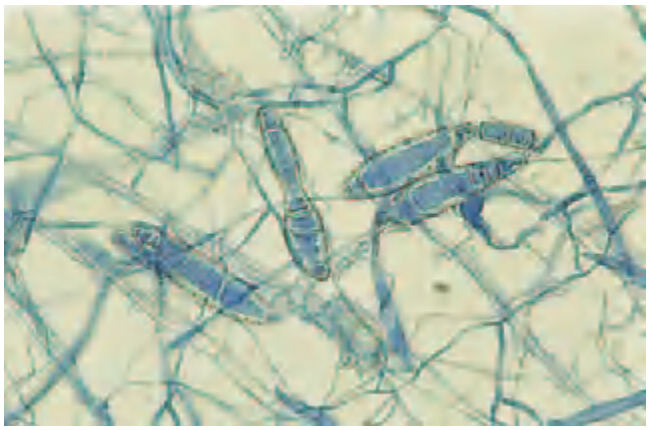


Fig. 31.18 (a) *Microsporum audouinii* colony: reverse of colony shown on right. (b) *Microsporum audouinii* microscopy, bright field. In many isolates chlamydoconidia, raquet hyphae and microconidia may be the only features of note. (c) *Microsporum audouinii* microscopy, bright field. In some isolates, macroconidia are observed. These are large, unevenly septate and may have a waisted appearance. (Courtesy of the Department of Medical Mycology, King's College London, St John's Institute of Dermatology, London, UK.)

M. audouinii (Fig. 31.18a–c). Colony: in many isolates the surface is white to tan with thin, sometimes silky growth, which has been compared to mouse fur. Other strains may have a thicker, downy white surface. The colour on the reverse of the colony is salmon pink to tan. Microscopy: in most isolates macroconidia are absent and the most characteristic features may be the presence of terminal and intercalary chlamydoconidia and racquet hyphae. However, in isolates where macroconidia are present, they are large, unevenly septate, variably rough and thick-walled, and often have a constricted centre and irregular shape. Physiological tests: *M. audouinii* grows poorly on polished rice grains.

M. audouinii var. *rivalieri* is a variant found mainly in Africa, but also reported from North America and Europe. The colony surface is white, with a distinctive ground-glass texture and radial or more complex cerebriform folding. Microscopically, macroconidia may be present, but the most characteristic feature is the presence of numerous pectinate hyphae. On primary culture, some isolates produce well-developed antler hyphae, which may cause confusion with *T. schoenleinii*. Subculture on to lactritmel agar may stimulate macroconidial production in these isolates and the characteristic small-spored ectothrix mode of *in vivo* hair infection will also aid in their correct identification.

M. canis (Fig. 31.19a,b). Colony: the surface is white, thinning towards the edge to reveal the yellow or orange reverse pigment. The texture may be cottony, with a buff centre caused by the abundant production of macroconidia; alternatively, the surface may be thinner, silky or patchily cottony and entirely white. Radial folds may be present. Microscopy: macroconidia are rough, particularly at the tip, with thick outer walls and up to 16 cells. They are spindle-shaped and may show a slightly bent apical beak. Physiological tests: *M. canis* grows well on polished rice grains. This medium also encourages macroconidial production.

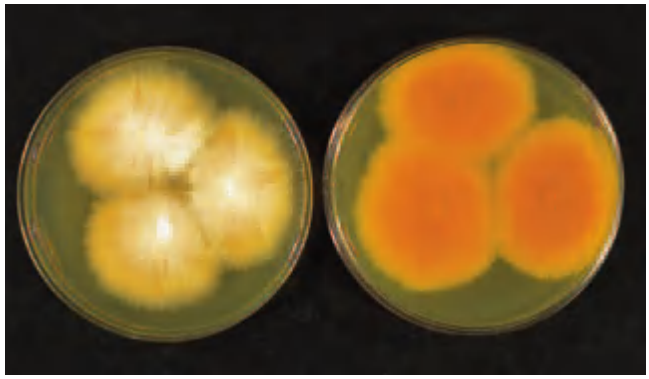
A glabrous variant (Fig. 31.20) has been described with heaped, leathery yellow or orange–brown colonies with feathery edges [5]; this mutant quickly reverts to the normal colonial form and produces typical macroconidia if cultured on rice grains.

M. canis var. *distortum* is a variety found in Australia, New Zealand and the Americas. The rough, thick-walled macroconidia are grossly distorted and bent.

M. equinum. Colony: the short surface mycelium is white to pale buff with regular deep radial grooves. The reverse is pink or salmon. Microscopy: the macroconidia are characteristic. They are rough and thick-walled but shorter and wider than those of *M. canis*, usually with one to four cells.

M. ferrugineum. Colony: restricted glabrous heaped colonies, yellow to rust in colour or more spreading, downy colonies similar to *M. audouinii*. Microscopy: thick 'bamboo' hyphae with prominent septa may be the only notable feature.

(a)



(b)

Fig. 31.19 (a) *Microsporum canis* colony; reverse of colony shown on right. (b) *Microsporum canis* microscopy, bright field. The macroconidia are characteristic, thick-walled and fusiform, often with a tilted, apical beak. They are rough with the most pronounced thickenings at the apical tip. (Courtesy of the Department of Medical Mycology, King's College London, St John's Institute of Dermatology, London, UK.)

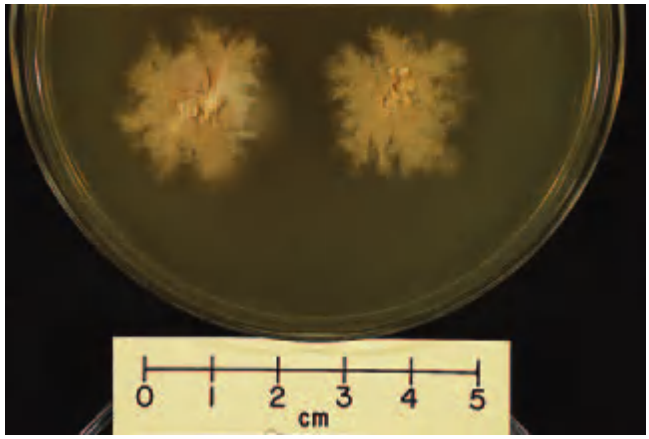
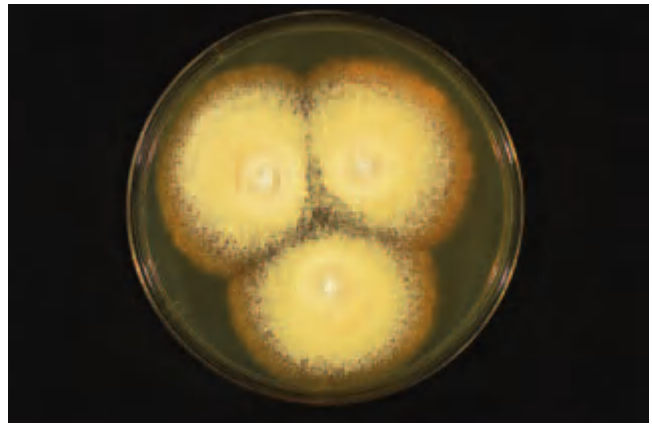


Fig. 31.20 *Microsporum canis* glabrous form colony. (Courtesy of the Department of Medical Mycology, King's College London, St John's Institute of Dermatology, London, UK.)

M. gypseum (Fig. 31.21a,b). Mating studies have demonstrated that the fungus traditionally known as *M. gypseum* is actually a complex containing three separate species: *A. fulvum* (Anamorph *M. fulvum*), *A. incurvatum* (Anamorph

(a)



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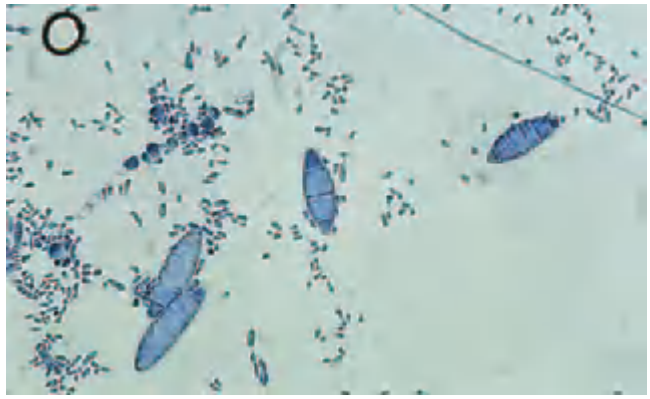


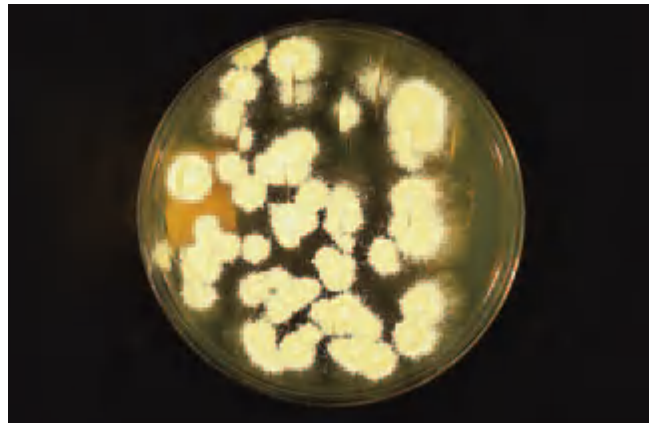
Fig. 31.21 (a) *Microsporum gypseum* colony. (b) *Microsporum gypseum* microscopy, bright field, the macroconidia are abundant and characteristic, with a symmetrical cigar shape and thin, finely roughened cell walls. (Courtesy of the Department of Medical Mycology, King's College London, St John's Institute of Dermatology, London, UK.)

M. gypseum) and *A. gypseum* (Anamorph *M. gypseum*). Colony: all the species produce rapidly growing colonies with a cinnamon or brown powdery surface. *M. fulvum* typically has a much thicker, more floccose surface texture; in *M. gypseum* the surface is almost completely flat. The reverse is yellow-buff to brown or may have red overtones. Microscopy: the numerous macroconidia are thin-walled, finely roughened over their entire surface and have up to six septa. The shape is very symmetrical, broadly fusiform with rounded ends, and has variously been described as cigar- or boat-shaped.

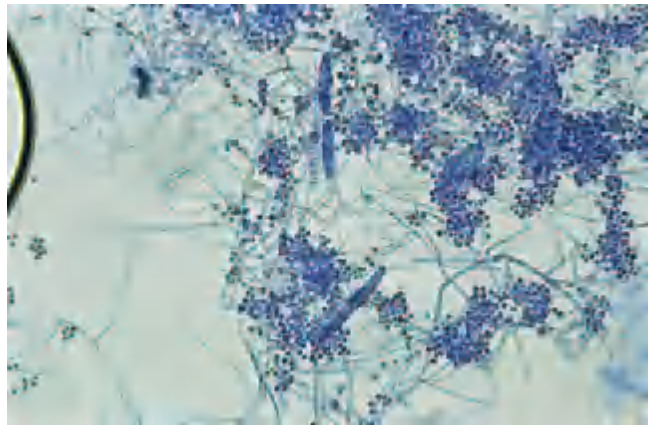
M. nanum. Colony: rapidly growing, flat powdery colonies with a buff surface and red-brown reverse. Microscopy: characteristic thin-walled rough obovate macroconidia with a single septum are abundantly produced.

M. persicolor. Colony: the surface of the colony is creamy buff, sometimes with pale pink tones. The texture is noticably thicker than that seen in *T. mentagrophytes* var. *mentagrophytes*. The reverse is buff to brown and may also

develop pink or reddish tones. Microscopy: very similar to *T. mentagrophytes* var. *mentagrophytes*. Many clavate to spherical microconidia are present, and arranged in grape-like clusters and along the hyphae. Young microconidia are pyriform and match-stick hyphae with an elongated basal cell carrying a microconidium at its tip may be observed. Tightly coiled, spiral hyphae are usually present. Thin-walled elongated macroconidia appear smooth on primary isolation media and usually contain six cells. Physiological tests: on medium free of sugar (1% peptone agar), *M. persicolor* colonies produce a pink surface colour; *T. mentagrophytes* var. *mentagrophytes* retains a white surface on this medium. On 3% salt agar, macroconidia are more obviously rough.



(a)



(b)

Fig. 31.22 *Trichophyton mentagrophytes* var. *mentagrophytes*. (a) Colony. (b) Microscopy, bright field. Round microconidia are arranged in clusters. Spiral hyphae and thin-walled, smooth, cylindrical macroconidia may also be present. (Courtesy of the Department of Medical Mycology, King's College London, St John's Institute of Dermatology, London, UK.)

Genus Trichophyton

Macroconidia are rarely formed by most of the anthropophilic species, and may not be particularly distinctive when they are. They are smooth and thin-walled. The size, shape and arrangement of the microconidia is useful in species identification, together with the presence of features such as coiled spiral hyphae, abundant chlamydospore production and special physiological requirements.

T. concentricum. Colony: the compact, heaped, folded colonies have a grey, tan or brown surface; initially glabrous, a thin short surface mycelium may develop. The reverse may be tan, brown or have reddish tones. Microscopy: conidia are absent. The hyphae may be swollen and distorted with numerous chlamydospores and occasional antler hyphae, or unremarkable. Physiological tests: 50% of isolates are stimulated by thiamine.

As the morphological features of this fungus are not very distinctive, it may be confused with other glabrous anthropophilic *Trichophyton* species, such as *T. yaoundei* or unpigmented isolates of *T. violaceum*. However, the clinical features of infection are so characteristic that they will aid in the identification.

T. equinum. Colony: in young cultures, the surface is very thin, revealing the reverse brown pigment. The reverse is initially brown in the centre with an outer yellow edge. As the culture matures, the surface texture thickens and becomes uniformly white and the reverse uniformly deep reddish brown. Microscopy: elongate to pyriform microconidia are arranged along the sides of the hyphae. Cylindrical smooth thin-walled macroconidia are rarely observed. Physiological tests: with the exception of some isolates from New Zealand and Australia, this fungus has a specific vitamin requirement for nicotinic acid.

T. gourvilii. Colony: the centre of the colony is garnet red to lavender, waxy, heaped, folded and surrounded by a flat white silky edge with an eyelash fringe. The reverse is cream to buff. Microscopy: clavate or pyriform microconidia are arranged along the sides of the hyphae.

T. megninii. Colony: the colony is very similar to downy *T. rubrum* isolates. The surface is white, developing pink or rose tones. The texture is velvety or downy, often with radial folds. The reverse is reddish brown to wine red. Microscopy: as in *T. rubrum*, pyriform microconidia are arranged along the sides of the hyphae. Physiological tests: when grown on a medium with an inorganic nitrogen source, this fungus has a specific requirement for L-histidine. Unlike *T. rubrum* it is urease positive.

T. mentagrophytes var. *mentagrophytes* (Fig. 31.22a,b). Colony: the colonies are fast growing with an intensely granular surface, which may be entirely white or develop a cream centre. The edge of the colony is thinner and may be spiky or stellate. The reverse is yellow, tan or red to brown. Microscopy: the spherical microconidia are

arranged in grape-like bunches and to a lesser extent along the hyphae. Coiled spiral hyphae are usually present, and in many isolates thin-walled, cylindrical macroconidia with up to eight cells may be present. Physiological tests: the fungus is urease positive and penetrates human hair *in vitro*.

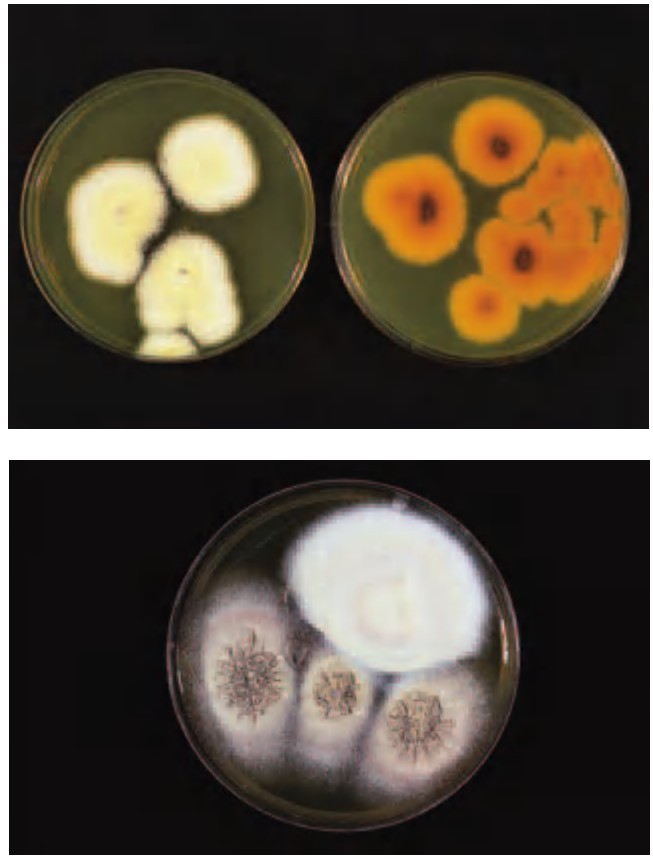
T. mentagrophytes var. *erinacei*. Colony: the rapidly growing colonies have a flat white intensely granular surface. The reverse is a bright canary yellow. Microscopy: elongate microconidia, even longer than those of *T. rubrum*, are arranged along the sides of the hyphae. Spiral hyphae and smooth thin-walled macroconidia may be present in some isolates. Physiological tests: unlike other variants of *T. mentagrophytes*, the fungus is urease negative, but will penetrate human hair *in vitro*. Some workers believe that this fungus should be regarded as a separate species, *T. erinacei*.

T. mentagrophytes var. *quinckeanum*. Colony: the surface is white, velvety or downy and often folded in the centre. The reverse is buff to cream. The colony has been reported to have a distinctive sour smell. Microscopy: pyriform microconidia are arranged along the sides of the hyphae. Physiological tests: produces a Wood's light-positive hair infection in mice with characteristic scutula.

T. mentagrophytes var. *interdigitale* (Fig. 31.23). Colony: the most typical isolates are rapidly growing with a white powdery surface, which develops a cream centre (Fig. 31.23a). A few isolates may develop a pinkish surface. The reverse is tan or reddish brown, often with a paler edge. Less typical downy forms have a fluffier white surface, sometimes slightly cream in the centre and folded (Fig. 31.23b). The reverse is pale cream to buff. Microscopy: powdery isolates may be very similar to *T. mentagrophytes* var. *mentagrophytes* with spherical microconidia arranged in bunches; spiral hyphae and macroconidia are present in some isolates. The fluffier downy isolates have pyriform microconidia arranged along the sides of the hyphae. Physiological tests: the fungus is urease positive and penetrates human hair *in vitro*.

The 'nodulare' form of *T. mentagrophytes* var. *interdigitale* has a predominantly glabrous, waxy surface devoid of aerial hyphae and feathery subsurface growth. Both the surface and reverse of the colony are orange–red in colour. Small areas of more typical white growth may be present. Nodular bodies are present on microscopical examination. This variety is relatively unstable, and may quickly sector out into a powdery or downy colonial form.

T. rubrum. This is probably the most morphologically variable dermatophyte species and several distinct colonial forms are regularly isolated. Only the most common will be described here.



(a)

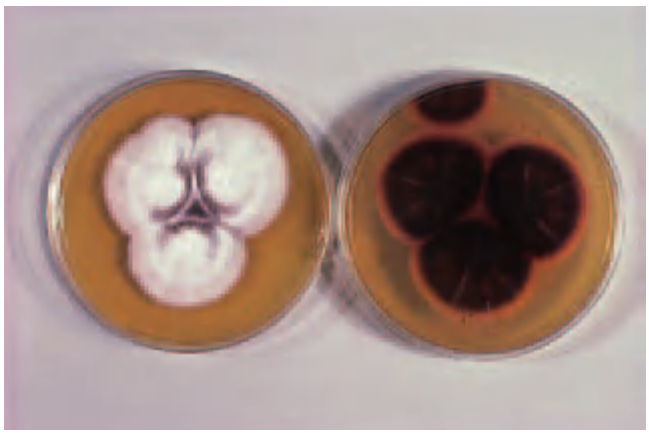
(b)

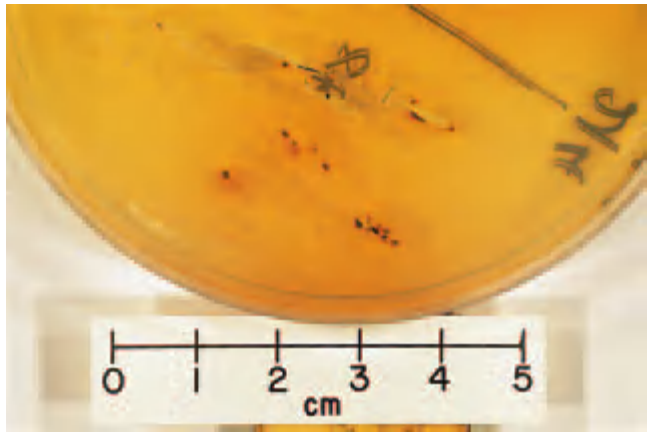
Fig. 31.23 *Trichophyton mentagrophytes* var. *interdigitale*. (a) Typical colony form; reverse of colony is shown on right. (b) More unusual colony forms. The upper colony is of the downy white form and the lower colonies show an intricately folded, beige form. (Courtesy of the Department of Medical Mycology, King's College London, St John's Institute of Dermatology, London, UK.)

1 *Downy form*. The most commonly isolated form in temperate zones (Fig. 31.24a,b). Colony: the surface of the colony is white, downy or cottony, and domed. The reverse of the colony is initially dark brown, usually with a paler cream border, but after incubation for 3–4 weeks produces the typical deep red pigment characteristic of this species. Microscopy: small tear-shaped, clavate or elongate microconidia are arranged along the sides of the hyphae. In some isolates microconidia may be scanty. Physiological tests: the fungus is urease negative and does not perforate human hair *in vitro*.

2 *Melanoid form* (Fig. 31.24c). Colony: similar to the downy form, but characterized by producing a brown melanoid pigment that diffuses into the medium and masks any red pigment on the reverse of the colony. Microscopy: small tear-shaped microconidia are arranged along the sides of the hyphae.

3 *Dysgonic form* (Fig. 31.24d). Colony: slow-growing tiny deep-red colonies with a brittle texture. This form is


(a)



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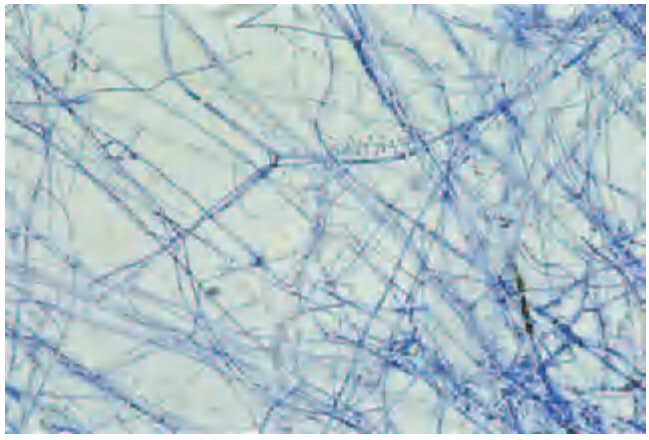
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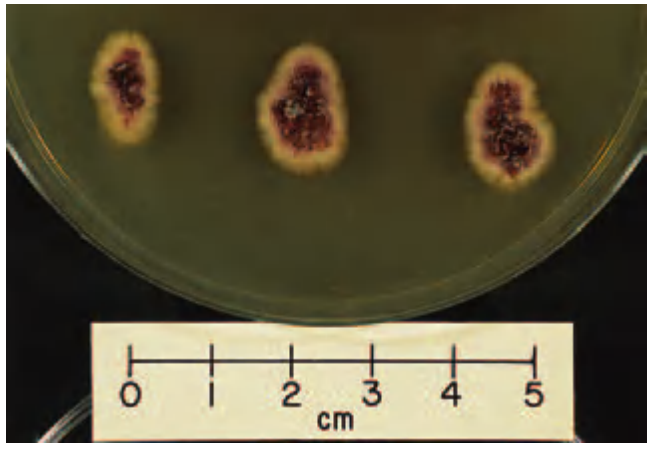

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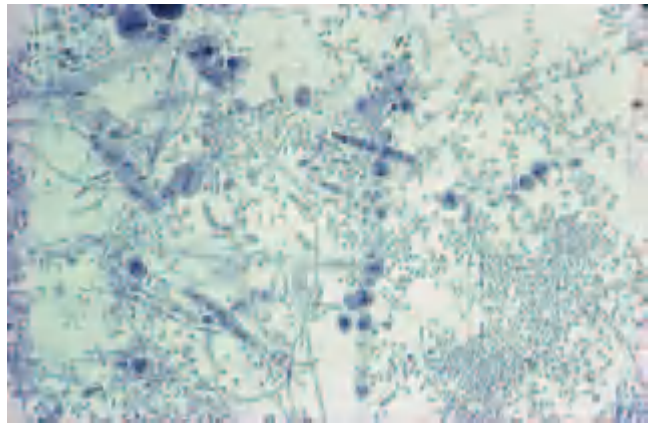
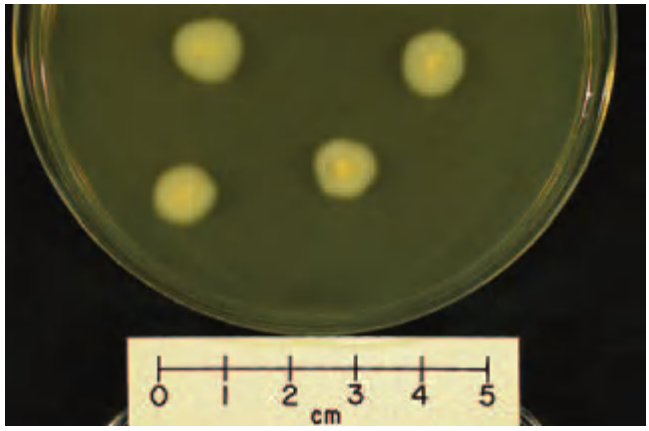

(f)

Fig. 31.24 *Trichophyton rubrum*. (a) Downy colony; reverse of colony shown on right. (b) Downy form microscopy, bright field. Clavate to elongate microconidia are arranged along the sides of the hyphae. They may be scanty in some isolates. (c) Melanoid colony form. A brown pigment diffuses into the agar medium. (d) Dysgonic colony form. Growth is initially very restricted and the tiny colonies a deep red. They usually revert to a more typical downy form within 2–3 weeks. (e) Granular form colony, with a powdery pink surface often raised and folded in the centre. (f) Granular form microscopy, bright field. Cylindrical, smooth-walled macroconidia are abundant and may become swollen as they mature with constricted septa. Microconidia and chlamydoconidia may also be abundant. (Courtesy of the Department of Medical Mycology, King's College London, St John's Institute of Dermatology, London, UK.)

relatively unstable and will quickly revert to the more typical downy form.

4 *Granular form* (Figs 31.24e,f). Colony: the surface is powdery or granular, cream to pink and often raised and folded in the centre. The reverse is red-brown. Microscopy: numerous smooth thin-walled cylindrical or pencil-shaped macroconidia are produced; some macroconidia may have constricted septa. Typical tear-shaped

(a)



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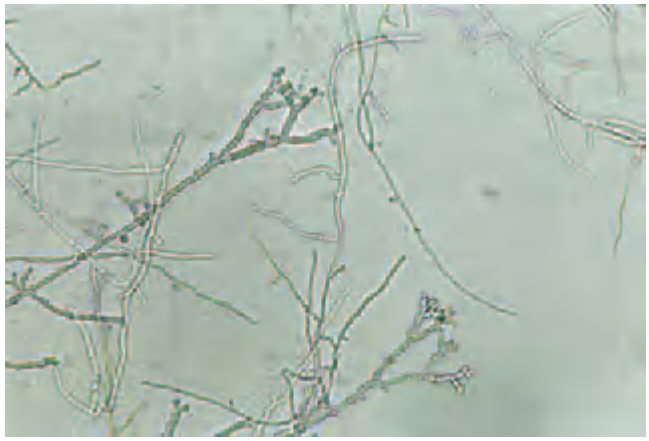


Fig. 31.25 *Trichophyton schoenleinii*. (a) Colony. (b) Microscopy, bright field. Typical antler hyphae may be observed by examining through the back of the culture plate with a × 10 or × 20 objective. The antlers branch dichotomously and have flattened tips. (Courtesy of the Department of Medical Mycology, King's College London, St John's Institute of Dermatology, London, UK.)

(a)

(b)

Fig. 31.26 *Trichophyton soudanense*. (a) Colony forms. A typical apricot yellow and a red isolate are illustrated. (b) Microscopy, bright field. The stiff hyphae with many arthroconidia and reflexive branching may be observed directly through the back of the culture plate. (Courtesy of the Department of Medical Mycology, King's College London, St John's Institute of Dermatology, London, UK.)

microconidia are also present. Physiological tests: this form is urease positive and may penetrate human hair *in vitro*.

5 *Yellow form.* The surface may be similar to the more usual downy form or it may be smooth, leathery and yellow. The reverse is yellow; the red pigment characteristic of *T. rubrum* is completely absent. In instances where microconidia are not observed it may be difficult to show that this is indeed a dermatophyte. However, pigmentation and sporulation may be enhanced on lactritmel agar.

T. schoenleinii (Fig. 31.25a,b). Colony: on primary isolation, the colonies may be glabrous or velvety, usually heaped and folded, and often with a fringe of hyphae at the edge submerged in the culture medium. The surface is white to cream and reverse pale. On repeated subculture, most isolates become downy. Microscopy: conidia are usually absent. Characteristic dichotomously branching hyphae with flattened tips, termed chandelier or antler hyphae, are present in fresh cultures. These may be readily observed by focusing on the back of the primary culture plate with a × 10 objective. Swollen distorted hyphae with many chlamydoconidia are also usually present.

T. simii. Colony: the surface is flat and granular, pale at the edges and buff or sometimes pink in the centre. The reverse is usually yellow to red-brown. Microscopy: many smooth-walled macroconidia are produced, often outnumbering the number of clavate to pyriform microconidia. The macroconidia are thin-walled, cylindrical or torpedo-shaped and are characterized by the development of constricted septa, and the fact that certain of the cells swell to produce endochlamydoconidia as they age.

T. soudanense (Fig. 31.26a,b). Colony: the colony is relatively slow growing, glabrous and leathery or brittle in texture, with a characteristic stellate or eyelash fringe around the edge. The colour is typically apricot, but

(a)

(b)

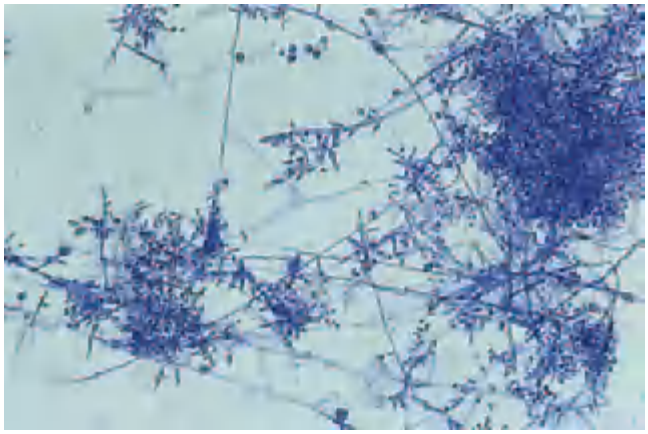


Fig. 31.27 *Trichophyton tonsurans*. (a) Colony; reverse of colony shown on right. (b) Microscopy, bright field. The microconidia are large and vary considerably in their shape. Chlamydoconidia are often abundant. Macroconidia and spiral hyphae are occasionally seen. (Courtesy of the Department of Medical Mycology, King's College London, St John's Institute of Dermatology, London, UK.)

isolates producing purple or red colonies are also common. Microscopy: when examined through the back of the primary culture plate using a × 10 objective, the hyphae appear stiff and 'brush-like'. They are very regularly septate, and the formation of arthroconidia produces a zig-zag appearance. Reflexive branching back towards the centre of the colony is a characteristic feature. Pyriform microconidia may be present.

T. tonsurans (Fig. 31.27a,b). Colony: the colony surface is velvety or powdery and may be grey, cream or yellow in colour, more rarely brown in the centre. Some isolates produce very sparse surface mycelium, so that the reverse brown pigmentation shows through. Circular or radial folds are often present. The reverse is typically chocolate brown, mahogany or yellow. Microscopy: the most characteristic feature is that the microconidia are noticeably larger than those of *T. mentagrophytes* or *T. rubrum* and very variable in shape. They range from clavate to elongate, and swollen 'balloon' microconidia and stalked, match-stick microconidia are also observed. In the majority of isolates, chlamydoconidia are numerous and in some isolates spiral hyphae and macroconidia are present. Physiological tests: this fungus has a specific vitamin requirement for thiamine.

T. verrucosum (Fig. 31.28a–c). Colony: this is a very slow-growing fungus, and after 2 weeks of incubation at 26°C the white or grey waxy colonies may still be barely visible. Growth is better at 37°C so, if cattle ringworm is suspected, incubation at both temperatures is recommended. Microscopy: examining the reverse of the primary plate under a × 10 objective, colonies incubated at 26°C show short hyphae with terminal chlamydoconidia. In contrast, colonies incubated at 37°C produce very characteristic long chains of chlamydoconidia. Clavate or elongate microconidia may be present along the sides of the hyphae. Rat-tailed macroconidia may be produced on depleted media. Physiological tests: most isolates have a requirement for thiamine and inositol. In a few, growth is enhanced by thiamine alone.

T. violaceum (Fig. 31.29). Colony: the slow-growing glabrous colonies have a waxy or leathery texture. Characteristically they are deep red in colour, but some isolates take several weeks to pigment, or retain unpigmented sectors. Occasionally, isolates fail to pigment at all. Microscopy: microconidia and macroconidia are usually absent. Chlamydoconidia and distorted hyphae may be present. Physiological tests: growth is stimulated by thiamine.

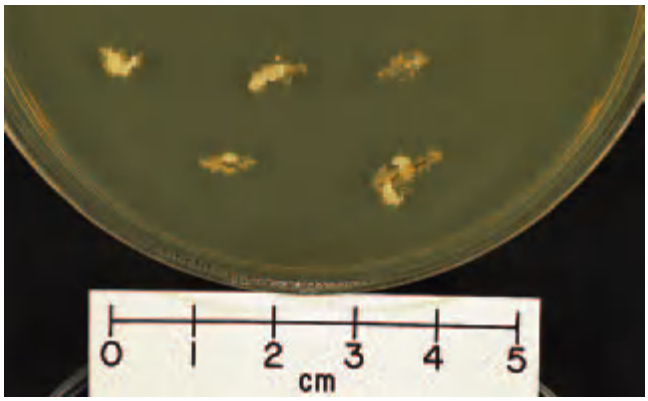
T. yaoundei. Colony: the colonies are initially glabrous, white to cream. As they age, the surface may develop a velvety texture and tan to brown colour; a diffusable brown pigment may be produced. Microscopy: irregular hyphae and chlamydoconidia may be present; clavate microconidia are rare. Physiological tests: the lack of vitamin requirements will distinguish this species from *T. verrucosum* and unpigmented isolates of *T. violaceum*.

Genus Epidermophyton

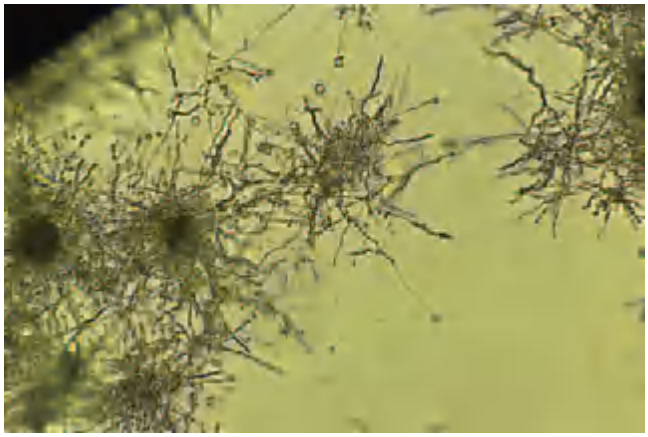
Identified by the characteristic macroconidia and lack of microconidia.

E. floccosum (Fig. 31.30a,b). Colony: this species grows rapidly to form velvety or suede-like colonies, which may remain flat or develop central or radial folds. The colour is typically khaki or olive green and some isolates produce tufts of floccose sterile white mycelium on the surface of the colony. Microscopy: large clavate macroconidia with a rounded apical end and up to six cells are rapidly formed. They are thin-walled and initially smooth, but may develop a few discrete thickenings as they age. Microconidia are absent. Chlamydoconidia are abundant and predominate in older cultures.

(a)



(b)



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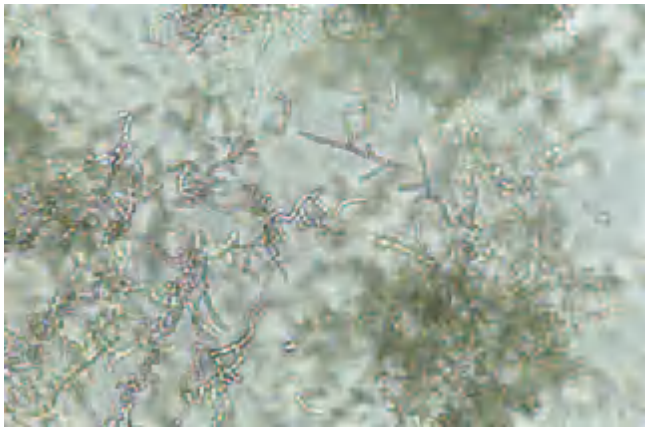


Fig. 31.28 *Trichophyton verrucosum*. (a) Colony. (b) Microscopy 26°C, bright field. Through the back of the culture dish, the small colonies are characterized by the development of hyphae with terminal swellings or chlamydoconidia. (c) Microscopy 37°C, bright field. Grown at a higher temperature, characteristic long chains of chlamydoconidia are observed. (Courtesy of the Department of Medical Mycology, King's College London, St John's Institute of Dermatology, London, UK.)

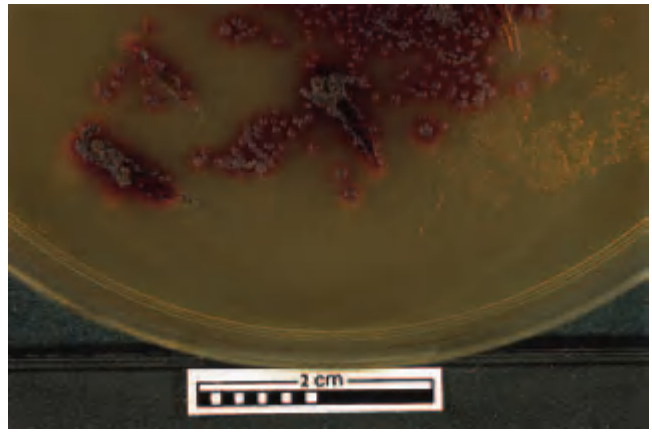
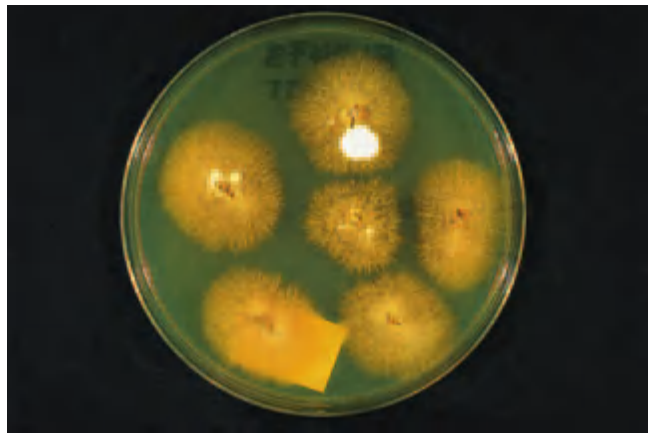
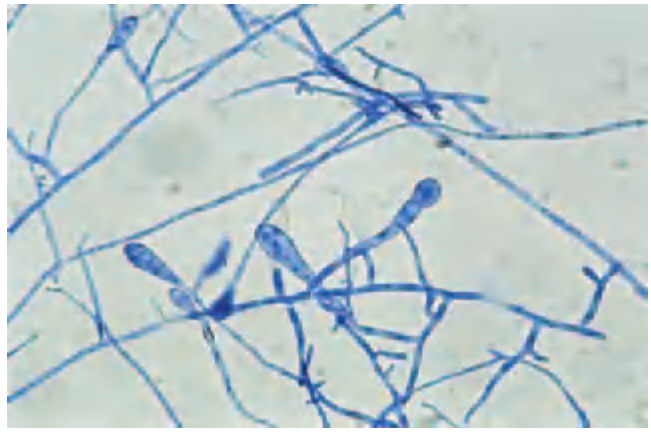


Fig. 31.29 *Trichophyton violaceum* colony. (Courtesy of the Department of Medical Mycology, King's College London, St John's Institute of Dermatology, London, UK.)



(a)



(b)

Fig. 31.30 *Epidermophyton floccosum*. (a) Colony. (b) Microscopy, bright field. The clavate macroconidia are characteristic. Microconidia are absent but chlamydoconidia are very common. (Courtesy of the Department of Medical Mycology, King's College London, St John's Institute of Dermatology, London, UK.)

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Therapy and management of ringworm infections

The treatment of fungal infection is now comparatively straightforward, and cure rates for many forms of dermatophytosis over 90%. In addition to treatment, some other management measures are generally helpful.

The identification of the causative agent is useful, particularly in tinea corporis and tinea capitis where treatment of an infected animal source is important in order to prevent other infections. In the case of tinea capitis, it will also provide information on the risk of spread to other children at home or in the school.

Prevention of dermatophytosis is not practicable except in situations where there is a high risk of spread to other individuals. These include shower rooms in industry or in the armed forces or schools. In the case of tinea pedis, improvement of hygiene in swimming baths may result in lower levels of infection. Frequent washing of changing room floors and walkways will remove infective material in skin scales. The provision of tolnaftate powder at a swimming bath and encouragement to use it prophylactically has been shown to reduce levels of toe cleft tinea pedis caused by *T. mentagrophytes* var. *interdigitale*, although it had little effect on *T. rubrum*. Clearly, infected individuals using these facilities should be encouraged to seek treatment. In industry or in schools, prompt treatment of infection combined with simple hygienic measures such as washing shower room floors with an antiseptic will be useful. It is less easy to prevent spread of tinea pedis in households; treatment of infection and care in keeping to personal towels are both sensible measures. Even with less care, family members often remain free of infection in spite of persistent cases of tinea pedis in their midst.

In the case of tinea capitis, it may be necessary to take preventative action [1]. This is particularly important if there is any evidence of an increasing number of cases of tinea capitis in schools. It is important to establish the nature of the infections, and whether the organisms are anthropophilic. There are no proven methods of ensuring eradication of infection in schools, but early identification of infected children and prompt treatment are probably the best approaches to adopt. An additional precaution is the use of a topical antifungal, which is likely to reduce spread while having little effect on the infection itself [1]. There is evidence that selenium sulphide shampoo may reduce the incidence of positive cultures in children receiving griseofulvin. The issue of keeping children off school remains controversial. The value of this measure in limiting spread has to be weighed carefully against its possible effect on compliance with surveillance and treatment. Therefore, this issue has to be considered in conjunction with the local situation. In one such outbreak in London, the policy adopted was to advise treatment for all infected children with griseofulvin plus selenium sulphide or ketoconazole shampoo, to allow them to attend school once on treatment, and to screen classes with scalp brushes if there were more than two children infected.

Therapeutic agents

The treatment of dermatophyte infections usually involves the use of oral terbinafine, fluconazole itraconazole, griseofulvin or one of several well-tried topical preparations (Table 31.7). All those noted have been shown to be effective in a substantial majority of patients, provided they are used regularly.

Terbinafine [2,3]. Terbinafine is a member of the allylamine antifungals, a newly developed group of drugs, which act by the inhibition of squalene epoxidase in the formation of the fungal cell membrane. This enzyme acts at an early stage in membrane biosynthesis, and the accumulation of squalene is thought to destabilize the cell membrane. The two main antifungal compounds are naftifine and terbinafine. Both are active *in vitro* against dermatophytes in addition to other fungi; terbinafine is also active against *Sporothrix schenckii*, some *Aspergillus* species and *Histoplasma capsulatum*, in addition to other fungi. *In vitro* there is little difference between the dosage at which the drug inhibits cell growth and that at which the fungal cell is killed (the drug is fungicidal rather than fungistatic). Terbinafine can be given topically or orally. When given orally, it is rapidly taken up into the stratum corneum and it persists in nails at high concentrations for several months. These may exceed the minimum inhibitory concentration 80 days after the end of therapy [4]. Terbinafine is given orally in a dosage of 250 mg/day. It has produced rapid and long-lasting remissions in both nail disease [5,6] and persistent tinea pedis, as well as tinea corporis. A smaller tablet form of 125 mg is available in some countries for treatment of children. The frequency of relapse is much lower than with griseofulvin. It also has activity against most of the agents of tinea capitis, particularly *Trichophyton* species, although it is not licensed for this indication in many countries [7]. There are few drug interactions reported for terbinafine, and side effects are uncommon. Some patients describe abdominal fullness and nausea. Taste loss may occur occasionally but is

Table 31.7 Topical antifungal agents used in dermatophyte infections.

Compound	Available as	Comments
Benzoic acid compound (Whitfield's ointment)	Ointment	Cheap
Undecenoates—various brands available	Ointment, powder	Cheap
Tolnaftate	Cream, powder, lotion	Cheap
Imidazoles		
Miconazole, clotrimazole, econazole, sulconazole,* ketoconazole, bifonazole*	Cream, powder, lotion, spray, shampoo (ketoconazole)	Broad spectrum including antibacterial (not ketoconazole)
Tioconazole nail solution*	Nail treatment	Expensive
Bifonazole urea*	Nail treatment	Expensive
Allylamines	Cream	Very rapid
Terbinafine, naftifine*		Expensive
Amorolfine*	Cream, nail lacquer	Can be used on nails Expensive
Cyclopyroxolamine*	Cream	Broad spectrum

* Availability varies in different countries.

reversible. Hepatic reactions, although reported, are exceptionally rare. Skin rashes including erythema multiforme or toxic epidermal necrolysis are also seen on occasion.

Itraconazole [8,9]. This is an orally active azole of the triazole series. It has similar activity to ketoconazole, but without the risk of hepatotoxicity. Its mode of action is through the inhibition of the cytochrome P-450-dependent demethylation stage in the formation of ergosterol on the fungal cell membrane. It is active *in vitro* against all the main superficial fungal pathogens including *Candida albicans*, as well as a wide range of fungi that cause deep infections from *Histoplasma capsulatum* to *Penicillium marneffei*. Itraconazole rapidly penetrates to the outer stratum corneum and is also found in sebum. It is avidly bound to keratin-containing tissues, and in nail, for instance, may persist long after cessation of therapy. It has been shown that after 3 months of 200 mg/day itraconazole, levels in the toenail persist for up to 6 months [10]. This feature allows a range of different dose regimens. These have evolved so that the initial treatments first described involving 100 mg/day itraconazole have been superseded by higher or intermittent (pulsed) therapy. It is active against a wide range of dermatophytes and is effective in regimens of 100 mg for 15 days in tinea cruris and corporis, or 30 days in tinea pedis. The currently preferred regimen uses 400 mg/day, given as two daily doses of 200 mg. In tinea corporis, 1 week of therapy is sufficient, and in tinea pedis 2 weeks. For onychomycosis, a regimen of 400 mg/day for 1 week every month for 3 months is usually given. Occasionally, longer periods of treatment are needed [11]. Although it is not licensed yet in many countries for the treatment of tinea capitis [12], it is effective in this indication. Side effects are not common but include nausea and headache. There is some evidence that its absorption is impaired in the presence of phenobarbital. It also interacts with coumarin anticoagulants, ciclosporin, rifampicin, digoxin, statins and astemizole and terfenadine. It should not be given together with the latter antihistamines, as they may cause cardiac arrythmias. Side effects are not common and mainly consist of nausea and abdominal discomfort. Hepatic reactions are exceptional.

Griseofulvin [13]. This is a metabolic product derived from several species of *Penicillium*, which was first isolated from *P. griseofulvum*. Its activity, which is fungistatic, is largely restricted to dermatophyte infections. The mode of action appears to be in part through inhibition of the formation of intracellular microtubules. Resistance to griseofulvin among dermatophytes is rare. The smaller particle size microcrystalline preparations of griseofulvin are better absorbed than those with larger particles, and the micronized form is now the standard preparation. Unlike itraconazole, griseofulvin is not firmly bound to keratin.

The usual human regimen is 10 mg/kg/day given in tablet form, or solution form for children. Treatment duration varies between 2 and 4 weeks for tinea corporis to over 1 year for onychomycosis of toenails. In tinea capitis, a single dose of 1–2 g griseofulvin has been reported to be effective in some patients with tinea capitis [14]. Drug interaction with phenobarbital and coumarin anticoagulants occur [13]. Headaches and nausea are common complaints on griseofulvin; however, serious side effects have been extremely rare. There are a few reports of apparent precipitation or exacerbation of systemic lupus erythematosus (SLE) and porphyrias by griseofulvin. Occasionally, urticarial rashes are seen and light sensitivity eruptions (distinct from lupus erythematosus and porphyria) have occasionally been reported.

The use of griseofulvin has largely been superseded in many countries by terbinafine or itraconazole, except in tinea capitis.

Ketoconazole [15]. This orally active imidazole is a broad-spectrum antifungal agent. In ringworm infections requiring systemic treatment, it offers an alternative agent and is given in a 200–400 mg/day regimen with food (for adults). Hepatitis is a proven complication, occurring in 1 in 10 000 patients. Because of this, ketoconazole is reserved for second-line therapy. At high doses, ketoconazole may also inhibit androgen biosynthesis [15].

Fluconazole [16]. Fluconazole is an orally active triazole antifungal used for the treatment of *Candida* infections and systemic mycoses. However, it also has activity against dermatophyte fungi. It is given in a regimen of 150 mg/week for 2–3 weeks for tinea corporis and tinea cruris, and somewhat longer for dry-type tinea pedis. It is also reported to be effective given in weekly doses in onychomycosis, although the exact length of treatment necessary is not clear as yet. There are fewer interactions than with itraconazole but, like the latter, side effects are rare and mainly confined to gastrointestinal discomfort. However, drug resistance in *Candida* species, particularly *C. krusei* and *C. glabrata*, have been described. There is *C. albicans* resistance in AIDS patients [17].

Topical applications. A great variety of topical applications have been used for the treatment of ringworm infections. The short list includes a few preferred preparations (Table 31.7), which have been soundly tested, and which in the authors' clinical experience and the published controlled trials are of very comparable effectiveness [18–22]. In all cases, allergic contact dermatitis is rare. Irritant effects may occur with any of them, especially on raw skin and in fissures between the toes. Benzoic acid compound ointment (Whitfield's ointment), full strength, is not advised for tender skin, such as the scrotum or the groins, and in such sites should only be used diluted to half-strength with its vehicle (emulsifying ointment). Magenta paint (Castellani's paint) is still used in some cases of inflammatory tinea pedis, particularly when bacterial infection coexists, although potassium permanganate followed by a topical antifungal is preferred. Imidazoles for topical use, such as clotrimazole, econazole and ketoconazole, are now well established as effective remedies in ringworm infections with an extremely low incidence of adverse reactions; other drugs in this group, miconazole, isoconazole, tioconazole and sulconazole are equally effective [23,24]. Alternatives include topical terbinafine and amorolfine. Terbinafine applied topically has been shown to produce responses in some dermatophyte infections in very short periods. For instance, 1 week of topical terbinafine was found to be more effective than 4 weeks of clotrimazole in tinea pedis. Amorolfine, a morpholine, is mainly used as a treatment for onychomycosis in the form of a 5% nail lacquer [25] applied after abrading the nail once or twice weekly.

Treatment regimen

The different syndromes of ringworm infections require different treatment regimens. The evidence base has only recently been reviewed in the case of some infections and among published clinical trials there are very few with long-term follow-up. Generally, topical therapies are used for localized or mild infections, oral antifungals for the more extensive infections. The newer oral azoles, such as fluconazole or itraconazole and terbinafine, are now the preferred oral treatments for extensive or severe dermatophytosis rather than griseofulvin. Although cheaper than the alternatives, griseofulvin is usually slower and, in many studies, less effective.

Tinea corporis. Localized tinea corporis, especially of recent origin, commonly responds to topical therapy applied twice daily, usually for about a month. Topical terbinafine often works in a shorter time (e.g. 2 weeks). In more widespread infections of recent onset, oral terbinafine or itraconazole will generally be preferred, and may be expected to clear the condition in about 2–3 weeks, depending on the dosage used. With griseofulvin, much longer term treatment is needed, for up to several months with extensive infections. With *T. concentricum*, treatment failures may occur with griseofulvin. Both terbinafine and itraconazole are effective in tinea imbricata, but the most appropriate regimen is not clear.

Tinea capitis. Topical therapy has little place in the management of this condition except as an adjunct to oral therapy. Griseofulvin should therefore be given. Although massive single-dose therapy and intermittent dose regimens (25 mg/kg twice a week) have had some success, in general, conventional continuous daily therapy is advisable (10 mg/kg). In small-spored ectothrix infections, griseofulvin for at least 6 weeks is usually adequate. In some *T. tonsurans* and *T. schoenleinii* infections, much longer courses and sometimes higher dosage (20 mg/kg/day) of griseofulvin therapy may be needed. With scalp kerions, careful removal of crusts using wet compresses should not be neglected, and the possibility of coexisting bacterial infection should be considered. If confirmed by swabs, systemic antibacterial chemotherapy should be instituted. In general, the kerions are less painful than their inflammatory appearance suggests, but analgesics may be needed. Occasionally, in children with extensive kerions, frequent attendance at the outpatient clinic where

skilled nursing is available may be of great value, and is much appreciated by the worried parents. Permanent hair loss from scarring is usually less than would be expected.

Both itraconazole and terbinafine are now licensed in a few countries for use in children, and are alternatives for certain infections such as those caused by *Trichophyton* species, although there are fewer data and, in some cases—particularly with terbinafine—they have appeared to be less effective in disease caused by *Microsporum* species. The best length of treatment for *T. tonsurans* and *T. violaceum* infections with terbinafine appears to be 1 month. There is some evidence that higher doses of terbinafine may be more effective for *Microsporum*. The appropriate length of treatment with either itraconazole or fluconazole is not established, although both appear to be effective against *T. tonsurans*. Ketoconazole shampoo or selenium sulphide can be used to prevent spread in the early phases of therapy, when used in combination with an oral treatment. In severely inflammatory forms, there has been some argument in favour of using oral steroids to inhibit the inflammatory response. While this view has its supporters, we tend to review all cases early after the institution of antifungal therapy, and only use oral steroids in severe cases with widespread ide reactions.

Tinea barbae. Beard infections usually respond satisfactorily to itraconazole or terbinafine, sometimes in combination with topical therapy over a period of 4–6 weeks. Fairly long-term follow-up is recommended, and late recurrences undoubtedly occur.

Tinea faciei. In localized cases, promptly diagnosed topical therapy seems to work well, especially with tolnaftate or one of the imidazoles. Where delay has occurred before the diagnosis is established, and especially when steroid therapy has modified the condition, terbinafine or itraconazole is generally preferred. Most cases will clear in 3 or 4 weeks, certainly in 6 weeks, but long-standing infections may occasionally need longer periods of treatment.

Tinea pedis. For very mild toe cleft changes and for prophylaxis at swimming baths, one of the topical preparations is recommended. Tolnaftate powder, for instance, has proven value, and the imidazoles are likely to be equally effective. For toe cleft changes that are more than trivial, a cream is generally preferred and any of the listed preparations can be confidently recommended for minor forms of tinea pedis. Azole preparations are cheap and are usually effective in up to 30 days, but topical terbinafine can be used for 1–7 days; it is more expensive. If the toe clefts are very inflamed and secondary bacterial infection is likely, a brief period with rest and bland applications may be necessary. Magenta paint initially used at half strength, potassium permanganate solution or aluminium chloride solution 20–30% twice daily have considerable advantages. Clearly, if there is any evidence of serious bacterial infection, swabs should be taken; if there is clinical evidence of cellulitis, patients should receive a systemic antibacterial antibiotic.

In dry-type tinea pedis, usually caused by *T. rubrum*, terbinafine or itraconazole are of great value. Speed of recovery is faster and relapse rates less than with griseofulvin. Treatments using terbinafine 250 mg/day for 2 weeks or itraconazole 400 mg/day for 1–2 weeks are usually given.

Tinea cruris. In cases of recent onset, topical therapy can be expected to be curative within 2–4 weeks. Any of the local applications listed is satisfactory, but benzoic acid compound ointment (Whitfield's ointment) should be prescribed at half strength. Tolnaftate, terbinafine and the imidazoles are better tolerated in the flexural areas, and if the diagnosis is in doubt terbinafine and the imidazoles have the advantage of being effective against *Candida* as well. Where the condition has been present for many months, or has spread to the pubic area, the natal cleft or the buttocks, and where topical steroids have been used, systemic treatment is strongly recommended. Terbinafine and itraconazole usually produce a remission in 1–2 weeks [26]. Some patients relapse even after this therapy, although it appears less likely to occur than with griseofulvin. A longer course of therapy may work in these recalcitrant cases.

Tinea manuum. Chronic ringworm infections of the palm are not easily cleared, and oral therapy is always needed. Itraconazole and terbinafine are both effective in this condition. Most cases clear with 2–4 weeks of treatment although it may be advisable to review the results a few months after the end of treatment. With griseofulvin, longer periods of treatment are necessary. Many patients will require 3 months of therapy and may even relapse after that.

Onychomycosis caused by dermatophytes. In general, fingernail infections with ringworm fungi respond satisfactorily to oral terbinafine 250 mg/day for 6 weeks or itraconazole 400 mg/day for 1 week, given monthly for 2–3 months. With griseofulvin [27], clearance may be expected in about 4 months, but longer treatment regimen, up to 8 months or even 1 year, are often needed. In the case of toenails, longer periods of treatment may be necessary; for example, terbinafine 250 mg/day for 3 months or itraconazole 400 mg/day for 1 week given monthly for 3–4 months. One large clinical trial has shown better efficacy with terbinafine than itraconazole [28]. Some, possibly 15% of patients, fail to respond to these drugs, and there is a strong clinical impression that results are much better

in younger patients in whom faster linear nail growth and relative absence of coexisting ischaemic or traumatic dystrophy are probably important factors. Poor peripheral circulation seems to have an adverse effect on treatment.

Avulsion of the nail or removal of the infected areas with a drill or burr as adjuncts to antifungals are occasionally valuable. The use of 40% urea cream under occlusive dressing is an alternative approach to treatment [29], particularly in oral treatment failures. The addition of the imidazole, 1% bifonazole, to the urea paste has produced good responses in some patients with involvement of the entire nail plate [30]. When a single great toenail is infected, these procedures are worthy of serious consideration. Unfortunately, there has been no reliable controlled evaluation of their worth, and avulsion is certainly not without its drawbacks. Topical therapy for nail infections has been used in the past with poor results, except in SWO caused by ringworm infection, where it may well be effective. Other topical agents reported to be effective —28% tioconazole, ciclopyroxolamine and amorolfine nail paint—have all produced remissions in some studies, although these are seldom frequent enough to encourage sole use of these preparations, except in early or superficial infections or as adjuncts to oral therapy. The use of combined treatment with either terbinafine or itraconazole with amorolfine may be more effective than oral therapy alone [31].

Steroid-modified ringworm. Whatever site is affected, it is often best to treat steroid-modified ringworm with oral therapy, allowing a few applications of topical steroid to continue until the terbinafine or itraconazole has begun to take effect. It is wise to use 1% hydrocortisone cream or at least a weaker steroid than that originally prescribed, and also to warn the patient about a possible rebound in spite of these measures. Follow-up to ensure steroid cream has been stopped and cure obtained is mandatory.

Treatment failures

Failure of topical therapy. Most failures of topical therapy are caused by inaccurate diagnosis or by inappropriate use of topical therapy (e.g. in hairy areas), or because the treatment is not used. Once or twice daily application for several weeks is usually required for success, and many patients, particularly if their symptoms are minor, will not achieve this unless they are carefully supervised and enthusiastically encouraged. Paradoxically, some non-fungal conditions may be improved considerably by one of the antidermatophyte preparations, and these remedies should not be used empirically to establish the diagnosis of ringworm infection. Many dermatoses respond, at least temporarily, to any bland application, and imidazole compounds in particular have considerable antibacterial properties.

Failure of oral therapy. When a patient fails to respond to terbinafine, fluconazole or itraconazole, the following points should be checked:

1 Is the diagnosis correct? If necessary repeat scrapings.

2 Has the patient been taking the tablets regularly?

3 Is the patient taking any potentially competitive drugs?

4 In spite of taking them correctly, is the patient failing to absorb the antibiotic? Estimation of itraconazole levels, which is sometimes poorly absorbed, may be helpful.

5 In some patients with onychomycosis, poor penetration of drugs into defined linear or nail edge areas of nail plate infection may account for treatment failure.

6 Is there coexisting pathology such as arterial disease?

7 Is a co-pathogen or secondary infection present? This should be considered in feet and in the case of kerions, and perhaps in groin infections too. In nails, the coexistence of non-dermatophyte fungus should be considered. *Scopulariopsis brevicaulis*, apart from causing infections of the toenails in its own right, may coexist with *T. rubrum* or *T. mentagrophytes* var. *interdigitale* and seems, at least on occasions, to cause failure of treatment. Nail removal may be indicated in this instance.

8 Antifungal resistance. This phenomenon is sufficiently uncommon among dermatophytes to make routine testing unnecessary [30], but where treatment failure occurs without other explanation, it is possible to estimate the sensitivity of the causal organism. This should be performed by a specialist laboratory. Apart from true resistance, tolerance, in which the organism apparently becomes clinically resistant to drug in the tissues but is sensitive *in vitro*, may also be important.

9 Reinfection. As ringworm fungi can frequently be isolated from the environment, when there are cases of ringworm of the scalp, and from clothing after laundering, it is highly likely that patients whose infection has been eradicated may be reinfected from these sources. Unfortunately, there is no proven way to avoid this.

Despite running through this checklist, dermatologists may not come up with an adequate explanation for treatment failure. In these situations, the use of one of the alternatives is a logical further step.

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Infections caused by *Scytalidium* species

Aetiology. *Scytalidium dimidiatum*, previously known as *Hendersonula toruloidea*, is a weak secondary pathogen of higher plants, found mainly in tropical areas, but also in the USA and the Mediterranean region. This grey to black mould is now recognized as the cause of ringworm-like infections of the palms, soles, toe webs and nails [1–4]. *S. hyalinum*, a variant non-pigmented form of *S. dimidiatum*, can also mimic tinea pedis and manuum and invade the nail plate [5]. These two moulds evoke the same clinical picture.

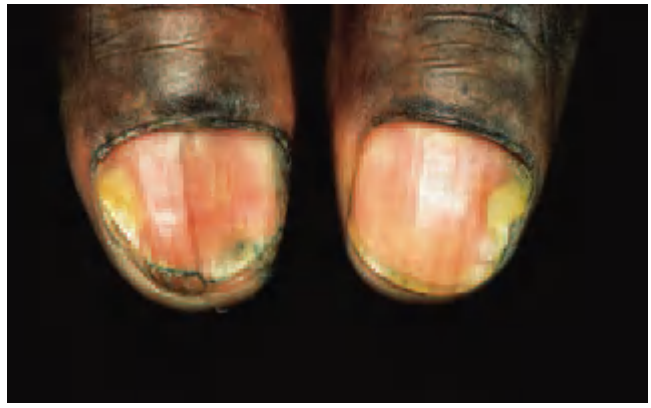

Fig. 31.31 Onychomycosis caused by *Scytalidium dimidiatum*: early onycholysis.

Although these infections were first diagnosed in the UK in patients who were immigrants from the West Indies, East Africa and the Indian subcontinent, reports from areas where they may be truly endemic, such as the Caribbean [6], West Africa [7–9] and Thailand [10], have shown that infection by *Scytalidium* species is extremely common. Infection has also been seen in Europeans who have merely visited an endemic area for a vacation.

Clinical features. These fungi are capable of producing toe cleft changes and involvement of the palms and soles. In this, they closely resemble the dry-type infection caused by *Trichophyton rubrum* affecting the palms or soles [5]. Lesions are often asymptomatic and only discovered on routine inspection. In fingernails, the nail changes start at the lateral and distal edges, and there may be extensive undermining of the nail without corresponding thickening of the nail plate (Fig. 31.31). The nails may fracture transversely in due course. Paronychia often accompanies these changes. Usually, yeasts are not present under the nail fold, suggesting that the changes are caused by *Scytalidium* alone. In the toenails, the changes are usually identical to those seen in dermatophyte infections. Occasionally, there may be increased pigmentation in the nail plate, but this should not be confused with idiopathic longitudinal pigmented streaking of the nail. This change is most prominent in white people with nail infections [11]. The infection is confined to areas of thickly keratinized skin, and involvement of less heavily keratinized areas, such as the groins, or dorsum of the hand or foot, is not found.

Laboratory diagnosis. Although pigmented brown hyphae have occasionally been observed in skin and nail

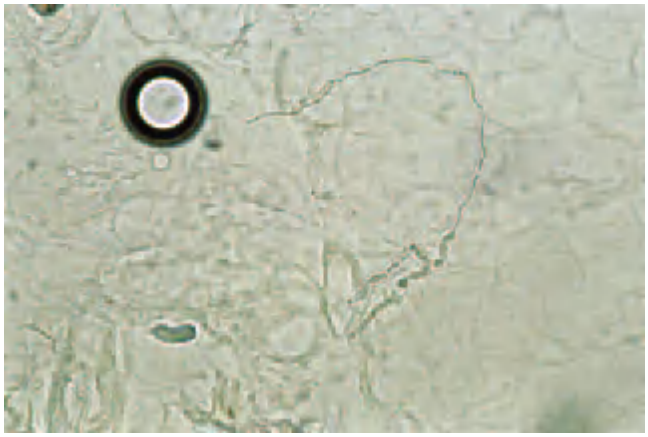

Fig. 31.32 Infection by *Scytalidium* species. Skin scales mounted in 30% KOH, bright field. The hyaline hyphae superficially resemble those of dermatophytes, but are very uneven in diameter. One- to two-celled arthroconidia may be observed. (Courtesy of the Department of Medical Mycology, King's College London, St John's Institute of Dermatology, London, UK.)

Fig. 31.33 *Scytalidium dimidiatum* colony forms. The fast-growing form (right) fills a 90-mm Petri dish in a few days and develops profuse aerial mycelium. The velvety, slow-growing form grows at the same rate as a dermatophyte. (Courtesy of the Department of Medical Mycology, King's College London, St John's Institute of Dermatology, London, UK.)

samples infected by *S. dimidiatum*, in the vast majority of cases the hyphae are hyaline and appear very similar to those of dermatophytes. Typically, however, they are more irregular, varying noticeably in width along the length of a single hypha [12] (Fig. 31.32). With experience, a preliminary diagnosis of *Scytalidium* infection may be made on the basis of direct microscopy alone.

Both *S. dimidiatum* and *S. hyalinum* are sensitive to cycloheximide, and this antibiotic must be excluded from the culture medium. As mixed infections by *Scytalidium* species and dermatophytes have been recorded, duplicate cultures with and without cycloheximide are ideal, and will allow the isolation of both dermatophyte and non-dermatophyte. Mixed infections of dermatophytes and *S. dimidiatum* and *S. hyalinum* have also been reported.

S. dimidiatum. Colony: variable colonial morphology [13] (Fig. 31.33). One form grows very rapidly and produces a high aerial mycelium, which completely fills a 90-mm Petri dish in a few days. The other common form grows more slowly, at about the same rate as a dermatophyte and does not produce aerial hyphae, but has a velvety surface texture. Both are pale initially, but darken to black and mouse grey, respectively, as they mature. Microscopy: branching chains of one- to two-celled brown arthroconidia are observed (Fig. 31.34). These are abundant in the fast-growing cultures, but may be scanty in the slow-growing form. Coiled hyphae and rough-walled hyphae are usually present in the slow-growing cultures.

S. hyalinum. Colony: the fungus grows rapidly, and in a few days produces a white to cream colony with a moderately high aerial mycelium and buff reverse (Fig. 31.35).

Fig. 31.34 *Scytalidium dimidiatum* microscopy, bright field. Chains of brown, one- to two-celled arthroconidia are characteristic. They may be scanty in the slow-growing form. (Courtesy of the Department of Medical Mycology, King's College London, St John's Institute of Dermatology, London, UK.)

Fig. 31.35 *Scytalidium hyalinum* colony. (Courtesy of the Department of Medical Mycology, King's College London, St John's Institute of Dermatology, London, UK.)

Microscopy: chains of hyaline one- to two-celled arthroconidia are produced.

Treatment. There is no reproducibly effective therapy, although individual patients may respond to treatment with tioconazole or econazole. For scaling sole lesions, the use of Whitfield's ointment may be very effective. Although both organisms may be sensitive *in vitro* to itraconazole or terbinafine infections seldom respond to these drugs clinically.

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Onychomycosis caused by other non-dermatophyte moulds

Definition. Broadly, the term onychomycosis describes any fungal infection of the nail plate. Ringworm infections, *Candida* infections and *Scytalidium* infections are considered separately, and these organisms are considered to be primary pathogens. However, a wide variety of other non-dermatophyte moulds have been reported from abnormal nails, most often toenails, and in such cases their significance needs very careful assessment [1]. Many of these putative pathogens are common in the environment, and may be isolated as contaminants, particularly on media free of cycloheximide. It is therefore essential in cases where such moulds are implicated in onychomycosis to correlate the morphological findings on direct microscopy with those of the isolate. A considerable proportion of dermatophyte infected nails with typical hyphae present on direct microscopy will fail to yield a dermatophyte on culture. In these instances, the isolation of a few colonies of a contaminating mould may be misinterpreted. In other instances, a non-dermatophyte mould may be isolated in addition to a dermatophyte, and once more, unless evidence suggestive of a mixed infection has been obtained on direct microscopy [2], in most instances this will represent simple contamination. Before the isolation of a non-dermatophyte can be considered significant, re-examination of the patient is essential in order to confirm the infection. A second direct examination will allow any unusual features of the fungus in the nail to be assessed. Atypical morphology, such as the presence of large numbers of fronding hyphae or even the production of characteristic conidia within the nail, may be present. In such instances, a second culture on medium free of cycloheximide may allow reisolation of the same mould and confirm the infection. Concurrent culture with cycloheximide is also recommended to confirm the absence of a dermatophyte, or it may in some instances prove the presence of a mixed infection, for nails rendered abnormal by a primary dermatophyte infection may occasionally be secondarily invaded by moulds. It is noteworthy that in unmixed infections, these non-dermatophytes, unlike *Scytalidium* species, are incapable of producing concurrent skin infection.

Using reliable criteria, one survey in Canada [3] of over 2500 isolates from infected nail samples found that *Scopulariopsis brevicaulis* made up 1.6% of the total, and that species of *Aspergillus* and *Fusarium* comprised a further 0.3% of the total. Similarly, a working group of the British Society for Medical Mycology [4] has estimated that approximately 5% of cases of onychomycosis are caused by non-dermatophyte moulds. Such data confirm the view that a few moulds are fairly regularly reported from a small percentage of the total cases of onychomycosis, and their isolation may suggest that they are playing some part in the pathology, although whether their removal with antifungal therapy will result in clinical recovery remains to be established. By far the most common of these isolates is *Scopulariopsis brevicaulis*, which does appear capable of attacking undamaged nails or ones showing only trivial abnormalities. In cases of superficial white onychomycosis, species of *Acremonium*, *Fusarium* and *Aspergillus* may be isolated rather than *Trichophyton mentagrophytes* var. *interdigitale*. Since 1990, *Onychocola canadensis* has been recognized as a cause of onychomycosis in nine subjects from Canada and New Zealand [5,6].

Scopulariopsis infections [2]

Scopulariopsis brevicaulis is a common saprophytic mould that does not attack the skin. When it causes nail dystrophy, the clinical features may be indistinguishable from those of a ringworm infection, but where there is heavy

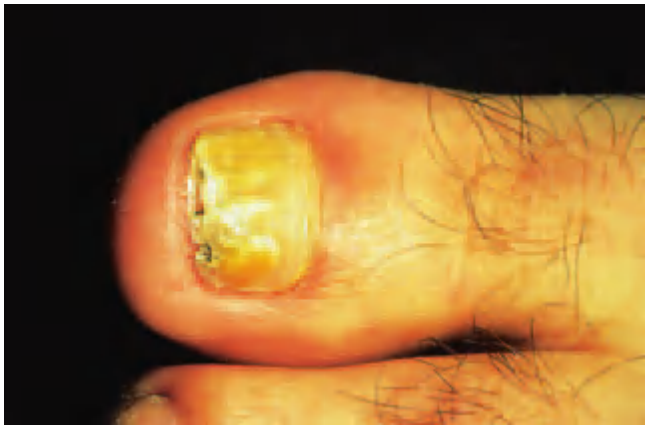


Fig. 31.36 Onychomycosis caused by *Scopulariopsis brevicaulis*.

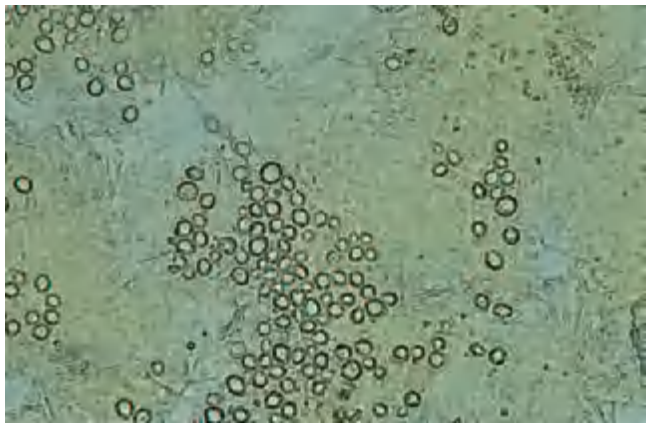
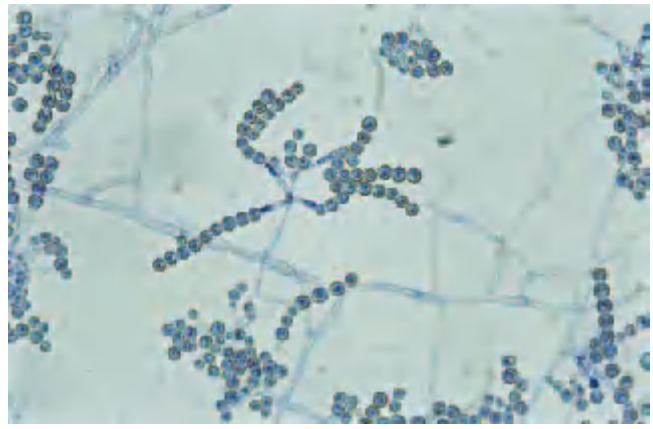


Fig. 31.37 Onychomycosis caused by *Scopulariopsis brevicaulis*. Nail mounted in KOH, bright field. The characteristic conidia are relatively thick-walled, oval or lemon-shaped with a truncate base. (Courtesy of the Department of Medical Mycology, King's College London, St John's Institute of Dermatology, London, UK.)

(a)



(b)

Fig. 31.38 *Scopulariopsis brevicaulis*. (a) Colony. On media free of cycloheximide, the colonies are initially waxy and deeply folded, but production of conidia rapidly produces a brown colour on the colony surface. (b) Microscopy, bright field. Chains of rough-walled conidia are formed from annellides. (Courtesy of the Department of Medical Mycology, King's College London, St John's Institute of Dermatology, London, UK.)

invasion its brown spores may discolour the nail, producing a cinnamon colour (Fig. 31.36), best seen end-on in the area of subungual hyperkeratosis. The great toenails are most often affected, but other toenails and, very occasionally, fingernails are involved. Dermatophyte infections of the skin and of the *Scopulariopsis*-infected nail plate itself may coexist.

Laboratory diagnosis. The distribution of the fungus in the infected nail material is often patchy, but where conidia are found they are quite distinctive, being approximately spherical or lemon-shaped with one flat basal facet. The thick cell walls and truncate bases of the conidia distinguish them from the arthroconidia of dermatophytes. The surfaces of the conidia appear smooth (Fig. 31.37). The mould is partially sensitive to cycloheximide and, in most instances, if cycloheximide-containing medium is used for isolation, the fungus will grow but remain compact, pale and intricately folded, producing few conidia.

Scopulariosis brevicaulis (Fig. 31.38a,b). Colony: on cycloheximide-free medium, the fungus grows rapidly to produce a powdery cinnamon brown surface, often with radial or cerebriform folds. The reverse is cream to brown. Microscopy: chains of basipetal conidia are formed from annellides. The conidia are rough, lemon-shaped or obovoidal with a truncate base.

Management. It is essential to search carefully for a coexisting dermatophyte infection, particularly if there are cutaneous changes. Treatment of pure *Scopulariopsis* infections is difficult. Occasionally, patients may respond to a topically applied lotion such as econazole. However, the most commonly used approach is to use 40% urea paste as a method of chemical nail avulsion and, following removal of the infected plate, an azole antifungal cream or lotion is applied daily to the nail bed until the new nail has completely formed. Itraconazole 400 mg/day for 1 week monthly for 3–4 months may be of help [7].

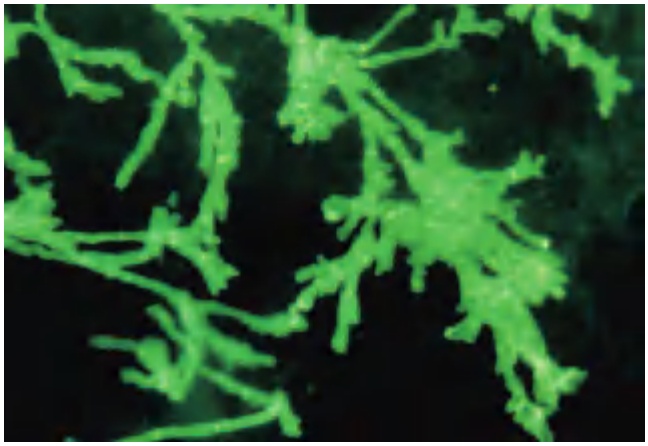


Fig. 31.39 Superficial white onychomycosis caused by non-dermatophyte moulds. Nail mounted in KOH and Calcofluor white, UV illumination. Bizarre, fronding hyphae may be observed (Courtesy of the Department of Medical Mycology, King's College London, St John's Institute of Dermatology, London, UK.)

Superficial white onychomycosis

Non-dermatophyte moulds that cause SWO produce a clinical picture identical to that seen in SWO caused by *Trichophyton mentagrophytes* var. *interdigitale*. However, one distinguishing feature is the lack of accompanying skin lesions.

Laboratory diagnosis. Direct examination of the nail material often reveals bizarre atypical hyphal forms (Fig. 31.39) and extensive fronding hyphae. However, some degree of fronding may be seen in dermatophyte infections. The most commonly isolated species, which include *Acremonium strictum*, *Aspergillus terreus* and *Fusarium* species [8], grow rapidly if cycloheximide is omitted from the culture medium.

Acremonium strictum. Colony: the rapidly growing colonies are slimy to waxy with a few central tufts of aerial mycelium and are pink, beige or orange in colour. Microscopy: elongate narrow phialides arise at right angles from the slender hyphae. The ellipsoidal conidia collect as a slimy ball at the apex of the phialide.

Aspergillus terreus. Colony: colonies are rapidly growing, powdery with a cinnamon brown surface and pale yellow reverse. Microscopy: the vesicle at the apex of the stout conidiophore bears metulae and phialides only on the upper two-thirds of its surface. Long chains of small smooth brown phialoconidia are produced, which form a columnar head.

Fusarium species. Colony: rapidly growing woolly colonies may have a pink, purple or pale brown surface and reverse. Microscopy: the genus *Fusarium* is characterized by the production from phialides of curved multicellular macroconidia, with a distinct foot cell at the base. Microconidia are also formed and are unicellular or bicellular, ovoid to ellipsoidal. They collect as slimy balls or chains at the apices of the phialides. Chlamydoconidia may also be present.

Management. Results of treatment are unpredictable, but a trial of therapy with amorolfine 5%, tioconazole 28% or removal of the nail with 40% urea is worth attempting.

Onychomycosis caused by Onychocola canadensis

This fungus was only recognized as a pathogen in 1990. Nails display yellow or grey discoloration and hyperkeratosis with a build-up of subungual debris. Direct microscopy reveals irregular hyaline, sometimes golden or brown hyphae, together with barrel-shaped or round arthroconidia. The fungus grows in the presence of cycloheximide as a very slowly developing, restricted, glabrous, pale-grey mould, which after 5–6 weeks eventually produces delicate chains of hyaline, waisted arthroconidia.

Management. A single patient treated with griseofulvin showed some clinical improvement after 6 months, but the direct microscopy remained positive.

Miscellaneous mould infections

In contrast to the fungi described above, an enormous variety of other moulds have been implicated in one or only very few cases of onychomycosis. These include *Pseudeurotium ovalis*, *Pyrenochaeta unguius hominis*, *Lasiodiploidea theobromae*, *Curvularia lunata* and many others [9]. Investigations of abnormal toenails, especially in elderly people, have shown that an appreciable minority are colonized by non-dermatophyte fungi, usually moulds, often *Aspergillus* species. Fingernails are much less often invaded. These moulds are generally accepted as existing purely saprophytically. Although they may conceivably add to the primary damage caused by ischaemia, trauma or a dermatosis, they are, in general, of little practical importance to the patient. For the dermatologist, their significance lies in the fact that they must be distinguished from dermatophytes. Moreover, a dystrophic nail caused by ischaemia, secondarily colonized by *Aspergillus* species, is likely to regrow abnormally even if the fungus is eliminated by avulsion. Unlike *Scopulariopsis* infections, secondary mould invasion often affects several nails and indeed all may be invaded.

In addition to causing SWO, *Fusarium* species may also cause proximal subungual onychomycosis and rarely can be isolated from interdigital tinea pedis.

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Candidosis

SYN. CANDIDIASIS; MONILIASIS; THRUSH

Definition. Candidosis is an infection caused by the yeast *Candida albicans*, or occasionally by other species of *Candida*. Superficial infections of the mucous membranes and skin are numerically most important, but more serious involvement of internal organs as in septicaemia, endocarditis and meningitis can also occur and these are considered in the section on systemic mycoses.

Aetiology [1]. *C. albicans* is an oval yeast 2–6 × 3–9 μm in size, which can produce budding cells, pseudohyphae and true hyphae. This ability to simultaneously display several morphological forms is known as polymorphism. Although hyphae are likely to be produced during the process of tissue invasion, yeasts without hyphae may also occur in invasive disease, particularly in infections caused by non-*albicans Candida* species. Apart from *C. albicans*, the genus *Candida* includes over 100 species, most of which are neither commensals nor parasites on humans. A few other species of *Candida*, for example *C. tropicalis*, *C. dubliniensis*, *C. parapsilosis*, *C. guilliermondii*, *C. krusei*, *C. pseudotropicalis*, *C. lusitaniae*, *C. zeylanoides* and *C. glabrata* (formerly *Torulopsis glabrata*) are occasional causes of human candidosis, particularly in AIDS patients and in patients in intensive care units.

Candida ecology and the commensal or parasite role [2]

Gastrointestinal tract carriage

Many species of animals and birds carry yeasts, often species of *Candida*, in their gut as part of the normal commensal flora and the human is no exception. *C. albicans* is a frequent, but not invariable inhabitant of the gastrointestinal tract. Colonization with *C. albicans*, or another species, may occur during birth directly from the birth canal, at some time during infancy or perhaps later in life. We lack good information on carriage rates at different ages. Very early colonization of the mouth seems more likely to be followed by frank pathological changes, but if the organism is acquired later it is usually established asymptomatically.

The literature on oral carriage rates is extensive and confusing, but in his review Odds [1] concludes that fewer than 26% of normal subjects carry yeasts in the mouth, and that the figure for *C. albicans* carriage is about 18%. Surveys of the oral flora of hospital patients tend always to give higher figures. Isolation rates of yeasts from faecal specimens and rectal swabs are also higher than those from oral samples. Odds suggests figures of nearly 47% for yeast carriage, and just under 41% for *C. albicans* on the basis of published studies.

If specialized techniques or repeated sampling are used, the proportion of healthy adults carrying *Candida* in the gastrointestinal tract may be demonstrably higher, even rising to two-thirds. Moreover, if antibacterial antibiotics effective against the resident gastrointestinal bacterial flora are given by mouth, the percentage of *Candida* carriers rises—as demonstrated by a single oral or rectal swab [3]. However, even then there remain some from whom *Candida* cannot be isolated. Clearly, the density of the gastrointestinal yeast flora varies from individual to individual, and influences the chances of isolation. Presumably, there is a spectrum from those with high levels through moderate carriers to those whose gut has no yeasts, or at least very low levels.

Studies of *Candida* serology and skin testing suggest that a substantial proportion of those not colonized by yeasts may have been exposed to *Candida* in the past. The practical implication of this is that normal individuals show a wide range in the density of carriage of *Candida* species as assessed, for instance, by mouth swabs. Extraneous factors such as oral antibiotic therapy are likely to increase not only the incidence of carriage, but also the number of organisms present and the chances of invasion of tissue.

Because the mouth and rectum are easily accessible for swabbing, gastrointestinal tract carriage of *Candida* is generally considered in these terms, but there is considerable evidence that the yeast colonizes other parts of the gastrointestinal tract.

Vaginal carriage [4]

The healthy vagina may be colonized by yeasts—most commonly *C. albicans*, sometimes *C. glabrata*—but only in a minority of women [5]. The percentage of vaginal carriers differs widely in different surveys, but a figure of 12.7% for *C. albicans* is probably accurate. Higher rates are found in hospital patients, even without vaginal disease [1].

Pregnancy and oral contraception have both been associated with elevated carrier rates, but so is the use of intrauterine devices [6].

Cutaneous carriage

Generally, neither *C. albicans* nor any other species of *Candida* is a permanent member of the normal flora of the skin. At the same time, it is clear from numerous surveys that skin adjacent to the body orifices and the skin of the fingers, which are in frequent contact with the mouth, often yield *C. albicans* and sometimes other species, particularly *C. parapsilosis* and *C. guilliermondii* [7]. In moist intertriginous sites, *Candida* may be a persistent colonizer in a few individuals [8]. Age and climate are important in this connection. Samples from the very young and the very old are more likely to yield *Candida*.

Carriage in other sites

The bronchial tree is not normally colonized by *Candida*, and where the organism is isolated from sputum specimens, at least in low amounts, it can be assumed that it has come from the mouth or oropharynx. It is apparent that swallowing a massive quantity of *Candida* cells will result in the transfer of these yeasts rapidly through the gut wall into the circulation, presumably via the portal vein and the liver [9]. Whether such passage of *Candida* cells occurs in normal situations is not known, but it may be an important portal of entry in the neutropenic patient.

C. albicans can occasionally be cultured from the environment, usually in situations where there are heavily infected subjects [1], human or animal; for example, it has been isolated from a nursery where there was an epidemic of oral thrush, from hospital bed linen, and from the air of dermatology clinics. Normally, however, *Candida* is not part of the air-borne microflora. Except for neonatal and conjugal infections, most cases of candidosis probably result from infection of the host by his or her own commensal yeasts. Further experience with typing [10] have tended to confirm the view that most infections are endogenous, and generally infection seems to follow a shift in the existing host–yeast relationship. This shift from commensal to parasite results from a variety of influences. To date, an increase in yeast virulence has not been shown to be important. Theoretically, different isolates of *C. albicans* might be expected to differ to a minor degree at least in their capacity to cause damage in the human host [11]. In practice, such variations are hard to demonstrate.

Genetic methods of typing *Candida* strains have provided a means of investigating the spread of organisms within individual patients, groups or hospital wards [12]. They have indicated that spread of predominant strains can occur either between individuals or in hospitals. In one well-documented outbreak, an isolate that resisted normal hand-washing procedures was the cause of a number of infections in an intensive care unit [13]. This indicates that strains carried by patients may be replaced by others with different biological characteristics. These techniques can now be used to determine important issues, such as the acquisition of drug resistance [14]. *C. albicans* may also demonstrate an unusual phenomenon known as phenotypic switching, whereby a strain may change morphology or another phenotypic character such as drug sensitivity in response to a change in growth conditions; such changes are reversible and not associated with genetic variation [15].

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Pathogenesis

Fungal virulence

In animal experiments, some *Candida* species have been shown to be less virulent than *C. albicans*, a finding that conforms well with clinical experience. Generally, the most common pathogen in skin disease is *C. albicans*, although increasingly other species are isolated in vaginal infections and from AIDS patients.

Enzymes and toxins

Factors such as the production of an acid proteinase by certain strains of *C. albicans* are also known to affect pathogenicity. Proteinase-negative strains are known to be less virulent [1]; laboratory-generated gene defective strains have not been shown to be less virulent.

Yeast–mycelial shift [2]

In oral and cutaneous candidosis, scrapings examined microscopically usually show *Candida* in both budding and mycelial forms. In histopathology of invasive candidosis, hyphae are usually present. This suggests that the production of hyphae may contribute to fungal virulence.

Adherence

The ability of yeast forms to adhere to the underlying epithelium is also an important prerequisite for tissue invasion [3–5]. Adherence of *Candida* to epithelial surfaces is mediated through a number of receptor interactions. *Candida* adhesins are either based on cell-wall mannan or protein components. Among the latter is a *Candida* surface C3d-binding protein [6]. It has also been shown that proteinase production is necessary for adherence.

Other factors

In vivo, a wide variety of factors have at various times been claimed to be important in stimulating mycelium formation [7]. Temperatures above 35°C, low oxygen tension, liquid media, non-sulphur-containing amino acids, a polysaccharide carbon source, serum and a pH of 7.5 are the most convincing factors in experimental studies [8]. However, it is difficult to relate these experimental results to the *in vivo* situation.

The effects of ecological pressures from other organisms are of considerable importance [9]. Both in the gastrointestinal tract and on the skin, removal of competing bacteria leads to an increase in yeast numbers, an important prerequisite to invasion. Work on the competition between *Candida* and bacteria in saliva suggests that a crucial factor is the amount of available glucose [9,10], and that if this is elevated and plentiful, as in diabetes, the bacterial flora will not inhibit the yeast [11]. Mechanisms other than nutrient depletion may possibly apply. In other situations (e.g. the finger web), bacteria, especially Gram-negatives, may act as co-pathogens rather than competitors, their presence enhancing the pathogenicity of the yeast. Once again the presence of bacteria may impair the ability of *Candida* to adhere to the underlying substrate [12].

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Host factors

Host factors involved in mucocutaneous candidosis are numerous. It has long been recognized that the very old, the very young and the very ill are susceptible to oral thrush. However, a variety of other factors are also involved, and many patients have more than one predisposing factor. In the mouth, carbohydrate levels are important; food debris, likely to be present in the mouth of the severely ill patient with inadequate oral hygiene, should not be ignored and may be as significant as diabetic saliva. In Sjögren's syndrome, *Candida* carriage and probable susceptibility to candidosis are high, a fact attributed to low saliva flow rates. Whether this correlates with changes in pH as has been suggested, or with IgA levels, or whether it simply leads to poor oral hygiene as the mouth is inadequately washed by saliva, is not known. High glucose levels in urine, general tissue fluids and sweat may make diabetics more susceptible to candidosis [1]. Phagocytosis is also impaired in diabetics. In practice, this feature is largely confined to *Candida* vulvovaginitis and balanitis.

Any form of local tissue damage may be important in the pathogenesis of candidosis [2]. Experimental removal of the stratum corneum facilitates the establishment of cutaneous candidosis, and with a given inoculum increases the severity of the response [3]. In the mouth, the wearing of dentures undoubtedly increases susceptibility, but whether this is primarily because of trauma, food debris

or the restriction in saliva flow is not clear. On the skin, maceration is of fundamental importance, and in experimental candidosis high moisture levels, usually provided by occlusion, are a prerequisite. Although several surveys have shown higher levels of *Candida* carriage on psoriatic and eczematous skin, and one other study [4] has claimed that *Candida* paronychia is more common in psoriatics, in general candidosis is not a common complication of either psoriasis or eczema. Indeed, Rebora *et al*. [3] found difficulty in colonizing such diseased skin with *Candida* without prior removal of the bacteria.

Furthermore, in experimentally infected guinea pigs there is increased epidermal cell turnover, which develops after *Candida* infection, possibly through a cellular immune mechanism. In this case, increased shedding of stratum corneum correlates well with recovery from infection [5].

Higgs and Wells [6] showed that some cases of chronic mucocutaneous candidosis had iron deficiency. With iron replacement therapy, their resistance to *Candida* infection increased. On the other hand, *in vitro* experiments indicate that unsaturated transferrin acts as an inhibitor to *C. albicans*. Iron reverses this effect.

Serum factors

Apart from transferrin, other serum factors affecting *C. albicans*, such as clumping factor, have been described [7]. Short of actual clumping, even the well-known effect of serum in encouraging *C. albicans* to produce germ tubes and mycelium may be disadvantageous. Davies and Denning [8] have shown that hyphae longer than 200 μm are poorly phagocytosed, and not readily killed by leukocytes. The presence of heavy persistent *Candida* infection has on some occasions led to the appearance of factors present in serum that, far from being advantageous, resulted in the inhibition of T-cell function; an effect demonstrable with other leukocytes *in vitro*, and that was reversed by anticandidal therapy [9]. It is likely that this is a circulating antigenic product of *Candida* such as mannan, which is known to affect immune responsiveness, blocking antibody or an immune complex.

Endocrine factors [10]

Apart from diabetes, a variety of endocrinopathies have been mentioned as susceptibility factors in candidosis. There is little doubt that Cushing's syndrome, whether spontaneous or iatrogenic, increases susceptibility to a wide range of infections including candidosis. The mechanism seems to be a direct suppression of immune mechanisms, especially T-cell function. In addition to these two conditions, familial endocrinopathy presenting with Addison's disease, hypoparathyroidism and hypothyroidism have all been found to occur in association with some cases of chronic mucocutaneous candidosis. Mutations on the *AIRE* (autoimmune regulator) gene have been identified in some patients [11]. Treatment of the endocrine abnormality does not improve the *Candida* infection and other factors are probably involved.

Immunological factors

Intensive investigation of patients with the syndrome of chronic mucocutaneous candidosis, and studies of a wide range of patients with primary immune defects, indicate clearly that in the defence against *Candida* infection, both superficial and deep-seated, cell-mediated immunity is of paramount importance, coupled with normal phagocytosis and killing by polymorphs and macrophages [12,13]. Circulating humoral antibodies or secretory IgA may have some role [14]. Absence of specific anti-*Candida* IgA salivary antibody in cases of chronic mucocutaneous candidosis was subsequently shown to be associated with depressed T-cell function, a factor now thought to be more important. However, in children wearing orthodontic appliances, the risk of candidosis is higher in those with low salivary IgA levels.

While systemic corticosteroids act to increase the susceptibility to candidosis by diminishing immune functions, the practical importance of topical steroids in this connection is not so well understood. However, there is evidence that an inflammatory response to *Candida*, which can be produced experimentally in humans [15] but not in the rat [2], by dead disintegrated *Candida* cells, as well as by living organisms, can be suppressed by topical steroids. The description of large granulomatous lesions in the napkin area of infants with candidosis treated with steroids suggests that it may also enhance the real susceptibility to the organisms, as might be expected if fewer lymphocytes and phagocytic cells are present.

The susceptibility of elderly and severely ill people, especially those with leukaemia, lymphomas and carcinomatosis, probably lies, in large measure, in the depression of cell-mediated immunity. In AIDS this is clearly the case.

Patients with defective T-lymphocyte function, such as those with AIDS, appear to be particularly susceptible to mucosal or cutaneous candidosis, but not systemic infections [16]. Congenitally T-cell-deficient mice (*nu/nu*) do not show reproducible increased susceptibility to systemic infection by *Candida*. In fact, some investigators have found heightened resistance, suggesting that T-lymphocyte activity alone does not account for resistance to systemic invasion [17]. By contrast, in patients with chronic mucocutaneous candidosis, the most consistent abnormalities have been those of T-lymphocyte function, particularly cytokine expression [9], even though some of

these are now thought to be secondary to immunoregulation induced by the infection.

Patients with defective neutrophil or macrophage function are susceptible to both superficial and systemic candidosis. The activity of neutrophils and macrophages in phagocytosis and killing of *Candida in vitro* has been demonstrated [18,19]. In addition, some cytokines such as interferon-γ appear to interact with these cells to enhance killing of the organism. It appears that there is therefore substantial interplay between different immune mechanisms in defence against candidosis.

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Candidosis and AIDS

In the untreated HIV-positive population, oral *Candida* carriage rates are generally high, and this has been confirmed by the finding that carriage rates are, for instance, higher in HIV-positive homosexual males than in a control group of HIV-negative homosexual men [1]. Another study of HIV-positive patients without clinical evidence of oral candidosis showed that 24% of 261 individuals were carrying *C. albicans* on the tongue or buccal mucosa. Colonization rates were higher in intravenous drug abusers, Center for Disease Control (CDC) group IV and in those with lymphopenia. In addition, patients with CD4 cell depletion and those with elevated β_2-microglobulin levels were more likely to be carriers [2].

The relationship between CD4 counts, as a guide to disease progression, and oral candidosis in AIDS patients has been studied by a number of authors. Oral thrush does appear to reflect viral load [3]. Both hairy leukoplakia and oral candidosis are markers for increased rate of progression to AIDS [4]. The presence of oral candidosis may also be a marker of survival in some patients. For instance, HIV-positive patients with oral candidosis but who have no other features of AIDS have a poorer survival rate than those without [5]. However, it is important to remember that immunologically related factors such as CD4 counts are not the only determinants of oral candidosis. Another factor implicated as a possible predisposing cause of oral *Candida* infection in AIDS patients is the salivary flow rate.

The evidence that persistent vaginal candidosis is associated with AIDS is less convincing.

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Histology [1,2]

The range of clinical manifestations caused by *C. albicans* and other *Candida* species is paralleled by the variety of pathological changes seen in inflamed tissues. However, there are certain generalizations that can usefully be made about histology of candidosis of epithelial surfaces. Fungal elements are almost always restricted to the outer layers of epithelium, including the stratum corneum. On the skin, particularly in acute infections, mycelium may be very sparse, and indeed yeast forms may be present in only small numbers. There seems also to be less likelihood of finding mycelium in infectious species other than *C. albicans*.

Apart from the presence of the fungus, acute oral candidosis is characterized by inflammatory changes with the formation of a pseudomembrane of epithelial and inflammatory cells [1]. In the oral epithelium and in the cutaneous epidermis, the inflammatory infiltrate consists predominantly of polymorphs, which may form microabscesses or subcorneal pustules. Splitting of the epidermis often follows. In the dermis, the inflammatory infiltrate is a mixture of lymphocytes, plasma cells (especially in the mouth) and histiocytes. In chronic cases, hyperplasia with parakeratosis and acanthosis of the epithelium is associated with a mixed chronic inflammatory infiltrate. In chronic cutaneous lesions, hyperkeratosis with acanthosis may be seen, and in *Candida* granuloma of the skin, a dense mixed cell infiltrate may include giant cells [3]. Although the matter is still somewhat controversial, it seems probable that in chronic oral cases, neoplastic change secondary to candidosis may develop as a late feature [4].

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Clinical syndromes of candidosis

Oral candidosis [1]

Acute pseudomembranous candidosis (oral thrush; acute pseudomembranous candidiasis) [2,3]. The characteristic sign of this condition is a sharply defined patch of creamy, crumbly, curd-like white pseudomembrane, which, when removed, leaves an underlying erythematous base. This membrane consists of desquamated epithelial cells, fibrin, leukocytes and fungal mycelium that attaches it to the inflamed epithelium. There may be one or many patches. The buccal epithelium on the cheeks, the gums or the palate may be affected. In immunocompromised patients, the tongue may be affected as well. In severe cases, extension to the pharynx or the oesophagus may occur, and erosion and ulceration are occasional complications.

The condition occurs most commonly in the first weeks of life, and the preterm infant may be especially susceptible. Apart from in neonatal oral candidosis (as distinct from *Candida* carriage), acute pseudomembranous candidosis is usually secondary to local or general predisposing factors. For instance, it may present in the neutropenic patient or those with AIDS [4–6]. In both cases, the clinical changes are often erosive with severe symptoms resulting in inadequate food intake because of pain. Extension of lesions to the buccal mucosa, tongue and oesophagus is common in these groups. Coincident oral infection with herpes simplex virus may occur in both groups [7]. Oral candidosis is the most common secondary infection in those with AIDS, and recurrent or more prolonged episodes are to be expected in these patients [8].

Acute erythematous candidosis (acute atrophic oral candidiasis) [9]. In this condition, there is marked soreness and denuded atrophic erythematous mucous membranes, particularly on the dorsum of the tongue. It may follow pseudomembranous candidosis, when traces of the residual membrane will often be found. It is especially associated with antibacterial antibiotic therapy, but may also develop in HIV-positive subjects. In these cases, the tongue is often markedly affected.

Chronic pseudomembranous candidosis. This does not differ clinically from the acute pseudomembranous variety but, as the name suggests, lesions are very persistent. It occurs principally in immunocompromised patients.

Chronic erythematous candidosis (chronic atrophic candidiasis; denture sore mouth; denture stomatitis) [10]. Some soreness in the epithelium in the denture-bearing area is said to affect nearly one-quarter of all denture wearers and most, if not all cases appear to be caused by candidosis. A similar problem may also occur in children wearing orthodontic appliances.

Elimination of *Candida* alone does not usually result in complete recovery, and it is likely that other factors such as chronic mechanical irritation and bacterial colonization have a role in the pathogenesis of this condition.

The condition is normally confined to the upper denture-bearing area, the palate and gums. The affected mucous membranes show a variable bright red or dusky erythema, fairly sharply defined at the margin of the denture. The epithelium is often shiny and atrophic, and there may be marked oedema, in some areas at least. In late cases, secondary papillomatosis may occur. There is often an associated angular cheilitis, and that is the feature that frequently brings the patient to seek dental or medical advice, for the symptoms from the palatal area are often minimal. The excess of female patients over males remains unexplained. The vast majority of patients of either sex are otherwise fit. Underlying defects of immunity are not to be expected in this syndrome. However, AIDS patients with erythematous candidosis may enter a chronic phase.

Chronic plaque-like candidosis (chronic hyperplastic candidiasis; Candida leukoplakia) [11]. Very persistent, firm, irregular white plaques occur in the mouth, commonly on the cheek or the tongue. Most patients are male and generally over the age of 30 years but the onset of the disorder is difficult to date, as symptoms are mild, only slight soreness and roughness being noticed. Around the hyperplastic

area, there may be a margin of erythema. Unlike the pseudomembrane of oral thrush, this plaque cannot be easily removed. In most cases, serious predisposing factors are not present, although this appearance, particularly an extensive form, may occur in patients with chronic mucocutaneous candidosis. Smokers appear to be particularly prone to develop this form of oral candidosis [12].

The significance of this condition lies in the fact that it must be differentiated from other types of leukoplakia as, although the affected areas may undergo malignant change [13,14], it may eventually clear with prolonged anti-*Candida* therapy.

Chronic nodular candidosis. This is a rare form, where the clinical appearance that usually affects the tongue is of a cobbled appearance. It is most often seen in certain patients with chronic mucocutaneous candidosis.

Angular cheilitis (angular stomatitis; perleche) [15]. Soreness at the angles of the mouth extending outwards in the folds of the facial skin is a well-known syndrome, not always associated with *Candida* infection. It is perhaps best considered as an intertrigo in which different organisms may play a part, *Candida* being the most common. Nutritional status and mechanical factors (e.g. the depth of the fold), the presence of moisture from persistent salivation or licking the lips may also be important. The yeasts involved clearly come from the mouth, and the association with denture stomatitis is important. Although the condition may present acutely, it is common to find a long history of soreness and cracking at the angles of the mouth and a fluctuating course is typical. Obviously, the oral cavity should be examined carefully in such cases and swabs taken from that site to establish the presence of *Candida* carriage, as well as from the affected skin at the angles.

Median rhomboid glossitis [16]. This condition, characterized by a more-or-less diamond-shaped area on the dorsum of the tongue with loss of papillae, occurs as an acquired condition. It has been regarded in the past as a developmental abnormality, but current opinion suggests that it is simply a variant of chronic plaque-like candidosis.

Candidosis, steroids and the mouth. Apart from systemic steroid therapy, local applications of steroids in the form of steroid creams, mouthwashes and lozenges for the treatment of aphthosis or lichen planus of the mouth may predispose to candidosis, sometimes occurring as a secondary invasion of the primary pathology. Similarly, steroid aerosols for asthma must be considered as at least a potential cause of diminished local immunity in this area.

Other conditions associated with Candida in the mouth. *Candida* can secondarily invade other oral conditions such as ulcerative lichen planus [17], leukokeratosis and white-sponge naevus. On the lips, invasion of traumatic cheilitis may complicate management. In all cases, the removal of *Candida* often speeds the recovery even though the yeast is only a contributory cause.

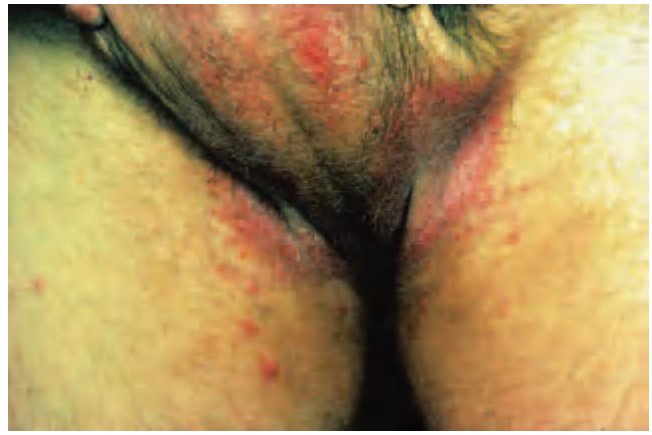

Fig. 31.40 *Candida* infection of the groins.

Candidosis of the skin and genital mucous membranes

Most cases of cutaneous candidosis occur in the skin folds or where occlusion from clothing or medical dressings produces abnormally moist conditions. Areas close to the body orifices [18] and the fingers, which are frequently contaminated with saliva, are also at risk.

Candida intertrigo (flexural candidosis). Any skin fold may be affected, especially in the obese subject. Signs are typically erythema and a little moist exudation starting deep in the fold (Fig. 31.40). As the condition develops, it spreads beyond the area of contact, usually developing the typical features of candidosis with a fringed irregular edge and subcorneal pustules rupturing to give tiny erosions, and then further peeling of the stratum corneum. Satellite lesions, pustular or papular, are classical. Soreness, and itching, which may on occasions be intense, is usual. Topical steroids, prescribed for relief of the latter symptoms, may modify the inflammatory signs and cause diagnostic confusion. Where the web spaces of the toes or the fingers are affected, marked maceration with a thick white horny layer is usually prominent. In the case of the hands, some abnormality, including wide fat fingers, appears to predispose to infection. In this particular syndrome, often known as erosio interdigitalis blastomycetica or interdigital candidosis, *Candida* and Gram-negative bacteria are often co-pathogens [19]. Apart from skin folds, macerated skin under rings and dressings may become infected with *Candida*.

The differential diagnosis of intertriginous candidosis includes tinea, seborrhoeic dermatitis, bacterial intertrigo,

flexural psoriasis, Hailey–Hailey disease and flexural Darier's disease. It is important to establish that the *Candida* species are present by taking a scraping or swab. Although it is useful to find mycelium, its absence does not exclude the diagnosis, and the culture of *Candida* from an inflamed lesion of a skin fold usually justifies instigation of anti-*Candida* treatment. Bacterial co-pathogens should be considered.

Vulvovaginitis (vulvovaginal thrush) [18,20]. This common condition presents with itching and soreness, and with a thick creamy white discharge. Most women with vaginal candidosis have no evidence of underlying disease.

It is more common in pregnancy. In the non-pregnant, it is said to be more prevalent in the premenstruum, but a fluctuating course not clearly related to the menstrual cycle is frequent. Although largely confined to sexually active subjects, it has been described in childhood, sexually inexperienced and elderly people. Typically, there is dusky red erythema of the vaginal mucosa and the vulval skin, with curdy white flecks of discharge, but on occasions the only sign is erythema. The rash may extend onto the perineum and into the groins. The perianal area is often affected. In extensive cases, subcorneal pustules may be seen peripherally. In pregnancy, the picture is modified by marked physiological leukorrhoea.

Candida vulvovaginitis may recur and in some it appears to be a chronic condition [21]. In chronic cases, the vaginal mucosa may become glazed and atrophic. There may be considerable vaginal soreness or irritation as well as dyspareunia. Management of the recurrent or chronic case is difficult; the condition causes considerable distress. It is important in such patients to evaluate the presence of *Candida* during repeated episodes where there are symptoms, to establish that recurrence of signs of disease is associated with recurrence of *Candida*. Although vaginal candidosis has been reported to occur with an increased frequency in women with AIDS, and in some cases the infection is resistant to therapy, this is not always the case; many patients present with an acute and treatable episode. In this it seems to differ from the situation seen with oral candidosis.

Candida balanitis [22]. The skin of the glans penis, especially in the uncircumcised, may sometimes be colonized by *Candida* asymptomatically [23]. When *Candida* balanitis develops, it is usual to find either abundant vaginal *Candida* carriage or frank vulvovaginitis in the sexual partner, although this is variable. In the mildest cases, transient tiny papules or pustules develop on the glans penis a few hours after intercourse, and rupture, leaving a peeling edge. Some may settle spontaneously without going through the full evolution. This mild form is usually associated with a little soreness and irritation. In some men, the condition continues in this intermittent form. In more severe and chronic cases, the inflammatory changes become persistent over the glans and the prepuce. Involvement of the groins sometimes coexists, especially in hot weather.

Trichomonas infection, although it usually produces watery brown discharge, and bacterial vulvovaginitis should both be considered in the differential diagnosis, and in pregnancy physiological leukorrhoea. Dermatoses affecting the vulva may mimic this condition (e.g. psoriasis, contact dermatitis, lichen sclerosus). In the case of balanitis, bacteria and herpes simplex require consideration, but few of the common venereal diseases are episodic like candidosis. Psoriasis and lichen planus, although sometimes fluctuating, should not be a cause of confusion, except with the chronic established lesion, in which case plasma-cell balanitis and erythroplasia must be excluded as must lichen sclerosus. The diagnosis in both sexes is confirmed by finding the organism, preferably in large numbers. However, even scanty amounts of *Candida* isolated from cases with typical clinical features demand active and sometimes prolonged therapy. In the male, it must be stated that failure to find the organism does not exclude the diagnosis if swabs or scrapings were not taken during the acute phase. It is wise to consider diabetes in cases of genital yeast infections, but florid persistent lesions spreading beyond the genitalia seem most likely to be associated with that condition. Although the large majority of patients with genital candidosis will not have diabetes, it is appropriate to test for glycosuria in persistent or recurrent cases.

Perianal and scrotal candidosis. Perianal and scrotal candidosis may occur with or independently of genital involvement. Although usually starting around the anal margin with non-specific erythema, soreness and irritation, subsequent spread along the natal cleft is common, with classical features developing as it extends. Involvement of the scrotum is usually in the form of a nondescript erythema and subcorneal pustules are rarely seen. Candidosis must be included in the differential diagnosis of unexplained erythema of scrotal skin. Secondary infection of flexural psoriasis with *Candida* may have to be considered.

It has been suggested that a more objective assessment can be provided by taking quantitative cultures to determine the density of *Candida* more accurately [24]. For practical purposes this is not necessary, and dense growth of organisms on swab culture or the presence of diagnostic clinical features such as satellite pustules are usually taken as indications for treatment.

Napkin candidosis (diaper candidiasis). C. albicans is commonly isolated from the moist skin of the buttocks and genitalia of the infant but is more prevalent where the skin is affected by napkin rash [24]. In some instances, the classical subcorneal pustules, a fringed irregular border

and satellite lesions are found. In these cases, there is little doubt that the organism is playing a pathogenic part, and it is likely to be found in the faeces [10,24]. In other nondescript cases of napkin eruption from which the organism is isolated, the role of the yeast is in doubt. Steroid creams applied to this site not only modify the clinical features but they are probably advantageous to *Candida*. Moreover, if the bacterial flora has been suppressed by a topical antibiotic, this will also favour the yeast. All these factors should be considered in any napkin rash.

In acrodermatitis enteropathica in which zinc deficiency has a central role, there may be a secondary *Candida* infection, particularly of the napkin area.

In all but the most trivial cases of napkin eruption, a moistened swab or a scraping should be taken to discover whether or not *Candida* is present on the affected skin. Some estimate of the density of colonization is also helpful. If *Candida* is present, particularly in large numbers, even if the features are non-specific, a trial of anti-*Candida* therapy is generally indicated.

Nodular or granulomatous candidosis of the napkin area (granuloma gluteale infantum) [25,26]. The clinical picture is that of a napkin eruption over the buttocks, genitalia, upper thighs and pubis, within which develop nodules, sometimes as large as 2 cm across, bluish or brownish in colour, reminiscent of Kaposi's sarcoma [25]. The primary napkin dermatitis may clear leaving only the nodules. Some examples have marked scaling and hyperkeratosis over the lesions, in others the epidermis appears to be normal. Histological changes are those of an intense dermal infiltrate with lymphocytes, eosinophils and histiocytes.

The natural history of this condition has not been elucidated. Successful management involves removal of microorganisms, avoidance of topical steroids and general measures to ensure adequate dryness in the region.

Candida paronychia

Candida species, not always *C. albicans*, can be isolated from the majority of cases of chronic paronychia [27,28]. The yeast is thought to have an aetiological role in this condition, but bacteria and irritant or allergic contact dermatitis also play a part, although the contribution of each varies from patient to patient.

This condition is chiefly found among those whose hands are frequently immersed in water, but in chefs and pastrycooks the presence of organic debris such as flour and other carbohydrates may be equally important. The condition is less common in the UK than formerly. Toenail folds are not usually affected. Some experimental confirmation of the role of *Candida* has been achieved by occluding the nail fold in the presence of the yeast, but fully developed chronic paronychia has not been produced experimentally.

Clinical features. Typically, several fingers are chronically infected, but one or all may be involved. The nail fold is red and swollen, and there is loss of the cuticle, and detachment of the nail fold from the dorsal surface of the nail plate, leading to pocketing. Occasionally, thick white pus may discharge; often force is needed to express it. The patient usually has marked tenderness, and spontaneous pain is an occasional feature. Nail dystrophy with buckling of the nail plate and some discoloration and onycholysis around the lateral nail fold frequently occur, but massive destruction of the nail plate is rare. Many patients, particularly those who are resistant to treatment, appear to have a poor peripheral circulation. A link with psoriasis has been reported [29].

Onychomycosis resulting from Candida

There are three main manifestations of *Candida* infection of the nail apparatus [30]. The most common is onycholysis (DLSO) associated with paronychia. Complete destruction of the nail plate is also seen in some patients with chronic mucocutaneous candidosis. In addition to these conditions, erosion (DLSO) of the distal and lateral nail plate of the fingernails, not usually progressing to total nail dystrophy, has been associated with *C. albicans* invasion of the nail [31]. This is not common, but when it occurs it is most often seen in women. Two important predisposing conditions are Raynaud's phenomenon or disease and Cushing's syndrome. The main clues that the yeast is a significant pathogen are erosion of the distal nail plate, presence of yeasts and hyphae in nail on direct microscopy and the isolation of *C. albicans*. Such cases respond well and completely to oral antifungals such as itraconazole. Very rarely, *Candida* may invade the nail plate in the neonatal period, sometimes causing an isolated nail dystrophy with evidence of penetration of the superior aspect of the nail plate (SWO). In addition to these conditions, *Candida* is not infrequently isolated from the undersurface of the nail plate in patients with onycholysis resulting from other causes. Antifungal therapy in these circumstances does not produce any improvement.

Differential diagnosis. It is usual in chronic paronychia to establish which organisms are present, and a platinum loop introduced into the nail fold may be more valuable than a swab for this. It must be plated out promptly. When nail plate involvement is suspected, clippings should be taken.

Congenital candidosis [32]

This, as the name implies, represents established candidosis, usually of the skin and birth membranes present at the time of birth, and following intrauterine infection. It is

quite distinct from oral thrush of the neonate in which the organism is acquired, at the very earliest, from the birth canal during delivery.

Factors associated with this condition have included prematurity, although this has not been noted in some cases, and the presence of an intrauterine foreign body, usually a contraceptive device. The amniotic fluid is often turbid at delivery [32,33]. The skin is the most common site for lesions, which are usually present at birth. The lesions are typically discrete vesicles or pustules on an erythematous base. The face and chest are first affected by the rash, which generally spreads over the next few days after delivery. In over 10% there is evidence of spread to deep sites such as the lungs. Although there has been a high level of mortality reported with such cases, the cause of death is usually related to other complications of prematurity rather than candidosis *per se*.

Such widespread skin infections are believed to follow contamination of the skin surface during birth, and the high incidence of intrauterine infection or vaginal candidosis associated with this disease would support this contention. Such cases are distinct from the more common neonatal systemic candidosis, a septicaemic illness associated with extreme prematurity, where skin involvement is not common.

Candida allergy [23]

There is no doubt that in normal subjects skin testing with *Candida* antigens and serological studies reveal evidence of antibodies, humoral and cellular, to *C. albicans* and to other *Candida* species. A variety of clinical features attributed to *Candida* allergy have been described and include urticaria, ordinary annular erythema, bullous annular erythema and generalized pruritus. Even palmoplantar pustulosis has been linked to delayed hypersensitivity to *Candida* antigen. In the case of urticaria, some association, not necessarily mediated by immune mechanisms, may exist between yeast carriage in the gut (or frank candidosis) and the wealing of the skin. Unfortunately, the fluctuating nature of urticaria, and the fact that *Candida* is difficult if not impossible to eliminate from the gut, make the response to anti-*Candida* therapy difficult to evaluate. The candidide situation in general is even more perplexing than that of dermatophytide, in that the cutaneous reactions have often been ascribed to normal gut carriage. The so-called ide eruptions are not specific morphologically, and even the enthusiast for *Candida* allergy claims only a small percentage of cases of annular erythema, for example, is causally associated with *Candida*. Observant open-mindedness with a hint of scepticism would seem to be the right approach in this difficult area.

The term *Candida* allergy or *Candida* syndrome is also used to describe a constellation of symptoms ranging from headache to malaise and depression, allegedly secondary to colonization of the gastrointestinal tract with yeasts. However, there is no objective evidence to connect these symptoms with the presence or absence of *Candida*.

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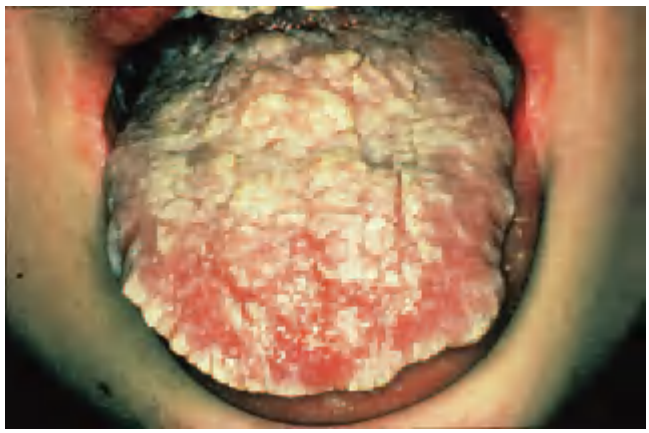

Fig. 31.41 Chronic oral candidosis.

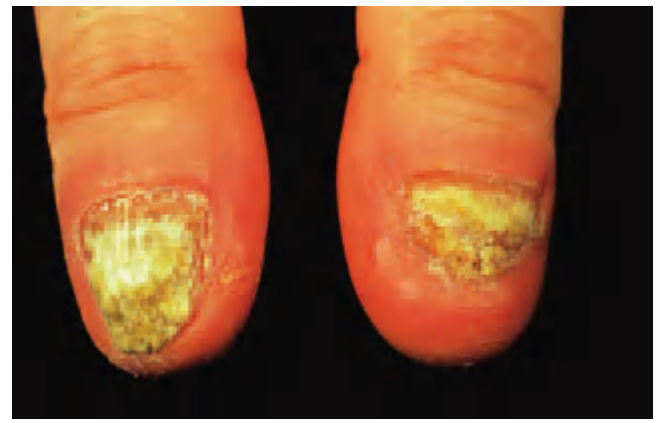

Fig. 31.42 *Candida* onychomycosis in a patient with chronic mucocutaneous candidosis.

Chronic mucocutaneous candidosis

Persistent *Candida* infection of the mouth, the skin and the nails, refractory to conventional topical therapy, is a distinct syndrome occurring as a more-or-less isolated feature. Sometimes it is associated with a variety of other infections, both cutaneous and systemic [1,2]. In the latter case, it may represent a manifestation of a primary defect in immune function, for example severe combined deficiency (Swiss-type agammaglobulinaemia).

Clinical features [1]. With minor variations, the syndrome consists of the following features, usually starting in infancy or early childhood:

1 Persistent oral thrush, responding only partially to conventional therapy, or relapsing promptly after apparently successful treatment. Chronic hypertrophic changes may follow (Fig. 31.41).

2 Cutaneous candidosis. Often intertriginous skin is involved, but also the face and the hands, and sometimes it is widespread over the trunk and limbs. In long-standing lesions, the cutaneous changes are often atypical, suggesting ringworm. In some patients, markedly thickened areas with gross hyperkeratosis may form. However, lesions may also develop as deep dermal nodules or small macules. Scalp involvement is not rare in this syndrome. Dermatophytosis in such patients may present in a similar manner.

3 Paronychia is commonly a feature, often with serious nail plate invasion and total dystrophic onychomycosis [3]. The important findings are nail invasion at an early age often proceeding to complete nail involvement (Fig. 31.42). Here, the nail plate is thickened and the whole terminal phalanx may become encased in hyperkeratotic infected skin.

Patients with this syndrome comprise a heterogeneous group, which was originally classified by Higgs and Wells [2,4] into several distinct categories using genetic and clinical criteria. It is probably best to exclude from the syndrome of chronic mucocutaneous candidosis those patients who present with a well-documented underlying immune defect, such as severe combined immunodeficiency or agammaglobulinaemia, where severe candidosis may form a minor part of the secondary infectious complications. In these patients, mucosal candidosis is usually overshadowed by other serious infections, such as recurrent pneumonia or aspergillosis. In contrast, in patients with chronic mucocutaneous candidosis (CMC), the skin and mucous membrane infections dominate the clinical pattern [1].

However, it is important to recognize that all patients with this syndrome may develop other infections, most commonly human papillomavirus infections (warts) and dermatophytosis, in addition to other features, such as recurrent aphthous ulcers, seborrhoeic dermatitis and alopecia areata.

The main body of CMC patients develop signs in early childhood, and usually *Candida* infection is the presenting feature [5]. While a number of different forms of immune defect have been described in these patients [6], the abnormalities are neither constant nor diagnostic and may reverse with antifungal therapy. Within the childhood-onset group, there are a number of different variants that show features in common. Such features should not be taken as inflexible markers of a particular type, as there is probably considerable overlap in clinical expression between the different groups. The different types are as follows:

1 *Autosomal recessive CMC* [7]. This usually starts in the first decade with persistent oral and nail plate infections. Generally, the health of these patients is good and they do not develop endocrine defects. They also tend to improve with increasing age.

2 *Autosomal dominant CMC* [8]. There are now a number of well-documented pedigrees of families with the dominant form of CMC. Generally, they are more severely affected than those with the recessive variety, and other

infections, such as dermatophytosis, may be particularly troublesome.

3 *Idopathic CMC* [4]. This form was named diffuse CMC by Higgs and Wells in children who had no evidence of genetic predisposition. Some of the original group have now produced affected offspring, and it is likely that some of these patients belong to the autosomal dominant group. Indeed, it is not possible to exclude the possibility that all may eventually be classified with these. However, it remains a useful subgroup to describe the most severely affected patients, who may have other infections and often develop bronchiectasis and pulmonary bullae. Their candidosis is also very severe with oesophageal involvement and the appearance of 'granulomas'. The term *Candida* granuloma was originally used to describe these severely affected patients, who may produce sheets of hyperkeratosis caused by *Candida* infection on the skin and scalp. It has been suggested that this appearance follows attraction of neutrophils into an area of infection, but because of defective function these are unable to destroy the invading yeasts. In practice, the main histological features are hyperkeratosis with only the occasional granuloma in the dermis. Rarely, patients have been reported from this group who develop other systemic diseases, such as cryptococcosis or miliary tuberculosis. Survival into adult life is still not universal in these children.

4 *CMC associated with endocrinopathy*. The majority of these patients appear to have the familial polyendocrinopathy syndrome [9,10]. Mutations of the autoimmune regulator gene appear to be correlated with this syndrome in many cases [10]. This is usually seen in early childhood, and occasionally the onset of *Candida* infection may predate the appearance of endocrine disease by as much as 10 years. The main cluster of endocrine abnormalities is hypoparathyroidism with hypoadrenocorticalism. In addition, other autoimmune abnormalities can occur, such as pernicious anaemia, vitiligo [11] and ovarian failure. This condition is also inherited as an autosomal recessive condition [12]. The severity of the patient's candidosis is very variable, and it is not uncommon to find that one affected sibling has extensive infection while another has only mild but chronic oral candidiasis.

A further group of CMC patients have CMC with associated hypothyroidism [13]. The inheritance of this abnormality is vertical, suggesting autosomal dominant transmission. Their clinical features are similar to other patients with endocrinopathy. It is important to recognize this group in view of their different genetic risk. A mutation has recently been mapped to chromosome 2p [14].

5 *Late onset CMC* [15,16]. Occasionally, adult patients are found to have the syndrome of CMC. The best-documented cases have been associated with a thymoma, but the occasional sporadic infection in a patient with no detectable abnormality may be recognized [3]. Patients with SLE occasionally develop the severe nail changes and oral manifestations of this condition. The sudden onset of chronic oral candidosis in an adult should be investigated as it may be the initial presentation of another condition such as HIV infection.

Immunological classification [1]. It is still not possible to correlate precisely defects of immune function with different clinical variants of the CMC syndrome, and indeed, with current investigative techniques, a substantial minority of cases have no demonstrable defect of immune function at all [5]. To date, a variety of defects of delayed hypersensitivity has been shown to be important [6]. Defects of phagocytosis or killing both in macrophages and polymorphs must be considered, but the much publicized myeloperoxidase deficiency, found in a few cases of systemic candidosis, has not been present in any patient with the chronic mucocutaneous syndrome.

In addition, it is known that certain antigenic components of *C. albicans*, such as mannan as well as some glycoproteins, are immunomodulatory [17]. Reversal of immune defects, such as absent delayed-type hypersensitivity to *Candida* antigens, has been seen with successful clearance of candidosis in CMC patients. It is therefore possible that some of the immunological changes may be secondary to the infection itself.

Diagnosis. The diagnosis of this condition normally requires the elapse of time and repeated failure to respond to conservative treatment. Confusion may occur with persistent ringworm infections, and indeed in some reported cases candidosis and dermatophytosis have coexisted. A family history is of obvious importance, and special note should be taken of other infections, cutaneous or systemic. Full endocrine investigation is also indicated.

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Fig. 31.44 *Candida albicans* colonies. (Courtesy of the Department of Medical Mycology, King's College London, St John's Institute of Dermatology, London, UK.)

Laboratory diagnosis

As *C. albicans* is a common commensal, the interpretation of cultural findings has to be related to the clinical appearances. A scanty growth of *C. albicans* from the skin or from a mucocutaneous site may be meaningless without evidence of infection from a positive direct microscopy.

On direct examination of skin or nail material, the oval thin-walled yeasts bud on a narrow base, and are usually accompanied by filaments, either true hyphae or pseudohyphae (Fig. 31.43). Occasionally, particularly when a non-*albicans* yeast is present, filaments may be absent. The size and shape of the yeasts observed may also suggest the presence of a non-*albicans* yeast; for example, the budding cells of *C. krusei* are noticeably larger and more elongate than those of *C. albicans*. Isolation and identification of *C. albicans* is simple. At 37°C, on media free of cycloheximide, colonies from swabs and skin samples usually appear within 1–3 days. However, growth from thicker skin and nail material can be slower, so plates should be held for a week before reporting as negative. Chromogenic agars have now been developed that allow the identification of *C. albicans* on primary culture. On Albicans ID agar (bioMerieux), the colonies of *C. albicans* are blue and all other yeasts cream or white. On Chromagar (Becton & Dickinson), colonies of *C. albicans*, *C. tropicalis* and *C. krusei* are green, blue and pink, respectively.

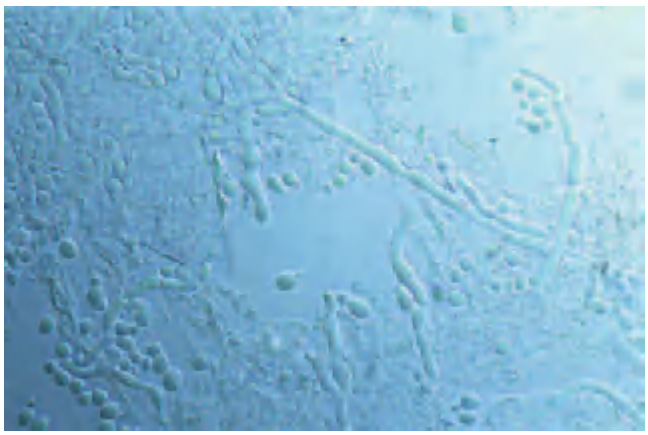

Fig. 31.43 Candidosis. Skin scales mounted in 30% KOH, Nomarski illumination, oil. Budding yeasts and slender filaments are observed. (Courtesy of the Department of Medical Mycology, King's College London, St John's Institute of Dermatology, London, UK.)

Candida albicans. Colony: the colonies on glucose–peptone agar are white to cream and soft in texture (Fig. 31.44). Some isolates may produce wrinkled 'rough' colonies and some may produce an obvious fringe of pseudohyphae around the edge of the colony. Microscopy: mounts from primary culture plates will reveal predominantly budding yeast cells. The production of filaments is best examined on depleted media, such as cornmeal agar, or rice extract agar supplemented with Tween 80. The morphology of *C. albicans* on these media allows identification, for in addition to filaments and budding yeasts, *C. albicans* produces rounded refractile vesicles, usually erroneously termed chlamydospores (8–12 µm diameter), at the sides and ends of the filaments (Fig. 31.45). These are produced within 24–96 h of incubation at 26°C. *C. albicans* also differs from most other species of *Candida* by the production of rudimentary true hyphae—germ tubes—when lightly inoculated into serum and incubated at 37°C for 2–4 h (Fig. 31.46). The only other species that is germ-tube positive and produces vesicles on depleted media is *C. dubliniensis*, a yeast associated predominantly with oral infections in HIV-positive patients.

Other Candida species. Colony: the different species produce colonies that vary slightly in texture, colour and production of obvious pseudohyphae. With experience,

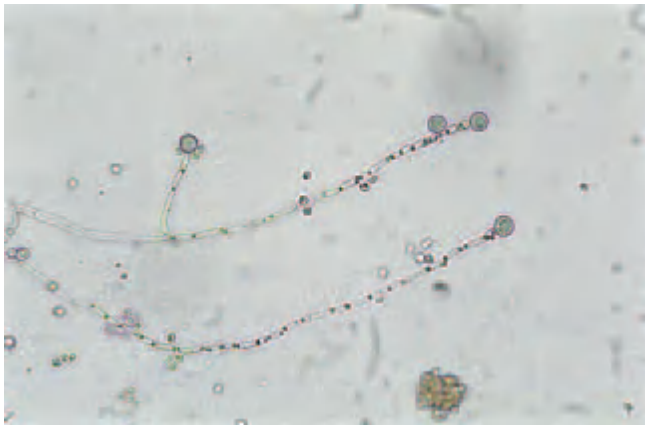

Fig. 31.45 Specific identification of *Candida albicans* can be made by the observation of filaments with thick-walled terminal vesicles when cultured on a depleted medium such as rice–agar supplemented with Tween. (Courtesy of the Department of Medical Mycology, King's College London, St John's Institute of Dermatology, London, UK.)

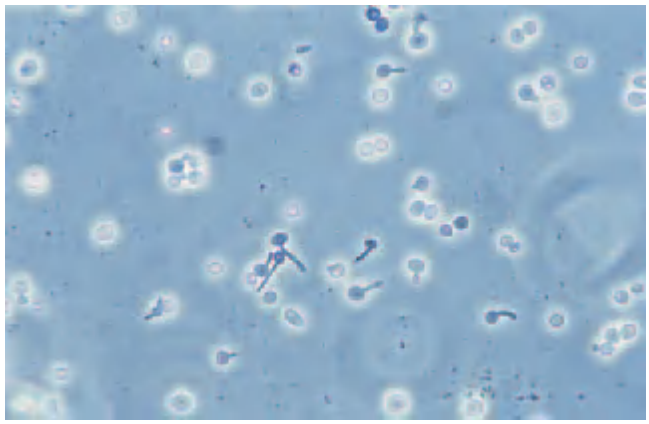

Fig. 31.46 A second method for specific identification of *Candida albicans* is the observation of germ tubes in serum after incubation at 37°C for 2–4 h (Courtesy of the Department of Medical Mycology, King's College London, St John's Institute of Dermatology, London, UK.)

these differences may be recognized on the primary culture plates, but specific identification always requires study both of the morphology and physiology of each isolate. Microscopy: the majority of pathogenic *Candida* species—*C. glabrata* is a notable exception—will produce filaments and budding yeasts, but not chlamydospores, on depleted media, and the appearance of these filaments and yeasts is subtly different and characteristic for each species. The presence or absence of filaments is a key characteristic that is necessary for the identification of all *Candida* yeasts. Physiological tests: a battery of physiological tests, such as sugar and nitrogen source assimilations, and determination of the presence or absence of urease, are used. The development of commercial yeast identification systems, such as the API 20C (bioMerieux) and the Auxacolour (Sanofi), have greatly facilitated this task, and such kits are widely used. It has become particularly necessary to speciate non-*albicans* yeasts, because of the realization that some of these species may show innate resistance to some antifungals; for example, *C. glabrata* and *C. krusei* are often resistant to fluconazole.

Treatment of candidosis

General principles [1]

In the treatment of candidosis, it is important to be aware of the necessity of altering both localized and general susceptibility factors. In the mouth, for instance, this involves frequent toilet in the seriously ill, and denture hygiene in other patients, whereas in *Candida* infections affecting the skin, careful drying of affected sites is important. In many cases, topical antifungal therapy alone is sufficient to produce a response, but in immunocompromised patients with oropharyngeal candidosis, oral systemic therapy may be necessary to treat concomitant oesophageal infection, as well as being the most effective treatment for oral candidosis in AIDS patients. In addition, oral antifungals are used to prevent systemic candidosis in neutropenic patients. Although the success of this approach is often contested, it is nonetheless a common practice. Apart from these indications, and CMC and onychomycosis, the main indications for systemic anti-*Candida* therapy are *Candida* septicaemia and deep-seated candidosis.

Therapeutic agents

The polyene antibiotics amphotericin, nystatin and natamycin are all highly effective against *Candida* species and most other yeast pathogens. Even though the polyenes have been used over many years, resistance by *C. albicans* and other *Candida* species, with the possible exception of *C. lusitaniae*, to these antibiotics is very rare. They are all safe to use topically, and contact dermatitis is rare. Of these drugs, only amphotericin is used systemically, and this must be given by intravenous infusion. Recently, intravenous lipid-associated amphotericin B compounds including a liposomal formulation (AmBisome), a colloidal dispersion (ABCD) and a lipid complex (ABLC) have been introduced. These compounds have the advantage of producing reduced renal toxicity. Gastrointestinal absorption of all the polyenes is limited; after oral administration, only 5–10% is taken up. The other important group of agents effective against *Candida* are the imidazoles. Clotrimazole, miconazole and econazole are the best known and, after a decade or so of topical use, significant resistance to them has not developed in *Candida* species [2]. Contact allergy, although reported, seems to be almost

as rare as reactions to the polyenes. The most useful treatments are with the two triazoles, fluconazole [3] and itraconazole [4], that are also effective in these conditions and have the additional advantage that hepatotoxicity, seen with ketoconazole, an alternative treatment, is exceptionally rare with both drugs. The usual daily doses are itraconazole 100–200 mg and fluconazole 100–400 mg or ketoconazole 200 mg. In addition, fluconazole can be given for systemic candidosis as an intravenous compound. A formulation of itraconazole in cyclodextrin solution provides better absorption in severely immunocompromised patients. Resistance to ketoconazole has been reported in CMC patients receiving long-term therapy with the drug. Similarly, primary resistance to fluconazole has been recorded with some *C. albicans* isolates, and particularly with *C. krusei*, *C. dubliniensis* and *C. glabrata*. Secondary drug resistance in *C. albicans* can occur in AIDS patients receiving fluconazole for long-term management of oropharyngeal candidosis [5]. However, *Candida* infection and resistance is less common in patients receiving highly active antiretroviral (HAART) therapy [6].

Flucytosine is an agent that is absorbed from the gut, is relatively safe and very potent against those strains of *Candida* that retain their sensitivity. Unfortunately, resistance developing during treatment is not uncommon, and this drug is now only occasionally used for systemic candidosis, usually in combination with intravenous amphotericin B.

Treatment of the different clinical forms

Oral candidosis. In infants, suspensions of nystatin, amphotericin or miconazole gel applied several times a day are usually adequate for treating oral thrush. In the adult patient, removal of the dentures with careful hygiene at night is important. Regular amphotericin lozenges, nystatin or amphotericin tablets or oral nystatin suspension are effective in non-immunocompromised patients. The duration of the treatment varies with the condition: 10–14 days may be enough in acute cases. For treatment of unresponsive and chronic cases, such as those with hyperplastic candidosis, the responses to topical therapy are often poor, and either fluconazole (100–200 mg/day) or itraconazole (100–200 mg/day) are more effective. Ketoconazole 200–400 mg/day is an alternative. In patients with chronic oral candidosis, a biopsy may be justified to exclude leukoplakia. Angular stomatitis usually responds to treatment of the primary oral condition, although a topical antifungal applied to the area may speed recovery.

Oral candidosis in patients with AIDS or CMC, by contrast, frequently fails to respond to topical polyene therapy. In these conditions, the best approach is to use oral ketoconazole [7,8], itraconazole [9] or fluconazole [10,11]. If possible, therapy should be given intermittently if there is a recurrence, because of the risk of resistance developing with continuous therapy. Treatment is usually given until there is symptomatic recovery, which is usually quicker with fluconazole than the capsule formulation of itraconazole. A new cyclodextrin solution of itraconazole is also quicker than the capsule form.

Genital candidosis. Acute vulvovaginitis is best treated with a single-dose topical preparation (pessary, ovule), such as clotrimazole, econazole or isoconazole. Longer courses of these compounds (e.g. 14 days), as well as the polyenes, such as nystatin, are also available. If there is coexistent involvement of the skin, a topically applied cream should also be used. Single-day oral therapy with either fluconazole 150 mg or itraconazole 600 mg have recently been introduced; both are more convenient but more expensive. Efficacy seems to be similar to that seen with topical drugs. There is no reliable method of curing recurrent vaginal candidosis.

Balanitis usually responds satisfactorily to topical antifungals applied several times a day, but if there is a source of infection in the sexual partner this should be treated appropriately, and diabetes, if discovered, obviously requires management. Conjugal cases need simultaneous and often prolonged therapy.

Flexural candidosis. Candida intertrigo requires specific topical therapy (azole or polyene creams) usually continued for about 2 weeks, but treatment may be required for longer periods, and is likely to fail if attention is not given to drying the affected area. In some patients with moist *Candida* intertrigo, potassium permanganate soaks are more effective. Attention should be given to treating concomitant bacteria; once again, potassium permanganate is useful for this purpose. In finger or toe web infections, topical antifungal therapy, combined with use of open footwear in the case of infections of the feet, is appropriate.

Napkin candidosis. In infants, rashes in the napkin area should be investigated for *Candida* and, if present, this can be treated topically. The antifungal should be combined with a general regimen for napkin dermatitis, with frequent napkin changes. In seborrhoeic dermatitis, a weak topical steroid is appropriate for the disseminated dry lesions, but steroids should be avoided on the napkin area itself.

Paronychia and onychomycosis. Candida paronychia requires prolonged topical therapy with frequent applications of polyenes, imidazoles or non-specific remedies, such as 4% thymol in chloroform. Lotions are probably preferable

to creams. There have been too few studies of either itraconazole or fluconazole to comment on their effectiveness in paronychia. Whatever anti-*Candida* regimen is chosen, it must be followed by general measures, such as ensuring adequate drying of the hands. The hands should be kept warm and a poor peripheral circulation improved if at all possible. In many patients, particularly in the chronic phases of paronychia, the role of *Candida* is more contentious and other factors such as irritant or allergic contact dermatitis may have a role. For this reason, in chronic cases, concomitant use of a topical corticosteroid is a logical approach. In proven *Candida* onychomycosis, fluconazole or itraconazole [9] offer a real hope of success.

Congenital candidosis. In congenital candidosis of the skin, topical therapy alone is required, but where there is systemic involvement, clearly amphotericin B or fluconazole should be considered.

Chronic mucocutaneous candidosis. Treatment of this condition depends critically on antifungal chemotherapy [12]. Attempts have been made to restore T-cell function, usually by the use of transfer factor [13], or thymosin, or grafting compatible lymphocytes from blood or marrow, or fetal thymic tissue [14], and non-specific measures such as restoration of normal iron stores when these are defective. Systemic anti-*Candida* therapy with fluconazole, itraconazole or ketoconazole is likely to be necessary, and may need to be prolonged and repeated.

Once a remission has been induced, maintenance therapy should not be used in view of the risk of antifungal resistance. In a few patients, reduction of the load of *Candida* antigen seems to result in restoration of normal immunological responses, such as delayed hypersensitivity. Attention must be given to any endocrine factors as, although such treatment is not likely to lead to improvement in the candidosis, it may have considerable importance on the child's health and development. Endocrine screening tests should be repeated, even if initially negative, as patients with endocrinopathy may develop endocrine disease years after the first appearance of candidosis. Where appropriate, parents should be given genetic counselling. The possibility of coexisting dermatophytosis should not be forgotten, but it should respond satisfactorily to itraconazole or terbinafine.

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Subcutaneous mycoses

Subcutaneous mycoses, or mycoses of implantation, are sporadically occurring infections caused by fungi present in the natural environment, which are directly inoculated into the dermis or subcutaneous tissue through a penetrating injury. They are seldom common even in endemic areas, and are mainly seen in the tropics, although, as many have long incubation periods, they may be seen in countries outside these endemic areas in patients who were originally infected elsewhere. The most common of these infections are sporotrichosis, mycetoma and chromoblastomycosis; rarer infections are phaeohyphomycosis, lobomycosis, rhinosporidiosis and subcutaneous zygomycosis.

The diagnosis of the subcutaneous mycoses is made initially by direct examination and examination of histopathological sections. Culture is not necessarily difficult, but identification of the more unusual pathogens may require the help of a reference mycological laboratory, as, with the rise in the number of immunocompromised patients in the population, an ever-increasing number of organisms have now been recognized as opportunistic pathogens. Additionally, some isolates, particularly from cases of eumycotic mycetoma and phaeohyphomycosis, may fail to sporulate on primary isolation, and special media or conditions of incubation may be required to encourage conidial production. The description of all the potential pathogens is outside the scope of this chapter, although brief descriptions of the most common isolates are included.

Laboratory methods

Collection of samples

Materials from patients thought to have subcutaneous mycoses are obtained from a variety of sources. Occasionally, superficial scrapings from a lesion may be useful, but generally pus or exudates discharging or obtained by aspiration, and samples of biopsied tissue, ideally both from the edge and from the centre of the lesion, are required for satisfactory diagnosis. All samples are placed in sterile containers for immediate despatch to the laboratory. To prevent drying out of the material tissue, biopsy specimens intended for culture must be placed in sterile saline or wrapped in moistened sterile gauze if they cannot be processed immediately. Delays in processing samples will increase the likelihood of bacteria or saprophytic fungi contaminating the samples.

Direct examination and histopathology

A simple potassium hydroxide mount may be enough to give a preliminary diagnosis in some cases. For example, typical organisms may be observed in superficial crusts from chromoblastomycosis lesions, and pus containing grains from mycetoma patients can be used to immediately differentiate eumycotic and actinomycotic disease. Small fragments of biopsy tissue may be similarly examined, but generally histopathological processing will be more informative. Of the specific fungal stains, the silver impregnation procedure (Grocott, Gomori) and PAS are most commonly used and give excellent results, but in some instances examination without a specific fungal stain may also be valuable to determine whether the infecting fungus is naturally pigmented (dematiaceous). Details of the appearances of individual mycoses are dealt with more fully in the relevant sections of this chapter and are well reviewed in standard textbooks [1–4].

Culture and identification of isolates

Generally, tissue samples should be finely divided, either by grinding or cutting into small pieces using sterile scalpel blades. The exception to this is material suspected of being infected with a zygomycete, where the largely aseptate hyphae are particularly fragile and will not survive such fine division. Although glucose–peptone agar alone can be used for primary isolation of the subcutaneous pathogens, a number of other media are also commonly used, including inhibitory mould agar (BBL) and brain–heart infusion agar (Difco), with or without the addition of 5–10% sheeps' blood. Antibacterial antibiotics, such as chloramphenicol (0.005%) and gentamicin (0.0025%) are usually incorporated into the agar, and cycloheximide may be added for the culture of *Sporothrix schenckii* and the agents of chromoblastomycosis. If sufficient material is available, incubation at 26–30°C and 37°C on a variety of media is recommended. Although many organisms will grow quite quickly, cultures should be held for 6 weeks before being reported negative. If isolates fail to sporulate on the primary culture plate, subculture on to potato dextrose agar (Oxoid) or half-strength cornmeal agar (Oxoid) and incubation in the light may be necessary to encourage conidial production.

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Sporotrichosis

Definition. An acute or chronic fungal infection caused by *Sporothrix schenckii* [1]. There are both cutaneous and systemic forms of sporotrichosis.

Aetiology. Sporotrichosis is caused by a single species, the dimorphic fungus *S. schenckii* [2]. It occurs in both temperate and tropical zones. Less than 20 cases of sporotrichosis diagnosed in the UK have been published. The disease was common in France between 1905 and 1920, and occasional cases are reported from other European countries. It occurs sporadically in North, South and Central America, Egypt, Japan and Australia [3] and has been particularly prominent in the mining areas of South Africa. The incidence, and possibly the geographical distribution, are dependent on climate.

In Uruguay, it has been shown that the incidence is highest in the autumn and first half of the winter (high humidity and temperatures between 16 and 22°C) [4]. These conditions favour saprophytic growth of *S. schenckii*. Sporotrichosis is rare in semiarid areas. The fungus grows on decaying vegetable matter, for example the timber in mines. It has been shown that the timber harbours the fungus before being taken underground [5], and that the source is probably the soil in the vicinity of the mines. *S. schenckii* could be recovered from the feet of mine workers who did not have sporotrichosis.

The disease may also occur in other groups occupationally exposed to the organism, such as workers using straw as packing material, forestry workers, florists or gardeners [6].

In most cases of cutaneous sporotrichosis, the fungus is introduced into the skin or mucous membrane by trauma, as in a minor puncture wound caused by a thorn or to a splinter, or perhaps an insect bite. Sporotrichosis is not

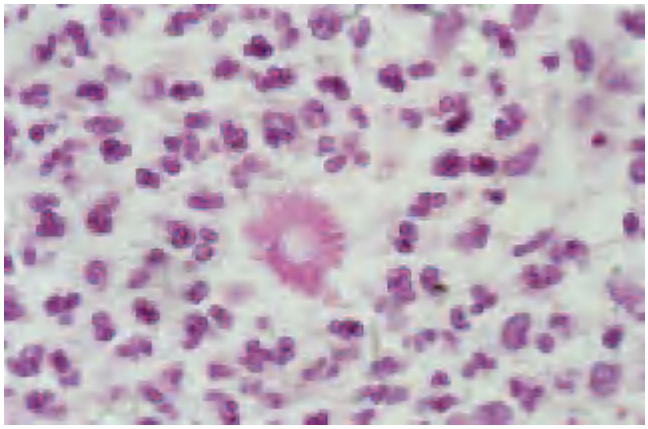

Fig. 31.47 Sporotrichosis: tissue section stained with haematoxylin and eosin. Organisms are usually very scanty but asteroid bodies, representing a foreign body tissue reaction, may be observed. (Courtesy of the Department of Medical Mycology, King's College London, St John's Institute of Dermatology, London, UK.)

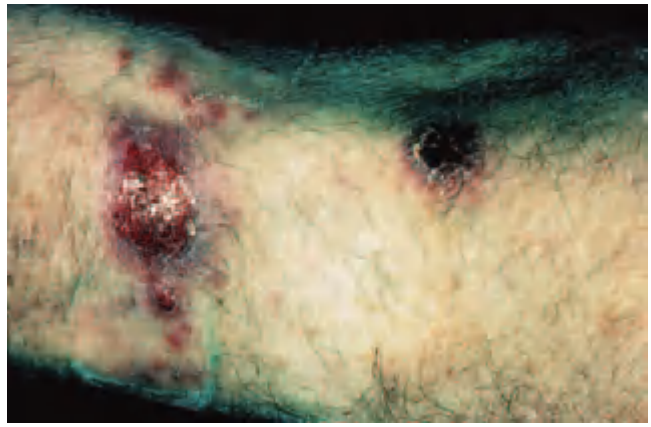

Fig. 31.48 Lymphangitic sporotrichosis.

contagious, although transmission has been recorded in a family from a cat, which also affected veterinary personnel. Adult males are, by their occupation, most exposed to the risk of infection. Systemic sporotrichosis is rare, and the portal of entry is thought to be the lung in these cases.

Unexplained areas of hyperendemicity have been described in certain countries, where unexpectedly high numbers of the local population develop cutaneous lesions of sporotrichosis and appear to be sensitized on skin testing with sporotrichin [7].

A family epidemic of cutaneous sporotrichosis was described among four children who became infected after playing in hay. On rare occasions it has been seen in young children. The incubation period is variable, but is usually 8–30 days.

Histology. *S. schenckii* may remain localized in the subcutaneous tissue, may spread locally in the subcutaneous lymphatics or, rarely, may be widely disseminated in the bloodstream after pulmonary infection. The immunological response of the host probably determines the form that the infection assumes [8]. The fungus provokes a mixed granulomatous reaction with neutrophil foci. The fungus is present in the tissue, usually in the form of small (3–5 μm) cigar-shaped or oval yeasts, and these may, on occasion, be surrounded by a thick radiate eosinophilic substance, which forms the distinctive asteroid bodies (Fig. 31.47) [9]. A mycelial form of the fungus in tissue has occasionally been reported [10].

Clinical features. The main clinical varieties of sporotrichosis are the cutaneous and the sytemic forms. In turn, cutaneous sporotrichosis is normally divided into two main types, the lymphangitic and fixed forms, but occasionally atypical varieties such as mycetoma-like or cellulitic forms may occur [2].

The most common type of sporotrichosis is the localized lymphatic variety, which follows the implantation of spores in a wound. This therefore usually occurs on exposed skin, often on the upper extremity [2,11], and is known as lymphangitic sporotrichosis. A nodule or pustule forms, which may break down into a small ulcer. Untreated, the disease usually follows a chronic course, which is characterized by involvement of lymphatics from the draining area and a chain of lymphatic nodules develops (Fig. 31.48). New nodules appear at intervals of a few days. These soften and ulcerate, and are connected by tender lymphatic cords [12]. A thin purulent discharge may come from the primary lesion and the earliest lymphatic nodules. As the disease becomes chronic, the regional lymph nodes become swollen and may break down. The primary lesion may heal spontaneously leaving the lymphatic nodes enlarged. The general health of the patient may not be affected.

The fixed variety, where the pathogen remains more or less localized at the point of inoculation, is less common [2,13]. The lesions may be acneiform, nodular, ulcerated or verrucous; the latter form is occasionally very extensive. Less commonly, there may be infiltrated plaques or red scaly patches. An ulcer may be gummatous or may simulate an epithelioma. The plaques may suggest leishmaniasis or tuberculosis. It is thought that this variety may reflect a high degree of immunity on the part of the patient. The variable morphology of this type is notable.

The reason for the difference in clinical behaviour of the two principal forms of cutaneous sporotrichosis is unknown, although changes in temperature sensitivity of the organisms [14] or in the host's immune response [2] have both been suggested. It is possible that some sporotrichosis infections are self-healing. Others are chronic and may mimic mycetoma or stasis ulcers. In

AIDS patients, multiple cutaneous lesions may develop, suggesting cutaneous spread.

The less common systemic form probably follows inhalation, and presents either with local pulmonary disease or focal or widely disseminated lesions in the joints, meninges and skin [15]. There is some evidence that systemic sporotrichosis occurs in patients with some defect in host defence, such as alcoholics. This is in contrast to the cutaneous variety, which occurs in perfectly healthy individuals. Where sporotrichosis has been reported in AIDS patients, the lesions have usually been widespread and have affected internal organs as well as the skin [16].

In the systemic type, which is rare, ulcerated nodules may develop anywhere on the body or mucous membranes, and visceral lesions may occur. No organ is immune and bones or joints may be involved. Occasionally, vascular lesions resembling polyarteritis nodosa may be found. If untreated, this type is fatal but systemic sporotrichosis is exceedingly rare.

Differential diagnosis. Sporotrichosis can simulate granulomatous lesions of almost any other origin, and the diagnosis must be considered in all cases when the initial lesions have followed an injury.

The main conditions that may resemble sporotrichosis are mycobacterial infections and leishmaniasis. The mycobacterial infection caused by *Mycobacterium marinum* (fish-tank granuloma) may closely resemble lymphangitic sporotrichosis.

Laboratory diagnosis. *S. schenckii* is very rarely present in quantity in infected tissues, and direct microscopy of clinical material is of little or no value in confirming a diagnosis because its presence may easily be overlooked. Fluorescent antibody techniques have been successfully employed in locating the pathogenic phase *in vivo* [17]. The fungus grows readily on common agar media.

S. schenckii. Colony: the colonies are leathery, moist and initially white or cream with a wrinkled surface. As the colonies age, they may become progressively darker until they are brown or black. Microscopy: the slender (2-µm) hyphae bear small, oval to pyriform, hyaline conidia produced along the sides of the hyphae and sympodially at the ends of delicate conidiophores arising at right angles from the hyphae. The arrangement of the conidia at the apex of the conidiogenous cell is often described as palmate or flower-like, with each conidium attached by a denticle to the small vesicle. In many strains, particularly when freshly isolated, oval, round or triangular dark brown thick-walled conidia are also produced, and it is partly the production of these conidia that results in the development of darkly pigmented colonies. However, pigmentation has also been reported to vary according to the culture medium and to increase with the addition of thiamine. Physiological tests: to confirm the identification, it is essential to convert this thermally dimorphic fungus to the yeast phase, as fungi that are non-pathogenic and morphologically very similar may be isolated as contaminants. This is best achieved on brain–heart infusion agar supplemented with sheeps' blood and incubated at 37°C. The yeasts are typically oval or cigar-shaped.

Treatment. While cases have been described where spontaneous remission has been seen to occur [18], it is the usual practice to treat patients with sporotrichosis. Potassium iodide in large oral doses is effective in the localized types, and should be continued for 3–4 weeks after clinical cure. It is cheap and effective, although side effects are common. A recommended schedule is five drops initially, increasing to 4–6 mL of saturated potassium iodide three times daily. Patient tolerance may require a lower maximum dose [19].

The alternatives are itraconazole 100–200 mg/day or terbinafine 250 mg/day. However, at these dosages the length of treatment is not significantly different to that used with potassium iodide [20]. However, it may be useful in patients who do not respond to the latter or in systemic cases. In the latter, treatment with intravenous amphotericin B or miconazole may also be helpful. As with chromoblastomycosis, the local application of heat may produce recoveries in some patients.

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Mycetoma

SYN. MADUROMYCOSIS; MADURA FOOT

Definition. A localized chronic infection caused by various species of fungi or actinomycetes, and characterized by the formation of aggregates of the causative organisms (grains) within abscesses. This results in severe damage to skin, subcutaneous tissues and bones of the feet, hands and other parts of the body, and grains are discharged to the surface through draining sinuses.

Aetiology [1]. Mycetoma may be caused by various species of fungi (eumycetoma) and aerobic actinomycetes (actinomycetoma), which occur as saprophytes in soil or on plants [2]. From these sources, they are implanted subcutaneously, usually after a penetrating injury [3,4]. The disease is largely confined to tropical and subtropical climates, usually among agricultural workers. Adult males are therefore most often infected. A few cases have occurred in Europe and North America, but in many such cases the patients have originated from the tropics and the infection was imported. These cases also illustrate clearly that the disease may not become troublesome until many years (20–30 years) after the initial injury. The condition, which is not contagious, is characterized by the presence of different coloured grains, which represent microcolonies of the organisms. The aetiological agents listed in Table 31.8 include only the most commonly isolated fungi.

The relative frequency with which the different species are encountered varies from country to country [5,6]. Actinomycetomas caused by *Nocardia* species are most common in Central America and Mexico. In other parts of the world, the most common organism is a eumycetoma agent, *Madurella mycetomatis*. The actinomycete, *Streptomyces somaliensis*, is most often isolated from patients originating from Sudan and the Middle East [7]. The causative organisms have been isolated from either soil or plant material, including thorns from *Acacia* bushes in endemic areas. It is unusual to find a clinically distinct predisposing abnormality in patients with mycetoma, although in the UK there is a striking preponderance of diabetics among mycetoma patients, although this has not been noticed elsewhere. It is thought that the implanted organisms survive in subcutaneous tissue because they are able to develop a number of adaptive changes—from cell-wall thickening to extracellular melanin deposition—which allow them to resist neutrophil attack.

Table 31.8 Aetiological agents of mycetoma.

Fungi	Actinomycetes
Dark grain	
Madurella mycetomatis	*Actinomadura madurae*
Madurella grisea	*Actinomadura pelletieri*
Leptosphaeria senegalensis	*Streptomyces somaliensis*
Curvularia lunata	*Nocardia brasiliensis*
	Nocardia otitidis-caviarum
	Nocardia asteroides
Pale grain	
Scedosporium apiospermum	
Neotestudina rosatii	
Acremonium spp.	
Fusarium spp.	

Histology [4,8]. The causal organisms produce a chronic inflammatory reaction leading to focal neutrophil abscess formation, with scattered giant cells and fibrosis. Grains in the form of white, yellow, red or black granules are found in the centre of the inflammatory response [9], and may be discharged in pus through multiple sinuses on to the skin surface. Secondary bacterial infection may occur but this is not common [10]. The destructive process slowly extends deeply into the underlying tissues, and invades muscle and bones. A haematoxylin and eosin preparation is sufficient to distinguish between eumycetoma and actinomycetoma.

Clinical features. The clinical features are essentially the same no matter which fungus or actinomycete is concerned [11,12]. Because trauma favours infection, most lesions are on the foot and lower leg, but they may occur anywhere on the body [13]. The earliest stage is a firm painless nodule but, with time, papules, pustules which break down to form draining sinuses, appear on the skin surface (Fig. 31.49). The whole area becomes hard and swollen, often without significant pain [14]. Extension to underlying bones and joints gives rise to periostitis, osteomyelitis and arthritis (Fig. 31.50). In advanced cases, destruction of bone within an infected area may be almost complete, and gross deformity may result [15]. There are usually multiple sinus tracts draining pus. These may remain open for months or may close and reopen, or may be replaced by new sinuses. The discharge may be purulent or seropurulent. The condition is comparatively painless and usually develops slowly (Fig. 31.51), but eventually results in gross swelling of the affected foot or other parts with serious deformity. Lymph node involvement is rare [16].

Imaging techniques contribute greatly to assessment of the destruction. Magnetic resonance imaging (MRI) provides the most comprehensive method [17].

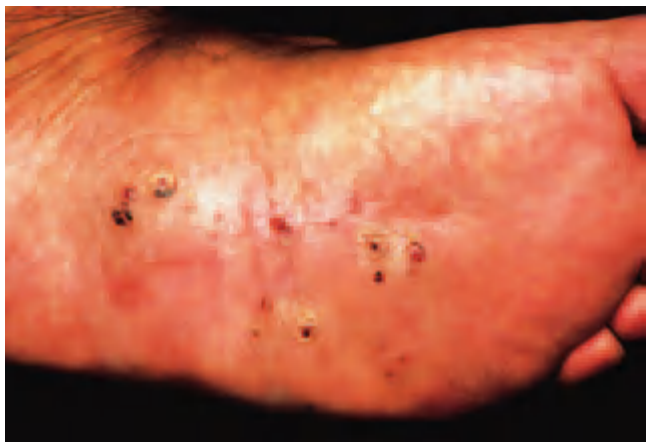

Fig. 31.49 Mycetoma caused by *Madurella grisea*.

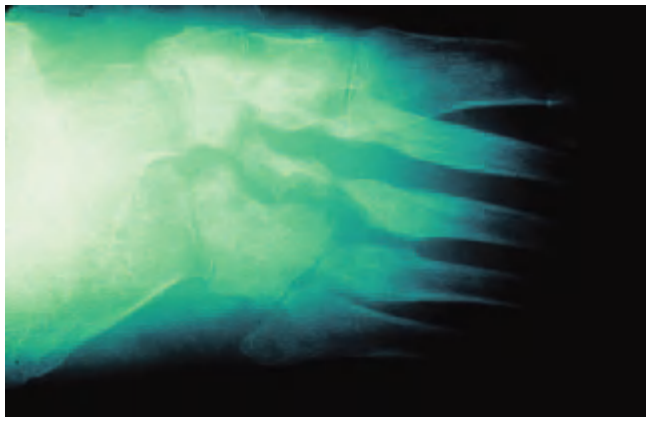

Fig. 31.50 Erosive X-ray changes in a mycetoma.

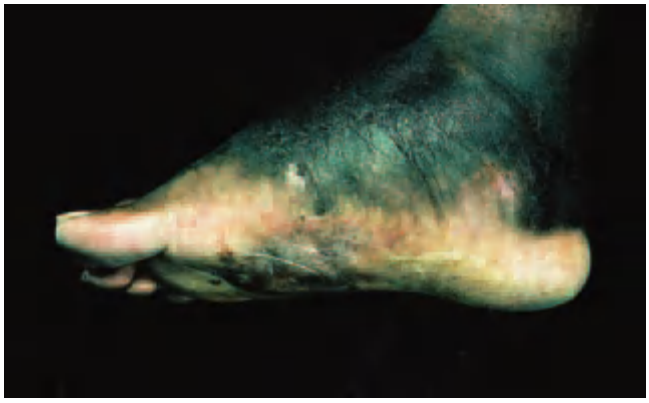

Fig. 31.51 Eumycetoma affecting the foot.

Differential diagnosis. Chronic osteomyelitis of bacterial or tuberculous aetiology may resemble mycetoma, particularly in the early stages. In early mycetoma, it may be necessary to incise pustules that represent foci of inflammation, necrosis and sinuses that have not yet ruptured through the skin; they often contain grains. Pus should be examined under the microscope for the presence of grains, which may then be processed for histology or examined directly in potassium hydroxide. If the infection is eumycotic, when crushed under the cover slip the grains will be seen to consist of masses of fungal mycelium with hyphae 2–6 µm in diameter. Chlamydoconidia are frequently formed at the periphery or in the centre of the grains. Actinomycotic grains will be seen to consist of masses of much narrower bacterial filaments 0.5–1.0 µm in diameter. If there are no discharging sinuses, biopsy may be required. In elephantiasis there are no sinus tracts.

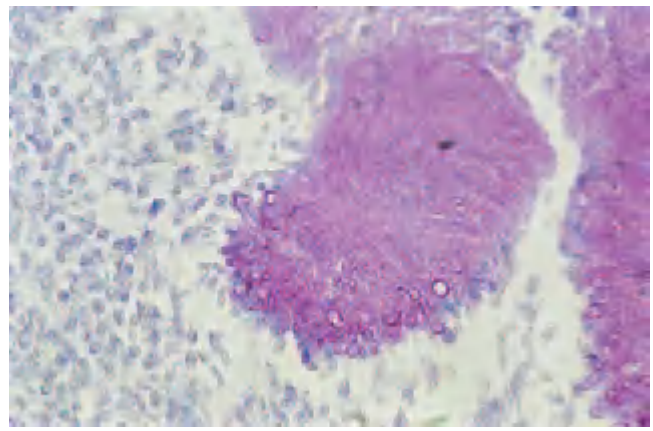

Fig. 31.52 Mycetoma: tissue section. Distinct hyphal filaments, stained pink with periodic acid–Schiff (PAS), are clearly visible in a pale-grained eumycetoma. (Courtesy of the Department of Medical Mycology, King's College London, St John's Institute of Dermatology, London, UK.)

Laboratory diagnosis. A tentative diagnosis sufficient to initiate treatment may be made on the basis of grain colour, texture and direct microscopic appearance [4]. For instance, black grains are always caused by fungi and red grains by an actinomycete. Eumycetomas with black grains are termed dark grain eumycetomas, and many of the fungal species responsible produce hard or brittle grains with a brown cement-like substance surrounding the hyphae. Eumycetomas with white or yellow grains are termed pale grain eumycetomas and most contain no cement and have a soft texture (Fig. 31.52).

In eumycotic disease, the final identification of the infecting fungus requires the isolation of the causal agent in culture. As the surfaces of the grains are frequently contaminated by bacteria, washing with saline containing antibacterials is recommended prior to inoculating the culture medium. Many of the grains may be non-viable. Primary isolates may require subculture on to nutritionally depleted media, such as half-strength cornmeal agar, to induce sporulation, and may fail to sporulate completely. Referral to a reference mycology laboratory for identification is recommended. Serology is helpful in some cases [18].

Only the two most frequently isolated species are described.

Madurella mycetomatis. Colony: the colonial form shows great variation. Colonies are initially pale and leathery, but after a few days become olive, ochre brown or grey in colour and may produce a diffusible brown pigment. Growth is faster at 37°C than 28°C. Microscopy: on nutrionally poor media, spherical conidia may be formed from flask-shaped phialides. Primary cultures may produce large chlamydoconidia but are otherwise usually sterile.

Scedosporium apiospermum. Colony: the colony grows rapidly with a floccose grey or brown–grey surface and white to dark grey reverse. Microscopy: oval, light brown, relatively thick-walled conidia with a truncate base are formed singly along the hyphae or in small groups from annellides. A second form of conidiation is seen in some isolates with the production of coremia—tufts of hyphae held together—which produce smaller hyaline annelloconidia at their tips. This is a homothallic species and the sexual phase with ascospores may be formed on primary culture. In these instances, the teleomorph is reported as *Pseudallescheria boydii*.

Treatment. Localized lesions that can be excised without residual disability are best so treated. In other cases, medical treatment should first be attempted, although chemotherapy of mycetomas caused by fungi has, so far, been found to be quite unsatisfactory in most cases, despite the fact that certain fungi have been found to be relatively sensitive *in vitro* to therapeutic agents such as amphotericin B.

Infection by species of actinomycetes may be susceptible to chemotherapeutic agents. The combination of dapsone with streptomycin or co-trimoxazole plus streptomycin has been reported to give good results [19]. An alternative second drug is rifampicin. Amikacin may also be used in recalcitrant *Nocardia* infections.

Among the fungal causes of mycetoma, *M. mycetomatis* is the most sensitive to therapy, as it responds to ketoconazole in about 60% of cases [1]. For the others, a trial of therapy with griseofulvin, terbinafine or itraconazole is worth attempting as, even though it may not be curative, the progress of the infection may be slowed [19]. Radical surgery, usually amputation, should be considered carefully. Removal of a limb may deprive the patient of livelihood in many countries and this will need to be taken into consideration. However, it remains the only effective means of removing the infection in some patients.

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Chromoblastomycosis

SYN. CHROMOMYCOSIS; VERRUCOUS DERMATITIS

Definition. A chronic fungal infection of the skin and subcutaneous tissues caused by pigmented fungi, which produce thick-walled single- or multicelled clusters (sclerotic or muriform bodies) in tissue, and which are characterized by the production of slow-growing exophytic lesions, usually on the feet and legs [1].

Aetiology. Chromoblastomycosis is caused by several fungi, the most common of which are *Phialophora verrucosa*, *Fonsecaea pedrosoi*, *F. compacta* and *Cladophialophora carrionii* (recent syn. *Cladosporium carrionii*) [2]. Other rare causes include *Rhinocladiella aquaspersa*. The nomenclature of these fungi has been reviewed by McGinnis [3].

The causal fungi have been isolated from wood and soil, and the infection usually results from trauma, such as a puncture from a splinter of wood [4]. The condition is usually found in rural communities [5]. It has been reported from Central, South and North America [6], Cuba, Jamaica, Martinique, and also from many other

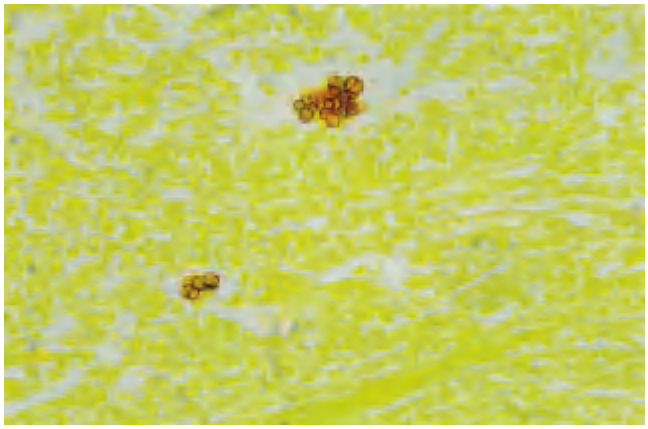

Fig. 31.53 Chromoblastomycosis: tissue section. The natural brown pigment of the fungal muriform cells is clearly visible. The cells divide by fission and may form septa in more than one plane of division. (Courtesy of the Department of Medical Mycology, King's College London, St John's Institute of Dermatology, London, UK.)

countries including India, South Africa, Madagascar, Australia and northern Europe. It is occasionally seen as an imported infection in the UK.

Adult male agricultural workers are most often affected, but the condition has been reported in children.

Histology. The histology is that of a foreign-body granuloma, with isolated areas of microabscess formation. In the organized granuloma, mainly within giant cells, groups of fungal cells may be seen. Because the cells are chestnut or golden brown in colour, they are easily distinguished in the infiltrate. The cells are characteristically divided in several planes of division by thick septa and are termed muriform or sclerotic cells (Fig. 31.53). There is marked pseudoepitheliomatous hyperplasia in the epidermis, and in some areas apparent transepidermal elimination of fungal cells, which can be found in the stratum corneum. The tissue between the granulomatous nodules shows chronic fibrosis. When ulceration has occurred there is usually secondary bacterial infection.

Clinical features [7,8]. The lesions are usually found on exposed sites (Fig. 31.54), particularly the feet, legs, arms, face and neck. A warty papule slowly enlarges to form a hypertrophic plaque [9,10]. In some lesions, the plaque is flat and expands slowly with central scarring. The early lesion may occasionally be an ulcer. Eventually, after months or many years, large hyperkeratotic masses are formed, and these may be as large as 3 cm thick (Fig. 31.55). Secondary ulceration may occur. The lesion is usually painless unless the presence of secondary infection causes itching and pain. Satellite lesions are produced by scratching, and there may be lymphatic spread to adjacent areas. Haematogenous spread has occurred but is rare, and brain abscesses have been described. Secondary infection may eventually lead after several years to lymphatic stasis with the production of elephantiasis. Some forms of the infection produce psoriasiform lesions. Squamous carcinomas may develop in chronic lesions.

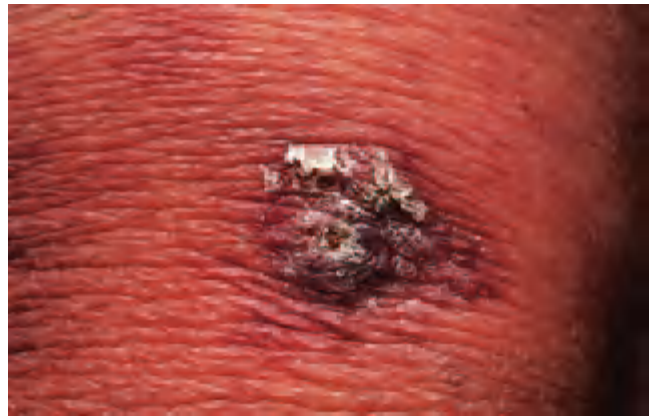

Fig. 31.54 Early lesion of chromoblastomycosis.

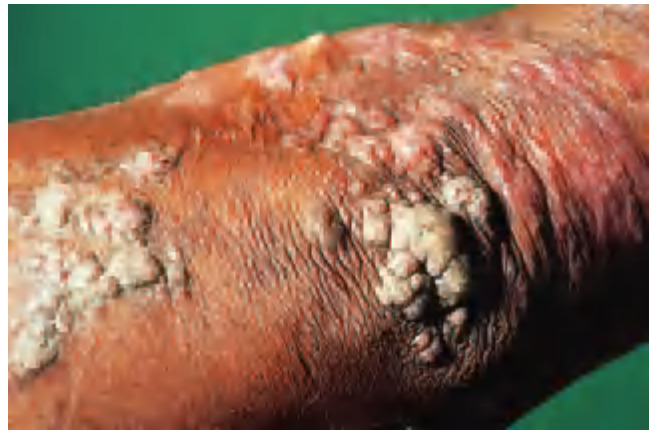

Fig. 31.55 Plaque-type chromoblastomycosis.

Differential diagnosis. The disease must be differentiated from blastomycosis (by the absence of a sharp border containing minute abscesses) and also the absence of pulmonary lesions, cutaneous tuberculosis, leishmaniasis, syphilis and yaws. Biopsy and culture of material for the associated fungi will establish the diagnosis.

Laboratory diagnosis. Irrespective of species, the pathogen can be seen in biopsy sections as deeply pigmented, thick-walled muriform or sclerotic cells. Occasionally, in superficial skin scrapings from the surface of the lesions, pigmented hyphae rather than sclerotic cells are seen. Multiplication *in vivo* is by splitting rather than budding, and this results in the production of single, two- or multiple-celled clusters.

In culture, the colonies of all species are dark grey–green to black and velvety or downy, with a black reverse. Three forms of conidial production are observed in the

most common agents of infection: acropetal budding, production of phialides and sympodial conidiation. Some agents are polymorphic, demonstrating more than one type of conidiation simultaneously, and this has caused some confusion in the nomenclature of these agents. They are named according to the dominant form of conidiation.

Phialophora verrucosa. Microscopy: the dominant form of conidiation is the production of flask-shaped phialides with a pronounced dark collarette at the apex. These are produced laterally or terminally. The hyaline thin-walled elliptical conidia are produced at the tip of the phialide in basipetal succession and collect as balls. On nutritionally weak media, a few sympodial or acropetal conidiogenous cells may also be observed.

Fonsecaea pedrosoi. Microscopy: the dominant form of conidiation is sympodial with the conidia confined to the upper part of the cell. The brown single-celled conidia are produced on short denticles and may in turn produce secondary conidia in a similar manner. Conidia produced by acropetal budding are also present in the majority of isolates, and some isolates will produce scanty phialides.

Cladophialophora carrionii. Microscopy: acropetal budding is dominant, producing long chains of pale, oval or lemon-shaped conidia. The chains branch at frequent intervals. On starvation media, such as half-strength cornmeal agar, bulbous phialides may be produced by the conversion of some of the cells within the branched chains.

Treatment. The main treatment of chromoblastomycosis involves the use of antifungal chemotherapy. Itraconazole with or without flucytosine is often successful, although responses to itraconazole alone are thought to be better if the causative organism is *C. carrionii* [1,11]. Flucytosine used on its own or combined with amphotericin B [12] may also be effective, but resistance to flucytosine may develop if it is used on its own. There is also evidence that terbinafine 250 mg/day may also be effective [13]. Tiabendazole is a further alternative, but is not well tolerated by patients because of gastrointestinal side effects. Other approaches to treatment have included the use of cryotherapy or the local application of heat [14]. The use of surgery is contentious; in larger plaques there is a risk in pursuing this approach as satellite lesions may develop around the excision site. Surgery is really only indicated in very small lesions, and even in these should be combined with chemotherapy.

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Phaeohyphomycosis

SYN. PHAEOMYCOTIC SUBCUTANEOUS CYST

Definition. Phaeohyphomycosis is a rare, and generally localized, subcutaneous or intramuscular infection, usually a cyst or abscess caused by a range of brown-pigmented (dematiaceous) fungi including *Exophiala jeanselmei*, *Exophiala dermatitidis*, *Bipolaris* species, *Alternaria alternata* and others that form pigmented hyphae in tissue [1]. Systemic forms of phaeohyphomycosis also exist.

Aetiology. The pathogen probably originates by implantation from an exogenous source, and occasionally fragments of plant tissue can be found in lesions. Infection begins with a firm, sometimes tender nodule, which may develop into a large cyst up to several centimetres in diameter. The overlying epidermis is not conspicuously thickened. There is no tendency towards lymphatic spread, and dissemination is exceedingly uncommon. Some patients are immunocompromised, usually through steroid therapy. An ever-increasing number of fungi have been reported as agents of phaeohyphomycosis: a review lists 104 species [2]. The most common causative organisms are shown in Table 31.9.

Table 31.9 Major aetiological agents of phaeohyphomycosis.

Exophiala jeanselmei	*Bipolaris* spp.
Exophiala dermatitidis	*Exserohilum* spp.
Cladophialopora bantiana	*Curvularia* spp.
Phialophora spp.	*Alternaria* spp.

Histopathology. The diagnosis should be confirmed by biopsy, and it is important to exclude other cystic structures such as Baker's cysts. The fungi can be seen in the inflammatory lining of the cyst wall. Specific fungal stains such as Grocott or PAS will mask the natural colour of the hyphae, but in haematoxylin and eosin sections the brown colour may be obvious. In some cases, however, the hyphae appear unpigmented and a specific stain for melanin, the Masson Fontana stain, must be used to reveal the presence of the fungal pigment. Beaded or moniliform hyphae are frequently reported, and sections through these structures may give the appearance of yeast-like structures.

Laboratory diagnosis. The organisms are not usually difficult to grow from the lesions, but the fact that so many different species may be involved, together with the failure of some primary isolates to sporulate, means that their identification may require the help of a specialist laboratory. The major dematiaceous pathogens are well illustrated and described in the review by Dixon and Polak-Wyss [3].

Exophiala jeanselmei. Colony: this fungus belongs to the group sometimes termed 'black yeasts'. The colony is initially glabrous or moist, and black in colour. As the culture matures, it becomes more filamentous and eventually is covered with a grey velvety mycelium. Microscopy: initially, the culture is made up of single cells, which are annellides reproducing by budding. When the filamentous stage has developed, the septate brown hyphae bear slender annellides producing elliptical conidia, which collect in a mass at the tip of the conidiogenous cell or slide down to form a row along the side of the annellide. Physiological tests: will not grow at 40°C.

Bipolaris species. Colony: the colonies grow rapidly. Initially downy and pale grey, the colour darkens to olive grey or black on both surface and reverse. Microscopy: the conidiogenous cells are geniculate, producing the brown multicellular phragmoconidia in a sympodial sequence. The hilum at the base of the conidium is only slightly protuberant.

Treatment. The usual treatment is excision, and although there are no published studies to establish efficacy, an appropriate antifungal such as itraconazole is often given after surgery.

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Lobomycosis

SYN. KELOIDAL BLASTOMYCOSIS; LOBO'S DISEASE

Definition. This rare disease is characterized by keloidal skin lesions that remain fairly well localized and apparently do not affect the general health of the patient [1].

Aetiology. The disease was first observed in 1931 in a patient from the Amazon valley and other cases have been seen there [2] and throughout Central and northern South America.

The causal fungus, which has never been isolated in culture, is *Lacazia loboi*. It is thought that the agent might be associated with water and gain entry through a wound [3]. In most cases studied, the disease has been present for periods of many years. Infections have been reported in fresh-water dolphins [4].

Histology. Fungi and giant cells are abundant in the lesions, which are granulomatous and apparently devoid of collagenous fibrosis. The fungus cells are usually round or lemon-shaped, sometimes joined one to the other with a narrow tubular neck. They measure about 8 μm in diameter and have a thick wall [5].

Clinical features [1,6]. Lesions may be found anywhere on the body, but are usually on exposed parts: legs, arms and face. They can, in most instances, be associated with injuries to the skin, and spread from one site to another is thought to be by autoinoculation following injury. There is no marked lymphangitis and no visceral dissemination. Old chronic lesions present as elevated crusted fungoid plaques. Squamous carcinomas may occasionally develop in chronic lesions [1].

Differential diagnosis. Clinically, the disease most closely resembles chromoblastomycosis. Microscopic examination of biopsy material will establish the diagnosis.

Laboratory diagnosis. The fungus has not been isolated in culture, and mycological confirmation depends on recognition of the characteristic cells of *Loboa loboi* in tissue. This is easily performed with potassium hydroxide mounts of epidermal crusts or sections, which need not be specially stained.

Treatment. There is no effective medical therapy for lobomycosis and where possible lesions are excised surgically.

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Rhinosporidiosis

Definition and aetiology. A chronic granulomatous mycosis caused by *Rhinosporidium seeberi*, inducing polyps of the mucous membrane. As the organism has never been isolated *in vitro*, its taxonomic position is not clear, nor can it be established that the organism is a fungus.

Rhinosporidiosis has occurred in many parts of the world on rare occasions, but is endemic in India and Sri Lanka [1]. In one review, 51 cases were described from Uganda [2]. Adult male workers are the persons most likely to be infected.

Histology. The histology is superficially like that of a nasal polyp but with conspicuous sharply defined globular cysts up to 0.5 mm in diameter. Occasionally, microabscesses may be found.

Clinical features. Vascular polyps, which may be pedunculated, occur on any mucosal surface [3]. The mucous membrane of the nose, the nasopharynx or the soft palate is involved in three-quarters of cases, and the conjunctiva or the lacrimal sac in a proportion of the others. Lesions are also found on other mucous membrane surfaces, such as the larynx, penis, vagina, rectum and sometimes also on the skin, where it is presumed to have spread from a primary site on the nearby mucous membrane [4]. They become hyperplastic and may reach an enormous size, extending from the nostrils to the pharynx or outwards over the lip [5]. The pink or red surface is lobulated and cauliflower-like. Close examination of the surface reveals small white spots, which represent mature sporangia of the fungus. The disease may last for many years. Spontaneous resolution has been observed rarely. It is not contagious. Obstruction to breathing is usually the chief complaint. On the genitalia, the lesions look like condylomas. If the eye is involved there is conjunctivitis and photophobia, and the weight of the polyps may cause eversion of the lid.

Differential diagnosis. Typical lesions are easily recognized by their pink–purple colour, friable consistency and the presence of the white sporangia within the polyp itself. Atypical lesions should be differentiated from warts, condylomas and haemorrhoids.

Laboratory diagnosis. The causative organisms cannot be cultured, and the diagnosis depends on histopathology —recognition of the sporangia seen on the surface of the polyp or in tissue sections. Depending on maturity, these may attain diameters of 0.5 mm, and can be readily seen by the naked eye as firm white cysts on or just below the surface. Microscopically, these are single, thick-walled and spherical, and when fully differentiated are packed with numerous rounded endospores, 6–7 μm in diameter. Immature and collapsed discharged sporangia are also present [6].

Treatment. Surgical removal resulting in complete eradication of the disease is the treatment of choice.

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Subcutaneous zygomycosis

SYN. BASIDIOBOLOMYCOSIS; SUBCUTANEOUS PHYCOMYCOSIS; CONIDIOBOLOMYCOSIS; RHINOENTOMOPHTHOROMYCOSIS

Definition. A localized subcutaneous and predominantly tropical mycosis characterized by chronic, woody swelling of subcutaneous tissue.

Aetiology. Subcutaneous zygomycosis caused by *Basidiobolus ranarum* was initially described in Indonesia [1,2], but cases have since been reported in Africa and South-East Asian countries. Subcutaneous zygomycosis caused by *Conidiobolus coronatus* (rhinoentomophthoromycosis) is another localized zygomycotic infection affecting animals and humans [3]. Reported from the West Indies, Africa, India and South America, infection may result in gross but non-painful facial swelling originating from the nasal mucosae or sinuses. In their natural environment, both fungi are associated with decaying vegetation and the gastrointestinal tracts of frogs.

Histology. The lesion is an eosinophilic granuloma lying deep in the subcutaneous tissue and largely replacing fat. Wide, sparsely septate hyphae, branching at right angles, are scattered throughout the granuloma [4,5] (Fig. 31.56) and there is often dense fibrosis.

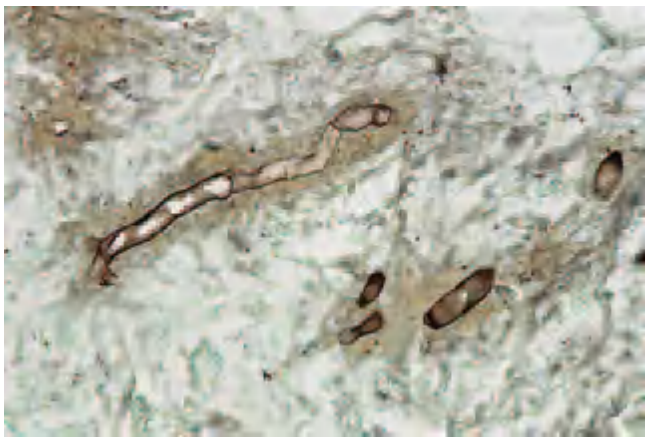

Fig. 31.56 Subcutaneous zygomycosis: tissue section. Wide, aseptate hyphae stained black with Grocott methenamine silver (GMS) are characteristic of infection by a zygomycete. (Courtesy of the Department of Medical Mycology, King's College London, St John's Institute of Dermatology, London, UK.)

Clinical features. There is a slowly spreading, painless subcutaneous swelling without other obvious clinical signs [6–8]. It may be single, or there may be multiple satellite lesions. The disc-shaped masses have a uniform hard consistency [9], and they do not pit.

The smooth rounded edge, which may be lobulated, can be raised up by inserting the fingers underneath it. Pain and tenderness may be absent or, less often, pronounced. The overlying skin may be tense, oedematous, desquamating, hyperpigmented or normal. Ulceration does not occur, and the regional lymph glands are not often enlarged [10].

In *Basidiobolus* infections, the lesion usually involves the limbs or limb-girdle areas and the infection is most often seen in children. The clinical features of *Conidiobolus* infections (rhinoentomophthoromycosis) are similar but affect the face, apparently spreading from the region of the inferior turbinates to involve the central facial tissues. It is mainly seen in young adults. Both subcutaneous infections are very disfiguring.

Differential diagnosis. Histological and mycological examinations are required for accurate diagnosis, but lymphatic oedema, which lacks the distinctive edge, subcutaneous malignant lymphoma, which grows more rapidly, and induration round an infection site, where there is pain and tenderness, have to be considered [11].

Laboratory diagnosis. The diagnosis is usually established histologically by biopsy, but culture is not difficult.

Basidiobolus ranarum. Colony: on cycloheximide-free media at 30°C, *B. ranarum* grows very rapidly as waxy cream or yellow colonies with many radial folds. Microscopy: the hyphae are broad, 8–20 µm in diameter and have few septa. After 10–14 days, sexual zygospores with a prominent beak may be produced. In addition, unicellular sporangia—sporangiola—are formed, which are forcibly ejected into the air from the tip of the sporangiophore.

Conidiobolus coronatus. Colony: the colonies are waxy white to grey, becoming more powdery and beige as a short aerial mycelium develops. Microscopy: wide, sparsely septate hyphae are present. Sporangiola are forcibly discharged, and impact on the sides and lid of the Petri dish. Some sporangiola may form small protuberances or villi all over their surfaces.

Treatment. Lesions usually respond to oral treatment with potassium iodides. These are given in similar doses to those used in sporotrichosis. There is some evidence that co-trimoxazole can be used in addition in conidiobolomycosis, and that itraconazole is also useful in this condition.

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Systemic mycoses

The systemic mycoses are fungal infections that involve deep structures, and that have the propensity to disseminate, usually via the bloodstream, from the original focus of infection. They include two main groups of disease: the endemic respiratory mycoses and the opportunistic systemic mycoses.

Infections caused by any of the respiratory mycoses usually follow inhalation of organisms. They therefore have a common mode of pathogenesis. In many cases, infections are asymptomatic and the primary infection

can only be detected in retrospect by a positive skin test, as in tuberculosis. These mycoses have defined endemic areas, which may have a characteristic climate or flora and fauna. The main endemic mycoses are histoplasmosis (classical and African types), blastomycosis, coccidioidomycosis, paracoccidioidomycosis and infection caused by *Penicillium marneffei*. The clinical manifestations of these infections are affected by the underlying state of the patient, and many of them develop in the presence of particular immunodeficiency states, notably AIDS. Cryptococcosis shares features of both respiratory mycoses and the second group, the opportunistic infections. However, as it can affect the healthy and is a primary respiratory infection caused by a fungus that occupies a specific ecological niche, it will be considered here with the respiratory infections.

The opportunistic systemic mycoses are those systemic infections that only occur in patients with some underlying predisposition. In contrast to the endemic mycoses, they may occur in any geographical area and their clinical manifestations are very variable, depending on the predisposition and mode of entry of the fungus.

Laboratory methods

The dimorphic fungi causing the respiratory mycoses are extremely hazardous to the laboratory worker, and must be handled in containment level 3 conditions. Laboratory infections and fatalities have been recorded. These organisms should never be cultured in Petri dishes, which pose too great a threat of aerosol dissemination. Cultures should be performed in capped bottles or tubes. The laboratory must be alerted to the possibility of a dimorphic pathogen when the specimen is submitted for examination.

Serological tests

Serological tests are of considerable value in the diagnosis of the systemic mycoses. In the endemic respiratory infections, immunodiffusion tests may demonstrate the presence of specific precipitin bands, for example, the H and M bands in histoplasmosis, and complement fixation tests are also routinely performed in suspected cases of histoplasmosis, coccidioidomycosis and paracoccidioidomycosis. The cross-reactivity of fungal antigens can be a problem, however, and this is true of antigens of *Blastomyces dermatitidis*, which cross-react with those of other dimorphic pathogens. In the opportunistic systemic mycoses, serology is also useful but may be more difficult to interpret. Many normal individuals will have detectable antibodies to *Candida* species, resulting from exposure in the environment, so that changes in titre have more significance than a single positive test. Additionally, many patients with opportunistic infections caused by *Candida* species or *Aspergillus* species will be unable to raise any antibody responses. For this reason, methods attempting the detection of antigen or fungal metabolites are currently of most interest, and are being developed in specialist laboratories. However, antigenaemia is transient and detection may require serial samples. These tests are not yet widely available. The situation is reversed in cryptococcosis, however, where the detection of antigen rather than antibody has proved to be virtually diagnostic, and commercial latex particle agglutination or enzyme-linked immunosorbent assay (ELISA) tests for cryptococcal antigen are routinely used.

Direct examination and histopathology

As with the subcutaneous infections, in some instances a simple wet mount of samples such as sputum or bronchoalveolar lavage fluid can show characteristic fungal structures. For example, observation of encapsulated yeasts in cerebrospinal fluid is diagnostic of cryptococcosis, and spherules of *C. immitis* may be detected in sputum. Histopathological investigations may allow the recognition of all the dimorphic mycoses, zygomycetes and *Cryptococcus*, but cannot distinguish some of the rarer pathogens such as *Fusarium* species and *Scedosporium apiospermum* reliably from *Aspergillus*.

Culture and identification of isolates

Suitable media are similar to those described for the subcutaneous fungi. Incubation should be performed at around 30°C and also at 37°C if sufficient material is available. Many of the opportunistic pathogens will grow in a few days, but some of the dimorphic fungi grow relatively slowly, and cultures should be held for a minimum of 4–6 weeks.

Isolation of any of the dimorphic pathogens is always considered significant. The identification of the five major dimorphic agents may, however, be complicated by the fact that in some cases they can be morphologically atypical or sterile. Exoantigen tests and nucleic acid probes for specific identification of these pathogens have now been developed. These techniques involve less handling of these pathogens and are far quicker than the traditionally used methods for converting the organisms to their parasitic phase *in vitro*.

The situation is rather different with the opportunistic infections, where the pathogens are widespread in the environment. The isolation of a few colonies of *Aspergillus* from a non-sterile site such as sputum may be difficult to interpret. However, the isolation of an opportunistic pathogen from a normally sterile site should always be taken seriously. The use of molecular diagnostic methods is beginning to increase, although all are still only available in specialist laboratories.

Histoplasmosis

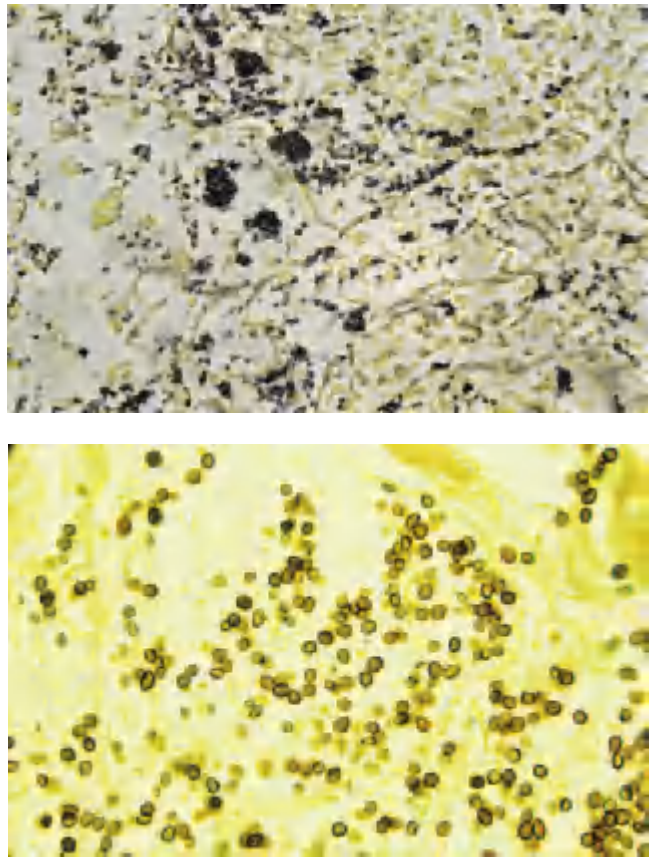
SYN. DARLING'S DISEASE; HISTOPLASMOSIS CAPSULATI

Definition. A highly infectious mycosis caused by *Histoplasma capsulatum* and affecting primarily the lungs, where it is generally asymptomatic. The fungus is intracellular, parasitizing the reticuloendothelial system and involving the spleen, liver, kidney, central nervous system and other organs. Rarely, the disease may become chronic, progressive and fatal.

Aetiology. Histoplasmosis results from infection with the dimorphic fungus, *H. capsulatum* var. *capsulatum*, or the closely related *H. capsulatum* var. *duboisii*. The two varieties differ in that in yeast phase they have different sizes, the *capsulatum* variety producing cells from 2 to 5 µm in diameter, the *duboisii* form 10–15 µm. The other important differences are in their epidemiology and clinical manifestations (see below). They show some subtle antigenic differences but their mycelial phases are identical.

The disease caused by *H. capsulatum* var. *capsulatum*, referred to here as histoplasmosis (small-form histoplasmosis), is widely distributed throughout the world, occurring in some 60 temperate and tropical countries in the Americas, Africa and Australasia [1]. It has been widely studied in the USA, where the number of human infections has been estimated at 30 million. It is highly endemic in the Mississippi and the Ohio valleys of the USA. In certain areas, more than 80% of the population are known to have acquired the infection, as revealed by cutaneous reactivity to histoplasmin [2]. Infections with the *duboisii* form, known as African histoplasmosis or large-form histoplasmosis, have been reported only from Africa. Infants and children are frequently infected, and among adults the rate is highest in male agricultural workers.

H. capsulatum exists as a saprophyte in nature, and has often been isolated from soil, particularly when contaminated with chicken feathers or droppings. Other birds, such as starlings, and bats have also been implicated in the establishment of saprophytic reservoirs of infection. The fungus has been demonstrated in the soil of caves inhabited by bats, and in endemic areas histoplasmosis is recognized as a hazard to speleologists. *H. capsulatum* var. *capsulatum* has been isolated from the organs and faeces of house-dwellings bats in Panama. Its spores are infectious not only to humans, but also to small animals such as dogs, cats and rats. The disease is not transmitted from human to human or from animal to human, but by the inhalation of air-borne conidia. Epidemics have occurred from time to time among people exposed to spore-charged atmospheres when exploring caves or cleaning out sites rich in the excrement of birds. Infection may follow introduction of spores through skin and mucous membranes, as in laboratory workers. Lymphoma appears to favour the development of the infection [3]. In addition, histoplasmosis is an important complicating infection in patients with AIDS [4,5].


(a)

(b)

Fig. 31.57 Histoplasmosis var. *capsulatum*. (a) Tissue section. The tiny yeasts, stained black with GMS are largely intracellular. (b) Oil immersion. The typical budding yeasts are clearly visible. Compare with *Penicillium marneffei* infection, Fig. 31.62. (Courtesy of the Department of Medical Mycology, King's College London, St John's Institute of Dermatology, London, UK.)

A sexual state (*Ajellomyces capsulatus*) has been described [6].

Histology. *Histoplasma* is predominantly an intracellular parasite, growing within the cells of the reticuloendothelial system as an oval yeast (Fig. 31.57). All phagocytic cells of the reticuloendothelial system are involved, including those in the liver, spleen, lymph nodes and bone marrow, so that the cytoplasm is swollen with masses of fungal cells. There is at first little tissue reaction; later, necrosis takes place to be followed by granulomatous changes and fibrosis. *H. duboisii* is usually distinctive in having a much larger tissue form, and it often elicits an inflammatory response in which giant cells predominate.

Clinical features [1]. Benign forms of the disease, which heal by calcification, are indistinguishable on X-ray from

tuberculosis. The spectrum of disease includes asymptomatic as well as symptomatic and benign infections, and the progressive disseminated variety with blood spread to all organs. Primary coin lesions have been demonstrated as well as areas of cavitation. All varieties are reminiscent of tuberculosis.

Skin lesions are more common with *H. duboisii* than with *H. capsulatum*. Indeed, whereas the skin is rarely affected in histoplasmosis, it is often involved in African histoplasmosis.

Although primary inoculation can rarely produce a local granuloma or ulcer, most skin lesions in histoplasmosis arise following dissemination from the primary pulmonary focus. Papules, ulcers, nodules, granulomas, abscesses, fistulae, scars and pigmentary changes may be seen, and there may be secondary involvement of the skin with osteomyelitis [3]. Involvement of the skin in some immunosuppressed patients may produce a condition resembling cellulitis [7].

Asymptomatic forms of histoplasmosis, indicated by the presence of positive skin-test reactivity without evidence of infection, are common in endemic areas [3]. It is likely that this form of exposure is the dominant pattern, unless other factors such as a massive inoculum (exposure in a bat-infested cave) or defective host defence are present.

The four main clinical varieties of histoplasmosis are acute pulmonary, acute disseminated, and chronic disseminated and pulmonary forms.

Acute pulmonary histoplasmosis. The patient has the usual symptoms of acute infection of the lungs, and X-ray examination of the chest reveals diffuse mottling or localized infiltration. However, this acute pulmonary form must be considered uncommon, as a great majority of people in endemic areas who have shown reactions to histoplasmin testing and are assumed to have acquired their infection by the pulmonary route have done so without developing recognizable signs and symptoms. Even in such cases, the organism is not limited to the lungs but is disseminated throughout all parts of the reticuloendothelial system. Associated erythema multiforme or erythema nodosum have been observed. This skin reaction occurs very early in the disease, but the association with histoplasmosis may not be apparent for several weeks.

Acute disseminated form. In this uncommon type, the lungs may be consolidated as a result of inhalation of many spores of *Histoplasma* and, although the pulmonary signs are prominent, there are also enlargement of the liver and spleen, fever, anaemia, loss of appetite and generalized enlargement of lymph glands. In such circumstances, any of the manifestations listed may be prominent, and the clinical features can be infinitely variable. Pulmonary manifestations may simulate miliary tuberculosis. Indurated granulomatous ulcers of the mouth, nose and larynx are often present and are distinctive [8]. Progressive emaciation, induced by gastrointestinal involvement, contributes to a fatal outcome after a course of weeks or months. Cutaneous or mucocutaneous granulomas are often seen in association with disseminated disease [9,10]. This is the form seen in patients with AIDS [11]. In AIDS patients, multiple small skin nodules may develop, the skin being more often involved than in other patient groups [4,5]. Often, papules have central softening.

Chronic pulmonary histoplasmosis. This usually occurs in adults, and also closely resembles tuberculosis with pulmonary involvement.

Chronic disseminated forms. These may appear months or years after a patient has left an endemic area. The most common clinical presenting features are oral ulceration and Addison's disease caused by adrenal infiltration. Mouth ulcers are large and may be chronic [8]; laryngeal involvement, ulceration or granuloma formation may also occur. Patients should be investigated for adrenal insufficiency, as this may appear for the first time during treatment. Ultrasound scans are useful for screening for adrenal enlargement [12].

Primary cutaneous histoplasmosis. This is very rare and appears after inoculation of the organism into the skin. The primary lesion is a nodule or indurated ulcer and there is often local lymphadenopathy [1].

Other forms of histoplasmosis. Other forms can be recognized. Dissemination may occur shortly after infection, or there may be a latent period of many years. Moreover, the severity of the condition may be influenced by various predisposing causes, including leukaemia, corticosteroid treatment, lymphoma, diabetes, carcinoma, AIDS and systemic collagen disease [11,13].

Diagnosis. The diagnosis of histoplasmosis is established by identifying the small intracellular yeast cells (2–5 μm) of *Histoplasma* in sputum, peripheral blood, bone marrow or in biopsy specimens. Lymph node aspiration may also be employed. Care should be taken in areas endemic for *Penicillium marneffei*, as the two organisms are of a similar size, although the latter shows characteristic septal formation rather than budding. The identity of the organism should be confirmed by culture. Some workers consider that cultures should be continued for up to 12 weeks before reporting negative results.

H. capsulatum. Colony: at 30°C the growth may initially be waxy, but surface mycelium usually develops to produce white or tan cottony colonies. Microscopy: two types of conidia are formed: large (8–15 μm), rounded or occasionally pear-shaped unicellular tuberculate macroconidia;

and small, oval, smooth or roughened microconidia. Physiological tests: ideally, cultural identification should be confirmed by demonstrating eluted *Histoplasma*-specific antigens, by using an exoantigen test or a nucleic acid hybridization test. However, if these techniques are not available, a suitable medium for conversion to the yeast phase is brain–heart infusion agar supplemented with 10% sheeps' blood, 1% glucose and 0.1% cysteine. Serological tests: the intradermal histoplasmin skin test is an epidemiological tool that is of no help in diagnosis because it is negative in many patients with disseminated histoplasmosis. A rising complement fixation titre indicates dissemination. Precipitins are also valuable because some antigens, designated H and M, correlate well with active or recent infection [14]. The histoplasmin skin test should not be performed before the serological test, as it may produce a rise in the serological titre. Several serological kits are now sold commercially for both complement fixation and double diffusion tests.

A significant development has been the use of a serological test for the detection of circulating *Histoplasma* antigens [15], which is particularly helpful in AIDS patients.

African histoplasmosis. The clinical appearances of African forms of histoplasmosis are variable, and the disease is sporadic and uncommon [16]. It is confined to the areas south of the Sahara and north of the Zambezi river. The most common sites clinically involved in African histoplasmosis are the skin and bone, although lymph nodes and other areas including the lungs may be affected [17]. Skin lesions range from small papules resembling molluscum contagiosum, to abscesses or ulcers [18]. It is useful to screen patients with a bone scan or X-rays to exclude bone foci of infection [19]. The course of the disease is usually chronic, although some patients appear to develop a more rapidly progressive disseminated type of infection. However, this form of histoplasmosis has only rarely been seen in AIDS patients. The diagnosis is confirmed by microscopy (direct or histopathology) and culture. Serology, using conventional tests, is often negative in African histoplasmosis.

Treatment. The choice of therapy for histoplasmosis has become considerably wider in recent years. For many disseminated or localized forms of the disease, oral itraconazole is highly effective [20], including the treatment of the disease in AIDS patients, where long-term suppressive therapy is usually needed. It appears that the use of HAART may reduce the requirement for maintenance therapy in some cases. Ketoconazole and fluconazole are alternatives [20]. Amphotericin B is useful and is used in those with widespread and severe infections, particularly where an intravenous drug is needed [3]. The acute pulmonary forms of histoplasmosis require no specific antifungal therapy.

In African histoplasmosis, there is some evidence that itraconazole or ketoconazole are effective. An alternative in severe cases is amphotericin B [18]. Some patients with solitary skin lesions may simply respond to excision without chemotherapy, although antifungals should be given where possible.

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Blastomycosis

SYN. NORTH AMERICAN BLASTOMYCOSIS; GILCHRIST'S DISEASE

Definition. A chronic granulomatous and suppurative mycosis caused by *Blastomyces dermatitidis*, affecting primarily the lungs but with disseminating forms affecting skin, bones, central nervous system and other sites.

Aetiology. The condition was originally thought to be restricted to the North American continent where it ex-

tends from Canada, particularly Quebec, through the USA with occasional cases in Mexico and Central America. The largest number of cases is seen in the Mississippi valley. Central Kentucky is an endemic area [1]. Blastomycosis, however, is now known to be widely distributed in Africa, with the largest numbers of cases coming from Zimbabwe [2,3], and cases have been reported from the Middle East [4], India [5] and Poland.

B. dermatitidis has only rarely been isolated from the environment. Studies suggest that its natural substrate may be wood debris or soil close to rivers or subject to flooding [6,7]. The fungus can grow in sterile soil in the laboratory, and it is believed that humans are infected by the inhalation of spores from a saprophytic source. However, primary skin infection also occurs, particularly in laboratory workers or pathologists. The incidence of infections tends to be highest in rural areas [1] and in agricultural workers. Human–human transmission does not normally take place. As with most of the systemic mycoses, adult males are most commonly affected, the majority being between the ages of 30 and 50 years. Indeed, some 86% of recorded cases are males. The fungus has also been recovered from domestic animals (e.g. the dog).

Histology. *B. dermatitidis* produces budding yeasts with a characteristic broad base to the bud in the tissues. The tissue reaction, and ultimately the course and prognosis, are determined by the immunological response of the patient. Primary lesions, usually pulmonary, sometimes cutaneous, develop 1–3 weeks after infection and are associated with regional lymphadenopathy. The skin lesions that follow bloodstream dissemination show marked epidermal hyperplasia, which may be pseudoepitheliomatous in degree. Intra- and subepidermal polymorphonuclear abscesses and a granulomatous infiltrate are found in the dermis. These include giant cells of Langhans' type, which contain the round or oval organisms with thick refractile walls. Disseminated skin lesions may also take the form of abscesses with organisms in their walls or within giant cells, and a non-specific granulomatous infiltrate.

Clinical features [8]. There are three forms of blastomycosis: primary cutaneous, pulmonary and disseminated.

Primary cutaneous blastomycosis. This is very rare and follows trauma to the skin and the introduction of fungus. The condition has been seen mainly in laboratory workers (e.g. pathologists carrying out necropsy examinations) [9]. After inoculation, an erythematous indurated area with a chancre appears in 1–2 weeks with associated lymphangitis and lymphadenopathy. There may be some constitutional reaction. There is a strong tendency towards spontaneous recovery.

Fig. 31.58 Cutaneous blastomycosis. (Courtesy of Dr M. James, Royal Berkshire Hospital, Reading, UK.)

Pulmonary blastomycosis. This is very similar to pulmonary tuberculosis. There may be no symptoms, or there may be low-grade fever, chest pain, cough and haemoptysis. Occasionally, erythema nodosum develops [8]. The pulmonary lesion may resolve, or there may be cavity formation with lung abscess. In most cases, other organs are also affected [10]. The disease, if untreated, may frequently disseminate and often progresses to death. Mild asymptomatic self-limiting infections, common in histoplasmosis and coccidioidomycosis, may occur [11], but are probably uncommon.

Disseminated blastomycosis. When the infection spreads from the chest, lesions develop in many organs, commonly the skin, bones and central nervous system [12]. Mucous membranes are rarely involved. One or many skin lesions may be present [13]. These are often symmetrical and usually on the trunk rather than on the exposed parts. Each consists of a papule or nodule that may ulcerate and discharge pus. The lesions enlarge at the periphery, and tend to show central scarring, which may be dense. Eventually, after a relentless progress for months, the lesion is serpiginous in outline, the borders are raised and warty (Fig. 31.58) and have a violaceous margin studded with miliary abscesses containing the organisms [8].

Other patients may present with nodules and abscesses. African patients with blastomycosis have a higher frequency of skin and bone involvement [2].

Differential diagnosis. The microabscesses are the distinctive clinical feature, but the chronic granulomas of the skin must be differentiated from tuberculosis, syphilis, leprosy, pyoderma gangrenosum and drug reactions resulting from bromides and iodides. Pulmonary lesions, which are invariably present, necessitate X-ray examinations of the chest and differentiation from tuberculosis

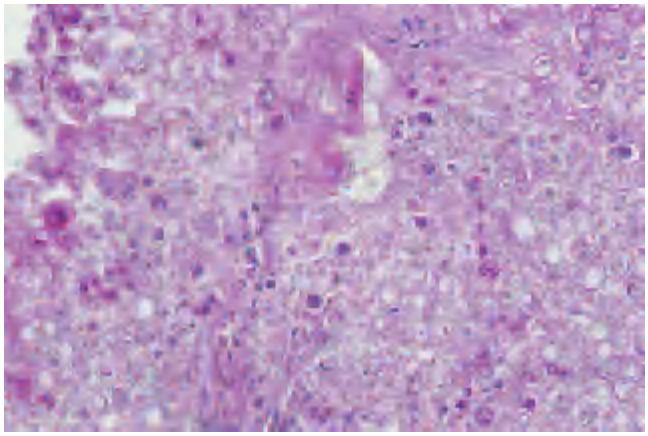

Fig. 31.59 North American blastomycosis tissue section. The large yeasts, stained pink with PAS, are characterized by the broad base of the buds. (Courtesy of the Department of Medical Mycology, King's College London, St John's Institute of Dermatology, London, UK.)

and other infections, and from neoplasia. The diagnosis of the skin lesions is established by direct microscopy of pus in 10% potassium hydroxide and confirmed by culture or biopsy.

Laboratory diagnosis. The fungus can be observed in potassium hydroxide mounts of pus or scrapings as rather thick-walled, rounded, refractile, spherical yeasts with broad-based buds. In tissue, sections must be scanned carefully to identify organisms with the characteristic broad bud (Fig. 31.59).

B. dermatitidis. Colony: in culture at 30°C, mycelium is developed, the colonies being initially waxy, then cottony and white to tan. Microscopy: small, rounded or pear-shaped conidia (2–5 µm) are produced on short stalks arising at right angles from the hyphae. Physiological tests: exoantigen tests or nucleic acid probes are available for safe and rapid identification of the organism. Alternatively, conversion to the yeast phase can be achieved on blood–glucose–cysteine agar. Serological tests: precipitating antibodies to *B. dermatitidis* are often present in the serum of infected subjects and a characteristic precipitin line, the E band, has been described in a high proportion of established cases [8].

Treatment. Amphotericin B is still widely used for the treatment of widespread disseminated forms of blastomycosis [8]. However, in most cases, itraconazole appears to be effective and has the advantage that it can be given orally [14]. The best regimen is not clear, but at least 400 mg should be given initially. Ketoconazole is an alternative therapy [15].

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Coccidioidomycosis

SYN. COCCIDIOIDAL GRANULOMA; VALLEY FEVER; SAN JOAQUIN VALLEY FEVER; DESERT RHEUMATISM

Definition. A (primary) respiratory fungal infection caused by *Coccidioides immitis*, which may become progressive and disseminated, with severe or fatal forms.

Aetiology [1]. Coccidioidomycosis, caused by *C. immitis*, is endemic in desert areas of the south-western states of the USA, and in parts of Central and South America [2]. Cases described outside this area are imported infections. The climate in endemic areas is characterized by high mean January and July temperatures and an annual rainfall of 12–50 cm. There is clear evidence that human infection may develop from very short residence in, or even a journey through, an endemic area, so that with increasing travel, cases of coccidioidomycosis are found in many parts of the world. Skin tests have shown that the incidence in endemic areas may be as high as 95%. It is a widespread and important disease only within these regions, affecting individuals of all ages. The fungus is a soil inhabitant; infection of humans and a wide variety of domestic and wild animals is acquired by inhalation of fungus-laden dust particles. The control of dust therefore

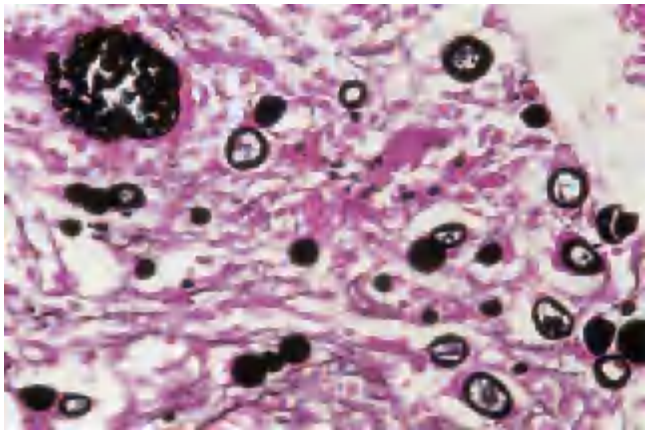

Fig. 31.60 Coccidioidomycosis tissue section. Spherules of various sizes are stained black with GMS. In the top left-hand part of the slide, freshly released endospores are visible. (Courtesy of the Department of Medical Mycology, King's College London, St John's Institute of Dermatology, London, UK.)

becomes important in prevention of the disease [3]. Primary infection of the skin is rare but is known to occur [4].

Histology. The inhaled spores (arthroconidia of the saprophytic mycelial phase) develop in the lung tissue to form spherules—large, round, endospore-containing structures, which when mature are usually 30–80 µm in diameter (Fig. 31.60). Between 2 and 6 weeks after exposure, the patient becomes sensitive to an intradermal skin test using the fungal antigen, coccidioidin. The primary lesion is associated with regional lymphadenopathy, but usually there is no further spread. If secondary dissemination occurs, granulomatous lesions with giant cells and epithelioid cells are produced. Usually in active lesions, spherules with endospores can be demonstrated with routine staining, but in lesions with immature, empty or degenerate fungal spherules this may be difficult or impossible. Spherules may be seen within the cytoplasm of histiocytes and in giant cells of the foreign-body type. The fungus can be easily demonstrated by the use of special fungus stains such as PAS or silver impregnation stains.

Clinical features [1]. The severity of coccidioidomycosis varies from a very mild, inapparent, upper respiratory tract infection to an acute, disseminated fatal disease. The primary pulmonary form, which is the most common form, is sometimes asymptomatic, but may simulate influenza or, occasionally, pulmonary tuberculosis. Erythema multiforme or erythema nodosum occurs from the third to the seventh week in some 3–25% of patients, particularly in females. In endemic areas, coccidioidomycosis is often the most common cause of erythema nodosum. There may be accompanying uveitis and arthralgia.

Pulmonary symptoms, when present, include pain resembling pleurisy, and often very sudden and acute shortness of breath, cough and associated pyrexia. Generalized aches, malaise and lassitude may occur, and there may be severe headache. An early generalized macular erythematous rash is seen in 10% of patients. The exceedingly rare primary skin lesions are painless, firm, indurated nodules often occurring 1–3 weeks after some form of local trauma. Regional lymphadenopathy develops but spontaneous healing follows after a few weeks [5].

Disseminated coccidioidomycosis is very uncommon and develops in fewer than 0.5% of infected individuals, usually in black, Filipino or immunosuppressed patients [6]. It may develop rapidly by blood spread of endospores to all organs, or insidiously from a pulmonary lesion after a period of quiescence. The death rate in acute disseminated disease, or with meningitis, is very high [7]. Disseminated lesions may occur in the skin, subcutaneous tissues, bones, joints and all organs. The skin lesions may appear as abscesses, granulomas, ulcers or discharging sinuses, particularly if there is underlying bone or joint disease [4].

Persistent and progressive pulmonary involvement and dissemination of infection are seen, including the appearance of multiple skin lesions in patients with AIDS [8]. Prolonged and progressive pulmonary infection may also occur in AIDS patients.

Differential diagnosis. The clinical manifestations of the disease are so varied that the condition must be differentiated from most chronic infectious conditions. Residence in, or travel through an endemic area might suggest the diagnosis.

Prognosis. The prognosis for the primary form is excellent; for the acute disseminated forms it is very poor indeed, with all stages in between.

Laboratory diagnosis. The large (usually 30–80 µm, exceptionally larger) globular spherules may be seen in potassium hydroxide mounts of sputum, cerebrospinal fluid or pus. Confirmation depends on the isolation of the fungus in culture.

C. immitis. Colony: cultures of *C. immitis* are mycelial, fast-growing, initially waxy then cottony and white to tan [9]. Microscopy: characteristic thick-walled arthroconidia separated from each other by alternate empty cells are observed. Physiological tests: exoantigen testing and nucleic acid probes are available for identification. If necessary, conversion can be achieved using modified Converse medium [10]. Serological tests: these are of value in diagnosis and prognosis of the disease. Thus, precipitins develop in some 90% of infected individuals within 2–4 weeks, but are short lived; complement fixing

(CF) antibodies are characteristic of more severe infections and increase to a maximum after 6 months. A rise of CF antibodies indicates dissemination while a decrease parallels clinical improvement.

Skin tests with coccidioidin are of little value in diagnosing infections. Positive reactions are of no diagnostic value in individuals from endemic areas, but may be helpful in subjects whose visits have been recent and brief [2]. Patients with coccidioidomycosis may cross-react to histoplasmin, but responses are usually much milder, and seldom cause confusion with the specific reaction to coccidioidin. Spherulin, derived from the tissue form of *C. immitis*, is reported to be superior to coccidioidin in detecting cutaneous hypersensitivity in both epidemiological and clinical settings [11]. In severe infections, cutaneous anergy is common [12].

Treatment. In the primary pulmonary infection, no specific therapy apart from rest is necessary. There is little evidence that the use of an oral azole, such as itraconazole, in patients with erythema nodosum is helpful in reducing symptoms, and it may aggravate the situation. For disseminated disease, the approach depends on the form of disease. Intravenous amphotericin B is used for many of the clinical forms of coccidioidomycosis [13], but alternatives are now becoming available. Oral ketoconazole, fluconazole and itraconazole [5] are effective in some forms of localized infection such as solitary disseminated skin lesions. Itraconazole may be effective in other disseminated forms of disease [14]. The most difficult to treat at present are meningitis and joint infections. Neither of these responds well even to newer therapies, although temporary improvements may be achieved. The use of lipid-associated amphotericin B preparations in coccidioidomycosis has not been widely assessed at present.

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Paracoccidioidomycosis

SYN. SOUTH AMERICAN BLASTOMYCOSIS; PARACOCCIDIOIDAL GRANULOMA

Definition. A chronic granulomatous fungal infection caused by *Paracoccidioides brasiliensis*, affecting the skin, mucous membranes, lymph nodes and internal organs [1].

Aetiology. Paracoccidioidomycosis has been reported from most Latin American countries, but the infection is most commonly found in Brazil, particularly in the state of Sao Paulo [2], Colombia and Argentina. The infection is not known in other continents. Adult males between the ages of 20 and 50 years are most frequently infected, although exposure rates are equal across the two sexes [3]. It is thought that the fungus occurs as a saprophyte on vegetation or in soil [4]. The disease is not transmitted directly from person to person. The condition is much more frequent in rural areas.

P. brasiliensis is likely to gain entry to the body after inhalation via the respiratory tract, as with the other dimorphic fungal infections. Susceptibility to *P. brasiliensis* may be related to HLA-A9. This antigen has been found more frequently in progressive pulmonary forms of the disease than in patients with extrapulmonary involvement. The inhibition of the yeast phase, the form seen in human infections, is at least partially dependent on the binding of oestrogen by the fungus, which may account for the marked sex difference in susceptibility.

Histology [5]. The reaction resembles that seen in blastomycosis, namely granulomas with pyogenic inflammation; giant cells are conspicuous and these frequently contain the rounded budding cells. Exceptionally, these may attain diameters of 60 μm. The tendency to produce many multilateral buds in tissue sections is diagnostic (Fig. 31.61). In the skin and mucous membranes, there is pseudoepitheliomatous hyperplasia with severe granulomatous inflammation; intraepithelial abscesses occur and these frequently communicate with the surface.

Clinical features. The most common site of infection is the lung (pulmonary form), although skin and mucous membranes (mucocutaneous form) or lymph nodes (lymphatic form) are also often involved. Many patients have a mixed type of infection with involvement of different

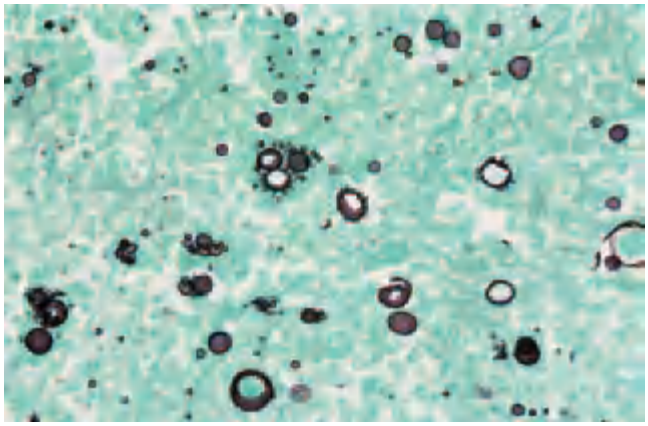

Fig. 31.61 Paracoccidioidomycosis. The yeasts, stained black with GMS, are characterized by the numerous peripheral buds produced. (Courtesy of the Department of Medical Mycology, King's College London, St John's Institute of Dermatology, London, UK.)

organ systems. In most patients, the disease is only slowly progressive.

Patients with pulmonary lesions present with weight loss and chronic cough. The lesions may be bilateral and nodular on X-ray, and there is often extensive fibrosis [6]. Mucocutaneous lesions may be present in patients with lung disease, or occur on their own. Oral or circumoral lesions are common in the mucocutaneous forms of paracoccidioidomycosis, although they may also occur in the nose, conjunctivae or anus. Lesions may be localized or diffuse. If in the mouth, a severe painful ulcerating stomatitis occurs. The ulcers become granulomatous and spread over the mucous membranes (the so-called 'mulberry-like erosion'). Lesions of the gums are common: they loosen the teeth, which are usually lost. The tongue may be involved. The skin lesions may begin at the mucocutaneous junction by direct extension from the mouth, or there may be satellite lesions from autoinoculation. Haematogenous or lymphatic spread results in subcutaneous abscesses. The cervical lymph nodes are sometimes enlarged early. They are palpable, painful, adherent to the overlying skin and may eventually suppurate with chronic sinus formation. If systemic spread occurs, the spleen, intestines, lungs and liver are involved; it is said that the intestines are often affected, with lesions eroding into the lumen [7]. Bone lesions have been seen and the adrenals may be destroyed. The central nervous system may also be affected [1]. Untreated, the disease was fatal in a few months to a few years in 43% of proved cases [6,7]. The extensive painful mouth lesions with loss of teeth interfere with feeding, and the patient becomes cachectic. Paracoccidioidomycosis is uncommon in AIDS patients, and widespread infections may develop in young adults or older children without recognizable predisposition.

Differential diagnosis. The frequency with which the mouth and gums are involved with loss of teeth, the fact that there is no central scar formation, and the presence of marked lymphadenitis and lymphadenopathy differentiates paracoccidioidomycosis from blastomycosis. Other conditions to be considered are tuberculosis, syphilis, histoplasmosis, actinomycosis, sporotrichosis, rhinoscleroma and leishmaniasis. The organisms are readily found in biopsy specimens or in scrapings from the mucous membrane lesions. Aspiration of pus from lymph nodes will also provide material for microscopic examination and culture.

Laboratory diagnosis. Pus, exudates and scrapings examined in potassium hydroxide mounts may show rounded refractile cells, which can be distinguished from *Blastomyces dermatitidis* when the characteristic multiple budding is seen. Yeasts range from 2 to 30 μm in diameter.

P. brasiliensis. Colony: growth is much slower and more restricted than that of *B. dermatitidis*. Initially flat or wrinkled and leathery, the colonies develop tufts of white to tan aerial mycelium. Microscopy: the hyaline unicellular pear-shaped conidia (3–4 μm) are borne directly on the hyphae or on short stalks. Very few conidia are produced. Physiological tests: an exoantigen test is available to identify the isolates; alternatively, conversion can be achieved on brain–heart infusion agar supplemented with 10% sheeps' blood. Serological tests: both complement fixation and immunodiffusion assays are useful in the diagnosis of this condition. A new antigen detection test is useful in monitoring therapy [8].

Treatment. The treatment of choice in most cases is itraconazole, which can produce remissions in 3–6 months [9]. Ketoconazole is an alternative [10]. Relapse is common, and long-term surveillance should be carried out. Some patients, particularly those with more rapidly progressive and extensive infections, may require amphotericin B [1].

Paracoccidioidomycosis is often associated with severe fibrosis, and in oropharyngeal lesions contractures or laryngeal strictures can occur during or after therapy.

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Infections caused by *Penicillium marneffei*

SYN. PENICILLIOSIS

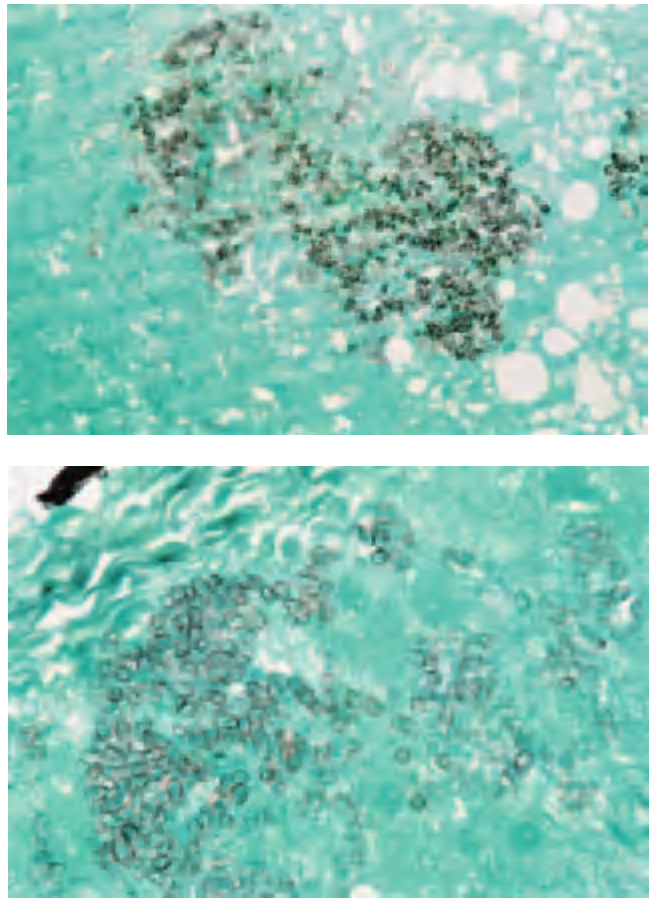
Definition. *Penicillium marneffei* is a recently recognized fungal pathogen that causes a disseminated mycosis in both healthy and immunocompromised patients [1]. There is a strong association with AIDS.

Aetiology. Although the causative organism is thought to originate from soil, it has not been isolated from this source. *P. marneffei* infections in humans are confined to South-East Asia, particularly Thailand, South China and Vietnam [2,3]. However, there are reports in other Asian countries, and imported cases have been seen in Europe and the USA [4]. Natural infections occur in bamboo rats, which are large, underground-dwelling rodents. Infections can occur in apparently healthy individuals, but it is a particular problem in severely immunocompromised patients in the endemic area.

Clinical features. It is not known if there is a subclinical form of *Penicillium* infection (cf. histoplasmosis). However, patients may present with respiratory symptoms, such as cough, chest pain and fever, or with signs of dissemination such as anaemia, multiple skin papules and hepatosplenomegaly. Skin lesions occur in over 50% of cases. They are small papules, ulcers or molluscum-like lesions. They are usually widely scattered on the face and trunk. *P. marneffei* infections are also seen in travellers to the endemic area. Left untreated, this infection is fatal.

Differential diagnosis. The main differential is with other disseminated mycoses, such as histoplasmosis and cryptococcosis, which can also be found in the endemic area in AIDS patients. Biopsy and, where necessary, culture will distinguish between the different causes.

Diagnosis. *Penicillium marneffei* forms characteristic cells which are divided by a septum in tissue (Fig. 31.62). It does not produce buds. However, most cells in biopsy material are small oval structures similar in size to *Histoplasma capsulatum*. Occasionally, larger banana-shaped cells are seen. The diagnosis can be made from appropriately stained biopsies, smears and blood films, although with experience the typical cells can be distinguished on simple stains such as leishmanin.


(a)

(b)

Fig. 31.62 Infection by *Penicillium marneffei*. (a) Tissue section. The tiny organisms are largely intracellular and look very similar to histoplasmosis at this magnification. (b) Oil immersion. The organisms divide by a central septum, rather than by budding. Sausage-shaped cells are also clearly visible. (Courtesy of the Department of Medical Mycology, King's College London, St John's Institute of Dermatology, London, UK.)

P. marneffei. Colony: in culture, *P. marneffei* grows rapidly on glucose–peptone agar as a green or greyish mould. It produces a diffusible red pigment. Microscopy: typical *Penicillium* conidiophores and phialoconidia are produced. Physiological tests: on glucose–peptone agar after incubation for 14 days at 37°C, the organism produces dry yeast-like colonies. The cells are oval to elliptical and reproduce by fission. Serological tests such as western blot are still only available in specialized centres.

Treatment. In severe cases, amphotericin B is necessary. However, there is usually a good response to itraconazole 200–400 mg/day, but this may have to be given for a long period to prevent relapse.

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Cryptococcosis

Definition. An acute, subacute or chronic infection caused by the encapsulated yeast *Cryptococcus neoformans*. There is a marked predilection for the brain and meninges, although the lungs and occasionally the skin and other parts of the body may be involved.

Aetiology. Cryptococcosis, unlike many other systemic mycoses, occurs throughout the world [1]. The condition is not excessively rare, and the diagnosis is frequently unsuspected. It is particularly associated with AIDS and is now seen regularly in these patients. Cryptococcosis is caused by a single species of fungus *C. neoformans*, which comprises two variants: *C. neoformans* var. *neoformans* and *C. neoformans* var. *gattii*. These correspond to cryptococcal serotypes known as A, D, AD and B and C, respectively [2]. Interest has been stimulated by the observation that in Europe and much of the USA the *neoformans* variety was dominant, whereas in much of the tropics including Africa the *gattii* form was more common [3]. With the spread of HIV infection, the *neoformans* variety is overwhelmingly found in AIDS patients. The *neoformans* variety exists as a saprophyte in nature, being particularly abundant in soils enriched with pigeon droppings. By contrast, the *gattii* variant has been isolated from leaf and bark debris from red gum trees. Under certain conditions sexual stages are formed. These have been named *Filobasidiella neoformans* and *Filobasidiella bacillispora*, corresponding to the *neoformans* and *gattii* varieties, respectively. Unusual among pathogenic fungi, the sexual stage is a basidiomycete. It is not known if spores produced by the sexual phase (basidiospores) constitute infectious propagules. Studies *in vitro* have shown that yeast cells of *C. neoformans* are susceptible to soil microorganisms, including bacteria and amoebae.

Animal–human, or human–human transmission of the disease has not been reported. Bird droppings act as an excellent culture medium, and probably play an important part in promoting multiplication of the fungus in contaminated soil and the provision of a significant reservoir of infection in the case of var. *neoformans*. The inhalation of small yeast forms which have been aerosolized is likely to be the main route of infection. It is assumed that var. *gattii* infections follow a similar route of infection, although the exact mode of pathogenesis is still not known.

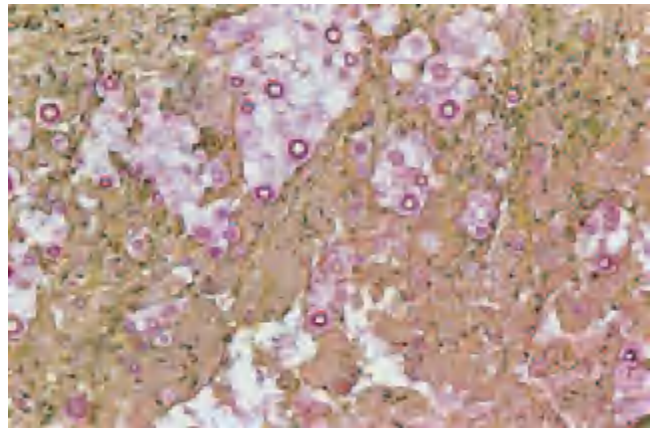

Fig. 31.63 Cryptococcosis tissue section. The mucicarmine stains the capsule specifically. The radiate spiny appearance is caused by shrinkage during processing. (Courtesy of the Department of Medical Mycology, King's College London, St John's Institute of Dermatology, London, UK.)

The disease usually occurs between the ages of 30 and 60 years, and is uncommon in childhood. Susceptibility is greatly increased by immunodeficiency states and neoplastic diseases, especially Hodgkin's disease. Recognizable predispositions include AIDS, malignant lymphomas, sarcoidosis, collagen disease, carcinoma and systemic corticosteroid therapy [4]. Cryptococcosis has also been associated with immunosuppression in patients following renal transplantation. However, the main underlying disease is AIDS [5]. The incidence of cryptococcosis in patients with established AIDS varies in different countries from 3–5% in the USA to 4% in the UK and over 12% in parts of Africa (e.g. Zaire) and of Thailand. This has resulted in an increase in the numbers of patients presenting with cryptococcal infection in many countries.

The respiratory tract is the usual portal of entry, but primary cutaneous lesions may occur. *C. neoformans* is unusual among pathogenic fungi in its predilection for invasion of the central nervous system. Strains of serotype D are more likely to be found in skin lesions which occur in 10–15% of cases of disseminated cryptococcosis.

Histology. There may be minimal inflammatory reaction. The characteristic lesion consists of encapsulated budding cells mixed with a network of connective tissue, which enlarges and compresses the surrounding tissues [6]. A specific stain for the capsule—mucicarmine—is available (Fig. 31.63). Alternatively, a granulomatous reaction without caseation may be seen [7]. These clusters of cells are

seen in most tissues of the body, but particularly in the central nervous system. In rare instances, cryptococci may proliferate in infected tissues in a non-encapsulated form. An acute inflammatory or granulomatous reaction is then seen, with overall resemblances to blastomycosis or histoplasmosis.

Clinical features [7]. Systemic involvement is usual, and the central nervous system manifestations often predominate, presenting as a chronic meningitis or as focal brain lesions simulating a tumour. There is low-grade fever and general decline in health, ending in coma and death, usually within a year but sometimes after a fluctuating course with periods of remission over many years. Pulmonary or urinary tract cryptococcosis may occur without involvement of the central nervous system when the prognosis is believed to be favourable, as it is in the rare cutaneous forms. In the disseminated disease, cutaneous lesions may precede or follow the signs of involvement of the central nervous system and lungs. These cutaneous and mucous membrane lesions, which occur in about 10 and 3% of cases, respectively, are seldom pathognomonic [8–10]. Most frequent are firm or cystic, slow-growing, subcutaneous, erythema nodosum-like swellings. Acneiform papules or pustules are characteristic of widespread systemic infection. They often occur around the nose and mouth. Any of these lesions may ulcerate or ulcers may develop in primarily unaffected skin, when they are often punched out with a rather distinctive rolled edge, or are multiple and resemble molluscum contagiosum. Direct extension of infection to the skin from bony lesions may occur, and mucosal lesions have been reported.

Often, the term primary cutaneous cryptococcosis is used erroneously to describe a solitary lesion of *Cryptococcus* on the skin, as in many such cases there is evidence of systemic spread, implying that the skin lesion has developed after bloodstream spread from a primary lung focus [4]. Documented cases of primary cutaneous infection by inoculation are exceptional.

In AIDS patients, the manifestations of cryptococcosis are not greatly different to those seen in other groups. However, often the symptoms of meningitis are minimal and there is evidence of wide dissemination, such as positive blood cultures or multiple skin lesions [1,11]. The skin lesions are often papules with central softening.

Differential diagnosis. Cryptococci may be recognized in smears of pus and of cerebrospinal fluid. When there is cutaneous involvement, cryptococci may be seen readily in and cultured from biopsy material. Their identity should be confirmed by culture. The diagnosis should particularly be considered when inflammatory nodules or ulcers develop in AIDS patients. However, similar lesions occur with other systemic mycoses, notably histoplasmosis and infections caused by *Penicillium marneffei*.

Laboratory diagnosis. The large (5–15 μm) budding cells with their characteristic capsules are best observed by direct microscopy of cerebrospinal fluid or pus in India ink or nigrosin mounts. Material suspected of containing *C. neoformans* should not be inoculated on to media containing cycloheximide, which inhibits growth. Incubation at 30°C for up to 4 weeks is sufficient.

C. neoformans. Colony: the growth is soft, cream to pale brown and usually mucoid. Isolation of *C. neoformans* is facilitated by its tendency to form brown colonies on media made selective by the addition of various melanin precursors (e.g. *Guizotia* seed or caffeic acid media). Microscopy: yeasts alone are formed; no filaments are produced. Physiological tests: identification is based on such cultural characteristics as the ability to grow at 37°C, urease production, phenoloxidase production, and ability to assimilate creatinine and various carbohydrates. As with the identification of *Candida* species, commercial kits are widely used to identify *Cryptococcus neoformans*. Serological tests: these are rapid, specific and useful, particularly in disseminated or central nervous system infections. Serodiagnosis is dependent on the detection of cryptococcal capsular antigen, using either a latex agglutination test or an ELISA assay. High titres are found in AIDS patients in serum and cerebrospinal fluid. However, non-AIDS patients with single, localized skin lesions are often antigen negative.

Treatment. The mainstay of treatment in the non-AIDS patient is intravenous amphotericin B combined with flucytosine [5]. This should be used in most cases, except in the occasional patient without serious underlying disease, who has focal infections, such as a skin lesion, and in whom there is no evidence of systemic spread, where fluconazole 400–600 mg/day may be used. In AIDS patients, the situation is more complicated as it is virtually impossible to induce complete remissions, necessitating maintenance therapy, although some patients on HAART appear to achieve remission [12]. The current strategy adopted by most units is to use amphotericin B with or without flucytosine for 7–14 days to induce remission, and this is followed by long-term oral maintenance with fluconazole 200–400 mg/day given as outpatient therapy. Itraconazole is an alternative for long-term therapy. The use of higher doses of fluconazole, triazoles combined with flucytosine or lipid-associated amphotericin B formulations as alternative initial treatments is being evaluated.

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Systemic candidosis

A general account of systemic candidosis is outside the scope of this text, but certain aspects do impinge upon the dermatologist, and are therefore considered [1,2].

In most cases of systemic candidosis, the causal organism originates in the patient's own gastrointestinal tract, and in patients with leukaemia or other serious illness a history of mucocutaneous candidiasis in the past is the indication for vigilance, and perhaps for prophylaxis with oral anti-*Candida* agents. Invasion by *Candida* along intravenous infusion lines is also important, and maceration or signs suggestive of cutaneous candidosis on adjacent skin should not be ignored. Drug addicts are particularly at risk.

Typical lesions start as macules, become papular or nodular, and may show a pale centre. Some are likely to be haemorrhagic and may break down to form ecthyma gangrenosum-like lesions. Subcorneal pustules are not a feature, but follicular invasion by *Candida* leading to pustules and nodules in the coarse hair-bearing areas of the scalp, beard, axilla and pubis may be characteristic of *Candida* septicaemia in heroin abusers [3]. Fever, diffuse muscle tenderness and an erythematous macular rash are regarded as an indication for prompt skin biopsy in any compromised patient. Histology of a skin lesion showing *Candida* cells in the dermis provides a rapid diagnosis, often before blood culture is positive. Unfortunately, only a minority of patients with *Candida* septicaemia manifest skin lesions, but when present they should not be ignored.

The treatment of systemic candidosis with intravenous amphotericin B or fluconazole drugs is beyond the scope of this volume. Satisfactory management may demand facilities for the measurement of blood levels of some of these agents (e.g. flucytosine) and a careful watch should be kept on renal function. With flucytosine or fluconazole, isolates of the *Candida* strain should be tested for sensitivity if the patient fails to respond. Wherever possible, the predisposing pathology should be treated, and where immunosuppression has been used this should be reduced to minimum levels if possible.

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Zygomycosis

SYN. MUCORMYCOSIS; PHYCOMYCOSIS

Zygomycosis is caused predominantly by species of *Rhizomucor*, *Absidia* and *Rhizopus*. *Cunnighamella bertholletiae* and *Saksenaea vasiformis* are less common causes. Although they are frequent in the natural environment, they are rare causes of invasive disease in patients made susceptible by poorly controlled diabetes, neutropenia or renal disease [1,2]. Fatal infections have been reported in patients with burns. Apart from invasion of necrotic burned areas, zygomycosis of the skin is uncommon.

Necrotizing infections of the skin associated with the application of dressings contaminated with *Rhizopus rhizopodiformis* [3] and *R. microsporus* from wooden spatulae have been described [4]. Cutaneous lesions have been described in patients with lymphoma and kidney transplants [2]. Zygomycosis is usually diagnosed in autopsy or biopsy sections, based on the recognition of the broad and generally non-septate hyphae. However, provided adequate samples are taken, they can be grown from tissue. Infections may respond to intravenous amphotericin, and recent results with lipid-associated amphotericin B formulations have been encouraging.

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Unusual causes of skin lesions among opportunistic systemic mycoses

Most of the organisms that can invade the immunocompromised patient may cause skin lesions. Some of these

infections, such as candidosis, zygomycosis and cryptococcosis, have been described previously. However, other organisms that can cause skin disease include *Aspergillus* [1,2], *Trichosporon* [3] and *Fusarium* [4]; all of these may affect the neutropenic patient.

Aspergillus and *Trichosporon* usually produce large, scattered necrotic lesions, although with the latter, smaller papules and pustules have been seen. *Fusarium* and, more rarely, *Acremonium* infection may produce target-like lesions, which may undergo central necrosis. In some cases of *Fusarium* infection, scattered skin lesions have been accompanied by digital cellulitis and SWO caused by the same organism.

Skin involvement has also been described in a variety of invasive infections affecting the paranasal sinuses such as those caused by *Exophiala dermatidis*. Skin lesions in these infections develop in severely sick patients. However, skin biopsy will sometimes reveal the true diagnosis. Treatment for these infections is usually amphotericin B. The response rates in both *Fusarium* and *Trichosporon* infections are low, and a lipid-associated amphotericin B formulation is often used instead.

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Cutaneous infection caused by *Pneumocystis jiroveci*

Pneumocystis jiroveci is an opportunistic fungal pathogen that is found in immunocompromised patients, including neonates, solid-organ transplant recipients and AIDS patients. *Pneumocystis* was previously regarded as a protozoan, but more recent DNA analysis has shown that it is best regarded as a fungus, although in certain structural features, such as its cell membrane, it differs from the fungal norm. Usually a pulmonary infection, it has rarely been found to cause skin lesions in AIDS patients [1]. The organisms stain with methenamine silver and appear as round, non-budding structures 5–10 µm in diameter. Treatment is with co-trimoxazole or pentamidine.

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Infections caused by *Pythium insidiosum*

Infections caused by *Pythium* species (swamp cancer, Florida horse leech) were first recognized in animals in 1884, affecting mainly horses and mules. Since 1987, a number of cases of human infection have been reported, nearly all of them from Thailand and in farmers exposed to swampy areas. Affected patients have usually had severe infections with ascending gangrene of the lower limbs. Most have had an underlying haemoglobinopathy such as thalassaemia [1]. The organisms appear to invade blood vessels with large, sparsely septate hyphae, 3–20 µm in diameter, similar to those seen in zygomycosis. It is now recognized, however, that the organism is not a true fungus and is probably more closely related to the algae. It is possible to isolate *P. insidiosum* on glucose–peptone agar, but production of the characteristic motile biflagellate zoospores, necessary to speciate the isolate, requires special media and expertise [2].

There is no known effective treatment, apart from high doses of amphotericin B and amputation.

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Protothecosis

Prototheca is generally accepted as a genus of achloric algae embracing three species of worldwide distribution: *P. wickerhamii*, *P. zopfii* and *P. stagnora*. The first two species are established as rare and opportunistic pathogens in humans [1]. Infections with green and blue-green algae, although recorded, are rarer still. Lesions confined to skin and subcutaneous tissues are generally located on exposed sites, and may be associated with trauma [2,3]. Papules, nodules, ulcers and multiple granulomatous lesions have all been described. In such cases, the organisms may be found in the dermis and epidermis. Protothecal bursitis, particularly of the olecranon bursa after injury, is also well documented, as are a few examples of widespread cutaneous, subcutaneous or deep infection in immunocompromised hosts including AIDS patients [4]. Colonization of nails has been reported, and *Prototheca* may occur as transients on the skin. Spontaneous recovery has occurred in one cutaneous infection. However, surgical excision is recommended for localized lesions, and systemic amphotericin B, ketoconazole [5] or itraconazole have proved effective on occasions.

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Glossary

anamorph an asexual state.
anthropophilic adapted to humans.
arthroconidium a spore resulting from the breaking up of a hypha into separate cells; characteristic of parasitic form of ringworm fungi.
asexual reproduction not involving prior union of two nuclei.
blastospore a spore formed by budding.
cerebriform complex folding similar to the brain surface.
chlamydospore a thick-walled cell, intercalary or terminal, containing stored food and able to function as a spore.
clavate club-shaped.
cleistothecium a reproductive structure associated with the sexual state of ringworm fungi.
conidiophore a specialized structure of varying complexity that bears conidiogenous cells.
conidium an asexual spore.
dermatophyte a ringworm fungus.
dimorphic having two distinct forms, which often correspond to saprophytic and parasitic phases, respectively.
downy fluffy.
ectothrix dermatophyte hair infection with hyphae inside the hair and a sheath of spores outside the hair.
endospore spore formed internally (e.g. a sporangiospore).
endothrix dermatophyte hair infection with fungus confined to the inside of a hair.
faviform waxy, restricted honeycomb-like growth of certain dermatophytes.
floccose cottony.
fusiform spindle-shaped.
geophilic soil-inhabiting.
glabrous smooth, leathery.
grain compact agglomeration of fungal or actinomycete elements formed *in vivo*.
granular texture similar to icing sugar.
hypha one of the branching filaments, septate or nonseptate, that make up the vegetative mycelium (q.v.) of moulds.
intercalary not terminal.
kerion an intensely inflammatory ringworm lesion.
macroconidium the larger of the two types of conidia in those fungi that bear large and small (microconidia) spores.
microconidium the smaller of the two types of conidia in those fungi that bear large and small conidia
mycelium the collective name for a mass of hyphae.
mycosis a fungal disease.
obovate inverted egg-shape.
pleomorphic strictly having two or more forms; used frequently to describe non-sporing (sterile) cultures of dermatophytes.
powdery with a texture like face powder.
pseudohyphae hypha-like structure produced by elongation of budding yeasts lying end to end.
pyriform pear-shaped.
sessile without a stalk.
spiral vegetative hypha assuming spiral forms.
sporangium asexual reproductive body in *Zygomycetes*.
spore a reproductive unit; formed sexually or asexually, sometimes multicellular.
sporophore a spore-bearing structure.
tuberculate covered with peg-like outgrowths.
zoophilic adapted to an animal host.

Chapter 32

Parasitic Worms and Protozoa

F. Vega-Lopez & R.J. Hay

Introduction

A parasite is conveniently defined as an organism that depends upon a living host for one or more of its essential metabolic requirements. Such a definition does not imply that the host must inevitably suffer in the process; indeed, the situation where two organisms benefit mutually from a close association represents one extreme of a wide range of relationships.

Many terms have been used to describe the relationships between parasites and their hosts, and a number are useful; but few can be given an exact or exclusive definition. It is not, for example, possible to draw a sharp line between so-called endoparasites living within the body, which, like some intestinal worms, may not invade the tissues, and ectoparasites living on the body surface, which, like the scabies mite, may in fact burrow into it. Similarly, when more than one species of host is successively infected during the life history of a parasite, they are not described in consistent terms. The definitive or final host is usually designated as the one in which the parasite reaches sexual maturity, and an intermediate host is one in which it undergoes larval development or an asexual phase. Thus, the human is definitive host for the so-called pork tapeworm *Taenia solium*, but may also act as an intermediate host in harbouring the bladder worm or cysticercus stage, which normally occurs in the pig. On the other hand, the human—as well as the sheep, the cow and the pig—is the intermediate host for *Echinococcus granulosus*, the hydatid cyst, and the dog, which harbours the tapeworm stage in its gut, is the definitive host. This logic is not ruthlessly applied. The human is usually regarded as the definitive host of the malarial parasite of the genus *Plasmodium*, though sexual maturity is reached only within the mosquito. In practice, the anthropocentric view usually prevails: when the life history of a parasite involves alternations of human and arthropod hosts, the human is designated the definitive host and the arthropod becomes the intermediate host or vector. A consequence of such illogicality is that the parasite now appears to be host specific only in respect of the vector, and not in respect of the so-designated definitive host. Humans share hospitality for *Plasmodium* spp. with other mammalian species, which are relegated to the status of reservoirs.

Parasites that affect humans exemplify a variety of life histories [1–10]. At one extreme are species that need not leave the host even from one generation to the next; *Sarcoptes scabiei* is an example of dermatological interest. At the other extreme are species that are only dependent on the host for the briefest contact, such as the female mosquito, which needs only a single meal of human blood before she can reproduce. In between these limits, there is a range of types of contact between parasite and hosts. Some forms spend part of their life history free, and only part as ectoparasites or endoparasites. Ticks, for example, while remaining for most of the time on their hosts, may drop off to lay eggs in the soil, and the larvae of hookworms hatch from the egg in the soil before burrowing their way through the skin to become gut parasites. Another category may be the many parasites that spend

all of their lives in the host, except for an egg or cyst stage that is transferred to another host without the intervention of any free-living phase; the roundworm, *Ascaris lumbricoides*, is such a form. Lastly, there are those parasites with one or more intermediate hosts or vectors. Examples of dermatological interest are the guinea-worm *Dracunculus medinensis*, for which the fresh-water crustacea of the genus *Cyclops* act as intermediate hosts, and *Loa loa*, a roundworm causing Calabar swellings, which is transmitted by flies of the genus *Chrysops*.

A number of biological considerations are of relevance to dermatological diagnosis and treatment. Cutaneous lesions may result from direct damage by or presence of the parasite, or occur in sites that are not themselves infected. In scabies, for example, extensive inflammatory lesions are found in regions other than those that actually harbour *Sarcoptes* spp. Skin disease due to parasites may be localized, or it may be only one manifestation of wider systemic infection. A parasite may make its first contact with the body via the skin, and may sometimes get no further, or the parasite may be ingested, when the skin lesions are either fortuitous, such as those caused by bladder worms, or serve as escape channels for propagation of the parasite, as are the ulcers caused by *Dracunculus* spp.

The principal groups of parasitic animals that cause skin disease are the protozoa, the helminth worms, which include the class Nematoda (roundworms) belonging to the phylum Nemathelminthes, the classes Trematoda (flukes) and Cestoda (tapeworms), both belonging to the phylum Platyhelminthes (Table 32.1), and the classes Insecta and Arachnida, both of the phylum Arthropoda.

The parasitic protozoa of dermatological interest include members of three classes. Belonging to the class Sarcodina is *Entamoeba histolytica*, an amoeba that infects the intestine causing amoebic dysentery, but which may occasionally invade the skin where it causes ulcers. Among the Flagellata (or Mastigophora) are classed the species of *Trypanosoma* that cause Chagas' disease, transmitted by species of 'kissing bugs', and African sleeping sickness, transmitted by tsetse flies: all these diseases have cutaneous manifestations. Other important flagellate parasites are the species of *Leishmania*, some responsible for systemic and others for superficial infections, which are also transmitted by insect vectors.

The Nematoda embrace both parasitic roundworms and forms that live free in water or soil. Both free-living and parasitic forms go through a similar series of moults during their life cycle, but in soil-living forms all these stages take place in a single environment. In comparing the life histories of parasitic species, it is convenient first to consider species such as *Ancylostoma*, *Necator* and *Strongyloides* in which the eggs hatch in the soil to produce free-living larvae. *Strongyloides stercoralis* is an example of particular interest, because it is capable either of undergoing a complete life cycle free in the soil, or of infecting humans or other animals. Female worms living in the soil produce partially developed eggs, which soon hatch into rhabditiform larvae. These larvae undergo a series of four moults while growing into adults, and this free-living cycle is essentially similar to that of any non-parasitic soil nematode. When environmental conditions become unfavourable, however, the rhabditiform larvae develop into more slender filariform larvae, which are non-feeding but infective to mammalian hosts. These larvae can infect cats and dogs by being eaten, but in humans they usually penetrate by way of the skin, where they cause a transitory 'ground' itch. They enter the bloodstream and are carried to the lungs, whence after penetrating the alveoli they pass up the bronchi and the trachea to the buccal cavity. Thus, they are swallowed, eventually reaching the intestine where they develop to adults. A third type of life cycle, which is completely parasitic, can occur by the hatching and development of the larvae in the gut lumen. At the filariform stage, the larvae burrow through the mucosa into the blood vessels, and hence make their way via the lungs back to the intestine, where they mature.

The life histories of *Strongyloides* spp. provide some of the models for other species. In the hookworm, *Ancylostoma duodenale*, for example, eggs that pass out with the faeces hatch, within 24 h in moist warm soil, to rhabditiform larvae. These larvae grow rapidly, moult twice and in about a week become filariform, the stage that is infective to humans. The young worms crawl to a high point of moist vegetation and wait for a new host. They penetrate the skin, enter blood or lymph vessels where they are

Table 32.1 Worms commonly causing cutaneous disease.

Nematodes (roundworms)
Necator americanus
Ancylostoma duodenale
Ancylostoma spp.
Strongyloides stercoralis
Enterobius vermicularis
Gnathostoma spinigerum
Trichinella spiralis
Dracunculus medinensis
Onchocerca volvulus
Mansonella streptocerca
Loa loa
Dirofilaria spp.
Wuchereria bancrofti
Brugia malayi and *B. timori*
Cestodes (flatworms)
Taenia solium
Echinococcus granulosus and *E. multilocularis*
Spirometra spp.
Trematodes (flukes)
Schistosoma mansoni
S. haematobium
S. japonicum
Schistosoma spp.
Paragonimus spp.

carried to the lungs, and undergo a migratory journey by way of alveoli, bronchi, trachea and buccal cavity to the small intestine. Here, a final moult occurs, and the young worm attaches itself to the intestinal wall, where it feeds and matures to an adult: by about 5 weeks after the original penetration of the skin it can produce new eggs. The American hookworm, *Necator americanus*, has a similar life history, and filariform larvae of other species, which do not infect the gut of humans, can nevertheless penetrate the skin and cause local 'creeping eruption'.

The problem of host infection has been solved in other ways by different species of nematodes. In the species *Ascaris*, the human roundworm, pairing of male and female worms occurs in the intestine of the host, and the eggs, each in a highly resistant capsule, pass out with the faeces. Growth and moulting of the embryo takes place within the egg, but the larvae do not hatch into the soil: the process is delayed until the eggs are ingested by a new host. After hatching in the intestine, the larvae burrow through the intestinal wall to reach the lymphatic or blood vessels and make the same tour through the body as species of *Strongyloides* or hookworm larvae. The threadworm or pinworm, *Enterobius vermicularis*, another intestinal parasite of humans, differs from *Ascaris* spp. in that the eggs are not deposited in the intestine, but discharged by the female after it has crawled out through the anus of the host, and in that the larvae undergo no migratory journey after ingestion by a new host.

In species of *Dracunculus*, the guinea-worm, the problem of reinfection is solved by the role of an intermediate host, *Cyclops* spp., which is ingested by the definitive host. The adult worms live in the connective tissue of humans and other vertebrates, especially the tissue just under the skin, and they can migrate from one site to another. The cutaneous lesion is a hole in the host skin through which a part of the female worm projects and, when the infected host skin gets in contact with water, sets free large numbers of larval worms. *Trichinella spiralis* is an intestinal parasite of the human and a number of other mammals. The young larvae are shed from the female and burrow through the host tissues to the blood vessels, where they are carried to all parts of the body. The vast majority of the larvae encyst in striated muscles, where they gradually become encapsulated. The life cycle can continue only if the infected muscle is eaten by another host: humans usually become infected by eating undercooked pork. The human parasites, *Wuchereria bancrofti*, which lives in the lymphatic vessels, and *Onchocerca volvulus* and *Loa loa*, which live in connective tissue, all produce microfilarial larvae in the host. Infection of new hosts is by blood-sucking or tissue-feeding insects, respectively, mosquitoes (*Anopheles* spp.), coffee flies (*Simulium* spp.) and deer flies (*Chrysops* spp.).

Trematoda that infect humans all belong to the order Digenea. Flukes are parasites of various cavities of the body, such as the intestine, the ducts associated with the alimentary canal, the bladder or the lungs. Eggs are discharged to pass out of the body, where their further development requires water and a mollusc. The egg is either eaten by a snail or it hatches into a free-swimming, ciliated larva, known as a miracidium, which finds its way into a snail. In the snail, the miracidium gives rise to a sporocyst, and an asexual reproductive cycle takes place, producing a number of larvae known as rediae. Within each redia, there may develop either a further generation of rediae or a number of motile larvae known as cercariae. Cercariae can enter a new host in a number of ways. In the sheep liver fluke, *Fasciola hepatica*, they form cysts on blades of grass and are ingested by the host. In the human liver fluke, *Clonorchis sinensis*, the cercariae penetrate the skin of fish, where they encyst as metacercariae. Humans are infected by eating uncooked, infected fish. In the various species of *Schistosoma*, however, the cercariae enter the human host by way of the skin. Of particular interest is the fact that cercariae of flukes parasitic in various birds and mammals, which cannot fully infect humans, can actually enter the skin and cause cutaneous symptoms known as cercarial dermatitis or swimmer's itch.

The Cestoda, or tapeworms, are entirely parasitic throughout their life histories, and have at least two hosts, one of which harbours the adult stage in the gut, and a second that harbours the bladder worm stage in the body cavity or tissues. Humans may, for example, become infected with the tapeworm stage of *Taenia solium*, of which the bladder-worm stage normally occurs in the pig, or by the bladder worm of *Echinococcus* spp., of which the tapeworm stage occurs in the dog and other mammals. Cysticercosis, which may affect the human skin, can occur also from *Taenia solium*. Cestodes belonging to the family Diphyllobothriidae, parasites of humans, other mammals and birds, have a so-called plerocercoid larva stage in copepod crustacea, fish or other aquatic animals. Larvae of this kind from intermediate hosts, such as frogs or snakes, may sometimes infect the skin of humans, causing a condition known as sparganosis.

Parasitic worms and protozoa cause a high proportion of the world's transmissible diseases, particularly in the tropics and subtropics, and they are responsible for some of the most dramatic and serious of the affections of the skin. Worms commonly causing cutaneous disease are shown in Table 32.1. In many instances, simple and effective preventive measures are available, which, when fully applied, should greatly reduce the world incidence.

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Infection with human nematodes

In these infections, the human is an obligatory host at some stage of the life cycle of the parasite. Helminths, including nematodes, may be long lived—up to 30 years for *Schistosoma* spp. and 17 years for *Onchocerca* spp. for example—and constant reinfection in endemic countries gives rise to heavy worm burdens. All nematodes must spend part of their life cycle outside the human body, either on soil or in water, or in an insect, crustacean or vertebrate intermediate host. *Strongyloides stercoralis* is the exception to this rule: autoinfection with this worm permits lifelong infections in humans. With some species of nematode, the worm is masked from immune recognition, and large worm burdens may be tolerated with remarkably little clinical effect. With others, inflammation, often in response to naturally dying worms or their progeny, causes severe disease. By contrast, some helminths make excessive demands on the body's nutritional reserves.

Onchocerciasis

SYN. BLINDING FILARIASIS; RIVER BLINDNESS; COASTAL ERYSIPELAS; MAL MORADO

Aetiology and epidemiology. Onchocerciasis is a filarial disease caused by *Onchocerca volvulus*. The worm affects inhabitants of certain areas in tropical Africa, from Senegal right across to Tanzania, and in Yemen, Central America, southern Mexico, Guatemala, Colombia, Ecuador and Venezuela [1]. The clinical manifestations of onchocerciasis in the New World show subtle differences in appearance and distribution, but the infection is otherwise the same [2–4]. The disease has been estimated to affect over 19 million people, of whom the vast majority live in Africa. The male adult worms measure 20–45 mm, and the female 230–700 mm in length; much longer than any other insect-borne filariae. Their progeny are sheathless microfilariae occurring in two sizes approximately 200 μm and 300 μm long.

The vectors of the disease are tiny, humpbacked black flies of the family Simuliidae (buffalo gnats). In Africa, the species *Simulium damnosum* is mainly, but not exclusively, responsible, causing very itchy bites as it transmits the disease. The larvae develop in the thoracic muscles of the flies, and 7 days after infection are fully developed in the labium of the proboscis.

Human infections with zoonotic onchocerca have been reported in the Crimean region, Illinois and Switzerland [5].

Pathology [6,7]. Mature worms and microfilariae are found in granulomatous dermal nodules (onchocercal nodules), often situated on the scalp of their hosts in Central America, but in Africa near bony prominences on the trunk and limbs or in the natal cleft. The nodules measure some 3–35 mm in diameter, and consist of an outer layer of fibroblasts, which contains the parasites in an organized, fibrinous exudate. Inflammatory cells and, sometimes, giant cells, tend to accumulate around the worms. Calcification may also occur.

Microfilariae migrate mainly in the dermis. Their death causes an inflammatory response. The longer the disease lasts, the more these changes are replaced by fibrosis and atrophy of dermis and epidermis [7,8].

The numbers of microfilariae vary greatly. In some instances, there is a dense, predominantly perivascular, reaction with mononuclear cells and eosinophils, but few microfilariae [9]. At its severest, this is accompanied by marked acanthosis and hyperkeratosis. The reason for this extreme reaction is unknown, but serum from patients with this form of onchocerciasis recognize a collagen antigen expressed by a specific nematode gene, suggesting that cross-reaction between antibodies to *Onchocerca* and human collagen might play a role in the pathogenesis of this condition [10]. Often in individuals with minimal clinical lesions and dermal inflammation, there is the highest density of dermal microfilariae (Fig. 32.1). In these patients, there is evidence of defective T-lymphocyte stimulation by certain filarial antigens, which can be reversed by treatment [11]. Conversely activation of T-cell-mediated pathways are associated with the highly inflammatory forms such as lichenified onchodermatitis (LOD) (see below)

Microfilariae also invade the eye, where they cause keratitis, posterior choroiditis, uveitis and optic neuritis, which can lead to blindness. Reports of microfilariae in blood have been rare and sporadic, and this finding is

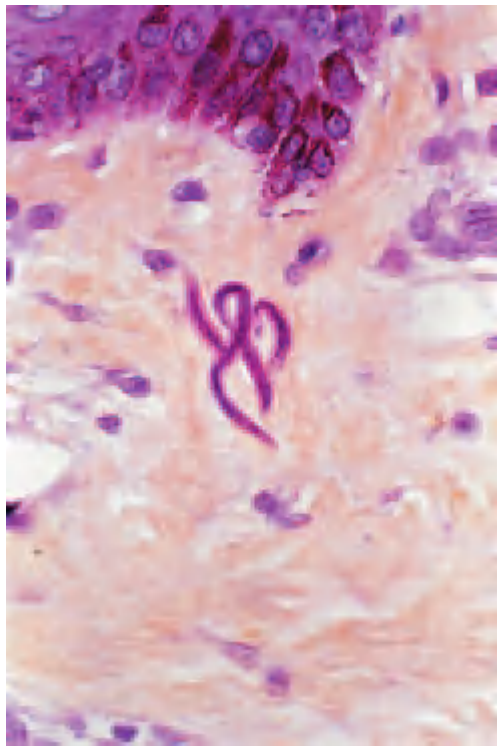

Fig. 32.1 Microfilaria of *Onchocerca volvulus* in the upper dermis. Note the absence of inflammation around the live organism. (Courtesy of Dr C. McDougall, Slade Hospital, Oxford, UK.)

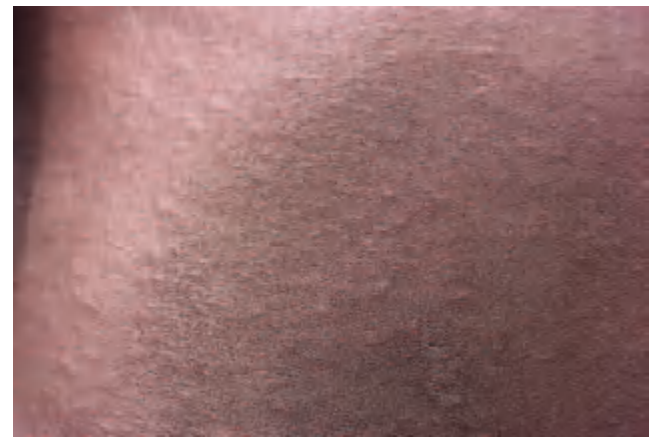

Fig. 32.2 Acute papular onchodermatitis in a Nigerian. Early in the disease the papules are usually urticarial.

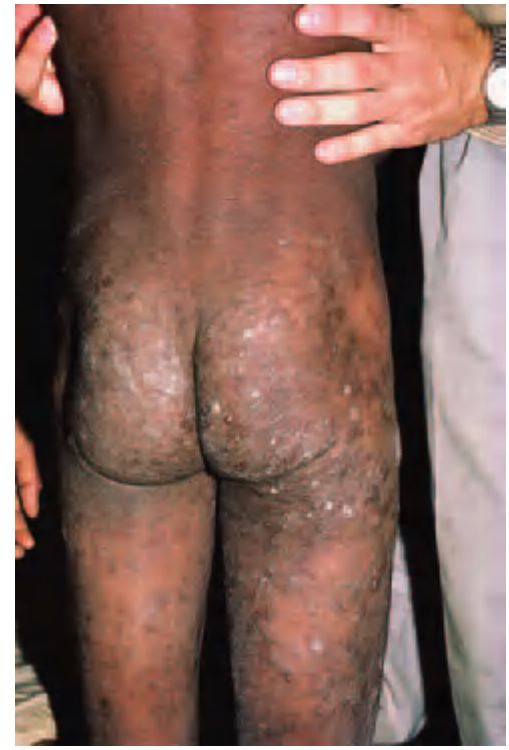

Fig. 32.3 Chronic papular onchodermatitis. Lesions are starting to lichenify.

usually associated with diethylcarbamazine (DEC) therapy [12]. In others, it is difficult to exclude the possibility of concomitant infection with other filarial worms.

Free microfilariae also penetrate superficial lymphatic vessels, and may be found in the urine, tears, sputum, cerebrospinal fluid (CSF) and, occasionally, in vaginal smears or irrigation sediment.

Clinical features [1,4,7,13]. The commonest symptoms and signs are pruritus, onchocercal dermatitis, nodules and, in areas of high endemicity, blindness. The disease may be detectable as early as 6 months of age, and presents with pruritus and a non-specific papular rash worsened by scratching.

In many patients, however, the skin may appear clinically normal, even when microfilarial counts in skin snips are found to be high. The skin changes seen in onchocerciasis vary with the age of the patient, the location of the infection on the skin surface and the geographical and climatic region where the infection occurs. Nonetheless, it is possible to define certain changes that are common features in onchodermatitis, although their prevalence varies from area to area. These changes have been classified as acute papular onchodermatitis (APOD) (Fig. 32.2), chronic papular onchodermatitis (CPOD) (Fig. 32.3), LOD, atrophy and hypopigmentation [13]. In children and in the earliest cases in endemic areas, the skin has an infiltrated appearance, with obliteration of surface markings. This is confined to one skin area and is often accompanied by the appearance of small, itching papules or pustules (APOD). The oedematous features are often more pronounced in Europeans with the disease, when it may appear as localized oedema [14]. In Europeans, blotchy erythema and urticated papules are common early signs. The early rash is usually seen on exposed sites, such as

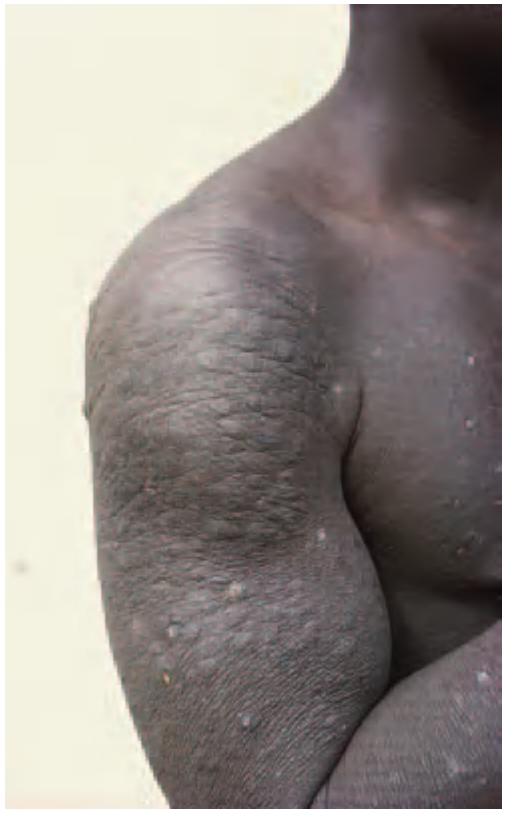

Fig. 32.4 Late lichenified onchodermatitis (pachyderma).

the shoulders and around the pelvis. In Central America, acute swelling on the face and cheeks with erythema and itching, known as erisipela de la costa, is also a manifestation of this acute phase. Patients may continue to present with this pattern over months and years in the early phases of the disease.

As the infection evolves, localized areas of scarring and CPOD (Fig. 32.3) are seen. These may coexist with the acute papular eruption, but chronic lesions are excoriated papules and flat-topped scars with hyperpigmentation and some lichenification. The buttocks and shoulders are common sites for this rash.

Lichenified onchodermatitis may well represent an extreme form of the last clinical pattern. When fully developed, it is a lichenified itchy rash confined to one limb (Fig. 32.4), commonly the leg, although sometimes two or more areas are affected [9,11]. The rash is composed of itchy papules and nodules, which become confluent. The lesion is characteristically hyperpigmented, and it is known in Arabic-speaking areas as Sowda. Gross enlargement of the regional lymph nodes is an important feature. Interestingly, it is found mainly in East Africa (Sudan [15], Ethiopia) and Yemen. It is less common in West Africa or South America. There is some evidence that this pattern of skin change is associated with very low microfilarial loads; it may also improve symptomatically over time with loss of itching and lichenification, but increasing microfilarial loads. LOD is mainly seen in teenagers and young adults.

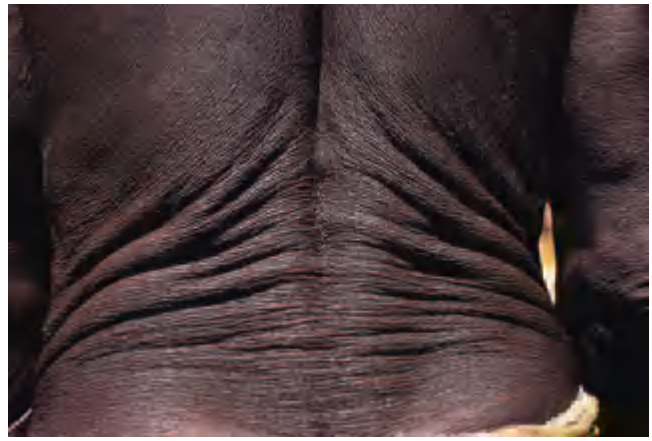

Fig. 32.5 Late onchocerciasis. Atrophy of skin and damage to supporting tissue cause the skin to sag in folds (lizard skin).

Atrophy (Fig. 32.5) is probably a consequence of long-standing onchocerciasis. It may develop after any of the patterns described previously, or arise from apparently normal but infected skin sites. The commonest sites to detect early atrophic changes are over the buttocks, shoulders or lower limbs. The skin becomes dry and shiny, with fine wrinkles resembling tissue paper. An extreme form of this secondary ichthyosis is known as lizard skin. It is believed that degenerative changes leading to loss of dermal elastic fibres, combined with other factors, such as massive inguinal lymphadenopathy, may give rise to the hanging groin, which is an apron-like fold of skin in the inguinal region [16] containing lymph nodes. Depigmentation is a common feature of late-stage onchodermatitis [17]. It is most commonly seen bilaterally over the pretibial region, but may affect the inguinal regions, bony prominences and the shoulders (Fig. 32.6). The patches of hypopigmentation are spotty, with islands of normal-appearing skin, but large coalescent sheets of depigmentation are present in late-stage disease. The name leopard skin is used to describe this change. While it is important to recognize that other causes of hypopigmentation, such as amyloid deposition, may also produce such changes in certain endemic areas, the presence of leopard skin in the community is used as an indicator of the prevalence of onchocerciasis in the population.

In many, if not most, patients with chronic onchocerciasis, it is possible to feel nodules containing the adult worms (Fig. 32.7). They are usually found over the pelvic or pectoral regions, although the top of the natal cleft is often a good site to find them. In South and Central American cases, the nodules are often found on the head.

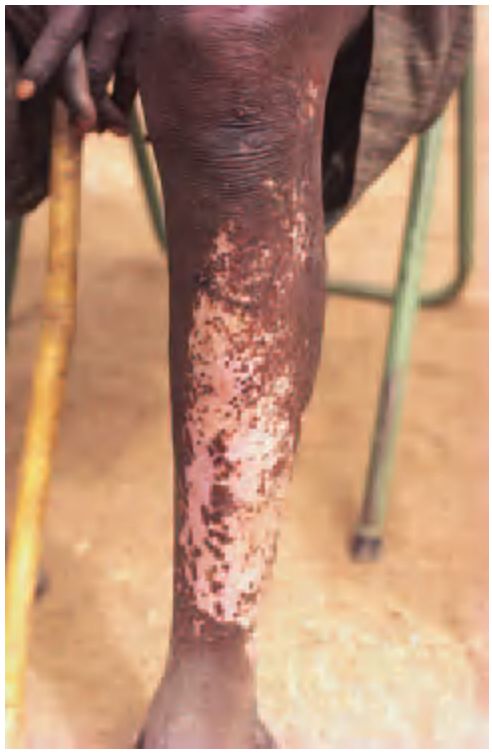

Fig. 32.6 Depigmentation over the shin in late onchocerciasis (leopard skin). This is common in African endemic areas. Note the stick for the blind.

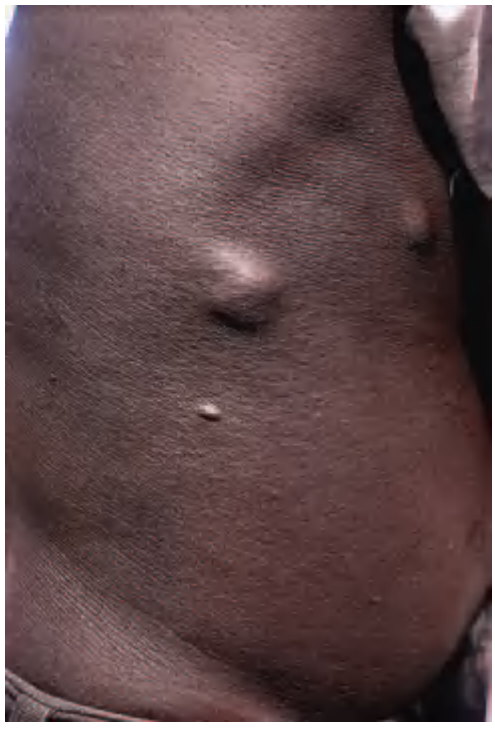

Fig. 32.7 Cutaneous oedema and cutaneous and subcutaneous nodules in a Nigerian with onchocerciasis.

Other clinical variants of onchocerciasis may occur. These include an acute urticarial eruption seen in Zaire and, in Central America, an inflammatory rash accompanied by hyperpigmentation known as 'mal morado'.

In endemic areas where onchocerciasis is found, the majority of the population may be affected; they will also have other skin diseases. There is little evidence that the presence of onchocerciasis affects the clinical appearances of these. However, it has been suggested that lepromatous leprosy [18] and widespread tinea corporis [4] are commoner in certain patients with onchocerciasis.

The major complication of onchocerciasis is severe visual impairment and blindness. It is the commonest cause of blindness in endemic areas. Ocular manifestations range from punctate and sclerosing keratitis, associated with the presence of microfilariae in the cornea and anterior chamber, to retinal pigmentation, optic atrophy, scarring and blindness. Onchocerciasis may result in blindness rates in endemic communities of 5–10% [19].

Prognosis. In endemic areas, the rate of infection increases up to the age of 50 years and no relative immunity is acquired. Symptoms increase in severity without treatment until atrophic changes are complete.

Diagnosis. Clinically, the diagnosis is usually evident, but other causes of prolonged pruritus and lichenification must be excluded, particularly scabies. Typical burrows may be hard to find in patients with scabies, and great tenacity is needed to demonstrate an acarus. Skin snips for active microfilariae are taken with the corneoscleral punch or by raising a little 'tent' of skin with a needle. This is then shaved off with a very sharp blade without bleeding, placed in normal saline in a microtitre well covered with transparent adhesive tape, or placed under a cover slip and examined microscopically 1–4 h later. The buttocks and legs are often most heavily infected, and are most likely to yield microfilariae. Nodules may be excised and examined histologically for adult worms and microfilariae. The white-cell count shows a leukocytosis with relative eosinophilia. The filarial immunofluorescence test or enzyme-linked immunosorbent assay (ELISA) is positive in 60–90% of cases.

Treatment. The treatment of onchocerciasis has been improved significantly by the development of the microfilaricide, ivermectin. This drug is given orally in a single dose of 100–200 μg/kg [20]. This results in a prolonged suppression of microfilarial counts in skin snips, and improvement in skin symptoms and reversible eye changes [21]. Microfilarial counts remain very low for 6 months, then rise slowly but do not reach pretreatment levels within 1 year. Patients may be retreated after 6–12 months. In patients with low parasite loads, such as travellers returning from an endemic country, about 30%

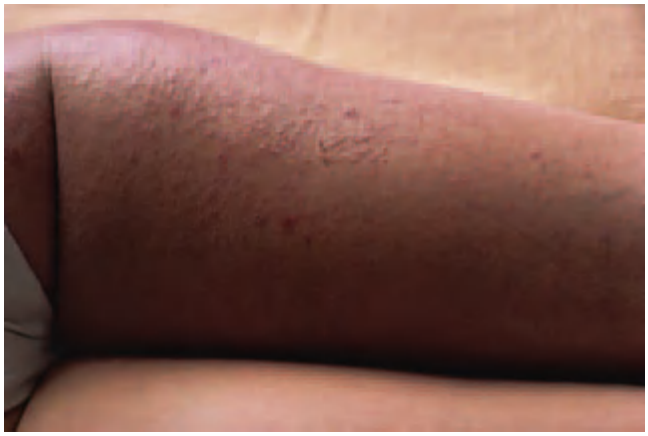

Fig. 32.8 Acute papular onchodermatitis in a European. Exacerbation and oedema are characteristic of the Mazzotti reaction following a dose of diethylcarbamazine.

will *not* relapse after each treatment [22]. The drug is well tolerated and side effects are seldom severe. Side effects that are seen include pruritus, skin oedema, arthralgia, malaise and fever. In particular, no acute eye changes accompany therapy [23].

The alternative drug regimen, now rarely used, involves the use of DEC, which may cause severe exacerbation of skin (Fig. 32.8) and eye disease, even blindness [24]. DEC kills the microfilariae and is given as follows:

1 first 3 days 1 mg/kg body weight once;
2 second 4 days 2 mg/kg body weight once;
3 second week 4 mg/kg body weight three times a day;
4 third week 4 mg/kg body weight three times a day.

In heavily infected patients, or in those with severe dermatitis or with eye involvement, prednisone should be given at a daily dose in adults of 40 mg, starting the day before DEC and continuing for a few days until the reaction has settled. Collapse and death have occurred in heavily infected patients during treatment. The sharp accentuation of symptoms after a single 50-mg dose of DEC may be used as a diagnostic test where skin snips are negative (Mazzotti's test). Repeated courses are usually necessary until the patient is symptom-free.

Ocular reactions need treatment with corticosteroid eye drops and mydriatics.

Suramin is a drug that kills adult worms (macrofilaricide). However, it can cause severe adverse reactions and is now seldom used.

There is still considerable controversy over the use of nodulectomy, usually combined with a microfilaricide. In South America, some studies have shown that nodulectomy alone without drugs may reduce microfilarial levels by over 60% by 5 months after surgery [25]. It may reduce the burden of eye disease but it does not cure the disease, nor reduce transmission.

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Streptocerciasis

Streptocerciasis in an infection caused by the filarial nematode, *Mansonella streptocerca*. The disease is seen mainly in parts of West and Central Africa in rainforest

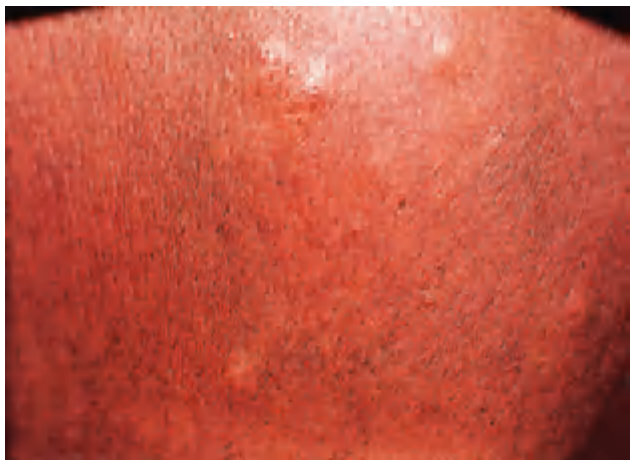

Fig. 32.9 Streptocerciasis. Pigmentary changes and nodules in a patient from Zaire. (Courtesy of the Armed Forces Institute of Pathology, Washington, DC, USA.)

areas, where it may be found in the majority of the population [1]. Chimpanzees in the endemic area may also be infected.

Adult worms of *M. streptocerca* can be found in the dermis, particularly around the upper trunk; microfilariae are also seen in the dermis.

The skin rash is rather similar to that seen with onchocerciasis, with acute or lichenified itching papules (Fig. 32.9). More widespread lichenification may also occur, and hypopigmented macules are common. Secondary enlargement of the local lymph nodes is seen in many patients. The diagnosis can be made by finding microfilariae in skin snips. These are less active than those of onchocerciasis, and the microfilarial tip may curl in a typical 'shepherd's crook' appearance. The main therapy is DEC.

Infections caused by two other *Mansonella* spp., *M. ozzardi* and *M. perstans*, are seen in Latin America and Africa, respectively, where the parasites are a cause of microfilaraemia; patients, however, are symptomless.

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Lymphatic filariasis

SYN. TROPICAL ELEPHANTIASIS

Aetiology and epidemiology [1]. This is a disease due to infection with the filarial worms *Wuchereria bancrofti*, *Brugia malayi* or *B. timori*, of which the first is the commonest. Most authorities agree that clinically the diseases caused by the two genera of filariae are indistinguishable. Infections due to *W. bancrofti* are more widespread than the others [2]. They occur between the latitudes of 40° north and 30° south. The areas with the highest incidence of infection are South-East Asia and sub-Saharan Africa. In the New World, there are fewer endemic foci: Guyana, Haiti and parts of Brazil. Control has been achieved in some other countries such as Taiwan and Japan. It is estimated that about 250 million people are infected. *Brugia malayi* is mainly confined to South-East Asia and as far north as Korea, particularly in rural rainforest areas [3]. The most restricted of this group is *B. timori*, which is found in certain of the Indonesian Islands [4].

Transmission and pathology [4]. The disease is transmitted by many species of anthropophilic mosquitoes of the genera *Culex*, *Aedes*, *Mansonia* and *Anopheles*. In ingested human blood in which microfilariae are present, the organisms lose their sheaths in the mosquito's stomach, and in less than 24 h have entered the thoracic muscles. Metamorphosis proceeds, and mature larvae migrate to the labella 10 days after infection of the insect. Here they are ready to be transmitted to the next human by biting.

In humans, larvae pass through peripheral lymphatics, develop and migrate centrally and eventually grow into adults, which mate in lymphatics proximal to lymph nodes. Fertilized females discharge their microfilariae, which may be found in peripheral blood 12 months after the initial infection. The discharge is cyclical and occurs principally at night. These microfilariae can pass the placental barrier. The adults are found coiled up in dilated lymphatics.

Immunity to filarial infections is complex. Otherwise healthy individuals from within the endemic area have both antibody and T-lymphocyte-mediated immune responses. By contrast, those with active infections and episodic microfilaraemia may show reduced cellular immunity, suggesting that antigens from the organisms may modulate immunity. The worms may also carry symbiotic bacteria of the genus *Wolbachia*. These are antigenic, although their contribution to inflammatory reactions is unknown.

Pathology. The presence of adult worms in the lymphatics with the resulting inflammatory response is the cause of the main pathological feature—lymphatic obstruction (Fig. 32.10). Leakage of lymph may contribute to tissue damage. Circulation of microfilariae in the bloodstream has remarkably little effect, although their entrapment in the lungs may cause tropical pulmonary eosinophilia.

Clinical features. Many of those infected do not appear to develop signs of infection, and such signs that occur vary considerably from patient to patient [5–7]. The first signs are often swelling, tenderness and erythema on the arms, legs or scrotum. Swellings may be firm, and fixed nodules and urticaria have also been described at this stage.

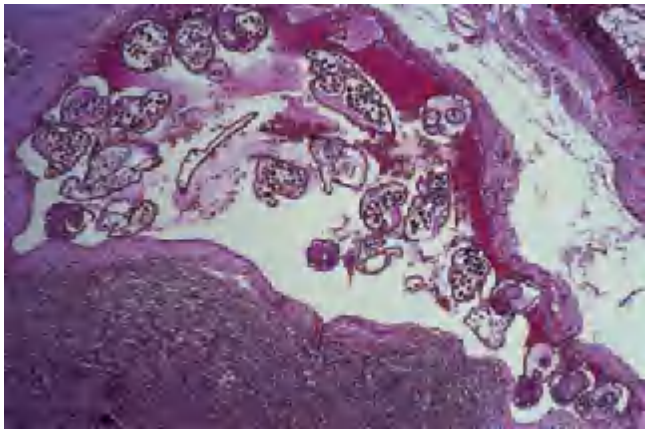

Fig. 32.10 Lymphatic filariasis (low power, H&E). Female adult *Wuchereria bancrofti* within lymph node sinus. Multiple cross-sections of worm are seen. (Courtesy of Professor S.B. Lucas, King's College, London, UK.)

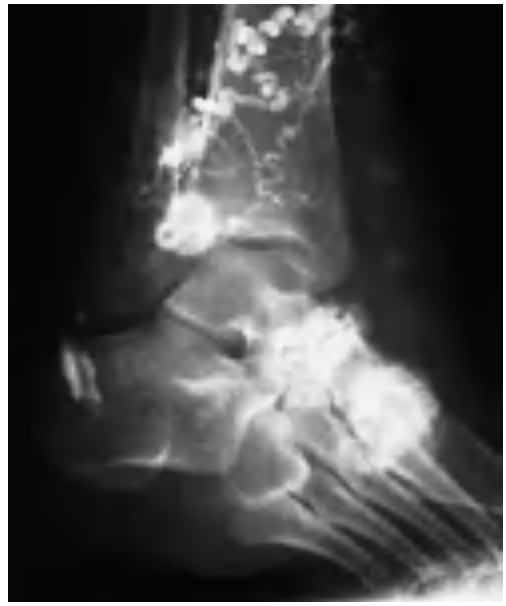

Fig. 32.11 Lymphangiogram showing tortuous dilated lymphatic vessels in the leg of a patient with lymphatic filariasis from Mauritius.

Cellulitis, which is common, may be mild or severe and is recurrent. In the severest form it presents with fever and sweats and the painful enlargement of lymph nodes, particularly the inguinal group. Lymphangitis can accompany some attacks. Milder forms of cellulitis with more localized erythema and tender swellings also occur repeatedly. Other complications include orchitis, which is commonly followed by hydrocoele and scrotal oedema, and recurrent epididymitis. Abscesses deep in the limb muscles, or more superficially located in lymphatics, occur.

Repeated attacks of oedema and cellulitis may be followed over a number of years by evidence of lymphatic obstruction (Fig. 32.11). In males, these commonly present as hydrocoeles, but lower leg oedema and elephantiasis may also develop. Hydrocoele or thickening of the scrotal skin is common in many endemic areas, and may affect up to 25% of the adult male population [8]. Limb oedema of a varying extent and nature is also common and passes through several grades of severity before becoming gross elephantiasis. This may be followed by recurrent episodes of secondary infection, and the appearance of warty thickening of the skin. The legs are usually affected, but arms, breast and genitalia may also be involved. A further complication is rupture of dilated abdominal lymphatics into the urinary tract, to produce episodic chyluria.

Diagnosis. In an endemic area, it may be possible to make the diagnosis on clinical grounds, before the stage at which microfilariae appear in the blood, as well as in the chronic condition. Biopsy of an enlarged lymph node may be diagnostic.

Microfilariae are demonstrated in the blood especially in acute cases, either in a thick blood film or by passing heparinized blood through a millipore filter, which retains the microfilariae, which can then be seen easily under the microscope. In the periodic form of filariasis, blood should be sampled between midnight and 02.00 hours.

An alternative procedure is to repeat blood films 1 h after a single dose of DEC 100 mg. This releases more microfilariae into the circulation. However, some cases of filariasis do not appear to develop detectable filaraemia.

Another approach to diagnosis is the use of serology, where an indirect immunofluorescence or ELISA is positive in a high percentage of those affected, although it is not specific for each organism. An antigen detection system is also used. A polymerase chain reaction (PCR)-based test has been applied to the detection of *W. bancrofti* genomic DNA in blood [9]. It is important to recognize the current deficiencies in the laboratory confirmation of this disease as no single test is even 90% accurate.

Filarial lymphangitis must be distinguished from bacterial lymphadenitis, with its signs of a portal of entry. Genital lesions may resemble lymphogranuloma venereum with adenopathy and oedema. The Frei test will be negative.

Treatment. The management and elimination of lymphatic filariasis has become the focus of a group of research units, governmental organizations, non-governmental organizations (NGOs) and charities collectively known as the Global Alliance for the Elimination of Lymphatic Filariasis. Two phases of their programme have been developed: parasite elimination and morbidity control. Parasite elimination depends on the use of chemotherapy, which is also used for the treatment of individual patients. DEC has long been the main treatment [10,11]. The dosage is the

same as for the treatment of onchocerciasis (see above), although higher doses at monthly intervals have also been given. The predominant effect of the drug is on the viability of microfilariae, but it has relatively little impact on adult worms. It may be necessary to repeat the course after a few months if microfilariae reappear in the blood.

No fatal complication has ever been reported from this use of DEC, but side effects occur, notably anorexia, nausea, vomiting, giddiness, headache, drowsiness and acute allergic reactions due to destruction of microfilariae and adult filariae.

Special care should be taken in areas where both lymphatic filariasis and onchocerciasis coexist, in view of the potentially serious nature of DEC reactions in the latter [8].

There is also experience with ivermectin, and it is effective in lymphatic filariasis. The drug works more rapidly than DEC, and microfilaraemia is reduced to 14–30% of pretreatment levels 6 months after therapy. There are also similar adverse reactions to ivermectin in patients with this condition. The dose is usually 400 µg/kg. Ivermectin does not kill adult worms, so recurrence of microfilaremia is common and further treatments are often necessary [12].

Morbidity control is approached through a combination of lower limb exercise and regular cleansing, combined with treatment of potential portals of entry of bacteria, such as infected web spaces. There is evidence that this can reduce limb swelling considerably, even in late stages. These approaches are being developed across a range of endemic areas. Surgical approaches may improve the appearance of affected limbs either in the early stages by creating a lymph node–venous shunt, or by removing subcutaneous tissue and grafting of split-skin onto a muscle bed (Charle's operation) [13] in established elephantiasis. Repeated drainage and surgery may be required for severe hydrocoeles.

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Loiasis

SYN. CALABAR SWELLINGS; FUGITIVE SWELLINGS; *LOA LOA* FILARIASIS; AFRICAN EYE WORM

Aetiology [1,2]. Human loiasis is restricted to the damp forest areas of West and Central Africa from 8° north to 5° south of the Equator, from the Gulf of Guinea across to the Great Lakes. It is particularly prevalent in the Cameroons and on the Ogowe River. Its distribution includes the coastal plain, and follows the Zaire River 500 miles inland. It is also found in southern Sudan. *Loa loa*, the eye worm, is transmitted to humans by blood-sucking tabanid flies of the genus *Chrysops* (deer fly, horse fly and mangrove fly), which bite by day, principally *C. silacea* and *C. dimidiata*. Infection is transmitted by the fly from person to person, and hill houses built at the level of the forest canopy or in cleared plantations are especially susceptible sites for the acquisition of the disease.

Pathology and clinical features [1,3]. Larvae are liberated from *Chrysops* spp. when it presses the labella against the skin to take a blood meal. They then enter the tissues through the puncture made by the proboscis. About 1 year after infection of the host, adult worms may appear under the skin or in the conjunctiva, but microfilariae in the blood are not discoverable until 5 months later [4]. The parasite moves about in fascial planes, from which microfilariae are released and travel up lymphatics to the bloodstream to be lodged in the lungs. The adult makes frequent journeys through the skin connective tissues, and has often been seen on the fingers, trunk, scalp, lingual frenulum, loose penile skin, eyelids, beneath the conjunctiva and in the anterior chamber of the eye [5]. These migrations may cause a pricking, itching, creeping sensation or may be symptomless, although when the parasite appears in the conjunctiva, considerable irritation is usual. When the eye is involved, unilateral palpebral oedema may develop and the worm may be seen actually crossing the eye (Fig. 32.12).

In certain patients, including expatriates who come to live in an endemic area, these wanderings cause temporary, shifting, oedematous swellings—Calabar swellings. These affect mainly the arm and hand (Fig. 32.13), although they may appear on any part of the body. They develop rapidly and may be painful or itchy, lasting for several days.

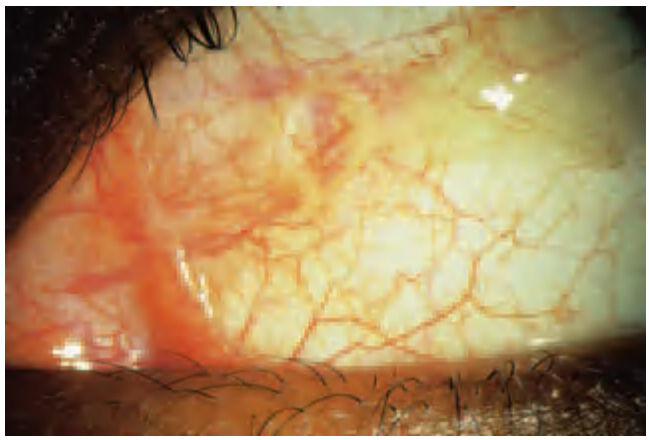

Fig. 32.12 *Loa loa*. Creamy white adult worm crossing the conjunctiva of a Nigerian patient.

Fig. 32.13 Calabar swelling of dorsum of left hand in a European patient with loaiasis. In this case no microfilariae were seen in the blood.

Allergic manifestations, such as eosinophilia and angio-oedema, are often more severe in visitors who originate from a non-endemic area. They have been correlated with high IgG and IgE levels, and increased lymphocyte blastogenesis to filarial antigens [6].

Adult worms may die and calcify. Additional complications reported in loiasis include encephalitis, meningitis and glomerulonephritis [7].

The life expectancy of adult worms is at least 4 years, and may be as much as 15 years. Cases in immigrants have been reported in Australia, Zimbabwe and in North America [5,8].

Diagnosis [3,4]. Clinical diagnosis, based on the presence of Calabar swellings, the sighting of adult worms and eosinophilia in a patient from an endemic area, is usually reliable. Microfilariae may be demonstrated in a sample of daytime blood as for *Bancroftian filariasis* (Fig. 32.14).

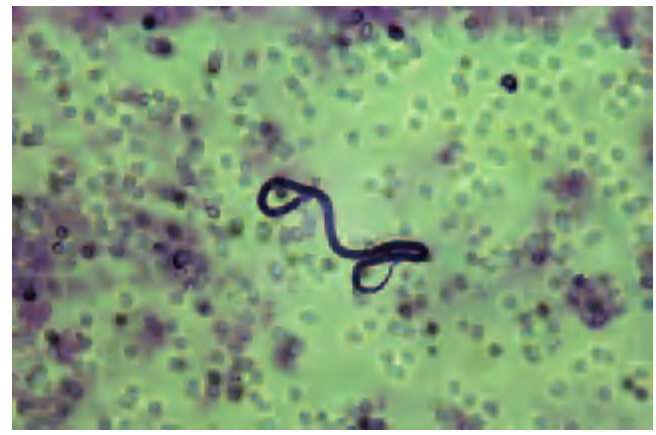

Fig. 32.14 Microfilaria of *Loa loa* stained with Giemsa on a micropore filter, after filtration of 10 mL blood taken at 12.00 hours. (Courtesy of Mr A.H. Moody, Hospital for Tropical Diseases, London, UK.)

Filarial serology by immunofluorescence or ELISA is usually positive, but not genus specific. It is particularly helpful in patients without microfilaraemia.

Treatment. One course of treatment with DEC is usually curative. Side effects are few and mild, although there may be an allergic reaction with one or more large Calabar swellings, fever, malaise, swelling of joints, joint pains and pruritus. There is a risk of encephalitis in heavy infections with headache, giddiness, vomiting, purpura and eosinophilia. Steroid therapy starting 1 day before DEC will prevent severe reactions as in onchocerciasis (see above) and is recommended for all microfilaraemic patients. After DEC therapy, elongated subcutaneous nodules, indicating the presence of adult worms, may appear [8].

Ivermectin has been recorded as producing good responses in loiasis, and reduces microfilaraemia [9]. It is given in doses of 200 µg/kg. While it is generally well tolerated, adverse events, such as impaired conscious state and arthralgia, can be seen in those with high levels of microfilaraemia [10]. Ivermectin does not kill adult worms, however.

Adult worms can sometimes be removed from the conjunctiva surgically.

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Dracunculiasis

SYN. DRACONTIASIS; GUINEA-WORM; MEDINA WORM; DRAGON WORM

Aetiology and epidemiology. Dracunculiasis is a chronic infection of humans due to the nematode, *Dracunculus medinensis* [1]. The disease occurs in India and West Africa as well as areas in East and Central Africa [2], Saudi Arabia, Yemen, Iran, Pakistan and the West Pacific. The disease was estimated to infect over 50 million people [3]. In some areas, it was particularly common: in Oyo state in Nigeria, for instance, it was found to infect 32% of a large survey population [4]. However, over the past 10 years there has been a highly successful campaign to eliminate this infestation, and the incidence of this disease has been reduced enormously

Pathology [5]. The adult female worm matures over a 1-year period in humans and discharges larvae through an ulcerated skin lesion. Millions of these larvae are produced, particularly on contact with water; these survive for 3–4 days and can develop further in copepods or water fleas (*Cyclops* spp. such as *C. leukarti*). After ingestion by the *Cyclops*, they pass through two developmental stages before reaching the infective third stage (L3) after 2 weeks. Humans are infected via drinking water containing infected *Cyclops* spp.; the larvae are released and penetrate the intestine. Further maturation occurs in the retroperitoneal space or other sites; mating occurs after about 3 months, and the males subsequently die. The females grow and migrate downwards, usually to the lower limbs. Aberrant migration can, however, occur [6]. The female penetrates the skin of the leg and can then discharge larvae after exposure to water. Each female contains 2–3 million larvae. Migration of the worm and larval forms is largely subclinical. Disease is associated with the presence of the adult female in subcutaneous tissue in the lower limbs.

Dracunculiasis is a disease found in poor rural populations. It can be spread in and around communal drinking or washing areas or wells.

Clinical features [1]. Immediately before the appearance of part of the adult female through the skin, there may be generalized symptoms such as fever, pruritus, urticaria and oedema [7]. Dyspnoea and diarrhoea may also occur. Usually, however, the first sign of the infection is the appearance of a small papule or vesicle, which expands and bursts over 4–5 days. When this occurs, commonly on the lower limb, there is intense localized itching. This is often followed by the emergence of part of the female worm through the skin (Fig. 32.15). The surrounding ulcer is covered with slough, which usually becomes secondarily infected. The worm itself is often palpable. Infections with two or more worms may also occur. Eventually, the worms may be resorbed or calcify.

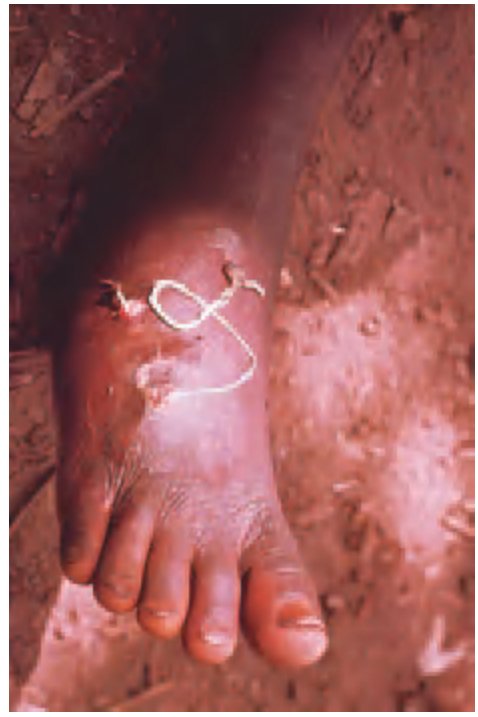

Fig. 32.15 Guinea-worm. Adult female *Dracunculus medinensis* emerging from the skin of a Nigerian patient. (Courtesy of Dr R. Muller, CAB International Institute of Parasitology, St Albans, UK.)

Secondary infection is very common, and may incapacitate the patient. It is a major cause of morbidity [7]. The common infecting organism is *Staphylococcus aureus*, but the open wound may also serve as a portal of entry for tetanus. Sometimes, *Dracunculus* may find its way into other sites [8], such as the knee joint, and cause intra-articular infection.

Diagnosis. The appearance of the worm under the skin is typical. However, the adult can be induced to shed larvae onto a glass slide, which can be examined microscopically, by applying water to the extruded segment. Worms may also calcify in tissue and can be visualized on X-ray [2]. There is usually an eosinophilia.

Treatment. The object of treatment is the removal of the worm. This is now facilitated by oral treatment with an oral benzimidazole, such as metronidazole or thiabendazole. After a few days, the inflammation lessens and it may be possible to extract the worm gently. It may be difficult to extract the worm if mebendazole is used [9]. The more traditional approach is to induce the worm to discharge larvae by applying water or ethyl chloride and to wind the free end around a matchstick. By gradually winding more and more of the worm onto the spool, the whole nematode can be recovered. It is important not to exert tension or the worm will break and cause severe allergic cellulitis. The procedure is therefore carried out slowly over a few days.

In addition, all cases should be treated with local antiseptics, tetanus toxoid and, if necessary, broad-spectrum antibiotics [7]. The drug treatment described above does not affect the larvae or prevent transmission. The latter is best accomplished by public health programmes designed to provide clean drinking water, by sieving or filtration to remove *Cyclops*. Chemical control of *Cyclops* using larvicides such as Temefos is also possible. Considerable progress has been made in the past decade in instituting effective public health measures for the control of dracunculiasis. Since 1986, the estimated prevalence has been reduced by 98% from an initial figure of 3.5 million [10].

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Enterobiasis

SYN. THREADWORM; PINWORM; SEATWORM; OXYURIASIS

Aetiology. *Enterobius vermicularis* is the commonest human intestinal worm, with a worldwide distribution. It is more prevalent in cold climates, and is associated with crowding and poverty. Children are most commonly affected, and females more than males. Whole families and communities, notably schools, may be infected [1]. Male and female worms develop in the caecum, becoming mature 2–8 weeks after ingestion of fertile eggs. Gravid female worms migrate to the anus, and at night crawl on the perianal skin where they lay up to 16 000 eggs and expire. The eggs mature within a few hours. Transmission is by ingestion of eggs, most commonly carried by fingernails, because of the itching during sleep. Hands may also become contaminated through sharing a bed or bedroom. Occasionally, transmission is airborne from infected dust, in which eggs may survive for up to 13 days. Adult worms live for 6–12 weeks.

Pathogenesis. Gravid female worms migrating on the skin cause intense itching, although not in all infected people. It is not known whether an allergic reaction is involved. Adult worms may burrow into the submucosa of the appendix or bowel and be associated with inflammation, although causation has not been clearly established. Female worms may migrate from the anus to the vagina, causing irritation and inflammation, and from there to the fallopian tubes or even peritoneal cavity, causing salpingitis and occasionally peritoneal nodules.

Clinical features. Anal and perineal pruritus at night, with sleeplessness and irritability, are the leading symptoms. Perineal intertrigo, nocturia, secondarily infected excoriations, localized urticaria [2], vulval irritation and mucoid discharge may occur [3]. Peritonitis and salpingitis [4,5] are described. It is important to realize, however, that a large number of infected children are asymptomatic.

Diagnosis. This may sometimes be made by seeing the 10-mm long female worms on the perineum at night, on toilet paper or in the stools. If possible, worms should be positively identified in a laboratory, to avoid confusion with proglotids of *Dipylidium caninum*. However, the best procedure is to wind a 6-cm strip of adhesive cellulose tape over the butt end of a test tube or a wooden spatula, sticky side outward. This is then rubbed over the perianal skin (preferably on waking) and the diagnostic eggs and adults stick to it. A drop of toluene is placed on a microscope slide and the tape is spread on it and examined microscopically.

Treatment. Of the several anthelminthic drugs available, mebendazole is probably the most effective, acting against all stages of the worm. In mass treatment campaigns, a single dose of 100-mg mebendazole cures over 90% of infections [6], but reinfection is common. More efficient is 100 mg twice daily for 3 days, repeated after 2 weeks. The whole family should be treated. In the interval, scrupulous attention should be paid to cleanliness of hands and nails on rising, after defaecation and before eating. After each dosing, the bed linen is changed, and the bedroom vacuum cleaned. Even so, relapses may occur and periodic retreatment may be needed. Pyrvinium 5 mg/kg,

piperazine 100 mg/kg and pyrantel pamoate 10 mg/kg are also effective.

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Ancylostomiasis

SYN. HOOKWORM DISEASE

'Ground itch', 'dew itch' and 'uncinarial dermatitis' all describe a variable and transient eruption due to skin penetration by larvae of the hookworms *Ancylostoma duodenale* and *Necator americanus*, and the roundworm *Strongyloides stercoralis*.

Aetiology. *Necator americanus* and *A. duodenale* are human hookworms very widely distributed in the tropics and subtropics. *Necator americanus* predominates in Central and South Africa, southern Asia and Melanesia, and is almost the sole hookworm in the New World and Polynesia. It rivals malaria in the store of misery and ill health that it creates [1]. *Ancylostoma duodenale* is the only human hookworm in Europe, the Mediterranean coast, central and northern Asia, and is more prevalent than *Necator* spp. in China, Japan and some parts of Indonesia.

Pathogenesis. The adult worms live in the jejunum with the head firmly attached to the mucosa and cause bleeding: *Necator americanus* 0.03 mL of blood per worm per day and *A. duodenale* 0.2 mL of blood per worm per day. They live for up to 5 years [2]. Bleeding leads to anaemia, hypoproteinaemia, digestive disturbances and retarded development [3]. Thousands of eggs are passed in the faeces. Eggs can survive varying periods of cold or drought, but under favourable conditions of warmth and humidity, hatch into motile rhabditiform larvae. After 5 days and further moults, the infective filariform larvae form. They migrate upwards through soil and grass and, after a period of contact of 5–10 min, can penetrate intact human skin. Walking barefoot is the commonest way of getting infected. Favourable places for transmission include soil around houses, places of work such as plantations and cultivated fields, and mines. Exceptionally, transmission occurs in England during a long hot summer, in playgrounds or picnic sites frequented by immigrants, and formerly in mines where temperatures are maintained above 20°C [4].

After penetrating the skin, larvae migrate within a day or two via the bloodstream to the lungs, pass up the bronchial tree, are swallowed and pass down the oesophagus, reaching the duodenum and jejunum, where they mature in 4–6 weeks. In passing through the lungs they cause acute alveolitis or pneumonitis.

Clinical features. Larvae penetrating the skin cause ground itch: severe pruritus accompanied by erythema and often a papular or papulovesicular rash [5]. The rash is most commonly on the feet, and may be accompanied by a generalized urticaria. The rash is more common with *Necator* infections, and may become secondarily infected as a result of scratching. Larvae passing through the lungs cause a syndrome of cough, wheeze and dyspnoea, which lasts for several days. Adult worms in the gut cause abdominal pain, diarrhoea and, occasionally, melaena. Later, features of iron-deficiency anaemia, with haemoglobin levels as low as 5 g/dL, and hypoproteinaemia develop with pallor, oedema, puffy face and listlessness. Changes in the texture of skin and hair resemble those seen in kwashiorkor [6].

Diagnosis. Clinical and circumstantial evidence point to a diagnosis of ground itch. Löeffler's syndrome is characterized by eosinophilia and patchy pneumonitis seen radiologically. Established infections are diagnosed by demonstrating characteristic eggs in the faeces.

Treatment. Ground itch is treated symptomatically with an antipruritic cream, such as crotamiton with 1% hydrocortisone, or oral antihistamines. Pulmonary symptoms, if severe, respond to a few days' corticosteroids. Established infections respond to a 3-day course of albendazole or mebendazole. Oral iron is given for iron deficiency.

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Strongyloidiasis

SYN. STRONGYLOIDAL GROUND ITCH; LARVA CURRENS

Strongyloides stercoralis is a widespread parasitic roundworm with a life cycle and distribution similar to that of the hookworm, but with important differences [1]. It

occurs in warm, especially damp, climates and is especially prevalent in South-East Asia.

Aetiology. Adult male and female worms, 3 mm long, live in the mucosal crypts of the duodenum and jejunum; eggs hatch quickly and rhabditiform larvae are passed in the faeces. In soil, they may either moult into infective filariform larvae, or set up a free-living cycle, with the production of more infective larvae. Infective larvae penetrate human skin, to establish new infections or augment existing ones. Alternatively, larvae mature in the gut and reinfect the patient by penetrating the mucosa or the perianal skin. This autoinfection is capable of maintaining the infection indefinitely, and predisposes to the syndrome of hyperinfection, in which extremely heavy worm loads build up and leave the confines of the gut, in patients who are immunosuppressed by corticosteroid drugs or Hodgkin's disease, or debilitated by advanced age, tuberculosis or other severe infection, ketoacidosis or burns [2].

Pathology [3]. Penetration of the skin by filariform larvae may cause dermatitis. Adult worms give rise to duodenitis and jejunitis, which may cause diarrhoea and malabsorption. Migrating larvae in the skin give rise to a weal-and-flare response, which follows the path of the larva. Hyperinfection causes severe enteritis with fluid loss, and paralytic ileus, pneumonia, meningoencephalitis and secondary Gram-negative bacterial septicaemia with shock and disseminated intravascular coagulation.

Clinical features. Ground itch of initial infection is similar to that seen in hookworm disease. Intestinal infection causes abdominal pain, diarrhoea and, if severe, weight loss or stunting of growth in children [4]. Associated allergic phenomena are common. Urticaria occurs in 66% of cases of strongyloidiasis among ex-Far-East prisoners of war, who have had the infection for over 45 years [5]: IgE levels are raised. Thirty per cent of these individuals also suffer from larva currens, the urticarial weal and flare of migrating subcutaneous larvae. Tracks are seen anywhere on the skin between knees and nipples (Fig. 32.16), but especially around the anus and buttocks. They move at a rate of several centimetres an hour and can traverse the abdomen in a single day, to be gone the next day: features that distinguish the rash from that of larva migrans (see below). Tracks may be several centimetres long or consist simply of one or more urticarial papules. Tracks may be linear or serpiginous [6].

Heavy infection causes severe diarrhoea, with fluid and electrolyte loss; signs of ileus may develop. Fever, abdominal distension, cough, dyspnoea, mental changes and unconsciousness may develop, and the patient may become shocked. Shock commonly indicates a complicating Gram-negative septicaemia. Cough, dyspnoea and chest signs suggest pneumonia. A widespread petechial or purpuric rash may be seen [7].

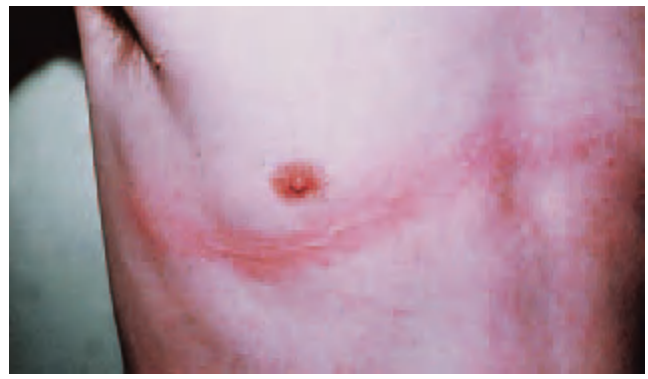

Fig. 32.16 Larva currens rash of *Strongyloides stercoralis*. The weal and flare will have disappeared in a few hours.

Diagnosis [8]. Larvae of *Strongyloides* spp. are demonstrated in the faeces, by one of several concentration or culture techniques. Diagnostic yield is increased by examining samples of jejunal juice, most conveniently obtained by a 'string test' (Enterotest capsule) or jejunal biopsy. In a few centres, a strongyloides antibody test is available. Except in the hyperinfection syndrome, eosinophilia is common and tests for malabsorption may be positive.

Treatment. Until recently, thiabendazole has been the drug of choice, given in a dose of 25 mg/kg body weight orally twice daily for 3 days, and repeated after 2 and 4 weeks. In unconscious patients or those with vomiting, the drug is given every 6 h by nasogastric tube. Side effects are common, and include headache, malaise, nausea and vomiting. Albendazole is also effective in a dose of 400 mg/day for 3 days, and is free of toxicity. Ivermectin in a single oral dose of 200 μg/kg body weight, to be repeated on day 7, is the currently recommended treatment at the Hospital for Tropical Diseases in London. Faecal and jejunal samples should be examined for larvae after 3 and 6 months. Mebendazole is an alternative.

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Infection with nematodes of other animals

Nematodes that do not normally parasitize humans are often unable to mature or develop fully, or to home to their normal site in the body. Biologically, the human is a dead-end host. The infective larvae tend to wander, causing one of several forms of larva migrans, or the adult worm migrates, causing migratory allergic phenomena. Worms reach unusual sites and give rise to eosinophilic granulomas, occasionally in important sites, such as the eye, causing blindness, or the lungs, causing radiological confusion. In other infections, full development may take place and humans act as accidental intermediate hosts.

Cutaneous larva migrans

SYN. CREEPING ERUPTION; SAND-WORM ERUPTION; PLUMBER'S ITCH; DUCK-HUNTER'S ITCH

Cutaneous larva migrans in a clinical term for a distinctive cutaneous eruption that has numerous causes. The prime features, as the name suggests, are that the lesions creep or migrate, and that they are due to the presence of moving parasites in the skin. Visceral larva migrans also occurs (see below).

Aetiology [1]. Causes of creeping eruption include *Ancylostoma brasiliense*, *A. caninum*, *A. ceylonicum*, *Uncinaria stenocephala* and *Bubostomum phlebotomum*. These are all hookworms of various animals, of which the first, the dog hookworm, is the commonest cause of creeping eruption in humans. *Anatrichosoma cutaneum*, a parasite of monkeys in the Far East, is a rare cause. *Strongyloides stercoralis* causes a distinctive form of cutaneous larva migrans. *Dirofilaria repens* and *Spirometra* spp. cause a subcutaneous granuloma that may migrate very slowly. *Gnathostoma* spp. and *Loa loa* cause migratory evanescent subcutaneous swellings. Cutaneous myiasis due to larvae of flies of the genera *Gasterophilus* and *Hypoderma* may cause a creeping eruption similar to that caused by the animal hookworms. Only the helminths that cause creeping eruption are considered further here.

Adult hookworms live in the intestines of dogs and cats, and their ova are deposited in the animals' faeces. Under favourable conditions of humidity and temperature, the ova hatch into infective larvae, which will penetrate human skin. Sandy, warm, moist, shaded areas are particularly favourable, and numerous infections are acquired by children in sandpits, plumbers under houses, farmworkers under outbuildings, hunters in hides, gardeners from the soil and seabathers from the sandy shore above the ebb and flow of the tides. The condition is common in all warm climates, and may occur in northern Europe during a hot summer. A case series in 44 travellers who mostly acquired the condition by direct skin contact with infested sand while on tropical beach holidays has recently been described [2].

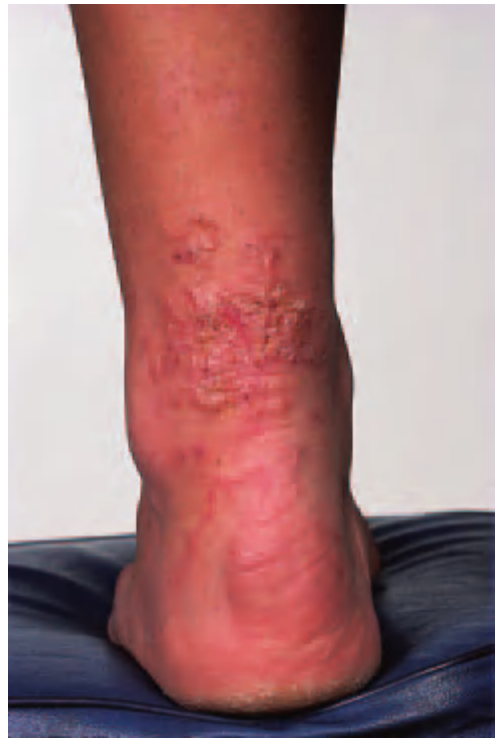

Fig. 32.17 Cutaneous larva migrans (creeping eruption). There are several tortuous indurated inflamed worm tracks, in some of which may be seen a blister that marks the head of the track.

Clinical [3]. The larvae may cause a non-specific dermatitis at the site of penetration where the skin has been in contact with infected soil. This is commonly the feet, hands and buttocks. They can then lie quiet for weeks or months, or immediately begin creeping activity with the production of a wandering thread-like line about 3 mm wide. This is exceedingly itchy, slightly raised, flesh-coloured or pink, and forms bizarre, serpentine patterns. Large numbers of larvae may be active at the same time, with the formation of a disorganized series of loops and tortuous tracks (Fig. 32.17).

The larvae advance at a rate of a few millimetres to a few centimetres daily, and are somewhat in front of the head of the track. The wanderings of an individual larva are usually confined to a relatively small area, but exceptionally it travels much further. Itching leads to scratching and secondary changes of dermatitis and bacterial infection. In later stages, these tracks are difficult to see, the path being marked by small itchy and discontinuous nodules.

The disease is self-limiting. Estimates for the natural duration of the disease vary considerably. This variation almost certainly depends on the species of larva observed,

and this is usually unknown. In one study, 25–33% of larvae died every 4 weeks, whereas in another (presumed due to *Ancylostoma brasiliense*) 81% of lesions disappeared in 4 weeks [4]. Some persist for many months.

Larva migrans can be accompanied by Löeffler's syndrome of pulmonary eosinophilia, particularly in severe infestations [5].

Diagnosis. The classic clinical picture of wandering, advancing, serpentine and itchy lesions is easily recognized, but may be atypical, hidden by vesicles and scaling, or spoiled by scratching and secondary infection.

Larva currens and migratory myiasis must be distinguished and, in the Orient, gnathostomiasis.

Biopsy in larva migrans is of little value, as the larvae have advanced beyond the clinical lesions.

Treatment. Ivermectin in a single dose of 200 µg/kg body weight seems best [6]. Albendazole 400 mg/day by mouth for 3 days is also effective. An alternative choice of treatment is the topical application of 10% thiabendazole. Either the commercially available oral preparation may be used directly [7], or two 0.5-g tablets of thiabendazole are triturated in 10-g petrolatum and applied twice daily. Well over 95% of the tracks clear within a week. Oral thiabendazole is less effective and more toxic.

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Visceral larva migrans: toxocariasis

Many non-human and human helminths may be found migrating in human organs at some stage of their life cycle, but the syndrome of visceral larva migrans is synonymous with the severe form of toxocariasis.

Aetiology. This infection is caused by *Toxocara canis*, *T. cati* and *T. leonensis*, the common roundworms of dogs, cats and wild carnivores. The domestic dog is the most important source of human infection, and the prevalence of infection in dogs may be high, reaching 73% in New York State and 100% in puppies in Brisbane [1]. Infection is intense in puppies because of transplacental infection, which is augmented by infection from breast milk and contaminated bed litter [2]. Eggs are passed in dog faeces. Humans are most commonly infected by ingesting eggs in soil, or in contaminated food or water. Children are especially at risk when playing in parks or other areas frequented by dogs, or from domestic puppies that have not been regularly wormed. Ova remain infective on soil for many months.

The incidence of human infections is not finally established, but skin tests on apparently healthy subjects suggest that at least 2% of the general population of the UK acquire the infection [2]. The incidence is higher in those in close contact with animals, especially under primitive living conditions. Of a rural population in Pennsylvania, 54% were infected [3].

Pathogenesis. In humans, the second-stage larvae migrate from the intestine to most parts of the body, but notably to liver, lungs, muscles and brain where they eventually die in eosinophilic granulomas.

Clinical features. Most human infections are asymptomatic, or at least unrecognized. Persistent eosinophilia is, however, probably invariably present [4]; counts of over 25×10^9/L are common. In a proportion of infected children, the full syndrome of visceral larva migrans develops. The essential features, apart from eosinophilia, are cough and dyspnoea, failure to gain weight, muscle pains and sometimes fever. The liver is enlarged. Hyperglobulinaemia is frequent. The syndrome is self-limiting after a few months if reinfection is prevented.

Since so many cases are undiagnosed, the incidence of cutaneous manifestations is unknown. Generalized pruritus and urticarial or papular eruptions of the trunk and legs are most frequently reported. Migrating panniculitis, although rarely reported, is distinctive and perhaps pathognomonic: substantial, tender, subcutaneous nodules vanish after 1 or 2 weeks [3,5].

In a minority of infected individuals, who have never experienced visceral larva migrans, a wandering larva causes an ocular granuloma simulating a neoplasm [6].

Diagnosis. This is reliably confirmed by biopsy of the liver or of a cutaneous nodule. Fluorescent antibody and ELISA techniques are helpful [7].

Treatment. Albendazole may prove to be the best treatment [8]. Cure rates are low with DEC or thiabendazole [9].

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Gnathostomiasis

Gnathostomiasis is an infection caused by *Gnathostoma spinigerum*, *G. hispidium* and *G. nipponicum*, the definitive host of which are cats, wild felines, dogs and certain other animals that eat fish, snakes and frogs. Human gnathostomiasis occurs throughout South-East Asia, east of and including Bangladesh, China, Japan, Indonesia and the Philippines. The greatest number of cases is in Thailand. There are also reports from Mexico [1].

Aetiology. Adult worms live in tumours in the stomach of the carnivore. Eggs are passed in the faeces, hatch in water and are ingested by a species of *Cyclops*, in which they transform further. When *Cyclops* is ingested by frogs, snakes or fish the larvae develop to the third stage in the flesh of the animals, which in turn are eaten by the definitive host, thus completing the cycle. Humans are infected either by ingesting *Cyclops* in water or by eating inadequately cooked flesh of an intermediate host. Worms removed from a person are most commonly third-stage larvae or immature adults, which measure 2–4 mm long and are rust brown in colour due to ingested blood. The head of the worm is crowned by 4–8 rows of hooklets (Fig. 32.18) and the anterior half of the body is covered in leaf-like spines. Rarely, a mature male worm, up to 12 mm long, has been found [2].

Pathogenesis. Larvae ingested by humans wander, mainly in subcutaneous tissues and muscles, causing deep tunnels, which form the sites of episodes of inflammation or abscess formation. Histology shows intense infiltration with neutrophils, plasma cells, chronic inflammatory cells and especially eosinophils. Less common sites of infection include the brain and eye.

Clinical features. The commonest presentation is of intermittent migratory subcutaneous swellings, several centimetres in diameter. They are firm, warm, red, painful and last up to 4 weeks, before disappearing and returning nearby. They occur most commonly on the upper parts of the body, including the orbit. Abscesses may develop subcutaneously or in muscle [3].

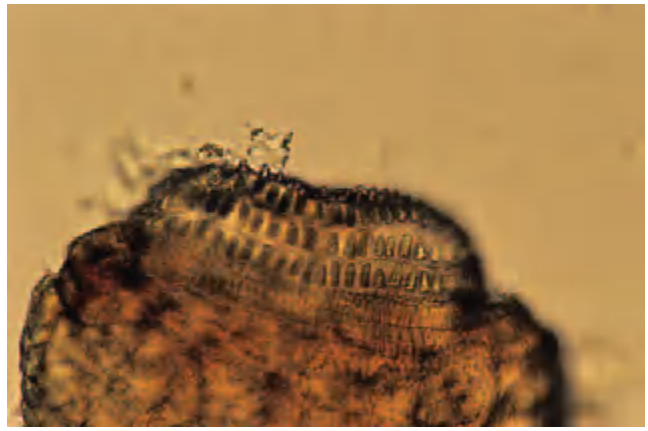

Fig. 32.18 *Gnathostoma spinigerum*. Head of adult worm that was extruded from a subcutaneous swelling in a patient from Bangladesh. The crown of hooklets is characteristic. (Courtesy of Dr P.L. Chiodini, Hospital for Tropical Diseases, London, UK.)

Fatal encephalomyelitis has also been described [4]. Isolated swellings may simulate inflammatory or neoplastic disease of other internal organs.

Diagnosis. Geographical history, clinical features and a peripheral eosinophilia suggest the diagnosis, which is confirmed by surgical extraction of the worm. Occasionally, a worm is expelled through the skin. A reliable serological test is available through some specialist centres.

Differential diagnosis. Other nematodes that may cause similar clinical pictures include *Lagochilascaris minor*, a cause of subcutaneous abscesses in Surinam and Central America, *Thelazia callipaeda*, which parasitizes the conjunctival sac in the Far East, and *Gongylonema pulchrum*, a cosmopolitan parasite of pigs, bears, hedgehogs and monkeys that causes migratory lesions in the oropharyngeal submucosa of humans [5].

Treatment. Albendazole in a dose of 400 mg/day is effective if given for 6 months. The shortest effective course has not been determined [6]. Other anthelmintics have not proven useful. Worms may be removed surgically. Treatment of worms of the face is important, to prevent ocular involvement [7].

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Dirofilariasis

Aetiology. Dirofilariasis is an infection by filarial nematodes of the genus *Dirofilaria*. There are two forms of the disease:
1 subcutaneous dirofilariasis caused by *D. tenuis* (*D. conjunctivae*), *D. ursi*, *D. subdermata* and *D. repens*;
2 pulmonary dirofilariasis caused by *D. immitis*, the dog heart worm.

Dirofilaria ursi and the related *D. subdermata* are natural parasites of bears and porcupines, respectively.

Subcutaneous dirofilariasis

Geographical distribution and life cycle. Most cases are reported from the southern USA, but there are occasional reports from Africa, Asia and South America. *Dirofilaria repens* is a subcutaneous parasite of dogs and cats and *D. tenuis* of raccoons in the USA. Transmission to humans is thought to be by mosquitoes.

Clinical features [1–3]. The lesion is usually a tender, occasionally migratory, subcutaneous nodule which develops over a few weeks. Common sites are eyelid, scrotum, breast, arm and leg. The worm may also be seen in the conjunctiva and is present within a foreign-body granulomatous reaction in the nodule (Fig. 32.19). Microfilariae are not found in the blood.

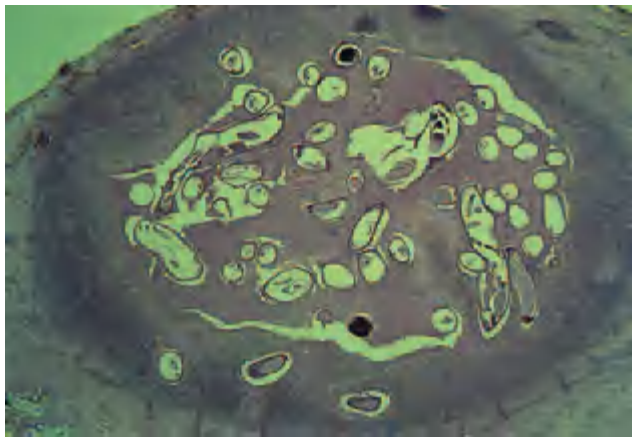

Fig. 32.19 Dirofilariasis. Low-power view of cold abscess from the cheek. It shows degenerate coiled *Dirofilaria* worm within an abscess, and surrounding lymphocytic infiltrate and fibrosis. (Courtesy of Professor S.B. Lucas, King's College, London, UK.)

Diagnosis and treatment [4]. This is made by extracting the worm from the lesion, or by identifying it in an excised specimen. Treatment is by surgical removal.

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Trichinosis

SYN. TRICHINIASIS; TRICHINELLIASIS

Trichinosis is an infection of intestine and muscle, with *Trichinella spiralis*, a natural parasite of a wide range of carnivores. The human is normally an end host. A variety of allergic phenomena characterize human infection. Trichinosis is distributed worldwide. It is an important disease both in Europe and in the USA and has been found in Africa, south of the Sahara.

Aetiology. Encysted larvae of *Trichinella spiralis* are ingested in meat, hatch in the duodenum, penetrate the submucosa, and within 5 days have matured and mated and started producing 200–2000 invasive larvae, which reach muscles where they become encysted and infective to a fresh host within 21 days. The adult worms live less than 2 months. Cysts may calcify, but the larvae remain viable for many years and can outlive their dead host by 10 days [1].

Humans acquire the disease by eating raw or undercooked meat infected by *Trichinella spiralis*—usually pork sausages in Germany and areas to which Germans have emigrated, bush pig in Africa, polar and black bear meat in Alaska and the Arctic. Entire polar expeditions have died of the infection after eating polar bear.

Pathogenesis. Intestinal infection causes partial villous atrophy and mucosal and submucosal inflammation. The deposition of larvae in muscles is associated with oedema, loss of cross-striations and basophilic degeneration (Fig. 32.20). The coiled larvae are surrounded by an inflammatory infiltrate of lymphocytes and macrophages until they become encapsulated.

Clinical features [2,3]. The disease may be symptomless or mild, but generally, after a moderate infection with the 'muscle worms', severe symptoms resembling acute food poisoning ensue rapidly. These are followed within a week by an acute illness with fever, generalized muscle pain and tenderness, sweating, periorbital oedema, conjunctivitis, some paralysis of the muscles of the tongue, jaw and

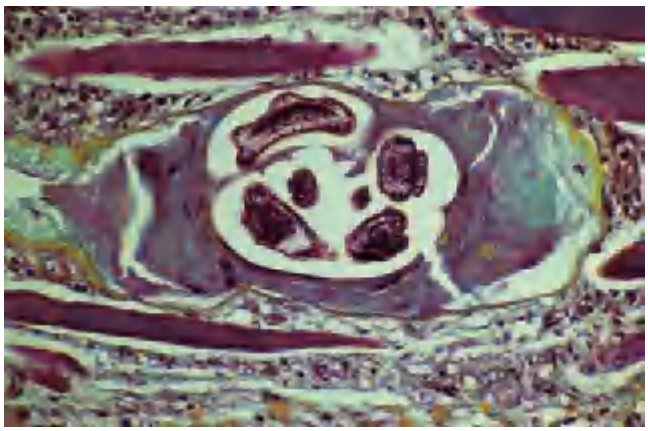

Fig. 32.20 Trichinosis. Medium-power view, Movat stain, showing *Trichinella* worm within a 'nurse cell' in skeletal muscle. There is surrounding oedema, muscle disruption and lymphocytic infiltrate. (Courtesy of Professor S.B. Lucas, King's College, London, UK.)

respiration, with a transient maculopapular rash of the extremities, and splinter haemorrhages beneath the nails.

In severe infections, there is involvement of the heart and central nervous system (CNS). A necrotizing vasculopathy equivalent to classic polyarteritis nodosa is described [4].

Diagnosis. Within a week of eating inadequately cooked meat, especially pork, clinical features suggest the diagnosis. Worms may be found in faeces in the second to fourth week of the infection, and after 4 weeks in biopsied muscle. The eosinophil count, erythrocyte sedimentation rate and serum creatine phosphokinase are all raised. After 3 weeks, antibodies become detectable. Bentonite flocculation and ELISA [5] are the tests most commonly used.

Treatment. Corticosteroids are life saving in suppressing allergic reaction at the height of larval spread. Mebendazole and thiabendazole reduce the severity of infection if given early enough in the acute disease, but albendazole is possibly more effective [6].

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Infection with trematodes

SYN. FLUKES; FLATWORMS

Trematodes are non-segmented, single-sex worms, flattened like a leaf and without a formal organ of attachment. Pairs of adult worms live in a hollow viscus (vein, gut, bile duct, lung), from whence eggs make their way into faeces, urine or sputum. The eggs must enter water, hatch and infect a species of snail, in which a cycle of development and multiplication occurs, resulting in the release of motile cercariae. These either penetrate human skin or enter a resting stage in aquatic plants, fish or crustacea, and are later eaten. Trematodes are important and common parasites of humans, especially in Africa and the Far East. They cause skin disease either as a result of cercarial penetration, by the ectopic deposition of adult worms or their eggs, or by causing allergic phenomena.

Schistosomiasis

SYN. BILHARZIASIS

Schistosomiasis or bilharziasis is a serious systemic disease due to different species of human schistosomes or blood flukes [1]. Rashes may occur during the invasive stage of this disease, when the skin is being penetrated by cercariae, and later there may be skin involvement at or near mucocutaneous surfaces, and less commonly at more distant sites on the trunk, following dissemination of ova.

A second group of non-human schistosomes cause cutaneous symptoms only. This situation follows penetration of cercariae into the skin, but further development of the flukes in humans is arrested and there are no sequelae. The condition 'swimmer's itch' or cercarial dermatitis is an example of this process.

Skin manifestations of this common disease of tropical and subtropical distribution are incidental features of the underlying disease. They may be grouped as follows [2]:

1 schistosomal dermatitis;
2 urticarial reactions in the early weeks of the disease;
3 paragenital granulomas and fistulous tracts;
4 ectopic cutaneous schistosomiasis.

Ectopic sites of egg deposition probably arise through migration of adults via the paravertebral venous plexus.

Aetiology [3]. Schistosomiasis is caused by the human blood flukes *Schistosoma mansoni*, *S. japonicum* and *S. haematobium*. Two other species, *S. mekongi* and *S. intercalatum*, are more rarely associated with infection in humans.

Humans infected with *S. mansoni* and *S. japonicum* excrete eggs in the faeces, and with *S. haematobium* excrete eggs in the urine. On contact with water, these eggs develop into miracidia, which undergo further development in certain aquatic snails. From these, free-swimming cercariae are released, which are capable of penetrating

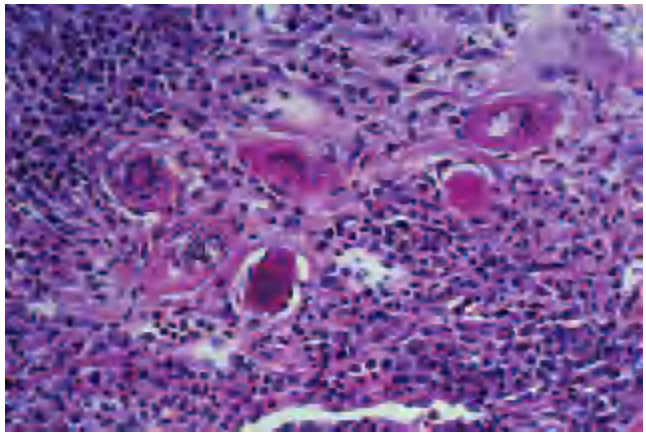

Fig. 32.21 Schistosomiasis of the vulva (medium power, H&E) showing six schistosome eggs with surrounding lymphoplasmocytic infiltration. (Courtesy of Professor S.B. Lucas, King's College, London, UK.)

human skin to produce the infection [4]. The organisms can pass rapidly through the epidermis, and enter the venous blood within 24 h of contact with human skin. The larvae are then carried through the heart and lungs, and mature into flukes in the intrahepatic portion of the portal system.

Finally, the mature flukes pass from the portal system into pelvic veins, where eggs are laid. *Schistosoma mansoni* and *S. japonicum* localize primarily in the veins around the rectum and colon, while *S. haematobium* invades vesical and, sometimes, rectal veins with the production of haematuria and other urinary symptoms. Ova work their way out of the veins into the tissues, where they cause the formation of granulomas in which there is a pseudotubercle arrangement of inflammatory cells rich in eosinophils and histiocytes, and occasional giant cells, surrounding the diagnostic ova [5]. Lesions occurring away from the characteristic sites of egg deposition are termed 'ectopic' (Fig. 32.21). Disease due to the commonest agent, *S. mansoni*, is endemic in Africa and South America (especially the Nile delta and North-East Brazil). *Schistosoma japonicum* occurs in the Far East, and *S. haematobium* extensively in Africa (especially in the Nile and Rift Valleys), Arabia, Malagasy and South-West India [6].

High prevalence rates in workers immigrant to temperate climates [1,7], outbreaks among foreign personnel employed in endemic areas and occasional case reports of the disease in individuals who have left those areas, reflect the frequency with which infections such as schistosomiasis are encountered outside their endemic area. Infections may also be seen in short-term visitors to an endemic zone, particularly if they have swum in an infected lake or river.

Clinical features. Skin involvement may occur either as a result of the initial penetration of the skin by water-borne, free-living cercariae (an intermediate stage in the life cycle), during an immune-complex-mediated phase of the infection, Katayama fever [8], or in the later stages of infection following ectopic localization of worms or ova [9].

1 *Schistosomal dermatitis.* Penetration by cercariae of parts of the epidermis in contact with water may pass unnoticed, or cause an itchy papular eruption indistinguishable from swimmer's itch (cercarial dermatitis due to non-human flukes). The symptoms of itching usually last only for a few hours after leaving the water, although mild erythema may persist for longer. In sensitized individuals, however, papules and itching persist for about a week [2].

2 *Urticarial reactions.* Four to eight weeks after penetration of the skin by cercariae, urticaria may occur. This is particularly severe in *S. japonicum* infection, together with fever, purpura, malaise, arthralgia, abdominal cramps, diarrhoea and enlargement of liver and spleen. In some areas, for example China and Japan, this feature is so prominent that the disease is called 'urticarial fever' or Katayama disease. Eosinophilia is also typical. The symptoms resolve in about 4–6 weeks.

3 *Paragenital granulomas and fistulous tracts.* In areas of high endemicity, cutaneous bilharziasis of the perineum and external genital regions is not uncommon [10,11]. This follows direct spread of adult flukes to adjacent vasculature. Granulomatous genital condylomas occur, and fistulous tracts with extensive firm masses, honeycombed by sinuses, are characteristically found on the perineum, groins or buttocks (Fig. 32.22).

4 *Ectopic cutaneous schistosomiasis* [12–14]. Ova may become deposited in the skin as well as in other ectopic sites, such as conjunctiva, lungs and CNS. They arise following embolism of ova from adults, which are localized in abnormal sites, such as the paravertebral plexus [2]. The trunk is almost invariably the site of ectopic cutaneous involvement. The primary lesion is a flesh-coloured, firm papule reaching a size of 2–3 mm, and ovoid in shape. These papules agglomerate to form slightly raised plaques with irregular contours. Later still, some plaques develop a mammillated surface, and deepen in colour but retain their irregular, ovoid contours. The skin over old nodules may be deeply pigmented and scaly, and may later ulcerate. The para-umbilical area is a common site [12] but other areas may be involved (Fig. 32.22) and, in some cases, the lesions have a segmental or zosteriform distribution [7,14]. With treatment, these lesions slowly disappear in about 5 months. A facial hypopigmented plaque is described.

The major complications of schistosomiasis are due to infections affecting the liver (fibrosis), intestinal involvement and bladder infection, which may lead to carcinoma of the bladder. Other sites of involvement include the kidneys, heart, CNS and retina [4].

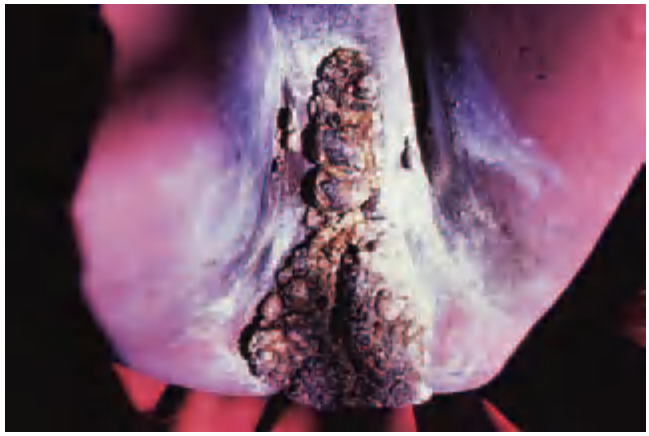

Fig. 32.22 Schistosomiasis of the vulva and anus. Condylomatous lesions containing granulomas around schistosome ova. (Courtesy of Professor G. Nelson, Liverpool School of Tropical Medicine, Liverpool, UK.)

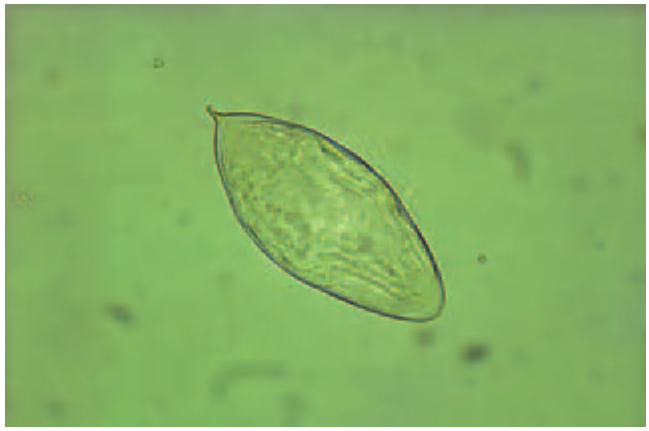

Fig. 32.23 *Schistosoma haematobium* ovum in urine. (Courtesy of Mr A.H. Moody, Hospital for Tropical Diseases, London, UK.)

Diagnosis. The characteristic ova may be found in stools or urine (Fig. 32.23). On occasions, rectal biopsy is an alternative method of finding ova. The latter have a characteristic morphology. Serological methods are useful for screening. Immunofluorescence and ELISA are commonly used. Ectopic cutaneous schistosomiasis is diagnosed by biopsy. Histology shows epithelioid cell granulomas containing degenerate ova (Fig. 32.21).

Treatment. Praziquantel is given as a single dose of 20 mg/kg twice in 1 day, except in infections due to *S. japonicum*, where 20 mg/kg three times in 1 day is administered [15]. Cure rates are high with this regimen, and there are few side effects such as abdominal discomfort and headache. Other drugs that are available include metrifonate for *S. haematobium* and oxamniquinine for *S. mansoni*. In early infections, the results of therapy are excellent, although reinfection is a continuing risk. Cercarial dermatitis resolves spontaneously. However, many of the complications of the infection such as hepatic fibrosis, portal hypertension and ureteric stenosis are irreversible, due to scar formation.

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Cercarial dermatitis

Cercarial dermatitis is the name given to a group of skin disorders having a common aetiology—penetration of the skin by free-living cercarial stages of non-human schistosomes [1]. There are a number of local names for these conditions, such as swimmer's itch, clam digger's itch, sedge pool itch, koganbyo and sawah itch. While the clinical features of the condition are similar whatever the aetiology, there are three main types of cercarial dermatitis.

1 *Fresh-water avian cercarial dermatitis* [2,3]. This follows penetration of the skin by cercariae of avian blood flukes. The intermediate hosts are fresh-water molluscs. The flukes belong to the genera *Trichobilharzia*, *Gigantobilharzia* and *Ornithobilharzia*. The condition has been described from many different parts of the world including North America, particularly the lakes region of the USA, Canada, Europe, Africa and the Far East [2,4]. In some countries, it affects patients with particular occupations such as rice farmers working in the paddyfields.

2 *Sea-water avian cercarial dermatitis* [5]. This follows invasion of the skin by blood flukes whose definitive hosts are sea birds. While it is recorded less frequently than infections caused by fresh-water species, it accounts for the condition, seen in the Atlantic seaboard of the USA, known as clam-digger's itch. The intermediate hosts are marine molluscs. The term 'sea bather's eruption' is used to describe a variety of different rashes that may develop after sea bathing. It is likely that it includes a number of different conditions from jellyfish dermatitis to eruptions due to toxic algae. A sea water form of cercarial dermatitis is therefore one cause of sea bather's eruption [1].

3 *Fresh-water mammalian cercarial dermatitis* [4]. This has been reported mainly from the Far East, and the definitive hosts for the schistosomes in this condition are mammals such as water buffaloes.

Attempts to find common features connecting the likely locations for cercarial infections have not been entirely successful. It is apparent, however, that areas endemic for cercarial dermatitis usually have abundant submerged vegetation harbouring the intermediate hosts. Hot spells of weather have also been associated with a higher risk of the development of symptoms [6].

Pathogenesis. The pathogenesis of cercarial dermatitis is not completely understood, although the kinetics of the clinical response suggest that sensitization is involved. The first phase of epidermal penetration is accompanied by dermal oedema, which is followed by a brisk neutrophil reaction.

Clinical features. Most forms of cercarial dermatitis have common features, although their intensity varies between different individuals [2]. The first sign of an infection is the development of a tingling sensation after contact with water. This lasts for about 1 h and there may be a fine macular erythema. After 10–15 h, there is usually a second phase with the appearance of multiple itchy papules with surrounding erythema. These may evolve into vesicles or oedematous lesions. The whole reaction takes about a week to resolve. The papules closely resemble small insect bites. There are no long-term sequelae.

Treatment. Treatment is entirely symptomatic. Although brisk rubbing with a dry towel seems sensible advice, there is no evidence that it prevents the second phase of responses [1]. Patients can be treated with antihistamines or topical applications such as crotamiton. Preventative measures are seldom called for as infections tend to be sporadic. Control of vegetation in endemic areas or of the snail population are possibilities, but seldom practised unless the more serious problem of schistosomiasis is also present.

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Paragonimiasis

Infections caused by the lung fluke, *Paragonimus westermani*, are found in the Far East, West Pacific and in parts of India and Central Africa [1]. Similar species, *P. africanus* and *P. peruviana*, cause disease in the Cameroons and Central and South America, respectively [2]. In China, two rare species, *P. szechuanensis* and *P. hueitungensis*, have been recorded as causes of migratory subcutaneous nodules in humans. The adult worms are found in the respiratory tract, from which eggs are coughed up and swallowed, thus entering the faeces. Miracidia are released on contact with water and seek and penetrate snails. These in turn are the first intermediate hosts, and liberate cercaria, which then enter the muscles of fresh-water crustaceans such as crayfish. Human infection results from ingestion of inadequately cooked crabs and crayfish. Ingested metacercaria penetrate the intestinal wall and make their way through the diaphragm to the lungs. Adult worms encyst in the lungs (Fig. 32.24) and cause a chronic cough with fever and sweats. Brown-stained sputum is characteristic. Flukes may also reach ectopic sites such as the peritoneum, brain or skin.

Skin lesions of paragonimiasis are large, mobile subcutaneous lesions, which develop into cold abscesses [3]. They can occur at any site including the conjunctiva, and may enlarge rapidly to reach a diameter of 10 cm or more. The larger lesions are often painful but they may rupture spontaneously.

The diagnosis can be confirmed by demonstrating the characteristic ova in sputum or in aspirates from cutaneous lesions.

This infection responds well to praziquantel in a dose of 25 mg/kg three times in a single day [4].

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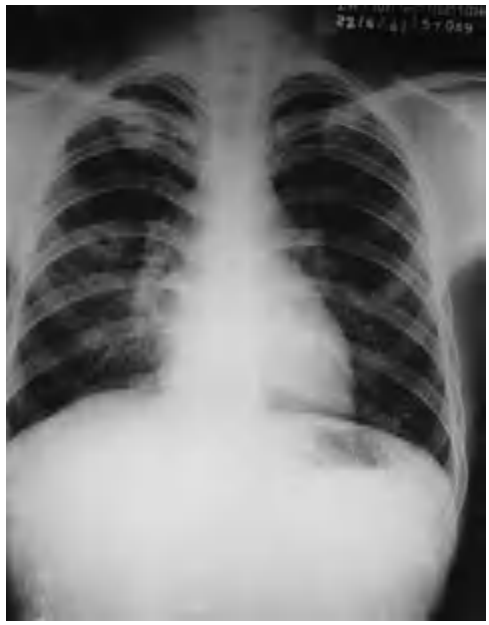

Fig. 32.24 Paragonimiasis. Chest X-ray showing three discrete opacities, in two of which cavitation is present, characteristic of the disease in Thailand. (Courtesy of Professor D.A. Warrell, Oxford Radcliffe Hospital, Oxford, UK.)

Infection with cestodes

SYN. TAPEWORMS

Tapeworms are flat, ribbon-like worms composed of a variable number of segments called proglottids. The anterior segment or scolex comprises the head, which carries hooks or suckers for attachment to the intestinal mucosa, and a narrow neck from which the proglottids develop. As the hermaphroditic proglottids mature, they become motile sacs full of eggs, which separate from the worm and pass in the faeces or wriggle through the anus. Adult tapeworms inhabit the intestinal lumen of a wide range of natural hosts. Eggs are taken up by an intermediate host and undergo often complex larval development; in some species, there may be two or more intermediate hosts, each supporting a different phase of larval development. The human is a natural host to certain tapeworms, and may be an accidental host to others. Generally speaking, infection with adult worms causes little or no disease, but infection with the larval stages may be serious [1].

Tapeworms that infect humans may be divided into two orders, Cyclophyllidea and Pseudophyllidea, within each of which certain species may cause skin disease.

Cyclophyllidea

Echinococcus granulosus and E. multilocularis. Tapeworms, respectively, of dogs and foxes. Larval stages cause echinococcosis, or hydatid disease in humans.

Taenia saginata. The beef tapeworm of humans. Causes taeniasis. No skin parasitization.

Taenia solium. The pork tapeworm of humans. Causes (i) taeniasis; and (ii) cysticercosis.

Multiceps multiceps. A tapeworm of dogs and wolves. Its larval stage (coenurus) may parasitize human brain and other organs [2].

Multiceps serialis. A tapeworm of dogs, wolves and foxes, whose larval stages may parasitize human muscle or subcutaneous tissue [3].

Multiceps brauni. A tapeworm of dogs whose coenurus may parasitize subcutaneous tissue and the eye in humans [2,4,5].

Pseudophyllidea

Spirometra spp. Tapeworms of carnivores. The larval forms (spargana) cause sparganosis in humans.

Diphyllobothrium latum. The fish tapeworm of humans. Causes diphyllobothriasis.

Echinococcosis

SYN. HYDATID DISEASE

Two species in the genus *Echinococcus* parasitize humans with the formation of hydatids, namely *E. granulosus* and *E. multilocularis* [6]. Adult *E. granulosus* lives in the intestine of the dog and, if ova are accidentally swallowed by humans or other animals, hydatid cysts develop. Sheep are the commonest intermediate hosts. Similarly, adult *E. multilocularis* lives in the bowel of red fox and arctic fox. Mice, voles and lemmings are the intermediate hosts.

Pathogenesis. Humans become infected by ingesting eggs in food or water that has been contaminated by, usually, dog faeces. In endemic countries, especially those where sheep rearing is not accompanied by strict regulations, children's hands readily pick up the eggs from the coats of dogs. Eggs hatch in gastric acid and penetrate the wall of the duodenum, and are distributed via the bloodstream, mainly to liver and lungs, but bones and any other organ may also be infected. The larvae develop into fluid-filled cysts whose germinal layer produces numerous protoscolices, capable of becoming the scolices of adult worms after ingestion by the definitive host.

Cysts of *E. granulosus* tend to grow slowly and bud inwards, producing daughter cysts. Those of *E. multilocularis* may bud outwards, and thus spread through the tissues like a cancer.

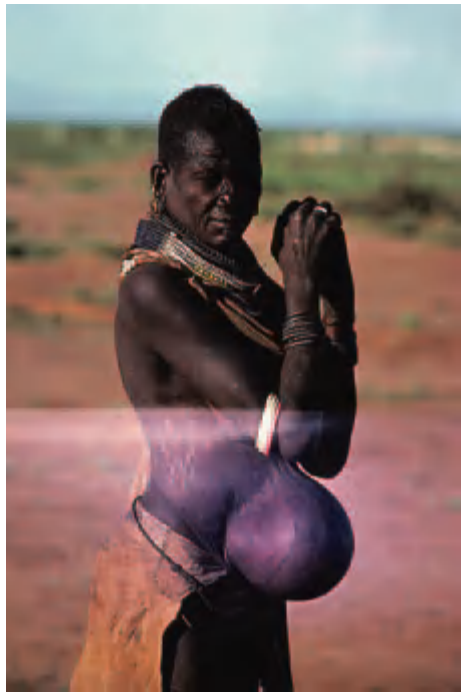

Fig. 32.25 Hydatid disease. Subcutaneous hydatid cyst presenting as a hernia, in a woman from Turkana, Kenya. (Courtesy of Dr C.N.L. MacPherson, Liverpool School of Tropical Medicine, Liverpool, UK.)

Clinical features. The commonest manifestation is an enlarged liver. Leakage of antigenic fluid from the cyst may cause wheeze, urticaria and eosinophilia. Rupture of the cyst may cause local signs and anaphylaxis. Hydatid cysts (Fig. 32.25) may be palpable in muscle or subcutaneous tissues as firm, painless swellings, often up to the size of an orange. They may be fluctuant. The overlying skin is normal.

Diagnosis. Clinical diagnosis is aided by X-ray or computed tomography (CT) examination of the lungs and sonographic ultrasound of the liver.

Excision of a subcutaneous cyst is conclusive. Great care must be taken not to spill any cyst fluid, which may give rise to further cysts. Complement fixation and ELISA are useful serological tests.

Treatment. This is essentially surgical. Formalin 2% or silver nitrate 0.5% should be used as a scolicidal adjunct [7]. Albendazole [8] is used in conservative management.

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Cysticercosis

SYN. LARVAL TAENIASIS

Aetiology. *Taenia solium*, the pork tapeworm, is responsible for producing human intestinal infection with the tapeworm (taeniasis), and the lodging of the larval stage (*Cysticercus cellulosae*) in numerous organs, especially subcutaneous tissue, muscle and brain, with the production of the disease cysticercosis.

In taeniasis, the adult *T. solium* lives attached to the wall of the small intestine and may reach a length of 7 m. Inadequately heated or frozen pork is the sole source of human infection with the adult worm, but humans and other primates may harbour the cysticercus stage.

Human infections with *Cysticercus cellulosae* are due to: ingestion of eggs in contaminated food or drink; eggs from their own intestinal infection being introduced into the mouth on dirty hands; or internal autoinfection as a result of vomiting—eggs must be digested in gastric acid.

Taenia solium is an important human parasite with a wide, although shrinking, distribution. It is most frequent in Eastern Europe, China, Manchuria, Pakistan, India, Mexico and Central and South America. Its prevalence depends upon insanitary human faeces disposal and the eating of undercooked pork.

Pathology. The cysticerci are found most frequently in subcutaneous tissue and muscle, but may occur in any organ of the body, especially the brain. The growing cyst provokes a non-specific inflammatory reaction, which may be followed by fibrosis and eventual calcification.

Clinical features. Adult worms in the intestine cause little or no reaction, although the passing of writhing fragments is distressing. The cysticerci form nodules in subcutaneous tissue muscles (rarely with widespread muscular enlargement), eye [1], eyelid [2], lungs and brain and other organs, which may seriously interfere with function depending on their position. Major exacerbation of symptoms, such as epilepsy or intracranial obstruction, coincides with death of the larvae. The disease in the skin is known as cysticercosis cellulosae cutis, and the subcutaneous nodules formed are 1–2 cm in diameter (Fig. 32.26). They are rubbery and firm, rounded and painless and may remain unchanged for many years. Their numbers

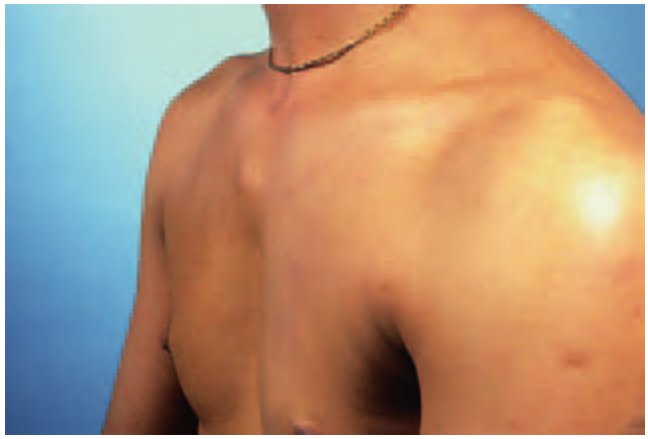

Fig. 32.26 Cysticercosis in a man from North India. A subcutaneous cyst is seen over the sternum. (Courtesy of Dr A.P. Hall, Hospital for Tropical Diseases, London, UK.)

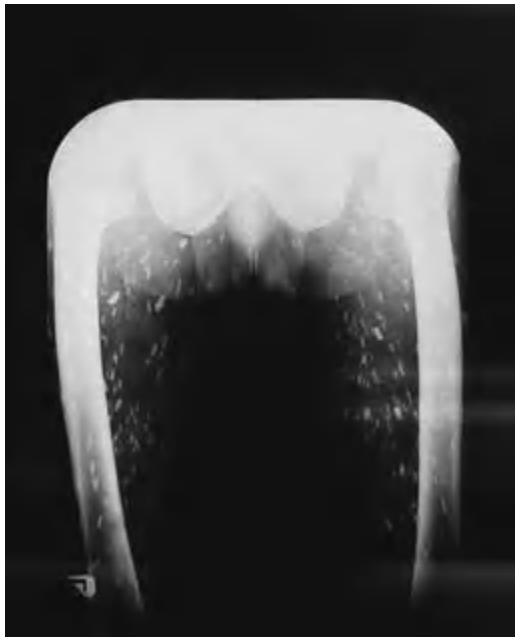

Fig. 32.27 Calcified cysticercal cysts in muscles of thighs and pelvis.

vary from one to hundreds, and when the diagnosis is entertained, search must be made for other lesions.

Diagnosis. *Taeniasis*: eggs in the stool cannot be differentiated morphologically from those of *T. saginata*, but examination of gravid proglottids allows exact identification. *Cysticercosis*: the histology of an excised cyst is diagnostic. Serology is helpful, but cross-reactions occur with hydatid disease.

X-ray examination frequently shows calcification in muscle (Fig. 32.27), although rarely in brain. CT shows typical appearances in brain and muscle.

Treatment. Subcutaneous cysticerci are important only in as much as they point to the possibility of more serious cerebral infection, which should be looked for. Individual subcutaneous cysts may be removed surgically if desired. Cerebral disease is treated with praziquantel 25 mg/kg daily for 10 days, under steroid cover. Adult tapeworms are treated with praziquantel in a dose of 10 mg/kg once. Obstructive lesions of the brain require surgical relief.

Prognosis is good in taeniasis, but in cysticercosis it is serious when vital organs are involved.

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Sparganosis

Sparganosis is a tissue infection with plerocercoid larvae or spargana of a number of species of pseudophyllidean tapeworms of the genus *Spirometra*. Patric Manson described the first case, in Amoy China in 1882. The Greek word sparganon means swaddling clothes, and describes the slender ribbon-like character of the larval worm. The infection is common throughout Asia, especially the Far East, but also occurs in Australia, the Americas and southern Europe.

Aetiology. Adult spirometra parasitize the gut of canines and felines. Eggs passed into water develop into procercoid larvae in copepod hosts of the genera *Diaptomus* and *Cyclops*. These are eaten by frogs, lizards, snakes, birds and some mammals, including mice and monkeys, in which the plerocercoid larvae develop, in muscle sheaths. Humans are infected either by the application of raw flesh to the skin or eye, usually as a medicinal poultice, or through eating uncooked flesh or drinking water containing infected copepods.

Pathogenesis and clinical features [1]. Ingestion sparganosis occurs a variable time after eating infected flesh, or drinking infected copepods. The larvae penetrate the intestine and develop into spargana, particularly in subcutaneous tissues and muscle. The invaded areas become oedematous and form painful lumps, in the centres of which the white, ribbon-like spargana move. Their death results in very intense inflammation with destruction of tissue and massive eosinophilia [2]. Clinically, the lesions can assume a more nodular consistency with an insidious onset; they may last for several years and can also migrate. Localized elephantiasis also results due to lymphatic invasion.

Application sparganosis. The spargana migrate into the inflamed part causing an immediate severe local pruritus.

Fig. 32.28 (a) Fibrous, encapsulated, cold abscess from the groin, which contained (b) a 22-cm long sparganum. (Courtesy of Professor S.B. Lucas, King's College, London, UK.)

Subsequently, signs of sparganosis may be very hard to differentiate from those of the primary inflammation for which the flesh poultice was applied. Redness, pain and swelling increase in severity over a few days or very few weeks, and the worms become localized in small nodules surrounded by pus (Fig. 32.28). Ocular sparganosis frequently results in panophthalmitis and loss of the globe.

Sparganum proliferum. This is a rare form in which the sparganum branches and divides, producing thousands of mainly subcutaneous spargana, which form subcutaneous nodules and itchy papules [3]. There may be a severe systemic illness with fever and eosinophilia.

Diagnosis. This is made from the history and by recovery of spargana after incision.

Treatment. This is by surgical removal and drainage.

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Infection with protozoa

Of the protozoa that give rise to skin disease or may cause changes in the skin indirectly, only *Leishmania* are natural parasites of the skin, in the sense that part of their life cycle must be spent in it. Even so, humans are often simply an accidental host in a zoonotic infection. *Entamoeba histolytica* may occasionally invade the skin, usually as an extension of an existing visceral lesion. Free-living amoebae, of the genus *Acanthamoeba*, may cause a primary lesion in skin, eye or ear, before invading the brain [1]. *Trypanosoma*, of the species that infect humans in Africa and America, may cause florid chancres soon after inoculation, but thereafter cause rashes indirectly. *Toxoplasma* causes an exanthem as part of the secondary stage of the infection, and *Trichomonas*, a mucosal parasite, causes inflammation of skin adjacent to the infected mucosa. Cutaneous manifestations of malaria, due to several species of *Plasmodium*, are simply a reflection of the severity of the systemic infection, or of drug toxicity.

Malaria

Malaria is caused by parasites of the genus *Plasmodium*, and is transmitted to humans by the bites of numerous species of mosquito belonging to the genus *Anopheles*. It causes a febrile systemic illness, which may be fatal in expatriates and in children in endemic areas in the tropics, and is a major cause of chronic ill health [2].

The mosquito bite can give rise to considerable skin reaction, and the disease itself to numerous cutaneous manifestations. In the early cold stage of benign tertian malaria (*P. vivax*) there is vasoconstriction and gooseflesh; in the hot stage, flushing of the face and to a less extent other parts of the skin, and in the sweating stage very profuse sweating. These manifestations are common to all diseases characterized by rigors caused by release of endotoxin or 'endotoxin-like' substances. Malaria commonly causes jaundice, and the skin in Europeans and Asians may have a curious grey or greenish hue. In severe malaria, there may be bleeding from the gums or gastrointestinal tract, and conjunctival petechiae may be seen, but cutaneous petechiae are rare. Herpes simplex and, occasionally, herpes zoster may develop.

Several of the drugs used in treatment of chemoprophylaxis cause skin problems. Chloroquine causes pruritus, especially in black people's skins, often severe enough to arrest treatment [3]. It responds to antihistamines, although the cause is unknown and there is never a rash. Various skin eruptions may occur, and psoriasis may be aggravated. Fansidar contains pyrimethamine and sul-

fadoxine. Epidermal necrolysis and Stevens–Johnson syndrome occur, sometimes fatally [4]. Quinine may cause rashes, notably toxic erythema and urticaria.

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Amoebiasis

Amoebiasis due to *Entamoeba histolytica* is arguably the third most important human parasitic infection, after malaria and schistosomiasis, being especially prevalent in South-East Asia and Central America, but the organism is found in all warm and temperate parts of the world where hygiene is inadequate [1,2].

Aetiology. *Entamoeba histolytica* inhabits the lumen of the human caecum, colon and rectum. Free-living trophozoites 10–60 μm in diameter, encyst and divide. Cysts passed in the faeces may survive up to 30 days, depending upon conditions of humidity and temperature, and survive chlorination. They are transmitted in contaminated water or food, especially salads, or by hands or flies, or by male homosexual intercourse. Ingested cysts that survive gastric acid complete the cycle. Isoenzyme electrophoretic analysis of cultured isolates suggest that pathogenic and non-pathogenic strains (zymodemes) of *E. histolytica* exist, but these cannot be distinguished morphologically [3].

Pathogenesis. Trophozoites of a pathogenic zymodeme may, under conditions that have not been determined, invade the mucosa of the large bowel, causing amoebic dysentery [4]. Amoebae that escape the bowel into the bloodstream may set up metastatic lesions, which develop into abscesses, most commonly in the liver. Cutaneous amoebiasis (Fig. 32.29) [5] develops when invasive amoebiasis escapes from the bowel to contiguous skin, usually around the anus or a colostomy, or after appendicectomy, or when amoebae are implanted in another mucosa, most commonly the vagina, cervix uteri or glans penis, and rarely in the mouth. Rupture or surgical intervention of an amoebic abscess is a less common source of cutaneous infection. Amoebae lyse the skin and subcutaneous tissues and mucosae involved, producing necrosis and gangrenous sloughing. *Entamoeba histolytica* is one of the most powerful organisms in terms of its lytic capacity, and this is mediated through amoebapores following the binding to the host's tissue in a lectin-like manner [6].

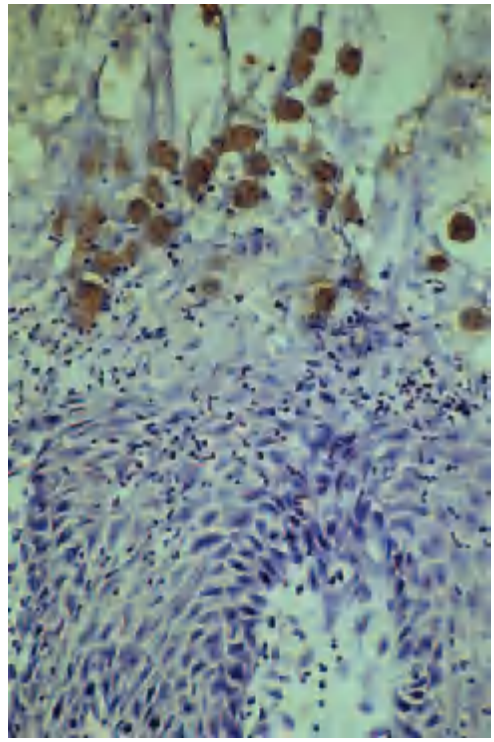

Fig. 32.29 Cutaneous amoebiasis. High-power view of skin biopsy, showing *Entamoeba histolytica* trophozoites on the epidermis, causing necrosis. The amoeba are stained with immunoperoxidase and are brown. (Courtesy of Professor S.B. Lucas, King's College, London, UK.)

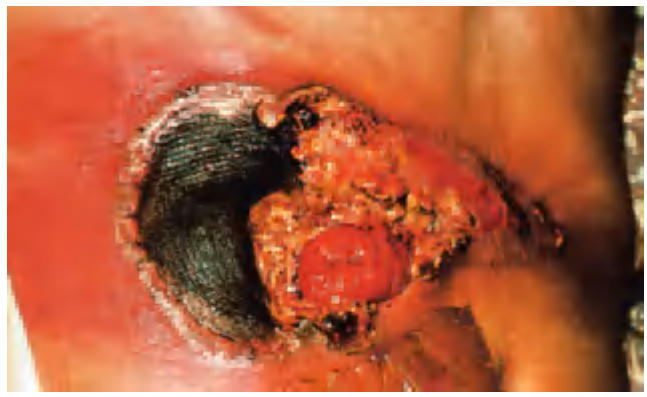

Fig. 32.30 Cutaneous amoebiasis. Rapidly spreading ulcer around a colostomy in a patient with intestinal amoebiasis. (Courtesy of Meddia, Amsterdam.)

Clinical features [5,7]. Commonly, one or more lesions appear at the anus or on the buttocks and spread as sloughing, coalescing ulcers [8] (Fig. 32.30). The course of the disease varies from less than 2 weeks to as long as 2 years, the more rapid and destructive lesions tending to occur in the young. The skin lesion itself is not diagnostic and is either a deeply invading ulcer or an ulcerated granuloma (amoeboma). It is usually seen as a serpiginous

ulcer with distinct, raised, thickened, often undermined, edges and with an erythematous rim about 2 cm wide, haemopurulent exudate and necrotic slough. It is intensely painful. Regional adenitis is usual.

All ages are affected. The vulva is particularly likely to be invaded in the infant with amoebic dysentery. Penile amoebiasis may occur in homosexual men [9], but invasive amoebiasis is not especially common in homosexual men or in patients with human immunodeficiency virus (HIV) infection [10].

Diagnosis. Cutaneous amoebiasis can spread very rapidly and terminate fatally, so early diagnosis is important. A solitary lesion may be mistaken for an epithelioma or for tuberculosis verrucosa cutis. On the penis when regional lymphadenopathy is present, syphilis or lymphogranuloma venereum may be confused. Examination of fresh material from the cutaneous lesion regularly discloses amoebae. Material should be taken from the edge of the ulcer avoiding necrotic tissue and examined at once under the microscope. The demonstration of motile trophozoites containing red blood cells is diagnostic. Histology of the ulcer edge will reveal amoebae, but the identification of the parasite in sections stained by haematoxylin and eosin may be difficult (Fig. 32.29). Amoebic trophozoites in faeces, biopsy, necropsy or abscess aspirate are revealed with much greater accuracy by immunofluorescence or immunoperoxidase staining. Serological tests are helpful, and the indirect immunofluorescent antibody test is positive in the serum of near 100% of patients with amoebic liver abscess, and in about 70% of patients with intestinal amoebiasis. Serial stool examinations should be performed.

The prognosis is serious in the neglected case, particularly in infants, but with early diagnosis and treatment it is good. It is important to appreciate that a history of dysentery is not essential to the diagnosis of amoebiasis of the skin.

Treatment. Treatment of invasive amoebiasis is with metronidazole [11]. The recommended adult dose is 800 mg orally three times a day for 10 days. This may be combined with diloxanide furoate 500 mg three times a day, or be followed by oral diiodohydroxyquin 650 mg three times a day for 21 days, to eliminate intestinal cysts.

Local cleaning of cutaneous ulcers with antiseptic solutions may be necessary.

Where a hepatic abscess needs to be drained, this is most safely done by needle aspiration.

Effective treatment is usually followed by complete healing of the skin without the need for plastic surgery.

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Trichomonads

Three trichomonads occur in humans. *Trichomonas vaginalis* invades the vagina, urethra and prostate and is pathogenic, causing trichomoniasis. *Trichomonas hominis* is found in the intestine and *T. tenax* in the mouth and occasionally the lung: neither is considered pathogenic [1].

Trichomoniasis

Trichomonas vaginalis is found worldwide affecting all races, but is eight times commoner in black people than in white people [2]. It invades the vagina and urethra in women, causing vaginitis and vulvitis with a characteristic pale-yellow, frothy discharge [3,4]. Vulval soreness and pruritus with inflammation of the surrounding skin are common, whereas infection of Skene's or Bartholin's glands with abscess formation rarely occurs.

Trichomoniasis characteristically causes a copious discharge with vaginal soreness or irritation and urinary frequency. The odour of the discharge is often unpleasant, although this feature is not specific. In many cases, bubbles can be seen in the discharge and the vaginal mucosal and cervical surfaces are infected and sometimes covered with punctate haemorrhages. The pH of the discharge is usually higher than the normal 4.5.

Although commonest in the second and third decades, the infection may occur at any age and has been reported in nearly 17% of babies aged from 1 day to 11 months. Many adults are asymptomatic carriers, particularly males. It can be isolated from up to 15% of men with non-specific urethritis. Discharge in males is scant.

The condition is frequently associated with gonorrhoea [5]. Transmission is usually by sexual intercourse, with an incubation period of 4–21 days. Occasional non-sexual transmission has been reported. In males, the condition occurs with non-specific urethritis in up to 5% of cases,

and balanitis may also occur [6]. The organism may be harboured in the prostate without symptoms.

Diagnosis. In women, diagnosis is usually easily confirmed by examination of a wet film by phase contrast or dark-field microscopy [7], but culture, usually in Feinberg–Whittington medium, gives the most reliable results. On the other hand, in males, examination of centrifuged urine or prostatic fluid following massage is only occasionally positive, and in many men it is not possible to confirm a clinical diagnosis. Examination of a stained dry film is neither easy nor reliable.

Sexual partners should always be examined, and in both sexes specimens taken to exclude other causes of sexually transmitted disease.

Treatment. Standard treatment is with metronidazole 400 mg twice a day for 5 days [8,9]. Alcohol should be avoided during treatment. Single-dose treatments have been advocated with this drug. Gastrointestinal disturbances are common. Benzimidazole drugs should be avoided in the first 3 months of pregnancy.

Clotrimazole has been shown to have some activity [6] and one 100-mg pessary daily for 6 days may be tried. Older remedies such as acetarsol pessaries or hydrargarphen pessaries, two a night for 3 weeks, are still valuable. Simple douching may relieve vaginal symptoms (20 mL of vinegar to 1 L of warm water).

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Trypanosomiasis

Protozoa of the genus *Trypanosoma* cause the widespread tropical disease trypanosomiasis. There are African and American forms.

African trypanosomiasis

SYN. SLEEPING SICKNESS

Aetiology and epidemiology. The disease is endemic in a belt running across Africa, limited approximately by lat. 15°N and lat. 15°S. *Trypanosoma gambiense* is the cause in West Africa, and the more virulent *T. rhodesiense* in East Africa to the east and south of Lake Victoria [1]. Occasional cases are imported into countries where the parasite is not endemic [2].

The human is the main natural host of *T. gambiense*, and the disease is transmitted by blood-sucking tsetse flies of the genus *Glossina*, the intermediate hosts *G. palpalis* and other related species are the most important. On the other hand, *T. rhodesiense* (which morphologically resembles *T. gambiense* but is biologically very different) is transmitted by *G. morsitans* and related species. The natural hosts are wild animals, notably antelope, and the human is a 'dead-end' host.

Age, sex, race and occupation have no influence on susceptibility to trypanosomiasis, except in so far as they affect exposure to tsetse flies. *Trypanosoma gambiense* sleeping sickness tends to be an endemic disease, affecting rural communities, with localized outbreaks, while *T. rhodesiense* sleeping sickness causes sporadic infections in herdsmen, hunters and tourists. In some parts of the 'tsetse fly belt' the incidence is high, and, as the same flies transmit bovine trypanosomiasis to livestock, farmers cannot keep cattle and poverty and malnutrition are rife.

Intrauterine transmission has been recorded infrequently. Preventive measures involved removal of entire villages to tsetse-free land. Mass survey and treatment were very successful in reducing the infection rate in Nigeria from 10.9% (1931–40) to 0.14% (1958) [1].

Pathogenesis. Trypanosomes develop, at the site of inoculation by the tsetse fly, from metacyclic forms to mature forms in about 10 days, and then enter the bloodstream. Within this time, the patient starts to develop an antibody response to the infection. The recognition of the trypanosomes in the skin causes the chancre. The systemic clinical illness coincides with invasion of the bloodstream. The early pathology is, thereafter, mainly in the lymph nodes, at first those draining the sore and then generally, with an increase in lymphocytes and plasma cells, but the appearances are not specific, and trypanosomes are not easily seen histologically. In *T. rhodesiense* infections, the lymphoplasmocytic infiltrate is also found in the myocardium, and this myocarditis may be fatal. In late trypanosomiasis, the meninges become invaded with the same infiltrate, and then the brain, especially around the basal ganglia. Gliosis and cerebral atrophy follow. The cause of these pathological changes is poorly understood, although it is known that there is a polyclonal B-lymphocyte activation with the production of very high levels of IgM, and circulating immune complexes [3].

Clinical features [4,5]. Within a few days of the infected bite, a trypanosomal chancre starts to develop (Fig. 32.31).

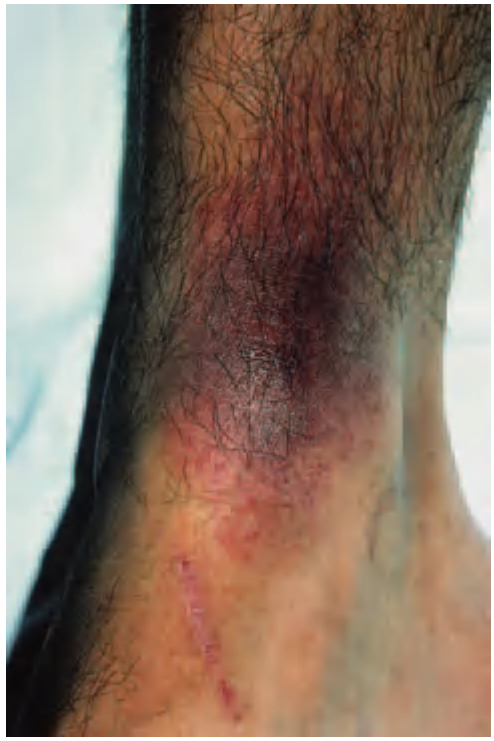

Fig. 32.31 Trypanosomal chancre due to *Trypanosoma rhodesiense* infection, appearing 6 days after the bite of the tsetse fly. The lesion is swollen, inflamed and haemorrhagic.

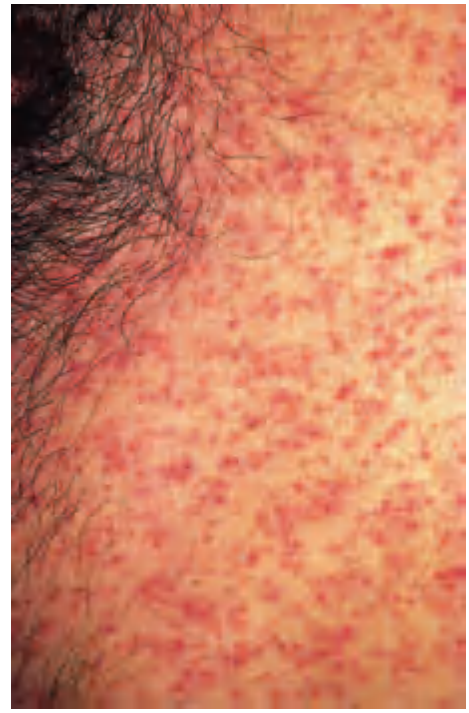

Fig. 32.32 Trypanosomal rash (same patient as Fig. 32.31). The maculopapular rash is becoming haemorrhagic.

It is a round, raised, red, hot, tender lesion, 2–5 cm or more in diameter, spreading to cover, for example, the entire surface of the forearm over the ensuing few days. There may be a tiny central punctum, and a blister with fluid rich in trypanosomes may appear on its surface. The chancre is present in 70–90% of people infected with *T. rhodesiense*, less regularly with *T. gambiense*, but fades within a few weeks. It is usually accompanied by local lymphadenopathy. The chancre heralds the onset of fever and systemic illness and generalized lymphadenopathy, which characterize the second phase of the illness. This is rapid and severe in *T. rhodesiense* infections, but gradual, mild, intermittent or even absent clinically in *T. gambiense* infections [6].

During this phase of the illness, there may be oedema of hands, feet and face, and transient erythematous or urticarial rashes, which are often circinate or annular, poorly defined, pale centrally, and commonest on the trunk. The rash may be haemorrhagic (Fig. 32.32). They are difficult to see in African skins. When the CNS is invaded, the patient experiences behavioural changes, alterations in sleep patterns, extrapyramidal signs and finally coma. These occur months after the onset of *T. rhodesiense* infections, if the patient has not died in the secondary phase, and 1–3 years after the onset of *T. gambiense* infections. At this stage, pruritus and excoriations from scratching are common, and the patient is emaciated.

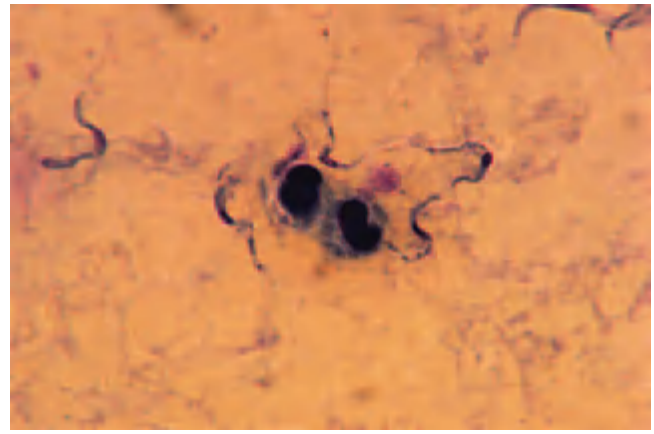

Fig. 32.33 Trypanosomes in a thick blood film, stained with Giemsa. (Courtesy of Dr P.L. Chiodini, Hospital for Tropical Diseases, London, UK.)

Death is often due to intercurrent infection due to the immune suppression.

Diagnosis. Within a few days of the onset of fever, trypanosomes may be demonstrated in simple thin blood films in *T. rhodesiense* infections. However, in *T. gambiense* infections, thick films (Fig. 32.33) or concentration techniques [7] may be necessary. A more profitable approach is puncture and aspiration of the enlarged posterior cervical lymph nodes. Trypanosomes are seen undulating

between the lymphocytes in the wet preparation, or well defined in a Giemsa-stained preparation. Cerebral involvement is characterized by raised protein in the CSF, containing IgM, and a raised cell count comprising lymphocytes and morula cells (plasma cells distorted by vesicles of IgM). Serological tests, including ELISA and immunofluorescence, may be helpful. Serum IgM levels are often grossly elevated, and there may be an anaemia. On diagnosis, a lumbar puncture is mandatory to establish whether the CNS has been invaded.

Treatment. A single course of suramin, preferably, or pentamidine isethionate is usually sufficient, if given before CNS invasion. Dosages are: suramin sodium 200 mg (test dose) i.v., followed by 1 g/week for five doses; pentamidine isethionate 4 mg/kg i.m. on alternate days for five doses. Both drugs are seriously toxic [8].

After CNS invasion melarsoprol is used [7,8], often with corticosteroids [9].

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American trypanosomiasis

SYN. CHAGAS' DISEASE; SOUTH-AMERICAN TRYPANOSOMIASIS; TRYPANOSOMIASIS CRUZI; CHAGAS–MAZZA DISEASE; SCHIZOTRYPANOSOMIASIS; OPILACAO

Definition. Chagas' disease is a parasitic disease of the tissues and blood caused by the flagellate *Trypanosoma* (*Schyzotrypanum*) *cruzi* and transmitted to humans and other mammals by blood-sucking bugs of the family *Triatomidae*. It occurs predominantly in rural areas in the tropical zones of the American continent.

Incidence. The insect vectors are widely distributed in the American continent from lat. 42°N in the USA to lat. 43°S in Argentina [1]. *Trypanosoma cruzi* attacks humans and other mammals, and the disease it produces can be regarded as a zoonosis. The area of distribution of the disease is more limited than the range of the reduviid bugs that transmit it, since those found at the two extremes of the continent are wild species, while the domestic types, concerned in the transmission of the infection to humans, occur between lat. 25°N in Mexico and lat. 28°S in Argentina [1].

Age does not influence the incidence of infection, although the acute forms are more frequently observed in children. The sexes are equally affected and there is no evidence of a racial factor. Occupation plays an important role because it is a rural disease and the vectors are found in rural dwellings, especially in huts or shacks with palm leaf roofs [2].

Aetiology. The disease is caused by *T. cruzi*, which bears some resemblance morphologically to the trypanosomes causing sleeping sickness in Africa. In the blood, the organism is 15–20 μm in length and of variable width, and has the typical undulant membrane and flagellum in an anterior position. The nucleus is central, the kinetoplast rod-shaped or oval and situated posteriorly. After transformation into the amastigote stage, *T. cruzi* multiplies only in tissue cells, being an obligatory tissue-cell parasite.

Vector. The disease is transmitted by blood-sucking insects of large size: Hemipteran, reduviid bugs (assassin or kissing bugs), belonging to the family *Triatomidae*, particularly *Panstrongylus megistus* (Brazil), *Triatoma infestans* (Southern Brazil, Uruguay, Paraguay, Bolivia, Southern Peru, Chile and Argentina) [1] and *Rhodnius proxlixus* (Venezuela, Colombia, Guianas and Central America). The larva, nymph and the adult insect can transmit the infection. They are active during the night. After ingestion, the trypanosomes multiply in the vector's intestine by longitudinal division, and within 3 or 4 weeks transform into the metacyclic form, which is infective to humans. Once the insect has been infected, it remains so for the rest of its life. The disease has many non-human reservoirs, including cats, dogs, monkeys, pigs, squirrels, rats, skunks, racoons, opossums, porcupines and armadillos. Transmission occurs by contamination through small cuts and abrasions on the skin, or through the normal mucous membranes of the eyes and lips when the vector, at the moment of biting, deposits its stools containing the infective metacyclic trypanosome [2]. The bite wound itself may provide the portal of entry [3].

Pathology. The tissues react almost immediately to the penetration of the metacyclic trypanosomes, producing oedema and cellular infiltration, which cause subcutaneous swelling. The infection spreads rapidly to the lymphatics, and the regional glands become oedematous and

Fig. 32.34 Chagas' disease. Unilateral oedema of the eyelids and orbit (Chagas–Mazza–Romaña's sign). (Courtesy of Professor M. Miles, London School of Hygiene and Tropical Medicine, London, UK.)

infiltrated with plasma cells and lymphocytes. The spleen and liver enlarge. The trypanosomes penetrate immediately into the cells of the reticuloendothelial system at the site of the inoculation and transform into the leishmania form, later returning to the interstitial spaces and blood in the form of trypanosomes, penetrating again into the cells to repeat the cycle in different organs and systems. The most striking invasion is that of the spleen macrophages, the Kupffer cells of the liver and the cells of the striated muscles [4]. The inflammation and scarring that follows invasion of the myocardium may have serious consequences.

Clinical features. The great majority of infections do not present any clinical manifestations in the early phase. Signs of early disease appear on the fifth day after inoculation: these are both local and general. Eighty per cent of the acute cases show the portal of entry in the conjunctiva, as evidenced by the 'eye sign' or 'Romaña's sign', also known as the 'ophthalmoganglionar complex' (oculoglandular complex), characterized by unilateral oedema of the eyelids and inflammation of the lacrimal gland (Fig. 32.34). Cutaneous inoculation results in the 'cutaneous adenopathy complex' or 'inoculation chagoma' and is less common. The general manifestations consist of moderate to high fever accompanied by headache, myalgia, weakness, particularly pronounced in children, in whom the disease may end fatally from acute meningoencephalitis or myocarditis. Hepatosplenomegaly, oedema and various forms of exanthem ('schizotripanides') are frequent [1]. Forms called oedematous, neuropsychiatric, meningoencephalitic, respiratory, gastrointestinal and pseudotyphoid have been described [2]. The subacute and chronic forms almost always present with heart manifestations—chagasic myocarditis—and digestive manifestations, such as mega-colon and mega-oesophagus. Megasyndromes are common in Brazil but absent in Venezuela. Congenital forms transmitted transplacentally or by the mother's milk are rare.

Prognosis. This is serious in acute cases in children, especially in the meningoencephalitic form, and when the myocardium is extensively involved. In the subacute and chronic forms it depends entirely on the degree of involvement of the heart. Sudden death by thromboembolic accidents and by blockage of the conduction system of the heart may occur. Chronic heart failure is frequently observed in the advanced cases.

Diagnosis. In the acute phase, the diagnosis is made by finding the parasite in the blood by direct examination, or by means of stained thick and thin smears, lymph-gland biopsy, blood culture, animal inoculation and by the so-called xenodiagnosis of Brumpt: the reduviid bugs grown in the laboratory and free from infection are allowed to bite the forearm of the subject under suspicion and feed on the blood, after which the faeces of these insects are examined for metacyclic forms between 30 and 60 days later [2]. In the subacute and chronic forms, laboratory tests are of great help, particularly those based on the complement-fixation test using antigen from culture forms of *T. cruzi* (Machado–Guerreiro's test).

Treatment. The acute stage (including congenital Chagas' disease and transfusion acute disease) should be treated with a trypanocidal drug, either nifurtimox (Lampit) given by mouth (8 mg/kg) for 60 or 90 days, or benznidazole (Rochagan), oral dose (6 mg/kg) for 30 or 60 days. A rare side effect is an exfoliative dermatitis. Both drugs produce anorexia, weight loss, headache and dizziness, gastric irritation and, occasionally, peripheral neuritis (12–30%). Allopurinol has recently been used [5].

Control. Improvement of environmental conditions should be attempted, especially those of the dwellings, eliminating palm leaf roofs. The insects can be destroyed with dieldrin and gamma benzene hexachloride. Chemotherapy of the infective cases may help to break the natural cycle of the disease.

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Leishmaniasis

The leishmaniases are a group of diseases caused by several species of the genus *Leishmania*. Each species tends to occupy a particular zoogeographical zone and the disease is endemic in 88 countries. It has been estimated that 1.5 million new cases of cutaneous leishmaniasis occur annually and more than 80% of the total of cases affect individuals in developing countries. Brazil, Iran, Afghanistan and Sudan suffer the highest prevalence and the disease is a priority for public health in all hyperendemic regions of the world. The species are morphologically identical, and are distinguished by isoenzyme pattern and DNA analysis. Monoclonal antibodies have also proved useful for rapid identification of isolates, especially in the field [1]. Clinical patterns are poor indicators of species, although certain disease characteristics may be commonly associated with a particular species [2]. *Leishmania* spp. undergo a cycle of development in the gut of female sandflies, of the genera *Phlebotomus* in the Old World, and *Lutzomyia* and *Psychodopygus* in the New World.

In its vertebrate host, the amastigote form of the parasite is found in cells of the reticuloendothelial system or in the dermis following severe parasite load and mononuclear cell necrosis. It is round or oval, 2–3 μm in diameter, with no protruding flagellum. The nucleus and kinetoplast stain deeply with the Romanovsky stains, giving the organism its characteristic appearance. In the sandfly and in artificial culture media, *Leishmania* spp. are the elongated promastigote stage, motile with an anterior flagellum.

Sandflies find their precise requirements for temperature and humidity in a wide variety of niches, commonly in rodent burrows, and crevices and holes in banks, trees and houses in the Old World, and in tree canopies and forest litter in the New World [3]. Infection is transmitted by the bite of the fly, usually at night and outdoors; however, infected vectors can take a blood meal during the day if disturbed and also are responsible for inoculating parasites indoors within the household environment. Commonly, the infection is zoonotic; one species of *Leishmania* may be associated with one, or many, natural vertebrate hosts, which provide the reservoir of infection. Humans are commonly accidental hosts, although there are situations in which they may be the reservoir in an anthroponotic cycle. For these reasons, human leishmaniasis has a very wide geographical distribution and range of climate and altitude (Fig. 32.35), and different epidemiological patterns (Table 32.2) [4].

Human leishmaniasis is usually classified as cutaneous or visceral, but the species that cause visceral disease may also cause skin lesions. In South and Central America, skin disease due to parasites of the *L. brasiliensis* complex may be complicated by the development of metastatic mucosal or mucocutaneous lesions. Mucosal disease is relatively rare with the other species [5].

Old World cutaneous leishmaniasis

SYN. ORIENTAL SORE; BOUTON D'ORIENT; DELHI BOIL; ALEPPO BOIL

Aetiology and epidemiology. Cutaneous leishmaniasis of the Old World is due to *L. major*, *L. tropica*, *L. aethiopica* and to *L. donovani infantum*, which is responsible for all the cutaneous disease on the northern Mediterranean littoral west of Greece and for some of the disease in North Africa [6,7] (Table 32.2). In endemic areas where transmission is stable, children are especially affected, and the cumulative rate of infection as determined by the presence of scars and positive leishmanin tests may approach 100%. In less stable situations, for example around oases, epidemics occur affecting all ages and sexes [8]. The disease is commonly imported into non-endemic countries by immigrants and returning travellers.

Pathogenesis. Sandflies inoculate the infective metacyclic promastigotes when taking a blood meal from the superficial vascular network in the human dermis. Inoculated promastigotes are taken up by histiocytes and newly immigrated monocytes, in which they multiply. Most inoculations do not seem to result in clinical disease as phagocytosis, and complement-mediated killing of leishmania parasites results in clearing of the infection. A minority of successful parasite inoculations result in localized or disseminated clinical cutaneous leishmaniasis. After a period of time, which depends on parasite species, size of inoculum, and the host's cellular immune response, a clinical lesion appears. This lesion comprises parasitized macrophages, lymphocytes and plasma cells, with little structure (Fig. 32.36) [9]. With time, piecemeal and focal necrosis of parasitized cells is found, probably the result of antibody-dependent cell-mediated immunity. The overlying epidermis becomes hyperkeratotic and breaks down, causing an ulcer whose surface is covered in a crust composed of hyperkeratotic debris, dried exudate, dead cells, and live and dead parasites. This activity continues for several months, while the lesion appears clinically static. In other, especially chronic, cases the more classical epithelioid cell, and sometimes

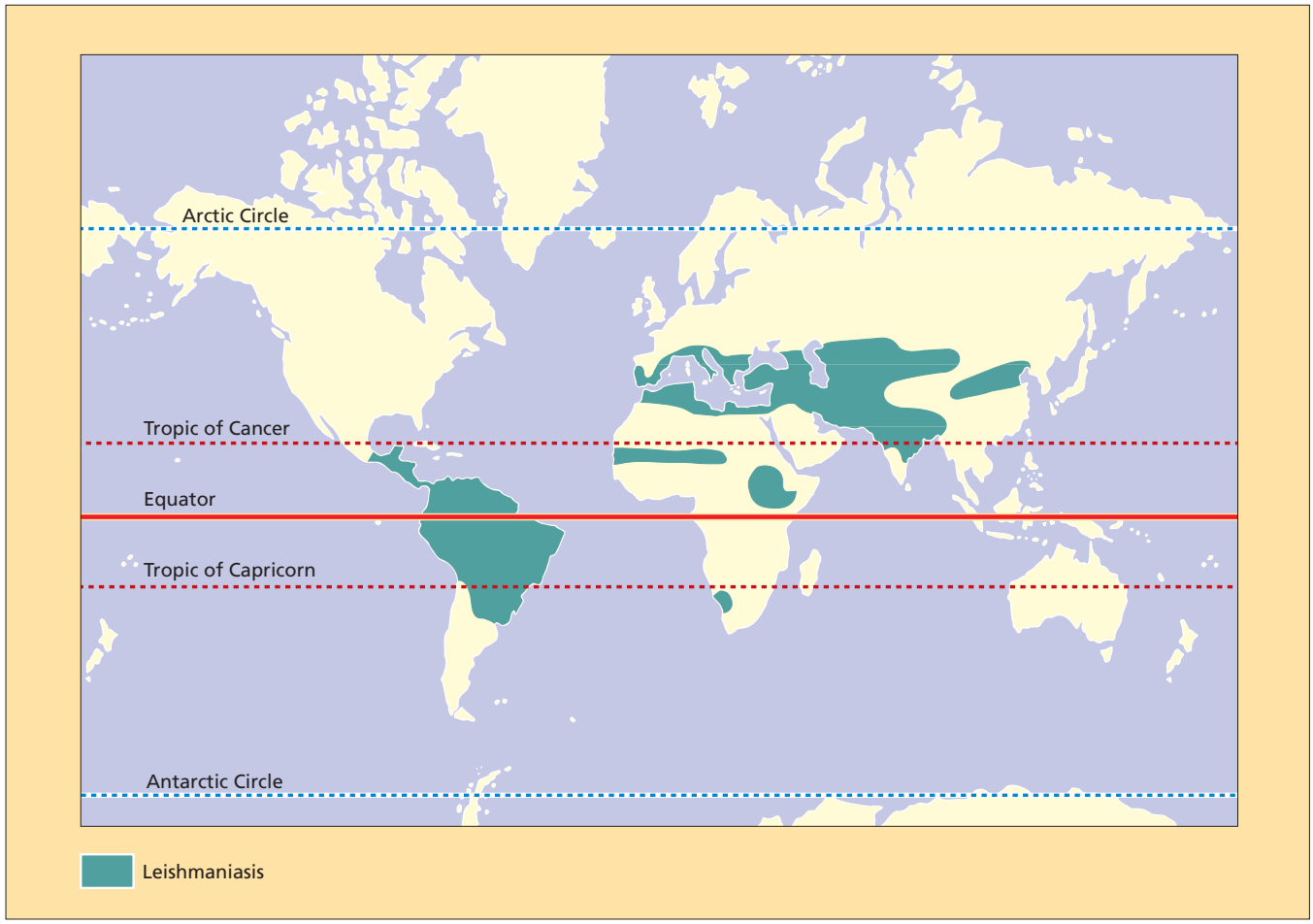

Fig. 32.35 World distribution of human leishmaniasis.

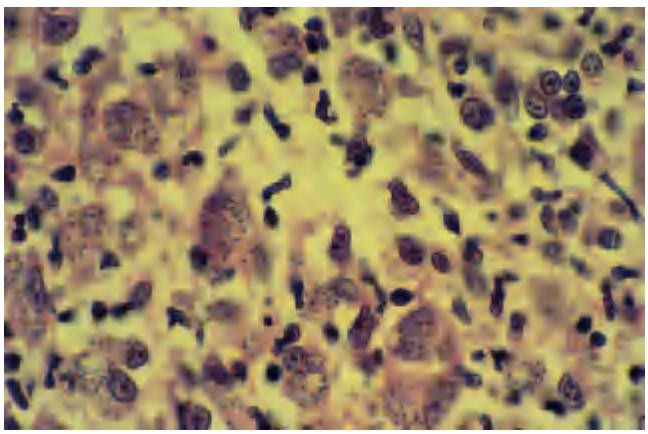

Fig. 32.36 Cutaneous leishmaniasis (high power, H&E); biopsy of early lesion, showing abundant amastigotes in macrophages, and a few plasma cells. (Courtesy of Professor S.B. Lucas, King's College, London, UK.)

giant cell granuloma, develops with relatively little necrosis, but similar epidermal changes (Fig. 32.37). In these cases, parasites are difficult to find [10]. Rarely, when cell-mediated immunity fails to develop, as in diffuse cutaneous leishmaniasis, histology shows masses of parasitized, often vacuolated, macrophages, with little or no lymphocytic infiltrate, and a normal or attenuated epidermis [11].

Clinical features [12]. All previously uninfected individuals are susceptible. The incubation period is usually measured in months, but ranges from a few days to over a year. One or more lesions occur on unclothed parts of the body, particularly on acral skin over bony prominences easily bitten by *Phlebotomus*, usually in a child. The face, neck and arms are the commonest targets. Lesions do not necessarily occur all at exactly the same time, but in endemic areas a family of children may all present with lesions and a history strongly suggesting infected sandfly bites all acquired in the same room on the same night.

The natural history of the lesions due to the four species tends to differ but there is much overlap, reflecting the variety in host response [2], so that lesions and their

Table 32.2 Epidemiology of leishmaniasis. (Courtesy of Weatherall *et al*. [4].)

Organism	Geography	Reservoir	Vector
Old World			
Leishmania donovani	North-East India, Bangladesh, Burma	Humans	*Phlebotomus argentipes*
L. infantum	Mediterranean basin, Middle-East, China, Central Asia	Dogs, foxes, jackals	*P. ariasi*, *P. perniciosus*
L. donovani (Africa)	Sudan, Kenya, Horn of Africa, ?Senegambia	?Rodents in Sudan, ?canines, ?humans	*P. orientalis*, *P. martini*
L. major	Semi-deserts in Middle East, North India, Pakistan, North Africa, Sudan, Central Asia	Gerbils (especially *Rhombomys*, *Meriones*	*P. papatasii*
L. major	Sub-Saharan savanna, Sudan	Rodents (especially *Arvicanthus*, *Tatera*)	*P. duboscqi*
L. tropica	Towns in Middle East, Mediterranean basin, Central Asia	Humans, ?dogs	*P. sergenti*
L. aethiopica	Highlands of Kenya, Ethiopia	Hyraxes (*Procavia*, *Heterohyrax*)	*P. longipes*, *P. pedifer*
New World			
L. chagasi	Central America, northern South America, esp. Brazil, Venezuela	Foxes	*Lutzomyia longipalpis*
L. mexicana mexicana	Yucatan, Belize, Guatemala	Forest rodents (especially *Ototylomys* and *Peromyscus yucatanicus*)	*Lu. olmeca*, *Lu. cruciata*
L. m. amazonensis	Tropical forests of South America	Forest rodents (especially *Proechimys*, *Oryzomys*)	*Lu. flaviscutellata*
L. brasiliensis brasiliensis	Tropical forests of South and Central America	?Forest rodents	*Psychodopygus wellcomei*, *Lutzomyia* spp.
L. b. guyanensis	Guyanas, Surinam, into Brazil, Venezuela	Sloths (*Choleopus*), arboreal anteaters (*Tamandna*)	*Lu. umbratilis*
L. b. panamensis	Panama, Costa Rica, Colombia	Sloths (*Choleopus*)	*Lu. trapidoi*
L. b. peruviana	West Andes of Peru, Argentine highlands	Dogs	*Lu. verrucarum*, *Lu. peruensis*

Table 32.3 Clinical features of cutaneous leishmaniasis. (Courtesy of Weatherall *et al*. [4].)

Parasite and lesion	Natural outcome	Treatment
Leishmania major		
Self-healing rural sores	3–5 months	Physical/topical/nil
	Disabling scars	Sb 20 mg/kg/day × 2–3 weeks
		(?Some unresponsive)
L. tropica		
Self-healing urban sores	10–14 months	Physical/topical/nil
		Sb 20 mg/kg/day × 2–3 weeks
Leishmaniasis recidivans	> 10 years destructive	Sb 20 mg/kg/day × 3–6 weeks
L. aethiopica		
Self-healing, nodular	2–5 years	Physical/topical/nil
Mucocutaneous	> 10 years destructive	Pentamidine 4 mg/kg/week × 8
DCL	Persists, disfiguring	Pentamidine 4 mg/kg/week × months
L. m. mexicana		
Self-healing	6–8 months	Physical/topical/nil
		Sb 20 mg/kg/day × 2–3 weeks
Chiclero ear	> 10 years, destructive	Sb 20 mg/kg/day × ?
L. m. amazonensis		
Self-healing	?Duration	?Sb 20 mg/kg/day × 3 weeks
DCL	Persists, relapses, disfiguring	Sb 20 mg/kg/day × months
L. b. brasiliensis		
Self-healing	?Duration, later mucocutaneous	Sb 20 mg/kg/day × 3–4 weeks
Mucocutaneous	Persists, destructive	Sb 20 mg/kg/day × 4 weeks, or amphotericin B
L. b. guyanensis		
Self-healing	?6–8 months	Sb 20 mg/kg/day × 3 weeks
Lymphatic nodules 'pian bois'	?Late espundia	If poorly responsive to Sb, use pentamidine
L. b. panamensis		
Self-healing	?Duration	Sb 20 mg/kg/day × 3 weeks
	?Late espundia	
L. b. peruviana		
Self-healing	?Duration	Physical/topical/nil
		Sb 20 mg/kg/day × 2–3 weeks

DCL, diffuse cutaneous leishmaniasis; Sb, antimony as pentavalent antimonial.

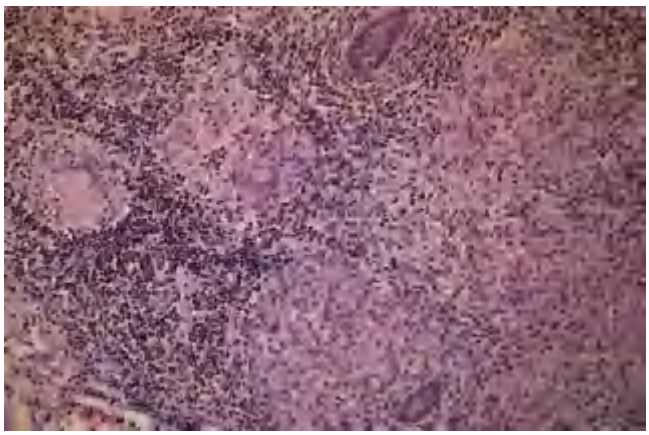

Fig. 32.37 Chronic cutaneous leishmaniasis. Granulomatous dermatitis without necrosis. There are no amastigotes to be found in this case, and the differential diagnosis may be difficult between the other granulomatous dermatitides. (Courtesy of Professor S.B. Lucas, King's College, London, UK.)

outcome are not always characteristic of the species (Table 32.3) [4]. The sequence of nodule, crusting, ulceration and healing with scar formation is common to all the self-healing sores.

Cutaneous leishmaniasis due to L. major: wet, rural or zoonotic cutaneous leishmaniasis [13,14]. After a short incubation period of less than 2 months, a red furuncle-like nodule appears at the site of inoculation (Fig. 32.38). After 2 weeks a central crust forms. The crust may persist (Fig. 32.39), or fall away revealing the underlying ulcer (Fig. 32.40). The ulcer and the raised, red margin enlarge over the next 2–3 months, and the lesion reaches a diameter of 3–6 cm. Multiple, small, secondary nodules (2–4 mm) sometimes occur around the lesion in lymphatics. Healing takes place in 2–6 months and leaves a scar. This type of cutaneous leishmaniasis is acquired in a rural area, where the infecting organisms are also rodent parasites and are poorly adapted to humans. It is an example of a zoonosis.

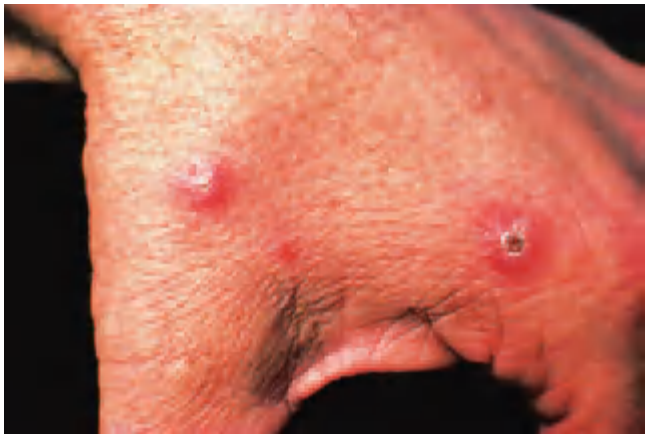

Fig. 32.38 Cutaneous leishmaniasis due to *Leishmania major*: early papules, one of which is starting to show central crusting.

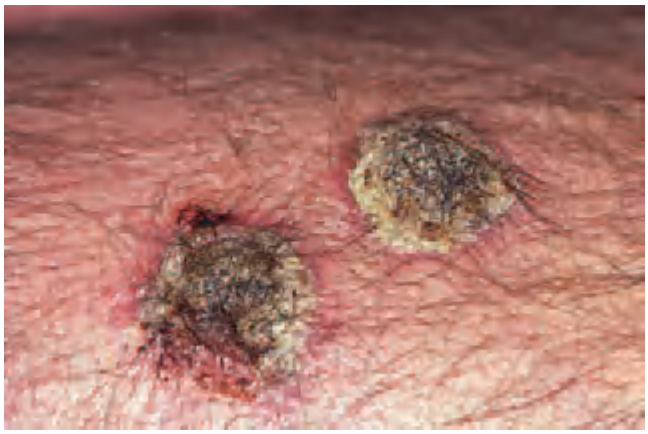

Fig. 32.39 Cutaneous leishmaniasis due to *Leishmania major* from Saudi Arabia, showing marked and persistent crusting.

Cutaneous leishmaniasis due to L. tropica: dry, urban or anthroponotic leishmaniasis [15]. After an incubation period of more than 2 months, a small, brownish nodule appears, which becomes a slowly extending plaque 1–2 cm in diameter in about 6 months. At this stage, shallow ulceration appears in the centre, which develops a closely adherent crust. Multiple secondary nodules occur much less frequently than in the 'wet' form. After 8–12 months, the lesion starts to regress and the ulcer heals, leaving a scar. The average time from nodule to scar is about 1 year, approximately twice as long as in the 'wet' form. Rare forms of viscerotropic infections by *L. tropica* have been described in war veterans who acquired the parasite in the Middle East and in cases of Indian kala-azar [16].

Cutaneous leishmaniasis due to L. aethiopica [11]. Lesions are most commonly central on the face, and single. Satellite papules accuminate into a large, spreading nodule that may not crust or ulcerate (Fig. 32.41). Lesions are seldom much inflamed, and heal over 2–5 years. If the sandfly bite has been on the mucosal border of the nose or mouth, primary mucocutaneous leishmaniasis (MCL) may develop, producing swelling of lips or nose, and persist for many years (Fig. 32.42), although without the gross destruction seen in Latin America caused by *L. brasiliensis*.

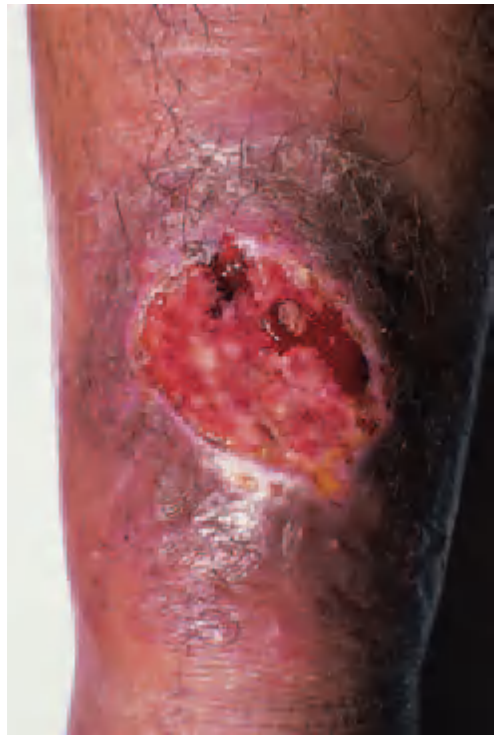

Fig. 32.40 Cutaneous leishmaniasis due to *Leishmania major* from Sudan. An ulcer with a raised edge.

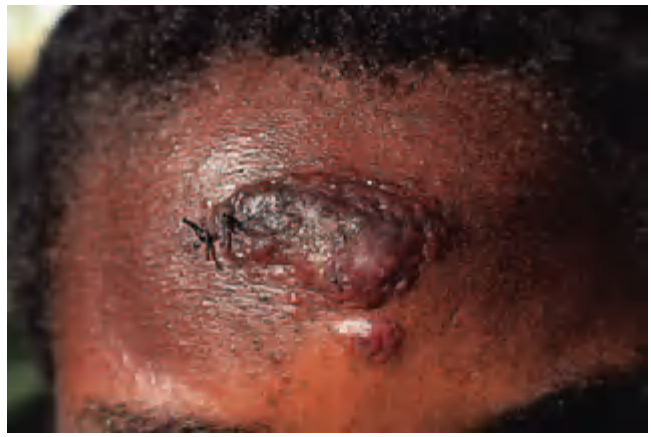

Fig. 32.41 Cutaneous leishmaniasis due to *Leishmania aethiopica* from Kenya. A large nodule with many satellite papules and abundant parasites.

Cutaneous leishmaniasis due to L. donovani infantum [7]. Whereas infants infected with this parasite tend to get visceral leishmaniasis, adults are more likely to develop

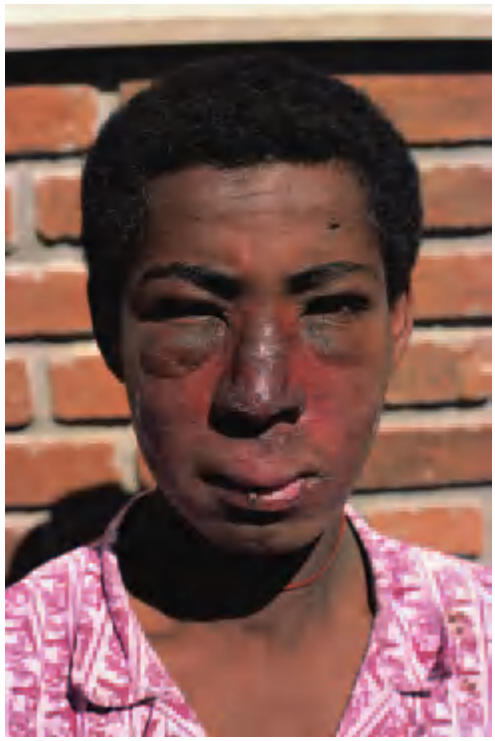

Fig. 32.42 Nasal involvement, and marked inflammatory oedema in leishmaniasis due to *Leishmania aethiopica* in Ethiopia.

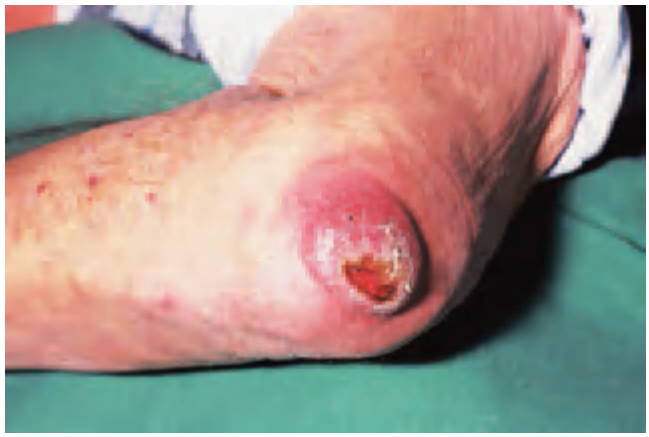

Fig. 32.43 Cutaneous leishmaniasis due to *Leishmania infantum*, from Spain. The fleshy nodule, with relatively little inflammation is characteristic.

simple self-healing cutaneous disease, without concurrent or subsequent visceral involvement. The appearance and evolution of the lesions is typically slow and mild, when compared with that of *L. major*, with which it coexists in North Africa [6] (Fig. 32.43). Solitary mucosal lesions have occasionally been reported [5].

In addition to the classical self-healing sores, there are two types of cutaneous leishmaniasis that are chronic, and may not heal spontaneously.

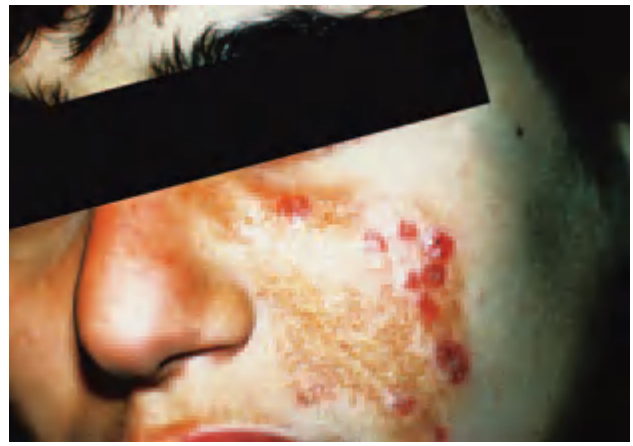

Fig. 32.44 Leishmaniasis recidivans (lupoid leishmaniasis) from Baghdad, showing active papules cropping in the edge of the scar of the healed sore. (Courtesy of Professor G. Rahim.)

Leishmaniasis recidivans: chronic leishmaniasis, lupoid leishmaniasis [10]. It has been estimated that approximately 4% of *L. tropica* infections from Iran and Afghanistan will develop this chronic form of the disease. Brown-red or brown-yellow papules appear, usually close to a scar of an old lesion of cutaneous leishmaniasis or actually in the scar. They coalesce and form a plaque closely resembling lupus vulgaris, even to the formation of apple-jelly nodules (Fig. 32.44). The lesions frequently worsen in the summer and may ulcerate or form concentric rings. Rare keloidal and verrucous forms on the lower limbs are described. A psoriasiform type also occurs and may cover large areas of the body.

The recidivans lesion is the result of a peculiar host reaction in which cellular immunity fails to sterilize the lesion, despite the presence of exaggerated hypersensitivity. Although not as destructive as lupus vulgaris, lupoid leishmaniasis may persist and spread slowly for many years [17]. Investigations to demonstrate the parasite or leishmanial DNA in the affected skin are commonly negative.

Diffuse cutaneous leishmaniasis: disseminated cutaneous leishmaniasis, leishmaniasis cutis diffusa. In the Old World this form of the disease is due to *L. aethiopica* and has certain characteristic features [11].

1 There is an initial lesion, which spreads locally, and from which the disease disseminates to other parts of the skin, often involving large areas (Fig. 32.45).
2 The lesions are nodules that do not ulcerate.
3 There is a superabundance of parasites in the lesions.
4 The histology is characteristic in that macrophages full of amastigotes predominate.
5 Internal organs are not invaded and there is no history of kala-azar.

Fig. 32.45 Diffuse cutaneous leishmaniasis due to *Leishmania aethiopica* in Ethiopia. The face is covered with infiltration and nodulation but there is no ulceration.

6 The leishmanin test and other tests of specific cellular immunity are negative.
7 The disease progresses slowly and becomes chronic.
8 Treatment produces only gradual improvement and relapse is the rule.

Under the influence of treatment, the histology changes towards the tuberculoid in a proportion of patients, and they may recover completely. Cases of coincident leishmaniasis and leprosy have been described, and show that the immune deficiency of each condition is specific [18].

Diagnosis. In endemic areas, or in travellers returned from endemic areas, the clinical diagnosis is not difficult in the case of typical sores. A positive diagnosis of cutaneous leishmaniasis (Old World and New World types) can be suggested, and in most cases confirmed, by the presence of one or more of the following criteria:
1 History of exposure to an endemic area in the previous weeks or months.
2 History of sandfly bites in the previous weeks or months.
3 History of high-risk activities such as sleeping outdoors, jungle or desert trekking.
4 Non-healing chronic nodular, violaceous ulcer for 4–6 weeks or longer.
5 Demonstration of amastigotes in Giemsa-stained smears from infected skin by direct microscopy.
6 Demonstration of intracellular amastigotes in the dermis of H & E sections of skin.
7 Presence of leishmanial granulomas in the dermis in H & E specimens.
8 Growth of promastigotes in Nicolle–Novy–MacNeal (NNN) culture medium from lesional specimens.
9 Demonstration of leishmanial DNA by the PCR.

Deeper, subcutaneous sores (the so-called volcano lesion), sores arising from lymphatic spread, or chronic sores in which scarring predominates may present difficulties. Confirmation is through demonstration of the parasite. Usually, this is best achieved by making a smear of material from the sore and staining it with Wright's, Giemsa or Leishman's stain on a microscope slide. The smear may be made from the exudate from the sore, and is often positive even if purulent because secondary bacterial infection is unusual. Alternatively, a slit-skin smear is made, as for leprosy (Chapter 29), being careful to avoid taking blood from the nodular part of the lesion. Parasites are usually readily seen in sores that have not yet started to heal, but are difficult to see thereafter. Alternatively, material may be obtained through a needle or with a dental broach [19].

Ideally, material should also be cultured on NNN or similar medium. At the time of taking the lesional skin biopsy for histological examination, a portion of it should be cultured, and dab smears made from the cut surface of the other portion before it is fixed. Leishmania are harder to see and identify in sections than in smears. In chronic leishmaniasis especially, histology may not be able to distinguish leishmaniasis from sarcoidosis, tuberculosis or other tuberculoid pathologies. However, in acute forms with or without the presence of amastigotes, the presence of a granuloma has a high diagnostic sensitivity.

In all forms of cutaneous leishmaniasis, the leishmanin test will be positive once the stage of crusting has been reached [19]. The test is negative in the diffuse anergic forms. The Leishmanin test also called the Montenegro test, particularly in Central and South America, is a suspension of 5×10^6 cultured promastigotes of *Leishmania* spp. (*L. major* is commonly used for cutaneous diagnosis in Old World leishmaniasis) per mL of 0.5% phenol saline: 0.1 mL is injected into the volar surface of the forearm and the result read at 48–72 h. The antigen is normally standardized so that an induration of 5 mm or more, measured by the ballpoint technique, is positive [1]. While interpreting the result in an individual patient, it is important to take into consideration the prevalence rate in the control population. This intradermal skin test is not useful for the diagnosis of current cutaneous leishmaniasis as a positive result may indicate previous sensitization. Moreover, there are also problems of cross-reactivity amongst different *Leishmania* spp. and therefore the Montenegro test is

not useful for particular epidemiological settings where infections by different *Leishmania* spp. overlap.

Molecular diagnostic tests to detect leishmanial DNA by PCR have been available for several years. Assays can be carried out by using nuclear DNA, and more recently the diagnostic sensitivity was significantly enhanced by using kinetoplast minicircle DNA [20]. The sensitivity of this test has been reported to be between 92% and 98% with 100% specificity by several authors [20]. A variety of clinical specimens, including cotton swabs and archival smears or paraffin-embedded skin sections, can be used as the DNA source for the PCR diagnosis. Ideally, the diagnosis of cutaneous leishmaniasis should achieve a species- and subspecies-specific level, as this has therapeutic and prognostic implications.

Treatment [21]. Most sores will heal spontaneously, but their duration cannot be predicted in an individual case. It is reasonable to try topical methods of treatment for simple sores, and to reserve the systemic use of pentavalent antimonials for problematic sores: these include sores where scarring would be disabling or severely disfiguring; sores that will not heal easily, for example on the lower leg or over a joint; sores involving mucosa or cartilage; or sores that might be due to parasites of the *L. brasiliensis* group.

Heating a sore to 40–42°C for several hours each day promotes healing but is technically difficult [22]. Small single sores may be frozen with carbon dioxide snow [23], curetted under local anaesthetic [24] or infiltrated with 1–2 mL sodium stibogluconate or meglumine antimoniate, on one or two occasions a few days apart. Careful attention to technique is essential [25]. Preliminary studies using the aminoglycoside aminosidine or paromomycin in an ointment look promising, but problems of formulation have yet to be solved [26].

Systemic treatment is with sodium stibogluconate or meglumine antimoniate by intravenous or intramuscular injection in a single daily dose of 20 mg antimony/kg, for as long as it takes to produce clinical and parasitological healing and a few days longer: usually 15–21 days [27]. Sores due to *L. brasiliensis* should be treated for the full 21 days [28]. *Leishmania aethiopica* is not sensitive to antimony at this dosage [29] and, when systemic treatment is justified, patients should be treated with pentamidine isethionate in a dose of 4 mg salt/kg once a week for as long as necessary [30]. Patients with diffuse cutaneous leishmaniasis require treatment for many months beyond clinical and demonstrable parasitic cure [30]. Leishmaniasis recidivans (lupoid) may respond to local infiltration after nodulectomy, or systemic antimonials. The additional use of steroids has helped some cases [14]. Severe scarring may require plastic repair. After healing, patients are normally immune to reinfection with the same species, although second sores in old age, or due to a parasite of a different zymodeme, have been reported.

It is clear that the available treatments for cutaneous leishmaniasis are far from being satisfactory. Even more, reported therapeutic failures with pentavalent antimonials have been described as an increasing problem in endemic regions for visceral leishmaniasis in India and also as an emerging problem in New World cutaneous leishmaniasis amongst returned travellers to the UK [31]. Novel approaches include combination therapeutic regimes using antimonials and immunostimulating agents. Intravenous treatment with pentavalent antimonials results in a number of common adverse reactions and side effects including hepatic, pancreatic, musculoskeletal and cardiac toxicity. Elderly patients seem to be more frequently and severely affected by these symptoms.

American cutaneous leishmaniasis and MCL

SYN. AMERICAN LEISHMANIASIS; SOUTH AMERICAN LEISHMANIASIS; ESPUNDIA; PIAN BOIS; UTA; CHICLERO'S ULCER; BUSH YAWS; PICATURA DE PITO

Aetiology and epidemiology. The site of development of leishmania in the gut of New World sandflies differs from that in Old World sandflies, and the parasites have been redesignated by the addition of the subgenus *vianna*, for example *Leishmania viannia brasiliensis* [32], but in this chapter the older, simpler terminology is retained, by which the parasites that cause disease in humans fall into the *L. brasiliensis* and *L. mexicana* complexes. American leishmaniasis is an endemic and mainly rural disease of damp, forested country in South and Central America [32]. It becomes epidemic among young people who go to work in the forests, 25% of young soldiers fighting in the jungle in certain areas and in villagers settled on land recently torn from the tropical forest. The optimum time for transmission is immediately after the rainy season.

Additionally, *L. b. brasiliensis* is becoming increasingly periurban [27], with a number of opportunistic hosts, including dogs and donkeys (whose true reservoir status is questionable). *Leishmania brasiliensis peruviana* is, by contrast, part of a mountainous zoonosis among peridomestic dogs, causing an endemic human infection that affects children especially. Vectors and reservoirs are given in Table 32.2. As increasing numbers of new species of parasite are identified, it is becoming clear that each is associated with its own complex of reservoir hosts and vector sandflies.

Pathogenesis. The pathology of the skin lesions does not differ significantly from that of Old World sores. The necrotic pattern, with ulceration of the overlying epidermis, is common [9]. Although recovery from an infection

confers lifelong immunity against reinfection with the same species of parasite, that immunity does not develop early enough or adequately to prevent the blood-borne metastatic spread of parasites of the *L. brasiliensis* complex, especially *L. b. brasiliensis* itself, to the mucosa of the nose, mouth, palate or larynx. Here, they may later start to multiply and be recognized immunologically, and cause severe destructive lesions, known as espundia (Portuguese: a sponge) [33]. Histology of the mucosal lesion [34] shows a collection of lymphocytes and plasma cells around small arterioles in the nasal submucosa. Occasional leishmania are present in the vascular endothelial cells. Oedema, congestion and proliferation of vascular endothelium progress, leading to desquamation and necrosis of the overlying mucosa and underlying cartilage. Endarteritis and thrombosis add to the tissue destruction. Vascular supply is so reduced that only fibrous tissue remains.

Clinical features [35]. The main types of American leishmaniasis are as follows.

Cutaneous leishmaniasis due to L. mexicana complex. The vector of *L. m. mexicana* bites humans reluctantly, so only those who spend long periods of time in the forest, such as chicle collectors, are at risk. The lesions behave like those of *L. major* or *L. tropica*. Most are on the side of the face or behind the ears (Table 32.3). Lesions on the pinna of the ear may invade cartilage, take many years to heal and destroy the pinna [36]. *Leishmania mexicana amazonensis* is extremely common in forest rodents, but the vector is not anthropophilic, so human infections are rare. A large proportion of them give rise to diffuse cutaneous leishmaniasis, which does not differ significantly from its counterpart in the Old World, due to *L. aethiopica* [29].

Cutaneous leishmaniasis due to L. brasiliensis complex [37]. Sores are often large deep ulcers, usually with a raised edge. Sores due to *L. b. guyanensis* are often fleshy and protuberant, usually on the limbs, often multiple, and resemble those of yaws, 'pian bois' [38]. This parasite and *L. b. panamensis* are especially associated with lesions along the draining lymphatics, but these may occur with any species. The lymphatic lesions may remain discrete small nodules, or may become inflamed and break through the skin to resemble the primary lesion. Lymphadenopathy is seldom marked.

American MCL [39,40]. Up to 40% of patients with sores due to *L. b. brasiliensis* and a very much smaller proportion with sores due to *L. b. panamensis* and *L. b. guyanensis* may develop mucosal lesions: 50% of mucosal lesions develop within 2 years of the appearance of the skin lesion, and 90% within 10 years. Delays of 35 years are recorded [33]. About 15% of patients with MCL give no previous history of a skin sore. The nasal mucosa is almost always affected, and in one-third of patients a second site is also involved, in the pharynx, palate, larynx or upper lip, in that order (Fig. 32.46). The usual initial lesion is a nodule on the inferior turbinate or septum, which causes stuffiness and obstruction. The destructive pathology perforates the septum and over years may destroy the nose, palate and lips (Fig. 32.47), which may become gross and protuberant, or scarred and constricted, causing difficulties in speech and eating. Death may supervene from secondary infection, starvation or laryngeal obstruction (Fig. 32.48). Spontaneous healing is virtually unknown.

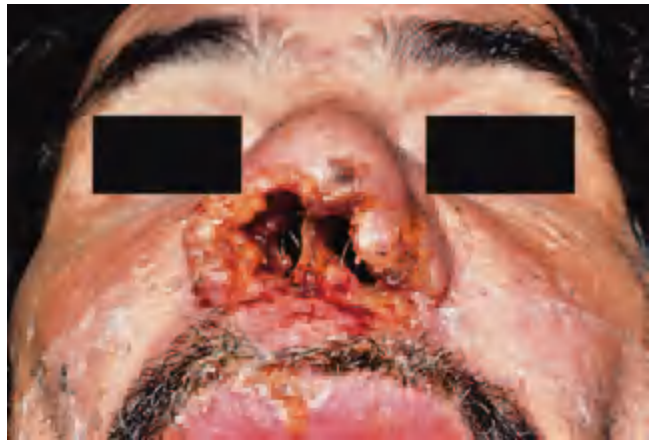

Fig. 32.46 Mucosal leishmaniasis due to *Leishmania brasiliensis* in Brazil. The nasal septum anteriorly is most severely affected. (Courtesy of Dr L. Bakos, Porto Alegre, Brazil.)

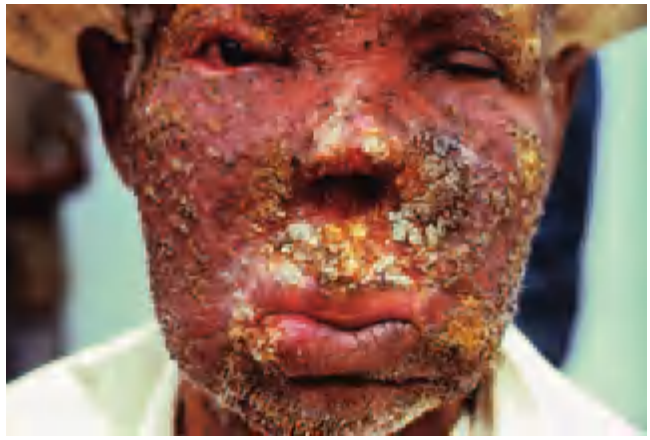

Fig. 32.47 Severe mucocutaneous leishmaniasis from Brazil. (Courtesy of Professor P. Marsden, University of Brasilia, Brazil.)

Cutaneous leishmaniasis due to L. b. peruviana: 'uta' [35]. Lesions are less severe than those of *L. b. brasiliensis*. They heal spontaneously and are not known to cause MCL.

Fig. 32.48 Mucosal leishmaniasis from Brazil. A fatal case, showing the extensive laryngeal involvement. (Courtesy of Professor P. Marsden, University of Brasilia, Brazil.)

Diagnosis. The principles are the same as for cutaneous leishmaniasis of the Old World, but the differentials of syphilis, yaws, rhinoscleroma, sporotrichosis, histoplasmosis, leprosy and, especially, blastomycosis must also be considered. Lesions of sarcoidosis, lupus vulgaris and cutaneous T-cell lymphomas (CTCLs) can also resemble cutaneous leishmaniasis. For the diagnosis of MCL, the nasal lesion must be sampled, after careful cleaning, for culture, as well as examined by impression Giemsa smear and histology. Problems of contaminating infection can be avoided by inoculating some of the material into a hamster.

Treatment [12]. This is summarized in Table 32.3. Lesions due to *L. b. guyanensis* are particularly liable to relapse. Lesions due to *L. b. brasiliensis* should be treated systemically for a week beyond parasitological cure, in order to prevent MCL from developing [28]. Previously untreated patients with MCL respond to pentavalent antimonials in a dose of 20 mg/kg/day, if given daily for 3–4 weeks [41]. Only 20% of relapsed patients will respond to the drug. Amphotericin is the drug of second choice, given in a dose of 1 mg/kg on alternate days for 2 months. Treatment that is inadequate in dose or duration leads to relapse and drug resistance. Secondary infection should be treated. Corticosteroids are useful to prevent laryngeal oedema that can otherwise complicate the start of treatment of laryngeal disease.

Cutaneous leishmaniasis in the returned traveller. Common and rare forms of cutaneous leishmaniasis are increasingly being described in non-endemic regions of the world. A recent retrospective survey at the Hospital for Tropical Diseases in London disclosed more than 50 new cases including Old and New World cutaneous infections by *L. tropica*, *L. viannia braziliensis*, *L. major* and *L. donovani* complex. Patients with infections acquired in the New World manifested a more severe clinical picture and therefore sought medical referral at an earlier stage. The diagnosis was established by all four standard investigations including Giemsa smears for direct microscopy, H&E histology, parasitological culture and molecular diagnosis by PCR. Intravenous or intralesional treatment with sodium stibogluconate and other less frequently used agents resulted in cure for most of these patients. Educational strategies to increase the awareness of cutaneous leishmaniasis as an emerging problem in the UK are being directed at general practitioners, dermatologists and the public.

Visceral leishmaniasis

SYN. KALA-AZAR; 'DEATH FEVER'; DUM-DUM FEVER

Leishmania donovani donovani and its close relative *L. donovani infantum* are, by contrast with the other species of *Leishmania* that infect humans, normally viscerotropic, and cause a severe systemic infection, which may be accompanied by cutaneous manifestations.

Aetiology. There are four main zoogeographical zones in which visceral leishmaniasis is found (see Table 32.2). Transmission is peridomestic and tends to be stable in the Mediterranean focus. Dogs are the reservoir. Young children are most commonly affected. Infected adults tend to develop self-healing skin sores. In Brazil, peridomestic transmission from raiding foxes affects older children. A similar age group is affected in East Africa, where transmission takes place outside the houses in the evenings. In India, where the human is the reservoir, epidemics occur every 15 years or so and all age groups, previously uninfected, are susceptible. Travellers and tourists of any group age are susceptible in any of the four zones.

Pathogenesis. In over 90% of cases, the infection is subclinical and cutaneous hypersensitivity and immunity develop [42]. In the others, especially in the malnourished, the parasite invades and multiplies in reticuloendothelial cells of the spleen, liver, lymphoid tissue, bone marrow and gut submucosa. This reticuloendothelial bombardment is associated with the overproduction of polyclonal IgG, specific antibody production, and the formation of high titres of immune complexes and various autoantibodies. The spleen and, to a lesser extent, the liver become

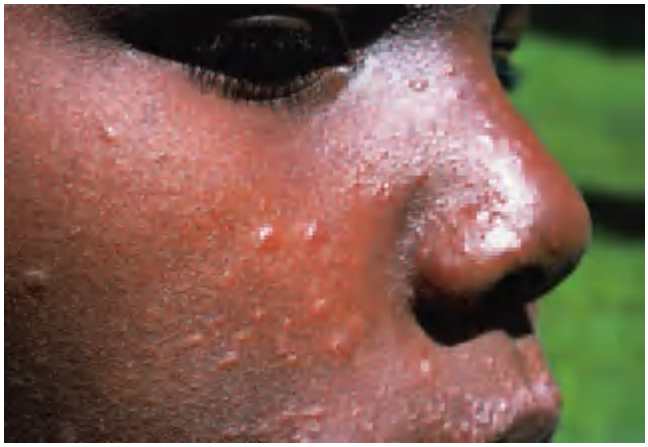

Fig. 32.49 Post-kala-azar dermal leishmaniasis. Typical facial papules in a Kenyan arising 6 weeks after treatment and healing spontaneously. (Courtesy of Dr J.D. Chulay.)

enlarged, and hypersplenism ensues, causing anaemia, leukopenia and thrombocytopenia. Organ function is usually well preserved until late in the disease, but specific and non-specific indices of cell-mediated immunity are depressed, and secondary infections are common and often fatal [43].

Clinical features [44]. After an incubation period of weeks to months, sometimes exceeding a year, fever develops, either insidiously or abruptly. The commonest additional symptoms are fatigue, discomfort from the presence of the enlarged spleen and cough, diarrhoea and epistaxis. Gross splenomegaly is the dominant physical sign; hepatomegaly, lymphadenopathy in some endemic zones, and signs of malnutrition, including pedal oedema, red, straight hair in Africans, and wasting also occur.

In a few cases in Africa, a primary skin sore has been described, like those of cutaneous leishmaniasis. Rarely, there may be an accompanying mucosal lesion. In Indian people especially, the skin of the face, hands, feet and abdomen becomes hyperpigmented, even black: kala-azar means black sickness. Despite epistaxis and sometimes jaundice, there is no evidence of cutaneous bleeding. In Iran, patients have been seen with numerous skin lesions [45].

Post-kala-azar dermal leishmaniasis (PKDL) (dermal leishmanoid). In 5% of East African patients, and 20% of Indian patients, a rash develops after the visceral disease has healed, either spontaneously or following treatment. A small proportion of patients with PKDL give no previous history of visceral disease. In Africa [46] the rash begins during convalescence, appearing on the cheeks, chin, ears and extensor aspects of forearms, buttocks and lower legs (Fig. 32.49). Usually, the rash comprises discrete papules, which on histological examination show a tuberculoid histology with scanty parasites. The leishmanin test is positive. The rash heals spontaneously over a few months. Presumably it represents the acquisition of specific cellular immunity that is clearing up scattered parasites that remained in the skin. Both cellular immunity and pentavalent antimonials are less efficient in the skin than in the viscera.

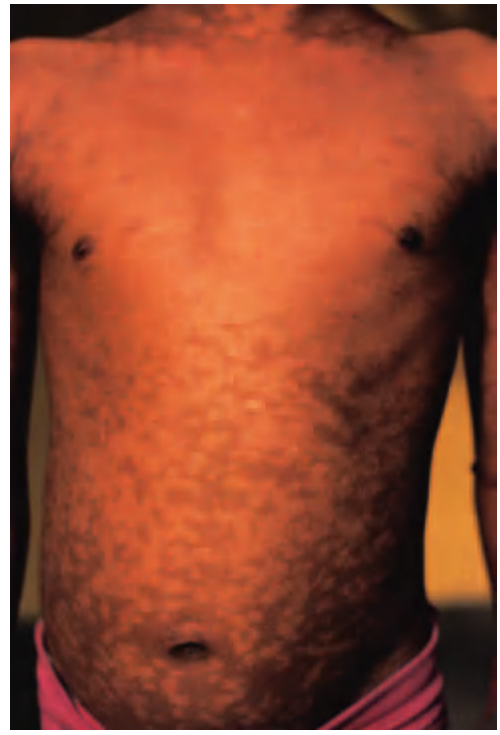

Fig. 32.50 Post-kala-azar dermal leishmaniasis in an Indian person showing the extensive hypopigmented macular rash.

In India, by contrast, the rash appears 1–2 years after recovery, as hypopigmented macules, similar in appearance and distribution to those of lepromatous leprosy (Fig. 32.50). After a variable period of years or months, diffuse nodulation begins to develop in these macules (Fig. 32.51). The rash is progressive over many years and seldom heals spontaneously. The tongue, palate and genitalia may be involved. There may be lymphadenopathy, but the viscera are spared and there are no features of relapse of the previous systemic infection. Presumably, this condition represents cellular immunity against a dermotropic mutant of *L. donovani*. PKDL is thought to represent the intraepidemic reservoir of infection of visceral leishmaniasis in India. Histology shows a poorly differentiated infiltrate of chronic inflammatory cells, with a variable number of leishmania in dermal macrophages [47]. The leishmanin test is usually negative, but becomes positive after successful treatment [48].

Diagnosis. In visceral leishmaniasis, parasites may be demonstrated in aspirates of spleen, bone marrow, liver or lymph node, in that order of likelihood (Fig. 32.52). In

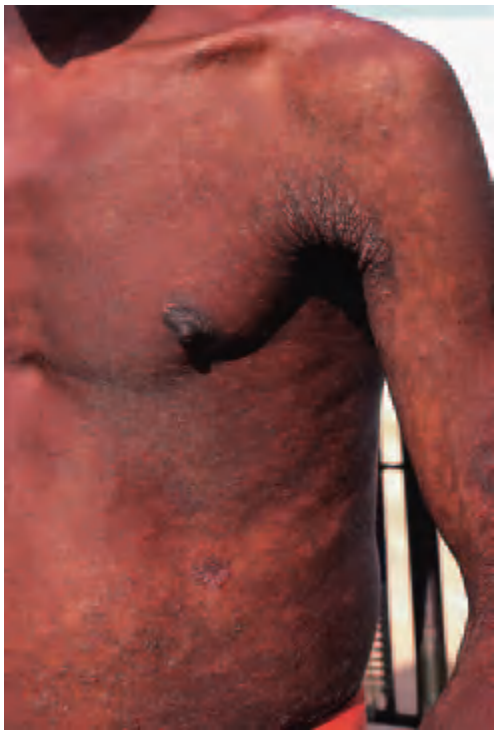

Fig. 32.51 Post-kala-azar dermal leishmaniasis in an Indian person. A later stage than that shown in Fig. 32.50. Papules are beginning to develop.

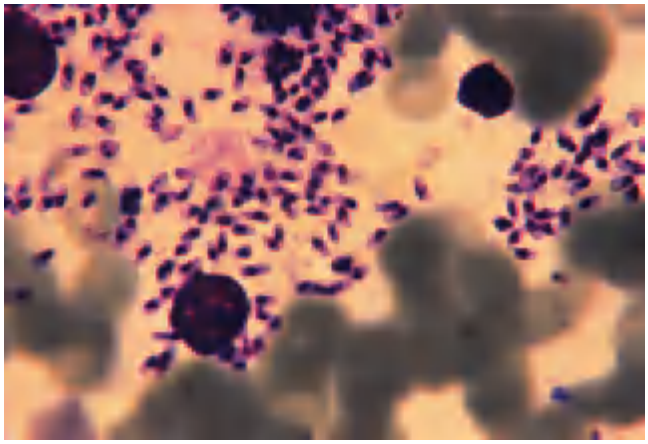

Fig. 32.52 Amastigotes of *Leishmania infantum* in a bone marrow smear from a patient with visceral leishmaniasis and the acquired immune deficiency syndrome. (Courtesy of Mr A.H. Moody, Hospital for Tropical Diseases, London, UK.)

PKDL, slit-skin smears are usually positive. Antibodies to *Leishmania* spp. may be demonstrated by a variety of techniques: indirect immunofluorescence, ELISA and direct agglutination tests are commonly performed [49]. The leishmanin test is negative, except in African PKDL.

Treatment. For visceral leishmaniasis, sodium stibogluconate is used, as for cutaneous leishmaniasis for 21–30 days, according to the endemic zone [27]. African PKDL does not require further treatment. Indian PKDL is treated with a further course of sodium stibogluconate.

Visceral leishmaniasis in patients with HIV infection [50]

The main area of overlap of these two infections is in southern Europe, especially Spain. Leishmaniasis may be acquired prior to or after the HIV infection, and may thus be primary or secondary to the HIV infection. In some patients, typical characteristics of fever and splenomegaly have not been present, and serological tests have been negative. On occasion, the parasite has been discovered by chance, for example in the biopsy of Kaposi's sarcoma, and disseminated dermatofibroma-like lesions containing amastigotes have been described in a patient with acquired immune deficiency syndrome (AIDS) coinfected with visceral *L. donovani* [51]. Aspirates of bone marrow and spleen show extremely heavy parasitization. Relapse and mortality rates are high. Treatment should be prolonged and monitored by splenic aspirates.

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Toxoplasmosis

Aetiology. The disease is caused by *Toxoplasma gondii*, a tiny sporozoon often assuming a crescentic shape, first identified in 1908 in a North African rodent, *Ctenodactylus gondii*. Cats are definitive hosts and a form of *Toxoplasma* cyst can be found in their faeces. Rodents and birds are the intermediate hosts. Larger mammals including humans are infected incidentally, by eating raw, infected meat or by ingesting oocysts in contaminated food or water.

Pathogenesis. The organism tends to invade the reticuloendothelial system and the endothelium of the blood vessels, forming granulomas with necrosis of affected tissues. Toxoplasmosis causes four types of disease in humans [1]:
1 an acute febrile lymphadenopathy;
2 fetal infection, causing brain damage;
3 ocular disease, usually due to reactivation of fetal infection;
4 disseminated disease in immunocompromised patients, including those with HIV infection, causing fulminating encephalitis.

Skin changes are uncommon and non-specific. In the congenital disease [1], macular and haemorrhagic eruptions predominate. Occasionally, abnormal hair growth and exfoliative dermatitis have been seen. In the acquired disease, macular, maculopapular, papular and haemorrhagic eruptions also occur and may be followed by scarlatiniform desquamation. A wide variety of other lesions have been described including bullae, nodules, livedo annularis, urticaria and an eruption like pityriasis lichenoides; conclusive evidence of a causal relationship is frequently wanting. A dermatomyositis-like syndrome is described [2,3].

Diagnosis is made on clinical evidence, and may be confirmed by demonstration of the organism in biopsy of lymph node, liver or spleen, bone marrow, or in cerebrospinal and ventricular fluid. Usually, the diagnosis is made serologically. Several methods are available, among them:
1 the Sabin–Feldman dye test, positive early and declining over 1–2 years, which measures mainly IgG antibodies;
2 direct agglutination of formalinized parasites—useful for screening, detects IgM and IgG antibodies;

3 indirect fluorescence—simple and safe, can be used to distinguish IgM from IgG antibodies, as can an IgM ELISA.

Treatment. The sulphonamides and pyrimethamine (Daraprim) act synergistically and are effective [4]. Severe side effects may occur due to interference with folic acid metabolism. For this reason, infections in immunologically normal individuals are not usually treated.

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Chapter 33

Diseases Caused by Arthropods and Other Noxious Animals

D.A. Burns

Mechanisms of skin injury by arthropods

Arthropods produce their effects on the skin by a variety of mechanisms [1–6], more than one of which may be implicated simultaneously.

Mechanical trauma

The puncture wound or laceration produced by the penetration of the skin seldom causes serious disturbance to the host. The nature of the trauma inflicted depends upon the structure of the mouthparts, which show wide variation between different species. There are two methods of feeding on blood: 'vessel feeders' insert the tip of their mouthparts into a capillary, and 'pool feeders' lacerate the skin, damage blood vessels and feed on the extravasated blood. Vessel feeders include sucking lice (Anoplura) and most mosquitoes, and pool feeders include stable flies and tsetse flies.

Injection of irritant, cytotoxic or pharmacologically active substances

An injected substance may contain pharmacologically active agents that produce local or, if in sufficient quantity, systemic effects. Salivary secretions and sting venoms may contain various enzymes such as hyaluronidase, proteases, peptidases and phospholipases; kinins; histamine-liberating agents; histamine; 5-hydroxytryptamine; or acetylcholine.

Injection of potential allergens

The vast majority of reactions to arthropod bites or stings depend upon the presence of specific antibodies to antigenic substances in the saliva or venom. Investigation of extracts of venom sacs and salivary glands from many species, using modern immunological techniques, has demonstrated the presence of numerous antigens, some specific for a single species, and others common to several related species or even to related genera.

The type of reaction provoked by an arthropod bite or sting in an individual patient largely depends on previous exposure to the same or related species. When an individual is bitten for the first time by a species whose salivary secretions contain no directly injurious substance, there is commonly no reaction. After repeated bites, sensitivity starts to develop, manifest by an itchy papule developing about 24 h after each bite and persisting for several days. With prolonged exposure, an immediate weal reaction occurs, to be followed by the delayed papular reaction. After a further period of exposure, the delayed reaction no

longer occurs, and eventually there is no reaction at all. The patient is then said to be immune. Mellanby [7] demonstrated this sequence of events with mosquito bites, and a similar response is seen with the bites of many other arthropods.

Some patients show a severe systemic hypersensitivity to arthropod allergens, manifest by anaphylaxis. The antigenic substances in the venoms of Hymenoptera (bees, wasps, hornets) are more likely to induce severe systemic hypersensitivity reactions than are the antigens of most other insects.

The capacity of a patient to respond to an antigenic stimulus is also an important factor in determining the reaction to an arthropod. The reactions of patients who are immunosuppressed, as a result of either disease or therapy, are modified. Examples of this include the occurrence of crusted scabies in immunosuppressed individuals, and the response to bites in patients with chronic lymphatic leukaemia, human immunodeficiency virus (HIV) infection, and Epstein–Barr virus-associated natural killer cell leukaemia/lymphoma (see p. 33.7).

Secondary infection

Bacterial infection may be introduced at the time of the bite, but commonly gains entry as a result of scratching, and may confuse the clinical picture. Compartment syndrome caused by streptococcal cellulitis complicating an insect bite has been described [8].

Invasion of the host's tissues

Certain flies cause myiasis, in which the host's tissues are invaded by larvae (see p. 33.8).

Contact reactions

Simple contact with the secretions of certain arthropods, or with their living or dead bodies, may provoke irritant or allergic contact reactions. For example, the secretions of blister beetles produce a severe irritant reaction, and repeated handling of cockroaches may induce contact urticaria and dermatitis.

Reactions to retained mouthparts

Persistent granulomatous papules or nodules may be provoked by retained mouthparts, for example those of ticks.

Transmission of disease

Many diseases have arthropod vectors, for example malaria (mosquitoes), leishmaniasis (sandflies) and typhus (lice).

Susceptibility to infestation or attack

There are a number of environmental and social factors that determine the range of arthropod species to which an individual is exposed.

Persons living and working in tropical climates tend to wear fewer clothes, and therefore expose larger areas of the body to bites and stings. Clothing itself is essential to the existence of the body louse, and areas of constriction of clothing affect the distribution of the skin lesions caused by certain mites (e.g. harvest mites).

Certain occupations carry an increased risk of reactions to arthropods [9]. Forestry workers, for example, may be exposed to the urticating hairs of the caterpillars of certain species of Lepidoptera, and dock workers handling foodstuffs may be attacked by mites infesting the cargo.

In some societies, humans are exposed to attack by the parasites of the domestic animals with which they cohabit.

Housing can influence exposure to arthropod attack in a number of ways. Overcrowded homes favour transmission of ectoparasites, such as lice and the scabies mite, and dilapidated housing provides an ideal habitat for bedbugs. Spiders and scorpions will take up residence in garages, outhouses and woodpiles.

The methods by which an arthropod is attracted to its host species include body heat, carbon dioxide in exhaled air (e.g. ticks, fleas, bedbugs), and displacement of air or vibrations caused by the host (e.g. fleas) [10]. Human sweat contains mosquito attractants, and anhidrotic subjects are unattractive to mosquitoes [11,12]. The human skin microflora may be responsible for producing compounds that attract mosquitoes and, as there is variation in the microflora between individuals, body odour probably contributes to susceptibility to biting [13]. Human odour also appears to play a part in attracting sandflies [14].

Pregnant women appear to be more attractive to mosquitoes than the non-pregnant [15,16].

There is also a suggestion of increased susceptibility to mosquito bites in patients with HIV infection receiving antiretroviral therapy and suffering from lipoatrophy [17].

Certain species of flies are attracted to skin ulcers and purulent material, in which they lay their eggs.

Insect pheromones play a part in attacks by large numbers of Hymenoptera. Honeybees, when stinging, emit an alarm pheromone from glands in their sting chambers, and this guides other bees to attack an intruder.

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Histopathology of arthropod bites and stings [1–3]

The histopathological changes associated with arthropod bites depend upon a number of factors, including the arthropod involved, the type of immunological reaction provoked and the duration of the lesion.

In papular urticaria, there is prominent papillary dermal oedema and a perivascular chronic inflammatory infiltrate with a significant admixture of eosinophils.

Bullous reactions develop beneath a more or less intact epidermis, and may be multilocular.

Chronic reactions often have a pseudolymphomatous appearance. The dermis contains a dense inflammatory infiltrate of lymphoid cells and histiocytes, with an admixture of eosinophils and plasma cells, and the presence of atypical mononuclear cells with hyperchromatic nuclei. Secondary lymphoid follicles with germinal centres are sometimes formed. Multinucleated cells may also occur. If retained mouthparts are present, there may also be giant cells of foreign-body type.

Additional histopathological features associated with particular arthropods are noted in the relevant sections of this chapter.

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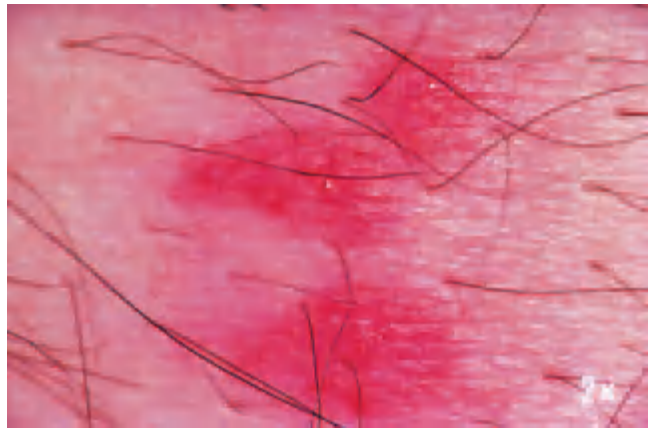

Fig. 33.1 Typical papular urticaria. In this case, in response to flea bites.

Clinical features of arthropod bites

The very large number of species of biting and stinging arthropods, their different feeding habits and the variation in individual patients' responses to the various irritants and allergens injected determine the diversity of clinical features. The type and distribution of lesions produced by individual arthropods are discussed in the relevant sections throughout this chapter.

The most frequently encountered response is papular urticaria (Fig. 33.1). Initially, an extremely itchy urticarial weal develops at the site of the bite, and this is succeeded by a firm pruritic papule, which usually persists for several days. The weal and papule may show a central haemorrhagic punctum, and the papule may be surmounted by a tiny vesicle. Lesions are often grouped in clusters, and develop in crops at irregular intervals.

The number and distribution of skin lesions produced by the bites depend upon the type of exposure and the feeding habits of the arthropod involved. New bites by the same species will often cause a recrudescence of activity in existing lesions.

Bullous reactions are common on the lower legs (Fig. 33.2), but may occur at other sites, especially in children. In the presence of lower limb venous hypertension, haemorrhagic or ulcerated lesions may develop. More severe local changes are sometimes found, with cellulitis and lymphangitis in the apparent absence of secondary infection.

Irritation is an almost inevitable symptom, and rubbing and scratching may increase the inflammatory changes and induce eczematization. When the bites are very numerous, or if the local reaction is severe, there may be fever and malaise.

Secondary infection is a common complication, and may be manifest as impetigo, folliculitis, cellulitis or lymphangitis.

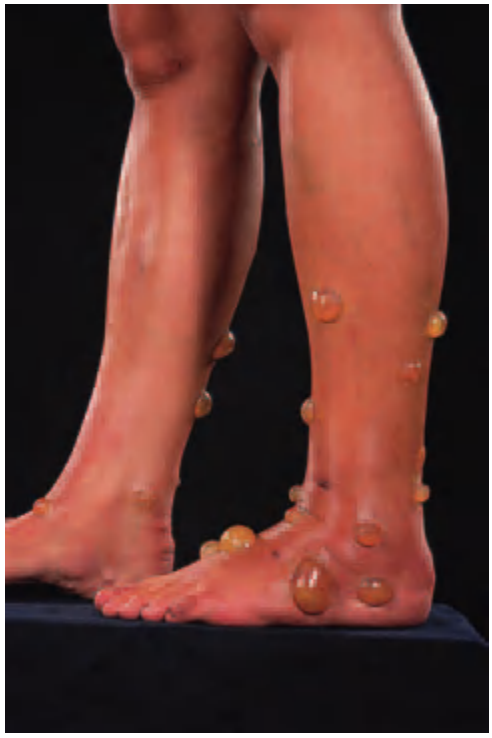

Fig. 33.2 Bullous lesions in response to arthropod bites. (Courtesy of Dr F.A. Ive, Durham, UK.)

Anaphylactic shock is unusual except after Hymenoptera stings, but is occasionally seen with some other arthropods.

Bite reactions may persist for months. Tick attachment sites, in which the mouthparts may be retained, are the most likely to persist, but so may bites of mosquitoes and other insects.

Diagnosis

The diagnosis of insect bites is often self-evident, for example when the patient has spent the afternoon in the garden on a hot day in summer and subsequently develops typical lesions on exposed areas of skin. However, difficulty arises when the source of the bites is not immediately obvious.

The distribution of the bites may provide a clue to their origin, for example localization to the abdomen and thighs in cheyletiellosis or contact with sarcoptic mange in dogs, and involvement of the legs below the knees when the lesions are produced by cat or dog fleas. Patients should be asked about domestic pets—not only their own, but also those in the homes of close relatives who are visited regularly, as ectoparasites associated with pet animals are often the source of persistent arthropod bites. If the bites are not localized, but scattered all over the body, consider reactions to arthropods biting in the patient's bedroom, such as bird fleas, bird mites or bedbugs. Enquire if the patient has recently moved house. It may

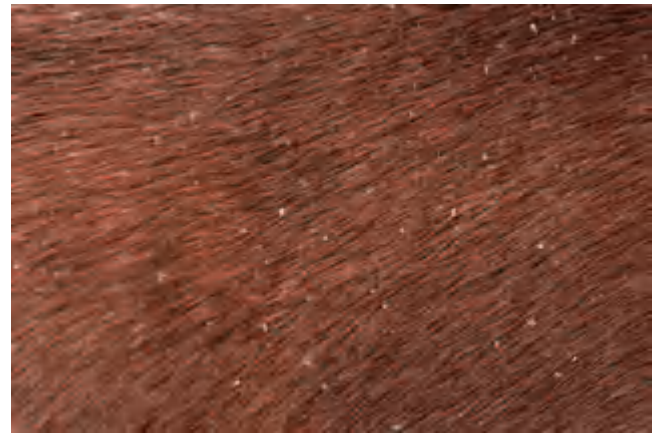

Fig. 33.3 Typical heavy scale in the coat of a dog suffering from *Cheyletiella* infestation.

be that the previous owners of the new home kept pet animals and have left a legacy of domestic flea infestation. Even if the house remained empty for a considerable time before the new owners took up residence, the flea population will be waiting in cocoons to emerge when the new occupants arrive. Adult fleas can survive starvation for variable lengths of time, depending upon species and environmental conditions [1,2]—a newly emerged and unfed dog flea, *Ctenocephalides canis*, will survive for approximately 60 days. In the absence of their natural hosts, such animal flea populations will not usually survive for more than a few months.

If the history and examination do not suggest a possible source for the problem, or if the dermatologist wishes to confirm a suspected source, the following procedures may be useful [3,4].

1 The patient's pet animals should be examined if possible for signs of skin disease. Cheyletiellosis and canine scabies produce characteristic changes on an affected animal [5]. Skin scrapings will confirm sarcoptic mange, and vigorous combing of scale from the coat of a dog suffering from cheyletiellosis (Fig. 33.3) will provide material in which *Cheyletiella* mites may be identified. If the animal cannot be examined, the patient should be provided with a sheet of black paper, and asked to collect brushings or combings from the animal's coat for subsequent examination.

2 If domestic infestation with cat or dog fleas is suspected, this can often be confirmed by examination of debris from the pet's bedding. The patient is supplied with a large polythene bag and instructed to place the pet's bedding in the bag and shake it vigorously for a few minutes. The bedding is then removed, and the bag is sealed and delivered to the dermatologist for microscopy of the debris. Macroscopically, flea eggs and faeces have a 'pepper-and-salt' appearance (Fig. 33.4), and the larvae are grub-like. For identification, adult fleas should be 'cleared' in 10%

Fig. 33.4 Typical 'pepper-and-salt' appearance of flea eggs and faeces in the debris from a cat's bedding.

potassium hydroxide for 24 h so that the majority of the pigment is removed and the anatomical details revealed. Cat and dog fleas are readily identified, but if unfamiliar species are encountered, the help of an entomologist with an interest in Siphonaptera should be sought. Correct identification of fleas is important so that proper control measures may be carried out [6].

3 If problems from bird fleas or bird mites are suspected, it is often of value to examine dust obtained with a vacuum cleaner from bedrooms. This is, however, time-consuming and requires some expertise.

4 It may be necessary to visit the patient's home to establish whether there are birds' nests under the eaves, which might be a source of fleas or mites, or to take specimens from household pets.

5 Mites that might have relevance to human dermatoses may be isolated from clothing, furnishings, or bedding by the techniques described by Hewitt *et al*. [7].

An entomologist is often invaluable in these situations, not only for identification of arthropods, but also to advise about their relevance to the situation. An arthropod discovered at the scene of the crime may only be an innocent bystander.

In some cases, in spite of extensive efforts, the source of the bites remains unknown, and the dermatologist can then only treat the problem symptomatically with oral antihistamines, topical antipruritics and insect repellents [8].

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Class Insecta

Mosquitoes, gnats, midges and flies (Diptera)

The order Diptera is one of the largest of the insect orders. Diptera are two-winged flies with a single pair of membranous forewings, and with hindwings modified as balancing organs (halteres). Most feed on nectar, plant exudates or decaying animal and vegetable matter, but some are blood-sucking, and some have larvae parasitic on humans. To the dermatologist, the Diptera are important as biting insects and as the cause of myiasis, in addition to their capacity to transmit disease.

The Diptera are usually classified in three suborders, based on characteristics shown by larvae, pupae and adults —the Nematocera, the Brachycera and the Cyclorrhapha [1]. Detailed information on the morphology, biology and medical importance of Diptera is provided in comprehensive texts by Kettle [2], and Lane and Crosskey [3].

Suborder Nematocera

The Nematocera are small flies with long, many-segmented, filamentous antennae. With a few exceptions, the medically important species are blood-suckers.

Family Culicidae (mosquitoes)

Mosquitoes have worldwide distribution. They are responsible for the transmission of malaria, filariasis, yellow fever and dengue fever. Human malaria is transmitted exclusively by *Anopheles* species. Both male and female mosquitoes will imbibe sweet juices from flowers or ripe fruit, but only the females pierce the skin and suck the blood of vertebrate animals. Most mosquitoes are nocturnal feeders, but a few species are diurnal. The eggs of mosquitoes are deposited on or near water, and adults develop via aquatic larval and pupal stages.

Family Psychodidae (sandflies)

These are tiny (2–3 mm long), hairy flies with lanceolate wings and long legs. They are widely distributed, especially in the tropics and subtropics.

Genus Phlebotomus. Species of *Phlebotomus* are vectors of cutaneous and visceral leishmaniasis in the Old World. *Phlebotomus* species are also vectors of sandfly or papatasi

fever. *Phlebotomus* bites cause a condition known as harara in Israel and the surrounding countries.

Genus Lutzomyia. Lutzomyia species are vectors of cutaneous and visceral leishmaniasis and bartonellosis in the New World.

Family Simuliidae [3,4]

Popularly known as blackflies, this family contains approximately 1300 species, whose distribution is worldwide. Blackflies are small (2–6 mm) flies with a characteristic humped thorax, and short, broad wings. They breed only in areas of fast-flowing water, and bite during the day.

Over large parts of the tropics, several species of blackfly are responsible for transmission of onchocerciasis—principally the *Simulium damnosum* complex (several closely related species) in West Africa, *S. neavei* in East Africa, *S. metallicum* in Venezuela and *S. ochraceum* in Guatemala. In temperate regions, the greatest problem caused by simuliids is their painful bites, and some species are such a persistent nuisance at certain times of the year that they may make large areas unpleasant to live or work in. In Yugoslavia, the notorious Golubatz fly, *S. columbaschense* (*S. columbaczense*), which bred in the Danube at Golubatz, caused both mortality among livestock and human misery until environmental changes eliminated it. In North America, the most troublesome biting species are *S. venustum*, which is holarctic and occurs from Alaska to Greenland and south to Texas and South Carolina, and *Prosimulium mixtum*, which occurs in the north-eastern USA and eastern Canada.

S. posticatum (the Blandford fly), formerly named *S. austeni* Edwards, is widely distributed throughout Europe and European Russia. In England, it is found in an arc running from East Anglia through Oxfordshire into Dorset. In the Stour valley area of Dorset, particularly in the region of Blandford Forum, the fly is present in sufficient numbers in summer to cause a problem [5–7]. It had not been known as a pest in the UK prior to the 1960s. The eggs are laid in cracks in vertical river banks, a short distance above the water [8]. The larvae are concentrated in stretches of fast-flowing water immediately downstream of barrages and weirs, where they attach themselves to weeds or stones and feed on phytoplankton. Adults hatch in May, and are on the wing in May, June and early July. Females require a blood meal before oviposition, and although they will bite various wild and domestic animals, they appear to prefer humans and dogs.

Family Ceratopogonidae (gnats; biting midges; 'punkies'; 'no-see-ums')

These small flies (1–3 mm in length) have a worldwide distribution, and are notorious as biting pests. The biting midges of the West Highlands of Scotland (the commonest species of which is *Culicoides impunctatus*), for example, are an intolerable nuisance, and pose a problem to the Scottish tourist industry [9]. Males and females feed on nectar, but most females require a blood meal for maturation of the ovaries and egg production. There are four genera that suck blood: *Culicoides*, *Leptoconops*, *Austroconops* and *Forcipomyia* (subgenus *Lasiohelea*). They breed in rivers, swamps and marshes, and often occur in swarms, which will readily attack any mammal in their vicinity. A few species enter homes and bite at night.

The genus *Culicoides* is widely distributed. *Leptoconops* species are largely restricted to the warmer parts of the Old and New World. *Austroconops* contains only one species, which is restricted to western Australia. *Lasiohelea* species are principally associated with tropical and subtropical rain forests.

Suborder Brachycera

The Brachycera are large, stout-bodied flies with short antennae, often composed of three segments, and never more than six.

Family Tabanidae

Many species of three genera of this family will attack humans—*Tabanus* (horse flies), *Chrysops* (deer flies) and *Haematopota* (clegs). They are large flies, and have a worldwide distribution. Only females suck blood. Tabanid flies act as vectors for loiasis and tularaemia, and some species may transmit anthrax mechanically [10].

Family Rhagionidae (snipe flies)

Species of *Symphoromyia* occurring in the Palaearctic and Nearctic regions are vicious biters. *Atherix* is another blood-sucking genus in the Nearctic and neotropical regions, and *Spaniopsis* is troublesome in Australia.

Suborder Cyclorrhapha

The antennae are composed of three segments, with a bristle (arista) carried dorsally on the last segment. The Cyclorrhapha is a large group of flies whose taxonomy is complex. Several families are of medical importance.

Family Chloropidae (eye flies; frit flies)

These are small flies about 2 mm in length. The adults of some species are attracted to open sores, body secretions and the eyes, particularly eyes with a copious discharge. *Hippelates* and *Siphunculina* species are associated with humans and can act as mechanical vectors of yaws, conjunctivitis and streptococcal skin infection.

Family Muscidae (house flies; stable flies)

This family includes the familiar house fly *Musca domestica* and the lesser house fly *Fannia canicularis*. These do not bite, but may act as mechanical vectors of disease. The muscids *Stomoxys calcitrans* (stable fly) and *Haematobia* species (horn flies) have mouthparts modified for sucking blood. They usually feed on large quadrupeds, but can inflict painful bites on humans.

Family Hippoboscidae (flat flies; louse flies; keds)

Members of this family are blood-sucking ectoparasites of birds and animals. Several species of ked have been recorded as biting humans [11,12].

Family Glossinidae (tsetse flies)

Many species are vectors of trypanosomiasis. They are confined to Africa south of the Sahara.

Members of several other families of Diptera are important in that their larvae may cause myiasis (p. 33.8).

Clinical features [13,14]. The clinical features of the bites of insects of this large and diverse order are variable. The nature of the pharmacologically active substances injected, and the degree of acquired allergic sensitivity to the antigenic substances in the saliva, are the main factors that determine the reaction. For most of the Diptera, the allergic component is by far the more important. The nature of any injected toxins is usually unknown and the effects attributable to them are usually slight. The clinical picture will also be influenced by the biting habits of the species concerned.

The reaction to mosquito bites is determined by previous exposure, and the sequence of events following multiple bites was elucidated by Mellanby [14]. In an individual not previously exposed, the bites produce no response. With subsequent bites, a delayed reaction occurs, consisting of pruritic weals, which develop approximately 24 h after the bites and persist for several days. After repeated bites for several weeks, the response changes, with the appearance of an immediate weal at the bite site. This resolves after about 2 h, to be replaced by the delayed reaction. Further exposure provokes the immediate reaction, but not the delayed response. Eventually, tolerance is acquired, and no reaction occurs. Studies of the bite reaction in relation to age have shown an increase in immediate reactions from early childhood to adolescence, and a decrease thereafter. The appearance and intensity of delayed reactions decreases with age [15]. It has been proved conclusively that the mosquito salivary glands are the source of the antigens responsible for the bite reactions [16].

Anaphylactic reactions to mosquito bites are rare [17]. Gaig *et al*. [18] reported a patient with a serum sickness-like illness associated with mosquito bites. Severe local reactions are not uncommon, and in highly sensitive subjects bullae, cellulitis and eczematization are often seen, especially on the legs. Gravitational factors probably play a role in the development of bullae on the legs [19]. Exaggerated hypersensitivity responses to mosquito bites have been reported in patients suffering from chronic lymphatic leukaemia [20–23]. However, although the clinical picture and histological features are typical of arthropod bites, in many cases patients do not recall being bitten [22,24]. Exaggerated responses to mosquito bites have also been described in patients with HIV infection [25,26], and a chronic pruritic eruption in patients with acquired immune deficiency syndrome (AIDS) in South Florida has been attributed to mosquito bites [27].

In recent years, there have been a number of reports from Japan of severe hypersensitivity to mosquito bites preceding the development of malignant histiocytosis [28–30]. This has now been characterized as a disease in which there is a triad of hypersensitivity to mosquito bites, chronic Epstein–Barr virus infection, and natural killer cell leukaemia/lymphoma [31–33]. It affects predominantly Japanese in the first two decades of life. The skin lesions are bullae, which develop at mosquito bite sites, undergo necrosis and heal with residual scarring. Accompanying the skin lesions are systemic features, principally high fever and general malaise. Affected individuals die of haemophagocytic syndrome (malignant histiocytosis).

Multiple sandfly bites are responsible for the syndrome known as harara (urticaria multiformis endemica), which occurs in Israel and surrounding countries [34]. Skin lesions occur on exposed parts of the body, and are composed of urticated papules and papulovesicles, and bullous lesions, frequently with secondary infection.

The bites of Simuliidae, which may be very numerous, are on exposed skin. The sites of the bites are often marked by a small blood crust with surrounding ecchymosis. Within a few hours, small, pruritic papules develop, and these resolve after several days. However, severe reactions with marked oedema of the limbs and constitutional upset occasionally occur, and in some cases nodules and discoid eczematous areas persist at the sites of the bites for several months [35]. The bites of the Blandford fly occur most frequently on the legs, and women are principally affected [6,7]. The bites often produce a severe local reaction, with oedema and blistering, and may be accompanied by systemic manifestations, including pyrexia, arthralgia and meningism.

The biting midges of the family Ceratopogonidae generally cause small, papular lesions on exposed parts of the skin, but wealing and bulla formation may occur in sensitized individuals. Weal-like lesions, papules and persistent nodules have been described following bites from *Leptoconops torrens* in California [36].

Midges of the family Chironomidae are closely related to ceratopogonids. These midges do not bite, but

hypersensitivity to their larvae, used as aquarium fish food and as bait, is well recognized [37], and includes contact urticaria [38] and protein contact dermatitis [39].

The bites of keds may be followed by the development of persistent pruritic papules [12].

The bites of horse flies and stable flies are often very painful and frequently become secondarily infected.

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Myiasis

Myiasis is the infestation of body tissues of humans and animals by the larvae of Diptera [1–6]. The various forms of myiasis may be classified from an entomological or a clinical point of view. Entomologically, flies may be classified into three myiasis-producing groups: obligatory, facultative and accidental. Obligatory myiasis producers always pass their larval stage parasitically in the body of an animal. Larvae of facultative myiasis producers usually develop on decaying flesh or vegetable matter, but may infest wounds. In accidental myiasis, the eggs or larvae of Diptera are ingested in food or drink, producing intestinal myiasis.

Clinically, myiasis can be classified according to the part of the body affected. Cutaneous myiasis includes wound myiasis and furuncular myiasis, in which larvae penetrate and develop within the skin. In nasopharyngeal myiasis, the nose, sinuses and pharynx are affected, and ophthalmomyiasis involves the eye, orbit and periorbital tissues. Intestinal and urogenital myiasis involve invasion of the alimentary tract or urogenital system.

The flies responsible for myiasis in humans include the following groups.

Family Muscidae

Eggs of *Fannia canicularis* (lesser house fly) and *Musca domestica* (house fly) may be deposited on ulcers and give rise to wound myiasis [7].

Family Calliphoridae (blowflies)

Genus Cochliomyia (Callitroga). These New World screwworms are distributed in North and South America. Cases of myiasis involve the larvae of only two species of *Cochliomyia*: *C. macellaria* and *C. hominivorax* (*americana*). The larva of *C. macellaria* is a facultative parasite, which may be responsible for secondary infestation of wounds. Larvae of *C. hominivorax* are obligatory parasites, which feed on living tissue and can penetrate unbroken skin [8–10], but they may also infest wounds.

Genus Chrysomya. The Old World equivalent of *Cochliomyia*. *Chrysomya bezziana*, the Old World screwworm, is important medically, as the larvae are obligate parasites in wounds.

Genus Cordylobia. Cordylobia anthropophaga, the 'tumbu' fly, is widespread in tropical Africa south of the Sahara [11], and most reported cases of tumbu fly myiasis are acquired in Africa [12,13]. There are, however, reports of myiasis acquired elsewhere, including Spain [14] and Saudi Arabia [15]. Tumbu fly myiasis occurring in two boys who had never been to Africa might have been acquired as a result of their father, who made frequent visits to Africa, bringing tumbu fly eggs back amongst his possessions [16]. *C.* (*Stasisia*) *rodhaini*, the only other species of *Cordylobia* known to infest humans, has a more limited distribution in tropical Africa, principally the rainforest areas. Extensive furuncular myiasis due to *C. rodhaini* has been reported in an Italian man who acquired the problem while working in Ethiopia [17]. Eggs are not laid on the host, but on sand or soil, especially if contaminated by urine or faeces. They may also be deposited on clothing and linen hanging out to dry. After hatching, the larva raises its cephalic end searching for a suitable host. In the wild, rats are the usual host, but around human habitation, dogs and humans are common hosts. The larva attaches itself by means of its oral hooks, and rapidly penetrates the skin. When development is complete, usually in 14–16 days, it drops to the ground to pupate.

Genus Auchmeromyia. Although strictly not a cause of myiasis, the larva of the fly *A. senegalensis*, the Congo floor maggot, is a blood-sucking parasite of humans. This fly occurs throughout tropical Africa, where it lives in native huts and lays its eggs in the soil of the floor. The larvae lie buried in the soil during the day, but emerge at night to feed on the sleeping occupants of the huts. Once engorged, they drop off the host and burrow back into the soil.

Larvae of members of the genera *Phormia* (black blowflies) [18–20], *Lucilia* (greenbottle) and *Calliphora* (bluebottle) may also be secondary invaders of wounds in man.

Family Sarcophagidae (flesh flies)

Genus Sarcophaga. There are occasional reports of members of this genus infesting wounds [21].

Genus Wohlfahrtia. These are similar to *Sarcophaga*. They are important myiasis-causing flies in camels and sheep. The larvae of *W. magnifica* may be deposited in the ear, eye or nose, and cause extensive destruction of healthy tissue. Delir *et al*. [22] reported an Iranian woman with a cavity in the left labium majus occupied by a number of *W. magnifica* larvae. *W. magnifica* occurs in south-eastern Europe, southern and Asiatic Russia, the Middle East and North Africa. *W. vigil* and *W. opaca* are North American species whose females deposit larvae on the skin of young animals, resulting in furuncular myiasis. Lesions are identical to those of *Dermatobia*. Human furuncular myiasis occurs only in young babies, as the larvae are unable to penetrate adult skin [23].

Family Oestridae

Genus Cuterebra (rodent or rabbit botfly). Rabbits and rodents are the natural hosts for the larvae of these flies, which are sometimes responsible for human furuncular myiasis [24–26]. Baird *et al*. [27] reviewed 54 cases of North American cuterebrid myiasis.

Genus Dermatobia (human botfly). Dermatobia hominis is the only species in the genus. It is a bluebottle-like fly found in the neotropical areas of the New World, extending from southern Mexico to northern Argentina. It occurs in areas where temperature and humidity are relatively high, principally lowland forests. *D. hominis* causes cutaneous myiasis in a wide range of mammalian hosts, including humans, and is particularly important as a parasite of cattle.

The female fly does not deposit her eggs directly, but uses other insects, such as day-flying mosquitoes and blood-sucking flies, as vectors to carry her eggs to the host. She grasps the insect vector in midair and deposits a number of eggs on its abdomen. When the vector subsequently feeds on a potential host, the eggs hatch and the larvae rapidly burrow into the skin (Fig. 33.5). Larval development lasts approximately 50–60 days, following which the larva emerges, drops to the ground and pupates. Human botfly myiasis should always be considered as a cause of boil-like lesions in patients who have recently returned from endemic areas [28–33].

Genus Gasterophilus (horse botfly). A form of migratory cutaneous myiasis known as 'creeping eruption' is caused by *Gasterophilus* larvae. The Gasterophilinae are mainly parasites of the alimentary tract of horses, but occasionally larvae of certain species of *Gasterophilus*, including *G. haemorrhoidalis* and *G. pecorum*, penetrate human skin.

Fig. 33.5 Third instar larva of *Dermatobia hominis* (the human botfly). Note the rows of backward-pointing spines.

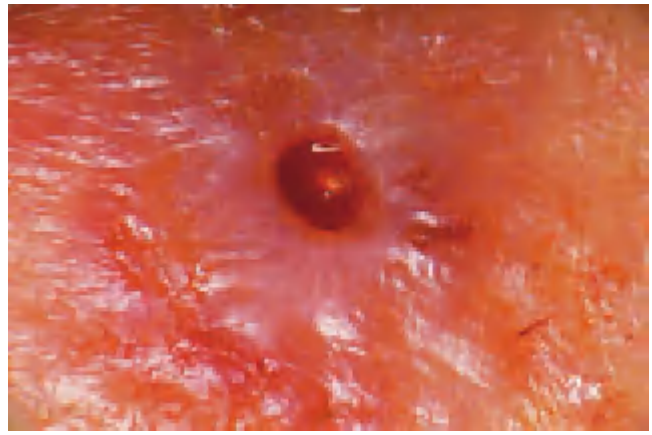

Fig. 33.6 Furuncle-like lesion produced by *Dermatobia hominis*. The tail of the larva is visible in the centre of the lesion.

Genus Oestrus (sheep nostril fly). Oestrus ovis, which develops in the nasopharyngeal passages of sheep and goats, and *Rhinoestrus purpureus*, which parasitizes horses, are occasionally responsible for human myiasis, especially ophthalmomyiasis [34,35].

Genus Hypoderma (warble flies). The larvae of *Hypoderma* species are obligate parasites of cattle. Man is an abnormal host for *Hypoderma*, and the larvae do not mature fully. After penetrating the skin, the larvae produce migratory subcutaneous swellings [36]. They may also invade the eye, producing severe damage. Marked eosinophilia may accompany infestation, and Starr *et al*. [37] reported a cattle rancher in whom an illness marked by pleuritis, pericarditis and myositis, and due to infestation with *H. lineatum*, mimicked the hypereosinophilic syndrome.

Fig. 33.7 Scanning electron micrograph of the spines on a *Dermatobia hominis* larva.

Clinical features [2,5,29]. The habits of the flies and their larvae determine the variations in the clinical manifestations for which they are responsible.

Traumatic or wound myiasis has been a serious complication of war wounds in tropical areas, and is sometimes seen in neglected ulcers or wounds in most parts of the world [38]. The eggs or larvae (maggots) can be seen, often in large numbers, in the suppurating tissues.

Obligatory cutaneous myiasis occurs in two main clinical forms; in both, there may be mild constitutional symptoms and eosinophilia. Both occur mainly on exposed skin—often the face, scalp, arms or legs. In the furuncular form, boil-like lesions develop gradually over a few days. Each lesion has a central punctum, which discharges serosanguineous fluid. The posterior end of the larva, equipped with a group of spiracles, is usually visible in the punctum, and its movements may be noticed by the patient (Fig. 33.6). The lesions are often extremely painful. The inflammatory reaction around the lesions may be accompanied by lymphangitis and regional lymphadenopathy. Once the larva has emerged, or has been removed, the lesions rapidly resolve. The flies causing furuncular myiasis in humans are *Dermatobia hominis*, *Cuterebra*, *Cordylobia anthropophaga*, *Cordylobia (Stasisia) rodhaini*, *Wohlfahrtia* species and *Hypoderma* species. The inflammatory nodular lesions produced by *Hypoderma* species are migratory.

The second principal clinical form is a creeping eruption, in which a tortuous, thread-like red line with a terminal vesicle marks the passage of the larva through the skin. The larva lies ahead of the vesicle in apparently normal skin. This form of myiasis is produced by *Gasterophilus* larvae.

Treatment. The larva of Cordylobia can often be expressed by firm pressure around the edges of the lesion, but the punctum may require enlarging surgically.

The larva of *D. hominis* has a bulbous anterior end equipped with rows of backward-pointing spines (Fig. 33.7), and cannot easily be expressed. Traditional methods

of treatment include occluding the punctum with pork fat [39,40], blocking the spiracles of the larva and stimulating premature extrusion. A similar result may be obtained with mineral oil, petrolatum or butter. Surgical management is most frequently recommended: the punctum is enlarged by cruciate incisions, and this enables removal of an intact larva [41]. The injection of lidocaine (lignocaine) underneath the nodule may be sufficient to push the larva out [42], and Li Loong *et al*. [43] also found that injection of 2 mL of 2% lidocaine into the blind end of the cavity facilitated non-surgical removal of the larva.

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Fleas (Siphonaptera)

Fleas are small (1–8 mm long), wingless, laterally compressed insects whose adults are blood-sucking ectoparasites of mammals and birds. Over 1500 species and subspecies are known. The larvae of fleas are not parasitic, but feed on organic material that they find in the nest or dwelling-place of the host [1,2].

The order Siphonaptera contains three families of medical importance.

Family Tungidae

This family contains tropical species that burrow in human skin (see Tungiasis, p. 33.13).

Family Pulicidae

Members of this family occur throughout the world, and some species transmit plague and murine typhus [3]. Cat fleas have been shown to be vectors of *Bartonella henselae*, the pathogen responsible for cat scratch disease and bacillary angiomatosis [4,5]. Many species are important

only for the irritability of their bites. The species most frequently parasitizing humans are the human flea, *Pulex irritans*, and the cat and dog fleas, *Ctenocephalides felis* and *C. canis*, but other species will bite humans in the absence of their normal host. The tropical rat flea, *Xenopsylla cheopis*, is the vector of bubonic plague.

The adult female flea lays her eggs during feeding on the host, and the eggs fall to the ground. Flea larvae feed on organic debris in their environment, and an important food source is the faeces of the adult flea. The larvae subsequently form cocoons, and under suitable conditions of temperature and humidity the life cycle may be completed in a few weeks. However, the cocoon stage can sometimes last as long as a year, and the flea may emerge only in response to vibrations produced by the movement of possible hosts.

In a household occupied by infested pet dogs or cats, fleas in various stages of development are found in the animals' bedding, and on carpets and soft furnishings.

Family Ceratophyllidae

Species in this family are mainly parasitic on rodents and birds. Bird fleas overwinter in cocoons in birds' nests, and emerge in spring. At this time, they can become household pests, as they may gain access to bedrooms from nests under the eaves.

Flea infestation in humans

Infestation with the human flea, *Pulex irritans*, occurs mainly in congested communities with low standards of hygiene. It is now rare in developed countries. Cat and dog flea infestation in the home is, however, common.

Animal fleas are common throughout the world, and persons in contact with domestic animals are frequently bitten. Severe attacks are sometimes experienced by individuals moving into empty premises previously occupied by pet cats or dogs. The vibration caused by footsteps triggers the emergence of fleas from their cocoons. Attacks are more likely to occur when the fleas do not have access to their usual host. Household infestations with bird fleas may occur from nests or nest boxes on or near the house [6], and similar problems may occur in the workplace [7]. An outbreak of papular urticaria in a nursery school was traced to an infestation with dog fleas of a fox's burrow beneath the building [8]. Similar problems were caused by *C. felis* entering houses from raccoons which had bred in the cavity between two houses [9], and by *P. simulans* originating from a skunk in a basement [10].

Clinical features [11,12]. Flea bites usually provoke typical papular urticaria in a sensitized individual. Occasionally, the reaction is more severe, and bullae may occur. The lesions may be grouped in lines or irregular clusters.

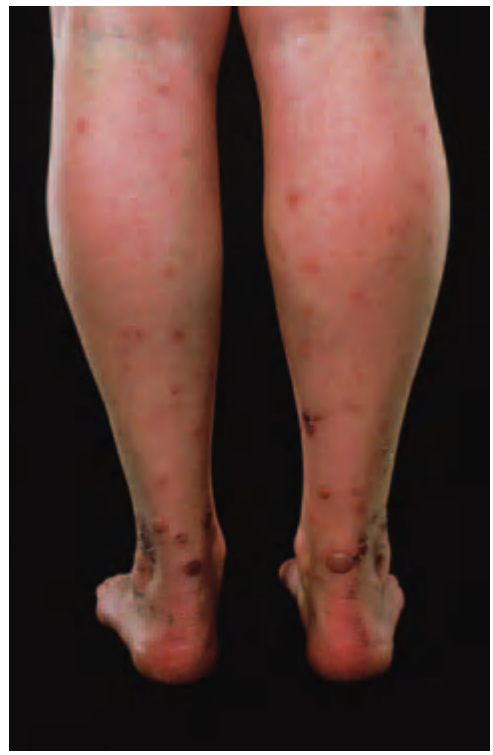

Fig. 33.8 Typical distribution of cat or dog flea bites on the legs.

Cat and dog flea bites occur predominantly on the legs below the knees, and are most profuse around the ankles (Fig. 33.8), but they can also occur on the forearms. They are much more common in women than men, as trousers and socks protect the legs. Bites from bird fleas tend to be more extensive, as the sleeping occupants of bedrooms usually provide larger areas of exposed flesh.

Confirmation of flea infestation [13]. If flea infestation from pet animals is suspected, this can be confirmed by microscopic examination of debris from the animals' bedding material (p. 33.4).

The principal sign of flea infestation in an affected animal is the presence of dried concretions of flea faeces on the animal's coat. Some animals will also have signs of flea allergy dermatitis. In dogs, this is usually manifest as areas of crusting and alopecia, most frequently on the lower back and the base of the tail. In cats, the clinical picture of flea infestation is more varied, most commonly a miliary dermatitis due, at least in part, to excessive grooming.

If fleas from another source are suspected of causing bites, it may be necessary to examine samples taken with a vacuum cleaner from rooms, or to visit the suspect premises.

It is important to identify the flea species responsible for an infestation, so that efforts at eradication may be accurately directed at the source [14]. Cat fleas (Fig. 33.9), dog fleas and common bird fleas may be readily identified

Fig. 33.9 *Ctenocephalides felis*, the cat flea.

after 'clearing' in 10% potassium hydroxide for 48 h [3], but the help of an entomologist should be sought.

Treatment. In domestic cat and dog flea infestations, treatment should be directed at the household as well as the affected animal. There are several proprietary preparations available for the treatment of pets, and others specifically for use on the animals' bedding, household carpets and soft furnishings.

Pest-control companies will deal with flea infestation from other sources.

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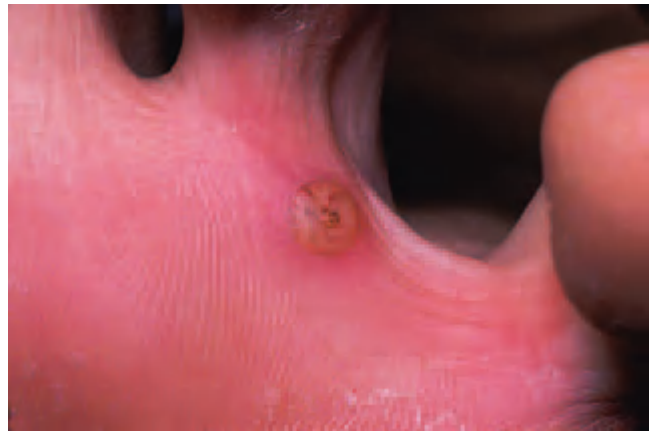

Fig. 33.10 Tungiasis, showing a characteristic lesion on the sole of the foot. (Courtesy of Dr N.H. Cox, Cumberland Infirmary, Carlisle, UK.)

Tungiasis

Aetiology. Tungiasis is caused by the sand flea *Tunga penetrans*, also known as the jigger, or chigoe. Originally a native of South America, it subsequently spread to Africa [1]. In recent years, tungiasis has reappeared in Mexico [2], where it was previously last recorded in 1948. The ease of world travel has contributed to tungiasis being encountered in non-endemic areas [1,3–8].

T. penetrans is the smallest known flea (1 mm long). Its larvae develop in dry, sandy soil, and development from egg to adult takes about 3 weeks in favourable conditions. The impregnated female flea burrows into the feet of large mammals, preferring humans and pigs. In humans, the fleas establish themselves between the toes, under the nails and on the soles. Once embedded in the skin, the flea's abdomen enlarges to the size of a pea, and large numbers of eggs are produced. The eggs are subsequently gradually extruded over a period of 2 weeks, and the female flea dies [9].

Pathology. Anatomical components of the flea are sufficiently distinctive to enable a diagnosis of tungiasis to be made histologically [10].

Clinical features [11,12]. The presence of the fleas causes intense irritation. At first, the site of penetration of the skin is visible only as a black dot, but soon an inflammatory nodule develops (Fig. 33.10). Secondary infection is common, and tetanus has often complicated tungiasis in the past. In severe cases, the feet may be honeycombed by multiple lesions, causing serious discomfort and disability.

Treatment. The flea should be completely removed from the skin. This can be accomplished by curettage and cautery of the residual cavity, or excision.

The unwary traveller may well acquire tungiasis, and those visiting endemic areas should be warned to wear stout shoes and not to sit on the ground.

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Bees, wasps and ants (Hymenoptera)

The adults of many species in this large order of insects have evolved a sting apparatus, and constitute the Aculeata group. Some use the sting in defence, and others use it offensively in hunting for food. Males have no sting apparatus. Humans are frequently stung by these insects, with reactions varying from local discomfort to fatal anaphylaxis.

The Hymenoptera are readily recognized by the narrow isthmus connecting the abdomen to the thorax. Some of the more important families include the following.

Superfamily Apoidea (bees)

Family Apidae (honeybees)

Honeybees possess a barbed sting. When humans are stung, the bee is unable to remove the sting. The sting and venom apparatus are avulsed from the bee's abdomen in its struggles, but the venom apparatus continues to function and pump in more venom.

'Africanized' honeybees, the product of interbreeding between bees from southern Africa and European species, have caused significant problems in recent years [1]. These aggressive ('killer') bees, which have characteristics of their African antecedents, including strong colony-defensive behaviour, have migrated northward from Brazil to the southern USA.

Family Bombidae (humblebees; bumblebees)

The sting is not barbed, and the bumblebee is therefore able to sting repeatedly. Most species are inoffensive, and only sting defensively when severely provoked.

Allergic reactions to bumblebee stings are much less common than reactions to the stings of honeybees.

Superfamily Vespoidea

Family Vespidae (social wasps)

This family includes wasps, yellow-jackets and hornets. Species of *Vespa*, *Vespula* and *Polistes* inflict painful stings. Wasps can also sting repeatedly, as they either have small barbs or none at all on their stings.

Superfamily Bethyloidea

These are small, solitary wasps. They sometimes become abundant in houses. They are parasitic on the larvae of Lepidoptera and Coleoptera. *Scleroderma domesticum*, *Epyris californicus* and *Cephalonomia gallicola* may inflict troublesome stings [2,3].

Superfamily Scolioidea

Family Formicidae (ants)

Many ant species are equipped with powerful stings, including the Australian jumper and bull ants [4,5], and *Solenopsis*, the fire ant. Fire ants, so called because of the burning pain of their stings, have been particularly problematic in recent years in the USA. There are several native species of fire ant in the USA, but it is the red and black imported fire ants *S. invicta* and *S. richteri*, inadvertently brought to the USA from South America, which are troublesome pests in the southern states [2,6–11]. *S. invicta* is also well established in two locations of the Brisbane area of Australia [12].

The fire ant first uses its powerful mandibles to grip its victim, and drives its non-barbed sting into the skin. It then rotates about the point of attachment of the mandibles and inflicts further stings in a circular pattern [9–11,13].

Although largely outdoor insects, fire ants may move into dwellings, causing problems for the inhabitants [14].

Species of *Pogonomyrmex* (harvester ants) may inflict multiple painful stings [2,15].

The sting

The mechanism of the sting is essentially similar in all species, although there are variations in detail. It consists of a dorsal sharp stylet and two ventrolateral lancets,

which may or may not be barbed. These structures enclose the venom canal, which communicates posteriorly with the venom sac. The venom is produced by a pair of coiled glands, which discharge into the venom sac.

Venoms [16–29]

The composition of venoms is complex. Pharmacologically active and antigenic substances are both present, and an individual's reaction to the sting is determined partly by the quantity of the former, and partly by the degree of acquired hypersensitivity to the latter. Hymenoptera venom contains vasoactive amines, small polypeptides and larger protein molecules. The components of vespid (wasps, yellow-jackets and hornets) venoms include histamine, serotonin, mast cell degranulating peptide, wasp kinin, phospholipases, hyaluronidase and antigen 5. The three major allergens in vespid venoms are phospholipases, hyaluronidase and antigen 5. The venom of the honeybee contains histamine, mast cell degranulating peptide, melittin, phospholipase A_2, hyaluronidase and acid phosphatase. The three proteins in honeybee venom which are important allergens are phospholipase A_2, hyaluronidase and acid phosphatase. In addition, the polypeptide melittin is also antigenic. Bumblebee venom appears to be chemically and antigenically related to honeybee venom [23].

Study of fire ant venom was impeded for many years by the extreme difficulty in obtaining sufficient amounts. The venom is composed of 90–95% water-insoluble piperidine alkaloids [24], which are not allergenic but are responsible for the local reaction at the sting site. When commercial-grade venom became available, several potent allergenic proteins were identified [10,25]. Antigenic similarity between fire ant venom, and bee and wasp venoms, has been demonstrated [26].

Allergy to Hymenoptera venom is mediated by immunoglobulin E (IgE) antibodies. The antigenic substances in the venom of many Hymenoptera are more liable to induce high degrees of hypersensitivity of the immediate type than are the antigens of most other insects.

Clinical features [16,17,27,28]. Reactions to bee and wasp stings may be classified as local or systemic. Both may have a toxic or a hypersensitive mechanism. The typical local toxic reaction produced by pharmacologically active components of the venom is burning pain, which may be very severe, followed by erythema and oedema. This local reaction subsides in a few hours. The systemic toxic effects of multiple stings include hypotension, generalized vasodilatation, severe headache, vomiting, diarrhoea and shock, and the cumulative effect of a large number of stings may be fatal, particularly in children.

In some cases, hypersensitivity produces only a more intense local reaction manifest as increased oedema, usually developing within the first 30 min, but occasionally delayed for several hours. If a generalized anaphylactic reaction occurs, this is usually within a few minutes of the sting. The manifestations of a generalized reaction may be classified as cutaneous (pruritus, erythema, urticaria and angio-oedema), respiratory (laryngeal oedema, bronchospasm) or vascular (tachycardia, hypotension, shock). These features may occur separately or in combination, and in varying degrees of severity.

Occasionally, late-onset reactions to stings occur [18]. Some of these also appear to be mediated by venom-specific IgE [29]. In some patients, an urticarial reaction develops several hours after the sting, and in others a serum sickness-like reaction occurs, with urticaria, joint swelling and arthralgia.

A patient with a foreign-body granuloma and IgE pseudolymphoma following multiple bee stings has been reported [30], and another with an eosinophilic foreign-body granuloma after multiple self-administered bee stings as treatment in traditional Korean medicine [31].

At least one-third of individuals developing systemic reactions give no personal or family history of atopy [32]. A study of a large number of boy scouts, average age 13 years, suggested that the incidence of reactions was not higher in atopic subjects [33], and later work, relying on history alone, confirmed that the frequency of sting reactions is similar in atopic and non-atopic populations [34].

Studies of fatalities following Hymenoptera stings [35,36] have shown the major cause of death to be respiratory tract obstruction from massive oedema and secretion.

Skin lesions produced by fire ants typically occur in clusters [9–13]. The site of attachment of the mandibles may be marked by two minute haemorrhagic puncta. The initial reaction to the sting is the development of a weal, followed within a few hours by a vesicle. The fluid in the vesicle gradually becomes cloudy, and after 8–10 h the typical lesion is an umbilicated pustule on a red, oedematous base. The pustule subsequently ruptures, forming a crust, and after several days the lesions heal, frequently leaving small scars. Systemic hypersensitivity reactions may also occur, and feature generalized urticaria and angio-oedema, wheezing, nausea and vomiting, and hypotension [9,37,38]. These manifestations may increase in severity with successive attacks, and fatal anaphylaxis can occur [11].

Treatment [28,39,40]. Local reactions to Hymenoptera stings may be treated with oral antihistamines. The treatment of choice for anaphylaxis is intramuscular epinephrine (adrenaline) (in adults, a dose of 0.5 mL 1 : 1000 solution should be administered, and repeated after about 5 min in the absence of clinical improvement, or if deterioration occurs after the initial treatment), followed by chlorpheniramine (10–20 mg, intramuscular or slow intravenous) and hydrocortisone (100–500 mg, intramuscular

or slow intravenous) [40]. Patients at risk of an anaphylactic response to Hymenoptera stings should wear a device such as a warning bracelet, in case they are discovered unconscious following a sting. They should also carry a sting emergency kit, and receive instruction in self-administration of epinephrine.

The introduction of venom immunotherapy has reduced the risk of anaphylaxis in Hymenoptera-sensitive patients. It is thought to exert its beneficial effect by stimulating the development of IgG (blocking) antibodies against the venom allergens. This prophylactic measure is indicated in patients with a history of life-threatening reactions to stings, positive skin tests and presence of venom-specific serum IgE. However, such therapy should only be carried out in specialized units.

Conventional advice with regard to honeybee stings is that the sting should be immediately scraped off, never pinched. A study by Visscher *et al*. [41] suggests that the method of removal does not affect the quantity of venom received and is therefore unimportant; the sting should simply be removed as rapidly as possible.

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Lice (Phthiraptera)

Lice are members of the order Phthiraptera. They are wingless, dorsoventrally flattened insects, which are obligate ectoparasites of birds and mammals. The Phthiraptera are highly host-specific and spend their entire lives on the host. Members of the suborder Anoplura are blood-sucking ectoparasites of mammals.

Humans are parasitized by three species of Anoplura: *Pediculus capitis*, the head louse; *Pediculus humanus*, the clothing or body louse; and *Pthirus pubis*, the pubic or crab louse. Head lice and clothing lice are morphologically almost identical, and are capable of interbreeding, but on the host they maintain their territorial preferences. *Pthirus pubis* is morphologically quite distinct from *Pediculus*. It is a louse that has no close relatives in the insect world, apart from a species living on gorillas. *Pthirus* is the correct zoological name for the crab louse—the name should

Fig. 33.11 *Pediculus capitis*, the head louse.

have been *Phthirus*, but a misprint was inadvertently accepted by the International Committee on Zoological Nomenclature [1].

Morphology and biology [1–10]

Pediculus capitis (head louse). The adult female is a greyish white insect 3–4 mm long (Fig. 33.11). The male is slightly smaller. The claws on the legs are adapted for clinging to hair.

During her lifespan of approximately 40 days, the female is capable of laying about 300 eggs at the rate of 7–10 daily. The eggs of the head louse are cemented to hair shafts with a chitinous cement material secreted by the female's accessory glands (Fig. 33.12). In temperate climates, in order to provide a suitable temperature for incubation, the eggs are attached to hair close to the surface of the scalp. They are oval, flesh coloured and have a lid (operculum) capping the free end of the egg. The operculum is pushed off by the emerging louse nymph. Once the louse has emerged, the empty egg case or 'nit' appears white, and is easier to see than the intact eggs close to the scalp surface. Eggs hatch in about 8 days and, following three moults, the louse nymph reaches maturity in approximately 10 days.

Pediculus humanus (clothing or body louse). This louse is almost identical in appearance to the head louse, and its development is similar. Its natural habitat is the clothing

Fig. 33.12 Head-louse eggs cemented to a hair shaft.

Fig. 33.13 *Pthirus pubis*, the crab louse.

of its host, and it only visits the skin to feed. Its eggs are cemented to clothing fibres, with a preference for clothing close to the skin. Seams are a favoured site for oviposition. It thrives in situations where normal hygiene is lacking. The clothing louse and its eggs will not survive high-temperature washing and ironing, and it is intolerant of temperature changes in its environment. It is therefore a parasite of individuals whose clothing is rarely changed or washed.

Pthirus pubis (pubic or crab louse). The crab louse is quite distinctive in appearance (Fig. 33.13) and habits from *Pediculus*. Its body is squat, and the second and third pairs of legs carry heavy, pincer-like claws. When static, the crab louse uses these huge claws to grip adjacent hairs close to the skin surface (Fig. 33.14). Its eggs are light brown in colour and, like those of the head louse, are cemented to the hair of the host (Fig. 33.15). It is adapted to living in hair of a particular density. Scalp hair, except at the scalp margins, is too dense, but the crab louse will colonize axillary hair, eyebrows, eyelashes, beard hair, and hair on the trunk and limbs, in addition to pubic hair.

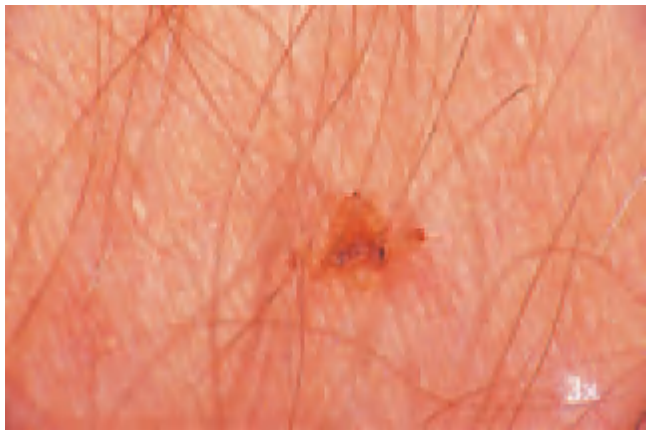

Fig. 33.14 Crab louse clinging to hairs on the abdomen.

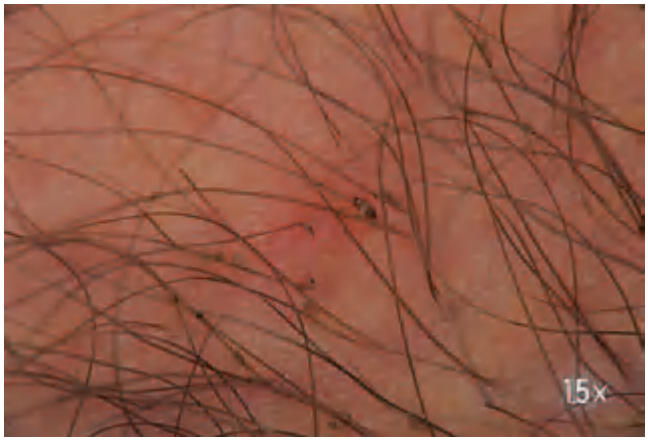

Fig. 33.15 Crab-louse eggs attached to abdominal hair.

It is mainly sedentary, but becomes active at night when the host is sleeping [11]. It moves by transferring its grip from one hair to another. The crab louse has difficulty moving when taken from its host, whereas head and clothing lice are quite mobile off the host.

Pthirus pubis is a specific parasite of humans, but its transfer to a dog has been recorded [12].

The Anoplura are vessel feeders (solenophages), introducing their mouthparts directly into a blood vessel to withdraw blood [13,14]. The components responsible for probing the skin and piercing a blood vessel are a group of stylets, which are kept withdrawn within the head unless the insect is feeding. In the front of the head is a small, snout-like tube, the haustellum, which is soft, eversible and armed with teeth. When the louse is about to feed, the haustellum is everted and the buccal teeth rotated outwards. The teeth cut into the epidermis, and the haustellum is driven into the skin. It eventually comes to rest with the buccal teeth fully everted, anchoring the mouthparts. Once fixed in the skin, a bundle of stylets is pushed forward through the opening in the haustellum by protractor muscles within the head of the louse [7] (Fig. 33.16). The

Fig. 33.16 Scanning electron micrograph of a crab louse, showing the protruded stylet bundle.

stylets are advanced into the dermis as a single bundle or fascicle, and probe for a small blood vessel. When the stylet bundle has pierced a blood vessel, feeding begins.

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Head lice (pediculosis capitis)

Prevalence and epidemiology [1,2]. The head louse has a worldwide distribution, and head louse infection is common both in developed and developing countries. However, precise data on current prevalence are relatively sparse.

In England, in the past, head lice were common in industrial conurbations. In 10 industrial cities, in 1941, about 40% of boys and 50% of girls younger than school age had head lice [3]. In contrast, infection rates in rural communities were low. A survey of schoolchildren in 1975 [4] showed an overall prevalence of 2.44%, with the highest rates in the more deprived central areas of large conurbations. Once again, the infection rate was higher in urban than in rural areas. However, in the early 1980s, there was a resurgence of infection, and the increase occurred mainly in middle-class, often professional families, especially in suburban and rural areas [5]. Hence, in more recent years, the head louse has become classless and cosmopolitan. It is of interest to note that in a recent survey in Jordan, there was a significant association between social class and infection rates, there being much higher infection rates in lower socio-economic classes [6].

High rates of head louse infection have been reported from the USA, Canada and several other countries; a review by Gratz [1] provides a comprehensive survey of published information relating to prevalence.

Head lice are more common on children, particularly in the age range 3–11 years, than on adults, and most surveys have shown that girls are more frequently infected than boys. Behaviour patterns in girls and boys at different ages probably influence rates of infection [7]. For example, in primary schools children are organized into small groups around desks, and head-to-head contact is frequent. In addition, hair contact is probably more likely between girls than boys. Older children tend to be more independent and more separated from their peers. The contribution of hair length to infection is contentious. Some studies have not shown any correlation between hair length and louse infection rates, but in others children with longer hair have had higher infection rates. A recent survey from Israel, in which detection of infection was by means of a louse comb rather than by direct visual inspection, found a significantly higher infection rate in children with long and medium-length hair than in those with short hair [8].

Several authors have noted a low incidence of head louse infection in black Americans [9–11], although infection rates in black Africans are high [1]. This might be related to specialization in the louse with regard to modification of the legs to grasp hairs of different cross-sectional shape [12], and consequent restriction on transfer between white people and negroes, and vice versa. It has also been suggested that the use of pomades by black Americans provides an environment unsuited to establishment of infection [9]. However, head lice are quite common in the Indian subcontinent, where hair oils and creams are frequently used [13], and a survey in Brazil found the same prevalence in blacks as in whites [14].

It is thought that the majority of head louse infections are acquired by direct head-to-head contact. Spread of lice is encouraged by poverty, poor hygiene and overcrowding. Overcrowding is perhaps the most important factor. Lack of hygiene alone does not encourage head louse infection.

There are conflicting opinions about the importance of fomites in transmission of head lice [5,15], and in practice the putative role of caps, scarves, combs and brushes is difficult to confirm or refute [16].

In Australia, an examination, employing a vacuum cleaner fitted with a filter, of classroom floors in schools in which there was an overall prevalence of head lice of 20.9% did not reveal any lice on the floors [17]. Hence, there is no requirement for antilouse measures on carpets and floors.

Clinical features. Although many individuals are asymptomatic [18], scalp pruritus is the characteristic manifestation of head louse infection. Secondary bacterial infection may occur as a result of scratching, and concomitant head louse infection must always be considered in cases of scalp impetigo. Pruritic papular lesions may occur on the nape of the neck, and occasionally a generalized non-specific pruritic eruption develops [19]. In severe, neglected cases, pus and exudate may produce matting of the hair—a state that has been termed ‘plica polonica’, from its prevalence in Poland in the early part of the 20th century. Matting of the hair can occur in the absence of louse infection, and it has been suggested that the term should be discarded [20].

The empty egg cases (‘nits’) are easily identified, and occur in greatest density on the parietal and occipital regions (Fig. 33.17). However, on naked-eye inspection, they may be confused with peripilar keratin casts (‘pseudonits’; hair muffs) [21,22] or dried globules of cheap hair lacquer.

Detection of adult lice and nymphs provides evidence of an ‘active’ infection, whereas the presence of eggs and egg cases alone merely indicates that infection has occurred at some time. The most reliable method of diagnosing current active infection is by detection combing [23], which has been shown to be superior to direct visual examination of the hair and scalp [8,24,25]. This is an important criterion for several reasons:

1 It is recommended that individuals who do not have evidence of active infection should not receive chemical treatment [23].

2 Participants in clinical trials of pediculicides should have live lice or ‘lice and eggs’ present on the head before enrolment, not just eggs alone [26].

Fig. 33.17 Numerous head-louse eggs and empty egg cases.

3 Children who do not have evidence of active infection may be inappropriately excluded from school [27,28].

Treatment [2,26,29,30]. The acetylcholinesterase-inhibiting insecticides malathion and carbaryl (carbaril) have been extensively used to treat head louse infection in the UK, although use of the latter declined markedly a few years ago following the release of data suggesting a potential carcinogenic effect of long-term oral administration of carbaryl to rodents [31]. Thereafter, it became a prescription-only medicine. These insecticides replaced lindane, following evidence of the development of resistance to organochlorines [32]. Lindane has been withdrawn from use in the UK. Malathion and carbaryl are efficient pediculicides and have good, but not complete, ovicidal activity [32–36]. It is recommended that lotion (alcoholic basis) and liquid (aqueous basis) formulations of malathion and carbaryl should remain on the scalp for 12 h before being washed off. Both insecticides are degraded by heat, and a hot-air hair dryer should not be used after their application. Treatment should be repeated after 10 days, because of the incomplete ovicidal activity. The second treatment should deal with any nymphs which emerge from surviving eggs.

Also effective as pediculicides are pyrethrins synergized with piperonyl butoxide, and the synthetic pyrethroids permethrin and phenothrin [37–39].

The formulation of the marketed products influences their efficacy, because the vehicle may also have pediculicidal activity [26,40,41]. Lotion and liquid formulations are preferable to shampoos, as the latter expose the insects to relatively low concentrations of insecticide which, in the long term, will favour the development of resistance. Preparations with an aqueous basis are less likely to irritate an excoriated scalp than alcoholic solutions, do not irritate the bronchi of asthmatics and are not flammable.

There have been a number of recent analyses of the effectiveness of available chemical methods of head louse eradication. A comparative assessment of the pediculicidal and ovicidal activity of five products marketed for head louse treatment in the USA (containing lindane, 1.0% permethrin, 0.5% malathion, and pyrethrin synergized with piperonyl butoxide), carried out on lice and eggs harvested from healthy Kuna Indian children in Panama, showed that 0.5% malathion was the fastest-killing pediculicide and the most effective ovicide, and that 1% permethrin was also highly effective [42].

A group of general practitioners in Oxford, England, employed an evidence-based approach to answering the question 'In children attending primary care with nits, what is the most effective treatment for eradication?', using several UK sources of information, and opted for permethrin [43].

A Cochrane Library review of interventions for head lice identified 71 trials of pediculicides, of which only four met the criteria for inclusion in the review. The study concluded that permethrin, synergized pyrethrin and malathion were effective in the treatment of head lice [26].

Hence, these analyses support the effectiveness of malathion, synergized pyrethrin and synthetic pyrethroids.

However, there is now evidence of widespread malathion and pyrethroid resistance in the UK [44–46], and resistance to these insecticides in other parts of the world [47–52]. In addition, there is evidence of the emergence of carbaryl resistance in the UK [46]. The restricted use of carbaryl in the UK in recent years may be a factor which has contributed to the delayed emergence of resistance in comparison with malathion and synthetic pyrethroids, which have been widely employed in over-the-counter preparations. Similarly, a factor in the continued pediculicide efficacy of malathion in a study in south Florida, USA, is probably the commercial failure, and therefore limited use, of previously marketed malathion preparations [53].

Therefore, choice of chemical treatment for head louse infection should be guided not only by evidence of pediculicidal activity from well-conducted clinical trials, but also by local patterns of resistance [54]. If treatment fails, efforts should be made to determine if resistance is responsible. From a practical point of view, if a correctly applied pediculicide has failed to eradicate an infection, a different pharmacological class of agent should be used—for example, change from a synthetic pyrethroid to malathion, or vice versa.

Family members should be examined, and treated if they show evidence of active infection.

Physical treatment is an alternative to the use of chemical agents and, in the UK, the 'Bug Busting' (Community Hygiene Concern, London, UK) wet-combing method has been promoted as a treatment for head lice. The technique involves ordinary shampooing of the hair, followed by the application of generous amounts of conditioner, and combing using a fine-tooth comb to remove lice. This procedure is repeated every 4 days for 2 weeks [55]. Comparison of the effectiveness of the Bug Busting method with chemical means of control is limited to a pilot study conducted by Bingham *et al*. [25] and a randomized controlled trial conducted by Roberts *et al*. [26,56]. The latter demonstrated that malathion lotion was twice as effective as the Bug Busting method, in an area with established intermediate resistance to malathion.

A battery-powered device, the 'Robi comb', which kills lice as it is used to comb through the hair, is also available.

Other treatments which have been employed to eradicate head lice include crotamiton [57], and topical [58] and oral ivermectin [59,60]. Although the results of oral ivermectin treatment were not impressive, it is likely that this is because ivermectin has no ovicidal activity, and two doses separated by an interval of 10 days would be more effective.

Oral therapy with co-trimoxazole has been reported to be effective in eradicating head lice [61,62]. This is probably because the antibiotic is ingested by the louse and affects its symbiotic bacteria. These bacteria are essential for synthesis of B vitamins, without which the louse cannot survive [63].

Tea tree oil and lavender oil are said to have pediculicidal activity, but have not been formally assessed.

Empty egg cases persist for some time until they are gradually worn away by repeated washing, but are otherwise difficult to dislodge. It has been claimed that a cream rinse containing formic acid may facilitate their removal [64], although this is disputed [29].

In an attempt to prevent repeated reinfection, and to discourage 'prophylactic' use of insecticides, a head-louse repellent containing piperonal has been marketed in the UK [65].

Guidelines for the management of head lice have been issued by the United Kingdom Department of Health [66], the Centers for Disease Control and Prevention (CDC) [67], the American Public Health Association [68], and the Canadian Paediatric Society [69].

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Fig. 33.18 Clothing lice and eggs.

Clothing/body lice (pediculosis corporis)

Prevalence and epidemiology [1–3]. Pediculosis corporis occurs throughout the world, although it is now uncommon in developed countries. The clothing louse is the louse of poverty and neglect, and flourishes in overcrowded, unhygienic situations on individuals who rarely remove their clothing. In the Western world today, those harbouring lice are mainly vagrants.

The number of lice and eggs on the clothing varies greatly. In most infected individuals the population is small, but in some there may be thousands of lice.

The clothing louse is the vector of epidemic typhus, trench fever and louse-borne relapsing fever. Epidemic typhus has been responsible for huge mortality in the past [4,5].

Clinical features [3,6]. In most infected persons, itching is the principal complaint. Pruritus is the result of sensitization to louse salivary antigens. Others, who have not become sensitized or have acquired tolerance to the bites, are asymptomatic. The body is often covered in excoriations, and there may be secondary bacterial infection. In those who have harboured clothing lice for long periods of time, the skin is often hyperpigmented (so-called 'vagabonds' disease', morbus errorum), and this is probably a postinflammatory phenomenon.

Lice and eggs should be sought in the clothing (Fig. 33.18).

Treatment. It is the clothing, not the patient, which requires treatment. Tumble-drying is a most effective means of killing both lice and eggs [2]. High-temperature laundering of undergarments and dry cleaning of outer clothing are also effective.

In dealing with large numbers of infected individuals, insecticides have been used to treat clothing. The emergence of lice resistant to dichlorodiphenyltrichloroethane (DDT) and lindane led to the introduction of malathion

dusting powder [7,8] and, more recently, permethrin-treated clothing has been shown to be toxic to clothing lice [9].

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Crab lice (phthiriasis pubis)

Prevalence and epidemiology [1–3]. Crab lice are transmitted by close physical contact, usually sexual. Although crab louse infection appears to be a common disorder among sexually active young adults, recent prevalence data are lacking.

Because many patients with crab louse infection who attend genitourinary medicine clinics are found to be suffering from other sexually transmitted infections (STIs) [4–7], screening for other STIs is indicated.

Clinical features. Itching, mainly in the evening and at night, is the principal symptom. Close inspection of affected areas will reveal lice grasping hairs close to the skin surface, and louse eggs attached to the hair shafts. Louse faeces are often visible as rust-coloured speckles on the skin and hair, and the underclothes may be spotted with altered blood.

When crab lice are discovered on the pubic area, other hairy areas of the body should be examined, as these lice may colonize eyebrows, eyelashes (Fig. 33.19), beard, axillae, areolar hair and the scalp margins [8–12]. In heavy infections in men, the hair on the trunk and limbs may be extensively colonized. A case has been reported in which the presence of an enormous population of lice was attributed to inappropriate use of topical steroids [13].

Blue-grey macules (maculae caeruleae) are occasionally seen on the skin [14–16], but their precise pathogenesis is unknown. Bullous lesions attributed to crab lice have been reported [17,18].

In children, crab lice may colonize the eyelashes and scalp [19–22]. Infection in children is usually acquired by close physical contact with infected parents. As an isolated finding, it is not indicative of sexual abuse, although this may occasionally occur [23].

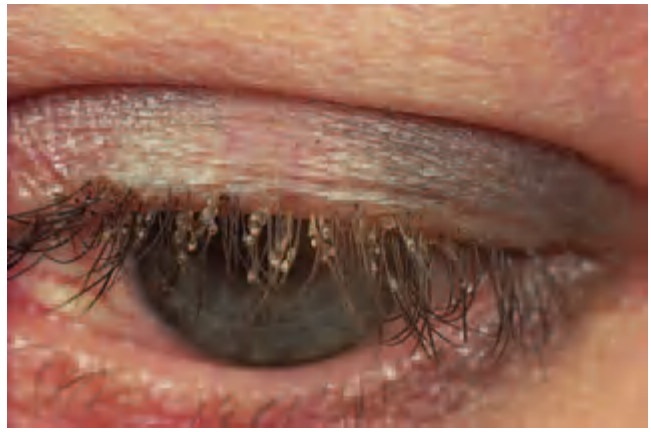

Fig. 33.19 Crab-louse eggs on the eyelashes.

Treatment [3,24–28]. Malathion, pyrethrins with piperonyl butoxide, pyrethroids and carbaryl may be used to eradicate crab lice. In view of the possibility of involvement of axillary and body hair, it is preferable to treat the whole of the trunk and limbs, and the scalp may also require treatment. Alcohol-based preparations may be irritating when applied to the scrotum, and an aqueous base is preferable. Treatment should be repeated after an interval of 7–10 days. All sexual contacts should also be treated.

Eyelash infection (phthiriasis palpebrarum) [29,30]. Although mechanical removal of lice and eggs with fine forceps [31] or epilation of the lashes with their attached eggs are obvious remedies, these procedures are uncomfortable, and are not recommended. Cryotherapy has been used to destroy crab lice on the lashes [32], and the use of fluorescein in concentrations of 10–20% is also said to be effective [33].

Any ointment might be expected to interfere with the respiratory function of the louse by blocking its spiracles, and the use of a thick application of petrolatum twice daily for 2–3 weeks has been recommended [34,35]. Yellow mercuric oxide ointment was frequently used in the past, and physostigmine ointment is also a popular remedy, particularly among ophthalmologists [30,36–38]. A drawback is the ocular effect of physostigmine, which causes pupillary constriction and paralysis of accommodation. Oral ivermectin, given as two doses a week apart, cured four patients with eyelash crab lice [39].

Argon laser phototherapy has also been employed [40].

Aqueous pediculicide preparations may theoretically be used to treat crab lice on the eyelashes, but proprietary preparations are not licensed for this purpose and, in an increasingly litigious society, it is therefore suggested that petrolatum is the treatment of choice.

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Bugs (Hemiptera)

Family Cimicidae (including bedbugs) [1–3]

All the Cimicidae are blood-sucking, temporary ectoparasites of birds and mammals. Two-thirds of the species in this family are parasites of bats. It has been suggested that Cimicidae became adapted to feeding on humans when cave dwellers took up residence alongside the bats.

Genus Cimex. *C. lectularius* (the common bedbug) is cosmopolitan, and common throughout Europe, North America, North Africa, North India, Siberia, North China, South Africa, Australia and South America. In recent years, bedbugs have been scarce in the UK, but an increase in the number of cases referred to Brighton Public Health Laboratory Service in 1999 suggested that they might be becoming more common [4].

C. pipistrelli (the bat bug), originating in a bat roost in a house, was responsible for itchy skin lesions in one of the house occupants [5].

C. hemipterus (the tropical bedbug) is less tolerant of low temperatures than *C. lectularius*. This bug is confined to tropical and subtropical regions, including India, Burma, Malaya, South China and Central Africa.

Genus Leptocimex. *L. boueti* has a limited distribution in West Africa, where it parasitizes humans and bats.

Genus Oeciacus. Several species are usually found on birds and in their nests, for example *O. hirundinis*, the martin bug [6] and *O. vicarius*, the swallow bug. They may invade houses from nests under the eaves, and will bite humans readily, but it is unlikely that they can complete their life cycles on human blood, or take up residence in houses as bedbugs do.

Genus Haematosiphon. *H. inodorus*, the only species in this genus, is also known as the Mexican chicken bug. As the name suggests, its major host is the chicken, but it can be a serious pest in human domiciles if these are close to chicken roosts.

Ecology [1–3]. Bedbugs are 4–5 mm in length, with dorsoventrally flattened, oval bodies, the forewings reduced to

Fig. 33.20 *Cimex lectularius*, the bedbug. (Courtesy of Oxford Scientific Films.)

scale-like pads, and the hindwings absent (Fig. 33.20). The mouthparts are modified into a proboscis adapted for piercing and sucking.

Female bedbugs deposit their pearly white, flask-shaped eggs in the crevices of floors and walls, in furniture, bed frames and mattresses. Each female lays about 300 eggs in her lifetime. The eggs hatch after about 10 days: the nymphal stage lasts approximately 6 weeks, during which time the bug moults five times.

Bedbugs normally feed at night, usually about an hour before dawn, but they may feed during the day if circumstances are favourable [7]. Searching for a food source is erratic, and is probably at random at distances greater than a few centimetres, but in the final approach to the host, both temperature and odour play a part in guiding the bug. Feeding time is relatively short (3–12 min). During feeding, the bedbug injects saliva containing an anticoagulant and anaesthetic. In the absence of a suitable food supply, however, adult bedbugs can survive starvation, in ideal circumstances, for a year or more [8].

In the absence of its usual host, *C. lectularius* will attack other animals, and Cimicidae normally parasitic on other hosts are similarly prepared to attack humans, invading houses from birds' nests or chicken runs.

Clinical features. The bites of the bedbug are painless, and the attention of the victim is only drawn to the bites by the reaction they produce. They commonly occur on the face and neck, hands and arms, but may occasionally be generalized. In the individual not sensitized by previous exposure, there may be no symptoms at any stage, and only a purpuric macule indicates the site of the bite. Late-onset reactions may occur in some cases [9]. In sensitized subjects, intensely irritating weals or papules surmounted by haemorrhagic puncta are the characteristic reaction. In some cases in which the reaction is severe, bullae predominate [10,11].

The bites of other Cimicidae are essentially similar, but their distribution depends on the method of exposure.

Bedbugs as vectors of disease [12]. It is not known with certainty that bedbugs act as vectors for any disease, but their possible role in the transmission of hepatitis B and C, and HIV infection, has been investigated [13–20]. Hepatitis B virus persists for up to 6 weeks in the bedbug's body [13,17,18]. It has been suggested that mechanical transmission to humans could occur via infected bug faeces, or when bugs are crushed during feeding. Hepatitis C virus RNA was not detected in bedbugs after feeding on blood with a high viral titre [17].

Initially, it was suggested that bedbugs might act as vectors for HIV [19], but it was later concluded that this is unlikely [20,21].

Haematosiphoniasis [22]. Haematosiphoniasis is the name given to the cutaneous lesions caused by the bites of *Haematosiphon inodorus* (the Mexican chicken bug). Polymorphic lesions, consisting of weals, papules, vesicles, pustules and scabs, occur predominantly on exposed parts of the body.

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Family Anthocoridae

The Anthocoridae are related to the Cimicidae. Bugs of this family are mostly predacious on other insects, but are known to bite humans occasionally. *Lyctocoris campestris* is a cosmopolitan species closely associated with humans, for example in haystacks and granaries [1]. *Anthocoris kingi* and *A. nemorum* will also bite humans [2]. Another anthocorid bug, *Dufouriellus ater*, attacked many workers in a clothing factory in north-east England [3].

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Family Pentatomidae

Palomena prasina (the green shield bug), a member of this family, has been reported as the cause of perioral blistering in a small child [1].

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Kissing bugs, assassin bugs and cone-nosed bugs (Reduviidae)

The majority of species of Reduviidae are predators on other insects, and are commonly called assassin bugs for this reason, but some attack humans and other animals. Most species are encountered in North, Central and South America, but some occur in Africa, the Middle and Far East, and in Australia. The subfamily Triatominae is the most important medically, and includes those species which feed exclusively by sucking the blood of vertebrate animals. Adult triatomines are large insects, commonly measuring 20–28 mm in length. They have an elongated head with a prominent proboscis and long, four-jointed antennae (Fig. 33.21).

Fig. 33.21 Cone-nose bug. (Courtesy of Oxford Scientific Films.)

The Triatominae are largely confined to the western hemisphere, with the majority of species being distributed in North, Central and South America. In the USA, *Triatoma sanguisuga* has the widest distribution, extending from the south-eastern and Mid-Atlantic states westwards, including Texas. Triatomines feed on a wide range of hosts, and domestic species feed on humans and domestic animals. They are of medical importance as vectors of *Trypanosoma cruzi* in Chagas' disease [1,2].

Ecology. In nature, triatomine bugs form colonies in the habitat of their host, for example a small mammal's nest or animal lair. In the south-western USA, infestations are often found in the nests of wood rats. Some species, however, have become totally domesticated, and live and breed in human dwellings, laying their eggs in cracks and crevices in the floors and walls. The young hatch as nymphs, which are miniature versions of the adults. Nymphs and adults hide in crevices during the day and emerge at night to feed.

Clinical features [3,4]. The bites of the predatory species of reduviid bugs (assassin bugs) are purely defensive, and are usually extremely painful [5,6]. The bites of the blood-sucking Triatominae, however, are painless—this is essential to the parasite if it is to feed undisturbed. In an individual not previously exposed to the bites, there will be little reaction, but with repeated exposure hypersensitivity develops, and reactions ranging from pruritic papules to haemorrhagic nodules and bullae may occur.

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Thrips (Thysanoptera)

Thrips ('thunder flies') are tiny, winged insects, 1–2 mm in length, and usually yellowish brown or black in colour. The name 'thrips' is derived from the Greek, meaning 'wood louse'. The order Thysanoptera ('fringe wing') comprises about 5000 species, with a worldwide distribution. The majority feed on plant juices, and some are important agricultural pests [1]. Some species are predatory on other arthropods. A few species appear able to suck blood, and there are a number of reports that thrips bite [2,3].

Most thrips, however, are unable to penetrate the human epidermis, and probably cause itching and prickling sensations only by their movement on the skin surface and their efforts to obtain water from perspiration.

Clinical features. Thrips bites, which occur on exposed skin, produce tiny puncta and small, pink macules or papules [2,4]. Large numbers of American soldiers in Hawaii developed hypoanaesthetic papular lesions surrounded by blanched halos, which, it was suggested, were caused by Cuban laurel thrips [5]. However, attempts to reproduce lesions by placing live thrips in contact with the skin were unsuccessful, and the cause of this distinctive dermatosis remains unknown [6].

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Beetles (Coleoptera)

Beetles are insects whose forewings are modified to form hard wing cases for the membranous or reduced hind wings. There are over 370 000 known species, but it is likely that many more await discovery. They are mainly terrestrial and the majority feed on decaying animal or vegetable matter, but some are predaceous on other insects. Several species may provoke skin lesions and are of interest to the dermatologist.

Vesicating species [1–4]

Family Meloidae (oil beetles, blister beetles)

Most of the beetles in this group only cause problems when crushed on the skin, but some may emit their vesicating fluid without being crushed. The family is large and widely distributed. Many species contain the irritant cantharidin, which commonly is called 'Spanish fly'. Contact with the skin produces an irritant dermatitis and bullae. Cantharidin has an undeserved reputation as an aphrodisiac, which is unfortunate for a chemical capable of producing severe toxicity. It has been used in blistering plasters and hair restorers, and in the treatment of warts and molluscum contagiosum.

Lytta vesicatoria is perhaps the best known of the blister beetles. It is a large, bright metallic green beetle, which lives mainly in the Mediterranean region, but is sporadically found further north, occasionally as far as England.

Other vesicating species include *Epicauta* spp. (USA, Mexico, India, Sudan, Senegal) [5], *Mylabris* spp. (Nigeria, India) [6,7], *Psalydolytta* spp. (Gambia) [8] and *Cylindrothorax melanocephala* (Gambia) [8].

Family Staphylinidae (rove beetles) [9–11]

The genus *Paederus*, found worldwide, includes many species containing a vesicant, pederin, which is chemically distinct from cantharidin. Pederin is released when the beetles are crushed, provoking an acute irritant contact dermatitis. A major outbreak of vesicular dermatitis on Okinawa in 1966 was traced to contact with the beetle *Paederus fuscipes* [12], and a number of other reports have documented *Paederus* dermatitis from several parts of the world [13,14], including an outbreak which occurred in a military unit training in the Arizona desert during heavy rain and flooding [15]. A plague of whiplash rove beetles (*P. australis*) forced evacuation of an aboriginal community in the Northern Territory of Australia [16]. *P. sabaeus* has been responsible for several outbreaks of dermatitis in Africa at the end of the rainy season [17–19].

Histopathological changes of *Paederus* dermatitis include intraepidermal and subepidermal blistering, epidermal necrosis and acantholysis [20].

It has been proposed that the biblical third, fourth and sixth plagues of Egypt might have been related to rove beetles and the bullous lesions they cause [21].

Family Oedemeridae [3]

Oxycopis vittata has been reported as causing a blistering dermatitis in Puerto Rico [22].

Sessinia species (coconut beetles) have caused blistering in the Gilbert Islands [7].

Thelyphassa lineata produced a bullous dermatosis in a large number of New Zealand Army personnel [23], and there is a report of blister beetle dermatosis in Hawaii caused by *T. apicata* [24].

Family Paussidae

Cerapterus concolor, an inhabitant of ants' nests, can eject a blistering liquid when disturbed [25].

Family Tenebrionidae (darkling beetles)

Many species inhabit wood, flour and grain stores. *Tribolium castaneum* (the 'rust-red flour beetle') has caused a pruritic eruption in workers handling infested jute packing bags [26]. The secretion of *Tribolium* species is mainly composed of quinones.

Species of *Blaps* can eject defensive secretions which are irritant and cause blistering.

Clinical features [2–4]. Usually, lesions are produced only when the beetle is crushed on the skin. A weal forms rapidly and is followed by a blister after 12–24 h. The blisters are sometimes linear 'whiplash dermatitis'. A characteristic feature is the development of kissing lesions, where a blister comes into contact with another area. Blisters induced in a small child by *Mylabris bifasciata* were associated with severe systemic manifestations of cantharidin poisoning [6].

Allergenic species

Family Dermestidae [27]

The beetles in this cosmopolitan family feed on hides, woollen materials and stored food. The adult beetles are not known to be directly injurious to humans, but their larvae are covered with hairs, which may cause skin lesions.

Papular urticaria in a child, caused by the larvae of *Dermestes maculatus* Degeer, has been reported, but it was uncertain whether the reaction to the hairs was irritant or allergic [28]. *Dermestes peruvianus* was responsible for dermatitis, vasculitis, cervical lymphadenopathy and pulmonary nodular interstitial infiltrates in a man whose bed was colonized by the beetles [29].

The irritating hairs from the larvae of carpet beetles (*Anthrenus* spp.) may also cause skin lesions [30,31]. There is also a report of the damaging effect of *Anthrenus* larvae on paraffin-embedded tissue specimens, especially the sectioned surfaces of hyperkeratotic lesions [32].

Clinical features. The skin lesions are not distinctive. Dermatitis, urticaria and papular urticaria may occur.

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Cockroaches (Dictyoptera)

Cockroaches are members of the order Dictyoptera, suborder Blattaria. They belong to one of the primitive orders of insects, being allied to crickets, grasshoppers, preying mantids and stick insects. Cockroaches were originally adapted to hot climates, but a number of species have established themselves in cool climates by living inside warm human habitations. They are active nocturnally, and are attracted to any organic material that may serve as food. This theoretically makes them potential mechanical vectors of pathogenic organisms.

The main pest species are *Periplaneta americana*, *P. australasiae*, *Blatta orientalis* and *Blatella germanica*.

Clinical features [1,2]. Inhalation of cockroach allergens is thought to play a part in some cases of allergic asthma, chronic rhinitis and conjunctivitis, and cockroach-specific IgE may be found in the serum of atopic subjects with a history of exposure to cockroaches. Three major allergens have been identified in crude extracts of *B. germanica* and *P. americana* [3], and work with the German cockroach (*B. germanica*) indicates that it is the cast skins and whole bodies of German cockroaches that contain the clinically relevant allergens; egg shells and faeces have little antigenic activity [4].

There are, however, few reports of skin lesions attributed to cockroaches. Contact urticaria and dermatitis have been described in laboratory workers and others handling cockroaches constantly [5–7], and urticated papules developed in a medical records clerk exposed to copious insect debris containing fragments of *B. germanica* when clearing old case notes from a derelict hut [8].

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Locusts (Orthoptera)

Sensitivity reactions, manifest as asthma and allergic rhinitis, are a recognized occupational hazard in those working with laboratory colonies of locusts [1,2]. The principal allergen appears to derive from the peritrophic membrane, which is present in the gut and surrounds faeces [2].

Contact urticaria to locusts has been reported by Monk [3] in a laboratory research worker who handled a large number of locusts. The patient produced a positive reaction to locust antigen on prick testing and a wealing reaction at the site of contact with a live locust.

Similarly, urticaria and worsening of asthma on exposure to grasshoppers have been described in an atopic research laboratory worker [4].

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Butterflies and moths (Lepidoptera)

Many members of this large order are of importance to the dermatologist because of the irritant properties of the hairs or spines of the caterpillars and sometimes of the adults. Skin lesions in the majority of cases are produced by a combination of mechanical and pharmacological effects [1,2]. The offending caterpillars are distributed through many different families [1,3]. Some of the species that have been recorded as causing damage to human skin are shown in Table 33.1.

Aetiology of skin lesions [1,2,16,17,26–29]. The term 'lepidopterism' is applied to the ill effects on humans of a structure or product of some part of a moth or butterfly at any stage of its life history. Some authors apply the term 'erucism' to injurious effects from caterpillars, and 'lepidopterism' to ill effects from adults. In the majority of cases, damage to human skin and mucosae occurs as a result of epithelial penetration by the 'hairs' (setae) of caterpillars. In addition to a foreign-body reaction, there is often an effect from venom. Setae develop from trichogen cells of the epidermis. They are hollow, and may function as sensory receptors or communicate with a poison gland cell and contain venom. They commonly have barbs, which hold them in place when they have penetrated the skin. In some families of moths, the caterpillars have clumps of much smaller setae known as 'dart hairs' or 'spicules', which are pointed at both ends and carry fine barbs. The point of attachment to the caterpillar is very narrow and easily fractured; hence, contact with the caterpillar may release huge numbers of these tiny darts. Such dart hairs are present in a number of species, including the brown-tail moth (*Euproctis crysorrhoea*) (Fig. 33.22) and the pine processionary caterpillar (*Thaumetopoea pityocampa*).

Table 33.1 Some Lepidoptera species responsible for skin damage.

Superfamily Noctuoidea
Family Lymantriidae (tussock moths)
- *Euproctis crysorrhoea* (the brown-tail moth): the most important urticating species in the UK [4]
- *E. edwardsi* (the mistletoe brown-tail moth) [5,6]
- *E. similis* (the yellow-tail moth) [7,8]
- *E. flava* (the oriental tussock moth)
- *Lymantria dispar* (the gypsy moth) [9]
- *Orygia pseudotsugata* (the Douglas fir tussock moth) [10]

Family Arctiidae (tiger moths)
- *Hyphantria cunea* [11]

Superfamily Notodontoidea
Family Thaumetopoiedae (processionary caterpillars)
- *Thaumetopoea* (*Cnethocampa*) *processionea* [12]
- *T. pinivora* [13]
- *T. wilkinsoni* [14]
- *T. pityocampa* [15–17]

Superfamily Zygaenoidea
Family Megalopygidae (flannel moths)
- *Megalopyge opercularis* [18,19]

Family Cochlididae (Eucleidae; Limacodidae)
- *Sibine stimulea* [20]

Superfamily Bombycoidea
Family Saturniidae
- *Hylesia* species [21,22]
- *Automeris io* (the bull's-eye moth) [23]
- *Hemileuca maia* (the buck moth) [24]

Family Lasiocampidae
- *Lasiocampa quercus*
- *Eriogaster lanestris* (the small eggar moth) [7]
- Dendrolimus punctatus [25]

Fig. 33.22 Caterpillar of *Euproctis crysorrhoea*, the brown-tail moth. (Courtesy of D. Fox/Oxford Scientific Films.)

Setae are also woven into cocoons, and the webs of the silk-spinning caterpillars.

Spines are an extension of the cuticle of the caterpillar and contain venom. The spines either have a terminal plug of inspissated material at their open ends, which is released by pressure, or a weak point at which the spine fractures to allow the venom to escape. Poisonous spines occur particularly on the caterpillars of the moth families Cochlididae (Eucleidae; Limacodidae), Saturniidae and Megalopygidae.

The venoms present in the setae and spines of caterpillars of a number of families of Lepidoptera have been studied, but not fully elucidated. Some contain histamine, histamine liberators, serotonin and proteases [14,30–33]. Lamy *et al*. [34] isolated a protein, thaumetopoein, from pine processionary caterpillar hairs. This has a direct effect on mast cells, leading to degranulation, and explains the urticating properties of these caterpillars. However, IgE-mediated hypersensitivity also appears to be responsible for some reactions to *Thaumetopoea*, and it has been suggested that the hairs should be considered as important airborne insect allergens [35].

In some species—for example, moths of the genus *Hylesia* (family Saturniidae)—irritating setae are carried by the adults. This genus is notorious for causing outbreaks of 'butterfly itch', 'moth dermatitis' or 'Caripito itch' [21] in tropical South America.

Clinical features [1,2,36]. Irritation may be experienced immediately after contact with the offending caterpillars, or may be delayed for hours or even days, depending on the species. Itching is followed by the development of small urticarial papules, sometimes surmounted by vesicles. Alexander [37] noted marked bruising in children who had been in contact with *E. crysorrhoea* caterpillars. Urticaria and eyelid oedema may also occur, and in severe eruptions there may be constitutional symptoms of malaise and mild pyrexia. The severity and distribution of the eruption depend mainly on the route and intensity of exposure, but the most common sites are the exposed parts of the body. Lesions usually resolve in a few days. When contact with caterpillars is suspected as the cause of a dermatosis, Sellotape stripping of affected areas and subsequent microscopy may be used to demonstrate setae [38].

Contact with *Megalopyge* caterpillars [18,19] produces immediate, intense, burning local pain accompanied by a spreading erythema around the puncture sites. The affected area becomes oedematous, and there is often lymphangitis and regional lymphadenopathy. The local changes may be accompanied by pyrexia, headache, nausea and vomiting, particularly in children [39].

In the eye, caterpillar setae may cause a variety of changes, ranging from conjunctivitis to ophthalmia nodosa [40,41] and even panophthalmitis.

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Class Arachnida

Arachnida are readily distinguished from insects, as the adults have no wings or antennae and possess four pairs of legs. Unlike insects, where the body is divided into three segments (head, thorax and abdomen), arachnids have only two, the cephalothorax, from which the legs arise, and the abdomen.

The Arachnida are classified in seven orders, only three of which are of medical importance:

1 Araneae (spiders)
2 Scorpiones (scorpions)
3 Acari (ticks and mites)

Spiders (Araneae)

The appearance of many of the larger spiders inspires terror or disgust, but very few of the many thousands of species are dangerous to humans. Spiders are, for the most part, shy and avoid contact with humans. Almost all are venomous and bite, but only a few have chelicerae strong enough to penetrate human skin, and in most cases the bites are trivial. The European tarantula, *Lycosa tarantula*, which inspired the tarantella in Italy in the Middle Ages, inflicts a temporarily painful but harmless bite. Some lycosid spiders in South America, for example *L. antibucana*, cause severe swelling and lymphangitis. In the USA, the term 'tarantula' is erroneously applied to the large 'bird' or 'crab' spiders of the family Theraphosidae, which attack only when vigorously provoked, and whose bite may be painful but is not dangerous. Some colourful species kept as pets, for example *Brachypelma smithi*, are among several that have urticating hairs capable of causing prolonged pruritus. Many spiders whose bites are dangerous and sometimes fatal are small, inconspicuous and unimpressive.

The clinical syndrome following the bite of a spider is known as arachnidism. The form of arachnidism caused by species of the family Loxoscelidae is known as loxoscelism, and that by widow spiders (*Latrodectus* species) latrodectism.

Fig. 33.23 *Latrodectus mactans*, the black-widow spider. (Courtesy of S. Camazine/Oxford Scientific Films.)

Fig. 33.24 *Atrax robustus*, the Sydney funnel-web spider (defensive posture). (Courtesy of Mantis Wildlife Films/Oxford Scientific Films.)

Air transport of crates of fruit and other materials may introduce exotic species to countries in which they are unable to multiply but can survive long enough to attack humans.

Arachnidism [1–4]

Family Theridiidae

Genus Latrodectus (widow spiders). Spiders of this genus are widely distributed throughout the world. *Latrodectus mactans* (Fig. 33.23), the black-widow spider, occurs throughout subtropical and tropical regions. Other species have a similar, but more limited range, but some extend to the temperate regions of Russia and Canada.

The female of *L. mactans* is glossy black, with a body length of 1.5 cm and a leg span of up to 5 cm. She normally spins her web in empty burrows or under stones, but may be found in dark corners of barns, garages, store rooms or outdoor lavatories. She bites humans only in self-defence. *Latrodectus* venom is considered to be one of the most potent toxins, exceeding that of snake venoms, but the dose injected is minute in relation to the body weight of a human victim. The toxins of all species of *Latrodectus* which have been studied appear to be closely related, and the symptoms from envenomation are similar.

Latrodectus hasselti, the red-back spider, is common in Australia [5]. A report from Fremantle documented 150 admissions for red-back spider bites over a 6-year period from 1982 to 1987 inclusive, and estimated the annual cases at between 830 and 1950 [6].

Latrodectus geometricus, the brown-widow spider, bites reluctantly, but is occasionally troublesome to vineyard workers in South Africa.

Clinical features (latrodectism) [1–3,7–10]. In the days of the outdoor lavatory, *Latrodectus* webs were often spun across the toilet seat, and this led to the frequent occurrence of bites on the buttocks and genitalia. The bite of *Latrodectus* species is fairly painless, but within a few minutes increasingly severe pain develops and becomes generalized. Cramp-like or colicky abdominal pain is particularly common. Puncta may be visible at the site of the bite, and there is local erythema and oedema. There is frequently profuse sweating, and neuromuscular involvement causes paraesthesiae, incoordination and paralysis. The pain begins to subside within 24 h, and other symptoms resolve within 2–3 days, although weakness and lethargy may persist for longer. However, without treatment the bite may be fatal in young children or in the elderly and frail.

Treatment. Species-specific antivenoms are available for *Latrodectus* bites, and there is evidence that red-back spider antivenom prevents toxicity of other widow spider venoms [11,12].

Family Dipluridae

Genera Atrax/Hadronyche (funnel-web spiders). The family Dipluridae contains several genera in Australia and New Zealand [5]. Funnel-web spiders are large, aggressive spiders (Fig. 33.24), which are nocturnal and predominantly insectivorous. They are widely distributed along the eastern seaboard of Australia. *Atrax robustus*, the Sydney funnel-web, normally lives under rocks and logs, but the spread of the Sydney suburbs into its habitat has provided similar hiding places under houses. Some species of *Hadronyche* inhabit trees.

Clinical features [4,13,14]. The bite of funnel-web spiders is invariably painful. From the majority of bites, especially those of female spiders, no general symptoms follow, and recovery is uneventful. However, the large amount of venom from male spiders may cause severe systemic

symptoms. Nausea and vomiting are early features, accompanied by abdominal pain, profuse sweating, piloerection, muscle fasciculation, lacrimation, excess salivation, dyspnoea and pulmonary oedema. Several fatalities were recorded prior to the development of an antivenom.

Treatment. The compression bandage-splinting method of first aid is effective in delaying onset of envenomation and may enhance local inactivation of venom. Severe reactions will require hospital admission and full supportive measures. Funnel-web spider antivenom is very effective.

Family Loxoscelidae

Genus Loxosceles ('fiddleback', 'violin', 'brown recluse' spiders). There are a number of species of *Loxosceles* in North and South America, with 13 in the USA, five of which are known to induce human skin necrosis: *reclusa*, *laeta*, *deserta*, *arizonica* and *rufescens* [4]. The most notorious is *L. reclusa*, the brown recluse spider, which is tan to brown in colour, with a dark-brown, violin-shaped marking on the dorsum of the cephalothorax—hence the names 'fiddleback' and 'violin' spider. *L. reclusa* is active mainly at night. Its natural habitat is in dark areas beneath rocks and in holes and caves. It is also found in homes, in areas that are dark, dirty and undisturbed, such as attics, cupboards and garages.

Loxosceles laeta also occurs widely in South America. *Loxosceles rufescens* is widespread in southern Australia.

Clinical features (loxoscelism) [1–4,8,15]. There are two distinct clinical forms of loxoscelism: necrotic cutaneous loxoscelism, and the much less frequent viscerocutaneous loxoscelism. The clinical manifestations depend upon the age and health of the victim, the amount of venom injected and the site of the bite—fatty areas such as the proximal thigh and the buttocks show more cutaneous reaction and extensive involvement of the entire subcutaneous layer.

In necrotic cutaneous loxoscelism, there is local damage to the skin and subcutaneous tissues, but systemic symptoms are mild. The bite of the spider is usually relatively painless. However, after an interval of minutes or hours, severe pain develops at the site, accompanied by erythema, oedema and a central bulla. In severe envenomation, a 'target' lesion is seen—central blue/purple discoloration surrounded by an ischaemic halo and an outer ring of erythema (the 'red, white and blue' sign). After 3 or 4 days, the central area becomes necrotic, and an eschar develops. The eschar is eventually shed, leaving an ulcer which may take a considerable time to heal. The size of maximum necrosis appears to be predictive of time to complete healing [15].

In viscerocutaneous loxoscelism, systemic involvement is indicated by pyrexia, severe malaise, restlessness and headache. Within 24 h of the onset of general symptoms, ecchymoses, jaundice, haematuria and haemoglobinuria indicate massive intravascular haemolysis, which may result in death [16].

Treatment [4,8,17]. Rest, application of ice compresses, and elevation (RICE therapy) help to reduce inflammation and pain. Although dapsone is said to be beneficial [17], its use is controversial [4].

Family Lycosidae (wolf spiders)

There are a few reports of bites by members of the genus *Lycosa* [4,18,19]. They usually cause only local pain, swelling and erythema, without cutaneous necrosis or significant systemic symptoms.

Other venomous species [3–5,20–23]

Spiders of several other families may cause unpleasant bites. Sac spiders of the genus *Chiracanthium* (family Clubionidae), which are found in many parts of the world, may cause local pain, oedema and small areas of necrosis [4,20]. *Tegenaria agrestis* (family Agelenidae), the hobo spider (previously known as the aggressive house spider), is a cause of necrotic arachnidism in the north-west USA [4,21,22]. Members of the families Gnaphosidae, Salticidae (jumping spiders), Sparassidae (huntsmen spiders) and Oxyopidae (lynx spiders), all occasionally bite humans, but the effects are usually mild, unless there is secondary bacterial infection.

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Scorpions (Scorpiones)

Scorpions are arachnids of the order Scorpiones, and are widely distributed in the tropics and subtropics. Their poisonous stings are responsible for considerable morbidity and mortality [1–3]. The venom is carried in the curved sting at the tip of the tail, which is swung over the scorpion's head to strike its prey. The principal components are neurotoxins [3,4], but some venoms also contain 5-hydroxytryptamine, histamine and kinins.

Many scorpions are quite harmless, and their stings of little consequence. Most of the dangerous species belong to the family Buthidae [5]. Species of *Androctonus* and *Buthus* are important in the Middle East and North Africa, and *Centruroides* species cause problems in the southern USA and Mexico. *Tityus* species are responsible for numerous episodes of envenomation in Brazil [6]. Throughout the world, many of the deaths from scorpion stings are in infants and young children.

Australia has a number of species of scorpions (Fig. 33.25), but their stings are relatively innocuous [7].

Fig. 33.25 Australian scorpion (*Urodacus* species). (Courtesy of Mantis Wildlife Films/Oxford Scientific Films.)

Clinical features [8–12]. The effects of scorpion stings may be local or systemic, and they vary according to the species responsible. The local effects are usually immediate severe burning pain and hyperaesthesia, and there may be marked swelling. Systemic effects include restlessness, profuse sweating, muscle spasms, difficulty with speech, marked increase in salivary and lacrimal secretion, nausea, vomiting, convulsions, hypertension, cardiac arrhythmias, myocarditis and pulmonary oedema. Death is usually due to respiratory or cardiac failure.

Treatment [7,9,12]. Ice packs should be applied, and the injection of local anaesthetic around the sting site will help to reduce the pain. Specific antivenoms are available.

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Ticks (Acari)

Ticks are large acarines, which are blood-sucking ectoparasites of vertebrates. They are important vectors of diseases such as tick-borne relapsing fever, a number of viral and rickettsial infections, and Lyme disease.

Morphology and biology [1]. Ticks are typical arachnids, possessing mouthparts referred to as the capitulum, an unsegmented body, and four pairs of legs in the adult. Larval ticks have three pairs of legs.

There are two major families: the Ixodidae (hard ticks) and the Argasidae (soft ticks). The term 'hard' refers to the dorsal chitinous shield or scutum, which is present in the Ixodidae but not in the Argasidae. In Ixodidae, the scutum covers the whole dorsum in the male, but only a small

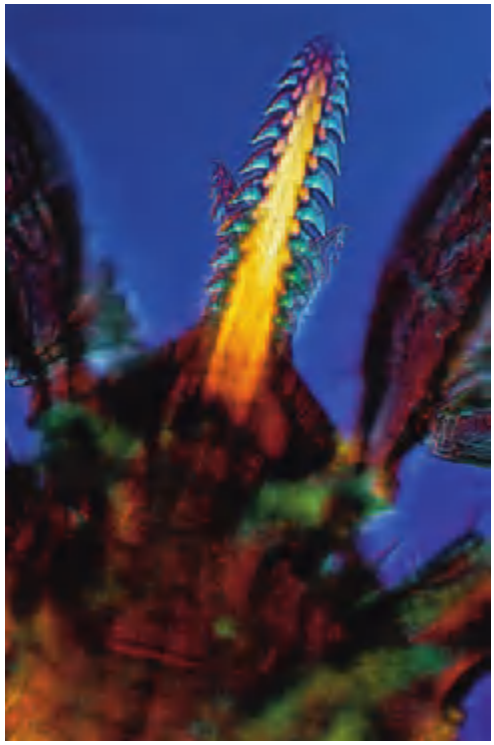

Fig. 33.26 Mouthparts of an *Ixodes ricinus* nymph, showing the toothed hypostome (interference contrast microscopy).

Fig. 33.27 Scanning electron micrograph of tick mouthparts.

anterior part in the female. In argasids, there is little difference between the sexes. The mouthparts of ixodid ticks project forwards and are easily visible from above, whereas those of the argasid ticks can only be seen from below. A conspicuous component of the mouthparts is the toothed hypostome (Figs 33.26 and 33.27).

Ixodid ticks have four stages in their life cycle: egg, larva, nymph and adult. The larva and nymph require blood meals before further development can occur, and the adult female (Fig. 33.28) also requires a blood meal before egg laying. The female lays one large batch of eggs and then dies. Some ixodids use one host for larval, nymphal and adult stages (one-host ticks), whereas others require two or, more usually, three separate hosts.

To find suitable hosts, the larvae, nymphs and adults climb low vegetation and raise the first pair of legs ('questing'), which carry sense organs (Haller's organ). These organs are sensitive to a number of stimuli, including the carbon dioxide in the exhalations of a potential host. If the host brushes past the vegetation, the tick will immediately grasp the animal's coat.

Argasidae undergo several nymphal stages, and the adult female feeds a number of times during her lifetime,

Fig. 33.28 *Ixodes ricinus*, the sheep tick (engorged female). (a) Dorsal view. (b) Ventral view.

(a)

(b)

laying several batches of eggs. Ixodid ticks feed on the host for several days, whereas argasids visit their hosts nocturnally to feed for only a few minutes. Argasids are mainly parasites of birds, bats and humans. Most ticks are essentially parasites of wild animals, and humans are incidental hosts.

When attaching itself to the host, the tick uses its toothed chelicerae to cut into the epidermis, before thrusting the hypostome into the opening and gradually penetrating the dermis. The hypostome becomes anchored by a protein cement, produced by the salivary glands, which forms a cone around the hypostome and interlocks with its teeth [1,2]. Argasids, being rapid feeders, do not attach themselves as securely as ixodid ticks.

Ticks as vectors of disease [1,3,4]. Within the large family of ixodid ticks, there are several genera of medical importance, including *Dermacentor*, *Haemaphysalis*, *Rhipicephalus*, *Amblyomma*, *Hyalomma* and *Ixodes*.

Dermacentor species act as vectors for a number of diseases, including Rocky Mountain spotted fever, Siberian tick typhus, Colorado tick fever and several types of viral encephalitis.

Haemaphysalis species may also carry Rocky Mountain spotted fever, Siberian tick typhus and Colorado tick fever.

Rhipicephalus sanguineus (the brown dog tick) transmits *Rickettsia conorii*, the causative organism of boutonneuse fever (Mediterranean spotted fever). *Rh. sanguineus* is normally confined to the tropics, but it may be encountered in temperate climates in centrally heated houses [5]. Ticks of the genus *Amblyomma* transmit *Rickettsia africae*, the organism responsible for African tick-bite fever [6].

Ixodes species are important vectors of certain haemorrhagic fevers and viral encephalitis, and also of Lyme disease (Chapter 27). They may also transmit babesiosis to humans [7]. The principal vectors of Lyme disease are the sheep tick *Ixodes ricinus* in Europe, and *I. dammini* (East coast) and *I. pacificus* (West coast) in the USA.

Various species of Argasidae may also act as vectors of disease, the most important being *Ornithodoros* species, which transmit tick-borne relapsing fever. In Israel, *O. tholozani* (the cave tick), which is endemic in the Middle East, is the vector of *Borrelia persica*, a causative agent of relapsing fever [8].

Pathology [3]. At the point of penetration of the tick mouthparts, there is coagulation necrosis of the epidermis and papillary dermis [9]. Surrounding the hypostome is the homogeneous cement [10]. The punctured epidermis shows parakeratosis, spongiosis and frequently pseudoepitheliomatous hyperplasia. There is marked dilatation of upper dermal blood vessels, and a dense perivascular infiltrate of neutrophils and lymphocytes. Histology of the bite site several weeks after removal of the tick shows a perivascular and periadnexal infiltrate of lymphocytes, plasma cells and histiocytes [11,12]. Foreign-body giant cells may also be present in the infiltrate. If the hypostome has been damaged during removal of the tick, fragments of the mouthparts may be seen.

Clinical features [3]. In the case of ixodid ticks, it is usually the parasite itself that attracts the patient's attention. Larvae, nymphs or adults may be discovered attached to the skin, and humans usually become accidental hosts when walking through, or sitting in, an area which contains ticks [13]. Larval ticks, sometimes referred to as 'seed ticks', are very small, and may go unnoticed unless present in large numbers [14,15]. An engorged adult female tick is the size of a large pea.

A papular urticarial response to ticks has been reported in berry pickers [16], and the author has seen papular urticaria developing within a few days of contact with numerous larval ticks of *I. ricinus*.

Autoeczematization has been reported in association with a tick-bite granuloma [17].

Temporary alopecia may develop around the sites of tick attachment to the scalp [12,18].

Bullae [19] and extensive bruising [20] at the feeding sites of argasid ticks have been reported, and anaphylaxis may be provoked by ixodid bites [21].

In boutonneuse fever, there is an eschar (tache noire; black spot) at the site of the bite of the infected tick, accompanied by a maculopapular rash, and African tick-bite fever is associated with multiple inoculation eschars, often located on the legs [6].

The bites of the cave tick, *O. tholozani*, produce characteristic deep red crusted papules or nodules, with a central punctum [8].

The colour of engorged ticks has led patients to suspect they were melanomas [22].

Tick paralysis [23,24]

Tick paralysis is an ascending flaccid paralysis probably caused by a neurotoxin injected by the feeding tick. Occasionally, bulbar paralysis, respiratory failure and death occur. The site of action of the toxin appears to be in the region of the neuromuscular synapse. If the tick is removed, all the signs usually resolve rapidly, but sometimes recovery is slow. Children are more frequently affected than adults.

Tick paralysis occurs in particular localities in association with specific ticks [3]. Offending species include *Dermacentor andersoni* and *D. variabilis* (USA); *Ixodes holocyclus* (Australia); *I. pilosus* (South Africa); *I. ricinus*, *I. hexagonus*, *Rhipicephalus sanguineus* (Europe).

Lyme disease

See Chapter 27.

Tick removal

Various methods for removal of ticks have been suggested, including the application of iodine, ether, chloroform, petrol and kerosene. Sherman [25] suggested a few drops of clear nail varnish, and Dolan and McKinsey [26] 2% lidocaine jelly. Karras [27] also found viscous lidocaine to be effective.

Ticks should not be removed by a sudden forcible movement, as this will often leave the mouthparts embedded in the skin. Gripping the tick with forceps or tweezers, as close to the skin as possible, and gentle traction usually succeeds when other methods have failed [28].

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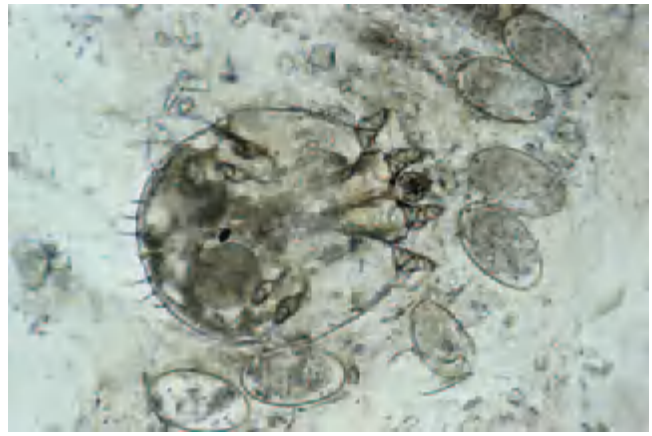

Fig. 33.29 *Sarcoptes scabiei*, the scabies mite. Female with eggs.

Mites (Acari)

Family Sarcoptidae

Scabies

Scabies in humans and other animals is caused by mites of the family Sarcoptidae, which includes *Sarcoptes scabiei*, the scabies mite, and *Notoedres cati*, a mange mite of cats.

The *Sarcoptes* causing scabies in humans and sarcoptic mange in many other animals are physiological variants of a single species, *S. scabiei*. Their host specificity is not complete, but they usually survive for only a short period on another host.

Human scabies

Human scabies has played a modest, but not insignificant role in history, and the story of scabies has been related in detail by Hebra [1], Beeson [2], Heilesen [3], Friedman [4] and Parish [5].

Morphology and biology of the scabies mite [3,6–12]. *Sarcoptes scabiei* var. *hominis* has an ovoid body, flattened dorsoventrally. The adult female measures approximately 0.4 mm long by 0.3 mm broad, and the smaller male 0.2 mm long by 0.15 mm broad. The body is creamy white and is marked by transverse corrugations, and on its dorsal surface by bristles and spines (denticles). There are four pairs of short legs; the anterior two pairs end in elongated peduncles tipped with small suckers. In the female, the rear two pairs of legs end in long bristles (setae) (Fig. 33.29), whereas in the male bristles are present on the third pair and peduncles with suckers on the fourth.

Copulation occurs in a small burrow excavated by the female. After copulation, the fertilized female enlarges the burrow and begins egg laying. The burrow is not confined

to the stratum corneum, but is inclined downwards into the epidermis. Eggs and mite faeces are deposited behind the female in the burrow. Approximately 40–50 eggs are laid by each female during a lifespan of 4–6 weeks, during which time she does not leave the burrow. Six-legged larvae emerge from the eggs after 3–4 days and escape from the burrow by cutting through its roof. The larvae then dig short burrows (moulting pockets) in which they transform into nymphs. After further moults, adult males and females develop.

The mites show a preference for certain sites in which to burrow, and appear to avoid areas with a high density of pilosebaceous follicles. The average number of adult female mites on an individual suffering from the common form of scabies is about 12 [13–15]. Only in crusted (Norwegian) scabies are large numbers of mites present.

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Prevalence and epidemiology [1–4]. Scabies affects all races and social classes worldwide, but accurate figures of its prevalence are difficult to obtain. A recent study has suggested that the prevalence is increasing in the UK, and that scabies is more prevalent in urban areas, the north of the country, in women and children, and that it is commoner in the winter than the summer [5]. The prevalence of scabies in developed countries shows cyclical fluctuations for which there is, as yet, no satisfactory explanation. War conditions are associated with a high prevalence, as in the Second World War. However, the number of cases was already rising before the outbreak of war. By the early 1950s it was declining, and it remained low until the mid-1960s, when there was a further upsurge [6–8]. The interval between the end of one epidemic and the beginning of another is approximately 10–15 years.

One suggested cause of the increased frequency of scabies in the 1960s was sexual promiscuity, but some authors believe this is unlikely, in view of a lack of correlation with trends in sexually transmitted diseases [7,9]. A proposed explanation for the epidemic cycles is the 'herd immunity' theory [2,7]. This suggests that an epidemic of scabies confers a degree of immunity, so that a further epidemic will not occur until a new, susceptible population has arisen. However, the persistent high prevalence of scabies in many underdeveloped countries, without any marked cyclical variation, is evidence against this view.

Scabies is most common in children and young adults, but may occur at any age, and in the UK in recent years it has become frequent in the elderly in residential and nursing-home environments. In a questionnaire survey of dermatologists in UK hospitals, respondents estimated that approximately 30% of all cases of scabies they encountered occurred in institutions such as care homes and hospitals [10]. Although some outbreaks are related to cases of crusted scabies, others appear to originate from residents who have ordinary scabies with many burrows, and therefore a large mite population, or from infected carers. Close contact between residents and carers in these homes is common—for example, carers often hold the hands of residents to provide support when walking.

The overall sex incidence is probably equal.

Whereas all racial groups are susceptible, there are some differences in prevalence, which are probably related to customs and social factors rather than inherent susceptibility. Some reports suggest that black Americans appear less susceptible [11,12], but this has been disputed [13]. In a study of a multiracial population in Hawaii [14], scabies was far more frequent in white people and Hawaiians than in Japanese and Filipinos, and this was thought to be related to family size and social customs.

Overcrowding, which is common in underdeveloped countries and is almost invariably associated with poverty and poor hygiene, encourages the spread of scabies.

Scabies is usually transmitted by close physical contact, such as prolonged hand-holding or the sharing of a bed. Indirect spread by clothing or bedding is unimportant, as demonstrated by the meticulous studies of Mellanby [15,16]. It is often suggested that fertilized female mites are responsible for transmission, although there is no firm evidence to support this contention, but it seems unlikely in view of their relatively small numbers and inclination to remain within their burrows. There are far greater numbers of immature mites on the skin surface, and their involvement in scabies transmission would appear more plausible.

A study from Sheffield, UK [17], showed that scabies was introduced into households mainly by schoolchildren and teenagers, especially by girls. The authors suggested

that the high incidence of scabies in teenage girls could be due to contact with younger children in large families, and the habit of holding hands. The commonest sources of infection were friends and relatives outside the home, and schools did not appear to play any appreciable part.

Away from the host, scabies mites survive for 24–36 h in room conditions (21°C and 40–80% relative humidity) [18], and live mites have been demonstrated in dust samples collected in the homes of infected patients [19].

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Immunology [1–5]. Allergic sensitivity to the mite or its products appears to play an important role in determining the development of lesions other than burrows, and in producing pruritus. However, the sequence of immunological events is unclear and requires further elucidation.

Evidence suggests that both immediate and delayed-type hypersensitivity are involved. Skin tests with mite extracts have given equivocal results, although positive immediate-type reactions to intradermal tests have frequently been obtained in patients within a few months of scabies infection. Normal IgE levels were reported in one series of scabies patients [6], but later studies have shown significantly elevated levels in many individuals [7–10].

Involvement of delayed-type hypersensitivity in the production of inflammatory papules and nodules is suggested by the histological changes and predominance of T lymphocytes in the cutaneous infiltrate [11,12].

Other immunological findings include high serum IgG and IgM, and low IgA [6,9] with levels returning to normal after treatment. IgM and C3 deposits have been demonstrated at the dermal–epidermal junction in the region of burrows [13,14], and circulating immune complexes have been found in the serum after treatment of scabies [15].

The frequency of human leukocyte antigen (HLA)-A11 was found to be higher among patients with scabies than in a normal population in Norway [16].

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Clinical features [1,2]. Itching is usually the most obvious manifestation of scabies. It is generally worst at night and when the patient is warm. The onset occurs 3–4 weeks after the infection is acquired, and coincides with a widespread eruption of inflammatory papules. Reinfection of a previously cured individual, however, provokes immediate symptoms [3].

The pathognomonic lesions of scabies are burrows, which appear as slightly raised, brownish, tortuous lesions (Fig. 33.30). The point of entry of the mite, the most superficial part of the burrow, has a slightly scaly appearance, and at the distal end there may be a tiny vesicle, adjacent to which is the female mite. There may be few or many burrows, and in patients with a good standard of hygiene they may be difficult to find. Burrows occur on the wrists, the borders of the hands, the sides of the fingers and the finger web spaces, the feet, particularly the instep

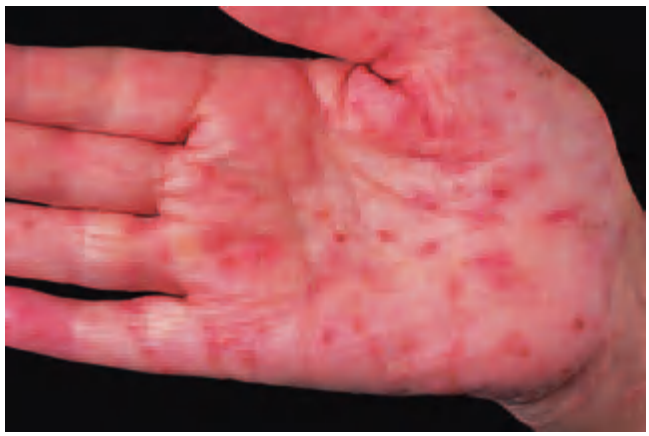

Fig. 33.30 Numerous scabies burrows on the palm.

and, in males, on the genitalia. They are often present on the palms and soles of young children and the elderly. In adults other than the elderly, burrows may occur on the palms in women, but they are less frequently found on the palms in men, particularly heavy manual workers. Burrows on the trunk are uncommon in adults, but may be found in the elderly and in infants. They may be seen on the head and neck in babies, but rarely in adults. The scalp was, however, involved in an adult who was applying a topical steroid for seborrhoeic dermatitis [4], and scalp involvement in ordinary scabies may be a reason for relapse [5]. The reason for this pattern of distribution of burrows is not understood, but the mites appear to prefer non-hairy skin and areas of low sebum production.

The pruritic papules that accompany the development of hypersensitivity occur predominantly around the axillae, in the periareolar regions, on the abdomen, particularly the periumbilical region, and on the buttocks and thighs. Histology shows epidermal spongiosis, with intraepidermal microabscesses containing neutrophils and eosinophils, and a dermal perivascular infiltrate of eosinophils, histiocytes and lymphocytes [6,7]. Indurated, inflammatory nodules sometimes occur, particularly on the axillae, groins, scrotum and penis. They are intensely itchy, and may persist for weeks or months after the scabies has been effectively treated [8–10]. The histological changes seen in these lesions may simulate lymphoma, with a dense, pleomorphic dermal infiltrate composed of plasma cells, eosinophils, lymphocytes, histiocytes and reticulum cells [6,11]. T lymphocytes are the predominant cells in the dermal infiltrate of both papular and nodular lesions [12,13].

Inflammatory papules or nodules, sometimes surmounted by burrows, on the male genitalia are characteristic of scabies (Fig. 33.31). The genitalia of males suspected of suffering from scabies should always be examined, as these lesions may provide an important diagnostic clue if burrows are difficult to find.

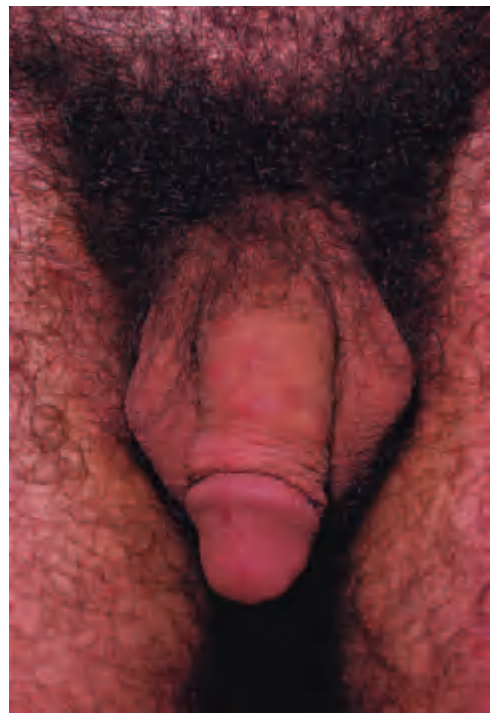

Fig. 33.31 Inflammatory papules on the penis in scabies.

Nail involvement in crusted (Norwegian) scabies is frequent, but it is uncommon in ordinary scabies [14]. Its presence may be a reason for relapse [15].

In addition to these primary manifestations, secondary features may frequently confuse the clinical picture. Eczematous changes are common, and may be widespread and severe. The inappropriate use of topical steroids may further modify the clinical picture to mimic other dermatoses (see crusted scabies)—so-called 'scabies incognito' [16]. Secondary infection, manifest as folliculitis or impetigo, may also be severe and extensive. In the tropics and subtropics, where nephritogenic strains of β-haemolytic streptococci may be responsible for secondary sepsis, glomerulonephritis occurs as a complication of scabies, but this must be exceedingly rare in temperate climates.

A bullous pemphigoid-like eruption may occur in association with scabies [17–24], and in many of the reported cases immunofluorescence studies showed immunoglobulin deposition in the basement-membrane zone of the bullous lesions. The demonstration of circulating antibodies against BP180 and/or BP230 in two patients with scabies and bullous lesions [23] indicates that scabies may induce true bullous pemphigoid.

Cutaneous vasculitis is an unusual presentation of scabies [25–27].

Scabies in babies. The clinical features of scabies in infants and young children differ in certain respects from those in

older children and adults [28,29]. In addition to the more extensive distribution of burrows mentioned above, vesicular and vesiculopustular lesions on the hands and feet are frequent, extensive eczematization is often present, and there may be multiple crusted nodules on the trunk and limbs.

Bullous lesions have been described in a child [30].

Scabies in the elderly. Burrows commonly occur on the palms and soles, and may be very numerous. Truncal papulosquamous lesions, often surmounted by burrows, are common. Secondary eczematization is often troublesome.

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Diagnosis. The typical history of pruritus with nocturnal exacerbations, and the distribution of the eruption of inflammatory papules, should suggest the diagnosis. The presence of genital lesions in males is pathognomonic. Absolute confirmation can only be made by the discovery of burrows and microscopical examination. A burrow is gently scraped off the skin with a blunt scalpel, and the material placed in a drop of 10% potassium hydroxide or mineral oil on a microscope slide. The presence of mites, eggs or fragments of egg shells confirms the diagnosis.

Epiluminescence microscopy may facilitate diagnosis [1], the mite in its burrow resembling a 'jet with contrail'.

Occasionally, burrows are difficult or impossible to find, and the diagnosis can then only be presumptive, based on the history, distribution of the papular eruption and the presence of contact cases within the family. However, in difficult diagnostic situations and atypical cases, polymerase chain reaction has been employed as a diagnostic tool [2].

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Treatment [1–3]. There have been many suggested remedies for scabies. Sulphur has been used for centuries, and sulphur ointment is still employed by some dermatologists. Used excessively, or in high concentration, it may cause irritation, but 10% sulphur in yellow soft paraffin is, in general, safe and effective. A concentration of 2.5% may be used for scabies in infants and young children [4]. Rotenone, an extract of Derris root, was employed in the 1940s [5,6], but frequently produced scrotal dermatitis.

There are several currently available scabicides. The choice of therapy is determined not only by efficacy and potential toxicity, but also by considerations such as cost, ease of application, the presence of secondary eczematization and the age of the patient.

Although for many years a hot bath and vigorous scrubbing of the sites of burrows was considered essential, Mellanby *et al*. [7] demonstrated that this was not necessary.

Benzyl benzoate. Although benzyl benzoate is now synthesized, it occurs naturally in balsams of Peru and Tolu; balsam of Peru has been used as a scabicide in the past. In

1937, the Danish dermatologist Kissmeyer [8] reported the effectiveness of benzyl benzoate in the treatment of 8000 cases of scabies, and it rapidly became popular [7,9–11]. Employed as a 25% emulsion, it should remain on the skin for 24 h. There are a number of suggested treatment regimens, but little has been published on their comparative efficacy. Most involve two or three applications, either within 24 h, on successive days or separated by intervals of a week. Benzyl benzoate is irritant, and patients should be warned about overuse.

Monosulfiram [12,13]. A 25% solution in industrial methylated spirit is diluted with two or three parts of water to form an emulsion immediately prior to application, as the suspension is unstable. It should be applied once daily for 2 or 3 days. Monosulfiram is chemically similar to disulfiram (Antabuse) and an Antabuse effect, with flushing, sweating and tachycardia, may occur if alcohol is ingested during or soon after treatment [14]. Monosulfiram-impregnated soap has been used as a prophylactic measure in communities where scabies was endemic [15–17]. Monosulfiram is no longer available in the UK.

Malathion. Malathion 0.5% in an aqueous base is employed as a scabicide [18,19]. It should be left on the skin for 24 h, with a second application after an interval of a week.

Permethrin. Permethrin 5% dermal cream is an effective scabicide [20–22]. It should be washed off after 8–12 h, with a second application after an interval of a week.

Gamma benzene hexachloride (lindane). A single application, washed off after 12–24 h, is usually recommended, but it has been demonstrated that a 6-h application is equally effective [23]. Topical lindane is absorbed through the skin, especially if the barrier function of the epidermis is compromised [24–27]. There are a number of reports of adverse neurological effects, principally seizures, attributed to lindane [24,26,28–31], but toxicity was usually the result of excessive topical application or accidental ingestion. A comparison of percutaneous absorption of lindane and permethrin concluded that 5% permethrin cream is at least 40 times less likely to cause toxic effects than 1% lindane lotion [32]. However, critical assessment of lindane as a scabicide led to the conclusion that it is safe if used correctly [33,34].

There are anecdotal reports from several parts of the world, including the UK and USA, of lindane treatment failures, suggesting the emergence of lindane-resistant scabies mites.

Lindane is no longer available in the UK.

Other topical treatments include thiabendazole [35,36] and crotamiton [37]. Both have limited scabicidal activity, and several applications on consecutive days are required.

Ivermectin [38,39]. Ivermectin is structurally similar to the macrolide antibiotics, but does not have antibacterial activity. It is, however, active against a number of ecto- and endoparasites. It has been extensively employed in veterinary medicine, and in humans is used to treat filarial disease, principally onchocerciasis. It is not licensed for use in scabies in humans. Glaziou *et al*. [40] compared oral ivermectin with topical benzyl benzoate for the treatment of scabies, and found that the former produced a higher cure rate. A comparison of the effectiveness of topical permethrin with oral ivermectin showed that a single application of permethrin is superior to a single dose of ivermectin, but two doses of ivermectin (with a 2-week interval between) are as effective as a single application of permethrin [41]. Comparison of ivermectin with lindane showed that they are equally effective [42]. It has also been reported that a specially formulated topical ivermectin preparation was effective in treating scabies [43]. Oral ivermectin has proved particularly useful in the treatment of crusted scabies (see below).

Ivermectin is apparently a safe drug with a low incidence of adverse effects. Many of the reported adverse effects have occurred in individuals given ivermectin for the treatment of filariasis, in whom serious reactions were thought to be related to death of the parasites [44]. A report suggesting a pattern of excess deaths in elderly people in a residential unit, who were given ivermectin to control a scabies outbreak, raised concerns about its safety [45]. However, the conclusions of this report were challenged [46,47], and other authors' findings regarding its safety are reassuring [48,49]. It also appears to be safe in children [50].

A single dose of 200 μg/kg body weight will be effective in many cases of ordinary scabies but, presumably because of a lack of ovicidal activity, higher cure rates are obtained with two doses separated by an interval of a week.

Because it is effective, inexpensive and easy to administer, ivermectin might prove particularly useful in the management of institutional outbreaks of scabies (see below). Leppard and Naburi [51] controlled an outbreak of scabies in a prison in Tanzania by giving ivermectin to 1153 prisoners.

In the Cochrane systematic review of the treatment of scabies, 13 randomized trials are included, assessing the effectiveness of benzyl benzoate, crotamiton, lindane, ivermectin, permethrin and sulphur [3]. No randomized controlled trials investigating malathion were identified.

In one small trial, ivermectin was associated with a significantly higher clinical cure rate at 7 days than placebo. Permethrin appeared to be more effective than

crotamiton for clinical and parasitic cure rates. Permethrin appeared to be better than lindane for clinical cure rates in two small trials, but had no advantage in the largest trial. There appeared to be no difference in clinical cure rates between crotamiton and lindane or benzyl benzoate and sulphur.

One small-scale placebo-controlled study suggested that ivermectin might be an effective treatment for scabies. Two small-scale studies, one comparing ivermectin with benzyl benzoate and the other ivermectin and lindane, found no difference in effectiveness between these drugs.

It was suggested that permethrin is the preferred treatment for scabies at the present time (based on comparisons with lindane and crotamiton)—the choice being based on 'small studies together with professional opinion and traditional reviews'.

A survey of dermatologists in the UK revealed that the majority used permethrin cream for treating scabies, and about half reported treatment failures with malathion [52].

In addition to the adverse effects of scabicides already mentioned, contact dermatitis to mesulphen, a scabicide used in Italy [53] and toxic epidermal necrolysis attributed to monosulfiram [54] have been reported.

Liquid scabicides are most conveniently applied with a 2-inch (5-cm) paintbrush. Scabicides should be applied to the whole body, except the head and neck, although the latter should be included if there is clinical evidence of involvement, and a non-irritant agent employed. Patients should be provided with written instructions explaining their treatment regimen and a warning against excessive use. They should be advised that itching will persist for a few days, but will usually resolve within 2 weeks. A topical antipruritic, such as crotamiton combined with hydrocortisone, may be used on residual itchy areas. All members of the family and close physical contacts should be treated, whether symptomatic or not. Disinfestation of clothing and bedding, other than by ordinary laundering, is not necessary.

Secondary infection should be treated with a systemic antibiotic. If eczematization is severe, a non-irritant scabicide should be used.

Treatment of infants and young children. Benzyl benzoate should be diluted with two or three parts water if used on infants and young children. Prolonged or repeated applications of benzyl benzoate or lindane should be avoided. Permethrin cream is probably the treatment of choice.

Scabicides in pregnancy. The literature is replete with cautionary advice relating to the use of scabicides in pregnancy, but having indicated which scabicides are best avoided authors rarely commit themselves to stating what they recommend. This is understandable in view of concern about potential toxic effects on the fetus, but to the present author's knowledge there is no documented evidence that any of the currently available scabicides has been responsible for harmful effects in pregnancy, and all must have been used on innumerable pregnant women.

Scabicides and breastfeeding. Published information regarding scabicides and breastfeeding is sparse [55]. There do not appear to be any data on levels of scabicides in human milk following their use on lactating women, hence any advice tends to be based on studies of percutaneous absorption and measurement of plasma levels. It would appear preferable to stop breastfeeding for a few days after treatment, to allow plasma levels of any percutaneously absorbed scabicide to fall, thereby reducing the likelihood of its ingestion in breast milk by the neonate.

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Crusted scabies

SYN. NORWEGIAN SCABIES

The appellation 'Norwegian' derives from the description in Norway by Danielssen and Boeck [1] of a type of scabies in which huge numbers of mites were present in lepers. Hebra referred to this as 'scabies Norvegica Boecki' [2]. It has been suggested that 'Norwegian' should be discarded and replaced by 'crusted' [3,4].

Crusted scabies is an infection with *Sarcoptes scabiei* var. *hominis* in which the mite population is enormous, and may number millions. The grossly thickened horny layer is honeycombed with cavities which contain large numbers of mites, and these are shed into the environment of the patient [5]. An undiagnosed case of crusted scabies may be the source of an outbreak of common scabies.

Aetiology and pathogenesis [6,7]. In common scabies, there are few mites, probably because scratching destroys the burrows. A good standard of hygiene may also help to control the mite population. In crusted scabies, the host's response to the mites is modified, allowing them to multiply.

Patients with skin anaesthesia secondary to sensory neuropathy or spinal injury [8] obviously do not perceive itch and therefore do not scratch, but many patients with crusted scabies show no demonstrable sensory loss. However, in many, itching is either absent or mild. Patients who are mentally retarded or suffer from dementia may develop crusted scabies [9], and Down's syndrome is a frequent association [3,10–13]. The reason for this association with mental abnormality is not completely understood, but lack of appreciation of pruritus may be important.

In some patients who are physically severely incapacitated, as a result of paresis [14,15] or severe arthropathy, the main reason for the development of crusted scabies is probably a physical inability to scratch in response to itching. It has also been described as a complication of dystrophic epidermolysis bullosa [16], in which an inability to scratch because of an absence of fingernails may have been a contributory factor, and in a patient with epidermolysis bullosa simplex [17].

Crusted scabies may develop in patients who are immunosuppressed, either as a result of disease [18,19] or therapy [20–22]. In recent years, there have been numerous reports of its occurrence in patients with HIV infection, and it is also an indicator of human T-cell lymphotrophic virus type I (HTLV-I) infection [23–25]. Crusted scabies has also resulted from inappropriate use of potent fluorinated topical steroids [26–28]. Suppression of sensitivity to the mites reduces itching, so there is less scratching and destruction of burrows.

The occurrence of crusted scabies in an otherwise healthy pregnant woman has been reported [29].

Clinical features. Large, warty crusts form on the hands and feet (Fig. 33.32), and the palms and soles may be irregularly thickened and fissured. Masses of horny debris accumulate beneath thickened and discoloured nails (Fig. 33.33). Erythema and scaling occur on the face, neck, scalp (Fig. 33.34) and trunk, and may generalize. The

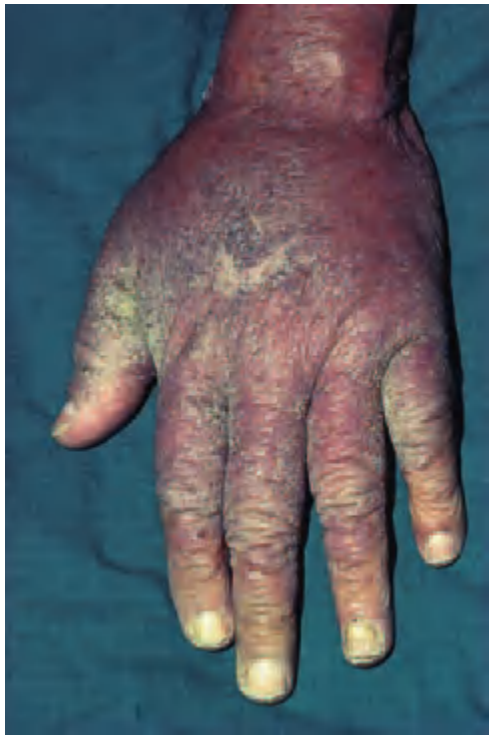

Fig. 33.32 Crusted (Norwegian) scabies.

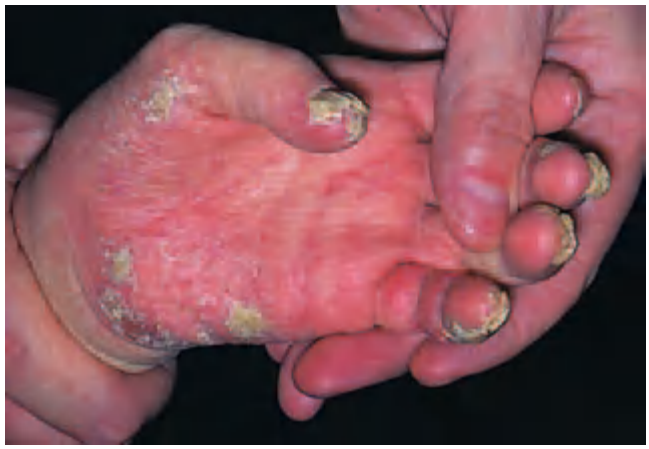

Fig. 33.33 Grossly dystrophic nails in crusted scabies.

extent of the erythroderma and the warty plaques varies greatly, and either may predominate. It has been suggested that *Staphylococcus aureus* colonizing burrows might play a part in initiating the erythroderma [30]. Itching is often absent or slight, but may occasionally be severe. Generalized lymphadenopathy is present in some cases, and blood eosinophilia is common.

Crusted scabies may masquerade as hyperkeratotic eczema, psoriasis, Darier's disease [31] and contact dermatitis [32].

The diagnosis is readily confirmed by examination of scrapings, which will be teeming with mites and eggs.

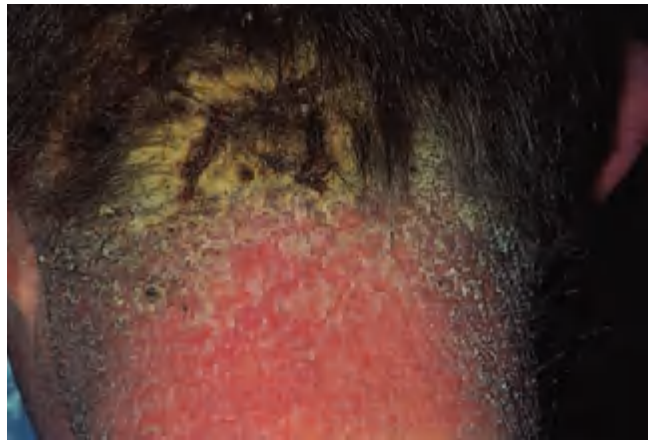

Fig. 33.34 Severe scalp involvement in crusted scabies.

Treatment. A patient with crusted scabies should be admitted to hospital for treatment. They may be treated with topical scabicides, but prolonged therapy involving several applications is often required, and incomplete response is not uncommon. In recent years, ivermectin has become the treatment of choice for crusted scabies, either alone or in combination with a topical agent [33–37]. Although there has not been a comparative study of various regimens which have been employed, it is likely that the most effective is two doses of ivermectin (200 μg/kg body weight), separated by an interval of a week, combined with a topical scabicide. The nails should be cut short, and a topical scabicide applied beneath their free edges.

Institutional outbreaks of scabies. There are numerous reports of outbreaks affecting both patients and medical personnel in hospitals and residential homes, and many of these are associated with undiagnosed cases of crusted scabies. Nursing and medical staff in contact with such a patient may develop the common type of scabies, but frequently the first lesions seen are pruritic papules on the limbs, without any clinical evidence of burrows. The presence of papules and nodules surmounted by burrows, on the abdomen, buttocks and limbs of several contacts of a case of crusted scabies has been described [38].

The management of an institutional outbreak of scabies requires control measures to deal with all residents/patients and health care workers [39–41]. In this situation, all the patients or residents should be examined to detect any cases of severe or crusted scabies, and such individuals should be isolated until cured. Any personnel coming into contact with such a patient should wear long-sleeved gowns and gloves. All individuals on an affected ward or in a residential home, and all medical and nursing staff and their families, should receive prophylaxis with a topical scabicide. Bedding should be laundered. It has

been suggested that during treatment of institutional outbreaks, particular attention should be paid to the nails, in view of the subungual persistence of mites [42]. Cases of crusted scabies should be treated as outlined above.

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Animal scabies

Transmission of animal scabies to humans is probably rare, because of the relative host specificity of the mites [1]. However, recurrent exposure to animal scabies mites can produce troublesome and diagnostically puzzling lesions.

Many varieties of *Sarcoptes scabiei* have been incriminated, including the following:

1 The mites causing sarcoptic mange in horses, cattle, buffalo, pigs, camels, monkeys, sheep and goats [2–7].

2 *Sarcoptes scabiei* var. *canis* commonly causes transient skin lesions in those in contact with infested dogs [8–14]. Exceptionally, scrapings from human skin have shown mites and eggs, and symptoms have persisted after contact with the animal has ceased [15]. Canine scabies has been experimentally transferred to humans [16]. Affected animals have areas of scaling and hair loss on the ears, face and limbs [17].

3 *Notoedres cati*, the cause of sarcoptic mange in cats, is almost unknown in the UK, but where it is endemic in the cat population, as in India [18] and Japan [19], human skin lesions may occur.

Clinical features. Skin lesions resulting from contact with animal scabies vary in extent and distribution, according to the mode of exposure. The eruption is usually composed of small, pruritic weals or papules, which are frequently excoriated and resemble human scabies, but without burrows. Lesions from contact with sarcoptic mange in dogs and notoedric mange in cats usually occur at sites of contact with the animal, principally the chest, abdomen, thighs and forearms.

Treatment. If contact with animal scabies is suspected, the diagnosis can only be confirmed by examining the suspect animal and obtaining skin scrapings from it. Affected animals should be treated by a veterinary practitioner.

Human skin lesions are self-limiting, and will resolve once contact with the affected animal has ceased, or it has been treated.

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Family Knemidokoptidae

Knemidokoptes mutans causes scaly leg in domestic poultry, and *Mesoknemidokoptes laevis* is a closely related mite which causes depluming itch in poultry; both have caused skin lesions in humans [1].

Family Psoroptidae

Mites of the family Psoroptidae cause mange in domestic animals. Species of *Chorioptes* and *Psoroptes* from cattle, horses and sheep have occasionally affected humans [1]. *Otodectes cynotis* is a common parasite in the ears of cats and dogs, and has been discovered in the ears of a patient suffering from otitis externa [2]. It was also considered to be responsible for a pruritic dermatosis in a patient whose dog was infested [3].

Family Listrophoridae

Listrophorus gibbus, a common parasite of the domestic rabbit [4], has been reported as causing papular urticaria in a child [5].

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Mites of stored products [1]

Family Acaridae

These mites attack flour, grain, dried meat, cheese and dried fruit.

Acarus siro is the most important pest of storage premises, and is found on flour, grain, and occasionally cheese. It may cause skin lesions on those who handle these products.

Tyrophagus putrescentiae [2–4] is mostly found in stored food with a high fat and protein content such as dried eggs, ham, herring meal, cheese, nuts and copra. *Tyrophagus longior* is found on cheese, grain, hay and copra [5].

Suidasia nesbitti is particularly associated with wheat pollards and bran, and has been recorded as causing dermatitis in humans [6].

Rhizoglyphus species occur on flower bulbs and have caused dermatitis in persons handling stored bulbs.

Family Carpoglyphidae

Carpoglyphus passularum (*lactis*) is found on all kinds of dried fruit, and may cause dermatitis [7,8].

Family Glycyphagidae

Glycyphagus domesticus is a widely distributed species, often found in large numbers on plant and animal remains in houses and stables. It has also been found in flour, wheat, hay, tobacco, cheese and ham. *Glycyphagus destructor* is often abundant in hay, straw and grain.

Pathogenesis of food-mite dermatitis. It has been suggested that the dermatitis caused by these mites, which are not haematophagous, results from irritation by mite products, either faecal or secretory [3]. However, the pathomechanics of the response do not appear to have been studied in detail.

Dockers and warehouse workers handling stored products are most at risk, but shopkeepers and domestic workers are occasionally affected.

Clinical features [9]. The eruption provoked by these mites is sometimes called 'copra itch' or 'grocer's itch', and is often composed of minute, intensely pruritic papules or papulovesicles on exposed parts of the body, principally on the head and neck, and forearms, but occasionally more widespread. The appearance of the eruption on the face may suggest an acute contact dermatitis.

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House-dust mites (HDM)

Dermatophagoides pteronyssinus, the HDM, was first discovered by Trouessart in dust shaken from tanned mammal skins [1]. It was subsequently established that it is widely distributed in the human environment in house dust and beds [2,3]. It occurs worldwide, and has been reported from all inhabited continents [4]. It is commonly associated with *Euroglyphus maynei* and *D. farinae*, which are related species in the same family, the Pyroglyphidae. In the USA, *D. farinae* appears to be more plentiful in house dust than *D. pteronyssinus* [5].

The largest numbers of mites are found in houses that are damp and inadequately heated [4]. Numbers vary seasonally, increasing in early summer to reach a maximum by early autumn. In the UK, numbers are low in winter and increase in spring, when temperature and relative humidity rise [6].

The main food of *D. pteronyssinus* is human skin scales [7]. Xerophylic moulds, especially *Aspergillus penicilloides*, are essential for the growth and survival of *D. pteronyssinus*. The moulds digest lipid in the scales which is toxic to the mites.

The major HDM allergens (Der p1 and Der f1) are present in the faecal pellets.

Role in atopic eczema [9–11]

The role of the HDM in the pathogenesis of atopic eczema remains controversial, although there is increasing evidence of involvement of HDM allergen in the disease [8–12].

Several studies have indicated that, in many individuals, the condition can be improved by techniques designed to reduce exposure to HDM allergen [13–18], although the benefits on clinical status appear to be greater in children than in adults [19], and it is not possible to predict which patients will benefit.

One study demonstrated that the houses of patients with moderate to severe atopic eczema had more HDMs than controls [20].

Measures to reduce the HDM allergen load include regular vacuum cleaning of carpets, or their removal, bedding covers made of material such as microporous Gore-Tex, and the use of acaricides, including benzyl benzoate and permethrin [21].

Hepple and Macmillan [22] have attributed a case of purpuric dermatosis to HDM allergy.

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Pyemotes mites

Pyemotes mites are all primarily parasites of insects or their larvae. They only affect humans when the latter come into contact with the food of their natural hosts.

The mite *P. tritici* preys on the larvae of many species of insect infesting grain, straw or hay, and stored foodstuffs. Another species, *P. ventricosus* preys on the larvae of wood-boring beetles, including the common furniture beetle *Anobium punctatum*. There has been some confusion about nomenclature of *Pyemotes* species [1].

Pyemotes mites have been responsible for attacks of dermatitis in those shovelling grain or coming into contact with infested straw [2] and husk rice [3]. The dermatitis has been referred to by a number of terms, including 'barley itch', 'grain-shovellers' itch', 'grain itch', 'straw itch', 'cotton-seed dermatitis' and 'acarodermatitis urticarioides'. *Pyemotes* dermatitis has been reported in shop workers coming into contact with wheat used for decorative purposes [4–6]. Dermatitis in workers in a food-mixing shed at a piggery was attributed to *P. herfsi* [7], and *P. zwoelferi* was incriminated in dermatitis acquired by contact with a package of everlasting flowers [8]. Dermatitis in a fisherman handling crab pots made of cherry wood was probably caused by *P. beckeri* [9].

An outbreak of dermatitis in a small hospital in Queensland, Australia, was attributed to *Pyemotes* mites originating in an adjacent grain storage facility [10].

Clinical features [11,12]. The lesions are urticated papules surmounted by vesicles; occasionally they may be bullous. They are often very numerous, and their distribution depends upon the mode of exposure. In grain handlers, they are usually on the forearms and neck, but they may be profuse around the waist and in the groins.

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Family Tydeidae

Dermatitis in eight woodworkers in Perugia, Italy, was attributed to contact with *Pronematus davisi* mites on wood imported from North America [1]. This mite has a worldwide distribution, and is widespread in North America, where it usually lives under bark.

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Plant mites

Some mites of the family Tetranychidae ('spider mites') cause cutaneous irritation or urtication in humans [1–4]. These mites are phytophagous and occur on every type of crop and ornamental plant. The name 'spider mites' is derived from the silk webbing they produce from palpal glands.

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Cheyletiella mites

Biology and epidemiology. Species of *Cheyletiella* mites are non-burrowing, obligatory parasites of certain mammals, predominantly dogs, cats and rabbits. The entire life cycle is completed on the host. Each egg is attached to a hair shaft by means of a fine thread, which is woven around it into a cocoon-like structure by the female mite. The adult mite develops via a larval and two nymphal stages. Adult mites move rapidly over the skin surface in pseudotunnels in keratinous debris. They use their hook-like

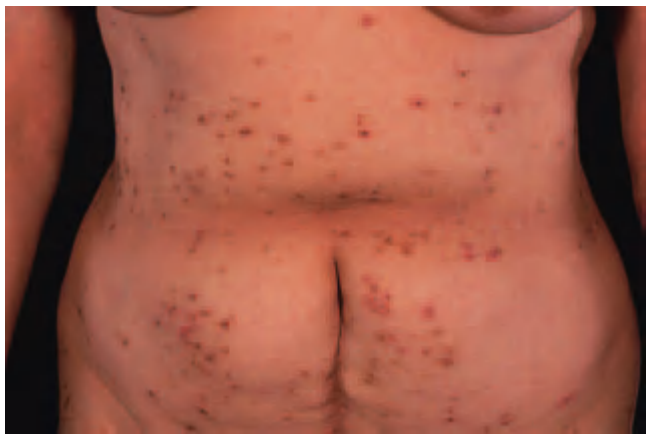

Fig. 33.35 Lesions on the abdomen produced by *Cheyletiella* mites from a pet dog.

Fig. 33.36 *Cheyletiella yasguri*.

palpi to attach themselves to the host while feeding on tissue fluids [1,2].

Cheyletiella mites were first reported as attacking humans by Lomholt [3] of Copenhagen, and in 1938 a case was reported from England [4]. It gradually became apparent that *Cheyletiella* infestation of dogs, cats and rabbits was common in most European countries, in the USA [5], in Canada [6] and in Australasia [7,8]. The distribution of these mites is likely to be worldwide. Many earlier reports incorrectly identified the species as *C. parasitivorax* when it was probably *C. yasguri*. It is now clear that *C. parasitivorax* is predominantly a parasite of rabbits, *C. yasguri* of dogs, and *C. blakei* of cats [9,10]. The three species are morphologically very similar, but distinguishable by the shape of a special sensory organ on the dorsal surface of genu I [10–12].

It is not clear from the limited information available whether the incidence of these mites is increasing, or whether infestation is becoming more frequently recognized. An investigation in the Netherlands [13] of 41 households, in which two or more cats were kept, showed *Cheyletiella* infestation of the animals in 27; 20% of the human contacts had skin lesions. Any age, breed or sex of animal may be affected. In dogs, cheyletiellosis is particularly common in boxers.

Most affected animals are asymptomatic, but some may suffer from pruritus. The most obvious sign of infestation is excessive dandruff, especially on the back, which is often known as 'walking dandruff' by veterinary dermatologists [14].

Clinical features in humans [15–17]. The typical clinical picture is of a large number of intensely itchy papules (Fig. 33.35). Surmounting the papules there may be tiny vesicles, and older lesions may show small areas of necrosis. Bullous lesions may occur [18,19]. The distribution of lesions corresponds to areas of contact with an infested animal, the abdomen and thighs being frequently involved as a result of an animal sitting on its owner's lap. The chest and arms may also be affected from carrying the animal.

In a patient with an extensive eruption, intradermal skin testing with an extract of *Cheyletiella* mites produced both immediate and delayed hypersensitivity responses [20].

Confirmation of the diagnosis [21]. The diagnosis may be confirmed by examination of combings from the animal's coat for the presence of mites. The suspect animal should be placed on a sheet of black paper, and the coat, particularly along the back, vigorously combed, preferably with a fine-toothed comb. The debris collected can then be examined microscopically (Fig. 33.36).

Treatment. The affected animal should be treated by a veterinary practitioner. Human skin lesions may be treated with a topical antipruritic. Once an animal has been treated effectively, there will be no further lesions on its owner.

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Harvest mites (Trombiculidae)

Harvest mites belong to the family Trombiculidae. More than 1200 species of trombiculids have been described, and many may attack human beings or livestock [1]. They are parasitic as larvae, but free-living as nymphs and adults. The larvae may cause troublesome dermatitis (trombidiosis; scrub itch), and some are important vectors of rickettsial disease. They have many common names throughout the world, for example orange tawny (Ireland), chigger, red bug (USA).

The eggs are laid in soil. The six-legged larvae which emerge climb onto low vegetation to wait for suitable vertebrate hosts. On the host, the larvae move to areas where the skin is thin, such as the ears, axillae, groins and genitalia. There they pierce the skin with their cheliceral claws and inject saliva, which has cytolytic properties, into the epidermis [2]. This action forms a tube-like canal (stylosome), through which the mites feed on tissue fluids and cell debris. Once engorged, they fall to the ground and develop into eight-legged adults via a nymphal stage. Nymphs and adults feed on vegetable debris and the eggs of insects and other arthropods.

Neotrombicula autumnalis, the European harvest mite, is widely distributed throughout Europe. In the UK [3], the larval mites are most numerous from May to October, with a peak in September. The most favoured natural host is the rabbit. *Neotrombicula autumnalis* is not known to transmit disease.

Eutrombicula alfreddugesi and *E. splendens* are the most common chiggers attacking man in the USA, and *E. batatas* is an important dermatitis-producing species in South America.

In South-East Asia, Australia and the Pacific Islands, trombidiosis is commonly caused by *E. wichmanni*, and species of *Odontacarus* and *Schoengastia* [4,5].

Species of *Leptotrombidium*, including *L. akamushi*, *L. pallidum* and *L. deliense*, are important vectors of scrub typhus (tsutsugamushi disease), caused by *Orientia tsutsugamushi* [6]. *L. akamushi* has a wide distribution, ranging from Japan and China southwards through South-East Asia to Indonesia and eastwards throughout the Philippines to New Guinea. *L. deliense* occurs in China, the Indian subcontinent, Malaya, Indonesia, the Philippines, New Guinea and Australia. The natural hosts of *L. akamushi* and *L. deliense* are rodents and insectivores. *L. subquadratum* has been reported as a cause of pruritus and dermatitis in dogs and humans in South Africa [7].

Clinical features [4,8,9]. Humans are infested while working in or walking through grass or low vegetation. The response to the bites of harvest mites appears to be determined by the irritant effect of the mites' saliva and an acquired hypersensitivity to salivary antigens. Within a few hours, erythematous macules appear at the sites of the bites, and these gradually develop into extremely itchy papules or papulovesicles.

The distribution of lesions is determined by the preference of mites for thin skin, and the clothing of the host. Lesions commonly occur around the feet and ankles, the groins and genitalia, the axillae, the wrists and antecubital fossae, and areas constricted by clothing, such as the waistline. In heavy infestations, the whole body may be covered in lesions.

Chigger bites on the penis in children are responsible for a seasonal acute hypersensitivity reaction in the USA known as the 'summer penile syndrome' [10].

Trombiculid mite bites have provided evidence to implicate a suspect in a murder investigation [11].

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Bird, rodent and reptile mites (Gamasida)

Family Dermanyssidae [1,2]

Dermanyssid mites are haematophagous parasites of birds and mammals. *Dermanyssus gallinae* (Fig. 33.37), the poultry mite, is a common parasite of domestic and wild birds. Poultry keepers, veterinary practitioners and others in direct contact with birds are sometimes attacked. Other dermanyssid mites responsible for dermatitis include *D. hirundinis* and *D. americanus*. Avian mites may enter buildings from birds' nests via windows, ventilation grilles or air conditioners, causing skin lesions on the occupants [3–7]. Mites on cage birds may cause similar problems [8]. Lucky *et al*. [9] reported itchy papular lesions related to contact with pet gerbils infested with *D. gallinae* and *Ornythonyssus sylviarum* (see below), and reviewed other reported cases of avian mite bites.

Liponyssoides sanguineus, the house mouse mite, is an ectoparasite of small rodents. It is of medical importance because it is the vector of *Rickettsia akari*, the agent causing rickettsial pox.

Family Macronyssidae [1]

Members of the Macronyssidae are haematophagous ectoparasites of birds, mammals and reptiles.

Fig. 33.37 *Dermanyssus gallinae*: comparison in size with the head of a match.

Ornithonyssus sylviarum (the northern fowl mite) and *O. bursa* (the tropical fowl mite) are pests of domestic and wild birds, and occasionally attack humans [10–13].

Ornithonyssus bacoti, although known as the tropical rat mite, is cosmopolitan, occurring in both tropical and temperate areas of the world. There are a number of reports of its effects on humans [14–17], including two groups of medical students in Lübeck, Germany [18] and Taegu, South Korea [19].

Ophionyssus natricis, a snake mite, caused skin lesions in a family owning a pet python [20].

Clinical features [2]. The clinical effects vary according to the route and severity of infestation and the degree of the host's response. Most commonly, there is a profuse eruption of small, intensely itchy weals or papules, sometimes grouped, and often asymmetrical. The lesions may have a central punctum, and vesicles occasionally occur in the centre of the papules, especially in children. Because of the intense pruritus, excoriations are common, and secondary infection may occur.

There is no characteristic distribution, as this is determined by the situation in which the bites are acquired. Those handling infested poultry tend to have lesions on the hands and forearms, whereas persons attacked by mites in bedding have more extensive bites. Occasionally, lesions are grouped adjacent to areas of tight clothing around the waistline.

In heavy infestations, the causative mites are often noticed by those affected, and any specimens obtained should be sent for identification to an entomologist familiar with Acari. When mite infestation is suspected, but no specimens are available, it may be necessary to visit the patient's home or workplace to determine the source of the problem.

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Follicle mites (Demodicidae)

Demodex folliculorum (Simon), the follicle mite, is an obligate parasite of the human pilosebaceous follicle. It was first discovered in cerumen by the anatomist Jakob Henle in 1841, but it was the dermatologist Gustav Simon who provided the first complete description of the parasite, under the name *Acarus folliculorum*, in 1842 [1,2]. The generic name *Demodex* was created for it in 1843 by the zoologist Richard Owen.

Morphology and biology [1,3–5]. *D. folliculorum* measures 0.3–0.4 mm in length, and has an elongated, striated abdomen, giving it a worm-like appearance (Fig. 33.38). A morphologically distinct species, *D. brevis* Akbulatova, has been recognized [6]. *D. folliculorum* occupies the hair follicle, and the smaller *D. brevis* the sebaceous and meibomian glands.

The lifespan of *D. folliculorum* is thought to be approximately 2 weeks [5]. The heart-shaped eggs hatch to produce hexapod larvae, and the eight-legged adults develop via two nymphal stages.

Follicle mites show a predilection for areas of high sebum production [7] and they have been shown to contain lipase [8]. They are most numerous on the forehead, cheeks, nose and nasolabial folds, but they are also found on the scalp, in the external ear, in eyelash follicles and meibomian glands, and on the upper chest and nipples. They have also been discovered on the penis, mons veneris, buttocks and in ectopic sebaceous glands in the buccal mucosa [9]. *D. folliculorum* assumes a head-down position in the follicle, often with the tip of the abdomen protruding from the follicular orifice. Follicle mites are quite motile, and migrate from follicle to follicle. Most infested follicles contain two to six mites, but occasionally they are much more numerous. Mites have been isolated from individuals of all ages, except neonates [10]. Transmission to infants probably occurs as a result of close maternal contact. The prevalence of both *D. folliculorum* and *D. brevis* increases with age [11,12] and it is likely that with adequate sampling techniques, mites could be discovered in some follicles in the entire adult population. The skin-surface biopsy technique is a useful method of assessing the population density and distribution of *Demodex* mites [13–15].

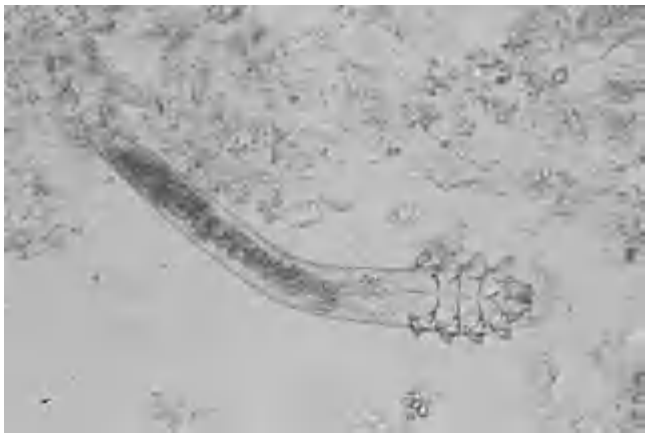

Fig. 33.38 *Demodex folliculorum*, the follicle mite.

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Pathogenicity. *D. folliculorum* has been implicated in the pathogenesis of a condition named pityriasis folliculorum [1–3]. This was originally described as occurring predominantly in middle-aged or older women who rarely washed their faces, but used large quantities of make-up

and cleansing creams. The lack of washing and use of facial cosmetics were considered to be aetiological factors, but a similar appearance has subsequently been described in women who washed their faces regularly [4,5]. This dermatosis is characterized by diffuse facial erythema and follicular plugs, which impart a 'nutmeg-grater' appearance to the skin. In reported cases, skin scrapings have contained unusually large numbers of *Demodex*, and the condition has responded to treatment with topical acaricides.

The question of the pathogenic role of *Demodex* in rosacea has prompted much debate in the past [6,7]. Although recent studies employing skin-surface biopsy have shown statistically significant increases in the density of *Demodex* mites in the facial skin of patients with rosacea compared with controls [8–12], it is still not clear whether rosacea merely provides a suitable environment for multiplication of the mites, or whether the mites play a role in initiating the disease. Skin biopsies taken from patients with rosacea, following topical therapy with sulphur, failed to show any correlation between clinical improvement and reduction in mite population [13]. In large studies of the histopathology of rosacea [14,15], *Demodex* was conspicuously absent from areas of inflammation in sections in which it was found.

It has been suggested that a local delayed hypersensitivity response to *Demodex* antigens might be partly responsible for the inflammatory component of rosacea [14], and the observation that most T cells in the granulomatous infiltrate surrounding extrafollicular *Demodex* are helper–inducer T cells [16] lends support to the hypothesis that the pathogenesis of rosacea involves a cell-mediated immune response.

Although extrafollicular *Demodex* or fragments of *Demodex* may be found in the granulomatous lesions of rosacea [17,18], its role in their induction has not been established. The mite may simply be displaced because the hair follicles have been destroyed by the inflammatory process.

A view that the beneficial effects of metronidazole in rosacea might be mediated through an action against *Demodex* [19] was not supported by the finding that mites can survive high concentrations of this drug *in vitro* [20].

Rosacea-like eruptions in which large numbers of mites could be demonstrated and which responded to therapy with acaricides [2,21–24] or metronidazole [25] have been described. The effectiveness of acaricidal treatment can be evaluated by skin-surface biopsy [26].

Demodex has been implicated in the causation of papular and papulopustular lesions in immunosuppressed individuals, including children with leukaemia [27–29], a patient with tumour-stage mycosis fungoides [30] and patients with HIV infection [31–34].

Facial lesions attributed to *Demodex* have been described in immunocompetent children, in the form of a localized scaly patch [35], and rosacea-like and pityriasis folliculorum-like lesions [36].

Demodex is present in eyelash follicles, and has been implicated in the pathogenesis of blepharitis in some patients [37–39], although its importance as a cause is disputed [40].

The observation of fungal spores [41] and *Mycobacterium leprae* [42,43] within *Demodex* mites has led to the suggestion that the mites may act as vectors for these organisms.

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Class Chilopoda (centipedes) and Diplopoda (millipedes)

Centipedes

Centipedes are elongated arthropods, with bodies composed of many segments, each bearing one pair of legs. They are nocturnally active carnivores, and feed on insects. Some of the giant species also feed on small mice and birds. The first pair of legs is modified, and provided with powerful hollow claws, which are used to grip prey and inject venom from poison glands in the basal segments of the legs.

The claws of smaller species of centipedes are unable to penetrate human skin, but some tropical and subtropical species, principally members of the orders Scutigeromorpha and the giant Scolopendromorpha, can inflict painful 'bites' [1–6]. The bites cause local pain, erythema and oedema, which may persist for several hours. Systemic symptoms include nausea, dizziness and pyrexia.

Fig. 33.39 Giant millipede. (Courtesy of M. Fogden/Oxford Scientific Films.)

Millipedes

Millipedes also have multisegmented bodies, and most segments bear two pairs of legs (Fig. 33.39). They feed mainly on decaying vegetable matter, and are generally regarded as harmless, but some large tropical species can cause injury to humans when acting defensively. The injurious effects of the defensive secretions of the giant spirobolid millipedes of tropical and subtropical zones are well known to the indigenous populations of these areas.

Millipedes have numerous 'repugnatorial' glands distributed along the body segments, which provide a chemical defence system, and it is the corrosive secretions of these glands which may cause burns on the skin. In the majority of species, these secretions ooze out and form droplets around the foramina of the glands, but a few species (*Spirobolida*, *Spirostreptida* and *Rhinocrichus*) are capable of squirting the fluid for some distance [7,8]. Millipede secretions contain benzoquinones and hydroquinones.

Clinical features of millipede burns [1,7,9–11]. Children often try to pick up millipedes, and are therefore at most risk of burns from the corrosive defensive secretions. If millipede secretions enter the eye, they produce a severe irritant conjunctivitis. Contact with the skin produces a local burning sensation and a yellowish-brown stain, which gradually darkens to deep mahogany or purple-brown. This colour is produced by oxidation of the quinones in the secretions. The lesions blister within a day or two, but in the absence of secondary infection, will heal and desquamate in 10–14 days. The discoloration may persist for months. In dark-skinned individuals, persistent hypopigmentation is a common sequel.

Treatment [7]. Skin lesions should be washed with copious amounts of water to remove any remaining secretions, and the area cleaned with alcohol (a solvent of

benzoquinones) if available. Blisters should be treated with a topical antiseptic. Ocular injuries should be dealt with by an ophthalmologist.

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Other noxious or venomous invertebrates

Leeches (Hirudinea)

Leeches are classified in the phylum Annelida (segmented worms), class Clitellata, in which they constitute the order Hirudinea. Fresh-water leeches were a popular method of bloodletting in Europe in the 18th and 19th centuries [1,2]. Although several species of leeches were used, the medicinal leech, *Hirudo medicinalis*, was the most popular. A large specimen of *H. medicinalis* may measure about 12 cm when fully extended. The body tapers towards each extremity, where it is provided with a muscular disc or sucker. Within the anterior sucker is the mouth, bordered by three jaws. Leeches attach themselves to the skin using these powerful jaws, and feed until engorged, when they release their grip and drop to the ground. Their saliva possesses anticoagulant, fibrinolytic, vasodilator and probably also anaesthetic properties. Some of the substances introduced by leeches during feeding are antigenic, and if sensitization to these substances develops, the reaction to the bite may be urticarial or bullous [3]. Multiple pseudolymphomas have occurred following application of leeches to the legs [4].

In recent years, there has been a revival of interest in the use of leeches for therapeutic purposes. They are being employed in microvascular surgery to salvage replants or skin flaps whose viability is threatened by venous congestion [5,6], and also for drainage of large haematomas. Unfortunately, the use of leeches carries the risk of introducing wound infection, most frequently with *Aeromonas hydrophila*, a Gram-negative rod, but occasionally other organisms are involved [7–10]. *Aeromonas* is part of the normal gut flora of the leech, where it is thought to be essential to aid digestion of a blood meal, as proteolytic enzymes are virtually absent from the leech gut. *A. hydrophila* is frequently susceptible *in vitro* to third-generation cephalosporins, aminoglycosides, trimethoprim–sulfamethoxazole, chloramphenicol, tetracyclines and several of the quinolones. It is often resistant to most penicillins, first-generation cephalosporins, amoxicillin–clavulanic acid, vancomycin and erythromycin [11,12]. Many plastic surgeons who use leeches employ antibiotic prophylaxis to protect against wound infection.

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Jellyfish, sea anemones, corals (Cnidaria)

The phylum Cnidaria [1–3] includes the jellyfish, sea anemones and corals. All are aquatic, and the majority are marine. Three of the four classes of the phylum have a medusa or 'jellyfish' stage in their life cycles. Cnidarians have tentacles bearing batteries of stinging cells (nematocysts) which are used for defence and capturing prey. Within each nematocyst is a spirally coiled thread that can be everted, uncoiled and forcibly ejected. In contact with prey, or with human skin, the nematocysts are discharged and the threads inject a venom. The nature and toxic effects of the venom vary with species. Many species inflict at least some discomfort on humans, and some are potentially dangerous [3–6].

Class Hydrozoa. This class includes the fire corals and free-floating members of the subclass Siphonophora. The Siphonophora are colonial organisms in which a number of individuals, specialized for different functions, are

structurally associated. Perhaps the best known siphonophoran is *Physalia*, the Portuguese man-of-war. This has the local name of 'bluebottle' in Australia. It has an air-filled float, which acts as a sail, and trailing tentacles. The nematocysts occur in 'batteries' or 'sting buttons' along the tentacles, and contact with them results in extrusion of numerous nematocysts and the inoculation of venom.

Class Cubozoa. Often referred to as 'box jellyfish'; several species are dangerous to humans [3]. The most notorious is *Chironex fleckeri*, which has been responsible for a number of deaths in Australian waters. Other dangerous species include *Carybdea rastoni* (the 'jimble'), and *Carukia barnesi* (the 'Irukandji') [7]. Another box jellyfish named 'Morbakka' has caused problems in the Moreton Bay area of South Queensland, Australia [8].

Class Scyphozoa. The medusa is the dominant form of the life cycle. Jellyfish of this class are distributed worldwide, and some have medical significance.

Class Anthozoa. This class contains several thousand species, including the sea anemones, the soft corals and the stony or true corals. Several species of sea anemone are known to inflict painful stings [2,3,9,10].

The reef-forming corals may cause injury to the skin with their nematocysts, or with their calcareous outer skeletons [11].

Clinical features [3,12,13]. Contact with *Physalia* tentacles usually results in a linear erythematous eruption accompanied by severe local pain. Because of the arrangement of 'sting buttons' of nematocysts, there is a beaded pattern of local small weals. In humans, pain and skin lesions are usually the limits of toxicity, but occasionally more severe reactions occur [14]. Haemolysis and acute renal failure in a 4-year-old girl [15], and fatalities, have been reported [16,17].

The local effects of box jellyfish tentacle contact are immediate severe pain, and linear weals with a white, ischaemic centre. Larger weals may have a typical 'cross-hatched' or 'frosted-ladder' pattern corresponding to the architecture of the tentacles. Partial or full-thickness skin necrosis may result. Box jellyfish may be responsible not only for local lesions, but also for severe systemic effects, which may result in death [3,7].

In addition to acute skin lesions, which are regarded as toxic in nature, there may be persistent or recurrent eruptions at the original sites of cnidarian envenomation [18–23], attributed to delayed hypersensitivity. Recurrent episodes may be single or multiple, and may take the form of erythema, urticarial lesions, papules or plaques. A delayed hypersensitivity response to jellyfish antigens has been demonstrated by a positive patch-test reaction to a nematocyst preparation from *Olindias sambaquiensis* [24].

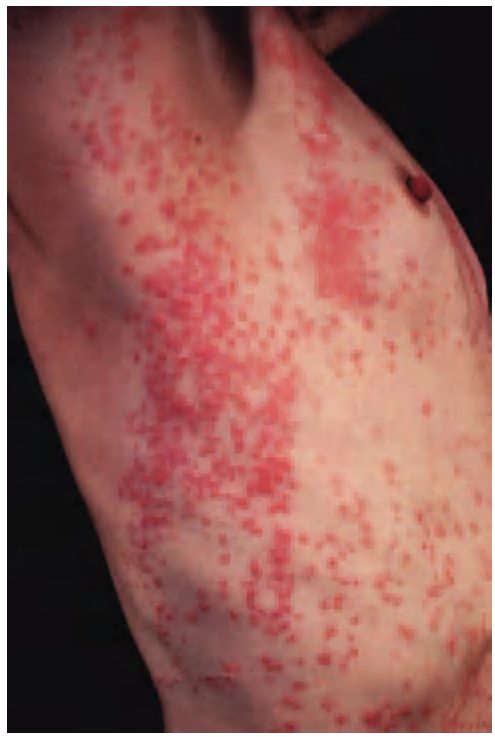

Fig. 33.40 Seabather's eruption. (Courtesy of Dr R. MacSween, Kingston, Ontario, Canada.)

Other reported sequelae of jellyfish stings include erythema nodosum [25], cold urticaria [26] and Mondor's disease [27].

Envenomation by fire corals usually produces immediate burning or stinging pain, followed by urticarial lesions at the site of contact. These may in turn be followed by a localized vesiculobullous eruption, and subsequently chronic granulomatous and lichenoid lesions [28–30]. Stinging of an aquarium shop worker by a stony coral, *Euphyllia picteti*, has been reported [31].

Seabather's eruption [32–37]. Itchy, erythematous papules and weals occur predominantly under swimwear, and lesions are usually concentrated in tight-fitting areas (Fig. 33.40). The organisms become trapped under the bathing costume, and discharge of nematocysts is triggered. It is probable that a similar clinical picture can be produced by different coelenterates in different waters. In Florida, the Gulf of Mexico and the Caribbean, *Linuche unguiculata* (thimble jellyfish) appears to be responsible, and evidence has recently been presented that all three free-swimming stages of this jellyfish can cause seabather's eruption [38]. Specific IgG antibodies against *L. unguiculata* antigen have been demonstrated by enzyme-linked immunosorbent assay (ELISA) in patients with seabather's eruption [39]. Cases in the Long Island region, New York, have been attributed to larvae of the sea anemone *Edwardsiella lineata* [32].

Pathology. The acute changes in the skin resulting from cnidarian stings consist of intracellular oedema of keratinocytes, many of which have pyknotic nuclei, and a lymphocytic infiltrate in an oedematous superficial dermis [40]. Nematocysts were visible penetrating the epidermis in a 5-year-old child who suffered fatal envenomation from *Chironex fleckeri* [41].

Histology of recurrent reactions shows a spongiotic vesicular dermatitis with a dense perivascular lymphohistiocytic infiltrate, often containing large numbers of eosinophils [20,42]. There is oedema of the papillary dermis. Immunohistochemical studies suggest that Langerhans' cells and helper T lymphocytes play a central role, and that type IV delayed hypersensitivity is involved in the pathogenesis of the lesions [42]. Epithelioid granulomas and large $CD30^+$ lymphocytes were present in a delayed reaction to a fire coral [43].

Treatment [3,44,45]. Inhibition of further discharge of nematocysts is an important aspect of first aid for some cnidarian stings. Vinegar inhibits discharge of the nematocysts of all the box jellyfish, and should be poured over the affected area of skin as soon as possible. However, in other jellyfish discharge is not inhibited, and may be provoked by vinegar.

The application of cold packs has been shown to provide relief of mild to moderate pain resulting from stings by *Physalia* and a number of species of jellyfish. An antivenom is available for use in *Chironex fleckeri* envenomation.

In Australia, protective clothing in the form of Lycra 'stinger suits' is extremely useful in the prevention of jellyfish envenomation.

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Sea mats (Bryozoa)

The Bryozoa are small, sedentary, colonial animals, which usually form mat-like encrustations on rocks, seaweeds or other surfaces. *Alcyonidium gelatinosum* occurs in the North Sea, where it can cause severe occupational dermatitis in fishermen who may have to remove large quantities from their nets. 'Dogger Bank itch' is an acute papular, occasionally bullous, contact dermatitis on the hands, arms and face [1–6], which may have a photoallergic component [7]. Hypersensitivity to another bryozoan, *Electra pilosa*, has also been described [7,8].

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Sea urchins (Echinoidea)

The Echinoidea, or sea urchins, form part of the phylum Echinodermata, which also includes the starfishes and sea cucumbers [1–3]. Sea urchins are usually spherical or ovoid, and are enclosed in a shell of closely fitting plates supplied with numerous moveable spines. The spines are formed by calcification of a cylindrical projection of subepidermal connective tissue. Situated between the spines are three-jawed pedicellariae, some of which are venomous. They are used to seize prey, and also in defence. In some species of sea urchins, the spines are also venomous.

Pathogenesis of skin lesions. Many species can cause unpleasant lesions of different types [4,5]—intense local pain and swelling following envenomation by spines or pedicellariae; secondary infection of the spine puncture wounds; development of implantation epidermoid cysts from fragments of epithelium driven into the wounds by the spines; late development of granulomatous skin lesions; synovitis, and joint damage if the spines penetrate joint cavities [6]. Occasionally, systemic upset accompanies the local changes.

Pathology [7]. In chronic lesions, a granulomatous inflammatory reaction predominates, with foreign-body or sarcoidal types the most frequent. Non-granulomatous chronic inflammation may also occur.

Clinical features [1,3–5]. Envenomation by sea urchins produces immediate burning pain, which may be very intense and persist for several hours. The degree of local swelling is variable, but is sometimes severe. In the absence of secondary infection, the puncture wounds heal within a week or two.

Delayed granulomatous reactions usually develop several months after the original injury, and take the form of bluish papules or nodules at the sites of penetration of the spines. On the digits, there may be diffuse fusiform swelling and limitation of movement. These lesions are very persistent if not treated.

A patient with a pruritic erythematous eruption on the knees and ankles following injury by a sea urchin produced a positive patch-test reaction to an extract of sea-urchin spines [8].

It has been suggested that *Mycobacterium marinum* may play a pathogenic role in some cases of sea urchin granuloma [9].

Treatment [4,5]. Immediate treatment consists of careful removal of spines and pedicellariae. Immersion of the affected area in hot water will provide pain relief. Local inhabitants in certain areas where sea-urchin injuries are common apply hot candle wax to the area [10]. The spines are difficult to remove surgically, but erbium–yttrium-aluminium-garnet (Er:YAG) laser ablation has proved effective [11]. If the spines have penetrated a joint, surgical exploration is advisable. The granulomatous lesions may be treated with intralesional steroid.

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Sponges (Porifera) [1,2]

Tedania ignis (the fire sponge) is capable of producing a severe dermatitis, and has also been reported as inducing erythema multiforme-like lesions of the face, palms and soles 10 days after contact [3]. Dermatitis may also be caused by several other sponges, including *Neofibularia nolitangere* (the poison bun sponge) and *Microciona prolifera* (the red sponge).

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Mollusca

The only important venomous univalve molluscs are cone shells of the genus *Conus* [1–3]. All the species of this genus possess a venom apparatus, and several species have caused human injury.

The stings are painful puncture wounds, with local ischaemia, cyanosis and numbness, the numbness quickly spreading to involve the whole body. The sting of some species, particularly *C. geographus* [2,4], may be fatal.

The very small floating mollusc *Creseis acicula* Rang has been incriminated as a cause of stings in bathers in Florida [5].

The tiny blue-ringed octopus (*Hapalochlaena maculosa*), a member of the Cephalopoda class of molluscs, and found mainly in Australian coastal waters, has been called the world's most deadly octopus. When agitated, the blue rings become very prominent. The bite of this octopus contains salivary toxins that may cause severe systemic symptoms culminating in death, usually from respiratory failure [6,7]. Cutaneous problems following *H. maculosa* bites include intense pruritus and urticaria [3,6,8].

Erythema, oedema and a burning sensation followed the bite of *Octopus apollyon*, succeeded by a persistent erythematous plaque and lymphoedema [9].

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Noxious or venomous vertebrates

Venomous fish [1–3]

Numerous species of fish are capable of inflicting painful or even dangerous stings by means of dorsal or caudal spines provided with complex venom glands.

Venomous species are not confined to tropical waters. The lesser weever fish, *Echiichthys vipera* [4,5], the spiny dogfish (*Squalus acanthias*) and several species of stingray occur on the Atlantic coasts, and can inflict serious stings.

In warmer waters, species of stingray, scorpionfish, catfish [6], rabbitfish, stonefish [7], the aptly named 'bearded ghoul', stargazers and toadfish are potentially dangerous. In many cases, injuries are the result of the victim inadvertently stepping on the fish in shallow water. The tail of the stingray carries serrated spines containing venom glands surrounded by an integumentary sheath. Treading on the fish results in a reflex 'whip' of the tail, which drives the spines into the skin, usually on the leg [8]. Several of these venomous species bury themselves in the sand in shallow waters, with their spines protruding, and are therefore a hazard to bathers.

Clinical features. Injuries commonly occur on the feet or legs, as a result of the victim stepping on the fish. Fish stings are usually immediately painful. They present as painful lacerations or puncture wounds. Intense pain may continue for several hours, and swelling and erythema around the wounds may simulate an infective cellulitis. With some species, systemic symptoms may occur. Stingray spines may cause lacerations, or may be driven into the skin and break off. If the integumentary sheath ruptures, envenomation occurs. In severe stingray wounds, the affected area appears dusky or cyanotic, and later becomes erythematous or mottled, with necrosis of underlying fat and muscle [9].

The inflammatory infiltrate in one case of stingray envenomation contained numerous mononuclear cells, many of which were TIA+, suggesting that an immunological reaction might contribute to the delayed healing commonly seen after stingray injury [10].

Treatment. The venom of the weever fish, like that of the stingray, stonefish and other venomous fish, is an unstable protein which is heat-labile, and hot water is very effective in treating the stings [3,11–13]. The injured part should be immersed in hot water (someone other than the

victim should gauge the temperature), and this will diminish the pain. An antivenom is available for stonefish stings.

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Snake bites

The highest incidence of snake bites is in South America, West Africa, the Indian subcontinent and South-East Asia [1,2]. In India, there are an estimated 10 000–50 000 deaths a year, and in Burma, snake bites cause about 1000 deaths a year [3].

The effects of snake envenomation vary according to the composition of the venom—for example, bites of the spitting cobra (*Naja nigricollis*) produce local swelling and necrosis, haematological abnormalities and complement depletion [4]; the venom of the Malayan krait (*Bungarus candidus*) contains a toxin (bungarotoxin) that interferes with transmission at the neuromuscular junction [5]; marked coagulation disturbances occur after envenomation by Australian brown snakes (genus *Pseudonaja*) [6]. Surveys of deaths from snake bite in Australia [7,8] have shown that the majority were due to brown snakes.

Treatment [8]. The first-aid and field management of victims of snake bites in Australia changed when the compression bandage–splinting method of first-aid treatment was introduced by Sutherland [9], and shown to be effective [10]. This method consists of the application of a firm compression bandage to the limb that has sustained the bite, and its immobilization by splinting. The centripetal flow of venom is markedly impeded by this procedure. The offending snake should be killed if possible, and kept for identification by a qualified herpetologist. If the snake cannot be identified, venom detection kits are used on swabs taken from the bite site to determine the appropriate antivenom. Unfortunately, there is limited availability of antivenoms in other parts of the world [3].

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Other animal bites

An enormous variety of other animals may occasionally bite humans. Most bites cause a variable degree of crushing and tearing of the skin, and the devitalized tissue readily becomes infected by the wide range of microorganisms found in the mouths of animals.

Dog and cat bites

The highest incidence of dog bites occurs in school-aged children [1], and boys are bitten twice as often as girls. In contrast, wounds caused by cats occur more commonly in girls [2].

Most infections which develop from dog and cat bites are polymicrobial, and include aerobic (*Staphylococcus* species, *Streptococcus* species and *Corynebacterium* species) and anaerobic (*Bacteroides fragilis*, *Prevotella*, *Porphyromonas*, *Peptostreptococcus*, *Fusobacterium* species and *Veillonella parvula*) organisms. Cat scratch disease, caused by *Bartonella henselae*, can follow a bite from a cat. There are a number of other potentially pathogenic organisms, including those described below.

Capnocytophaga (formerly dysgonic fermenter type 2) [3–10]

Capnocytophaga canimorsus is part of the normal oral flora of healthy dogs, cats and a number of other animals.

The majority of reported *Capnocytophaga* infections have been associated with exposure to animals, about 80% following exposure to or bites from dogs. Previous splenectomy and alcoholism are predisposing factors, but infection may occur in perfectly healthy persons.

The spectrum of illness ranges from local wound infection to fulminant septicaemia. Skin lesions include a localized eschar at the site of the bite, cellulitis, non-specific macular or maculopapular lesions, erythema multiforme [4], petechiae, purpura fulminans and symmetrical peripheral gangrene. The more severe changes occur as a consequence of septicaemia and disseminated intravascular coagulation [8–10].

Confirmation of infection depends upon identifying intracellular bacilli on direct microscopy by Gram staining of blood films and buffy coats, and isolation from blood and tissue cultures [5]. The organism is sensitive *in vitro* to most penicillins, cephalosporins, erythromycin, tetracyclines and clindamycin.

Eugonic fermenting bacteria (EF-4)

Organisms belonging to this *Pasteurella*-like group are frequently present in the oral and nasal fluids of dogs. EF-4 bacteria have been isolated from abscesses caused by animal bites [11], but only rarely cause any human pathology.

Pasteurella multocida [3,5,12,13]

This is an aerobic Gram-negative coccobacillus, which is also a normal component of the oral flora of dogs and cats. Bites or scratches which become infected are usually complicated by inflammation and a purulent discharge. Abscess formation, tenosynovitis, septic arthritis and osteomyelitis may also occur.

Pasteurella multocida is sensitive to penicillins, cephalosporins, tetracyclines and ciprofloxacin.

Seal finger [14–16]

Seal finger may be encountered wherever sealing takes place, especially around Greenland, Newfoundland and Spitzbergen, but it also occurs in the Falkland Islands and South Georgia. In Denmark, the disease occurs sporadically from the bites of seal pups, but it is also acquired by handling dead animals. A case has been reported in a veterinary surgeon from Norfolk, UK, after he had performed a necropsy on a seal [15]. It is common in the spring in seal trainers at the New England Aquarium in Boston, Massachusetts, and although the aetiological agent has not been established with certainty, *Mycoplasma* species were isolated from an infected seal trainer, who responded to treatment with tetracycline [16].

The usual clinical picture is of a painful, swollen, slightly erythematous finger. There are usually no constitutional symptoms. Many cases resolve spontaneously with no sequelae, but in others joint involvement may lead to synovitis, osteitis, fibrosis of periarticular tissues and disfiguring arthropathy.

Rodent bites

There are a number of reports of anaphylaxis following rodent bites [17–19].

Human bites

Human bites are quite common, clenched fist injuries ('fight bites') being the most prevalent, and may introduce dangerous bacterial infection [3]. Necrotizing fasciitis caused by group A streptococci has resulted from a human bite on the calf (at a Bavarian Oktoberfest!) [20]. Transmission of herpesvirus types 1 and 2, and of hepatitis B and C, has also been documented. An epidemic of hepatitis B was traced to a carrier in a residential institution for the mentally retarded who regularly bit his fellow residents [21]. Biting is also a possible transmission mode for HIV infection [22].

A traumatic neuroma following a human bite on the forearm has been reported [23].

The possibility of physical abuse should be considered in children with human bites. However, most bites in children are inflicted by other children [24].

Treatment [1,25,26]. All animal and human bites are potentially dangerous, and thorough irrigation with normal saline, exploration and debridement are required. Prophylactic antibiotics are given in some cases. If infection develops, appropriate antibiotics for *Pasteurella multocida*, staphylococci and streptococci should be administered.

Rabies should be considered as a possible sequel to any animal bite if this occurs in countries in which the disease is endemic.

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Chapter 34

Disorders of Keratinization

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The molecular genetics of keratinizing disorders

Classification of keratinizing disorders. The term 'disorders of keratinization' refers to a broad spectrum of skin disorders where there is abnormal differentiation of the epidermis and/or appendages, often with aberrant formation of the cornified envelope [1]. These disorders may have associated epidermal fragility, and there is clinical and pathological overlap with inherited and acquired blistering disorders (see Chapters 40 and 41). Epidermal and/or adnexal defects may exist in isolation or can also be associated with additional extracutaneous features. The pathogenesis of many of the acquired disorders included in this chapter is poorly understood and may prove to encompass a variety of infective, inflammatory or other causes. However, many disorders of keratinization are inherited as single-gene Mendelian traits, and understanding their aetiology has permitted re-evaluation of their classification. Traditionally, this group of diseases has been classified according to clinical, histological and ultrastructural findings. As the majority of the genetically determined disorders are uncommon in the population, the morphological approach has been beneficial to the practising clinician and offers a logical pathway to diagnosis when confronted with a patient with an

unknown disorder. Remarkable advances have been made in molecular genetic technology during the past decade or so, stemming from the development of the polymerase chain reaction (PCR) technology and related techniques from the late 1980s onwards [2]. This technology facilitates rapid amplification and DNA sequencing (decoding) of genes and parts thereof, using minute amounts of patient DNA as the starting material. This, coupled with the recent advances in the mapping and near-complete sequencing of the entire human genome, have led to a rapid increase in understanding the basic molecular defects responsible for inherited disorders of keratinization, and these advances have made possible a new, molecular mechanism-based approach to their classification, which complements the pre-existing morphological classification system (Table 34.1). These molecular genetic and biological insights have in many cases confirmed the accuracy of the original clinical distinctions. As knowledge increases, however, the association of mutations in one gene with a distinct phenotype has become more complicated, as illustrated below.

Genotype–phenotype correlation. A good example of phenotypic heterogeneity arising from mutations in a single gene is that of keratin K1. Heterozygous dominant negative mutations in suprabasal keratins K1 and K10 were initially reported to be the genetic basis of bullous ichthyosiform erythroderma of Brocq (BIE) [3,4]. These mutations were strongly clustered in parts of the keratin molecule that are known to be critical for keratin assembly and function (see Intermediate Filament Mutation database; http://www.interfil.org). In an early genetic study of a family with a quite typical BIE mutation in K1, there were mildly and severely affected persons within one family, all of whom had inherited the same mutation [5]. Later, in a family originally diagnosed by Brocq himself as having a consistently milder BIE phenotype, a mutation was found in a region of the K1 protein, linker L12, where mutations in other keratins produced milder phenotypes [6]. Later still, larger deletion and insertion mutations have been identified in K1 that produce primarily palmoplantar keratoderma [7,8]. The latter phenotype is easily confused with the Vörner form of epidermolytic palmoplantar keratoderma (EPPK) resulting from K9 mutations [9]. Certain mutations have also been associated with mild annular [10] and polycyclic erythematous forms of BIE [11]. More recently, a frameshift mutation affecting only the V2 domain of K1 was shown to consistently produce a phenotype closely resembling ichthyosis hystrix of Curth–Macklin in an African American kindred [12]. In contrast, an almost identical frameshift in K1 produced a very much milder striate keratoderma phenotype in a British Caucasian kindred [13]. In each of the phenotypes associated with these K1 mutations, there is histological evidence of epidermolytic hyperkeratosis (EHK) and ultrastructural evidence of suprabasal tonofilament disruption; however, the tissue distribution and severity of EHK is quite variable. Similar complexity of genotype–phenotype correlation has been identified in disorders caused by mutations in desmosomal proteins and connexins.

There are a number of lessons from these studies. First, mutations affecting different parts of a gene (and thus specific protein domains) can lead to radically different phenotypes. Secondly, there can be phenotypic variation between families carrying similar mutations, and even within one family where all affected persons have the same mutation. The source of phenotypic variation is presumed to be a result of a combination of unknown genetic modifying factors and environmental influences. Thirdly, there can in some instances be ethnic variation in phenotypes resulting from similar or identical mutations. In this case, there is possibly a greater scope for variation in both genetic background and environmental factors. As time goes on and more cases are studied at the molecular level in close consultation with experienced clinicians, greater insights will be gained into the molecular basis and classification of these diseases, as well as the subtle functions not just of proteins but of individual protein domains in epithelial biology.

The biology of keratinization revealed through genetics. Over the last decade, a great deal has been learned about the basic cell biology of epidermal differentiation and keratinization through the study of genetic disorders of this biological system. The various classes of molecules shown to be involved in this system, along with their respective genetic diseases, are listed in Table 34.1. Some of the defective molecules have a mainly structural role in maintaining the mechanical integrity of the epidermis and its appendages in the face of persistent physical trauma. The keratin intermediate filament cytoskeleton has been shown to be a major player in providing mechanical strength for epithelial cells. To date, mutations in 18 keratin genes are linked to cell fragility syndromes affecting the epidermis, adnexae and other epithelia [14]. Similarly, mutations in keratin-associated proteins, such as desmosomal proteins and molecules involved in the cross-linking of keratins during cornification, such as loricrin, have been linked to other keratinizing disorders [15]. Defects in molecules involved in regulating the movement of ions and other small molecules between cells of the epidermis have also been linked to a range of keratinizing disorders, including gap junction proteins [16] and calcium pump molecules [17]. Calcium metabolism plays an important part in the control of epidermal differentiation [18], as evidenced by the phenotype of Darier's disease. Similarly, there is a range of enzymes involved in lipid metabolism, which is integral to the production of the cornified cell envelope (a highly cross-linked protein–

Table 34.1 Known gene defects in disorders of keratinization.

Disorder	Genes affected	Further information
Keratin disorders		
Annular epidermolytic ichthyosis variant of BCIE and cyclic ichthyosis	*KRT10, KRT1*	Suprabasal keratin 10 (chr 17q12–q21) for annular variant; keratin 1 for cyclic ichthyosis (chr 12q11–q13)
Bullous congenital ichthyosiform erythroderma (BCIE)	*KRT1, KRT10*	Suprabasal keratins 1 and 10 (chr 12q11–q13 and 17q12–q21)
BCIE naevus	*KRT10, KRT1*	Keratin 10 (chr 17q12–q21) and keratin 1 (chr 12q11–q13)
Diffuse non-epidermolytic palmoplantar keratoderma	*KRT1*	Keratin 1 (chr 12q11–q13)
Epidermolytic palmoplantar keratoderma	*KRT9*	Keratin 9 (type I keratin; chr 17q12–q21). Keratin specific for palm and sole skin
Focal non-epidermolytic palmoplantar keratoderma	*KRT16*	Keratin 16 (chr 17q12–q21). Constitutive expression in palm and sole epidermis and other sites
Pachyonychia congenita type 1 (PC-1; Jadassohn–Lewandowsky form)	*KRT6A, KRT16*	Dominant-negative mutations in differentiation-specific keratins K6a (chr 12q11–q13) or K16 (chr 17q12–q21)
Pachyonychia congenita type 2 (PC-2; Jackson–Lawler form)	*KRT6B, KRT17A*	Dominant-negative mutations in differentiation-specific keratins K6b (chr 12q11–q13) or K17 (chr 17q12–q21)
Steatocystoma multiplex	*KRT17A*	K17 (chr 17q12–q21). Some cases appear to be allelic variant of PC-2
Ichthyosis bullosa of Siemens (IBS)	*KRT2E*	Epidermal keratin 2 (chr 12q11–q13). Expressed in late suprabasal cells of epidermis
Ichthyosis hystrix (Curth–Macklin)	*KRT1*	Frameshift mutation in V2 domain of keratin 1 (chr 12q11–q13)
Striate palmoplantar keratoderma	*KRT1*	Frameshift mutation in V2 domain of keratin 1, almost identical to IHCM defect, above (chr 12q11–q13)
Desmosome proteins		
Dilated cardiomyopathy with woolly hair and keratoderma	*DSP*	Desmoplakin 1 (chr 6p2)
Ectodermal dysplasia with skin fragility	*PKP1*	Plakophilin 1 (chr 1q)
Naxos disease	*JUP*	Plakoglobin, component of desmosome and adherens junction (chr 17q21)
Striate palmoplantar keratoderma	*DSG1, DSP, KRT1*	Desmoglein 1, a desmosomal cadherin (chr 18q12.1) Desmoplakin 1, role in attachment of intermediate filaments to the desmosome (chr 6p2)
Cornified cell envelope proteins		
Loricrin keratoderma (Vohwinkel's syndrome: ichthyotic/Camisa variant)	*LOR*	Loricrin, component of cornified cell envelope (chr 1q21). One pedigree presented as progressive symmetric erythrokeratoderma (PSEK)
Gap junction proteins		
Clouston's syndrome (hidrotic ectodermal dysplasia 2)	*GJB6*	Connexin 30 (chr 13q12)
Erythrokeratoderma variabilis (EKV)	*GJB3*	Connexin 31 (chr 1p35.1)
EKV with erythema gyratum repens	*GJB4*	Connexin 30.3 (chr 1p35.1)
Palmoplantar keratoderma and deafness	*GJB2*	Connexin 26 (chr 13q11–q12)
Vohwinkel's syndrome (classic variant, with deafness)	*GJB2*	Connexin 26 (chr 13q11–q12)

(*continued overleaf*)

Table 34.1 (*cont'd*)

Disorder	Genes affected	Further information
Calcium pump defects		
Darier's disease	*ATP2A2*	Sarcoplasmic/endoplasmic reticulum calcium ATPase (SERCA2) (chr 12q24.1)
Hailey–Hailey disease	*ATP2C1*	Calcium transporting ATPase (chr 3q21–q24)
Metabolic and enzyme defects		
Chanarin–Dorfman syndrome	*CGI-58*	CGI-58 (chr 3), CGI protein of the esterase/lipase/thioesterase subfamily
CHILD syndrome (congenital hemidysplasia, ichthyosis and limb defects)	*NSDHL, EBP*	3β-hydroxysteroid dehydrogenase, an enzyme in cholesterol biosynthesis (chr Xq28). Mouse mutant, bare patches Mutations also reported in 3β-hydroxysteroid-δ8, δ7 isomerase
Haim–Munk syndrome	*CTSC*	Cathepsin C (see below)
Lamellar ichthyosis (LI1, LI2, LI3)	*TGM1*	LI1, keratinocyte transglutaminase I (chr 14q11.2) cross-linking enzyme in cornified envelope formation LI2 (chr 2q33–q35) LI3 (chr 19p12–q12)
Netherton's syndrome	*SPINK5*	Serine protease inhibitor LEKTI (chr 5q32)
Papillon–Léfèvre syndrome	*CTSC*	Cathepsin C, a lysosomal protease (chr 11q14.1–14.3)
Refsum's disease	*PAHX*	Phytanoyl-CoA hydroxylase (chr 10pter–p11.2), a PTS2 protein
Rhizomelic chondrodysplasia punctata type I	*PEX7*	Encoding the peroxisomal matrix protein with type 2 peroxisome targeting signal (PTS2) receptor (chr 6q22–q24)
Richner–Hanhart (tyrosine transaminase deficiency)	*TAT*	Tyrosine aminotransferase (chr 16q22)
Sjögren–Larsson syndrome	*FALDH* (also known as *ALDH10* or *ALDH3A2*)	Fatty aldehyde dehydrogenase (chr 17p11.2). Microsomal enzyme that catalyses medium and long-chain aliphatic aldehyde oxidation
X-linked icthyosis (steroid sulphatase deficiency)	*STS* (also known as *ARSC*)	Arylsulphatase C gene (chr Xp22.32)
X-linked recessive chondrodysplasia punctata	*ARSE*	Arylsulphatase E gene (chr Xp22.3) resulting in steroid sulphatase deficiency
X-linked dominant chondrodysplasia punctata (CDPX2) or Conradi–Hünermann syndrome	*EBP*	Emopamil binding protein, 3β-hydroxysteroid-δ8, δ7 isomerase. Role in cholesterol biosynthesis (chr Xp11.22–p11.23). Mouse model, tattered
Secreted protein		
Mal de Meleda	*ARSB*	Encodes SLURP-1 (chr 8q24.3)

lipid barrier structure), during the terminal differentiation of the epidermis. Proteins involved in this process include transglutaminase-1, which controls cross-linking of keratins and other structural proteins [19], SPINK5, which is a protease inhibitor of unknown specificity [20], as well as a range of enzymes important in lipid synthesis and modification. Finally, some completely unexpected molecules have been turned up by positional cloning efforts, such as SLURP-1, a novel secreted protein whose absence leads to mal de Meleda [21].

In conclusion, the field of keratinizing disorders as it stands today represents a close marriage between clinical and morphological observations and molecular and cell biology. This union of medicine and science has led to improved classification and diagnosis, including first trimester prenatal genetic testing, accurate genetic counselling and hopefully in the future, an informed mechanistic approach to the design of new therapeutic agents for this group of diseases.

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Ichthyosis

Definition. Ichthyosis describes dry, rough skin with scaling over much of the body (Greek *ichthys/ikhthus*, fish + -osis). The ichthyoses are a clinically and genetically heterogeneous group of skin disorders, characterized by a diffuse, uniform, generally persistent pattern of scaling without mucosal involvement or extracutaneous disease. They are divided into congenital or genetic forms, namely primary ichthyoses, a number of rare ichthyosiform or ichthyotic syndromes, and individual cases that do not fit into either category, and acquired ichthyosis which is a complication of several systemic and malignant diseases (Table 34.2). They range in severity from mild ichthyosis vulgaris to erythrodermic forms and severe, often lethal, harlequin ichthyosis. Epidermal fragility is a feature of specific keratin mutations, while pruritus and atopy are prominent signs in Netherton's syndrome.

Ichthyosis is classified as a disorder of keratinization or cornification resulting from abnormal epidermal differentiation or metabolism. Defective epidermal desquamation is a feature of some ichthyoses while a prominent inflammatory component occurs in others, usually associated with epidermal hyperproliferation. Ultrastructural and molecular studies have informed a more accurate diagnosis and classification of the ichthyoses, shed light on pathogenetic mechanisms, and indirectly revealed a great deal about the structure and function of the normal epidermis.

History and classification. The first historic reference to ichthyosis appears in an Indian text in 250 BC, where there is mention of 'Ekakushtha, skin disease like scales of a fish' [1]. Reports of the 'porcupine men' in the 1730s highlighted the severity and familial occurrence of hystrix-type ichthyosis [2]. The first account of a harlequin (ichthyosis) fetus was written in 1750 [3]. In his treatise, *On Cutaneous Diseases*, Willan classified ichthyosis as a 'squamous disease' [4] and attempts at genetic classifications followed [5]. Brocq [6] first used the label 'congenital ichthyosiform erythroderma', and distinguished between bullous and non-bullous ichthyosiform erythroderma. The characteristic histological features of bullous ichthyosiform erythroderma were described by Lapiere [7], and

Table 34.2 Congenital and acquired ichthyoses.

Ichthyosis vulgaris (syn. autosomal dominant ichthyosis)
X-linked recessive ichthyosis (steroid sulphatase deficiency)
Non-bullous ichthyosiform erythroderma
Lamellar ichthyosis
Harlequin ichthyosis
Bullous ichthyosiform erythroderma (syn. epidermolytic hyperkeratosis)
Ichthyosis bullosa of Siemens (see erythrokeratolysis)
Ichthyosis hystrix
Ichthyosiform syndromes
Netherton's syndrome (syn. ichthyosis linearis circumflexa)
Sjögren–Larsson syndrome
Neutral lipid storage disease (syn. Chanarin –Dorfman syndrome)
Refsum's disease
Kallman's syndrome
Multiple sulphatase deficiency syndrome
X-linked dominant ichthyosis (syn. Conradi–Hünermann syndrome)
IBIDS (syn. Tay's syndrome, trichothiodystrophy, PIBIDS)
KID syndrome (keratitis, ichthyosis, deafness)
CHILD syndrome (congenital hemidysplasia, ichthyosiform erythroderma, unilateral limb defects)
Ichthyosis follicularis with alopecia and photophobia (IFAP)
Congenital ichthyosis variants
Isolated genetic syndromes with ichthyosis (case reports)
Acquired ichthyosis
Drugs (e.g. nicotinic acid, hypocholesterolaemic agents, maprotiline)
Chronic hepatic disease, renal failure, thyroid and parathyroid disease
Malabsorption states
Sarcoidosis, leprosy
Acquired immune deficiency syndrome (AIDS)
Lymphoma and other malignancies

subsequently termed epidermolytic hyperkeratosis [8]. Cockayne [5] regarded sex-linked ichthyosis as a separate entity, and lamellar ichthyosis as a recessive condition. Wells [9] differentiated X-linked and autosomal dominant ichthyosis vulgaris in an epidemiological survey. Recognition of ichthyosiform syndromes such as Refsum's disease, Netherton's and Sjögren–Larsson syndromes has come through astute clinical observation.

Early classifications depended on descriptive analogies, such as ichthyosis larvata, tarda, mitis and inversa. Wells and Kerr [9] defined groups of ichthyoses with autosomal recessive, sex-linked and autosomal dominant inheritance patterns, and clearly established X-linked recessive ichthyosis as a separate entity. Esterly [10] identified four categories of ichthyosis; major primary forms (ichthyosis vulgaris, recessive X-linked ichthyosis, bullous ichthyosis and congenital ichthyosiform erythroderma), ichthyosiform syndromes, related disorders of cornification and acquired ichthyoses.

Frost and van Scott [8] used epidermal kinetic data to characterize hyperproliferative (erythrodermic) and retention ichthyoses (ichthyosis vulgaris, X-linked ichthyosis). A numerical approach to 'disorders of cornification' lists 24 conditions (DOC 1–24), including the congenital ichthyoses and diverse diseases such as Darier's disease, peeling skin syndrome and the erythrokeratodermas [11]. Anton-Lamprecht and Schnyder [12] detailed subtle ultrastructural features of congenital ichthyosiform erythrodermas, and subdivided them into types 1–5. Traupe [13] identified four main categories: isolated vulgar ichthyoses, including ichthyosis vulgaris and X-linked recessive ichthyosis; associated ichthyoses of the vulgar type, such as Refsum's disease; isolated congenital ichthyoses, such as harlequin fetus, non-bullous ichthyosis and epidermolytic ichthyoses; and associated congenital ichthyoses, such as Sjögren–Larsson and Netherton's syndromes, IBIDS and X-linked dominant ichthyosis.

Elucidation of the underlying molecular abnormalities in ichthyoses will lead to a more logical and mechanistic classification and reveal previously unsuspected heterogeneity.

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The epidermis in health and ichthyosis. Epidermal differentiation is characterized by the synthesis and post-translational modification of many structural proteins, in particular, the proteins constituting the cornified cell envelope and enclosed aggregated keratin filaments, which are the major components of the stratum corneum. Envelope precursors, such as involucrin, loricrin, small proline-rich proteins and envoplakin, are synthesized late in stratification and then cross-linked by the action of transglutaminase enzymes, which are synthesized in the granular layer. The corneocyte protein envelope is linked covalently to an outer ceramide layer, the lipid envelope, which also contains a variety of membrane-associated glycoproteins such as the integrins. Desmosomes are

modified in the stratum corneum to form an electron-dense plug, the corneosome. In normal skin, desmosome density and cohesion lessens in transit from lower to upper stratum corneum, but in hyperkeratotic states this does not occur [1]. Keratin macrofibrils are aggregated by interaction with filaggrin (filament aggregating protein), a basic histidine-rich protein stored as profilaggrin in keratohyaline granules. Keratin intermediate filaments are the major stress-bearing cytoskeletal proteins of mammalian epithelial cells, the product of two gene families encoding type I (acidic) and type II (neutral-basic) polypeptides, which are coexpressed in particular pairs in a tissue-specific and differentiation-related manner.

The intercellular spaces of the stratum corneum contain lipid-rich multilayered lamellae, which are secreted by lamellar or Odland bodies, present in large numbers in the cytoplasm of the granular layer. At the granular–corneal junction, the lamellar body gravitates to the apex of the granular cell, and secretes its disc-like contents into the intercellular spaces [2]. The lipid-rich layers are redistributed into multilayered lamellae, composed of alternating electron-dense and electron-lucent lipid bands. Evidence suggests that these structures are formed by the condensation of liposomes under the influence of ceramides (sphingolipids that contain the n6 essential fatty acid, linoleic acid), which span the layers acting as rivets. They are also rich in non-polar lipids; free sterols including cholesterol sulphate, free fatty acids and triglycerides, and contain hydrolytic enzymes [3,4]. Conversion to cholesterol by cholesterol sulphatase, present on the cell membrane surface, leads to breakdown of the intercellular lipid lamellae and resultant desquamation [5]. Stratum corneum barrier function is dependent on the intercellular lipid lamellae, and increased transepidermal water loss is a characteristic feature of ichthyosis [6].

The importance of lipid metabolism in epidermal structure and function was first noted in 1929, when an animal model deprived of dietary essential fatty acids developed hyperkeratosis, abnormal desquamation and increased transepidermal water loss [7]. In the 1950s, the lipid-lowering drugs nicotinic acid and triparanol caused a reversible ichthyosis in some patients [8]. An inherited enzyme deficiency was identified in the 1960s as the cause of Refsum's disease [9] and cholesterol sulphatase deficiency in patients with X-linked recessive ichthyosis was reported in 1976 [10]. Sjögren–Larsson syndrome, another ichthyosiform disorder with neurological disease, is associated with fatty alcohol defects [11], while peroxisomal dysfunction, specifically abnormal sterol biosynthesis, has been identified in patients with Conradi–Hünermann and CHILD syndromes [12,13].

Disordered keratinization also results from alterations in structural proteins, including individual keratins, cornified envelope proteins and keratin-associated proteins (Table 34.1). Enzyme and metabolic defects (e.g. loss of transglutaminase activity in lamellar ichthyosis) and abnormalities in gap junction proteins (connexin mutations in the keratitis–ichthyosis–deafness (KID) syndrome) have been identified in diverse ichthyoses [14]. Several ichthyoses are associated with hyperproliferative and inflammatory features. Chronic barrier damage induces keratinocyte DNA synthesis and results in epidermal hyperplasia [15], with knock-on effects on the activity of cytokines, growth factors, calcium gradients, adhesion molecules and lytic enzymes. The identification of a serine protease inhibitor mutation in Netherton's syndrome and defects in lipoxygenase activity in an erythrodermic ichthyosis provide further insights into the occurrence of inflammatory changes [16].

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Congenital ichthyoses

Ichthyosis vulgaris (MIM 1467000)

SYN. AUTOSOMAL DOMINANT ICHTHYOSIS

Ichthyosis vulgaris is the most common of the inherited ichthyoses, with a reported incidence of 1 in 250 in an

English population study of 6051 healthy schoolchildren [1]. It is an autosomal dominant condition, and in the majority of affected individuals it is considered mild and may clear completely in the summer months. It appears to be more common in temperate climates and has an equal sex distribution. There is said to be a close association between ichthyosis vulgaris and atopic diseases; 37–50% of people who have ichthyosis vulgaris show features of atopic disease [1–3]. However, the difficulty in distinguishing ichthyosis vulgaris from the xerosis of atopic eczema on clinical grounds may result in an overestimate of both its frequency and its correlation with atopic eczema [4].

Histopathology. Histology of affected skin shows a mild hyperkeratosis and, usually, a diminished or absent granular layer in the epidermis. The dermis is normal. Features of keratosis pilaris may be seen. Electron microscopy reveals scanty and fragmented keratohyaline granules in granular layer cells, whereas the keratin filaments appear normal [5]. The proposed association between ichthyosis vulgaris and atopic eczema has been questioned on histological grounds, as eczematous features are found in biopsies of atopic xerosis [6]. Furthermore, ultrastructural study of xerotic lesions in 49 patients with atopic eczema and dry skin showed typical features of ichthyosis vulgaris in only two [4].

Aetiology and pathogenesis. Biochemical studies indicate that, in affected skin only, uptake of radiolabelled histidine by the granular layer is reduced [7]. Histidine is necessary for the synthesis of profilaggrin, the high-molecular-weight precursor of filaggrin, which is a major component of the keratohyaline granule and necessary for keratin filament assembly. Profilaggrin is virtually absent from the epidermis and from cultured keratinocytes (in those patients with no granular layer or keratohyaline granules) in ichthyosis vulgaris [7,8], and expression of filaggrin mRNA is reduced [9]. Cultured keratinocytes from unaffected skin formed thickened layers, with small keratohyaline bodies, and failed to react with monoclonal antibody to filaggrin [10]. Keratin expression and markers of differentiation are normal [11], and proliferative activity is reduced [12]. *In vitro* transfection studies using antisense profilaggrin RNA produced more widespread effects than occur in ichthyosis vulgaris [13], and a primary abnormality of the profilaggrin gene has not been shown by linkage analysis or mutational studies. There may be selectively impaired post-transcriptional control of profilaggrin synthesis [9], or the profilaggrin gene may be influenced by other mutated genes [8]. In addition, a mouse mutant lacking profilaggrin expression has been shown to be a good animal model for ichthyosis vulgaris, adding further circumstantial evidence of involvement of this gene and/or protein system in the human condition [14].

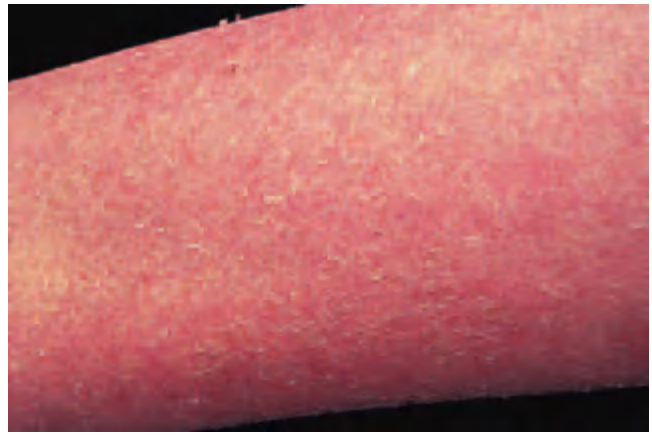

Fig. 34.1 Ichthyosis vulgaris.

Amino-acid breakdown products of filaggrin and some of their metabolites are able to retain water in the outer stratum corneum, and their deficiency may contribute to the scaling [15]. No consistent lipid abnormality has yet been found in ichthyosis vulgaris, although stratum corneum ceramides are reduced in atopic eczema, in lesional and xerotic skin [16]. A defect in serine proteases involved in the degradation of desmoglein 1, a transmembrane desmosomal protein, has been reported [17].

Clinical features. The skin may appear dry and scaly in the neonatal period, but more usually scaling is obvious from 2 months onwards and may be further delayed. The scale is white or grey, small, flaky or branny, and semi-adherent with turned-up edges (Fig. 34.1). It is most pronounced on the extensor surfaces of the arms and lower legs, and characteristically spares the flexural creases. The trunk, especially the abdominal wall, is often mildly affected and the nappy (diaper) area is spared. Facial scaling, generally forehead and perioral, mild dandruff and involvement of the pinnae are seen in some patients. The palms and soles are usually free of scale, but palmoplantar hyperlinearity (linear grooves crossing perpendicularly to the thenar and hypothenar eminences), a reflection of mild hyperkeratosis, is a helpful feature in many ichthyosis vulgaris patients, whether they have coexistent eczema or not [18]. It also occurs in atopic eczema without ichthyosis [4,19]. Keratosis pilaris is a common associated feature of both atopic eczema and ichthyosis vulgaris, and favours the extensor aspects of the upper arms and thighs.

Symptoms of ichthyosis vulgaris are few, mainly dryness or roughness of the skin and the cosmetic effect. In isolated ichthyosis vulgaris, pruritus is not a problem, but in patients who also have eczema, flexural lichenification and pruritus with excoriation are additional features. In these patients, a definite diagnosis of ichthyosis vulgaris as distinct from atopic xerosis can only be made on skin

histology. There is a marked seasonal variation in most patients, with improvement in warm and sunny weather, possibly as a result of ambient humidity. Many sufferers (38% of 169 patients) report a gradual improvement in adolescence [1], although a small number worsen with age. Reports of ocular manifestations and testicular cancer in ichthyosis vulgaris have not been verified, and may have arisen from inclusion of X-linked ichthyosis cases [20,21].

Diagnosis. Ichthyosis vulgaris may be mistaken for atopic xerosis, eczéma craquelé, acquired ichthyosis, Refsum's disease and a mild autosomal recessive variant reported in five of eight siblings [22].

Genetics. Ichthyosis vulgaris is an autosomal dominant disease with variable penetrance, such that disease severity can vary between generations, and affected siblings. Despite the fact that this condition is relatively common [1], an unequivocal gene locus awaits identification. The highly repetitive structure of the profilaggrin genes means that mutation analysis is difficult, a factor that has hampered attempts to link these genes to the disorder, despite compelling evidence from studies of a mouse model lacking this gene [14]. When ichthyosis vulgaris occurs with atopic eczema, gene linkage or contiguous gene defects are possible causes.

Treatment. As a general measure, avoiding low humidity environments is of benefit to all ichthyosis patients. Regular emollient application is recommended for those with ichthyosis vulgaris, and if provided with samples of a variety of suitable preparations, patients can make their own choice as to the most acceptable and appropriate for a given situation. Many do not require treatment in the summer as they spontaneously improve. In drier, colder seasons, mild and moderately affected subjects may opt to use a light emollient, such as aqueous cream, which can also be applied as a soap substitute. More severely affected individuals may prefer paraffin-based (mixtures of white soft and liquid paraffin) or cetostearyl alcohol-containing emollients, of which there are many proprietary brands. It should be borne in mind that greasy emollients such as emulsifying ointment have adverse effects on certain fabrics and washing machines.

Emollients need to be applied at regular intervals, but while morning and evening treatments are convenient for most patients, application during the day may not be possible for people with a busy work or academic routine. Assistance from carers and at school should be arranged for severely affected children. Emollient bath oils and a variety of soap substitutes are available. Cetomacrogol additives may enhance the antipruritic effect of bath oils. Bubble bath, astringent and other irritant products should be avoided.

Keratolytic agents, such as 1–5% salicylic acid, may be added to emollient cream bases, to encourage shedding of scale, but in practice they tend to be too irritant for regular usage. The risk of systemic toxicity (salicylism) precludes their widespread application, especially in young children who have a high surface area relative to body size. Alpha-hydroxy acids, such as lactate, glycollic, malic, mandelic, citric, pyruvic, gluconic and tartaric acids, 5–10% in an oil, lotion, cream or hydrophilic ointment base are said to enhance corneocyte shedding by virtue of their effect in breaking intercellular bonds [23]. They have become popular additives in many commercial skin-care products ('fruit acids') in recent years, and may be less irritant although more expensive than salicylic acid compounds. Beneficial effects from topical 12% ammonium lactate lotion have been reported [24]. Urea-containing (5–10%) emollients improve epidermal hydration, lyse keratin and are bacterostatic [25,26]. Topical retinoids are generally too irritant. The activity of keratolytic and urea treatments can be enhanced by occlusion under tubular dressings or sleep suits. In practice, they should be applied as tolerated for 2 weeks or so to produce a mild exfoliation, which can then be maintained with less frequent application. Mechanical exfoliation can be achieved with a loofah while bathing. Dandruff is not a problem for most ichthyosis vulgaris sufferers, but if present can be controlled with a tar or salicylic acid-containing shampoo.

Patients with both ichthyosis vulgaris and atopic eczema will need appropriate eczema therapy with the addition of topical anti-inflammatory or immunomodulatory preparations as required. Topical steroids and immunosuppressive agents do not benefit ichthyosis vulgaris but oral evening primrose oil, which contains essential n6 fatty acids, produced a slight improvement in some [27]. Systemic retinoid therapy is not necessary or appropriate for ichthyosis vulgaris, and in patients with associated atopic eczema would be likely to exacerbate the eczema.

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X-linked recessive ichthyosis (MIM 308100)

X-linked recessive ichthyosis (XLRI) affects male offspring who inherit an X chromosome bearing a steroid sulphatase genetic mutation from their asymptomatic carrier mother. Although the ichthyosis is rarely a significant problem, XLRI is an important disease for many reasons. It may be associated with extracutaneous manifestations and obstetric complications. The underlying lipid metabolic defect and the pathogenesis of the ichthyosis have been elucidated. The gene locus for steroid sulphatase (*STS*) has been identified at the distal end of the short arm of the X chromosome.

Incidence. Wells and Kerr [1], in a large epidemiological study in 1966, differentiated XLRI from ichthyosis vulgaris and defined their clinical and genetic features. They estimated its incidence in the UK at 1 in 6190 males. A not dissimilar incidence has been reported in other countries, based on clinical diagnostic criteria. In a Danish population study of placental *STS* deficiency, a predicted incidence of XLRI of 1 in 2000 males was derived [2]. XLRI has a worldwide distribution in all ethnic groups.

Aetiology and pathogenesis. In the 1970s, *STS* deficiency was identified as the cause both of XLRI and placental sulphatase deficiency, confirming them as a single disease entity [3,4]. Fibroblasts, epidermal cells, leukocytes, nail, hair bulbs, amniocytes and testicular tissue can all be assayed to reveal a functional and immunological enzyme deficiency. The enzyme substrate, cholesterol sulphate, is elevated in many tissues, including serum, red blood cell membranes, stratum corneum and nail matrix, but serum cholesterol levels are normal, as its main synthetic enzyme is hydroxymethylglutamyl-CoA reductase. Lipid analysis of normal epidermis shows a gradual decline in cholesterol sulphate (which stabilizes lipid bilayers) from 6% in the granular layer to 3% in the stratum corneum. A concomitant rise in cholesterol, which triggers stratum corneum intercellular lipid bilayer disintegration and desquamation, reflects the increasing activity of membrane-based steroid sulphatase at the corneal–granular layer junction. In XLRI, cholesterol sulphate accounts for 12–30% of stratum corneum lipids [5–7]. Calorimetric studies have identified a failure of the normal liquid–crystalline transition phase of stratum corneum intercellular lipids in XLRI, presumably because of the polar subgroups of cholesterol sulphate [8].

Steroid or cholesterol sulphatase is one of two isomers of aryl sulphatase C, a membrane-bound microsomal enzyme, and is responsible for hydrolysing sulphate groups from cholesterol sulphate and certain other steroids. The sulphated forms of some steroid sex hormones, such as 17-hydroxyprogesterone, oestrone and dehydroepiandosterone, are also increased in patients with XLRI [9]. Testosterone sulphate is reduced, but testosterone and dihydrotestosterone levels are normal, as synthesis can be mediated by a desaturase enzyme system. Pituitary gonadotrophins, prolactin and sex steroid binding globulin are normal. The altered sex hormone profile may in part explain the abnormal testicular development in some XLRI patients.

Evidence of a direct causal link between elevated cholesterol sulphate levels and scaling is compelling. Topical application of cholesterol sulphate in the hairless mouse induced a reversible retention ichthyosis, and a threefold increase in stratum corneum thickness, after 1 week [10]. The scaling cleared within 3 days of stopping the treatment, and did not occur if other sulphated substrates of the enzyme were applied. Topical cholesterol prevented this effect, and also temporarily reduced

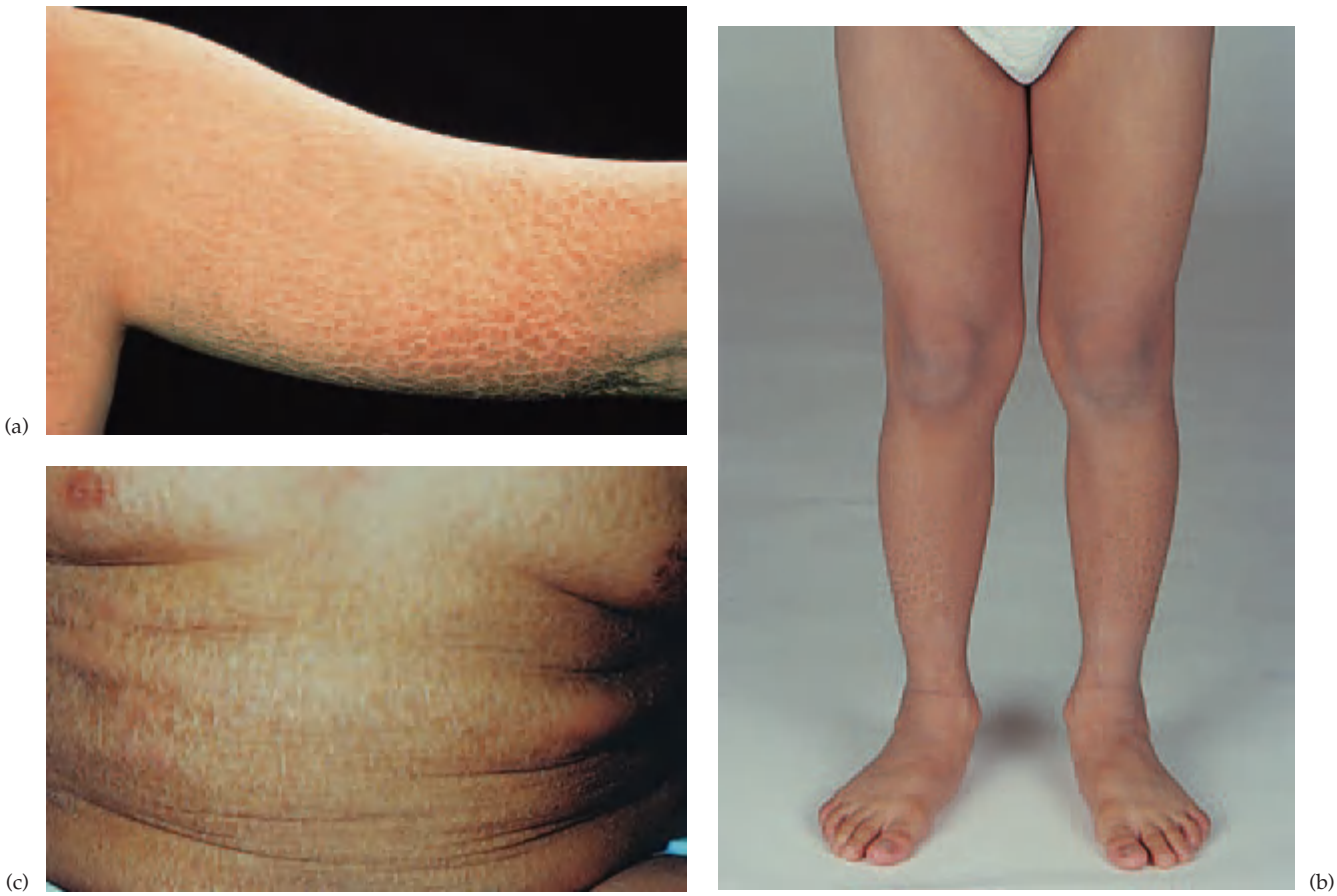

Fig. 34.2 X-linked recessive ichthyosis (XLRI). (a) Scaling on the arm; (b) on the legs; and (c) on the trunk.

the scaling of XLRI but not of other ichthyoses. Many cholesterol-lowering drugs have caused ichthyosis as a side effect [11].

Histopathology. Affected skin in XLRI shows an expanded stratum corneum without parakeratosis or acanthosis. The granular cell layer is usually normal, but may be mildly thickened or, rarely, diminished, making histological differentiation from ichthyosis vulgaris difficult. Ultrastructurally, the keratohyaline granules are normal or small, in contrast to ichthyosis vulgaris, but are more numerous. Desmosomes are more persistent than normal, and corneal melanosomes more prominent [12,13]. Kinetic studies have shown normal rates of cell turnover.

Clinical features. In 75% of cases, scaling is evident within the first week of life [14], but 6% develop scaling after the age of 1 year [15]. A Danish study of 76 patients revealed onset of light flaky scaling before 1 month of age, with more typical scale by 6 months in all but two children [16]. A prominent peeling episode at this stage was characteristic. The scaling tends to increase throughout childhood, often spreading up from the lower legs to the trunk. It stabilizes in the teens with little subsequent change, and in most patients scaling diminishes in the summer months. There is considerable variation in the severity of scaling between families, and even in some instances within affected kindred. Pruritus is unusual.

Scaling in XLRI is most prominent on the extensor surfaces of the upper arms (Fig. 34.2a), the outer thighs and around the lower legs (Fig. 34.2b). Typically, the scale is medium to large, polygonal, adherent, dull and light to dark brown, depending on skin type (Fig. 34.2c). The posterior and lateral neck, upper and lateral abdominal wall and pre-auricular facial skin are commonly affected with adherent, dark grey scale and, in contrast to ichthyosis vulgaris, the flexures may be involved. The face, scalp, axillae, flexor aspects of the limbs and dorsal hands and feet may show light grey scaling but the palms and soles are spared. Rarely, a fine white scaling is the predominant sign, and leads to a delay in diagnosis. In one study the average age of diagnosis was 10.3 years [14].

Extracutaneous features of XLRI. A variety of extracutaneous abnormalities have been noted in some patients with XLRI. An increased incidence of testicular maldescent,

abnormalities of sperm count or motility, and testicular cancer have been reported in patients with XLRI [16–19]. Of a group of 76 patients, nine had testicular maldescent and three developed testicular cancer in normally descended testes (one had bilateral cancer) [16,19]. Inguinal hernia appears to be more common, and unilateral renal agenesis was reported in half of those with cryptorchidism, all of whom had features of Kallmann's syndrome [14].

Corneal dot, thread-like or comma-shaped opacities, detected with the slit-lamp microscope, occur in 50–100% of adult patients, and to a lesser degree in 24% or more of female carriers, but are usually of no functional significance [15,16,20,21]. They are thought to be a result of stromal deposits on the posterior surface of Desçemet's membrane [21].

Perinatal manifestations of steroid sulphatase deficiency. It was noted in the 1970s that low urinary oestriol excretion in the third trimester of pregnancy was not invariably associated with intrauterine growth retardation. These pregnancies often ended in a prolonged labour, and the underlying defect, placental *STS* deficiency, was identified. Coincidentally, *STS* deficiency was noted in boys with XLRI [3].

Prolonged labour may occur in up to one-third of patients with XLRI. In a group of 33 patients, four had a spastic paraplegia or paraparesis, apparently as a result of perinatal complications related to prolonged labour, requiring obstetric intervention [14]. In each case, a younger male sibling with XLRI was neurologically normal.

XLRI and contiguous gene defects. Kallmann's syndrome describes the association of XLRI with hypogonadotropic hypogonadism, anosmia and a variety of neurological defects, including nystagmus and mirror movements of the hands and feet (synkinesis) [22]. It affects between 1 in 10 000 and 1 in 60 000 of the population, and may be misdiagnosed as XLRI until adult life because of delayed diagnosis of hypogonadism. Adult patients may suffer from obesity and osteoporosis. Renal anomalies and cleft palate have also been reported in Kallmann's syndrome. Developmental delay and spastic paraplegia appear to be more common in Kallmann's syndrome than in isolated XLRI. Kallmann's syndrome is caused by a large deletion of the short arm of the X chromosome proximal to and including the *STS* gene. The features of Rud's syndrome (X-linked ichthyosis, obesity, hypogonadism, mental retardation, epilepsy and endocrinopathies) can, in large part, be attributed to Kallmann's syndrome or to perinatal complications in patients with XLRI [23].

Larger X chromosome deletions distal to and including the *STS* gene may lead to XLRI associated with mild mental retardation, mild chondrodysplasia punctata or short stature [24]. Epiphyseal stippling of long bones, larynx and vertebrae may occur transiently in early childhood in the chondrodysplasia variant, while dysplastic features may be detected on X-rays later in life. Hypoplasia of cartilage and distal phalanges has been noted in affected males, and carrier females may be of short stature. Sparse, brittle hair occurred in two patients with large X chromosome deletions [14].

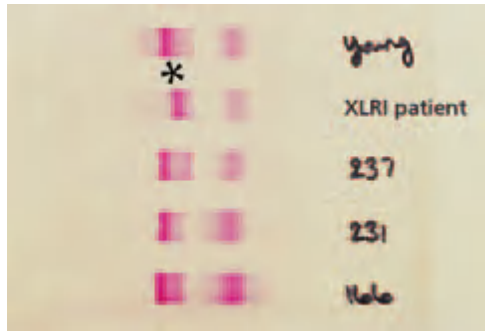

Fig. 34.3 Serum electrophoresis, showing 'fast' band in XLRI patient (compared to controls).

Diagnosis. Raised serum cholesterol sulphate in patients with XLRI can be detected on serum lipoprotein electrophoresis [25]. Cholesterol sulphate carries a stronger electronegative charge than cholesterol, resulting in increased mobility of the β low-density lipoprotein fraction (a 'fast' band 2 mm beyond that of controls) towards the anode (Fig. 34.3). This simple screening test is not widely available and equivocal results (1 mm difference) should be followed up with the definitive test, *STS* assay, which is available in regional laboratories. Enzyme activity can be measured in leukocytes or skin fibroblasts, and is much reduced or absent in XLRI [26]. Serum cholesterol levels are normal in XLRI.

Chromosomal analysis using high-resolution G-banding will detect and quantify significant Xp deletions where clinical evidence of contiguous gene defects exists. Southern blot analysis can be used to identify specific gene deletions, or mutations at and distal to the *STS* gene locus. PCR amplified testing for exons in the Kallmann's syndrome gene is the most sensitive test for this condition. Fluorescent *in situ* hybridization (FISH) analysis has been used to detect a common deletion of the *STS* gene [27].

Clinically, XLRI may resemble ichthyosis vulgaris or mild lamellar ichthyosis. A Sardinian kindred with a similar phenotype but normal *STS* activity has been reported [28].

Genetics. Linkage of XLRI and the Xg red blood cell group in the 1960s was an early example of chromosome localization identified by tracking linked traits in family studies [29]. The association of XLRI with stunted growth, hypogonadism and anosmia has enabled mapping of the

relevant genes on the short arm of the X chromosome (Xp). Gene mapping in families with X to Y translocations placed the *STS* gene at the Xp 22.3 locus [30]. The Kallmann's syndrome gene has been mapped proximal to this, while deletions distal to the *STS* gene may cause mental retardation, chondrodysplasia punctata and short stature, placing relevant genes towards the pseudoautosomal region at the tip of the X chromosome [24,31].

The virtual absence of immunoreactive *STS* in XLRI patients is matched by a complete deletion of the *STS* gene on Southern blot analysis of genomic DNA in up to 90% of cases using specific Xp complementary DNA (cDNA) probes [14,32]. Point mutations of the gene have been identified [33]. There is considerable genetic heterogeneity between XLRI and contiguous gene syndromes, with sizeable DNA loss (3.4%, up to 2 megabases) detected by flow cytometry in some [34] and in others evidence of X–Y translocations [35].

Isolated XLRI is generally a mild disease and few families are interested in prenatal diagnosis. However, placental *STS* deficiency is a risk factor in affected pregnancies, and highlights the importance of identifying carrier females. Kallmann's and other contiguous gene defects are more significant and, in these families, genetic assessment and heterozygote detection must precede genetic counselling. Prenatal diagnosis of XLRI is based on maternal urinary oestriol levels, or chorionic villus steroid sulphatase assay. Southern blot analysis and PCR can detect *STS* gene deletion or contiguous gene mutations, while high-resolution G-banding will identify large Xp deletions. FISH analysis can also rapidly identify female carriers [27].

Carrier detection. Obligate carriers show no consistent cutaneous features but corneal stromal deposits are detected on slit-lamp examination in some [20]. Lipoprotein electrophoresis is normal in obligatory female carriers. *STS* levels in leukocytes, fibroblasts or hair roots are higher in normal females than in normal males, because the Lyon effect (inactivation of one X chromosome in normal female cells) does not apply to the *STS* gene [36]. Therefore, female carriers would be expected to have 50% of the *STS* values of non-carrier females. Indeed, 30 of 31 obligate carriers had a leukocyte *STS* level below the 2.5 percentile of normal females, indicating enzyme heterozygosity [36]. However, partial X inactivation was evident in other studies, enzyme values in the range of 40–86% in known carriers were obtained. Leukocyte *STS* assay, using oestrone sulphate as substrate, proved the most reliable biochemical test for heterozygote detection [37]. Visual assessment of stained hair roots to detect *STS* has also been used. Southern blot hybridization of leukocyte DNA provides an accurate measure of the anticipated 50% *STS* gene dosage in carriers, but is applicable only to the 90% of XLRI families with complete gene deletion [38]. FISH analysis, a technically less demanding diagnostic technique, is currently the method of choice for carrier detection in XLRI families where a gene deletion is the underlying defect [27]. In the remaining 10% of cases where the gene is not deleted, PCR of the individual exons of the gene and mutation detection by direct DNA sequencing or another technique is necessary to find the mutation. Somatic and germinal mosaicism for the *STS* gene deletion in a carrier has been reported [39].

Treatment. The same principles apply to treatment of XLRI as have been outlined for ichthyosis vulgaris. Most patients achieve an acceptable level of control of their scaling and dryness with daily emollient application, and may improve sufficiently in the increased humidity of temperate summers to forgo any therapy. Keratolytic and urea-containing preparations are generally less irritating than in ichthyosis vulgaris. In severe XLRI, short or intermittent courses of oral retinoid therapy may be considered. A topical receptor-selective retinoid, tazarotene, showed promising results in a small number of patients [40]. Topical application of cholesterol reversed the effect of cholesterol sulphate in hairless mice [9], and a 10% cholesterol cream improved scaling in 18 of 20 patients after 3–5 weeks [41]. Abnormalities of genital or secondary sexual development should be investigated by an endocrinologist and appropriate treatment planned. Short stature warrants early investigation, including a radiological check of long-bone epiphyses. Neurological and developmental assessments will detect those patients with neurological damage or Kallmann's syndrome and help identify special educational needs.

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Multiple sulphatase deficiency (MIM 272200)

This is an exceedingly rare autosomal recessive disorder caused by deficiency of two or more of the seven microsomal sulphatase enzymes, usually including aryl sulphatases A, B and C. This leads, in infancy, to a combination of features of mucopolysaccharidosis type 2 (aryl sulphatase B deficiency), metachromatic leukodystrophy (aryl sulphatase A deficiency) and XLRI [1].

Developmental delay and failure to thrive occur from early infancy with features of Hurler's syndrome (coarse facies, stunted growth, hepatomegaly and skeletal defects) becoming evident in the first year of life. A positive urine spot test for glycosaminoglycans (GAGs) suggests a lysosomal storage disorder. A mild ichthyosis and progressive neurological degeneration evolve in the second or third year but the phenotype varies according to the degree of reduction of each enzyme [2,3]. The neurological disease is often fatal in childhood.

Multiple sulphatase deficiency is confirmed by enzyme assays on fibroblasts, fresh leukocytes or serum, and fibroblast iduronate sulphatase activity is reduced. Urinary sulphatides and GAGs (heparan and dermatan sulphate) are elevated. Prenatal diagnosis by enzyme assay of amniocytes is possible.

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Collodion baby

This accurate if outdated term is used to describe the transient appearance at birth and in the neonatal period of a baby who, in general, subsequently develops ichthyosiform erythroderma [1] (although a variety of unrelated disorders may ensue). It was reported sporadically in the 19th century [2], and familial, self-healing cases and localized forms have been noted [3,4]. There are no reliable figures on incidence and it may be overlooked or misdiagnosed in some cases.

Aetiology and pathogenesis. The collodion membrane

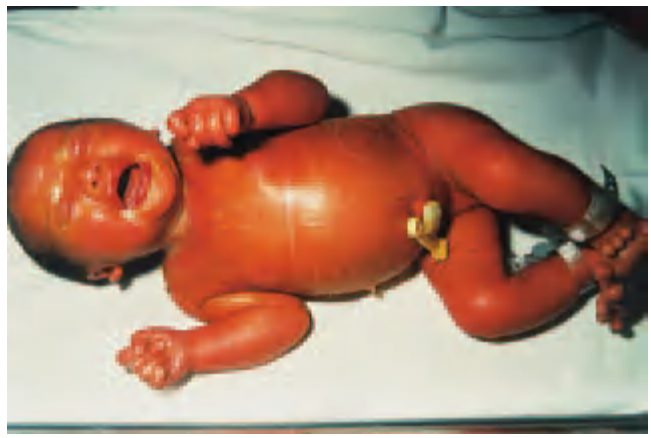
forms in the latter half of the third trimester, but at birth the defective stratum corneum barrier is exposed and the membrane desiccates and peels off. The association between fetal periderm, which evolves in the second month of gestation and dissolves with the onset of epidermal differentiation in the sixth month, and the neonatal collodion membrane, is unknown. Periderm does not express profilaggrin nor contain keratohyalin granules, which are present in the collodion membrane. In fetal skin biopsies of lamellar ichthyosis and harlequin ichthyosis, the periderm was normal in appearance [5].

Histopathology. Light microscopy of skin in the early neonatal phase of a collodion membrane shows a compact hyperkeratosis with a thick eosinophilic periodic acid–Schiff stain (PAS)-positive stratum corneum. However, the epidermis is attenuated because of a reduced granular layer. The mid- and lower epidermis and the dermis are usually unremarkable.

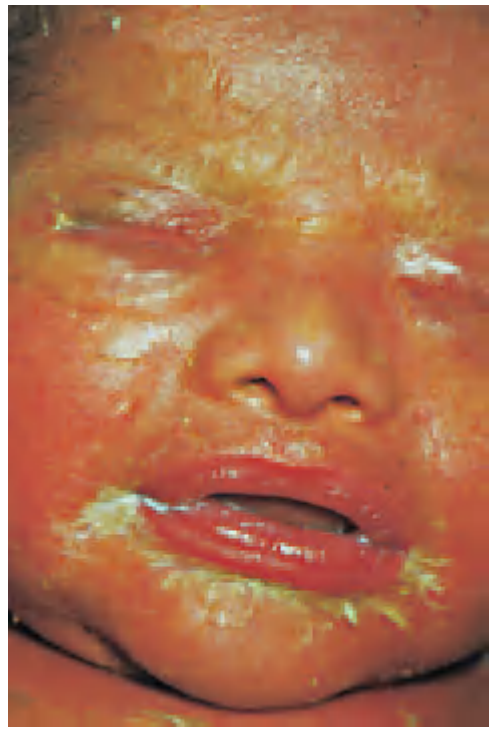
Electron microscopy features in the early neonatal phase have varied. In one case, cells of the upper two-thirds of the stratum corneum were convoluted and irregular in shape, with prominent nuclear debris and dense intracytoplasmic granules. Lamellar bodies were numerous in the intercellular spaces and desmosomes were well preserved [6]. Repeat skin biopsy at 16 months showed that, in spite of apparent 'self-healing', the ultrastructural changes persisted. Another report indicated that the ultrastructural features on the 15th day of life were predictive of the outcome, with a self-healing case showing relatively normal epidermal ultrastructure, while an infant who developed erythrodermic ichthyosis showed continuing dysplastic changes [7].

Clinical features and prognosis. Premature delivery may be slightly more common but is not a significant problem. At birth, the typical collodion baby presents a striking and characteristic clinical picture with a generalized glistening, taut, yellowish film stretched over the skin (Fig. 34.4a). It resembles a clingfilm wrap or sausage skin, although it may variously be described as a 'plastic skin', 'parchment-like' or 'as if dipped in hot wax'. Normal skin markings are obliterated, the eyelids and sometimes the lips are tethered and everted (ectropion and eclabion), the pinnae may be flattened and the nostrils obstructed (Fig. 34.4b). Sausage-shaped swelling of digits may result from acral extension of the membrane and, rarely, constricting bands encircle the limbs or digits. General examination is usually normal and movement is minimally restricted.

The collodion membrane desiccates and cracks around flexures during the first days of life (Fig. 34.5), and is usually completely shed within the first few weeks of life. It appears incomplete or localized in some infants, and may peel away only to reform, this pattern being repeated over a period of up to 12 weeks. In most cases, shedding reveals an erythrodermic ichthyosis.



(a)



(b)

Fig. 34.4 (a) Collodion baby, day 2. (b) Facial features in collodion baby.

Previously common and often lethal complications of a collodion membrane, and the associated erythroderma, were renal failure and neurological sequelae of hypernatraemic dehydration [8], hypothermia and bacterial sepsis. Affected infants require intensive nursing care in humidified incubators to control body temperature, prevent infection and combat electrolyte upset and dehydration. Increased absorption of topical agents through the skin may lead to systemic toxicity, and topical steroids should be avoided. Improved neonatal care has resulted in a reduction in neonatal mortality from 33% in the 1970s

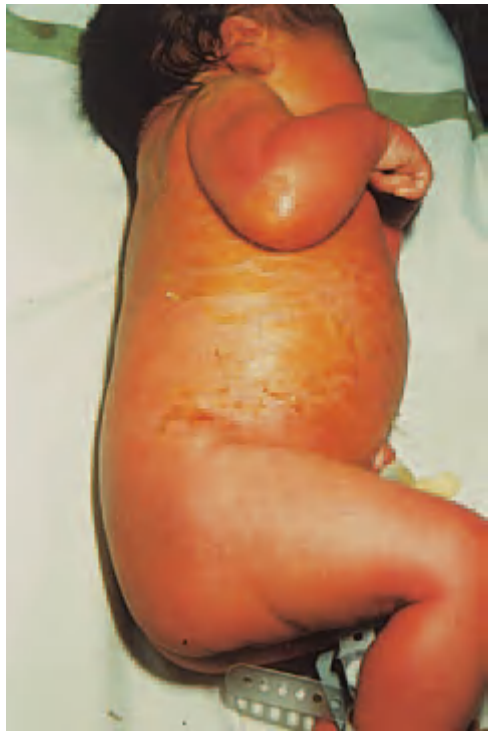


Fig. 34.5 Early shedding of membrane.

to less than 11% in one review [9], and in uncomplicated cases mortality is now negligible [10].

Sequelae and genetics. In 60–80% of these infants, the features of non-bullous ichthyosiform erythroderma or, less often, lamellar ichthyosis become apparent [9,10]. The severity of the subsequent ichthyosis cannot be predicted from the duration or complications of the collodion membrane. The rare autosomal dominant form of lamellar ichthyosis, and a kindred with apparent autosomal dominant non-bullous ichthyosiform erythroderma, have also presented with collodion membrane [11,12]. A minority of patients with lamellar ichthyosis, or non-bullous ichthyosiform erythroderma, appear not to have a collodion membrane at birth.

Occasional cases of trichothiodystrophy (IBIDS), neutral lipid storage disease, Sjögren–Larsson syndrome, Conradi–Hünermann disease and autosomal dominant loricrin keratoderma [13] have presented as collodion babies but its occurrence in other forms of ichthyosis, such as XLRI and bullous ichthyosiform erythroderma, is doubtful. Of collodion babies, 10–20% subsequently have normal skin, so-called self-healing collodion baby or 'lamellar ichthyosis of the newborn' [14]. This autosomal recessive condition has been attributed to a compound heterozygous transglutaminase mutation where the inactive *cis* form of the enzyme converts to an active *trans* form in an extrauterine environment [15]. Collodion membrane presentation has also been reported in anhidrotic ectodermal dysplasia [16], Gaucher's disease type 2, a disorder of sphingolipid metabolism resulting from β-glucocerebrosidase deficiency [17,18] and Neu–Laxova syndrome [19]. A single case associated with palmoplantar keratoderma was observed by one of the authors and another was included in a report of 10 collodion babies in the Thai literature [20].

Differential diagnosis. A collodion baby is generally easily distinguished from the more severe harlequin fetus or harlequin ichthyosis presentation, but occasional cases with intermediate features have been recorded. These cases have been referred to as 'chrysalis babies'. Restrictive dermopathy, or the 'stiff baby syndrome', produces a generalized taut, thick, tethered and unyielding skin at birth, which does not dessicate in the neonatal period. Its persistence causes respiratory failure and early neonatal death. Infective causes of desquamation such as staphylococcal scalded skin should be included.

Management. Skin biopsy is not usually performed at this stage, but hair analysis, blood film microscopy and hearing tests should be arranged. Collodion babies should be nursed in a special care baby unit in a humidified incubator. Cleansing with warm water and sterile aqueous cream or antiseptics daily, and barrier nursing, reduces the risk of infection (associated with skin barrier dysfunction, emollient use and high humidity). An emollient, such as sterile white soft paraffin in single-dose containers, is usually applied 4-hourly to keep the membrane pliable and reduce transepidermal water loss. Analgesics may be required before handling. Intravenous lines should be avoided and regular skin swabs carried out. Signs of skin or systemic sepsis (including *Candida* and *Pseudomonas*) should be investigated and treated immediately, but prophylactic antibiotics are unnecessary. Poor sucking and weight loss may necessitate nasogastric tube feeding, and a higher than normal fluid and calorie requirement can be anticipated. Exposure keratitis resulting from ectopion can be prevented by the regular use of lubricating drops and ointments, and ophthalmological advice should be sought. Nasal obstruction can be improved by gentle probing, and constricting bands on the limbs should be divided if causing acral pressure effects. Systemic retinoids have rarely been used in severe cases. Every effort must be made to allow the parents to nurse and bond with their baby and their involvement from the beginning will enhance their confidence in managing at home.

The need for continuing neonatal care, once the membrane is shed, depends on the baby's condition, but most can be discharged within the first 4 weeks on a continuing emollient regimen. Accurate information on the condition and its prognosis should be available from regional neonatal and dermatology centres, and is necessary to allow carers and family to plan management. The details

and outcome of an individual case, including transglutaminase mutation detection, will be important for genetic counselling of the family, which should be arranged on discharge.

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Non-bullous ichthyosiform erythroderma (MIM 242100)

Non-bullous ichthyosiform erythroderma (NBIE) is a rare and usually severe autosomal recessive inflammatory ichthyosis. There are few data on incidence, but an English population study estimated it to be 1 in 300 000 [1]. It occurs in all races, more so when consanguineous marriage is common. NBIE is more common than lamellar ichthyosis, but they were regarded as a single disorder until the 1980s, when clinical, histological and biochemical features that differentiated them were reported. NBIE is also referred to as erythrodermic lamellar ichthyosis. A Swedish kindred with autosomal dominant NBIE has been reported [2].

Aetiology and pathogenesis. NBIE is characterized by epidermal hyperplasia with increased mitoses, prominent PCNA staining [3] and increased expression of hyperproliferative keratins K6/K16/K17. *In vitro* studies of NBIE keratinocytes grown in organotypical culture at an air–liquid interface showed hyperkeratosis, and more marked parakeratosis, than with normal control keratinocytes [4]. There are no consistent changes in epidermal lipid content in NBIE. Although alkanes, a saturated hydrocarbon group, may be raised in certain hereditary ichthyoses, they are neither sensitive nor specific for any one type [5]. Assay of stratum corneum enzymes highlighted differences between the autosomal recessive ichthyoses. In NBIE scale, the lamellar body enzyme, β-glucosidase, was reduced while butyrase levels were maintained, and the opposite pattern pertained in lamellar ichthyosis [6].

Abnormal intracellular cytoplasmic accumulation of keratinocyte transglutaminase 1 has been reported in a subset of patients with NBIE [7]. Whereas transglutaminase activity in some patients with lamellar ichthyosis was entirely absent, intermediate levels were found in this subset of NBIE patients. Recently, mutations in two lipoxygenase enzymes, lipoxygenase-3 (ALOX3) and 12-lipoxygenase (ALOX12B), have been identified in six Mediterranean families affected by NBIE, known to be linked to chromosome 17p13.1 [8]. These two lipoxygenases are mainly expressed in epithelial cells including suprabasal keratinocytes, and are involved in the maintenance of the cutaneous permeability barrier and possibly in terminal differentiation. Lipoxygenases are involved in essential fatty acid and phospholipid metabolism, which provides the lamellar body-derived membranes responsible for the permeability barrier. Linkage to chromosome 3 has been reported, and this locus also appears to hold the gene for Chanarin–Dorfman syndrome [9].

Histopathology. Light microscopy of skin sections reveals compact hyperkeratosis and moderate increase in stratum corneum thickness. There is variable mild parakeratosis and acanthosis, a normal or prominent granular layer, increased mitoses and an accentuated broad rete ridge pattern. A mild upper dermal lymphocytic infiltrate and prominent dermal blood vessels may be present. Lipid vacuoles in the stratum corneum were noted in a family with autosomal dominant NBIE, and sweat glands were normal below the level of the stratum corneum [2].

PAS staining of frozen sections showed positivity in cell membranes of the stratum corneum and granular layer and in the basement membrane, which is absent in normal skin and in other ichthyoses, with the possible exception of Netherton's syndrome [10]. Kinetic studies, using labelled thymidine, confirmed an increased epidermal

turnover rate in NBIE, similar to that seen in psoriasis, and in contrast to the relatively normal epidermal kinetics of lamellar ichthyosis [11]. This was unaffected by retinoid therapy [12].

Electron microscopy reveals abnormal lamellar bodies, which are retained in the corneal layer. In the autosomal dominant variant, there was, in addition to increased mitotic activity, a reduced level of keratohyalin and tonofilaments, and lipid vacuolation in the stratum corneum [2]. The expanded granular layer showed normal lamellar body structure. Ultrastructural features more typical of harlequin ichthyosis have been found in several patients with severe NBIE [13]. Classification of autosomal recessive ichthyosis congenita into five subtypes, based on ultrastructural findings, highlights the clinical, ultrastructural and genetic heterogeneity of NBIE [14–19].

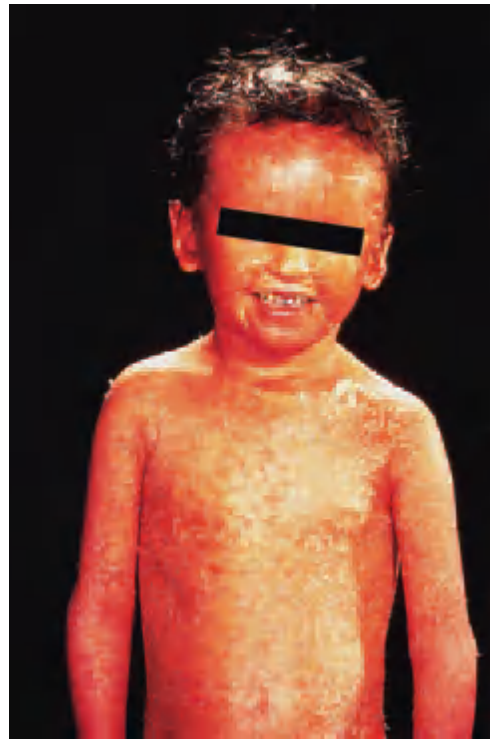
Clinical features. NBIE in over 90% of cases presents at birth with a collodion baby appearance (Figs 34.4 & 34.5). The few in whom this is not a recorded feature are erythrodermic from birth, and some are premature. After shedding of the collodion membrane, generalized scaly erythroderma is apparent and persistent (Figs 34.6a,b). Erythroderma may lessen while scaling increases in early childhood but there is considerable interindividual variation in severity.

Typically, scaling affects all areas including the scalp, ears, face, flexures, palms and soles. The scale of NBIE is white or grey, thin, superficial and semi-adherent. It appears feathery on the face, arms and trunk but may be lamellar or plate-like on the lower legs. Scaling may be cyclical, with build-up and shedding over periods of 2–4 weeks and, rarely, clinically normal skin may evolve in limited sites. Palmoplantar hyperkeratosis occurs in up to 70% of patients, and can cause recurrent painful fissures, digital contractures and loss of pulp volume. Scalp involvement may lead to tinea amiantacea and patchy cicatricial alopecia, especially on the temporal scalp.

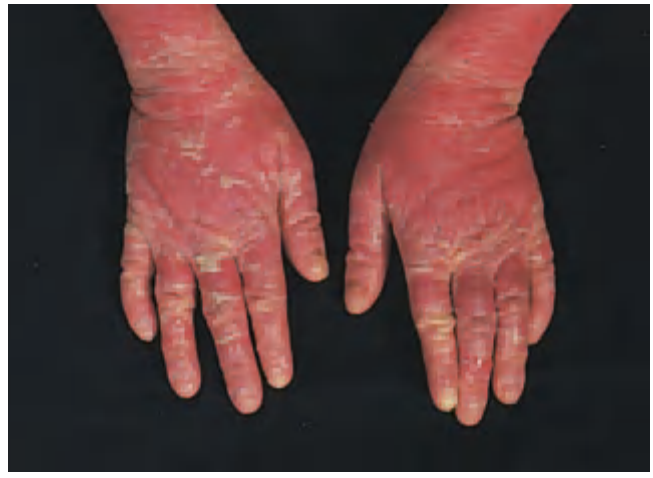
Ectropion improves during infancy, but persists into adult life in 30% and, if untreated, may lead to exposure keratitis and even blindness [20]. Loss of eyebrows and lashes in severe cases accentuates the ocular problem. Hypoplasia of the nasal and aural cartilages may result from compression and scarring, increasing the cosmetic burden.

A mild nail dystrophy consisting of ridging, subungual hyperkeratosis or hypoplasia occurs in up to 50% of patients, but hair, teeth and mucosal surfaces are normal. Nail growth and skin healing are rapid. In most patients, sweating is absent or markedly reduced in childhood, and care is needed to avoid hyperpyrexia during intercurrent illness, leisure pursuits or in hot climates. Sweat gland function improves in adolescence, and in patients treated with retinoids. Hypohidrosis is therefore thought to be a result of sweat duct obstruction by the hyperkeratotic stratum corneum. Pruritus is not uncommon and NBIE often deteriorates in summer weather. Coexistent eczema causes severe pruritus. Cutaneous infections are rare, although there have been reports of widespread fungal infection in patients with congenital ichthyosiform erythroderma [21,22]. Mildly affected patients may present with an intertrigo-like pattern, mild palmar hyperkeratosis and subtle facial tightness.

Many affected children are of short stature, but may catch up with a delayed growth spurt in adolescence. NBIE may limit a child's ability to take part in sports, but swimming and less vigorous activities should be



(a)



(b)

Fig. 34.6 Non-bullous ichthyosiform erythroderma: (a) in a 4-year-old-boy; and (b) same child.

encouraged. Psychological problems often arise at school because of insensitive comments and reactions of others. However, in general, children with NBIE seem to cope well with their disability, and academically achieve on a par with their peers.

Congenital reticular ichthyosiform erythroderma. Three cases of a variant of NBIE have been described [23]. They developed enlarging areas of normal skin which accounts for the alternative names, 'ichthyosis en confetti' and 'ichthyosis variegata'. Specific ultrastructural changes were reported and one affected woman developed hyperpigmented macules on the limbs [24].

Diagnosis. Classic NBIE presents a characteristic clinical picture enabling differentiation from classical lamellar ichthyosis. Other causes of congenital erythroderma and collodion membrane presentation need to be considered in the neonatal period. Collodion presentation of loricrin keratoderma associated with ichthyosiform erythroderma was seen in two Japanese siblings and their father [25]. Congenital infections such as candidiasis, congenital psoriasis, Netherton's syndrome, immunodeficiency disorders, trichothiodystrophy (IBIDS) and neutral lipid storage disease may mimic the cutaneous signs of NBIE in the neonate. There have been sporadic cases of coexistent congenital ichthyosiform erythroderma and psoriasis [26,27].

Genetics. Classical NBIE is an autosomal recessive condition and therefore more likely to occur in societies where consanguineous marriage is common. In a personal series of 25 patients with NBIE, there were five sibling pairs and seven patients, including three Caucasians, were the offspring of consanguineous parents. The risk of further affected children for the parents of the proband is 1 in 4 for each child. Affected individuals should not have affected children, and their offspring have a 50% risk of carrier status.

A non-consanguineous Swedish kindred with typical features of NBIE in a mother and her two daughters may have a previously undescribed autosomal dominant variant, or may have occurred because of pseudodominance [1]. This theory proposes that the mother's parents and her unrelated husband were each heterozygous carriers of the recessive gene; the incidence of heterozygosity was estimated at 1.8–3.2 in 1000 population.

Prenatal diagnosis is possible by fetoscopy and fetal skin biopsy with amniocyte pelleting at 17–22 weeks to detect premature or abnormal keratinization or abnormal inclusions [28,29], but it is far from satisfactory for two reasons [14,30]. First, phenotypic heterogeneity can exist between members of the same family, so that the severity of the proband may not reflect that of the affected fetus. Secondly, normal interfollicular keratinization is established only at 24 weeks' gestation and shows a regional pattern of evolution. To avoid errors, multiple skin biopsies from different sites including the scalp are recommended. The identification of a specific genetic mutation in the proband will allow first trimester prenatal diagnosis based on chorionic villus sampling at 10–12 weeks' gestation.

Treatment. The principles of emollient and keratolytic treatments for patients with NBIE are much the same as those outlined for treatment of ichthyosis vulgaris. Because of the inflammatory nature of the condition, the potential for irritation with topical treatment is high, and keratolytics and topical retinoids are rarely used. Topical steroids are ineffective and readily absorbed but antifungals may be helpful. Hypohidrosis with the attendant risk of hyperpyrexia may be aggravated by the occlusive action of ointments. Prevention of sunburn and sunstroke in children is important.

Systemic retinoids are effective in many disorders of keratinization, and have been shown to be helpful in reducing scaling, pruritus and erythema in most patients with severe congenital ichthyosis including NBIE [31]. For many patients, this may allow a more active role in daily activities, such as schooling, sport and socializing. The recommended starting dose of acitretin is 0.5–0.75 mg/kg/day, tending to higher doses in younger children. A response is apparent within 2–3 weeks, and the maintenance dose is titrated down to the lowest effective level between 0.1 and 0.5 mg/kg/day. Effective doses tend to be lower than in the treatment of other disorders of keratinization. Because of potential toxicity and the chronicity of the disease, intermittent therapy is preferred (e.g. 3 months on, 3 months off). Patients with ectropion or corneal damage may not be able to tolerate the side effects of retinoids, and peeling of palmar skin may induce an unpleasant hypersensitivity. Rare cases of skeletal toxicity have been reported with retinoid therapy [32], but long-term use of etretinate in 42 children, 14 with NBIE, did not cause significant skeletal abnormalities [33]. Pretreatment baseline selective skeletal survey was recommended for all patients, with follow-up studies restricted to those with pretreatment lesions or who develop musculoskeletal symptoms. Older children and adults must be advised of the teratogenicity of retinoids and, where appropriate, contraceptive measures undertaken. The period of mandatory contraception is less with isotretinoin compared to acitretin but it is less effective.

A small open trial on the effect of 4 weeks' treatment with oral ciclosporin in congenital ichthyosis (three cases with NBIE and two with lamellar ichthyosis) showed no benefit [34]. Topical tacrolimus ointment 0.1% was associated with dramatic improvement in one case but increased absorption led to potentially toxic blood levels on daily application [35]. Evening primrose oil has been helpful in occasional cases.

Patients and families may benefit from contact with other affected people and patient support groups exist in several countries. Advice to carers and teachers, careers advice and ongoing support assists children and young adults in coping with the educational, occupational and social problems resulting from their chronic skin disease.

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Lamellar ichthyosis (MIM 242300, 601277, 146750)

Of the two major autosomal recessive ichthyoses, lamellar ichthyosis (LI) is less common than NBIE, with an incidence of approximately 1 in 500 000. It has a worldwide distribution. In its severe form it is easily recognized, but heterogeneity exists and it may be confused with other ichthyoses. The so-called 'alligator boy' reported by Fox in 1884 probably suffered from LI [1].

The term 'lamellar ichthyosis' (Latin *lamella*, plate) was, in the early 20th century, used for any congenital ichthyosis excluding harlequin fetus and, until the 1960s, it also referred to the collodion baby phenotype. In the European literature, the prefixes erythrodermic or non-erythrodermic (lamellar ichthyosis) correspond to NBIE and LI [2]. Evidence for clinical, histological and biochemical heterogeneity in autosomal recessive ichthyosis helped distinguish between NBIE and LI [3,4] and specific genetic mutations have been found in a proportion of LI patients. An autosomal dominant pattern of inheritance of LI has been described [5].

Aetiology and pathogenesis. The main histological changes point to a disorder of cornification or terminal epidermal differentiation. Reduced skin barrier function was evident in studies of transepidermal water loss, and paralleled stratum corneum lipid defects [6]. Scale lipid analysis in severe LI showed a mild but significant rise in sphingolipids (ceramides) and free sterols, a pattern similar to that of normal palmoplantar skin [3].

Cornification involves the construction of the cornified envelope from intracellular protein precursors including loricrin and involucrin. These are cross-linked in the granular layer by the action of transglutaminase, forming γ-glutamyl-lysine isopeptide cross-links. Three cases of autosomal recessive LI examined immunohistochemically showed a high expression of abnormally distributed loricrin and involucrin in keratinocyte cytoplasm, with diminished cytoplasmic transglutaminase staining [7].

Genetics. Genetic studies of inbred and outbred families with severe LI revealed complete genetic linkage to the region on chromosome 14q11 containing the transglutaminase 1 candidate gene, *TGM-1* [8]. There was striking homozygosity at this locus, compatible with recessive inheritance, and the evidence was further strengthened by the identification of several mutations in the *TGM-1* gene [9,10]. These mutations were shown to greatly reduce or ablate transglutaminase activity [9]. Homozygous or compound heterozygote mutations of the *TGM-1* gene were found in all these families and have since been reported in mild localized LI [11]. However, there is biological heterogeneity; 13 of 23 families with a clinically similar phenotype had no evidence of linkage to the *TGM-1* gene locus [12]. Linkage to chromosome 2q33-35 [13], to chromosome 19p12–q12 [14] and to chromosome 19p13.1–p13.2 has also been reported [15]. There is close genotype–phenotype correlation in those families with linkage to these three sites.

An autosomal dominant keratoderma with ichthyosiform erythroderma in a kindred reported by Camissa [16] is a result of a loricrin mutation [17] (cf. Vohwinkel's syndrome).

Classical LI is an autosomal recessive disorder, and the same principles apply in the counselling of families as outlined for NBIE. Because of the rare occurrence of autosomal dominant LI (see below), examination of any relatives with skin disease is indicated, and in non-consanguineous families with a single affected child, the implications of dominant transmission should be borne in mind.

Histopathology. Light microscopy of the skin in LI shows striking, compact orthohyperkeratosis with variable mild focal parakeratosis, and a stratum corneum thickness at least twice that of NBIE. The granular layer appears normal or increased, the remainder of the epidermis is normal, and overall epidermal thickness is slightly increased. There may be mild papillomatosis, extension and blunting of rete ridges, and dilatation of dermal capillaries reminiscent of psoriasis.

Histochemical techniques to identify glycoconjugates and free-sterol localization showed a staining pattern similar to that of normal skin [3]. One group reported faint PAS positivity in the stratum corneum [2]. Kinetic studies surprisingly revealed a near-normal transit time, in contrast to the hyperproliferative epidermis of NBIE and psoriasis, and LI is therefore classified as a retention ichthyosis [4].

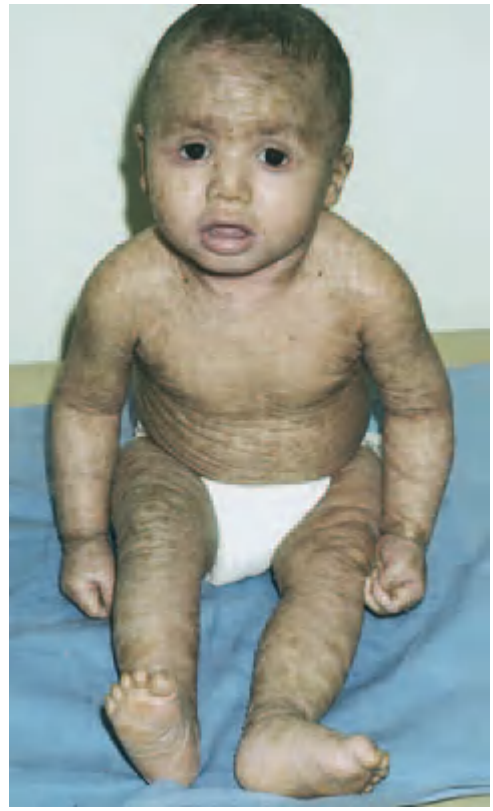

Fig. 34.7 Lamellar ichthyosis, severe.

Electron microscopy features in LI are variable. Niemi *et al*. [18] reported finding prominent cholesterol clefts or crystals in the stratum corneum, lipid droplets in corneocytes and a thin or absent cornified envelope in nine affected patients with clinical features of LI, from seven Finnish kindreds. These ultrastructural signs led to the subclassification of ichthyosis congenita type 2. Various other changes including abnormal membrane structures and vesicles within lamellar bodies have been noted in patients with a reticulated form of LI, also called ichthyosis congenita type 3 [19].

Clinical features. At birth, most affected infants present as collodion babies, and after shedding the membrane, show a less intense erythroderma than infants with NBIE—an important and persistent distinguishing feature. Scaling occurs within the first month of life and may affect the whole skin surface, or localize to the scalp, abdomen and lower legs.

The scale in LI is typically large, dark brown or grey and firmly adherent (Figs 34.7 & 34.8). In severely affected individuals, the thick, rigid scale is intermittently shed, causing deep and painful fissures, especially around

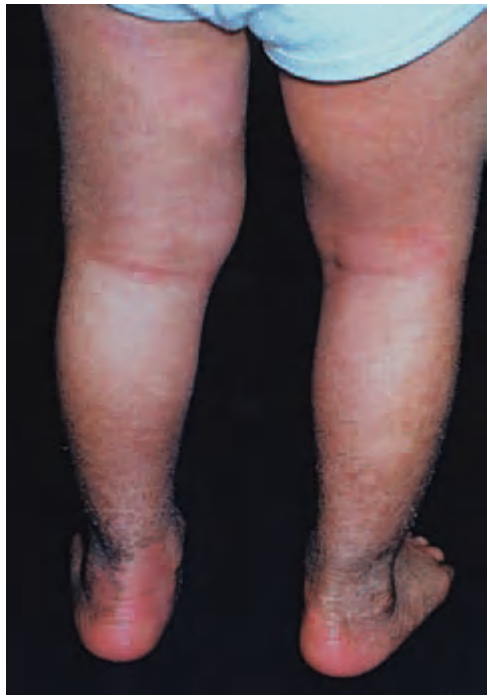

Fig. 34.8 Lamellar ichthyosis, mild (same patient as Fig. 34.4a,b).

flexures and on the digits, palms and soles. Limitation of joint movement, flexion contractures and digital sclerodactyly may result. Additional features in some patients are palmoplantar keratoderma, scarring alopecia, persistent ectropion, and congenital hypoplasia of aural and nasal cartilages. Erythroderma is absent or mild in LI. Pruritus rarely occurs, and sweating is severely impaired. The hair shaft, teeth and mucous membranes are not affected, and growth and intellectual ability are normal. Extracutaneous manifestations have not been reported. Severe forms of LI seldom improve with age, and psychological problems resulting from the cosmetic effects and limited mobility can lead to isolation, depression and poor school performance.

In mild LI (Fig. 34.9), the typical plate-like scale may only occur on the lower legs, upper arms, and possibly the forehead and trunk [11,18]. These patients may also have fine white branny scales on the flexures and neck. They have focal hypohidrosis, usually normal palms and soles, and tend to improve in summer months. Cyclical shedding or peeling may occur.

Autosomal dominant lamellar ichthyosis (MIM 146750). Traupe *et al*. outlined the clinical, ultrastructural and biochemical features of an ichthyosis that clinically resembled LI, but that showed an autosomal dominant transmission in four members, two male and two female, through three generations of a German family [20]. These patients had non-erythrodermic lamellar-type generalized scaling from birth, palmoplantar hyperkeratosis

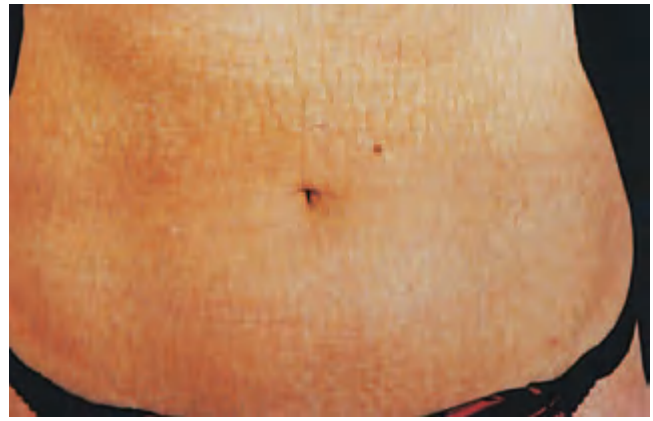

Fig. 34.9 Lamellar ichthyosis, adult with mild disease.

and lichenification of the dorsa of the hands and feet and major flexures. They did not have a collodion membrane at birth, and pruritus was a problem in one child. The light microscopical features were similar to those of classical LI. The electron microscopy findings in two of them differed from those of autosomal recessive LI, and included normal tonofilaments and keratohyaline granules, a prominent transforming zone at the granular–corneal junction and sparse corneocyte lipid inclusions.

Since then, reports of a similar disorder in separate families (French and Swedish) have appeared, although in these cases, a collodion baby phenotype and subsequent mild erythroderma were notable features [21,22]. Of the 32 collodion babies reviewed by Larregue *et al*. [21], 10% were said to have developed autosomal dominant LI, but the disease phenotype is not clearly defined. Lipid analysis of plantar scale from two patients with autosomal dominant LI revealed a different profile compared to that of classical LI [23].

Diagnosis. Differential diagnosis includes XLRI and ichthyosiform erythrodermas with collodion presentation. DNA-based mutational analysis of the *TGM-1* gene, using PCR, requires only a blood sample.

Treatment. Mild LI can be controlled with regular emollients and keratolytics as outlined for the treatment of ichthyosis vulgaris. Topical calcipotriol has been efficacious in LI [24] and beneficial effects of a 10% urea lotion and topical *N*-acetylcysteine have been reported [25,26]. A trial of oral retinoid therapy is indicated in severe LI. Of six patients with typical severe LI, five had a marked improvement, while the sixth had a moderate response with reduction of scaling, pruritus and skin tenderness [27]. The main side effects were cheilitis, epistaxis and hair loss in one. In three of them, low-dose therapy was effective. The management of systemic retinoid therapy is detailed under the heading of treatment of NBIE. A

topical receptor-selective retinoid, tazarotene 0.05% gel, has also produced good results [28].

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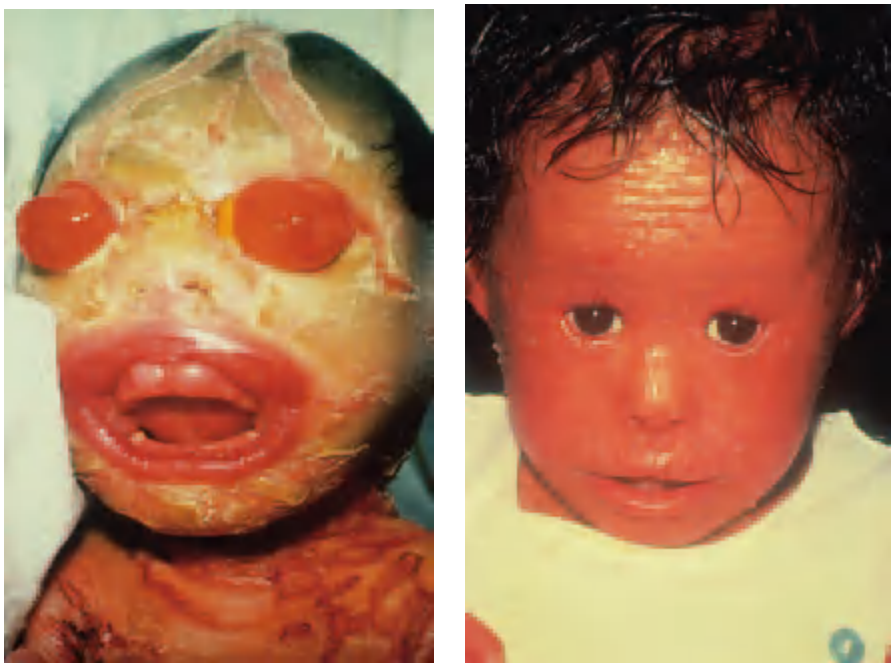
Harlequin ichthyosis (MIM 242500)

Harlequin ichthyosis (HI) describes a severe erythrodermic ichthyosis that causes a distinctive and alarming appearance at birth. The skin patterning and lethality prompted the label of 'harlequin fetus' but, as survival is possible, the term HI is a more appropriate name. This was one of the first genodermatoses to be recorded. An affected baby, who survived for 2 days, was described by Oliver Hart, a Charleston pastor, in his diary of 1750, published in 1896 [1]. HI is, fortunately, a very rare occurrence (approximately five cases in the UK annually) and was invariably associated with stillbirth or early neonatal death until Lawlor's report of a survivor in 1985 [2,3]. Other survivors have been reported since, with most eventuating in a severe erythrodermic ichthyosis, although one was mildly affected [4–9]. Most cases are sporadic with autosomal recessive inheritance, but some kindred have had several affected children [2,8–10].

Aetiology and pathogenesis. Defects in keratin expression and epidermal lipid deposition were reported in the 1970s [11,12]. HI cultured keratinocytes show excessive cornification and failure of desquamation. A study of 10 clinically similar cases from eight separate families revealed defective lamellar bodies (replaced by small vesicles) and intercellular lipid lamellae in all of them. There was abnormal, although variable keratin and filaggrin expression, suggestive of genetic heterogeneity [13,14]. Three subtypes were evident: type 1 cases had a normal keratin profile and positive profilaggrin staining but absent filaggrin expression; type 2 displayed a hyperproliferative keratin pattern in suprabasal cells (prominent K6/16 and reduced K1/10); type 3 had suprabasal K6 and 16 expression and absence of profilaggrin staining and keratohyaline granules, except in intraepidermal sweat ducts. Filaggrin was not expressed in any form of HI; in types 2 and 3, profilaggrin cannot be converted to filaggrin because of a block in post-translational processing [14]. A primary epidermal defect was suspected, specifically defective dephosphorylation secondary to abnormal protein phosphatase activity. In type 2 HI, abnormal expression of protein phosphatase 2Ac, a widely distributed serine–threonine protein phosphatase whose gene is located on chromosome 11 was found [15]. Low reactivity was also seen in type 1 cases [15]. However, in neither type 1 nor type 2 HI have these observations been backed up by molecular genetic evidence.

The expression of a calcium-dependent neutral protease, calpain 1, is reduced in HI epidermis but not in other epidermal disorders [16]. Calpain 1 plays an important part in epidermal differentiation via its role as a regulator of signal transduction and cytoplasmic protease activity. It plays a part in profilaggrin processing and in the activation of transglutaminase and phospholipase



(a) (b)

Fig. 34.10 Harlequin ichthyosis: (a) neonate; (b) aged 18 months.

C. Again no defects in this or related genes have been reported to date.

Histopathology. Skin biopsy shows marked, compact orthohyperkeratosis extending down into dilated hair follicles and pilosebaceous units. Parakeratosis is marked in type 3 HI (see above) and may occur in types 1 and 2. Usually, no other specific changes are noted on light microscopy, and the basal and spinous layers appear relatively normal. In some cases, vacuoles are seen in the stratum corneum and the granular layer is reduced in thickness. Rarely, papillomatosis and a dermal inflammatory infiltrate are present. Pilosebaceous and sweat glands are preserved and non-keratinizing mucous membranes are normal.

Electron microscopy of 10 cases, including one fetal skin biopsy, revealed multiple vacuoles, lipid droplets and cellular remnants in corneocytes in all cases [13]. Keratohyaline granules were abnormal in types 2 and 3. Lamellar bodies in spinous and granular cells were either absent or abnormal in all, and the intercellular lipid lamellae at the granular–corneal junction were not formed. Immunohistochemical staining of the cytoplasmic vesicles seen in granular layer cells suggested that they were abnormal lamellar granules. In fetal biopsies, large abnormal mitochondria in keratinocytes have been noted at 16 weeks' gestation, prior to keratinization [17]. Adnexal keratin plugging at 18–20 weeks preceded interfollicular changes, and a thickened cornified envelope was also evident.

A skin biopsy from a 2-year-old survivor showed histological and ultrastructural features similar to those of severe NBIE with more pronounced lamellar body defects [10]. However, there was a persisting defect in filaggrin synthesis.

Clinical features. The affected infant, usually premature, sometimes stillborn, is encased in a rigid, taut, yellow-brown, adherent skin, a hyperkeratotic 'coat of armour', covering the whole body surface. Deep fissures occur prenatally over the scalp and soon after birth, the inflexible 'cast' splits, producing further red fissures and a skin pattern resembling a harlequin's costume. The head may appear microcephalic, and facial features are distorted because of severe ectropion, conjunctival oedema, which obscures the eyes, and eclabium (everted lips) (Fig. 34.10a). The scalp feels boggy, and the nose and external ears are tethered and appear rudimentary. Oedematous hands and feet may either be encased in hard mitten-like casts, or covered with a mucoid membrane, but the digits are well formed underneath. Additional congenital defects have been found in some cases.

Movement is restricted, and respiratory insufficiency results from limited chest expansion and sometimes coexistent skeletal deformity. Absence of effective sucking causes feeding difficulties leading to hypoglycaemia, dehydration and renal failure. Temperature instability and infection commonly supervene, and may lead to rapid demise. However, several survivors have been reported in recent years [2–10]. In these cases, intensive nursing and medical care prolonged survival until the plate-like scale was shed over a period of weeks. Early retinoid therapy was instituted in some cases and in all but one

a severe ichthyosis resembling NBIE was the eventual outcome. One survivor, at 9 years of age, was reported to be of normal intelligence and had discontinued retinoid therapy [4]. Another, at age 9 years, had severe ichthyosiform erythroderma, a nutritional osteomalacia, short stature and limb contractures but was bright and attending mainstream school (Fig. 34.10b) (F. Lawlor, personal communication, 2002) [2,3].

Genetics and prenatal diagnosis. HI is an autosomal recessive disorder. However, it has been suggested that some cases may result from a sporadic new dominant mutation with parental mosaicism in families with recurrent cases [2,10,13]. The uniform HI phenotype contrasts with its genetic heterogeneity. Each family may possess a different genetic defect, but within families disease expression is consistent.

Detailed genetic counselling is required for affected families, and prenatal diagnostic testing in future pregnancies is available in selected centres. In the past, this depended on the identification on light microscopy of premature keratinization by the 20th to the 22nd week of gestation [18]. Earlier diagnosis is possible with electron microscopy, which shows atypical intraepidermal vesicles at 18 weeks' gestation, during the periderm phase and before the onset of cornification [19]. Amniocentesis at 17 weeks' gestation has also shown intracellular lipid vesicles in clumped shed keratinocytes, presumably derived from follicular epidermis [20]. Ultrasound detection of amniotic fluid debris in HI has been noted [21]. It is hoped that identification of specific genetic mutations will allow first trimester diagnosis and accurate prognosis in individual families.

Despite the disproportionately high incidence of affected offspring in some families, HI is regarded as autosomal recessive and the extended family should be advised of the genetic risk of intermarriage. HI has been reported in one non-identical twin [22] and in two twin pairs [10,23].

Differential diagnosis. The distinctive clinical features of HI are unlikely to be confused with the less severe presentation of the collodion baby, but a small proportion of affected neonates fall between the two presentations. These may in the past have been referred to as 'chrysalis babies'. The early neonatal appearance of HI may resemble that of restrictive dermopathy, but in the latter the tight thick skin persists and skeletal and facial abnormalities are evident. A variant of infantile systemic hyalinosis and the 'stiff skin syndrome' (congenital fascial dystrophy) also present with tight skin.

Treatment. Up to the 1980s, the outcome was uniformly bleak with death resulting in the first days or weeks of life. The potential for survival of HI babies presents families and carers with the dilemma of providing intensive neonatal care while accepting the outcome of severe lifelong ichthyosis. The family should be informed of the implications of the condition, encouraged to consider all options and supported in the part they wish to play. Staff unfamiliar with the startling and distressing deformity also need to be enlightened about the evolution and practical problems associated with HI. If survival seems possible and intensive care is available, a care plan should be drawn up within the first day of life and support provided for staff in their difficult role. The facilities of a neonatal intensive care unit are required to cope with the predictable problems of hypothermia, feeding and respiratory difficulties, dehydration, electrolyte and renal complications and sepsis. Regular paraffin-based emollient and oil baths are required from day 1 onwards. The apparent benefit of early retinoid therapy is difficult to assess and not all survivors have received it [8]. Early introduction of acitretin accelerates shedding of hyperkeratotic plates. Later, staged plastic surgery may improve the cosmetic result, and intermittent retinoid therapy may reduce the degree of disability.

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Bullous ichthyosiform erythroderma (MIM 113800)

Bullous ichthyosiform erythroderma (BIE) is a rare autosomal dominant disorder of keratinization that, in its early phase, is associated with blistering. It was first described by Brocq in 1902 [1]. The incidence is thought to be less than 1 in 100 000, although it is likely that some mild cases go unrecognized. A characteristic histological picture of hyperkeratosis with lysis and tonofilament clumping in granular layer keratinocytes characterizes this condition, and BIE may also be known as 'epidermolytic hyperkeratosis'. To date, all investigated cases of BIE have been shown to result from mutations in particular keratin genes, with good correlation of phenotype and genotype as skin lesions occur in sites where the affected keratin is expressed.

Aetiology and pathogenesis. The aggregation of tonofilaments in suprabasal keratinocytes in BIE is suggestive of an underlying genetic defect of keratin synthesis or degradation, involving keratins K1 and/or K10, as they are distributed only in the suprabasal compartment in normal epidermis [2]. Immunoelectron microscopy, using highly specific keratin monoclonal antibodies, showed selective involvement of K1/K10 in the aggregated tonofilaments suprabasally, while the non-aggregated filaments seen in basal cells consisted of K5 and K14 [3]. These data pointed to a primary genetic defect in K1 or K10 [3]. Increased filaggrin reactivity was also evident on immunohistochemistry and protein blotting, but was preceded by keratin filament aggregation, suggesting that the aggregation was independent of the action of profilaggrin. In some cases, there appeared to be defective keratin–filaggrin interaction because of premature cell death, abnormal filaggrin processing and structural alteration in keratin interaction points. Affected fetuses have been shown to develop suprabasal tonofilament clumps at a stage of skin development where keratohyalin granules are not yet expressed, implying that filaggrin changes are secondary [4]. There are also alterations in the staining pattern and electron density of cornified envelope proteins, thought to be secondary to the keratin defects [5]. Loricrin staining was prematurely expressed and associated with keratin aggregates. Trichohyalin reactivity, not normally found in epidermis, was found in granular cells.

Genetic linkage studies confirmed autosomal dominant inheritance, and revealed linkage to either of the keratin gene clusters on chromosomes 12q and 17q [6–8]. Transgenic mice carrying mutant K10 developed skin abnormalities similar to BIE [9], and transgenic mice expressing a severely truncated K10 protein displayed a BIE-like phenotype in heterozygotes and a more severe phenotype in homozygotes [10]. Several groups have described mutations in the highly conserved regions of K1/K10, predominantly involving point mutations resulting in amino acid substitutions within the specialized sequences of the ends of the rod domains [11–18; see also Intermediate Filament Mutation Database, http://www.interfil.org]. These conserved regions are critical for filament integrity and assembly, and the mutations disrupt higher filament assembly in a dominant-negative fashion, leading to collapse of the network and filament aggregation around the nucleus. Most mutations occur within the conserved sequence motif at the beginning of the helical rod domain, with a particular arginine codon in K10 being most vulnerable, the 'hotspot arginine' [13,15]. Specific mutations involving different amino acid substitution within the 2B rod domain of K1 have been associated with the rare annular migratory variant of BIE [19].

Identification of the gene abnormality in a parent can permit prenatal diagnosis by direct gene sequencing from a chorionic villus sample earlier than by prenatal skin biopsy. In a genetic study of 21 American families, the presence or absence of palmoplantar keratoderma (PPK) was used to subset the patients [20]. Of the six families with PPK, four had K1 mutations whereas eight of the 15 families without PPK had K10 mutations.

Histopathology. Skin biopsy shows marked epidermal acanthosis and hyperkeratosis. In the cells of the prominent and degenerate granular layer, and in the upper spinous layers, there are multiple perinuclear vacuoles and large clumped keratohyaline granules. Inter- and intracellular spaces form as a result of suprabasal cytolysis or cell rupture, and a split with oedema in the granular layer marks the site of a blister (Fig. 34.11). These features together are described by the term 'epidermolytic hyperkeratosis'. In mild forms of the disease, these changes may be subtle. The basal keratinoyctes are normal and there is a mild upper dermal lymphocytic infiltrate. The epidermis is hyperproliferative and the number of basal keratinocyte mitoses approaches that of psoriatic erythroderma [21].

Electron microscopy reveals clumped keratin tonofilaments dispersed around the keratinocyte nucleus. Desmosomes are disrupted to a variable degree, and clefts between keratinocytes are associated with oedema and acantholysis. The ultrastructural tonofilament changes precede the vacuolation in spinous and granular cell layers [2,22]. EHK is not unique to BIE but is seen in ichthyosis bullosa of Siemens, some cases of ichthyosis hystrix,

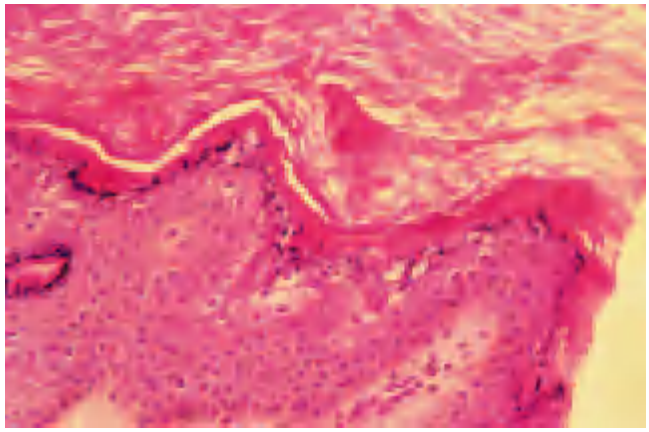


Fig. 34.11 Bullous ichthyosiform erythroderma: histological features of epidermolytic hyperkeratosis.

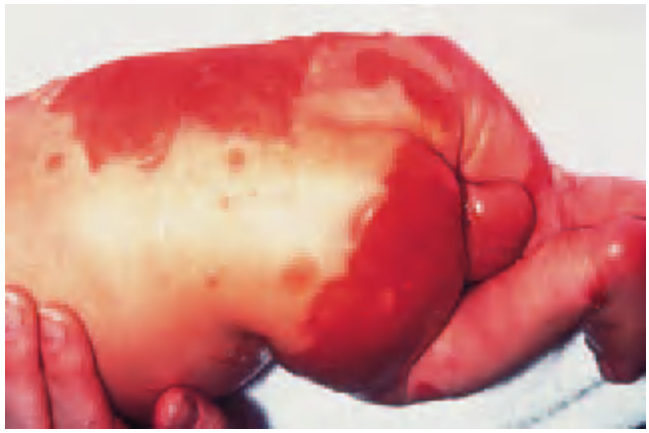


Fig. 34.12 Bullous ichthyosiform erythroderma, neonate.

Vorner's palmoplantar keratoderma, a subgroup of epidermal naevi, and as an incidental finding in a variety of unrelated lesions such as solitary acanthoma, dermatofibroma, melanocytic, actinic and inflammatory lesions, in the walls of epidermal cysts and even occasionally in normal oral mucosa [23,24].

Clinical features. BIE typically presents with epidermolysis (fragile skin), which gives way to gradual evolution of hyperkeratosis. A mild generalized erythroderma is present at birth. Flaccid blisters, peeling and superficial erosions at sites of minor trauma or friction are apparent within the first few hours of life (Fig. 34.12). Frequent misdiagnoses at this stage include staphylococcal scalded skin syndrome and epidermolysis bullosa. However, the baby is generally apyrexic and well, and focal hyperkeratosis may hint at the diagnosis. In the past, many of these infants developed severe infection, dehydration and malnutrition leading to a considerable mortality, but with intensive neonatal care their prognosis has greatly improved. The superficial erosions heal rapidly without scarring, and easy blistering ceases in the first few months

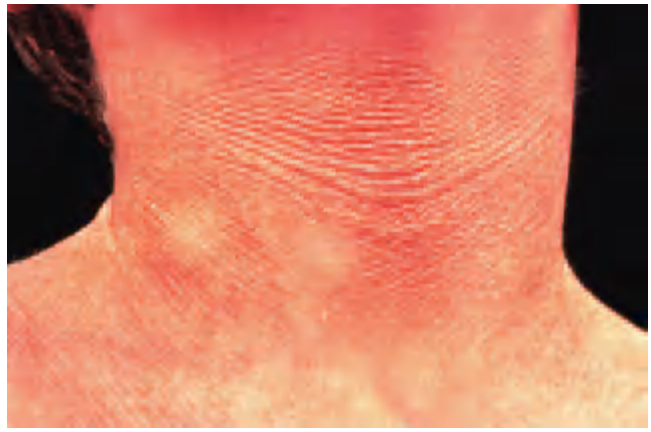


Fig. 34.13 Bullous ichthyosiform erythroderma, neck.

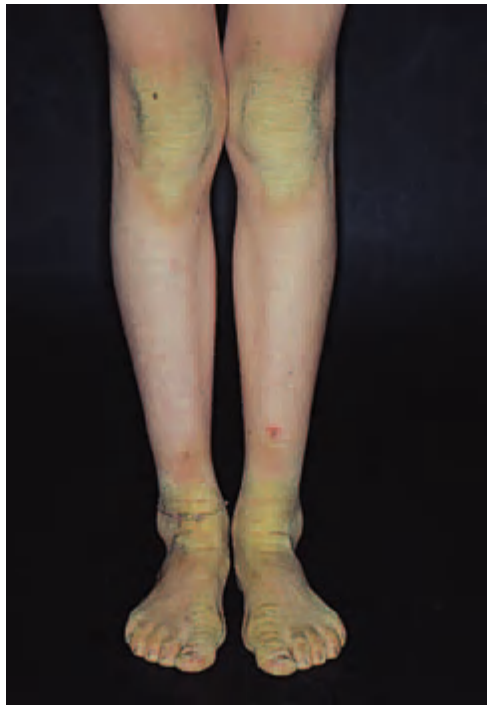
of life. Localized blistering at sites of trauma (the nappy/diaper area, thighs, knees) or infection continues through childhood. Erythroderma fades while the characteristic grey waxy scale progress.

Increasing hyperkeratosis is obvious from early childhood and is most prominent around the anterior neck, flexures, abdominal wall, infragluteal folds and scalp (Figs 34.13 & 34.14). Yellow–brown, waxy, ridged or corrugated scale builds up in skin creases, sometimes forming spiny (hystrix) outgrowths. Cobblestone-like keratoses occur at other sites such as the dorsal hands and feet, and over the trunk. Verrucous plaques may coat bony prominences, scalp and areolae, and chunks are easily dislodged, leaving tender erosions where scale slowly accumulates again. Skin colonization by *Staphylococcus*, brevibacterium and possibly fungi produces a distinctive and embarrassing body odour. Repeated skin infections, causing blisters, pustules or cellulitis, especially in macerated flexural areas, are a troublesome complication in some children. The central face is mildly affected but scalp involvement can be severe and cause patchy alopecia. Spontaneous blistering virtually disappears by adolescence and only a mild erythema persists. Some mildly affected individuals have transient blistering in infancy with focal hyperkeratosis thereafter.

Palmoplantar hyperkeratosis develops in approximately 60% of patients with BIE and may result in recurrent painful fissures, contractures, sclerodactyly and foot deformity with impaired function. It does not relate to disease severity. Nail dystrophy is rare, although curvature may result. Severely affected children may be of short stature, although many catch up in adolescence.

An unusual variant of BIE, characterized by recurring, migrating, truncal annular and polycyclic plaques in association with more typical flexural lesions has been reported [25]. Histological features of EHK and keratin K10 or K1 mutations, similar to those of BIE, have been identified and it has been termed annular epidermolytic hyperkeratosis [19,25,26].

(a)



(c)

(b)

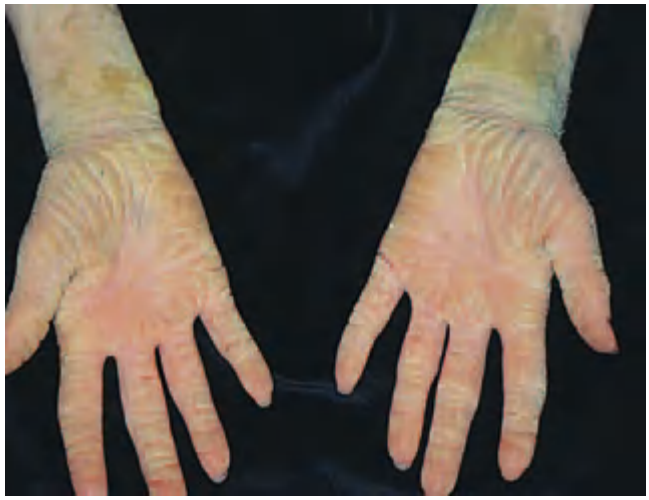


Fig. 34.14 Bullous ichthyosiform erythroderma: (a) arms; (b) palms; and (c) legs.

Evolution of BIE is variable, but in common with other autosomal dominant skin disorders it tends to improve with age. BIE sufferers may have significant physical and psychological morbidity. Visible scaling, skin fragility, keratoderma and odour can lead to social and occupational problems. Mild learning difficulties in some patients may be related to perinatal complications.

Naevoid BIE. There have been several reports of individuals with an asymmetrical linear, focal or naevoid lesion (including comedo and systematized naevi) showing histological features of EHK, who have had a child with generalized BIE [27–29]. The limited or naevoid disease expression in the parent, which is distributed in Blaschko's lines, is suggestive of a genetic somatic mutation of keratins K1 or K10 at an early stage in embryonic life, producing phenotypic and gonadal cell mosaicism [27]. K1/K10 mutations have been found in keratinocytes from affected but not unaffected sites in the parent [30]. The parental lesions may be overlooked or misdiagnosed.

Differential diagnosis. In the neonatal period, other blistering disorders such as epidermolysis bullosa, staphylococcal scalded skin syndrome, herpetic infection and incontinentia pigmenti must be excluded by clinical, histopathological and microbiological assessment. In older patients, ichthyosis hystrix, ichthyosis bullosa of Siemens and non-epidermolytic epidermal naevi may resemble BIE.

Genetics. At least half of cases of BIE have no family history of the disease and are presumed to have suffered a new keratin gene mutation. However, both parents of an affected child should be carefully examined for focal keratotic lesions suggestive of somatic and gonadal mosaicism. In the absence of suspicious parental lesions, further siblings should not be at risk, but an affected parent will transmit the condition in an autosomal dominant fashion to their offspring, who will have generalized disease. The occurrence of inter- and intrafamilial variation in disease severity further complicates genetic assessment. A mildly affected parent may have a severely affected child, either because they have improved with age or because they have a mosaic expression. The reverse can also happen with an attenuated form of familial BIE appearing in the next generation, or variation in severity among affected offspring. It is postulated that a benign simultaneous polymorphism in keratin or keratin-associated protein genes has a modifying effect on the phenotypic expression of the disease in these families [14].

Prenatal diagnosis, based on identification of the characteristic ultrastructural changes on fetal skin biopsy, can be carried out at around 20 weeks' gestation, using ultrasound-guided fetoscopy [31]. Tonofilament clumping is the earliest morphological abnormality, occurring during the second trimester, and precedes the formation of keratohyalin granules and stratum corneum [32]. It is now possible to apply DNA screening techniques to identify specific K1 and K10 gene mutations in chorionic villus samples, following direct gene sequencing of the index case [15].

Treatment. Emollients are of limited value in BIE as the scale is often waxy and macerated. Keratolytic preparations (salicylic acid, α-hydroxy acid or propylene glycol compounds) reduce hyperkeratosis on exposed sites but their irritancy limits patient tolerance. Patients are best placed to decide which, if any, they wish to use and their needs will change over time. Regular use of antiseptic washes and appropriate systemic antibiotics may be required to control repeated cutaneous bacterial and fungal infection and associated body odour. Sensitivity testing of *Staphylococcus aureus* isolates, and cyclical rotation of long-term antibiotics, are indicated for those requiring long-term antibiotic treatment. Topical calcipotriol produces a slight reduction in scaling at the cost of skin irritation [33]. Retinoid therapy is beneficial in some patients, but significant reduction in scaling is often associated with unacceptable skin fragility, blistering and tenderness [34] (for details of acitretin dosage and surveillance, see treatment of NBIE, p. 34.19).

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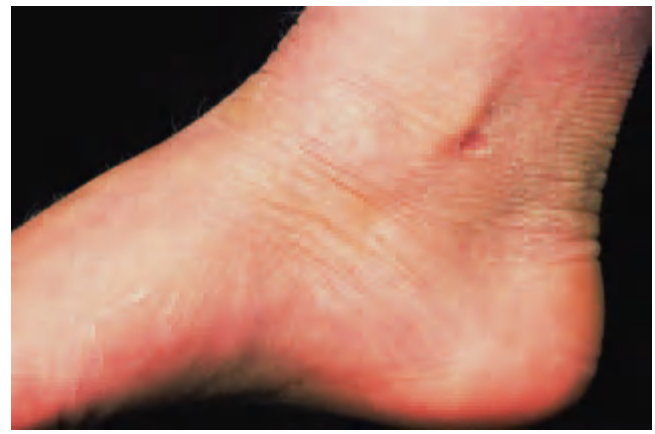

Fig. 34.15 Ichthyosis bullosa of Siemens.

Ichthyosis bullosa of Siemens (MIM 146800)

A mild variant of BIE was described by a Dutch dermatologist, Siemens, in 1937 in a large Dutch kindred [1]. The concept was revived by Traupe who confirmed autosomal dominant inheritance [2] and the phenotype was described in detail in additional Dutch kindreds [3]. Ichthyosis bullosa of Siemens (IBS) is probably less common than BIE, but some milder cases may escape detection.

Aetiology and pathogenesis. In addition to keratins K1 and K10, the high suprabasal keratinocytes express a further type II keratin K2e, a protein of molecular weight 65.8 kDa encoded by a 2.6-kb RNA species [4,5]. As the site of EHK in IBS correlates with its expression sites, K2e was recognized as a likely target gene [6]. Linkage analysis of two affected Dutch families showed linkage with the type II gene cluster on chromosome 12 [7]. Direct sequencing of PCR products of keratin K2e showed point mutations in the highly conserved helix termination motif in a five-generation kindred and a sporadic UK case [8]. Three different K2e mutations were found in four Dutch families, including the descendents of Siemens' original kindred [9]. Several K2e rod domain mutations have been reported in other patients [10–13]. The identical substitution of a glutamic acid with a lysine in helix 2B rod domain of K2e has been found in the majority of IBS cases, including a number of sporadic cases (Intermediate Filament Mutation Database, http://www.interfil.org), indicating that this is a mutation hotspot.

Histopathology and pathogenesis. On histological examination, features of EHK are confined to the prominent granular layer and the upper spinous layer. Basal and suprabasal keratinocytes appear normal. Sites of 'mauserung' (moulting) reveal intracorneal blistering with orthohyperkeratosis above and below the split. Electron microscopy shows granular cell oedema with thick bundles and some clumps of tonofilaments [2].

Clinical features. The characteristic features are mild neonatal disease, or delayed onset, with episodes of superficial blistering persisting through childhood and sometimes into adult life. These occur predominantly on the flexures, shins and abdomen, and quickly rupture to produce annular peeling. There is variable, grey, rippled hyperkeratosis on the limbs and lower trunk, with flexural accentuation and mild hypertrichosis in some. IBS is less severe than BIE, and may resemble the flexural lichenification of atopic eczema. Circumscribed patchy scaling occurs elsewhere, and focal desquamation or moulting of scale, which Siemens called 'mauserung', is seen at the flexures and acral sites, especially the dorsal hands and feet (Fig. 34.15). Palmoplantar blistering is associated with hyperhidrosis and is more severe in summer, but PPK and skin odour are absent. Erythroderma does not occur in IBS, but sudden deterioration with diffuse erythema and peeling resulting from staphylococcal infection has been observed.

A similar ichthyosis, also caused by K2e mutations, has been reported under the title of ichthyosis exfoliativa [14,15]. This and IBS are now regarded as a single entity [7]. An autosomal recessive form of exfoliative ichthyosis (without epidermolytic hyperkeratosis) in an inbred Bedouin family has been documented [16].

Diagnosis. This condition may be mistaken for other autosomal dominant ichthyoses, ichthyosis vulgaris, the dominant variant of lamellar ichthyosis and mild BIE. In certain phases, epidermolysis bullosa simplex, peeling skin syndrome, infected atopic eczema or staphylococcal scalded skin syndrome may be suspected. Prenatal diagnosis, although possible, is rarely an issue. Molecular diagnosis can be performed using whole blood.

Treatment. Emollients and mild keratolytic preparations suffice in most, and often appear to induce an impressive remission. A beneficial effect from 12% lotion of ammo-

nium lactate has been reported in IBS [17]. Avoidance of friction and measures to reduce hyperhidrosis are indicated. Antibiotics should be used to treat skin infection and may prevent episodic widespread blistering. Some cases responded well to low-dose retinoid therapy [18].

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Ichthyosis hystrix (MIM 146590)

The subgroup of ichthyosis hystrix (IH) encompasses a number of rare conditions, characterized by spiny hyperkeratotic scale similar to that of BIE. They differ from BIE in that blistering is not a feature, erythroderma is mild or absent, limited or naevoid forms are more common and few show the histological features of BIE. They are autosomal dominant disorders.

History and nomenclature. The first documented kindred with familial IH was the Lambert family of Suffolk, who between 1731 and 1851 had 11 affected members in four generations [1]. The first, Edward Lambert, attended the Royal Society of Medicine in 1731 and some of his affected descendents, known as the 'porcupine men', appeared in circuses, billed as 'a new species of man'. A review in the 1950s showed that, contrary to reports, females were also affected and the ichthyosis was autosomal dominant [2]. Their skin, normal at birth, developed dark warty scaling after 7 weeks of age. There was no blistering, and the face, palms and soles were spared. The severity of the ichthyosis varied among family members and lessened in later generations.

Similar cases of ichthyosis were reported during the 19th century, and in 1954 Ollendorff-Curth and Macklin described two teenage brothers who had congenital verrucous scale on the scalp, neck and limbs, PPK and keratoses on the lips, ears, nipples and buttocks [3,4]. Histological examination of their skin showed acanthosis, hyperkeratosis and swollen hydropic granular layer keratinocytes. Affected relatives spanning five generations had a variable phenotype and it was regarded as an autosomal dominant condition.

Other variants include an isolated case reported by Bafverstedt [5] with striking hystrix scaling on the face, IH gravior of Rheydt (two patients with ichthyosiform erythroderma, PPK and deafness) now known as HID syndrome [6,7]. HID syndrome is allelic with KID syndrome and caused by the same connexin 26 mutation [8]. Zeligman proposed that, on histological grounds, many cases of IH were variant BIE [9]. A single case of a biphasic ichthyosis (typical IH followed by centrifugal scaly lesions in middle age) was described [10]. IH shows considerable phenotypic heterogeneity [11].

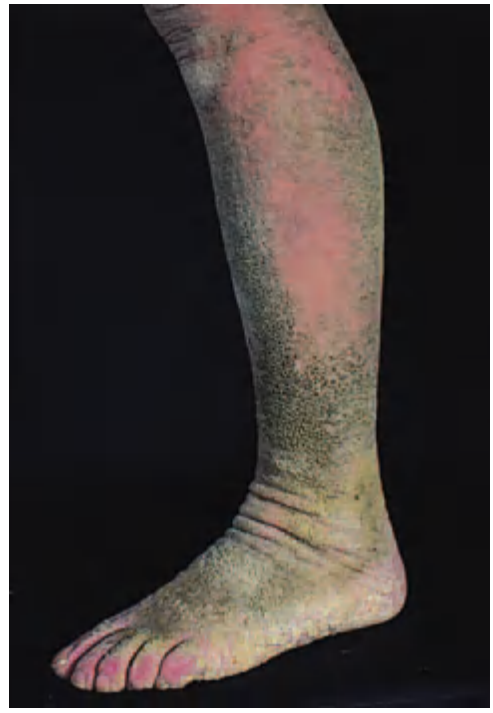
Aetiology and pathogenesis. Features suggestive of abnormal keratin expression in middle and upper spinous keratinocytes, from both affected and unaffected skin, were noted [12] but other groups reported normal epidermal keratin labelling [13] and absence of linkage to the keratin gene clusters on chromosome 12q and 17q in a mildly affected family [14]. The electron microscopy features of thick, continuous, perinuclear shells of haphazardly arranged intermediate filaments, flanked by a region rich in ribosomes, are suggestive of a disorganized keratin intermediate filament network [15]. Binucleate cells and perinuclear vacuolation are common, although epidermal proliferation rates are normal. Recently, a novel keratin mutation affecting the variable tail domain (V2 domain) of keratin 1 has been described in an African American family with severe mutilating PPK diagnosed

as IH of Curth–Macklin [16]. This led to a distinctive cytoskeletal abnormality (unlike that of EHK), with failure of intermediate filament bundling, retraction of the cytoskeleton from the nucleus and failure to translocate loricrin to the desmosomal plaques at the cell periphery. Interestingly, a British Caucasian family with an almost identical frame-shift mutation in K1 presented clinically with striate keratoderma of the palms and focal keratoderma of the soles, a phenotype much milder than and quite distinct from that seen in the African American kindred [17]. Interracial differences in genetic modifiers may explain this phenotypic disparity. IH is both clinically and genetically heterogeneous.

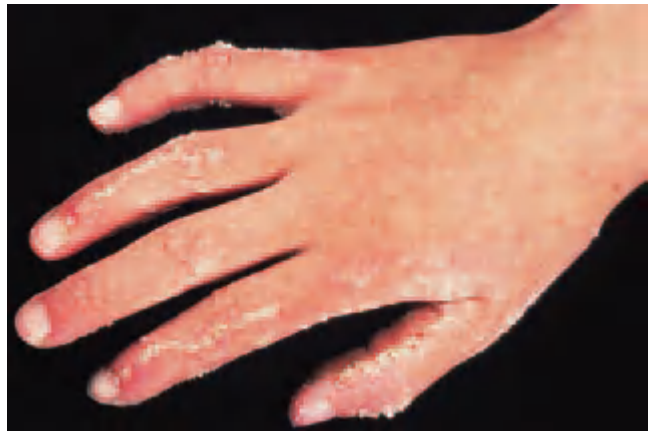
Histopathology. Early reports identified the histological features of EHK [9] but the phenotype of these cases is not clearly defined and epidermolysis is typically absent. Light microscopy shows orthohyperkeratosis, patchy parakeratosis, acanthosis and papillomatosis. Scattered vacuolated and binucleate keratinocytes in the upper epidermis are characteristic. The granular layer is reduced and contains rounded and some vacuolated cells. Electron microscopic studies of Curth–Macklin type IH highlighted a characteristic continuous perinuclear tonofilament shell (in contrast to the clumped filaments in EHK) in the upper spinous and granular layers, resulting in three distinct cytoplasmic compartments [12,15,18,19]. That inside the tonofilament shell contained ribosomes, mitochondria and deformed lamellar bodies, while the band outside had normal tonofilament structure terminating on desmosomes. Conspicuous vacuoles (some of which contained lipid material) were present in 30%, and double nuclei in 10% of spinous and granular keratinocytes. Similar changes were seen in clinically uninvolved skin, and persisted with retinoid therapy [19]. An unusual histological finding in a family of eight with IH was the presence of cornoid lamellae [20].

Clinical features. Affected cases may present at birth with a generalized or naevoid scaly erythema without blistering or skin fragility. However, delayed onset in infancy or childhood has been noted. Hystrix ('porcupine spine') scaling, often a muddy brown or grey colour, accumulates during childhood and affects extensor aspects of the limbs (Fig. 34.16a), truncal areas to variable degrees and flexures to a lesser extent than in BIE. Mild scaling may occur at other sites including the scalp, and PPK, diffuse or striate, affects most patients. This may lead to functional impairment, contractures and nail dystrophy. Scaling stabilizes or improves slightly in adulthood. Naevoid lesions follow the lines of Blaschko, and are accentuated by summer tanning of unaffected skin (Fig. 34.16b). There is little seasonal variation, and disturbances of sweating are rare.

IH of Rheydt was reported in two unrelated sporadic cases [6,7]. Generalized scaling, more pronounced on the face and limbs, developed from birth and was associated with profound deafness and PPK. This is now known as HID syndrome.



(a)



(b)

Fig. 34.16 Ichthyosis hystrix: (a) adult male; and (b) naevoid acral lesions in Blaschko's lines in a child.

The development of multiple keratoses and squamous cell cutaneous carcinoma in two patients may have been linked to prior carcinogenic treatments (poorly documented), but a cancer proneness related to IH or EHK cannot be excluded [21,22].

Genetics. Where a positive family history is available, all types of IH have been inherited as an autosomal dominant trait [2,4,12]. There is considerable inter- and intrafamilial variation, and the occurrence of naevoid forms also complicates genetic counselling.

Treatment. Non-greasy emollients are used by some patients, while others prefer keratolytic preparations such as salicylic acid or propylene glycol compounds to reduce hystrix scaling. Their use is not influenced by the fragility or malodour that occurs in patients with BIE. Topical calcipotriol or retinoid may be helpful. Systemic retinoid therapy, intermittent or continuous, is beneficial in some [19] but not in others [20] (for details of acitretin dosage and surveillance, see therapy section of NBIE, p. 34.19).

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Netherton's syndrome (MIM 256500)

Netherton's syndrome (NS) is the most common of the multisystem ichthyosiform syndromes, and comprises an ichthyosiform dermatosis (primarily episodic peeling) with a variable erythroderma, hair shaft defects and atopic features. It is an autosomal recessive condition with a worldwide distribution, and an incidence similar to or greater than NBIE, perhaps more than 1 in 100 000. In the absence of a family history, diagnosis may be delayed because of the gradual evolution and heterogeneity of the clinical features. Misdiagnosis and a high neonatal mortality rate in the past have contributed to an underestimate of its incidence.

Netherton's original patient, reported in 1958, was a young girl with a generalized, scaly, erythematous 'dermatitis', paroxysmal pruritus and a hair shaft defect subsequently identified as trichorrhexis invaginata (TI) [1]. Later reports noted the association of TI with migratory double-edged scaly lesions termed ichthyosis linearis circumflexa (ILC) [2]. ILC had been described by Comel in 1949, but there was no comment on that patient's hair [3]. TI is a pathognomonic finding in NS, while the skin manifestations are variable.

Aetiology and pathogenesis. Although genetic mutations of the serine protease inhibitor Kazal type 5 (*SPINK5*) gene have been identified in several NS patients [4–6], the pathogenetic mechanisms of NS are poorly understood. Clinical and histopathological features point to an intermittent disruption of epidermal and hair shaft maturation and keratinization. Electron microscopy shows premature lamellar body secretion and abnormal lipid processing in the intercellular space, which accounts for the severe impairment of the stratum corneum permeability barrier in NS [7]. This leads to an increase in epidermal DNA synthesis and turnover, further disrupting lipid metabolism. In the hair follicle, the TI lesion coincides with a bulge of external root sheath cells, which invaginate the hair shaft at the level of the keratogenous zone [8]. Failure to convert sulphydryl groups to disulphide bonds in the cortical cells of the hair at this level may contribute to the focal softening [9]. The intermittent nature of the hair shaft defect and the migratory pattern of lesions of ILC is, as yet, unexplained. Retinoid therapy induces deterioration in most patients with NS, and a parallel exists in a transgenic mouse model with negative retinoic acid receptors, which also develops erythroderma and poor barrier function. Impaired transcription of differentiation-relevant retinoic acid receptor genes in NS has been suggested [10].

Some features of atopic eczema are seen in NS and the skin permeability barrier is disrupted in both. Histological changes in NS include spongiosis and exocytosis as seen in atopic eczema, but immunohistochemical markers differed [11]. Raised total and specific IgE levels are characteristic [12,13]. Other immune function tests have usually shown only minor and inconsistent abnormalities. The *SPINK5* gene is located adjacent to a cytokine gene cluster

and research efforts are now focusing on the genetic mechanisms of atopy and IgE responses.

The *SPINK5* gene is composed of 33 exons spanning over 61 kb on the distal long arm of chromosome 5q32. It encodes a serine protease inhibitor proprotein, also called LEKTI, which is thought to be necessary for epidermal cell growth and differentiation. *SPINK5* transcripts are expressed in the upper stratum spinosum, the stratum granulosum and in hair follicle and sebaceous gland epithelium. The substrates and mode of activation of the *SPINK5* gene product are unknown. The resultant peptides appear to exert an inhibitory effect on epidermal serine proteases that mediate corneocyte desquamation (perhaps by targetting desmoglein 1) and indirectly help to maintain the epidermal permeability barrier [14]. Elevated trypsin-like proteolytic activity in the stratum corneum in NS provides support for this hypothesis and helps to explain the prominent inflammatory nature of the cutaneous lesions. In NS patients with severe erythroderma, the trypsin levels were higher than in those with a mild phenotype. Homozygous frameshift and splicing *SPINK5* mutations were associated with more severe disease than downstream nonsense mutations, which caused milder ILC-type lesions [5].

Histopathology. The histological features vary with the type and phase of the lesion sampled. Hyperkeratosis is mild, in contrast to other ichthyoses, but parakeratosis and a reduced or absent granular layer occur at the spreading border of a lesion. Eosinophilic material may collect within the corneal and granular layers in ILC lesions. An intracorneal split at the site of degenerative parakeratotic corneocytes was noted by Comel [3] and others. Psoriasiform epidermal hyperplasia, papillomatosis and a mixed perivascular inflammatory infiltrate occur in older ILC lesions and in the more diffuse, scaly erythroderma. Acute erythroderma in NS is accompanied by pronounced inflammatory changes with spongiosis, exocytosis, intraepidermal microabscesses and upper epidermal eosinophilic necrolysis, which may lead to a subcorneal split. Features of a non-specific dermatitis may be reported.

Ultrastructural studies in NS have identified inclusion bodies (possibly lysosomes) containing finely granular material in suprabasal keratinocytes, reduced numbers of tonofilament–keratohyalin structures and desmosomes and abnormal lamellar bodies [7,10]. Intercellular lipid lamellae in the stratum corneum were, as a result, disorganized and even absent in places. Lesions of ILC and erythroderma may show similar epidermal changes of retarded keratinization and eosinophilic granular material between and within cells [10].

Microscopy of the scalp and eyebrow hair in NS shows, in a variable proportion of intact hairs, the 'bamboo' nodal dilatation consisting of a bulbous distal hair end invaginating a concave dilated proximal hair terminal (Fig. 34.17). The proportion of scalp hair affected varies from 5 to 50%, and the only clue to its presence may be ragged cupped proximal hair ends, where the fragile node has fractured, 'golf tee hairs' [15]. Hair sampling may have to be repeated several times, and clipped hairs, especially eyebrows, may be the most informative. Pili torti and trichorrhexis nodosa also occur. Scalp biopsies have shown early nodal deformity occurring at the keratogenous zone within the hair follicle and variable perifollicular inflammatory changes [8–10].

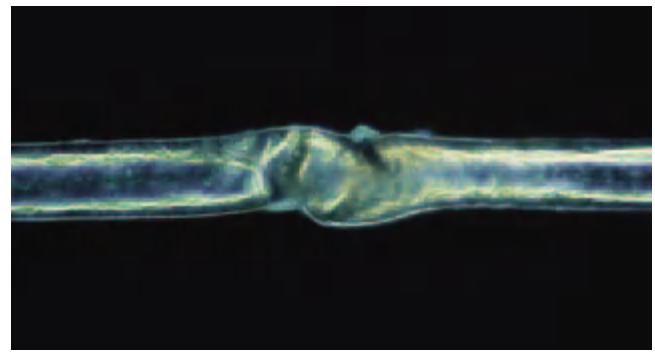

Fig. 34.17 Trichorrhexis invaginata.

Clinical features. Generalized erythroderma of variable intensity is usually evident at or shortly after birth, and desquamation and scaling quickly develop (Fig. 34.18). A minority is mildly affected. Collodion membrane is not a feature, and the infant is usually born at term with average birth weight. Common complications in the neonatal period and infancy, resulting from epidermal barrier disruption, are temperature instability, skin and systemic infection including fungal sepsis and hypernatraemic dehydration. Hypernatraemia in infancy is more common in NS than in other congenital erythrodermas [16,17]. Severely affected infants often suffer from marked failure to thrive in the first year or so, and may have mild diarrhoea. This occurs even with dietary supplementation and, although malabsorption is a recognized though rare complication of erythrodermas ('dermopathic enteropathy'), it is more pronounced in NS. Jejunal villous atrophy was found in one of three NS infants who had biopsies (non-gluten sensitive and resolving spontaneously at 10 months of age) [13] and in three of five patients in another report [18]. In fact, most of these infants begin to put on weight in their second year, although they may remain below the 25th centiles for height and weight. The erythroderma tends to improve also, but can recur unpredictably. Infant mortality in NS was, in the past, significant and often attributed to 'Leiner's syndrome' or other congenital erythrodermas. A rare late complication is dilated cardiomyopathy [19].

During childhood, approximately half of NS patients

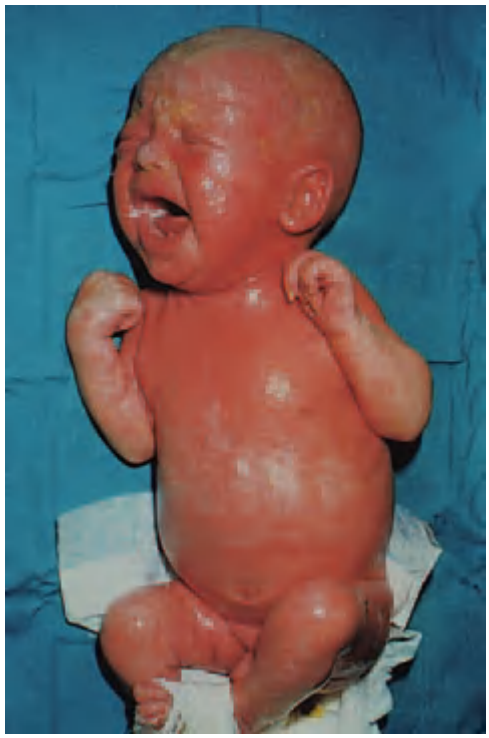

Fig. 34.18 Netherton's syndrome, erythrodermic neonate.

develop lesions of ILC on the trunk and limbs, but they may still be at risk of acute erythroderma. A typical ILC lesion is an erythematous, exfoliating or scaly, annular or polycyclic, flat patch with an incomplete advancing double edge of peeling scale (Fig. 34.19). ILC is episodic, with migrating lesions, often in a cephalocaudal pattern, each lasting a few days. Lesions without the double-edged scaly margin are commonly seen. While many patients have recurrent ILC every few months, some have infrequent lesions. In severe NS, a fluctuating erythroderma persists, which may be triggered by intercurrent illness, and rarely pustular lesions are superimposed. Between acute attacks, the skin may look surprisingly normal. In a literature review of 43 cases, ILC was recorded in 30, while ichthyosiform erythroderma was the predominant skin lesion in 13 [12]. Many patients are distressed by prominent facial, particularly perioral erythema and peeling. Pruritus or burning irritation may be troublesome, and another feature reminiscent of atopic eczema is flexural lichenification. Impaired sweating can lead to hyperpyrexia. Bacterial and yeast colonization of the skin and human papilloma virus (HPV) viral warts are common in NS. Chronic blepharitis and ectropion may lead to a keratitis. Mild mental impairment in a minority of NS patients may be related to neonatal complications.

There is gradual improvement with age in most patients, but those with chronic erythroderma may develop painful and disabling flexural oedema and papillomatosis of the axillae, groin, vulva and lower legs [12,13]. This is

Fig. 34.19 Ichthyosis linearis circumflexa.

a premalignant lesion with pseudoepitheliomatous histology; carcinoma of the vulva has been reported in a 63-year-old woman [20]. There are two reports of squamous skin cancer in adult males with NS [21,22]. A progress report 21 years on in the first of these reveals that he developed multiple skin cancers, including a single basal cell carcinoma, on photoexposed sites [23]. He had a history of widespread chronic viral warts and oncogenic HPV types were isolated from skin lesions. The other patient developed eight skin cancers, the first on the scalp at age 27. There is no mention of warts in this report but he was an outdoor worker.

Hair defects. The major diagnostic clue in NS is the hair shaft defect known as trichorrhexis invaginata (Fig. 34.17), but it is often missed in infancy, because scalp hair growth is poor, and attributed to erythroderma. In childhood, scalp, eyebrow, eyelash and even body hair remains sparse, slow growing, lustreless and brittle, and patchy traumatic alopecia results from normal wear and tear. Hair growth improves with age, but in many it is unruly or short and spiky, and some patients may opt to wear a wig. A few older patients have clinically normal, although microscopically defective hair. Broken hair shafts at follicular orifices produces a peppered appearance, especially on the limbs. A small proportion of patients have a nail dystrophy, ranging from thickening to pterygium formation in individual nails.

Atopic features. Many patients with NS have a personal or family history of atopy, especially hay fever or asthma. The question as to whether they may have atopic eczema is controversial. The pruritus, flexural accentuation, periods of remission and raised IgE are suggestive; however, the skin lesions are not clinically eczematous, histological features are not consistent and they do not respond to appropriate eczema therapy. Recurrent urticaria and facial angio-oedema, triggered by certain foodstuffs, are

common complications, although the incidence varies [12,13]. The most common food allergens are nuts and fish, and it can manifest in childhood or even in infancy.

Diagnosis. The diagnosis of NS was suspected prenatally in one case because of ultrasound detection of amniotic fluid debris [24]. The triad of congenital erythroderma, poor hair growth and failure to thrive in infancy, or the detection of ILC suggests the diagnosis. In milder cases without a family history, diagnosis is delayed until the specific hair shaft defect of TI is detected. Atopic features in childhood are associated with positive skin prick tests, and high specific serum IgE tests to common airborne and food allergens. Total IgE levels peak, often at very high values, in early childhood and then may fall towards the normal range [5,12,13]. Minor IgG subclass deficiencies have been noted. Lymphocyte subpopulations are normal, though evidence of T- or B-cell activation and reduced natural killer cell numbers have been found in a few [13]. Impaired lymphocyte mitogen responses were noted in one case [21]. Transient aminoaciduria and neutrophil function defects were identified in one patient [12]. C1 esterase inhibitor levels were normal in eight patients studied, and complement C3 or C4 were raised in three of them [13].

In infancy, the differential diagnoses include erythrodermic atopic or seborrhoeic eczema, staphylococcal or candidal infection, non-bullous ichthyosiform erythroderma (NBIE), psoriasis, hyper-IgE syndrome, immunodeficiency states, zinc or biotin deficiency, cystic fibrosis and protein metabolic disorders. In older children and adults, NBIE is the usual diagnosis, but others have included atopic eczema, familial peeling skin syndrome, pemphigus foliaceus and erythrokeratoderma.

Genetics. NS is an autosomal recessive disorder with several reports of affected siblings and a proportion of patients coming from consanguineous families. The clinical manifestations may vary between siblings, and may be less severe in female sufferers. Several *SPINK5* mutations have been identified in NS, but in up to 34% mutations have not yet been found. Close genotype–phenotype correlation has been reported by three groups [5,14,25] but not by another [6]. Prenatal diagnosis may be requested by parents of severely affected offspring, but, prior to molecular diagnosis, was unreliable. Mutational analysis of *SPINK5* gene on a chorionic villus sample in one case and amniotic fluid in another successfully predicted an unaffected fetus in both [5,25].

Treatment. In the neonatal period, intensive medical, nursing and nutritional care must be available to manage erythroderma and its complications and, specifically, to prevent hypernatraemic dehydration and failure to thrive. Frequent occlusive emollients, such as paraffin mixture, provide a partial skin barrier, which reduces insensible loss that contributes to hypernatraemia. Regular skin and eye swabs and stool culture will guide decisions on the need for antimicrobial therapy; staphylococcal, Gram-negative and candidal isolates are common. Nasogastric tube feeding is often required for several months and a gastrostomy is occasionally necessary. Topical steroids are ineffective, and should be avoided as the erythroderma and high surface area at this age contribute to rapid systemic steroid toxicity.

The day-to-day treatment of older patients with NS is similar to that of other ichthyosiform erythrodermas. Regular emollients are helpful, and patients tend towards greasy paraffin-based products. Excessive use in one patient led to a granulomatous lymphadenopathy [26]. Ammonium lactate lotion 12% has been recommended [27]. Keratolytics are poorly tolerated, but intermittent mild topical steroid therapy may help to lessen facial erythema and antifungal creams improve intertrigo. Topical or systemic antibiotics are often required in childhood for skin and respiratory infections. Antipruritics are only partially effective. Significant improvement in the cutaneous features was reported with topical tacrolimus 0.1% application [28] but there may be significant percutaneous absorption [29].

A peculiar feature of NS is the deterioration induced by systemic retinoid therapy, which is usually beneficial in other erythrodermic ichthyoses [9,12,13,23]. Retinoids are known to aggravate atopic eczema. Some patients with ILC do benefit from low-dose therapy [30]. Psoralen with ultraviolet A (PUVA) therapy has produced variable results [22,31]. Methotrexate and ciclosporin A were ineffective [23,32]. Dermabrasion and subsequent excision of papillomatosis lesions on the lower leg, with split-skin grafting, was performed in an adult patient [13]. Grenz ray therapy has been used in the past, and recently laser ablation of hypertrophic areas has been suggested. A trial of topical protease inhibitors in a group of NS patients is underway [14].

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Sjögren–Larsson syndrome (MIM 270200)

Sjögren–Larsson syndrome (SLS) is a rare autosomal recessive condition comprising congenital ichthyosis, spastic diplegia and mild to moderate mental retardation. In addition, a characteristic retinopathy has been noted. Although this syndrome may have been described some years before, credit goes to Sjögren and Larsson, Swedish psychiatrists, for their detailed monograph in 1957. They reported a clinical and epidemiological study of 28 institutionalized patients from 13 families, many of them consanguineous, in an area of north-west Sweden where the condition is common [1]. Common ancestry for most of these was traced back to the 17th century, and a founder mutation introduced to the area in the 13th century has been proposed [2]. Over 200 cases worldwide have been reported, and it occurs in all races. The incidence in Sweden has been estimated at 1 in 100 000 rising to 1 in 10 000 in the north-west region of Vasterbotten [2]. In the UK, the estimated incidence of 1 in 300 000 may be an underestimate [3].

Aetiology and pathogenesis. A defect in essential fatty acid metabolism in plasma phospholipids, involving δ6-desaturase deficiency, was reported in the 1980s [4,5]. Rizzo *et al*. [6,7] demonstrated elevated plasma hexadecanol (C16) and octadecanol (C18) long-chain fatty alcohols, because of a deficiency of fatty alcohol : NAD oxidoreductase (FAO). FAO was assayed in leukocytes and cultured skin fibroblasts and the fatty aldehyde dehydrogenase component (FALDH) of this two-part enzyme is predominantly affected. Reduced enzyme levels in the absence of clinical signs were found in obligate carriers [7,8]. FAO activity combines an alcohol dehydrogenase converting fatty alcohols to fatty aldehydes, and microsomal FALDH oxidizing medium- and long-chain fatty aldehydes to fatty acids. The histochemical demonstration of absent alcohol–hexanol dehydrogenase in the epidermis (Fig. 34.20) and jejunal mucosa in SLS, but not in other ichthyoses, provided further evidence of the importance of abnormal fatty alcohol metabolism in SLS [8]. The neurological defects result from abnormal lipid development in myelin, specifically in the glycerol ether pathway, a side arm of the fatty alcohol cycle, and plasmalogen deposition.

The 31-kb FALDH gene (*FALDH3A2*) is located on chromosome 17p11.2, close to the neurofibromatosis-1 gene [9]. Several different mutations, including deletions, insertions and point missense mutations have been reported [10–12]. FALDH is a 485 amino acid membrane-bound protein with a hydrophobic carboxy-terminus, which is necessary for microsomal membrane anchoring.

Histopathology. Skin sections show orthohyperkeratosis, acanthosis and papillomatosis. The granular cell layer is normal or increased, and there may be mild upper dermal inflammatory change. Kinetic studies in one patient indicated a hyperproliferative epidermis [13]. Ultrastructurally, atypical membranous structures have been reported in spinous and granular layer cells, associated with numerous, large lamellar bodies some of which were irregular or disc-shaped. A proportion contained granular

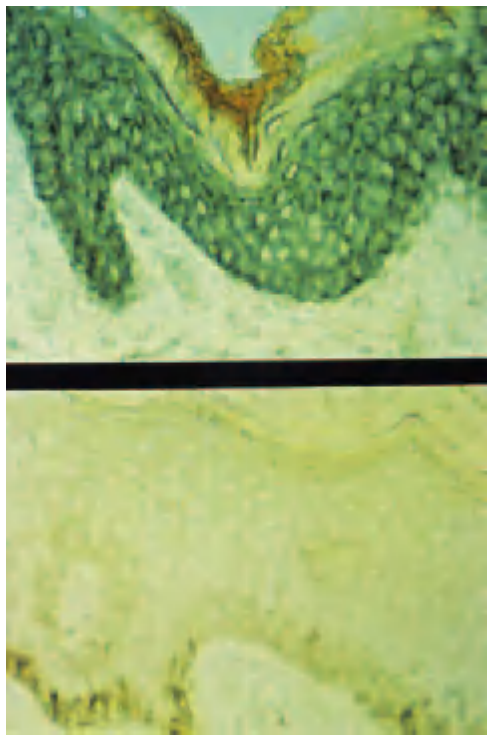

Fig. 34.20 Sjögren–Larsson syndrome, negative staining for alcohol dehydrogenase in the skin, lower panel.

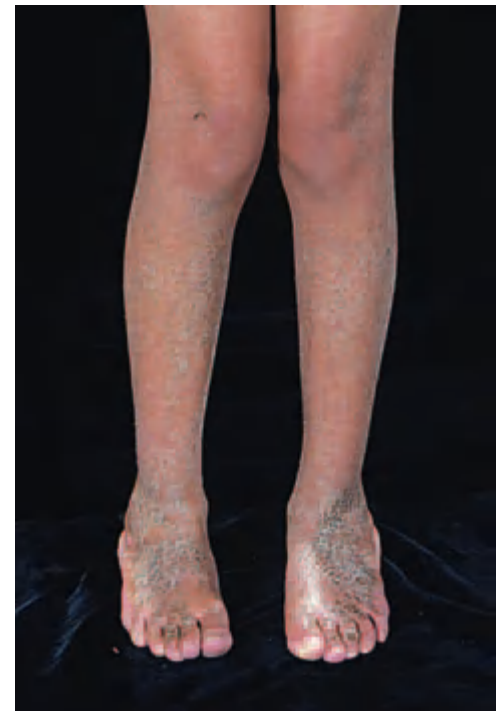

Fig. 34.21 Sjögren–Larsson syndrome, lamellar scaling on legs in a child. (Courtesy of Professor J.I. Harper, Great Ormond Street Hospital for Children, London, UK.)

material in addition to lipid lamellae [14]. Membranous inclusions persisted into the corneal layer and increased numbers of mitochondria were present in the basal epidermal cells.

Clinical features. Collodion baby presentation has been reported [15,16], but usually the skin is dry and mildly erythrodermic at birth, and scaling develops within the first 3 months of life. Thereafter, a mild erythema persists and a variable degree of scaling develops, consisting of diffuse peeling on the trunk and more pigmented, lamellar-type ichthyosis on the lower limbs. Scaling tends to follow a cyclical pattern of accumulation and shedding, and predominantly affects the limbs and face (Fig. 34.21). A velvety orange or brown lichenification, sometimes topped with verrucous hyperkeratosis, is most obvious in and around the flexures, neck and periumbilical folds. This characteristic feature may even be noted during the first year of life, and is helpful in diagnosis. Lichenification becomes prominent and is embarrassing to older children, in whom it may also restrict the mobility of already hypertonic limbs. Skin infections are rare, but scratch marks on the trunk reflect the persistent pruritus that SLS patients suffer.

Neuro-ocular features. Variable neurological dysfunction is obvious in early infancy, with delayed motor milestones and evolution of upper motor neurone signs (a non-progressive spastic paraparesis) in the legs and rarely the arms also. Most patients learn to walk unaided or with crutches in early childhood. Altered posture and movement predispose to kyphoscoliosis, dislocated hips and short stature. Development of speech is delayed and seizures are a rare complication. Mild to moderate learning disability is the rule and, although many SLS patients were institutionalized in the past, most can achieve limited independence. They are notable for their cheerful, friendly disposition. Patchy leukodystrophy and myelination defects have been reported on CT and MR scanning and in post-mortem studies in SLS [12,17].

Ocular signs were reported in 1980, and consist of glistening dots on the fovea and parafovea of the retina, which develop during childhood and which do not seem to interfere with vision [18]. They are detected in up to 80% of patients and may fade with advancing age. They may be caused by deposition of lipofuscin pigment granules in the specialized retinal epithelium [19].

Diagnosis. The cutaneous and retinal features are characteristic and quite unlike those of other ichthyosiform syndromes. Biochemical assay of cultured fibroblasts from a skin biopsy or of leukocytes to identify reduced FAO activity, in particular FALDH, confirm the diagnosis. Histochemical analysis of hexanol dehydrogenase in skin is also diagnostic. Assay of plasma C16 and C18 fatty alcohols can be used to assess the effect of dietary interventions. The main differential diagnoses are congenital ichthyosiform erythrodermas with neurological signs, neurocutaneous disorders such as neutral lipid storage

disease, hystrix-like ichthyosis and deafness (HID) syndrome and a neuroichthyotic condition with absent laboratory markers of SLS described in one patient [20].

Genetics. Although rare outside northern Sweden, SLS is a severe autosomal recessive disorder and fully penetrant [2]. Many families seek prenatal diagnosis in subsequent pregnancies, and relations of affected consanguineous families may also request an assessment of their risk. Although FAO is reduced in most obligate carriers, this assay does not allow accurate identification of carrier status. In contrast, the fibroblast FALDH component of FAO was significantly reduced in 10 of 11 heterozygotes [21], and combination of the two enzyme assays was deemed useful in carrier detection. Prenatal diagnosis by fetal skin biopsy was successful in detecting premature keratinization at 20–22 weeks [22]. Accurate first and early second trimester diagnosis based on FALDH and FAO deficiency in cultured chorionic villus cells and amniocytes has been reported [23]. Mutational analysis of the FALDH gene on a chorionic villus sample will be the ideal test, provided the index case mutation is known.

Treatment. The abnormal fatty acid profile in plasma phospholipids in three SLS patients prompted treatment with a 6-month course of essential fatty acid supplements, but there was minimal improvement in the skin or neurological features [5]. An early report of the beneficial effects of a diet rich in medium-chain triglycerides on the skin manifestations in SLS [24] has been followed by further small trials with mixed results. Reduction of total fatty intake (to 30% of total calorie intake) with essential fatty acid supplements resulted in significant improvement in the skin and neurological features (and in plasma fatty alcohol levels) in two infants after some months but was less effective in older children [16,25]. This approach failed in another study [26].

Regular emollient and keratolytic therapy may help. Retinoid (etretinate) therapy proved effective in relieving scaling and disabling lichenification in several patients [16,27]. Three children and two adults assessed by one of the authors (MRJ) also responded well, but tolerance developed after approximately 3 months, and intermittent therapy may be a better option. Intensive physiotherapy and extra tuition in early childhood clearly improve motor and social development in SLS, and orthopaedic treatment of skeletal deformities of the legs is beneficial in some cases. The discovery of a role for leukotrienes in SLS led to a trial of a 5-lipoxygenase inhibitor in one patient with a partial response [28].

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Refsum's disease (MIM 266500)

Refsum's disease (RD) is a very rare autosomal recessive neurocutaneous disorder, caused by defective fatty acid

metabolism. Refsum, a Norwegian neurologist, first defined it as a clinical entity in 1946, and called it 'heredopathia atactica polyneuritiformis' [1].

Aetiology and pathogenesis. In the early 1960s, accumulation of a storage product identified as a branched-chain 20-carbon fatty acid was reported [2]. Impaired oxidation of phytanic acid, a long-chain 20-carbon branched fatty acid (3,7,11,15-tetramethylhexadecanoic acid), in cultured skin fibroblasts, was demonstrated in 11 patients with RD [3]. Asymptomatic heterozygote carriers possessed 50% phytanic acid oxidase levels, pointing to autosomal recessive inheritance.

Phytanic acid is derived from plant chlorophyll and, to a lesser extent, animal sources (phytol) in the diet, and cannot be synthesized by human tissues. In health, it is barely detected in serum (1 mg/100 mL) but in RD it accounts for 5–30% of serum lipids, and levels rise to over 60 mg/100 mL. In lipid-rich tissues, it replaces other fatty acids and binds to sterols, resulting in lipid vacuoles in the basal epidermis. It interferes with membrane structure and function. The genes for two enzymes involved in α-oxidation of phytanic acid to pristanic acid have been cloned and their protein products localized to peroxisomes [4]. Mutations in the first of these genes, phytanoyl-CoA 2-hydroxylase (*PAHX*), are responsible for most, but not all, cases of adult RD. The *PAHX* gene is located on chromosome 10p13.

Histopathology. Skin biopsy changes are similar to those of ichthyosis vulgaris but without the typical ultrastructural findings. An important feature is the presence of lipid droplets in the basal and suprabasal layers of the epidermis (also seen in neutral lipid storage disease). Their significance may only be appreciated after special lipid stains are used. Kinetic studies in one patient with advanced disease showed a hyperproliferative pattern [5]. Electron microscopy reveals enlarged distorted mitochondria [6].

Clinical features. Diagnosis is often delayed until early adult life. Neurological features develop in adolescence or the early twenties, and progress slowly over a period of some months or years. Failing vision and night blindness result from progressive retinitis pigmentosa, and cataracts may also develop. Sensorineural deafness, tinnitus and, in some, anosmia occur in the early stages. Progressive weakness, foot drop and loss of balance are caused by cerebellar ataxia. A mixed sensorimotor polyneuropathy (type IV) with hypertrophied peripheral nerves and an elevated cerebrospinal fluid (CSF) protein are characteristic findings. In the early stages of evolution, the neurological symptoms and signs of RD may fluctuate, and patients may be labelled as clumsy and neurotic. Consequent delayed diagnosis may result in severe neurological impairment, wasting and depression, and a high mortality has occurred in the past. Some patients develop a cardiomyopathy with serious conduction defects [7], and skeletal defects have been noted in others.

The ichthyosis, which either coincides with or postdates the onset of neurological signs, resembles ichthyosis vulgaris with a fine white scaling, most noticeable over the lower trunk but also affecting the limbs. In late untreated cases, lamellar scaling develops.

Infantile Refsum's disease. This is an autosomal recessive peroxisomal disorder with several enzyme abnormalities including phytanic acid oxidase deficiency. It manifests in early infancy with neurodegenerative disease and signs similar to those seen in adult RD, but ichthyosis is an unusual feature.

Genetics. Diagnosis of a new case of RD should prompt intensive family screening for other presymptomatic cases [8]. Carrier heterozygotes may have marginally elevated phytanic acid levels and show intermediate values for phytanic acid oxidase [3]. Prenatal testing by amniocentesis and culture of amniocytes to assay phytanic acid oxidase and, more recently, by a molecular genetics approach in the first trimester using chorionic villus biopsy are theoretically possible, but the availability of effective dietary therapy may reduce the demand for this approach [9]. It has been suggested that all families with retinitis pigmentosa should be screened for RD [8].

Treatment. Exclusion of sources of chlorophyll in the diet is mandatory in the treatment of RD. The major dietary exclusions are green vegetables (phytanic acid) and animal fat (phytol), and the aim of dietary treatment is to reduce daily intake from the usual level of 50 mg/day to less than 5 mg/day. Rapid weight loss should be avoided, as it mobilizes tissue phytanic acid, which can lead to acute clinical manifestations [10]. A high carbohydrate intake ensures adequate calories and, when instituted in the early stages of the disease, blood levels of phytanic acid fall rapidly, followed by clearance of the ichthyosis and, to a variable extent, reversal of recent neurological signs. Retention of vision and hearing is less certain but has been reported [11]. Lifelong strict adherence to the diet is necessary, and recurrence of scaling is an obvious marker of rising phytanic acid levels. Plasmapheresis has been used to reduce phytanic acid levels rapidly in acutely ill patients at diagnosis [10,12].

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IBIDS syndrome (MIM 601675)

SYN. TAY'S SYNDROME;
TRICHOTHIODYSTROPHY E, F

This rare and heterogeneous genodermatosis belongs to a group of disorders that has in common a hair defect termed trichothiodystrophy. The trichothiodystrophies have been classified into subtypes A–H, two of which (IBIDS and PIBIDS) feature skin lesions. The acronym IBIDS describes *i*chthyosis, *b*rittle hair, *i*mpaired intelligence, *d*ecreased fertility and short *s*tature [1]. In 1968, a sibling pair with brittle hair, intellectual impairment, short stature and trichorrhexis nodosa was reported [2]. Reduction of sulphur-containing amino acids in the hair (Greek *thio*, sulphur) was a central feature of the disorder [2,3]. In 1971, Tay reported three Chinese siblings (of cosanguineous parents) who also had a generalized ichthyosiform erythroderma and progeric facies [4]. Decreased fertility, in an affected Amish kindred, was added to the list of features of the syndrome [5]. Other rare genetic disorders such as the Marinesco–Sjögren syndrome are variants (BIDS), and misreporting of IBIDS cases has occurred [6]. This is an autosomal recessive syndrome and occurs worldwide. UV-induced DNA repair defects have been demonstrated in some patients and recent genetic and molecular advances help to explain the phenotype of this and other DNA repair defect syndromes [7].

Aetiology and pathogenesis. Reduced levels (approximately 50% of normal) of hair sulphur and sulphur-containing amino acids, cysteine, methionine and proline are the hallmark of trichothiodystrophy, but circulating amino acid levels are normal. The cornified envelope of stratum corneum cells is cysteine-rich, and sulphur-rich amino acids form hair-specific matrix proteins that cross-link keratin fibres in the hair shaft.

DNA repair studies on skin fibroblasts and lymphocytes from patients with IBIDS with (PIBIDS) and without photosensitivity have shown markedly reduced levels of duplicative and unscheduled DNA synthesis on UV exposure [8–10]. The response pattern of nucleotide excision repair defects was similar to that seen in xeroderma pigmentosum (XP) complementation group D. In contrast to classical XP, PIBIDS and XP group D patients do not develop skin malignancies. The DNA repair gene *ERCC2/XPD* can correct the photosensitivity of both IBIDS and XP group D and different mutations within this helicase gene, specific to each disorder, have been identified [11]. IBIDS is caused by mutations that alter the transcriptional role of *ERCC2*, while XP is caused by mutations that mainly affect the repair role of the gene. *XPD* mutations account for 95% of PIBIDS. Defects in two other genes, *TTDA* and *ERCC3/XPB*, underlie the photosensitivity in a small number of IBIDS cases [11,12].

Further DNA studies in patients with typical IBIDS revealed three subgroups: one with a normal UV response (for which no gene mutation has been identified); one showing an XP group D response pattern; and a third with reduced clearance of 6–4 photoproducts, reduced DNA repair synthesis and normal cell survival [13]. The patient reported by Jorizzo *et al*. [1] subsequently developed photosensitivity and was found to have a DNA repair defect, which complemented all XP types [14]. There is no correlation between the severity of the DNA repair defect and the clinical features. DNA repair-deficient transgenic and knock-out mouse models have been produced, including one that mimics IBIDS with photosensitivity [15]. The growth defects, brittle hair and nails and neurological abnormalities are not features of nucleotide excision repair defects, and may be caused by impairment of the transcription function of *XPD* and *XPB* gene products leading to reduced RNA synthesis [16].

Histopathology. In most cases, skin biopsy has shown changes similar to those of NBIE with hyperkeratosis, focal parakeratosis, acanthosis and a normal or reduced granular layer. Ultrastructural features include perinuclear vacuoles and abnormal tonofilaments. Hair microscopy shows wavy hair shafts with pili torti, trichorrhexis nodosa and trichoschisis (transverse fractures). Polarizing light reveals characteristic alternating zig-zag light and dark bands, which give rise to the term 'tiger tail' hair. This defect may also occur in inherited amino acid and zinc deficiencies. Scanning electron microscopy highlights flattening and irregular ridging of the shaft.

Clinical features. IBIDS typically presents in a low-birthweight premature infant with a collodion membrane or

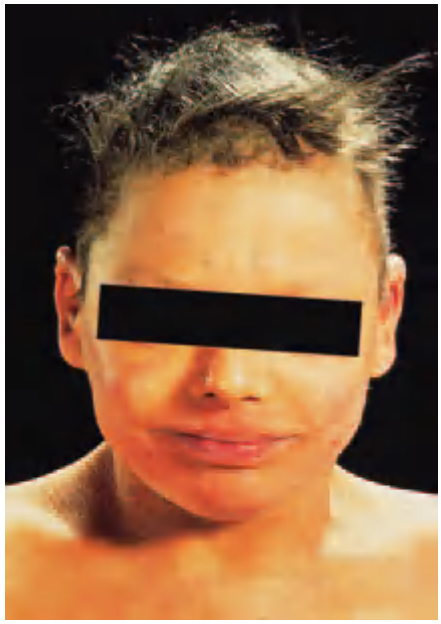

Fig. 34.22 IBIDS/trichothiodystrophy, 18-year-old male. (Courtesy of Professor J.I. Harper, Great Ormond Street Hospital for Children, London, UK.)

congenital erythroderma, which evolves during infancy into an ichthyosis. Skin manifestations vary widely from generalized fine scaling, which may have a delayed onset, to an erythrodermic hypohidrotic ichthyosis resembling congenital ichthyosiform erythroderma. Additional features in some patients are eczema, palmoplantar hyperkeratosis, pulp atrophy and flexion contractures, hypoplastic aural cartilage and nail dystrophy [1]. An elfin-like and aged face resulting from fat atrophy, prominent ears and chin recession is typical (Fig. 34.22).

Scalp and eyebrow hair is sparse, short and unruly, but its growth may improve with age. Mild to moderate intellectual impairment is the rule, and hypogonadism leads to delayed puberty and infertility in most adult patients. Severe growth failure is usual and cataracts, skeletal defects, otosclerosis, dental anomalies and neurological signs (microcephaly, cerebellar dysfunction, seizures, nerve deafness, autism) have been described [17,18]. Abnormal myelination may account for the wide range of neurodevelopmental problems. An increased incidence of asthma has been noted and bronchiectasis developed in one patient, although no immune defect was found [1]. Early death from sepsis may occur. A friendly disposition is characteristic.

Marked photosensitivity and photophobia were reported in a review of 15 patients with features of IBIDS [10]. In this group, neurological disease and cataracts were more common and hypogonadism less common than expected. Photosensitivity occurs in 50% of IBIDS patients [1].

Diagnosis. Amino acid analysis and microscopy of hair, DNA repair studies and phototesting are essential for diagnosis. Immune studies and growth hormone assay are generally normal and skin histology is non-specific. The main differential diagnoses are NS, SLS, NBIE, Cockayne and other progeric syndromes.

Genetics. The clinical heterogeneity of this syndrome appears to result from the variety of DNA repair gene mutations and diverse mutations within the critical functional area of the *ERCC2*/*XPD* DNA repair gene [11,12]. The *XPD* gene maps to chromosome 19q13.2–13.3 while the *XPB* gene is located on chromosome 2q21. IBIDS and its variants are autosomal recessive disorders. Successful prenatal diagnosis has been reported in two families by identifying defective DNA repair in amniocytes taken at 21 weeks' gestation and trophoblasts at 9 weeks' gestation, as well as on fetal hair analysis [19]. Prenatal DNA studies are relevant only to the 70% of families with DNA repair defects.

Treatment. Emollients are helpful in improving skin comfort and suppleness. The influence of retinoid therapy and keratolytics on the ichthyosis has been disappointing. Sun avoidance and sunscreens should be used in photosensitive patients. Growth hormone treatment failed in one patient, and the effect of sex hormone therapy is unknown. Physiotherapy and splinting may reduce the severity of digital contractures.

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X-linked dominant ichthyosis (MIM 302960)

SYN. HAPPLE'S SYNDROME; CONRADI–HÜNERMANN–HAPPLE SYNDROME; X-LINKED DOMINANT CHONDRODYSPLASIA PUNCTATA TYPE II/ICHTHYOSIS/CATARACT SYNDROME

X-linked dominant ichthyosis (XLDI) is a distinctive skin disorder occurring in a mosaic pattern in females, often associated with skeletal and ocular defects. It is usually lethal *in utero* in affected males. The characteristic features were described by Happle in 1979, and it is now referred to as Happle's syndrome or Conradi–Hünermann–Happle syndrome [1]. It is one of the variants of chondrodysplasia punctata (CP), a group of genetic disorders that have in common a congenital punctate epiphyseal and skeletal calcification which affects growth. CP was first described by Conradi in 1914. There are three other subgroups of CP: an autosomal recessive rhizomelic type; an autosomal dominant form without cutaneous disease, now referred to as Conradi–Hünermann syndrome [2]; and an X-linked recessive variant.

Aetiology and pathogenesis. A deficiency of a peroxisomal enzyme, dihydroxyacetone phosphate acyltransferase (DHAPAT), was identified in cultured fibroblasts from patients with both rhizomelic chondrodysplasia punctata and XLDI [3,4]. DHAPAT is responsible for synthesis of plasmalagen phospholipids and glycolipids. An animal model, the 'bare patches mouse', has an X-linked dominant disorder with a phenotype and peroxisomal defect similar to that of Happle's syndrome [5]. Accumulation of 8(9)-cholesterol and 8-dehydrocholesterol in tissue samples from seven XLDI patients suggested a defect in C8-C7 isomerization, which is catalysed by sterol-Δ8-isomerase, an emopamil-binding protein [6]. Functional mutations of the candidate gene, located at Xp11.22–p11.23, have been confirmed in these patients. There was no obvious genotype–phenotype correlation and lyonization of X-linked genes at this site may influence the severity of the clinical phenotype as well as causing mosaicism. Similar mutations have been found in the X-linked dominant 'tattered mouse' [7], whereas the 'bare patches mouse' phenotype is caused by a mutation of the gene coding 3β-hydroxysteroid dehydrogenase, which maps to Xq28 [8]. Abnormalities of sterol metabolism have been implicated in other genetic skeletal dysplasias, possibly by interfering with hedgehog (HH) signalling pathways. The Indian HH protein is necessary for vertebrate skeletal development and mutations cause chondrocyte degeneration, affecting epiphyseal growth plates, and ectopic calcification. Ectopic epiphyseal and sometimes epidermal calcification are recognized features of X-linked dominant ichthyosis. Rhizomelic CP is caused by three different peroxisomal enzyme mutations, including two involved in phospholipid biosynthesis [9].

Histopathology. Biopsy of ichthyotic skin shows changes similar to those of ichthyosis vulgaris, but without the typical ultrastructural features. There is orthohyperkeratosis with a reduced granular layer, mild acanthosis and a light perivascular inflammatory infiltrate in the upper dermis in childhood. Older lesions show prominent perifollicular atrophy. Epidermal calcification, needle-like inclusions in granular keratinocytes and reduced numbers of Langerhans' cells, some of which are degenerate, have been reported [10]. Electron microscopy reveals persistent desmosomal structures in the stratum corneum layer. Abnormal degenerate mitochondria and vacuolated lamellar bodies were seen, and the dilated intercellular spaces contained disordered lipid lamellae and debris [3].

Clinical features. Affected babies are typically female, premature and born with either a collodion membrane or generalized ichthyosiform erythroderma. Within the first year, generalized linear and swirling patterns of erythroderma and scaling, following the lines of Blaschko, are established (Fig. 34.23). Intervening areas of skin are unaffected. Palmoplantar hyperkeratosis and nail dystrophy may occur. Recurrent infections, especially in the flexures, can be troublesome, and scalp and eyebrow hair growth is sparse and lustreless. The ichthyosis improves with age and the residual signs are often so subtle in adult life that an affected mother may be missed. Signs to be sought in adults include swirls of fine scale, linear pigmentary change, follicular atrophoderma mainly on the limbs and cicatricial alopecia, all in a Blaschkoid distribution. An adult patient had persistent ichthyosis and also developed psoriasis in Blaschko's lines [11].

Other variable features include rounded or asymmetrical facies with frontal bossing, a broad flat nasal bridge, congenital asymmetric cataracts in 60% of patients

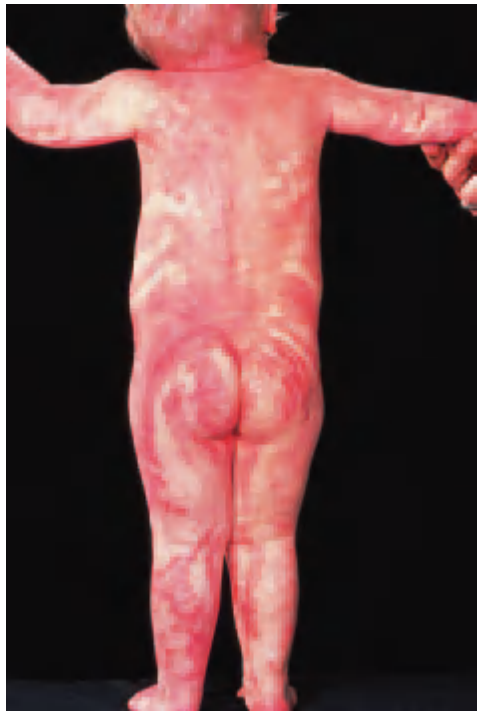

Fig. 34.23 X-linked dominant ichthyosis in a 2-year-old girl. (Courtesy of Dr D.J. Atherton, Great Ormond Street Hospital for Children, London, UK.)

(mosaic lens involvement), short stature, asymmetrical or, rarely, symmetrical shortening of limbs [12], kyphoscoliosis, supernumerary digits and other skeletal defects. Stippled calcification of long-bone epiphyses is a characteristic but not universal radiological finding in the neonatal period, and usually resolves by adulthood. Patients have normal or mildly impaired intellectual development and neural hearing loss has been reported [11,12].

Genetics. The mosaic pattern of X-linked dominant ichthyosis reflects the effects of the two populations of keratinocytes that result from the X chromosome alleles: one normal, the other mutated (functional mosaicism). This X chromosome mutation is compatible with survival in female embryos, because of the Lyon effect of X inactivation allowing expression of either allele in a given somatic cell. It shows variable penetrance in females and is generally lethal in male embryos. However, male patients with cutaneous and skeletal features have been reported, and at least one had the Kleinfelter karyotype [13,14]. The spontaneous improvement with age may reflect progressive elimination of mutant cells by adjacent normal cells, which have a growth advantage. However, clinical severity may worsen in successive generations [13,15].

Autosomal recessive rhizomelic CP can cause cataracts but rarely affects skin. An X-linked recessive variant may represent XLRI with contiguous gene defects. Genetic counselling must include assessment of all members of the extended family, looking for dysmorphism, residual skin signs, subclinical cataracts and a history of radiological abnormalities. Fetal warfarin or hydantoin toxicity and congenital rubella can mimic CP syndromes.

Prenatal testing, assaying DHAPAT, has been successfully used in one family. Ultrasound scans in the second trimester may detect skeletal and other defects. The variability of disease expression and improvement with age make decisions on prenatal diagnosis difficult but mutational analysis of chorionic villus biopsy should simplify the process.

Treatment. Emollients are helpful and antimicrobial therapy may be needed for skin infections. Some patients may opt to use a wig. Clofibrate, a peroxisome inducer, did not help one patient [15]. The effect of retinoids is unknown and the need for treatment diminishes with age. Appropriate orthopaedic procedures may be indicated for skeletal anomalies.

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Neutral lipid storage disease (MIM 275630)

SYN. CHANARIN–DORFMAN SYNDROME

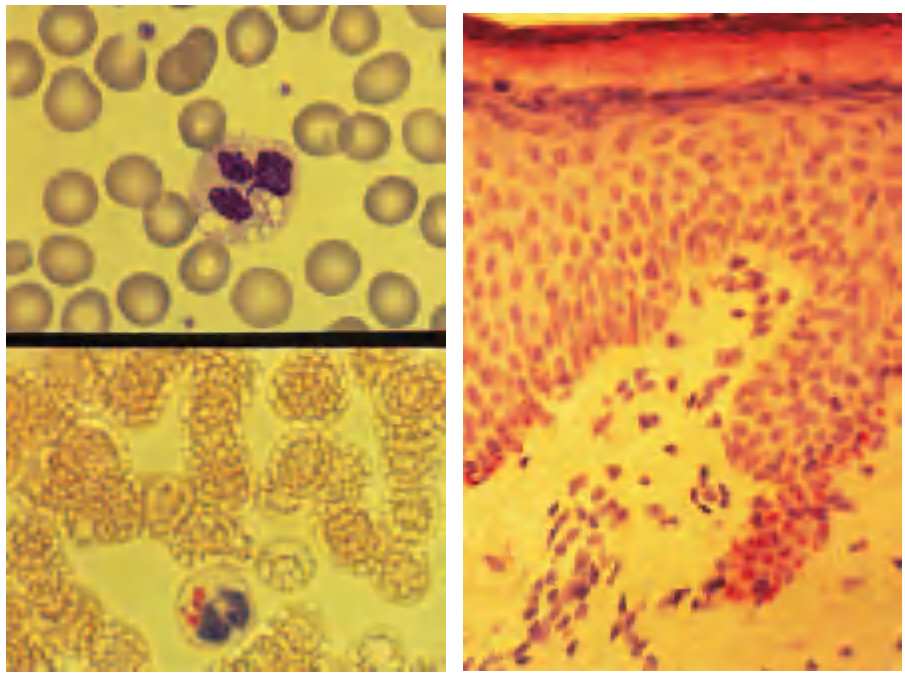
The association of an autosomal recessive congenital ichthyosis and leukocyte lipid vacuolation affecting two sisters was first described in 1966 [1]. Dorfman reported four cases including a follow-up of the two sisters and recognized that this was a specific multisystem lipoidosis [2]. Chanarin, describing a similar case, referred to it as neutral lipid (triglyceride) storage disease (NLSD) [3]. The triglyceride deposition in white blood cells and several organs results in a combination of skin, hepatic, muscle and ocular abnormalities. There are more than 30 reported cases of NLSD, mainly in people of Mediterranean or Arabic descent, many from consanguineous families [4,5].

Aetiology and pathogenesis. Serum lipid analysis is normal in NLSD and scale lipids show a raised triglyceride content [6]. Histochemical studies on cultured fibroblasts and keratinocytes confirmed that the stored lipid was neutral lipid triacylglycerol or triglyceride [3]. Increased fibroblast triglyceride synthesis with a complete failure of endogenous triglyceride breakdown was demonstrated [6,7]. Exogenous triglyceride metabolism was normal and dietary lipid restriction was unhelpful. A defect in recycling of mono- or diacylglycerols from triglycerides to phospholipids or in long-chain fatty acid oxidation was suspected [8].

Linkage in several families with NLSD to a locus (the *NCIE2* locus) at chromosome 3p21 led to the identification of mutations in the *CGI-58* gene in 13 patients [9]. CGI-58 is one of a large family of proteins, many of them enzymes, with a characteristic α/β-hydrolase fold. Its function is unknown but it is widely expressed in tissues such as skin, muscle, liver and brain.

Histopathology. A notable feature of NLSD (seen to a lesser extent in heterozygote carriers) is the presence of lipid droplets, visible on light microscopy, in circulating polymorphs (neutrophils, eosinophils and basophils) and monocytes but not in lymphocytes, red cells or platelets (Fig. 34.24a). The vacuoles are oil red O and Sudan black positive and this feature is termed 'Jordan's anomaly'. Electron microscopy shows non-membrane-bound cytoplasmic lipid droplets.

Biopsies of muscle, liver and skin and cultured fibroblasts also reveal numerous cellular lipid droplets. Skin biopsy shows acanthosis and hyperkeratosis, and closely packed lipid droplets of varying size are seen in basal (Fig. 34.24b), granular and adnexal (sweat gland and duct) keratinocytes and in dermal fibroblasts, smooth muscle cells and endothelium. Lipid vacuoles are seen in the epidermis, but not in other tissues, in RD. Ultrastructurally, vacuoles may be seen in upper epidermal layers and arrector pili muscles [6]. Epidermal lamellar bodies and intercellular lipid lamellae are disrupted by globular electron lucent inclusions [10]. Lipid vacuoles are present in muscle fibres and marrow. Liver biopsy reveals hepatocyte fatty vacuolation, lobular fibrosis in late-stage disease and normal Kupffer cells.



(a) (b)

Fig. 34.24 Neutral lipid storage disease: (a) lipid vacuoles (lower panel, oil red-O positive) in neutrophils; and (b) in basal keratinocytes. (Courtesy of Dr B. Lake, Institute of Child Health, London, UK.)

Clinical features. Clinical features are variable [4–6,9]. Affected newborns are either collodion babies or erythrodermic. The pattern of skin disease thereafter resembles mild to moderate NBIE with fine white scale on an erythematous background and lamellar scaling on the legs. Scaling may diminish in warm weather and with advancing age. Pruritus is often troublesome and hypohidrosis may occur. Mild ectropion and flexural lichenification are common, and palmoplantar hyperkeratosis (with nail dystrophy) and scalp alopecia have been reported.

Muscle involvement ranges from an asymptomatic or subclinical myopathy with elevated muscle enzymes in most patients, to marked proximal myopathy in a few late cases. Hepatomegaly, abnormal liver enzymes and fatty infiltration of the liver are common, even in childhood. Liver biopsy is more sensitive than biochemical markers in detecting the degree of involvement. Splenomegaly and malabsorption, resulting from intestinal mucosal lipid deposition, are occasional features. Cataracts of the nuclear type may be detected from infancy in over 50% of cases but rarely affect vision. Retinal disease, nerve deafness, ataxia, microcephaly, neuropathy, short stature and mental retardation have been reported, but most patients are intellectually normal. Prognosis depends on the pattern and degree of organ involvement.

Diagnosis. The diagnosis is confirmed by microscopy of a peripheral blood smear, which shows lipid droplets in granulocytes (Jordan's anomaly) [1]. Careful inspection of a fresh blood film may also be used to detect carriers and should be a routine investigation in all patients with congenital ichthyosis [11]. Moderate elevation of muscle and hepatic enzymes is usual but raised urinary creatine with normal serum muscle enzymes has been noted [5]. Liver biopsy changes are noted above. Muscle biopsy reveals lipid droplets in muscle fibres and EMG signs of myopathy are detected.

Gaucher's disease type 2, muscle carnitine deficiency and Wolman's disease should be excluded, as they share some of the features of NLSD. Lipid vacuoles are seen in the epidermis, but not in the blood smear, in RD.

Genetics. Most NLSD families have come from Mediterranean regions and the majority are of Arab descent. The majority of patients have consanguineous parentage. The disease is clearly autosomal recessive and the asymptomatic heterozygote carriers may be identified by detection of lipid vacuoles in myeloid leukocytes, especially eosinophils on a fresh blood film [12]. This screening test should be offered to members of the extended family. Prenatal diagnosis using fetal blood microscopy, or skin biopsy at 20 weeks' gestation, is possible and identification of the *CGI-58* mutation in an affected family should allow first trimester diagnosis by chorionic villus sampling and molecular genetic analysis.

Treatment. Emollients are helpful and retinoid therapy, either low-dose continuous or intermittent courses, improves the cutaneous features. Dietary manipulation to reduce intake of long-chain fatty acids and increase medium-chain fatty acids has been reported to benefit two patients, but one was also receiving retinoid therapy [5,13]. In another case, dietary treatment was ineffective [6].

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KID syndrome (MIM 148210) and HID syndrome (MIM 602540)

The combination of *k*eratitis, *i*chthyosis and *d*eafness was first reported in 1915 as a generalized congenital keratoderma with ocular and mucosal involvement [1]. The acronym KID was coined in 1981 to highlight the main features of the syndrome [2]. However, the skin disease combines features of a hystrix-like ichthyosis and an erythrokeratoderma, and keratitis is not present in all cases. The pattern of inheritance is uncertain, as most cases have been sporadic. It has a worldwide distribution and at least 70 cases have been recorded in the literature, some under different terms. A change in terminology has been suggested but not yet accepted.

HID syndrome describes *h*ystrix-like *i*chthyosis and *d*eafness. It was originally reported in two patients from Rhedyt in Germany [3] but is now regarded as an allelic variant of KID.

Aetiology. Mutations in gap junction proteins called connexins have been reported in various epidermal diseases including hidrotic ectodermal dysplasia (connexin 30), erythrokeratoderma variabilis with and without deafness (connexin 31 and 30), Vohwinkel's syndrome (connexin 26) and non-syndromic hearing loss (connexin 26 and 31). Connexins are universal membrane proteins that form inter- and intracellular channels for ion and molecule transfer, which is the basis of all cellular communications. Similar defects were considered likely in KID and to date three different missense mutations of connexin 26 (GJB2) have been reported in 10 patients [4,5]. KID and HID share the same connexin 26 mutation [6].

Histopathology. Skin biopsy shows marked orthohyperkeratosis and acanthosis, focal parakeratosis and papillomatosis. Fungal and bacterial elements are frequently present within the keratin, and perinuclear vacuolation with keratohyaline clumping are a minor feature. Proliferating keratoses should be examined for signs of pseudoepitheliomatous hyperplasia and malignancy. There is a mild upper dermal inflammatory infiltrate with plasma cells, and atrophic or plugged hair follicles reflect the widespread alopecia.

Ultrastructural study has shown irregular clumped tonofilaments in lower epidermal layers with perinuclear distribution in the granular layer (similar to changes noted in IH) and indented keratinocyte nuclei [7]. Intercellular membrane-bound granules have been noted.

Clinical features. Many affected neonates have generalized erythema and some also have diffuse scaling and a leathery skin. The typical skin changes gradually develop during infancy with linear and spiny hyperkeratosis around the flexures, elbows and knees, and hystrix-like scaling on the limbs [7]. Scattered follicular hyperkeratoses appear on the trunk. Typical feature are the evolution of symmetrical well-demarcated hyperkeratotic plaques on the scalp, ears, face (Fig. 34.25) and occasionally the trunk and limbs, and, in some patients, thick perioral rugae, and an aged or leonine facies [8,9]. Keratotic, hyperplastic nodules may develop on the scalp, face, trunk and lower legs, and *in situ* and invasive squamous cell carcinoma arising within these dysplastic lesions have been reported in several KID patients in adult life [4,10–12]. Squamous cell carcinoma of the tongue has occurred in two children [13,14] and a 28-year-old had a fatal malignant fibrous histiocytoma [15]. Multiple hair follicle tumours occurred in an adult with KID syndrome [16].

Most patients have extensive scarring alopecia of the scalp and loss of eyebrows, lashes and body hair resulting from follicular hyperkeratosis. A reticulated PPK resembling grained leather is a characteristic feature, and progressive nail dystrophy and shedding may occur. Acneiform eruptions on the upper trunk are common, and

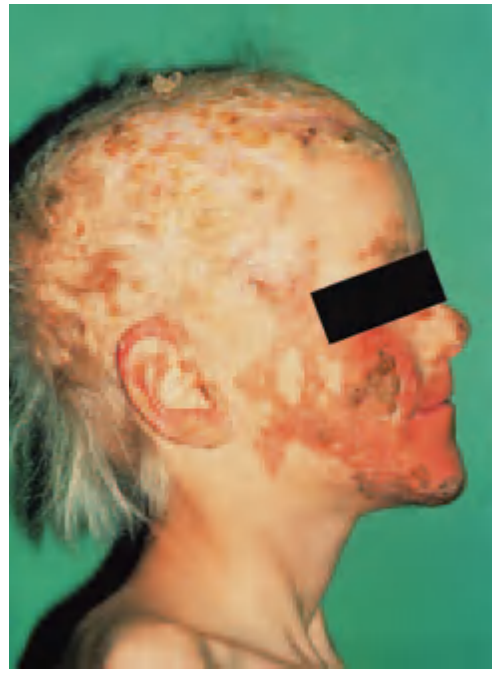

Fig. 34.25 KID syndrome in an 8-year-old boy. (Courtesy of Dr D.J. Atherton, Great Ormond Street Hospital for Children, London, UK.)

chronic deep abscesses and discharging sinuses are a distressing late complication in some. Chronic cutaneous granulomatous fungal and candidal infections may develop and contribute to the alopecia, nail dystrophy and body odour. Death in infancy from overwhelming infection has been reported in several patients with KID syndrome [17]. No specific immune defect has been identified. Premature caries, oral leukoplakia, short stature, breast hypoplasia and cryptorchidism are occasional complications.

Congenital sensorineural deafness is evident during infancy in most patients. In typical KID syndrome, progressive corneal vascularization occurs in childhood, often after a febrile illness, and leads to blindness by adolescence. Delayed onset of the keratitis has been reported [18]. A progressive peripheral neuropathy has occurred in several adults with KID [8]. Intellect is unaffected and it is no surprise that the combined disabilities of deafness, blindness and disfigurement impose severe limitations and hardship on the individual.

The cutaneous features of the HID syndrome vary from a diffuse hyperkeratosis with pruritus to a generalized hystrix hyperkeratosis with mild PPK. Multiple squamous cell skin cancers occurred in an adult patient [6]. The deafness runs a similar course to that of KID syndrome and mild punctate keratitis has been noted in some patients (evidence that HID and KID are a single disorder).

Diagnosis. KID/HID syndrome is a clinical diagnosis, supported by audiological and ophthalmological evidence

of neurosensory deafness and keratitis. In spite of the occurrence of chronic skin infections, consistent immune defects are not found. The differential diagnosis includes congenital erythrokeratoderma with deafness, IH and unusual ectodermal dysplasias. Typical HID syndrome must be differentiated from SLS.

Genetics. Most reported cases of KID/HID syndrome have been sporadic, but autosomal dominant inheritance was evident in two families with KID [11,19] and one with HID syndrome [6]. A report of two sisters of consanguineous ancestors affected with KID syndrome pointed to autosomal recessive transmission [20] but this sibship and half-sibs affected with KID could also be explained by gonadal mosaicism [21]. First trimester prenatal molecular diagnosis on chorionic villus sampling is possible where the connexin mutation in the index case in a family has been defined.

Treatment. Early and frequent audiology and eye assessment should be performed to enable treatment such as hearing aids, cochlear implants and speech therapy. Corneal transplant for advanced keratitis has usually failed [19]. Keratolytics and emollients have a limited role. Antiseptic baths and cleansers, intermittent antibiotic therapy and systemic antifungal agents all play an important part in controlling skin infections and odour, and regular bacteriology screening of the skin should guide the choice of antimicrobial treatment. Cleansing, débridement and grafting of hyperplastic lesions may be needed and may reduce the potential for malignant transformation. Mohs microsurgery is appropriate for invasive malignancies. Systemic retinoids have been tried in several patients with variable success. The potential of acitretin to reduce the skin cancer risk provides further justification for its use. Isotretinoin aggravated the keratitis in one patient [22]. PUVA phototherapy was unhelpful in a few adult patients [7].

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CHILD syndrome (MIM 308050)

The acronym CHILD describes a very rare disorder comprising *c*ongenital *h*emidysplasia with *i*chthyosiform erythroderma and unilateral *l*imb *d*efects, mainly skeletal hypoplasia [1]. The skin lesion more often resembles a unilateral inflammatory epidermal naevus, rather than an ichthyosis. Happle suggested that it is a unique inherited naevus determined by an X-linked dominant mutation, as the female : male ratio is 28 : 1 and skin involvement may occur in Blaschko's lines [2]. Over 30 cases have been reported since the 1960s [3].

Aetiology. Keratin expression studies indicate a hyperproliferative epidermis [4]. Abnormal fibroblast activity, increased prostaglandin E_2 synthesis and defective peroxisomal structure and function in lesional skin were reported and similarities with XLDI (Happle's syndrome) noted [5,6]. Indeed, abnormal 3β-hydroxysteroid-Δ8,Δ7-isomerase activity has been found in one case while reduced NAD steroid dehydrogenase (NSDHL) has also been reported [7,8].

Histopathology. The epidermis is acanthotic with areas of hyper- and parakeratosis. Neutrophilic collections in the stratum corneum and a dermal lymphocytic inflam-

matory reaction are suggestive of psoriasis. Hair follicles are plugged, and foamy macrophages may be seen in distended dermal papillae. Ultrastructural features include lipid vacuoles in granular layer keratinocytes, keratin filament defects, disrupted mitochondria, patchy disruption of lamellar bodies, vacuolated intercellular lamellae and lamellated structures in fibroblasts [4,6,9].

Clinical features. The skin lesions are usually noted in the first days of life as an inflamed, hyperkeratotic, crusted or thickened plaque covering a large area or most of one side of the body, with sharp demarcation at the midline. Linear bands of normal skin on the affected side and of ichthyotic scaly red skin on the 'normal' side may occur, and suggest a mosaic somatic mutation [1,4]. The flexures on the affected side are preferentially involved, and the head is usually spared. The skin lesions may progress in the first year of life and then improve with time. Unilateral alopecia and nail dystrophy may occur. Various other defects, some of which may prove lethal, include congenital heart disease, spina bifida and renal defects [9]. The most common skeletal defect is ipsilateral limb hypoplasia, and calcific stippling of epiphyses in infancy has been reported. A sibling of an affected patient had bilateral limited skin disease in the absence of extracutaneous features [10]. Bilateral symmetrical lesions were reported in one patient with a novel NSDHL mutation [11]. The lesions may be mistaken for an epidermal naevus, lichen striatus or linear psoriasis. Cataracts do not occur.

Genetics. The theory of X-linked dominant inheritance is convincing and explains the apparent lethality in male embryos [2]. The predominantly unilateral and mosaic distribution is attributed to the Lyon effect of random X chromosome inactivation. An early teratogenic insult and syndromes associated with limb reduction defects must be included in the differential diagnosis.

Treatment. Emollients and keratolytics are helpful. Urea-containing emollient, retinoid therapy and methotrexate have improved the skin lesions in individual patients [2,9].

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Ichthyosis follicularis with alopecia and photophobia (MIM 308205)

Isolated follicular ichthyosis is an ill-defined and controversial entity and may overlap with keratosis pilaris and coexistent ichthyosis vulgaris. On the other hand, the syndrome of ichthyosis follicularis with alopecia and photophobia (IFAP) is a well-recognized but very rare ectodermal disorder, which was first reported by MacLeod in 1909 [1]. Fewer than 20 cases have been recorded.

Histopathology. Skin biopsy shows follicular plugging and orthohyperkeratosis with a normal granular layer (which is thickened at the infundibulum), effaced rete ridges and thin dermis. Absence of sebaceous glands, atrophy of hair follicles with perifollicular lymphocytic infiltrates and reduced numbers of sweat glands are characteristic findings [1,2]. No specific ultrastructural features have been noted, although a psoriasiform lesion showed reduction in desmosomes, and electron microscopy of the cornea in an adult revealed a thickened basement membrane and absent Bowman's capsule [3].

Clinical features. The phenotype is variable, but patients have a striking facial similarity. One presented at birth with a collodion membrane [2]. All have generalized non-inflammatory follicular keratoses, persistent non-cicatricial scalp and body alopecia, and severe photophobia from birth. The keratotic papules are most pronounced on the knees, elbows and fingers, and follicular spiny projections develop over extensor surfaces. Generalized xerosis and cheilitis, lamellar scaling, skin infections and pruritus are common, and the keratoses may improve with age. Pregnancy-related vulvitis occurred in one patient and her affected daughter developed psoriasiform plaques in early childhood [3]. Teeth, nails and sweating are generally normal, although one infant had natal teeth [4], and nail dystrophy does occur [2,3]. Palmoplantar erythema was present in one case [2]. Severe photophobia, reduced visual acuity, nystagmus and head tilt are caused by

punctate keratitis, which leads to corneal erosions and vascularization. Occasional features include atopy [1,2,4], recurrent chest infections, growth and psychomotor retardation, hypotonia and seizures. Hearing is normal.

Diagnosis. IFAP must be distinguished from the keratosis pilaris variants, keratosis follicularis spinulosa decalvens (KFSD) and keratosis pilaris rubra atrophicans facei, which are associated with inflammatory scarring alopecia of the scalp and eyebrows. Ocular disease is prominent in KFSD, the KID syndrome and IFAP, but palmoplantar hyperkeratosis is not a feature of IFAP. Skin histology helps to exclude other congenital ichthyoses, such as ichthyosis vulgaris. An autosomal recessive congenital atrichia with papular lesions has been reported [5]. Hereditary mucoepithelial dystrophy/dysplasia shares certain clinical traits with IFAP, but the striking mucosal changes do not occur in IFAP [6].

Genetics. X-linked recessive inheritance was proposed in a family with three affected male siblings [1]. However, two girls with typical lesions were reported, and, as one had an affected father, autosomal dominant transmission was suggested [7]. This pattern was evident in an affected Japanese mother and daughter [3].

Treatment. Keratolytics, urea preparations and emollients are used. Topical calcipotriol may improve psoriasiform lesions. Oral retinoid (vitamin A) therapy produced a partial response in one case, while topical retinoid proved too irritant [2]. Early and regular ophthalmological assessment is necessary.

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Isolated genetic syndromes with ichthyosis

There are several reports of individuals or small groups of cases with congenital ichthyosis occurring in association with extracutaneous defects that do not fit within the classification of inherited ichthyoses discussed above. These are discussed under headings indicating the main systemic features.

Ichthyosis associated with neurological and ocular disorders

In 1983, Zunich and Kaye [1] reported a child with migratory ichthyosiform erythroderma, retinal colobomas, neurological disease, fine sparse hair and dental abnormalities—the acronym CHIME derives from *c*oloboma, *h*eart disease, *i*chthyosis, *m*ental retardation and *e*ar defects. A further four cases have been described [2,3] and occurrence in a sibling pair suggests autosomal recessive inheritance. Generalized pruritus, erythema and scaling occurred within the first month, and figurate red scaly patches developed on the head and body in early childhood [3]. Characteristic facial dysmorphism and other skeletal defects were noted, and neurological features included seizures and developmental delay. Degenerative changes in the myelin sheaths of cutaneous nerves have been detected ultrastructurally. Impaired epidermal maturation is associated with a distinctive perinuclear oedema and nuclear pyknosis in upper granular keratinocytes. A similar syndrome of generalized ichthyosis, mental retardation, hypotonia and craniofacial anomalies occurred in a Turkish boy of consanguineous parents [4]. Abnormal nerve myelination also occurred in a patient with ichthyosis associated with congenital sensory neuropathy [5].

Generalized ichthyosis with mental retardation and spasticity was noted in a single patient in whom SLS was excluded [6], and a similar syndrome in identical twins was also associated with cortical atrophy, epilepsy and a hearing defect [7]. An inbred Swedish family was reported where two siblings and an aunt and uncle had an ichthyotic syndrome with mental retardation, alopecia, eclabion and ectropion [8]. Ichthyosis was noted in a patient with Dubowitz syndrome, which causes microcephaly and growth retardation [9], and in a boy with microcephaly and lentigines, diagnosed as LEOPARD syndrome [10].

Retinitis pigmentosa associated with congenital ichthyosis and other defects was reported in two women [11], and an adult female patient had ocular albinism, Noonan's syndrome and ichthyosiform erythroderma (with collodion baby presentation) [12].

An infant with ichthyosis and deafness may have had KID syndrome but he died of malnutrition brought about by Hirschsprung's disease [13]. A patient with ichthyosis, deafness and mental retardation had, in addition, dental and skeletal defects and developed thyroid cancer [14]. A family with a variable syndrome of unspecified deafness, microphthalmos and ichthyosis is recorded [15].

Ichthyosis associated with renal disease

Passwell reported three siblings of a consanguineous family whose skin was red with fine scaling, atrophic changes and small blisters over the dorsal hands and feet. Skin biopsy revealed vacuolation in basal keratinocytes, reminiscent of neutral lipid storage disease, and collagen disruption. They had a generalized aminoaciduria, dwarfism and mental retardation [16].

Congenital ichthyosis has also occurred with renal parenchymal disease, growth retardation and hypogonadism in three siblings of another family [17]. A possibly autosomal dominant syndrome of renal disease, prolinuria, nerve deafness and a poorly defined ichthyosis affected a third family [18]. Fanconi's syndrome with jaundice occurred with congenital ichthyosis [19].

Ichthyosis and skeletal defects

The ICE syndrome, reported in five subjects in four generations of one family, consisted of *i*chthyosis vulgaris, fullness of the *c*heeks and thinning of the *e*yebrows [20]. Other dysmorphic features occurred, and skeletal abnormalities included kyphoscoliosis. Accessory ribs, cortical thickening, arthrogryposis and osteopetrosis have been recorded in individual patients with ichthyosis [14,20–23].

Ichthyosis with immune defects

Patients with ichthyosiform erythroderma associated with defective chemotaxis have been described [24]. Abnormal T cells, hypogammaglobulinaemia, neurological defects, eczema and fungal infection were reported in an infant boy who died at 9 months (cf. Ommen's syndrome) [25]. Three patients with congenital ichthyosiform erythroderma and IgM or IgG deficiencies had recurrent respiratory infections [26].

Ichthyosis and cancer

Apart from the increased incidence of skin cancer in KID and Netherton's syndromes, the occurrence of both in the same patient is rare. A youth with an ill-defined ichthyosis, micropinnae, universal alopecia and ectropion developed a scalp squamous cell carcinoma [27, case 2]. The predisposition to testicular cancer in XLRI is likely to be related to the endocrine dysfunction in that disorder. Other non-cutaneous malignancies (e.g. thyroid cancer and medulloblastoma) have been associated with inherited ichthyosis, but may be coincidental [14,28].

Miscellaneous

Ichthyosiform erythroderma from early infancy has been reported in 50% or more of patients with Shwachman's syndrome. Its main manifestations are exocrine pancreatic insufficiency, growth retardation and bone marrow hypoplasia with neutropenia [29,30]. Granular droplets in keratinocytes and defective lamellar bodies were seen ultrastructurally [29]. Migratory ichthyosis and pruritus associated with type 2 diabetes mellitus occurred in a large consanguineous family [31]. A sibship with an autosomal recessive ichthyosis, developmental delay and cirrhosis [32], a single case of ichthyosis, hepatomegaly and cerebellar degeneration [33] and a syndrome of erythrodermic ichthyosis associated with PPK, hypogonadism and hepatosplenomegaly have been reported [34]. Two related inbred Moroccan families with diffuse nonerythrodermic ichthyosis, scarring alopecia, sclerosing cholangitis and eosinophil vacuolation have shown linkage to chromosome 3q27–q28 [35]. An autosomal dominant syndrome in four generations of a family included ichthyosis, abnormal platelet function, asplenism, migraine, fatigue and dyslexia [36]. Ichthyosis has been present in some patients with ectodermal dysplasias [37,38] and two reports of ichthyosis vulgaris-like scaling associated with follicular atrophoderma, hypotrichosis and woolly hair have been published [39,40].

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Acquired ichthyoses

Acquired or late-onset ichthyosis is a rare and significant occurrence, as it is generally associated with underlying pathology such as malignancy. It presents with features similar to ichthyosis vulgaris and must be distinguished from both it and RD in which scaling starts in early adult life.

Ichthyosis associated with malignancy

The most commonly reported malignancy that produces ichthyosis is Hodgkin's disease, and the skin lesions as a rule occur simultaneously or after the lymphoma is diagnosed [1,2]. The fine scaling affects the trunk and limbs, spares the flexures and histologically resembles ichthyosis vulgaris with orthohyperkeratosis and reduced or absent granular layer. It clears with effective anticancer treatment and may be an early marker of subsequent recurrence. It may be associated with pruritus. Reduced skin lipogenesis, as measured by radiolabelled carbon uptake in lipid groups except sterols, paralleled the severity of the ichthyosis and contrasted with results in ichthyosis vulgaris in one study [3]. Production of transforming growth factor (TGF-α) by the tumour has been proposed [2].

Ichthyosis has also been reported in association with non-Hodgkin's lymphoma [4], mycosis fungoides [5–7], multiple myeloma [8], carcinoma of breast, lung, cervix [9] and liver [10], leiomyosarcoma [11] and Kaposi's sarcoma [12]. It preceded by 2 years the development of lymphomatoid papulosis in one case [13], and occurs in patients with acquired immune deficiency syndrome (AIDS), with or without demonstrable malignancy [14,15].

Ichthyosis and non-malignant disease

Ichthyosis may occur with chronic metabolic derangement such as malnutrition [6], malabsorption [3,5], essential fatty deficiency, which is extremely rare [16], and Shwachman's syndrome (pancreatic insufficiency) [17]. In these conditions, there is a disturbance of lipid and possibly vitamin absorption; because epidermal structure and integrity are dependent on complex lipid interactions, disordered epidermal maturation and desquamation, and permeability barrier dysfunction ensue. It occurs in renal failure with or without secondary hyperparathyroidism [6,18] and is an occasional feature of hypopituitarism [4], hypothyroidism [5] and diabetes [19,20]. Ichthyosis may rarely occur in connective tissue diseases such as systemic lupus erythematosus [21] and dermatomyositis without associated malignancy [22]. It has been noted in patients with the granulomatous diseases, sarcoidosis [23] and leprosy [24], following bone marrow transplant [25], and in association with Haber's syndrome [26] and eosinophilic fasciitis [27]. A single case of ichthyosiform erythroderma

with lichenoid features, starting at 10 years old and proving fatal at 28 years old, was reported [28]. No underlying cause was identified.

Drug-induced ichthyosis

The cholesterol-lowering drugs triparanol and nicotinic acid induced ichthyosis in a few patients [29,30]. Normal desquamation depends on the conversion of cholesterol sulphate (which maintains the structure of intercellular lipid lamellae in the subcorneal layers) to cholesterol, by cholesterol sulphatase, located on keratinocyte cell membranes. This enzyme is unaffected by hypocholesterolaemic agents but cholesterol constitutes 25% of stratum corneum lipid. Keratinocytes lack low-density lipoprotein receptors, which may explain why so few treated patients show this complication. HMG CoA (hydroxymethylglutaryl coenzyme A) reductase inhibitors are also a rare cause of ichthyosis. Ichthyosis and variable effects on hair have been attributed to certain butyrophenones, the phenothiazine dixyrazine, maprotiline, cimetidine (an antiandrogen), allopurinol, hydroxyurea and clofazamine [31–34].

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Pityriasis rotunda

Definition. Pityriasis rotunda describes a rare, persistent, large, sharply defined, circular patch of ichthyosiform scaling with no inflammatory changes. This name is preferred to pityriasis circinata, under which Toyama described the condition in 1906, and to acquired pseudoichthyosis [1].

Aetiology. Pityriasis rotunda is relatively common in the Far East, where it accounts for some 0.2% of dermatological cases [1]. It has been reported also in South African Bantus [2], in an Egyptian [3] and in West Indians living in London [4]. It typically occurs in black patients, but has been described in caucasians [5]. Its true incidence and geographical distribution are unknown. It is possible that a genetic factor is involved, but systemic illness (including tuberculosis) and pregnancy favour the development of lesions, which may have been latent [2]. It may also be a cutaneous marker of malignancy, including hepatocelluar carcinoma [6,7].

Pathology. The histological changes are unimpressive and resemble those of ichthyosis vulgaris.

Clinical features. The lesions of pityriasis rotunda are often almost perfectly circular, sharply defined patches

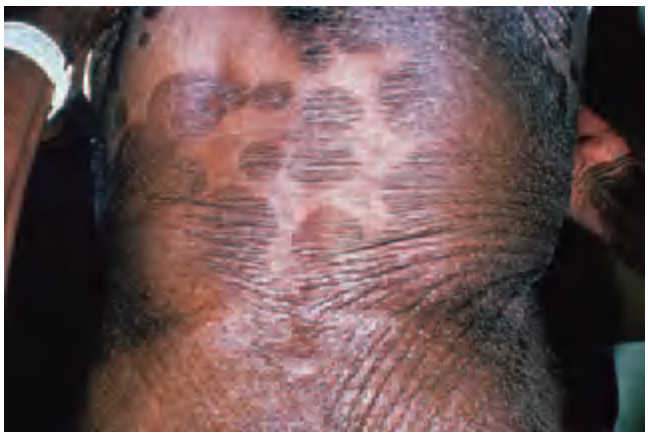

Fig. 34.26 Pityriasis rotunda.

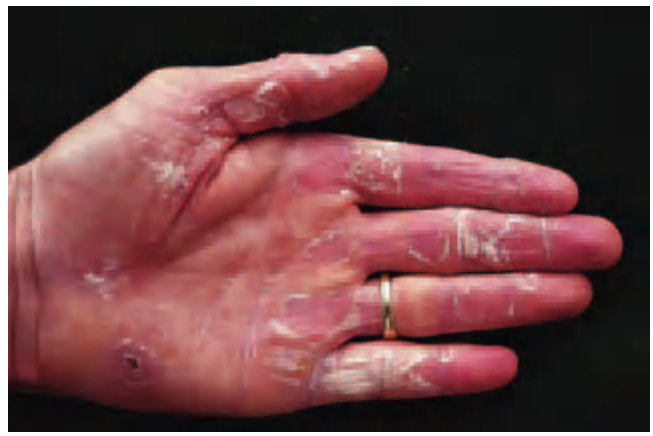

Fig. 34.27 Erythrokeratolysis exfoliativa of palms.

of dry skin with ichthyosiform scaling, usually 2–3 cm in diameter but sometimes much larger (Fig. 34.26). They are commonly situated on the buttocks, thighs, abdomen, back or upper arms, and may be solitary or multiple. They develop between the ages of 25 and 45 years (7 and 76 years are the reported extremes) and remain unchanged throughout life.

The age of onset, distribution, strikingly circular outline and absence of inflammatory change should suggest the diagnosis. In prereticulotic eruptions, the lesions show atrophy and telangiectasia. Dermatophytosis can be excluded when necessary by the microscopy of scrapings.

Treatment. Emollients and topical keratolytics may help, but topical steroid and antifungals do not. Where an underlying cause is found, appropriate therapy should clear the lesions.

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Peeling skin syndromes (MIM 270300)

Periodic peeling of the superficial layers of the skin resulting from damage to the stratum corneum has widely differing aetiologies. Histologically, there is cleavage within the stratum corneum and some alteration in the staining properties of defined layers. Involvement of the most superficial layer of the stratum spinosum is suggestive of pemphigus foliaceus. A few cases and families have been reported with either generalized skin peeling (deciduous skin, familial continual skin peeling or shedding) or acral peeling. In Oudsthoorn disease (erythrokeratolysis hiemalis), the peeling is more pronounced and is associated with erythema.

Acquired peeling of the palms

The most common condition encountered is *keratolysis exfoliativa*. This affects the palms of young adults, usually in the summer months. This suggests that it may be related to sweating. Lesions appear as tiny white rings or 'air bubbles', which soon rupture and peel off ('ringed keratolysis') (Fig. 34.27). Attempts to identify a specific fungal or bacterial agent proved negative [1]. Emollients are usually prescribed but are not very effective.

Cases are seen where the peeling is not seasonal. In these patients, the peeling episode may be preceded by a few days by intense itching of the palms. Histologically, there is minimal spongiosis and it may represent a *forme fruste* of hand eczema. The use of degreasing chemicals may produce similar damage to the stratum corneum, by affecting intercorneocyte adhesion.

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Familial peeling skin syndrome

Variously known as keratolysis exfoliativa congenita [1] or deciduous skin [2], the label 'familial continual skin peeling' was suggested in 1969 in a case report of four affected siblings [3]. Two further kindreds and a number

of individual cases have since been described and some authors prefer the title peeling skin syndrome [4–8]. The peeling was generalized and variations in the salient features among reported cases led to the identification of type A [2–4,6] and type B [5,7] inflammatory peeling skin syndrome [9]. Two affected families were consanguineous [3,4] and the occurrence of affected siblings also points to autosomal recessive inheritance. A familial, predominantly acral peeling has been reported [10]. The paucity of reported cases makes estimation of the frequency difficult but it occurs worldwide.

Aetiology. A defect in profilaggrin or a site-specific keratin with resultant abnormal keratin filament aggregation has been suggested [10]. Evidence for a desmosomal abnormality and altered vitamin A metabolism has been put forward [11]. Reduced trytophan with aminoaciduria was reported in one case [5].

Histopathology. Mild hyperkeratosis with loose irregular stratification at follicular orifices and a normal granular layer thickness are common findings [4], although psoriasiform acanthosis was noted in one case [5]. Kinetic studies suggested a hyperproliferative disorder [3], but this has been disputed [6]. The split exists at the corneal–granular interface and ultrastructurally intercellular disruption occurs above the lower two layers of stratum corneum, within the stratum lucidum. At this site, intercellular lamellae are irregular and fragmented, keratohyalin granules are abnormal and desmosomes may be normal [10] or reduced [4]. Lamellar bodies are aggregated in the upper granular layer, but other cytoplasmic structures are normal. A patient with adult-onset disease was found to have intracellular keratinocyte cleavage with globular lipid deposits between corneal cells at all levels [6]. Immunofluorescence studies were normal in two cases [5,12].

Clinical features. Generalized superficial peeling starts at birth or in early childhood and is then persistent or periodic in most affected people. Collodion membrane and blisters do not occur in this condition, although vesicles were noted in one case [8]. Peeling is not preceded by fever or erythema, and can be produced by rubbing intact skin, especially if pre-soaked in water. Exfoliating flakes and peeling sheets of stratum corneum spread across the trunk, limbs and occasionally face, leaving mildly erythematous intact skin. Mild pruritus is a problem for some patients and patchy hyperpigmentation has been noted. The palms and soles are either spared or mildly thickened without peeling, and hair, nails and teeth are usually normal. However, one patient did have severe palmoplantar subcorneal blistering, ichthyosis and keratotic cheilitis [11]. The acral variant occurred in an adult male with lifelong episodic peeling of the dorsal and volar aspects of the hands and feet, and to a lesser extent in a niece and nephew [10]. Two patients had easily plucked hair [5,12], another shed nails as well [13] and a woman of 26 was stunted with hypogonadism and anosmia [5]. Developmental delay was noted in one case [14]. Some cases are more severely affected in the summer [2,8,10,12], but generally there is only slight seasonal variation. Shedding occurred in a cephalocaudal pattern for a week once a year in an Indian boy [13].

Diagnosis. Several unrelated skin disorders eventuate in skin shedding, but differentiation from peeling skin syndrome is generally not a problem. IBS (ichthyosis exfoliativa) produces transient blisters and erosions on a background of flexural hyperkeratosis and typical histopathology. An autosomal recessive form of exfoliative ichthyosis (without epidermolytic hyperkeratosis) in an inbred Bedouin family has been documented [15]. It shares some of the clinical features of familial peeling skin syndrome type A. In epidermolysis bullosa simplex superficialis and Weber–Cockayne variant, subcorneal or basal layer blisters occur with friction but there is no continual peeling, the histology is characteristic and they are autosomal dominant [16]. Peeling lesions without double-edged scale do occur in NS, but inflammatory lesions, atopy and hair defects should enable accurate diagnosis. Acquired keratolysis may complicate tinea (the original definition of keratolysis exfoliativa, an id reaction mainly affecting the palms), staphylococcal or streptococcal infection, atopic eczema or retinoid therapy.

Treatment. Minimizing immersion in water is recommended. Absorbing powders or aluminium antiperspirants may help, especially in the acral variant, by reducing sweating and friction. Keratolytic and urea creams speed up shedding. Topical and oral steroids, emollients and tar, oral retinoids [14], methotrexate and UVB phototherapy are among those agents tried without success.

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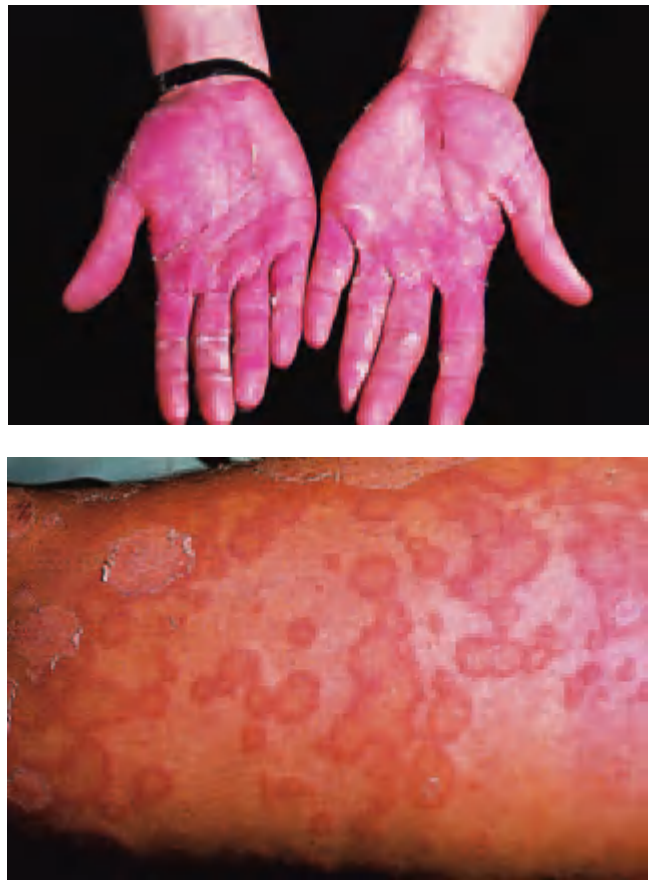
Oudtshoorn disease (MIM 148370)

SYN. KERATOLYTIC WINTER ERYTHEMA; ERYTHROKERATOLYSIS HIEMALIS

This rare epidermal disorder, characterized by recurrent skin peeling, palmoplantar erythema and seasonal variation, was originally described as erythrokeratolysis hiemalis in 1977. It has been observed in at least 35 white or mixed-race related South African families of European descent originating from the Oudtshoorn district of Cape Provence [1,2]. The incidence in this population is 1 in 7000. Cases have since been identified in several other countries, and a familial link to the Oudtshoorn cluster is evident in most. It is an autosomal dominant disorder with variable penetrance and linkage to chromosome 8p22-p23 has been reported in five South African and one German kindred [3]. The genetic mutation may have arisen in a French immigrant in the late 1700s. Over 400 descendants are affected.

Histopathology. Biopsy of the advancing edge of a lesion shows focal cellular oedema, necrobiosis of the Malpighian layer and absence of the overlying granular layer, through which the Malpighian layer is ejected. It forms a parakeratotic wedge, which becomes sandwiched within the hyperkeratotic stratum corneum and is shed. Hyperproliferative features are evident in the basal layer—so-called basaliosis [2].

Clinical features. Symmetrical keratolysis of the hands and feet may begin at any age from infancy to early adult life but it is not usually present at birth (Fig. 34.28a). Cyclical centrifugal peeling (sometimes preceded by erythema multiforme-like papules) at several sites on the palms and soles is a constant feature, and may spread to the dorsal hands and feet, and the interdigital spaces. Episodes may be preceded by itch and hyperhidrosis and are associated with pustulation. Palmoplantar erythema develops, and is followed by the evolution of superficial opaque dry blebs, which peel or can be pulled away, leaving a red base with intact markings. A second wave may begin at the centre of a lesion, resulting in gyrate and polycyclic annular erythema, which eventually resolves. Cycles repeat every few weeks and the palms and soles appear normal between attacks. Similar rosette lesions may arise on the lower legs, knees and rarely thighs (Fig. 34.28b), upper arms and shoulders. Truncal lesions were reported in one patient [2]. The father of a typical case apparently had involvement of one interdigital space only [4].


(a)

(b)

Fig. 34.28 Oudtshoorn disease: (a) palmar lesions; and (b) truncal lesions.

A frequent precipitant is cold dry weather and, although in South Africa it is most active in wintertime, it may be perennial in temperate climates. Other triggers include febrile illness, stress and menstruation, and it improves in pregnancy and with age.

Diagnosis. The differential diagnosis includes familial peeling skin syndrome (keratolysis exfoliativa congenita), pustular bacterids, erythrokeratoderma en cocardes and variabilis, and Weber–Cockayne epidermolysis bullosa simplex.

Treatment. There is no effective treatment, and topical keratolytics, retinoids and steroids may aggravate the condition. Urea, tar, antiperspirants and oral retinoids have been tried.

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Erythrokeratoderma

Erythrokeratoderma (or erythrokeratodermia) is the association of localized hyperkeratotic plaques with circumscribed areas of persistent but variable erythema. Many associations and possible syndromes have been reported. There is clinical overlap with KID and transgredient keratoderma syndromes. Identification of underlying genetic defects in gap junction proteins in some erythrokeratodermas (Table 34.1) has led to re-evaluation of their classification [1], but reliable classification on clinical grounds remains challenging.

Erythrokeratoderma variabilis (MIM 133200)

SYN. MENDES DA COSTA'S SYNDROME

Mendes da Costa described a mother and daughter with relatively fixed hyperkeratotic plaques and erythematous areas with geographical margins that changed by the hour [2]. The inheritance is usually autosomal dominant, but recessive inheritance is reported [3,4].

Aetiology. There is a disease locus near the rhesus cluster on chromosome 1 [5], at which several genes encode members of the connexin family. Connexins are the constituents of gap junctions, intercellular channels that allow traffic of ions and small molecules between adjacent cells [6]. Mutations have been identified in gap junction beta-3 (*GJB3*), encoding connexin 31, in several pedigrees of erythrokeratoderma variabilis (EKV) [7–9]. Homozygous missense mutations in connexin 31 causing recessive EKV have also been reported [4]. The mechanisms by which impaired protein trafficking [10] or gap junction function give rise to the cutaneous abnormalities remain unknown. Connexin 31 mutations are not found in all pedigrees of EKV [9,11]. Other mutations in *GJB3* cause autosomal dominant or recessive deafness, in isolation or with peripheral neuropathy [12–14]. In a family with EKV associated with unusual rapidly evolving erythematous lesions resembling erythema gyratum repens, a mutation of *GJB4* (encoding connexin 30.3) was found [15]. This phenotype appears to be specific to mutations in *GJB4*, but other mutations in this gene present as more typical EKV [16].

Pathology. Histology is non-specific: orthohyperkeratosis or parakeratosis, with acanthosis and papillomatosis. Immunohistochemistry shows aberrant staining for basal cytokeratins in the stratum corneum, improved by etretinate [17]. There is an increase of suprabasal staining for involucrin [18]. Connexin 31 is expressed in an abnormal perinuclear distribution, rather than at the cell membrane [10]. Reduced numbers of keratinosomes within the stratum granulosum, restored by isotretinoin, and clumped tonofilaments have been reported [19]; the latter were not confirmed in other cases [20,21].

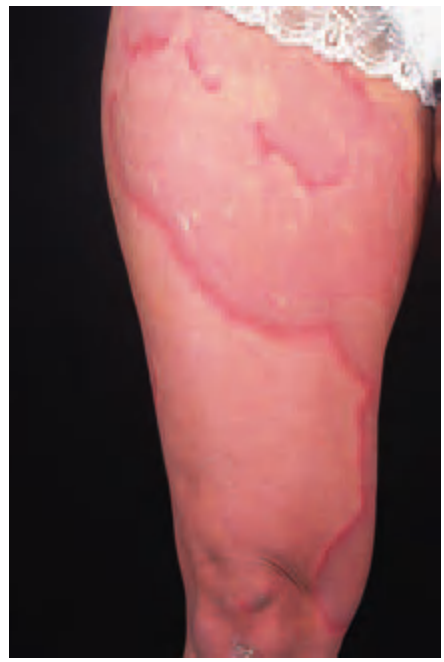

Fig. 34.29 Erythrokeratoderma variabilis: migrating polycyclic erythematous lesions.

Clinical features [21–25]. Onset is usually in infancy. The manifestations vary within a family and within the individual. There are two types of lesions. Relatively fixed well-demarcated keratotic and erythematous plaques show a predilection for extensor surfaces. These extend and regress in area, thickness and degree of erythema. Secondly, transient erythematous polycyclic or comma-shaped macular lesions occur at any site (Fig. 34.29). These may be triggered by trauma, irritation or temperature change, and evolve in shape over hours. They last days or weeks, fading *in situ* or migrating slowly, leaving a residual fine scale. Improvement may be seen after extended sun exposure. In some cases the erythema is annular or 'en cocarde' (Degos' syndrome) [26,27]; in others, it may resemble erythema gyratum repens [15,16,28]. Palmoplantar involvement in EKV may take the form of mild scaling or peeling [23], but transgredient keratoderma resembling Greither's syndrome is recorded [29]. The condition persists throughout life, but may improve at

puberty or worsen during pregnancy or with oral contraceptives [30]. Migratory polycyclic erythematous plaques suggestive of EKV have also been reported in two families with the same heterozygous point mutation in the keratin 1 gene [31].

Treatment. Acitretin is now the treatment of choice [32]. Isotretinoin may also be helpful [19]. Successful use of bath PUVA has been reported [33]. Non-sedating antihistamines have been reported to benefit pruritic erythematous lesions [34].

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Progressive symmetrical erythrokeratoderma (MIM 602036)

SYN. GOTTRON'S SYNDROME

In progressive symmetrical erythrokeratoderma (PSEK) [1,2], fixed plaques of hyperkeratotic erythema, which gradually extend during childhood, resemble those of EKV, but migratory erythema is not seen. PSEK is more common than EKV, and probably also heterogeneous. Approximately half the cases are familial with autosomal dominant inheritance [3], while the remainder are sporadic.

Aetiology. In a Japanese pedigree, lesions suggestive of PSEK were associated with honeycomb keratoderma, and an insertional mutation in loricrin was found, of the same type as those found in honeycomb keratoderma with ichthyosis [4]. This is probably an exceptional finding, as histological findings were more consistent with loricrin keratoderma, of which PSEK is not otherwise a feature.

Pathology [5,6]. The epidermis is acanthotic with a preserved granular layer. The stratum corneum is hyperkeratotic with a basket-weave pattern and foci of parakeratosis. The variable presence of perinuclear vacuolation of keratinocytes further suggests heterogeneity. Ultrastructurally, the granular cells contain swollen mitochon-

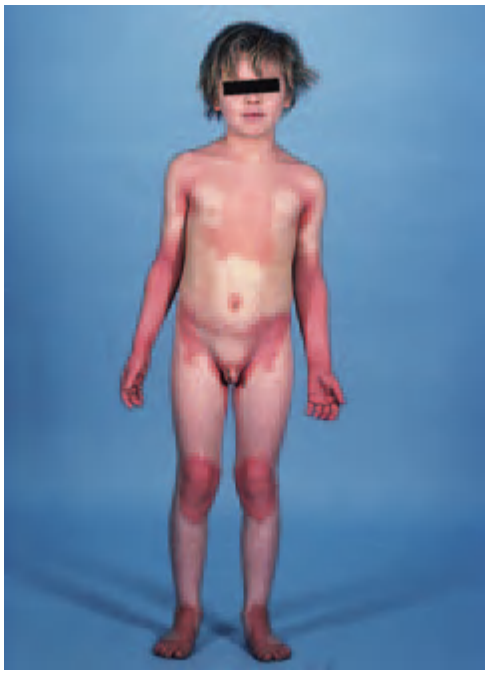

Fig. 34.30 Symmetrical progressive erythrokeratoderma: sharply demarcated 'geographical' orange–red plaques. (Courtesy of Dr A.G. Smith, North Staffordshire Hospital, Stoke-on-Trent, UK.)

dria, and corneocytes show lipid-like vacuoles, both of which are reduced by etretinate therapy. Labelling studies show increased epidermopoiesis with shortening of the interphase [7,8].

Clinical features [3,9,10]. The skin is usually normal at birth. Large, geographical but symmetrical fine scaly plaques with an orange–red erythema appear in infancy (Fig. 34.30). There is little pruritus. The shoulder girdle, cheeks and buttocks are most often affected with limited plaques on the ankles and wrists. Keratoderma may be present. Hair and nails are usually normal, but one case showed thickened nails [11]. The plaques extend during childhood but become fixed or occasionally remit. Erythroderma present at birth [12], and onset delayed to 17 years [13], have been recorded. A family with mal de Meleda keratoderma first presenting with inguinal lesions was originally diagnosed as PSEK [14].

Treatment. Limited data suggest that etretinate and acitretin are effective [13,15] although etretinate was reported in one patient to cause generalization of the erythema [12]. PUVA treatment has been reported [16].

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Other erythrokeratoderma syndromes

Erythrokeratoderma with sensorineural deafness [1] may be a form of the KID syndrome (see above), now known to be caused by mutations in connexin 26 [2,3]. Schnyder's syndrome (asymmetrical erythrokeratoderma with deafness, peripheral neuropathy, muscle atrophy and mental retardation, and occasionally keratitis) [4–6] and overlapping syndromes may be pathogenetically related. In a five-generation Canadian pedigree, erythrokeratoderma appearing in infancy and clearing in later life was associated with late-onset ataxia and neuropathy (Giroux–Barbeau syndrome, MIM 133190) [7,8]. The defective gene maps to the connexin gene cluster at 1p34–p35 [8]. A sporadic case of a boy with atypical erythrokeratoderma mainly localized to periorificial regions also had acral involvement and pachyonychia [9]. Vakilzadeh and Rose [10] described a boy with slowly migrating orange–brown plaques over the buttocks and legs from the age of 1 year, without large zones of erythema and without fixed plaques, leading the authors to separate this disorder from both EKV and PSEK. Faninger [11] reported a case of localized hyperkeratosis

resembling symmetrical interdigital keratoderma, but with marked underlying erythema.

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Folliculocentric keratotic disorders

Keratosis pilaris (MIM 604093)

Keratosis pilaris [1,2] is characterized by keratinous plugs in follicular orifices with varying degrees of perifollicular erythema. Mild forms, appearing in childhood and reaching a peak incidence in adolescence, can be regarded as physiological. Mevorah *et al*. [3] recorded its presence in 44% of 155 normal people, but few were markedly affected. Prevalences of 2.7–4% are recorded in schoolchildren from various countries [4–6]. Nutritional deficiency may have caused a higher prevalence in postwar Germany [7]. It is often seen in ichthyosis vulgaris [3]. It was present in 72% of 54 atopic black children with eczema [8], but in a group of white children only 37% of patients with keratosis pilaris had a personal history of atopy [9], and it is a poor discriminator of atopic eczema [10].

Aetiology. Follicular hyperkeratosis is a feature of several syndromes (see below) but keratosis pilaris in isolation may be inherited as an autosomal dominant trait with variable penetrance. One locus is suggested by the occurrence of more severe forms with translocations and deletions of chromosome 18p [11–13]. An X-linked dominant form in women has been suggested [14].

Pathology. The follicular orifice is distended by a horny plug which may contain one or more twisted hairs. There may be mild inflammatory changes in the dermis. Lectin staining did not demonstrate abnormal keratinization [15].

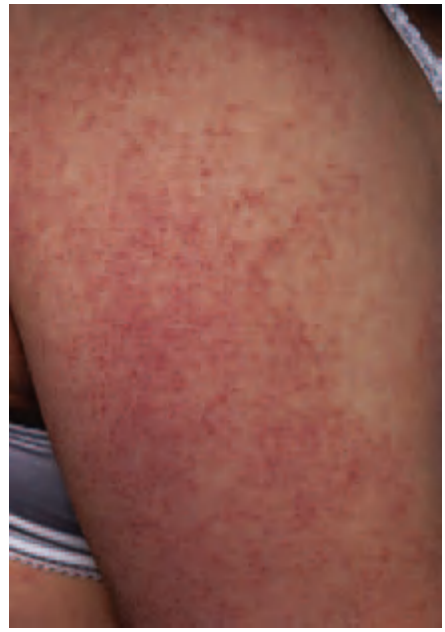

Fig. 34.31 Keratosis pilaris on the extensor aspect of the upper arm.

Clinical features [9] (Fig. 34.31). Small grey–white plugs of keratin obstruct the mouths of the follicles, entrapping the body hair. Extensor surfaces of the upper arms (92%), thighs (59%) and buttocks (30%) are most commonly involved. Occasional cases are generalized. Uneven involvement of a given area is usual, with some follicles completely spared, while adjacent ones are grossly plugged. Individual follicles show a long strand of keratin glinting when examined in side light (antenna sign). Perifollicular erythema is often present, and may be psychologically distressing for the patient [16]. The age at onset was in the first decade in 51%, the second decade in 35% and the third decade in 12%. Improvement in the summer months was noticed in 49% [9]. Improvement with age is common, occurring at a mean age of 16 years [9]. The term keratosis rubra pilaris is sometimes used when redness is marked. The erythematous component without plugging is also seen. Severely affected follicles may show a tiny pustule.

Associations. Keratosis pilaris is seen in association with ichthyosis vulgaris and in atopic xeroderma rather than atopic eczema *per se* [3]. Keratosis pilaris (or 'follicular ichthyosis') also occurs with Noonan/cardio-facial-cutaneous syndromes [17–20], renal insufficiency [21], prolidase deficiency [22], Down's syndrome [23] and various mental deficiencies, in which it overlaps with trichostasis spinulosa [24,25], and in Fairbanks' [26] and Olmsted's [27] syndromes. A syndrome of hypotrichosis

and leukonychia is recognized [28,29]. Follicular hyperkeratoses occur in monilethrix, pachyonychia congenita and ectodermal dysplasias [30–36]. Follicular hyperkeratosis may be seen during systemic steroid [37] or lithium therapy [38].

Keratosis pilaris with atrophy [39–43]. Keratosis pilaris is sometimes succeeded by atrophy. The nosology is debated [39,40] as only keratosis follicularis spinulosa decalvans can be distinguished genetically at present. *Ulerythema ophryogenes* or *keratosis rubra pilaris faciei atrophicans* shows prominent facial erythema with involvement of the eyebrows and scalp and prominent atrophy, with simple keratosis pilaris on extensor surfaces, and may occur in Noonan's syndrome [20,40,44,45]. The late stage of a previously active case shows fine follicular atrophy. The condition is thought to be inherited as an autosomal dominant [40]. *Atrophoderma vermiculatum* is rare, and affects the cheeks and preauricular regions with a combination of keratotic papules giving way to an atrophic worm-eaten appearance, and may be recessively inherited [40,46].

Erythromelanosis follicularis faciei et colli. This comprises the triad of well-demarcated erythema, hyperpigmentation and follicular plugging on the cheeks and neck [37,47]. Patches of red-brown skin with follicular plugging and a granular feel are found on the cheeks and pre-auricular region, spreading onto the neck anterior to the angle of the mandible. The majority of cases are in Asian men [48], but cases have been reported from the Middle East [49], and women are also affected [50]. Associated keratosis pilaris on the arms suggest that it is a pigmented variant of keratosis pilaris, and overlap with ulerythema ophryogenes is also reported [51]. Juhlin and Alkemade [52] report a woman with centrifacial erythrosis pigmentosa peribuccalis which moved onto the cheeks, and argued that these entities are also the same. Unilateral cases occur [53,54]. Reported dermal calcium deposition [55] has not been confirmed as a specific histological feature [48]. A report of possible autosomal recessive inheritance in a consanguineous family [56] is inconclusive.

Follicular ichthyosis. The capacity of this term to describe an entity distinct from keratosis pilaris is doubtful. IFAP is discussed above. A report of follicular hyperkeratosis distinguished from keratosis pilaris may be Noonan's syndrome [57].

Treatment. Simple emollients are rarely effective in keratosis pilaris. One recommended routine is based on initial control of the inflammatory component with a topical steroid, followed by 2% salicylic acid in 20% urea cream and an abrasive sponge [16]. Systemic retinoids are ineffective, and calcipotriol was not effective in nine patients [58], but benefit from topical tazarotene has been claimed [59].

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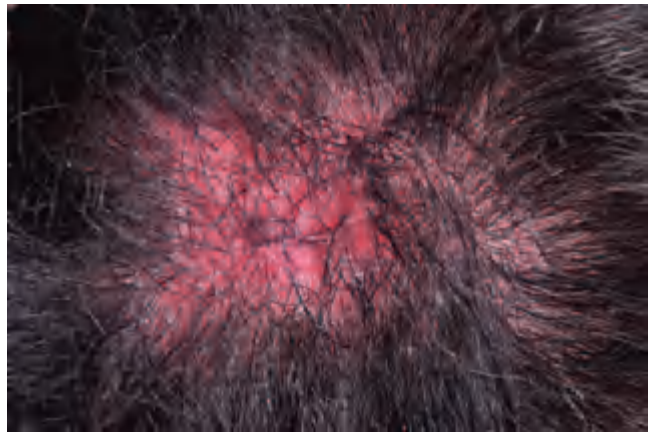

Fig. 34.32 Keratosis follicularis spinulosa decalvans showing atrophy and loss of scalp hair.

Keratosis follicularis spinulosa decalvans (MIM 308800)

KFSD [1,2] is an X-linked recessive disorder mapped to a locus at Xp21.13–p22.2 [3,4]; there may also be an autosomal form [3] and sporadic cases are reported. Keratotic follicular papules develop on the scalp in the first few years of life [5–9]. Progressive scarring alopecia follows with variable degrees of inflammatory change (Fig. 34.32), resembling folliculitis decalvans (see Chapter 63). Erythema and plugging of eyebrow follicles, follicular hyperkeratosis and prominent cuticles are seen. Ocular signs include blepharitis, ectropion and corneal dystrophy. Variable focal plantar keratoderma may be present [10]. Female heterozygotes may exhibit a phenotype that is usually mild [7,9]. The cutaneous and ocular features overlap with ichthyosis follicularis and photophobia (see above) in which palmoplantar involvement is absent [11,12]. Other associations reported include Noonan's syndrome [13], and with deafness [14], cutis laxa, big pinnae and clinodactyly [15], and aminoaciduria high in aspartic acid [16]. Treatment is generally unsatisfactory. *Staphylococcus aureus* is occasionally found in the inflamed lesions but improvement does not follow extensive appropriate antibiotic therapy. Retinoids, either topically or systemically, produce little improvement [17] but were helpful in one report [8].

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Other folliculocentric disorders

Lichen spinulosus (syn. keratosis spinulosa). This appears to have become uncommon in Western practice. Typical grouped lesions appear predominantly in childhood as crops of minute follicular papules, each with a projecting keratinous spine [1,2], and without erythema, chiefly about the neck, buttocks, trochanteric regions, abdomen, thighs, popliteal spaces and extensor aspects of the arms (Fig. 34.33). The face, hands and feet are usually spared.

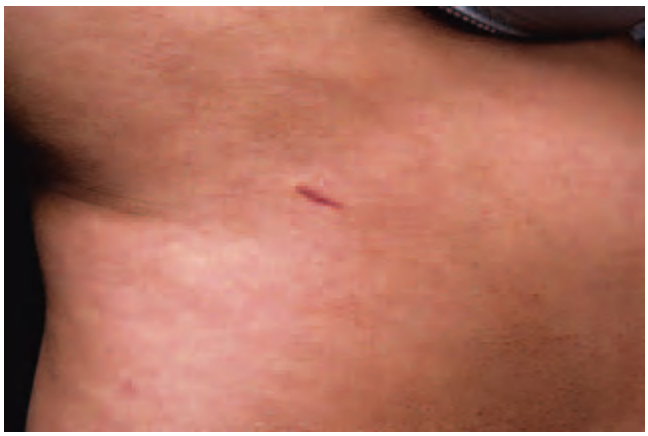

Fig. 34.33 Lichen spinulosus: even flesh-coloured grouped keratotic papules.

Similar appearance may arise in lichen planus, seborrhoeic dermatitis and reactions to dermatophytes, syphilis and tuberculosis. Friedman [2] studied 35 cases and concluded that it was probably a reaction pattern to several pathogenic processes. Many cases previously described as lichen spinulosus show follicular atrophy and loss of scalp hair, and would currently be termed ulerythema ophryogenes. One case was associated with Crohn's disease [3] and one case was considered to be a reaction to omeprazole [4]. In patients with human immunodeficiency virus (HIV), follicular lesions termed 'PRP-like' or 'lichen spinulosus-like' appear to be more filiform and florid than the disorder described here [5].

Phrynoderma. This condition, also now rare, is a distinctive form of follicular keratosis associated with nutritional deficiency first reported among prisoners in Beijing province [6]. Horny plugs with perifollicular papules are seen on the elbows, knees, neck and posterior axillary fold. The lesions are 2–3 mm in diameter and easily distinguished from keratosis pilaris. Adjacent skin may be pigmented and scaly. Hypovitaminosis A was the most likely cause, but deficiencies of other factors, such as calories and vitamins B and E, have also been incriminated.

Keratosis follicularis squamosa (Dohi). This is an acquired disorder of follicular hyperkeratosis with a surrounding scale 'like lotus leaves on the water', well-recognized in Japan, but apparently unusual elsewhere [7]. The condition responds to antibiotics.

Disseminate and recurrent infundibulofolliculitis. This striking eruption of unknown cause has been reported almost exclusively in young black male adults [8,9]. Recent reports are few. Profuse, monomorphic, tiny follicular papules with a variable degree of follicular plugging occur mainly over the trunk and back. There is no erythema. The epithelium of the upper follicle is oedematous and in parts spongiotic, and is surrounded by a predominantly lymphocytic infiltrate. Immunofluorescence was negative [9]. Both recurrent and chronic cases have been described. It has been suggested that it is a reaction pattern of atopic eczema in black people. The condition is resistant to therapy, but five of six cases responded to oral vitamin A [9], and a young Indian woman responded to photochemotherapy [10].

Familial dyskeratotic comedones [11–14]. This is an autosomal dominant condition characterized by scattered comedo-like lesions. The lesions appear around puberty, showing a predilection for the trunk, arms, legs, face and the shaft of the penis. The glans, and palms and soles are spared. The comedones can be picked out without producing bleeding. The lesions reform over a few weeks, and the condition gradually worsens with time. The lesions usually

lack any inflammatory signs, but around puberty approximately 50% may show concomitant acne. Histologically, there is a lamellar keratin plug with patchy parakeratosis; there may be acantholysis and scattered but not universal evidence of dyskeratosis. A naevus comedonicus is usually unilateral and the lesions are more closely packed [15]. Retinoid therapy has proved unrewarding.

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Pityriasis rubra pilaris

Pityriasis rubra pilaris (PRP) is a heterogeneous group of disorders that have in common circumscribed follicular keratoses, branny scale and an orange-red erythema, and PPK [1–5]. Classification is debated [6–8] but that of Griffiths [6] has been most widely used. There is a bimodal age of onset [9,10], but juvenile and adult forms of PRP, and indeed their variant forms, may be unrelated disorders. Incidence was approximately 1 in 5000 among patients presenting to a specialist dermatology centre.

Aetiology. The causes are unknown. Familial cases (MIM 173200) are rare [11,12]. Epidermal thymidine labelling is increased [13–15] from an average normal 3% to 27%, and the rate of growth of nails is faster than normal (although not so fast as in psoriasis). An infective aetiology is suggested, especially in the juvenile form [16–19]. Human leukocyte antigen (HLA) phenotype frequencies in 31 Finnish PRP patients did not differ significantly from those in a control population [19]. A PRP-like eruption is seen in patients with HIV [20].

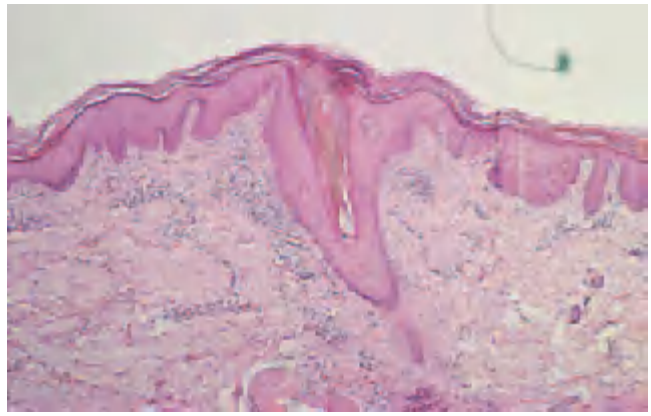


Fig. 34.34 Histopathology of pityriasis rubra pilaris: follicular plugging, acanthosis with exaggerated follicular shoulders, spotty parakeratosis and mild upper dermal inflammatory infiltrate.

Pathology [13,21,22]. The histology of classical adult PRP is distinctive, but varies with the stage of the process, and may differ from site to site. Affected follicles are filled with dense horny plugs and there are foci of parakeratosis in the perifollicular shoulder and interfollicular epidermis (Fig. 34.34). At other sites, basket-weave hyperkeratosis overlies a prominent granular layer and there is little parakeratosis, but there may also be attenuation of granular and horny layers. Dermal capillaries are dilated, but not tortuous, and there is a lymphohistiocytic dermal infiltrate. Unlike psoriasis, the acanthotic epidermis is not thinned above the dermal papillae, and there is no neutrophil infiltration. In discriminating PRP from psoriasis, follicular plugging and an increased granular layer in PRP may be valuable signs [22], but focal acantholysis also occurs. In one study there was increased staining of keratinocytes for β-D-galactose [23]. Expression of keratins K6/K16, a marker of epidermal proliferation, was present in affected epidermis in familial cases [12]. Circumscribed juvenile PRP shows dense lamellated hyperkeratosis with a normal or increased granular layer and little acanthosis. There is little capillary dilatation, and a sparse histiocytic dermal infiltrate. The pattern of keratin components seen by protein gel electrophoresis indicated a rapid epidermal turnover, as in normal skin, following adhesive-tape stripping of the stratum corneum, which contrasts markedly with that found in psoriasis [24]. Ultrastructural changes of uncertain significance have been reported [13,25].

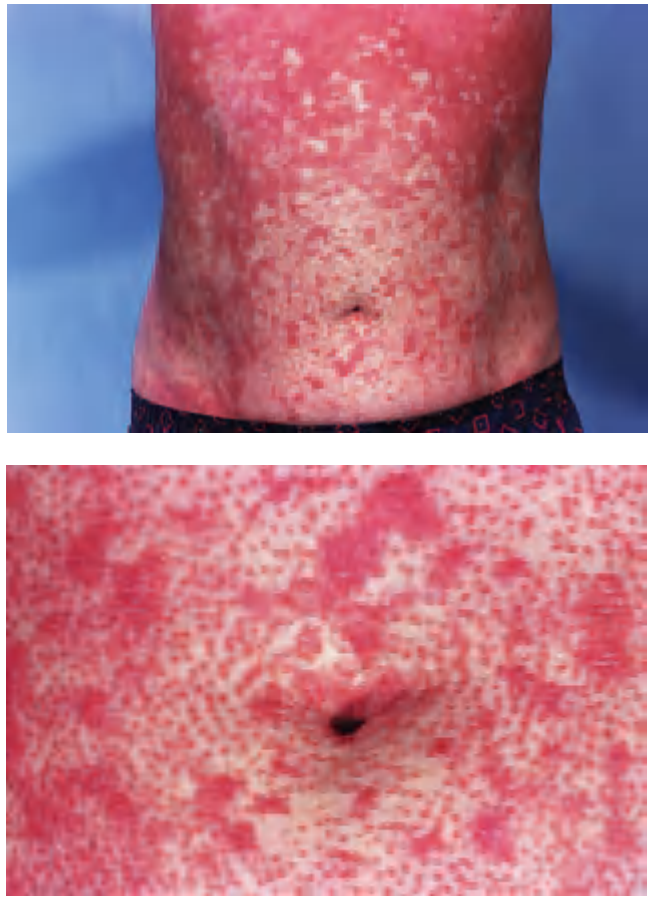
Clinical features. In view of the clinical and histological heterogeneity, confident diagnosis of PRP necessitates

Table 34.3 Some differences between pityriasis rubra pilaris and psoriasis.

	Pityriasis rubra pilaris	Psoriasis
Age at onset	Bimodal	Second decade
Scalp scaling	Furfuraceous	Adherent
Keratoderma	Constant	Less common
'Islands' of pale skin	Constant	Less common
Nail changes	No salmon patches	Present
Nail growth rate	Moderate increase	Marked increase
Epidermal kinetics	Moderate increase	Marked increase
Munro microabscesses	Absent	Common
Response to UVB	Poor	Good
Response to corticosteroids	Poor	Positive
Response to methotrexate	Variable	Good
Seronegative arthropathy	Rare	Common

strict criteria, and in the early or late stages of disease distinctive findings may be lacking. Repeated observation and multiple biopsies may be necessary. Psoriasis, notably follicular psoriasis in children [26], may present difficulties, but these are resolved by the clinical course or histology of psoriasis. Some differences between psoriasis and PRP are indicated in Table 34.3. Atypical forms of PRP must be regarded as provisional diagnostic categories.

Type I: Adult onset, classical. The most common and recognizable form, classical adult PRP affects the sexes equally with highest incidence between 40 and 60 years of age. The eruption usually starts without obvious precipitating factors as an erythematous, slightly scaly macule on the head, neck or upper trunk. Further macules appear within a few weeks, showing profusion of erythematous perifollicular papules with a central keratotic acuminate plug. Follicular lesions appear singly at first, and then coalesce to form groups of two, three or more (Fig. 34.35a,b). Irritation is initially absent, but may be pronounced as the disease spreads. Interfollicular erythema appears, and the follicular lesions are gradually submerged in sheets of erythema with a slight orange colour, which typically spreads from head to feet [6]. The face becomes uniformly erythematous and mild ectropion may follow. Prolonged erythema may give rise to peripheral oedema, and in the elderly precipitate high-output cardiac failure. The scalp shows diffuse bran-like scaling. The palms and soles become hyperkeratotic and yellow (PRP 'sandal'; Fig. 34.36). Erythroderma frequently develops within 2–3 months. In most cases, sharply demarcated islands of unaffected skin 1 cm in diameter remain as a helpful diagnostic sign [27]. Islands of deeper erythema are sometimes seen. The nails are thickened and discoloured distally, showing splinter haemorrhages, but unlike psoriasis there is no dystrophy of the nail plate and pitting is minimal [28] (Fig. 34.37). Spontaneous resolution occurs in 60–80% of patients in 1–3 years, but the condition may persist indefinitely [9,10]. The eruption resembles seborrhoeic dermatitis as it resolves. Relapses are rare [29].



(a)

(b)

Fig. 34.35 Pityriasis rubra pilaris type I: (a) cephalocaudal spread of follicular papules; and (b) follicular papules beginning to coalesce.

Type II: Adult-onset, atypical. This uncommon variety affects some 5% of patients. Follicular hyperkeratosis is prominent in some areas, while more lamellar scaling may be seen elsewhere, especially on the legs. Many patients show areas of eczematous change. The orderly caudal progression seen in type I does not occur and there is less tendency for the disease to become erythrodermic.

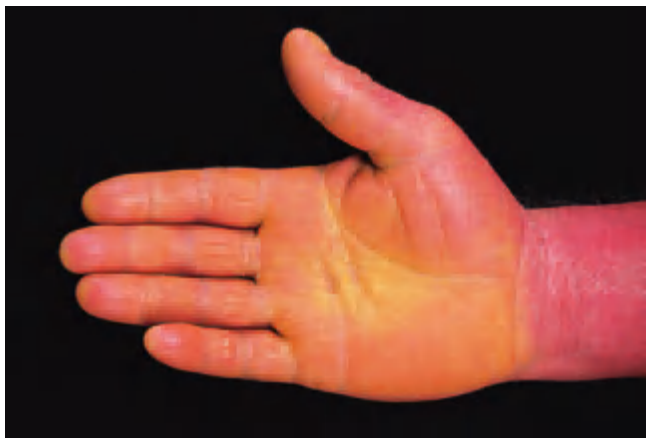


Fig. 34.36 Pityriasis rubra pilaris (PRP) type I: the PRP 'sandal'.

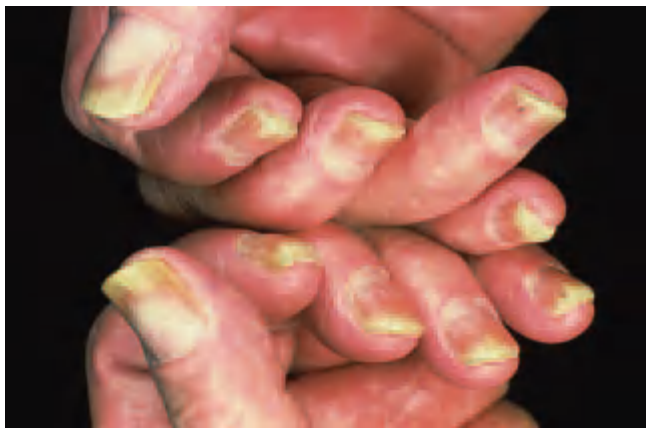


Fig. 34.37 Pityriasis rubra pilaris type I: thickening of the nails, subungual hyperkeratosis and splinter haemorrhages.

Type III: Juvenile-onset, classical (Fig. 34.38). The onset is between the age of 5 and 10 years. It resembles type I PRP, but may rapidly follow acute infection [16–18], and spontaneous clearing is usual within 1–2 years [7,30,31]. One case appeared to show a change from type III to type IV [32]. The atypical varieties described below are less exanthematic and have a poorer prognosis.

Type IV: Juvenile-onset, circumscribed. Several years after birth, well-demarcated plaques of follicular plugging with variable degrees of erythema appear on the knees and elbows (Fig. 34.39). A few scattered scaly erythematous macules are often found on the trunk or in the scalp. Some cases also show marked PPK. The histological changes are more reminiscent of psoriasis, but lack neutrophil microabscesses, and evolution to psoriasis is not reported. Circumscribed juvenile PRP must also be differentiated from the erythrokeratodermas. The prognosis is uncertain but some cases clear in the late teens. *Keratosis circumscripta*—prominent follicular papules on the knees, elbows, nape of the neck, and posterior axillary folds—reported in

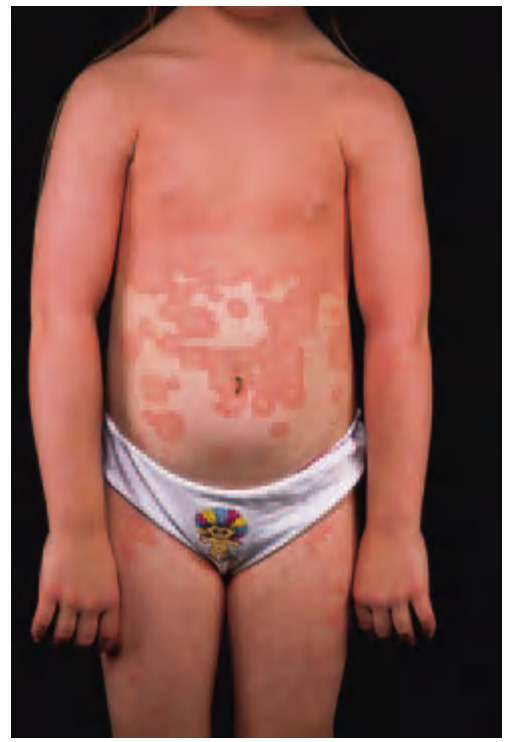


Fig. 34.38 Pityriasis rubra pilaris type III: orange-red erythema with cephalocaudal spread.

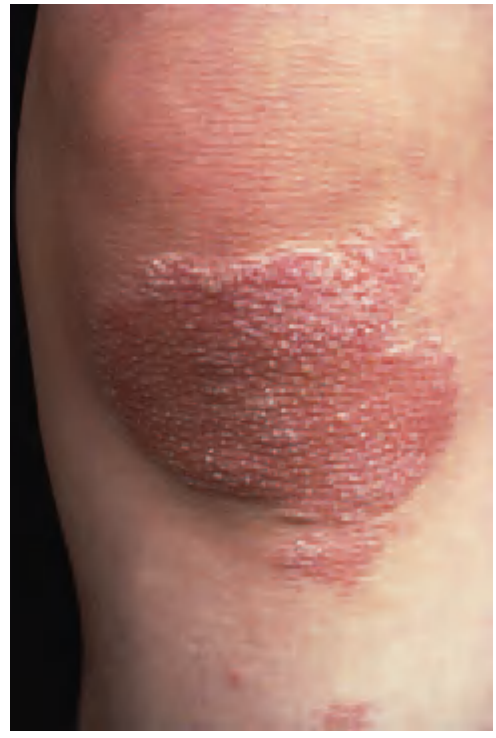


Fig. 34.39 Pityriasis rubra pilaris type IV (circumscribed juvenile PRP) showing well-demarcated plaques of follicular plugging.

African patients is probably identical to localized juvenile pityriasis rubra pilaris [33–35].

Type V: Juvenile-onset, atypical. Patients in this group show erythema and hyperkeratosis at birth or in the first few years of life. Keratoderma is common, and follicular plugging and erythema suggest a diagnosis of PRP. The group overlaps with poorly defined ichthyotic disorders and erythrokeratoderma. Several patients have shown a scleroderma-like change of the digits. There is little tendency for the disorder to clear spontaneously. Some cases within this group are clearly familial [12].

PRP and immunodeficiency. A PRP-like eruption associated with HIV infection and responding to antiretroviral therapy is recognized [36–39]. The term *type VI PRP* has been proposed [39]. Some cases resemble classical PRP, but others show a filiform pattern of keratoses on the face and upper trunk and often have marked acne conglobata [36–39]. Hypogammaglobulinaemia [40] has been reported in an isolated case.

Investigation. There are no diagnostic laboratory tests for PRP. Plasma vitamin A and carotenoid levels are normal [41] and reduced serum retinol-binding protein has been disputed [42,43]. Elevated cellular retinol-binding protein (CRBP) and cellular retinoic acid-binding protein (CRABP) levels similar to those found in plaques of psoriasis are reported [44]. Elevation of parathyroid hormone level [45] was not confirmed in five patients (W.A.D. Griffiths, unpublished data). Takematsu *et al*. [46,47] reported a normal level of leukotriene B_4 (LTB_4) and low levels of anaphylotoxins in scale extracts from PRP, within the range found for normal and non-inflamed skin, and differing from psoriatic scale. Shvili *et al*. [48] reported activated suppressor T cells and impairment of helper T-cell function.

Associated disorders. Many associations of uncertain significance have been reported. PRP has preceded leukaemia [49], metastatic carcinoma [50] and Sézary syndrome [51]. Conversely, Sézary syndrome and chronic T-cell lymphomas can mimic PRP [52,53]. A PRP-like eruption may also be seen in dermatomyositis (reviewed in [54]). Seronegative arthritis is recognized [55–57]. A patient with classical adult-onset PRP (type I) and lichen planus, alopecia universalis, vitiligo and chronic viral hepatitis C was reported [58]. Another patient with type I PRP developed Kaposi's varicelliform eruption from herpes simplex virus (HSV) type I [59]. Photosensitivity and worsening with UVB and UVA have been noted [60,61]. Other reported associations have been reviewed [3].

Treatment. Intensive topical and supportive treatment is needed for the erythrodermic state. Rest and emollient applications reduce exfoliation, and help to restore the skin barrier. Topical and systemic corticosteroids are ineffective. No systematic trials have been conducted, but oral retinoids are widely used. In the erythrodermic phase, acitretin or isotretinoin are used [62–65]. Results with systemic retinoids are unpredictable, with some patients showing dramatic clearing while others appear to be resistant. In patients who respond, the natural history of the disease appears to be shortened [63]. In children, isotretinoin produced the best response [31]. Topical vitamin D analogues are reported to be beneficial [67]. Methotrexate has been effective as an alternative or adjunct to oral retinoids [63,68,69], but may be less efficacious in PRP than in psoriasis [3]. Phototherapy may exacerbate the condition, but narrow-band UVB, UVA1, PUVA, bath PUVA and extracorporeal photopheresis have all been reported as beneficial [68,70–73]. Phototherapy may be combined with acitretin [74,75], and capsaicin was used to relieve phototherapy pruritus [76]. Success [77–79] and failure [63,80] with ciclosporin are reported. Antiretroviral therapy, of value in the PRP-like eruption of HIV disease [81], did not help three non-HIV cases [82]. Oxholm *et al*. [83] reported a patient receiving cytostatics, retinoids, PUVA and ciclosporin who developed a squamous cell carcinoma of the parotid.

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Darier's disease and related disorders

Darier's disease (MIM 124200)

SYN. KERATOSIS FOLLICULARIS; DARIER–WHITE DISEASE

Darier's disease, described independently by White and Darier in 1889, is an autosomal dominant condition characterized by a persistent eruption of hyperkeratotic papules, histological examination of which shows suprabasal acantholysis with a distinctive overlying dyskeratosis [1,2]. Expressivity is variable but penetrance complete in adults [3]. Sporadic cases are common. It has a worldwide distribution. Reported prevalence varies from to 1 in 100 000 in Denmark [4] to 1 in 30–35 000 in northern England and Scotland [3,5].

Aetiology. Darier's disease is caused by mutations in the *ATP2A2* gene at chromosome 12q24.1, which encodes the sarco- and endoplasmic reticulum calcium ATPase type 2 (SERCA2) [6–10]. SERCA2 is member of a family of ion pumps that maintain high calcium concentration in the endoplasmic reticulum [11–13]. It has two isoforms: SERCA2a is expressed in cardiac and smooth muscle, whereas SERCA2b is more widely expressed, including in epidermis. Darier's disease is caused by both nonsense and insertion and/or deletion mutations, likely to produce haploinsufficiency, and missense mutations, likely to result in an abnormal expressed protein [6–9].

Pathology. In the earliest papular lesions, lacunae appear above the basal layer [1,2], and extend irregularly throughout the Malpighian layer. Small groups of cells around the lacunae become separated from their neighbours, enlarge and present a darkly staining nucleus surrounded by clear cytoplasm and a glistening ring simulating a membrane. These 'corps ronds' show premature partial keratinization (dyskeratosis); they give rise to the grains, small cells with shrunken cytoplasm, seen in the upper layers of the epidermis. This abnormal terminal differentiation appears also to be distinct from apoptosis [14]. Lesions are not exclusively follicular [15], as acantholysis and dyskeratosis appear to occur preferentially around sweat ducts and mucous and salivary glands as frequently as around follicular openings. With the electron microscope, the lacunae can be seen to result from changes in the tonofilaments, which become separated from the desmosomes [16]. Immunocytochemical studies confirm that desmosomal proteins of affected cells are not localized to the membranes but diffusely distributed in the cytoplasm [17–19] and their intra- and extracellular domains are dissociated [20]. Defects in SERCA2 may produce these changes as a result of impaired processing of cell membrane proteins in the endoplasmic reticulum.

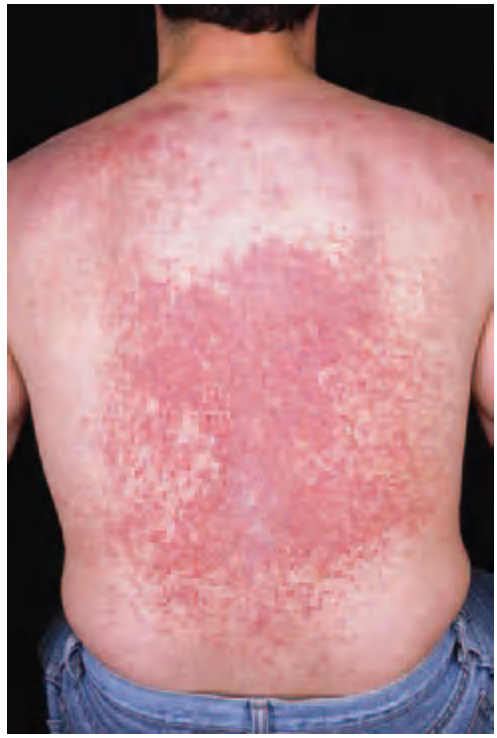

Fig. 34.40 Darier's disease: profuse keratotic papules in the seborrhoeic region of the back.

Focal acantholytic dyskeratosis also occurs in other conditions, such as solitary dyskeratoma, and transient and persistent acantholytic dermatoses. Hailey–Hailey disease (chronic familial benign pemphigus; see Chapter 40), may overlap clinically and histologically, although there is more suprabasal clefting and acantholysis, and grains and corps ronds are less evident, in Hailey–Hailey disease.

Clinical features [1,3]. The distinctive lesion of Darier's disease is a firm rough papule, which is skin-coloured, yellow-brown or brown. Seborrhoeic areas of the trunk (Fig. 34.40) and face, particularly the scalp margins, temples, ears and scalp, are most often involved. Many lesions are subtle; the occurrence of multiple minute acanthomas is easily overlooked. Flat and freckle-like lesions may appear as pale macules in pigmented skin [21]. Coalescent papules form irregular warty fissured plaques or papillomatous masses, which, in the flexures, become vegetating

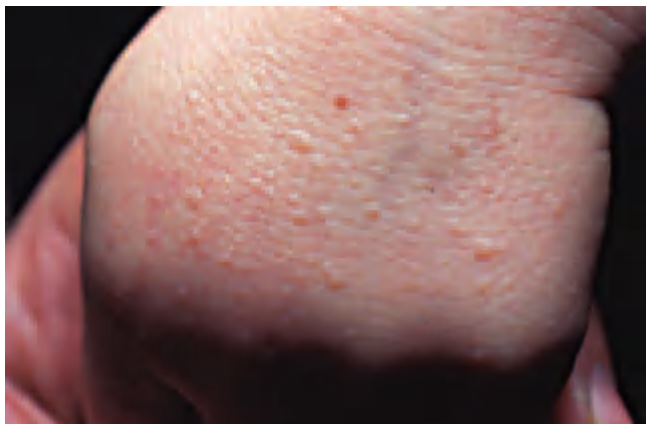

Fig. 34.41 Darier's disease: acrokeratosis verruciformis in a 4-year-old child.

and malodorous [1]. Flexural involvement most notably affects the anogenital region, the groins and the natal cleft. On the scalp, the heavy crusting simulates seborrhoea, but has a characteristic spiny feel to palpation. Loss of hair is exceptional. The external auditory meatus may be blocked by keratotic debris [22]. Limb involvement usually takes the form of scattered papules, but confluent lesions on lower legs and arms may be a problem [23]. On the dorsa of the hands and feet, discrete papules are clinically indistinguishable from acrokeratosis verruciformis of Hopf [24,25]. These may be the earliest manifestations of the disease (Fig. 34.41) [3]. In Darier's disease, the palms and soles may show minute pits or, in older subjects, punctate or filiform keratoses [25,26]. Lesions of the mucous membranes are uncommon, but white umbilicate or cobblestone papules on the palate resembling nicotinic stomatitis may be seen [27]. Lesions of the tongue, buccal mucosa, epiglottis, pharyngeal wall, vulva, oesophagus or rectum may occur, as may gingival hypertrophy [28–30]. Confluent buccal lesions may simulate leukoplakia. Characteristic nail changes include red or white longitudinal bands of varying width, often ending in a pathognomonic notch at the free margin of the nail. The nails are often brittle.

The majority of patients first become aware of lesions in the second decade [1], although minor lesions or nail or palmar changes may be detected earlier [3]. The condition is typically exacerbated by heat and light, especially sunburn, and lesions can be experimentally induced by UVB exposure [31]. The disease usually runs a chronic relapsing course, and general health is normally unaffected. Exacerbations of keratosis follicularis have also been reported following steroids in naevoid disease [32]. Spontaneous remissions do occur.

Clinical variants. Most patients have the classical seborrhoeic distribution of papules, but there is considerable variation in the severity, from isolated nail or palmar changes to universal and grossly disfiguring involvement. A minority of patients have predominantly vesicobullous [33], flexural or erosive disease or hyperkeratotic lesions, particularly of the distal limbs [23]. The most malodorous cases occur in these patients. Some patients present with multiple comedones or nodulocystic acne with deep pitted scars, and typical histology of Darier's disease may be found in these lesions [34]. Haemorrhagic macules occasionally seen on the hands and feet seem to represent a true genetic variant, as they occur consistently within families [35] and may be caused by specific mutations [8]. Atypical or unusually severe Darier's disease is usually a result of missense mutations [7,8].

Acantholytic dyskeratotic epidermal naevi. Following the lines of Blaschko, these are commonly of late onset and display photoaggravation, suggesting they are a naevoid form of Darier's disease [32,36,37]. It has now been shown that is the case in at least some such naevi [38], a finding that implies the potential for transmission of the disorder if the gonads are affected by somatic mosaicism.

Associated features. Despite the wide expression of SERCA2, the phenotype of Darier's disease is largely confined to the skin. However, patients have an increased susceptibility to herpes simplex [39]. Kaposi's varicelliform eruption has occurred [40,41], as has poxvirus infection [42]. There may also be an increased incidence of chronic pyogenic infection [43]. There is evidence for and against a defect in cell-mediated immunity [44–47]. Salivary duct narrowing can cause recurrent salivary gland swelling, and subclinical narrowing may be common [27,48,49]. Most patients are of normal intellect, but clinical experience suggests that mild degrees of learning difficulty are common. There are numerous reports of cases of Darier's disease with a range of neuropsychiatric disorders, including a high prevalence of epilepsy [1,4,50–52]. Transgenic mice haplo-insufficient for SERCA2 display impaired cardiac contractility [53] and an increased incidence of gastro-oesophageal and other squamous cancers [54]. However, SERCA2 function in humans appears to be largely compensated by other genes or epigenetic factors, as there is no evidence of a consistent cardiac problem in Darier's disease [55] and an increased incidence of cancer has not been documented.

Differential diagnosis. In mild forms, acne and seborrhoeic dermatitis may be confused, unless the warty papules are carefully sought. Confluent lesions resemble discoid eczema and may respond to treatment for this. Flexural Darier's disease may overlap clinically and histologically with benign familial pemphigus (Hailey–Hailey disease) but patients with intertriginous Darier's disease have changes typical of Darier's disease elsewhere,

Table 34.4 Focal and follicular keratoses.

	Age of onset	Distribution	Morphology	Associated features
Keratosis pilaris				
Physiological	Childhood or adolescence	Extensor limbs	Horny follicular plugs	None or erythrocyanosis
Ichthyotic	Early childhood	Extensor limbs	Horny follicular plugs	Ichthyosis—autosomal dominant type
Keratosis pilaris atrophicans (including atrophoderma vermiculatum)	Childhood	Eyebrows, cheeks	Erythema, follicular plugs, alopecia	Miliary cysts
Keratosis pilaris spinulosa decalvans	Childhood	Face, scalp, trunk	Follicular plugs, scarring alopecia	
Phrynoderma	Any age; usually childhood	Elbows, thighs, buttocks	Horny follicular plugs	Skin dry, pigmented
Pityriasis rubra pilaris	Childhood or middle life	Especially dorsa of fingers, knees, elbows; may be widespread	Fine, red papules with central horny plug	Plaques of erythema and scaling; palmoplantar keratoderma
Darier's disease	Usually above 10 years	Seborrhoeic areas	Yellow-brown, greasy papules	Nail and palmoplantar lesions
Kyrle's disease	50–70 years	Mainly arms and legs	Large irregular horny plugs	

and the age of onset is usually earlier. In Dowling–Degos disease or acanthosis nigricans, lesions are flexural and pigmented. In confluent reticulate papillomatosis (see below), the lesions are flat and largely confined to the upper trunk. Other follicular keratoses are listed in Table 34.4. The harshness on palpation distinguishes the disorder from many visually similar disorders such as the reticular erythematomucinous syndrome and prurigo pigmentosa [56].

Treatment [57]. Many patients with mild disease require no treatment other than emollients, simple hygiene and advice to avoid sunburn. Topical tretinoin and isotretinoin, adapalene and tazarotene have been reported as effective [58–61]. In practice, irritancy limits the value of most topical preparations and extra emollients are needed. Antiseptics may help with infected plaques, which may respond to topical steroid–antibiotic combinations. For those with more severe disease, oral retinoids are usually effective. Both acitretin and isotretinoin may be used [62,63]. Dermabrasion in limited areas may prove useful [64]. Severe inflammatory exacerbations of Darier's disease occur in some patients, and have responded to ciclosporin [65,66]. Knulst reported 2 and 6 months' remission in two patients treated with topical 5-fluorouracil [67].

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Transient and persistent acantholytic dermatosis

SYN. GROVER'S DISEASE; PAPULAR ACANTHOLYTIC DERMATOSIS

These papular acantholytic dermatoses mainly affect the trunk in middle-aged or elderly people, and typically present as an eruption of pruritic papules or papulovesicles with focal acantholytic dyskeratosis on histology [1–4]. Distinction between transient and persistent forms of disease may be artificial [2,4].

Aetiology. The cause is unknown. Heat and sweating are predisposing factors [5,6]. The condition has been regarded by some as a minimal expression of Darier's disease [7] but mutations in the *ATP2A2* gene were not found in four patients [8].

Pathology. Many conditions show histology of focal acantholytic dyskeratosis [9]. In transient acantholytic dermatosis, the histology mimics Darier's disease, pemphigus and Hailey–Hailey disease, and there is also a spongiotic form in which acantholytic cells are contained within spongiotic foci in the epidermis [2,5,10]. Acantholysis may only be related to the acrosyringium in a subset of cases [11,12]. Darier-type [2] or pemphigus-type histology [5] appears to predominate in the more persistent type of lesion. Dermal eosinophilia and degranulation is sometimes seen [10]. Immunofluorescent studies are negative [13]. Electron microscopic studies have shown intradesmosomal separation, diminution in the number of desmosomes and perinuclear aggregation of tonofilaments [14]. Cells with the electron microscopic features of corps ronds have also been seen [15]. In a study of the focal

acantholytic dermatoses, Hashimoto *et al*. [16] reported that the attachment plaque proteins dissolved and diffused into the acantholytic cells. Internalized desmosomal structures were seldom found in acantholytic cells of non-immune diseases.

Clinical features. Transient acantholytic dermatosis presents as an acute eruption of pruritic discrete greyish pink papules or papulovesicles. Lesions most commonly occur on the trunk, and mostly affect middle-aged or elderly men, especially those with a fair skin. The initial lesion may be mistaken for a solar keratosis. The disease may occur on a background of pre-existing skin disease [17]. It is common in hospitalized patients [18]. The rash is usually transient, lasting from 2 weeks to several months. Exposure to sun [1,2], ionizing radiation [19] and 2-chlorodeoxyadenosine [20] have been noted as precipitating factors. An association with internal malignancy has been reported several times [10,19,21,22], but may be non-specific.

The prognosis is variable, and the disease may run a chronic relapsing course. Most patients with persistent disease are men with significant solar damage.

Differential diagnosis. Darier's disease and Hailey–Hailey disease are distinguished by the late onset of scattered truncal lesions without a tendency to confluence, and the absence of family history. Pemphigus is clinically distinct and is also excluded by negative immunofluorescence, although coexistence with pemphigus foliaceus has been recorded [23]. Other conditions in which focal acantholysis can occur include actinic keratoses or PRP [24], and these may need to be differentiated.

Treatment. In mild cases, symptomatic treatment of pruritus and topically applied steroids may be all that is required. The successful use of calcipotriol is recorded [25]. In more troublesome cases, etretinate [2,26], isotretinoin [27], systemic steroids [5] and PUVA [28] have been used.

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Acrokeratosis verruciformis

Acrokeratosis verruciformis of Hopf [1] is characterized by multiple flesh-coloured or lightly pigmented papules on the dorsa of the hands and feet and other sites. Its existence as an independent entity has been debated [2–4] and recent genetic data suggest that it is allelic with Darier's disease [5].

Aetiology. The lesions are typical of acral lesions in Darier's disease, but may occur as an isolated autosomal dominant trait. Causative mutations in *ATP2A2*, the gene implicated in Darier's disease, have been found in a pedigree of acrokeratosis verruciformis, but the occurrence of

similar lesions in other conditions (see below) suggests that there could be multiple causes.

Pathology. Hyperkeratosis, acanthosis and a prominent granular layer may be accompanied by papillomatosis and discrete pointed epidermal upgrowths said to resemble church spires. It has been claimed that the absence of suprabasal clefts distinguishes this entity from Darier's disease [2], but in practice lesions from the latter do not show always show clefting [4].

Clinical features. Flat or convex skin-coloured warty papules are present on the dorsa of the hands and feet, on the knees and elbows, and on the forearms [6]. Small groups or isolated papules may develop in other sites. Friction of the lesions may cause blister formation. The eruption affects both sexes and is usually present at birth or appears in early childhood; however, the onset may be delayed until the fifth decade [7]. Transformation to squamous cell carcinoma has been reported [2,8]. Nail or palmar lesions may suggest the diagnosis of Darier's disease, even in the absence of the rash [5,6]. In addition to Darier's disease, cases have been recorded in association with Hailey–Hailey disease [9], naevoid basal cell carcinoma syndrome [10], congenital poikiloderma [11], and steatocystoma multiplex and hypertrophic lichen planus [12]. The condition resembles extensive plane warts. In more severe cases, epidermodysplasia verruciformis can be differentiated by histopathology and virological studies (see Chapter 25).

Treatment. Systemic treatment of isolated acrokeratoses is not usually justified, but oral retinoid treatment failed in one case [13].

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Other focal disorders

Perforating keratotic disorders [1]

The nature and number of perforating (epidermal elimination) disorders is uncertain. They present as keratotic papules, but epidermal involvement may be secondary to dermal disease. A case has been made for unifying some or all disorders because, with the exception of elastosis perforans serpiginosa, all have been reported in association with diabetes mellitus or renal failure [2]. The term acquired perforating dermatosis has been proposed.

Kyrle's disease (hyperkeratosis follicularis et parafollicularis in cutem penetrans). Keratinous 1-cm nodules are seen mainly on the limbs (Fig. 34.42). Kyrle's case was a young diabetic female in whom keratotic nodules appeared around the axillae and later became generalized [3].

Acquired perforating dermatosis. This may be synonymous with Kyrle's disease [4–6], and is most often seen with diabetes or before, during or after dialysis for renal failure [7]. Eleven per cent of 72 British patients on renal dialysis developed a perforating dermatosis [8]. Trauma from scratching is thought to initiate the lesions. Histology shows follicular and non-follicular lesions with broad or narrow ulcer craters, and evidence of perforation of both collagen and elastic fibres. Degenerate collagen, elastic tissue and keratin are seen mixed with an unidentified

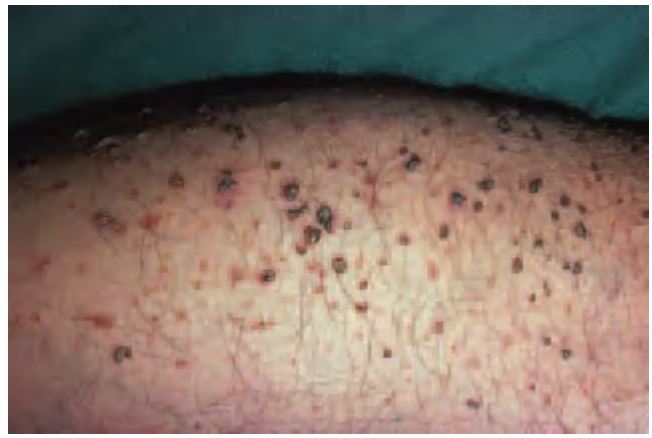

Fig. 34.42 Kyrle's disease: large keratinous plugs on the thigh.

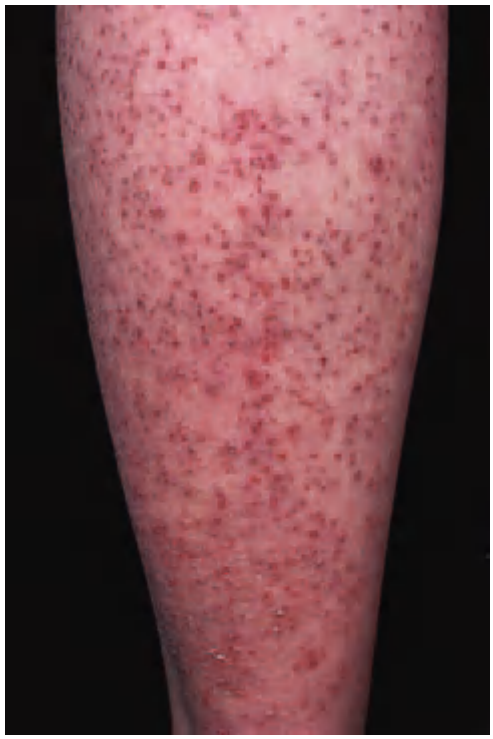

Fig. 34.43 Flegel's disease: polygonal keratotic lesions on legs.

clear material, which has been regarded by some as an accumulation of a metabolite [2]. Lucke *et al*. [9] reported two cases of a disorder characterized by transepidermal elimination of negatively birefringent needle-shaped crystals similar to monosodium urate. In most cases of acquired perforating dermatosis, lesions could be cleared by treatment with potent topical or intralesional steroids. Topical tretinoin was also helpful in reducing the lesions. Successful use of allopurinol has been reported [10].

Flegel's disease (hyperkeratosis lenticularis perstans). This is inherited as an autosomal dominant condition (MIM 144150). Lesions differ markedly from Kyrle's disease [11]. In the third or fourth decade, 2–3 mm keratotic papules with discrete irregular margins ('cornflake sign', Rowland–Payne) appear over the calves and extensor surfaces of the ankles (Fig. 34.43). Lesions may spread to the arms and the concha of the ears. The keratotic scale separates from many lesions, leaving a non-exudative red base. Irritation may be severe. Histologically, there is hyperkeratosis, sometimes with foci of parakeratosis. The underlying epidermis alternates between atrophy and acanthosis, and there is a dermal infiltrate of mononuclear cells [11,12]. Despite the strong genetic component in the disorder, no reports identifying a candidate gene have appeared to date. The profusion of lesions and poor response to cryotherapy, topical and systemic retinoids, and to 5-fluorouracil make management difficult.

Reactive perforating collagenosis (see Chapter 46). This affects children, with the formation of 2–5-mm papules, usually on the limbs. Lesions in all stages of eruption and resolution are present at one time [13].

Perforating folliculitis. This affects the limbs of young adults with erythematous follicular papules, 2–8 mm diameter, which are usually asymptomatic. Histologically, a plug of keratin disrupts the infundibular portion of the follicular epithelium [14].

Elastosis perforans serpiginosa (see Chapter 46). This presents as grouped arcuate or serpiginous keratotic papules and is associated with Down's syndrome, disorders of connective tissue and penicillamine treatment. Histologically, amorphous masses that bind elastic tissue stains can be seen traversing the epidermis.

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Porokeratosis

Porokeratoses are characterized by marginate scaling lesions, histologically showing a column of parakeratotic keratinocytes (the coronoid lamella). Various forms are recognized, but terminology and classification are debated [1,2]. Some forms appear to be premalignant [3].

Aetiology. Loci at chromosomes 12q23.2–24.1 and 15q25.1–26.1 have been reported in familial disseminated superficial (actinic) porokeratoses (MIM 175900) [4,5]. The latter

locus includes a candidate gene, basonuclin [5]. The centrifugal progress of individual lesions is thought to reflect the migration of a clone of abnormal cells [6]. There is keratinocyte dysplasia and Otsuka *et al*. [7,8] have reported aneuploidy and chromosomal abnormalities in lesional keratinocytes. The tumour suppressor protein p53 is over-expressed in the coronoid lamella [9–11]. Cytogenetic anomalies in fibroblasts, particularly chromosome 3, are also recorded [12]. An association with immunosuppression [1] suggests impaired immunity is permissive, perhaps by reduced immune surveillance of dysplasia, but the possibility of an infective aetiology [13] remains.

Pathology [14]. Lesions may or may not involve the eccrine sweat duct. The characteristic histopathology is seen in the edge of the lesion. The stratum corneum is hyperkeratotic, and at the raised border a column of poorly staining parakeratotic stratum corneum cells, the cornoid lamella, is seen running through the surrounding normal-staining cells. The underlying keratinocytes are oedematous with spongiosis, shrunken nuclei and a moderate dermal lymphocytic infiltrate under the lamella [14]; a lichenoid reaction pattern may be present. The central area of a lesion is usually atrophic, but may occasionally show gross hyperkeratosis [15]. Cornoid lamellae may also be found in other conditions, such as viral warts, some ichthyoses and naevoid hyperkeratoses.

Clinical features

Disseminated forms. Clinical distinction between the various forms of disseminated porokeratosis may not be justified [16]. *Disseminated superficial actinic porokeratosis* (DSAP) is the most common presentation, with very many lesions of up to 10 mm predominantly in sun-exposed sites in middle-aged individuals, especially those with sun-sensitive skin (Fig. 34.44). They are easily mistaken for actinic keratoses, with which they may coexist. Lesions were not induced by artificial light exposure [17], but have been provoked by photochemotherapy [18]. No evidence that skin cancer arises in the porokeratotic lesions was found in one study of 29 patients [19]. *Disseminated superficial porokeratoses of immunosuppression* are recognized after renal, hepatic, cardiac and bone marrow transplantation, and in AIDS [1]. The distribution is similar to DSAP, but a history of sun exposure is less likely [20]. *Disseminated superficial porokeratosis of childhood* may be inherited as an autosomal dominant condition, but sporadic cases are seen. Widely disseminated, flat lesions usually begin in childhood, the majority between the ages of 5 and 10 years, but may be present at birth or may first appear at puberty or later. Palmoplantar lesions may be associated (porokeratosis palmaris et plantaris disseminata) [21]. Widespread lesions appeared first at the age of 1 month in a male infant with craniosynostosis and other congenital abnormalities [22].

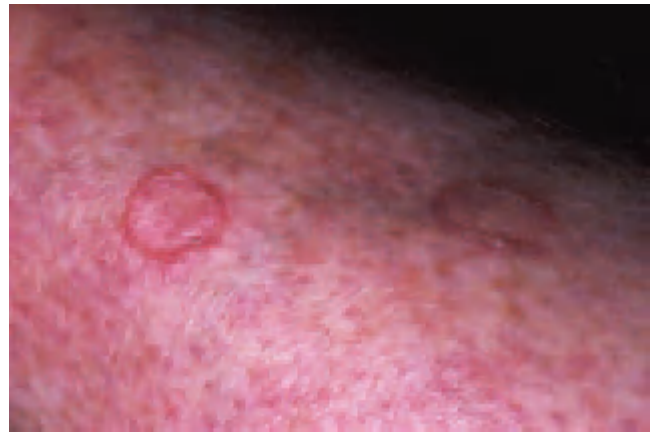

Fig. 34.44 Disseminated superficial actinic porokeratoses: annular keratotic lesions with a raised margin.

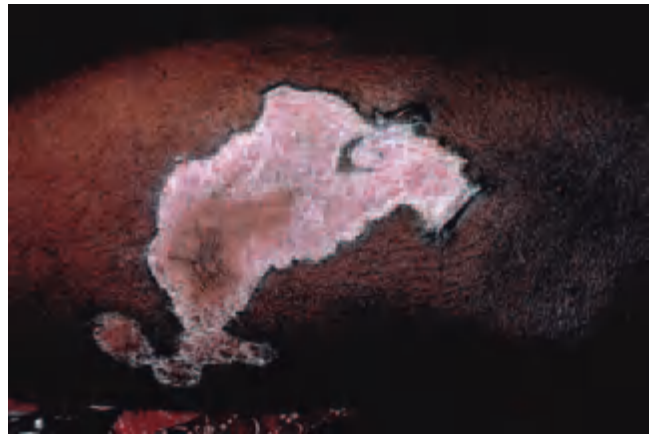

Fig. 34.45 Porokeratosis of Mibelli.

Porokeratosis of Mibelli [23,24]. The eponym Mibelli is sometimes used generically for porokeratoses, but usually refers only to the form with single or scanty and larger lesions. These develop as annular dry plaques (Fig. 34.45) surrounded by a raised, fine keratotic wall and sometimes also a furrow. Lesions are most common on the limbs and by centrifugal spread may achieve several centimeters in diameter. The centre is usually atrophic but may be hyperkeratotic [15]. The face, genitalia, oral mucosa and cornea may also be affected. The condition may be familial, inherited as an autosomal dominant with onset in childhood (MIM 175800), or sporadic and of later onset.

Giant porokeratoses (up to 20 cm in diameter with a surrounding wall of 1 cm). These are very rare [25], and are most often found on the foot. Large lesions are said to have the highest malignant potential [3,26,27].

Palmoplantar porokeratosis (of Mantoux). Parakeratotic hyperkeratosis histologically reminiscent of the cornoid lamella occurs in some punctate keratodermas, but the absence of marginate lesions distinguishes from true porokeratosis [28]. Nonetheless, annular lesions of palms and soles with a cornoid lamella are recognized [21,29].

Linear porokeratosis [27,30,31]. Linear porokeratoses showing typical cornoid lamellae and following the lines of Blaschko usually appear in childhood. These lesions probably result from a predisposition to porokeratosis in an abnormal clone of epidermal precursors. Malignant degeneration and metastasis has been reported in this variety [28,32]. Linear accentuation of disseminated actinic porokeratosis is reported [33,34].

Treatment. Treatment of disseminated superficial porokeratoses is usually unnecessary, but cryotherapy, carbon dioxide and pulsed dye laser therapy have all been used [35,36]. Keratolytics offer little relief but successful use of tacalcitol has been reported [37]. In some cases 5-fluorouracil ointment is effective [38,39]. Consistent results appear to be given by etretinate, but the symptoms may not justify treatment [40].

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Minute and filiform keratoses

Clinical discrimination of multiple minute and filiform keratoses remains unsatisfactory, but a number of entities have been described [1]. Filiform palmoplantar keratoses are also recognized (see below).

Filiform keratoses. Multiple discrete fine keratotic lesions, variously described as spiked, filiform or hairy, have been reported, including familial [2] and sporadic [3], follicular and non-follicular [4], drug-associated [4,5] and myeloma-associated [6,7] cases. Filiform keratoses occur

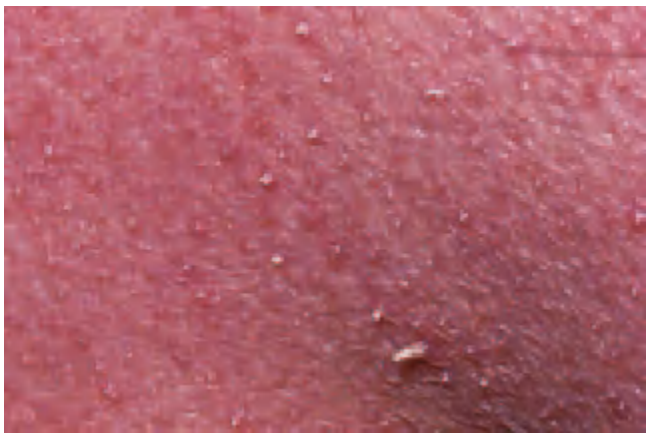

Fig. 34.46 Digitate hyperkeratosis. (Courtesy of Dr F.A. Ive, Dryburn Hospital, Durham, UK.)

with a PRP-like eruption and acne conglobata in association with HIV infection [8].

Minute aggregate keratoses [9]. This is characterized by the truncal distribution of multiple minute keratotic papules. Morphologically, these may be spicular or dome-shaped, and aggregation of the latter may create the impression of annular and crateriform lesions. Histologically, there are focal areas of hyperkeratosis and orthokeratosis with no dermal infiltrate. Odland bodies are present on electron microscopy of lesional skin.

Multiple minute digitate hyperkeratoses (Fig. 34.46). Goldstein [10] reported a 32-year-old black patient with multiple small finger-like projections on the anterior chest and anterolateral aspects of the arms and legs. The non-follicular lesions were less than 1 mm in diameter and 1–2 mm in length. Family history was negative. Familial cases with probable autosomal dominant inheritance [11,12], or sporadic and transient [13–15] cases occur. The condition has been seen following X-irradiation [11,16]. Histologically, there are focal areas of compact orthohyperkeratosis with few dermal changes and keratohyalin granules, which were thought to be smaller than normal [12], athough Pujol found columnar parakeratosis resembling porokeratosis [16]. One case associated with carcinoma of the larynx cleared following surgery [17].

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Miscellaneous circumscribed keratotic disorders

Waxy keratoses of childhood. Three children in two families were reported with a disorder consisting of generalized discrete domed keratotic papules, which were flesh-coloured or yellowish [1]; two young patients reported earlier with 'disseminated hypopigmented keratoses', appear to be identical [2]. Histological findings were marked orthokeratotic hyperkeratosis, tenting of the epidermis and mild acanthosis. Differential diagnosis includes the leukodermic macules in Darier's disease in dark skin [3].

Facial Afro-Caribbean childhood eruption. A monomorphic, mildly hyperkeratotic, papular facial eruption in black children was reported by Marten *et al*. [4] in 1976. Further cases in children were termed granulomatous perioral dermatitis [5]. Williams *et al*. [6] suggested the name and acronym FACE. The eruption shows a predilection for the perioral and periorbital regions and nose. The condition is of unknown cause, and does not appear to be a rebound phenomenon from the use of topical steroids. Histology shows peri-follicular inflammation with foci of granuloma formation. It does not respond to topical steroids, but resolution within a year without scarring was usual.

Florid cutaneous papillomatosis [7,8]. This term was used to describe the appearance of multiple acuminate keratotic papules in association with an underlying gastric adenocarcinoma. The first patient also had acanthosis

nigricans and eruptive seborrhoeic warts (Léser–Trelat sign). Worret's case also had acquired hypertrichosis lanuginosa from metastatic bronchial carcinoma.

Hyperkeratosis of the nipple [9]. Marked hypertrophy of the nipple and areola was noted in association with a T-cell lymphoma, which resolved following chemotherapy.

Knuckle pads [10,11]. These are classified with the fibromatoses (see Chapter 46). Nevertheless, it appears that the dry, rather fleshy lesions occurring over the knuckles and interphalangeal joints differ from the acanthotic grossly hyperkeratotic lesions seen in association with some keratodermas. In Morginson's series of 30 patients [10], seven showed hyperkeratosis, keratodermas and fissuring of varying degree involving the palms and soles. Confusion sometimes occurs with pachydermodactyly (see Chapter 46). Knuckle pads may be seen also in the Papillon–Léfèvre syndrome, and in epidermolytic keratoderma resulting from keratin 9 mutation [12]. The *Bart–Pumphrey syndrome* (MIM 149200) is an autosomal dominant condition associating knuckle pads, leukonychia and mixed sensorineural and conductive deafness [13].

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Palmoplantar keratodermas

Classification of palmoplantar keratodermas

PPKs are a diverse group of hereditary and acquired disorders defined by excessive epidermal thickening of palms and soles. Many keratoderma syndromes are restricted to palms and soles, but other ectodermal or systemic abnormalities may be associated. Palmoplantar involvement may also be seen in generalized disorders of keratinization such as ichthyosis vulgaris, epidermolysis bullosa or EHK. Genetic defects have been identified in some inherited keratodermas (Table 34.1), but clinically homogeneous entities may have distinct molecular pathogenesis, and different mutations in one gene can give rise to distinct syndromes. Consequently, although a number of classifications of keratodermas have been published [1–7], none unite satisfactorily clinical presentation, pathology and molecular pathogenesis. Inherited keratodermas described in this chapter are outlined in Table 34.5, but many isolated reports of unusual or unique associations are necessarily excluded.

Keratodermas are often grouped by clinical pattern as diffuse, focal (areate), striate or punctate, but there are no absolute boundaries between these groupings. The presentation of a single disease may vary with site, age, gender or occupation. Plantar skin tends to be more severely or diffusely affected than palmar skin. In assessing an isolated case of keratoderma, it may be inappropriate to confine the differential diagnosis to one clinical grouping. However, the following definitions may offer some guidance. In *diffuse keratodermas*, the whole of the palmar or plantar epidermis, usually including the centripalmar skin and the instep, is abnormally but uniformly thickened. In *focal (areate or nummular) keratoderma*, the areas of palmoplantar skin under most pressure are disproportionately thickened, for example at either end of the metatarsal arch, the sides or points of the toes, or the margins of the heel. Focal lesions may be painful. *Striate keratoderma* overlaps clinically with focal keratoderma, but the lesions are conspicuously longitudinal, particularly on the fingers, where keratoderma overlies flexor tendons. *Punctate (papular or disseminated) keratoderma* consists of multiple scattered discrete round lesions, not bearing a consistent relationship to pressure points.

Transgredient keratoderma extends beyond palmoplantar skin, contiguously or as callosities on pressure points on the fingers or knuckles, or elsewhere. Confluent hyperkeratosis may extend round whole digits. *Cicatrizing keratodermas* (the term 'cicatrizing' is suggested in preference to the more emotive 'mutilating') are those in which constricting bands appear around digits, usually distal to proximal interphalangeal joints. Such constrictions ('pseudo-ainhum') are found in many severe transgredient keratodermas, and are not diagnostic of any one syndrome. *Hyperhidrosis* is also a commonly used descriptor, as many keratodermas, particularly on the feet, are spongy and malodorous. There may be a real increase in sweat excretion, or simply water retention and microbial overgrowth in abnormally keratotic and porous stratum corneum.

Table 34.5 Prinicipal hereditary palmoplantar keratodermas (fuller descriptions and references are given in the text).

Type	Eponym(s)	Inheritance (presumed)	Gene or locus	Onset (years)	Transgredient/ cicatrizing	Comments/special features
Keratodermas and ectodermal dysplasias						
Diffuse group						
Epidermolytic keratoderma	Vörner	AD	Keratin 9	0–3	N	Most common but histology needed to confirm
Diffuse non-epidermolytic keratoderma*	Thost–Unna	AD	some 12q11–q13; Keratin 1	2–5 or later	N	Likely to be heterogeneous
Loricrin keratoderma	Camisa; variant Vohwinkel	AD	Loricrin	2–5	Y	Mild ichthyosis; honeycomb pattern keratoderma
Autosomal dominant transgredient keratoderma*	Greither; Sybert	AD	some 1p	3–8	Y	Likely to be heterogeneous
Keratoderma with scleroatrophy	Huriez	AD	4q23		Y	Squamous carcinomas
Mal de Meleda		AR	*SLURP-1*	0–3	Y	Dermatophyte infection common
Autosomal recessive transgredient keratoderma*	Gamborg–Neilsen	AR	–	8–10	Y	Likely to be heterogeneous
Palmoplantar and periorificial keratoderma	Olmsted	?AR	–	0–1	Y	Periorificial and flexural erythema and hyperkeratosis
Focal or areate group						
Focal/areate/nummular keratoderma*	Wachters	AD	–			Includes painful hereditary callosities Likely to be heterogeneous
Focal keratoderma with oral leukokeratosis		AD	Keratin 16	3–5	N	Oral leukokeratosis
Pachyonychia congenita type 1	Jadassohn–Lewadowsky	AD	Keratins 6a, 16	3–5	N	Oral lesions, follicular keratoses
Pachyonychia congenita type 2	Jackson–Lawler	AD	Keratins 6b, 17	3–5	N	Natal teeth, multiple cyst, follicular keratoses
Striate keratoderma	Brunauer–Fuhs–Siemens	AD	Desmoplakin Desmoglein Keratin 1		N	
Hidrotic ectodermal dysplasia	Clouston	AD	Connexin 30		Y	Nail and hair dystrophy

Keratodermas with extracutaneous features						
Keratoderma with oesophageal carcinoma	Howel–Evans	AD	17q23		N	Focal PPK with oral lesions
Striate keratoderma, woolly hair and arrhythmogenic cardiomyopathy	Naxos disease	AR	Plakoglobin		N	
Striate keratoderma, woolly hair and dilated cardiomyopathy		AR	Desmoplakin		N	
Cicatrizing keratoderma with hearing loss	Vohwinkel	AD	Connexin 26	5–10	Y	Papular lesions becoming confluent, starfish keratoses. Mild hearing impairment
Keratoderma with prelingual deafness		AD	Connexin 26	0–5	Y	Mild diffuse PPK but profound deafness
Mitochondrial hearing loss with keratoderma		Matrilineal	*A7445G*		N	Variable mild focal PPK
Keratoderma with neuropathy*		Varies	–		N	Peripheral neuropathy; spastic paralysis
Keratoderma with periodontitis	Papillon–Léfèvre	AR	Cathepsin G		N	Severe periodontal and other pyogenic infections
Keratoderma with eyelid cysts	Schöpf–Schulz–Passarge	AR	–		N	Diffuse keratoderma, hypotrichosis, nail fragility, loss of deciduous teeth, adnexal tumours
Oculocutaneous tyrosinaemia	Richner–Hanhart	AR	Tyrosine aminotransferase		N	Corneal ulcers, painful keratoses, progressive mental impairment
Punctate group						
Punctate keratoderma*	Brauer–Buschke–Fischer	AD	–	10–40	N	Possible association with malignancy in some families
Punctate keratoderma of palmar creases		AD	–	10–40	N	Palmar creases, sometimes marginal lesions Patients usually of African origin
Acrokeratoelastoidosis	Costa	AD	–	Childhood	N	Marginal crateriform papules with elastorrhexis
Focal acral keratoderma	Dowd	AD	–	Childhood	N	Marginal crateriform papules without elastorrhexis or palmar creases
Papuloverrucous keratoderma	Touraine; Jakac–Wolf	AR	–	2–6	N	Follicular keratoses; dysplastic teeth

* These are pragmatic clinical groupings likely to encompass a variety of genetically distinct syndromes.

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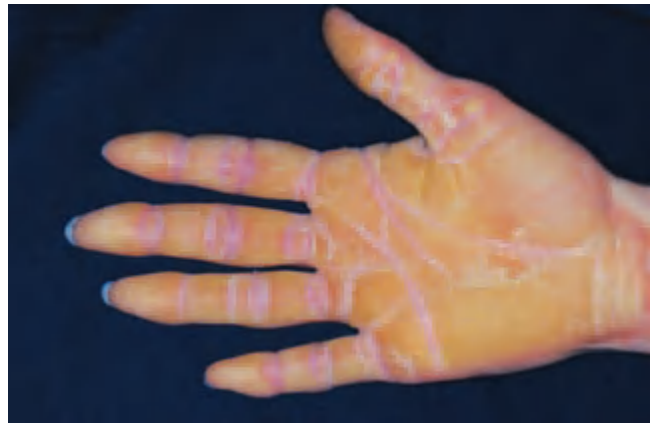

Fig. 34.47 Diffuse epidermolytic keratoderma (Vörner) caused by keratin 9 mutation.

Diffuse keratodermas

Epidermolytic palmoplantar keratoderma (MIM 144200)

SYN. VÖRNER'S KERATODERMA

Vörner described diffuse palmoplantar keratoderma with an autosomal dominant inheritance, clinically indistinguishable from that described by Thost and Unna but with histological features of EHK in the affected palms and soles [1]. Thost's original family in fact had epidermolytic histology; indeed Vörner's is probably the most common form of diffuse keratoderma [2,3]. A prevalence of 4.4 in 100 000 was found in Northern Ireland [4].

Aetiology. Epidermolysis with tonofilament clumping suggested an intermediate filament defect, and the type I epithelial keratin 9 (K9), preferentially expressed in palmoplantar skin, was a strong candidate [5,6]. Linkage of epidermolytic PPK to the type I keratin gene cluster on chromosome 17 and causative mutations in highly conserved regions of K9 have been demonstrated, including in Vörner's original pedigree [7–11]. Most mutations are in the helix initiation peptide, but a 3-bp insertion in the helix termination motif has also been identified [12]. In a pedigree with subconfluent diffuse keratoderma and only mild epidermolysis on histology, a splice-site mutation causing insertion of 18 amino acids into the 2b rod domain of keratin 1 was identified [13]. Disruption of intermediate filament integrity consequent on these mutations is predicted to reduce the resilience of the cytoskeleton to minor external trauma, leading to blistering and hyperkeratosis. Possible autosomal recessive inheritance was reported in two children born to consanguineous parents [14].

Pathology. Histologically, Vörner's PPK shows epidermolytic change in suprabasal keratinocytes, with large tonofilament aggregates visible on electron microscopy. There are secondary changes in the expression of markers of cornified envelope formation [15]. The morphological appearance of keratin filament bundles in palmoplantar epidermis is different from other epidermis, with thicker bundles in a distinct orientation, so care must be undertaken in the assessment of filament aggregation [8]. A pedigree with EPPK resembling Vörner PPK but with an unusual ultrastructure, showing tonotubular keratin, has been reported [16].

Clinical features [1,17–19]. Diffuse keratoderma develops in infancy. In adults, there is confluent keratoderma, sparing dorsal surfaces, with a sharp demarcation and erythematous edge (Fig. 34.47). Blistering is not a major feature, but a history of blisters [19] or fissuring of the palms may hint at reduced structural strength. Hair, teeth and nails are normal, but knuckle pads and nail changes were found in Vörner's original families [1], many of whom have K9 mutations. Families with a tendency to develop internal solid tumours [20] or breast and ovarian cancer [21] probably represent coincidence.

Treatment. Response to oral retinoids is good, but excessive peeling may be a problem [22]. Topical calcipotriol has been helpful [23].

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Non-epidermolytic palmoplantar keratoderma

SYN. THOST–UNNA KERATODERMA

Thost and Unna separately described keratoderma characterized by even, thick, yellow hyperkeratosis over the whole palm and sole [1,2]. The eponym refers specifically to non-epidermolytic keratoderma, although the original Thost family is now known to have epidermolytic keratoderma [3]. It is inherited as an autosomal dominant disorder but may be genetically heterogeneous.

Aetiology. Studies of a family from Bothnia in northern Sweden and three English pedigrees showed linkage centromeric to the type 2 keratin gene cluster on chromosome 12 [4–6], but the cluster itself was excluded. In another family with diffuse PPK, a mutation occurred in a highly conserved lysine residue in the V1 domain of keratin 1 [7]. This residue is thought to be important in cross-linking in the cornified envelope formation [8].

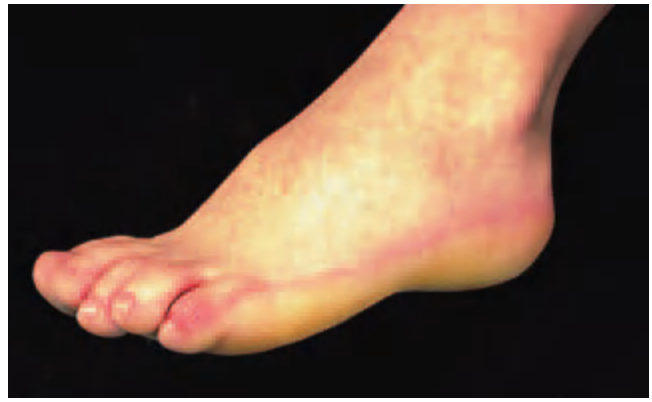

Fig. 34.48 Thost–Unna keratoderma: even yellow hyperkeratosis of sole with red border.

Pathology. The histological changes are non-specific: orthokeratotic hyperkeratosis, hypergranulosis or normogranulosis and moderate acanthosis [2]. There is usually a mild perivascular infiltrate. A biopsy serves mainly to exclude epidermolytic keratoderma. Although vesiculation secondary to dermatophyte infection may be a confounding factor, the large Bothnian pedigree of diffuse PPK showed no evidence of true epidermolysis in 91 biopsies [9].

Clinical features [10,11]. The condition may present in the first few months of life and is usually obvious by the age of 4 years. It rarely appears in the third decade. An even, very thick, yellow hyperkeratosis occurs over the whole of the foot, starting on the heel and anterior arch, spreading later to the palms (Fig. 34.48). There is a sharp cut-off at the wrist, and no tendency to spread to the extensor surfaces. The margins show a livid red border, which can be seen also to underly the hyperkeratosis. Hyperhidrosis is usual, and dermatophyte infections and pitted keratolysis are frequent. The nails are usually normal, but may be thickened without evidence of dystrophy. Hair and teeth are normal.

Treatment. Keratolytic therapy, such as 6% salicylic acid in white soft paraffin, or a gel of 6% salicylic acid in 70% propylene glycol may be used. Occlusion with polythene for a few nights enhanced the efficacy of these preparations. Benzoic acid compound ointment is mildly keratolytic, and is useful in reducing fungal and bacterial overgrowth. Topical retinoids have little effect. Acitretin may be effective for patients with marked functional impairment, but response is unpredictable and in some

patients the loss of the thick keratin leaves the foot markedly hypersensitive.

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Transgredient keratodermas

Loricrin keratoderma (MIM 604117)

SYN. VARIANT VOHWINKEL'S SYNDROME; MUTILATING KERATODERMA WITH ICHTHYOSIS; CAMISA'S SYNDROME

In two related pedigrees, Camisa and Rossana delineated a diffuse transgredient honeycomb keratoderma with annular constrictions around digits, accompanied by a mild ichthyosis (Fig. 34.49) [1–3]. In true Vohwinkel's syndrome, there is impaired hearing but no generalized ichthyosis [4].

Aetiology. The disorder is caused by mutations in the gene encoding loricrin, a glycine-rich cornified envelope protein [3–6]. Several different single nucleotide insertions have been identified in this gene, but all shift the reading frame and lead to expression of an abnormal protein with a foreign, arginine-rich C-terminal peptide containing nuclear recognition signals [4]. The mutant protein is transported to the nucleus, where it can be identified from the upper spinous layer upwards, and is thought to interfere with regulation of cornification

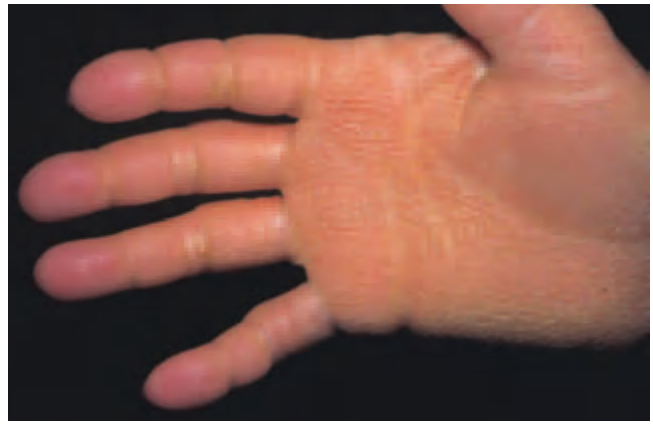

Fig. 34.49 Loricrin keratoderma.

[7]. In one Japanese father and son, a loricrin mutation analogous to that producing human disease produced a phenotype resembling progressive symmetrical erythrokeratoderma [8]. Transgenic mice in whom loricrin has been knocked out are largely asymptomatic [9], but mice expressing a pathogenic loricrin mutation showed generalized scaling, thickened footpads and a constricting band causing autoamputation of the tail [10,11].

Pathology. A particular feature is the presence of retained nuclei in the thickened stratum corneum [1]. Immunoelectron microscopy shows the presence of loricrin in these nuclei [3,4]. Camisa noted elevated serum levels of the lysosomal enzyme β-glucuronidase [2].

Clinical features [1–6]. Generalized desquamation may be noted at birth, and a collodion baby has been reported [6]. However, the ichthyosis is generally mild and may pass unnoticed. A rugose keratoderma develops during childhood, gradually extending to confluence, with a 'honeycomb' pattern. The edges of the keratoderma are diffuse (in contrast to true Vohwinkel's syndrome) and cicatricial bands (pseudo-ainhum) may develop around digits. Knuckle pads and warty keratoses have been reported, but are not a prominent feature. There are no consistent extracutaneous features.

Treatment. The successful use of isotretinoin has been reported [1].

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Autosomal dominant transgredient keratoderma

SYN. GREITHER'S SYNDROME; PALMOPLANTAR KERATODERMA TRANSGREDIENS ET PROGREDIENS

Transgredient autosomal dominant keratodermas are distinguished by involvement of the extensor surfaces of hands, knees and elbows, including the Achilles tendon. Greither described a syndrome with gradual onset and a tendency to improve in the fifth decade [1], but cases reported under this eponym are likely to be genetically heterogeneous [2]. There is clinical overlap with erythrokeratoderma [3]. One pedigree mapped to chromosome 1p [4], but this was not confirmed in another family [5].

Pathology. In Greither's syndrome, the changes on light microscopy are non-specific, with orthohyperkeratosis and absence of granular cell degeneration. Immunohistochemical staining with the marker Ki-67 showed pronounced proliferation of keratinocytes [6]. Beylot-Barry *et al*. [7] found numerous desmosomes and abnormal imbricated cell–cell junctions on electron microscopy.

Clinical features. Onset of Greither's syndrome is at 8–10 years old, and it may improve with age. There is diffuse but transgredient hyperkeratosis with patchy lesions of knees and elbows. Erythema at the margins and hyperhidrosis may be present. Some patients experience Raynaud-like vasomotor disturbances.

Sybert's keratoderma. A more severe transgredient keratoderma reported by Sybert *et al*. [8] resembled mal de Meleda but had dominant inheritance. Onset was earlier than in Greither's. Glove and stocking hyperkeratosis, including autoamputation of toes, extended also to the elbows, knees, posterior aspects of the forearms, shins, groins and natal cleft. Histologically, excessive accumulation of lipid-laden cells was seen in stratum corneum. Electron microscopy showed keratohyalin granules that were abnormal in distribution and structure. Abnormal filaggrin staining suggested that the association of filaggrin and keratin filaments in the stratum corneum was disturbed. Isotretinoin was used with benefit.

Other transgredient keratodermas. Magro *et al*. [9] reported several cases with a milder phenotype clinically resembling that of Sybert, but characterized ultrastructurally by perinuclear accumulations of ribosomes and abnormal keratohyaline granules. In one case, a father and child were affected. The histological features were felt to resemble IH of the Curth–Macklin type. Sprecher *et al*. [10] described an African American family with a more severe, dominant disorder of keratinization diagnosed as Curth–Macklin IH. The main feature was a gross palmoplantar hyperkeratosis, with cobbled papular hyperkeratoses mainly over extensor surfaces. Ultrastructural studies showed retraction of the cytoskeleton to the nucleus and failure of loricrin transport to the cell membrane. They identified a causative frameshift mutation in the V2 domain of Keratin 1 [10]. Linkage to keratin gene clusters has been excluded in another family with IH Curth–Macklin [11].

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Keratoderma with scleroatrophy (MIM 181600)

SYN. HURIEZ SYNDROME

This rare autosomal dominant transgredient keratoderma, first reported in three Franco-Belgian families, is

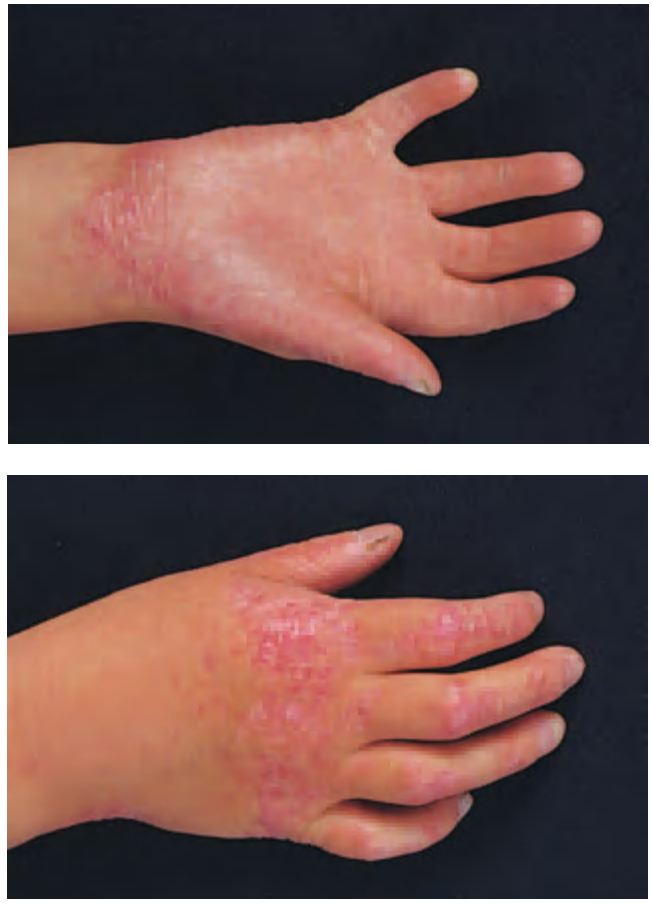
characterized by scleroatrophy of the fingers and a high frequency of squamous carcinomas in affected skin [1–4].

Aetiology. The causative gene maps to chromosome 4q23, but has not been identified [5]. Excision repair of UV damage to lymphocytes was normal [6].

Pathology [6]. Acanthosis, an accentuated granular layer and orthohyperkeratosis were seen in keratodermatous skin. There was no dermal infiltrate, and connective tissue was normal. On electron microscopy, the dermal–epidermal junctions and desmosomes were normal, but dense bundles of tonofilaments were seen in all epidermal layers. The granular layer showed large, coarse, clumped keratohyalin. In the scleroatrophic area, similar changes were seen, with the addition of thinning of the elastic fibres, which on electron microscopy had irregular borders and looked non-homogeneous. There is a reduction in Langerhans' cells in affected palmar epidermis [3,7].

Clinical features [1–4,6,7]. Palms are more often affected than the soles, the keratoderma lacks an underlying erythema, and dermatoglyphics are often absent (Fig. 34.50a). Atrophic parchment-like skin over the dorsal surface of the hands, associated with diffuse keratoderma, is present from birth (Fig. 34.50b). Dense hyperkeratosis gives a pseudosclerodermatous appearance with nail atrophy. Nail changes include hypercurvature, longitudinal ridging, onychorrhexis and koilonychia. Squamous cell carcinomas of the affected skin developed in six cases, and internal malignancy was the cause of death in six out of 33 deaths in the original report. One of the original families was re-examined and reported in 1995 [6]. Only two of the 23 deaths in the family resulted from internal malignancy.

Other scleroatrophic keratodermas. Pujol *et al.* [8] and Vahlquist *et al.* [9] reported cases of sclerosing keratoderma associated with ichthyosis, and bizarre striate keratoses of the flexures. Inheritance appears to be autosomal recessive. A scleroatrophic keratoderma has been reported in association with sex reversal in a 46,XX subject with a male phenotype [10].



(a) (b)

Fig. 34.50 Huriez syndrome: (a) keratoderma; and (b) atrophy skin over dorsa of hand and sclerodactyly. (Courtesy of Dr M. van Steensel, Department of Dermatology, University of Maastricht, the Netherlands.)

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Mal de Meleda (MIM 248300)

SYN. KERATODERMA PALMOPLANTARIS TRANSGREDIENS; ACROERYTHROKERATODERMA

Mal de Meleda is a rare autosomal recessive transgredient keratoderma named after the Croatian island of Meleda (Mljet) where it was described [1,2]. It has been reported from other sites in the Mediterranean littoral; maritime dissemination is inferred.

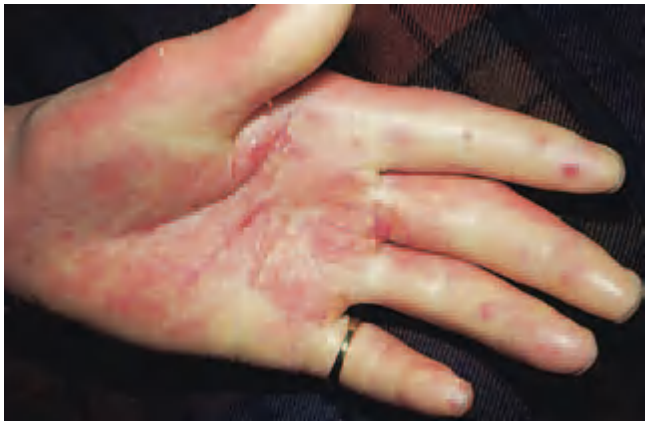

Fig. 34.51 Mal de Meleda.

Aetiology. Mal de Meleda is caused by homozygosity for mutations in the ARS (component B) gene, encoding SLURP-1 (secreted Ly-6/uPAR related protein 1) [3–6], a member of a superfamily of secreted and receptor proteins implicated in transmembrane signal transduction, cell activation and cell adhesion, which has homologues to reptilian and amphibian toxins. The mechanism of disease remains obscure. Families from Croatia (including Meleda), Algeria and Tunisia share very few ancestral haplotypes [3,6,7], indicating founder effects. Almost all cases occur in consanguineous pedigrees.

Pathology. There is a greatly thickened corneal layer, increased stratum lucidum, with marked acanthosis, pseudospongiosis, and a prominent perivascular lymphohistiocytic infiltrate. Sweat glands are enlarged. Electron microscopy showed a less abrupt than normal transition from stratum granulosum to stratum corneum [8].

Clinical features [2,9–12]. Onset is in early childhood, and the development of hyperkeratosis is preceded by erythema. Patches of waxy ivory–yellow hyperkeratosis (Fig. 34.51) extend across the whole palms and soles, and on to the dorsal surfaces of hands and feet. Similar lesions of knees and elbows may develop. The erythematous component often persists in central palms and soles, with hyperhidrotic maceration and malodour. Fungal superinfection is common and should be excluded [10]. Circumferential hyperkeratosis of fingers may lead to sclerodactyly and digital constrictions; nail changes include hypercurvature, thickening and koilonychia [10–12]. Angular cheilitis is common. There is clinical overlap with Olmsted's syndrome, keratosis lichenoides chronica striata and progressive symmetrical erythrokeratoderma [3,12].

Treatment. Oral retinoids are effective but the hyperkeratosis may respond better than the erythema [12–16].

Other autosomal recessive transgredient keratodermas. Other pedigrees of autosomal recessive transgredient PPKs, such as the mutilating keratoderma with knuckle pads identified by Gamborg-Nielsen [17,18], are reported. Some such cases may prove to be forms of mal de Meleda, but multiple disease entities are likely and linkage to the *SLURP-1* locus, or mutations of the ARS coding sequence, have not been found in pedigrees with this phenotype [19,20]. Akiyama *et al*. [21] reported siblings with a recessive transgredient keratoderma in whom linkage excluded mutation in the epidermal differentation complex.

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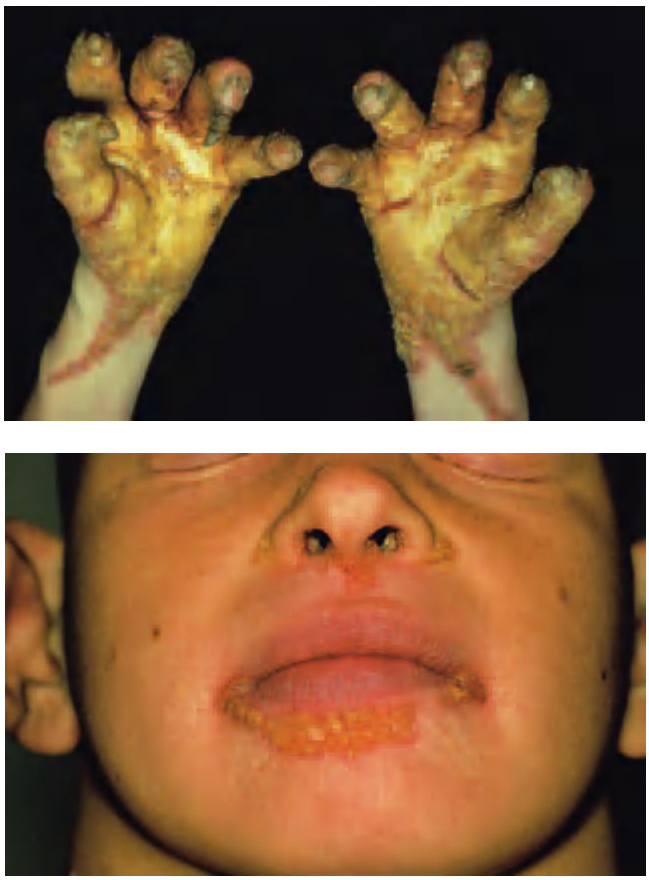

(a)

(b)

Fig. 34.52 Olmsted's syndrome: (a) gross keratoderma with striate features; and (b) periorificial hyperkeratosis. (Courtesy of Professor R.K. Winkelmann, Mayo Clinic, Scottsdale, AZ, USA.)

Congenital palmoplantar and perioral keratoderma

SYN. OLMSTED'S SYNDROME

The inheritance of this rare severe transgredient keratoderma with periorificial lesions is uncertain [1–4]. Most cases are male and sporadic, although in one case the mother was also affected [5]. The pathogenesis is unknown, but there is cytochemical evidence of hyperproliferation of the epidermis [6,7]. Onset is in the first year of life, with symmetrical, sharply defined palmar and plantar keratoderma surrounded by erythema, and flexion deformities, constriction or spontaneous amputation of the digits (Fig. 34.52a). Other abnormalities include periorificial erythema and warty hyperkeratosis (Fig. 34.52b) and linear keratoses on the flexor forearms [3,4]. Universal alopecia, nail and tooth anomalies and joint laxity and corneal dystrophy have been reported [8]. The condition can be confused with acrodermatitis enteropathica, hidrotic ectodermal dysplasia of the Clouston type, mal de Meleda and Vohwinkel's keratoderma. Etretinate has been used in several cases with variable effect [9,10]. Topical tretinoin slightly improved the keratosis but proved irritant in one case [11].

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Focal keratodermas

SYN. WACHTERS' KERATODERMA; PALMOPLANTAR KERATODERMA VARIANS

Focal, areate or nummular, and linear or striate keratodermas have been distinguished. The occurrence of both areate and striate forms within a family led Wachter [1] to suggest a single entity, keratoderma varians. Although focal and striate may coexist (Fig. 34.53), several distinct disorders can now be discriminated clinically and genetically. The pattern and severity depends on both the underlying defect and environmental factors, such as the stresses on the tissue. Blisters may be a feature [2]. Striate forms are particularly but not uniquely associated with desmosomal defects (see below). Focal keratoderma may also be associated with other cutaneous or ectodermal disorders, including Dowling–Meara epidermolysis bullosa simplex, or with disease in other systems. Focal keratoderma with oesophageal carcinoma (Howel-Evans' syndrome) and keratodermas with deafness are described separately.

Painful hereditary callosities [3–5]. Plantar callosities of sufficient size are inevitably painful, and the term is probably non-specific. Painful callosities are a feature of conditions corresponding to keratoderma nummularis of Brunauer and Fuhs and keratoderma areata of Siemens, but also pachyonychia congenita and type II oculocutaneous tyrosinaemia (Richner–Hanhart syndrome).

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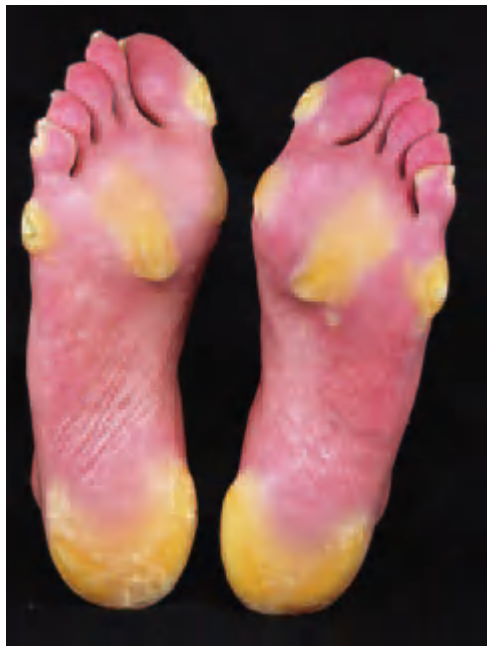
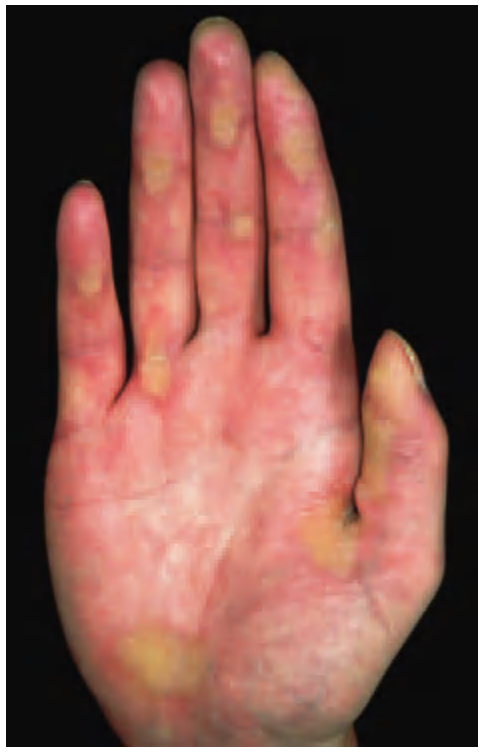


(a)



(b)

Fig. 34.53 Focal keratoderma (keratoderma areata/striata): (a) focal masses of keratin predominantly on pressure points; and (b) striate keratotic lesions on palms in the same patient.

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Focal keratoderma with oral leukokeratosis (MIM 600962)

Focal non-epidermolytic keratoderma, inherited as an autosomal dominant trait, may be associated with white plaques on the sides of the tongue and buccal mucosa. This syndrome is clinically and genetically a mild variant of pachyonychia congenita; subtle associated nail changes include splinter haemorrhages and a widening of the onychocorneal band, and causative mutations in the helix initiation motif region of keratin 16 identified [1]. An isolated patient with leukoplakia and florid oral papillomatosis, and keratoderma without nail changes has been recorded [2]. Oral lesions without nail changes are also seen in Howel-Evans' syndrome [3].

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Pachyonychia congenita

SYN. JADASSOHN–LEWANDOWSKY SYNDROME; JACKSON–LAWLER SYNDROME

Pachyonychia congenita (PC) is characterized by subungual hyperkeratosis of the distal nails and focal palmoplantar hyperkeratosis. A large number of associations have been reported [1], but only the simplest clinical classification into PC-1 (Jadassohn–Lewandowsky) and PC-2 (Jackson–Lawler) syndromes is borne out genetically [2].

Aetiology. Autosomal dominant inheritance is usual, but a recessive form is reported [3]. Tonofilament aggregates seen on electron microscopy suggest an intermediate filament disorder [4,5]. The distribution of lesions in PC-1 corresponds to the expression patterns of keratins K6a and K16, and causative mutations have been found in both these genes [5–8]. By contrast, K17 is constitutively expressed in the pilosebaceous unit and basal appendage keratinocytes, with lesser basal expression in palmoplantar skin and a number of other minor epithelial populations, but not in mucosae [9–11]. Point mutations in the K17 gene have been reported from many families with PC-2 [2]. Identical mutations may also present as isolated steatocystoma multiplex with or without mild nail

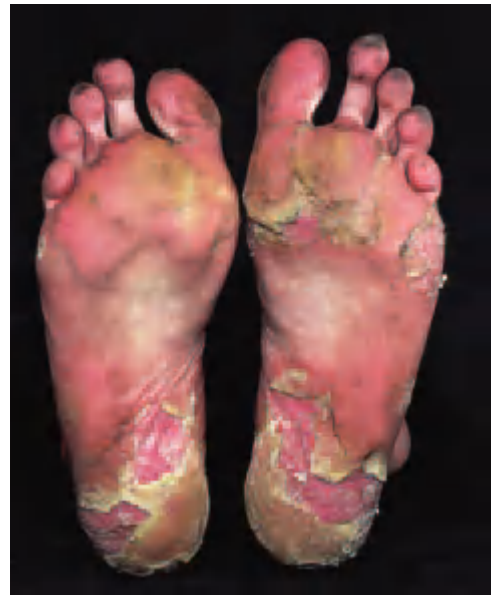
changes [12]. Mutations in the K6b isoform of keratin 6 also cause PC-2, suggesting this is the expression partner keratin of K17 [13]. The prominent nail involvement of pachyonychia reflects the expression of these keratins in the ventral nail [14].

Pathology. Palmoplantar epidermis shows gross hyperkeratosis with alternating ortho- and parakeratosis. Acanthosis is present with patchy hypergranulosis, in which large and misformed keratohyalin granules are present, but there is no gross epidermolysis [4]. In PC-2, the cysts may be keratinous epidermoid cysts, eruptive vellus hair cysts or true steatocysts. Different histologies may be seen within a family, an individual, or even a single cyst.

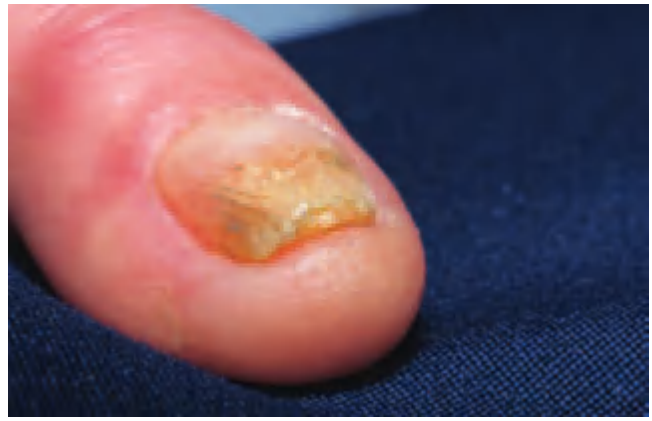
Clinical features [1,15,16]. Hyperkeratosis of the nail bed appears in the first year or two of life, followed by focal thickening of palms and soles. Late onset has been termed pachyonychia congenita tarda [17–19]. Frictional blisters may occur on the feet, especially in hot weather in childhood. In adults, focal hyperkeratosis may produce marked pain on walking. Severity varies, even within families. The mildest nail changes are similar to those seen in focal keratoderma with oral leukokeratosis, with which PC-1 is allelic.

PC-1 (Jadassohn–Lewandowsky type; MIM 167200). Thick yellow keratoses are found on sites of pressure (Fig. 34.54a), associated with wedge-like thickening of distal finger- and toenails (Fig. 34.54b), keratosis pilaris and follicular keratoses on the knees and elbows. Patchy white thickened areas are seen on the tongue and oral mucosa (oral leukokeratosis). Severe oral lesions resemble candidiasis [20]. Laryngeal involvement may produce hoarseness and in infancy even fatal respiratory obstruction [21]. Kansky *et al*. [14] have given the frequency of these changes as follows: palmoplantar keratoderma 89%, pachyonychia 69%, follicular hyperkeratosis 53%, hyperhidrosis 53%, leukokeratosis 30% and blisters 19%. Squamous carcinoma has been reported in a persistently ulcerated area [15].

PC-2 (Jackson–Lawler type; MIM 167210). Findings are similar to PC-1 but palmoplantar keratoses are possibly less severe. Despite the absence of mucosal lesions, hoarseness is a feature. Teeth are present at birth in the majority of cases [22]. Unruly hair and milia may be seen in infancy, and adults have protuberant eyebrows. Multiple epidermal cysts appearing after puberty include both epidermoid and steatocysts. Axillary cysts may mimic hidradenitis suppurativa [23]; extensive and infected vulval, scrotal or scalp cysts also cause significant disability for some patients. Within families, some patients may have only nail changes and some only cysts.



(a)



(b)

Fig. 34.54 Pachyonychia congenita: (a) keratoderma on weight-bearing areas; and (b) typical wedge-shaped nail.

Other clinical variants. For a review of reported associations of PC see Feinstein *et al*. [1], although the classification they propose has been superseded. All mutations yet found, even in previously suggested variants, correspond to either PC-1 or PC-2 phenotypes [2]. Nonetheless, thickening of the nails may occur in a variety of ectodermal dystrophies and some suggested PC variants may merit further genetic study. Involvement of the nails alone has been reported [24,25]. Heterozygous missense mutations in the connexin 30 gene, normally associated with Clouston's syndrome (see below), have been identified in a number of families with pachyonychia-like nail changes and no other phenotype [26]. Schafer and Brunauer reported corneal leukokeratosis [27]; Buckley and Cassuto [28] and Tidman *et al.* [29] flexural pigmentation and amyloid.

Treatment. Emollients and keratolytics may help kerato-

derma in milder cases. Acitretin 25–35 mg/day make the keratin more flexible and less pronounced without complete clearing [30,31], but treatment is generally unsatisfactory [4]. Retinoids produce a degree of flattening of the nails if given for prolonged periods. Surgical excision of the keratotic masses is sometimes attempted, but recurrence around the margins is frequent.

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Striate keratoderma (MIM 148700)

SYN. BRUNAUER–FUHS–SIEMENS

Striate keratoderma in isolation, usually inherited as an autosomal dominant trait, can be caused by defects in at least three different genes.

Aetiology. Autosomal dominant striate keratoderma was mapped to the desmosomal cadherin cluster on 18q12.1 in a German pedigree [1]. In a Dutch family in whom linkage data favoured this locus, an N-terminal deletion mutation predicted to cause haploinsufficiency was identified in the desmoglein 1 gene [2]. Similar mutations were reported by Hunt *et al*. [3]. Earlier, Armstrong *et al*. [4] had found linkage to 6p21 in another pedigree and identified a heterozygous nonsense mutation in the desmoplakin gene. Other nonsense mutations in desmoplakin also produce the phenotype, which is again thought to result from haploinsufficiency [5]. Compound heterozygosity for nonsense and missense mutations in desmoplakin were found in two patients with keratoderma, skin fragility and woolly hair [6]. Other mutations in desmoplakin cause recessive and dominant cardiomyopathy with or without keratoderma (see p. 34.97). Striate keratoderma has also been reported in two pedigrees with frameshift mutations in the V2 tail domain of keratin 1 which may be important in cross-linking to cornified envelope proteins [7].

Pathology. In the family studied by Armstrong *et al*. [4], electron microscopy of involved skin showed abnormal bunching of keratin filaments and reduction in the peripheral keratin network, with loss of connections with desmosomes. A proportion of desmosomes were small and rudimentary and the intercellular spaces were widened. Uninvolved skin was normal.

Clinical features. As the name implies, there is a linear pattern of skin thickening on the palms and flexor aspects

of the fingers (Fig. 34.53b). However, lesions on the soles may be more areate or confluent, and striate lesions can be seen in affected members of pedigrees in which other patterns of keratoderma predominate. The presence of other features, especially woolly hair, should be specifically sought, and the possibility of cardiac disease considered.

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Hidrotic ectodermal dysplasia (MIM 129500) [1]

SYN. CLOUSTON'S SYNDROME

This autosomal dominant ectodermal dysplasia, characterized by dystrophic nails and sparse hair, is described in Chapter 12 but is mentioned here because a papillomatous and fissured transgredient keratoderma is a significant feature, and because the disorder is now known to be caused by mutations in gap junction beta-6, encoding connexin 30 [2,3].

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Keratodermas with extracutaneous features

Extracutaneous features in cases of hereditary keratoderma are often reported. Unusual associations with well-recognized syndromes may be coincidental, and in isolated cases it is rarely possible to establish their significance. Some associations are tabulated in Table 34.6. Readily recognizable or clinically important syndromes are described below.

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Table 34.6 Associations of keratoderma. References are given only where not provided in the relevant section of the text.

Bone and muscle	
Arachnodactyly	Haim–Munk syndrome
Pes planus	Keratoderma with neuropathy
Acro-osteolysis	Papillon–Léfèvre, Haim–Munk, Olmsted, and Bureau–Barrière syndromes; [1]
Clinodactyly	[2]
Ankylosing spondylitis	[3]
Albers–Schonberg	[4]
Amyotrophy	[5,6]
Hyperostotic spondylosis	[7]
Hair and nail	
Hypotrichosis or atrichia	Schöpf–Schulz–Passarge syndrome; [1,8,9]
Alopecia	Olmsted syndrome [10;11]
Steel hair	[12]
Curly or woolly hair	Naxos disease Keratoderma, woolly hair and dilated cardiomyopathy Noonan's and cardio-facial-cutaneous syndromes [13,14]
Rolled and spiral hair	[15]
Heliotrichosis	[16]
Premature canities	[17]
Onychogryphosis	Haim–Munk syndrome
Leukonychia	[8,12]
Onychodystrophy	Pachyonychia congenita
Nail psoriasis	Punctate keratoderma [18]
Teeth	
Hypodontia	Schöpf–Schulz–Passarge syndrome
Dysplasia	Jakac–Wolf syndrome Olmsted's syndrome Punctate keratoderma [19]
Natal teeth	Pachyonychia congenita
Periodontosis	Haim–Munk, Papillon–Léfèvre syndromes; [1]
Anodontia	Papillon–Léfèvre syndrome
Pigment	
Mottled	Pachyonychia congenita Epidermolysis bullosa [11,20]
Incontinentia pigmenti	[21,22]
Hyperpigmentation	[23]
Vitiligo	[24,25]
Dermatopathia pigmentosa reticularis	[5,26]
Hypomelanosis of Ito	[27]
Nervous system	
Impaired hearing or deafness	Keratoderma with prelingual deafness Cicatrizing keratoderma with impaired hearing Keratoderma with impaired hearing caused by mitochondrial mutation Haim–Munk syndrome [12]
Charcot–Marie–Tooth	[28]
Spastic paraplegia	Keratoderma with neuropathy Bureau–Barrière syndrome
Friedreich's ataxia	[29]
Eyes	
Corneal ulcers/dystrophy	Richner–Hanhart syndrome Pachyonychia congenita [10,30–34]
Deuteranopia	Buschke–Fischer–Brauer syndrome [35]
Photophobia	Richner–Hanhart syndrome
Glaucoma	[36]

(*continued overleaf*)

Table 34.6 (*cont'd*)

Metabolic	
Tyrosinaemia	Richner–Hanhart syndrome
Myxoedema	[37,38]
Hyperlipidaemia	[39]
Sphingomyelinuria	Bureau–Barrière syndrome [40]
β-Glucuronidasaemia	Loricrin keratoderma [41]
Abnormal cystine metabolism	[15]
Cirrhosis	[42]
Glucocorticoid insufficiency	Allgrove's syndrome [43]
Malignancy	
Basal cell epithelioma	[44]
Squamous carcinoma	Huriez syndrome; [45,46]
Epithelioma cuniculatum	[47]
Malignant melanoma	Greither's syndrome [48]
	Papillon–Léfèvre syndrome [49]
	Mal de Meleda [50]
Colon	[17,51,52]
Bronchus	[53–57]
Oesophagus	Howel-Evans' syndrome; [58]
Breast	Epidermolytic keratoderma [52,59]
Ovarian	Epidermolytic keratoderma [59]
Myeloma	[60]
Acanthosis nigricans	[61]
Cardiac	
Total anomalous pulmonary venous connection	[62]
Cardiomyopathy	Keratoderma, woolly hair and dilated cardiomyopathy
	Cardio-facio-cutaneous syndrome [13]
Endomyocardial fibrodysplasia	Naxos disease [63]
Arrhythmogenic right ventricular cardiomyopathy	Naxos disease
Miscellaneous	
AIDS	[64,65]
Acrocyanosis	[66,67]
Angiodysplasia	[68]
Atopy	[69]
Benign familial pemphigus	[70]
Calcinosis	[71]
Clubbing	Bureau–Barrière syndrome [72]
Epidermal cysts	Pachyonychia congenita
Polycystic kidney and liver	[73]
Darier's disease	[74]
Dermatophytosis	[75,76]
Epidermolysis bullosa	[77]
Granuloma annulare	[78]
Hydrocystomas	Schöpf–Schulz–Passarge syndrome
Ichthyosis	Loricrin keratoderma
	Cardio-facial-cutaneous syndrome [13,79]
Ichthyosis hystrix	[80]
Lichen nitidus	[81]
Lichen planus	[82,83]
Lipomas	Richner–Hanhart syndrome
Lupus erythematosus	[84–86]
Peptic ulcers	Buschke–Fischer–Brauer syndrome [35]
Perianal leukokeratosis	[87,88]
Pulmonary fibrosis	[89]
Rapp–Hodgkin syndrome	[90]
Rosacea	Haber's syndrome [91]
Truncal lesions	[92]

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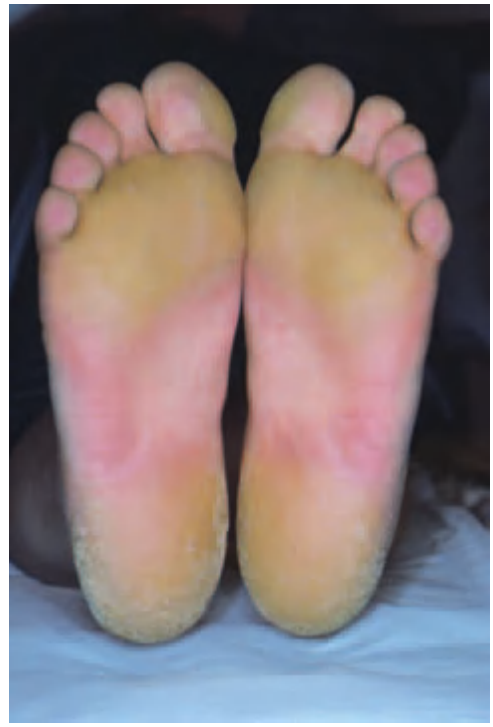
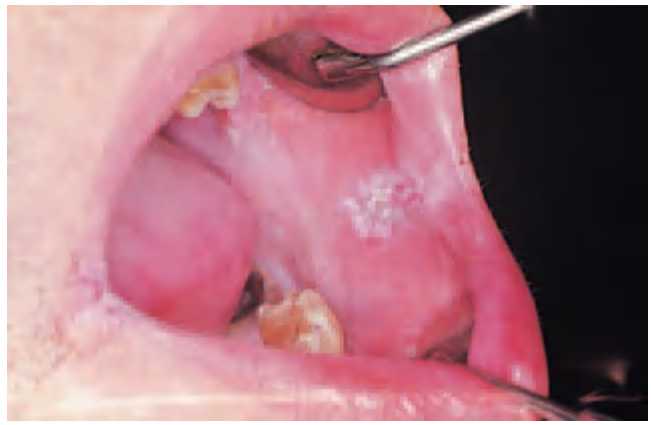
Keratoderma with oesophageal carcinoma (MIM 148700)

SYN. HOWEL-EVANS' SYNDROME; TYLOSIS WITH OESOPHAGEAL CANCER

Howel-Evans described two families of autosomal dominant keratoderma associated with later development of oesophageal cancer [1]. The term tylosis has been used for this syndrome, but was originally synonymous with (diffuse) keratoderma, and should not be used to describe the syndrome without qualification. Clinical reappraisal has shown that this should be considered a focal PPK, as the lesions predominantly affect pressure points of the sole (Fig. 34.55a), and less so the palm [2,3]. There is variable oral leukokeratosis (Fig. 34.55b) and follicular prominence, but the disorder can be distinguished from PC type 1 by the absence of even mild nail changes [3]. Thirty-seven per cent of the original affected family members developed oesophageal cancer 30–40 years later. A further extensive German American family has been reported, also with an increased (38-fold) risk of oesophageal cancer [3]. In both families, the disorder maps to chromosome 17q23 [3,4], a locus named *TOCG* (for tylosis with oesophageal cancer gene). Envoplakin, a cornified envelope precursor whose gene is in this region, has been excluded by mapping [5,6]. The region is commonly deleted in oesophageal carcinomas [7], but despite sequencing of several candidates in the region, the tumour suppressor gene which this implies has not yet been identified [8].



(a)



(b)

Fig. 34.55 Howel-Evans' syndrome: (a) keratoderma; and (b) oral mucosal lesions. (Courtesy of Professor W.R. Tyldesley, Liverpool University School of Dentistry, Liverpool, UK and Dr M.S. Lewis-Jones, Ninewells Hospital, Dundee, UK.)

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Keratoderma, woolly hair and cardiac disease

The occurrence of congenital heart disease in patients with keratoderma has been reviewed [1]. The possibility of cardiomyopathy or conduction disorders should be particularly considered in patients with keratoderma and woolly hair. Defects in proteins of the desmosomal plaque are common to the two clearly identified genetic syndromes.

Naxos disease (MIM 601214). An autosomal recessive syndrome of arrhythmogenic right ventricular cardiomyopathy, keratoderma and woolly hair was reported in seven pedigrees from the Greek island of Naxos [2,3]. These families have been found to share a 2-bp deletion causing premature termination in the gene encoding plakoglobin [4], a cell junction protein found in association with desmosomes in the epidermis and in striated and cardiac muscle. Homozygous but not heterozygous individuals show an increased incidence of arrhythmias, cardiac failure or sudden death [5]. A similar autosomal dominant syndrome has been reported [6]. The association may be genetically heterogeneous [7].

Keratoderma, woolly hair, and dilated cardiomyopathy (Carvajal syndrome; MIM 605676). In three Equadorian pedigrees, striate keratoderma and woolly hair were associated with dilated left ventricular cardiomyopathy developing in teenage years. Histology of keratoderma showed wide intercellular spaces, clustering of desmosomes and a collapsed intermediate filament network [8]. Affected cases were all homozygous for a deletion mutation producing a premature stop codon in the tail of the desmoplakin gene [9].

Another mutation in desmoplakin, in an N-terminal domain that binds plakoglobin, causes dominant arrhythmogenic right ventricular cardiomyopathy without cutaneous phenotype [10]. Skin fragility and woolly hair resulting from compound heterozygosity for nonsense and missense mutations in desmoplakin are also reported [11].

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Keratoderma and hearing impairment (MIM 148350)

The association of disordered keratinization with impaired hearing is most commonly caused by defects in genes encoding members of the connexin family of gap junction proteins [1], but mitochondrial defects may also be responsible [2].

Keratoderma and prelingual deafness. Premature termination codons in connexin 26 are the single most common cause of non-syndromic autosomal recessive deafness [1,3–5]. Connexin 26 is expressed in the cochlea where it may permit the recycling of potassium to endolymph [5]. In skin, connexin 26 is found in palmoplantar epidermis and sweat glands, and is up-regulated in conditions such as psoriasis [6,7], but patients homozygous for mutations causing non-expression of connexin 26 have no discernible cutaneous phenotype. However, in several pedigrees with diffuse or transgredient autosomal dominant keratoderma and varying degrees of prelingual deafness, missense mutations in connexin 26 have been found [8–11]. Other mutations in connexin 26 cause cicatrizing keratoderma with impaired hearing (see below) and KID syndrome [12,13]. Mutations that cause skin disease may exert a transdominant effect, disrupting gap junction communication by interfering with the function of other epidermal connexins [10].

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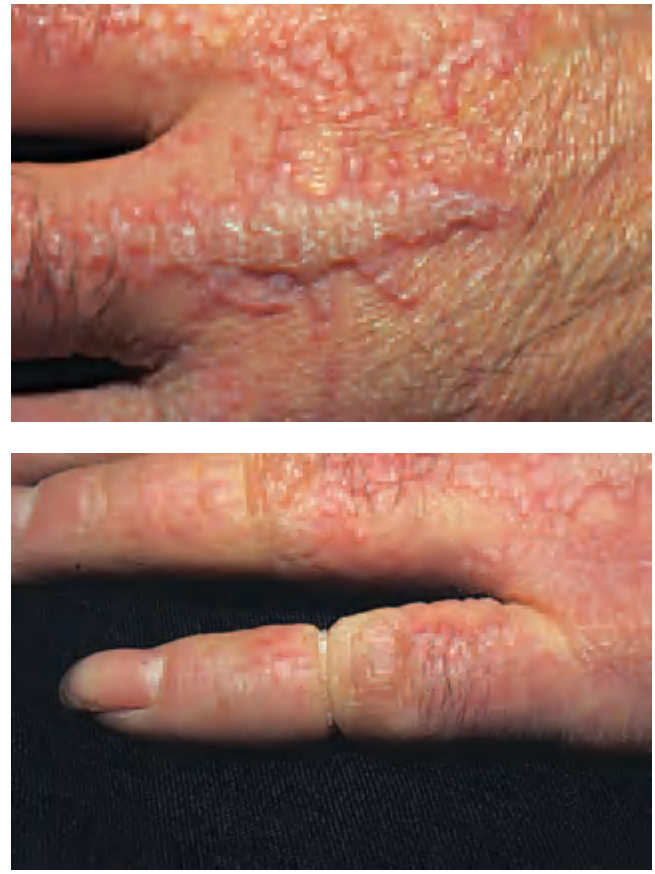
Cicatrizing keratoderma with hearing impairment (MIM 124500)

SYN. KERATOMA HEREDITARUM MUTILANS; VOHWINKEL'S SYNDROME

Vohwinkel [1] and Wigley [2] independently reported honeycomb-like keratoderma associated with stellate keratoses on the knuckles and the formation of circumferential bands around digits ('pseudo-ainhum'). Vohwinkel's family also had moderate sensorineural deafness [3], and subsequent cases have confirmed autosomal dominant inheritance [4–7].

Aetiology. In three unrelated English, Spanish and Italian pedigrees with true Vohwinkel's syndrome, Maestrini *et al*. [8] found the same mutation, D66H, in the gap junction beta-2 gene encoding connexin 26. This mutation was also found in another English family [9]. Other mutations in the same gene cause KID syndrome or keratoderma with prelingual deafness (see above). The probable mechanism, transdominant inhibition of gap junction function, can be reproduced *in vitro* [10], but the reason for the less profound deafness but more severe cutaneous phenotype with this specific mutation is not understood.

Clinical features [1–8,11]. PPK begins in childhood as shiny or translucent papular hyperkeratosis, gradually becoming confluent on hands and feet. Striate lesions may be seen in some individuals. Warty papules on the knuckles and other extensor sites coalesce into the pathognomonic 'starfish' keratoses (Fig. 34.56a). The edge of the keratoderma at the wrists and Achilles tendon consists of spiky digitate hyperkeratotic projections onto normal skin, sometimes showing koebnerization. This contrasts with the diffuse edge seen in loricrin keratoderma [10]. Multiple keratoses on digits produce circumferential hyperkeratosis, which predisposes to the formation of cicatricial bands (Fig. 34.56b) and auto-amputation. The little finger and fifth toe are most commonly affected. A high-tone sensorineural hearing loss [6] is probably present from birth, but is relatively subtle and may escape detection in childhood unless specifically sought. It does not appear to be progressive. A reported association with craniofacial anomalies [11] proved coincidental [8].


(a)

(b)

Fig. 34.56 Cicatrizing keratoderma with deafness: (a) 'starfish' lesions; and (b) pseudo-ainhum.

Treatment. Vohwinkel's syndrome has been successfully treated by etretinate [7] and the cicatricial bands released surgically [12].

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Keratoderma with hearing impairment caused by mitochondrial mutation (MIM 590080)

In a Scottish family, Reid *et al*. [1] reported familial progressive post-lingual deafness caused by specific mutation in mitochondrial DNA encoding a serine transfer RNA. The same point mutation (A7445G) was identified in a New Zealand family who also had keratoderma, and in a previously reported Japanese pedigree of keratoderma and deafness [2,3]. One of the authors (CSM) has examined members of the original Scottish family, confirming variable plantar keratoderma (Fig. 34.57). A further French pedigree of this association has been reported [4].

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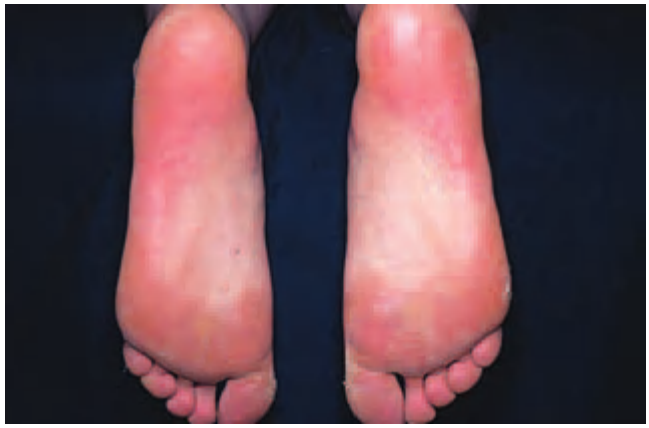

Fig. 34.57 Mitochondrial keratoderma with deafness.

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Keratoderma with neuropathy

Various reports associate neuropathy or spastic paralysis with keratoderma. These include striate keratoderma with spastic paraplegia, pes cavus and mental retardation in four brothers [1]; autosomal dominant punctate keratoderma and spastic paralysis [2]; autosomal dominant focal keratoderma with nail dystrophy and motor and sensory neuropathy [3], and Charcot–Marie–Tooth disease [4]. Atypical erythrokeratoderma with deafness has also been associated with peripheral neuropathy [5]. Connexin genes seem good candidates for causative mutations [6].

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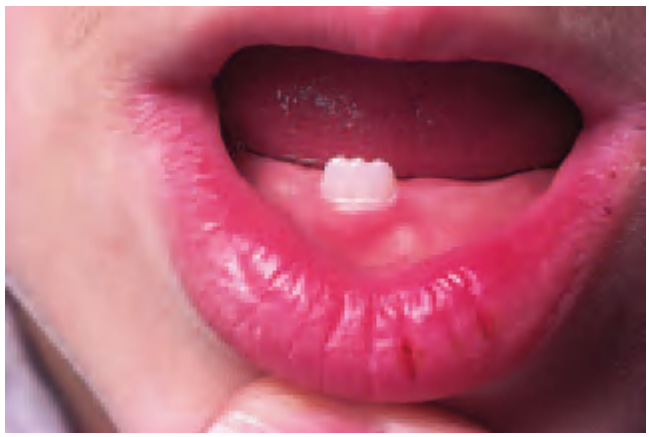
Keratoderma with periodontitis (MIM 245000)

SYN. PAPILLON–LÉFÈVRE SYNDROME

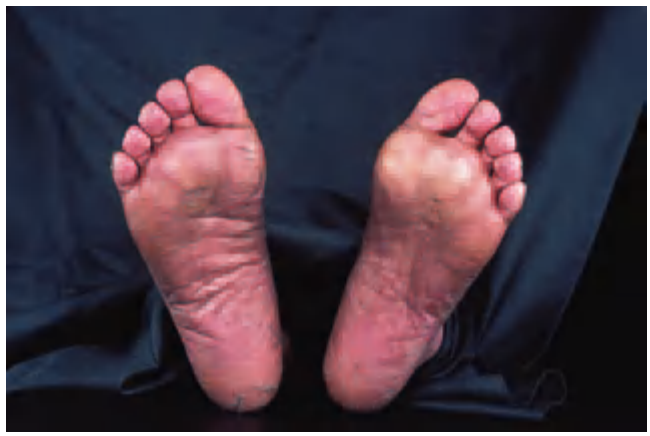
In this syndrome, redness and thickening of the palms and soles is associated with periodontosis and frequent pyogenic skin infections. The prevalence has been estimated as 1–4 in 1 million [1].

Aetiology. Neutrophil phagocytosis and reactivity to T- and B-cell mitogens are impaired [2–4]. Inheritance is recessive, and the condition is caused by homozygous mutations in the gene encoding the lysosomal protease cathepsin C [5]. This finding explains the predisposition to pyogenic infection, but the mechanism of keratoderma is not established.

Pathology. Histopathological changes are non-specific, but show hyperkeratosis with irregular parakeratosis and a moderate perivascular infiltrate [6]. Electron microscopic findings include lipid-like vacuoles in the corneocytes and granulocytes, reduction in tonofilaments and irregular keratohyalin granules. These changes improve during retinoid therapy [7].



(a)



(b)

Fig. 34.58 Papillon–Léfèvre syndrome: (a) loss of dentition; and (b) diffuse plantar hyperkeratosis.

Clinical features [8,9]. Periodontosis resulting in severe gingivitis (Fig. 34.58a) in children leads to the loss of deciduous teeth by the age of 4–5 years unless treated; permanent teeth may be lost in the same fashion. Transgredient palmoplantar keratoderma, preceded by erythema, appears in the first year of life (Fig. 34.58b), and spreads to dorsal surfaces and up the Achilles tendon. Psoriasiform plaques on the knees and elbows may be present, but in a survey of 47 patients cutaneous involvement was not related to the severity of periodontal disease and did not correlate with age [9]. Virulent Gram-negative organisms invade the alveolar socket, usually including *Actinobacillus actinomycetemcomitans* [10–12]. Frequent pyogenic infections of the skin and internal organs occur. Associated hyperhidrosis causes an unpleasant odour [13]. The hair is usually normal but may be sparse [14]. Dural calcification, especially in the attachment of the tentorium and choroid, has been noted in some cases.

Haim–Munk syndrome (MIM 245010). This variant syndrome combines the features of Papillon–Léfèvre syndrome with onychogryphosis, arachnodactyly and acro-osteolysis [15,16]. The syndrome is allelic with Papillon–Léfèvre syndrome, and all reported cases may be members of a single family of Cochin Jews [17]. Van Steensel *et al*. [18] reported a mother and daughter with a syndrome resembling Haim–Munk syndrome, but with hypotrichosis and an unusual linear and reticulate keratoderma, apparently not caused by mutations in cathepsin C.

Treatment. Before the advent of retinoids, dental clearance and antibiotic therapy was advised. Etretinate [14,19,20], isotretinoin [21] and acitretin [7] have all been successful in improving the keratoderma, lessening the gingival inflammation and saving the teeth.

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Schöpf–Schulz–Passarge syndrome (MIM 224750)

SYN. KERATODERMA WITH EYELID CYSTS, HYPODONTIA AND HYPOTRICHOSIS

In this rare autosomal recessive syndrome, diffuse palmoplantar keratoderma is associated with hypotrichosis, nail fragility and early loss of deciduous teeth [1,2]. Hydrocystomas of the eyelids but also follicular and other adnexal tumours occur in older patients [3,4].

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Oculocutaneous tyrosinaemia (MIM 276600) [1–5]

SYN. TYROSINAEMIA TYPE II; RICHNER–HANHART SYNDROME

Tyrosine aminotransferase deficiency causes palmoplantar keratoderma, dendritic corneal ulcers and progressive mental impairment.

Aetiology. This autosomal recessive condition is caused by homozygous defects of the tyrosine aminotransferase gene at 16q21.1–q22.3 [6]. Deficiency of the enzyme leads to increased levels of serum tyrosine [6–8]. Urinary reducing substances and aminoaciduria are found.

Pathology. Biopsy shows acanthosis with hyperkeratosis and hypergranulosis. At ultrastructural level, the keratinocytes contain clumped tonofilaments with adherent globoid keratohyalin granules resembling 'dew drops on a blade of grass' [9].

Clinical features (Fig. 34.59). In the first year of life, photophobia and corneal ulcers occur, and the diagnosis may be made by slit-lamp examination showing tyrosine crystals in ocular lesions [10]. Corneal lesions may be misdiagnosed as herpes simplex keratitis [11]. A year or two later, erythematous areas appear on the pressure-bearing areas of the soles, followed by painful circumscribed hyperkeratoses, making the child walk on the toes. Onset of the keratoderma may be delayed until the second decade

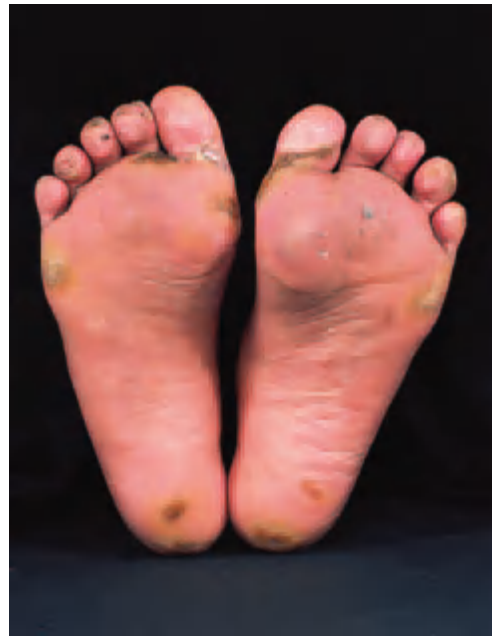

Fig. 34.59 Oculocutaneous tyrosinaemia (Richner–Hanhart syndrome). Callosity-like hyperkeratoses.

[12]. The keratoses vary from gross keratoderma to dry lamellar patches. Bullous lesions and hyperhidrosis are sometimes seen. Unless correctly treated, behavioural problems arise within a few years and progressively worsen, ending in inanition or death. Chitayat *et al*. [13] reported two siblings with tyrosinaemia, only one of whom showed signs of the Richner–Hanhart syndrome.

Treatment. Early institution of a diet low in phenylalanine and tyrosine causes prompt resolution of the ocular and cutaneous symptoms and prevents the development of mental disorder [4,8,14–16].

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Punctate and porokeratotic keratodermas (MIM 148600)

SYN. BRAUER–BUSCHKE–FISCHER KERATODERMA

Punctate keratodermas differ from focal ones in showing a random distribution of small rounded papular lesions, but clinical differentiation is not always possible. The various terms used for morphological patterns of punctate keratoderma—keratoma dissipatum; keratoderma punctata, papulosa; disseminated clavus; papulotranslucent acrokeratoderma—probably do not justify distinction [1]. Excepting pedigrees with parakeratotic histology, the delineation of entities is uncertain.

Punctate keratoderma [1–3]. This autosomal dominant condition has a much later onset than other hereditary keratodermas, with lesions appearing in the second or third decades or later. Linkage to keratin loci has been excluded in two unrelated pedigrees of punctate keratoderma [4]. The sexes are equally affected with an incidence reported as 1.2 in 100 000 [1]. Pinpoint, hard keratotic papules, initially translucent but later opaque and warty, appear on the palms and soles (Fig. 34.60). In many families, small

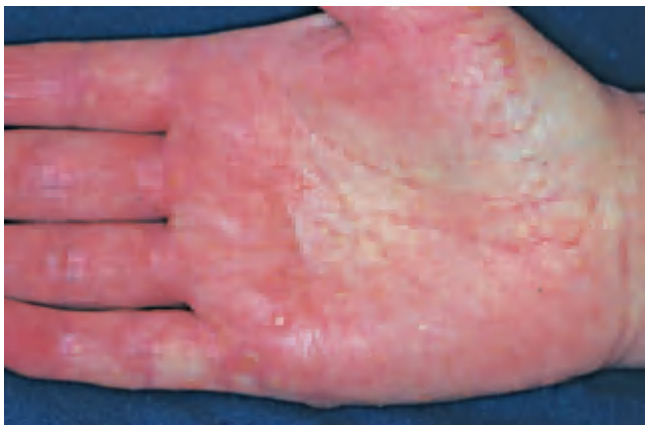
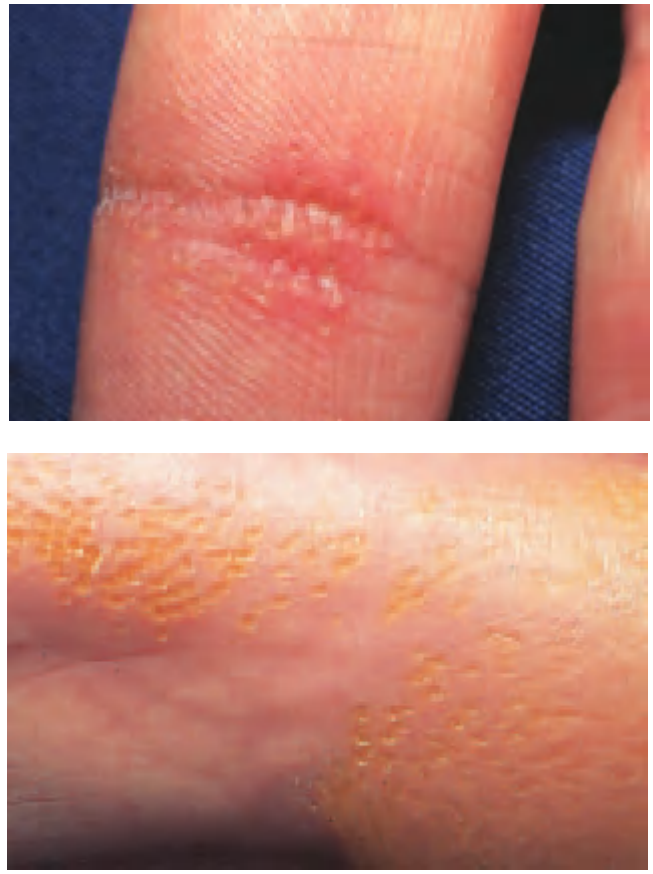


Fig. 34.60 Punctate keratoderma: small even keratotic papules on the palms.



(a)

(b)

Fig. 34.61 (a) Punctate keratoderma of the palmar creases; and (b) plantar lesions in the same patient.

and large lesions coexist, including broader focal plantar callosities. Lesions are more florid in manual workers. There is no hyperhidrosis. In most cases, punctate lesions are orthokeratotic on histology. Some pedigrees show crateriform lesions or keratoses that can be picked out; histology of these lesions shows parakeratosis [5,6]. The term porokeratosis of Mantoux has been used, but the parakeratosis is columnar rather than lamellar. A linear distribution of punctate lesions is seen in porokeratotic eccrine ostial and dermal duct naevus (see Chapter 15). Multiple associations of punctate keratoderma have been described, including association with diverse Lynch type II malignancies [6–8]. Topical retinoids and calcipotriol have only a slight effect on softening the keratoses but may be tried. Results with systemic retinoids are better but variable. Etretinate 0.5–1 mg/kg/day produced good results in three patients, moderate in four and no effect in two patients [9]; acitretin was rapidly effective in another case [10].

Punctate keratoses of the palmar creases [10–13]. This is characterized by hard warty lesions of the finger and palmar creases (Fig. 34.61a), often with a clavus-like lesion at the medial border of the distal palmar crease. The absence of marginal lesions distinguishes this entity from marginal

papular acrokeratodermas. It is inherited as an autosomal dominant trait and has been reported mainly in patients of African origin. Lesions may coexist with punctate or nummular keratoderma (Fig. 34.61b) [14].

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Filiform keratodermas

SYN. MUSIC BOX SPINE KERATODERMA

Fine keratotic lesions that project a millimetre or so from the palmoplantar surface are variously described as filiform, spiked, spiculate, spiny, minute digitate, minute aggregate and music box spine keratodermas. Like disseminated filiform keratoses, large morphological differences within this group probably reflect distinct aetiologies. Lesions may be inherited as an autosomal dominant trait, when they appear in the second or third decade [1]. They may be sporadic, and may involve other parts of the skin or palms and soles alone. Histology may show compact orthohyperkeratosis or parakeratosis resembling porokeratosis [2]. Attempts have been made to provide a unifying clinical classification based on histological features and distribution [3–5]. Tosti *et al*. [6] found dyskeratotic foci in the nail matrix. Hashimoto *et al*. [7] demonstrated the presence of hair-type keratin immunostaining in the lesions, suggesting that spiny keratoderma may represent ectopic hair formation. Reported associations include polycystic kidneys and liver [8], Darier's disease [3,9], epidermodysplasia verruciformis [10], renal failure [11], tuberculosis [12], hyperlipidaemia [13] and malignancy including nodular melanoma [5], carcinoma of the oesophagus [14] and lymphoproliferative disorders [15]. Profuse filiform keratoses are also associated with multiple myeloma and with HIV-associated PRP.

Treatment. Keratolytics are usually prescribed but are rarely successful. Etretinate gave variable slight improvement [10] or good results [6]. Topical 5-fluorouracil ointment cleared the lesions temporarily in one patient [2] but failed in another [8].

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Marginal papular keratodermas [1,2]

The relationships between marginal papular acrokeratodermas are debated, but Rongioletti *et al*. [1] suggest a pragmatic division into the hereditary type with elastorrhexis (acrokeratoelastoidosis), or without it (focal acral hyperkeratosis), and the acquired type (degenerative collagenous plaques).

Acrokeratoelastoidosis [2–4]. Costa [3] reported 13 cases with cornified and umbilicated papules distributed along

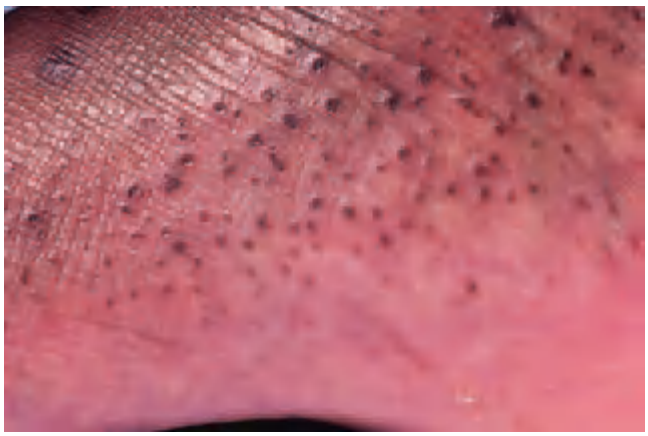

Fig. 34.62 Focal acral hyperkeratosis: crateriform punctate keratoses at the margin of the sole (Wallace's line).

the borders of the hands and feet (Fig. 34.62). He noted fragmentation and rarefaction of elastic fibres in the dermis, and introduced the term acrokeratoelastoidosis. Fiallo *et al*. [5] argued that the primary defect is in the elastic tissue.

Focal acral hyperkeratosis. Dowd *et al*. [6] reported 15 cases with oval or polygonal crateriform papules along the borders of the hands and feet but without solar damage or elastorrhexis, and termed these focal acral hyperkeratosis. However, eight of Costa's 13 patients [3] appear identical. One patient illustrated by Dowd *et al*. [6] also had marked punctate keratoses of the palmar creases, suggesting a relationship. Many patients with these disorders are of Afro-Caribbean origin, but a Filipino patient with focal acral hyperkeratosis and hearing loss has been reported [7].

Degenerative collagenous plaques [8–11]. These are firm plaques, sometimes concave, forming a linear band principally around the web of the thumb and index finger at the margin of the volar and dorsal surfaces. There is marked clinical and histological evidence of solar damage. Pathogenesis and a possible relationship with knuckle pads is discussed by Abulafia and Vignale [11].

Mosaic acral keratosis. Jacyk and Smith [12] reported African patients with widespread polygonal papular lesions over the ankles and shins under the title mosaic acral keratosis. It is not a marginal keratoderma [13] but is included here for convenience, as Costa's case 13 [3] had similar features.

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Miscellaneous keratoderma syndromes

Papillomatoverrucous palmoplantar keratoderma. The association of a florid warty keratoderma, dysplastic teeth and follicular keratoses was reported by Jacak and Wolf in four siblings in one family, with a possible autosomal recessive mode of inheritance [1]. Baran and Juhlin [2] reported a similar case, which responded to etretinate.

Keratosis multiformis. Under this title, Salamon and Marinkovic [3] presented a patient with gross warty PPK, shiny atrophic skin on the dorsa of the feet and hands, follicular keratoses, punctate pigmentation around the neck, forearms and buttocks, and skeletal abnormalities. The parents were consanguineous.

Acral poikiloderma of Weary. A curious, dry, leather-grained appearance of the palms and papular keratotic lesions on the dorsa of the hands is seen in the Weary syndrome [4,5]. This condition overlaps clinically and may be allelic with Kindler's syndrome.

Acro-osteolysis with keratoderma (Bureau–Barrière syndrome) [6,7]. Marked diffuse keratoderma is associated with osteolysis in the forefoot area, polyneuropathy of the lower legs and painless ulcers of the feet. Finger clubbing is a feature of this syndrome [8–10]. Cases associated with benign symmetrical lipomatosis [11] and angiodysplasia [12] are reported.

Aquagenic syringeal acrokeratoderma. Several patients are reported in whom a subtle keratoderma is revealed by sweating or immersion [13–16]. Patients typically present with a hand immersed in water to demonstrate the signs [16]. The painful whitish papular lesions are associated with dilated acrosyringeal ostia.

Symmetrical interdigital keratoderma. This is a sporadic condition of the hands, in which thickening of the interdigital spaces occurs from the second decade. The absence of occupational or other factors and the poor response to corticosteroids or keratolytics were said to be features supporting the diagnosis [17,18].

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Keratodermas and associated disorders

Many of the disorders reported in association with keratoderma in isolated cases may be fortuitous, but those that occur repeatedly may be significant. Table 34.6 lists many of them according to the systems involved.

Keratoderma and cancer

Cancers may arise in keratodermatous skin. Squamous and verrucous carcinomas are common in Huriez's syndrome [1], and isolated cases are reported in mutilating keratoderma [2], porokeratosis [3] and Clouston's syndrome [4]. Melanoma has occurred in different keratodermas [5–7]. Predisposition to internal cancer may be part of a keratoderma syndrome, of which the Howel-Evans' syndrome (see p. 34.96) is best known. A reported association between epidermolytic keratoderma caused by keratin 9 mutation and breast and ovarian cancer [8–10] is not a general feature of this syndrome. Familial punctate keratoderma has been reported with a variety of malignancies [11–13].

Acquired keratoderma may be paraneoplastic. In addition to tripe palms (see p. 34.108), and Bazex's acrokeratosis paraneoplastica (see Chapter 59), reports include acquired diffuse PPK with cancer of the bronchus [14–16], and filiform PPK with cancer of the breast, colon and kidney [17–19].

Carcinogens, of which the best documented example is arsenic, may produce both keratoderma and internal malignancy [20,21]. One survey showed that palmar keratoses occur four to five times more frequently in patients with cancer than in controls [22]. An increased incidence of keratoses in patients with lung or bladder cancer has been debated [23–25]. Smoking [23] and papillomavirus infection [24] are suggested culprits. Keratoses associated with cancer are histologically distinct from arsenical keratoses [26].

Chemotherapeutic agents used in cancer treatment commonly cause palmar erythema and may cause keratoderma [27].

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Other acquired keratodermas

Callosities or more extensive thickening of plantar epidermis is a common concomitant of obesity [1], and symptomatic plantar hyperkeratosis occurs with age or orthopaedic problems.

Keratodermas caused by other dermatoses. Palmar or plantar lesions occur in a wide range of dermatoses [2]. In psoriasis, both diffuse gross and centripalmar hyperkeratosis are seen. A scalloped margin (*Festonné*), Caro–Senear lesions (depressed plaques) on the sides of the fingers and involvement of the knuckles may suggest the diagnosis. The lesions of Reiter's disease are compact, heaped up and resemble the heads of nails (keratoderma blenorrhagica). The even yellow hyperkeratosis of PRP is associated with an acute follicular eruption in adults and by lesions on the knees and elbows in children. Extensive hyperkeratotic eczema may be difficult to distinguish on clinical and histological grounds from keratoderma but marked itching may indicate eczema. Trichophytosis, especially resulting from *Trichophyton rubrum*, may be unilateral and lacking in inflammatory signs. Keratoderma may be seen in crusted scabies (Fig. 34.63). The tendency of secondary syphilis lesions to involve the palms is well known, and

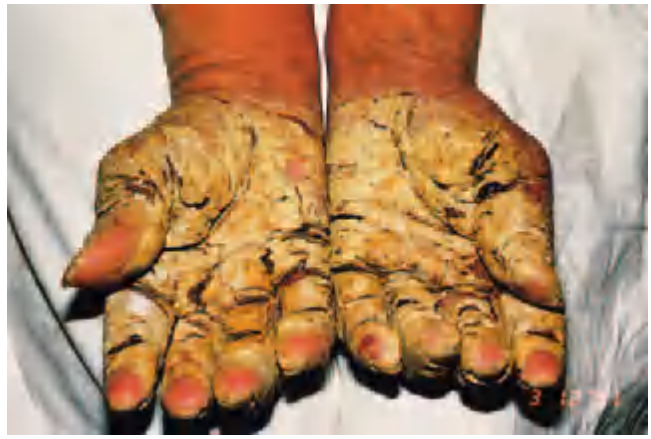

Fig. 34.63 Norwegian scabies causing keratoderma. (Courtesy of Dr N. Walker, Oxford Radcliffe Hospital, Oxford, UK.)

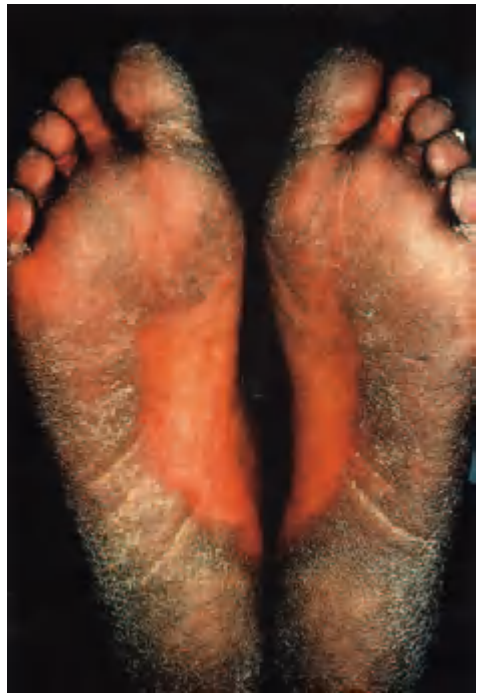

Fig. 34.64 Keratoderma produced by lupus erythematosus. (Courtesy of Dr I. Sarkany, Royal Free Hospital, London, UK.)

hyperkeratotic late syphilides may be warty or focal [3]. In late yaws, keratoderma may induce a peculiar crab-like gait in those affected. In immunocompromised patients, viral warts may be confluent on the palms or soles. Lupus erythematosus may show dry and atrophic [4], hypertrophic (Fig. 34.64) [5] or ulcerative [6] palmar lesions. In lichen planus, warty lesions may be mistaken for viral warts, and it and lichen nitidus may mimic punctate keratoderma [7]. Keratoderma may be seen as a result of hypersensitivity to drugs such as iodine. Keratoderma may result from tegafur [8], glucan [9], lithium [10] and halogenated weed-killers [11], and dioxin intoxication

[12]. Arsenicals induce irregular warty keratoses, or more even glassy lesions, still occasionally seen [13].

Keratoderma climactericum (Haxthausen's disease) [14,15]. The specificity of this syndrome described in women over the age of 45 is uncertain, as many patients are obese. Pressure areas of the heel and the forefoot are involved first (Fig. 34.65). Erythema and heavy hyperkeratosis with fissuring make walking painful. The condition slowly extends to become confluent. Later, the central palms may be affected. Symptoms may be worse in winter. Deschamps *et al*. [15] excluded endocrine dysfunction, contact dermatitis and fungal infection, and found normal serum vitamin A levels. However, Wachtel [16] described three young women in whom an identical condition arising following bilateral oophorectomy was reversed by oestrogen replacement. Laurent *et al*. [17] implicated keratinization of the acrosyringium by the finding of composite keratohyaline granules in the granular cells of the interductal granular cells, believed to serve as a marker for acrosyringeal differentiation [18]. Low-dose etretinate produces improvement in several weeks. In this age group, hypertension, cardiovascular disease or lipid abnormalities may prove contraindications. In one report, topical 0.05% oestradiol in a water-in-oil base was successful where keratolytics and emollients had failed [19].

Myxoedema. Palmoplantar hyperkeratosis with myxoedema, improving with treatment, has been reported on several occasions [20,21].

Lymphoedema and other circulatory disorders. In chronic lymphoedema, the skin overlying the lymphoedematous area first becomes diffusely thickened, and then develops a velvety papillomatous surface, which is ultimately covered by large irregular warty projections (lymphostatic verrucosis; mossy foot) [22–24]. The condition may simulate chromoblastomycosis. Lymphoedematous keratoderma occurs most characteristically in filariasis, but may develop in chronic lymphoedema of any origin. Histologically, there is hyperkeratosis, acanthosis and papillomatosis. The dermis is oedematous with dilated lymphatics, conspicuous new-vessel formation, some sclerosis and a variable infiltrate of inflammatory cells. Both the hyperkeratotic component and the lymphoedema improved in three cases given etretinate 0.6 mg/kg/day [22]. Keratoderma is also reported in association with acrocyanosis and livedo reticularis [25].

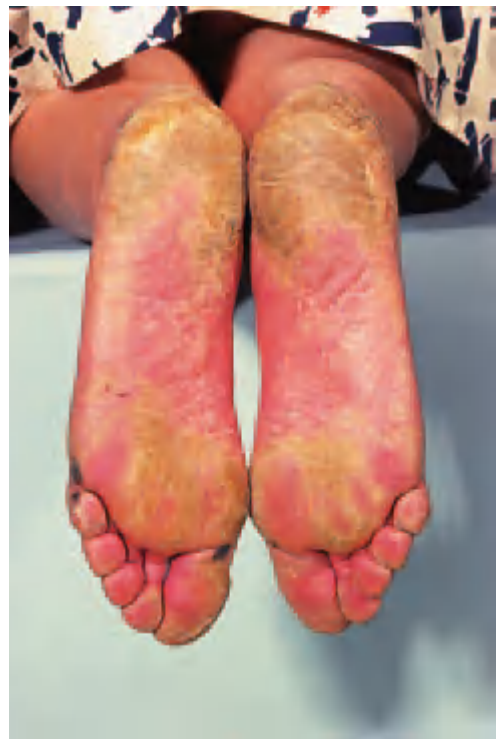

Fig. 34.65 Keratoderma climactericum.

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Acanthosis nigricans [1–3]

Skin affected by acanthosis nigricans is hyperpigmented, with papillomatous hyperkeratosis giving a velvety texture. Neck and flexures are most severely affected. Palms may be involved by papillomatous hypertrophy ('tripe palms').

Aetiology. Acanthosis nigricans has a variety of known causes whose common mechanism is likely to be stimulation of tyrosine kinase growth factor receptor signalling pathways in epidermis [4]. In insulin resistance syndromes, high levels of circulating insulin directly or indirectly activate the insulin-like growth factor 1 receptor (IGF1R) [5,6]. IGF1R is a transmembrane protein related to the insulin receptor, which is present in many tissues, including keratinocytes and some ovarian compartments. Specific activating mutations in fibroblast growth factor receptors (FGFRs), and tyrosine kinase receptors, are associated with acanthosis nigricans in Beare–Stevenson syndrome (FGFR2), Crouzon's syndrome with acanthosis nigricans (FGFR3) and thanatophoric dwarfism (FGFR3) [7]. Tumour-derived growth factors, in particular transforming growth factor-α acting through the epidermal growth factor receptor (EGFR), are presumed to be involved in malignant acanthosis nigricans [8–11], although anti-insulin receptor antibodies have also been implicated [12].

Pathology. Hyperkeratosis and irregular spiky papillomatosis alternating with areas of attenuation are seen [3,13].

Clinical features [1,3,13]. The essential clinical features are common to all forms of the disease, but vary in distribution and degree. In congenital forms, skin lesions may be present at birth, but usually develop during childhood or puberty. The earliest changes are usually pigmentation, dryness and roughness of the skin, which in the affected areas is grey–brown or black, palpably thickened and covered by small papillomatous elevations, which give it a velvety texture (Fig. 34.66). As the thickening increases, the skin lines are further accentuated and the surface becomes mammillated or rugose, and larger warty excrescences develop. The sites most commonly involved are the axillae, the back and sides of the neck, the anogenital region and the groins, but the other flexures, the submammary region, the umbilicus and, in some cases, almost the entire skin may be affected. The distal extremities are usually spared. Involvement of the mucous membranes is uncommon, but the oral mucous membrane may show a velvety pattern of delicate furrows [14].

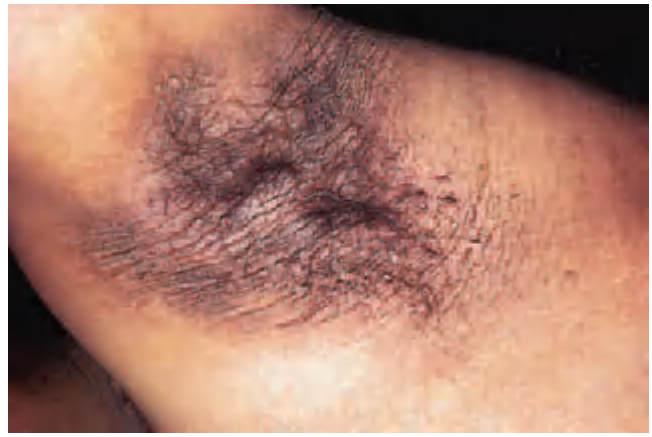

Fig. 34.66 Benign acanthosis nigricans: velvety thickening with skin tags.

Inherited forms of acanthosis nigricans. Acanthosis nigricans without other abnormalities may be inherited as a Mendelian dominant trait (MIM 100600) [15,16], but acanthosis nigricans has been reported in many genetic syndromes [1]. Known causes include insulin receptor defects such as leprechaunism, Rabson–Mendenhall syndrome, lipodystrophies and other causes of hyperinsulinaemia, and activating mutations of FGFRs [4].

Benign acquired acanthosis nigricans. The term 'pseudo'-acanthosis nigricans is obsolete, as it is clear that this condition differs only in severity from other forms. As a complication of obesity, it is seen most often in adults [17,18], but also occurs in childhood [18], and is likely to become more common with increasing obesity in prosperous countries. Small patches of pigmentation and velvety thickening, often with multiple skin tags, are present in all or any body folds, especially the axillae (Fig. 34.66), groins and natal cleft. Stuart [19] examined 1412 unselected American high school children and found acanthosis nigricans in 7%, which correlated well with severe obesity. In a study of native Americans, subjects affected by acanthosis nigricans had twofold higher fasting insulin levels than weight-matched controls [18]. With weight

reduction, the skin changes may slowly regress, although the pigmentation often persists. In the tropics, the condition may occur in those who are not overweight.

HAIR–AN syndrome. The triad of *h*yper*a*ndrogenism, *i*nsulin *r*esistance and *a*canthosis *n*igricans in women is known as the HAIR–AN syndrome [2,6], and may be seen with insulin resistance of various causes. Chronic hyperinsulinism is thought to induce ovarian hyperandrogenism [6], and *in vitro* ovarian tissue from hyperinsulinaemic diabetic women responds to supraphysiological insulin concentrations by enhanced steroidogenesis [20]. The finding of pubic hair before the age of 8 years (premature adrenarche) with acanthosis nigricans was associated with insulin resistance [21].

Autoimmune acanthosis nigricans. Acanthosis nigricans disorder may occur in autoimmune disease, including systemic lupus erythematosus, caused by antibodies to the insulin receptor [2,22].

Drug-induced acanthosis nigricans. Nicotinic acid [23,24] and fusidic acid [25] have induced the cutaneous changes of acanthosis nigricans. Acanthosis nigricans has also been reported as a complication of stilboestrol therapy in young males [26] and as a complication of oral contraceptive therapy. Triazinate, which is a folic acid antagonist, has also been reported to cause acanthosis nigricans in two patients [27]. Acanthosis nigricans with insulin resistance has been reported in patients receiving treatment with protease inhibitors [28].

Malignancy-associated acanthosis nigricans. This is comparatively rare, and lesions are more severe and extensive. Pigmentation is conspicuous and is not confined to hyperkeratotic areas. Thickening of the palms is frequent and the nails may be brittle or ridged. The hair may be shed. Irritation is common and may be severe. The mucous membranes and mucocutaneous junctions are involved in at least 50% of the cases, and warty papillomatous thickening around the lips and eyes may be a presenting symptom (Fig. 34.67). The sexes are equally affected. There is usually an underlying adenocarcinoma, especially of stomach, but other tumours are sometimes found, including those of oesophagus, rectum, bronchus, urinary tract, bile duct and thyroid [1]. Acanthosis nigricans may precede other symptoms by as many as 5 years, but the interval is usually shorter. Removal of the tumour may be associated with regression of the clinical signs, but relapses are common. Rendon *et al*. [29] provide a practical algorithm for investigating these patients. Malignant acanthosis nigricans has very rarely occurred in childhood—rapidly progressing lesions and mucous membrane involvement are useful warning signs. An unusual source of diagnostic confusion is an associated hypertrophic osteo-arthropathy simulating pachydermoperiostosis.

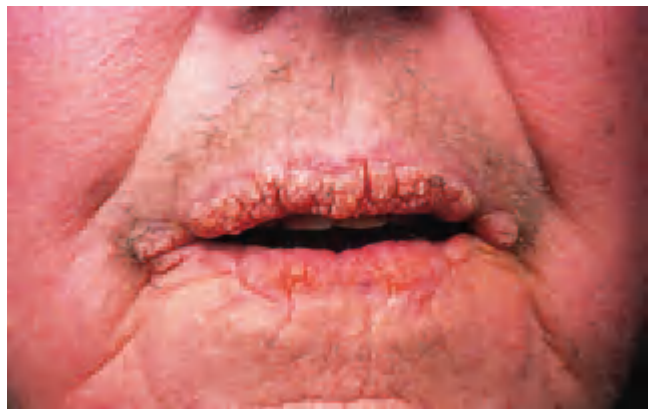

Fig. 34.67 Malignant acanthosis nigricans: warty thickening of the oral margins in a patient with carcinoma of the breast.

Tripe palms. Velvety rugose thickening of the palms, resembling tripe (the villous lining of ruminant stomach), is almost always associated with internal malignancy [30,31]. By contrast, familial keratoderma associated with malignancy is compact and non-rugose. An elevated level of epidermal growth factor was described in a patient with tripe palms and carcinoma of the bronchus [32]. Tripe palms with malignancy may occur alone (25%) or associated with acanthosis nigricans [33].

Naevoid acanthosis nigricans [34]. This rare variety is unilateral and localized and is not associated with endocrine abnormalities.

Treatment. Treatment is of the underlying cause, or is otherwise symptomatic and of little help. Removal of the tumour in the malignant form may allow some improvement but is rarely complete. A case of hereditary benign acanthosis nigricans improved dramatically with etretinate [35].

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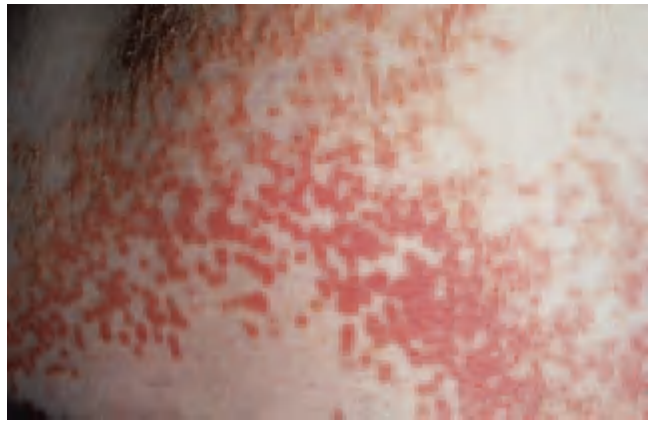

Fig. 34.68 Confluent and reticulate papillomatosis: red–brown reticulate papules with a fine scale in the central area of the chest. (Courtesy of Professor R.J. Hay, St John's Institute of Dermatology, London, UK.)

Confluent and reticulate papillomatosis [1]

SYN. GOUGEROT–CARTEAUD SYNDROME

This syndrome of mild truncal hyperkeratosis is included here in view of its improvement with retinoids, but there is stronger evidence of an infective aetiology.

Aetiology. Most cases are sporadic, although a genetic predisposition has been proposed [2]. The hyperkeratosis may represent an abnormal response to microbial products. *Pityrosporum orbiculare* has been implicated [3], but anti-yeast therapy is unreliable. Response to several antibiotics supports a bacterial contribution [4].

Pathology. Histologically, hyperkeratosis and papillomatosis are present without acanthosis. Amyloid has been reported [5].

Clinical features [1,6]. The condition is seen predominantly in girls, beginning around puberty. Flat dry papules up to 5 mm in diameter commonly appear between the breasts and in the interscapular area. Neighbouring papules become confluent in the centre of the affected areas, but only partially so at their periphery to form an irregular network (Fig. 34.68). The lesions gradually extend over the breasts and up and down the epigastrium and back, sometimes reaching the shoulders and the sides of the neck. They cause no symptoms and little disfigurement. The age of onset and the distribution of lesions differentiate the condition from acanthosis nigricans, athough their coexistence in childhood has been noted [7]. Darier's disease and reticulate pigmentary disorders [8] (see Chapter 39) must also be considered.

Treatment. Various antibiotics may be effective [4,9,10] especially where PAS-positive materials are present in the stratum corneum [11]. Minocycline has been most used [4]. The response to antifungal agents is variable, even if yeasts are demonstrated [12,13]. Systemic or topical retinoids, or topical vitamin D analogues may also be effective [14–16].

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Chapter 35

Psoriasis

C.E.M. Griffiths, R.D.R. Camp & J.N.W.N. Barker

Definition. A common, chronic, disfiguring, inflammatory and proliferative condition of the skin, in which both genetic and environmental influences have a critical role. The most characteristic lesions consist of red, scaly, sharply demarcated, indurated plaques, present particularly over extensor surfaces and scalp. The disease is enormously variable in duration, periodicity of flares and extent. Morphological variants are common.

Epidemiological aspects

Incidence and prevalence

Accurate figures concerning epidemiology and morbidity of psoriasis are difficult to obtain given that diagnostic criteria have never been validated, different methodologies have been employed and patient ascertainment techniques have varied. Nevertheless, it is clear that psoriasis is a very common disease. Most robust prevalence data comes from northern Europe and Scandinavia where studies of white people indicate population prevalence between 1.5 and 3% (Table 35.1) [1–9], although prevalence as high as 4.8% has been reported [10]. There are considerable racial variations, with most other populations having a lower prevalence of disease. In China, psoriasis is estimated to affect 0.3% of the population [7], while the disease has not been observed in Samoans [8] or Latin American Indians [9]. It appears to be more common in East than West Africa. Climate appears to affect psoriasis prevalence, with higher rates recorded in single countries at greater latitudes from the Equator [11].

Table 35.1 Worldwide studies on prevalence of psoriasis.

Place and reference	Sample size	Percentage with psoriasis
Faroes [1]	10 984	2.84
Sweden [2]	159 200	2.3
UK [3]	2180	1.56
UK [4]		1.48
Croatia	8416	1.5
US [5]	20 749	1.4
US [6]	7514	1.4
China [7]	670 000	0.3
Samoa [8]	12 569	0
South America [9]	25 000	0

The incidence of the disease (the number of new cases occurring in a given population in a defined time) has only been accurately assessed in a single study. This indicated that 60 individuals per 100 000 per year were seeking medical care for psoriasis for the first time [12]. The study also provided support for seasonal variation, with 68% of cases first diagnosed in winter and spring months.

All figures quoted above relate primarily to psoriasis vulgaris (chronic plaque psoriasis). Estimates of disease variants are much less robust. They probably account for approximately 10% of all cases.

Age of onset

Considerable variation exists between studies in age of onset, perhaps in part reflecting the lack of strict criteria used. Lomholt [1] reported average age of onset as 12

years in his study in the Faroe Islands. In a large USA survey [5], the average age of onset was 28 years, while in the largest study reported in China, average age of onset was 36 years [7]. It has been reported that 35% of cases have disease onset before age 20 years and 58% before age 30 [8]. In a recent UK study [4] of a defined population, mean age of onset was 33 years with the mode in the second decade. Seventy-five per cent had disease onset before the age of 46 years.

However, these studies hide the fact that it appears that psoriasis has a bimodal distribution of age of onset. In a German study, two peaks were identified: the larger, early peak between 16 and 22 years and the later one at 57–60 years [13]. Several other studies including from the UK [14] broadly support this observation. Those individuals with early onset appear, in general, to have more severe disease and are much more likely to have an affected first-degree relative with psoriasis (see below) [1,5,15].

Sex effects

Males and females are equally affected by psoriasis vulgaris. Many studies indicate that age of onset is younger in females. Thus, one German study demonstrated a peak age of onset of 22 years in males and 16 years in females in early-onset disease [13]. However, results of studies are highly dependent on sampling techniques used and are variable in their results. There is no evidence that the disease is phenotypically different between the sexes.

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Aetiology and pathogenesis

Genetic epidemiology

There is overwhelming evidence that psoriasis has an important genetic component. Lomholt's [1] classic epidemiological study of psoriasis in the Faroe Islands (1963), in which he examined more than 10 000 inhabitants, made the key observation that the incidence of psoriasis was much greater amongst first- and second-degree relatives of patients than unaffected control subjects.

A further large-scale study performed in Sweden supported these data, showing the prevalence of psoriasis to be 7.8% in first-degree relatives, compared with a prevalence of 3.14% in matched controls and 1.97% in the overall population [2]. Based on population data, several investigators have calculated the risk for a child to develop psoriasis. In a German study, the risk was 14% if one parent was affected, 41% if both parents affected and 6% if one sibling affected, compared to 2% when no parent or sibling was affected [3]. Henseler and Christophers [4] demonstrated that the bimodal peak in disease onset (see above) could be taken as evidence for the existence of two pathogenetically distinct forms of the disease, similar to the model for diabetes mellitus. Thus, type 1 is hereditary, strongly HLA associated (particularly HLA-Cw6), early onset and more likely to be severe. Type 2 is sporadic, HLA unrelated, of late onset and usually mild. A recent study in Iceland has confirmed many of these data [5]. However, others have suggested that the true situation is more complex [6] and certainly there are many individuals in extended family pedigrees with late-onset disease.

Support for these population studies comes from analysis of various family pedigrees in which psoriasis appears throughout multiple generations [7]. Although some authors have argued that the data are most consistent with an autosomal dominant pattern of inheritance with reduced penetrance and others that the best fit is a double recessive model, most regard the data as consistent with a polygenic or multifactorial pattern (see below). Interestingly, the development and severity of psoriasis may be influenced by the sex of the contributing parent. Thus, several studies have noted evidence for a preferential paternal effect, while one Scottish study further showed earlier age of onset when the disease was inherited from the father, consistent with 'genetic anticipation' [8].

Perhaps the most robust data supporting a genetic basis to psoriasis come from studies examining concordance for

the disease in twins. Examination of individuals from the Danish Twin Registry has shown concordance for psoriasis in 64% of monozygotic (identical) twins compared to 15% for dizygotic twins, corresponding to an estimated heritability of 91% [9]. Very similar figures (73% and 20%, respectively) were found in the retrospective study of Farber *et al.* [10] although in more recent Australian studies lower concordance rates were observed: 35% in monozygotic twins compared to 12% in dizygotic twins [11]. Of interest, when monozygotic twins are concordant for psoriasis the age of onset, distribution of the disease and severity are very similar, suggesting that genetic factors have a role in these parameters. However, it is self-evident from the data that concordance rates do not reach 100%, even when older twins are examined, indicating that the environment plays a key part in disease expression. Based on the variable extent and pattern in which it is inherited through families, it is suggested that psoriasis represents a spectrum of genetic diseases. At one end are the rare families in which changes in a single gene may be sufficient to cause the disease. At the opposite end of the spectrum is the more common form in which an obvious family history may be lacking. In these individuals, it is likely that changes in multiple genes, interacting both with each other and the environment, are required for disease expression [12].

All the above studies have concentrated upon chronic plaque psoriasis, the most common variant. Little is known of the epidemiology of other forms. Guttate psoriasis (see below) is almost invariably HLA associated [13] and thought to be closely linked pathogenetically to type 1 plaque psoriasis.

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Environmental risk factors

Present evidence indicates that interactions between genes and the environment are important in disease causation. Many environmental factors have been linked to psoriasis, and have been implicated in, for example, initiation of the disease process and exacerbation of pre-existing disease. However, conclusive evidence is so far lacking.

Trauma

Psoriasis at the site of an injury is well known (Koebner phenomenon; see below). A wide range of injurious local stimuli, including physical, chemical, electrical, surgical, infective and inflammatory insults has been recognized to elicit psoriatic lesions [1].

Infection

Acute guttate psoriasis is strongly associated with preceding or concurrent streptococcal infection, particularly of the throat [2]. There is evidence that streptococcal infection may be important in chronic plaque psoriasis [3], and that treatment with rifampicin and penicillin may lead to clearance of skin lesions. Further, acute episodes of guttate psoriasis are much more common in individuals with a family history of plaque psoriasis [4] and one-third of cases of guttate psoriasis progress to the chronic plaque form [5]. Guttate and chronic plaque psoriasis share strong HLA associations, particularly with HLA-Cw6.

Human immunodeficiency virus (HIV) infection has also been associated with psoriasis (see below).

Drugs

There are many drugs reported to be responsible for the onset or exacerbation of psoriasis [6]. Chief amongst these are lithium salts, antimalarials, β-blocking agents, non-steroidal anti-inflammatory drugs (NSAIDs), angiotensin-converting enzyme (ACE) inhibitors and the withdrawal of corticosteroids. However, their risk has never been formally assessed in controlled epidemiological studies. The adverse effect of β-blockers is based on early experiences with practolol [7], although data implicating those in current usage are lacking. Likewise, the risk of withdrawal of systemic or potent topical corticosteroids requires careful re-evaluation.

Anecdotal personal experience of the authors and questioning of colleagues have suggested that β-blockers and NSAIDs have little, if any, adverse effects on psoriasis but that the effect of lithium salts or antimalarials may be severe. Patients with unstable psoriasis should receive appropriate advice before travelling to countries where antimalarial prophylaxis is required.

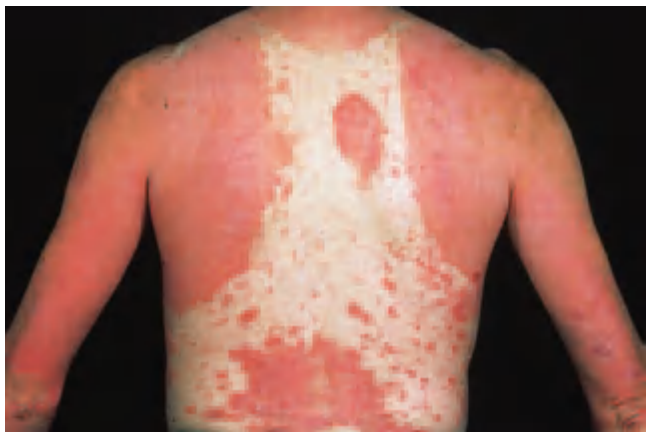

Fig. 35.1 Psoriasis exacerbated by sun exposure. (Courtesy of St John's Institute of Dermatology, London, UK.)

Sunlight

Although sunlight is generally beneficial, in a small minority of patients, psoriasis may be provoked by strong sunlight (Fig. 35.1) and cause summer exacerbations in exposed skin. In a questionnaire study of 2000 patients in Sweden, the prevalence of photosensitivity in psoriasis was estimated at 5.5% [8]. Approximately 40% of these patients gave a history of polymorphic light eruption (PLE) with psoriasis appearing as a secondary phenomenon with PLE lesions. The remainder of the photosensitive psoriatics slowly developed psoriasis after sun exposure with PLE. Photosensitive psoriasis was associated with skin type I, advanced age and female sex. Photochemotherapy (PUVA) can be helpful in these patients.

Metabolic factors

The early onset of psoriasis in women, with a peak around puberty, changes during pregnancy and provocation of psoriasis by high-dose oestrogen therapy potentially indicates a role for hormonal factors in the disease. A questionnaire study has provided data from 65 females who had one or more pregnancies after the diagnosis was made. Psoriasis improved in approximately 40% of pregnancies, and worsened in 14% [9]. In contrast, in the 3-month postpartum period, 11% improved and 54% deteriorated. Thus, if psoriasis changes in pregnancy, it is more likely to improve than worsen, while in the postpartum period it is more likely to deteriorate. These results have been broadly supported in more recent studies [10]. Although rare, generalized pustular psoriasis precipitated by pregnancy has repeatedly been reported [11].

Hypocalcaemia (e.g. following accidental parathyroidectomy) has been reported to occur in severe forms of psoriasis, particularly generalized pustular psoriasis [12,13] and may be a predictor of poor outcome.

Psychogenic factors

Considerable clinical evidence exists for the role of stress in onset and exacerbation of psoriasis. Seville [14] reported consistent links between major stressful life events and disease manifestation. In a recent UK study, over 60% of a sample of psoriasis patients believed stress was a principal factor in the cause of their psoriasis [15]. Gupta [16] reported that several psychocutaneous characteristics, including more exacerbations and worse disease, correlated with stress reactivity. However, not all studies have supported these observations and prospective epidemiological studies, using appropriate psychometric instruments, are required to answer these important issues.

It is without doubt, however, that psoriasis has a detrimental effect on the psychosocial quality of life of patients and that stress management programmes significantly shorten the time to clearance with standard therapies [17]. Furthermore, psoriasis in patients who are categorized as being high or pathological worriers is less likely to clear with photochemotherapy (PUVA) than in those patients with low worry [18].

Alcohol and smoking

It has long been suspected that both cigarettes and alcohol have a detrimental effect on psoriasis. Although recent large epidemiological studies are not conclusive, support for an association is observed [19]. When controlled for confounding variables, studies suggest that alcohol may exacerbate pre-existing disease but does not appear to induce psoriasis [20]. This effect seems greater in men than women. Heavy drinkers tend to have more extensive and inflamed disease [21,22]. Increased alcohol consumption is a recognized stress response. Excess drinking is undoubtedly also a consequence of the disease and leads to treatment resistance and reduced therapeutic compliance. Abstinence has been reported to induce remission [23].

In the Rochester incidence study [24], female patients at first diagnosis smoked more than a random sample of the population, in contrast to male patients who were comparable. These data were confirmed by Naldi [25] in a case–control study. In women who smoked more than 15 cigarettes/day, the odds ratio for association with psoriasis was 3.9 (men = 1.4). Most striking is the link between smoking and pustular forms of psoriasis, particularly palmoplantar pustulosis, a disease most frequently observed in females (see below). Individuals smoking more than 15 cigarettes/day had an odds ratio of 10.5 for association with palmoplantar pustulosis.

Acquired immune deficiency syndrome

The association between severe psoriasis, psoriatic arthropathy and HIV infection is well recognized [26–29]. In a study of 13 HIV-positive psoriasis patients followed over 2.5 years, psoriasis was found to flare severely or to appear *de novo* in explosive form as features of HIV infection developed. The prognosis of acquired immune deficiency syndrome (AIDS) in patients with psoriasis also appeared poor, nine out of 13 patients having died during the course of the above 2.5-year study [26]. The mechanism of worsening of psoriasis in these circumstances is unclear. Furthermore, the knowledge that psoriasis may be aggravated by AIDS, a disease in which the helper T cell is the major target, and the evidence that psoriasis may be greatly improved by ciclosporin, which inhibits helper T-cell function, create a paradox that remains to be fully explained.

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Pathogenetic mechanisms

The cardinal features of lesional psoriatic skin are:
1 Epidermal hyperproliferation with loss of differentiation
2 Dilatation and proliferation of dermal blood vessels
3 Accumulation of inflammatory cells, particularly neutrophils and T lymphocytes.
A vast array of growth factors, cytokines, inflammatory mediators and other biological markers have been shown to be altered in lesional psoriatic skin. Far more contentious is whether any of these alterations persist in non-lesional skin.

Modern molecular techniques such as microarray gene profiling allow a more comprehensive analysis of transcriptional changes involved in various stages of disease progression and will provide new insights into disease pathogenesis and potentially mechanisms of drug activity [1].

Epidermal proliferation

A variety of techniques have demonstrated that the increased keratinocyte proliferation observed in psoriasis is a consequence of an increase in the proliferating cell compartment in the basal and suprabasal levels of the epidermis, and not because of shortened cell cycle time. The number of cycling cells is increased approximately sevenfold [2]. These changes are not specific for psoriasis as, for example, increased numbers of proliferating keratinocytes are also seen in wound healing and atopic dermatitis. Multiple growth factors, which experimentally have been shown to modulate keratinocyte proliferation, are present in lesional skin [3]; in particular, transforming growth factor-α (TGF-α) appears to be an important autocrine mediator of these events [4].

Vascular changes

Vertical dermal capillary loops in lesional skin are dilated, elongated and twisted. Image analysis quantification of immunostained microvessels has demonstrated a four-fold increase in endothelium of superficial but not deep microvasculature, indicating that these changes are confined to the upper plexus [5]. These vascular changes occur early in lesional development [6]. Autoradiographical and immunohistochemical studies have demonstrated proliferating endothelial cells in pustular and plaque forms of psoriasis, with a proliferation index of approximately 3% [5], indicating that vascular growth, or angiogenesis, is an important component of this process.

Using various *in vivo* models of angiogenesis, it has been demonstrated that epidermal keratinocytes are the primary source of angiogenic activity [7]. These cells produce an array of soluble mediators with angiogenic activity including interleukin-8 (IL-8), TGF-α, tumour necrosis factor-α (TNF-α), thymidine phosphorylase and endothelial cell-stimulating angiogenesis factor and, perhaps most importantly, vascular endothelial growth factor (VEGF). VEGF is overexpressed in psoriatic epidermis as are its receptors on lesional psoriatic microvasculative [8]. Transgenic mice, which overexpress VEGF in basal epidermis, have an expanded superficial dermal vasculature similar to that observed in psoriasis [9]. Interestingly, some patients with erythrodermic or severe plaque psoriasis have evidence of systemic capillary leak such as proteinuria. In such patients, circulating VEGF is detectable and correlates with proteinuria [10].

Angiopoietins 1 and 2 and their receptor Tie 2 are involved in the stabilization of blood vessels, once formed. Altered regulation of these molecules has been reported in psoriasis [11].

In addition to vascular growth, dermal capillaries contribute to the inflammatory process actively through surface expression of molecules involved in leukocyte homing, induced by inflammatory mediators such as histamine, neuropeptides, IL-1 and TNF-α. Importantly, E-selectin is induced and intercellular adhesion molecule-1 (ICAM-1) up-regulated on dermal vessels in lesional tissue, thus providing a mechanism for skin homing T lymphocytes to accumulate within lesional dermis and epidermis [12].

Molecular genetics

At least eight total or partial genome scans have been reported in psoriasis, using a variety of genetic statistical approaches [13]. Eight loci giving statistical evidence of linkage to psoriasis have been identified (Table 35.2) [14–21], and several others provide partial evidence of linkage. Given the complex nature of psoriasis pathophysiology, many potential candidate genes reside at each of these genetic loci. Genetic replication and fine mapping constitute key steps still required before gene identification becomes a reality. However, much progress has been made in gene identification at *PSORS1*, which has been consistently observed across studies [13]. This locus resides within the major histocompatibility complex (MHC) on the short arm of chromosome 6, as predicted by many HLA association studies. Genetic analysis localizes the critical interval to an approximately 200 kb region containing approximately eight known genes [22]. Three genes stand out as potential psoriasis susceptibility genes: HLA-C, HCR [23] and corneodesmosin [24].

Table 35.2 Genetic loci significantly linked to psoriasis.

Designation	Chromosomal locus	Reference
PSORS1	6p21.3	[14]
PSORS2	17q	[15]
PSORS3	4q	[16]
PSORS4	1q	[17]
PSORS5	3q	[18]
PSORS6	19q	[19]
PSORS7	1p	[20]
PSORS8	16q	[21]

PSORS, psoriasis susceptibility locus; p, chromosome short arm; q, chromosome long arm.

The putative gene at *PSORS1* is undoubtedly the major genetic determinant for psoriasis, perhaps accounting for 35–50% of the heritability of the disease. However, psoriasis is genetically complex and how *PSORS1* interacts with other genes, and potentially the environment, are important issues yet to be addressed. Recent evidence indicates that palmoplantar pustular psoriasis is genetically distinct from type 1 psoriasis vulgaris which, in turn, appears genetically identical to guttate psoriasis with respect to *PSORS1* [25].

Immunology and inflammation

There is considerable evidence that T lymphocytes have an important role in the development of plaques of psoriasis:

1 Early influx of T cells into expanding lesions [26,27]
2 Strong association with the MHC, particularly HLA-Cw6 [28]
3 Ablative (albeit temporary) effect of anti-T-cell therapy [29]
4 Increased antigen presentation in psoriatic plaques [30]
5 Anecdotal evidence of development of psoriasis after syngeneic bone marrow transplant [31]
6 Change in phenotype to lesional psoriatic skin in non-lesional psoriatic skin transplanted on to severe combined immunodeficient mice and injected with autologous T cells [32].

Those T cells involved in psoriasis pathogenesis express particular markers, including memory (CD45RO), activation (HLA-DR and CD25) and skin homing (CLA) surface receptors [33]. Th1 cytokines predominate, with a key role postulated for interferon-γ (IFN-γ) [34].

A critical immunological question is that, if T cells are fundamental to the disease process, what triggers their activation? Evidence has been presented implicating conventional antigens [35] and bacterial superantigens [36]. One hypothesis is that bacterial superantigens initiate the process, and that molecular mimicry between bacterial proteins and keratin 17 leads to activation of autoreactive T cells and thus disease persistence [37].

These postulated immunological mechanisms reflect changes in acquired immunity. It is increasingly clear that innate immune mechanisms involving neutrophils, monocytes and keratinocytes, in which there is a rapid non-specific response to a limited number of invariate features associated with pathogens, are important in psoriasis pathogenesis [38]. These concepts are supported by many parallels with Crohn's disease including the sharing of a genetic locus [39], the postulated role of bacteria in both diseases and the response to therapy targeted at TNF-α [40], a key mediator of innate immunity.

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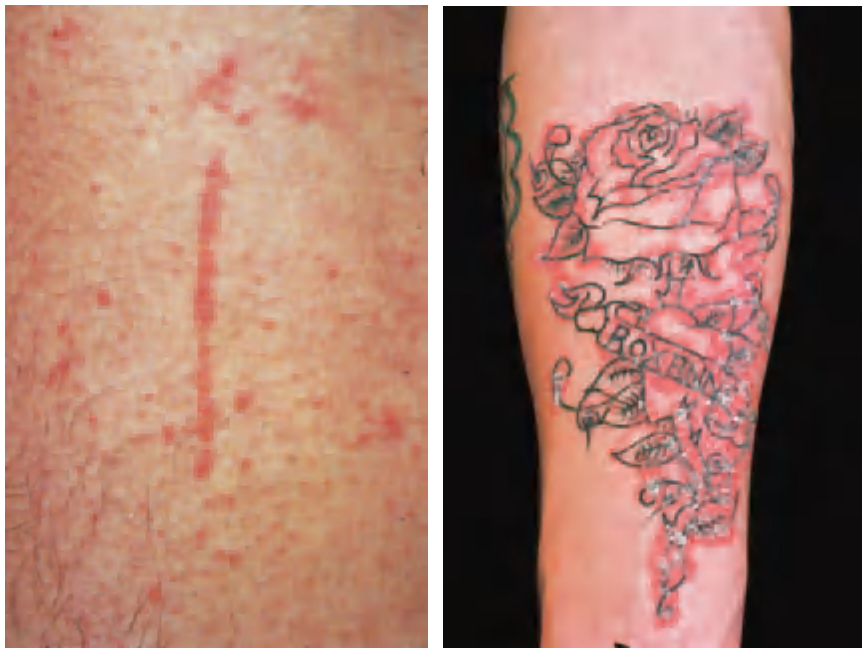

(a) (b)

Fig. 35.2 (a,b) Psoriasis: Koebner's phenomenon. (Courtesy of St John's Institute of Dermatology, London, UK.)

Koebner and reverse Koebner phenomena [1]

Psoriasis is one of several conditions in which various types of trauma may elicit the disease in previously uninvolved skin (Koebner reaction) (Fig. 35.2) [2]. The Koebner reaction usually occurs 7–14 days after injury [3], and the reported incidence has varied between 38 and 76% of patients with psoriasis [4]. In a given patient, an all-or-none phenomenon occurs at multiple sites of injury (if psoriasis occurs at one site of injury it occurs at all sites of injury) [5,6]. Clearing of existing psoriasis following injury has been observed and termed the reverse Koebner reaction [5]. This reaction also obeys an all-or-none rule, and the Koebner and reverse Koebner reactions are mutually exclusive [5]. These observations suggest the presence of a circulating element controlling the expression of the disease throughout the skin, and lend support to the previous observation that serum from patients recovering from active psoriasis inhibits the Koebner reaction [7]. Using a standardized injury, one study found that 25% of patients gave a Koebner reaction and 67% a reverse Koebner reaction [5].

The Koebner reaction is often thought to be more frequent in actively spreading severe psoriasis. Although this may be true, it has yet to be established by prospective studies [1]. The reaction does, however, appear to be a marker for a subgroup of patients with a tendency to early onset and early relapse after various forms of therapy [8].

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Histopathology

Early changes

Vasodilatation, papillary oedema and leukocyte infiltrates appear to precede epidermal changes in early developing lesions [1]. Compact hyperkeratosis, disappearance of the granular layer and slight epidermal hyperplasia follow. Mitotic figures in keratinocytes, and leukocytic infiltration in spongiotic foci, are seen in the lower half of the epidermis. Scattered mounds of parakeratosis, set in a still predominantly orthokeratotic stratum corneum, appear, with or without neutrophils. In the Malpighian layer, neutrophils may accumulate to form the characteristic spongiform pustules of Kogoj (Fig. 35.3) [2]. Epidermal hyperplasia with rete ridges of even length and prominently dilated, tortuous papillary capillaries associated with mixed mononuclear and neutrophil infiltrates are seen [1,3].

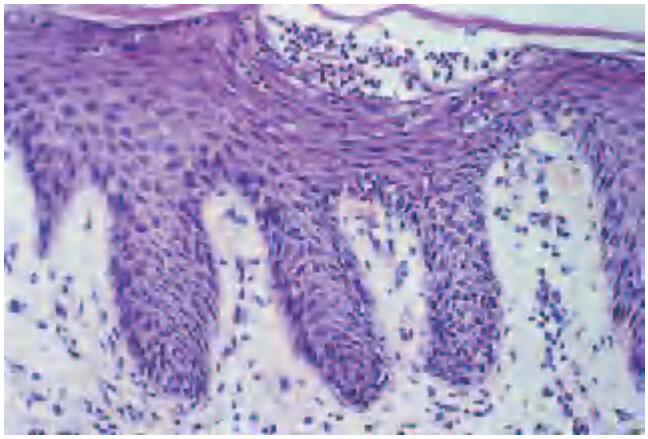

Fig. 35.3 Psoriasis: intra-epidermal spongiform pustule. H&E, × 100. (Courtesy of St John's Institute of Dermatology, London, UK.)

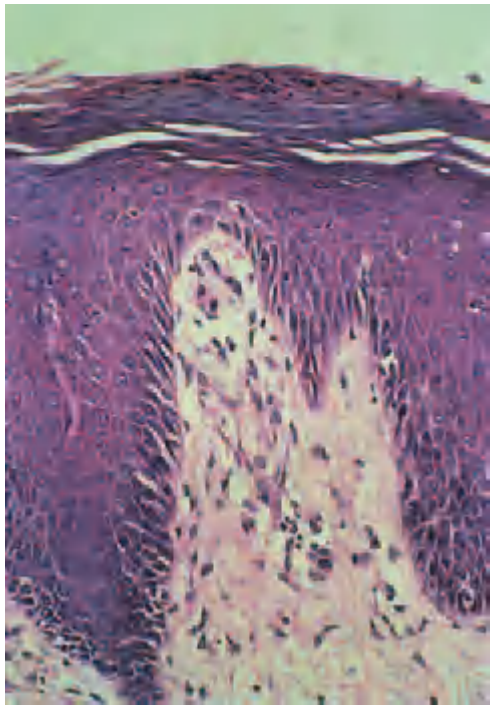

Fig. 35.4 Psoriasis: Munro microabscess formation in lesional stratum corneum. H&E, × 200. (Courtesy of St John's Institute of Dermatology, London, UK.)

Changes in fully developed plaques

There is parakeratosis associated with focal orthokeratosis and Munro microabscess formation (Fig. 35.4), near absence of the granular layer, spongiform pustules in the Malpighian layer [2], hyperplasia with elongation of rete ridges and suprapapillary epidermal thinning (Fig. 35.5). The rete ridges are often clubbed, branched or fused at their bases, with mononuclear leukocyte infiltrates in the lower half of the epidermis. Dilated, tortuous papillary blood vessels almost touch the undersurface of the thinning suprapapillary epidermis and are surrounded by a mixed mononuclear and neutrophil infiltrate, as well as extravasated erythrocytes. Invasion of the epidermis with leukocytes takes place particularly in the suprapapillary region [1,3,4].

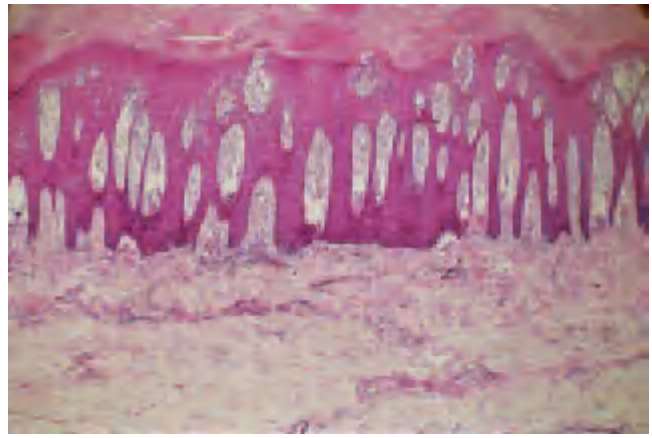

Fig. 35.5 Psoriasis: irregular epidermal hyperplasia with suprapapillary thinning. H&E, × 50. (Courtesy of St John's Institute of Dermatology, London, UK.)

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Clinical features

Modes of onset

The first manifestation of psoriasis may occur at any age. The common ages of onset, and the tendency for females to develop psoriasis earlier than males, are described above. Its duration may vary from a few weeks to a whole lifetime. The course is unpredictable and the variations numerous. Certain patterns are, however, more common than others.

The patterns of onset in childhood, including congenital psoriasis, are discussed below [1]. Acute guttate attacks characteristically occur in this age group. Nail changes may herald the development of psoriasis elsewhere, or remain localized for several years. Most forms of psoriasis present before the fourth decade, although pustular psoriasis of the palms and soles is extremely rare before adult life.

Post-traumatic psoriasis is not uncommon in young, athletic men, who develop psoriasis initially at the site

of injury, later elsewhere. Minor lacerations of the legs during shaving are believed to precipitate psoriasis in some women. Flexural varieties make their appearance either alone or following a pre-existing intertrigo from other causes. Flexural lesions become increasingly common in obese middle-aged subjects. Psoriasis entirely limited to the groins, perineal and perianal regions may develop insidiously and often remains undiagnosed for several years.

In old age, psoriasis may appear unexpectedly for the first time, either spontaneously or following a pre-existing skin disease. Onset at the age of 108 years has been reported [2].

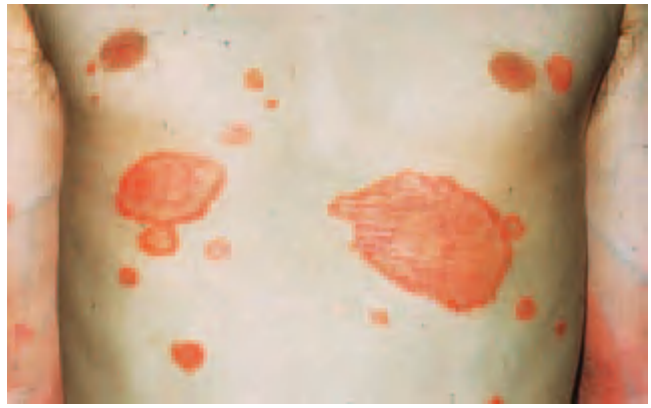

Fig. 35.7 The 'salmon pink' colour of psoriatic lesions. (Courtesy of St John's Institute of Dermatology, London, UK.)

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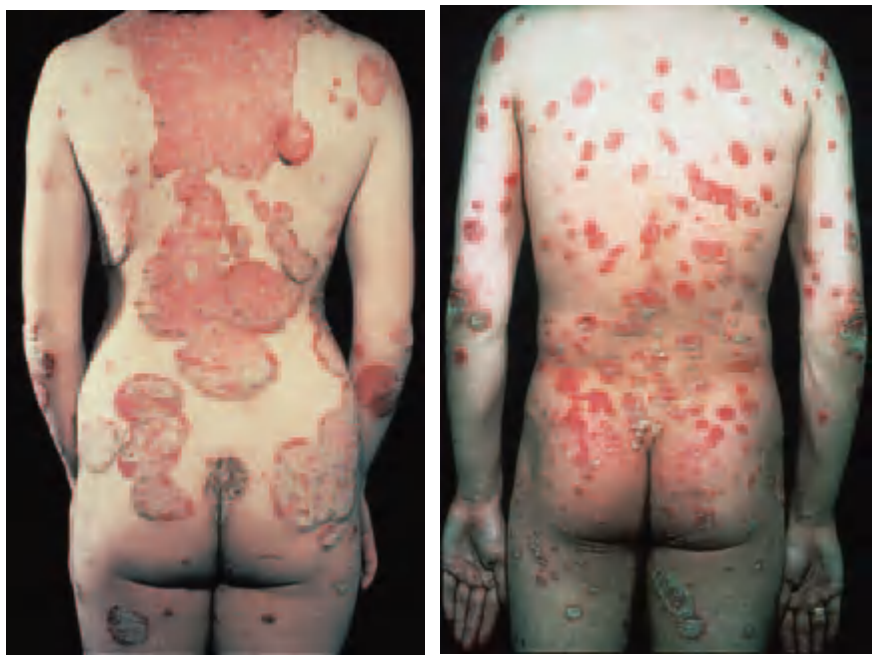
Morphology of common chronic stable plaque psoriasis (psoriasis vulgaris) [1,2]

The appearance of a typical lesion is characteristic (Fig. 35.6). The diagnostic features may not all be present at the same time or in every case, and are sometimes obscured or evanescent.

The colour, a full rich red (often referred to as 'salmon pink') (Fig. 35.7) has a particular depth of hue not normally seen in eczema, seborrhoeic dermatitis or lichen simplex. This quality of colour is of special diagnostic value in lesions on the palms, soles and scalp. On the legs, a bluish tint is often present, but this differs from the violaceous hue of lichen planus. In the fair-skinned individual, the colour is less rich and almost magenta pink. In dark-skinned races, the quality of the colour is lost (Fig. 35.8).

The amount of scaling is variable. It may, as in rupioid forms, be waxy yellow or orange-brown. A similar colour occurs in nails ('oil drop sign'), but most psoriatic lesions are surmounted by the very characteristic silvery white scaling, which varies considerably in thickness (Fig. 35.8). The successive removal of psoriatic scales usually reveals an underlying smooth glossy red membrane with small bleeding points where the thin suprapapillary epithelium is torn off (Auspitz's sign) (Fig. 35.9). When scaling is not evident, it may often be induced by light scratching, a useful sign in diagnostically uncertain lesions.



(a) (b)

Fig. 35.6 (a,b) Extensive chronic plaque psoriasis. (Courtesy of St John's Institute of Dermatology, London, UK.)

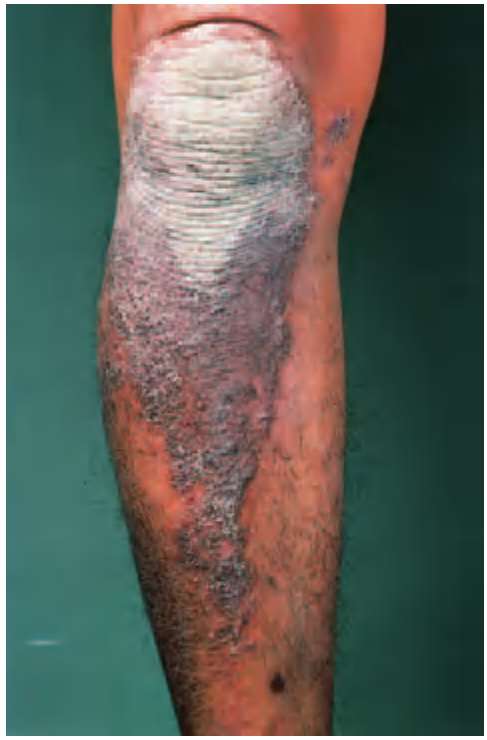


Fig. 35.8 Psoriasis: in the darker-skinned individual, the characteristic red colour is lost, although silvery scaling is readily seen. (Courtesy of St John's Institute of Dermatology, London, UK.)

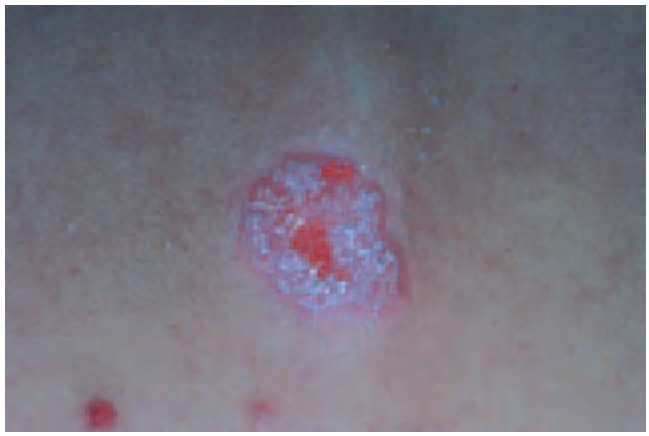


Fig. 35.9 Auspitz's sign: removal of the thinned suprapillary epidermis, by gentle scraping, reveals vascular bleeding points.

Psoriatic lesions exhibit a considerable degree of uniformity, modified little by site except on the palms and soles. The colour remains consistent, although the scaling varies in degree.

The lesions are well defined, with a sharply delineated edge. When they merge, annular and gyrate figures may be produced. This definition is of special diagnostic value on the scalp and penis, when other evidence of psoriasis is absent, and in the flexures.

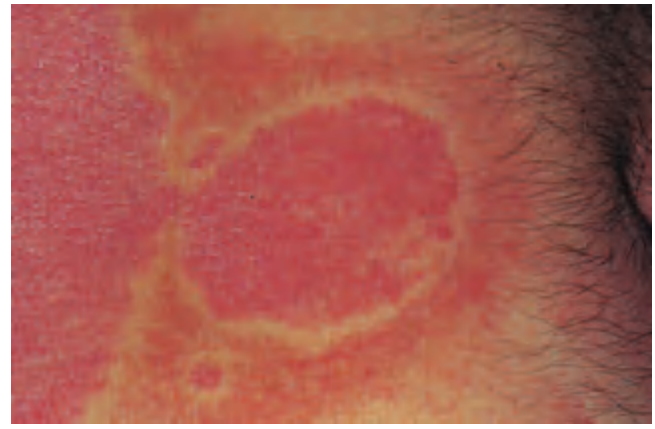


Fig. 35.10 Woronoff's ring: vasoconstriction around active plaques of psoriasis.

The epidermal thickening characteristic of the psoriatic process causes the lesions to be raised from the adjoining skin, and easily palpable. When the hyperkeratosis is removed by thorough washing or treatment, this character may sometimes be lost temporarily.

Discs and plaques of varying sizes are often found on the trunk and limbs. They vary in diameter from one to several centimetres and are oval or irregular in shape. There may be any number of lesions or only a single one and, when multiple, may be symmetrically distributed. Large plaques form by their coalescence and are commonly seen on the legs and sacral region. When plaques occur across the line of joint movement, fissuring may occur.

The psoriatic plaque may be encircled by a clear peripheral zone, the halo or ring of Woronoff (Fig. 35.10) [3].

Clinical variants

Guttate psoriasis

This describes the shower of small lesions, appearing more or less generally over the body, particularly in children and young adults, and after acute streptococcal infections (Fig. 35.11). In the early stages, there may be little scaling. The lesions are from 2 or 3 mm to 1 cm in diameter, round or slightly oval. They are scattered more or less evenly over the body, particularly on the trunk and proximal part of the limbs, rarely on the soles but not infrequently on the face, ears and scalp. The lesions on the face are often sparse, difficult to see and disappear quickly. Although guttate lesions are normally profuse, there are occasionally no more than half a dozen present on the body, and in the early stages the colour is not specific. The diagnosis is made chiefly on the nature of the scaling, the general distribution and evidence for preceding infection. In one series, only 1.9% of all affected psoriatics showed this form [2].

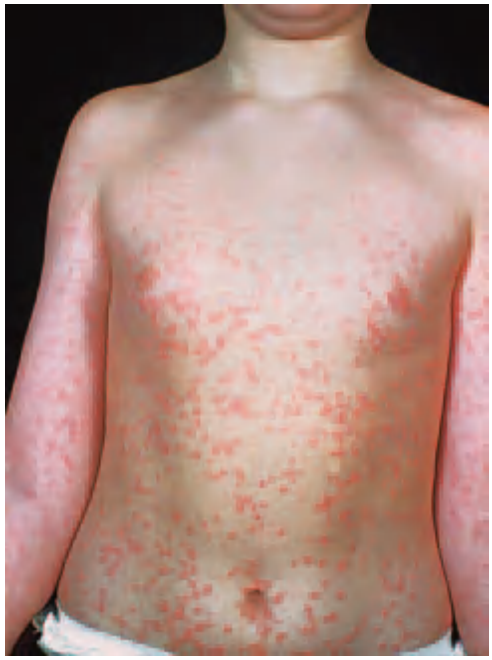


Fig. 35.11 Guttate psoriasis. (Courtesy of St John's Institute of Dermatology, London, UK.)

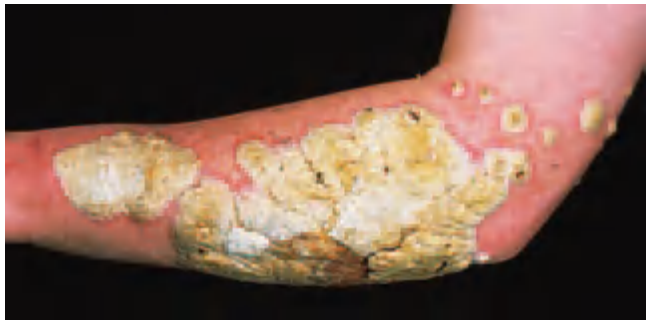


Fig. 35.12 Elephantine psoriasis: large plaques with gross hyperkeratosis. (Courtesy of St John's Institute of Dermatology, London, UK.)

Rupioid, elephantine and ostraceous psoriasis

These terms describe plaques associated with gross hyperkeratosis. Rupioid psoriasis refers to limpet-like cone-shaped lesions. The term elephantine psoriasis might be used to describe unusual but very persistent, thickly scaling, large plaques that sometimes occur on the back, limbs, hips or elsewhere (Fig. 35.12). Ostraceous psoriasis, an infrequently used term, refers to a ring-like hyperkeratotic lesion with a concave surface, resembling an oyster shell.

'Unstable' psoriasis

This term, which has no aetiological connotation, may be usefully employed to describe phases of the disease in which activity is marked and the course and immediate outcome unpredictable; for example, in stages when a previously stable and chronic form is exacerbated by inappropriate management and threatens to become erythrodermic or pustular, or when localized pustular or ill-defined erythematous lesions appear spontaneously for the first time. Patients may develop such unstable phases repeatedly, settling back again into the classical forms of the disease. Withdrawal of intensive systemic or topical corticosteroid therapy, hypocalcaemia, acute infection, overtreatment with tar, dithranol or UV irradiation, and perhaps severe emotional upset, may precipitate this condition.

Pustular psoriasis

See below.

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Erythrodermic psoriasis [1–3]

Two forms exist [4]. In the first form, chronic lesions may evolve gradually into an exfoliative phase, and can be regarded as extensive plaque psoriasis involving all, or almost all, the cutaneous surface (Fig. 35.13). There are usually some areas of uninvolved skin. The psoriatic characteristics are retained, mild treatment is well-tolerated and the prognosis is good.

The second form is part of the spectrum of 'unstable' psoriasis (Fig. 35.14). It may occur at any time, either presenting suddenly and unexpectedly, or be ushered in by a period of increasing intolerance to local applications, UV therapy, and of loss of control over the disease. It is more frequent in arthropathic psoriasis [5]. Generalized pustular psoriasis may revert to an erythrodermic state. It can be precipitated by infections, hypocalcaemia, antimalarials, tar [6] and classically by withdrawal of corticosteroids [7]. The characteristics of the disease are often lost, the whole skin is involved, the patient may be febrile and ill, the course is often prolonged, relapses are frequent and there is an appreciable mortality. In contrast to the stable form, itching is often severe.

Metabolic complications of erythroderma [2]

Persistent universal inflammation of the skin may have important consequences for thermoregulation, haemody-

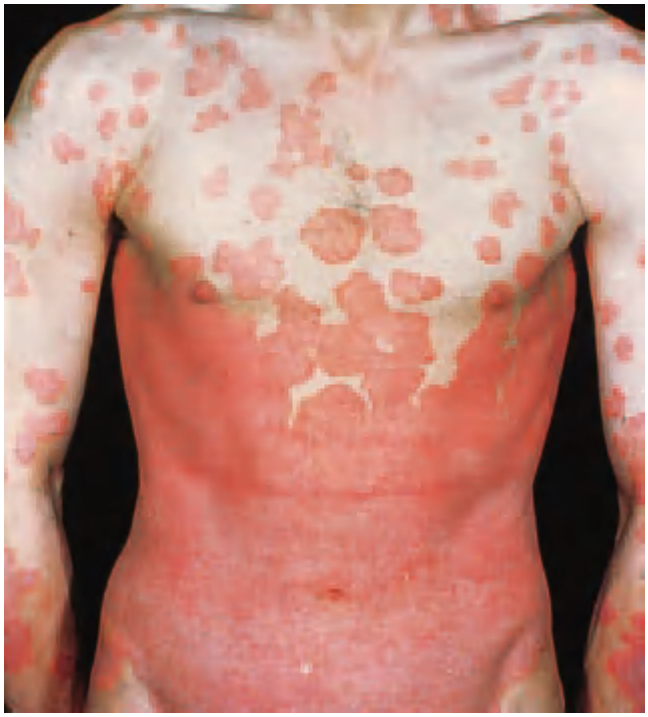

Fig. 35.13 Extensive chronic plaque psoriasis with coalescence of lesions and the potential to evolve into an erythrodermic form. (Courtesy of St John's Institute of Dermatology, London, UK.)

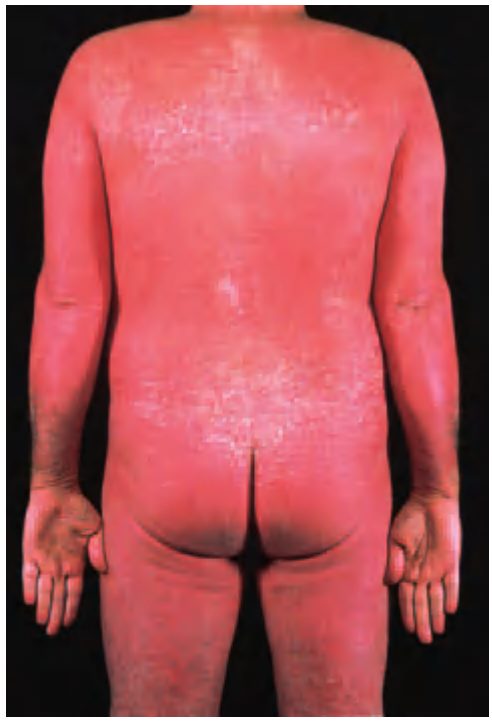

Fig. 35.14 Acute unstable erythrodermic psoriasis. (Courtesy of St John's Institute of Dermatology, London, UK.)

namics, intestinal absorption, protein, water and other metabolism.

Under normal environmental conditions, radiant and convective heat loss from the body surface is increased, occasionally leading to dangerous hypothermia [7]. An increase in metabolic activity provides compensatory increases in body heat production, but at the expense of tissue catabolism and muscle wasting if prolonged. At the same time, the psoriatic or erythrodermic skin is hypohidrotic or anhidrotic [8], because of intraepidermal occlusion of the sweat duct [9]. Hyperthermia is a hazard in very high (e.g. tropical) ambient temperatures.

Skin blood flow, blood volume and cardiac output may all be increased, and if these changes persist, they may lead to failure of a cardiovascular system already compromised by hypertension, myocardial or valvular heart disease, or anaemia (particularly in old people). A healthy cardiovascular system will tolerate the increased metabolic demand for years. Malabsorption (dermatogenic enteropathy) may occur, reverting as the psoriasis remits, but earlier reports of structural small bowel changes have not been confirmed [10].

The principal loss in the profuse scaling of exfoliative psoriasis is of protein (keratin) but some iron is also lost. In fulminating psoriasis, further protein loss may be attributable to enteropathy, as well as leakage from the circulation into the skin [11]. Eventually, hypoalbuminaemia may contribute to the oedema caused by the skin inflammation itself, or cardiac failure. Mild anaemia is prone to develop, because of a combination of iron loss and possibly impaired absorption and utilization of iron. Serum and red cell folate and serum B_{12} may also be low.

The barrier efficiency of the skin in psoriatic erythroderma is impaired, the chief effect being increased transepidermal water loss. The urine output tends to drop and, if water intake is inadequate for any reason, dehydration results.

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Modification by site

Scalp

Often, very thick plaques develop, especially at the occiput. The whole scalp may be diffusely involved, or multiple discrete plaques of varying size may be seen [1]. A morphological entity consisting of plaques of asbestos-like scaling, firmly adherent to the scalp and associated hair, has been termed pityriasis (tinea) amiantacea [2] (Fig. 35.15). It is most common in children and young adults, and is best regarded as a non-specific reaction pattern, which may be seen in other scaling scalp conditions. It may be an early manifestation occurring before the other stigmata of psoriasis. Hair loss, sometimes cicatricial, is seen in pityriasis amiantacea. Otherwise, common scalp psoriasis is not a frequent cause of alopecia, although it may occur [3]. Psoriatic erythroderma is associated with severe hair loss, as is vigorous local treatment. Hair-shaft abnormalities have been described on electron microscopy [3], but the rate of hair growth is normal [4].

Penis (Fig. 35.16)

A solitary patch on the glans of the uncircumcised male lacks scales, but its colour and well-defined edge are usually distinctive. Where confirmatory signs elsewhere are absent, a diagnostic biopsy may be necessary, as it may resemble erythroplasia or Zoon's plasma cell balanitis (see Chapter 68).

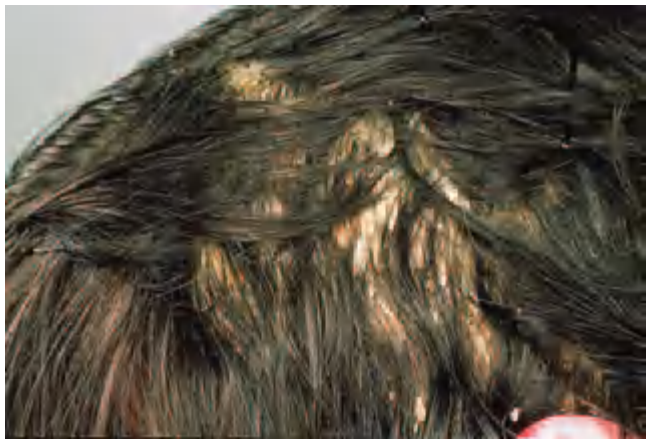

Fig. 35.15 Pityriasis amiantacea in a patient with psoriasis. (Courtesy of St John's Institute of Dermatology, London, UK.)

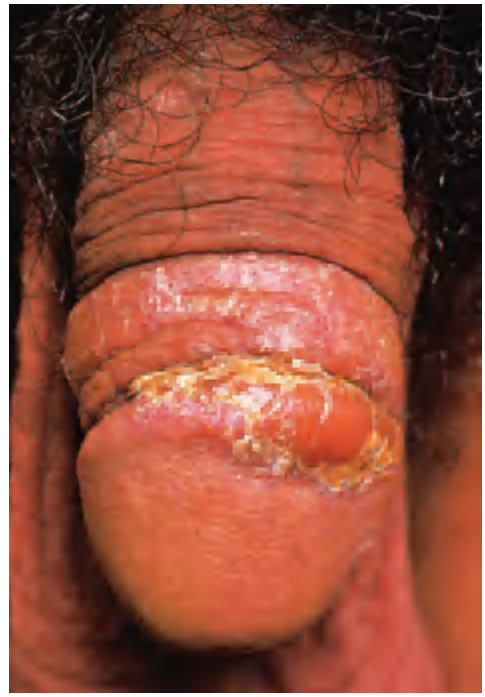

Fig. 35.16 Psoriasis: circumcised penis. (Courtesy of St John's Institute of Dermatology, London, UK.)

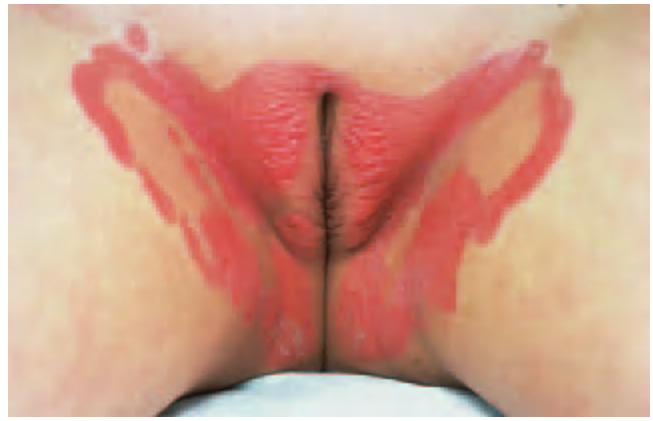

Fig. 35.17 Psoriasis: vulval region. (Courtesy of St John's Institute of Dermatology, London, UK.)

Flexural (inverse) psoriasis

Psoriasis involving the groins, vulva (Fig. 35.17), axillae, submammary folds, gluteal cleft and other body folds is more common in older adults than children. The frequency with which the genital area alone is involved appears to be low, but this area is not uncommonly involved together with other areas [5].

Scaling is greatly reduced or absent, and an assured diagnosis may therefore be difficult. Flexural psoriasis may occur as a primary disorder or as a Koebner phenomenon on top of infective or seborrhoeic intertriginous

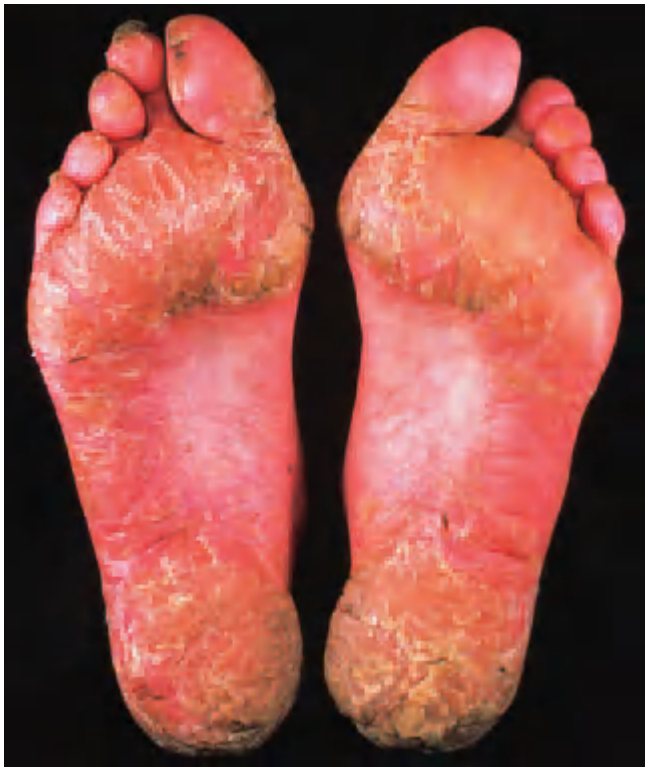

Fig. 35.18 Psoriasis of soles. (Courtesy of St John's Institute of Dermatology, London, UK.)

dermatoses. Failure to respond to antibacterial or antifungal preparations should arouse suspicion. Although the lesions are themselves anhidrotic [6], the effect of hyperhidrosis of the surrounding skin, maceration and friction alter the appearance of the psoriasis, which retains its characteristic colour. The surface has a glazed hue and fissuring at the depth of the fold is common, especially in the gluteal cleft. The edges of the lesions are usually well-defined, unless secondary infection or medicament dermatitis, both quite common events, have occurred. Psoriasis of the retro-auricular fold or the external auditory meatus may be particularly difficult to distinguish from infective or seborrhoeic dermatitis.

Hands and feet [7]

On the palms and soles (Fig. 35.18), psoriasis may present as typical scaly patches on which a fine silvery scale can be evoked by scratching; as less well-defined plaques resembling lichen simplex or hyperkeratotic eczema; or as a pustulosis. Mixed forms occasionally occur. It may often be difficult to distinguish the psoriasis from eczema, with which it may sometimes alternate. A sharply defined edge at the wrist or forearm (Fig. 35.19) and absence of vesiculation are helpful. On the dorsal surface, the knuckles frequently show a dull red thickening of the skin. Elsewhere on the hands and feet, psoriasis retains its typical

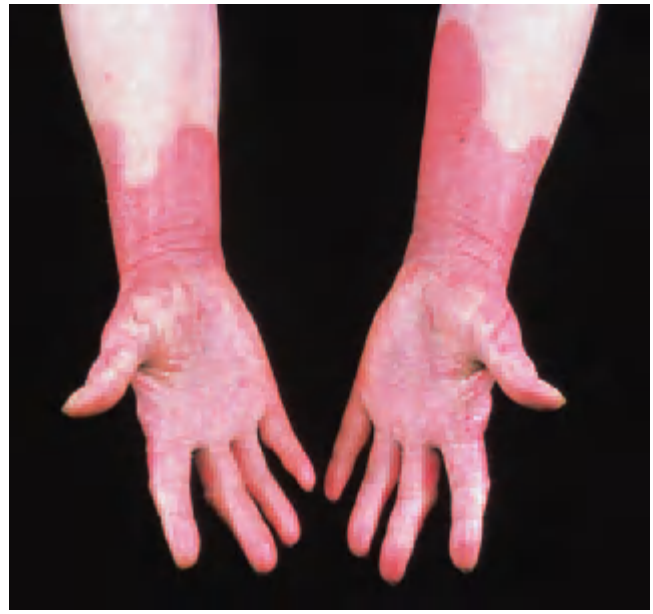

Fig. 35.19 Psoriasis of palms and fingers with sharply demarcated edge on forearms. (Courtesy of St John's Institute of Dermatology, London, UK.)

character. There may be a relationship to trauma or occupational irritants.

Nail involvement [8,9]

This is seen in association with all types of psoriasis of the skin, and is frequently present with psoriatic arthropathy [10,11]. Figures for its incidence vary considerably. Minor degrees of involvement (e.g. pitting) are difficult to define and may occur in apparently normal subjects. If looked for carefully, nail changes are present in 25–50% of all cases [12]. There is no sex predilection, but patients over 40 years of age are affected twice as often as those under 20 years. A recent study has shown that nail disease is more likely to be severe if psoriasis is early onset and familial [13].

Although pitting (Fig. 35.20) is the most frequent change seen, discolouration, subungual hyperkeratosis (Fig. 35.21) and onycholysis are common, and splinter haemorrhages occur. Longitudinal biopsy of the nail bed and matrix has clarified understanding of these changes [14,15]. Pits, ridges and grooves are a result of psoriasis of the nail matrix, whereas onycholysis, subungual hyperkeratosis and splinter haemorrhages are attributable to disease of the nail bed or hyponychium [16]. Circular areas of discolouration of the nail bed and hyponychium may resemble an 'oil drop' below the nail. Histologically, these are areas of psoriatic change in the hyponychium [14]. *Candida* species frequently contaminate the psoriatic nail and bed, but dermatophytes are rare. In one series, 19 of 105 patients with candidal paronychia were found to have psoriasis [17].

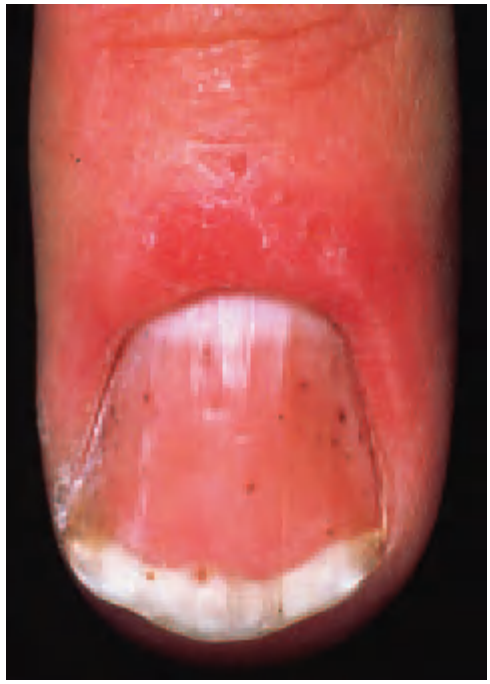

Fig. 35.20 Fingernail pitting in psoriasis. (Courtesy of St John's Institute of Dermatology, London, UK.)

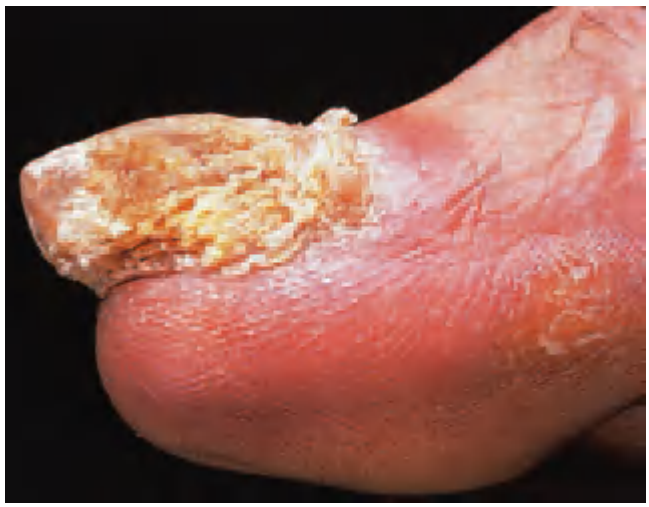

Fig. 35.21 Subungual hyperkeratosis in psoriasis. (Courtesy of St John's Institute of Dermatology, London, UK.)

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Psoriasis in children [1–4]

Psoriasis is quite common in children, although congenital psoriasis is very rare [5]. Guttate psoriasis is discussed below. Apart from the common forms, several other patterns of psoriasis occur in childhood. Interdigital tinea is uncommon in children and a toe cleft intertrigo may be psoriatic. Other flexural forms also occur (Fig. 35.17). The disease may mimic chronic blepharitis or perleche, usually unilaterally, with a small plaque of psoriasis on one eyelid extending to the lid margin, or on the cheek at the angle of the mouth. Psoriasis involving the face appears more common in children than adults [6]. In an Australian study of 1262 children with psoriasis, 26% had a psoriatic rash in the napkin area and facial involvement occurred in 38% [7]. The disease often first appears in the scalp [4], where it may present as pityriasis amiantacea (Fig. 35.15). An indolent pustular acrodermatitis, sometimes of only one digit, usually eventually proves to be psoriatic. More extensive chronic lesions of the hands and feet may occur with persistent dryness, hyperkeratosis and fissuring. Pitting of the fingernails may be the only manifestation for months or even years. Follicular psoriasis occurs on the extensor prominences of elbows and knees. A child with apparently true psoriasis in a unilateral linear distribution has been reported [8].

All the more serious forms of the disease occur in childhood but are rare. Erythrodermic psoriasis [9] may be intractable for years and may or may not become pustular. Generalized pustular psoriasis is well documented in childhood [10,11]. Arthropathic psoriasis is rare but has been reported.

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Atypical forms [1,2]

In a disease as common and variable as psoriasis, atypical forms are obviously frequent. Many unusual localizations have been recorded, including digital and interdigital forms. Verrucous lesions particularly affect the legs. A follicular form, especially in children, may be confused with pityriasis rubra pilaris but this form seems to be more common in the elderly [3,4]. A lichenoid variety has been reported to involve the flexures or the extremities in a 'glove and stocking' distribution [5].

Linear and zonal lesions

Linear psoriasis may occur in the presence of other typical lesions, as part of the Koebner phenomenon. Zonal lesions may represent a Koebner reaction at a site of herpes zoster. True linear psoriasis in the absence of lesions elsewhere is extremely unusual. It may be confused with inflammatory linear verrucous epidermal naevus (ILVEN) (see Chapter 15) or may occur as a Koebner response on verrucous epidermal naevi of the non-inflammatory type [5]. True psoriasis arranged in linear bands unilaterally has also been described [6].

'Seborrhoeic psoriasis'

There is no reason why a genetically constituted psoriatic should not develop seborrhoeic dermatitis. Lesions involving the scalp, eyebrows and the region of the ears are often of this type, having features of both diseases or changing during the course of observation. Difficulties also occur in the flexures as in the 'napkin psoriasis' of infants [7] and in obese, middle-aged or elderly patients.

Mucosal lesions

True mucosal involvement by psoriasis appears to be rare, but has been associated with cutaneous involvement by pustular, erythrodermic and plaque forms [8–12]. Various lesions have been described, including grey, yellowish, white or translucent plaques or annular forms, diffuse areas of erythema and the geographic tongue [8,10,12]. The association of both psoriasis and geographic tongue (benign migratory glossitis) with HLA-Cw6 provides further evidence that the two disorders are related [13].

Ocular lesions

Blepharitis, conjunctivitis, keratitis, xerosis, synblepharon and trichiasis have been recorded. Chronic uveitis has been found, particularly in patients with psoriatic arthritis [14]. Uveitis was also reported in patients with generalized pustular psoriasis or psoriatic arthritis, who were receiving treatment with methotrexate. It was unclear whether methotrexate contributed to the ocular lesions [15].

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Disease associations

Studies have reported association between psoriasis and many other diseases, both cutaneous and systemic. The most frequently described is seronegative arthritis and this is discussed elsewhere.

Henseler and Christophers [1] analysed data from more than 40 000 patients and calculated expected and observed

incidence rates of associated disorders. For many diseases, particularly heart disease, hypertension and diabetes mellitus, they were able to confirm the results of smaller earlier studies showing positive association. Of particular note was the under-representation of patients with atopic dermatitis within the psoriasis population.

Although not observed in the above study, an increased prevalence of psoriasis in patients with Crohn's disease (relative risk = 7) has been reported. Further, a family history of psoriasis (10% versus 2.9% in controls) was frequently observed in Crohn's disease patients [2,3]. These observations of altered relative risk for atopic dermatitis and Crohn's disease in psoriasis patients may be of great relevance to understanding the genetic and immunological mechanisms underlying these important conditions.

Patients with psoriasis are at an increased risk of developing malignancy, particularly non-melanoma skin cancer and lymphoproliferative cancers. The risk is greatest for those with severe disease and probably reflects those treated with systemic agents and phototherapy [4]. There is no good evidence that psoriasis, *a priori*, is associated with an increased incidence of malignancy.

Acquired autoimmune blistering diseases have been reported in association with psoriasis, particularly bullous pemphigoid [5]. Based on a small series of patients, it has been suggested that treatment of psoriasis, especially phototherapy, triggers the bullous disease. Vitiligo is a further cutaneous autoimmune disease seen more frequently in psoriasis [6].

Psoriasis has been reported rarely to occur more frequently in certain metabolic disorders including gout [7], although whether this is a true association requires formal epidemiological study. It has been suggested that gout may be precipitated by systemic antipsoriatic therapy [8]. Hypocalcaemia has been reported in association with severe and pustular forms of psoriasis, including certain syndromes [9] and following thyroidectomy [10].

Chronic recurrent multifocal osteomyelitis is an unusual sterile inflammatory entity of unknown cause, characterized by pain and swelling in affected bones. Association with pustular and non-pustular forms of psoriasis has been reported [11,12]. Closely related to this entity is the SAPHO (synovitis, acne, pustulosis, hyperostosis, osteitis) syndrome most frequently described in the radiological and rheumatological literature [13].

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Complications

These are uncommon.

Infection

Secondary infection of psoriatic lesions is rarely a problem except during topical steroid therapy under occlusive dressings, when folliculitis and furunculosis are a hazard. However, staphylococci are carried by 50% of psoriatics, especially on the lesions [1]. This relative 'resistance' of psoriatic skin to infection despite the carriage of staphylococci is probably in part caused by the presence of endogenous antimicrobial peptides—cathelicidins and β-defensins—in the skin [2]. This may prove to be a problem if a surgical procedure is to be carried out through a psoriatic plaque. Because of exfoliation, these patients may disseminate infections in hospital wards. A series of postoperative deaths resulting from sepsis was caused by a psoriatic anaesthetist carrying *Staphylococcus aureus* [3]. Rarely, flexural psoriasis may become clinically infected, especially if fissuring occurs (e.g. in the natal cleft).

Itching

This is very variable in psoriasis, ranging from complete absence to severe pruritus in a minority of patients. It is more common in unstable forms. One study from Poland reported that 80% of patients complain of itching [4]. Pustular and erythrodermic patterns are more usually accompanied by sensations of burning or tightness. Often, the degree of itching reflects the emotional state of the patient and, if severe, may be a symptom of anxiety or depression.

Arthritis

See below.

Alcoholism

Heavy drinking was found significantly more commonly in male patients with severe psoriasis than in other groups with the disease, and could be a symptom of stress caused by severe skin disease [5,6].

Nephritis and renal failure

The role of streptococcal infection, especially in the throat, in provoking acute guttate psoriasis is discussed above. It is exceptionally rare for post-streptococcal guttate psoriasis to be associated with glomerulonephritis. One such case has been reported [7], as well as a case of concomitant onset of diffuse psoriasis and mesangiocapillary glomerulonephritis [8]. Renal failure brought about by acute tubular necrosis may rarely result from the oligaemia after loss of albumin into and from the skin in acute pustular psoriasis [9].

Hepatic failure

Severe abnormalities of liver function may occur in erythrodermic or pustular psoriasis, and are likely to be related to drugs, alcohol intake and oligaemia [5,6,10,11].

Apical pulmonary fibrosis

This has been established as a non-articular complication of ankylosing spondylitis, and has been reported in association with a case of psoriatic spondylitis [12]. Two further patients with chronic plaque psoriasis, one with peripheral arthropathy and one free of joint disease, have been reported with apical pulmonary fibrosis typical of that found in association with ankylosing spondylitis. Extensive investigations and follow-up observation showed no evidence of other disease [13].

Amyloidosis

Amyloidosis of the secondary type is a rare sequel of arthropathic, generalized pustular and severe non-pustular psoriasis [14–17]. It is an additional cause of renal failure in association with psoriasis, and may follow an aggressive fatal course [16].

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Laboratory findings

There is no constantly present laboratory abnormality in uncomplicated psoriasis. The erythrocyte sedimentation rate (ESR) is unaffected. Modest hyperuricaemia may be found and has been attributed to enhanced epidermopoiesis. The occasional finding of low folate levels can be similarly explained [1]. The laboratory abnormalities associated with erythrodermic psoriasis and arthropathic psoriasis are described in the relevant sections. Immunoglobulins are generally normal, but selective IgA deficiency [2] and monoclonal IgG gammopathy [3] are documented in association with psoriasis.

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Differential diagnosis

The characteristics already defined are usually sufficient to enable the diagnosis to be made, but doubt may arise in atypical cases, in particular sites, and when psoriasis is complicated by or alternates with other diseases. In seborrhoeic dermatitis, the lesions are lighter in colour, less well-defined and covered with a dull or branny scale. Eczema at times develops a psoriasiform appearance, especially on the legs. Hyperkeratotic eczema of the palms is a common cause of misdiagnosis. Colour, scratch-evoked scaling and well-defined margins are suggestive of psoriasis, and nail changes may be diagnostic. Lichen planus should give rise to difficulty only when the two

diseases alternate or coexist, especially when present as hypertrophic lesions on the legs, as penile lesions and on the palms. The violaceous colour, glistening surface and presence of oral changes are usually decisive. Lichen simplex can resemble psoriasis closely, particularly on the scalp and near the elbow. The intensified skin markings, rather ill-defined edge and the marked itching are characteristic, and the point of the elbow tends to be avoided. Pityriasis lichenoides chronica can closely resemble guttate psoriasis, but the lesions are usually less evenly scattered, have a brownish red or orange-brown colour and are capped by an opaque soft 'mica-like' scale. Candidiasis shows a glistening deep red colour suggestive of psoriasis, particularly in the flexures, but scaling tends to be confined to the edge, and small satellite pustules and papules are usually evident outside the main area. Tinea cruris has a well-defined, often polycyclic edge, but *Trichophyton rubrum* infections, especially of the palm, cause difficulty. If corticosteroids have been applied, scaling may be absent and the diagnosis must be made by microscopy and culture.

Less common causes of confusion are pityriasis rubra pilaris and secondary syphilis. The resemblance to pityriasis rubra pilaris may be close, especially in the erythrodermic phase. The colour is generally less distinct, and dark red follicular lesions are apparent, and the acquired palmar and plantar keratoderma has a yellow-orange tinge. The psoriasiform lesions of syphilis may cause difficulty to the inexperienced; condylomas, mucosal lesions and other signs of the disease are usually found, if sought. Porokeratosis of Mibelli on the palms and soles, patches of Bowen's and Paget's disease and penile erythroplasia may resemble psoriasis, but the lesions are usually solitary except in chronic arsenical poisoning. A biopsy may be necessary. The rare recurrent circinate erythematous type of psoriasis of Bloch and Lapiere may pose considerable diagnostic difficulties. It is to be distinguished from erythema annulare centrifugum, and from the annular migratory necrolytic erythema associated with carcinoma of the pancreas [1], and sometimes with subcorneal pustular dermatosis. The distribution, course and histology will usually be sufficiently decisive to distinguish these. Psoriasiform drug eruptions must be distinguished from psoriasis.

Parakeratosis pustulosa is an eczematoid eruption seen in young children and commonly mistaken for psoriasis, atopic dermatitis or tinea. It affects the skin around one or more fingernails or toenails, causing subungual hyperkeratosis and thickening of the free edges of the nail. Scaling is more marked than pustulation, the course is often protracted and recurrences are the rule, whatever the treatment. A large series has been reported [2]. Histology shows hyper- and parakeratosis, acanthosis, papillomatosis and a marked infiltrate around dilated capillary loops [3].

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Course and prognosis [1–5]

This remains as unpredictable as it was 150 years ago. 'Psoriasis is at all times and under all forms a very troublesome and, often, an intractable disease, but it is rarely dangerous to life' [6]. 'It is impossible to say, in any particular case, how long the disease will last, whether a relapse will occur, or for what period of time the patient will remain free from psoriasis' [7]. Guttate attacks carry a better prognosis than those of a slower and more diffuse onset, and have longer remissions after treatment [3]. Few studies have assessed the long-term prognosis for first episodes of guttate psoriasis. In one study, only five (33%) of 15 patients followed up 10 years after an initial episode of guttate psoriasis had developed chronic plaque disease [8]. At the other extreme, erythrodermic and pustular forms carry an appreciable mortality and arthropathic forms a considerable morbidity. Early onset and a family history of the disease appear to worsen the prognosis [2].

Among environmental factors, sunlight and hot weather are favourable [1,2,4]; pregnancy had no effect in approximately half of patients [2,4], but improvement was more common than worsening. The influence of stress or 'worry' is more difficult to determine. Patients' beliefs on the importance of stress are probably dependent on cultural and linguistic differences. Sixty per cent of patients studied in Manchester, UK, believed that stress was an important trigger of their psoriasis [9]. In one series [10], 50% reported worsening with 'worry', in others 33–42% reported worsening [1,4]. Common experience suggests that stress is of considerable importance in some patients, but may be too easily accepted as a general cause of variations in this disease.

Complete remissions of psoriasis over 1–54 years were reported by 39% of patients in a large series [4], often without treatment. An even higher figure applied to Japan [11], but lower figures are also quoted [12].

In one follow-up study of 'napkin psoriasis', two out of 67 had developed true psoriasis in 5.4 years [13]; four developed seborrhoeic dermatitis. In another study [14], 123 infants were reviewed 5–13 years later. Of 71 who had shown psoriasiform napkin eruptions, 12 had developed psoriasis; of 40 who had a predominantly seborrhoeic pattern of flare, none had shown later signs of psoriasis but 15 (37%) had atopic eczema. Most of the psoriatic cases occurred within the first 3 months of life.

Relapse

Relapse is the rule, however completely the lesions are treated and by whatever method. Only three of 260 patients in one series [2] were clear for 5 years or more and most of the rest for only 6 months. In another series [15], only three out of 95 were clear for 5 years or more and 11.5% relapsed rapidly. A 7-year follow-up of 142 patients [3] indicated that intensive outpatient treatment gave longer remissions than those treated at home, or the presumably more severe cases admitted to hospital. Guttate lesions had the best prognosis.

There is no doubt that even severe cases can be maintained in prolonged remission by the use of methotrexate, PUVA, ciclosporin or oral retinoids.

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Management

Every psoriatic patient presents an individual problem. Treatment depends upon age, sex, occupation, personality, general health, intelligence and resources, as well as the type, extent, duration and natural history of the disease. Extensive psoriasis may be ignored by the phlegmatic, yet trivial lesions on exposed areas can be ruinous for the sales executive or artiste. With this in mind, an assessment tool for psoriasis severity has been developed —the Salford Psoriasis Index—which takes into account physical extent of disease, psychosocial difficulty and previous therapy as a means of measuring difficulty in treatment [1]. Reassurance and emotional support are invaluable, stressing the non-contagious and benign nature of psoriasis, the possibility of spontaneous remission, and the availability of a wide range of therapeutic weapons for all psoriatic seasons. Fears for the future of children need to be allayed. The physician must take a long-term view. Treatment must always be appropriate to its severity and importance in that individual. It should never be more unpleasant, intolerable or dangerous than the disease itself. Its details must be commensurate with the patient's intelligence, physical capacity, time and socio-economic circumstances.

General and non-specific measures

Attention to the patient's general, physical and psychological health is always worthwhile. Mild anaemia, minor but untreated arthritis, an anxiety state or depression, especially in the elderly patient, may all critically lower the patient's tolerance of his or her disability. Physical extent of psoriasis and psychosocial disability produced by the disease do not correlate [2]. Rest, mild sedation, removal from a troublesome environment, a holiday or a short stay in hospital may all help to turn the therapeutic tide. The importance of talking to patients, trying to allay their concerns, coupled with advice on how to handle negative beliefs about their disease cannot be overestimated. A study of cognitive–behavioural therapy (CBT) as an adjunct to pharmaceutical therapies in patients with psoriasis showed a significantly greater reduction in psoriasis severity in the CBT group as compared to pharmaceutical therapy alone, both at the end of 6 weeks' intervention and 6 months later [3]. Indeed, high worry appears to have a significant detrimental effect on response to PUVA therapy and is the best predictor of outcome [4]. Harmless placebos may give comfort and should not be despised.

Diet is unimportant. Diets rich in zinc [5] and turkey meat [6] or low in tryptophan [7], protein [8] or calories [9] do not influence the disease. Spa treatment, involving rest and relaxation in an area where high sunlight exposure is possible, such as the Israeli Dead Sea coast, can undoubtedly induce remissions [10].

General approach

Most stable discoid psoriasis should first be approached with outpatient topical therapy, which disrupts the patient's routine as little as possible. Tar preparations and vitamin D analogues are appropriate, but corticosteroids can be used for localized psoriasis. If necessary, dithranol can be introduced later but is more difficult to handle. If sunlight or UVB phototherapy are available, light can be added at this stage or earlier. Special routines may be necessary for the scalp. If the psoriasis is severe and

extensive and the above initial measures have failed, more intensive tar or dithranol therapy should be considered, in a day-care unit or a hospital if such facilities exist, with or without UV phototherapy. The indications for intralesional corticosteroid injections, PUVA therapy, retinoids, cytotoxic drugs and ciclosporin are discussed in the appropriate sections below but, in general, the more hazardous measures should be restricted to those patients whose psoriasis is physically, socially, economically or emotionally disabling, and in whom conventional and conscientious topical therapy has failed. Each of the available modalities is discussed in detail below. The management of psoriatic erythroderma has been reviewed [11].

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Local therapy

Tar [1,2]

Coal tar is a complex mixture of thousands of substances produced by primary condensation during the carbonization of coal [3]. Some 400 known substances comprise 55% of tar by weight [2,3]. Standardization is impossible and, because great variation in biological activity of various samples of tar has been demonstrated [4], therapeutic results achieved in different centres may not be comparable.

Tar has been used in topical therapy for more than a century. It is assumed to have an antimitotic effect but this is not proven [5]. Its use in psoriasis was popularized by Goeckerman [6] and, for more than half a century since, his regimen of daily application of 2–5% crude coal tar, combined with a tar bath and UV light, has been a mainstay of in-patient treatment [7]. In skilled hands, substantial clearing of stable discoid psoriasis can be achieved in 3–6 weeks in 80% of patients [7]. Many modifications of Goeckerman's regimen have been advocated, utilizing alcoholic extracts of tar (e.g. coal-tar solution) in cream or ointment bases, tar gels [8], etc., which are 'cleaner' and easier to handle, but it seems that the cruder the tar extract, the more effective it is [2]. Concentrations of coal-tar solution up to 10% can be incorporated in various vehicles for outpatient therapy, and many commercial creams, lotions, ointments, gels and shampoos containing tar extracts are available throughout the world.

Controversies surrounding the roles of tar and UV light have not yet been fully resolved [2]. Tar alone is certainly active in psoriasis [9], as is UVB alone [10]. Coal tar seems to sensitize the skin to UVA but not to UVB [11] and phototoxicity is of photodynamic type [12,13]. Nevertheless, UVB is more valuable than UVA in conjunction with tar [14] and probably UVB erythema thresholds prevent UVA exposure sufficient to cause photosensitization in the Goeckerman regimen [15].

Despite a huge literature, it is remarkably difficult to quantify success rates with tar regimens in terms of percentage of patients cleared, the number of days of treatment needed to achieve clearance or the length of remission [2,7]. Only one placebo-controlled trial of coal tar was found in a recent systematic review [16]. This short 4-week trial showed that 5% liquor carbonis detergens was more effective than emollient vehicle [17]. Exorex®—a new formulation of 1% coal tar in esterified fatty acids was no more effective than crude coal tar in a head-to-head comparative study [18]. Recent attempts at short-contact crude coal-tar treatment have shown that daily 1-h applications of 30% crude coal tar in yellow soft paraffin are effective in improving psoriasis, but less so than daily 23-h treatment with 5% crude coal tar in yellow soft paraffin. It was concluded that the former has no place in in-patient management, but that it may have a limited role in certain outpatients [19]. A combination of 5% crude coal tar and dithranol was found to be as effective as dithranol alone when used in short contact treatment of psoriasis, but was recommended in preference to the latter, as less irritancy was encountered [20]. Others have found that tar and dithranol combination regimens do not enhance the clearance rate of psoriasis and that they offer little benefit over dithranol alone [21,22].

The safety of tar has been regarded as one of its great virtues. In spite of the evidence that increased levels of 1-hydroxypyrene, polycyclic aromatic hydrocarbons and mutagenic activity (as determined by the Ames plate assay) may be detected in the urine of patients following 3 days of therapeutic exposure to coal tar [23], systemic toxicity is unknown. Primary irritation is uncommon except in unstable psoriasis, and on the face, genitalia and in the flexures. Allergic contact dermatitis does occur, but

is rare. Folliculitis is the most common side effect. Notwithstanding the undoubted carcinogenicity of coal tar in the skin of experimental animals [24] and human workers chronically exposed to tar, long experience dictates that the risk from therapeutic tar products is small [1,24]. There are certainly case reports of various scattered skin tumours developing in patients treated previously with tar [25–27], but some of these patients had been exposed to other known carcinogens. Reports of carcinoma at the site of local coal-tar treatment are few but significant [28–31]. It may, therefore, be wise to avoid prolonged application of coal tar to the anogenital area, including the scrotum, sites that have been involved in at least two case reports. In spite of negative results in several other series [32–34], a case–control study has shown that there was a significantly greater risk of skin cancer in psoriatic patients treated with high-exposure coal tar and UV light therapy, than in matched patients treated with smaller dosage therapy [35]. This association was confirmed by further epidemiological studies in which patients receiving multiple Goeckerman regimens were compared with age- and sex-matched controls [34]. Another study involved 719 psoriatic patients in the west of Scotland, all of whom had received intermittent topical coal-tar therapy over a 10-year period, but no cytotoxic drugs, ionizing radiation or prescribed UV radiation. No increase in malignancy of skin, bladder or any other organ was found in the psoriasis patients over that in the general population [35]. The increased incidence of malignancy [36,37] may, therefore, depend on exposure to high-dose UVB. It would therefore appear prudent to place patients who have received repeated intensive Goeckerman regimens under careful surveillance. The benefits of repeated Goeckerman regimens in patients with difficult psoriasis may, however, outweigh the risk of skin malignancy, which should be easy to detect and treat.

Other contraindications to tar therapy do exist. Erythrodermic or generalized pustular psoriasis will infrequently tolerate even the weakest tars. Pre-existing folliculitis or severe acne are also possible contraindications.

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Dithranol (anthralin) [1,2]

The value of chrysarobin, a tree-bark extract, in psoriasis was discovered accidentally [3] a century ago. A synthetic derivative, dithranol (1,8-dihydroxy-9-anthrone) was

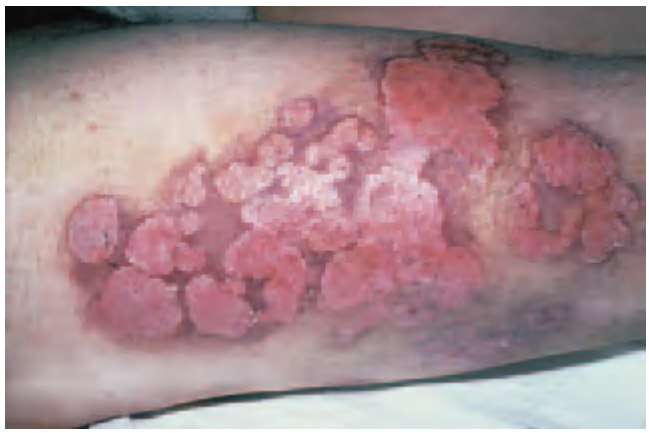

Fig. 35.22 Psoriasis partially treated with dithranol, showing brownish staining. (Courtesy of St John's Institute of Dermatology, London, UK.)

introduced by Unna in 1916 [4] but is unstable. The role of salicylic acid in stabilizing dithranol formulations was also an accidental discovery, and led to the development of the Ingram regimen [5], which has played a central part in psoriasis management since, especially in Europe. After a tar bath in which scales and the previous applications are removed, suberythema UVB is given, and the lesions then precisely covered with dithranol paste. The initial concentration is 0.05 or 0.1%, increasing cautiously up to 4% according to response, and aiming to avoid irritation of the normal or psoriatic skin [5–7]. The paste is kept in position with tubular gauze or stockingette. After 18–22 h, the cycle is repeated and can be on an in-patient or day-care basis. In skilled hands, most patients with discoid psoriasis can be cleared in 3 weeks, leaving deep brown staining (Fig. 35.22) of the treated skin, which soon disappears after treatment is stopped. Dithranol paste is not suitable for the head and neck, flexures or genitalia, where it is liable to spread and is too irritant; it is highly irritant if accidentally introduced into the eyes. It also stains bed linen and clothing irreversibly.

In the early 1980s, disenchantment with the side effects of cytotoxic and PUVA therapy stimulated a resurgence of interest in dithranol [2], its chemistry and pharmacology [8–10], pharmacokinetics and percutaneous absorption [11,12], and mode of action [2,13,14]. Attempts were made to modify its formulation [15] to allow easier application and removal, and relatively stable cream formulations introduced that are effective, although less so than the classical paste [16–18]. Low-strength formulations may also be active yet less irritating and staining [19–21]. Kinetic studies showing penetration of the full epidermis in 100 min or less [11,22] encouraged the notion that 'short-contact' therapy may be effective and less irritant, while being easier and more convenient for the patient. Dithranol application periods as short as 10 min/day [22–27] have been effective. One study has even shown that immediate removal of dithranol is as effective as removal at 20 min [28]. Another study showed that a 2-h short-contact regimen using dithranol in Lassar's paste was as effective as a standard 24-h Ingram regimen, but that both of these were more effective than 10–20 min contact periods using dithranol in soft paraffin base. Higher concentrations (up to 12%) applied twice daily for 30 min were surprisingly well-tolerated, but provided no advantage over 2% dithranol in Lassar's paste applied for 2 h once daily. The latter schedule was therefore recommended as optimal for home use in well-motivated patients [29]. A randomized controlled trial from the UK [30] showed that dithranol in Lassar's paste applied once daily as per the Ingram regimen was as effective as twice daily applications in clearing psoriasis in in-patients, although nursing time was longer for the twice daily group. A comparative study of short-contact dithranol versus in-patient treatment or UVB phototherapy reported that short-contact dithranol was the most cost-effective option [31].

Combination of short-contact dithranol with broad-band UVB appears to have little advantage over short-contact dithranol alone [27,32] or broad-band UVB alone [33,34]. However, dithranol or calcitriol in combination with narrow-band UVB (311 nm) were equally effective [35] and short-contact dithranol had a cumulative UVB sparing effect when used in combination with 311 nm narrow-band UVB [36].

Attempts to address the two main side effects of dithranol usage—local staining and irritation—have led to the development of combination therapy and new formulations of dithranol.

Dithranol in 0.0125% clobetasol propionate (quarter-strength Dermovate) ointment was reported to produce more rapid clearing than dithranol in Lassar's paste. The relapse period was similar in the two groups, although folliculitis was an important side effect in the steroid group [37]. In contrast, a combination of dithranol and fluocinonide in Lassar's paste, although causing more rapid initial clearing and reducing irritancy, did not reduce total clearance time when compared with dithranol in Lassar's paste alone. In this study, the steroid combination was also associated with a more rapid relapse rate [38]. Swinkels *et al.* [39] combined short-contact dithranol with clobetasol-17 propionate, each used once daily, and found that this accelerated the improvement of psoriasis produced by dithranol alone. Micanol is a microcrystalline formulation of 1% dithranol that releases the active medication at skin surface temperature [40]. This formulation reduces staining of fabrics significantly, but skin staining can still occur. A novel aqueous gel-based lipsome entrapped formulation of dithranol appears, in an open study at least, to produce no irritation and minimal staining [41].

Notwithstanding these developments, any form of dithranol therapy requires careful control and explanation

if the patient is not to become quickly disenchanted. The drug has the great virtue of lacking systemic toxicity, although if very high concentrations become general, continued vigilance will be necessary. Allergic contact dermatitis is extremely rare but has been documented [42]. Overall, the relative impracticality of dithranol therapy as compared to topical vitamin D analogues indicates that use of this effective and safe therapy will probably decline, particularly for outpatient use.

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Topical corticosteroids

Topically applied corticosteroids are of established value in psoriasis [1,2]; in the USA, they are still the mainstay of topical therapy [3]. In appropriate concentrations, they are the treatment of choice on the face and neck, flexures and genitalia, where neither dithranol nor tar are well-tolerated, even in low concentrations. Diluted topical steroids are also used in unstable, erythrodermic and generalized pustular psoriasis, in preference to tar or dithranol, although bland emollients may be more suitable. On the scalp and other parts of the body, they can be tried if tar has failed and dithranol is inappropriate or unsuccessful. Corticosteroids have the merits of ease of application and removal, lack of irritancy and the absence of staining of skin or linen. The hazards of therapy are now well known, and enhancement by polythene occlusion will magnify and hasten side effects. Topical steroids under occlusion do have a limited place in the management of recalcitrant psoriasis of the scalp, hands, feet and other areas. Superior results have been claimed with topical steroids occluded by a hydrocolloid dressing as opposed to plastic film [4]. Apart from the cutaneous adverse effects, plasma cortisol levels are easily suppressed by the most potent preparations or high doses [5,6]. As little as 7 g/day of 0.05% clobetasol propionate or 0.05% betamethasone dipropionate was sufficient to suppress

morning plasma cortisol levels in 20% of patients [7]. These unwanted effects, and evidence of tolerance [8] induced by intensive therapy, have stimulated use of less frequent applications [2,3,5,9,10]. Thus, once daily applications of 0.1% halcinonide cream were as effective as thrice daily applications [2], and 0.05% clobetasol propionate used on alternate days, or even less frequently, induced and maintained remissions for up to 5 months [9]. A novel regimen of topical high-potency corticosteroid—betamethasone dipropionate—is to apply the agent three times over a 24-h period each week [10]. This so-called 'weekend therapy' was shown to maintain improvement in psoriasis in up to 60% of patients so treated. Another regimen [3] using fluticasone propionate ointment once daily for two consecutive days per week maintained control of psoriasis for up to 10 weeks.

Newer formulations of corticosteroids, particularly foams, are easier to apply than traditional creams or ointments and can be used for scalp, truncal or limb psoriasis [11]. There is evidence that intensive treatment of discoid psoriasis with the most potent preparations can induce generalized pustular psoriasis [12–14]. With less potent or diluted preparations, the volume can be increased *pro rata*. Potent preparations are likely to be needed on the scalp and knuckles particularly; conversely, the flexures and inner thighs need much weaker products, if striae formation is to be avoided. Their usefulness in conjunction with UVB phototherapy has been questioned [15]. Hydrocortisone (except as the butyrate ester) [16] is too weak to be of value, except perhaps in combination with tar for facial lesions.

Intralesional corticosteroid therapy

Triamcinolone hexacetonide (5 mg/mL) or triamcinolone acetonide (10 mg/mL) can be infiltrated intradermally into localized psoriatic lesions by needle injection. This is a valuable technique in troublesome, small, resistant lesions on the backs of hands, especially the knuckles, intensely pruritic small plaques or lichenoid lesions. The effect is long-lasting and repetition of the injection may be unnecessary for several months. In treatment of psoriasis of fingernails, the nail fold can be injected, but results are disappointing and the procedure may be painful.

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Vitamin D analogues

The naturally occurring, active metabolite of vitamin D_3, 1α,25-dihydroxyvitamin D_3 (calcitriol) [1], and three synthetic analogues, calcipotriol [2–4], 1α,24-dihydroxyvitamin D_3 (tacalcitol) [5,6] and 1α,25-dihydroxyvitamin D_3 (maxacalcitol) [7], have all been shown to be effective when applied topically in psoriasis. The mechanism of action of these agents is via vitamin D receptor-mediated effects on the proliferation and differentiation of epidermal keratinocytes [1,8] and on the immunological features of psoriasis, including shifting the Th1 cytokine profile of plaques towards a Th2 cytokine profile [9]. The introduction of topical vitamin D analogues into clinical practice in the early 1990s [10] undoubtedly transformed first-line management of psoriasis. Topical formulations of calcipotriol and other vitamin D analogues are probably the most widely prescribed active topical therapy for plaque psoriasis. Systematic reviews [11,12] of calcipotriol therapy for psoriasis attest to its equivalence or superiority to other available topical therapies apart from potent topical corticosteroids [11]. The most widely prescribed analogue in current use, calcipotriol (50 μg/g) ointment, has been reported to be at least as effective as 0.1% betamethasone valerate ointment [13,14] and more effective than short-contact dithranol therapy [15] in plaque psoriasis. Calcipotriol (50 μg/g) ointment has also been shown to be effective and safe in children when administered in amounts up to 45 g/week/m^2 [16]. Side effects of calcipotriol include local irritation, which may affect up to 20% of patients, and can be particularly troublesome on the face,

leading to the need for withdrawal of treatment [14–16]. Vitamin D and its analogues all have the potential to affect systemic calcium homeostasis with hypercalciuria and hypercalcaemia [17]. Calcipotriol (50 μg/g) ointment was found to cause no significant changes in serum total adjusted calcium when used in amounts up to 100 g/week [18,19] or 50 g/week/m^2 [18] in adults, and up to 45 g/week/m^2 in children [16]. However, subsequent work showed significant rises in 24-h urinary calcium levels with calcipotriol ointment 100 g/week [19]. Significant rises in both serum and urinary calcium levels were also seen with high doses of calcipotriol ointment of up to 300 g/week [20,21]. It would therefore be prudent to restrict the amount of calcipotriol (50 μg/g) ointment used per week to less than 100 g or 50 g/m^2, and to monitor serum and urinary calcium levels carefully should these doses be exceeded.

New vehicles for calcipotriol have been introduced and calcipotriol cream appears to be slightly less effective than the ointment formulation [22] but cosmetically more appealing. Combining calcipotriol monotherapy applied in the morning with a super-potent topical corticosteroid such as halobetasol ointment applied in the evening for 2 weeks was superior to either drug used twice daily [23]. Based on this observation, a stable ointment formulation of calcipotriol 50 μg/g and betamethasone dipropionate (0.5 mg/g) has been investigated and now licensed for therapy. Used twice daily, this combination shows superior efficacy to either calcipotriol or betamethasone alone [24] with better clearance and faster onset of action. Once daily application of the combination appears no less effective than when applied twice daily [25]. Whether withdrawal of the combination following treatment leads to an increase in rebound or pustular relapse remains to be ascertained.

Long-term treatment of chronic plaque psoriasis with calcitriol (3 μg/g) ointment confirmed previous shorter term studies indicating the efficacy of this natural vitamin D_3 metabolite [1]. The relative efficacy of this agent compared with topical calcipotriol, corticosteroids or dithranol is currently unclear, although the relapse rate following withdrawal of calcitriol ointment appeared lower than that after topical corticosteroid therapy [1]. No statistically significant changes in serum or urinary calcium levels were found, even in patients using large quantities of the ointment to treat up to 35% of the body surface area for 3 months [26]. Transient local skin irritation, occasionally necessitating withdrawal of treatment, may occur but calcitriol 3 μg/g ointment is better tolerated than calcipotriol ointment for treatment of face and flexures [27].

Tacalcitol 4 μg/g ointment applied once daily is effective for the treatment of chronic plaque psoriasis [6]. A systematic review [12] indicated that it was probably inferior in efficacy to calcipotriol 50 μg/g ointment. A long-term 18-month study in 197 patients using tacalcitol once daily demonstrated efficacy and safety with no evidence of effect on calcium homeostasis [28], although 5.9% of patients discontinued because of skin irritation. Maxacalcitol 25 μg/g ointment applied once daily for 8 weeks is an effective treatment for chronic plaque psoriasis and may be more effective than once daily application of calcipotriol 50 μg/g ointment [7].

Calcipotriol and talcalcitol have been combined with other therapies. Calcipotriol ointment enhances the efficacy of PUVA and UVB phototherapy [29,30]. As UVA partly inactivates calcipotriol [31] and UVB is absorbed by calcipotriol [32], it is recommended that calcipotriol is not applied until after phototherapy sessions. Tacalcitol ointment when combined with PUVA is UVA-sparing [33] and calcitriol is UVB-sparing in combination [34]. Calcipotriol 50 μg/g ointment used in combination with methotrexate enables lower cumulative doses of methotrexate to be used [35].

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Vitamin A analogues

Retinoids, with their pleiotropic effects on cellular proliferation and differentiation, would appear to be an ideal topical preparation for psoriasis. Early studies were performed with topical all-*trans*-retinoic acid (tretinoin). Efficacy was reported but local irritation was a major problem [1,2]. The development of retinoic acid receptor (RAR) selective retinoids facilitated a revisitation of the role of topical retinoids. Tazarotene is a synthetic retinoid, whose main metabolite, tazarotenic acid, binds to RARs β and γ [3]. Tazarotene in a 0.05 or 0.1% gel applied once daily for 3 months is significantly more effective than vehicle in the treatment of chronic plaque psoriasis [4,5]. The main drawback of tazarotene is local irritation at the site of application, so much so that various strategies have been devised using once daily application of a potent topical corticosteroid, such as mometasone furoate or clobetasol propionate to alleviate this problem [6,7]. More recently, a cream formulation (0.05 and 0.1%) of tazarotene has been developed. A study [8] involving 1303 patients treated once daily with tazarotene cream reported significant reduction in clinical severity of psoriasis—the 0.1% formulation was more effective but less well-tolerated. Tazarotene is probably best reserved for thick, recalcitrant plaques of psoriasis.

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Topical or intralesional cytostatic therapy

Several compounds have been reported to be effective, but side effects are common and usage complicated by the practical difficulties encountered in the preparation and handling of cystostatic agents. Topical mechlorethamine (nitrogen mustard) has demonstrable activity as a 0.01–0.05% aqueous solution, the chief limiting factor being an 80% chance of allergic contact sensitization [1,2].

The chance of this hazard can be delayed and lessened by combining treatment with UVB phototherapy [3]. Thiotepa 0.4% ointment under occlusion can be effective but carries a risk of leukopenia [4]. Fluorouracil 5%, as a cream or ointment, can clear psoriasis but painful erosive necrolysis of the epidermis and dermal inflammation are common [5]. Weekly pulse doses of fluorouracil given intralesionally have been found to be effective. Treatment was well tolerated and associated with only minimal toxic effects,

including hyperpigmentation, and in one patient moderate local irritation [6]. An injectable gel formulation of fluorouracil and epinephrine has been used also [7]. The alkylating agent lomustine has been tried as a 0.1% ointment. Undoubted efficacy was unfortunately accompanied by severe and persistent pain because of irritation of unaffected skin [8]. Hydroxyurea has been found to be ineffective topically [9]. Topical methotrexate is discussed below.

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Occlusive dressings alone

Improvement or clearing of psoriasis lesions has been described following prolonged occlusion with various tape products, including sticking plasters, although different tapes varied markedly in their effectiveness [1,2]. These findings have been confirmed in a prospective bilateral comparison study in which prolonged application of an adhesive hydrocolloid occlusive dressing was found to be superior to twice daily applications of a potent topical corticosteroid, and as effective as erythemogenic UVB treatment. Side effects included hyperpigmentation, pain on removal of dressings resulting from hair traction and, in a minority, a Koebner response or offensive odour [3]. Further evidence came from a 3-week study when occlusion alone was as effective as the potent topical corticosteroid—fluocinonide ointment [4]. Mechanism of action may relate to normalization of the permeability barrier [5]. This treatment appears to have potential in the management of limited psoriasis.

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Treatment of the scalp

Psoriasis of the scalp can be intractable and resistant to therapy. A recent development is that of corticosteroid-containing shampoos. Tar-containing shampoos should be the first approach, carried out daily if necessary. Tar lotions or gels may be added, rubbed in at night and shampooed out the following morning. A coconut oil-based tar and salicylic acid pomade applied at bedtime, sometimes occluded overnight with a polythene shower cap, and shampooed off in the morning, is commonly used in the UK. Cream formulations of dithranol can be useful, but care should be taken to avoid irritation of the ears and eyes. Dithranol may also cause unacceptable staining of fair hair. Calcipotriol scalp application may also be of value.

If these measures fail, corticosteroid scalp lotions, gels or foams should be tried, but even the most potent (e.g. clobetasol propionate 0.05% alcoholic solution) is useless if painted on the surface of thickly heaped-up psoriasis. In these circumstances, the scalp should be copiously drenched overnight (or throughout 24 h if possible) with the coconut oil-based tar and salicylic acid pomade or similar preparation, which is shampooed out once or even twice a day. Two or three days of such treatment generally brings about marked improvement, allowing corticosteroid or calcipotriol scalp lotion to be substituted.

UV phototherapy

UVB

Goeckerman [1] first thoroughly documented the ability of crude coal-tar applications followed by exposure to UV radiation to clear psoriasis. Much later, it became clear that broad-band (290–320 nm) UV radiation (BBUVB) alone, if given in mildly erythemogenic dosage, was capable of clearing psoriasis [2–5] and can be as effective as PUVA [6]. In addition, continued maintenance BBUVB therapy after initial clearance with BBUVB significantly increased the duration of disease control, even though maintenance treatment was given at modest frequency (an average of six treatments per month) [7].

UVB therapy three times weekly is sufficient [2], and twice daily treatment is of no extra value over once daily treatment [8]. The benefit of additional tar therapy is accepted [8,9], but doubt has been cast on the value of adding topical steroid therapy [10,11] or short-contact dithranol to a UV regimen. The known carcinogenicity of

BBUVB limits enthusiasm for phototherapy. While some studies have not shown an increased skin cancer risk in UVB-treated psoriasis patients [12–14], one study suggested that high levels of exposure to BBUVB are associated with an approximately fourfold increase in the risk of genital tumours in men [15]. Protection of the genital area from BBUVB exposure would therefore be prudent in these patients.

Philips TL-01 fluorescent lamps emit a narrow-band UVB (NBUVB) at 311 ± 2 nm. Irradiation with this source has been found to be superior to conventional BBUVB in psoriasis, producing longer remissions, a lower incidence of burning and possibly a lower risk of UV carcinogenesis [16–21]. The effectiveness of NBUVB appears to be similar to that of PUVA, but it is more convenient and also probably less carcinogenic [20]. The use of higher intensity (100 W) TL-01 lamps has confirmed the superiority of narrow-band over conventional broad-band therapy, and has allowed shorter, more convenient exposure times [22]. In a randomized controlled trial, 100 patients with psoriasis were allocated to either twice weekly PUVA or NBUVB. Clearance of psoriasis occurred in a significantly greater proportion of patients on PUVA (84%) than with NBUVB (63%) and with significantly fewer treatments (16.7 versus 25.3, respectively) [23]. However, another trial of NBUVB three times weekly was of equivalent efficacy to PUVA [24]. Several studies have examined the optimal number of NBUVB treatment sessions per week. Twice-weekly treatment produced equivalent improvement in psoriasis to four times weekly, but with only 16 as compared to 32 exposures [25]. Three times weekly appears to be the optimum regimen for efficacy in that two NBUVB sessions weekly took 50% longer to clear psoriasis compared to three times weekly (88 versus 58 days, respectively) [26]. An interesting development is home NBUVB treatment based on patient training—all patients who took part in the study preferred home- over hospital-based treatment [27]. Application of dithranol also provided a substantial additional benefit [22]. The combination of NBUVB with etretinate decreased the number of treatments and the UV exposure required for clearing, but was associated with a more rapid relapse than seen in NBUVB monotherapy [27,28]. NBUVB radiation may emerge as the UV therapy of choice in psoriasis, although its long-term safety remains to be confirmed by objective clinical studies. Unlike BBUVB, TL-01 therapy has been reported to cause asymptomatic or painful blistering at the sites of psoriatic lesions towards the middle of a treatment course. This side effect appears to be very unusual, and usually resolves with continued narrow-band treatment, although this may need to be briefly interrupted or restricted [29].

A retrospective study of 1488 psoriasis patients treated for 4 weeks at the Dead Sea Clinic from 1983 to 1986 by sun exposure and bathing in mineral-rich sea has been carried out. Nearly three-quarters improved by 90% or more, results consistent with those of a prior prospective study of 110 patients. The treatment is said to be cost-effective and pleasant, the combined costs of travel, accommodation and nominal medical fees usually being less than that of in-patient treatment for the clearing of psoriasis [30].

In general, UVB therapy is valuable for discoid psoriasis and may be especially valuable in guttate and 'seborrhoeic' patterns. It is usually of little value in psoriatic erythroderma and generalized pustular psoriasis, and may aggravate these forms of the disease.

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Psoralen photochemotherapy

History. Experience with coal-tar and UV therapy of psoriasis, and psoralen photochemotherapy of vitiligo, led to the suggestion that psoriasis might benefit from the same approach [1]. The first report of successful treatment of psoriasis was ignored [2] but a decade later the effectiveness of topical psoralens followed by long-wave UV radiation (UVA) in resolving plaque psoriasis was confirmed [3,4]. Within 2 years, the first report of successful use of oral 8-methoxypsoralen (8-MOP) and UVA [5] led to intense interest and the coining of the terms 'photochemotherapy' and 'PUVA' [2,6–9]. Multiple studies soon confirmed the efficacy of oral [10–18] and topical [12,19–21] PUVA therapy in various patterns of psoriasis. In the USA, Food and Drug Administration approval of PUVA therapy for severe psoriasis was granted in May 1982. In the UK, official approval is still withheld, and no psoralen preparation has a product licence. Nevertheless, PUVA is widely used in the UK. With the introduction of narrow-band UVB phototherapy and the risk-averse practice of medicine prevalent in the USA, there is a significant reduction in the number of patients receiving PUVA per annum. The National Ambulatory Medical Care Survey revealed an 85% reduction in PUVA use from 1993 to 1998 [22].

Methodology. Dosage of 8-MOP is arbitrary, as is the time interval before irradiation. Different pharmaceutical preparations of 8-MOP differ markedly in bioavailability [23,24], and there are patient variations in the rate and extent of absorption [25]. In addition, there is no simple correlation between achieved plasma levels and therapeutic response [26], although patients responding unsatisfactorily are more likely to have deviant blood levels [27,28]. Liquid formulations of 8-MOP have been reported to produce higher, earlier peak levels of drug in the plasma and more reproducible plasma concentrations [29,30].

Table 35.3 Initial dose of UVA according to skin type [6].

Type	Description	Initial dose (J/cm^2)
I	Always burn, never tan	0.5
II	Always burn, then slight tan	1.0
III	Sometimes burn, always tan	1.5
IV	Never burn, always tan	2.0
V	Moderately pigmented	2.5
VI	Deeply pigmented	3.0

Dietary influences may be important [31], absorption being delayed and reduced by a fat-rich meal. Other photoactive drugs should be avoided. Standard oral dosage using 8-MOP tablets is 0.6 mg/kg [9], given 2 h before irradiation. High-intensity fluorescent UVA tubes are used, and initial UVA dosage is based on skin type (Table 35.3). Some clinicians start with somewhat smaller doses. Treatment is given two to four times weekly. UVA dosage is increased by increments of 0.5–1.5 J/cm^2 according to response. Persistent tenderness or erythema of uninvolved skin may call for temporary reduction of UVA dosage, or cessation of treatment for a few days. Once substantial clearance has been achieved, the frequency of treatment can be reduced, so that maintenance treatment (usually the last UVA dose in the clearance phase) is given once every 1–4 weeks. Alternatively, the treatment may be stopped in many cases if the psoriasis remains clear. In either case, clearance schedules may have to be resumed to control relapses. A cost-effective modified UVA dosage schedule leading to an increased clearance rate and reduced cumulative UVA dose, and therefore possibly a lower incidence of long-term cutaneous side effects, has been proposed [32]. In this study, initial and incremental UVA doses were maximized to near erythemogenic levels by weekly testing for the minimal phototoxic dose, by using an automated skin testing UVA irradiation unit. However, the value of repeated minimum UVA phototoxicity dose testing in reducing the cumulative dose of UVA and improving the clearance rate has been questioned [33].

Eye protection [34,35]. During irradiation, UVA-opaque goggles must be worn. For the remainder of that day, UVA-blocking sunglasses should be worn outdoors (except when driving at dusk) and indoors during the daylight hours or under artificial fluorescent lighting. There is a wide variation in the efficacy of commercially available sunglasses, and the screening efficiency should always be tested with a radiometer. Detailed information is provided in published reviews [34,35].

Patient selection [6,23]. In many departments, only vertical UVA irradiation units are available as they occupy

less floor space than horizontal units, and they save time, as the entire skin is irradiated simultaneously. Some elderly or infirm patients may encounter difficulty standing in a vertical unit for a prolonged period. Contraindications to the use of PUVA are evidence of renal, hepatic or severe cardiovascular disease, cataract formation, or pre-existing light-aggravated disease such as systemic lupus erythematosus (SLE), porphyria and multiple melanocytic naevi, particularly in the presence of a family history of malignant melanoma. However, a history of previous summer exacerbation of psoriasis involving exposed areas is not necessarily a contraindication; some such patients do well with cautious PUVA treatment [36]. Previous exposure to inorganic arsenic or radiotherapy or a history of cutaneous malignancy are relative contraindications. The treatment should not be given in pregnancy nor to children under 18 years, except in the most compelling circumstances. Because the long-term carcinogenic hazard is uncertain, PUVA should only be considered as a primary treatment in those patients over 55 years of age where psoriasis covers at least 20% of the body surface, and who cannot be controlled by conventional topical therapy. In patients under 55 years or with less widespread psoriasis, other considerations may justify therapy according to individual circumstances. PUVA is of no value for psoriasis in areas where UVA access is impossible, such as the scalp (except in the bald) or certain body flexures.

Results. Therapeutic results have been uniformly good to excellent in psoriasis vulgaris. Clearance rates of up to 90% have been reported [11,13,16–18], substantial clearance being achieved by 15–25 treatments to a total of 100–200 J/cm^2. Less spectacular success rates have probably reflected selection of severe resistant cases [10,15,37] or use of lower 8-MOP or UVA doses [12,38]. The use of four treatments weekly in a European cooperative trial achieved complete clearing in 65%, and substantial improvement in another 29% in approximately 3200 patients, with a mean of 20 exposures in 5–6 weeks, a mean UVA clearance dose of 7 J/cm^2 and a cumulative UVA dose to clearance of about 100 J [18]. Although success was comparable in large US cooperative studies [13,16] in which three treatments weekly were given, higher clearance UVA doses (13–14 J/cm^2), higher cumulative doses (up to 200 J) and 10–12 weeks were needed. The European regimen of four treatments weekly possibly achieved its antipsoriatic action before increasing pigmentation necessitated higher UVA doses.

PUVA is also of value in generalized pustular psoriasis, erythrodermic psoriasis, palmoplantar pustulosis and nail psoriasis [39], but success rates are much lower in these atypical patterns of disease. The value of maintenance therapy is disputed, being thought to be of value by some authors [13,40–42] but not by others [18]. A useful compromise is to give maintenance treatment for 2 months. If the psoriasis remains clear, PUVA is stopped. Low-dose PUVA maintenance is possible after clearance has been achieved by some other modality (e.g. dithranol) [43].

Patient monitoring. Regular blood counts, renal and liver function tests are not necessary, but should be carried out occasionally as clinical circumstances demand. Eye examination, ideally by an ophthalmologist, before and at 6–12-month intervals during maintenance treatment is a prudent precaution. Long-term supervision of patients should not be entirely delegated to ancillary staff, and a thorough clinical examination of the skin at regular intervals, say every 3 months, is indicated.

Combined therapy. The simultaneous use of etretinate or acitretin and PUVA is discussed below. Dithranol and PUVA have been used together [39] and sequentially [43]. In extremely severe erythrodermic or generalized pustular psoriasis, a cytotoxic drug may be given concurrently. Methotrexate in combination with PUVA is effective; however, there is an inevitable increased risk of skin cancer [44,45]. Topical corticosteroids may be used concurrently, especially on areas inaccessible to UVA. However, it is unresolved whether this combination results in shorter remission times [46,47]. Calcipotriol combined with PUVA is more effective than PUVA alone and results in less UVA exposure [48]. Although rarely used, PUVA and UVB used together has been reported effective in patients unresponsive to either PUVA or UVB alone [49].

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Adverse effects [1]. Erythema and frank 'sunburn' are the most common effects, and are seen at some stage in at least 30%. Nausea affects approximately 12% of patients and pruritus approximately 25%. A mild facial dermatitis resembling seborrhoeic dermatitis and involving the glabella, cheeks and nasolabial folds affects approximately 5% of patients. It is not very responsive to topical corticosteroids. Pigmentation is the most common cutaneous change observed, and is dose related. It may be diffuse, poikiloderma-like or in a naevus spilus-like pattern [2,3], producing gross freckling (PUVA lentigines) [4]. The melanocytes are abnormal within these lentigines, with large melanosomes and lipid accumulations [5]. These changes may be partially reversible. The nails may pigment [6] and photo-onycholysis has occurred [7,8]. Bullae occur occasionally and several cases of generalized pemphigoid have been reported. Hypertrichosis may be a problem in females. Lichenoid eruptions are documented [9] and histologically, in apparently unaffected skin, colloid or amyloid bodies may be found near the dermal–epidermal junction [10,11]. The incidence of actinic keratoses is controversial, ranging from 1.4% [12,13] or less [14] to over 50% in California [15]. A case of superficial actinic porokeratosis is on record [16].

Itching is a common problem, occurring in up to 25% of patients [17]. Severe cutaneous pain is a rare but well-recognized associated phenomenon [18,19]. The pain starts 4–8 weeks after onset of PUVA therapy, and sometimes after treatment has been stopped. Attacks may last from 15 min to several hours, and can be provoked by scratching or pressure. The buttocks, limbs and abdomen are particularly affected, especially at night. The pain is not associated with itching. It settles over a few weeks.

The concurrent administration of other photoactive drugs increases the chances of unpleasant erythematous reactions [20]. Worsening or new eruptive psoriasis, resulting from a Koebner phenomenon, occurs in about 2% of patients. A few reports of a lupus erythematosus-like syndrome [21,22] have stimulated several studies of antinuclear antibody levels during PUVA therapy, with normal findings in one study [20] but modestly raised antibody levels in others [23–25]. Circulating immune complexes may be raised [26].

No cataracts unequivocally attributable to PUVA have been reported in humans [27], although they have been induced in experimental animals by massive dosage [28]. However, bilateral punctate cortical opacities, not present prior to therapy, have been reported [29,30], and the animal changes have been in an anterior cortical location [28]. A patient, with previously normal eyes, developed cataract 4 years after a 28-month course of PUVA [31].

Liver function tests only rarely become abnormal, and no changes were found in liver biopsies after 2 years of PUVA therapy [32]. Nevertheless, there have been rare reports of hepatotoxicity [23,24,33]. Psoralens are known to induce liver microsomal enzymes [34]. The possibility of chromosomal changes has attracted inevitable attention, and the published data are conflicting. Striking increases in sister chromatid exchange frequency *in vitro* induced by 8-MOP concentrations likely to be found *in vivo* have been reported [35], but earlier workers did not find such changes [36]. Unscheduled DNA synthesis is apparently not increased in normal human skin by PUVA [13] or in psoriatic skin [37].

Various abnormalities of immune function have been recorded. Reduction in circulating T-lymphocyte numbers and function is documented [38], but there are reports of previously depressed T-cell numbers returning to normal with PUVA therapy [26,39]. However, a reduction in circulating helper–inducer T cells has also been associated with long-term therapy [40]. Inhibition of lymphocyte DNA synthesis occurs, and the effect has been demonstrated to be an immediate one on circulating lymphocytes *in vivo* [41]. Delayed hypersensitivity responses are undoubtedly reduced and delayed [38,42–45], perhaps caused by Langerhans' cell depletion [46] or damage [47] in the irradiated skin.

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The carcinogenic hazard. It is undisputed that solar UV radiation is a major aetiological factor in squamous and basal cell carcinoma and malignant melanoma in humans. Tumours have been induced in the skin of hairless albino mice by PUVA exposure using both 8-MOP and 5-MOP [1]. An early report suggested that PUVA therapy accelerated the development of skin tumours in patients with xeroderma pigmentosum [2], and it appeared to have an obvious promoter effect in a patient previously exposed to X-irradiation, arsenic and several cytotoxic drugs, who developed 25 basal or squamous cell carcinomas, the first within 21 months of onset of PUVA therapy [3].

There is now substantial literature dealing with the incidence of skin tumours in groups of PUVA-treated patients. Although certain studies have failed to show a clear relationship between PUVA and tumour development [4–6], long-term follow-up of a large US cohort has provided conclusive evidence for the carcinogenicity of PUVA [7]. In this study, an initial cohort of 1380 PUVA patients was followed up for a mean of 13.2 years. Squamous cell carcinoma (SCC) developed in one-quarter of patients exposed to high doses of PUVA, giving a relative risk of SCC of 5.9-fold on comparison with patients receiving low-dose PUVA. High-dose PUVA was regarded as a total of over 299 treatments, low-dose less than 160 [7]. Precise UVA doses were not given, but taking an average dose of 11 J/cm^2 after clearing, the high-dose group can be estimated to have had more than approximately 3200 J and the low-dose group less than 1760 J. The latter figure may therefore be taken as a cumulative dose, which should ideally not be exceeded. However, a study in Northern Ireland, where there is a high population of sun-sensitive Celtic subjects, indicated increased risk for non-melanoma skin cancer (including particularly basal cell carcinoma) with cumulative UVA doses above only 250 J/cm^2 [8]. Therefore, far more conservative UVA limits may be needed with certain populations, and safety limits may be better expressed as numbers of treatments rather than cumulative UVA doses. In the Northern Ireland study, a cumulative UVA dosage of 250 J/cm^2 equated with approximately 100 treatments. The US study showed that fair-skinned persons (skin types I or II; Table 35.2) had an approximately twofold higher risk of SCC than those with skin types III or IV. Overall, there was no substantial increase in the risk of basal cell carcinoma with high-dose PUVA in the US study [7]. Metastatic SCC was seen in seven patients, but two of these were elderly and had had little PUVA. Four were younger (41–57 years) and had had moderate- to high-dose PUVA, although methotrexate or ionizing radiation may have played an additional part [7].

The substantially increased risk of SCC with high-dose PUVA therapy has been supported by a large Swedish study [9]. The male genitalia appear particularly to be at risk [10–12]. In a prospective cohort study [7,12] of 892 men first exposed to PUVA in 1975–76, 24 (2.7%) had developed a total of 51 genital neoplasms. It appears that increased risk is associated with high-dose PUVA in association with UVB and coal tar. Shielding of the genitalia during PUVA therapy reduces the risk.

PUVA lentigines may exhibit cytologically atypical melanocytes [13]. There is an increased risk (8.4-fold) of malignant melanoma in patients who have received PUVA—the 1380 patient cohort study of patients who first received PUVA in 1975–76 calculated that high-dose PUVA (more than 250 treatments) and passage of time were contributing factors [14,15]. PUVA is best avoided in those predisposed to malignant melanoma (e.g. those with numerous melanocytic naevi or atypical moles) and a family history of melanoma.

There is no evidence of any internal carcinoma hazard, but acute leukaemia [16,17] and a preleukaemic state [18] have been reported. In addition, a patient transformed from myelodysplasia to fatal acute myeloid leukaemia after 4 months of PUVA [19].

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PUVA using other psoralens

There has been interest in 5-MOP as a substitute for the standard 8-MOP in PUVA therapy. The two forms have been compared [1], and it has been reported that 0.6 mg/kg 5-MOP is as effective as the same dose of 8-MOP [2]. Higher doses of 1.2 mg/kg were more effective, but produced more erythema [2]. The main advantage of 5-MOP lies in better gastrointestinal tolerance, nausea occurring only rarely [1,2]. It has also been shown that therapeutic doses of 5-MOP are associated with a lower incidence of phototoxic reactions than 8-MOP [3]. It may therefore be preferable to 8-MOP in PUVA therapy, particularly in light-sensitive patients and subjects with 8-MOP intolerance. There is no evidence that 5-MOP is less photocarcinogenic than 8-MOP [4].

Trimethylpsoralen has been used to good effect in PUVA baths (see below). Use of 3-carbethoxypsoralen has been advocated because it is non-carcinogenic in mice [5].

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PUVA therapy with topically applied psoralens

A desire to avoid some of the side effects of oral treatment, especially in patients with localized forms of psoriasis, reactivated interest in the use of 8-MOP topically. A lotion or emulsion containing 0.1–1% 8-MOP has been used, and the time interval before UV irradiation seems to be relatively unimportant, periods as short as 5 min giving results as good as those with a delay of up to 2 h [1]. If extensive areas of skin are treated with topical 8-MOP in an oil-in-water emulsion, blood levels comparable to those achieved during oral therapy are found [2], so that the usual precautions to protect the eyes must be taken and little advantage is incurred. Local treatment can be given two to five times weekly, the dose of UVA being slowly increased according to response.

Trimethylpsoralen (TMP) has also been used topically to the whole body in a bath, combined with UVA, initially mainly in Finland and Sweden [3–5]. TMP is used at a concentration of 0.33 mg/L [6]. Comparisons of TMP baths with oral 8-MOP PUVA have shown that the response and relapse rates are similar. Nausea and headache occurred in the group using systemic treatment but not in the bath group, but short-term local cutaneous side effects, such as pruritus, were more common in the bath group [7,8]. Benefits have also been claimed for a combination of TMP bath PUVA with oral etretinate [9] and acitretin [10]. One report has suggested that TMP bath PUVA carries a lower risk for skin cancer than oral 8-MOP PUVA, possibly because the doses of UVA are 15–20 times lower with bath PUVA [11]. However, the data are preliminary and may be confounded by the fact that there were fewer high-dose PUVA patients among the bath group, that maintenance treatment was not given and that the face (an important site of SCC in the oral PUVA group) was not treated in the bath PUVA patients. It is prudent to conclude that, as yet, there is insufficient evidence that bath PUVA is safer. While no excess risk of skin cancer has been reported with bath PUVA, both keratoses and lentigines are common [12].

Bath PUVA with 8-MOP, at a concentration of 2.6–3.7 mg/L, has been successful [8,13]. A comparison of 8-MOP bath PUVA and oral PUVA found no difference in efficacy between the two, but bath delivery required 50% less UVA [13]. Although plasma levels of psoralen have been reported as either undetectable or very low after bath PUVA, a relationship between plasma 8-MOP levels and severity of psoriasis has been found, raising the possibility of adverse systemic reactions in patients with extensive disease [14]. The practice of not using UVA-screening spectacles following bath PUVA [13] may therefore need to be reassessed in such patients. Bath temperature should remain constant from treatment to treatment, 37°C seems optimal with a bath time of 15 min—followed immediately by UVA; local head and foot treatment may require up to 40 min before UVA. Guidelines issued by the British Photodermatology Group provide protocols for delivery of bath PUVA [6].

Psoriasis of the fingernails has been successfully treated with topical 1% 8-MOP solution and UVA two to three times weekly [15].

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Systemic therapy

For practical purposes, the alternatives are corticosteroids, antimetabolites, retinoids, ciclosporin and the new biological therapies. Photochemotherapy is discussed above.

Methotrexate

The beneficial effect of aminopterin on psoriasis was first observed in 1951 [1]. Safe regimens were soon developed [2], and aminopterin was replaced by its more stable analogue, methotrexate, which may be given orally, intramuscularly or intravenously. In cancer patients, absorption of an oral dose was found to be complete [3], but variable degrees of malabsorption are found in psoriatics even with small doses, 32–98% of the oral dose being absorbed, and the degree of absorption correlating well with D-xylose absorption [4]. Excretion is largely (95%) by the kidney, but there is extensive enterohepatic cycling [5,6]. The drug is 50–70% bound to plasma albumin [3,7]. Methotrexate inhibits DNA synthesis by competitive inhibition of dihydrofolate reductase [8], and may thus exert an antimitotic action on the epidermis. Recently, *in vitro* studies showed that methotrexate was 10–100 times more effective at inhibiting the proliferation of lymphoid cell lines than cultured keratinocytes, suggesting that lymphoid cells may be a more important cellular target than epithelial cells in psoriasis [9]. In regimens for psoriasis, methotrexate also inhibits polymorphonuclear leukocyte chemotaxis [10]. These actions may explain its clinical effects.

Controlled trials have suggested that topical methotrexate is ineffective in psoriasis [11,12] in spite of evidence for local absorption [13]. In contrast, significant improvement was subsequently noted following the use of a topical methotrexate gel containing the penetration enhancer, laurocapram. It was therefore suggested that topical methotrexate may be effective in psoriasis if adequate percutaneous absorption is provided for a sufficient period [14].

Oral therapy is given once weekly, occasionally fortnightly. Daily regimens are dangerous and have been abandoned. For a 70-kg adult, an initial test dose of 5–10 mg is given to avoid early toxicity. Maintenance doses should be achieved by gradual increases of 2.5–5 mg/week, and usually range between 7.5 and 30 mg/week. Methotrexate may be given as a single weekly oral dose, or divided into three parts given 12 h apart over 24 h [15]. Parenteral therapy is equally safe, similar doses being given intramuscularly or intravenously every 7–14 days. In the elderly, the effective dosage of methotrexate is below the above range, and toxicity may be more readily encountered with higher dosage, probably owing to reduced renal clearance. Patients over 80 years have been adequately treated with as little methotrexate as 2.5 mg/week [16].

Before treatment, renal, hepatic and marrow function must be shown to be normal. If renal function is impaired, a reduced dosage of methotrexate may be given with extreme care and regular monitoring. Routine liver-function tests should be supplemented by a liver biopsy, which may be delayed for 2–4 months until it is established that methotrexate is effective and tolerated, and that long-term treatment will be carried out. Many centres are now starting to use an assay of serum levels of the aminopropeptide of type III procollagen (PIIINP) as an alternative to liver biopsy (see below) [17,18]. Anaemia, thrombocytopenia and leukopenia are contraindications to therapy, as are active infection, peptic ulceration, ulcerative colitis past or present, alcoholism, immunodeficiency, pregnancy, lactation and an unreliable patient [15].

Initial dosage should always be cautious (at the lower end of the therapeutic range). Note should always be taken of concurrent therapy with drugs that may displace methotrexate from plasma albumin, such as aspirin, NSAIDs and sulphonamides, including co-trimoxazole [19], as has been reviewed [15]. In addition to the drugs

reviewed, frusemide (furosemide) has induced severe toxicity in one patient [20] and a profound fatal leukopenia in another (D.H. Jones, personal communication), probably by interfering with tubular secretion of the drug. Diuretic therapy should be avoided if possible, and used only with great caution if cardiac failure threatens. Special caution is needed if corticosteroids are being given orally, because the toxic effects of the two drugs on the intestinal tract and defence against infection may be additive [21].

Clinical response is usually evident in 7–14 days, but maximal response may take 4–8 weeks. Generalized pustular psoriasis (if acute) may respond within 48 h. As soon as acceptable control is achieved it may be possible to lower the dosage or to extend the interval between doses. It is prudent to accept less than 100% control; quite small doses (e.g. 7.5–10 mg or less weekly) may afford adequate control, especially in the elderly patient. Subsequent minor fluctuation in activity can be treated by other means. In the treatment of erythrodermic or pustular psoriasis where gross oedema, especially of the legs, is common, the temptation to use diuretics, especially frusemide (furosemide) [20] should be resisted. As the psoriatic inflammation is controlled, a spontaneous diuresis will follow.

Laboratory control of treatment is essential. Initially, the haemoglobin, leukocyte and platelet counts should be shown to be within normal limits; weekly, but later less frequent counts, say monthly or even less often, are adequate. Maximal myelosuppression occurs 7–10 days after an oral dose. The liver enzymes give the simplest guide to hepatic function, and serum albumin, liver-function tests and blood urea or creatinine levels should be checked every 3–4 months during maintenance therapy, although the value of liver enzyme measurements in predicting significant hepatotoxicity is controversial [22]. Liver biopsy should usually be undertaken not less frequently than after every 1.5 g of cumulative methotrexate dosage [15,22]. However, the need for repeated follow-up liver biopsies in carefully selected and monitored patients who have no other risk factors for hepatotoxicity has been questioned, especially in view of the morbidity and cost associated with liver biopsy, and the low yield of pathological findings leading to discontinuation of methotrexate [23].

Numerous toxic effects of methotrexate therapy are recognized. In one long-term study, 73% of patients had side effects, most frequently abnormal liver-function tests, nausea and upper gastrointestinal symptoms [24]. Oral regimens commonly provoke transient anorexia, nausea and dyspeptic pain. Many patients feel slightly unwell for 24 h or so after each dose. Bursting headaches, lasting a day or so, may follow large parenteral doses. Burning sensations in the psoriatic plaques, lasting several days, are not uncommon after full doses, and herald rapid resolution of lesions. Toxic effects on the marrow include leukopenia, thrombocytopenia and, rarely, folate-deficient megaloblastic anaemia. Folic acid given regularly during treatment with methotrexate can prevent nausea and reduce the chances of bone marrow suppression. A recent UK audit [25] of folic acid prescribing during methotrexate therapy indicated the preferred regimen to be 5 mg/day every day including the day of methotrexate dosing. Modest thrombocytopenia ($100–125 \times 10^9$/L) and low to normal white cell counts ($3.5–4.5 \times 10^9$/L) do not necessarily preclude safe long-term treatment if the counts remain stable.

It is now established beyond all doubt that methotrexate is hepatotoxic, causing fibrosis and cirrhosis, the incidence of which has varied in different series [15,26,27]. One report described cirrhosis and liver failure leading to liver transplantation in three patients receiving largely unsupervised methotrexate treatment for psoriasis, although no information was given about other potential aetiological factors [28]. In general, the incidence of cirrhosis is low with total dosage of less than 1.5 g. Higher incidences of fibrosis and cirrhosis have been reported by Danish authors in patients receiving higher cumulative dosage or longer exposure, findings that have conflicted with the data of others [15]. These higher incidences in Denmark may possibly be explained by a higher average age and previous intake of hepatotoxins, such as arsenic, vitamin A and alcohol [29].

Pre-existing liver disease adds to the risk from the drug, and both functional and structural abnormalities have been demonstrated frequently in severe psoriatics being assessed prior to methotrexate therapy. In one series, premethotrexate liver biopsies showed that steatosis, periportal inflammation and focal necrosis were all found with a statistically significant higher grading among psoriatic patients than controls [26]. Other risk factors include impaired renal function, diabetes, obesity and increasing age [11,15,29–31]. The presence of chronic hepatitis B or C infection is also likely to be a risk, and should be excluded prior to methotrexate therapy.

The clinical course of cirrhosis induced by methotrexate may, however, not be aggressive, some patients being able to continue on the drug without worsening of liver biopsy findings [27,32]. Generally, it is an indolent, slowly developing process that will be detected by serial liver biopsies, when the hazards of stopping and continuing therapy can be weighed against each other. Fatty change and mild inflammatory infiltrate can be ignored, as can the mildest stage of fibrosis if the need for methotrexate is compelling. Progressively more severe damage in serial biopsies demands withdrawal of the drug, as do the findings of advanced fibrosis or cirrhosis, but the serial biopsies may show apparent reversibility or fluctuation of changes [23]. At present, liver biopsy remains the gold standard for the exclusion of significant hepatotoxicity, as indicated in the guidelines of Roenigk *et al.* [15]. However, there is now compelling evidence that 3-monthly monitoring of serum levels of PIIINP may permit dispensing with liver biopsy

altogether in approximately 70% of patients. Careful work by researchers in Manchester, UK, and Aarhus, Denmark, [17,18,33] has established that serum levels of PIIINP accurately reflect liver pathology. If serum levels of PIIINP remain within the normal range liver histology is normal; there are occasions when high serum levels of PIIINP occur with a normal liver biopsy—in such circumstances patients can continue on methotrexate but hepatoxicity is monitored by regular (1.5 g cumulative dosage of methotrexate) liver biopsy.

Another focus of anxiety has concerned the possible hazard of the development of malignant disease. Metastasizing SCC of the skin has been described in a patient on long-term methotrexate [34]. Furthermore, long-term follow-up of a large cohort of patients on PUVA, and other treatments for psoriasis, has suggested a relative risk of 2 : 1 for SCC of the skin in those who have had high-dose methotrexate exposure (a probable cumulative dosage of more than 3 g over 4 years or more) versus low or no exposure. This risk was independent of PUVA therapy [35]. Careful examination of the skin at intervals would therefore be prudent in any patient on high cumulative dosage of methotrexate.

Anagen alopecia, cutaneous erosions, ulceration and bleeding are rare with weekly dose regimens [36]. Other uncommon side effects include epidermal necrolysis [36], candidiasis [36], folliculitis, ataxia [37], keratoconjunctivitis [38], depression and other psychotic symptoms [21], reactivation of tuberculosis [39] and other pulmonary illnesses [40]. Gastrointestinal bleeding has been reported. Fatal complications of therapy [21] have included rapidly progressive renal failure [41] and septicaemia, as well as the consequences of irreversible marrow or hepatic failure. Death has followed a single intravenous injection in a patient with severe renal failure. The majority of the published deaths are attributable to absolute or relative overdosage [21]. Renal damage is not a recognized hazard of conventional antipsoriatic dosage [41]. Oligospermia is an important hazard in men [42] and may persist long after the drug is withdrawn. Methotrexate osteopathy is a little-recognized complication of long-term low-dose treatment, affected patients presenting with the triad of severe pain localized to the distal tibia, osteoporosis and compression fractures of the distal tibia. The condition is readily confused with psoriatic arthropathy and, as the only treatment is said to be withdrawal of methotrexate, it is important that it should be recognized [43].

Despite these dangers, methotrexate has a secure place in the treatment of severe psoriasis that is physically or socially disabling, and which is resistant to conventional topical therapy and photochemotherapy. It is particularly valuable in the chronic erythrodermic and generalized pustular forms, where it may be life-saving, and for weaning such patients off systemic steroids. It is useful in intractable non-pustular forms of psoriasis of the hands and feet. Nevertheless, it has long-term hazards and it should never be used as an easy substitute for topical therapy. It should rarely be used in the first half of life, but this is sometimes inevitable, and the use of methotrexate (0.2–0.4 mg/kg/week) in children with severe psoriasis has been reported [44]. It is abortifacient and teratogenic in early pregnancy [45] and fertile patients should take contraceptive precautions. Conception should not be allowed within 3 months of stopping treatment, but is probably safe after that time [46].

In the event of accidental overdosage or unexpected acute toxicity, folinic acid should be given intramuscularly in full dosage (10 mg/m^2) and repeated every 6 h orally or parenterally as tolerated by the patient [15]. After the first dose, subsequent administration of folinic acid should ideally be governed by the serum methotrexate level [15]. Its effectiveness in counteracting the haematological toxicity of methotrexate diminishes with increasing delay.

Methotrexate has been combined successfully with various other therapies such as UVB phototherapy [47–49], PUVA [50] and etretinate [51], in the hope of reducing dosage and therefore toxicity of each modality, while maintaining efficacy. Methotrexate and etretinate should only be used with caution because of the risk of hepatitis. Combining methotrexate with ciclosporin [52] appears to be effective in patients (particularly those with psoriatic arthritis) in whom either drug as monotherapy is poorly tolerated and/or ineffective. This combination approach is analogous to that practised by rheumatologists. Reactivation of UV-induced erythema by methotrexate [47–49] ('erythema recall') may be a problem. Colchicine and methotrexate together have been used in generalized pustular psoriasis [53], and methotrexate can be used to maintain clearance induced by PUVA or a dithranol regimen [54]. However, in view of a report of possible cancer induction, care should be exercised in using PUVA and methotrexate concomitantly [55].

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Hydroxyurea

Hydroxyurea is an antimetabolite that has been used principally for the treatment of malignant disease, particularly chronic myeloid leukaemia. The active drug, which is converted *in vivo* from its parent, blocks the conversion of ribonucleotides to deoxyribonucleotides by interfering with the enzyme ribonucleoside diphosphate reductase, thereby inhibiting DNA synthesis in proliferating cells [1,2]. Hydroxyurea was first recommended for psoriasis by Yarbro in 1969 [3,4]. It is quickly and well absorbed and excreted by the kidney. Bone marrow suppression is a common side effect of treatment with hydroxyurea, leukopenia is seen in most treated patients. Profound anaemia and thrombocytopenia occur less frequently, although a fall in haemoglobin to 110 g/dL is common [5–8]. Macrocytosis is almost universal. Irreversible bone marrow failure and death have not been reported. Because it is teratogenic, hydroxyurea must be avoided during pregnancy. Compared with methotrexate, it has the virtue of being a less frequent cause of anorexia, nausea and hepatoxicity. In the three largest case series of patients with

psoriasis treated with hydroxyurea [1,9,10], the reported satisfactory response rates have ranged from 45 to 80%. Clinical response is slow, and may become evident only over several weeks [4]. A therapeutic trial should therefore last at least 2 months. It is only modestly effective in palmoplantar pustulosis [11], and is less effective than methotrexate overall. That it may be a valuable reserve drug for patients needing systemic treatment and who are resistant to methotrexate or develop side effects, has been confirmed by a report of its use in 85 patients [1]. Hydroxyurea may be effective when other systemic drugs have failed, but is a less potent antipsoriatic agent. Its use has been advocated in combination with methotrexate [12], ciclosporin [13] and acitretin [14].

Regimens should rarely exceed 0.5 g three times daily, and sometimes 0.5 g once or twice daily long-term suffices for therapy [1,2]. A cutaneous vasculitis resulting from the drug has been reported [9,15]. Other recently recorded side effects include diffuse hyperpigmentation, actinic psoriasis, alopecia and psychological effects [1].

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Retinoids

Vitamin A has long been recognized to have profound effects on epithelial differentiation, and the toxicity of hypervitaminosis A is well known. Deficiency causes cutaneous hyperkeratosis and squamous metaplasia of mucous membranes. This knowledge stimulated development of synthetic derivatives, and the term 'retinoid' has been applied to a family of natural and synthetic analogues of vitamin A [1,2].

Etretinate [3–6]

This analogue was first reported in 1975 by Ott and Bollag [7] to have antipsoriatic efficacy, and many subsequent reports have confirmed this [8–13]. In a dosage of 1 mg/kg/day, resolution of psoriasis vulgaris [9,10], pustular [10,14] and erythrodermic psoriasis [14] has been demonstrated. The usual initial dosage is between 0.5 and 1 mg/kg/day, and daily doses of 0.75–1 mg/kg/day are generally required for exfoliative and plaque psoriasis [3]. With the higher dosage level, side effects are inevitable (see below) [10,12,14]. Fortunately, response to higher dosage (1 mg/kg/day) is often rapid in generalized pustular psoriasis, beginning within days [14], and lower dosage of between 0.5 and 0.75 mg/kg/day may be sufficient to maintain control [3]. It has been regarded as the treatment of choice for generalized pustular psoriasis of the Zumbusch type, and need not necessarily be given continuously to maintain disease clearance [15]. Psoriasis vulgaris may be less responsive, and is often best treated by a combination of etretinate with another modality [3], allowing lower dosage of the retinoid or greater therapeutic effectiveness. Thus, corticosteroid cream [13,16], dithranol [17,18], tar [14], selective UVB phototherapy [11,19] and PUVA [20–22] all appear to have been successfully combined with etretinate, allowing maintenance dosage of 0.3–0.6 mg/kg/day or even lower. However, a randomized double-blind comparison of PUVA–etretinate and PUVA–placebo in chronic plaque psoriasis failed to show significant differences between the two regimens [23], although this could have been because of the small number of patients studied [24,25]. A subsequent randomized double-blind multicentre study showed that patients receiving PUVA–etretinate appear to undergo an additional response when compared with the PUVA–placebo group, but again this did not reach statistical significance [26], possibly for the reason given above [24,25]. A proportion of patients with palmoplantar pustulosis will improve with full dosage [10] or in combination with PUVA [27,28].

The combination of long-term methotrexate and etretinate has been reported to be useful in difficult cases, and the short-term use of this combination has been reviewed [29]. During a switch from methotrexate to etretinate, combination treatment may be justified for up to 8 weeks while the therapeutic effects of etretinate become established [6]. However, extreme caution should be exercised in view of the potential for toxic hepatitis and increased blood levels of methotrexate [6].

Etretinate has been used with success in children with generalized pustular psoriasis or psoriatic erythroderma [30,31]. The potential skeletal toxicity of retinoids in

childhood has been reviewed [30,31], and includes premature epiphyseal closure, growth retardation and hyperostosis during prolonged high-dose treatment, although this appears to be less common with etretinate than with isotretinoin treatment [31]. It has been argued that etretinate may be effective in childhood generalized pustular psoriasis if given in short intermittent courses (unlike the prolonged high dosage needed for keratinizing disorders), and that under these circumstances it may not be associated with skeletal changes and may be the treatment of choice if the only alternatives are methotrexate and systemic steroids [30]. However, retinoids should not be given to children except in compelling circumstances.

Side effects of etretinate are usually inevitable, but are often a nuisance rather than a real danger. The drug is lipophilic and progressively accumulates in the subcutis. After withdrawal, it disappears from the epidermis within 1 week, but remains in the subcutis for months and it is detectable in the plasma for up to 140 days after cessation of treatment [32]. Etretinate is teratogenic [17] and is strictly contraindicated in pregnancy. Fertile women must be warned of the teratogenicity and must maintain effective contraception during treatment and, in view of its lipophilicity, for 2 years after cessation of treatment [6]. There is no evidence for carcinogenicity or mutagenicity [14,17,33]. Effects on serum lipids are well known. The serum triglyceride level becomes elevated in approximately 75% of patients, and serum cholesterol in approximately 25%, although high-density lipoprotein cholesterol is unchanged [14]. The lipid abnormalities induced by etretinate, particularly the hypertriglyceridaemia, may be alleviated by concomitant administration of fish oils [34,35]. Minor elevations in serum levels of enzymes reflecting liver function occur in a minority of patients, but are often not of importance, and return to normal when the retinoid is withdrawn [14]. However, in one follow-up study of patients on long-term etretinate, clinically evident hepatitis and cirrhosis each occurred in 1% of patients [36]. In contrast, in a prospective study of patients receiving long-term etretinate, serial liver biopsies failed to show any significant pathology during treatment [37]. Prolonged retinoid treatment has been associated with radiographical spinal changes, including anterior spinal ligament calcification, osteophytes, bony bridges and disc abnormalities, resembling diffuse idiopathic skeletal hyperostosis (DISH). These changes may be asymptomatic or associated with back or neck stiffness [38]. Prior and periodic repeat spinal radiographical assessment should therefore be considered if long-term treatment is to be carried out. Other musculoskeletal changes are well recognized, and include arthralgia, objective arthritis, stiffness and myalgia, which can affect 25% of patients [6].

Additional clinical side effects are frequent and dose related [14,16]. Dryness of the lips, nose, eyes, mouth, throat or vagina is common, and full dosage may induce painful exfoliative cheilitis, urethritis, balanitis, gingivitis, peeling of the fingertips and corneal ulceration. Rhagades, palmoplantar desquamation, burning sensations in the skin, especially of the face, pruritus, skin atrophy, increased hair loss, epistaxis, increased bruising and widespread erythema are all very well recognized. Paronychia may be severe and purulent [10,16], forcing withdrawal of therapy. Rare complaints are of lethargy, headache, loss of taste and smell, nail plate thinning, increased sweating and generalized oedema [39,40]. Dark adaptation failure may cause night blindness.

To summarize, despite the high incidence of nuisance side effects, etretinate has been a valuable addition to the antipsoriatic weaponry, especially in generalized pustular psoriasis. The drug should not be used in children except in compelling circumstances nor in young women unless essential. Active liver disease and pre-existing hyperlipidaemia are contraindications to treatment. Etretinate has now been superceded in many countries by acitretin, which has a shorter half-life.

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Isotretinoin (13-cis-retinoic acid)

Isotretinoin was reported to improve generalized pustular psoriasis, but additional therapy was required to produce satisfactory control during maintenance treatment. Isotretinoin was also found to be less effective than etretinate in the treatment of chronic plaque psoriasis [1]. However, it may have a place in the management of psoriasis in fertile females who urgently need treatment, in view of its short half-life [2], and has been advocated in combination with PUVA in this patient group [3].

Acitretin

This is the main active metabolite of etretinate. Being a free acid as opposed to an ester as in the case of etretinate, acitretin has the great advantage of decreased lipophilicity. It is therefore not sequestered in the adipose tissue, and has an elimination half-life of approximately 50 h compared to more than 80 days for etretinate [4,5]. Several clinical trials showed that the clinical efficacy and side effects of acitretin are similar to those of etretinate [6–11]. The greatly reduced half-life of acitretin compared with etretinate suggested that it would have clinical advantages over the latter, especially for women of child-bearing potential. Accordingly, marketing of etretinate ceased in the UK in 1993 and acitretin took its place. However, in an unpredictable number of patients, reversed metabolism of acitretin to etretinate has been found to occur [12]. It has therefore been essential for women on acitretin to avoid pregnancy during and for 2 years after the course, as in the case of etretinate. A further comparative study [13] confirmed the equal efficacy of etretinate and acitretin in psoriasis, but in this study etretinate was better tolerated both objectively and subjectively, and to an extent that was statistically significant. Limited recent experience also indicates that the occasional patient previously controlled on etretinate may not do well on acitretin but benefits from transfer back to etretinate once again [14]. Thus, the great advantages initially perceived for acitretin have not been realized in practice. If reversed metabolism to etretinate only occurs in 50% of subjects, albeit unpredictably [12], and the levels of etretinate thus obtained are low, this may confer a theoretically lower risk of fetal abnormalities in women becoming pregnant inadvertently before expiry of the 2-year period. The use of acitretin in fertile women therefore has a theoretical advantage, but it seems to have no major advantages over etretinate in other patients. In combination with PUVA, acitretin has been shown to be therapeutically superior to PUVA with placebo. Acitretin in a regimen of 50 mg/day for 2 weeks followed by up to 10 weeks of 25 mg/day combined with PUVA significantly reduced the number of PUVA treatments required for clearance and the cumulative dosage of UVA (by 40%) [15]. These results were confirmed by Tanew [16], in that acitretin at 1 mg/kg/day in addition to PUVA reduced the total UVA dosage and time to clearance. Similarly, acitretin enhances the efficacy of broad-band UVB in that the number of subjects who improve or clear with the combination therapy is significantly greater than with UVB alone: 60 versus 24% in one study [17] and 74 and 35%, respectively, in another [18]. Acitretin may also reduce the photo-ageing effects of

phototherapy and act as a chemopreventive against the development of cutaneous malignancy. This benefit has not been proven, but extrapolates from the known effects of retinoids on photo-aged skin and as chemopreventive agents in kidney transplant recipients [19,20]. A review of acitretin combination therapy with UVB or PUVA has recently been published [21].

The side effect profile of acitretin is generally similar to that of etretinate [5–10,22–24]. Although apparently 1.5% of patients on acitretin may develop a toxic hepatitis, there is no histological evidence of hepatoxicity on liver biopsy [25]. The starting daily dosage in adults is usually 25 mg, the optimum being about 50 mg (0.66 mg/kg/day) depending on therapeutic response and side effects.

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Ciclosporin

The antilymphocytic effects of ciclosporin, a cyclic undecapeptide derived from the fungus *Tolypocladium inflatum* Gams, were first described in 1976 [1]. The ability of ciclosporin to clear the skin lesions of psoriasis was first noted in four patients in 1979, as an incidental finding during a trial of this drug in inflammatory arthritis [2].

This information appears to have been somewhat disregarded until 1984, when the dramatic therapeutic effect of ciclosporin was again noted in a single patient with otherwise unresponsive psoriasis [3]. Subsequently, several case reports appeared [4–10], followed by unequivocal evidence for therapeutic efficacy in the form of double-blind placebo-controlled trials with both high [11] and lower [12,13] dosage. The mechanism of action of ciclosporin in psoriasis is not entirely certain, but is likely to be related to its inhibitory effects on T-cell activation [14], a possibility that has substantially affected attitudes towards pathogenic mechanisms in psoriasis.

Ciclosporin is highly lipophilic, but is active orally and metabolized in the liver by the cytochrome P-450 system. A series of consensus conferences on its use in psoriasis have been held and the proceedings published [15–17]. Briefly, a twice daily oral regimen is recommended. The side effects associated with ciclosporin (see below) demand that it should be given only to patients with sufficiently severe disease, in whom less toxic forms of treatment have been unsuccessful. Such treatment should include conventional topical therapy, if possible carried out in an in-patient department or day-treatment centre on at least one occasion, UVB, PUVA and possibly a retinoid. However, the prolonged use of high-dose PUVA may predispose certain patients to skin malignancy, and constitute a relative contraindication to ciclosporin. The choice between ciclosporin and methotrexate is not straightforward, the latter being thoroughly tried, relatively safe in the right hands and much cheaper, but currently requiring repeated invasive investigation in the form of liver biopsies. There has, to date, been no published head-to-head comparison of the two drugs in the treatment of psoriasis. Ciclosporin should not be given to unreliable patients or if regular

monitoring for side effects is not possible. Other major exclusion criteria include renal dysfunction, uncontrolled hypertension, past or present malignancy, history of epilepsy, acute infections, other immunosuppressive therapy, concomitant therapy with nephrotoxins, previous serious side effects from ciclosporin and known hypersensitivity. Minor exclusion criteria include abnormal liver function, previous therapy that may predispose to skin malignancy, malabsorption, drug or alcohol abuse, and concomitant treatment with drugs that affect the metabolism of ciclosporin. NSAIDs are often used by patients with psoriatic arthropathy, and may enhance the nephrotoxicity of ciclosporin (see below). Other drugs interacting with ciclosporin are described in a consensus report [17] and elsewhere [14], and include anticonvulsants which induce hepatic cytochrome P-450 and thus enhance metabolism of ciclosporin, which may never reach therapeutic blood levels [18].

An initial daily oral regimen of 2.5 mg/kg equally divided in two doses has been recommended. Improvement may be seen within days, but if this does not occur within 2 weeks, the dosage may be increased gradually to a maximum of 5 mg/kg/day [14,17]. Maintenance dosage should be reduced to the minimum that allows adequate control and, as for methotrexate, the aim should not be to achieve complete clearance. Withdrawal of ciclosporin in patients with severe psoriasis is usually associated with relapse within weeks but, with few exceptions [19], has not been associated with the severe rebound phenomenon seen following withdrawal of systemic steroids. In patients with moderately severe chronic psoriasis, the relapse rate (41% at 6 months) following cessation of ciclosporin therapy (5 mg/kg/day) was no greater than that seen with dithranol or PUVA [20]. A systematic review of therapies for severe psoriasis [21] concluded that 'ciclosporin is a well-tested treatment for severe psoriasis and in the short term is probably more effective than other forms of systemic therapy'. Ideally, ciclosporin should be used for short courses of 3–4 months' maximum duration [22,23]. Only in exceptional circumstances should ciclosporin be used as continuous therapy for periods exceeding 6 months. The accepted modern regimen (intermittent short courses of ciclosporin) is effective for at least 2 years—most patients require less than four courses of treatment over this time with good control of the disease and no significant side effects [23]. A Japanese study that compared intermittent with continuous ciclosporin for psoriasis showed that an intermittent regimen was probably safer [24].

The most important side effects associated with ciclosporin are dose-related hypertension and nephrotoxicity. The blood pressure may rise sharply within weeks of starting treatment, and plasma creatinine levels may increase or glomerular filtration rates decrease within the same period [14]. Immunosuppression associated with the long-term use of ciclosporin may increase the risk of cutaneous malignancy, especially in patients who have previously had high-dose UV irradiation, PUVA, Goeckerman regimens or arsenic. SCCs of the skin have been reported in patients receiving ciclosporin for psoriasis [14]. A prospective 5-year survey of 1252 European patients with psoriasis who had on average received ciclosporin for 1.9 years [25] found that ciclosporin produced a sixfold increase in risk for developing non-melanoma skin cancer (mainly SCC). The risk was compounded by contributions from PUVA and other immunosuppressants such as methotrexate. There was no increase in non-cutaneous malignancies. Lymphoproliferative disorders are an important risk of high-dose immunosuppressive treatment in transplant recipients, although these diseases were not more common in transplant recipients receiving ciclosporin than in those not receiving it [14]. Eight malignant lymphomas developed in more than 6000 patients receiving ciclosporin for autoimmune disorders, although a causal relationship was not proved [14]. Overall, there is no clear association between ciclosporin treatment and a risk of other internal malignancies, although cases have been reported [26,27] and vigilance is essential. The finding of cervical intraepithelial neoplasia associated with possible human papillomavirus infection underlines the need for cervical smears in female patients on ciclosporin, perhaps every 6 months [14,27]. Human papillomavirus-associated penile carcinoma has also been reported [28]. Other side effects include elevated serum potassium and uric acid levels, decreased serum magnesium, mild normochromic normocytic anaemia, gum hyperplasia, hypertrichosis, acral paraesthesia or hyperaesthesia, tremor, altered liver-function tests and gastrointestinal intolerance [14]. Gum hyperplasia is associated with poor dental hygiene and regular dental check-ups are recommended. The hyperplasia may respond to treatment with azithromycin [29].

Regular monitoring is therefore essential during ciclosporin therapy, and has been reviewed [14,17]. It was recommended in an earlier review that ciclosporin should be used only in patients with normal glomerular filtration rates, and that this investigation should be repeated every few months [14]. However, the last consensus conference [17] recommended serum creatinine measurements every 2 weeks for the first 6 weeks, then monthly for the duration of ciclosporin treatment. Great care should be exercised in preventing sustained rises in serum creatinine to more than 30% above baseline, even if the level remains within the normal range. Should this rise occur, an estimation of serum creatinine should be repeated within 2 weeks, and the dosage of ciclosporin reduced if the elevation is sustained. Ciclosporin treatment may be continued if the serum creatinine then falls to within the 30% range, but if not, treatment should be stopped. It appears that rigorous adherence to the above protocol should prevent

significant renal injury. Irreversible renal structural changes may occur but will be minor and of no functional significance, and there have been no cases of progressive deterioration of renal function after stopping ciclosporin if these guidelines are followed. Inherent in the protocol is the need to establish a stable pretreatment serum creatinine, by carrying out at least two independent estimations. Persistent diastolic blood pressure above 95 mmHg is an indication for dosage reduction or, if this precipitates a relapse, treatment with a calcium-channel antagonist such as nifedipine is the preferred option [30]. Diltiazem and verapamil are not recommended as they inhibit the metabolism of ciclosporin [17]. Potassium-sparing diuretics are also best avoided as ciclosporin may raise serum potassium levels [17]. The occurrence of malignancy would usually lead to withdrawal of ciclosporin, but this may not be an absolute rule if, for example, a cutaneous basal cell carcinoma is easily treated and the need for ciclosporin is compelling. There is no evidence that monitoring of serum trough levels of ciclosporin is indicated during treatment of psoriasis unless there is doubt about compliance and/or absorption of the drug [31].

Ciclosporin is now marketed in a new microemulsion formulation (Neoral®), which provides more predictable absorbance following oral administration, better bioavailability and improved therapeutic efficacy in severe psoriasis [32]. This is now the formulation of choice.

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Systemic glucocorticosteroids [1]

The glucocorticosteroids (steroids) have shown themselves to be double-edged weapons. The fluorinated forms such as triamcinolone and betamethasone have more effect on psoriasis than prednisolone [2,3]. When triamcinolone, 12–20 mg/day, is given for the first time, clearance of the psoriasis is rapid but the disease usually eventually 'breaks through', necessitating progressive increases in dosage and incidence of side effects [4]. If withdrawal is attempted, the psoriasis tends to relapse often promptly [4] and may 'rebound'. 'Rebound' may take the form of widespread small-patterned eruptive psoriasis often involving the face and backs of hands. Erythrodermic or generalized pustular phases may be precipitated [1,5]. Systemic steroids should not be used in the routine care of psoriasis. They do have a role in the management of persistent, otherwise uncontrollable erythroderma that is causing metabolic complications and in fulminating generalized pustular psoriasis of the von Zumbusch type [6] if other drugs are contraindicated or ineffective. Associated

psoriatic arthropathy is not an indication *per se*, but steroids may occasionally be needed, and in high dosage (prednisolone 40 mg/day initially), to control hyperacute polyarthritis that is threatening severe irreversible joint damage. Patients with psoriasis who have concomitant psoriatic arthritis controlled with low-dose steroids often have active labile skin disease that is difficult to control [7].

Psoriasis may remain labile and treatment resistant for many months after the withdrawal of systemic corticosteroids [8].

6-Thioguanine

6-Thioguanine is closely related to 6-mercaptopurine. The observations of one group [9] led to studies confirming that thioguanine appears to be effective in psoriasis [10]. Further experience in 81 patients was reported [11]. This drug may prove to be a useful alternative when other forms of treatment have failed. In 21 patients with severe psoriasis that had failed to respond to other systemic therapies, 14 of 18 had greater than 90% improvement in psoriasis [12]. Treatment was for an average of 15 months and regimens ranged from 20 mg twice weekly to 120 mg/day. Bone marrow toxicity is common, and is usually inevitable if an effect on psoriasis is to be seen. Increased liver enzymes are also seen and veno-occlusive disease of the liver may be a consequence of therapy [13], but preliminary evidence suggests that 6-thioguanine does not induce hepatic fibrosis [11]. Clearance of psoriasis correlates with depletion of T cells in the skin [14].

Fumaric acid esters (fumarates)

For more than 20 years fumarates have been used extensively in northern Europe, particularly German-speaking countries, for the treatment of moderate to severe psoriasis [15,16]. The commercially available preparation of fumarates, Fumaderm, comprises a mixture of dimethylfumarate and the calcium magnesium and zinc salts of monoethylfumaric acid. After ingestion, dimethylfumarate is hydrolysed to monomethylfumarate—the main active metabolite. Clinical trials [17–19] attest to the efficacy of fumarates. The drug is introduced gradually, starting at 30 mg/day, building up over several weeks to a maximum dosage of 240 mg three times daily. It is estimated that if they tolerate the drug then approximately 57% of patients will achieve a 70% reduction in severity of psoriasis. Two-thirds of treated patients develop gastrointestinal symptoms such as dyspepsia and diarrhoea; one-third of patients develop flushing. In most patients these side effects settle down over time. Lymphocyte counts fall in nearly all treated patients, sometimes by 50% [17,19]. Renal function and liver function should be monitored but impairment is unusual. The mechanism of action of fumarates appears to be an ability to promote the secretion of Th2 cytokines [20], such as IL-10, which are beneficial in psoriasis.

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Miscellaneous therapies

Sulfasalazine

Sulfasalazine (sulphasalazine) is an anti-inflammatory agent, 5-{[*p*-(2-pyridylsulfamoyl)phenyl]azo}salicylic acid, commonly used in the treatment of inflammatory bowel disease. One open study and one randomized controlled trial provide evidence that sulfasalazine for 8 weeks at 3–4 g/day can produce marked improvement in about

one-third of patients [1,2]. Approximately 25% of patients find the side effects of headache, nausea and vomiting disabling. Oligospermia, pruritus and haemolytic anaemia may occur. Sulfasalazine is a useful alternative systemic therapy for psoriasis.

Azathioprine

This is a synthetic purine analogue synthesized by attaching 6-mercaptopurine to an imidazole ring—*in vivo* it is converted to its active metabolite 6-mercaptopurine by hepatic xanthine oxidase. Several uncontrolled or case studies [3–5] describe efficacy in psoriasis but, in the absence of data from controlled trials, it is best to conclude that there is no good evidence that azathioprine is an effective treatment for psoriasis. The most important side effect is bone marrow suppression.

Mycophenolate mofetil

Following ingestion, mycophenolate mofetil (MMF) is hydrolysed to its active metabolite—mycophenolic acid. Mycophenolic acid inhibits inosine 5′-monophosphate dehydrogenase, a key enzyme in *de novo* purine synthesis —this results in blockade of T- and B-cell proliferation. Dosage is 1–2 g/day increased to a maximum of 4 g/day. MMF is only moderately effective as monotherapy for psoriasis [6–8], but its place in the therapy of severe psoriasis is probably in combination with ciclosporin as a ciclosporin-sparing agent [9,10], used at an average dosage of 1–2 g/day. Side effects include gastrointestinal symptoms and bone marrow suppression.

Tacrolimus and pimecrolimus

Despite the undoubted efficacy of ciclosporin in the treatment of psoriasis, its long-term use is limited by nephrotoxicity and hypertension. In an effort to find drugs that have a similar mechanism of action, namely blockade of calcineurin phosphatase and consequent inhibition of T-cell activation, a number of drugs structurally dissimilar to ciclosporin, but with a similar mechanism of action, have been investigated.

Tacrolimus and pimecrolimus, both of which are derived from species of the soil fungus *Streptomyces*, have been trialled for the treatment of severe psoriasis. Oral tacrolimus at a dosage of 0.05–0.15 mg/kg/day can significantly improve severe psoriasis in the short term (10 weeks) [11,12]. Side effects include paraesthesia, headache and minor elevations in serum creatinine and blood pressure. Tacrolimus is rarely used for the treatment of psoriasis, but is a useful alternative.

Oral pimecrolimus is under clinical trial development for the treatment of severe psoriasis following the highly promising results of a 4-week trial [13]. Side effects were minimal, with no effect on either blood pressure or serum creatinine.

Biological therapies

Biological therapies directed at selected targets integral to the pathogenesis of psoriasis are the logical progression of the biotechnological revolution. This arises from a more detailed knowledge of the roles of T cells, pro-inflammatory cytokines and Th1 cytokines in psoriasis. Several of these therapies are under active development for psoriasis and two, alefacept and efalizumab, are already approved for this indication in the USA. Furthermore, the use of these selective therapies allows detailed investigation of the immune processes involved in psoriasis. Two main approaches are under development: (i) targeting of T cells; and (ii) cytokine modulation [14].

T-cell targeting

Case reports of the efficacy of monoclonal antibodies to CD4 (expressed by T cells) as therapy for psoriasis provided initial encouragement that a T-cell targeted approach would be effective in the management of psoriasis [15,16]. An IL-2 diphtheria fusion toxin (Denileukin diftitox) that specifically targets and lyses cells which express the high affinity IL-2 receptor—predominantly T cells—can significantly and rapidly improve psoriasis. Side effects including coagulopathy have hindered its development as a therapy for psoriasis, but its demonstrable efficacy further underlined the key role that T cells have in psoriasis [17].

Most investigational approaches involve blockade of T-cell binding to antigen-presenting cells, a process mediated by co-stimulatory molecules, thereby inhibiting T-cell activation. Alefacept, a lymphocyte function-associated molecule-3 (LFA-3)–IgG1 fusion protein, blocks CD2–LFA-3 binding, and also apoptoses peripheral lymphocytes belonging to the $CD45RO^+$ memory effector subset. Controlled trials indicate that alefacept, whether delivered by intravenous or intramuscular route once weekly over a 12-week course, significantly improves psoriasis in approximately 30% of subjects [18,19]. A small proportion of patients may go into long-term remission. In the short to medium term, alefacept appears to be safe; it was the first biological agent to be licensed for the treatment of psoriasis.

Efalizumab is a humanized monoclonal antibody to CD11a (LFA-1). CD11a is expressed on leukocytes. Efalizumab blocks T-cell binding to ICAM-1 on antigen-presenting cells and endothelium, thereby inhibiting T-cell activation and T-cell trafficking from peripheral blood into the skin. It is administered once weekly subcutaneously. Results are similar to those reported for alefacept in that 30% of patients show significant clinical improvement, but it has a faster onset of action [20].

Daclizumab, a humanized monoclonal antibody to the α subunit of CD25, blocks binding of IL-2 to activated T cells. Early trials indicate a moderate beneficial effect on psoriasis [21]. Basiliximab is a chimeric human–mouse antibody to CD25. This is already licensed for the treatment of acute solid organ graft rejection, where it is used in combination with ciclosporin. This same combination is effective in severe psoriasis, but seemingly only in those cases where disease is rapidly progressive, such as generalized pustulosis [22,23].

Not all biological therapies are effective, despite good scientific rationale for use. For instance, T-cell adherence to endothelium via cutaneous lymphocyte-associated antigen (CLA)–E-selectin binding is considered a critical step in skin inflammation. However, a placebo-controlled trial of a humanized antibody to E-selectin in psoriasis was unable to demonstrate any efficacy despite adequate blood levels [24].

Cytokine blockers

TNF-α is a ubiquitous pro-inflammatory cytokine involved in inflammation. Anti-TNF-α blockers initially developed for therapy of rheumatoid arthritis are in advanced trials for psoriasis. The two main agents are infliximab, a chimeric human–murine IgG antibody to TNF-α; and etanercept, a dimeric fusion protein consisting of the extracellular portion of the human p75 TNF-α receptor linked to the Fc portion of human IgG1. A serendipitous observation of the efficacy of infliximab for psoriasis in a patient with concomitant Crohn's disease and psoriasis [25] led to placebo-controlled trials. These trials show that infliximab delivered intravenously at 5 mg/kg on three occasions at 0, 2 and 6 weeks is a highly effective therapy for severe psoriasis—approximately 85% of treated subjects achieve significant clinical improvement [26,27]. In the management of rheumatoid arthritis, infliximab is combined with methotrexate—this combination is also effective for psoriasis [28] and may reduce the occurrence of infusion reactions. Infliximab can be associated with reactivation of pulmonary tuberculosis.

Etanercept is less effective than infliximab and is given twice weekly by self-administered subcutaneous injection —approximately 30% of patients achieve significant benefit from 12 weeks treatment [29,30]. It is approved for use in psoriatic arthritis.

Cytokines

Plaques of psoriasis contain a predominance of Th1 cytokines such as IL-2, IL-12 and IFN-γ. Systemic administration of Th2 cytokines such as IL-4 or IL-10 appears to neutralize the Th1 bias and improve psoriasis. IL-10 was the first Th2 cytokine to be used for treatment of psoriasis. Phase II trials show that subcutaneous injections of recombinant IL-10 given either daily or three times weekly produce a mean reduction in psoriasis severity of 50% [31,32]. This response is associated with a Th2 cytokine shift and, when used as maintenance therapy, length of remission correlates with T-cell production of IL-4 [33]. Recently, systemic administration of IL-4, in an open study, has demonstrated very significant reduction in clinical severity of psoriasis [34].

Zidovudine (azidothymidine, AZT)

The skin lesions of patients with therapy-resistant AIDS-associated psoriasis have been reported to clear with oral zidovudine [35,36]. This drug may be the treatment of choice for retinoid-resistant AIDS-associated psoriasis, as therapies such as methotrexate, ciclosporin and PUVA may be contraindicated.

Somatostatin

Following uncontrolled reports of the efficacy of somatostatin in psoriasis, a double-blind placebo-controlled study of intravenous somatostatin suggested benefit in recalcitrant psoriasis [37].

Liarozole

Liarozole, a member of the imidazole family and an inhibitor of retinoic acid 4-hydroxylase, belongs to a new class of drugs, the retinoic acid metabolism blockers. It delivers a retinoid-like effect by increasing endogenous levels of naturally occurring all-*trans*-retinoic acid and other retinoids upstream of retinoic acid 4-hydroxylase. The advantage of liarozole over acitretin is that the raised levels of retinoic acid return to normal within a few days of cessation of therapy. Early trials [38,39] indicate that liarozole is effective for chronic plaque psoriasis. Side effects are 'retinoid' in nature (teratogenicity, hyperlipidaemia and mucocutaneous symptoms).

Troglitazone

The thiazolidinediones are ligands of the nuclear hormone receptor peroxisome proliferator activated receptor-γ (PPARγ). Troglitazone, a member of this family, is used to treat diabetes mellitus. A small open study established that oral troglitazone therapy improved psoriasis accompanied by normalization of the histological features of psoriasis [40]. Hepatotoxicity enforced the withdrawal of troglitazone but further studies in psoriasis are being performed with rosiglitazone.

Gluten-free diet

Studies, primarily from Sweden [41,42], have established

that approximately 16% of patients with psoriasis have IgA and IgG antibodies to gliadin. In a further study [43], 33 psoriasis patients with IgA antibodies to gliadin (15 of whom had evidence of a lymphocytic infiltrate in the duodenal epithelium) were placed on a gluten-free diet for 3 months. All 33 patients had significant improvement in psoriasis severity while on the diet. These fascinating results indicate that in a very few patients a gluten-free diet may be worth trying if antigliadin antibodies are present.

Photodynamic therapy

Photodynamic therapy has been investigated for the treatment of small plaques of psoriasis. Using 5-aminolaevulinic acid as the topical photosensitizer has produced improvement in the treated plaques, but use is limited by local pain at the site of treatment [44,45]. Further work is required to ascertain the value of photodynamic therapy for treatment of psoriasis—if larger plaques could be treated in a relatively painless manner then this would be an advance.

Lasers

Recalcitrant plaques of psoriasis have been treated with lasers. Local destruction of psoriatic epidermis using CO_2 laser resurfacing gave mixed results [46,47]; further investigation is required. Pulsed dye laser (585 nm) therapy appears to be more effective than the CO_2 laser; indeed some plaques treated with pulsed dye laser remain in remission for a year or more [48,49].

Excimer laser-generated 308-nm UVB radiation is the laser source most likely to be used for routine management of psoriasis. The UVB source is handheld and delivers high-intensity UVB selectively directed to plaques, thereby sparing uninvolved skin. Controlled trials show it to be safe and effective for localized plaques, and it requires fewer treatments than conventional phototherapy [50,51].

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Dialysis and related therapies [1,2]

The clearing of incidental psoriasis during haemodialysis for uraemia was reported in 1976 [3]. Others then recorded similar experiences with both haemodialysis and peritoneal dialysis [4–6]. It soon became clear that dialysis could favourably influence psoriasis in patients with normal renal function [1,6–9] and that peritoneal dialysis is more effective than haemodialysis [1,9,10], possibly because substances of higher molecular weight can be removed in larger quantities [2].

Success rates with dialysis have been variable. Although some patients clear completely, others do not improve, and successfully treated patients may relapse quickly afterwards [4,8]. Not all have achieved success [11] and, confusingly, there are several reports of psoriasis worsening or appearing *de novo* during chronic haemodialysis for renal disease [12–14].

Plasmapheresis and leukapheresis were ineffective, findings that led to the suggestion that there is no pathogenic circulating factor or leukocyte abnormality in psoriasis [15,16].

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Pustular forms of psoriasis

Neutrophilic accumulation in the epidermis is a characteristic histological feature of all types and patterns of psoriasis, but in clinical practice the term 'pustular psoriasis' is reserved for those forms of the disease in which macroscopic pustules appear.

It is convenient to separate two main types of pustular psoriasis: localized and generalized. In the localized forms, the disease is confined to the hands and feet and tends to be chronic. In the generalized forms, the whole body may be involved and the course is subacute, acute or even fulminating and life-threatening.

A convenient classification is as follows.

1 Localized pustular psoriasis:
  (a) chronic palmoplantar
  (b) acrodermatitis continua
2 Generalized pustular psoriasis:
  (a) acute
  (b) of pregnancy
  (c) infantile and juvenile
  (d) circinate
  (e) localized (not hands and feet).

Localized pustular psoriasis

Palmoplantar pustulosis

SYN. CHRONIC PALMOPLANTAR PUSTULAR PSORIASIS; PUSTULOSIS PALMARIS ET PLANTARIS; PERSISTENT PALMOPLANTAR PUSTULOSIS

Definition. A common condition in which erythematous and scaly plaques studded with sterile pustules persist on the palms or soles. The disease is chronic and very resistant to treatment.

Pathogenesis. The relationship of palmoplantar pustulosis (PPP) to psoriasis vulgaris is controversial [1,2]. Sometimes the presence of typical psoriasis elsewhere, or a personal or strong family history of psoriasis, or the future development of psoriasis vulgaris, establishes the relationship. However, typical PPP often occurs in the absence of such evidence [1–3]. This, and the absence of immunogenetic associations characteristic of psoriasis (see below) in such patients, suggest that some forms of PPP may represent a separate and distinct entity. Furthermore, PPP is more common in females, unlike psoriasis vulgaris there is no seasonal variation, and it tends to start at a later age [2].

HLA antigens. HLA-B13 and -B17 are not associated with PPP [4–6]. Three potential candidate genes for psoriasis susceptibility reside within *PSORS1* locus on chromosome 6, HLA-Cw6, *HCR WWCC* and the *CD5N5*. A recent immunogenetic study demonstrated categorically that PPP is not associated with any of the three candidate genes —indicating that it is a distinct disorder [7]. Combining the results of these and other studies, it may be concluded that there is no predominant HLA locus associated with PPP [2].

Provocative factors. PPP usually starts without obvious provocation. Septic foci have been blamed [1,8,9] but their removal may not cure the eruption [8]. The disease has appeared for the first time after several months of treatment with lithium [10]. Japanese otolaryngologists remain interested in the tonsils as a site of relevant focal infection [11]. Smoking has also been reported as a possible provoking factor [12]. An immunohistochemical study of biopsies of palmar skin revealed an altered staining pattern for nicotinic acetylcholine receptors in PPP—the authors suggested that an abnormal response to nicotine in patients with PPP resulted in inflammation [13].

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Clinical features [1–3]. PPP is a disease of adults and is rare in children. It usually starts in the fifth or sixth decade, although sometimes earlier. In most series, there has been a preponderance of women [4]. The disease presents with one or more well-defined plaques. On the hands, the thenar eminence is the most common site. Less commonly, the hypothenar eminence or the central palm or the distal palm are involved. On the feet, the instep, the medial or lateral border of the foot at the level of the instep, or the sides or back of the heel are involved. Less frequently, the distal sole or the whole sole is implicated. Digital lesions are uncommon. A striking symmetry of the lesions on the hands or feet is common, but sometimes a solitary lesion persists for weeks or months before others appear.

The affected area is dusky red and often scaly. Removal of scale (e.g. by treatment) leaves a glazed dull-red surface. Within this plaque, numerous pustules are present, usually 2–5 mm in diameter. Fresh pustules are yellow; older ones are yellow-brown or dark brown as the pustule dries. Eventually, the desiccated pustule is exfoliated. Normally, pustules in all stages of evolution are seen (Fig. 35.23). Itching is variable; more often the patient complains of 'burning' discomfort in the lesions.

Associations. A significant incidence of hyper- and hypothyroidism and the presence of thyroid antibodies has been found in association with PPP [5–7]. A greater tendency to develop diabetes was found in a Japanese study [8]. Various arthropathies are also associated [9], including chronic recurrent multifocal osteomyelitis [10,11], sternoclavicular involvement [12,13], pustular arthro-osteitis, axial and peripheral arthritis [9,14]. The association of some of these conditions with PPP may represent part of the spectrum of SAPHO syndrome [15]. More than

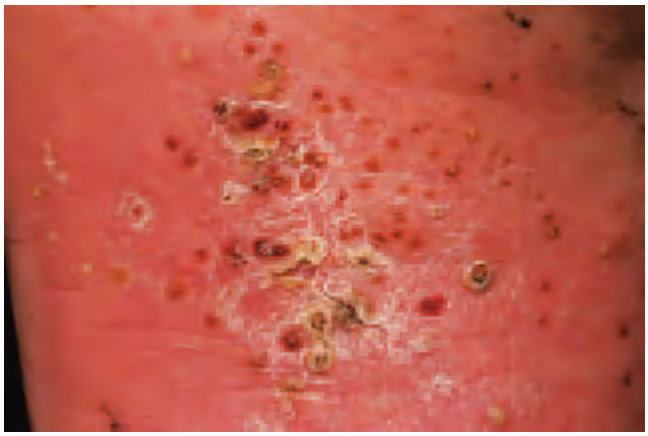

Fig. 35.23 Palmoplantar pustulosis. Note pustules in different stages of evolution. (Courtesy of St John's Institute of Dermatology, London, UK.)

90% of patients with PPP are current or previous smokers [5,16]. Some patients have antigliadin antibodies [5].

Differential diagnosis. Tinea and eczema are the most common alternatives. Tinea is usually asymmetrical or unilateral. The toe clefts may be involved. Acute vesiculopustular tinea is more common in hot weather. Microscopy and culture confirm the diagnosis. Secondary infection of eczema may be pustular but is more painful, and Gram stains and culture of pustule contents will establish the diagnosis. Chronic allergic contact dermatitis caused by rubber in footwear should not cause difficulties. Typically, the insteps are spared. The chronic acropustulosis seen in black infants does not occur in adults, and affects the digits and dorsal aspects of the extremities as well as the palms and soles [17,18].

Prognosis. The usual course is prolonged. Sometimes spontaneous remission does occur but is more often temporary than permanent. Slow spread or extension may be refractory to all treatment.

Pustular bacterid

This term was first used [19] to describe an acute monomorphic eruption of sterile pustules occurring on the hands and feet (Fig. 35.24). Whether it is a distinct entity or merely an acute variant of PPP is unclear. The term 'bacterid' implies that the eruption is provoked by a remote bacterial infection.

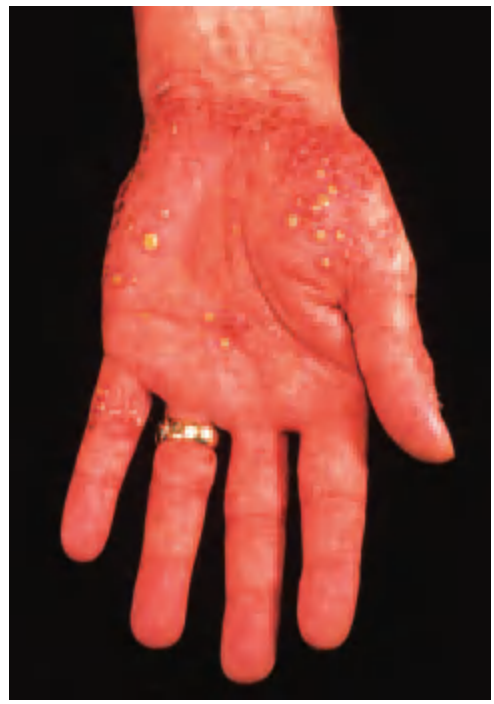

Fig. 35.24 Acute palmoplantar pustulosis. (Courtesy of St John's Institute of Dermatology, London, UK.)

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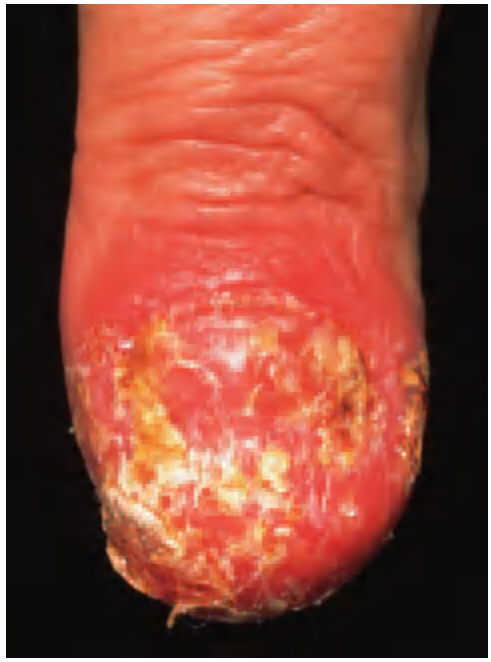

Fig. 35.25 Acrodermatitis continua with destruction of nail plate. (Courtesy of St John's Institute of Dermatology, London, UK.)

Acrodermatitis continua

SYN. ACROPUSTULOSIS; PUSTULAR ACRODERMATITIS; ACRODERMATITIS PERSTANS; DERMATITIS REPENS; ACRODERMATITIS CONTINUA OF HALLOPEAU

Definition. A chronic, sterile, pustular eruption affecting initially the tips of fingers or toes that tends slowly to extend locally but which, in adults, may evolve into generalized pustular psoriasis.

Clinical features. Whereas PPP is a disease of middle life, acrodermatitis may be seen in children. It is rare in young adults and, unlike PPP, not infrequently begins in old age. It is more common in females.

The first lesion starts on a finger or thumb more often than on a toe. Onset is often related by the patient to minor trauma, or infection at the tip of the digit. The skin over the distal phalanx becomes red and scaly, and pustules develop. The nail folds and nail bed may be involved, leading to nail dystrophy. The proximal edge of the lesion is bordered by a fringe of undermined epidermis, irregular, often sodden and sometimes preceded by a line of vesiculopustules. Removal of scale or desiccation of pustules may leave a brighter red, glazed, very sore and painful digit. Slow proximal extension is the rule but this may be spread over years. Eventually, other digits may be involved. The nail plate may be completely destroyed (Fig. 35.25). Bony changes can occur with osteolysis of the tuft of the distal phalanx [1]. The free end of the digit may become wasted and tapered, mimicking scleroderma. In such digits, the circulation may be secondarily affected so that discomfort is greatest in cold weather.

Acrodermatitis continua may evolve into generalized pustular psoriasis, especially in the elderly [2]. The tongue may become involved with fissuring or the annulus migrans of pustular psoriasis [3].

Differential diagnosis. In the earliest stage, staphylococcal infection, pulp infection, herpetic whitlow, tinea or contact dermatitis may be suspected. Candidiasis is only likely to be a problem in the immunocompromised. Parakeratosis pustulosa [4] should be considered in children.

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Histopathology

The changes are essentially psoriatic, but the central feature is a fully developed, large pustule within the epidermis, unilocular and full of neutrophils (Fig. 35.26). Spongiform pustules may be found in the wall of the larger unilocular pustule. There is some overlying parakeratosis. The acrosyringium is involved in the inflammation, and there are at times large numbers of eosinophils and mast cells present [1].

Management

Effective therapy is elusive and treatment is often as disappointing for the physician as for the patient. In view of the finding that PPP is an immunogenetically distinct dis-

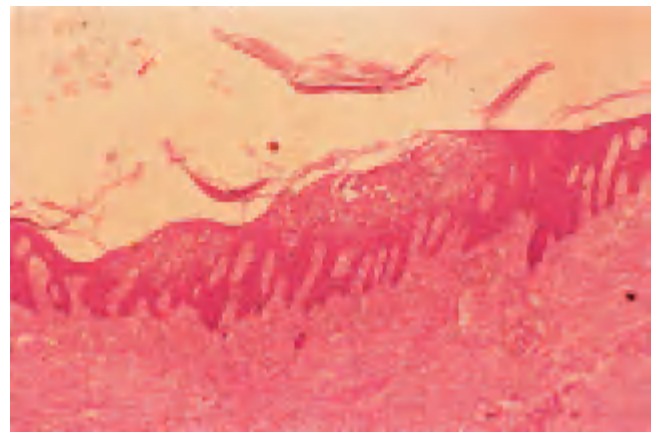

Fig. 35.26 Pustular psoriasis: intraepidermal pustule packed with neutrophils. (Courtesy of St John's Institute of Dermatology, London, UK.)

ease from psoriasis vulgaris [2], it is perhaps unsurprising that using traditional therapies for the treatment of PPP is not ideal. The choice of treatment is influenced by its side effect profile. It is usual to start with topical therapy but topical treatments alone tend to be ineffective for PPP [3]. Superpotent topical corticosteroids may be beneficial in the short term. Hydrocolloid gel occlusion can enhance efficacy of moderate potency steroid cream, which is applied every third day up to a maximum of 4 weeks [4,5]. Atrophy, particularly of the skin around the medial longitudinal arch, is a significant risk. There are no published controlled trials to support efficacy of coal tar or dithranol [3]. Tar-impregnated occlusive bandages may be helpful for acrodermatitis continua. Neither calcipotriol nor tazarotene have been formally evaluated for the treatment of PPP. Studies of topical psoralens in either soak, paint or gel form have failed to demonstrate superiority over placebo [6]. Open studies, particularly for 8-MOP soaks, indicate efficacy; in one study the majority of patients achieved remission [7].

Systemic therapies offer the best opportunity for remission. Oral retinoids either alone or in combination with oral PUVA are the best of the second-line therapies [8–11]. Etretinate at a dosage of 0.6 mg/kg/day produces objective improvement [8,9] in at least two-thirds of PPP patients—an efficacy that is matched by acitretin [10]. Liarozole—an imidazole derivative that blocks metabolism of all-*trans*-retinoic acid and thus boosts endogeneous levels of retinoids, may be effective—as shown in a small placebo-controlled study [12]. Oral PUVA is effective [9,13] and the response is enhanced by combination with etretinate (Re–PUVA) [13–15]. Various other forms of oral therapy have been used. Placebo-controlled trials of clomocycline 170 mg three times daily [16] or tetracycline 250 mg twice daily [17] have demonstrated efficacy in PPP. Ciclosporin at the low dosage of 2.5 mg/kg/day significantly improved PPP in most patients [18]—this placebo-controlled trial confirmed observations made in earlier open trials [19,20]. Dosage as low as 1 mg/kg/day may be effective [21]. Colchicine, known to influence neutrophil function, has been claimed to be effective [22] but randomized controlled trials have not confirmed this [23,24]. Methotrexate is occasionally beneficial, but an open study refutes this claim [25]. Anecdotal evidence exists for dapsone [26] and clofazimine [27], and grenz ray therapy may be a useful adjunct [28]. Oral corticosteroids should be used with extreme caution; triamcinolone in a dosage of 6 mg/day or less initially and 2–4 mg as maintenance may be effective.

Oral tetracycline and topical betamethasone valerate [29], and a combination of oral propylthiouracil and methotrexate [30], have been advocated for treatment of acrodermatitis continua, as has low-dose ciclosporin [31].

Remission of pustulosis in three obese patients after jejuno-ileal shunt operations leading to marked weight reduction awaits confirmation [32].

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Generalized pustular psoriasis

Definition. Generalized pustular psoriasis (GPP) is an uncommon variant of psoriasis in which an acute, subacute or occasionally chronic eruption has sterile pustulosis as its central feature.

Relationship to psoriasis vulgaris. GPP is an extreme form of psoriasis in which all the main pathological features of the disease are accentuated. Its relationship to psoriasis vulgaris is clear, because patients may have phases of ordinary psoriasis before or after the GPP [1]. Family data are similar to those found in psoriasis vulgaris [2,3]. In addition, methotrexate, etretinate, PUVA and ciclosporin A are effective in both psoriasis vulgaris and GPP.

Provocative factors. Provocation is most obvious in the acute forms. Von Zumbusch's original patient [4] was provoked by irritating topical therapy. Coal tar [5] and dithranol [2] may provoke pustulation if injudiciously continued when the psoriasis is intolerant. Other documented factors have been infection [2,6], pregnancy (see below) and hypocalcaemia associated with hypoparathyroidism [7–9]. Drugs implicated have included salicylates [10], iodide [11], lithium [12], phenylbutazone and oxyphenbutazone [13] and progesterone [14], terbinafine [15–17] and amfebutamone (bupropion) prescribed to assist with cessation of smoking [18]. The most important drug provocation is by corticosteroids. There is substantial evidence that withdrawal of systemic steroid therapy can precipitate GPP [1,2]. Intensive topical therapy with strong corticosteroids under occlusion has also been implicated [2,19,20]. Withdrawal of ciclosporin therapy has also been documented to induce GPP [21,22]. Chronic, previously stable acrodermatitis continua has been converted to GPP by high-dose oral prednisolone followed by sudden withdrawal [23].

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HLA antigens. There is a strong positive correlation of GPP with HLA-B27 [1,2]. The association of GPP with polyarthritis [1,2] may partly explain this finding. A Japanese study has reported an association between HLA CW1 and HLADQβ*0303 and GPP [3].

Histopathology [2,4]. In acute GPP, there is intense inflammation. The earliest infiltrate is lymphocytic. Intense papillary and epidermal oedema cause spongiosis. The arrival of masses of neutrophils leads to spongiform pustule formation (Kogoj) and abscesses that quickly become macroscopic. There is acanthosis with elongation of rete ridges [2]. The stratum corneum soon becomes parakeratotic and the subcorneal pustule is shed as epidermal turnover is accelerated. Essentially, the same features are seen in subacute as in chronic patterns but in a less intense form.

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Acute generalized pustular psoriasis (von Zumbusch)

Clinical features [1–3]. Two main groups have been distinguished [1]. In the first, typical psoriasis of early onset develops into pustular psoriasis after some years, often after provocation by steroid withdrawal or other extraneous factors. In the second, the onset of psoriasis is later in life and usually atypical, acral [4] or flexural [2,4] in distribution. A rapid and apparently spontaneous progression to the generalized pustular form follows.

The eruption may be ushered in by a sensation of burning. The skin becomes dry and tender. These warning signs—not always present—are followed by an abrupt onset of high fever and severe malaise. Pre-existing lesions become fiery and develop pinpoint pustules (Fig. 35.27). Sheets of erythema and pustulation spread to involve previously unaffected skin, the flexures and genital regions being particularly involved. Any configuration or variety of pustular exanthems may occur—isolated pustules, lakes of pus, circinate lesions, plaques of erythema with pustular collarettes or a generalized erythroderma. Waves of pustulation may succeed each other, subsiding into exfoliation of the dried pustules.

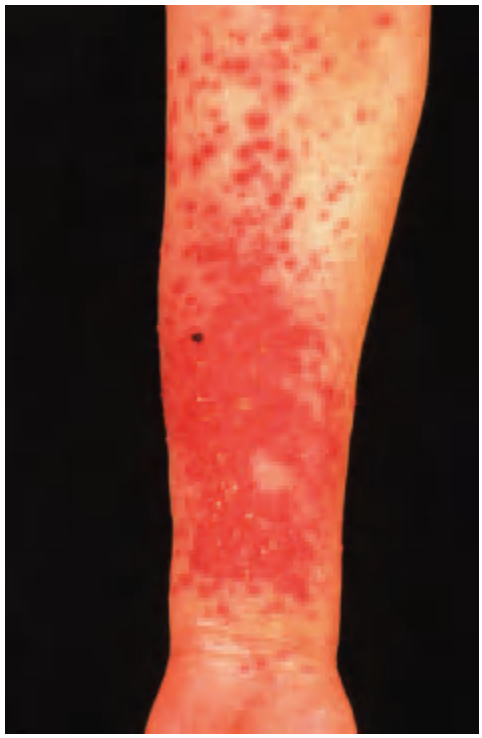

Fig. 35.27 Acute generalized pustular psoriasis. (Courtesy of St John's Dermatology Centre, London, UK.)

The nails become thickened or separated by subungual lakes of pus. The buccal mucosa and tongue may be involved, the lesions on the latter being clinically and histologically indistinguishable from 'geographic' tongue [1,5,6]. Persistent fissured tongue has also been associated with GPP and geographic tongue [7]. If the patient does not die of exhaustion, toxicity or infection, a remission may occur within days or weeks, the psoriasis returning to its normal state, or erythroderma develops. Relapses are common.

Complications. In the absence of effective treatment, death can occur in the acute stage. Hypoalbuminaemia may be profound, perhaps because of a sudden loss of plasma protein into the tissues [8]. In one patient, albumin half-life was shortened to 4 days (normal 11–12 days) [8]. Hypocalcaemia may be a consequence of the hypoalbuminaemia [1,9]. The consequent oligaemia can cause acute and fatal renal tubular necrosis [10]. There may be evidence of liver damage or even jaundice, perhaps caused by a combination of oligaemia, general toxicity and drugs [10,11]. Cholestatic jaundice of uncertain pathogenesis, closely related to acute episodes of GPP, has been described [12]. Deep-vein thrombosis in a leg can cause fatal pulmonary embolism. Staphylococcal infection may complicate GPP, usually because of hospital ward cross-infection. *Staphylococcus aureus* may be grown from pustules and rarely from blood cultures. However, claims that most GPP is caused by staphylococcal bacteraemia [13] were not substantiated [14].

Inflammatory polyarthritis is common. In one large series, one-third of patients were eventually affected [1]. Malabsorption may be a feature of the acute episode [9,15] and may further contribute to hypocalcaemia [9]. The absorption of therapeutic drugs may be impaired. Amyloidosis is a rare complication [16,17]. The obstetric complications of GPP in pregnancy are discussed below.

If GPP lasts more than a few days, gross hair loss may follow from all areas of the body. Occasionally, a telogen effluvium follows 2–3 months after the height of the illness.

Laboratory findings. There may be an absolute lymphopenia at the onset of GPP [18]. A polymorphonuclear leukocytosis quickly follows [1,18]. Plasma albumin, zinc [19] and calcium may be abnormally low. The ESR is usually raised. Malabsorption partially explains these findings. Hyperlactataemia is probably secondary to hyperproliferation [20].

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Generalized pustular psoriasis of pregnancy [1–4]

SYN. IMPETIGO HERPETIFORMIS

Definition. A rare eruption, occurring especially in pregnancy, with the features of generalized pustular psoriasis, but with a tendency to be symmetrical and grouped, and often starting in the flexures. Constitutional disturbance may be severe.

Pathogenesis. The worsening of pustular psoriasis just before menstruation is well recognized [5,6] and challenge with progesterone [7] or clomifene (clomiphene) [5] has produced pustular exacerbations in such patients. The syndrome was first described by Hebra [8] and an endocrine cause is suspected. The claims that impetigo herpetiformis stands as an entity separate from GPP have been restated [3,9].

Clinical features. The disease is rare; by 1982 less than 200 cases were documented [2]. Onset is usually in the last trimester of pregnancy, but may be earlier, and has been recorded in the first month of pregnancy [6] and in the first day of the puerperium [10]. The disease tends to persist until the child is born, and occasionally long afterwards [6]. There is one report of familial disease [11]. Essentially, the features are of a GPP, usually of flexural onset and with a marked tendency to symmetry, and sometimes grouping of areas of pustulation. Constitutional disturbance is characteristically severe with fever, and death may occur, attributable to cardiac or renal failure. Delirium, diarrhoea, vomiting and tetany have been described. The eruption usually starts in the inguinogenital region and other flexures, with minute pustules arising on an acutely inflamed area of skin. These extend centrifugally, drying in the centre, or form plaques in which eroded greenish yellow pustules become fetid, crusted or vegetating. Condyloma-like lesions may form in the flexures [12]. The eruptions may become widespread. As individual areas heal, they leave a reddish brown pigmentation. The tongue, buccal mucosa and even the oesophagus may be involved, with circinate or erosive lesions following short-lived pustules.

The more severe and long-standing the disease, the greater are the risks of placental insufficiency leading to stillbirth, neonatal death or fetal abnormalities [3,9,13].

Prognosis. Characteristically, the disease recurs in subsequent pregnancies [2,14]. Recurrence has been described in up to nine pregnancies, and on subsequent use of oral contraceptives [2,3]. In one case, the disease continued unabated despite termination of the pregnancy [6].

Laboratory findings. Hypocalcaemia has often been reported [1,6]. Lowered levels of serum vitamin D have been found, probably attributable to its malabsorption [2].

Treatment. This is discussed with that of other forms of GPP (see below). In one case, where termination failed to halt the disease, a mestranol–ethynodiol combination orally was effective when other measures had failed [6].

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Infantile and juvenile pustular psoriasis

All forms of pustular psoriasis are rare in childhood. Five cases were seen in one series of 479 children with psoriasis [1], and one case of GPP in another series of 112 [2]. In a series of 104 cases of GPP in patients of all ages, there were only five children [3]. Although GPP can begin at any age in childhood, in over 25% of certain series onset has been in the first year [4,5]. The disease may begin in the first few weeks of life and two cases of congenital GPP have been described [5].

In contrast to psoriasis vulgaris in childhood [6] and GPP in adults [3], a male preponderance is seen in GPP of childhood (about 3 : 2) [4,5]. Infantile cases are usually benign. Systemic symptoms are often absent and spontaneous remissions occur [4,5]. In at least one-third of infantile cases, a history of an eruption diagnosed as seborrhoeic dermatitis [7], napkin dermatitis or sudden-onset napkin psoriasis [8] is obtained [4,9]. More severe forms with fever and toxicity do occur, necessitating active treatment. Rarely, pustulosis has supervened on a congenital erythroderma [4,10].

The majority of children are aged 2–10 years at onset. The disease may be of Zumbusch pattern, but annular and circinate forms are the most common [4,9,11]. Onset of Zumbusch-type psoriasis may be abrupt with toxicity, and an erythrodermic background can become generalized rapidly (Fig. 35.28). Attacks often settle within a few days, but repeated waves of inflammation may follow [4]. Systemic steroid therapy carries the hazard of disseminated infections with varicella and other viruses [9]. In older children, the disease resembles that in the adult and may be of any of the recognized patterns.

The prognosis may be variable [3] but has been generally good in two series [9,12]. Treatment is discussed below.

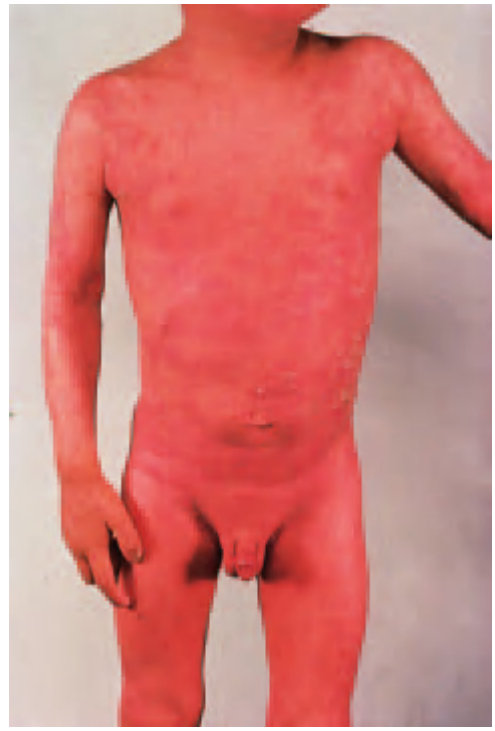

Fig. 35.28 Juvenile pustular psoriasis. (Courtesy of St John's Institute of Dermatology, London, UK.)

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Circinate, annular and linear pustular psoriasis

Annular and other patterned lesions may be seen in acute GPP, but are more characteristic of the subacute or chronic forms of widespread pustular psoriasis [1,2]. Lesions begin as discrete areas of erythema, which become raised and oedematous. Slow centrifugal spread may mimic erythema annulare centrifugum [3,4]. Pustules appear peripherally on the crest of the advancing edge, become desiccated and leave a trailing fringe of scale as the lesion slowly advances.

Some authors have separated a related pattern, well described by Lapière as recurrent circinate erythematous

psoriasis [5,6]. It was originally described in 1907 as 'recurrent circinate erythema'. It may occur alone (in the complete absence at any stage of recognizable psoriasis) or as a phase in what is clearly generalized pustular psoriasis.

Linear forms of pustular psoriasis are occasionally observed within the context of more generalized pustulosis [7,8].

Localized forms of GPP

These must be distinguished from PPP or acropustulosis. The term 'psoriasis with pustules' is perhaps more appropriate. One or more plaques of psoriasis vulgaris may develop pustules (e.g. after excessively irritant topical therapy).

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Differential diagnosis. Subcorneal pustular dermatosis of Sneddon and Wilkinson remains a controversial entity [1,2]. Acute generalized exanthematous pustulosis (AGEP) is perhaps the most important differential, occurring as an acute, spontaneously healing reaction to drugs, usually antibiotics [3]. It is probable that some cases previously reported as drug-induced GPP (see above) may in fact have been AGEP. In infantile acropustulosis, the process does not become generalized and is not associated with constitutional disturbance [4,5]. The distinction between GPP and pustular lesions in Reiter's disease is probably academic. Acute pemphigus foliaceus can mimic subacute GPP, but histological and immunofluorescence testing will distinguish the two. The wasting, glossitis and anaemia associated with the migratory necrolytic eruption of glucagonoma should allow easy differentiation. Occasionally, the bowel bypass syndrome [6,7], Sweet's syndrome [8] and Behçet's syndrome will cause difficulty. Staphyloderma, rampant impetigo or candidiasis in the immunosuppressed or pustular drug eruption (e.g. caused by halides) should be remembered.

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Management [1]. The treatment of acute GPP requires admission to hospital, removal of possible provocative factors, general support measures and topical and usually systemic drug therapy.

Withdrawal of provocative factors. Tar or dithranol can be withdrawn abruptly, but massive overdosage with potent topical corticosteroids requires more care. The application of serially diluted topical steroids over several days may be the safest course, and is preferable to substitution of oral or parenteral corticosteroid, however temporary. Infection, where present, should be treated rigorously with the appropriate antibiotic, usually erythromycin or flucloxacillin. Rarely, when GPP in pregnancy is threatening maternal life, termination or early delivery may be indicated.

General measures. If there is no immediate metabolic threat in acute GPP, and generally in subacute forms, initial treatment should be conservative [2]. This is particularly so in infancy and childhood [3]. Bed rest in hospital, mild sedation, bland local applications with fluid and protein replacement may promote spontaneous reversion to a quieter erythrodermic psoriasis or even psoriasis vulgaris [2]. This approach is particularly apt if a provocative factor has been at play [2]. However, such a course has to be weighed against the risk of repeated waves of pustulation that may exhaust the patient, and the hypostatic and thrombotic hazards of prolonged bed rest, particularly in the elderly patient. Excessive heat loss must be prevented by maintaining an adequate ambient temperature, avoiding cool draughts of air. A low-reading thermometer is essential. Fluid intake should be increased so that the daily urine volume remains adequate.

Topical therapy. Often, completely bland creams or lotions are best. Weak corticosteroid creams may be helpful in subacute forms. Tar [4] and dithranol are contraindicated.

Systemic therapy. Most cases of GPP require systemic therapy. Retinoids are probably the treatment of choice. A

recent survey of 385 Japanese patients with GPP [5] reported that acitretin was effective in more than 80% of cases. Response to high doses of acitretin (1 mg/kg/day) may be rapid [6] and lower doses of 0.5–0.75 mg/kg/day may be sufficient to maintain control [7]. Disease control can sometimes be achieved with intermittent therapy [8]. Combination of etretinate with PUVA is beneficial [9].

PUVA therapy is effective in acute and subacute GPP [9–12]. Very ill patients may have to be treated in the horizontal position. Small doses of UVA should be given initially three or four times weekly; the dose of UVA is slowly increased.

Methotrexate is probably as effective as acitretin but no comparative studies are available [2]. In fulminating GPP, small (7.5–10.0 mg) intravenous doses, repeated every 5–7 days may be safest. The intramuscular route can be used, but the intravenous or intramuscular dosage should rarely exceed 0.3 mg/kg/week. Oral therapy is less predictable, because of variable absorption. Sudden unexpected toxicity from repeated methotrexate doses may follow, because of improved absorption of the drug as the GPP subsides. Orally, dosage of 0.2–0.4 mg/kg/week should suffice, starting at the lower end of the range. If the patient is very ill, renal function may have to be monitored daily if methotrexate overdosage is to be avoided. Methotrexate has been used with success in children with GPP [13].

Control of GPP has been achieved with very high dosage of ciclosporin alone (9–12 mg/kg/day), but toxicity prevented prolonged treatment at these dose levels. With lower dosage, the addition of topical steroids allowed adequate control [14]. However, ciclosporin (5–7 mg/kg/day) failed to alleviate GPP in a renal transplant recipient during periods of prednisolone withdrawal [15]. In contrast, a case of GPP was reported to respond rapidly to ciclosporin 7.5 mg/kg/day, and was successfully maintained in remission at 3.5 mg/kg/day [16]. Three patients, including two children, were successfully treated with low-dose (1–2 mg/kg/day) ciclosporin; the lesions cleared within 4 weeks of starting therapy [17].

Razoxane has been effective in acute GPP [18] but is rarely used now. Hydroxyurea is less effective [19]. Colchicine has been used either alone [20,21] or in combination [22] with methotrexate. 6-Thioguanine has also been used successfully [23].

In the subacute and chronic forms of GPP, the use of dapsone (50–200 mg/day) [24–26] can be considered, and may be particularly valuable in atypical variants and children [2,27]. Oral or parenteral corticosteroid should be used only when urgent control of metabolic complications is needed [2]. The short-term effects of prednisolone (30–40 mg/day) are excellent [2,28], but serious relapses are liable to occur as the dosage is reduced unless another form of therapy (e.g. methotrexate or acitretin) is given simultaneously [2].

Biological agents have been used occasionally and to excellent effect. It appears that these therapies are perhaps well-suited to rapid control of GPP. The TNF-α blockers, infliximab and etanercept, and basiliximab, an antibody directed at the IL-2 receptor, have all been reported to rapidly control acute GPP [29–32]. It is likely that these therapies will become the treatment of choice in cases of fulminant disease.

Cytotoxic drugs, etretinate and PUVA cannot be used in GPP of pregnancy unless termination has become inevitable. Fulminating disease in pregnancy is best treated with prednisolone, the drug that carries the least hazard for the fetus, but ciclosporin has been used safely for treatment of impetigo herpetiformis [33]. Methotrexate, retinoids, PUVA or combination therapy may be needed after delivery to allow weaning off the steroid or ciclosporin [34].

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Prognosis. There is a paucity of data on the long-term prognosis of GPP. Von Zumbusch's patient [1] survived many acute episodes over a number of years, and perhaps had the good fortune to live before potent (and dangerous) remedies were available. Ryan and Baker [2,3] reported on the prognosis in 155 patients with all types of GPP. Thirty-four of 106 patients followed up had died, and 26 of these deaths were attributable to the disease or its treatment. GPP developing from acropustulosis (acrodermatitis continua) had the worst prognosis, seven out of 11 patients having died and a further one remaining severely disabled. To some extent, this particularly poor outlook reflected the age at onset of these patients, who were predominantly elderly. However, death was a direct result of GPP in all of these cases, resulting from cardiac failure or respiratory infection during uncontrolled pustular psoriasis. In general, patients with preceding ordinary psoriasis had a better prognosis than those with atypical prepustular psoriasis [2,3].

The better prognosis of GPP of pregnancy reflects the abrupt removal of the main provocative factor by childbirth or, *in extremis*, termination of the pregnancy [4,5]. GPP of childhood also carries a more benign prognosis [6], providing oral corticosteroids and methotrexate can be avoided [7]. Khan *et al*. [7] stressed the hazard of fatal virus infections in corticosteroid-treated children and advocated bland topical therapy, if necessary in hospital, for up to 3 months in anticipation of spontaneous remission. In their patients, where oral corticosteroids were avoided, growth and development progressed unimpaired despite GPP [7].

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Psoriatic arthritis

Definition. An inflammatory arthritis associated with psoriasis of the skin and/or nails, with usually a negative serological test for rheumatoid factor and the absence of rheumatoid nodules [1].

Epidemiology. Like psoriasis of the skin, good population studies remain to be performed and thus estimation of population prevalence is difficult and highly variable, depending on the study. Historically, arthritis prevalence amongst psoriasis patients has been estimated at 2.6–7% [2,3]. However, more recent large questionnaire-based studies have indicated that the real prevalence may be much higher. Thus, a Scandinavian study revealed arthritis in 30% [4] of psoriatics and in the USA, 23% (www.npf.org). In general, it appears that the more severe the skin disease, the greater the prevalence of arthritis [5,6]. Further, nail disease is more frequent in cases with arthritis. A review of population-based studies estimated the population prevalence of psoriatic arthritis at 0.02–0.1% [7]. There appears to be a stronger association with generalized pustular psoriasis [6] or erythrodermic psoriasis [8] and arthritis.

The age of onset for psoriatic arthritis is, in general, later than for the skin disease, with peak age of onset being the fourth decade. Biodi-Oriente *et al*. [9] reported psoriasis predating arthritis in 68% of cases occurring at the same time in 11%, and following it in 21%. There is a rare but well-recognized juvenile-onset form of psoriatic arthritis [10], with age of onset between 9 and 12 years. Psoriatic arthritis appears more common in individuals with type 1 early-onset psoriasis vulgaris.

In contrast to rheumatoid arthritis, where females predominate 3 : 1, in psoriatic arthritis the sexes appear equally affected.

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Aetiology and pathogenesis

Genetics. Familial clustering of psoriatic arthritis has been reported [1] although much less frequently than for cutaneous psoriasis. There is no evidence that psoriatic arthritis follows Mendelian patterns of inheritance. A large number of HLA association studies have been performed [2]. In general, results concur with studies of cutaneous disease, with HLA Cw6, B13, B17 and DR3 occurring most frequently. A specific association with psoriatic arthritis, not seen in the cutaneous form, is HLA-B27, seen particularly in spondyloarthritis (see below). Genome scans have recently been reported with evidence for a susceptibility locus on chromosome 16q [3]. *CARD15*, a molecule involved in macrophage–monocyte cell signalling, has been implicated as a candidate gene at least in some patients [4]. This molecule has also been implicated in Crohn's disease but not in cutaneous psoriasis.

Environmental factors. Studies of families in which psoriatic arthritis aggregates suggest an important environmental component to disease pathogenesis [5]. Increased immunoreactivity to streptococcal antigens has been reported in sera of patients [6], but establishing a pathogenic link has proved elusive and appears much more tenuous than for the skin disease. An increased prevalence of psoriatic arthritis has been reported in HIV [7] and hepatitis C infection [8], and antibodies to enterobacterial antigens are also recorded [9].

Trauma as a precipitating event has also been noted. Interestingly, trauma appears to be more important in psoriatic compared to rheumatoid and other inflammatory forms of arthritis [10]. Neuropeptides and the nervous system have been implicated in these events [11].

Pathogenetic mechanisms. As for cutaneous psoriasis, T cells probably have a key role in arthritis pathogenesis. Those implicated possess activation and memory surface markers but, unlike skin, do not express the skin homing molecule CLA [12]. Thus, when skin and joint manifestations coexist, different populations of T cells mediate disease at different sites. Intra-articular clonal expansion of CD8-expressing T cells have been observed, but putative antigens remain elusive. As observed in the skin, the morphology of blood vessels in psoriatic arthritis is altered with the presence of dilated tortuous vessels and evidence of angiogenesis [13]. Interestingly, these features are different from that seen in rheumatoid arthritis.

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Clinical features. In one series of 180 patients, the mode of onset was studied, and skin lesions were found to precede arthritis in 65%, arthritis antedated skin lesions in 19%, and in 16% skin and joint involvement occurred almost simultaneously. The peak age of onset of arthritis in this series was 40–60 years [1].

Clinical subgroups. Psoriatic arthritis is not accompanied by rheumatoid-type nodules. The Moll and Wright

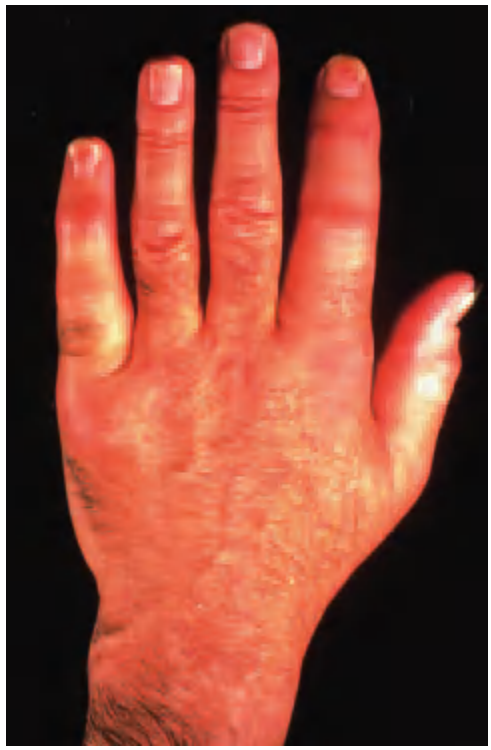

Fig. 35.29 Psoriatic arthritis, showing peripheral oligoarthropathy with sausage-like digital swelling. (Courtesy of St John's Institute of Dermatology, London, UK.)

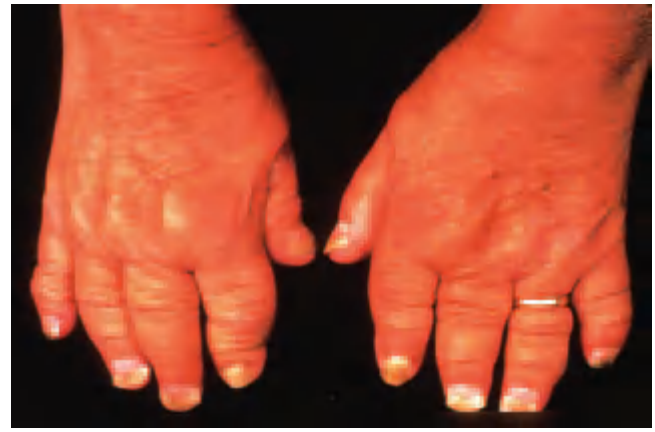

Fig. 35.30 Arthritis mutilans showing gross digital foreshortening. (Courtesy of St John's Institute of Dermatology, London, UK.)

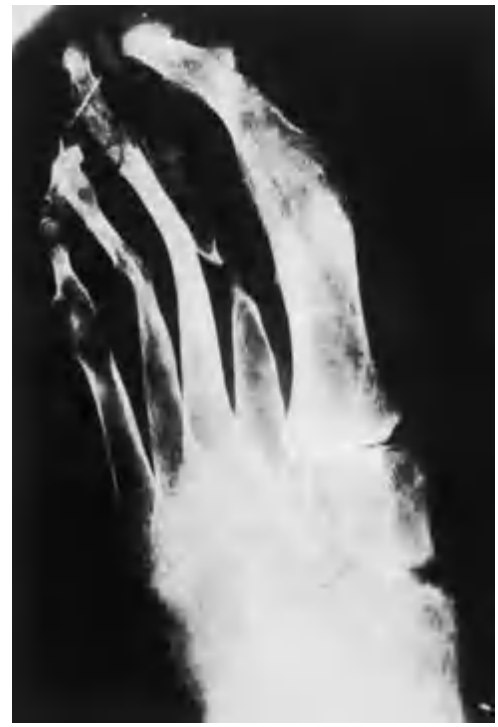

Fig. 35.31 Arthritis mutilans: osteolysis and bony ankylosis. (Courtesy of Royal London Hospital, London, UK.)

classification includes five clinical groups, which often overlap [2,3].

1 Predominantly peripheral mono- or asymmetrical oligoarthritis is the most common form, and often overlooked. An appearance similar to low-grade gout, as well as sausage-like swelling of one or more digits (dactylitis) resulting from terminal and proximal interphalangeal joint involvement and flexor sheath synovitis are recognized (Fig. 35.29).

2 Predominantly distal interphalangeal arthritis, the well-recognized classical form, but less common than previously emphasized.

3 Predominantly symmetrical, rheumatoid-like, rheumatoid factor-negative polyarthritis, usually less severe than rheumatoid arthritis.

4 'Arthritis mutilans', a relatively uncommon, severely deforming arthritis involving fingers and toes predominantly. Gross osteolysis may cause digital foreshortening and ankylosis (Figs 35.30–35.32).

5 Predominantly axial arthritis: psoriatic spondylitis and/or sacroiliitis, with or without variable peripheral arthropathy. Spinal involvement may be clinically silent, but radiological examination suggests that it may affect about one-third of all cases of psoriatic arthritis. Clinically, this form may involve: (i) both spine and sacroiliac joints, as in idiopathic ankylosing spondylitis; (ii) sacroiliac joints alone; and (iii) spine alone. It may be less disabling than the idiopathic form [3,4].

Several more recent clinical studies have indicated a need to reclassify psoriatic arthritis. In two studies, each involving 100 patients, three subgroups were proposed, any of which may include the classical features of psoriatic arthritis, such as distal interphalangeal joint involvement, dactylitis or spondylitis [5,6].

1 Asymmetrical arthritis usually, but not always, involving a small number of joints with few erosions, infrequent deformity and good preservation of function.

Fig. 35.32 Arthritis mutilans: gross osteolysis of metatarsal heads and phalanges. Note pencil-in-cup changes at metatarsophalangeal joints. (Courtesy of Royal London Hospital, London, UK.)

2 Symmetrical polyarthritis, frequently erosive, deforming and functionally disabling, but distinguished from rheumatoid arthritis by association with distal interphalangeal joint involvement, spondylitis and negative rheumatoid factor (titre less than 1 : 80).
3 Predominant spondylitis, similar to ankylosing spondylitis, possibly accompanied by peripheral arthritis but behaving independently of it [6].

Cervical spinal involvement is well recognized [7,8] and may be primarily ankylosing in nature or inflammatory and rheumatoid-like [9]. Both forms may be associated with cord or nerve-root compression related to intervertebral subluxation and/or fusion, and neurological deterioration may require surgical stabilization [8,10–13].

Temporomandibular joint involvement may manifest as local pain, often aggravated by eating [14,15] and may progress to ankylosis requiring surgical management [16]. Orthopantomographical examination showed that 31% of patients with psoriatic arthritis had radiographical changes in the condyle of the temporomandibular joint, as compared with 13% of controls [17]. Computed tomography may reveal changes not visible on conventional radiography [18].

Sternal joint involvement is becoming increasingly recognized but is unusual as an initial manifestation [19,20].

Nail involvement. Psoriasis of the nails occurs in about three-quarters of psoriatic patients with arthritis, but only in about one-third of those with skin lesions alone [1,21,22]. The distal and mutilating forms of arthritis are particularly associated with severe nail dystrophy, and the distal joints and nails affected are often but not necessarily correlated in the same digits [22]. All types of nail involvement may occur [23].

Extra-articular features. These occur less frequently than in rheumatoid arthritis. Subcutaneous nodules are not seen, and tendon sheath effusions are uncommon. In contrast, inflammatory eye lesions are common, conjunctivitis being reported to occur in 20%, uveitis in 10%, and episcleritis and keratoconjunctivitis sicca in about 2 and 3%, respectively [24]. Cardiac involvement similar to that seen in ankylosing spondylitis has been reported [25].

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Laboratory findings. The most important serological feature is the negative test for rheumatoid factor, particularly in patients with distal and mutilating arthritis. In patients with psoriatic arthritis of the rheumatoid type, about one-quarter had a positive test or a test that fluctuated between positive and negative [1]. Some of these patients probably represent the coincidental association of psoriasis and rheumatoid arthritis, but a weakly or intermittently positive rheumatoid factor occurs in approximately 5% of the normal population [2] and should not necessarily lead to the diagnosis of rheumatoid arthritis. Other reported laboratory abnormalities, such as anaemia, raised ESR and C-reactive protein, transient leukocytosis, and raised immunoglobulin levels, most consistently IgA, have been reviewed [3,4]. It has been concluded that none of these is sufficiently specific to contribute to diagnosis, management or prognostic evaluation [4]. The conflicting reports of the association between hyperuricaemia and psoriasis are outlined above. Antinuclear antibodies have been reported as both positive and negative [3], but in an American study of 1285 patients they were found to have little predictive value [5].

Histopathology. The histopathologies of psoriatic and rheumatoid arthritis appear to be similar, except that characteristic rheumatoid granulomas have not been found and there may be more fibrosis [6,7] and vascular changes [8] in the psoriatics. In spite of these possible differences, synovial biopsy usually has no place in the routine clinical management of psoriatic arthritis [4].

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Radiological changes [1–3]. The changes may be indistinguishable from those of rheumatoid arthritis: local demineralization, narrowing of joint spaces, articular erosion of varying degree and soft-tissue swellings. Atypical features include destructive changes in the terminal interphalangeal joints, a tendency to hypertrophic changes and absence of generalized demineralization.

In the distal type of psoriatic arthropathy, early changes may consist only of minimal 'fluffiness' and osteoporosis of the distal phalanx, but gross destruction eventually occurs. Four characteristic signs of psoriatic arthropathy, seen in one controlled series [1], were:

1 A destructive distal interphalangeal arthropathy—bony ankylosis of the interphalangeal joints
2 Destruction of the interphalangeal joints with abnormally wide joint spaces and sharply demarcated adjacent bony surfaces
3 Destruction of the interphalangeal joint of the great toe with bony proliferation of the distal phalanx
4 Resorption of tufts of the distal phalanges of hands and feet (uncommon).

In arthritis mutilans, the joint changes are widespread. The 'opera-glass hand', in which the fingers can be pulled in and out, results from gross destruction and absorption of the bones. The heads of metacarpals and metatarsals may completely disappear, leaving a tapered bone looking like a sharpened pencil. Such gross osteolysis may be followed by bony fusion (Figs 35.31 & 35.32).

Intermittent hydrarthrosis may occur. Sacroiliac changes similar to those of ankylosing spondylitis are common [4–6]. Syndesmophytes and calcification of the interspinous ligaments are also seen [6]. Cervical changes including apophyseal sclerosis or joint narrowing, and calcification of the anterior ligament, are common [7], and there is a tendency to posterior fusion of the cervical vertebrae [3]. Paravertebral ossification of the lumbar and thoracic regions may occur more laterally in psoriasis than in spondylitis [8].

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Differential diagnosis. This has been reviewed in detail elsewhere [1]. One of the subgroups of psoriatic arthritis may be clinically indistinguishable from rheumatoid arthritis. As a weakly or intermittently positive rheumatoid factor occurs in 5% of the normal population [2], this should not necessarily lead to the diagnosis of rheumatoid arthritis. Gout may be simulated, especially if the onset is acute and monoarticular, or if widespread psoriasis is associated with hyperuricaemia. Ankylosing spondylitis may be similar, but the onset tends to be later, peripheral

involvement is more common, and the arthritis does not necessarily begin in the spine. The acute Heberden's node of osteoarthritis may cause confusion, and distinction from Reiter's disease may be difficult or impossible.

Treatment. Treatment follows the general lines of management of inflammatory polyarthritis, and is best supervised by a rheumatologist. Assessment of efficacy of therapies for psoriatic arthritis is hindered by inexact definition of the condition, the variable clinical presentation and lack of validated outcome measures. The treatment of psoriatic arthritis has been recently reviewed [1].

Symptomatic treatment. Mild arthritis can usually be controlled with NSAIDs. There is concern that NSAIDs may exacerbate the skin lesions of psoriasis [2,3], although a randomized controlled trial showed no worsening of psoriasis in patients treated with the NSAID nimesulide [4]. Cyclo-oxygenase-2 (COX-2) selective inhibitors are effective but, as with traditional NSAIDs, caution should be exercised in the elderly and those with impaired renal function.

Systemic glucocorticosteroids are not recommended for the long-term treatment of psoriatic arthritis not only because of the well-recognized side effects but also because chronic glucocorticosteroid use can make psoriasis more labile and withdrawal can on occasion lead to a rebound pustular flare [2,5]. Intra-articular injections of glucocorticosteroid are used to treat monoarthritis [6].

Disease-modifying antirheumatic drugs (DMARDs). Ascertaining effectiveness of DMARDs in the management of psoriatic arthritis is complex [1]. The clinical subgroups respond differently, for instance axal involvement associated with HLA-B27 has a relatively poor response to treatment [7]. The most commonly used DMARDs for psoriatic arthritis are methotrexate, ciclosporin and sulfasalazine although there are few randomized controlled trials.

Methotrexate is the most widely used of the DMARDs for psoriatic arthritis—particularly as it is effective for the skin lesions, and is amenable to combination with other DMARDs to enhance efficacy. Only two randomized controlled trials provide evidence [8,9], one [8] used parenteral injections of high-dose methotrexate (1–3 mg/kg)—a dose probably too toxic. A second study [9] showed that methotrexate 7.5–15 mg/week was superior to placebo only in physician assessment of arthritis. Thus, the data imply that methotrexate is beneficial for synovitis but there is no evidence of benefit for axial disease.

Ciclosporin is probably less effective than methotrexate for the treatment of psoriatic arthritis but evidence is mainly accrued from open studies. In an 18-week open study [10], ciclosporin 4.8 mg/kg/day benefited psoriatic arthritis but the effect was less marked than for the skin lesions. In a trial comparing methotrexate to ciclosporin [11], ciclosporin 3–5 mg/kg/day produced significant improvement in clinical and serological measures of severity of psoriatic arthritis. An Italian study [12] found that ciclosporin was more effective than either sulfasalazine or placebo in reducing a variety of clinical measures of severity. Long-term use of ciclosporin may control progression of radiological damage in peripheral joints [13].

Sulfasalazine has been subject to more open trials and randomized controlled trials than either methotrexate or ciclosporin for the treatment of psoriatic arthritis. Despite encouraging results from open studies and one short (8-week) study [14], this promise has not been substantiated by most randomized controlled trials [1,15,16]. Overall, the evidence suggests that sulfasalazine has a small beneficial effect on peripheral synovitis, particularly pain [17], but whether efficacy is enhanced by increasing the daily dosage above 3 g is unclear [1,18]. Axial disease is not benefited [1].

Gold salts (oral auranofin) and intramuscular sodium thiomalate are used to treat psoriatic arthritis [19,20]—on the evidence sodium thiomalate appears to be the better of the two, but less effective than methotrexate [21,22]. Occasional exacerbation of the skin lesions of psoriasis by gold salts can occur [23].

A variety of other DMARDs have been investigated and advocated for the treatment of psoriatic arthritis, none of which has been subject to good randomized controlled trials. Leflunomide (a pyrimidine synthesis inhibitor effective for rheumatoid arthritis) appeared to have some benefit in psoriatic arthritis in both the short term (3 months) and long term (2 years) in a longitudinal study of eight patients [24].

Antimalarials, particularly chloroquine [25], may be of limited benefit, but this class of drug can, on occasion, exacerbate psoriasis. Mycophenolate mofetil has shown some initial promise [26], but the efficacy of colchicines is variable; however, one randomized controlled trial has demonstrated benefit [27]. Open studies suggesting that etretinate is effective have been reviewed [28], but a randomized controlled trial demonstrated only a modest effect [28]. PUVA, oral and extracorporeal, was reported to improve peripheral joint arthritis [29,30], but had no effect on axial disease [30]. A limited randomized controlled trial of azathioprine versus placebo showed benefit [31]. Success has been reported for other drugs including 6-mercaptopurine [32], D-penicillamine [33], systemic 1,23-dihydroxyvitamin D_3 [34] and 2-chlorodeoxyadenosine [35].

Biological agents. The introduction of biological agents into the therapy of rheumatoid arthritis has revolutionized the management of that disease. Unsurprisingly, the same agents have been trialled, and in one case approved for the treatment of psoriatic arthritis. The main biological agents

to have been trialled in psoriatic arthritis are blockers of TNF-α and of T-cell activation. The two main anti-TNF-α blockers are infliximab, a chimeric human–murine anti-TNF-α IgG1 antibody, and etanercept, a dimeric fusion protein consisting of the extracellular portion of the human p75 TNF-α receptor linked to IgG1. Infliximab significantly improved psoriatic arthritis in small open studies either as monotherapy [36] or in combination with methotrexate [1]. Etanercept has been subject to good randomized controlled trials [37]; 25 mg administered subcutaneously twice weekly over 12 weeks produced significant improvement in 87 and 23% of patients treated with etanercept and placebo, respectively. An open trial has reported that axial arthritis is also improved by etanercept [38]. Blockade of T-cell activation by inhibition of co-stimulatory molecule binding is under rigorous investigation in psoriasis. Alefacept (licensed for treatment of psoriasis) is an LFA-3 IgG1 fusion protein that blocks LFA-3–CD2 binding and apoptosis circulating $CD45RO^+$ memory effector T cells. A small study of 11 patients demonstrated clinical improvement in 64% of patients [39]. It is highly likely that more biological agents, particularly blockers of pro-inflammatory cytokines, will be approved for treatment of psoriatic arthritis.

Surgery. The place of surgery has been reviewed [40,41]. In spite of past reluctance to perform elective surgical procedures in view of perceived risks of infection, a review of 41 orthopaedic operative procedures and 54 other surgical procedures in patients with psoriasis and arthritis revealed a low prevalence of wound sepsis and other complications. It was therefore suggested that elective surgery should not be withheld from these patients [40]. Such procedures might include joint prosthesis and cervical spine stabilization, and the use of digital distraction lengthening and bone grafting for severe arthritis mutilans has also been described [41].

Prognosis. A 10-year follow-up study suggested that psoriatic arthritis produced less pain and disability than rheumatoid disease [42]. Excluding the arthritis mutilans group, in this study 30% lost no time off work, only 3% had more than a total of 1 year off work in 10 years, and many patients showed little or no radiological deterioration. Thus, it is usually perceived that psoriatic arthritis may be a mild disease, and that the descriptions of mutilating digital disease and occasional severe spondylitis may give a false impression of the usual prognosis in these patients. However, in a Canadian study of 220 patients with psoriatic arthritis, deforming erosive arthropathy was found in 40% of cases. The concept that psoriatic arthritis is often a benign arthropathy was therefore challenged [43]. Indicators of poor prognosis include younger age at onset, extensive skin involvement, polyarticular synovitis, HIV infection, high ESR at presentation, large numbers of effusions and association with HLA B27, B39 and DLW3 [1,44].

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Chapter 36

Non-Melanoma Skin Cancer and Other Epidermal Skin Tumours

R.M. MacKie & A.G. Quinn

Introduction

The complexity of the cellular composition of the skin means that the range of tumours that can arise within the skin is very wide. This chapter deals chiefly with the benign and malignant tumours arising from epidermal keratinocytes. Non-melanoma skin cancers and related premalignant lesions are dealt with in a separate section in view of their clinical importance and the overlap in the epidemiology, pathogenesis and management of these tumours. Chapter 37 is devoted to appendage tumours, Chapter 38 to tumours arising from the melanocyte and Chapter 53 to soft-tissue tumours.

A *tumour* is an abnormal mass of tissue, the growth of which exceeds and is uncoordinated with that of normal tissues. Although most tumours retain a resemblance to the normal tissue from which they arise, they can show an extraordinary variation in their structure and it is this variation that causes difficulties in some cases in establishing a definitive pathological diagnosis. Most of the keratinocyte-derived tumours described in this chapter are *benign*, which is the term used to describe tumours where the cells remain at their site of origin forming a single mass of tumour cells. *Hamartomas* are difficult to distinguish from true benign tumours clinically. They are not true tumours and best considered as a localized overproduction of one or more elements of a tissue but without the progressive growth characteristics of a tumour. *Malignant* tumours are composed of cells that have acquired the ability to invade through a basement membrane and this is associated with the capacity to metastasize to other organs by the lymphatics and blood vessels. In addition, malignant tumours frequently show more rapid growth and less differentiation than benign tumours, which is reflected histologically by higher mitotic rates, cellular and nuclear pleomorphism and abnormal mitoses. Differentiation between benign and malignant tumours is one of the major responsibilities of a dermatopathologist. The distinction, however, can be

difficult with small tissue samples and is not absolute, which means that it is vital that there is good communication between the clinician and pathologist, particularly when the pathology report suggests biological behaviour that is not in keeping with the clinical impression.

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Non-melanoma skin cancer and related premalignant lesions

Non-melanoma skin cancer (NMSC) is the most common human cancer. The term encompasses basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) of the skin, which are both derived from epidermal keratinocytes. Although these tumours are clinically and pathologically distinctive, they share some characteristics and are frequently classified under the term non-melanoma skin cancer for health care planning, cancer registry reporting and epidemiological purposes. In contrast to other common epithelial cancers, NMSCs rarely metastasize, which means that the case fatality rate for these cancers is low. This low mortality from NMSC has contributed to the widespread underreporting of this cancer to disease registries in many countries and makes it impossible at present to quantify accurately the morbidity and health care costs associated with this disease. Nevertheless, given the high prevalence of NMSC and the frequent occurrence of multiple primary tumours in affected individuals, there is little disagreement amongst dermatologists that NMSC is an important and frequently underestimated public health problem.

Patients at risk for development of NMSC are also predisposed to the development of actinic keratoses (AK) and Bowen's disease, which are premalignant lesions that show some of the histological characteristics of SCC. The prevalence of AK and the multiplicity of lesions within individual subjects is considerably greater than that for NMSC. While there is some controversy about the premalignant potential of AK and Bowen's disease and their relationship to SCC, these lesions are in themselves an important clinical problem for two reasons. First, they need to be distinguished from SCC and, secondly, the scaling and inflammation associated with these lesions means that they are the cause of some morbidity in their own right.

Epidemiology and risk factors for non-melanoma skin cancer development

Epidemiological surveys have a key role in the generation of incidence and prevalence data for NMSC in populations, quantification of the clinical impression of increasing skin cancer incidence and identification of environmental and host factors important in NMSC development.

Incidence and mortality

Up-to-date accurate incidence figures for NMSC in different geographical regions are difficult to obtain as there are relatively few population-based studies. Giles *et al*. [1], in an Australian postal survey of 31 000 individuals, conducted in 1985, reported 652 BCCs and 160 SCCs and an increased incidence of SCCs from 166 to 250 per 100 000 over the 5-year period, and an 11% increase in the incidence of BCCs [2]. In the USA, a population-based study [3] quotes an incidence of 38 SCCs per 100 000 population, with a 3 : 1 male : female preponderance. Miller and Weinstock [4] have estimated that in 1994 there were 1 million new cases of NMSC in the USA. Mortality from NMSC in the USA is estimated at $0.44/10^5$ per year [5], with the main cause of death being metastases from SCC. There are a few recorded deaths from BCC, most of these being related to refusal of surgical treatment. The annual cost of treating NMSC in the USA has been estimated at over $500 million [6].

The incidence of NMSC has increased dramatically over the last 30–40 years in many populations worldwide. In addition to the study by Giles in Australia showing a 50% increase in the incidence of SCC and an 11% increase in the incidence of BCCs between 1985 and 1990 [2], Miller and Weinstock have reported a threefold increase in NMSC incidence in the USA over the past two decades with a continuing rise at a rate of 8% per year [4]. Increases in NMSC incidence have also been reported in Europe. In Wales, a population-based study has shown that the crude incidence for NMSC has increased from 173.5 to 265.4 per 100 000 population per annum between 1988 and 1998 [7]. Although differences in the methodologies between reported population-based studies make it difficult to directly compare NMSC incidence in different countries, comparison of age-specific incidence rates of BCCs in two studies from Sweden and Australia indicate that the rate in northern Europe is approximately 3–4 times less than that seen in the Australian population [1,7,8].

Most studies indicate that BCCs account for more than 70% of the cases of NMSC in areas with both high and low ambient sun exposure. Although a ratio of 4 : 1 BCC : SCC has been described as a relatively consistent finding in studies of NMSC incidence in non-immunosuppressed white-skinned individuals, closer examination of the available information shows that that this ratio differs between countries with low and high ambient sun exposure, which reflects a disproportionate increase in SCC relative to BCC with increasing sun exposure. In some groups such as white Maryland fisherman with very high occupational ultraviolet radiation (UVR) exposure, the ratio of BCC : SCC is almost 1 : 1 [9].

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Environmental risk factors

Ultraviolet radiation

UVR is now recognized as by far the most important and best understood risk factor for NMSC development. An association between sun exposure and NMSC was first suggested by Thiersch and Unna at the end of the 19th century and substantiated by the work of Hyde [1] and Dubreuilh independently at the beginning of the 20th century [2]. Since then, a large body of information from epidemiological, clinical and experimental observations has been generated to substantiate the proposed causal link between the sun and NMSC development. This evidence includes the increased frequency of NMSC in areas of high ambient sun exposure; the latitude gradient in the annual age-adjusted incidence in the USA for cutaneous SCCs, with an increasing incidence the nearer one gets to the equator because of greater levels of the UVB component of terrestrial sunlight [3]; the increased incidence of NMSC in sun-sensitive people, which is dramatically highlighted by the differences in NMSC risk between albinos and non-albinos in countries such as Tanzania with high ambient sun exposure [4]; the association between NMSC and 'benign' sun-related conditions such as photoageing and solar telangiectasia; and the marked increase in NMSC incidence with increasing age resulting from cumulative sun exposure, which reflects both the intensity and duration of this exposure [3,5]. The strength of the evidence led the International Agency for Research on Cancer to conclude in 1992 that sun exposure was carcinogenic in humans and that it has a causal role in NMSC development [6].

The increasing incidence of NMSC over the last 30 years is largely the result of increased recreational sun exposure and there are many parallels between the changing epidemiology of NMSC with that other well-known 20th century epidemic, smoking-related lung cancer. Sunbathing, like cigarette smoking, became popular in the early half of the century with the popularization of the bronzed look by Coco Chanel in the 1930s. Although the development of sunbathing as a popular leisure pursuit has lagged behind cigarette smoking, changes in attitudes about the desirability of a tan, coupled with increased leisure time, the introduction of paid holidays and the development of cheap package holidays have seen a marked increase in the level of individual sun exposure in the latter half of the 20th century. In parallel with smoking-related lung cancer, the incidence rate for NMSC has lagged behind the changes in carcinogen exposure, which means that the current clinical impression of increasing NMSC incidence is likely to be a prelude to reporting on a more substantial scale over the next 30–40 years.

The relationship between exposure to UVR and skin cancer development is complex. Epidemiological studies have had an important role in the identification of differences between BCC and SCC with respect to age and pattern of sun exposure. Migrant studies have established that high sun exposure in childhood is especially important in determining NMSC risk and that that there is a sharp change in relative risk of NMSC between arrival before and after 10 years of age [7]. Although the basis for this age effect is still unclear, an important consideration is the possibility that the skin is more susceptible to the carcinogenic effects of UVR in childhood. The concept that the response of the skin with respect to cancer susceptibility may be qualitatively different in early life is supported by the observation that susceptibility to melanocytic naevus formation is also greatest during this period [8]. Although both BCC and SCC increase with increasing ambient sun exposure, there is a proportionately greater effect of increasing sun exposure on SCC risk [9]. Other observations that suggest that the relationship between sun exposure is not the same for BCC and SCC include the greater preponderance of BCCs on intermittently sun-exposed areas, the plateauing of BCC but not SCC risk after moderate solar exposure, and the finding that for occupational sun exposure SCC but not BCC risk is related to hours of exposure, whereas BCC risk but not SCC risk is increased by sun exposure occurring during holidays [6,10].

UVR comprises a broad band of energy extending from 200 nm to visible light in the lower 400 nm range (see Chapter 24). The UV part of the solar electromagnetic spectrum is subdivided into three broad regions: UVA, UVB and UVC. Although UVB is the main wave-band responsible for skin cancer induction, there is increasing interest in the carcinogenic potential of UVA. Exposure to UVA has increased considerably over the last 20 years for two reasons. First, UVB blocking sunscreens have allowed sunbathers to spend longer in the sun and, secondly, the desire to achieve a tan has led to the growth in popularity

of UVA sunbeds. Experimental evidence suggests that UVA is carcinogenic [11] but it has been difficult to assess the risk of NMSC development from commercial tanning equipment, as people who tend to use sunbeds also tend to have greater levels of exposure to natural sunlight. Support for a role for UVA in NMSC induction in humans comes from recent reports of both precancerous lesions and NMSC in some individuals in areas of skin exposed almost exclusively to artificial UVA sources [12,13].

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Photochemotherapy (PUVA) and UVB phototherapy

PUVA and UVB phototherapy are widely used by dermatologists and are recognized as highly effective treatments for a variety of skin diseases. On theoretical grounds, repeated exposure of the skin to artificial UVR or PUVA would be expected to result in cumulative actinic damage and an increased risk of NMSC. Although a recent meta-analysis has estimated excess skin cancer incidence in patients treated with UVB phototherapy between −0.6 and 2 extra skin cancers per 100 patients treated per year [1], this in itself is insufficient evidence to definitively establish that phototherapy for psoriasis and other dermatological problems increases skin cancer risk. Given the links between sun exposure and NMSC, however, it is prudent to ensure monitoring and accurate record keeping of cumulative doses of UV, particularly with the newer phototherapeutic modalities such as narrow-band UVB lamp (TL01) and high-dose UVA1 regimens while this uncertainty remains.

In marked contrast to the lack of clinical evidence of carcinogenicity of UVB phototherapy, there is strong evidence that PUVA increases the risk of developing SCC. The carcinogenic potential of PUVA in humans was first described in 1979 [2] and there is now a substantial amount of information documenting the long-term clinical effects of PUVA [3,4]. NMSC risk in PUVA-treated patients is correlated with cumulative UVA dose and, although earlier data suggested that PUVA may increase susceptibility to both BCCs and SCCs, more recent studies indicate that the increased skin cancer risk is almost exclusively a result of increased SCC risk. Although at a population level it is clear that high-dose PUVA (defined as more than 200 treatments or 2000 J/cm^2) is associated with a 14-fold (95% CI 8.3–24.1) increase in NMSC incidence rate compared to low-dose patients [4], there is evidence that the risk is not uniformly distributed in high-exposure patients, which suggests that other factors may have an important role in modifying risk [5]. In this study, clinical review of patients exposed to more than 2000 J/cm^2 revealed that only 50% of patients had SCCs or premalignant lesions. Interestingly, none of the 13% of patients in this study without PUVA lentigines had dysplastic lesions, which suggests that the absence of lentigines may be helpful in the identification of patients at low risk of PUVA malignancy.

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Chemical carcinogens

The importance of exogenous carcinogens in human skin carcinogenesis was first suggested by Sir Percival Potts, based on observations of an increased incidence of scrotal cancers in chimney sweeps [1]. This hypothesis was supported by observations made by Volkmann in 1874 of a high incidence of NMSC in workers exposed to tar and mineral oil. These observations, and the occurrence of NMSC in other occupational groups exposed to aromatic hydrocarbons at work, served as a stimulus for the large body of experimental studies with chemical carcinogens in animals, which have provided considerable insight into the biology of cancer. The epidemiology of skin cancers

resulting from the occupational environment has been extensively reviewed [2]. Many aspects of occupational skin cancers parallel observations made in animal chemical carcinogenesis models. The prevalence of industrial skin cancer is determined by the potency of the carcinogens and by the thoroughness of the measures used to protect workers from them. The likelihood of an individual developing tumours is influenced by the duration of the exposure. An inverse relationship has been established between the age at first exposure and the length of the latent period following exposure to cutting oils and some other industrial carcinogens [3]. The long latent period between exposure and NMSC development and the observation that cancers can develop without a requirement for ongoing exposure means that it is likely that many cases of occupational-induced skin cancers are not recognized and therefore, by implication, the published figures are likely to reflect a lowest approximation of the true incidence.

Arsenic is another important chemical carcinogen implicated in NMSC development. The association between arsenic administration and the subsequent development of both cutaneous and systemic malignancies was first recognized in 1887 by Sir Jonathan Hutchinson. Unlike aromatic hydrocarbons where exposure was frequently occupationally related, arsenic exposure in the first half of the 20th century was more often caused by the ingestion of medical arsenic in the form of potassium arsenite (Fowler's solution) used to treat asthma and psoriasis [4]. Today, arsenic exposure most frequently occurs because of high arsenic levels in well water from either natural sources or as a result of contamination from mining waste [5].

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X-rays and thermal radiation

Physical agents other than solar radiation are less frequent causes of NMSC but are an important aetiological factor in some subject groups. The carcinogenic effects of X-rays on the skin were first recognized by Frieben in 1902. NMSCs resulting from X-rays still occur in some at-risk occupational groups such as dentists, radiographers, physicians and engineers. Other at-risk groups include patients treated with Grenz rays for other dermatological conditions such as scalp ringworm, and patients who have received radiotherapy for the treatment of ankylosing spondylitis [1], lymphomas and other malignancies. Exposure to X-rays in childhood appears to be an important risk factor for BCC development [2]. The long latent period between exposure to ionizing radiation and NMSC development means that cases of radiation-induced NMSC may be overlooked if a careful history is not taken, particularly if they occur on sun-exposed sites. Patients who develop large numbers of BCCs within an irradiated field should be examined for signs of the naevoid basal cell carcinoma syndrome (Gorlin's syndrome) as some patients with this syndrome show a marked increase in susceptibility to ionizing radiation-induced BCCs [3,4].

Chronic exposure to thermal radiation is also recognized as a risk factor for NMSC development. Most of the evidence comes from studies of different cultural groups where an increased incidence of NMSC has been linked to common practices within these groups. Examples include Kangri cancer in the people of the Kashmir, resulting from repeated contact of abdominal skin with an earthenware brazier containing burning charcoal [5]. Additional clinical signs implicating thermal radiation include erythema ab igne and/or thermal keratoses, which frequently co-localize with thermal-induced cutaneous SCCs [6,7].

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Human papillomavirus

The association between human papillomavirus (HPV) and squamous cell neoplasia is best established for cervical and anogential cancers, which have served as a useful paradigm for unravelling the complex relationship between HPV and cancer development. HPV infection of mucosal keratinocytes is common and the prevalence is increased in woman at high risk of cervical cancer. Epidemiological HPV typing studies had a key role in defining two distinct groups of genital HPV types that show marked differences in their strength of association with cancer development. 'High-risk' types (HPV16, 18, 31, 33 and 35) were found to be strongly associated with cancer

development while 'low-risk' types (HPV6, 11, 42, 43 and 44) were not [1]. HPV typing studies to date have not generated convincing evidence that implicates high-risk genital HPV types with the development of most cutaneous squamous cell neoplasms. An association has been identified between HPV16 and two unusual clinically distinctive cutaneous squamous cell neoplasms, periungal SCC and palmoplantar Bowen's, and it is likely in these tumours that the oncogenic effects are mediated by mechanisms similar to those operating in mucosal keratinocytes [2].

In spite of the absence of a link between high-risk genital HPV types and NMSC, there is compelling evidence of a link between cutaneous viral warts and NMSC. This association was recognized from observational studies of patients with the rare inherited condition epidermodysplasia verricuformis (EV) many years before the epidemiological studies linking HPV infection to cervical cancer [3]. Patients with EV develop extensive cutaneous plane and common warts at an early age and in later life frequently develop SCCs on sun-exposed areas. Although the genetic basis for EV is still unclear, HPV typing suggests that there may be an aetiological link between HPV and skin cancer development as over 90% of the EV-associated skin cancers contain HPV types 5 and 8. The clinical similarities between EV and the skin phenotype seen in immunosuppressed organ transplant recipients has led to speculation that HPV may contribute to the increased risk of NMSC development in these patients. The development of new approaches that allow detection of a wide range of HPV types has provided some new insights into the potential role of HPV in NMSC development. In a recent study, HPV DNA was detected in more than 80% of NMSC from immunosuppressed patients [4]. In contrast, less than 40% of NMSC from immunocompetent individuals contain HPV DNA. In this study, HPV DNA was detected in SCCs, BCCs and premalignant lesions in both immunocompetent and immunosuppressed patients and the most common HPV types identified were of the EV type. Cutaneous HPV types were more common in tumours from immunosuppressed patients compared to immunocompetent patients, and in the immunosuppressed patients the cutaneous HPV types were frequently found as mixed infections with EV-type papillomaviruses.

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Host susceptibility factors

Familial cancer syndromes

Interindividual differences in the susceptibility to NMSC development have been recognized for many years and epidemiological studies have identified a number of phenotypic features, such as hair colour, skin colour, freckling tendency and ability to tan, which show a consistent correlation with NMSC risk. Genes that determine inherited susceptibility to NMSC development can be divided broadly into two main types. The first type are genes associated with rare, highly penetrant cancer predisposition syndromes and includes conditions such as the naevoid basal cell carcinoma syndrome (NBCCS), Gorlin's syndrome (MIM 109400), Bazex's syndrome (MIM 301845) and xeroderma pigmentosum. The second type are multiple low-penetrant genetic loci that may contribute to susceptibility in the general population. Evidence for the importance of these latter genes has come from quantitative trait loci mapping of other cancers in murine models. Although mapping of similar loci in humans is difficult, association studies provide some evidence to support a role for high-frequency low-penetrant traits such as DNA damage repair capacity and xenobiotic metabolism in BCC susceptibility.

Naevoid basal cell carcinoma syndrome [1,2]

SYN. BASAL CELL NAEVUS SYNDROME; GORLIN'S SYNDROME

Definition. An autosomal dominant familial cancer syndrome in which affected individuals are predisposed to the development of multiple BCCs at an early age and a variable combination of other phenotypic abnormalities including a highly characteristic facies (with large forehead), bifid or otherwise misshapen ribs, vertebral and other skeletal anomalies, pits of the skin of the palms and soles, dysgenesis of the corpus callosum, calcification of the falx cerebri (at an earlier age than is seen in non-affected individuals) and macrocephaly.

Aetiology and incidence. Population-based studies suggest that the prevalence of this disorder in the UK is approximately 1 in 56 000 of the population [3]. The high rate of new mutations and the variable expressivity of the condition, however, makes full ascertainment difficult, particularly in mildly affected individuals where there is no family history of the condition. Although NBCCS differs from other autosomal dominant cancer syndromes in that many of the associated features are developmental abnormalities, the presence of multiple BCCs at an early age is consistent with the 'two hit model' for inherited cancers first proposed by Knudson. The gene for this syndrome maps to chromosome 9q22.3–3.1 and the frequent

loss of heterozygosity of this region in DNA from both sporadic and familial BCCs indicates that the gene is a tumour-suppressor gene [4]. The NBCCS gene was identified in 1996 with the identification of mutations in the *PATCHED* (*PTCH1*) gene in the germ line of NBCCS patients and in sporadic BCC tumour samples [5]. *PTCH1* is the human homologue of PTC, which was first identified as a key regulator of the evolutionarily conserved Hedgehog (Hh) signalling pathway in elegant genetic studies of embryonic segmentation and imaginal disc specification in *Drosophila*. This finding was the first reported example of a link between genes important in development and cancer, and provided a completely new insight into the molecular pathways important in the development of this common skin cancer. The importance of Hedgehog signalling during normal development explains many of the other phenotypic abnormalities seen in patients with NBCCS and these features are consistent with findings from studies of heterozygote *PTCH1* knock-out mice [6].

Clinical features [7]. The skin manifestations of the syndrome are varied and include BCCs, skin tags, palmoplantar pits, milia, epidermoid cysts and lesions that clinically resemble dermal naevi. Skin lesions including BCCs may be present at birth or develop in infancy but more frequently develop between puberty and 35 years of age. The number and type of skin lesions is very variable both within and between families and there is a marked difference between white people and African Americans in the number of BCCs [8]. It is not uncommon to find affected individuals with several hundred lesions. With the exception of the pits that are localized only on the palms and soles, skin lesions can occur in any region. The eyelids, nose, cheeks and forehead are the usual sites, but the neck, trunk and axillae are quite frequently involved. The scalp and limbs are usually spared.

The individual lesions are smooth surfaced, rounded, elevated papules, flesh-coloured or pigmented, varying in size from 1 to 15 mm in diameter. The lesions tend to increase in size and number up to late adolescence. There may be fine telangiectasia and milium-like bodies just below the surface. Tumours of the axillae, neck and eyelids tend to be pedunculated. Most lesions appear to behave in a relatively benign fashion with barely discernible growth and/or evidence of clinical progression. As is the case for patients with sporadic BCCs, some patients with NBCCS develop more aggressive tumours, which can be more difficult to treat and may cause significant morbidity or, rarely, death resulting from extensive invasion and/or recurrence following treatment. The proportion of NBCCS patients who develop very aggressive tumours and the risk factors for this have not been established. Aggressive tumours appear to occur more frequently on the eyelids or nose, and can cause gross destruction. In one study, four of five cases with aggressive BCCs in a series of 36 NBCCS patients received radiotherapy as the initial therapy, which suggests that radiotherapy may be a contributing factor to tumour aggressiveness in some NBCCS patients [9]. A variety of other skin manifestations have also been described, including multiple epidermoid cysts, milia and palmoplantar pits. The pits are a useful diagnostic feature that occur in about 65% of adults with NBCCS but are relatively rare in children. They are characterized by small, more or less circular pits, which may have an erythematous base and are usually 1–2 mm deep.

Other diagnostically useful phenotypic abnormalities in NBCCS patients include jaw cysts, a highly characteristic facies (broad nasal root, hypertelorism, frontal bossing), bifid or otherwise misshapen ribs, vertebral and other skeletal anomalies, dysgenesis of the corpus callosum, calcification of the falx cerebri (at an earlier age than is seen in non-NBCCS individuals) and macrocephaly [2]. The dental cysts are usually multiple, occurring in one or or both jaws, and are odontogenic keratocysts [10]. Skeletal abnormalities include spina bifida occulta, bifid or splayed ribs, scoliosis or kyphosis, and occur with one-third of the frequency of the cysts or the basal cell naevi [11]. Less common associated anomalies include syndactyly, shortened metacarpals, cleft lip and palate, bicornuate uterus, hypogonadism in males, lymphatic cysts of the mesentery, ocular abnormalities including dystopia canthorum, cataracts and congenital blindness, and a variety of neurological disorders [12–17]. In addition to BCCs, the syndrome is associated with an increased susceptibility to other neoplasms including rhabdomyosarcoma, ovarian and cardiac fibromas and, in particular, medulloblastoma. Approximately 3% of NBCCS patients develop medulloblastomas, and approximately 3% of patients with medulloblastomas have NBCCS [18].

Pathology [19]. The histopathological appearance of BCCs from patients with NBCCS are indistinguishable from those seen in sporadic BCCs. The tumours induce a fibrous stroma as occurs with trichoepithelioma or nodular BCC, and the lesions may become papular or pedunculated. Deeper penetration, ulceration and invasion can occur, with lymphocytic infiltration. There may be pigmentation in and around the masses. The presence of calcification and the general architecture can resemble trichoepithelioma. Palmoplantar pits show focal absence of the stratum corneum with vacuolization of the spinous layer. At an ultrastructural level, pits show evidence of premature desquamation with a reduction in desmosomes and tonofibrils resulting from delay in maturation of the epidermal basal cells [20,21]. BCC has developed in palmar pits [22–24].

Diagnosis. In many cases, the skin lesions resemble melanocytic naevi, von Recklinghausen's neurofibromatosis or skin tags rather than BCC, and their true nature

may be suspected only because of associated features or family history. The correlation between the clinical and pathological features of the range of skin lesions seen in NBCCS patients is still poorly understood, which makes it difficult to draw firm conclusions about the natural history of the different skin lesions in these patients.

Treatment. The large number of lesions in patients with NBCCS means that primary excision of all lesions is not always practicable. Radiotherapy is contraindicated as many patients show an accelerated rate of development of new BCCs within an irradiated field, and where recurrences do occur they frequently are more aggressive and difficult to manage than the initial primary tumour. Surveillance of NBCCs patients who have developed BCCs can be useful for the early detection and treatment of new lesions. Although no controlled trials have established that reduced sun-exposure can reduce the rate of BCC development in NBCCs patients, the reduced prevalence of BCCs in African Americans with this syndrome suggests that advice on reducing sun exposure is important [8].

Treatment of individual lesions should be guided by anatomical location, tumour size, clinical appearance and histology, with primary excision the treatment of choice for BCCs on the central face near critical structures. For superficial BCC on the trunk, approaches such as curettage and cautery or cryotherapy are useful. While the recurrence rate is potentially greater with these therapies, they are an effective, convenient alternative for small or superficial BCCs distant from critical sites in patients with large numbers of lesions. Where the presence of large numbers of superficial lesions limits the acceptability of conventional therapies, then photodynamic therapy with a systemic or topical photosensitizer and an appropriate laser or non-laser light source can be a useful and effective treatment option. Other non-surgical approaches that can be useful in the management of superficial lesions at non-critical sites include topical 5-fluorouracil and imiquimod formulations. These approaches have been shown to induce histological clearing of some BCCs and can reduce but not replace the need for more conventional therapies in patients with large numbers of lesions [24,25]. The value of systemic chemoprevention strategies in the management of patients with NBCCs is still unclear. A few studies suggest that systemic retinoids (isotretinoin (> 4 mg/kg) and etretinate (0.7–1 mg/kg)) may reduce the rate of development of new BCCs [26,27]. The clinical benefits, however, appear small relative to those seen in patients with multiple cutaneous SCCs.

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Follicular atrophoderma and basal cell carcinoma

SYN. BAZEX–DUPRÉ–CHRISTOL SYNDROME

This syndrome is a rare genodermatosis that also

predisposes affected individuals to multiple BCCs [1,2]. Additional clinical features that allow distinction from NBCCS include follicular atrophoderma, hypotrichosis and hypohidrosis. Follicular atrophoderma is present at birth or in early childhood, and shows as 'ice-pick marks', enlarged follicular ostia on the dorsa of hands, elbows, feet and face. The follicular changes are not caused by injury or inflammation but there may be facial eczema soon after birth. There may be anhidrosis of the face and head, and hypotrichosis. The BCCs appear on the face in the second or third decade and resemble cellular naevi [3].The absence of male–male transmission is suggestive of X-linked inheritance, and this has been confirmed by linkage analysis, which has mapped the gene to Xq24–q27 [4]. The association between BCCs and clinical abnormalities of the hair follicle is of interest as BCCs have the same cytokeratin profile as a subpopulation of follicular keratinocytes [5]. The importance of the Hedgehog signalling pathway in BCC development in patients from affected families with this disorder is not yet known.

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Rombo syndrome

Rombo syndrome is a very rare autosomal dominant syndrome first described in 1981 (MIM 180730). Affected individuals develop vermiculate atrophoderma, milia, hypotrichosis, trichoepitheliomas and peripheral vasodilation in addition to BCCs [1,2]. Although there are some similarities with Bazex's syndrome (follicular atrophoderma and milia), there are a number of distinctive features including cyanotic discoloration of the hands and lips in childhood, and telangiectasia. The genetic locus for Rombo syndrome has not yet been mapped.

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Self-healing epitheliomas

SYN. MULTIPLE SELF-HEALING EPITHELIOMA OF FERGUSON-SMITH

This condition is an autosomal dominant condition first described by Ferguson-Smith in the 1930s, characterized by the intermittent development of spontaneously regressing skin tumours histologically identical to well-differentiated SCCs.

Incidence and aetiology. The incidence is unknown but the condition is very rare. Two large Scottish kindred are well described in the literature [1–3], and accurate genetic pedigree analysis has suggested that the condition may have arisen in these two families from a single mutation around 1790. The gene has been mapped to chromosome 9q22–q31 in these families but has not yet been identified [4]. Other sporadic cases have been reported. The lesions develop most frequently on light-exposed skin and it is postulated that UVR is an important co-factor in the development of these tumours.

Clinical features [5]. Patients usually develop their first lesions in the second decade, and each patient tends to have a fairly specific pattern of development, duration and evolution. Knowledge of the 'normal' pattern for the patient is of great value in the management of individual lesions.

The lesions develop predominantly on exposed skin and may cluster around the nose or ears. In the majority of reported cases, one or more lesions have been present in the scalp, a site rarely affected by keratoacanthoma. A small, raised, red nodule is the first sign of a new lesion. This may grow over 2–4 weeks to a diameter of 2–3 cm and may become crusted or ulcerated. The lesion then may remain unchanged for 1–2 months, and then gradually shrink, leaving behind a very characteristic and unsightly crenellated scar (Fig. 36.1).

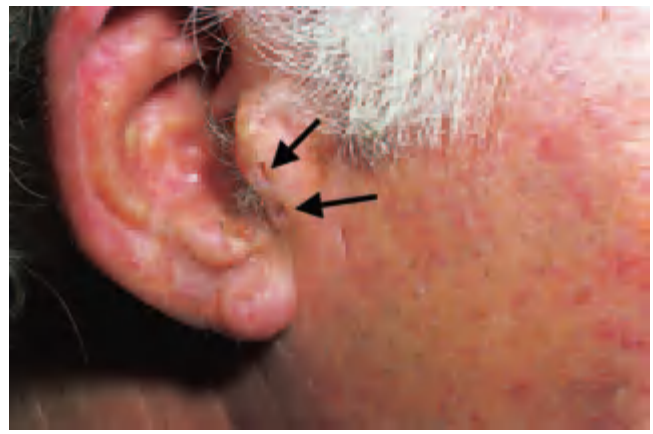

Fig. 36.1 Scarring seen in patient with multiple self-healing squamous epitheliomas of Ferguson-Smith.

Lesions develop singly or in crops. In one case they were strikingly confined to half of the body [6].

Pathology. The lesions have features that are indistinguishable from invasive SCCs, but are quite distinct in most cases from multiple keratoacanthoma with which they should not be confused. The epidermis may be ulcerated, and demonstrates marked cellular atypia and loss of polarity. Invasive tongues of epithelial cells will be seen at the base of the lesion and isolated invasive clumps of cells may be seen detached from the main tumour mass, which is still adherent to the epidermis. There is no marked 'shouldering' of the lesion by normal keratinocytes as is seen in keratoacanthoma, and the leukocyte abscesses characteristic of the older keratoacanthoma are absent.

Management. Although spontaneous involution does occur, the resultant scar is unsightly and the end results of shaving or curetting the lesions at an early stage in their development are more acceptable. Cryotherapy of a lesion in the early stages produces an excellent result.

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Xeroderma pigmentosum

This is a rare autosomal recessive disorder characterized by extreme sun sensitivity, which is associated with a marked increase in skin cancer susceptibility, with affected individuals developing multiple precancerous lesions and skin cancers at an early age (see Chapter 12). From a historical perspective this condition is important as it is one of the key pieces of evidence that highlighted the carcinogenic potential of UVR and was the first model in humans that supported the somatic mutation theory of the initiation of cancer. Recent evidence from studies of other genetic sun-sensitive syndromes in humans has challenged the original assumption that the increased cancer susceptibility in xeroderma pigmentosum (XP) patients is exclusively the result of persistent DNA lesions caused by defective DNA repair following exposure to UVR. The new data have come from elegant studies of patients with trichothiodystrophy (TTD) who show photosensitivity and defective nucleotide excision repair that resembles that seen in XP patients [1]. In contrast to XP patients where there is a more than 2000-fold increase in skin cancer incidence, TTD does not appear to be associated with skin cancer. Although the basis for the differences in NMSC susceptibility between XP and TTD has not yet been established, a number of XP-specific changes have been identified that are helping to shed new light on the mechanisms of ultraviolet carcinogenesis. These include differences in the repair of some photoproducts, in the nature of DNA damage induced, and in the effects of UVR on the immune response to tumour cells.

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Muir–Torre syndrome

SYN. HEREDITARY NON-POLYPOSIS COLORECTAL CANCER

This autosomal dominant syndrome originally described in 1967 is characterized by the presence of one or more sebaceous neoplasms in association with internal malignancies, most frequently carcinoma of the colon. The clinical and pathological features overlap with hereditary non-polyposis colorectal cancer (HNPCC) syndromes and these disorders have now both been shown to be caused by germ-line mutations in genes involved in DNA mismatch repair [1]. Tumours in patients with Muir–Torre syndrome are characterized by alterations in the length of DNA sequences called microsatellites and this microsatellite instability has been identified in sebaceous neoplasms from patients with Muir–Torre syndrome [2]. A number of other skin tumours including SCC, BCC, keratoacanthoma and AK have also been described in patients with this syndrome but the significance of these findings has been difficult to establish as the high frequency of undiagnosed NMSC in the population make it hard to differentiate a real increase from an increase resulting from ascertainment bias. The recent identification of microsatellite instability in skin tumours other than sebaceous neoplasms indicate that the NMSC noted in previous clinical studies of Muir–Torre kindreds are more likely to reflect a true increased susceptibility and not simply a result of ascertainment bias [3,4].

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Other cancer susceptibility modifying genes

In addition to the rare, highly penetrant skin cancer predisposition syndromes described above, there is increasing evidence that other genetic loci can contribute to sporadic NMSC risk. The importance of these so-called modifying genes has been highlighted in studies using mouse cancer models in which genes have been identified that markedly reduce the rate of cancer development in mice carrying germ-line mutations in known tumour-suppressor genes [1,2]. It is likely that similar, as yet unidentified genes in humans account for the marked variations in the susceptibility to BCC development seen both within and between families with NBCCS. At present, identification of these high-frequency low-penetrant genes in humans is based on educated guesswork based on consideration of factors that might contribute to NMSC development. Epidemiological studies have already identified a number of complex phenotypic traits such as skin colour, ethnicity and freckling tendency, which are associated with an increased risk of NMSC development [3]. In addition to the well-recognized importance of differences in skin pigmentation, variations in UVR, DNA repair capacity and xenobiotic metabolism have been implicated as important modifiers of sporadic NMSC risk [4]. The complexity of this area is well illustrated in a recent population-based case–control study of the *XRCC1* arginine to glutamine (arg399gln) polymorphism [5]. The *XRCC1* gene is important in base excision and single-strandbreak repair and the arg399gln polymorphism is associated with decreased DNA repair capacity. For NMSC, the overall effect of the polymorphism is a reduction of NMSC risk. This contrasts with the findings in many other cancers where the polymorphism is associated with an increased cancer susceptibility. Comparison of subjects, however, with marked differences in sun exposure in the same study has revealed that the impact of the polymorphism on NMSC risk is dependent on sun exposure and that it is associated with an increased risk in subjects with high exposure and a reduced risk in subjects with low exposure. While the basis for this differential effect is still unclear, it may reflect differences in the apoptotic capacity of keratinocytes in these different patient groups. A delay of repair in keratinocytes capable of apoptosis may increase the likelihood of elimination of abnormal cells, whereas a delay of repair in apopototic-deficient keratinocytes may favour persistence of abnormal cells and the development of further genetic changes.

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Chronic injury and scarring

It has been recognized for many years that NMSC can arise at sites of chronic inflammation and/or scarring. Although there is a substantial literature on this subject, it is difficult to assess the risk as there are no prospective studies of patients with conditions recognized as being associated with NMSC development. Conditions linked to NMSC development include burns [1,2], discoid lupus erythematosus [3], necrobiosis lipoidica [4,5], lupus vulgaris and skin fistulae resulting from discharging sinuses. A particularly strong clinical association has been identified between patients with recessive dystrophic Epstein–Barr virus (EBV) and SCC development [6,7]. The basis for the association between deficiency in type VII collagen resulting from germ-line gene mutations and SCC risk in dystrophic EBV patients is not known. In contrast to other forms of EBV, fibroblast collagenase is increased in dystrophic EBV and this has recently been shown to be associated with marked elevation of urinary excretion of basic fibroblast growth factor [8]. Further studies of SCC development in patients with dystrophic EBV may provide new insight into the long-recognized association between wounding and SCC development.

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Immunosuppression

Immunosuppressed patients show a marked increase in susceptibility to NMSC development, with an earlier age of onset and a higher incidence of multiple primary tumours relative to immunocompetent patients. This marked increase in NMSC incidence in these patients is powerful evidence of the importance of the immune system in limiting NMSC development in humans. The cumulative incidence for NMSC uncorrected for age has been shown to vary between 27 and 40% after 20–25 years of immunosuppression in different populations within Europe [1,2]. In Australia, the cumulative incidence appears to be significantly higher after only 10 years of immunosuppression, highlighting the importance of UVR as a co-factor for cancer development in these patients [3]. The risk of NMSC development in renal transplant recipients, which is the best-studied group of immunosuppressed patients, is very variable between different centres as a result of differences between populations including the age distribution of the transplanted patients, the duration of transplantation and the ambient sun exposure of the country. In the UK, a 50-fold increase in the risk of developing SCCs and a fivefold increase in BCC risk has been described in renal allograft recipients [1]. Even greater increases in risk have been described in another European study with a 250-fold increase in SCC incidence and a 10-fold increase in the incidence of BCCs [4]. Epidemiological studies have established that in immunosuppressed patients there is a close association between the development of NMSC and premalignant lesions and the presence of viral warts [5]. The viral warts and skin cancers both preferentially co-localize to areas of sun-exposed skin, although there are some interesting differences between immunocompetent and immunosuppressed patients in SCC distribution with a greater proportion on the hands and forearms in immunosuppressed patients [6].

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The molecular and cellular biology of non-melanoma skin cancer

NMSC is unique among human cancers in that the main aetiological factors have been identified and the accessibility of the skin has facilitated analysis of the clinical, pathological and molecular characteristics of these tumours. Advances in molecular and cell biology over the last 10 years has seen an enormous growth in the amount of descriptive data cataloguing changes at the DNA, RNA and protein level in NMSC [1]. While this information in itself has provided an insight into the basis for some of the clinicopathological differences between BCCs, SCCs and related premalignant lesions, a fuller understanding of the biology of NMSC will be critically dependent on approaches that integrate emerging molecular data with the clinical and epidemiological aspects of this important disease. This section outlines current concepts and summarizes some of the more important advances in the biology of NMSC, which have important clinical implications. Topics discussed include cancer genetics, multistage carcinogenesis, UV carcinogenesis and the role of HPV infection in NMSC development.

Cancer as a genetic disease

Cancers are, with few exceptions, clonal; they are derived from a single somatic cell and have accumulated a series of changes that lead to complex and persistent changes in gene expression and cell behaviour. Although it has long been thought that these phenotypic changes require the stepwise accumulation of growth-advantageous heritable changes, direct evidence of the importance of genetic alterations in tumorigenesis has only come within the last decade [2]. Genes important in cancer development can be broadly divided into three categories:

1 Proto-oncogenes that encode for proteins that regulate cellular proliferation and differentiation. These genes are inappropriately activated in cancer cells by point mutations, gene amplification or chromosome translocation.

2 Tumour suppressor genes that maintain a normal phenotype by limiting growth, invasiveness and other features of malignant cells. Mutations are recessive at the cellular level, which means that the effects of alterations in these genes are only seen when both copies are inactivated.

3 Mutator genes that encode for proteins that play a critical part in maintaining genomic integrity. The importance of this class of genes in determining cancer susceptibility was first recognized in studies of patients with rare autosomal cancer susceptibility syndromes such as XP, Bloom's syndrome and ataxia telangiectasia where there

are abnormalities in the recognition, response and/or repair of DNA damage [3]. Further evidence of the importance of 'mutator' genes has come with the demonstration of instability of dinucleotide repeats in a number of common cancers that are caused by either germ-line or somatic mutations in enzymes important in mismatch repair [4]. More recently, a number of groups have shown that genetic factors also influence genetic stability at a chromosome level and there is increasing evidence that the destabilizing of the genome by mutations in genes that normally maintain chromosomal stability plays an important part in the development of some cancers [5].

Molecular genetic analysis of human NMSC have to date focused on four main areas: the role of genes identified in other human cancers; the mapping of chromosome losses; the mapping and positional cloning of familial NMSC susceptibility genes; and comparisons of genetic changes in SCCs with AK and Bowen's disease [1]. As has been the case for other epithelial cancers such as breast and colon cancer, most of the genes implicated to date in NMSC development are tumour-suppressor genes. DNA sequencing has identified mutations in the *p16* and *p53* tumour-suppressor genes. Comparison of the mutational spectra of these genes in NMSC and internal malignancies has confirmed the importance of UVR-induced mutagenesis in NMSC development [6]. Although the *p53* gene has been linked to genetic instability in other cancers, the mutation frequency in BCC and SCC appears broadly similar, which raises interesting questions about the functional effects of *p53* mutations in keratinocytes. Loss of heterozygosity studies have revealed that BCCs and SCCs show marked differences in the pattern and extent of chromosome loss. BCCs differ from SCCs and other epithelial neoplasms in that chromosome losses are largely confined to a single chromosome arm, 9q. Subsequent studies have confirmed that the gene for the NBCCS maps to chromosome 9q and that the high frequency of loss in sporadic BCC reflects the importance of the *PATCHED1* tumour-suppressor gene in BCC development. SCCs show more widespread losses with frequent loss of 9p, 13q, 17p, 17q and 3p [1]. Although the high frequency of allelic loss on these chromosome arms suggests that these regions may contain one or more genes important in the development of cutaneous SCCs, with the exception of *p16* on 9p and *p53* on 17p chromosome, the identities of the candidate tumour-suppressor genes on these chromosome arms are unknown.

Multistage carcinogenesis in the murine skin model

Mouse skin has, for more than 50 years, played a critical part in the development of the concept of multistage carcinogenesis that has underpinned studies of the biology and molecular genetics of the carcinogenic process. While there are important differences between murine and human skin in the response to both chemical carcinogens and UVR, many of the basic concepts identified using this system have been shown to be generally applicable to many human cancers including NMSC. Observational studies of skin tumour induction by chemical carcinogens led to the concept of 'initiation', 'promotion' and 'progression', which represent different stages of the carcinogenic process [7]. 'Initiation' is characterized by the acquisition of an irreversible change in a cell that in the presence of appropriate growth selection pressures ('promotion') can clonally expand to form a benign tumour (papilloma). The probability of papilloma formation within a given mouse strain is dependent on the nature of the carcinogen, the dose applied and the time course over which the mouse is observed. In the murine two-stage skin carcinogenesis model, 'initiation' is accompanied by mutations in the H-*ras* proto-oncogene and the position and type of mutation within this gene is carcinogen-specific. Dimethylbenzanthracene (DMBA)-induced skin tumours predominately have a mutation at the middle adenosine of Ha-*ras* codon 61 (C<u>A</u>A → C<u>T</u>A)s, whereas methylnitrosurea (MNU)-induced tumours have a G → A transition at codon 12 [8]. This concept of a 'signature' mutation in critical target genes identified in the murine model has underpinned the studies of mutation spectra in the *p53* tumour-suppressor gene and other genes in UVR-induced human NMSC.

The latency period for tumour formation following the application of an initiator is significantly reduced by the application of 'promoters' such as 12-*O*-tetradecanoylphorbol-13-acetate (TPA) and other phorbol esters. In contrast to an 'initiator', a 'promoter' generally has to be applied repeatedly and the frequent visible consequences of promoter application, such as hyperkeratosis and scaling of the skin, subside if the application is discontinued. The observation of latency has parallels with the recent observations in humans that clones of *p53* mutant keratinocyte exist within the normal sun-exposed epidermis many years before clinical lesions become detectable [9].

Initiation and promotion, for example using DMBA and TPA, result in the development of multiple papillomas, which rarely progress to invasive carcinoma. The rate of progression of papilloma to carcinoma can be increased by application of the initiator to a papilloma after it has developed or by repeated application of the initiator to 'normal' skin before promotion. Progression is distinct from promotion in that it is considered to reflect accumulation of additional genetic changes and is generally regarded as irreversible. Support for this concept comes from studies of mouse skin tumours, which have established that the transition from benign papilloma to carcinoma is accompanied by an increase in the number of genetic abnormalities in the tumours. This requirement to accumulate additional genetic changes to facilitate tumour progression can occur without further application

of an initiator in tumour cells that show 'genetic instability' as this increases the probability of additional genetic changes, which allow histological progression, invasion and metastasis.

Differences between mouse strains and between species in both their susceptibility to cancer induction and the types of tumours induced by identical regimens highlight the importance of other genetic factors in determining cancer susceptibility. The well-defined mouse model system has allowed mapping of these 'modifier' genes and it has now been established that these genes frequently exert their effect by acting in combination and that the same allele can exert opposite effects in different strains of mice [10]. These observations highlight the difficulties in interpreting results from cancer gene association studies in humans.

Ultraviolet radiation mutagenesis and DNA repair

The overwhelming evidence from clinical and epidemiological studies implicating UVR as the most important skin carcinogen makes it easy for us to answer the question, 'Does the sun cause skin cancer?' Answering the question, 'How does the sun cause skin cancer?' is much more challenging and from the information available at present it is still unclear which one or combination of the multitude of effects that UVR has on the skin is critical for all of its carcinogenic properties.

The UV part of the solar electromagnetic spectrum is subdivided into three broad regions:

- UVC (200–280 nm)
- UVB (280–315 nm)
- UVA (315–400 nm).

UVC is widely used in *in vitro* studies of the effects of UVR but is not relevant to human skin cancer as it is efficiently attenuated by the Earth's atmosphere. Although it accounts for less than 10% of the spectral energy of sunlight, UVB is the main waveband responsible for sunburn and skin cancer induction. UVA differs from UVB in a number of ways. It is the main (more than 90%) component of terrestrial sunlight but is less biologically active than UVB. Both UVB and UVA are complete carcinogens in that they are both capable of inducing benign papillomas and SCCs in murine skin.

The effects of UVR on the skin are complex and it is likely that a number of these effects contribute to its initiating and promoting properties. Exposure to both UVB and UVA cause genetic changes in many biological systems [11]. Dose for dose, UVB is a much more efficient mutagen than UVA and the types of mutations induced by these different wavebands are distinct. The action spectra for DNA damage and skin cancer induction are very similar for UVB and closely coincide with the absorption spectra of DNA, which suggests that direct DNA damage by UVB is an important contributor to its carcinogenic effect. Cyclobutane or pyrimidine dimers and the 6-4 photoproduct are the predominant photolesions induced by UVB and these are the preferential sites for UVB-induced mutagenesis [12]. For UVA, the spectra for DNA damage diverges from that of DNA absorption and it has been inferred that DNA damage by wavelengths above 347 nm is not caused by direct absorption by DNA but is more likely a consequence of indirect effects caused by the generation of reactive oxygen species [13]. The types of DNA damage associated with exposure to UVA are DNA strand breaks and DNA protein cross-links.

The mutagenic effects of UVR on keratinocytes within the skin are dependent on the amount and wavelength of the exposure, cellular antioxidant defences [14], the effectiveness of DNA repair mechanisms and the characteristics of the target keratinocyte. Studies in *Escherichia coli* have demonstrated that UVB induces a characteristic spectrum of mutations that is sufficiently distinctive to serve as a molecular 'signature' or 'fingerprint' of DNA damage [15]. This 'fingerprint' is characterized by the presence of C → T transitions at dipyrimidine sites, either singly (C → T) or as a tandem double bases substitution (CC → TT). The identification of mutations that show this molecular fingerprint in human NMSC [6] and in mouse skin tumours induced by UV provides important evidence at the molecular level of the importance of UVB as a mutagen in skin carcinogenesis [16]. Considerably less is known about the characteristics of mutations induced by UVA. As the DNA damage with UVA is predominately indirect, it is more difficult to extrapolate findings from *in vitro* studies using bacteria or mammalian cells. *In vivo* studies using a transgenic mouse model have shown a predominance of GC → AT transitions at non-pyrimidine dimer sites, which is consistent with the proposed involvement of oxidative DNA damage [17].

Mutations induced by UVR are a result of persistence of unrepaired photoproducts at the time of DNA replication. During DNA replication, the DNA polymerase complex misreads the photoproduct on the template strand and this leads to the insertion of a default adenine residue at this position. At subsequent cell divisions, this adenine pairs with thymine and the net result is the conversion of a cytosine base to a thymine base on the originally damaged strand. A number of studies have shown that there appears to be a close relationship between photoproduct formation and carcinogenesis in that enzymatic repair of photoproducts by endogenously activated photolysase [18] or by topical application of T_4 endonuclease in liposomes [19] reduces the incidence of tumour formation. Although these studies are consistent with the original XP paradigm, which directly links unrepaired DNA lesions, mutations and cancer, recent observations from studies of patients with TTD indicate that the marked increase in susceptibility to UV carcinogenesis seen in XP patients is a

result of other effects and not simply a reflection of an increased mutation rate [20]. Detailed comparisons between XP and TTD cells have revealed a number of differences in the repair efficiency and mutational spectrum, but it is still unclear which of these underpin the differences in cancer susceptibility between these syndromes [21,22].

Immunological effects of ultraviolet radiation

The importance of the immune system in human skin carcinogenesis is dramatically illustrated by the marked increases in NMSC incidence in immunosuppressed patients. UVR, in addition to its mutagenic and other direct effects on keratinocytes, has been shown in murine models to exert an immunosuppressive effect that interferes with the ability of the immune system to eliminate UV-induced skin tumours. These observations and the importance of immunosuppressants as a risk factor for NMSC development in humans has led to speculation that UV-induced immunological injury may be an important contributor to the carcinogenic effects of UVR. In mice, skin tumours induced by UVR differ from chemical carcinogen-induced skin tumours in that they are highly immunogenic and are rejected when transplanted into genetically identical recipient mice. The importance of UV-induced immunosuppression in UV carcinogenesis was first recognized in the 1970s when Kripke [23] made the seminal observation that irradiation of recipient mice abolished the ability to reject the transplanted tumours. This work and subsequent studies established that immunosuppression could be transferred to unirradiated animals by adoptive transfer of splenic lymphocytes and that UVR exerted similar effects on the normal immunological reactions to sensitizing chemicals such as dinitrochlorobenzene in contact hypersensitivity reactions. Further investigation of the immunological effects of UVR using skin contact hypersensitivity has revealed that there are marked differences between mice strains in their susceptibility to UVR-induced immunosuppression. Genetic studies have demonstrated that the UV-susceptibility phenotype is dominantly inherited and two genetic loci have been identified that are thought to mediate this effect [24].

The significance of UVR-induced immunosuppression in humans is still unclear. There are some similarities with the findings in mice in that UV irradiation decreases the ability to mount a delayed-type hypersensitivity response when the immunization occurs on exposed skin and there appears to be interindividual differences in the susceptibility to this effect [25–27]. One study suggests that the UV-susceptibility phenotype is more common in patients with NMSC and that 50% of such patients develop hapten-specific tolerance using this test system [28]. While these observations raise the possibility that exposure to UVR may interfere with the ability of the immune system to eliminate UV-induced skin tumours in humans, the clinical importance of this effect is unclear. The observation that pharmacological inhibition of the immune system has a profound clinical effect on NMSC development suggests that the impact of UVR-induced immunosuppression on NMSC development may not be as great as that seen in murine models. However, further work is required to better understand the impact and clinical significance of other, more subtle aspects of the effects of UVR on cutaneous immunity and the implications of these effects in determining NMSC susceptibility in humans.

Human papillomaviruses

The subdivision of HPV types, based on clinical biology and epidemiological studies of anogenital cancers, played a critical part in the dissection of the molecular mechanisms of HPV carcinogenesis. This allowed identification of the characteristics specifically associated with the carcinogenic properties of the high-risk HPV types [29]. Cell biology and molecular studies have shown a good correlation between high- and low-risk HPVs and their ability to transform primary human keratinocytes [30]. The major transforming proteins of the high-risk genital HPVs are the E6 and E7 proteins, which target and inactivate tumour-suppressor genes including *p53* and the retinoblastoma gene.

Clinical and epidemiological studies have also provided compelling evidence of a link between cutaneous viral warts and NMSC and recent molecular studies have allowed analysis of HPV types. Although the increased prevalence of HPV infection in NMSC from high-risk organ transplant recipients is less compelling compared to the information from studies of other HPV-associated cancers, there are some other pieces of evidence that point to a possible direct role for HPV in NMSC development. Genetic analysis of squamous cell neoplasms from immunocompetent and immunosuppressed patients has revealed that there are significant differences between these two patient groups, with significantly less chromosome loss in SCCs from immunosuppressed patients [31]. Further support for a causal role for HPV in NMSC development has come from recent molecular studies that have shown that the E6 protein from some cutaneous HPVs blocks the epidermal apoptotic response to UVR by targeting the pro-apoptopic Bak protein for proteolytic degradation [32]. This finding and the demonstration of an inverse correlation between Bak protein levels and HPV positivity in cutaneous SCCs suggests that cutaneous HPV may promote SCC development by blocking the normal epidermal apoptopic response to UVR [33].

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General principles in the management of patients with non-melanoma skin cancer

Many aspects of the management of patients with BCC and SCC are common to both tumour types and these general principles are discussed in this section. Tumour-specific issues are discussed in the treatment section for the relevant tumour. Management of patients with NMSC requires early detection and accurate diagnosis, selection of the appropriate treatment modality based on the clinical and/or pathological findings, consideration of patient-specific risk factors and institution of preventative measures if appropriate.

Detection and diagnosis

Early detection of NMSC is critically dependent on a good awareness of risk factors and the characteristics of tumour development in at-risk groups. Although most patients with NMSC initially present with a lesion requiring a therapeutic intervention, the high prevalence of benign skin disease and the increasing use of medical screening examinations means that there are opportunities for identifying at-risk individuals sooner than they might present with an obvious clinical lesion. Superficial BCCs on the back, Bowen's disease on the leg and AK are not uncommonly either not noticed or dismissed as a normal consequence of ageing. Although early detection of such lesions may have little impact on the clinical prognosis of the identified tumour, the ability to identify at-risk individuals means that advice on preventative measures such as sun awareness and protection can be initiated much earlier than otherwise would have been the case.

Selection of appropriate therapeutic modality for tumour treatment

The aims of any treatment directed against an NMSC is the removal or destruction of the primary tumour mass and, in the case of SCC, the prevention of metastasis. A broad range of therapeutic options are available to achieve these aims and while surgical excision is frequently the treatment of choice, there are a number of reasons why an alternative treatment may be preferred on some occasions. Treatment selection is dependent on a good understanding of the clinical and/or pathological aspects

of NMSC that affect prognosis and clinical experience of the pros and cons of the different therapeutic modalities. The different modalities used in current practice include curettage and cautery, cryosurgery, radiotherapy, photodynamic therapy, laser surgery, conventional surgical excision and Mohs' micrographic surgery (described in detail in Chapter 78). Specific issues with respect to these therapies from a NMSC perspective are outlined below.

Cryosurgery. This modality has been recommended for the treatment of AK, Bowen's disease, superficial BCC, small nodular BCC and small well-differentiated SCC. While freezing with liquid nitrogen is a quick and relatively tolerable procedure that does not require anaesthesia, it can be associated with significant morbidity, particularly when tumours selected for treatment require prolonged freeze times to ensure adequate treatment. This form of treatment is considered in more detail in Chapter 77.

Curettage and cautery. This modality can be used for the same spectrum of lesions as cryotherapy. Curettage with traditional curettes is critically dependent on the friable nature of the tumours, which leads to a selective removal of the abnormal tissues. This differential effect on tumour tissue is an effective way of delineating the extent of some tumours and can be useful before standard or Mohs' excision of some BCCs to define more accurately lateral tumour spread within the epidermis [1]. When used therapeutically it is important that the stroma and surrounding dermis are charred with diathermy or cautery to a depth of 1 mm following initial curettage and that this is repeated a further twice with curetting of the charred tumour base. As the procedure does not divide the upper dermis connective tissue network, healing is usually predictable and occurs in most cases with minimal scarring.

Radiotherapy. Most NMSCs are sensitive to ionizing radiation and radiotherapy offers the potential to treat large areas of tumour and a surrounding rim of normal skin with minimal tissue damage. The effectiveness and cosmetic end result of this therapy is critically dependent on the treatment regimen administered. This operator dependence, which makes comparison of published studies difficult, is also an important contributor to the misconceptions that some physicians have about the value of this approach. Radiotherapy can be an effective cosmetically acceptable treatment for NMSC including BCC, SCC and premalignant lesions such as Bowen's disease. Although it is often stated that radiotherapy is best suited for elderly patients, the inconvenience and practical difficulties of frequent outpatient appointments required for a full fractionated course needs to be taken into account when radiotherapy is considered as an alternative to conventional surgical approaches. In addition to a primary therapy, radiotherapy is also an important adjuvant therapy following excisional surgery for the treatment of residual microscopic disease and as a prophylaxis against systemic metastases. Situations where radiotherapy is best avoided include NMSC on the lower limbs, ear and eyelid, recurrent tumours, lesions previously treated with radiotherapy, tumours with poorly defined clinical margins and patients with multiple NMSCs and severe actinic damage. The technical details of radiotherapy are discussed elsewhere.

Photodynamic therapy. The development of topically active photosensitizing agents has led to studies on the role of photodynamic therapy (PDT) for the treatment of NMSC. This therapy appears particularly effective for AK of the face and scalp and for the treatment of Bowen's disease, where advantages have been demonstrated over other therapies with respect to tolerability and cosmesis [2,3]. The value of PDT for the treatment of BCC is still under investigation. Studies of superficial BCC suggest that a 96% complete clearance rate can be achieved with two treatments 7 days apart [4]. As with other destructive therapies, PDT appears less effective for nodular BCC with inconsistent clearance rates. One of the main advantages of PDT over existing therapies is its potential for the treatment of large and/or multiple lesions on challenging anatomical sites such as the scalp [5].

Laser therapy. Like PDT, this therapy is still under investigation to determine optimal methods of use and compare efficacy rates to conventional therapies. The most widely used laser for the treatment of NMSC and related premalignant lesions is the carbon dioxide (CO_2) laser where the principal chromophore is tissue water. One application of the CO_2 laser has been as an alternative to scalpel excision. Although laser excision can seal small blood vessels, lymphatics and nerve endings, which may reduce bleeding, swelling and postoperative pain, the tissue damage induced may interfere with wound healing and hinder the assessment of margins in the excised specimen. Developments in CO_2 laser technology have increased interest in the use of this approach to selectively vaporize tissues and a number of studies have examined the effectiveness of this modality for the treatment of superficial BCCs and premalignant lesions. Although a full assessment of the efficacy of CO_2 lasers for the treatment of NMSC will require studies with longer follow-up than those available at present, clinical studies have demonstrated excellent short-term results and suggest that the tolerability and cosmetic results may be superior to destructive therapies.

Conventional surgical excision. This is regarded by many as the treatment of choice for primary NMSC. Excision with primary closure, local rotational or advancement flaps or full-thickness graft to repair the defect, when carried out by a trained operator, usually produces a good cosmetic

result and provides the pathologist with a specimen that allows confirmation of the completeness of excision and identification of histological factors associated with increased risk of local or systemic recurrence. Although undertreatment because of lateral or deep tumour extension may be identified in conventionally processed surgical specimens, there is potential to miss cases of incomplete excision as only a small proportion of the tumour edge is examined using conventional histopathological techniques [6].

Mohs' micrographic surgery with pathological control of excision margins [7,8]. This integrated surgical and pathological technique allows precise definition and excision of primary tumours growing in continuity. It is now well established that this approach offers advantages over conventional surgical excision in the treatment of both BCC and SCC of the skin in terms of local recurrence and, in the case of SCC, for metastatic disease. While there are at present differences in practice between individual countries in the threshold for recommending Mohs' surgery, current recommendations are that it is the treatment of choice for recurrent NMSC and primary NMSC with high-risk clinical and/or pathological features for tumour recurrence. Other indications include tumours at high-risk sites (central face, eyelids) and tumours at sites where maximal preservation of normal tissue is important. The Mohs' technique is described in detail in Chapter 78.

Selection of the optimal treatment modality

The selection of the most appropriate therapy for a patient is determined by three key factors: tumour size, tumour location and the likely tumour characteristics based on clinical and, where available, pathological assessment. Low-risk NMSC and related premalignant lesions include AK, Bowen's disease and superficial BCC. These lesions can usually be adequately dealt with using curettage and cautery, cryotherapy or PDT. Although the recurrence rate for these types of lesions with these modalities when used appropriately is slightly higher than that achieved with surgical excision, this needs to be balanced against the fact that these less invasive procedures are relatively simple to carry out, often associated with less short-term morbidity and more predictably give a good cosmetic result compared to excision and suturing. Excellent cure rates for curettage and cautery and/or cryotherapy have also been reported for small (less than 1 cm) nodular BCCs and well-differentiated slow-growing SCCs on sun-exposed skin [9,10]. For intermediate-risk NMSC (tumours less than 2 cm, well-defined clinical margins), the location of the tumour is an important determinant of treatment choice. A specific advantage of surgical excision over other destructive therapies is the provision of tissue for histological examination, which provides confirmation of the diagnosis, information on the adequacy of excision and may allow recognition of histological features associated with a high risk of local recurrence and risk of metastasis. For BCC, these features include location on the central face and a morphoeic histological pattern. For SCC, depth of invasion greater than 4 mm or extension into subcutaneous fat, poor differentiation and perineural involvement have all been associated with increased risk of local recurrence and metastatic disease [11]. For high-risk NMSC, the treatment of choice is Mohs' surgery.

For the management of most NMSC a treatment plan can be defined based on a clear understanding of the pros and cons of the different treatment modalities and a careful consideration of the tumour characteristics. In some cases, such as high-risk patients with multiple NMSCs, high-risk tumours, recurrent tumours or incompletely excised NMSC, optimal selection of therapy may be best achieved in the context of a multidisciplinary tumour clinic with input from dermatologists, plastic surgeons, oncologists and radiotherapists.

Chemoprevention and management of high-risk patients

The surgical treatment of high-risk NMSC differs from that of high-risk patients with many other common cancers such as colon, breast and bladder cancer in that it is not possible to completely remove the target organ. While excision or destruction of lesions is well suited for the management of small numbers of NMSCs or related premalignant lesions, these approaches become increasingly impractical and distressing for high-risk NMSC patients with multiple lesions. Examples of patient groups where this problem arises include patients with NBCCS, immunosuppressed organ transplant recipients, high-dose PUVA patients and patients with severe actinic damage. From our current understanding of the epidemiology and biology of NMSC, the number of high-risk patients is likely to increase considerably over the next 25 years as a result of the changing age structure of the population and increased recreational sun exposure. The management of patients with multiple NMSCs is a considerable therapeutic challenge, which is not helped by the limited number of treatment options available and the lack of controlled clinical studies.

Topical 5-fluorouracil is a valuable therapy for the treatment of superficial BCC and for patients with multiple AK. For reasons that are still not understood, 5-fluorouracil acts on both clinically detectable lesions and subclinical lesions, which means that application to a contiguous area of skin may target a greater number of lesions than would be achieved using destructive therapies of visible clinical lesions. Although there is some evidence to suggest that 5-fluorouracil may reduce the rate of development of new AK, there is no conclusive evidence at

present favouring a role for 5-fluorouracil in the prevention of NMSC [12,13].

A number of systemic approaches have been investigated as chemopreventive agents for high-risk skin cancer patients. Oral retinoids are used to treat patients with multiple SCCs where the rate of new SCC development makes management by surgical intervention difficult. Although oral retinoids show clinical efficacy, there are many unanswered questions on their mode of action and long-term effects as there are very few controlled trials on their use. Etretinate has been shown to be superior to placebo in the treatment of high-risk patients with AK, some of whom also had at least one NMSC [14].

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Basal cell carcinoma [1–3]

SYN. BASALIOMA; RODENT ULCER

Definition. A malignant tumour that rarely metastasizes, composed of cells similar to those in the basal area of the epidermis and its appendages. The histology of the tumour and the surrounding stroma is characteristic.

Incidence and aetiology. BCC is the most common malignant tumour of the skin and the most common cancer in some countries, including the USA and Australia. Although the prevalence of this tumour increases within a population as exposure to sunlight increases, the distribution of the lesions does not correlate well with the area of maximum exposure to UVR in that BCCs are common on the eyelids, at the inner canthus and behind the ear, but uncommon on the back of the hand and forearm. The palm, sole and vermilion of the lips are rarely, if ever, involved. The basis for the different susceptibility of skin at different sites to BCC development is not known.

BCC is more common in males than females. A population-based incidence study in Minnesota gives annual incidence figures for males and females of 175 and 124 per 100 000, respectively, [4], and a recent Australian survey gives an incidence in that country of 849 and 605 per 100 000 for males and females, respectively, in 1990 [5], while figures from Hawaii show an incidence of 576 per 100 000 for males and 298 in 100 000 for females [6].

A Canadian case–control study has identified outdoor occupations (particularly farming), freckling, and Scottish or Irish descent as particular risk factors [7]. The Australian case–control study by Kricker *et al*. [8,9] of 226 patients with BCC suggests that the tumour is more common in those born in Australia than in immigrants, that southern European ancestry is protective, and that poor tanners are more at risk than those who tan easily. The presence of large numbers of naevi, freckles and solar elastosis all add to the BCC risk, while a past history of acne is protective [8,9]. A large European study of 1549 southern European patients with BCC reports that those with fair or red hair, those who tan poorly and those who have a history of childhood sunburn are at greater risk, and that acute episodes of intense burning sun exposure are a greater risk factor than cumulative lifetime sun exposure [10,11]. The study by Gallagher *et al*. [12] of 226 Canadian males with BCC again finds pale skin, the presence of freckles and childhood exposures to be risk factors.

BCC is extremely uncommon in dark-skinned races, and less common in Chinese, Japanese and other oriental populations than in white populations [13,14]. Although it may occur at any age from childhood, more than three-quarters of patients are over 40 years old. It occurs earlier and multiple tumours are more common in those with a fair freckled complexion. On the lower leg, the incidence in women is three times as great as in men [13]. BCC appears to arise more frequently and at a younger age in patients who are immunosuppressed. These lesions are frequently aggressive [15]. It is occasionally seen adjacent to leg ulcers [16].

BCC may arise in skin damaged by sunlight and ionizing radiation. It may occur in burn scars [17] or vaccination scars [18,19]. Arsenic salts are also a proven cause [20]. BCC has been reported in identical twins [21]. The increased risk of BCC development in naevus sebaceus and other adnexal hamartomas is well recognized [22–24].

The identification of mutations in the *PTCH1* gene has provided a completely new insight into the pathogenesis

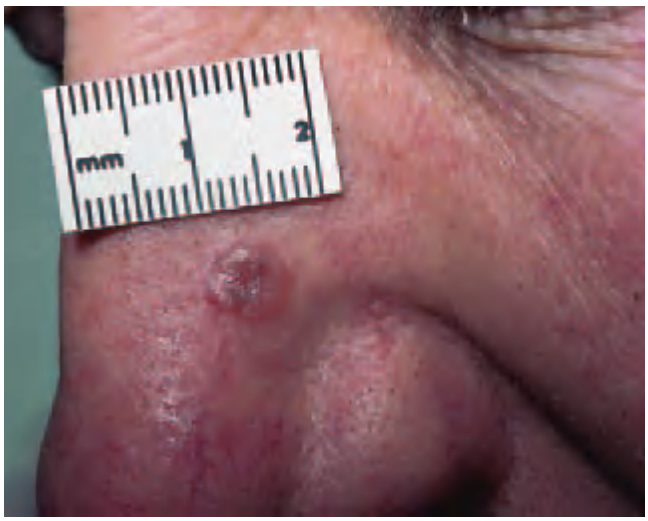

Fig. 36.2 Typical early basal cell carcinoma on the nose.

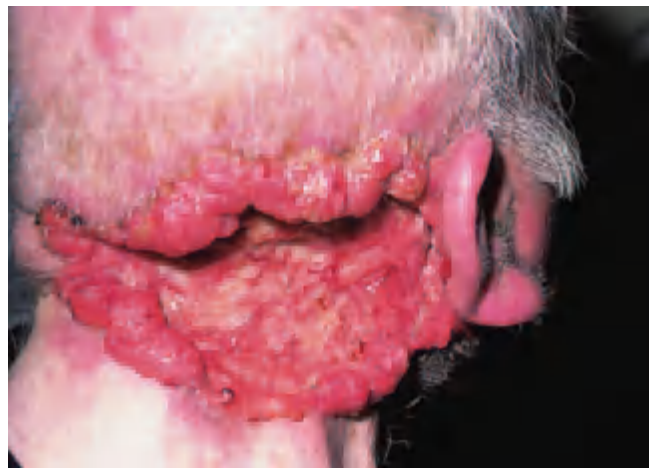

Fig. 36.3 Extensive ignored basal cell carcinoma on the back of the neck in an elderly man presenting to a British hospital in 1988.

of this common skin cancer and points to a key role for the Hedgehog (Hh) signalling pathway in its pathogenesis (see above and [25,26]).

Histogenesis. Theories about the nature and origin of the cells of BCC have been put forward at intervals over the last 80 years or more. The histological variability does not accord with a derivation from any individual epithelial structure, and is now generally considered to stem from the pluripotentiality of immature cells of the epidermis. It is thus capable of maturing towards any of the epithelial structures, and its behaviour is governed, as is the normal immature cell, by the connective tissue in its proximity. Thus, the stroma dependence, the range of histological patterns and the way these merge with the more organized hamartomas are explained. It has been rightly emphasized that the stroma is an essential part of the neoplastic process and it must also be removed in treatment.

Clinical features [27]. The early tumours are commonly small, translucent or pearly, raised and rounded areas covered by thin epidermis through which a few dilated superficial vessels show (Fig. 36.2). Tiny flecks of pigment may be seen with a hand lens. Other modes of presentation are a small pearly erythematous lichenoid papule or plaque, as a keratotic and slightly indurated area, or as a small and superficial ulcer resembling an excoriation by a fingernail. It may occasionally be pedunculated and telangiectatic, resembling a pyogenic granuloma.

The more advanced tumours have as wide a variety of forms as the early lesions and tend to maintain the same pattern of growth throughout their course. One common type grows slowly as a well-marginated expanding nodule or thickened plaque. The thinned epidermis closely covers the tumour and may periodically scale or erode and crust. In this variety, ulceration occurs relatively late, and may re-epithelialize and break down several times before becoming permanent. The surface contour usually becomes more irregular as the lesion grows. The degree of vascularity varies. There may be surface telangiectasia over a flesh-coloured mass or the tumour may be pink or red in colour. Pigment, when present, is usually unevenly distributed through the tumour. Some or all of the component nodules may have cystic centres, which add to the translucent appearance; the cystic parts may be more deeply pigmented than the peripheral parts.

Less commonly, the tumour spreads only superficially. It is bounded by a slightly raised thread-like margin, which is irregular in outline and may be deficient at part of the circumference. The epidermis covering the central zone is usually atrophic and may be scaly. This, combined with an increased vascularity, gives a resemblance to Paget's disease of the nipple. There may be a series of thickened papular islands of growth within the margin, and these may be crusted or eroded. Superficial tumours are often pigmented.

The atypical rodent ulcer has an indurated edge and base, but no thread-like margin. The edge is usually raised above the normal level but in some areas, particularly in the nasolabial furrows, it may be flush with the surface. The floor of the ulcer is depressed below the skin surface, fleshy in appearance and not very vascular. However, there is more or less inflammation around the tumour. Such an ulcerated lesion may have begun as a nodule, but more frequently it is crusted or eroded from an early stage of its evolution. If left, the tumour and its following ulcer may spread deeply and cause great destruction, especially around the eye, nose or ear (Fig. 36.3). There may be wide extension in the periorbital tissues; the bones of the face, the skull and even the meninges may be invaded, and

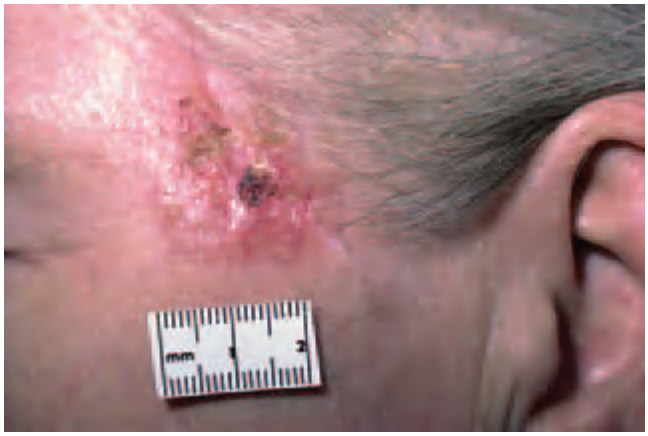

Fig. 36.4 Recurrent basal cell carcinoma that has arisen on the basis of pre-existing morphoeic basal cell carcinoma that was incompletely excised.

advanced cases amply justify the title 'ulcus terebrans' (penetrating ulcer).

The morphoeic or sclerodermiform BCC is uncommon, and is so named because dense fibrosis of the stroma produces a thickened plaque rather than a tumour. The exact margin of the lesion is impossible to define, but palpation reveals a firm skin texture that extends irregularly beyond the visible changes (Fig. 36.4) [28]. The surface is smooth and may be slightly raised above, or sometimes slightly depressed below the normal level. The colour is yellowish and has been compared with old ivory. Ulceration is uncommon and only very superficial when it does occur. Many patients, and doctors, may take little notice of this type of BCC until its slow extension produces a sizeable lesion.

The majority of BCCs arise on the head and neck, with a particular predilection for the upper central part of the face. The morphoeic type occurs almost exclusively on the face. The superficial type, however, is found mainly on the trunk. The palms and soles are rarely affected. BCCs may be multiple.

Post-irradiation tumours of the scalp [29] and those that occur in sun-damaged skin of the face may be multiple and show various stages of development. A few cases of genuine BCCs have been reported to arise from the epidermis over histiocytomas, but the not uncommon basaloid buds seen in sections of histiocytoma are of doubtful significance.

The typical BCC runs a slow progressive course of peripheral extension, which produces the thread-like margin, the nodule with a central depression or the expanding rodent ulcer. Some tumours grow at so slow a rate that they are, for all practical purposes, benign. This is true for many of the superficial lesions and some of the nodular cystic lesions also. There may be spontaneous fluctuation in size, and areas of scarring can be found within many superficial tumours. A patient who has had one BCC treated should always be followed up, not only for local recurrence but also to detect fresh tumours arising elsewhere. There is no recognized premalignant stage of BCC equivalent to solar keratoses or Bowen's disease for SCC.

Rapid growth is so uncommon as to throw doubt on the accuracy of the patient's history. Invasive rodent ulcers, if neglected, may cause death. This is preceded by prolonged mutilation of the face or scalp [30], with destruction of the nose or eye and exposure of the paranasal sinuses or the skull, dura or brain. A few giant exophytic tumours have occurred on the back [31].

In rare cases, the tumour may disseminate [32–37]. When the ulceration involves the airway, fragments of tumour cells and stroma may be inhaled and become implanted in the lungs [35]. Authentic cases of bloodstream metastasis are on record in which, for example, deposits in the viscera or spinal column have caused the presenting symptoms of the terminal illness. Other cases have spread via lymphatics to the regional lymph nodes before disseminating.

Pathology [38,40]. The tumour cells resemble those of the basal layer of the epidermis and the matrix cells of the appendages, in the relatively small amount of cytoplasm they possess and in their ability to interact with the dermis adjacent to them. Their nuclei are compact, rather darkly staining and closely set. Their cytoplasm stains poorly and the cell margins are rather indistinct. Adjacent cells are connected by bridges. The sparsity of keratin fibrils gives these connections a different appearance from the 'prickles' of the Malpighian layer, but the presence of desmosomes and tonofibrils has been shown by electron microscopy. The interaction with the dermis, which is one of the principal functions of the normal epidermal basal cell, produces the characteristic marginal palisade of tumour cells and the well-organized stroma that surrounds it. The dependence of the tumour on its stroma has been shown by transplantation experiments [41]. The cells within the palisade usually show little evidence of organization or differentiation. Mitotic figures may be frequent, and it is speculated that the combination of large numbers of mitoses and a slow growth rate result from a high rate of apoptosis. Data on cell kinetics indicate that a considerable proportion of cells in the tumour die fairly rapidly [42]. Bizarre and atypical cells occur commonly in arsenic-induced tumours [20]. In some tumours, the cells may become acantholytic and amyloid may be identified [38].

In early lesions, the tumour buds can be seen arising from the epidermis. In very small lesions, multiple buds have been seen. These very soon become confluent, and the three-dimensional examination of superficial BCC shows a coherent margin of tumour with a reticular pattern of growth along the interpapillary ridges and larger,

more discrete masses centrally [39]. As the tumour progresses, the masses extend into the dermis, and may separate from each other and from their point of origin. Growth in one area may be accompanied by involution of the tumour in nearby areas leaving an atrophic epidermis. A common site of origin in humans and in the experimental tumours of the rat is the junction between a pilosebaceous duct and the epidermis. From here the tumour may extend along the epidermis and down the duct. It is difficult to prove a purely adnexal origin for BCC, but some lesions behave as though this were so. In all considerations about the origin of the tumour, one must remember that the tumour can either sever its connection with epithelial structures or establish a secondary connection to structures to which it has grown close.

The variability of the natural history of BCCs is reflected in its pattern of growth. Most tumours are composed of rounded expansile islands. These throw out small buds that grow in the same way to produce multilobular masses with thin strands or septa of fibrous tissue penetrating them [39,40]. In some regions, a limited capacity to grow around and enclose adjacent connective tissue may be associated with a reticular or cystic pattern of growth. The capacity to invade in thin strands is often accompanied by an excessive and almost exclusive fibroblastic response, in contrast with the lymphocytic response around the expansile masses. Invasive strands may spread for long distances along nerve sheaths. BCC is truly invasive in only a small proportion of cases. In these, the tumours show no tendency to grow as rounded masses, have no palisade or organized stroma, and penetrate the dermis and deeper structures, destroying them as they go. Such tumours are almost always ulcerated, usually from an early stage. In the less invasive tumour, ulceration occurs when the epidermis is replaced by the tumour. An eroded, vegetating type of growth is rather uncommon.

Most BCCs provoke a round-cell inflammatory reaction of some degree. It increases in extent with ulceration and is often conspicuous in the papillary body, with superficial patterns of growth. Mast cells are often present in numbers among the fibroblasts of the stroma, and Langerhans' cells have been demonstrated within and near the tumour. This infiltrate has recently been correlated with the aggressive nature of the tumour [43].

The diversity of histological patterns of BCC is caused in part by features that have no direct bearing on the clinical course of the tumour. Not infrequently, melanocytes proliferate within the tumour. The melanin they produce causes the tumour to be pigmented, and numerous melanophages collect in the stroma, and sometimes in cystic cavities. Mucin is commonly found in the stroma, particularly at the margin of the tumour, and may be encysted within it. Cystic cavities also form when the centrally placed cells undergo necrosis. There is no evidence that such cavities represent glandular differentiation. Evidence of true sebaceous or sweat gland differentiation has been seen, but is very rare. Within some tumours there are strands of fusiform cells with more abundant eosinophilic cytoplasm, which may form whorls or keratinizing cysts, and which probably represent rudimentary differentiation towards hair roots. Citrulline can be demonstrated as a histochemical confirmation in such cases but does not help in the sometimes difficult separation from trichoepithelioma. Histochemical and electron microscopy investigations show little evidence of differentiation of the tumour cells. However, *in vitro* culture of tumour cells from nodular tumours produces evidence of keratinization after 30 days, suggesting that the cells possess the biochemical mechanisms for keratinization but that some factor, possibly dermal in origin, inhibits them.

Diagnosis. The common nodular type of tumour has a distinctive appearance when it is more than a few millimetres in diameter. In the initial stages it may be hard to separate from a melanocytic naevus (especially when pigmented), molluscum contagiosum or senile sebaceous hyperplasia without the aid of a biopsy. Naevi can be distinguished if hairs grow from the surface, and in molluscum contagiosum and sebaceous hyperplasia there is a central keratin-filled pit. Scaling or crusting on the surface can cause confusion with warts, keratoacanthoma, SCC or molluscum contagiosum. In all cases, the debris should be removed, and this is easily done in BCC. The friable, relatively avascular tissue beneath is characteristic, and if fragments are removed and smeared on a slide the diagnosis can be confirmed by cytology. Darkly pigmented, ulcerated tumours are occasionally confused with malignant melanoma. The margin of BCC is usually rolled, telangiectatic and multinodular, and there is no pigmented halo. The colour tends to be more definitely brown, in contrast with the dusky greyish brown of malignant melanoma.

Perhaps the most difficult problems (although least crucial from the patient's viewpoint) are found with superficial BCCs. Casual inspection may suggest that these are patches of eczema, psoriasis or Bowen's disease. When the scale is removed and the edge stretched, the thread-like margin will reveal the true diagnosis [44]. Careful inspection will almost always rule out eczema or psoriasis, which the patient's history will have also made unlikely. There are some cases, however, where distinction from Bowen's disease can be made only after biopsy. The consistency of a morphoeic BCC may resemble morphoea; the outline is usually less sharp and the evolution more gradual and relentless. A recently described elastotic nodule on the anterior crus of the antihelix of the ear in sun-damaged skin may resemble a nodular BCC on cursory examination.

Clinical diagnostic accuracy in the diagnosis of BCC, widely regarded by most dermatologists as being the

easiest tumour to recognize, is surprisingly poor. One study reported a diagnostic accuracy rate of 70% for academic dermatologists, 65% for dermatologists in private practice and 64% for residents [45].

Treatment. The aims of any therapy selected for the treatment of a BCC is to ensure complete removal and destruction of the primary tumour to prevent local recurrence and the need for further therapeutic intervention. The enormous differences in the natural history and biology of the different subtypes of BCC and the large number of treatment modalities available for the removal and destruction of skin tumours means that it is difficult to draw up rigid guidelines for the management of this common cancer. Successful management of BCC requires a clear understanding of the clinicopathological factors that affect prognosis and a good theoretical and practical knowledge of the strengths and limitations of the many different treatments available for the treatment of BCCs. From published series on treatment outcomes it is clear that successful treatment can be achieved by any one of the large range of therapies, subject to appropriate matching of the treatment to the tumour characteristics [46,47]. In most cases, treatment selection is usually based on a clinical assessment which considers a number of factors that are known to influence tumour prognosis. These factors include tumour size, tumour location, clinical subtype and ability to define tumour margin. In addition to the tumour characteristics, other factors such as the patient's age, adequacy and success of previous treatments and coexisting medical conditions that influence tumour biology or treatment tolerability need to be considered. For reasons that are still unclear, BCC recurring following radiotherapy are particularly difficult to eradicate by conventional surgical excision and this needs to be taken into account when selecting the most appropriate therapy [48].

Destructive therapies used appropriately with careful tumour selection can offer an effective alternative to surgical excision for small primary tumours at non-critical sites. A number of studies have shown that curettage and cautery of low-risk BCCs can give cure rates of up to 97% [49]. Similar high cure rates have also been reported for cryotherapy for low-risk BCCs [50,51]. Tumour size has an important effect on prognosis for BCCs and there is good evidence that the recurrence rate following curettage and cautery or cryotherapy increases significantly with increasing size [52,53]. In addition to recurrence risk, it is also important to bear in mind that the morbidity associated with cryotherapy also increases with increasing size.

Conventional surgical excision with predetermined margins based on the clinical characteristics of the tumour is regarded by many as the most appropriate therapy for most nodular BCCs and provides a specimen for histological examination and assessment of the lateral and deep margins. Information from studies of Mohs' surgical specimens have provided useful information about the probability of achieving complete excision in tumours with predetermined margins in different sized BCCs. For BCCs less than 2 cm in diameter with well-defined clinical margins, a 3-mm margin will clear the tumour in 85% of cases and a 4–5-mm margin in 95% of cases [54,55]. Although it has been estimated that careful inspection of the common nodular and plaque forms of the tumour with a loupe allows the margin to be determined to within 0.5 mm of the histologically proven border, inaccuracies in the clinical assessment of tumour margins is an important cause of incomplete excision of nodular BCCs as underestimation of tumour size can lead to overlap of the predetermined margin with lateral extension of the tumour [38]. Small ulcerated nodular BCCs, which present as non-healing erosions, not infrequently extend several millimeters beyond the clinically defined margin. For these tumours and others where the margin is less clearly defined, curettage prior to excision is a useful technique for more accurately defining the true borders of the BCC [56]. Even in experienced hands there is a risk that nodular BCCs with apparently well-defined clinical margins may have infiltrated more extensively, leading to incomplete excision with residual tumour. In some cases, strands of cells extend along the fine nerves of the skin for a considerable distance beyond the obvious clinical edge of the tumour [57]. The outlook is poor when cartilage, bone or the orbit have been invaded.

Although a clinical recurrence is not inevitable in patients with incompletely excised BCCs, there is a significant risk which is dependent on the extent of the infiltration and aggressiveness of the tumour based on histological assessment. It is well recognized that total removal of a BCC is not an absolute requirement to effect cure and that many incompletely excised BCCs do not recur [58,59]. Based on information generated over the years on residual tumour in re-excision specimens and recurrence rates of incompletely excised tumours, it may be reasonable in cases where there is incomplete excision of the lateral margin only, not to re-excise if the BCC is a primary tumour on a non-critical site with a non-aggressive histology. For all other cases and in cases where the surgical defect has been repaired using a skin graft or local flaps, immediate re-excision with frozen section control or using Mohs' micrographic surgery is the treatment of choice [60–62].

The management of morphoeic BCC, large BCCs (more than 2 cm), some smaller nodular BCCs with poorly defined clinical margins and recurrent BCCs needs to take into account the increased likelihood of subclinical extension. In the absence of either frozen section control or Mohs' surgery, these tumours will require large predetermined margins; even a 5-mm margin will only give complete excision of 82% of morphoeic BCCs [54].

Management of recurrent BCCs is a difficult problem as cure rates are consistently poorer than those achieved for primary tumour. Mohs' surgery is an important treatment option for the treatment of high-risk BCCs as it offers consistent high cure rates for even the most difficult BCCs. For primary BCCs, 5-year cure rates of 99% have been reported [63]. For recurrent BCCs treated with Mohs' surgery, the reported 5-year cure rate in a large review was 94% [64]. The proportion of BCCs treated using Mohs' surgery varies considerably between different countries as it is a relatively specialized technique and is more resource-intensive than simple surgical excision. Tumour characteristics that warrant consideration of Mohs' surgery include BCCs at high-risk sites (nasolabial fold, periocular and nose), BCCs larger than 2 cm, morphoeic, infiltrative or micronodular BCCs and recurrent BCCs [46].

Basisquamous or metatypical basal cell carcinoma [65,66]

This term is used for tumours that on pathological study appear to have features of both BCC and SCC. The biological significance is that this pathological pattern is associated with a significantly higher incidence of metastatic spread [67]. The pattern in these lesions is of small aggregates of cells lacking classic palisading and embedded in dense and profuse fibrous stroma. The cells are larger with a larger paler nucleus than in the classic BCC and have a more eosinophilic cytoplasm.

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Squamous cell carcinoma

Definition. A malignant tumour arising from the keratinocytes of the epidermis.

Incidence and aetiology. The epidemiology and risk factors important for cutaneous SCC development have been described in detail in the previous sections on NMSC. SCC of the skin is a heterogeneous disease both aetiologically and clinically, with different risk factors implicated in its development in different populations. The epidemiology of the disease has changed over the last 50 years, with a decrease in the importance of occupational exposure to chemical carcinogens and an increase in the proportion of cases caused by recreational sun exposure. In addition, new diseases such as HIV infection, and therapeutic advances such as the introduction of effective immunosuppressive therapies to prevent rejection of transplanted organs, and PUVA therapy have resulted in the emergence of new populations that are highly susceptible to cutaneous SCC development [1,2].

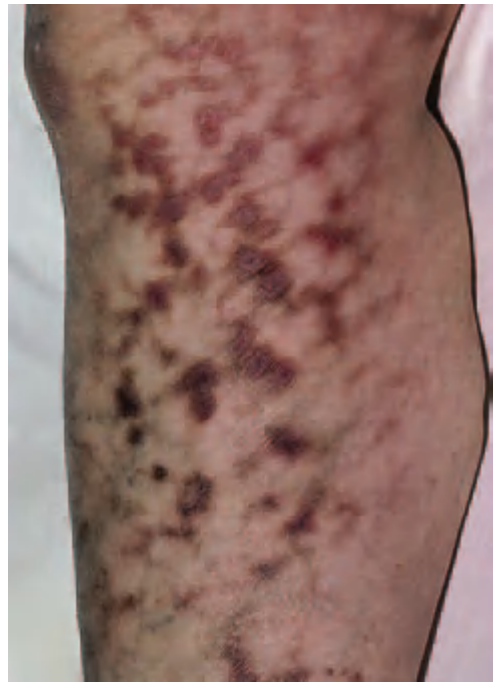

Fig. 36.5 Area of erythema ab igne on the lower leg of an elderly female.

Cutaneous SCC is predominately a disease of white populations and is especially prevalent in this group in areas of high ambient sun exposure [3,4]. Although the incidence is low in non-white populations, SCC is still the most common skin cancer in these populations but shows differences in the anatomical location of the tumours, in recognized aetiological factors and in prognosis [5]. Factors implicated in the pathogenesis of cutaneous malignancy in Africans and African Americans include trauma, albinism, burn scars, ionizing radiation, chronic inflammation and chronic discoid lupus erythematosus [5,6]. There is a high incidence in albinos in Tanzania but no evidence of an increased incidence in vitiliginous skin of black people [6,7]. Additional aetiological factors implicated in cutaneous SCC development in some populations include chronic exposure to thermal radiation and chronic scarring. Radiant heat from coal and peat fires may cause SCC in women who habitually sit with their legs close to the fire [8,9]. The preceding lesion is called erythema ab igne (Fig. 36.5). SCC is also an occasional complication of long-standing chronic granulomas such as venereal granulomas, syphilis, lupus vulgaris and leprosy and lupus erythematosus, chronic ulcers,

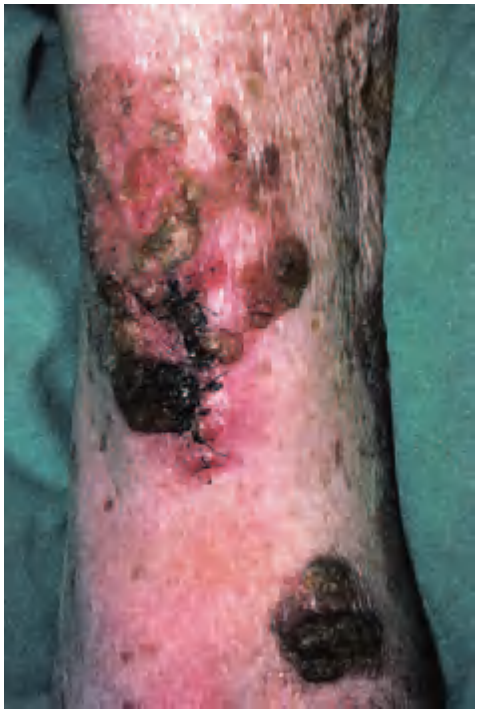

Fig. 36.6 Multiple invasive squamous cell carcinomas in a patient with a history of exposure to arsenic.

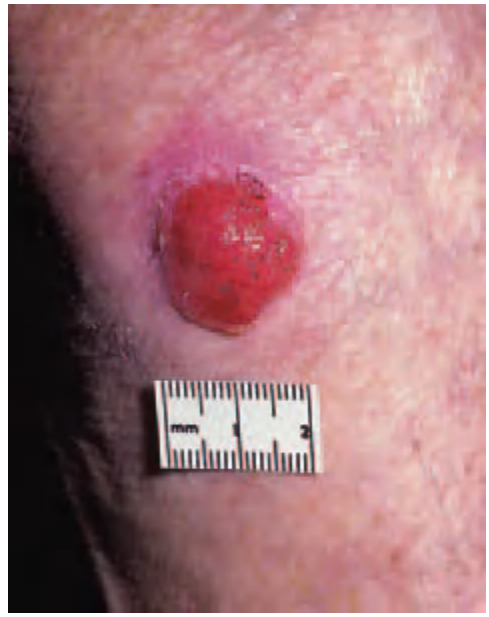

Fig. 36.7 Raised erythematous invasive squamous cell carcinoma in an elderly patient on a light-exposed site.

osteomyelitis sinuses, old burn scars and hidradenitis suppurativa. It may complicate scarring dermatoses such as poikiloderma congenitale, dystrophic epidermolysis bullosa [10] and porokeratosis of Mibelli [11].

Clinical features (Figs 36.6 & 36.7). SCC does not often arise from healthy-looking skin. Commonly, there are signs of photodamage: solar elastosis of the dermis, hyperkeratosis, irregular pigmentation and telangiectasia, or leukokeratosis and fissuring of the lip. The first clinical evidence of malignancy is induration. The area may be plaque-like, verrucous, tumid or ulcerated, but in all cases the lesion feels firm when pressed between the finger and thumb. The limits of the induration are not sharp and usually extend beyond the visible margin of the lesion. The resistance to pressure is much greater than that given by an inflammatory lesion or benign epithelial hyperplasia.

The tissue around the tumour is inflamed and the edge is an opaque yellowish red colour. The better-differentiated tumours are usually papillomatous and are capped by a keratotic crust in the earlier stages. This may be shed later to reveal an ulcer or eroded tumour with an indurated margin and a purulent exuding surface that bleeds rather easily. The outline may be rounded, but is often irregular, and in premalignant lesions the induration and elevation is often asymmetrical at first. On mobile structures such as the lip or genitalia the presenting sign may be a fissure or small erosion or ulcer which fails to heal and bleeds recurrently.

The most common sites for SCC are those most exposed to the sun. They occur on the backs of the hands and forearms, the upper part of the face and, especially in males, on the lower lip and pinna.

The histological susceptibility of the scrotum in chimney sweeps, mule spinners and capstan-lathe operators was a result of the retention of the carcinogen on the skin surface. The relatively high incidence of lesions on the lower leg in the natives of tropical countries is related to the frequency of ulcers and scars. The nailbed is an uncommon site, which may be overlooked until the lesion is large enough to produce radiographical changes in the distal phalanx [12].

The evolution of SCC is usually faster than that of BCC, but is conspicuously slower than that of keratoacanthoma, which may attain the same size in as many weeks as SCC does in months or even years. Tumours arising in keratoses on the dorsum of the hand are particularly indolent and late in metastasizing. Early ulceration, and the absence of tumid outgrowth, are usually a result of an anaplastic lesion [13], and are more commonly seen on the lip and genital area than elsewhere. Regional nodes may become enlarged, either as a result of infection of the ulcer or from metastases. In the latter case, they feel harder, are more irregular and become fixed to the adjacent tissues. Spread by the bloodstream is uncommon [14].

Pathology [15–17]. SCC is a tumour that may arise in any epithelium, and its behavour in the skin is essentially similar to its behaviour in the respiratory tract and elsewhere. Because of the accessibility of the skin, the precancerous

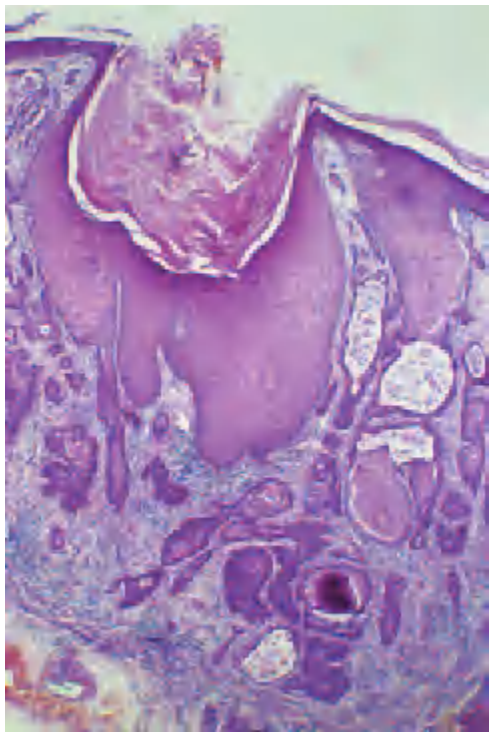

Fig. 36.8 Pathological features of well-differentiated early invasive squamous cell carcinoma, showing differentiated keratinocytes invading the underlying dermis.

changes that lead to the tumour are more easily observed and followed.

Potentially precancerous conditions include actinic keratoses, Bowen's disease and leukoplakia. Invasive SCC begins when atypical keratinocytes breach the dermal basement membrane and invade the dermis (Fig. 36.8). The distinction is thus architectural rather than cytological, and is based on the presence of descending strands of morphologically malignant keratinocytes, which can no longer be regarded as distorted interpapillary ridges. The distinction may be further complicated by the phenomenon of pseudoepitheliomatous hyperplasia [15], which may occur at an ulcer margin or over certain inflammatory or neoplastic states in the dermis (see below).

The cells of SCC vary from large well-differentiated polygonal cells with vesicular nuclei, prominent nucleoli and an abundant cytoplasm containing numerous tonofibrils and well-developed intercellular bridges, through to completely anaplastic cells with basophilic cytoplasm, which provide no cytological evidence of their origin. Some tumours have large bizarre cells, in others the cells may have a clear, almost vacuolated cytoplasm and in yet others the cells may be spindle-shaped. Well-differentiated tumours show areas of maturation that form parakeratotic horny pearls and individually keratinized cells, and also dyskeratosis, with lacunae and lumina that contain shed rounded degenerating cells. The latter appearance is pseudoglandular, and is termed adenoid or acantholytic SCC [16,17].

Most tumours invade as coherent strands and columns, and reproduce the same pattern in their metastases. Many are composed of cells uniform in type and showing only moderate mitotic activity. They stimulate an inflammatory reaction in the dermis. The capillary pattern is abnormal and the number of vessels considerably increased [18]. Increasing anaplasia is associated with hyperchromatic nuclei, decreasing eosinophilia and tonofibril formation in the cytoplasm, and lessened intercellular adhesions. The cell outlines may be rounded or spindle-shaped. Mitotic figures become more frequent, and abnormal mitoses can be found. Even in extensively ulcerated tumours, the connection with the epidermis is usually maintained, and the origin can be traced to atypical epidermal cells, which may enable a distinction to be made from an anaplastic amelanotic melanoma. Its origin from an area of abnormal epidermis distinguishes it from keratoacanthoma. In rare instances, SCC may appear to arise in a keratinous cyst. Many reported instances of this occurrence, however, can now be considered as proliferating trichilemmal cysts.

Local extension of SCC may occur around nerves, sometimes for considerable distances, and may require extensive surgery [19]. Biological differences in the aggressiveness of SCCs arising in different locations and/or resulting from different aetiological factors are well recognized [20]. It is unusual for SCC originating in an AK on the hand or arm to show evidence of anaplasia or to metastasize until well advanced. In a Scandinavian series [21], fewer than 8% of tumours of the upper limb metastasized. Lesions of the vermilion of the lip, and to a lesser extent of the ear, metastasize much earlier even when they are relatively well differentiated. Those elsewhere on the face appear to be less aggressive. SCC of the external genitalia is also inclined to early invasion and metastasis. Spread is almost always by the lymphatic route.

Various ways of predicting the likelihood of metastasis from the histological features have been suggested. One that has been widely used is Broders' classification based on the proportion of differentiated to atypical tumour cells. From the practical point of view, this method needs to be supplemented by the depth of invasion. For tumours of the hand, for instance, metastasis is unlikely when the penetration does not extend deeper than the sweat coils [16]. At the two extremes of differentiation this criterion does not apply. A well-differentiated lesion such as 'epithelioma cuniculatum' may invade the soft tissues of the foot extensively without metastasis [22,23], while a completely undifferentiated tumour, of the lip for instance, may disseminate at an early stage.

Epithelioma cuniculatum [24] *and verrucous carcinoma* [25]. There are several uncommon tumours that are so well

differentiated that the diagnosis may be in doubt if the unrelenting course is not taken into account. One such has been reported as the 'epithelioma cuniculatum' [22]. There is a soft bulbous mass with a squashy consistency on the distal part of the sole of the foot. Multiple sinuses open on the surface and, when pressed, greasy, rancid and foul-smelling material can be expressed. It is possible that the appearance of a vegetating pyoderma may at times be caused by the same process. In such cases, the distinction from pseudoepitheliomatous hyperplasia may be very difficult. A few examples of 'giant condyloma acuminatum' have eventually become low-grade SCC [26,27].

In both the oral cavity and on the genital mucosa [28], a strikingly verrucous lesion may develop [25,29]. These lesions, because of the site involved, may become massive, moist, cauliflower-like and often malodorous because of secondary infection. The clinically apparent relentless growth contrasts with the pathologically less aggressive appearance characterized by a lack of mitotic figures and a well-demarcated lower margin with no strands of cells becoming detached from the main bulk of the lesion.

At the other extreme, anaplastic SCC rarely may arise from skin not showing a premalignant lesion and in a form very difficult to recognize. The lesion is a red papule or nodule, relatively fast growing and looking inflammatory rather than neoplastic. It tends to ulcerate early. It may resemble a keratoacanthoma, but the central keratin core is usually absent. Induration is present, but may be less marked than in well-differentiated tumours. It can infiltrate deeply and metastasize quite early. It has been designated 'squamous cell carcinoma *de novo*' [30].

Squamous cell carcinoma following immunosuppression after organ transplantation. Recipients of organ transplants receiving immunosuppressive therapy have a much higher than expected incidence of SCC [1,31,32]. The development of carcinomas is directly related to time from transplantation, and appears to be independent of the immunosuppressive regimen used. The normal ratio of BCC : SCC is reversed, and SCC is more common. The lesions are most numerous on sun-exposed sites and are frequently multiple. They may clinically be deceptively banal, and resemble either keratoacanthoma or actinic keratosis. All such lesions should be regarded with suspicion in transplant patients, and biopsied to establish their true nature. Female transplant recipients also have a much higher than expected incidence of genital premalignancy.

Careful regular supervision of transplant patients by a dermatologist is required, and advice on sun avoidance should be part of the post-transplant care regimen.

Diagnosis. The indurated well-differentiated SCC arising in skin damaged by sunlight presents no problems in diagnosis. The distinction from keratoacanthoma is usually easy, as the rate of growth and domed appearance of keratoacanthomas are characteristic. On occasions, however, a tumour develops like a typical keratoacanthoma, but proves by its progress to be an SCC [33]. In such cases, the histology of the early stage may not be conclusive one way or the other. The most important clinical distinction is between a poorly differentiated carcinoma arising *de novo* from normal skin, and an inflammatory ulcer or granuloma on the one hand, or an amelanotic melanoma or BCC on the other. The characteristic induration and opaque colour are the most important signs but any doubt is usually clarified by biopsy. Warty lesions such as viral warts or seborrhoeic keratoses are not indurated and are frequently multiple.

Treatment. The aims of any therapy selected for the treatment of cutaneous SCCs are to ensure complete removal and destruction of the primary tumour and to prevent metastasis. From published series on treatment outcomes it is clear that these aims can be achieved by any one of a range of therapies subject to appropriate matching of the therapy to the tumour characteristics [34]. The relative effectiveness of different therapies, however, cannot at present be determined as there are no prospective randomized trials examining different approaches for clinically matched tumours. Treatment selection in clinical practice is based on an assessment of tumour characteristics that have been shown to be important in determining the level of therapy required and in identifying tumours with a poor prognosis. Although there are considerable differences in clinical practices in different countries, it is possible to make some generalizations. Destructive therapies used appropriately with careful tumour selection can offer an effective alternative to surgical excision for small (less than 1 cm) slow-growing well-differentiated SCCs on sun-exposed sites. For tumours with similar characteristics between 1 and 2 cm in diameter, surgical excision with a 4-mm margin is an appropriate starting point but it may be necessary to consider wider margins, subject to other factors such as poorly defined clinical margins and tumour depth [35]. Tumour size has an important effect on the probability of both local recurrence and metastatic risk, with a doubling of local recurrence risk and a threefold increase in metastatic risk for SCCs greater than 2 cm. In addition to tumour size, other criteria used in the selection of appropriate therapy include the location of the tumour, the likely aetiological factor and histopathological characteristics [34,36,37]. UVR-associated SCCs on the ear, lip, scalp, eyelids and nose have a worse prognosis than UVR-associated SCCs at other sites. The basis for this difference has not been established but it is possible that some of the increased risk for cutaneous tumours may result from technical considerations at the time of surgery. SCCs on non-sun-exposed sites where aetiological factors other than UVR exposure are important are also associated with a worse prognosis. It has long been recognized

that SCCs at sites of scarring, ulcers, chronic sinuses or previous thermal or ionizing radiation injury have a worse prognosis. SCCs arising in areas of Bowen's disease are also thought to have greater malignant potential. Although deaths resulting from metastatic cutaneous SCCs are more common in immunosuppressed patients, it is not clear if this increase is brought about by differences in the biology of SCCs in these patients or a reflection of the marked increase in the prevalence of SCCs in this group, which in itself could lead to more deaths from metastatic disease. Histopathological characteristics associated with a worse prognosis include tumour depth, degree of differentiation and presence of perineural involvement. SCCs extending into the subcutaneous fat or greater than 4 mm in depth are almost eight times (45.7% metastatic rate) more likely to recur than SCCs confined to the upper dermis (6.7% metastatic rate). Poorly differentiated tumours have a doubling incidence of local recurrence and a threefold increase in metastatic rate [34]. Histological evidence of perineural involvement is also associated with a worse prognosis. The worse prognosis and difficulties in managing recurrent SCCs highlight the importance of adequate initial treatment based on accurate clinical assessment and appropriate selection of therapy.

It is essential that the planning of treatment for cutaneous SCCs takes into account these prognostic factors. While destructive therapies such as curettage and cryotherapy have a role in the treatment of small low-risk SCCs, surgical excision is the treatment of choice for high-risk lesions less than 1 cm in diameter and for all lesions greater than 2 cm in diameter. Radiotherapy is rarely the treatment of choice but may be indicated for some very large or rapidly enlarging tumours or in patients where aggressive surgical management may not be tolerated. Radiotherapy may also have a role as an adjuvant therapy in some high-risk SCCs where there are concerns about residual microscopic disease. Mohs' micrographic surgery offers advantages over conventional surgical excision and is widely regarded as the treatment of choice for high-risk SCCs as it reduces the risk of local recurrence and metastatic disease.

The final results of any of the methods depends on the experience of the person using it rather than the technique itself. In experienced hands, all the techniques give 5-year cure rates of approximately 90% in a wide variety of SCC at different sites.

Prevention. Patients presenting with SCCs or related premalignant lesions on sun-exposed skin should be advised about the importance of reducing exposure to solar radiation. In high-risk patients, regular follow-up and targeted treatment of small low-risk tumours with cryotherapy and other destructive therapies may help reduce the frequency of tumours requiring surgical excision. Although intermittent 5-fluorouracil use may improve skin texture and reduce the rate of development of AK, there is no published evidence at present that this is associated with a decrease in the rate of development of invasive SCCs. In patients such as organ transplant recipients and patients with XP, where the rate of new SCC development makes surgical management difficult, then it may be necessary to consider treatment with systemic retinoids to reduce the rate of development of new lesions and help target surgical excision to retinoid unresponsive tumours. Etretinate and isotretinoin have both been shown to reduce the rate of development of new lesions in XP patients [38,39]. More recently, acitretin has been shown to reduce the rate of development of new SCCs [40]. In contrast to cytotoxic drugs, retinoids do not appear to eliminate neoplastic clones from the epidermis and discontinuation of therapy is associated with the rapid growth of numerous dysplastic lesions that were growth inhibited but not eliminated by retinoid therapy.

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Premalignant epithelial lesions

Premalignant epithelial lesions are conditions that can be recognized clinically or histopathologically and are associated with an increased risk of cancer development. Although premalignant lesions frequently share many of the histopathological changes seen in invasive cancers, the ability to order lesions on the basis of severity does not in itself imply that the lesions identified represent consecutive changes in a neoplastic process [1]. The histopathological changes seen in premalignant lesions include nuclear pleomorphism, increased mitotic rate, abnormal mitotic figures and abnormal differentiation. In the skin, a number of premalignant epithelial lesions have been identified and there is convincing clinical and epidemiological evidence of an association between many of these lesions and an increased risk of NMSC. Some lesions, such as AK and leukoplakia of mucosal surfaces, may show relatively little evidence of cellular atypia, whereas others, including Bowen's disease and erythroplasia of Queyrat, can show marked dysplasia of the epidermis that is histologically indistinguishable from the changes seen in well-differentiated SCC. Premalignant lesions are distinguished from their invasive counterparts by the absence of histological invasion with the microscopical features of intraepidermal carcinoma confined above the dermal–epidermal junction. In addition to the epidermal changes, a common feature of many premalignant lesions is the presence of a chronic inflammatory cell infiltrate in the papillary dermis immediately beneath the abnormal epidermis [2]. The importance of premalignant lesions as indicators of increased NMSC risk is well illustrated by AK, Bowen's disease, tar keratoses, ionizing radiation keratoses and arsenical keratoses, which are frequently found in patients with NMSC or at high risk of developing this type of cancer. With the exception of arsenical keratoses, which are the result of systemic carcinogen exposure, all of the other premalignant lesions localize to areas of skin exposed to carcinogen and these areas are the same as those at risk of NMSC development. Premalignant lesions frequently develop before the development of invasive cancers and can be useful in identifying individuals at high risk of NMSC development.

Conventional models of multistage carcinogenesis, such as the human colon cancer model and murine skin cancer models, are based on tumour systems that show an orderly progression through well-defined clinicopathological changes. In these models, cancer development is indirect, progressing through discrete clinicopathological changes and this is supported by molecular studies, which have shown that 'early' lesions have less genetic abnormalities than 'late' lesions. Other tumours develop in the absence of any recognizable precursor lesions, that is, they arise directly. Clinical observation suggests that most human cancers including cutaneous SCCs may not progress through intermediate stages and that progression of AK and Bowen's disease to invasive SCC may be the exception rather than the rule [1]. A full consideration of the natural history of most premalignant lesions including AK and Bowen's disease is difficult as therapeutic removal or destruction provides evidence of what the lesion looks like but destroys any chance of consideration of future behaviour. Notwithstanding these limitations, a number of longitudinal studies indicate that AKs frequently undergo spontaneous regression and have a low potential for developing into invasive SCCs [3,4]. Support for the hypothesis that most AKs are not likely to progress into invasive SCCs comes from molecular studies, which have shown that AKs frequently show more extensive chromosome losses than SCCs, in contrast to findings in the colon cancer model where indirect cancer development as part of a linear progression process is the norm [5,6]. These findings do not undermine the importance of regular skin examination of high-risk skin cancer patients and the treatment of lesions based on clinical need but they do not support the concept that aggressive treatment

of some types of premalignant lesions such as AK will prevent cancer development in these patients.

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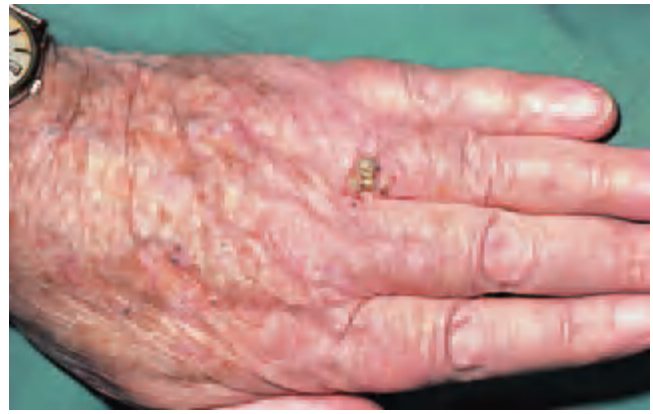

Fig. 36.9 Multiple actinic keratoses on the dorsum of the hand of an outdoor worker.

Actinic keratosis [1–3]

SYN. SOLAR KERATOSIS; KERATOSIS SENILIS

Definition. Hyperkeratotic lesions occurring on chronically light-exposed adult skin, which are focal areas of abnormal proliferation and differentiation that carry a low risk of progression to invasive SCC.

Aetiology and incidence. The great majority of AKs occur on sun-exposed sites in fair-skinned people who have had excessive exposure to solar UVR [4]. Lesions with similar clinical and histological features may be induced by ionizing radiation or radiant heat and in workers exposed to pitch and other products of coal distillation.

The prevalence of these lesions is high in many countries and is influenced by the amount of ambient UV, the proportion of susceptible individuals in the population, the age structure of the population and the time spent in outdoor occupations and recreations. In the UK, a recent study has reported an overall prevalence of 15.4% in men and 5.9% in woman over the age of 40 years and 34% and 18% in men and woman, respectively, aged 70 years and over [5]. In areas with high ambient UVR levels such as Australia, a prevalence rate of 43% with 18% (of a population of 197) having more than 10 AKs is recorded [3]. Longitudinal studies in patients with AK have established first that there is a high probability of developing new lesions and, secondly, that many lesions undergo spontaneous resolution [6]. Although the rate of progression of an individual AK to invasive SCC has been estimated to be low (less than 0.1%), the presence of AK is an important biomarker of excessive UV exposure and increased NMSC risk [7].

Clinical features [8–10]. These lesions occur usually in middle-aged or elderly subjects on habitually sun-exposed areas such as the face, scalp and dorsa of the hands. The sides of the neck are involved in both sexes, but the ears predominantly in men. The vermilion of the lower lip but not often of the upper lip may also show keratosis, with a much higher incidence in men than women. Lesions are usually multiple and comprised of either macules or papules with a rough scaly surface resulting from disorganized keratinization and a variable degree of inflammation. Lesions vary in size from less than 1 mm to over 2 cm and are usually asymptomatic. In many individuals, the number of lesions can be better appreciated by skin palpation, which is a sensitive way of detecting the characteristic roughness associated with smaller lesions. Many of these small lesions may pass unnoticed by most patients, and the diagnostic changes often only appear later as a dry, rough, adherent and often yellow- or brown-coloured scale (Fig. 36.9). The adherent scale can only be picked off with difficulty, revealing a hyperaemic base with punctate bleeding points. In some cases, scaling may be prominent and in time may become thick and horny. The edge of the keratosis is usually sharply demarcated and the reddening is usually closely confined to the area immediately below the area of abnormal scaling. The flat, atrophic or lichenoid variety is most commonly seen on the face.

Many patients give a history of relapsing and/or remitting lesions, which can often disappear either spontaneously or after sun avoidance and use of sunscreens.

Pathology. The boundary between unaffected and affected epidermis is a sharp line that slopes upwards and inwards, and there is a similar margin where the appendage ducts perforate the epidermis as funnel-shaped columns of orthokeratosis. The epidermal cells have a paler cytoplasm and mature through an absent or diminished granular layer to form a parakeratotic scale of varying thickness. There is usually some acanthosis, and the more dysplastic lesions show epidermal hypertrophy with hyperkeratosis and parakeratosis (Fig. 36.10). The interpapillary ridges may be reduced in number and

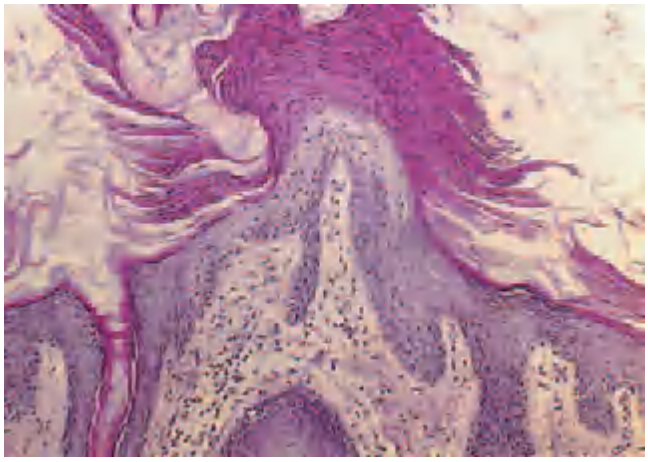

Fig. 36.10 Pathological features of actinic keratoses showing alternating parakeratosis and hyperkeratosis.

broader than normal. The affected zone tends to grow under the normal epidermis and around the ductal epithelium, and may separate from it by a cleft. The basement membrane is intact but basaloid cells may form multiple buds at the junction; the combination of clefting, budding and papillomatosis produces a Darier-like change. Within the epidermis there may be a simple dysplasia or a range of abnormalities up to a picture indistinguishable from Bowen's disease. These are the Bowenoid AK.

The papillary vessels are irregularly increased and there is a lymphoid infiltrate beneath the lesion. There is a variable degeneration of dermal collagen and deposition of material staining like elastin in the upper half of the dermis, except for a narrow band at the basement membrane; this change is more or less uniform, unlike the discontinuous keratosis.

The flat type of AK, most common on the face, may resemble discoid lupus erythematosus. The distinction is made by the altered epidermal cells, deficient granular layer and parakeratosis, the band-like rather than perivascular inflammatory reaction, and the absence of immunoglobulin in the basement membrane region. Occasionally, the appearance may appear pseudoepitheliomatous [8] or similar to lichen planus [9].

The occurrence of funnel-shaped columns of normal epidermis, derived from appendage ducts that appear to be trying to cover the diseased epidermis like an umbrella, suggests an effort at biological compensation [10]. It must be remembered, however, that in keratoses and Bowen's disease, sleeves of dysplastic cells growing down appendage ducts may survive damage by freezing or cytotoxic applications. The presence of an inflammatory response appears to be a warning sign of early malignant transformation [11].

Diagnosis. The diagnosis is usually based on clinical findings which take into account the morphology of individual lesions and the clinical setting. For lesions less than 3 mm, clinical discrimination from an early SCC may be difficult. This diagnostic uncertainty, particularly for small lesions, is one of the reasons why it is difficult to establish accurate rates of progression for AK to SCC. Clinical pointers favouring the diagnosis of an early invasive SCC include the presence of tenderness, induration or a raised shoulder that extends beyond the area of disorganized scaling. Other diagnoses that need to considered, particularly in patients with large confluent areas of erythema and scaling, include discoid lupus erythematosus. The brown colour of lichenoid AK, particularly when these lesions have only minimal scaling, can sometimes cause these to be mistaken for focal areas of lichen planus. When AK is pigmented, it may resemble a superficial seborrhoeic keratosis, but can usually be distinguished from such lesions by the lack of organization of the hyperkeratosis. Bowen's disease on the exposed areas usually has a more irregular contour and a more erythematous base.

Treatment. Management of patients with AK needs to take into account the clinical impact of individual lesions, the probability that the clinical diagnosis is likely to be correct, the significance of the presence of AK with respect to NMSC risk and the importance of general advice such as sun avoidance and sunscreen use. Although AKs are frequently asymptomatic, the skin roughness can cause considerable distress and can be complicated by bleeding and pain because of low-grade skin trauma leading to detachment of the overlying scale. The similarities between AK and SCC mean that there is always a small risk, particularly for small lesions less than 3 mm, that the lesion may not be an AK. Effective management of this risk requires a careful clinical assessment, a therapy plan and and clear communication with the patient. Cryotherapy is the treatment of choice for small numbers of superficial lesions and generally gives excellent cosmetic results. Other destructive therapies such as curettage and cautery can be useful for larger lesions and have the advantage of providing a specimen for histological assessment. Where there is significant diagnostic uncertainty then lesions are best excised for pathological examination of the base to be certain that the lesion is not an early invasive SCC.

In many patients, the number of lesions or the rate of development of new lesions makes management more difficult using approaches such as cryotherapy. For patients with extensive clinical lesions, a number of approaches are available that allow treatment of large areas of AK in severely photodamaged skin. Many of these treatments offer the added advantage that they also target early lesions, which means that a more sustained clinical effect may be achieved. These treatments can be subdivided into two broad groups based on their ease of use. The first group includes topical 5-fluorouracil and diclofenac in hyaluron gel, which have been shown

to be effective therapies for AK [12–14]. Although 5-fluorouracil is a very effective therapy, the marked local inflammation that commonly develops after 2–4 weeks of treatment makes it unacceptable to many patients. Once weekly application for 9 weeks with 5-fluouracil has been shown, in a small study, to reduce the treatment-induced inflammation while maintaining efficacy [15]. A recent study has surprisingly reported greater efficacy and fewer side effects in patients treated with 0.5% fluorouracil cream compared with 5% fluorouracil cream [16]. The relative effectiveness and tolerability of 5-fluorouracil and diclofenac in hyaluron gel have not, however, as yet been formally addressed in a clinical trial. A number of other approaches including retinoids and the immune modifier imiquimod are currently being investigated as topical therapies for AK [17–19]. The second group of therapies involves procedures that are normally carried out in the office or clinic setting and includes PDT therapy, dermabrasion and chemical peels. PDT with topical 6-aminolaevulinic acid has been shown to be an effective well-tolerated therapy for patients with widespread photodamage and AK [20]. A recent comparison of PDT with cryotherapy has established that PDT is as effective as cryotherapy and superior to the latter in patient satisfaction and cosmetic result [21]. Dermabrasion and chemical peels have been widely used in some countries for the treatment of AK and severe photodamage. There is some evidence that this approach may provide more long-term effective prophylaxis against AK [22].

The demonstration that regular sunscreen use reduces the rate of development of new AK indicates that continuing UVR exposure plays an important part in promoting the development of clinical lesions and highlights the importance of ensuring that patients with AK are provided with practical advice on sun-avoidance strategies [23].

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Bowen's disease [1,2]

Definition. A form of intraepidermal SCC characterized by a persistent, non-elevated, red, scaly or crusted plaque with a small potential for invasive malignancy. Progressive growth is usual but spontaneous partial regression occasionally occurs.

Aetiology and incidence. Most cases of typical Bowen's disease in white populations are found on the lower legs of elderly women. The distribution in the context of differences between men and women in coverage of the lower leg by clothing and molecular epidemiological evidence of UVR-specific *p53* mutations in typical Bowen's disease suggests that exposure to solar radiation is an important cause of these lesions [3]. Bowen's disease is uncommon in individuals with pigmented skin and, in these individuals, aetiological factors other that UVR exposure may be important [4].

In the past, arsenic exposure was also important [5]. Although fewer than 5% of a large series of patients with Bowen's disease gave a history of ingestion of arsenic-containing medications, arsenic was found in a significantly higher proportion of the patients' skin than in that of the controls [6]. The possible sources of arsenic vary in different localities. Agricultural workers may be exposed

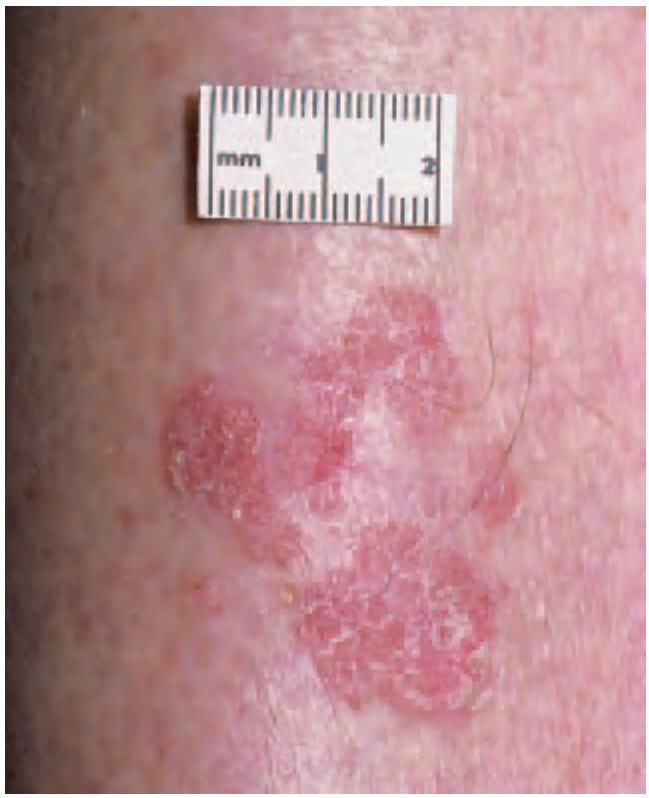

Fig. 36.11 Area of Bowen's disease on lower leg.

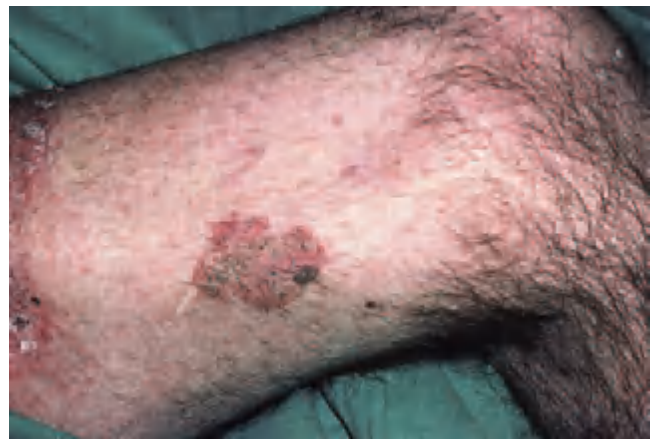

Fig. 36.12 Bowen's disease on the lower leg of a patient with a history of arsenic contact.

to arsenic salts used as a fungicide, weedkiller, sheep dip or pesticide, and they frequently take inadequate precautions against accidental ingestion or inhalation. It may be a hazard in smelting and other industrial processes. In some countries, notably parts of Argentina, Bangladesh and Taiwan, the water supply has been contaminated [7].

Clinical features [8,9]. Although the lesions may occur anywhere on the skin surface or on mucosal surfaces, they are most frequently found on the lower legs of elderly women. The initial change is a small, red and slightly scaly area, which is symptomless and gradually enlarges in a somewhat irregular fashion. The scale is white or yellowish, detached without much difficulty to give a moist, reddened and at times granular surface, but without producing bleeding (Fig. 36.11). The margin is well demarcated and the lesion slightly raised; the surface is usually flat, but may become hyperkeratotic or crusted. Ulceration is usually a sign of development of invasive carcinoma, and may be delayed for many years after the appearance of the intraepidermal change. Persistent superficial ulceration may, however, be the early clinical evidence of Bowen's disease of palmar skin without invasion. There may be several lesions, either widely spread or sometimes close and becoming confluent with extension.

When there is good evidence of chronic arsenicalism (Fig. 36.12), either from the history or because of associated changes such as pigmentation or punctate palmoplantar keratoses, the possible evolution of a visceral malignancy, especially of the lung, should be borne in mind. Although studies in the 1950s suggested that there was a significant link between the presence of Bowen's disease on the skin and internal malignancy [10–14], more recent studies using carefully selected control populations have failed to confirm the results of these earlier studies [15–19].

Pathology [20]. The normal epidermis is replaced by abnormal keratinocytes, which show disordered differentiation and loss of epithelial polarity. There is variable acanthosis, with increase in the length and thickness of the interpapillary ridges but retention of a distinct dermal–epidermal junction. The atypical cells have hyperchromatic nuclei, often larger than normal, giving an irregular appearance to the epidermis. Giant forms and multinucleate cells are seen and mitotic figures can be frequent (Fig. 36.13). There is a conspicuous disturbance of epidermal organization, and cells keratinize prematurely and lose their intercellular connections. The surface is formed by a thickened, loose, parakeratotic scale. The papillary body shows an inflammatory infiltrate that is often quite dense. In some cases, the proliferating cells may be surrounded by relatively normal epidermal cells to give a 'Borst–Jadassohn' appearance. The epidermis above the ducts of appendages may be normal, as in AK, but the cells of the lesion of Bowen's disease often grow down around the ducts like a collar. The condition can become invasive, and when it does it is always squamous cell in type. Arsenical Bowen's disease is said to be characterized by the presence of numerous vacuolated atypical cells. Electron microscope features have been described [21–24].

Diagnosis. The condition must be distinguished from lichen simplex, psoriasis and other papulosquamous

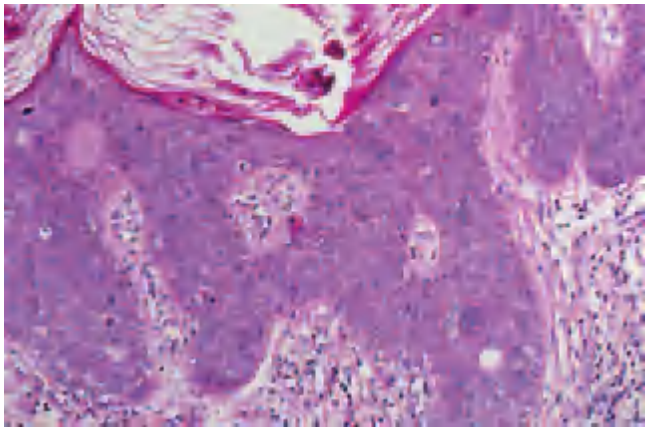

Fig. 36.13 Typical pathological features of Bowen's disease showing loss of polarity of the epidermis and the presence of atypical mitoses and giant cells.

dermatoses. If the diagnosis is uncertain on the first examination, the lack of improvement when steroids are applied is suggestive of Bowen's disease. The superficial ('pagetoid') type of BCC can produce a very similar appearance, but can usually be differentiated by the finely elevated, 'thread-like' margin. Bowen's disease and superficial BCC can be seen in the same patient. Differentiation from the flat type of solar keratosis may be impossible.

Treatment [24]. Destructive therapies such as curettage and cautery, or cryotherapy are widely used in clinical practice and usually effective. Comparison of the relative effectiveness of different therapies and regimens is difficult as the published studies do not fully control for factors such as site and size and there are inconsistencies between treatment regimens between different centres. Cryotherapy is an effective therapy with a recurrence rate when used optimally of less than 10% at 12 months. Regimens used include single freeze–thaw cycles, single freeze–thaw cycles repeated on more than one visit and multiple freeze–thaw cycles repeated at a single visit [25–27]. Prolonged single freeze cycles for larger lesions is painful and may be better performed under local anaesthesia. Slow healing can be a problem, particularly for larger lesions on the lower leg. Curettage and cautery is widely used in practice but poorly studied. Reported recurrence rates are higher than those described with cryotherapy but these findings are difficult to interpret as the treatment regimens and equipment used are not well described. Surgical excision is a useful approach, particularly for larger lesions where wound healing following destructive therapies can be slow.

Local cytotoxic agents such as 5-fluorouracil can be applied to good effect. Treatment regimens vary and include once daily application of a 5% cream for 4–8 weeks or more prolonged treatment using a once weekly application. There is some evidence that occlusion may increase efficacy. Recurrences are common, and may come from extensions of the carcinoma *in situ* around appendage ducts that were not affected by treatment. Current studies suggest that PDT, using a topical photosensitizer such as aminolaevulinic acid and a laser or non-laser light source may also be an effective method of treatment [27,28].

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Arsenical keratosis

Definition. A corn-like, punctate keratosis caused by arsenic, characteristically affecting the palms and soles, which may progress to SCC.

Incidence. A considerable proportion of any population exposed to chronic arsenic intoxication develops keratosis, the frequency increasing with the degree of intoxication and its duration [1]. There is great individual variation in tolerance, and it is not possible, on present data, to construct a precise dose–response curve. The problem is greatest in parts of Bangladesh, West Bengal and Taiwan resulting from well water contamination [2].

Clinical features. The keratoses usually begin on the palms or soles as small areas of hyperkeratosis resembling corns. These enlarge, thicken and increase in number. The fingers, backs of the hands and more proximal parts of the extremities may be involved. Induration, inflammation and ulceration occur when the lesion becomes malignant. There may be areas of Bowen's disease in other sites and multiple BCCs, mainly of the trunk, may occur in association.

Pathology. A range of changes may be seen from a benign-looking hyperplasia or dysplasia, through mild or moderate atypia, to frank Bowen's disease [3–5]. There is no microscopic feature that allows a positive diagnosis of arsenic as the cause. In most lesions there is no elastotic degeneration of the upper dermis.

Diagnosis. The palmar lesions have to be differentiated from the various types of punctate keratosis, such as disseminated punctate keratoderma (see Chapter 34), which usually appears in early life, and Darier's disease and lichen planus, which usually have characteristic lesions elsewhere. Plantar warts differ in being papillomatous.

Treatment. The multiplicity of the keratoses makes treatment difficult. Where it is necessary, the use of a keratolytic ointment and trimming down of the surface is helpful. Two recent case reports suggest that oral acetretin may be beneficial [6]. All affected patients should be examined periodically for evidence of malignant change and for signs of visceral malignancy.

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Disseminated superficial 'actinic' porokeratosis

This disorder was first recognized in Texas [1,2], and is common in Australia [3]. It appears on sun-exposed areas of white-skinned individuals, becomes more prominent in summer and may improve in winter. New lesions have been provoked by exposure to a UV sun lamp [4]. The tendency to develop these lesions is inherited as an autosomal dominant [4]. The preponderance of females in reported cases has been attributed to their greater tendency to seek help for skin problems. The average age at which Texan patients first notice it is about 40 years, and its frequency in members of affected families increases with age. There are UK patients with multiple lesions who have never lived abroad, and the true role of the sun in the aetiology of the condition has been questioned, as has its degree of premalignant potential [5,6]. Genetic studies have mapped a gene, *DSAP1*, for this condition to chromosome 12q23.2–24.1 and a Chinese family with disseminated superficial 'actinic' porokeratosis (DSAP) has recently been reported with a second affected locus, *DSAP2*, on chromosome 15q25.1–26.1 [7].

Clinical features [2]. The lesion begins as a 1–3 mm conical papule, brownish red or brown in colour, and usually around a follicle containing a keratotic plug. It expands and a sharp, slightly raised, keratotic ring, a fraction of a millimetre thick, develops and spreads out to a diameter of 10 mm or more. The skin within the ring is somewhat atrophic and mildly reddened or hyperpigmented, but a hypopigmented ring may be seen just inside the ridge. The ridge itself is sometimes darkly pigmented. The central thickening usually disappears, but it may persist with an attached scale, follicular plug or central dell. Sweating is absent within the lesions. Sun exposure may cause them to itch. In sunny areas, lesions may be present in very large numbers and may change from a circular to a polycyclic outline. In less sunny climates, like the UK, patients have fewer lesions, which tend to remain circular (Fig. 36.14). In a few cases, the centre of the area has become considerably inflamed and covered by thick hyperkeratosis, or has even ulcerated and crusted. The disorder affects areas exposed to sunlight, appearing mainly on the distal extremities and arising more frequently on the lower legs in women than men. The malar

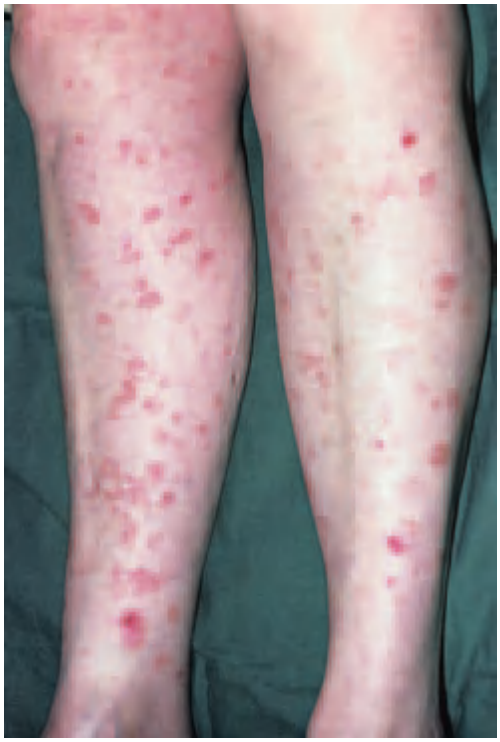

Fig. 36.14 Disseminated superficial actinic porokeratosis on the lower legs.

regions and the cheeks may be affected. It has not been seen on areas habitually covered by clothes, or on the scalp, palms or soles.

Pathology [8]. There is no microscopic feature that separates this disorder from porokeratosis of Mibelli (see Chapter 34), and both have been explained as the result of localized clones of abnormal epidermal cells [8], an idea supported by the successful autotransplantation of the disseminated superficial variety [4].

The distinctive pathological feature of porokeratosis is the cornoid lamella at the margin. This is a narrow column of altered or parakeratotic keratin, seated in a slight depression in the epidermis and directed obliquely inwards in some cases. It may involve the ostia of follicles and sweat ducts. The granular layer of the indented epidermis is usually missing and there may be dyskeratotic cells. The epidermis enclosed by the ridge is usually thinned, the interpapillary ridges and dermal papillae may be flattened, and the basal cells may show liquefaction degeneration. In addition to solar elastosis, decrease in collagen and telangiectasia, the upper dermis may have a non-specific inflammatory infiltrate with vascular proliferation, oedema and fibrosis. Malignant change has not been recorded.

Diagnosis. Porokeratosis is distinguished from other dermatoses by its sharp margin and history of outward expansion. The rim of DSAP is very much smaller than in Mibelli's porokeratosis and never contains a cleft. The onset of Mibelli's porokeratosis is often in childhood, and the lesions are usually solitary or few in number and do not necessarily affect exposed parts. Where the central keratosis and inflammation are prominent, the disseminated superficial variety may be mistaken for solar keratosis if the marginal ridge is not noticed.

Treatment. Lesions respond satisfactorily to cryotherapy with liquid nitrogen, but new lesions tend to develop [2,3].

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Cutaneous horn [1]

This is a clinical diagnosis. Horny plugs or outgrowths may be caused by various epidermal changes, such as epidermal naevus, virus wart, molluscum contagiosum, keratoacanthoma, seborrhoeic keratosis, or marsupialized trichilemmal or epidermoid cyst (Fig. 36.15). In most of these cases, the primary diagnosis is suggested by the

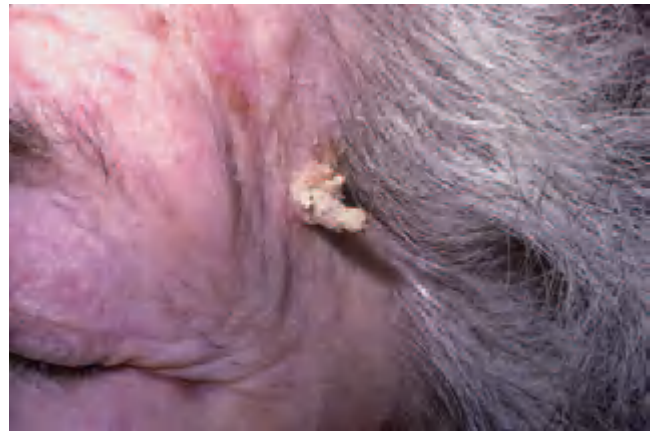

Fig. 36.15 Typical cutaneous horn. Underlying this lesion, a carcinoma *in situ* was identified after biopsy.

appearance and clinical course and, in most, the horn has a friable quality.

Clinical features. Clinical examination shows a hard, yellowish brown horn, often curved and having circumferential ridges, which is surrounded either by normal-looking epidermis or by an acanthotic collarette. Recurrent injury may cause the base to be inflamed; a combination of inflammation and induration beneath the horn is suggestive of malignant transformation. The lesions are most common on the exposed areas—particularly the upper part of the face and the ears. They are commonly single, but may be multiple; it is usual to find some more typical solar keratosis or other evidence of solar damage. Nodular AKs, which are largely confined to the dorsum of the hand and forearm and in which the histology may show an almost pseudoepitheliomatous picture, occupy a position midway between cutaneous horns and the more usual flat AKs.

Pathology. The gradual continuing development from relatively normal-looking skin to a hard keratotic protrusion resembling an animal horn in miniature is the result of dysplastic epidermal changes similar to those in a solar keratosis. Histologically, there is usually no atypicality or loss of polarity of the epidermal cells, but the granular layer is deficient or absent. In long-established lesions there may be budding from the basal layer, indicating early development of an SCC.

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Erythroplasia of Queyrat [1–3]

This condition is described with the genital disorders (see Chapter 68). The histological appearance and natural history suggest that the lesion is Bowen's disease of the mucosa of the penis. However, its prevalence only in the uncircumcised indicates a different and locally acting cause.

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Bowenoid papulosis of the genitalia [1]

This entity is fully discussed in Chapter 68. It is likely that some of the cases previously described as Bowen's disease [2,3], frequently multifocal, of the genital area were in fact Bowenoid papulosis. The lesions regress spontaneously over time and aggressive surgery is therefore not required [4,5]. There are reports of the presence of viral particles and of certain HPVs in a small number of cases to date.

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Intraepidermal carcinoma of the eyelid margin

This condition (see Chapter 64), which may resemble a banal warty lesion in its early stages, represented about 6% of all eyelid malignancies in one series [1]. Occupational exposure to oils and grease may be important. The dysplastic changes seen on biopsy may not be sufficiently severe to warn of the dangers of inadequate treatment. One clue is the way the intraepidermal carcinoma invades the deepest ciliary adnexae, causing loss of eyelashes and nodularity of the margin on clinical examination. SCC may supervene and complete excision is essential.

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Leukokeratosis of the lips

SYN. ACTINIC CHEILITIS [1]

This disorder is an AK that occurs on the vermilion border (see Chapter 66). The patient almost always gives a history of recurrent sunburn of the lips, and the lower lip is predominantly affected. It has been suggested but not proven that cigarette smoking may also be contributory. Some observers have not found a correlation [2], but others claim that this is the reason for the high incidence in men. The use of lipstick by women may be protective [3], especially in preventing dehydration. It is common experience that a hot, dry wind potentiates the burning effect of the sun. Actinic cheilitis is relatively common in renal transplant recipients [4].

The lower lip shows persistent dry scaling, a tendency to fissure and atrophic changes beneath and around the keratosis.

Treatment. Removal of the affected area by shaving through the superficial dermis and allowing healing by secondary intention often produces a good result.

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Post-ionizing radiation keratoses

These may occur in an area of scarring following radiotherapy or excessive fluoroscopy where there is obvious dermal damage. They may also be seen in radiologists, surgeons, dentists and others who have exposed their skin to frequent small doses of X-rays and where the dermis is less grossly changed, although such cases are now rare. The epidermal changes are similar to solar keratosis. Histologically, the dermis shows a much more extensive replacement of collagen by scar and elastotic material, obliterative changes in the vessels and, at times, the presence of abnormally large and irregular fibroblasts (Fig. 36.16).

Tar keratoses [1–4]

These are now very rare entities. In the past, they were seen in workers with tar and pitch. There were small keratotic plaques, not unlike plane warts, or flat seborrhoeic keratoses on the face and hands, which have the microscopic features of benign acanthomas. These usually disappeared when the exposure ceased. There were also lesions resembling solar keratoses, which persisted and a few became malignant. Other lesions with the appearance of keratoacanthomas were seen. Their course was usually more prolonged and, particularly on the scrotum, a relatively high proportion became malignant.

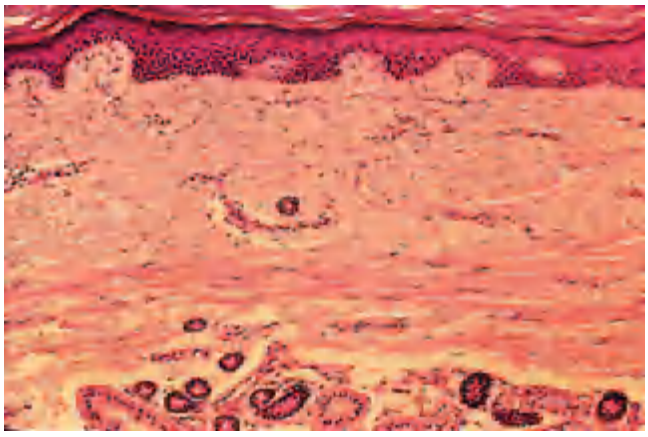

Fig. 36.16 Pathological appearance of radiodermatitis showing a scarred dermis with loss of skin appendages.

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Benign epidermal tumours

Seborrhoeic keratosis

SYN. SEBORRHOEIC WART; SENILE WART; BASAL CELL PAPILLOMA

Definition. A benign tumour, frequently pigmented, more common in the elderly and composed of epidermal keratinocytes.

Aetiology and incidence. Multiple seborrhoeic keratoses may be a familial trait, with an autosomal dominant mode of inheritance [1]. It has been suggested that the lesion is a naevoid tumour; its occasional association, in the same patient, with the fibroepithelial type of BCC [2] is said to support this concept. A genetically determined predisposition, based perhaps on a mosaic pattern of aberrant response to epidermal growth factors and inhibitors [3], would explain those cases where a profuse eruption follows an inflammatory dermatosis [4] or occurs as a manifestation of visceral malignancy, usually cancer of the gastrointestinal tract. The latter is known as the sign of Leser–Trélat [5].

Seborrhoeic keratoses are very common in white races and are often of little concern to the patient, being accepted as a harmless and inevitable consequence of ageing. Males and females are equally affected. The seborrhoeic keratoses may be large and have a tendency to crumble on covered truncal skin. A flat variant is more common on the light-exposed skin of the face and may be confused with early lentigo maligna. The keratoses usually appear in the fifth decade in a temperate climate but may develop earlier in tropical regions. There is little tendency to spontaneous disappearance and new lesions may continue to appear for many years.

Stucco keratosis [6] is probably a non-pigmented variant of seborrhoeic keratosis, occurring principally on the limbs.

Seborrhoeic keratoses are uncommon in black and Indian people. Multiple tumours of the face found in dark-skinned races, and termed dermatosis papulosa nigra, have a similar histology to seborrhoeic keratosis, but appear earlier in life [7].

Clinical features. Seborrhoeic keratoses occur on any body site. They are usually asymptomatic but may be itchy. They are most frequent on the face and the upper

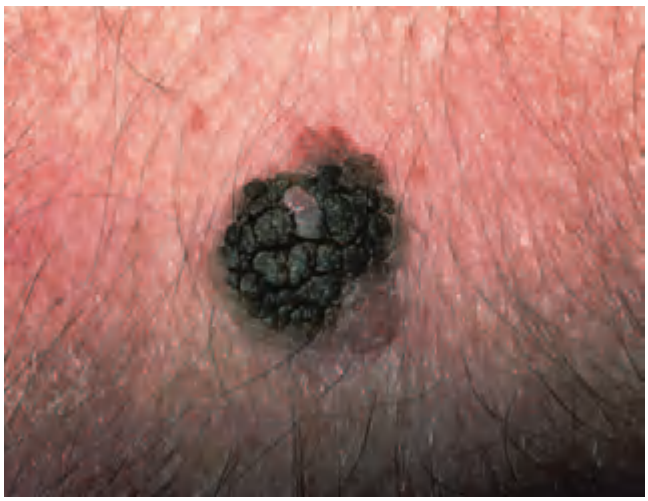

Fig. 36.17 Clinical illustration of basal cell papilloma showing dull, non-reflective, hyperkeratotic surface. This contrasts with melanocytic lesions.

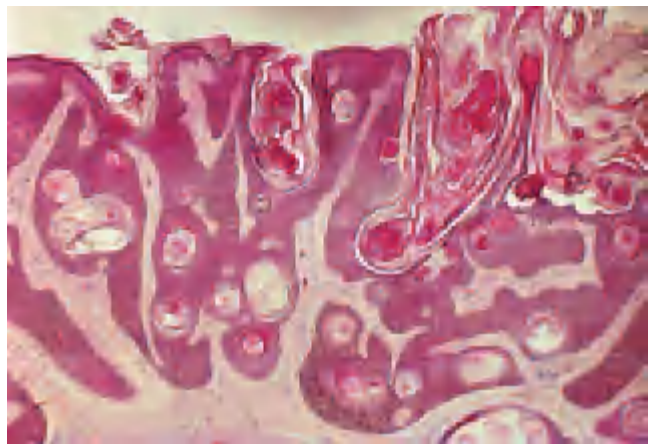

Fig. 36.18 Histology of classic basal cell papilloma showing hyperkeratotic surface and numerous horn cysts.

trunk. The first evidence is slight hyperpigmentation. On the hand and face, seborrhoeic keratoses may remain superficial for a long period, and can be mistaken for melanocytic lesions. It may be difficult to distinguish superficial seborrhoeic keratoses from lentigo maligna and pigmented AK. More florid examples may be pedunculated or acanthotic, smooth-surfaced, domed and heavily pigmented, but in contrast to melanocytic naevi do not reflect light and usually have plugged follicular orifices on the surface, giving an almost cerebriform appearance. Most seborrhoeic keratoses have fewer hairs than the skin they arise from. The most common appearance is that of a very superficial verrucous plaque which appears to be stuck on the epidermis, varying from dirty yellow to black in colour and having loosely adherent greasy keratin on the surface (Fig. 36.17). The shape is round or oval and multiple lesions may be aligned in the direction of the skin folds. The size varies from 1 mm to several centimetres. The smallest lesions are placed around follicular orifices, particularly on the trunk. On the eyelids and major flexures, seborrhoeic warts may be pedunculated and less keratotic. Irritation or infection causes swelling, sometimes bleeding, oozing and crusting, and a deepening of the colour because of inflammation. An eruption of seborrhoeic keratoses may be precipitated by an inflammatory dermatosis [4] or severe sunburn.

Seborrhoeic keratoses usually increase in number over the years, and some elderly patients have very large numbers.

Pathology [8]. The essential change is an accumulation of normal keratinocytes between the basal layer and the keratinizing surface of the epidermis. Melanocytes may proliferate among these immature keratinocytes and transfer melanin to them. The dermal papillae may be elongated. Focal keratinization may occur within the mass of immature cells to produce horn cysts, which enlarge, may coalesce and can be carried to the surface by the tide of epidermal cells. If the formation and discharge of horn cysts is excessive, a verrucous surface will be formed. Marked papillomatosis will also cause an irregular 'church steeple' outer border which retains keratin. If, in contrast, the main mass of the lesion is composed of immature cells, the surface will be smooth and rounded, and the melanocyte population and degree of pigmentation will vary, so that the lesions may be surprisingly pigmented. The parenchymal cells are rather small and polygonal, possessing tonofibrils and intercellular bridges, and they are arranged in an orderly fashion.

The most common pathological type is the solid variant, in which a mass of immature keratinocytes is seen mainly above the level of the surrounding epidermis (Fig. 36.18). Occasional cystic areas containing fragments of stratum corneum are seen in these areas. A rarer variant is the hyperkeratotic variety, which may be clinically mistaken for an AK. The reticular form is a third variant composed of strands of keratinocytes; this type is frequently seen as a flat lesion on the face.

If a seborrhoeic keratosis becomes irritated, or develops a pattern of apparently inverted growth, frequently in association with a hair follicle opening, the pathological differential diagnosis may include an early invasive SCC. An irritated seborrhoeic keratosis shows focal areas of whorls of keratinocytes in so-called squamous eddies, but mitotic figures are rare, and the base of the lesion shows a clear separation from dermal tissue, with no single-cell invasion (Fig. 36.19).

Diagnosis. The superficial type of seborrhoeic keratosis has to be distinguished from simple and malignant lentigo (see Chapter 38) and from AK, especially on the

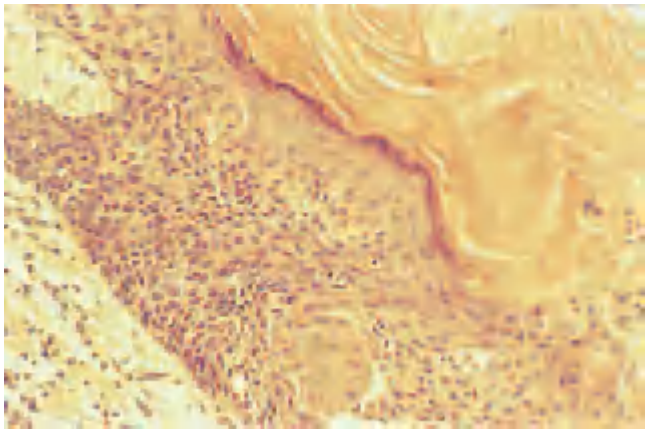

Fig. 36.19 Histology of irritated basal cell papilloma. The squamous eddies are clearly seen in this illustration.

face. The patterned fine fissures on the surface may be helpful. The pigmented domed variety may closely resemble a melanocytic naevus, but the surface is less lustrous and the follicular orifices are plugged. An inflamed keratosis may be confused with a malignant melanoma. If the lesion is treated with a topical antibiotic and occluded for 3–5 days the diagnosis may become obvious, but if clinical doubt persists an excision biopsy and pathological examination is indicated. Pigmented BCCs may also have to be considered in the differential diagnosis. They are usually rather irregular with a rolled edge, a thin shiny epidermis with telangiectases and a depressed or ulcerated centre.

Treatment. Removal with a small sharp curette leaves a flat surface that becomes covered by normal epidermis in a week. Cautery or diathermy should be used as little as possible to avoid scarring. Satisfactory results can be obtained by freezing briefly, a technique especially suitable for large superficial lesions, or by carefully painting the surface with pure trichloracetic acid and repeating if the full thickness is not removed on the first occasion. Seborrhoeic keratoses tend to recur, and it is often wise to encourage patients to accept them rather than to keep returning for further treatment.

Melanoacanthoma

This term has been used for a very rare lesion, originally described by Bloch as 'non-naevoid melanoepithelioma, type 1', and has been considered to be a benign neoplasm composed of epidermal keratinocytes and large dendritic melanocytes [9]. The current general view is that this is not a discrete entity. Some deeply pigmented acanthotic seborrhoeic keratoses contain, dispersed among the parenchymal cells, numerous dendritic melanocytes, which are demonstrable by the dopa technique [10]. Normally they transfer melanin to the surrounding immature keratinocytes. However, if irritation or inflammation caused the parenchymal cells to become more mature, the transfer of melanin would be impeded and pigment might be retained in the melanocytes, producing a microscopic appearance similar to that described as melanoacanthoma.

Stucco keratosis [6,11]

This title has been given to small rough whitish keratotic plaques that are easily lifted off the skin with a fingernail and come away without causing bleeding. They are situated principally on the extremities, especially the ankle region, and occur in middle-aged or elderly persons. They have the same stuck-on appearance of seborrhoeic warts and a similar microscopic architecture. Basaloid cells and horn cysts are not seen and the histology is more that of a regular spiky papillomatosis, with loose lamellated hyperkeratosis capping the epidermis. If treatment is called for, curettage or cryotherapy are effective.

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Dermatosis papulosa nigra

Definition. A pigmented papular eruption of the face and neck caused by a naevoid developmental defect of the pilosebaceous follicles, with histology resembling seborrhoeic keratoses. The condition is most common in black races.

Aetiology [1]. This lesion is probably genetically determined. The incidence in black people rises from about 5% in the first decade to over 40% by the third, and is rather higher in females than males.

Clinical features [1–3]. The individual lesions are black or dark brown, flattened or cupuliform papules 1–5 mm in

diameter. They are rare under the age of 7 years, after which they increase steadily in frequency, number and size. They are most numerous in the malar regions and on the forehead. They are rare on the lower parts of the face and the chin, but in a few individuals may be found on the neck, chest and back [2].

Pathology [1,4]. The lesions, which are naevoid developmental defects of the pilosebaceous follicles, show irregular acanthosis and hyperkeratosis, and somewhat resemble seborrhoeic keratoses.

Treatment. Treatment is seldom requested. Removal with the diathermy or cautery is effective.

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Skin tags

SYN. SOFT WARTS; ACHROCHORDON

Definition. A common benign lesion composed of loose fibrous tissue and occurring mainly on the neck and major flexures as a small soft pedunculated protrusion.

Incidence and aetiology. These lesions are very common, particularly in women at the menopause or later. They are frequently found together with seborrhoeic keratoses.

Clinical features. The lesions are pedunculated and may have a long stalk. They vary in size and are about 2 mm in diameter on average. They are round, soft and inelastic. The colour may be unchanged, but they are frequently hyperpigmented. The most common site is on the sides of the neck, where they may be mixed with typical small sessile seborrhoeic keratoses. When more profuse, they can extend on to the face or down to the back and chest. Similar lesions may be found in and around the axillae and groins.

Pathology. The protruding mass is connected to the skin by a narrow pedicle. The bulk of the lesion is loose fibrous tissue, similar to that of the papillary dermis. The epidermis is thin, and the basal cell layer is flat and often hyperpigmented. Melanocytic proliferation and naevus cells are not usually seen and the majority of such lesions probably come within the seborrhoeic keratosis spectrum. However, there is an overlap with melanocytic naevi and neurofibromas. Some skin tags may be the last remnants of a pre-existing melanocytic naevus.

Diagnosis. The lesions are unmistakable. They are smaller than the average pedunculated melanocytic naevus or the lesions of neurofibromatosis.

Treatment. Both cautery and cryotherapy with liquid nitrogen are effective.

Haber's syndrome

Definition. A familial condition characterized by a persistent rosacea-like eruption, associated in some cases with keratotic plaques on the trunk and limbs.

Incidence. A family in which five members were affected was originally described [1]. Another case, with 15 affected relatives, has been described from Japan [2]. The rosacea-like eruption appears in childhood, and the keratotic lesions somewhat later. The mode of inheritance seems to be a simple autosomal dominant.

Clinical features. The cheeks, nose, forehead and chin are permanently flushed. The skin surface shows a combintion of erythema and telangiectasia, prominent follicles, comedones, small papules, some of which are scaly, and tiny atrophic pitted areas. There is little fluctuation in the erythema, although sunlight may aggravate it. The warty lesions occur mainly on the trunk and thighs and are static, scaly or keratotic, flat and non-indurated plaques.

Pathology. The facial eruption shows perivascular inflammation leading to fibrosis, acanthosis and parakeratosis of the epidermis, distortion of pilosebaceous complexes with dilated follicular orifices, and proliferation of immature glands and basal cell strands. The warty lesions are produced by papillomatosis, acanthosis in the interpapillary ridges and dyskeratosis with areas of pale-staining cells giving a parakeratotic stratum corneum. Mitotic figures are present, but there is no evidence of malignancy.

Treatment. The facial eruption was controlled in the young patient in the first family and in the Japanese patients by steroid creams locally. The warty lesions respond to radiotherapy. Simple destructive measures are also effective.

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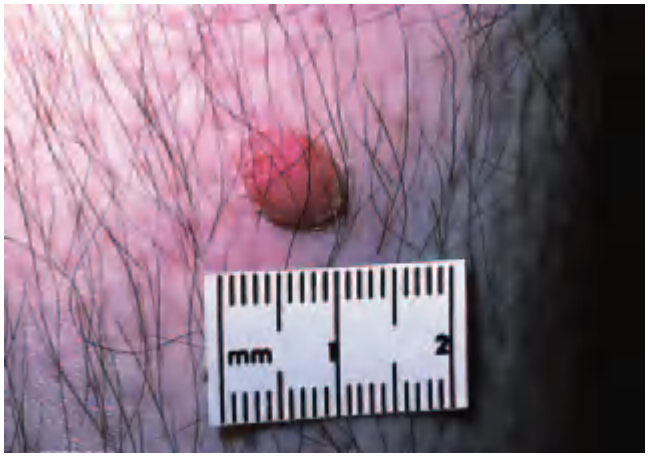

Fig. 36.20 Clinical illustration of clear cell acanthoma.

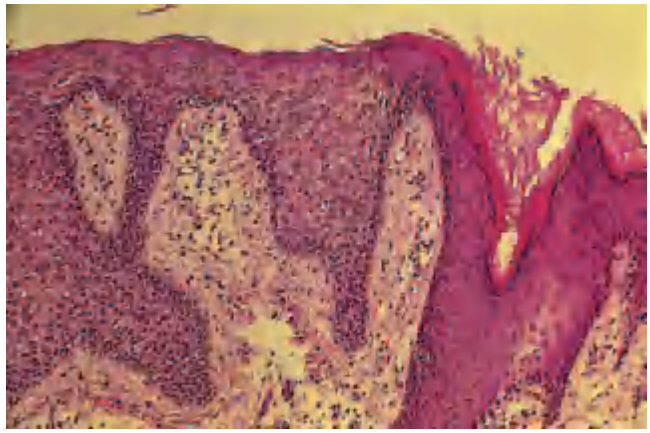

Fig. 36.21 Pathology of clear cell acanthoma of Degos, showing sharp margin between normal skin to the right and epidermis involved with the clear cells to the left.

Clear cell acanthoma [1–3]

SYN. DEGOS' ACANTHOMA; ACANTHOME A 'CELLULES CLAIRES'

Definition. A scaly plaque or nodule that has a characteristic accumulation of clear glycogen-containing cells in the epidermis.

Incidence and aetiology. Clear cell acanthoma is a relatively uncommon condition of adults. The sexes are equally affected [3]. The cause is unknown [4].

Clinical features (Fig. 36.20) [1,3,5]. The lesion is usually solitary. It is a slightly elevated to dome-shaped plaque or nodule with an abrupt margin and a wafer-like scale adherent at the periphery, which leaves a moist or bleeding surface when removed. The colour varies from pink to brown, but is most characteristically red with vascular puncta and it blanches on diascopy. It varies from 3 to 20 mm in diameter, and occurs most commonly on the lower limbs. The duration may be of many years, and there are usually no symptoms. The diagnosis can be suspected on the clinical evidence. The lesion may be mistaken for a histiocytoma, seborrhoeic keratosis or pyogenic granuloma.

Pathology [1,6,7]. The epidermis is thickened and papillomatous with sharply demarcated areas of light-coloured cells, which contrast with the normal basal cells below and Malpighian cells around them (Fig. 36.21). The cytoplasm of the clear cells contains an abundance of glycogen, which on electron microscopy is seen to displace tonofibrils [7,8]. The cells do not have the enzymes characteristic of eccrine sweat glands. There is intercellular oedema and an infiltrate often containing many polymorphonuclear leukocytes. The papillary body is oedematous and the superficial capillaries and veins are increased in number. There may be syringomatous sweat gland elements and evidence of sebaceous differentiation beneath the lesion [9].

Treatment. Excision is often needed to confirm the diagnosis [1].

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Keratoacanthoma

SYN. MOLLUSCUM SEBACEUM

Definition. A rapidly evolving tumour of the skin, composed of keratinizing squamous cells originating in pilosebaceous follicles and resolving spontaneously if untreated.

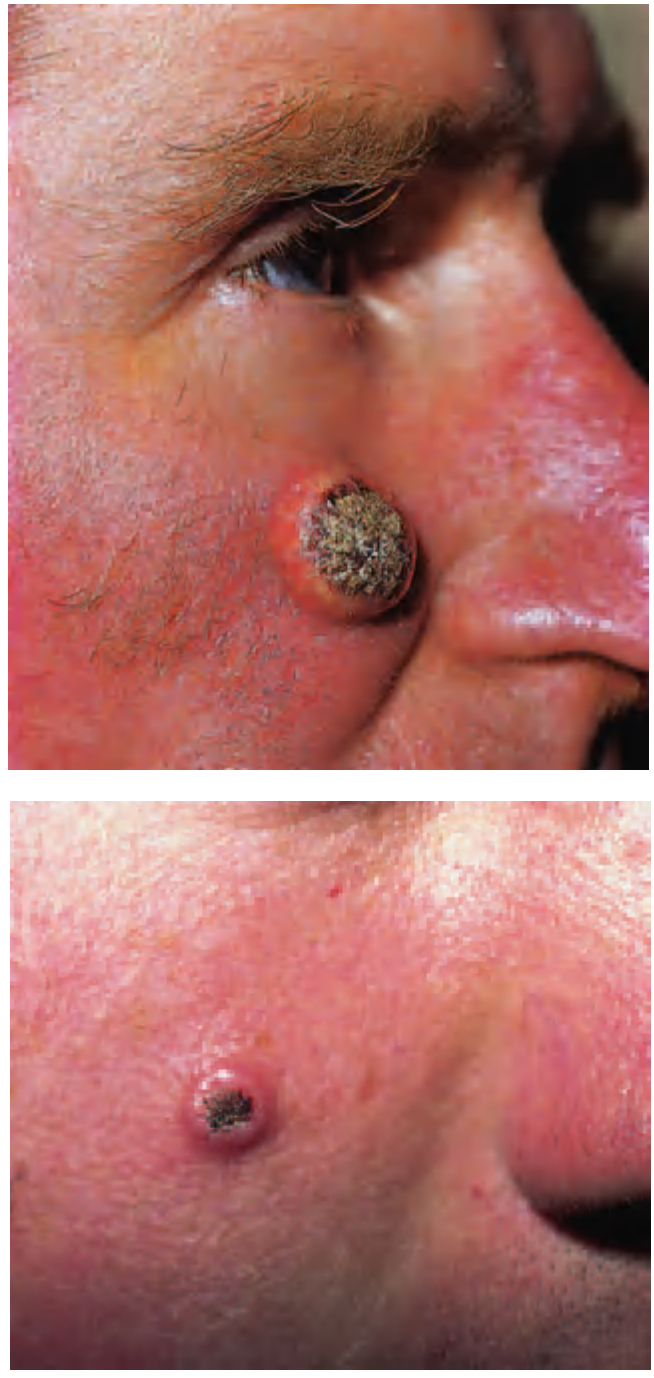
Incidence. Keratoacanthoma is relatively common, and in white races tends to occur with about one-third of the frequency of SCC, despite differences in climate [1]. It is uncommon in dark-skinned races and in the Japanese [2].

Males are affected about three times more often than females. The adjusted age distribution shows that it is most frequent in middle life and does not increase in incidence in old age, unlike basal and squamous cell carcinomas.

Aetiology. The epidemiological data suggest that incidence is related to sun exposure, and the localization of the tumours mainly on the head and upper limb supports this. Contact with tar and mineral oil has also been shown to cause an increased incidence [3,4] and very similar lesions have been produced in animals by painting with carcinogenic hydrocarbons. In some cases, the lesion follows injury to the skin, which suggests that infection may play a part in its origin, a view supported by the occurrence of multiple keratoacanthomas in skin grafts of patients with the tumour in the recipient site [5], the donor site [6] or both [7]. Proof of a viral cause is lacking. Cases are reported of keratoacanthoma associated with carcinoma of the larynx [8], multiple internal malignancy [9], leukaemia [10], deficient cell-mediated immunity [11] and in transplant recipients.

Clinical features [1,12,13]. The first evidence of keratoacanthoma is a firm, rounded, flesh-coloured or reddish papule, which may resemble molluscum contagiosum or, if keratotic, a virus wart. The patient rarely seeks advice at this stage. There is then a rapid growth phase and in a few weeks it may become 10–20 mm across. There is no infiltration at the base. The epidermis over the nodule is smooth and shiny; the lesion is skin-coloured to red with telangiectases just beneath the surface. The centre contains a horny plug or is covered by a crust which conceals a keratin-filled crater (Fig. 36.22). As the lesion matures, the accumulating keratin expands the outermost part making the edge overhang the base somewhat, but the radial symmetry is usually well preserved. The keratin may project like a horn or it may soften and break down. Spontaneous resolution is achieved by the epidermal covering receding towards the base and the horny core being shed. The base is revealed as irregular and puckered and the edge may remain as soft but thickened epidermis, either as a continuous rim or a series of tags. The process of spontaneous healing usually takes about 3 months.

A small proportion of keratoacanthomas grow to much larger dimensions—50 mm or more in diameter being not exceptional on the forearm. One lesion on the chest became over 150 mm across [14]. In some cases, the maximum size may be reached in a month or two; others may enlarge for many months. After growth ceases, involution may not occur for some months or may occur at part of the periphery while growth continues elsewhere. There may be recurrences after curettage or excision, more frequently in lesions on the lips and fingers and when treatment is carried out in the early stages [15]. Recurrence may happen after spontaneous resolution [16].



(a) (b)

Fig. 36.22 Typical keratoacanthomas, both found on the face, showing raised margin and central keratin-filled crater.

The most frequently affected area is the central part of the face: the nose, cheeks, eyelids and lips. The dorsum of the hand, the wrist and the forearm are commonly affected; the thigh, chest, shoulder and scalp less so; and the anogenital area uncommonly except in those exposed to occupational hazards. Lesions have occurred in the subungual region [17,18], in the vermilion of the lips [15] and on the buccal mucosa.

In most cases, the tumour presents as a solitary lesion. Multiple or recurrent tumours are more likely to be present in several circumstances. Recurrent lesions occur in the patient who has been exposed to pitch or tar [3] and in rare cases as a familial disorder, although there are reasons to keep this Ferguson-Smith type as a separate entity (see below). There are a few cases of eruptive keratoacanthoma recorded. Multiple lesions have occurred with defective cell-mediated immunity and also as part of Torre's syndrome, with multiple internal malignancies [9] and with sebaceous adenomas (see Chapter 37).

Pathology. The distinctive features are best seen when the fixed specimen is being cut before processing or in sections under low magnification. The tumour has a symmetrical, more-or-less globular form and is situated in the dermis, usually extending down no deeper than the sweat glands, although deep penetration has occasionally been recorded. The epidermis around the tumour is normal or slightly acanthotic, but becomes thinned as it rises over the tumour. A narrow spur of connective tissue separates the epidermis from the proliferating squamous cells, except where the two connect at the mouth of the keratin-filled crypt. Serial sections of an early lesion have shown connection of the masses of squamous cells with the upper part of a hyperplastic follicle [19].

The histological features vary with the stage of evolution. The early lesion is composed of a mass of rapidly multiplying squamous cells. These are large and rather pale with vesicular nuclei, prominent nucleoli and frequent mitoses. Hyperchromatic cells, atypical mitotic figures, individual cell keratinization and other evidence of loss of polarity may be found. The marginal cells invade the surrounding dermis aggressively, while those more centrally placed keratinize to form a branched core of keratin that communicates with the surface. The stroma is vascular and is infiltrated with round cells and histiocytes.

Resolution occurs through maturation of the hyperplastic masses. The accumulating keratin dilates the central pore, the epidermal lips recede from the centre and the lesion opens like a flower bud. When the horn is finally shed, the irregular epithelium beneath it replicates the scalloped outline of the active mass. The cells take on the morphology of epidermis, and a scar is formed, which is depressed and may have papillomatous tags at the margin, the remnants of the epidermal lip. Older lesions frequently show clusters of leukocyte microabscesses at the base. Thus, the pathological features vary with the stage of evolution of the keratoacanthoma and, if an adequate specimen is not submitted, it may be impossible for the reporting pathologist to confidently rule out early invasive SCC. Keratoacanthomas may also rarely progress to SCC. In one case [20], it may have been precipitated by treatment with oral methotrexate for a recurrence. The conjunction of two independent lesions in sun-damaged skin may account for the finding of a BCC in the scar of keratoacanthoma in this and other cases.

Experimentally produced lesions differ in their form, depending on whether the hair follicles are in anagen or telogen when the proliferation begins [21,22]. Virus-like particles have been seen under electron microscopy [23].

Diagnosis. The most important differential diagnosis is to distinguish keratoacanthoma from SCC. In most cases, the more rapid evolution to a relatively large size, the regular crateriform shape and keratotic plug, the undamaged surrounding skin and the younger age of onset make a distinction relatively easy for the clinician. Spontaneous healing adds support to the diagnosis of keratoacanthoma. The problem is made more difficult in sunny areas where actinic damage and SCC are more common, and the most important single point is the history of rapid growth. The differential diagnosis includes cutaneous horn and hypertrophic AK, viral wart, molluscum contagiosum, pseudoepitheliomatous hyperplasia and granulomas of various types. Secondary deposits from non-cutaneous malignancies can also occasionally mimic keratoacanthoma.

Treatment. The end result of leaving the tumour to regress is usually a rather unsightly scar. Curettage and coagulation of the base, or excision and suture, produce a much more acceptable result. Excision is desirable if the diagnosis is in doubt, because curetted specimens yield poor sections. Radiotherapy shortens the course and improves the scar, and can be used in patients who refuse surgery. A total of 2000 cGy in two closely spaced doses of adequate penetration can be given.

The application of 5-fluorouracil ointment twice daily may reduce the time taken for natural resolution and diminish the scarring [24]. If there is real doubt about the diagnosis, surgical removal or radiotherapy should be carried out as for SCC, and the patient followed up.

Generalized eruptive keratoacanthoma [9,25]

A small number of cases of widely disseminated lesions, some of them typical keratoacanthomas, have been reported. Both sexes have been affected. The primary lesions are flesh-coloured to red dome-shaped follicular papules 1–3 mm in size and affecting particularly the face, where they may be confluent, the trunk and the roots of the limbs. Itching is a prominent symptom, and ectropion and narrowing of the mouth may be produced by the keratotic facial change. Scattered among the papules are larger, more typical keratoacanthomas, which resolve spontaneously. The palms and soles are spared, but the oral and laryngeal epithelium can be involved.

Pathology. Histological examination shows the papules to consist of a dilated and plugged follicle duct with

acanthotic follicular epidermis around it; the mucosal lesions are irregular acanthosis; and the nodules are keratoacanthomas, but with no inflammatory changes.

Management. The nodular lesions heal in a few months. The papules are not influenced by cytotoxic drugs, but one case responded to topical retinol [25] and current trials of the synthetic retinoids are in progress.

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Pseudoepitheliomatous hyperplasia [1]

Aetiology. Epidermal hyperplasia is an early and essential feature in the healing of any breach of the skin surface. Under ordinary circumstances, this is coordinated with the repair of the dermis, and the down-growths are eventually broken up [2]. When the dermis is diseased, however, a persistent and much more extensive hyperplasia may occur. This is seen, for instance, at the margin of chronic leg ulcers, over chronic granulomas such as lupus vulgaris, tuberculosis verrucosa cutis, insect-bite granulomas and halogen granulomas and, in a rather unusual form, over a small proportion of histiocytomas. It is also a component of some cases of lupus erythematosus and of lichen planus of the hypertrophic type. It may occur in association with tumours, particularly granular cell myoblastoma and malignant melanoma.

Clinical features. The appearance will vary with the primary disorder. Granulomas may be covered by a thickened, warty or heaped-up epidermis, perhaps best seen in chromomycosis. In chronic ulcers, the margin is heaped-up, often giving the appearance of being rolled, and has an irregular surface. The edge is not usually indurated to the extent that occurs in SCC. It is characteristic that the hyperplasia will subside as the ulcer is treated and heals. It is wise to remember that an ulcer whose margin has been affected by pseudoepitheliomatous hyperplasia in the past may eventually be the cause of metastasizing SCC.

Pathology. The nature of the primary disorder modifies the picture greatly. In simple ulcers and inflammatory lesions—by far the most common causes—there is disturbance of the upper part of the dermis, often with young fibroblasts and a rather myxomatous connective tissue stroma replacing the normal dermal collagen. Columns of prickle cells grow down into the dermis in an irregular fashion. In some areas, there is maturation of the central parts of the columns to produce horny pearls. The general appearance is that of invasive proliferation of the epithelium. The individual cells, however, do not show the atypical features that suggest malignancy. The columns may be penetrated by inflammatory cells, a feature that is not seen in malignant proliferations. In most instances, a weighing of dermal against epidermal changes suggests that the former are the cause and not the consequence of the latter.

Diagnosis. A good-sized biopsy from a representative area of the lesion is essential.

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Cysts

Nomenclature. The term *sebaceous cyst* should be used only to describe steatocystoma multiplex, which contains oily sebum. Histological examination of all other cysts reveals the lining wall to be keratinous in nature. Keratinous cysts can be divided into two types, those with a lining identical in its stratification with epidermis and pilosebaceous duct, and those with a lining resembling the external root sheath of the follicle. The latter variety is less common, and is often familial, multiple and largely confined to the scalp [1]. This type is the trichilemmal cyst [2].

The cysts found in Gardner's syndrome are epidermoid in type [3] and are characterized by their appearance in childhood. There is no genetic overlap between trichilemmal cysts, cysts of Gardner's syndrome or steatocystoma multiplex, although all have an autosomal dominant mode of inheritance.

Histogenesis. Steatocystoma multiplex is most likely to be a genetically determined failure of canalization between the sebaceous lobules and the follicular pore. The common epidermoid cyst is the result of squamous metaplasia in a damaged sebaceous gland. Milia may result from either keratinization within the sebaceous anlagen ('collars') of vellus hair follicles or cystic dilatation of an interrupted sweat duct. Trichilemmal cysts may be caused by survival of fragmented segments of the hair root during catagen.

The following cysts are described in this section or elsewhere in the book:

1 Keratinous cysts, both epidermoid and trichilemmal
2 Dermoid (see Chapters 64 and 66)
3 Milium
4 Steatocystoma multiplex
5 Eccrine hidrocystoma (see Chapter 37)
6 Apocrine hidrocystoma (see Chapter 37)
7 Bartholin's cyst (see Chapter 68)
8 Myxoid cyst of the skin (see Chapter 62)
9 Branchial cyst (see Chapter 15).

Epidermoid cyst

SYN. EPITHELIAL CYST (SEBACEOUS CYST IS A MISNOMER)

Definition. A cyst containing keratin and its breakdown products, surrounded by an epidermoid wall.

Incidence and aetiology. Epidermoid cysts are common, most frequently affecting young and middle-aged adults. They are rare in childhood. Many are the result of inflammation around a pilosebaceous follicle, and they are frequently seen following the more severe lesions of acne vulgaris. Some may result from deep implantation of a fragment of epidermis by a blunt penetrating injury. Those that occur as a part of Gardner's syndrome and of the NBCCS are probably caused by a developmental defect.

Clinical features. An epidermoid cyst is situated in the dermis and raises the epidermis to produce a firm elastic dome-shaped protuberance that is mobile over the deeper structures. It is tethered to the epidermis, and there may be a central keratin-filled punctum. The spherical form can be felt where the skin is sufficiently lax. Cysts near the surface, as in the ear lobe or scrotum, are yellowish or white. The size varies from a few millimetres to 50 mm or so. The common sites are the face, neck, shoulders and chest, which are areas favoured by acne vulgaris. Lesions may be solitary but are commonly multiple. They enlarge slowly and may become inflamed and tender from time to time. Suppuration may occur. Cysts that follow acne and have been subject to recurrent inflammation may be difficult to remove completely. Calcification of the contents of epidermoid cysts cannot usually be detected clinically; when it occurs in multiple cysts of the upper part of the trunk it can give a confusing picture on a chest X-ray.

Traumatic inclusion cysts usually occur on the palmar or plantar surfaces, buttock or knee. A history of penetrating injury is not always obtained.

Pathology. An epidermoid cyst is unilocular and spherical, unless flattened by firm tissue beneath it. There may be an obvious connection with the surface by a keratin-filled duct, but this is probably less common than surgical texts would suggest. The cyst is situated within the dermis. The lining wall reproduces the layers of the epidermis, although attenuated in large cysts. The keratin is lamellated and birefringent. Cholesterol clefts may be seen. The basal layer may be flattened and surrounded by fibrosis, or may show papillary indentations similar to the epidermis. Some cysts have a chronic inflammatory or foreign-body type of reaction around them, at times producing (or caused by) partial disruption of the wall. Occasionally, a hair shaft may be found coiled up within the cyst. These cysts probably result from inflammatory destruction of the sebaceous matrix cells and connective tissue investment of the gland and subsequent re-epithelialization of the abscess cavity, or from squamous metaplasia following impaction of a hair shaft within the sebaceous gland.

Diagnosis. The uncomplicated cyst can usually be diagnosed with confidence. Other benign and rounded dermal tumours may be mistaken for epidermoid cysts, and inflammatory granulomas such as cutaneous leishmaniasis may mimic an inflamed cyst (Figs 36.23 & 36.24).

Treatment. A cyst that has not recently been inflamed can be dissected out. An inflamed cyst is better incised, drained and phenolized.

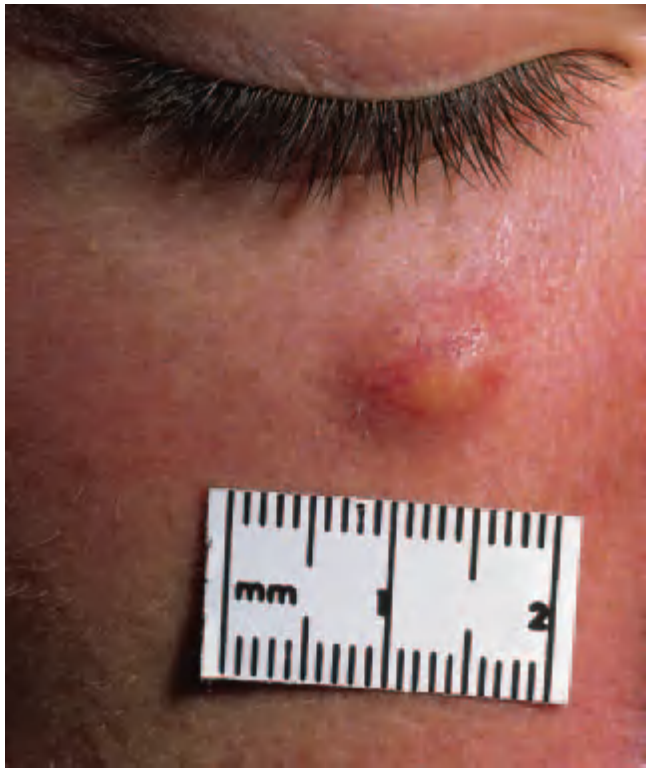

Fig. 36.23 Calcified cyst just below the eyelid margin.

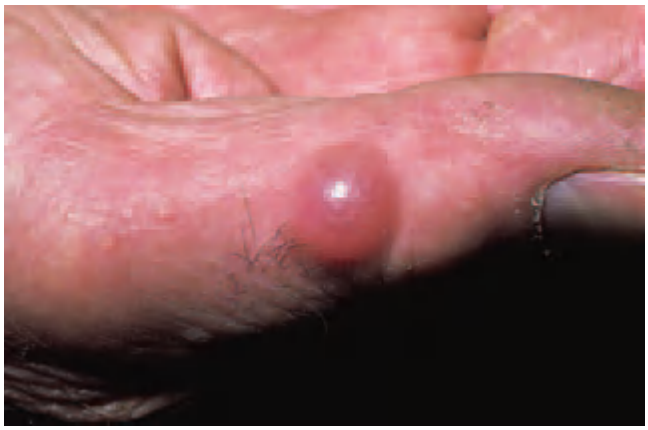

Fig. 36.24 Inclusion cyst following trauma to the thumb.

Trichilemmal cyst

SYN. PILAR CYST

Definition. A cyst containing keratin and its breakdown products, usually situated on the scalp, with a wall resembling external hair root sheath [4].

Incidence and aetiology. This is quite a common condition, and accounts for about 5–10% of keratinous cysts seen in surgical pathology services. Women are affected more frequently than men. It is seen mainly in middle age [5] and is inherited as an autosomal dominant [1,6].

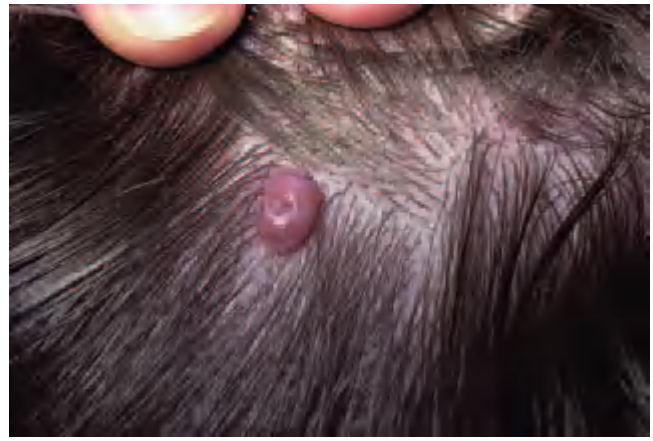

Fig. 36.25 Clinical illustration of typical pilar cyst on the scalp.

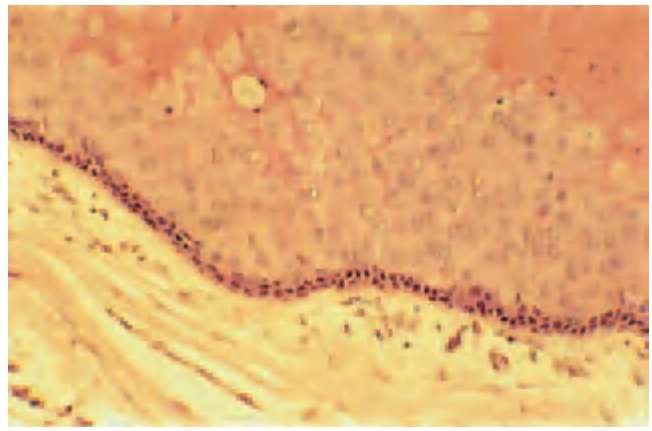

Fig. 36.26 Pilar cyst showing typical pathological features (see text).

Clinical features. The lesion occurs mainly on the scalp, and is a smooth, mobile, firm and rounded nodule (Fig. 36.25). Larger lesions may be lobular and multiple cysts are commonly found. Tenderness occurs with inflammation, and the surface may break down with infection. The cyst wall may fuse with the epidermis to form a crypt (marsupialized cyst), which can occasionally terminate by discharging its contents and healing spontaneously [6]. In contrast, the contents may protrude above the surface to form a soft cutaneous horn.

Pathology. Trichilemmal cysts differ from epidermoid cysts in the way the lining cells mature. They do not flatten and form a granular layer, and keratinization seems to occur mainly in the region of the cell membrane. The cells appear to disintegrate at the inner margin of the lining. The contents are not brightly birefringent lamellae, but may calcify (Fig. 36.26).

The wall of a trichilemmal cyst may become ruptured and the contents invaded by granulation tissue. The reaction is much less acute than in ruptured epidermoid cysts and produces proliferation rather than destruction of the

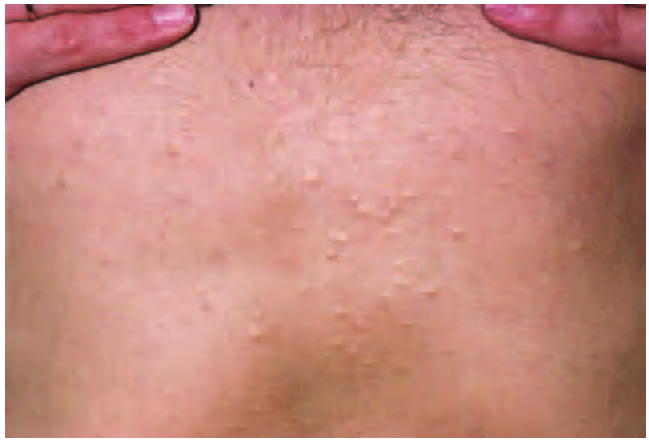

Fig. 36.27 Clinical illustration of steatocystoma multiplex on the chest.

wall. The proliferation may be progressive and simulate, clinically and histologically, a well-differentiated SCC [7]. Cases of proven malignant degeneration in scalp cysts are very rare.

Treatment. Uncomplicated cysts shell out of the dermis with remarkable ease. Proliferating cysts need to be excised with a margin because they will recur if tissue is left behind.

Steatocystoma multiplex

SYN. SEBOCYSTOMATOSIS; HEREDITARY EPIDERMAL POLYCYSTIC DISEASE

Definition. Multiple cysts in the dermis having sebaceous gland lobules in their wall and containing sebum.

Incidence and aetiology. It is a very uncommon condition, which usually begins in adolescence or early adult life [8]. The condition is inherited as an autosomal dominant in many cases [9,10]. The sexes are affected equally [11].

Clinical features. Multiple smooth compressible nodules are present within the dermis, varying in diameter from a few millimetres to 20 mm or more (Fig. 36.27). They usually appear or become larger at puberty. The trunk and proximal part of the limbs are most commonly involved, particularly the presternal area. No punctum is usually apparent over the cyst, but there may be widespread comedones [12]. The more superficial lesions may have a yellowish colour. If pricked, an oily fluid can be expressed. Some lesions become inflamed, suppurate and heal with scarring.

Pathology. The cyst is situated in the mid-dermis. The wall is thin and composed of keratinizing epithelium. In some sections, lobules of sebaceous glands can be seen to form part of the wall or to empty by ducts into the cyst. The contents are oily, and are composed of the unsplit esters of sebum [13]. They may contain hairs. Hair roots and, occasionally, sweat glands may be found connected with the cyst, and the whole complex is joined to the epidermis by a short strand of undifferentiated cells [14].

Treatment. The number of cysts makes excision impractical in most cases. There is no reason, apart from cosmetic, for treating them.

Milium

Definition. A small subepidermal keratin cyst.

Incidence and aetiology. Milia are quite common at all ages from infancy onwards. Many arise in undeveloped sebaceous glands. This may occur in young women as an eruptive phenomenon, and is sometimes a sequel to sunbathing. Others may arise in the proximal part of divided sweat ducts. The cause of the duct damage is usually avulsion accompanying an acute subepidermal bulla, particularly in second-degree burns, epidermolysis bullosa, porphyria cutanea tarda and bullous lichen planus. They may also follow dermabrasion and occur in areas of chronic topical corticosteroid-induced atrophy. Destruction of skin appendages by radiotherapy may result in a ring of milium-like lesions at the margin of an area treated with tumour doses. These, unlike other forms, can be expressed easily.

Clinical features. The lesions are white or yellowish, rarely more than 1 or 2 mm in diameter and appear to be immediately beneath the epidermis. They are usually noticed only on the face, and occur in the areas of vellus hair follicles, on the cheeks and eyelids particularly. Those that follow blisters are scattered more or less at random in the affected area (Fig. 36.28).

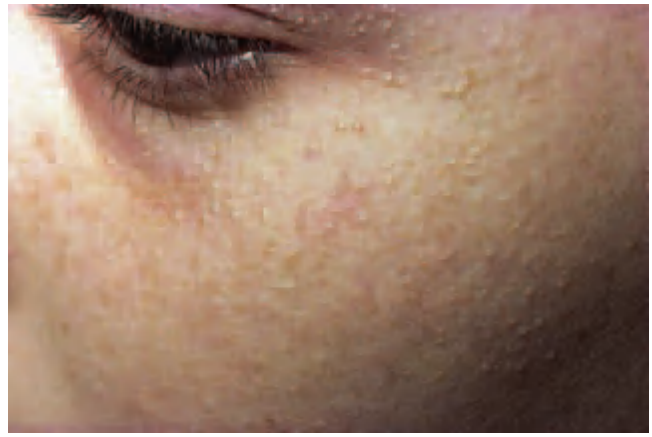

Fig. 36.28 Multiple milia on the upper cheek area.

Pathology. The lesion is so easily treated that specimens for histological examination are uncommon. However, the milia that follow blistering can often be traced to eccrine sweat ducts in serial sections. Those at the margin of an irradiated area are usually situated in the distorted remnant of the pilosebaceous duct. The much more common milia of the face are found within the undifferentiated sebaceous collar that encircles many vellus hair follicles. The white milium body is composed of lamellated keratin.

Diagnosis. Milia are recognized as groups of small uniform spherical white papules with a smooth non-umbilicated top. They are usually whiter and more translucent than syringomas, which appear clinically to be more deeply situated in the skin. Milia tend to occur in isolation and are not associated with papules, comedones and cysts such as may be seen in closed comedones associated with acne and chloracne. Trichoepithelioma may rarely cause confusion, but tend to be larger, more multilobulated structures even on clinical examination.

Treatment. Incision of the epidermis over the milium with a cutting edge needle or sharp-pointed scalpel and squeezing out the contents is usually effective. Recurrence is uncommon. Spontaneous disappearance occurs in many milia in infants.

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Premalignant fibroepithelial tumour (of Pinkus)

Definition. A premalignant tumour composed of cells resembling those of BCC arranged in a thin honeycomb around a prominent overgrown papillary stroma.

Incidence. Relatively uncommon. Several examples have arisen in areas treated by radiotherapy for ankylosing spondylitis [1,2]. The author has seen one case on the chest of a patient with multiple postarsenical BCC.

Clinical features. The tumour is sessile with a domed surface and is firm and flesh-coloured. Most of the recorded lesions have been found on the abdomen or loins. There may be seborrhoeic keratoses or BCCs, or both, elsewhere [3]. Increase in size, when it occurs, is slow. The tumour is most likely to be diagnosed as a fibroma.

Pathology. The outline is domed and the surface is formed of normal epidermis. The bulk of the tumour is composed of considerably enlarged dermal papillae, more cellular and fibrotic than normal, which are surrounded by strands of small dark cells that extend down from the underside of the epidermis. Small buds of cells may arise from the strands and enlarge to form BCC, replacing part or all of the tumour [4].

Treatment. The lesions should be surgically excised.

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Chapter 37

Tumours of the Skin Appendages

R.M. MacKie & E. Calonje

Introduction

The anatomical relationships of the epidermis and dermis are fully discussed in Chapter 3. The skin appendages are of particular interest in examining this relationship, in that they clearly show a morphological, and also in some instances functional, interrelationship. The appendage tumours discussed in this chapter either differentiate towards or arise from the pilosebaceous apparatus (including the apocrine gland) and eccrine sweat glands [1–9].

The pilosebaceous apparatus can be divided into the hair follicle, the adjacent sebaceous gland and in some body sites the apocrine glands. Small strips of smooth muscle, the arrector pili muscle, are also found in association with these structures.

The pilosebaceous apparatus is concentrated in the head and neck area, with the pilar element predominant on the scalp and the sebaceous element in the face, chest and upper back areas. Thus, tumours arising from these structures are found predominantly in these sites.

The eccrine sweat glands are, in contrast, found on all body sites and are composed of a double-layered, deeply situated secretory structure and a more superficial excretory duct winding through the dermis and spiralling through the epidermis to reach the outer surface.

The excretory (ductal) portions of the eccrine and apocrine glands are identical and cannot be differentiated on morphological grounds unless the apocrine duct can be identified entering the hair follicle. To complicate matters further, the apocrine duct rarely opens directly into the epidermis, and there are no histochemical or immunohistochemical stains that allow distinction between eccrine and apocrine tumours. From this, it can be inferred that adnexal tumours showing ductal differentiation may be

either eccrine or apocrine, and distinction is not possible unless there is concomitant follicular differentiation. In recent years, it has therefore been proposed that the classification of adnexal tumours should follow a more logical approach that takes this into consideration [6]. It has become apparent that tumours traditionally considered to be of eccrine differentiation, such as cylindroma, spiradenoma and mixed tumour (so-called chondroid syringoma), may show either line of differentiation and this is probably most often apocrine. Even a classical eccrine tumour such as poroma has been described occasionally as differentiating towards the apocrine duct [7].

A wide range of cells make up the secretory and excretory components of the appendage ducts, the hair follicles and the sebaceous glands. As each cell type capable of dividing can give rise to a tumour as a result of inappropriate transfer of genetic material and cell division, it follows that an equal number of tumours are theoretically possible. The great majority of these appendage-derived tumours are relatively benign, with behaviour and prognosis similar to that seen in basal cell carcinoma. Thus, although local recurrence is well recorded, metastases are rare, with the exception of the malignant eccrine and apocrine gland-derived tumours and sebaceous carcinoma. It is important to take into account that malignant adnexal tumours with metastasis are over-reported in the literature and that this has led to overestimation of their true malignant potential.

Appendage tumours are relatively rare, and their clinical appearance is commonly non-specific. The great majority are not diagnosed as such until after excision and pathological study. Classification systems for these lesions tend to be controversial, but in general the system groups lesions together according to their morphological similarity to normal appendage structures.

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Hair-follicle tumours

A large number of tumours are theoretically capable of arising from the hair follicle and matrix, depending on the exact type of cell and its situation within the dermis. A representative selection of these tumours will be described here. For a pathologically comprehensive list, the reader is referred to specialized publications [1,2]. Recent studies on the role of the sonic hedgehog gene and related proteins in basal cell carcinoma (see Chapter 36) have been extended to hair-follicle tumours [3]. The patched gene is located on chromosome 9q22.3, and loss of heterozygosity has been identified in sporadic trichoepitheliomas [4]. Overexpression of Gli-1, which is integral to this pathway, has been observed in trichoepitheliomas in mice [5].

β-Catenin plays a key role in signal transduction and subsequent tissue modelling, and mutations in the β-catenin gene have been recorded in pilomatricomas [6,7].

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Inverted follicular keratosis [1–3]

Definition. A localized area of hyperkeratosis found in association with the pilosebaceous orifice. A number of these lesions arise as a result of infection of the infundibulum of the hair follicle by human papillomavirus (HPV). It is likely that a majority of these lesions may be regarded as the most superficial tumour of the follicular infundibulum (see below), arising as the result of irritation.

Clinical features. In common with many of the lesions described in this chapter, this lesion presents as a solitary papule on the head and neck area. It may reach a considerable size, be inflamed and may cause pruritus.

Pathology. The pathological features show an endophytic lesion connected to the infundibulum of the hair follicle. Irritated keratinocytes form whorls of cells, so-called 'squamous eddies', and keratin cysts. All of these features may give rise to problems with the differential diagnosis of squamous cell carcinoma, especially on small biopsies. This can be relatively easily distinguished on low-power examination, as there is no individual cell invasion into the dermis. At higher power, mitotic figures may be seen, but they are not abnormal mitoses. The appearances are

identical to an irritated seborrhoeic keratosis, but the latter is exophytic.

Management. Local surgical excision is generally needed, for both diagnostic and therapeutic purposes. Occasionally, the lesions recur [3].

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Dilated pore [1]

SYN. WIENER'S PORE

Definition. An area of expanded follicular infundibulum with a dilated poral opening extending down to subcutaneous fat [2].

Clinical features. The pore is a comedo-like lesion found mainly on the head and neck area of the elderly.

Pathology. There is a wide, crater-like cavity, from which acanthotic areas of follicular epithelium radiate. The follicle is lined by outer root-sheath epithelium, and there is little evidence of a sebaceous gland or a well-formed emerging hair.

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Tumour of the follicular infundibulum

Definition. This lesion may be considered the hair-follicle equivalent of the eccrine dermal duct tumour (p. 37.20).

Clinical features. These lesions are usually found on the facial skin and may be relatively large, irregular nodules. They are usually biopsied or excised to obtain a diagnosis, as the clinical appearance is not specific. It has been suggested that they can be divided into four main groups: solitary lesions; those in association with Cowden's disease; multiple eruptive tumours; and follicular infundibulum-like changes in the epidermis [1].

Pathology [2–4]. The pathology is that of a large, horizontally orientated plate of small, dark cells situated in the superficial dermis, usually with multiple connections to the overlying epidermis. The cellular detail is focally similar to that seen in the trichilemmoma, with large numbers of small polygonal cells with clear cytoplasm contained within a palisaded border. Basaloid cells are often seen. The resemblance to basal cell carcinoma is striking, but the stromal element is lacking.

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Pilar sheath acanthoma [1]

Clinical features. These lesions are very rare and are most commonly seen on the upper lip area of the elderly [2,3].

Pathology. The pathology is that of an expanded area of the outer root-sheath epithelium within an irregularly branched cystic cavity, with large lobules of epithelial cells radiating outwards from this cavity area.

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Trichoadenoma [1–5]

Definition. A rare benign tumour, with multiple cystic structures closely resembling the infundibular portion of the hair follicle.

Clinical features. This lesion presents as a non-specific nodule, usually on the face, although there are some reports of lesions on the buttocks.

Pathology. The lesions are in the upper dermis, and on light-microscope scanning power give the impression of a cluster of cysts. On higher power, these cyst-like structures have an appearance similar to the infundibular portion of the hair follicle but turned through 90°; no recognizable hair shafts are seen.

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Comedo naevus [1–3]

Definition. A rare abnormality of the follicular infundibulum presenting as a group of comedo-like lesions.

Clinical features. These lesions are rare and are seen on the head and neck area. They may be present at birth or develop throughout adult life. They appear as a cluster of comedos or as a single giant lesion.

Pathology. A rudimentary pilosebaceous follicle is present, with a large overlying keratin-filled crater. The surface of the keratinous material oxidizes to give the blackhead-like appearance.

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External root-sheath tumours

Trichilemmal cyst

Definition. A cyst apparently arising from the external root sheath, containing keratin and breakdown products [1,2].

Clinical features. These lesions are mainly seen on the scalp and are relatively common. They may be familial, inherited by autosomal-dominant transmission [3]. Females are affected more often than males. They clinically present as firm nodules, which may become infected or inflamed after minor trauma. They are commonly multiple.

Pathology. These cysts are well circumscribed in the dermis and lined by two or three layers of small, dark keratinocytes. There is then an abrupt transition, towards the centre of the lesion, to large, pale cells with features of root-sheath cells. A granular cell layer is absent. The centre of the cyst contains keratin debris. Some lesions are hybrid and show focal changes of an epidermoid cyst, with formation of a granular cell layer.

Management. These are commonly excised to obtain a diagnosis. Lesions which are shelled out may recur [4].

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Proliferating trichilemmal cyst

SYN. PILAR TUMOUR

Clinical features. The tumour presents as a rapidly growing large nodule, commonly on the head and neck area of the elderly. Some lesions are more than 10 cm in diameter. The history of rapid expansion frequently gives rise to concern about malignancy. Malignant change has been rarely reported in these lesions.

Pathology. These lesions may arise from pre-existing trichilemmal cysts, and remnants of a classic trichilemmal cyst may be present [1,2]. The architecture is lobular and expansile, without an infiltrative growth pattern. Tumour lobules are cystic and composed of pale squamous cells with mild atypia. However, tumour cells in the periphery of the lobules may display marked cytological atypia. Prominent abrupt pilar keratinization towards the centre of the lobules is a typical feature. In addition, however, there are areas of squamous epithelium containing both squamous eddies and mitoses. If there is frank invasion into adjacent structures in association with tumour necrosis, the diagnosis of a malignant trichilemmal cyst may be appropriate [3,4]. The diagnosis is often very difficult in small samples, and ideally the whole tumour should be submitted for histological examination to avoid confusion with a squamous cell carcinoma.

Management. Local recurrence takes place and complete excision is therefore necessary.

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Trichilemmoma [1–3]

Definition. This lesion is considered to be a proliferation of the external root sheath of the hair follicle [4,5].

Clinical features. Clinically, these lesions are small, non-specific papules on facial skin; they present in young and middle-aged adults. Their importance lies in the fact that patients with Cowden's syndrome or multiple hamartoma and neoplasia syndrome [6–13]—which is

associated with a very high incidence of breast, thyroid and gastrointestinal carcinomas—have large numbers of trichilemmomas. The diagnosis of multiple trichilemmomas should therefore stimulate a search for other evidence of Cowden's syndrome. This includes a characteristic 'cobblestone' appearance of the oral epithelium, multiple skin tags, squamous papillomas and sclerotic fibromas (storiform collagenomas). Mutations of the *PTEN* gene on chromosome 10q23 are found in Cowden's syndrome [14,15].

Pathology. These lesions are well-circumscribed, lobular tumours extending down from the epidermis and often connected to a hair follicle. Tumour cells display prominent clear cytoplasm secondary to the deposition of glycogen. The presence of glycogen can be confirmed with a positive periodic acid–Schiff (PAS) stain, which becomes negative after treatment with diastase. There is an irregular enclosing PAS-positive, diastase-resistant membrane. In a number of cases, there is prominent hyperplasia of the surface epithelium, with hypergranulosis, clumping of keratohyalin granules and hyperkeratosis. This indicates induction of some lesions by HPV. A viral aetiology has been confirmed by demonstration of HPV DNA by polymerase chain reaction [16]. Trichilemmomas are often found within a naevus sebaceus.

A variant of trichilemmoma, described as desmoplastic trichilemmoma, has been reported [16]. The periphery of this lesion has histological features identical to those of ordinary trichilemmoma, but towards the centre there are strands of squamous cells embedded in a desmoplastic stroma. This results in an infiltrative appearance that is often confused with a squamous cell carcinoma, particularly in small biopsy samples.

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Trichilemmal carcinoma [1–4]

Definition. A very rare tumour with metastatic capacity, usually arising in sun-exposed skin of the elderly.

Clinical features. This lesion presents as a solitary, expanding, often ulcerating lesion on the face. It may be clinically diagnosed as basal cell carcinoma. Multiple tumours have exceptionally been described [5]. Trichilemmal carcinoma may arise exceptionally from a trichoblastoma and in the context of a naevus sebaceus [6].

Pathology. These lesions invade downwards from the epidermis or outer root-sheath areas in a multilobular and infiltrative fashion. They may have a surrounding PAS-positive membrane, and there is central trichilemmal keratinization. There is a high mitotic rate, with abnormal mitoses present. The diagnosis of trichilemmal carcinoma should only be made in the presence of clear evidence of trichilemmal differentiation. The presence of clear cell change is not enough to make this diagnosis. Most malignant cutaneous tumours with clear cell change are squamous cell carcinomas and often show at least focal evidence of keratinization.

Management. Surgical excision with clear margins is the treatment of choice.

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Hamartomas and hair germ tumours and cysts

Hair-follicle naevus [1,2]

Clinical features. These naevi are very rare and are recognized as plaque-like lesions with small tufts of hairs. They present in children and may be congenital. The so-called

'faun tail naevus' is a hair-follicle naevus on the sacral skin. Rare cases occur following Blaschko's lines [3].

Pathology. The pathology of this entity consists of a group of normal vellus hair follicles clustered together.

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Eruptive vellus cyst

Definition. Occlusion and cystic dilatation of vellus hair follicles.

Clinical features. These present as small red or brown papules on the chest, commonly in the second decade of life [1]. They are usually multiple, and family clusters have been reported [2]. They are commoner than expected in patients who also have pachonychia congenita [3,4].

Pathology. Cysts are located in the mid-dermis, and are lined by squamous epithelium. They contain vellus hair and keratin debris. Biopsies from some lesions show features indistinguishable from steatocystoma, with absence of vellus hairs. This finding suggests that there is an overlap with steatocystoma multiplex [5].

Management. If treatment is requested, the lesions may clear after application of topical retinoids. Curettage and laser therapy may also be effective, but it is easy to cause scarring.

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Trichofolliculoma [1]

Definition. This lesion is a hamartoma of the pilosebaceous follicle, which results in several hairs being formed within the follicular opening and all protruding onto the epidermal surface from the one pilosebaceous orifice [2–6].

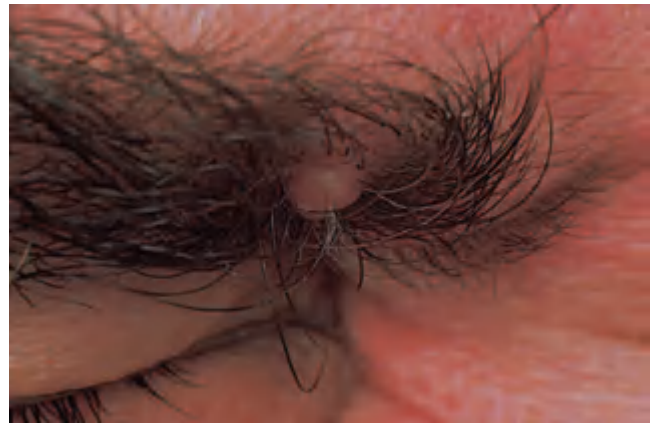

Fig. 37.1 Typical example of a trichofolliculoma, with a small tuft of hairs in the centre.

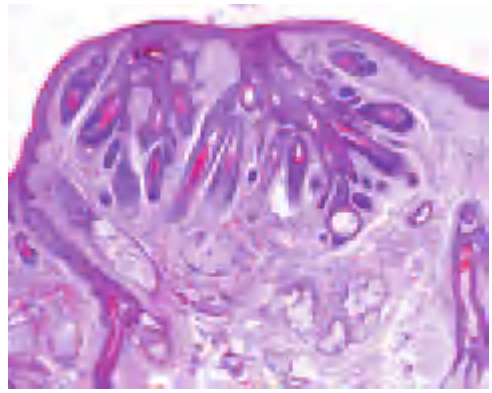

Fig. 37.2 Trichofolliculoma. A large central follicular structure from which immature follicular structures radiate.

Clinical features. Most cases occur in young adults. Clinically, lesions can be recognized as small, raised nodules with two or three hairs protruding together in a small tuft (Fig. 37.1).

Pathology. The pathological appearance is that of a dilated and abnormally large pilosebaceous canal containing numerous, poorly formed hairs, with several pilosebaceous-like structures opening into the canal (Fig. 37.2). Malignant change has been suggested in a single case with perineural invasion [7]. The so-called folliculosebaceous cystic hamartoma is considered to be a variant of trichofolliculoma in a late stage of development [8].

Management. Surgical excision is recommended.

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Trichoepithelioma [1]

SYN. EPITHELIOMA ADENOIDES CYSTICUM; BROOKE'S TUMOUR

Definition. A hamartoma of the hair germ composed of immature islands of basaloid cells with focal, primitive follicular differentiation and induction of a cellular stroma.

Clinical features. The presentation of a solitary lesion is that of a smooth nodule, usually on the face, which clinically resembles a non-ulcerated basal cell carcinoma. Most affected patients are young adults. Multiple lesions, which are inherited by autosomal-dominant transmission, are seen as multiple small, pearly lesions, mainly on centrofacial skin (Fig. 37.3).

Pathology [2–5]. The pathology is identical for solitary or multiple lesions and consists of lobules of small, dark cells, often with a degree of peripheral palisading surrounding a central area of eosinophilic amorphous material (Fig. 37.4). Occasionally, hair shaft-like structures can be seen in these central areas. A fibrous cellular stroma is seen around the cellular lobules. There is frequently a strong resemblance to basal cell carcinoma, and at times the differential diagnosis between the two can be very difficult. However, the stroma induced in trichoepithelioma is distinctive and contains clefts, and there is absence of retraction artefact between tumour cells and the surrounding stroma. The gene for multiple trichoepitheliomas has recently been mapped to a locus on chromosome 9p21 [6]. The commoner sporadic cases of trichoepithelioma have, in a proportion of cases, deletions

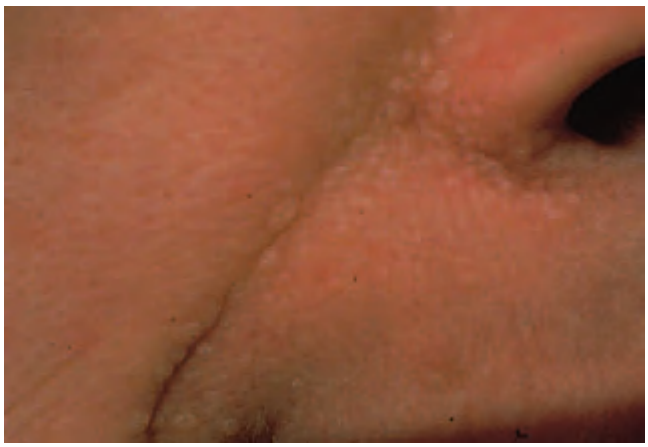

Fig. 37.3 Multiple trichoepitheliomas on the central face.

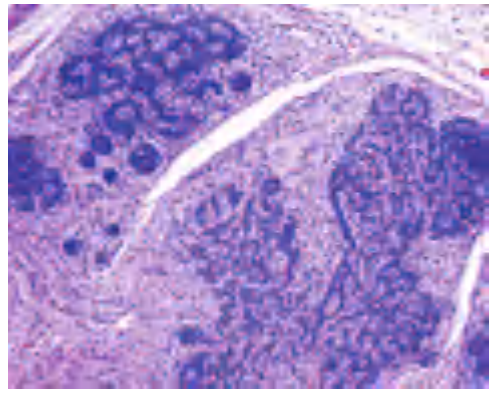

Fig. 37.4 Trichoepithelioma. A lobular basaloid tumour with induction of stroma and immature follicular differentiation.

at chromosome 9q22.3, the site of the human homologue of the *Drosophila* patched gene [7]. Familial basal cell carcinomas and some cases of sporadic basal cell carcinomas also show this deletion.

In multiple lesions, which are present in epithelioma adenoides cysticum [8–12], larger lesions may be yellow, pink, or sometimes bluish from pigmentation, and there may be dilated blood vessels over the surface. Individual tumours reach a limiting size, but the numbers may increase over the years. Continued growth or ulceration raises the suspicion of change to basal cell carcinoma [13].

Treatment. Any suspicion of malignant change calls for adequate excision and histological examination. The only other reason for treatment is cosmetic. Partial destruction is usually followed by regrowth.

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Desmoplastic trichoepithelioma [1–3]

SYN. SCLEROSING EPITHELIAL HAMARTOMA

These two terms were introduced almost simultaneously. The US group of Brownstein and Shapiro used the term 'desmoplastic trichoepithelioma' [2], while MacDonald, Wilson-Jones and Marks in the UK suggested the term 'sclerosing epithelial hamartoma' [3].

Definition. A slowly expanding plaque of tissue containing hair follicle-like structures.

Clinical features. Lesions are found mainly on the face of young patients and have a depressed centre and a raised, rolled edge in many cases, causing clinical confusion with basal cell carcinoma. To date, more females than males have been reported with the condition.

Pathology. Tumours are symmetrical on scanning magnification. The three features that characterize this lesion are large numbers of small, keratin-filled cysts, strands and ribbons of small, dark, epithelioid cells, and a dense fibrous stroma surrounding the first two structures. Perineural invasion is not a feature.

The striking palisading of the basal cell carcinoma is absent. There is, however, a considerable similarity to the sclerosing variant of basal cell carcinoma, although the number of cysts is very much greater in the desmoplastic trichoepithelioma. Distinction from microcystic adnexal carcinoma may be impossible in a small and superficial biopsy. The latter, however, shows a diffuse infiltrative pattern, with prominent perineural invasion.

Occasional desmoplastic trichoepitheliomas are combined with a benign melanocytic naevus [4].

Treatment. Local excision is effective in the majority of cases.

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Solitary giant trichoepithelioma [1,2]

This is a rare condition with a dramatic clinical presentation that may cause concern about a rapidly growing malignancy. It has also been described under the name 'trichoblastic fibroma'. Trichoepithelioma and giant trichoepithelioma represent the more mature end of the spectrum of trichoblastoma. These tumours are described separately because they represent distinctive clinicopathological entities. However, it should be remembered that histological overlap is often seen.

Clinical features [3–5]. The clinical presentation is of a very large, polypoid lesion presenting on the lower trunk, frequently in the perianal area, with a history of recent rapid growth. The lesions may cause considerable discomfort because of their size. They affect both sexes equally.

Pathology. The pathology shows the features of the smaller, classical trichoepithelioma but the lesions are much larger, deeper and are often located in the subcutaneous fat. An oedematous myxoid stroma is frequently seen and focally, various stages of follicular differentiation are identified. Mitotic figures are frequent, but abnormal mitoses are not seen.

Management. Excision is required, both to confirm the diagnosis and because of discomfort. Malignant change in these lesions has not been reported.

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Trichoblastoma [1–4]

SYN. TRICHOGENIC FIBROMA; TRICHOBLASTIC FIBROMA

Definition. Tumours of the hair germ composed of follicular germinative cells.

Clinical features. These are deeply or superficially situated dermal nodules, found—as is common with follicular tumours—on the head and neck.

Pathology. Nests of basophilic basaloid cells with a lobular architecture and prominent induction of stroma are seen in the dermis and/or subcutaneous tissue. Focal evidence of follicular differentiation is seen, but this usually consists of less mature structures than those seen in trichoepithelioma. Mitotic figures are frequent. Usually, the tumour is not connected to the epidermis. According to the degree of follicular differentiation and the amount of stroma induced, lesions have been subclassified into different categories, including trichogenic fibroma and trichoblastic fibroma. However, all tumours in this category are best classified as trichoblastomas. Some tumours may display sebaceous and even ductal (apocrine) differentiation [5].

Management. Behaviour is benign, but complete excision is often desirable to exclude a basal cell carcinoma.

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Cutaneous lymphadenoma [1–6]

Definition. This entity was first described in 1987 [1], and to date there are around 35 reported cases in the literature. Follicular, sebaceous and ductal differentiation has been demonstrated.

Clinical features. The lesions are seen mainly on the head and neck area, and present as non-specific papules or nodules. Both sexes are affected equally. The preoperative clinical diagnosis is frequently basal cell carcinoma or an intradermal naevus.

Pathology. The tumour consists of nests and lobules of basaloid cells in the reticular dermis, with no connection to the epidermis. These aggregates of cells are embedded in a fibrous stroma. Tumour cells are bland and display focal peripheral palisading. A striking feature is the presence of prominent infiltration of tumour lobules and nests by T lymphocytes and histiocytes (Fig. 37.5). These inflammatory cells are mainly located in the centre of the tumour lobules. No cellular atypia is seen, and mitotic figures are rare. Focal areas of keratinization are seen in some cases.

Individual lymphadenomas show varying differentiation towards sebaceous, eccrine and pilar structures, and there is therefore continuing debate as to their exact ontogeny [2–6]. It has been suggested that cutaneous lymphadenoma represents a variant of trichoblastoma [4].

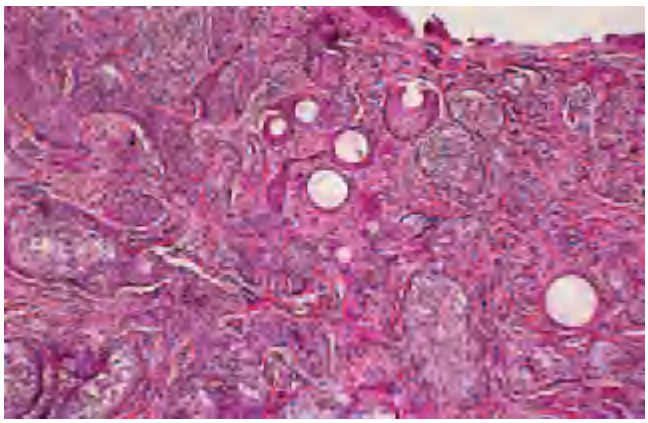

Fig. 37.5 Lymphadenoma. Nests and lobules of epithelial cells with prominent infiltration by lymphocytes.

Treatment. Local excision is recommended. The behaviour is entirely benign.

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Basaloid follicular hamartoma [1–4]

Definition. A hamartoma consisting of a proliferation of basaloid cells, with frequent involvement of hair follicles.

Clinical features. These lesions are usually small multiple facial papules. They may be present in isolation or inherited as an autosomal-dominant trait [4].

Pathology. A multifocal proliferation of cords, strands and nests of basaloid cells is seen, with frequent connections to the epidermis. Basaloid cells focally replace neighbouring hair follicles. In addition, immature follicular bulbs may also be seen.

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Hair matrix tumours

Pilomatricoma [1–4]

SYN. BENIGN CALCIFYING EPITHELIOMA OF MALHERBE; TRICHOMATRICOMA; PILOMATRIXOMA

Definition. A benign tumour considered to be a hamartoma of the hair matrix composed of cells resembling those of the hair matrix, hair cortex and inner root sheath. The cells usually undergo 'mummification'.

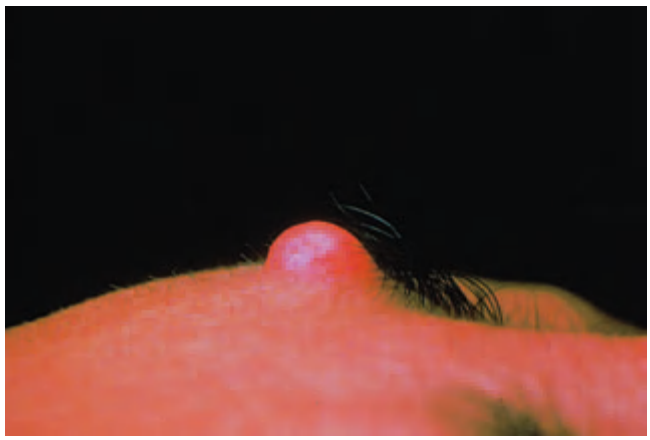

Fig. 37.6 Pilomatricoma. Small red firm papule.

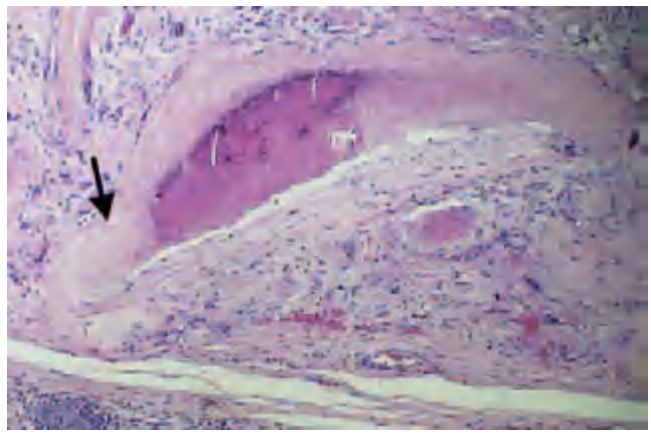

Fig. 37.7 Pilomatricoma. Lobules of basaloid cells intermixed with pale pink areas containing ghost cells.

Incidence. This lesion makes up around 20% of all hair follicle-related tumours in most series and is therefore the commonest hair-follicle tumour. It may occur at any age from infancy and is frequently seen in children [5]. The majority of patients are under 20 years of age, and females are affected more often than males. A number of familial cases are recorded, and an association with myotonic dystrophy has been reported [6].

Clinical features [7–13]. The lesion is usually a solitary, deep, dermal or subcutaneous tumour 3–30 mm in diameter situated in the head, neck or upper extremity (Fig. 37.6). Very large tumours are occasionally seen. The skin over the tumour is normal and the lesion has a firm to stone-hard consistency and a lobular shape on palpation. In adult life, there may be quite a short history [4] and there is usually no evidence of a preceding cyst. It may be subject to periodic inflammation and can present as a granulomatous swelling. Rare ulcerated lesions may show transepithelial elimination [14]. Malignant change has been reported (see below).

Pathology [15–22]. The tumour is situated in the dermis, and is composed of well-circumscribed, rounded islands giving a lobulated contour. The outer cells are small, and their rounded nuclei crowded together make this region deeply basophilic. Normal mitotic figures can usually be seen and are often numerous. The cytoplasm is scanty and the cell margins indistinct, but intercellular connections can be seen. Towards the centre of the mass, the cytoplasm becomes more abundant and eosinophilic. The nuclear outline persists, but the chromatin is sparse and clumped in dark granules; then, all the basophilic material disappears, leaving a mummified 'ghost cell' (Fig. 37.7). The ultrastructure and histochemical characteristics of these cells mark them as hair-matrix cells maturing towards cortex or root sheath [3,21,22]. The central areas often calcify, and calcium can be demonstrated in the basophilic areas of the tumour. In older lesions, the basophilic cells may be much reduced, or disappear entirely. Melanin may be present, and dendritic melanocytes have been found between the tumour cells. The stroma that encapsulates the masses usually contains inflammatory and foreign-body giant cells, and occasionally ossifies.

Recent studies have shown that 75% of pilomatricomas show activating mutations of the β-catenin gene [23–25]. The sites of β-catenin expression within pilomatricomas suggest that this may affect cell–cell adhesion [26].

Diagnosis. The diagnosis can be suspected if a subcutaneous nodule feels hard and lobular. The presence of calcium salts may be apparent on radiographs, but these can also be deposited in other cysts and tumours of the skin. The microscopic picture is, however, diagnostic.

Malignant change is recorded in several cases, and appears to arise chiefly in large pilomatricomas that have been present for many years (see below).

Management. Local excision is required for benign lesions, as there is a tendency for local recurrence. Wider excision will be needed if malignancy is suspected.

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Pilomatricarcinoma [1–4]

Definition. The malignant counterpart of the pilomatricoma, possessing metastatic potential.

Clinical features. A rapidly expanding firm nodule. Around 70 cases are reported in the literature, and the average age of the patients is around 70 years. Males are more often affected than females.

Pathology. Many pilomatricarcinomas appear to arise on long-standing benign pilomatricomas. Definition of malignancy is usually very difficult on histological grounds. Malignant tumours usually have a very large predominant basaloid component, an infiltrative growth pattern and extensive tumour necrosis. In addition, there are numerous abnormal mitotic figures, and both lymphatic and vascular invasion may be seen. There can be metastases to distant organs such as the lungs, bone and lymph nodes [5–8]. At least two cases have proved fatal.

Management. Wide local excision is usually curative, but follow-up is required because of the possibility of metastatic spread.

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Lesions of the hair-follicle mesenchyme

Trichodiscoma [1]

Definition. This lesion is a hamartomatous proliferation of the mesodermal component of the *Haarscheibe* described by Pinkus [1]. The *Haarscheibe* is considered to be a slowly reacting mechanoreceptor associated with the hair follicle.

Clinical features. The clinical appearance of the trichodiscoma is that of multiple, discrete, flat-topped papules 2–3 mm in diameter. They occur mainly in the central area of the face. Familial cases are recorded [2,3]. Multiple trichodiscomas, trichofolliculomas and acrochordon-like lesions have been described as part of the Birt–Hogg–Dubé syndrome [4]. Interestingly, the acrochordon-like lesions display the histological features of either trichodiscomas or trichofolliculomas [5].

Pathology. A discrete but non-encapsulated area of myxoid, poorly cellular stroma with focal collagen deposition is seen in the dermis, associated with a proliferation of blood vessels, some of which are thick-walled. Pilosebaceous units are often seen on both sides of the myxoid stroma. Trichodiscomas and trichofolliculomas usually show histological overlap.

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Perifollicular fibroma [1,2]

The clinical appearance of these lesions has not been well described. The pathology is that of a striking fibrous proliferation around a relatively normal pilosebaceous apparatus.

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Fibrofolliculoma

Definition. Rare lesions of perifollicular connective tissue [1].

Clinical features. These lesions usually first appear in middle age and tend to affect the upper part of the body. Multiple lesions are seen in the Birt–Hogg–Dubé syndrome, which is an autosomal-dominant condition recently mapped to chromosome 17p11.2 [2–5]. In this syndrome, fibrofolliculomas are seen in association with trichodiscomas, acrochordon-like lesions, renal tumours most commonly chromophobe carcinoma and spontaneous pneumothorax [6,7]. Colonic neoplasms do not seem to be increased in this syndrome, as previously suggested [6].

Pathology. Histology shows multiple, small, poorly formed pilosebaceous follicles set in a very striking fibrous stroma. There is also an obvious proliferation of the outer root sheath similar to that seen in the perifollicular fibroma.

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Sebaceous gland tumours [1]

The following tumours or tumour-like conditions of sebaceous glands are considered elsewhere in the book:

1 Naevus sebaceus (Chapter 15);
2 Senile sebaceous hyperplasia (Chapter 43);
3 'Sebaceous' cyst (Chapter 36);
4 Steatocystoma multiplex (Chapter 36).

The two main conditions discussed in this section are sebaceous adenomas and sebaceomas, and sebaceous carcinoma. The old term 'sebaceous epithelioma' is no longer used, as it causes confusion with the exceptionally rare basal cell carcinoma with sebaceous differentiation.

Sebaceous adenomas and sebaceomas [1–4]

Definition. Benign tumours composed of incompletely differentiated sebaceous cells of varying degrees of maturity. Sebaceous adenoma and sebaceoma are described together, as they do not have distinctive clinical features, and although histological separation is possible in most cases, there is also some degree of overlap.

Incidence and aetiology. These are fairly rare tumours [4]. The solitary type may occur in either sex, and most cases have been in elderly patients. They may be associated with a cutaneous horn [5]. There is no evidence that actinic radiation or other recognized carcinogens are to blame.

Patients with multiple benign sebaceous tumours (other than sebaceous hyperplasia) should be suspected of having the Muir–Torre syndrome, associated with multiple visceral malignancies [6–17]. The latter include gastrointestinal malignancies, especially colonic and, more rarely, renal neoplasms. The internal malignancies tend to be fairly low grade, and often patients develop them earlier in life than the equivalent neoplasm in the general population. The sebaceous neoplasms tend to develop later in life. Patients with Muir–Torre syndrome may also develop sebaceous keratoacanthomas, and the diagnosis of one of these tumours should raise the possibility of the syndrome. Microsatellite instability has been reported in the Muir–Torre syndrome [18,19], and it has been proposed that loss of MLH1 or MSH2 proteins in the skin lesions may be a marker of patients who carry the syndrome and are therefore at risk of systemic malignancy [20,21]. The loss of expression of MLH1 and MSH2 may be demonstrated by immunohistochemical methods [20].

Clinical features. The tumour is rounded, raised and may be either sessile or somewhat pedunculated (Fig. 37.8). It is usually less than 10 mm in diameter, but older lesions may form plaques or ulcerate. Occasional tumours are more deeply located and appear cystic. The colour may be fleshy or of a waxy, yellowish hue, and the surface may be verrucose. The common situation is the face or scalp, and it may occur on the eyelid. It usually grows slowly, but a sudden increase in growth rate can occur.

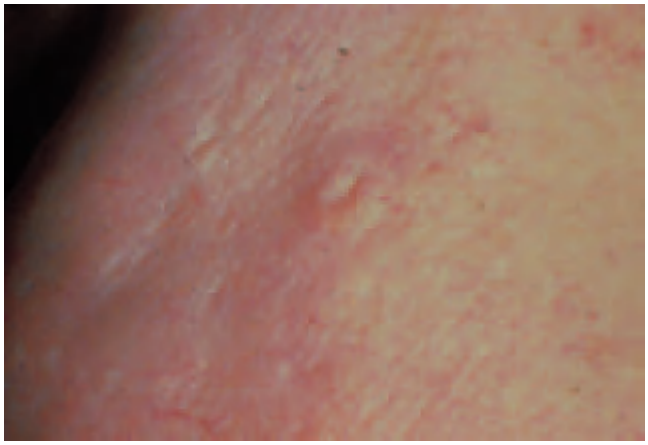

Fig. 37.8 Sebaceous adenoma. Small yellowish papule.

Diagnosis. A yellow-tinged facial nodule may be suggestive, but clinical differentiation from other epithelial tumours, especially basal cell carcinoma, may be impossible. The microscopic diagnosis is more certain when fat can be demonstrated, but sebaceous differentiation can usually be distinguished in ordinary sections.

Pathology [3,5,14,22]. The tumours are multilobular and usually connected to the epidermis. The lobules are well-defined, and are composed of variable numbers of small, basophilic, sebaceous matrix cells peripherally and larger cells—mature sebaceous cells—containing cytoplasmic fat globules. The proportion of immature, transitional and mature sebaceous cells may vary widely from one area to another. In sebaceous adenoma, mature sebaceous cells predominate towards the centre of the lobules, whilst in sebaceoma, immature basaloid sebaceous cells predominate, occupying large areas of the lobules. In both tumours, there may also be cystic spaces lined by a thin layer of eosinophilic material similar to the intraglandular sebaceous ducts. The outline of the tumour is less regular than the normal sebaceous glands, and may be frankly irregular. However, some sebaceous adenomas closely mimic the normal sebaceous gland, except for an increase in the number of immature sebaceous cells. Mitotic figures are frequent in the immature sebaceous cells, and this feature should not be regarded as evidence of malignancy. Larger and deeper tumours with cystic degeneration usually represent sebaceomas, but adenomas may also be seen. Some of these tumours have atypical histological features [23]. The cystic space contains abundant holocrine (sebaceous) material. It has been suggested that these cystic sebaceous tumours are a marker for the mismatch, repair-deficient subtype of Muir–Torre syndrome, which has a high risk of internal malignancies [23].

Treatment. The best treatment is surgical excision.

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Superficial epithelioma with sebaceous differentiation [1–4]

This is a rare tumour that has no distinctive clinical features and presents as a solitary papule on the face or trunk of adults. Occasionally, lesions are multiple. Histological features consist of a multifocal plate-like proliferation of basaloid cells with focal sebaceous differentiation and connections to the epidermis.

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Sebaceous carcinoma [1–3]

Definition. A malignant tumour composed of cells showing differentiation toward sebaceous epithelium.

Incidence. The variable incidence reported for this tumour reflects the differing diagnostic criteria of different workers. It is, however, rare, comprising less than 1% of all skin malignancies. The tumour has been reported following radiodermatitis, and in a patient with multiple arsenical skin cancers. It is likely that a number of sebaceomas with high mitotic activity have been reported in the past as sebaceous carcinomas.

Clinical features [4–12]. The tumour is solitary, firm, sometimes translucent and covered with normal or slightly verrucose epidermis. The colour may be yellow or orange. The face and scalp [13] are the commonest sites, especially the eyelid (Fig. 37.9). The evolution may be very slow, and a size of 5 cm or more may be reached after many years without metastasis. Some tumours grow rapidly and invade early, but metastasis is uncommon [14,15]. In the absence of the yellow colour there is no feature to indicate the diagnosis clinically. Sebaceous carcinomas may occur in immunosuppressed organ-transplant patients, and these tumours are associated with microsatellite instability [16]. Sebaceous carcinoma may be associated with the Muir–Torre syndrome [17].

Fig. 37.9 Sebaceous carcinoma. Ulcerated yellowish lesion of the eyelid.

Pathology. The same problem of terminology exists with sebaceous carcinoma as with the adenomas. Basal cell carcinoma with sebaceous differentiation is not included in the description of sebaceous carcinoma. It is uncommon for the lesion to be aggressively invasive on the skin, although it frequently is when situated on the eyelid [4–8]. There are however, individual case reports of aggressive lesions on the axillary skin [18].

The essential feature is cytological evidence of sebaceous differentiation. The proportion of cells showing fat globules and the degree of cytoplasmic vacuolation are variable. The undifferentiated cells are of moderate size, with round, centrally placed nuclei and rather basophilic cytoplasm, and they tend to group themselves in masses of a multilobular configuration. The differentiating cells tend to be more central. There are, in addition, cytological features of malignancy and evidence of an infiltrative growth pattern. Mitotic figures including atypical forms are frequent. Pagetoid infiltration of the epidermis is frequent, particularly in tumours arising in the eye [4].

Treatment. Complete surgical excision is required [9]. Reports of excellent results with Mohs surgery suggest that this may be the treatment of choice [19].

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Apocrine gland tumours [1]

Apocrine hidrocystoma [2]

SYN. APOCRINE CYSTADENOMA

Definition. A lesion produced by cystic dilatation of apocrine secretory glands.

Incidence. The lesion is not uncommon, but is most often seen in ophthalmological or surgical clinics. It occurs in adult life, in no particular age group. Males and females are equally affected.

Clinical features [3–6]. The lesions are solitary or occasionally multiple well-defined, dome-shaped, translucent nodules [7]. The surface is smooth and the colour varies from a skin colour to greyish or blue-black. The pigmentation may affect only part of the cyst. The commonest site is around the eye, particularly lateral to the outer canthus (Fig. 37.10). It has also been reported on the penis [1]. There are no symptoms. The cyst increases slowly in size, and may become 10 mm or more in diameter.

Pathology [8–10]. Large cystic cavities are found in the dermis if the lesion has been dissected out carefully. Commonly, the cyst is punctured and has collapsed before fixation. The cavities are lined by cuboidal or high-columnar apocrine secretory cells with decapitation secretion and a peripheral layer of myoepithelial cells (Fig. 37.11). Papillary projections or solid buds of secretory cells may break the smooth contour of the cyst lining. The secretory cells may contain pigment [5,6], which is neither melanin nor haemosiderin. The secretions in the cysts may be coagulated and stained using the PAS technique. There is a well-organized fibrous stroma. Electron microscopy confirms the apocrine nature of the secretory epithelium [11].

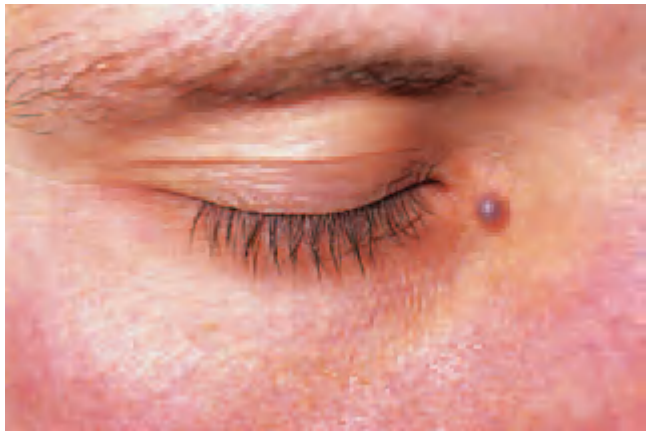

Fig. 37.10 Apocrine hydrocystoma. Cystic translucent papule on the right inner canthus.

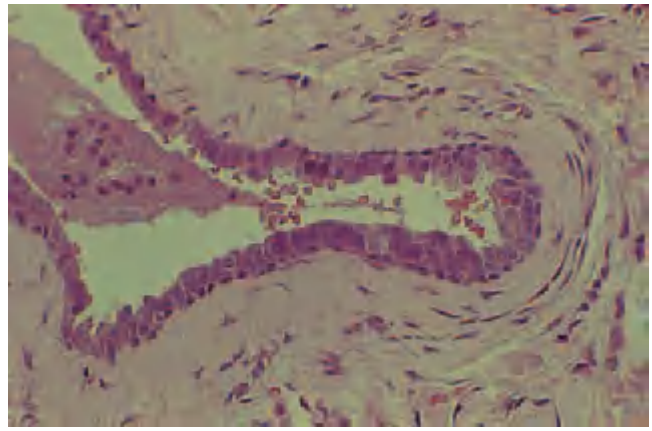

Fig. 37.11 Apocrine hydrocystoma. Cystic cavity lined by cuboidal cells with pink cytoplasm and decapitation secretion.

Diagnosis. Basal cell carcinoma is usually of a firmer consistency, less regular in its surface contour, and has surface telangiectases. The cystic nature of the lesion, which can often be shown by transillumination, separates it from blue naevi and malignant melanoma when pigment is present.

Treatment. The tumour is cured by surgical removal, which is commonly also needed for diagnosis.

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Syringocystadenoma papilliferum [1,2]

Definition. An exuberant proliferating lesion, commonly seen on the scalp in association with an organoid naevus, and showing differentiation in an apocrine pattern [3].

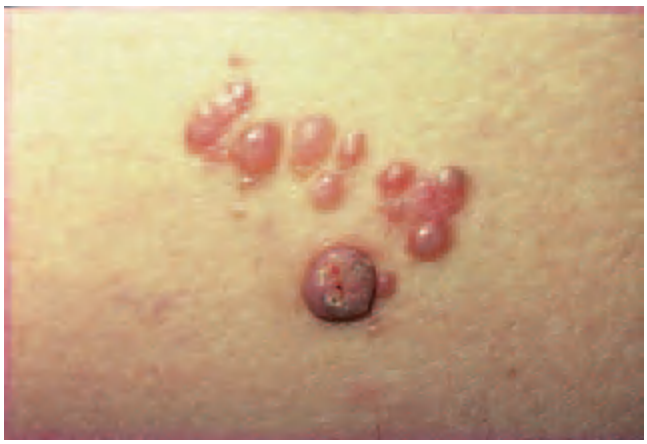

Fig. 37.12 Syringocystadenoma papilliferum. Papular lesion with superficial erosion.

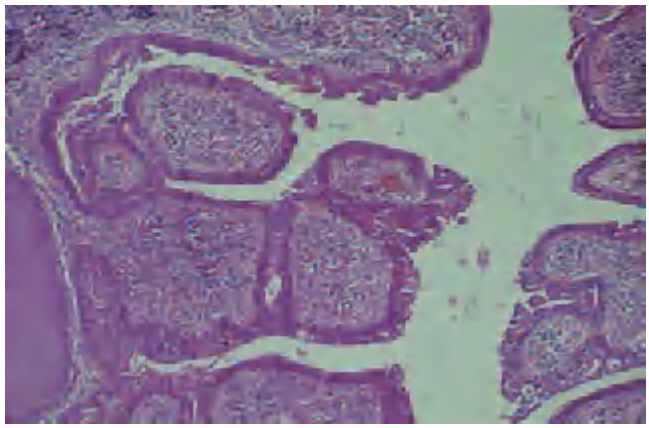

Fig. 37.13 Syringocystadenoma papilliferum. Papillary projections with a fibrovascular stroma.

Clinical features [4]. These lesions may be present at birth, but the majority are seen on the face and scalp of young adults. There is frequently a history of papillomatous expansion of a small pre-existing lesion at or around puberty. There may be a pre-existing organoid naevus. The lesion is composed of multiple papules, some of which are translucent and pigmented (Fig. 37.12).

Pathology [5–8]. The epidermal surface shows papillomatous expansion, and from these areas cystic invaginations are seen. The cystic structures are lined by papillae that have a lining of a double layer of columnar epithelium, which shows an apocrine pattern of secretion (Fig. 37.13) [9,10]. The underlying stroma is rich in plasma cells [11]. Occasionally, basal cell carcinoma or a squamous cell carcinoma develops on a pre-existing syringocystadenoma papilliferum. Development of an apocrine carcinoma is exceptional. Recent molecular biological studies have identified loss of heterozygosity at chromosome 9q22, the locus of the patched gene [12].

Management. Surgical excision is recommended, both to confirm the diagnosis and for cosmetic reasons.

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Hidradenoma papilliferum

Definition. A skin tumour of the anogenital area of adult females, composed of frond-like papillae lined by apocrine epithelium.

Incidence. This is an uncommon tumour, which occurs predominantly in women. In one large series, the subjects were exclusively white, and 75% were between the ages of 25 and 40 years. It occurs four times as commonly on the vulva as in the perianal area [1].

Clinical features [2,3]. The patients usually seek advice for a lump in the vulval or perianal area, which may be symptomless or, less frequently, may be tender or liable to bleed. The tumour is rounded, freely mobile, often elevated and may feel firm, soft or even cystic. It may range in size from 1 to 40 mm. The commonest site is the labium majus, but it may occur elsewhere on the vulva or perianal area and, exceptionally, in other sites such as the eyelid [3].

Occasionally, the epithelial surface will ulcerate and the tumour becomes everted to form a reddish-brown papillary mass, which may be suspected of being malignant [1]. Malignant transformation, however, has not been reported.

Pathology. The tumour is well-circumscribed and located just below the skin surface. It is usually spherical in shape

and enclosed by compressed connective tissue stroma. The tumour is composed partly of slender fronds of connective tissue lined by one or two layers of epithelial cells, and partly of glandular structures. The epithelial cells have histochemical characteristics in keeping with an apocrine origin [4,5]. The lesion may receive a pathological diagnosis of adenocarcinoma, but follow-up studies indicate that it is benign.

Diagnosis. The tumour is usually mistaken for a cyst, polyp, angioma or haemorrhoid. A prolonged history and a firm, spherical form make the last three diagnoses unlikely.

Treatment. Simple excision is curative.

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For erosive adenomatosis of the nipple, see Chapter 67.

Apocrine tubular adenoma [1–3]

Definition. A rare tumour usually arising on the scalp.

Clinical features. These are usually large, slowly expanding lesions on the scalp. The lesion often arises in association with a naevus sebaceus.

Pathology. Clusters of tubular structures are seen in the dermis, with a lining of cells showing decapitation secretion. There is no surrounding inflammatory response. Cytological atypia and an infiltrative margin are absent. As with many adnexal tumours, often one finds histological overlap between tubular apocrine adenoma and papillary eccrine adenoma [3,4].

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Apocrine carcinoma [1–3]

Definition. A malignant adnexal carcinoma showing clear evidence of apocrine differentiation—large cells with abundant pink cytoplasm and decapitation secretion.

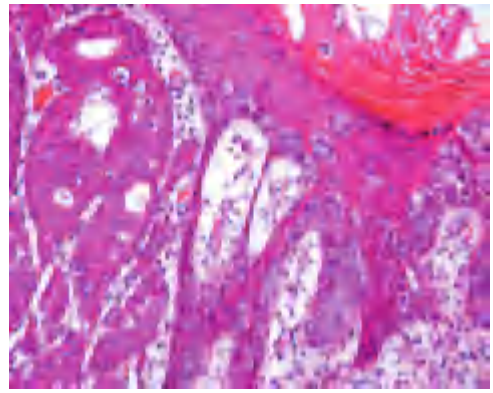

Fig. 37.14 Apocrine carcinoma. Prominent glands with decapitation secretion. Note the epidermotropism.

Clinical features. This is a rare entity. Lesions have been reported mainly from the head and neck area, including the eyelid and external ear, anogenital skin and also the axilla [4]. It is not possible on morphological grounds or with the help of immunohistochemistry to separate a cutaneous axillary apocrine carcinoma from an apocrine breast carcinoma spreading or invading the skin by direct extension. It is therefore important always to rule out a primary breast tumour. Some tumours arise within a naevus sebaceus [5]. The tumour presents as a nodule, usually measuring more than 1 cm in diameter. Rare cases may be bilateral [6]. There is a predilection for females, and patients are middle-aged or elderly. Metastatic spread to regional lymph nodes and internal organs occurs in up to a third of the cases [7].

Pathology. Three histological patterns may be seen: tubular, tubulopapillary and solid (Fig. 37.14). The degree of differentiation varies, and the diagnosis is often difficult in poorly differentiated tumours. Mitotic figures, local invasion and nuclear pleomorphism all suggest a malignant lesion. The most specific pathological feature is the presence of decapitation secretion [1]. Some cases are associated with prominent pagetoid spread, particularly those presenting on genital skin [8]. Tumour cells are positive for gross cystic disease fluid protein-15 (GCDFP-15) [9], and they show variable positivity for oestrogen and progesterone receptors.

Treatment. Wide excision and close follow-up are required.

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Eccrine gland tumours [1]

Eccrine gland-derived lesions make up a large and relatively common group of appendage tumours. Hidroacanthoma simplex, dermal duct tumour and eccrine poromas form a fairly homogeneous family derived from eccrine duct and pore. Eccrine syringofibradenoma probably also belongs in this subsection. Eccrine hidradenoma, although closely related, has features suggesting both secretory and ductal differentiation, which makes the term 'acrospiroma' misleading, and this is perhaps best kept in a separate category.

Malignant tumours of sweat glands are relatively rare, but important to recognize. Their morphology and behaviour are variable.

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Eccrine hidrocystoma [1–7]

Definition. A tumour produced by mature, deformed eccrine sweat units, whose secretions dilate the ducts. Lesions are usually situated on the face and are often multiple.

Incidence and aetiology. This is a rare tumour that occurs mainly in middle-aged women. It was formerly reported as being more common in those who had to work exposed to heat, such as cooks. A report indicating that the lesion is usually solitary and situated close to the eyelid underlines the problem of differentiating eccrine from apocrine hidrocystomas [1].

Clinical features [1,7]. The lesions are largely confined to the cheeks and eyelids. They may seem to be cystic on examination, and there is frequently a history of enlargement when the skin is exposed to heat. The lesions may be multiple and pigmented [8].

Pathology [2–4]. The general features are similar to those of syringoma, but secretory cells are usually found and the stroma tends to be inflammatory, rather than fibrosing. The histochemical reactions are eccrine in pattern [5,6].

Treatment. Diathermy or excision produce satisfactory results.

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Hidroacanthoma simplex [1–3]

Definition. An intraepidermal tumour derived from the eccrine duct epithelium, which could be considered an intradermal eccrine poroma.

Clinical features. Hidroacanthoma simplex is a verrucous plaque or ring with a hyperkeratotic, usually brown surface. It often mimics a flat seborrhoeic keratosis. Ulceration or elevation of the lesion suggests a dermal component. From the few reports available, it appears that the limbs are more likely to be involved than the trunk or head.

Pathology. Nests of clearly discrete, small, rounded cells are seen within the normal epidermal cells. They are smaller and more cuboidal than surrounding keratinocytes and are rich in glycogen and the glycolytic enzymes. These lesions may be confused with intraepidermal or clonal seborrhoeic keratoses, demonstrating what has in the past been called the 'Borst–Jadassohn phenomenon' [4]. The individual cells in these lesions are larger and less rich in glycogen. However, for the diagnosis to be made, ductal differentiation should be demonstrated.

Management. Excision is recommended both to confirm the diagnosis and for management. Malignant change has been reported in hidroacanthoma simplex [5–7]. If this is suspected, wider excision and a period of follow-up is advisable.

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Eccrine poroma [1,2]

Definition. A tumour arising from the eccrine duct epithelium in the region of the dermo-epidermal junction.

Clinical features [1–10]. This lesion is one of the easiest of the appendage tumours to recognize in the clinic. The great majority of these lesions are found on the palms and soles (Fig. 37.15), in contrast to other skin-appendage tumours, which tend to be concentrated around the head and neck area. They are moist, exophytic lesions, pink or red in colour, and may reach 1–2 cm in diameter.

Pathology [11–14]. These lesions are relatively easy to diagnose, with a clear margin between adjacent, normal epidermal keratinocytes and a population of smaller cuboidal cells, usually with darker nuclei protruding down into the underlying dermis (Fig. 37.16). The cells are strongly PAS-positive and are similar to those seen in the dermal duct tumour [15]. Recent reports, however, have stressed the fact that some poromas may show either sebaceous or apocrine differentiation [16,17]—highlighting the fact that adnexal tumours with ductal differentiation may be either eccrine or apocrine, as the ducts of both structures are identical.

Malignant change has been recorded on many occasions and may be subtle (see below). Any degree of cytological atypia should alert the pathologist to this possibility.

Management. Benign eccrine poromas are treated by surgical excision.

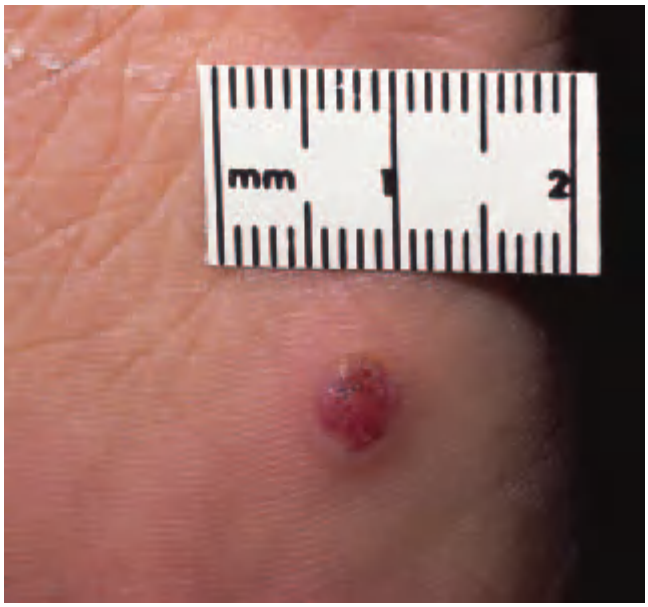

Fig. 37.15 Poroma. Note the red, shiny surface, which often leads to misdiagnosis of a pyogenic granuloma.

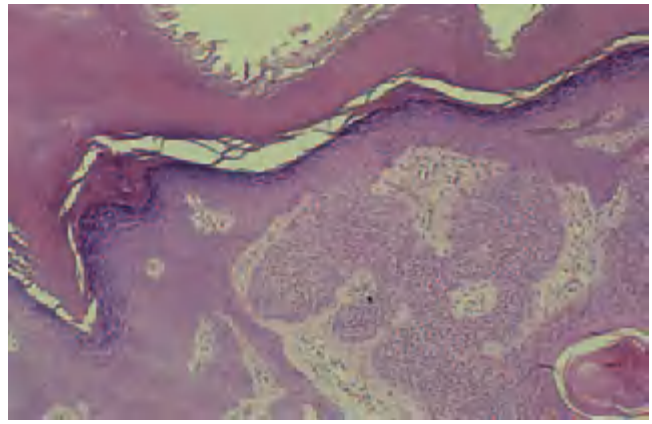

Fig. 37.16 Poroma. Note the clear demarcation between the tumour and the neighbouring epidermis.

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Eccrine dermal duct tumour [1,2]

Definition. A benign proliferation of the eccrine dermal duct situated in the papillary dermis.

Clinical features. The clinical picture is that of a dermal nodule, occasionally with verrucous change overlying it.

Pathology. The pathology is similar to that of the hidroacanthoma simplex, but the nests of tumour cells making up the lesion are located in the dermis. The cells are small, cuboidal, regular and stain strongly with PAS. An intraepidermal component may be seen, confirming that this lesion is part of the spectrum of eccrine poroma.

Management. Excision is required for diagnostic and therapeutic purposes.

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Eccrine syringofibroadenoma [1]

Clinical features. This is a rare entity, and may present as a solitary nodule on the arms or legs.

Pathology. A network of epithelial cells extends down from the epidermis, forming a mesh-like structure in the underlying epidermis. These cords are composed of smaller cells than in the overlying epidermis, and may contain ductal structures. This mesh is surrounded by a fibrovascular stroma. Unlike basal cell carcinoma, there is no palisading [2,3]. Often, syringofibroadenomatous hyperplasia of sweat ducts is seen in the background of other tumours, a healing ulcer, stasis, or a reparative process after a bullous disease [4–6]. In small biopsies, this type of hyperplasia may be confused with a syringofibroadenoma.

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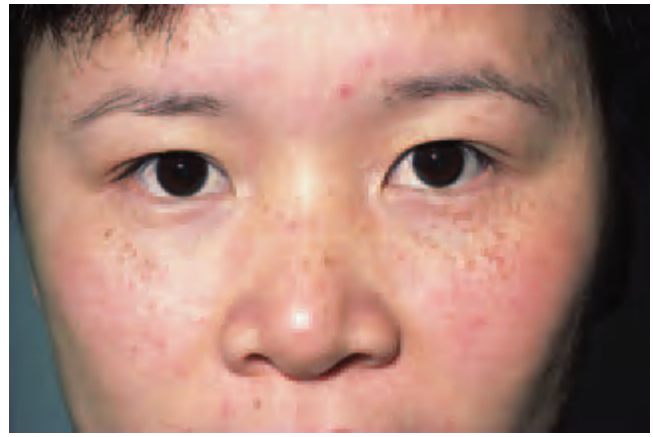

Fig. 37.17 Multiple syringomas on upper cheek area.

Syringoma [1–3]

SYN. HIDRADENOMES ERUPTIFS; SYRINGOCYSTADENOMA; SYRINGOCYSTOMA

Definition. A benign skin tumour that is usually multiple. The histology is characteristic.

Incidence. It is an uncommon tumour, and is more common in females than males. It is most likely to appear at adolescence, and further lesions may develop during adult life. It does not appear to be hereditary.

Clinical features [4–11]. The individual small dermal papules [12] are skin-coloured, yellowish or mauve, but sometimes appear translucent and cystic. The surface may be rounded or flat-topped and the outline sometimes angular. Rarely, injury to the surface will allow a drop of clear, watery fluid to escape. They vary in size from 1 to 5 mm, but most are less than 3 mm. In most cases, there are multiple tumours, and they tend to have a bilateral symmetry in distribution. The front of the chest, face and neck are the chief areas affected. A few lesions are usually found on the eyelids when the cheeks are involved (Fig. 37.17). The lesions are present more often than expected in patients with Down's syndrome [13] and may erupt dramatically (Fig. 37.18) [14].

Pathology [15–17]. The lesion has a characteristic architectural pattern on light-microscope scanning power. Collections of convoluted and cystic ducts are seen in the upper half of the dermis. Most are lined by a double layer of cells similar to, but flatter than, those that line normal eccrine ducts. The lumina contain amorphous debris. A characteristic feature is the tail-like strand of cells projecting from one side of the duct into the stroma, giving a resemblance to a tadpole or comma (Fig. 37.19). The ducts may be enclosed in a fibrous stroma similar to the

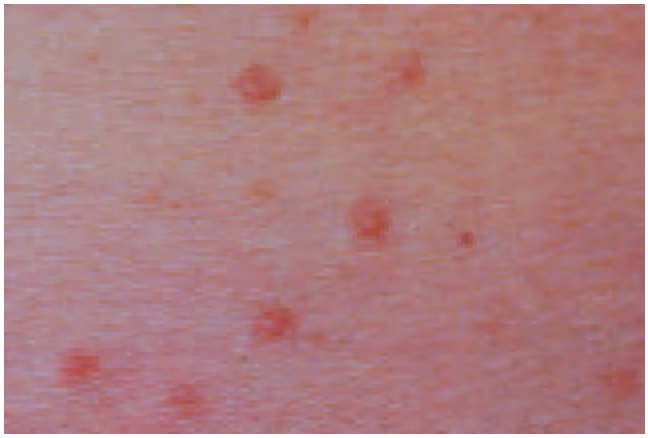

Fig. 37.18 Eruptive syringomas. Multiple tiny brownish or red lesions are often seen on trunk and limbs.

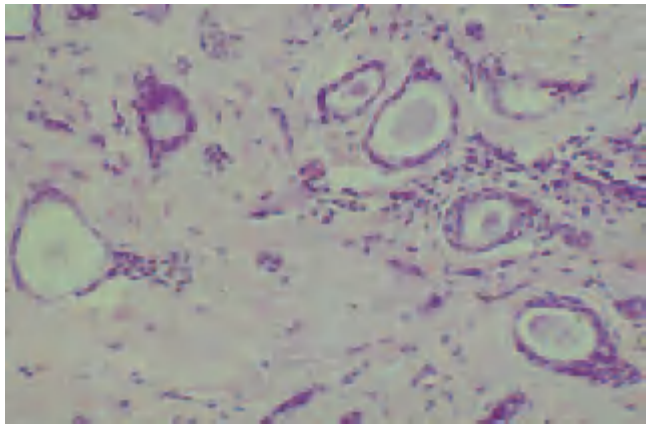

Fig. 37.19 Syringoma. Typical ductal structures with a tadpole appearance.

hair-follicle hamartomas, but in most cases it is narrower and less cellular. When the stroma is dense, it may be difficult to differentiate from the morphoeic basal cell carcinoma, in which, however, well-developed duct structures are not associated with cellular strands.

Diagnosis. Syringoma is most likely to be confused with trichoepithelioma on the face. The syringomas tend to be smaller, rather less superficial, more flat-topped and disposed more evenly over the cheeks and eyelids, rather than favouring the nasolabial creases. There is no family history. Lesions on the lids may be mistaken for xanthelasma, but lack the orange colour. Those erupting on the trunk may be mistaken for disseminated granuloma annulare.

Treatment. The main reason for treatment is cosmetic. Careful destruction with diathermy can produce good cosmetic results.

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Papillary eccrine adenoma

Definition. A solitary nodule, usually on the limbs of darker-skinned individuals.

Clinical features. This rare lesion was first described in 1977 [1]. It presents in a non-diagnostic manner as a slowly growing nodule on the limbs.

Pathology. The lesion is in the papillary dermis and consists of ductal structures which may resemble either eccrine or apocrine tissue. Dilated ducts form a complex honeycomb-like structure.

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Eccrine hidradenoma [1]

Definition. A relatively rare tumour of sweat gland origin.

Clinical features [2]. This is an uncommon tumour, found mainly in adults, and is excised more commonly in

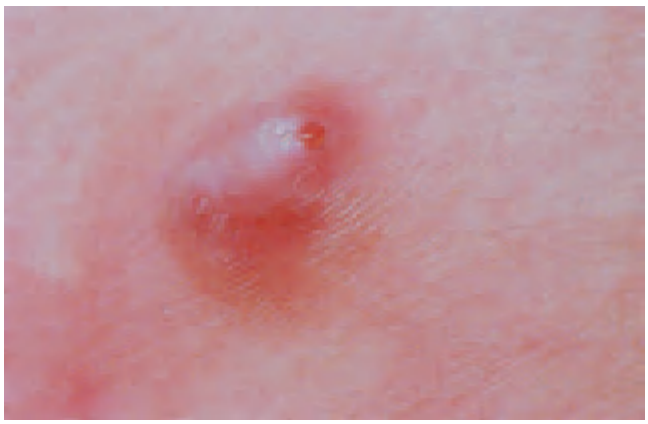

Fig. 37.20 Hidradenoma. Red/brown irregular papule.

women than in men. The tumours are firm dermal nodules 5–30 mm in size, and may be attached to the overlying epidermis, which can be either thickened or ulcerated (Fig. 37.20). Growth is slow and there may be a history of serous discharge. The lesions are usually solitary and are most likely to be found on the scalp, face or anterior trunk.

Pathology [3–6]. The tumour may connect with the epidermis. It forms lobulated, circumscribed masses and is composed of two cell types—polygonal cells, whose glycogen content may give the cytoplasm a clear appearance; and elongated, darker and smaller cells, which may occur at the periphery. Often, tumours do not contain cells with clear cytoplasm, and the name 'clear cell hidradenoma' is therefore misleading. Cuboidal or columnar cells are seen lining duct-like spaces and clefts. The histochemical reactions [7] and fine structure [8] indicate an eccrine origin, with features of both secretory and duct cells. In cases with a connection to the epidermis, the superficial component displays poromatous features.

Malignant transformation is very rare, and the diagnosis relies on identification of the pre-existing benign component [9–12].

Diagnosis. When the tumour is attached to the epidermis, the diagnosis may be suspected on clinical grounds, especially if there is a history of discharge. Ulcerated lesions may resemble basal cell carcinoma. Dermal nodules are non-diagnostic by clinical inspection.

Treatment. Surgical excision will cure benign lesions. Local recurrences are rarely seen [13]. Malignant eccrine hidradenoma may metastasize.

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Eccrine or apocrine/follicular tumours

In recent years, it has become apparent that a number of adnexal tumours that were regarded as exclusively showing eccrine ductal differentiation often display ductal apocrine differentiation. Because of the close relationship between the apocrine and the pilosebaceous unit, these tumours may also show evidence of focal follicular and even sebaceous differentiation [1,2]. The list of tumours with potential to display apocrine ductal differentiation continues to expand and even includes rare examples of poromas showing apocrine differentiation (see p. 37.19).

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Cylindroma [1–5]

SYN. TURBAN TUMOUR; SPIEGLER'S TUMOUR

Definition. A skin tumour of uncertain origin with a characteristic histology (see below) that usually manifests as nodules or tumours of the scalp.

Incidence. This is an uncommon tumour, affecting females about twice as frequently as males. It is frequently familial and an autosomal-dominant gene determines its inheritance [6,7]. It has been reported to follow radiotherapy epilation of the scalp. The onset is usually in early adult life, but may be in childhood or adolescence.

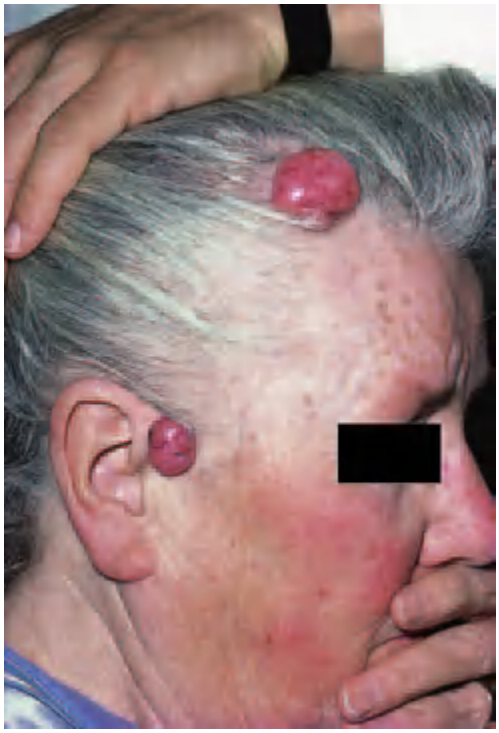

Fig. 37.21 Cylindroma. Two large tumours on the head of an elderly woman.

Clinical features [8,9]. The tumours are frequently multiple, smooth, firm, pink to red in colour and often somewhat pedunculated (Fig. 37.21). The lesions may be familial, and a suppressor gene has recently been identified on chromosome 16q, loss of which appears to be associated with cylindroma development [10,11]. The rate of growth is slow and often seems to cease when a certain size has been reached. Some tumours become 50 mm or more in diameter, but most are smaller. Pain is an occasional symptom. The commonest site is the scalp and adjacent skin. Tumours on the scalp may be almost hairless when pedunculated, but the smaller lesions form dermal nodules with little loss of overlying hair. Multiple tumours have attracted much attention in the literature, but solitary lesions are not uncommonly seen by surgical pathology services. A proportion of lesions occur on the face and neck away from the scalp margin; in fewer than 10% of cases, are they situated on the trunk and limbs. When the lesions are multiple, new tumours arise over the years. In some patients, there may be an admixture with trichoepithelioma, either in separate tumours or sometimes in the same tumour. This is a clear indication that these tumours are likely to show ductal apocrine follicular differentiation rather than ductal eccrine differentiation.

Pathology [12–18]. The tumours have a rounded outline and are composed of closely set mosaic-like masses ('jigsaw-puzzle' appearance) and columns of cells that are

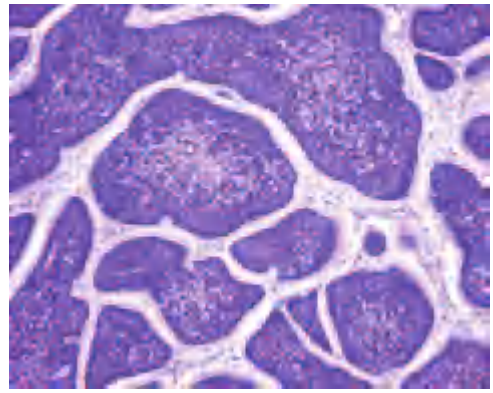

Fig. 37.22 Cylindroma. Classical jigsaw-puzzle architecture, with tumour lobules displaying a thick basal membrane.

invested by a hyaline basal membrane of variable thickness. Thin bands of stroma (Fig. 37.22) separate tumour lobules from one another. The cells are of two types—one large, with a moderate amount of cytoplasm and a vesicular nucleus; and the other small, with little cytoplasm and a compact nucleus. The small cells tend to be peripheral; they also surround duct-like spaces or masses of hyaline material within the tumour lobule. There are strong immunohistochemical similarities between cylindromas and spiradenomas, and they may coexist in the same individual [19,20].

Diagnosis. The multiple type on the scalp is most likely to be confused with tricholemmal cyst, which is, however, usually smoother, firmer and more mobile. Small tumours are difficult to diagnose, and must be distinguished from trichoepithelioma, steatocystoma, or basal cell carcinoma if solitary. Large, pedunculated and lobular tumours are almost unmistakable.

Treatment. Surgery is the treatment of choice. Extensive involvement of the scalp may require wide excision and replacement of the whole area by a graft.

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Spiradenoma [1,2]

SYN. ECCRINE SPIRADENOMA

Definition. A benign tumour of sweat gland origin, which is usually solitary and is distinguished by its histology (see below).

Incidence. It is relatively uncommon, appears mainly in young adults, equally in both sexes and is rarely familial.

Clinical features [3,4]. The lesion is usually solitary and painful and consists of a firm, rounded, bluish, dermal nodule 3–50 mm in diameter [13]. The usual site is on the front of the trunk and proximal limbs.

Pathology [5,6]. The tumour is lobular, with two cell types in the islands (Fig. 37.23). Larger, paler cells may be grouped around lumina, and smaller, darker cells form the periphery. Small, tubular structures or cystic spaces may occur, and large, thin-walled, dilated vascular channels are also present [7,8]. The lobules are surrounded by condensed connective tissue, which may encroach on the islands as hyaline droplets. Degenerative changes in old tumours are often prominent. Necrosis and degeneration often obscure the histological features, and only focal areas display the typical features of a spiradenoma. Old tumours with degenerative changes tend to be very large. Malignant transformation may occur and usually presents in long-standing tumours [9–14]. The diagnosis of a malignant spiradenoma is often only made after a residual benign component is identified.

Diagnosis. Clinical differentiation from other dermal tumours and cysts may be made if the tumour is a firm, domed elevation of a dark-blue colour.

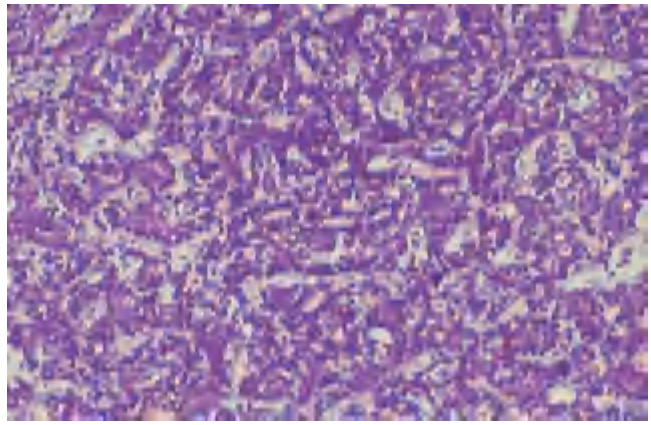

Fig. 37.23 Eccrine spiradenoma. Ductal structures and intermixed pale and dark cells.

Treatment. Surgical excision should be complete, as there may be recurrence.

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Mixed tumour of the skin [1]

SYN. CHONDROID SYRINGOMA

Clinical features [1–4]. This tumour is usually found on the head and neck, followed by the trunk and the extremit-

ies, as a solitary nodule. The lesions are frequently large and nodular, sometimes with a diameter of 5–10 cm, and occur most commonly in middle-aged males. Local recurrence is rarely seen.

Pathology [5–11]. This is usually a fairly large, multilobulated tumour located in the dermis and/or subcutaneous tissue. Tumour lobules are separated by fibrous septa. A myxoid, hyalinized or chondroid stroma is variably seen in all tumours. The epithelial component consists of nests and strands of cells with pink cytoplasm and vesicular nuclei with a single, inconspicuous nucleolus. Cytological atypia is absent, and mitotic figures are sometimes seen. Tubular structures and ductal differentiation are frequently seen. Larger tumour cells with a plasmacytoid appearance are a frequent finding and suggest myoepithelial differentiation. Ductal structures usually have a peripheral layer of flattened myoepithelial cells. Immunohistochemical studies reveal positivity for keratin and focal positivity for S100 and smooth muscle actin, confirming myoepithelial differentiation. Areas more suggestive of apocrine and follicular differentiation are identified in some tumours [7,8,12,13]. These cellular areas are set in a dense stroma, and on low-power magnification a rather lace-like or trabeculated pattern may be present. The stroma stains positively with Alcian blue, indicating the presence of chondroitin sulphate and hyaluronic acid. Focal calcification, mature fat and bone formation may also be seen. Rare tumours composed exclusively of myoepithelial cells should be regarded as myoepithelioma.

Malignant chondroid syringomas have been reported [15–22], including a case with metastasis [23].

Management. Local excision is recommended. If there is any suspicion of malignancy, wide excision and follow-up are required.

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Sweat gland carcinomas, including ductal apocrine/follicular carcinomas

These lesions can be divided into two broad groups. The first group represents the situation in which malignant change develops in a pre-existing, apparently benign lesion, such as hidradenoma, mixed tumour, spiradenoma, cylindroma and eccrine poroma. The latter is the most commonly recorded example of such malignant progression [1,2]. In most adnexal tumours, with the exception of malignant eccrine poroma, the diagnosis usually requires identification of a benign component. Even when there is unmistakable cytological evidence of malignancy, the biological behaviour of malignant tumours of skin appendages is generally relatively benign, with local recurrence being much more common than cutaneous metastases.

The second group of carcinomas consists of lesions that develop as carcinomas *ab initio*. The primary eccrine carcinomas include microcystic adnexal carcinoma, eccrine epithelioma (regarded by many as part of the spectrum of microcystic adnexal carcinoma), aggressive digital papillary adenocarcinoma, mucinous carcinoma and adenoid cystic carcinoma. Lymphoepithelioma-like carcinoma of the skin is also included in this group.

A recent review of 60 sweat gland carcinomas reported 41 porocarcinomas, three syringomatous carcinomas, eight ductal carcinomas, five adenoid cystic carcinomas and three mucinous carcinomas [1]. The rarity of sweat gland carcinomas makes it difficult to say whether or not this distribution is the norm, but porocarcinoma does appear to be a relatively common lesion.

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Eccrine gland carcinomas

Malignant eccrine poroma [1,2]

SYN. POROCARCINOMA

Definition. A malignant tumour with metastatic potential arising from intraepidermal eccrine duct epithelium. In up to 18% of cases, tumours arise from a pre-existing benign eccrine poroma [3].

Clinical features [4–7]. These are relatively common malignancies (0.01–0.005% of all cutaneous tumours), arising most often on the lower limbs (44% of cases) in older patients, with an average age at presentation of 73 years. Females are more commonly affected than males. The lesion presents as an endo-exophytic tumour, which is often ulcerated. Tumours may attain a very large size and are frequently long standing. Local recurrence is seen in 17% of cases. Regional lymph-node metastases and systemic metastases occur in 19% and 11% of patients, respectively [3]. A small number of patients present with multiple lesions, and it is not clear whether this represents epidermotropic metastasis or true multifocality [1,3,8].

Pathology [3,9–11]. Tumours show multiple connections to the epidermis, and a pre-existing benign eccrine poroma may be present. *In-situ* lesions are seen occasionally [3,12]. The tumour infiltrates the dermis and the subcutaneous tissue in nests and lobules composed of relatively small cells that do not have a basaloid appearance. Peripheral palisading is absent. Ductal differentiation is necessary for the diagnosis to be made. This may be demonstrated by the use of immunohistochemical stains for carcinoembryonic antigen (CEA) and epithelial membrane antigen (EMA). A PAS stain may also be used, but this only highlights the ducts in very well-differentiated tumours forming ducts with a cuticle. Comedo necrosis is often present. Clear cell change and squamous differentiation may be seen, but do not tend to be prominent.

Poor prognostic factors are a large number of mitotic figures, lymphovascular invasion, tumour depth greater than 7 mm and an infiltrating rather than a pushing border [3].

Treatment. Wide excision and follow-up are required. Two recent series including a total of 93 cases suggest that these lesions may have less metastatic capacity than had been previously suggested [3,13]. Mohs micrographic surgery is useful in those cases with a prominent infiltrative growth pattern [14].

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Malignant hidradenoma

SYN. HIDRADENOCARCINOMA; MALIGNANT ACROSPIROMA

Definition. A malignant tumour traditionally regarded as displaying eccrine differentiation and arising from a pre-existing hidradenoma.

Clinical features. These lesions are most often recorded as red, ulcerated nodules on the face hands or feet. They are commonest in older adults, but cases are recorded in children [1–4]. They may be very aggressive and pulmonary metastases have been recorded.

Pathology. Large clusters of glycogen-rich clear cells are present in some cases, but others may resemble basal cell carcinoma [5–9]. Focal necrosis may be present, and the range of mitoses is highly variable. Squamous differentiation may be prominent [10].

Treatment. Wide local excision is recommended. Mohs surgery has been used successfully for lesions on the foot [11]. Follow-up is essential, as the lesions may recur locally and/or metastasize.

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Aggressive digital papillary adenocarcinoma

Definition. A rare tumour found on the hands and feet, with a high risk both of local recurrence and metastasis. Prior publications have described both a benign, aggressive digital papillary adenoma and a carcinoma [1,2], but the lack of pathologically diagnostic or prognostic differentiating features suggests that all lesions in this category should be treated as carcinomas.

Clinical features. Both sexes are affected and at any age. The lesion presents as a non-diagnostic asymptomatic nodule on the fingers, toes, palms or soles. Delayed diagnosis is frequent [1–4].

Pathology [1,2,5]. The lesions are obviously cystic on low-power examination, and have papillary projections into the cystic cavities, Ductal and tubuloalveolar structures are also present. There may be focal necrosis and both nuclear hyperchromatism and a high mitotic count. In some cases, a tubular architecture tends to predominate and papillary projections may not be so prominent. Histological features do not allow accurate prediction of behaviour, as tumours with low-grade histology may metastasize [2].

Tumours may invade surrounding soft tissues and blood vessels and can destroy bone.

Treatment. Wide local excision and follow-up are recommended in view of the high recurrence rate, both locally and via metastatic spread [1,2,6]. It has been suggested that sentinel lymph-node biopsy is appropriate for these lesions [6].

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Eccrine or apocrine/follicular carcinomas

Malignant cylindroma [1–7]

Definition. A rare tumour, which develops from a pre-existing benign dermal cylindroma.

Clinical features. These unusual tumours develop as expanding nodules, usually on the scalp. They may be suspected by expansion of a previously static dermal cylindroma or turban tumour. They have been reported in familial cases of cylindromas [1,2].

Pathology. These lesions have the characteristic architecture of a dermal cylindroma, with deeply basophilic small cells surrounded by an eosinophilic basement membrane [3–6]. In addition, however, there is marked nuclear atypia, irregularity of cell size and an infiltrative growth pattern. Mitotic figures, both normal and abnormal, are present.

Treatment. Wide local excision and follow-up are required.

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Malignant eccrine spiradenoma

SYN. SPIRADENOCARCINOMA

Definition. A rare tumour, which usually arises in a pre-existing spiradenoma.

Clinical features. Sudden expansion of a pre-existing nodule is the most likely presentation [1]. A recent study of

12 cases reports the commonest site as the trunk, with limbs and head and neck less frequently involved [2]. The sex distribution appears equal, and the likely age at presentation is in the seventh decade.

Pathology [2–4]. These lesions usually show evidence of origin from a pre-existing benign spiradenoma. Necrosis, a high mitotic count, loss of the dual cell population and an infiltrative growth pattern are features that raise the possibility of malignant transformation.

Treatment. Excision and follow-up are required. Up to 20% of these tumours have been reported to metastasize [2–5].

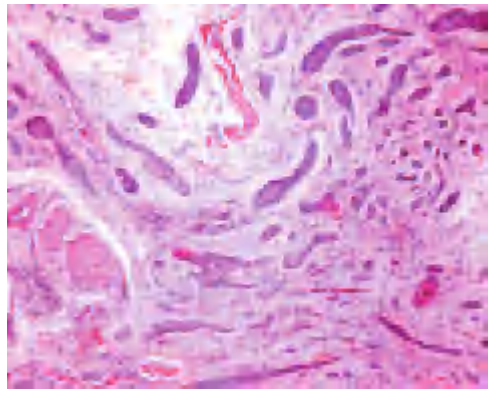

Fig. 37.24 Microcystic adnexal carcinoma. Strands and small nests of bland epithelial cells with an infiltrative growth pattern.

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Microcystic adnexal carcinoma

SYN. SCLEROSING/SYRINGOMATOUS SWEAT DUCT CARCINOMA; MALIGNANT SYRINGOMA

Clinical features. This tumour is relatively rare, has an equal sex incidence and a predilection for the central area of the face, often as an inconspicuous, elevated or depressed sclerotic plaque or nodule in the upper lip area [1–4]. The trunk is also rarely involved. The age range is very wide, but young and middle-aged patients are more frequently affected. If the lesion is not promptly treated, or if local recurrence occurs, the lesions may present with pain or a burning sensation because of perineural spread. Cases have been reported both in patients with generalized immunosuppression and in sites of previous radiotherapy [5–7]. The rate of local recurrence is very high (up to 40%).

Pathology [8,9]. The salient histological features are the presence of cords of cytologically banal epithelial cells with focal, variable ductal differentiation set in a very sclerotic desmoplastic stroma [2–4]. Horn cysts are seen in many cases and pilar and sebaceous differentiation may also occur (Fig. 37.24) [8,9,11]. Superficial areas show a resemblance both to the syringoma and desmoplastic trichoepithelioma. The diagnosis can therefore be impossible if only a small, superficial biopsy is evaluated, as clues to the correct diagnosis reside in an infiltrative growth pattern and prominent perineural invasion. Cytogenetic analysis of a case of microcystic adnexal carcinoma has shown a deletion on chromosome 6q (23–25) [12].

Management. The importance of this tumour is that perineural permeation is common, and for this reason microscopically controlled surgical excision is recommended. Mohs surgery has been recommended as the surgical approach of choice.

Metastatic spread is very rare, but extensive local recurrence can be a major problem. Tumours may rarely extend into the brain as a result of perineural invasion.

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Eccrine epithelioma [1–4]

SYN. BASAL CELL CARCINOMA WITH ECCRINE DIFFERENTIATION; SYRINGOID ECCRINE CARCINOMA

Freeman and Winkelmann, who considered it to be a basal cell tumour with eccrine differentiation [1,2], first described this rare tumour in 1969. However, the tumour does not represent a basal cell carcinoma with eccrine differentiation [3]. Some authors have proposed that it is part of the spectrum of microcystic adnexal carcinoma. At least 12 cases are currently reported in the world literature. The lesion has some resemblance to both benign syringoma and to dermal cylindroma.

Clinical features. Two-thirds of the cases so far reported have occurred on the scalp as large, non-specific, sometimes ulcerated nodules. They may be painful, due to their position in the deep dermis.

Pathology. The tumour consists of cords and clusters of small, dark-staining, cuboidal basophilic cells set in a very dense stroma. The cells are cytologically abnormal, with a high nuclear/cytoplasmic ratio, and mitotic figures are seen. These features occur in the lower part of the dermis, extending into the subcutaneous fat. The islets of cells have a surrounding PAS-positive membrane.

Management. Wide local excision is required. Follow-up is essential, as repeated local recurrences are common. In one case, metastasis to a local lymph node was recorded.

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Mucinous carcinoma

Definition. A rare, adnexal, mucin-producing carcinoma arising on the head and neck area in more than 90% of the cases.

Clinical features. The most frequently described clinical presentation is that of a grey nodule on the face of an elderly male, often in the periorbital area [1–5]. Rare tumours are bilateral [6]. An important clinical differential diagnosis is from a cutaneous secondary deposit from a more common site for mucinous carcinoma such as the stomach and breast [7]. The distinction between a primary skin tumour and a metastasis cannot be made on the basis of the histological and immunohistochemical findings and has to rely on clinicopathological correlation and additional studies to rule out an internal primary. In the case of a suspected metastatic mucinous breast carcinoma, staining for oestrogen and progesterone receptors is not useful, as primary cutaneous mucinous carcinomas are often positive for these markers [8].

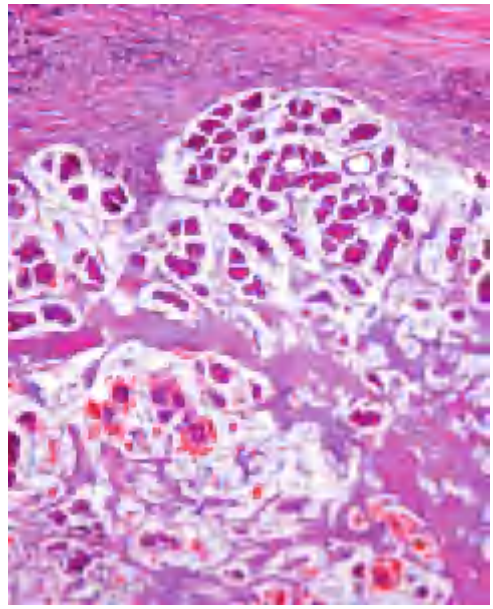

Fig. 37.25 Mucinous carcinoma. Nests of tumour cells surrounded by pools of mucin.

Pathology. These lesions are relatively deeply situated and consist of clusters of cells with pink cytoplasm and some degree of cytological atypia. The central cells are paler and surrounded by darker-staining cells arranged in a palisaded fashion. Broad, fibrous septa run between these cytologically malignant cells, and both cells and septa are separated by lakes of mucin (Fig. 37.25) [9,10]. The mucin stains with diastase-resistant PAS, and acid Alcian blue (pH 2.5).

Management. Wide local excision, possibly with microscopically controlled excision margins, is recommended. Extensive metastatic spread and invasion of bone is very rare [11,12]. Local recurrence is often seen and the risk of metastatic spread to regional lymph nodes increases after a recurrence.

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Adenoid cystic carcinoma

SYN. PRIMARY CUTANEOUS ADENOCYSTIC CARCINOMA

This is a particularly rare variant of adnexal carcinoma, which has only been recognized as an entity since 1975. Adenoid cystic carcinomas arise relatively frequently from salivary glands, and direct spread or even metastasis from this site should be ruled out before the diagnosis of primary cutaneous adenoid cystic carcinoma is made. Around 20 cases are presently recorded in the literature.

Clinical features [1,2]. These lesions are non-specific, sometimes painful, nodules on the head and neck area. The pain is attributed to perineural spread. Rarely, tumours develop elsewhere in the skin including the scrotum [3].

Pathology [4–7]. The pathology is that of large masses of cells with mild or no cytological atypia, arranged in a distinct adenoid or cribriform pattern. The cystic spaces are occupied by mucin, which stains with Alcian blue (pH 2.5). The lesion occupies the middle to deep dermis and may extend to the subcutaneous tissue. A more solid variant may be seen occasionally. Many of these tumours show at least focal evidence of myoepithelial differentiation.

Management. The management of these lesions is by wide local excision. Local recurrence is common and metastasis to the lung and regional lymph nodes has rarely been reported [5,8–10]. Metastatic spread to the lungs has also been reported many years after removal of the primary cutaneous tumour [11]. Erosion of bone at the primary site has also been recorded.

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Lymphoepithelioma-like carcinoma

Lymphoepitheliomas are well-recognized tumours of the nasopharynx, and an entity with similar histological features has also been observed in the skin [1]. However, the latter is not associated with Epstein–Barr virus (EBV) infection and its behaviour appears to be less aggressive than that of upper respiratory tract lesions [2,3].

Clinical features. The clinical appearance is of non-specific nodules on the head and neck area of older patients. The trunk and vulva are also rarely involved.

Pathology. The pathological features are those of a very dense infiltrate of inflammatory mononuclear cells, including lymphocytes and histiocytes, with small strands and nests of atypical epithelial cells. Inflammatory cells extensively infiltrate nests and strands of tumour cells, and the epithelial nature of these cells is often not immediately apparent unless more or less intact nests of epithelial cells are found. Confusion with a lymphoma is therefore a possibility, and often immunostaining for keratin and lymphoid cells is necessary to distinguish the two populations of cells. Cytological atypia is usually present, and mitotic figures are common. Focal evidence of adnexal differentiation may be seen [4–7]. Some tumours appear to be arising from a squamous cell carcinoma. It has therefore been suggested that this is not a distinctive entity but a morphological pattern in various cutaneous carcinomas [8].

Treatment. Surgery followed by radiotherapy is recommended. However, the lesions are aggressive, and both local recurrence and distant metastases, with one tumour-associated death, have been recorded [5,7].

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Paget's disease of the nipple [1]

Definition. A progressive, marginated, scaling or crusting of the nipple and areola due to invasion of the epidermis by malignant cells, which are currently thought to originate in the intraduct carcinoma of the breast that frequently accompanies the condition.

There is a strong current view that Paget's disease arises from apocrine duct-derived epithelial cells.

Incidence and aetiology [2]. Paget's disease of the nipple is an uncommon occurrence, considering the frequency of breast cancer [3,4]. In one series, it occurred in fewer than 3% of breast cancers. It occurs chiefly in women, although rare cases have been recorded in men [5]. It is rare before the fourth decade and is most frequent in the fifth and sixth. Published cases suggest that the disease is more common in Anglo-Saxon countries. The current view is that the majority of cases of Paget's disease arise from either invasive or *in-situ* ductal carcinoma in the deeper breast tissue.

Clinical features [6,7]. The early changes may be minimal, with a small, crusted and intermittently moist area on the nipple giving a brownish stain on clothing, or producing itching, pricking or burning sensations. Less often, there is a serous or blood-stained discharge from the nipple, or a lump may be noticed in the breast (Fig. 37.26). The surface changes persist and gradually spread to produce an eczematous appearance. The nipple, areola and, at a later stage, skin of the breast are erythematous and moist or crusted (Fig. 37.27). The change is sharply marginated and may spare a segment of the areola. The edge is slightly raised and irregular in outline. If the crusts are removed, a red, glazed, moist or vegetating surface is revealed. Itching may be a prominent symptom and excoriations may be found in the established lesion. Some areas may

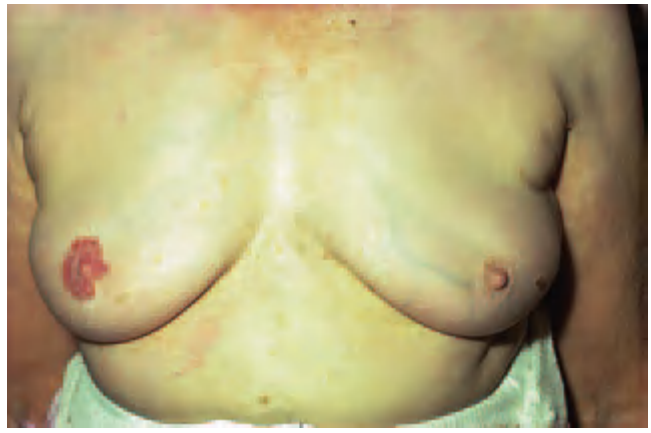

Fig. 37.26 Paget's disease of the nipple. Distant clinical view, showing unilateral lesion.

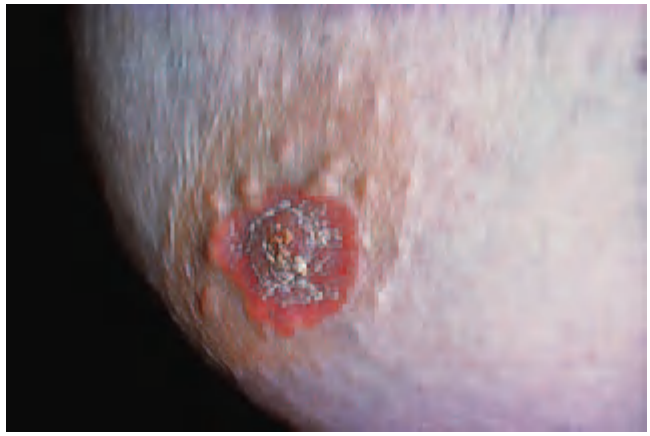

Fig. 37.27 Paget's disease of the nipple. Close-up view, showing erythema and well-marked lateral edge of the lesion.

be ulcerated. The change is confined to one nipple. The nipple itself may be retracted, and a subjacent mass or a lump deeper in the breast may be felt. The regional glands should be examined; they are rarely enlarged when a mass cannot be felt, but are enlarged in more than half the cases with a detectable tumour. The rate of spread of the skin changes is slow, and patients often wait a year or more before seeking advice. The change may occasionally involve not only the skin of the breast but also spread on to the chest wall.

Pathology [8–10]. The epidermis is thickened, with papillomatosis, enlargement of the interpapillary ridges and hyperkeratosis or parakeratosis on the surface (Fig. 37.28). Within the epidermis, characteristic Paget's cells are dispersed between the prickle cells. They vary in number, and when profuse the Malpighian layers may be disrupted and the surface covered by a crust. There is a chronic inflammatory reaction in the upper dermis. In the later stages, the epidermis may be atrophic or eroded.

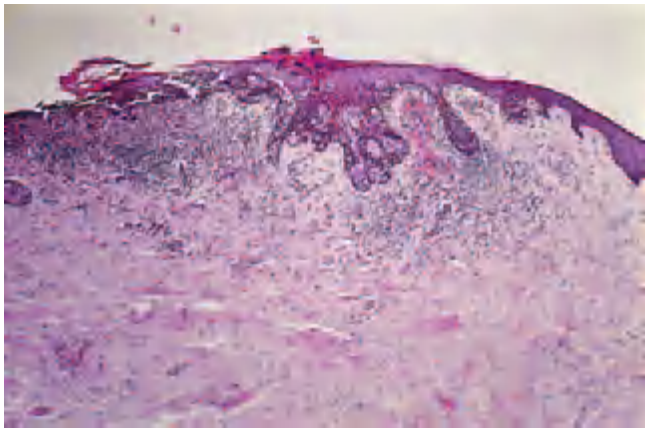

Fig. 37.28 Pathology of Paget's disease of the nipple, showing epidermal ulceration, colonization of the epidermis by large pale Paget's cells and an underlying brisk lymphocytic infiltrate.

On scanning microscopy, the differential diagnosis may include superficial spreading malignant melanoma.

The Paget's cells have a clear, abundant cytoplasm and do not establish intercellular bridges with the adjacent normal keratinocytes. Both the cells and their nuclei are rounded; the nuclei are vesicular or hyperchromatic with a high nuclear/cytoplasmic ratio. The cytoplasm PAS is positive and diastase-resistant [11], which indicates the presence of neutral polysaccharides and supports the glandular origin of the cells [12]. Staining with antibodies to CEA is also positive [13,14]. The cells are distributed singly among the prickle cells, or in clusters in a pattern similar to that seen in superficial spreading melanoma. The Paget's cells may also be seen in appendage ducts, so that it can be impossible to determine if these cells are migrating from these ducts to the epidermis, or invading downwards into the ducts from the epidermis.

An underlying breast carcinoma, if present, is not always seen on biopsy, as it may be deeply set. Careful examination of the amputated breast may show an intraduct carcinoma, sometimes of quite small dimensions, situated most usually distally, but sometimes in the terminal ducts, and often appearing to spread between the two layers of epithelial cells of the duct. The cells may accumulate within and distend the ducts and spread in both directions. A number of ducts are usually involved. At a later stage, the carcinoma becomes invasive and behaves like classic breast carcinoma.

Diagnosis. The principal differential diagnosis is eczema of the nipple. This is frequently bilateral and runs a more fluctuating course, improving in response to local treatment and spreading rapidly when irritated. Eczema lacks the sharp, raised and rounded margin and the superficial induration of Paget's disease. In doubtful cases, biopsy will be required. Bowen's disease and superficial basal cell carcinoma may also produce a similar clinical picture. They are both very uncommon on the nipple and can be differentiated histologically. Psoriasis and erosive adenomatosis of the nipple may also need to be considered in the clinical differential diagnosis, and again a biopsy to obtain pathology will clarify the situation. The chief pathological problem is to distinguish Paget's disease from superficial malignant melanoma. Paget's disease cells will be CEA-positive, EMA-positive and Cam 5.2-positive, while those of melanoma will be positive for Melan A mart melanoma antigens [13,14]. Positivity to antibody to S100 protein is not useful, as although it is positive in the great majority of melanomas, it is also positive in a proportion of Paget's disease. The absence of melanophages and the presence of neutral mucopolysaccharides in the cells are also helpful.

Treatment [15]. All patients should have a mammogram or ultrasound to establish whether or not there is deeper pathology in the underlying breast, as this will help determine the extent of surgery required. Surgery should be carried out as for carcinoma of the breast. In patients with no evidence of an underlying breast carcinoma, conservation may be a realistic option [16,17].

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Extramammary Paget's disease [1]

Definition. A marginated plaque resembling Paget's disease clinically and histologically, but occurring in sites rich in apocrine glands, such as the vulva, anogenital region and axilla.

There is currently controversy as to how often this condition arises on the background of an underlying carcinoma, and how often it arises primarily in the epidermis or apocrine ductal tissue of the affected area. This has given rise to the concept of primary and secondary extramammary Paget's disease [2].

Incidence and aetiology. This is a rare disease. It occurs more frequently in women and starts usually in the fifth decade or after. The current view is that in about 75% of cases, extramammary Paget's disease arises as a primary intraepidermal neoplasm, possibly from apocrine gland ductal cells or from keratinocyte stem cells. In the remaining 25%, an underlying primary adenocarcinoma is found. These cases are referred to as secondary Paget's disease.

Clinical features. The lesion has many features in common with Paget's disease of the nipple. The margin is sharp, rounded and slightly raised, and encloses an area that is somewhat erythematous or distinctly red. The surface may be scaly, and small, greyish crusts may cover erosions. Itching is a prominent feature and there may be excoriations or lichenification. Variable hyperpigmentation may be present, adding to the pathological confusion between extramammary Paget's disease and superficial spreading melanoma. In a proportion of cases, there may be leukoplakia.

The appearance varies somewhat according to the site. The commonest area involved is the vulva [3–5] (Fig. 37.29), followed by the perianal area, which is more frequently affected in men than women, the scrotum, penis and axilla [6,7]. The first symptom, especially in vulval lesions, is itching and burning, which may be persistent and spread. Quite often it is regarded as a dermatitis, and may be irritated by topical therapy. The mucosal surfaces of the labia are frequently a rather more vivid red than the skin when both areas are involved, and the change may spread to the thighs, mons pubis and into the vaginal introitus. There may occasionally be a papillomatous surface. Perianal lesions may extend up into the anal canal. Lesions on the scrotum spread to the thigh or onto the shaft of the penis. Very occasionally, extramammary Paget's disease may be present on the eyelids or ears. Characteristic clinical features include the relentless progression, despite all local applications, and the sharp margin. Eventually, one area may become thickened and ulcerated as evidence of invasion downwards. Lymph node or distant metastases can occur.

Although most of the cases in which a primary carcinoma is found result from an underlying sweat gland adenocarcinoma, it is necessary to examine the patient for evidence of an adenocarcinoma of the cervix and rectum.

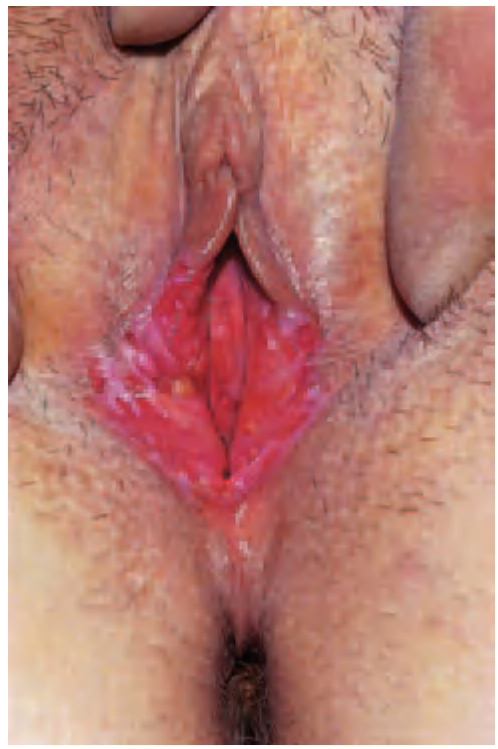

Fig. 37.29 Extramammary Paget's disease of the vulva showing inflamed eczematous presentation.

Pathology. The changes in the epidermis are essentially similar to Paget's disease. The cells stain positively for acid as well as neutral mucopolysaccharides. They may contain melanin granules. Immunohistochemistry shows cells positive for CEA and Camp 5.2 and other low-molecular-weight keratins such as CK7. GCDFP-15 is a marker of apocrine epithelium [8] and is frequently strongly expressed in primary vulval or perianal Paget's disease with no detectable underlying malignancy.

Diagnosis. The differential diagnosis from eczema, intertrigo and pruritus vulvae is made by the steady spread, lack of response to topical anti-inflammatory agents and the sharp and extending margin. Bowen's disease is usually more raised and verrucous, and superficial basal cell carcinoma has a thread-like margin. It may be difficult to differentiate leukoplakia or Bowen's disease of the mucosal surfaces, and biopsy may be required. As with mammary Paget's disease, superficial spreading melanoma is an important pathological differential diagnosis.

Treatment. Adequate tissue sampling and other investigations are essential to establish whether or not there is an associated underlying malignancy requiring surgical excision. If an underlying malignancy is present, it should

be excised together with all clinically abnormal epithelium. If no underlying malignancy is detected on careful examination, the entire affected area of epithelium should be excised. Mohs surgery with careful control of excision margins may be useful, as a common cause of recurrence is inadequate excision of the lesion [9,10].

Promising results are reported with photodynamic therapy, but larger series and longer periods of follow-up are required [11].

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Merkel cell tumours [1]

SYN. TRABECULAR CELL CARCINOMA OF SKIN; PRIMARY NEUROENDOCRINE CARCINOMA OF THE SKIN

Definition. An aggressive and frequently lethal tumour thought to arise from the cutaneous Merkel cell, a neuroendocrine cell [2].

Incidence and aetiology. The first definitive report of Merkel cell tumour dates from 1977 [2], although there are reports in 1972 of 'trabecular cell carcinoma of skin' [1], which is almost certainly synonymous. De Wolf-Peeters *et al*. [3] were the first to suggest the use of the term 'Merkel-cell tumour'. More than 2000 cases have been recorded to date. This is a rare tumour of the elderly, with a high concentration of primary tumours on sun-exposed sites. An unexpectedly high proportion of Merkel cell tumours arise in association with either squamous cell or basal cell carcinomas, or in patients who have a past history of such lesions. These facts suggest that excessive ultraviolet exposure may play an aetiological role in the development of Merkel cell tumours.

Clinical features [4]. The lesions appear to have few distinctive features, and are described as raised, reddish-blue nodules, which may develop on any body site, although the head and neck area is over-represented in terms of surface area.

Pathology [5,6]. The cells making up the tumour may be either a solid mass or a more diffuse collection of cells, initially situated in the mid-dermis. They are intensely basophilic, with abundant mitotic figures and also many apoptotic cells. Lymphatic and vascular invasion is frequently present. On light microscopy, they may resemble small lymphocytes or a poorly differentiated metastatic deposit, particularly of small cell carcinoma of lung or of naevoid melanoma. The cells are argyrophilic, with sparse cytoplasm, dispersed chromatin and inconspicuous nucleoli.

Electron microscopy [7] is required for positive identification of the multiple, round, secretory granules that pack the cytoplasm of these cells. There may be a dense lymphoid infiltrate.

Immunohistochemistry is useful in confirming the diagnosis. Merkel cells show a characteristic 'dot' positivity with antibodies to low-molecular-weight keratins such as Camp 5.2 and CK20.

Treatment. Surgical excision is required [8], but metastases occur early and 30–50% of patients may die from metastases. Arterial limb perfusion has been used for lesions on limbs and may be beneficial [9]. Merkel cell tumours are considered to be radiosensitive, and trials of postoperative radiotherapy suggest a survival advantage [10]. There are ongoing studies of the benefit of sentinel lymph-node biopsy and full lymph-node dissection if the sentinel node is positive for limb lesions.

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Chapter 38

Disorders of the Cutaneous Melanocyte

R.M. MacKie

Introduction

Factors responsible for variation in cutaneous pigmentation are discussed in Chapter 39. Melanin pigment is synthesized and distributed to adjacent cells by cutaneous melanocytes, which are found in normal skin in the basal layer of the epidermis. Melanin synthesis and distribution is accelerated by exposure to UV radiation. Cutaneous pathology attributable to the melanocyte may arise as a result of overproduction of melanin by a normal quota of melanocytes as in the simple freckle, or by an increased number and altered distribution of cutaneous naevomelanocytes as in melanocytic naevi, or as a result of malignant transformation of the melanocyte as in malignant melanoma.

The freckle or ephelis

Definition. A pale-brown, macular lesion, usually less than 3 mm in diameter with a poorly defined lateral margin which appears and darkens on light-exposed skin sites during periods of UV exposure.

Clinical features. Simple freckles are commoner in children, and in individuals of all ages who are red- or fair-haired and fair-skinned (Fig. 38.1). They fade away almost completely during the winter months.

The clinical distinction between a freckle and a lentigo is that the lentigo persists in the absence of UV stimulation and on biopsy the lentigo will be seen to have a linear increase of melanocytes at the dermal–epidermal junction.

Pathology. The simple freckle shows no anatomical abnormality on biopsy [1,2]. It arises as a result of temporary overproduction of melanin by a normal quota of melanocytes due to stimulation by UV radiation. It has been claimed that the melanocortin 1 receptor gene is the major freckle gene, and that *MC1R* gene variants are required for the development of freckles [3].

Diagnosis. This is usually obvious with the presence of regular macular brown lesions on light exposed skin. The freckles and café-au-lait spots of neurofibromatosus (Chapter 12) are commonly on the trunk and axilla, and other features of neurofibromatosis may be present. An isolated patch of tinea nigra (Chapter 31) could rarely cause confusion but is likely to be larger than a freckle,

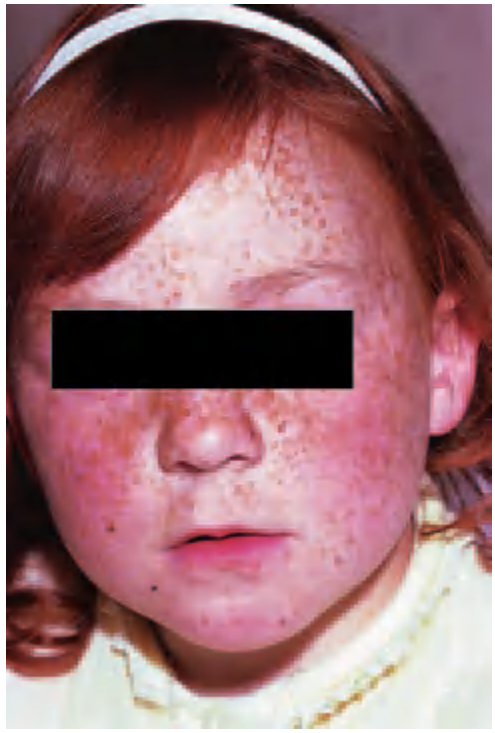

Fig. 38.1 Multiple freckles on a young girl with red hair.

and solitary. In contrast, freckles are usually present in reasonable numbers rather than as solitary lesions.

Management. No treatment is needed for these benign lesions, and their biological significance lies in the fact that they have been identified in case–control studies as an independent risk factor for melanoma [4].

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Lentigines

These lesions are also macular increases in melanin pigmentation on the skin, but they persist throughout the year, and on microscopy have an increase in the number of melanocytes at the dermal–epidermal junction for the body site in question.

Lentigines can be divided into simple lentigines, actinic lentigines, psoralen UVA (PUVA) lentigines, and the more recently described ink-spot lentigo. In the case of the first three variants, excessive exposure to natural or artificial UV radiation is the major aetiological factor.

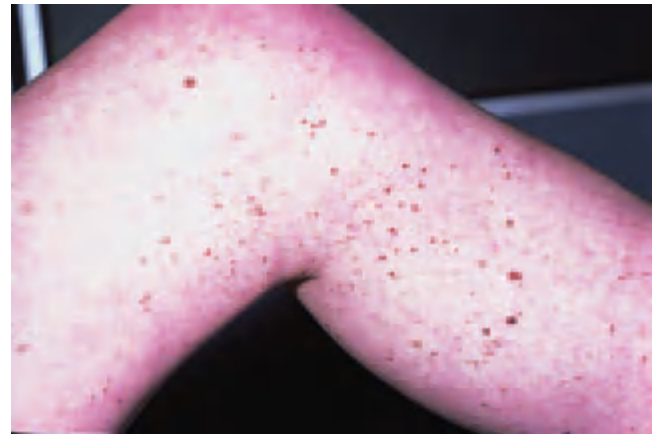

Fig. 38.2 Multiple lentigines on a young woman with cardiac defects.

Simple lentigo [1]

Definition. A brown macule arising as a result of an increased number of melanocytes at the dermal–epidermal junction without evidence of proliferation of these melanocytes downwards into the dermis.

Aetiology and incidence. Multiple benign lentigines occurring as an isolated phenomenon are very common, particularly in those with red hair, and skin with a high phaeomelanin/eumelanin ratio. Lentiginosis is a characteristic feature of a number of rare but potentially serious hereditary multisystem syndromes (Chapter 12).

Clinical features. A lentigo is a macular area of brown or brown-black pigmentation, usually circular or oval, although several individual lentigines may coalesce. There may be slight scaling of the surface, but the skin markings are unaltered. The pigmentation is usually light brown and fairly uniform. Any area of the skin, the mucocutaneous junctions or the conjunctivae may be affected (Fig. 38.2).

Pathology. There is a linear increase in the number of melanocytes along the dermal–epidermal junction. There is more melanin than normal in the adjacent epidermis and stratum corneum, and melanophages are abundant in the papillary body. The papillae and interpapillary ridges may be elongated.

Lentigines usually appear in childhood and may increase in number in the second and third decades. Rarely, they may erupt profusely [2] or occur in vast numbers [3]. They may fade or disappear over the course of years. Lentigines are found in the Peutz–Jeghers syndrome [4–6] and in centrofacial lentiginosis. The majority of lentigines remain static or disappear spontaneously in adult life.

If, however, very large numbers of lentigines are present and there is no history of excessive sun exposure, the possibility of one of the multisystem disorders should be considered [7–11]. These include the LEOPARD syndrome (*l*entigines, *e*lectrocardiogram anomalies, *o*cular anomalies, *p*ulmonary stenosis, *a*bnormal genitalia, *r*etardation of growth and *d*eafness), the NAME syndrome [7] and the LAMB syndrome [9]. The patient should be fully investigated for potentially serious systemic asssociations in such cases.

Diagnosis. Lentigines are distinguished from freckles by their darker colour, comparative sparseness and scattered distribution, and by the fact that they do not darken or increase in number on sun exposure, and do not disappear during the winter months.

It is often impossible to distinguish lentigines from flat junctional or compound naevi on clinical grounds.

Treatment. As these lesions are usually multiple, and have no premalignant potential, the patient should be reassured. Excision or even shave biopsy is likely to leave a residual scar more obvious than the lesion itself. Laser therapy may be effective if treatment is considered essential [12].

Solar or actinic lentigo

Definition. A macular area of brown pigmentation appearing after either acute or chronic sun exposure.

Clinical features. In younger patients, solar lentigines are most commonly seen on sun-exposed sites, such as the face in both sexes and the shoulders in males. They are macular, tan coloured and may be very large with a striking irregular border. There is frequently a history of acute sunburn, followed by the sudden appearance of large numbers of these irregular and unsightly macular lesions. In the UK they are rare before the age of 12 years, but in sunnier countries they may appear at a very young age.

Solar lentigines are also seen on older fair skinned patients who have had chronic sun exposure. The backs of the hands and the face are common sites. Once again the lesions are large and macular, have an irregular edge and are usually a uniform shade of brown. They are situated in an area of obviously sun-damaged epidermis.

Pathology. The pathological features of solar lentigo are similar to those of the smaller simple lentigines. There is a linear increase of melanocytes at the dermal–epidermal junction, but no cytological atypia of these melanocytes, and no budding down of these cells into the underlying dermis. There is frequently associated actinic damage to the adjacent dermal collagen.

Treatment. Because of the large size and unsightly appearance of some actinic lentigines, patients frequently request treatment. Prevention of further UV-induced damage should be encouraged by sun avoidance and the use of a high sun protection factor, broad-spectrum sunscreen. With these measures, there is often some spontaneous resolution of existing lesions. The use of cryotherapy may also be effective, but this should be used lightly to avoid scarring.

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Photochemotherapy (PUVA) lentigo [1,2]

Lentigines associated with PUVA therapy are a well-recognized complication of long-term use of PUVA therapy. They are relatively large, macular, pigmented lesions, which develop on the skin of patients receiving photochemotherapy. The number of melanocytes in the relevant body site are increased, and on ultrastructural examination there are morphological abnormalities of the melanosomes. Follow-up of PUVA-treated patients in the USA have indicated that PUVA lentigines are a marker of patients at increased risk of both melanoma and non-melanoma skin cancer [3–5].

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Ink-spot lentigo

Definition. A small (less than 5 mm in diameter), densely black macule, usually on sun-exposed skin [1].

Clinical features. These are relatively rare lesions but, as both doctors and the public become more expert at suspecting and diagnosing very early melanoma, such lesions may give rise to concern, partly because of their very dark pigmentation, and also because they may have an irregular lateral margin. They are usually solitary intensely pigmented macules with an irregular lateral margin (Fig. 38.3).

Pathology. The pathology of the lesion is that of a lentigo, with a linear increase in melanocytes in the basal layer of the epidermis, and an associated increase in melanin pigmentation both in the basal cells of the epidermis and also lying free in the underlying epidermis. The melanocytes are normal, and there is no evidence of cellular atypia.

Management. These lesions are commonly excised to obtain a pathological diagnosis because of their clinical resemblance to possible early melanoma.

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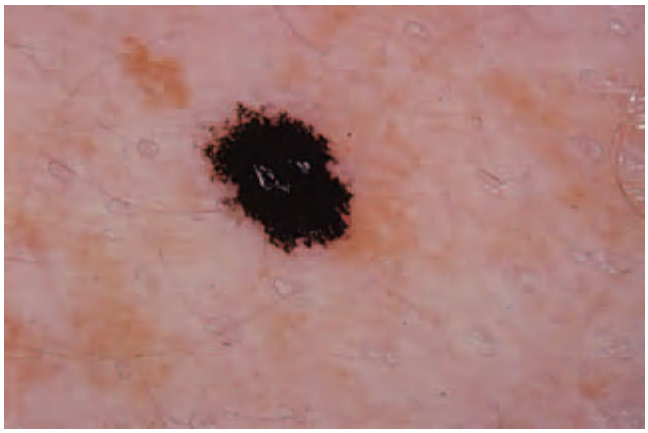

Fig. 38.3 Ink-spot lentigo.

Mucosal melanotic lesions

Essential melanotic mucosal hyperplasia

Relatively large, macular, melanotic lesions may develop on the oral mucosa or genital mucosa [1–3]. These lesions may slowly expand laterally to reach a diameter of several centimetres with a strikingly irregular lateral border. The pigmentation is usually relatively uniform. The vital point concerning these lesions is the fact that early and even moderately advanced oral or genital mucosal melanoma may look deceptively benign. A tissue diagnosis is therefore essential.

Clinical features. These lesions are relatively large macular areas of uniform brown or grey pigmentation. They may have slowly expanded to reach a large diameter over several years.

Pathology. The pathology of these lesions is usually much less dramatic than their clinical appearance [4,5]. There is a clear increase of melanin pigment in the basal layer keratinocytes with some overspill into the dermis, resulting in pigment-laden macrophages. The melanocyte count is relatively normal with only a slight linear increase and no junctional activity.

Treatment. No treatment is required if an incisional biopsy of an appropriate area has confidently excluded melanoma. This can, however, be extremely difficult, and the patients may require long-term follow-up.

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Labial melanotic macules [1,2]

Definition. Flat areas of benign non-progressive melanin pigmentation on the lips.

Clinical features. Labial melanotic macules usually affect the lower lip in the central third. More females than males seek treatment for these lesions. The site suggests that excessive exposure to natural UV radiation may be an aetiological factor.

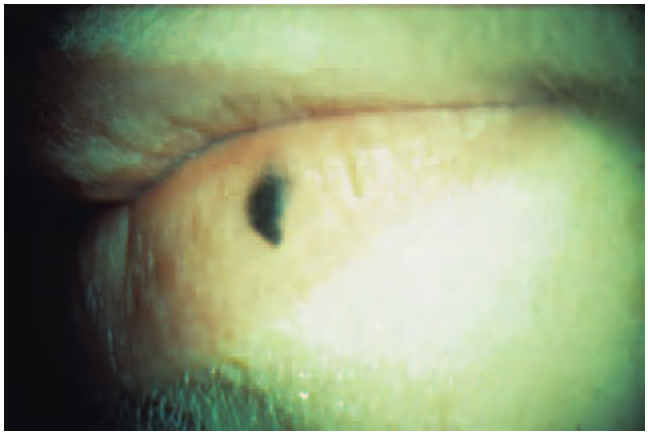

Fig. 38.4 Melanotic macule of the lower lip.

The natural history is of the relatively rapid appearance of a brown macule on the lower lip in a young adult. The macules rarely become larger than 1 cm in diameter, and are usually single lesions (Fig. 38.4).

Pathology. The pathology is that of linear increase in melanin pigment in the basal cells. Malignant transformation has not been reported in these lesions.

Treatment. Reassurance is all that is needed on medical grounds. If removal is requested for cosmetic reasons, cryotherapy, use of the infrared coagulator or laser therapy may all be effective [3].

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Melanocytic naevi

Epidemiology. Acquired melanocytic naevi are extremely common, and the great majority are benign with little malignant potential. Only a very small proportion progress to melanoma.

A broad initial subdivision of melanocytic naevi can be made into those appearing after birth—acquired naevi—and those present at or shortly after birth—congenital melanocytic naevi. In the UK, Australia and US 1–3% of infants examined in the first month of life have melanocytic naevi [1,2]. The great majority of individuals have acquired naevi which appear throughout childhood and puberty, so that in the third decade young white adults in the UK have 20–50 naevi. Thereafter, these naevi slowly disappear throughout life and by the ninth decade very few melanocytic naevi remain [3].

From studies in the cities of Brisbane, Sydney and Melbourne in Australia, which all have a marked latitude gradient, it appears that naevi appear earlier and in larger numbers in white skinned children in Brisbane, which is closest to the equator, but that by the early teenage years the numbers of naevi in children in these cities have equalized [4,5]. Similar studies looking at Italian schoolchildren in Europe also show higher naevus counts in those who have had greater sun exposure [6]. Patients with atopic dermatitis have significantly lower naevus counts than age-matched controls for reasons that are not yet understood [7].

The interaction between genetic susceptibility to naevi development and environmental stimuli is currently a subject of active research particularly using monozygotic and dizygotic twin pairs as models. These studies show very strong correlation of naevus counts in monozygotic twins, suggesting a strong genetic influence for total numbers of naevi [8–10]. Much of the current interest in and search for genetic and environmental factors affecting naevus development relate to the fact that large numbers of banal melanocytic naevi are the most significant risk factor yet identified for development of malignant melanoma [11,12].

Terminology commonly used in describing melanocytic naevi is included in Table 38.1.

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Table 38.1 Terms commonly used in the description of melanocytic naevi.

Melanocyte	A pigment-producing cell characterized by its ability to synthesize melanosomes. Contains the enzyme 3,4-dihydroxyphenylalanine (DOPA)
Theque	A group of melanocytes (generally four or more) in contact with the basal layer of the epidermis but budding downwards into the dermis
Freckle	An area of increased melanin pigmentation. The only histological abnormality is an excess of melanin pigment. The lesion would therefore appear to be the result of functionally overactive melanocytes. These lesions are stimulated by UV irradiation
Lentigo	An area of increased melanin pigmentation which shows histologically a linear replacement of keratinocytes in the basal layer of the epidermis by melanocytes. This replacement does not reach the level of theque formation; if this were the case, the term junctional naevus would be appropriate
Junctional activity	The presence at the dermal–epidermal junction of theques of melanocytes
Junctional naevus	A pigmented or cellular naevus in which the main histological feature is that of junctional activity. A few naevus cells are usually observed scattered in the underlying dermis
Compound naevus	A pigmented or cellular naevus in which the histological features include both junctional activity and the presence of naevus cells in the dermis. Such naevi usually contain melanin
Intradermal naevus	A cellular naevus in which there is little or no abnormality of melanocytes in the epidermis. The main feature is the presence of packets of naevus cells in the dermis. Melanin pigmentation is often absent and such naevi may be clinically non-pigmented

Acquired melanocytic naevi

SYN. CELLULAR NAEVUS; NAEVOCYTIC NAEVUS; MOLE

Definition. A benign cluster of melanocytic naevus cells arising as a result of proliferation of melanocytes at the dermal–epidermal junction. These may all remain in contact with the basal layer of the epidermis, giving rise to the junctional naevus. In other naevi some of the naevus cells may have become detached from the basal layer giving rise to the compound naevus. The end stage of this process is when there are no naevus cells attached to the epidermis and all are lying free in the dermis. This pattern is the intradermal naevus.

Aetiology and incidence. Melanocytic naevi are almost universal, and the great majority appear after birth [1]. The presence of large numbers is associated with childhood sun exposure [2]. Individuals with Turner's syndrome have larger than average numbers of naevi, as do children who have been treated for leukaemia [3].

The prevalence of melanocytic naevi varies with age [4–6]. They increase in frequency gradually during childhood and adolescence, and then more slowly during early adult life, to a plateau in middle age. During old age their prevalence falls [7,8]. The incidence of pigmented naevi on the palms, soles and genitalia has been studied in a large series of normal young men [9], and more than 10% of the sample were found to have one or more.

Clinical features [6,10]. Melanocytic naevi have a wide range of clinical appearances.

The **junctional** naevus is most often seen on the palms and soles and is a macular brown lesion, which may show pigment lying along the normal skin markings. It may have a slightly irregular lateral margin because of this,

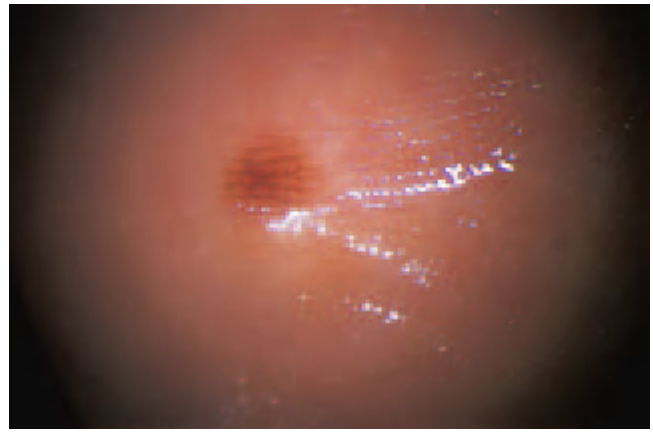

Fig. 38.5 Junctional naevus on the sole of the foot. Note the continuity of the skin markings.

and may have a large diameter of up to 10 mm. The pigmentation tends to be uniform and regular (Fig. 38.5).

The **compound** naevus is usually raised above the epidermal surface and may be round or oval. The colour varies with the natural pigmentation of the patient and may be very dark. There is usually little if any pigment on the flat surrounding epidermis in a classic non-dysplastic compound naevus (Fig. 38.6). In late childhood and adolescence, compound naevi often become elevated, giving rise to concern. It is important to recognize that elevation and the transformation of a macular melanocytic naevus to a palpable papule is not a sign of malignant change but a normal maturation pattern of these naevi. This elevation is often accompanied by loss of visible melanin pigment.

The **intradermal naevi** are frequently raised, dome-shaped, non-pigmented nodules, most commonly seen on the face (Figs 38.7 & 38.8). There are often some overlying telangiectatic vessels, and outgrowth of one or two coarse terminal hairs is common [7,8].

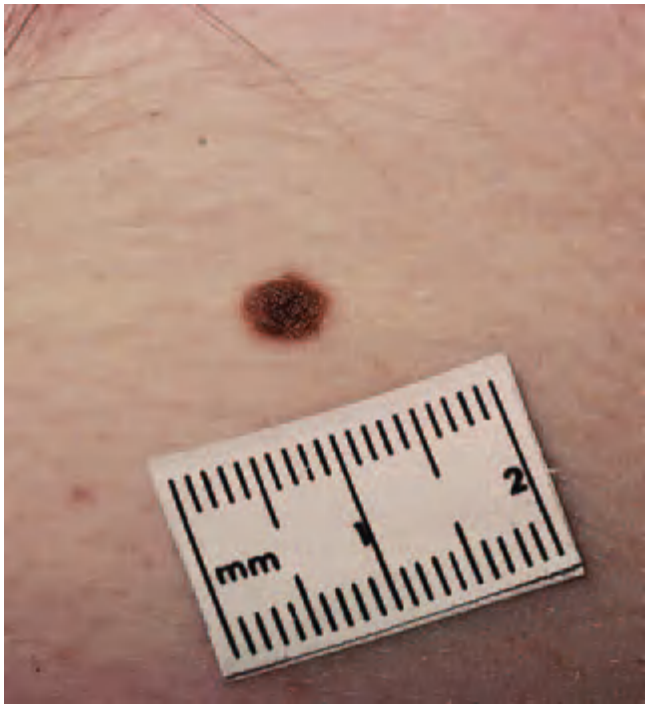

Fig. 38.6 Small compound naevus on the trunk of a young adult.

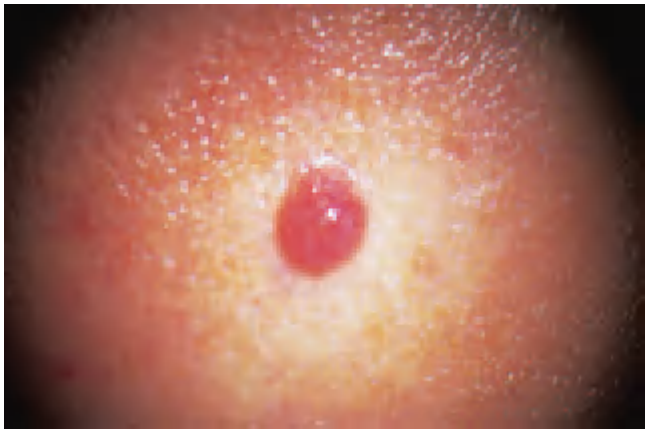

Fig. 38.7 Intradermal naevus. Note the relative lack of pigmentation on this naevus by comparison with Figs 38.5 and 38.6.

The other type of intradermal naevus usually seen only in adult life is a sessile or pedunculated, soft skin tag-like lesion. There is frequently no excess of pigment, or at the most a light-brown surface. They are often seen in the axillae, the groins and on the neck.

It is not uncommon for a naevus on the face or neck to suddenly become swollen and inflamed. Examination shows a tender, firm nodule beneath the naevus, which will usually resolve in a few weeks. This event may follow the plucking of hairs from the naevus or other physical irritation. If the naevus is excised, a foreign-body granuloma will be found in the vicinity of one of the hair roots [11–13]. Fragments of hair shaft can often be demonstrated. The inflammation may recur and leave a fibrous nodule, or one that goes on to calcification or even ossification.

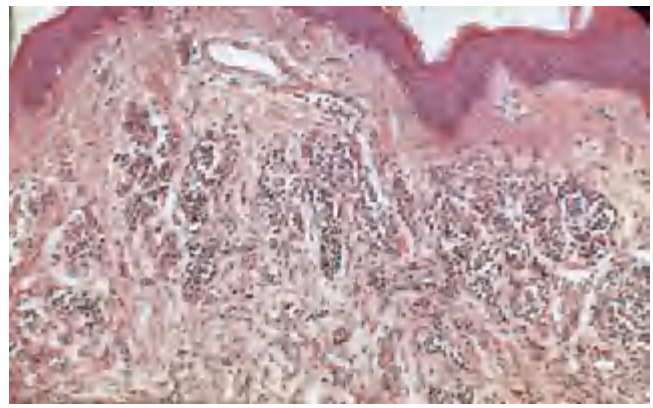

Fig. 38.8 Histology of intradermal naevus. Note the normal overlying epidermis and the maturation of dermal naevus cells, with neural appearance at lower levels.

A small proportion of usually compound melanocytic naevi will show a predominant population of cells with a high volume of foamy cytoplasm. These are called balloon cell naevi because of their pathological appearance [14–16]. The pathological picture is striking, but there is no known biological significance. There is also a malignant counterpart of balloon cell melanoma, but the balloon cell naevus is not a precursor to balloon cell melanoma.

Naevi of the skin adjacent to the eye may be associated with a melanocytic tumour of the iris. Ocular melanosis is also a feature of the naevus of Ota (p. 38.16).

Conjunctival naevi are similar in their behaviour and histology to cellular naevi of the skin. Some lesions involve both the opposed surfaces of the upper and lower eyelid so that when the eyes are shut the naevus takes its normal rounded shape. This shows that the site of the naevus was determined during the period when the lids were fused, i.e. between the second and sixth month of fetal life.

Naevi of the nail matrix or bed may show as a longitudinal brown stripe on the underside of the nail plate (Chapter 62).

Pathology. The possible pattern of evolution of pigmented naevi has been deduced by pathological examination of a large number of lesions removed at different ages [17,18]. In childhood, over 90% of naevi are junctional and show melanocyte proliferation at the dermal–epidermal junction to form small clusters of cells that indent both the overlying epidermis and the underlying papillae [19,20]. The cells have abundant cytoplasm containing melanin granules. The majority of naevi on the palms and soles, and also on the vulva [21], appear to be junctional naevi.

The next stage occurs when some of these melanocytes migrate into the dermis, where they form nests and columns of cells. The speed with which this can occur, even in adult life, is shown in one case of eruptive cellular naevi, where biopsy of a lesion not more than 3-weeks old showed a band of densely packed cells in the papillary dermis [22].

In the compound naevus both junctional proliferation and dermal cells are present. The dermal cells accumulate in the papillary body and extend more deeply around appendages and neurovascular bundles. The more superficial cells (type A) remain recognizable as naevus cells, continuing to form melanin, which is taken up by melanophages in the stroma. The deeper cells (type B) are smaller and usually contain no melanin, although they have been shown to possess tyrosinase and premelanosomes [23,24]. The more superficial cells may throw the epidermis into a series of folds by expanding dermal papillae. The deeper cells are arranged as a band (type B) or as arborizing columns in the deeper dermis, when the cells become spindle shaped (type C).

If the junctional melanocytes stop proliferating, and the overlying epidermis returns to normal, the naevus becomes *intradermal*. Many intradermal naevi have neuroid tissue in their deeper parts, and some are composed of little else. These neural areas in the deeper areas of intradermal naevi are sometimes referred to as Masson's naevic corpuscles, after Pierre Masson who first evolved the theory of evolution of melanocytic naevi [18]. The similarity of these naevic corpuscles to Meissner's corpuscles, the sensory nerve endings found in large numbers on the fingertips, has been confirmed by electron-microscopic studies [20]. The deeper parts of intradermal naevi give a strongly positive cholinesterase reaction, and even the type A cells may react [20,25]. The stroma around the dermal naevus cells is loose and fibrillar, the nests of cells are often enclosed by flattened cells that resemble endothelium and may give an erroneous impression of naevus cells in vessels. Multinucleated naevus cells are commonly seen, but mitotic figures are rare and occur only in the type A cells. It is not uncommon to find an occasional 'ballooned' naevus cell, and in rare instances the entire naevus may be composed of balloon cells with vacuolated cytoplasm [15].

Many intradermal naevi show features very similar to nerve tissue with a sparse naevus-cell population, which is fibrillar in configuration. Schwann cells may be observed in such lesions, and cholinesterase-positive fibres can be demonstrated [26]. These observations give support to the view that naevi are basically hamartomas of both melanocytic cells and neural tissue.

The end stage of a melanocytic naevus is a flesh-coloured, pedunculated skin tag in which very few naevus cells are observed [27]. Pigment is sparse, and fat cells may be present.

Compound and intradermal naevi show related abnormalities of other structures. Pilosebaceous follicles may be large and distorted, dermal collagen may appear disturbed or displaced by fat cells, the vascular supply may be increased and there is frequently a network of non-myelinated nerve fibrils [28]. Hairs from the large follicles may pierce the wall of the follicle and produce a granulomatous foreign-body reaction. Calcification, and even ossification, can follow [11–13].

Diagnosis [29]. The clinical differential diagnosis of melanocytic naevi includes freckles, lentigines, non-melanocytic lesions such as seborrhoeic keratoses and dermatofibroma and, most importantly, early malignant melanoma.

Freckles are usually relatively easy to clinically distinguish from naevi because of their seasonal variation, but it may be clinically impossible to differentiate clinically between lentigines and small junctional naevi.

In older adults, there may be difficulty in clinical differentiation between seborrhoeic keratoses (Chapter 36) and larger papillomatous compound naevi. The seborrhoeic keratosis usually has a 'stuck-on' appearance with its bulk above the normal skin contour, and the colour is usually more grey-brown than the typical melanocytic naevus. In addition, the surface is usually dull and pitted, with a tendency to crumble, and does not reflect light in the same way as the naevi.

The most important clinical differential diagnosis is from early malignant melanoma. Any pigmented lesion in an adult that is growing or changing in any way should be examined carefully. A history of very rapid growth over days rather than weeks and tenderness suggests the development of an underlying granuloma rather than malignant change. Features strongly suggestive of an early malignant melanoma either developing *ab initio* or in a pre-existing naevus are an irregular outline to the lesion and the presence in the lesion of several shades of brown and black. Either of these features, particularly in association with a history of recent growth or change and a history of altered sensation in the pigmented lesion, are indications for excision biopsy with a narrow margin of normal skin and pathological examination.

The techniques of dermatoscopy and of computerized diagnosis are discussed in the section on malignant melanoma (p. 38.35). Several groups have produced useful atlases of the clinical dermatoscopic appearances of melanocytic naevi and the differences between these naevi and malignant melanoma. While both sensitivity and specificity for accurate differentiation between benign and malignant melanocytic lesions have improved greatly in the past decade, the technique is not as accurate as the gold standard of pathology, so excision biopsy and pathological examination is still required in most cases. Excision may not, however, be required if the differentiation is between a pigmented lesion of melanocytic origin

and one in which the pigment is not melanin as in an angioma or incidental as in a seborrhoeic keratosis. In both of these conditions the dermatoscopic appearance is reliably consistent and enables accurate diagnosis without the benefit of pathology.

Management. The great majority of junctional, compound or intradermal naevi are not premalignant lesions, and removal is therefore not required on medical grounds, although a few may merit local excision on cosmetic grounds. There is no evidence to support suggestions that naevi on sites of friction such as the waistband should be removed because of a greater risk of malignant change. Naevi on the palms, soles and genitalia are more frequently of the junctional or compound type than those elsewhere. The incidence of melanoma relative to the prevalence of naevi in these sites does not, however, suggest that these lesions have a greater malignant potential than naevi in other sites, and therefore prophylactic removal is neither necessary nor logical.

If a melanocytic naevus is excised for whatever reason, it should always be sent for pathological examination. In general, scalpel excision with a narrow margin of 1–2 mm of normal surrounding skin is recommended and preferred to shave biopsy, which frequently fails to completely remove the deeper dermal cells [30,31]. When this occurs, residual naevus cells may proliferate and give rise to a pathological picture very like an early melanoma. This picture has been termed 'pseudomelanoma' or, more appropriately, a traumatically activated naevus. This can give rise to needless anxiety and is avoidable.

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Spitz naevus [1,2]

SYN. SPINDLE AND EPITHELIOID CELL NAEVUS; JUVENILE MELANOMA

Definition. A compound naevus variant, seen most commonly in children, which has distinctive pathological features. These features may make the pathological differential diagnosis from malignant melanoma extremely difficult.

Incidence. Spitz naevi are usually diagnosed in the first two decades. Although Spitz naevi can be diagnosed in the eighth and ninth decades, this is unusual, and the pathological differential diagnosis should be carefully considered. The sexes are equally affected. Spitz naevi comprise less than 1% of melanocytic naevi removed from children [3].

Clinical features. The naevus usually appears in early childhood as a firm, rounded, red or reddish-brown nodule. A small proportion may show a surrounding halo [4]. The colour is due to excessive vascularity and the naevus can usually be bleached by firm pressure or diascopy to show the residual degree of true melanin pigmentation (Fig. 38.9).

The lesions usually grow rapidly over a period of 3–6 months and may reach diameters of 1–2 cm. The surface

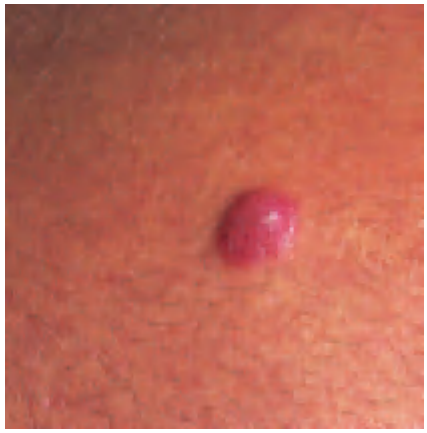

Fig. 38.9 Spitz naevus showing a uniform red facial lesion.

can remain smooth, with a thin fragile overlying epidermis. This may cause bleeding and crusting after minor injury.

The commonest sites for Spitz naevi are the face, particularly the cheeks, and the legs, but other areas may be affected. After rapid initial growth they may remain static for years.

A striking and unusual appearance is that of *multiple Spitz naevi* or *agminate Spitz naevi* [5–10]. This entity appears to be composed of a large number of pathologically independent small Spitz naevi in the same anatomical area. The individual Spitz naevi develop rapidly and thereafter remain relatively static. The pattern is similar to that seen in the satellite lesions that develop around a pyogenic granuloma, and is more common in children than in adults.

Spitz naevi in adults may occur on any site and tend to be more deeply pigmented than those in children. They are well-demarcated, firm, dome-shaped lesions.

Pathology [11,12]. The Spitz naevus is a compound naevus variant. There is frequently a degree of epidermal acanthosis overlying the naevus cells, in the absence of any upward epidermal invasion by naevus cells. The melanocytes at the dermal–epidermal junction are often separated from the underlying dermis by a cleft, and may be associated with amorphous pink globules. These are thought to be degenerating keratinocytes and are called *Kamino bodies*. They are frequently seen in Spitz naevi, but their presence is neither totally sensitive nor specific for Spitz naevi, as they may also be present in early melanoma.

The Spitz naevus cells may be either spindle shaped and stream into the dermis in interlacing bundles, or epithelioid and arranged in clusters with giant and multinucleated naevus cells among them. Mitotic figures may occur but abnormal mitoses are not seen. Mitotic figures are rarer in the deeper naevus cells, and their presence should alert the observer to the possibility that the lesion is in fact a spitzoid melanoma. The deepest naevus cells show some degree of maturation and are usually smaller than those seen at the dermal–epidermal junction. The dermal vessels are usually dilated, and the stroma may be oedematous and infiltrated with lymphocytes. Melanin is rarely abundant, and may often be absent [13–15].

The important and difficult pathological differential diagnosis is the separation of true benign Spitz naevi from spitzoid malignant melanoma. Two useful studies have recently tried to identify pathological factors that may help in this situation. Crotty and colleagues [16] have identified symmetry of the lesion from side to side, the presence of Kamino bodies and the uniformity of cell nests or sheets in the dermis as features of benign Spitz naevi. In contrast, they identify abnormal mitoses, mitotic counts of over $2/mm^2$ and deep mitoses as suggestive of spitzoid melanoma. Spatz *et al*. [17] have identified age over 10 years, diameter over 10 mm, ulceration, invasion to subcutaneous fat and mitotic activity of over $6/mm^2$ as suggestive of spitzoid melanoma rather than Spitz naevi.

Diagnosis. Most Spitz naevi in children are red rather than brown, and are likely to be confused clinically with vascular tumours, pyogenic granuloma, histiocytoma, juvenile xanthogranuloma or granulomas such as lupus vulgaris. When the surface is warty, distinction from an epidermal naevus or occasionally even a common wart may be difficult. Pigmented Spitz naevi may be clinically indistinguishable from compound melanocytic naevi or spindle cell naevi of Reed (see below).

The main problem with the accurate diagnosis of Spitz naevi arises when a pathologist is sent a naevus without an adequate history and, in particular, without being given the age of the patient. In this situation it can be easy to overdiagnose melanoma on the pathological appearance. It is therefore very important for the clinician and pathologist to liaise well in arriving at the correct diagnosis of suspected Spitz naevi. Malignant melanoma is rare before puberty, although it does occur, but the balance of probabilities in spitzoid lesions excised in the first decade of life lies with the lesion being a true Spitz naevus rather than a spitzoid melanoma. This is particularly true if the cell type is predominantly spindle. In the case of lesions removed from adults, the pathological differential becomes very much more difficult, and it may be necessary to admit uncertainty and recommend a period of follow-up after complete scalpel excision. It is worth remembering that one of the original 12 cases identified by the late Sophie Spitz as Spitz naevus rather than melanoma did in fact later metastasize [1].

The concept of a Spitz naevus with a capacity for metastasis to the draining regional lymph nodes but not beyond has been proposed. Six patients who had an initial diagnosis of malignant melanoma later modified to Spitz

naevus had elective lymph node dissection. In all six cases Spitz-type naevus cells were found in the nodes with no evidence of metastasizing malignant melanoma beyond these nodes on short-term follow-up [18].

Treatment. Local excision with a narrow margin of 1–2 mm of normal skin is usually required to confirm the clinical diagnosis. Local recurrence has been recorded in both isolated and agminate lesions [19].

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Pigmented spindle cell naevus of Reed [1]

Definition. A heavily pigmented, predominantly junctional naevus. This naevus is considered by some to be a variant of a Spitz naevus rather than an entity in its own right.

Spindle cell naevus of Reed was first described in 1975 [2] and it is important to be aware of its existence when considering a possible diagnosis of malignant melanoma, as it may cause confusion on both clinical and pathological grounds.

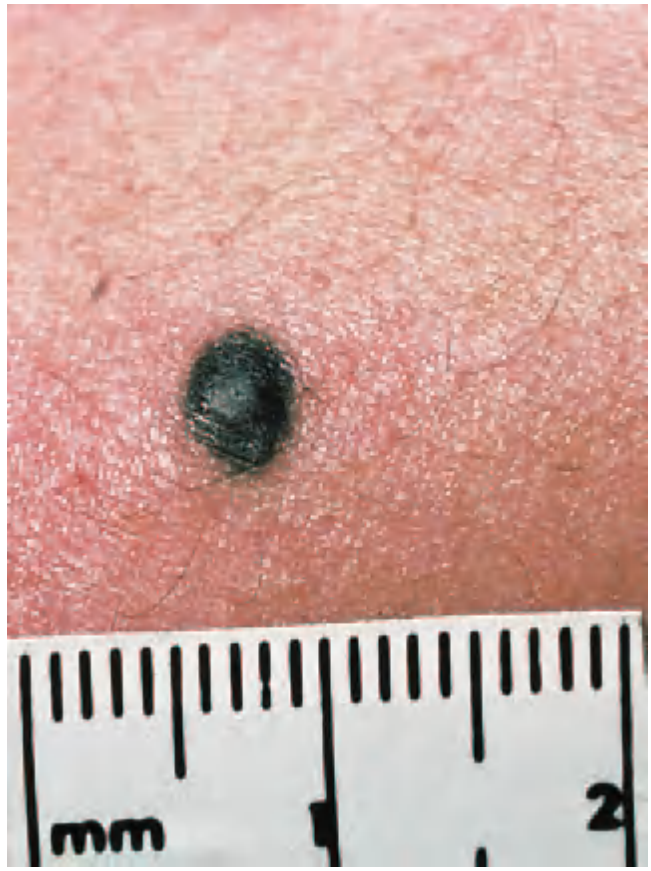

Fig. 38.10 Pigmented spindle cell naevus of Reed. A deeply pigmented but regular lesion on the thigh of a young female.

Clinical features. The majority of patients reported are young females, and the lesions are most commonly seen on the thighs [2]. They are densely pigmented, irregularly shaped dark-brown or black nodules and are usually isolated (Fig. 38.10).

Pathology [3,4]**.** The lesions show well-demarcated junctional melanocytic activity with large quantities of melanin pigment. Spindle-shaped melanocytes proliferate downwards towards the dermis, but there is no upward movement of naevus cells through the epidermis, and usually very little, if any, intradermal component. Some naevus cells may be seen in the papillary dermis, but these naevi do not involve the reticular dermis. A sparse lymphocytic infiltrate is seen at the base of the naevus cells, but the lesion is relatively small and circumscribed. As with Spitz naevi, symmetry is an important feature.

Treatment. This lesion should be narrowly excised for pathological diagnosis.

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Desmoplastic naevus [1,2]

Definition. A firm, predominantly intradermal naevus with a characteristic thick, collagenous stroma surrounding melanocytic naevus cells.

As with spindle cell naevi of Reed, these naevi may be considered as a subset of Spitz naevi.

The age of affected patients and the body site suggests that these lesions are not precursors to the desmoplastic melanoma (p. 38.31).

Clinical features. Desmoplastic naevi may show little or no clinically visible melanocytic pigmentation, and may appear as pink or red, firm, raised nodules. The lesions may be woody hard, and the clinical differential may include a keloid, although there is no history of injury (Fig. 38.11).

Pathology. This lesion was well described by Barr *et al*. in 1980 [1] and has a very striking and characteristic pathological appearance. The lesions are predominantly intradermal, and a relatively small number of naevus cells will be found embedded in thick collagen fibres. The naevus cells are usually distributed singly through the stroma rather than in clumps, and may be very large and bizarre, with copious cytoplasm, which may contain inclusions. The nuclei look unusual but not frankly malignant, and mitotic figures are rare. Mitotic figures if present are normal [2] (Fig. 38.12).

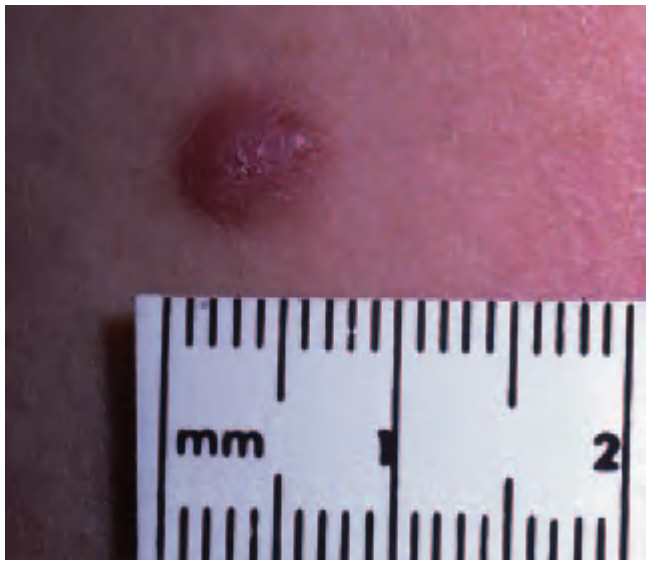

Fig. 38.11 Clinical appearance of desmoplastic naevus. Note the red, keloid-like appearance.

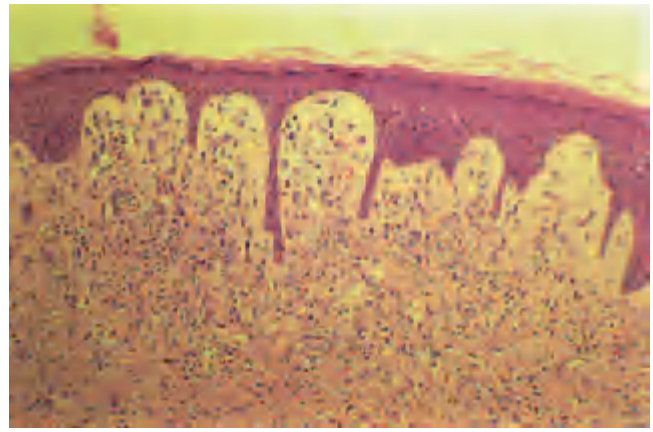

Fig. 38.12 Histology of desmoplastic naevus. Note the presence of cytologically unusual naevus cells set in a dense collagenous stroma.

Treatment. Excision is usually required to establish a diagnosis. Incomplete excision is common due to the unexpected extent of the dermal infiltration of the naevus cells.

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Halo naevus [1]

SYN. SUTTON'S NAEVUS

Definition. A melanocytic naevus surrounded by a depigmented halo of otherwise normal skin.

Incidence and epidemiology. Halo naevi are relatively common, particularly in older children and young teenagers. They are frequently multiple. Circulating anti-melanoma antibodies [2] have been detected in a proportion of patients with these lesions, but their role in the development of the halo and the subsequent disappearance of the naevus is not established.

Clinical features [3–5]**.** These lesions have a characteristic appearance and progression. A halo of depigmentation will appear around a pre-existing melanocytic naevus, and on white skin this will usually be seen during the summer months when the rest of the epidermis has acquired a tan, showing the non-tanned halo in sharp contrast (Fig. 38.13). The back is the commonest site and several naevi may develop haloes simultaneously, while other adjacent naevi remain unchanged. Over the next

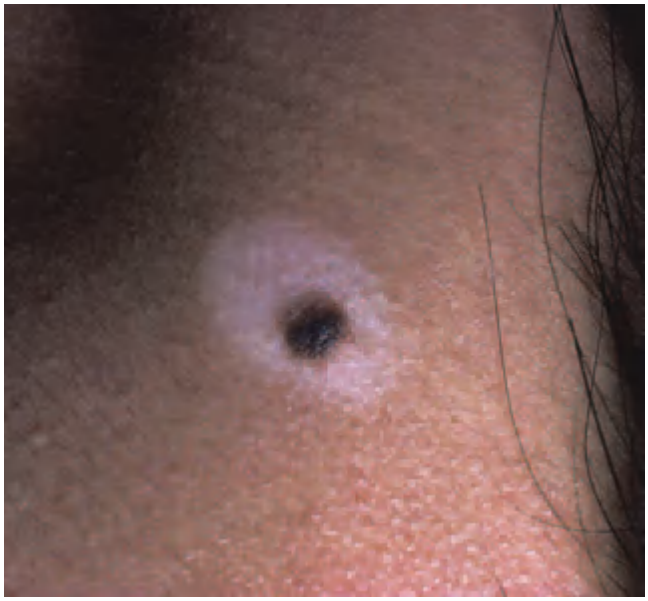

Fig. 38.13 Clinical appearance of a halo naevus.

few months, the central naevus will gradually disappear leaving a macular area of non-pigmented skin. This depigmented area may persist for years and only gradually return to a normal colour. On biopsy, all traces of the original naevus will be found to have disappeared.

Pathology [6]**.** These lesions are variants of compound melanocytic naevi, and at the time of appearance of the halo they show a very striking lymphocytic infiltrate admixed with the intradermal naevus cells. The use of the antibodies to S 100 protein and NKIC3 will reveal a loss of epidermal melanocytes in the halo area.

Management. Reassurance rather than excision is recommended in young people, particularly if the lesions are multiple. The patient should be warned that the depigmented areas will burn badly in sunlight because of the lack of melanocytes and should be advised to use a sunscreen.

In older patients, the differential diagnosis may include an early superficial spreading melanoma with surrounding depigmentation. In this case the surrounding area of depigmentation is usually irregular, and the central pigmented area may also be irregular in both shape and pigmentation. Obviously if there is any clinical doubt, excision biopsy and pathological confirmation must be obtained.

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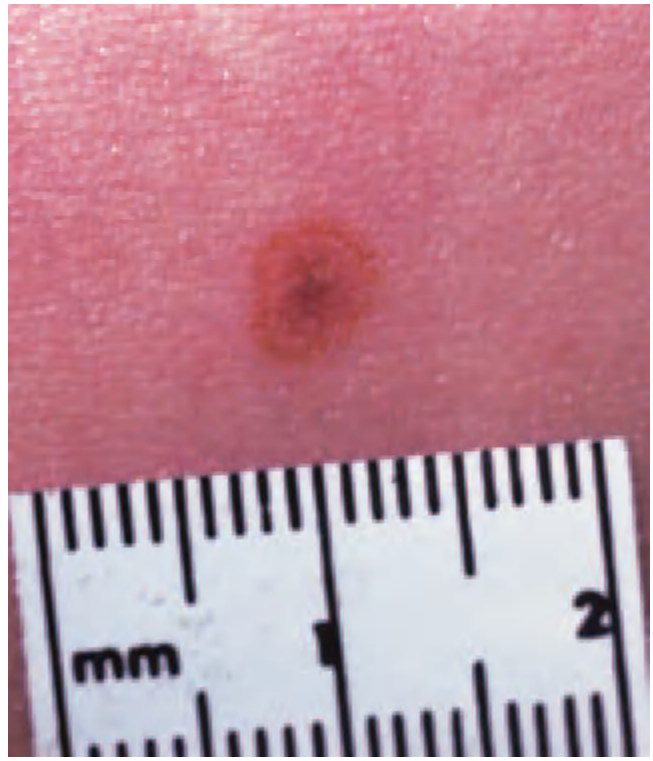

Fig. 38.14 Cockade naevus (naevus en cocarde). Note the darker outline to this lesion.

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Cockade naevus

SYN. KOKARDENNAEVUS; NAEVUS EN COCARDE

This rare variant of the pigmented naevus was first described by Mehregan and King in 1972 [1]. Since then, several further cases have been described [2,3]. The lesion is named because of its resemblance to a rosette. All cases so far reported are in young patients with multiple target-like naevi with concentric circles of increased melanin pigmentation. The central lesion in all cases would appear to be a junctional naevus (Fig. 38.14).

REFERENCES

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Meyerson's naevus [1]

This name is used to describe a melanocytic naevus that

has developed a surrounding inflammatory reaction. The naevus may be pruritic, and there may be overlying scaling.

Clinical features. These lesions present as melanocytic naevi with associated epidermal scaling and a halo of inflammation. The original report was of multiple naevi developing this associated inflammatory reaction simultaneously. Four cases have recently been described of this inflammatory reaction developing around atypical naevi [2]. The central naevus may disappear, leaving a depigmented area [3].

Pathology. The pathology is usually that of a banal, usually compound, naevus with associated spongiotic dermatitis in the overlying dermis.

Treatment. These lesions are frequently excised as the appearance of inflammation in a pre-existing naevus gives rise to concern that the naevus is undergoing malignant change. If this is not a concern, they will settle to a normal naevus appearance after 1–2 week's application of a moderately potent topical steroid.

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3 Ramon R, Silvestre JF, Betlloch I *et al*. Progression of Meyerson's naevus to Sutton's naevus. *Dermatology* 2000; **200**: 337–8.

Speckled and lentiginous naevus

This term is recommended in preference to the term naevus spilus, which is frequently confused with Becker's naevus, a non-melanocytic proliferation (Chapter 39).

Clinical features. Speckled and lentiginous naevus is a relatively rare entity [1]. The lesion may be several centimetres in diameter and is clinically a combination of a flat, macular, lentiginous component, often of a darker shade than the surrounding skin, with even darker central lentigo-like lesions. In addition to these features there are elevated darker-brown areas (Fig. 38.15). It may also coexist with a blue naevus [2].

Pathology. Pathological examination shows, as the clinical appearance suggests, a large lentiginous area with superimposed individual compound naevi.

Management. There have been reports of malignant change in these lesions [3–6]. In view of this and the relative rarity of the lesions, and of their cosmetic appearance, local excision should be considered if this is feasible. This is often not practical as the area involved would require grafting and it may be more practical to photograph the lesion for future reference, and to only excise it if there are subsequent signs of growth or change.

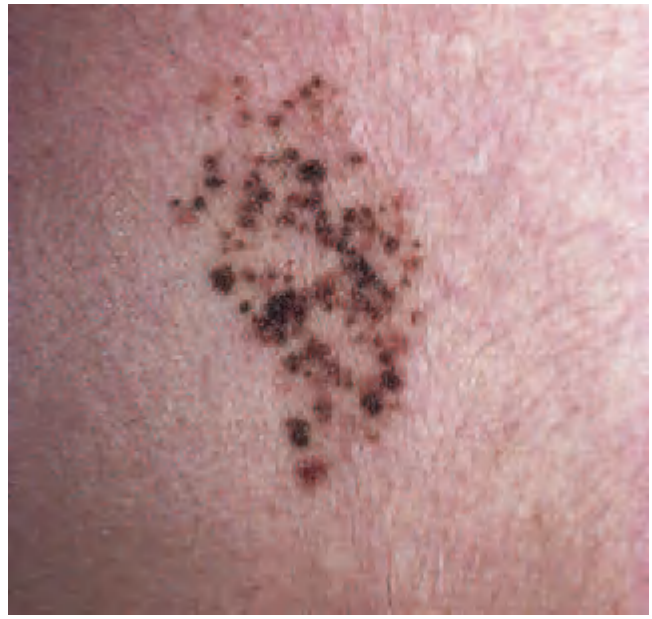

Fig. 38.15 Speckled and lentiginous naevus. Note the variation in colour of this lesion.

REFERENCES

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Dermal melanocytic naevi

All the melanocytic naevi described in the preceeding pages are believed, on the basis of biopsies from multiple lesions in patients at varying ages, to have developed from epidermal melanocytes that completed their migration from the neural crest to the dermal–epidermal junction in fetal life—the so-called 'abtropfung' (dropping down) theory.

The lesions described below differ in that they are believed to arise from dermal melanocytes that have become arrested in the dermis during fetal life and tissue modelling and have never reached their normal site in the basal layer of the epidermis. Many mammals have a physiologically normal population of dermal melanocytes but

these are not commonly observed in human dermis, with the possible exception of the Mongolian spot [1].

Experimentally induced melanocytic tumours in animals frequently have a morphological resemblance to these dermal naevi [2,3].

Mongolian spot

Definition. Macular blue-grey pigmentation present at birth on the sacral area in normal infants of darker-skinned races.

Incidence. These are present in over 90% of infants of Mongoloid race, and have been found in about 1% of white European infants, the incidence being highest in the Mediterranean region. The incidence in other races lies between these extremes. It has been found in some 80% of East African infants [4].

Clinical features. The pigmentation is macular, diffuse and more or less uniform, slate blue to grey and usually relatively faint. The patches are usually rounded or oval in shape, up to 10 cm or so in diameter, and usually single but occasionally multiple. The lumbosacral region is the common site, and the buttocks, flanks or even shoulders may be affected in extensive lesions. The pigmentation develops in fetal life, increases in depth for a period after birth and then diminishes. It usually disappears during the first decade, but has occasionally persisted into adult life.

Pathology. Melanocytes are dispersed in a ribbon-like pattern between the collagen fibres and around the neurovascular bundles of the dermis. They run parallel to the skin surface and contain very fine granules of melanin. There is no disturbance of the pattern of collagen and elastic fibres. Melanophages are not found. The last two characteristics enable it to be differentiated from blue naevus.

Management. No treatment is needed.

Blue naevus and cellular blue naevus [5]

Definition. An area of blue or blue-black dermal pigmentation produced by aberrant collections of pigment-producing but benign melanocytes.

Incidence and aetiology. Blue naevi are relatively common. A ratio of 2.5 : 1.0 of female to male patients in a recent series probably reflects the relative degree of either anxiety or wish for removal. Blue naevi are thought to arise because of arrested migration of melanocytes migrating towards the dermal–epidermal junction.

Clinical features. There is an area of diffuse blue pigmentation, usually slightly raised and smooth surfaced. Blue naevi may be found on any site but patients with facial naevi most often request excision for cosmetic reasons.

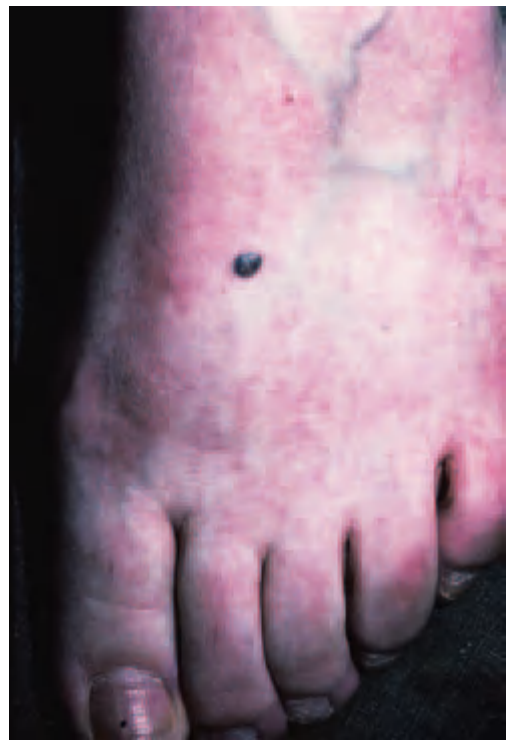

Fig. 38.16 Clinical appearance of cellular blue naevus on the dorsum of the foot.

The cellular blue naevus is seen most often on the extremities, particularly the dorsa of the hands and feet (Fig. 38.16), the buttocks and the face. The onset may be before birth, but lesions frequently first appear around puberty. Progressive growth is rare, and malignant transformation very rare [5,6] (p. 38.17).

Pathology. In the common or classic variety, bipolar and dendritic melanocytes lie singly or in masses in the dermis (Fig. 38.17). They tend to be profuse in the lower dermis and are often concentrated around appendages or in the perivascular and perineural areas. Deeper tissues may be involved. The melanocytes are relatively inconspicuous, containing fine granules of melanin dispersed through their cytoplasm. There are varying numbers of melanophages in which the melanin granules are coarse and more closely clumped.

The cellular blue naevus is composed of the same elements as the common blue naevus, but in addition possesses islands of larger cells arranged in a neuroid ('pigmented neurofibroma') or sarcomatoid fashion. The appearance may raise suspicions of malignant melanoma, but the lack of mitotic activity, vascularity or inflammatory reaction, the regularity of the cells and the absence of junctional proliferation in continuity with the cellular masses enable the distinction to be made [7–9].

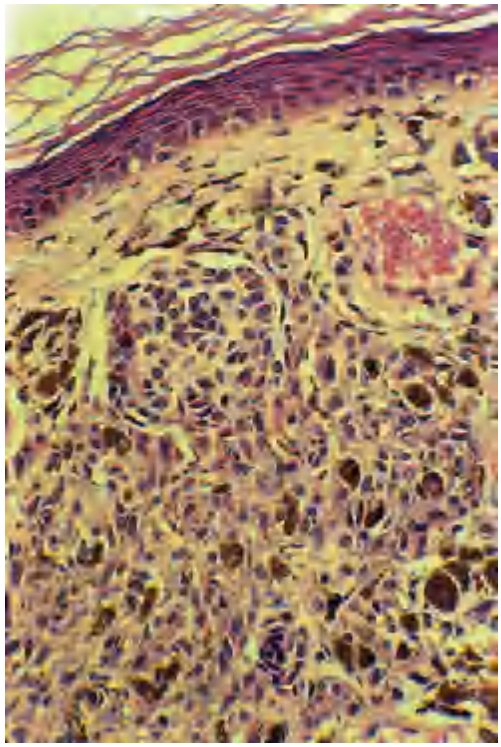

Fig. 38.17 Histology of blue naevus. Note the normal overlying epidermis with spindle cells and dense pigmentation in underlying dermis.

The compound blue naevus is a more recently described entity [10,11] with additional dendritic cells in the overlying epidermis. This lesion may clinically be very similar to early malignant melanoma.

Multiple epithelioid blue naevi may be associated with the Carney complex (Chapter 59). This is a genetically transmitted multitumour syndrome involving both blue naevi and lentigines, and also cardiac myxomas, endocrine tumours and schwannomas [12].

A blue naevus may be present in association with a compound naevus, and the resulting lesion is then called a *combined naevus* (see below).

Malignant blue naevus is a very rare entity, and in some cases it is not possible to differentiate between classic malignant melanoma and malignant change within a blue naevus. Malignant blue naevus appears to develop more often on the scalp, and pathologically have a sheet-like growth pattern. Necrosis and atypical mitotic figures are diagnostic features which will distinguish these lesions from benign classic or cellular blue naevi [13].

Diagnosis. The condition is characterized by its colour and must be differentiated from other dermal melanoses. It is a relatively static, non-progressive lesion.

Treatment. None is needed. Excision may be justified on cosmetic grounds. Rare malignant blue naevi should be widely excised as these tumours are aggressive and have a high recurrence rate

Naevus of Ota [14,15]

SYN. NAEVUS FUSCOCAERULEUS OPHTHALMOMAXILLARIS

Definition. An extensive, blue, patch-like area of dermal melanocytic pigmentation of the sclera and the skin adjacent to the eye due to the presence of dermal melanocytes [16].

Incidence. This disorder is not uncommon in Asian people but is comparatively rare in other races. Unlike the Mongolian spot, it is not usually visible at birth, becomes progressively darker in childhood and persists in adult life.

Clinical features. The pigmentation is often speckled and is composed of deeper bluish and more superficial brownish elements, which do not always coincide. The two colours are perhaps best seen in the eye, where the affected sclera is blue and the conjunctiva brown. The brown pigmentation is patchy and may be patterned in a reticular or geographical way; the blue pigmentation is more diffuse. The areas involved are the eyelids, the bulbar and palpebral conjunctiva and the sclera, and the cheeks, forehead, scalp, alae nasi and ears. The mucosa of the palate and cheeks may also be affected. The distribution is usually restricted to the first and second divisions of the trigeminal nerve, but rarely patches may occur on the trunk [1].

The pigmented spots usually appear in childhood and increase in number and extent to become confluent in some areas [17]. There is one report of the onset following trauma, and in another the ocular pigmentation became much more pronounced after an attack of conjunctivitis. The distribution is usually, but not always, unilateral.

In very rare instances malignant melanoma has developed in naevus of Ota [5].

Pathology [18,19]. The features are the same as those of Mongolian spot.

Treatment. Laser therapy may be of value, and cosmetic camouflage may also be useful.

Naevus of Ito [20]

This type of dermal melanocytosis involves the acromioclavicular region and the upper chest and, like the naevus of Ota, is largely confined to the Japanese (Fig. 38.18).

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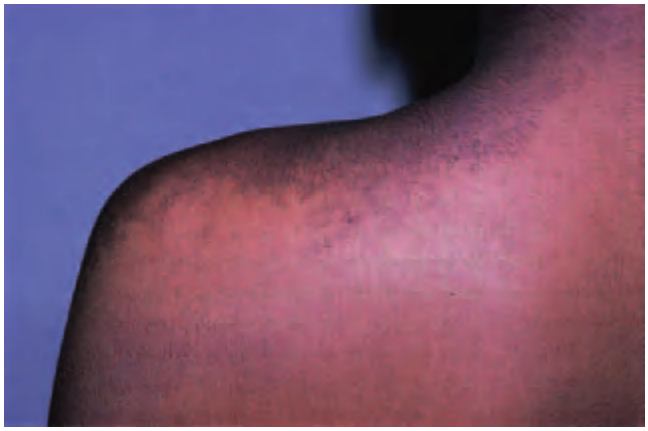

Fig. 38.18 Naevus of Ito, showing typical distribution over shoulder area.

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Naevus fusco-caeruleus zygomaticus

A number of cases of this entity have been described from China and Japan [1]. The lesions are speckled naevi on the upper cheek, and microscopy shows bipolar pigment-bearing cells in the upper dermis only, in contrast to the naevus of Ota in which pigment-bearing cells are seen throughout the dermis.

REFERENCE

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Malignant blue naevus [1]

Definition. A rare malignancy often confused with melanoma.

Pathology. Malignant cells of melanocytic origin are seen in the deeper dermis with no overlying abnormality of epidermal melanocytes. Mitotic figures are rare [2], but the presence of any at all should suggest the diagnosis. Necrosis within the lesion is another important diagnostic sign, which is not seen in benign blue naevi.

Clinical features. Malignant blue naevus usually arises in a cellular blue naevus, and the scalp is the commonest site (Fig. 38.19). Expansion of a previously identified blue naevus should suggest the diagnosis. Metastases do occur and can cause death [3].

Treatment. Wide surgical excision is required.

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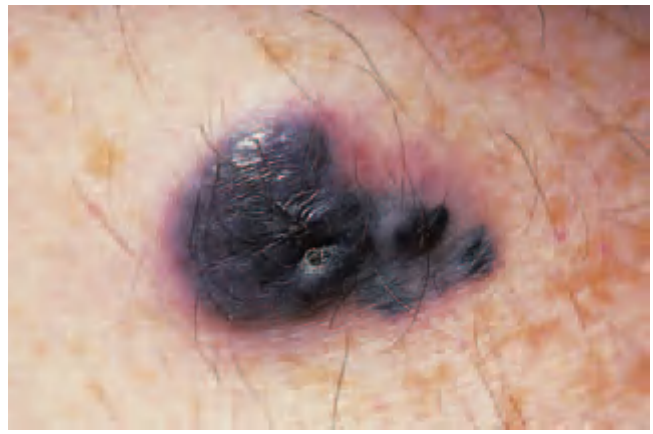

Fig. 38.19 Malignant blue naevus which has arisen in a previous cellular blue naevus. This lesion subsequently metastasized to lymph nodes.

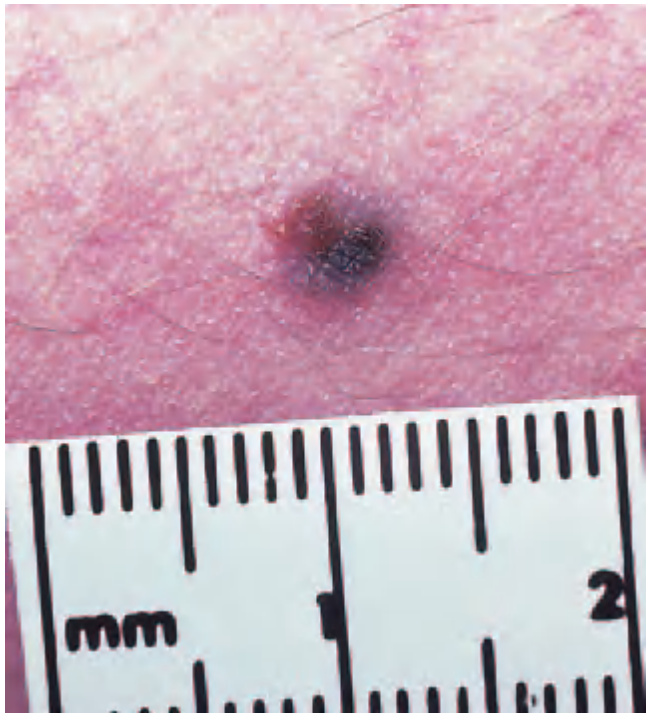

Fig. 38.20 Combined naevus showing typical combination of pale-brown and deeper blue-black pigmentation.

Combined naevus [1]

Definition. A melanocytic naevus formed by a combination of epidermally and dermally derived naevus cells.

Clinical features. Combined naevi show clinical evidence of their dual origin in that they are multicoloured, having both a sandy brown component and a blue-black component. They are frequently relatively large and may have an irregular border (Fig. 38.20). This trio of features means that they are frequently mistaken for early melanoma.

Pathology [2]**.** The essential pathological feature of a combined naevus is the combination of some degree, usually slight, of junctional activity at the dermal–epidermal junction together with the presence in the dermis of the heavily pigmented bipolar dendritic cells characteristic of a blue naevus.

Treatment. Excision biopsy and pathological examination is usually necessary to confirm the clinical diagnosis and exclude the possibility of melanoma.

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Deep penetrating naevus

Clinical features. This naevus variant is rare. Clinically it may be a deep blue or black colour with a diffuse irregular lateral margin. The clinical differential diagnosis is therefore frequently melanoma.

Pathology. This naevus frequently has features of both a compound and a blue naevus, making it a variant of the so-called combined naevus, but with minimal junctional activity. The diagnostic feature is the presence of clusters of widely separated but deep naevus cells throughout the dermis. Frequently these clusters are around the skin appendages. The cytology is of a spindle cell population and mitotic figures are rare [1].

REFERENCE

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Congenital melanocytic naevus

Incidence and epidemiology [1,2]**.** One to three per cent of all newborns have a pathologically confirmed congenital melanocytic naevus [3], although clinical studies have suggested that twice as many infants have pigmented lesions clinically compatible with this diagnosis [4]. In addition, there is a subsection of naevi that develop in the first 5 years of life but that were not present at birth which have clinical and pathological features much more compatible with congenital naevi than with acquired naevi. These naevi are frequently referred to as congenital-type or early-onset naevi.

Congenital pigmented naevi have been arbitrarily divided into three size ranges. Small lesions have maximum diameters of less than 1.5 cm, intermediate-sized lesions have maximum diameters between 1.5 and 20.0 cm and giant lesions have diameters of over 20 cm. The great majority of congenital naevi are small, although the published studies in the literature, particularly in relation to the malignant potential of congenital naevi, mainly relate to the giant, or garment, type [5–8].

Clinical features. At birth, congenital naevi may be very pale macular lesions, which may enlarge, darken and develop terminal hair over a period of years (Figs 38.21 & 38.22). Early-onset or congenital-type naevi may first become visible in the 5 years after birth.

Small and medium-sized congenital naevi usually grow less rapidly than the infant so that their surface area relative to the whole body surface area is reduced, but they frequently darken with age and may develop outgrowths of coarse terminal hair. There is frequently a striking increase both in pigmentation and hair growth at puberty.

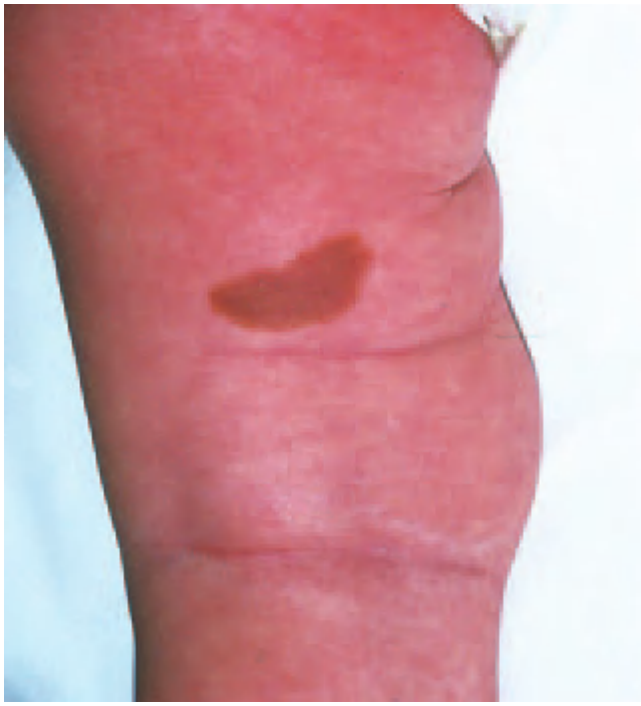

Fig. 38.21 Small congenital naevus on the leg of a neonate.

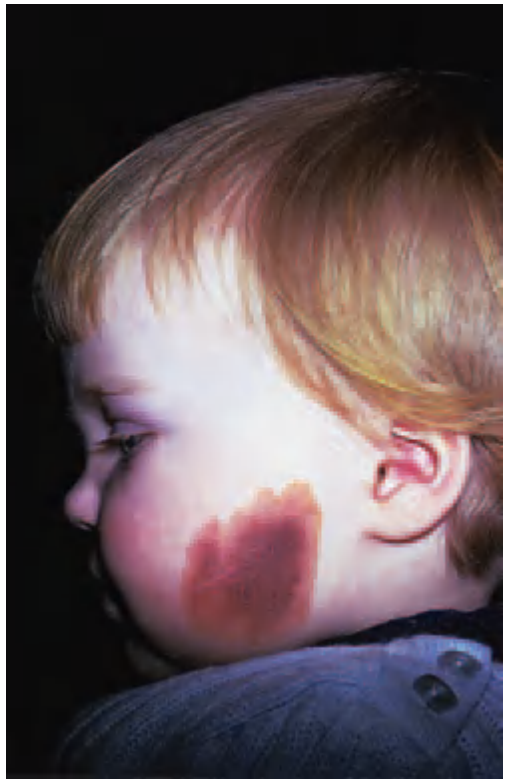

Fig. 38.22 Medium-sized congenital naevus on the cheek of a toddler.

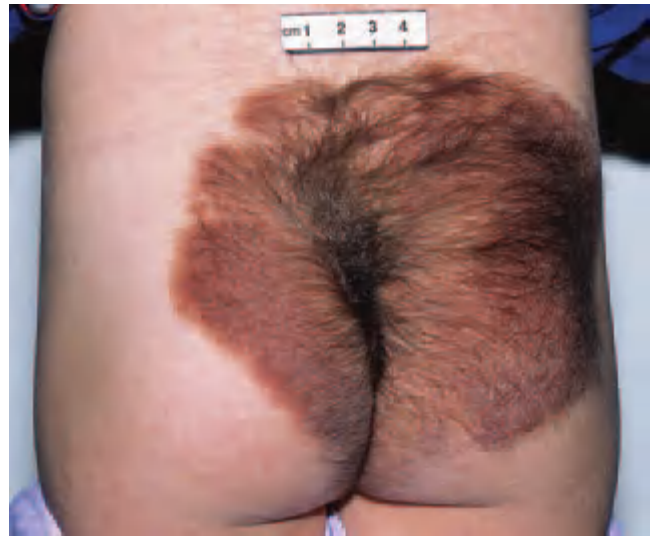

Fig. 38.23 Giant or garment congenital naevus on the lower back area of a child.

The rare giant, garment or bathing-trunk naevus is obvious at birth and distressing to parents. The common site is the lower back and thigh area and a very large proportion of the infant's surface area may be involved. There may also be large numbers of smaller congenital naevi present on the infant's skin. As the infant grows the surface may become rugose or warty and nodules can develop within a large naevus. The hairy component, which occurs in 95% of lesions, tends to become more prominent in late childhood, but at this stage the naevus itself ceases to thicken and may become paler. The hair growth pattern may have a 'vortex' distribution, often centred on the midline in giant naevi of the back (Fig. 38.23).

There may be associated abnormalities such as meningeal involvement, spina bifida or meningocoele when the naevus is over the vertebral column, or club-foot and hypertrophy or atrophy of the deeper structures of a limb. Other hamartomas, such as vascular naevi, lipomas or von Recklinghausen's disease, may be found in patients with extensive congenital pigmented naevi [9].

Pathology [10–13]**.** The pathological features of a congenital melanocytic naevus are the presence of an increased number of melanocytes in the epidermal basal layer in a lentigo-like pattern, a relatively cell-free papillary dermis approximating to a Grenz zone, and aggregates of dermal naevus cells in the lower areas of the dermis. This contrasts with the intradermal component of acquired melanocytic naevi in which the bulk of the intradermal naevus cells are found in the papillary dermis.

In congenital naevi, naevus cells are found not just around but also infiltrating the skin appendages. The presence of these cells in the skin appendages is a relatively specific feature of congenital naevi [13].

Many congenital melanocytic naevi are hamartomas because of the presence of increased numbers of hair follicles and other skin appendages. Large congenital melanocytic naevi over the posterior midline are frequently associated with intracranial melanosis, and over the lower spine area they may be found in association with spina bifida occulta.

Management. There are two main problems to be considered in managing these lesions. The first is the potential of these lesions for malignant change and the resulting need for prophylactic removal [14–17], the second is the cosmetic concern, particularly in the case of the giant lesions.

There are many case reports in the literature of malignant change in giant pigmented naevi, but these reports are likely to overestimate the true frequency of this occurrence because of the tendency to report positive events. The best study involving a large population of patients followed for many years comes from Scandinavia and reports a lifetime incidence of malignant change of 4–6% [5]. A British study has reported that 50% of the cases of malignant change in congenital naevi occur prior to puberty [7]. Thus, there is a significant risk of malignant change in a giant congenital naevus and prophylactic removal, if practical and feasible, is justified. The time at which malignant change is recorded in giant naevi is in contrast with that seen in the small congenital naevi; in small congenital naevi malignant change has only been reported after puberty [14].

The giant congenital melanocytic naevi are a difficult surgical problem, but shaving of the lesion in the neonatal period, and the use of tissue expanders to create additional normal epidermis to use in grafting are both valuable techniques.

A number of centres have advocated deep curettage or shave in the early neonatal period [18]. The object is to remove as many melanocytic naevus cells as possible, and thus both improve the cosmetic appearance and reduce the risk of development of malignant melanoma by reducing the total number of naevus cells present. Despite the necessary trauma of the procedure, it appears to be well tolerated by the infant and does in many cases reduce the degree of pigmentation, at least temporarily. The shave is rarely deep enough to remove the hair follicles and therefore the hair-bearing element of the lesion is less affected. There is a tendency, however, for the naevi to repigment, and the procedure has not been carried out on a large enough sample, or followed for a long enough period of time, to make any judgement as to whether or not it alters the risk of malignant change. Those who perform the procedure state that the best results are obtained if the procedure is carried out as soon as possible after birth—preferably in the first week of life. Follow-up of 16 children treated in this way as neonates reports that, after a decade of observation, the cosmetic results are good, and that no child has yet developed malignant melanoma [19].

The other valuable technique is the use of tissue expanders [20]. Once the required degree of epidermal expansion is achieved, the normal epidermis is harvested and used as an autologous graft to cover a defect created by the removal of an area of giant melanocytic naevus. This approach has meant that naevi that were previously considered unresectable because of their large surface area can now be removed, frequently by serial excisions, and the resulting defects grafted using the epidermis grown up *in vivo* using the tissue expanders.

Long-term follow-up of children with large congenital naevi that are not excised is essential. The naevus should be examined carefully for malignant change, which is more often detected by palpation than by observation. If the area at the base of the neck is involved, a computed tomography (CT) scan or magnetic resonance imaging (MRI) of this area is wise, as leptomeningeal involvement is particularly common in this site. Any textural change in a giant naevus should be biopsied, but many of these are minor, degenerative, cystic changes rather than the development of malignancy. However, malignant change may also develop in the underlying involved areas of the nervous system and may be impossible to detect at an early stage.

In the case of small and medium-sized congenital naevi, the situation is more confused [14,21]. Available data would suggest that there is a very small risk of malignant change. Current practice in many centres is to remove congenital naevi in children referred as soon as the child can tolerate local anaesthesia.

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Clinically atypical naevus

SYN. DYSPLASTIC NAEVUS

Definition. A melanocytic naevus, usually compound, identified on histological examination by the presence of architectural atypia (lentiginous melanocytic hyperplasia, bridging of junctional nests and focal elongation of epidermal rete ridges) and cytological atypia of naevus cells.

These naevi may be seen in patients in a sporadic or a familial setting. In the familial setting, they are a major risk factor for melanoma. In a sporadic setting they appear to be a marker of an individual at some increased risk of developing malignant melanoma, either on the naevus or on normal skin of the affected individual.

Incidence and epidemiology [1–3]**.** The term dysplastic naevus was first used by Elder *et al*. [4,5] as a pathological description of a sporadically occurring melanocytic naevus, which was clinically larger and more irregular than banal naevi and showed a constellation of pathological features that also distinguished it from common or banal naevi. Three years earlier, Clark *et al*. [6] and Lynch *et al*. [7] had separately but almost simultaneously described families in which multiple primary melanomas were much more common than expected and who also had large numbers of unusual naevi—the BK mole syndrome or FAMM syndrome (*f*amilial *a*typical *m*ultiple *m*ole *m*elanoma syndrome). Crutcher and Sagebiel [1] estimate the prevalence of dysplastic naevi in Californians at 8%, and figures of 2–4% are reported from other geographical areas.

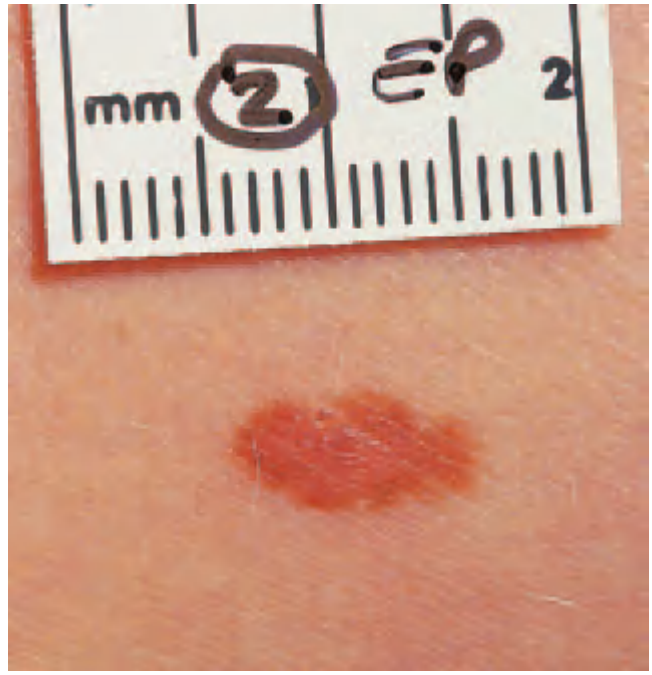

Fig. 38.24 Clinical features of dysplastic naevus in a young woman whose father and grandfather both died of melanoma. Note the size, irregular edge and irregular pigmentation.

In 1984, the National Institutes of Health (NIH) Consensus Conference [8] suggested that patients with dysplastic naevi could usefully be divided into four broad categories, A–D, on the basis of personal and family involvement (Table 38.2). This is a useful working classification as the risk of malignant melanoma in individuals in the A and B categories is increased by about ×90, while it is much higher, at ×400–500 in the D category [9].

Clinical features [10–13]**.** The original description of dysplastic naevi indicated that these were lesions larger than 5 mm with an irregular edge, irregular pigmentation and a degree of inflammation (Fig. 38.24). A number of subsequent studies have reported that these features are neither totally specific nor totally sensitive for the pathological features described. Because of this lack of complete

Table 38.2 National Institutes of Health (NIH) Consensus Conference classification of 'dysplastic' naevus patients.

Patient		Personal history of melanoma	Family history of multiple naevi	Family history of melanoma
A	Multiple dysplastic naevi	No	No	No
B	Multiple dysplastic naevi	No	Yes	No
C	Multiple dysplastic naevi	Yes	No	No
D*	Multiple dysplastic naevi	Yes	Yes	Yes

* The number 1, 2, 3, etc., after D denotes the number of affected relatives.

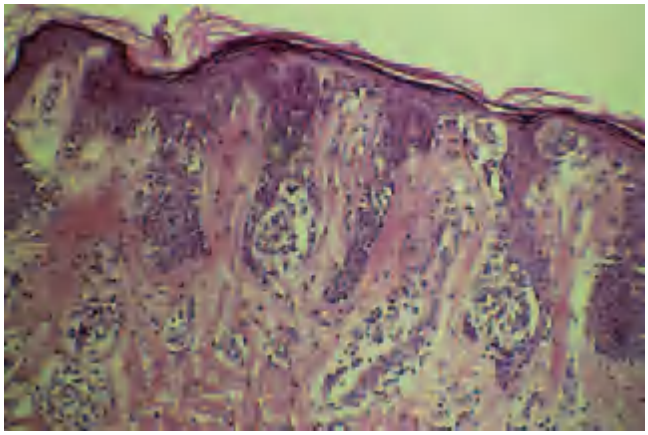

Fig. 38.25 Histological features of dysplastic naevus showing lentiginous melanocytic dysplasia, fibroplasia of the papillary dermis and melanocytic atypia.

correlation, it is suggested that the term 'clinically atypical' naevus be used for the clinical presentation [14] and 'dysplastic' naevus for those that fulfil the pathological criteria.

Pathology [15–21]**.** The great majority of dysplastic naevi are variants of acquired compound melanocytic naevi, although features described in dysplastic lesions may be seen in junctional naevi, in some congenital naevi and, occasionally, in Spitz naevi and variants.

The specific pathological features described in dysplastic naevi can be divided into architectural features, cytological features and features indicative of a host response to the naevus cells [22]. The architectural features are lentiginous melanocytic hyperplasia, fusion of individual nests of naevomelanocytes and associated elongation of epidermal rete ridges (Fig. 38.25). The cytological abnormalities are the increase in the nuclear to cytoplasmic ratio of individual melanocytes, an increase in nuclear staining and occasional normal mitotic figures in melanocytes. Most groups would not make the diagnosis on architectural features alone but consider melanocyte cytological atypia an essential feature for the diagnosis. The three pathological features indicating a host response are the presence of a lymphocytic infiltrate, a degree of fibroplasia of the collagen of the papillary dermis and a relative increase in the vascularity of the underlying dermis [19,22].

Treatment [23–26]**.** Many atypical naevi are difficult to distinguish from early malignant melanoma on clinical grounds, and therefore require an excision biopsy with a 2-mm margin of normal skin and pathological examination. It is essential to establish whether or not the patient has a family history of melanoma as, if this is the case, the risk of melanoma development is very much greater, and the threshold for excision of clinically atypical naevi needs to be lower than for those with no such history. In patients with no family history but large numbers of atypical naevi, a reasonable plan is to excise the most clinically atypical naevus. If this is not melanoma, then the remaining naevi can be recorded either with conventional photography, or with digital imaging, and the patient reviewed at intervals, according to the degree of concern. Changing naevi should be excised to obtain a pathological diagnosis, but static although atypical naevi may be safely observed. This approach results in excision of very thin melanomas. There is no logic in removing all atypical naevi to prevent development of melanomas, as melanoma can develop on clinically normal skin in these individuals.

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Melanocytic proliferations associated with lichen sclerosus

A recent paper has recorded the presence of pigmented patches in the genital skin of women affected by lichen sclerosus et atrophicus [1]. Biopsy of these lesions has shown the lesions to be atypical melanocytic naevi. There is no obvious explanation for the development of these naevi in lichen sclerosus et atrophicus, but it is important to be aware of this assocation as clinically the lesions may suggest malignant melanoma.

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Malignant melanoma of the skin

Definition. A malignant tumour arising from the epidermal melanocyte.

Incidence and mortality [1]**.** From 1950 to the mid-1990s there was a steady rise in the incidence of malignant melanoma of the skin in Australia, New Zealand, North America and Europe.

In Australia, numbers of new cases rose steadily to over 40 per 100 000 population per annum for males and to 30 per 100 000 population per annum for females in 1995. Since 1995 there has been a stabilization of the annual incidence in women of all ages, and a slight decline in melanoma incidence in younger females. However the incidence continues to increase in males, and is most marked in older males. The most rapid rate of increase by body site is for the head, neck and upper limb in males and the trunk in females. Lesions greater than 1.5 mm thick are increasing in incidence most rapidly in older males [2]. A similar pattern is seen in New Zealand [3].

In the USA, the SEER programme reported a trebling of melanoma incidence in males aged 45–64 years over the 30-year period 1969–99, from 13.5 to 40.0 per 100 000 population per annum, and a fivefold increase in older males aged over 65 years, from 18.8 to 91.9 per 100 000 population per annum. Incidence rates for females aged 45–64 years and for those aged over 65 years have also risen but less steeply than for males, while the incidence of melanoma in younger adults of both sexes aged under 45 years has only risen slightly over a 40-year period [4].

In Scotland, the incidence trebled in males of all ages over the 20-year period 1979–98, from 3.5 to 10.6 per 100 000 population per annum, and nearly doubled for females of all ages, from 7.0 to 13.1 per 100 000 population per annum over the same time period [5].

In the Stockholm/Gottland area of Sweden there was an average increase in incidence of 5% per year from 1976 to 1994. In the latter part of the 1990s this rate of increase levelled off in males but not in females [6].

Melanoma mortality has not risen at the same rate as melanoma incidence. In the USA, the increase in melanoma-attributable mortality has only been observed in males aged 65 years and over, in whom it trebled between 1969 and 1999. Over the same time period, melanoma mortality in both sexes aged below 45 years at diagnosis declined slightly [7]. In Scotland, melanoma mortality over the time period 1979–98 remained static in males of all ages at 1.9 per 100 000 population per annum and fell very slightly for females from 1.90 to 1.85 per 100 000 population per annum [5].

The rising incidence suggests continuing effects of past or present exposure to aetiological factors, most marked in older males. Static mortality figures can be attributed to patients presenting for surgery with thinner primary tumours.

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Aetiology

Malignant melanoma is an example of a malignancy strongly influenced by environmental factors that develop in a genetically susceptible host. The main identified environmental aetiological agent is UV radiation.

UV radiation

Large case–control studies carried out in different continents all indicate that intense burning sun exposure of unacclimatized white skin is a major risk factor for

cutaneous malignant melanoma [1–3]. However the exact dose of UV irradiation which increases melanoma risk, the timing in life of this excessive UV exposure and the exact wavelengths of the UV spectrum which are most likely to induce melanoma are not yet established. The sun exposure-related risk appears to be greatest for intense intermittent exposure [4–10] of non-sun-acclimatized skin rather than continual, occupational sun exposure. Episodes of severe sunburn appear to be risk factors in 19 of 22 published studies [11,12]. The typical melanoma patient is an indoor office worker [13] who is not exposed to regular daily sunlight but who enjoys one or two holidays each year in an area of high UV intensity. Case–control studies from Denmark [4] and Canada [8,9,14] have confirmed this, and have also incriminated outdoor hobbies such as sailing and swimming as risk factors for melanoma.

Migration. Studies of age at migration from Europe to a sunnier climate such as Israel [15] or Australia [16] indicate that exposure to intense UV at a young age may be particularly important. A comparison of native-born Israelis and Australians with those who arrived in these countries after the age of 5 years indicates that the melanoma incidence is higher in the native-born group.

Use of artificial UV sources. Several studies now incriminate the use of sunbeds and sunlamps as a weak but significant risk factor, suggesting that longer-wave artificial UVA may play a part in the aetiology of melanoma in addition to exposure to natural sunlight [17–21]. However, these studies may be confounded by the fact that those who use sunbeds are also those who spend excessive amounts of time trying to acquire a tan in natural sunlight.

The use of sunscreens and melanoma risk. Studies suggesting that the use of sunscreens or even the wearing of hats are statistically significant risk factors for melanoma require to be interpreted with care. They are likely to be confounding factors in that those likely to use sunscreens and hats are those with a phenotype associated with increased melanoma risk in the form of sun-sensitive skin [6,22].

Hormonal. Studies have been carried out to establish whether or not use of the oral contraceptive is a risk factor for melanoma in women [23]. Two recent large reviews find no significant association with use of the modern low-dose oral contraceptive [24,25]

Socio-economic status. Two studies have now shown that melanoma is more prevalent in those of high socio-economic status, but the converse applies to mortality, in that patients in lower socio-economic groups are more likely to die of melanoma even after controlling for the well-recognized prognostic factors, particularly tumour thickness [26].

Occupational. A number of studies have suggested that the risk of melanoma is slightly increased in pilots and other airline crew members. A recent study of 10 032 pilots showed a relative risk of 2.3 (CI 1.7–3.0) [27]. The explanation for this may be the greater than average opportunity for recreational sun exposure.

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Genetic susceptibility to melanoma

Patients with sporadic melanoma are more frequently fair skinned, fair or red haired and blue eyed, with a tendency to burn easily and tan poorly, if at all, on exposure to sunlight [1–6]. They also have large numbers of banal naevi, a tendency to freckle and more atypical or dysplastic naevi than control subjects [7,8]. These phenotypic characteristics are influenced by several genes. The melanocortin 1 receptor gene (*MC1R*) gene on chromosome 17 codes for production of dark eumelanin, found in darker haired, darker skinned white people, or for phaeomelanin, which is the melanin variant found in fair skinned red heads. *MC1R* polymorphisms are very much more common in freckled redheads and it has been suggested that this gene may be a major determinant of the freckling tendency [9].

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Familial melanoma and melanoma susceptibility genes

Around 2% of melanoma patients have a proven positive family history of melanoma in one or more first-degree relatives. A higher percentage give a positive family history on first questioning, but this requires to be pathologically confirmed as non-melanoma skin cancer or a benign melanocytic lesion may be confused by patients and their relatives with true melanoma.

The major melanoma susceptibility gene identified to date is the *CDKN2A* gene, which is located on chromosome 9p21. Mutations in this gene are found in 10–30% of melanoma patients with a positive family history, with a higher prevalence of mutations in families with more than two affected members. The function of the wild-type *CDKN2A* gene is to control entry of cells into the G1 phase of the cell cycle and to prevent or delay entry of damaged cells into the cycle to allow time for repair of damaged DNA. It thus acts as a tumour suppressor gene. Mutated *CDKN2A* does not act as a break on the cell cycle in this way, and allows uncontrolled entry into the cycle of cells with damaged DNA, and subsequent proliferation and extension of DNA damage [1–3].

A number of cases of familial melanoma who have abnormalities of chromosome 9p do not have a detectable *CDKN2A* mutation, suggesting that there may be other melanoma susceptibility genes in this area.

A large number of different mutations in the *CDKN2A* gene have been found in familial melanoma patients with certain mutations been more prevalent in different geographical areas, suggesting a founder effect. For example, the 113 insert R *CDKN2A* mutation is preferentially found in Swedish families [4].

There appears to be marked geographical variation in the penetrance of *CDKN2A* mutations worldwide with the greatest penetrance observed in areas of highest UV exposure, implying a genotype–environment interaction. Overall penetrance of *CDKN2A* mutations is 30% at age 50 years, rising to 67% at age 80 years, but analysis of patients in Europe, North America and Australia shows lowest penetration in Europe and highest in Australia, where 90% penetrance is observed at age 80 years [5].

In addition three families worldwide have been found to have mutations in the *CDKN2A* binding domain of *CDK4* [6]. This is an oncogenic mutation.

In addition to *CDKN2A* and *CDK4* mutations, one US group has published evidence that melanoma susceptibility gene(s) are located on chromosome 1 [7], but this has not yet been confirmed outside the USA, and no candidate gene has been identified.

The melanocortin 1 receptor gene (*MC1R*) is a further candidate melanoma susceptibility gene. This gene is highly polymorphic and certain polymorphisms have been reported as being strongly associated with the melanoma susceptible phenotype of red hair. Many redheads have two or more *MC1R* polymorphisms, a phenomenon not observed in non-redheaded subjects [8]. Once hair colour is controlled for, *MC1R* polymorphisms still appear to be associated with increased melanoma risk [9], and may also interact with *CDKN2A* mutations [10].

The *BRAF* gene has also been identified as an oncogene in a proportion of patients with sporadic cutaneous malignant melanoma. *BRAF* encodes a *ras*-regulated kinase that controls cell growth and malignant transformation

mediated by the kinase pathway. Somatic mutations in *BRAF* have been identified in two-thirds of melanoma samples examined [11] and also in other tumour types. *BRAF* mutations are also found in benign melanocytic naevi of the congenital, compound, intradermal and dysplastic varieties in 82% of samples examined, indicating that *BRAF* mutations alone are not sufficient for full transformation to malignant melanoma [12]. Germline *BRAF* mutations are not found in the peripheral blood of patients with familial melanoma, either in those who do or do not have *CDKN2A* mutations [13].

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Clinicopathological variants of primary malignant melanoma [1]

In 1969, Clark *et al*. [2] suggested that, using a combination of clinical and pathological features, malignant melanoma could be divided into three main subsets; the superficial spreading melanoma, the nodular melanoma and the lentigo maligna melanoma. In 1975, Reed *et al*. [3] added a fourth group, the acral lentiginous or palmoplantar malignant melanoma.

There is some controversy as to whether or not these subsets are completely discrete entities, and it has been established that the clinico-pathological variant is not an independent determinant of prognosis [4]. However, the four subtypes have distinct clinical features, thus giving rise to a different range of conditions to be considered in the differential diagnosis in the early growth phase.

There are two simple systems devised to aid clinical diagnosis of melanoma by naked-eye inspection. Both apply mainly to the superficial spreading variant of malignant melanoma. These are the American ABCD categories and the Glasgow seven-point check-list. The American ABCD mnemonic is A = asymmetry, B = irregular border, C = irregular colour and D = diameter over 1 cm. The Glasgow seven-point check-list is divided into three major and four minor features. These are:

Major features:
1 Change in size
2 Change in shape
3 Change in colour.

Minor features:
4 Diameter more than 5 mm
5 Inflammation
6 Oozing or bleeding
7 Mild itch or altered sensation.

It is suggested that any lesion with one major feature in an adult be considered for removal, and that the presence of additional minor features should add to clinical suspicion.

Now that the majority of melanomas are recognized and removed at an early growth stage, it is clearly essential that all dermatologists in training learn to recognize such lesions.

Superficial spreading melanoma [5]. This is by far the commonest type of melanoma on white skin. Superficial spreading melanomas present most frequently in a patient in the fourth or fifth decade. The commonest sites are the female leg and the male back (Fig. 38.26), but any body site may be involved. Early presentation is of an irregularly shaped, brown lesion, usually still macular, but with clear colour variation within the lesion. Shades of brown, black, red and grey or white may be present. At this stage the lesion may still be very small—only 4–5 mm in diameter, but there may be a history of growth or change, and of subtle altered sensation, often described as a new awareness of the lesion. At this stage, the lesion will almost certainly be in the early horizontal growth phase, but as growth continues the lesion will become palpable, indicating that the lesion has now progressed to the vertical growth phase. If the melanoma is developing in a pre-existing naevus, which occurs in approximately 50% of lesions, the irregular appearance of the growing melanoma may contrast strikingly with the more regularly pigmented and outlined residual naevus component.

Partial regression may cause central pigment loss while extension continues peripherally. This pattern of growth may result in a crescentic area of dense blue-black pigmentation with some adjacent inflammatory response and a central area of thin grey or white atrophic epidermis. Elevated nodules and a history of bleeding are associated with advanced lesions.

The main differential diagnosis here is between an early melanoma and a benign but atypical melanocytic naevus.

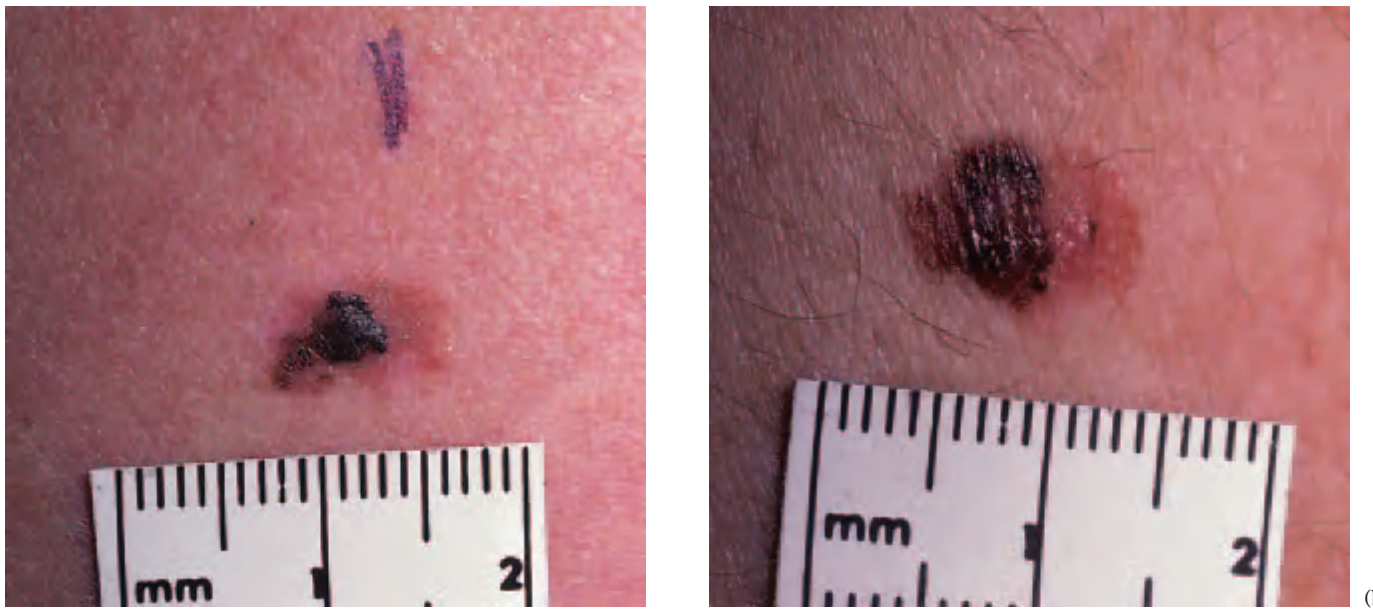

Fig. 38.26 (a,b) Two early superficial spreading malignant melanomas. Note the size, the irregular edge and the irregular pigmentation.

A history of growth or change strongly suggests early melanoma, as does a size of 6 mm or greater, but other clinical features may be very similar in atypical naevi and early melanomas, and an excision biopsy may be needed.

The relatively rare verrucous variant is more difficult to diagnose clinically. It presents as a raised, crusted, changing, pigmented lesion [6]. The differential diagnosis here may be a seborrhoeic keratosis, a pigmented actinic keratosis or a pigmented squamous cell carcinoma.

Nodular melanoma. This variety presents most commonly in the fifth or sixth decade and occurs more frequently in males than in females. The trunk is a common site. These lesions grow rapidly and because of this, and the fact that they are commonly deep tumours by the time they are excised, they have a poor prognosis. This, however, relates to tumour thickness not to the nodular nature of the lesion *per se*.

The lesion presents clinically as an elevated, dome-shaped polypoid or even pedunculated structure and the predominant colour may be reddish brown. (Fig. 38.27) Melanin pigment may be sparse in these lesions and a raised red central area, with only a peripheral brown ring of melanin, is a common clinical pattern. Ulceration and bleeding from the lesion occur frequently. This variety of malignant melanoma is misdiagnosed prior to surgery more frequently than either a superficial spreading melanoma or a lentigo maligna melanoma. The reason for this is probably the rapid growth and relative lack of melanin pigment, which may lead to confusion with vascular lesions.

Lesions to consider in the differential diagnosis are angioma or pigmented basal cell carcinoma. Histiocytoma or sclerosing angioma may also cause clinical confusion. The latter are usually a yellow-brown colour, due to both iron pigment and melanin and are well tethered to the overlying epidermis, giving the so-called dimple sign—if the lesion is compressed laterally, the epidermis is seen to be tethered to the underlying dermis. However, this is not specific, and an excision biopsy should be carried out if there is any clinical concern.

Lentigo maligna melanoma [7]. In this histogenetic variant, the preceding horizontal or *in situ* growth phase is the lentigo maligna (Hutchinson's melanotic freckle; melanosis circumscripta precancerosa of Dubreuilh). By comparison with the horizontal growth phase of the superficial spreading melanoma, this is a much more prolonged period of lateral extension. Most occur on the face, commonly on the upper cheek, temple or forehead. Ocular structures may be involved in the process. A small proportion of lentigo maligna melanomas are observed on extrafacial exposed sites such as the hand or leg. Patients tend to be older than those presenting with the other types of melanoma and many of the risk factors suggest that the aetiology of this variety of melanoma has a greater similarity to squamous cell carcinoma than to the other melanoma variants.

Initially the lentigo maligna is a flat, brown or black, irregularly shaped lesion. These lesions will grow very slowly, over months or years, and there may be central regression while the peripheral margin continues to extend. In time, a raised central nodule will develop (Fig. 38.28) indicating transition to the vertical growth phase.

Two lesions that may require inclusion in the differential diagnosis of early lesions are pigmented actinic

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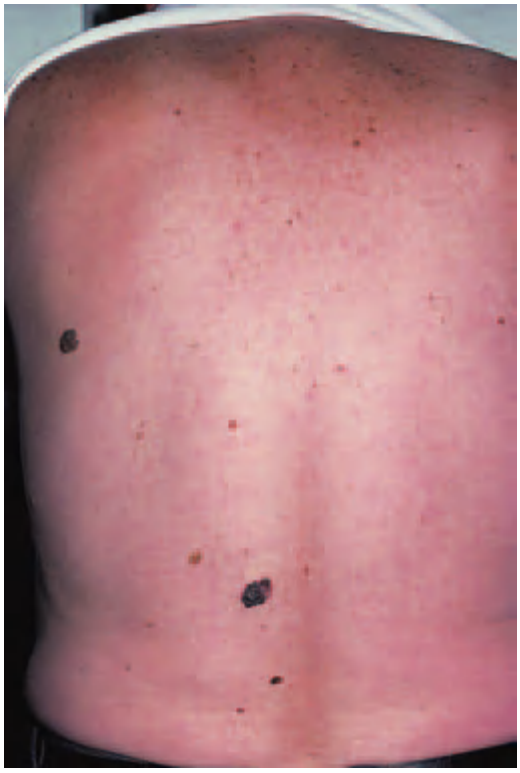

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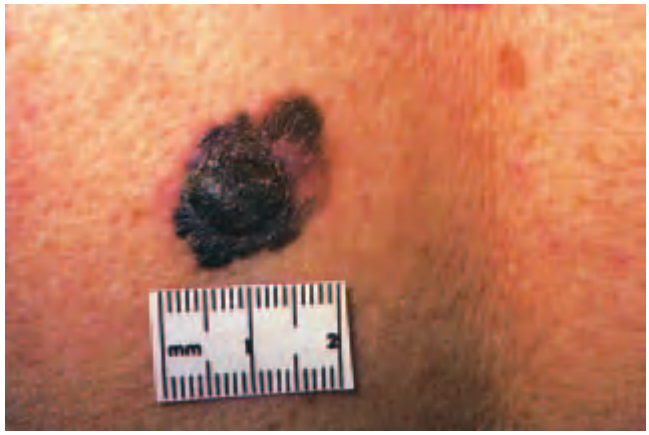


Fig. 38.27 (a) Distant and (b) close-up view of malignant melanoma on the lower back of a male patient. The second large lesion in the distant view is a seborrhoeic keratosis. Note the fact that here a nodule has developed in a pre-existing superficial spreading malignant melanoma.

keratoses and the flatter variant of seborrhoeic keratoses. Both tend to have more surface scaling, lack a visible melanin pigment network and have a dull, non-reflective surface.

Acral lentiginous melanoma (palmoplantar malignant melanoma) [3,8]. This type of melanoma comprises around 10% of all melanomas on white skin but over 50% of all melanomas on darker-skinned races [9]. The lesions are found mainly on the sole of the foot but also on the palm

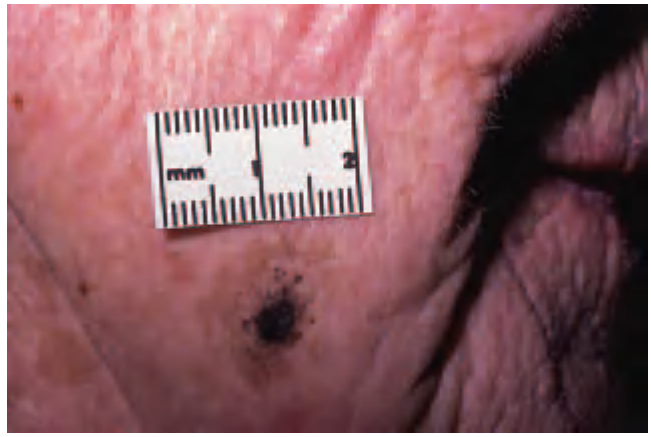


Fig. 38.28 Lentigo maligna melanoma. Note the elevated nodule in the centre of macular pigmented area.

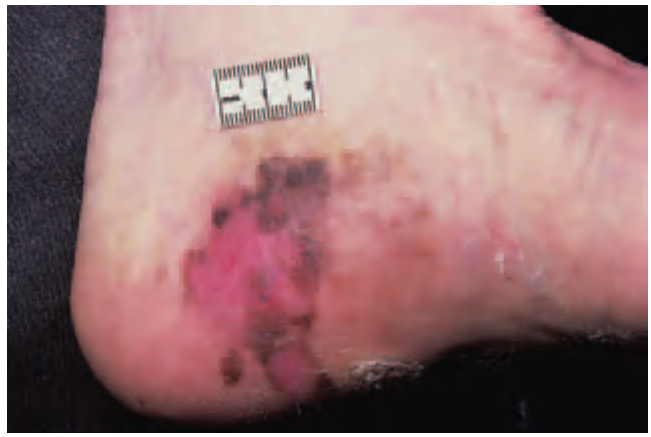


Fig. 38.29 Acral lentiginous melanoma on the sole of the foot.

of the hand, and are characterized, as their name would suggest, by a large, macular, lentiginous pigmented area around an invasive raised tumour. Approximately 50% of all melanomas on the foot come into this category (Fig. 38.29).

The clinical differential diagnosis may include a plantar wart, which is a common cause of delayed diagnosis, and black heel (talon noir) (Chapter 22), due to haemorrhage into the superficial layers of the epidermis. Any tender growing nodule on the sole of the foot should give rise to concern that the lesion is a melanoma and a biopsy considered.

Subungual malignant melanoma [10]. These lesions are commonly diagnosed at a late stage in development because of earlier confusion with a benign melanocytic lesion, a traumatic haemorrhage under the nail, pyogenic granuloma [11], persistent paronychia, a fungal infection or even a subungual wart. Any pigmentation of the nail bed should be examined with great care, particularly if there is

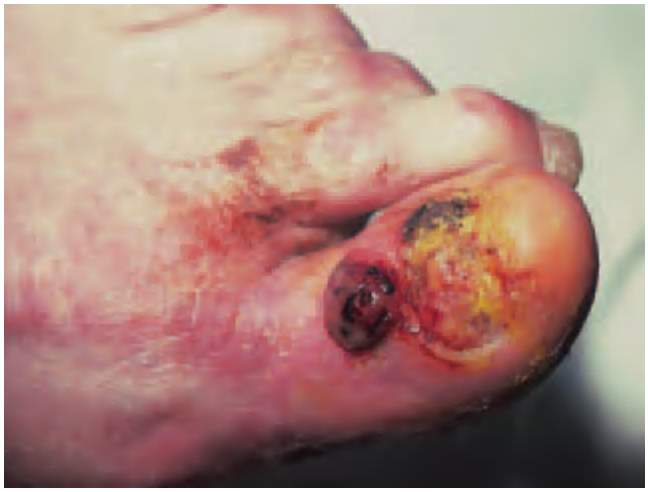


Fig. 38.30 Subungual melanoma causing destruction of the nail. Note the pigmentation on the nail fold.

full-length involvement of the nail and if the nail fold is also affected. This is known as Hutchinson's sign.

As the melanoma continues to grow, the nail is destroyed (Fig. 38.30).

Mucosal melanoma. Mucosal melanomas are rare, but can be seen in the oral cavity, on the genital mucosa and in the perianal area. The most common presenting feature of mucosal melanoma is the presence of extensive, irregular macular pigmentation. This may be extensive but spotty and may extend laterally for years before becoming elevated. Such lesions should be biopsied without delay, although clinically they may look deceptively benign (Fig. 38.31).

Secondary melanoma with no obvious primary site [12]. About 5% of cutaneous melanomas present as an isolated, usually non-pigmented, subcutaneous or dermal nodule with no primary source of the tumour apparent. In such a situation, the possibility of an ocular or mucosal primary tumour should be carefully investigated.

A further possibility in such a situation is that the primary lesion has undergone spontaneous regression, and examination of the skin distal to the secondary nodule may reveal a depigmented area suggestive of regression. In many cases, the site of origin is never identified.

Depigmentation in relation to malignant melanomas. Haloes of depigmentation are occasionally seen around primary malignant melanoma. As they may also occur around benign pigmented lesions, their presence is not diagnostic of malignant melanoma. The haloes around benign lesions tend, however, to be more symmetrical, whereas those around a neoplastic lesion may be highly irregular. The significance of this is not yet clear, but they may be

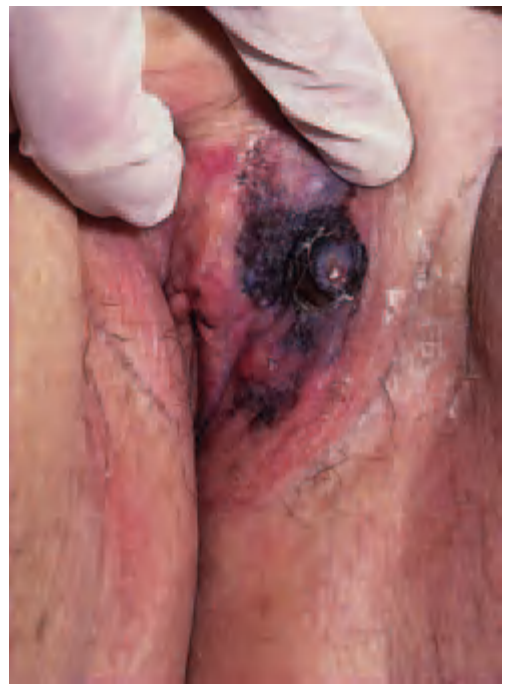


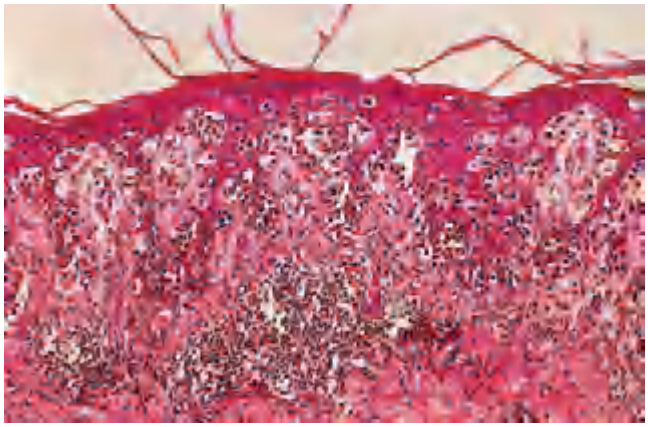
Fig. 38.31 Vulvar melanoma. This lesion is obviously deeply invasive and has a poor prognosis.

related to the immunological mechanisms known to be active, particularly in patients with early disease. It has been suggested but not yet confirmed that depigmentation around a primary tumour may be associated with a good prognosis.

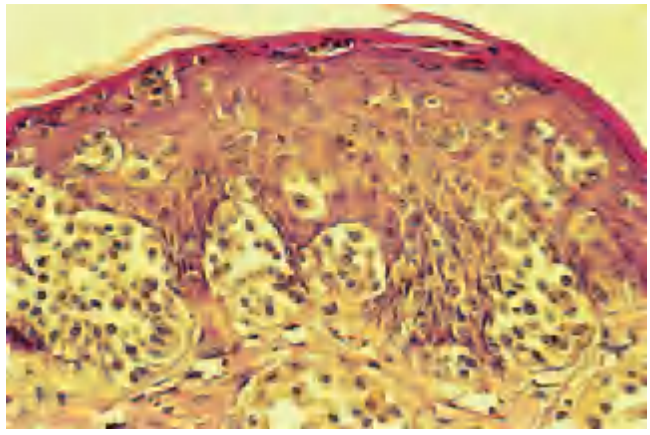
Multiple primary malignant melanomas [13,14]. At present around 5% of patients who have already had one melanoma diagnosed will develop a second and possibly a third or further primary melanoma. For patients who have had a thin melanoma diagnosed, the risk of a second primary melanoma is greater than the risk of the first melanoma metastasizing. Patients who have a family history of melanoma comprise about 50% of those who develop multiple primary melanomas, and a small number will have mutations in the *CDKN2A* gene. An importance consequence of this high incidence of second primary tumours is in follow-up regimes (p. 38.37). It is vital to look for a second primary melanoma on routine follow-up visits with as much if not more suspicion than it is to palpate for enlarged lymph nodes.

Pathology

Essential diagnostic features of malignant melanoma. The essential pathological feature for the diagnosis of primary cutaneous malignant melanoma is the presence of cytologically malignant melanocytes invading the dermis. Similar cells may also be seen in the overlying epidermis



(a)



(b)

Fig. 38.32 (a,b) Histology of superficial spreading melanoma showing striking pagetoid invasion of the overlying epidermis.

and also in the epidermis lateral to the invasive component. Additional supportive microscopic evidence that the lesion is melanoma rather than a benign melanocytic naevus is the presence of ulceration, a lack of maturation of the cells comprising the dermal component, the presence of a lymphocytic infiltrate, the presence of atypical mitoses, particularly in the deeper melanocytic cells, and apparent angiogenesis at the base of the lesion.

Superficial spreading or pagetoid melanoma [5]. The essential pathological features are the presence of a focus of malignant melanoma cells invading the dermis with areas of *in situ* malignant change in the adjacent epidermis. This consists of the presence of cytologically atypical melanocytes in the suprabasal layers of the epidermis, both singly and in clumps (Fig. 38.32). On H&E sections, the pattern may be very similar to that seen in extramammary Paget's disease, and the term pagetoid melanoma may therefore also be used to describe this lesion.

The verrucous variant [6]. This is characterized by gross hyperkeratosis and also epidermal hyperplasia. The significance of this lesion is the fact that it is not usually recognized clinically because of the hyperkeratosis, and it may be confused with both benign and malignant lesions derived from the keratinocyte, such as a seborrhoeic keratosis or a squamous cell carcinoma.

Nodular melanoma. The nodular melanoma has the pathological features of a focus of invasive melanoma cells in the dermis with direct contact with the immediately overlying epidermis, and no morphological abnormality apparent in the adjacent epidermis on either side of the invasive nodule. An alternative term therefore is primary malignant melanoma with no recognizable adjacent *in situ* or horizontal growth phase [1]. These lesions frequently grow relatively rapidly. There is a tendency to use the term nodular melanoma inappropriately for any primary melanoma that has a visible nodule. This is incorrect usage, as superficial spreading, acral and lentigo maligna melanomas can all develop elevated nodular areas in the course of later growth.

Lentigo maligna melanoma [7]. This variant of melanoma is the most distinct. It is found on chronically light-exposed skin, usually the face, and has a long preinvasive or horizontal growth phase during which there is striking lentiginous replacement of the basal keratinocytes by atypical melanocytes, but no downward invasion into the underlying dermis, which will show actinic damage of the dermal collagen. During this phase, the names **lentigo maligna**, Hutchinson's melanotic freckle and premalignant melanosis of Dubreuilh are all appropriate. There is also often extensive colonization of the hair-follicle epithelium by atypical melanocytes. After a variable period of time, invasion into the underlying dermis will take place. The site of such early invasion in its earliest stages may be marked by a lymphocytic infiltrate. Once obvious dermal invasion is present, the name **lentigo maligna melanoma** is appropriate.

Acral lentiginous melanoma [8]. About 50% of melanomas arising on the non-hair-bearing areas of the palms and soles have pathological features that do not allow them to be easily classified into Clark's original three variants. This was recognized by Reed who introduced the term acral lentiginous melanoma in 1975. The essential pathological features are the presence of an extensive area of lentiginous change in the epidermis around the focus of invasive primary melanoma. Very often this lentiginous area is very easy to identify, but the invasive focus is small and difficult to find, requiring cutting of many sections. The basal keratinocytes are replaced by cytologically malignant melanocytes, and there is often an associated inflammatory flare of lymphoid cells in the underlying dermis. An important feature is the presence of skip areas, with foci of relatively normal epidermis in areas of gross lentiginous change. This feature makes it particularly

important to examine the excision specimen thoroughly to determine whether or not the lesion has been completely excised.

Primary melanomas arising on the mucosal surface of the oral cavity, the vulvovaginal and the rectal areas have some features in common with acral lentiginous melanomas, and the term palmoplantar mucosal melanoma is sometimes used to describe the entire group. Extensive lentiginous change is frequently visible, both clinically and pathologically, and the focus of invasion may be very difficult to find, even in the presence of obvious metastases.

Desmoplastic neurotropic and myxoid variants [15–18]. The desmoplastic variant of malignant melanoma is frequently seen in association with chronically sun-damaged skin and overlying lentigo maligna in the epidermis. As the name suggests, this is a combination of malignant melanocytes in association with extremely dense desmoplastic change of the dermis. The stromal change in the dermis is usually much more obvious than the malignant melanocytes, which may be few in number. The pathological importance of this variant is the fact that it can be difficult to be absolutely certain that excision is complete, and local recurrence is a common problem. Two studies have reported that malignant melanocytes in these lesions stain less reliably with the antibodies NKI C3 and HMB 45, both antibodies used commonly to identify melanoma cells on tissue sections. One study suggests that desmoplasia is associated with a statistically significantly better survival [19], while another finds no survival difference [15].

A pathological variant sometimes coexisting with the desmoplastic pattern is the neurotropic melanoma [20]. In this variant, the pattern of metastatic spread is along the cutaneous nerve trunks. This is seen particularly in lesions on the head and neck area, and may cause severe, relentless pain. As with the desmoplastic variant, completeness of excision can be difficult to determine.

Myxoid melanoma is a rare variant in which there is a striking myxoid stroma in the dermis surrounding malignant spindle cells. The morphological features have some features in common with desmoplastic melanoma [21].

Naevoid melanoma (minimal deviation melanoma, small cell melanoma) [22,23]. A further pathological variant is the so-called naevoid, minimal deviation or small cell melanoma. These lesions lack epidermal involvement, are fairly well defined at their lateral margins, and the small naevoid cells in the dermis, which make up the bulk of the tumour, show partial differentiation. However, careful examination will reveal the presence of abnormal mitoses in naevomelanocytes. These lesions may be confused with compound naevi.

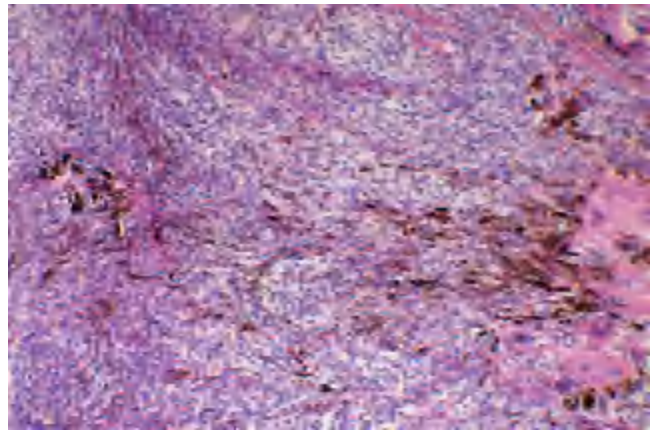


Fig. 38.33 Pathology of melanoma of the soft parts. Note the eosinophilic cytoplasm and also the pigmentation.

Animal-type melanoma. This is a rare pathological variant of melanoma which, as the name suggests, has some morphological similarities to melanoma found in grey horses. Blue-black nodules are the clinical presenting feature, and the pathology shows heavy dermal melanin pigmentation with sheets of atypical spindle cells, which may be difficult to visualize without bleaching because of the quantity of pigment present. The epidermis is usually, but not always, involved and mitotic figures may be difficult to find. Metastases to both regional nodes and to distant organs may occur [24].

Melanoma of the soft parts (clear cell sarcoma). This is a further rare pathological variant of malignant melanoma. The tumours usually arise on the tendons and aponeuroses. The ankle appears to be a relatively common site, and the tumours generally appear in young people. There appears to be no epidermal component, which gives rise to diagnostic confusion with various types of sarcoma, but the malignant cells contain premelanosomes and melanosomes. Plump, pale spindle cells with clear cytoplasm are seen in the tendons (Fig. 38.33). They may be deceptively bland on microscopy as mitotic figures are difficult to find, but both local recurrence and distant metastases are relatively common [25–27].

Wide excision and amputation may be required.

Vulvar and vaginal melanomas. These tumours are also discussed on page 38.29. They are rare variants of melanoma, which usually present late with vaginal bleeding. They are relatively common vulvar tumours, and the average age at presentation is in the seventh decade, significantly older than for cutaneous melanomas. A mass will be present and on biopsy the majority of the tumours are of the nodular type of melanoma. Vascular invasion and nodal involvement are both common at the time of diagnosis.

The prognosis is poor, presumably related to the late stage at presentation [28,29].

Differential diagnosis. There are two quite distinct problems in pathological differential diagnosis of primary malignant melanoma. The first is the benign melanocytic naevus and the second is non-melanocytic but malignant tumours, either primary or secondary. These are more often a problem when a clinically indeterminate large nodule is excised.

The differentiation between benign and malignant melanocytic lesions rests on both the pattern of involvement and the cytological features of individual cells. The association of cytologically atypical melanocytic cells in the upper layers of the epidermis with apparent proliferation at the dermal–epidermal junction and invasion of the underlying dermis by atypical melanocytic cells is a malignant pattern. The cells in the deeper areas of the dermis will show no maturation such as is seen in a benign naevus with dermal involvement. The cytological characteristics of malignancy are a high nuclear to cytoplasmic ratio, intense nuclear staining, size variation between adjacent cells and the presence of abnormal mitotic figures.

Two of the more difficult pathological differential diagnoses in this area lie between the halo naevus [30] or Spitz naevus and malignant melanoma. It is unusual for a melanoma to elicit as intense a lymphocytic response as the halo naevus, but a careful search should be made through the lymphocytic infiltrate for cytologically malignant cells, particularly if the clinical information available does not suggest a halo naevus.

The differentiation between malignant melanoma and Spitz naevus can be extremely difficult. Features suggesting that the lesion is a melanoma and not a Spitz naevus are an asymmetrical lesion with a poorly defined lateral margin, the presence of abnormal mitoses in the melanocytic cells, lack of any maturation or differentiation in the deeper naevus cells, and an epithelioid cell pattern with striking lack of adhesion of one cell to the other. These features are not absolute, and there are times when it may be necessary to state that a firm diagnosis cannot be made on pathological grounds. In such cases excision and a period of follow-up are common practice.

A range of antibodies are currently in routine diagnostic use. They will confirm the melanocytic nature of the lesion, but cannot differentiate between benign and malignant melanocytic lesions. These antibodies include antibody to S 100 protein, HMB 45 and melan A/MART-1 [31].

Pathological prognostic features [1,32]. A large number of pathological features have been suggested as offering prognostic information. Tumour thickness was established by Alexander Breslow as the most valuable prognostic guide [33]. Blocks are cut from the apparently thickest area of the primary melanoma and the slides cut from this block are examined using an ocular micrometer to measure the distance between the overlying epidermal granular layer and the deepest invasive area of the primary lesion (Fig. 38.34). This figure in millimetres is the Breslow or tumour-thickness measurement and should be included in all pathology reports of primary melanoma. Thin primary melanomas are associated with females, a family or personal history of melanoma, large numbers of benign naevi and one or more atypical naevi, suggesting that educating those at greatest risk of developing a melanoma does result in earlier diagnosis [34].

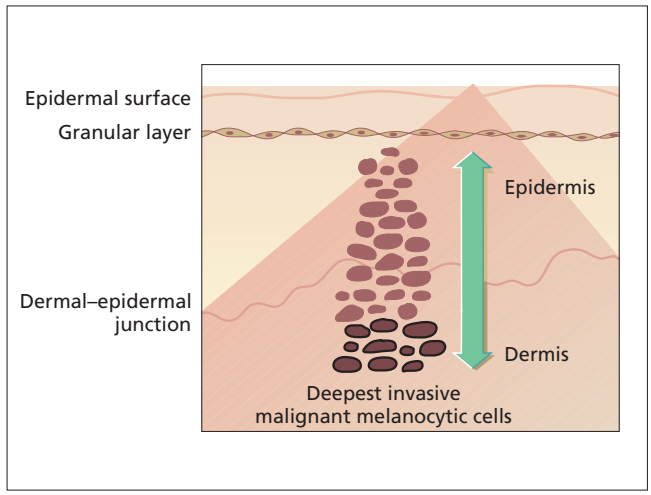


Fig. 38.34 Malignant melanoma thickness measurement (Breslow). The pathologist measures in millimetres the distance between the granular layer in the epidermis and the deepest invasive melanoma cell. (From Breslow [33].)

Ulceration, even if only microscopic, is an additional and independent, poor prognostic sign, and the mitotic count also varies inversely with survival [35]. The presence of tumour cells in vessels is a poor prognostic sign associated with both local and distant recurrence. Prominent tumour vascularity at the base of the primary melanoma has also been recorded as a statistically significant prognostic sign, lesions with increasing tumour vascularization showing a higher incidence of metastatic spread [36].

The levels of invasion into the dermis introduced by Clark *et al*. [2] are a similar way of relating extent of penetration of the primary lesion to prognosis. Clark's levels are as follows:

1 intraepidermal or *in situ*
2 a few cells in the papillary dermis
3 occupation and expansion of the papillary dermis by melanoma cells
4 invasion of the reticular dermis
5 invasion into fat

Five-year survival figures fall steadily with the deeper levels [37].

Regression in and around a primary melanoma is a sign of disputed prognostic value. The first reports associated regression in thin, primary melanomas with a poorer-than-expected 5-year survival [38], but since that time there have been several papers from other parts of the world both confirming and refuting this observation [39,40]. Part of the apparent disagreement may relate to the problem of definition of regression. This should include dermal change similar to either granulation tissue formation or scarring, a lymphocytic response, pigment-filled macrophages and free melanin, and also the presence of at least a few degenerating malignant melanoma cells.

There are currently a number of models available of melanoma prognosis designed to be applied to individual patients to give an accurate indication of the outlook for that patient. The best established and validated of these is the Clark model [41]. As these models are developed on series of patients in very different geographical areas who have varied phenotypic characteristics, it is necessary to validate them in different geographical areas before they are generally applied.

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Prepubertal melanomas [1]

Malignant melanoma is extremely rare before puberty, although the incidence rises steadily in the second and third decades. Children with giant congenital naevi are at increased risk of developing melanoma, and approximately half of all the reported cases of prepubertal melanoma appear to have arisen in giant congenital naevi [2].

Very occasionally, melanomas may be present in neonates either spontaneously or as a result of transplacental metastases [3].

For pathologists, the difficult diagnosis is between the true Spitz naevus, commoner in children than adults, and

the spitzoid melanoma. This can be extremely difficult and there are occasions when it is virtually impossible, even if several expert opinions are sought [4]. In such situations, reasonably wide excision and careful follow-up is usually the safest compromise.

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American Joint Committee on Cancer (AJCC) tumour node metastasis (TNM) staging system for cutaneous melanoma

The most recent TNM staging system for melanoma published by the AJCC is outlined in Table 38.3.

A provisional review [1] was followed by validation on a sample of over 17 000 patients [2] and the final version then published [3].

The major changes are, firstly, that Clark levels of invasion are not used in primary melanomas thicker than 1 mm. The overriding importance of tumour thickness has firmly established that Clark levels offer no additional information for these thicker tumours. Secondly, the presence of ulceration in patients with stage 1 or 2 disease advances the stage. In the N category, total number of affected nodes and their identification on clinical or pathological grounds replace gross dimensions of these nodes. In this section, data obtained as a result of sentinel lymph-node biopsy is also included (p. 38.36). In the M category, the site of distant metastases is now included, as is the presence of elevated lactic dehydrogenase.

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Management of cutaneous malignant melanoma

This can logically be divided into clinical diagnosis, biopsy confirmation, definitive surgical excision, appropriate treatment of draining lymph nodes, routine follow-up of patients with melanoma apparently confined to the

Table 38.3 Current tumour node metastasis (TNM) classification for cutaneous melanoma.

Tumour T classification	
T1: ≤ 1 mm	a, no ulceration b, ulcerated or Clark level 4
T2: 1.01–2.00 mm	a, no ulceration b, ulcerated
T3: 2.01–4.00 mm	a, no ulceration b, ulcerated
T4: > 4 mm	a, no ulceration b, ulcerated
Node N classification	
N1: 1 lymph node	a, micrometastases b, macrometastases
N2: 2–3 nodes	a, micrometastases b, macrometastases c, in transit metastases or satellites without metastatic nodes
N3: > 4 metastatic nodes or combinations of satellites and or in transit lesions	
Metastases M classification	
M1: Distant skin, subcutaneous tissue or nodal metastases	Normal LDH
M2: Lung metastases	Normal LDH
M3: All other visceral metastases	Normal LDH
Any distant metastases with elevated LDH	Elevated LDH

LDH, lactate dehydrogenase.

primary site, management of nodal disease, management of patients with distant metastases and palliative care [1]. Dermatologists will mainly be involved with patients with stages 1 and 2 melanoma, but it is necessary to have a reasonable understanding of the likely further management of these patients by surgeons and oncologists. In the UK there is currently a policy to manage patients with stages 3 and 4 melanoma in specialized melanoma units in cancer treatment centres by a multidisciplinary team as part of a managed clinical network.

UK guidelines are available for the management of all stages of melanoma [2] and similar guidelines have been published for the USA [3] and the Netherlands [4]. Such guidelines are valuable provided they are regularly updated as new information becomes available.

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Clinical diagnosis. Risk factors for melanoma are described on p. 38.23. The most likely patient is a white adult with pale skin which burns easily, and who has a history of excessive sun exposure. Males are most likely to have melanoma on the trunk, and females on the lower limbs. A positive family history is a strong risk factor, as is a personal history of a previous primary melanoma. Patients with large numbers of benign melanocytic naevi are also at increased risk. The patient will give a history of a new or pre-existing pigmented lesion that is changing in size, shape or colour. Some early melanomas have slight altered sensation described by patients as a minor itch. The melanoma is likely to be 5–6 mm in diameter and to have an irregular lateral outline. It may be composed of several shades of brown, black, red and blue.

The two commonest clinical differential diagnoses are benign melanocytic naevi in younger adults and seborrhoeic keratoses in older adults. Benign naevi are usually smaller than melanoma, have a regular oval or circular outline, and are a uniform shade of brown. Seborrhoeic keratoses are dull, non-reflective lesions, which have a hyperkeratotic surface and a tendency to crumble. They are usually multiple and found mainly on the trunk.

Dermatoscopy (epiluminescence microscopy). This technique involves the examination of the surface of the pigmented lesion at moderate magnifications using the hand-held dermatoscope, having first 'cleared' the epidermal surface with oil. With this technique it is possible to see the distribution of melanin in the epidermis and superficial dermis in great detail. The technique is currently widely used in certain European countries, such as Germany and Austria, and in Australia. There are now three published atlases giving detailed descriptions of the dermatoscopic appearance of malignant melanoma, of benign melanocytic naevi and of other non-melanocytic pigmented lesions which may require to be included in the differential diagnosis [1–3]. Few dermatoscopic features are totally specific for melanoma but certain are found more frequently in melanoma than in benign naevi. These include peripherally situated black or brown dots and globules, a blue-white 'veil' appearance over the lesion, irregular pseudopods of pigment and asymmetric parallel linear extensions of pigment at the margin referred to as 'radial streaming'. A lace-like melanin pigment network is seen in both benign and malignant melanocytic lesions and is therefore not a useful discriminating feature. This network can, however, be seen to be broadened and irregular in melanoma. Some non-melanocytic lesions have a characteristic appearance on dermatoscopy, including vascular lesions and basal cell carcinomas. Angiomas are relatively easy to identify with the small capillaries being clearly seen through the epidermis. Basal cell carcinomas often have a characteristic clover leaf pattern of bluish pigmentation, which represents dermally situated melanin or altered blood trapped within the basal cell carcinoma cell nests. Seborrhoeic keratoses show clearly the keratin pits, which can be seen with the naked eye on their surface.

The technique of dermatoscopy is simple but interpretation of the patterns visualized requires some training and experience [4]. The best approach is to use the hand-held dermatoscope with a camera attachment (Dermaphot™), and record all lesions to be excised both with a conventional camera and with the Dermaphot™. These two images can then be studied when the pathology of the lesion is established.

There are also currently a number of computerized image analysis systems in development to aid preoperative diagnosis of malignant melanoma. These include the Mole Max system™ and spectrophotometric intracutaneous analysis using the siascope [5]. The absolute value of these machines in increasing both sensitivity and specificity of preoperative diagnosis of melanomas, thus reducing the number of unnecessary removals of benign naevi in routine practice, is not yet established.

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Biopsy. All patients with suspected malignant melanoma should have an excision biopsy of the lesion carried out with a narrow surrounding cuff of 1–2 mm of clinically normal skin. This will enable the pathologist both to confirm the diagnosis and also to measure the thickness of the melanoma, which is an essential guide to further management. In rare situations when an excisional biopsy is not practical, such as a large possible melanoma on the face, an incisional biopsy from the area of the lesion which appears to be most invasive is acceptable, provided any necessary definitive surgery follows within 1–2 weeks. Punch biopsies should not be routinely performed in suspected melanoma as a false tumour thickness may be obtained due to biopsy trauma and there is a theoretical risk of displacing melanoma cells deeper into the dermis. The surgeon should measure accurately the clinical excision margins, as biopsy samples shrink by 20–30% during fixation in formalin and the pathologist may report a narrower margin than was excised. It is the clinical rather than the pathologically measured excision margins that should be used in decisions concerning further surgery.

This biopsy should be ribboned by the pathologist and examined in total. Features required in the biopsy report are the diagnosis, the apparent completeness of excision, the tumour thickness, histogenetic type, presence of ulceration, presence of regression and an estimate of the number of mitoses both normal and abnormal in the tumour. Clark levels add little prognostic information for thicker primary melanomas, but should also be included, particularly for melanomas less than 1 mm in thickness, as Clark level 4 lesions in this thickness range appear to have a worse prognosis than level 3 lesions. It is also important to report the presence of regression if observed as this may influence decisions on the width of definitive excision.

In some cases there will be pathological evidence of a pre-existing benign melanocytic naevus on which the melanoma has developed. In these cases the pathologist may feel it necessary to give two tumour thicknesses, one measuring the entire thickness of the lesion and one measuring only to the deepest obvious tumour cell, ignoring any deeper apparent naevus cells.

Definitive surgical treatment to the primary site. Once the diagnosis of primary malignant melanoma is established, and the thickness of the melanoma has been measured, the definitive excision can be planned. The extent of this excision will relate to the tumour thickness. At present, if the diagnosis is of a level 1 or *in situ* melanoma, a margin of only 2–5 mm of surrounding normal skin is considered adequate. This may have been included in the diagnostic biopsy and therefore no further surgery may be necessary [1].

Invasive melanomas up to 1 mm thick require an excision margin of 1 cm, those 1–2 mm deep require a margin of 2 cm of clinically normal skin, and thicker tumours require a maximum margin of 3 cm of clinically normal skin [1]. There is no evidence that a wider margin of clinically normal skin improves survival for patients with thicker tumours. Most melanoma excisions can be closed directly, and skin grafts are nowadays rarely needed. Thus melanoma surgery is commonly a day case procedure carried out under local anaesthesia.

Patients with lesions on the fingers and toes may require amputation through the distal joint to achieve adequate clearance.

Further investigations. There is currently no evidence to support extensive staging investigations other than sentinel node biopsy (see below) for patients with stage 1 or 2 melanoma [1].

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Sentinel node biopsy. In the past decade, Morton and his colleagues have initiated large clinical trials to establish whether or not the technique of sentinel lymph-node biopsy, to assess the need for further surgery to the lymph-node basin, confers a survival advantage for patients with primary malignant melanoma still apparently confined to the primary site [1]. The results are awaited.

The principle behind the technique is the observation that a proportion of patients with thicker melanomas will have occult lymph-node metastases that are not clinically detectable on palpation. Studies on animal models have suggested that the drainage of tumour cells into a nodal basin such as the axilla or groin follows an orderly pattern with the most distal node, henceforward referred to as the sentinel node, trapping tumour cells first, prior to spread proximally to the other nodes in the area [2]. Thus, sampling this sentinel node would determine the need for further nodal surgery. A negative sentinel lymph-node biopsy would indicate that the proximal nodes would be clear of tumour and therefore that full node dissection was unnecessary. In contrast, a sentinel node containing tumour cells would indicate that the more proximal nodes might contain tumour and that a full lymph node dissection of the area was justified [3–8].

The technique requires three technical skills. These are lymphoscintigraphy to identify the lymphatic drainage pattern from the site of the primary melanoma, the surgical skills involved in injecting radiolabelled colloid and/or blue dye at the site of the primary melanoma to identify the sentinel node using a hand-held gamma probe (neoprobe), and the pathological skills to identify

what may be very small numbers of melanoma cells within a node biopsy and differentiating these melanoma cells from benign naevus cells which are found in around 10% of lymph nodes. There are detailed recommended protocols available for the handling of sentinel node biopsies to obtain maximum information using both conventional haematoxylin and eosin staining and also relevant antibodies in immunohistochemistry [9].

The technique of sentinel node biopsy is thus labour intensive and therefore expensive.

Careful studies of the frequency of positive sentinel nodes in melanomas of increasing thickness have established that melanomas less than 1 mm thick or of Clark levels 2 and 3 rarely yield positive sentinel nodes so the technique is not justified in these thin tumours. There is an increasing yield of positive sentinel nodes in thicker tumours, with a yield of around 30% positivity in patients with primary melanomas greater than 3 mm thick. In most published series, the yield of non-sentinel nodes containing melanoma following a positive sentinel node is 15–20%. At present sentinel node biopsy is a valuable staging technique in centres that have the trained personnel and resources to perform it. Results of the two large trials currently nearing completion will determine whether or not advancing the time at which the diagnosis of melanoma in the draining nodes is made offers the patient a survival advantage. Until these results are available, sentinel node biopsy should be considered a technique under evaluation rather than the current standard of care. It has, however, become a required investigation for entry into some adjuvant trials.

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Follow-up after surgery for stage 1 or 2 melanoma. Patients who have had surgery for primary melanoma with no evidence of spread beyond the primary site have traditionally undergone a period of hospital-based follow-up at varying intervals for a varying number of years. The three main purposes of this follow-up are to detect any local recurrence around the scar of the excised melanoma, to palpate the local draining nodes for any clinically detectable evidence of nodal spread and to examine the rest of the skin surface for a second primary melanoma. Accepted intervals and duration of follow-up are 3-monthly intervals for 3–5 years. As, however, there is no evidence that this routine follow-up examination advances the time of diagnosing metastatic spread, and the majority of recurrences are detected between such visits, these intervals can be interpreted according to the needs of individual patients and the geographical situation. All patients should be taught how to look for local recurrence, how to palpate the relevant area for enlarged nodes, and be made aware of the clinical features which would suggest a second primary melanoma. They should have information about an appropriate contact in case they detect possible recurrence between regular appointments.

Patients with only an *in situ* melanoma do not require to be placed on a follow-up regime but can be discharged after appropriate surgery.

Management of clinically involved lymph nodes. Patients who have palpable regional lymph nodes are highly likely to have metastatic spread in these nodes. Normal practice is to carry out a fine-needle aspirate or an open node biopsy to obtain pathological confirmation. If the pathology shows melanoma cells, a CT scan of the chest, abdomen and pelvis should be arranged to establish whether there is spread beyond the draining nodes. It is not normal practice in the UK to include a routine head and neck scan in asymptomatic patients, although this is a requirement prior to entry into some trials of adjuvant therapy. The patient should then have a full node dissection of the involved nodal basin. The number of nodes involved has been shown to affect prognosis and so this should be reported by the pathologist, as should the total number of nodes excised. Thereafter the patient should be followed up at 3-monthly intervals, or considered for randomization into ongoing trials for stage 3 disease. Appropriate investigations such as chest X-ray and CT scans should be arranged according to signs and symptoms.

Adjuvant therapy for patients with stages 2 and 3 melanoma. At present there is no proven effective adjuvant non-surgical therapy for these patients which has been shown to increase overall survival time. There have been several well-conducted randomized controlled trials using interferons and vaccines. Trials of interferon (IFN) have been in progress for the past decade and results of these trials involving around 5000 patients have been published

[1–7]. The dose of IFN, treatment schedule and duration of therapy is very variable, ranging from 1 million units given subcutaneously thrice weekly for 6 months to high-dose regimes involving megaunits of IFN given daily intravenously for 4 weeks and thereafter high maintenance doses for 11 months. Although some of these trials report early results of an increased disease-free interval in the IFN-treated group, only one trial has shown an effect on overall survival time from diagnosis [2], although the confirmatory study proved negative [5]. At present, patients with stage 2 or 3 melanoma should be considered for entry into available trials of IFN.

Trials of vaccines given as adjuvant therapy have not yet shown any survival benefit. Vaccines used have included an allogeneic tumour vaccine [8] and two vaccinia viral lysates [9,10]. None have shown improved survival, although tests of immune function have indicated an immune response to the virus.

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Management of patients with stage 4 disease

This will be mainly carried out by an oncologist who is part of a melanoma management team and who has an interest in melanoma. Even when stage 4 disease is obvious, accurate staging is still worthwhile, as if the disease burden is limited to, for example, one lung or one area of the gastrointestinal tract, further surgery to these isolated lesions may offer worthwhile palliation. This also applies to isolated cerebral metastases, and patients who are otherwise fit with cerebral metastases should be rapidly referred to a neurosurgical unit for evaluation for surgery, usually followed by radiotherapy.

The AJCC TNM staging revision has clearly indicated that patients with metastatic spread to certain areas, including the lungs and soft tissue, have a better outlook than those patients with spread to the liver or central nervous system. Lung and soft tissue lesions tend to be more responsive to chemotherapy, but even for these patients such responses are rarely complete and tend to be of short duration.

No chemotherapeutic agent gives a high proportion of complete responses in melanoma. The current chemotherapeutic agent of choice is dacarbazine (DTIC), which gives around a 20% overall response rate [1–3]. With modern antiemetics DTIC is relatively non-toxic and can be given as a day case, usually at 3-week intervals. Patients should be assessed for response after 4–6 courses. There is no evidence that combination therapy with DTIC and other chemotherapeutic agents or with IFN increases the response rate or the duration of response achieved by DTIC alone [4,5].

Patients with recurrent disease confined to one limb may obtain an extended disease-free interval with arterial perfusion [6–11] or infusion with melphalan or tumour necrosis factor-α, but a large controlled trial has demonstrated no survival benefit for this treatment used in an adjuvant or prophylactic setting for thick, poor-prognosis primaries on a limb.

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Radiotherapy. Malignant melanoma is traditionally

regarded as a radioresistant tumour. Radiotherapy has little part to play in the management of primary tumours, although it has been recorded in the past that the lentigo maligna melanoma variant is relatively radiosensitive, and radiotherapy has been used to treat elderly and infirm patients with these lesions [1,2].

Radiotherapy can be of considerable value in the palliation of metastatic disease in relieving pain from bony metastases. Intracerebral metastases can also be palliated by radiotherapy used in combination with systemic steroids [3,4]. Radiobiological studies have indicated that there is a large 'shoulder' effect when melanoma cells are irradiated. This term describes the observation that, if a given dose of radiation is divided into several small fractions, only a small proportion of the cells are killed and the remainder quickly proliferate. In contrast, if the same total dose of radiation is divided into a smaller number of larger fractions, a higher proportion of the cells are killed each time and the end result is more favourable.

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Melanoma, pregnancy and female sex hormones

Several large case–control studies and a meta-analysis suggest that oral contraception will not affect the outcome for women who have had stage 1 or 2 melanoma excised [1]. A recent prospective observational study of hormone replacement therapy (HRT) in women who have had melanoma shows no adverse effect of HRT, which can therefore be prescribed according to clinical need [2].

Primary melanoma diagnosed during pregnancy does not carry a worse prognosis than melanoma diagnosed in the non-pregnant state, although two studies show that melanomas diagnosed in pregnancy are significantly thicker than melanomas diagnosed in non-pregnant age-matched females [3,4]. Patients who develop stage 3 or 4 melanoma while pregnant require to be managed by an expert team. There is no evidence that termination of the pregnancy will alter the prognosis for the mother, but there is the possibility that the infant may have in its circulation melanoma cells transmitted from the mother through the placenta.

There is no evidence to suggest that pregnancy after melanoma therapy alters the prognosis, which continues to be determined mainly by tumour thickness.

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Prospects for primary and secondary prevention of melanoma

Melanoma is currently increasing rapidly in incidence in most countries for which adequate data are available. In some parts of the world there appears to be stabilization of the incidence rate in younger females. Mortality rates are not rising as rapidly as incidence rates and in some sections of the population are relatively static. This implies that patients are seeking medical help and thus receiving surgical excision earlier in the growth phase of their primary melanoma when the lesion is thinner and thus associated with a better prognosis.

Secondary prevention of melanoma is prevention of deaths from melanoma and thus is aimed at earlier diagnosis. Campaigns to encourage earlier presentation for treatment have been associated with a significant reduction in patient delay prior to seeking medical advice about a new or changing pigmented lesion, and also in a significant reduction in thickness of primary melanomas excised [1].

Primary prevention of melanoma is prevention of new cases developing and depends on knowledge of the aetiological agent and the capacity to avoid that agent. Although the exact relationship between melanoma and UV exposure is not fully established, cancer societies in many countries are introducing campaigns advocating a reduction in sun exposure, particularly for those who have the established risk factors, which include large numbers of banal naevi, dysplastic naevi and a family history of melanoma [2]. In view of the epidemiological evidence that excess sun exposure in early life leads to a greater risk of melanoma in adult life, much of this publicity is currently aimed at children and those responsible for their care.

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Chapter 39

Disorders of Skin Colour

S.S. Bleehen & A.V. Anstey

The colour of the skin [1–3]

Normal skin colour is dependent on haemoglobin (in both the oxygenated and reduced state), carotenoids and melanin pigment. The major colour determinant is melanin, and racial and ethnic differences in skin colour are related to the number, size, shape, distribution and degradation of melanin-laden organelles called melanosomes. These are produced by the melanocytes (Fig. 39.1) and are transferred to the surrounding epidermal keratinocytes. The wide variety of skin colour occurring in humans can be objectively measured by reflectance spectrophotometry [1,4].

Two types of melanin pigmentation occur in humans [2]. The first is *constitutive* skin colour, which is the amount of melanin pigmentation that is genetically determined in the absence of sun exposure and other influences. The other is *facultative* (inducible) skin colour or 'tan', which results from sun exposure. Increased pigmentation can also be due to endocrine causes, such as occur in pregnancy, and to interaction of light and hormonal effects, as seen in melasma (chloasma) and Addison's disease.

Variations in the degree of pigmentation occur in various regions of the body and are different in the various ethnic groups. In black people, the abdomen is the darkest and the lumbar region the lightest. In white people, the darkest area is the upper thigh and the lightest the lumbar region [5]. Females are generally lighter than males. In some ethnic groups, a sharply demarcated linear border is seen between more and less pigmented skin. This occurs in the Japanese [6] and black Americans [7], and is most noticeable on the anterior aspect of the arm between a dark lateral portion and a more lightly pigmented medial area. It is also seen in the lower legs and on the chest [5].

A blue colour is seen in the Mongolian spot that can occur on any part of the body, although most commonly in the sacral region. These spots fade after birth, but can persist in certain sites as in the naevus of Ota (see p. 39.42). The blue colouration of the skin is due to an optical effect and the presence of brown pigment in the dermis. It results from decreased spectral reflectance in the 'red' region compared with normal skin, and there is a subtractive mixing of colours [8]. Dermal melanocytes and pigmentation are commonly found in mammals and are seen in primates such as the vervet monkey [9] and the mandrill. The function of such blue coloration in sociosexual communication is explained in Chapter 4. Its development is dependent on androgens [10].

The carotenoids are yellow pigments that are exogenously produced and can be obtained only from plants in

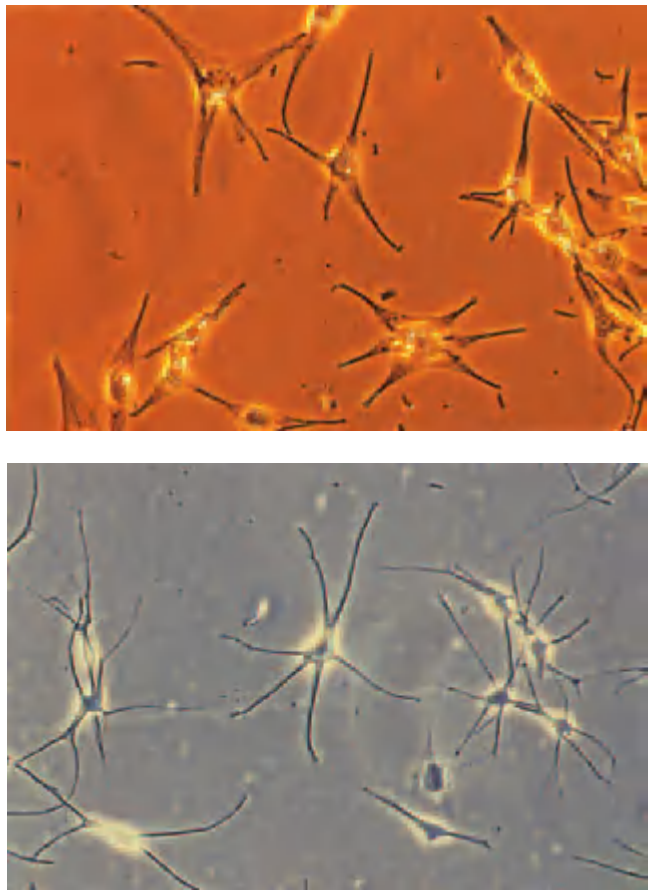

Fig. 39.1 (a,b) Melanocytes in culture. (Courtesy of Professor P. Friedmann, Royal Liverpool University Hospital, Liverpool, UK.)

the diet. These are to be found in the epidermis as well as the subcutaneous fat.

The evolution of pigmentary systems and their variety throughout the animal kingdom are reviewed in Chapter 2.

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The melanocyte [1–4]

Epidermal melanin unit

Melanin pigmentation in the skin in humans is a dual process, which involves not only the production of melanosomes within the melanocyte, termed *melanogenesis*, but also the distribution and transfer of these pigment granules to surrounding epidermal keratinocytes. Each epidermal melanocyte is surrounded by a group of keratinocytes with which it maintains functional contact, the whole being an epidermal melanin unit [1,5]. Although the number of active epidermal melanin units varies considerably in the different regions of the body (Fig. 39.2), the number of keratinocytes served by each melanocyte remains constant [6]. A single melanocyte supplies melanosomes to a group of about 36 keratinocytes.

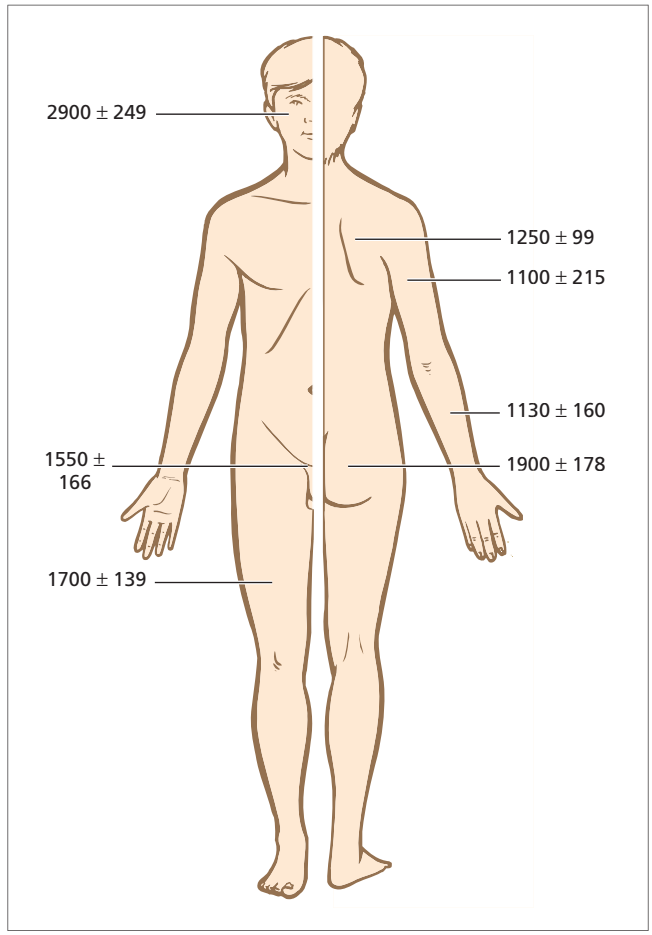

Fig. 39.2 Regional variation in the distribution of epidermal melanocytes. The figures are mean values per mm^2 ± standard error of the mean. (From Rosdahl & Rorsman [8].)

The concept of the epidermal melanin unit as a structural and functional unit, like the nephron of the kidney, has proved useful in the understanding of disorders of melanin pigmentation in humans. This concept has also been extended to classes of vertebrates other than mammals, and has been applied to reptiles and amphibia [7]. The epidermal melanocytes of frogs possess the capacity not only to produce melanin but also to rearrange the melanin granules within the cell and to produce an adaptation of skin colour to the background—a melanophore action [7]. In addition, fish, amphibia and reptiles have specially large pigment cells called chromatophores or melanophores, which lie in the dermis and have the capacity to disperse or aggregate the pigment granules which they contain [3]. The skin remains light when the pigment is aggregated in the centre of the melanophores and dark when it is dispersed to their periphery.

Three different mechanisms may be involved in the control of colour change. First, the pigment cell may act as an independent effector and respond directly to the stimulus of light; there is evidence that this can occur in some fish and amphibia [3] and the tanning processes of human skin, both immediate and delayed, can be considered to be analogous. Second, the movement of pigment within a melanophore may be under nervous control. The melanophores of fish are innervated by postganglionic sympathetic fibres, which are undoubtedly able to mediate contraction of the pigment and thus lighten the skin. A similar mechanism accounts for the rapid colour change of the chameleon. It has been claimed, but is not commonly accepted, that nervous mechanisms also play a part in the darkening of chromatophores in fish. Third, the activity of pigment cells may be under humoral influence [3]. Pituitary hormones that cause expansion of melanophores or promote the formation of melanin in epidermal melanocytes occur in fish, amphibia, reptiles and mammals. There is evidence of a lightening hormone in the amphibian pituitary, and a substance of similar function, known as melatonin, occurs in high concentration in the mammalian pineal body.

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Distribution of melanocytes

Melanocytes can be found in nearly every tissue but are most common in the epidermis, hair follicles, dermis, eye, around blood vessels, peripheral nerves and the sympathetic chain, and in the lining of the coelomic cavity. They are also present in the leptomeninges and inner ear. It is estimated that the total epidermal melanocyte population in a person is about 2×10^9 cells. The melanocyte mass forms a tissue with a volume of 1.0–1.5 cm^3 [1]. The distribution of epidermal melanocytes in different parts of the body varies, the population density in the face and genital areas being greater than in the trunk (Fig. 39.2) [1,2]. The range is from $2900 \pm 249/mm^2$ for the face to $1100 \pm 215/mm^2$ for the upper arm [1]. There are no significant sexual or racial differences. The differences in colour between white, oriental and black skin are due to the amount and arrangement of the melanosomes produced by the melanocytes. Ultrastructural studies [3–5] indicate that skin colour in the different races is largely determined by the size, packaging, distribution and degradation of melanosomes within the keratinocytes.

A reduction in the number of melanocytes occurs with ageing [6–8]. The melanocyte density decreases by 6–8% per decade. The density of melanocytes is about twofold higher in exposed than in non-exposed skin [2].

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Embryology and affinities

Melanocytes are remarkable in that in spite of their ubiquity they all arise from the neural crest [1]. This is a region of the embryonic ectoderm that originates from the margins of the neural plate at the time when it sinks in to form the tubular central nervous system. The neural crest gives rise also to some of the dorsal root and cranial ganglia and other miscellaneous structures. The dependence

of melanin formation on melanocytes of neural crest origin has been demonstrated experimentally in both amphibia and mammals [2,3].

Ultrastructural studies on early human embryos have shown the presence of melanocytes in the epidermis by the eighth week of gestation; by the 10th week these cells contain melanosomes showing early melanization [4]. Dendritic melanocytes have been identified in the black fetus at the 10th week using the silver impregnation technique [5].

The position and differentiation of melanocytes in the epidermis are influenced by keratinocytes. In cultured fetal skin equivalents, the melanocytes are grouped and distributed both basally and suprabasally, whereas in neonatal skin equivalents they are singly distributed among basal keratinocytes only [6].

It is generally accepted that melanocytes in the skin and hair continue to reproduce themselves by cell division, although mitotic melanocytes are rarely seen *in vivo*. Mitotic non-neoplastic melanocytes have been observed in the skin of mice and humans [7]. Stimulation of the mitosis of melanocytes occurs following UV irradiation [8]. The mitotic index of these cells is much lower than that of the keratinocytes.

Okun and co-workers presented morphological, enzymatic and histochemical evidence to support a histogenetic relationship between melanocytes and mast cells [9,10]. However, most pigment-cell biologists believe that these cells are quite distinct and of different embryonic lineage, the mast cell being of mesenchymal origin whereas the melanocyte is derived from the neural crest. For a long time, the Langerhans' cell was thought to be related to the melanocyte [11,12], but this dendritic cell is of bone marrow origin [13]. Langerhans' cells have been found in mouse skin deprived of its neural crest component [14].

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Fine structure of melanocytes

Melanocytes form a network of dendritic cells in the basal layer of the epidermis (see Fig. 39.10). They are also found in the external hair root sheaths and in the bulbs of hair follicles. These secretory melanocytes behave as unicellular glands producing melanosomes that are transferred to surrounding epidermal keratinocytes—a cytocrine activity [1]. Some do not transfer their melanosomes but redistribute them from the perinuclear zone into the dendrites and then back again. These non-secretory melanocytes are melanophores. Melanocytes may also be found in the dermis, particularly in some mammals.

The donation of pigment has been studied *in vivo* by electron microscopy [2,3] and *in vitro* using time-lapse cinematography (Fig. 39.3) [4,5]. The transfer of melanosomes involves the active participation of keratinocytes. Cell cultures have shown that melanocytes are rather inactive and non-mobile, and become dendritic in relation to keratinocytes. The tip of the dendrite of the melanocyte becomes embedded in the cytoplasm of the keratinocyte and the end becomes pinched off. A package of melanosomes is transferred to the keratinocyte, which acts as a phagocyte [6].

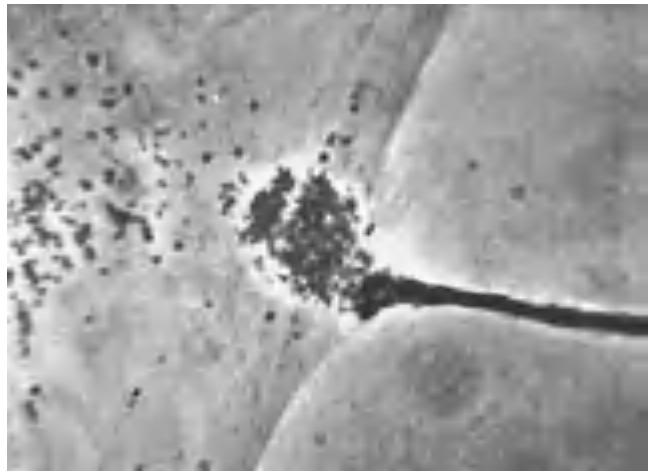

Fig. 39.3 Transfer of melanin granules from a melanocyte to an epidermal cell in a guinea-pig ear skin culture. (From Cruickshank & Harcourt [5].)

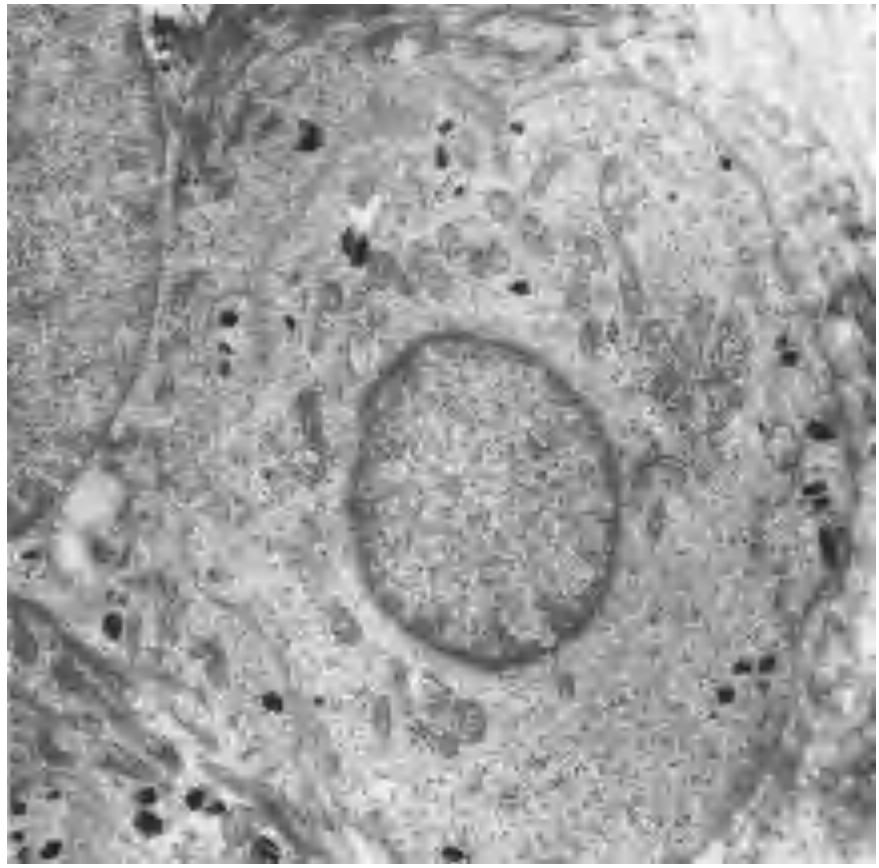

Fig. 39.4 Melanocyte in the basal layer of the epidermis. × 12 000.

Several theories have been suggested for the post-transfer digestion of melanosome complexes within the keratinocytes and their subsequent packaging. Experimental studies indicate that the melanosomes are packaged according to size, the larger ones as single units, the smaller ones as complexes of two or more [7].

On electron microscopy, the melanocyte is readily distinguishable from the keratinocyte by the lack of desmosomes and tonofibrils and by a more lucent cytoplasm (Fig. 39.4) [8].

The characteristic feature of the cell is the presence of special cytoplasmic organelles, the melanosomes, on which melanin is formed by the action of the enzyme tyrosinase. The developing melanosomes show varying degrees of electron density, the more fully melanized being very dense. Four stages of melanosomal development are recognized (Figs 39.5–39.7) [9]. Stage 1 is a membrane-bound, spherical vesicle derived from the Golgi apparatus. This vesicle may show tyrosinase activity or contain filaments that have a periodicity of particles along their length of 7 nm, characteristic of melanofilaments.

How the structural proteins and the enzyme tyrosinase are organized in these early melanosomes is uncertain, but according to the classical theory tyrosinase is produced on membrane-bound ribosomes and transferred via the endoplasmic reticulum to the Golgi apparatus,

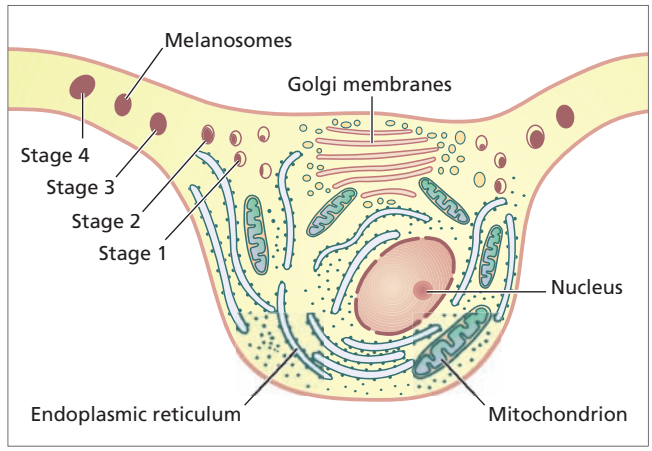

Fig. 39.5 Fine structure of a melanocyte. (From Jimbow *et al.* [12].)

where it accumulates in vesicles derived from the Golgi apparatus [10]. Stage 2 melanosomes are oval in shape and show numerous melanofilaments with and without cross-linking. In stage 3, the internal structure of the melanosomes is partially obscured by the deposition of melanin. By stage 4, the mature melanosome appears electron dense. Ultrastructural studies have shown that the fully melanized melanosomes are not as amorphous as

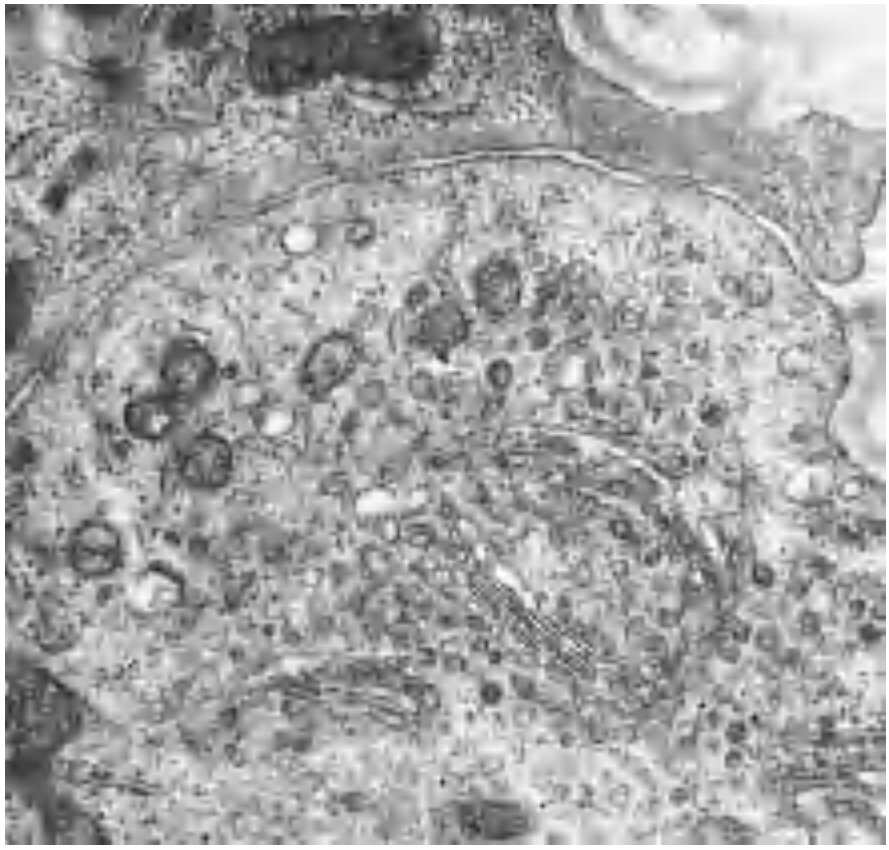

Fig. 39.6 Portion of a melanocyte in the basal layer of the epidermis of a tyrosinase-negative albino. Early stages of development of melanosomes in relation to the Golgi apparatus. Fine cytofilaments within cell. × 28 000.

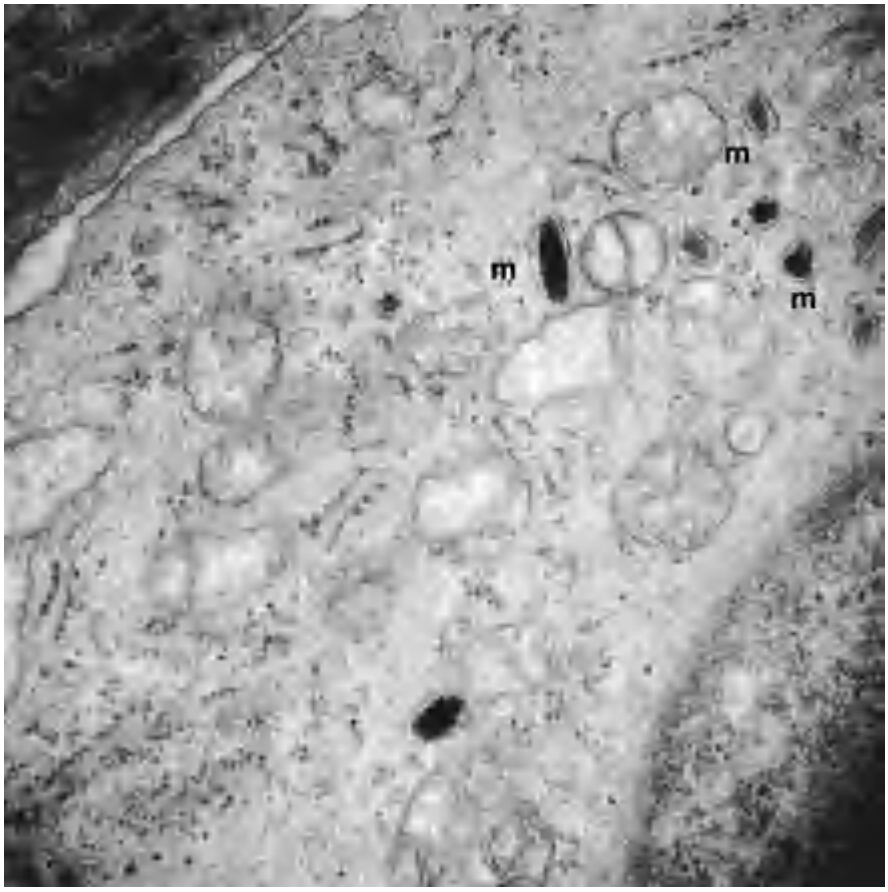

Fig. 39.7 Portion of a melanocyte in the basal layer of normal skin showing melanosomes (m) in various stages of development in the cytoplasm. × 28 000.

previously considered but contain spherical microvesicles called vesiculoglobular bodies [11]. These are involved in the organization of the melanosomes and are to be found in both the ellipsoidal filamentous eumelanosomes and the spherical phaeomelanosomes of human red hair [12]. The vesicular bodies are the key unit for the development of macromelanosomes [13,14].

The subcellular components of melanocytes have been isolated by density-gradient ultracentrifugation and the various fractions examined by electron microscopy and analysed for enzyme activity. The proof that melanosomes are the site of melanogenesis came from these studies, which also showed that the smooth and rough membranes as well as the melanosomes of the cells have tyrosinase activity [15,16].

Melanocytes also contain fine cytoplasmic filaments about 100 nm in diameter (Fig. 39.6). These are particularly prominent in the melanocytes of the pale skin of freckled and albino subjects [8]. Studies on tanning reactions in human skin indicate that they are concerned with the movement of dendrites and melanosomes within the melanocyte and the transfer of these organelles to the epithelial cells [17,18].

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Culture of human melanocytes

The culture of human pigment cells was at first frustrated by the problem of separating them from keratinocytes, which enjoyed the proliferative advantage, and by the fact that melanocytes would not multiply *in vitro* without the presence of mitogenic factors [1,2]. Selective plating of melanocytes was achieved by the addition of 12-*O*-tetradecanoyl phorbol 13-acetate (TPA) to culture media containing a mixed population of skin cells, and cholera toxin was shown to potentiate their mitogenic activity [3].

Melanocytes derived from both newborn foreskin and adult facial or truncal skin have been maintained in a tissue culture medium supplemented with epidermal growth factor, triiodothyronine, transferrin, insulin, cholera toxin and bovine hypothalamic extract dialysed to remove a keratinocyte growth factor present in the crude extract. After 3–4 weeks, pure melanocyte populations could be harvested and serially passaged up to six times over several months, with successive doubling of the cell numbers 10 or more times [4]. Such cultures have been used to study melanogenesis. For example, it has been shown that UV radiation from a solar simulator directly induces pigment formation in human melanocytes *in vitro*. There is a dose-related increase in melanin per cell and in uptake of ^{14}C-dopa, but an inhibition of growth. There are increases in the length and number of dendritic processes and in the number of melanosomes [5].

Melanocytes from melanomas and naevi have also been successfully maintained *in vitro* [6]. The melanocytes from uninvolved skin of subjects with vitiligo proved very difficult to culture [7], but they have been successfully isolated and seeded by adding the enzyme catalase to the medium and thereafter keeping the concentrations of calcium and TPA low [8].

Large-scale cultivation of human pigment cells appears possible by using collagen-coated Sephadex beads (Cytodex 3) as a microcarrier surface [2].

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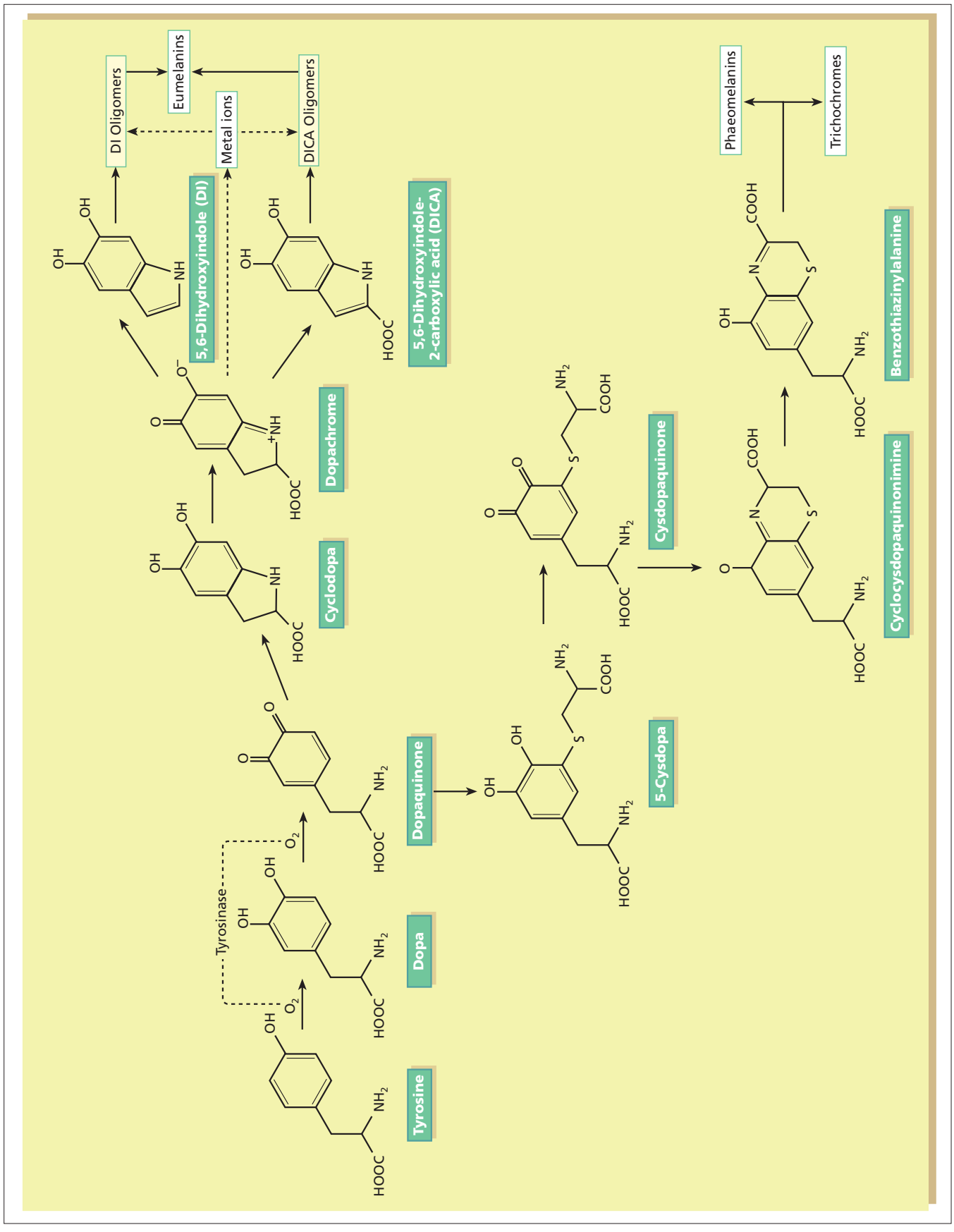

Fig. 39.8 A simplified overview of the major metabolic pathways in the synthesis of melanins and trichochromes. (From Prota [1].)

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Biochemistry of melanogenesis

Melanins are usually classified into two main groups: the black and brown eumelanins, which are insoluble, and the yellow and reddish-brown phaeomelanins, which are alkali soluble (Table 39.1). Eumelanins arise by oxidative polymerization of 5,6-dihydroxyindoles; phaeomelanins are chemically distinct, in that they contain sulphur in addition to nitrogen and are formed from cystein-*S*-yl-dopas (Fig. 39.8). However, the situation is complicated by the fact that some phaeomelanin-like pigments may be structural variants of eumelanins [1]. Thus, in the presence of metal ions, black insoluble eumelanin may be oxidized chemically or photochemically to a soluble form (melanin-free acid), which is light in colour [2,3]. A further complication is that red human hair contains, in addition to phaeomelanins, small amounts of intensely coloured pigments known as trichochromes [1,4], which were originally isolated from the red feathers of New Hampshire hens. Trichochromes are sulphur-containing pigments of a well-defined structure, of which six variants have so far been identified (Fig. 39.9).

Both eumelanins and phaeomelanins are derived from tyrosine, by the same initial steps. Tyrosine is oxidized to 3,4-dihydroxyphenylalanine (dopa) by the copper-containing enzyme tyrosinase, which also catalyses the further oxidation to dopaquinone (Fig. 39.8). Three distinct forms of active tyrosinase have been isolated from mouse melanoma. Two, T_1 and T_2, with similar molecular weights of 66 600 and 56 700, are soluble; one, T_3, is insoluble [5]. Recently, it has been found that not only tyrosinase is involved in melanogenesis but also the tyrosinase-related proteins TRP-1 and TRP-2 [6,7]. It has also been proposed that a peroxidase is involved in the initial conversion of tyrosine to dopa [8].

Table 39.1 Main types of epidermal melanin pigments. (Courtesy of Prota [1].)

Eumelanins	Black or brown nitrogenous pigments, insoluble in all solvents, which arise by oxidative polymerization of 5,6-dihydroxyindoles derived biogenetically from tyrosine via dopa
Phaeomelanins	Alkali-soluble pigments, ranging from yellow to reddish-brown; most of them contain sulphur in addition to nitrogen and arise by oxidative polymerization of cystein-*S*-yl-dopas via 1,4-benzothiazine intermediates
Trichochromes	A variety of sulphur-containing phaeomelanic pigments with a well-defined structure, characterized by a $\Delta^{2,2'}$-bi(1,4-benzothiazine) chromophore

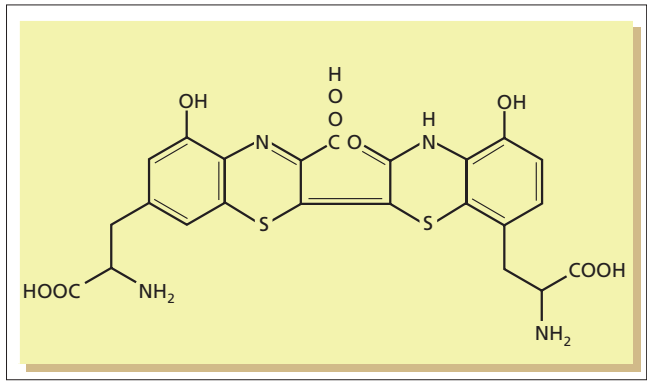

Fig. 39.9 Structure of trichochrome B, one of six trichochromes so far identified.

From dopaquinone the eumelanin and phaeomelanin pathways diverge. Eumelanins arise by oxidative polymerization of 5,6-dihydroxyindoles. In the classical Raper–Mason scheme, dopaquinone undergoes cyclization to cyclodopa (leukodopachrome), which is rapidly oxidized to dopachrome [9,10]. Dopachrome then becomes rearranged to form 5,6-dihydroxyindole (Di) or, in smaller amounts, 5,6-dihydroxyindole-2-carboxylic acid (DiCA). It was proposed that 5,6-indolequinone then polymerized by repeated condensations at the 3 and 7 positions.

The process is now believed to be more complicated [1,4,11,12]. Certain metal ions, such as copper, zinc and iron, are found in high levels in pigmented tissues and have long been thought to be involved in melanin pigmentation. It appears that zinc, copper, cobalt, nickel, and to a lesser extent iron, manganese and calcium, all catalyse the rearrangement of dopachrome to form DiCA rather than Di. The ratio of DiCA to Di determines the extent to which these intermediates take part in the subsequent polymerization process to form eumelanins. The final stages of conversion of Di, DiCA or mixed oligomers to eumelanins is little understood.

Most of the knowledge of the chemistry of the phaeomelanins comes from study of red hen feathers, although the pigments in human red hair are similar. Phaeomelanins have a complex structure made up of benzothiazole and tetrahydroisoquinoline units (Fig. 39.8) linked together by carbon bonds.

The biosynthesis of phaeomelanins and trichochromes involves the addition of the SH group of cysteine to dopaquinone to form cysteinyldopa, of which two forms have been characterized: 5-cystein-*S*-yl-dopa (5-cysdopa) and 2-cystein-*S*-yl-dopa (2-cysdopa). Dopaquinone will also link with glutathione to form colourless glutathione-dopa. The addition of cysteine or glutathione to quinones

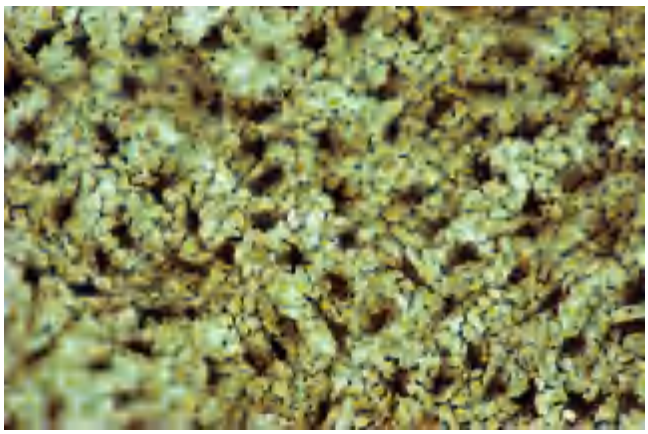

Fig. 39.10 Epidermal sheet of forearm skin incubated in dopa to show melanocytes.

are each fast non-enzymatic reactions that, in a sense, sidetrack the metabolic pathway leading to eumelanin formation. Glutathionedopas may be enzymatically converted to cysteinyldopas. Cysteinyldopa can be detected in the plasma and urine of patients with melanoma [13]. Prota [1] has reviewed these pathways and discussed their significance.

Melanocytes can be demonstrated by incubation of the skin in dopa (Fig. 39.10). Incorporation of labelled tyrosine into the cytoplasm of melanocytes has been shown by autoradiography [14]. Eumelanosomes and phaeomelanosomes appear to be morphologically different [14,15].

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Endocrine and paracrine influences

In many vertebrates, α-melanocyte-stimulating hormone (α-MSH) is the major hormone controlling melanin pigmentation [1]. This peptide is derived from a large precursor protein produced by the pituitary, pro-opiocortin [2]. In mammals, including humans, so-called 'β-MSH' is an extraction artefact [1,3] and is derived from β-lipotrophin, a precursor molecule for the opiate peptides (Fig. 39.11). Both α-MSH and β-MSH contain the same heptapeptide sequence

. Met . Glu . His . Phe . Arg . Trp . Gly .

which has a melanogenic effect. For maximal melanocyte-stimulating activity, the whole sequence is necessary [4]. γ-MSH, which has five of the amino acids in the sequence, has been shown to have some activity.

There is considerable evidence from studies with mouse melanoma cells [5,6] that MSH interacts with membrane receptors [7], leading to activation of adenylate cyclase (and formation of cyclic AMP) and increase in tyrosinase and melanin formation. The peptide β-endorphin and its derivatives met-enkephalin and melanotrophin-potentiating factor (MPF), which all lack the heptapeptide, do not activate this second messenger in mouse melanocytes [4]. In lizard skin, MPF potentiates the effect of α-MSH [8].

The mode of action of MSH on human melanogenesis is far less clear. Pigment formation in response to MSH has not been achieved *in vitro*. There is, however, evidence

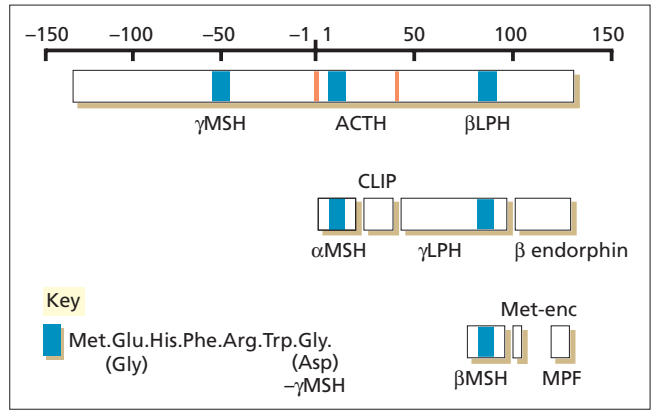

Fig. 39.11 Schematic representation of adrenocorticotrophic hormone (ACTH)/β-lipotrophin (β-LPH) precursor. MPF, melanotrophin-potentiating factor; MSH, melanocyte-stimulating hormone.

that MSH receptors are present, since cyclic AMP can be elevated [9]. The demonstration that an analogue of diacylglycerol (DAG) increases both the melanin content of cultured human melanocytes [10] and the incorporation of dopa suggests that DAG and the receptors linked to phospholipase C are also implicated in the intracellular signals [5,11]. Calmodulin antagonists both increase melanogenesis and decrease cell proliferation in cultured melanoma cells [12].

The culture of melanocytes *in vitro* has made it possible to investigate the possible role of local as well as systemic factors. In this respect, it is important to differentiate an effect on melanocyte proliferation from actions on the synthesis of melanin and its transfer to surrounding keratinocytes, which are mainly responsible for pigmentation.

As well as α-MSH, which can be synthesized not only by the pituitary but also within normal and abnormal pigment cells [13], basic fibroblast growth factor (bFGF) [14–16] is a naturally produced mitogen. Of a range of membrane-derived mediators of inflammation, only leukotrienes C_4 and D_4 have proved capable of stimulating melanocyte proliferation; arachidonic acid, prostaglandins D_2 and E_2, and leukotrienes B_4 and E_4 are ineffective [17]. The cytokines interleukin (IL)-1α, IL-6 and tumour necrosis factor-α (TNF-α) inhibit both melanocyte proliferation and melanogenesis [18].

The addition to melanocyte cultures of media in which keratinocytes have been incubated has been shown to increase melanocyte yield, total melanin and melanocyte dendricity. Because the addition of bFGF or other known mitogens has no effects in this system, it seems probable that other keratinocyte-derived factors influence melanocyte behaviour [19].

Many amphibians are able to adjust the colour of their skin rapidly to the external environment. Frogs placed on a dark background respond by the skin darkening due to dispersal of melanosomes within the melanophores. Later, there is an increase in melanogenesis. When they are placed on a light background, there is an aggregation of pigment granules within the melanophores. The epidermal melanocytes and dermal melanophores of frogs and other amphibians are extremely responsive to α-MSH and other melanotrophic hormones [20].

In humans, MSH stimulates melanogenesis, and an increase in the pigmentation of the skin is seen in a number of disorders where there are elevated levels of this polypeptide. Marked hyperpigmentation of the skin occurs in Nelson's syndrome (Fig. 39.12) and in Addison's disease. A darkening of black skin has been detected within 24 h of injection with MSH [21,22].

Evidence from animal experiments suggests that oestrogens, but not androgens, increase skin pigmentation. In mammals, pituitary and ovarian hormones are potent stimulators of melanogenesis [23].

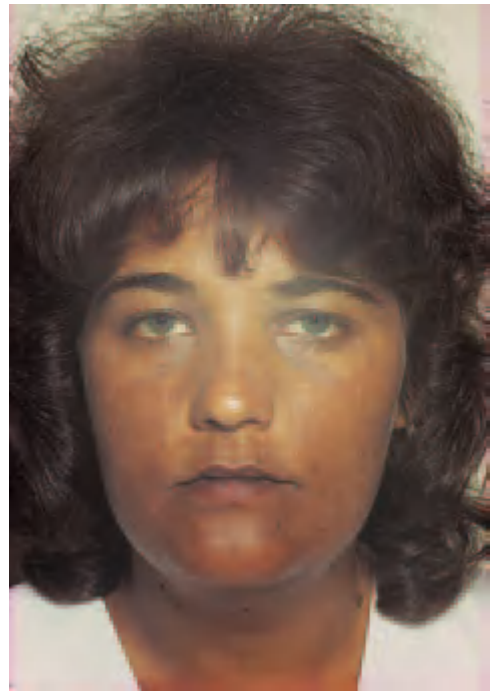

Fig. 39.12 Diffuse hyperpigmentation with darkening of hair and mucous membranes in a woman with Nelson's syndrome following bilateral adrenalectomy.

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Melatonin

The aggregation of melanin within the chromatophores and consequent lightening of the skin in the frog can be achieved by 5-methoxy-*N*-acetyl-tryptamine, known as melatonin [1]. This substance has been isolated from bovine pineal glands, although it is also present in much lower concentration in the hypothalamus and peripheral nerves [2]. Its action on frog chromatophores resembles that of epinephrine (adrenaline), norepinephrine (noradrenaline), acetylcholine, serotonin and triiodothyronine, but melatonin is by far the most potent, being 10^5 times as effective as norepinephrine [3].

There is conflicting evidence about the action of melatonin on mammalian epidermal melanocytes. On the one hand, a visible lightening of the skin has been produced within 2 days in melanotic dogs by treatment with 1 mg/day of the hormone [4]. On the other hand, large doses of melatonin have failed to alter the skin pigmentation of a human subject [5] or to cause any change, macroscopic or microscopic, in guinea-pig epidermis [6].

It is now unequivocally established that in seasonally breeding mammals the daily pattern of melatonin secretion by the pineal gland provides an endocrine measure of daylength and mediates its effect on reproductive function. Humans show a clear daily rhythm, and a fall in nocturnal serum melatonin occurs during prepuberty and pubescence [7,8]. Melatonin has been advocated for alleviating jet lag. A hypothesis that a decrease in melatonin secretion initiates puberty is discussed in Chapter 69.

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Biological significance of melanin

Melanin is widespread throughout the animal kingdom, where it appears to serve a variety of functions concerned with the protection of tissue and the gross coloration of animals. It is generally assumed that its major function in humans is protection of the lower layers of the skin against UV light. As keratinizing epidermal cells move outwards to become the stratum corneum, they carry with them melanosomes, which they have received from the melanocytes. The stratum corneum of oriental and black people is flecked with melanin, although this is not ordinarily so in white people.

If human pigment has such adaptive significance, we might expect to find that, among the races of the world, pigment is geographically distributed in relation to solar intensity. It appears to be generally true that pigmentation is greatest in the tropics and reduced in temperate zones, reappearing to some extent in northern races subjected to prolonged snow glare [1]. However, there are exceptions, for example native Americans are not notably different in skin colour throughout the whole continent, and Tasmanians are dark even though they live in a temperate climate.

The damaging role of UV light is well illustrated by the high incidence of epidermal carcinoma in Europeans exposed to the tropical sun. The evolutionary usefulness of pigmentation may be twofold. On the one hand, it protects against damage by sunburn. On the other, since it efficiently absorbs UV radiation and is readily activated to a free radical by incident light, it may serve to eliminate genetically damaged cells by a phototoxic mechanism.

Not all the effects of pigmentation are advantageous. There is no doubt that pigmentation increases the heat load in hot climates, so that black people absorb 30% more heat from sunlight than do white people, although this factor may be offset by more profuse sweating [2,3]. In addition, in cold climates pale skin has the advantage that heat loss by radiation is reduced.

A further disadvantage of pigmentation is that it vitiates against the synthesis of vitamin D, so that in areas of poor nutrition black children are more liable to rickets than white children. Thus, loss of pigmentation may facilitate vitamin D synthesis in temperate climates. It might be presumed that the retention of pigment in Arctic

latitudes, while providing a protection against snow glare, is only permitted by natural selection because of the high-fat diet in these areas.

Since pigmentation appears to be not entirely advantageous to life in the tropics, other hypotheses about its biological significance have been advanced. For example, Wassermann [4,5] has suggested that the major adaptation of black people to tropical Africa is in the ability to survive malaria, multiple parasites and tropical diseases under the hazards of intense solar radiation and, more often than not, poor nutrition. He suggests that diseases, not climatic conditions, are the primary selective factors, and lists evidence that black Africans, in comparison with white people, show increased reticuloendothelial activity and increased serum γ-globulin fractions. These features are inversely related to the size and activity of the adrenal cortex. Because of their primary decrease in adrenocortical function, black people show increased MSH and adrenocorticotrophic hormone (ACTH) activity, which enhances melanogenesis. Pigmentation might thus be a secondary phenomenon.

One of the most important properties of melanin is its free radical character. Electron spin resonance (ESR) studies show that melanin belongs to a class of so-called stable free radicals [6,7]. Skin irradiated with UV light shows an increase in free radicals, and ESR studies have shown that following irradiation a different type of signal is produced that is more apparent in white than in pigmented human skin [8]. Other studies also indicate that melanin acts not only in an optical fashion by diffusing and absorbing light, but also as a trap for electrons and possibly free radicals. Melanin can oxidize reduced NADH *in vitro* and can also participate in other oxidation–reduction reactions [9].

Because melanin is phagocytized by leukocytes, it can be circulated around the body. Melanin granules can be found in about 75% of the skin-draining lymph nodes in Bantu, but in only about 20% of similar nodes in white people. Thus, melanin circulating through the body may influence intracellular metabolism, and on these grounds could be regarded as a hormone [4,5].

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Pathogenesis of disorders of melanin pigmentation

Disorders of melanin pigmentation can be divided on morphological grounds into two types. The first is hypermelanosis, where there is an increased amount of melanin in the skin. This excess may be confined to the epidermis, when the skin appears browner than normal, or it may be present in the dermis, producing a slaty-grey or blue appearance. The second type is hypomelanosis, where there is a lack of pigment in the skin, which therefore appears white or lighter than the normal colour. Amelanosis is the term applied when there is a total lack of melanin in the skin. Hypermelanosis and hypomelanosis can be generalized and diffuse, or may be localized and circumscribed. Sometimes, localized areas may have a segmental or dermatomal pattern. The term 'depigmentation' is used to describe a loss of pre-existing pigment from the skin. Leukoderma is a white skin that may be congenital or acquired and can be due to a variety of aetiological factors. Examination of the skin with a source of long-wave UV light, for example Wood's lamp, is often helpful in localizing abnormal variations in melanin pigmentation in the skin and as an aid to the diagnosis of various disorders [1].

Changes in pigmentation can arise in a number of ways and can be due to a variety of genetic and environmental factors. Abnormalities may involve:

1 formation of melanosomes in melanocytes;
2 melanization of melanosomes;
3 secretion of melanosomes into keratinocytes;
4 transport of melanosomes in keratinocytes with and without degradation in lysosome-like organelles.

It is also pertinent to consider non-melanin pigmentation as a cause of cutaneous colour changes, as discussed at the end of this chapter.

Light and electron microscopy studies have considerably advanced our knowledge as regards the pathogenesis of many disorders of melanin pigmentation in humans. Only a few examples of pigmentary disorders are given here. In vitiligo, there is an absence of secretory melanocytes in the amelanotic areas. In piebaldism, in the amelanotic areas there is a complete lack of melanocytes. This probably results from a failure of migration of melanoblasts derived from the neural crest. Alternatively, it could be due to a failure of the cells to differentiate into melanocytes. In the hyperpigmented areas of human piebaldism, abnormalities are found in the formation and melanization of melanosomes. As with many of the disorders of pigmentation, more than one of the biological processes may be affected. Genetic studies carried out on mice show that white spotting is related to the action of approximately 70 genes at 40 loci [2,3]. It is therefore not surprising that there are so many genetically determined disorders of pigmentation in humans, with various modes

of inheritance. Genetic factors are involved in the migration of melanoblasts and their development and differentiation in the skin. The morphology of the melanocytes, the structure of the melanosome matrix, tyrosinase activity and the type of melanin synthesized are all under genetic control. Also, the patterns of melanosome transfer and of their subsequent degradation are determined by different genes. Melanosomal abnormalities occur in a wide variety of disorders. Giant spherical pigment granules (macromelanosomes) are found in the skin of patients with neurofibromatosis [4,5], naevus spilus [6], lentiginoses, X-linked recessive ocular albinism and Hermansky–Pudlak syndrome [7]. Abnormal giant melanosomal complexes due to a fusion of melanosomes are found within melanocytes in Chédiak–Higashi syndrome [8].

Defective melanization of melanosomes occurs in oculocutaneous albinism. In this group of inherited disorders, melanocytes are present but there is decreased or absent synthesis of tyrosinase and marked diminution in the biosynthesis of melanin. In tyrosinase-positive albinism, melanin synthesis can be induced *in vitro* when the skin or hair bulbs are incubated in tyrosine and dopa. In the tyrosinase-negative type this does not occur. There are various possibilities why there is defective melanization and it is possible that in the tyrosinase-positive type there is active inhibition *in vivo* of tyrosinase. Defective melanization occurs in untreated patients with phenylketonuria because of what is believed to be competitive inhibition of tyrosinase by the elevated levels of phenylalanine. Darkening of the hair is seen when these patients are put on diets that are low in phenylalanine.

Melanocytes can be lost from the skin as a result of such physical causes as thermal burns and ionizing radiation. Certain chemicals, particularly substituted phenols [9], have a selective destructive effect on functional melanocytes. Many of these compounds, for example the monobenzylether of hydroquinone, can produce in humans a permanent depigmentation of the skin, such as seen in vitiligo (Fig. 39.13). Acquired hypomelanosis may be due to a number of inflammatory disorders of the skin in which melanocytes may be lost and destroyed. Also, failure of the transfer of melanosomes from the melanocyte to surrounding keratinocytes can occur and probably accounts for the hypomelanosis seen in lesions of psoriasis and in eczema.

Hypermelanosis similarly can be due to many factors, both genetic and acquired. It can be due to an increased number of melanocytes in the skin such as occurs in the dermal melanocytoses: the naevus of Ota, the naevus of Ito and the Mongolian spot. Many of the hypermelanotic disorders are due to an increase in melanogenesis due to genetic factors. Some may be induced by UV light, hormones and chemical compounds. Rarely, patients with metastatic malignant melanoma develop a generalized hypermelanosis of the skin and mucous membranes due to numerous pigment-containing cells in the dermis [10,11].

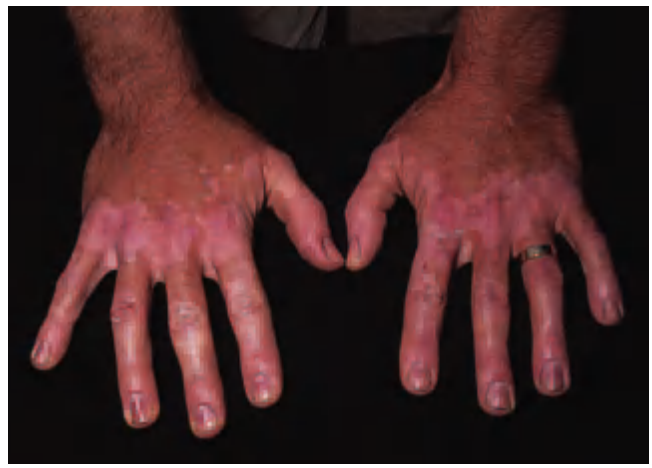

Fig. 39.13 Occupational vitiligo due to tertiary-butylphenol.

An ultrastructural study [12] has shown that in some white patients with diffuse hypermelanosis there is a tendency for the melanosomes to be dispersed singly in the keratinocytes rather than aggregated in melanosomal complexes. Large non-aggregated melanosomes, as seen in black skin, are found in tanned white skin treated with trimethylpsoralen and exposed to long-wave UV radiation [13].

Finally, the degradation of melanosomes may vary in different disorders of pigmentation. Autophagocytosis of melanosomes occurs in melanocytes in Chédiak–Higashi syndrome [8] and is seen in naevus depigmentosus [14].

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Normal pigmentation, racial variation and response to sun exposure

Genetic factors play the primary role in determining the degree of pigmentation that is normal for the individual, i.e. *constitutive* skin colour, as well as the response to exposure to sunlight, i.e. *inducible* skin colour [1]. Considerable variation in skin colour exists among humans, the main racial groupings being Caucasoid (white), Mongoloid (oriental), Negroid (black) and Australoid (aboriginal) (see Chapter 69). It has been estimated that three to four gene pairs account for the variation in colour between black and white people in the USA. Racial differences in melanocyte morphology are apparent, but the population density of melanocytes in a particular skin site remains relatively constant. The main cytogenetic differences lie in the size, shape and distribution of the melanosomes, particularly their packaging within the keratinocytes. Ultrastructural studies have shown that in white people the melanosomes are small and tend to be in membrane-bound complexes containing three or more within the keratinocytes [2,3]. The ellipsoidal melanosomes of aboriginals and black people are larger, about 1 μm in length, and tend to be distributed as singlets rather than being aggregated. These larger melanosomes can be found intact in the stratum corneum. The melanosomes in the complexes in white people show degradative changes even in the basal layer of the epidermis and are presumably broken up by lysosomal enzymes [4]. Whether melanosomes are individually dispersed or aggregated in melanosomal complexes appears to depend on the size of the melanosome [2].

The melanin in the skin has a photoprotective role [5]. Melanin acts as a neutral density filter reducing all the wavelengths of light. The superior photoprotection of the black epidermis is due not only to its increased melanin content but also to the packaging and distribution of the melanosomes [4].

A classification of sun-reactive skin types based on sunburn and tanning history is now in general use and has stood the test of time (Table 39.2) [6].

Two types of pigmentation of the skin in humans occur in response to sun exposure [1,7]. The first is immediate pigment darkening, referred to as the Meirowsky phenomenon. This is best observed in those with hyperpigmented skins and is most effectively induced by long-wave UV light (UVA). It is transient and, although rapidly induced, soon fades. The second is the increased pigmentation that follows the erythemal response. This is the delayed tanning reaction and can be seen 48–72 h after the exposure of the skin to UV light.

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Hypermelanosis

Familial progressive hyperpigmentation (MIM *145250) [1]

Familial progressive hyperpigmentation has been reported in a black family where diffuse macular areas of hyperpigmentation were present at birth and increased in size and number with age. Pigmented macules also involved mucosal surfaces. Four individuals in two generations were affected. Skin biopsy revealed increased melanin pigment, but normal melanocyte density in the epidermis. Ultrastructural examination revealed an

Table 39.2 Classification of sun-reactive skin types.

Skin type	Sun sensitivity	Pigmentary response
I	Very sensitive, always burn easily	Little or no tan
II	Very sensitive, always burn	Minimal tan
III	Sensitive, burn moderately	Tan gradually (light brown)
IV	Moderately sensitive, burn minimally	Tan easily (brown)
V	Minimally sensitive, rarely burn	Tan darkly (dark brown)
VI	Insensitive, never burn	Deeply pigmented (black)

increased number of melanin granules that were larger than normal [1].

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Periorbital melanosis

Some darkening of the skin around the eyes is not uncommon. Familial periorbital hyperpigmentation is characterized by dark circular areas around the eyes, and is determined by an autosomal dominant gene [1]. Increased pigmentation is first noted below the lower eyelids at the approach of puberty. There is wide variation in its ultimate extent and intensity.

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Lentiginosis

The histological and clinical features of lentigo, together with other lesions in which the number of melanocytes is increased, are fully described in Chapter 38. A lentigo is a benign pigmented macule in which there is an increased number of melanocytes. The term 'lentiginosis' is applied when lentigines are present in exceptionally large numbers or in a distinctive distribution. The following clinical syndromes can usefully be differentiated.

Generalized lentiginosis. Lentigines are commonly multiple but appear singly or in small crops at irregular intervals from infancy onwards. Their pathogenesis is unknown and in the great majority of cases no genetic factor is demonstrable.

Unilateral lentiginosis (zosteriform lentiginosis). Lentigines may occur on one side of the body [1]. Cases have been reported with and without associated neurological abnormalities [2–4]. The lentigines can be zosteriform and occur in a dermatomal-like distribution [5–7]. These cases are usually without central nervous system abnormalities and are of a naevoid nature. Lentigines have also been reported within naevoid hypopigmentation [8]. A case of unilateral lentiginosis with contralateral naevus depigmentosus has been reported [9].

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Eruptive lentiginosis [1–3]. Lentigines increase in number with age [4]. Very large numbers of lentigines may develop rapidly over the course of a few weeks, usually in adolescents and young adults. The lesions may be telangiectatic at first, but rapidly become pigmented and subsequently evolve as cellular melanocytic naevi.

Multiple lentigines syndrome (LEOPARD syndrome, MIM #151100) [5–9]. A syndrome has been characterized in which multiple lentigines are associated with a wide range of developmental defects. It is determined by an autosomal dominant gene with variable expressivity.

Lentigines are present at birth or first appear early in life and increase in number until puberty. They are most numerous on the neck and upper trunk, but occur all over the body, including the scalp, genitalia, palms and soles. Cardiac abnormalities are frequent—sometimes pulmonary or subaortic stenosis but more commonly conduction defects [10].

Several patients with this syndrome have died at an early age from obstructive cardiomyopathy [7]. Growth tends to be retarded. Ocular hypertelorism and mild mandibular prognathism are the most usual of a variety of skeletal abnormalities. Inconstant features are deafness and genital abnormalities. The deafness, which may be profound, is of sensorineural type. The genital abnormalities include gonadal hypoplasia, hypospadias and delayed puberty. This very variable syndrome has been named LEOPARD syndrome, comprising *l*entigines, *e*lectrocardiographic abnormalities, *o*cular hypertelorism, *p*ulmonary stenosis, *a*bnormalities of the genitalia, *r*etardation of growth and *d*eafness.

Histological studies of the lentigines show an increase in pigment in the epidermis with an increased number of melanocytes that are glutted with melanosomes [6]. Macromelanosomes are found in the multiple lentigines syndrome [11].

Many case reports of hereditary generalized lentiginosis are insufficiently detailed to allow their precise classification. In one family, fixation nystagmus is mentioned as an associated defect. It is possible that some such cases are examples of the very variable LEOPARD

syndrome, but the existence of more than one genotype for generalized lentiginosis is not excluded.

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Centrofacial lentiginosis (MIM 151000) [1–3]. This uncommon syndrome is apparently determined by an autosomal dominant gene. Small brown or black macules appear during the first year and increase in number up to the age of 8 or 10 years. Their distribution is restricted to a horizontal band across the centre of the face. The mucous membranes are not involved.

Associated defects include coalescence of the eyebrows, a high-arched palate, absent upper median incisors, sacral hypertrichosis, spina bifida and scoliosis. Mental retardation is frequent and many affected individuals are epileptic.

A somewhat similar disorder of multiple lentigines in a centrofacial distribution, sparing the mucosae, but also with lesions on the buttocks, palms and soles, has been reported in black people [4]. Inheritance is dominant. There have been no systemic changes.

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Peutz–Jeghers syndrome (MIM 175200)

SYN. PERIORIFICIAL LENTIGINOSIS

Aetiology. Peutz–Jeghers syndrome is an autosomal dominant disorder characterized by lentigines on the lips, buccal mucosa, fingers and toes in association with intestinal polyps [1–3]. Study of a large pedigree [4] demonstrated the variability of the manifestations; clinically normal carriers and monosymptomatic cases are recognized. Peutz–Jeghers syndrome is caused by mutations in a novel serine threonine kinase; the gene has been mapped to chromosome 19p13.3 [5].

Pathology. The pigmented macules show an increase in the amount of melanin in the basal layer of the epidermis. Polyps are found throughout the gastrointestinal tract. They are most numerous in the jejunum and ileum and less frequent in the colon, rectum, stomach and duodenum. In general, the polyps are benign hamartomas. They may show histological rather than biological evidence of malignancy [1,6]. The true malignant potential of the polyps is not as great as in some other genetically determined syndromes with colonic polyps but is not negligible. Malignancies, usually fatal, have involved mainly the gastrointestinal tract (stomach, duodenum, jejunum, colon, rectum, pancreas). There also seems to be an increased incidence of malignancy in other organs (breast, ovary and also some less common types). In one series, there were 16 fatal malignancies in 72 cases with an average age at death of 36 years [7,8]. In another series, 15 of 31 cases had malignancies [9].

Clinical features [1,2,4,6]. Both sexes and all races may be affected. About 40% of cases have no family history and are presumed to be new mutations. The pigmented macules usually appear in infancy and early childhood, but may be present at birth or may develop later in life. The oral mucous membrane is almost constantly involved. Round, oval or irregular patches of brown or almost black pigmentation 1–5 mm in diameter are irregularly distributed over the buccal mucosa, gums, hard palate and lips, especially the lower lip. The pigmented macules on the face are smaller, often under 1 mm, and darker, and are concentrated around the nose and mouth. Larger macules may be present on both aspects of the hands and feet and may be conspicuous on palms and soles. The oral pigmentation is usually permanent, but the macules on the lips and skin may fade after puberty. Rarely, the nails may be pigmented, diffusely or in longitudinal bands. In one case, new pigmented lesions appeared preferentially in areas that had previously had psoriasis [10].

Symptoms attributable to the polyps usually occur between the ages of 10 and 30 years, but may occur in early childhood or be delayed until later adult life. The most common symptoms are repeated attacks of abdominal pain caused by intestinal obstruction. Rectal bleeding is common and haematemesis may occur with gastric or duodenal polyps. Many patients are anaemic. Although there have been several reports [9] of an association with intestinal cancers, the risk is small and the prognosis is similar to that of the general population [11].

Mucosal and facial pigmentation without evidence of intestinal polyposis may be found in relatives. Indistinguishable pigmentary changes beginning in adult life also occur sporadically in individuals without intestinal involvement. In three generations of one family, facial and mucosal lentiginosis occurred without polyposis [12].

Associated abnormalities. Clubbing of the fingers has been noted in many cases. Of women with this syndrome, 10% have ovarian tumours. A granulosa–theca cell tumour of the ovary has been associated in several cases. Precocious puberty in both sexes has been associated with hormone-secreting tumours [8,13]. Lentiginosis of Peutz–Jeghers distribution has been found in association with intestinal haemangiomatosis, which was the source of recurrent severe haemorrhage [14].

Diagnosis. The mucosal pigmentation is the most constant feature of the syndrome. It may require differentiation from that of Addison's disease, in which there is also diffusely increased pigmentation elsewhere. Freckling occurs in those of fair complexion, but the macules are light-influenced, are not periorificial in distribution and do not involve the mucous membranes.

In Cronkhite–Canada syndrome (see below) the volar aspects of the fingers are diffusely pigmented but the mucous membranes are spared. Examination of relatives may assist the diagnosis. At a stage when the polyps are already giving rise to symptoms they may not always be radiologically detectable.

Treatment. In many cases, it may be appropriate to undertake regular endoscopic examinations of the upper gastrointestinal tract and of the whole colon, together with barium follow-through studies of the small intestine every 2 years or so. A pelvic examination should also be done. In view of the generally benign nature of the polyps, routine radical surgery is not required. Individual polyps may require endoscopic or surgical removal. Prophylactic colectomy has sometimes been advocated for cases with numerous colonic polyps.

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Cronkhite–Canada syndrome (MIM 175500) [1–6]

Cronkhite–Canada syndrome is a rare syndrome of unknown origin, in which diffuse pigmentation of the palms and the volar aspects of the fingers and macular pigmentation of the dorsa of the hands are associated with gastrointestinal polyposis [1–4,6] (see Chapter 59). The skin changes are assumed to be the result of malabsorption associated with the protein-losing enteropathy.

Diarrhoea, abdominal pain and weight loss, beginning in adult life, are the presenting manifestations. Alopecia, patchy at first but becoming total, begins a few months later, and dystrophic changes in the nails develop at the same stage. The nail dystrophy is distinctive but not pathognomonic and could be explained by the formation of ventral nail in the absence of normal nail production by the matrix [4]. Exceptionally, the nail changes may precede gastrointestinal symptoms by months or years [5].

Hyperpigmentation is present in more than 85% of patients [2]. It consists of light to dark brown lentigo-like macules ranging in size from a diameter of a few millimetres to 10 cm. These hyperpigmented macules are scattered but are most numerous on upper and lower extremities, face, palms and soles. The mucosal surfaces are usually spared, although the buccal mucosa is occasionally affected. In some patients hyperpigmentation is generalized. Treatment of the malabsorption leads to reversal of hyperpigmentation in most cases.

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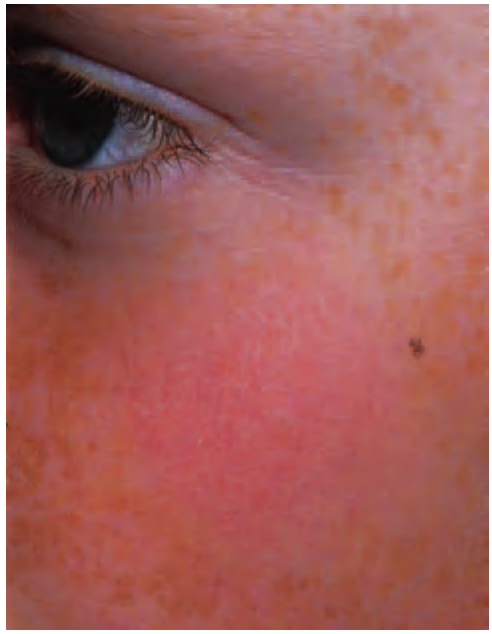

Fig. 39.14 Freckles, one area of which has been bleached by a superimposed patch of pityriasis alba.

Ephelides

SYN. FRECKLES

Freckling is probably determined by an autosomal dominant gene [1]. It is most frequent in individuals with red or blonde hair and blue eyes, particularly in those of Celtic extraction. Red-haired individuals with fair skin (and freckles) have a significantly higher incidence of the gene encoding melanocortin receptors [2,3].

Pathology [4]. There is no increase in the number of melanocytes in the pigmented macules but their melanosomes are long and rod-shaped, like those found generally in dark-skinned people. They form melanin more rapidly after exposure to sunlight than do those in the surrounding pale skin, which are spherical and often granular, and are of the type usually found in fair- and red-haired individuals. With the light microscope, the only abnormality detectable is an increase in the quantity of melanin in the epidermis.

Clinical features (Fig. 39.14). Freckles first appear at about the age of 5 years as light-brown pigmented macules on light-exposed skin. They increase in number, size and depth of pigmentation during the summer months and are smaller, lighter and fewer in number in the winter. They may be cosmetically disfiguring or may enhance appearance, but are not otherwise of significance.

The incidence of melanocytic naevi is increased in freckled individuals.

Treatment. Freckles seldom require treatment and may sometimes be regarded as a desirable cutaneous feature. However, they are amenable to removal by laser for those who desire it [5,6]. Solar lentigines may be improved in appearance by topical treatment which includes retinoic acid [7].

Freckles in various syndromes. Freckles are a feature of a number of inherited and acquired disorders described in this chapter. These include xeroderma pigmentosum [8], neurofibromatosis, Moynahan's syndrome and progeria. The lesions in the various forms of lentiginosis (see above) must also be differentiated. Their distribution and the lack of relationship to light exposure should be noted.

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Cutaneous lentiginosis with atrial myxomas (MIM 160980) [1–4]

SYN. NAME SYNDROME; LAMB SYNDROME

This is a rare syndrome comprising various cutaneous pigmented lesions, particularly freckles, cutaneous myxomas, atrial myxomas, which are sometimes bilateral, other cardiac lesions (see Chapter 59) and cerebral artery aneurysms. NAME syndrome comprises *n*aevi, *a*trial myxomas, *m*yxomas of the skin and *e*phelides. Blue naevi occur in LAMB syndrome [4].

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Laugier–Hunziker syndrome [1,2]

This rare syndrome of unknown aetiology has no known genetic basis. It is characterized by macular pigmentation of the lips and buccal mucosa together with linear black streaks of the nails. Onset is usually in adult life. There have been no systemic changes. The differential diagnosis of striate melanonychia is considered in Chapter 62.

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Penile melanosis/vulvovaginal melanosis [1–3]

Acquired, irregular, brownish or slaty-brown discoloration of the glans or shaft of the penis or of the vulva and vagina may give rise to fears of malignant potential. Histologically, there is only an increase of pigment without any increase or atypia of the melanocytes.

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Incontinentia pigmenti (MIM #308300)

SYN. BLOCH–SULZBERGER SYNDROME; BLOCH–SIEMENS SYNDROME

Definition. Incontinentia pigmenti is a complex hereditary syndrome in which vesicular, verrucous and pigmented cutaneous lesions are associated with developmental defects of the eye, skeletal system and central nervous system [1].

Aetiology. The condition is not excessively rare and cases have been reported from many countries [2].

Most pedigrees are small, but from the accumulated genetic data [2–5] it appears that this syndrome is due to an X-linked dominant trait that is usually lethal in males. More than 95% of the reported cases are females, the few males being probably the result of spontaneous mutations and mosaicism of the X chromosome [6,7]. Initial studies indicated that the gene was on chromosome Xp11.2 [8], but subsequent studies confirmed the locus to be on Xq28 [9,10].

Incomplete forms of the syndrome are found in some female relations [4].

Pathology [2]. The bullae are situated beneath the horny layer or within a spongiotic epidermis. The dermis shows non-specific inflammatory changes with a cellular infiltrate, including numerous eosinophils. The infiltrate extends into the epidermis, and the contents of the bullae may consist predominantly of eosinophils (Fig. 39.15). The lichenoid papules show hyperkeratosis, acanthosis and oedema of the basal layer, many cells of which are degenerate. Macrophages laden with melanin are present in the upper dermis. In the warty lesions, the hyperkeratosis is further increased, and within the irregularly acanthotic epidermis are hyaline bodies representing individual cell keratinization. The epidermal changes at this stage may suggest pseudoepitheliomatous hyperplasia. The pigmented patches show diminution or absence of pigment in the basal cells and large quantities of melanin in melanophages in the upper dermis. The epidermis may be normal or slightly acanthotic.

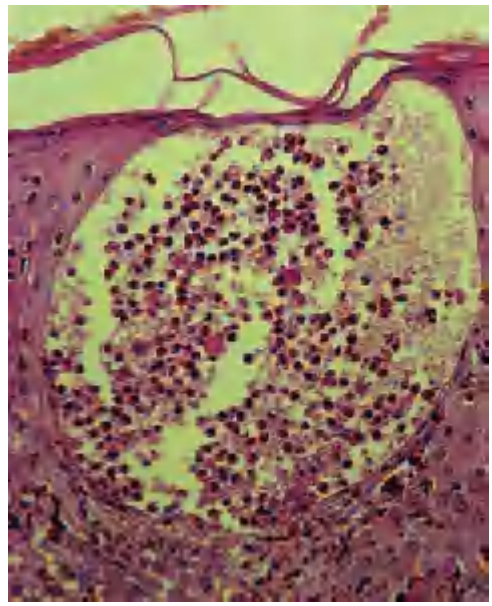
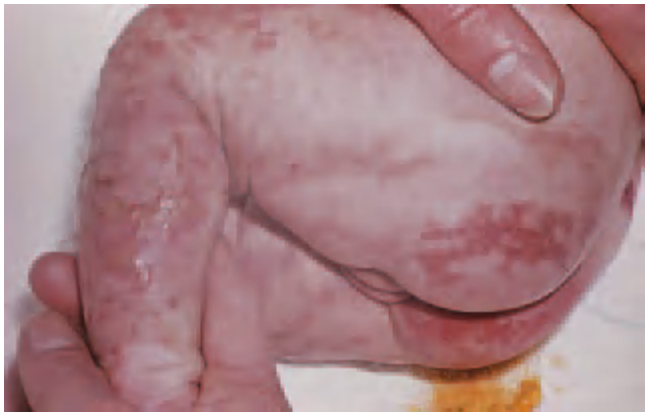


Fig. 39.15 Incontinentia pigmenti. Intraepidermal vesicle containing eosinophils. The spongiotic epidermis has been invaded by an inflammatory infiltrate that includes many eosinophils. Dyskeratotic cells are present.

Ultrastructural studies [11,12] show that, particularly in the early stages, there are many dyskeratotic cells in the epidermis. In addition to eosinophils, there are activated lymphocytes, basophils and mast cells, especially in the upper dermis [13]. In all three stages, melanophages are present.

Clinical features [2,14–16]. The skin changes are often present at birth, have usually developed before the end of the first week and rarely appear after the first 2 months. Three clinical stages are recognized: (i) bullae, (ii) papular and warty lesions, and (iii) pigmentation. However, their sequence is irregular, their duration variable and they

(a)



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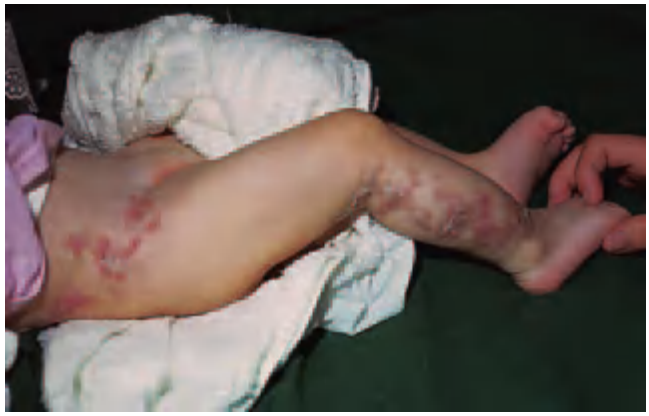

Fig. 39.16 Incontinentia pigmenti: (a) linear groups of blisters in a child aged 3 weeks; (b) linear warty lesions on the lower leg of the same child aged 3 months.

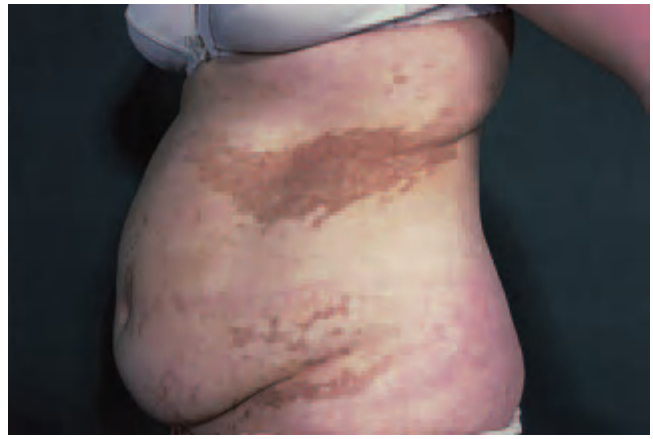

Fig. 39.17 Slate-grey pigmentation on the abdomen of a woman who had blistering lesions in childhood and who gave birth to a child with typical incontinentia pigmenti.

may overlap. It is possible that the earlier inflammatory stages can occur *in utero* and not progress after birth.

Clear tense bullae, often in linear groups (Fig. 39.16), develop on the limbs in recurrent crops; less often they are generalized. The crops continue for a few days or for a month or two. They are accompanied or followed by smooth red nodules or plaques, often irregularly linear, on the limbs and trunk. The plaques may be extensive and may precede the bullae. They may be bluish-purple in colour and may ulcerate. Linear warty lesions may appear on the dorsa of hands and feet, particularly on the fingers and toes. Warty lesions around the nails with underlying lytic bone lesions have occurred in adolescence [17]. The pigmentation, which may be the only abnormality, may be present from the outset or may appear as the inflammatory lesions are subsiding, although not necessarily in the same sites; inflammatory lesions can develop in areas that are already pigmented. Activity may rarely persist into adult life [14]. The pigmentation, ranging in colour from blue-grey or slate to brown (Fig. 39.17), is characteristic of the syndrome, and the bizarre 'splashed' or 'Chinese figure' distribution is diagnostic. Multiple, linear and macular telangiectases have occasionally been present [18].

Peripheral eosinophilia, up to 50%, is usual when acute inflammatory skin changes are present. There is evidence of both neutrophil and lymphocyte dysfunction, and altered immunological reactivity is observed in some patients [3,19].

The inflammatory lesions are uncommon after the age of 6 months but may be followed by atrophy or sclerosis. The pigmentation persists for many years, slowly fading until it is imperceptible by the second or third decade. Hypopigmented and atrophic streaks are not uncommonly found in the later stages of incontinentia pigmenti. They may also occur in young children. They may be anhidrotic [13]. Such lesions may be the only remaining sign of childhood disease and may then be of importance in counselling parents who already have an affected child. The hair is usually normal, but in about 25% of cases patches of cicatricial alopecia, resembling pseudopelade, are present from birth or develop in infancy at or near the vertex. The nails are usually normal but may be small and dystrophic. A case of keratoacanthoma developing within a pigmented area of incontinentia pigmenti was speculated to represent a late manifestation of the disease [20].

In over half the reported cases, organs other than the skin have also been involved.

Dental defects are frequent: delayed dentition, partial anodontia and cone- or peg-shaped teeth are the most usual. The absence of teeth, especially the upper lateral incisors and premolars, has been recorded in otherwise unaffected siblings and in the mother who may likewise appear normal.

Ocular defects [2,21] are found in about 30% of cases, many patients being blind. The defects include strabismus, cataract, uveitis, optic atrophy, retinal vascular abnormalities

and a condition resembling retrolental fibroplasia. Microphthalmia also occurs.

Central nervous system disorders [2] occur in about 25% of cases. These include mental retardation, slow motor development, spastic tetraplegia and diplegia, microcephaly and epilepsy.

Skeletal abnormalities [2] are less common and are usually minor, although skull and palatal defects are reported.

Diagnosis. The combination of bullae with linear nodular or warty lesions in a female infant is pathognomonic. During a purely bullous phase, infantile pemphigoid must be excluded. Both conditions present with blood and tissue eosinophilia, but in infantile pemphigoid the eruption remains monomorphic and the bullae, in irregular clusters, commonly develop on the hands, feet, face and genitalia and are not followed by the characteristic pigmentary changes. Epidermolysis bullosa and other bullous eruptions of infancy should not cause difficulty. At a later stage when only the splashed pigmentation is present, it has to be differentiated from post-inflammatory pigmentation of other types and from other genetically determined pigmentary disorders. Incontinentia pigmenti achromians (hypomelanosis of Ito) is a completely separate disease (see p. 39.52). Biopsy of the skin in the blistering phase is often of help in establishing the diagnosis (see Fig. 39.15) with the presence of many eosinophils in the epidermis and dermis.

Treatment. Usually no treatment is necessary other than the control of secondary infection. Systemic therapy with corticosteroids or sulfapyridine (sulphapyridine) is usually unsuccessful. Skilled dental supervision will minimize the cosmetic disability. As with other serious genetically determined disorders, family counselling should be offered.

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Fanconi's syndrome (MIM #227650) [1–9]

SYN. PANCYTOPENIA WITH CONGENITAL DEFECTS

Fanconi's syndrome is a rare autosomal recessive condition characterized by widespread mottled skin pigmentation, petechiae, microcephaly, genital hypoplasia, generalized hyperreflexia, internal strabismus and normal intelligence [1,2,8]. The full syndrome occurs more frequently in boys than in girls.

Chromosome breakages occur in a high proportion of phytohaemagglutinin-stimulated lymphocytes in most of the patients studied. A DNA-repair defect is implicated [4].

Clinical features [1,2,8]. The age of onset is usually between 4 and 10 years, and either cutaneous or haematological abnormalities may be the presenting manifestation. In 85% of cases, there is generalized, dusky or olive-brown pigmentation, often most intense on the lower trunk, in the flexures and on the neck. Scattered over the dusky areas are often depigmented macules of 'raindrop' type and macules of darker pigmentation. Rarely, only café-au-lait macules are present.

A constant feature is progressive hypoplastic anaemia with neutropenia and thrombocytopenia, usually presenting as an increased bleeding tendency [7]. The haematological manifestations appear earlier in males. The pancytopenia usually causes death in 2–5 years. In recent years, treatment with anabolic steroids has improved survival, and histocompatible bone marrow transplantation is also to be considered. Haematological defects may be

present in otherwise normal siblings. There is an increased incidence of acute leukaemia and other neoplasms [3].

Affected children are usually of slender build with short broad hands with tapering fingers. The thumbs are often rudimentary, with aplasia of the radii. Microcephaly, mental retardation and hypogonadism are frequent and other developmental defects occur. Few patients survive to adult life, although this is recorded [2].

Diagnosis. The diagnosis of Fanconi's anaemia is made on clinical grounds and by haematological assessment. The association of pigmentation of very similar type with pancytopenia is seen only in dyskeratosis congenita. Prenatal diagnosis is now possible by demonstrating increased spontaneous and induced chromosomal breakage in cultured fetal amniocytes or chorionic villous cells [9].

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Albright's syndrome (MIM #174800) [1–7]

Albright *et al*. [1] described a syndrome in 1937 characterized by polyostotic fibrous dysplasia, skin pigmentation and (in females) precocious puberty.

Aetiology. The cause is unknown. Simple monostotic and polyostotic fibrous dysplasia affects the sexes equally and is relatively common. Fibrous dysplasia with associated pigmentation is unusual and is more frequent in females than in males. The full syndrome with precocious puberty occurs only in girls [2,3].

Pathology [4]. In the majority of patients, the number of melanocytes is not increased either in the lesions or in normal skin, and in split-skin preparations the giant pigment granules characteristically seen in Malpighian cells and melanocytes in neurofibromatosis are rarely to be found.

Clinical features [1,4–7]. Cutaneous pigmentation usually develops between the ages of 4 months and 2 years,

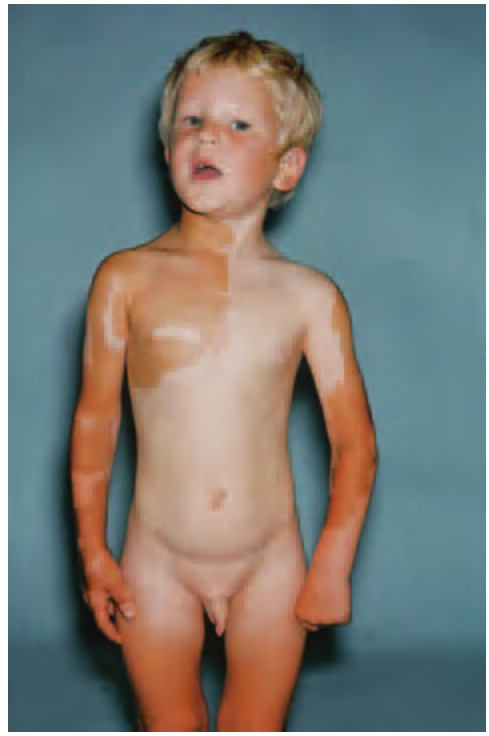

Fig. 39.18 Large pigmented macules in a child with Albright's syndrome. (Courtesy of Professor N.R. Rowell, Leeds General Infirmary, Leeds, UK.)

but may be present at birth. Extensive light-brown patches, often with an irregular or serrated margin, occur mainly on the trunk, buttocks and thighs, but may rarely involve the face and neck. They tend to be asymmetrical and to be most extensive on the side showing the most severe bone involvement (Fig. 39.18).

The bone lesions usually reveal themselves during the first decade by aching pain, pathological fractures and secondary deformities [3]. Bony overgrowth at the base of the skull may produce defective vision or proptosis. Serum calcium and phosphorus are normal but alkaline phosphatase may be elevated if the bone lesions are numerous. In females, precocious puberty, manifested by breast enlargement or by vaginal bleeding and growth of pubic hair, occurs below the age of 5 years in about 50% of cases and between 5 and 10 years in 30%. Growth in childhood is accelerated but the epiphyses unite prematurely.

Other developmental abnormalities may be associated. The prognosis for life is good and the pathological fractures unite normally.

Diagnosis. There is no single clinical feature of the pigmented lesions that reliably differentiates Albright's syndrome from neurofibromatosis, in which bone lesions and endocrine disturbances may also occur. The presence of many café-au-lait macules, freckles in the axillae and Lisch nodules on the iris are diagnostic for neurofibromatosis.

Giant pigment granules may also rarely be found in Albright's syndrome.

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Other hereditary disorders with hypermelanosis

Increased pigmentation is an incidental or inconstant feature of many other genetically determined syndromes characterized predominantly by ectodermal dysplasia or diffuse connective-tissue defects. Such conditions are described in other chapters but are briefly mentioned below in differential diagnosis. There are also a number of unusual syndromes of which pigmentation is the most conspicuous or the only manifestation. The interrelationships, classification and nomenclature of some of these syndromes, of which few examples have been reported, are not reliably established [1,2].

Naegeli–Franceschetti–Jadassohn syndrome (MIM *161000) [3–11]

SYN. NAEGELI SYNDROME

This rare syndrome, inherited as an autosomal dominant condition, is known in one large Swiss family [3]. A very similar condition with associated onychodystrophy is described in an English family [4].

Reticulate pigmentation develops during the second or third year in a previously normal child. It may become very extensive and is not preceded by any inflammation. Often the neck and axillae are particularly affected. The fine network of hyperpigmentation differs from the irregular splashes and whirls seen in incontinentia pigmenti. Keratoderma of the palms and soles is usual. Hypohidrosis with intolerance to heat is common. The hair and nails are normal, except in the English family where the fingernails and toenails are of almond shape. The teeth may be normal or defective, with yellow discoloration of the enamel. Mental and physical development is normal. In addition to pigmentary incontinence, varying amounts of colloid–amyloid bodies have been found in the superficial dermis [5].

A number of cases have been described that show a combination of some of the features of Naegeli–Franceschetti–Jadassohn syndrome and of incontinentia pigmenti [6–8].

Reticulate hyperpigmentation may be associated with alopecia, nail changes and growth retardation [7] and there may be a history of blisters [9]. There may or may not be sweating defects [10]. Reticular pigmentation with milia has also been described as a variant of Naegeli–Franceschetti–Jadassohn syndrome [11].

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Mendes da Costa syndrome (MIM *302000) [1,2]

SYN. DYSTROPHIA BULLOSA; TYPUS MACULATUS

This rare syndrome, determined by a sex-linked recessive gene, is known only in a single family in Amsterdam [1,2]. The affected individuals, all boys, are normal at birth. They develop tense bullae, irregularly scattered on trunk and limbs, between the ages of 2 months and 3 years. Soon after the bullae begin to appear the hair is lost, and conspicuous coarsely reticulate pigmentation develops on the face and limbs in association with macular atrophy. Some patients are physically and mentally retarded and the expectation of life is poor.

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Cantú's syndrome (MIM 114620) [1]

This is inherited as an autosomal dominant. Brown macules develop in adolescence on the face, forearms and feet. The palms and soles are hyperkeratotic.

REFERENCE

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Dyskeratosis congenita (MIM #305000) (see Chapter 12) [1–4]

Reticulate hyperpigmentation, most conspicuous on the neck, chest and thighs, develops between the ages of 5 and 13 years [1]. It is usually preceded by nail dystrophy and accompanied or followed by leukoplakia of the oral, ocular and anal mucous membranes [2,3]. The skin has a poikilodermatous appearance with atrophy and prominent telangiectasia. Haematological abnormalities are common [4].

The condition is inherited as a sex-linked recessive, although autosomal dominant pedigrees are described. There is an increased risk of malignant disease [2,3].

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Dermatopathia pigmentosa reticularis (MIM *125595) [1–5]

Since the first description in 1958 [1], 10 cases have been reported [2,3]. The condition is probably inherited as an autosomal dominant [4]. Onset is usually in early childhood or from birth. The most striking change is widespread reticulate pigmentation with pigmentary incontinence and sometimes liquefaction degeneration of the basal layer. Associated findings have included a variable combination of alopecia, nail changes, palmoplantar hyperkeratosis and loss of dermatoglyphics. The genetics of the disorder are uncertain. An isolated case from the Netherlands also presented ainhum-like constrictions of the digits [5].

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3 Maso MJ, Schwartz RH, Lambert C. Dermatopathia pigmentosa reticularis. *Arch Dermatol* 1990; **126**: 935–9.
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Becker's syndrome [1–4]

This is different from Becker's naevus (see Chapter 15). It consists of discrete or confluent brown macules on the neck and forearms, present from early infancy in three sisters. There was no atrophy or telangiectasia. In another case, somewhat similar mottled pigmentation of neck and elbows appeared at the age of 10 years [2].

Two other syndromes defy classification: diffuse pigmentation of the trunk and neck, beginning in the first year, with later development of small white macules in the pigmented areas [3]; and diffuse pigmentation with conspicuous macular depigmentation on the trunk, associated with macular and reticulate pigmentation of the neck [4].

REFERENCES

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Acromelanosis [1–12]

Diffuse hyperpigmentation of the dorsal aspects of fingers and toes is not uncommon in individuals of dark complexion [1]. It has been reported in mulattos and white, black and oriental people. A simple dominant gene is implicated. There may be more than one genotype. The pigmentation begins in infancy or childhood and increases in depth and extent. There may be increased pigmentation in the flexures of the finger joints and in the larger joint flexures. The condition must be differentiated from hyperpigmentation induced by repeated trauma. Sporadic cases presenting in infancy with progressive hyperpigmentation of the fingers and toes are reported as 'acromelanosis progressiva' [2] and acromelanosis [1,3]. Some examples of acropigmentation show a reticulate pattern [4].

Reticulate acropigmentation of Kitamura [5–9]

Previously reported only in Japan, this is now recognized to be worldwide [5–8]. The condition is inherited as an autosomal dominant and in the first two decades a network of freckle-like areas of pigmentation develops on the dorsa of the hands. They may subsequently involve most

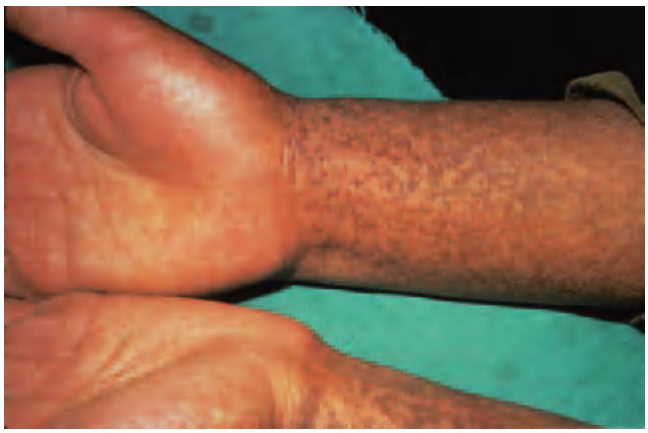

Fig. 39.19 Reticulate acropigmentation of Kitamura. (Courtesy of Dr W.A.D. Griffiths, St John's Institute of Dermatology, London, UK.)

parts of the body (Fig. 39.19). Palmar pits and breakages of epidermal ridge pattern are found. Several individual cases and families have been reported with features of both Kitamura's disease and reticulate pigmented anomaly of the flexures (Dowling–Degos disease) [9–11]. Histologically, the pigment macules show epidermal atrophy and an increased number of melanocytes.

Symmetrical dyschromatosis of the extremities (MIM *127400) [12–14]

SYN. ACROPIGMENTATION OF DOHI

This has been reported mainly from Japan, where it is not uncommon. It appears to be determined by an autosomal dominant gene. An identical or closely similar syndrome has been described in European [12], Afro-Caribbean and Indian patients [13]. During infancy or early childhood, mottled pigmentation with areas of depigmentation develops on the dorsa of the hands and feet and sometimes on the arms and legs. The face is spared, apart from a few scattered, small, discrete, pigmented macules.

A symmetrical acroleukopathy reported in a Japanese mother and daughter [14] began soon after birth around the nail folds and reached the distal interphalangeal joints by adolescence.

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Hereditary universal melanosis [1–4]

A number of rare or even unique clinical pictures have been reported with such names as melanosis diffusa congenita, universal acquired melanosis (carbon baby) [4], familial progressive hyperpigmentation, familial diffuse melanosis, generalized pigmentation and dyschromatosis universalis. The relationship between these various entities and their inheritance is often in doubt. Pigmentation is usually present from early infancy but it may be progressive. It is often diffuse and generalized but may later become rather mottled.

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Reticulate pigmented anomaly of the flexures (MIM 179850) [1]

SYN. DOWLING–DEGOS DISEASE

This disorder of pigmentation combined with epidermal changes is considered in Chapter 12. Cases showing features of this and of reticulate acropigmentation, suggesting that there is some overlap in pathogenesis, are discussed above [1].

REFERENCE

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Zosteriform reticulate hyperpigmentation [1,2]

The description of this disorder is enshrined in its name. There may be an associated change in the texture of the skin within the lesions.

REFERENCES

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Human chimera with pigment anomalies

True human chimeras, formed from more than one zygote, with pigment anomalies are described [1].

REFERENCE

1 Findlay GH, Moores PP. Pigment anomalies of the skin in the human chimaera. *Br J Dermatol* 1980; **103**: 489–98.

Schimke immuno-osseous dysplasia (MIM #242900) [1]

Schimke immuno-osseous dysplasia is a rare autosomal recessive spondylo-epiphyseal dysplasia characterized by short stature, unusual facies, hyperpigmented macules, proteinuria with progressive renal failure, lymphopenia with recurrent infections and cerebral ischaemia. There is no effective treatment for patients suffering from this syndrome other than supportive measures.

REFERENCE

1 Boerkoel CF, O'Neill S, Andre JL *et al*. Manifestations and treatment of Schimke immuno-osseous dysplasia: 14 new cases and a review of the literature. *Eur J Pediatr* 2000; **159**: 1–7.

Neurofibromatosis (MIM *162200) (see Chapter 12)

Café-au-lait marks are present in 90% of patients with neurofibromatosis, particularly in those with NF-1, and may appear early. They are round or oval patches of light-brown pigmentation. They are also found in 10% of normal subjects. The presence of one or two is not diagnostic in the absence of other signs of the disease but if six or more are present, with a diameter of 5 mm or more, the probability of neurofibromatosis is high.

Extensive melanotic macules can also occur and resemble those seen in Albright's syndrome; however, these tend to be confined to a particular site and are on either side of the midline. Axillary freckling is common in neurofibromatosis and is an aid to the diagnosis. Lisch nodules and iris hamartomas are present in most patients over the age of 6 years (Fig. 39.20). Giant pigment granules (macromelanosomes) are found in the café-au-lait macules (Fig. 39.21).

NF-1 accounts for 85% of all neurofibromatosis. The NF-1 gene has been identified on the proximal long arm of chromosome 17 [1,2]. It is inherited as an autosomal dominant trait with variable penetrance and expression, and a spontaneous mutation rate of around 50%. NF-2 has the same mode of inheritance, high spontaneous mutation rate, high penetrance and variable expression as NF-1. The NF-2 gene is located near the centre of the long arm of chromosome 22 [3].

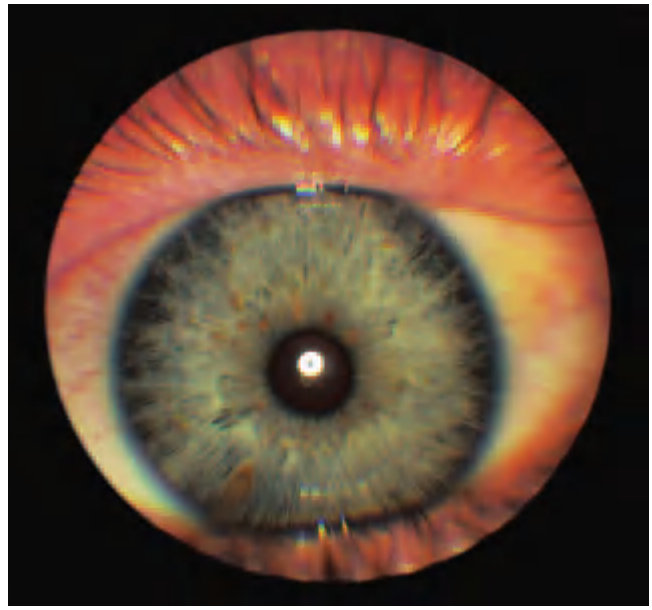

Fig. 39.20 Lisch nodules in the iris.

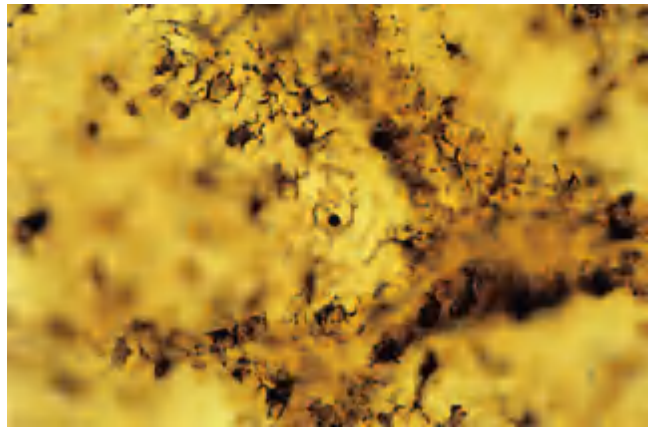

Fig. 39.21 Giant pigment granules in epidermal melanocyte in neurofibromatosis.

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Werner's syndrome (MIM #277700) [1–3]

Werner's syndrome is a rare autosomal recessive disorder characterized by primary growth retardation, features of premature ageing and an increased prevalence of malignancy [1]. Localized or diffuse hyperpigmentation is commonly seen [1–3]. Less commonly, depigmented spots with greying of the hair are present [1–3]. The gene for Werner's syndrome (*WRN*) has now been cloned and sequenced, and mutational analysis has confirmed that most cases are caused by one of three major mutations in the *WRN* gene [4].

REFERENCES

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Gaucher's disease and Niemann–Pick disease (see Chapter 57)

Pigmentation of two types occurs in adults with Gaucher's disease: brown patches of chloasma type on the face, neck and hands; and symmetrical pigmentation of the lower legs with a sharp lower margin and an irregular upper margin. There may also be a brown wedge-shaped thickening of the bulbar conjunctiva.

In the acute infantile form of Gaucher's disease, the skin is not pigmented, but in Niemann–Pick disease there is diffuse brown pigmentation, most marked on the face.

Xeroderma pigmentosum (see Chapter 12) [1]

Freckle-like pigmentation of the face and other exposed skin begins in infancy or early childhood. The light- or dark-brown macules are associated with telangiectases, small white atrophic spots and later with keratoses and tumours. The freckled sun-exposed skin with associated severe photosensitivity in a young child is a striking clinical phenotype not easily overlooked.

REFERENCE

1 Kraemer KH, Lee MM, Scotto J. Xeroderma pigmentosum: cutaneous, ocular, and neurologic abnormalities in 830 published cases. *Arch Dermatol* 1987; **123**: 241–50.

Hypermelanosis in endocrine disorders

Some of the mechanisms by which endocrine glands influence melanogenesis are discussed on pp. 39.10–39.11. Here are considered clinical syndromes showing endocrine-induced pigmentary changes (see also Chapter 59).

Addison's disease [1–3]

Pigmentation is rarely absent in Addison's disease, but may be slight in cases of rapid onset. It is diffuse but is most intense on areas exposed to light, and is accentuated in the flexures, at sites of pressure and friction, and in the creases of palms and soles. Normally pigmented areas, such as the nipples and genital skin, darken. Pigmentation of the buccal mucous membrane is almost invariable, and the conjunctival and vaginal mucous membranes may also be involved. However, less distinctive patterns of pigmentation are not exceptional [2], and in any unexplained melanosis adrenal function should be carefully evaluated. Vitiligo-like lesions may also occur in Addison's disease [3].

The hypermelanosis is the result of increased secretion of melanotrophic hormones by the pituitary. Affected patients have elevated plasma levels of β-MSH-like immunoreactivity.

REFERENCES

1 Deutsch S, Mescon H. Melanin pigmentation and its endocrine control. *N Engl J Med* 1957; **257**: 22–6, 268–72.
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Acromegaly

Pigmentation of addisonian pattern is present in some cases of acromegaly, and may be a striking feature.

Cushing's syndrome [1–4]

Pigmentation of addisonian pattern has been noted in 10% of reported patients with Cushing's syndrome. It is an indication of secretion of ACTH and β-MSH by the pituitary and should suggest the probable presence of a pituitary tumour. After adrenalectomy, progressive hypermelanosis develops in a proportion of patients, about 10%, in spite of adequate hormone replacement therapy. Only in half of these patients is the sella turcica enlarged [1,2]. These patients with Nelson's syndrome [3] show marked hypermelanosis, with the mucous membranes also being involved. The hair is often darker and there are sometimes multiple lentigines and longitudinal pigmented bands in the nails. Very high levels of both β-MSH and ACTH are found in the plasma [4].

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Hyperthyroidism

Pigmentation occurs in about 10% of patients with primary thyrotoxicosis [1]. It is usually diffuse and is broadly of addisonian pattern, although involvement of the mucous membranes is uncommon and pigmentation of nipples and genital skin is less striking. The eyelids are occasionally conspicuously pigmented (Jellinek's sign). Some patients show chloasmal rather than diffuse pigmentation. The incidence of vitiligo is increased. Diffuse pigmentation was present at birth in the infant of a thyrotoxic mother [2].

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Pregnancy and menstruation

Increased pigmentation is almost invariable in pregnancy and is most marked in brunettes. A blotchy hypermelanosis of the face involving the cheeks, forehead and chin is frequently seen. This was called chloasma, but the term 'melasma' is now preferred (see p. 39.40). The pigmentation may involve the neck and is associated with darkening of the nipples, the linea alba to form the linea nigra, and the anogenital skin. The pigmentation usually fades after parturition, but may persist for months and years. The same pigmentation can be idiopathic and familial and is particularly seen in those who tan readily when exposed to bright sunlight [1,2]. It is noted by some women to be more apparent just prior to menstruation [3].

Oral contraceptives

Melasma (chloasma) (see p. 39.40) is frequently seen in women on oral contraceptives. No one oral contraceptive appears to be more liable than any other to cause pigmentation in predisposed subjects. The hypermelanosis is made more apparent with sun exposure. These patients also develop the same pigmentation when pregnant [4]. The pigmentation takes a long time to fade after discontinuing oral contraception and, as after pregnancy, it may never fade completely.

The mechanism is not fully elucidated and although MSH may be involved it plays a minor part. Oestrogens and progesterone are involved in the increased pigmentation but other factors are also implicated [2]. In a study of idiopathic melasma it was suggested that some of the patients had mild ovarian dysfunction [5]. Plasma concentrations of MSH are normal in patients with idiopathic melasma [5] and in those on oral contraceptives [6].

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Phaeochromocytoma

Pigmentation of addisonian pattern occurs in some cases of malignant phaeochromocytoma. Hypertension, headaches, profuse sweating, palpitation and apprehension will suggest the diagnosis, which is established by the abnormal plasma catecholamines.

Carcinoid syndrome

Hyperpigmentation of the skin has been noted in a number of patients with this syndrome.

ACTH administration [1,2]

A small proportion of patients treated with ACTH in high dosage (120 units/day) develop pigmentation of addisonian pattern. The pigmentation, which is accompanied by a combination of addisonian and Cushingoid manifestations, fades when the dose is reduced.

The incidence of melanosis appears to be rather higher in patients treated with tetracosactrin [2].

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Hypermelanosis in other systemic disorders

Increased pigmentation is an inconstant feature of a wide variety of systemic disorders and may be associated with malignant disease. In most instances, the mechanism is

obscure although, in some, elevated levels of β-MSH-like immunoreactivity are found. A genetic predisposition may be present in those affected. The hypermelanosis may be diffuse or localized. It may be confined to the epidermis, when the skin appears brown in colour, or it may be in the dermis, when often the skin is a slaty-grey or blue colour. Pigments other than melanins may also be present.

Chronic infections [1]

Pigmentation may occur in many chronic infections, but it is difficult to determine the relative responsibility of the infection and of malnutrition and other factors. It has been associated particularly with malaria, kala-azar, schistosomiasis and tuberculosis, but is occasionally seen in other chronic infections. Diffuse, light-brown pigmentation is a feature of the later stages of subacute bacterial endocarditis. It has been suggested [1] that the activity of the reticuloendothelial system is inversely related to adrenocortical activity. With stimulation of the reticuloendothelial system by these chronic infections and consequent reduced adrenocortical activity, this would lead to enhanced pigmentation of the skin.

REFERENCE

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Neoplastic disease [1–5]

In cachectic states there may be diffuse hyperpigmentation of the skin as in Addison's disease. The mechanism is uncertain. In the ectopic ACTH syndrome, which may occur in patients with oat cell carcinoma of the bronchus, pigmentation is usual. The tumour has been shown to produce a distinct MSH-like compound [1].

In an adult, acanthosis nigricans (see Chapter 34) is associated usually with internal malignancy, almost invariably an adenocarcinoma. The hypermelanosis affects the axillae, nipples and umbilicus, which also show a warty papillomatosis. These skin changes may later become generalized. The mucous membranes are frequently involved.

A diffuse dermal melanosis, having a slaty-blue colour, can occur secondary to melanoma and melanogenuria [2,3]. Ultrastructural studies on this rare condition have shown in one patient [4] single-cell metastases disseminated widely through the skin; in another [5] the dermal histiocytes contained many lysosomal bodies containing electron-dense granular material, presumably melanin.

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Lymphomas [1–3]

Pigmentation is an uncommon manifestation of lymphomas, occurring in 10% of cases of Hodgkin's disease and in 1 or 2% of cases of lymphosarcoma and lymphatic leukaemia. The pigmentation is of addisonian type, but allegedly without involvement of the mucous membranes. Malnutrition may be a factor and post-inflammatory pigmentation after scratching may modify the clinical pattern. Diffuse progressive hyperpigmentation can also be a manifestation of mycosis fungoides [1,2]. A number of different clinical patterns for early mycosis fungoides have been described, including pigmented purpura-like lesions [3] (see Chapters 48 & 54).

Several of the cytostatic drugs used for the treatment of these disorders can also produce increased pigmentation of the skin (see Chapter 73).

REFERENCES

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Diseases of the nervous system [1–3]

Pigmentation, usually conforming to the addisonian pattern, occurs in some diseases of the nervous system, particularly those involving the diencephalon and the substantia nigra. Intense pigmentation is a feature of Schilder's disease [1] but some increase in pigmentation is not uncommon in hepatolenticular degeneration [2] and in ependymomas. It is occasionally noted in chronic schizophrenia. In post-encephalitic parkinsonism, it may be diffuse but may be melasmal. Pigmentation may sometimes develop after intense and prolonged emotional stress [3].

REFERENCES

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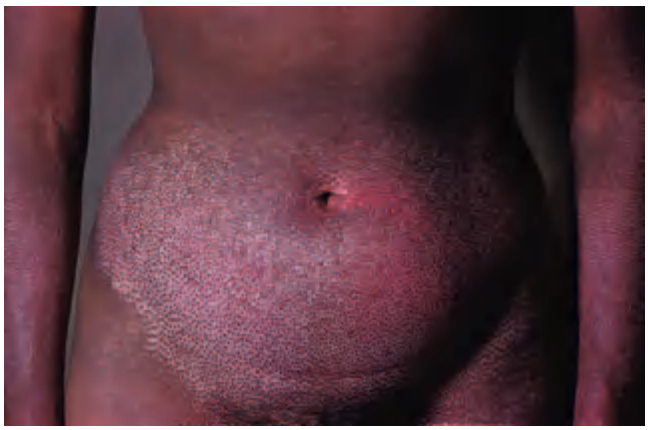

Fig. 39.22 Generalized pigmentation in a woman aged 33 years with systemic sclerosis.

Rheumatoid arthritis and Still's disease [1,2]

Pigmentation, usually generalized, is occasionally observed in rheumatoid arthritis and is a more frequent feature of Still's disease. It may sometimes be caused by medication taken to treat the rheumatoid arthritis, such as minocycline [1] or methotrexate [2].

REFERENCES

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2 Toussirot E, Wendling D. Methotrexate-induced hyperpigmentation in a rheumatoid arthritis patient. *Clin Exp Rheumatol* 1999; **17**: 751.

Systemic sclerosis, scleroderma and morphoea [1–9]

Generalized pigmentation in systemic sclerosis and scleroderma may be intense and diffuse or of addisonian type, but without mucous membrane involvement [1]. It may involve predominantly the face and limbs but is often far more extensive than the scleroderma (Fig. 39.22). Hyperpigmentation in systemic sclerosis is seen most commonly in patients with pigmented skin, and is less common in whites [2]. Keratinocyte endothelin-1 production has been implicated as playing a central role in the pathogenesis of cutaneous hyperpigmentation in systemic sclerosis [3], as has local expression and systemic release of a stem cell factor [4]. Levels of soluble cell surface L-selectin are elevated in systemic sclerosis with diffuse hyperpigmentation [5].

Pigmentation may also be a conspicuous feature of morphoea [6] and is occasionally the presenting symptom (Fig. 39.23). Hyperpigmentation is sometimes a feature of atrophoderma of Pasini and Pierini [7], and has also been reported in the linear atrophoderma of Moulin [8]. Prominent post-inflammatory hyperpigmentation has been reported in a case of porphyria cutanea tarda with idiopathic myelofibrosis and CREST syndrome [9].

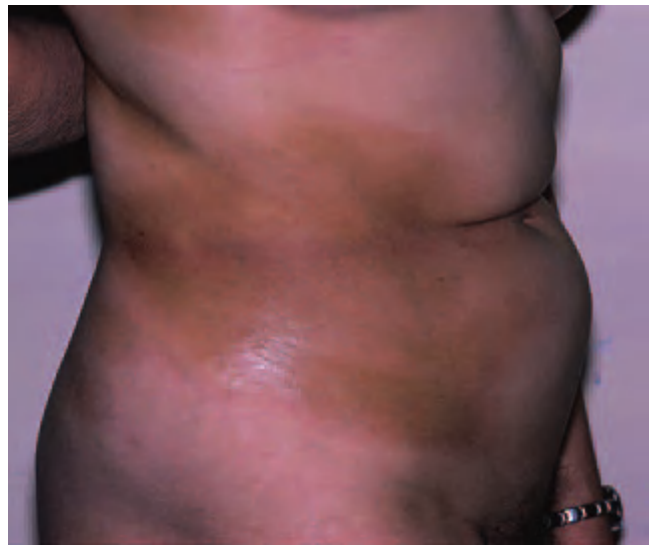

Fig. 39.23 Morphoea. Hyperpigmentation was the presenting symptom.

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Dermatomyositis and lupus erythematosus [1,3]

Diffuse pigmentation may accompany or follow the cutaneous lesions of dermatomyositis [1]. Acanthosis nigricans has also been reported in association with dermatomyositis [2]. In systemic lupus erythematosus, diffuse pigmentation of light-exposed skin occurs in about 10% of cases. It may gradually darken, although the disease is controlled by treatment. Longitudinal melanonychia may occasionally be a feature of systemic lupus erythematosus [3].

REFERENCES

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Multiple organ failure [1]

Patients with multiple organ failure who survive for long periods are susceptible to hyperpigmentation. Renal failure, hepatic failure and polypharmacy may all contribute to this. An unusual case of intense green colour in a patient with multiple organ failure was attributed to dyes in the liquid tube feeds [1].

REFERENCE

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Renal failure [1–4]

Chronic renal disease with nitrogen retention is frequently accompanied by increased pigmentation of the skin. This hypermelanosis is diffuse and brown in colour. It is most intense on the hands and face. Hyperpigmented macules are common on the palms and soles [3]. Elevated levels of β-MSH are found in the plasma of these patients [1,2] and cause the excess production of melanin in the skin. The increased levels of β-MSH-like immunoreactivity are due to slow clearance by the kidney rather than increased production by the pituitary. Lipochromes and carotenoids deposited in the skin may also play a part. Paradoxically, hypopigmentation with acquired lightening of hair is sometimes a feature of chronic renal failure [4].

REFERENCES

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Anaemia [1–8]

Hyperpigmentation of the skin occurs in vitamin B_{12} deficiency and is more common in dark-skinned races [1]. A diffuse brown pigmentation is also seen occasionally in patients with folic acid deficiency [2,4]. Pigmentation of the fingertips and nails of a patient with B_{12} deficiency has been reported [5]. The pigmentation seen in association with B_{12} deficiency often has a rather dappled and mottled appearance, and particularly affects the face, hands and feet [3,5,7]. Sometimes, only the fingers are affected. Treatment with vitamin B_{12} reverses the pigmentation of the skin to normal [7,8]. Pigmentation also occurs in megaloblastic anaemia associated with pregnancy [2]. In the haemolytic anaemias, hypermelanosis and haemosiderosis may develop on the lower legs.

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Hepatic cirrhosis

A diffuse hypermelanosis is seen in patients with cirrhosis due to many aetiological factors. It is particularly striking in patients with primary biliary cirrhosis, when it may occur at an early stage. The excess melanin is dispersed widely in the epidermis [1]. No significant difference from normal controls is observed in the levels of MSH-like peptides. Lichen planus may be associated with primary biliary cirrhosis [2], and as lesions resolve they leave slaty-brown hypermelanotic macules.

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Haemochromatosis (see Chapter 57)

Pigmentation, bronzed or slaty-grey in colour, involves first the exposed skin but later generalizes [1]. It is present in some 90% of cases [2], but may not be conspicuous. The diagnosis should be suspected when pigmentation of this pattern occurs in middle-aged men, is supported by the finding of an enlarged liver and diabetes, and is confirmed by the high level of serum iron [1–3]. Hyperpigmentation

is reversible with phlebotomy [3], and a single case with high serum ferritin showed no post-inflammatory hyperpigmentation with sclerotherapy for spider veins [4].

REFERENCES

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Amyloidosis (see Chapter 57)

Localized pigmentation, often symmetrical, is seen in both lichen and macular amyloidosis [1,2]. The macular type of amyloidosis is often mistaken for banal post-inflammatory hyperpigmentation, but the lesions often have a distinctive 'ripple' pattern, and microscopic studies reveal the presence of amyloid. Melanophages are found in the papillary dermis. The melanin contained in these dermal cells is derived from degenerating basal keratinocytes and melanocytes [1,3]. Macular amyloidosis is seen most commonly on the upper back (interscapular areas), chest, buttocks, forearms and shins.

REFERENCES

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Vitamin A deficiency (see Chapter 57)

Severely malnourished patients with the pathognomonic ocular lesions of vitamin A deficiency also show cutaneous changes. In children, dry skin is the main manifestation of vitamin A deficiency and may be associated with hyperpigmentation of the face and limbs. In adults there is dryness and scaling of the skin with abundant desquamation associated with generalized hyperpigmentation. Conjunctival pigmentation has been noted particularly in the oriental races and may be striking, especially in the lower fornix and bulbar conjunctiva.

Pellagra (see Chapter 57) [1]

Hyperpigmentation is frequent in pellagra, and is confined to sun-exposed sites. It follows the onset of the dermatitis that characterizes this condition. Following erythema and sometimes bullae on sun-exposed skin, the skin becomes mildly oedematous with brown scales and haemorrhagic crusts. The exposed skin becomes hard, dry and cracked and in extreme cases is black in colour. The sites of involvement are the face, neck, dorsa of hands and feet, and sometimes the forearms. These changes are seldom seen elswhere.

REFERENCE

1 Dumitrescu C, Lichiardopol R. Particular features of clinical pellagra. *Rom J Int Med* 1994; **32**: 165–70.

Malabsorption syndromes

In sprue and other malabsorption syndromes, pigmentation is of common occurrence and may sometimes be prominent [1,2]. It may be of addisonian type but without involvement of the mucous membranes, or may occur in well-defined patches on the face and neck and occasionally on the trunk. The scaly inflammatory plaques (see Chapter 57) that may develop in these syndromes are usually followed by intense pigmentation.

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Vagabond's disease

This classically occurs in those in whom lack of food is combined with lack of cleanliness, and heavy infestation with pediculi. The pigmentation is basically of addisonian pattern and the mucous membranes may be involved.

The pathogenesis is uncertain, but the hypermelanosis is probably post-inflammatory and related to the scratching from the pediculosis infestation. Areas of hypomelanosis occur and there is a decrease in the number of melanocytes that show degenerative changes [1]. Adrenal function is in most cases normal [2].

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Peripheral neuropathy with dysproteinaemia, skin changes and endocrinopathy

SYN. CROW–FUKASE SYNDROME; SHIMPO'S SYNDROME; PEP SYNDROME; POEMS SYNDROME

This multisystem disorder characterized by polyneuropathy, dysglobulinaemia, anasarca, pigmentation,

scleroderma, hypertrichosis, endocrinopathy, hepatosplenomegaly and lymphadenopathy is discussed in Chapter 57.

Hypermelanosis of drug origin [1–6]

Pigmentation may be induced by a wide variety of drugs [1,2]. Several mechanisms are involved in drug-induced changes of pigmentation of the skin. These include increased melanin synthesis, increased lipofuscin synthesis, deposition of drug-related material and post-inflammatory hyperpigmentation [6]. For example, the phenothiazines, particularly chlorpromazine, react with melanin to form drug–pigment complexes, probably due to a 'charge transfer reaction'. In contrast to melanin, the chlorpromazine–melanin complexes are not metabolized by the body. Imipramine hyperpigmentation is thought to be produced by a similar mechanism [7]. Many drugs induce hypermelanosis as a non-specific post-inflammatory change in predisposed subjects. The pigmentation following fixed drug eruptions is of this type. Other drugs induce pigmentation more directly: in the case of arsenic it is believed that it combines avidly with sulphydryl groups in the epidermal cells and promotes the action of tyrosinase. A post-inflammatory hyperpigmentation of the skin is seen following the resolution of drug-induced lichenoid reactions. Oestrogens stimulate melanin production, and drug-induced hyperpigmentation may be seen with the combined oral contraceptive [5]. Hyperpigmentation in AIDS patients may occur as a complication of drug therapy, most notably with zidovudine which causes pigmentation of nail, skin and oral mucosa.

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Chlorpromazine and related phenothiazines [1–10]

Bluish-grey pigmentation of the sun-exposed areas of the skin is seen in a small percentage of patients receiving high doses of chlorpromazine for long periods [1,2]. The pigmentation is cumulative and some develop a purplish tint. Related phenothiazines may cause a similar effect, but chlorpromazine is usually implicated [3]. Some of those affected also develop cataracts, corneal opacities and pigmentation of the conjunctivae [4]. The nail beds are also affected in severe cases [2]. Sun exposure is a factor. The mechanism is uncertain, as discussed above, but probably involves drug–melanin complexes. There is extensive deposition of melanin-like material throughout the reticuloendothelial system and involving the parenchymal cells of internal organs. The pigment found in the cells of the dermis stains as for melanin [1,2]. Electron microscopy studies [5] show increased melanin in the epidermis and perivascular macrophages in the dermis that contain electron-dense particles. Radioactively labelled chlorpromazine is found to localize in tissues containing melanin [6]. It is believed that this drug or some metabolite is bound to melanin in the tissues [9]. The level of immunoreactive β-MSH in the plasma of these patients is within the normal range [7].

The administration of penicillamine as a copper-chelating agent has diminished the pigmentation in some cases [8]. It ultimately slowly fades after phenothiazine therapy is stopped.

A blue-grey pigmentation of the sun-exposed areas of skin has been reported following treatment with low-dose trifluoperazine [10].

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Hydantoin [1,2]

Phenytoin (diphenylhydantoin) is the prototype of the hydantoin derivatives. Some 10% of patients receiving hydantoin preparations develop pigmentation of the face and neck, resembling chloasma, which fades in a few months when the drug is stopped. It has been suggested that hydantoin exerts a direct action on the melanocytes; it has been shown to expand melanophores in amphibian larvae.

A patient on this drug developed pigmentation of addisonian type and other evidence of hypoadrenalism [2].

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Arsenic (see Chapter 73)

Prolonged ingestion of inorganic arsenic may result in diffuse pigmentation, most intense on the trunk, where macular areas of depigmentation within areas of hyperpigmentation produce the distinctive 'raindrop' appearance [1]. Many cases also show arsenical keratoses, but the severity of the two manifestations of arsenic poisoning is not necessarily proportionate and either may be present alone.

REFERENCE

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Antimalarial drugs [1–5]

About 25% of patients receiving chloroquine or hydroxychloroquine for several years develop bluish-grey pigmentation on the face and neck and sometimes the lower legs and forearms. With continued therapy, the areas darken, particularly oval patches on the shins, which increase in size. A blue-black colour may develop. Also, these patches are more pigmented in the light-exposed areas. The nail beds may be affected diffusely or in transverse bands and the hard palate may be bluish-grey. Bleaching of the colour of the hair occurs and when associated with pigmentation of the skin should suggest the diagnosis [4]. Corneal and retinal changes may develop following pigmentation of the skin due to antimalarials [3]. Chloroquine has been shown to have an affinity for dermal melanin [4]. A yellowish pigmentation of the skin is common with mepacrine [5]. Pigmentation appears to result from complexes of melanin, haemosiderin and mepacrine, in combination with sulphur [5]. Quinine and quinidine may also produce a generalized pigmentation [3,6].

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Antitumour agents [1–7]

Long-term administration of busulfan (busulphan) produces a diffuse brown pigmentation, particularly in non-white people with a dark complexion. Less commonly, Addison's disease is simulated [2,3]. Light and electron microscopy studies suggest that busulfan has both a stimulatory and a toxic effect on melanocytes [4]. Both busulfan and doxorubicin cause mucous membrane pigmentation. Other cytostatic drugs that may produce hyperpigmentation include cyclophosphamide, bleomycin, fluorouracil, hydroxyurea, daunorubicin, methotrexate, mithramycin, mitomycin, thiotepa and Adriamycin [6,7]. Topical cytostatic drugs that produce localized hyperpigmentation include carmustine, mechlorethamine and fluorouracil. Patients on cyclophosphamide [5], bleomycin, daunorubicin, doxorubicin and fluorouracil can develop banded or diffuse pigmentation of the nails. Hair pigmentation may be induced by methotrexate, and pigmentation of the teeth may be seen with cyclophosphamide.

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Fixed eruptions [1–6]

Circumscribed areas of slate-brown pigmentation commonly follow the erythematous and bullous stages of fixed eruptions (see Chapter 73) but almost universal brown pigmentation has followed the long-continued ingestion of phenolphthalein [3]. Fixed eruptions are particularly frequent in black people. More or less symmetrical, discrete patches are usually seen but the melanosis may be diffuse or melasmal, and the mucous membranes may be involved [4,5].

The slate-brown colour in fixed drug eruption is due to pigmentary incontinence with melanophages in the upper dermis [6].

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Post-inflammatory hypermelanosis

Hypermelanosis commonly follows acute or chronic inflammatory processes in the skin. The intensity and persistence of the hypermelanosis are greater in dark-skinned subjects. The degree of inflammation appears to be of less significance in determining the pigmentary response than the nature of the dermatosis, for it may be frequent and severe after some conditions and slight after others [1]. Disorders where there is disruption of the basal layer of the epidermis, such as lichen planus or lupus erythematosus, frequently develop areas of slate-brown hypermelanosis. Similarly, in fixed drug eruptions, hyperpigmentation occurs owing to damage of cells in the basal layer. There is pigmentary incontinence with melanophages in the upper dermis [2]. In the late phase of chronic graft-versus-host reaction, there is a poikilodermatous appearance with hyperpigmentation [3].

Hypermelanosis of the epidermis may also occur in inflammatory disorders, but more frequently there is hypomelanosis of the skin. This results from an increased mitotic rate of keratinocytes and diminished transfer of melanosomes from the melanocyte to these cells, which also exhibit a reduced transit time from the basal layer to being shed on the skin surface. Very frequently in inflammatory disease in the skin, hypermelanosis and hypomelanosis occur together, often with a slaty-blue colour due to the presence of melanophages in the upper dermis. There may be an associated loss of functional melanocytes in the skin [4].

The cause of the pigmentation is usually obvious, although the preceding lesions have sometimes not been noticed by the patient or have been transitory or clinically imperceptible. The pattern and distribution of the pigmentation will sometimes allow a retrospective diagnosis, as in lichen planus, herpes zoster, dermatitis herpetiformis and papular urticaria. Pigmentation is often conspicuous after lichenoid drug eruptions, and is a feature of lipomelanic reticulosis.

An unexplained, but not excessively rare, clinical syndrome has been reported in some dark-skinned white people [5]. A small irregular patch of hypermelanosis of the interscapular skin is often intensely pruritic. It seems likely that this condition is in fact notalgia paraesthetica [6,7] (see Chapter 60).

Reticulate pigmentation following the vascular network is characteristic of erythema ab igne (see Chapter 22), which may occur at any site regularly exposed to the heat of a fire or a hot-water bottle. A reticulate pigmentation is also seen in prurigo pigmentosa, a dermatosis mostly occurring in Japan [8].

Post-inflammatory hyperpigmentation may occur following trauma to the skin. It can occur following dermabrasion and particularly in those who are racially pigmented. Unusual patterns may declare their origin, for example the tooth-mark pattern on an ill-treated child [9] or the symmetrical pigmentation of the sides of the chin in a patient who, as a nervous tic, chews the buccal mucosa [10].

In late secondary syphilis, especially in women, so-called syphilitic leukoderma is occasionally seen. Diffuse hypermelanosis of the sides and back of the neck and the shoulders is mottled with depigmented macules 1–2 cm in diameter. The Wassermann reaction is always positive. A deep-blue or slate-grey hyperpigmentation is seen in late pinta (see Chapter 30).

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Tanning and specific effects of UV light [1–9]

The increased melanin pigmentation of human skin following exposure to sunlight or UV light from various sources is known as 'tanning'. Two separate reactions are recognized: immediate pigment darkening and delayed tanning reaction. Immediate pigment darkening is induced by UV light, particularly UVA (320–400 nm). Visible light

(400–700 nm) is less effective. The reaction is rapid and can be induced in a matter of a few minutes. It reaches a maximum 1–2 h following irradiation and slowly decreases between 3 and 24 h [1]. Ultrastructural studies have shown that in this reaction there are alterations in the distribution of pre-existing melanosomes within the keratinocytes and melanocytes [2–4]. Delayed tanning involves the formation of new melanosomes and is a gradual process that occurs 48–72 h following irradiation of the skin. Alterations in the distribution of 10-nm cytofilaments in the melanocytes are seen in both types of reaction to UV light [2,3]. In delayed tanning, the dopa reaction and tyrosinase activity are markedly increased, and the melanocytes are increased in number and have well-developed dendrites. The minimal UV dose required for the stimulation of melanogenesis varies in the three spectral regions [5].

Tanning and DNA damage are closely associated. Repeated suberythemal doses of UV light induce tanning but have also been shown to induce DNA damage. Skin phototypes II and IV develop similar degrees of DNA damage, but repair is faster for skin type IV [6]. Tanning salon exposure has also been demonstrated to induce cyclobutane pyrimidine dimers and p53 protein expression in epidermal keratinocytes, changes linked with the early stages of cutaneous carcinogenesis [7]. It is widely believed by lay people that a tan provides good protection against sunburn. However, tanned skin has been shown to be less effective against formation of DNA photoproducts than constitutive pigmentation [8] and has a sun protection factor of 3–5 at best. Population-based surveys reveal that tanning is still popular, particularly with the young, but that episodes of sunburn remain common [9,10].

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Photodynamic and phototoxic reactions [1–5]

Drugs and other chemicals with photodynamic and phototoxic activity potentiate the pigmentogenic effect of UV light. Tanning follows the sunburn-like reactions to drugs such as demethylchlortetracycline and imipramine, but does not occur after photoallergic reactions [3].

If the photodynamic agent is applied directly to the skin, the intensity of the pigmentary response is greatly enhanced. Transient hyperpigmentation has been reported due to photodynamic therapy in acne [4] and localized scleroderma [5]. Hypermelanosis may sometimes be heavy and persistent following photodynamic and phototoxic reactions. The more or less diffuse patterns of pigmentation so induced are considered below, together with other facial melanoses. Two distinctive clinical syndromes are Berloque dermatitis and phytophotodermatitis.

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Phytophotodermatitis [1–3]

SYN. MEADOW DERMATITIS; STRIMMER DERMATITIS; WEEDWACKER DERMATITIS

This is an inflammatory and pigmentary reaction of the skin to light, potentiated by furocoumarins in plants (Fig. 39.24). All the plants reliably recorded as inducing this reaction in humans have been shown to contain furocoumarins, including cow parsley (*Anthrisus sylvestris*) and giant hogweed (*Heracleum sphondylium*) [1,2]. The reaction occurs in those exposed to sunlight after these plants have been crushed on the skin. There is some individual variation in susceptibility but with adequate exposure most will react. If the inflammatory phase is severe, bullae are formed, but in milder cases only the pigmentary changes are conspicuous and follow the irregular pattern of the points of contact of the plant stems and leaves with the uncovered skin. Serial dilutions of psoralens may, in exceptional cases, be needed to distinguish photoallergy from phototoxicity [3].

Common clinical patterns for phytophotodermatitis include a bizarre network of pigmented streaks on the legs

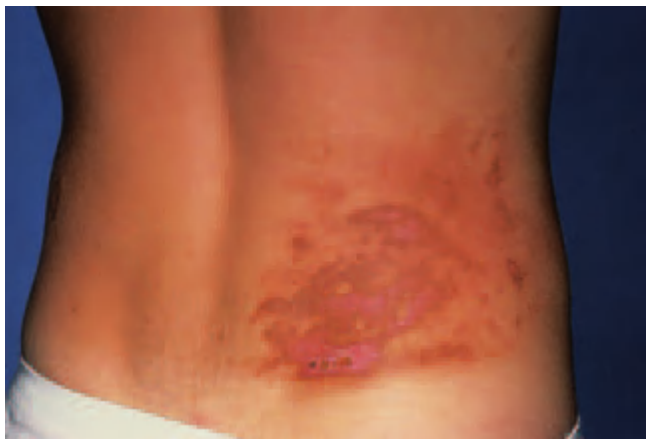

Fig. 39.24 Phytophotodermatitis. Linear, streaky pigmentation following an acute blistering reaction caused by giant hogweed and sunlight.

or arms (meadow dermatitis), and much finer spots and small streaks on forearms and legs from contact with plant material during strimming (strimmer dermatitis). Squeezing limes outside when preparing cold drinks can cause blistering of the hands if carried out on sunny days. Handling celery either at harvest or when it is sold can cause phytophotodermatitis of the fingertips if it takes place in direct sunlight.

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Berloque dermatitis (Fig. 39.25) [1–8]

Berloque dermatitis results from the potentiation of UV-stimulated melanogenesis by 5-methoxypsoralen (bergapten) in bergamot oil contained in perfumes. The term arose from the method of applying perfume to the sides of the neck and upper chest in a pendant shape (*berloque* is French for pendant). The action spectrum for this reaction includes wavelengths of UV light above 320 nm. There is wide individual variation in susceptibility, and the reaction occurs in only a small proportion of those exposed [5]. This variation depends on the readiness with which the bergapten is absorbed, the quantity applied, and the intensity and duration of exposure to UV light. Susceptibility is increased by stripping the horny layer [6]. Hot humid conditions favour absorption.

The pigmentation occurs in susceptible subjects who have been exposed to light after the application of perfume. The distribution of the lesions is therefore variable but their configuration is usually distinctive. Deep-brown

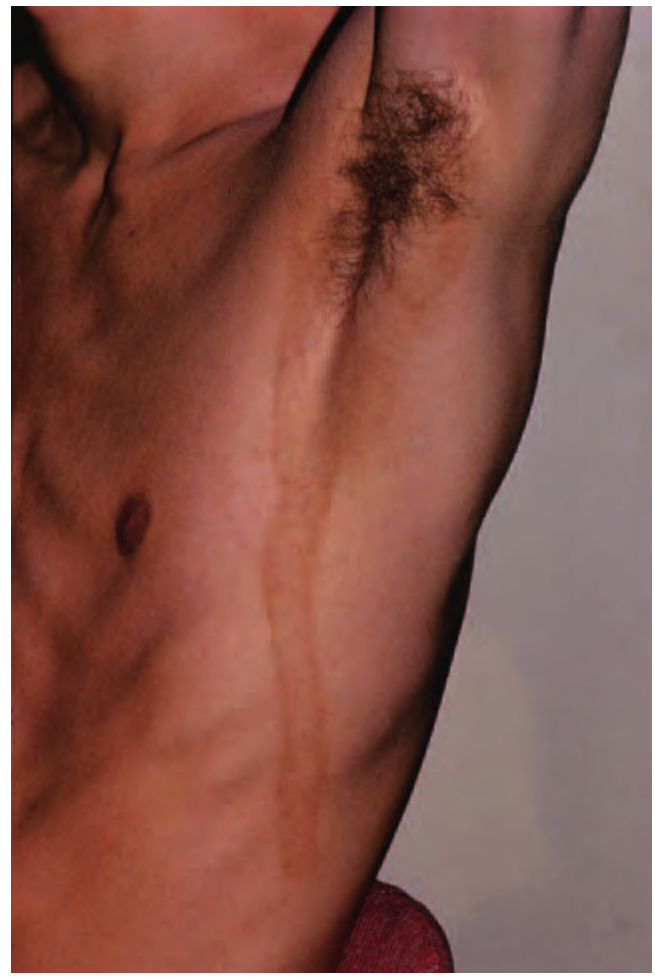

Fig. 39.25 Berloque dermatitis.

pigmentation follows the pattern formed by the trickle of the droplets of perfume over the skin from their points of application. The pigmentation fades after weeks or months. The condition is now much less frequent, although it is a continuing cosmetic problem [7].

Following the application of psoralens to the skin and irradiation with long-wave UV light, there is an increase in the number of functional melanocytes. These cells are more dendritic and more dopa-positive. There is an increase in melanogenesis and in white skin the distribution pattern of the melanosomes in the keratinocytes is changed from the aggregated to the non-aggregated form [4,8].

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PUVA lentigines [1–6]

These pigmented macules develop in all the treatment-exposed areas in patients who are on long-term photochemotherapy with psoralens and UVA (PUVA) [1]. They vary in appearance and may be numerous in number and small in size. Occasionally, larger irregular lentigines are seen, some with a stellate configuration [2] (Fig. 39.26). PUVA lentigines are usually permanent and show little tendency to remit. A less common clinical pattern is localization of lentigines to sites previously affected by psoriasis, creating an appearance not unlike a naevus spilus [3]. The histology is that of a lentigo. The melanocytes are hypertrophic and some may be cytologically atypical [4]. Similar melanocytic macules have been reported following use of a sunbed [5]. PUVA has also been reported to cause hyperpigmentation of the nails [6].

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Erythema dyschromicum perstans [1]

SYN. ASHY DERMATOSIS OF RAMIREZ; LICHEN PIGMENTOSUS

This clinical syndrome of unknown origin was reported first from El Salvador in 1957, then from Venezuela [2], and subsequently from many other countries. It is sometimes called lichen pigmentosus. Ramirez observed a cutaneous eruption in Salvadorians that caused ashy discoloration of the skin, such that affected individuals were called *los cenicientos* (the ash-coloured ones). The exact relationship to lichen planus is uncertain but there are close similarities and both conditions may coexist [3,4]. It has occurred in both sexes from childhood to old age, and is not uncommon.

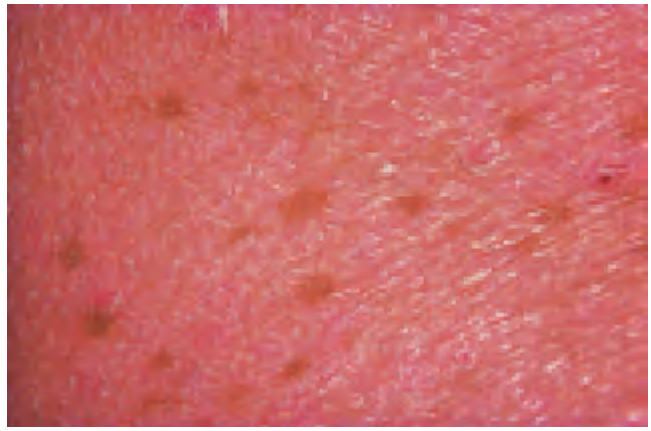

Fig. 39.26 Psoralen and UVA (PUVA)-induced freckles in a patient on long-term treatment.

Histologically, the active border shows vacuolar degeneration of the basal cells. The epidermis contains much pigment and there is pigmentary incontinence; the dermal vessels are sleeved with an infiltrate of lymphocytes and histiocytes, and there are many melanophages [5]. Ultrastructural studies [5,6] show vacuoles within the cytoplasm of basal and suprabasal keratinocytes that contain many melanosomal complexes. One study found IgM cytoid bodies on direct immunofluorescence [7].

Clinically, the condition is characterized by numerous macules of varying shades of grey with a red, slightly raised and palpably infiltrated margin. They vary in size and tend to coalesce over extensive areas of the trunk, limbs and face. Against the general greyish background are macules of hypomelanosis or hypermelanosis. The condition is persistent and slowly extends, but causes no symptoms.

The pigmented macules resemble very closely the lesions of late pinta, but the negative dark-field examinations, negative serological tests for syphilis and lack of response to penicillin are important features that allow the dermatologist to exclude this treponematosis.

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Facial melanoses

Hypermelanosis involving predominantly the face and

the neck is relatively common and often presents a complex diagnostic problem. Several more or less well-defined clinical syndromes can be recognized, but many transitional forms defy classification. The causes of the pigmentation are often obscure.

Genetic and racial factors are important, the increased pigmentation occurring more frequently in those with dark skins, especially oriental people. Endocrine factors play a major role in melasma and are implicated to some degree in other melanoses. External agents (light and photodynamic chemicals) are essential factors in the occupational melanoses but are also concerned in Riehl's melanosis, erythrosis and poikiloderma of Civatte. Other unknown factors are certainly implicated, and wide individual variation in susceptibility must be postulated.

Cosmetics may occasionally cause facial melanosis. Facial melanosis is, of course, also a conspicuous feature of addisonian pigmentation.

Melasma (Figs 39.27 & 39.28) [1–3]

SYN. MASK OF PREGNANCY; CHLOASMA

This common acquired hypermelanosis is seen mainly in women, and occurs exclusively on the sun-exposed skin of the face. The majority of cases are attibuted to pregnancy or the combined oral contraceptive pill. In the context of pregnancy melasma is regarded as a normal physiological change, along with darkening of the nipples and linea nigra. It is not uncommon at any time during the years of reproductive activity and has been attributed, without acceptable proof, to a variety of ovarian disorders. The rarity of melasma in post-menopausal women on oestrogen-containing hormone replacement therapy and the fact that men are occasionally affected suggests that oestrogen alone is not the causative agent. Thus, an endocrine mechanism is postulated but its nature is unknown.

The hypermelanosis affects the upper lip, cheeks, forehead and chin and becomes more apparent following sun exposure. The areas are brown in colour and are bilateral and frequently symmetrical. In some women it may be noticeable premenstrually. After pregnancy or after stopping oral contraceptives the condition may fade but is often persistent. Melasma-like hyperpigmentation has been reported from use of phenytoin or mephenytoin (hydantoins).

Up to 10% of cases of melasma are seen in men, particularly Latin Americans and those from the Middle East or Asia.

A variety of topical treatments are effective at lightening melasma [4,5], but these treatments should be combined with assiduous sun-protection measures if the reduced pigmentation is to be maintained.

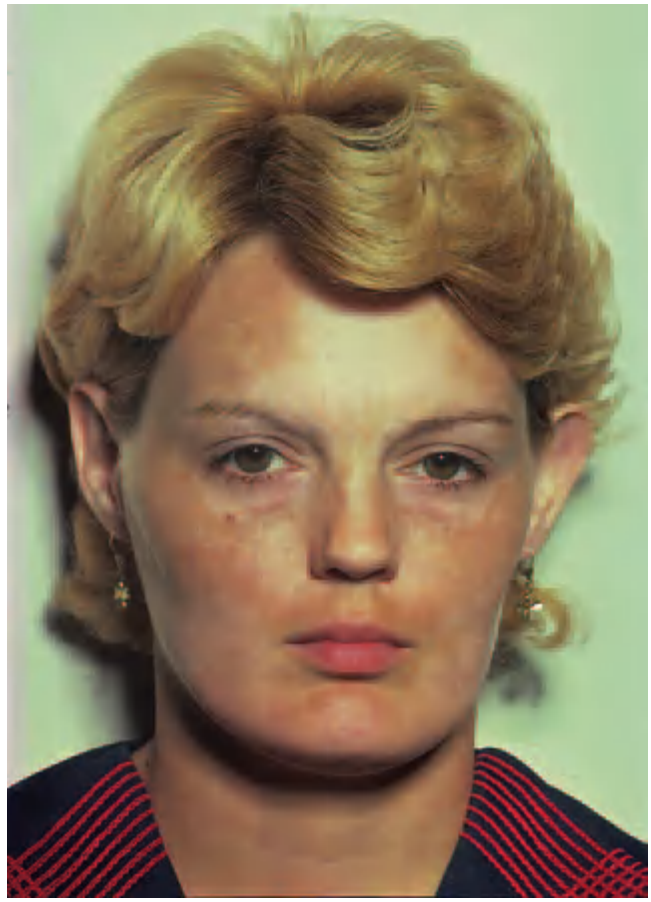

Fig. 39.27 Melasma.

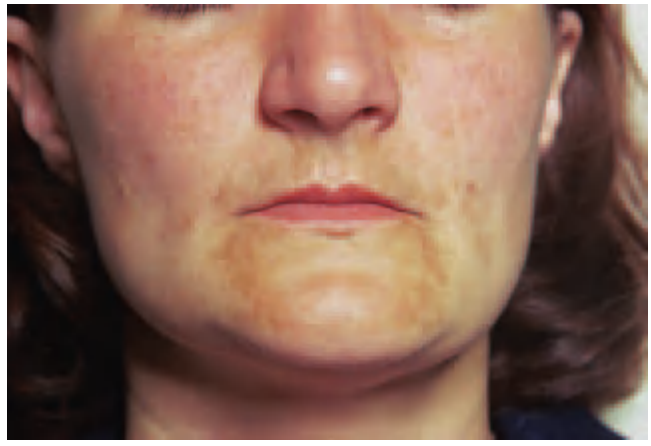

Fig. 39.28 Melasma.

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Riehl's melanosis

SYN. MELANODERMATITIS TOXICA; PIGMENTED COSMETIC DERMATITIS; FEMALE FACIAL MELANOSIS

A distinctive pattern of pigmentation was common in Vienna between 1916 and 1920 [1]. It was again frequently seen in Europe and Asia during and after the Second World War. It has occurred in Argentina and in the South African Bantu [2]. The condition is more frequent in women, and tar derivatives and fragrances are suspected to be the cause [3]. Patients in Japan and elsewhere may show positive patch tests to cosmetics or their ingredients; the disease is then called 'pigmented cosmetic dermatitis' [4,5]. Nutritional and other factors may be involved, for some cases occur in children and in others there is no history of contact with cosmetics. Workers handling coal-tar products, such as pitch, asphalt and creosote or mineral oils, may develop diffuse melanosis of exposed skin through the photodynamic action of anthracene, phenanthrene and other substances [4].

Histologically, in the early stages, there is liquefaction degeneration of the basal layer of the epidermis and a perivascular or band-like dermal infiltrate. There is pigmentary incontinence. Later, the epidermis appears normal but many melanophages are present in the upper dermis [6]. Ultrastructural studies show intercellular and intracellular oedema of keratinocytes and a multilayered basal lamina, as well as many melanophages in the dermis [4].

Brownish-grey pigmentation develops quite rapidly over the greater part of the face but is more intense on the forehead and temples. Smaller pigmented macules, often perifollicular, lie beyond the indefinite margin. The pigmentation may extend to the chest, neck and scalp, and occasionally involves hands and forearms. Horny plugs fill the follicles and there may be some scaling. Unexplained constitutional symptoms are occasionally noted [1]. Where a contact cause can be implicated, removal of the cause leads to slow improvement over many months.

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Poikiloderma of Civatte (Fig. 39.29) [1]

This occurs in middle-aged women. The milder forms are common and patients often do not seek medical advice. The distribution implicates exposure to light, and it is probable that photodynamic substances in cosmetics are an important factor. The age incidence suggests that an unknown endocrine factor or age change may also play some part. Reddish-brown reticulate pigmentation with telangiectasia and atrophy develops in irregular, more or less symmetrical patches on the lateral cheeks and the sides of the neck but spares the area shaded by the chin. Treatment with a tuneable dye laser is effective at clearing the telangiectasia of poikiloderma of Civatte, but care is needed as it may also cause scarring and may even worsen the appearance.

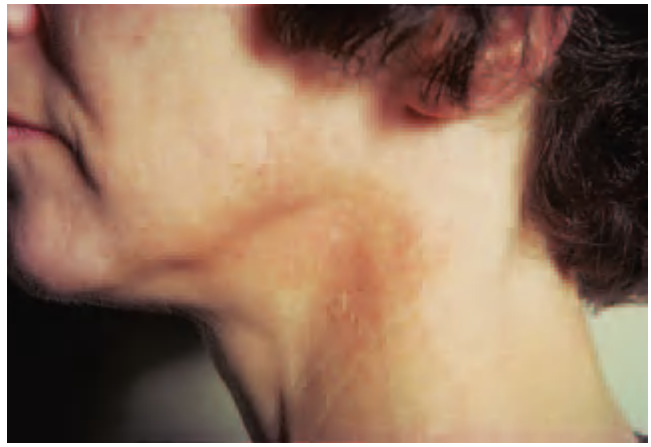

Fig. 39.29 Poikiloderma of Civatte on side of neck.

REFERENCE

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Erythrose péribuccale pigmentaire de Brocq [1–4]

SYN. ERYTHROSIS PIGMENTATA FACIEI

This syndrome occurs predominantly in middle-aged women but has been reported in men. A photodynamic substance in cosmetics is probably responsible. Diffuse brownish-red pigmentation develops more or less symmetrically around the mouth but spares a narrow perioral ring. It may extend up the centre of the face to the forehead and in some cases there are well-defined patches of pigmentation over the angles of the jaw and the temples [3]. The erythematous component, and hence the intensity of the pigmentation, may fluctuate over short periods. The pigmentation is usually persistent but tends gradually to fade if the cause is eliminated.

A similar post-inflammatory hyperpigmentation is seen in some patients with perioral dermatitis and may be the result of topical steroid therapy [4].

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Erythromelanosis follicularis of the face and neck [1–5]

This syndrome, of unknown origin, was originally described in Japan but may not be uncommon in white people. The affected individuals have been men, young or middle-aged at the time of onset [1–3], although it has been reported in adult females [4,5].

Histologically, there is slight hyperkeratosis. The hair follicles are enlarged and contain lamellar horny masses. The sebaceous glands are also enlarged. The epidermis overlying the affected follicle is flattened and contains excess melanin. In the dermis, an inconspicuous lymphocytic infiltrate surrounds dilated vessels.

The clinical picture is distinctive. A background of reddish-brown pigmentation with telangiectasia is studded with pale follicular papules. The hairs are lost from the majority of affected follicles in the vellus region, but less conspicuously from the terminal hair of scalp or beard. The pigmentation involves the skin in front of, beneath and behind the ear, extending to the side of the neck. It spreads slowly, is persistent and is not influenced by treatment.

The distribution and lack of clinical follicular keratosis or scarring readily distinguish erythromelanosis from the various forms of keratosis pilaris and from other facial melanoses.

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Dermal melanocytosis

SYN. CERULODERMA

Hyperpigmentation of the skin may be due to the presence of functional fusiform and dendritic melanocytes that lie in the dermis [1]. Although dermal melanocytes are common in other mammals, they are not often seen in humans. These cells have failed to reach their proper location in the basal layer of the epidermis in their migration from the neural crest of the developing embryo. Several conditions are grouped under the term 'dermal melanocytosis'. In all of them, the affected areas have a slate-brown or blue colour (ceruloderma) due to an optical effect from the pigment lying in the dermis.

Mongolian spot (Fig. 39.30) [1–4]

Mongolian blue spots are seen in 90% of oriental babies and less frequently in black babies. The usual site of involvement is the lumbosacral region. The spots are poorly circumscribed areas of slate-brown or blue-black pigmentation that are sometimes extensive and may be mistaken for bruises. A case of generalized dermal melanocytosis of the newborn has been described [2]. Mongolian blue spots usually fade in early childhood, although the aberrant extrasacral spots can persist [3]. The dermal melanocytes in persistent Mongolian spots have an extracellular sheath [4], as also seen in the naevus of Ito.

Naevus of Ota

SYN. NEVUS FUSCOCAERULEUS OPHTHALMOMAXILLARIS; OCULODERMAL MELANOCYTOSIS

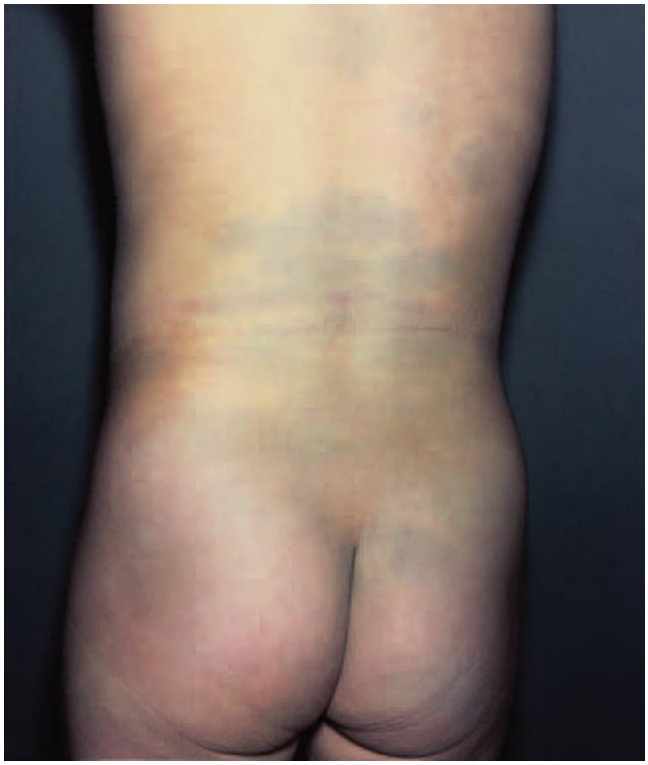
In naevus of Ota, the hyperpigmentation affects one side of the face in the area supplied by the ophthalmic and maxillary divisions of the trigeminal nerve [5,6]. Occasionally, it is bilateral. It is usually congenital but may appear later in life. It is more prevalent in the Japanese but is observed in other races. The colour is variable, but is usually either slate-brown or blue. The sclera is involved and there may be hyperpigmentation of the cornea, iris, retina, ocular muscles and orbit [7] (Fig. 39.31). Sometimes, there is pigmentation of the hard palate. An ipsilateral sensineural deafness occurring in a patient with naevus of Ota has been reported [8].

Naevus of Ota does not improve with time. Malignant change in the cutaneous lesions of naevus of Ota is extremely rare. However, melanomas are more common in the choroid, iris, orbit and brain of these patients [9]. A bilateral acquired dermal melanosis of the face resembling naevus of Ota has been described [10]. Promising results with the Q-switch ruby laser have been reported in the treatment of naevus of Ota, with multiple treatments increasing the response rate [11].

Naevus of Ito (Fig. 39.32) [4,12]

In this condition, the increased pigmentation affects the area supplied by the posterior supraclavicular and lateral brachial cutaneous nerves. It is common in the Japanese.

(a)



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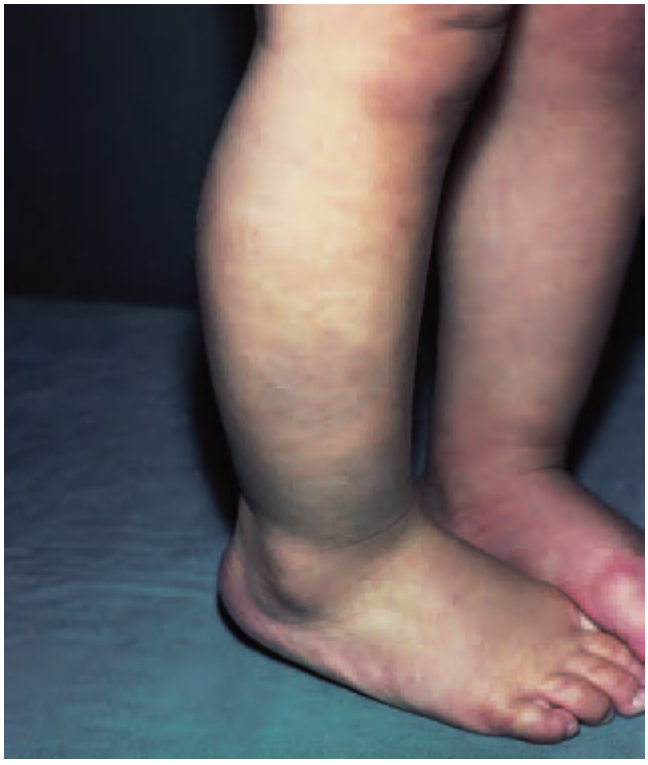
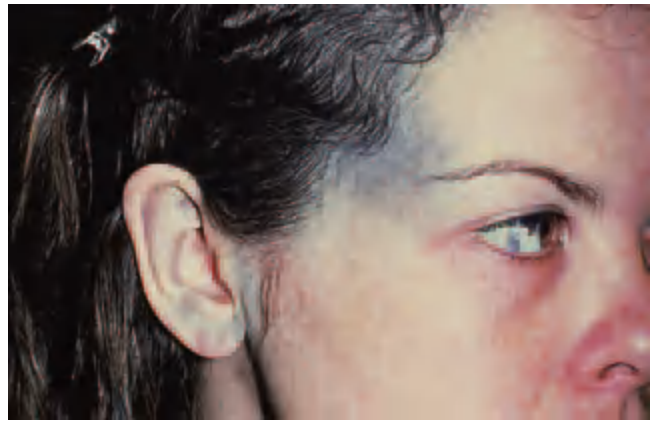


Fig. 39.30 Mongolian spot: (a) extensive blue coloration on the back of an oriental child; (b) involvement of the legs in the same child.



(a)

(b)

Fig. 39.31 (a) Naevus of Ota in a white subject. (b) Marked blue coloration of the sclera in the same patient.

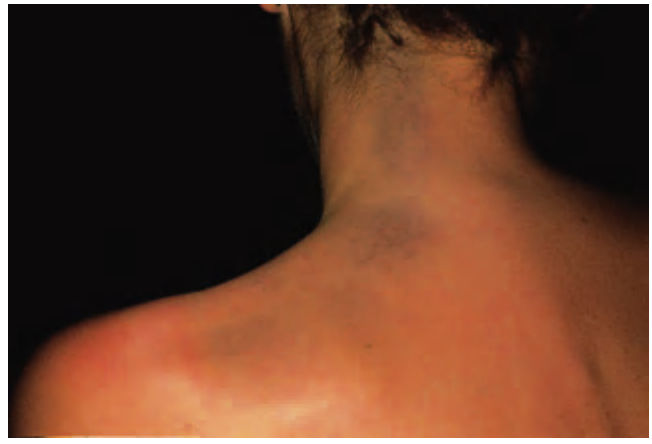


Fig. 39.32 Naevus of Ito.

Blue naevus (see Chapter 38) [1]

These commonly occur on or near the dorsa of hands and feet, usually early in life. Malignant transformation does not occur in the common blue naevus. However, the cellular blue naevus may rarely undergo malignant change.

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Disseminated dermal melanocytosis [1]

Progressive dermal melanocytosis has been described in a patient who developed profuse bluish bruise-like spots in childhood. The woman died in the fifth decade from melanoma.

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Hypermelanosis associated with other cutaneous lesions

Hypermelanosis is a characteristic feature of urticaria pigmentosa (see Chapter 47) but the mechanism of its production is unknown. The possible relationship between melanocytes and mast cells is discussed on p. 39.4. Tyrosinase-positive cells have been found in the upper dermis in some cases. In the childhood type, the light-brown macules often exceed 2 cm in diameter and the lesions are frequently nodular. In the adult types, the smaller and more numerous macules are purplish-brown in colour and not palpably infiltrated, and often fail to urticate on friction. They are usually widely distributed over the trunk and limbs.

The differential diagnosis of hypermelanosis

The very large number of conditions associated with widespread or localized hypermelanosis cannot readily be classified. The present classification is based on the colour of the skin and on various causative factors. The hypermelanosis may be due to genetic and naevoid factors (Table 39.3) or it is acquired and due to a variety of factors (Table 39.4).

The areas of hypermelanosis may be circumscribed or may be diffuse with intensification of the normal pattern of pigmentation. Hypermelanosis confined to the face and neck is considered on pp. 39.39–39.42. In acquired circumscribed patches of hypermelanosis, a post-inflammatory origin should be considered (see p. 39.45).

Treatment of hypermelanosis

Hypermelanosis, particularly affecting areas on the face, can be the cause of marked cosmetic disability and give rise to much mental distress. Treatment depends essentially on establishing the cause and if possible reversing the conditions that have given rise to the hypermelanosis. In the majority of cases, topical therapy has no place,

Table 39.3 Hypermelanosis due to genetic and naevoid factors.

Brown colour	Grey, slate or blue colour
Ephelides (freckles)	Mongolian spot
Lentigines	Naevus of Ota
Multiple lentigines syndrome	Naevus of Ito
Peutz–Jeghers syndrome	Blue naevus
Café-au-lait and freckle-like macules in neurofibromatosis	Diffuse melanocytosis
	Incontinentia pigmenti (Bloch–Sulzberger syndrome)
Melanotic macules in Albright's syndrome	Naegeli–Franceschetti–Jadassohn syndrome
Acanthosis nigricans, juvenile type	
Xeroderma pigmentosum	
Fanconi's syndrome	
Dyskeratosis congenita	
Familial progressive hyperpigmentation	

Table 39.4 Acquired hypermelanosis.

Causative factor	Brown	Grey, slate or blue
Metabolic	Liver disease	Haemochromatosis
	Haemochromatosis, hepatolenticular degeneration, biliary cirrhosis	
	Porphyria	
	Porphyria cutanea tarda and variegata, erythropoietic (congenital) porphyria	
Endocrine	ACTH and MSH-producing pituitary and other tumours	
	Addison's disease	
	ACTH therapy	
	Pregnancy	
	Contraceptive pill and oestrogens	
	Melasma (chloasma)	
Chemical	Arsenic	Minocycline
	Busulfan, bleomycin, cyclophosphamide	Fixed drug eruptions, barbiturates, phenolphthalein
	Adriamycin	Phenothiazines
	Psoralens	Chlorpromazine
	Berloque dermatitis	
	Phytophotodermatitis	
Physical	UV light, ionizing radiation, trauma	
Nutritional	Kwashiorkor	Chronic nutritional deficiency
	Pellagra	
	Sprue	
	Vitamin B_{12} deficiency	
Post-inflammatory	Eczema	Pinta
	Lichen planus, lupus erythematosus	Erythema dyschromicum perstans
	Lichen and macular amyloidosis	
	Systemic sclerosis, morphoea	
Tumours	Malignant melanoma	Metastatic melanoma with melanogenuria
	Acanthosis nigricans with adenocarcinoma	
	Malignant tumours	

ACTH, adrenocorticotrophic hormone; MSH, melanocyte-stimulating hormone.

although some who are perturbed about their cosmetic disability will demand treatment with a skin-bleaching preparation. Because in many cases exposure to sunlight intensifies the pigmentation, a photoprotective preparation should be prescribed and applied during sunny weather. Cosmetic camouflage may also be indicated.

A number of compounds have been used in skin-bleaching preparations and of these hydroquinone is the most safe. Preparations containing 2% hydroquinone, although not very effective, are of help in producing cutaneous depigmentation [1]. Although higher concentrations of hydroquinone are more potent, these preparations frequently irritate the skin and may produce, if used for long periods of time, an exogenous ochronosis and pigmented colloid millium [2,3]. A formulation of hydroquinone and retinoic acid has some effect in depigmenting human skin and is of use in the treatment of hypermelanotic conditions such as melasma [4–6]. It is not very effective for post-inflammatory hyperpigmentation. Topical tretinoin has been found to be effective in the treatment of actinic lentigines ('liver spots') in photodamaged skin [7] and also improves melasma [8]. The monobenzylether of hydroquinone is responsible for many therapeutic and cosmetic disasters and the compound should be used only to bleach away the remaining pigmented areas in patients with extensive vitiligo [9]. Several other substituted phenols, such as 4-isopropylcatechol, can produce cutaneous depigmentation; however, this compound and others are irritant and may produce sensitization [10].

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Hypomelanosis

Genetic and naevoid disorders

A number of genetically determined or naevoid conditions are characterized by localized and/or generalized hypomelanosis of the skin. These are listed in Table 39.5.

Albinism [1–10]

There are many distinct types of oculocutaneous albinism (OCA), each of which is characterized by partial or complete failure to produce melanin in the skin and the eyes. The classification is rapidly changing with the advent of advances in molecular genetics (e.g. rufous OCA is now TRP-1 gene-related OCA or type III OCA). Melanocytes are present in normal distribution but fail to synthesize melanin adequately. These conditions are inherited as autosomal recessive disorders; one rare type with apparent autosomal dominant inheritance is now felt to be due to quasi-dominant pedigree patterns or to partial expression of OCA II in OCA I heterozygotes (Table 39.5). The gene encoding tyrosinase has been localized to chromosome 11 [3] and many different mutations are now recognized for OCA [4]. The gene for type II OCA has been mapped to chromosome 15q11.13 [5]. Tyrosinase-negative albinism is characterized by hair bulbs that, after plucking and incubation with tyrosine, fail to produce darkening. In tyrosinase-positive albinism, the hair bulbs do darken in this test and the precise metabolic defects have yet to be ascertained. The tyrosinase-positive types are the most common. Ultrastructural studies of skin and hair show that in tyrosinase-negative albinos most of the melanosomes are stage 1 and stage 2 without any melanization. Other types may show up to stage 3.

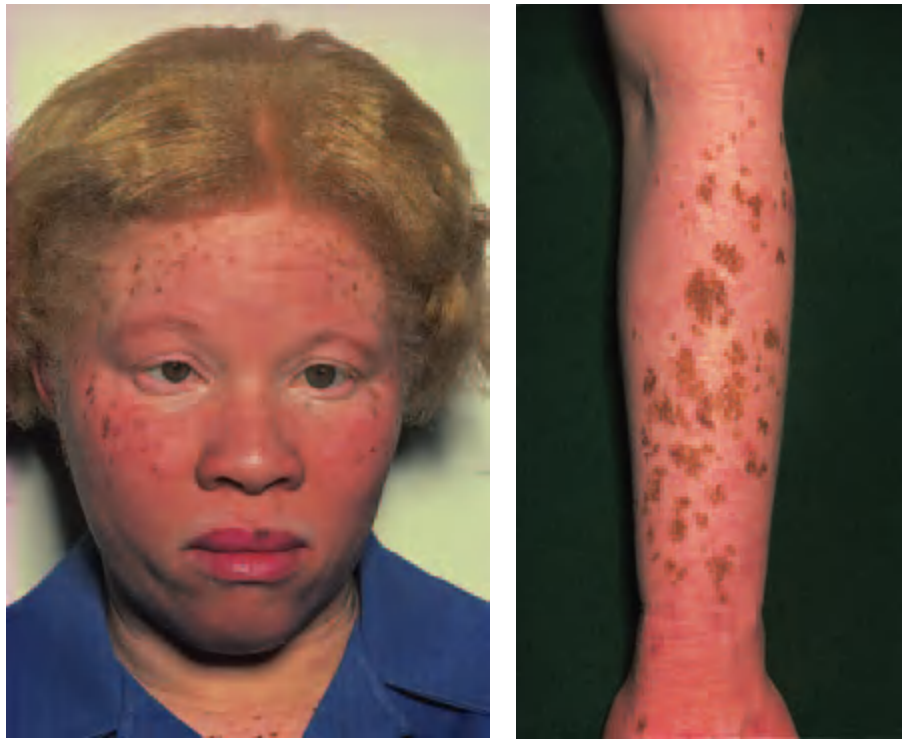
In ocular albinism, only the eyes are clinically involved, although careful investigation of the melanocytes in the skin does show some changes. There are four different types, two X-linked, one dominant and one recessive. Carrier females of the X-linked types may show irregular retinal pigmentation. In two types there is an associated deafness, the melanocytes apparently failing to play a protective role in the ear. In most albinos this defect leads to little or no change in ear function.

Incidence. Albinism is found in all races and the prevalence varies considerably. In the UK, the incidence is

Table 39.5 Hypomelanosis due to genetic and naevoid factors (MIM numbers in parentheses).

Oculocutaneous albinism (OCA)	
Tyrosinase negative (type IA, #203100)	Recessive
Yellow mutant (type IB, #606952)	Recessive
Temperature-sensitive (type 1TS; included in IB #606952)	Recessive
Tyrosinase positive (type II, *203200)	Recessive
Brown	Recessive*
Minimal pigment (203280)	Recessive
Platinum	Recessive†
TRP-1 gene-related (type III) (was rufous OCA, #278400)	Recessive
Hermansky–Pudlak syndrome (203300)	Recessive
Chédiak–Higashi syndrome (#214500)	Recessive
Autosomal dominant	Dominant‡
Ocular albinism	X-linked
With deafness	X-linked, recessive, dominant
Albinoidism (*126070)	Dominant§
Cross syndrome (*257800)	Recessive
Piebaldism (#172800)	Dominant
Waardenburg syndrome (#193150, #193510)	Dominant
Phenylketonuria (*261200)	Recessive
Vitiligo	Polygenic
Tuberous sclerosis (#191100)	Dominant
Achromic naevus	
Incontinentia pigmenti achromians	

* Brown OCA is currently included as a type of OCA II.
† Platinum OCA may be an alleleic variant of minimal pigment OCA.
‡ Dominant OCA probably does not exist: instances appear to be due to quasi-dominant pedigree patterns or to partial expression of albinism II in OCA I heterozygotes.
§ The term 'albinoidism' is applied to both pigmentary dilution (MIM *126070) and OCA II.



(a) (b)

Fig. 39.33 (a) Tyrosinase-positive oculocutaneous albinism in a black woman aged 40 years. (b) Dark-brown freckles on light-exposed areas.

estimated at 1 in 20 000. In the USA, the incidence of albinism is estimated at 1 in 39 000 in Caucasians and 1 in 28 000 in Afro-Caribbeans. In some countries it is more common, particularly where there is a tendency towards inbreeding and especially in isolated communities. The Cuna tribe on the San Blas islands off the coast of Panama have the highest incidence of albinism in the world (63 per 10 000). In Nigeria, the incidence of albinism is much higher in the south [6]. There are no adequate studies of the incidence of the different genotypes of OCA in the different races.

Clinical features. In all races there is marked dilution of the pigmentation of the skin, hair and eyes. In tyrosinase-negative OCA the skin is pink in colour, the hair is white and the patients show a prominent red reflex. This is the most severe variant of OCA.

In tyrosinase-positive OCA, some pigment is formed and with increasing age is to be found in the iris, skin and hair, the latter often developing a flaxen-yellow colour. These patients may also tan and in black people the skin has a yellowish-brown colour that with age develops dark-brown freckles, particularly in sun-exposed areas (Fig. 39.33). Also in this type, the iris is less translucent and in black people may be brown in colour.

In both types, patients have photophobia; often they have a characteristic facial expression due to apparent squinting. Errors of refraction are common, especially in the tyrosinase-negative type (OCA IA), and almost all patients have horizontal or rotatory nystagmus, sometimes with head nodding. In the tyrosinase-positive type, visual acuity may improve as patients get older and they may have less severe nystagmus [7]. There are abnormalities of the optic pathway. Foveal hypoplasia occurs in the tyrosinase-negative type [7].

In the yellow mutant type of albinism, the newborn resembles the tyrosinase-negative type, but by the age of 1 year the hair is yellow-red in colour. Hair bulbs incubated in tyrosine plus cysteine produce an intensification of the yellow-red phaeomelanin. This type of albinism is prevalent in the Amish communities in the USA [8].

The other types of albinism listed in Table 39.5 have pigment changes described by their names. Each has a rather distinctive racial predisposition.

In temperate climates, the prognosis for the albino is good, the visual defects constituting the greatest disability. In the tropics the fate of albinos is grim. At an early age [9] most of them develop in solar-exposed skin many actinic keratoses, squamous cell carcinomas and, occasionally, melanomas. Some die young from these tumours [6].

Treatment. No treatment is possible other than prescribing photoprotective preparations and limiting sun exposure, vigorous enforcement of which from early childhood can be very helpful. The regular examination of all albinos for the early detection and treatment of premalignant and malignant conditions of the skin is advisable,

especially in the tropics. Prenatal diagnosis of albinism has been reported [10].

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*Albinoidism (MIM *126070)*

Albinoidism is the name applied to families where there is some partial defect in melanin production in the skin but only minimal changes in the eyes. The biochemical basis of this is uncertain. Several families are described with this type of albinism [1,2]. Although there is hypopigmentation of the skin and hair, it is not as marked as in OCA. Slight tanning is reported and the hair-bulb test is positive. A diffuse punctate pattern of iris transillumination is seen. The eyes are usually normal, but there may be photophobia. In one large Swiss pedigree there was high-grade myopia [2]. The condition appears to have autosomal dominant inheritance, but in some families it is recessive.

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Hermansky–Pudlak syndrome (MIM #203300)

Hermansky–Pudlak syndrome is a rare type of OCA associated with a haemorrhagic diathesis [1]. About 250 cases have been reported, most of whom are from Puerto Rico or the south of the Netherlands [1]. Two different mutations in the gene for Hermansky–Pudlak syndrome have been identified. Tyrosinase-positive OCA occurs in association with a bleeding tendency and deposits of a ceroid-like pigment in the cells of the reticuloendothelial system [2]. The bleeding tendency is attributed to a storage-pool platelet defect. The platelets have decreased numbers of dense granules and reduced levels of serotonin and ADP [3]. Pulmonary fibrosis, granulomatous colitis and lupus nephritis have been associated [4]. There is no defect in circulating lymphocytes or neutrophils [5]. Two cases of Hermansky–Pudlak syndrome have been complicated by systemic lupus erythematosus [6].

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Chédiak–Higashi syndrome (MIM #214500)

Chédiak–Higashi syndrome is a rare autosomal recessive disorder characterized by hypopigmentation of the skin and eye [1]. The skin is fair, the retinae are pale and the irides translucent. The hair is light blonde or silvery grey. These children are very susceptible to bacterial and viral infections, and intractable respiratory and cutaneous infections usually prove fatal before the age of 10 years. Longer survival is possible but later the lymph nodes, spleen and liver are enlarged and a malignant lymphoma develops. A similar condition is seen in Aleutian mink [2], Hereford cattle [3] and the beige mouse [4].

The hereditary defect concerns membrane-bound organelles of various cell types and is due to mutations in a gene encoding a protein known as lysosomal trafficking regulator. The melanocytes contain giant pigment granules (Fig. 39.34), which arise by autophagocytosis and fusion of large melanosomes that show degradative changes within the cells [5]. Similar defects of granules and other organelles occur in white cells and platelets. Cytoplasmic inclusions are present in a variety of cells of neuroectodermal origin. The white cells are defective in combating infection and if these children survive infancy, they usually die later from a malignant lymphoma.

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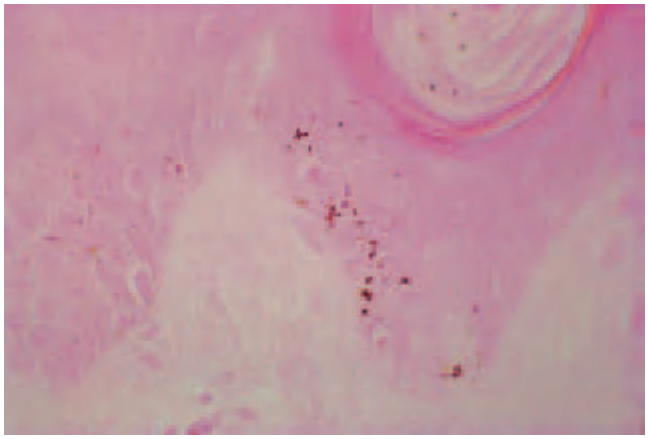

Fig. 39.34 Chédiak–Higashi syndrome. Large pigment granules in the epidermis as seen by light microscopy. Fontana stain, × 40.

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Griscelli syndromes type I (MIM #214450) and type II (MIM #607624)

Griscelli syndrome type I comprises partial albinism with neurological deficiency due to mutations in the myosin type V gene.

Griscelli syndrome type II, due to mutations in the *RAB27A* gene, combines partial albinism and immunodeficiency [1], but is distinct from Chédiak–Higashi syndrome. It is inherited as an autosomal recessive condition. In addition to pigmentary dilution, there is immune deficiency and the affected children are prone to recurrent pyogenic infection. There is hypogammaglobulinaemia and defective cell-mediated immunity with lymphohistiocytosis and haematophagocytosis.

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Prader–Willi syndrome (MIM #176270) and Angelman syndrome (MIM #105830) [1]

Both syndromes are associated with mental retardation, abnormal behaviour and hypopigmentation. In both there are deletions of the same region of chromosome 15, with deletion on the paternal chromosome in Prader–Willi syndrome and the maternal in Angelman syndrome.

REFERENCE

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*Cross' syndrome (MIM *257800)*

SYN. OCULOCEREBRAL SYNDROME WITH HYPOPIGMENTATION

Cross' syndrome is one of the 'silvery hair' syndromes and is characterized by generalized hypopigmentation associated with ocular anomalies, mental and physical retardation, ataxia and spasticity [1]. It is probably determined by an autosomal recessive gene [2,3]. The pigmentary and ocular defects are manifest from birth. The hypopigmentation resembles albinism: blood tyrosine levels are normal and the light-coloured hair pigments poorly in tyrosine solution. The ocular defects include microphthalmos, a small opaque cornea and coarse nystagmus. Spasticity soon becomes evident, and physical and mental development is retarded [3].

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Piebaldism (MIM #172800) [1–11]

Piebaldism is a rare autosomal dominant condition characterized by stable areas of vitiligo-like amelanotic skin associated with a white forelock [2,3]. The incidence of piebaldism is estimated at less than 1 in 20 000. Both sexes are affected equally, and no race is spared. A similar condition of 'white spotting' is seen in mice and results from deletion or mutation of the c-*kit* proto-oncogene that codes for an embryonic growth factor called Steel factor [4]. Missense and frameshift mutations of the *kit* proto-oncogene, which encodes the cellular receptor tyrosine kinase for the mast cell/stem cell growth factor, are responsible for a range of phenotypes with piebaldism [5,6].

The plurality of defects revealed by electron microscopy suggests that a number of different gene loci are concerned. Ultrastructural studies have shown either an absence of melanocytes and melanosomes in the hypomelanotic areas or sometimes reduced numbers of abnormal large melanocytes. In the hypermelanotic islands in the areas of hypomelanosis, melanocytes are present that produce normal melanosomes but also abnormal spherical and granular melanosomes [9]. When transferred to the

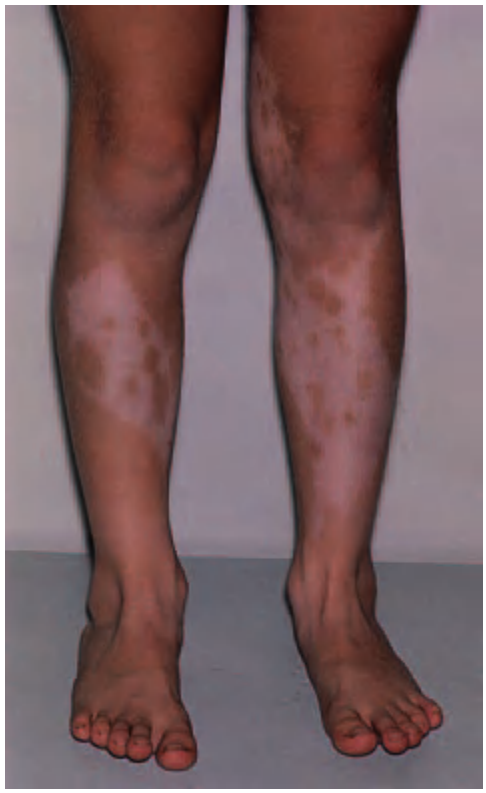

Fig. 39.35 Piebaldism. The lesions had been present from birth.

keratinocytes, these show abnormal degradation and fusion.

Clinical features. Patches of skin totally devoid of pigment are present at birth and usually remain unchanged throughout life. Most common is a frontal median or paramedian patch, associated with a mesh of white hair (white forelock); rarely, this may be the only lesion. Often, white patches occur on the upper chest, abdomen and limbs, bilaterally but not necessarily symmetrically (Fig. 39.35). Occasionally, they are found on the face, particularly the chin. The hands and feet, as well as the back, remain normally pigmented. Islands of normal or hypermelanotic skin occur in the white areas, or less often on normal skin.

Piebaldism can easily be distinguished from vitiligo where the lesions are acquired later in life and their configuration and distribution are quite different. In piebaldism, there is almost invariably a white forelock and the pattern of arrangement of the lesions is quite characteristic. Also the presence of islands of normal pigmented skin in the hypomelanotic areas is typical. If the interpupillary distance is increased or the patient is deaf, the diagnosis of Waardenburg's syndrome (see below) must be considered. The patterns of hypomelanosis as seen in the localized and systematized types of naevus depigmentosus differ from piebaldism. Microscopy of the skin in naevus depigmentosus reveals normal numbers of melanocytes with sometimes rather stubby dendrites [9]. A progressive variant of piebaldism has been described in association with a novel mutation in the *kit* gene [11].

Treatment. Photoprotective preparations should be prescribed to protect the amelanotic areas from burning with sun exposure. Cosmetic camouflage or skin dyes may be helpful for some patients. Skin grafts, minigrafts and grafts of autologous cultured melanocytes have some promise [12,13]. PUVA therapy is generally disappointing, as are topical corticosteroids.

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Tietz's syndrome (MIM #103500)

Tietz reported a six-generation pedegree with the constant association of total absence of pigment in the skin and hair, normal eyes, complete deaf-mutism and hypoplasia of the eyebrows [1]. An autosomal dominant gene appeared to be implicated. There is some doubt that this syndrome is a distinct entity.

The analogy with a syndrome in cats, in which severe deafness is associated with total absence of skin pigment but normal eye colour, suggests that Tietz's syndrome probably represents a 'generalized white spot' rather than albinism.

REFERENCE

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Waardenburg's syndrome (MIM #193150) [1–11]

Waardenburg's syndrome (WS) is a rare autosomal dominant condition characterized by lateral displacement of the inner canthi and the lacrimal puncta, prominent nasal root and medial eyebrows, congenital deafness and heterochromic irides. The pigmentary changes are a 'dappled' appearance of the skin, a white forelock, which may be conspicuous or only a few strands, and premature greying of hair, eyebrows and cilia. A few patients show piebaldism; pigment-free patches may be large and multiple or small and inconspicuous.

WS has been reported in both black and white people. The incidence has been estimated at 1 in 42 000 in the general population and 1–2% among the congenitally deaf. Variable expression and penetrance explain milder or incomplete phenotypes. The skin lesions so clearly resemble those of piebaldism that a similar pathogenetic mechanism is likely. Some abnormality of the development of neural crest derivatives is postulated.

Four variants of WS have been described. Type I is the classic form, while type II lacks dystopia canthorum but has a high incidence of congenital sensorineural deafness and heterochromia. Type III resembles type I but is associated with limb abnormalities in addition to dystopia canthorum. Type IV, like type III, is autosomal recessive and is characterized by associated Hirschsprung's disease and, in some cases, by more extensive hypopigmentation [7].

A number of different mutations of the *PAX*-3 gene on chromosome 2q35 have now been reported in different forms of type I and type III [4]. None of the cases of type II have been linked to 2q markers but type IIA is now known to be due to mutations in the *MITF* gene. Mutations in the endothelin-3 gene [10] and in endothelin-B genes have been reported in type IV, and mutations in the *SOX10* gene have also been implicated as causing WS [11]. Types IIB and IIC are further subdivisions linked to genes mapping to chromosomes 1p and 8p, respectively. Ultrastructural studies on the amelanotic skin show an absence of melanocytes [5]. In the pigmented areas, there are abnormalities of the melanocytes and melanosomes.

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Piebaldism in association with congenital nerve deafness [1] has been reported in two brothers with no other manifestation of WS. It has been suggested that the condition may be genetically distinct.

REFERENCE

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Ziprkowski–Margolis syndrome [1,2]

Ziprkowski–Margolis syndrome is a rare X-linked recessive syndrome that occurs in males. It was first reported in 14 members of an Egyptian–Jewish family with males showing deaf-mutism, heterochromic irides and piebald-like hypomelanosis of skin and hair. The skin appears completely amelanotic at birth, but pigmented macules develop on the extremities, trunk and scalp. The hair usually remains white. Linkage studies indicate the gene locus to be on Xq, probably in the region Xq13–26 [3].

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Hypomelanotic macules of tuberous sclerosis

In this neurocutaneous disorder (see Chapter 12), transmitted as an autosomal dominant trait, hypomelanotic macules are found in about 90% of affected babies [1–3]. These macules are usually multiple, irregularly scattered and frequently have a lance–ovate shape: the configuration of an ash leaf (Fig. 39.36). The macules are the earliest manifestation of this disorder and are of diagnostic significance in a baby with fits, especially infantile spasms [1]. They are best identified in the fair skinned with the aid of a Wood's lamp. Electron microscopy of the macules shows the presence of normal or reduced numbers of

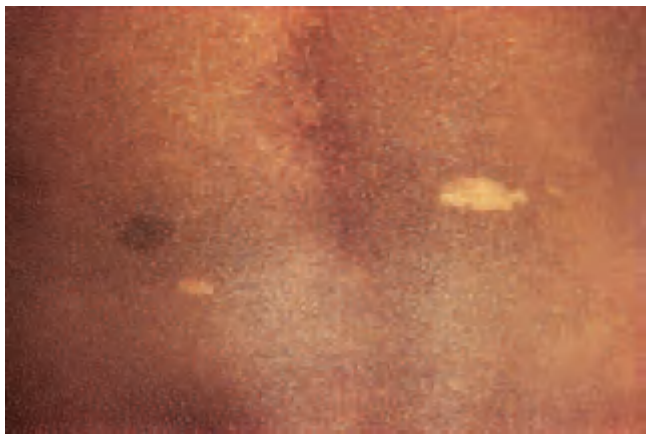

Fig. 39.36 Ash-leaf-shaped hypopigmented macules in tuberous sclerosis.

melanocytes that have poorly developed dendrites and contain fewer and smaller melanosomes than normal [2]. The gene responsible for tuberous sclerosis has been localized to 9q34 (*TSC1*) and 16p13.3 (*TSC2*) [4,5].

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Naevus depigmentosus

SYN. ACHROMIC NAEVUS

This is a circumscribed area of depigmentation, usually present at birth and changing little thereafter. The lesions are often single but may be multiple, circumscribed [1], and rounded, dermatomal or in whorls and streaks resembling incontinentia pigmenti achromians of Ito (see below). Histology may show either normal or reduced numbers of melanocytes. A functional defect in melanocytes, with morphological abnormalities of melanosomes, has been identified [2]. Apart from a few reports of associated findings, this is an isolated naevoid abnormality of the skin.

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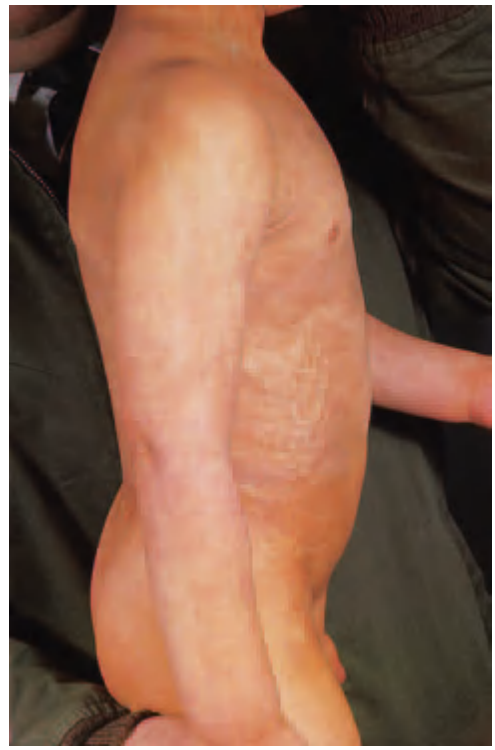

Fig. 39.37 Incontinentia pigmenti achromians of Ito.

Incontinentia pigmenti achromians of Ito (MIM *300337) [1–7]

SYN. HYPOMELANOSIS OF ITO

This neurocutaneous disorder is characterized by bizarre whorled areas of depigmented skin that are variable in extent and may be unilateral or bilateral. The areas of hypomelanosis occur along Blaschko's lines [6] (Fig. 39.37). The appearances resemble the late stages of incontinentia pigmenti, but this is clearly a quite separate disease without the preceding inflammatory stages and without the sex-linked inheritance of incontinentia pigmenti. There is no basal layer damage and no pigmentary incontinence. Most cases are sporadic, although familial cases have been reported. Mosaicism involving the X chromosome has been found [6]. The white streaks are usually present at birth but may progress thereafter. Eventually, they may repigment. There may be associated disorders in the musculoskeletal system, teeth, eyes and central nervous system [2]. Convulsions and mental deficiency occur commonly in the reported cases [4]. The skin lesions have to be distinguished from the more bizarre-shaped depigmented naevi and from focal dermal hypoplasia where the skin also shows atrophic changes.

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Vogt–Koyanagi syndrome

SYN. HARADA'S DISEASE

Aetiology. This complex syndrome affects the skin, eyes, inner ears and meninges. It is rare but widely distributed. Most cases occur in the third and fourth decades but children may be affected. The cause is unknown but an abnormal response to a virus and immunological mechanisms have been postulated. Of interest is the report of the condition occurring in a patient following an operation for metastatic malignant melanoma [1]. In one study, cellular hypersensitivity to uveal pigment was confirmed by leukocyte migration tests [2].

Pathology. Electron microscopy of depigmented skin shows an absence of melanocytes, with replacement by Langerhans' cells and by indeterminate dendritic cells, as in vitiligo [3,4]. Colloid–amyloid bodies are also found at the dermal–epidermal junction [3]. Inflammatory skin lesions are characterized by a chronic, mixed inflammatory cell infiltrate [5].

Clinical features [6,7]. A prodromal febrile episode, which may be trivial or severe with encephalitic or meningitic symptoms and lymphocytosis of the cerebrospinal fluid, is followed after a week or two by bilateral uveitis, often with choroiditis and optic neuritis. Shortly after the establishment of uveitis, deafness and/or tinnitus of labyrinthine origin develops in over 50% of cases. As the uveitis begins to subside, and usually within the first 3 months, vitiligo, poliosis and alopecia may develop. Poliosis, which occurs in 80% of cases, may be limited to the brows and lashes or may involve scalp and body hair extensively. Vitiligo, present in about 60% of cases, is usually symmetrical. Rarely, it may precede the uveitis, even by as much as 3 years. Two cases of vitiligo following a plaque-type inflammatory erythema have been reported [8]. Halo naevi may be present [9]. Alopecia areata occurs in 50%; occasionally the hair loss is diffuse.

The pigmentary changes tend to be permanent. The uveitis, which may take a year or more to clear, may result in total blindness, but most cases show some recovery of visual acuity, although it is seldom complete [10]. Hearing is usually completely restored.

Diagnosis. The association of vitiligo with loss of pigment in brows and lashes and with the residual ocular defects should clearly differentiate this syndrome from any other.

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Alezzandrini's syndrome [1,2]

Alezzandrini's syndrome has only been reported in a small number of cases. The syndrome is characterized by unilateral facial vitiligo associated with unilateral retinal degeneration, white hair, poliosis and deafness.

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Vitiligo [1–3]

Aetiology. Vitiligo affects all races and has a long history [4]. It is stated that it occurs in 1% of the world's population [2]. An epidemiological survey on the island of Bornholm in Denmark [5] found the prevalence to be 0.38%. It is likely that this figure applies also to other countries in north-west Europe. The incidence of vitiligo in those with racially pigmented skins is higher (and the social impact greater), although reliable figures are not available. There is a preponderance of females in most series based on outpatient attendances, but the frequency in the population is probably the same in both sexes [5].

Table 39.6 Disorders associated with vitiligo.

Thyroid disease* (hyperthyroidism and hypothyroidism [7])
Pernicious anaemia*
Addison's disease* [8]
Diabetes mellitus* [9]
Hypoparathyroidism*
Myasthenia gravis*
Alopecia areata
Morphoea and lichen sclerosus
Halo naevus*
Malignant melanoma* [10]

* Autoantibodies demonstrable.

Fig. 39.38 Vitiligo. Epidermal sheet of marginal depigmented area showing marked reduction in number of melanocytes.

Between 30 and 40% of patients have a positive family history [2], and a genetic factor is undoubtedly involved. Inheritance may be polygenic or determined by an autosomal dominant gene of variable penetrance. Vitiligo has been reported in monozygotic twins [6].

Various theories have been suggested for the aetiology of vitiligo; the same mechanism may not apply to all cases.

- *Autoimmune hypothesis*: this is based on the clinical association of vitiligo with a number of disorders also considered to be autoimmune (Table 39.6). Organ-specific autoantibodies to thyroid, gastric parietal cells and adrenal tissue are found in the serum more frequently in patients with vitiligo than in the general population [11,12]. A complement-fixing antibody to melanocytes has been found in the serum of several patients who in addition to vitiligo had alopecia areata, mucocutaneous candidiasis and multiple endocrine insufficiencies [11]. Antibodies to normal human melanocytes have been detected using a specific immunoprecipitation assay [13,14], and have a cytolytic effect [15]. T-cell profiles are abnormal in vitiligo, with a decrease in T-helper cells [16–18].
- *Neurogenic hypothesis* [19]: this suggests that a compound is released at peripheral nerve endings in the skin that may inhibit melanogenesis and could have a toxic effect on melanocytes. Although vitiligo may sometimes occur in a dermatomal distribution and electron microscopy shows abnormalities of terminal portions of peripheral nerves, there is little support for this hypothesis. However, recent studies on neuropeptide and neuronal markers in vitiligo suggest that neuropeptide Y may have a role [20].
- *Self-destruct theory of Lerner* [2]: this suggests that melanocytes destroy themselves due to a defect in a natural protective mechanism that removes toxic melanin precursors. This hypothesis is based on the clinical features of vitiligo and on experimental studies of cutaneous depigmentation by chemical compounds that have a selective lethal effect on functional melanocytes [21]. These compounds can produce a leukoderma indistinguishable from idiopathic vitiligo.

It has been suggested that defective keratinocyte metabolism plays a major role, with low catalase levels in the epidermis of vitiligo [22]. A new hypothesis involving defective tetrahydrobiopterin and catecholamine biosynthesis has been put forward to explain the pathogenesis of this disorder [23].

Pathology. There is a marked absence of melanocytes and melanin in the epidermis. Histochemical studies [24] show a lack of dopa-positive melanocytes in the basal layer of the epidermis (Fig. 39.38). Recent immunohistochemical studies with a large panel of antibodies show only an occasional melanocyte in lesional skin [25]. Electron microscopy studies [9,26,27] confirm the loss of melanocytes, which appear to be replaced by Langerhans' cells. In the epidermis of areas around the margins of vitiligo are abnormalities of keratinocytes [9] as well as degenerating melanocytes. There is increased cellularity of the dermis and occasional colloid amyloid bodies are found. In inflammatory vitiligo, where there is a raised erythematous border, there is an infiltrate of lymphocytes and histiocytes. This infiltrate is also found in the marginal areas of some biopsies [27].

Clinical features [2,3]. Vitiligo can begin at any age, but in 50% of cases it develops before the age of 20 years. The condition is gradually progressive, sometimes extending rapidly over a period of several months and then remaining quiescent for many years.

Hypomelanotic macules are usually first noted on the sun-exposed areas of skin, on the face or on the dorsa of hands (Fig. 39.39). These areas are prone to sunburn. Rarely, itching in the absence of sunburn may occur. Damage to the 'normal' skin frequently results in an area of depigmentation—an isomorphic or Koebner phenomenon (Fig. 39.40).

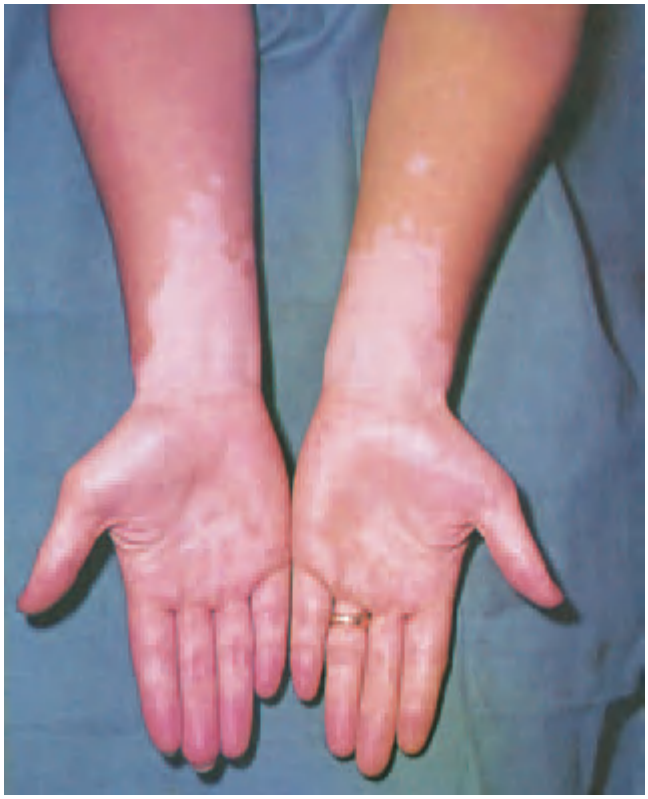

Fig. 39.39 Vitiligo.

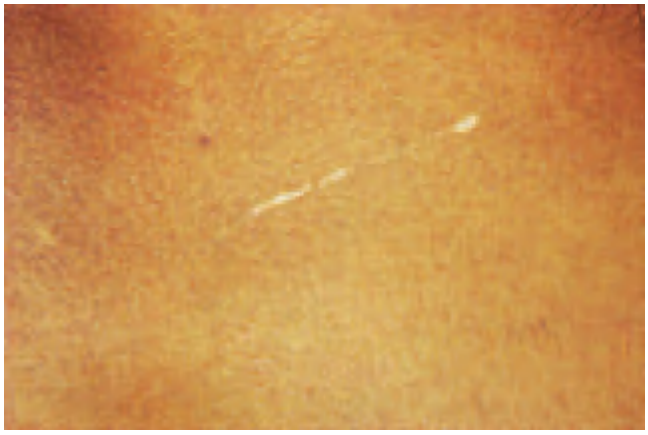

Fig. 39.40 Isomorphic or Koebner phenomenon at site of a scratch in a patient with vitiligo.

The amelanotic macules in vitiligo are found particularly in areas that are normally hyperpigmented, for example the face, axillae, groins, areolae and genitalia. Areas subjected to repeated friction and trauma are also likely to be affected, for example the dorsa of hands, feet, elbows, knees and ankles. The distribution of the lesions is usually symmetrical, although sometimes it is unilateral and may have a dermatomal arrangement (Fig. 39.41). Rarely, there is complete vitiligo, although a few pigmented areas always remain.

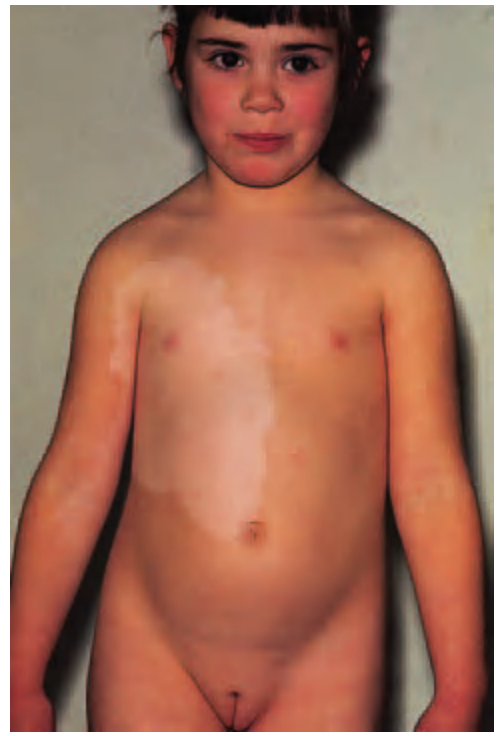

Fig. 39.41 Segmental vitiligo.

The pigment loss may be partial or complete, or both may occur in the same areas (trichrome vitiligo) (Fig. 39.42).

The macules have a convex outline, increase irregularly in size and fuse with neighbouring lesions to form complex patterns. The hairs in the patches frequently remain normally pigmented, but in older lesions the hairs too are often amelanotic. The margins of the lesions may become hyperpigmented. The main symptom is the cosmetic disability, although some patients present because of sunburn in the amelanotic areas. Vitiligo commonly starts in children, who are more likely to show segmental vitiligo, autoimmune diseases or to have a family history of canities [28].

Spontaneous repigmentation is noted in about 10–20% of patients, most frequently in sun-exposed areas. It is usually seen in younger patients, the repigmentation being quite trivial and mainly perifollicular.

In addition to premature greyness of the hair, uveitis also rarely occurs [29]. Careful examination of the ocular fundus may show abnormalities [30]. There have also been suggestions of an increased incidence of deafness [31].

Associated disorders. A number of conditions occur in association with vitiligo and are listed in Table 39.6. Halo naevi [2,3] occur not infrequently and often antedate the onset of vitiligo. Areas of depigmentation sometimes develop in patients with malignant melanoma [10].

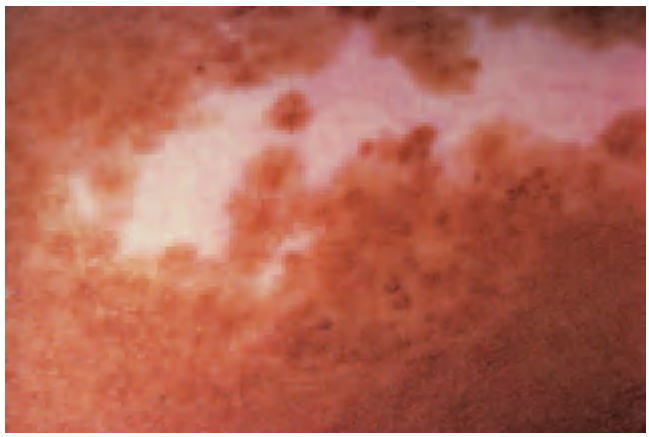

Fig. 39.42 'Trichrome' vitiligo.

Vitiligo with uveitis, central nervous system involvement and premature greying of the hair occurs in the Vogt–Koyanagi syndrome (see p. 39.53).

Diagnosis. The distribution, age of onset and hyperpigmented border will suggest the diagnosis. In piebaldism, the lesions are present at birth, are usually confined to the head and trunk, and rarely show a hyperpigmented border. Careful examination of the texture of the unpigmented skin should exclude lichen sclerosus and scleroderma. Post-inflammatory leukoderma, which is frequent in the darker races, shows an irregular mottling of hyperpigmented and hypopigmented blotches. Hypomelanosis of the affected skin is commonly seen in pityriasis alba, producing slightly scaly areas with rather ill-defined edges on children's faces. Hypopigmented slightly scaly macules are seen in pityriasis versicolor. These areas often fluoresce a golden yellow when examined under a Wood's lamp. The hypomelanotic macules in leprosy are anaesthetic.

Treatment. The treatment of vitiligo is unsatisfactory and in most cases the patient is best advised to seek effective cosmetic camouflage for the lesions on exposed skin. In sunny climates, the prescription of sunscreens is often necessary.

Treatment with systemic psoralens, 4,5',8-trimethylpsoralen, 8-methoxypsoralen or 5-methoxypsoralen, combined with exposure to sunlight or to light sources providing high-intensity long-wave UV light, is effective in a proportion of cases [3,32,33]. The patient is instructed to take the psoralens in a dose of 0.6 mg/kg 2 h before carefully controlled graduated exposure to sunlight, preferably around midday. Therapy is continued for at least 6 months and in some for several years. In the majority of patients, the areas retain the pigment long after psoralen therapy has been discontinued. The use of topical applications of psoralens is hazardous and may result in untoward blistering of the skin. Khellin has also been used with UVA [34].

Narrow-band UVB phototherapy has been found to be effective and safe for vitiligo [35].

In some patients, the more potent topical corticosteroid preparations, 0.1% betamethasone valerate and 0.05% clobetasol propionate, are effective in producing repigmentation of areas of vitiligo, but often at the price of some atrophy [36].

In those patients with extensive vitiligo and only a few residual areas of hyperpigmentation, skin-bleaching creams, such as 20% monobenzylether of hydroquinone, are of use [37].

The use of grafting techniques, minigrafts and autologous cultured melanocytes is interesting but may be limited by the Koebner phenomenon [38–40]. Minigrafting has been carried out with success in some patients with more widespread vitiligo [41]. A systematic review of autologous transplantation methods in vitiligo has recently been performed [42].

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Halo naevus [1,2]

SYN. SUTTON'S NAEVUS; LEUKODERMA ACQUISITUM CENTRIFUGUM

Definition and aetiology. Leukoderma acquisitum centrifugum designates the development of a halo of hypomelanosis around a central cutaneous tumour. This tumour is usually a benign melanocytic naevus but may be a neuroid naevus, a blue naevus, a neurofibroma, or a primary or secondary malignant melanoma [1]. The phenomenon, which is not uncommon, is usually seen in children or young adults of either sex.

Halo naevi occur with increased frequency in patients with certain organ-specific autoimmune disorders, as does vitiligo (see above), with which it is often associated. An immunological association of halo naevus with cutaneous malignant melanoma exists. Antibodies against the cytoplasm of malignant melanoma cells are found in the serum of patients with halo naevi [3]. Multiple halo naevi may occur in patients with melanoma.

Pathology [1,4]. Most halo naevi are compound naevi. There is frequently a lymphocytic infiltration of the naevus and the constituent cells may show damage. Ultrastructural studies show the apposition of mononuclear cells with naevus cells that show cytotoxic changes [5]. In the depigmented halo, there is an absence of melanocytes, but Langerhans' cells are present [6]. Melanophages are often present in the dermis.

Clinical features [1,7]. Circular areas of hypomelanosis occur around pigmented naevi, particularly on the trunk, less commonly on the head and rarely on the limbs. Multiple lesions are common, the halos being about 0.5–1.0 cm wide and developing simultaneously or at intervals around several, but not all, naevi (Fig. 39.43). The condition is usually seen in young people. The naevus tends to flatten and may disappear completely. The depigmented areas often persist, but may pigment after many years. Eczema around naevi (Meyerson's naevi) is discussed in Chapter 38.

Treatment. Normally none is required. The usual diagnostic criteria must be applied if there is any possibility that the central tumour is a melanoma. It should be remembered that a halo around a benign naevus is relatively common, whereas malignant melanoma is rare, and a melanoma surrounded by a halo is extremely rare. Mutilating surgery must never be undertaken without preliminary histological examination by an experienced pathologist.

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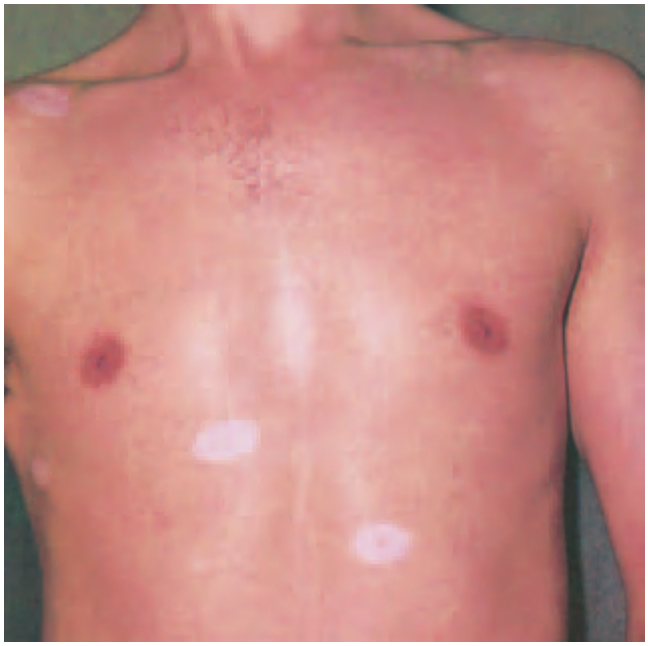
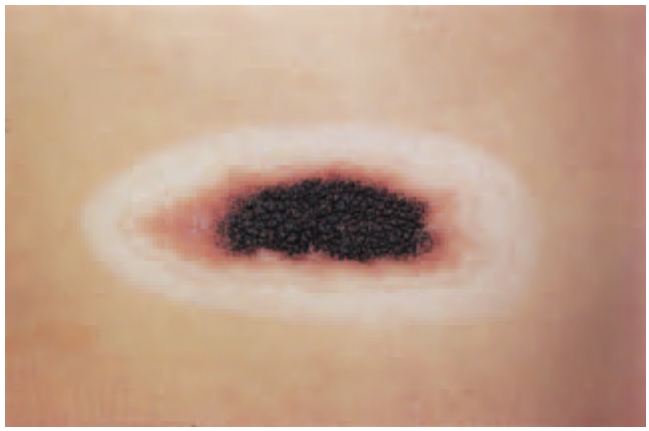
Acquired hypomelanosis

The disorders in which there is frequently an acquired loss of melanin pigment not due to genetic factors are shown in Table 39.7.



(a)



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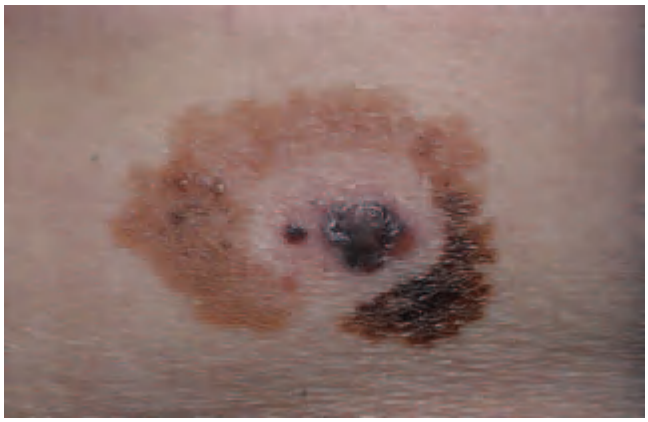

(c)

Fig. 39.43 (a) Multiple halo naevi in a young man who also had vitiligo. (b) Unusually large halo naevus. (c) Halo phenomenon developing within a malignant melanoma that later proved fatal.

Table 39.7 Acquired hypomelanosis.

Endocrine factors
Hypopituitarism*
Addison's disease†
Thyroid disease†
Chemical factors (occupational and therapeutic)
Monobenzylether of hydroquinone†
Monomethylether of hydroquinone
p-tertiary-butylphenol†
p-tertiary amylphenol†
Chloroquine and hydroxychloroquine
Arsenic‡
Nutritional factors
Chronic protein deficiency§
Pernicious anaemia§
Post-inflammatory and infections
Eczema (pityriasis alba)‡
Psoriasis‡
Pityriasis versicolor‡
Pinta‡, syphilis‡, yaws‡
Leprosy‡
Sarcoidosis‡
Lupus erythematosus‡
Lichen planus‡
Neoplasms
Halo naevus†
Malignant melanoma†
Miscellaneous
Idiopathic guttate hypomelanosis‡
Vogt–Koyanagi–Harada syndrome†

* Diffuse loss of pigment: lack of melanocyte-stimulating hormone.
† Circumscribed areas: vitiligo-like lesions.
‡ Partial loss of pigment in circumscribed areas.
§ Loss of pigment in hair.

Chemical depigmentation

A number of chemicals can produce cutaneous depigmentation when applied to the skin [1,2]. Several substituted phenols produce an occupational leukoderma in workers coming in contact with them (see also Chapter 21). Of these, *p*-tertiary-butylphenol is the most important [2–4]. Occupational leukoderma occurs in workers in contact with the monobenzylether of hydroquinone [5]; this compound is used in the treatment of hypermelanosis and can produce confetti-like areas of depigmentation in the treated areas [6] (Fig. 39.44). The monomethylether of hydroquinone can induce a similar leukoderma [7]. Several phenolic germicidal preparations can produce depigmentation of the skin [4]. 4-Tertiary-butylcatechol is also a cause of occupational leukoderma [8], and this may follow contact sensitization [9]. The areas most likely to be affected in occupational leukoderma are the dorsa of the hands (see Fig. 39.13), but other areas are involved, not necessarily in contact with the chemicals. The depigmented areas frequently enlarge, and new ones appear

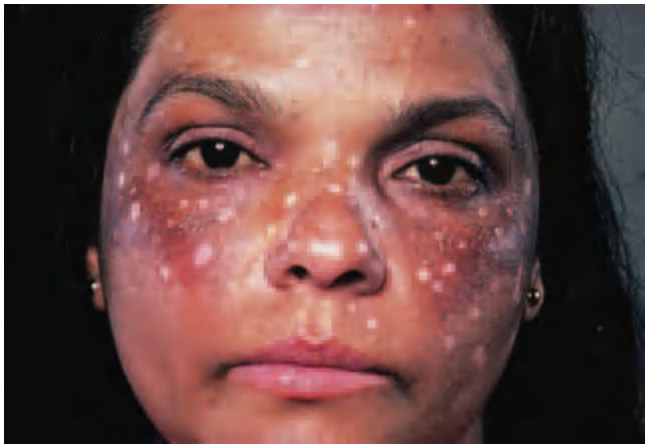

Fig. 39.44 Depigmentation on the face following treatment of melasma with monobenzylether of hydroquinone. (Courtesy of St John's Dermatology Centre, London, UK.)

even after the patient is no longer in contact. The areas may or may not repigment. Treatment with psoralens is usually ineffective. In the hypomelanotic and amelanotic areas, there is often an almost complete absence of melanocytes [3,4]. Experimental studies [1,10] indicate that these substituted phenols have a selective lethal effect on functional melanocytes.

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Post-inflammatory and infections

Hypomelanotic areas occur following the resolution of areas of eczema and psoriasis (Fig. 39.45). These are also seen in pityriasis lichenoides and cutaneous T-cell lymphoma [1].

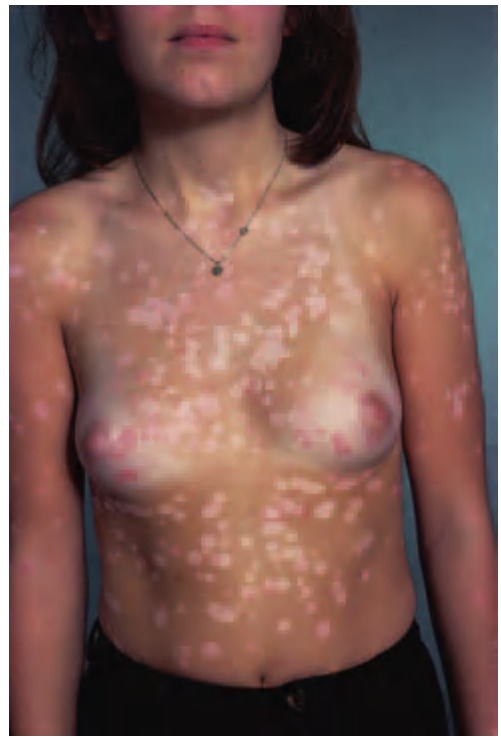

Fig. 39.45 Hypopigmentation in a girl with resolving psoriasis.

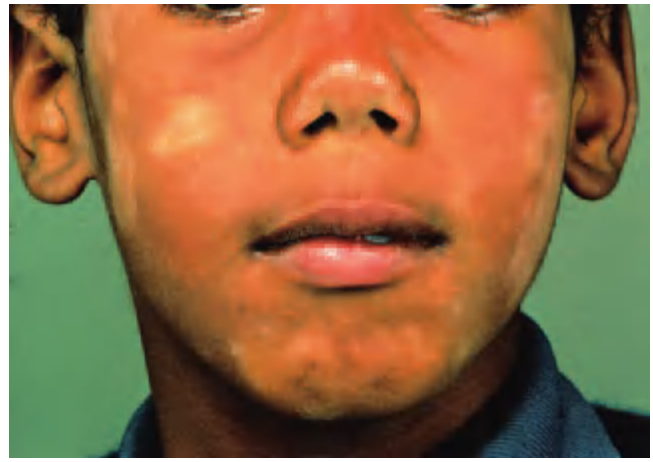

Fig. 39.46 Pityriasis alba. (Courtesy of St John's Institute of Dermatology, London, UK.)

The superficial eczema known as pityriasis alba (see Chapter 17) commonly presents with white, somewhat scaly, and not so well-defined areas of skin, which are most noticeable on the cheeks of racially pigmented children (Fig. 39.46).

Hypopigmented macules occur in the superficial fungal infection pityriasis versicolor, a condition frequently mistaken for vitiligo. Hyperpigmented areas are also present. It is suggested that the fungus forms oxidation

products of unsaturated fatty acids of skin surface lipids that inhibit the tyrosinase activity of melanocytes [2]. Other mechanisms are suggested, including the fungus acting as a sun barrier in a thickened stratum corneum. Light and electron microscopy studies of hypopigmented macules [3,4] and of hyperpigmented areas [5] have been unhelpful in determining the mechanisms involved and are confusing. The lack of sunburn in the pale areas may be explained by the fact that the causative yeast produces pityriacitrin, an indole compound that has a broad spectrum of ultraviolet absorption [6].

In a number of inflammatory disorders of the skin, there are areas of hypomelanosis and in these there may be a loss of functional melanocytes. This loss is seen in lupus erythematosus and lichen planus. Hypopigmentation is seen in sarcoidosis [7,8] and leprosy [9]. A leukomelanoderma occurs in syphilis.

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Idiopathic guttate hypomelanosis [1–3]

This clinical entity, also known as disseminate lenticular leukoderma [4], can be mistaken for vitiligo. It is common. The lesions in white people most frequently occur in sun-exposed areas of the limbs. Solar damage is a factor in these cases. Non-actinic lesions occur in black people and may be on the trunk in unexposed areas [1].

Clinically, the lesions are porcelain-white macules, usually 2–6 mm in size but sometimes much larger. The borders are sharply defined, often angular and irregular. The skin markings are normal. Histologically, there is a decrease in pigment granules. Histochemical and ultrastructural studies [5,6] show a reduction in the number of melanocytes, many of which lack mature melanosomes. It has been suggested that this disorder results from an age-related somatic mutation of melanocytes.

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Symmetrical progressive leukopathy [1]

This has been reported from Japan and Brazil, where it is relatively common. Punctate leukoderma develops in young adults, symmetrically on the front of the shins and on the extensor aspects of the arms, and less often on the abdomen and interscapular region. It is persistent.

REFERENCE

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Cutanous lymphoma [1,2]

Cutaneous T-cell lymphoma may sometimes show prominent hypopigmentation. In poikilodermatous mycosis fungoides, clinical lesions are characterized by widespread poikiloderma rather than plaques or nodules. On clinical examination there is alternating increase and decrease in pigmentation associated with epidermal atrophy. In hypopigmented mycosis fungoides, the areas of hypopigmentation are more prominent than in poikilodermatous mycosis fungoides [1,2].

REFERENCES

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Endogenous non-melanin pigmentation [1]

A variety of substances that are normal constituents of the body may, if present in excess or in an abnormal form or site, give rise to alterations in skin colour. Other substances formed only by patients with certain metabolic defects may also produce pigmentary changes. Special stains of histological specimens, or techniques such as spectroscopy, may help to identify the nature of exogenous and other non-melanin pigments.

Haemosiderosis (see Chapter 48)

The deposition in the tissue of the iron-containing pigment haemosiderin is commonly the result of the local destruction of red blood cells, but also occurs in haemochromatosis. The presence of haemosiderin stimulates melanogenesis, and hypermelanosis may dominate the clinical and histological picture. Such is the case in haemochromatosis (see Chapters 57 & 59). In the much more frequent conditions in which haemosiderin is derived locally from red blood cells, the pigmentation is orange–red at first, later fading through ochre and tawny shades.

Hypostatic haemosiderosis

Haemosiderosis of the lower legs is extremely common in the presence of venous insufficiency. Recently involved areas show grouped points of reddish pigment, but recurrent extravasation of red cells combined with increasing hypermelanosis soon produce a more or less uniform deep brown or coppery colour. The pigmentation usually persists even if the venous insufficiency is relieved.

Sickle-cell anaemia and congenital haemolytic anaemia

Haemosiderosis and melanosis may give rise to conspicuous pigmentation of the lower leg in the third decade or earlier.

Schamberg's disease and related disorders [2] (see Chapter 48)

Haemosiderosis without clinically evident hypermelanosis is seen in Schamberg's disease and other types of capillaritis. Reddish-brown plaques with cayenne-pepper points beyond their margins are present on the legs and thighs and sometimes on the arms.

Small patches of haemosiderosis, most numerous on the lower legs but progressively involving thighs and buttocks, are characteristic of drug reactions to ureides. Haemosiderosis of the trunk is a feature of some reactions to clothing.

Jaundice

Jaundice results from the staining of the skin with bilirubin, which has a great affinity for elastic tissue, hence the early involvement of the sclerae. The range of yellow shades produced by bilirubin may be modified by the presence of biliverdin, which adds a greenish hue. Bronzing is the effect of added melanin pigmentation and is often seen in jaundice of long duration. The sclerae are not involved in carotenaemia or in mepacrine pigmentation.

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Bronze baby syndrome [1–3]

This striking grey-brown discoloration of the skin of neonates follows phototherapy for hyperbilirubinaemia and is often associated with evidence of liver dysfunction. The serum is also brownish. The nature and origin of the pigment are uncertain. The changes are reversible unless there is some underlying liver disease.

REFERENCES

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Riboflavinaemia [1]

Yellow skin and hair have been described in a patient with myeloma, due to riboflavin being avidly bound by a monoclonal antiflavin antibody.

REFERENCE

1 Farhangi M, Osserman EF. Myeloma with xanthoderma due to an IgG monoclonal anti-flavin antibody. *N Engl J Med* 1976; **294**: 177–83.

Carotenaemia [1]

Carotene, a lipochrome, contributes a yellow component to the colour of normal skin. In the presence of excessive blood carotene levels, this yellow component is increased, and is most conspicuously accentuated where the horny layer is thick on the palms and soles. The sclerae are not discoloured. The most striking coloration is seen in food faddists who overindulge in oranges or carrots. Some increased yellowness is seen in conditions with hyperlipaemia, diabetes, nephritis and hypothyroidism, and where conversion of carotene to vitamin A is impaired by an inborn metabolic error [2] or by hepatic disease. However, it is now more commonly seen in young women drastically reducing their weight and eating foodstuffs with high carotene content [3,4].

Carotenaemia is seen in patients on oral supplements of β-carotene as a photoprotective agent in erythropoietic protoporphyria [5,6] and in those taking carotenoids that contain canthaxanthin.

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Ochronosis (see Chapter 57)

In alkaptonuria, a deficiency in homogentisic acid oxidase causes accumulation of homogentisic acid throughout the body. Ochronosis is the term used to describe the pigmentary changes that occur in connective tissue in patients with alkaptonuria [1]. The term was coined by Virchow in 1866 for the ochre-like (pale yellow) colour of the connective tissue when viewed down a microscope. Ochronosis is present in about 75% of patients with alkaptonuria, and the majority show some pigmentation. Most frequent is darkening of the ear cartilages and of the sclerae and conjunctiva. Less often the axillary skin is pigmented and there is brown mottled pigmentation of the face, sometimes in butterfly distribution, and of the neck and trunk. Rarely, pigmentation of the palmar and plantar skin is seen [2]. Examination of the urine establishes the diagnosis.

REFERENCES

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Exogenous pigments

A wide variety of chemicals either from industrial or medicinal exposure can produce discoloration of the skin. Some of these may not only produce an alteration of pigmentation by being deposited in the dermis but may also result in an increase in the amount of melanin in the skin. Of importance are the metals silver, gold, mercury and bismuth, which are cumulatively deposited in the dermis and can produce permanent disfiguring pigmentation. A number of drugs can cause discoloration of the skin. These include the antimalarials, the phenothiazines, clofazimine and minocycline. Of less importance is the transient staining of the skin produced by picric acid, dinitrophenol and chemical dyes.

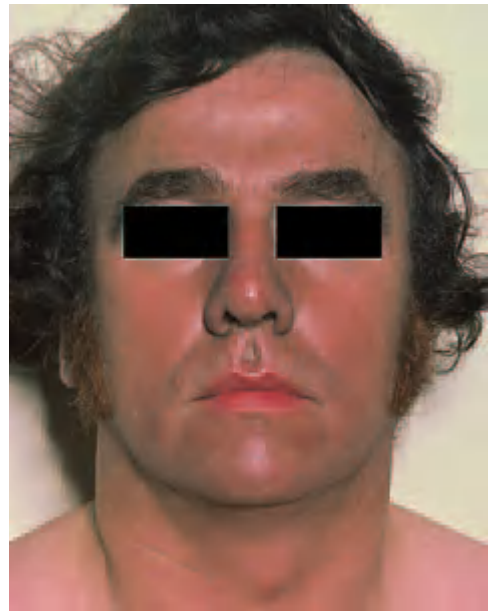

Fig. 39.47 Occupational argyria.

Metals

Argyria [1–8]

Silver may be deposited in the skin either from industrial exposure or as a result of medication with silver salts [2–4]. Blue macules have appeared at sites of acupuncture needles [6]. Cases have followed the use of silver salts for the irrigation of nasal, oral and urethral mucous membranes and the excessive use of an oral smoking remedy containing silver acetate [2,7]. 'Food supplements' may also contain colloidal silver [8]. The pigmentation is usually a slate-grey colour and may be clinically apparent after a few months, but usually takes many years to develop and depends on the degree of exposure. The hyperpigmentation is most apparent in sun-exposed areas of skin, especially the forehead, nose and hands (Fig. 39.47). In some patients, the entire skin has a slate blue-grey colour. The sclerae, nails and mucous membranes may become hyperpigmented. Light and electron microscopy studies [1,5,6,8,9] show silver granules in the dermis that are most numerous in relation to the basal lamina of the eccrine sweat glands, and in the dermal elastic fibres. Furthermore, silver particles may be seen lying free within the cell cytoplasm of epithelial cells of the secretory segment of eccrine sweat glands and in mast cells [8,9]. Silver granules are readily visible with dark-field illumination. X-ray-dispersive microanalysis confirms that the granules contain silver [1,6]. Silver is widely deposited in the tissues as well as in the skin. The diagnosis of argyria is established by skin biopsy. The pigmentation is permanent; treatment with depigmentary preparations is not effective.

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Chrysiasis [1–5]

Chrysiasis and chrysoderma are terms used to describe permanent pigmentation of the skin due to parenteral administration of gold salts. Excessive administration of gold leads to its deposition in connective tissue. Chrysiasis has not been observed in any patient who has received less than 50 mg/kg of gold thiosulphate, and it has not failed to develop in any patient receiving more than 150 mg/kg. It may first develop after a few months or after a long latent period. The pigmentation is blue-grey or may show a purplish hue, and is limited to light-exposed skin and to the sclerae [3]. The oral mucous membrane is not affected. The diagnosis is confirmed histologically on microscopy with dark-field illumination and on electron microscopy with electron probe microanalysis [4]. The granules of gold are larger and more irregular than those of silver. The pigmentation is permanent [5].

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Mercury [1–4]

Repeated applications of mercury-containing compounds can produce localized hyperpigmentation of the treated areas [1–3]. Systemic administration of mercury results in gingival hyperpigmentation. The pigment is observed in the upper dermis around capillaries and associated with collagen and elastic fibres. Electron microscopy shows an increase in melanin pigmentation and the metal is present as granules in dermal macrophages [1,3]. A case report of homicidal subcutaneous injection of metallic mercury resulted in widespread skin lesions, remote from the radiologically visible mercury; these appeared at 40 days and began to clear at 6 months [4].

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Bismuthia

The administration of bismuth at regular intervals over a period of years has often been practised, yet generalized pigmentation is extremely rare. The diffuse grey pigmentation resembles that of argyria and involves also the sclera and the oral and sometimes the vaginal mucous membrane [1].

A distinctive blue-black line occurs at the gingival margin. This is due to deposition of bismuth that reacts with hydrogen sulphide formed by bacteria in the mouth [2].

REFERENCES

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Drugs

Mepacrine [1,2]

Pigmentation of the skin is first noticed a few days after the administration of mepacrine commences and may persist for several weeks after it ceases. The dye is deposited in the skin. A bright-yellow or greenish-yellow colour develops first and remains most prominent on the face, hands and feet, but occurs diffusely with accentuation in the skin flexures. The sclerae are sometimes affected, which may mimic jaundice [2]. The melanin-containing pigment induced by antimalarials is discussed in Chapter 73.

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Clofazimine (Lamprene) [1–4]

This synthetic riminohenazine dye used in the treatment of leprosy produces an initial redness of the skin due to an accumulation of the drug. Later, with prolonged treatment, a violaceous brown colour develops that is most noticeable in lesional areas [1]. Histochemical studies indicate a ceroid-lipofuscin pigment as well as clofazimine inside macrophage phagolysosomes [2,3]. Reddish-blue pigmentation has been reported within scarred areas of lupus erythematosus in one patient [4].

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Hydroxyurea [1]

Nail pigmentation has been reported in association with use of hydroxyurea and most commonly consists of longitudinal melanonychia. Occasionally all 20 nails are affected and there is associated hyperpigmentation of the skin.

REFERENCE

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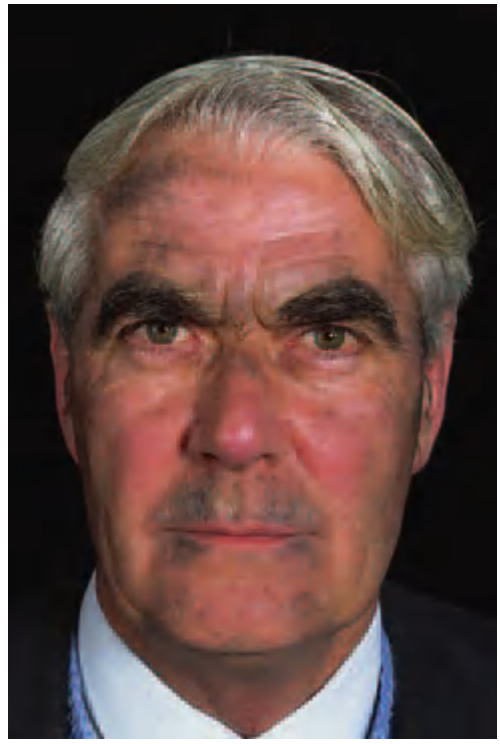
Minocycline [1–8]

Long-term therapy with minocycline may result in pigmentation, but this is generally agreed to be rare. Three types of cutaneous pigmentation are seen in patients treated with minocycline [6] (Fig. 39.48):
1 a focal type with well-demarcated blue-black pigmentation at sites of previous inflammation as first described in acne scars [1];
2 a more diffuse and generalized pigmentation that is most apparent in sun-exposed areas of skin and nails [2], but may also involve the sclera [5];
3 a more persistent brown-grey change most prominent on sun-exposed sites.
The pigmentation usually occurs following prolonged courses and high doses of this drug. Histological studies show the presence of brown-black granules in the upper


(a)

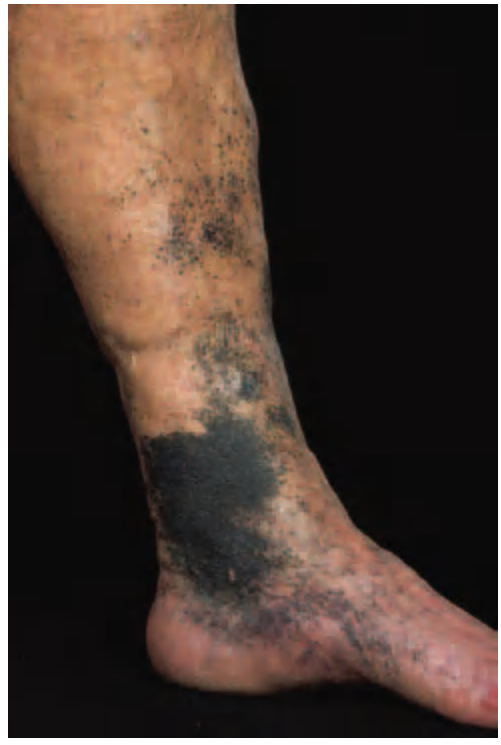

(b)

Fig. 39.48 (a) Hyperpigmentation of the skin in sun-exposed areas of the face due to long-term therapy with minocycline. (b) Blue-black pigmentation on the lower legs in the same patient.

dermis that stain for iron [1,3]. Electron microscopy reveals electron-dense material in dermal macrophages and X-ray microanalysis confirms the presence of iron [4]. Partial resolution of the pigmentation occurs after the drug is stopped [6]. Similar blue-black pigmentation of the legs has resulted from treatment with the 4-quinolone antibiotic pefloxacin [7] and the tetracycline antibiotic methacycline [8].

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Amiodarone [1–5]

Amiodarone is a drug used for prolonged periods in the treatment of ventricular tachycardia. It induces photosensitivity in more than 50% of patients; however, fewer than 5% develop cutaneous hyperpigmentation [1–5]. A grey-blue pigmentation of the face and other sun-exposed areas is a rare late effect of this drug, and may also involve non-exposed sites (Fig. 39.49) [1]. Yellow-brown granules are present in dermal histiocytes. Ultrastructural studies show membrane-bound dense lysosomal bodies in macrophages that probably contain degradation products of the drug bound to lipofuscin [1,2]. Dose reduction or withdrawal of amiodarone can lead to complete disappearance of the pigmentation [5].

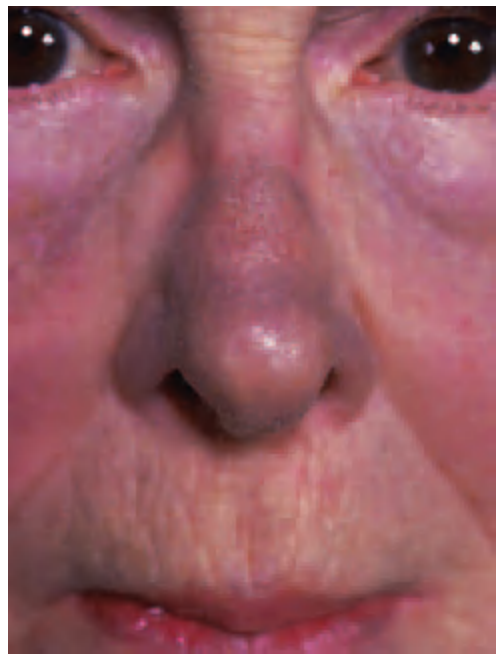

Fig. 39.49 Bluish pigmentation on the nose caused by amiodarone therapy.

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Picric acid, dinitrophenol and other chemicals

Picric acid, self-administered by malingerers to simulate jaundice, stains the skin yellow. Dinitrophenol, formerly used in industry and as a metabolic stimulant, also produces yellow staining of the skin and of the sclerae. Trinitrotoluene, santonin and acriflavine also stain the skin yellow.

Tattoos

Accidental tattoos

Pigmented particles may be accidentally introduced as contaminants of wounds or may, at high velocity, penetrate previously intact skin.

Superficial abrasions contaminated with chemically inert particles may be followed by disfiguring tattoos. Such irregularly spattered pigmentation is quite commonly seen after road accidents and blast injuries. Some particles may eventually be extruded, but the disfigurement is often permanent. Small lesions may be excised and larger areas treated by dermabrasion, the results of which depend on the depth to which the particles have penetrated.

Collier's stripes [1]

These are a very distinctive occupational mark in coalminers. The bluish grey, linear or angular stripes develop at the sites of abrasions. The commonest sites are the forehead, bridge of the nose, wrists and elbows. Histologically, particles of coal dust up to 100 μm in diameter are

seen at all levels in the dermis. They tend to be grouped around blood vessels.

Therapeutic agents

Iron salts. The use of solutions of ferric sulphate and ferric chloride in the treatment of dermatitis has been followed by a reddish-brown tattoo [2,3]. The pigmentation may disappear after a few months or may persist indefinitely [4].

Occupational contact with iron salts [5] produced red-brown punctate perifollicular pigmentation of the forearms in a man employed in pickling metal in hydrochloric acid.

Gentian violet (pararosaniline chloride). This has, exceptionally, given rise to a tattoo when applied to a wound of the face [6].

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Decorative tattoos (see also Chapter 22) [1–5]

History and prevalence. From ancient origins the practice of tattooing has developed along more or less parallel lines in most countries. Tattoos have been used to accentuate beauty, as a permanent adornment, or to make a statement. Occasionally tattoos serve to accentuate aggression or ugliness in order to make the wearer more intimidating. Tattoos with words or a name as a symbol of dedication or devotion have always been popular. Tattoos have also been used for more sinister motives. Tattoos were used as a means of identification by the Nazis in the Second World War for members of concentration and labour camps as well as for members of the SS. Formerly associated with religious ceremonies, fertility and marriage rites, tattooing in contemporary westernized civilizations thus fulfils a number of diverse functions and in so doing it survives and flourishes.

Contemporary life finds tattooing more popular than ever [1], even among the elite [2]. Tattoos are no longer the exclusive preserve of street gangs, prisoners and members of the armed forces [1,2]. Not all who submit to tattooing are emotionally unstable, immature individuals. Indeed, tattooing is viewed by many as an acceptable fashion accessory like any other, and is increasingly popular in Western societies with the young and with women, as well as the more traditional male stereotypes [1,2]. Tattooing and body piercing are now so common that health care workers are advised to maintain a non-judgemental attitude to tattoos [1], even in the face of the unexpected [4]. The decision to have a tattoo may be taken when an individual is in no position to make such a life-long commitment, for example when intoxicated, under peer pressure or when mentally unwell [5]. Tattoos may also be a manifestation of deliberate self-harm [6].

Another contemporary trend is the use of temporary black henna 'tattoos' [3,7]. These are not true tattoos but represent application of a black dye to produce a tattoo-like appearance that lasts for a few days. Unfortunately, a high concentration of the well-known contact sensitizer paraphenylenediamine is usually present in these 'tattoos', which results in a risk of contact allergy [3,7].

Techniques and materials. The professional tattooist uses an electric needle to introduce particles of pigment into the dermis; the amateur, often a child, pricks particles of soot or Indian ink into skin with any pointed object. The individual's choice of design may be motivated by subconscious psychological factors. The pigments commonly employed include:

- blue-black (carbon);
- red (cinnabar and vegetable dyes);
- light blue (cobaltous aluminate);
- green (chromic oxide or chromium sesquioxide);
- yellow (cadmium sulphide);
- brown (ochre, iron oxides).

Complications of tattoos

Unhappiness with the tattoo. Many regret having a tattoo, which may cause a significant psychological, social and financial burden [8].

Introduction of infection. Significant infection of tattoos is now unusual, and pyogenic infection, although the most frequent, is seldom serious. Erysipelas and gangrene, necessitating amputation, are mentioned in the older literature. Syphilis and tuberculosis have been inoculated by the tattoo needle, and small outbreaks have been traced to an infected operator. The tattooing of many people in rapid succession has been suspected of transmitting infective hepatitis. Also there is the risk of transmitting retrovirus infection. The transmission of leprosy is suspected [9]. Both vaccinia and warts have developed in recently inflicted tattoos.

Allergic reactions to pigment. Once the initial inflammatory changes have subsided, by far the most frequent reaction observed in tattoos is the development of allergic sensitivity to one of the pigments.

Fig. 39.50 Lichenoid reaction in red areas of a tattoo.

In most cases, the tattoo pigment itself, or a derived compound formed locally in the tissues, provokes the development of hypersensitivity, which is manifest clinically by the sudden onset of irritation, swelling and redness in a part of the tattoo a few weeks or many years after its infliction. In recent years, lichenoid tattoo reactions have been reported; these appear to be confined entirely to the red areas (Fig. 39.50) [10]. These resemble the reactions to cinnabar (mercuric sulphide); although this pigment has now been replaced by vegetable dyes, cases do still occur [11].

The allergic reaction can remain localized but may become generalized as a patchy eczematous eruption or an exfoliative dermatitis. In some cases, the primary sensitization is induced by some other contact with the metal, and the reaction in the tattoo accompanies or follows an attack of contact dermatitis.

Mercury [12]. The red areas of the tattoo are affected. The reaction may eventually subside spontaneously, but the risk of a generalized eruption is high. The tattoo reaction may be accompanied by erosions of the oral mucosa in contact with amalgam dental fillings [13]. Patch tests are positive to mercuric chloride and ammoniated mercury but not necessarily to cinnabar.

Chrome [14]. The green areas are affected. The patient is often primarily sensitized by exposure to cement. Patch tests with 0.5% potassium dichromate are positive.

Cobalt [15]. The light-blue areas are affected. In three patients, the tattoo reaction was accompanied by the simultaneous development of uveitis [16]. Patch tests are positive with 2% cobalt chloride.

Manganese [17]. A reaction in the purple areas of a tattoo was due to manganese.

Carbon [18]. A case is reported of a reaction in the black areas of a tattoo, presumably to carbon particles.

Light-induced reactions [19]. A high proportion of yellow tattoos develop redness and swelling only on exposure to sunlight, and the same phenomenon is occasionally observed in red tattoos. The mechanism is uncertain, although the yellow pigment, cadmium sulphide, has photoconducting properties.

Localization of skin disease in tattoos

Some skin disorders show a predilection for tattooed skin, in which they may appear first or be accentuated. Syphilis in the secondary or tertiary stage has often been observed in tattoos but tends to spare the red areas, apparently deterred by the mercury. Lichen planus and psoriasis may be localized in tattoos but show no colour predilection. Lupus erythematosus is more rarely seen. A sarcoidal granuloma in a tattoo may be the presenting manifestation of generalized sarcoidosis [20]. Melanoma has been reported in a tattoo [21], although the association may be fortuitous. Foreign-body granulomas of sarcoid type are extremely unusual after decorative tattoos, but have been reported in ochre tattoos [22]; ochre has a high silica content.

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Treatment of tattoos [1–9]. The removal of a tattoo may become essential on account of the development of one of the complications considered above, most commonly an allergic reaction within the tattoo. Some cases will settle with intralesional or even topical steroids, but more often excision of the offending area of tattoo, followed if necessary by grafting, is the only satisfactory treatment to secure elimination of all particles of pigment.

Far more frequently, removal of a tattoo is sought on aesthetic or cosmetic grounds, often only a few weeks after its infliction. If the area involved is small and simple or serial excision without grafting is practicable, this is undoubtedly the treatment of choice. If grafting is essential, the inevitable cosmetic imperfections of grafts are such that alternative procedures may be considered. Salabrasion using table salt is of use [6]. Some good results have been achieved with lasers, but scarring, at times quite troublesome, is likely to remain. The best results are with Q-switched red or near-infrared laser systems [7]. Infrared coagulation has also been used [8]. The keratotome [9] gives moderately good results and at least partially obliterates the design. For very extensive tattoos, dermabrasion or chemosurgery [4] have been advocated. The choice of technique should be influenced by personal predilections, and the experience of the plastic surgeon consulted. The patient should be warned that there is usually some residual pigment following superficial abrasion and there may be scarring.

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Chapter 40

Genetic Blistering Diseases

R.A.J. Eady, J-D. Fine & S.M. Burge

Introduction

The hereditary blistering disorders described in this chapter, although uncommon, may have a dramatic impact on the patient and their family, and severe economic consequences for the relatives and health services. These diseases have been the subject of intensive study in recent years, and the discovery of the causative genes underlying Hailey–Hailey disease, and all the major types of epidermolysis bullosa (EB), has increased our knowledge not only of the pathogenesis of these disorders, but also of the normal biology of the skin. This is exemplified by the way the graded severity of the clinical features, and associated structural changes in the dermal–epidermal junction, of the dystrophic forms of EB can be explained by the nature of the mutations in the *COL7A1* gene encoding the structural protein, collagen VII [1]. The strategies used to track down the genetic causes of Hailey–Hailey disease and EB provide interesting contrasts. In most forms of EB, the candidate genes and proteins were flagged up by earlier ultrastructural and immunohistochemical studies of the skin of affected patients before linkage and mutation analysis pinpointed conclusively the locus and identity of the causative gene. There were no similar clues to discovering the causative gene, *ATP2C1*, in Hailey–Hailey disease. Indeed, before it was found that mutations in *ATP2C1* could result in Hailey–Hailey disease [2], most dermatologists or skin biologists were unaware of its existence.

Knowledge of the ultrastructure and molecular composition of the epidermis and dermal–epidermal junction is necessary for understanding the tissue and molecular pathology that underlies this group of disorders.

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Epidermolysis bullosa

[R.A.J. Eady & J-D. Fine, pp. 40.1–40.32]

Definition and classification

EB comprises a group of genetically determined skin fragility disorders characterized by blistering of the skin and mucosae following mild mechanical trauma. The alternative term therefore is *mechanobullous diseases* [1]. The descriptive term *epidermolysis* is illogical because epidermal disruption is not the primary change in two of three main categories of EB. However, the name *epidermolysis bullosa*, as originally used by Koebner [2] in 1886, is now so well established in the literature that it is still the preferred term.

Classification of this complex and heterogeneous group of disorders is difficult, and not helped by the large variety of names and eponyms that have traditionally been used. Early classification was based largely on the mode of inheritance and clinical studies involving relatively few patients and families [3, reviewed in 4]. While these early observations were clearly important in establishing EB as an entity, a major step forward was made by Pearson [5] who used electron microscopy to show that the ultrastructural level of tissue cleavage (blister formation) in the skin is distinctive in the three major groups of EB: EB simplex, junctional EB and dystrophic EB. Other studies have revealed a number of associated ultrastructural abnormalities, which have also proved to be important in the diagnosis and classification of EB [6–9]. In addition, the application of immunohistochemical studies, particularly a specialized form of immunofluorescence microscopy,

has had a major role in differentiating certain forms of EB, and in helping to uncover the underlying molecular abnormalities by demonstrating specific antigenic changes in the dermal–epidermal junction of patients with different forms of the disease [10,11]. Since 1991, the molecular basis of virtually all subtypes of EB has been established [12].

The most comprehensive classification scheme, based on the recommendations of the Subcommittee of the National EB Registry (USA), and an international consensus group [13,14], has attempted to incorporate molecular and clinical findings, eliminate unnecessary eponyms, and combine certain phenotypes that cannot be distinguished by modern molecular analysis. It is still not clear whether a revised classification, based entirely or largely on the new molecular genetic findings, will provide a more practical or clinically useful alternative to the current one, although it is inevitable that this issue will be reviewed periodically. It is also possible that the concept of keeping all the currently recognized forms of EB under one umbrella could change. For example, a more genotypically based classification might reclassify most subtypes of EB simplex as part of a larger group of 'keratin diseases', and include the different subtypes of dystrophic EB with the group of inherited 'collagen diseases'. Nevertheless, the increasing knowledge of the molecular basis of EB will doubtless continue to be crucial for enabling accurate diagnosis, mainly for genetic counselling and prognosis.

A suggested working classification is shown in Table 40.1.

Table 40.1 Classification of epidermolysis bullosa (EB).

Type of EB	Inheritance
EB simplex (EBS) (intraepidermal blisters)	
More common forms	
EBS of hands and feet (Weber–Cockayne)	AD (rarely AR)
EBS herpetiformis (Dowling–Meara)	AD
EBS Koebner	AD (rarely AR)
Less common forms	
EBS associated with neuromuscular disease	AR
EBS with mottled pigmentation	AD
EBS superficialis	AD
EBS Ogna	AD
Junctional EB (JEB) (lamina lucida blisters)	
More common forms	
JEB gravis (Herlitz)	AR
JEB mitis (non-Herlitz; non-lethal; generalized atrophic benign EB)	AR
Less common forms	
JEB with pyloric atresia	AR
Inverse JEB	AR
Progressive JEB	AR
Cicatricial JEB	AR
Dystrophic EB (DEB) (sublamina-densa blisters)	
AUTOSOMAL RECESSIVE INHERITANCE	AR
More common forms	
Severe generalized, mutilating DEB (Hallopeau–Siemens)	
Mild, non-mutilating generalized/localized DEB	
Less common form	
Inverse DEB	
AUTOSOMAL DOMINANT INHERITANCE	AD
More common form	
Classical DEB (Cockayne–Touraine; Pasini)	
Less common forms	
Pretibial DEB	(may be AR)
EB pruriginosa	
Bart's syndrome	
Transient bullous disease of childhood	
Disorders of uncertain cause, possibly not EB	
Mendes da Costa disease	XR
Kallin's syndrome	?

AD, autosomal dominant; AR, autosomal recessive; XR, X-linked recessive.

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Prevalence and incidence

The most accurate data available on the incidence and prevalence of EB are derived from the National EB Registry (USA) project, a longitudinal study of approximately 3300 patients within the continental USA [1]. The incidence and prevalence of EB are estimated to be 19.60 per million live births and 8.22 per million population, respectively. Similarly, the incidence and prevalence rates for EB simplex are 10.75 and 4.60; junctional EB 2.04 and 0.44; dominant dystrophic EB 2.86 and 0.99; and recessive dystrophic EB 2.04 and 0.92, respectively. Comparison of these data with those derived from two smaller populations (e.g. in Norway [2], Finland [3], Croatia [4], Northern Ireland [5] and Scotland [6]) suggests little if any differences reported across the major types and subtypes of EB (reviewed in [1]). These data suggest that there is no gender, racial, ethnic or geographical predilection for EB. It should be remembered, however, that these reported rates probably underestimate the true prevalence and incidence of EB, especially the clinically milder forms, because of recruitment or selection bias.

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Epidermolysis bullosa simplex

EB simplex is the most frequent form of EB, accounting for at least 50% of patients enrolled by the National EB Registry (USA) [1]. Given the recognized underreporting of EB simplex, it is likely that at least two-thirds of all EB patients have this form of EB. The inheritance is chiefly autosomal dominant, and it is common to see affected individuals in three generations. Rarely, EB simplex may be transmitted as an autosomal recessive trait.

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Molecular pathology [1,2]

In all forms of EB simplex, blister formation is intraepidermal and generally begins with the disruption of basal keratinocytes. Genetic linkage analysis [3] and transgenic mouse experiments [4] led to the discovery that mutations in the basal keratin pair, K5 and K14, could result in EB simplex. It was shown that expression of mutant keratins in cultured cells gave rise to dense keratin aggregates [5]. Similar aggregates or keratin filament clumps were seen in the basal epidermis (Fig. 40.1) [6,7] or cultured keratinocytes [8] of patients with the Dowling–Meara form of EB simplex. Immunoelectron microscopic studies labelled the abnormal filament clumps with K5 and K14 antibodies [9]. In general, a correlation exists between the position of the mutation on the *KRT5* or *KRT14* genes and the resulting phenotype (Fig. 40.2). For example, the most severe form of EB simplex, the Dowling–Meara subtype, is usually caused by missense mutations in the initiation or termination peptides of the rod domains [10,11], which are evolutionarily highly conserved and thought to have a critical role in keratin filament assembly and structural integrity. Mutations in *KRT5* and *KRT14* have also been described in Weber–Cockayne EB simplex [12–14]. In this

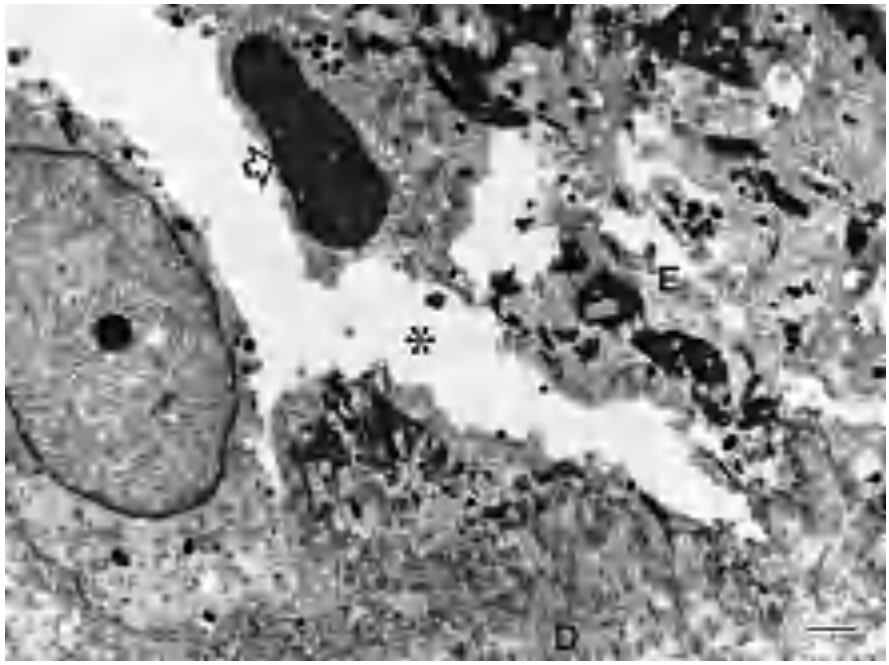

Fig. 40.1 Electron micrograph showing blister formation in epidermolysis bullosa simplex (Dowling–Meara). A split (*) is present in the epidermal basal layer (E), which contains electron-dense tonofilament (keratin) clumps (arrow). D, dermis; Bar = 1 μm.

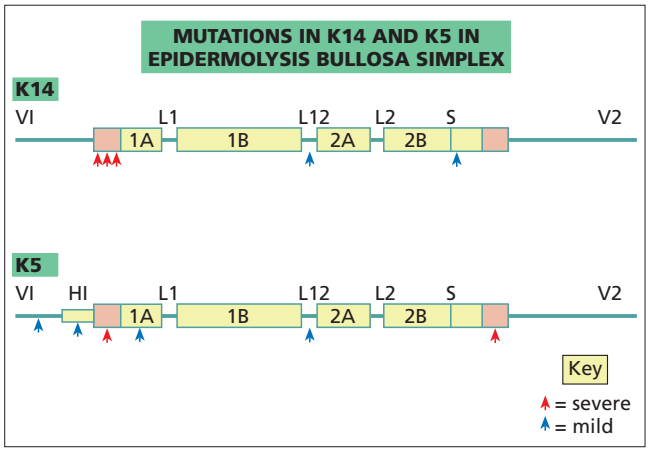

Fig. 40.2 Schematic representation of the type II (keratin 5) and type I (keratin 14) proteins, with position of mutations (arrowed). Each keratin has an α-helical rod domain (boxed areas) with head and tail domains at each end. The red boxes represent the highly conserved helix boundary sequence motifs. The mutations causing Dowling–Meara epidermolysis bullosa simplex occur in these boundary peptides and are known to be highly disruptive to keratin filament assembly. (Modified from a figure provided by Professor E.B. Lane.)

subtype of EB simplex, which is milder than the Dowling–Meara form, mutations occur outside the highly conserved boundary motifs, and chiefly in other parts of rod domain or the L12 linker region [13]. In the Weber–Cockayne or Koebner variants of EB simplex and in the form of EB simplex associated with mottled pigmentation, the basal cell keratin filaments are not consistently abnormal and do not show the major changes that characterize Dowling–Meara EB simplex. A heterozygous C to T transition at base position 71 in the non-helical VI domain of *KRT5*, causing a proline to leucine substitution, has been reported in three unrelated families with EB simplex and mottled pigmentation [15,16]. The cause of the pigmentary changes is unknown. Recessive forms of EB simplex would appear to be very rare; however, at least two families with autosomal recessive EB simplex with a Weber–Cockayne phenotype have been recognized [17,18]. In three cases with widespread blistering, more in keeping with a Koebner phenotype, normal keratin filaments were absent in the basal epidermal layer as was K14 protein expression [19–21]. However, K5 expression appeared normal. These cases were thought to represent the first functional knockouts of K14. Subsequently, a large kindred with EB simplex was described, also with ablation of K14, caused by a homozygous splice-site mutation [22]. A further autosomal recessive form of EB is associated with muscular dystrophy, and on occasion other abnormalities affecting the central nervous system. The ultrastructural level of tissue separation begins at a very low level in the basal cells, just above the hemidesmosomes and adjacent basal plasma membrane (Fig. 40.3) [23–28]. The level of cleavage in this form of EB may appear, in part, to be within the lamina lucida, therefore these ultrastructural findings, together with the clinical similarities of this form of EB with non-Herlitz junctional EB (see below), have led to the description of 'pseudojunctional EB' [28]. Immunofluorescence microscopy of skin from affected individuals shows diminished or absent staining for plectin [25–27], a 500-kDa protein, which is distributed among a variety of tissues, including

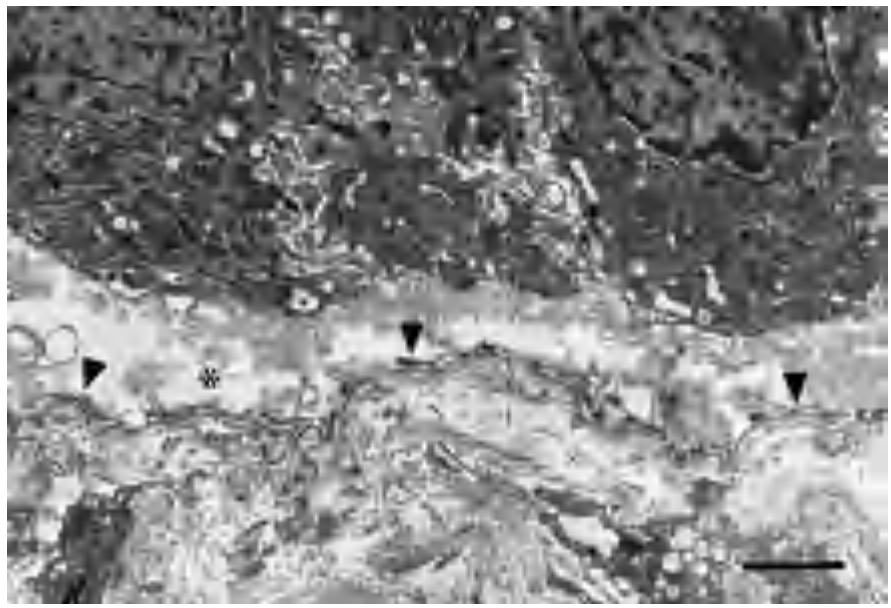

Fig. 40.3 Electron micrograph showing low level of intraepidermal blister formation in epidermolysis bullosa simplex associated with muscular dystrophy. The split (*) is above hemidesmosomes (arrowheads) and associated plasma membrane. Bar = 2 µm.

stratified squamous epithelia, nerve and muscle [29,30]. Homozygous mutations in the plectin gene, *PLEC1* on chromosome 8q24, have been described in several families with the disease [26,27, reviewed in 31] and in two unrelated children with EB simplex associated with mucosal lesions in the respiratory tract, but without evidence of concurrent myopathy [32]. The rarer, autosomal dominant, Ogna form of EB simplex has also been found to be caused by a *PLEC1* mutation [33].

Certain patients, who might otherwise have been diagnosed as having a form of junctional EB, by virtue of their clinical presentation or molecular findings, have been found to have an intraepidermal level of tissue cleavage in their skin, and have therefore been classified (or reclassified) as having EB simplex. This applies mainly to patients with EB associated with pyloric atresia [34,35], but has also been described in patients whose mutations result in deletions of the cytoplasmic domains of collagen XVII [36] or β4 integrin [37].

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Clinical subtypes

The various clinical subtypes of EB simplex are as follows.

Epidermolysis bullosa simplex of hands and feet (Weber–Cockayne)

This is the most common type of EB. The palms and soles (Fig. 40.4) are mainly affected, with the exception of the sides of the toes, where blistering may be particularly painful. Many patients have blisters only on the feet, and a minority (approximately 10%) will have blisters at other sites, such as the waist or neck, especially in hot weather and after friction from clothing or other sources. In the large majority of patients, blistering starts in childhood,

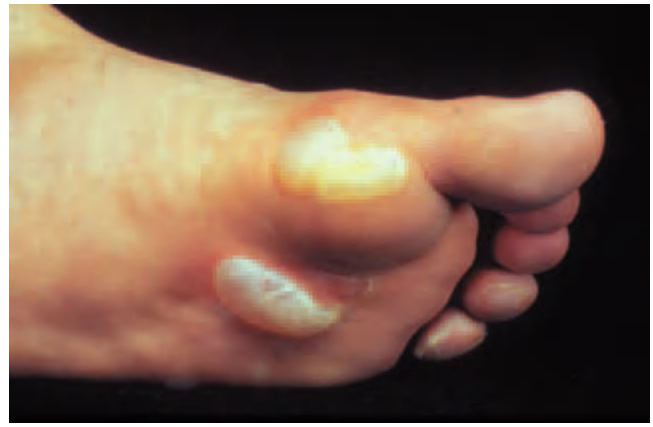

Fig. 40.4 Blisters on a foot in epidermolysis bullosa simplex (Weber–Cockayne).

but there are reports of the onset being delayed until early adult life, and brought out by strenuous physical activity [1]. The condition is always worse in warm weather. Hyperhidrosis of the feet is common; this increases friction, which also exacerbates blistering. The blisters heal without clinically significant scarring or milia formation. Calluses on the balls of the feet and the heels are very common, especially in adults. Troublesome blistering or ulceration of the oral mucosa is rare, although infants may have occasional small intraoral lesions. The hair and teeth are normal; nail dystrophy is infrequent, and is usually localized and mild when it does occur.

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Koebner epidermolysis bullosa simplex [1,2]

This is one of the two major subtypes of generalized EB simplex. Although usually mild, approximately 60% of patients have localized scarring and approximately 16% have milia. Development of hair and teeth and nails is normal. The nails rarely may be involved by blisters, but are only temporarily shed. Blisters appear within the first year and may be present at birth. In infancy, they commonly appear on the occiput, back and legs, while in childhood, the hands and feet are often affected, although the palms and soles are not preferentially involved, as in Weber–Cockayne EB simplex. In common with other forms of EB simplex, blistering is worse in warm weather. Although blistering occurs throughout life, some patients are alleged to improve after puberty.

In the authors' experience, the Koebner subtype of EB simplex is rare in comparison with the Weber–Cockayne or Dowling–Meara forms of EB simplex. Approximately

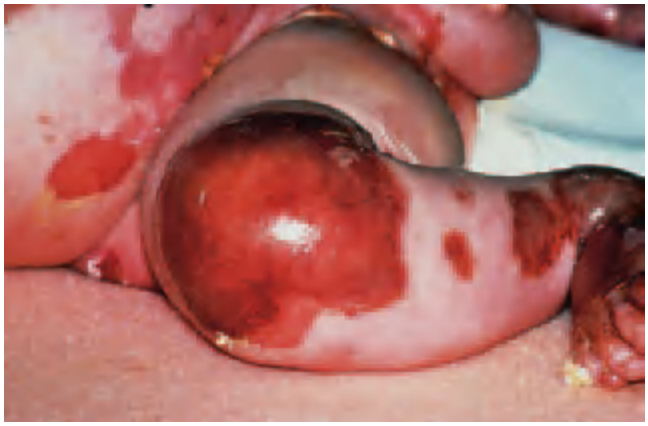

Fig. 40.5 Extensive erosions in a neonate with epidermolysis bullosa simplex (Dowling–Meara). (Courtesy of Dr A. Highet, York District Hospital, York, UK.)

10% of patients with the Weber–Cockayne form of EB will at some time have experienced blistering at sites other than the palms and soles (see above). Such individuals were recognized by Cockayne [2]. In the autosomal recessive cases, oral blistering with dental caries may be a feature, and nail dystrophy is common.

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Dowling–Meara epidermolysis bullosa simplex

SYN. EPIDERMOLYSIS BULLOSA HERPETIFORMIS

In 1954, Dowling and Meara [1] described four unrelated children (aged 3–7.5 years) with unusual trauma-induced or spontaneous blistering. The blisters healed without leaving scars, and tended to occur in groups that were reminiscent of those seen in dermatitis herpetiformis. Similar cases have since been described [2–10]. In infancy, blistering may be severe and extensive (Fig. 40.5) with involvement of the mucous membranes, shedding of nails and formation of milia. The differential diagnosis at this age may include both the junctional and generalized recessive dystrophic forms of EB. Therefore, a diagnostic skin biopsy is mandatory. After several months, blistering of the palms and soles becomes more frequent, as it does elsewhere. The distinctive feature of this condition is spontaneous herpetiform, annular or arcuate blistering on the trunk, limbs and neck (Fig. 40.6). However, when the blistering is severe and widespread, this pathognomonic grouping of lesions may not be obvious, so the correct diagnosis may be missed. Healing of the blisters may leave mild hyperpigmentation; localized atrophic scarring affects approximately 40% of patients, and milia are seen in approximately 20%. Irregular hyperkeratosis of the palms and soles, eventually developing into a confluent keratoderma (Fig. 40.7), first appears in childhood, and may rarely lead to a flexion deformity of the hands, associated with a severe keratoderma [5]. The general condition tends to improve with age [2]. Clearing of skin lesions has been noted in some patients with a fever, and after warm saline soaks [2].

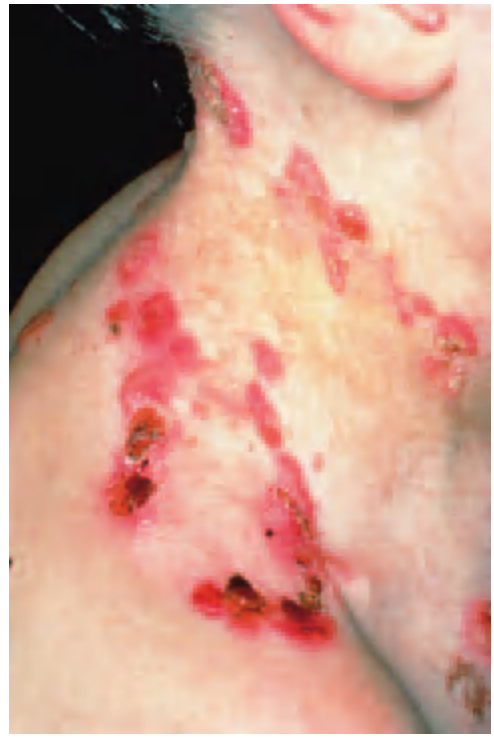

Fig. 40.6 Grouped blisters on erythematous base in epidermolysis bullosa simplex (Dowling–Meara).

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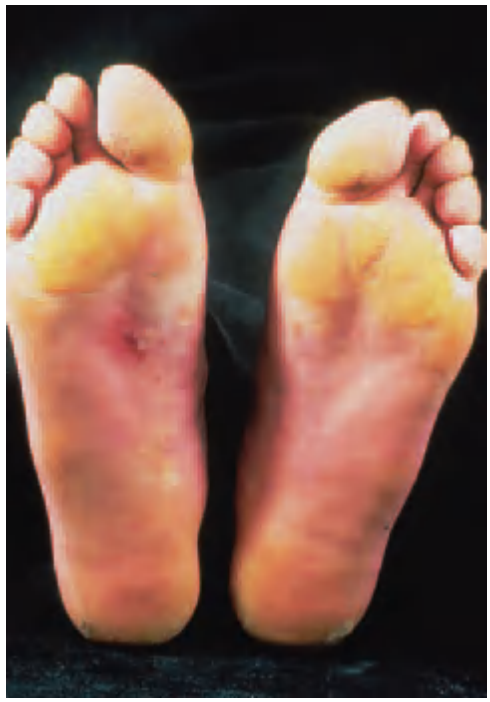

Fig. 40.7 Hyperkeratosis of the soles in epidermolysis bullosa simplex (Dowling–Meara).

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Epidermolysis bullosa simplex Ogna (Gedde-Dahl)

This autosomal dominant condition was named after the village in Norway where the first affected family originated [1]. There is seasonal blistering of hands and feet, and occasionally elsewhere. This rare subtype of EB is distinguishable by a generalized bruising tendency, haemorrhagic bullae and onychogryphotic great toenails [1].

REFERENCE

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Epidermolysis bullosa simplex with mottled pigmentation

This rare condition can be distinguished from other forms of EB simplex by the associated pigmentary changes [1–5], which are present at birth or appear during infancy. There is a reticulate pattern of small tan-coloured macular lesions, which fade with age. They may cover the entire skin surface but preferentially involve the neck, upper trunk or extremities. Blistering may be localized, mimicking Weber–Cockayne disease, or become more generalized. Punctate keratoses on the palms and soles have been noted in some cases [2,3]. Mild localized skin atrophy and nail dystrophy are also features of the condition [5].

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Autosomal recessive epidermolysis bullosa simplex with neuromuscular disease

Several families have been described in which skin fragility and blistering are associated with a neuromuscular disorder, chiefly muscular dystrophy [1–5], myasthenia gravis [3] or spinal muscular atrophy [6]. The blisters, which affect the skin and oral mucosa, are present at birth or soon afterwards. Muscle weakness and wasting may be severe and evident in early childhood, or milder and detectable later in life. Mental retardation has been reported [2], as has early death [1]. The widespread blistering is associated with atrophic scarring, milia, nail dystrophy and alopecia. Two children with homozygous null mutations developed supraglottic scarring and hoarseness; one required a tracheostomy [7].

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Epidermolysis bullosa simplex superficialis

Epidermal cleavage is typically just beneath the stratum corneum. This autosomal dominant condition, reported in

seven patients [1], is characterized by the presence of superficial erosions rather than intact blisters, similar to those seen in pemphigus foliaceous. Healing results in localized atrophic scarring or post-inflammatory hyperpigmentation. The finding of mutations within the type VII collagen gene, *COL7A1*, in one kindred with EB superficialis [2], suggested that the diagnosis was an atypical form of dystrophic EB rather than EB simplex in these cases. Further molecular studies are needed to clarify whether other patients with EB superficialis also have mutations in *COL7A1*.

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Kallin's syndrome

The single report on this disorder [1] included two sisters whose surname was Kallin. Both had blistering chiefly of the hands and feet, nail dystrophy, absent teeth and alopecia. One sister was partially deaf. Light microscopy showed a mid-epidermal cleavage in the skin of one sister, and a substratum corneal split in the other. From the limited information available, it is uncertain whether Kallin's syndrome is a distinct form of EB.

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Lethal autosomal recessive epidermolysis bullosa simplex

A kindred of 13 Sudanese patients has been reported with the autosomal recessive form of EB simplex [1]. Blistering was present at or very shortly after birth and was generalized, with no associated scarring or milia, and with a predilection for the more distal portion of the limbs. The oral mucosa was only mildly affected, and the nails, teeth and hair were not affected. Most of the affected children died during the first 2 years of life; only one patient reached adolescence.

Electron microscopy of the skin of these patients was reported to reveal a paucity of tonofilaments in the basal epidermal cells. A published electron micrograph is reminiscent of the ultrastructural features seen in an unrelated case of North African origin whose autosomal recessive EB simplex was found to be caused by a homozygous null mutation in the keratin 14 gene [2].

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Junctional epidermolysis bullosa

All the variants of this disorder are characterized by autosomal recessive inheritance and by blister formation at the level of the lamina lucida. Conventionally, junctional EB is divided into two main categories: the Herlitz (or lethal) and non-Herlitz (non-lethal) forms. The terms *lethal* and *non-lethal* are no longer recommended in this context because it is well recognized that non-Herlitz subtypes of junctional EB, or forms of dystrophic or simplex EB, may also have a lethal outcome, even in infancy. The term *indeterminate* junctional EB has been used to classify infants who have diagnostic biopsy evidence of junctional EB, but who have not lived long enough to allow clinical segregation into the Herlitz or non-Herlitz subtypes. The term *EB atrophicans* has also been used to describe patients with junctional blistering and atrophic scarring [1]. We do not recommend the use of this term because other forms of EB may be associated with atrophic scarring, and the abbreviation 'EBA' could potentially cause confusion with its more usual association with EB acquisita.

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Molecular pathology [1,2]

Electron microscopy shows that the level of tissue separation in all forms of junctional EB is through the lamina lucida of the basement-membrane zone immediately beneath the plasma membrane of basal epidermal cells (Fig. 40.8a). The hemidesmosomes tend to be sparse and very small, especially in the more severe forms of the disease (Fig. 40.8b) [3–5]. In addition, the hemidesmosome subbasal dense plates may be indistinct or attenuated [4,5], and the association between hemidesmosomes and the basal keratinocyte keratin filament network is reduced [5]. Keratinocytes from junctional EB patients have shown similar ultrastructural changes *in vitro* [6,7] or after grafting on to nude mice [8]. These hemidesmosome abnormalities are most prominent in the Herlitz form of junctional EB and the subtype associated with pyloric atresia. Although the latter is normally classified as a form of junctional EB, the ultrastructural level of cleavage is not consistently restricted to the lamina lucida, and may occur intraepidermally at a level just above the basal plasma

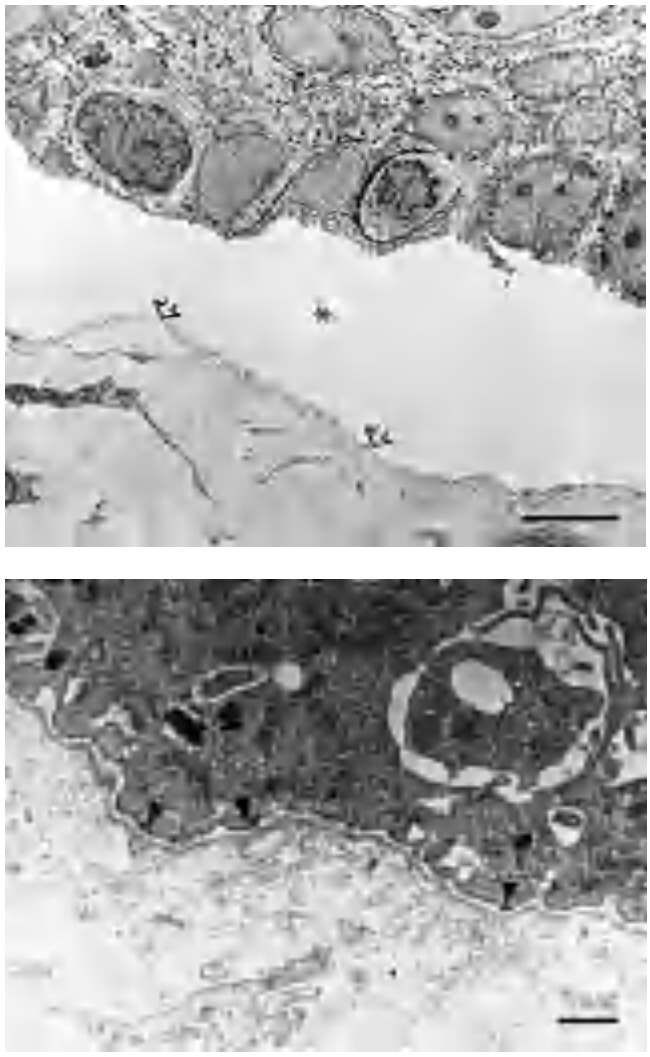

Fig. 40.8 Electron micrographs of dermal–epidermal junction in Herlitz junctional epidermolysis bullosa. (a) A clean split (*) is present at the level of the lamina lucida. A row of closely apposed basal keratinocytes is at the top of the split, and a continuous lamina densa (open arrowheads) is below. Bar = 5 µm. (b) In intact skin, hemidesmosomes (arrowheads) are sparse and much smaller than normal. Bar = 1 µm.

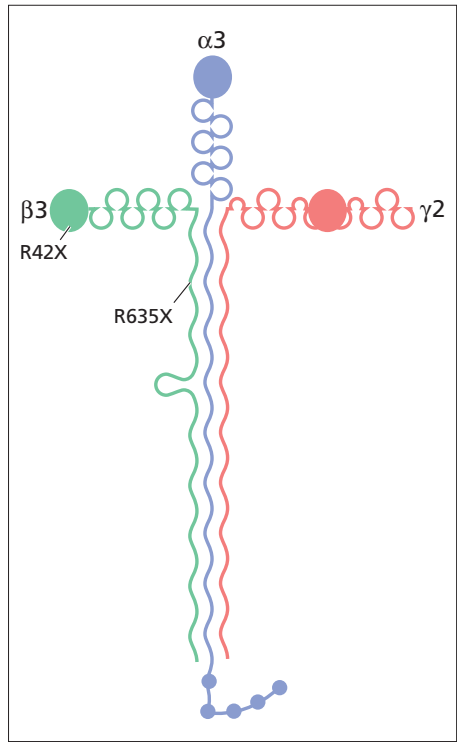

Fig. 40.9 Schematic representation of laminin 5, a heterotrimer comprising α3, β3 and γ2 chains encoded by the *LAMA3*, *LAMB3* and *LAMC2* genes, respectively. The relative positions of two premature stop codon mutations giving rise to R42X and R635X on the β3 chain are shown. These mutations together account for about 50% of all laminin 5 mutations underlying junctional epidermolysis bullosa. (Courtesy of Professor J.A. McGrath, St John's Institute of Dermatology, London, UK.)

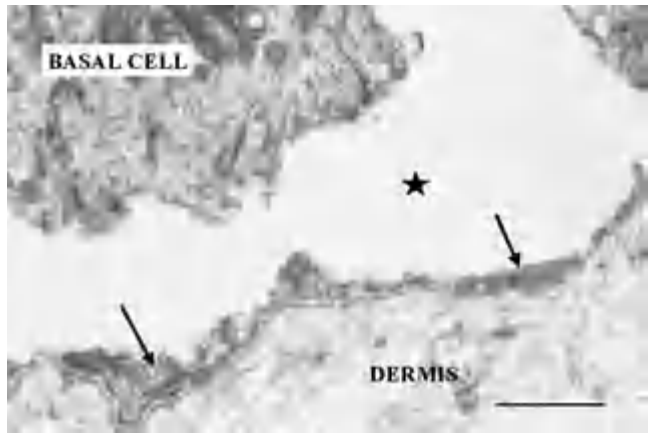

Fig. 40.10 Epidermolysis bullosa with pyloric atresia. A split (star) is present at a very low level in the basal epidermal layer, leaving fragments of basal cells at the base. Bar = 2 µm.

membrane of the basal keratinocytes (Fig. 40.9) [9]. This is similar therefore to the level of tissue disruption occurring in the skin of knockout mice with ablation of the β4 integrin subunit [10]. It may also resemble the ultrastructural abnormality seen in patients with autosomal recessive EB simplex resulting from defects in plectin (see p. 40.5) [11–13]. In the non-Herlitz forms of junctional EB, the hemidesmosome ultrastructure is variable, and individual hemidesmosomes may show little if any discernible abnormality [4].

Immunofluorescence microscopy indicated an abnormality in the expression of the anchoring filament protein laminin 5 in the skin of patients with Herlitz junctional EB and in certain patients with non-Herlitz phenotypes [14–16]. Molecular analysis subsequently showed that the Herlitz form of the disease may be caused by mutations in any of the three laminin 5 genes, *LAMA3*, *LAMB3* and *LAMC2* (Fig. 40.10), encoding the α3, β3 and γ2 polypeptide

chains, respectively, which co-polymerize to form the heterotrimeric laminin 5 protein. The mutations reported so far in Herlitz junctional EB have been homozygous or compound heterozygous premature termination codon mutations [17–20]. These would be expected to result in the production of unstable RNA transcripts and a severely truncated non-functional protein, leading to reduced adhesion at the dermal–epidermal junction and marked skin fragility. The majority of mutations have been found in the *LAMB3* gene, with evidence for mutational hotspots leading to recurrent mutations R42X and R635X [21]. The mutation R635X was found in seven of 24 (29%) mutant alleles in a study of 12 British families with Herlitz junctional EB [22]. The mutation represents a C-to-T transition at a CpG dinucleotide and probably results from deamination of 5-methylcytosine to thymine, a recognized cause of human genetic disease [22].

Non-Herlitz junctional EB (also known as generalized atrophic benign EB; GABEB) may also result from laminin 5 gene pathology [23,24]. In a family with non-Herlitz EB, there was a premature termination codon mutation in exon 3 of one *LAMB3* allele and a missense mutation in exon 7 in the other allele. Exons 3 and 7 encode part of the domain VI on the short arm of the β3 chain. Because this globular domain is thought to be involved with the interaction between laminin 5 and other basement-membrane proteins, such as laminin 6, these mutations might therefore cause destabilization of the macromolecular network involved in adhesion at the dermal–epidermal junction [23].

Other patients with non-Herlitz junctional EB may instead have mutations in the *COL17A1* gene encoding another anchoring filament component, collagen XVII (also known as the 180-kDa bullous pemphigoid antigen [BP180] or BPAG2) [25,26]. The strong similarity in the clinical phenotype of non-Herlitz junctional EB patients with either collagen XVII or laminin 5 gene pathology suggests that the attribution of GABEB is not specific to a particular genotype. Evidence for the role of collagen XVII in odontogenesis is provided by the finding of a combination of a glycine substitution mutation in the helical domain of one *COL17A1* allele, and an internal duplication in the other allele, in a patient with fairly mild skin changes but severe dental abnormalities [27]. The patient's offspring inherited the glycine substitution mutation but had normal second *COL17A1* alleles. Interestingly, although their skins were clinically normal, they had inherited the dental anomaly.

Patients with the subtype of junctional EB associated with pyloric atresia may have a reduced expression of the α6β4 integrin in their skin, as shown by indirect immunofluorescence [28–30]. Staining for other antigens, including laminin 5, is usually normal. The α6β4 integrin is a hemidesmosome-associated heteropolymer and receptor for laminin 5. Knockout mouse experiments with targeted removal of the β4 and α6 subunits showed that homozygous (–/–) mice manifested widespread epithelial separation from the underlying stroma and major ultrastructural changes in the hemidesmosomes [10,31,32]. Mutations in genes for the β4 and α6 integrin chains, *ITGB4* and *ITGA6*, have been shown to underlie this form of EB [33–36] and, in some cases, the phenotype may be predicted by the nature of the mutations.

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Clinical subtypes

Junctional EB has the following subtypes.

Herlitz junctional epidermolysis bullosa [1,2]

SYN. EPIDERMOLYSIS BULLOSA LETALIS; EPIDERMOLYSIS BULLOSA ATROPHICANS GENERALISATA GRAVIS

Blistering and erosions are present at or soon after birth and rapidly become generalized. The absence of blistering at birth is consistent with the diagnosis. The whole skin is extremely fragile and lifting or turning the baby may cause extensive blistering or peeling away of the epidermis. Eroded areas are often very slow to heal. Healing may result in atrophic scarring. Milia are not generally seen, although they may occur after secondary infection.

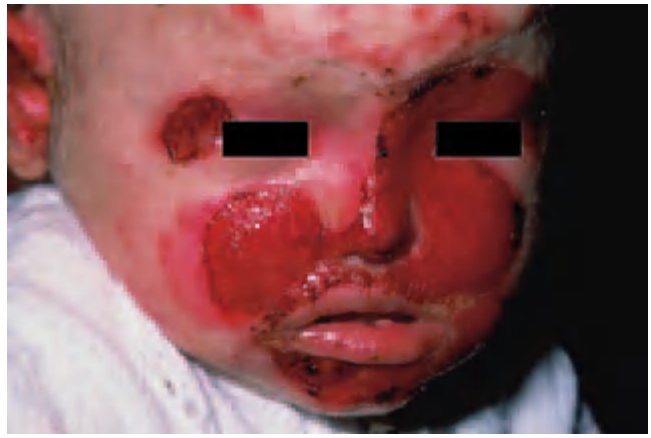

Fig. 40.11 Facial erosions in junctional epidermolysis bullosa (Herlitz).

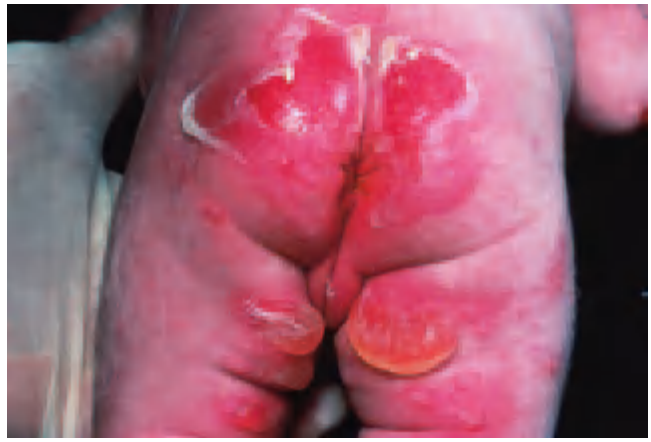

Fig. 40.12 Junctional epidermolysis bullosa (Herlitz).

Involvement of the oral and pharyngeal mucosa is frequent and may be severe; hoarseness and stridor may indicate laryngeal or supraglottic involvement [3,4]. Vesicles have been reported in the trachea and bronchioles post-mortem [5,6]. Many infants die early in infancy with overwhelming infection, but those surviving the first few months will often develop distinctive lesions characterized by non-healing crusted erosions containing exuberant granulation tissue [1,7]. These typical lesions occur symmetrically around the nose and mouth (Fig. 40.11) but also in other sites including the neck, trunk and buttocks (Fig. 40.12). The combination of chronic infection and loss of protein and iron from the skin, in addition to poor feeding, contributes to impaired healing and refractory anaemia [8]. The teeth show abnormal enamel formation, but normal dentine [9], and as a result are malformed, pitted and lost prematurely. Following blistering and erosions, the formation of granulation tissue on the nail folds and nail bed leads to shedding of the nails and bulbous changes of the fingertips (Fig. 40.13).

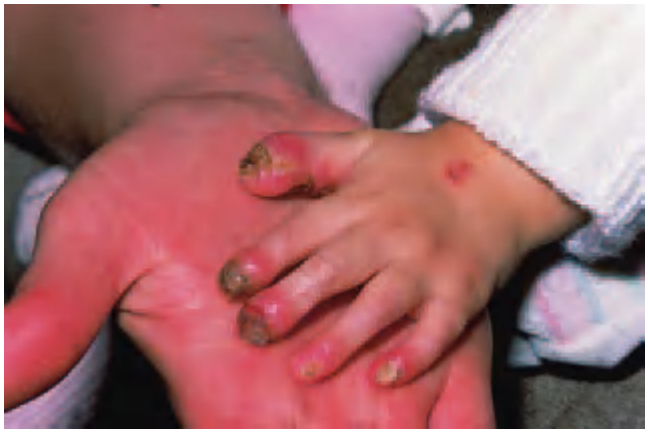

Fig. 40.13 Nail changes in junctional epidermolysis bullosa (Herlitz).

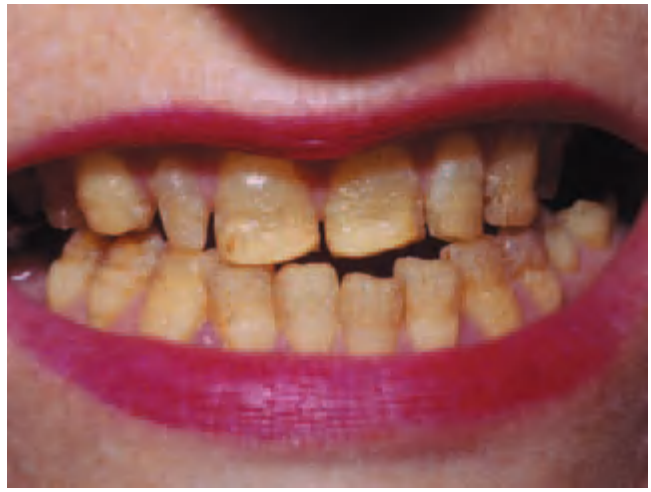

Fig. 40.14 Pitting and discoloration of teeth in non-Herlitz junctional epidermolysis bullosa.

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Generalized non-Herlitz junctional epidermolysis bullosa

SYN. EPIDERMOLYSIS BULLOSA ATROPHICANS GENERALISATA MITIS; GENERALIZED ATROPHIC BENIGN EPIDERMOLYSIS BULLOSA (GABEB)

Hashimoto *et al.* [1] first described this condition in 1976. Hintner and Wolff [2] coined the acronym GABEB. The early clinical course may be similar to the Herlitz form of junctional EB with generalized skin fragility and blistering, but the patients usually survive to adulthood [2–8]. Although blistering persists, there is gradual lessening in severity of the disease with age. Mucous membranes are involved, but less severely than in the Herlitz form of junctional EB. The teeth show severe enamel defects (Fig. 40.14) and may fail to erupt normally. The nails are dystrophic and frequently missing, especially on the toes. Approximately 3–5% of patients may develop a degree

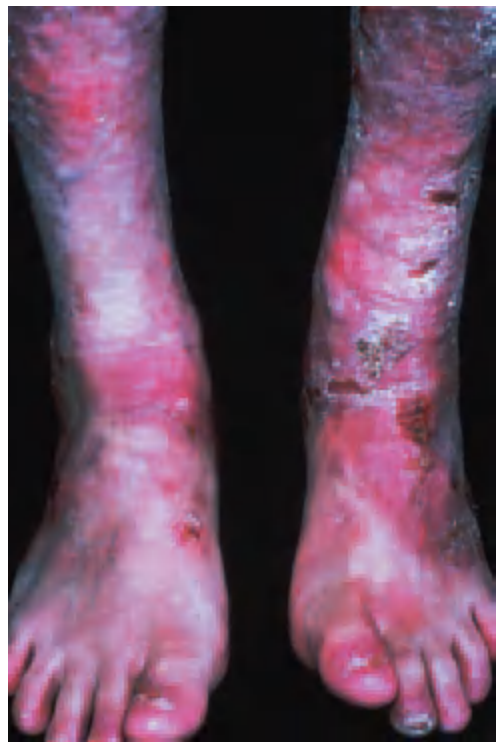

Fig. 40.15 Atrophic scarring on lower legs and toenail dystrophy in non-Herlitz junctional epidermolysis bullosa.

of pseudosyndactyly, clinically suggestive of dystrophic EB. These patients were originally said to have 'cicatricial' junctional EB (see below). Typically, the lesions in non-Herlitz junctional EB heal with atrophic scarring, which can easily be mistaken for the scarring seen in dystrophic EB, especially on the lower legs (Fig. 40.15) or backs of the hands. An important sign of this form of EB is the poor hair development; the alopecia affects the scalp (Fig. 40.16),

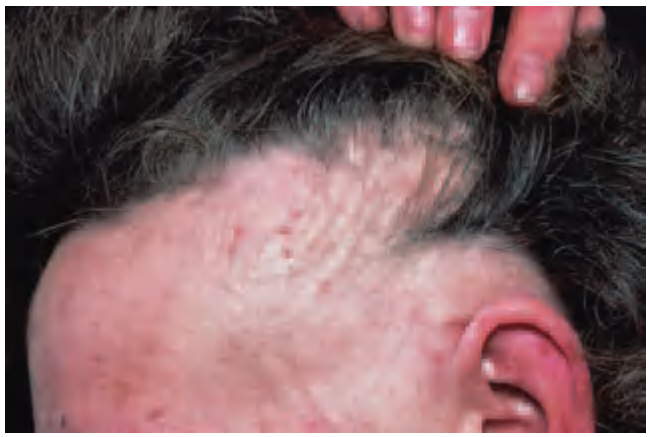

Fig. 40.16 Alopecia in non-Herlitz junctional epidermolysis bullosa.

eyebrows and eyelashes, and body hair is also sparse or absent. Pigmented naevi, or acquired macular hyperpigmented lesions with irregular borders, are common [2–4]. Oesophageal stricture [2], laryngeal involvement [3], oral erosions [2,3,6], corneal ulcers [6] hypoacusis [1,2] and urethral stricture [9] have all been reported.

A more localized form of non-Herlitz junctional EB has been recognized [10,11]. Typical clinical manifestations include nail dystrophy, dental enamel changes and blistering involving the lower legs and feet only [9]. In a second report of two affected sisters, the skin was generally fragile, but the atrophic changes were most noticeable on the lower legs and dorsa of the feet. The nails were dystrophic, but hair and teeth appeared normal [11]. Chronic painful erosions associated with hyperkeratosis were present on the soles. In the rare form of 'inverse' non-Herlitz junctional EB [12,13], the whole skin is fragile and blistering starts during the neonatal period. Later, the lesions affect chiefly the groin, perineum and axillae (inverse sites). Healing may result in small atrophic white streaks. Dysplastic teeth, erosions of the cornea and feet (Fig. 40.17) and nail dystrophy, are all features. Squamous cell carcinoma, similar to that occurring in dystrophic EB (see below), may also occur in non-Herlitz junctional EB [14–16], at times with a fatal outcome. Keratoacanthoma has also been reported [17].

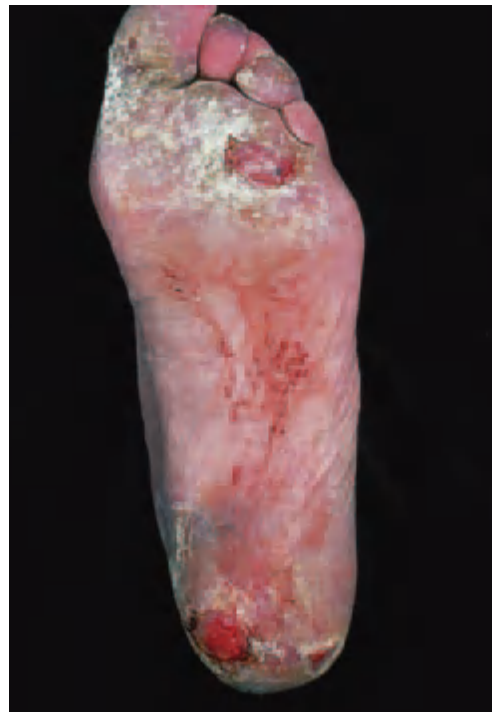

Fig. 40.17 Hyperkeratosis with erosions on soles in non-Herlitz junctional epidermolysis bullosa.

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Junctional epidermolysis bullosa with pyloric atresia

This rare disorder is normally included as a subtype of junctional EB, although, not uncommonly, the true level of blistering has been found to be in the cytoplasm of basal keratinocytes, just above the plasma membrane, rather than within lamina lucida. These cases therefore might more appropriately be classified as EB simplex (see p. 40.10). Over 50 patients with this disorder have been reported [1], yet only a few have survived beyond the first few months of life. Blistering is usually present at birth, following a pregnancy complicated by polyhydramnios. The lesions are usually widespread and can result in atrophic scarring. The teeth are hypoplastic, lacking normal enamel, and the nails are dystrophic. Early attempts at feeding result in vomiting, which is not bile-stained. In a series of five patients [2], four died at the age of 1–2 months; the fifth survived for over 4 years, but had constant haematuria and dysuria and recurrent urinary tract infections. Hayashi *et al.* [1] have made a strong case for surgical correction of the congenital pyloric atresia. Of the five patients in their report, four (aged 17 months to 16 years) were moderately well, despite complications such as retarded growth and hydronephrosis. The fifth patient died of respiratory distress, probably caused by aspiration, and had renal complications. The variable clinical outcome in this disorder will probably be explained, to some degree, by the nature of the mutations affecting either the α6 or β4 integrin subunits [3].

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Progressive junctional epidermolysis bullosa

SYN. EPIDERMOLYSIS BULLOSA PROGRESSIVA

This condition was originally named EB dystrophica–neurotrophica by Gedde-Dahl because of the association of partial deafness [1]. The onset is delayed until childhood or adolescence, and nail dystrophy is a common presentation. Blistering occurs on the hands and feet. Later, knees and elbows are involved. Progressive atrophic changes lead to early loss of fingerprint patterns and mild finger contractures. The tooth enamel may be defective and the tongue papillae may disappear [2]. The oral mucosa is sometimes involved. The ultrastructural changes are said to be distinctive and show widening of the lamina lucida with deposition of amorphous material. The hemidesmosomes are ultrastructurally normal [2–4]. The molecular basis is unknown.

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Cicatricial junctional epidermolysis bullosa

Three patients have been reported in whom blistering had healed with scarring and resulted in loss of nails, alopecia, syndactyly and contractures. The oral mucosa was involved and there was stenosis of the anterior nares [1]. Based on more recent findings [2], this rare phenotype is included under the heading of non-Herlitz junctional EB. The evidence that this form of EB has a distinct genotype awaits confirmation.

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Dystrophic epidermolysis bullosa

The dystrophic forms of EB are characterized by skin fragility, blistering, scarring, nail changes and milia formation. Unlike the other types of EB, there are both major autosomal recessive and autosomal dominant subtypes. Recent studies have shown a number of genotypic and phenotypic differences between these two major subtypes of dystrophic EB, and a number of newer clinical variants have emerged. However, the definition of the subtypes of dystrophic EB is somewhat arbitrary, representing more quantitative than qualitative phenotypic differences [1].

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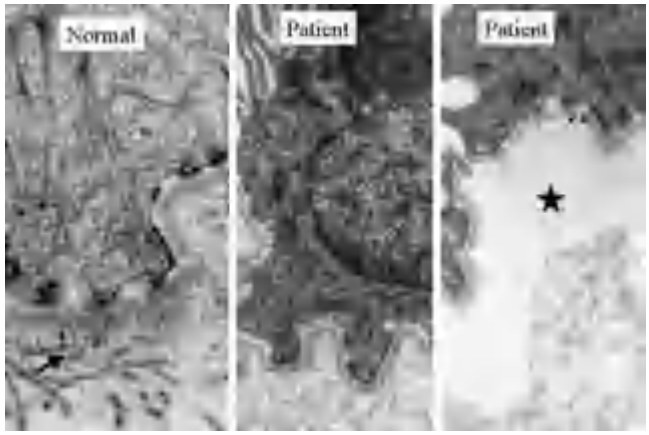
Molecular pathology [1–3]

In contrast to EB simplex or junctional EB, in which



(a) (b) (c)

Fig. 40.18 Electron micrographs demonstrating blister formation in dystrophic epidermolysis bullosa. (a) Anchoring fibrils (arrow) are present in the dermal–epidermal junction in normal skin, (b) but are absent in patient's skin. (c) Early blister formation (star) beneath the lamina densa (double arrows).

several genes are now recognized in the pathogenesis of these disorders, both autosomal dominant and recessive forms of dystrophic EB are caused by mutations in a single gene, *COL7A1*, which encodes the anchoring fibril protein, type VII collagen.

Ultrastructurally, the level of blistering or tissue cleavage in all dystrophic forms of EB is immediately below the lamina densa of the epidermal basement membrane, at a site normally occupied by anchoring fibrils (Fig. 40.18) (see Chapter 3 for a fuller description of these and other structures in the basement-membrane zone) [3].

Quantitative electron microscopy and immunoelectron microscopy have shown that anchoring fibrils in dystrophic EB are reduced in number, morphologically altered or completely absent [4,5]. Immunofluorescence staining of the skin of patients using antitype VII collagen antibodies showed that the normal bright linear staining is absent in severe generalized recessive dystrophic EB, but present in dominant dystrophic EB [6–8]. In the milder or more localized form of recessive dystrophic EB, the immunoreactivity may be attenuated or normal in intensity. In the 'inverse' form of recessive dystrophic EB, type VII collagen is normally expressed, but the anchoring fibrils are structurally abnormal [9]. These ultrastructural and immunohistochemical findings indicated that type VII collagen was the candidate gene for at least the recessive forms of dystrophic EB and probably for the dominant form too. These clues were supported by genetic linkage of both dominant and recessive forms of dystrophic EB with the type VII collagen gene locus [10–13], which had been mapped to chromosome 3p21 [14]. Other studies showing abnormalities of collagenase in skin and dermal fibroblasts from patients with recessive dystrophic EB indicated that the collagenase gene was also a candidate [15]. However, this was not borne out by subsequent linkage analysis [16,17].

Cloning and sequencing of the human type VII collagen gene (*COL7A1*) and cDNA revealed that the gene is highly complex, containing a total of 118 exons within approximately 32 kb of genomic DNA [14,18–21]. Type VII collagen is a homotrimer ($\alpha_1[VII]_3$) in which each pro-α chain has a large amino-terminal non-collagenous domain (NC-1), a central collagenous domain of Gly-X-Y repeats with several interruptions, and a small carboxy-terminal non-collagenous domain (NC-2). The formation of antiparallel dimers involves cleavage of the NC-2 domain [22]. Anchoring fibrils consist of laterally associated aggregates of the dimers.

Numerous *COL7A1* mutations have been documented. The most severe (Hallopeau–Siemens) subtype of recessive dystrophic EB is caused by premature termination codon mutations on both *COL7A1* alleles [23–25]. Heterozygote carriers of these mutations are phenotypically normal, and it is presumed that a truncated polypeptide, encoded by the mutant allele, is unable to take part in triple helix formation without its collagenous domain, leaving the wild-type polypeptide free to form normal trimers [1]. Ultrastructural morphometric analysis has shown that the number of anchoring fibrils is reduced to about half the normal value in the heterozygotes [26]. In the milder forms of recessive dystrophic EB, typically a premature termination codon mutation on one allele combines with a missense mutation or in-frame deletion on the second allele [27]. The net result is thought to result in synthesis of type VII collagen molecules, which assemble into unstable and relatively weak anchoring fibrils.

Detailed studies correlating clinical, ultrastructural and immunofluorescence changes with different combinations of mutations in *COL7A1* have helped with the understanding of the phenotype diversity in recessive dystrophic EB [28,29]. Dominant dystrophic forms of EB have been shown exclusively to be associated with glycine substitutions within the triple helical collagenous domain of the type VII molecule, characterized by a Gly-X-Y repeating amino-acid sequence [1,30]. These mutations are thought to have a dominant negative effect on the processing or function of the normal gene product. The amino-acid substitutions are likely to destabilize the triple helix, impair the normal secretion of the molecules and make them susceptible to intracellular degradation. Assuming equal expression of both normal and mutant alleles, only approximately 13% of the triple-helical molecules will be normal [1]. This would help to explain the ultrastructural observations of reduced numbers of anchoring fibrils, some of which appear normal [4,5].

In the absence of a positive family history, it is often difficult to determine whether a single patient with mild to moderately severe dystrophic EB will have autosomal recessive or *de novo* dominant disease. Recent molecular

studies of *COL7A1* have established that the vast majority of such cases are recessive in nature. Nevertheless, a small number of *de novo* dominant patients have been documented. Three patients with *de novo* dominant disease were found to have the same glycine substitution mutation, G2043R in *COL7A1*. This mutation is the most common *COL7A1* mutation in dominant dystrophic EB throughout the world. These cases emphasize the importance of molecular analysis in providing accurate genetic counselling in patients with apparent sporadic dystrophic EB [31,32].

In addition to their occurrence in classical forms of dominant dystrophic EB, glycine substitution mutations have been demonstrated in rarer variants including Bart's syndrome [33], pretibial dystrophic EB [34] and EB pruriginosa [35,36]. Other types of *COL7A1* mutations may also occur in EB pruriginosa [36].

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Clinical subtypes

Dystrophic EB has the following subtypes.

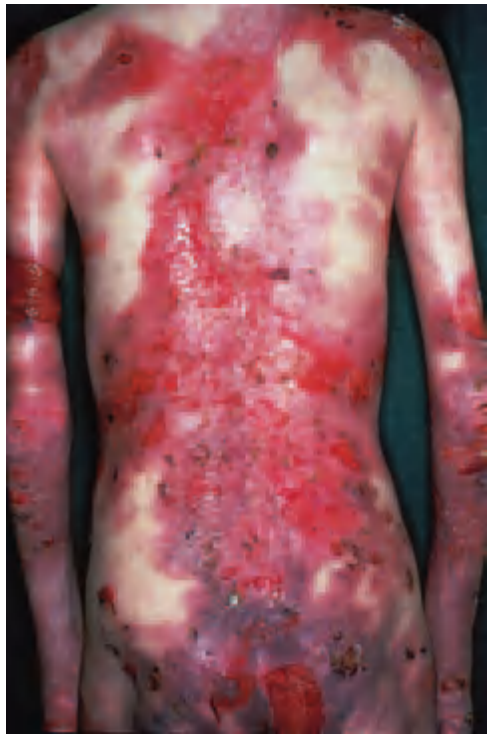

Fig. 40.19 Extensive lesions on the back in generalized recessive dystrophic epidermolysis bullosa.

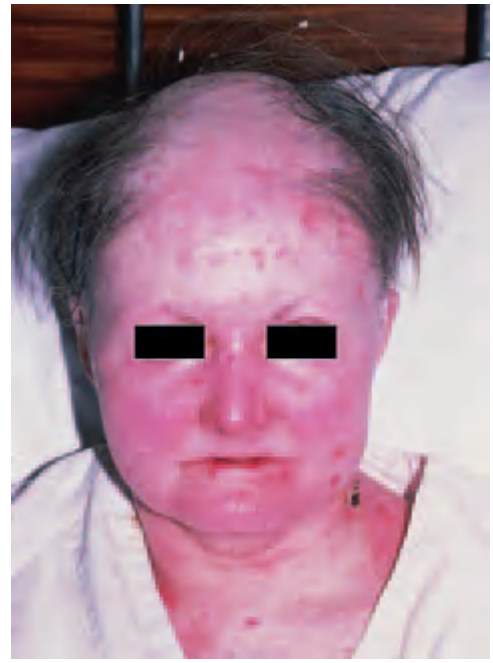

Fig. 40.20 Scarring alopecia in generalized recessive dystrophic epidermolysis bullosa.

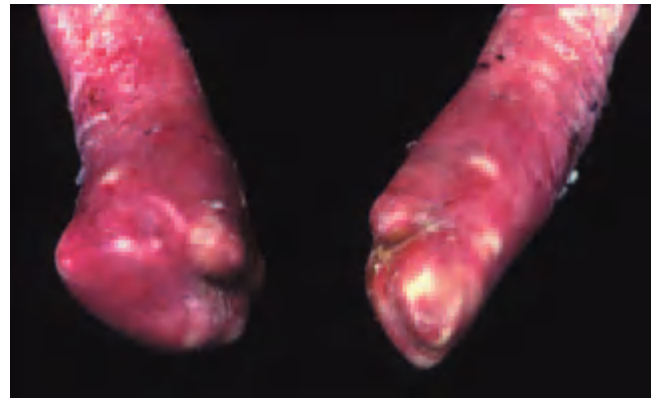

Fig. 40.21 Mitten hand deformity in generalized recessive dystrophic epidermolysis bullosa.

Autosomal recessive forms

Severe generalized recessive dystrophic epidermolysis bullosa (Hallopeau–Siemens) (syn. polydysplastic epidermolysis bullosa; epidermolysis bullosa dystrophica generalisata gravis) [1]. Bullae are present at birth or appear in early infancy. The clinical presentation may include localized absence of skin ('Bart's syndrome') especially affecting the hands, feet and lower legs in a glove or sock-like distribution [2]. The skin can be extremely fragile in this form of EB. Blisters develop spontaneously or after the mildest trauma on any part of the skin and may be haemorrhagic. Healing lesions leave atrophic scars like cigarette paper; thicker scars may occur particularly over the large joints, such as the knees. Milia formation is a constant feature. Although the whole of the skin is fragile and at high risk of developing blisters, the main sites of predilection are those subjected to repeated friction and other forms of physical trauma. These include the knees, elbows, hands, feet, back of the neck, shoulders and over the spine (Fig. 40.19). Ulcers over the spine or shoulders may heal extremely slowly. Chronic erosions and ulcers tend to become covered with a slough, often associated with heaped-up crusting and scaling, increasing the risk of secondary infection. Pruritus is frequent, and constant rubbing and scratching may induce blisters.

The scalp is often involved. Hair growth on the scalp and body is impaired and scarring alopecia may occur (Fig. 40.20). During childhood, repeated blistering with progressive scarring causes fusion of adjacent fingers and toes. If left untreated, the digits then undergo progressive contractures and gradually become encased in a cocoon-like covering of thin scar tissue (Fig. 40.21). Disuse of the hands results in bony resorption and muscle atrophy.

Non-cutaneous epithelia are also at risk of developing blisters, erosions and scars. Oral lesions may be severe, leading to ankyloglossia and microstomia. Patients are often unable to protrude the tongue outside the mouth, or to open the mouth normally. The gums are fragile, and gentle tooth brushing may induce epithelial disruption with bleeding. The lingual papillae are lost and the surface of the tongue becomes smooth, shiny and atrophic.

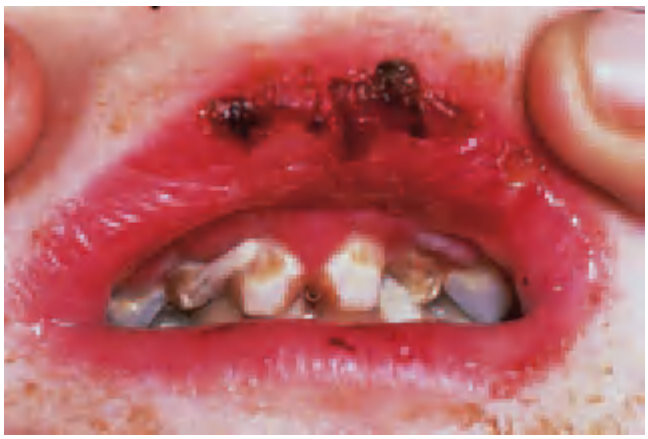

Fig. 40.22 Dental changes and blistering on lips in generalized recessive dystrophic epidermolysis bullosa.

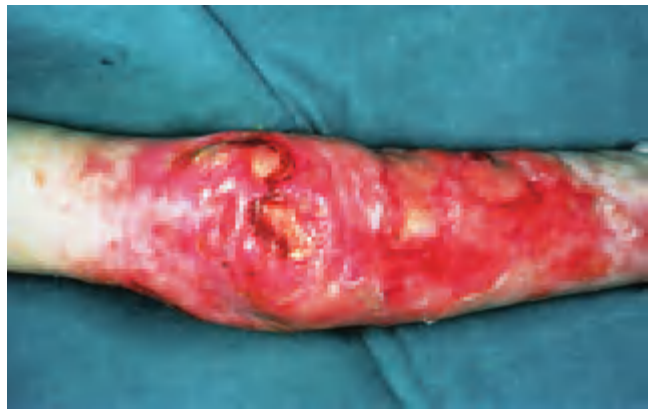

Fig. 40.23 Squamous cell carcinoma arising in an area of chronic scarring in a patient with generalized recessive dystrophic epidermolysis bullosa.

Although the evidence for a primary abnormality of dental enamel is questionable, the teeth are at a high risk of developing caries (Fig. 40.22) because of prolonged exposure to food. This stems from a reduced ability to chew the food normally and diminished circulation of saliva. Oral secretory immunity may be compromised [3]. In one series, the frequency of caries in the recessive dystrophic form of EB was about five times greater than in dominant dystrophic EB [4]. The loss of dentition has several ramifications. First, the intake of solid food is impaired, with potential consequences affecting the patient's nutrition and tendency to suffer with constipation. Secondly, there is a secondary loss of bone within the alveolar ridges of the jaw, preventing later corrective dental treatment such as the use of tooth implants.

Oesophageal involvement is a serious and invariable complication of this form of EB [5–8]. It may occur very early in life, even in infancy, and by the age of 20–30 years will have affected most patients. Blistering in the oesophagus may cause acute pain and dysphagia, manifesting with difficulty in swallowing solids. With time, partial or complete obstruction may result from oesophageal stricture, caused by scarring and fibrosis; or from web formation [8]. Stricture occurs more frequently in the upper third of the oesophagus, and may be multiple. In time, the oesophagus is thought to shorten as a result of fibrosis and is then at additional risk from gastro-oesophageal reflux [6]. Rare complications of oesophageal involvement include spontaneous perforation [7] and bringing up an oesophageal cast. Oesophageal involvement is another cause of poor nutrition.

Perianal blistering, erosions and painful fissures are common in childhood. Later, anal stenosis from scarring may develop. These changes will contribute to a child's reluctance to defaecate, leading to faecal retention, abdominal pain and bloating. Chronic constipation and eventual faecal impaction are also common. A low-fibre diet adds to this complication [5,6].

The main ocular complications include symblepharon, which in its more severe form may involve joining of the lid margin to the peripheral cornea; limbal broadening, which is often asymptomatic; and corneal opacity, possibly resulting from recurrent corneal erosions [9,10].

General physical development is retarded. Most patients are very thin and have a short stature. Some blood vitamin and trace metal levels are low [11] and immune function may be impaired because of reduced natural killer cell activity [12]. Severe refractory multifactorial anaemia adds to management problems.

An important sequela of this form of EB is the development of squamous cell carcinomas. These are often multiple primary tumours which, histologically, are usually well differentiated. They may be difficult to identify clinically at an early stage, appearing as a non-healing erosion or crusted or hyperkeratotic lesion. In keeping with other scar carcinomas, these tumours behave aggressively and often metastasize, eventually with a fatal outcome. Life-table analysis from the National EB Registry [13,14] indicates the high probability of death within 5 years of diagnosis of the first squamous cell carcinoma. Patients as young as 13 years may be at risk of developing cancer [15]. These tumours usually arise in any chronically scarred area of skin (Fig. 40.23). Less frequently, they may occur in the oesophagus [16] and mouth. The large majority of carcinomas are on the limbs, often in areas of chronic non-healing ulceration [17]. The tumours tend to recur locally, despite primary treatment using an apparently wide-surgical excision. Recurrences and metastases are generally unresponsive to chemotherapy or radiotherapy. There is also an increased risk of developing malignant melanoma [13], but the incidence of other internal malignancies does not appear to be increased. Systemic amyloidosis is a

further complication [18,19] that may involve internal organs such as the heart or kidneys.

Most patients experience a delay in development of secondary sexual changes. Despite the severity of the skin disorder, sexual function may be sufficiently normal in some female patients to undergo an uncomplicated pregnancy with the vaginal delivery of a normal healthy child (R.A.J. Eady & S. Bewley, unpublished observations 1996) [20].

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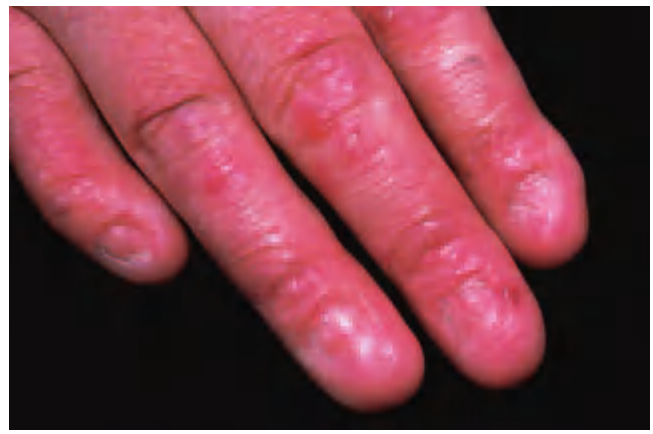

Fig. 40.24 Nails in localized recessive dystrophic epidermolysis bullosa.

Non-Hallopeau–Siemens dystrophic epidermolysis bullosa. The condition shares several cutaneous and extracutaneous features with the more severe, Hallopeau–Siemens form of recessive dystrophic EB, but is generally much milder. The skin and mucosae are very fragile, but lesions, including nail changes, milia and atrophic scarring, tend to be more localized, and similar to those seen in classical dominant dystrophic EB (Fig. 40.24). Growth retardation and anaemia are usually mild. Pseudosyndactyly, oesophageal involvement and squamous cell carcinoma may also occur, but these complications are usually milder or less frequent than in Hallopeau–Siemens dystrophic EB.

Inverse recessive dystrophic epidermolysis bullosa [1,2]. The primary areas of blistering and scarring include the groins, axillae, neck (Fig. 40.25) and lumbar area. Traumatic corneal erosions and oesophageal lesions are common. Nail dystrophy, mucous membrane involvement and dental changes are similar to those in the generalized form of the condition. Patients are also at risk of developing squamous cell carcinoma.

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Autosomal dominant forms

Classical dominant dystrophic epidermolysis bullosa (syn. hyperplastic (Cockayne–Touraine) and albopapuloid (Pasini) variants). A problem with most classifications of EB, including a more recent one [1], is the convention of subdividing most cases of dominant dystrophic EB into the mutually exclusive Cockayne–Touraine or Pasini variants. In 1928, Pasini described a single family whose EB

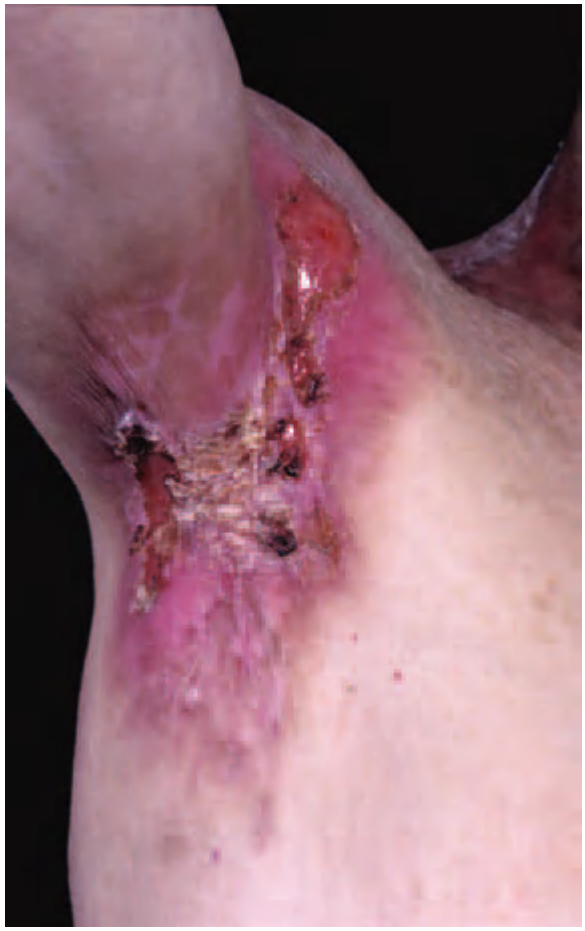

Fig. 40.25 Scarring and erosions affecting the axilla and neck in the inverse form of recessive dystrophic epidermolysis bullosa.

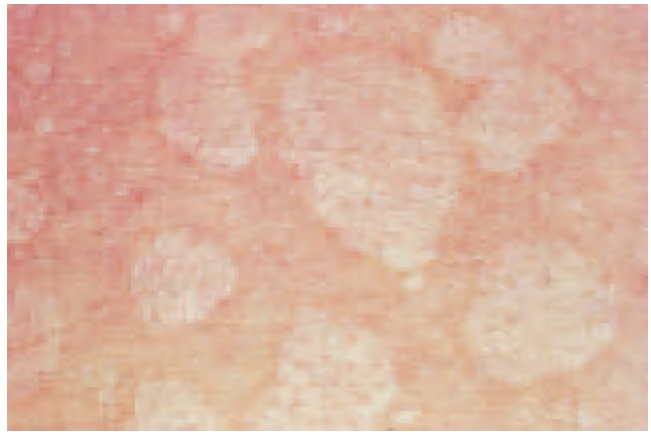

Fig. 40.26 Albopapuloid lesions on the lower back of a patient with dominant dystrophic epidermolysis bullosa.

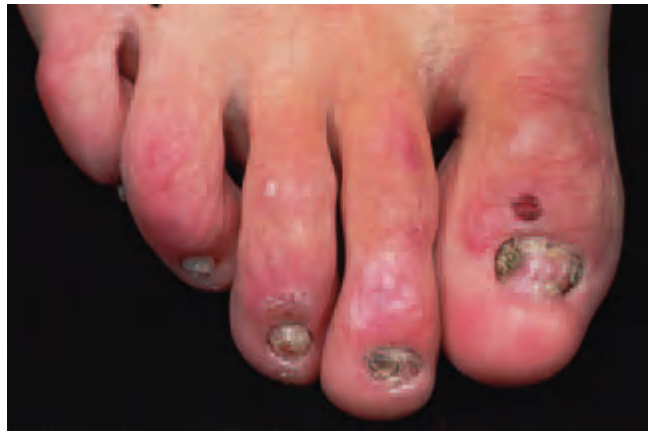

Fig. 40.27 Nail changes and scarring of skin on backs of toes in dominant dystrophic epidermolysis bullosa.

was distinguished by the presence of numerous white papules that he called 'albopapuloid' lesions. In other respects, it is unclear how such individuals can confidently be distinguished from those with the so-called 'Cockayne–Touraine' phenotype. It has been said that one form tends to be more severe than the other, but the issue is clouded by the fact that albopapuloid lesions, which are most often seen on the trunk (Fig. 40.26), are probably not specific, and variations in the onset and severity of the disease have been described, even within the same kindreds [1,2]. Differences in ultrastructural and biochemical findings have also been reported (see [3] for review). The histogenesis of albopapuloid lesions is unclear, and reports have alluded to both epidermal and dermal abnormalities, including alterations of collagen and elastic tissue (reviewed in [2]). To avoid further confusion, the time has come to abandon these eponymous descriptions and to regard these so-called variants of dominant dystrophic EB as belonging to a continuum. The main feature of dominant dystrophic EB is that the skin is generally less fragile than in the Hallopeau–Siemens form of recessive dystrophic EB. Blisters usually follow sharp knocks or glancing blows rather than mild friction, and therefore can be difficult to induce for a diagnostic skin biopsy. They mainly occur in skin overlying bony prominences, such as the knees and ankles, and dorsa of the hands or feet. The most consistent findings are localized scarring with milia formation and dystrophic nails. Nail dystrophy is probably the most important diagnostic feature of the disease, especially in adults, because many patients have only limited scarring, which becomes less noticeable with age. The nail plates, particularly of the large toes, are often diminutive (Fig. 40.27) or entirely absent, where the normal nail is replaced by atrophic scar tissue. Blistering in the mouth is usually mild and the teeth are generally normal. However, perianal lesions may cause considerable pain, especially in children.

Clinically, it is often impossible to distinguish this form of dominant dystrophic EB from the localized recessive dystrophic forms, making genetic counselling impossible in the absence of a positive family history or accurate molecular diagnosis.

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Congenital localized absence of skin (syn. Bart's syndrome). In 1966, Bart described a kindred with localized absence of the skin over the lower legs associated with cutaneous blistering and mucous membrane and nail involvement [1]. The condition, which appeared to follow an autosomal dominat mode of inheritance, was thought to be form of EB simplex [2]. However, localized absence of the skin has been reported by others in association with simplex [3], junctional [4,5] and dystrophic EB [6]. In view of these findings, congenital localized absence of the skin should be regarded now as a manifestation of EB, instead of a separate entity or syndrome. The original family described by Bart has since been shown to have dominant dystrophic EB, caused by a glycine substitution mutation in *COL7A1* [7].

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Pretibial dystrophic epidermolysis bullosa and epidermolysis bullosa pruriginosa. In 1946, Kuske [1] reported a patient with itching, blisters, atrophy and scarring on the shins. There were further reports of similar patients [2,3]. In one family with a dominant transmission of the disease, the clinical features were variable [3]. Several authors have referred to this condition as pretibial EB [4–6], given the tendency for the lesions to develop in the pretibial areas.

In 1994, McGrath *et al*. [7] delineated a group of eight patients with a highly distinctive phenotype in which the overriding symptom is severe pruritus. The authors named the condition 'EB pruriginosa' to highlight this combination of clinical features. EB pruriginosa presents either at birth with mild acral blistering and erosions, or during infancy or childhood. Violaceous papular and nodular lesions, often in a linear arrangement, are mainly confined to the shins (Fig. 40.28) and forearms, although rare lesions may occur on the trunk. In adults, the lesions are chiefly lichenified plaques. Histologically, a split may be evident at the dermal–epidermal junction, although frank blisters are rarely seen. Apart from scarring with milia, toenail dystrophy is a consistent finding in adult patients.

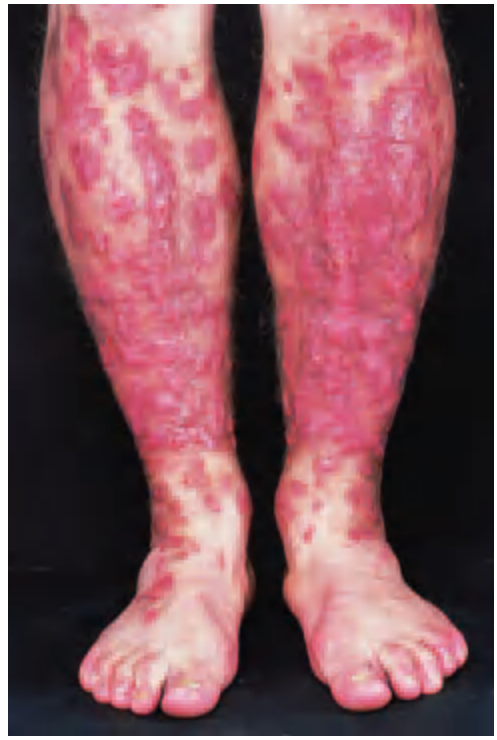

Fig. 40.28 Violaceous lesions in a partly linear distribution in a patient with epidermolysis bullosa pruriginosa.

Most cases are sporadic. However, both autosomal recessive and dominant inheritance is recognized [8]. The cause of the severe pruritus is unknown; however, a number of patients have raised blood levels of immunoglobulin E (IgE) (R.A.J. Eady, unpublished observations 1997), suggesting a possible atopic background. Clinically, EB pruriginosa has to be distinguished from lichen simplex, hypertrophic lichen planus, Nékam's disease, cutaneous amyloidosis and dermatitis artefacta [9]. It shares several features with the pretibial form of dystrophic EB, but is clinically much more striking.

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Transient bullous dermolysis of the newborn. In 1985, Hashimoto *et al.* [1] reported a newborn with blistering developing on the extremities soon after birth. The bullae quickly resolved and there was apparently no scarring or milia formation. The name 'transient bullous dermolysis of the newborn' was coined to describe this uniquely self-limited clinical course associated with a sublamina densa level of cleavage. Ultrastructurally, the basal epidermal keratinocytes were shown to contain electron-dense stellate bodies. The skin condition resolved completely and a year later there were only mild residual pigmentary changes. Later, Fine *et al.* [2] used immunofluorescence and immunoelectron microscopy to show that these intracellular inclusions contained type VII collagen, and that the underlying dermal–epidermal junction usually lacked normal anchoring fibrils and type VII collagen staining (Fig. 40.29). The phenotype of these patients resembled a mild dominant or localized recessive form of dystrophic EB, and included small numbers of tense blisters, milia and mild focal atrophic scarring. Fine *et al.* [2] further demonstrated that these immunohistochemical features tended to revert to that of normal non-EB skin, showing intense uniform linear immunostaining of the dermal–epidermal junction with antibodies to type VII collagen, at about the time most blister formation had ceased. It was thought that this phenomenon represents a transient secondary abnormality in packaging, transport or incorporation of a presumably mutated type VII collagen into the dermal–epidermal junction during early infancy in these patients.

The clinical and microscopic features were later confirmed by Schofield *et al.* [3] in other patients. Smith and Sybert [4], however, described similar ultrastructural and immunocytochemical findings in a patient with recessive dystrophic EB whose prognosis was poor. Phillips *et al.* [5] also showed that the presence of intraepidermal type VII collagen in infancy was not always predictive of a good clinical outcome.

One of the kindreds reported by Fine *et al.* [2] has since been shown to have a *COL7A1* mutation typical of dominant dystrophic EB [6]. *COL7A1* mutations have also been reported in other cases [7].

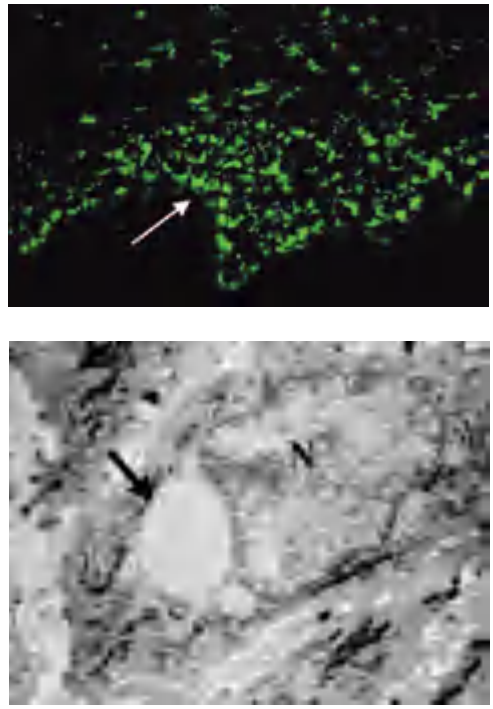

Fig. 40.29 Transient bullous dermolysis of the newborn. (a) Indirect immunofluorescence micrograph showing granular staining in the basal and suprabasal layers with LH7.2 (anticollagen VII) antibody, yet absence of the normal linear staining at the dermal–epidemal junction (arrow). (b) Electron micrograph showing a large intracellular inclusion (arrow) beneath a basal cell nucleus (N).

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Diagnosis

Despite the impressive advances in the molecular genetics of different forms of EB, the initial diagnosis still relies largely on a careful clinical examination, enquiry into the family history and establishing the level of blister formation [1]. Because the clinical features may be unhelpful or even misleading, especially in a neonate, the diagnosis will often rely on microscopic analysis of a skin biopsy. Electron microscopy, performed in a laboratory with appropriate experience and skills, is still the best method for evaluating skin samples. Immunohistochemistry, particularly indirect immunofluoresence microscopy, is also important, if not essential. Ideally, tissue should be acquired at the same time for both electron microscopy and immunohistochemistry.

Skin biopsy

The main objectives of skin biopsy are first to establish the level of blistering or tissue separation and, secondly, to search for other clues that may be indicative of the underlying disorder and therefore helpful in the diagnosis. The importance of the correct biopsy technique cannot be overstressed. Most blisters that are clinically evident, and especially those with bloodstained contents, are often more than 12 h old and therefore too old for diagnostic purposes. Older blisters may cause severe diagnostic difficulty because false-negative immunostaining caused by proteolytic antigen degradation, re-epithelialization under the blister roof and multiple cleavage planes may all occur. A sample of non-blistered skin that has been gently rubbed to produce a mild erythema is preferable, because this will usually contain a cleavage plane with few if any secondary changes.

Because the diagnostic signs are mostly seen in and around the dermal–epidermal junction, shave biopsy samples are preferable to thicker specimens obtained by ellipse or punch biopsy methods. Care must be taken to ensure that a sufficient amount of dermis is present, to allow examination of the entire dermal–epidermal junction. It is often better to take two or three small pieces for different types of examination, such as electron microscopy and immunofluorescence. Attempts to subdivide a larger biopsy specimen can result in detachment of the epidermis from the dermis and spoil the sample for critical microscopic analysis. The samples should be immediately immersed in suitable fixative for electron microscopy, or in a freezing liquid, such as isopentane precooled with liquid nitrogen, after embedding in OCT Tissue-Tek Compound (Miles Inc, Diagnostics Division, IN 46515, USA), for immunofluorescence. The samples can then be stored in a –70°C freezer or in liquid nitrogen until required for analysis. Michel's transport medium can be used for both immunofluorescence and electron microscopy [2], although the ultrastructural preservation will be variable and often inadequate for detailed electron microscopic analysis.

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Electron microscopy

The chief purpose is to demonstrate the level of tissue separation or blistering [1,2]. As indicated in the sections on molecular pathology of EB subtypes, the split is intraepidermal in EB simplex, in junctional EB it is through the lamina lucida, just below the lowermost plasma membrane of basal cells, and in dystrophic EB it is beneath the lamina densa. Other ultrastructural features important for diagnosis are that hemidesmosomes are generally sparse and small in the more severe forms of junctional EB [3,4] and anchoring fibrils are reduced in number, absent or structurally abnormal in dystrophic forms of EB [5–7]. A clear distinction cannot be made between the dominant and localized recessive dystrophic forms, even with morphometric analysis of anchoring fibrils [3]. Intraepidermal electron-dense stellate bodies are a marker of transient bullous dermolysis of the newborn (Fig. 40.29). In the Herlitz form of junctional EB and in the form of EB associated with pyloric atresia, hemidesmosome plaques are often minute, and subbasal dense plates are severely attenuated or absent.

In EB simplex, the most striking changes are seen in the Dowling–Meara form, where tonofilament clumping in basal keratinocytes (Fig. 40.1) is pathognomonic [8]. In the rare generalized or Koebner autosomal recessive forms of EB simplex, the tonofilaments may be severely depleted or absent from the basal cells. In EB superficialis, the cleavage level is usually subcorneal. Despite their value in diagnosis in most instances, the ultrastructural features in a given diagnostic biopsy sample can be difficult to interpret. Briggaman [9] has illustrated how the level of cleavage may appear to vary, not only between skin samples from the same patient but also within the same sample.

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Antigen mapping

As an alternative to electron microscopy, the level of blister formation can be determined using indirect immunohistochemical staining [1–3]. The aim is not to look for reduced expression of skin antigens, but to stain the dermal–epidermal zone using antibodies to proteins that are strongly expressed in both normal skin and skin from patients with different forms of EB. For example, sera from bullous pemphigoid patients or, preferably, an anti-BP230 antibody can be used to stain the lower surface of basal cells (containing hemidesmosomes), and antikeratin 14 antibody to stain the cytoplasm of basal epidermal cells. Anti-type IV collagen antibody will stain the lamina densa of the epidermal basement membrane. In EB simplex, all antibodies (except antikeratin) stain only the base of the split. Antikeratin stains the roof and the floor (but this is difficult to see in low-level separations). In junctional EB, antikeratin and bullous pemphigoid antibodies stain the roof; whereas anti-type IV collagen staining is on the floor. In dystrophic EB, all antibodies stain only the roof of the split.

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Use of specific antibody probes

This method can be very valuable in diagnosis when used together with electron microscopy or antigen mapping. The purpose is to demonstrate a reduction in or absence of expression of certain antigens in the dermal–epidermal junction, which may be indicative of specific abnormalities in either junctional or dystrophic forms of EB [1]. Several relevant studies have already been referred to under the sections on molecular pathology of EB subtypes.

In Herlitz and some non-Herlitz cases of junctional EB, caused by laminin 5 mutations, abnormal staining for laminin 5 can be shown using monoclonal antibodies GB3 [2] and K140 [3] (Fig. 40.30). In non-Herlitz junctional EB (generalized atrophic benign EB) with BP180 defects,

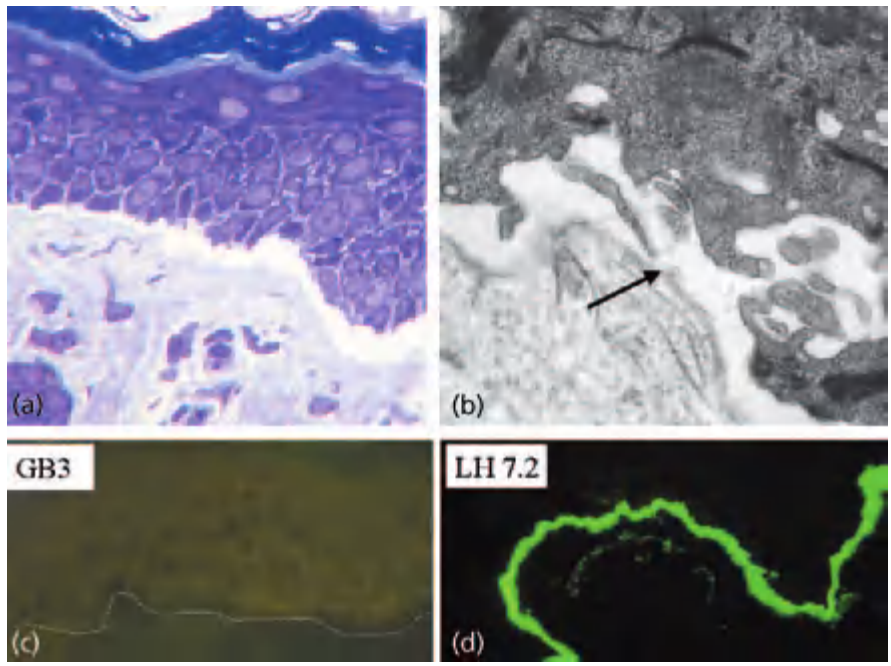

Fig. 40.30 Combined use of (a) light microscopy, (b) electron microscopy, and (c,d) indirect immunofluorescence microscopy for the diagnosis of Herlitz junctional EB. (a) A split in a semi-thin (1 μm thick) resin section has occurred in (b) the lamina lucida, just above the lamina densa (arrow). (c,d) In frozen sections, (c) GB3 (antilaminin 5) staining is negative, whereas (d) LH7.2 (anticollagen VII) staining is normal.

staining is reduced with anti-BP180, but not with anti-laminin 5 antibodies [4]. Antibodies to the α6 or β4 integrin chains will show reduced staining in the skin of patients with EB associated with pyloric atresia [5].

The monoclonal antibody 19-DEJ-1, recognizing 'uncein', an anchoring filament antigen possibly representing a protein with homology with a non-muscle myosin (J-D. Fine, unpublished data), shows reduced or absent staining in all forms of junctional EB and in approximately 25% of individuals with recessive dystrophic EB [6,7]. LH 7.2 monoclonal antibody, reacting with the amino terminal of the type VII collagen molecule is probably the most widely used antibody for the diagnosis of recessive dystrophic EB [8]. In cases of EB simplex associated with muscular dystrophy, reduced or absent staining will be found using antibodies to plectin, or HD1 (an antigen that is homologous with plectin) [9–11].

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Molecular diagnosis

With the discovery of at least 10 distinct genes underlying different variants of EB, DNA-based techniques have had an increasingly important application in the diagnosis and prenatal diagnosis of EB. The information gained from molecular diagnosis is especially useful for genetic counselling and prognosis. When a patient is first seen in the clinic or neonatal unit, it is important to make provision for molecular diagnosis in the management plan, and obtain venous blood or cheek mucosa brushings (collected in ethylenediaminetetra-acetic acid tubes, and *not* in heparin or citrate) for subsequent DNA extraction and analysis in the laboratory.

An example of the power of moleular diagnosis is the ability to discover whether a patient has a dominant or recessive form of dystrophic EB, where neither the family history, a skin biopsy nor the clinical phenotype has been able to provide the information. In a cohort of some 180 families in which distinct *COL7A1* mutations had been identified, there was evidence of only one case derived from a *de novo* germ-line-dominant mutation in a parent [1]. This implies that the large majority of apparently sporadic 'new' cases, with no known family history of EB, are likely to have a recessive rather than a dominant form of dystrophic EB [1]. However, the presumptive *de novo* occurrence of a glycine substitution mutation has also been reported [2,3]. The possibility of germ-line mutations inherited in patients with 'sporadic' dominant dystrophic EB should also be considered [4]. Molecular diagnosis can be valuable in the differentiation of Herlitz from non-Herlitz EB (e.g. in a child) where the skin biopsy findings, including the immunofluorescence results, are equivocal.

The developments in the molecular genetics of the dystrophic and junctional forms of EB have already had a major impact on prenatal diagnosis. First trimester DNA testing is now an option for couples at risk of having affected children (see Chapter 13). Knowledge of mutation 'hotspots' within a population can reduce the time and expense of extensive screening for mutations that might otherwise be necessary [5]. The issue of mutation screening of family members of affected individuals, or unrelated partners, often arises during genetic counselling. In relatives not known to be at high risk of either being a carrier of a recessive gene and therefore of having an affected child, genetic screening may not be offered, or even encouraged. However, there are rare instances where prior screening may have averted an affected pregnancy [6].

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Differential diagnosis

Differentiating EB from non-EB, or one form of EB from another, can be very difficult, especially in the neonatal period. At this stage, the following disorders may need to be included in the differential diagnosis of EB: bullous congenital ichthyosiform erythroderma; staphyloccocal scalded skin syndrome; bullous impetigo; incontinentia pigmenti; neonatal herpes simplex; autoimmune bullous disease, such as pemphigus or herpes gestationis, acquired transplacentally; aplasia cutis; focal dermal hypoplasia; Gunther's disease; and Kindler's syndrome.

In infants, older children or adults, some autoimmune bullous diseases, such as bullous pemphigoid, cicatricial pemphigoid or linear IgA disease may show overlapping features with junctional EB or Dowling–Meara EB simplex (e.g. EB acquisita may resemble dystrophic EB). Usually, however, the timing of the onset of blistering will allow inherited EB to be distinguished from the autoimmune immunobullous disorders. Pachyonychia congenita, skin peeling syndrome and ichthyosis bullosa of Siemens may rarely be confused with EB in older children or adults.

Shabbir's syndrome also has to be considered in the differential diagnosis of EB. This disorder, described by Shabbir *et al.* [1], included 22 patients from 13 mostly consanguineous Pakistani families. It starts in infancy and affects both sexes. Chronic erosive lesions affect the face, mainly around the nose and mouth, and, to a lesser extent, the limbs, trunk and genitalia. The nails are also involved and the third constant feature is hoarseness. The teeth may be notched. In a detailed study of three children with Shabbir's syndrome (or laryngo-onychocutaneous syndrome), Phillips *et al.* [2] emphasized the additional feature of conjunctival lesions, which were also constant in their patients. They also thought that the condition may represent a distinctive form of junctional EB because two patients had transient blisters in the neonatal period, the ulcers appeared in sites of repeated rubbing or trivial trauma, and hemidesmosomes in some of their patients showed ultrastructural and immunohistochemical abnormalities consistent with junctional EB.

Another recently recognized disorder that must be distinguished from EB is an autosomal recessive form of ectodermal dysplasia associated with congenital skin fragility, caused by mutations in the plakophilin 1 gene [3,4]

Mendes da Costa disease [5] is often classified as a form of EB simplex. The pathogenesis of this rare X-linked disorder, reported in a Dutch family, is still poorly understood. Although blisters are seen, they are not trauma induced [6]. Without further evidence, the case for continuing to classify this disorder as a form of EB is questionable.

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Treatment

There is no specific treatment for any form of EB, and the mainstay of clinical management is based on protection and avoidance of provoking factors. In the more severe forms of EB, it should be remembered that the whole skin and other stratified squamous epithelia, including the oral mucosa, are extremely fragile and vulnerable to blistering from the slightest friction or scrapes. In the milder forms, blistering may not always result from mild friction and may only follow sharp knocks to the skin. Major challenges include the treatment of the neonate with severe generalized disease and the older child, adolescent or adult with the chronic disability that accompanies the severe form of recessive dystrophic EB.

Management of neonates and infants

Because severe blistering and erosions may be associated with junctional, dystrophic or simplex forms of EB in the neonate, an early objective is to establish the diagnosis from an appropriate skin biopsy (see above). This may be particularly relevant for a newborn with Dowling–Meara EB simplex, where the clinical appearance may be confused with Herlitz junctional EB or even dystrophic EB, suggesting a much graver prognosis. The early management of neonates with EB should, where possible, be undertaken in a specialist neonatal or paediatric unit, which has the expertise, staff and resources to manage these vulnerable babies. A key to successful treatment is expert nursing care. Paediatric nurse specialists with experience of caring for babies and children with EB are often best placed to help with coordinating hospital treatment, training parents and non-specialist nurses at other centres to handle and treat the patients, and prepare for the child's return home. In these specialist centres [1], babies with EB are nursed on thick foam pads, which are covered by a silk sheet. This allows the babies to be held, fed and nursed without subjecting them to undue trauma. The erosions are cleaned with sterile normal saline and covered in comfortable non-adherent dressings. Some EB specialists may prefer to use a topical antiseptic such as stabilized hydrogen peroxide cream (Hioxyl, Quinoderm, UK) or 1% chlorhexidine cream, rather than topical antibiotics, chiefly because of the risk of emergence of antibiotic-resistant bacteria. Another preference is to treat open

wounds with 1% silver sulfadiazine cream (Flamazine, Smith and Nephew, UK) or an ointment containing polymyxin B or bacitracin. The topical antibiotic mupirocin is not recommended for regular use, especially in hospital practice, because of the emergence of mupirocin-resistant *Staphylococcus aureus* [2,3]. However, its use for short periods (up to 7 days) in the home, for localized infected areas, is normally safe and effective [4]. Among the newer dressings now favoured for use in children and older patients are Mepitel and Mepilex (Molynycke, Luton, UK). Mepitel is a porous, mildly adherent silicone-based material, which can be left in place for up to 7 days. Any exudate is usually able to pass through the holes in this dressing to be absorbed by a secondary gauze dressing, which can be changed more frequently. Mepilex has a foam backing which provides more protection where needed.

Management of severe generalized recessive dystrophic epidermolysis bullosa

Patients with the more severe forms of recessive dystrophic EB will often survive into middle age and will therefore require continuing care throughout life [5]. Ideally, they should be seen at 6-monthly intervals in a multidisciplinary clinic with expertise to help with the particular needs of these patients. Special precautions should be taken in the use of adhesive tapes, sphygmomanometer cuffs, tourniquets and any other instruments or appliances that might lead to blister formation or shearing of the skin or mucous membranes. The following systems require particular attention.

Oral and dental care [6,7]

Microstomia, intraoral fibrosis and tethering of the tongue make access and examination of the teeth and mucosa difficult. Treatment should start in early childhood, so the involvement of a paediatric dentist with specialist knowledge of the dental complications affecting children with EB is important. Wherever necessary, reconstructive measures should be applied to permanent and primary teeth, to maintain function. These include treatment of caries, and meticulous cleaning of tooth surfaces. Crown placement and even tooth implants (in adults) have been used succesfully in some patients. More frequent preventive measures include daily fluoride supplements and the use of a mouthwash containing sodium fluoride and aqueous chlorhexidine (G. Roberts, personal communication, 1996).

Gastrointestinal tract and nutrition [8–12]

Dysphagia and pain on swallowing are common. Oesophageal strictures may be demonstrated by X-ray examination (including barium swallow and cine radiography)

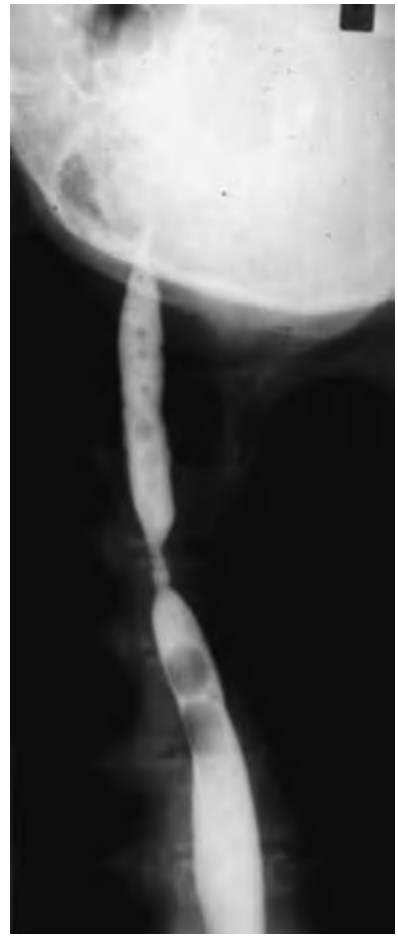

Fig. 40.31 Barium swallow radiograph showing constriction in the upper oesophagus in recessive dystrophic epidermolysis bullosa.

(Fig. 40.31) or by endoscopy. Oesophageal spasm, often accompanying an acute obstruction, can sometimes be relieved by administration of calcium-channel blocking agents. More permanent blockage requires an endoscopically guided balloon dilatation [8], which will usually have to be repeated, perhaps several times each year. More radical treatment has included surgical excision of the stricture followed by anastomosis, and colonic interposition [9]. Most patients have gastro-oesophageal reflux, which should be treated with a proton pump inhibitor to prevent further damage to the lining of the oesophagus with the risk of secondary scarring and oesophageal shortening. Constipation is inevitable and often chronic in these patients. The cause is complex and associated in some degree with inadequate fibre in the diet. A high-fibre diet is therefore important, and patients who have difficulty in eating sufficient fibre may benefit from nutritional supplements such as Enrich (Abbot Laboratories Ltd, Maidstone, Berks, UK). Osmotic and stimulant laxatives, as well as faecal softeners, may all have a role and be prescribed according to an individual patient's

needs. Lactulose is often the first choice of laxative to be used in treating constipation in children and adults.

Anal blistering and erosions contribute to the constipation and faecal retention, especially in children. Glycerol suppositories used in conjunction with a topical anaesthetic preparation may help. If faecal impaction occurs, more drastic measures, including manual removal of faeces under general anaethesia, may be required.

Trying to ensure adequate nutrition with a balanced diet is especially important to maintain growth in children [10,11]. A deficiency of vitamins and trace elements (including zinc and iron) is frequent [12]. Comprehensive nutritional supplementation is only partly effective in maintaining adequate growth, and controlling anaemia and wound healing. The advice of an EB dietitian is essential. Feeding through a gastrostomy allows appropriate nutrition in addition to the administration of supplements such as iron, zinc and multivitamins, which children may find difficult to take by mouth [13]. Gastrostomy feeding can be delivered overnight in the home [13]. Parenteral nutrition has also been used [10].

Eyes

External abrasions should be dealt with urgently; they usually require topical treatment with an antibiotic and anaesthetic. Scarring of the lids following blistering may result in inadequate lid closure and loss of normal protection to the eyes. Plastic surgical reconstruction may be indicated. Artificial tears are a useful lubricant.

Musculoskeletal system

Although early exercises and physiotherapy may be helpful, the progress of finger and hand contractures with eventual mitten-type deformity is virtually inevitable. Contractures and tight tethering by scar tissue may also affect elbows and knees. Surgical release of the contracted fingers is a highly specialized procedure and requires skin grafting and postoperative splinting [14–16]. The benefit from surgery is only temporary because most patients need further surgical treatment within a few years. The feet may be involved in a similar process, but a 'degloving' procedure is not recommended, because the foot deformities do not usually prevent the patients from standing or walking.

Anaemia

All patients with the more severe forms of recessive dystrophic EB are anaemic, and the picture is that of an anaemia of chronic disease. Despite the administration of oral iron supplements, the iron stores are usually low as assessed by serum ferritin levels. In patients with widespread lesions and secondary infection, the serum ferritin may not accurately reflect the need for supplementary iron. Instead, the serum iron level may be a better indicator of the requirement for iron replacement in these patients. Parenteral iron is painful if given intramuscularly, especially where the muscles are thin and wasted. Anaphylaxis is a potential risk of intravenous administration. Venofer (Synar-Med, UK), an iron hydroxide preparation, can be given intravenously, and has been used repeatedly in several dystrophic EB patients, with a good response and no serious side effects [17,18]. The haemogobin levels generally increased, and the patients' sense of well-being improved. Transfusion of packed red cells may be required, especially when the blood haemoglobin level falls below approximately 7.00 g/dL, or when the patient becomes short of breath and more easily fatigued than usual.

Bony abnormalities

Virtually all patients have bony changes, mainly osteoporosis [19]. The cause is multifactorial, and is related to poor nutrition, relative immobility in some patients and previous treatment with systemic glucocorticoids. This last point is especially relevant in older patients. Regular checking of bone density, especially of the hips and spine, usually by dual-energy X-ray absorptiometry, is now part of routine management. Treatment with calcium supplements and a biphosphonate may be indicated.

Systemic treatment

Long-term systemic corticosteroid treatment is not used now because of the high risk of complications, and phenytoin, which had appeared to control blistering in certain patients in an open study [20], did not prove to be more effective than placebo in a controlled trial [21]. Other systemic drugs that have been tried with mixed results in small numbers of patients include vitamin E [22,23], minocycline [24], ciclosporin [25,26] and retinoic acid [27]. Although, theoretically, the systemic use of a retinoid such as isotretinoin or acetretin might reduce the risk of squamous cell carcinomas in these patients, there is no evidence yet in support of this presumably lifelong treatment. In addition, in a recent phase 1 trial of low-dose isotretinoin in recessive dystrophic EB, many of the patients treated complained of increased mechanical fragility, blistering and/or itching as the dosage approached 0.5 mg/kg/day (J-D. Fine, unpublished data).

Skin grafting

Autologous split-thickness skin grafts have had short- to longer term beneficial effects in the treatment of chronic ulcers or erosions in patients with generalized recessive dystrophic EB [28] or pretibial EB [29,30]. The treatment

was found to be more effective when allogeneic keratinocytes were added to the split-skin grafts [30]. Cultured keratinocytes have also been used successfully in the treatment of junctional EB [31,32]. Repeated applications of autologous [31] or maternally derived [32] cells were used in the treatment of facial erosions in three children, and allogeneic keratinocytes were effective in promoting re-epithelialization of extensive erosions on the trunk and upper limbs of an infant [33]. Similar benefit was seen in a patient with recessive dystrophic EB [34]. The effects of applying allogeneic keratinoyctes to split-skin graft donor sites on the thigh were studied in 10 patients with severe recessive dystrophic EB [35]. There was no overall difference in the rate of wound healing, in comparison to similar non-treated sites. However, the treatment was effective in relieving pain in several patients.

Skin bioequivalents have also been used in the treatment of EB simplex [36], junctional EB [37,38] and dystrophic EB [37], with mixed results. Concerns have been raised about the relative efficacy, especially in the long term, of treatment with bioequivalents, including the commercially available Apligraf (Novartis), until more comprehensive data based on controlled trials become available [39]. Anecdotal evidence from the National EB Registry suggests that such treatments are often either ineffective or any benefits may be relatively short-lived (J-D. Fine, unpublished data).

Pain management

Patients with EB frequently experience severe pain, which is unresponsive to conventional treatment with non-opiate-based or non-steroidal anti-inflammatory agents. Unfortunately, systemic opiates are addictive and tend to exacerbate chronic constipation, making their chronic use highly undesirable. However, recent experience has found that the use of topical opiates, including diamorphine, may be effective in the treatment of pain in EB patients, reducing the need for powerful systemic analgesia (E. Pillay, F. Keane and R.A.J. Eady, unpublished data). Its use is particularly beneficial when chronic pain is associated with chronic ulcers and erosions, accompanied in some patients by squamous cell carcinoma. Amitriptylline is useful in pain management in both adults and children [40]. Amitriptylline and cognitive–behavioural techniques were effective in relieving chronic pain and discomfort in an 11-year-old child with junctional EB [41]. Oral midazolam 0.33 mg/kg administered 20 min prior to baths and dressing changes substantially improved the patient's tolerance of wound care [41].

Cancer and recessive dystrophic epidermolysis bullosa [42]

Squamous cell carcinomas are expected to occur in nearly every patient with Hallopeau–Siemens disease, as well as in a minority of patients with non-Hallopeau–Siemens and inverse forms of recessive dystrophic EB (Figs 40.32 & 40.33). Meticulous surveillance, preferably with the aid of serial photography, should be performed regularly (at

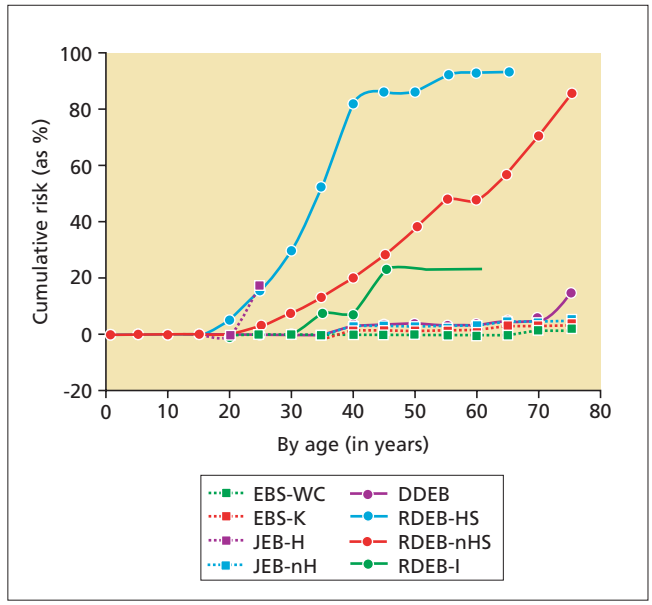

Fig. 40.32 Cumulative risk of death from squamous cell carcinoma in different forms of epidermolysis bullosa. EBS-WC, epidermolysis bullosa simplex (Weber–Cockayne); EBS-K, EB simplex (Koebner); JEB-H, junctional EB (Herlitz); n-H, non-Herlitz; DDEB, dominant dystrophic EB; RDEB-HS, recessive dystrophic EB (Hallopeau–Siemens); n-HS, non-Hallopeau–Siemens; RDEB-I, inversa. (J-D. Fine, unpublished data, 2002.)

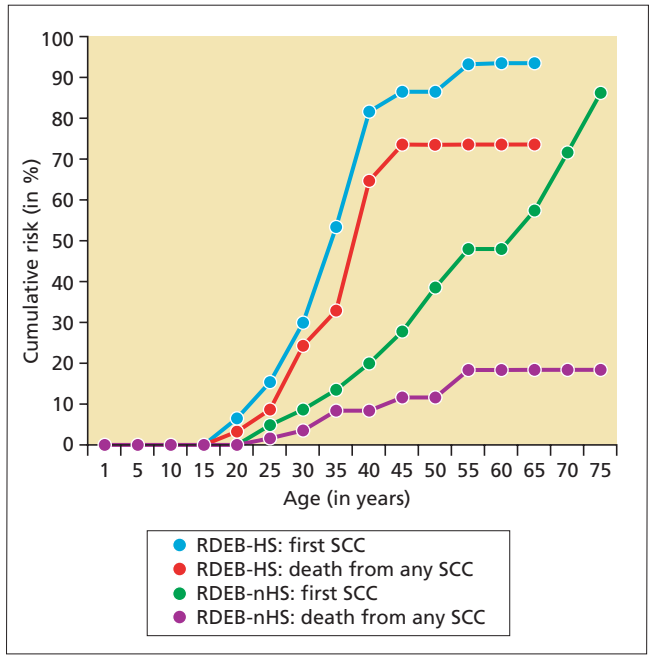

Fig. 40.33 Cumulative risk of developing first squamous cell carcinoma (SCC), and death from SCC in recessive dystrophic epidermolysis bullosa. (J-D. Fine, unpublished data, 2002.)

least every 6 months), from the age of 10 years, and any suspicious lesion should be immediately biopsied. Those lesions that fail to reveal cancer histologically, and yet remain atypical in appearance or healing pattern, such as a non-healing erosion, should be re-biopsied, because it is possible to miss an early squamous cell carcinoma, given the tendency of these tumours to be well differentiated histologically and to show only focal areas of neoplastic change. Wide surgical excision is recommended, and careful serial follow-up examinations should be implemented, seeking possible local or regional recurrences. Although still unproven, there may be a role for sentinel node biopsy in the management of these patients. There is also no evidence yet in support of using Mohs technique instead conventional wide surgical excision. Regional metastases, even if extensive, may benefit from at least partial surgical debulking, to reduce the size of non-healing, painful, malodorous or chronically infected lesions. Neither chemotherapy or radiotherapy has been shown to provide lasting benefit in the treatment of primary or secondary tumours. However, radiotherapy, like surgery, may be used for reducing the tumour mass. It does not appear to make blistering worse (J-D. Fine, unpublished data, 2002).

Treatment of epidermolysis bullosa simplex

Heat and humidity lower the threshold for blistering in patients with EB simplex, and measures to reduce both these factors are therefore important. Patients with Weber–Cockayne or Dowling–Meara EB simplex should wear well-fitting well-ventilated shoes, preferably with a soft inner lining. Cotton socks are preferable to wool or synthetic fibres, and double-layer sports socks provide extra protection from friction and absorb sweat well. The application of aqueous solutions containing alcohol or glutaraldehyde [43] has been found useful, but is not necessarily recommended as glutaraldehyde is potentially irritant and toxic. Iontophoresis and the application of aluminium chloride hexahydrate [44] have also been used in attempts to suppress sweating. However, in a controlled trial of 20% aluminium chloride hexahydrate for the treatment of Weber–Cockayne EB simplex, there was no difference between the active drug and placebo in suppressing blistering [45]. The observation that oral tetracycline may have been effective in reducing the rate of blistering in two patients with EB simplex [46] requires further evaluation [47].

Newer forms of treatment, including gene therapy

Newer, specific, methods of treating EB have been slow to emerge. However, it is likely that genetically engineered growth factors and other cytokines that are able to influence wound healing will soon be available for clinical trials, or even clinical practice. Such advances could clearly have an important impact on the management of chronic erosions in junctional and dystrophic EB, although their potential role in the treatment of lesions in internal organs, such as the oesophagus, may be less clear. There is a pressing need for an effective means to halt and possibly reverse the relentless progression of digital fusion and hand contractures seen in recessive dystrophic EB.

Although currently unavailable, gene therapy [48–53] is nevertheless a realistic goal for the future treatment of more severe autosomal recessive forms of EB. There are numerous obstacles, but each is potentially surmountable, given time and sufficient resources. Different methods of introducing DNA into skin or skin cells *ex vivo* are currently being explored. The objective is to introduce one normal allele into somatic cells that, in recessive forms of EB, would have two mutant genes. The strategy includes finding effective and safe methods for targeting 'normal' genes into the right place (e.g. the nucleus of an epidermal stem cell) and keeping the gene activated under controlled conditions. The introduced gene must be able to undergo transcription and translation in the synthesis of an appropriate product, such as a basement-membrane protein, which then has to be secreted by the cells and incorporated into the extracellular matrix in a way that will allow it to be functionally effective. The gene may be at risk of being rapidly degraded, neutralized (by autoantibodies), shed (inside a differentiating keratinocyte) or being otherwise inactivated.

For autosomal dominant disorders, including dominant dystrophic EB or EB simplex, the strategy is different. Under these conditions, rather than introduce a further normal gene, the objective is to try to inactivate or nullify the action of the mutant gene, which usually exerts a 'dominant-negative' effect on its normal paired allele. A major approach involves antisense DNA and RNA strategies [54], which currently are being explored particularly for use in the treatment of cancer.

A direct result of the recent advances in the molecular genetics of different forms of EB has been the development of DNA-based first-trimester prenatal diagnosis. This has already been used for the benefit of many couples at high risk of having affected children (see Chapter 13). The introduction of preimplantation genetic diagnosis will broaden the available options in the overall management of those affected by EB.

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Hailey–Hailey disease

SYN. FAMILIAL BENIGN CHRONIC PEMPHIGUS

[S.M. Burge, pp. 40.32–40.36]

Hailey–Hailey disease (McKusick No. 16960) is a rare intraepidermal blistering disease that is inherited as an autosomal dominant. The condition, which was described by the Hailey brothers in 1939, is characterized by recurrent vesicles and erosions usually affecting the neck, axillae and groins [1].

Aetiology. Hailey–Hailey disease is caused by mutations in *ATP2C1*, a gene on chromosome 3q21 that encodes a P-type calcium-transport adenosine triphosphatase (ATPase). This is the human homologue of an ATP-powered pump (PMR1) that sequesters calcium into the

Golgi in yeast. A number of mutations have been described but no phenotypic correlations identified [2–5]. An autosomal dominant pattern of inheritance has been confirmed in family studies [6,7]. Darier's disease, a condition that shares many clinical and pathological features with Hailey–Hailey disease, is caused by mutations in a gene that encodes another calcium ATPase located in the sarco-endoplasmic reticulum (SERCA) (see Chapter 34).

Pathogenesis. Calcium pumps have a key role in maintaining epidermal integrity, but it is not yet clear how loss of one functional allele of *ATP2C1* leads to the changes in adhesion that typify Hailey–Hailey disease. Calcium ATPases in the Golgi are important for protein sorting, processing and glycosylation, and cytosolic calcium is involved in cell signalling. The cellular processes that may be affected by the mutation in Hailey–Hailey disease include gene transcription, post-translational modifications of adhesion proteins, trafficking of adhesion proteins and the assembly of adhesion junctions.

The adhesion of cultured keratinocytes from patients with Hailey–Hailey disease is abnormal [8–10] and regulation of cytoplasmic calcium is impaired [2]. Plasminogen activation may potentiate acantholysis [11,12]. Acantholysis is reduced *in vitro* by corticosteroids, serine protease inhibitors and vitamin D_3 analogues, but not by retinoids [10,13].

UVB provokes acantholysis in patients and has been used to detect carriers of the disease gene [14]. The adhesion of cultured keratinocytes from Hailey–Hailey disease is impaired by UVB, but no more than the adhesion of keratinocytes from normal individuals. This suggests that other factors may be necessary for UVB to provoke acantholysis *in vivo* [15].

Sellotape stripping, friction, freezing, irritants, inflammation and suction induce acantholysis in the normal-looking skin of affected patients. Cutaneous bacterial or yeast infections may exacerbate disease [7,16].

Pathology. Acantholytic clefts and bullae form above the basal cells. The suprabasal cells separate partially from one another, so clusters of loosely coherent cells float in the bullae. Widespread partial acantholysis gives the epidermis the appearance of a 'dilapidated brick wall'. No intercellular deposits of IgG and complement are present in the epidermis.

The primary event appears to be dissolution of the desmosomal attachment plaque [17]. Tonofilaments separate from desmosomal plaques and aggregate in perinuclear whorls [18–20].

The components of desmosomes, adherens junctions, gap junctions and the cytoskeleton are distributed normally in uninvolved skin. Desmosomal components, E-cadherin and connexins are internalized in acantholytic cells [12,21–23] and extracellular epitopes of cadherins are lost [24]. P-cadherin, an adhesion protein expressed by basal cells in normal skin, is expressed by suprabasal acantholytic cells in Hailey–Hailey disease and other acantholytic conditions [25].

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Clinical features. The condition usually presents in the third or fourth decade [1,2]. Flaccid vesicopustules, crusted erosions or expanding circinate plaques appear in areas exposed to friction such as the sides of the neck, axillae, groins and perineum. Involvement may be restricted to one site but can be generalized [3,4]. Lesions extend peripherally, healing in the centre (Fig. 40.34). Flexural disease may be hypertrophic and malodorous with soft, flat, moist vegetations and fissures (rhagades) (Fig. 40.35). Itch and pain are common and flexural disease may be disabling, particularly if the groins are affected [2]. Even mild disease may reduce quality of life [5]. Asymptomatic longitudinal white bands are present in the nails of some patients (Fig. 40.36) [2] and fine palmar pits have been documented in one patient [6]. Mucosal involvement is rare, but conjunctival, oral, oesophageal and vaginal involvement have been described [2,7].

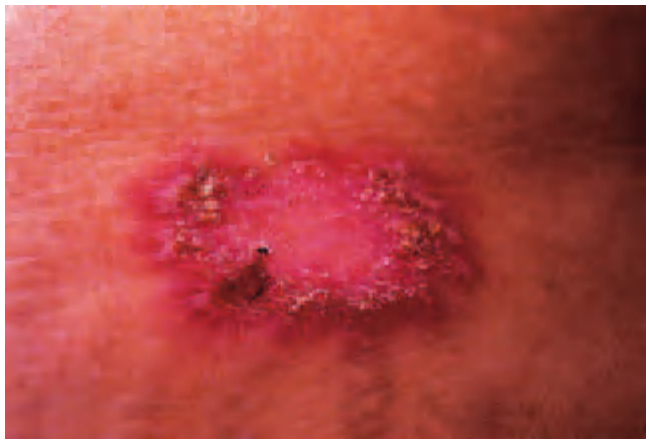

Fig. 40.34 Hailey–Hailey disease: spreading annular plaque with a crusted rim.

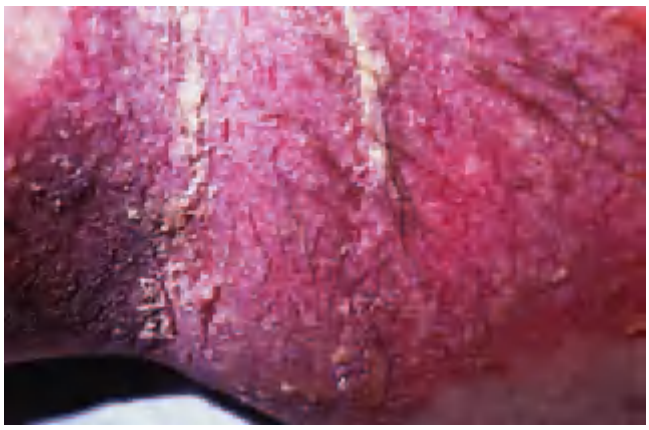

Fig. 40.35 Hailey–Hailey disease: typical hypertrophic malodorous axillary plaque with painful fissures (rhagades).

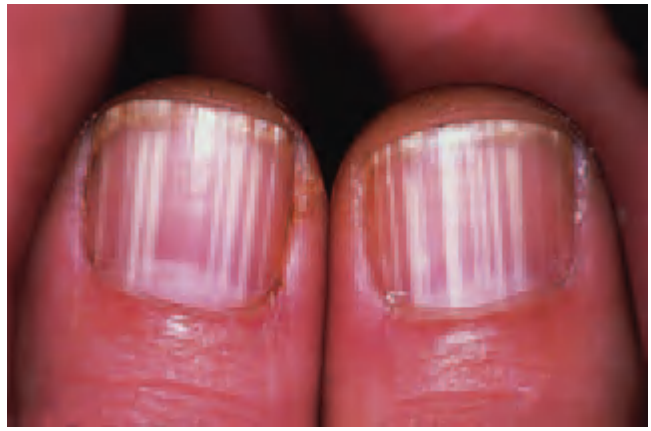

Fig. 40.36 Hailey–Hailey disease: longitudinal white bands in the nails may be a helpful diagnostic sign.

Complications. Herpes simplex virus causes painful exacerbations, which may be difficult to differentiate from vesicular Hailey–Hailey disease [8,9].

Contact dermatitis, both irritant and allergic, may exacerbate Hailey–Hailey disease [10,11], but the overall frequency of positive patch tests is probably not increased [12].

Rarely, carcinomas have arisen in skin affected by Hailey–Hailey disease, sometimes in association with human papillomavirus (HPV) [13–16].

Prognosis. Long remissions are common and many patients improve in old age [1,2].

Clinical differential diagnosis. Misdiagnosis is frequent [17,18]. Lesions may simulate impetigo, impetiginized eczema, *Candida* intertrigo or tinea corporis. Hypertrophic vulval lesions may suggest malignancy [2]. Diagnostic difficulties are compounded because Hailey–Hailey disease may respond to treatments such as antibacterials or topical steroids that are used for some of these conditions. Longitudinal white bands in the nails may confirm the diagnosis [2,19].

Vegetating flexural disease occurs in both pemphigus vegetans and Darier's disease. Oral lesions distinguish pemphigus vegetans. Darier's disease is characterized by hyperkeratotic papules as well as a distinctive nail dystrophy (see Chapter 34).

Localized perineal papules and plaques with an acantholytic histology have been reported in patients without other features of Hailey–Hailey disease [20–22]. The relationships between this condition, Hailey–Hailey disease and Darier's disease might be clarified by genetic studies.

Histological differential diagnosis. Hailey–Hailey disease must be differentiated from Darier's disease and pemphigus. Epidermal hyperplasia and suprabasal separation occur in both Darier's disease and Hailey–Hailey disease, but acantholysis tends to be more widespread in fully developed lesions of Hailey–Hailey disease, whereas dyskeratosis with corps ronds and grains is more prominent in Darier's disease [23]. In pemphigus, the acantholytic cells are less well preserved and immunoglobulin and complement are deposited between the keratinocytes.

Investigations. The diagnosis should be confirmed by skin biopsy. Skin swabs should be cultured if infection is suspected but herpes simplex virus may be difficult to culture and Tzank smears, biopsy, electron microscopy or polymerase chain reaction have been recommended if this infection is suspected [24,25]. Patch testing should be considered in patients with long-standing disease.

Treatment. Loose, cool clothing will reduce friction and sweating. Absorbent pads may be helpful to keep flexures dry and thus reduce bacterial overgrowth.

No controlled therapeutic trials have been performed.

Eighty-six per cent of 58 patients found combinations of moderate to potent topical corticosteroids with antibacterial agents effective in one series. Topical steroids were most effective if applied promptly to early lesions [2]. Very potent topical corticosteroids (clobetasol propionate) with antibiotics and/or antifungals controlled disease in seven patients, but the skin atrophied in four patients who had continued to apply the steroid [26]. Potent steroids may be required for severe disease, but the strength of steroid should be reduced if possible. Rarely, systemic corticosteroids may be required for widespread disease [3,18,27].

The role of antiseptics, antibiotics and/or topical antifungal agents as steroid-sparing agents is unproven, but long-term anti-staphylococcal treatment appears to be helpful [2,18,28]. Topical tetracycline, fusidic acid and imidazoles may be added to a topical corticosteroid. Low-dose oral tetracyclines, erythromycin or flucloxacillin should also be considered. Oral treatment of herpes simplex should be considered in patients with unresponsive painful disease.

Although ultraviolet light may exacerbate Hailey–Hailey disease, PUVA was effective in six patients [29,30] and suberythemal UVB controlled both psoriasis and coexisting Hailey–Hailey disease in one patient [31]. Superficial (grenz) rays produced remissions of several months in six patients [32].

Recommendations for many treatments have been made on the basis of individual cases and evidence for the efficacy of any of the following is poor: ciclosporin topically and orally (3–4 mg/kg/day) [33–35], dapsone [36], methotrexate [37], thalidomide [38], oral calcitriol [39] and a topical vitamin D_3 analogue [40]. Oral retinoids have been prescribed with variable outcomes [41,42]. Botulinum toxin [43] reduced axillary sweating and improved disease in one patient.

The long-term benefit of any surgical approach is equally uncertain, but many have been recommended for recalcitrant disease including cryosurgery [18], full-thickness excision with or without split-thickness grafting [44,45], dermabrasion [46], carbon dioxide laser vaporization [47], erbium:YAG laser ablation [48], electrodesiccation [49] and breast reduction [50].

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Linear acantholytic dermatosis

A linear acantholytic dermatosis has been described affecting one side of the body and following the lines of Blaschko [1,2]. This pattern might be explained by cutaneous mosaicism for the *ATP2C1* mutation just as mosaicism for *ATP2A2* may underlie segmental Darier's disease [3].

A patient with a family history of Hailey–Hailey disease had mild generalized disease, but superimposed on this background she had pronounced erythema and blistering arranged in a unilateral pattern following the lines of Blaschko. The authors hypothesize that the individual has a germ-line mutation affecting one allele but, in addition, a post-zygotic mutation affects the other allele resulting in loss of heterozygosity. The linear manifestations may be more severe because keratinocytes in this area are homozygous for the mutation [4].

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Chapter 41

Immunobullous Diseases

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Introduction

The bullous diseases discussed in this chapter, although uncommon, have a dramatic impact on the patient and their family and have severe economic consequences for the family and health services. These diseases have been the subject of intensive investigation in recent years, and the study of both the genetic and autoimmune diseases has made major contributions to our knowledge of the biology of the skin. The identification of the target antigens for the autoantibodies in the autoimmune bullous diseases has led to the discovery of many components of the desmosome and the adhesion complex linking the epidermis to the dermis (Fig. 41.1; also see Fig. 41.11). In parallel with this work has been the realization that mutations of these same proteins are the basis of some of the genetic bullous diseases. The molecular biology of the genetic abnormalities is beginning to reveal how the fine structure of these proteins enables them to perform their function (see Chapter 40).

The immunological diseases are classified largely by their clinical presentation, histopathology and immunopathology. The increased use of immunoblotting and immunoelectron microscopy to define these diseases has revealed that the target antigens and the specific epitopes may be common to more than one clinical entity. Thus, the clinician is still the final arbiter for diagnosis.

A comprehension of the ultrastructural anatomy and composition of the areas under discussion greatly facilitates understanding the diseases that produce chronic blistering of the skin and mucous membranes (see Chapter 3).

The immunobullous diseases are characterized by pathogenic autoantibodies directed at target antigens whose function is either cell–cell adhesion within the epidermis, or adhesion of stratified squamous epithelium to dermis or mesenchyme. These target antigens are components of desmosomes or of the functional unit of the basement-membrane zone known as the adhesion complex and are shown in Figs 41.1 and 41.11. The clinical, immunopathological and immunogenetic features of these diseases are shown in Tables 41.2, 41.3, 41.5 and 41.6. Dermatitis herpetiformis is the one possible exception, as the relevant target antigen has not yet been identified.

The most important techniques for the investigation of patients with immunobullous disease are histopathology, and direct and indirect immunofluorescence. Research techniques such as immunoblotting and immunoelectron microscopy may refine the diagnosis in the individual patient but do not replace the clinician [1].

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Intercellular adhesion in the epidermis

Adhesion between keratinocytes is mediated predominantly by cell adhesion molecules of the cadherin family localized in two specialized intercellular adhesion junctions: desmosomes (*maculae adherentes*) and intermediate or adherens junctions (*zonulae adherentes*). The desmosomes are small electron-dense structures that link the

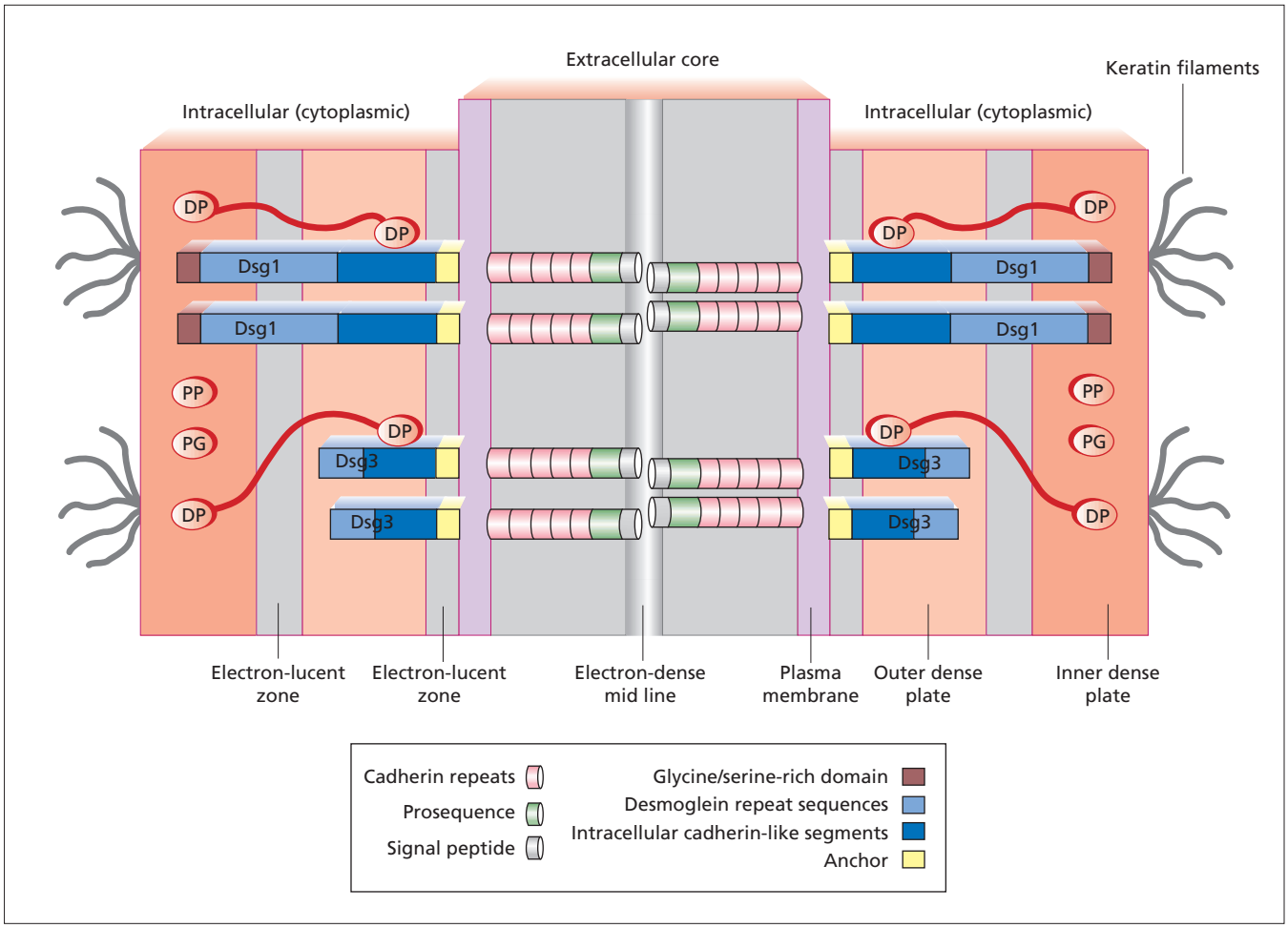

Fig. 41.1 Diagrammatic representation of the molecular components of the desmosome. DP, desmoplakin; Dsg1, desmoglein 1; Dsg3, desmoglein 3; N, amino terminal; PG, plakoglobin; PP, plakophilin. (Courtesy of Dr J. Allen, Oxford Radcliffe Hospital, Oxford, UK.)

intermediate filament within cells to the plasma membrane and to adjacent cells. The possible arrangement of desmosomal components is illustrated in Fig. 41.1. The major adhesion components of the desmosome are the desmosomal cadherins, desmogleins and desmocollins. The cadherins are transmembrane glycoproteins each having an extracellular domain, a transmembrane domain and a cytoplasmic domain that links to the cytoskeleton. Adhesion is probably regulated by complex interactions between the cytoplasmic domains of cadherins and cytoplasmic proteins such as catenins or plakoglobin [1–3]. For a detailed discussion see Chapter 3.

The desmoglein subfamily comprises at least three related proteins: desmogleins 1, 2 and 3. Desmoglein 1 is recognized by sera from patients with the autoimmune blistering disease pemphigus foliaceus and some with pemphigus vulgaris. It is also the target of protease-mediated damage by staphylococcal exotoxins [4]. Desmoglein 3 is the target antigen in pemphigus. The desmocollins are also a family of proteins that exist in more than one isoform. Desmocollin 1 is recognized by sera from some patients with immunoglobulin A (IgA) pemphigus.

The expression of desmosomal cadherins varies during differentiation, and expression in human skin differs from that in mucosal epithelium. Desmoglein 3 is expressed only in the basal and suprabasal layers of the epidermis whereas desmoglein 1 is found throughout the epidermis, particularly in the higher layers [5–7]. In mucosae, desmoglein 3 is strongly expressed throughout, whereas desmoglein 1 is expressed only weakly [8,9]. In neonatal epidermis, the distribution of desmogleins resembles that of the adult mucosa [10,11].

Desmosomes have well-defined submembranous plaques containing non-glycosylated proteins plakoglobin, desmoplakins 1 and 2 and plakophilin. Plakoglobin, present in both desmosomes and adherens junctions, may interact with cadherins to regulate adhesion [12,13]. Desmoplakins 1 and 2 belong to a multigene family of

intermediate filament organizing proteins, which includes the bullous pemphigoid antigen (BP230), present in the hemidesmosomes of the basement-membrane zone, and plectin, a widely distributed intermediate filament associated protein [12]. Less well-characterized plakins localizing to the desmosome are envoplakin and periplakin [14]. Plakin autoantibodies are present in the blistering disease, paraneoplastic pemphigus, a condition that is associated with lymphoid malignancies, thymomas or poorly differentiated sarcomas [15]. Keratin intermediate filaments insert into the desmosomal plaque, where their amino termini interact with the carboxy termini of desmoplakin. Desmoplakins and plakoglobin, and possibly also plakophilin 1, are attached to the desmosomal cadherins and to each other in a complex arrangement [16,17].

Adherens junctions

Epithelial cadherin (E-cadherin) is present in adherens junctions. Interactions between cytoplasmic domains on E-cadherin and cytoplasmic proteins called catenins are essential for normal adhesion. Plakoglobin, which is similar in structure to β-catenin, may also form complexes with E-cadherin [12]. Vinculin and α-actinin, cytoplasmic proteins present in adherens junctions, may link to bundles of actin microfilaments to influence the organization of the filaments. These are not currently identified as target antigens in immunobullous diseases.

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Intraepidermal immunobullous diseases

Blisters form within the epidermis in the pemphigus group of immunobullous diseases. The antibodies in these diseases react with intercellular adhesion molecules. Immunoreactants are deposited between keratinocytes, intercellular bridges disappear and keratinocytes separate from one another, a change known as acantholysis.

Pemphigus

Definition. Pemphigus is derived from the Greek, *pemphix*, meaning blister or bubble. The term 'pemphigus' once covered most of the bullous eruptions of the skin, but diagnostic tests have improved and the bullous diseases have been reclassified. A number of distinct subgroups of pemphigus have emerged and many of the autoantigens have been identified. The antibodies are directed against epidermal cadherins, a family of calcium-dependent cell–cell adhesion molecules. The two major subtypes, pemphigus vulgaris and pemphigus foliaceus, are distinguished by the level of cleavage within the epidermis. Splitting is suprabasal in pemphigus vulgaris and its rare vegetating form, pemphigus vegetans. Blistering is more superficial in pemphigus foliaceus and related subtypes.

The classification of pemphigus, its clinical features, immunopathology and immunogenetics are summarized in Tables 41.1–41.3.

Table 41.1 Types of pemphigus.

Pemphigus vulgaris
variant: pemphigus vegetans
Pemphigus foliaceus
variant: pemphigus herpetiformis
variant: pemphigus erythematosus
Induced pemphigus
Intercellular IgA dermatosis
Paraneoplastic pemphigus

Table 41.2 The intraepidermal immunobullous diseases: clinical features.

Disease	Patients	Cutaneous distribution	Mucosal involvement	Lesions	Disease associations	Treatment	Prognosis
Pemphigus vulgaris	Middle age	Scalp, face, flexures, may be generalized	Always oropharynx, conjunctiva, genital	Flaccid blisters, erosions, flexural vegetations	Autoimmune disease, thymoma	Steroids, immunosuppressives, dapsone	Variable, may remit
Pemphigus vegetans	Middle age	Flexural	Oral	Vesicles, pustules, erosions, vegetating plaques		Steroids, immunosuppressives, dapsone	Variable, may remit
Pemphigus foliaceus	Middle age	Scalp, face, chest, upper back, rarely generalized 'seborrhoeic'	None	Scaly papules, crusted erosions, erythroderma		Steroids (topical, intralesional, systemic), immunosuppressives	Benign but chronic
Endemic pemphigus foliaceus	Children, young adults	Head, neck, generalized	Uncommon	Flaccid blisters, erosions, verrucous lesions, erythroderma		Steroids, immunosuppressives, antimalarials	Chronic mortality < 10%
Intercelluar IgA dermatosis	Adults children	Axillae, groins, face, scalp, proximal limbs	Uncommon	Flaccid pustules annular or circinate configuration	IgA monoclonal gammopathy	Dapsone	Chronic indolent
Paraneoplastic pemphigus	Adults, children	Upper body, palmo-plantar	Severe mucositis	Polymorphous, bullae, erosions, 'target lesions'	Lymphoproliferative disease, Castleman's, other malignancies	Tumour resection, steroids, immunosuppression	Very poor

Table 41.3 The intraepidermal immunobullous diseases: immunopathology and immunogenetics.

							Immunogenetics
Disease	Direct IMF	Isotype	Target antigens	Antigens (kDa)	Epitopes	Location	MHC class I and II
Pemphigus vulgaris/ pemphigus vegetans	Intercellular	IgG, (few IgM, IgA)	Desmoglein 3 Sometimes desmoglein 1 desmocollins	130	Amino-terminal of extracellular domain	Desmosome	DRB1*0402 DRB1*14
Pemphigus foliaceus	Intercellular	IgG	Desmoglein 1 Sometimes desmocollins	160	Amino-terminal of extracellular domain	Desmosome	HLA-DRB1*14
Endemic pemphigus foliaceus	Intercellular	IgG	Desmoglein 1 Sometimes desmocollins	160	Amino-terminal of extracellular domain	Desmosome	Several susceptibility alleles, all with same amino acid sequence in *DRB-1* gene DRB1*0102 DRB1*0404, *1402 or *1406
Paraneoplastic pemphigus	Intercellular and subepidermal	IgG	Plakins (desmoplakin, envoplakin BP230, periplakin)		Various	Desmosomes, BMZ; stratified, simple and transitional epithelia	Unknown

BMZ, basement-membrane zone; HLA, human leukocyte antigen; IMF, immunofluorescence; MHC, major histocompatibility complex.

Pemphigus vulgaris

Aetiology. Pemphigus vulgaris affects all races and both sexes [1]. It is a disease of middle age that affects children rarely, but patients are younger at presentation in India than in Western countries [2].

Pemphigus vulgaris accounts for approximately 70% of all cases of pemphigus and may be the most common autoimmune blistering disease in eastern countries, such as India, Malaysia, China and the Middle East [2,3]. The Jewish race, especially Ashkenazi Jews, have an increased susceptibility to pemphigus vulgaris [1]. In South Africa, pemphigus vulgaris is more common in Indians than in black or white races [4]. Pemphigus is less common in the West.

Predisposition to pemphigus is linked to genetic factors. First-degree relatives of patients with pemphigus vulgaris are more susceptible to the development of autoimmune diseases than controls [5,6] and have a higher incidence of circulating antidesmoglein antibodies [7]. Certain major histocompatibility complex (MHC) class II genotypes, in particular alleles of HLA-DRB1*04 and DRB1*14 subtypes, are common in patients with pemphigus vulgaris across racial barriers [8–11]. These alleles produce amino acid substitutions in the HLA-DRB1 peptide-binding sites, which may influence antigen presentation and recognition by T cells [11,12]. Susceptibility may also be determined by genes encoding immunoglobulins [13]. Pemphigus occurs in patients with other disorders characterized by immunological disturbances. Thymoma or myasthenia gravis have been reported in a number of patients; some have all three diseases [1]. Pemphigus may develop in patients with lupus erythematosus (see p. 41.16). Bullous pemphigoid (BP) and pemphigus have coexisted [14]. Pemphigus has been reported in patients with lymphoproliferative diseases such as Castleman's tumours (see p. 41.22). Viral DNA (herpes simplex, Epstein–Barr virus, human herpesviruses 6 and 8) has been detected in some skin biopsies or peripheral blood mononuclear cells from pemphigus patients [15,16] and pemphigus has coexisted with HIV infection [17].

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Pathogenesis. Autoantibodies against the surface of keratinocytes occur in pemphigus and both clinical and experimental observations indicate that the circulating autoantibodies are pathogenic [1].

Pemphigus vulgaris antigen. The pemphigus vulgaris antigen, also known as desmoglein 3, is a desmosomal cadherin involved in mediating intercellular adhesion in the epidermis [2]. The antibody binds to an extracellular domain on the amino-terminal region of desmoglein 3 where it may have a direct effect on the function of the desmosomal cadherins [3,4].

Desmoglein 3 is found in desmosomes [4] and possibly elsewhere on the cell membrane of keratinocytes [5]. It is detected early in keratinocyte differentiation, primarily in the lower epidermis [6–9] and is expressed more strongly in buccal mucosa and scalp skin than in skin from the trunk [10]. This contrasts with the pattern of expression of the pemphigus foliaceus antigen, desmoglein 1, which is present throughout the epidermis, more intensely in the upper layers, but only weakly expressed in mucosae [11].

Where both desmogleins are expressed, one molecule is able to compensate for the loss of function of the other [12] and the distribution of lesions in different forms of pemphigus is consistent with the distribution of the desmogleins. Those pemphigus vulgaris patients with only desmoglein 3 antibodies tend to have lesions limited to the mucous membranes [13–15], where the relative lack of desmoglein 1 is unable to compensate and prevent

acantholysis. Pemphigus vulgaris patients with both desmoglein 3 and desmoglein 1 antibodies develop widespread mucocutaneous blistering [13,15,16] with skin blisters confined to the suprabasal epidermis, the location where both cadherins appear to be essential to maintain cell–cell adhesion. In cases evolving from mucosal dominant to mucocutaneous pemphigus vulgaris or from pemphigus vulgaris to pemphigus foliaceus, or more rarely vice versa, the shift in clinical features correlates with changes in the reactivity of the serum against the pemphigus antigens [17–21]. Although there is homology between desmogleins 1 and 3, the antibodies are not thought to be cross-reactive. One interpretation for this phenomenon is epitope spreading (tissue damage from a primary autoimmune or inflammatory response results in exposure of new epitopes on the same or another molecule to produce a secondary autoimmune response) [22]. However, a dual antibody response is not necessarily a feature only of late disease and may be present from the onset in mucocutaneous pemphigus vulgaris. Conversely, cases of antidesmoglein 3 mucosal pemphigus vulgaris may have neither clinical nor serological progression over many years of follow-up [23]. Antidesmoglein 1 antibodies are more common in Indian patients, suggesting that antibody profile does not simply reflect disease duration but is determined by other, possibly racial factors [23].

Pemphigus vulgaris sera may also contain autoantibodies to desmocollins [24,25]. Antibodies to non-cadherin antigens have also been reported. Antidesmoplakin in addition to antidesmoglein antibodies occurred in one patient but were not thought to be pathogenic [26]. Others report antibodies to cholinergic receptors and claim pathogenicity [27]. Although interesting, given the association of pemphigus with myasthenia gravis, this conclusion is disputed [28].

Antibodies. Patients with active disease have antibodies of both IgG1 and IgG4 subclasses, but the IgG4 antibodies are pathogenic [29,30]. Autoantibody production is T-cell dependent; autoreactive Th1 and Th2 cells specific for desmoglein 3 occur in pemphigus vulgaris [31]. Antibody–antigen complexes are found on desmosomes in early pemphigus lesions [32]. Immunohistological studies have revealed abnormalities in the staining pattern for desmosomal components, possibly secondary to the binding of the autoantibodies [12,33].

The pathogenicity of pemphigus vulgaris antibodies is suggested by several lines of evidence. Most studies have shown a correlation between disease activity and titre of antibody [34,35]. Transplacental transfer of maternal pemphigus vulgaris antibodies may cause transient blisters in the newborn [36]. In the neonatal mouse model, passive transfer of pemphigus vulgaris IgG causes suprabasal acantholysis [37]. Blistering is prevented by prior absorption of antibodies with the extracellular domain of the pemphigus vulgaris antigen [38]. Acantholysis can be induced in mice by antidesmoglein 3 antibodies alone but is greatly enhanced by addition of antidesmoglein 1 antibodies [39]. Pemphigus antibodies can induce acantholysis in mice deficient in complement, but the presence of complement amplifies blistering [40].

Complement and inflammatory mediators. Pemphigus IgG added to a skin organ culture or to cultures of epidermal cells induces acantholysis without requiring complement [41], but complement enhances pathogenicity. Pemphigus antibody fixes components of complement to the surface of epidermal cells [42]. Antibody binding may activate complement with the release of inflammatory mediators [43] and recruitment of activated T cells [44]. Complement activation in pemphigus is increased by interleukin-1α (IL-1α) and tumour necrosis factor-α (TNF-α) [45]. IL-1, thromboxane B_2 and leukotriene B_4 are present in blister fluid [43]. TNF-α and IL-6 are found in serum and lesional skin of pemphigus patients [46]. Their role in acantholysis is unknown.

Proteases. Several lines of evidence suggest that the plasminogen–plasmin system may be involved in the acantholytic process. Plasminogen activators and plasmin activity can be detected in the fluid taken from pemphigus blisters [47,48]. Keratinocytes in lesional epidermis may express tissue plasminogen activator when stimulated by contact with plasma [49]. Proteinase inhibitors, antibodies to plasminogen activators and inhibitors of plasminogen activators block the acantholysis induced by pemphigus antibodies in experimental models [47,50]. However, acantholysis induced by pemphigus antibodies occurs in plasminogen activator knockout mice, indicating that plasminogen activation is not a prerequisite [51]. The activity of plasminogen activator does not always correlate with disease activity in models of pemphigus [52], nor does proteolysis account for all the ultrastructural changes seen in epidermal cells injured by pemphigus vulgaris antibodies [53], but plasmin may amplify epidermal damage.

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Pathology. The earliest changes consist of intercellular oedema with loss of intercellular attachments in the basal layer. Suprabasal epidermal cells separate from the basal

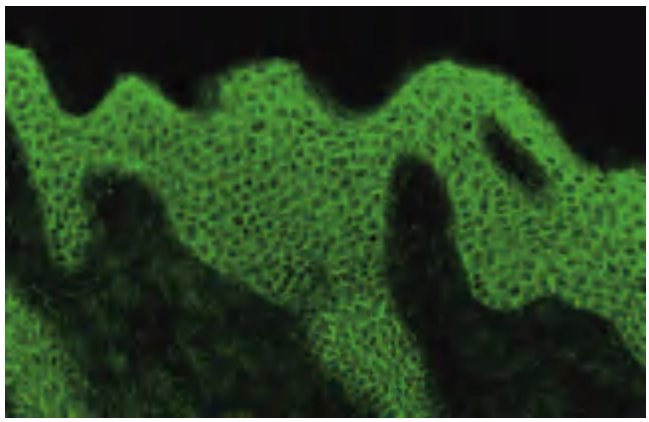

Fig. 41.2 Immunofluorescence showing intercellular IgG throughout the epidermis of a patient with pemphigus vulgaris.

cells to form clefts and blisters. Basal cells remain attached to the basement membrane but separate from one another and stand like a 'row of tombstones' on the floor of the blister. Blister cavities contain some acantholytic cells. A smear taken from the base of a blister or an oral erosion (Tzanck preparation) contains acantholytic cells. Clefting may extend into the walls of adnexae. Blistering is preceded by eosinophilic spongiosis in some cases. The superficial dermis has a mild superficial mixed inflammatory infiltrate which includes some eosinophils [1].

Electron microscopy has shown that widening of the intercellular space is followed by splitting of the desmosome junctions. When the cells separate from each other, the intracellular cytokeratin tonofilaments retract around the nucleus and the desmosomal plaques disappear. The attachment of basal cells to the basement membrane is not affected [2,3].

The diagnosis of pemphigus is confirmed by direct immunofluorescence, which shows IgG deposited on the surface of keratinocytes throughout the epidermis, in and around lesions (Fig. 41.2). IgG1 and IgG4 are the most common subclasses. Complement components (C3), IgM and IgA are present less frequently than IgG. Direct immunofluorescence may be the most sensitive method for diagnosing oral pemphigus (Table 41.5) [4].

Circulating pemphigus autoantibodies are detected by indirect immunofluorescence in over 80% of patients. The use of more than one substrate improves sensitivity, oesophageal substrate being preferable for the detection of desmoglein 3 antibodies [5]. A disadvantage of immunofluorescence methods is the difficulty distinguishing pemphigus vulgaris from pemphigus foliaceus on the staining pattern. Recombinant desmogleins (desmogleins 1 and 3) have been used recently to develop a sensitive and specific enzyme-linked immunoabsorbent assay (ELISA) for serodiagnosis of pemphigus [6,7]. Using ELISA, over 95% of pemphigus vulgaris patients have detectable antidesmoglein 3 antibodies and approximately 50% have antidesmoglein 1 antibodies. In appropriate dilutions, ELISA can be used to monitor disease activity [8].

Antibodies may be detected in patients without pemphigus [9]. Pemphigus-like circulating intercellular antibodies have been reported in conditions such as thermal burns [10], toxic epidermal necrolysis [9], penicillin reactions [11] and in first-degree relatives of relatives of pemphigus patients [12,13].

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Clinical features. All patients have mucosal lesions, but pemphigus vulgaris presents with oral lesions in 50–70% of patients. These may precede cutaneous lesions by months or be the only manifestation of the disease [1–3]. Intact bullae are rare in the mouth. More commonly, patients have ill-defined, irregularly shaped buccal or palatal erosions, which are slow to heal (Fig. 41.3). The erosions extend peripherally with shedding of the epithelium [4]. Other mucosal surfaces may be involved including the conjunctiva [5], nasal, pharynx [6], larynx, oesophagus [7,8], urethra, vulva [9] and cervix [10].

Most patients develop cutaneous lesions. Involvement may be localized or generalized, but the disease has a predilection for the scalp, face, axillae, groins and pressure points (Figs 41.4 & 41.5). Flaccid blisters filled with

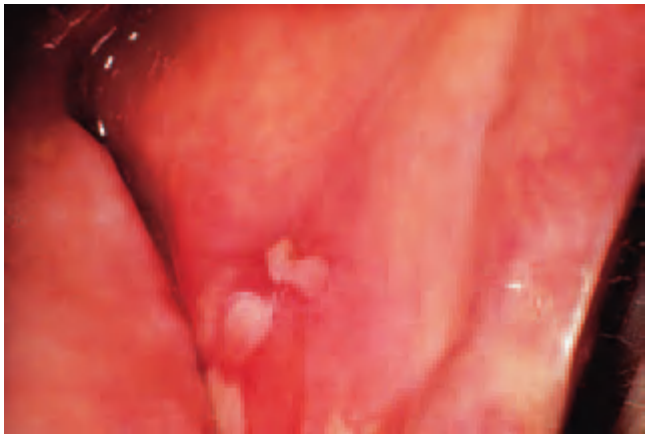

Fig. 41.3 Pemphigus vulgaris. Erosions in mouth. (Courtesy of Dr R.J. Pye, Addenbrooke's Hospital, Cambridge, UK.)

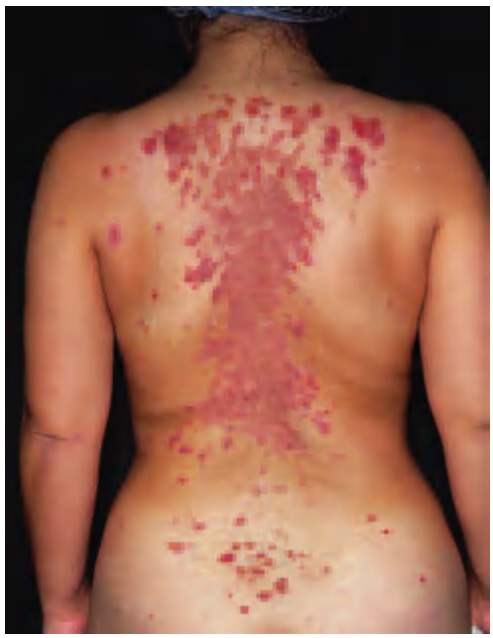

Fig. 41.4 Pemphigus vulgaris. Erosions and healing areas on the back. (Courtesy of Dr R.J. Pye, Addenbrooke's Hospital, Cambridge, UK.)

clear fluid arise on normal skin or an erythematous base. The contents soon become turbid or the blisters rupture producing painful erosions which extend at the edges as more epidermis is lost. At this stage, firm sliding pressure with a finger will separate normal-looking epidermis from the dermis producing an erosion (Nikolsky's sign). Nikolsky's sign is positive in pemphigus and more rarely in toxic epidermal necrolysis. Blisters can also be extended by vertical pressure, a phenomenon that occurs in many blistering diseases. Healing occurs without scarring but pigmentary change and acanthomas may occur in resolving lesions [11].

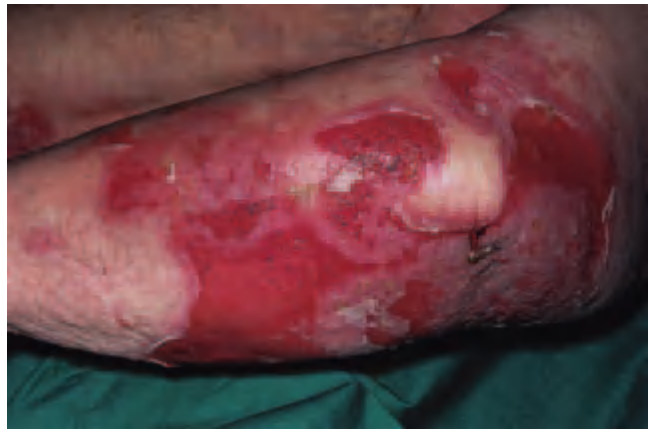

Fig. 41.5 Pemphigus vulgaris. Flaccid bullae and erosions on the forearm. (Courtesy of Dr R.J. Pye, Addenbrooke's Hospital, Cambridge, UK.)

Lesions in skin folds readily form vegetating granulations, and flexural pemphigus vulgaris merges with its variant pemphigus vegetans. Nail dystrophies, acute paronychia and subungual haematomas have been observed in pemphigus [12,13].

Severe pemphigus in pregnancy may be associated with fetal prematurity and death, but it is difficult to separate the effects of treatment from those of the disease. Generally the baby is healthy [14], although neonatal pemphigus may occur with mucosal or mucocutaneous lesions which are generally short-lived [15–17].

Prognosis. The severity and natural history are variable, but before treatment with steroids most patients with pemphigus vulgaris died [18]. Treatment with systemic steroids has reduced the mortality to between 5 and 15% [2,19], but some of these patients succumb to complications of therapy. Morbidity and mortality are related to the extent of disease, the maximum dosage of prednisolone required to induce remission and the presence of other diseases [2,18,20–22]. Disease activity generally decreases with time and most relapses occur in the first 2 years after diagnosis [23]. The outlook is worse in Jews [19] and in older patients [22].

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Pemphigus vegetans

Definition. Pemphigus vegetans is a rare variant of pemphigus vulgaris that is characterized by vegetating erosions, primarily in flexures. Two subtypes are recognized: Neumann pemphigus vegetans and Hallopeau pemphigus vegetans. These may be considered to form a clinical spectrum from the severe Neumann type to the mild Hallopeau type [1].

Aetiology/pathogenesis. Antibodies react with the 130-kDa pemphigus vulgaris antigen and possibly other antigens in both types of pemphigus vegetans [2–6]. Antibodies in the Hallopeau type also react with desmocollins 1 and 2 [7].

Complement fixation might stimulate the marked infiltration of neutrophils and eosinophils that is so typical in pemphigus vegetans [3].

Pathology. The vegetating lesions are hyperkeratotic, papillomatous and acanthotic. Some suprabasal clefts may contain eosinophils but few acantholytic cells are present. Intraepidermal eosinophilic abscesses may be present in older lesions. Early lesions in the Neumann type show suprabasal acantholysis and intraepidermal vesicles without eosinophils. Eosinophilic spongiosis or eosinophilic microabscesses are common in the early pustular lesions of the Hallopeau type [8]. The dermis contains a heavy infiltrate of lymphocytes and eosinophils with a few neutrophils.

Direct immunofluorescence demonstrates intercellular IgG, sometimes with C3. Circulating intercellular antibodies can be detected in most patients by indirect immunofluorescence (Table 41.5).

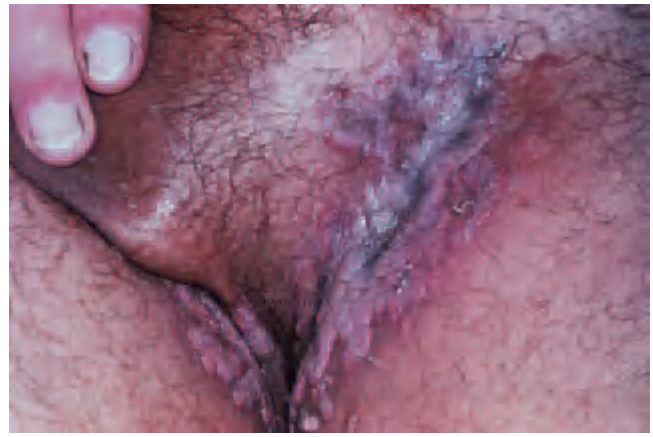

Fig. 41.6 Pemphigus vegetans. Vegetations with no evidence of blistering. (Courtesy of Dr R.J. Pye, Addenbrooke's Hospital, Cambridge, UK.)

Clinical features. The disease starts at a slightly earlier age than pemphigus vulgaris. Involvement of the oral mucosa is almost invariable. Lesions are primarily flexural although vegetations may occur at any site (Table 41.4) [8].

Neumann type (Fig. 41.6). Vesicles and bullae rupture to form hypertrophic granulating erosions, which bleed easily. The lesions evolve into vegetating masses exuding serum and pus. The edges are studded with small pustules. Erosions at the edge of the lesions induce new vegetations. In time, the vegetations become dry, hyperkeratotic and fissured.

Hallopeau type (syn. pyodermite végétante, pyoderma vegetans). Pustules rather than vesicles characterize early lesions but these soon progress to vegetating plaques. As in the Neumann type, the vegetations are studded with pustules. In one patient, pemphigus foliaceus preceded the onset of pemphigus vegetans of Hallopeau [9].

Prognosis. The course of Neumann type of pemphigus vegetans is similar to pemphigus vulgaris but is generally prolonged. The Hallopeau type is more benign and spontaneous remission is possible.

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Differential diagnosis of pemphigus vulgaris and pemphigus vegetans. Patients with mucosal lesions present to dental surgeons, oral surgeons and gynaecologists. Erosions may simulate acute herpetic stomatitis, erythema multiforme, aphthous ulcers or bullous lichen planus. Bullae are transient in the mouth and biopsies of erosions may not be diagnostic. Smears taken from the base of an erosion may show acantholytic cells (Tzanck's preparation). Direct immunofluorescence is the most accurate way to diagnose mucosal pemphigus [1]. Specimens may be posted to a suitable laboratory in Michel's medium if facilities for snap freezing and storage of the tissues are not available [2]. Indirect immunofluorescence may be a useful confirmatory test.

The diagnosis is less difficult when the patients have cutaneous blisters or erosions. Blisters in pemphigoid are tense and may be haemorrhagic. A smear taken from the base of a blister in pemphigoid (Tzanck's preparation) has no acantholytic cells. The diagnosis of pemphigoid is confirmed histologically by showing subepidermal bullae with immunoreactants in the basement-membrane zone.

Acute erythema multiforme is a short-lived disorder that may blister, but is easily differentiated from pemphigus histologically. Blistering in dermatitis herpetiformis is subepidermal and direct immunofluorescence of involved and uninvolved skin shows a granular deposition of IgA in the basement-membrane zone.

Vegetating pustular lesions in flexures must be differentiated from chronic infections or Hailey–Hailey disease (benign familial chronic pemphigus). Vegetating plaques mimicking pemphigus vegetans have been seen in IgA pemphigus [3] and paraneoplastic pemphigus [4]. The hyperkeratotic lesions of chronic pemphigus vegetans may simulate cutaneous tumours. The histology may be misinterpreted if immunofluorescence studies are not performed [5].

The histological differential includes Darier's disease, Hailey–Hailey disease and Grover's disease (transient acantholytic dermatosis). These conditions have distinctive clinical features in addition to negative immunofluorescence studies. Eosinophilic spongiosis may be an early histological manifestation of either pemphigus or bullous pemphigoid [6]. Immunofluorescence studies are needed to confirm the diagnosis.

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Treatment of pemphigus vulgaris and pemphigus vegetans. The introduction of corticosteroids has greatly reduced mortality, but a significant morbidity remains [1]. Numerous steroid regimens, with and without immunosuppressive agents, have been recommended but sound clinical evidence for many of these regimens is lacking because the rarity of pemphigus has precluded controlled trials. Treatment has been the subject of a number of reviews [2–4].

Monitoring activity of disease. In the acute phase, the progress of the disease should be evaluated by the clinical findings. Once blistering stops and erosions heal, changes in the titre of circulating pemphigus antibody may be helpful in gauging the dosage of steroids [5,6]. Direct immunofluorescence studies of normal skin have also been recommended to predict remission or relapse [6].

Topical therapy. Patients who present with oral disease and mild cutaneous involvement may remain in this localized phase for months. Potent topical or intralesional steroids may reduce the requirement of oral steroids. Good oral hygiene, including treatment of periodontal disease, is important.

Opportunist infection is the major cause of death in patients with widespread blistering who are also immunosuppressed. Potassium permanganate and topical antiseptics may help reduce the risk of cutaneous infection,

while topical nystatin, amphotericin or one of the imidazoles will reduce the risk of oral *Candida*.

Systemic therapy. Prednisolone with an adjuvant is the preferred treatment for pemphigus vulgaris [3]. Prednisolone 1.0–1.5 mg/kg/day in combination with topical or intralesional steroids is sufficient to control disease in many patients. The dosage should be titrated to the clinical response [7] but it is important to stop oral steroids when the disease is inactive rather than maintain patients on a homoeopathic dose [8].

Patients with generalized disease may require more aggressive immunosuppression to suppress blistering, but the major difficulty in managing these patients is achieving a balance between the adverse effects associated with high-dose steroid therapy and those of poorly controlled disease. High dosage of prednisolone of 120–240 mg/day has been recommended for severe pemphigus, but the risks are considerable [1,9,10]. Prednisolone 60–100 mg/day or intravenous pulses of either 1 g methylprednisolone or 100 mg dexamethasone are safer alternatives [8,11,12].

A number of immunosuppressive agents have been recommended as adjuncts to oral steroids [2–4]. Azathioprine is widely used in a dosage of 2.5 mg/kg/day. The combination of prednisolone and azathioprine is more effective than prednisolone alone, both in terms of mortality and remission [3,13,14]. Azathioprine may be an effective monotherapy in mild cases, although the therapeutic effect is delayed for 3–5 weeks.

Cyclophosphamide alone is not effective in pemphigus, but cyclophosphamide 1–3 mg/kg/day is an effective alternate to azathioprine in combination with steroids. The combination is more effective than steroids alone [3,4,15]. Monthly intravenous pulses of cyclophosphamide with dexamethasone combined with low-dose oral cyclophosphamide have been used with great success [11,14,16]. Remission was maintained with low doses of oral cyclophosphamide [11].

Tetracycline in combination with prednisolone has been reported as useful in an uncontrolled study [17]. A small controlled study showed superiority over prednisolone and azathioprine [18].

Oral or intramuscular gold in addition to steroids reduces mortality and increases the number of patients in remission [3,4].

Ciclosporin (cyclosporin) alone is not helpful in the acute phase of the disease. Ciclosporin 5 mg/kg/day has been used in combination with steroids, particularly in patients with haematological abnormalities [4,19–21]. However, a comparative study found no advantage over prednisolone alone [22]. Topical ciclosporin mouthwash has been helpful in severe oral pemphigus [23].

Dapsone has been advocated as an adjunct in some patients with mild disease [15,24].

Methotrexate is seldom used as there were concerns about toxicity with the high doses that were used [4]. One retrospective review of the literature suggested that methotrexate neither reduced mortality nor changed the number of patients in remission [3]. Others have found that moderate dosage of methotrexate (10–17.5 mg/week) permitted withdrawal of prednisolone in steroid-dependent patients [25].

Mycophenolate mofetil (2 g/day) has been found helpful as a steroid-sparing agent in some [26–28].

Plasmapheresis reduces the titres of autoantibody, but concomitant immunosuppression with steroids or cyclophosphamide is needed to prevent a rebound increase in the synthesis of antibody [4,29]. Sepsis is a serious complication.

Other unproven therapies tried for resistant cases of pemphigus include psoralen with ultraviolet A therapy (PUVA) and extracorporeal photophoresis [4]. High-dose intravenous immunoglobulin is capable of inducing rapid remission but the benefit is short-lived [30,31]. Acitretin has been used in conjunction with prednisolone in pemphigus vegetans [32].

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Pemphigus foliaceus and its variants

Definition. Blistering in this group of autoimmune diseases is high in the epidermis, either in the granular layer or just beneath the stratum corneum.

Aetiology. Pemphigus foliaceus is less common worldwide than pemphigus vulgaris and in most parts of the world probably accounts for only 10–20% of cases of pemphigus [1–6]. One of the pemphigus vulgaris susceptibility alleles (HLA-DRB1*14) may also be associated with pemphigus foliaceus [7]. Endemic pemphigus foliaceus, also known as fogo selvagem ('wild fire'), is common in rural parts of South America, particularly certain states of Brazil [8]. It is probably triggered by an environmental factor (see below). Pemphigus foliaceus is also more common than pemphigus vulgaris in Mali, Libya and rural Tunisia and in South Africa, where it predominantly affects black races [6,9,10].

Pathogenesis. Experimental evidence suggests that autoantibodies in all forms of pemphigus foliaceus are pathogenic.

Pemphigus foliaceus antigen. Sera from all forms of pemphigus foliaceus recognize epitopes located in the extracellular aminoterminal domain of desmoglein 1, a 160-kDa desmosomal cadherin [11–14]. The epitopes recognized by autoantibodies in endemic pemphigus foliaceus may differ from those recognized in non-endemic pemphigus foliaceus [15]. Rare cases of pemphigus foliaceus evolving into pemphigus vulgaris develop antibodies to desmoglein 3 [16–21]. A small subset of pemphigus foliaceus sera have both desmoglein 3 and desmoglein 1 antibodies in the absence of clinical evolution [22]. Some sera, particularly from endemic pemphigus foliaceus, also contain autoantibodies directed against desmocollins 1 and 2 [23,24]. Cases of pemphigus foliaceus with antibodies to desmoplakin [25] and to keratinocyte cholinergic receptors [26] have also been reported. Their significance is unknown.

Localization of antigen. Immunoelectron microscopy has demonstrated that the antibodies bind exclusively to desmosomes [27,28]. Pemphigus foliaceus antigen (desmoglein 1) is expressed more strongly in skin from upper torso than in specimens from the lower torso or scalp [29]. In culture, the antigens are only expressed by stratified keratinocytes [30]. Although direct immunofluorescence may be positive around keratinocytes throughout the epidermis, pemphigus foliaceus sera bind to significantly more desmosomes in the upper epidermis than the lower epidermis, the reciprocal of the pattern with pemphigus vulgaris sera [31], so the pattern of binding correlates with the histological level of split in the epidermis. Antibody binding may have a direct effect on the function of the desmosomal cadherins in the upper epidermis, causing detachment of keratinocytes. Desmoglein 1 is present but only weakly expressed in mucosae [32], accounting for the lack of mucosal involvement in pemphigus foliaceus (Fig. 41.1).

Antibodies. A large epidemiological study of Brazilian pemphigus foliaceus found that only patients with disease had circulating autoantibodies. The titre correlated both with the extent and activity of the disease [33]. Recently, using more sensitive ELISA techniques, anti-desmoglein 1 antibodies have been detected in unaffected individuals living in an endemic area. Subsequent development of pemphigus foliaceus in some of these individuals was preceded by a marked increase in antibody titres [34]. The pathogenic autoantibodies in all forms of pemphigus foliaceus are predominantly in the IgG4 subclass [12,35,36]. Immunohistological staining for desmosomal components appears abnormal in skin from patients with pemphigus foliaceus, possibly altered by binding of autoantibodies (Table 41.5) [37,38].

Pathogenicity. Purified IgG fractions induce loss of cell adhesion in skin organ cultures and neonatal mice with

the typical histological findings of pemphigus foliaceus. Complement is not required. Antigen-specific immunoadsorption of the autoantibodies prevents blisters [39,40].

Proteases. Proteolysis may augment the acantholytic process as in pemphigus vulgaris (see above). High concentrations of plasminogen induce foliaceus-like acantholysis in cultured skin. Pemphigus foliaceus antibodies stimulate epidermal cells to secrete plasminogen activator, but secretion is reduced by corticosteroids. Antibodies against the plasminogen activator, urokinase, block acantholysis induced by pemphigus foliaceus IgG [41].

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Pathology. In early lesions, vacuoles form in the intercellular spaces in the upper levels of the epidermis. These coalesce to form clefts and superficial bullae high in the granular layer or immediately below the stratum corneum. Bullae contain fibrin, some neutrophils and scattered acantholytic keratinocytes. Eosinophilic spongiosis [1] or neutrophilic spongiosis [2] may precede blisters. Frank neutrophilic pustules have been described [3]. Older lesions are acanthotic, papillomatous and hyperkeratotic with focal parakeratosis. Dyskeratotic cells in the granular layer of older lesions distinguish pemphigus foliaceus from pemphigus vulgaris [4]. A mixed inflammatory infiltrate of eosinophils and neutrophils occupies the superficial dermis.

Direct and indirect immunofluorescent findings are usually indistinguishable from pemphigus vulgaris with intercellular IgG and C3 throughout the epidermis. Occasionally, intercellular staining is restricted to the upper layers of epidermis, both on direct and indirect immunofluorescence [5]. Rarely, intercellular IgA is detected by direct immunofluorescence [6]. Indirect immunofluorescence is positive in over 85% of sera but immunoblotting is less sensitive (43%) (Table 41.5) [7].

Electron microscopy demonstrates loss of desmosomes, detachment of keratin tonofilaments and dyskeratosis [4].

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Clinical features. Pemphigus foliaceus is less severe than pemphigus vulgaris. Most cases are idiopathic but penicillamine and other drugs containing thiol groups (e.g. captopril) have been implicated (see p. 41.18). The onset is usually insidious with scattered scaly lesions involving the 'seborrhoeic' areas: scalp, face, chest and upper back (Figs 41.7 & 41.8). Localized disease slowly extends. Blistering may not be obvious because the cleavage is superficial and the small flaccid blisters rupture easily. Scales separate leaving well-demarcated crusted erosions surrounded by erythema, sometimes with small vesicles along the borders. Erosions are both painful and offensive. Eventually, the patient may become erythrodermic with crusted oozing red skin (Fig. 41.9). Oral lesions are uncommon (Table 41.4) [1].

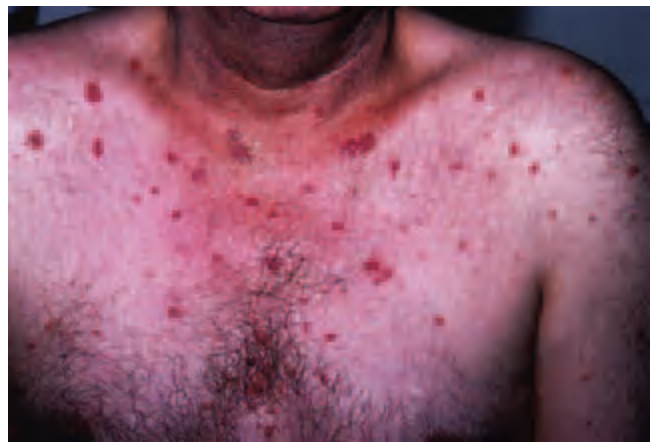

Fig. 41.7 Pemphigus foliaceus. Well-demarcated crusted lesions scattered over the chest.

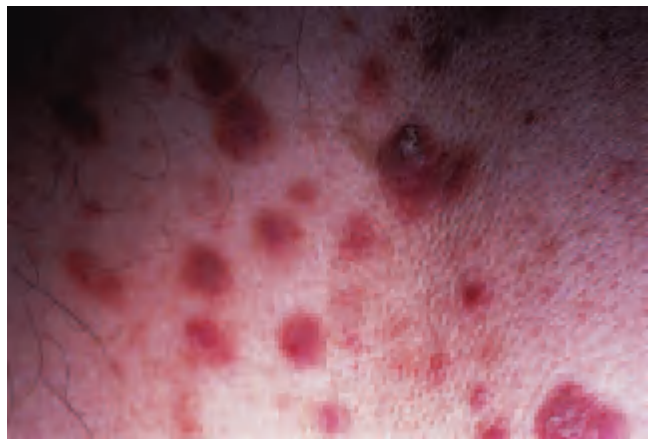

Fig. 41.8 Pemphigus foliaceus. Sharply demarcated areas of erythema, crusting and scaling with no obvious bullae.

Although the antibodies in pemphigus foliaceus can cross the placenta, the neonate is not usually affected [2]. In two cases in which the neonate did develop pemphigus foliaceus, both mother and neonate had very high antibody titres [3,4].

Clinical variants of pemphigus foliaceus

Pemphigus resembling dermatitis herpetiformis

A rare and atypical variant of pemphigus resembles dermatitis herpetiformis in its early phase (pemphigus herpetiformis) was first described by Jablonska and is the subject of a recent review [5]. Widespread clusters of pruritic papules and vesicles develop on an erythematous background. Biopsies show subcorneal pustules,

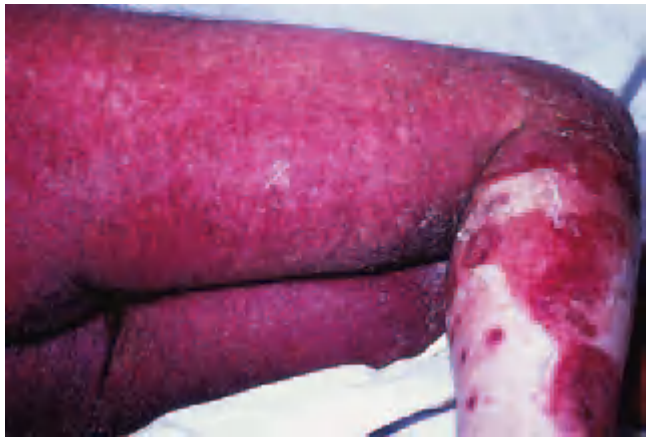

Fig. 41.9 Pemphigus foliaceus. This man became erythrodermic and then developed widespread painful erosions.

eosinophilic spongiosis or features of dermatitis herpetiformis without acantholysis, but immunofluorescence studies reveal intercellular staining. Patients possess circulating IgG intercellular autoantibodies which recognize either desmoglein 1 [6,7] or desmoglein 3 [7,8] or neither antigen [7]. The condition usually evolves into classical pemphigus foliaceus but has also been described preceding pemphigus vulgaris [6]. In general, the clinical course is benign.

Pemphigus erythematosus (Senear–Usher syndrome)

Pemphigus erythematosus is a variant of pemphigus foliaceus originally described by Senear and Usher [9–11]. Patients have immunological features of both lupus erythematosus and pemphigus (granular IgG and C3 at the basement-membrane zone, intercellular IgG and C3 in the epidermis and circulating antinuclear antibodies) [12]. The antibodies recognize the pemphigus foliaceus antigen, desmoglein 1 [13]. Progression to systemic lupus erythematosus is rare. Pemphigus erythematosus may be associated with myasthenia gravis or thymoma [12,14].

Erythematous scaly lesions over the nose and cheeks in a butterfly distribution simulate cutaneous lupus erythematosus or seborrhoeic dermatitis. Sunlight may exacerbate the disease. Lesions on the trunk, either localized or generalized, are similar to those in pemphigus foliaceus. Rarely, oral mucosa is involved.

Differential diagnosis. Pemphigus foliaceus may resemble seborrhoeic dermatitis or impetigo, but the histological and immunological features are diagnostic. Pemphigus erythematosus needs to be distinguished from both seborrhoeic dermatitis and chronic cutaneous lupus erythematosus. Pemphigus may simulate dermatitis herpetiformis both clinically and histologically, but immunopathological studies differentiate the diseases. Histological features may not be diagnostic in the early stages. Eosinophilic spongiosis may be an early manifestation [15]. Immunofluorescence studies should always be performed if pemphigus is suspected.

Treatment. These superficial forms of pemphigus usually respond to potent topical or intralesional steroids or, if control is inadequate, prednisolone 20–40 mg/day. Azathioprine or cyclophosphamide are effective adjuncts to oral steroids in severe cases. Hydroxychloroquine 200 mg twice daily has also been recommended as adjuvant therapy [16]. Intravenous immunoglobulin has been reported as effective in resistant cases [17,18].

Dapsone 100–300 mg/day may be effective as a monotherapy or given in combination with steroids [19]. Dapsone 100–300 mg/day is the treatment of choice for pemphigus with dermatitis herpetiformis-like lesions (pemphigus herpetiformis), but retinoids have been suggested as a second-line therapy in these patients [20,21]. Mycophenolate mofetil has been used as a steroid-sparing agent [22,23].

Nicotinamide 1.5 g/day, combined with either tetracycline 500 mg four times daily or minocycline 100 mg/day, appeared effective in superficial pemphigus in one uncontrolled study [24] but these results were not substantiated [25]. High-dose intravenous immunoglobulin has been successfully used in severe pemphigus foliaceus resistant to other therapies [18].

Prognosis. Pemphigus foliaceus is a benign but chronic disease that responds well to treatment and may remit. Prior to the introduction of steroids, the disease pursued a chronic course over many years [1]. There are rare reports of pemphigus foliaceus evolving both clinically and immunopathologically into pemphigus vulgaris [26–31]. Pemphigus erythematosus may persist for years as localized disease. The clinical course is often similar to pemphigus foliaceus.

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Endemic pemphigus foliaceus

SYN. FOGO SELVAGEM (WILD FIRE); BRAZILIAN PEMPHIGUS FOLIACEUS

One form of pemphigus foliaceus is endemic to certain parts of South America. Histologically and immunopathologically it resembles the non-endemic form. It is distinguished by its unique epidemiological features, including geographical, temporal and familial clustering of cases, high prevalence in the young, and association with certain HLA haplotypes [1].

By 1987, more than 15 000 cases had been registered, clustered in certain states of Brazil [1–4]. Endemic foci have also been reported in Columbia, El Salvador, Paraguay and Peru [1,5]. An endemic focus has also been observed in rural Tunisia [2–4].

Aetiology. Epidemiological evidence suggests that endemic pemphigus foliaceus is precipitated by an environmental factor, possibly a biting insect. The disease is endemic in newly developed jungle areas of Brazil that are being used for agriculture, but endemic foci are eradicated by urbanization. Rural labourers are at greatest risk. The incidence of disease is greatest at the end of the rainy season when insects are most abundant. Black fly (family Simuliidae) bites are a risk factor for the disease [1]. Chronic exposure to black fly antigens may trigger the formation of antibodies that cross-react with epidermal antigens but this hypothesis has not been proved experimentally. Patients are exposed to numerous biting insects and infestations of parasites are common so other vectors may be important.

No infectious agent, chemical toxin or pollutant has been isolated.

A significant number of cases have an affected family member [1]. In one Brazilian population, the susceptibility allele was identified as HLA-DRB1*0102. In two other Brazilian populations different alleles of the HLA-DRB1 gene (DRB1*0404, *1402 or *1406) have been linked to the development of endemic pemphigus foliaceus [5,6]. All alleles involved in predisposition to disease share the same amino-acid sequence in the *DRB1* gene. Inheritance of this sequence may determine susceptibility when individuals are exposed to the appropriate environmental agent [1].

Pathogenesis. Passive transfer studies demonstrate the pathogenicity of the antibodies [7]. Like idiopathic pemphigus foliaceus, these are of the IgG4 subclass. Sera recognize epitopes located in the extracellular amino-terminal domain of desmoglein. The epitopes involved may be different from those in non-endemic disease [8]. Some sera also contain autoantibodies directed against desmocollins 1 and 2 [9,10]. Autoantibodies bind to oral mucosa as well as skin [11]. Mucosal involvement clinically is rare but there may be ultrastructural abnormalities (e.g. widening of the intercellular spaces and desmosomal changes [12]).

Using sensitive ELISA techniques, it is now clear that the prevalence of antidesmoglein 1 antibodies is high

among normal subjects living in an endemic area. The onset of the disease is preceded by a sustained antibody response. These findings support the concept that the production of antibodies against desmoglein 1 is initiated by exposure to an unknown environmental agent [13].

Clinical features. Endemic pemphigus foliaceus affects children and young adults, with a peak incidence in the second and third decades, whereas other forms of pemphigus foliaceus affect middle-aged adults (Table 41.4) [14,15].

Patients present with flaccid bullae, which rupture easily leaving superficial erosions. Nikolsky's sign is positive. The head and neck are involved at first. The burnt appearance and burning sensation, particularly on sun exposure, gives the disease its popular name, fogo selvagem, Portuguese for 'wild fire'. The disease slowly spreads acrally and may become generalized. Oral mucosa is usually spared.

Some patients develop widespread bullae with pyrexia, arthralgia and malaise. Generalized erythroderma may supervene. Chronic disease is frequent, with disseminated verrucous lesions that simulate prurigo nodularis. Plaques may vegetate. Hyperpigmentation is a feature of inactive disease.

Growth retardation, common in affected children, responds to treatment with oral corticosteroids. Adults who were affected in childhood may have azoospermia. Patients may show signs of chronic depression [14,15].

Although antibodies to desmoglein 1 cross the placenta, the disease is rarely transmitted from affected mothers to the neonate [16], except in rare cases with high-titre antibodies [17]. Desmoglein 3 is more highly expressed in neonatal than adult skin and this may be protective [18].

Treatment. Treatment is similar to other forms of pemphigus foliaceus. Topical steroids are effective in localized disease or as an adjunct to systemic treatment. Most patients respond to systemic steroids alone, but verrucous plaques may be resistant to therapy. Immunosuppressive agents, gold and antimalarials have been recommended [14,15].

Prognosis. Before the advent of corticosteroids, 40–60% of untreated patients died. Now less than 10% die, often as a result of the complications of treatment. Spontaneous remissions have been reported.

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Induced pemphigus

Drugs may exacerbate or induce pemphigus. Drugs containing a sulphydryl group (thiol drugs) such as penicillamine and captopril are the best studied, but pemphigus can also been attributed to non-thiol drugs including other angiotensin-converting enzyme (ACE) inhibitors (e.g. enalapril [1], ramipril [2], fosinopril [3]) and other drugs such as nifedipine, the penicillins, cephalosporins, pyrazolon derivatives and rifampicin [4]. Patients treated with interferon may develop autoimmune pemphigus [5].

Pemphigus has also been induced by radiotherapy [6] and thermal burns [7]. Apparently dietary factors, particularly vegetables of the *Allium* group, have triggered pemphigus [8]. Human herpesvirus 8 DNA sequences

have been reported in peripheral blood mononuclear cells and skin from pemphigus patients [9,10]. Their significance is disputed [11].

Aetiology and pathogenesis. Alleles of HLA-DR4 predispose to pemphigus vulgaris and a susceptibility allele is also carried by individuals with drug-induced pemphigus [12]. Drugs may act to trigger disease in genetically predisposed individuals. Thiol drugs provoke acantholysis *in vitro*, possibly by increasing the activity of plasminogen activators. An active amide group in the molecule of non-thiol drugs may be responsible for inducing disease [4].

Clinical features. Pemphigus foliaceus or pemphigus erythematosus are the most common patterns induced by drugs. Drug-induced pemphigus vulgaris and pemphigus vegetans are rare. Most patients have circulating autoantibodies with the same antigenic specificities as in other forms of pemphigus [13,14].

Prognosis. Forty to 50% of patients with thiol-drug-induced pemphigus, but only 15% of the cases induced by non-thiol drugs recover spontaneously when the drug is withdrawn [4].

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Intercellular IgA dermatosis and subcorneal pustular dermatosis

These conditions share clinical and histological features. Immunofluorescence studies were negative in classical subcorneal pustular dermatosis. Although there is overlap, the relationship between the diseases has not been defined so they are considered separately here.

Intercellular IgA dermatosis

SYN. IgA PEMPHIGUS FOLIACEUS; INTRAEPIDERMAL NEUTROPHILIC IgA DERMATOSIS; IgA HERPETIFORM PEMPHIGUS; INTERCELLULAR IgA VESICULOPUSTULAR DERMATOSIS

More than 50 cases have been reported of patients presenting with vesicopustular or vesicobullous eruptions with intraepidermal antikeratinocyte IgA detected in perilesional skin on direct immunofluorecence. These comprise a heterogeneous group clinically, histologically and immunologically. Some may be variants of subcorneal pustular dermatosis (see below), others may be a form of pemphigus, but the relationships between these conditions have still to be clarified [1,2].

Pathology. A neutrophil-rich polymorphonuclear infiltrate in the epidermis is observed. Two types are distinguished based on the level of pustule formation and IgA deposition [1]: the subcorneal pustular dermatosis type (subcorneal pustules) and the intraepidermal neutrophilic type (intraepidermal pustules). However, microabscesses at various levels have been observed and may depend on the age of the lesion [2]. Acantholysis is usually sparse or absent but is occasionally pronounced, mimicking either pemphigus vulgaris or pemphigus foliaceus histologically.

Pathogenesis. The hallmark of these disorders is the intercellular IgA deposition, present at many different epidermal levels or throughout the epidermis. Circulating IgA is either undetectable or present in low titre [2–4]. Desmocollin 1, a desmosomal component located mainly in the upper epidermis, has been identified as the target antigen in cases with subcorneal pustules [5–7]. In patients with the intraepidermal neutrophilic type, antigens resembling desmoglein 1 [5,8] or desmoglein 3 [7,9–11] have been implicated in a few cases. In others cases the target antigen could not be identified. Standard immunoblotting is frequently negative, probably because the target epitopes are conformation dependent [7,12].

Clinical features. The disease chiefly affects adults although childhood cases have been reported [1,2]. Patients with both types have flaccid vesicles or pustules

arising on either erythematous or normal skin. The lesions may be pruritic and show a circinate or annular configuration with central clearing and evolve to crusted or scaly erythematous macules. The sites of predilection are the axillae and groins. Other sites are elsewhere on the trunk, face, scalp and proximal limbs. In some cases, the flaccid pustules resemble subcorneal pustular dermatosis of Sneddon–Wilkinson (see below). Others may resemble pemphigus foliaceus or pemphigus herpetiformis [13–15]. Flexural oozing verrucous plaques mimicking pemphigus vegetans have been described in a child [16]. Nikolsky's sign is usually negative and mucosal involvement is unusual. Most run a chronic indolent course.

The most frequently reported association is monoclonal IgA gammopathy in the subcorneal type [17,18], a feature it has in common with classical subcorneal pustular dermatosis. Other cases have been linked with human immunodeficiency virus (HIV) infection, Crohn's disease, gluten-sensitive enteropathy, rheumatoid arthritis [2] and thiol drugs [19].

Treatment. These neutrophilic dermatoses respond well to dapsone [3,4,20] but poorly to steroids [3]. Other reported therapies are etretinate [3,20,21], isotretinoin [22], PUVA [21], immunosuppressives [14], plasmapheresis [23] and colchicine [10,24].

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Subcorneal pustular dermatosis

SYN. SNEDDON–WILKINSON DISEASE

Definition. A chronic relapsing pustular eruption, mainly involving the trunk, which affects women over 40 years of age. Pustules are subcorneal.

Background. This disorder was separated from bullous impetigo in 1956 [1,2]. The exact nosological position of subcorneal pustular dermatosis remains controversial. Some cases may be a variant of pustular psoriasis, whereas others appear to overlap with the subcorneal pustular variant of IgA pemphigus.

Pathogenesis. The pathogenesis is obscure. The salient feature is subcorneal accumulation of neutrophils. Culture of the pustules is sterile. Subcorneal pustular dermatosis has been reported in association with various types of immune dysfunction. Monoclonal gammopathy, usually IgA (occasionally IgG), has been repeatedly reported. The paraproteinaemia is usually benign but IgA myeloma also occurs. Other reported associations are pyoderma gangrenosum, inflammatory bowel disease and rheumatoid arthritis [3–7]. The condition has also been observed at the injection site of recombinant human granulocyte–macrophage colony-stimulating factor in a patient with IgA myeloma [8]. Excess production of TNF-α has been implicated in the pathogenesis of neutrophil activation [9].

In classic subcorneal pustular dermatosis, immunofluorescence studies are negative. However, a possible subgroup with identical clinical and histological features to the 'classic' type have intercellular IgA deposition in

the upper epidermis [10,11]. Desmocollin 1 is the target antigen in these cases. There are also examples of 'classic immunofluorescence-negative' cases in whom intercellular epidermis IgA deposits were detected on repeat immunofluorescence testing [11], in one case after a latent period of many years [12]. The relationship between the intercellular IgA dermatoses, regarded as part of the pemphigus spectrum, and classic subcorneal pustular dermatosis remains unclear.

Pathology. Biopsies from early lesions show a perivascular inflammatory infiltrate with neutrophils and occasional eosinophils. Neutrophils migrate through the epidermis, without forming spongiform pustules, to collect beneath the stratum corneum in subcorneal pustules. The pustules sit on the surface of the epidermis rather than being an integral part of it. A few acantholytic cells may be found in old lesions [1]. Ultrastructural studies show cytolysis of single cells and invasion by neutrophils [13].

Both direct and indirect immunofluorescence studies are negative in classic cases [14], but recently some cases have been described with clinical features resembling classic subcorneal pustular dermatosis but with intercellular IgA within the epidermis [15–17].

Clinical features. The disease is more common in women and usually affects individuals between 40 and 50 years of age. The eruption occurs mainly in flexures and on the flexor aspect of the limbs [1,18,19]. The face is almost never affected, nor are the mucous membranes. The primary lesion is an oval pea-sized flaccid pustule, which arises on normal skin or a slightly erythematous base. Characteristically, pus accumulates in the lower half of a fully developed pustule, leaving clear fluid in the upper half (Fig. 41.10). Pustules rupture easily and tend to coalesce, forming annular or serpiginous patterns with a scaly edge. The eruption fades to leave faint hyperpigmentation, but successive waves of pustules pass across the previously affected areas. The intervals between active and quiescent phases varies from several days to several weeks.

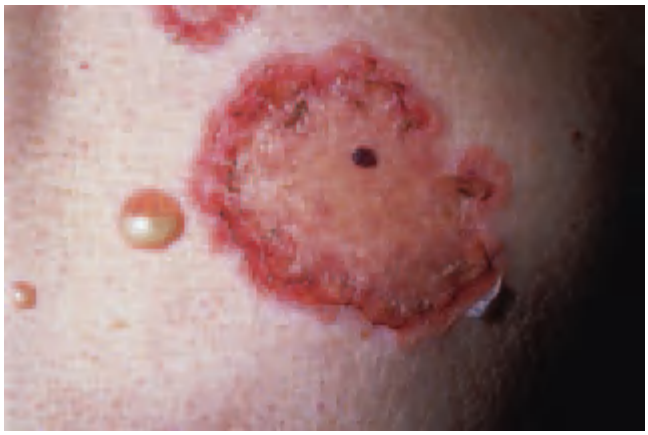

Fig. 41.10 Subcorneal pustular dermatosis. Annular lesions with a scaly margin and surrounding pustules. Pus has accumulated in the lower half of the flaccid pustule leaving clear fluid in the upper half.

Prognosis. The condition is benign but chronic, with an average duration of 5.8 years [1]. Myeloma obviously worsens the outlook.

Diagnosis. The differential diagnosis includes impetigo, pustular psoriasis, pemphigus foliaceus, dermatitis herpetiformis, intercellular IgA dermatosis and acute generalized exanthematic pustulosis.

Pathogenic organisms are cultured from pustules in impetigo and the condition responds to antibiotics.

Pustular psoriasis, either of the acute von Zumbusch type with small pustules or the spreading annular type, may resemble subcorneal pustular dermatosis. Spongiosis is not a feature of subcorneal pustular dermatosis, but spongiform pustules that are an integral part of the epidermis are characteristic of pustular psoriasis [20]. Subcorneal pustular dermatosis, unlike pustular psoriasis, responds to dapsone. Some authors consider that subcorneal pustular dermatosis is part of the spectrum of pustular psoriasis [21]. 'Atypical cases' reported as examples of subcorneal pustular dermatosis may be unusual presentations of pustular psoriasis.

Biopsies from early lesions of pemphigus foliaceus may show subcorneal pustules with very little acantholysis. Direct immunofluorescence will show intercellular IgG in the epidermis in pemphigus.

Acute generalized exanthematic pustulosis is distinguished by its acute onset in a febrile patient with a history of exposure to a candidate drug. The histology shows spongiform pustules [22].

Treatment. Dapsone 50–150 mg/day is the treatment of choice. Although the response is slower than in dermatitis herpetiformis, most patients obtain partial, if not complete relief. Sulfapyridine and sulfamethoxypyridazine have been used as alternatives. Treatment can often be weaned or stopped without relapse. Some cases respond to potent topical corticosteroids [23] or oral steroids [9], but in general steroids are ineffective even in large doses. Etretinate [6,16,24] and acitretin [25] have been used. Isotretinoin was found ineffective at a dosage of 0.5 mg/kg/day [26]. Broad-band UVB [27], narrow-band UVB [28,29], PUVA [16,30] and Re-PUVA have also been reported as effective. Colchicine [31] and topical tacalcitol [32] have been recommended. In cases associated with myeloma, the skin lesions may improve when the paraprotein is reduced by chemotherapy [17].

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Paraneoplastic pemphigus

A distinctive form of pemphigus has been described in association with a variety of underlying neoplasms [1], most commonly B-cell lymphoproliferative disorders but also thymoma, sarcomas and carcinomas [2,3]. Some cases have been linked with the use of fludarabine chemotherapy [4,5]. The clinical features overlap with erythema multiforme and lichen planus pemphigoides. Patients have severe mucosal erosions and polymorphous cutaneous signs including blisters, erosions particularly on the upper body and palmoplantar target lesions (Table 41.4) [1,2,6–10]. In two-thirds of cases, paraneoplastic pemphigus occurs with an existing neoplasm; in the remainder the neoplasm is detected after the mucocutaneous disease has occurred [2]. Biopsies show necrosis of keratinocytes or vacuolar interface dermatitis in addition to suprabasal clefting with acantholysis [11], but the specificity of these histological findings has been questioned [12].

Direct immunofluorescence reveals immunoglobulin and/or complement at the basement-membrane zone as well as on the surfaces of keratinocytes. Indirect immunofluorescence is positive in both non-stratifying (simple and transitional) epithelia and stratifying epithelia (Table 41.5) [13].

Antibodies are predominantly antiplakin antibodies of the IgG1 subclass. Their pathogenicity has been established by passive transfer studies. The autoantibodies recognize a complex of antigens on immunoblotting and immunoprecipitation. These are members of the plakin family of proteins and include desmoplakin 1 (250 kDa), envoplakin (210 kDa), the 230 kDa BP antigen and a 190-kDa antigen, thought to be periplakin [1,14–17] and plectin (500 kDa) [18]. Antiplakin antibodies are not specific to paraneoplastic pemphigus and have also been detected in patients with severe erythema multiforme [19], BP [20] and pemphigus foliaceous [21,22]. Antidesmoglein antibodies have been detected in paraneoplastic pemphigus in some [18,23–25] but not all cases [26]. Paraneoplastic pemphigus is a multisystem disease. Passive transfer of paraneoplastic pemphigus sera to mice produces autoantibody deposits in skin, upper digestive and respiratory tract epithelia, kidney, urinary bladder, smooth and striated muscle [27].

Paraneoplastic pemphigus is generally refractory to all treatments. Oral steroids, azathioprine, ciclosporin, mycophenolate mofetil and plasmaphoresis have been tried [1,2,8,9,28,29]. Most patients deteriorate inexorably, with death usually secondary to sepsis, gastrointestinal bleeding, multiorgan or respiratory failure [2,28]. Cases associated with benign or low-grade neoplasia such as thymoma or Castleman's disease [8,30–32] may remit partially after surgical removal of the neoplasm.

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Structure of the dermal–epidermal junction

The basal keratinocytes of the epidermis are separated from the underlying dermis by the basement membrane, a two-layered structure on electron microscopy comprising the *lamina lucida*, the major components of which are laminins, and the *lamina densa*. Above the lamina lucida, straddling the plasma membrane of the epidermal basal cells are discrete electron-dense structures, the *hemidesmosomes*. Fine structures, the *anchoring filaments*, traverse the lamina lucida, particularly in the region of the hemidesmosomes, and appear to terminate in the lamina densa, rich in both laminin 5 and type IV collagen [1]. Beneath the lamina densa and appearing to embed in the upper dermis are curved structures, the anchoring fibrils, composed of type VII collagen (Fig. 41.11) [2].

The intracellular plaque of the hemidesmosomes contains a 230-kDa polypeptide, a member of the plakin family known as BP230 or BPAG1 as it binds to sera of patients with bullous pemphigoid (BP) [3]. Other components of the intracellular plaque are plectin (MW 500 kDa) and the less well-characterized antigens HD1, IFAP300 and P200. The intracytoplasmic keratin intermediate filaments (keratin types 5 and 14), organized into *tonofilaments*, loop down and insert into the hemidesmosomes where they interact with the carboxy-terminals of BP230 and plectin.

The transmembrane components of the hemidesmosome include BP180/collagen XVII or BPAG2 and $\alpha 6\beta 4$ integrin (Fig. 41.11). Collagen XVII (MW 180 kDa, also known as

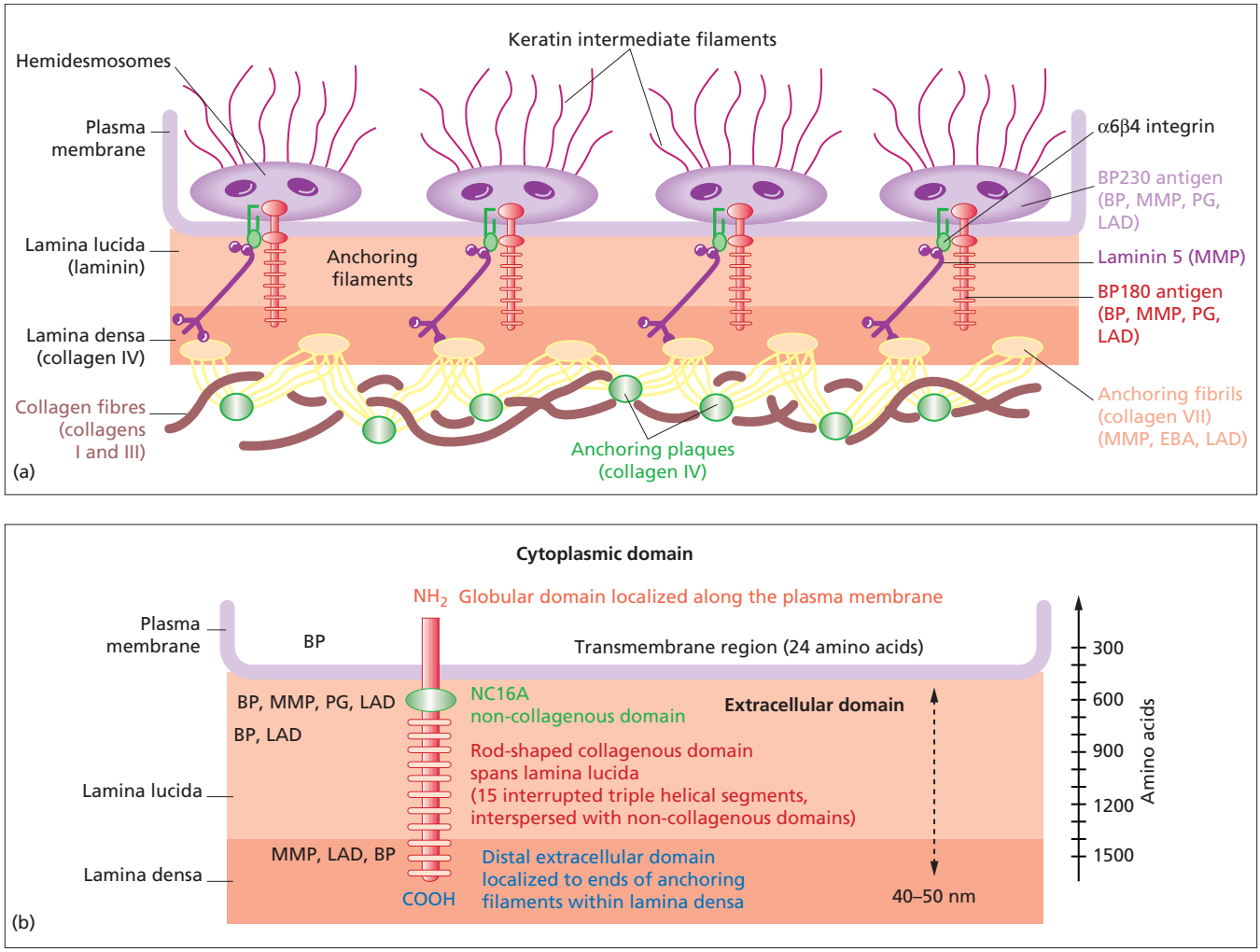

Fig. 41.11 The dermal–epidermal junction. (a) The structure of the adhesion complex of the basement-membrane zone. (b) The structure of BP180/collagen XVII, showing sites of antigen binding. BP, bullous pemphigoid; EBA, epidermolysis bullosa acquisita; LAD, linear IgA disease; MMP, mucous membrane pemphigoid; PG, pemphigoid gestationis. (Courtesy of Dr J. Allen, Oxford Radcliffe Hospital, Oxford, UK.)

BP180 as it binds BP sera) comprises an intracellular globular domain, where its NH_2 terminal interacts with the NH2 terminal of BP230 [4], with additional; stabilizing interactions with both plectin and β4 integrin [5]. The long extracellular collagenous domain of collagen XVII is shed by the physiological action of proteases [6] and interacts both with α6 integrin [5] and with the B3 chain of laminin 5 in the region of the anchoring filaments. Laminin 5 also interacts with other laminin isoforms, with both β4 and α6 integrin [5], as well as being the principal ligand for type VII collagen, the main component of the anchoring fibrils. Hence, laminin serves as a bridge between the transmembrane hemidesmosomal molecules and the dermal matrix molecules.

These structures collectively form the *adhesion complex* of the dermal–epidermal junction, with continuity running from the keratin filaments within the epidermal cells via the hemidesmosomes, the anchoring filaments and through to the anchoring fibrils embedded in the dermis. In normal skin, mechanical stability and adhesion between the epidermis and dermis depends on the integrity of the adhesion complex components. Mutations of these molecules produce skin fragility and blistering (see Chapter 40). Autoantibody-mediated diseases have been described in relation to BP230, BP180, laminin 5, type VII collagen and type IV collagen and these are considered in this chapter.

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Subepidermal immunobullous diseases

These bullous diseases include a number of clinical entities (Table 41.4). However, there is clinical overlap and it is not uncommon for individual patients to be difficult to classify clinically (Fig. 41.12). Similarly, the histology and immunofluorescence are not always distinctive, and the identification of the target antigens for these diseases has demonstrated that not only are the antigens and their specific epitopes common to many of the entities, but also often multiple within a patient. In addition, new antigens are still being described. It seems likely that many as yet poorly characterized or undiscovered molecules within the anchoring complex of the basement-membrane zone can be the targets for autoantibodies in the subepidermal blistering diseases. The expectation that perhaps the immunogenetic constitution of the individual might determine the disease has been only partially fulfilled. Thus, the clinical overlap is reflected in immunopathological and immunogenetic overlap (Fig. 41.12) and is shown in Tables 41.5 and 41.6.

Table 41.4 The subepidermal immunobullous diseases.

Bullous pemphigoid
variant: pemphigoid nodularis
variant: localized pemphigoid
variant: localized vulvar pemphigoid
variant: pemphigoid vegetans
variant: lichen planus pemphigoides
Mucous membrane pemphigoid
variant: oral pemphigoid
variant: Brunsting–Perry pemphigoid
Pemphigoid gestationis
Linear IgA disease
variant: chronic bullous disease of childhood
variant: linear IgA disease of adults
variant: dermal associated linear IgA disease
variant: linear IgA mucous membrane pemphigoid
variant: mixed immunobullous disease
Epidermolysis bullosa acquisita
Bullous systemic lupus erythematosus
Dermatitis herpetiformis

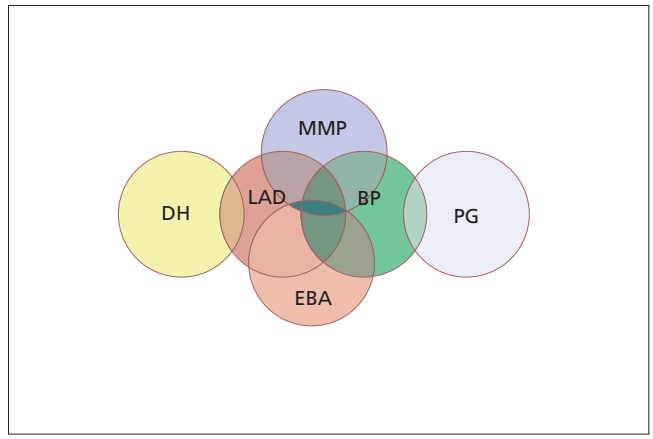

Fig. 41.12 The clinical and immunopathological overlap between the subepidermal blistering diseases. BP, bullous pemphigoid; DH, dermatitis herpetiformis; EBA, epidermolysis bullosa acquisita; LAD, linear IgA disease; MMP, mucous membrane pemphigoid; PG, pemphigoid gestationis.

The subepidermal autoimmune bullous diseases are, with the exception of dermatitis herpetiformis, characterized by autoantibodies directed against components of the adhesion complex (Fig. 41.11). The use of the patient's sera to identify these antigens and their genes has made a major contribution to cell and molecular biology. The mechanisms by which the autoimmune process is initiated and by which the combination of antibody with antigen results in blistering are in the process of being elucidated. However, evidence is accumulating that the autoantibodies are pathogenic.

Bullous pemphigoid

SYN. PEMPHIGOID

Definition. A blistering disease of elderly people, which often starts with pruritus and urticated and erythematous lesions; later large tense blisters develop both on erythematous and on normal skin and there may be mucosal involvement with blisters and erosions. The blisters are subepidermal and intact epidermis forms the roof. Autoantibodies, chiefly IgG, to the epidermal basement-membrane zone are found in the skin and blood [1].

The clinical features, immunopathology and immunogenetics are summarized in Tables 41.5 and 41.6.

REFERENCE

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Aetiology. Bullous pemphigoid is an affliction of elderly people, with onset usually after 60 years of age, but the condition can occur in those under 40 years, and more than 60 cases have been described in children, the three

Table 41.5 The subepidermal immunobullous diseases: clinical features.

Disease	Patients	Cutaneous distribution	Mucosal involvement	Lesions	Associations	Treatment	Prognosis
Bullous pemphigoid	Elderly (few infants and children)	Trunk, limbs, flexures	Common, minor	Urticated plaques, tense blisters, (milia)	Nil	Steroids, dapsone, immunosuppressives	3–6 years' duration
Mucous membrane pemphigoid	Middle–old age	Infrequent (30%)	Major, severe	Erosions, blisters, gingivitis, milia **Scarring**	Autoimmune disease	Steroids, dapsone, immunosuppressives	Chronic
Pemphigoid gestationis	Pregnant women	Umbilicus, generalized	Minor	Urticated plaques, tense blisters	Autoimmune thyroid disease	Steroids	Remits postpartum
Linear IgA disease							
Chronic bullous disease of childhood	Children	Perineum, face, trunk, limbs	Majority, (few severe)	Urticated plaques, annular lesions, tense blisters		Dapsone, sulphonamides	3–4 years' duration (few persist)
Adult linear IgA disease	Young adults to elderly	Trunk, limbs	Majority, (few severe)	Urticated plaques, tense blisters, papulovesicles	Ulcerative colitis, lymphoma	Dapsone, sulphonamides	3–6 years' duration (few persist)
Epidermolysis bullosa acquisita	Adults and children	Generalized, variable	Some, (few severe)	Urticated plaques, tense blisters, milia **Scarring**	Inflammatory bowel disease	Steroids, dapsone, immunosuppressives	Persists
Bullous SLE	Adults	Generalized, variable	Minor	Urticated plaques, tense blisters	SLE	Dapsone	Transient
Dermatitis herpetiformis	Young adults (some children and elderly)	Symmetrical, elbows, knees, buttocks	Minor	Papulovesicles	Gluten-sensitive enteropathy, lymphoma	Dapsone, sulphonamides, gluten-free diet	Persists

SLE, systemic lupus erythematosus.

Table 41.6 The subepidermal immunobullous diseases: immunopathology and immunogenetics.

		BMZ antibodies						Immunogenetics	
Disease	Direct IMF	Isotype	Binding to split skin	Target antigens	Antigens (kDa)	Location	Structure	MHC class I and II	MHC class III
Bullous pemphigoid	Linear BMZ	IgG (few IgA)	Epidermal (Few dermal)	BP230 BP180	230 180 200 Others	Hemidesmosome Transmembrane	Dense plaque Dense plaque	DQ7 (males)	
Mucous membrane pemphigoid	Linear BMZ	IgG, IgA	Epidermal	BP180 BP230 α6β4 integrin ?	180 230 120 205 45	Lamina lucida Hemidesmosome Hemidesmosome	Anchoring filament	DQ7	
			Few dermal	Laminin 5 Collagen VII	600 290	Lamina lucida Lamina densa	Anchoring filament Anchoring filament		
Pemphigoid gestationis	Linear BMZ	IgG	Epidermal	BP230 BP180	230 180	Hemidesmosome Transmembrane	Dense plaque	A1, B8, DR3/4	C4 null
Linear IgA disease (CBDC and adult LAD)	Linear BMZ	IgA	Epidermal (majority)	BP180 (shed ectodomain) LAD285 BP230	180 (120/97) 285 230	Hemidesmosome and lamina lucida		A1, B8, CW7, DR3	TNF2 (some homozygous)
			Dermal (minority)	Collagen VII Other	Collagen VII 285	Lamina densa	Anchoring fibril		
Epidermolysis bullosa acquisita	Linear BMZ	IgG	Dermal	Collagen VII (anchoring fibril)	290	Lamina densa	Anchoring fibril	DR2	
Bullous SLE	Linear BMZ	IgG, IgA	Dermal	Collagen VII (anchoring fibril) Others	290	Lamina densa Lamina densa	Anchoring fibril	DR2	
Dermatitis herpetiformis	Granular dermal papillae	IgA	Negative	Unknown ?epidermal tissue transglutaminase		Upper dermis		A1, B8, DR3 DQw2	TNF2 TNFB*1

BMZ, basement-membrane zone; CBDC, chronic bullous disease of childhood; IMF, immunofluorescence; LAD, linear IgA disease; MHC, major histocompatibility complex; SLE, systemic lupus erythematosus.

youngest being 10 weeks or less at onset of their disease [1–4]. The risk of developing BP increases with age and is higher in men [5]. Bullous pemphigoid is the most common immunobullous disease in western Europe. In France and Germany, the incidence of BP is estimated to be 6–7 cases per million population per year and is similar in Singapore [6–8]. However, in other countries of the Far East, BP appears to be less common, and more likely to develop in Indians than Chinese [8–10]. Recent work suggests that in northern Europeans HLA-DQ7 may be associated with BP but only in men, not women [11,12]. This association does not exist in Chinese or Japanese patients [13,14].

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Pathogenesis. Bullous pemphigoid provides one of the best models for an autoimmune disease. The disease is characterized by IgG autoantibodies to hemidesmosome-associated proteins within the adhesion complex (Fig. 41.11). The target antigens have been characterized and their genes cloned (see below). The autoantibodies have been shown to be pathogenic and complement to be necessary for blister formation [1,2].

The two major BP antigens are BP230 and BP180, which are associated with hemidesmosomes (Fig. 41.11) and are the products of genes located on different chromosomes [3].

BP230, also known as BPAG1, was the first to be characterized and has a molecular weight of 230 kDa [4,5]. BP230 is intracellular and localized to the dense plaque [6]. The gene for BP230 has been cloned and resides on the short arm of chromosome 6 [7,8]. The portions of BP230 antigen that are the target for the autoantibodies (immunodominant epitopes) are located chiefly at the carboxy terminal, which mediates the interaction of the keratin intermediate filaments with the hemidesmosome [9,10].

BP180, also known as BPAG2 and collagen XVII, has a molecular weight of 180 kDa [4,11] and is a transmembrane molecule with collagenous domains and a long extracellular portion, which is shed under physiological conditions (Fig. 41.11) [12,13]. The gene for BP180 has been cloned and is situated on chromosome 10 [3,12]. It is located in the hemidesmosome and the extracellular portion interacts with the anchoring filaments [6,14]. The extracellular region adjacent to the transmembrane portion, the NC16A domain, is the immunodominant epitope; however, other epitopes are found in many regions of the molecule, including the intracellular region, the shed collagenous ectodomain and the carboxy terminal (Fig. 41.11) [6,15–19]. This extracellular location makes it a likely candidate for pathogenic autoantibodies.

There are reports of other target antigens in individual patients, the most common being one of 200 kDa weight, which has been described associated with the epidermis and dermis [4,20].

Two animal models have demonstrated that the autoantibodies in BP are pathogenic. In the first model, injection of BP autoantibodies into rabbit cornea produced subepidermal blisters and immune deposits of IgG and C3 along the basement-membrane zone [1]. Other attempts were unsuccessful until molecular biology demonstrated that the chief epitope differed in mice and humans. Antibodies were raised to the immunodominant mouse epitope of BP180, and these antibodies produced immunopathological BP in neonatal mice [2].

The formation of blisters begins with autoantibody deposition, which binds C3 along the dermal–epidermal junction [21]. These antibodies are directed at BP180 and BP230 and are mainly of the IgG subclass, predominantly IgG1 and IgG4 isotypes [22]. There is a change with disease duration and remission in the relative amounts of inflammatory IgG1 and less inflammatory blocking IgG4 [23]. The pivotal role of complement has been demonstrated using the mouse model that had been used previously to deduce the autoimmune basis of BP [2]. Mice depleted of complement by pretreatment with cobra venom factor or a genetic C5-deficient mouse strain did not develop blisters following the injection of pathogenic rabbit BP180 antibodies, and $F(ab')_2$ fragments of the IgG antibody that cannot bind complement did not produce

disease when injected into animals [24]. Blister formation in C5-deficient mice could be restored if fragments of C5a were injected with the pathogenic anti-BP180 IgG. C5a fragments are thought to stimulate the recruitment of neutrophils to the site of inflammation [24]. The importance of neutrophil recruitment in the pathogenesis of this disease has been shown using the mouse model. Mice depleted of neutrophils by pretreatment with an antineutrophil serum become resistant to the pathogenic effects of BP180 antibodies [25], indicating that the inflammatory response in BP is in part mediated by neutrophils. The role of proteases in blister formation has been shown using mouse models either genetically deficient for neutrophil elastase or with elastase inhibitors, and by demonstrating that elastase can cleave BP180 *in vitro* and *in vivo* [26]. Eosinophil infiltration occurs [27] and releases a 92-kDa gelatinase (gelatinase B or MMP-9) at the blister site that can cleave BP180 [28]. Mice genetically deficient for gelatinase B did not produce blisters after infusion with antibodies to BP180, unless reconstituted with neutrophils from normal mice [29].

All these data taken together suggest a mechanism for blister formation. Autoantibodies bind to the BP antigens and activate complement. Complement components set off an inflammatory cascade attracting leukocytes, degranulating mast cells and releasing inflammatory mediators. The activated inflammatory cells release lysosomal enzymes and proteases, cleaving the target antigens and disrupting the hemidesmosomes, resulting in blister formation.

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Pathology. The blister in BP is subepidermal with an intact and often viable epidermis forming the roof. The blisters may contain numerous eosinophils and neutrophils. Biopsies of blisters and from erythematous areas of skin show a dermal inflammatory infiltrate containing many eosinophils and neutrophils with lymphocytes and histiocytes; eosinophilic spongiosis may also be seen. There are patients with BP in whom the dermal infiltrate is so intense in the papillae that it cannot be distinguished from dermatitis herpetiformis. Old blisters may

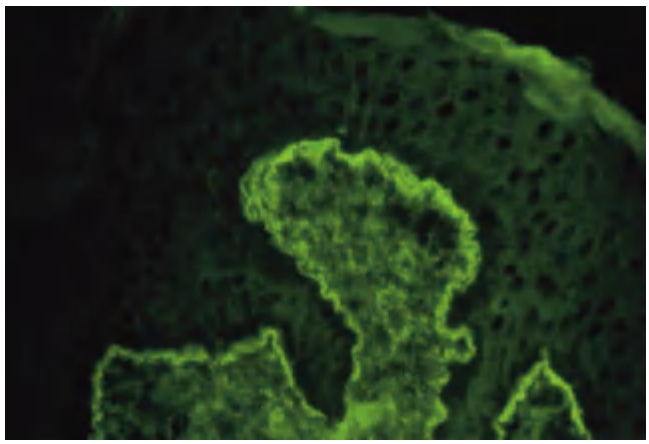

Fig. 41.13 Immunofluorescence showing IgG at the basement-membrane zone in a patient with pemphigoid. (Courtesy of Dr R.J. Pye, Addenbrooke's Hospital, Cambridge, UK.)

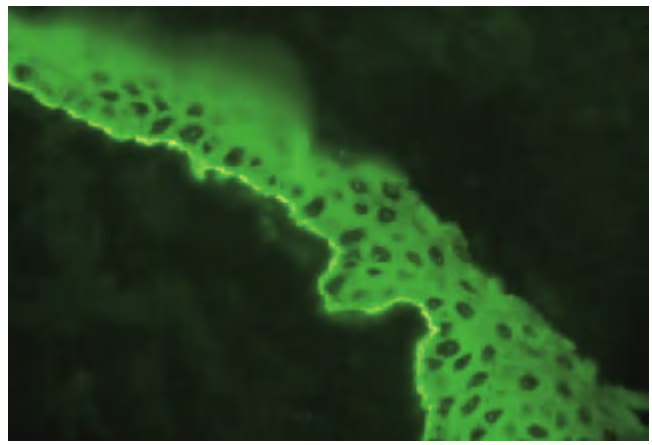

Fig. 41.14 Split-skin substrate with pemphigoid sera showing immunofluorescence of the roof of the split. (Courtesy of Dr J. Allen, Oxford Radcliffe Hospital, Oxford, UK.)

demonstrate re-epithelialization along the base giving an artefactual intraepidermal blister. Biopsies taken from apparently normal and non-inflamed skin are non-diagnostic or normal.

The findings with immunofluorescence are summarized in Table 41.6 and in a review [1]. Positive direct or indirect immunofluorescence is essential to confirm the clinical and histological diagnosis.

Direct immunofluorescence studies should not be performed on a blister, as the immunoreactants are often lost from the roof of a blister. They are best performed on a perilesional biopsy (within 2 cm of a lesion). The biopsy for immunofluorescence can also be taken from clinically uninvolved skin, the front of the thigh or flexor forearm, if this is more convenient or there are no active lesions, and from mucosal surfaces [2,3]. A 3–4-mm punch biopsy is ideal, and need not be deep. The biopsy will show either IgG and C3, or C3 alone along the basement-membrane zone (Fig. 41.13); deposition of IgA and IgM may also occur. The patient's biopsy can be split with 1 molar sodium chloride (salt-split) to provide additional information as to the localization of the target antigens, as the immune deposits should be associated with the hemidesmosomes, and thus present on the epidermal side of the split (roof of the artificial blister) [1,4]. The raising of a suction blister in the patient can give similar information but is rather cumbersome [5].

Indirect immunofluorescence can be performed on blood, blister fluid or urine (although less often positive), the latter two being useful substitutes for blood with an uncooperative child or adult [6,7]. About three-quarters of BP patients have a circulating IgG autoantibody to the basement-membrane zone. False-positives are rare, and the finding of circulating antibodies is diagnostic. The circulating autoantibodies in BP react with the epidermal side of normal human skin that has been split by prolonged incubation with salt or suction (Fig. 41.14) [5,8,9]. The use of salt-split skin increases the sensitivity of autoantibody detection and differentiates patients with BP from those with epidermolysis bullosa, and is to be recommended as a routine technique [8]. There are rare dermal binding BP patients and these can only be identified with immunoelectron microscopy or immunoblotting [10].

Recently, the use of ELISA techniques to detect antibodies against specific epitopes has been used as a research tool, and in time this may have a routine diagnostic application.

There is a change with time from inflammatory IgG1 to less inflammatory blocking IgG4 associated with diminution in disease activity, even though an overall diminution in titre may not be seen [11].

Occasionally, patients with BP have pemphigus-like antibodies, and the diseases may coexist. This may relate to the homology between BP230 and desmoplakin [12,13].

Immunoelectron microscopy demonstrates that the autoantibodies are deposited in the lamina lucida *in vivo* [14], but in contrast bind to the target antigens in association with the dense plaque (antibodies to BP230) and hemidesmosome surface (antibodies to BP180) *in vitro* [15].

Immunoblotting demonstrates that the majority of patients have circulating autoantibodies that react with the BP230 and BP180 antigens. The individual patient may react with either or both [16,17]. There is some suggestion that patients who have autoantibodies to BP180 may have more severe or prolonged disease [18–20]. A clinical pattern indistinguishable from BP may be seen in association with other target antigens [21].

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Clinical features. Bullous pemphigoid commonly starts with itching and a non-specific rash. The itch may continue for days to years before the rash appears. The non-specific rash often starts on the limbs and may be either urticaria-like or occasionally eczematous and rarely may simulate vesicular eczema. When urticarial, the prodrome lasts 1–3 weeks before blisters occur; when eczematous, the blisters may not develop for several months. Severe irritation with a faint dusky erythema in a figurate pattern may sometimes precede blister formation (Fig. 41.15). These changes may closely resemble erythema multiforme or dermatitis herpetiformis. Sudden generalization of the true eruption of BP follows the prodromal phase and most of the body may be affected within a week.

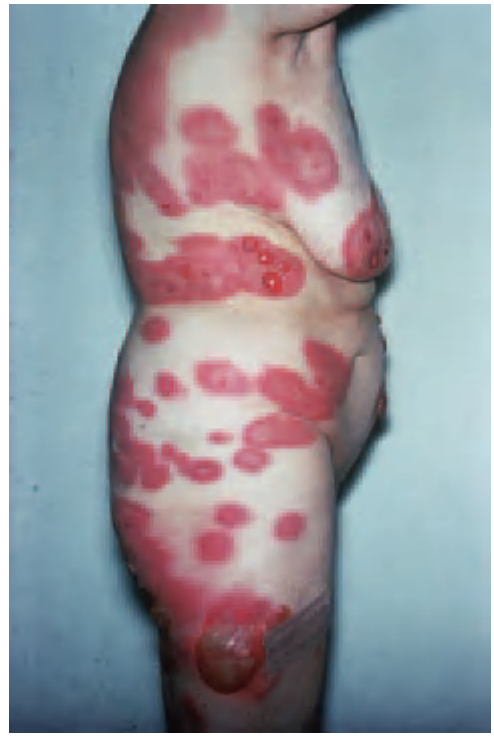

Fig. 41.15 Bullous pemphigoid. Figurate erythema with large tense bullae. (Courtesy of Dr R.J. Pye, Addenbrooke's Hospital, Cambridge, UK.)

Blisters may arise on erythematous and on normal skin and may be associated with oedema. The blisters are tense and dome-shaped, obtaining a diameter of many centimetres (Figs 41.15 & 41.16). They appear mainly on the flexural aspects of limbs and on the central abdomen. Their contents are usually clear serous exudate, although occasionally this is bloodstained. The blisters are tough and may remain intact for several days, the contents often becoming jelly-like with coagulated fibrin. In some blisters, the fluid is reabsorbed and the epithelium settles back in place like a skin graft. Those that do rupture leave erosions which heal rapidly, leaving mild post-inflammatory changes. Erythema may persist at the sites of previous blisters for many weeks or months. Milia may be profuse during the healing phase (Fig. 41.17). Mucosal lesions occur less frequently and are less severe than in mucous membrane pemphigoid and pemphigus vulgaris and are usually confined to the mouth. The oral lesions consist of small blisters which, like those of the skin, may remain intact and, if they rupture, heal rapidly.

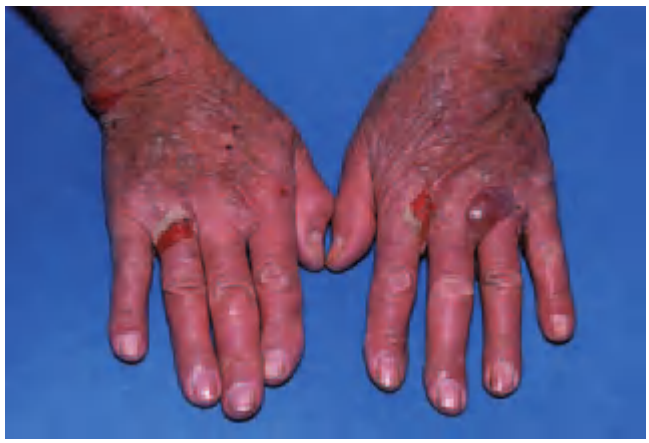

Fig. 41.16 Bullous pemphigoid. Tense haemorrhagic bullae. (Courtesy of Dr R.J. Pye, Addenbrooke's Hospital, Cambridge, UK.)

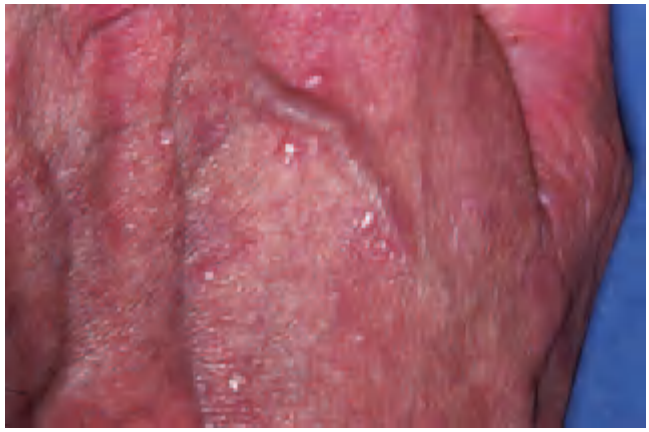

Fig. 41.17 Bullous pemphigoid. Milia at sites of severe blistering. (Courtesy of Dr R.J. Pye, Addenbrooke's Hospital, Cambridge, UK.)

The acute phase is usually accompanied by leukocytosis and eosinophilia, but fever is uncommon and, in spite of extensive blistering (Fig. 41.15), the patients' general condition remains good. Fresh crops of small blisters may continue to occur even after apparent control has been achieved with treatment.

Pemphigoid nodularis. This entity presents great diagnostic difficulty. Patients present with intensely itchy nodules, suggesting a diagnosis of prurigo nodularis. Blisters are rarely reported by the patient or seen, but when present are diagnostic. The eruption may be generalized or localized to the shins [1]. It may occur in children [2]. The immunopathology and antigens are the same as in ordinary pemphigoid [3]. Treatment is often difficult [1].

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Localized pemphigoid. An unusual variant is the localized form of the disease, which occurs in 5–30% of patients with BP. This form is usually limited to the lower extremities and responds well to treatment [1–3]. Localized disease may progress to the generalized form.

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Localized vulvar pemphigoid. This rarely reported entity is characterized by recurrent blistering confined to the vulva of young girls, which does not result in scarring [1,2]. A localized desquamative vaginitis has also described [3].

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Pemphigoid vegetans. This is a rare variant with circumscribed hypertrophic lesions with crusts or erosion, and pustules or vesicles at the periphery. The lesions chiefly affect intertriginous areas [1–3].

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Lichen planus pemphigoides. Bullous pemphigoid can occur in the setting of lichen planus in both adults and children, tense subepidermal blisters arise from the lesions of lichen planus and normal skin. The blistering usually responds rapidly to treatment and is short-lived [1–5]. The disease has immunofluorescence findings identical to BP although there are antibodies to a characteristic epitope of BP180 (see Chapter 42) [6].

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Induced BP and associated diseases. There are no well-defined causal agents, although a number of agents have been associated with the development of BP. Several drugs have been implicated [1], including frusemide [2], spironolactone [3], sulfasalazine, penicillins [4–6] and penicillamine [7]. These patients tend to have a younger average age than those in the idiopathic group. A case–control study suggests that antipsychotic drugs and aldosterone antagonists are associated with the development of BP [8]. Whether or not the drugs are exerting a direct effect on the immune system is not yet known.

Local irritation and damage to the skin have all been implicated in the induction of BP [9]. UV radiation or PUVA have been described as precipitating or exacerbating BP [10–14]. Other physical agents including thermal burns, wounds, localized trauma, skin grafts and radiotherapy have also been reported to induce BP in normal skin [9,15]. There have been a number of case reports of BP associated with radiotherapy for breast cancer [16,17]. Topical 5-fluorouracil has induced BP, but the role of topical chemical irritants such as dithranol (anthralin) and tar is less clear. Tetanus immunization has been reported to induce BP [18]. The mechanisms may be alteration or exposure of epitopes of adhesion complex proteins, or a change in the host immunological response.

Bullous pemphigoid is associated with certain other diseases; however, as it occurs in an elderly population, these patients often have other disorders at the same time. To determine whether the associations truly exist, prospective age-controlled studies are necessary. There are many individual case reports of BP in association with autoimmune diseases, although a case–control study did not show an overall association [19]. However, other systemic diseases have been reported in association with BP. These include diabetes mellitus [20,21], rheumatoid arthritis [22–24], ulcerative colitis [25–27] and multiple sclerosis [28,29]. There may be an association with neurological diseases [30]. More than 40 reports of BP in patients with psoriasis have been published, the blisters may be localized to the psoriatic lesions or independent of them, and in some instances therapeutic anthralin or UV radiation appeared to be the trigger [11,31]. A case–control study suggested an association between psoriasis and BP [32]. Bullous pemphigoid can occur in the setting of lichen planus (see above and Chapter 42).

There is controversy about the association between BP and malignancy. Initially, most large series concluded that there is no or only a very small increase in incidence of malignancy in BP patients compared with age- and sex-matched controls, although the association may exist in individual patients [33]. However, a large series of more than 1000 BP patients in Japan showed a 5.8% incidence of malignancy (with gastric carcinoma being the most common), which was significantly higher than that of age-matched controls [34]. A similar incidence was reported in Chinese patients with BP [35,36] and in Italy [37]. The carcinoma may express the BP antigens and evoke an immune response.

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Differential diagnosis. It may not be possible to diagnose accurately the early pruritus, urticaria-like, eczematous and erythematous prodromal eruptions. The possibility of BP should always be considered in the elderly patient with unexplained itch or irritable fixed erythematous lesions. The lower leg in elderly people seems particularly prone to develop blisters, and it must be remembered that eczema or oedema at this site may blister.

When blisters have appeared, it is usually possible to differentiate BP from pemphigus vulgaris on clinical grounds alone. The large, tense, tough blisters of BP can be distinguished from the smaller, flaccid, more easily broken blisters of pemphigus, and the severe mucosal lesions of pemphigus vulgaris are a further distinguishing feature. Clinically typical cases of BP may be found to be linear IgA disease or epidermolysis bullosa acquisita on investigation. More atypical cases of BP with small or absent blisters and/or annular lesions may resemble dermatitis herpetiformis, linear IgA disease, erythema multiforme and a final differentiation must then be on histological grounds. Direct and indirect immunofluorescence should confirm the diagnosis.

A more difficult task may be separating mucous membrane pemphigoid from BP. The generalized eruption of mucous membrane pemphigoid may be clinically and histologically indistinguishable from BP, and BP may evolve into mucous membrane pemphigoid [1]. However, involvement of the mucous membranes with scarring is characteristic of mucous membrane pemphigoid.

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Prognosis. Untreated BP runs a chronic self-limiting course over a number of months or years. Remission may occur within a few months or the eruption may continue for many years. The disease duration is usually 3–6 years, with most patients achieving complete remission off all treatment. Bullous pemphigoid can be fatal, particularly in the active blistering phase in elderly people, and about one-third of untreated patients died. The features that predict a poor prognosis are age, generalized disease and low albumin, and mortality is associated with high doses of steroids [1–5]. Localized disease is very responsive to treatment and more of these patients appear to go into remission.

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Treatment. The aim of treatment is to suppress disease activity with the minimum dosage of drugs necessary. BP patients are elderly, commonly on many drugs and very susceptible to adverse drug reactions and side effects. During prolonged treatment, it is advisable to aim for the presence of a blister once every few weeks so as to be certain that the patient is not being overtreated. The treatment of BP has recently been the subject of a systematic review and guidelines have been produced [1,2].

Topical and systemic corticosteroids are the mainstay of treatment. For localized BP, very potent topical steroids are worth trying first. Topical corticosteroids should be considered in all patients with BP, they aid control and may reduce the dosage of systemic agents. The recom-

mended initial dosage of prednisolone is 20 mg/day or 0.3 mg/kg/day in localized or mild disease, 40 mg/day or 0.6 mg/kg/day in moderate disease and 50–70 mg or 0.75–1 mg/kg/day in severe disease. Measures to prevent osteoporosis should be implemented from the start of systemic steroid therapy, whenever practicable. For mild to moderate disease, tetracycline and nicotinamide should be considered. Corticosteroid dosage can often be reduced over the course of a few weeks to 15–20 mg/day and thereafter more slowly. The majority can be managed on less than 10 mg/day prednisolone, which can be slowly withdrawn. We use a reducing regimen of 1 mg/month reduction once the dosage is below 10 mg/day. Immunosuppressants cannot be recommended routinely, but should be considered if the steroid dosage cannot be reduced to an acceptable level. Azathioprine is the one best established; methotrexate may be considered in patients with additional psoriasis [1].

There may be occasional flares which will require temporary increases in therapy.

Corticosteroid therapy has lowered the morbidity from the disease considerably and most patients achieve remission off all therapy. The mortality of BP still remains at 15–20%, and is nearly always treatment-related. However, treatment is essential to control this distressing disease.

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Mucous membrane pemphigoid

SYN. CICATRICIAL PEMPHIGOID; BENIGN MUCOSAL PEMPHIGOID; OCULAR PEMPHIGUS; SCARRING PEMPHIGOID

Definition. A chronic blistering disease of the mucosa, which may involve the skin, and usually results in permanent scarring of the affected area, particularly the conjunctiva. Recently, this entity has been defined on the basis of the clinical picture and renamed mucous membrane pemphigoid [1]. In the previous edition it was called cicatricial pemphigoid. The new entity includes patients formerly diagnosed as having oral pemphigoid and some linear IgA disease and epidermolysis bullosa acquisita patients, and excludes Brunsting–Perry pemphigoid. Brunsting–Perry pemphigoid will, however, still be discussed in this section, as some patients have mucosal involvement and identical cutaneous signs.

The clinical features, immunopathology and immunogenetics are summarized in Tables 41.5 and 41.6.

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Aetiology. Mucous membrane pemphigoid is a disease of late middle to old age [1,2], but can affect children and teenagers and is more common in females [3,4]. The annual incidence in western Europe is approximately 1 in 1 million [3,4] and is probably less in China and the East [5,6].

There is an association with HLA-DQ7 (DQB1*0301) in all types of mucous membrane pemphigoid [7–16].

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Pathogenesis. Mucous membrane pemphigoid is assumed to have a pathogenesis similar to BP. Some but not all patients have circulating autoantibodies, usually of low titre, that recognize proteins in the adhesion complex. The

reasons for the localization of mucous membrane pemphigoid to mucosal areas and limited areas of skin, and the scarring pattern are still not understood (see below). The antigens are identical to those of BP in many patients, although the binding site of the autoantibodies seems to be associated more with the anchoring filament than the hemidesmosome.

The major autoantigens in mucous membrane pemphigoid are all components of the basement-membrane zone (Fig. 41.11), and are associated with the hemidesmosome, the anchoring filament, and the anchoring fibrils (see below). There is an animal model for the pathogenicity of autoantibodies against laminin 5 (an anchoring filament component) [1] and *in vitro* models for other antibodies in mucous membrane pemphigoid [2–4].

Immunoblotting and immunoprecipitation have shown multiple target antigens (summarized recently in [5]). Many patients' autoantibodies target the BP antigens BP230 and BP180 [6,7]. BP180 is considered to be the major antigen, and numerous different epitopes, including the shed ectodomain, have been characterized as targets for the autoantibodies (Fig. 41.11) [8–11]. Some patient's antibodies bind to the α6 or β4 subunits of the α6β4 integrin [4,12–14]; a minority with dermal binding antibodies with salt-split skin target laminin 5 [15] or collagen VII [5,16].

The autoantibodies in mucous membrane pemphigoid may be IgG and/or IgA, and the presence of a dual antibody response is a marker for more severe disease [17–20]. The reason for the scarring is unclear. The demonstration of the autoantibodies is more difficult than in BP, and other mechanisms may be involved. Many patients share target antigens and HLA-DQ7 with BP and thus the scarring cannot be attributed solely to the site of the immune reaction or to differing immunogenetics. The nature of the inflammatory response and the cytokine network activated is a current focus for investigation, and probably determines the outcome of the lesions.

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Pathology. Histological examination of a blister is helpful only if it is intact and recent. Biopsy of an erosion is rarely helpful. Blisters in the mouth and on the skin show subepithelial or subepidermal blister formation, but often lack distinctive and diagnostic features. There are usually fewer eosinophils present in the cutaneous lymphohistiocytic infiltrate than in BP. At a later stage there is fibrosis, the distinctive feature of mucous membrane pemphigoid. The conjunctiva shows invasion of the epithelium by inflammatory cells and an appearance of granulation tissue in the submucosa. The corneal epithelium may later be transformed into an epidermis-like structure.

The findings with immunofluorescence are summarized in Table 41.6 and there is a detailed review [1].

The site for biopsy for direct immunofluorescence often presents a problem. The involvement of mucosal surfaces may mean that there is no perilesional area accessible to the dermatologist. However, it is worth taking a 3–4-mm punch biopsy or shave biopsy from uninvolved skin and from the inner lower lip [2]. The help of other specialities is needed to take biopsies from bulbar conjunctiva and other mucosal surfaces. The direct immunofluorescence

findings are of linear basement-membrane zone IgG or C3, and less commonly IgA and IgM [3,4]. Not all patients with the clinical disease have positive immunofluorescence; in one series, the conjunctiva was most frequently positive [2].

With indirect immunofluorescence, the serum in mucous membrane pemphigoid does not always contain detectable circulating autoantibodies, the use of salt-split skin increases the sensitivity of the technique, and often demonstrates the presence of IgA autoantibodies that are not detected on intact skin [5–7]. The majority of sera bind to the epidermal aspect of split skin (Fig. 41.14). However, there are some that bind dermally [5–7], and these usually have circulating antibodies to laminin 5 [8], or rarely collagen VII [7]. The use of intact or salt-split mucosa does not improve the overall sensitivity [9]. The IgG autoantibodies are most commonly detected and are usually of the IgG1 and IgG4 isotypes, with IgG4 being present in nearly all cases [10]. The IgA autoantibodies are present in a minority of cases and are all IgA1 [5].

The immunoelectron microscopy data suggest that the antigens of mucous membrane pemphigoid are within the lamina lucida or associated with the lamina densa [11–13]. Thus, the antigens or their epitopes do seem to differ in their location from those of BP.

There are multiple target antigens including BP180, BP230, α6β4 integrin, laminin 5 and collagen VII (summarized recently in [7]), explaining the variation in immunofluorescence patterns.

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Clinical features. The striking features are the recurring blisters on either a mucous membrane or an area of skin often near one of the orifices (Fig. 41.18) [1], together with the tendency for scars to form at these sites. The initial site may be any mucous membrane including the conjunctiva, the oral mucosa and those of the nose, larynx, pharynx, oesophagus, penis (Fig. 41.19), vulva, vagina and anus.

Oral lesions occur in the majority of patients [1]. In the mouth, vesicles or small blisters, which remain intact for some time, may be seen and when erosions form they are slow to heal. Persistent extensive erosions may be present

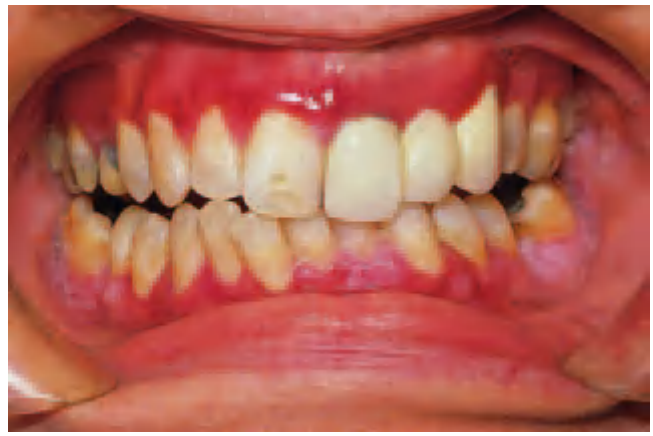

Fig. 41.18 Mucous membrane pemphigoid. Erosions around the gingival margins. (Courtesy of Dr R.J. Pye, Addenbrooke's Hospital, Cambridge, UK.)

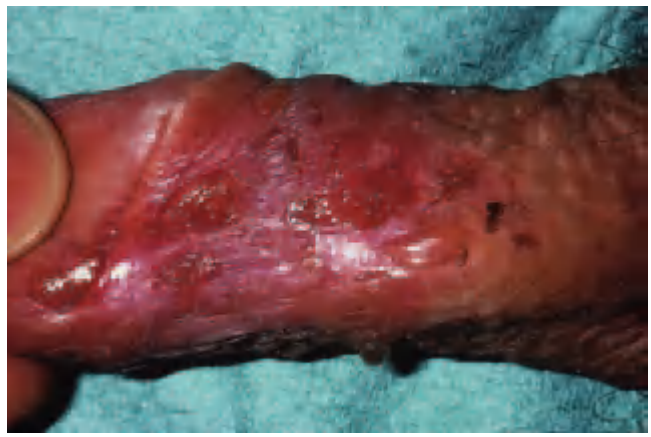

Fig. 41.19 Mucous membrane pemphigoid. Recurrent bullae and ulceration of the penis resulting in some scarring. (Courtesy of Dr R.J. Pye, Addenbrooke's Hospital, Cambridge, UK.)

in the buccal mucosa and especially the palate. Desquamative gingivitis with eroded bleeding gums and occasionally blisters is common (Fig. 41.18). Localized oral pemphigoid was the name previously given to patients in whom there were only oral lesions without scarring. Adhesions may develop between the buccal mucosa and the alveolar process and around the uvula and tonsillar fossae. Extension of the disease to the pharynx and oesophagus causes dysphagia and may give rise to strictures, which can result in weight loss often necessitating surgical intervention [2]. The disease can involve the larynx manifesting with hoarseness and, in rare cases, may give rise to strictures causing stridor and even asphyxiation requiring surgical intervention [3]. Deafness from involvement of the middle ear has been reported [4].

The genitals are involved in half of female patients, with blisters and erosions of the vulva [5]. Scarring leads to obliteration of the vulval architecture with labial fusion, introital shrinkage and end-stage scarring that may be indistinguishable from lichen sclerosus [6]. The penis may be involved with blisters and erosions and adhesions may form between the prepuce and the glans penis.

Conjunctival lesions may start in one eye but will later involve both. At first, there may be a simple conjunctivitis causing redness, soreness and discomfort, and this may last for years, with alternating periods of activity and remission. Occasionally, episodes of blistering may be associated with pain and discomfort, and blisters or erosions may rarely be visible on the tarsal conjunctiva. Scarring can also occur without any preceding symptoms. There is progressive scar tissue formation, with forniceal shrinkage, linear scarring, formation of symblepharon, adhesions between the palpebral conjunctiva and corneal involvement. It becomes difficult to move the eyes. The conjunctiva becomes shrunken and dry and the lower lids become inverted causing entropion (Fig. 41.20). In the final stages, the cornea becomes dry and opaque, the 'statue eye'. The conjunctivae are eventually affected in many patients, but other areas may be involved for several years before the eyes become affected.

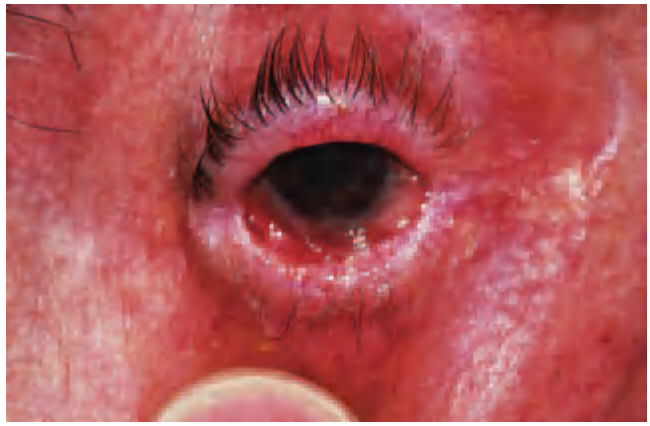

Fig. 41.20 Mucous membrane pemphigoid. Severe scarring and blindness. (Courtesy of Dr R.J. Pye, Addenbrooke's Hospital, Cambridge, UK.)

Two types of skin lesion may occur, the most common of which is a generalized bullous eruption such that an initial diagnosis of BP is made [7]. The second is a localized erythematous plaque, which becomes the site of recurrent blisters with subsequent scarring and hyperpigmentation. These localized lesions are often near affected mucosal surfaces. The scalp may be involved and the scarring and atrophy produce permanent alopecia [8].

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Localized oral pemphigoid. These patients were previously regarded as a variant of BP, as they had disease confined to the mouth, and without scarring.

Brunsting–Perry pemphigoid. In 1957, Brunsting and Perry [1] described a group of patients who developed disease localized to the scalp or face, with grouped subepidermal bullous skin lesions that leave scars and may result in permanent alopecia. In the initial description, the patients did not develop mucous membrane involvement. However, in many such patients mucosal involvement does ensue and they are best diagnosed with mucous membrane pemphigoid.

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Associated diseases. There is an association with autoimmune disease, both organ- and non-organ-specific [1]. There is also an association with lichen sclerosus [2] with which it may share clinical similarities in the genital area as well an association with HLA-DQ7 (DQB1*0301) [3,4]. There is no overall association with malignancy [5], apart from patients with laminin 5 antibodies [6]. Most of the case reports of malignancy are associated with laminin 5 mucous membrane pemphigoid [7,8].

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Prognosis. Mucous membrane pemphigoid is a chronic debilitating and mutilating disease. It can affect the general health causing blindness, weight loss, respiratory, sexual and urinary problems. Impairment of vision is the most important complication, with some patients becoming blind in both eyes. In rare cases, patients may die from laryngeal stenosis or complications of treatment. Unlike BP, it does not appear to be self-limiting, and prolonged remissions are rare [1,2] except in localized oral or skin disease [3]. The disease often extends over many years with periods of activity and extension followed by quiescent phases. Very rarely, carcinoma has arisen in chronic oral or oesophageal lesions [4].

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Differential diagnosis. The oral lesions, which may appear first, are difficult to differentiate from pemphigus vulgaris or from erosive lichen planus. Desquamative gingivitis may be a manifestation of mucous membrane pemphigoid or lichen planus. The clinical signs elsewhere differentiate these conditions, but there are patients in whom initial differentiation may be impossible.

End-stage scarring of the conjunctiva may resemble scarring that can occur as a result of severe infective conjuctivitis, chronic allergy, reactions to topical drugs, erythema multiforme and toxic epidermal necrolysis, epidermolysis bullosa or burns. Similarly, the end-stage scarring of the genital region may mimic the more common lichen sclerosus and erosive lichen planus. The history of the mode of onset and the evidence of other active lesions should be helpful in diagnosis. The generalized skin eruption is indistinguishable from that of BP; however, the presence of mucosal lesions and scarring favour the diagnosis of mucous membrane pemphigoid. Fixed scaly patches near the face and scalp may resemble pemphigus erythematosus.

Histological examination of a recent blister but not an erosion is helpful. Direct immunofluorescence on perilesional or clinically uninvolved mucosa and skin and indirect immunofluorescence are diagnostic if positive.

Treatment. Treatment is difficult and a systematic review has demonstrated how little evidence there is for the treatments used [1,2]. The disease activity fluctuates without treatment, and most treatments modify disease activity rather than totally suppressing it [3]. Treatment approaches have recently been summarized by an international consensus [4].

Local treatments are crucial and may be sufficient to control the disease to an acceptable level [3,5].

Systemic treatments are required for severe mucosal and laryngeal lesions and the control of generalized bullous eruptions, but are not always successful. The best evidence is for the use of cyclophosphamide in severe ocular disease, and for dapsone or sulfonamides in moderate to severe disease [1,2,6–8]. Dapsone and sulfamethoxypyridazine or sulfapyridine may be of value in controlling oral and cutaneous blistering and ocular disease [9,10]. Azathioprine is used but there are no trials to support this. There are recent reports that systemic tetracyclines alone or combined with nicotinamide may be helpful for oral lesions [11]. Recently, the use of intravenous immunoglobulins has been advocated [4,12]. The usual approach is to start with the least toxic therapies, in mild to moderate disease. In rapidly advancing disease threatening sight or airway, more aggressive treatment is needed.

Oral lesions are often helped by local treatment with topical steroids, as mouthwashes, sprays or applications, or tetracycline mouthwashes. The sprays and mouthwashes may also help the pharynx and oesophagus. Tetracyclines and nicotinamide can be helpful [5]. Oesophageal strictures may necessitate dilatation, which gives excellent results. Tracheotomy, which may need to be permanent, can be life-saving if there is stridor.

The management of ocular disease needs to be performed by an ophthalmologist with experience in treating mucous membrane pemphigoid, and includes topical steroids and subconjunctival injections of corticosteroid suspension and mitomycin [13] that may be temporarily effective for conjunctival disease, but neither these treatments nor systemic dapsone, cyclophosphamide, intravenous immunoglobulins and/or corticosteroids will halt

the progress in every case. Surgery to the lashes, division of adhesions and grafting may be required. Some patients will become blind.

Genital lesions may respond to potent topical steroids or to the combination of topical steroid and tetracycline. Vulval adhesions may require surgical division, and a Fenton's procedure to enlarge the introitus may be required in sexually active patients. Circumcision may be required in men.

Persistent skin erosions on the scalp or face can be helped by potent topical steroids.

The role of mucosal grafts is controversial and in the eye may have an adverse effect [14].

Mucous membrane pemphigoid is frustrating for the patient and the physician, and the patients endure many years of discomfort and morbidity, and rarely mortality from the disease and its treatment.

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Pemphigoid gestationis

SYN. HERPES GESTATIONIS

Definition. Pemphigoid gestationis is an intensely pruritic bullous eruption that may develop in association with pregnancy or rarely the trophoblastic tumours, hydatiform mole and choriocarcinoma. The clinical features, immunopathology and immunogenetics are summarized in Tables 41.5 and 41.6.

Aetiology. Pemphigoid gestationis is a rare condition that may affect from 1 in 10 000 to 1 in 60 000 pregnancies [1,2]. In western Europe the incidence is approximately 0.5 per million population [3,4]. It does occur in Afro-Caribbeans, but is very rare in the Far East [5].

The disease arises only in the presence of paternal derived tissue, the fetus, and rarely hydatiform mole or choriocarcinoma, and thus tissue expressing HLA antigens from the father [6–8]. The fathers are more often HLA-DR2 than the control population [9]. It is considered that an HLA mismatch between mother and fetus triggers an immune response that cross-reacts with the maternal skin. There is clinical evidence of placental insufficiency (see below), and immunohistochemical findings of immune activation in the placenta [10,11], and affected mothers have high titres of antibodies to HLA class 1 antigens [12].

The mothers frequently manifest the autoimmune haplotype, HLA-B8, -DR3 and -DR4 [6,13,14], and this association has been verified in a Mexican population [15]. They also have, as predicted for this HLA haplotype, a linkage disequilibrium with certain immune response genes and thus a high incidence of the C4 null allele, which influences clearing of immune complexes [16]. The immunogenetics of the mothers increases susceptibility to the development of pemphigoid gestationis.

Pemphigoid gestationis is associated with other autoimmune diseases (see below) implying an autoimmune basis [6,17,18].

The clinical course of pemphigoid gestationis may be modified by changes in oestrogen and progesterone levels; exacerbations may occur with oral contraceptives and the severity may vary during the menstrual cycle [6,18].

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Pathogenesis. The autoantibodies are directed at the same hemidesmosome target antigens as in BP, namely BP180 and, less commonly, BP230 [1,2]. The extracellular region of BP180 adjacent to the transmembrane portion, the NC16A domain (Fig. 41.11), is the immunodominant epitope [3], and the antibody response seems to be restricted to this region [4–6]. This extracellular location makes it a likely target for pathogenic autoantibodies. The same epitopes are recognized by the autoantibodies and T cells [5]. There is a report of a target antigen of 200 kDa in an individual patient [7].

An animal model has demonstrated that autoantibodies to BP180 are pathogenic and require complement (see p. 41.24) [8,9].

The autoantibodies react with the basement membrane of amnion placenta from the second trimester onwards and are found in the fetal skin and cord blood [10–13]. The autoantibodies are IgG antibodies of the IgG1 and IgG3 subclasses [14,15]. These IgG1 antibodies avidly bind C3, and often this binding is detected rather than the IgG antibodies themselves. There is a single case report of IgA antibodies [16].

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Pathology. The histopathology of the early urticated lesions of pemphigoid gestationis shows epidermal and papillary dermal oedema with occasional foci of eosinophilic spongiosis. The bullous lesions are subepidermal and contain numerous eosinophils. The split is through the lamina lucida.

The findings with immunofluorescence are summarized in Table 41.6. Direct immunofluorescence studies show that in all active cases of pemphigoid gestationis there is C3 deposition at the basement-membrane zone. In some cases, IgG is also found. C3 and IgG deposition are found in the placenta and fetal skin [1–4].

Indirect immunofluorescence studies demonstrate binding of C3 to the basement-membrane zone; this serum factor was known as the HG factor. Although conventional immunofluorescence techniques are able to demonstrate IgG in only approximately 25% of cases, it is now clear that the autoantibody is an IgG of the IgG1 subclass [5,6]. The autoantibodies bind to the epidermal side of salt-split skin [7].

Immunoelectron microscopic studies have confirmed that IgG is deposited along the basement-membrane zone chiefly within the lamina lucida and localized to proximal part of the anchoring filament [8–10].

Immunoblotting techniques have shown that the major antigen recognized by the circulating autoantibodies is BP180 [11,12].

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Clinical features. Pemphigoid gestationis may begin at any time between 4 weeks' gestation and 5 weeks' postpartum, with the majority presenting in the second and third trimester [1,2]. Almost half of cases develop in the first pregnancy. There is a high risk of recurrence in subsequent pregnancies, the onset is likely to be earlier than in the previous one and the disease may be very different in severity. In many cases, the disease becomes relatively quiescent in late pregnancy, only to flare severely immediately postpartum [1]. Usually, the disease lasts several weeks to months, the average is 6 months, but sometimes it can continue for years afterwards [2]. The likelihood of prolonged disease is increased by older age, multiparity and mucosal involvement [3].

Pemphigoid gestationis is intensely itchy. The condition usually begins around the umbilicus, and then spreads to the abdomen, thighs, limbs, palms and soles (Fig. 41.21). Involvement of the oral cavity is relatively rare. Early in its course, the eruption consists of urticated papules, plaques, target lesions and annular wheals, associated with marked pruritus. Subsequently, vesicles and larger blisters appear (Figs 41.21 & 41.22).

Neonatal pemphigoid gestationis may occur in 3% of pregnancies [2], with positive direct immunofluorescence in the neonate [4,5], resulting from transfer of antibodies across the placenta. It usually resolves rapidly without treatment [2,4,5].

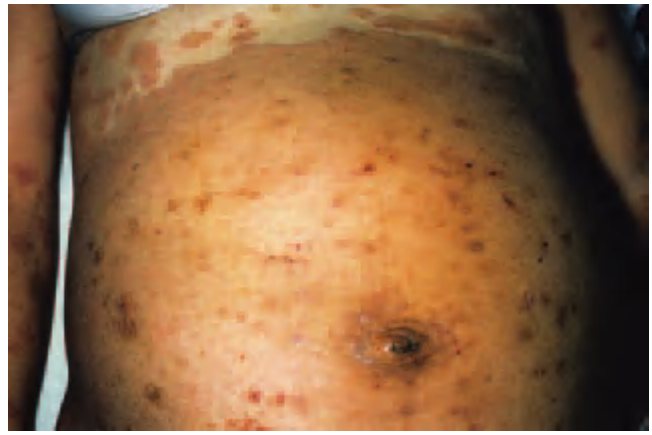

Fig. 41.21 Pemphigoid gestationis. Early pruritic erythematous stage. (Courtesy of Dr P. Hudson, Peterborough Hospital, Peterborough, UK.)

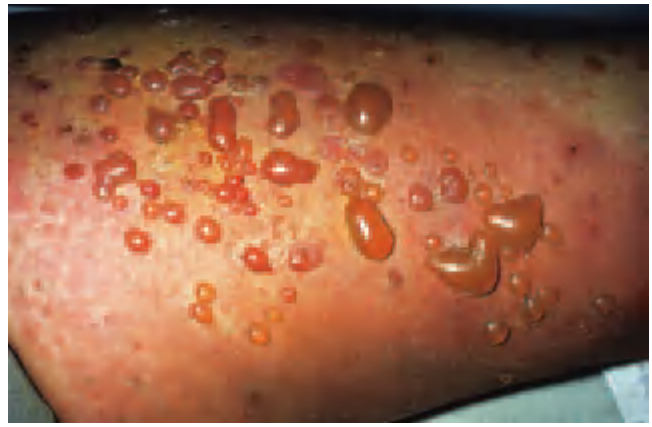

Fig. 41.22 Pemphigoid gestationis. Bullae arising on urticated erythematous skin on the thigh. (Courtesy of Dr P. Hudson, Peterborough Hospital, Peterborough, UK.)

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Associated diseases. Pemphigoid gestationis is associated with other autoimmune diseases, 14% in a recent study [1], particularly with Graves' disease (10%), hypothyroidism, vitiligo, alopecia areata and autoimmune thrombocytopenia [1–3].

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Prognosis. Pemphigoid gestationis tends to improve postpartum, but it may be weeks, months or years before there is complete resolution. In rare cases, the disease may evolve into BP [1]. There are often flares with menstruation. There are usually dramatic flares with the oral contraceptive, which is contraindicated while the disease is still active.

There are reports of persistent disease postpartum and these cases are more likely to have previous disease and to be older [1,2].

Once pemphigoid gestationis has occurred, it is likely to recur in subsequent pregnancies, and may be more or less severe. Approximately 8% of subsequent pregnancies are spared [3]. Although a change in partner does not increase the risk of developing pemphigoid gestationis, it is unclear whether it alters the risk of recurrence [3]. Patients should be counselled as to the risk of recurrence, but not advised from having further pregnancies because they have had pemphigoid gestationis.

The modern view is that pemphigoid gestationis is associated with premature delivery and a risk of low birth weight [4–6]. Deliveries from mothers with pemphigoid gestationis should take place in departments of obstetricians that have facilities for special care of the newborn.

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Differential diagnosis. The main problem is the differentiation of pemphigoid gestationis from the much more common urticarial eruption that begins in later pregnancy, termed polymorphic eruption of pregnancy (see Chapter 70). This usually begins in the stretch marks and almost never blisters. The histopathology often differentiates the two conditions, and immunofluorescence is negative in polymorphic eruption of pregnancy.

Treatment. In mild cases of pemphigoid gestationis, topical potent or very potent steroids can be successful, and this was so in approximtely 20% in a recent retrospective study [1]. They are often combined with a systemic antihistamine (suitable for use in pregnancy) [1]. Once the blisters develop systemic steroids are usually necessary. Moderate disease responds to prednisolone 20–30 mg/day, severe disease may need prednisolone 40–80 mg/day. Prednisolone can usually be reduced fairly rapidly to a much lower maintenance dosage. Because postpartum exacerbations are so frequent, it is worth increasing the corticosteroid dosage temporarily at the first sign of a flare. Plasmapheresis can be considered in the most severe cases [2]. The role of dapsone is unclear and the drug can cause haemolytic disease in the neonate [3]. There is only anecdotal support for the use of pyridoxine [4].

Postpartum treatment can be a problem if the mother wishes to breastfeed, as the drugs pass into the breast milk. Antihistamines can cause drowsiness in the baby, steroids at high doses (more than 40 mg/day prednisolone) can cause adrenal suppression, and dapsone can cause haemolysis. Paediatricians should therefore be consulted in this situation. In the non-breastfeeding woman there are reports of the successful use of tetracyclines, sometimes with nicotinamide [5–7]. Immunosuppressive treatment and immunomodulating treatments such as intravenous immunoglobulins have also been used [8–10].

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Linear IgA disease

SYN. CHRONIC BULLOUS DISEASE OF CHILDHOOD; JUVENILE DERMATITIS HERPETIFORMIS; JUVENILE PEMPHIGOID; LINEAR DERMATITIS HERPETIFORMIS; LINEAR IgA BULLOUS DERMATOSIS

Definition. Linear IgA disease is a chronic acquired subepidermal disease of children and adults, with cutaneous and mucosal involvement, characterized by IgA basement-membrane antibodies. The disease responds to dapsone and has a tendency to remit.

Two main clinical syndromes are distinguished: chronic bullous disease of childhood, beginning in childhood, and adult linear IgA disease, beginning any time in adult life. They differ in their age of presentation and to some extent regarding their clinical signs, but there is much overlap, and the immunopathology and immunogenetics are common to both diseases. Clinical features, immunopathology and immunogenetics are summarized in Tables 41.5 and 41.6.

Aetiology. Linear IgA disease affects all ages, from babies of a few months to the elderly. The majority of children present while toddlers or preschool children. Teenagers and young adults also present with the disease and there is a second peak over 60 years [1]. Linear IgA disease is one of the less common subepidermal blistering diseases in western Europe with an incidence of less than 0.5 per million, chiefly adults [2,3]. It is more common in China where it is about one-third as common as BP [4], and is reported from South-East Asia [5–7]. Moreover, one-third of Chinese patients are children [4]. There seem to be more children with the disease in developing communities (e.g. China, Malaysia, Sri Lanka, India, Thailand, Tunisia, Mali) and black children in South Africa than in western Europe [8–15]. The sex incidence is about equal or there may be a slight excess of female patients.

There is a strong association between linear IgA disease and the extended autoimmune haplotype HLA-B8, -CW7 and -DR3 in UK and black South African patients and possession of this haplotype is associated with an early disease onset [11,16]. This extended haplotype is in linkage disequilibrium with a high producing allele of TNF, and this association exists in linear IgA patients and confers a worse prognosis [16].

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Pathogenesis. The autoantibodies in linear IgA disease are IgA, which is unusual for an autoimmune disease, and usually IgA1 and monomeric [1–3]. However, IgG antibodies can also be detected by immunoblotting techniques, although their antigen repertoire is more limited [4–6].

The IgA antibodies are directed at a number of different target antigens within the adhesion complex (Table 41.5; Fig. 41.11). The major antigen in linear IgA disease is BP180/collagen XVII and its shed ectodomain, formerly known as LAD1, with molecular weights of 97 and 120 kDa (Fig. 41.11). There are also antibodies to BP230 and a unique antigen LAD285, which has a molecular weight of 285 kDa [5–10]. The autoantibodies recognize many different epitopes on BP180, including the NC16A domain (Fig. 41.11) [11–13]. T-cell responses to BP180 have been demonstrated [14]. Collagen VII, the anchoring fibril component, is a rare antigen and is almost never associated with a mechanobullous scarring phenotype, unlike classic epidermolysis bullosa acquisita (see below) [15–18]. There are other unidentified dermal antigens [6,19].

There is indirect evidence that the antibodies are pathogenic, in that they cause splitting of skin in culture and binding of neutrophils to the basement-membrane zone [20,21].

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Pathology. The histological features are not specific for the condition. The subepidermal vesicles may contain numerous eosinophils suggestive of pemphigoid. In some blisters, neutrophils predominate and dermal capillary microabscesses are seen, suggesting dermatitis herpetiformis. Others show subepidermal blisters with non-specific features. An old blister will give misleading results. In a child, it is not always worthwhile performing a biopsy on a lesion, as direct immunofluorescence will give the diagnosis and is often easier and less traumatic to perform. The findings with immunofluorescence are summarized in Tables 41.6 and a detailed review has been published [1].

Direct immunofluorescence can be performed on clinically uninvolved skin, and the back is often convenient (and out of sight) in a child. The forearm is the least satisfactory site [2] and mucosal biopsies from the mouth, but not necessarily the conjunctiva, are also positive [3]. In all cases there is linear deposition of IgA along the basement-membrane zone. There may also be other immunoreactants, IgG, IgM or C3, on direct immunofluorescence [4,5]. Direct salt splitting of the biopsies or the raising of suction blisters in patients shows that the deposition of autoantibodies can be associated with the epidermal aspect of the artificial blister, with the dermal aspect or both [6,7].

The significance of the rare linear granular pattern of IgA deposition at the basement-membrane zone is still unclear [4]. Some patients with this pattern have true dermatitis herpetiformis but others may have autoantibodies to unusual target antigens.

Indirect immunofluorescence for IgA basement-membrane zone antibodies is more often positive in children (approximately 80%) than adults (approximately 30%) [5]. The titres are usually low, of the order of 1 : 5 or 1 : 10, but occasionally much higher. The use of normal human skin split through the lamina lucida with suction or, more commonly, 1 molar salt increases the sensitivity and gives additional information as to the site of the target antigen. The majority of sera demonstrate binding to the epidermis, implying an antigen associated with hemidesmosomes or the upper lamina lucida; a few have a combined pattern, and a larger minority bind to the dermal aspect of the artificial blister, suggesting a lower lamina lucida or dermal antigen [5,6,8].

Blister fluid is an alternative to serum for indirect immunofluorescence and may be easier to obtain in a child [9]. However, urine did not prove a practical alternative [10].

The presence of IgG autoantibodies on direct or indirect immunofluorescence causes problems with disease definition, and has been used to define a further entity, mixed immunobullous disease (see below) [11–13].

Immunoelectron microscopy studies have shown that the immunoreactants and target antigens are either associated with the hemidesmosomes, within the lamina lucida, in the subbasal lamina zone or in a mirror-image pattern on each side of the lamina densa [14–20].

Immunoblotting studies have demonstrated a variety of target antigens, in keeping with the multiple localizations found with split skin and immunoelectron microscopy studies. The antigens include both epidermal and dermal associated antigens, and the major one is BP180 (see above).

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Clinical features (Figs 41.23 & 41.24). The clinical features of children and adults are described separately as they are distinctive.

Chronic bullous disease of childhood. The mean age of onset is under 5 years, it is usually acute and the initial attack more severe than subsequent recurrences. Symptoms vary from absent or mild pruritus to severe burning. The face and perineum are involved, particularly in younger children. The perioral area, the eyelids, ears and scalp may be affected. The involvement of the perineum and vulva (Fig. 41.23) has been mistaken for sexual abuse in some patients. The eruption may spread to the trunk, thighs, limbs, hands and feet. The lesions comprise urticated plaques and papules, and annular polycyclic lesions often with blistering around the edge, the 'string of pearls' sign. Large blisters may develop and become very extensive, they are occasionally haemorrhagic, and usually arise on previously normal skin. Papules and vesicles also occur.

Mucosal involvement is common. The mouth may be involved, with ulcers and erosions, and hoarseness may indicate pharyngeal involvement. There can be nasal stuffiness and bleeding. The eyes are often sore or gritty and there is conjunctivitis [1]. The children who progressed to conjunctival scarring and blindness are most appropriately diagnosed with mucous membrane pemphigoid [1–4].

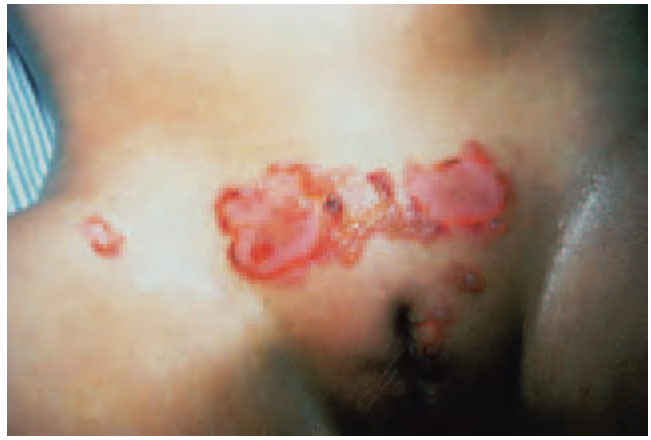

Fig. 41.23 Chronic bullous dermatosis of childhood. Cluster of blisters with new blisters forming around an older lesion (string of pearls). (Courtesy of Dr R.J. Pye, Addenbrooke's Hospital, Cambridge, UK.)

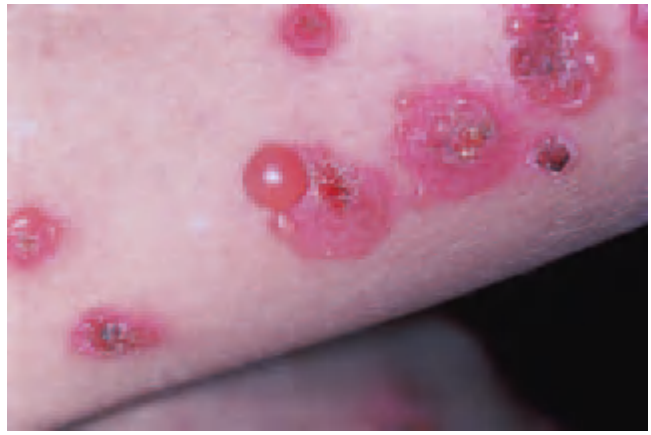

Fig. 41.24 Linear IgA disease. Intact tense bullae on the thigh and annular lesions. (Courtesy of Dr P. Hudson, Peterborough Hospital, Peterborough, UK.)

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Linear IgA disease of adults. This commences at any age from the postpubertal teenager to the ninth decade, most commonly after the age of 60 years. The onset may be insidious or, more usually, abrupt. Symptoms vary from mild pruritus to severe pruritus and burning. The trunk is almost always involved, and the limbs, face and scalp, hands and feet are commonly affected. The lesions comprise urticated plaques, papules and vesicles, and blisters. The blisters may arise from normal skin (Fig. 41.24) or from urticated plaques and can be haemorrhagic. The characteristic annular lesions with blistering around the edge are less common than in children (Fig. 41.24). Milia are almost unknown.

Mucosal involvement is common [1]. The mouth may be involved, with ulcers and erosions. Hoarseness indicates pharyngeal involvement. There is often nasal stuffiness, crusting and bleeding. The eyes are often sore or gritty. Involvement of the genitals and also the vagina can occur. Those few patients who progress to scarring, including blindness, are most appropriately diagnosed with mucous membrane pemphigoid [2,3].

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Dermal associated linear IgA disease. There does not seem to be a mechanobullous scarring phenotype for linear IgA disease when associated with dermal antigens including collagen VII [1,2]. Classic IgA epidermolysis bullosa acquisita with antibodies to collagen VII is very rare and progresses to a mucous membrane pemphigoid-like phenotype [3,4].

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Linear IgA mucous membrane pemphigoid. Patients with typical clinical signs of mucous membrane pemphigoid who have linear IgA on direct immunofluorescence should, following the International Consensus on Mucous Membrane Pemphigoid, be regarded as having mucous membrane pemphigoid [1]. Interestingly, this has been described in several children and some adults, and the case of linear IgA desquamative vaginitis is also best regarded as such [2–8].

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Mixed immunobullous disease. A small number (14) of patients with a dual antibody response of IgA and IgG autoantibodies have been studied. This immunopathological finding was seen in both children [1,2] and adults [3]. In most cases, the patients had a clinical picture compatible with linear IgA disease and a good response to dapsone or sulfonamides. The exact position of this entity is still unclear, but for practical purposes the patients are best managed as for linear IgA disease.

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Induced linear IgA disease and associated diseases. A number of precipitating factors are observed (namely infection and antibiotics (penicillins)) in approximately one-quarter of adults and more children [1,2], and the presence of building work in the home in approximately half of adult patients and three-quarters of the children [3]. The significance of these findings is unclear. Drug-induced linear IgA disease is commonly reported, vancomycin being the drug most frequently implicated [4–6] and diclofenac and other non-steroidal anti-inflammatory drugs less

commonly [7–12]. However, a large range of drugs has been reported [9,13,14]. Local skin trauma has initiated the disease in some cases [1,2,15].

Patients with linear IgA disease were originally thought to have dermatitis herpetiformis, but it is now clear that this is a totally distinct disease and there is no overall association with gluten-sensitive enteropathy [1,16,17]. There is an association with ulcerative colitis and other inflammatory bowel disease in a small number of patients [18]. There is no overall association with autoimmune disease, although autoantibodies are common [1].

There is an increased incidence of lymphoproliferative disorders in adults with linear IgA disease, which may occur after remission of the skin disease [2,19,20]. There are a number of case reports of various cancers in association with linear IgA disease, of which bladder and renal cancer are the most common, but there is no overall increase [2,21,22].

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Prognosis. Spontaneous remission occurs in the majority of patients after an average of 3–6 years, the TNF genotype of the patient influencing disease duration [1–3]. Initially, there were no reports of chronic bullous disease of childhood extending beyond puberty, but cases have now been documented [2,4]. Some of these patients are women of childbearing age. In pregnancy, often there is improvement or remission of the disease from the second trimester, and the women may be able to discontinue all drugs. However, there is usually a relapse at approximately 3 months postpartum [5]. There does not appear to be any fetal damage [5].

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Differential diagnosis. In the young infant, bullous impetigo may resemble the initial lesions, but its response to antibiotics differentiates it. Genetic epidermolysis bullosa is often present at birth and the family history further differentiates it. Bullous papular urticaria rarely affects the face or genital region and is usually of short duration. Childhood BP may give a similar clinical picture, but the deposition of IgG and C3 at the basement-membrane zone is diagnostic. The adult disease is frequently confused with atypical erythema multiforme, neurotic excoriations and nodular prurigo, dermatitis herpetiformis and, most commonly, BP. Histology is helpful and direct immunofluorescence is essential for diagnosis.

Treatment. A few patients have mild disease and can be controlled with topical steroids alone. The treatment of children can be difficult, because side effects limit the dosage of drugs used, but the drugs used are identical in

children and adults. The recent favourable reports of erythromycin suggest that this should be tried as first-line treatment in children [1]. Dapsone in regimens starting at less than 0.5 mg/kg, which often means giving it as 25 mg on alternate days or less in young children and 25–50 mg/day in an adult, may be slowly increased to a dosage of 1 mg/kg or a little more in a child and 100–150 mg in an adult to keep the patient comfortable and without significant side effects. Too rapid an increase in the dosage often results in haemolytic anaemia, which does not reach its maximum for a month. A fall in haemoglobin with a low mean corpuscular volume (MCV) indicates iron deficiency (resulting from intravascular haemolysis) rather than pure haemolytic anaemia. Patients at risk of glucose-6-phosphate dehydrogenase deficiency should be screened prior to treatment. Met-haemoglobinaemia is common, reaching a steady state after approximately 2 weeks, and may cause cyanosis, breathlessness and angina. Hepatitis, the dapsone syndrome (lymphadenopathy and hepatitis) and agranulocytosis are serious, usually early complications. Motor neuropathy may occur. Most complications occur in the first 3 months. Sulfonamides are alternatives. Sulfapyridine is often poorly tolerated and may cause an allergic reaction, hepatitis or agranulocytosis, and is used at a dosage of 250 mg/day to 3 g/day, which usually controls the eruption rapidly, but the dosage may need frequent adjustment. Sulfamethoxypyridazine (adult dose 250 mg/day to 1.5 g/day) is an alternative, which is often better tolerated. Dapsone and sulfonamides can be combined. Some patients do not respond to either of these, and corticosteroids may need to be added. A few patients are very difficult to control and may need azathioprine or ciclosporin. Success has been reported in small numbers of patients with other antimicrobials. These include tetracyclines and nicotinamide/niacinamide [2–4], penicillins [5–7] and recently erythromycin [1]. Colchicine has been used successfully in children and adults [8–13]. The cutaneous lesions are always much more responsive than the mucosal lesions, which can be treated with topical steroids (see p. 41.39).

In view of the ultimate spontaneous recovery in the majority of patients, attempts should be made to avoid overtreatment and the production of side effects with steroids.

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Epidermolysis bullosa acquisita

SYN. ACQUIRED EPIDERMOLYSIS BULLOSA; DERMOLYTIC PEMPHIGOID

Definition. Epidermolysis bullosa acquisita (EBA) is a rare condition in which patients may have chronic acquired trauma-induced subepidermal blistering or a clinical picture indistinguishable from BP. There is a distinctive immunopathology, and the disease is defined in terms of the target antigen (collagen VII). However, there are patients with the same clinical pattern in whom antibodies to collagen VII cannot be identified [1], and antibodies to collagen VII are found in patients with mucous membrane pemphigoid (see above) [2,3]. It is interesting that this acquired mechanobullous disease was named for its clinical resemblance to genetic dystrophic epidermolysis bullosa (see Chapter 40) and that the molecular basis of both these diseases is collagen VII. The clinical features, immunopathology and immunogenetics are summarized in Tables 41.5 and 41.6.

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Aetiology. EBA can occur at any age. It has been described in children and adults [1–5]. The original reports from the USA included many African American patients, and it may be more common in African races and orientals [6–9]. It is one of the rarest subepidermal bullous diseases in western Europe, with an incidence of about 0.25 per million, but may be more common in the Far East [7–11].

There is an association with HLA-DR2 in the USA [6] but not in Korean patients [12].

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Pathogenesis. Collagen type VII, the major component of the anchoring fibrils, is the target antigen recognized by autoantibodies from patients with EBA [1]. Collagen type VII comprises a globular amino non-collagenous domain (NC1) and a collagenous triple helix (Col-1), and the gene is located to the short arm of chromosome 3 [2]. The autoantibodies in EBA are directed at epitopes chiefly within the fibronectin-like region at the globular amino non-collagenous NC1 domain [3–7], although antibodies to the collagenous triple helix and NC2 and can be demonstrated [8,9].

The autoantibodies are IgG, and are of all the IgG isotypes, although the IgG1 and IgG4 isotypes may predominate in the chronic mechanobullous forms [10–12]. Some of the antibodies bind complement [12,13].

There is evidence that the autoantibodies are pathogenic. Complement-binding autoantibodies from patients with EBA bind to skin and attract neutrophils to the basement-membrane zone [14,15] and also induce blistering in the presence of neutrophils in sections of human skin [16]. There has been an animal model in which the immunopathological features and some histological features of the disease were induced in neonatal mice using serum from a single patient [17].

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Pathology. The blistering is subepidermal, but the precise histological findings depend on the stage of the disease. In inflammatory disease, there is a heavy predominately neutrophil infiltrate. In the mechanobullous non-inflammatory phase, the infiltrate is usually absent or sparse. The findings with immunofluorescence are summarized in Table 41.6 and a detailed review has been published [1].

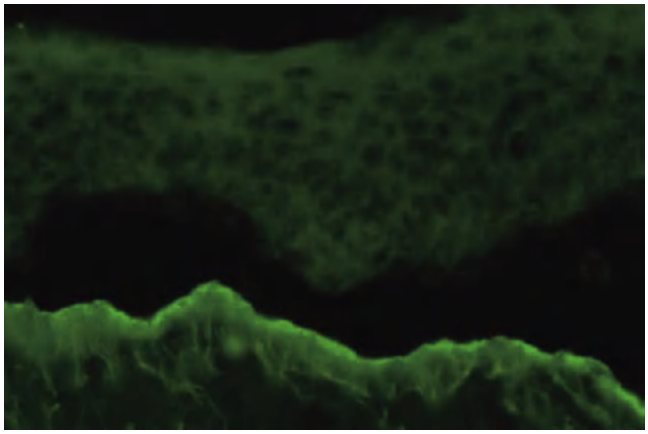

Fig. 41.25 Epidermolysis bullosa acquisita. Indirect immunofluorescence showing dermal binding of autoantibodies to salt-split skin. (Courtesy of Dr J. Allen, Oxford Radcliffe Hospital, Oxford, UK.)

On direct immunofluorescence, linear IgG at the basement-membrane zone is found in all patients, and linear IgA and IgM may also be seen. C3 has been reported in most cases. The basement-membrane staining may be broader than that seen in BP. Patients' skin split through the lamina lucida with suction (applied *in vivo*) or with 1 molar salt demonstrates the IgG antibodies to be bound to the dermal aspect of the blister [2].

Positive indirect immunofluorescence has been demonstrated in approximately half of patients tested with circulating autoantibodies binding to the basement-membrane zone. However, if skin is separated through the lamina lucida using 1 molar sodium chloride, or suction, and then used as substrate, the fluorescence is seen on the dermal aspect of the artificial blister (floor of the split skin) (Fig. 41.25) [3]. EBA serum is negative on toad skin [4,5]. An ELISA technique is more sensitive, but is not in routine use [6].

Electron microscopy has shown dermolysis and cleavage in the upper dermis with preservation of the basal lamina, but no reduction in the number of anchoring fibrils [7]. Amorphous material has been found beneath the basal lamina, sometimes in a band-like distribution [7–9].

Immunoelectron microscopy has shown that the IgG was deposited in the upper dermis beneath the basal lamina and within the sublamina densa zone [7]. Immunogold studies demonstrate that the autoantibodies bind to the non-collagenous ends (NC1 domain) of the anchoring fibrils and elsewhere [10,11].

Immunoblotting and ELISA techniques demonstrate that EBA autoantibodies recognize proteins of 290 and 145 kDa shown to be collagen VII, and that the immunodominant epitopes are within the NC1 domain, but that other regions are immunogenic (see above).

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Clinical features. Early in the disease, clinical manifestations may be very variable and may mimic a number of bullous dermatoses. Blisters may be serous or haemorrhagic, tend to be localized to areas of trauma, especially on the dorsa of the hands, tops of the feet and elbows, and heal with scarring, milia and hyperpigmentation (Fig. 41.26). Nails may be dystrophic but are often normal. Some patients have disease indistinguishable from BP,

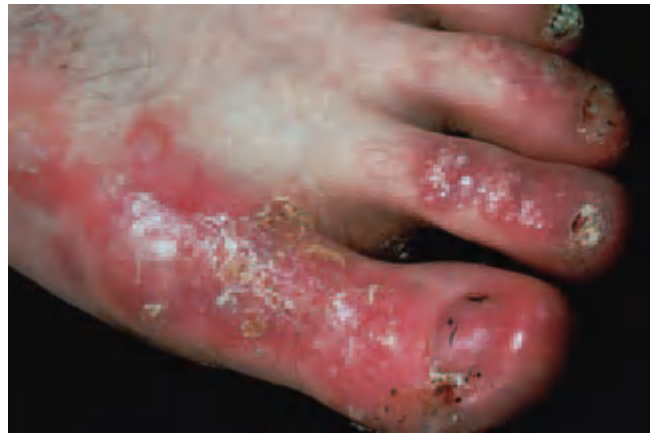

Fig. 41.26 Epidermolysis bullosa acquisita. Milia and scarring and dystrophic nails. (Courtesy of Dr S. Wakelin, St John's Dermatology Centre, London, UK.)

although some of these evolve into a more typical mechanobullous picture [1,2]. Mucosal involvement is variable but both erosions and intact blisters may be present in the mouth, larynx and oesophagus, and may cause dysphagia and laryngeal stenosis, and ocular involvement and blindness have been reported. Those patients in whom mucosal symptoms predominate are now regarded as having mucous membrane pemphigoid [3].

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Induced EBA and associated diseases. A number of conditions have been associated with EBA: inflammatory bowel disease, ulcerative colitis and Crohn's disease [1–6]. Collagen VII is expressed in human colon, and autoantibodies to collagen VII react with the epithelial mesenchymal junction; moreover, antibodies to collagen VII are present in Crohn's disease and to a lesser extent in ulcerative colitis, suggesting that cross-reactivity and epitope spreading may explain this association [7]. There are reports of EBA in association with multiple myeloma, amyloidosis and lymphoma [8–13]. Individual cases have been associated with carcinoma [14–16]. The association with systemic lupus erythematosus is discussed below (see p. 41.54). Drug-induced EBA has been described [17].

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Prognosis. The prognosis is very variable. Those patients with a BP-like picture may go into remission. However, patients with mechanobullous disease tend to have disease that is difficult to suppress and is very prolonged.

Differential diagnosis. Cases of EBA are often confused with dominant dystrophic epidermolysis bullosa, BP or porphyria cutanea tarda. Clinically, the mechanobullous epidermolysis bullosa acquisita patients most closely resemble mild dominant dystrophic epidermolysis bullosa, but the lack of family history, late onset and positive direct immunofluorescence distinguish them. The lesions on the hands may mimic porphyria cutanea tarda but this can be ruled out by porphyrin studies. Bullous pemphigoid presents the greatest diagnostic problems, because the direct immunofluorescence may be similar in these conditions. The conditions may be separated by using salt-split skin or toad skin as a substrate for indirect immunofluorescence and the additional finding on electron microscopy of cleavage beneath the basal lamina and the deposition of IgG in the dermis.

Treatment. The rarity of the condition has precluded controlled trials but the mechanobullous condition is characterized by resistance to the usual treatment modalities. A recent systematic review identified only 10 reports of studies on two or more patients (20 adults and 11 children) [1] and much of the information on treatment is anecdotal. Corticosteroids, azathioprine, ciclosporin, other immunosuppressants, vitamin E, gold, dapsone and sulfonamides have been reported to give inconsistent benefit, intravenous immunoglobulins and photopheresis have both had occasional success [2]. Steroids in combination with dapsone or sulfonamides are probably the best first-line treatment, certainly in children [1].

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Bullous systemic lupus erythematosus

SYN. VESICULOBULLOUS SYSTEMIC LUPUS ERYTHEMATOSUS

Definition. An autoimmune blistering condition, often transient, that occurs in the setting of systemic lupus erythematosus [1,2]. There is some controversy as to whether the term bullous systemic lupus erythematosus (BSLE) should include all subepidermal autoimmune bullous diseases that arise in patients with systemic lupus erythematosus or should be reserved for those patients with dermal antigens [2,3].

The clinical features, immunopathology and immunogenetics are summarized in Tables 41.5 and 41.6 and a review has been published [2].

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Aetiology. BSLE occurs only in patients with systemic lupus erythematosus. It affects young adults, chiefly women, often of African or Hispanic descent, and has been reported in children [1,2]. It is very rare in western Europe, with an incidence of 0.2 per million [3,4] and has been reported from China and Singapore [5,6]. In the USA, there is an association with HLA-DR2 [7].

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Pathogenesis. The bullous disease is mediated by autoantibodies to the basement-membrane zone, as demonstrated by positive direct immunofluorescence at the basement-membrane zone. The autoantibodies initially were demonstrated to react with collagen VII and to bind to fibronectin-like domains of the NC1 terminal [1,2]. However, as more cases have been studied it has become obvious that other dermal and epidermal antigens can also be involved, and in some cases no circulating autoantibodies can be detected [3–7]. Basement-membrane autoantibodies have been detected in patients with systemic lupus erythematosus without blisters, although other groups have not confirmed this [3,4,8].

Both IgG and IgA autoantibodies are involved [4,5].

The target antigens and immunogenetic susceptibility are in many patients shared with EBA, and yet in general they differ in clinical presentation. The reasons for these marked differences in the clinical phenotype are intriguing but unexplained.

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Pathology. Histologically, the bullae are subepidermal with a neutrophilic infiltrate, occasionally resulting in microabscesses resembling dermatitis herpetiformis.

The findings with immunofluorescence are summarized in Table 41.6. Direct immunofluorescence shows linear bands of IgG, IgA, IgM and C3 in the basement-membrane zone. With indirect immunofluorescence, circulating antibodies, when present, may bind to the basement-membrane zone and to either the dermal or the epidermal aspects of split skin, or may be absent [1,2].

Immunoelectron microscopy studies have demonstrated that circulating IgG autoantibodies bind below the lamina densa [3].

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immunologically heterogeneous bullous disorder. *J Invest Dermatol* 1993; **100**: 28S–34S.
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Clinical features. The onset of the disease is usually in patients with established systemic lupus erythematosus. There is widespread blistering, which may include both vesicles and larger tense blisters, and there may also be erythematous macules. All cutaneous sites may be involved. Mucosal lesions are uncommon. In some patients, the eruption is photosensitive. Post-inflammatory hyperpigmentation may occur. The occurrence of the bullous eruption is not related to flares of the systemic disease, and shows clinical similarities to BP and dermatitis herpetiformis. The classical epidermolysis bullosa phenotype of a mechanobullous eruption with milia and scarring (see above) is rare [1,2]. In many patients, the disease is transient.

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Associated disease. BSLE by definition only occurs in the setting of systemic lupus erythematosus. Vesiculobullous skin eruptions are uncommon but well recognized in patients with systemic lupus erythematosus, occurring in less than 10% of patients with systemic lupus erythematosus, while true BSLE was reported in 1 in 73 British and 1 in 186 Italian patients [1,2]. The classic widespread bullous skin eruption appears to be unrelated to the other systemic manifestations, exacerbations or the severity of the systemic lupus erythematosus [3–6]. There are many reports of other autoimmune diseases: pemphigus, BP, linear IgA disease, dermatitis herpetiformis and reactive bullous diseases, erythema multiforme and toxic epidermal necrolysis in association with systemic lupus erythematosus, but all the subepidermal ones are best regarded as BSLE [7].

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Prognosis. Most patients have a transient eruption. However, patients with the rare mechanobullous and scarring picture have a poorer prognosis.

Differential diagnosis. The presence of blistering in a patient with systemic lupus erythematosus can be caused by photosensitivity, acute lupus or a drug eruption. The histopathology and immunopathology will distinguish BSLE.

Treatment. Some of these patients appear to have responded to steroids used to control their systemic lupus erythematosus. Dapsone has been shown to be very effective in those patients with steroid-resistant blistering [1,2]; methotrexate has also been reported to be helpful [3].

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Dermatitis herpetiformis

SYN. DUHRING–BROCQ DISEASE

Definition. Dermatitis herpetiformis (DH) is a rare, intensely pruritic, chronic, recurrent, papulovesicular disease. The eruption is symmetrical and pleomorphic, consisting of erythematous, urticarial, papular, vesicular or bullous lesions (Fig. 41.27). There is an underlying gluten-sensitive enteropathy that may be asymptomatic.

The characteristic clinical and immunopathological features are shown in Tables 41.5 and 41.6.

Aetiology. Dermatitis herpetiformis is a disease of all ages. In Italy and Hungary the disease commonly presents in childhood [1,2], in the UK in young and middle-aged adults, with a slight male preponderance, and in southern Sweden it may present in old age [3]. The incidence is over 3000 per million in Ireland, 200–390 per million in Sweden, 110 per million in Scotland and Finland, and probably less elsewhere in Europe [3]. DH is rare in the Far East.

There is a family history of DH or coeliac disease in 10.5% of patients [4]. The disease has been reported in monozygous twins [5].

All patients have an underlying gluten-sensitive enteropathy, although this may be asymptomatic. Others will

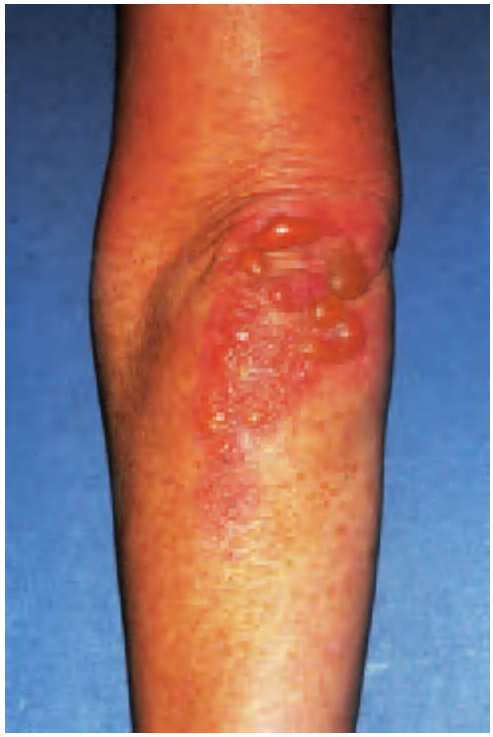

Fig. 41.27 Dermatitis herpetiformis. Intact tense bullae on the elbow. (Courtesy of Dr R.J. Pye, Addenbrooke's Hospital, Cambridge, UK.)

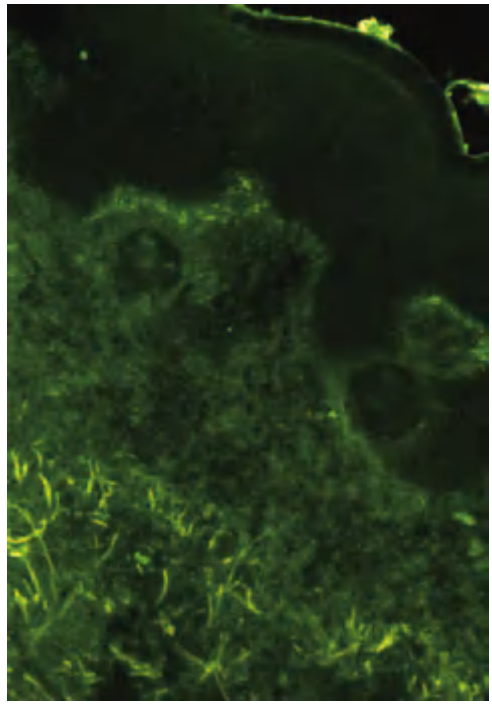

Fig. 41.28 Dermatitis herpetiformis. Direct immunofluorescence demonstrating granular IgA deposition in the dermal papillae. (Courtesy of Dr J. Allen, Oxford Radcliffe Hospital, Oxford, UK.)

have been investigated for abdominal pain, and may be misdiagnosed. There is an association with exposure to infection with adenovirus, as has been observed in coeliac disease [6].

HLA studies in patients who on clinical and immunological criteria have DH, have shown identical findings to coeliac disease. There is a very strong association with DR3 and DQw2 [7–10].

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Pathogenesis. The characteristic finding is deposition of IgA in a granular pattern in the papillary dermis (Fig. 41.28), although IgM, IgG and C3 may be found. The IgA deposits are gluten-dependent, and are slowly cleared from the skin once gluten is removed from the diet [1,2]. The mechanism by which gluten causes the IgA deposition in the skin is still unknown, although non-immunological binding of gliadin to reticulin has been shown [3]. The IgA deposits are often but not exclusively associated with the microfibrils [4,5]. The antigen within normal human skin to which IgA antibodies from DH sera bind is still unknown.

The IgA deposits have been shown to be chemoattractant to neutrophils [6]. C3 has been demonstrated in the papillary dermis of both lesional and perilesional skin. Properdin and factor B have been found and support the suggestion that complement is activated via the alternative pathway [7]. C5 and fibrin are often detected in similar sites [8]. The activated fraction, C5a, is highly chemotactic for neutrophils and may contribute to the inflammatory change at the papillary tip. Lymphocytes also play a part with the neutrophils in initiating an inflammatory cascade (reviewed recently in [9]).

Characterization of the IgA deposits has shown the IgA

to be almost exclusively IgA1 and to be both monomeric and polymeric, with J chains and secretory components present [10–12]. These data suggest that the IgA is derived from mucosa and serum.

In 1967, the link with gluten-sensitive enteropathy (coeliac disease) was established [13]. Further studies showed that the small bowel changes of villous atrophy were secondary to gluten sensitivity and responded to a gluten-free diet [14]. The gluten-sensitive enteropathy is present in all patients, although difficult to demonstrate in some [15]. Patients were found to have antireticulin antibodies and, in addition, antigluten or antigliadin antibodies [15–19]. IgA endomysial antibodies, directed at smooth muscle, are frequently found in DH and coeliac disease and fall with the introduction of a gluten-free diet [20,21].

The most exciting development of recent years has been the recognition that autoantibodies and T-cell reactions to tissue transglutaminases, and in particular transglutaminase 2, are relevant to the pathogenesis of coeliac disease [22]. These antibodies have been demonstrated in DH [23–25]. In addition, it is now clear that the previously recognized antireticulin and endomysial antibodies are associated with these antibodies [26], and require transglutaminase 2 to bind to tissues [27]. The tissue transglutaminases cleave gliadin to antigenic peptides and this may contribute to their role in pathogenesis [28]. There is a difference in autoantibody profile between DH and coeliac disease, in that there are antibodies to epidermal transglutaminases in DH but not coeliac disease [29]. The IgA precipitates in the dermis contain epidermal transglutaminases [29]. However, the precise chain of events leading to IgA deposition in the skin and blistering is still to be unravelled [9].

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Pathology. Diagnostic histological changes are best seen in the vicinity of early blisters or in lesions that have not yet blistered. Neutrophils and eosinophils accumulate within the dermal papillae and form microabscesses. The surrounding collagen is degraded, resulting in detachment of the epidermis and a subepidermal vesicle. Multilocular vesicles may coalesce to form blisters; at that stage the cellular infiltrate is mixed and distinction from pemphigoid may be difficult.

The characteristic immunofluorescence findings are shown in Table 41.6 and Fig. 41.28. Direct immunofluorescence is always positive [1]. However, sometimes when there is a high degree of clinical suspicion, serial sections and multiple biopsies may be necessary to confirm the diagnosis. The biopsy (a 3–4-mm punch biopsy is suffi-

cient) should be taken from clinically normal skin. The forearm or buttock is usually suitable. There are granular deposits of IgA in the dermal papillae (Fig. 41.28). There may also be C3 and IgG.

The diagnostic significance of the rare linear granular pattern of IgA deposition at the basement-membrane zone is still unclear [2]. Some patients with this pattern have true DH and others may have autoantibodies to unusual target antigens.

Indirect immunofluorescence is negative for basement-membrane zone or dermal autoantibodies. However, if monkey oesophagus is used, IgA endomysial antibodies may be detected [3].

Immunoblotting studies are negative.

Electron microscopy shows that the blisters are subepidermal and can occur beneath the basal lamina. In the lesions, the basal lamina may be fragmented or lost. However, in adjacent skin, the basal lamina may be thickened and reduplicated. The basal cells show cytolysis, but these changes are probably secondary to the effects of the inflammatory cells [4].

Ultrastructurally on immunoelectron microscopy, the IgA deposits appear to be closely associated with the dermal microfibrillar bundles [5,6]. However, immunogold studies have shown that not all of the IgA is associated with any recognizable structure [6].

Gastrointestinal investigations. All the abnormalities found in coeliac disease may be found in DH [7]. A full blood count may reveal anaemia. The additional signs on the blood film depend on whether it is caused by iron deficiency or folate deficiency. There may also be Howell–Jolly bodies on the film, indicating splenic atrophy [8]. There may be antireticulin antibodies and antigliadin antibodies as well as antiendomysial antibodies. A jejunal biopsy will demonstrate signs of gluten-sensitive enteropathy in almost all cases; these signs may be a raised intraepithelial lymphocyte count or, in more severe cases, a flat biopsy.

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Clinical features. DH presents mainly between the ages of 20 and 55 years, but does present both in childhood and old age. The onset may be acute or gradual, and pruritus is usually the first and predominant symptom. Early lesions on the skin are erythematous papules, urticarial wheals or groups of small vesicles often excoriated so rapidly that it may be impossible to find one intact. The vesicles are usually grouped together on plaques of erythema but, rarely, blisters 1–2 cm in diameter occur (Fig. 41.27). This happens more frequently in relapses when suppressive treatment has been discontinued. Papules without blistering are not uncommon and eczematous changes, which may be lichenified, are sometimes seen. Progressive pigmentation of the sites of the skin lesions occurs in some patients.

The distribution of the lesions is characteristic. The extensor aspects of the limbs, especially the knees, just below the point of the elbows, buttocks and the natal cleft, are affected in the majority of patients (Fig. 41.27). The axillary folds, shoulders, trunk, face and scalp are all frequently involved. Oral lesions are common but asymptomatic [1].

Provocation or exacerbation by iodides, either by mouth or by patch test, is not specific for DH and is now considered outmoded as a diagnostic test [2,3]. Skin cleansers containing iodine and iodine-containing preparations must be avoided, as they can exacerbate DH.

There may be a feeling of malaise with the acutely active disease. In addition, constitutional symptoms caused by the gluten-sensitive enteropathy can be present. The patient may experience bouts of abdominal pain, constipation and diarrhoea, and be undernourished. Patients are often tired and lack a feeling of well-being.

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Associated diseases. There are often associated autoimmune diseases, particularly thyroid disease, pernicious anaemia and diabetes [1,2]. There is an association with thyroid disease in up to 30% of patients [3]. A variety of organ-specific and non-organ-specific autoantibodies have been detected in patients with DH, notably antithyroid antibodies [4].

Lymphoma is a well-recognized complication of DH as are other malignancies [5–11]. Moreover, the protective role of a gluten-free diet for the lymphomas has been established [11,12].

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Differential diagnosis. The diagnosis should be suspected when any persistent pruritic symmetrical eruption resists topical treatment. In view of the pruritus and involvement of the axillary folds and buttocks, many patients are thought to have scabies, but the absence of burrows or of contact cases should help with the diagnosis. The most difficult diagnostic problem is the group of patients with chronic exudative eczema, papular urticaria and chronic prurigo, some of whom may be dapsone-responsive. The histology and the lack of IgA deposition should help to establish the correct diagnosis.

Treatment. The treatment of DH has been reviewed recently [1]. Dapsone is the most widely used treatment. The dosage needed for the average case is 100–200 mg/day but a few may require 400 mg/day. It is wise to start at 25–50 mg/day in an adult and slowly increase to a dosage that keeps the patient comfortable and without significant side effects. Too rapid an increase in the dosage often results in haemolytic anaemia, which does not reach its maximum for a month. A fall in haemoglobin with a low MCV indicates iron deficiency (resulting from intravascular haemolysis) rather than pure haemolytic anaemia. Patients at risk of glucose-6-phosphate dehydrogenase deficiency should be screened prior to treatment. Methaemoglobinaemia is common, reaching a steady state after about 2 weeks, and may cause cyanosis, breathlessness and angina. Hepatitis, the dapsone syndrome (lymphadenopathy and hepatitis) and agranulocytosis are serious, usually early complications. Motor neuropathy may occur. Most complications occur in the first 3 months. Sulfapyridine 1.5 g/day is an alternative in patients who cannot tolerate dapsone; however, a few may not be controlled even on 4 g/day [2,3]. Side effects include nausea, lethargy, haemolytic anaemia and bone marrow suppression. The long-acting sulfonamide, sulfamethoxypyridazine, is an alternative treatment; usually 0.5–1.5 g/day is sufficient to control DH, the incidence of side effects increasing with dosage above 1 g/day [4]. Although systemic corticosteroids are in the main ineffective and not indicated, topical steroids may be helpful in lessening symptoms. Heparin, with or without tetracyclines in combination with nicotinamide (niacinamide), has been advocated for patients who cannot tolerate dapsone or sulfonamides [5,6].

A gluten-free diet is the treatment of choice in the long term. It has been shown not only to improve the enteropathy, but also to allow discontinuation of drug therapy. The patients gain weight, lose their abdominal symptoms and often feel generally much better. In order to obtain strict adherence to the diet, the patient needs to be highly motivated, intelligent and leading a regular life. Sometimes it may be wise to postpone starting the diet until a more settled period. Wheat must be avoided, but oats are not damaging [7,8]. Unlike patients with coeliac disease, ingestion of small quantities of gluten does not always precipitate symptoms. The help of a dietitian and the Coeliac Society are essential. It is usually many months and sometimes years before patients are able to reduce their dapsone requirements. Often dapsone can be discontinued altogether after 2–3 years on a strict gluten-free diet, but some patients take much longer [9]. Reintroduction of gluten in selected patients produced a relapse in skin lesions [10,11]. After 5–10 years the gluten-free diet protects patients from lymphoma, and this is an additional reason to recommend it [12].

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Prognosis. The disease runs a very long course with exacerbations and remissions [1]. Ten per cent of patients experience remissions. Acute infection and even emotional disturbances may precipitate an attack. A strict gluten-free diet will result in remission of the skin and the gut.

Interestingly, patients with DH on a normal diet or a gluten-free diet do not have a decreased life expectancy, despite the increase in lymphoma, and there may be a reduction in ischaemic heart disease [2–5].

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Chapter 42

Lichen Planus and Lichenoid Disorders

S.M. Breathnach & M.M. Black

Definition of lichenoid eruptions

The term 'lichenoid' is used by clinicians to describe a flat-topped, shiny, papular eruption resembling lichen planus (LP), or by histopathologists to describe a type of tissue reaction consisting principally of basal cell liquefaction and a band-like inflammatory cell infiltrate in the papillary dermis [1]. The prototype of all lichenoid eruptions is LP itself but a number of other diseases may develop a lichenoid tissue reaction [2,3].

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Pathogenesis

LP is thought to be an immunologically mediated disorder, not least because a lichenoid eruption may be seen as part of graft-versus-host disease (see below). Cloned murine autoreactive T cells produce a lichenoid reaction in recipient animals following injection [1]. T cells, both $CD4^+$ and $CD8^+$, accumulate in the dermis, while $CD8^+$ T cells infiltrate the epidermis, in LP lesions; it has been proposed that $CD8^+$ cytotoxic T cells recognize an antigen (currently unknown) associated with major histocompatibility complex (MHC) class I on lesional keratinocytes and lyse them [2–6]. T cells and keratinocytes express interferon-γ (IFN-γ) and interleukin-6 (IL-6) [2], and T cells also express lymphocyte function associated antigen-1 (LFA-1) [4] and secrete IFN-γ *in vitro* [7]. Mononuclear cells infiltrating the skin, the majority of which are $CD8^+$, as well as basal keratinocytes, express tumour necrosis factor-α (TNF-α) and TNF-R1 [7]. Activated T cells secreting IFN-γ induce keratinocyte expression of human leukocyte antigen (HLA)-DR [8], and the presence of epidermotropic T cells correlates with that of HLA-DR expressing keratinocytes and Langerhans' cells [9]. It has been proposed that keratinocyte cytokines up-regulate expression of cell surface adhesion molecules on, and migration by, T cells [10–12]. $CD1a^+$ Langerhans' cells and factor $XIIIa^+$ cells are increased in LP [4,13,14] and may be involved in antigen presentation to T cells. Vascular endothelial expression of the adhesion molecules intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) is also elevated [4]. Infiltrating $CD8^+$ T cells, as well as keratinocytes, express a variety of different chemokines [15–17]. RANTES (regulated upon activation, normal T-cell expressed and secreted) secreted by T cells may trigger mast cell degranulation with consequent release of TNF-α, which in turn up-regulates lesional T-cell RANTES secretion; such mechanisms may contribute to chronicity of T-cell infiltration and clinical disease [18]. Mast cell degranulation [19], and T-cell secretion of matrix metalloprotein 9 [20], may contribute to basement membrane disruption, enabling migration of $CD8^+$ T cells into the epithelium.

There may be a genetic susceptibility to idiopathic LP. Familial cases are reported [21–26], and a familial incidence of 10.7% was quoted in one series [24]. LP has also been reported in monozygotic twins [27,28]. An association with HLA-3 and HLA-5 has been documented [29],

although others found no such association [30,31], as have associations with HLA-B7 [21], HLA-28 in Jews with LP and carbohydrate intolerance [32], HLA-DR1 [33] and HLA-DR10 [34]. Genetic heterogeneity in LP has led to a suggestion that idiopathic cutaneous, and purely mucosal, LP may have a different pathogenesis [35]. Anxiety and depression may be risk factors for the development of LP [36].

An epidemiological association of LP with hepatitis C virus (HCV) infection has been recorded, especially in patients from Italy, certain parts of France, Spain, Japan and Pakistan [37–43], and HCV RNA has been isolated from lesional skin in patients with LP and chronic HCV infection [44,45]. Thus, an HCV-related product has been postulated as a possible antigen in LP. However, no association between LP and HCV infection has been noted in patients from Northern Europe including the UK, the USA or Nepal [46–50]. It has been suggested that the observed geographical differences with regard to HCV infection and LP could be related to immunogenetic factors such as the HLA-DR6 allele, significantly expressed in Italian patients with oral LP and HCV infection [37,38].

Another putative antigen in oral LP is mercury in dental amalgam. Eighty-seven per cent to 97% of patients with oral LP associated with dental amalgam fillings benefit from amalgam removal, but only 28–39% have positive patch test reactions to amalgam or inorganic mercury [51–54]. Patients who improve following removal of amalgam, but in whom patch testing is negative, are presumed to have an irritant reaction to amalgam. A recent study reported that the presence of amalgam or of gold is not associated with an increased risk of oral LP, but corrosion of amalgams, and a 'galvanic effect' from dissimilar dental materials in continuous contact with the mucosa (bimetallism) are associated with an elevated risk of oral LP [55].

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Incidence

LP has a worldwide distribution with no overt racial predisposition. LP represented about 1.2% of all new patients in London [1] and Turin [2], 0.9% in Copenhagen [3] and 0.38% in India [4]. Hypertrophic cases were reportedly common in Nigeria [5]. Both oral and cutaneous LP have rarely been reported in childhood [3,6–12]. Familial cases are recorded (see above).

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Histology [1,2]

The earliest finding is an increase in epidermal Langerhans' cells [1], associated with a superficial perivascular infiltrate of lymphocytes and histiocytes, impinging on the dermal–epidermal junction (DEJ). Mild spongiosis is followed by vacuolar alteration and clefting along the DEJ, with accumulation of necrotic keratinocytes (colloid bodies) [3].

The characteristic histological changes are best seen in biopsies of fully developed LP papules [4] (Fig. 42.1). The centre of the papule shows irregular acanthosis of the epidermis, irregular thickening of the granular layer, and compact hyperkeratosis. The mid-epidermal cells appear larger, flatter and paler than usual [4]. In oral LP, epithelial proliferation is increased [5]. Parakeratosis is rarely found in idiopathic LP, in contrast to some drug-induced lichenoid tissue reactions. A focal increase in thickness of the granular layer and infiltrate corresponds to the presence of Wickham's striae [6]. Degenerating basal epidermal cells are transformed into *colloid bodies* (15–20 μm diameter) which appear singly or in clumps [7–9]. The rete ridges may appear flattened or effaced (*'saw-tooth' appearance*), and focal separation from the dermis may lead to

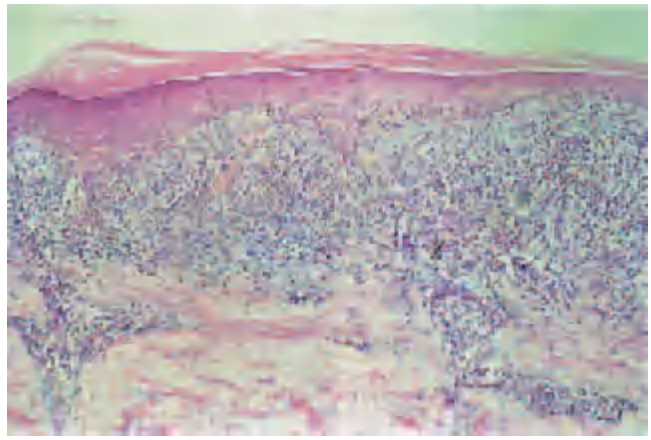

Fig. 42.1 Lichen planus, typical histology. H&E, × 40. (Courtesy of St John's Institute of Dermatology, London, UK.)

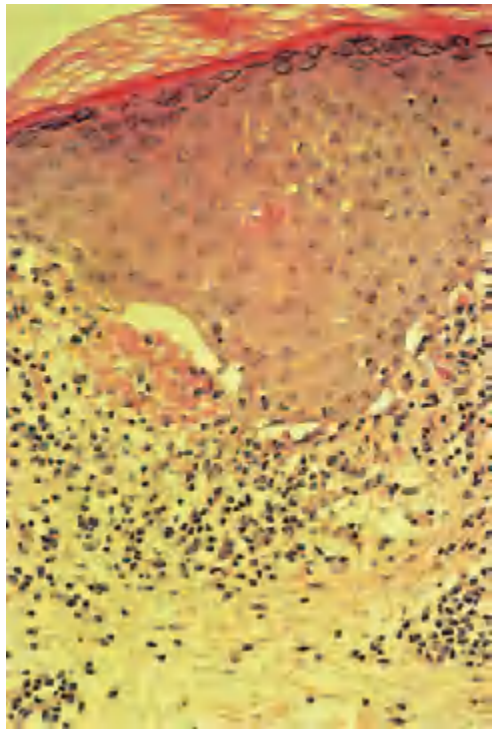

Fig. 42.2 Lichen planus. Photomicrograph to show clumps of cytoid bodies. H&E, × 100. (Courtesy of St John's Institute of Dermatology, London, UK.)

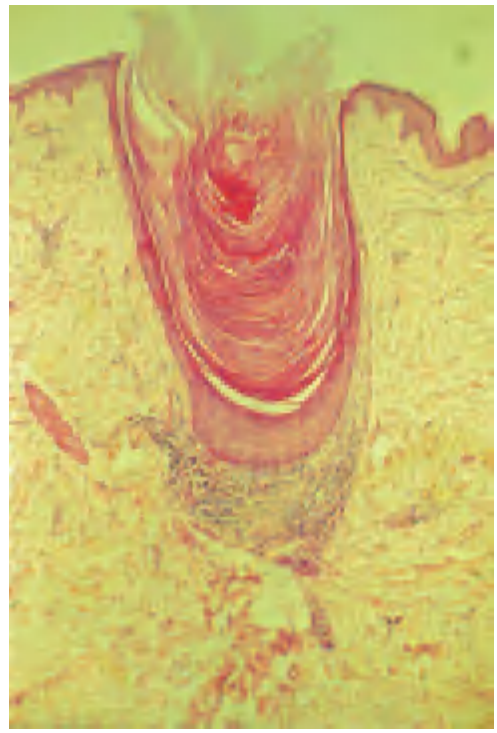

Fig. 42.3 Lichen planus. Photomicrograph of follicular lesion. Scanning view. H&E, × 20. (Courtesy of St John's Institute of Dermatology, London, UK.)

Max Joseph spaces (Fig. 42.2). In older or hypertrophic lesions, the number of colloid bodies is considerably reduced. In 'active' LP, a *band-like infiltrate* of lymphocytes and histiocytes, rarely admixed with plasma cells [10,11], obliterates the DEJ. Epidermal melanocytes are absent or considerably decreased in number [4], while *pigmentary incontinence* with dermal melanophages is characteristic. When the disease is becoming inactive, the infiltrate, with melanophages, becomes sparser and arranged around papillary blood vessels, which may show ectasia and surrounding fibroplasia.

In hypertrophic LP, the epidermis may show a pseudoepitheliomatous appearance with extreme irregular acanthosis. Follicles may be expanded and at times have a 'cyst-like' appearance. The infiltrate may not appear very 'band-like', but serial sections will usually show foci of basal cell liquefaction and colloid-body formation, often around the follicular epithelium. Long-standing cases usually demonstrate coexistent dermal fibrosis adjacent to the inflammatory changes.

In atrophic LP, the epidermis may be greatly thinned almost to the level of the granular layer; although relative compact hyperkeratosis remains. The rete ridges are usually completely effaced with relatively few colloid bodies. The papillary dermis shows fibrosis and loss of elastica.

In follicular lesions (Figs 42.3 & 42.4), an infiltrate extends around, and may permeate, the base of the hair follicle epithelium, with follicular keratin plugging [12,13].

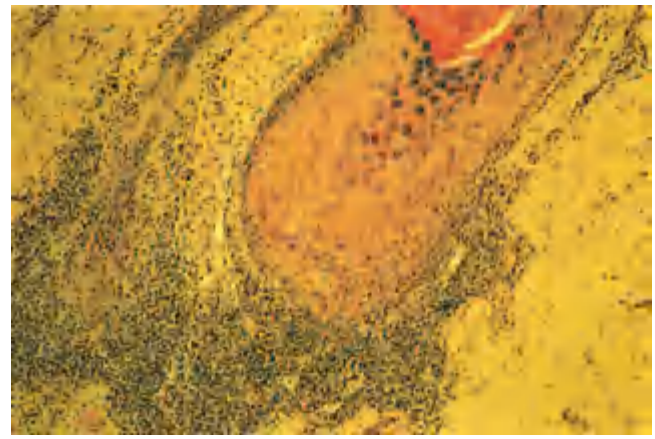

Fig. 42.4 Lichen planus. Photomicrograph of follicular lesion. Higher power, H&E, × 40. (Courtesy of St John's Institute of Dermatology, London, UK.)

In mucosal LP, the epithelium is usually thinned with parakeratosis, although both types of keratinization may be seen [14]; the epithelium may resemble epidermis from skin, plasma cells may be prominent in the 'band-like' infiltrate, and colloid bodies are fewer than in typical cutaneous papular LP. The erythematous subtype of oral LP is associated with increased cell proliferation compared

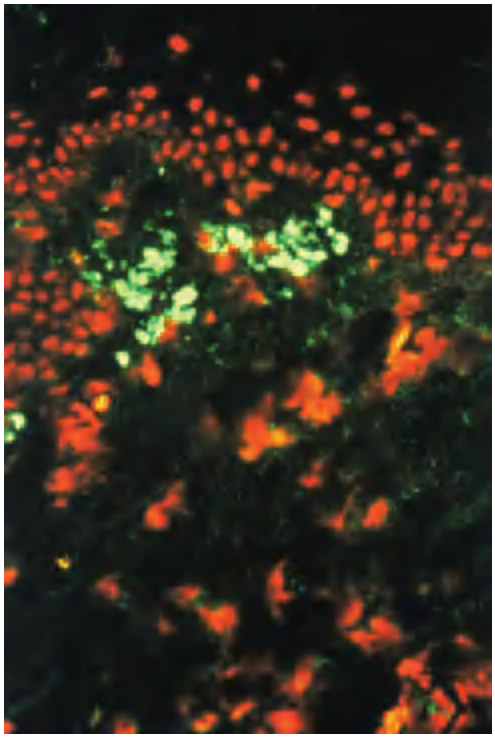

Fig. 42.5 Lichen planus. Photomicrograph of direct immunofluorescence. Bright fluorescence of cytoid bodies with anti-IgM × 100. (Courtesy of St John's Institute of Dermatology, London, UK.)

with the reticular form [15]. Moderate or severe epithelial dysplasia on oral biopsy should probably be regarded as an increased risk for subsequent cancer development [16].

Bullous LP is rare; blister formation takes place predominantly between the basal lamina and cytomembranes of basal keratinocytes (i.e. intrabasal) [7], such that there is a wide separation between the epidermis and infiltrate.

Direct immunofluorescence (IMF) shows globular deposits of IgM (Fig. 42.5), and occasionally IgG and IgA, representing apoptotic keratinocytes [17,18], around the DEJ and lower epidermis, with fibrin deposition at the region of the DEJ. Direct IMF studies may be useful in differentiating LP from lupus erythematosus or LP pemphigoides [19,20], and can be carried out on routine histological material [21].

A clinicopathological study of lichenoid dermatitis concluded that it was usually possible to provide a specific diagnosis [22]. Occasionally, lichenoid dermatitis can become generalized and clinically mimic an exfoliative dermatitis; such eruptions are usually triggered by drugs [23].

Benign lichenoid keratoses (BLKs) are usually solitary but may be multiple, and show characteristic lichenoid infiltrates of lymphocytes, occasional parakeratosis, and apoptotic bodies in the epidermis without nuclear atypia of keratinocytes [24]; rarely, the histology may show features of mycosis fungoides [25]. Malignant melanoma may be associated with a lichenoid tissue reaction [26], and melanoma *in situ* with lichenoid regression may mimic a BLK histologically [27].

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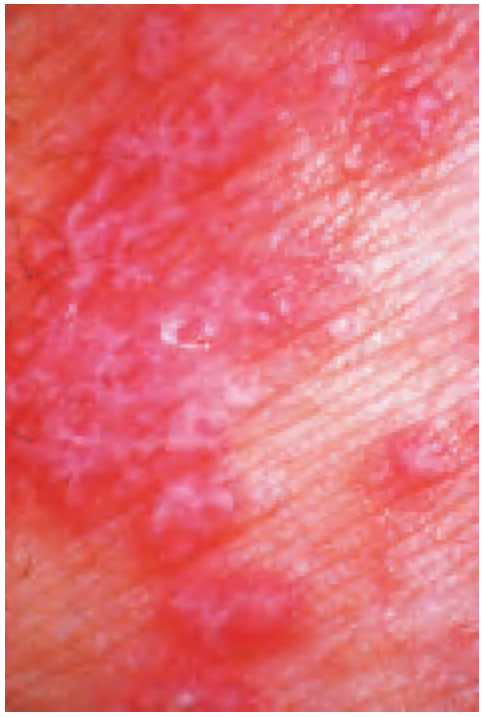

Fig. 42.6 Lichen planus. Close up to show Wickham's striae. (Courtesy of St John's Institute of Dermatology, London, UK.)

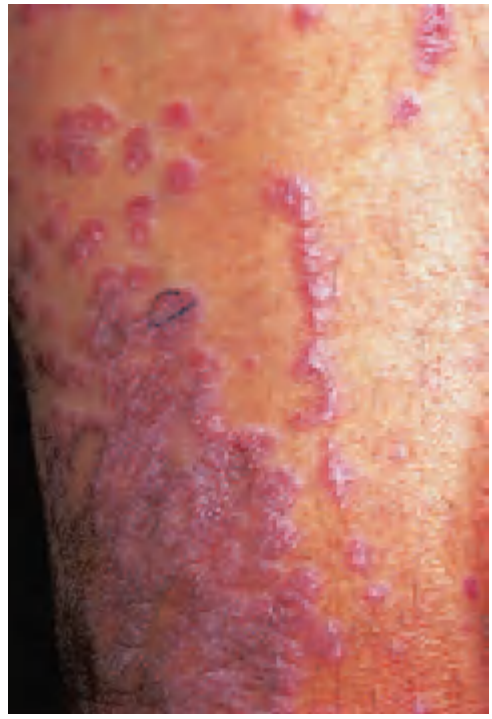

Fig. 42.7 Lichen planus papules showing Koebner effect. (Courtesy of St John's Institute of Dermatology, London, UK.)

Clinical features

LP is characterized by shiny, violaceous, flat-topped polygonal papules which retain the skin lines, and which vary in size from pinpoint to a centimetre or more across; they may be closely aggregated or widely dispersed. The size of the papules is often fairly uniform in an individual patient, but minute and large papules coexist in some cases. White lines, known as Wickham's striae [1] (Fig. 42.6), may traverse the surface of the papules. Papules can remain discrete or appear in groups, in lines or in circles. Linear lesions often appear along scratch marks or in scars (Koebner phenomenon) (Fig. 42.7), while annular lesions may be formed either by groups of papules arranged in rings or by single, large papules clearing in the centre and leaving an active margin. Annular lesions are especially common on the penis (Fig. 42.8) and rarely may be the predominant type of lesion present, leading to atrophy later [2].

A variant in which groups of 'spiny' lesions resembling keratosis pilaris develop around hair follicles (lichen planopilaris) (Fig. 42.9) is not uncommon. Lichen planopilaris more often forms only a minor feature of the disease, but occasionally this type of lesion may predominate.

Although a few cases evolve rapidly and clear within a few weeks, the onset is usually insidious. In most cases, the papules eventually flatten after a few months, often to be replaced by an area of pigmentation that retains the shape of the papule and persists for months or years.

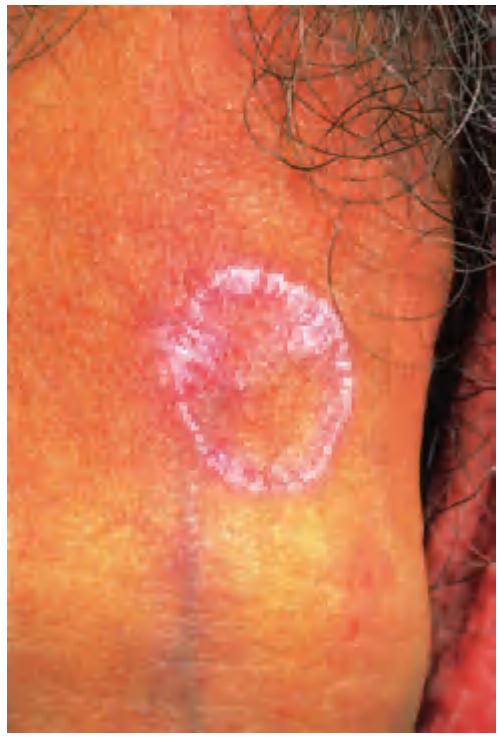

Fig. 42.8 Lichen planus. Annular lesion on shaft of penis. (Courtesy of St John's Institute of Dermatology, London, UK.)

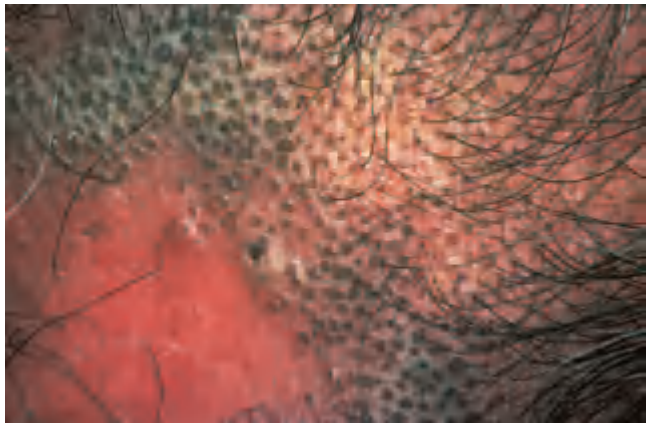

Fig. 42.9 Lichen planopilaris. Hyperpigmented follicular 'plugged' lesions in frontal scalp hairline. (Courtesy of St John's Institute of Dermatology, London, UK.)

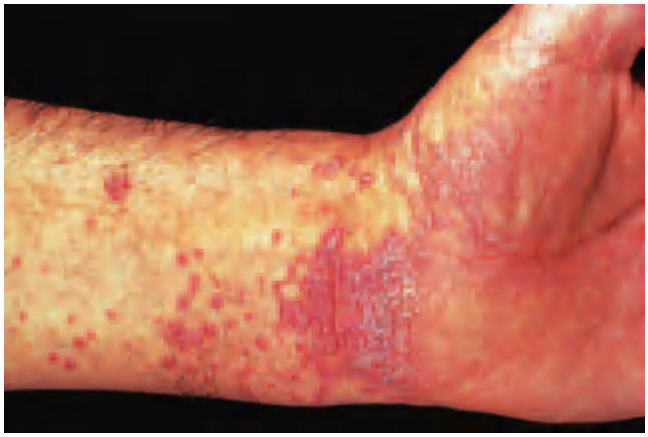

Fig. 42.10 Lichen planus. Classical eruption on volar aspect of wrist. (Courtesy of St John's Institute of Dermatology, London, UK.)

There may be a gradual change in colour from pink to blue to black. The residual pigmentation may be intense, especially in dark-skinned races, or almost imperceptible in fair-skinned individuals. New papules may form while others are clearing. Some papules persist much longer, enlarge and thicken, and develop a roughened surface with a prominent violaceous hue, so-called hypertrophic LP. Such lesions may resolve with atrophy or scarring. More warty lesions are seen occasionally. Areas of pigment loss are described in black South Africans [3]. Colocalization of LP and vitiligo has been reported [4].

LP can affect any part of the body surface, but is most often seen on the volar aspect of the wrists (Fig. 42.10), the lumbar region and around the ankles. The ankles and shins are the commonest sites for hypertrophic lesions. When the palms and soles are affected, the lesions tend to be firm and rough with a yellowish hue (Fig. 42.11) [5,6]. A rare erosive flexural variant of LP has been described [7]. Isolated lesions of LP have been reported to involve one or

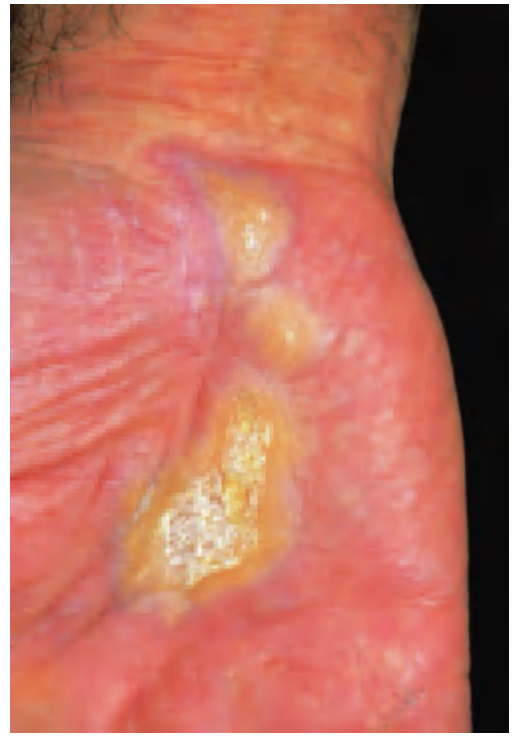

Fig. 42.11 Lichen planus of palm showing hyperkeratosis and a yellow colour. (Courtesy of St John's Institute of Dermatology, London, UK.)

both eyelids [8,9] or the lips [10–12]. Milia have been recorded in LP [13], and LP was confined to a radiation therapy site in one patient [14].

Mucous membrane lesions are very common, occurring in 30–70% of cases, and may be present without evidence of skin lesions. They are, however, much less common in black people. The buccal mucosa and tongue are most often involved, but lesions may be found around the anus, on the genitalia, in the larynx and, very rarely, on the tympanic membrane of the ears or even in the oesophagus. White streaks, often forming a lacework, on the buccal mucosa are highly characteristic (Fig. 42.12). They may be seen on the inner surface of the cheeks, on the gum margins or on the lips. On the tongue, the lesions are usually in the form of fixed, white plaques, often slightly depressed below the surrounding normal mucous membrane, especially on the upper surface and edges (Fig. 42.13). Ulcerative lesions in the mouth are uncommon, but may be the site of epitheliomatous transformation (Fig. 42.14). There may be striking pigmentation of oral LP in darkly pigmented races [15]. Diabetes is a possible associated disease of oral LP [16,17], and candidiasis may coexist with LP in some patients.

Itching is a fairly consistent feature in LP and ranges from occasional mild irritation to more or less continuous, severe itching, which interferes with sleep and makes life almost intolerable; occasionally, itching is completely

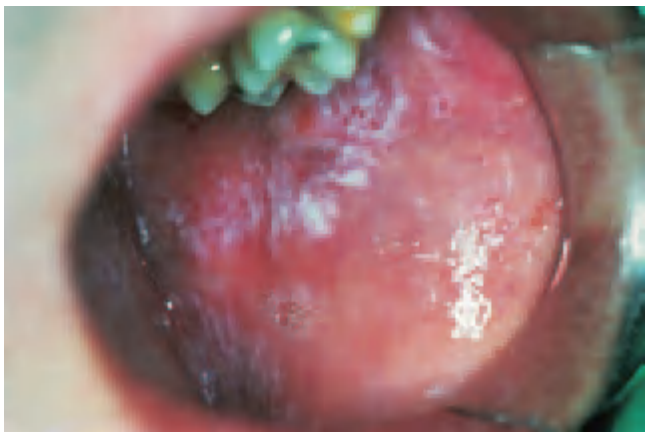

Fig. 42.12 Lichen planus on buccal mucosa showing a lacework of white streaks. (Courtesy of St John's Institute of Dermatology, London, UK.)

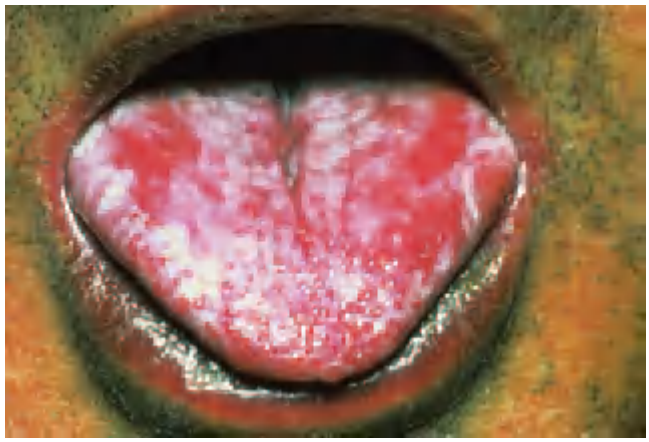

Fig. 42.13 Lichen planus of tongue showing irregular fixed white plaques. (Courtesy of St John's Institute of Dermatology, London, UK.)

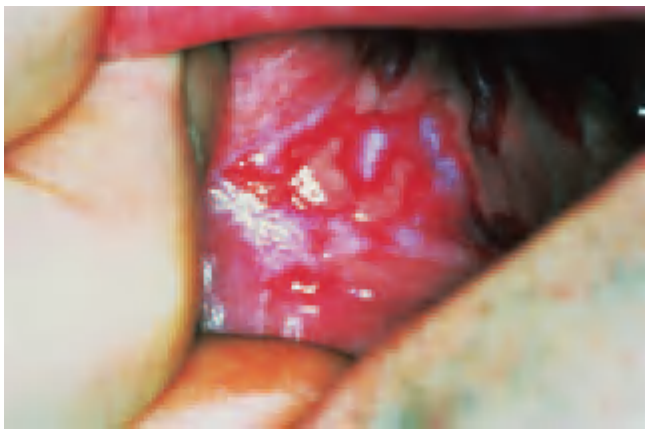

Fig. 42.14 Severe erosive lichen planus of buccal mucosa. (Courtesy of St John's Institute of Dermatology, London, UK.)

absent. Hypertrophic lesions usually itch severely. Paradoxically, there is seldom evidence of scratching, as the patient rubs, rather than scratches, to gain relief. Itching at sites without visible skin lesions can occur. Burning and stinging are less common complaints. In the mouth, the patient may complain of discomfort, stinging or pain; ulcerated lesions are especially painful. Great discomfort may be caused by hot foods and drinks.

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Variants

LP principally involving mucous membranes

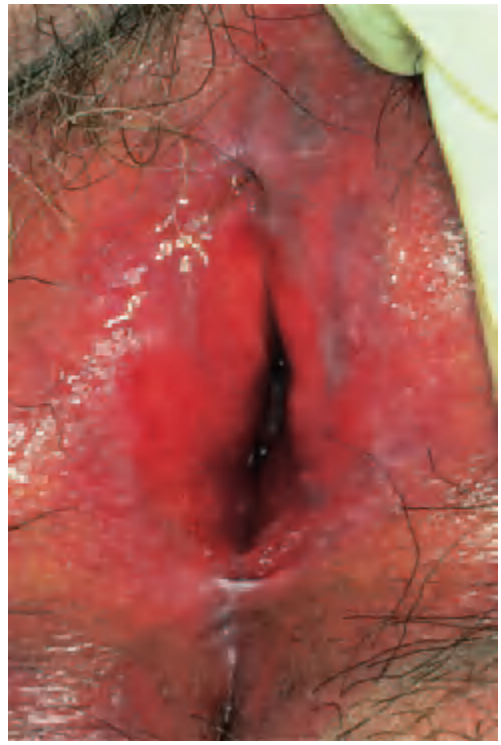
Lesions confined to the mouth, or with minimal accompanying skin involvement, are not uncommon [1–5], and account for about 15% of all cases [1]. The prevalence of oral LP was 1.5% among the villagers of Kerala in southern India [6], possibly related to chewing tobacco, and ranges between 0.5% and 2.2% of the population in other epidemiological studies [2,7]. The lesions do not differ from those found in connection with skin lesions, but, being confined to the mouth, may lead to great difficulty in diagnosis. They are often referred first to a dental surgeon. Distinct clinical subtypes such as reticular, atrophic, hypertrophic and erosive forms are well recognized; more than one type may be present [2]. On the tongue and

buccal mucosa, they are most likely to be mistaken for leukoplakia and on the gum margin for gingivitis or chronic candidiasis, or the latter may coexist. Other conditions that must be excluded are 'smoker's patches', which characteristically involve the palate, and white-sponge naevi, in which the mucous membrane is thickened, irregularly folded and feels soft to the touch. These occur mainly on the floor of the mouth and histologically many of the prickle cells are vacuolated. It is important to bear in mind the possibility of a lichenoid drug reaction in patients with oral lichenoid changes (see below). Oral lichenoid reactions may be asymmetrical on the buccal mucosa and occur adjacent to dental amalgam fillings. If patch testing reveals mercury allergy, changing to another type of filling may prove beneficial [8–13].

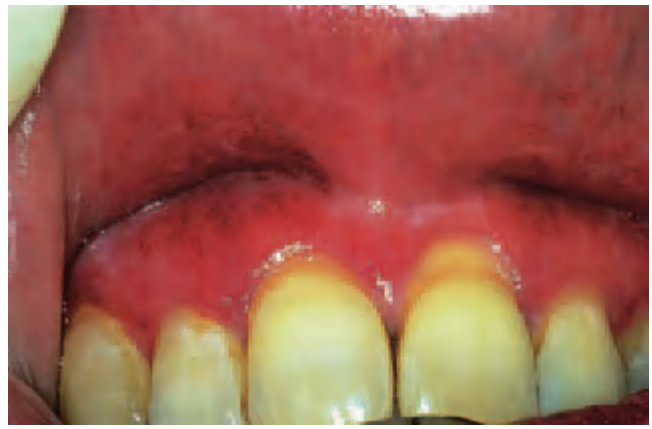
Very occasionally, LP lesions extend to the larynx or oesophagus [14–18]. Oesophageal LP may result in dysphagia and the formation of benign strictures.

In young men, the lesions are sometimes restricted to the genitalia and/or the mouth [19,20]. Genital lesions, which are usually characteristic, may be present on the penile shaft (see Fig. 42.8), glans penis, prepuce or scrotum. Ulceration is very unlikely, and syphilis can usually be excluded without difficulty; the presence of buccal mucosal lesions will usually confirm the diagnosis. Circumcision may be helpful [19].

Lesions on the female genitalia are fairly common [21–27]; they may occur alone, be combined with lesions in the mouth only, or be part of widespread involvement. The clinical presentation of LP of the vulva spans a spectrum from subtle, fine, reticulate papules to severe erosive disease accompanied by dyspareunia, scarring and loss of the normal vulvar architecture. The condition should be distinguished from lichen sclerosus or leukoplakia, but this may be difficult when there is coexisting atrophy or vaginal stenosis. The association of erosive LP of the vulva and vagina with desquamative gingivitis has been termed the *vulvovaginal–gingival syndrome* [20,22] (Fig. 42.15). Coexisting vulval lichen sclerosus and lichenoid oral lesions have been described [28].



(a)



(b)

Fig. 42.15 Vulvovaginal–gingival syndrome. Showing (a) vulvitis and (b) gingivitis in the same patient. (Courtesy of Dr S. Neill, St John's Institute of Dermatology, London, UK.)

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Hypertrophic LP

This usually develops during the course of a subacute attack, but occasionally only hypertrophic or warty lesions are found. They most often occur on the lower limbs, especially around the ankles; venous stasis has been put forwards as an explanation (Fig. 42.16). The development of hypertrophic lesions greatly lengthens the course of the disease, as they may persist for many years. When such lesions eventually clear, an area of pigmentation and scarring may remain and there is often some degree of atrophy. They must be distinguished from lichen simplex chronicus and lichen amyloidosus (papular). Multiple cutaneous horns overlying hypertrophic LP are recorded [1], as are keratoacanthoma [2,3] and malignant transformation [4] arising in hypertrophic LP, as well as metastatic squamous cell cancer [5].

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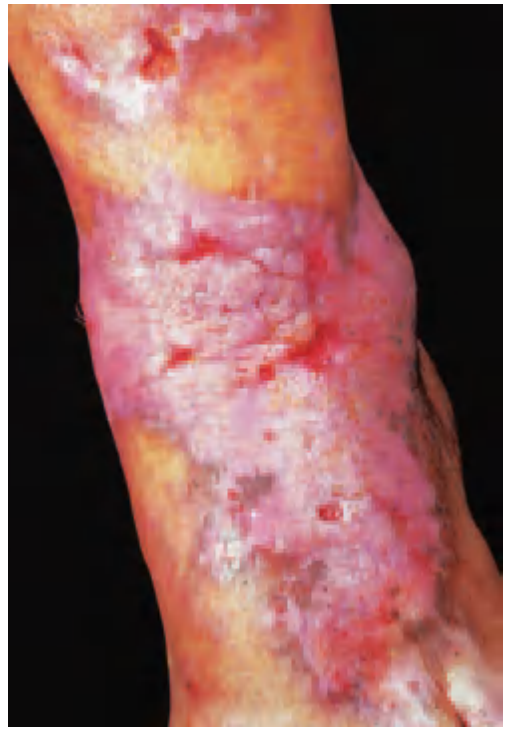

Fig. 42.16 Hypertrophic lichen planus of great chronicity occurring on lower leg and ankle. (Courtesy of St John's Institute of Dermatology, London, UK.)

Follicular LP

SYN. LICHEN PLANOPILARIS

Follicular lesions usually appear during the course of typical LP, but occasionally they predominate and diagnosis may then be difficult. Presentation with alopecia of the trunk is recorded [1]. Follicular lesions occurring in the scalp are accompanied by some scaling and are likely to lead to a scarring alopecia (Fig. 42.17). Very rarely, the scalp alone is involved. The clinical, histological and IMF overlap between the so-called Graham Little–Piccardi–Lassueur syndrome and LP with follicular involvement (lichen planopilaris) has recently shown them both to be variants of LP [2–5]. Follicular LP must be distinguished by biopsy from keratosis pilaris, Darier's disease, follicular mucinosis, lichen scrofulosorum and, in the scalp, from lupus erythematosus.

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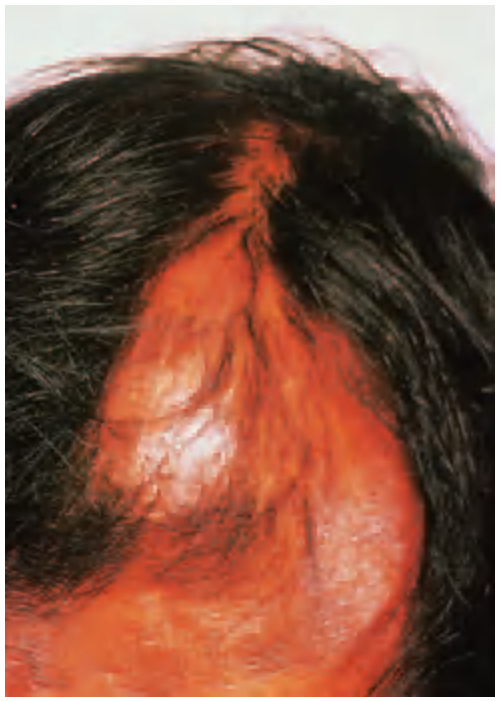

Fig. 42.17 Lichen planus of scalp leading to large areas of cicatricial alopecia. (Courtesy of St John's Institute of Dermatology, London, UK.)

Linear LP

Linear lesions as a Koebner effect are frequently found in LP. Isolated linear lesions, usually made up of small papules in close apposition, sometimes becoming confluent, are rare [1,2]; they are more common in childhood [3]. Linear LP lesions are usually only a few centimetres in length, but long, narrow linear lesions extending the whole length of a limb may occur. Such cases may overlap with epidermal naevi, and the term lichenoid epidermal naevus has been introduced [3]. Multiple linear LP lesions following the lines of Blaschko have been reported [4,5], and multiple linear LP was documented in a human immunodeficiency virus (HIV) patient [6]. Segmental LP was colocalized with vitiligo in one case [7]. Zosteriform LP has been described [8–11] (Fig. 42.18). The histology of linear or zosteriform LP is characteristic, and enables distinction from other linear dermatoses such as lichen striatus, linear naevi and linear psoriasis.

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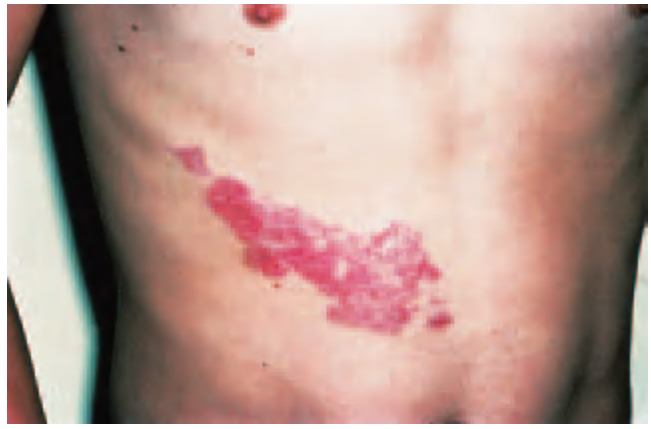

Fig. 42.18 Lichen planus, zosteriform lesion on chest wall. (Courtesy of St John's Institute of Dermatology, London, UK.)

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Actinic LP

SYN. LICHEN PLANUS SUBTROPICUS

'Actinic' or (sub)tropical LP generally occurs in children or young adults with dark skin living in tropical countries; virtually all cases originate from the Middle East, East Africa or India [1–4]. Lesions occur on exposed skin (usually the face) as well-defined annular or discoid patches, which have a deeply hyperpigmented centre surrounded by a striking hypopigmented zone (Fig. 42.19). Erythematous actinic LP has been associated with oral erosive LP and chronic active hepatitis [5]. Sunlight exposure appears to be central to the pathogenesis of actinic LP [6], although evidence for photo-induction of lesions in actinic LP is still lacking [7]. Actinic LP may mimic melasma [8]. There is a histological spectrum comprising a form with features of classical idiopathic LP; an intermediate form (lichenoid melanodermatitis) with foci of spongiosis and parakeratosis; and a more overtly eczematous type [9]; all share striking pigmentary incontinence. Some of these 'hybrids' of actinic LP may not be mere variants of LP. Actinic LP has been treated with acitretin and topical corticosteroids [10].

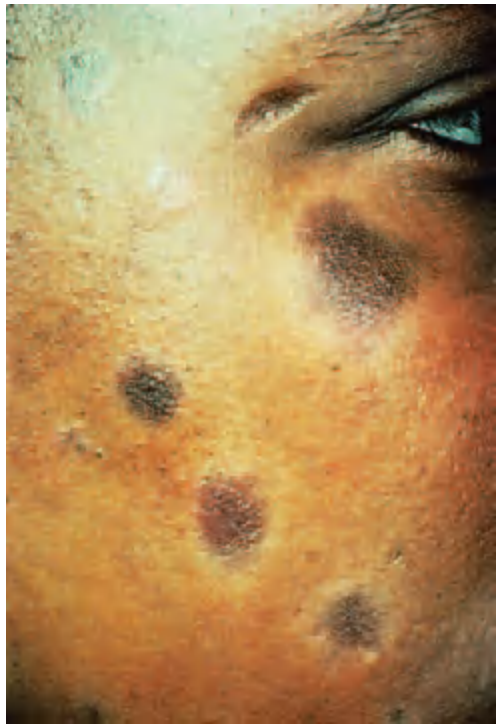

Fig. 42.19 Lichen planus actinicus, showing well-defined pigmented nummular patches on face. (Courtesy of St John's Institute of Dermatology, London, UK.)

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LP pigmentosus [1–3]

This is a pigmentary disorder seen in India or in the Middle East, which may or may not be associated with typical LP papules. The macular hyperpigmentation involves chiefly the face, neck and upper limbs, although it can be more widespread, and varies from slate grey to brownish black; it is mostly diffuse, but reticular, blotchy and perifollicular forms are seen [3]. The duration at presentation ranged from 2 months to 21 years in one series [3]. Occasionally, there is a striking predominance of lesions at intertriginous sites, especially the axillae [4]. The mucous membranes, palms and soles are usually not involved, but involvement of mucous membranes has been observed [5]. LP pigmentosus has been anecdotally reported in association with acrokeratosis of Bazex [6].

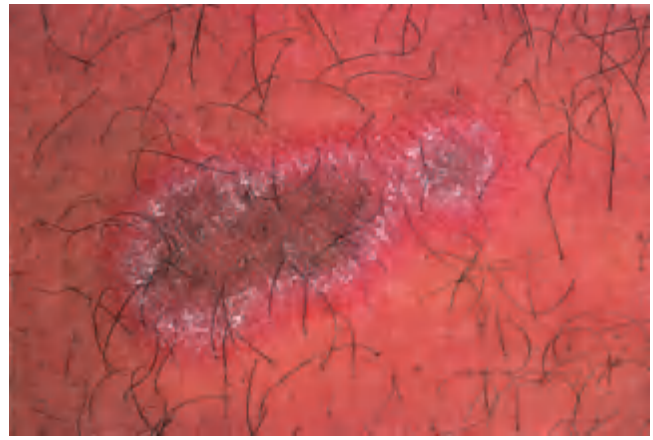

Fig. 42.20 Annular lichen planus.

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Annular LP

Although small annular lesions are common in LP, cases showing a few large annular lesions only are unusual. They may be widely scattered, and usually have a very narrow rim of activity and a depressed, slightly atrophic, centre (Fig. 42.20). Much less often, the margin is wide, and the central area is quite small. Annular lesions are characteristically found on the penis (see Fig. 42.8), sometimes associated with lesions on the buccal mucosa. The differential diagnosis includes granuloma annulare.

Atrophic LP

Lesions tend to be few in number; the atrophy may be the result of faded annular lesions [1], or resolved hypertrophic lesions on the lower legs especially. The histology

is likely to be non-specific, but allows lichen sclerosus or guttate morphoea to be excluded.

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Guttate LP

Lesions are widely scattered and remain discrete, may be all small (1–2 mm across), or larger (up to 1 cm) (Fig. 42.21), and individual lesions seldom become chronic. Guttate psoriasis must be differentiated.

Acute and subacute LP with confluence of lesions

In these forms, small lesions are widely distributed; where they become confluent, eczema may be simulated. Colour changes may be marked, with individual lesions initially red but progressing rapidly to black as they fade. Successive crops may occur, such that the total time for clearance may be little different from other forms; a small minority clear in under 3 months. Differential diagnosis includes pityriasis rosea in the earliest phase, and eczema later; drug-induced lichenoid eruptions may present in this fashion.

LP of the palms and soles

Although lesions on the volar aspect of the wrists or at the ankles occur in more than 50% of cases of LP, lesions on the adjacent palms and soles are less common, lack the characteristic shape and colour of lesions elsewhere, and are firm to the touch and yellow in hue [1,2] (see Fig. 42.11). They may be broadly sheeted or show up as punctate keratoses [3]. Vesicle-like papules are recorded [4]. Itching may be absent. When such changes occur in isolation, diagnosis is very difficult; syphilis, psoriasis, callosities and warts must be exluded.

A rare, very chronic form of LP involves large, painful indolent ulcers on the sole of one or both feet [5], with gradual permanent loss of toenails; there may be secondary webbing of the toes [6]. The sole may resemble lichenified dermatitis or psoriasis rather than LP before the ulcers appear. The onset is insidious and there may be no other evidence of LP, although cicatricial alopecia has been associated in some cases.

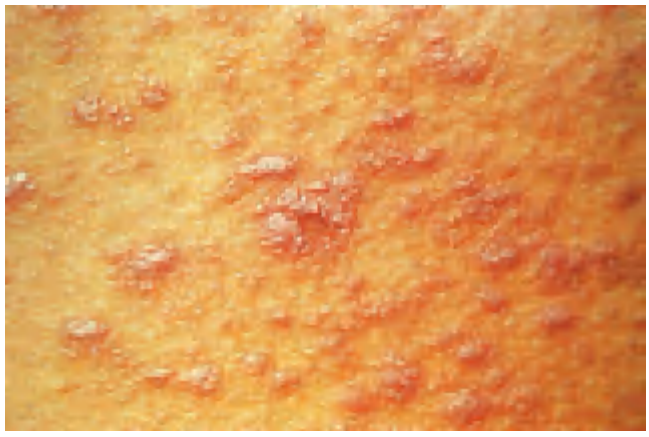

Fig. 42.21 Guttate lichen planus. (Courtesy of St John's Institute of Dermatology, London, UK.)

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Complications

Hair. Alopecia is uncommon in LP, but most often occurs in small areas on the scalp, producing patches of atrophic cicatricial alopecia [1–5] (see Fig. 42.17). It results from follicular destruction by the inflammatory infiltrate, with scarring. Areas of alopecia may continue to appear, or to extend, for months after the skin lesions have faded. The final result is one of pseudopelade [2,5]; this is probably best considered as a clinical entity due to a number of independent conditions, of which LP is only one. Lichen planopilaris is more common in women and about half will develop involvement of glabrous skin, mucous membranes or nails [1]; it may occur in children [3]. Tumid forms of LP follicularis have been described in which clusters of milium cysts and comedones develop [6]. LP pilaris has been reported in association with dermatitis herpetiformis [7].

Nails. Nail involvement occurs in up to 10% of cases, but is usually a minor feature of the disease [8,9]. The majority of cases present during the fifth or sixth decades; long-term permanent damage to the nails is rare [10]. Fingernails are more frequently affected than toenails [10], with initial involvement of two or three fingernails before subsequent spreading to the remaining digits. The most common changes are exaggeration of the longitudinal lines and linear depressions (Fig. 42.22), due to slight thinning of the nail plate. These changes usually occur in the context of severe generalized LP, although skin lesions may not be

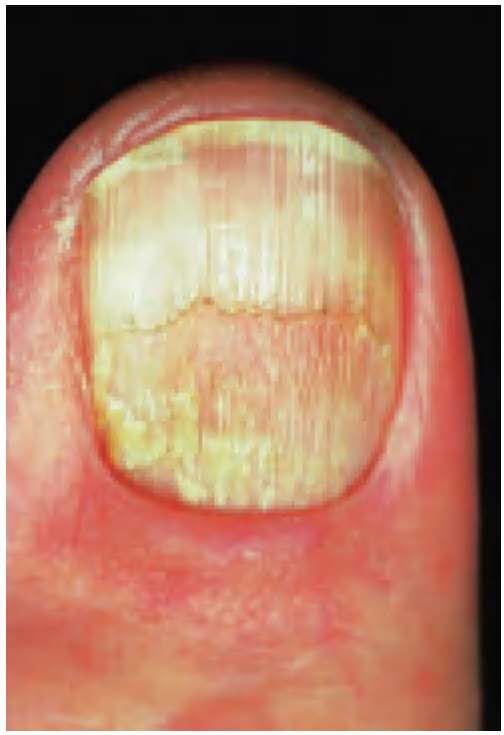

Fig. 42.22 Lichen planus of thumbnail showing thinning of nail plate and longitudinal lines. (Courtesy of St John's Institute of Dermatology, London, UK.)

seen in the vicinity of the affected nail. Elevated ridges may be seen on the nail [9]. Adhesion between the epidermis of the dorsal nail fold and the nail bed may cause partial destruction of the nail (pterygium unguis) (Fig. 42.23). Rarely, the nail is completely shed; there is usually clinical evidence of LP at the base of the nail before shedding. Nails may partially regrow or be permanently lost (Fig. 42.24); the nails of the great toes are the ones most often affected.

LP has been shown to cause childhood idiopathic atrophy of the nails [11]. LP of the nails in childhood is rare [12], but may overlap with the condition of twenty nail dystrophy of childhood (idiopathic trachyonychia); the exact relationship is unclear [13–18]. The rare variant of LP that causes ulceration of the soles is often accompanied by permanent destruction of several toenails. LP of the nail bed may give rise to longitudinal melanonychia [19], hyperpigmentation, subungual hyperkeratosis or onycholysis [9], or changes mimicking the yellow nail syndrome [20,21].

Mucous membranes. Squamous cell cancer developing on mouth lesions is uncommon, but is a potential danger, especially with ulcerated lesions [21–30], although the incidence varies greatly in different series. Lesions may occur on the lip (Fig. 42.25), the buccal mucosa or the gum margin. Squamous cell cancer arising on LP cutaneous

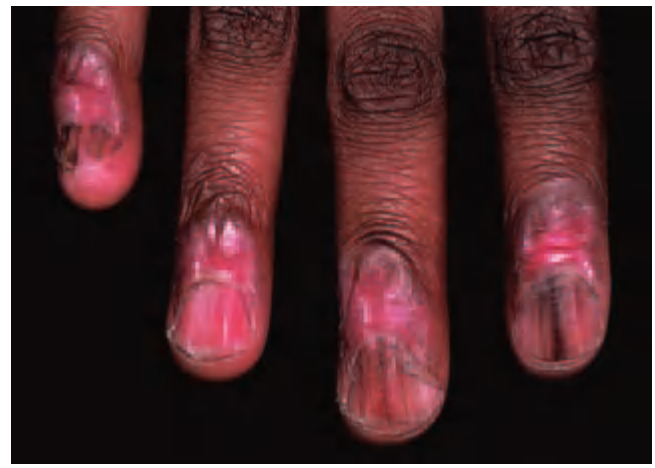

Fig. 42.23 Severe lichen planus of fingernails showing involvement of nail fold areas and early pterygium formation. (Courtesy of St John's Institute of Dermatology, London, UK.)

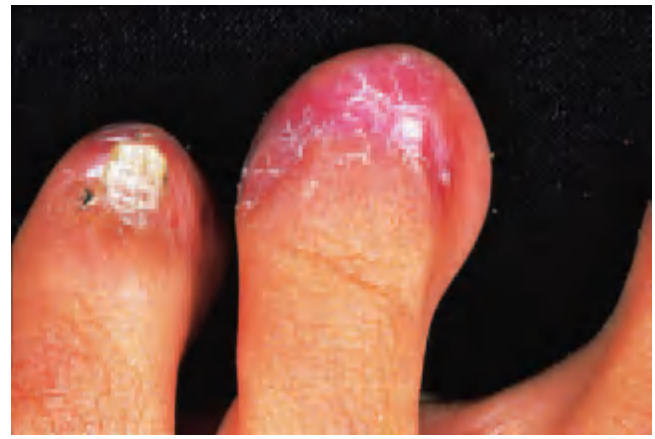

Fig. 42.24 Severe destructive lichen planus of toenails. (Courtesy of St John's Institute of Dermatology, London, UK.)

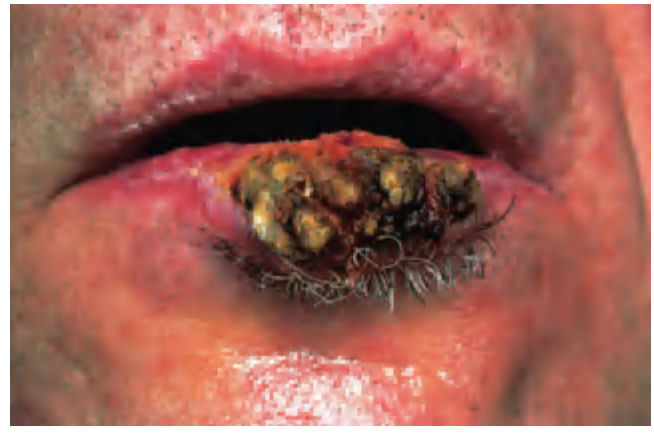

Fig. 42.25 Squamous carcinoma on lower lip developing at site of lichen planus cheilitis. (Courtesy of St John's Institute of Dermatology, London, UK.)

lesions [31] and anogenital lesions [32,33] is definitely a rare phenomenon. Cicatricial conjunctivitis [34] and lacrimal canalicular obstruction are recorded [35].

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Associated conditions

Idiopathic LP has been reported in association with diseases of altered or disturbed immunity, including ulcerative colitis [1–4], alopecia areata [2,4,5], vitiligo [4], dermatomyositis [6], morphoea and lichen sclerosus [7], systemic lupus erythematosus [8,9], pemphigus [8] and paraneoplastic pemphigus [10,11]. In addition, LP has been observed in association with thymoma [5,8,12,13], myasthenia gravis [3,4,13], hypogammaglobulinaemia [5,14] primary biliary cirrhosis [15–17], especially in those treated with penicillamine, and primary sclerosing cholangitis [18]. The literature with regard to LP and HCV infection is reviewed in the section on pathogenesis above. In Italy, possibly because of a higher prevalence of hepatitis B virus (HBV) and HCV infection, LP patients seem more prone to develop liver disease including chronic active hepatitis [19–23]. A high prevalence of anticardiolipin antibodies has been documented in patients with HCV-associated oral LP [24]. Elsewhere, the association between LP and chronic active hepatitis or primary biliary cirrhosis is unusual and probably coincidental [25–27]. Overall, the majority of patients with LP live to old age, despite an association with autoimmunity [28].

LP has also been associated with diabetes mellitus [29]. Anecdotally, LP has occurred in patients with Castleman's tumour (giant lymph-node hyperplasia) [30] or with generalized lichen amyloidosus [31]. LP has been described in certain tattoo reactions, particularly in those areas where there is coexisting mercury hypersensitivity to the injected dye [32,33].

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Differential diagnosis

Typical cases of LP need be distinguished only from lichenoid eruptions induced by drugs or colour developer. Less typical cases of LP may be mistaken for plane warts, eczematous eruptions with lichenification from scratching, pityriasis rosea, lichen simplex chronicus [1] and other lichenoid eruptions such as papular lichen amyloidosus. Occasional cases of LP without itching must be distinguished from secondary syphilis.

The differential diagnosis of the special variants has already been mentioned; in case of doubt, a biopsy should establish the diagnosis. Although erythema dyschromicum perstans (ashy dermatosis) has a characteristic clinical appearance, it has been regarded as simply a macular variant of LP (LP pigmentosus) [2,3].

Prognosis [4–8]

Occasional cases clear in a few weeks, but skin lesions more usually subside within 9 months in about 50% of cases, and in 85% have cleared within 18 months, unless treated with systemic corticosteroids or potent topical steroids. Itching disappears first, then papules flatten, to be replaced by a corresponding area of post-inflammatory hyperpigmentation.

If hypertrophic patches develop, they are likely to persist for many more months, and occasionally for 20 years or more. The development of large, annular lesions is also a poor prognostic sign. Hair fall is usually permanent. Mucous membrane lesions clear more slowly than those on the skin and may remain visible for years after all evidence of the skin lesions has cleared [8]. Only 13% of patients with oral LP under follow-up in a large series went into remission [9], although mucous membrane lesions in Indian people were reported to be short-lived and without a tendency to malignancy [10]. About one case in five relapses, and frequent attacks occur in a small minority of cases.

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Treatment

A large number of different forms of medication have been advocated, without adequate controlled trials [1]. Symptomatic treatment is usually sufficient, and largely consists of the use of the fluorinated topical steroid creams and ointments. These should be of the 'potent' variety (e.g. fluocinonide 0.05%, clobetasol proprionate 0.05%) to have any real chance of being effective. They are recommended for use for comparatively small areas, but in a diluted form (e.g. 1 : 4 in white soft paraffin) can cover much larger areas. Oral antihistamines such as promethazine hydrochloride, trimeprazine tartrate, brompheniramine maleate or hydroxyzine hydrochloride may be helpful in counteracting pruritus. If hypertrophic lesions form, they may be treated by using occlusive dressings of tar or flurandrenolone tape, or by the use of topical steroid preparations under polythene occlusion. Occasionally, intralesional injections of a suitable steroid preparation may be of great value. Skin grafting has been used for ulcerative lesions on the soles [2]. Topical calcipotriol is of limited use [3].

Systemic corticosteroids, in the form of adrenocorticotrophic hormone (ACTH) or tetracosactrin (Synacthen®), or prednisolone at 15–20 mg daily for about 6 weeks and thereafter gradually reduced, may be of great value in treating the 5% of severe cases with marked irritation, ulcerative mucous membrane lesions, or progressive nail destruction or alopecia [4]. Such doses are sufficient to retard growth in children [5]. Some relapse is liable to occur on discontinuation of systemic steroids, but the disease is self-limiting and corticosteroid therapy eases the patient through the worst part of its course.

Other agents used in treating severe cutaneous and erosive LP have included acitretin [6], itraconazole [7], metronidazole [8–10], low-molecular-weight heparin (enoxaparin) [11,12], narrow-band ultraviolet B phototherapy [13], oral or bath photochemotherapy with psoralen and UVA (PUVA) [14–16], Re-PUVA (retinoids with PUVA; this combination, however, has anecdotally induced dramatic hyperpigmentation) [17], cyclophosphamide [18], azathioprine [19–21], methotrexate [22], recombinant IFN-α-2b [23], basiliximab [24] and systemic ciclosporin (cyclosporin) [25–27]. Topical and systemic ciclosporin have been used to treat ulcerative LP of the feet [28,29]. Systemic ciclosporin [30,31] and thalidomide [32,33] have been helpful in management of lichen planopilaris of the scalp.

Mucous membranes. Treatment of oral lesions has been reviewed [34,35]. Topical lidocaine (lignocaine) gel or diphenhydramine may alleviate discomfort, and topical tetracycline may be useful [36]. Topical corticosteroids, such as triamcinolone in Orabase®, clobetasol propionate as an ointment or a paste [37–41], corticosteroid lozenges (Corlan®), betamethasone (Betnesol®) mouthwashes 0.5 mg three to four times daily [41], or fluticasone propionate spray [41], are often beneficial. Vaginal hydrocortisone suppositories have been advocated [42,43]. The use of silastic prosthetic devices to enhance the delivery of topical corticosteroids to mucosal surfaces (e.g. vagina and oral) has been documented [44]. Intralesional injections may be used but are painful [45]. Reactivation of human papillomavirus may occur at genital sites with topical steroids [46]. Extensive ulcerative lesions should be treated with systemic steroid preparations, but the starting dose will need to be higher than for treatment of skin lesions.

Initial reports of the efficacy of griseofulvin [47] have not stood the test of time [48,49]. Dapsone [50], hydroxychloroquine [51], retinoids, either topical in the form of retinaldehyde [52], isotretinoin gel (0.1%) [53], or tazarotene [54], or systemic as with etretinate [55], isotretinoin [56] or acitretin [57], and thalidomide [58], have all had their advocates. Topical ciclosporin for chronic mucosal LP has been of variable benefit and is expensive [59–63]. The heparinoid sulodexide given systemically was judged as effective as topical ciclosporin [64].

Oral ciclosporin can be effective [65]. There has been a spate of recent papers on the merits of topical tacrolimus in oral, genital and perianal mucous membrane LP [66–74]. Carbon dioxide and Nd : Yag laser therapy [35], as well as the 308-nm UVB excimer laser [75], have been utilized in the treatment of oral LP. Surgical excision of persistent ulcers has been recommended [76], and malignancy demands immediate surgery combined with radiotherapy.

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'Mixed' LP/discoid lupus erythematosus disease patterns

Discoid lupus erythematosus (DLE) and LP are usually considered as distinct entities with characteristic clinical, histopathological and immunopathological features, with basement membrane deposition of IgG in DLE [1,2]. However, similarities between LP and DLE have been noted [3]. In addition, there have been several reports of patients showing overlapping features of both disorders [4–11]. Chronic atrophic DLE-like lesions on the head, neck and upper trunk may accompany reticular white lesions in the oral cavity, and combinations of lichenoid or verrucous lesions are seen. Eyelid involvement is recorded [12]. The association of extensive generalized LP with subacute cutaneous DLE has been documented [13]. Both ciclosporin [13] and acitretin [14] can be of benefit in treating LP/DLE overlap syndrome.

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Bullous LP and LP pemphigoides

Lichen ruber pemphigoides was first described by Kaposi in 1892 [1]. Bullous LP and LP pemphigoides were in the past differentiated solely on clinical and histological criteria [2], but can now be differentiated using IMF procedures and immunoelectronmicroscopy [3,4]. In bullous LP, blisters arise only on or near the lesions of LP, as a result of severe liquefaction degeneration of the basal cell layer [5]. Histologically there is subepidermal bulla formation with typical changes of LP, and direct and indirect IMF is negative [3]. The eruption of is usually only of short duration [3].

In LP pemphigoides [6–9], the LP tends to be acute and generalized and is followed by the sudden appearance of large bullae on both involved and uninvolved skin (Fig. 42.26). Occasionally, even in LP pemphigoides, blisters may arise only on the lesions of LP [10]. LP pemphigoides has been precipitated by PUVA [11]. An LP pemphigoides-like eruption has been reported to overlap with paraneoplastic pemphigus [12,13]. In LP pemphigoides, the histology shows a subepidermal bulla with no evidence of associated LP [3]. Direct IMF shows linear basement-membrane-zone deposition of IgG and C3 in perilesional skin [3,9]. Immunoelectron-microscopic studies reveal deposition of IgG and C3 in the base of the bulla and not in the roof as found in bullous pemphigoid [14].

Immunoblotting data have revealed that circulating autoantibodies in LP pemphigoides react with an epitope within the C-terminal NC16A domain of bullous pemphigoid 180-kDa antigen, and also with a 200-kDa antigen

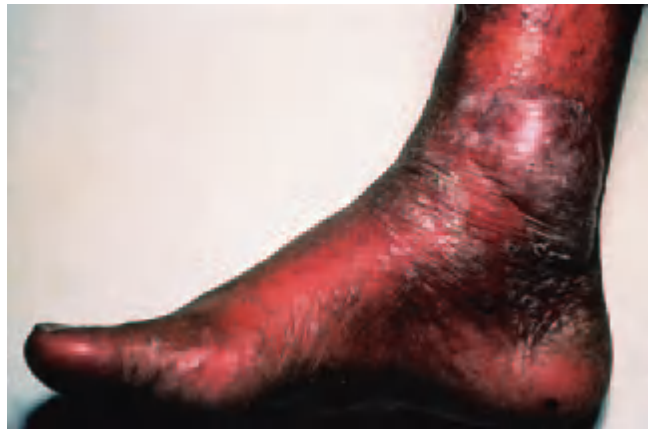

Fig. 42.26 Lichen planus pemphigoides. Large bulla arising on and around vicinity of lichen planus around ankle. (Courtesy of St John's Institute of Dermatology, London, UK.)

detected in bullous pemphigoid [15–20]. It seems that epidermal damage from liquefaction degeneration in LP exposes basement-membrane antigens, and consequent stimulation of autoantibody production.

The mean age of cases of LP pemphigoides is lower than that of classical bullous pemphigoid, and the course of the disease also tends to be less severe. Nevertheless, some cases require treatment with systemic steroids or azathioprine and fatalities occur [9]. A combination of corticosteroids and acitretin has been used [20,21].

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Symptomatic lichenoid reactions

Lichenoid reactions occur in persons handling developer used in the processing of colour films. Many drugs may produce an eruption identical with or similar to LP.

LP-like contact dermatitis due to contact with colour developing agents and methacrylic acid esters

An LP-type eruption was reported in up to 25% of persons exposed to chemicals in colour developer [1–5]. Lesions began in areas of contact with the developer, but sometimes extended widely; the mucous membranes were usually spared. Resolution was slow, and lesions persisted for months, with residual pigmentation lasting for a year or more. The responsible chemicals were substituted paraphenylene diamines. Current automated equipment minimizes contact with these, and LP-like eruptions due to this source are now rare [5]. Two types of reaction were observed—acute (eczematous) and subacute (lichenoid)—but either evolved into the other. It is not clear why exposure to colour developers caused a spongiotic dermatitis in some patients and a lichenoid dermatitis in others [5]. Patch-test reactions were usually positive to the substituted paraphenylenediamine and were eczematous in nature, but might become lichenoid [4].

LP-like lesions have developed on sites exposed to methacrylic acid esters used in the car industry [6]. As dental devices contain methacrylic acid esters, it is possible that methacrylic acid esters may be one of the causative agents in oral LP [6]. Other inducers of contact lichenoid eruptions include dental restorative materials, musk ambrette, nickel, aminoglycoside antibiotics and gold.

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Lichenoid eruptions due to drugs

The reader is also directed to Chapter 73, Table 73.8, as well as to information on individual drugs. The mechanisms by which drugs induce a lichenoid tissue reaction are unknown, but they may develop as a result of autoreactive cytotoxic T-cell clones directed against a drug/class II MHC antigen complex, such that keratinocytes and

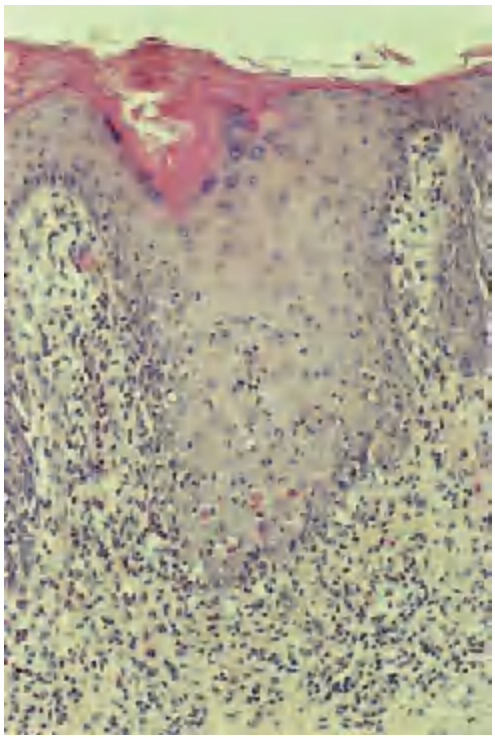

Fig. 42.27 Lichenoid drug eruption (gold). Photomicrograph showing the presence of higher level cytoid bodies with several eosinophils amongst the lichenoid infiltrate. H&E, × 20.

Langerhans' cells are viewed by the immune system as 'non-self'. Cloned murine autoreactive T cells produce a lichenoid reaction in recipient animals following injection [1]. The presence of epidermotropic T cells correlates with that of class II MHC (HLA-DR) expressing keratinocytes and Langerhans' cells in lichenoid eruptions [2]. Macrophage migration inhibition factor (MIF) assays are significantly increased in lichenoid drug eruptions [3].

Histologically, the pattern of an LP-like eruption can be indistinguishable from idiopathic LP, although the cellular infiltrate tends to be more pleomorphic and less dense; helpful histological features indicative of a drug reaction include the following: focal parakeratosis; focal interruption of the granular layer (Fig. 42.27); cytoid bodies situated higher in the granular and cornified layers; presence of a few eosinophils; exocytosis of lymphoid cells into the upper epidermis; and a deeper perivascular infiltrate [4]. Later, there may be scarring with destruction of the sweat glands. The histopathology of photodistributed, as opposed to non-photodistributed, lichenoid drug eruptions has been shown to be often indistinguishable from that of idiopathic LP [5]. Occasionally, the degree of lymphoid epidermotropism may simulate mycosis fungoides [6]. The IMF findings in lichenoid drug eruptions are identical to those in idiopathic LP [7].

Lichenoid drug eruptions tend to be extensive, and may develop weeks or months after initiation of therapy; they

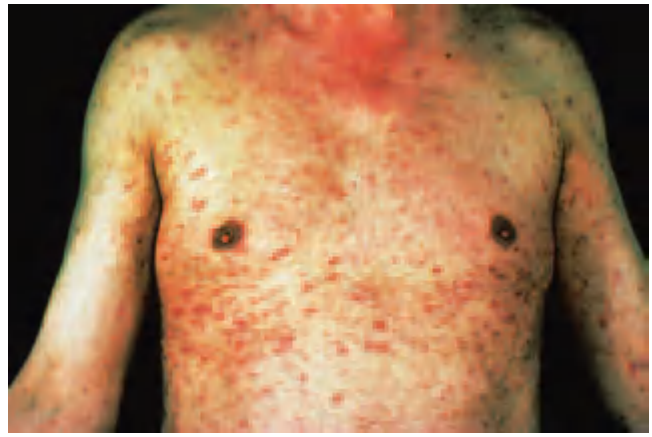

Fig. 42.28 Diffuse psoriasiform lichenoid drug eruption due to β-blocker administration. (Courtesy of St John's Institute of Dermatology, London, UK.)

may progress to an exfoliative dermatitis [8,9]. Lesions may be rather more psoriasiform than in idiopathic LP (Fig. 42.28), and oral involvement is rare. Long-lasting deep hyperpigmentation, alopecia and skin atrophy with anhidrosis due to sweat gland atrophy may develop. Resolution of the skin eruption may be slow after cessation of therapy, on average from 1 to 4 months, but up to 24 months with gold [9].

The list of drugs causing LP-like eruptions is already long and continues to increase steadily. Gold is probably the most common drug producing an LP-like eruption [10]; oral involvement tends to be rarer in LP-like drug eruptions, but occasionally it can be severe and involve the oesophagus [11]. Mercury-induced lichenoid eruptions are recorded [12], and may be or particular relevance in oral LP (see above). During the Second World War, millions of troops took mepacrine to prevent malaria, and many cases of an LP-like eruption occurred [13]. Mepacrine (quinacrine) lichenoid eruptions may be followed by skin cancers, up to 34 years later. Photodistributed lichenoid lesions [9] may be seen with quinine and quinidine [6,14,15], demeclocycline [16] and other tetracyclines, thiazide diuretics [17] (Figs 42.29 & 42.30), furosemide (frusemide), diazoxide, amlodipine [18], chlorpromazine, carbamazepine, 5-fluorouracil, pyritinol and ethambutol [19]. Other drugs implicated include streptomycin, isoniazid [20], pyrazinamide [21], pyrimethamine [22], metropromazine, levopromazine, amiphenazole, methyldopa, β-blocking agents including propranolol [23], oxprenolol [24] and labetalol [25], sulphydryl drugs such as penicillamine [26], tiopronin [27], captopril [28–30] and enalapril [31], non-steroidal anti-inflammatory drugs (NSAIDs) [32] including acetylsalicylic acid [33], naproxen [34] and salsalate [35], levamisole [36], proton pump inhibitors [37], chlorpropamide and tolazamide [38], carbamazepine [39], simvastatin [40] and pravastatin [41], antihistamines

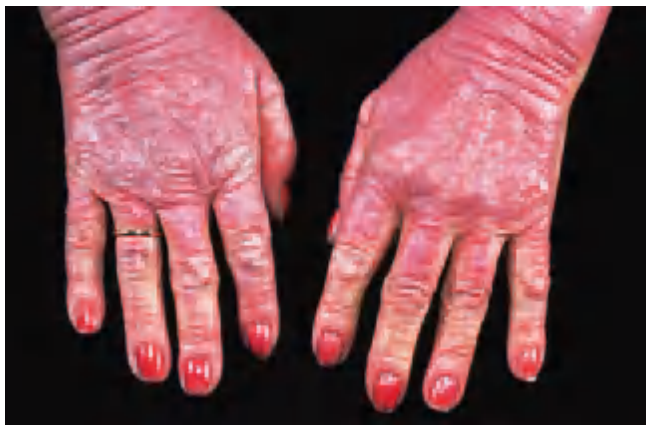

Fig. 42.29 Lichenoid photodermatitis occurring in a patient with a long history of thiazide ingestion. (Courtesy of Dr D.H. McGibbon, St John's Institute of Dermatology, London, UK.)

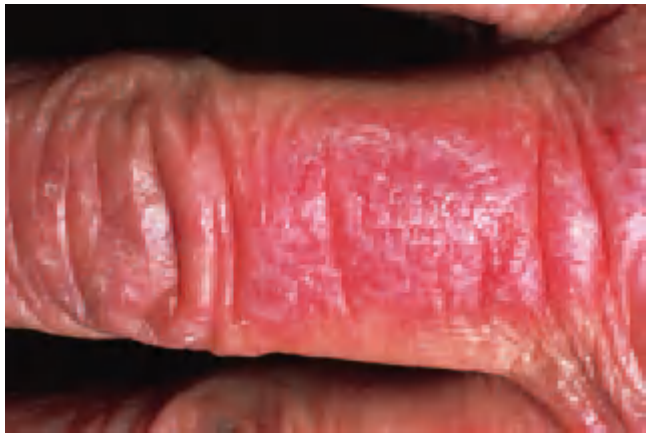

Fig. 42.30 Close-up of dorsum of finger shown in Fig. 42.29.

[42] including chlorpheniramine [43], roxatidine and ranitidine [44], isotretinoin [45], alendronate [46], PUVA therapy [47], sildenafil [48], sparfloxacin [49], imatinib [50], intravenous immunoglobulin [51], ursodeoxycholic acid given for neonatal hepatitis [52], and hepatitis B vaccination [53–59]. Lichenoid reactions have been documented at the sites of injection of granulocyte colony-stimulating factor [60]. Ulcerative lesions may occur with hydroxyurea [61,62], methyldopa, propranolol and lithium carbonate. Oral LP lesions are associated with drugs metabolized by major cytochrome P450-enzymes [63]. Oral involvement may be caused by NSAIDs, gold salts, penicillamine, sulphonylureas, angiotensin-converting enzyme (ACE) inhibitors, methyldopa, allopurinol, ketoconazole, antiretroviral agents including zidovudine [64], clopidrogel [65] and lithium carbonate [66]. Social use of betel nut is relatively common in India and South-East Asia; the product that is chewed, betel quid, is a mixture of substances, including the areca nut and betel leaf, and is associated with oral LP [67,68]. An LP pemphigoides-like eruption has been reported following administration of captopril, cinnarizine [69] and simvastatin [70]. Bullous lesions are recorded with labetalol and tiopronin; LP pigmentosus with gold; and exfoliative dermatitis with nifedipine. Lichenoid photoeruptions have been described in advanced HIV infection; black patients are disproportionately affected and all were taking potential photosensitizing drugs [71]. Hydroxyurea has induced a lichenoid chronic graft-versus-host disease-like acrodermatitis [72].

Treatment. Treatment is to withdraw the drug; with gold eruptions, dimercaprol (BAL) or ethylene diamine tetraacetic acid (EDTA) may be used. Subsequent treatment is symptomatic, but severe cases may require corticosteroid therapy as outlined for idiopathic LP.

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Nékam's disease [1,2]

SYN. KERATOSIS LICHENOIDES CHRONICA; POROKERATOSIS STRIATA LICHENOIDES; LICHEN RUBER MONILIFORMIS; LICHEN VERRUCOSUS ET RETICULARIS

The variety of synonyms used implies that there is no complete consensus of agreement about this rare disorder. The great majority of cases are adults between the ages of 20 and 40 years [2], although children are occasionally affected [3]. Nékam's disease is characterized by violaceous, papular and nodular lesions typically arranged in a linear and reticulate pattern (Figs 42.31 & 42.32), most marked on the extremities and buttocks, and accompanied by a seborrhoeic dermatitis-like eruption on the face. Nékam's original case was also associated with palmoplantar keratoderma [4]. The individual lesions are erythematous verrucous papules covered by a hyperkeratotic plug that can only be removed with difficulty, revealing irregular indentations and prominent capillary loops [1,5]. In extensive Nékam's disease, the lesions tend to be

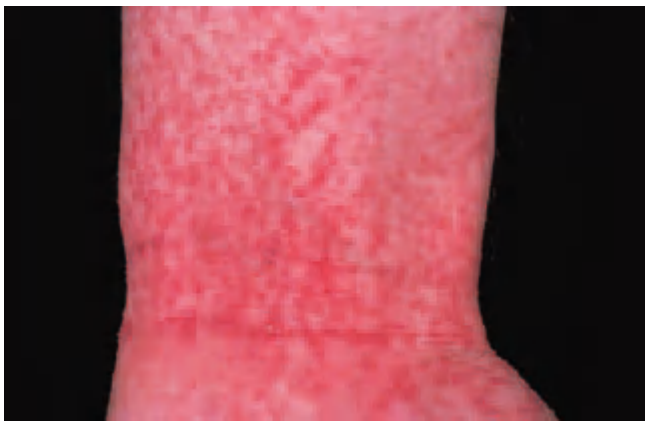

Fig. 42.31 Nékam's disease. Reticulate keratotic erythematous papules on volar aspect of wrist. (Courtesy of St John's Institute of Dermatology, London, UK.)

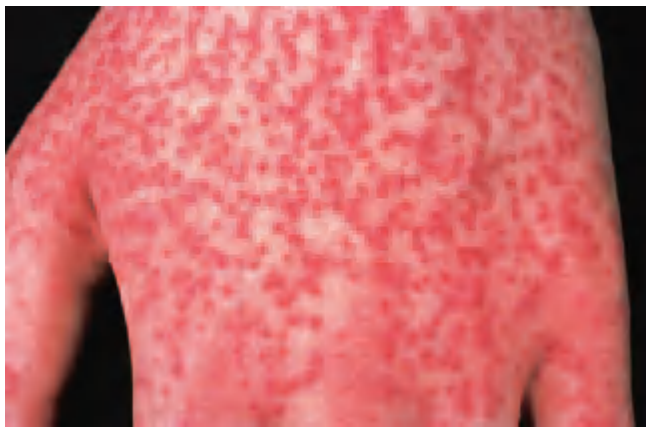

Fig. 42.32 Nékam's disease. Same patient as shown in Fig. 42.31. Involvement on dorsum of hand. (Courtesy of St John's Institute of Dermatology, London, UK.)

symmetrical bilaterally, mainly involving the antecubital fossae, extensor forearms, lumbosacral area and buttocks, posterior thighs, popliteal fossae, and less commonly the oral cavity and genitalia. Oral manifestations occur in 50% of patients, recurrent aphthous ulcers, larger chronic ulcers or erythrokeratotic papules being the commonest oral features [2]. The nails can become thickened, longitudinally ridged and prone to paronychia [6]. Cases have followed trauma [7] and erythroderma [8]. A limited variant of Nékam's disease presenting with erythematous hyperkeratotic papules and plaques on the face, clearing in the summer months, has been described in two young siblings [9].

Histologically, changes are often non-specific and consistent with a chronic dermatitis, but lichenoid features can be seen [1,5]. Some authors [1] believe that the condition is an unusual variant of LP, while others [10] consider that it is a distinct entity. A case of Nékam's disease associated with porokeratotic histology and amyloid deposition may also point against the view that Nékam's disease is a subset of LP [11]. A possible association of Nékam's disease with glomerulonephritis and lymphoproliferative disorders has been commented on [2]. The course of the dermatosis is chronic and progressive and very resistant to therapeutic approaches, but has shown a favourable response to photochemotherapy [12] and etretinate [13].

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Lichen nitidus [1]

Lichen nitidus is a rarer condition than idiopathic LP and is clinically characterized by the presence of pinpoint to pinhead-sized papules, which are usually asymptomatic, flesh coloured, with a flat, shiny surface.

Aetiology. The view that lichen nitidus represents a variant of LP tends to be supported by the fact that early tiny LP papules may be clinically and histopathologically indistinguishable from lichen nitidus [2,3]. Immunophenotypic studies also reinforce the association between LP and lichen nitidus [4]. However, some authorities favour a separation into two dermatoses, because of histopathological differences, or differences in cytokine expression in lichen nitidus [5]. Surprisingly, direct IMF studies in lichen nitidus have given negative results [6,7]. However, ultrastructural studies have shown identical changes in lichen nitidus and LP [6].

Histology. The histology of a typical papule is characteristic. The papule is formed by an intense infiltrate situated

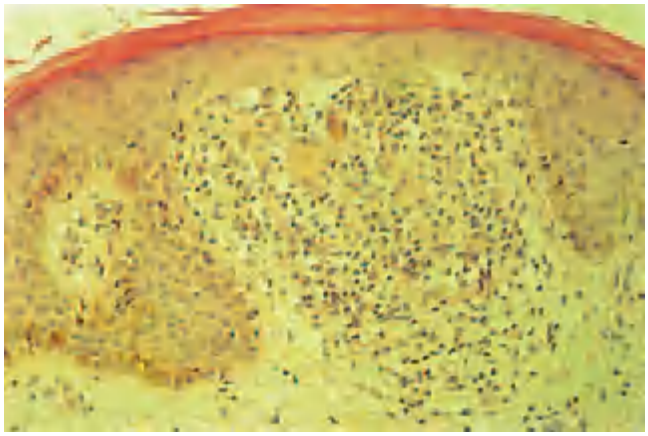

Fig. 42.33 Lichen nitidus. Typical histology showing the focally dense infiltrate containing a few giant cells. H&E, × 100. (Courtesy of St John's Institute of Dermatology, London, UK.)

Fig. 42.34 Lichen nitidus. Close-up of aggregated pinhead-sized papules. (Courtesy of St John's Institute of Dermatology, London, UK.)

immediately below the epidermis and is well circumscribed. The infiltrate consists of lymphocytes and histiocytes and there are often a few Langhans' giant cells (Fig. 42.33). Sometimes, plasma cells are numerous in the infiltrate [8]. The overlying epidermis is flattened and sometimes there is liquefaction degeneration of the basal cell layer. The rete ridges at the margin of the infiltrate are elongated and tend to encircle it. Although tuberculoid in appearance, there is never true tubercle formation or caseation. The histology of a palmar lesion may show a deep parakeratotic plug, which distinguishes it from the palmar lesions of LP [9]. Perifollicular granulomas can occur in spinous and follicular lichen nitidus, which may simulate lichen scrofulosorum [10]. Perforating lichen nitidus has also been described [11].

Incidence. In its characteristic monomorphic form, lichen nitidus is rare, but lesions of lichen nitidus occurring in association with LP are more common [3]. The age incidence tends to be lower than that of LP. Most cases occur in children or young adults. Familial lichen nitidus has rarely been observed [12].

Natural history. Typical lichen nitidus may clear in a few weeks or last a very long time, and may show little or no response to treatment. There have been no large series reporting the natural history of this disorder. With our present knowledge, its course is unpredictable.

Clinical features. Typical lichen nitidus papules are minute, pinpoint to pinhead sized, and have a flat or dome-shaped, shiny surface. They usually remain discrete, although they may be closely grouped (Fig. 42.34). They are found on any part of the body but the sites of predilection are the forearms, penis (Fig. 42.35), abdomen, chest and buttocks. The eruption is sometimes generalized [13,14]. When the palms or soles are involved, the changes can be those of a confluent hyperkeratosis resembling chronic fissured eczema, or there may be multiple, distinctive, minute papules [15,16]. On the palms, the minute papules can become purpuric [9] and may occasionally resemble pompholyx [17]. Such cases may lack lesions of lichen nitidus elsewhere, so a biopsy is essential to confirm the diagnosis [9,15].

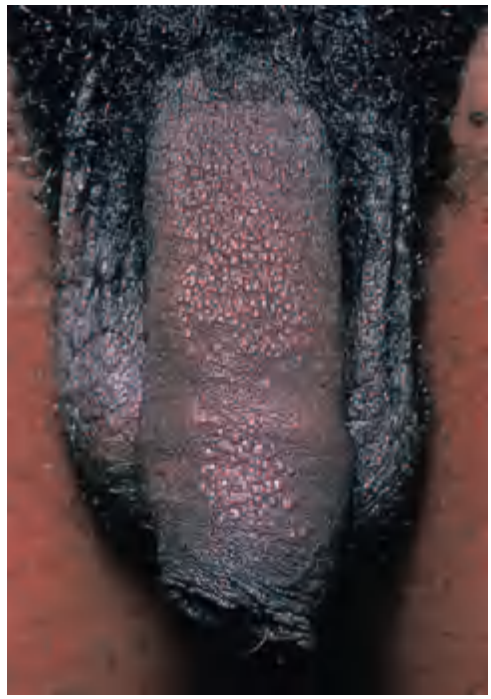

Fig. 42.35 Lichen nitidus. Aggregates of pinhead-sized papules on shaft of penis. (Courtesy of St John's Institute of Dermatology, London, UK.)

Linear lichen nitidus has been described, but is exceptionally rare [18]. The development of lesions along

scratch marks is not uncommon. The lesions are flesh coloured or reddish brown. Although intense pruritus can occur [14], the lesions are generally quite symptomless.

Coexistence with LP is common, and Wilson and Bett [3] claim that lesions clinically identical to those of lichen nitidus can be found in 25–30% of all cases of LP. Nail pitting may coexist with lichen nitidus [19], or the affected nails may appear rough due to increased linear striations and longitudinal ridging [15,20].

Mucous membrane lesions occur occasionally and are much rarer than in LP. Krook [21] described a generalized case as having mucosal lesions mainly on the hard palate and maxillary alveolar margins, which consisted of fairly closely grouped, greyish yellow, round, sharply demarcated, discrete papules up to 1 mm in diameter; many were petechial. In other cases, lesions occur that are similar to those in LP.

Lichen nitidus must be distinguished from lichen scrofulosorum [10], where there are grouped follicular papules in small patches on the trunk, and from keratosis pilaris, where there are horny follicular papules mainly on the extensor surface of the limbs. In cases of doubt, a biopsy usually clarifies the diagnosis.

Lichen nitidus has been described in association with Crohn's disease [22], trisomy 21 and congenital megacolon [23].

Treatment. As the disease is often asymptomatic and eventually self-limiting, no treatment is required in most cases, but fluorinated topical steroid preparations may be recommended if treatment is demanded, for example for lesions on the penis, and can be dramatically successful [24]. Clearance of generalized lichen nitidus has been described with sun exposure [25], PUVA [26] and astemizole [13,27,28]. Acitretin can lead to a gradual improvement in palmoplantar lichen nitidus [29].

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Graft-versus-host disease (see also Chapter 56)

Haematopoietic cell transplantation is the preferred therapy for a certain life-threatening diseases of the lymphohaematopoietic system [1], including acute leukaemias, aplastic anaemia and certain immunodeficiency disorders, as well as for some inborn errors of metabolism. Graft-versus-host disease (GVHD) occurs when lymphoid cells from an immunocompetent donor are introduced into a histo-incompatible recipient incapable of rejecting them, and is a major obstacle to successful transplantation. Moderate to severe acute GVHD affects 9% to 35% of patients undergoing standard allogeneic bone marrow transplantation, despite using HLA-matched sibling donors and immunosuppression after grafting [2]. The incidence of chronic GVHD is approximately 40% to 50%. Patients with stages 2, 3 and 4 acute GVHD had median survivals of only 5.4, 3.6 and 2.5 months, respectively, while the overall 10-year mortality rate of patients with chronic GVHD was 42% in one recent series [2]. A systemic autoimmune syndrome resembling GVHD, termed autologous GVHD, may follow autologous or syngeneic bone marrow transplantations and ciclosporin therapy [3–6]. Blood transfusions involving transfer of unirradiated immunocompetent cells into immunodeficient children or adults, including those with malignancy, are an important cause [7–12]. GVHD has followed liver trans-

plantation [13–15]. GVHD can also occur after materno–fetal cell transfer (engraftment) in immunodeficient children [16,17]. GVHD has been reported rarely to develop 'spontaneously' in response to a disseminated carcinoma [18,19].

The main targets of GVHD in humans are the skin, the gastrointestinal tract and the liver. GVHD is of importance to the dermatologist since skin manifestations, amongst them lichenoid eruptions, are prominent; in addition, cutaneous GVHD provides us with a unique biological model for the study of lymphocyte-mediated skin disorders [20–22].

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Pathogenesis of GVHD

Genetic factors may influence the risk of development of acute and chronic GVHD [1,2]. There is an increased frequency of HLA-A1-B1 and -B2 in chronic GVHD with scleroderma-like complications [3]. $CD4^+$ T cells, of both Th1 and Th2 type, as well as $CD8^+$ Tc2 type, mediate and regulate GVHD [4,5]; T cells are also involved in the pathogenesis of syngeneic or autologous GVHD [6,7] and transfusion-related GVHD [8]. Viral infection may have an adjunctive role [9,10]. Host dendritic cells, rather than alloantigen expression by host epithelium, play a critical role in triggering T-cell-mediated GVHD before they disappear [11–15]. Langerhans' cells are reduced in number, and appear to be targets for destruction, in acute GVHD [16–19]. Keratinocytes express certain minor non-HLA histocompatibility antigens not expressed by haemopoietic cells, which may explain in part why the skin is a particular target organ for GVHD [20]. Host endothelial cells may also be targeted in chronic GVHD [21]. Cytokines are intimately involved in the pathogenesis of GVHD [22–24]. The use of mutant mice lacking critical proteins has helped map out the molecular pathways by which GVHD targets organ damage [25]. Donor T-cell-derived TNF-α is required for GVHD [26], and neutralization of TNF-α and IL-1 prevents acute GVHD in a murine model [11]. Polymorphisms for TNF-α and TNF receptor genes [27,28], and for IFN-γ and IL-6 genes [29], affect the outcome of bone marrow transplantation. IL-5 [30], IL-18 [31] and macrophage MIF [32] are up-regulated in acute GVHD. The chemokines MIP-1α, MIP-2, MCP-1 and MCP-3 may contribute to the preferential recruitment of inflammatory cells into the skin [33]. Absence of IFN-γ promotes the development of chronic GVHD and autoimmunity [34]; IL-10 and IFN-γ may be critical mediators for the development of autologous GVHD [35]. Fibrosis in sclerodermatous GVHD may be driven by infiltrating transforming growth factor (TGF) -β1-producing donor mononuclear cells as critical effector cells, with C–C chemokines playing an important role [36]. Apoptotic keratinocytes arise in the skin of bone marrow transplant patients due to both GVHD and the effects of conditioning regimes; keratinocyte damage in GVHD is mediated by both cytotoxic T-cell-dependent and -independent mechanisms [37].

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Clinical manifestations [1–3]

GVHD that develops between 1 week and 3 months after transplantation is termed acute, while that appearing after 3 months is termed chronic. The severity of the reaction, clinically and histologically, varies from mild to severe and provides a basis for a grading of 1–4. Grades 2–4 carry a mortality exceeding 75%. Early diagnosis of GVHD can be difficult, as drug reactions, viral infections and cutaneous reactions to radiation therapy may have clinical and histological similarities [1]. Survival of patients receiving marrow/stem cells from one antigen mismatched related donor is inferior to that of controls with HLA-identical related donors [4]. Risk factors for acute cutaneous GVHD in one recent series were a diagnosis of chronic myeloid leukaemia, HLA disparity, receipt of more than one stem cell transplant, conditioning regimens that include total body irradiation, and GVHD prophylaxis regimens other than ciclosporin plus methotrexate [5]. GVHD has been reportedly triggered by use of contrast media [6], and followed use of roquinomex [7].

Acute GVHD

The earliest cutaneous features are accompanied by a fever and include a malar flush, erythema of the palms or soles, and a generalized erythematous morbilliform rash.

Occasionally erythematous to violaceous follicular papules [8], a pustular acral erythema [9], or an ichthyosiform rash [10] occur. The rash can be more severe with scarlatiniform features. Rarely, serious toxic epidermal necrolysis [11] or a severe exfoliative erythroderma may occur.

Watery diarrhoea may develop within days to weeks after the cutaneous lesions, its severity often paralleling that of the skin involvement; it may become bloody and protracted. Liver involvement is expressed clinically by jaundice and hepatomegaly with tenderness. Monitoring of total bilirubin, stool output, extent of rash and overall clinical stage of GVHD is important during the first 40 days after bone marrow transplant in formulating the prognosis of early acute GVHD in allogeneic bone marrow transplant patients receiving ciclosporin [12].

The differential diagnosis of acute GVHD includes drug reactions, e.g. to ciclosporin, use of recombinant human cytokines [13], the eruption of lymphocyte recovery (ELR) [14,15] and opportunistic infections. The ELR presents as an erythematous maculopapular rash usually between 14 and 21 days, and coincides with the earliest return of lymphocytes to the peripheral circulation after marrow ablation. The histological findings in ELR are non-specific, but the diagnosis can be suspected from the association of an increased peripheral lymphocyte count with the development of a transient erythematous maculopapular rash. Eruption of lymphocyte recovery occurs in more than 50% of cases undergoing intensive marrow-aplasia-inducing chemotherapy [14]. Dyskeratosis congenita in children may simulate GVHD [16]. The differences can usually only be established by histology and cultures.

Histology [17]. Characteristic histopathological features are present in all patients with acute GVHD. The epidermis shows focal vacuolar alteration of the basal layer with a few lymphoid cells at the dermal–epidermal interface. 'Satellite' lymphocytes often abut ovoid eosinophilic bodies called 'mummified' cells, so-called satellite cell necrosis [18]. However, the presence of dyskeratotic keratinocytes and satellite cell necrosis is not specific for GVHD [19]. Coagulative necrosis and acantholysis in the lower layers of the epidermis and pilosebaceous units may also be present. It has recently been shown that apoptosis contributes to the keratinocyte destruction in GVHD [20]. The numbers of dermal and epidermal mononuclear inflammatory cells correlate positively with the probability of developing more severe acute GVHD [21]. Immunoglobulin M deposits may occur at the DEJ [22].

Chronic GVHD

Chronic GVHD presents between 3 and 14 months post-haematopoietic stem cell transplant in approximately 20% of matched sibling transplants and 40% of matched unrelated donor recipients. Involvement of the skin, liver, eyes, mouth, upper respiratory tract, oesophagus, lower gastrointestinal tract and skeletal muscles is common. Patients may develop chronic GVHD *de novo* in about 15% of cases, or as a gradual progression from continuously active acute GVHD, or following resolution of acute GVHD.

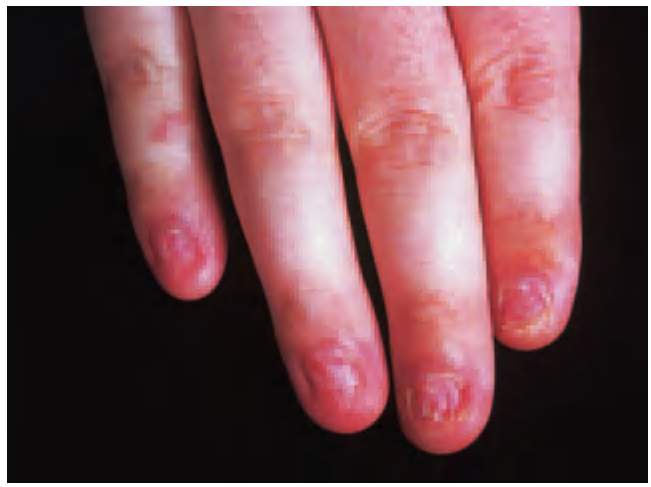

Fig. 42.36 Lichenoid graft-versus-host disease showing marked nail involvement. (Courtesy of Dr C.T.C. Kennedy, Bristol Royal Infirmary, Bristol, UK.)

The initial eruption is usually lichenoid, and may involve the oral cavity [23,24] with mucoceles [25], skin, and nails [26] (Fig. 42.36), sometimes causing a scarring alopecia. Hyper- or hypopigmentation are often prominent features and total leukoderma has been described [27]. The cutaneous changes can be generalized or localized. The localized forms can be linear or whorled; in the latter, the lesions occur in the lines of Blashko [28,29]. It is not clear whether this linear distribution is due to viral infection or cellular mosaicism [30]. Dermatomal chronic GVHD at the site of previous herpes zoster has been described [31]. The development of chronic GVHD solely in an area of piebaldism suggests that piebaldism-affected skin is immunologically different from normal skin [32].

Chronic GVHD may resemble Sjögren's syndrome, lupus erythematosus, dermatomyositis or polymyositis [33,34]. A severe cicatrizing conjunctivitis mimicking cicatricial pemphigoid has been documented [35]. A GVHD-like condition can occur after fluorouracil administration for metastatic carcinoma [36], and has been described in a patient with Hodgkin's disease associated with serological features of paraneoplastic pemphigus and systemic lupus erythematosus [37]. Crusted scabies may cause a confusing clinical picture if it complicates chronic GVHD [38].

The late phase of chronic generalized GVHD may result in a disabling type of sclerodermatous skin reaction, which develops after about a year. There is severe poikiloderma with widespread cutaneous sclerosis, contractions, malabsorption, wasting, alopecia and areas of ulceration

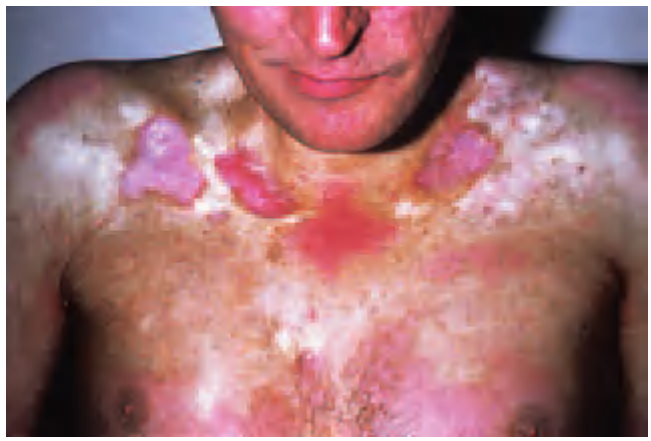

Fig. 42.37 Chronic graft-versus-host disease. Seven years post-transplant, showing widespread sclerosis and focal areas of ulceration. (Courtesy of Dr C.T.C. Kennedy, Bristol Royal Infirmary, Bristol, UK.)

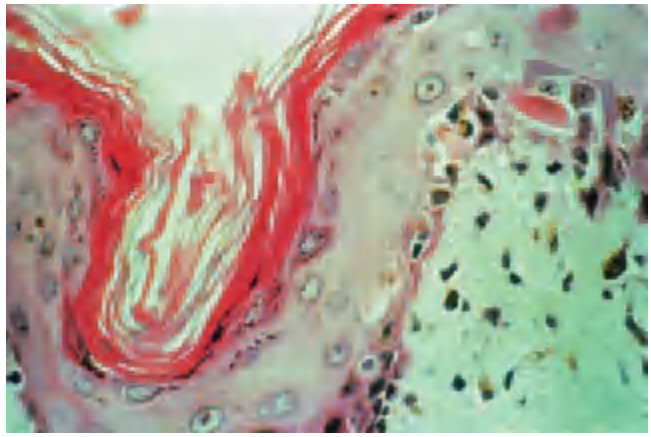

Fig. 42.38 Graft-versus-host disease. Histology showing cytoid bodies and liquefaction degeneration of the basal layer. Note the virtual absence of inflammatory infiltrate. H&E, × 100. (Courtesy of Dr P.H. McKee, UMDS, Guy's and St Thomas' Hospitals, London, UK.)

[39] (Fig. 42.37). Bullous changes [40], changes of lichen sclerosus et atrophicus [41] and dermal mucinosis [42] are recorded.

Chronic cutaneous GVHD is associated with a decreased number of melanocytic naevi [43]. Squamous cell carcinoma development in an indolent ulcer in chronic GVHD has been reported [44]. Other systemic complications include progressive hepatic fibrosis, autoimmune haemolytic anaemia, lung fibrosis and obstructive bronchiolitis [1]. The mortality of chronic GVHD is about 10%.

Histology [45]**.** In the earlier phase of chronic GVHD, the epidermis is acanthotic with hyperkeratosis. The changes at the dermal–epidermal interface closely resemble LP, although the infiltrate is not as dense and may contain eosinophilis (Fig. 42.38). Involvement of pilar units, vessels, nerves and sweat glands is not uncommon. In the final stages of the disease, the epidermis becomes atrophic and gross fibrosis involves the dermis, skin appendages, or even the subcutis.

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Treatment of GVHD

The future success of bone marrow transplantation depends on the extent to which GVHD can be prevented or modified, as treatment of established GVHD is difficult. Prophylactic regimes [1–4] include use of ciclosporin or tacrolimus [5] with methotrexate, and lymphocyte depletion of donor infusions using alemtuzumab (CAMPATH-1H), a humanized monoclonal antibody directed against lymphocyte CD52 antigen [6]. A new approach in the prevention of acute GVHD involves use of genetically manipulated donor T cells expressing the herpes simplex virus thymidine kinase (HSV-tk) suicide gene [3,7,8]; acute GVHD may be effectively controlled by ganciclovir-induced elimination of the transduced cells. Extensive vitiligo has, however, followed ganciclovir treatment [9]. Systemic steroids remain the standard regime for the treatment of acute GVHD. When this approach fails, patients with GVHD require secondary therapy [1–3,10–13] such as mycophenolate mofetil [14,15], sirolimus (rapamycin) or humanized or chimeric monoclonal antibodies directed against cytokines or their receptors. The latter include infliximab (anti-TNF-α); anti-IFN-γ; antibodies directed against activated T cells, including basiliximab and daclizumab (IL-2 receptor antagonists), visilizumab and ABX-CBL; antibodies to adhesion molecules (such as LFA-1) or targeting distal effector mechanisms (such as Fas ligand); and tolerance-induction agents such as cytotoxic T-lymphocyte antigen (CTLA)-4 Ig and anti-CD40 ligand. Pentostatin may also be useful [16]. Intravenous immunoglobulin is of uncertain benefit in the prevention of GVHD [17,18]. IL-18 has the capacity to modulate acute GVHD when administered either to the donor or the recipient [19].

Initial treatment of chronic GVHD has tended to be ciclosporin and prednisolone [20]. For refractory cases, combined mycophenolate mofetil and tacrolimus, both systemically and topically [21], etretinate [22] and hydroxychloroquine [23] may be helpful. Thalidomide has been used successfully as an adjunct in the therapy of chronic, but not acute, GVHD [24–26], but use of this drug in GVHD has been followed by severe cutaneous ulceration [27]. Low-dosage UVB therapy, both broad-band [28,29] and narrow-band [30], can be successful as an adjunctive therapy in chronic oral and cutaneous GVHD, and UVA-1 phototherapy [31,32] has been advocated for sclerodermatous chronic GVHD. Photochemotherapy (PUVA and bath PUVA) may similarly clear skin lesions in chronic GVHD [33–36]. Extracorporeal photochemotherapy involves the reinfusion of a patient's own white cells following exposure to 8-methoxypsoralen and UVA *ex vivo*, and is a safe and effective adjunctive therapy for both acute and extensive chronic cutaneous GVHD resistant to conventional therapy [37–39]. Addition of an overnight incubation period may further improve results [40]. The effects on systemic involvement are more variable.

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Chapter 43

Disorders of the Sebaceous Glands

N.B. Simpson & W.J. Cunliffe

Structure and distribution

The sebaceous gland [1] is holocrine; its secretion is formed by the complete disintegration of the glandular cells. The cells are replaced by cell division at the periphery of the lobes or acini of the glands, with the consequence that differentiating cells are displaced towards the centres of each acinus. The average transit time of the cells, from formation to discharge, has been given as 7–25 days in the human gland [2], a figure similar to that estimated for the rat [3,4]. However, the dynamics of the human gland are complicated. The gland consists of a series of lobes, each with a duct lined by a keratinizing squamous epithelium. The lobule ducts converge towards the main sebaceous duct, which normally opens into the pilary canal, whose epithelium is continuous with the surface epidermis. Within any one glandular unit, the acini vary in differentiation and maturity: some are completely undifferentiated, showing little or no lipid accumulation in any of their cells, and some are full of lipid-laden cells that extend to the outer periphery of the acinus [5]. New acini can apparently arise from the walls of the ducts, grow into sebaceous units and fuse with adjacent ones. Three proliferative regions were recognized by Plewig *et al*. [6,7] using ^{3}H-thymidine autoradiography. The duct displayed fast cellular migration with a renewal time of 2–4 days. An undifferentiated cell pool, with a renewal time of 4–7 days, could be distinguished from the differentiating lipid-producing cells in the glandular fundus, with a replacement time of more than 14 and probably 21–25 days [8]. The synthesis and discharge of the lipid contained in the sebaceous cells require more than a week [9].

Sebaceous glands occur over much of the body, although not normally on the palms or soles, and only sparsely on the dorsal surfaces of the hand and foot. Sebaceous glands are largest and most numerous on the face, scalp, upper trunk, in the external auditory meatus and on the anogenital surfaces. On the scalp, forehead, cheeks and chin, for example, there are between 400 and 900 glands/cm^2; elsewhere there are fewer than 100 glands/cm^2 [10–12].

In a number of sites, sebaceous glands open directly to the surface of the skin, and not by way of a hair follicle.

Examples of such glands are the Meibomian glands of the eyelids and the Tyson's glands of the prepuce [13]. Free sebaceous glands are also found on the mucocutaneous surfaces of the female genitalia, the areolae of the nipples, and ectopic sites such as the tongue and the cervix uteri [14]. Free sebaceous glands in the margin of the upper lip are often visible to the naked eye as pale-yellow bodies, which vary in size from minute specks to about 1.5 mm in diameter; they are known as Fordyce's spots [15].

Many mammals have specialized aggregations of sebaceous units that function as scent glands [16–19]. Some such glands also include tubular 'apocrine' units (Chapter 45). Of special interest as possible models for the study of compounds that affect sebaceous activity [20] are the costovertebral organs of the golden hamster [13,20–23], the supracaudal gland of the guinea pig [24,25], the abdominal gland of the gerbil [26] and the preputial glands of many species of rodents [27].

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Development

The development of the sebaceous glands is closely related to the differentiation of hair follicles and epidermis [1,2]. In about the third week of fetal life, the epidermis consists of a single layer of undifferentiated cells, but by the fourth week an outer periderm and a basal stratum germinativum can be distinguished. Between the 10th and 12th weeks, a stratum intermedium becomes apparent, and at about the same time developing hair germs are quite distinct (Chapter 3). In the following weeks, the follicles extend downwards into the dermis and the rudiments of the sebaceous glands appear on the posterior surfaces of the hair pegs; by 13–15 weeks, the glands are clearly distinguishable.

The cells at first contain glycogen. This lingers at the periphery of the gland, but is quickly lost at the centre, where large lipid drops are visible at 17 weeks [3–5]. At the point of their origin from the follicle, centrally positioned cells degenerate to form a lumen, and surrounding cells keratinize to form the sebaceous duct [6]. The glands become multi-acinar by the formation of buds on the peripheral wall.

Sebaceous glands are functional from their formation; sebum is the first demonstrable glandular product of the human body. Their development and function before birth and in the neonatal period appear to be regulated by maternal androgens and by endogenous steroid synthesis by the fetus [7]. Hydroxysteroid dehydrogenases and 5α-reductase, which reduces testosterone to 5′α-dihydrotestosterone (5′α-DHT), are present after 16 weeks [8,9]. The glands reach a peak of activity in the third trimester, and their secretion forms part of the vernix caseosa. The vernix lipids resemble sebum in their content of fatty acids, squalene and wax esters, but also contain

sterols and sterol esters [10]. Sebaceous glands remain active in the neonatal period, but then involute and remain quiescent until puberty [11].

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Ultrastructure, histochemistry and immunocytochemistry of the sebaceous gland and duct

Undifferentiated sebaceous cells at the periphery of the gland are rich in ribonucleoproteins and stain with basic dyes [1]. As the cells move towards the centre of each lobe they contain more lipid and become progressively acidophilic. All the cells have numerous mitochondria, usually appearing as short or wavy rods. The undifferentiated cells contain coarse, osmium-staining particles around the nucleus; as differentiation proceeds, these particles increase in number and size and develop lipid droplets in their centres, which gradually enlarge. This complex corresponds to the Golgi body: at completion of sebaceous synthesis it is no longer recognizable.

In studies with the electron microscope [2–4], the undifferentiated cells at the periphery of the gland can be seen to rest upon a basement membrane, and to be connected with each other by desmosomes. The membranes of the granular endoplasmic reticulum are coated with ribosomes, and there are in addition particles of ribonucleoprotein and glycogen scattered free in the cytoplasm. At this stage, the Golgi zones are usually inconspicuous; the nucleus is relatively very large. Differentiation of the cell becomes evident with the appearance of one or more small sebum vacuoles within it. During the active phase of lipid synthesis, the cytoplasm becomes packed with smooth-surfaced membranes of the endoplasmic reticulum. In some partially differentiated cells, a large Golgi zone becomes apparent; typically, it consists of parallel, smooth-surfaced, thick membranes, slightly dilated cisterns and small vesicles. The Golgi appears to be the centre where lipid aggregates to form sebum vacuoles. At an early stage of sebaceous transformation, one of the cisterns in the Golgi zone becomes more dilated than the others, and forms the centre of the developing sebum vacuole. At a later stage, the smooth membranes of Golgi apparatus and the endoplasmic reticulum become orientated around the edge of the developing vacuole, forming a sort of 'husk'. The fully differentiated cells contain very large sebum vacuoles, which compare in size with the nucleus; the cell may have a complement of more than 60 (Fig. 43.1). In the final stages of differentiation, the mitochondria become widely separated, indicating that their numbers have decreased, and the nucleus becomes irregularly shaped, with clumping of the nucleochromatin and dispersal of the nucleolar material. Lysosomes are prominent in peripheral and other cells in the early stages of differentiation, but are found at all stages [2]. They may be concerned with hydrolysing precursors of sebaceous lipids or the breakdown of mature cells.

The sebaceous cells of prepubertal and hypogonadal males are qualitatively similar to those of normal adults, even though the glands are smaller [1].

Immunocytochemical techniques, supported in some instances by investigating messenger RNA (mRNA) expression of the peptide, performed both on human skin biopsies and on immortalized sebocytes, have also helped in our understanding of the hormonal and cytokine control of the sebaceous gland and duct in health and disease [3].

Androgen receptors are present both in the gland and the duct [4]. Peroxisome proliferator-activated receptors (PPARs) are a subfamily of former so-called orphan receptors within the non-steroid receptor family of nuclear hormonal receptors. There are three subtypes (PPAR-α, γ and δ) all of which are expressed by sebocytes, with PPAR-γ 1 gene expression being much greater than in the epidermis; this subtype is also expressed in the ductal cells of normal skin and of comedones. In the sebaceous gland these receptors are located in basal and early differentiated sebaceous gland cells [5] and are likely to be important for sebocyte formation of the intracellular fused lipid droplets that constitute the holocrine secretion of differentiated cells. They may also inhibit skin inflammation by diverse mechanisms not necessarily related to lipid metabolism [6].

Sebocytes are target cells for several neurohormones. Immunocytochemical studies have shown that human sebocytes express melanocortin (MC)-1 receptors and are target cells for α-melanocyte-stimulating hormone (α-MSH) [7].

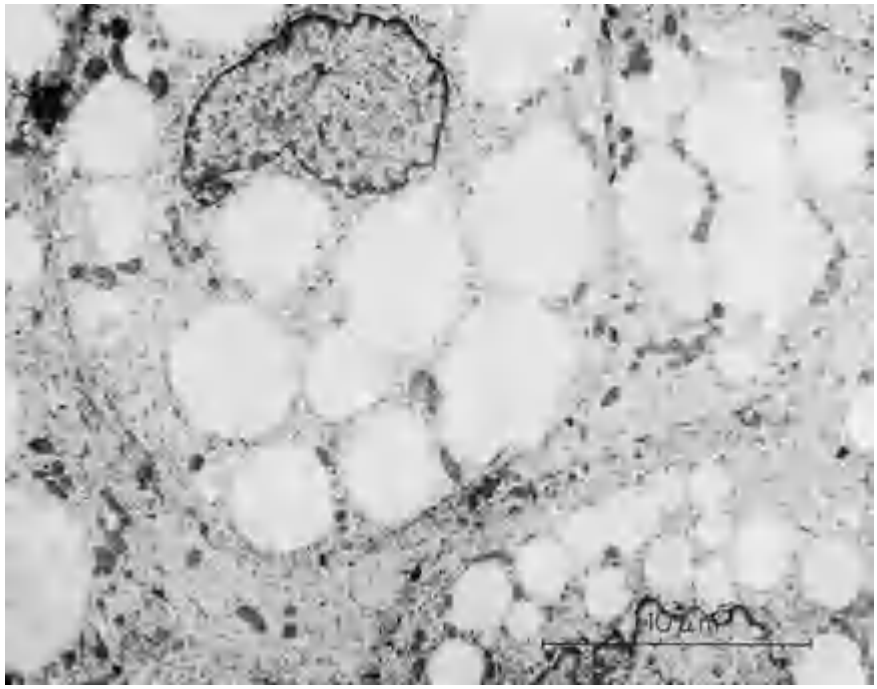

Fig. 43.1 Transverse section of the sebaceous gland of a 24-week fetus. The cytoplasm of the cells is honeycombed with spaces occupied by lipid droplets, which have been leached away during processing. (Courtesy of Professor A.S. Breathnach, St John's Institute of Dermatology, London, UK.)

The sebaceous gland constitutively expresses other cytokines without any influence of external factors. Interleukin-1 (IL-1) is present in the normal human sebaceous gland [8] and mRNA for IL-1-α, IL-1-β and tumour necrosis factor-α (TNF-α) are also present in the sebaceous glands. Cultured human sebocytes also express IL-1-α at the mRNA and protein levels. The presence of such cytokines may relate to the development of inflammation [9].

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Composition and biosynthesis of sebum

Sebum is a complex mixture of lipids, which varies widely from species to species [1–3]. The analysis of human sebum is complicated by several factors. The principal difficulty is that the surface film contains not only sebum, but also lipid from the keratinizing epidermis and possibly from eccrine glands. In addition, the pure sebaceous secretion undergoes degradation as it passes through the ducts, or on the skin surface as a result of bacterial lipase activity [4]. Some material, for example, hydrocarbons, may also be acquired from environmental sources.

Surface lipid can be collected by simple non-invasive tests, such as wiping the skin with a sponge soaked in an organic solvent such as hexane or ether [5]. However, skin biopsies are necessary to investigate sebum synthesis and the analysis of pure sebum. Incubation of isolated human sebaceous glands showed that acetate and glucose appeared to be equally efficient as substrates for triglycerides but not for squalene [6].

An unusual feature of sebaceous lipogenesis is a partial or complete inhibition of cholesterol biosynthesis at some point in the pathway. Thus, in human and in some other animal glands, there is little or no conversion of squalene to cholesterol, and squalene remains a major product.

In vivo studies suggest that the synthesis of some sebaceous lipids is indirect, with newly synthesized fatty acids becoming first incorporated into phospholipids and later recycled into non-polar lipids. In human scalp, the label of intradermally injected ^{14}C acetate is immediately taken up

Table 43.1 Comparison between constituents of sebum and epidermal lipid.

Constituents	Sebum (%)	Epidermal lipid (%)
Glycerides (plus free fatty acids)	57.5	65
Wax esters	26.0	—
Squalene	12.0	—
Cholesterol esters	3.0	15
Cholesterol	1.5	20

by squalene, wax esters and triglycerides, but as the cells mature the proportion in wax esters increases [7].

Human skin surface lipid consists of glycerides, free fatty acids, wax esters, squalene, cholesterol esters and cholesterol. Lipid production varies according to site, for example 5–10 μg/cm^2 were recovered from the trunk and limbs of subjects who washed 3 h prior to extraction, compared with 150–300 μg/cm^2 from the forehead [8]. When amounts were in the range 5–10 μg/cm^2, the skin surface lipid contained virtually no wax esters or squalene. However, as the quantity of surface lipid increased, so did the proportion of wax esters and squalene, while at the same time the proportions of cholesterol esters decreased. The proportion of each of the constituents became nearly constant when the amount of lipid reached 50–100 μg/cm^2.

These results are consistent with the view that wax esters and squalene are produced by the sebaceous glands only, and not by the epidermis. When the surface lipid is as low as 4–10 μg/cm^2 no sebum is present, and this level of lipid represents that contributed by the epidermis. However, when the surface lipid is greater than 100 μg/cm^2, its composition approximates to that of sebum. The percentage proportions of constituents are shown in Table 43.1. It may be concluded from these figures that the sebaceous glands do not, to any great extent, convert squalene to sterols, whereas in the epidermis squalene synthesized in the lower layers is rapidly and totally converted to sterols, either to precursors of vitamin D or to cholesterol. Squalene is unique to sebum and is virtually unique to humans [2].

Between birth and sexual maturity, surface lipid undergoes two distinct changes [9,10]. Shortly after birth it resembles adult sebum, presumably because maternal hormones have activated the sebaceous glands. Thereafter and up to 8 years of age, the wax esters and squalene remain low, and epidermal lipids, i.e. cholesterol and its esters, are high. In this age range, sebum constitutes less than half the total surface lipid of the forehead, compared with 95% or more in the adult. Between 8 and 10 years of age, the wax esters and squalene rise to about two-thirds of the adult level, and between 10 and 15 years the composition comes to resemble that of the adult.

Free fatty acids constitute 10–30% of the human skin surface fat [11–13], but occur in only small amounts in the skin lipids of most other animals. This difference is presumably due to the rather unique bacterial flora of humans, in particular *Propionibacterium acnes*, and its lipase action on sebaceous triglycerides. Analysis of pure sebum from isolated human sebaceous glands showed the presence of triglycerides, but not free fatty acids, monoglycerides or diglycerides [14,15]. It thus seems that, prior to secretion, all the fatty acids are combined as triglycerides, which are subsequently subjected to lipolytic activity by enzymes present in the sebaceous ducts and on the skin surface. This conclusion is reinforced by the demonstration that the skin surface can hydrolyse triglycerides of exogenous origin; when ^{14}C-labelled tripalmitin was spread on the back, labelled free fatty acids were isolated from the surface fat 3 h later [7].

The fatty acid components [1–3,16] have both odd- and even-numbered carbon chains up to C25 in length, although more than half are C16 and C18 compounds. They are both saturated and unsaturated, and of particular interest is the presence in both classes of unusual branched chains. These are of two kinds, one having an even number of carbons with the methyl group attached to the penultimate (iso series), the other having an odd number of carbons with the methyl group attached to the antepenultimate (antiso series). Such branches are present in the chains of the wax esters, which are virtually limited to 18 carbons and produced only by the sebaceous glands and, in higher proportion, in the longer chains of the sterol esters, which probably arise from both sebaceous glands and epidermis.

It is possible to modulate sebum composition as a result of dietary, hormonal or drug manipulation. Although various effects have been ascribed to diet, there is no evidence from either humans or experimental animals that any components of sebum are directly derived from ingested fats. In humans, most of the unsaturated fatty acids in the surface film are Δ6 compounds, whereas dietary lipids are Δ9 compounds [3]. Prolonged starvation of human subjects [17,18] decreased the rate of sebum synthesis by about 40%, without any decrease in the actual amount of squalene, which thus rose as a proportion of the total surface lipid.

Administered hormones can also influence the composition of the skin surface fat. In rats, testosterone, at the same time as increasing the amount of sebaceous secretion (see below), increases the ratio of palmitate to stearate and the ratio of oleate to stearate; oestrogens and antiandrogens antagonize these effects [19–21]. In female patients prescribed co-cyprindiol (35 μg ethinyl estradiol and 2 mg cyproterone acetate [CPA]) there is a significant increase in sebaceous linoleate, which might explain in part the anticomedogenic effect of the therapy [22]. A

reduced sebaceous linoleate may induce comedogenesis. Oral isotretinoin not only significantly reduces sebum production, but produces a tremendous change in lipid composition. There is a great reduction in sebaceous-related lipids (i.e. squalene, wax esters and fatty acids) [23].

For comprehensive discussions of lipid biosynthesis in the sebaceous glands, the reader is referred to detailed references [3,24].

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Functions of sebum

Several functions have been ascribed to sebum, but they are by no means undisputed. In humans, it has been stated that the lipid film both controls moisture loss [1] from the epidermis and protects the skin from fungal and bacterial infection. The colonization of the skin by *P. acnes* may have an immunomodulatory role. Aggregations of holocrine glands play an important part in scent production in many mammals, and components of sebum may possibly contribute to body odour [2].

It was believed that the sebaceous lipids were essential factors for the barrier function of the skin. This is clearly not so. A healthy prepubertal child who produces no sebum has no impaired barrier function. Certain surface free fatty acids markedly reduce the growth of pathogenic organisms, such as *Staphylococcus aureus*, *in vitro* [3], and suppression of sebaceous gland activity by isotretinoin maybe followed by impetigo towards the end of a 4-month course [3]. Circumstantial evidence supports the view that sebum, or at least the product of its hydrolysis, is fungistatic. Fungi causing tinea pedis preferentially colonize areas that are not supplied with sebaceous glands: ringworm of the scalp becomes rare after puberty, when sebum production increases.

Propionibacterium acnes is unique to humans and this fact may equate with the rather unique composition of human sebum.

Shuster [4] made the interesting suggestion that the capacity to develop delayed immune hypersensitivity may be augmented and maintained by the *P. acnes*, which colonizes sebaceous glands in adults. A sequel of this may be an enhanced immunoregulatory effect, producing some protection against cancers such as leukaemia and melanoma, which occur with less frequency in acne patients [5].

The sebaceous gland has also been shown to secrete vitamin E into the upper layers of facial skin. This mechanism may in part serve to protect skin surface lipid and the upper stratum corneum from harmful oxidation [6].

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Measurement of sebaceous activity and sebum production

Various methods have been used for collecting lipids from human skin, and for measuring their production [1]. They include swabbing by pads soaked in solvent [2], washing lipid solvents over areas of skin circumscribed by rings, caps or apertures of bottles [3–6] and absorption on paper [7,8]. Another method is removal by pressing a ground-glass plate on the skin followed by photometric assessment [9–14]—for both stages an instrument known as a Lipometer®/sebometer has been devised [15]. The rate of sebum production has been calculated from the squalene content of skin biopsies [16]. Analysis of the ratio of wax esters/(cholesterol plus cholesterol esters) may provide an indirect measure of lipid synthesis per sebaceous cell [17–19].

A simple, practical, but time consuming, method for measuring human sebaceous secretion is to place a pad of specially absorbent cigarette papers for 3 h on a delimited area of the forehead, and then to extract the sebum with diethyl ether. In view of circadian changes in secretion [20], the measurement should be carried out between standard times. It does not give the absolute sebum production rate, which is indefinitely sustainable [21], but it is valuable for comparative purposes, and provides more reproducible results than many other methods. The method that follows was originally devised by Strauss and Pochi [7,8,14].

1 Two areas on either side of the forehead (2.0 × 3.5 cm) are delineated by pre-cut Micropore® tape.

2 A pad of four or five cigarette papers is placed carefully, to avoid creasing, over the forehead and held in place by a gauze pad and a stocking-weave bandage encircling the head (Fig. 43.2).

3 In order to remove the accumulated surface lipids, two or three pads are so applied for 10–15 min and then discarded. After 30–40 min, close examination of the final paper in contact with the forehead will reveal a follicular pattern of sebum emerging from the follicles.

4 A pad of papers of known weight (previously prepared by washing in ether and being allowed to dry) is then applied. At the end of a 3-h collection period, the lipid-containing papers are then reweighed [22].

Control papers must be used to control for variation in environmental factors (such as humidity), which may influence the weight of the papers. Precision in weighing techniques is essential. The weight of sebum multiplied by the time of collection and divided by the area of collection provides a figure, which is referred to as the sebum excretion rate (SER).

The sustainable rate of sebum production on the forehead can be measured by first depleting the follicular reservoir by an application of an aqueous gel of bentonite clay, into which a rectangle of non-woven polyester cloth is pressed. The cloth is removed after 14 h, and the sebum is then collected for 3 h on two discs of clay, each 2 cm in diameter. The lipid is extracted and quantified by thin-layer chromatography [23–25] or by weighing [26]. The method also makes possible an estimation of the extent of the follicular reservoir [26]. According to Saint-Leger and Cohen [27], the forehead can be defatted with 70% ethanol and the rate of sebum excretion is then linear.

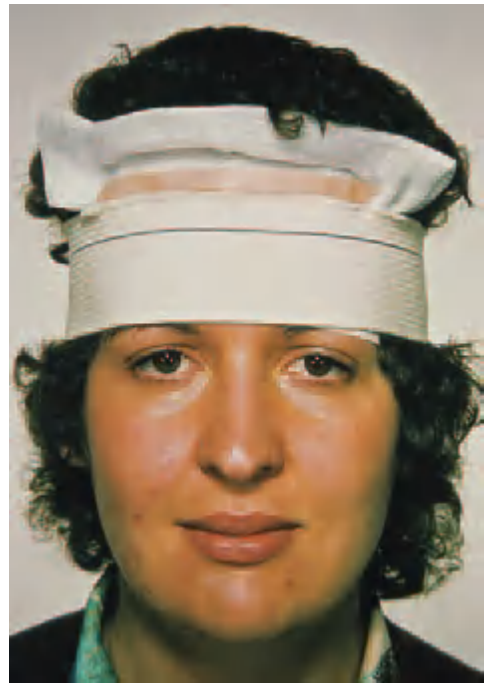

Fig. 43.2 Patient with a firm but comfortable headband which is holding in place the special absorbent papers for measurement of sebum production.

The introduction of a sebum-absorbent tape (Sebutape®) has made it possible to observe the lipid output of individual follicles [28,29]. Computerized image analysis has been used for quantification [30–32].

Several authors have described methods for the isolation, from skin biopsies, of whole human glands [33,34] or sebaceous cells [35], and their cultivation *in vitro* for study of their activity. These techniques reflect reasonably well the *in vitro* situation. In particular, the sebocyte culture system has provided much information on the hormonal and cytokine control of the sebaceous gland [36]. Sebum production in the rat has been measured by total immersion of animals in lipid solvents [37], by changes in hair fat lipid [38,39], or by absorption of lipid on paper from areas denuded of hair [40]. To study responses to hormones, the size of the sebaceous glands has also been estimated from histological sections using planimetry [41]. Mitotic activity, estimated after injecting the rats with colchicine, which arrests mitoses in the metaphase, has also been used as a measure of glandular activity [41]. Other experimental models, such as the preputial glands of rodents

[42], which can be dissected out and weighed, or the visible costovertebral glands of the hamster [43,44], to which hormones can be topically applied, have been reviewed by Ebling [1].

When interpreting the results of animal experiments it is important to realize that the reactions of supposed homologues of the sebaceous glands may vary not only from species to species but also within species. Thus, the responses to hormones of the preputial and sebaceous glands of the rat may not be identical. Moreover, because of the miscellaneous parameters involved, it is also important to understand the relationships between the different facets of sebaceous activity. The rate of secretion of sebum depends on two factors: the synthetic capacity of each sebaceous cell and the rate of production of the cells. The size of the glands depends partly on both these things, but also of critical importance is the time taken for each cell to mature and pass through the gland, i.e. the turnover time or cell life. If, for example, the rate of production of cells were doubled, with a consequent increase in sebum production, no alteration in gland size need occur if at the same time cell life were halved. As a general principle, it seems to be true that, the greater the mitotic rate, the lower the turnover time [45]; but in practice the changes do not keep pace with each other, and glands under stimulation do increase in size as well as in rate of secretion.

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Endocrine control of sebaceous gland activity [1]

The link between sebaceous gland activity and puberty has been recognized for many years [1]. Much pioneering work was performed on the rat, which has a simple unilobular sebaceous gland, and on the Syrian hamster, whose flank organ is a good model for the human sebaceous gland. The development of techniques to grow human sebocytes and ductal cells in culture [2–4] has confirmed and built on previous observations of human physiological and pathological states. This section will concentrate on the human sebaceous gland, with reference to animal work where the evidence in humans is lacking or uncertain.

Androgens

Androgens are responsible for the development and maintenance of sebum secretion in both sexes. They are without doubt the most important hormones controlling sebaceous gland activity. The level of sebum excretion at birth is similar to that in adults [5]. There is a significant correlation between maternal and neonatal sebum excretion rate (SER) perinatally. This observation suggests an important role for the maternal hormonal environment on the infant's sebaceous glands [6]. The sebaceous glands regress to become minute during the prepubertal period, but undergo vast enlargement at puberty, when the sebum output of males increases more than fivefold [7]. Sebum production remains essentially unchanged in both sexes until around the age of 60 years, when it declines [8]; paradoxically, in old age the sebaceous glands become larger because cell turnover is decreased [9].

The most effective androgens are the 17β-hydroxy group (testosterone, 5α-dihydrotestosterone (5α-DHT) and 5α-androstene-3β-17β-diol). Sebaceous glands possess many enzymes for the interconversion of androgens, notably the relatively weak adrenal androgens dehydroepiandrosterone and androstenedione, to testosterone and DHT. The latter conversion requires the enzyme 5α-reductase, which is thought to be of pivotal importance in the development of sebaceous glands and acne [8]. There are two isoforms of this enzyme, and it is the type-2 isoenzyme that is important for most androgen action in sexual organs [10–12]. However, sebocytes [11] and epithelia [13] in the pilosebaceous unit possess the type 1 isoenzyme, and individuals who are genetically deficient in type 2 5α-reductase develop normal sebaceous glands and suffer from acne [14,15]. Androgens exert their effect in target cells via the androgen receptor, which has similar binding affinities for testosterone and DHT. The androgen receptor has been found by immunohistochemical localization in human sebaceous glands in basal and differentiating sebocytes, and in the keratinocytes of the pilosebaceous duct and hair follicle, but not in keratinocytes elsewhere [16–19]. There is evidence from cell culture experiments that androgens stimulate the growth of sebocytes and other components of the pilosebaceous unit by action on specific stromal components, and interact with retinoic acid to regulate directly sebocyte differentiation [16]. Administration of testosterone dramatically increases the size of the sebaceous glands and the sebum output of prepubertal boys (Fig. 43.3). In adult males the glands are almost but not completely maximally stimulated by endogenous androgen [20–23]. Adrenal androgens increase sebum production [23,24] but appear to require conversion to testosterone within the sebaceous gland.

Eunuchs secrete about half as much sebum as normal males, but substantially more than prepubertal boys [25].

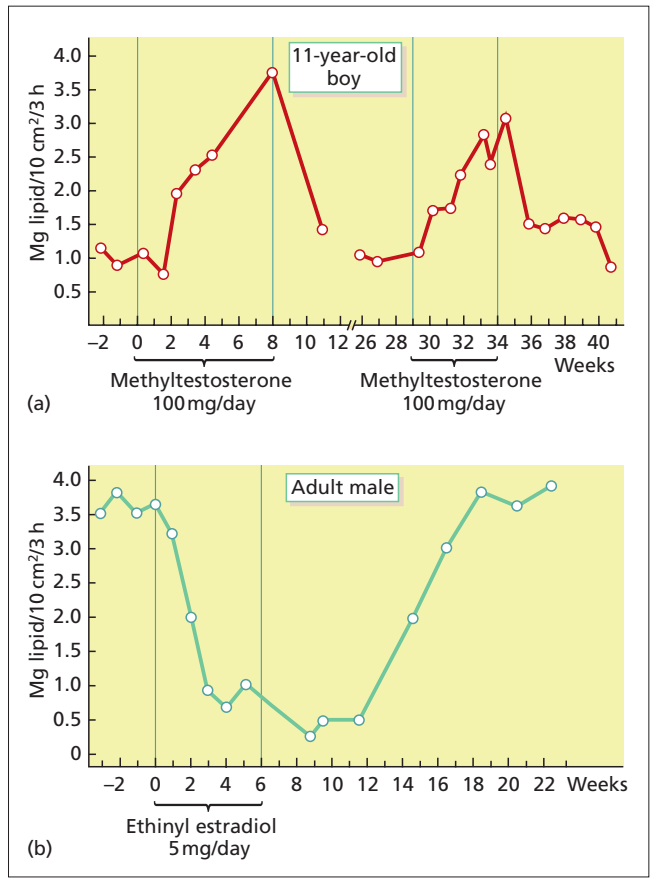

Fig. 43.3 (a) Sebum output of an 11-year-old boy given two courses of methyltestosterone orally (100 mg/day). Sebaceous secretion promptly rose with androgenic stimulation and quickly declined to the original level when the drug was stopped. (b) Suppression of sebum production in an adult male given 5 mg of ethinyl estradiol orally daily for 6 weeks. In this subject the decrease was readily detectable in 2 weeks and was nearly maximal after 3 weeks. Sebum production returned to pre-oestrogen levels approximately 11–12 weeks after discontinuation of oestrogen. (From Strauss *et al*. [23].)

Sebum production by eunuchs is quantitatively correlated with the urinary excretion of 17-hydroxycorticoids and 17-oxosteroids [26]; thus, the activity of the sebaceous glands of eunuchs appears to be dependent on adrenal androgens.

The secretion of sebum by adult women is only a little less than that of normal men. Up to the age of 50 years it is greater than in castrated men, but after that age it falls [7]. This pattern, and the fact that women do not normally produce more adrenal androgens than men, suggest that sebaceous glands are affected by extra-adrenal sources of androgen. Evidence also implicates secretion or conversion of androgens and oestrogens in the ovary and conversion in the skin [27]. However, there is only a small reduction in skin-surface lipid following bilateral oöphorectomy [25].

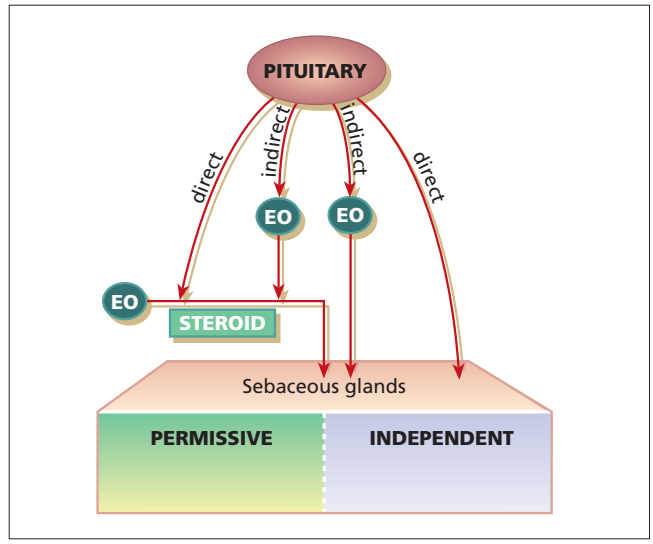

Fig. 43.4 Possible ways in which pituitary hormones may affect the sebaceous glands. The effect may be direct or indirect, and in addition may be either independent or permissive, in the sense that the pituitary hormone facilitates the response of another hormone, for example a steroid. EO, endocrine organ.

Progesterone

The effect of progesterone on sebaceous glands has been a matter of dispute. The fluctuation of sebum production in women during the menstrual cycle has been blamed on progesterone [28], but this has not been proved experimentally. Progesterone administration can produce acne [29], and when given to elderly women it increases sebum production [30], but no such effect could be demonstrated in young women [31,32]. Progesterone is a competitive inhibitor of 5α-reductase and might be expected to reduce sebaceous gland activity; in humans its sebosuppressive effect is minimal [33–35]. Experiments in the rat showed varied responses, depending upon when progesterone was administered in relation to birth, puberty, castration and oöphorectomy [35–39].

Adrenocortical hormones

Adrenal androgens have been discussed above. Sebum production fell after adrenalectomy for Cushing's syndrome [24]. Adrenocorticotrophic hormone (ACTH) causes hypertrophy of sebaceous glands in prepubertal human males and postpubertal human females [40], and increases the size of sebaceous glands [37,41] and sebum production [42] in hypophysectomized and gonadectomized rats.

There is little information on the effect of glucocorticoids on sebaceous gland activity. Hydrocortisone given to a prepubertal boy caused enlargement of sebaceous glands [40]. Sebum production is decreased in adrenal insufficiency, but replacement of glucocorticoids has no effect [24, 43].

Pituitary hormones

The pituitary has a major effect on sebaceous gland activity (Fig. 43.4). The mechanisms are different in the human and rat particularly in respect of pro-opiomelanocortin peptides, which seem to dominate in the rat but probably have little effect in humans. The pituitary acts indirectly through its various target glands, and as a result of a direct action by some of its hormones on sebaceous glands. Gonadotrophins stimulate sebum secretion in the human male [44], but probably do not have any direct independent action on the sebaceous gland.

ACTH has an effect through adrenal androgens (see above). Patients with hypopituitarism and those with isolated growth hormone deficiency have low levels of sebum [45], while patients with acromegaly show increased sebum secretion [46,47]. Growth hormone levels can be raised in prepubertal boys by supplemental testosterone administration, through increased growth hormone-releasing hormone secretion [48].

The effect of growth hormone may be mediated by insulin-like growth factors such as somatomedin C [49], which has been suggested as a mediator of the induction of 5α-reductase [50].

Alpha-melanocyte-stimulating hormone (α-MSH) is an important stimulator of sebaceous gland growth and development in the rat [51,52] and has synergistic action alongside testosterone [38,52,53]. Alpha-melanocyte-stimulating hormone is a member of the pro-opiomelanocortin peptide family, which includes ACTH. However, there is no evidence for a sebotrophic role for α-MSH in the human, despite slight elevations of plasma concentrations in Cushing's disease [54]. At the local level the sebocytes expressed MC-1 receptor; the precise relevance of this is not clear [55].

There remains some circumstantial evidence for a pituitary sebotropic hormone in humans. The drug levodopa decreases the seborrhoea of Parkinsonism, but has no effect in normal subjects [56]. The increase in sebaceous gland activity in pregnancy [57], lactation [58] and after taking phenothiazine drugs could be due to a pituitary-derived sebotrophic factor [1].

Oestrogens

Oestrogens undoubtedly depress sebaceous activity, especially in pharmacological doses. They decrease the size of sebaceous glands when injected into rats [59–61] or when given orally to adult human males [42], and have also been shown to reduce sebum production in both animals [62–64] and humans [23,65–68]. On the grounds that it was not possible to demonstrate a local, as distinct from a systemic, effect by topical application of oestrogen ointment to the human forehead [23], it has been suggested that oestrogens may act by reducing endogenous androgen production [44]. This view that they suppress gonadotrophin secretion by the pituitary receives support from the finding that sebum-suppressing doses of oestrogen reduced the levels of testosterone in the plasma and urine of normal men [68], although not from the evidence that they suppressed sebum secretion in eunuchs [26].

Evidence from animal experiments favours the hypothesis that oestrogens act peripherally and directly upon the sebaceous glands [60,69–73]. However, in humans oestrogens are very likely to influence hormonal levels by some systemic action through the pituitary–gonadal axis.

Hormonal actions on sebocytes in culture

Data from sebocytes in culture have supported the *in vivo* evidence presented in the previous sections. Several groups [2,74–78] have made significant contributions. Zouboulis's group [76–78] has established an immortalized human sebaceous gland cell culture system that has been passaged over 50 times; cells have been cloned and show no signs of senescence after 4.5 years *in vitro*, whereas normal human sebocytes can only be grown for 3–6 passages. These immortalized sebocytes have large cytoplasm profiles with abundant organelles, including vacuoles and myelin figures, which indicate lipid synthesis. The cells express molecules typically associated with human sebocytes such as keratins 7, 13 and 19. Functional studies have revealed that the synthesis of the sebaceous lipids is virtually identical to that of the human sebaceous gland cells. They have also showed an increased cell proliferation after the addition of 5α-DHT and a significant inhibition in the proliferation of these immortalized cells after the addition of retinoids, in particular 13-*cis*-retinoic acid (13-*cis*-RA).

These culture systems have demonstrated that the skin is a factory of androgen metabolism [76–78]. Studies on immortalized sebocytes have demonstrated that the four major enzymes involved in the intracellular activation and deactivation of androgens are: (i) 3β-hydroxysteroid dehydrogenase Δ^{4-5} isomerase (Δ^5-3β-HSD), (ii) 17β-hydroxysteroid dehydrogenase (17β-HSD), (iii) 5α-reductase and (iv) 3α-hydroxysteroid dehydrogenase (3α-HSD). Three-beta-hydroxysteroid dehydrogenase Δ^{4-5} isomerase (isotype 1), which converts dihydroepiandrosterone to androstenedione, is almost exclusively located in the sebaceous glands. Sebaceous glands express isoforms 2 and 3 of 17β-HSD and thus are able to reversibly convert androstenedione to testosterone. Five-alpha-reductase isotype 1, which irreversibly metabolizes testosterone to 5α-DHT, is also predominantly expressed in the sebaceous glands [13]. Zouboulis's group also demonstrated that corticotrophin-releasing hormone (CRH) is a sebaceous gland autocrine hormone and is a byphasic regulator of lipogenesis in human sebocytes [79]. This evidence was obtained from sebocyte cell culture experiments and suggests that human sebocytes possess a complete CRH/CRH-receptor system. These proteins are expressed at the mRNA and protein level. Could it be, in part, that the influence of stress on acne is explained by this local hormonal pathway?

In contrast, keratinocytes have different expression and metabolic rates of some of these enzymes. For example, sebocytes are able to synthesize testosterone from adrenal precursors and to inactivate them in order to maintain androgen homeostasis, whereas keratinocytes are responsible for androgen degradation. These unique expressions of different androgen activity in different cutaneous cells suggests that there may be differentially programmed duties of skin cell populations for androgen metabolism [76–80].

In addition to androgens, other physiological and pharmacological candidates have been reported to control the development of sebocytes and to stimulate the proliferation of human sebocytes. Growth factors such as epidermal growth factor (EGF), transforming growth factor-α (TGF-α) and basic and fibroblast growth factor are paracrine and autocrine mediators of the proliferation and differentiation of a wide variety of cells [81,82]. Studies on hamster sebocytes have shown that these growth factors have mitogenic activity and act as antilipogenic factors [82].

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Retinoid control of sebaceous gland activity

Interest in retinoid metabolism within sebocytes and the sebaceous gland has been stimulated by the extreme clinical effectiveness of 13-*cis*-RA (isotretinoin) in severe acne. Other retinoid drugs including retinoic acid and all-*trans*-RA (tretinoin) have been shown to have a clinical effect in acne. Retinoids exert their effect through cell proliferation, lipid synthesis and keratin expression.

Sebocyte proliferation and lipid synthesis are suppressed when cells are cultured in the absence of vitamin A [1]. Pharmacological quantities of 13-*cis*-RA or all-*trans*-RA also suppressed sebocyte proliferation and lipid synthesis in a dose-dependant manner [2]. 13-*cis*-Retinoic acid down-regulated the expression of keratins 5, 6, 14 and 16 and up-regulated keratin 7, whereas all-*trans*-RA down-regulated keratin 5, 6 and 16 expression and up-regulated the expression of keratin 19 [2]. Recent studies have suggested that all-*trans*-RA may be the active metabolite of isotretinoin within cells following enzymic conversion from 13-*cis*-RA [3]. Evidence comes from the preferential binding of all-*trans*-RA to retinoic acid receptors (RARs) [3]. Figure 43.5 illustrates probable interconversion of retinoids within cells.

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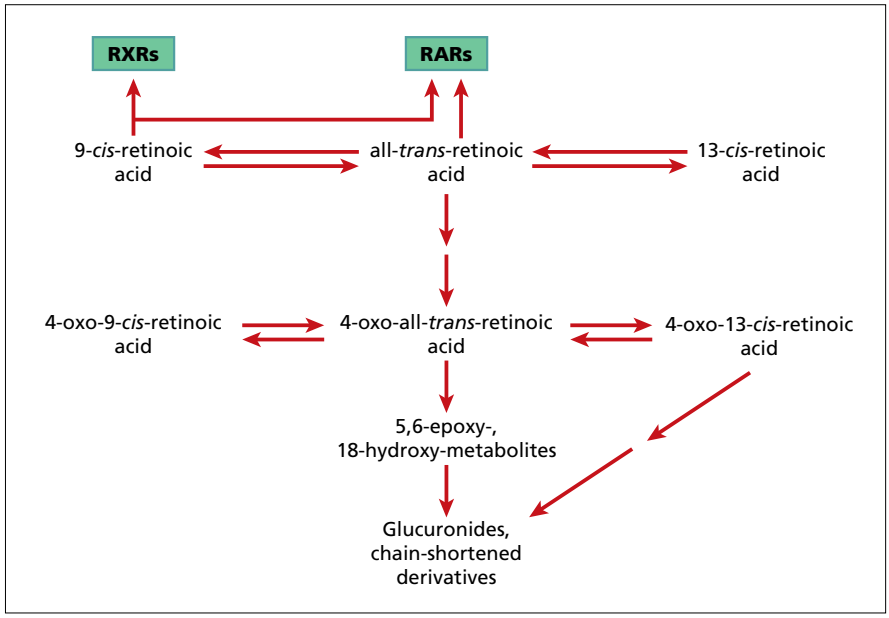

Fig. 43.5 The likely retinoid pathways of isotretinoin metabolism in the sebaceous gland. RAR, retinoic acid receptor; RXR, retinoid X receptor. (Reproduced with the kind permission of Dr U. Wiegand, Switzerland.)

2 Zouboulis CC, Korge B, Akamatsu H *et al*. Effects of 13-*cis*-retinoic acid, all-*trans*-retinoic acid, and acitretin on the proliferation, lipid synthesis and keratin expression of cultured human sebocytes *in vitro*. *J Invest Dermatol* 1991; **96**: 792–7.
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Inhibitors of sebaceous activity

Acne is associated with an increased sebum secretion and proliferative activity of sebaceous glands. Much effort has therefore gone into developing treatments for acne, which reduce sebaceous gland activity.

Possible mechanisms include reducing the circulating levels of serum androgens through an effect on the pituitary, adrenal or gonads, or by affecting the transport of androgens. Alternatively, the pharmacological/physiological suppression of androgens could be achieved through a direct effect on sebocyte metabolism. Such mechanisms include blocking enzyme activity (5α-reductase type 1, Δ^5-3β-HSD, cytochrome p450), or by blockage of androgen or retinoid receptors.

The effect of topically applied hormones shows a considerable species difference between animals and humans. Some topical therapies significantly reduce sebum excretion in animals but have no effect in the human. The most likely explanation is anatomical, because the animals under investigation have sebaceous glands that are situated very close to the epidermis; the human sebaceous gland is relatively deep in the dermis and connects to the epidermis by a long pilo-sebaceous duct, which would make it more difficult for these compounds to reach the gland itself. Clinical benefit does not occur until sebum suppression achieves a minimum of 30%.

Co-cyprindiol (Dianette® and Estelle 35®), which contains 35 μg ethinyl estradiol and 2 mg cyproterone acetate (CPA), reduces sebum excretion by 28% [1–3]. When combined with additional CPA (100 mg/day) from the fifth to the 14th days of cycle, the sebum suppression rises to 68%.

CPA appeared to be ineffective when applied topically in 50% dimethylsulfoxide (DMSO) or in cetomacrogol [4–5], but to have some effect in ethanol [6]. Various other agents have been proposed for topical effectiveness [7–12] including 17α-propyltestosterone, 17α-mesterolone and flutamide, all of which have been shown to be of no clinical benefit in patients with acne. Inocoterone, another non-steroidal receptor blocker, reduces sebaceous gland activity when applied topically to rat and hamster sebaceous glands [13,14], and appears to lack systemic effects. In humans, topical inocoterone produced only a small reduction in sebum excretion in adult males, and a minor improvement in clinical acne [15]. Seventeen substituted α-chloro and 17β-sulphinyl steroids have been suggested as inhibitors of sebaceous activity [16], but have been disappointing in humans. Spironolactone, given systemically, has been shown to inhibit the hamster flank organ [17], and, given topically, to block androgen activity in sebaceous glands of the hamster pinna [18]. However, there was no effect on sebum excretion when applied topically to humans [19]. In contrast, spironolactone given orally significantly reduces sebum excretion in humans in a dose-dependent manner: there is a reduction of around 30% with 100 mg/day, and a reduction of 60–70% with 200 mg/day [20]. Oral administration of the H_2-receptor antagonists ranitidine and cimetidine reduces sebum excretion in humans [21], but not to a clinically significant level, and these drugs lack effect topically [22].

Substances that inhibit the conversion of testosterone to DHT, without blocking attachment to the intracellular receptor, also reduce sebum production [23]. A reduction in the rate of sebum excretion by topically applied progesterone [24,25] may involve such a mechanism. Topical progesterone only has a relatively small and temporary sebosuppressive effect in humans; this is likely to be of no clinical significance to the patient with acne.

Certain derivatives of vitamin A, in particular isotretinoin (13-*cis*-RA) have marked effects on the sebaceous glands when given systemically. They have been shown to reduce the size of the hamster flank organ [26] and human sebaceous glands [27], in which they profoundly inhibit sebum excretion [28–30]. Isotretinoin reduces 5α-reductase activity in human liver and skin [31–33], and reduces the binding capacity of the androgen receptor in back skin [33]. Isotretinoin reduces the synthesis of DNA and the incorporation of a lipid precursor ^{14}C-acetate in human sebaceous glands *in vitro* [34,35]. The metabolism of retinoids in the human sebaceous gland has been described above (see also section on oral isotretinoin below). Topical retinoids, in contrast to certain oral retinoids, have no effect in reducing sebum production or excretion.

It has been assumed that topical antibiotics do not influence sebum production or sebum excretion. However, it has been shown that topical erythromycin plus zinc acetate (Zineryt®) reduces SER by about 20% (using Sebutape® technology) in contrast to topical erythromycin alone [36]. The mechanism for this is unclear, but may relate to the drug affecting sebum outflow from the duct.

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Acne vulgaris

Definition. Acne is a chronic inflammatory disease of the pilosebaceous units. It is characterized by seborrhoea, the formation of comedones, erythematous papules and pustules, less frequently by nodules, deep pustules, or pseudocysts and, in some cases, is accompanied by scarring.

Four major factors are involved in the pathogenesis: (i) increased sebum production, (ii) hypercornification of the pilosebaceous duct, (iii) an abnormality of the microbial flora especially colonization of the duct with *P. acnes*, and (iv) the production of inflammation.

Natural history. The condition usually starts in adolescence and frequently resolves by the mid-twenties [1]. Prevalence data shows some variation from study to study, which may relate to the population studied and the time when the study was performed. In one study prevalence of significant acne was 56% in boys and 45% in girls aged between 14 and 16 years, being moderate to severe in 11% [2]. A peak in prevalence and severity occurs between 14 and 17 years in females, when 40% are affected, and 16 and 19 years in males, when 35% are affected [1]. A study from the USA [3] indicated that the prevalence by the mid-teens was virtually 100%. On the other hand only about 20% of sufferers needed the help of a physician. In those patients with very mild disease the problem is referred to as physiological acne. Acne develops earlier in females than in males [1,4], which may reflect the earlier onset of puberty. Significant prepubertal acne is only rarely found to be a cutaneous marker of an endocrine abnormality, such as adrenogenital late-onset syndrome. Mild, comedonal acne can be the first sign of pubertal maturation; significant comedones usually precede inflammatory lesions by 2–3 years [5,6]. Some subjects show small non-inflamed lesions by the age of 8–9 years [1]. Site of involvement is linked to the age of onset of the disease with inflammatory lesions in the midline of the face presenting early in sexual maturation [5].

After the age of somewhere between 20 and 25 years the acne resolves slowly [7]. However, in 7–17% of individuals clinical acne persists beyond the age of 25 years [8] with physiological acne in females having a prevalence of 24% [9]. A study from Denmark suggested that there has been a decrease in the prevalence of acne in females, and

this may relate to the widespread use of oral contraceptives [10]. On the other hand, some clinicians consider that they are now seeing an increase in the number of patients with mature acne. In a recent study [8], 25% of acne patients referred to an acne clinic had a mean age of 24 years. Most had acne persisting from adolescence, but 8% had late-onset (age over 25 years) acne. This may be a reflection of a more demanding and articulate group of mature acne patients [11]. At the age of 40 years, significant lesions are still present in 1% of males and 5% of females [7]. On the other hand, questionnaire-based studies in France [12] and in the USA [13] have shown that as many as 80% of patients treated for acne have some level of disease activity that persists into the 30–40 year age range.

Factors that underlie the resolution of acne are not understood, nor is the relative persistence in females. Recent studies on the natural history of acne are limited, because improved treatment has modified the prevalence, severity and age of presentation to dermatological clinics [14].

Genetic factors. Several studies have shown that genetic factors influence susceptibility to acne [15,16]. A survey in Germany [17] showed that acne had been present in one or both parents of 45% of schoolboys with acne but in only 8% of parents of boys without acne. A genetic influence is confirmed by the very high concordance between monozygotic twins, in whom the SER is virtually identical. Comedone numbers are also similar in identical twins but not in dizygotic twins, which suggests a genetic role in comedone formation [16]. Furthermore, in three pairs of identical twins, severe nodular acne developed at approximately the same time in each pair. On the other hand, in less than half of affected dizygotic twins did both twins have acne [17]. Patients with persistent acne have a strong family history of persistent acne, in contrast to patients with adolescent acne [8].

The decreased incidence of atopic dermatitis in acne sufferers [18] may be genetically determined, but it could be otherwise explained. Patients with eczema have a low sebum excretion. The association of very severe acne with the XYY syndrome [19,20] has been recorded.

Racial studies provide an insight into genetic and environmental factors. Acne in black Americans is less evident than in white Americans, who, in turn, have more severe acne than Japanese [21]. The incidence of acne is said to be low in Inuits, who eat a diet rich in fish, but increases markedly when they change to a 'Western' (Canadian) diet with more saturated fats. Similar changes have been noted in Japanese people who emigrate to Hawaii and consume an American-style diet [21].

Since the last edition of this textbook, there has been a dramatic increase in knowledge about the human genome. The authors know of several clinical/laboratory groups who are exploring the links between acne and its inheritance. It is essential that these workers relate their laboratory data to a more focused description of the disease rather than just the term acne. For example, patients with acne persisting into their thirties have a strong family history of this event [8]. Acne severity, distribution, site of the lesions, scarring and response to treatment could also be genetically determined.

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The size of the problem [1]. A person is more likely to develop acne than any other disease [2]. The major burden of acne is experienced during the teenage years, but acne may continue as a clinical problem into the twenties and older. Data are more reliable for school-aged children than for those in the later teens or older because of the ease of data capture.

Studies of European schoolchildren in Switzerland in 1931 [3], Newcastle upon Tyne, England, in 1971 [4] and Glasgow, Scotland, in 1989 [2] have shown a consistent level of maximum prevalence, approaching 100% for 16–17-year-old boys and 85–100% in 16-year-old girls. However, the same period has seen a major reduction in severity. In the 1931 study, 57% of boys and 19% of girls had severe acne [3]. These figures had fallen to 30% and 20% in 1971 [4] and changed to 35% and 13% respectively in a further study in Newcastle upon Tyne in 1981 [5]. By 1989, the Glasgow study showed no schoolchildren with severe acne, only 1.8% of boys with moderate acne and no girls with worse than mild acne [2]. Only the Newcastle upon Tyne and Glasgow studies were randomized cross-sectional views. Similar prevalence levels were found in New Zealand [6] and Southern Australia [7], but both countries showed significantly larger numbers of school students with the more severe grades of acne than were found in the UK. Unfortunately, most studies have been affected by selection bias due to place of work, educational institution or hospital/surgery attendance. Questionnaire-based surveys in the USA and the UK [8,9] have shown a lower prevalence, as might have been expected from the Glasgow study, which found clinical acne in 18% of boys, many of whom denied the presence of spots.

The clinical problem of acne in older patients in their twenties and thirties appears to be increasing [8–12], but better epidemiological data are required.

The size of the problem is also influenced by patients' beliefs and perception [13,14]. Twelve per cent of teenage boys denied the presence of clinical acne [2] and, in another study, 49% of patients believed their acne to be curable within 6 months [13].

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Aetiology of acne

The four major factors involved in the aetiology of acne are:

1 seborrhoea
2 comedo formation (comedogenesis)
3 colonization of the duct with *P. acnes*
4 inflammation.

Seborrhoea

Patients with increased sebum production complain of seborrhoea (greasy skin). Active sebaceous glands are a prerequisite for the development of acne. Acne patients, male and female, excrete, on average, more sebum than normal subjects [1], and the level of secretion correlates reasonably well with the severity of the acne (Fig. 43.6) [2,3]. Sebaceous activity is predominantly dependent on androgenic sex hormones of gonadal or adrenal origin [4–6]. Abnormally high levels of sebum secretion could thus result from high overall androgen production, increased availability of free androgen, due to a relative reduction of sex hormone binding globulin (SHBG) or an amplified target response mediated either through 5α-reduction of testosterone or an increased capacity of the intracellular receptor to bind androgens.

There is general agreement that plasma testosterone levels are not abnormally high in males with acne [6–8]. In females with acne, the situation is more complicated. Some investigators have found testosterone levels to be normal [9–11], while others have found raised levels [12–15], albeit often lower than in males with no acne whatsoever. Most studies have shown that mean SHBG

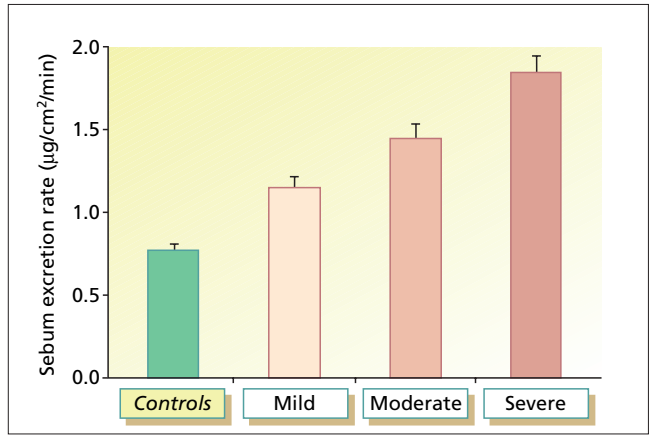

Fig. 43.6 Correlation between acne severity and sebum excretion.

levels are significantly below normal, with free testosterone consequently above normal. However, for every endocrine assay, there has been a considerable overlap between the values found in acne patients and normal ranges. Lawrence *et al.* [12] found that only 41% of their acne patients had free testosterone levels above normal. Lucky *et al.* [13] measured a number of androgens and their precursors, as well as SHBG, and found that 52% of non-hirsute women with acne had at least one abnormal hormone level. Cibula *et al* [16] found that 81% (73 of 90 patients) had an elevation of at least one androgen hormone of the four that they measured. In their study, 21% had hirsutism and 50% had polycystic ovarian syndrome, but there was no correlation between the severity of acne and abnormalities of the sex hormones. Darley *et al.* [17] examined 38 women with acne and found high serum testosterone in 26%, low SHBG in 45% and high prolactin in 45%, but 24% had no hormonal abnormality at all. Peripheral androgen metabolism may be important, for example increased androsterone metabolism has also been reported in females with normal circulating androgen levels [15]. Insulin may affect SHBG, thereby influencing androgen clearance [18]. However, post-meal transient hyperinsulinaemia does not seem to play a role in hyperandrogenaemic acne patients [19].

Thus, on reviewing published papers, it would seem that androgenic hormonal balance is disturbed to some degree in 50–75% of female acne patients. However, this does not establish a causal link and at least a quarter of all cases remain unexplained. Furthermore, in many of the reports the patients were older than the modal value for all female acne patients, and not infrequently had other features of endocrine disease, such as significantly irregular menstruation and hirsutism. There are no correlations between the severity of acne, hirsutism and menstrual irregularity [20]. Moreover, if the development of acne were simply related to systemic hormone levels, it should have a similar frequency on the face, back and chest, but this is not so. In general, acne patients are not endocrine misfits.

The fact that acne does not occur simultaneously on all susceptible sites is consonant with the finding that sebum excretion varies from follicle to follicle (Figs 43.7 & 43.8) [21]. In acne patients, there is marked heterogeneity in individual follicular sebum excretion. This allows us to hypothesize that certain follicles may be prone to acne [22]. An enhanced peripheral response to androgens must thus be considered as a probable factor in many subjects. The possible role of increased 5α-reduction of testosterone to its more active metabolite 5α-DHT is supported, both by the demonstration that sebaceous glands in acne-prone regions show abnormally high 5α-reductase activity *in vitro* [23], and by the finding of abnormally high amounts of 5α-androstanediols in the urine of female acne patients [9]. Data on androgen receptors in acne suggest that

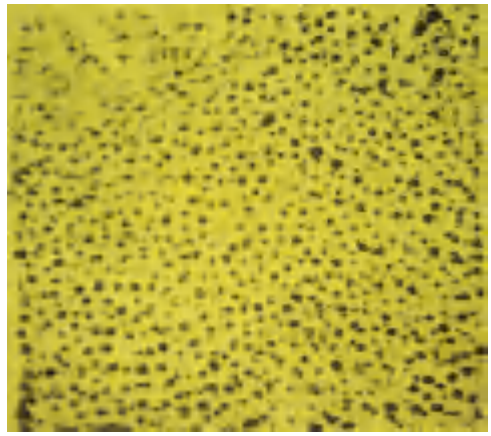

Fig. 43.7 Homogeneous sebaceous outflow in a normal subject.

Fig. 43.8 Heterogeneous sebaceous outflow in an acne subject.

androgen action on the sebaceous gland may be independent of serum hormone levels [24]. There are two forms of 5α-reductase [25]. It is likely that 5α-reductase type I is the most relevant in acne for two reasons. First, finasteride, an inhibitor of type II 5α-reductase, does not reduce sebum production [26]. Second, patients with a deficiency of type II 5α-reductase have normal sebum levels [26]. Regional differences in the activity of type I 5α-reductase in isolated sebaceous glands from various body sites also support the end-organ hyper-responsiveness theory for acne [27–30].

In the authors' clinical practice and that of other acne centres [31], it is usually not necessary to investigate for an endocrinopathy. An endocrine evaluation may be indicated for adult females, with a sudden onset of severe acne; with acne that has proven resistant to conventional therapy especially in the presence of hirsutism; with very irregular menstrual periods or signs of hyperandrogenism. Androgen evaluation may also be warranted in women who experience relapse shortly after starting isotretinoin therapy. A medical history and physical examination should be performed before embarking upon relevant blood tests. Polycystic ovarian syndrome is the

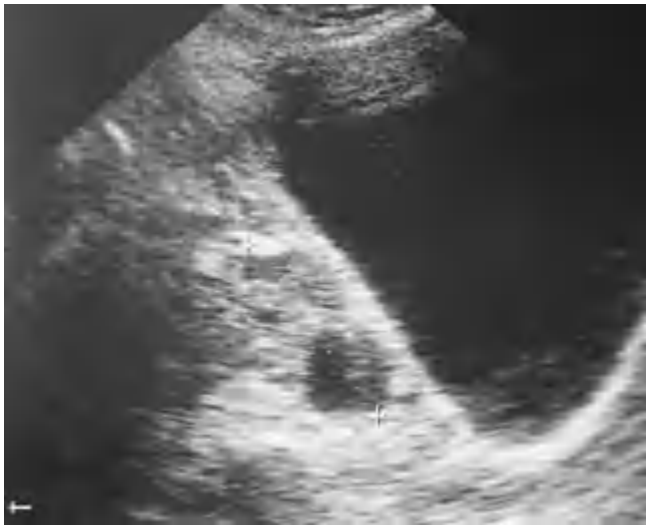

Fig. 43.9 Ultrasound of the pelvis showing polycystic ovaries.

most frequently associated hormonal disease [32], and this can be detected by ultrasonography (Fig. 43.9). In most acne clinics, the majority of female patients with acne have no other clinical features of the syndrome, which consists of hirsutism, infertility or irregular menstruation [11]. There is no correlation between the presence of ovarian cysts and the severity of the acne [33]. Late-onset adrenal hyperplasia due to a partial deficiency of 21-hydroxylase should be considered in patients with persistent problems with their acne [34]. This enzyme deficiency results in a need to maintain cortisol levels, and so produces a shunting in the steroid biochemical pathways that results in an increase in androgen production. The disorder may uncommonly be a cause of severe acne in boys [35]. It is very rare to find virilizing tumours that present as acne alone. Thus, it is not often necessary to measure sex steroid levels, as this information usually contributes little to the patient's management. When thought necessary, appropriate initial tests should include measurement of total testosterone (ideally free testosterone, but only a few laboratories can measure this hormone), SHBG, androstenedione, dehydroepiandrosterone (DHEA), prolactin and follicle-stimulating hormones (FSHs) and luteinizing hormones (LHs) [36]. Since there are diurnal and menstrual variations in sex hormone levels it is important to relate the results to the time at which the blood was taken in relationship to the menstrual cycle and, for consistency, the test is best performed at 09.00. For reliability and repeatability, the tests should be performed in the luteal phase of the menstrual cycle (within 2 weeks prior to the onset of menstruation). If late-onset congenital adrenal hyperplasia is suspected, then a 09.00 cortisol and 17α-hydroxyprogesterone measurement should be performed. Clinicians should remember that hormonal therapy might also interfere with the results.

Either the adrenal gland or the ovary may produce excess androgens. Serum dehydroepiandrosterone sulphate (DHEAS) levels can be used to screen for an adrenal source of excess androgen production. Clinicians should check local normal values, but patients with a serum DHEAS greater than 21.7 μmol/L may have an adrenal tumour. Some adrenal tumours may also produce testosterone. Values of DHEAS in the range of 10.8–21.7 μmol/L may be seen with congenital adrenal hyperplasia, which is often associated with a slightly raised cortisol and a 17α-hydroxyprogesterone level of greater than 12.8 μmol/L.

An ovarian source of excess androgen can be suspected in cases where the serum total testosterone is elevated. Serum total testosterone in the range of 520–700 nmol/L or an increased LH : FSH ratio (greater than 2–3) is often seen in patients with polycystic ovarian disease. Greater elevations in serum testosterone may indicate an ovarian tumour.

The possibility that other hormones may affect the sebaceous glands, either directly or by enhancing their response to androgens, should not be neglected. In acromegaly, the rate of sebum excretion is high and correlates with skin thickness and growth hormone levels [37]. The SER is low in individuals with isolated growth hormone deficiency, and therefore is not associated with acne [38]. In clinical practice, these endocrinopathies are rarely encountered as presenting features in the dermatological clinic.

Sebaceous lipid composition

Irrespective of the rate of sebum excretion, could acne be related to a change in skin lipid composition? Sebum consists of a mixture of squalene, wax and sterol esters, cholesterol, polar lipids and triglycerides [39]. As the sebum moves up the duct, bacteria, especially *P. acnes*, hydrolyse the triglycerides to free fatty acids. The role of individual lipid components in causing acne is uncertain. Lipids may be involved in ductal hypercornification, or may be essential to the growth (stimulation and inhibition) of bacteria. Sampling of skin-surface lipids has shown that patients with acne tend to have higher levels of squalene and wax esters, lower levels of fatty acids [40–42], and a more frequent occurrence of particular free fatty acids [43,44]. Linoleic acid is significantly reduced in epidermal and comedonal lipids, and this may relate to ductal hypercornification.

Comedone formation (comedogenesis)

An important feature in the aetiology of acne is the presence of ductal hypercornification, which can be seen histologically as microcomedones, and clinically as blackheads, whiteheads and other forms of comedones such

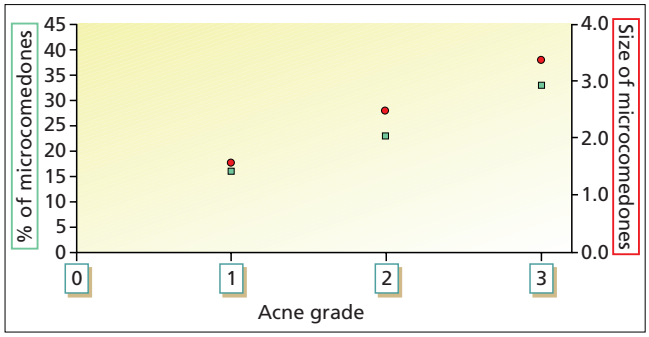

Fig. 43.10 Correlation between the number and size of microcomedones and acne severity.

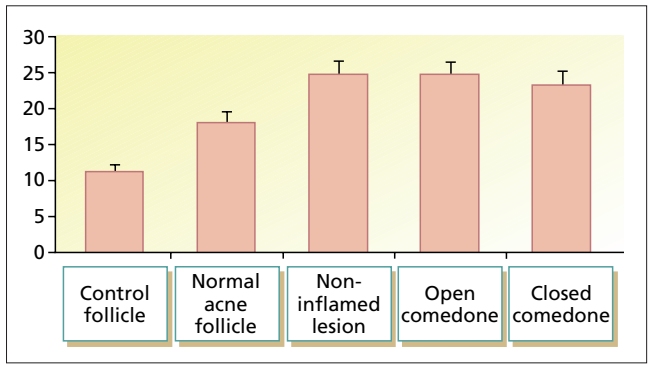

Fig. 43.12 Uptake of Ki-67, a marker of keratinocyte proliferation, in control skin, microcomedones and clinical comedones.

Fig. 43.11 Scanning electron microscopy of a microcomedo that has been sampled from an acne-prone skin using the skin-surface biopsy technique.

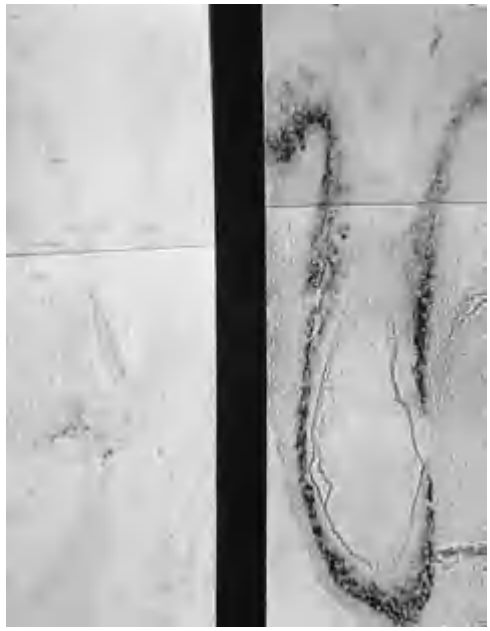

Fig. 43.13 *In situ* hybridization for keratin 6 (a marker of hyperproliferation) demonstrates little activity in a normal follicle (left) and considerable activity in a comedo (right). (Courtesy of Dr D.B. Holland, Leeds General Infirmary, Leeds, UK.)

as macrocomedones. There is a significant correlation between the severity of acne and the number and size of follicular casts (microcomedones), the presence of which is a measure of comedogenesis [45] (Fig. 43.10). Follicular casts (microcomedones) can be sampled by applying cyanoacrylate gel to the skin surface, followed by pressing a glass microscopic slide on top for 1 min [46,47]. The sample can be analysed by low-power microscopy or by digital image analysis [46,47] (Fig. 43.11).

Comedones are due to abnormalities in the proliferation and differentiation of ductal keratinocytes. They represent the retention of hyperproliferating ductal keratinocytes/corneocytes in the duct. The hyperproliferation has been confirmed by showing an increase in ^{3}H-thymidine labelling of comedones [48] and increase in the Ki-67 labelling (a marker of cell turnover) of ductal keratinocytes (Fig. 43.12) [49]. Ki-67 labels nuclear antigen expressed by cells in the late G1, S, M and G2 phases of the cell cycle [50]. This technique has also shown an increase in the proliferation of ductal keratinocytes of 'non-affected' follicles, which were biopsied as clinically 'normal' follicles from an area affected by acne [49]. This fits with the histological observation of microcomedones being found in 30% of tissue sections of clinically 'normal' skin taken from skin adjacent to acne lesions. Further evidence of ductal hyperproliferation is the presence of keratins 6 and 16 (keratin markers of hyperproliferation) in microcomedones and comedones (Fig. 43.13) [51]. The primary abnormality that gives rise to hypercornification is not related to changes in keratin expression [51,52]. There is as yet no evidence to suggest that comedogenesis

may be related to failure of ductal keratinocytes to separate. Studies of involucrin expression and desmosomes, which are features of terminal differentiation, have shown no difference between follicles from acne and control biopsies [53].

Several factors have been implicated in the induction of keratinocyte hyperproliferation, and include sebaceous lipid composition, androgens, local cytokine production and bacteria.

Of the abnormal sebaceous lipids in acne patients, the linoleate levels may be relevant. Examination of polar lipids recovered from comedones shows that the acyl ceramides contain only 6% linoleate among the esterified fatty acids, compared with 45% in normal human epidermis [54,55]. Similarly, linoleic acid is reduced in sebum from acne subjects, but returns to normal with resolution of acne following treatment with isotretinoin [56] and antiandrogens [57]. In animal experiments, a low linoleate produces hypercornification, which may parallel the increased scale found in comedones. In these animals, a low linoleate produced a decreased epidermal barrier function, which might have rendered the comedonal wall more permeable to inflammatory substances. Membrane-coated granules [58–60] are probably more related to barrier permeability than cell separation, and are decreased in comedones, but the significance of this is as yet unclear.

Other lipids have been incriminated; in particular, free fatty acids and squalene have been blamed for inducing comedones [61,62] in the rabbit-ear model [63]. The development of a human model for comedogenesis has, however, suggested that the rabbit model is inappropriately over reactive [64]. Laboratory animals do not develop whiteheads or inflamed acne lesions, even though the rabbit ear readily produces comedones [65]. The rhino mouse is an alternative useful model for comedogenesis [66]. From experiments in the rhino mouse, it has been suggested that comedone formation may be associated with an abnormality in apoptosis (programmed cell death) [67]. Evidence is accumulating to propose that androgens may play an important role in comedogenesis. There is a correlation between comedone numbers in early acne and DHEAS levels [68]. Cells of the pilosebaceous duct have androgen receptors [69], and 5α-reductase type I is also present in these cells both in health and in disease [70–72]. Antiandrogen drugs, such as CPA in the drug co-cyprindiol (Dianette® and Estelle 35®), reduce comedones. Co-cyprindiol also increases the sebaceous linoleate concentration [57], and thus antiandrogen therapy could modulate comedogenesis both directly and indirectly by influencing sebaceous lipid.

Cytokine production by ductal keratinocytes is also likely to be important. Kealey and colleagues have developed an excellent *in vitro* model for growing the duct [73–75]. IL-1-α is present in many comedones at levels that are likely to be biologically and pathologically relevant [76]; IL-1-α induces comedogenesis (Fig. 43.14). Furthermore, EGF markedly disrupts the duct comedo *in vitro* [75]. Kealey and colleagues have extended their studies, and provided further supporting data to show that the isolated, maintained infundibulum is also a good culture model for studying the effects of inflammatory cytokines on the pilosebaceous duct, and that IL-1-α acts on the fundibular keratinocytes to induce cornification [76]. They have also shown that EGF and TGF-α inhibit sebum secretion [77].

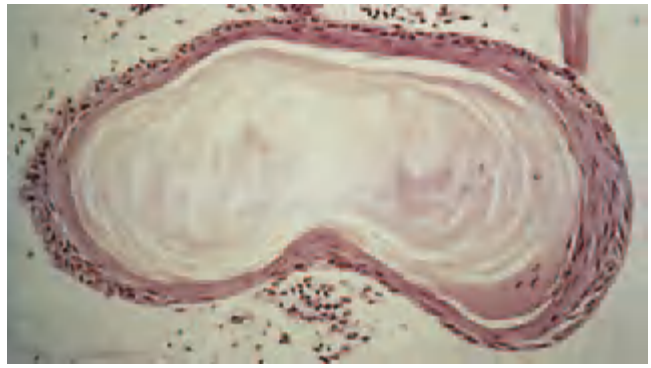

Fig. 43.14 An *in vitro* comedo, induced by interleukin-1-α (IL-1-α). (Courtesy of Dr T. Kealy, Cambridge University, UK.)

Bacteria are probably not involved in the initiation of comedones. Electron microscopy of early non-inflamed lesions taken from prepubertal and early pubertal individuals has demonstrated few or no bacteria [78]. Quantification of bacteria from comedones suggests that follicular colonization may be unrelated to comedogenesis [79]. Biopsy and culture of early non-inflamed lesions has shown that 30% of these are without bacteria [80], suggesting that ductal bacteria are not needed for the initiation of cornification in the development of comedones.

Comedones are temporary structures. Using markers of cell cycling (Ki-67) and keratinocyte proliferation, it has been shown that, like the hair follicle, normal pilosebaceous follicles and comedones undergo cyclical growth [81]. Extracted blackheads refill over 2–6 weeks. Functionally, some comedones are blocked [82], but others can become blocked temporarily following skin hydration [83], and this obstruction is associated with a decrease in outflow of sebum. Such observations could help to explain tropical acne and premenstrual flare of acne [84].

Certain external chemicals may contribute to comedogenesis. These substances include the ingredients of some cosmetics such as isopropyl myristate, propylene glycol, and D and C red dyes [85]. It has been suggested that the excretion of products from the sebaceous gland occurs through an organized acellular tubular conduit—the sebolemmal sheath produced by the sebaceous duct cells; rupture of this sheath may contribute to comedogenesis [86]. However, this concept has yet to be confirmed by others.

Relationship between *P. acnes* and acne

Acne is not infectious. The three major organisms isolated from the surface of the skin and the pilosebaceous ducts of patients with acne are *P. acnes*, *Staphylococcus epidermidis* and *Malassezia furfur* [87]. There are three major subgroups of the propionibacteria—*P. acnes*, *P. granulosum* and *P. avidum*. Almost certainly *P. acnes* and, to a lesser extent, *P. granulosum* are the most important. Nevertheless, as they live in association with *S. epidermidis* and *M. furfur*, the latter organisms probably have some control over the growth of *P. acnes* [88].

Adolescence and its attendant seborrhoea are associated with a significant increase in *P. acnes* numbers [89], but there is little or no relationship between the number of bacteria on the skin surface and the severity of acne [90–92]. There is a much closer relationship between follicular organisms recovered from 4 mm punch biopsies and the severity of the disease [93]. In a study in which the cutaneous microflora of patients with persistent and late-onset acne were compared with individuals with adolescent acne and normal control volunteers without acne [93], the microflora consisted in the main of *Propionibacterium*, staphylococci and *Malassezia*, and at all sites there were significantly more *Propionibacterium* spp. than the other two microorganisms. Female facial skin and male back skin showed significantly higher numbers of microorganisms in the upper parts of the follicles from patients compared with control volunteers. In all, 26 papules and 48 normal follicles were biopsied and analysed [93]. There was a bimodal distribution of microbial colonization, with about 90% of normal follicles and about 10% of acne follicles having no detectable viable microorganisms. There were fewer microorganisms in normal follicles than in inflamed lesions. Although the presence of microorganisms, especially *P. acnes*, cannot be deemed to be singularly responsible for the onset of the inflammatory lesion, the significant difference between the number of inflamed lesions, which were colonized, when compared with normal follicles, lends support to the theory that these microorganisms may be involved in the inflammatory process at some point.

It is possible that the number of microorganisms increases at each stage as the follicle progresses from normal to comedone and on to an inflamed lesion. There is a 10-fold increase in the number of organisms found in inflamed lesions [93]. The biological significance of this is uncertain. It seems plausible that microorganisms might contribute to the inflammatory process but, conversely, an inflamed lesion may simply provide an enriched environment for the proliferation of cutaneous microorganisms. The microenvironment within the pilosebaceous unit produced by the bacteria is probably more important than their absolute numbers for the development of acne lesions. *In vitro*, it has been shown that oxygen tension, pH and nutrient supply markedly affect the growth of *P. acnes*, and the bacterial production of active substances such as lipases, proteases, hyaluronate lyase, phosphatase and smooth muscle contracting substances [94–96]. *In vivo*, the pH of blackheads markedly varies between 3.6 and 6.7 [97], and this is likely to affect the bacteria. Oxygen tension is also likely to be important. *Propionibacterium acnes* grows well at low oxygen tensions. In the presence of light at high oxygen concentrations, *P. acnes* grows well, but growth is inhibited because of photodamaging reactions involving excess oxygen and endogenous microbial porphyrins [98]. These factors could determine whether or not a follicle develops into a non-inflamed comedo and, subsequently, into an inflamed lesion.

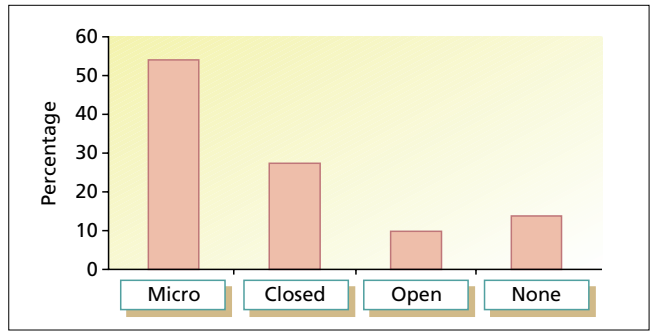

Fig. 43.15 Most, but not all, early inflamed lesions are associated with a microcomedo or clinical comedo.

The once-fashionable 'lipase' theory for acne [99] no longer has much support, because injection of fatty acids into the skin produces only mild inflammatory reactions [100]. Lipids are not found in the dermis in the early inflammatory infiltrate of acne, and a specific lipase inhibitor produced no improvement in acne [101].

Propionibacterium acnes is non-motile but easily colonizes the duct. Just how this event occurs is unknown. To colonize, *P. acnes* organisms must clump; free fatty acids aid clumping, and so bacterial lipases may be necessary for clumping and ductal colonization [102].

Mediation of inflammation

The precise factors that induce inflammation in acne lesions are unknown, but the subject has been well reviewed by Webster [103]. A microcomedo or comedo is present in 88% of early inflamed papules (Fig. 43.15). Duct rupture is seen in only 33% of papules at 36 h after the onset of clinically detectable inflammation, but by 72 h duct rupture has occurred in 67% [104]. Thus, in early inflammation pro-inflammatory mediators move through the duct wall into the dermis (Fig. 43.16). In papules, helper T cells are the first inflammatory cells to be seen [104,105].

The dermal inflammation of acne is not caused by the presence of bacteria in the dermis, as these are rarely

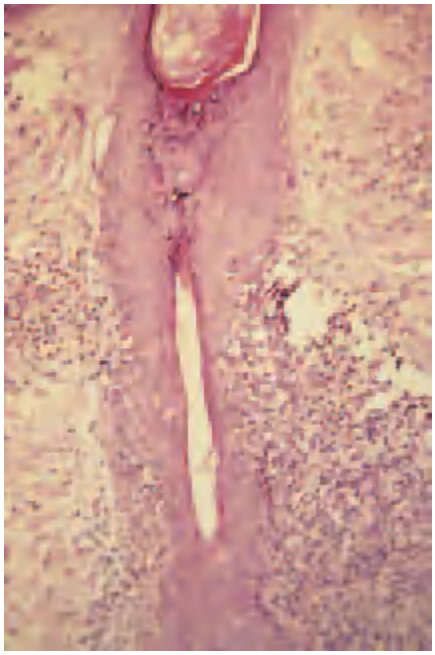

Fig. 43.16 An early inflamed papule (6 h). Note spongiosis and a lymphocytic infiltrate but no obvious rupture of the duct.

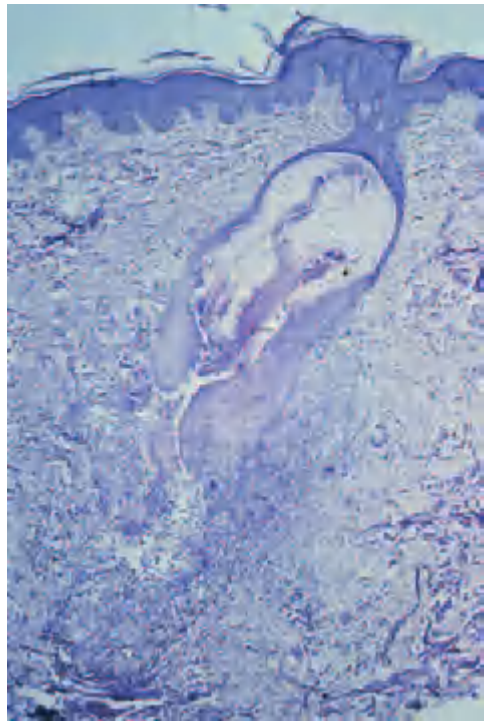

Fig. 43.17 A late-stage papular nodular lesion (7 days). Note total disruption of the duct and a macrophage, giant cell reaction.

demonstrable by routine and immunofluorescence methods [105]. It probably results from biologically active mediators that diffuse from the follicle, where they have been produced by *P. acnes*.

As the lesions progress, timed biopsies using a bank of inflammatory markers have shown that, prior to obvious duct rupture, the inflammation represents a classical type IV immunological reaction to as yet not fully identified antigens [106]. Later, in moderate and severe inflammation there is disruption of the duct and a macrophage giant cell foreign-body reaction (Fig. 43.17). Direct immunofluorescence studies have shown that there is activation of the classical and alternative complement pathways in early non-inflamed and in inflamed lesions [107,108].

The microorganisms, especially *P. acnes*, are an obvious source of antigenic stimuli. *In vitro*, *P. acnes* produces many enzymes, including three proteases, lipase, phosphatases and hyaluronate lyase, all of which might, in theory, be implicated in the development of inflammation [94,95]. *In vitro*, *P. acnes* has little effect in modulating peripheral blood mononuclear cell derived IL release or keratinocyte-derived cytokine release [109]. *Propionibacterium acnes*, in particular its cell wall fraction, is a potent chemoattractant for polymorphonuclear and mononuclear cells [110–113]. Recent research has shown two mechanisms of lymphocyte activation by *P acnes* cells; the activation is both antigen and mitogen driven [114]. These results are consistent with the histological evidence of inflammation in acne lesions. There is also increasing evidence to support the involvement of toll-like receptors in acne inflammation. Toll receptors recognize 'abnormal' organisms. In a way, *P. acnes* can be looked upon as 'abnormal', as it is not often present in follicles from subjects without acne. The toll receptors in turn regulate the production of cytokines which may contribute to acne inflammation. *Propionibacterium acnes* also produces a prostaglandin-like substance [115] which might be involved, as non-steroidal anti-inflammatory drugs have an anti-acne effect [116].

Cytokines are known to play a role in inflammatory acne. Ductal corneocytes constitutively produce interleukins (including IL-1-α and IL-β) and TNF [77].

The sebaceous gland also expresses several pro-inflammatory cytokines at steady state, without any influence of external factors such as bacteria. IL-1 is present in normal sebaceous glands and mRNA for IL-1-α, IL-β and TNF are also present in the sebaceous glands, and these cytokines may be involved in inflammation [117].

Leukotriene B4 (LTB4) is a pro-inflammatory mediator synthesized from arachidonic acid. Synthesis of LTB4 is catalysed by 5-lipoxygenase and is increased by inflammatory mediators including complement fragments, TNF-α and interleukins. Leukotriene precursors are synthesized in the sebaceous gland [118]. LTB4 induces recruitment and activation of neutrophils and monocytes. It also stimulates the production of a number of pro-inflammatory cytokines and mediators that augment and prolong tissue inflammation. These events are

independent of bacteria. Limited data from pharmacological inhibition studies support a role for LTB4 in the pathogenesis of neutrophil-mediated tissue damage. A preliminary, small-scale clinical study of an oral anti-inflammatory agent that specifically blocks the formation of LTB4 [119] showed a 70% reduction in inflammatory lesions at 3 months in patients with acne. These data support the suggestion that bacterial involvement may not always be necessary for expression of inflammation.

Some investigators have focused on the systemic immunological response as a possible factor in acne inflammation. Circulating immune complexes have not been demonstrated in sera from acne patients [120]. Skin testing with a heat-killed suspension of *P. acnes* demonstrated that subjects with severe acne produced a greater inflammatory response at 48 h than other subjects, suggesting that the host response may be important [121]. Observed changes in neutrophil chemotaxis may be a secondary event [122]. *Propionibacterium acnes* polypeptides are detected in the serum of acne patients but not in normal individuals [123]. This host response is of uncertain significance. Some lipids are likely to get into the dermis when the duct ruptures and may act as irritants. Other lipids such as linoleic acid can down-regulate neutrophil oxygen metabolism and phagocytosis [124]. Acne-prone sebaceous glands contain less linoleic acid than those of non-acne controls and this could contribute to the inflammation [56]. One group [125] reported elevated IgE levels that related to clinical severity, but another group found no changes in total IgE or its subclasses [126]. It is uncommon to see females with very severe acne, and it has been proposed that females muster a better defence mechanism than males against *P. acnes* [127]. In summary, acne patients are not usually immunological misfits, but some immunological reactions may verge on the abnormal in a very small number of patients. For example, some patients with acne fulminans show a markedly exaggerated delayed hypersensitivity to *P. acnes* [128].

It had been suggested that persistent mature acne could be explained by an abnormal humoral response to *P. acnes*. However, neither a deficient nor heightened humoral response to *P. acnes* accounts for persistent adult acne [93].

Hormones can also influence inflammatory processes, and in several other biological/clinical situations androgens are known to be pro-inflammatory; there is no evidence for this in acne.

Probable sequence of pathological events in acne

Microcomedones are the earliest observable abnormality. There is much debate as to whether the seborrhoea in certain acne-prone follicles, or comedogenesis, is the initial trigger. Microcomedones can be found in 30% of biopsies taken from apparently normal looking skin from an acne-prone site, and 85% of early papules are associated with a comedone. Colonization of the duct with *P. acnes* and the production of inflammation are late stages in the development of acne, even though it is often the inflammation and its severity which brings the patient to the clinic.

The role of drugs, in particular retinoids, in reducing comedones is discussed in detail in the therapy section. Most publications on oral and topical antimicrobial therapy of acne clearly show a significant reduction in comedonal lesions. This reduction is very similar to that seen with topical retinoids. The Leeds group have published a paper demonstrating that a significant number of biopsies from normal looking skin of acne patients without any evidence of microcomedones or ductal hyperproliferation have a significant inflammatory cell infiltrate around the follicle (in particular $CD3^+$, and $CD4^+$ cells and macrophages). Such cells are significantly suppressed by antimicrobial therapy, and so such therapies will reduce comedones [129].

Mechanisms inducing acne scarring

Scarring is a consequence of abnormal resolution or wound healing following the damage that occurs in the sebaceous follicle during acne inflammation. A cell-mediated immune response has been found to be involved in these inflammatory events, but such a response not only contributes to the clearance of antigen but also to tissue damage. Previously, no attention has been paid to the influence that this response may have on the resolution of acne lesions. The inflammatory response has been implicated as an important component in the development of scars [130]. Holland *et al.* [131] investigated the differences in cell-mediated immune responses in developing and resolving inflamed lesions between those acne patients who were prone to scarring and those with the same degree of inflamed acne who were not prone to develop scarring. The numbers and activation states of lymphocytes, macrophages and endothelial cells were examined in biopsies of timed inflamed lesions of known duration at less than 6 h, 24 h, 48 h, 72 h and 6/7 days using standard immunohistochemical methods.

Clear differences in the cellular infiltrate present in lesions from the two groups of patients were identified. In acne patients who were not prone to scarring, the time course was typical of a type IV delayed hypersensitivity response. In developing lesions there was significant angiogenesis and vascular adhesion molecule expression, with a large influx of activated $CD4^+$ T cells, macrophages ($CD68^+$) and Langerhans' cells ($CD1a^+$). Cell recruitment peaked at 48 h, after which there was a decrease in leukocytes, cellular activation and a return to normal levels of blood vessels and vascular adhesion molecules in resolving lesions. Of the $CD4^+$ T cells, 50% were skin homing

memory effector cells ($CD45RO^+$, CLA^+) and naïve cells ($CD45RA^+$) cells, whilst the remainder were unclassified ($CD45RO^-$, $CD45RA^-$, CLA^-), which suggests that effective resolution occurred by both non-specific/innate and adaptive immune mechanisms.

In lesions from acne patients who were prone to scar, a predominantly adaptive immune response was present, which was persistent and up-regulated in resolving lesions. The number of $CD4^+$ T cells were approximately half of those found in lesions of non-scarrers, but a high percentage of these cells were skin homing memory/effector cells, suggesting that these patients were sensitized to the causative antigen(s). In developing lesions, although the numbers of macrophages, blood vessels and vascular adhesion molecules were high and similar to those present in lesions of non-scarrers, the numbers of Langerhans' cells and the level of cellular activation was low and comparable to levels found in normal skin, indicative of an ineffective response. However, in resolving lesions there was an up-regulation of the response with greater cellular activation, and a further influx of macrophages and skin homing memory/effector cells. Certainly, the strong macrophage presence represents a dominant force in this response. Thus, it may be interpreted that, in patients prone to scarring, there is a chronic delayed-type hypersensitivity reaction provoked by a persistent antigen which these patients are initially unable to eliminate.

The different inflammatory cell profiles elicited by the two patient groups could explain the different qualities of repair observed. Lymphocytes and macrophages secrete an extensive array of cytokines and growth factors that are known to modulate dermal fibroblast recruitment, proliferation and phenotype, and will affect fibroblast functions such as wound remodelling and contraction, both contributory factors in scarring. This model suggests that the type and magnitude of the inflammatory response in 'resolving' lesions from patients with such a dominant macrophage presence, would lead to abnormal healing and pathological scarring. It is possible that the management of either numbers or activation states of inflammatory cells during the development and resolution stages of acne may help to control scarring.

Resolution of acne

This can be considered in two ways, resolution of individual lesions and resolution of the disease as a whole. The evolution of acne has received considerable attention; its resolution has been largely ignored. Limited studies suggest that the resolution is not related to reduction of sebum production or changes in surface bacteria [88]. The relationships between ductal hypercornification, inflammatory mediators, changes in the host response and resolution are obscure. Pierard [21] has shown that individual sebaceous glands function at different rates in acne patients. Resolution may be associated with specific changes in these acne-prone hypersecreting glands. Resolution of individual lesions could relate to cytokine activity within the pilosebaceous duct. For example, EGF and TGF-α are *in vitro* not only associated with disruption of the follicle but also with inhibition of sebaceous secretion [78]. Could this switch off an acne-prone follicle—albeit temporarily—and convert it into a non-acne-prone follicle?

Biological significance of acne, sebum and *P. acnes*

Activity of the sebaceous glands is unlikely to be essential for healthy skin, because prepubertal skin appears perfect unless severely challenged by soap and water! Yet the ubiquity of both hypersecretion of sebum and the presence of *P. acnes* suggests that their apparent undesirability may be outweighed by some selective advantages: the possible biological role of sebum is discussed above and it has been suggested that *P. acnes*, which enhances immune responses, may provide protection against malignant haematological disease [132], although not against solid tumours [133]. Independent of bacterial colonization, there is now evidence that the sebaceous gland is an immunocompetent organ [134].

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Clinical features

Acne is a polymorphic disease, which occurs predominantly on the face (99% of sufferers) and, to a lesser extent, occurs on the back (60%) and chest (15%) [1]. In young men, it affects mainly the face, and in older males the back is also significantly affected. Seborrhoea is a frequent feature [2,3]. We have recently (unpublished observations) investigated the importance of the symptoms of acne to the patient. To our surprise seborrhoea was as important to the patient as the inflammatory papules.

Non-inflamed lesions (comedones) develop earlier than inflamed lesions in younger patients [4]. Comedones may be blackheads (open comedones), in which the black colour may be due to the presence of melanin (not dirt or oxidized sebum), whiteheads (closed comedones) (Fig. 43.18) and the so-called intermediate non-inflamed lesions, which show features of both blackheads and whiteheads (Fig. 43.19) [5]. There are also several subtypes of comedone that can easily be missed by the physician, but which may markedly influence response to therapy [6]. These non-inflamed lesions may be part of the primary acne process or secondary to some external influence. Comedonal lesions called 'sandpaper comedones' consist of multiple very small whiteheads and are found most often on the forehead (Fig. 43.20). There may even be as many as 500 such lesions, which feel rough to the touch—a fact that is often appreciated by the patient. Macrocomedones are large whiteheads or blackheads (usually whiteheads) greater than 1 mm in diameter. Both macrocomedones and sandpaper comedones respond poorly to conventional topical treatments (see below). 'Submarine comedones' are large comedonal structures

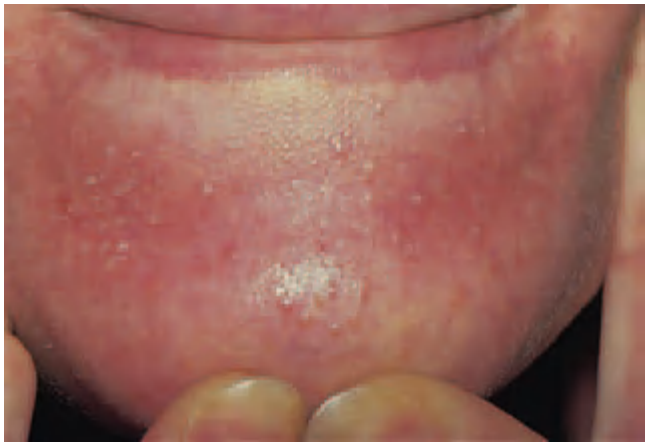

Fig. 43.18 Multiple whiteheads (closed comedones); only seen clearly on stretching the skin.

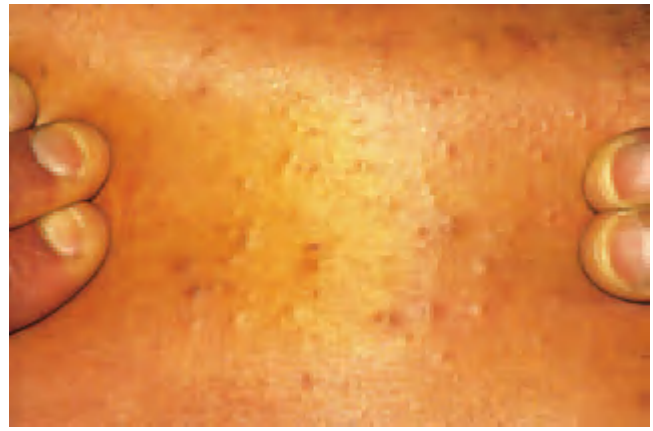

Fig. 43.19 Multiple whiteheads and blackheads, which are made more apparent by stretching the skin.

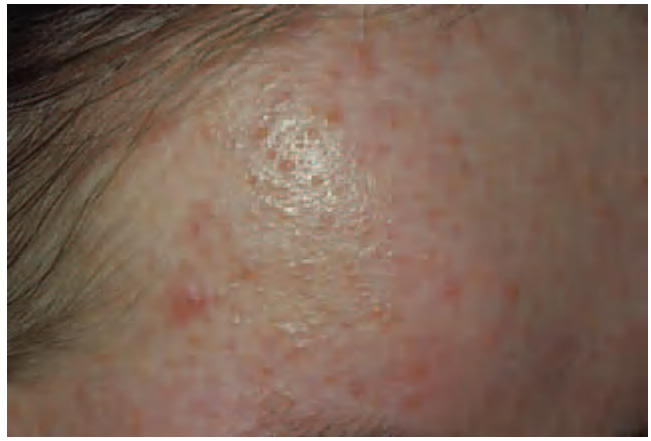

Fig. 43.20 A patient with sandpaper acne. Note the very small and multiple whiteheads.

greater than 0.5 cm in diameter and occur fairly deep in the skin; they are frequently the source of recurrent inflammatory nodular lesions (Fig. 43.21). Secondary comedones may be produced after exposure to dioxins (chloracne), pomades (pomade acne), topical steroids and other drugs (drug-induced acne).

Inflammatory lesions may be superficial or deep, and many arise from non-inflamed lesions [7]. The superficial lesions are usually papules and pustules (5 mm or less in diameter) (Fig. 43.22), and the deep lesions are deep pustules and nodules (Fig. 43.23). The term nodulo-cystic acne is incorrect. Acne 'cysts' are not true cysts because they are not lined by an epithelium. It is more appropriate to describe such lesions as nodules [8].

Nodules more frequently occur in males and, if exudative or haemorrhagic, are particularly disfiguring and messy (Fig. 43.24). Nodules may extend over areas of a few to many centimetres, and may be remarkably deep with very little surface involvement. Sinus track acne is due to sinus formation between nodules and/or deep

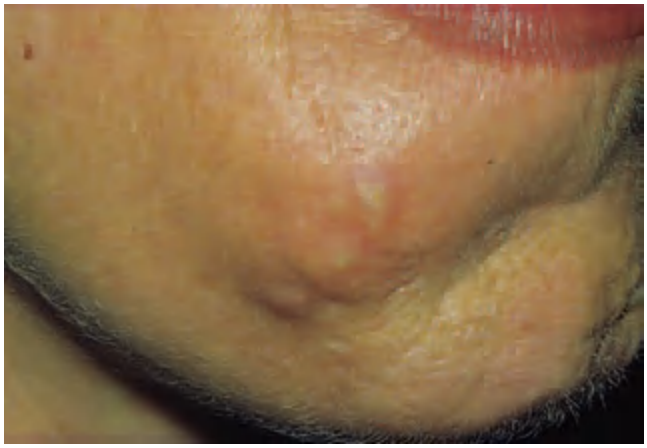

Fig. 43.21 This patient had submarine comedones requiring stretching the skin in order for them to be detected.

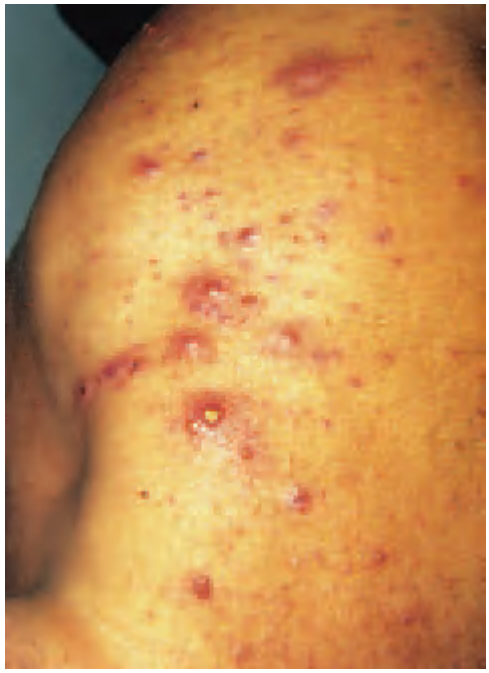

Fig. 43.22 Multiple superficial papules.

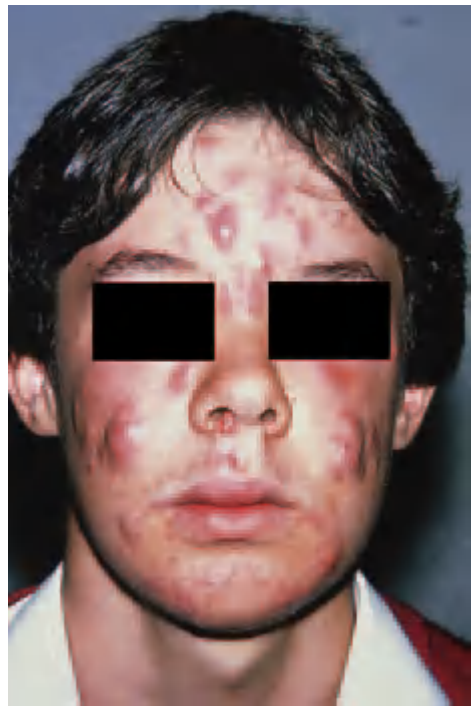

Fig. 43.23 Deep inflammatory nodules.

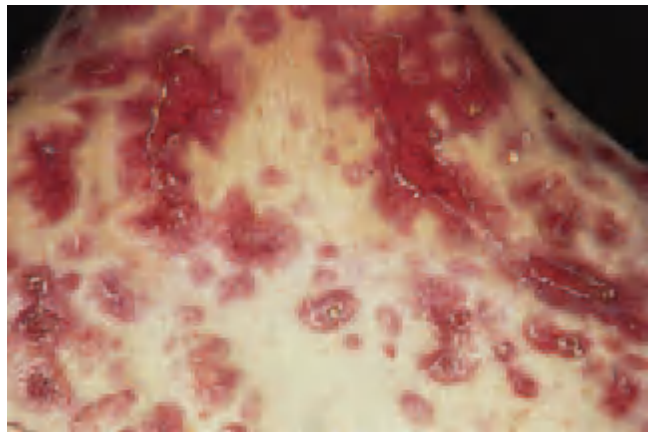

Fig. 43.24 Exudating haemorrhagic lesions.

pustules and leads to devastating cosmetic effects and scarring [9,10]. These lesions can be very tender and are very chronic and resistant to treatment. Although such lesions, like other acne lesions, have a relatively slow onset over a few days, sometimes patients acutely develop large nodules within a 24-h period, or an acute exacerbation of their sinus track disease. There is usually no obvious reason for this flare up, but eruptive and severe inflammatory acne has been reported to be precipitated by glandular fever [11]. Itching is a rare symptom of acne, but may be seen earlier on in therapy, and is possibly due to the release of histamine-like compounds from *P. acnes* [12]. Pyogenic granulomas develop very infrequently [13,14], and occur predominantly in patients with very severe disease of the trunk. They can also be precipitated during the early phase of treatment with oral isotretinoin. Nodules, including haemorrhagic nodules, are also a feature of acne conglobata, which is characterized by extensive acne and is found particularly on the trunk. There are many grouped polyporous comedones, which are frequently inflamed and develop scarring. Acne conglobata is characteristically a chronic disorder, and may last up to 40–50 years of age.

Inflammatory macules are often not recognized as a physical sign of acne; these represent regressing lesions that may persist for many weeks and contribute markedly

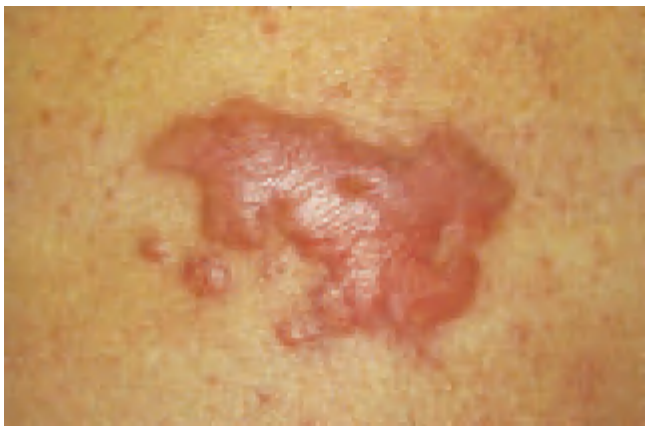

Fig. 43.25 Post-acne keloid scar.

to the general inflammatory appearance [5]. Although the classification of lesions may be helpful in choosing the appropriate management, it must not be forgotten that inflammatory lesions frequently may change from one type to another.

Scarring usually follows deep inflammatory lesions,but may often happen after superficial lesions in scar-prone patients [15]. Close inspection of acne skin under a bright light can reveal some scarring in up to 90% of patients who attend a dermatologist [16], but significant (socially noticeable) scarring occurs in about 22% of sufferers. Scars may show increased collagen (hypertrophic scars and keloids) or be associated with loss of collagen (i.e. ice-pick scars, depressed fibrotic scars, atrophic macules and perifollicular elastolysis). Keloids (Fig. 43.25) are the least common, and are most prevalent on the trunk. Technically, hypertrophic scars do not extend beyond the extent of the original inflammation, but keloids do. Some scars are difficult to classify in their earlier phases of development and should be classified as intermediate scars; with time they may then become more obviously hypertrophic or keloid scars, or perhaps in some instances become atrophic and hardly noticeable. Atrophic macular scars are frequently multiple, and normally retain a purple colour for many months before becoming white and less conspicuous (Fig. 43.26). Ice-pick scars are self-explanatory; they are small jagged atrophic scars 1–2 mm in size—including depth. They often exceed 50 in number, and are most evident on the cheeks. A common type of scarring on the back and chest consists of relatively inconspicuous small, follicular, macular and almost, but not quite, atrophic lesions—so-called perifollicular elastolysis [16]. This sign may be seen occasionally in subjects who have no clinical evidence of acne. The natural genesis of scars is not known and is a subject that should be investigated.

Calcification is a rare complication of scarring [17,18]. Persistent post-inflammatory hyperpigmentation is a

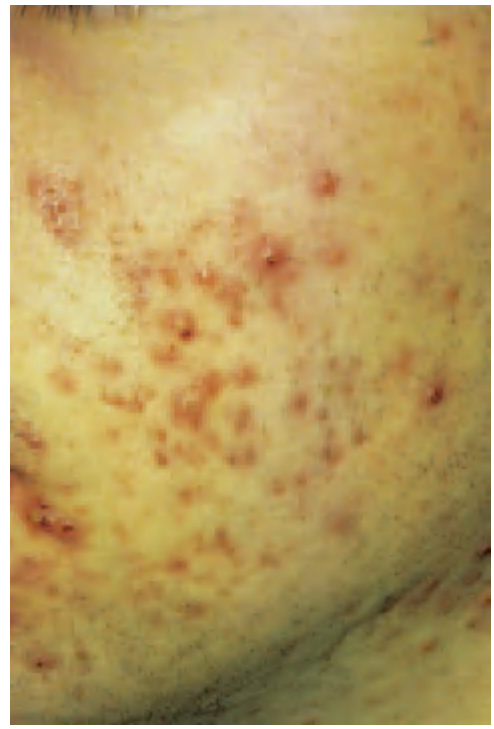

Fig. 43.26 Vascular atrophic macular scars.

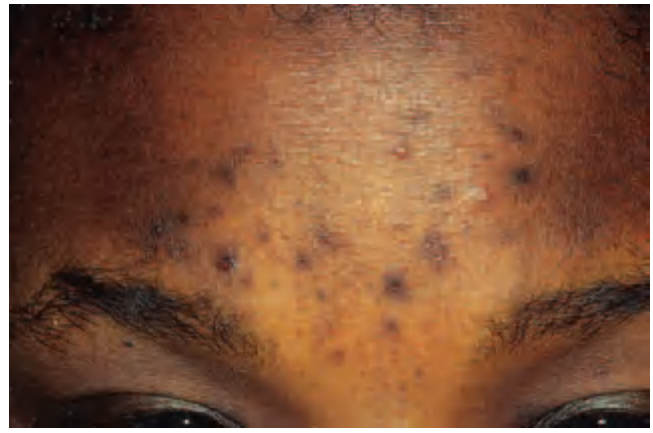

Fig. 43.27 Post-inflammatory hyperpigmentation.

common feature of pigmented skin and may be more disabling than the original disease (Fig. 43.27).

Associated features. Certain diseases that occlude the follicular pores, for example hidradenitis suppurativa [19] and dissecting folliculitis (perifolliculitis capitis abscedens et suffodiens) [20] of the scalp may accompany acne, and are classified as the follicular occlusion triad when accompanied by acne conglobata. All conditions have in common a deep, recurrent, chronic folliculitis that results in abscess formation, sinus track formation and scarring. These diseases are discussed later in this chapter.

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Physiological and environmental factors that influence acne

There are many myths about factors that might help or aggravate acne.

Diet

A wealth of folklore has blamed acne on certain foods, in particular chocolate and pork fat, but scientific proof is lacking. Chocolate, for example, appears to have no significant influence [1–3]; severe dietary restriction resulting in marked weight loss reduces seborrhoea, but cannot be considered as routine treatment [4]. Acne occurs less frequently in Zambia, Nigeria and Japan [5], where diets differ markedly from those in Western Europe, but the lower incidence could be due to other environmental or genetic factors. A detailed epidemiological study of Kitavan islanders of Papua New Guinea and Aché hunter-gatherers of Paraguay failed to find a single male or female with significant acne [6]. The authors proposed that the absence of acne was due to dietary factors, but these are closed communities in which genetic factors must be important. These authors suggest that the diet in the Western civilization has a high glycaemic index, which in turn can trigger insulin and insulin-like growth factor that influence androgens and retinoids. This could thereby induce seborrhoea, comedones and acne. The possible effect of nutrition on the age of puberty may be relevant, as acne is more likely after the start of sexual development, and this occurs when the body weight attains about 48 kg [7]. The trend of increased weight among children and earlier puberty may be reflected in early clinical acne [8]. A personal study of 100 acne patients found no link between acne severity, caloric intake, carbohydrates, lipids, proteins, minerals, amino acids or vitamins.

Premenstrual flare

About 70% of women complain of a flare 2–7 days premenstrually [7,8]. It is unlikely that any possible variation in sebum excretion during the menstrual cycle [9] could be substantial enough to explain the flare. Possibly it is related to a premenstrual change in the hydration of the pilosebaceous epithelium [10]. Progesterone and oestrogen also have both pro- and anti-inflammatory effects [11]. Up-regulation of aspects of the inflammatory response would make some teleological sense at this vulnerable time.

Sweating

Up to 15% of acne patients notice that sweating causes a deterioration in their acne, especially if they live or work in a hot humid environment; for example, for a cook, ductal hydration may be the responsible factor [12].

Ultraviolet radiation

Patients and doctors alike accept that natural sunlight often improves acne, but there is no scientific evidence for this belief. The cosmetic effect of tanning may be the entire explanation. Artificial UV radiation appears to be less satisfactory than natural radiation, and psoralen and UVA (PUVA) have been reported to very uncommonly induce acne lesions [13]. Furthermore, UV radiation may enhance the comedogenicity of sebum [14,15]. Recently several new light therapies for acne have been investigated and these are discussed later.

Occupation

Hydration of the ductal stratum corneum may induce acne in such occupations as catering and steam cleaning. Patients dealing with oil may develop an acneiform oil folliculitis, particularly on their trunks and limbs, but

usually need their overalls to be very heavily contaminated. The induction of chloracne by accidental release of halogenated hydrocarbons or other chemicals is discussed elsewhere in this chapter.

Smoking and acne

One study has shown a linear relationship between acne prevalence and the number of cigarettes smoked daily [16].

Psychosocial effects of acne

Data from the older literature suggests that it is unlikely that stress alone induces the formation *de novo* of acne lesions [17,18]. A recent paper, however, in which acne grade was assessed before and during exams would suggest that stress can induce acne [19]. In addition, acne itself induces stress, and the 'picking' of the spots will aggravate the appearance [19]. This is particularly obvious in young females who present with acne excoriée [20]. Questionnaire studies have shown that many acne patients experience shame (70%), embarrassment and anxiety (63%), lack of confidence (67%), impaired social contact (57%) and a significant problem with unemployment [21,22]. Severe acne may be related to increased anger and anxiety [23].

Appearance is an important factor in social and emotional functioning. When people first meet each other, it will often be their appearance and mostly their face, which draws attention. From psychosocial research it is known that physically attractive strangers attributed more positive qualities such as friendliness, intelligence and higher social skill levels to each other than were attributed by physically unattractive strangers. This effect is strongly reinforced through television commercials and advertisements, in which flawless facial skin is the only model that guarantees social success.

There has been a renewal of interest in the psychological effects of acne and other skin diseases over the past 10 years. Several groups have developed simple questionnaires to better understand the impact of acne in inducing anxiety, depression and impaired quality of life. These questionnaires can be very helpful in the clinic; they take only a few minutes for the patient to complete and can help the physician to quantify the psychological and social effects of the disease [24–26], and allow an appreciation of the overall response to therapy [27,28]. In most research, a combination of generic and dermatology-specific questionnaires have been used [29–39] to assess the effect of facial disease on the psychosocial behaviour of the patient and the modulating effects of treatments. General health measures that have been used to assess a variety of diseases include the Short-Form 36 (SF-36) and the General Health Questionnaire (GHQ). These tools allow comparison between skin diseases and a spectrum of other diseases. Questionnaires that relate specifically to acne include the Cardiff Acne Disability Index (CADI) and the Assessment of the Psychosocial Effects of Acne (APSEA) from Leeds and the Acne Quality of Life Scale (Acne-QoL) [28,33,34,36,37,39]. Comparisons with other chronic illnesses have shown that acne patients have levels of social, psychological and emotional disability that are similar to those reported by patients with 'more serious' diseases such as asthma, epilepsy, diabetes or arthritis. Acne also affects patients' functional abilities. Patients are also prone to embarrassment and social withdrawal, depression, anxiety and anger. In addition, younger acne patients are subject to bullying, teasing and stigmatization from their peers. There are still widely held beliefs in some communities that acne is a penalty for 'impure' thoughts or deeds.

We consider the use of quality of life and psychosocial questionnaires essential to adequately understanding just how the disease is affecting the patient, and to better understand the progress of the disease. For example, Newton *et al.* [40] demonstrated in 111 patients that treatment with oral isotretinoin or combined oral and topical antibiotics subsequently improved quality of life. Similarly, Kellett and Gawkrodger demonstrated significant psychological and emotional effects of acne which improved with oral isotretinoin [41].

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Differential diagnosis

Acne is rarely misdiagnosed. The commonest mistaken diagnosis is rosacea, which occurs in older patients and lacks comedones, nodules, cysts or scarring. Occasionally, patients may have both rosacea and acne (Fig. 43.28). The presence of facial flushing that is induced by heat, hot food or alcohol is a useful pointer towards a diagnosis of rosacea. Rosacea patients may also have ocular involvement, but rarely have truncal lesions. In females, confusion with perioral eczema is possible, but in these patients the lesions itch, the skin is dry and there are no comedones. Whiteheads (closed comedones) may be confused with milia. Milia are predominantly infraorbital in distribution and are whiter. They are very common and can occur in association with, although unrelated to, acne. Acneiform drug eruptions are discussed in this chapter and in Chapter 73. Folliculitis due to Gram-negative organisms can complicate acne therapy [1], and the rare folliculitis due to *Candida* may also present as multiple pustular eruptions, as may *S. epidermidis* folliculitis. Demodex folliculitis can present as non-responsive acne. It is difficult to diagnose since many people have this mite in their normal pilosebaceous follicles. The best diagnostic help is the therapeutic response to metronidazole or topical permethrin. Localized pustular eruptions may be due to animal ringworm, and some infections with zoopilic fungi may result in kerion formation. Rarely, dermatitis herpetiformis may present as a vesicular pustular facial eruption, but it is very itchy. Linear IgA disease can also present very uncommonly as a papular facial rash without comedones. Biopsy, including immunofluorescence studies, is essential to confirm this particular diagnosis. *Pityrosporum* folliculitis presents on the upper trunk as moderately ill-defined superficial plaques, among which

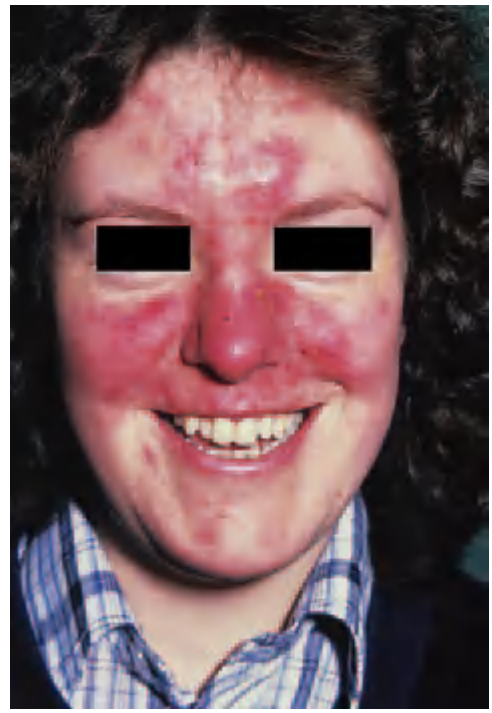

Fig. 43.28 A patient who, having had acne vulgaris since the age of 14 years which never resolved, developed at the age of 35 years obvious rosacea.

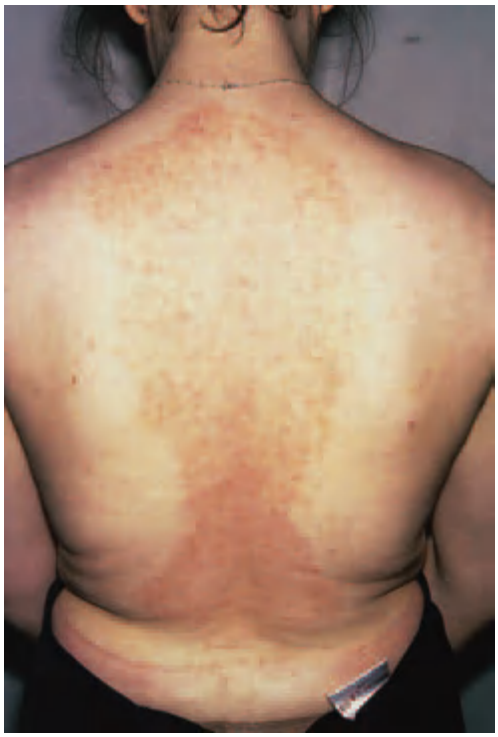

Fig. 43.29 Typical distribution of *Pityrosporum* folliculitis.

are scattered many papules or pustules (Fig. 43.29). It is likely, but unproven, to be a host reaction to *M. furfur*, which is a normal skin commensal [2,3]. *Pityrosporum* folliculitis does not usually respond well to isotretinoin [4], and response to topical imidazoles is often poor. Plane warts, particularly on the face, can also cause confusion, as can pseudofolliculitis barbae. Rare diseases that may produce difficulties include acne agminata (granulomatous rosacea) and tuberous sclerosis. Acne agminata presents as a facial rash in the acne age group. The lesions are light brown in colour (somewhat darker in black skin) and on diascopy may reveal an apple jelly colour [5]. Tuberous sclerosis lesions are relatively monomorphic papules, often with a brownish appearance. A micropapular, sarcoidal facial eruption has been reported to be due to the selective perifollicular absorption of oils present in certain bubble gums [6]. The severe papulo-pustular eruption associated with zinc deficiency can be mistaken for marked acne, and several cases have been reported after prolonged intravenous feeding without zinc supplementation [7]. Acne necrotica (varioliformis) is associated with itching and smallpox-like scars, usually on the trunk. Biopsy shows a necrotizing lymphocytic folliculitis [8]. It can be mistaken for severe acne excoriée, but the response to isotretinoin can be excellent [9]. Behçet's disease may produce an acneiform eruption. A dental sinus can be confused with a persistent facial acne nodule (Fig. 43.30). Epidermoid cysts may become inflamed and be mistaken

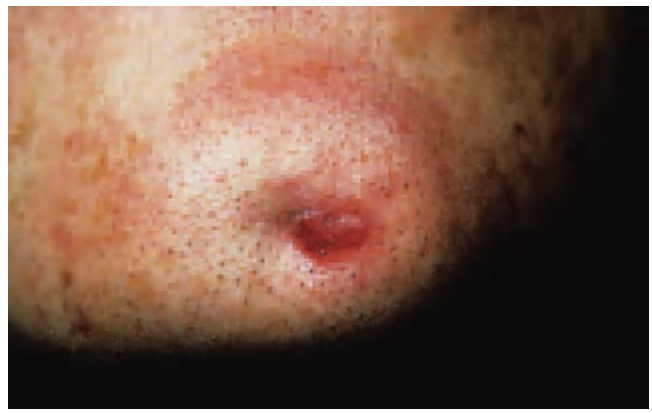

Fig. 43.30 A persistent 'acne nodule' due to a dental sinus.

for acne nodules. Of course, acne may coexist alongside one of these alternative diagnoses.

Acne scarring can mimic scarring due to hydroa vacciniforme, ulerytherma ophryogenes, acne keloidalis [10,11], varioliform atrophy and porphyria cutanea tarda.

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Treatment

General principles of acne treatment

The management of acne starts with education. Treatment procedures involve detailed patient discussion, acne assessment and appropriate prescribing based on the history, acne severity, lesion type, psychological effects of the disease and cause of the disease [1–3]. The cause of the acne should be discussed, as should the goals and outcome (including patient expectations) of therapy. Patient leaflets are essential. The patient should be told that in

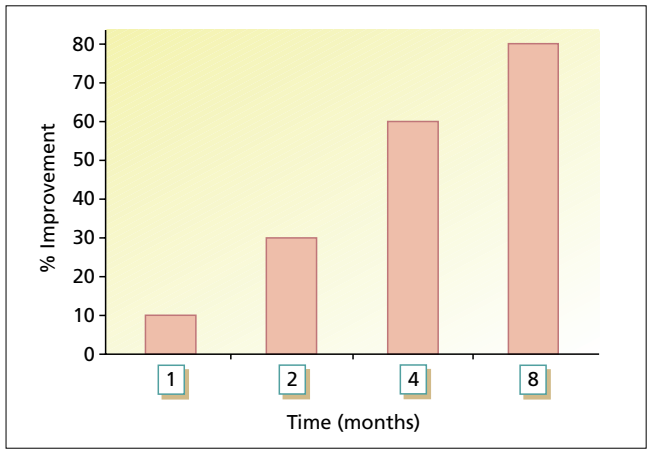

Fig. 43.31 The anticipated rate of improvement with therapy other than oral isotretinoin in the absence of significant clinically resistant *Propionibacterium acnes*.

mild cases the acne will persist for 4–6 years, but in severe cases the natural history could be in excess of 12 years. The patient, however, should be informed that, if the acne does not respond well to a reasonable trial of oral antibiotics and appropriate topical therapy, oral isotretinoin would probably be prescribed. Such therapy is an almost guaranteed success [4]. However, because of cost, teratogenicity and other side effects of isotretinoin, many patients will appropriately receive a variety of alternative oral and topical treatments. For 35 years these have been the standard therapy. Appropriate patient expectations for these treatments would be little improvement after 1 month of therapy, 20% improvement at 2 months, 60% at 6 months and 80% at 8 months (Fig. 43.31).

Acne grading

Grading is very useful in the assessment of acne in the clinic. A grading scale similar to that shown in Figs 43.32–43.35 is recommended. A good light and palpation, as well as inspection, are required [5]. The acne can be graded on a 0–10 scale on the face, back and chest. Little practice is required to become reasonably efficient, and it does not matter if the grading scale used is somewhat different from the published techniques, so long as the observer is consistent. Lesion counts are essential for clinical trials but not for use in the day-to-day clinic [6].

Choice of therapy

This is largely determined by the severity and extent of the disease but should be tempered by patient choice and cost. Patients with mild acne usually receive topical therapy alone; patients with moderate acne receive oral and topical therapies; patients with severe acne should immediately receive oral isotretinoin unless contraindicated.

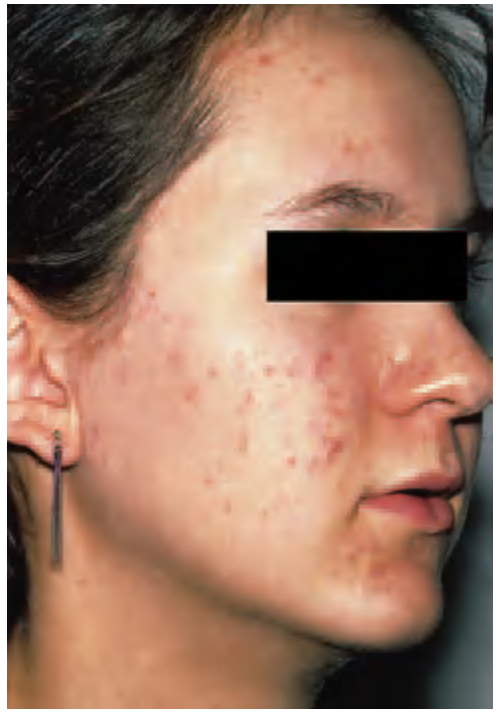

Fig. 43.32 Mild acne.

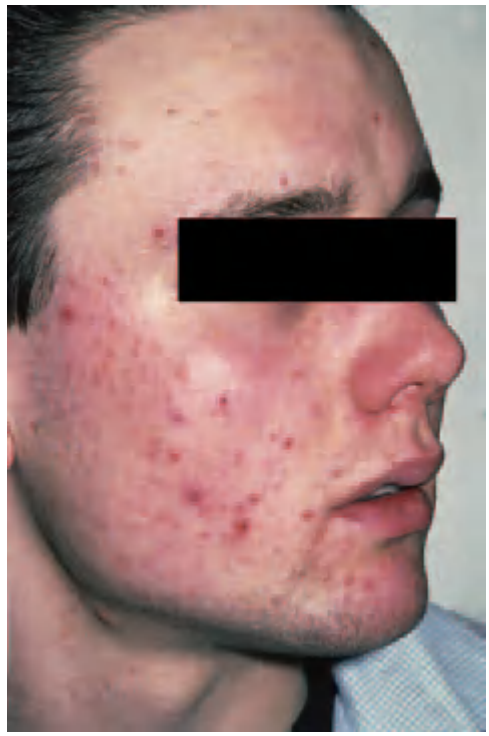

Fig. 43.33 Mild to moderate acne.

The severity assessment should include not just the extent of the inflammatory and comedonal lesions, but also the presence of scarring, the psychological effects of the disease, and the degree of success or failure with previous

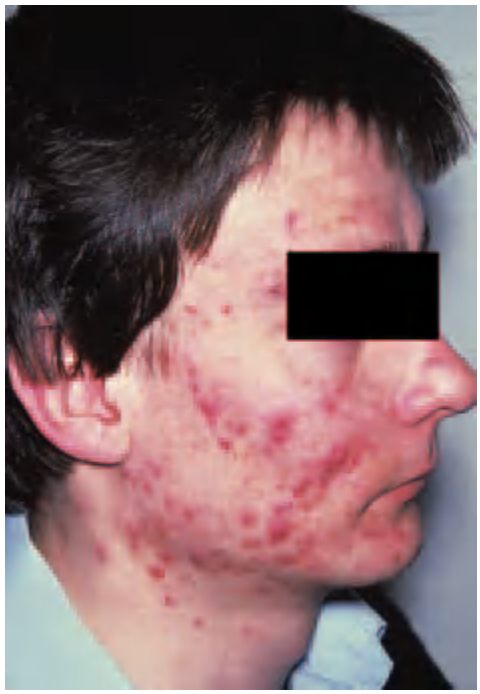

Fig. 43.34 Moderate acne.

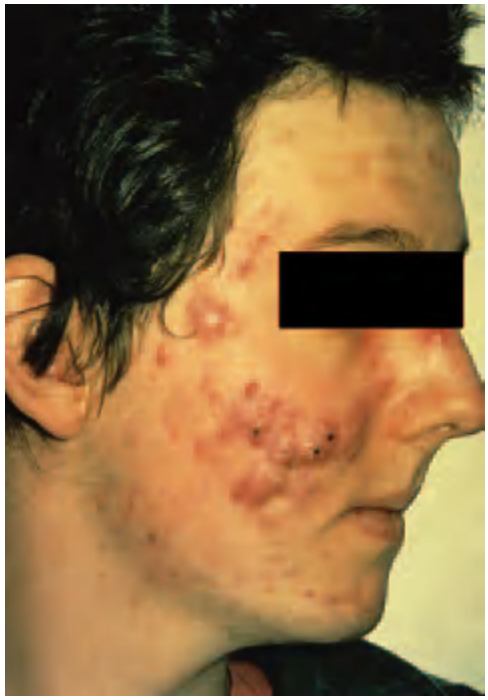

Fig. 43.35 Severe acne.

treatment. A family history of persistent acne may also influence the choice of therapy.

The choice of treatment should also be based on a logical understanding as to how the treatments influence the aetiology of acne.

Table 43.2 Choice of topical treatment.

Predominantly anticomedonal
Adapalene
All-*trans*-retinoic acid (tretinoin)
Azaleic acid
Isotretinoin
Predominantly antimicrobial
Azaleic acid
Benzamycin® (benzoyl peroxide/erythromycin)
Benzoyl peroxide
Clindamycin
Duac® (benzoyl peroxide/clindamycin)
Erythromycin
Tetracycline
Zineryt® (erythromycin/zinc)
Predominantly anti-inflammatory
Adapalene
Nicotinamide
Topical antibiotics

Topical treatment (Table 43.2)

The most widely used topical drugs are benzoyl peroxide, retinoids, antibiotics and azaleic acid, either as monotherapy or in combinations [7–9]. Patients with predominantly inflamed lesions should receive topical benzoyl peroxide, antibiotics or azaleic acid. However, because of the central role of the microcomedone, a topical retinoid should probably be added for most patients [1,8,9].

Benzoyl peroxide is supplied in concentrations of 2.5%, 5% and 10%, either alone or in combination with imidazole, hydroxyquinolone, glycolic acid or zinc lactate [10–14]. Despite the wide range of concentrations of benzoyl peroxide in gels, creams or washes there are few dose–response studies. The value of some combined therapy is uncertain, although a miconazole (2%)/benzoyl peroxide (5%) combination may be marginally better than benzoyl peroxide alone [14]. Fixed combinations of benzoyl peroxide with topical antibiotics are clinically superior to the antibiotic alone [15].

Topical antibiotics include tetracycline, erythromycin and clindamycin [16–21]. They are used in concentrations of 1–4%, usually in a cream or lotion base. Topical tetracycline is probably the least effective topical antibiotic and may fluoresce under UV light. Combinations of antibiotics with zinc or benzoyl peroxide are superior to single therapies [20–23]. Clinical experience with azaleic acid has not delivered the improvement suggested by the original clinical trials [9,24,25].

Patients with predominantly non-inflamed lesions should have topical retinoids as the first choice. Most topical retinoids are very similar in their clinical benefit. The major difference lies in the increased tolerability with the more recently (within the last 10 years) developed formulations. Retinoic acid (vitamin A acid) is available in 0.01–0.05% concentrations as either a gel or a cream

[26–30]. Recently, new formulations have been developed: the so-called microsponge or polymer formulations [27–29]. The newer formulations are less irritant than the original formulation. Isotretinoin is a second-generation retinoid; a 0.05% topical formulation [31–32] similar in efficacy to benzoyl peroxide [31] and topical tretinoin [32]. A third-generation retinoid, adapalene, has a greater benefit/risk ratio than tretinoin [33–37]. In the USA and a few other countries, there is a fourth-generation retinoid on prescription for acne called tazarotene [38,39]. Adapalene has a significant anti-inflammatory action in the first few days of therapy [40]. Patients with mixed lesions should be prescribed anticomedonal therapy at night and anti-inflammatory therapy in the morning. Even patients with predominantly inflammatory acne should be prescribed a topical retinoid as part of their regime, given the fact that a microcomedone or comedone is a central and early feature of most inflammatory lesions [9]. Topical therapy should be prescribed alone for mild acne, in conjunction with appropriate oral acne therapy for moderate acne, and as maintenance therapy after oral therapy has stopped.

In many acne patients topical therapy may be necessary for many years. It is also important to stress to the patient that topical therapy must, if appropriate, be applied to the trunk, as well as to the face. It is necessary to apply the topical therapy not just to the spots but also to the whole of the site prone to acne. The reason for this relates to the observation that the apparently normal skin adjacent to acne lesions is likely to have many early microscopic lesions, in particular microcomedones. The concept of spot prevention must be stressed to the patient.

Mechanisms of action

Benzoyl peroxide is primarily antimicrobial [11,41] and rapidly reduces both surface and ductal *P. acnes* [41]. It also reduces the number of non-inflamed lesions, and is anti-inflammatory [11], but it is unlikely that it significantly affects sebum production [42,43]. Vitamin A acid and other retinoids act by removing non-inflamed lesions, making the microenvironment less favourable for the development of inflammation [9,44]. Tretinoin binds to cytosolic retinoid acid-binding protein (RAR) with high affinity, but adapalene does not bind at all [45]. Tretinoin has high affinity for all nuclear receptors, but adapalene has selective affinity for RAR-β and RAR-α [45]. Some of the actions are receptor modulated. Adapalene also has anti-inflammatory actions, notably against leukotriene [46]. It, like tretinoin, reduces, *in vitro*, the functions of toll receptors (type 2) that are involved in the production of pro-inflammatory cytokines. Topical antibiotics have some effect on the non-inflamed lesions by reducing perifollicular lymphocytes which are involved in comedogenesis [1,9,]. They also significantly reduce numbers and function of *P. acnes* [47–49]. Some topical antibiotics also have a direct anti-inflammatory action; for example, erythromycin in a benzoyl peroxide/erythromycin combination (but not benzoyl peroxide alone) had an antioxidant effect on leukocytes [50]. Azaleic acid (1 : 2 heptanedicarboxylic acid) is not sebosuppressive; it has been reported to reduce the numbers and function of *P. acnes* [51,52], but recent studies have thrown doubt on this observation. Azaleic acid reduces comedones by normalizing the disturbed terminal differentiation of keratinocytes in the follicle infundibulum [53].

A detailed analysis of 144 clinical trials of topical antimicrobial therapy rejected over 50% because of poor trial design [54]. Adequate conclusions could not be drawn from the remaining data because of the different protocols, but benzoyl peroxide emerged as a successful treatment and was probably similar in effectiveness to topical erythromycin and clindamycin, with topical tetracycline less effective. The clinical benefit of topical erythromycin can be improved by combining it with either zinc or benzoyl peroxide [20–23,55–57]. Comparative studies between topical and oral antibiotics were often biased, due to the use of less oral antibiotic than is currently recommended. The general clinical impression is that topical therapy appears less effective than oral treatment, providing the correct oral dose is prescribed. However, a large randomized controlled trial in a primary care (general practitioner) setting showed that topical Benzamycin® and its components given separately (erythromycin and 5% benzoyl peroxide) were more effective than oral tetracycline and minocycline [58].

There has been an alarming increase in worldwide resistance of *P. acnes* to antibiotics [59–62]. There is evidence to show some correlation between *P. acnes* resistance and clinical failure, and this is in part explained by variation in comedonal levels of antibiotic after topical application [63]. It is important to note that, should a strain of *P. acnes* be reported microbiologically resistant, it does not necessarily mean that the acne will be clinically resistant to such therapy. If the concentration of the same antibiotic at the relevant skin site is equal to or greater than the minimal inhibitory concentration (MIC) of that same *P. acnes* strain, the patient will be clinically responsive. Many antibiotics with anti-acne properties have additional non-antimicrobial anti-inflammatory mechanisms of action [64], which may partly offset problems with antibiotic resistance.

Up to 61% of patients referred to special acne clinics in Leeds, UK, had resistant *P. acnes* [60,65]. Resistance is most frequently seen to erythromycin and clindamycin, less so to tetracycline and doxycycline (Fig. 43.36). Multiple resistances are seen in 18% of patients. Resistance to minocycline is rare (1%). In 2002, as a consequence of a change in antibiotic prescribing policies, the levels of resistance had fallen to 56% from 61% [66]. There were

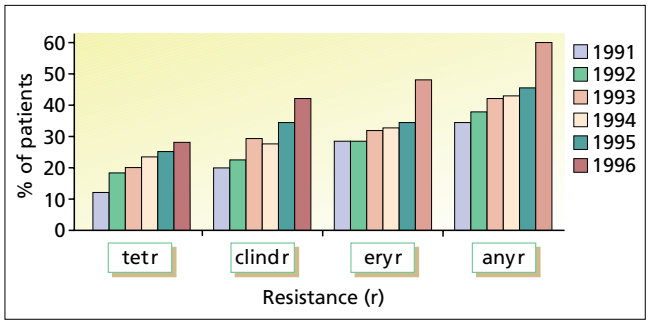

Fig. 43.36 Increase in the prevalence of resistant *Propionibacterium acnes* in Leeds, UK. Note the resistance of *P. acnes* to several antibiotics. r, resistance; tet, tetracycline; clind, clindamycin; ery, erythromycin.

also significantly greater numbers of resistant *P. acnes* on the skin of close contacts of acne patients who use antibiotics compared with controls [67]. Given the fact that the resistance is due to a mutant gene [68], it is likely that *P. acnes* resistance is going to last for many years. Benzoyl peroxide alone significantly reduces *P. acnes* resistance [69]. The combination of topical benzoyl peroxide with oral antibiotics and a topical combination of erythromycin and benzoyl peroxide are associated with the least resistance both *in vitro* and *in vivo* [69]. Physicians should also avoid prescribing dissimilar oral and topical antibiotics. Other topical treatments such as azaleic acid and topical retinoids are not antibiotics, and are therefore not associated with resistance.

Topical nicotinamide 4% also does not induce *P. acnes* resistance. Nicotinamide has anti-inflammatory actions [70]. Double-blind studies have shown it to be better than the vehicle alone against inflamed lesions, although the improvement with the placebo was considerable (32–76%) [71]. A comparison of 4% nicotinamide gel demonstrated it to be similar in efficiency to 1% clindamycin gel [72].

The efficacy of other topical treatments has not been established by controlled studies. Sulphur is a long-standing anti-acne therapy, which may be both comedogenic and comedolytic [73–75]. Sulphur is unpopular because of its smell, and is rarely used. Salicylic acid in several formulations is probably useful [76], but the many formulations of resorcin appear to be totally ineffective [77]. A few topical preparations contain weak corticosteroids but proof of their efficacy is lacking. However, potent steroids such as clobetasol propionate (Dermovate®) applied twice a day for 5 days can dramatically reduce the inflammation of a severely inflamed nodule [78]. There have been clinical data published on the potential value of traditional 'herbal' medicines from the eastern hemisphere. So far the clinical benefits of certain plant alkaloids have not been established [79]. It is very important that all new treatments are validated for safety and efficacy against standard medicines before their release to patients.

In conclusion, topical therapies, alone or in combination, should be used for patients with mild inflammatory acne. Retinoids should be the first choice for treatment of comedonal acne. In mild inflammatory acne a topical retinoid should be used in the evening and an anti-inflammatory agent in the morning [9]. Topical therapies, especially retinoids, should also be used in conjunction with oral antibiotics in patients with moderate and severe acne [1,9,80], and as maintenance treatment after cessation of oral therapy [1,9].

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Oral therapy

Oral treatments for acne include antibiotics, hormones, isotretinoin and, occasionally, steroids [1]. Other drugs such as dapsone [2], clofazimine, and vitamin A acid (10–20 mg/day) [3] are very occasionally used; there is very little evidence for their effectiveness. Oral zinc is discussed later on in this section.

Oral antibiotics are the most widely prescribed oral therapy worldwide. Tetracyclines (tetracycline, oxytetracycline, doxycycline, lymecycline, minocycline and azithromycin) are the antibiotics of choice [4–11], but erythromycin is preferable in the female who is, or might, become pregnant or is breastfeeding [12]. Trimethoprim (400–600 mg/day), which is similar in efficacy to tetracycline [13], can be reserved as a third-line antibiotic [14]. Oral clindamycin, most helpful because of its lipid solubility, should not be used routinely because of the possible risk of pseudomembranous colitis [15].

Not all patients respond in the same way; it is clear that young males with marked seborrhoea and truncal acne respond less well than females with purely facial acne [10]. Patients who require antibiotics should be given 1 g/day of tetracycline or erythromycin in appropriately divided doses [16]. The major disadvantage of tetracycline (and less so of erythromycin) is the need to take the tablet with water (not milk) half an hour before food: otherwise there is reduced absorption [17]. Thus, daily doxycycline (100 mg/day) or lymecycline (408 mg/day) or the more expensive minocycline (100 mg/day), which are better absorbed, may enhance patient compliance. Recent data, however, have also shown that the absorption of minocycline is reduced by food [18]. In the Western world, minocycline is very extensively used but it should not be the first-line treatment. A large randomized controlled trial in primary care practice in the UK demonstrated that oral minocycline and oral tetracycline were of similar efficacy, and so given the cost and the increased side effect potential of oral minocycline, minocycline should not be the first choice of oral antibiotic therapy in acne [19]. Indeed, the same study showed that topical therapies such as benzoyl peroxide and combined topical benzoyl peroxide and erythromycin were of similar efficacy. However, this study did not include a topical retinoid nor combined oral and topical therapy.

Oral therapy should be given in combination with topical therapy for a minimum of 6 months [16]. There should be 20% improvement by 2 months, 60% by 4 months and 80% by 6 months. With 1 g/day, relapse is less likely than with smaller doses [16,20]. However, if there is no improvement after 2–3 months, then alternative therapy is necessary. In patients with non-responding disease, minocycline (100 mg) is more effective than tetracycline [21]. Limited dose–response studies have shown that doubling the dose of minocycline to 200 mg/day is more effective than continuing on an average dose of 100 mg where acne has not responded [21]. Daily doses of doxycycline (100 mg), minocycline (100 mg) and lymecycline (408 mg) are equally effective, provided *P. acnes* is not resistant to doxycycline and lymecycline [22–25]. Sixty per cent of patients who attended an acne clinic in Leeds, UK, were found to harbour resistant *P. acnes*. Within this subgroup, 20% had *P. acnes* resistant to tetracycline and doxycycline [26]. When acne recurs it is safe to prescribe repeated courses of the same antibiotics if the previous course was successful.

Oral treatment will be required in the following groups of patients: those with moderate and moderate/severe acne; patients who are significantly depressed, even if the acne is physically mild; patients with body dysmorphic disorder; and patients with scarring or who are prone to scarring. Patients who are likely to develop post-inflammatory pigmentation should also receive oral therapy sooner rather than later, since such pigmentation is usually very persistent and very difficult to treat. Patients with acne fulminans and patients with Gram-negative folliculitis may also benefit from oral antibiotics. However, in the latter two groups, oral isotretinoin is the preferred treatment. If isotretinoin is not available, trimethoprim is the preferred antibiotic for Gram-negative folliculitis.

There is very little scientific information to guide physicians about the precise duration needed for optimum oral antibiotic therapy, whether or not combined with topical therapy. Likewise, there are very few data on the rate of relapse on stopping oral therapy even if adequate topical therapy is continued, as it should be. Available data definitely supports the use of combined oral antibiotics with topical therapies—especially a topical retinoid [27]. There are several potential mechanisms of action for oral antibiotics; obviously they have antibacterial activity, but they also have direct effects in reducing inflammation [27–34]. Tetracycline and erythromycin are bacteriostatic, especially in larger doses. In smaller doses (500 mg/day or less), oral antibiotics do not reduce the number of organisms, but they do affect their function. The antibiotics can also inhibit various enzyme activities and modulate chemotaxis, lymphocyte function and pro-inflammatory cytokines, in particular IL-1-α expression [33,34].

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Side effects of topical treatments and oral antibiotics

Topical agents. Many topical preparations produce a mild primary irritant dermatitis (Fig. 43.37) [1,2] and the patient must be warned, so that treatment is not stopped prematurely. Indeed, with some preparations such as benzoyl peroxide and retinoids, the total absence of skin irritation should lead the physician to suspect that the topical therapy is not being used correctly. If a primary irritant reaction occurs, the product should not be used for a few days and the dermatitis should be treated with moisturizers and/or a low potency steroid cream temporarily. Thereafter, the acne preparation can be restarted at a somewhat reduced frequency of application. Some topical therapies have a comparatively lower irritant profile than others. For example, azaleic acid is relatively non-irritant [3]; adapalene is less irritating than tretinoin [4–6];

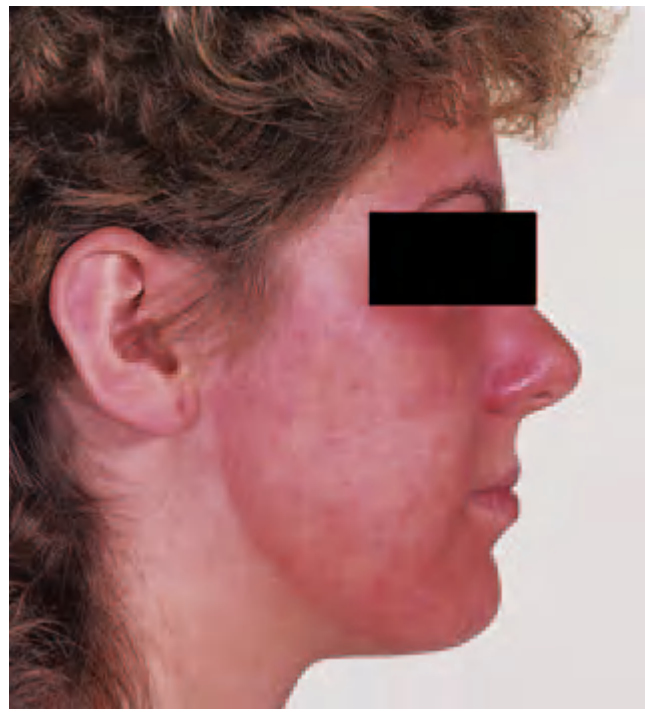

Fig. 43.37 A typical primary irritant dermatitis from topical anti-acne therapy.

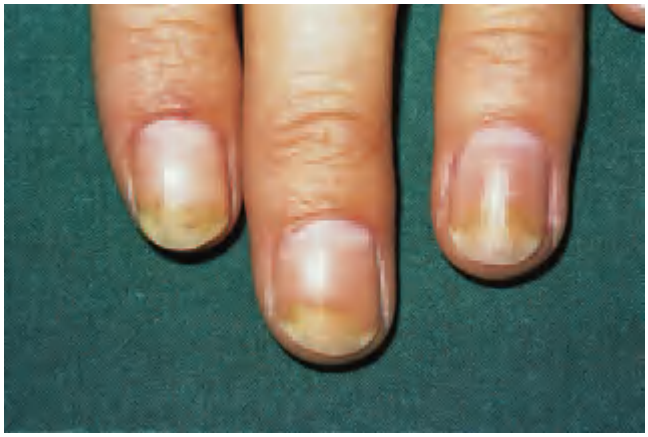

Fig. 43.38 Photo-onycholysis due to doxycycline.

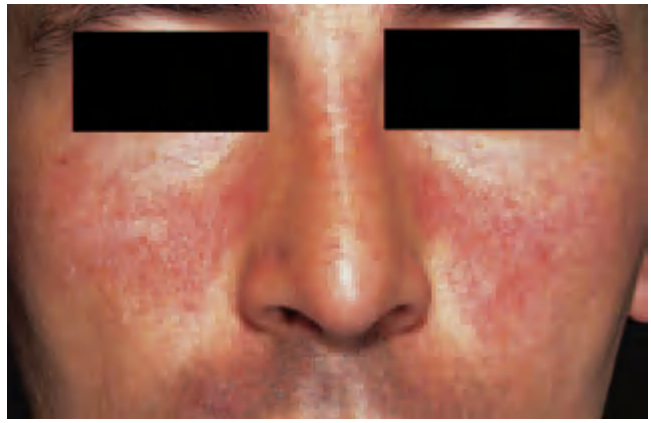

Fig. 43.39 A phototoxic reaction in a patient on doxycycline.

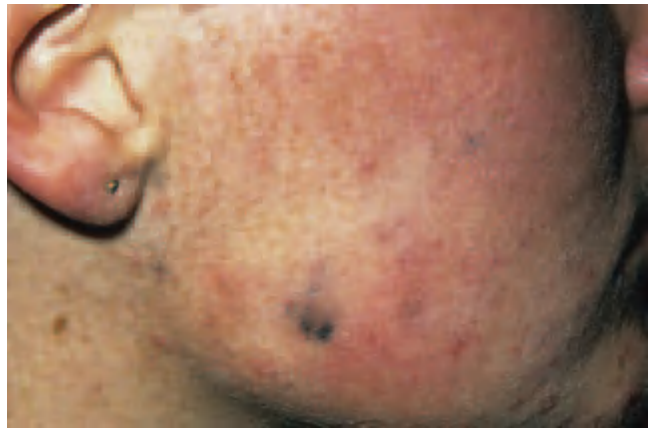

Fig. 43.40 Minocycline pigmentation in acne scars.

the newer formulations of tretinoin (microsponge or polymer based) are less irritating than the early formulations [7–9]. Certain antibiotic/benzoyl peroxide combinations are less irritating than benzoyl peroxide alone [10], which is possibly due to the anti-inflammatory action of the antibiotic. True allergic contact dermatitis is extremely rare with any of the topical anti-acne preparations. From animal studies and much clinical experience there is no evidence to support the claims that benzoyl peroxide and vitamin A acid induce skin carcinomas, and continued use of these two drugs is recommended [11,12]. Benzoyl peroxide bleaches clothes and hair and the patient must be informed of these inconvenient side effects. Significant systemic absorption of topical retinoids does not occur [13,14]. Nevertheless, it is prudent to stop topical retinoid therapy should a female patient become pregnant. The patient should also be told that she should avoid becoming pregnant whilst on topical retinoids.

Oral antibiotics. Oral tetracycline and erythromycin are both relatively safe [15,16]. Gastrointestinal effects, especially colic and diarrhoea, may occur in 5% of patients, but are easily controlled with a combination of diphenoxylate hydrochloride and atropine sulphate (Lomotil®). Vaginal candidiasis occurs in 6% but is rarely a problem; it is important to treat the patient and her partner with appropriate anticandidal therapy. Significant candidiasis can be helped by the prophylactic use of intravaginal clotrimazole cream mid-cycle.

Uncommon complications of oral tetracycline therapy include onycholysis (Fig. 43.38) [17], oesophagitis with ulceration [18], fixed drug eruptions [19] and photosensitivity (Fig. 43.39), including porphyria-like cutaneous changes [20], especially with the longer-acting tetracyclines. Doxycycline causes a phototoxic rash in up to 3% of patients, especially at doses greater than 100 mg/day, when exposed to significant sunshine [21]. Widespread drug eruptions are rare except with trimethoprim, where the incidence is 2.5% [22]. Tetracyclines, especially minocycline, may produce benign intracranial hypertension [23–25], which presents with headache, loss of concentration and sometimes papilloedema, and quickly disappears on stopping therapy. This side effect is dose dependent and the patient should be warned of this potential problem. Minocycline produces a blue-black pigmentation in a dose-dependent way, and in the skin this presents in three forms: pigmentation in inflamed acne lesions, in scars (acne and non-acne) (Figs 43.40 & 43.41) and, more rarely, generalized dark-grey discoloration [25–33]. The pigmentation is due to a melanin–drug complex and lasts for an average of 8–15 months post therapy. It lasts longer in older patients [31]. If therapy is required, local lesions can be treated reasonably successfully with the Q-switched ruby laser [31]. The brown-grey pigmentation due to minocycline may also occur in the nails, oral mucous membranes [33] and sclera [34] (Fig. 43.42). At these sites, the pigmentation tends to last for longer than it does in the skin. When present in the mucous membranes, only a small percentage of affected patients are aware of its presence [35], particularly if the tongue is affected. Even more uncommon but quite dramatic is black breast milk due to minocycline therapy [36,37].

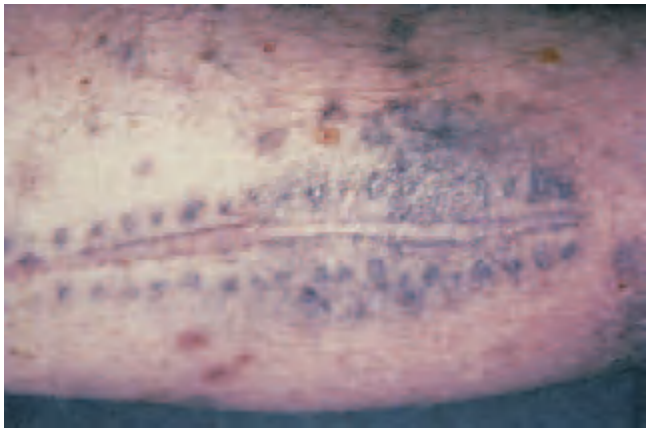

Fig. 43.41 Minocycline pigmentation in non-acne scars.

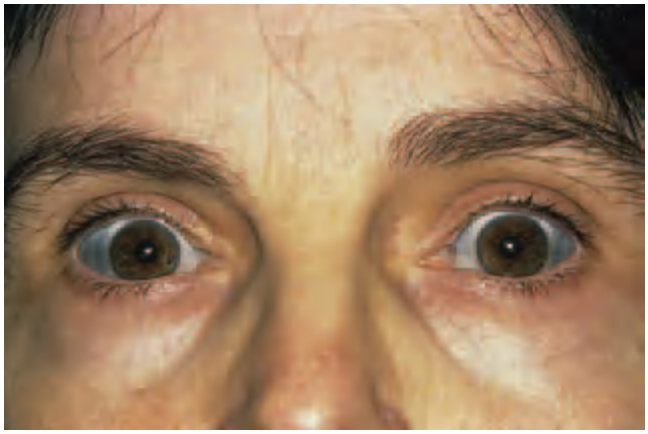

Fig. 43.42 Minocycline pigmentation in the sclera.

Minocycline has been used in a large number of acne patients worldwide. Reports of serious systemic minocycline-induced side effects have prompted much debate [38–42]. The serious side effects are of three types, all of which are relatively uncommon. Hypersensitivity syndrome reactions (including pulmonary eosinophilia) and serum sickness-like reactions occur within 3 months of treatment, and are characterized by fever, malaise and arthralgia, possibly with major organ involvement. The late-reaction pattern occurs much later, usually at about 6–48 months. These patients, predominantly female, present with a symmetrical polyarthritis or polyarthralgia in the small joints. Some of these patients have concomitant liver disease, which may occur in the absence of joint symptoms. A lupus facial rash may also be present, and occasionally lupus rashes occur at the body sites. A liver biopsy if appropriate shows chronic active hepatitis, and serology for lupus is usually positive. Very rarely the liver damage is devastating resulting in death or needing liver transplantation [43]. Thus, minocycline should be avoided in patients with a personal or family history of systemic lupus erythematosus. We recommend that every 3 to 6 months the patient's liver function, antinuclear antibody (ANA) and perinuclear antineutrophil cytoplasmic antibody (pANCA) be checked, even if there are no symptoms, and obviously earlier if necessary. Any patient with any of these iatrogenic side effects should be advised to avoid all classes of tetracycline antibiotics. Pseudomembranous colitis is an exceedingly rare consequence of oral antibiotic therapy, and was a particular problem with long-term oral clindamycin treatment, but oral clindamycin is virtually no longer used in acne therapy.

The clinical significance of a possible interaction between oral antibiotics and the contraceptive pill is unclear. There is a small risk of failure of contraception [44–46]. All sexually active females should be made aware of this problem. Tooth discoloration from tetracycline does not occur in patients treated after the age of 9 years, when the permanent teeth are established. Should therapy be required in pregnancy, oral erythromycin is safe; topical acne therapy has very rarely been implicated as a cause of fetal deformity. In pregnancy, the safest therapies are therefore topical benzoyl peroxide and/or topical erythromycin [47]. The increasing problem of *P. acnes* resistance is discussed above.

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Hormonal treatments

Various oral hormonal regimens have been recommended for reducing sebaceous gland activity. Hormonal treatments are indicated usually when standard antibiotic regimens have failed, when concomitant menstrual control or contraception and acne therapy are required, and when oral isotretinoin is inappropriate or not available. Topical therapy should be prescribed with hormonal regimens.

Table 43.3 Suppressive effects of oral drugs on sebum excretion rate (SER) at 3 months' treatment.

Dianette®*	28%
Dianette®* + 50 mg CPA	42%
Dianette®* + 100 mg CPA	67%
Spironolactone 100 mg	35%
Spironolactone 200 mg	70%
Isotretinoin 0.5–1.0 mg/kg/day	92%

CPA, cyproterone acetate.
* Dianette® is 35 μg ethinyl estradiol +2 mg CPA.

Hormonal regimens include: prednisolone plus oestrogen; oestrogens plus antiandrogens; and spironolactone [1–8]. Low-dose glucocorticosteroids (i.e. 2.5 mg prednisolone on waking and 5 mg on retiring) to suppress adrenal androgens, with or without a contraceptive pill, will reduce sebum production by up to 50% with a concomitant improvement in acne [1]. Cyclical oestrogen (30 μg) with medroxyprogesterone acetate (5 mg for 7 days) is also of benefit [2].

Antiandrogens are a logical approach to the treatment of acne, as they suppress sebum production to an extent that depends on the drug and dose prescribed (Table 43.3) [4–8]. The antiandrogen CPA is prescribable in most European countries, but not in the USA. Clinically effective topical antiandrogens are not available, although it appears possible to reduce sebum production slightly by topical applications [9,10]. Co-cyprindiol (Dianette® and Estelle 35®) is an oral contraceptive that ameliorates acne. It is as effective as 1 g/day of oral tetracycline over a 6-month period, although it is slower in action [11]. It is also of potential benefit in women with acne resistant to other therapies [6]. In males, 25 mg CPA has been used with success, but it reduces libido and produces gynaecomastia and possible azoospermia. In women, the side effects of CPA with oestrogen are different from those of conventional contraceptive pills that contain lower amounts of oestrogen. Recently it has been suggested that, because of the risk of deep venous thrombosis associated with the higher oestrogen content [12], once the acne is brought under control then the co-cyprindiol formulations should be replaced by a birth pill containing a lower dose of oestrogen. Yasmin® (drospirinone 3 mg, ethinyl estradiol 30 mg) is one possibility, and a comparative study [13] has shown that Yasmin® is similar to co-cyprindiol in its efficacy against acne. Another possibility is to prescribe one of the triphasic pills such as Trinordiol® (ethinyl estradiol/levonorgestrel in varying concentrations), which suppresses sebum excretion by 20%. In the past few years, clinical trials have shown the benefit of other oral contra-

ceptives in acne. These include Belara® (30 µg ethinyl estradiol and 2 mg chlormadinone acetate), which has been registered in some European countries for a few years [14]. In the USA, a placebo-controlled clinical trial showed the benefit of a low oestrogen dose oral contraceptive (20 µg of ethinyl estradiol and 100 µg of levonorgestel) [15]. Co-cyprindiol is more likely than the lower dose pills to cause weight gain [5].

For how long CPA (2 mg) combined with 35 µg ethinyl estradiol (co-cyprindiol) can be given is uncertain. We know that many physicians have patients on these preparations for many years. Given the recent evidence [12], it is prudent to change to a lower oestrogen-containing pill when the acne has been brought under control. Because co-cyprindiol reduces sebum production only by about 30%, it is likely that it acts by an additional mechanism, such as a direct effect on comedogenesis, which is also androgen-mediated [16]. The clinical efficacy of this combination can be enhanced by giving an extra 50 mg or 100 mg CPA from the fifth to 14th day of the cycle [17]. At this dosage, the reduction in sebum production is 50–67%. Spironolactone is an effective treatment (it is not a contraceptive), but is more likely to be prescribed for females over 30 years of age. Its effects are dose dependent, and it is usually prescribed at a dose of 100–200 mg daily for 6 months [18–20]. The main side effects are menstrual irregularity, occasional fluid retention and, rarely, melasma. A question mark remains over its long-term use because of a theoretical increase in breast cancer, which has been shown in animal but not human studies [21]. All hormonal regimens should be combined with appropriate topical therapies. Effective hormonal regimens seem to have a dual mechanism of action, suppressing gonadotrophin release and having an additional peripheral effect on the sebaceous gland [22].

For the patient with intractable moderate or severe acne, or if appropriate antiandrogens are unavailable, isotretinoin is the treatment of choice. Isotretinoin is more effective than co-cyprindiol for acne patients [4].

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The patient with slow response or failure of response to treatment

There are several reasons as to why some patients show a slow response or no response to therapy. These include poor education of the doctor or patient, poor compliance, *P. acnes* resistance and Gram-negative folliculitis. Other explanations include incorrect diagnosis, the fact that certain acne subtypes respond poorly and side effects of therapy.

Poor compliance

Chronic disorders are associated with poor compliance and acne is no exception [1]. In a study that assessed acne patients after 18 weeks of treatment, compliance was less than 40% both for oral and topical treatment. Young age, smoking and excess alcohol were risk factors for poor compliance. Ways of improving compliance include better education of patients and doctors, and the constant reminding of patients that acne is a chronic disease which responds slowly to treatment, and that it is necessary to apply topical treatment not just to the acne spots but to the whole of the acne-prone skin. More time spent with patients and the development of nurse-led clinics could also help to improve compliance.

Propionibacterium acnes resistance

Resistance of *P. acnes* to commonly used antibiotics is a further reason for failure of adequate response. *Propionibacterium acnes* resistance has been recognized in most Western countries [2–6] (see Fig. 43.36). *Propionibacterium acnes* resistance has risen dramatically, and in 2003 the prevalence rates in a pan-European study [4] were lowest in Hungary (50.8%) and highest in Spain (93.6%). The incidence in the non-hospital community in the UK is 20%. Resistance is seen to tetracycline and doxycycline in 20% of subjects (see Fig. 43.36) and these antibiotics share a similar resistance profile [4]. Resistance to erythromycin is the most common, and these organisms share a cross-resistance to clindamycin [2–4]. Resistance to trimethoprim occurs in 12%, and multiple resistances are found in 24% of patients with resistant *P. acnes* [3]. Resistance to minocycline is relatively uncommon [3,4]. It should be emphasized that microbiological resistance does not necessarily equate with clinical resistance. Clinical resistance will occur if the MIC of the *P. acnes in vitro* exceeds the concentration of the antibiotic in the pilosebaceous duct. The concentration of ductal antibiotics varies considerably [6]. There are several factors that contribute to a less than optimal concentration of the drug in and around the pilosebaceous duct. Poor compliance will reduce drug availability, and a high sebum excretion is likely to wash out what might otherwise be an effective drug concentration [7]. A low tissue drug concentration will encourage the acquisition of antibiotic resistance by *P. acnes*. The incidence of *P. acnes* resistance in non-antibiotic-treated close contacts (i.e. mother, father, girl/boyfriend) is 50% [8], and thus may account for the apparent difficulty in treating some of our younger acne patients who have older siblings who have had antibiotics to treat their acne.

There are no data relating to failure of clinical response in patients who have been treated with an antibiotic to which their resident *P. acnes* have high levels of resistance; the authors suspect that the figure is probably of the order of 20%. The reasons are complex and include the fact that antibiotics also have some direct anti-inflammatory actions. There is clinical evidence that, in some patients, a change to an antibiotic to which the *P. acnes* are sensitive will bring about clinical benefit.

Molecular studies have demonstrated that the resistance of *P. acnes* to erythromycin and clindamycin is due to a mutation [9]. The same is likely to be the situation with tetracycline [10]. This means that resistance is likely to persist even after the selective pressure of that specific antibiotic has been removed. Thus, clinicians must develop strategies to prevent *P. acnes* resistance, and to use therapies that may reduce the resistant organisms where present. The authors' recommended strategies include the following:

1 Prevent overuse of a particular oral or topical antibiotic. A 6-month course of oral therapy should be adequate in most patients. When further oral antibiotics are required and the initial clinical response was good, re-use the same drug.

2 Avoid prescribing different oral and topical antibiotics at the same time.

3 Resistance may be avoided by using topical retinoids and azaleic acid, which do not promote *P. acnes* resistance *in vitro*.

4 Topical benzoyl peroxide and certain benzoyl peroxide/antibiotic combinations may be helpful because they appear to reduce the induction of antibiotic resistance by *P. acnes in vitro* and *in vivo* [11–12].

Propionibacterium acnes is, contrary to belief, quite an easy organism to grow in the laboratory, but many hospital microbiology departments do not provide information on resistance patterns in *P. acnes*. Therefore, clinicians must be alert to possible clinical resistance to a particular oral and/or topical antibiotic, which should be suspected in four circumstances:

1 If the patient's acne fails to respond when compliance is thought to be good.

2 If the patient's acne relapses after an improvement while still on therapy.

3 If the patient has had multiple courses of oral and topical antibiotics.

4 If the patient has a history of poor compliance with therapy.

Fortunately, *P. acnes* resistance to minocycline is uncommon (1%), but the authors' laboratories have shown that MIC levels to minocycline are gradually increasing and this should be seen as a warning for the future. When *P. acnes* resistance is suspected, alternative therapy may be necessary depending upon the circumstances. Options include alternative oral and topical antibiotics (including high-dose antibiotics), topical retinoids, antiandrogens and oral isotretinoin.

High-dose antibiotics (such as minocycline 200 mg/day or trimethoprim 600 mg/day) have been shown to be successful in overcoming apparent resistance [13]. These doses will increase the drug concentration in the duct, where it will act as a better antimicrobial agent, and in the dermis, where it will enhance the drug's anti-inflammatory action. In the USA, minocycline is frequently prescribed at 200 mg/day, even to the so-called normal acne patient, but our practice is to routinely use half that dose. In a female patient whose acne fails to respond, and in whom contraception or menstrual control is also required, combined co-cyprindiol plus additional CPA (50/100 mg) taken from the fifth to the 14th day of the cycle will often be beneficial [14].

Gram-negative folliculitis due to *Klebsiella*, *Escherichia*, *Proteus*, *Serratia* or *Pseudomonas* organisms may be the cause of apparent failure to respond [15]. Clinically, this may present with an acute flare of many pustules, the development of nodules, or simply as the deterioration of ordinary acne. Bacteria from the skin and nose of these patients must be sampled with a moistened swab. In this

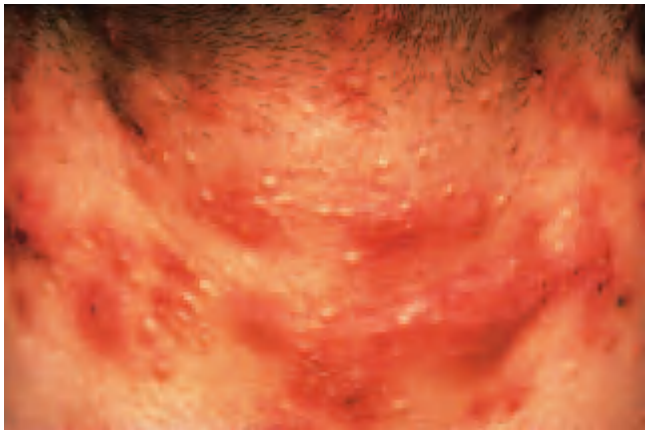

Fig. 43.43 Multiple macrocomedones: a frequent cause of persistent inflammatory acne.

situation, hospital microbiology departments should be able to identify the offending organism. The current antibiotic should be stopped and oral isotretinoin prescribed (0.5–1.0 mg/kg/day). An alternative is oral trimethoprim (200–300 mg twice a day), but relapse is more common after antibiotic therapy and after oral isotretinoin.

Certain subtypes of acne are more frequently associated with clinical failure. As discussed above, some patients have specific types of comedones. Patients with sandpaper comedones respond poorly to the more standard antibiotic/topical retinoid therapy and frequently require oral isotretinoin (0.5 mg/kg/day for 4–6 months). Patients with macrocomedones (Fig. 43.43) require physical treatment with gentle cautery under a local anaesthetic (EMLA®) [16,17]. Ill-advised prescription of isotretinoin to patients with multiple macrocomedones may precipitate a bad flare of acne, which may produce significant scarring. This disease flare probably relates to the release of large quantities of inflammatory mediators due to death of *P. acnes* organisms within the duct system. Similar treatment with gentle cautery is also required for patients with submarine comedones, but in contrast to those patients with macrocomedones who respond very well to this physical treatment, only about 50% of patients with submarine comedones show a satisfactory response.

Patients with severe inflammatory acne such as acne fulminans, acne conglobata and sinus tract disease also respond badly to standard therapy.

Most other non-responding patients will respond successfully to isotretinoin [18].

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Oral isotretinoin

Oral isotretinoin (13-*cis*-RA; Roaccutane®; Accutane® in the USA) revolutionized the treatment of acne when it was introduced in the UK in 1983. Two decades later, it remains the most clinically effective anti-acne therapy, producing long-term remission in many patients.

Mechanism of action

Isotretinoin is the only treatment that has an effect on all the major aetiological factors involved in acne [1–6]. It significantly reduces elevated sebum production, comedogenesis, and surface and ductal colonization with *P. acnes*; it is also anti-inflammatory.

Oral isotretinoin dramatically reduces sebum excretion by the order of 90% within 6 weeks of the patient receiving 0.5–1.0 mg/kg/day. Isotretinoin has an effect on sebocytes, but may act as a pro-drug with metabolites that have greater intracellular activity. Isotretinoin has at least five biologically important metabolites: 13-*cis*-4-*oxo*-retinoic acid (4-*oxo*-isotretinoin), all-*trans*-RA (tretinoin), all-*trans*-4-*oxo*-retinoic acid (4-*oxo*-tretinoin), 9-*cis*-retinoic acid and 9-*cis*-4-*oxo*-retinoic acid (see Fig. 43.5).

Studies of SER in sufferers of severe acne have shown that, within 4 weeks, 4-*oxo*-isotretinoin (30–60 mg/day orally) produces a mean reduction of 70% of that achieved by 30–60 mg/day of oral isotretinoin (N. Shear, personal communications).

In vitro studies of human sebocyte proliferation in cell culture, keratin 7 induction in pig sebocytes, HL-60 cell differentiation, the limb bud assay and the production of hypervitaminosis A in rats, have shown that isotretinoin and its three main metabolites; tretinoin, 4-*oxo*-isotretinoin and 4-*oxo*-tretinoin have comparable activities. In the human sebocyte proliferation assay, which is the most relevant model for the anti-acne effect, all three isotretinoin metabolites inhibit sebocyte proliferation at slightly lower concentrations than isotretinoin. All three metabolites have similar activity in the limb bud assay, which defines teratogenic potential, and in the hypervitaminosis A assay, which predicts the overall side effect potential. It is reasonable therefore to conclude that all three metabolites may contribute to the overall efficacy and safety, and side effects, of isotretinoin. These four compounds activate retinoid receptors RAR-α, RAR-β and RAR-γ in SZ 95 sebocytes, but only tretinoin and 4-*oxo*-tretinoin bind to RAR-γ, which is the receptor that is thought to be important in retinoid treatment of acne. Incubation of SZ 95 human sebocytes with isotretinoin led to significantly higher intracellular concentrations of tretinoin than isotretinoin [7]. The incubation with tretinoin generated very high intracellular concentrations of tretinoin and negligible concentrations of isotretinoin. These data suggest that tretinoin may be the active intracellular form of isotretinoin and prompted Tsukada *et al.* [7] to conclude that isotretinoin should be considered as a pro-drug. Differences in the plasma concentrations of these metabolites could therefore explain the differences in the intensity of the therapeutic response and the severity and/or occurrence of side effects in individual patients.

Just how oral isotretinoin influences a significant reduction in comedogenesis (by up to 80% or more) is uncertain [3]. Oral isotretinoin has no direct antimicrobial action, but by dramatically reducing SER and the size of the pilosebaceous duct it markedly alters the microenvironment within the duct. The result is a $\log_3$ reduction in *P. acnes*—a suppression much greater than that seen with oral and topical antibiotics [4,5]. Oral isotretinoin also modifies monocyte chemotaxis, which in part explains the anti-inflammatory effects of the drug [6]. The significant reduction in the *P. acnes* population also contributes to the reduction in acne inflammation.

Clinical benefit of oral isotretinoin

Almost all patients who receive oral isotretinoin will be free from acne by the end of 4–6 months of treatment. Recent clinical experience suggests that the long-term cure rate may be lower than was initially thought by dermatologists when isotretinoin became prescribable in the mid 1980s [1,8–10]. One explanation is that isotretinoin is being used to treat patients with less severe acne, who then have high expectations of a totally acne-free life, whereas the initial cohorts of patients had severe disease and were less concerned by the reappearance of a few spots. Furthermore, some of the early reported 'cures' may have been due to the fact that patients had eventually grown out of their acne.

Table 43.4 Indications for and success of isotretinoin in various acne-related conditions.

	Success		
Diagnosis	Excellent	Moderate	Limited
Severe acne	√		
Moderate acne*	√		
Mild acne*	√		
Acne fulminans*†	√		
Rosacea	√		
Rosacea fulminans*†	√		
Acne conglobata			√
Gram-negative folliculitis		√	
Hidradenitis suppurativa			√
Vasculitis acne			√
Dissecting scalp cellulitis			√
Steatocystoma multiplex			√
Oil acne		√	
Fordyce's disease		√	

* Especially if associated with scarring and/or psychological problems.
† Also needs pre-isotretinoin therapy with oral steroids.

The clinical effectiveness of isotretinoin in acne and acne variants is summarized in Table 43.4. When isotretinoin was first introduced, its prescription was restricted predominantly to patients suffering from severe nodular acne (Figs 43.44–43.46) [1–3]. With increasing clinical experience, use of the drug has been expanded worldwide to include less severely affected patients who have responded unsatisfactorily to what have been called conventional treatments, including long-term antibiotics and/or appropriate topical antimicrobial or retinoid-like therapies [8–13]. Failure of conventional treatment may occur for many reasons, including resistance of *P. acnes* to antibiotics [14].

The risk of teratogenicity has led some physicians to restrict the prescription of isotretinoin in female patients to those with severe acne only. However, there are convincing published data [9–12] to show that isotretinoin should be prescribed for patients with moderate acne who are failing to respond to conventional therapy, for whatever reason. Acne may produce scars in 30% of patients with moderate disease, and significant psychological morbidity in 12–13%. Thus, any failure of conventional

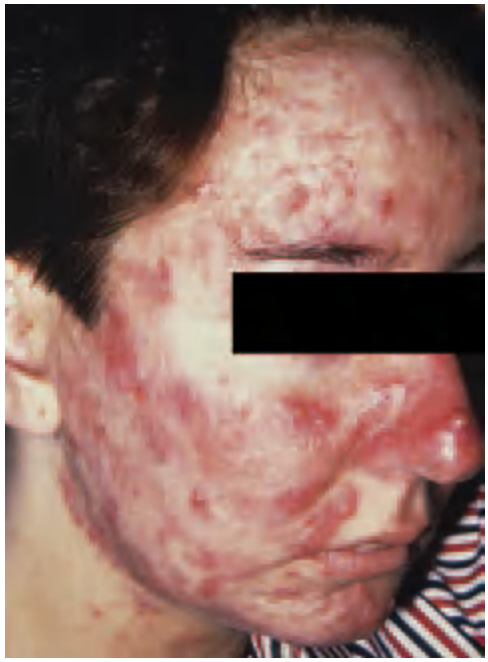

Fig. 43.44 A patient with severe acne before treatment with oral isotretinoin.

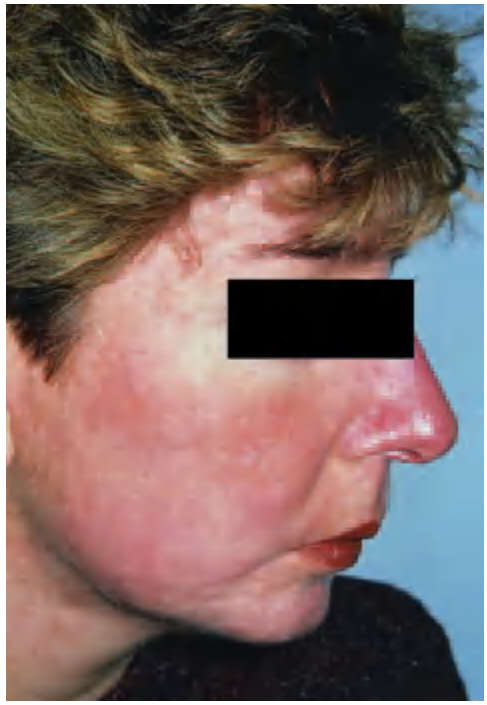

Fig. 43.45 The same patient at 3 months of treatment with isotretinoin.

treatment should be followed by a course of isotretinoin unless specifically contraindicated. In the UK, the National Institute for Clinical Excellence (NICE), a government-supported group, has provided guidelines for primary care physicians concerning referral to a consultant dermatologist. Providing the guidelines are adhered to, then in most instances the role of the dermatologist will be to prescribe oral isotretinoin, but some dermatologists may consider high-dose antibiotics plus appropriate topical therapy such as topical retinoids.

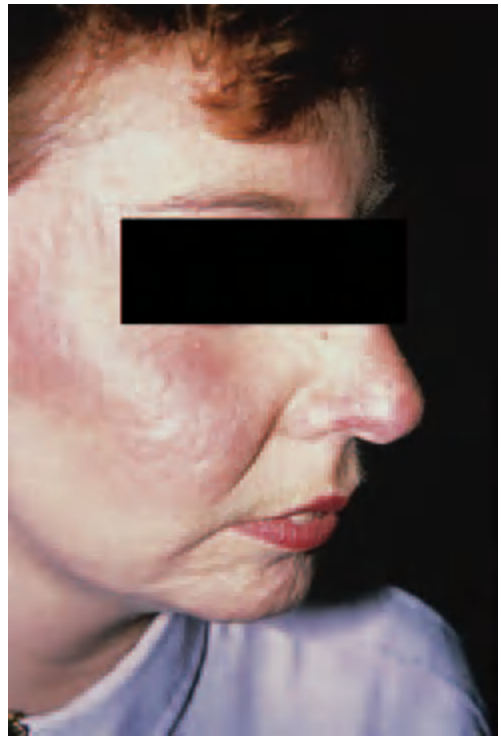

Fig. 43.46 The same patient 3 years after treatment with isotretinoin.

The definition of poor response should be made against objective or semi-objective criteria. The authors recommend the use of a clinical acne scoring system [15], and both quality of life and psychological profile indexes [16]. Physical and psychological severity of acne and local financial pressures will all play a role in the decision whether to prescribe isotretinoin. Conventional anti-acne treatment that fails to produce any improvement over 3 months should be changed. Some physicians take the failure of three successive treatment courses as an absolute indication for oral isotretinoin. There is abundant evidence to show that isotretinoin significantly reduces the psychological problems associated with acne [17,18].

A small number of patients with mild acne have disproportionate psychological effects when compared with the majority of acne sufferers. These patients may have a condition called body dysmorphic disorder and should be considered for the prescription of isotretinoin [19].

Age should not be a barrier to the use of isotretinoin. A very small number of neonates or juveniles with acne that had not responded to all appropriate topical or oral therapy have been treated successfully with isotretinoin, the usual dose being 0.5 mg/kg/day [20]. Some pre-adolescent youngsters, even under 10 years of age, develop

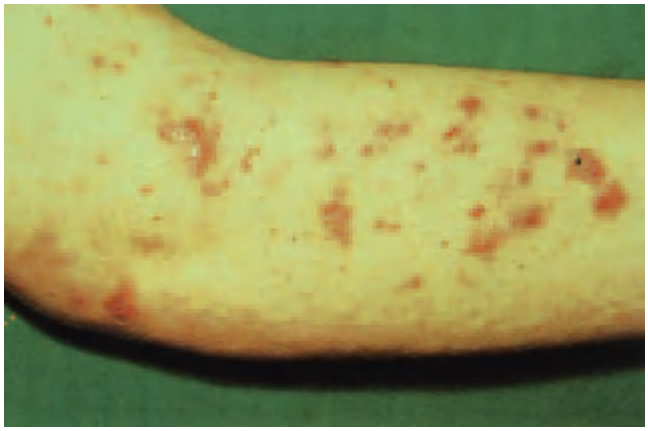

Fig. 43.47 The unusual extent of acne in a patient with Apert's syndrome.

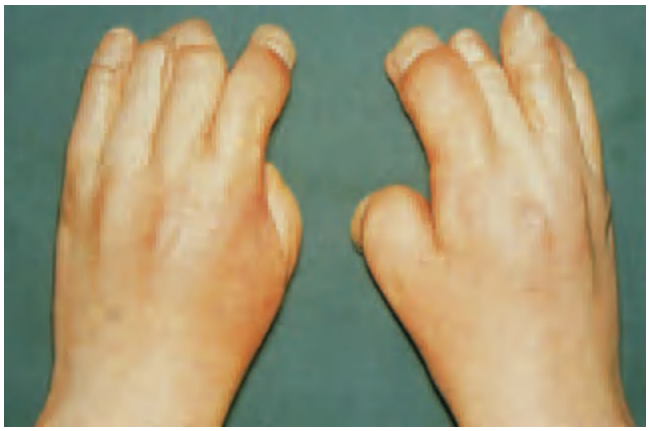

Fig. 43.48 The typical appearance of the fingers of a patient with Apert's syndrome.

troublesome acne with scarring. Oral isotretinoin should be prescribed for paediatric acne patients if there are sufficient clinical indications [21]. Apert's syndrome is a rare disorder associated with a hyperresponse of the epiphyses (Figs 43.47 & 43.48) and sebaceous glands to androgens, which results in premature epiphyseal fusion, particularly of the long bones and skull, and in acne respectively. These patients, presumably because of the hypersensitivity of the sebaceous glands to androgens, respond poorly to conventional therapy, and are therefore often treated successfully by oral isotretinoin [22].

Most dermatologists are treating increasing numbers of patients with acne that has persisted beyond the age of 25 years. The reasons for this change in the age/referral pattern are unclear, but may reflect increased expectations for cure based on the widely known clinical effectiveness of isotretinoin. Although the acne severity in these patients is not usually as great as it was when they were 15–25 years old, the persistence of the disease results in an increased risk of scarring and disproportionate psychological distress [23]. Isotretinoin is an important treatment in this age group. Data from a clinic in Leeds, UK, show that an adult with acne persisting at the age of 30 years is likely to have acne for at least a further 10 years. Small, intermittent-dose isotretinoin therapy (see below) may be appropriate for this subgroup of patients, but relapse often occurs quickly following a successful acne-free interval while on therapy.

Isotretinoin for patients with significant systemic disease. Patients with significant systemic disease can be treated with oral isotretinoin [24,25]. The authors feel that these patients fall into three subgroups, and recommend three appropriate protocols (Table 43.5) to minimize any negative effect in the associated disorder. In all instances it is necessary that a careful check be made by the dermatologist and/or the relevant physician at monthly intervals to ensure that there are no significant clinical or laboratory changes in the systemic disease.

1 Patients in Group 1 are those patients for whom there is evidence to show that the full dose of isotretinoin can be safely given.

2 Patients in Group 2 are those patients for whom there is limited information but, on balance, the drug probably does not cause any change in the associated disorder. These patients usually can start on a dose regimen of 0.25–0.5 mg/kg/day. If all is well, the dose can be increased at 2-monthly intervals to 0.5 mg/kg/day, and beyond if required, and therapy usually maintained for 24 weeks.

1 Protocol A: standard regimen	**2** Protocol B: initially half the standard regimen	**3** Protocol C: once-a-week regimen with gradual dose increase
Crohn's disease	Chronic renal failure	Behçet's syndrome
Diabetes mellitus	Renal dialysis	Cerebellar spongiform encephalopathy
Epilepsy	Hypertriglyceridaemia	Idiopathic thrombocytopenic purpura
Spina bifida	Immunosuppression	Leukaemia
Ulcerative colitis	Manic depressive psychosis	Mitochondrial degeneration
	Myalgic encephalopathy	Paroxysmal nocturnal haemoglobinuria
	Motor neurone disease	Polymyalgia rheumatica
	Multiple sclerosis	

Table 43.5 Isotretinoin dose schedules that may be most appropriate for patients with significant systemic disease.

3 Group 3 includes patients who have rare diseases, or where not much information exists.

In these uncommon circumstances, it is recommended that therapy begins at 20 mg isotretinoin/week. The dose is increased by 20 mg each week so that at the end of 7 weeks patients are taking 20 mg/day. The cycle can then be repeated to achieve a higher dose, so that by the end of a further 7 weeks they are taking 20 mg twice a day. In this group of diseases, it is particularly important that the dermatologist links with the appropriate physician so that a very careful clinical and, where appropriate, laboratory measurement is made of the associated disease. The authors recommend publication of these cases to help other similarly affected patients.

Isotretinoin in the treatment of acne variants. These diseases are very rare, and represent a small but essential indication for oral isotretinoin. This group includes patients with acne fulminans, rosacea fulminans, Gram-negative folliculitis, dissecting cellulitis of the scalp, hidradenitis suppurativa and acne conglobata.

Patients with acne fulminans and rosacea fulminans respond to oral isotretinoin [26,27]. The best response in these conditions is obtained by starting with a course of prednisolone 0.5–1.0 mg/kg for 4–6 weeks [26,27]. The steroids can usually be reduced gradually over the following 2 weeks, and isotretinoin can be introduced at a dosage of 0.5 mg/kg body weight/day and this can be increased gradually to 1 mg/kg/day according to the response.

Patients with acne conglobata and Gram-negative folliculitis usually do not require oral steroids, and can be started immediately on oral isotretinoin at a dose of 0.2 mg–1.0 mg/kg/day [28]. Hidradenitis suppurativa is a distressing disease that is difficult to treat. The response to isotretinoin is variable [29,30]. However, it may be worth trying a course of oral isotretinoin in patients who have not responded to hormonal regimens or long-term high-dose antibiotics such as minocycline. Dissecting cellulitis of the scalp also responds variably to oral isotretinoin, but a 4-month course ought to be tried [31].

Steatocystoma multiplex does not respond well to isotretinoin, which does not reduce the size of the non-inflamed cysts. However, while the inflammatory component of this disease may improve, it may also respond equally well to long-term oral antibiotics [32]. Other uncommon diseases related to acne that may respond to isotretinoin are oil acne [33], especially where there is an inflammatory component, and extensive Fordyce's disease [34]. See Table 43.4 for a summary of the acne-related indications for oral isotretinoin.

Recommended doses and duration of therapy. Most physicians prescribe a dose within the range 0.5–1.0 mg/kg body weight/day. There are variations in the way treatment is started [35–38]. Treatment regimes usually begin at 0.5 mg/kg/day and may be increased to 1.0 mg/kg/day, but in some centres treatment is started at 1.0 mg/kg/day. Published data suggests that optimal benefit is achieved by the higher dose. Absorption of isotretinoin is markedly affected by the presence of fat, which accompanies the drug in the intestine. Pharmacokinetic studies show that absorption can be doubled by taking isotretinoin with, or after, a meal compared with the fasting state [37]. The authors would advise patients to take their capsules along with the largest meal of the day. The majority of physicians, whether they start on a higher or lower dose, will adjust the dose according to the response and the presence or absence of side effects.

The duration of therapy varies from centre to centre. The range is usually 16–30 weeks, with a mean between 16 and 20 weeks. Studies to derive a cumulative dose for maximum benefit and reduced relapse rate [36] have confirmed that there is a definite effect of both dose and duration of therapy but that there is no *a priori* pharmacokinetic reason to support the concept of accumulation of drug or a cumulative dose effect. Post-therapy relapse is minimized by treatment courses that amount to a total of at least 120 mg/kg, but there is no added benefit when 150 mg/kg is exceeded [36]. Typically, this total dose can be achieved by 4–6 months at 0.5–1.0 mg/kg/day. The duration of therapy should be adjusted to give at least 90% clearing of acne based upon acne scoring techniques followed by 4 weeks of consolidation.

Demographic factors, such as age, sex and duration of acne, may also govern the rate of response and relapse. For example, males with more truncal acne and more severe acne, or who have had acne for less than 7 years, fail to respond as well as, and relapse more quickly than, female patients with predominantly facial acne and those with less severe acne.

Eighty-five per cent of patients who receive a dose of 0.5–1.0 mg/kg/day are virtually clear of their acne by 16 weeks. Thirteen per cent require 5 or 6 months to clear, and 3% require a longer course. Fewer than 1% of patients may need up to 12 months of continuous therapy, and it is the authors' experience that these patients are usually sons and daughters of physicians and lawyers! Low-dose courses of isotretinoin are successful in mature adults with persistent and late-onset acne. Typical treatment consists of 0.5 mg/kg/day taken 1 week out of 4 for a period of 6 months. Ninety-one per cent will be clear of acne using this regimen [39] but relapse is disappointingly frequent. Furthermore some patients wish to stay on the drug for many years at this lower dosage because of its benefit and relative lack of side effects. Some of these patients are almost addicted to this regime, which clearly would be totally inappropriate for a female of reproductive potential.

Table 43.6 Side effects of isotretinoin and their management.

Side effect	Management if disease is: Mild	Moderate	Severe
Cheilitis Facial dermatitis Discoid dermatitis Xeroderma	Lubricant	Intermediate steroid ointment	Potent steroid ointment combined with antiseptic and oral antibiotic
Nasal dryness and soreness	Lubricant	Nasal mupirocin	Nasal mupirocin + oral antibiotic
Blepharoconjunctivitis	Lubricant	Mild steroid/antibiotic combination	Antibiotic eye ointment + oral antibiotics
Arthralgia and myalgia	Nil	Paracetamol Aspirin Non-steroidals	Paracetamol Aspirin Non-steroidals
Headache	Nil	Paracetamol, dose reduction	Consider BIH Stop therapy
Pyogenic granuloma	Nil	Potent steroid ointment ± cautery and curettage	Potent steroid ointment ± cautery and curettage

Note: if in doubt reduce the dose of or stop isotretinoin.
BIH, benign intracranial hypertension.

What are the reasons for a slow response to isotretinoin? Analysis of slow responders to isotretinoin shows that the cause is due to the presence of macrocomedones (see Fig. 43.43) in 70% [40], nodular acne in 15% and unknown in about 5%. It may be necessary to stretch the skin to detect macrocomedones. These must be sought prior to starting isotretinoin, and treated by light cautery. This is best conducted after the application to the skin of a local anaesthetic cream, such as EMLA®, for 60 min beneath an occlusive dressing. Thereafter, the areas are touched gently with light cautery [41]. This procedure should initially be performed on a test area of 10 cm^2, so as to ensure that the patient does not develop any disproportionate scarring or, in the case of black skin, hypo- or hyperpigmentation. An acne flare early in treatment often needs dose reduction and possibly the addition of oral steroids. This observation may also contribute to a slow response [42].

When macrocomedones are not the cause of the poor response, the dosage of isotretinoin should be carefully considered. Patients may be given an increased dose providing that the side effects are tolerated, but if the acne is very inflammatory, then a significant reduction in the dose of isotretinoin and addition of oral steroids may be required (e.g. 0.5–1.0 mg/kg/day for 2–3 weeks) Some female patients with hormonal dysfunction, due, for example, to polycystic ovarian syndrome, may need additional treatment with a hormonal preparation such as co-cyprindiol.

Persistent deep pustules in about 1% of patients may be due to *S. aureus*, and bacterial swabs should always be sent from these patients, whose lesions respond to antistaphylococcal therapy.

Table 43.7 Some uncommon side effects of isotretinoin.

Achilles tendonitis
Acne fulminans
Depression
Diarrhoea
High-tone deafness
Mood changes
Night blindness
Sticky palms
Urticaria
Vasculitis

Some patients have multiple reasons for the slow response, and compliance with the prescribed regime must always be considered. The presence of mucocutaneous side effects (see below) is usually a good indicator of absorption.

Further courses of therapy are usually successful when required. There is no contraindication, apart from pregnancy and other significant side effects, to re-prescription, and there is no tachyphylaxis. Some patients have needed two or three courses, and fewer than 3%, in the authors' experience, have required up to five courses, usually, with no signs of cumulative toxicity.

Side effects

Isotretinoin has many side effects (Tables 43.6 & 43.7). In particular it is very teratogenic [43]. Fifty per cent of pregnancies spontaneously abort, and of the remainder about half of the infants are born with cardiovascular or skeletal deformities. The authors recommend that a negative (if

possible blood) pregnancy test be obtained on the first or second day of the period with treatment being started the day after the negative result is available. Adequate counselling about the risks of pregnancy and teratogenicity is essential, even in a 10-year-old girl. It is best that someone who is experienced in family planning issues should give the counselling. Female patients must acknowledge risk by signing a document to indicate that they have been informed of the teratogenic hazard. In the USA, the guidelines are even more stringent, requiring two negative blood pregnancy tests before starting therapy, and monthly negative blood pregnancy tests before the pharmacist is allowed to dispense the next month's supply. In the UK, very similar guidelines have recently been introduced; consult the British Association of Dermatologists (London) if practising in the UK.

Mood changes including depression are common among adolescents and may occur in patients who are being treated with isotretinoin. Two studies that looked at spontaneous reports of side effects for the Food and Drug Administration (FDA) in the USA [44,45] found little or no increase in psychiatric disease including depression and suicide over the background prevalence in the adolescent population. A further study of general practice databases in Canada and the UK showed similar findings [46]. The authors recommend that clinicians should be aware that patients might develop mood changes and clinical depression during their 4–6-month treatment with isotretinoin, and in the first few months post therapy, and should enquire about symptoms at each clinic visit. A suggested short questionnaire with good stringency is:

Over the past 2 weeks have you consistently …

1 Been feeling unusually sad or fed up?

2 Lost interest in things that used to interest you?

3 Felt any more short tempered or irritable than you used to?

Discussion about the teratogenicity and recognized side effects should be recorded in the notes at each visit, even witnessed by the patient, and patients given appropriate documentation. If significant depression is identified, then a psychiatric referral may be indicated. Increased aggression has been identified in some male patients and the FDA in the USA has advised clinicians to warn potential patients about this side effect. If there is any doubt, the drug must be stopped.

Most other side effects of oral isotretinoin are predictable and rarely interfere with the patient's management [2,8–13]. They are rendered tolerable by modification of the dose and/or additional symptomatic therapy. Table 43.6 shows the common and uncommon side effects and strategies for their optimum management.

An acne flare early in the course of isotretinoin occurs in 6% of subjects, and in half of these is clinically important [42]. The physician must inform the patient that should there be an acne flare (or any other concern whatsoever), then they must immediately call the dermatology department, as sometimes these flares can be devastating both physically and psychologically. Risk factors for this flare include the presence of macrocomedones in two-thirds and nodules in almost one-third of patients [42]. Should a patient flare badly, oral prednisolone should be given in a dose of 0.5–1.0 mg/kg/day over a period of 2–3 weeks, and the dose slowly decreased over the next 6 weeks. When the acne flares, the isotretinoin should either be stopped or reduced to a dosage of 0.25 mg/kg/day depending on the extent of flare. If stopped, the drug can be slowly reintroduced at a dose of 0.25 mg/kg/day, and then increased or decreased as necessary.

The mucocutaneous side effects can usually be minimized by the very regular use of moisturizers and lip salves, but occasionally retinoid dermatitis, a severe retinoid cheilitis or conjunctivitis occur (Figs 43.49 & 43.50), often complicated by secondary infection with *S. aureus*. These patients may need treatment with an intermediate-strength steroid ointment combined with an antiseptic. If there is impetiginization, oral antistaphylococcal therapy such as

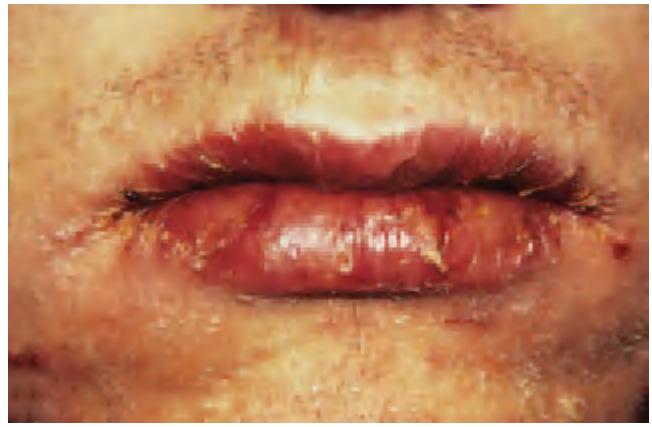

Fig. 43.49 Patient with troublesome cheilitis due to oral isotretinoin.

Fig. 43.50 Patient with troublesome conjunctivitis due to oral isotretinoin.

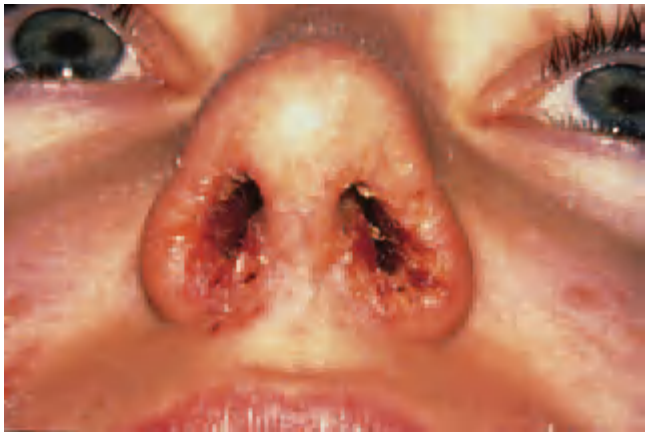

Fig. 43.51 Patient with troublesome nasal crusting (and *Staphylococcus aureus* infection) due to oral isotretinoin.

flucloxacillin and/or topical mupirocin 2% ointment may be required [47]. A nasal preparation of mupirocin can be used to eradicate nasal carriage of staphylococci (Fig. 43.51).

Significant systemic effects are uncommon, and mainly consist of headaches, which may uncommonly be an early feature of benign intracranial hypertension, and arthralgia. Tetracyclines, including doxycycline and minocycline, must not be prescribed with isotretinoin, as both drugs may produce benign intracranial hypertension [48]. Systemic side effects are usually well controlled by dose reduction and concomitant the use of non-steroidal anti-inflammatory drugs or aspirin. There is a long list of very uncommon systemic side effects (see Table 43.7 and Chapter 73); a detailed review of these is beyond the scope of this chapter.

There is much debate as to whether liver function tests and lipids should be monitored while on therapy. Elevations in these tests occur in almost all patients and rapidly return to pretreatment levels after therapy has been stopped [1,2,49]. It is, however, essential to carry out these tests before starting therapy. Published evidence suggests that the laboratory tests need not be repeated except in groups at risk, such as diabetics and patients with known familial hypertriglyceridaemia [12,49]. The reader is referred to an excellent detailed overview on the many side effects of oral isotretinoin [50].

Cost-effectiveness. Oral isotretinoin is clearly more effective than oral antibiotics in acne of all grades of severity. However, its relative expense and side effects have deterred some physicians from prescribing it. Cost-effectiveness comparisons in the UK [51,52], France [53], New Zealand [54] and Australia [55] have shown that a 4–6-month course of isotretinoin is significantly cheaper than a 3-year therapeutic regimen of rotational courses of antibiotics and topical treatment. In fact, only patients treated with isotretinoin achieved complete clearance of acne when assessed 3–5 years post-treatment [43]. Funding bodies should look more logically at the way isotretinoin is prescribed, so that it can be prescribed appropriately in acne to prevent the many physical and psychological problems of the disease.

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Other oral treatments

Before the advent of the retinoids and antiandrogens, several other oral treatments were used, and may occasionally be tried in difficult cases of acne if the newer drugs are contraindicated, unobtainable or ineffective. Oral zinc is of some value [1–6]. Two double-blind studies showed a significant benefit, particularly with zinc gluconate (200 mg/day). Comparison with minocycline 100 mg/day showed that the antibiotic improved acne by 63% at the end of 3 months—in contrast to an improvement of 32% with 30 mg/day of elemental zinc—but there was no placebo in the study. Certain non-steroidal anti-inflammatory drugs, such as ibuprofen and benoxaprofen, have been shown to reduce inflamed lesions [7]. More recently, a new 5-lipoxygenase inhibitor has, in a small pilot study, been shown to reduce inflamed lesions and seborrhoea, but with little effect on comedones [8]. Clofazimine (200 mg three times a week) has been shown to improve acne fulminans [9], but should not be given as a first option. Dapsone (100–300 mg/day for 6 months) has also been tried with varied success [10,11]; it is much less effective than isotretinoin [11].

Oral vitamin A has been advocated [12,13]. Doses of less than 40 mg/day are not effective. In our experience, oral vitamin A proved considerably less effective than 1 g/day of either tetracycline or erythromycin. The side effects of oral vitamin A are similar to oral isotretinoin, and the period of therapy should not exceed 6 months.

Oral prednisolone (0.5–1.0 mg/kg body weight/day) should be prescribed in patients with severe inflammatory acne vulgaris and in acne fulminans and pyoderma faciale [14]. The steroids should be prescribed at this dosage for 2–4 weeks, and then gradually reduced over a further 2–4-week period. In patients with acne fulminans and pyoderma faciale, it is preferable to prescribe the steroids for 2–4 weeks before prescribing isotretinoin. Oral steroids in similar doses are also indicated in patients whose acne flares badly while taking oral isotretinoin [14]. If such patients have many macrocomedones, they should be urgently treated with light cautery under a local anaesthetic cream such as EMLA® [15].

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Physical modalities for treating active acne

Some of the physical modalities used as an adjunct to treatment require considerable skill. The many abrasive materials, usually based on polyethylene and aluminium oxide, are of little or no value. Facial saunas, heat and massage probably worsen the condition by precipitating the development of inflamed lesions. Removal of comedones can, however, be aided by hot compresses. Comedone removal can be surprisingly uncomfortable, and a variety of specially shaped tools, particularly for blackhead removal, are available. Some patients have very visible closed comedones, which often become inflamed. For these lesions, the eccentrically placed pore may be widened with a small blade under a good light, which allows enucleation of the cornified plug with the comedo remover. The limitations of comedonal extraction include incomplete extraction, refilling and the risk of tissue damage. Light cautery after the application of a local anaesthetic (EMLA®) [1] has been shown to help patients with multiple macrocomedones; these are usually whiteheads but occasionally blackheads (up to 1.5 mm diameter), and chloracne can be improved [1,2]. The EMLA® is applied for 60–75 min beneath an occlusive dressing. The cautery is used at a very low setting so as to produce little or no pain. The tip of the cautery should be just sufficiently warm to char paper towelling. The aim is to produce very low-grade thermal damage so as to stimulate the body's own defence mechanisms to eradicate the comedo. The actual cautery procedure takes 5–10 min; the treatment of each lesion takes 1–2 s and is associated with very little scarring or post-inflammatory pigmentation. This therapy is more effective than topical tretinoin for macrocomedones [3].

Until recently there has been little objective assessment of treatment by UV radiation. Broad-spectrum sunlamp therapy is probably not as good as natural sunlight: both provide only short-term benefits in acne. A combination of blue light (peak at 415 nm) and mixed blue and red light (peaks at 415 and 660 nm) was investigated in 107 patients with mild to moderate acne [4]. The light sources were portable and the treatment performed daily for 15 min over a 12-week period. At 12 weeks of active treatment there was a mean improvement of 76% with blue-red light therapy; this was significantly superior to the improvement seen from blue light, benzoyl peroxide and the control white light. The final mean improvement in comedones from exposure to the blue-red light was 58%—again better than that achieved by the other active treatments, although the differences did not reach significant levels [4]. The lamp is commercially available as the DermaLux® lamp.

Topical amino laevulinic acid (ALA) plus broad-band light (550–700 nm) has been shown to produce statistically significant clearance of inflammatory acne for at least 20 weeks after multiple treatments, and 10 weeks after a single treatment [5]. The therapy produced acute damage to the sebaceous glands, resulting in significant sebum suppression for up to 20 weeks post-therapy; this was associated with a significant decrease in *P. acnes* for many weeks. Similar long-term benefits in facial acne were achieved using a combination of ALA and polychromatic visible light (600–700 nm) [6].

Laser therapy with the NLite laser, which emits light at 585 nm, has recently been reported in a small randomized controlled trial to produce a 50% improvement in acne grade and lesion counts by 12 weeks after a single treatment [7]. In general, these regimes also significantly suppress a range of comedonal and pro-inflammatory cytokines [5,8]. Furthermore, there is a differential cytotoxic effect, in that cutaneous bacteria, including *P. acnes*, are more susceptible to short-term damage from, for example, photodynamic therapy, than keratinocytes [9]. These observations could explain some of the action of 'light' therapy regimes.

Superficial freezing with liquid nitrogen will hasten the resolution of chronic fluctuant nodular lesions and is comparatively painless [11]. Two freeze–thaw cycles of 15–30 s each are recommended, depending on the size of the nodule. It is uncertain how this treatment works, but it probably invokes an inflammatory reaction, so breaking down the indolent tissue surrounding the lesion. Cryotherapy is probably preferred to intralesional steroid injections in the treatment of older (7 or more days) nodular lesions, whereas intralesional steroid is preferred in lesions less than 7 days old [11]. Triamcinolone, 2.5 mg/mL, may be administered from a syringe with a 30-gauge needle [11,12]. Placement too superficially or too deeply may cause atrophy; 0.025–0.1 mL should be injected into the middle of the lesion, causing slight distension. Aspiration before the steroid injection is desirable but not always possible because of the nature of the fluctuant nodular lesions, which are not true cysts. Aspiration is best performed from the lower part of the nodule to facilitate drainage, with the steroid being injected into the upper part and then gently massaged into the lesion.

Deep X-ray treatment must not be prescribed because of its carcinogenic risk. Superficial X-ray therapy (no more than 8.1 Grays given in fractionated doses to any one area of skin in a lifetime) has been advocated, but is of questionable benefit.

Chemical peels [13,14]. Some dermatologists in certain countries use light chemical peels to help remove comedones as well as possibly helping superficial scarring and hyperpigmentation. Peeling agents include α-hydroxy acids (glycolic acid), salicylic acid and trichloroacetic acid. Chemical peels are supposed to promote desquamation and may help dislodge comedonal plugs. There is limited scientific evidence to support the use of chemical peels.

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Treatment of scars

Response to treatment is variable and sometimes not that successful. Some scars will become less conspicuous over a period of many months. Recent interest in the pathogenesis of wound healing and scars may pave the way for new oral and topical therapies. The expansion of dermatological surgery and new lasers hold some promise. Surgical/laser therapies for scars are probably best performed when the acne is under good control. Treatment of facial scars associated with loss of tissue may include excision, planing and filling techniques. Such techniques are rarely used for scars on the trunk.

Treatment of atrophic scars

Excision of scars. Small, well-defined scars can sometimes be satisfactorily excised [1].

Dermabrasion and laser resurfacing [2–7]. These may be of value for depressed scars of even depth, but multiple ice-pick scars of irregular depth respond badly. Dermabrasion involves the use of a high-speed wire brush or diamond fraise to plane the skin under local or general anaesthesia. It is best avoided in summer because of the risk of post-inflammatory hyperpigmentation. Hypopigmentation can also occur in some patients. Postoperative care is very important, and should include the use of a topical sunscreen and prophylaxis with oral aciclovir to prevent herpes simplex infection. Improvement ranges from 30% to 75%; the patient's estimate of improvement often surpasses that of the surgeon. In the past 5 years laser resurfacing has taken over from dermabrasion. An increasing array of lasers is used for this practice and the reader is referred to specialized texts. Although scientific data on their precise benefit are limited, the future outlook may be promising [6,7].

Collagen injection. Injections of purified bovine dermal collagen to augment tissue defects are of limited benefit, but have been shown to help soft scars that are easily stretched [8–10]. Deep ice-pick and fibrotic scars show little improvement. Hypersensitivity, which is rare, must be excluded by waiting 42 days after an intradermal test before the collagen is injected. Technical expertise is necessary for a successful outcome. It is best to overfill the scar above the normal skin contours; even so, repeated treatments every 18 months may be needed. Recollagenation of acne scars refers to a technique in which an implant of freeze-dried irradiated human cadaver fascia lata is placed in an intradermal pocket at the site of each scar through a needle hole to elevate the depressed epidermis [11]. A further alternative is the injection of autologous fat into atrophic scars.

Gelatin matrix implant. One or two injections of this preparation have been shown to help scars and the improvement was maintained over 2 years [12].

Chemical peeling. Chemical peeling has been used in the treatment of atrophic acne scars. Expertise is required for such a procedure. Several chemical agents are used, including α-hydroxy acids, glycolic acids and resorcinol. The reader is referred to detailed texts on how, when and why to use chemical peels [13–15].

Multiple treatments. If several approaches are required, it is probably best to excise the larger scars and then re-plane the skin surface by dermabrasion or carbon dioxide lasers. Refilling with collagen or autologous fat may then be necessary. In older patients with much loss of tissue, facelifts may help.

Treatment of hypertrophic and keloids scars

Keloids (see Fig. 43.25) and hypertrophic scars also vary in their response to therapy, but several options are worth

trying. These include steroids, either potent topical steroid creams or triamcinolone depot injections, excision, cryotherapy or topical application of silicon gels. There are several papers that testify to both the benefit and pitfalls of such therapy [16,17]. Potent steroids such as clobetasol propionate need to be applied carefully to the scar, usually twice daily, avoiding adjacent skin to prevent atrophy of the perilesional skin. Each treatment should be used initially for 2 months. Intralesional triamcinolone (2.5 mg/mL—0.05–0.1 mL) injections into the scars can be tried at monthly intervals for a few months and the decision about subsequent therapy based on the response. Excision is frequently followed by recurrence, which may be larger than the original lesion. Double-blind studies are needed to confirm the optimum therapy for hypertrophic and keloid scars. It is important to remember that some scars improve with time and without treatment. Vascular keloids may benefit from therapy with the pulsed tunable dye laser [18]. Silicone gel sheeting applied for 12/24 h per day for at least 2 months to young hypertrophic and keloid scars has been reported to be of benefit [19]. Such sheets are available without prescription in many countries but adequate trials are lacking.

Many patients have multiple scars, and since multiple treatments are available then different treatments could be used for different scars—perhaps with some not being treated to act as an internal control. This approach might determine the natural resolution of the patient's scars.

Cosmetic camouflage. Although certain cosmetics may induce acne, it is not unreasonable, and is often psychologically necessary, for the female acne patient to use some form of cosmetic camouflage. She should be advised that she can wear light, non-greasy make-up. When scarring is a physical and psychological problem, cosmetic camouflage may be essential. In certain countries, professional advice is available, and in the UK these cosmetics are available on prescription. Make-up is often needed for the post-inflammatory increase in pigmentation, which may occur in the skin of dark-skinned people and may persist for years. Indeed, where this risk occurs, even mild acne should be treated aggressively with long-term antibiotics. Topical all-*trans*-RA and azaleic acid may be of possible therapeutic benefit in reducing post-inflammatory pigmentation, but therapy has to be continued for many months.

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Uncommon associations with acne

Under this heading we have included a miscellaneous group of either distinct diseases or unusual physical features which may coexist with acne. In some, the association is unquestionable, but in others the association is debatable. In many of these clinical situations much more research is required to provide clarity. For no reason other than simplicity we have listed these associations alphabetically.

Acne excoriée

This variant (Fig. 43.52) occurs predominantly in females. Two subgroups exist: one with some primary inflammatory acne lesions, and another with almost none. Both groups usually consist of females who 'fiddle' with the skin to exacerbate even the smallest lesions. There is often some personality or psychological problem [1,2]. The disease merges into dermatitis artefacta. A contact dermatitis needs to be excluded [3]. Treatment with oral antibiotics such as oxytetracycline 0.5 g twice daily, or for better compliance lymecycline, one tablet daily, for several months and advice not to pick the spots is of considerable benefit to females with mild acne. By markedly reducing the number of lesions, the regimen leaves the patient fewer to 'play' with. Topical treatment tends to irritate the skin and aggravate the problem. In the group with virtually no acne spots, trifluoperazine hydrochloride (5–30 mg/day) or pimozide (2 mg twice a day) and appropriate psychotherapeutic support may help.

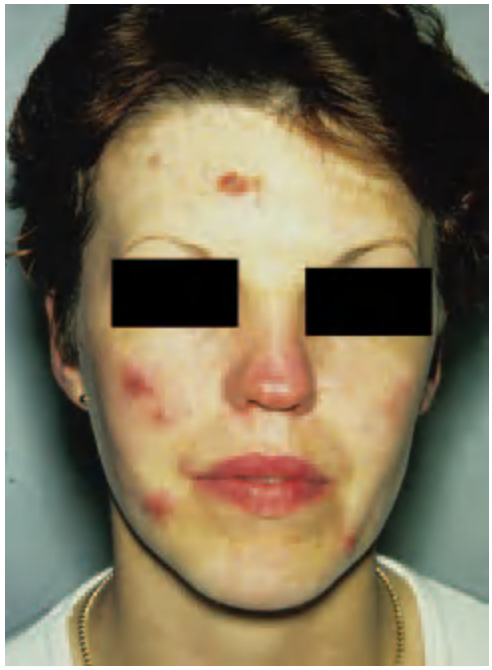


Fig. 43.52 A patient with acne excoriée.

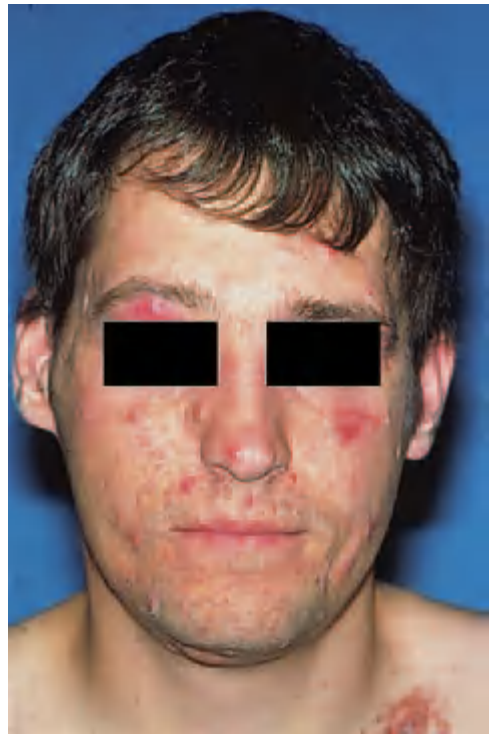
Apert's syndrome

There is an association between acne and Apert's syndrome [4,5] (see Figs 43.47 & 43.48). These subjects develop early epiphyseal closure, which, like acne, is an androgen-mediated event. The characteristic facial abnormalities are: hypertelorism, a flattened occiput, proptosis due to shallow orbits, prognathism, a parrot-beaked nose and fused shortened digits. Two genetic mutations on receptor 2 fibroblastic growth factor have been defined as a cause of this syndrome [6].

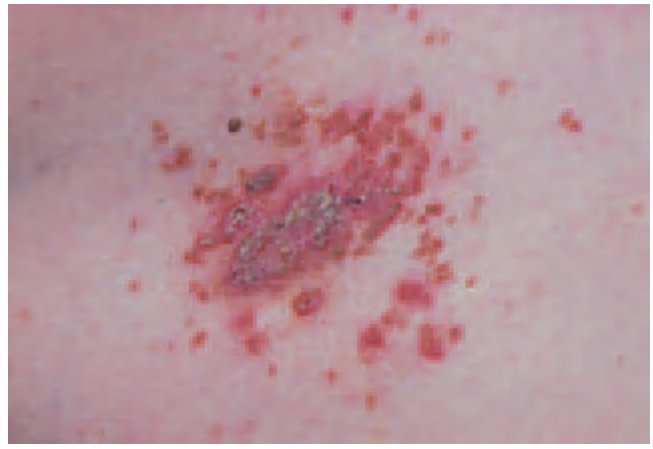
Consequently, the patient has a characteristic appearance as well as extensive acne, which often occurs at unusual sites such as on the arms (see Figs 43.47 & 43.48). The acne responds relatively less well to oral antibiotics, and patients frequently need a course of isotretinoin [7,8].

Body dysmorphic disorder and acne

A small number of patients with body dysmorphic disorder have acne as their prime symptom [9]. The acne is usually very mild, and the patient's complaint is out of all proportion to the physical signs. These patients require much support; they are often depressed or obsessional and have a significant risk of suicide [2]. Unfortunately, they usually tolerate psychiatric treatment badly, and the dermatologist must treat the acne enthusiastically with one of the more effective therapies such as minocycline 100–200 mg/day for 6 months. Isotretinoin given for 4 months is the preferred therapy. The authors consider that 'relapse', either real or perceived, is common and requests for further isotretinoin are also common [10]. This subject is dealt with in greater detail in Chapter 61.



(a)



(b)

Fig. 43.53 (a) A patient with acne conglobata, which can coexist with Darier's disease (b).

Darier's disease

This disease is discussed in detail in Chapter 40, but it is possibly associated with acne; some patients with Darier's disease have significant nodular acne that can be very difficult to treat with antibiotics, oral isotretinoin or acitretin. The variable penetrance of Darier's disease means that sometimes the clinical features are relatively inconspicuous, such that Darier's disease may be initially missed in patients with severe nodular acne (Fig. 43.53).

Table 43.8 Drugs reported to cause acne or acne-like eruptions.

Hormones and steroids	*Antituberculous drugs*
Gonadotrophins	Isoniazid
Androgens	Rifampicin
Anabolic steroids	
Oral and topical steroids	*Miscellaneous*
	Chloral hydrate
Halogens	Cyanocobalamin
Bromides	Disulfiram
Iodides	Lithium
Halothane	Psoralens (with UVA)
	Quinine
Anti-epileptic drugs	Sulphur
Diphenylhydantoin (phenytoin)	Thiouracil
Phenobarbitone	Thiourea
Troxidone	

Two patients with prominent nodular and comedonal lesions on the face and scalp showed histological features of Darier's disease on examination of a comedone [11].

Drug-induced acne/acneiform eruptions

The many drugs that have been incriminated as possible aggravators of acne are listed in Table 43.8 [12–34]. Much of the evidence consists of isolated case reports, and many of the reported reactions are idiosyncratic. Only those substances that definitely induce acne or acneiform eruptions will be discussed.

Corticosteroids, orally, topically, intranasally, intrathecally and ACTH by injection, may provoke an acneiform reaction (Fig. 43.54) [17–21]. The precise mechanism is uncertain. Corticosteroids induce cornification in the upper part of the pilosebaceous duct, but do not affect the number of surface bacteria [17,19]. Steroid acne is usually, but not invariably, more monomorphic than true acne vulgaris; however, both inflammatory and non-inflammatory lesions may be present on the face, back and chest.

Androgens including anabolic steroids and gonadotrophins may precipitate acne, especially in athletes who take performance-enhancing drugs (Fig. 43.55) [22–25]. In the former group, both testosterone and stanazolol have been shown to increase sebum excretion and the surface population of *P. acnes* [25]. Contraceptive pills that reduce SHBG levels may also result in deterioration of pre-existing acne.

Antiepileptic drugs, especially phenytoin, have been incriminated in case reports in the past, but a study of severe epileptics taking several different anticonvulsants showed that they were at no more risk of acne than the normal population, but some patients with severe epilepsy showed features of hypogonadism [26].

Isoniazid, especially in patients who slowly inactivate the drug, provokes an acneiform rash [27]. A small number of patients receiving PUVA treatment have been reported

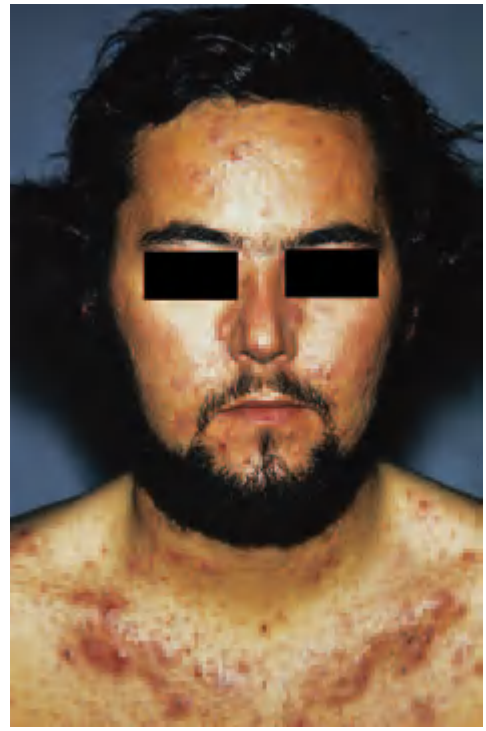


Fig. 43.54 A patient with acne due to oral steroids.

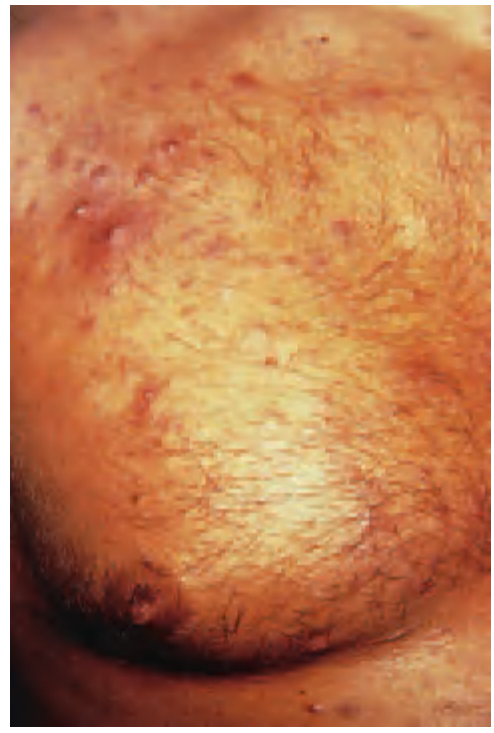


Fig. 43.55 A patient with acne due to anabolic steroids.

to develop a perioral dermatitis and/or an acneiform eruption on the face [29,30].

An acneiform eruption has also been described in patients taking amineptine [15,16,31]. Most reported cases

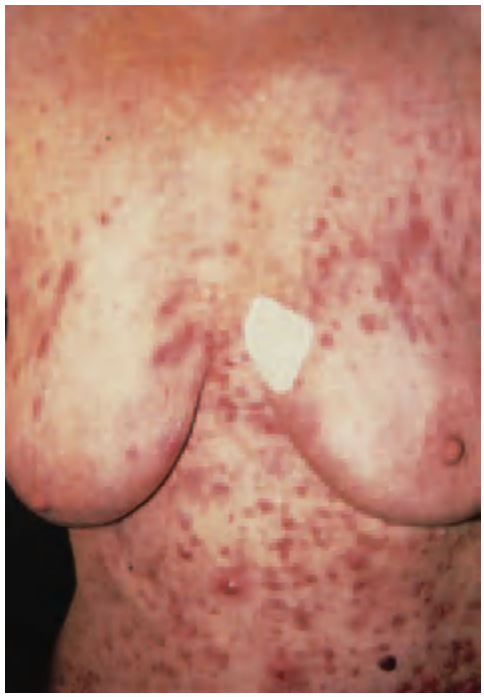


Fig. 43.56 A patient with acne due to lithium. (Courtesy of Dr V.M. Yates, Royal Bolton Hospital, Bolton, UK.)

have involved adult females. Comedonal lesions are the most prevalent and inflammatory lesions are usually absent or few in number. The pathomechanism is unknown; the drug contains no halogenated substances. The drug should be withdrawn but the response is variable and oral isotretinoin (0.5–1.0 mg/kg/day) plus physical treatment of the comedones appears to be the most appropriate treatment.

A follicular acneiform eruption has been reported in cancer patients treated with the anti-EGF receptor antibody ZD 1839 [32]. The consistency of lesion morphology and timing following monotherapy with this antibody suggest a direct biological effect of the antibody. Histological examination of the lesions, which occur within a few weeks of receiving the antibody, has demonstrated a superficial dermal inflammatory cell infiltrate surrounding a dilated follicular infundibulum.

Iodides and bromides used to be a common cause of follicular pustules that were marked by the rapidity of onset after starting these preparations [33,34]. In contrast to acne vulgaris, all people and all ages were affected. Lithium is currently still an occasional cause of iatrogenic acne (Fig. 43.56).

In all cases, the risks and benefits must be assessed, and the causative drug should be stopped if possible. Appropriate topical or systemic acne therapy, according to the severity of the condition, is often successful.

Endocrine acne

The role of the endocrine system in the aetiology of acne is discussed elsewhere in this chapter. Most female patients do not have evidence of virilism and require no further investigation. The term endocrine acne should be reserved for cases of acne associated with significant clinically manifest endocrine disease such as Cushing's disease, late-onset congenital adrenogenital syndrome and polycystic ovarian syndrome. The latter is the commonest cause of 'endocrine' acne. Also reported is the so-called SAHA syndrome (*s*eborrhoea, *a*cne, *h*irsutism and *a*lopecia), which can be associated with polycystic ovarian syndrome, cystic mastitis, obesity and infertility [35]. The association of these clinical features should also alert the physician to exclude an androgen-producing tumour.

Externally induced acne

Cosmetic acne

This variant is reported more commonly in the USA [36] than in Europe and elsewhere, perhaps because of the greater use of potentially comedogenic cosmetics in the USA. The lesions characteristically occur in the perioral area of mature females, especially those who had acne as adolescents and have used cosmetics for a long time. The rabbit-ear model, which is oversensitive for humans, has shown that some cosmetics, especially those containing lanolin, petrolatum, certain vegetable oils, butylstearate, lauryl alcohol and oleic acid, are comedogenic. Many cosmetics, especially in the USA, are now screened by the rabbit-ear test and appropriate cosmetics are labelled as being non-comedogenic [36–37]. Patients should be warned that switching to a non-comedogenic cosmetic does not bring rapid clinical results in cosmetic acne. Treatment with topical retinoids or benzoyl peroxide is usually successful.

Pomade acne

Pomades are greasy preparations used to defrizz curly Negroid hair. The rash is similar to cosmetic acne and consists predominantly of many non-inflamed lesions around the forehead and other areas where greasy pomades may extend onto the hairless skin (Fig. 43.57) [38]. It may also coexist with true acne vulgaris. The rabbit-ear model has shown that certain pomades are comedogenic. Restriction of the use of pomades is essential, and the treatment of choice is with topical retinoids.

Detergent acne

This uncommon form of acne develops in patients who wash many times each day, in the mistaken hope of

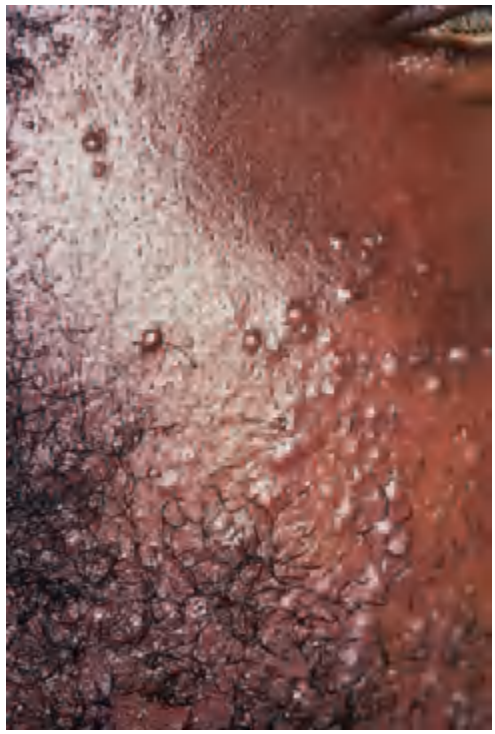


Fig. 43.57 A patient with pomade acne.

improving their existing acne. Trauma and the alkalinity of soap are likely to be involved in the mechanism. Pustular and papular lesions are most noticeable [39]. Several bacteriostatic soaps contain weak acnegenic compounds, such as hexachlorophene.

Folliculitis on the scalp (dissecting cellulitis of the scalp/folliculitis decalvans) and acne

Scalp folliculitis

About 1% of acne patients complain of, or are found on examination to have, small papules or pustules in the scalp. In patients with moderate and severe acne, it is not unusual to see inflammatory papules, pustules and nodules in and around the hairline in the occipital area. Despite the frequent occurrence of this association, there have been few clinical and research studies.

Follicular pustules in treated acne patients are also seen in subjects with Gram-negative folliculitis. Patients receiving treatment with oral isotretinoin may develop a pustular scalp folliculitis, which is either due to *S. aureus* infection or may arise for unknown reasons; in the latter instance they can be quite persistent for several weeks after stopping therapy. If due to a *S. aureus* infection, response to therapies such as oral flucloxacillin is very successful. Significant, very persistent scalp folliculitis associated with an acneiform eruption has been recorded in patients with cyclical neutropenia [40].

Folliculitis decalvans

Folliculitis decalvans is a chronically progressive disorder of the hairy scalp that leads to scarring, alopecia and atrophy [41–43]. The aetiology is unknown. In some patients, it is associated with very severe acne (often acne conglobata) and hidradenitis suppurativa, forming part of the so-called poral occlusion triad. In others, the disease occurs by itself and may possibly have an infectious aetiology; sometimes *S. aureus* may be identified in the lesions. When this occurs, appropriate oral antibiotics are necessary; the greater tissue penetration of oral clindamycin or rifampicin may help, possibly combined with topical mupirocin [44]. In other instances, therapies including oral antibiotics or oral isotretinoin can be tried, but the response is often very poor. Differential diagnosis of folliculitis decalvans in the younger patients includes pustular psoriasis, erosive pustular dermatosis of the scalp, folliculitis keloidalis nuchae, tufted folliculitis and trauma.

Dissecting folliculitis of the scalp

SYN. PERIFOLLICULITIS CAPITIS ABSCEDENS ET SUFFODIENS

This condition is more frequently seen in Afro-Caribbean males [45–47]. It is a chronically progressive inflammatory disease of the scalp similar to nodular acne of the face and trunk. The common pathogenesis of this disorder, the associated severe acne and the occasional concomitant hidradenitis suppurativa is occlusion of the follicular pores and a subsequent granulomatous response to the ruptured duct contents. The lesions characteristically last many years and are cosmetically very unpleasant, painful and foul smelling. It has been reported to occur with marginal keratitis [45]. Response to therapy is poor. Options include acne-type oral antibiotics, often in higher than average doses (such as minocycline 100 mg twice daily, trimethoprim 300 mg twice daily), and oral and topical isotretinoin; success has been reported with oral zinc sulphate, 135 mg three times a day [46,47]. Many different treatments have been tried, including potent topical, intralesional and systemic steroids and widespread surgical excision with skin grafting.

Granulomatous/lymphoedematous acne

This is sometimes reported as solid facial oedema in association with acne (Fig. 43.58). Solid symmetrical or asymmetrical facial oedema is likely to be due to pre-existing hypoplastic lymphatics. The disorder is frequently progressive, and the associated acne must be treated aggressively to minimize the swelling, which can become permanent. High-dose antibiotics or oral isotretinoin are usually mandatory [48], and often need to be combined with a short or intermittent course of oral steroids; how-

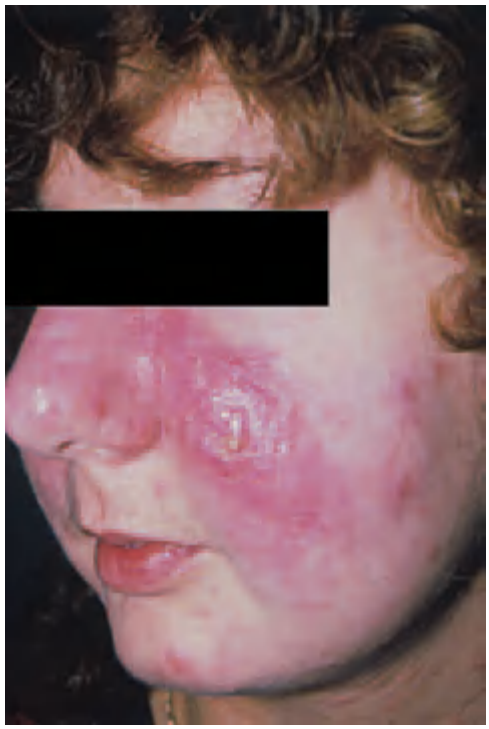


Fig. 43.58 A patient with granulomatous acne.

ever, the problem may be precipitated by oral isotretinoin. Clofazimine may help [48].

Extensive localized acne may also be due to an extensive granulomatous reaction to the mediators of acne inflammation. The precise mechanism producing localized granulomatous acne is not known. The clinical picture is usually that of deep, very well-demarcated lesion(s), especially on the cheeks. Response to therapy is slow and sometimes unsatisfactory—antibiotics and isotretinoin are of limited benefit; oral steroids are also often required.

These patients often have recurrent relapses and therefore long-term follow-up is recommended.

Hidradenitis suppurativa

This entity is described in more detail in Chapter 27. However, given its occasional association with severe nodular acne, often of the conglobate type, a brief note is necessary. There is often a family history and the onset is usually in late adolescence; the disease may persist up to the age of 40 or 50 years [49–54]. There are very occasional reports of early- or late-onset disease. It is a persistent disease that affects the axillae, breasts, and the genital and perianal areas, and may sometimes spread extensively on to the buttocks and lower back. There is clinical evidence of comedones (often polyporous), papules, pustules, deep nodules, large abscesses, sinus track formation and scarring. There is much discharge from the inflammatory lesions, which makes the simple activities of sitting, walking, working and sexual relationships at times almost impossible. Pain is a common feature; the foul smell is often dreadful both for the patient and close associates. Thus, the disease produces a high degree of morbidity, higher than for previously studied skin diseases, which correlates with disease intensity as expressed by new lesions per month [51].

It is primarily a disorder of the follicles at these sites, especially of the apocrine units, which become occluded. It is not a primary disease of the apocrine gland. Aetiological factors such as hyperandrogenism, obesity, smoking and local irritation (e.g. from excessive sitting) are not consistently associated with the disease, but in some patients may be relevant aggravating factors.

Treatment is usually very disappointing. Therapeutic options include long-term antibiotics as used in acne but in high doses, such as minocycline at 100 mg twice daily, trimethoprim 300 mg twice daily; co-cyprindiol plus additional CPA (100 mg/day taken from the fifth to the 14th day of the cycle); topical retinoids; topical antiseptic washes; oral isotretinoin; oral zinc; and potent topical, intralesional and intermittent pulsed oral steroids (the dose of steroid prescribed depending upon the severity of the inflammation). Combinations of such therapy may also be tried. At the moment, there are no good clinical data to indicate which therapy should be prescribed first and in what order. More recently, finasteride 5 mg/day has been reported to be successful [53] as has infliximab [54].

Infantile and juvenile acne

Infantile and juvenile acne, which mainly affects males, presents as facial acne in children between 3 and 24 months, and may last up to 5 years of age (Fig. 43.59) [55–65]. The lesions are more localized than in adults and particularly affect the cheeks. The individual lesions may include not just comedones, papules and pustules, but also both nodules and scarring. In the neonatal period, the differential diagnosis is neonatal cephalic pustulosis [66]. This disorder usually presents in the first 3 weeks of life, and is characterized by papular/pustular lesions especially on the cheeks. It may be associated with *Malassezia sympodialis*. Treatment is often not required for this self-limiting disorder, but a topical anti-fungal cream helps.

A study of 29 patients with infantile/juvenile acne over a period of 25 years [55] showed that the median age of onset was 9 months; the disease was mild in 24%, moderate in 62% and severe in 14%. In 59% the acne was predominantly inflammatory. Five patients (17%) were left with scarring (Fig. 43.60). It is important to note that this single study was from a specialist acne centre, and therefore the data may not reflect completely the overall clinical pattern of patients with infantile acne. It is thought that infantile/juvenile acne initially results from

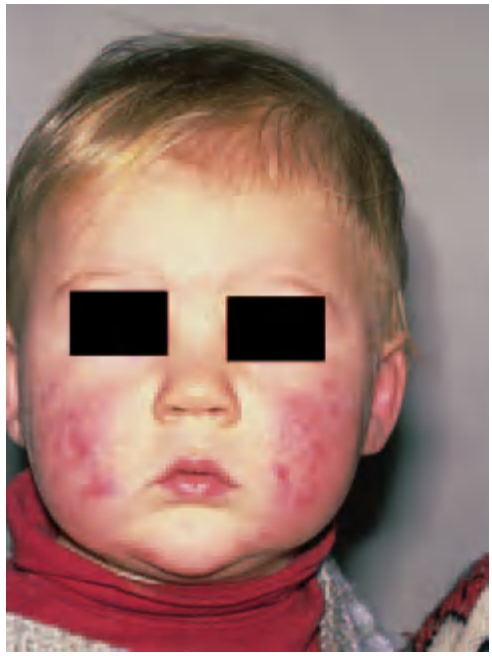


Fig. 43.59 A patient with infantile acne.

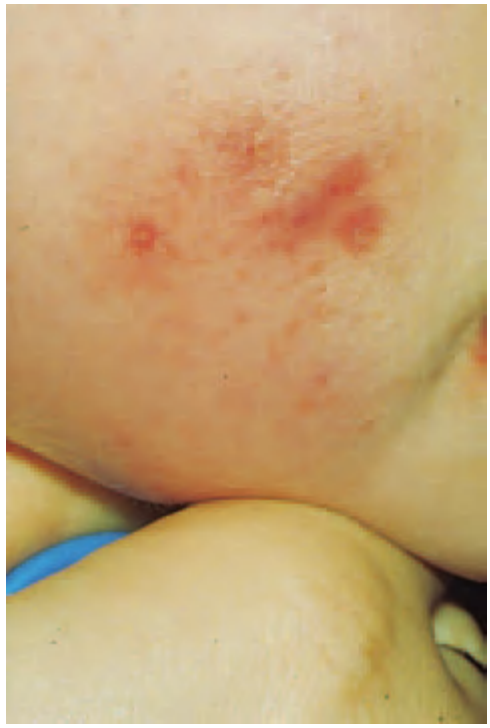


Fig. 43.60 A patient who has scarring as a consequence of infantile acne.

transplacental stimulation of the adrenal gland, as most sufferers have elevated plasma adrenal androgens [57]. Sebaceous glands are unique, in skin, in having enzymes capable of converting the adrenal androgen dehydroepiandrosterone to androstenedione and testosterone. It is uncertain why the acne should sometimes last for several years. Infantile acne is very rarely associated with other clinical features of androgen excess such as hirsutism or premature closure of epiphyses; very occasionally, there may be transient or more persistent high plasma levels of testosterone, LHs and FSHs. An associated virilizing tumour or underlying congenital adrenal hyperplasia is extremely rare. If the child is otherwise well and there are no other abnormal features, no endocrine investigations are required. However, such investigations may be appropriate in a patient who develops acne between 5 and 8 years of age. Occasionally, a drug such as phenytoin has been incriminated, but the evidence is weak [60].

The principles of treatment are the same as for patients with adult acne, except that the tetracycline group of drugs is not prescribed because of the risk of discoloration of permanent dentition. For mild disease, topical therapies such as topical retinoids, benzoyl peroxide, topical erythromycin or clindamycin are recommended. Perhaps the preferred choice is a combination of a topical retinoid and a topical antimicrobial agent. For moderate disease, a topical retinoid and/or benzoyl peroxide combined with oral erythromycin (as ethyl succinate, 125 mg three times a day) for 6 months is essential until lesions have totally disappeared. Alternatives include oral trimethoprim (100 mg twice daily) [55]. Infantile acne may take several months to resolve—the more severe the disease the longer the disease lasts [55]. Isotretinoin is rarely needed, and only for severe non-responding cases [61]. Patients with infantile acne may develop significant acne as teenagers [62–65].

Mechanical acne

SYN. ACNE MECHANICA

This term covers a mixed group of disorders in which the acne occurs at the site of physical trauma, as indicated by the pattern of the lesions [67–69]. Examples are so-called fiddler's neck, which occurs on the neck of violin players, and is also characterized by the presence of lichenification and pigmentation. Headbands (as worn by sports-people and hippies) and tight bra straps are other causes. Continuous friction from turtleneck sweaters may localize acne to the neck [68]. The mechanism of mechanical acne is unclear. Most patients have a tendency to develop acne, and its localization may be caused by an irritant dermatitis of the upper part of the pilosebaceous duct or excessive hydration at that site. Adolescent patients lying in bed for a long time, for example following a fractured femur in the orthopaedic ward, may develop a flare of acne—so-called 'immobility acne'. This is probably due to a change in the environment of the skin, which may enhance bacterial colonization of the duct [69]. Treatment of these conditions is the same as for other forms of acne but, in addition, advice on removal of the causative stimulus is essential.

Occupational acne

Oil and tar acne

This acneiform eruption occurs in areas of skin that are in contact with oils and crude tars [70–73]. It is now much less uncommon because of improved working practices. However, outbreaks do still occur. In a controlled study of 55 workers in a tar distillation plant, 18% in the study group and 4% of the control group had periorbital comedones [71].

Not surprisingly, men are more often affected than women. The skin may show conspicuous comedones and only occasionally do frank inflammatory lesions arise; these are usually superficial. Lesions can occur within 6 weeks of exposure on almost any site, but the thighs and lower arms are especially prone. It has been suspected, but not proven, that individuals with acne vulgaris are more likely to develop oil acne. The commonest oils involved are the impure paraffin mixtures used in the engineering industry. Petroleum products can affect oilfield and refinery workers; workers exposed to heavy coal-tar distillates, especially pitch and creosote, may also develop acne. Dichlorodiphenyltrichloroethane (DDT), asbestos and heavy water distillate has caused acne in some patients.

The treatment is removal from the source of the disease and the use of topical retinoids. If significant inflammatory lesions are present, then topical and oral antimicrobials may help. Very infrequently, oral isotretinoin has been successfully prescribed [73].

Chloracne

This variant is part of a syndrome that follows exposure to certain toxic, chlorinated hydrocarbons. Chloracne lesions consist of multiple comedones; inflammatory lesions are infrequent [74–89]. Comedones are often localized on both sides of the face (Fig. 43.61), especially the temporal regions, but in more severe cases may occur on other parts of the body. Other skin lesions may also occur, including porphyria-like changes, pigmentation, hypertrichosis and palmar and plantar hyperhidrosis. Ophthalmic chloracne may occur, due to the Meibomian gland involvement. Systemic abnormalities are less frequent, and include fatigue, anorexia, neuropathy, impotence, disturbed liver function and hyperlipidaemia. Often the chloracne and the systemic disturbances may last for many years following exposure [78,81,83,88]. Persistent chloracne, goitre, headache, broken teeth, anaemia and arthritis were more prevalent in patients compared to controls in a 14-year follow-up study following exposure to polychlorinated bihenyls and polychlorinated dibenzofurans [88].

Chloracne has been reported following exposure to chlornaphthalenes, polychlorbiphenyls, polychlorinated dibenzofurans, chlorophenol contaminants, trifluoromethyls, pyrazole derivatives and chlorobenzenes. Contamination often follows an explosion resulting in the uncontrolled liberation of the chemical [74,80,84]. The chloracnegens have been identified in the blood [80,87,89]. They have not been identified in the pilo-sebaceous apparatus, but in one instance exposure to dioxin was reported to produce a hyperproliferative reaction of the cutaneous epithelium with squamous metaplasia of the pilosebaceous duct, with subsequent atrophy of the sebaceous gland [85].

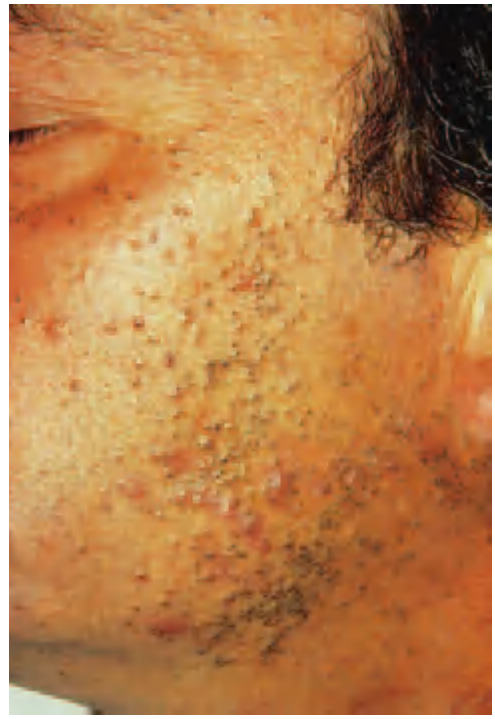


Fig. 43.61 A patient with multiple blackheads typical of chloracne.

The skin lesions are relatively persistent and resistant to treatment. Topical therapy with retinoids such as adapalene and tretinoin are worthy of a therapeutic trial; long-term oral antibiotic therapy may be needed for the inflammatory lesions. Oral isotretinoin does not help. This is not surprising, since the sebaceous gland has already undergone atrophy [86]. Gentle cautery under local anaesthetic cream (EMLA® applied for 60–75 min under polythene occlusion) produces excellent results [90]. Litigation is frequent when the contamination follows an industrial accident.

Osteoma cutis

Calcification, i.e. osteoma cutis, is an uncommon complication of acne and usually needs no treatment [91–93]. The calcification presumably occurs in areas of inflammation and presents as small, 2–4 mm persistent papules, which

are slightly firm to touch and usually skin or ivory coloured. They are occasionally associated with hyperpigmentation. The lesions are often suspected to be persistent closed comedones. A biopsy will reveal calcified trabecular bone formation surrounded by a perivascular proliferation, sometimes with increased fibrous tissue formation. The only successful treatment is carbon dioxide laser therapy. This is associated with quite a considerable local inflammatory response and so it is best to treat a small test area first before proceeding to treat all lesions.

Pilosebaceous naevoid disorders

Some of these disorders are only tenuously linked with the pilosebaceous system; they are described in more detail in Chapter 15.

Acne and non-acne naevi

Patients have been described with symmetrical areas of normal skin set in the midst of severe acne on the back [94], or with acne localized to one side of the back [95]. A reduced rate of sebum excretion with a reduction in surface bacteria has been demonstrated in the normal (non-acne) areas.

Comedo naevus

SYN. NAEVUS COMEDONICUS; NAEVUS FOLLICULARIS; NAEVUS UNILATERALIS COMEDONICUS

This uncommon naevus is usually a developmental defect of the hair follicles [96–102]. The associated sebaceous glands may be normal, hypoplastic or hyperplastic. In one case, however, the sweat duct was the origin of the lesions [98]. Lesions usually occur on the scalp, face and trunk, and occasionally at unusual sites such as the penis. The individual lesions are large comedones, often grouped or linear in arrangement (Fig. 43.62). Occasionally, inflammatory acne lesions may be found. Although usually present at birth, they can appear much later in life [102]. The symptoms are mainly cosmetic, but at times can be psychologically and physically devastating. An association with epidermolytic hyperkeratosis has been reported [101]. Treatment is usually only of limited success. Topical retinoids are a logical treatment. Twelve per cent aqueous ammonium lactate solution has been reported to be of benefit. Gentle cautery can help the less severe cases [102].

Familial comedones

This uncommon genetic disorder shows autosomal inheritance. The earliest lesions are monoporous, but later the face may be extensively involved with polyporous comedones and cysts, and scarring may follow. New lesions may continue into middle age.

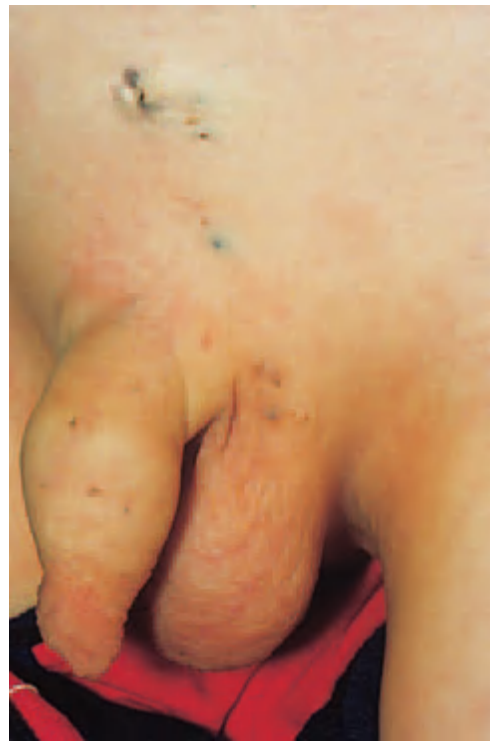


Fig. 43.62 A patient with a comedo naevus (predominantly consisting of blackheads) on the lower abdomen.

Pyogenic granulomas in acne

Pyogenic granulomas are a rare complication of healing severe nodular lesions [108], and this occurs more frequently following isotretinoin therapy [109]. The lesions can either be left alone or, if single, treated with cautery; if multiple, they will usually respond to clobetasol priopionate (Dermovate®) cream topically twice daily applied carefully to the lesions over a 2–3-week period.

Sebaceous naevus

SYN. NAEVUS SEBACEUS OF JADASSOHN

This is an organoid naevus, consisting of a mixture of relatively normal-looking epidermis, dermis, sweat and sebaceous glands. It usually presents on the scalp as an area of alopecia associated with a pinkish yellow, fleshy swelling [103–107]. At puberty, the sebaceous glands enlarge and the epidermis becomes verrucous. Co-occurrence with aplasia cutis has been reported [104]. Trichoepithelioma and eccrine syringoadenoma has been reported to develop in naevus sebaceus [106]. Unusual haematopoietic proliferation at birth that spontaneously resolved at 4 months has been documented [107]. Lesions occurring in the midline are often associated with mental subnormality and

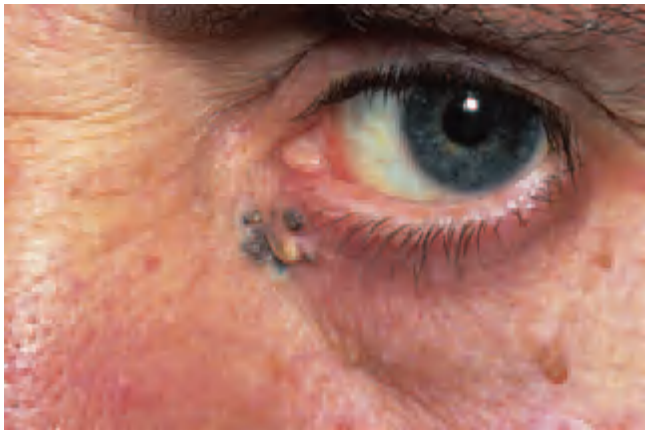


Fig. 43.63 A patient with senile comedones.

epilepsy. Excision is usually recommended because of malignant change into a squamous or basal cell carcinoma in later life [105].

Seborrhoea

Excessive grease production is an uncommon reason for referral, but many patients with severe acne complain bitterly of seborrhoea. In a recent unpublished personal survey, we demonstrated that many patients found seborrhoea to be as important a problem to the patient as inflammatory lesions. It can persist after acne has regressed [110]. Patients with acromegaly or parkinsonism, especially the post-encephalitic type, often have seborrhoea. Antibiotic and desquamating agents used in the treatment of acne do not influence the seborrhoea, but oral isotretinoin, CPA combined with oestrogen (cocyprindiol) and spironolactone all significantly reduce the seborrhoea. Physicians have to decide whether the patient's distress justifies the use of these systemic drugs.

(Acne with) solar comedones

SYN. SENILE COMEDONES; FAVRE–RACOUCHOT SYNDROME

These are seen in elderly people, especially in the periorbital areas (Fig. 43.63). Most patients have had high exposure to UV radiation, and the solar damage to the supporting dermis allows the pilosebaceous duct to become more easily distended with impacted corneocytes. The clinical presentation is that of multiple, open, and sometimes closed, comedones superimposed on a sun-damaged skin, usually symmetrically affecting the periorbital areas and the cheeks; occasionally the lesions are unilateral [111]. Similar lesions may be seen in pseudoxanthoma elasticum and after radiotherapy. In patients with isolated lesions, the edge of the adjacent skin may be mistaken for the pearly edge of a basal cell carcinoma. The lesions are easily removed with a comedo expressor, but they slowly recur. A topical retinoid to suppress the formation of future comedones may help. Gentle electrocautery can eliminate the smaller comedones [90].

'Tropical' acne (hydration acne)

Troops in the Second World War suffered badly when posted to the Far East, but US Marines in Vietnam were relatively spared, possibly because acne-prone individuals were not selected for service [112]. Certain occupations may aggravate pre-existing acne; for example, workers in a hot, humid environment, such as cooks and pressers, are at risk. It is thought that hydration of the pilosebaceous duct pores may accentuate blockage of the duct and so precipitate inflamed lesions [113]. A similar explanation may apply to 'Mallorca acne', in which small, follicular papules appear, especially on the upper trunk, during or after a holiday in a hot, humid environment. Potentially comedogenic sunscreens may be an additional factor in these patients [114]. These patients often need prolonged treatment as the event often precipitates or exacerbates troublesome pre-existing acne. Treatment options are the same as for acne vulgaris.

'Virally' induced acne

Acne can occur at unusual sites and at unusual ages with little involvement of the commonly affected sites. An acneiform rash has been reported at the site of previous herpes zoster infection. Histology revealed follicular occlusion and the disease was quite persistent [115].

A very small number of patients with severe acne and significant glandular fever responded poorly to oral antibiotics and oral isotretinoin. It was proposed that the viral illness in some way played an important role in the poor response [116].

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Severe acne variants

Six severe acne variants will be discussed in this section. For ease of reference, they are discussed alphabetically.

Acne conglobata

This is a most uncommon but severe form of acne, found particularly in males; the lesions usually occur on most of the trunk and upper limbs. In contrast to ordinary acne, facial lesions are less common. The condition usually appears in early teens, but unlike other forms of acne, becomes increasingly active in the second to third decades of life. It is characterized by multiple inflammatory papules and tender nodules which frequently fuse to form multiple draining sinuses (Figs 43.64 & 43.65) [1]. Grouped, multiple, fused blackheads and extensive scarring are also features. In some patients, the scarring is very mutilating [2]; in addition, malignant change may occur in

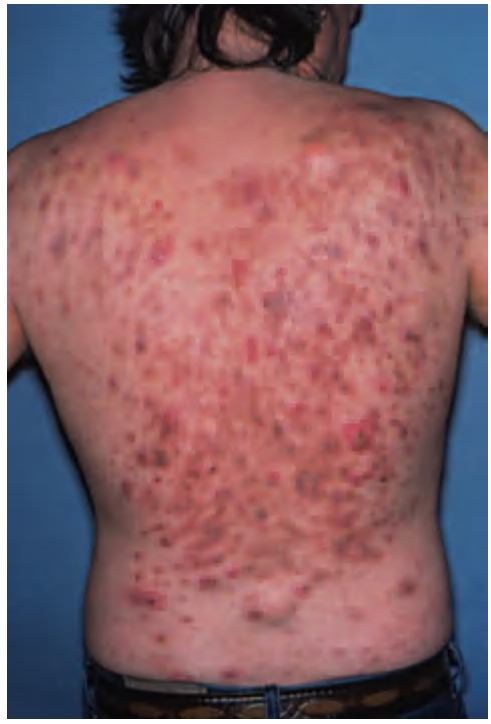

Fig. 43.64 A patient with extensive acne conglobata.

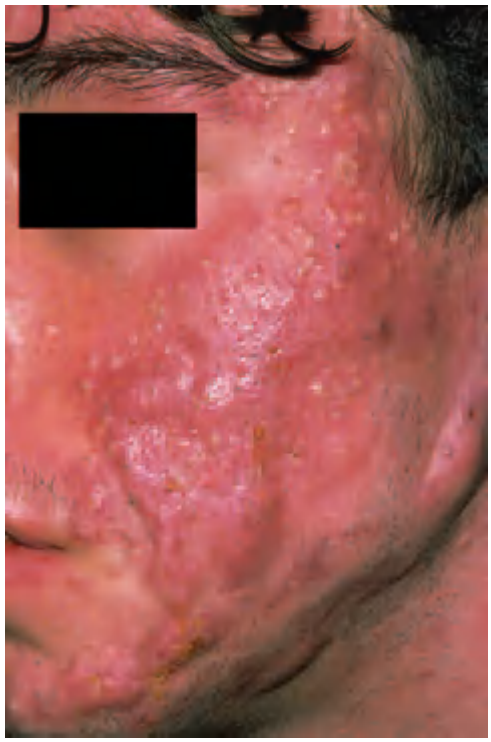

Fig. 43.65 Sinus formation in a patient with acne conglobata.

chronic scars [3]. Familial cases have been reported. Uncommonly it is associated with hidradenitis and folliculitis decalvans, which is a rare and chronic progressive hair disorder that produces scarring alopecia and atrophy [4]. Significant scarring is an inevitable consequence. Acne conglobata may persist to 40–50 years of age. Therapy is difficult; options include long-term high-dose antibiotics, colchine, dapsone and topical therapy. Oral isotretinoin (1 mg/kg/day) for 4–6 months is the treatment of choice. Isotretinoin may need to be combined with oral antibiotics such as erythromycin or trimethoprim. Concomitant short intermittent courses of oral steroids may be required to control acute exacerbation. Surgery may be required [2,5].

Acne fulminans

This was originally described as an acute form of febrile ulcerative acne conglobata. It is an uncommon, immunologically induced, systemic disease in which the offending antigen is *P. acnes*. The patients are predominantly young males who quite suddenly develop extensive inflammatory lesions, especially on the trunk (Fig. 43.66) [6–29]. Associated features are fever, polyarthropathy, marked leukocytosis (even a leukaemoid reaction), weight loss, anorexia and general malaise. Painful splenomegaly [19], erythema nodosum [20] and bone pain due to aseptic osteolysis have also been reported [17,21]. Bone involvement is common [22]; in a series of 24 patients, 48% had

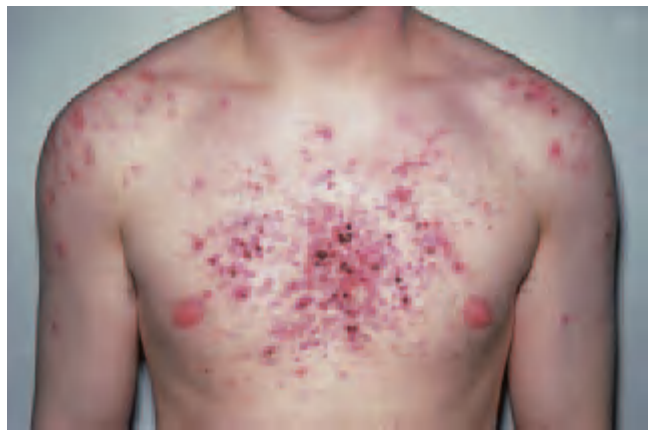

Fig. 43.66 A patient with severe truncal acne who had acne fulminans.

lytic bone lesions on X-ray and 67% showed increased radiolabel uptake; 25% showed destructive lesions resembling osteomyelitis [21,22]. The prognosis for bone lesions is good, and chronic sequelae, if any, are mild leading to sclerosis and hyperostosis [23]. Blood cultures from the pustular lesions are universally sterile. Skin tests with *P. acnes* demonstrate a very extensive, immediate and delayed reaction, the immunohistology of which reveals a type III or type IV hypersensitivity reaction [23].

Testosterone treatment, either legal or illegal, or oral isotretinoin may induce acne fulminans [24,25]. An acne fulminans-like picture has been reported in association with Epstein–Barr virus infection. Thus, patients with a sudden exacerbation of previously relatively mild acne should be checked for infectious mononucleosis [26].

Oral prednisolone therapy is required urgently (0.5–1.0 mg/kg/day), decreasing to zero over 6 weeks. The acute myalgia, arthralgia and fever can also be helped by oral salicylates or non-steroidal anti-inflammatory drugs and graduated physical exercise. The underlying skin condition requires high-dose antibiotics or oral isotretinoin (0.5 mg/kg/day), which should be started after 4–6 weeks of steroids and is the treatment of choice [23,27–29]. Topically, crusts need to be removed by soaking the skin with emollient oil, followed by the use of a potent steroid/antiseptic cream for 2–3 weeks.

Gram-negative folliculitis

This is a complication of long-term treatment of acne with antibiotics (usually taken orally, uncommonly by the topical route) [30–34]. It presents either as a sudden eruption of multiple, small follicular pustules (Fig. 43.67) or with nodular lesions. In the authors' clinic, 35% presented as a worsening of acne that had been under good control. Microbiological sampling from the nose and lesions reveals one or more Gram-negative organisms, including

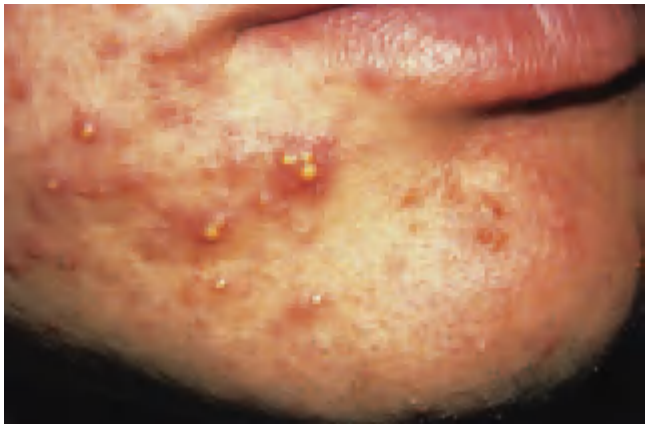

Fig. 43.67 A patient with the typical multiple pustules of Gram-negative folliculitis.

Klebsiella, *Escherichia coli*, *Proteus* or *Pseudomonas*. Therapy usually involves stopping the current antibiotics and replacing them with either ampicillin (250 mg four times a day) or trimethoprim (600 mg/day). However, the response may be slow and relapse is common. Isotretinoin is the treatment of choice; relapse following oral isotretinoin is less frequent than in patients receiving oral antibiotics.

Of our acne patients who present with many pustules (i.e. pustular folliculitis), about 1% have significantly high counts of *S. epidermidis*, and very occasionally this may cause signifant folliculitis [35]. Therapy usually requires stopping all antibiotics and using topical benzoyl peroxide, which is particularly helpful.

Pyoderma faciale

SYN. ROSACEA FULMINANS

This was initially believed to be a variant of acne but it is suggested that it is more related to rosacea (Chapter 44) [36–40]. However, there is still much debate, and further clinical and basic research is required on this devastating facial dermatosis. It is uncommon, and occurs in patients who usually have mild skin disease that suddenly erupts producing many pustules and nodules, especially on the face. It mainly affects post-adolescent women (aged 20–40 years), often following a period of stress (Figs 43.68 & 43.69). Comedones are rare, and facial flushing frequently precedes the acute illness. In contrast to acne fulminans, there are usually no systemic symptoms. The reason for the sudden flare is unknown. Rosacea fulminans has been reported in association with Crohn's disease—the significance of which is unclear [38]. The daily ingestion of high-dose vitamin B supplements has been reported to be associated with the sudden onset of rosacea fulminans [39].

Treatment consists of minocycline (100–200 mg/day) plus intralesional steroids or liquid nitrogen to the nodules, but the best treatment is perhaps oral isotretinoin (0.5 mg/kg) for 4–6 months (see Fig. 43.69) [36–39]. To minimize an acute exacerbation, oral prednisolone (0.5–1.0 mg/kg body weight/day decreasing to zero over 4 weeks) should be prescribed initially for 2–3 weeks

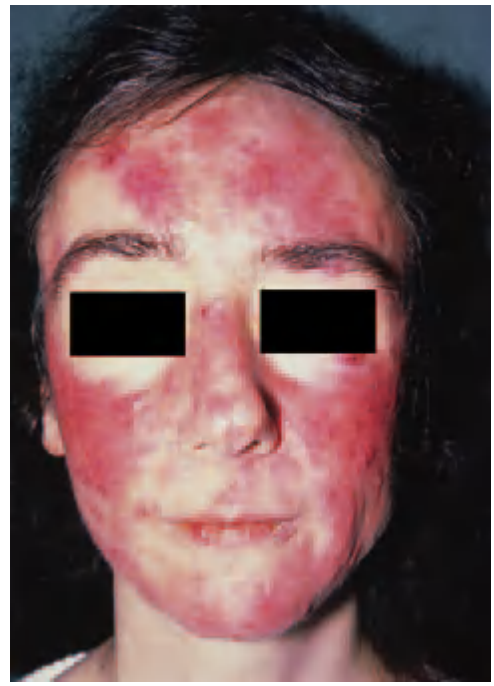

Fig. 43.68 A patient with rosacea fulminans.

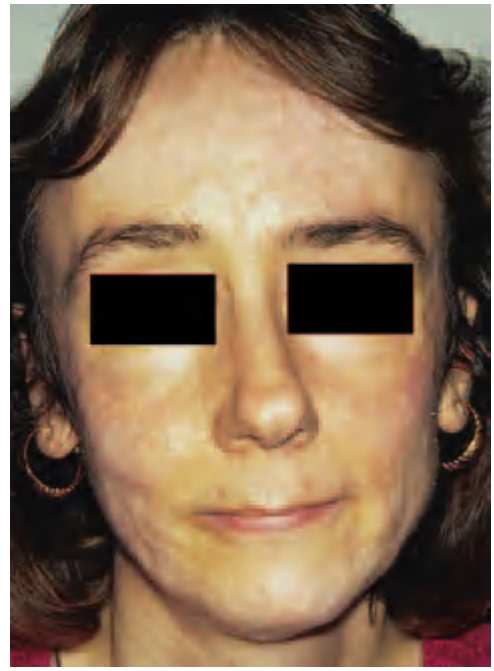

Fig. 43.69 The same patient as in Fig. 43.68 after 4 months treatment with oral isotretinoin.

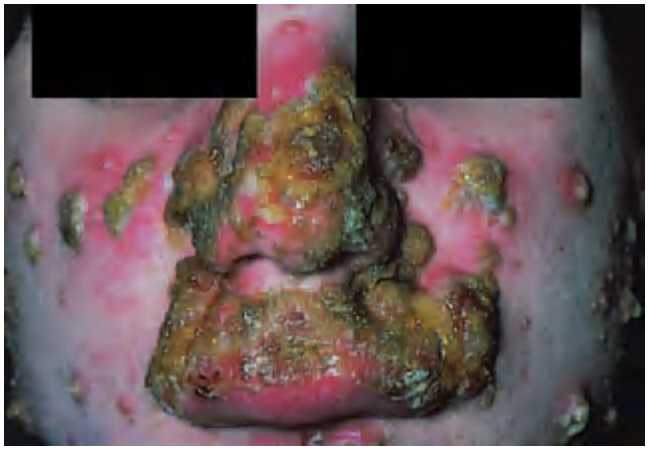

Fig. 43.70 A patient with very significant vasculitic acne.

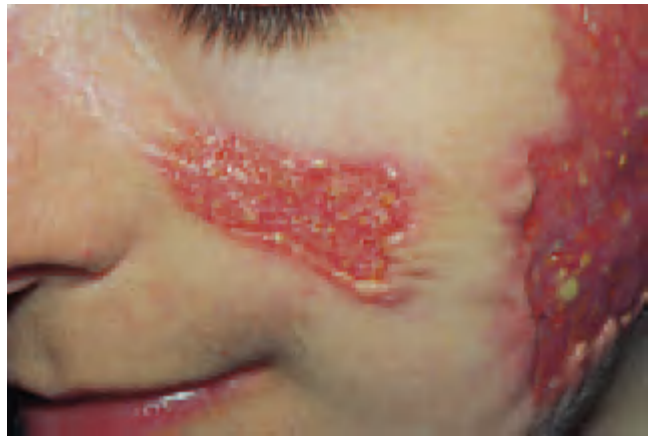

Fig. 43.71 Pyoderma gangrenosum-type scarring in a patient who had suffered from vasculitic acne.

before starting oral isotretinoin, which can then be taken at the same time. Alternatives include oral metronidazole and dapsone [40]. The prognosis is difficult to assess, but scarring is infrequent. Recurrence occurs more frequently than was believed some 5 years ago.

SAPHO syndrome

This acronym represents a syndrome of *s*ynovitis, *a*cne, *p*ustulosis, *h*yperostosis and *o*steitis [41,42]. In adults, and occasionally in children, chronic recurrent multifocal osteomyelitis can be associated with certain skin disorders. Severe acne is one of the less frequently associated disorders. The syndrome may be under recognized by dermatologists, since the skin manifestations in some patients can be quite mild. The disease may represent an immune reaction to a particularly skin or bacterial antigen.

Vasculitic/pyoderma gangrenosum acne

A few patients, who previously had very mild acne, have developed the sudden onset of severe vasculitic, pyoderma gangrenosum-like lesions (Fig. 43.70). Very significant scarring is the inevitable consequence (Fig. 43.71). The mechanism of this devastating acne is probably an immunological reaction to *P. acnes*. Such patients appear to be unresponsive to oral isotretinoin alone, but settle to some extent with oral steroids and azathioprine (200 mg/day) over a 3–4-month period [43].

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Ectopic sebaceous glands

These are commonly seen in the mouth—the so-called Fordyce spots—as multiple, symmetrical, barely elevated, discrete, yellow papules on the buccal mucosa [1]. They are present in 25% of the population over the age of 35 years, and are usually asymptomatic. When extensive they can, on the lip, be quite disfiguring and do respond to oral isotretinoin [2]. There are no adequate data that indicate whether or not they relapse post-therapy.

Similar lesions are common on the penile shaft, especially on the ventral surface, and at this site inflamed acne lesions may be seen, but usually the patient needs no more than reassurance. Other sites are occasionally affected such as the areolar area of the breast [3].

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Sebaceous gland hyperplasia, adenoma and carcinoma

Sebaceous gland hyperplasia

The sebaceous glands sometimes become prominent in middle-aged or elderly people. In white people they produce numerous yellowish pink papules, each 1–3 mm in diameter. They are seen especially on the forehead and temples, and are of no clinical significance. They also are present occasionally on the light-exposed skin of renal transplant patients who are receiving ciclosporin (cyclosporin) [1]. Treatment is rarely requested, but cosmetic camouflage may be used. If requested and appropriate, some physical treatments such as gentle cautery, cryotherapy, trichloroacetic acid, and carbon dioxide and pulsed dye laser may be used [2]. Sometimes, but very uncommonly, the lesions are diffuse, producing a yellowish hue to the skin. In such patients, oral isotretinoin has been reported to be of considerable benefit [3]. Co-cyprindiol (Dianette® and Estelle 35®), with or without additional oral CPA, will also produce regression of sebaceous hyperplasia whilst on therapy. A therapeutic trial of oral isotretinoin may help to differentiate between sebaceous hyperplasia and multiple early basal cell carcinomas in transplant recipients, and may avoid multiple biopsies if there are many lesions.

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Sebaceous gland tumours

These are very uncommon. The adenomas in particular may be associated with a systemic tumour.

Sebaceous adenoma

This is a benign tumour composed of incompletely differentiated sebaceous cells. It occurs in both sexes and is seen mainly in elderly patients on the face or scalp [1]. The pink or waxy yellow tumours are round, raised, sessile or pedunculated; they are usually 10 mm or less in size, but may form plaques and ulcerate. Excision is the best treatment, but they are radiosensitive. Very infrequently, sebaceous gland adenomas can be associated with multiple visceral carcinomas. The internal tumours are usually

of relatively early onset (45 years) and include adenocarcinoma of the colon, breast, ovary and prostate [2,3]. This association is referred to as the Muir–Torré syndrome, which is linked to the same chromosomal region as the familial cancer syndrome [4]. Such patients are characterized by the concurrent or sequential development of sebaceous gland tumours (adenoma, epithelioma or carcinoma) and at least one internal malignancy. With the Muir–Torré syndrome microsatellite instability can often be demonstrated in tumour DNA as a result of an inherited mutation in one of several known mismatch repair genes; however, the role of microsatellite instability in sporadic sebaceous carcinoma has until recently not been demonstrated. Of the nine tumours recently reported, five tumours were from four renal transplant recipients and four were from otherwise healthy individuals [5].

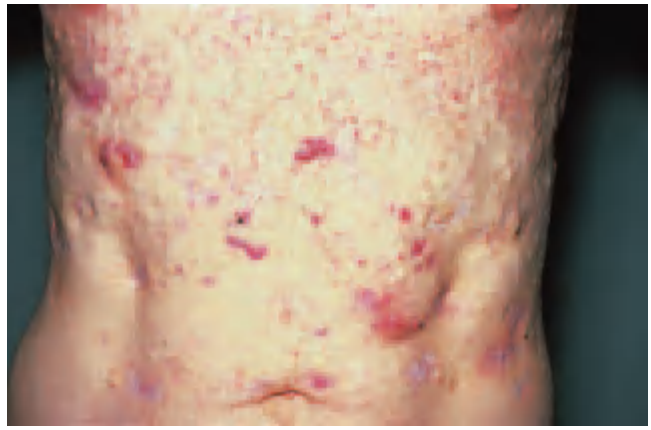

Fig. 43.72 A patient with extensive steatocystoma multiplex. There are both inflammatory lesions and non-inflammatory cysts.

Sebaceous carcinoma

This is a very uncommon malignant tumour usually involving men over the age of 40 years. It presents as a solitary, firm tumour, yellow–orange in colour, especially on the face and scalp. Sebaceous carcinomas have a well-recognized association with the Muir–Torré syndrome. The tumour grows slowly, but those arising in the eyelid (from the Meibomian glands) have a greater predilection for metastasizing [6,7]. Treatment is by excision or radiotherapy [7].

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‘Sebaceous’ (epidermoid) cysts and steatocystoma multiplex

The classical ‘sebaceous’ cyst (wen) is an epidermal structure; strictly, it should be referred to as an epidermoid cyst, and it is discussed in Chapter 36. However, true sebaceous cysts occur as so-called steatocystoma multiplex, a naevoid condition that histologically shows a mixture of a keratinizing epithelium and sebaceous lobules attached to the epidermis by a thin epidermal strand [1–3]. Steatocystoma multiplex is uncommon, and in some patients is associated with type 2 pachyonychia congenita (PC-2 or Jackson–Lawler syndrome), in which natal teeth are also a feature [4–6]. Histologically, the cysts in PC-2 may be true steatocysts, eruptive vellus hair cysts or keratinous cysts, even in the same family or individual [7–9]. To date, mutations in the Ia domain of keratin 17 (K17) have been found in all cases [9,10]. In some families with clinically and histologically typical steatocystoma multiplex, mutations in the K17 gene are also found [10]. In these families, close inspection shows that some but not all members have nail changes, which are usually but not always milder than those of PC. Familial steatocystoma multiplex has also been associated with natal teeth in the absence of nail dystrophy [11], and it seems likely that these cases are also due to keratin gene mutations. However, in a case of steatocystoma multiplex/eruptive vellus hair cyst (EVHC) and in another of EVHC, mutations in K17 were not found along the Ia domain [10], and hence it is likely that steatocystoma multiplex is genetically heterogeneous.

The lesions are multiple, smooth, elastic, yellow dermal swellings varying from a few millimetres to 20 mm in size (Fig. 43.72). They appear or enlarge at puberty, and mainly occur on the trunk or limbs. They last indefinitely, and whether they resolve with old age is uncertain. Inflamed lesions due to rupture of the cysts are common and, when extensive, can produce the so-called steatocystoma multiplex suppurativa, which mimics acne conglobata. Treatment is very difficult [1]; excision of the larger cysts is possible, but total removal of all cysts is impractical because of their number. Tetracycline (1 g/day) or minocycline (100–200 mg/day) for 3–6 months is required if the lesions suppurate. Topical therapy is of limited benefit. Oral isotretinoin is of some help in reducing inflammation, but does not affect the primary disease process.

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Chapter 44

Rosacea, Perioral Dermatitis and Similar Dermatoses, Flushing and Flushing Syndromes

J. Berth-Jones

This chapter brings together a range of dermatoses presenting with facial eruptions and/or flushing. It includes rosacea, the rosacea-like eruptions and carcinoid syndrome.

Rosacea

Definition. Rosacea is a disease lacking an entirely satisfactory definition. It is a chronic disorder affecting the facial convexities, characterized by frequent flushing, persistent erythema and telangiectasia, interspersed by episodes of inflammation during which swelling, papules and pustules are evident [1]. However, not all cases fit this description since not all features are always present. A recent attempt to define diagnostic criteria [2] concluded that the presence of one or more of the following signs with a central face distribution is indicative of rosacea: flushing, non-transient erythema, papules and pustules, telangiectasia. Clearly, if all individuals with one or more of these features are to be included, rosacea is both a common and highly heterogeneous entity.

Many authorities have expressed the view that vascular changes, particularly flushing, are the initial and constant feature, followed by progression to inflammatory changes (papulation and pustulation) and that the development of chronic lymphoedema, thickening of affected skin and rhinophyma are late complications. However many cases do not seem to demonstrate such a clear pattern of evolution.

Nomenclature. The term 'acne rosacea' is used synonymously with rosacea but is better avoided. It reflects the occurrence in both diseases of facial papules and pustules. However, the epidemiology, aetiology and pathology of rosacea are quite distinct from acne vulgaris. The latter is primarily a disorder of pilosebaceous units but it is not clear to what extent the same is true of rosacea.

Epidemiology. Rosacea is a very common disease. It is much more common in fair-skinned than darker-skinned individuals, although it does occur in black people [3]. Meaningful figures on prevalence are scarce, but in Swedish 'white-collar' workers the figure is probably about one in 10 [4], representing about 1–3% of dermatological consultations. Women are more commonly affected than men, although the development of rhinophyma is not common in women, who generally experience less severe disease than men. It is predominantly a disease of young to middle-aged adults, but it can occur occasionally in children [5].

Pathogenesis. The cause, or causes, of rosacea remain uncertain. In contrast to acne vulgaris, rosacea is not associated with seborrhoea [6]. Marks [1] has proposed that damage to dermal connective tissue, often caused by solar irradiation, may be the initiating event. This may result in dysfunction of the unsupported facial blood vessels with consequent endothelial damage, leakage, oedema and inflammation. Others have argued for the central role of abnormal vascular reactivity [7]. The association of rosacea with migraine seems to support this hypothesis [8].

As there is no associated sweating, it has been argued that flushing in rosacea is mediated by released vasoactive

substances rather than a neural reflex mechanism [9], but this cannot yet be taken as established and both mechanisms may play a role. Proposed mediators included serotonin, bradykinin, prostaglandins [10], substance P, opioid peptides and gastrin. Blood levels of substance P were raised in some patients but not consistently [11]. Opioid peptides have been proposed as mediators of flushing in rosacea on the basis of the suppressive action of the opioid antagonist naloxone [12].

It is often stated that rosacea is associated with gastrointestinal symptomatology, although there is little evidence to support this [13–15]. No consistent evidence of gastritis was obtained in a controlled endoscopic study [16]. An association between jejunal mucosal atrophy and rosacea has also been proposed [17] but has not been confirmed [18].

In recent years, the possible role of *Helicobacter pylori* infection of the gastric mucosa has been the subject of particular controversy. A high prevalence of this infection has been reported in patients with rosacea [19,20], reaching up to 100% in one uncontrolled series [20]. In controlled studies prevalence rates have sometimes been similar to controls [21–24] and sometimes higher than controls [15,25–27]. It has been suggested that the prevalence of seropositivity in patients with rosacea might be artificially reduced as a result of antibiotic treatment [15], increasing the difficulty in drawing conclusions from these data.

The role of *H. pylori* in rosacea might be clarified if it could be established that eradication of the organism cured the disease, but the available data are inconclusive in this regard. There are anecdotal reports of impressive responses. A patient who had suffered from rosacea for 9 years cleared and remained free of the disease 2 years later [28]. A case of granulomatous rosacea of 4 years duration resolved after eradication of *H. pylori* and remained clear 3 years later [29]. Significant improvement was seen in an uncontrolled trial of *Helicobacter* eradication, which studied 22 patients with rosacea and evidence of *H. pylori* infection [24]. In a placebo-controlled trial of *Helicobacter* eradication in 44 *H. pylori*-infected patients with rosacea, the disease abated in almost all the patients in both treatment groups, although none were cured [30]. There was no significant difference between placebo and active treatment at the 60-day end point, although improvement was somewhat greater in the active limb. In an open-label study comparing the response of rosacea to a *Helicobacter* eradication regimen in groups of patients with and without evidence of *Helicobacter* infection, both groups were improved when assessed at 3 and 6 weeks with a somewhat larger response being seen in those with *H. pylori* infection [26]. Szlachcic *et al*. [27] treated 53 *H. pylori*-infected patients with rosacea with an eradication regimen, and reported clearing of rosacea within 2–4 weeks in 51 cases. The clinical improvement was accompanied by resolution of gastritis and reduction in serum levels of gastrin, interleukin-8 (IL-8) and tumour necrosis factor-α (TNF-α), possible mediators of the vascular changes in rosacea.

A range of different eradication regimens were used in these studies but all contained antibiotics known to be effective in rosacea. Antibiotics used in treatment of rosacea are all potentially effective in treatment of *H. pylori*. Whilst these do have anti-inflammatory properties and may therefore work by other mechanisms, it remains an interesting and plausible hypothesis that suppression of *H. pylori* might partially explain their efficacy.

A potential role has often been proposed for the follicle mites *Demodex folliculorum* and *D. brevis* in the pathogenesis of rosacea. Infestation with these mites is extremely common in the general population, reaching up to 100% of subjects in some studies [31]. These organisms have traditionally been considered harmless commensals, but there is increasing evidence that they are potentially pathogenic, especially when present in very high numbers. Eruptions strongly resembling rosacea and associated with the presence of large numbers of *D. folliculorum* have been reported under the title of rosacea-like demodicosis [32,33]. These cases have improved following treatment to eradicate the mite.

Several investigators have reported increased numbers of *D. folliculorum* in the facial skin of patients with rosacea relative to controls [31,34–38]. *Demodex* mites have also been demonstrated in the dermis associated with an inflammatory response and undergoing phagocytosis by multinucleate giant cells. This phenomenon has been observed both in localized and in more widespread facial eruptions resembling rosacea [39,40]. Furthermore, *D. brevis* is often present in the eyelid in hair follicles, eyelash follicles and meibomian glands [41,42], and is often reported in association with periocular pathology including blepharitis and meibomianitis [43–45]. These observations would suggest that the presence of *Demodex* mites might also play a role in some of the ophthalmic complications of rosacea. Against a central role for *Demodex* is the relatively infrequent observation of the mites (in 19% or less of the biopsies) in some of the larger histological studies of rosacea [46–48]. However in a histological study specifically examining the prevalence of mites these were observed in 51% of patients with rosacea, and perifollicular inflammation was observed around infested hair follicles [49].

Further insight into the role of *Demodex* in the pathogenesis of rosacea might be gained by investigating the effects of eradication of this organism, but there has been limited formal study of this. In a small left/right comparative study permethrin cream and topical metronidazole both yielded similar results [50]. In a parallel group study permethrin was superior to placebo and equivalent to metronidazole in reducing papules and erythema [51]. Some improvement has been reported in an uncontrolled study

using crotamiton [37]. Benzyl benzoate reduces mite numbers but seems to be irritant in patients with rosacea [52]. A florid rosacea-like facial eruption associated with *Demodex* and accompanied by dermal inflammatory response and phagocytosis of the mites responded to metronidazole [40]. This is not easy to explain as metronidazole is not considered to be mitocidal [53]. However the mites may be associated with bacteria, both in their gut and on their skin [37], providing a potential microbial target for antibiotics.

Recently, rosacea has been reported as a manifestation in the skin of human immune deficiency virus (HIV) infection [54], and the same is true of rosacea-like demodicosis [33,55].

Clinical features. Rosacea is a polymorphic disease with several variants, each of which may require a different approach to treatment. The areas characteristically affected are the central convex areas of the face (nose, forehead, cheeks and chin) (Fig. 44.1). Occasionally, the scalp, upper chest, back and even the limbs may be involved [56]. In cases of rosacea showing the classical pattern of progression the onset is most often marked by vascular changes, notably episodic flushing usually unaccompanied by sweating. Erythema, which is accompanied by a burning sensation, gradually becomes more persistent, is easily triggered by minor irritants, and is associated with increasingly prominent telangiectasia. More advanced cases show follicular and non-follicular papules and pustules without comedones followed by persisting tissue thickening due to oedema, fibrosis and glandular hyperplasia, leading ultimately to a *peau d'orange* appearance and rhinophyma (Figs 44.2–44.4).

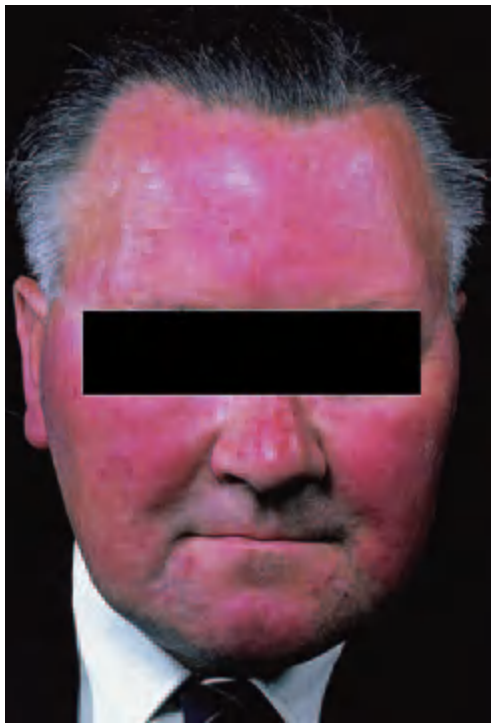

Fig. 44.1 Erythema mainly involving the convex areas of the face in a patient with rosacea. (Courtesy of Professor M. Greaves, Singapore General Hospital, Singapore.)

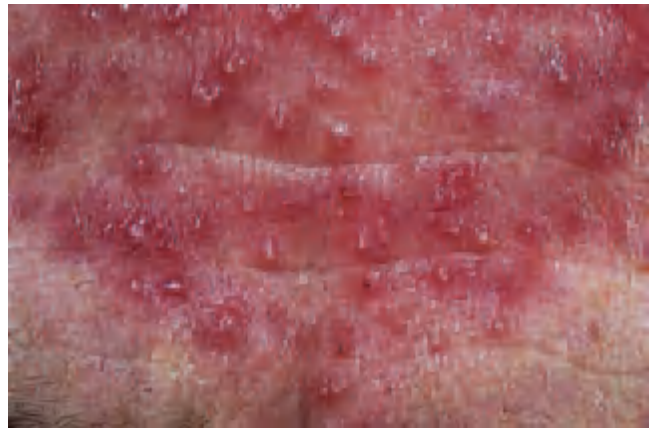

Fig. 44.2 Erythema, papules and pustules affecting the forehead in classical rosacea. (Courtesy of Professor M. Greaves, Singapore General Hospital, Singapore.)

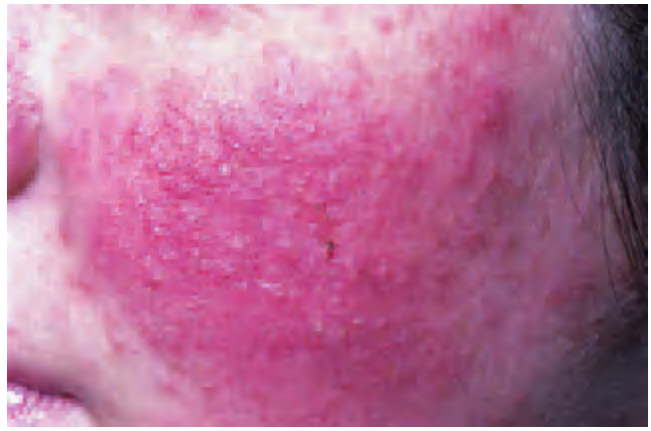

Fig. 44.3 *Peau d'orange* appearance of advanced rosacea. (Courtesy of Professor M. Greaves, Singapore General Hospital, Singapore.)

Factors which trigger flushing include emotion and stress [57], hot drinks [58], alcohol [12] and other vasodilating drugs, and spicy food. Despite traditional beliefs to the contrary it is the heat, not the caffeine content of hot drinks, which causes flushing [58]. Aggravating factors include the use of topical steroids on those occasions when they are used (usually in error) to treat rosacea. Sun exposure may worsen or improve rosacea [59].

The classical progression of rosacea is summarized in Table 44.1. Many cases do not follow this pattern. Some show predominantly the vascular features (erythematotelangiectatic rosacea), others develop mainly inflammatory lesions (papulopustular rosacea), others develop mainly chronic thickening and induration and still others

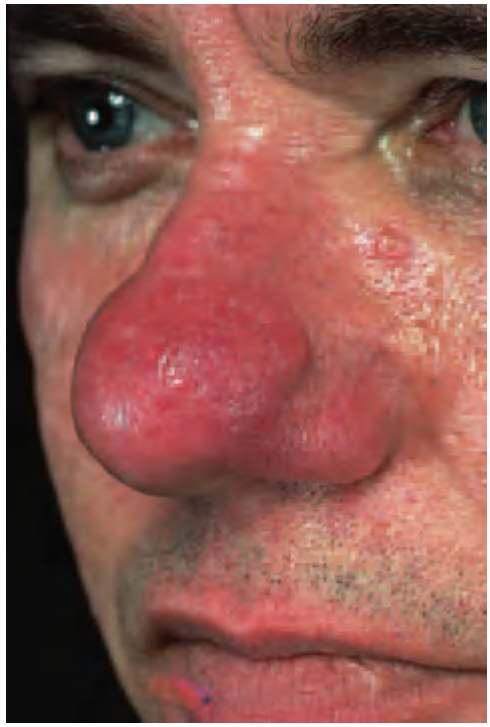

Fig. 44.4 Rosaceal rhinophyma. (Courtesy of Professor M. Greaves, Singapore General Hospital, Singapore.)

Table 44.1 Rosacea: clinical progression.

Early	Episodic flushing Mild telangiectasia Transient oedema
Progressive	Papules Pustules Sustained oedema Extensive telangiectasia
Late	Induration Rhinophyma

develop only rhinophyma. Each of these patterns may occur in isolation or in any combination.

Complications. Rosacea, usually of long duration, is associated with several important complications.

Chronic lymphoedema. This is a relatively rare complication of rosacea which can affect any part of the face and the ears (Fig. 44.5). In time this may develop into a coarsening of the features known as leonine facies. A characteristic pattern of lymphoedema of the upper half of the face developing as a complication of chronic rosacea has been termed chronic upper facial erythematous oedema or Morbihan's disease [60]. The orbital skin is often affected resulting in severe eyelid swelling and sometimes ectropion [61,62]. Histological examination reveals features of

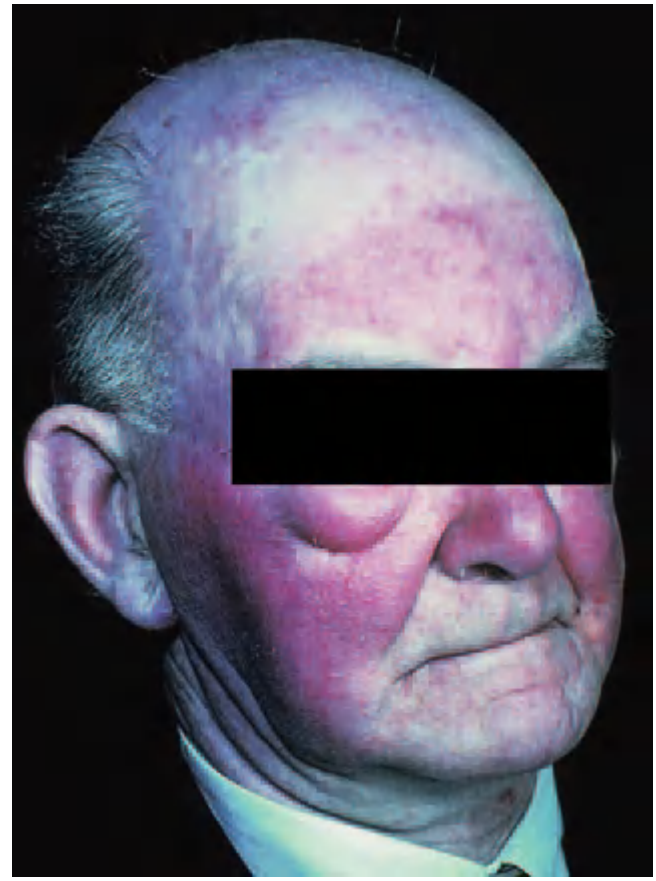

Fig. 44.5 Chronic lymphoedema in a patient with a long history of rosacea. (Courtesy of Professor M. Greaves, Singapore General Hospital, Singapore.)

lymphoedema and inflammatory cell infiltration of variable intensity.

Eye involvement. Ophthalmological complications are common, occurring in over 50% of patients with rosacea [63], although the pathogenesis is still not well understood. These include a sensation of grittiness or irritability of the eyes, often accompanied by visible reddening of the conjunctiva. Blepharitis, episcleritis, chalazion and hordeolum are also common. Rosacea keratitis is a more serious and quite common complication, occurring in 5% of patients including children [64]. The conjunctivitis, keratitis and other complications seem likely to be at least partly secondary to reduced tear secretion and Meibomian gland dysfunction which result in an unstable tear film [65,66].

Histopathology [46,47,49,67]. The histological features are predominantly dermal and tend to reflect the clinical features. Thus, telangiectasia is indicated by the presence of dilated superficial capillaries. Lymphatic channels may also be dilated but tend to be located rather deeper in the mid-dermis. Solar elastosis is commonly present and often

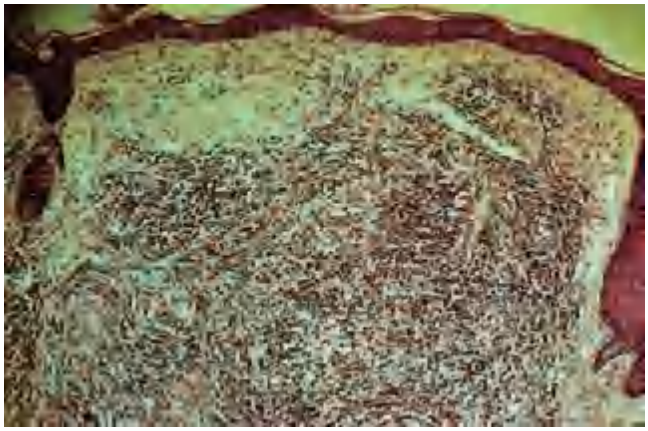

Fig. 44.6 Histological appearance of granulomatous rosacea (H&E × 40). (Courtesy of Professor M. Greaves, Singapore General Hospital, Singapore.)

prominent. The intensity and pattern of inflammation is variable, ranging from a mild perivascular lymphohistiocytic infiltrate in erythematotelangiectatic cases to more intense infiltration, which may be perifollicular, interfollicular and perivascular in papular rosacea. Some lesions show a granulomatous appearance (Fig. 44.6) and foreign-body type giant cells may be observed. Pustules are evidenced by polymorph accumulation in the upper parts of hair follicles. Areas of necrosis are occasionally conspicuous, sometimes marking the remnants of inflamed hair follicles. *Demodex folliculorum* has been observed in up to 51% of cases in one series [49] and may densely populate the pilosebaceous follicles. However, the mites have not consistently been associated with inflammation.

Differential diagnosis. Important differential diagnoses include acne vulgaris, lupus erythematosus, perioral dermatitis, seborrhoeic dermatitis and nasal sarcoidosis. Although acne vulgaris and rosacea are quite distinct diseases, there are occasional patients in whom the distinction is difficult. Since both conditions are common, it is to be expected that, by chance, both will occasionally occur in the same patient. Acne vulgaris affects a younger age group and often has an extensive distribution over the face, neck and trunk whereas extra-facial rosacea is rare. Typical acne vulgaris lacks the redness, telangiectasia and flushing of rosacea, whilst rosacea lacks the comedones and seborrhoea characteristic of acne vulgaris [68].

Scarring, scaling and follicular plugging are not features of rosacea and therefore readily distinguish it from facial discoid lupus erythematosus. However, patients are often referred to the dermatology clinic with a 'butterfly' erythema and a tentative diagnosis of systemic lupus erythematosus (SLE). The latter is not pustular and is usually associated with systemic symptoms. In some cases, lupus serology and a skin biopsy for histological and immunofluorescent examination may be necessary.

The pattern of the rash in seborrhoeic dermatitis differs markedly from that of rosacea. The former, but not the latter, characteristically involves the scalp, retroauricular area, eyelids and nasolabial folds. That scaling is not normally a feature of rosacea but is the rule in seborrhoeic dermatitis may also be helpful. However, rosacea and seborrhoeic dermatitis often seem to occur concurrently.

Nasal sarcoidosis (lupus pernio) superficially resembles rhinophymatous rosacea and both are granulomatous. However, sarcoidosis often affects the nasal septum (causing nasal obstruction); additionally, the surface of the thickened nose in lupus pernio, although telangiectatic, is smooth and lacks the rugose *peau d'orange* surface which characterizes rhinophyma. Patients with lupus pernio almost invariably have evidence of multisystem disease.

Demodex folliculitis can clearly mimic rosacea but is generally considered to be a separate entity.

The possibility of carcinoid syndrome should be considered when the symptoms are predominantly vascular and unusually severe (see p. 44.16).

Prognosis. The duration of the disease and the eventual outcome are highly variable and difficult to predict. In a follow-up study on 70 patients after 6 months treatment with tetracycline, two thirds had relapsed after a mean follow-up period of 2.6 years [69]. In a questionnaire survey of 92 patients 10 or more years after a diagnosis of rosacea, 48 of whom replied, 25 still had active disease whilst 23 had cleared [70]. In those patients in whom the rosacea had resolved, the duration of the disease had ranged from 1 to 25 years. There is no evidence that treatment affects the likelihood of resolution. When it persists, rosacea usually follows a fluctuating course. In males, and less often in females, the persistence of rosacea may result in chronic thickening and induration of the face (leonine facies) and rhinophyma. Eye involvement is usually mild and reversible, though occasionally ocular keratitis can lead to severe scarring and even corneal perforation [71]. Most symptoms of rosacea can usually be successfully controlled (see below) but the flushing is often impossible to suppress.

Treatment. Papulopustular rosacea responds well to treatment in the majority of cases, but improvement may be gradual and so perseverance is sometimes required. Relapse is often prompt when treatment is discontinued [69]. It is important to avoid irritants such as strong soaps and alcohol-based cosmetic cleansers. Although many patients say that their rosacea improves in the sun, solar exposure should probably not be encouraged in view of the marked photodamage often seen in these patients and the possible role of this elastotic change in the pathogenesis.

Papulopustular rosacea. Both topical and systemic modalities can be highly effective and patients often have a

particular preference for one route or the other. Effective oral agents include tetracyclines (e.g. tetracycline or oxytetracycline 250 mg twice daily) and erythromycin 250 mg twice daily. Higher doses are often prescribed in the belief that they are more effective, although there is little evidence that this is true. More recently developed tetracyclines such as minocycline, lymecycline and doxycycline are often used and offer the advantages of once daily administration and lower potential for interaction with dietary calcium, enabling them to be taken with food. Ampicillin appears superior to placebo but less effective than tetracycline [72]. Oral metronidazole can also be effective [73], although this can cause peripheral neuropathy if used for more than 3 months. Development of Gram-negative folliculitis has been reported as a rare complication of broad-spectrum antibiotic treatment of rosacea [74].

Oral isotretinoin (10–60 mg/day) is an alternative in resistant rosacea [75] and can even improve rhinophyma [76]. This is most often used in relatively low dosage in rosacea, partly due to concern about the potential to worsen ocular disease. Treatment may need to continue for several months and particular caution is required with this teratogenic drug in fertile female patients.

Topical treatment with metronidazole 1% cream is effective [77]. A 0.75% gel formulation is also available and is preferred by some patients. Tetracycline and erythromycin are also available in topical formulations, although these are lotions developed for treatment of acne vulgaris and they can prove irritant on skin affected by rosacea. Clindamycin gel, also developed for the treatment of acne, may be better tolerated. Additional topical therapies reported as effective include azelaic acid 20% cream and 15% gel, 0.025% retinoic acid and 10% sulphur cream.

Combinations of topical and systemic treatment are often used. There is little point in discontinuing treatment before 3 months and in many cases it is necessary to continue for several years.

Treatments directed at eradication of *H. pylori* or *Demodex* are discussed above. The final place of these modalities will be determined when the pathogenic role of these organisms has been established or excluded. On current evidence, the author would suggest that these treatments may prove helpful in individual cases where there is reason to believe that these organisms may be playing a role.

Flushing. It is important to explain to patients with papulopustular rosacea that none of the above measures will significantly suppress the troublesome flushing, or the burning discomfort which often accompanies this. Flushing and burning are the most difficult features of rosacea to treat. Non-cardioselective β-blockers such as propranolol 40 mg twice daily or nadolol 40 mg daily [78] are often used but generally provide rather limited benefit. Clonidine 50 μg twice daily and the related but less sedative drug rilmenidine 1 mg daily may also provide some modest improvement, perhaps due to a non-specific vasoconstrictor effect [79]. On occasions, removal of telangiectasia with vascular lasers or intense pulsed light can be surprisingly beneficial in reducing flushing and burning.

Cosmetic camouflage may also be helpful for patients with persistent facial redness. The British Red Cross provide cosmetic camouflage clinics free of charge throughout the UK in association with hospital dermatology departments (British Red Cross Beauty Care and Camouflage Service, 9 Grosvenor Crescent, London SW1 7EJ, UK).

Telangiectasia. The advent of vascular lasers and intense pulsed light sources has provided a range of highly effective treatments for ablation of telangiectasia [80–82].

Lymphoedema of rosacea. Treatment is far from satisfactory. Reduction of the inflammatory component of rosacea by broad-spectrum antibiotics may slow down progression. Jansen and Plewig [60] have suggested the use of low-dose isotretinoin 0.1–0.2 mg/kg/day over a period of 2–4 months, which may be combined with ketotifen 1–2 mg daily and a potent H_1 antihistamine. Marked reduction in facial swelling was reported in one case treated with a reducing course of prednisolone, starting at 30 mg daily, and metronidazole 400 mg/day over a 4-month period, followed by metronidazole 200 mg/day [83]. For established leonine facies, regular facial massage may help. In cases of severe eyelid oedema, surgical debulking of the tissue has proved helpful [84].

Rhinophyma. This is discussed below (p. 44.8).

Ocular rosacea. Ocular rosacea is most frequently treated with systemic tetracyclines. A comparison of doxycycline 100 mg/day and tetracycline 1 g/day showed improvement in both treatment groups. The tetracycline was significantly more effective at 6 weeks, but the difference between groups was insignificant at 3 months [85]. In another trial, a topical ophthalmic formulation of fusidic acid appeared more effective than systemic oxytetracycline [86]. The use of retinoids should be avoided in patients with eye involvement. Patients also find regular application of a liquid paraffin eye ointment symptomatically helpful.

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Rhinophyma and other phymas

The phymas are localized swellings of facial soft tissues due to variable combinations of fibrosis, sebaceous hyperplasia and lymphoedema [1]. They develop almost entirely in males. The commonest is rhinophyma, a swelling of the nose which may become grossly distorted in contour (Fig. 44.7). Other areas which may be affected include the forehead (metophyma) (Fig. 44.8), chin (gnathophyma), eyelids (blepharophyma) and ears (otophyma) [2]. In many cases rhinophyma develops in patients with a long history of other features of rosacea, and it is often regarded as a complication or 'end stage' of the disease. However, rhinophyma is sometimes also seen in patients who do not have any history of other manifestations of rosacea. Occasionally rhinophyma is complicated by the development of a malignancy and this can be difficult to recognize [3].

It is likely, but not proved, that active treatment of rosacea may inhibit the development of rhinophyma. Unfortunately neither systemic nor topical treatments for rosacea have any useful impact on established rhinophyma. One exception is systemic isotretinoin, which can significantly reduce the bulk of rhinophyma although it does not restore normal skin contours [4]. Treatment of rhinophyma and other phymas therefore usually involves surgical removal of excess tissue or other means of physical ablation. Remodelling can often be successfully achieved simply by paring off the excess tissue with a scalpel. Electrosurgery is an inexpensive alternative method. Excision and vaporization with argon, carbon dioxide or Nd : Yag lasers is effective. Other treatments have included cryotherapy and ionizing radiation [5]. The latter approach is probably most useful in cases with coexisting malignancy.

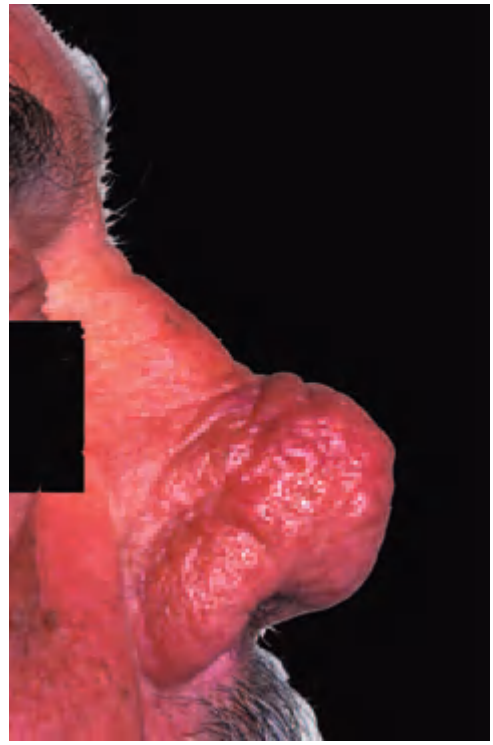

Fig. 44.7 Rhinophyma. (Courtesy of Dr I. Ahmed, University Hospitals Coventry and Warwickshire NHS Trust, Coventry, UK.)

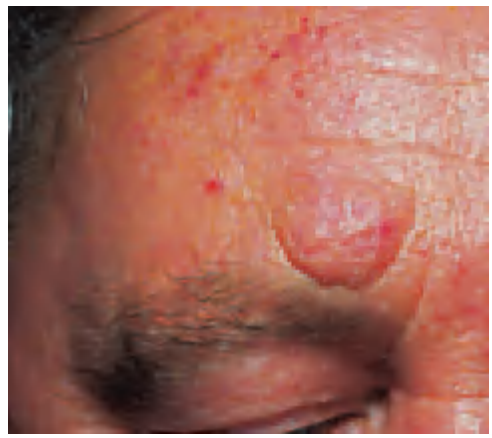

Fig. 44.8 Metophyma.

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Corticosteroid-induced rosacea

The use of potent topical corticosteroids on the face often results in a papulopustular eruption accompanied by erythema which may closely resemble rosacea (Fig. 44.9) [1,2]. Patients of all age groups and either gender are susceptible, although this seems to happen rather more often in females. It is usually necessary to apply potent corticosteroids for 8 weeks or more before steroid rosacea develops. If application of the steroid continues, fixed erythema and telangiectasia develop, further increasing the similarity to idiopathic rosacea. Patients experience exquisite sensitivity of the involved skin to the slightest irritant: itching, burning and intense redness being the major complaints. Whenever the corticosteroid is discontinued, the eruption flares, leading to a state of dependence. Patients affected by steroid rosacea often fail to recognize the causal link between the corticosteroid treatment and the rash. On the contrary, the application of the corticosteroid usually produces prompt, if transient, improvement in the symptoms, creating the illusion of significant benefit.

On occasions, even 1% hydrocortisone may provoke steroid rosacea in children [3]. The use of steroid nasal spray may also be responsible [4]. A granulomatous eruption described as resembling rosacea developed 9 months into therapy with topical tacrolimus 0.1% ointment [5]. This resolved on treatment with doxycycline and did not recur when the tacrolimus was reintroduced.

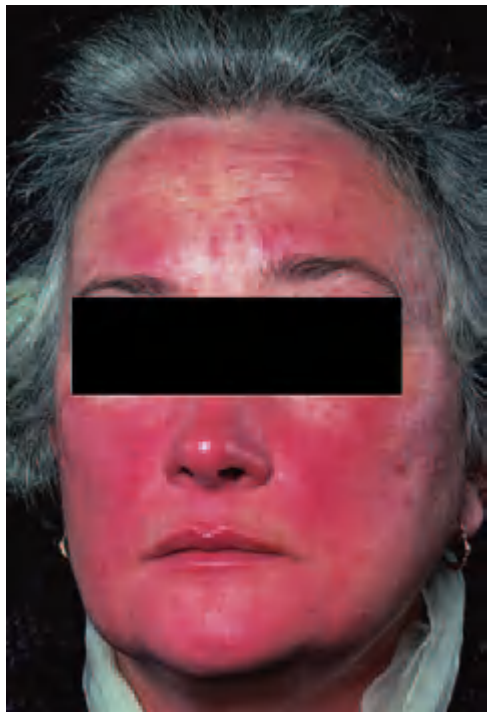

Fig. 44.9 Corticosteroid-induced rosacea. (Courtesy of Professor M. Greaves, Singapore General Hospital, Singapore.)

Treatment. The first and most important step is withdrawal of the causative topical corticosteroid. Patients must be advised to anticipate a flare of the rosacea at this stage. In order to reduce the severity of this flare it is often necessary initially to introduce a less potent steroid. The author has found that a topical or systemic antibiotic, used in the same way as in idiopathic rosacea, can also be very useful in the early stages of steroid withdrawal. Topical application of tacrolimus 0.075% ointment proved helpful in three cases [6]. Steroid rosacea may take several weeks or even months to subside but eventually complete resolution can be anticipated.

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Perioral dermatitis

Definition. Perioral dermatitis is a persistent erythematous eruption consisting of tiny papules and papulopustules with a distribution primarily around the mouth [1]. A similar eruption involving the eyelids and periorbital skin has been termed periocular dermatitis [2,3].

Epidemiology. First described in the late 1950s and 1960s, it became a commonplace diagnosis in the 1970s [1]. Over the past decade there has been an apparent fall in new cases—possibly attributable to a decline in the use of potent topical steroids on the face. It almost entirely affects young adult females, the age range tending to be somewhat younger than that of rosacea and occurrence in childhood more frequent. It has a worldwide distribution.

Aetiology. Although infectious agents and infestations including *Candida* spp. [4], *Demodex* [5] and fusiform bacteria [6] have been incriminated, none has been confirmed to play a significant role. A variety of primary irritant

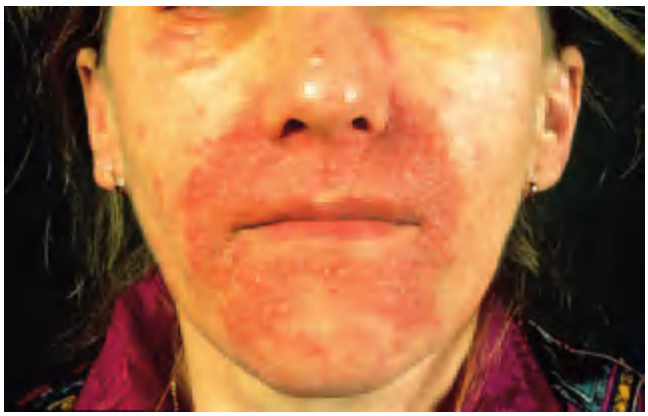

Fig. 44.10 Perioral dermatitis. (Courtesy of Professor T. Luger, Münster, Germany.)

and allergic contact factors have been proposed but not substantiated, including toothpaste and intimate contact with a partner's beard stubble [2]. Despite the prevalence among young female adults, there is no evidence to incriminate the oral contraceptive pill. Cosmetic products, especially foundation, may play a role, possibly resulting from an occlusive effect [7]. Topical corticosteroid therapy is known to be an important aetiological factor. Prescribed initially for trivial facial eruptions, regular application of potent topical corticosteroids leads to papulation and pustulation in the 'muzzle' area of the face [8,9]. Even brief exposure may occasionally cause the disease [8]. The more potent the corticosteroid the more likely it is to cause perioral dermatitis, although even hydrocortisone may very occasionally be sufficient [10]. The use of inhaled corticosteroids for treating asthma, particularly from nebulisers, may also cause perioral dermatitis [11]. Systemic corticosteroids may be an additional triggering factor [12]. Periocular dermatitis may be caused by corticosteroid eye ointment [3].

Clinical features. Characteristically, the eruption begins abruptly in the nasolabial areas, spreading rapidly to the perioral zone but sparing the lip margins (Fig. 44.10). The course of the condition may be continuous, intermittent or remittent. Occasionally it may spread to the forehead, eyelids and glabella; rarely, there may be periocular lesions alone. Pruritus, burning and soreness are prominent symptoms. The lesions consist of monomorphic small papules and pustules occurring against a background of redness and variable scaling. The papules may occur in recurrent crops and are usually less substantial than those of rosacea. Strong soaps, sunlight and even contact with water may cause discomfort.

Histopathology. There is not a large amount of data published on the histology of perioral dermatitis, probably because of concern over the risk of scarring from facial biopsies. One study of 26 cases [13] showed a perivascular and perifollicular mononuclear cell infiltrate with mild eczematous changes. In another study of 36 patients similar features were observed but, in addition to epidermal spongiosis, oedema of the papillary dermis was prominent. There was often perifollicular inflammation and some follicular pustules were observed. Granulomatous infiltration was observed in only two cases and *Demodex* mites were also rarely present [14].

Differential diagnosis. The clinical picture of perioral dermatitis is distinctive. The important differential diagnoses include rosacea, seborrhoeic dermatitis, contact allergic dermatitis, late-onset acne vulgaris, acne agminata and facial Afro-Caribbean childhood eruption (FACE, see below). Unlike rosacea, there is usually no telangiectasia or flushing in perioral dermatitis. Seborrhoeic dermatitis, like perioral dermatitis, affects the nasolabial area, but is not usually circumoral and the scalp, ears and eyebrows are commonly involved. Contact dermatitis does not usually spare the immediate perioral area, but may present a problem which can only be resolved by patch testing. Acne vulgaris usually shows evidence of comedones, large papules and cysts in a wider distribution and responds more slowly to treatment than perioral dermatitis. Acne agminata may be difficult to distinguish if confined to the perioral area but can be differentiated histologically, if necessary, as the lesions are more consistently granulomatous. Similarly, FACE may be difficult to distinguish when the lesions are predominantly perioral, although they do not spare the perilabial skin as in perioral dermatitis and pustules do not occur. FACE occurs in Afro-Caribbean children and, unlike perioral dermatitis, seems to occur often in males.

Prognosis. Most patients experience permanent remission after a fairly short course of broad-spectrum antibiotics [15]. Relapses occur in a small minority [16]. However, if untreated and especially if the provoking topical corticosteroids are continued, perioral dermatitis can persist for years [17].

Treatment. The most important measure is usually to discontinue the application of topical corticosteroids. Other applications, including cosmetics, should also be stopped. The patient must be warned that an initial flare may develop after withdrawal of a topical corticosteroid. A 4-week course of oral tetracycline is usually all that is required. Topical tetracycline is also effective [18], as is topical metronidazole cream 1% [19] and topical erythromycin [20].

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Acne agminata

SYN. LUPUS MILIARIS DISSEMINATUS FACIEI; ACNITIS; FACIAL IDIOPATHIC GRANULOMAS WITH REGRESSIVE EVOLUTION (FIGURE)

Acne agminata is seen mainly in young adults and adolescents of either gender, although a case has been reported in a 71-year-old Japanese woman [1]. It presents as multiple, monomorphic, symmetrical, reddish-brown papules on the chin, forehead, cheeks and eyelids (Fig. 44.11). The lesions may cluster around the mouth or on the eyelids or eyebrows so that the term 'agminata' is appropriate, although paradoxically, in many cases, the lesions are widely disseminated around the face and the term 'disseminatus' seems more applicable. Diascopy of larger lesions often reveals an apple-jelly nodule-like appearance indicating their granulomatous histology, which also shows central caseation. The lesions are not consistently related to hair follicles [2]. This eruption tends to be self-limiting, resolving completely over a few months or up to 2 years. In some cases there is scarring. There are reports of similar eruptions having an extra-facial distribution but this seems to be very rare [3].

The clinical picture in classical cases of acne agminata is quite distinctive and does not closely resemble rosacea or acne vulgaris since the other features of these diseases are not present. The synonym 'lupus miliaris disseminatus' results from a historical classification of this condition as a presentation of tuberculosis. It now seems most unlikely to be tuberculous in aetiology and more likely that this condition is a distinct entity. The recently proposed acronym 'FIGURE' (facial idiopathic granulomas with regressive evolution) is perhaps more appropriate as it avoids linking the condition to acne or tuberculosis [4].

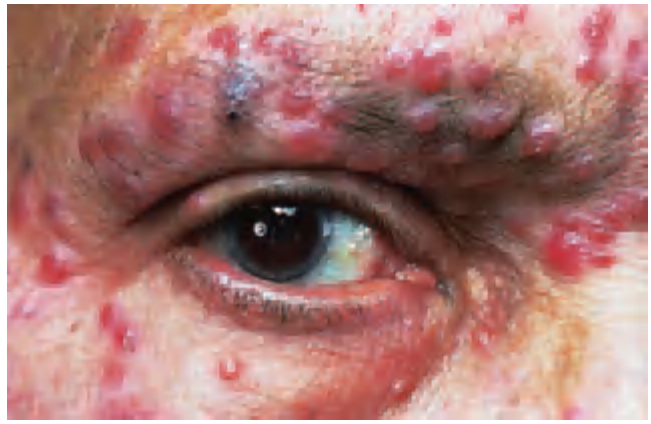

Fig. 44.11 Acne agminata. (Courtesy of Professor M. Greaves, Singapore General Hospital, Singapore.)

The aetiology remains unknown. It has been considered by some to be a variant of rosacea and may represent a self-limiting variant of the granulomatous form of this disease. Whilst the distribution of lesions is similar the natural history and the tendency to affect male and females approximately equally argue against this being a form of rosacea. It can be difficult to distinguish from micropapular sarcoidosis.

The response of acne agminata to tetracyclines has been variable, as has the response to isotretinoin. Dapsone may be effective [5], and a good response to low-dose prednisolone has been reported [6]. In one case the use of clofazimine 100 mg three times weekly was followed by complete resolution within 8 weeks [7].

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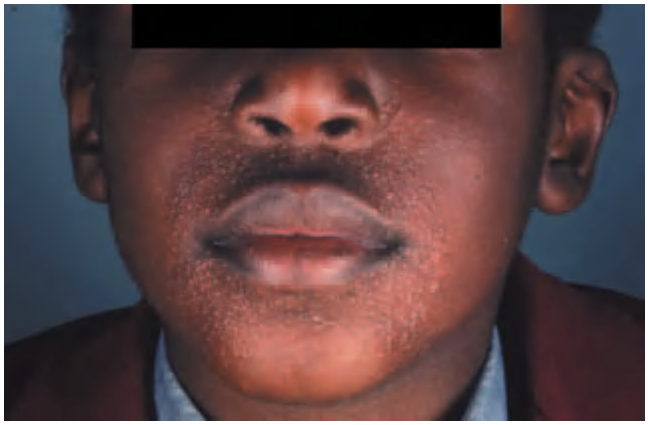

Fig. 44.12 Facial Afro-Caribbean childhood eruption (FACE). (Courtesy of Professor H.C. Williams, Queen's Medical Centre, Nottingham, UK.)

Granulomatous perioral dermatitis in children

SYN. FACIAL AFRO-CARIBBEAN CHILDHOOD ERUPTION (FACE); GIANOTTI-TYPE PERIORAL DERMATITIS; GRANULOMATOUS PERIORIFICIAL DERMATITIS; SARCOID-LIKE GRANULOMATOUS DERMATITIS

This eruption, which is seen in prepubertal children, may represent a juvenile form of perioral dermatitis or of acne agminata. It is considered relatively common in Afro-Caribbean children giving rise to the acronym FACE (Fig. 44.12) [1] (see also Chapter 69).

This is a papular eruption that is generally confined to the face, with lesions clustering around the mouth, eyes and ears [1–4]. In contrast to perioral dermatitis it does not spare the narrow zone bordering the lips and pustules are not seen. The histology has been variously described as showing non-specific inflammation with hyperkeratosis or, more often, as granulomatous, with the inflammatory changes often, but not invariably, being perifollicular. Blepharitis has occasionally been present. A series of cases with typical facial lesions accompanied by more disseminated lesions involving the trunk, limbs and labia majora has recently been described [5].

Complete resolution usually occurs after a few months, either spontaneously or in response to treatment. In some cases small, pitted scars have been reported. Treatment with systemic erythromycin or topical metronidazole seems to have hastened resolution in several cases.

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Pyoderma faciale

SYN. ROSACEA FULMINANS

Although pyoderma faciale is also known as rosacea fulminans it is not yet clear whether this condition is a variant of rosacea or acne vulgaris or a separate entity.

Pyoderma faciale affects mainly adult females. This is a sudden severe eruption of pustules and cystic swellings, which may be interconnected by sinuses (Fig. 44.13). Marked erythema and oedema are usually present. Comedones are usually absent or inconspicuous, as are other features of acne vulgaris or rosacea [1,2]. There is often no preceding history of acne. Some cases have developed during pregnancy, suggesting that hormonal factors may play a role. As the name implies, the eruption is usually confined to the face, involving the cheeks, chin, nose and forehead. Localized forms may be confined to the cheeks, jaw line or chin. Culture of the purulent discharge may be sterile or may yield a growth of commensal organisms including *Staphylococcus epidermidis* and *Propionibacterium acnes*. This investigation can be helpful in excluding Gram-negative infection. Significant scarring develops in many cases.

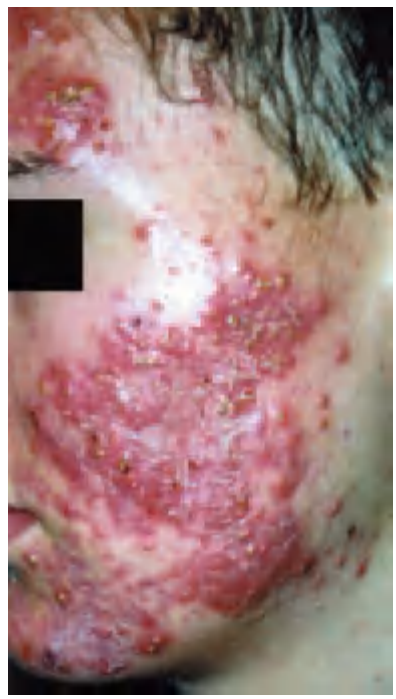

Fig. 44.13 Pyoderma faciale. (Courtesy of Dr G. Dawn, Carlisle, UK.)

In view of the distressing nature of this disease and the risk of severe scarring it is usually treated initially with systemic corticosteroids. In one series 10 of the 20 cases were hospitalized to commence treatment with prednisolone at 1 mg/kg/day, before adding isotretinoin 0.2–0.5 mg/kg/day. The corticosteroid was tapered off over 2–3 weeks and the isotretinoin continued for 3–4 months [2]. Others have used moderately potent topical corticosteroids combined with systemic isotretinoin [3], application of Vleminckx packs (containing sulphur, calcium polysulphide and calcium thiosulphate), UVB, benzoyl peroxide, systemic antibiotics [1], or dapsone [4].

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Flushing and flushing syndromes

SYN. BLUSHING; HOT FLUSHES; HOT FLASHES

Flushing is intermittent redness, often accompanied by a sensation of warmth or burning due to cutaneous vasodilatation. This is usually most evident on the face and neck but less conspicuous changes may occur over the entire body. Flushing may arise from the action of a circulatory vasodilator substance, for example histamine, or it may be caused by changes in the neurological control of the cutaneous vasculature in the affected areas. In the face, neck and upper trunk, where flushing is most apparent, vascular tone is predominantly influenced by autonomic vasodilator nerve fibres rather than by relaxation of vasoconstrictor tone [1]. These fibres are found in somatic nerves supplying the affected skin, including the trigeminal nerve [2]. Since autonomic nerve fibres also supply sweat glands, neurally activated flushing is frequently associated with sweating ('wet flushing') whereas flushing due to circulating vasodilator mediators usually does not involve sweating ('dry flushing'). The presence or absence of sweating has therefore been proposed as a clinical guide to the mechanisms of flushing [3]. This is not entirely reliable in practice and it should be noted, in particular, that severe sweating occurs in some cases of carcinoid syndrome. Causes of flushing are summarized in Table 44.2.

Table 44.2 Causes of flushing.

Cause	Proposed mediator(s)
Physiological	Autonomic
Menopausal	Autonomic
Drug induced	Various
Alcohol	Acetaldehyde
Chlorpropamide and alcohol	Acetaldehyde
Food	Autonomic
Scombroid fish poisoning	Histamine
Carcinoid syndrome	Serotonin
	Prostaglandins
	Bradykinin
	Histamine
Mastocytosis	Histamine
Thyrotoxicosis	Thyroxine
Medullary carcinoma of the thyroid	Prostaglandins
	Calcitonin
Pancreatic tumours	Vasoactive intestinal peptide
Insulinoma	?
POEMS syndrome	?

Physiological flushing

Flushing develops as part of the normal thermoregulatory response in a hot environment or following exercise. A similar mechanism is responsible for facial flushing due to hot drinks, which cause a rise in temperature of blood in the oral cavity, which in turn leads, by a countercurrent heat-exchange process involving the internal jugular vein and internal carotid artery, to a rise in temperature of blood perfusing the hypothalamus [4].

Emotionally triggered flushing due to embarrassment or anger may be a problem in some patients in whom the threshold for this response may be low or the reaction itself unusually intense or extensive. It is often associated with telangiectasia and with sweating and can be a significant social handicap. Such patients are occasionally referred for investigation to exclude an underlying carcinoid tumour.

Explanation, accompanied if necessary by the β-blocker propranolol, may alleviate the symptom, which is essentially due to exaggeration of a normal response. Transthoracic endoscopic sympathectomy can be effective, but seems justifiable only in the most severe cases and perhaps those with concurrent severe palmar hyperhidrosis [5,6]. This procedure can result in compensatory hyperhidrosis at other sites, Horner's syndrome and other complications.

Menopausal flushing

About 80% of menopausal women develop troublesome flushing often associated with sweating. Attacks, which are often preceded by a feeling of heat, may be provoked by emotion, exertion and hot food or drink. The mechanism remains imperfectly understood, but it is likely that the endocrine changes associated with the menopause result in a disturbance of thermoregulation and that the flushing and sweating represent a hypothalamic response

Table 44.3 Drugs which cause flushing.

5-HT_3 receptor antagonists: odansetron, ramosetron, tropisetron
ACE inhibitors: captopril, enalapril, lisinopril, perindopril, ramipril
Beta-3 adrenoceptor agonists: fluvoxamine, mirtazapine
Calcium channel blockers: nifedipine, verapamil
Chlorpropamide*
Disulfiram*
Ethanol
Fumaric acid esters
Gold
Hydralazine
Metronidazole*
Nicotinic acid
Nitrates: isosorbine mononitrate/dinitrate, glyceryl trinitrate
Phentolamine
Pilocarpine
Prostacyclin
Prostaglandin E
Sildenafil and vardenafil
Venlafaxine

ACE, angiotensin-converting enzyme.
* With ethanol.

to reduce body temperature [7]. A similar syndrome may also occur in men with prostatic cancer receiving treatment by gonadotrophin-releasing hormone analogues such as buserelin [8].

Menopausal flushing usually improves with oral or transdermal oestrogen replacement therapy. Combined oral contraceptives are effective and even the use of progestogens alone may be beneficial. Non-hormonal approaches to management include the use of clonidine 0.05 mg twice daily or selective serotonin reuptake inhibitors (SSRIs) [9].

Flushing caused by drugs

Numerous drugs cause flushing as an unwanted side effect, most frequently those listed in Table 44.3. There seems to be considerable variation between individuals in susceptibility to this side effect. It is not surprising that vasodilating drugs such as calcium antagonists and sildenafil may do this. Flushing occurs in an estimated 12% of patients taking sildenafil and may be accompanied by headache [10].

Fumaric acid esters, used in treatment of psoriasis, produce flushing in about one third of patients [11]. Some state that this regularly occurs 20–60 min after each dose, but in others the timing is not consistent. Flushing episodes may be quite severe but are usually very evanescent, lasting for only a couple of minutes. They may be accompanied by headache. Some patients do not notice this flushing at all, whilst occasionally it is so severe that the drug cannot be tolerated. The flushing may sometimes be reduced by addition of pentoxifylline (oxypentifylline), perhaps due to antagonism of TNF-α by the latter drug [12].

Flushing is observed as part of generalized vasodilation in reactions to gold therapy for rheumatoid disease which have been termed 'nitritoid reactions' [13]. These occur most commonly with gold sodium aurothiomalate but have also been reported with other formulations. The reaction may develop after several years of regular treatment and may be more severe if angiotensin-converting enzyme (ACE) inhibitors are used simultaneously. This phenomenon may be accompanied by hypotension and has occasionally been complicated by stroke or myocardial infarction. It is usually quite benign.

A reduction in the normal flushing response induced by systemic or topical nicotinic acid has been proposed as the basis of a diagnostic test for schizophrenia [14].

Flushing associated with alcohol intake

Most information on alcohol-evoked flushing in otherwise healthy individuals has been acquired by study of Japanese, Chinese and Korean volunteers, since a majority of these oriental genotypes show extensive flushing in response to low doses of alcohol [15]. The high prevalence of this reaction in occidentals is associated with higher plasma levels of acetaldehyde, the initial metabolite of ethanol. Acetaldehyde may act partly by causing histamine release from mast cells [16]. Harada *et al*. [17] demonstrated deficiency of an isoenzyme of liver aldehyde dehydrogenase (low K_m aldehyde dehydrogenase ALDH-1) in 50% of Japanese and showed that these, but not other, Japanese individuals developed flushing after alcohol intake. This population can be detected using an ethanol patch test, which shows erythema due to accumulation of acetaldehyde in the ethanol-treated skin [18]. In a Caucasian population patch testing with acetaldehyde proved more reliable [19]. Symptoms can be alleviated by aspirin [20] and also by antihistamines, H_1 and H_2 antagonists being most effective used in combination [21].

The chlorpropamide–alcohol flush is a special type of alcohol-induced flushing, occurring in patients receiving this oral antidiabetic sulphonylurea drug. Even small amounts of alcohol provoke intense flushing within a few minutes of ingestion [22]. There is no associated sweating, and no systemic symptoms. The abnormality is dominantly inherited, and is associated with familial non-insulin-dependent diabetes and with a low frequency of diabetic complications. The flush is mediated by elevated acetaldehyde plasma levels, but release of prostaglandins is also involved since aspirin and other non-steroidal anti-inflammatory agents block the flush [23].

Flushing associated with food

It is a matter of common experience that eating spicy foods causes facial flushing, usually associated with sweating. This type of flushing, termed gustatory, is due

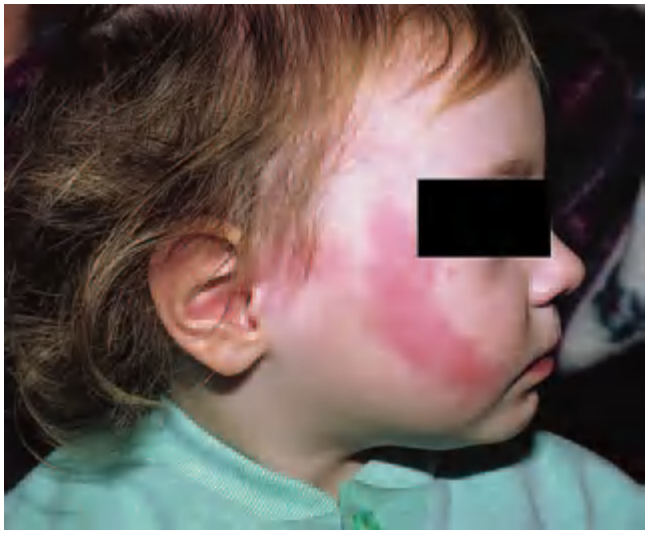

Fig. 44.14 Unilateral gustatory flushing. (Courtesy of Professor M. Greaves, Singapore General Hospital, Singapore.)

to a nerve reflex involving autonomic neurones carried by the branches of the trigeminal nerve. Sour foods may also cause a similar response that, curiously, may be unilateral, as demonstrated by a child in whom the right (but not the left) side of the face manifested a 'slapped cheek' appearance (without sweating) a few seconds after sucking an acid drop (Fig. 44.14).

Monosodium glutamate has a reputation for causing flushing associated with sweating and faintness ('Chinese restaurant syndrome'). Although first described by Kwok [24], his account did not include flushing; this was added to the symptom complex by later authors [25]. A more recent study involving oral challenge of volunteers with and without a history of previous monosodium glutamate reactions by both monosodium-l-glutamate and its cyclized derivate monosodium-l-pyroglutamate failed to provoke flushing over a range of doses, although burning and tightness of the skin was noted in some volunteers [26]. Similar negative results have subsequently been reported [27]. Flushing due to monosodium glutamate, if it exists at all, must be an extremely rare occurrence.

Scombroid fish poisoning

The scombroid families of edible fish include tuna and mackerel, but non-scombroid fish including dolphin and herring have occasionally been reported to cause this syndrome [28]. Scombroid fish poisoning, which is the commonest form of ichthyotoxicosis worldwide, is due to the ingestion of fish which has 'gone off', usually due to having been left on the fishmonger's counter in a warm atmosphere for several hours. Ingestion of the affected fish causes flushing, heat, sweating, vomiting and diarrhoea. That the symptoms are due to histamine intoxication is indicated by recent studies of the histamine content of affected fish and measurement of urinary histamine excretion in affected individuals [29]. Bacterial biosynthesis (by histidine decarboxylation) is thought to be the source of histamine in the spoiled fish.

Patients poisoned in this way should be treated with a combination of H_1 and H_2 antihistamines. Epinephrine (adrenaline) and corticosteroids may be required in severe cases.

Other causes of flushing

Persistent flushing is sometimes observed in thyrotoxicosis as part of a picture of generalized vasodilatation. Mastocytosis is discussed elsewhere (Chapter 47). Medullary carcinoma of the thyroid [30] and certain pancreatic tumours [31] have been found to cause attacks of flushing. There are also single case reports of the association of flushing with an insulinoma [32] and the POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M-protein, skin changes) [33]. These may therefore cause confusion with the carcinoid syndrome, which may also present with flushing (see below).

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Carcinoid syndrome

The carcinoid syndrome results from secretion of a variable and diverse range of endocrinologically active substances by a malignant carcinoid tumour and its metastases. It may present with cutaneous features alone so it is of particular importance that dermatologists remain alert to this disease.

The term 'Karzinoid' was first used in 1907 to denote an intestinal tumour which behaved less aggressively than the more common adenocarcinoma [1]. A variety of other terms have been used to describe these tumours, which are probably derived from a primitive endocrine stem cell. Some of these reflect staining characteristics (argentaffinoma, enterochromaffinoma), others reflect their functional capacity to secrete a range of hormonally active substances (neuroendocrine tumours, amine precursor uptake and decarboxylation tumours (APUDomas)).

The tumours are variable in their degree of malignancy and in the pattern of hormones they secrete. Clinical manifestations are also highly dependent on the anatomical situation in which they arise, as their secretory products are substantially metabolized during passage through the liver and lungs when these organs lie downstream of the circulation from the tumour.

Carcinoid tumours are found most commonly in the embryological mid-gut (appendix, small bowel), especially in the appendix where they may cause appendicitis. Estimates of the prevalence of appendiceal carcinoids range between 0.03% and 0.69% [2]. Most are asymptomatic and only a minority metastasize. Small bowel carcinoids are also common, whereas foregut (stomach, pancreas, biliary tract) and hind-gut (colon and rectum) tumours are relatively rare. Occasionally, carcinoid tumours arise outside the intestinal tract (lung, ovary, testis).

The low levels of endocrine activity associated with most carcinoid tumours are asymptomatic, probably as a result of rapid hepatic metabolism of endocrine products in portal blood. The symptoms of the carcinoid syndrome normally develop as a consequence of metastasis to the liver, although pulmonary carcinoids release hormonal products directly into the systemic circulation and can therefore cause symptoms without metastases. The considerable range of products with potential for endocrine activity known to be produced by carcinoid tumours includes 5-hydroxytryptamine (5-HT, serotonin), 5-hydroxytryptophan, histamine, dopamine, kallikrein, prostaglandins, tachykinins (neuropeptide K, substance P), gastrin, motilin, somatostatin, calcitonin and pancreatic polypeptide [2,3].

Clinical features. The cardinal features of carcinoid syndrome are flushing, diarrhoea, asthma and right-sided cardiac dysfunction. The relative prominence of these varies considerably between patients. Flushing and diarrhoea are the most common symptoms.

Flushing is observed in 80% of cases and may develop long before other symptoms. This is usually episodic and may be spontaneous or precipitated by exercise, alcohol, stress or meals. Certain foods, especially those containing tyramine or catecholamines (red wine, chocolate, blue cheese) are especially likely to induce flushing.

The character of the flush can vary considerably and seems to depend particularly upon the site of origin of the tumour. Mid-gut tumours usually produce diffuse, transient flushes of pink to red colour, lasting 2–10 min, and affecting the face, neck, arms and upper chest. The flush is often mingled with areas of pallor, especially as it resolves (Fig. 44.15) [4]. Foregut carcinoids tend to produce slightly more prolonged and violaceous flushes, sometimes associated with a permanent cyanotic hue, facial telangiectasia, watery eyes and injected conjunctivae [2]. Gastric carcinoids are often associated with increased histamine secretion and bright red, patchy 'geographic' flushing (Fig. 44.16) [5]. Bronchial carcinoids may result in particularly severe episodes of fiery violaceous-red flushing lasting up to 2 weeks and associated with profuse lacrima-

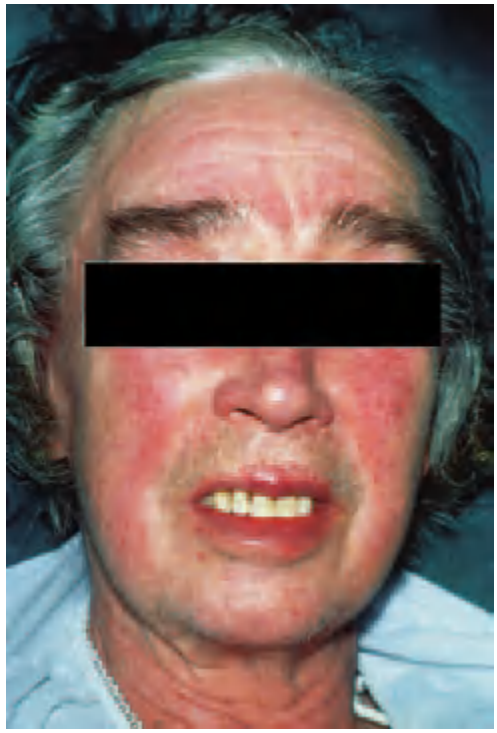

Fig. 44.15 Violaceous flushing, probably caused by the combined actions of 5-hydroxytryptamine (5-HT, serotonin) and vasoactive peptides. (Courtesy of Professor M. Greaves, Singapore General Hospital, Singapore.)

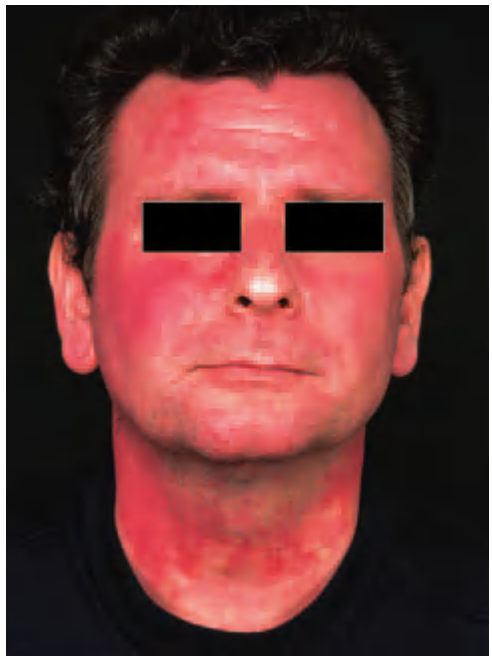

Fig. 44.16 Histamine evoked 'geographical' pattern of flushing due to foregut carcinoid tumour. (Courtesy of Professor M. Greaves, Singapore General Hospital, Singapore.)

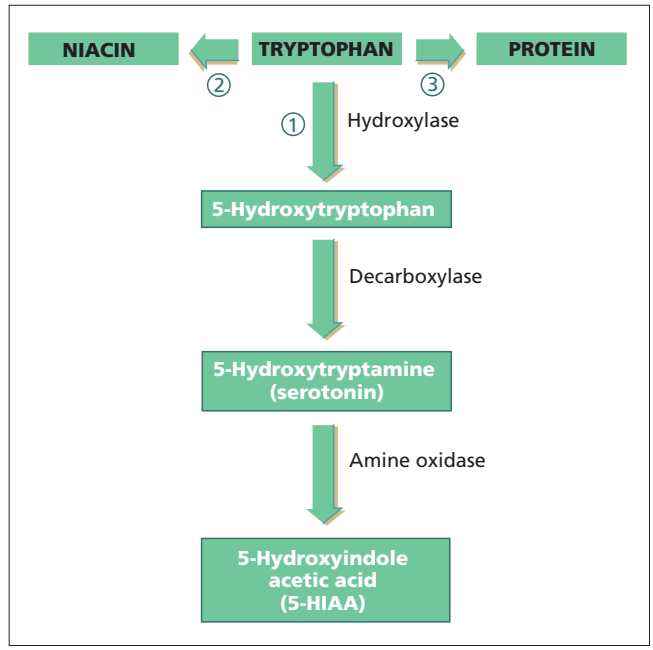

Fig. 44.17 Pathways for transformation of tryptophan to 5-hydroxytryptamine (5-HT, serotonin) (pathway 1); niacin (pathway 2); and protein (pathway 3).

tion, salivation and sweating, nasal congestion, swelling of the salivary glands, facial oedema, tachycardia, increased cardiac output and hypotension [6]. In contrast, rectal carcinoid tumours very rarely result in the carcinoid syndrome, tending to present with local symptoms such as bleeding, pain, constipation or pruritus ani.

The pathophysiology of the flushing is not fully understood. It is likely that histamine plays a major role in the distinctive bright red, geographical flushing associated with foregut (especially stomach) carcinoids [5]. The cause of the more classical flushing of mid-gut carcinoids is less clear. Serotonin, the major product of these tumours, seems unlikely to be the primary mediator. Serotonin infusions do not consistently induce flushing, and flushing is not consistently associated with a rise in serotonin [7]. Serotonin antagonists inhibit the diarrhoea associated with the carcinoid syndrome but not the flushing. It seems more likely that carcinoid tumours may release kallikrein, which may produce flushing by acting on kininogen to release bradykinin [8]. Other proposed mediators of flushing include prostaglandins [9] and substance P [7].

A photosensitive eruption resembling pellagra may occur as part of the carcinoid syndrome and is believed to result from diversion of tryptophan metabolism away from synthesis of niacin (Fig. 44.17). Additional cutaneous manifestations reported in association with carcinoid tumours have included scleroderma [10], pyoderma gangrenosum [11] and pruritus [9]. Fixed facial erythema, telangiectasia and lymphoedema may give rise to an incorrect diagnosis of rosacea [12].

Gastrointestinal symptoms are common. An estimated 76% of patients develop watery (secretory) diarrhoea [2]. This seems likely to be mediated substantially by serotonin. Abdominal pain is often reported and arises from a range of causes including altered motility, bowel obstruction, intussusception or appendicitis. Cardiac involvement results from the development of right-sided endocardial fibrosis which may lead to pulmonary stenosis, tricuspid incompetence and congestive cardiac failure. The pathogenesis of the fibrotic changes is unknown. The asthma associated with carcinoid syndrome is a less constant feature than the flushing and the diarrhoea, occurring in about 25% of cases [2]. The episodes of wheezing often coincide with flushing and/or diarrhoea.

Diagnosis. The clinical diagnosis is not difficult in patients with advanced disease who present with flushing, diarrhoea, wheezing, weight loss and a large liver. Early recognition of the carcinoid syndrome is not so easy and some cases have been misdiagnosed for years as suffering from benign causes of flushing. These symptoms may even be dismissed as psychogenic in origin.

The diagnosis is usually confirmed by determining the urinary excretion of 5-hydroxyindole acetic acid (5-HIAA), the major metabolite of serotonin. The normal excretion is rate is up to 10 mg (150 µmol) in 24 h. In carcinoid syndrome the level often exceeds 40 mg daily and may be much higher, especially after flushing episodes. However levels can vary considerably from day to day. If attacks are infrequent, it may be helpful to wait until a flushing episode occurs before performing the urine collection. Foods containing serotonin, such as avocados, aubergines, bananas, pineapples, plums, tomatoes and walnuts, should be avoided for 3 days before the urine collection is made, in order to avoid false positive results. The elevation of 5-HIAA due to these is usually only marginal. Various drugs including bromocriptine, caffeine, levodopa, paracetamol, phenothiazines and salicylates may also cause marginal changes in 5-HIAA excretion or interfere with the assay, so the laboratory should be advised about the patient's drug intake.

Further confirmation of the diagnosis may be obtained by induction of the flushing, which can usually be provoked by alcohol ingestion (4 mL of 45% ethanol) or the infusion of norepinephrine (noradrenaline) 6 µg. This response to norepinephrine can be blocked by phentolamine (5–15 mg i.v) [13].

If hepatic involvement is evident by abdominal palpation there is little point in elaborate attempts to locate the primary tumour, unless it is suspected to be causing obstruction. Many imaging techniques have been employed to investigate the extent of liver and lymph node metastases, including angiography, ultrasound, endoscopic ultrasound, computed tomography (CT) scanning and positron emission tomography [2]. Octreotide receptor imaging using radiolabelled octreotide can be used to localize both primary and secondary tumours [14].

In some cases further investigation may be indicated to exclude additional neuroendocrine tumours. Carcinoid tumours, especially those of foregut origin, may occur in association with multiple tumours of the pancreas, parathyroid and pituitary as a feature of type I multiple endocrine neoplasia [15]. This condition is inherited as an autosomal dominant trait.

Table 44.4 Food items which may cause flushing in carcinoid syndrome.

Alcohol
Aubergine
Avocado
Bananas
Chocolate
Hickory nuts
Kiwi fruit
Pecan nuts
Pineapples
Plums
Red wine
Spicy foods
Tomatoes
Walnuts

Prognosis. About one-fifth of patients with the carcinoid syndrome undergo a protracted course. In the remainder, deterioration can be rapid. The mean survival in one series was 8 years, the longest survivor living for 20 years [16].

Treatment. Alcohol and foods which may exacerbate symptoms (listed in Table 44.4) should be avoided, as should exercise and stress. Nicotinamide supplements are often provided to reduce the risk of pellagra.

A range of pharmacological agents have been employed with variable degrees of success in providing control of symptoms. Serotonin antagonists such as cyproheptadine, ketanserin and methysergide, and the inhibitor of serotonin synthesis parachlorophenylalanine, can help control the diarrhoea but these are less effective against flushing [17]. Codeine phosphate and loperamide can also be useful for reducing diarrhoea. Clonidine has been reported to suppress flushing at low doses (0.05 mg twice daily) [18] and higher (antihypertensive) doses (0.4 mg/day) [19]. Antihistamines, both H_1 and H_2 types [20], are effective in blocking the flush of foregut carcinoids, especially gastric carcinoids, due to the dominant role of histamine in carcinoids at this location. Corticosteroids can be highly effective in controlling prolonged flushing associated with bronchial carcinoids [6]. Alpha-adrenoceptor blockers such as phentolamine and phenoxybenzamine have been helpful in improving flushing, diarrhoea and wheezing in some cases [21].

Octreotide, a somatostatin analogue given by subcutaneous injection at total daily dosage of 50–600 μg, lowers plasma levels of serotonin and tachykinins and relieves both flushing and diarrhoea [22]. The requirement for subcutaneous injections two or three times daily has been a disadvantage, but a long-acting depot injection is now available and can be used at the dose of 20 mg i.m. every 28 days. In some cases treatment for 6–12 months has resulted in partial or complete tumour regression [23]. Another somatostatin analogue, lanreotide, is also now available in depot formulation.

Surgical excision of carcinoid tumours is performed when possible. In metastatic disease, reduction of tumour mass can be useful in reducing symptoms and a similar effect can often be achieved by hepatic artery ligation or embolization [24]. Some patients have had multiple embolizations over a number of years. This treatment is based upon the dependence of metastatic malignant tissue, but not healthy liver parenchyma, on an intact hepatic arterial blood supply. Chemotherapy with agents such as streptozotocin, dacarbazine, adriamycin and 5-fluorouracil has also been employed [2]. All these 'tumour ablative' interventions run the risk of provoking an acute carcinoid crisis (profound flushing, bronchospasm and shock), due to massive release of mediators. This can be prevented or treated with intravenous octreotide [25]. Interferon-α has also proved helpful in reduction of symptoms and 5-HIAA levels in some cases, but side effects include flu-like symptoms and bone marrow suppression [26].

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Chapter 45

Disorders of Sweat Glands

I.H. Coulson

Comparative anatomy and physiology

Sweat glands are described as merocrine; unlike the holocrine sebaceous glands, their cells are not destroyed in the process of secretion. Merocrine glands have been further subdivided into two major types, usually known as apocrine and eccrine. The nomenclature is attributed to Schiefferdecker [1,2], who believed that secretion by apocrine glands involved decapitation of the apical cytoplasm, in contrast with eccrine glands, in which no breakdown of any cellular material occurs. Such a distinction between modes of secretion has been denied [3–5]. However, in the rabbit chin gland [6] and the lemur antebrachial organ [7], large portions of secretory epithelium do appear to be sloughed during secretion. In the axillary organ of humans, although some authors have claimed that decapitation of apical cells can sometimes occur [8], most believe this to be abnormal. The favoured view is that secretion occurs by small portions of apical cytoplasm becoming pinched off [9].

Even though the mechanisms of secretion may be debatable, there are a number of characteristic differences between the two types of gland (Fig. 45.1). The alternative designations of 'epitrichial' (where the sweat duct opens into the hair follicle) for 'apocrine', and 'atrichial' (where the duct does not enter the hair follicle) for 'eccrine', are not entirely satisfactory, because glands which on developmental and histochemical grounds must be classed as apocrine do not invariably open into the hair ducts. On balance, therefore, there is no strong case for abandoning the well-established terms.

The terminology has become further complicated by the use of 'apoeccrine' to describe a distinct type of tubule present in the human axilla. The axilla contains not only typical eccrine and apocrine elements, but numbers of large, irregularly shaped glands which cannot be assigned to either category, although they have some characteristics of each [10]. Such glands consistently occur in adults, but not in children, and become apparent between the ages of 8 and 14 years. Whether their precursors are apocrine or eccrine is unclear, but their ducts do not open into hair canals.

Apocrine glands occur in all known orders of mammals except whales, elephants, sea cows and scaly ant-eaters, although in some species only as part of specialized aggregates [11]. When dispersed, their density varies widely, ranging from 20 to 30/cm^2 in the pig to over 2000/cm^2 in Zebu cattle [5].

Eccrine glands occur in the footpads of many mammals; the exceptions again include whales, sea cows, elephants and scaly ant-eaters, with the addition of bats. Such glands probably serve to moisten the surface of the skin to improve their grip.

In hairy skin, however, eccrine glands are found only in tree shrews, Old World monkeys, apes and humans. The evolution of eccrine glands in primates is discussed in Chapter 2. They appear to replace, but not to evolve from, apocrine glands. Only in humans do eccrine glands

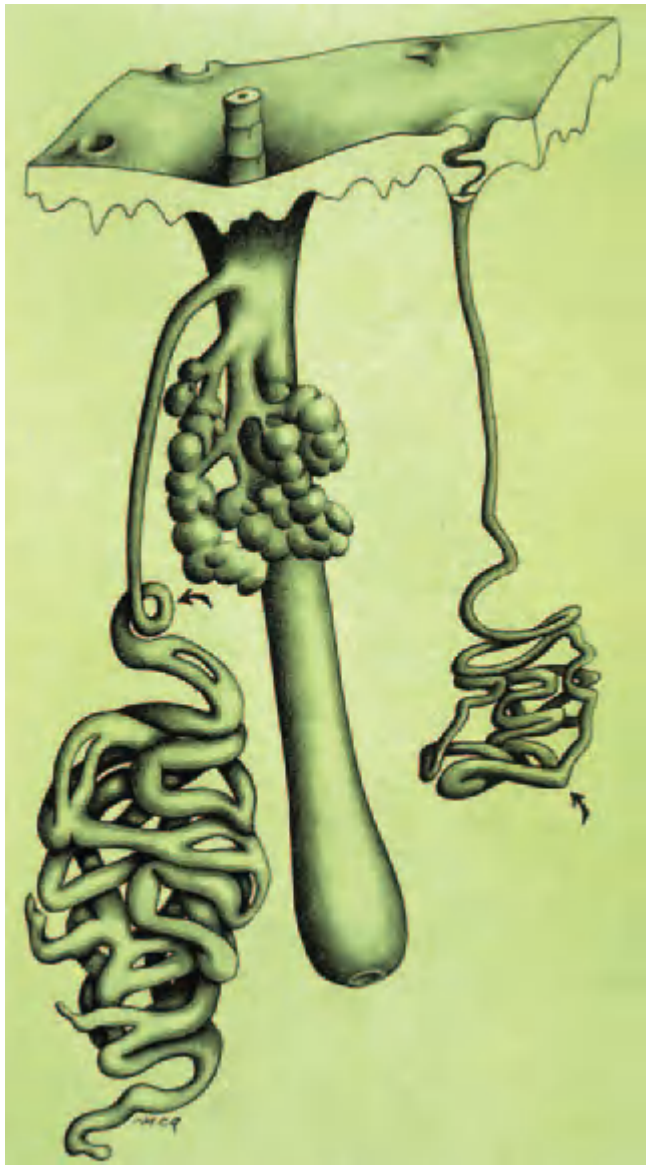

Fig. 45.1 An apocrine, sebaceous and eccrine gland and their relationships to the hair follicle. (Courtesy of Dr W. Montagna.)

completely replace apocrine glands over the major areas of hairy skin. In the human embryo, such glands develop later than those on the friction surfaces, and thus should probably be placed in a different category and distinguished from mammalian footpad glands in general.

Specialized glands, i.e. aggregations of secreting units, are not only widespread amongst mammalian orders but, in different species, can be found in almost every area of the body, from the head to the rump and the extremities [11]. Some—for example, the chin and anal glands of the rabbit—contain only tubular units [12,13]; others—for example, the supracaudal gland of the guinea pig, the flank organ of the golden hamster, the abdominal gland of the gerbil and the preputial glands of rodents—are purely sebaceous. Both types of unit may be associated, as in the muzzle glands of certain bats [14], the side glands of shrews, in which batteries of tubular glands underlie the sebaceous elements [15], and the inguinal glands of the rabbit, which consist of a discrete pair of each type [16].

Similar glandular aggregations occur in primates [17]. In humans, rudiments of apocrine glands attached to each follicle appear during development, but survive to become functional only in the axillae, the genital area and the areolae.

In animals, two main functions, thermoregulation and odour production, are performed by apocrine glands. The first is carried out by glands dispersed over the general body surface or, in some species, limited to areas such as the scrotum. Odour production is a property of specialized aggregates, although possibly not exclusive to them.

The extent to which the glands respond to environmental heat loads, and the exact nature of the control mechanisms, have been studied mainly in domestic animals. They vary widely. In horses, oxen and camels, the glands secrete in response to a rise in ambient temperature, but in pigs, dogs and deer they do not [18]. Apart from the primates, Equidae and some Bovidae, sweat glands appear to play a minor role in the control of body temperature in warm conditions [5,19], although they may cool local areas, such as the scrotum in sheep [20]. By sympathetic denervation of the skin, it has been shown that sweating is under adrenergic nervous control, even in species which lack a demonstrable nerve supply. In addition, in most species studied, the glands also respond to administration of epinephrine (adrenaline), although in contrast with human eccrine glands they are much less sensitive to acetylcholine. Although various interpretations have been made of the experimental results, it is now accepted that apocrine sweating is, in general, controlled by adrenergic nerves, and that in some species—for example, the horse—epinephrine from the adrenal medulla supplements the sweating caused by exercise, although not that caused by heat exposure [18,19].

Odour production is known to occur in 15 out of 29 mammalian orders, but has received detailed study in only a few species. Chemical signals serve a number of social purposes, of which the marking of territory, the maintenance of social hierarchy, alarm signals and individual, group or species recognition are only a few [13,21–23]. They are also concerned with sexual attraction, either of the female by the male, as has been well established, for example, in the boar [24], or of the male by the female, as in the hamster [25] and the rhesus monkey [26,27].

Notwithstanding social pressures to devalue its impact, odour is undoubtedly important in human communication [28], as Havelock Ellis recognized in his comprehensive and entertaining, if almost entirely anecdotal, review in 1905 [29]. The odorous steroids 5-alpha-androsterone and 5-alpha-androsterol, known to act as pheromones in

pigs, have been found in axillary sweat, as well as in human urine, plasma and fatty tissue [30–34]. The role of odour in human social behaviour is discussed in Chapter 4.

The limited evidence available suggests that at least some of the tubular glands of apocrine type are, like the sebaceous glands, controlled by hormones. In the rabbit, all three sets of apocrine glands are stimulated by androgens and inhibited by oestrogens [35].

It seems likely that the human apocrine glands of the axillary and pubic regions are similarly under some androgenic control [36]. The glands do not become active until puberty, at the same time as the development of the sexual hair with which they are associated.

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Anatomy and physiology of human eccrine glands [1–4]

Human eccrine sweat glands have two distinct functions: they allow body cooling by evaporation, and have thus contributed in a major way to adaptation to a hot environment by humans (major illness or death may ensue with sweat gland failure, even in temperate climates); they also moisten the skin on the palms and soles at times of activity, and thus improve their grip. Apocrine glands are responsible for body odour.

Eccrine sweat glands are distributed over the whole skin surface, including the glans penis and foreskin, but not on the lips, external ear canal, clitoris or labia minora. The number varies greatly with site, from 620/cm^2 on the soles and about 120/cm^2 on the thighs to 60/cm^2 on the back [5]. The total number on the body surface is between 2 and 5 million, and is the same in black people as in white people. It has been calculated that the weight of the eccrine glands totals 100 g. The glands vary in size from person to person by a factor of five, and this probably accounts for individual as well as regional differences in sweat rate (maximal individual gland secretion rates ranging from 2 to 20 nL/min/gland).

Embryologically, sweat glands are derived from a specialized down-growth of the epidermis at about the third month of intrauterine life on the palms and soles and at about 5 months elsewhere, and they resemble adult glands by 8 months. Sweat glands are morphologically normal at birth, but may not function fully until about 2 years of age. No new eccrine glands develop after birth. Unlike the apocrine glands, they have no developmental relationship with the pilosebaceous follicle, although some glands may eventually come to open into the follicular

Fig. 45.2 Section of a secretory coil of an eccrine sweat gland stained with osmium. The coil contains three types of cell: (i) serous or clear cells (S) containing finger-like processes and bordering a canaliculus (c); (ii) mucous or dark cells (M); and (iii) myoepithelial cells (me). D, dermis; L, lumen of coil. (Courtesy of the late Professor A.S. Breathnach, St John's Dermatology Centre, London, UK.)

neck. The gland consists of a secretory coil in the lower dermis and subcutaneous tissue, and a duct leading through the dermis to the intraepidermal sweat duct unit. Apoeccrine glands have features of both eccrine and apocrine glands, but seem to be nearer to eccrine in function. They open onto the surface, and produce a copious watery fluid. They may account for 10–45% of adult axillary glands [6].

The secretory coil contains three types of cell: large clear cells, which are the main secretory cells, small dark cells, which resemble mucus-secreting cells of other organs but whose function is not known, and myoepithelial cells [7] (Figs 45.2 & 45.3). The large and small cells of the secretory coil, unlike those of the duct, are attached to the basement membrane, although individual sections may at times suggest a double layer. Outside the basement membrane are the longitudinally arranged myoepithelial cells, whose function is probably to support the gland, but they may also help propel the sweat towards the surface. They respond to cholinergic stimuli. The function of the coil is to produce from plasma a watery isotonic secretion which can subsequently be modified by the duct. Ultrastructurally, the large clear cells are characterized by the presence of many mitochondria and by both intricate basal infoldings and intercellular canaliculi. Paranitrophenyl phosphatase activity, which reflects catalytic activity of Na-K-ATPase, is evident in the basal infoldings but not the intercellular canaliculi, suggesting that the basal areas are the sites of active ion transport requisite for sweat secretion. The classical theory suggests that acetylcholine passively increases entry of sodium into the cell, and this is then pumped out by the sodium pump into the intercellular canaliculi rather than directly through the luminal margin. However, there are other theories [4]. Fluid secretion is believed to be mediated osmotically, but the mechanism by which water moves has long been obscure. However, recently a membrane protein with water-transporting properties has been described in a range of tissues, including the human eccrine sweat gland [8]. The sodium pump in the gland can achieve a pressure up to 500 mmHg [9]. During active secretion, and in certain pathological conditions, well-marked histological changes occur in the gland [10]. Many different monoclonal antibodies can be shown to react with different portions of the sweat glands [11].

The duct consists of two or more layers of relatively uniform cuboidal cells. About one-third of the coil has this histology, as well as the uncoiled part passing up to the epidermis. The basal cells are rich in mitochondria and their entire membranes are rich in Na-K-ATPase activity, suggesting that sodium pumping occurs along the entire duct membrane and performs an active part in modifying the secretion produced by the coil.

It has been suggested that sweat glands do not cool the skin only by evaporation of heat from the surface, but also act as heat pipes. According to this theory, evaporation of the fluid at the base of the duct allows water vapour to pass up the duct and condense nearer the surface, and thence return to the deeper parts by capillary action. Such systems are a very effective way of transferring heat quickly [12].

The intraepidermal sweat unit is lined by a layer of specialized cells which may sometimes be distinguished only with difficulty from the surrounding epidermis. On the palms and soles, it has a well-developed coil structure that is not so apparent in other sites.

The techniques for studying the function of the eccrine sweat glands [12–14] include the following:

1 Collection of sweat in bags or pads at rest, after heat, or after injection or iontophoresis of pilocarpine or other cholinergic agonists.

2 Direct measurement of water loss.

3 Microcannulation of the duct or coil [15].

4 Measurement of electrical potentials and electrical resistance of the skin, which depends on both the sweat

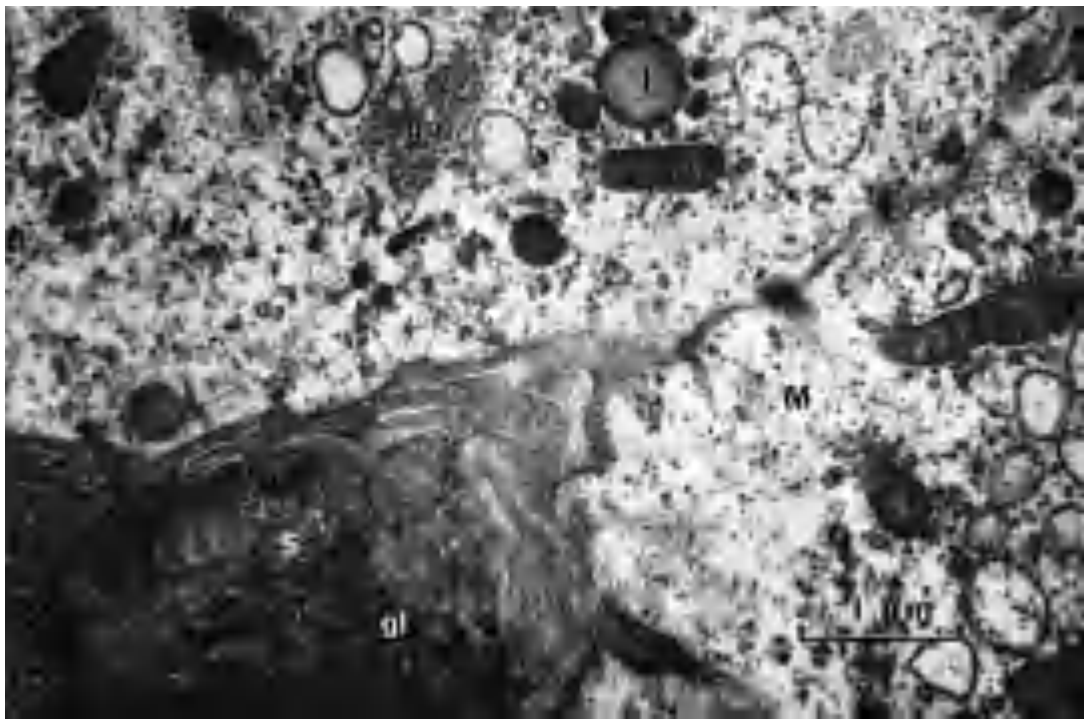

Fig. 45.3 Portions of two mucous (dark) cells (M), showing a Golgi complex (go) and lipid globules (l) and a serous (clear) cell (S) with glycogen granules (gl). (Courtesy of the late Professor A.S. Breathnach, St John's Dermatology Centre, London, UK.)

present on the epidermis and the column present within the duct [16,17].

5 Visualization of the individual sweat droplets. This may be achieved by direct microscopy, by *in vivo* staining, by forming plastic impressions [18] or by indicators which become coloured on contact with water, such as the starch/iodine technique [19], bromophenol blue [13], quinizarin [20] and the food dye edicol ponceau. The plastic or silicone impression techniques are probably the most reliable, and can produce a permanent record. A simple modification of the starch/iodine test is to dry the skin, paint it with 2% iodine in alcohol, allow it to dry, and then press the skin against a good-quality paper. The starch in the paper reacts with iodine in the presence of water, so that each sweat droplet shows up as a minute dark spot. Alternatively, the starch may be suspended in castor oil (50 g in 100 mL) and painted onto the iodine-treated skin (Fig. 45.4). Special dry starch/iodine powders can be dusted directly onto the skin [21].

6 Isolated glands. Recently, it has become possible to isolate single eccrine glands (and also hair follicles, sebaceous glands and apocrine sweat glands) by the relatively simple technique of shearing tissues with scissors [22,23]. This allows the physiology, biochemistry and tissue-culture behaviour to be studied *in vitro*.

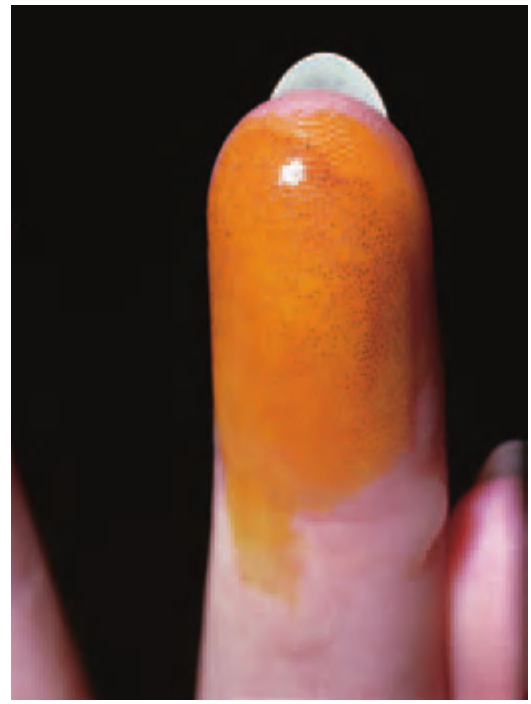

Fig. 45.4 Starch iodine test on the finger, showing individual sweat droplets. (Courtesy of Dr R.H. Champion, Addenbrooke's Hospital, Cambridge, UK.)

Control of eccrine sweating [1–4]

Eccrine glands alter their activity in response to thermal, osmotic, mental and gustatory factors. When the core temperature of the body rises above a certain level, termed

the temperature set point, eccrine sweating is initiated. Thermosensitive receptors are present both in the preoptic area and the anterior hypothalamus, and, in experimental animals, warming of these areas of the brain activates functions to facilitate cooling, including sweating, panting and vasodilatation. Conversely, cooling the same areas initiates shivering. Different receptors respond to heat and cold. Microelectrode recording has demonstrated that the firing rate of the warm sensitive receptors is increased not only by the local receptor temperature, but also by a rise in skin temperature, indicating the effect of local skin and spinal thermoreceptors. The effect of core temperature rise is about nine times more efficient than skin temperature in stimulating sweating. The efferent pathways from the hypothalamus involve nerve fibres relaying in the medulla, lateral horn of the spinal cord and sympathetic ganglia [2].

Thermoregulatory sweating occurs especially on the upper trunk and the face [24], but also occurs over the whole body surface, including the palms and soles. The hypothalamic thermal set point is also influenced by alterations in blood osmotic pressure. Hyperosmolarity results in an elevation of the thermal set point and reduced sweating (as sweat is hypotonic, this is a response to conserve further water loss).

The centres and pathways controlling mental sweating are not fully known, but responsible centres within the frontal region of the brain have been identified. Mental stimuli produce sweating, especially on the palms and soles, perhaps to improve the grip at times of activity. Mental activity also produces some general increase in sweating over the body surface. The activity may be emotional or intellectual—for example, mental arithmetic.

Innervation of the eccrine sweat gland

The efferent sudomotor pathway consists of the cerebral cortex to the hypothalamus, hypothalamus to medulla, medulla (mostly crossed) to the lateral horn of the spinal cord, then to the sympathetic ganglia, and finally from the ganglia to the sweat gland as postganglionic non-myelinated fibres.

The functioning of the eccrine sweat gland is dependent on intact non-myelinated C fibres of sympathetic nerves. Glands deprived of their postganglionic nerve supply soon cease to respond to any stimuli, although they remain histologically normal. The main sympathetic nerve supply of sweat glands is unusual in being cholinergic. Recent work in rats has shown that there is a complex interrelationship between the developing sweat glands and peripheral nerves. The glands influence the nerves to produce the appropriate neurotransmitter [25]. Adrenergic agents and nerve stimulation also increase sweat-gland activity [26–28], and a single isolated eccrine gland can respond to both cholinergic and adrenergic stimuli. The ratio of maximal secretory rates for human sweat glands *in vitro* and *in vivo* is 5 : 1 : 1 for cholinergic, alpha-adrenergic and beta-adrenergic stimulation, respectively. The adrenergic nerve supply seems to play little part in the normal control of eccrine sweating in humans. Vasoactive intestinal peptide (VIP), calcitonin gene-related peptide, atrial natriuretic peptide and galinin immunoreactivity can be found in human axillary periglandular neurones, but whether physiologically relevant concentrations are present remains to be established [29].

Other factors may modify the quantity and quality of sweat in the presence of an intact sympathetic nerve supply—for example, local temperature [30], hormones, circulatory changes, and axon and spinal reflexes. Sweat coils contain androgen receptors [31], and androgens may be at least partly responsible for the increase in sweating around puberty, and for the greater activity in males. Androgens do not play a significant role in the day-to-day regulation of eccrine sweat gland activity.

By these mechanisms, the quantity and quality of the sweat may be varied greatly. Under basal conditions, there may be few or no impulses passing to the sweat gland. Some insensible perspiration always occurs, partly due to transepidermal water loss and partly to sweat gland activity. Only the latter can be suppressed by atropine. Under maximal stimulation, the body can produce up to 12 L in 24 h, or for short periods 3 L in 1 h; this rate exceeds the ability of humans to drink [32].

The composition of sweat [4,33] varies greatly from person to person, time to time and site to site. It has a basic similarity to the plasma from which it is derived. The sweat duct is largely responsible for the modification in sweat constituent concentration which occurs, and this will therefore vary according to how rapidly the sweat is passing through the duct. The most important constituents are sodium, chloride, potassium, urea and lactate. Sweat is hypotonic and this is largely due to reabsorption of sodium in the duct. At increased sweat rates, the sodium concentration rises, presumably because there is reduced time for ductal reabsorption. The normal sodium concentration is between 10 and 20 mmol/L at low sweat rates, and up to 100 mmol/L at high rates. Aldosterone can increase ductal sodium reabsorption and in Addison's disease high sweat sodium can be demonstrated (70–80 mmol/L). Antidiuretic hormone may reduce sweat rates in humans, but it also induces local vasoconstriction.

An increase in sweat electrolytes occurs in cystic fibrosis, and is sufficiently constant to be a most useful diagnostic test [34]. The basic defect seems to be an abnormal diminished permeability of many cells to chloride ions [35–37]. The gene responsible has been identified [38]. Sweat may be collected after intradermal injection or iontophoresis of pilocarpine or methacholine (Mecholyl), or

after heating. In normal children, it is not unusual to have a sweat sodium level above 60 mmol/L, but the majority of children with cystic fibrosis have levels greater than this, often above 90 mmol/L. Sometimes a normal level is present, but the normal fall in sweat sodium concentration after deoxycorticosterone acetate (DOCA) or aldosterone is not seen. In adults, the normal levels are higher, and the test is of much less value. Initial suggestions that partial forms and carriers of cystic fibrosis could be diagnosed in this way have not been substantiated. An increase in sweat potassium has been reported in infants with apparent life-threatening events ('near-miss sudden infant death syndrome') [39].

Lactate is found in a concentration of 4–40 mmol/L, which greatly exceeds the concentration found in plasma. It is formed in the gland from glucose from the blood. It is interesting to speculate whether urea and lactate can act to moisturize the stratum corneum.

Glucose is present in small quantities only (usually 0–3 mg/100 mL, although levels up to 11 mg/100 mL may be found). High sweat glucose may be found in uncontrolled diabetes and this may create a favourable environment for skin infections. The pH is 4–6.8.

The concentration of these substances varies greatly in health and disease. Such changes seldom give rise to any symptoms referable to the skin, but may help in the understanding of disease.

A variety of other substances may be found in sweat, including pharmacologically active substances and inhibitors, antigens, antibodies and drugs [4]. Some of these seem to be excreted, and have no special function; others may have a definite function—for example, a urokinase-type plasminogen activator may play a part in digestion of glycoprotein plugs in sweat pores [40]. Active excretion or secretion of drugs such as griseofulvin and ketoconazole may contribute to their efficacy.

Atopic dermatitis patients often have IgE antibodies against an antigen found in their own sweat. The importance of this in the pathogenesis of the disease is uncertain [41].

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Hyperhidrosis [1,2]

Hyperhidrosis is the excessive production of sweat, and can be a major inconvenience to sufferers. In theory, when there is over- or underproduction of sweat it should be possible to determine whether the change is in the sweat glands, due to pharmacologically active agents acting on the gland, to abnormal stimulation of the sympathetic pathway between the hypothalamus and the nerve ending, or to overactivity of one of the three different 'centres' responsible for thermoregulatory, mental and gustatory sweating. Any difficult case should be approached from first principles in this way. In practice, most cases of hyperhidrosis fall into the clinical groups outlined below.

Generalized hyperhidrosis

There is marked physiological variation in thermoregulatory sweating from person to person in the absence of disease. An increase in the temperature of blood bathing the hypothalamus increases heat loss by sweating and vasodilatation. Some instability of the sweat regulating centre is caused by many febrile conditions, so that sweating may occur at times when there is no fever. This instability may persist for days, or even months, after the fever has subsided, and in some cases is such a prominent feature that the term 'sweating sickness' has been used [3]. Generalized sweating may occur in disorders of unknown aetiology, which alter the setting of the thermoregulatory centre, and may be associated with episodic hypothermia [1]. Generalized sweating can occur with a wide range of medical and neurological disorders, but seldom in the absence of other neurological symptoms or signs (Table 45.1). Thermoregulatory sweating occurs during or after many infective processes, and may be the presenting manifestation of malaria, tuberculosis, brucellosis, lymphoma, subacute bacterial endocarditis, etc. Night sweats are often part of the clinical picture. A similar mechanism may account for the hyperhidrosis associated with alcohol intoxication or gout, and after vomiting. The mechanism of generalized hyperhidrosis which may be associated with diabetic autonomic neuropathy, hyperthyroidism, hyperpituitarism, hypoglycaemia, obesity, the menopause and malignant disease is unknown. Increased sweating has been documented in some patients with Parkinson's disease, but others have noted the combination of patchy anhidrosis and compensatory hyperhidrosis, suggesting autonomic dysfunction. Paroxysmal sweating, tachycardia and headaches strongly suggests phaeochromocytoma. Hypertension is noted during attacks. Two sisters have been reported who had generalized sweating in a thermal pattern, but induced by cold [4]. Hyperhidrosis is seen in association with peripheral neuropathies, as in familial dysautonomia, or the Riley–Day syndrome, a recessively inherited disorder of Ashkenazi Jews comprising an absent axon reflex flare after histamine injection, pupillary meiosis, diminished tendon reflexes, diminished pain sensation and absent fungiform papillae of the tongue. Excess sweating is thought to be due to sweat centre excitability. Congenital autonomic dysfunction with universal pain loss is similar, but individuals are not Ashkenazi, have complete absence of pain sensation with accidental self-mutilation, corneal opacities and episodic fever. Cold-induced profuse sweating has been reported with a peripheral motor and autonomic neuropathy. Generalized hyperhidrosis may be associated with brain lesions (diencephalic lesions, malformations of the corpus callosum, microgyria) and may be accompanied by episodic hypothermia. Some drugs—for example, fluoxetine—are able to cause generalized hyperhidrosis. In many cases of generalized hyperhidrosis of the thermal type, but with no obvious underlying disease, the aetiology remains unknown, even after extensive investigation.

Table 45.1 Causes of generalized hyperhidrosis.

Febrile infective illnesses
Tuberculosis, malaria, brucellosis, endocarditis, etc.
Metabolic diseases
Diabetes, hyperthyroidism, hyperpituitarism, hypoglycaemia
Menopause
Underlying solid malignancy and lymphoma
Parkinson's disease
Congestive heart failure
Cold-induced generalized hyperhidrosis
Neurological disorders
Peripheral neuropathies
Familial dysautonomia (Riley–Day)
Congenital autonomic dysfunction with universal pain loss
Cold-induced profuse sweating
Brain disease
Episodic hypothermia with hyperhidrosis
Generalized hyperhidrosis without hypothermia
Drugs
Fluoxetine

Palmoplantar, axillary and craniofacial ('emotional') hyperhidrosis

Emotional or mental activity increases sweating, especially on the palms, soles, axillae and to a lesser extent, groin and face. It should be emphasized that mental activity devoid of any clear emotional content may provoke sweating. There may be some generalized increase in sweating. Thermal stimuli and physical effort increase this effect in many cases. Most cases of hyperhidrosis presenting to the dermatologist are of this type, affecting

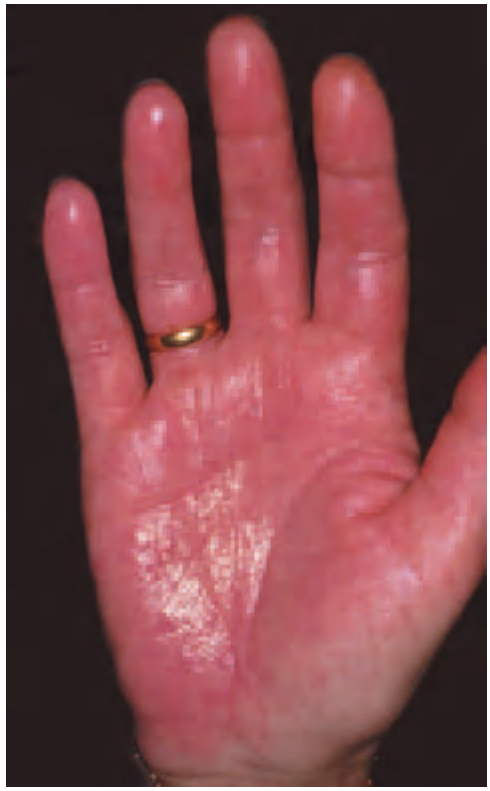

Fig. 45.5 Disabling palmar hyperhidrosis.

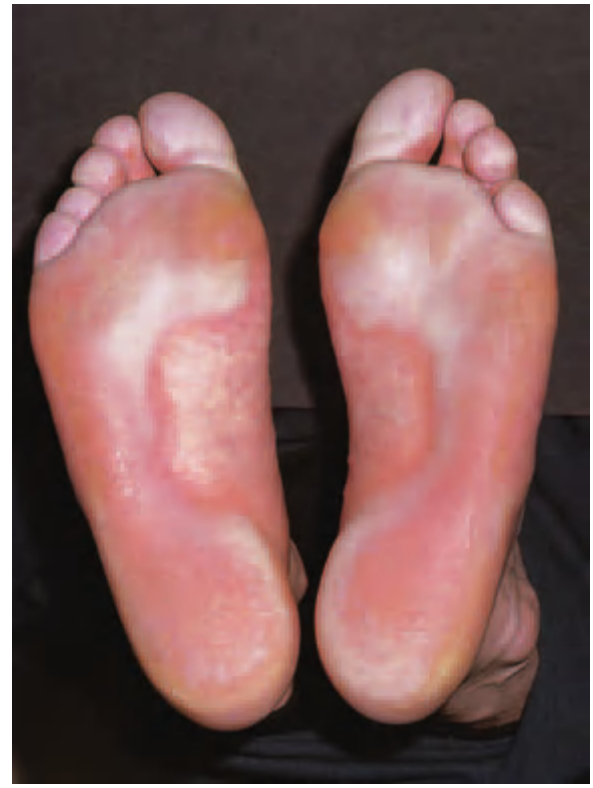

Fig. 45.6 Symmetrical lividity. Hyperhidrosis of the feet, with cool macerated soles and pitted keratolysis. (Courtesy of Dr R.H. Champion, Addenbrooke's Hospital, Cambridge, UK.)

especially the palms, soles and axillae, and may affect up to 1% of the population in the UK. The head, neck and scalp may be affected in craniofacial hyperhidrosis in the absence of other areas being affected. Although mental or emotional factors are the usual trigger for this type of sweating, and in some patients deep-seated emotional disturbances may be found, in many there seems to be some facilitation of the nervous pathways causing physiological mental sweating.

The sweating of the palms and soles may be either continuous or phasic [5]. When continuous it is worse in the summer, and not so clearly precipitated by mental factors. When phasic, it is usually precipitated by minor emotional or mental activity, and is not markedly different in summer and winter. The hands may be cold, and show a tendency to acrocyanosis. Hyperhidrosis may be associated with Raynaud's phenomenon and reflex sympathetic dystrophy [6], or may follow cold injury.

Hyperhidrosis may be a significant disability, in that sweat drips from the hands onto the floor (Fig. 45.5), rusting of metal objects may be an industrial problem, or clothing may be saturated. This disorder occurs in either sex, and commonly begins in childhood or around puberty. Frequently there is a family history, and it is one component of various syndromes in which palmoplantar keratoderma occurs (Chapter 34). It also occurs with the nail–patella syndrome (Chapter 62). Hyperhidrosis may persist for some years, but there is a tendency to spontaneous improvement after the age of 25 years. Apart from the embarrassing nature of the disorder, complications include pompholyx (Chapter 17) and contact dermatitis. Control of plantar hyperhidrosis may reduce the exacerbations of contact dermatitis to footwear constituents.

Sweating affects the hands, feet and axillae in any combination, but only a minority of patients with axillary hyperhidrosis also have involvement of the palms and soles. Troublesome hyperhidrosis of the feet occurs especially in young adult men. When this is associated with vasomotor changes, so that the sodden skin is also cold and cyanotic, the name 'symmetrical lividity' is sometimes applied (Fig. 45.6). The condition of pitted keratolysis (Chapter 27) of the feet, due to infection with *Micrococcus sedentarius*, is associated with hyperhidrosis.

Axillary sweating may be continuous, or more commonly phasic, and may or may not be aggravated by heat or mental activity. It is uncommon before puberty. Axillary sweating on undressing is very common. Axillary hyperhidrosis is due to overactivity of eccrine glands, unlike axillary odour which is mainly apocrine in origin. Craniofacial hyperhidrosis is often phasic, occurs in middle age and may be exacerbated by heat, exercise and eating, but unlike true gustatory hyperhidrosis, not

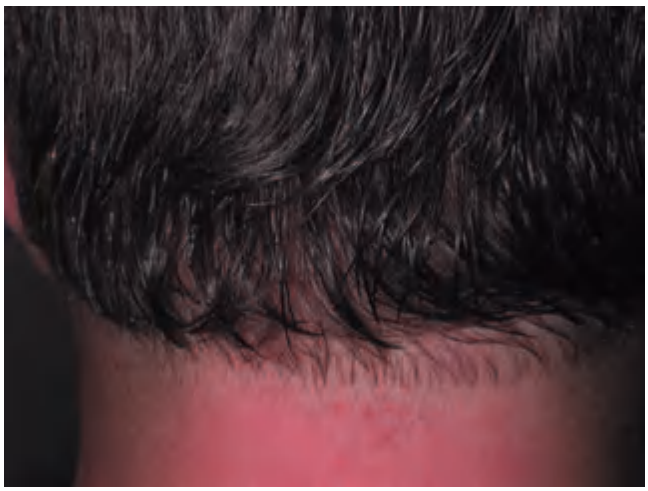

Fig. 45.7 Craniofacial hyperhidrosis producing persistent saturation of the hair.

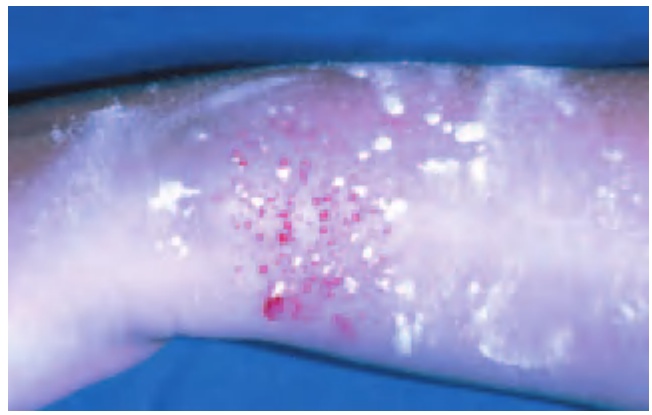

Fig. 45.8 Idiopathic circumscribed hyperhidrosis on the wrist (indicated by edicol ponceau powder, which turns scarlet on hydration). The rest of the patient's sweating and neurological examinations were normal.

exclusively so. Sweating sufficient to soak the hair is an additional embarrassment (Fig. 45.7).

Localized and asymmetrical hyperhidrosis

The causes of localized hyperhidrosis are outlined in Table 45.2.

Excessive sweating may be due to neurological lesions involving any part of the sympathetic pathway from the brain to the nerve ending. It may be the presenting symptom, but it is quite exceptional for this to occur as an isolated phenomenon in the absence of other neurological symptoms or signs. Such lesions may be within the central nervous system [1,7–9] (cortex, basal ganglia or spinal cord), the sympathetic pathway and ganglia, or in the peripheral nerves. It must be remembered that the distribution of the sympathetic nerves does not exactly correspond with sensory dermatomes. One sympathetic grey ramus may supply 10 or more sensory segments, and one white ramus extends over at least five. Asymmetrical sweating may also occur reflexly from visceral disturbances [10], adjacent to an area of anhidrosis or due to axon reflex stimulation, around a leg ulcer, for example [7], or around glomus tumours, blue rubber bleb naevi or sudoriparous angioma [11]. Compensatory hyperhidrosis occurs in normal sweat glands when those elsewhere are not functioning because of neurological or skin disease, or after sympathectomy (see also Ross's syndrome). Functional sweat gland naevi have been reported [12], but must be distinguished from sweat gland hypertrophy associated with local hyperhidrosis of some other aetiology. There are some bizarre cases of hyperhidrosis which cannot be explained in these ways. Areas of skin which may be localized [13] (Fig. 45.8), termed idiopathic circumscribed hyperhidrosis, or as extensive as one-half of the body [14], may sweat continuously, or, more commonly, with mental activity. They may represent functional naevi, where the eccrine glands show increased sensitivity to cholinergic neurotransmitters. Sometimes, some psychological disturbance accounts for the distribution [15], but more often such cases remain a mystery. In the absence of other neurological symptoms or signs, they are seldom a manifestation of a progressive neurological lesion.

Table 45.2 Causes of localized hyperhidrosis.

Spinal cord injury
Hyperhidrosis associated with autonomic dysreflexia
Hyperhidrosis due to orthostatic hypotension
Intrathoracic neoplasia
Gustatory hyperhidrosis
Frey's syndrome
Granulosis rubra nasi
Functional and true sweat gland naevi
Sweating associated with local skin disorders
Glomangioma
Blue rubber bleb naevi
Pachydermoperiostosis
Pretibial myxoedema
POEMS syndrome
Burning feet syndrome
Compensatory
After sympathectomy, or with partial anhidrosis
Idiopathic unilateral circumscribed hyperhidrosis

POEMS, polyneuropathy, organomegaly, endocrinopathy, M protein, skin changes.

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Gustatory hyperhidrosis (Table 45.3)

Sweating on the lips, forehead and nose after eating certain foods occurs physiologically in many people. Hot spicy foods are the most likely cause. The central connections of this reflex are not fully known. Gustatory hyperhidrosis also occurs in pathological conditions involving the autonomic nervous system. Localized areas of intense hyperhidrosis may occur on the face [1], and even on the knee [2]. These disorders are very rare, usually start in childhood and are not progressive (Fig. 45.9). Their nature is little understood.

Also uncommon is gustatory hyperhidrosis due to a lesion within the central nervous system [3].

Much the commonest cause is damage to the sympathetic nerves around the head and neck. After damage to sympathetic nerves, regeneration occurs not only from the proximal ends of the damaged sympathetic nerves, but also from damaged or undamaged parasympathetic nerves [4,5]. In this way, abnormal connections are made. Thus, the reflex arcs which normally allow chewing or taste stimulation to cause parotid or gastric secretion may cause sweating in a localized zone corresponding to the area of the skin in which the sympathetic innervation has been damaged. The commonest site is within the distribution of the auriculotemporal nerve, following injury, abscess or operation in the parotid region (auriculotemporal or von Frey's syndrome) [6–8]. Submental gustatory sweating [9,10] follows injuries involving the chorda tympani, and sweating in the distribution of the greater auricular nerve commonly follows radical neck surgery [11]. On the upper arm, fibres from the vagus may cause gustatory sweating after cervical sympathectomy [12].

Gustatory sweating may occur in diabetes as part of a widespread autonomic neuropathy [13,14]. It has also followed herpes zoster [15].

Gustatory sweating is by no means uncommon, and occurs in 50–80% of patients subjected to operations on the parotid gland [16,17]. Usually the symptoms appear 4–7 months after operation, and either persist indefinitely or wane after 3–5 years. The stimuli required to initiate the reflex vary, as does the severity. Sometimes chewing, without taste sensation, is the most important stimulus. In many cases, it is merely a curiosity, but in others it can be a significant disability. As well as sweating there is usually

Table 45.3 Classification of gustatory hyperhidrosis.

Idiopathic
Central
Post-herpetic
Post-peripheral nerve injury
Parotid surgery, injury and abscess
Auriculotemporal
Chorda tympani
Greater auricular
Cervical sympathectomy
Peripheral autonomic neuropathy
Diabetes mellitus

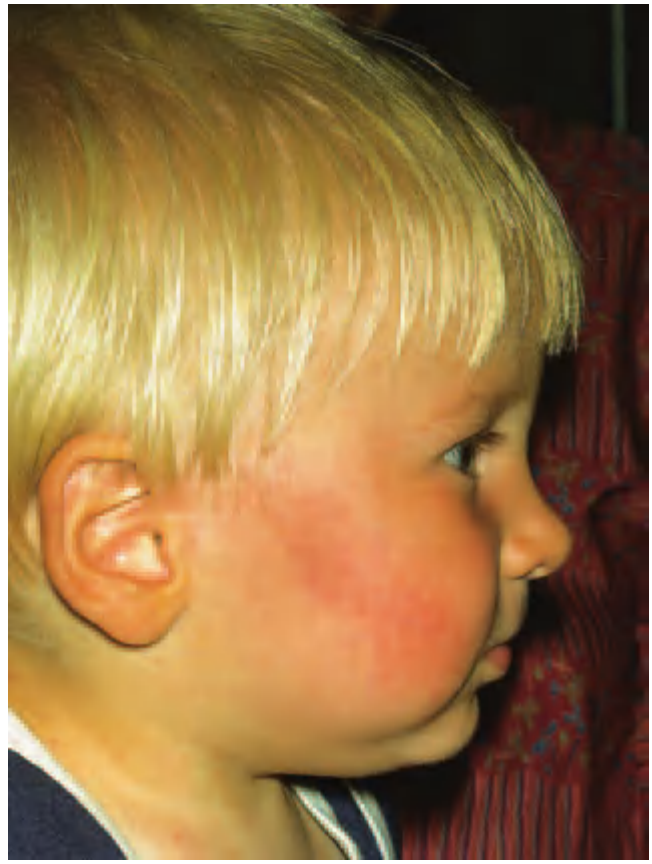

Fig. 45.9 Auriculotemporal or von Frey's syndrome without any neurological abnormality and not preceded by surgery or injury. Cheek flushing and sweating was precipitated by eating. (Courtesy of Dr P. Hudson, Peterborough District Hospital, Peterborough, UK.)

vasodilatation, which rarely occurs by itself in the absence of visible sweating.

Treatment of severe cases may require surgical interruption of the parasympathetic pathway—for example, section of the glossopharyngeal nerve within the skull, or tympanic neurectomy [4]. Excision of the auriculotemporal nerve is usually followed by recurrence. Topical therapy with aluminium chloride [18], topical glycopyrronium bromide [19] or botulinum toxin may be helpful.

Olfactory hyperhidrosis, in which the trigger stimulus is olfactory in origin, has also been recorded [20].

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Treatment of hyperhidrosis

In many patients all that is necessary is simple reassurance and explanation of the nature of the disorder, and that it is likely to improve spontaneously, perhaps in several years. Topical and systemic treatments are by no means satisfactory and, at best, only temporarily suppressive.

Topical treatment

Topical anticholinergics. Atropine-like drugs may be absorbed sufficiently to produce a beneficial local effect without associated systemic side effects, but none of those at present available can be relied upon to do so [1]. Poldine methosulphate, 1–4% in alcohol, suppresses experimentally induced sweating, but unfortunately is less valuable on the palms, soles and axillae [2]. Topical 0.5% glycopyrronium bromide cream has been successfully used in gustatory hyperhidrosis in diabetics.

Eccrine duct blocking agents. These drugs act by impeding the delivery of sweat to the skin surface. Formalin 1% soaks have long been used for treatment of hyperhidrosis of the feet, but are unsuitable for the hands and axillae. Glutaraldehyde 10% in a buffered solution, pH 7.5, swabbed onto the feet three times weekly, has helped some patients [3], but may cause allergic sensitization and stains the skin, so that it is suitable only for the feet. For axillary hyperhidrosis (as opposed to bromhidrosis) the most commonly used topical applications are aluminium (or other metal) salts. Aluminium chloride, the first to be introduced, is in many ways the best, but may be irritant to the skin and damage clothes. Many other salts—for example, the chlorhydrate—are in use in cosmetic preparations [4]. Improved results can be achieved by applying 20% aluminium chloride in absolute ethanol at night, when the axilla is dry, with or without polythene occlusion, at first nightly and later every 1–4 weeks [5,6]. Commercial preparations are available. Mild irritation of the skin from such therapy may be helped by a weak topical steroid. The same treatment can also be tried on the hands and feet, or other localized areas of hyperhidrosis, but usually with rather less success. The mode of action of aluminium salts is uncertain, but they can be shown to affect both the duct and secretory coil [7].

Iontophoresis. One of the more satisfactory methods of controlling hyperhidrosis of the hands and feet is by iontophoresis, either using tap water or anticholinergic drugs such as glycopyrronium bromide [8–11]. The mode of action of tap water iontophoresis is not known. It is more effective than using saline, and duct occlusion does not occur. Direct current is usually used, with each palm or sole being treated for 30 min with 20 mA initially three times a week, but once euhidrosis is established, maintenance treatments once a month only may be required. Alternating current is less effective, but may usefully be combined with direct current (alternating current offset) to produce a safer, more comfortable treatment [12]. Once control has been achieved, a single treatment may prove effective for some weeks. Minor systemic side effects due to absorption of anticholinergic agents, such as dry mouth and eye symptoms, are not uncommon, and can be avoided if tap water alone is used. The author's practice is to initiate thrice-weekly treatment on a hospital outpatient basis, and if this is successful, a small battery-operated home unit can be purchased for maintenance

therapy [13]. Less frequent treatment will then be required. When the sweating is controlled, the associated lividity, coolness and oedema improve. Similar treatment has also been used for the axilla, but is less often needed because topical applications are more effective in this site.

Botulinum toxin A injection. This compound produces prolonged blockade of neuronal acetylcholine release at the neuromuscular junction and in cholinergic autonomic neurones and has been used to treat dystonic conditions for many years. In recent years, intradermal injection of various sites has been used to produce marked reduction of sweating in hyperhidrotic areas produced by a variety of conditions [14–17]. Different preparations of botulinum A toxin have different activities, and dose schedules differ for each product. 0.1 mL of appropriately diluted botulinum toxin administered by high intradermal injections can be given to 1 cm^2 areas of skin appropriately anaesthetized—topical eutectic lignocaine/prilocaine is sufficient for axillary skin, but palms and soles require regional nerve blockade. Each axilla usually requires 12 injections, hands 20 and each foot 24–36 injections. It will produce reduction in sweating within 48 h and the benefit will last for up to 8 months in axillary and 6 months in palmar hyperhidrosis [18]. Reinjection seems to be effective, and to date resistance has not been seen in hyperhidrosis, although it eventually occurs in 5% of patients treated intramuscularly for dystonia. Botulinum toxin has been used for idiopathic circumscribed and gustatory hyperhidrosis, including Frey's syndrome, the hyperhidrotic areas in Ross's syndrome, and frontal and craniofacial hyperhidrosis. Slight transient reduction of thenar and hypothenar muscle power is a minor problem after palmar injections [18].

Systemic drug treatment

Atropine-like drugs have been used to block the effect of acetylcholine on the sweat glands, but their side effects are often more troublesome than the hyperhidrosis itself. These include dryness of the mouth, constipation and disturbances of vision, due to paralysis of accommodation, but more serious side effects, for example glaucoma, hyperthermia and convulsions, can occur. Atropine itself is seldom employed. Propantheline may be prescribed in doses of 15 mg three times daily, increasing, if tolerated, to as much as 150 mg daily [19], but overall the results are disappointing. Ganglion-blocking drugs can inhibit sweating, but side effects from hypotension are usually too troublesome. Calcium-channel blockers, such as diltiazem [20] have helped some cases. In cases with a pronounced emotional factor, sedative or tranquilizing drugs are often useful, but psychiatric treatment may be necessary. Both clonazepam [21] and amitriptyline have helped isolated cases of unusual localized hyperhidrosis.

Surgical treatment

Sympathectomy, when complete, causes anhidrosis, whether performed cervically, transaxillary or endoscopically [22–25]. Sweating may return after a period of some years, due either to regeneration of sympathetic fibres or to fibres which do not pass through the sympathetic ganglia [26]. The open approach has been largely replaced by an endoscopic procedure, which may be successful in treating palmar, axillary and craniofacial hyperhidrosis. A pneumothorax is induced, and an operating endoscope inserted into the thorax via a small axillary incision, allowing visualization of the sympathetic trunk. Interruption of the sympathetic fibres between the second and fourth thoracic ganglia can be achieved by surgical transection, radiofrequency ablation, phenol destruction, cautery or clipping [27] (the latter technique has the potential advantage of partial reversibility). Most surgeons treat both sides at a single session. With both the open and endoscopic approaches, satisfactory reduction of palmar hyperhidrosis is achieved in over 95% of cases; it is a little less successful for axillary hyperhidrosis. In a series of 650 patients treated endoscopically, the initial failure rate was 2%, and there was recurrence in 2%; overall, 98% were satisfied with the result [28]. Large case series using endoscopic techniques in children show it to be an acceptable option, with a low recurrence rate [29]. Complications of sympathectomy include haemothorax, pneumothorax, chylothorax, nipple sensitivity and Horner's syndrome. There are rare instances of transient or permanent bradycardia complicating the technique. Other disadvantages are that the palms or soles may become excessively dry, and irritant eczema after sympathectomy has been reported [30]. Postoperative compensatory hyperhidrosis is a problem, particularly in warmer climates, as it may occur in up to 80% of those treated, affecting the trunk, legs and face, where it may be gustatory. It is usually mild and preferable to severe palmar hyperhidrosis, but rarely is disabling. In five patients who had undergone a clipping procedure who developed compensatory hyperhidrosis, removal of the clips resulted in return of the palmar sweating and abolition of the compensatory hyperhidrosis [27]. It has been suggested that ablation at the level of the third thoracic ganglion does not produce this side effect. Abolition of severe facial blushing may be a desirable consequence, and resolution of palmar eczema has been reported after endoscopic sympathectomy. In general, only those patients in whom a severe disability is arising from the hands or axillae warrant surgery, and in these selected cases the results can be very gratifying. Endoscopic sympathectomy has been used successfully in the treatment of severe craniofacial hyperhidrosis [31]. Pedal sympathetic denervation requires removal of the second lumbar sympathetic ganglion; bilateral operations will usually result in ejaculatory impotence, so it is best avoided.

Axillary hyperhidrosis may be greatly helped by local excision of the axillary vault [32,33]. Variations of this technique include subcutaneous curettage of the axillary skin [34] and tumescent liposuction of the axillae [35].

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Anhidrosis

Anhidrosis is the absence of sweat from the surface of the skin in the presence of an appropriate stimulus. This may be caused by an abnormality of the sweat gland itself, or at any level in the nervous pathway. There are many causes [1], and a number of the more important of these are listed in Table 45.4.

A full account of the assessment of sympathetic nerve activity is beyond the scope of this book [2–10].

Extensive anhidrosis may impair heat regulation to such a degree that hyperpyrexia occurs on exposure to heat. It characteristically occurs in anhidrotic ectodermal dysplasia and in otherwise normal premature or full-term infants under the age of 1 month [11]. It may be associated with compensatory hyperhidrosis of the remaining functionally active glands. It has been reported as an isolated finding [12,13]. Cessation of sweating is the cause of heat hyperpyrexia. The anhidrosis associated with ichthyosis may be more apparent than real. Localized areas of anhidrosis are of little clinical importance, except that they may help in the diagnosis of neurological lesions or leprosy. Sweat gland function can be a useful way to assess damage to the sympathetic nervous system—for example, in patients with postural hypotension [2,10,14]. Sweat retention is the cause of miliaria (see below), and plays an important part in producing crises of irritation in patients with atopic dermatitis, eczema and other dermatoses. It also occurs in psoriasis, where sweat duct blockage, and perhaps also impaired ductal absorption, occurs [15].

Ross's syndrome [16]

This rare syndrome consists of widespread hypohidrosis combined with patchy, sometimes very striking, compensatory hyperhidrosis (Fig. 45.10), together with tonic pupils (appearing asymmetrical and irregular in their outline, constricting and dilating slowly to light and dark,

Table 45.4 Classification of anhidrosis.

Brain lesions
Organic lesion at any level
Hyperthermia
Spinal cord and peripheral nerve lesions
Organic lesions, e.g.:
Syringomyelia
Leprosy
Sympathectomy
Diabetes mellitus
Alcoholism
Congenital sensory neuropathy with anhidrosis
Other causes of autonomic neuropathy
Ross's syndrome
Ganglion-blocking and anticholinergic drugs
Botulism
Sweat gland lesions
Aplasia
Congenital ectodermal dysplasia
Ichthyosis
Any cause of atrophy (e.g. acrodermatitis chronica atrophicans)
Mepacrine eruption
Scleroderma
Myelomatosis
Lymphoma
Sjögren's syndrome
Incontinentia pigmenti
Fabry's disease
Plugging of the eccrine duct
Miliaria
Eczema and atopic dermatitis
Lichen planus
Psoriasis
Uncertain
Neonatal
Sweat gland fatigue
Idiopathic acquired anhidrosis

respectively) and loss of deep tendon reflexes (Holmes–Adie syndrome). Patients with the Holmes–Adie syndrome often show asymptomatic changes in sweating [17]. The anhidrosis may be quite localized—for example, mainly on one palm, mimicking a *Trichophyton rubrum* infection [18]. When the anhidrosis is extensive, remaining areas of functioning eccrine glands may show compensatory hyperhidrosis. Cardiac sympathetic denervation which may be asymptomatic has been shown to develop [19]. The compensatory hyperhidrosis may be striking and severe enough to require therapy, for example with iontophoresis [20] or botulinum toxin injection [21], although eventually it may be lost as complete anhidrosis develops. The changes are due to selective degeneration of the sympathetic pathways [21].

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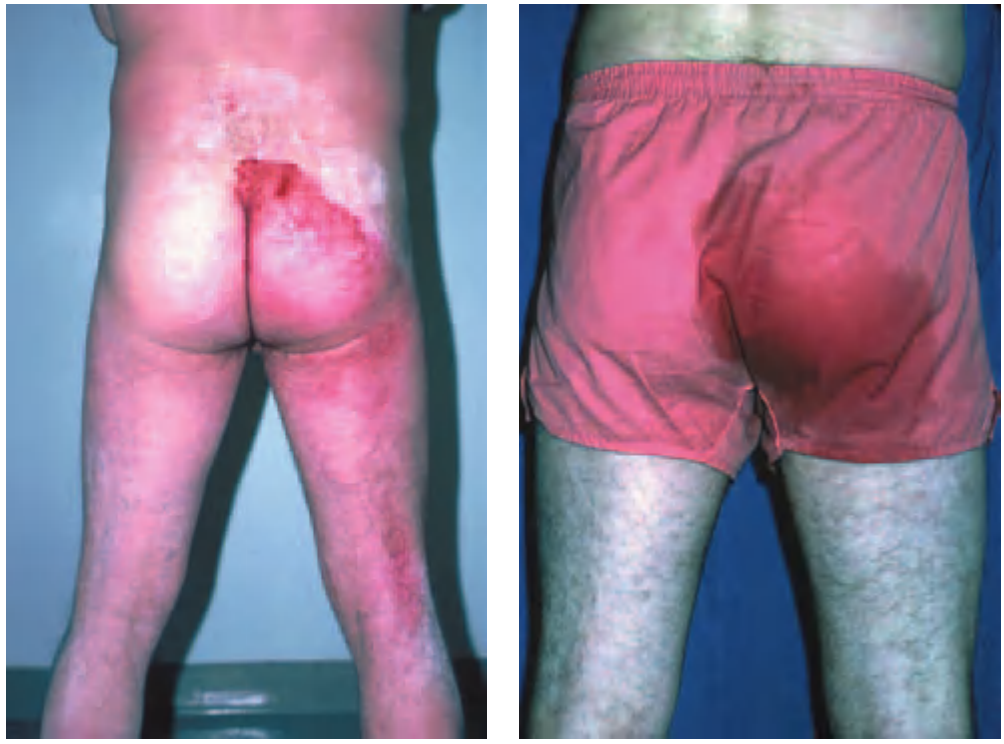
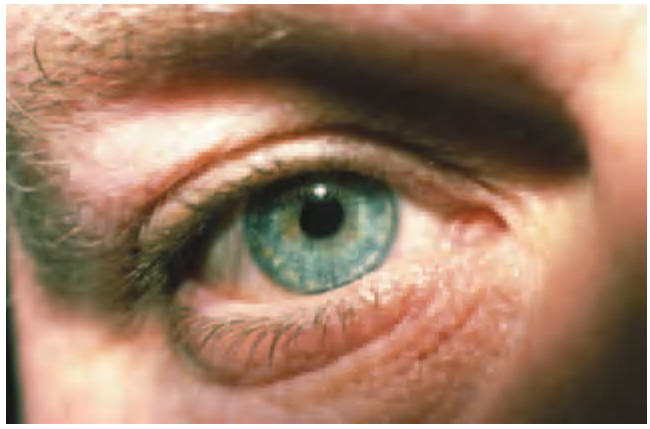
Miliaria

Aetiology and pathology [1–3]. The three forms of miliaria—miliaria crystallina (sudamina), miliaria rubra (prickly heat) and miliaria profunda—occur as a result of either obliteration or disruption of the eccrine sweat duct. They differ in clinical form due to the different levels at which obliteration occurs, although some authorities have suggested that disruption of the duct rather than obliteration is responsible [4]. In miliaria crystallina, the obstruction is very superficial within the stratum corneum and the vesicle is subcorneal. In miliaria rubra, the later changes include keratinization of the intraepidermal part of the sweat duct, with leakage and then formation of a vesicle around the duct. In miliaria profunda, there is rupture of the duct at the level of or below the dermal–epidermal junction.

Miliaria crystallina can easily be produced experimentally by minimal non-specific epidermal injury and profuse sweating [5]. It is often seen in febrile illnesses associated with profuse sweating. It occurs commonly in



(a) (b)



(c)

Fig. 45.10 Ross's syndrome. (a) There is generalized anhidrosis, with large islands of severe compensatory hyperhidrosis (delineated with edicol ponceau powder, which turns red in the presence of water). (b) The hyperhidrosis is sufficient to soak the underclothes, with consequent embarrassment. (c) An abnormal pupil, showing an irregular outline and meiosis. It responds sluggishly to light.

infants due to a delay in patency developing in the sweat ducts. In a large Japanese study, it was identified in 4.5% of babies, with a peak frequency at 1 week [6].

The incidence of miliaria rubra is highest in hot, humid conditions, but it may occur in desert regions, affecting up to 30% of people exposed to these climatic conditions [7]. It may begin within a few days of arrival in a tropical climate, but is maximal after 2–5 months. There is a striking variation in individual susceptibility. Infants are especially prone. Lesions may be produced experimentally in susceptible subjects by epidermal injury. They can be reproduced regularly by occlusion of the skin under polythene for 3–4 days, following which anhidrosis lasts for about 3 weeks. Prolonged exposure of the skin to sweat achieves the same effect. The first event may be an increase in the skin flora, perhaps with *Staphylococcus epidermidis* being responsible for producing an extracellular polysaccharide substance or slime which blocks the lumen of the sweat duct [1,8]. The parakeratotic plugs which are a notable feature of the later stages of the disease are not the primary cause of the obstruction, but arise in the repair process, and may further aggravate the obstruction. Leakage of sweat into the epidermis is responsible for the final production of the lesions, and for their further aggravation.

Miliaria profunda is due to more severe damage to the sweat duct, and usually follows repeated attacks of miliaria rubra. It may be reproduced by experimental injury [7].

Clinical features of the three types of miliaria are as follows.

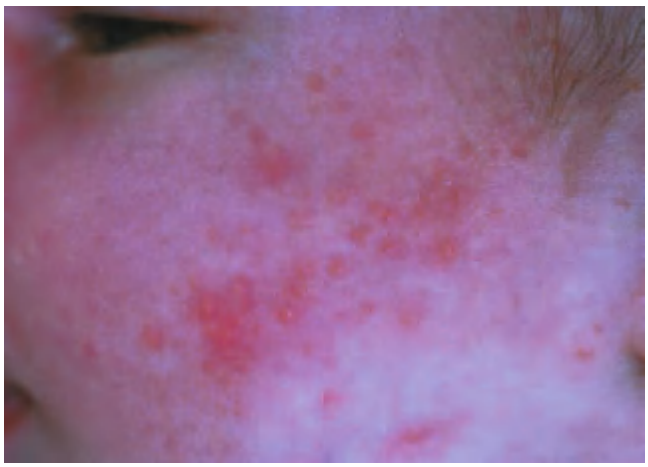


Fig. 45.11 Miliaria rubra on a baby's cheek. (Courtesy of Dr Richard Logan, Bridgend General Hospital, Bridgend, Mid Glamorgan, UK.)

Miliaria crystallina. Clear, thin-walled vesicles, 1–2 mm in diameter, without an inflammatory areola are usually symptomless and develop in crops, mainly on the trunk. In persistent febrile illnesses, recurrent crops may occur. The vesicles soon rupture, and are followed by superficial branny desquamation.

Miliaria rubra. The typical lesions develop on the body, especially in areas of friction with clothing, and in flexures. They may also commonly be seen after occlusive therapy with polythene. The lesions are uniformly minute erythematous papules, which may be present in very large numbers. Miliaria rubra is common on the trunk in hospitalized patients, who have to be nursed on their backs on bedding that has waterproof occlusive membranes below the sheets (Fig. 45.11). Characteristically, the lesions produce intense discomfort in the form of an unbearable pricking sensation. Relief is often instantaneous when the stimulus to sweating is abolished by a cool shower. Outbreaks on the legs in miners working in tropical climates have been reported [9]. In infants, lesions commonly appear on the occluded skin of the neck, groins and axillae, but also occur elsewhere.

Miliaria profunda. This nearly always follows repeated attacks of miliaria rubra, and is uncommon except in the tropics. The lesions are easily missed. The affected skin is covered with pale, firm papules 1–3 mm across, especially on the body, but sometimes also on the limbs. There is no itching or discomfort from the lesions.

Patients often refer to polymorphic light eruption as 'prickly heat', but the relationship of the rash to light, particularly on newly exposed sites, is usually straightforward.

Natural history. The course depends mainly on environmental factors. If continued sweating occurs, recurrent episodes lasting a few days are usual, but discomfort may be continuous. However, after a few months some degree of acclimatization occurs, and the disorder becomes less prevalent.

The most important complications of miliaria are secondary infection and disturbance of heat regulation. Secondary bacterial infection is common and sometimes serious. This may present as impetigo. In other cases, the pustules are more clearly related to sweat ducts, although in *pustular miliaria* factors other than bacterial infection are concerned [10]. Periporitis staphylogenes [11] is the name given to multiple staphylococcal abscesses superimposed on miliaria rubra in young infants. In most cases of miliaria rubra, the changes are reversible if further sweating is avoided, but permanent damage to the sweat duct may occur, especially after miliaria profunda.

Treatment. The only really effective prevention or treatment for miliaria is avoidance of further sweating. Even if this is achieved only for a few hours a day, as in an air-conditioned office or bedroom, considerable relief is experienced. For the very susceptible person, a move away from tropical climates may be essential. Avoidance of excessive clothing, friction with clothing, excessive use of soap and contact of the skin with irritants will reduce the incidence. The large number of treatments advocated for prickly heat is the best indication of their relative ineffectiveness if sweating is not reduced. In the absence of gross secondary sepsis, the effect of topical or systemic antibiotics or other antibacterial preparations on established miliaria is disappointing, but they may have some role in prophylaxis [1]. Oral ascorbic acid 500 mg b.d. was found to diminish the severity of miliaria, as was the degree of subsequent anhidrosis in experimentally induced disease [12]. Calamine lotion is probably as effective as anything for the relief of discomfort, but because of its drying effect, a bland emollient, for example oily cream, may subsequently be required to prevent further epidermal damage. Isotretinoin was reported to help a recalcitrant case of miliaria profunda [13].

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The role of sweating in some other dermatoses

The role of sweating in pompholyx or dyshidrosis is discussed in Chapter 17, in Grover's disease or transient acantholytic dermatosis in Chapter 34 and in cholinergic urticaria in Chapter 47.

Disorders associated with abnormal eccrine histology

Neutrophilic eccrine hidradenitis

Necrosis of the eccrine epithelium and secretory coil with a dense surrounding neutrophilic infiltrate is seen in a variety of clinical entities (Table 45.5).

Chemotherapy-induced neutrophilic eccrine hidradenitis. The most commonly reported variant occurs during cancer chemotherapy [1–3], and has been reported in adults and children. The clinical presentation is of painful erythematous papules and plaques arising on the limbs, neck, face and ears 8–10 days after the start of chemotherapy, often associated with fever and a neutropenia. Cases featuring only erythematous swelling of the periorbital areas [4] and the ears [5] have been described. The eruption lasts for about 10 days, resolving without therapy, and only rarely recurs at subsequent chemotherapy exposures [6]. No one chemotherapeutic agent has been identified as the culprit; indeed, most cases have arisen after administration of a cocktail of chemotherapeutic agents given for myeloproliferative disorders, lymphomas and solid tumours. It has been reported after granulocyte colony-stimulating factor [7]. The histological changes have been experimentally induced in healthy volunteers given intradermal bleomycin, suggesting that a direct toxic effect of the drug on the eccrine gland is responsible [8]. In a case of recurrent chemotherapy-triggered disease, dapsone prophylaxis was effective [9].

Table 45.5 The classification of neutrophilic eccrine hidradenitis.

Chemotherapy-induced eccrine hidradenitis
Infectious neutrophilic hidradenitis
Palmoplantar hidradenitis
Neutrophilic eccrine hidradenitis with HIV infection and Behçet's disease

HIV, human immunodeficiency virus.

Neutrophilic eccrine hidradenitis (NEH) and other diseases. NEH has recently been associated with Behçet's disease [10], and has been reported in association with human immunodeficiency virus (HIV) infection [11].

Infectious neutrophilic eccrine hidradenitis [1]. The sweat glands are resistant to infection, and there are few reports of bacterial hidradenitis. *Serratia* and staphylococcal hidradenitis have been reported in immunocompromised hosts. Enterococci have been cultured from an otherwise healthy woman with hidradenitis on the trunk.

Idiopathic recurrent palmoplantar hidradenitis

This disorder, first described in 1994, is probably more common than the literature suggests [12]. Tender, erythematous plaques develop on the soles and occasionally the palms of children; it has been reported between the ages of 18 months and 15 years [13]. It may mimic a vasculitis. Attacks, lasting up to 3 weeks, are more frequent in autumn and spring. Resolution occurs spontaneously, and in almost half of the cases, the condition is recurrent. Vigorous exercise has been implicated in initiation of some attacks; exposure to cold, damp footwear was believed to be important in another small series [14]. Histology shows eccrine epithelial necrosis, dense infiltration of the periglandular dermis with neutrophils and sometimes abscess formation. Rest, cool compresses, topical and oral steroids have been used as symptomatic treatment.

Syringosquamous metaplasia

Syringosquamous metaplasia is a histopathological term describing the transformation of normal cuboidal duct epithelium into cells with an eosinophilic cytoplasm and a larger more irregular nucleus, so that in some areas it seems that ducts appear in islands of squamous epithelium mimicking squamous carcinoma, or as dilated structures reminiscent of syringomas. The eccrine gland coils are not affected [15]. The histological changes may be seen around areas of cutaneous ulceration of diverse causes, such as burns and arterial ulcers, but also adjacent to pyoderma gangrenosum and extravasated chemotherapy sites [16]. It may represent a non-specific reaction pattern.

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Drugs and eccrine glands

A number of drugs are concentrated and secreted by eccrine glands, and in part this may account for their therapeutic effect. Drugs known to be secreted include sulfaguanidine, sulfadiazine, amphetamines, iodides, phenytoin, phenobarbital, carbamazepine, griseofulvin, ketoconazole, fluconazole, ciprofloxacin, diamorphine, cocaine and nicotine. Thiotepa excretion may result in hyperpigmentation of the skin where it is occluded under bandages.

Coma-induced eccrine necrosis

Necrosis of the eccrine glands is the most consistently reported feature of drug-induced coma, whether it be caused by barbiturates, benzodiazepines, narcotics or antidepressants. Similar changes are seen in blisters resulting from coma induced by hypoglycaemia or neurological events, suggesting that the changes are due to pressure rather than the drug *per se*. Areas not usually subject to pressure are the areas that usually show these changes. Early features are necrosis of the secretory coil; later, the duct may be similarly affected. Subsequently, epidermal spongiosis, and subepidermal and intraepidermal blisters form with minimal dermal inflammatory infiltrate.

Radiation-induced eccrine damage

High-dose radiation (> 50 Gy) resulting in radiation dermatitis will abolish eccrine function. Lower doses of radiation will reduce eccrine function within 2 weeks of exposure, reaching a nadir at 8 weeks and recovering to a final dose-dependent deficit by 30 weeks. Radiation-induced keratoses have been described that block the eccrine duct, resulting in milia-like lesions. Histologically, dilated eccrine orifices filled with keratin were identified. Resolution occurred a few months after completion of the radiotherapy.

Disorders with sweat gland cellular inclusions

Accumulation of substances within the secretory cells occurs in a number of metabolic conditions, and their identification in skin biopsies can be used diagnostically. In the Hurler and Sanfilippo types of mucopolysaccharidosis, membrane-bound vacuoles may be seen in the secretory cells [1]. Intracytoplasmic lipid occurs in Sandhoff and Niemann–Pick lipid storage disease [2]. Secretory cell inclusions are seen in Fabry's disease, fucosidosis [3] and Kanzaki disease [4], and in amaurotic idiocy, maltase deficiency and adrenoleukodystrophy [5]. Periodic acid–Schiff (PAS)-positive granules in the outer duct cells characterize Lafora's myoclonic epilepsy [6].

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Granulosis rubra nasi [1–3]

The pathogenesis of this rare disease is obscure. Most cases are genetically determined, but the mode of inheritance is uncertain.

The disease usually starts in childhood, from the age of 6 months to 10 years. Excessive sweating may precede other changes by several years. Diffuse erythema first appears on the tip of the nose, gradually extends, and may involve the cheeks, the upper lip and the chin. The erythema is covered by small beads of sweat, which may also be evident over a wider area. Small red macules and papules, and sometimes vesicles, later form at the sweat duct orifices. The condition usually subsides spontaneously at puberty, but may persist indefinitely. In such

cases, telangiectasia becomes a conspicuous feature, and small cysts may be present. Many of those affected have poor peripheral circulation and hyperhidrosis of the palms and soles. Response to treatment is usually disappointing. A single case has been associated with phaeochromocytoma [4].

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Apocrine sweat glands

Anatomy and physiology [1–4]

Apocrine sweat glands derive their name from the way their secretion appears, on light microscopy, to be derived by pinching off parts of the cytoplasm. They are epidermal appendages, and develop as part of the pilosebaceous follicle in the fourth to fifth month of intrauterine life. In the embryo, they are present over the entire skin surface, but most glands subsequently disappear, so that in the adult the characteristic distribution in the axillae, perianal region and areolae of the breasts is found. So-called ectopic glands may be found elsewhere. The mammary glands and glands in the external auditory meatus are modified apocrine glands. Apocrine glands are poorly developed in childhood, and begin to enlarge with the approach of puberty. The activity of the glands is androgen-dependent, and the glands show marked testosterone 5α-reductase activity [5]. The glands are larger than eccrine glands, and in the dissected specimen are visible to the naked eye. They are situated in the subcutaneous tissue. Each consists of a tubule and a duct. The latter is often quite short, and opens into the neck of the hair follicle above the sebaceous gland. Despite their embryological origin from the hair follicle, some apocrine glands eventually come to open on the surface of the skin. The secretory coil is a simple convoluted tube. It is lined by a single layer of columnar or cuboidal cells resting on a basement membrane. The free edge of the cells may show the appearance of apocrine secretion. Electron microscopy shows that this may be partly an artefact, but eccrine, apocrine and even holocrine secretion may all be found in places [3,6,7] (Fig. 45.12). The apocrine duct closely resembles the eccrine duct, and consists of a double layer of cuboidal cells. Outside the basement membrane of the gland and duct is a longitudinal layer of myoepithelial cells. Their function is to support the duct and to propel the secretion to the surface, and waves of peristalsis have been seen in them [8]. Where the duct opens into the neck of the hair follicle, there is the equivalent of the acrosyringium of the eccrine duct, although it is less obvious [9].

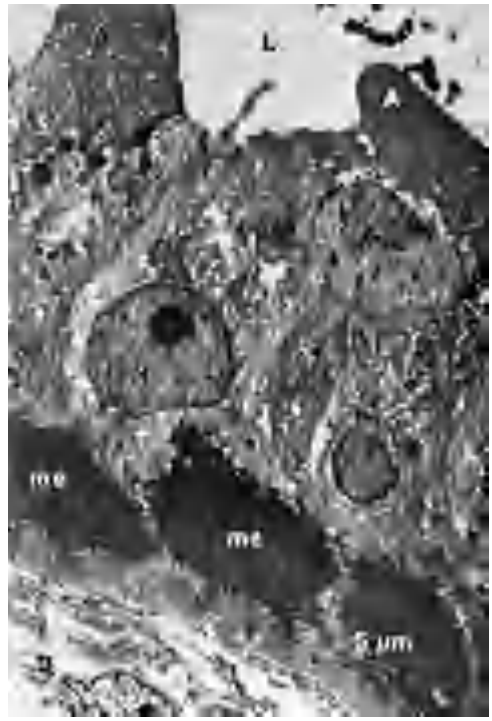

Fig. 45.12 Section of a secretory coil of an apocrine gland from the human axilla; lying next to the basement membrane are myoepithelial cells (me), followed by cuboidal secretory cells, with prominent nuclei (N) and apical caps (A), projecting into the lumen (L). D, dermis. (Courtesy of the late Professor A.S. Breathnach, St John's Dermatology Centre, London, UK.)

Apocrine glands secrete very small quantities of an oily fluid, which may be coloured. This secretion is odourless on reaching the surface, and bacterial decomposition is responsible for the characteristic odour; *trans*-3-methyl-2-hexanoic acid, which is water-soluble, is one of the substances which contributes to the odour [10]. The glands have no thermoregulatory function in humans, although they may play some part in human olfactory communication. The epithelium of the secretory coil produces its secretion continuously, with some variation depending on hormonal factors—for example, menstruation and pregnancy. The ducts have an adrenergic sympathetic nerve supply and are also stimulated by circulating epinephrine. Nervous control of secretion is unimportant, and it is even disputed whether the glands have any motor innervation [4,11]. Expulsion of apocrine sweat may occur continuously or be provoked by emotional stimuli. It seems possible that histologically normal apocrine glands may fail to produce any secretion, and that only the axillary glands in humans are important in producing body odour [12].

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Abnormal sweat odour (bromhidrosis and osmidrosis) [1–3]

Odour of the skin in humans is, to a large extent, determined by apocrine gland secretion, although there are other sources. Sebaceous secretion has some odour, and decomposition products of keratinization, especially in the presence of hyperhidrosis, produce offensive smells. Eccrine secretion is usually odourless, but various substances may be excreted in it—for example, garlic, drugs, arsenic. Characteristic odours may be associated with various uncommon amino-acidurias (see below). Old textbooks of medicine report that sweat has a characteristic odour in gout, diabetes, scurvy, typhoid and other diseases [4]. Cases of generalized bromhidrosis associated with nasal foreign bodies have been recorded in children [5,6], and the symptom may be a clue to premature puberty. Other patients complaining of body odour may be suffering from paranoia or phobias (monosymptomatic delusions of malodour) or from organic lesions of the central nervous system.

Apocrine secretion is odourless as it reaches the surface, apart from excreted substances such as garlic. Bacterial decomposition liberates fatty acids, etc., with characteristic smells. This process occurs only after some hours, and frequent removal of apocrine sweat prevents its decomposition. A strong axillary odour tends to be associated with a richer bacterial flora, and especially with more corynebacteria [7,8]. Increased axillary pH may facilitate the overgrowth of these bacteria, and some deodorants may help by acidifying the axillary skin.

There is marked individual and racial variation in body odour, and what is socially acceptable varies greatly with race and social upbringing. Recent studies have demonstrated histological differences between normal and bromhidrotic apocrine glands; in the bromhidrotics, the apocrine glands were larger and more numerous [9]. Elevated activity of type I 5α-reductase activity has been shown in those with bromhidrosis [10].

Treatment of axillary bromhidrosis includes omission of foodstuffs like garlic from the diet, frequent washing of the axillary regions and local antibacterial substances [2]. There is little evidence that measures used to control axillary eccrine hyperhidrosis—for example, aluminium salts and anticholinergic drugs—have much effect on the apocrine glands, although excessive eccrine excretion may favour the spread of apocrine secretion. Surgical excision of axillary subcutaneous tissue by a variety of surgical techniques (axillary shave and subsection of subcutaneous glands, laser ablation, ultrasound ablation and liposuction), which removes both eccrine and apocrine glands, has been performed with good effect in those dissatisfied with conservative measures [11,12].

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Fish odour syndrome (trimethylaminuria)

This disorder results from excessive amounts of the offensively smelling tertiary amine trimethylamine appearing in the both eccrine and apocrine sweat, breath and urine and imparts an unpleasant rotting fish smell to sufferers [1]. Affected individuals are unable to oxidize this substance, which is produced by the intestinal bacterial degradation of choline and carnitine in food to the odourless trimethylamine N-oxide. This can occur as a primary problem, as a result of a mutation in the flavin-containing monooxygenase 3 (*FMO3*) gene [2]. The ability to N-oxidize trimethylamine is distributed polymorphically,

and sufferers are homozygous for an allele which determines this impaired reaction. One per cent of the population are heterozygous carriers of the allele. Secondary trimethylaminuria can occur when there is an increased burden of trimethylamine, and is seen when there is an increased production of trimethylamine (TMA) from its precursors by gut bacteria, in conditions such as blind loop syndrome, uraemia and liver disease.

The unpleasant odour, which is often worse after eating seafood, during periods of stress and during menstruation, can be the source of much distress, rejection and resentment. Sufferers are sometimes unaware of their smell, which may be intermittent and may not be detected by physicians when consulted. Trimethylaminuria was found in 7% of a series of individuals who perceived themselves to be malodorous [3]. The condition can be diagnosed by direct estimation of TMA in the urine; both affected individuals and heterozygous carriers have abnormal elevated excretion of TMA after an oral TMA challenge. A diet low in carnitine and choline may help. Short courses of metronidazole or neomycin may temporarily reduce the bacteria that degrade the carnitine and choline in the gut.

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Chromhidrosis [1,2]

Apocrine sweat may be tinged with a yellow, green or blue hue in up to 10% of the population, but only rarely does it occur to the striking degree that merits the term chromhidrosis (Fig. 45.13). Most commonly blue-black, yellow or green, it results from the secretion of lipofuscins in apocrine sweat, and may be associated with the secretion of coloured breast milk. The more oxidized lipofuscins appear deeper in colour; the lighter-coloured pigments may fluoresce. The diagnosis can be confirmed by finding lipofuscin pigment granules that may fluoresce on fluorescence microscopy in the apocrine secretory cells. The secretion of coloured sweat starts at puberty and persists until there is a gradual regression of apocrine function in old age. Coloured sweat may be discharged from the glands in response to exercise and emotional stimuli, and after manipulation of the skin. The axillae are the most frequently affected sites, although facial [3] and areolar chromhidrosis [4] are recorded. Topical capsaicin has satisfactorily reduced facial and nipple chromhidrosis.

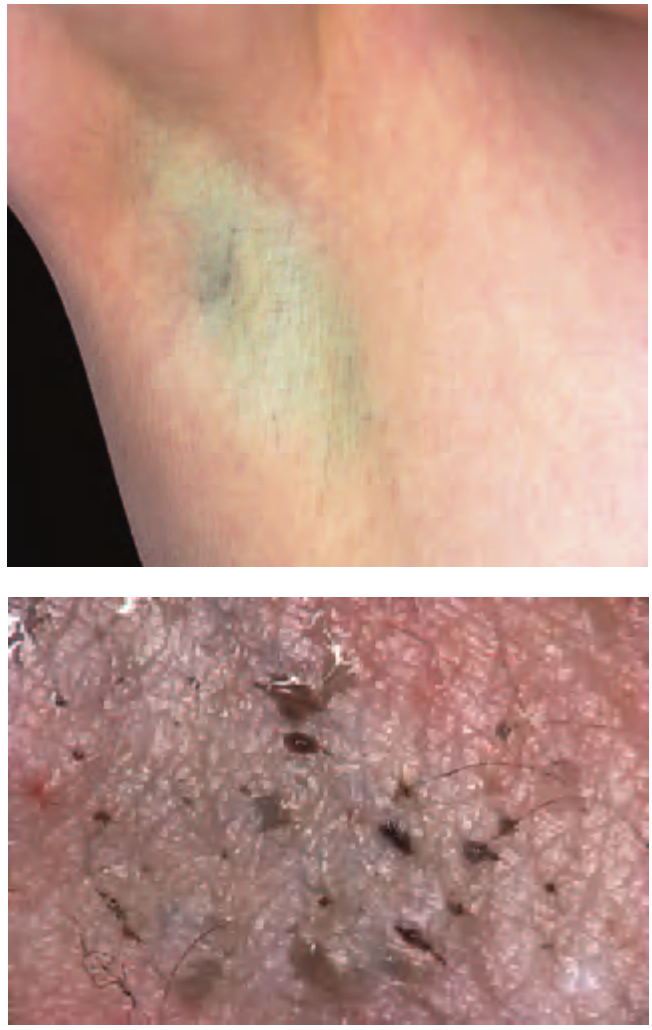

Fig. 45.13 Axillary chromhidrosis. (Courtesy of Dr D. Shuttleworth, Essex County Hospital, Colchester, UK.)

Pseudochromhidrosis refers to the coloration of otherwise colourless sweat when it reaches the surface of the skin due to dyes, paints or chromogenic or porphyrin-producing bacteria on the skin. Blue pseudochromhidrosis has been reported in workers occupationally exposed to copper salts. An outbreak of red pseudochromhidrosis occurred in a group of flight attendants who had new red-dyed labels put into their uniforms [5]. Erythromycin eradicated a presumed bacterial facial pseudochromhidrosis of the face in a young girl [6]. Eccrine chromhidrosis is usually due to exogenous dyes and is usually weak in hue. A case of red pseudochromhidrosis resulting in red staining of underwear was attributed to eating excessive quantities of a snack containing a red food dye [7]. Dark perspiration has been reported to occur in alkaptonuria (ochronosis).

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Fox–Fordyce disease

Aetiology and pathology [1]. Fox–Fordyce disease is a disorder of the apocrine glands comparable to prickly heat of the eccrine glands. The aetiology is unknown. Obliteration of the apocrine duct at the infundibulum is felt to be the cause. The earliest visible change histologically is a small vesicle in the apocrine duct [2]; early changes may be seen most easily in transverse histological sections. This progresses to an inflammatory lesion, followed by rupture and plugging of the duct. Apocrine sweat retention therefore follows. Hormonal influences are important, but there is little evidence of a primary hormonal abnormality.

Clinical features. The disease occurs mainly in women soon after puberty, but can be postmenopausal [3]. It can occur in males or in children, and has been reported in females with Turner's syndrome and in identical twins [4]. Itching, which may be intense, occurs in the axillae, and to a lesser extent in the anogenital region and around the breasts. Objectively there may be little to see at first, but later skin-coloured, or slightly pigmented, dome-shaped, follicular papules develop (Fig. 45.14). Hair loss in the axillae usually ensues. The itching is often provoked by those emotional stimuli which normally cause apocrine secretion. The disease runs a very prolonged course, and may persist until the menopause. Some remission may occur in pregnancy.

Treatment. Response to treatment is unsatisfactory. Topical and intralesional steroids provide some benefit, but their use is limited by atrophy. Topical clindamycin is reported to have been of help [3]. Treatment with four to six weekly doses of ultraviolet radiation (UVR), sufficient to cause exfoliation, helps some patients [5]. Topical retinoic acid may also be helpful [6], as may oral contraceptive agents [7,8], and oral retinoids [9]. Other cases are sufficiently severe to require electrocautery [10] or surgical excision of the affected skin, or subcutaneous removal of the apocrine glands [11].

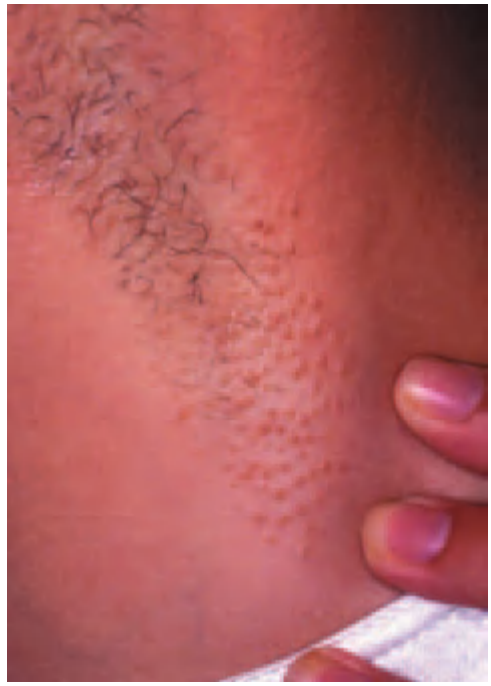

Fig. 45.14 Axillary Fox–Fordyce disease.

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Chapter 46

Disorders of Connective Tissue

N.P. Burrows & C.R. Lovell

Introduction

The connective tissue of the normal skin is discussed in Chapter 3.

Diseases which predominantly affect the cutaneous connective tissue (collagen, elastin and ground substance) can be divided into three main groups.

1 Genetic abnormalities that affect connective tissue formation or metabolism. Examples include Ehlers–Danlos syndrome (EDS) (which affects collagen), pseudoxanthoma elasticum (PXE) (elastic tissue) and the mucopolysaccharidoses (ground substance).

2 Acquired metabolic or degenerative disorders, such as scurvy and solar elastosis, which are liable to affect people with no genetic defect if the environmental cause is present.

3 Inflammatory 'collagen vascular' or 'connective tissue' diseases, which damage connective tissue as a result of complex immunological reactions involving autogenous antigens. This group includes systemic lupus erythematosus, rheumatic fever, systemic sclerosis and dermatomyositis. Both genetic and acquired factors (including the possibility of infective agents) may play some part in producing these conditions, which are fully discussed in Chapter 56.

The attempt to classify the pathological changes according to whether ground substance, collagen, elastin or cellular components are mainly or wholly involved is not always easy, and may have been inaccurate in the past.

In this chapter, some of the genetic and acquired diseases which affect mainly collagen or elastin are discussed. Disorders of the ground substance are discussed elsewhere (see myxoedema, cutaneous mucinosis, myxoid cyst and mucopolysaccharidoses).

There are, in addition, many other disorders, including developmental defects, reactive or scarring conditions and benign or malignant neoplasms, which may involve the connective tissue.

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Cutaneous atrophy

Atrophy of the skin is a term which is applied to the clinical changes produced by a decrease in the dermal connective tissue. It is characterized by thinning and loss of elasticity. The skin usually appears smooth and finely wrinkled, and it feels soft and dry. Veins or other subcutaneous structures may be unduly conspicuous. There is often associated loss of hair follicles, and telangiectasia may also be present, due to the loss of connective tissue support of the capillaries. There may or may not be an associated atrophy of the epidermis.

Atrophy of the skin occurs in varying degree in a large number of skin conditions, and the underlying histological changes are also variable, because the several components of the connective tissue may be involved to a different degree. Atrophy that includes subcutaneous tissue or even deeper structures is referred to as *panatrophy*.

The main causes of cutaneous atrophy are as follows.

1 Generalized cutaneous thinning:
  (a) ageing;
  (b) rheumatoid disease;
  (c) glucocorticoids (exogenous or endogenous).
2 Poikiloderma.
3 Atrophic scars (striae).
4 Anetoderma:
  (a) primary;
  (b) secondary to another inflammatory disease.
5 Chronic atrophic acrodermatitis (borreliosis).
6 Follicular atrophoderma.
7 Vermiculate atrophoderma.
8 Atrophoderma of Pasini and Pierini (probably morphoea).
9 Atrophic naevi.
10 Panatrophy:
  (a) local panatrophy;
  (b) facial hemiatrophy.

Generalized cutaneous atrophy

The skin becomes increasingly thin and atrophic in elderly people, and both the epidermis and the dermis are affected [1] (see Chapter 70 for further details). As a result, the aged skin becomes fragile, translucent, lax and wrinkled, with a tendency to easy bruising.

Dermal thickness is considerably decreased in the elderly [1]. Wound healing is delayed in the elderly because of a decrease in the numbers and synthetic capability of fibroblasts [2]. With increasing age, both keratinocytes and fibroblasts show a decreased response to various growth factors [3].

Ageing and wrinkles

Wrinkles may be defined as creases or furrows in the skin surface. They are generally distinguished from the lax pendulous folds of skin which occur in conditions such as PXE and cutis laxa, but the distinction is somewhat arbitrary, because loss of dermal elastic tissue is common to all these conditions. Deepening of the furrows occurs with advancing age [4]. Histologically, there is epidermal thinning, decrease in chondroitin sulphate and deposition of abnormal elastic tissue in the papillary dermis [5].

Wrinkles can be classified into three morphological types [6].

1 *Crinkles*. This is a very fine wrinkling which occurs in aged skin, even in areas protected from sunlight. These fine wrinkles disappear when the skin is slightly stretched. They are caused by deterioration of elastin, especially the vertical subepidermal fine elastic fibres which keep the epidermis in tight apposition to the dermis [7,8]. Ultrastructural studies have shown that even in normal people the elastic fibres begin to deteriorate from the age of 30 years onwards, regardless of the amount of sun exposure, although sunlight undoubtedly increases the damage [9]. Crinkles are seen in a marked form in mid-dermal elastolysis (see below).

2 *Glyphic wrinkles*. These creases are an accentuation of the normal skin markings. They occur on skin which has been prematurely aged by elastotic degeneration caused by sunlight, for example on the sides and back of the neck (see actinic elastosis).

3 *Linear furrows*. These are long, straight or slightly curved grooves that are usually seen on the faces of elderly people. They include the horizontal frown lines along the forehead, the 'crows' feet' radiating from the lateral canthus of the eye and the creases from the nose to the corners of the mouth.

The facial skin has a remarkably complex and dense intradermal elastic tissue mesh. This sheath of elastin is unique to the face, not being found in such complexity elsewhere. In youth, the linear furrows caused by facial muscle contraction disappear due to elastic recoil, but in older people they become permanent. There is some controversy regarding the histology of these linear furrows. Several groups have claimed that the linear wrinkles cannot be distinguished by light or electron microscopy from the surrounding skin, and Kligman *et al*. [6] claim the furrow is merely a configurational change like the crease in an old glove. Tsuji *et al*. [8], however, claim that the upper dermis in the furrow shows less elastotic change than the surrounding skin. Other authors [9,10], on the other hand, claim that the trabeculae of the retinacula cutis (which anchors the dermis to the underlying fascia)

are broader and much shorter underneath the wrinkles than in the surrounding skin. The hypertrophy of these subcutaneous septa is probably related to repetitive mechanical stimuli generated by the facial muscles over the years.

Wrinkles are a characteristic feature of photodamaged skin (Chapter 24). Cigarette smoking is also a potent, independent cause of wrinkling. The so-called 'cigarette face' is characterized by pale, grey, wrinkled skin with rather gaunt features, so that heavy smokers can often be recognized from their facial appearance alone. Heavy smokers are five times more likely to be wrinkled than non-smokers of the same age, and cigarette smoking probably has at least as much effect on facial wrinkles as sun exposure [11,12]. The pathogenesis of these deleterious effects on facial skin is unknown, but causative factors might include ischaemia due to the vasoconstriction induced by nicotine or sympathetic nerve stimulation, decreased tissue oxygenation, increased tissue carboxyhaemoglobin, increased platelet aggregation, decreased prostacyclin formation and reduced collagen deposition [12]. Both UVA and tobacco smoke may cause wrinkling through additive induction of matrix metalloproteinase-1 (MMP-1) expression [13].

Treatment of wrinkles. See Chapter 77.

Idiopathic mid-dermal elastolysis

Several cases have been described in which idiopathic loss of the elastic fibres in the mid-dermis has led to widespread wrinkling of the crinkle type in an otherwise healthy young or middle-aged woman (Fig. 46.1) [14,15]. The exact relationship between this condition and other elastolytic disorders such as acquired cutis laxa (p. 46.19) and anetoderma (p. 46.11), is uncertain. Maghraoui *et al.* [16] have distinguished post-inflammatory elastolysis, with or without features of cutis laxa, from non-inflammatory elastolysis. Inflammatory triggers may include UV radiation, insect bites and borreliosis. Localized elastolysis adjacent to varicose veins has also been reported [17].

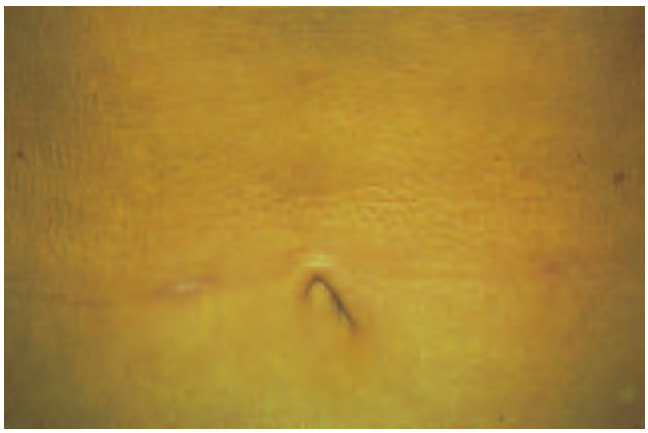

Fig. 46.1 Idiopathic mid-dermal elastolysis. (Courtesy of Dr L. Ostlere, St George's Hospital, London, UK.)

Ultrastructural studies of mid-dermal elastolysis demonstrate elastic fibres engulfed by macrophages [18]. Immunological studies of affected skin show a non-specific profile of immune activation [19]. Localized areas may clinically resemble PXE, although they are histologically distinct [20,21].

The histology of idiopathic mid-dermal elastolysis is similar to that of post-inflammatory elastolysis and cutis laxa (PECL), which occurs in young African girls (see below). Those lesions are preceded by inflammatory lesions, but the lesions of idiopathic mid-dermal elastolysis may also occasionally be preceded by erythema, urticaria or a burning sensation, and the two conditions are similar, if not identical.

No definite treatment exists but topical retinoic acid (0.01% gel) produced some cosmetic improvement in one patient [19].

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Post-inflammatory elastolysis and cutis laxa

PECL is a distinctive severe variant of anetoderma (p. 46.11), which occurs predominantly in black girls living in a tropical climate [1–3]. It has a prolonged course, with relapsing inflammatory phases lasting for months or years. In the acute phase, there are firm, infiltrated plaques or rings, with a collarette of scale, and these progress to leave a diffuse, fine, wrinkled skin with the appearance of premature ageing. In some cases, most of the body surface may be involved. There is no internal involvement, and no preceding infection, such as syphilis or tuberculosis. Histological examination shows destruction of the elastic fibres in the upper and mid-dermis.

It is thought that PECL is a reaction to arthropod bites because some patients have eosinophilia, other family members may suffer from papular urticaria, the lesions show a predilection for exposed parts and no new lesions develop when the patient is in hospital. There is a resemblance to erythema chronicum migrans (Chapter 27).

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Atrophic skin with rheumatoid disease

In rheumatoid patients over the age of 60 years, especially women, the skin on the dorsa of the hands may become thin, loose, smooth, inelastic and transparent, so that the details of veins and tendons are clearly seen. The change is generalized but is seldom conspicuous except on the hands and forearms. Histologically, the dermis is thinned but shows no distinctive changes.

There is a significant association between transparent skin, rheumatoid arthritis and osteoporosis, and it is assumed to form part of a general connective tissue defect [1]. Steroid therapy is not a factor but it will potentiate the problem [2]. Skin collagen is structurally abnormal [3]. A reported association with PXE may be coincidental [4].

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Glucocorticosteroid-induced atrophy

Both systemic and topical glucocorticoid therapy can produce cutaneous atrophy by a dose-related pharmacological effect. The effect is more severe with the more potent steroids (as assessed by the vasoconstrictor assay test) but both fluorinated and non-fluorinated topical steroids can cause atrophy. The effect is most marked when potent steroids are applied topically under an occlusive dressing. The skin becomes thin, fragile and transparent, and striae may develop (see below) (Fig. 46.2).

Severe dermal atrophy can follow injection of intralesional steroids, such as triamcinolone acetonide (particularly if the higher concentration of 40 mg/mL is used, instead of the more usual 10 mg/mL, which is less likely to cause atrophy) (Fig. 46.3).

The earliest histological change is marked thinning of the epidermis, with flattening of the rete ridges and decreased corneocyte size [1]. This is followed a few weeks later by thinning of the dermis, which can be measured by skinfold calipers, ultrasonography or a radiographic technique [2–4].

The epidermal thinning probably results from a reduction of mitotic activity in the germinal layer [5], but the mechanism by which dermal thinning is produced is uncertain.

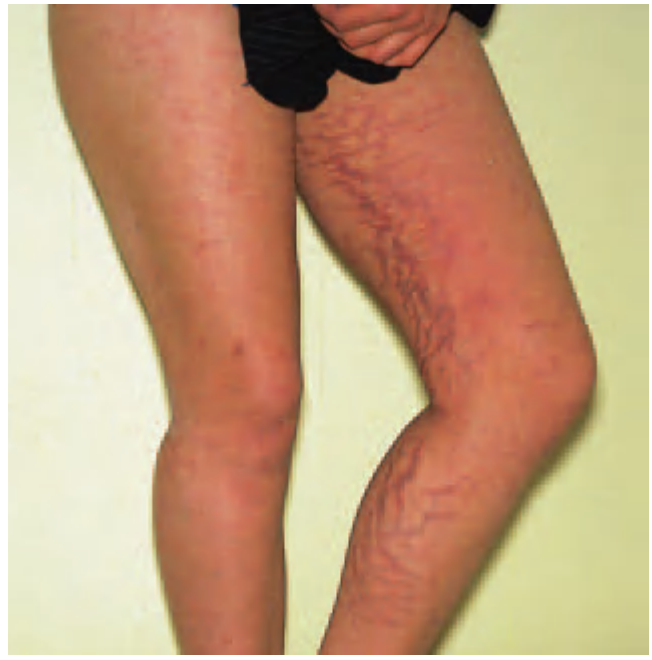

Fig. 46.2 Striae of the legs due to long-term application of a potent topical steroid in a young woman with psoriasis.

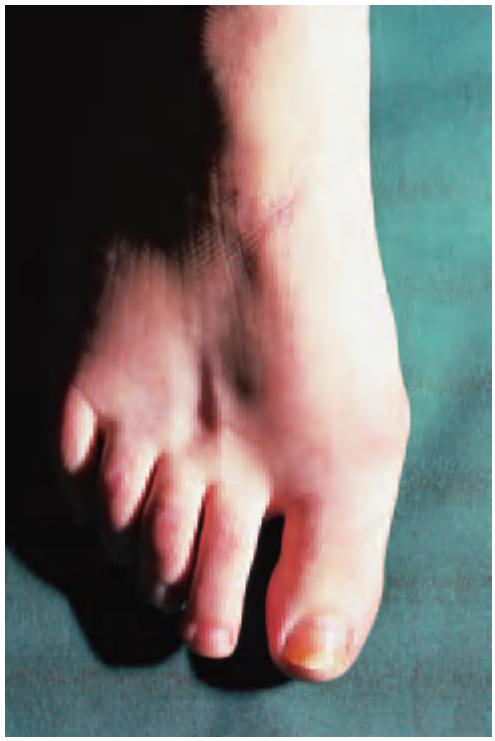

Fig. 46.3 Localized atrophy due to injection of a steroid (triamcinolone, 40 mg/mL) into the skin between the second and third metatarsals.

Loss of dermal ground substance leads to a reorganization of the dermal architecture. The spaces between the collagen and elastic fibres become smaller, so that the dermis becomes more compact but thinner [6]. Steroids are known to inhibit the formation of glycosaminoglycans [7,8]. The fibroblasts become shrunken, although their numbers do not decrease, but the number of mast cells is markedly reduced.

Topical steroids also inhibit the activity of enzymes involved in collagen biosynthesis [9,10], and they have been shown to depress synthesis of types I and III collagen *in vivo* [11–13]. Type III collagen synthesis is preferentially reduced in fibroblast cultures [14]. They can also depress collagenase production and collagen breakdown [15], and the rate of collagen turnover is probably decreased. Even a weak steroid, such as hydrocortisone, can suppress the stimulatory effect of cyclic nucleotides on collagenase production. Studies of the effect of topical steroids on collagen and elastic fibres *in vivo* have given conflicting results [6,16,17]. Collagen microfibrils may form globular microfibrillar bodies, although the changes are not specific for steroid atrophy [18]. These ultrastructural changes can develop in the early stages before there is clinical or histological evidence of atrophy. Digestion of collagen fibrils in the endocytic vesicles of fibroblasts may be involved in the production of steroid-induced atrophy [15].

Capillaroscopic studies have shown that steroid-induced vasoconstriction involves the superficial capillary network, and prolonged superficial ischaemia could also play a role in producing atrophy [10].

Treatment. It has been suggested that local and oral vitamin C therapy might help restore the normal skin thickness [19].

Concurrent application of retinoic acid may partially prevent the epidermal atrophy due to steroids [20].

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Achenbach's syndrome [1–4]

SYN. PAROXYSMAL HAEMATOMA OF THE FINGER

This syndrome presents with the sudden spontaneous onset of one or more painful haematomas in the fingers,

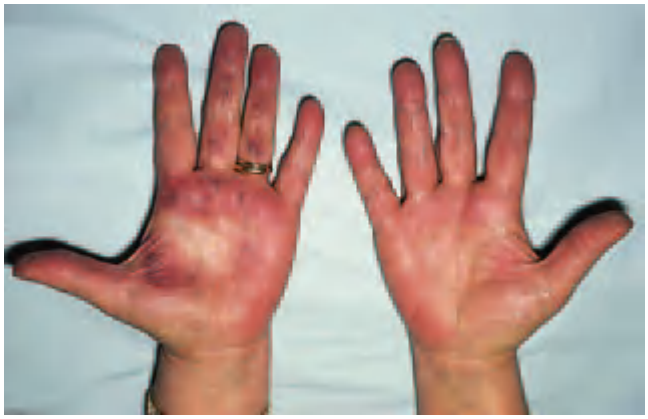

Fig. 46.4 Achenbach's syndrome. (Courtesy of Dr J. Verbov, Royal Liverpool University Hospitals, Liverpool, UK.)

usually in a middle-aged female (Fig. 46.4). It may recur at intervals for several years. The cause is unknown—there is no evidence of vasculitis or amyloid on skin biopsy, and the condition, although troublesome, has a good prognosis. It may be mistaken for easy bruising due to steroid atrophy.

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Striae

SYN. STRIAE ATROPHICANS; STRIAE DISTENSAE; 'STRETCH MARKS'

Definition. Striae are visible linear scars which form in areas of dermal damage produced by stretching of the skin. They are characterized histologically by thinning of the overlying epidermis, with fine dermal collagen bundles arranged in straight lines parallel to the surface.

Aetiology. The factors which govern the development of striae are poorly understood. Many authors have suggested that striae develop as a result of stress rupture of the connective tissue framework [1], but others disagree. It has been suggested that they develop more easily in skin which has a critical proportion of rigid cross-linked collagen, as occurs in early adult life [2]. They are common during adolescence [3], and they seem to be associated with rapid increase in size of a particular region. They are very common over the abdomen and breasts in pregnancy, and they may develop on the shoulders in young male weight lifters when their muscle mass rapidly increases [4]. They are a feature of Cushing's disease, and they may be induced by local or systemic steroid therapy [2,5]. The effects of glucocorticoids on the dermal connective tissue are outlined above. Together with other steroid effects, striae have been reported in human immunodeficiency virus (HIV)-positive patients receiving the protease inhibitor, indinavir [6].

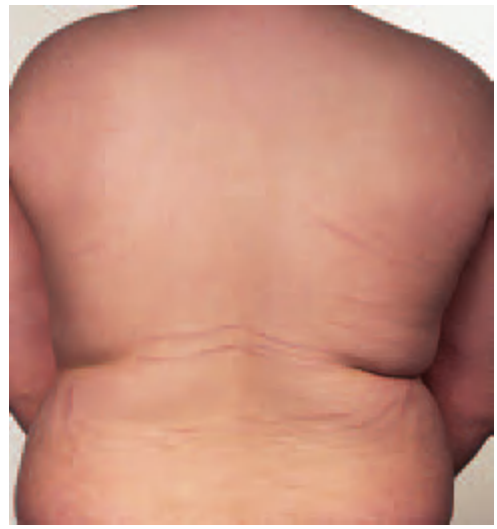

Fig. 46.5 Striae due to obesity in a young man.

The importance of genetic factors in determining susceptibility of connective tissue is emphasized by their presence as one of the (minor) diagnostic criteria for Marfan's syndrome (MFS) [7], but they are commonly absent in pregnancy in EDS.

Pathology. In the early stages, inflammatory changes may be conspicuous; the dermis is oedematous and perivascular lymphocytic cuffing is present. In the later stages, the epidermis is thin and flattened [8]. The dermal collagen is layered in thin eosinophilic bundles, orientated in straight lines parallel to the surface in the direction of the presumed stress. Scanning electron microscopy shows amorphous sheet-like structures [9,10]. With Luna's stain, the elastic fibres are numerous, close together, fine and straight, in the same direction as the collagen bundles [9]. On scanning electron microscopy in collagen-free preparations there is an abundance of thin, curled and branched elastic fibres. The histology is that of a scar.

Clinical features. Striae are very common, and occur in most adult women, as they readily develop at puberty or during pregnancy. Adolescent striae may first develop soon after the appearance of pubic hair. The commonest sites are the outer aspect of the thighs and the lumbosacral region in boys (Fig. 46.5), and the thighs, buttocks and breasts in girls, but there is considerable variation, and other sites, including the outer aspect of the upper

arm, are sometimes affected. Early lesions may be raised and irritable, but they soon become flat, smooth and livid red or bluish in colour. Their surface may be finely wrinkled. They are commonly irregularly linear, several centimetres long and 1–10 mm wide. After some years, they fade and become inconspicuous.

The striae in Cushing's syndrome or those induced by steroid therapy may be larger and more widely distributed, and involve other regions, including sometimes the face. In pregnancy, the striae appear first and are most conspicuous on the abdominal wall, and later on the breasts, but may involve most or all of the pubertal sites [11].

The striae induced by topical steroid therapy occur particularly in the flexures, but may appear in other sites if occlusive plastic films increase absorption [12,13]. They may disappear or become less conspicuous when treatment is stopped.

Usually, striae are only a cosmetic problem, but occasionally, if extensive, they may ulcerate or tear easily should the patient be involved in an accident.

Diagnosis. The diagnosis of striae is usually simple. The possibility of Cushing's syndrome must be considered, although this is rarely the cause. In linear focal elastosis the lesions are yellow and palpable (p. 46.26).

Treatment. In the case of common adolescent striae, the patient may be reassured that in time they will become less conspicuous. Numerous unproven remedies are available from cosmetic companies.

Some cases appear to respond to treatment with topical tretinoin [14]. The erythema of 'younger' striae is claimed to respond to the 585 nm pulsed dye laser [15].

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Congenital reticulate scarring

Three children have been described who presented at birth with vesicles, deep erosions and erythematous patches. The vesicles were generalized, but spared the palms, soles and face, superficially resembling 'scalded skin syndrome'. Healing at around 3 months was followed by fragile reticulate scars; the affected areas were anhidrotic [1]. Two further children with this condition had epilepsy and delayed intellectual and motor milestones [2]. Histological examination showed that the reticular dermis was partially replaced by collagenous scar tissue, and eccrine glands were absent. The differential diagnosis includes Goltz syndrome, Rothmund–Thomson syndrome, acrodermatitis chronica atrophicans and aplasia cutis [1,2].

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Localized cutaneous atrophy

Focal facial dermal dysplasia

Scar-like depressions on the face are a feature of this syndrome, which may be a variant of the Setleis syndrome (Chapter 12) [1,2].

REFERENCES

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Atrophic scars and pseudoscars

Atrophy may result from the destruction of connective tissue by trauma or by inflammatory changes. The distribution and character of the atrophic lesions may be so distinctive as to betray their origin, and is sometimes of considerable importance in diagnosis. Viral infections, such as varicella, can leave widespread, small, circular, atrophic scars [1]. The scars left by tertiary syphilis, certain tuberculides and some deep mycoses, especially sporotrichosis, are usually completely atrophic. Lupus erythematosus may also leave atrophy without clinical evidence of sclerosis. Lupus vulgaris and the chronic follicular

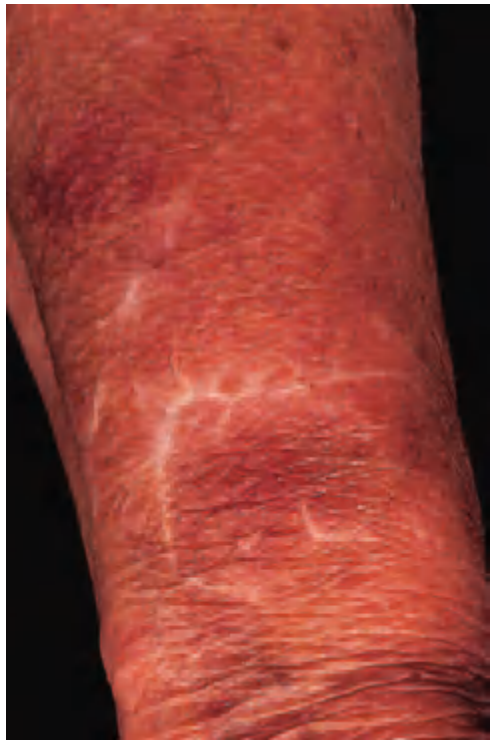

Fig. 46.6 Stellate pseudoscars on the forearm of an elderly woman. There was no history of trauma.

pyodermas, and some cases of lupus erythematosus, leave a combination of atrophy and sclerosis, in which the latter predominates. Lesions that have been treated by intralesional steroid injections may also leave atrophic scars.

Exposure to ionizing radiation gives rise to a very striking combination of atrophy, pigmentation and telangiectasia (Chapter 76).

The wide atrophic scars which follow injuries in EDS (p. 46.31) emphasize the importance of constitutional factors in determining the pattern of dermal response to a known external injury.

REFERENCE

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Stellate and discoid pseudoscars [1,2]

Stellate pseudoscars are white, irregular or 'star-shaped' atrophic scars (Fig. 46.6). They are common on light-exposed skin, particularly on the extensor aspects of the forearms, often in association with senile purpura. These are seen in 20% of patients aged 70–90 years, and a much less common presenile form occasionally occurs before the age of 50 years. These pseudoscars are secondary to mild trauma, and are probably always preceded by haemorrhage into the dermis.

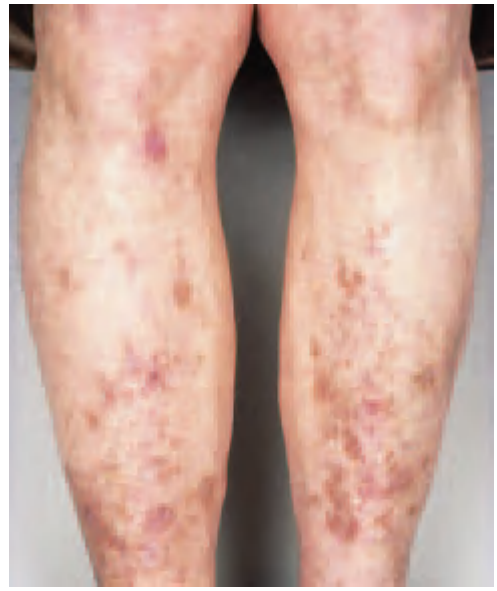

Fig. 46.7 Brown pseudoscars of the legs due to diabetic dermopathy. There was no history of trauma.

Stellate scars following trivial trauma can also occur in other conditions which cause fragile skin, for example porphyria cutanea tarda and prolonged use of potent topical steroids.

Brown pseudoscars may also develop over the shins of diabetic patients with no history of trauma (Fig. 46.7).

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Spontaneous atrophic scarring of the cheeks

SYN. VARIOLIFORM ATROPHY; ATROPHIA MACULOSA VARIOLIFORMIS CUTIS

This is a very rare condition in which spontaneous scars develop on the cheeks (Fig. 46.8) in young adults [1,2] or children [3]. The shallow atrophic lesions have sharp margins and may be linear, rectangular or varioliform. They may be preceded by slight erythema and scaling. Histology shows mild loss of collagen or elastic fibres; there may be thickening of the stratum corneum [4]. Familial cases are recorded [1,5]. The differential diagnosis includes vermiculate atrophoderma (p. 46.9), chickenpox scars and artefact.

REFERENCES

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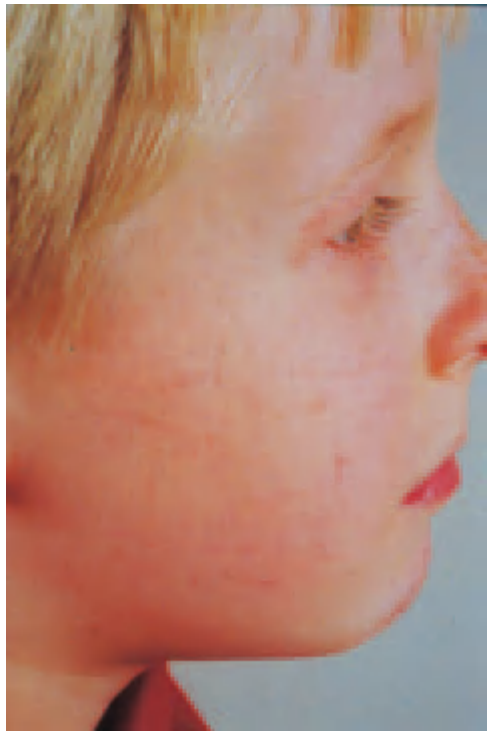

Fig. 46.8 Spontaneous atrophic scarring of the cheeks (varioliform atrophy). (Courtesy of Dr S. George, Amersham Hospital, Amersham, UK.)

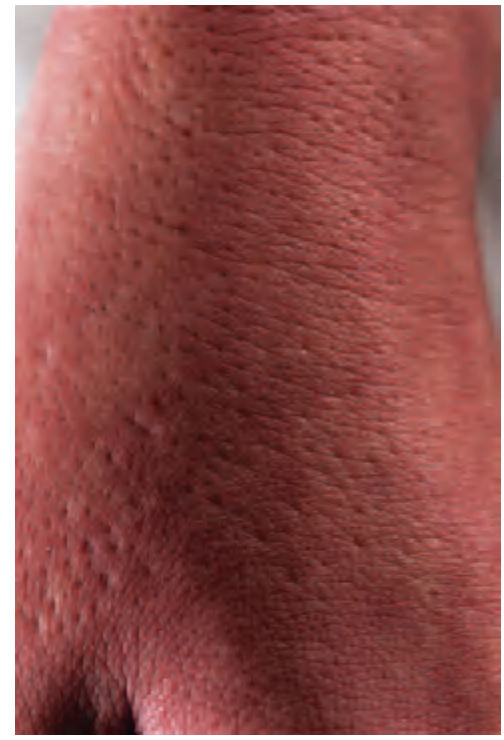

Fig. 46.9 Follicular atrophoderma in Conradi's syndrome. (Courtesy of Dr D.A. Burns, Leicester Royal Infirmary, Leicester, UK.)

2 McCoriston LR, Roys HC. Atrophia maculosa varioliformis cutis. *Arch Dermatol* 1951; **64**: 59–61.
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Atrophoderma

Follicular atrophoderma

In this distinctive syndrome dimple-like depressions at the follicular orifices are present from birth or early life, usually on the backs of hands (Fig. 46.9) and feet and sometimes in the elbow region.

Histology shows widened follicular ostia with thickening of the connective tissue sheath of the follicle.

It appears to be due to a variety of genetic defects and it may be associated with the following conditions [1]:

1 calcifying chondrodysplasia (Conradi's syndrome) (Chapter 12);
2 Bazex syndrome (Chapter 12) [2];
3 hyperkeratosis palmoplantaris, follicular keratosis or palmoplantar hyperhidrosis.

It may also occur as an isolated defect of limited extent.

REFERENCES

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Vermiculate atrophoderma

This rare condition has been described under a variety of other names, including atrophoderma reticulatum, folliculitis ulerythematosa reticulata and honeycomb atrophy. It is a characteristic reticulate or 'honeycomb' type of atrophy, which seems to develop as a late reaction to inflammation around horny follicular plugs on the cheeks (Fig. 46.10). The condition is now regarded as part of the keratosis pilaris syndrome, and is further discussed in Chapter 34.

Familial focal facial dermal dysplasia

Atrophic macules occur on the temples in this rare autosomal dominant disease (Chapter 12).

Hallermann–Streiff syndrome

There may be focal atrophy of the scalp skin in this condition (Chapter 15) [1].

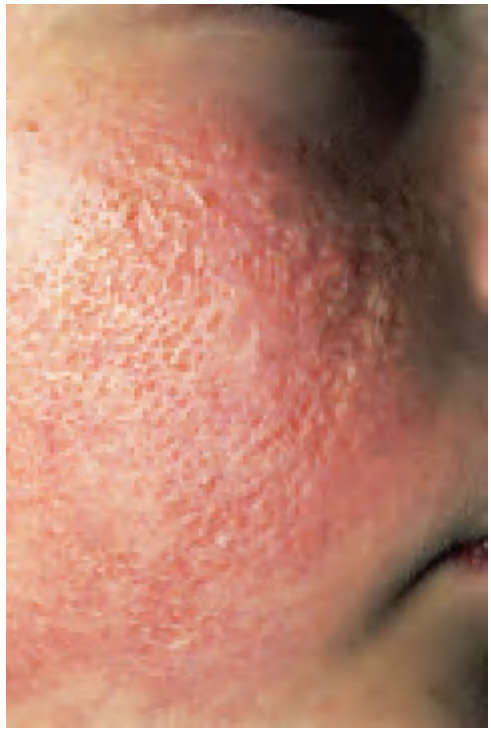

Fig. 46.10 Vermiculate atrophoderma on the cheek of a child. (Courtesy of Dr P. Frosch, Heidelberg, Germany.)

REFERENCE

1 Grattan CEH, Liddle BJ, Willshaw HE. Atrophic alopecia in the Hallermann–Streiff syndrome. *Clin Exp Dermatol* 1989; **14**: 250–2.

Atrophoderma of Pasini and Pierini

Definition. This condition appears to be an atrophic variant of morphoea (Chapter 56) in which one or more patches of skin become bluish and sharply depressed, with no surrounding erythema [1–3].

Aetiology. The cause is unknown. No genetic factor has been reliably incriminated, although familial cases have been reported [4], and morphoea and atrophoderma of Pasini have occurred in siblings with phenylketonuria [5].

Pathology [3]. The histological changes are slight. There may be increased pigmentation of the basal layer. During the earlier stages, the collagen in the lower dermis may be oedematous, and elastic tissue clumped and scanty. There may be a dermal perivascular infiltrate consisting of macrophages and T lymphocytes. Immunofluorescence studies may show IgM and C3 staining in the dermal blood vessels [6]. Later, the oedema subsides and there is some reduction in the total thickness of the dermis. Collagen bundles appear homogeneous and clumped in the reticular dermis. Eventually there may also be some epidermal atrophy.

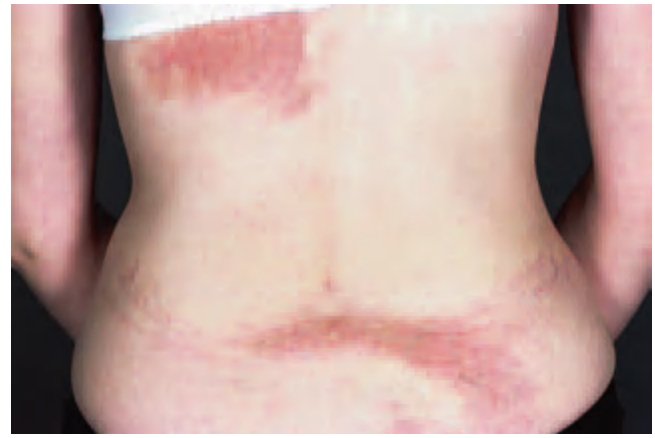

Fig. 46.11 Atrophoderma of Pasini and Pierini. (Courtesy of Dr D.A. Burns, Leicester Royal Infirmary, Leicester, UK.)

Clinical features [3,7,8]. The lesions, which may be single or multiple, range in size from 2 cm to many centimetres in diameter, and are round or oval in shape, but may become confluent to form irregular patches (Fig. 46.11). They are smooth, slate-coloured or violet brown, and are slightly depressed below the level of the entirely normal surrounding skin. The back is almost always involved, the chest and abdomen frequently, and the proximal parts of the limbs occasionally. The patches extend very slowly, increase in number for 10 years or more, and then usually persist unchanged. The eventual development of sclerodermatous changes within the patches has been observed, as has the presence in the same patient of lesions typical of atrophoderma and of morphoea.

Diagnosis. Clinical differentiation from morphoea, possibly an academic exercise, is based on the ivory-white, indurated plaque with an oedematous lilac ring so characteristic of the latter. Histologically, sclerosis may be prominent in morphoea and is usually absent in atrophoderma.

Serological tests for *Borrelia burgdorferi* are negative [3].

Treatment. None is of proven efficacy, but psoralen and UVA (PUVA) has helped some patients.

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Linear atrophoderma

Pigmented atrophic bands follow Blaschko's lines [1] on the trunk, arms and legs. Histologically, collagen bundles are normal or thickened; the apparent atrophy may be due to loss of fat. The condition may reflect mosaicism for an autosomal lethal gene [2].

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Anetoderma

SYN. MACULAR ATROPHY

Definition and nomenclature. The term anetoderma (*anetos* = slack) refers to a circumscribed area of slack skin associated with a loss of dermal substance on palpation and a loss of elastic tissue on histological examination.

'Primary' anetoderma implies that there is no associated underlying cutaneous disease, whereas 'secondary' anetoderma can be attributed to some associated condition.

In the past, cases of primary anetoderma were divided into the *Jadassohn–Pellizari* type, in which the lesions are preceded by erythema or urticaria, and the *Schweninger–Buzzi* type, in which there are no preceding inflammatory lesions. This is now of historical interest only, because in the same patient some lesions may be preceded by inflammation and others may not, and the prognosis and histology are identical in the two types [1–3].

Primary anetoderma

Aetiology. The cause is unknown. Familial cases are reported [4,5] and there is an association with inherited bony or ocular abnormalities. The Blegvad–Haxthausen syndrome comprises anetoderma, blue sclerae and osteogenesis imperfecta (OI) (p. 46.41).

The histology of anetoderma suggests that the basic abnormality is focal elastolysis [1,6,7]. This may be secondary to the release of elastase from the inflammatory cells, which are probably always present in the early stages. Metalloproteinases are increased in lesional skin [8].

Complement activation may be involved, as C3 is deposited on the remaining elastic fibres [9]. It has been suggested that decay-accelerating factor (DAF) and vitronectin (an inhibitor of the membrane-attack complex) may protect elastic fibres against this type of damage [10]. Abnormalities in the protective system could play a role in primary anetoderma. Fibrinolytic activity may also be reduced in anetoderma [11].

Secondary anetoderma

This arises in association with another identifiable disease, but the atrophic areas do not always develop at the sites of the known inflammatory lesions. They are soft, round or oval areas which occur mainly on the trunk.

Syphilis. The lesions occur in association with secondary, latent, congenital or tertiary syphilis, but even where cutaneous syphilitic lesions are present the atrophy develops independently on the trunk, and not at the sites of the lesions.

Anetoderma has also been reported in five patients with false-positive syphilis serology, three of whom also fulfilled the criteria for the antiphospholipid syndrome [12].

Lupus erythematosus. Anetoderma has occurred in association with systemic or chronic discoid lupus erythematosus, not always in relation to the lesions. Biopsy shows a focal loss of elastic tissue, and a perivascular infiltrate with prominent plasma cells [1,2]. Generalized elastolysis (cutis laxa) has also occurred [13]. Anetoderma is also associated with lupus profundus [14,15] and discoid lupus with hereditary complement (C2) deficiency [16].

Some cases of primary anetoderma have direct immunofluorescent findings similar to those of either chronic cutaneous or systemic lupus erythematosus, even though there may be no other features of lupus erythematosus [17,18].

No antibodies have been demonstrated against elastic fibres [18].

Other diseases [2]. Some of the other reported associations may be coincidental, but it is probable that many inflammatory diseases may occasionally be complicated by anetoderma. It has been reported in association with leprosy [19], urticaria pigmentosa [20], pityriasis versicolor [21], granuloma annulare [22], lymphoma [23] and other conditions. Localized anetoderma-like changes on histology have been reported in association with pilomatricoma [24], dermatofibroma [25] and hamartomatous congenital naevi [26]. Penicillamine-induced anetoderma has also been reported [27].

Localized anetoderma may occur in premature infants, possibly due to the application of transcutaneous oxygen monitoring devices [28,29].

Post-inflammatory elastolysis and cutis laxa, described in African children, may follow arthropod bites (p. 46.4).

Pathology [2,6]. During the early stages, the dermis is oedematous, and a lymphocytic infiltrate (predominantly helper T cells) surrounds the blood vessels and appendages

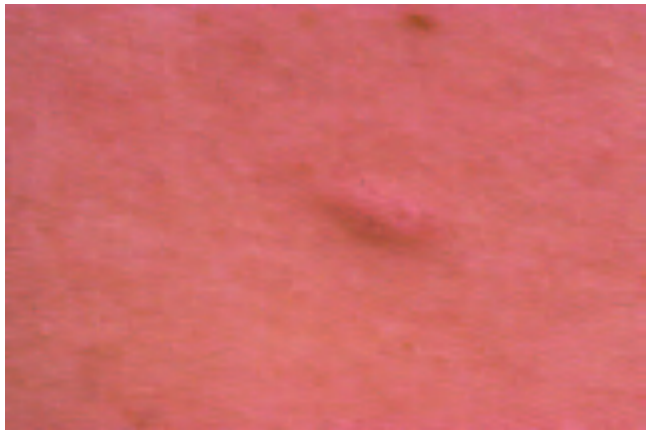

Fig. 46.12 Primary anetoderma. (Courtesy of Dr J. Ellis, Princess Margaret Hospital, Swindon, UK.)

[1,7]. Plasma cells and histiocytes, with some granuloma formation, may also be seen. Later, the oedema and perivascular infiltrate subside and elastic fibres become scanty. The persistence of fine, irregular or twisted elastic fibres is common. The dermal collagen may also be diminished, but the fragmentation and disappearance of elastic tissue is the essential change, beginning superficially in the subpapillary zone and extending downwards. Electron microscopy shows phagocytosis of elastic fibres by macrophages [30,31].

Clinical features [2]. This rare disorder occurs mainly in women aged 20–40 years, but is occasionally reported in younger and older patients of both sexes. It is perhaps more frequent in central Europe than elsewhere, which suggests a possible relationship to chronic atrophic acrodermatitis (due to *Borrelia* sp.) in some cases. In the most usual form, crops of round or oval, pink macules 0.5–1.0 cm in diameter develop on the trunk, thighs and upper arms, less commonly on the neck and face and rarely elsewhere. The scalp, palms and soles are usually spared. Each macule extends for a week or two to reach a size of 2–3 cm. Sometimes, there are larger plaques of erythema, and nodules have also been reported as a primary lesion [32]. Slowly, each lesion fades and flattens from the centre outwards to leave a macule of wrinkled, atrophic skin, which yields on pressure, admitting the finger through the surrounding ring of normal skin (Fig. 46.12). The colour varies from skin colour to grey, white or blue. The number of lesions varies widely, from less than five to 100 or more. The lesions remain unchanged throughout life, and new lesions often continue to develop for many years. If the lesions coalesce they form large atrophic areas, which are indistinguishable from acquired cutis laxa [2].

In some cases, the lesions are initially urticarial weals which, after a succession of exacerbations and remissions, perhaps continuing for many weeks, are succeeded by atrophy. They may become confluent, to cover large areas, especially at the roots of the limbs and on the neck.

Diagnosis. The white cicatricial lesions of 'white spot disease' (Chapter 56) around the base of the neck and shoulders should not be confused with anetoderma.

Histological examination establishes the diagnosis. Focal dermal hypoplasia and atrophic scars (e.g. following varicella) must also be considered.

Acquired cutis laxa is probably a variant of anetoderma.

The diagnosis of 'primary' anetoderma can be established only by excluding the presence of any of the diseases known to be associated with 'secondary' atrophy, e.g. perifollicular elastolysis (p. 46.20).

Treatment. Penicillin and the antifibrinolytic drug ε-aminocaproic acid have been advocated [33], but Venencie *et al.* [2] studied 16 patients and found no treatment was beneficial once the atrophy had developed. Colchicine may prevent some atrophic changes [34].

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Acrodermatitis chronica atrophicans

SYN. CHRONIC ATROPHIC ACRODERMATITIS; LATE-PHASE LYME BORRELIOSIS

Definition. This is a late skin manifestation of Lyme borreliosis (Chapter 27). It is characterized by the insidious onset of painless, dull-red nodules or plaques on the extremities, which slowly extend centrifugally for several months or years, leaving central areas of atrophy.

Aetiology. The condition is due to infection with a spirochaete, *Borrelia burgdorferi sensu lato*, which is transmitted by ticks [1]. The disease occurs mainly in northern or central Europe, Italy and the Iberian Peninsula. Occasional cases occur in other parts of Europe and Africa, but it is very rare in the UK, America, Australia and Asia [2]. These geographical variations are related to different strains of the organism [3–5]. *Borrelia afzelii* is the predominant species associated with acrodermatitis chronica atrophicans. This species is transmitted by ticks in Western Europe, but is rare in the USA, where *Borrelia burgdorferi sensu stricto* predominates.

Pathology [6]. During the early stages, there is non-specific dermal oedema with perivascular inflammatory infiltration. Subsequently, the epidermis becomes atrophic and the epidermal appendages are destroyed. Beneath a subepidermal zone of degenerate connective tissue lies a dense, band-like infiltrate, predominantly consisting of lymphocytes, histiocytes and plasma cells. Ultimately, the infiltrate is reduced to narrow bands between collagen fibres. In some patients, scleroderma-like changes may develop [7,8]. *Borrelia afzelii* has been cultured from the atrophic skin [7] but culture is usually negative. *Borrelia afzelii* can be identified by polymerase chain reaction (PCR). The organism may be resistant to attack by the complement system and may lurk in immunologically protected areas such as fibroblasts and endothelial cells. Expression of cytokines, such as interferon-γ (IFN-γ), is impaired [9].

Clinical features [10]. Most cases occur in country dwellers between the ages of 30 and 60 years.

The onset is usually insidious, and constitutional symptoms are exceptional. Painless, dull-red or bluish red nodules or plaques, more or less infiltrated, develop on the feet or legs, and less often on the forearms and hands. The lesions themselves are typically painless, but there may be associated acral pain or paraesthesiae. Erythema chronicum migrans (Chapter 27) may have been present at the same site some years earlier. Extension to the trunk and the greater part of the body, including the face, is sometimes seen. Single or multiple lesions may be present. They slowly extend centrifugally, the active inflammatory stage persisting for months, years or even decades. Marginal extension may continue once the central areas have already entered the atrophic phase, in which the skin is smooth, hairless and tissue-paper-like, dull red, pigmented or poikilodermatous (Fig. 46.13).

Subcutaneous nodules may develop around the knees or elbows, and fibrous bands along the ulnar margin of the forearms. Gaiter-like sclerosis of the lower third of the legs, often accompanied by ulceration, is a further complication. Morphoea of the trunk and lichen sclerosus et atrophicus (both genital and extragenital) have also been reported as associated lesions [2,11], and it is interesting that *Borrelia* antibodies have been found in five of 10 patients with morphoea [12], although others have not confirmed this [13].

In some cases, involvement of the joint capsule or bone results in limitation of movement of the joints of the hands and feet, or of the shoulders.

Very rarely, squamous carcinoma has developed in the atrophic skin, and lymphoma has also been reported in the non-affected skin [14,15].

Other late syndromes of Lyme borreliosis (lymphocytoma, neurological, etc.) have been fully reviewed by Steere [1].

Diagnosis. The appearance of erythema chronicum migrans may be similar, but the evolution of the annular lesions establishes the differentiation. In the atrophic

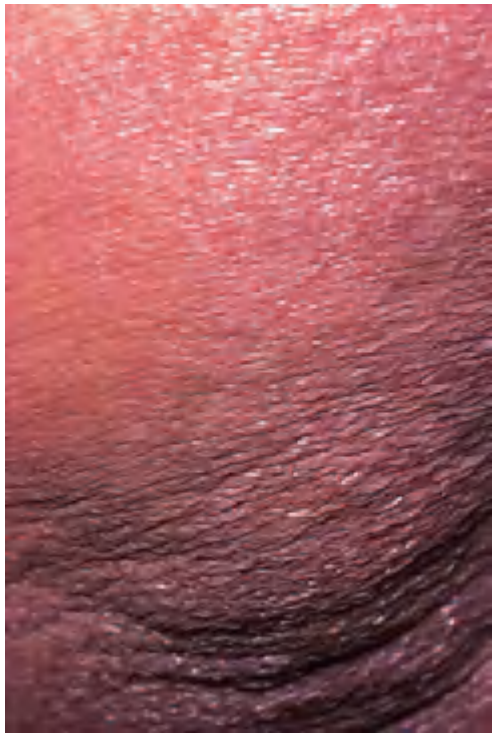

Fig. 46.13 Atrophic skin of the knee in acrodermatitis chronica atrophicans. (Courtesy of Dr T. Robinson, University College Hospital, London, UK.)

stage, diagnosis is usually readily made, and can be confirmed histologically.

Immunoblotting, using *B. afzelii* flagellar antigen (41 kDa) is confirmatory [5]. Serology is used to confirm the diagnosis of Lyme disease, but false-negative and false-positive results are common. In chronic atrophic acrodermatitis, however, the antibody titre is very high. Serology may be positive on enzyme-linked immunosorbent assay (ELISA) but negative on immunoblotting, particularly in patients with neurological disease [16]. A high titre of antibodies may reflect occult central nervous system involvement, when the antibodies can also be demonstrated in colony-stimulating factor [17].

When it occurs on the lower legs, the condition can mimic venous insufficiency [18], with thick, cyanotic, itchy skin.

Treatment. Oral antibiotics should be given for 1 month, for example doxycycline or amoxicillin in standard doses [1]. The improvement occurs gradually, several weeks after the course of treatment, but there may be no response if treatment is delayed until atrophy has developed. If the antibody titre is high, or there are clinical features of systemic disease (e.g. neuroborreliosis), intravenous penicillin G, ceftriaxone or cefotaxime should be given for 3 weeks [17].

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Local panatrophy

Definition and aetiology. Local panatrophy is a rare disorder involving partial or total loss of subcutaneous fat and atrophy of overlying skin, sometimes associated with atrophy or impaired growth of muscle or bone. A primary neurogenic disturbance has been postulated but not proved. The syndrome may represent the end result of more than one pathological process, but many cases may be due to a variant of morphoea.

The atrophic areas exhibit a reduced sympathetic response and aberrant production of non-esterified fatty acids after stimulation with norepinephrine (noradrenaline), and it has been suggested that there may be a primary abnormality of the sympathetic nervous system [1].

Two groups of cases can be differentiated.

1 *Panatrophy of Gower*: no scleroderma or other sclerotic process accompanies or follows the loss of subcutaneous tissue. Most cases have occurred in women, usually in the second to fourth decades.

2 *Sclerotic panatrophy*: either typical morphoea or similar

sclerotic change in dermal collagen precedes the atrophy [2].

Clinical features of the two groups are as follows.

Panatrophy of Gower [3]. Sharply defined areas of atrophy, irregular in size, shape and distribution, develop over a period of a few weeks, without preceding inflammatory stages. In each affected area, the subcutaneous tissue disappears and the overlying skin appears atrophic but is otherwise normal. There may be a single area of atrophy or two or more. In size they range from 2 to 20 cm across, and in shape they are very variable but are sometimes triangular or quadrangular. Most lesions have occurred on the back, buttocks, thighs or upper arms, but some have involved forearms or lower legs. The atrophy reaches its maximum extent within a few months and then remains unchanged indefinitely.

Sclerotic panatrophy. Atrophy of the subcutis, and sometimes of underlying muscle and bone, may follow clinically and histologically typical morphoea, especially when the process begins in childhood and involves a limb (Chapter 56).

Sclerotic panatrophy may also occur in the absence of morphoea. The sclerosis involves subcutaneous tissue and muscle, and dense, sclerotic, scar-like, linear bands develop along a limb, or encircle the trunk in a metameric distribution, or encircle a limb. These lesions have also usually occurred in childhood. They cease to progress after a few months and, although new areas may be involved, most lesions have been solitary.

It is possible that Gower's panatrophy and linear morphoea are at the ends of a continuous disease spectrum. The histology of linear morphoea reveals thickened bundles of collagen, which appear to be intact on B-scan ultrasound imaging [4].

In the differential diagnosis of panatrophy, the various forms of *panniculitis* must be excluded. The preceding inflammatory changes are the single most distinctive feature, but they are not always easy to distinguish.

Facial hemiatrophy

SYN. PARRY–ROMBERG SYNDROME

Definition and aetiology. Facial hemiatrophy is an atrophic dysplasia of the superficial facial tissues, but the underlying muscles, cartilage and bone may also be affected. The cause is unknown, but it may be a disorder of the sympathetic nervous system in some cases. Other cases have followed lupus panniculitis [5].

There is no evidence that it is usually genetically determined, but it appears to be hereditary in a few pedigrees. Some cases have been associated with syringomyelia, epilepsy or cerebrovascular disease, but in 90% of cases no such association is demonstrable. The sexes are equally affected.

Clinical features [6–8]. This rare disease usually starts within the first two decades. The first manifestation is usually increased or decreased pigmentation in irregular patches on cheeks, forehead or lower jaw. Occasionally, there may be premonitory muscle spasms or neuralgia. Progressive atrophy gradually develops in the affected sites, involving skin, subcutis, muscle and bone, and may extend in area—and sometimes in depth—for months or years with temporary remissions. The skin becomes dry, thin and atrophic, but may be scar-like and adherent in some areas. When the atrophy is fully developed, the contrast between the sunken, haggard, pigmented affected half of the face and the unaffected half is dramatic. The hair may be lost in the frontoparietal region on the affected side but is often normal; occasionally, localized canities is an early change. A variety of neurological signs have been reported, of which Horner's syndrome is the most frequent. Heterochromia of the iris has developed at the same time as the facial atrophy in about 5% of cases, and other ocular changes may also be present [9]. There can be ipsilateral cerebral atrophy [10].

The atrophy may remain limited both in extent and depth. It may be confined to the distribution of one division of the trigeminal nerve or involve the whole of the side of the face, sharply demarcated at the midline. Rarely, it may be bilateral, and very rarely may involve half the body, usually on the same side as the face but exceptionally the opposite side—crossed hemiatrophy. The atrophy may, in such cases, begin on the trunk or a limb and only later involve the face.

The degree of bone atrophy as established radiologically is usually much less than the clinical appearance suggests, and is severe only in some cases of early onset. In such cases, the cerebral cortex may also be affected, and contralateral epilepsy may result.

Scleroderma of the 'sabre-cut' paramedian form may be associated with some degree of facial hemiatrophy, especially if it begins early in life. However, it is a more superficial process than progressive facial hemiatrophy. The skin in scleroderma is bound down and adherent, and loss of hair and pigmentary changes are conspicuous. In progressive facial hemiatrophy, the skin may remain mobile and grossly normal. The two processes have been confused frequently in the literature, and may coexist [11].

Diagnosis. When the cutaneous involvement is early and conspicuous, the diagnosis presents few difficulties. Hypoplasia following radiotherapy given in infancy, perhaps in treatment of a naevus in the region of the temporomandibular joint, could cause confusion. If the skin changes are slight, or of later onset, physiological asymmetry, unilateral mandibular agenesis, hemihypertrophy

and atrophy secondary to facial paralysis must be excluded. Hemihypertrophy is always congenital. When the limbs are involved, infantile hemiplegia and lipodystrophy must also be considered.

Treatment. Plastic surgery using large buried pediculated flaps of dermis and fat, or silicone implants, offers some cosmetic benefit [5,11–13].

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Scleroatrophic syndrome of Huriez

This autosomal dominant congenital syndrome is discussed in more detail in Chapter 34. It comprises a triad of diffuse scleroatrophy of the hands, mild palmoplantar keratoderma and hypoplastic nail changes [1–4]. Scleroatrophy is accentuated on the palms and fingers, which are tapered as in sclerodactyly; however, Huriez syndrome is congenital, and Raynaud's phenomenon is absent. The acral hyperkeratosis is associated with dry skin, resulting in painful fissures in winter months. Nail changes include prominent lunulae, elongated cuticles, longitudinal and transverse ridging, increased longitudinal curvature [5] and V-shaped notches [6]. Squamous carcinoma may develop in the scleroatrophic skin, sometimes as early as the third or fourth decades of life [1,6]; fatal metastases may occur [7].

Histology shows marked orthokeratosis, acanthosis with a prominent granular cell layer, and mild fibrosis of the upper and mid-dermis. Elastic fibres are reduced. Epidermal Langerhans' cells are reduced in number, perhaps contributing to the risk of malignant change [6].

Patients should be followed throughout life, with early excision of suspected malignancies. Acitretin reduces the painful hyperkeratosis [7] and could reduce the incidence of skin cancer.

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Localized abdominal wall atrophy

Congenital cutis laxa (p. 46.18) may rarely be confined to an area such as the abdomen. There may be other associated defects, for example dysplasia of the abdominal muscles, deformity of the thorax or mediastinal hernia. This condition must be distinguished from *centrifugal abdominal lipodystrophy* (Chapter 55) and the *prune belly syndrome*, in which wrinkled abdominal skin due to underlying abdominal muscle deficiency is associated with malformation of the urogenital tract [1,2].

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Poikiloderma

Poikiloderma is a descriptive term, often somewhat loosely applied. Atrophy, macular or reticulate pigmentation and telangiectasia are the essential features. Depigmentation, miliary lichenoid papules, fine scaling and small petechial haemorrhages are less constantly present.

Congenital poikiloderma

Poikiloderma may occur as an apparently primary abnormality in certain genetically determined syndromes, including the Rothmund–Thomson syndrome, dyskeratosis congenita (Chapter 12) and the Mendes da Costa syndrome (Chapter 34).

Several other syndromes have been described in which poikiloderma is a prominent feature [1].

Hereditary sclerosing poikiloderma of Weary [2]

This rare autosomal dominant syndrome was described in a large black family. Generalized poikiloderma, which developed in early childhood, was accompanied by sclerosis of the palms and soles, and linear hyperkeratotic and sclerotic bands developed in the flexures of the arms and legs.

Weary–Kindler syndrome

Hereditary acrokeratotic poikiloderma of Weary [1–3]. This autosomal dominant condition produces vesicopustules of the hands and feet, which start at the age of 1–3 months and resolve in childhood. There is also a widespread eczema, and the gradual appearance of poikiloderma, which persists into adult life. Keratotic papules develop in childhood on the hands, feet, knees and elbows, and these also persist indefinitely. Mucosal involvement is frequent. Histological examination shows an intraepidermal cleft [4].

Kindler syndrome [4,5]. This may be a variant of hereditary acrokeratotic poikiloderma [6], although acral blistering is present at birth. Poikiloderma is progressive, resulting in thin, wrinkled skin without surface markings. Cutaneous atrophy is most pronounced on the hands and feet. Photosensitivity is common and, like other cutaneous features, tends to improve with time. However, recurrent acral blisters have been described in a 46-year-old Japanese male [7]. Colloid bodies that show IgM deposition on direct immunofluorescence have been described [8]. Ultrastructural studies show separation of the sub-basal lamina. Activated fibroblasts are present in the subepidermal region, suggesting a transient mechanobullous dermatosis, and enabling distinction from epidermolysis bullosa [9]. Detailed immunohistochemical and ultrastructural analyses indicate that Kindler syndrome is not a variant of dystrophic epidermolysis bullosa [10]. Some cases have been reported which do not fit clearly into either Weary's or Kindler's syndromes [11].

Diffuse and macular atrophic dermatosis [12]

This rare condition is characterized by the presence from birth of generalized poikilodermatous changes that give the appearance of prematurely sun-damaged skin. The facies, hair and skeleton are normal. Biopsy shows thinning of the epidermis, with large hyaline bodies in the superficial dermal collagen, and these stain positively with periodic acid–Schiff (PAS) and elastin stains. Electron microscopy shows that these globular structures consist of microfibrillar material, and the adjacent fibroblasts may be degenerative.

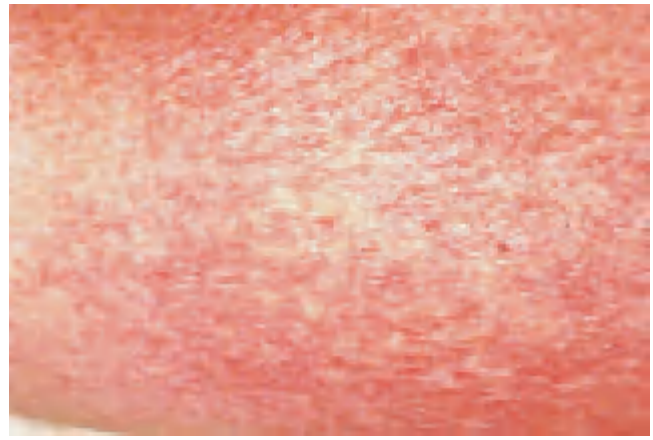

Fig. 46.14 Poikiloderma in a prelymphomatous eruption. The patient eventually developed cutaneous T-cell lymphoma.

Degos–Touraine syndrome [13]

In this condition, incontinentia pigmenti is accompanied by poikiloderma of light-exposed areas, often with gastrointestinal symptoms. Both gastrointestinal and skin manifestations are said to disappear following treatment with diiodohydroxyquine. Small bullae on the extremities have been described, but the initial bullae appear on the face. Hyperpigmentation follows a chronic erythrodermatous phase.

Acquired poikiloderma

Poikiloderma may occur as a pattern of cutaneous response to injury by cold, heat or ionizing radiation [14]. So-called poikiloderma of Civatte (Chapter 39) is a similar reaction mediated by photosensitizing chemicals in cosmetics. Some inflammatory dermatoses, such as lichen planus, may also give rise to poikilodermatous changes.

Poikiloderma is also a feature of some inflammatory 'connective tissue' diseases, and is particularly characteristic of dermatomyositis. It is also seen in lupus erythematosus and rarely in systemic sclerosis. Poikiloderma occurs as a manifestation of some lymphomas, especially mycosis fungoides (Fig. 46.14).

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Disorders of elastic fibres

The capacity of the skin to adapt to local or general changes in body size and contour, and to allow for movement of head and limbs and a wide range of facial expression, depends upon its tension, elasticity and tensile strength. These properties may be congenitally defective or modified by ageing or disease [1–5].

Tension. The tension of the skin—its resistance to deforming forces—is provided by abundant elastic fibres, and is reduced when they are defective or degenerate. Tension decreases with age.

Elasticity. The elasticity of the skin is the measure of its ability to resume its original shape after deforming forces have ceased to act. There is wide individual variation, but a tendency to decrease with age. Several diseases such as cutis laxa decrease cutaneous elasticity.

Tensile strength. The tensile strength of the skin is the degree to which it can be elongated before it tears. It is greatest in infancy and decreases with age, but is also abnormally low in diseases associated with collagen defects such as EDS and Cushing's syndrome [5].

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Lax skin

Increased laxity of the skin due to ageing (accelerated by dermal photodegradation) is of course extremely common, but cutaneous laxity can occasionally be due to marked weight loss (especially after gross obesity) or can follow recovery from severe oedema. Less commonly, the skin may become lax due to localized or generalized defects in elastic tissue resulting from other causes, and these may be grouped as follows.

1 Generalized elastolysis (cutis laxa):
(a) congenital;
(b) associated with other inherited disorders (PXE, SCARF syndrome (*s*keletal abnormalities, *c*utis laxa, *c*raniostenosis, *a*mbiguous genitalia, *r*etardation and *f*acial abnormalities), de Barsy syndrome, geroderma osteodysplastica);
(c) acquired (numerous associated disorders, for example inflammatory skin disease, multiple myeloma, systemic lupus erythematosus, hypersensitivity reactions, complement deficiency, penicillamine therapy.)

2 Localized elastolysis:
(a) anetoderma—(i) primary; (ii) secondary to syphilis, tuberculosis, sarcoidosis, bacille Calmette–Guérin (BCG) vaccination, etc.; (iii) PECL (possibly due to insect bites);
(b) blepharochalasis;
(c) chronic atrophic acrodermatitis (due to *Borrelia*);
(d) granulomatous slack skin (due to lymphoma).

Generalized cutis laxa [1]

SYN. GENERALIZED ELASTOLYSIS; GENERALIZED ELASTORRHEXIS; GENERALIZED DERMATOCHALASIS

Definition. Cutis laxa is characterized clinically by lax, pendulous skin and histologically by loss of elastic tissue in the dermis. It is a heterogeneous condition, with several causes and associations, and it may be inherited or acquired.

Aetiology. Cutis laxa may be *inherited*, either as an autosomal dominant or autosomal recessive trait [2]. Occipital horn syndrome was originally described as X-linked recessive cutis laxa and subsequently EDS type IX, but is now classified with Menkes' syndrome as a condition in which secondary changes in connective tissue are caused by abnormal copper metabolism [3–5] (p. 46.40).

Cutis laxa may also be *acquired* following inflammatory skin disease [6], and it has occurred in babies born to women taking penicillamine [7]. An immunological pathogenesis has been suggested in some acquired cases because of the rare associations with drug hypersensitivity, complement deficiency, systemic lupus erythematosus and multiple myelomatosis [8–10]. Amyloidosis seems to provoke cutis laxa in some cases [11], and it is known that amyloid can coat elastic fibres [12,13].

Several studies suggest a biochemical defect in elastin in cutis laxa. In one patient, there was a greatly increased activity of a neutral protease which degraded tropoelastin [14]. In other cases, the production of elastin by skin fibroblasts was reduced, as measured by elastin messenger RNA (mRNA) and desmosine levels [15–17]. Mutations have been identified in the elastin gene in several patients with autosomal dominant cutis laxa [18,19] and recently in fibulin-5 (a microfibrillary protein) in the more severe, autosomal recessive form [20].

Pathology. The skin is of normal thickness, but the elastic fibres are sparse, short, fragmented and clumped, particularly in the upper dermis, and they show granular degeneration [15]. The elastic fibres are deficient in elastin but their microfibrils appear normal [4,17]. Similar changes in elastic fibres may occur in the lungs and aorta.

Various ultrastructural changes have been described, including separation of the elastin microfibrils from the amorphous matrix, the presence of a 'wood-grain' pattern and aggregation, fragmentation and clumping of the elastic fibres [6,17,21].

Clinical features. In this rare condition, the skin becomes inelastic and hangs in redundant folds. The face and neck are often affected, which produces a 'bloodhound' appearance of premature ageing. The internal elastic tissues may also be affected, and emphysema and cardiovascular abnormalities occur in some types.

Hereditary forms [22,23]

Various clinical types have been described [24,25]. In the *autosomal dominant* form, the skin changes may develop at any age but tend to present later than in the recessive form. Those presenting in adult life usually have no internal defects, and the life expectancy is normal [25]. When the condition presents in infancy there is intrauterine growth retardation, delayed fontanelle closure and ligamentous laxity [26]. The skin changes may be preceded by episodes of oedema, usually within the first 2 months of life, and the child may look aged by the end of the second year. Affected males may be impotent, with infantile genitalia and scanty body hair. Pulmonary emphysema due to a loss of elastic tissue in the lungs is common [2].

In the commoner, but more severe, *autosomal recessive* form there is a characteristic facies with downward slanting palpebral fissures, a broad flat nose, sagging cheeks and large ears. There are prominent skin folds around the knees, abdomen and thighs [25]. Herniae, diverticula, severe pulmonary emphysema and cor pulmonale are important complications. Dental caries, aortic aneurysm and osteoporosis may also occur. These children have a short lifespan.

The *de Barsey syndrome* is a rare type in which cutis laxa is accompanied by retarded psychomotor development and corneal clouding due to degeneration of the tunica elastica of the cornea [27–29]. Growth is retarded and there may be pseudoathetoid movements.

Congenital cutis laxa has also been associated with SCARF syndrome [30], osteoporosis [31] and geroderma osteodysplastica, which is characterized by skeletal abnormalities including joint hypermobility, wormian bones and osteoporosis [32].

Acquired forms [33]

Cutis laxa may rarely develop at any age following episodes of urticaria or angio-oedema, extensive inflammatory skin disease (such as systemic lupus erythematosus or erythema multiforme) or febrile illness. It may also follow hypersensitivity reactions such as penicillin allergy [18].

Cutis laxa has also been reported in association with complement deficiency, sarcoidosis, syphilis, multiple myeloma [8–10] and the Klippel–Trenaunay syndrome [4]. Focal elastolysis can also occur in association with lupus erythematosus [34] and severe rheumatoid arthritis [35].

There may be widespread, massive folds of lax skin, or the changes may be mild and confined to a limited area, in which case it cannot be distinguished from anetoderma. Purpura may follow slight trauma and fibrotic nodules may form over bony prominences. Organs other than the skin may also be involved. Emphysema, gastric fibromas and tracheobronchomegaly have been reported [36].

In acquired cutis laxa, dermal elastic tissue is markedly reduced, although collagen is normal. Fibroblasts express increased elastolytic activity (cathepsin G). Levels of serum α_1-antitrypsin and elastase inhibition are decreased [37].

Post-inflammatory elastolysis and cutis laxa also appears to develop as a distinctive syndrome in African children, with clinical features intermediate between anetoderma and cutis laxa [38] (p. 46.4). This condition might represent an unusual reaction to an arthropod bite, as the lesions are preceded by urticaria or multiple red papules, which slowly enlarge to form rings 2–10 cm in diameter.

Diagnosis. The diagnosis, which is suggested by finding loose skin that recoils only slowly after stretching, may be confirmed by histology.

In EDS, the skin is hyperextensible but not lax, and it recoils quickly. In PXE, the skin may be lax, but it is yellowish and the face is usually spared. It is distinguished histologically by the presence of calcification. There may be circumscribed folds of lax skin in neurofibromatosis, and loose folded skin may also occur in leprechaunism, Patterson syndrome, trisomy 18 and wrinkly skin syndrome, but these conditions are distinguished by their associated features.

In Costello's syndrome there is skin laxity with joint hyperextensibility, but the elastin fibres are normal under

both light and electron microscopy [39]. The other features of this rare syndrome include poor postnatal growth, developmental delay and a distinctive facies with macroglossia, bilateral ptosis, epicanthic folds and posterior rotation of the pinnae, with prominent helices and thickened lobes.

In severe actinic damage, there may be marked skin laxity due to damage to elastic fibres.

Treatment. Plastic surgery ('face-lift') may reduce the cosmetic disability. Investigations for emphysema are indicated, with referral to a pulmonary physician if necessary.

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Perifollicular elastolysis

Anetoderma-like changes in a perifollicular distribution have been described in three women aged 30–40 years [1]. The lesions were small, grey–white, finely wrinkled, round or oval areas, each with a central hair follicle. Some exhibited a balloon-like bulge above the surface. They occurred on the upper trunk, neck, earlobes and arms. Histology showed a non-inflammatory perifollicular loss of elastin fibres, and it was suggested that the lesions might have been caused by an elastase-producing strain of *Staphylococcus epidermidis* [2]. Similar changes are more commonly seen in acne scars (Chapter 43) [3].

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Granulomatous slack skin

This rare disease is characterized by the slow development of pendulous folds of lax erythematous skin, which on histological examination contains a dense granulomatous

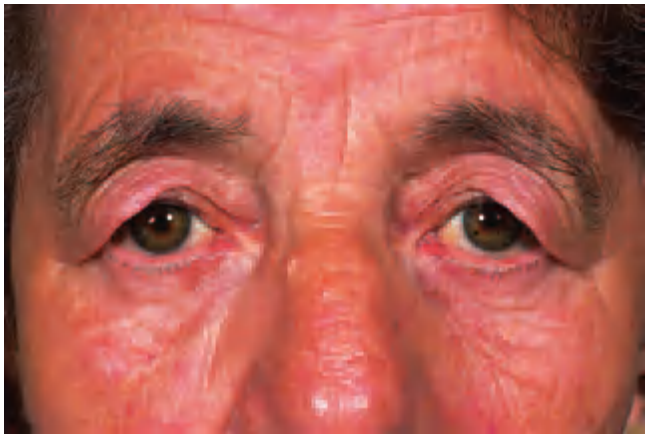

Fig. 46.15 Blepharochalasis. (Courtesy of Dr D.A. Burns, Leicester Royal Infirmary, Leicester, UK.)

dermal infiltrate, with destruction of dermal elastic tissue. It is now considered to be a type of lymphoma (Chapter 54).

Blepharochalasis [1–3]

Definition. Laxity of the eyelid skin due to a defect in the elastic tissue.

Aetiology. The cause is unknown. Most cases are sporadic, but some pedigrees show autosomal dominant inheritance. Some cases may be a localized form of post-inflammatory elastolysis, and in one patient, blepharochalasis followed angio-oedema [4].

Pathology [3]. In the early stages there may be a mild dermal lymphocytic infiltrate, and in the later stages the elastic tissue in the lids becomes decreased and fragmented. A recent case report described IgA deposition in the residual elastic fibres, implying that an immune mechanism may be involved [5].

Clinical features. Blepharochalasis is an uncommon condition that usually develops insidiously around the time of puberty. Repeated transient attacks of painless swelling of the eyelids lasting for 2 or 3 days are followed by laxity, atrophy, wrinkling and pigmentation, predominantly of the upper eyelids (Fig. 46.15). There may be multiple telangiectases. These changes produce an appearance of tiredness, debauchery or premature ageing.

Reduplication of the mucous membrane of the upper eyelid is associated with blepharochalasis in about 10% of cases, and this may make the eyelids appear thick.

Blepharochalasis is occasionally a manifestation of generalized cutis laxa, and it may form part of Ascher's syndrome (see below). Laxity of the eyelid skin also occurs in EDS but other features of this syndrome will also be present.

Diagnosis. The many other causes of eyelid swelling must be excluded (Chapter 64). Ptosis is easily distinguished because the skin appears normal.

Treatment. Plastic surgery can be performed, but the condition may recur [2].

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Ascher's syndrome

Ascher's syndrome is the association of blepharochalasis with progressive enlargement of the upper lip due to hypertrophy and inflammation of the labial salivary glands [1–4]. The lip feels soft and lobulated and there may be excessive salivation. In some cases, the accessory lachrymal glands are also affected, with increased thickness of the eyelids. Enlargement of the thyroid has also been reported.

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Pseudoxanthoma elasticum

SYN. SYSTEMATIZED ELASTORRHEXIS; GRÖNBLAD–STRANDBERG SYNDROME

Definition. PXE is an inherited disorder characterized by generalized fragmentation and progressive calcification of elastic tissue in the dermis, blood vessels and Bruch's membrane of the eye. This leads to laxity of the skin, arterial insufficiency and retinal haemorrhage.

Aetiology. Until recently the basic defect was unknown. Because the pathology affects elastic fibres the genes responsible for elastin and microfibrillary proteins were initially studied, but linkage analysis excluded these early candidate genes [1,2]. Positional cloning identified candidate genes on chromosome 16p13.1 and mutations have subsequently been identified in the *MRP6/ABCC6* gene [3–5]. This is a member of the ATP-binding cassette (ABC) family and acts as a transmembrane transporter. Mutations in the gene affect transport of anionic peptides [6]. *ABCC6*

is expressed primarily, if not exclusively, in the liver and kidneys and absence of normal *ABCC6* may allow certain metabolic compounds to accumulate resulting in progressive calcification of elastic fibres. This suggests that PXE may in fact be a primary metabolic disorder with secondary involvement of elastic fibres [7]. It is not clear whether any genotype/phenotype correlation exists.

The inheritance of PXE has been controversial over the past few years, and historically at least five genetic groups have been described [8–10]. With molecular testing it is now apparent that most cases are autosomal recessive and no confirmed autosomal dominant form has yet been shown [7]. Clinical features of PXE can be seen in unambiguously identified heterozygous carriers, and this explains some earlier reports of different clinical types and modes of inheritance.

Pathology [11–17]. In the fully developed skin lesions, the elastic fibres in the mid-dermis are clumped, degenerate, fragmented and swollen, and the abnormal fibres stain positively for calcium. The collagen fibres are also abnormal, being split into small fibres.

Similar changes occur in the connective tissue of the media and intima of the blood vessels, Bruch's membrane of the eye, and in the endocardium and pericardium. The heart may occasionally be enlarged, with extensive calcification [18], and pulmonary calcification has been reported [19]. Calcification may occur in other viscera [20].

The vascular involvement may be generalized but may involve predominantly the larger arteries, the mesenteric and visceral arteries, or those of the extremities [21]. Calcification of the internal elastic lamina of the arteries leads to vascular occlusion. Hypertension, angina, myocardial infarction, cerebrovascular accidents and recurrent mucosal haemorrhages may result. The changes in Bruch's membrane give rise to angioid streaks, and rupture of the retinal vessels to haemorrhages and choroiditis.

The complete syndrome consists of the distinctive skin lesions, retinal changes (angioid streaks) and vascular disturbances. The characteristic skin changes and angioid streaks have also been reported as isolated findings, but this is unusual, and in patients with angioid streaks but no obvious skin abnormalities, a biopsy of normal-looking skin will often show histological changes in the elastic tissue [16]. The relative severity of the cutaneous, ocular and vascular changes determines the wide variations in the clinical picture.

Skin changes. The skin lesions are characteristic. They consist of small (1–3 mm), yellowish papules in a linear or reticular pattern, in confluent plaques, although the changes are sometimes very subtle. The skin is soft, lax and slightly wrinkled, and may hang in folds, especially in elderly people. There may be a slightly pebbly surface, which has been variously described as a 'cobblestone', 'Moroccan leather' or 'chicken skin' appearance (Fig. 46.16). The sites of predilection are the sides of the neck, below the clavicles, the axillae (Fig. 46.17), abdomen, groins, perineum and thighs. Reticulate pigmentation on the abdomen may occur [22]. Numerous acneiform lesions have been reported [23]. Although usually limited, the eruption may occasionally involve most of the body. It may develop in early childhood, and usually does so before the age of 30 years, but it may also first appear in

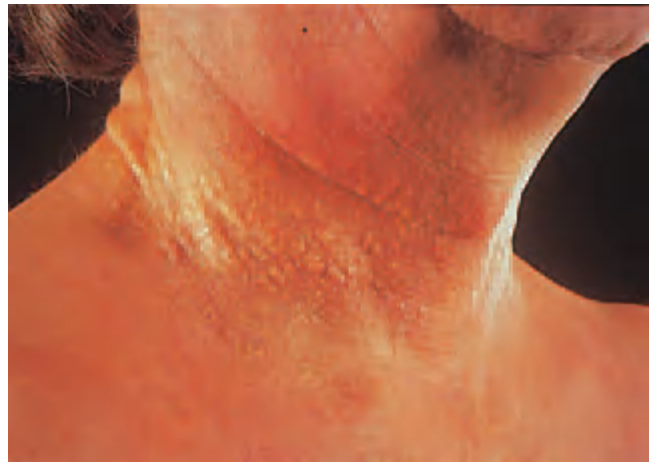

Fig. 46.16 Pseudoxanthoma elasticum, showing the typical 'chicken skin' appearance involving the neck.

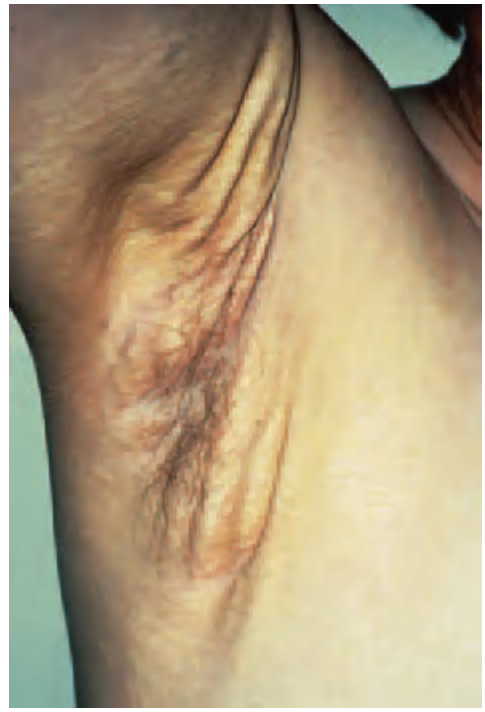

Fig. 46.17 Pseudoxanthoma elasticum of the axilla, showing the characteristic yellow discoloration of the skin and the loose folds. The changes in this condition are often much more subtle than in this patient.

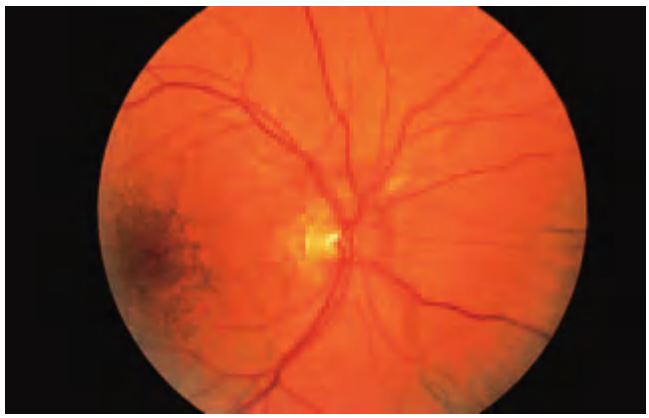

Fig. 46.18 Angioid streaks of the retina in pseudoxanthoma elasticum. (Courtesy of Professor D. Easty, Bristol Eye Hospital, Bristol, UK.)

old age. It usually persists unchanged indefinitely. Similar changes may occur in the soft palate, inside the lips and in the mucous membranes of stomach, rectum and vagina. In the mouth, the lesions may mimic sebaceous glands (Fordyce spots). Rarely, chronic granulomatous nodules have developed in the skin lesions [24].

Occasionally, there may be spontaneous perforating lesions, with transepidermal elimination of the fragmented elastic fibres. These present as hyperkeratotic papules, which leave a bleeding surface when dislodged.

Cardiovascular changes. The arteries throughout the body are affected. There may be intermittent claudication with diminished peripheral pulses, and there is accelerated atheroma, often with hypertension [25]. The circulatory disturbances are detectable by plethysmography or oscillometry, and angiography may show angiomatous malformations, aneurysmal dilatation, and narrowing or occlusion of peripheral or visceral arteries [26]. Signs of arterial degeneration may be seen by the age of 30 years, and death may result from cerebral haemorrhage, coronary occlusion or massive haemorrhage into the gut [27]. Cardiomyopathy has been reported [28,29].

Arterial involvement may not be clinically manifest until adult life, but intermittent claudication and angina have occurred in early childhood. Some patients, however, survive to old age.

Mitral valve prolapse occurs in about 5–8% of the normal population. In one series of 14 patients with PXE, 11 had mitral valve prolapse [30], but these individuals probably had an overlap with Marfanoid features [31].

Ocular changes. Angioid streaks [32,33] of the retina are seen as slate-grey, poorly defined streaks radiating from an incomplete greyish ring, surrounding the nerve head (Fig. 46.18). They are bilaterally symmetrical, and usually first appear between the ages of 20 and 40 years. There may be no impairment of vision, but progressive visual failure may occur, and haemorrhages and choroiditis occasionally result in total blindness.

Other associated ocular findings include small, raised, pearly white *drusen*, or punched-out atrophic areas in focal areas of dehiscence of Bruch's membrane [34]. There may also be speckled yellowish mottling at the posterior pole, and this change, which has been called 'leopard spotting', may antedate the angioid streaks [35]. About 50% of patients also have a random scattering of small, round pigment dots throughout the macula and optic nerve [36]. These may resemble a string of pearls in some cases, and they are best seen on fluorescein angiography.

Abnormal visibility of the choroidal vessels has been present in some apparently unaffected members of some families with PXE [37].

Obstetric risk. There is an increased risk of miscarriage in the first trimester, possibly related to failure of placental development [38], and abdominal striae develop during pregnancy in virtually all patients [39]. Opinions differ regarding the risk to the mother. Berde *et al.* [40] reviewed the literature and concluded that there was a serious risk of cardiovascular complications during pregnancy, but Viljoen *et al.* [39] reported 54 pregnancies in which there were no serious maternal complications. Subsequent reports also agree that whilst skin manifestations may worsen, the risks of pregnancy have been overstated [41].

Associated abnormalities. In most cases of PXE the serum calcium and phosphate levels are normal, but in a few patients the phosphate levels are increased, with mild hypercalcaemia and abnormalities of vitamin D metabolism [20,42]. The biochemical changes resemble those of tumoral calcinosis [43], although the clinical changes are those of PXE. This seems to be a distinctive rare type of PXE which may be associated with renal failure in other members of the family. Some of these patients also have systemic sclerosis [44].

Other patients have been reported with multiple calcified cutaneous nodules, with angioid streaks and hyperphosphataemia, but without pseudoxanthoma [45].

Skin changes of PXE and/or angioid streaks are occasionally seen in patients with osteitis deformans (Paget's disease). Pseudoxanthoma elasticum has also been reported in association with *osteoectasia*, which is characterized by dwarfism, bizarre radiographic changes and elevated serum alkaline phosphatase levels [46].

The development of both clinical and histopathological PXE-like changes, involving skin, eyes and vasculature, in sickle cell disease and β-thalassaemia has been well documented [47]. The abnormalities are most probably acquired and related to the consequences of the primary disease. The clinical features are of later onset and milder than in inherited PXE.

Table 46.1 Diagnostic criteria for pseudoxanthoma elasticum (PXE). (From Lebwohl *et al*. [17].)

Major criteria
1 Flexural yellow cobblestone lesions
2 Characteristic histological features of lesional skin, using elastic tissue and calcium stains (e.g. van Gieson and von Kossa)
3 Angioid streaks in the retina
Minor criteria
4 Characteristic histological changes in non-lesional skin
5 Family history of PXE in first-degree relatives

The typical features of PXE have been reported in a patient with true MFS but it is likely that this is a chance association [48].

Diagnosis. The clinical and histological changes of PXE are often distinctive, and the diagnosis is usually readily made when skin lesions are present. The disseminated form of dermatofibrosis lenticularis (Buschke–Ollendorff) can be clinically similar and juvenile elastoma, which is a feature of this condition, shows thickened elastic fibres on histology. If laxity of the involved skin is extreme, other forms of dermatochalasis must be excluded.

In cases without skin lesions, the diagnosis may be difficult and attempts have been made to establish diagnostic criteria [1,17]. These are summarized in Table 46.1. It should be suspected in obliterative arterial disease of early onset and in unexplained gastrointestinal haemorrhage. The presence of angioid streaks or mucosal lesions should be sought. A skin biopsy from the side of the neck may be helpful, even if there are no clinically evident changes, although the characteristic histological changes are not necessarily diagnostic [17]. Soft-tissue or vascular calcification may be detectable radiologically [49] and angiography may be helpful [26]. Ultrasound can detect early renal parenchymal calcification although its prognostic significance remains uncertain [50].

Definitive diagnosis is made by molecular analysis of the *ABCC6* gene. This also provides a means for prenatal and presymptomatic testing in families at risk for recurrence [7]. Emerging evidence also suggests that heterozygosity for an *ABCC6* mutation (*R1141X*) confers a fourfold risk of developing coronary artery disease [51].

Treatment. It is important that the condition is accurately diagnosed so that appropriate genetic advice may be given. The most important aspect of treatment is to ensure that complications from vascular involvement are prevented or dealt with speedily by the appropriate specialist. Ophthalmologists will recommend that the patient learns to use an Amsler grid in the early detection of visual loss. Patients should avoid any activity that might cause sudden increase in blood pressure or contact injury to the eyes. Laser photocoagulation may be helpful in preventing further retinal haemorrhage. Cardiovascular risks should be minimized with control of blood pressure and serum lipids, and avoidance of smoking. The cosmetic appearance of the skin lesions may be improved by plastic surgery. Restriction of dietary calcium has been tried with apparent benefit in some cases [43], but this treatment remains controversial.

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Perforating PXE

Transepithelial elimination (TEE) of altered elastic fibres can occasionally occur in generalized hereditary forms of PXE (see above), but it can also occur as a localized acquired defect in patients who do not have the other features of PXE [1]. These localized lesions usually occur in the periumbilical area in obese, multiparous black women, and it is possible that this represents a response to repeated cutaneous stretching [2,3]. A similar lesion on the breast was reported in a patient undergoing haemodialysis [4].

Clinically, there is a well-demarcated, hyperpigmented plaque which slowly enlarges. The surface may be atrophic, grooved, fissured or verrucous, and compression of the edge of the lesion may produce a liquid discharge.

It seems likely that most cases previously described as perforating serpiginous elastosis in association with PXE were really examples of perforating PXE [5]. The histology of the two conditions is similar, but in perforating PXE there is TEE of altered basophilic, calcified, elastic fibres, which are short, fragmented, curled and predominantly in the mid-dermis, whereas in perforating serpiginous elastosis the fibres are abnormally large, non-calcified, eosinophilic and straight.

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Pseudo-PXE

Skin changes which are virtually identical to those of PXE can rarely be produced by penicillamine, although the systemic features do not occur [1]. The skin changes can be explained by the known effect of penicillamine in inhibiting collagen and elastin cross-linking, with the production of vastly increased amounts of abnormal elastin in the dermis [2]. Transepidermal extrusion of elastin has been reported in this condition [3].

Saltpetre-induced disease mimicking PXE

A condition which resembles the skin changes of PXE clinically, histologically and ultrastructurally has been described in a group of elderly farmers, who years earlier had spread a fertilizer containing a mixture of various nitrates (Norwegian saltpetre) [4,5]. The patients developed cutaneous ulcers, which quickly healed to leave yellowish-white papules and plaques. None of the patients had a positive family history or other signs of PXE.

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Williams–Beuren syndrome

The Williams–Beuren syndrome is a developmental disorder characterized by premature laxity of the skin, congenital heart disease (notably supravalvular aortic stenosis), metabolic abnormalities and dysmorphic facial features, which include baggy connective tissue around the eyes, full cheeks, prominent lips and dental malocclusion [1]. Delayed motor and perceptual development are sometimes masked by above-average language skills allied to a 'cocktail party' personality [2].

In situ hybridization techniques have revealed both inherited and new deletions at the elastin locus on chromosome 7 [3]. Multiorgan involvement occurs as a consequence of contiguous gene deletions and at least 14 genes may be involved [4]. An 'epidemic' of the Williams' syndrome was reported in the UK following the administration of excessive doses of vitamin D to prevent rickets in pregnant women [5]. Vitamin D is known to down-regulate elastin gene expression [6].

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Linear focal elastosis

SYN. ELASTOTIC STRIAE

This condition is characterized by asymptomatic, yellow, linear bands arranged horizontally on the lower back [1–3]. Superficially, the lesions resemble striae distensae, but they are palpable rather than depressed and yellow rather than purplish or white. Although the two conditions are generally unrelated, linear focal elastosis has been reported adjacent to striae distensae in one case [4]. The condition was originally described in elderly males [1], although it has been reported in a young black male whose father was similarly affected [5]. It may be commoner than is suggested by the paucity of reports. Ultrastructural studies reveal active elastogenesis. The middle and lower dermal collagen is separated by bluish grey, fine, fibrillar material, which is composed of thin, wavy elastic fibres and fragmented elastic fibre bundles. The elastic fibres are near to, or even in contact with, fibroblasts [6], and elastogenesis may occur in response to local trauma, perhaps following the development of striae distensae [7].

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Actinic elastosis

SYN. SOLAR ELASTOSIS

Definition. This is a degenerative change in the dermis caused by prolonged exposure to electromagnetic (usually solar) radiation. It is characterized clinically by yellowish discoloration and histologically by degeneration of elastic fibres.

Aetiology. Solar elastosis usually results from prolonged exposure to sunlight, but it can also result from infrared (IR) radiation [1,2]. It is related to the cumulative dose of radiation, as it is more common in older people, outdoor workers and in sunny climates. There is, however, considerable variation in susceptibility between individuals. Fair-skinned people are the worst affected, although the condition can occur in black people [3,4]. Severe elastosis may occur in photosensitized skin, for example in porphyria cutanea tarda. UVB wavelengths are the most likely to cause solar elastosis, although UVA and PUVA therapy can also accentuate it [5,6].

Ageing normal skin becomes atrophic, with fewer elastic fibres [3]. In contrast, sun-damaged ('photo-aged') skin exhibits hypertrophy of elastin tissue, secondary to a prolonged inflammatory process [7]. Skin on the back of the neck exposed to chronic UV radiation shows partially degranulated mast cells in close apposition to fibroblasts. Metalloproteases produced by mast cells and macrophages degrade skin collagen [8].

Pathology [9,10]. At an early stage, there is a perivenular lymphohistiocytic infiltrate, with degranulating mast cells [7,11]. The vessel walls become thickened due to deposition of a basement-membrane-like material [4]. The

elastic fibres of the upper and middle dermis then become curled and fibrillar to form thick, irregular masses [12]. At a later stage, the elastotic degeneration becomes more diffuse, forming long swollen bands of irregular texture, with finely granular elastin and dense microfibrillar masses. Actinic elastosis originates in elastic fibres rather than collagen, as shown by the findings that the abnormal fibres stain with antielastin antibody HB8, disappear with elastase but resist collagenase, and have a high desmosine content.

In the early stages of actinic elastosis, there is also an increase in collagen and in glycosaminoglycans, although ultimately the collagen decreases. Eventually, the fibrous network degenerates into an amorphous elastotic mass, and the dermal blood vessels become sparse and tortuous [3,4]. The increased dermal glycosaminoglycans are deposited on the elastotic material in the superficial dermis [13].

Clinical features. The condition is more common in later life. In temperate climates, it is rare before the fourth decade, but it starts earlier and is more severe in sunnier climates. The light-exposed areas are affected, particularly the forehead and the back of the neck. Mild degrees of elastosis may not be apparent until the skin is pinched up, when it may assume a wrinkled appearance. Elastosis is usually more advanced in the tissue than the clinical appearance would suggest.

The affected skin is diffusely thickened and yellowish (Fig. 46.19), and on the neck it may be divided by well-defined furrows into an irregular rhomboidal pattern (cutis rhomboidalis nuchae). There may also be more sharply marginated, thickened plaques on the face or neck. These are usually, but not always, symmetrical.

When the skin around the orbits is affected, it is often studded with numerous comedones, and this has been called the *Favre–Racouchot syndrome* (Fig. 46.20). Favre–Racouchot syndrome is usually confined to facial skin and is bilaterally symmetrical, but unilateral and circumscribed forms have been reported [14]. The term actinic-comedonal plaque has been suggested for similar lesions which can rarely occur on other parts of the body, such as the forearm [15,16].

Skin which is affected by actinic elastosis is likely to develop other signs of sun damage, including irregular pigmentation, wrinkling, scaling, solar keratoses and malignancy. This range of changes due to chronic sun damage has been called *dermatoheliosis* [17].

Actinic elastosis may also be complicated by actinic granuloma (see below).

Photodamage is markedly exacerbated in smokers [18].

Diagnosis. Plane xanthoma, PXE and colloid milium may sometimes cause confusion, but the combination of the clinical and histological features is distinctive.

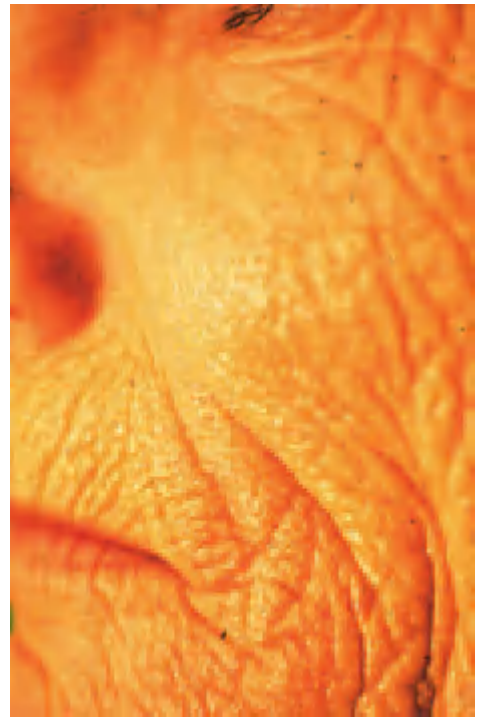

Fig. 46.19 Actinic (solar) elastosis, showing the characteristic yellowish discoloration, thickening and wrinkling of the facial skin.

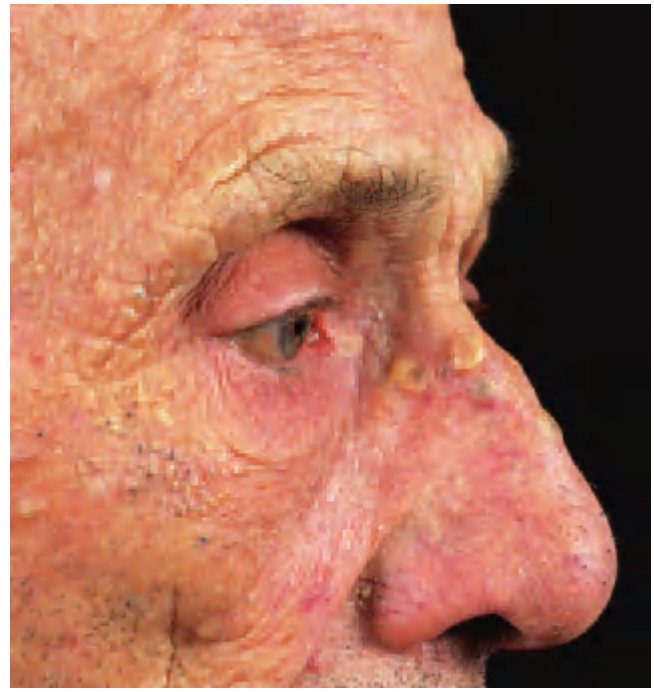

Fig. 46.20 Favre–Racouchot syndrome, showing comedones and actinic elastosis. (Courtesy of Professor R. Marks, St Vincent's Hospital, Melbourne, Victoria, Australia.)

Treatment. Sunscreens protect against the development of photodamage both in humans and animals [19]. In hairless mice exposed to UVB radiation, synthesis of subepidermal collagen has been demonstrated in animals protected with a sunscreen [20]. Topical application of α-hydroxy acids ('fruit acids'), i.e. lactic, glycolic and citric acids, led to a modest improvement in photodamaged skin [21]. More impressive results have been obtained with topically applied tretinoin cream [22,23]. A double-blind study [24] demonstrated a decrease in papillary dermal collagen type I in photodamaged skin, and subsequent treatment with 0.1% tretinoin cream for 10–12 months resulted in an 80% increase in dermal collagen. Several studies have shown clinical and histological improvement after prolonged use [19]. Tretinoin may also repair skin changes due to intrinsic ageing [24,25]. Similar results have been obtained in double-blind trials of topical isotretinoin [26] and tazarotene cream [27]. There has been interest in the use of so-called non-ablative lasers, including the 1320 nm Nd : YAG and 1540-nm erbium glass lasers, which are claimed to wound the upper dermis without epidermal damage [28].

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Digital papular calcific elastosis

Digital papular calcific elastosis (DPCE) is an acquired papular eruption in which keratoderma is associated with changes in dermal connective tissue. Predominantly it affects the radial aspect of the index finger, first web space and ulnar aspect of the thumb [1]. Histologically there is hyperkeratosis, with sawtoothing of the rete ridges. The dermal collagen fibres are thickened and arranged haphazardly; there are basophilic elastotic masses, often containing calcium, in the upper reticular dermis. Cases are sporadic, unlike the clinically similar disorders acrokeratoelastoidosis and focal acral hyperkeratosis (Chapter 34) [2]. The distribution suggests photodamage; the condition has been reported entirely from geographical areas with high solar irradiation. Digital papular calcific elastosis has been regarded as a variant of actinic elastosis [3]. However, in DPCE, the elastotic process relatively spares the papillary dermis and the basophilic areas containing calcium differ from the changes in actinic elastosis. Squamous carcinoma has been reported, arising from the lesion [4].

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Actinic granuloma

SYN. O'BRIEN'S GRANULOMA

Definition. This is an annular inflammatory reaction with a giant cell dermal infiltrate, which develops in an area

of actinic elastosis. Some authors feel that this is not a specific entity, and the changes could be a feature of granuloma annulare or some other granulomatous disease that happens to occur on light-exposed skin [1]. Others point out that a similar granulomatous reaction to elastotic material can occur in pinguecula of the eye [2]. A recent histopathological study supports histological distinction of the two conditions [3]. There is minimal or no lysozyme activity in the histiocytes in the inflammatory area of actinic granuloma, in contrast with those of granuloma annulare, which exhibit abundant lysozyme activity [4].

The condition is more common in sunny countries, and fair-skinned or freckled subjects are particularly susceptible. A similar condition has been described in dark-skinned people under the name of granuloma multiforme (Chapter 57).

Pathology [3–6]. A biopsy taken radially across the thickened edge of the lesion shows three distinct zones in the dermis. In the external 'normal' skin, there is actinic elastosis. In the thickened annulus, there is a histiocytic and giant cell inflammatory reaction in relation to elastotic fibres, and in the centre, within the annulus, little or no elastic tissue remains. The cellular infiltrate slowly expands outwards, leaving behind a central area from which elastic fibres have been removed by 'elastoclasis'.

The epidermis may be normal or it may show signs of actinic damage.

Clinical features. Lesions develop in the exposed 'weather-beaten' skin of patients after the third decade, particularly in fair-skinned or freckled subjects. They start insidiously as small, pink papules, which progress slowly to form an annulus of firm superficial dermal thickening. This is smooth, slightly raised and measures 0.2–0.5 cm in width. The ring may expand up to 6 cm in diameter. The centre may become slightly atrophic, and variable depigmentation may occur. The lesions are usually asymptomatic, but a sunburn reaction may provoke severe erythema and irritation.

Diagnosis. The condition must be distinguished from granuloma multiforme, granuloma annulare, serpiginous perforating elastosis, Miescher's disciform granuloma, sarcoidosis and necrobiosis lipoidica [7]. The lesions of actinic granuloma are confined to light-exposed skin, and the infiltrate lacks the tidy palisaded arrangement that is normally seen with granuloma annulare. Rarely, granuloma annulare can occur in an actinic distribution [8,9].

Treatment. Infiltration of the annular edge of the lesions with triamcinolone may be effective. Sunscreens should be used to prevent further damage.

Isotretinoin (0.5 mg/kg/day) arrested the development of lesions in an elderly male [10].

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Elastofibroma [1–5]

Elastofibroma occurs predominantly in elderly women, and in most cases is situated beneath the lower angle of the scapula. The painless or slightly tender swelling, from 2 to 10 cm in diameter, is often discovered fortuitously. It may enlarge slowly, displacing neighbouring structures, and it can be clinically confused with a sarcoma. This is a benign lesion, however, despite the fact that it is poorly circumscribed. The growth is composed of mature fibrous tissue, containing fibres which stain as elastic fibres. The lesions may be solitary or multiple.

Histologically, the lesion contains abundant large elastic fibres, some broken into irregular masses, and large amounts of relatively acellular collagen. The elastic fibres are composed of true elastin surrounded by a large amount of hydrophilic material forming an orderly array of tubules [4]. It is generally regarded either as a type of reactive hyperplasia, or as a hamartoma. It is cured by simple excision.

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Elastoderma

Elastoderma is a very rare condition which is due to excessive elastogenesis. A young woman developed a localized defect of the skin of one arm, which became pendulous and lax, but lost its elastic recoil. Histological

and biochemical investigation showed this was due to accumulation of excessive elastin, with derangement of elastin fibrillogenesis [1].

In a further case, clinically uninvolved skin showed thin elastic fibres on haematoxylin and eosin staining [2].

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Marfan's syndrome

Definition. This is an autosomal dominant inherited disorder of connective tissue with variable clinical manifestations, both between and within families, and a prevalence of one in 5000–10 000 [1]. Up to 30% of cases are new mutations [2]. The full syndrome is characterized by aortic dilatation, ectopia lentis and skeletal abnormalities [3].

Aetiology. Mutations in the fibrillin-1 (*FBN1*) gene, located on chromosome 15q21.1, cause MFS [4]. Fibrillin is one component of the elastin-associated microfibrils, which are especially important in the ciliary zonule of the eye (the suspensory ligament of the lens). Patients with Marfan's syndrome (MFS) show a striking lack of fibrillin in their skin and on culture of their dermal fibroblasts [5,6]. Mutations in *FBN1* probably exert their effect by dominant-negative mechanisms, but recent studies also suggest altered susceptibility to proteases and disturbances of elastic fibre homeostasis [7].

Pathology. The cardiovascular lesions are the most important. Fragmentation and sparsity of elastic fibres, with accumulation of mucinous material, occur in the media of the aorta [8–10]. These changes lead to aortic incompetence, dissecting aneurysm, or rupture of the aorta [11]. Mitral incompetence is common [12]. Dermal elastic fibres are narrower than normal and more resistant to neutrophil elastase [13].

Clinical features [3,9,14,15]. Despite recent advances in mutation detection, the diagnosis of MFS is primarily clinical and relies on the Ghent nosology [3]. The full syndrome comprises skeletal, ocular and cardiovascular defects. The patient is often, but not invariably, exceptionally tall, but the skeletal proportions are abnormal. The extremities are long, the excess being greatest distally, giving rise to arachnodactyly, and the length of the hallux is often particularly conspicuous. The skull is dolichocephalic, the paranasal sinuses are large and the palate high and arched [16]. Lax capsules result in unstable or hyperextensible joints, kyphoscoliosis, pectus excavatum and flat foot. Muscles may be underdeveloped and hypotonic, and subcutaneous fat is sparse.

The common ocular abnormalities [17] include ectopia lentis (usually upward), a trembling iris, myopia and retinal detachment; less frequent are blue sclerotics and heterochromia of the iris.

Aneurysmal dilatation of the ascending aorta is the most important abnormality of the cardiovascular system, and aortic and mitral incompetence are common. Aortic dilatation may begin in childhood. Mitral valve prolapse occurs in 80% of cases [18].

Skin changes may be under-reported. Serpiginous perforating elastosis may occur [15]. In a recent study [19], striae atrophicae were observed in 7% of children and 35% of adults. Other features include papyraceous scars and skin hyperextensibility [20]. Several patients have been described with concomitant EDS and MFS [21].

Other abnormalities are frequent—nerve deafness occurs in 6%; pulmonary malformations are often reported at autopsy; renal abnormalities are manifest as proteinuria and raised blood urea [14].

The prognosis is related to the severity of the cardiac defects, the localization and progression of which are dependent on haemodynamic stresses [9,22]. Survival beyond the fifth decade is unusual, and some cases die in childhood. The average age at which dissection of the aorta develops is 30 years. Early death from cardiovascular disease may occur, even in apparently mild cases, and the correlation between cardiac and skeletal problems is poor [23–25].

Diagnosis [3,26]. The full syndrome is unmistakable, but diagnostic certainty is impossible in the partial forms. Clinical features are divided into major and minor according to their specificity. To make a diagnosis major criteria must be present in two organs and involvement in a third is required [3].

Simple screening tests that may be helpful include the thumb sign (positive if the thumb when completely opposed in the clenched hand projects beyond the ulnar border), the wrist sign (positive if the thumb and little finger overlap when wrapped around the opposite wrist) and the ratio of the lower segment (pubic ramus to floor) to the upper segment (height minus lower segment), but this ratio varies with age and sex.

Some tall people have high, arched palates and some degree of arachnodactyly. This is probably of no consequence in many cases, although a marfanoid habitus in women may be associated with mitral valve prolapse [18,27].

Joint hypermobility may also be associated with mitral valve prolapse [28]. Other causes of joint hypermobility, such as homocystinuria, may be confused with the partial forms of the syndrome. Homocystinuria should be considered in marfanoid patients with myopia or downward ectopia lentis. Urine screening is unreliable; blood levels of methionine and homocysteine should be measured. Prompt diagnosis and treatment reduce the risk of coronary artery or cerebrovascular thrombosis [29].

The marfanoid habitus has been reported in association with distal pigmentation, neuroma of the eyelids and tongue, medullary carcinoma of the thyroid and phaeochromocytoma [30] (see also multiple endocrine neoplasm syndrome (Chapter 59)).

Congenital contractural arachnodactyly is another fibrillinopathy, which is caused by mutations of the fibrillin-2 gene [31]. It is primarily an orthopaedic condition unrelated to MFS [32,33]. It produces multiple joint contractures, arachnodactyly, kyphoscoliosis, distorted pinnae and dolichostenomelia (long, thin limbs), but there are no cardiovascular complications.

Management [26]. Patients should be seen by an ophthalmologist and an orthopaedic surgeon, and they should be reviewed regularly by a cardiologist. Beta-blockers may be used to retard the development of aortic dilatation, and surgical replacement before the diameter exceeds 5.5–6.0 cm is recommended [10,34].

Oestrogen therapy has been used to prevent excessive stature in female patients [35].

Pregnancy is inadvisable, because of the 50% risk of inheritance in the fetus, and because of the risk of acceleration of aortic degeneration and vascular rupture. A pregnant patient with no cardiac signs needs monthly checks from the third month. Those with aortic or mitral valvular disease or dilatation of the aortic root are at high risk during pregnancy [36,37].

The majority of *FBN1* mutations are unique to one affected individual or family, but despite this and the presence of sporadic cases, prenatal and preimplantation diagnosis is feasible [2].

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Disorders of collagen

Ehlers–Danlos syndrome

SYN. CUTIS HYPERELASTICA

Definition. EDS is a heterogeneous group of inherited disorders of connective tissue. Estimates of its prevalence vary between 1 : 560 000 and 1 : 5000 [1]. For many

patients the symptoms are so mild that they may not be recognized. The hallmarks of EDS are fragility of the skin and blood vessels, hyperextensibility of the skin, and joint hypermobility [2]. The original classification divided EDS into 11 clinical types; however, in 1986, the International Nosology of Heritable Disorders of Connective Tissue redefined EDS into subtypes I–VIII and X [3]. It is now clear that certain phenotypic subtypes (EDS types I and II) overlap and some patients do not fit neatly into one category. Progress in molecular biology has been rapid in recent years, enabling further subdivision of some types [4].

Aetiology. Specific molecular and biochemical abnormalities have been identified in several types (see Table 46.2) [5,6]. Attempts should be made to delineate the clinical, biochemical and, if possible, molecular abnormalities in a patient with EDS in view of the widely differing prognosis between different types. Defects predominantly involve collagen, although a fibronectin defect has been reported in type X [7], and more recently mutations in tenascin-X have been found to cause a newly recognized autosomal recessive form of EDS.

Pathology [8,9]. Skin histology is variable and often within normal limits. Typically, there is a loose, disordered dermal collagen network. Elastic fibres are usually increased and orientated irregularly. The 'pseudotumours' seen in type I EDS consist of fat and mucoid material in fibrous capsules; they may be calcified. Bone mineralization is decreased, and the collagen fibres are irregular. Adventitial defects of small arteries and inadequate support from the surrounding connective tissue account for the vascular vulnerability in vascular EDS (type IV) [10,11]. Although bruising can be explained on the basis of skin and blood vessel fragility, a few patients also exhibit both ultrastructural and functional platelet defects [12,13]. Clotting factor deficiencies have been only rarely reported. Electron microscopy of dermal collagen consistently shows irregularities of fibril shape and size, although reliable subclassification of the more common subtypes is not possible [14]. By contrast, arthrochalasia type EDS is characterized by angular fibrils in cross-section, and dermatosparaxis by grossly distorted, hieroglyphic fibrils. Biomechanical studies confirm increased skin elasticity and hyperextensibility, particularly in classical EDS (type I) [15,16].

Clinical features. These are summarized in Table 46.2. The india-rubber men and circus contortionists who are affected by EDS turn the syndrome to their advantage. More details are given in the accounts of each type.

Classical type (EDS I/II)

This subgroup, which is inherited as an autosomal dominant, includes both EDS type I (gravis) and II (mitis).

Pathology. Histology may be within normal limits; alternatively there may be thin, weakly polarized, dermal collagen bundles. Elastic fibres may be irregular and relatively increased [8,9]. At ultrastructural level, collagen bundles are of variable size with abnormally large, composite 'cauliflower' fibrils, reflecting abnormal fibrilogenesis [14,17,18]. Linkage to *COL5A1* was originally identified in a British family with EDS II, and analysis of further families subsequently showed that EDS I and II are allelic [19,20]. Up to half of all classical EDS patients have mutations in *COL5A1* or *COL5A2*, which encode the α_1 and α_2 chains of type V collagen, respectively. Although quantitatively minor (approximately 2–5% of dermal collagen), collagen V plays an important role in the regulation of type I collagen diameter [21]. Missense and exon skipping mutations with dominant-negative effects or mutations giving rise to haploinsufficiency may occur [22,23]. Genetic heterogeneity is apparent with reports of classical EDS caused by a mutation in the collagen I gene [24]. Furthermore, knock-out experiments with mice suggest other extracellular matrix components such as decorin, fibromodulin, thrombospondin-2, lumican and biglycan may be important [25,26].

Clinical features. The skin is soft, velvety and hyperextensible (Fig. 46.21) but retains its normal recoil. The skin on the palms and soles may be redundant, like a loose glove. The skin is not usually otherwise lax until later in life, when redundant folds occur on the eyelids (blepharochalasis), face and limbs. Secondary cutis laxa has been described on the lower back of a patient with mild classical EDS [27]. Striae do not develop during pregnancy. Trivial lacerations form gaping wounds that heal very slowly to leave broad, atrophic 'cigarette paper' scars (Figs 46.22 & 46.23). Sutures may tear out repeatedly. Blue-grey, spongy tumours (molluscoid pseudotumours), due to accumulation of connective tissue, may form on the skin, especially in scars or over pressure points. Smaller, firm, subcutaneous nodules (spheroids), which show calcification on X-ray develop on the shins and forearms in up to a third of patients.

Easy bruising may be the presenting symptom, and pigmentation due to haemosiderin deposition is often found on areas of repeated trauma.

The facies may be distinctive, with widely spaced eyes, a wide nasal bridge, and epicanthic folds. The sclerae are sometimes blue.

There is marked joint hypermobility, which can impair walking, especially during pregnancy. Subluxation of the large joints may occur, and genu recurvatum and kyphoscoliosis are frequent [28]. Muscle tone is often poor, and hernias develop. Pedal piezogenic papules are seen more frequently. Diaphragmatic eventration and gastric torsion have been reported [29]. Symptomatic bladder diverticula may develop [30]. Varicose veins may develop in

Table 46.2 Clinical and molecular subtypes of Ehlers–Danlos syndrome.

EDS type	Synomym	Villefranche classification*	Mode of inheritance	Clinical features	Ultrastructural findings	Molecular defect
I II	Gravis Mitis	Classical	AD	Soft, velvety, hyperextensible skin; easy bruising; atrophic scars; hypermobile joints; pseudotumours	'Cauliflower' fibrils	*COL5A1* & *COL5A2* (& *COL1A1*) mutations
III	Hypermobile	Hypermobility	AD	Hypermobile joints; minimal skin abnormality	As above	?
IV	Acrogeric or ecchymotic	Vascular	AD	Thin skin; easy bruising; small joint hypermobility; vascular and bowel ruptures	Small variable fibrils	*COL3A1* mutations
V	X-linked	Other form	XLR	Resembles mild classical type; bruising more pronounced	–	?
VI	Ocular-scoliotic	Kyphoscoliosis	AR	Soft, hyperextensible skin; hypermobile joints; scoliosis; ocular fragility; keratoconus	Small collagen bundles; fibrils normal or similar to classical type	Lysyl hydroxylase mutations
VIIA, B	Arthrochalasis multiplex congenita	Arthrochalasis	AD	Floppy infant; congenital hip dislocation; hypermobile joints; soft skin; normal scarring; short stature	Angular fibrils	A & B: *COL1A1* & *COL1A2* mutations, respectively, result in loss of exon 6 (Procollagen *N*-proteinase/*ADAMTS2* cleavage site)
VIIC	Dermatosparaxis	Dermatosparaxis	AR	Markedly hypermobile joints; very soft and extremely fragile skin; easy bruising	Hieroglyphic fibrils	Procollagen *N*-proteinase (*ADAMTS2*) mutations
VIII	Periodontal	Other form	AD	Severe periodontitis; pigmented pretibial plaques and scarring	Small fibrils in some patients	Occasionally collagen III deficient
X	Fibronectin	Other form	AR	Similar to mild classical type	Large, irregular fibrils	Fibronectin deficiency abnormality
–	Progeroid	Other form	AR	Atrophic scars; lax skin and joints; aged appearance; short stature; osteopenia; mental retardation	–	*XGPT1* mutations
–	Tenascin-X	–	AR	Similar to mild classical type but no scarring	Normal fibrils but reduced density	Tenascin-X mutations

* The Villefranche classification simplifies EDS into six major types. The other types have been provisionally grouped under 'other forms' until more is known about their molecular basis.
AD, autosomal dominant; AR, autosomal recessive; EDS, Ehlers–Danlos syndrome; XLR, X-linked recessive.

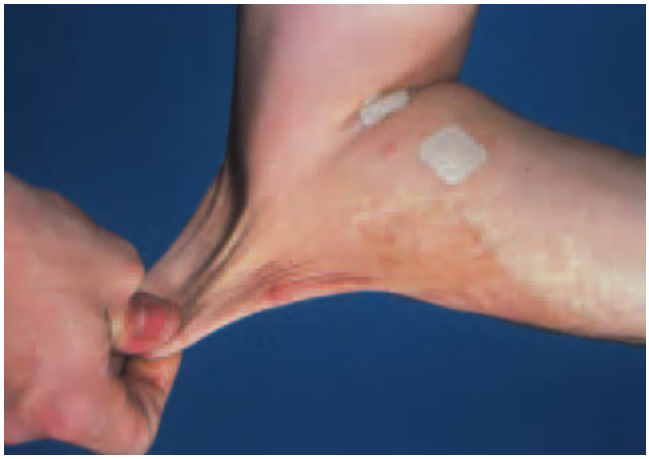

Fig. 46.21 Cutaneous hyperextensibililty in classical Ehlers–Danlos syndrome.

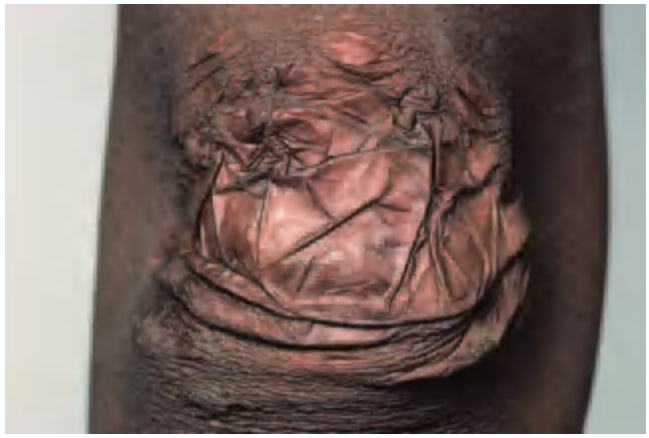

Fig. 46.22 Atrophic scarring of the elbow in classical Ehlers–Danlos syndrome.

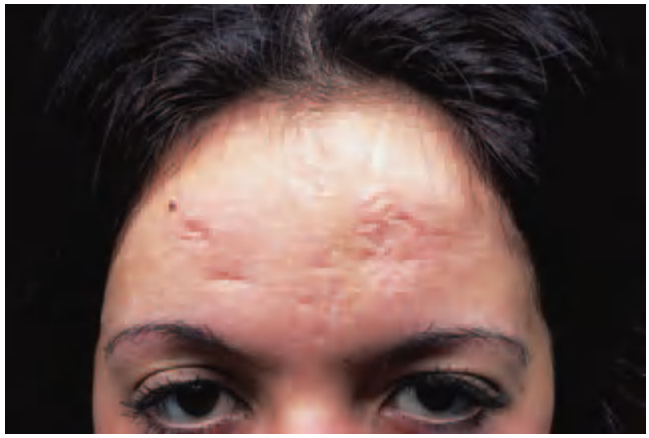

Fig. 46.23 Scarring of the forehead in classical Ehlers–Danlos syndrome.

early life. Prematurity due to ruptured fetal membranes is common.

As physical and mental development are normal, life expectancy is not reduced, hence large family pedigrees are not unusual. A mild variant of classical EDS has been described in 9% of a general dermatology population less than 50 years old, and merges with benign hypermobility syndrome and the normal spectrum [31]. A simple clinical scoring system, based on an assessment of joint hypermobility, skin extensibility and bruising might be useful in predicting which members of the general population are likely to produce poor scars following cutaneous surgery [32].

Hypermobility type (EDS III)

Hypermobile EDS and benign joint hypermobility syndrome (BJHS) are autosomal dominant and considered by some authors to be the same disorder. Revised criteria have been proposed for their diagnosis [33]. The Beighton score is a useful, quick method for assessing global joint hypermobility, and an adult score of four or more out of nine either currently or historically is considered hypermobile [34]. The genetic defect is not known but ultimately molecular analysis will determine whether these two groups are genetically heterogeneous. There is one report of a family with hypermobile EDS phenotype due to collagen III deficiency, as occurs in vascular EDS [35]. The ultrastructural changes resemble those in classical EDS. The skin is only minimally affected by scarring and hyperextensibility, whereas joint mobility is markedly increased, and dislocation and joint pains are common [36,37]. A study of a small number of hypermobile patients showed they were resistant to the effects of intradermal or topical local anaesthetic compared with BJHS patients or controls, suggesting that the disorders are distinct [38]. However, the criteria used to diagnose the hypermobile group were not clearly documented. In the authors' experience, patients with classical EDS may also be resistant to local anaesthetic.

Vascular type (EDS IV)

This very severe form is inherited as an autosomal dominant. Cases previously reported as autosomal recessive inheritance were probably due to sporadic mutations [39–41]. It is rare, the prevalence being between one in 10^5 and one in 10^6 [39].

Pathology. The condition is characterized by an abnormality of the synthesis, secretion or structure of type III collagen due to an abnormality of the collagen III gene (*COL3A1*) [6,42]. Segregation studies using polymorphic restriction sites in the gene may be of use in prenatal diagnosis [43]. The syndrome is biochemically heterogeneous

[5]. Several changes have been reported, the most common of which are point mutations (substituting other amino acids for glycine residues in the triple helical domain). Exon-skipping mutations are nearly as common; small genomic deletions within one exon and multiexon deletions have also been described [5,6,44]. It has been suggested that the region of the type III collagen molecule where mutation occurs may be linked with the clinical severity [6], although this has not been found in other studies [44].

These abnormalities all result in abnormal structure, synthesis or secretion of type III procollagen. Often, the skin is reduced to 25% of normal thickness, with small collagen fibre bundles. Fibril diameter is markedly variable in some patients [45]. In many patients, the fibroblasts contain prominent rough endoplasmic reticulum containing abnormal type III procollagen [45,46]. Cell strains from other individuals show markedly reduced extracellular accumulation of procollagen and collagen but without intracellular accumulation, perhaps due to rapid degradation of mutant chains [47]. Bizarre elastic fibres are often abundant.

The condition affects tissues rich in type III collagen, notably arterial media, bowel and uterus. Interestingly, type III collagen production by fibroblasts is decreased in some patients with ruptured cerebral aneurysm, even though they have no other stigmata of EDS [48]. The collagen deficiency in these patients does not appear to arise from *COL3A1* mutations, but may relate to abnormal post-translational modification or altered collagen metabolism [49].

Clinical features. The major clinical features are spontaneous rupture of large arteries, colon and gravid uterus. Dissecting aortic aneurysm is a common cause of sudden death [50]. Spontaneous carotid–cavernous fistula can also occur, resulting in unilateral exophthalmos [51]; it may respond to surgical repair or embolization [52]. Repair of rupture of the colon (usually sigmoid) is complicated by tissue friability and peritoneal contamination [53]. In one series complications of pregnancy led to death in the peripartum period in 12 of 81 women who had a total of 183 pregnancies [44]. Seven died following vessel rupture and five following uterine rupture.

Other features include prematurity (due to rupture of friable placental membranes), low birth weight, short stature, easy bruising (which may lead to the mistaken accusation of child abuse) [54] and pneumothorax [55,56]. Elastosis perforans serpiginosa is seen more commonly in this EDS subtype.

Two phenotypic groups are recognizable. In the *acrogeric* type, individuals appear prematurely aged with thin, translucent, fragile skin (Fig. 46.24), a hollow-eyed appearance, thin, peaked nose and thin lips. Easy bruising predominates in the *ecchymotic* type, often falsely suggesting a primary disorder of coagulation [13]. Unlike other forms of EDS, the skin is not hyperextensible, and joint hypermobility is chiefly restricted to the small joints of the hands and feet. Surface veins are usually readily visible. There is a tendency to form keloid scars.

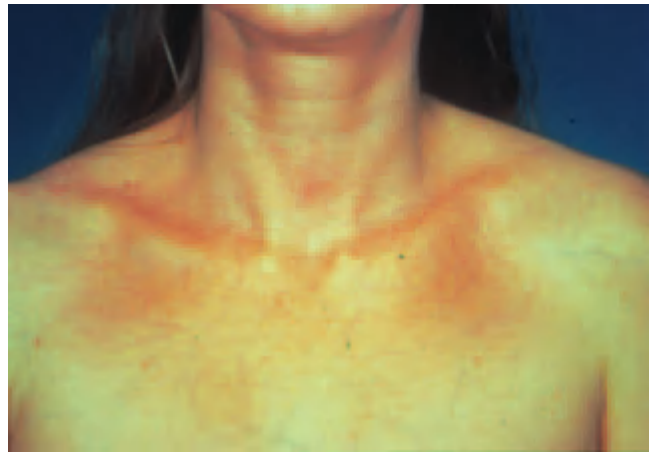

Fig. 46.24 Cutaneous atrophy in vascular (acrogeric) Ehlers–Danlos syndrome.

The largest case series to date of 220 index cases of vascular EDS patients and 199 affected relatives showed the median survival as 48 years, with 25% of index cases having their first significant complication by 20 years [44]. Most deaths follow arterial dissection or rupture, mainly of the thoracic and abdominal vessels. Milder variants may occur, presenting with cardiac features in later life [57].

X-linked type (EDS V)

Two families have been described as type V EDS. Clinically, it resembles mild classical EDS, but bruising is more marked. However, it is distinguished by X-linked inheritance [58]. The biochemical defect is unknown, and skin collagen cross-links are normal [59]. Lysyl oxidase activity has been reported to be reduced in one family [60], but these patients appear to form a clinically distinct subgroup. In other families, the lysyl oxidase levels have been normal [59]. Until a precise genetic or biochemical abnormality is found, the status of this type must remain in question [5].

Kyphoscoliosis type (EDS VI; ocular-scoliotic)

This autosomal recessive condition was the first true disorder of collagen structure to be described [61–63]. The biochemical abnormality in most, but not all, patients, is a deficiency of lysyl hydroxylase [62]. Different mutations in the lysyl hydroxylase gene (*PLOD*) have been identified in unrelated families. One is homozygous for a stop codon at residue 319 (R319X) [64]. In another, duplication of 180 base pairs in the coding sequence of the complementary DNA resulted in decreased enzyme function [65], and a further family revealed a compound heterozygote

combining a 3-bp deletion and an amino acid substitution (G678A) [66].

Deficiency of the enzyme leads to reduced hydroxylation of lysyl residues in types I and III collagen in skin; hydroxylysine-containing cross-links are not formed [67]. Lysine-derived cross-links appear not to be as stable as those derived from hydroxylysine; the former do not mature as rapidly to stable intermolecular cross-links [68]. Types II, IV and V collagens are hydroxylated normally, which suggests that there may be different isoenzymes or different affinities of a single enzyme for specific collagen types [5]. Detection of abnormal pyridinoline cross-links in urine can be used as a diagnostic aid [69].

Clinical features include soft, velvety, hyperextensible skin and increased joint mobility. Scoliosis is common. Eye manifestations include microcornea, glaucoma, keratoconus and ocular fragility. Some patients have a marfanoid habitus. Bleeding may occur from major wounds, and there may be delayed motor development [70].

The kyphoscoliotic type of EDS appears to be rare, with less than two dozen cases reported in the literature [5]. Because it is inherited recessively, after the birth of an affected child there is a 25% risk of recurrence in each successive pregnancy. Measurement of lysyl hydroxylase activity in amniotic fluid enabled the prediction of a phenotypically normal heterozygous infant in a family at risk [71].

Some patients respond to treatment with ascorbic acid, which regulates collagen biosynthesis [72].

Arthrochalasia type (EDS VIIA and B; arthrochalasis multiplex congenita)

This rare autosomal dominant condition, like OI, results from mutations causing defects in type I collagen. Phenotypic overlap therefore occurs.

All or part of exon 6 of the *COL1A1* or *COL1A2* gene is deleted in types A and B, respectively, resulting in a defect in the cleavage sites of the substrate pro-α_1(I) or pro-α_2(I) chains [73–77]. Mutations appear to affect cross-link formation, decreasing tensile strength of tissues rich in type I collagen. Partially processed molecules accumulate in the dermis and other tissues, where they interfere with tissue function without much effect on fibrillar organization [73,77].

Arthrochalasis is characterized clinically by extreme joint hypermobility and multiple dislocations affecting both large and small joints [27]. Bilateral hip dislocation presents a major surgical problem. Some individuals have a short stature. There may be a chubby facial appearance due to lax facial tissues, and a depressed nasal bridge [77].

Dermatosparaxis type (EDS VIIC)

This very rare autosomal recessive form is characterized by extreme skin fragility (Fig. 46.25), bruising, droopy skin, joint laxity, umbilical hernia and blue sclerae [78–81]. The condition is akin to dermatosparaxis, a disorder causing fragile skin in animals [82,83]. It is caused by homozygous mutations in the gene encoding procollagen I *N*-terminal peptidase (*ADAMTS2*); the enzyme that excises the *N*-propeptide of type I and II procollagens [84]. Collagen fibrils from affected children and animals are small, with a bizarre hieroglyphic-like appearance in cross-section; they are ribbon-like in longitudinal section [5].

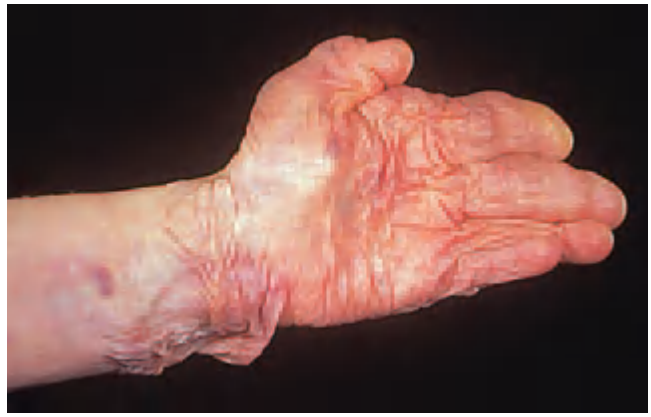

Fig. 46.25 Extreme cutaneous fragility and laxity in dermatosparaxis.

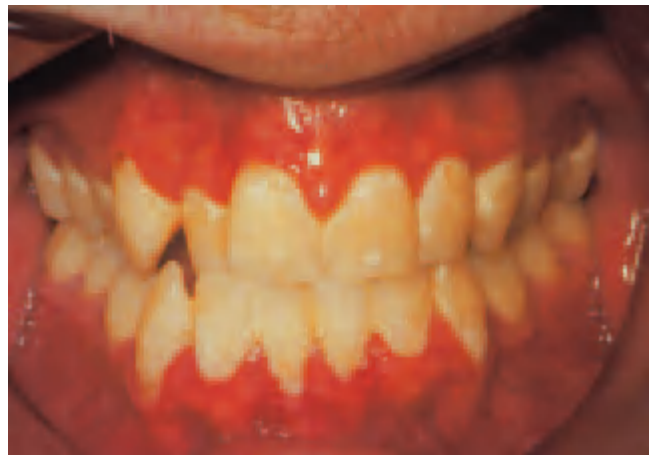

Fig. 46.26 Premature periodontal recession in periodontitis type Ehlers–Danlos syndrome (VIII).

Periodontitis type (EDS VIII)

This type has features similar to classical EDS but there is often only moderate small-joint hypermobility. The distinguishing clinical features are premature periodontal recession (Fig. 46.26), resulting in loss of teeth by the third decade, and heavily pigmented, pretibial plaques (Fig. 46.27) [85,86]. It is inherited as an autosomal dominant. Little is known about the biochemical defect,

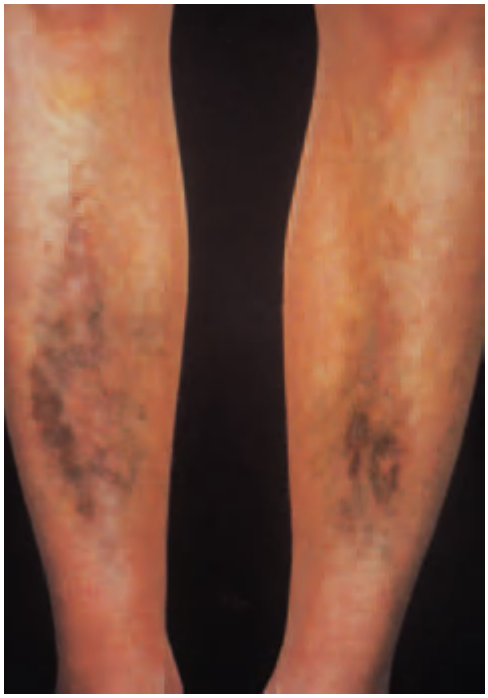

Fig. 46.27 Pigmented pretibial plaques in periodontitis type Ehlers–Danlos syndrome (VIII).

although there is a reduced proportion of type III collagen in skin [87]. Some patients have small collagen fibrils [86].

EDS IX (occipital horn syndrome)

This is an X-linked recessive disorder allelic to Menkes' syndrome and is no longer considered a variant of EDS [3]. It was formely known as X-linked cutis laxa or 'occipital horn syndrome' and has been reclassified as a disorder of copper transport (p. 46.40).

Fibronectin-deficient type (EDS X)

Only one family has been identified to date with this autosomal recessive disorder. Skin and joint changes are mild, but bruising occurs readily due to defective platelet aggregation [7]. This defect is reversed *in vitro* by adding purified fibronectin to the assay. Some patients have composite fibrils in the dermal collagen, possibly due to a defect in fibronectin interactions [88].

Progeroid EDS

A rare association of EDS with progeroid facies, short stature, osteopenia and mental retardation is recognized [89]. Patients lack the full phenotype of progeria (p. 46.59) and do not fit in to the more well-defined progeroid syndromes. Galactosyltransferase I activity is reduced in patients' fibroblasts due to mutations in the *XGPT1* gene [90]. This enzyme is involved in the synthesis of glycosaminoglycans, suggesting that they may be involved in the process of senescence. The phenotype of decorin/biglycan double knock-out mice is similar to human progeroid EDS and occurs as the result of impaired binding of glycosaminoglycans to decorin and biglycan [25].

Tenascin-X-deficient type EDS

Tenascin-X deficiency causes a recently identified, clinically distinct, autosomal recessive form of EDS [91]. Patients have hyperextensible skin, bruising and joint laxity, but no scarring. The gene for tenascin-X overlaps the steroid 21-hydroxylase gene, and it was originally identified as a candidate gene for EDS in a patient with a contiguous-gene deletion giving rise to both 21-hydroxylase deficiency and EDS [92]. Tenascin-X is the first EDS gene that does not encode a fibrillar collagen or collagen-modifying enzyme. It is a large extracellular matrix protein that appears to be an essential regulator of collagen deposition by dermal fibroblasts [93].

Associated syndromes

Various unclassified forms of EDS overlap with other disorders, such as OI, PXE, MFS [94], renal tubular acidosis and medullary sponge kidney [95], and osteolysis of the terminal phalanges.

Diagnosis

The diagnosis is mainly clinical; a scoring system may be helpful in doubtful cases [96]. Confirmation of the subtype can require a combination of electron microscopy of dermal collagens, protein chemistry analysis from cultured fibroblasts and mutation detection. Immunofluorescent staining of fibroblasts for retained type III collagen may be a faster and cheaper method for the diagnosis of the important type IV EDS [97]. Similarly, the finding of reduced type III procollagen aminopropeptide in the serum of some, but not all, patients with EDS IV may help diagnosis [98]. Chorionic villus sampling may enable prenatal diagnosis of abnormalities of type I (and II) collagen [99]. Measurement of the ratio of urinary lysyl and hydroxylysyl pyridinolines is a non-invasive reliable diagnostic test for kyphoscoliosis type EDS [69].

EDS should be distinguished from cutis laxa, in which the skin hangs in flaccid redundant folds. In EDS, redundant skin folds may develop in late adult life, but they are usually limited to the elbows and the skin around the eyes. Hyperelastic skin is a feature of Turner's syndrome (Chapter 12), but the dwarfism, cubitus valgus and webbed neck are distinctive. Hyperelastic skin with abnormal elastic fibres in the papillary dermis has been reported in the rare cartilage–hair hypoplasia syndrome [100].

Treatment

All patients should receive genetic counselling. Treatment is highly unsatisfactory, although some features of EDS VI may respond to oral ascorbic acid [71]. Patients with type IV EDS should be advised to avoid pregnancy and trauma, including physical contact sports, and to avoid activities, such as trumpet playing, which raise intracranial pressure by the Valsalva effect. Bleeding should be managed conservatively if at all possible. The fragility of blood vessels makes arteriography and surgical procedures dangerous and difficult. Surgeons must be made aware of the patient's diagnosis prior to surgery. Sutures should be buttressed, and tension avoided. Although re-excision of ugly scars can give a good cosmetic result it is not generally recommended [101].

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Occipital horn syndrome

SYN. X-LINKED CUTIS LAXA; EHLERS–DANLOS SYNDROME TYPE IX

In this rare X-linked recessive disorder, affected males have a defect in distribution of intracellular copper to copper-dependent enzymes, as in Menkes' syndrome [1]. Lysyl oxidase is a major copper-dependent enzyme, and its activity is markedly decreased in some patients [2], resulting in defective collagen cross-links. Serum copper and caeruloplasmin levels are low [1]. The disorder, like Menkes' syndrome, is caused by mutations in the gene (*ATP7A*) encoding for Cu^{2+}-transporting adenosine triphosphatase (ATPase) α-polypeptide [3,4].

Clinical manifestations include the development of bladder diverticula during childhood, inguinal herniae, mild laxity of skin and skeletal defects such as short humeri and clavicles. Bony occipital horns appear during adolescence [2]. Other features include mild chronic diarrhoea and orthostatic hypotension.

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Prolidase deficiency

Definition. Prolidase (peptidase D) is involved in the latter stages of degradation of endogenous and dietary proteins and is particularly important in collagen catabolism. Deficiency of prolidase is a rare inborn error of collagen metabolism, associated with chronic skin ulceration and mental retardation.

Aetiology. The deficiency is inherited as an autosomal recessive [1,2]. Mutations in the prolidase gene (*PEPD*) result in loss of prolidase activity [3]. Some siblings of patients have the enzyme deficiency without clinical manifestations [4].

Pathology. Light and electron microscopy of cultured fibroblasts from affected patients suggest necrosis-like cell death with abnormal morphology and increased cytosolic vacuolization, and abnormal plasma membranes and mitochondria [3]. Large amounts of imidodipeptides are excreted in the urine [5,6], and the proline/hydroxyproline ratio in collagen is increased.

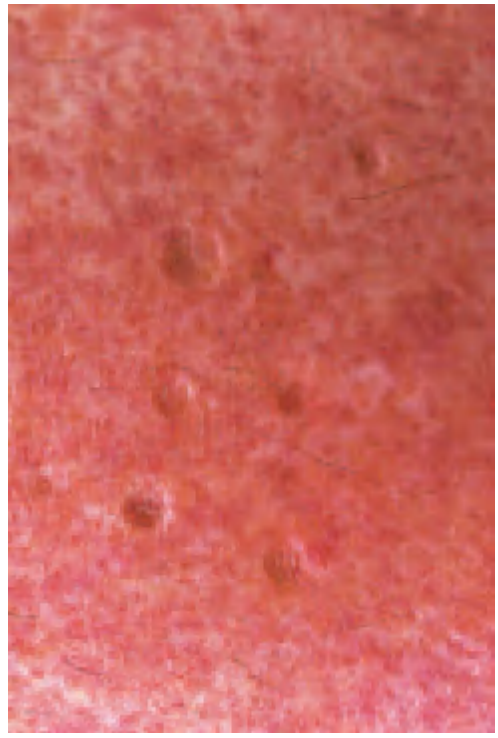

Fig. 46.28 Pitted skin in prolidase deficiency. (Courtesy of Dr D.A. Burns, Leicester Royal Infirmary, Leicester, UK.)

Abnormal laboratory findings include mild anaemia, thrombocytopenia and hypergammaglobulinaemia.

Clinical features [7]. Most patients are mentally defective, with an abnormal facies, but there is no characteristic or consistent pattern. Skin changes occur in about 85% of cases. The skin may feel spongy, with pitting and scarring, especially on the legs (Fig. 46.28). The skin is fragile and leg ulcers are common. Occasionally, there may be photosensitivity, telangiectasia, purpura, premature greying and lymphoedema.

Splenomegaly, recurrent infections and obesity or a protuberant abdomen occur in about 30% of cases.

Diagnosis. This is confirmed by the finding of massive imidodipeptiduria with prolidase deficiency in the red cells, white cells or cultured fibroblasts. Mutations can be detected in the gene encoding for prolidase [3].

Treatment. Topical proline has been successfully applied to the leg ulcers [8]. Oral proline administration produces no clinical improvement. Enzyme replacement by transfusion of prolidase-containing red cells is a possibility, perhaps using manganese activation of the enzyme before transfusion [9]. Pulsed corticosteroids may help [10]. Apheresis exchange has improved skin ulceration in two patients [11].

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Osteogenesis imperfecta

Definition. This term is applied to a heterogeneous group of heritable disorders characterized by osteoporosis with fractures, due predominantly to type I collagen abnormalities. Patients may also have blue sclerae (Fig. 46.29), deafness, skeletal deformity, abnormal dentine formation (dentinogenesis imperfecta), mild joint hypermobility, hernias, mitral valve prolapse, arterial fragility and thin, fragile skin [1,2].

Aetiology. Approximately 80–90% of patients with OI, who fit into types I–IV, have mutations in one of the type I collagen genes (*COL1A1*, *COL1A2*) [3]. The aetiology of the remainder is unclear. A variety of mutations are seen but very few families share the same mutation. Furthermore, considerable intrafamilial variation of phenotype occurs in type IA [4].

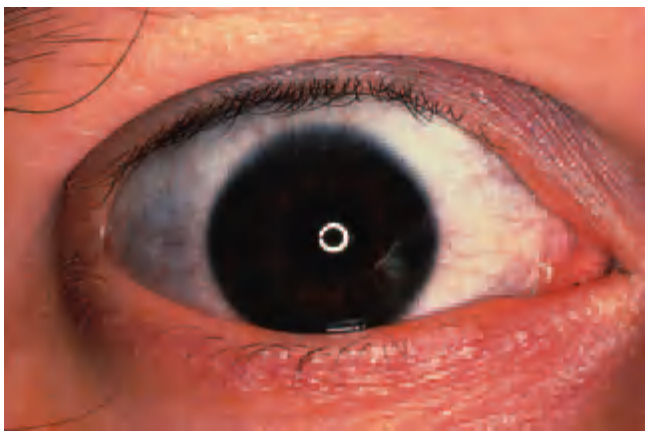

Fig. 46.29 Blue sclera in osteogenesis imperfecta.

Pathology [5]. The bones are markedly collagen deficient, and often have a distorted architecture. The dermis is thin, with a relative increase of argyrophil and elastic fibres, and a deficiency of adult collagen [6].

Clinical features [1,2,5]. The following broad groups exist, although some patients are difficult to classify.

Type IA: Classic form. This is the commonest form. It is inherited as an autosomal dominant, although sporadic cases also occur [7]. Fractures are common in childhood. The sclerae are blue or grey, and easy bruising and early onset deafness are common, but skeletal deformity is absent or mild. Joint laxity is common. The incidence of mitral valve prolapse is increased, and the aortic valves are thin and occasionally incompetent [8–10]. A few patients (type IB) have dentinogenesis imperfecta, but this is more common in the type IV group. Most patients have increased skin collagen, with an increased ratio of type I/type III [6]. Other patients have an abnormal α_2 chain, which is unduly susceptible to proteolysis by pepsin [11].

Type II: Lethal perinatal form. This is the rarest form. There are multiple fractures *in utero* and infants rarely survive for more than a few days after birth [12]. Avulsion of the limbs may occur during delivery due to a generalized connective tissue fragility. Radiography shows beaded ribs, crumpled femora and little skull calcification.

This form has been subdivided on the basis of rib and limb bone abnormalities [6,13]. Inheritance is usually autosomal dominant. Multiple recurrence of gonadal mosaicism can mimic autosomal recessive inheritance [14].

Type III: Progressively deforming form. In this condition, there are fractures *in utero* or at birth, and the long bones are thin and occasionally cystic. As the child grows older, progressive scoliosis and bowing of long bones cause crippling deformities. The sclerae are blue in childhood but become normal in the adult. The inheritance is uncertain, but the disease may be genetically heterogeneous.

Some patients with this form seem unable to synthesize α_2 chains [7,15].

Type IV: Mild form with normal sclerae. This condition is similar to type I in clinical features and inheritance, but the sclerae are not blue, dentinogenesis imperfecta is frequent and deafness is rare.

Diagnosis. Patients with short extremities and a large skull may be confused with achondroplasia, but bone fragility and thin skin do not occur in achondroplasia.

Prenatal diagnosis of the more severe forms is possible, using ultrasonography from week 16 [16]. The skin of patients with OI is stiffer and less elastic than normal skin, and these differences in mechanical properties may prove useful in diagnosis and prognosis [17]

Treatment. This is essentially an orthopaedic problem, although many children die of respiratory infections [18]. Medium-term studies show clinical improvement with the use of biphosphonates [2]. Somatic cell therapy, using allogenic bone marrow and mesenchymal stromal cell transplantation have been used [19,20].

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Pachydermoperiostosis (see also Chapter 12)

SYN. PRIMARY (IDIOPATHIC) HYPERTROPHIC PULMONARY OSTEOARTHROPATHY; TOURAINE–SOLENTE–GOLÉ SYNDROME

In this rare condition [1,2], inheritance is autosomal dominant, with variable penetration. Digital clubbing is associated with cylindrical thickening of legs and forearms, hypohidrosis, seborrhoea, sebaceous gland hyperplasia and folliculitis. X-rays reveal symmetrical, irregular periosteal ossification, predominantly affecting the distal ends of long bones. Histology shows cutaneous sclerosis and hyalinosis, with perivascular infiltration by lymphoid cells in the dermis [2]. Additional clinical features include carpal and tarsal tunnel syndrome, chronic leg ulceration and calcification of the Achilles tendon [3]. Cultured dermal fibroblasts synthesize increased amounts of collagen and α_1(I) procollagen mRNA, and exhibit up-regulation of transcriptional activity of the α_1(I) procollagen gene promoter [4]. Proteoglycan synthesis is also affected [5].

When conventional treatments fail, intravenous pamidronate may help rheumatological manifestations [6].

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Relapsing polychondritis

SYN. ATROPHIC POLYCHONDRITIS; SYSTEMIC CHONDROMALACIA

Definition. In this non-infective condition, focal inflammatory destruction of cartilage is accompanied by fibroblastic regeneration. It is characterized by (i) recurrent chondritis of the pinnae; (ii) chondritis of nasal cartilage; (iii) inflamed cartilage in the larynx, trachea or respiratory tract; (iv) ocular inflammation; (v) cochlear or vestibular lesions; and (vi) non-erosive arthritis. Three or more of these features are required for the diagnosis [1].

Aetiology. Relapsing polychondritis has been recorded as rare, but recent reports suggest that it is not so uncommon but is easily overlooked. The cause is unknown, but the association with rheumatoid arthritis, lupus erythematosus, vasculitis, Behçet's disease and Hashimoto's disease suggests that autoimmune mechanisms may be concerned (see also MAGIC syndrome, p. 46.45). Other reported associations include ulcerative colitis, Crohn's disease, psoriasis, glomerulonephritis, Sjögren syndrome,

thymoma, ankylosing spondylitis, myeloproliferative disorders and following intravenous injections [2–7]. Cutaneous manifestations have been reported in a patient treated for prostatic adenocarcinoma with goserelin, a luteinizing hormone releasing analogue [8].

Relapsing polychondritis probably overlaps with Wegener's syndrome. Auricular chondritis has been described in some patients with the latter [9], and cANCA, an antibody once regarded as specific for Wegener's syndrome, has been reported in patients with relapsing polychondritis [10].

Antibodies to type II collagen have been detected in the serum in acute polychondritis, and granular deposits of IgG, IgA, IgM and C3 at fibrochondrial junctions have indicated a possible role of immune-complex deposits [11–15]. Antibody production is T-cell dependent and major histocompatibility complex (MHC) restricted; the arthritis in experimental animal models can be suppressed by synthetic type II collagen peptides [16]. The intravenous injection of papain into rabbits produces loss of cartilage rigidity, manifested by floppy ears [17], and it has been suggested that local protease activity may play some part in causing relapsing polychondritis [18]. Cartilage oligomeric matrix protein (COMP) is decreased and cartilage matrix protein (matrilin-1) increased. Both revert to normal levels during successful therapy [19].

Pathology [20]. Areas of damaged cartilage, which have lost the normal basophilic staining, are separated by areas of predominantly lymphocytic infiltration. Later, the fragments of cartilage are surrounded and replaced by abundant granulation tissue and even nascent cartilage. Occasionally there is evidence of vasculitis [21].

Clinical features [1,22–24]. The condition affects both sexes equally and usually begins between the ages of 30 and 50 years. Chondritis ultimately involves three or more sites in most patients but may be limited to one or two for long periods. The following tissues may be involved in decreasing order of frequency: auricular, joint, nasal, ocular, respiratory tract, heart valves and skin [25,26]. During the acute stage, the affected area is swollen, red and tender, and may be mistaken for cellulitis (Fig. 46.30). Sparing of the ear lobe is a useful differentiating sign. Serous otitis media can occur, and there may be loss of hearing even in the absence of chondritis [27]. Involvement of the nasal cartilage leads to obstruction and later to a saddle-nose deformity (Fig. 46.31). Cutaneous and systemic vasculitis, cerebral aneurysms, superficial thrombophlebitis and toxic erythema have been described [1,21,24,28,29].

The joint changes, usually affecting the smaller peripheral joints, may simulate rheumatoid arthritis [30]. Involvement of the larynx, trachea or bronchi produces respiratory embarrassment and recurrent infection. Permanent tracheostomy may be required [20,27]. An

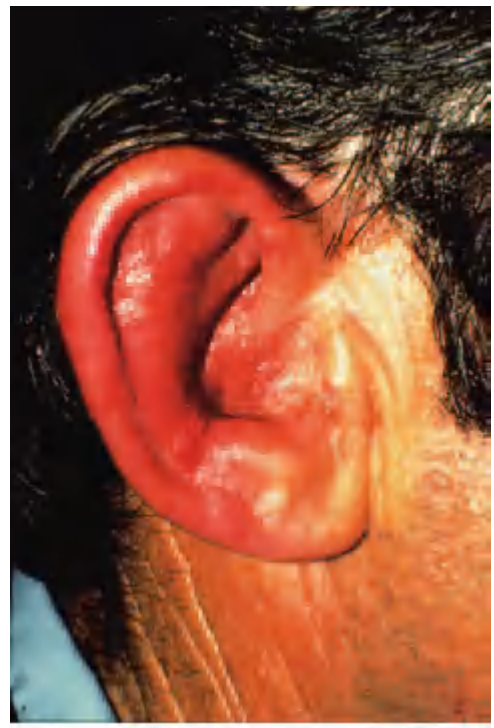

Fig. 46.30 Relapsing polychondritis, showing inflammation of the pinna.

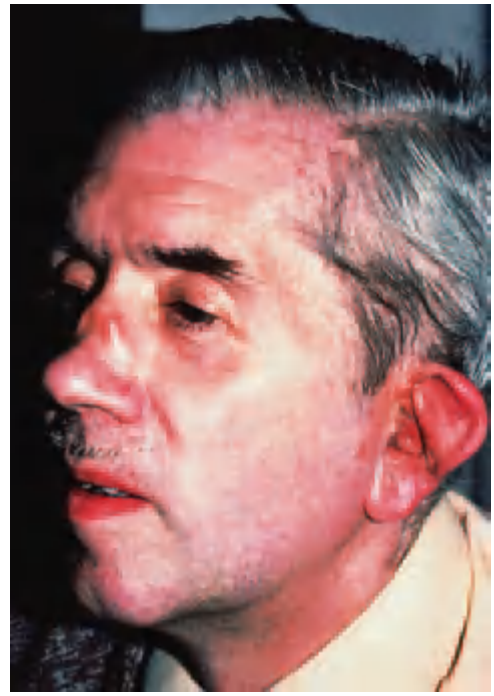

Fig. 46.31 Relapsing polychondritis: late stage, showing damage to the cartilage of the ear and nose. (Courtesy of Dr D.M. Wilkinson, Ackton Hospital, Pontefract, UK.)

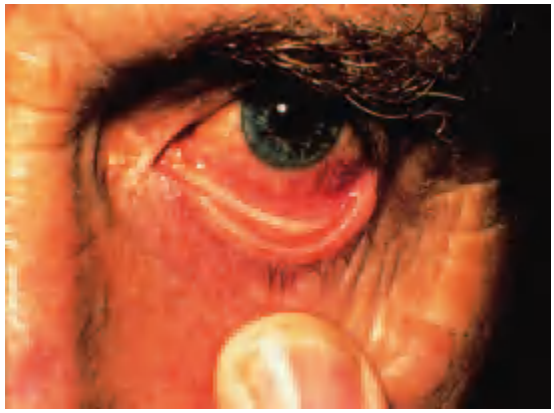

Fig. 46.32 Relapsing polychondritis, showing ocular involvement. (Courtesy of Dr N. Cox, Cumberland Royal Infirmary, Carlisle, UK.)

association with granulomatous lung disease has also been described. Ocular abnormalities are found in some cases—episcleritis, conjunctivitis and iritis (Fig. 46.32), or more rarely keratoconjunctivitis sicca or chorioretinitis. Proptosis occurs in 3% of cases [31,32]. Involvement of the heart valves may cause serious complications, including sudden valve rupture, even in a patient otherwise in remission [1,33,34].

The course of the disease is extremely variable [7]. Relapses are the rule, but they vary in frequency and severity. Some cases continue to relapse for over 20 years, but others become inactive within a short period. Pregnancy does not appear to affect the course of the disease, although complications are more frequent [35]. Deformity of the ears and nose is common, but in general the disease is a source of discomfort and disfigurement rather than a threat to life. Plasma viscosity or erythrocyte sedimentation rate is usually raised and anaemia is frequent. The rheumatoid factor and antinuclear factor are often positive. Leukocytosis is inconstant, but eosinophilia is found in 40% of cases. Lupus erythematosus cells may be present. The characteristic biochemical finding is the increased urinary excretion of acid mucopolysaccharides during each relapse.

Radiological abnormalities are not pathognomonic, but evidence of extensive destruction of joint cartilage without changes in adjacent bone is suggestive. In some cases, the changes are indistinguishable from rheumatoid arthritis.

Diagnosis. Polychondritis may present to the dermatologist as 'chronic otitis externa with cellulitis of the pinna'. The diagnosis is established by biopsy, or by other associated changes, and by the examination of urine for acid mucopolysaccharides. Wegener's granulomatosis and lethal midline granuloma can produce a similar histology, but in these two conditions the involvement is more purely destructive.

Treatment. The progression of the acute relapse can be controlled with corticosteroids. An initial daily dose of 30 mg prednisone can be gradually reduced and finally discontinued as remission develops. Remissions may also be induced with indometacin or dapsone [13]. Colchicine is also helpful in some patients [36]. Immunosuppressive agents such as methotrexate and ciclosporin [15] may have a role. Pulsed intravenous cyclophosphamide has been used for renal disease [37]. Remission has followed autologous stem cell transplantation [38].

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MAGIC syndrome

At least 13 patients have been described with features of both relapsing polychondritis and Behçet's syndrome [1]. The term MAGIC syndrome (*m*outh *a*nd *g*enital ulcers with *i*nflamed *c*artilage) has been used for this overlap syndrome. The underlying immunological defects are still unclear, but circulating immune complexes and autoantibodies to elastic tissue have been suggested as possible factors [1,2].

Aortic valve disease has been associated with the syndrome [3], and features of the MAGIC syndrome have been described in an HIV-positive individual [4].

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Fibromatoses

Fibrous overgrowth of dermal and subcutaneous connective tissue occurs most readily in certain sites and at certain ages, and some of the resulting syndromes are clinically and histologically distinctive and well defined. There are some cases, however, that defy precise classification, and others in which histological criteria may be a poor guide to prognosis. Invasiveness and a high local recurrence rate may or may not be associated with a tendency to metastasize. The borderline between simple overgrowth and a benign tumour may be equally difficult to define.

Fibromatosis is a benign fibrous tissue proliferation, which is intermediate between benign fibroma and metastasizing fibrosarcoma. The lesions of fibromatosis tend to infiltrate and recur when removed, but they do not metastasize. The term should not be applied to reactive fibrous proliferation, or to keloid, which is usually secondary to injury. The lesions in fibromatosis may be single or multiple, and the likelihood of recurrence after surgical removal varies with the location of the lesion and the age of the patient. The fibromatoses occur in two major groups.

1 Superficial fibromatoses (fascial fibromatoses):
(a) palmar (Dupuytren's);
(b) plantar;
(c) penile (Peyronie's);
(d) knuckle pads.

2 Deep fibromatoses (non-metastasizing fibrosarcoma). These are rapidly growing tumours that usually involve the musculature or aponeuroses. Their tendon-like consistency accounts for their alternative name of desmoid tumours.

These conditions are discussed in more detail elsewhere (Chapter 53).

Palmar fibromatosis

SYN. DUPUYTREN'S CONTRACTURE

Definition. This is a fibromatous hyperplasia of the palmar aponeurosis, which is characterized by nodular thickening of the fascia with associated flexion contractures of one or more digits (Fig. 46.33).

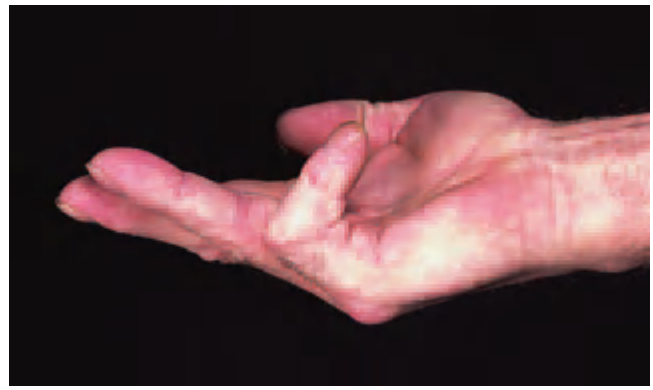

Fig. 46.33 Palmar fibromatosis (Dupuytren's contracture). (Courtesy of Dr D.A. Burns, Leicester Royal Infirmary, Leicester, UK.)

Aetiology. The condition seems to be due to a reactive proliferation of fibroblasts with no inflammatory component, and the basic cause is obscure. Free radical production secondary to ischaemia may be involved, and the concentration of hypoxanthine substrate capable of releasing free radicals is greatly increased in the affected tissue [1]. Localized ischaemia has been thought to play a part, and in animal studies allopurinol (a competitive inhibitor of xanthine oxidase) has been shown to limit the damage associated with acute ischaemia [2]. High concentrations of free radicals are toxic, but in low concentration they stimulate fibroblast proliferation [1]. The contractures, which are a late complication, appear to follow the conversion of the fibroblasts to contractile myofibroblasts [3].

Palmar fibromatosis is often familial, and may be inherited as an autosomal dominant trait [4].

Some families are described in which there is a predominantly female expression [5]. The prevalence in the general adult population is around 2–6% [6], but it may approach 20% or more in elderly males [7–9], in diabetic patients and in patients with acquired immune deficiency syndrome (AIDS). It is relatively rare in black and oriental races.

Associated disorders. The condition occurs more commonly in patients with alcoholic cirrhosis, epilepsy [10] and diabetes mellitus [9,11], but the prevalence is decreased in rheumatoid arthritis [12].

Palmar fibromatosis is also associated in about 5% of patients with other fibrosing conditions, such as knuckle pads, Peyronie's disease, keloid scarring or plantar fibromatosis [13], and this has been termed the *polyfibromatosis syndrome*. Other conditions which have been less convincingly claimed to be associated with Dupuytren's contracture include periarthritis of the shoulder, chronic lung disease, gout, trauma and ulnar nerve damage [14]. Phenytoin appears to stimulate fibrosis in the polyfibromatosis syndrome [15] and it may also cause gingival hypertrophy by stimulating fibroblasts and increasing collagen production [10,16].

There is one case report of a girl aged 14 years who developed Dupuytren's contracture while receiving growth hormone therapy for hypopituitarism [17].

Pathology [18]. Fibroblasts in Dupuytren's contractures are identical to those in normal palmar fascia. However, there are more of them in Dupuytren's contractures and they tend to be clustered around narrowed microvessels [19]. In the early stages, there are nodules in the subcutaneous tissue, or within the fascia, composed of proliferating fibroblasts with irregular hyperchromatic nuclei, but with no excess of collagen. Later stages are characterized by the presence of myofibroblasts which have a fibrillary ultrastructure in the cytoplasm and seem to have some other properties of smooth muscle. The nuclei are deeply indented, and these constrictions may be related to the contractile properties of the cell. The cell also has surface membrane differentiations which provide attachment to neighbouring cells and stroma. Myofibroblasts have also been identified in the normal aorta and in granulation tissue, hypertrophic scars, keloids, liver fibrosis,dermatofibroma, etc. [3], in which their contractile properties may be important. The advanced stages of Dupuytren's contracture are characterized by dense, fibrous connective tissue with a few elongated cells. An increased concentration of type III collagen is present in the nodules [20].

Clinical features. The age of onset is generally between 30 and 50 years, and the disease is less common and progresses more slowly in women [14]. The earliest sign is the development of a palmar nodule, usually in the ulnar half of the hand. There are usually no symptoms, but there may be a dull ache or tingling. Insidious progression of the fibrosis over several years causes flexion contractures of the affected fingers. There is often puckering of the overlying skin. Eventually, the function of the hand becomes impaired due to fixed flexion of one or more digits. If left untreated, there may be some improvement after many years.

Diagnosis. There are few diagnostic difficulties. There may be a histological resemblance to fibrosarcoma, but this is more pleomorphic, with larger nuclei and more mitoses. Juvenile aponeurotic fibroma may produce palmar or plantar nodules, but Dupuytren's contracture does not occur in young children.

Treatment. The advice of an orthopaedic or plastic surgeon should be sought. Complete removal of the palmar aponeurosis is generally recommended [21].

A recent study recommends subtotal fasciectomy and direct closure [22]. Some preliminary results suggest that allopurinol may be helpful, by decreasing free-radical production [23], and it has been suggested that vitamin C might prevent progression of the disease by acting as a free-radical scavenger [7]. Many other non-surgical approaches have been tried, including continuous slow skeletal traction, radiotherapy, dimethyl sulfoxide, vitamin E, steroid injections and interferon, although none has been proven to be clinically useful [24]. However, placebo-contolled trials of collagenase injections look very promising [25].

Another suggestion, which has yet to be tested clinically, is the use of immunosuppressive therapy as an adjunct to surgery, on the grounds that the presence of CD3 lymphocytes and the expression of MHC class II proteins in the affected tissue imply that Dupuytren's disease is a T-cell-mediated autoimmune disorder [26].

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Camptodactyly

Camptodactyly is a non-traumatic flexion deformity affecting the proximal interphalangeal joint of one or more fingers [1]. Congenital camptodactyly may be familial, associated with non-inflammatory arthropathy [2]. Additionally, other serous membranes undergo fibrosis. Clinical features include *c*onstricting pericarditis *a*nd *p*leuritis (*CAP syndrome*) [3,4]. Familial camptodactyly of later onset has been described in association with an inflammatory arthritis with erosive changes [5]. *Blau's syndrome* encompasses familial camptodactyly, granulomatous arthritis, uveitis and an erythematous eruption [6]. In one family, taurinuria was associated [7]. Sporadic cases of camptodactyly have been linked with accelerated growth and osseous maturation, unusual facial appearance (including large ears, small mouth, broad forehead and hypertelorism), a hoarse, low-pitched cry and hypertonia (*Weaver's syndrome*) [8]. Other associated features include pectus excavatum and scoliosis. The underlying biochemical abnormality is unknown, although there may be a primary deficit in synthesis or deposition of type VI collagen in synovium. Treatment, if required, is surgical [1,9].

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Streblodactyly

Streblodactyly [1] is inherited as a sex-limited autosomal dominant character. The affected females show from birth a flexion deformity at the metacarpophalangeal joints of the thumbs and the proximal interphalangeal joints of the little fingers. Some fingers show swan-neck deformities and hyperextensible metacarpophalangeal joints. In one family there was an abnormal α-amino acid in the urine.

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Plantar fibromatosis [1,2]

SYN. LEDDERHOSE'S DISEASE

This is a much rarer condition than palmar fibromatosis. The lesions, which occur most often on the medial half of the mid-foot, present as one or more nodules, which may

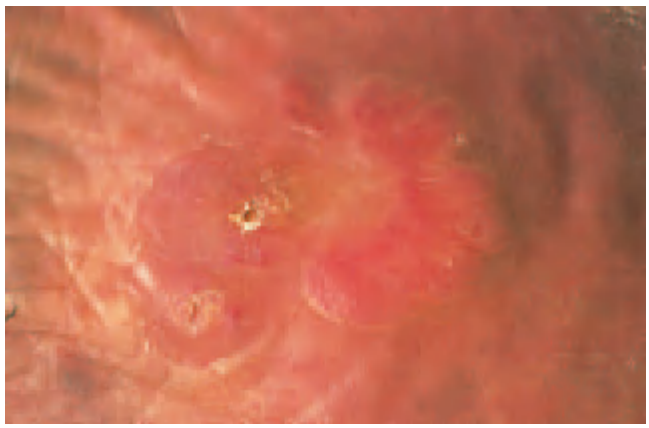

Fig. 46.34 Plantar fibromatosis. (Courtesy of Dr J. Ellis, Princess Margaret Hospital, Swindon, UK.)

become painful and may ulcerate (Fig. 46.34). They rarely produce contractures, but they tend to be locally invasive and to recur. Total excision of the lesion and the entire plantar fascia seems to give the best results, with the lowest incidence of recurrence. The differential diagnosis includes keloid and fibrosarcoma, and in younger patients aggressive infantile fibromatosis and aponeurotic fibroma must also be considered [3]. Similar nodules have been described symmetrically affecting the anteromedial heel pads in children. They are asymptomatic and may resolve spontaneously [4,5]. Surgery is contraindicated.

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Penile fibromatosis

SYN. PEYRONIE'S DISEASE; PLASTIC INDURATION OF THE PENIS; FIBROUS SCLEROSIS OF THE PENIS

Definition. Penile fibromatosis is characterized by one or more irregular dense fibrous plaques in the penile shaft.

Aetiology. Penile fibromatosis may occur as an isolated abnormality, or as one component of polyfibromatosis in association with palmoplantar fibromatosis, keloids and knuckle pads. Atheroma predisposes to the condition, and it is now thought that the association with the use of β-adrenoreceptor blocking drugs is probably attributable to concomitant atheroma [1,2]. There may be a genetic factor, but reliable studies of the mode of inheritance are lacking. The condition is rare below the age of 20 years, and the highest incidence is between 40 and 60 years. It is much less common than palmar or plantar fibromatosis.

Pathology [3]. The thickened plaque shows cellular fibroblastic proliferation surrounded by dense masses of collagen. Calcification and ossification may occur. The process appears to begin as a vasculitis in the areolar connective tissue beneath the tunica albuginea, whence it extends to adjacent structures.

Clinical features. The disease presents with painful erections and curvature of the erect penis due to a thickened subcutaneous plaque, rubbery or hard, usually on the dorsal aspect of the penis in its distal third. The erectile deformity may make vaginal penetration impossible, and pain or anxiety about performance may cause secondary impotence. Fibrosis of the underlying cavernous erectile tissue may lead to a constriction or 'waisting' of the penile shaft, leading to flaccidity of the distal portion.

The course is unpredictable [4]. The pain generally subsides within a few months, but the fibrous plaque may resolve, remain unchanged or progress [5].

The severity of the disease and the response to treatment can now be evaluated by high-resolution ultrasonography [6], computed tomography [7] or magnetic resonance imaging of the erect penis [8]. If necessary, an erection can be induced by the intracavernosal injection of papaverine [9].

Treatment. Many treatments have been tried, but there is little evidence that vitamin E, potassium aminobenzoate, orgotein, radiotherapy, ultrasonic therapy or intralesional steroids affect the long-term outcome, although they may relieve the pain [4]. Clostridial collagenase injections have given promising results [10]. Surgery is probably the treatment of choice, using Nisbet's operation, in which ellipses of normal tunica albuginea are excised from the side of the shaft, opposite the point of maximum curvature. A semi-rigid penile prosthesis may also be inserted.

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Knuckle pads [1–4]

SYN. HOLODERMA

Definition. Knuckle pads are circumscribed thickenings overlying the finger joints. The term is a misnomer as most lesions occur over the proximal interphalangeal rather than the metacarpophalangeal joints (knuckles).

Aetiology. The condition is usually sporadic but several pedigrees have shown an autosomal dominant inheritance. The age of onset and the distribution of the lesions tend to be more or less constant in each family, but show interfamily variation. The condition is not rare but the true prevalence is uncertain, as most patients ignore the lesions. Knuckle pads are thought to be idiopathic in children, although they occur at sites prone to picking, chewing or 'knuckle cracking' [4].

Pathology [1]. The epidermis is grossly hyperkeratotic and acanthotic. The dermal connective tissue is hyperplastic and individual collagen fibres may be obviously thickened. Histologically, the changes resemble those of palmar fibromatosis.

Clinical features [2,3]. Flat or convex, smooth, circumscribed keratoses develop slowly and almost imperceptibly over the course of months or years. In some patients they become very much raised and obviously indurated, but in others the dermal component is not clinically apparent. They are most commonly seen over the dorsa of the proximal interphalangeal joints, but occasionally develop over the knuckles or the distal interphalangeal joints. Any single site or combination of sites may be involved. Sites other than the hands are not often affected, but similar lesions on the knees were also present in one family [2].

The age of onset is variable but it is more common after the fourth decade. In some individuals, the lesions may not be conspicuous until they have been present for some years.

An association between Dupuytren's contracture and other fibromatous lesions has been recorded in some families. In one large family, knuckle pads were associated with sensorineural deafness and with leukonychia [5]. Two affected individuals also had palmoplantar keratoderma.

Another family has been described with knuckle pads in association with oesophageal cancer, hyperkeratosis and oral leukoplakia [6].

In differential diagnosis, occupational callosities, Heberden's nodes of osteoarthritis, pachydermodactyly, granuloma annulare, erythema elevatum diutinum and rheumatoid nodules must be excluded.

Treatment. There is no satisfactory treatment. Excision may be followed by keloidal scarring.

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Pachydermodactyly [1–7]

This is a benign fibromatosis of the fingers that usually affects young adult males (Fig. 46.35). It produces a symmetrical diffuse swelling of the skin around the dorsal aspect and sides of the proximal phalanges of the index, ring and middle fingers. Pachydermodactyly has been recently reported in women [4,5] and two young girls, one of whom had tuberous sclerosis and the other EDS [6]. It may be associated with bilateral carpal tunnel syndrome [2] and varioliform atrophy [8]. A distal variant has been described in an elderly woman, who also presented with nodules over the extensor aspects of the elbows [9]. Affected families have been reported [10].

It has been suggested that repeated rubbing of the fingers or mechanical injury to the joints may contribute to the condition [3,6], but pachydermodactyly must be distinguished from occupational callosities, obsessive 'chewing pads' and true knuckle pads [11,12].

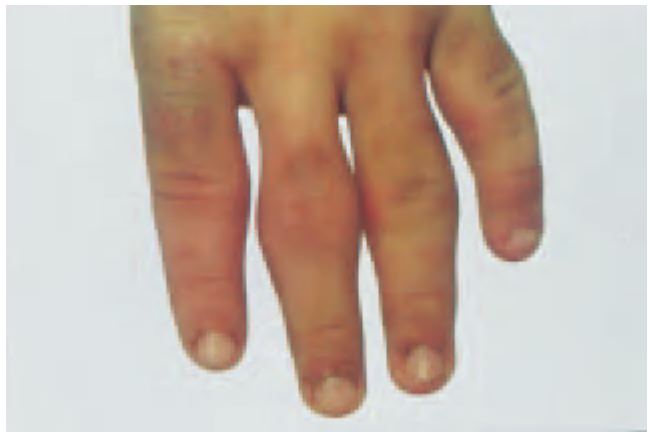

Fig. 46.35 Pachydermodactyly. (Courtesy of Dr A. Chamberlain, Churchill Hospital, Oxford, UK.)

Histology of the dermis shows marked thickening, with extension of collagenous fibres into the subcutaneous tissue. Types III and V collagen are increased, and electron microscopy shows increased numbers of fine-diameter collagen fibres.

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Juvenile fibromatoses

The term juvenile fibromatosis has been applied to a group of disorders occurring in infants and children, and characterized by proliferative activity of the fibroblasts [1–6]. There is a tendency to local recurrence but, unlike fibrosarcomas, they do not metastasize. The group includes a number of well-defined clinical entities that affect the skin:

1 infantile myofibromatosis;
2 fibrous hamartoma of infancy;
3 juvenile hyaline fibromatosis;
4 infantile digital fibromatosis;
5 calcifying aponeurotic fibroma;
6 giant cell fibroblastoma.

These conditions are described in Chapter 53.

Juvenile hyaline fibromatosis

SYN. SYSTEMIC HYALINOSIS; PURETIC SYNDROME

Definition. This is a disorder of glycosaminoglycan synthesis, which is characterized clinically by skin papules or tumours, gingival enlargement, osteolytic lesions and joint contractures, and histologically by deposition of amorphous hyaline material.

Aetiology. The cause is unknown, but increased chondroitin synthesis has been demonstrated in skin fibroblasts cultured from the tumour tissue [1]. The disease is very rare and occurs sporadically, but it has occurred in siblings.

Pathology [1–4]. The skin lesions contain 'chondroid' cells embedded in amorphous eosinophilic ground substance in the dermis. In the early lesions, this consists of glycosaminoglycans, but in the later lesions the matrix is mainly composed of chondroitin sulphate [5]. The dermal collagen is decreased and the collagen fibrils are fewer and thinner than in normal skin. The hyaline material may also be present in the muscles and bones. Absence of pro-α_2 chains and type III collagen has been demonstrated in affected skin [6].

Clinical features [4,7–10]. Skin lesions are present at birth or develop in early childhood. There may be small, pearly papules or nodules, particularly on the face or neck. Large subcutaneous tumours may also occur, particularly on the scalp. These may be hard or soft, fixed or mobile, and they may ulcerate. Gingival hypertrophy is commonly present, and flexion contractures of the fingers, elbows, hips and knees may develop. Osteolytic lesions can occur in the skull, long bones or phalanges. The musculature is poorly developed. The condition persists into adult life and the joint contractures are disabling. Infantile systemic hyalinosis is probably an extreme variant, leading to death in infancy.

Treatment. This is unsatisfactory. The tumours do not respond to radiotherapy, and they may recur after excision [11]. Joint contractures may respond to intralesional steroid injections in the early stages and they may also respond to systemic steroids and physiotherapy.

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Other benign fibrous cutaneous nodules

Nodular fasciitis

See Chapter 53. In this condition, there is fibroblastic proliferation of one or more nodules, usually on the limbs or trunk.

Collagenoma

Multiple fibrous dermal nodules with coarse, collagen fibres may develop as sporadic cases (*eruptive collagenoma*) or as a genetic disorder with a dominant inheritance (*familial cutaneous collagenoma*) (Chapter 15).

Collagen naevi

See Chapter 15.

Albopapuloid form of epidermolysis bullosa

SYN. PASINI'S SYNDROME

This rare form of epidermolysis bullosa is characterized by the development of ivory-white papules on the trunk, which histologically show connective tissue hyperplasia. Epidermolysis bullosa is discussed in Chapter 40.

Buschke–Ollendorf syndrome

Extensive nodular fibrosis may occur in the Buschke–Ollendorf syndrome (Chapter 15), in association with juvenile elastoma and osteopoikilosis.

Fibrous digital nodules

In addition to giant cell synovioma and infantile digital fibromatosis, fibrous nodules in the digits may be due to acquired digital fibrokeratoma, fibrous papule of the finger, dermatofibroma (Chapter 53) or the Koenen tumour (Chapter 12).

Infantile stiff-skin syndromes

Several rare syndromes have been described in which hard, stiff skin and joint contractures develop in early life. The relationship between these conditions is uncertain at present.

Systemic hyalinosis

In infantile systemic hyalinosis the skin becomes diffusely thickened and hard in the first few weeks of life, with limited joint mobility. Other characteristic features include small nodular thickenings of the perianal region, ears or lips, and gingival hypertrophy. There may also be hyperpigmentation, joint contractures, osteopenia, diarrhoea, frequent severe infections and growth failure. The prognosis is poor, and survival beyond the age of 2 years is unlikely [1].

The tissues show widespread deposits of hyaline material with the general staining properties of collagen.

Clinically, this syndrome appears distinct from juvenile hyaline fibromatosis (see p. 46.50), but it is possible that it represents a more severe form of the same condition, as some cases have been described with features of both conditions [2,3].

Winchester's syndrome

Diffusely stiff skin may also occur in Winchester's syndrome [4–6]. This is a rare autosomal recessive disease of infancy characterized by joint contractures, gingival hypertrophy, dwarfism, destructive small-joint arthritis and corneal opacities. In this condition, however, the prognosis is relatively good, and many patients survive into adult life.

Previously, similar cases have been described as *hereditary contractures with sclerodermatoid changes of skin* and *stiff-skin syndrome* [7], with increased mucopolysaccharides in the skin.

The skin changes resemble those of scleroedema of Buschke but are distinguished by their early onset. The condition must also be distinguished from sclerema neonatorum, but this is a disorder of subcutaneous fat rather than the skin.

Congenital fascial dystrophy

SYN. STIFF-SKIN SYNDROME

This hereditary connective tissue disorder is characterized by mild hirsutism, limitation of joint mobility affecting gait and localized areas of stony-hard skin, which are otherwise normal in appearance [8]. It appears in early infancy, and is only slowly progressive. The condition affects the deeper skin and fascia, which is much thicker than normal, and tends to be most pronounced on the buttocks and legs, with a sharp demarcation of subcutaneous sclerosis at the inguinal canal. Unlike morphoea, no inflammatory changes are seen on histology. Electron microscopy of the skin shows large collagen fibres, and bundles of aggregated microfibrils [8]. Thickening of the thoracic fascia may cause hypoventilation due to thoracic underdevelopment, but there are no other systemic features of this disease.

The condition appears to be analogous to the tight-skin mouse [9].

Infantile restrictive dermopathy

This is a very rare autosomal recessive disorder, which is probably due to a primary defect in collagen metabolism

[10,11]. It presents at birth with a taut, shiny skin, which restricts movement of the joints. The birth is premature due to ruptured fetal membranes, and the facies is characteristic, with a small, fixed, round, open mouth, micrognathia, small nose, low-set ears and widely spaced cranial sutures. The joints are all fixed in flexion, and gross restriction of the respiratory movements causes death within hours, or at most weeks. The epidermis shows hyperkeratosis and parakeratosis, and the keratohyaline granules are abnormal. The dermal–epidermal junction is flat, with a thin dermis, and a thick layer of subcutaneous fat. The eccrine and pilosebaceous glands are underdeveloped. The collagen bundles appear stretched, and orientated in parallel lines, as they are in a tendon.

The basic defect has not been identified. Immunohistochemistry shows increased expression of 48- and 56-kDa keratins. Their significance is unclear [12].

Prenatal diagnosis would be desirable, but biopsy specimens from a 20-week-old fetus were normal on light and electron microscopy [13].

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Other causes of diffuse fibrosis

Environmental and drug-induced scleroderma
(see also Chapter 56)

A variety of environmental triggers may stimulate a localized or diffuse scleroderma-like reaction in a genetically susceptible host. Important causes are listed in Table 46.3. In most cases, the fibrotic process continues after withdrawal of the external stimulus. Sometimes, the ensuing clinical pattern resembles idiopathic forms of scleroderma (see Chapter 56).

Table 46.3 Cutaneous fibrosis due to chemical exposure.

Vinyl chloride
Silica dust
Organic solvents:
Aromatic hydrocarbons (e.g. toluene, benzene)
Aliphatic hydrocarbons:
Chlorinated (e.g. trichlorethylene, perchlorethylene)
Non-chlorinated (e.g. naphtha-*n*-hexane)
Epoxy resins
Toxic oil syndrome
Urea formaldehyde foam insulation
Breast augmentation (paraffin, silicone)
Drugs:
Reactions to local injection:
Phytomenadione, pentazocine, heparin
Reactions to systemic therapy:
Bleomycin
L-tryptophan (eosinophilia–myalgia syndrome)
Carbidopa and L-5-hydroxytryptophan
Penicillamine
Valproate sodium
Cocaine
Appetite suppressants (diethylpropion hydrochloride, amphetamine)
Diltiazem

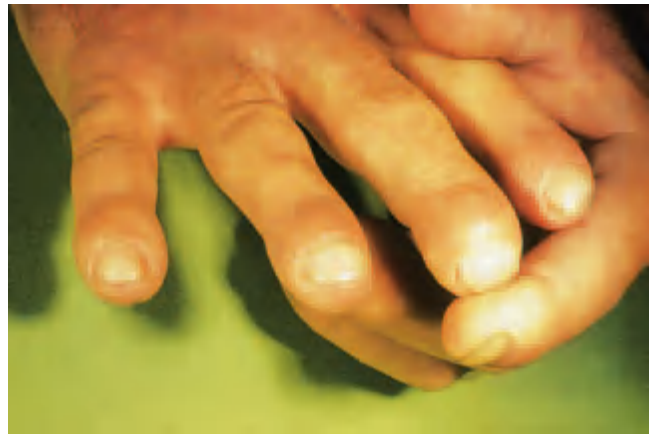

Fig. 46.36 Vinyl chloride-induced osteolysis affecting fingertips.

Exposure to *vinyl chloride monomer* occurs in workers involved in polyvinyl chloride (PVC) production. One-third of male operatives in a British factory developed a clinical syndrome that included Raynaud's phenomenon, dyspnoea, cutaneous sclerosis, pulp atrophy and radiological evidence of acro-osteolysis (Fig. 46.36) [1]. Genetic marker studies have demonstrated an increased incidence of human leukocyte antigen (HLA) -DR5 in affected individuals; severe disease is linked with B8 and DR3 [2]. A similar syndrome has been reported in gold miners

exposed to silica dust [3], and in workers exposed to organic solvents, such as trichlorethylene [4] and perchlorethylene [5], which are structurally similar to vinyl chloride. Exposure to epoxy resin results in an acute syndrome of cutaneous sclerosis, muscle weakness, arthralgia, impotence, lung and oesophageal involvement [6]. The causative agent appears to be a cyclohexylamine.

Toxic oil syndrome is a multisystem illness, reported in Spain in 1981. Acute fever, severe but transient pulmonary oedema, myalgia, and a pruritic exanthem and eosinophilia were followed after several months by widespread cutaneous sclerosis in 30% of cases [7,8]. The syndrome was probably due to ingestion of imported rapeseed oil mixed with an aniline denaturant, designed to make the oil unfit for human consumption. Toxic oil syndrome bears a striking resemblance to the *eosinophilia–myalgia syndrome* [9–11], linked with consumption of L-tryptophan; this is used as a 'food supplement' to treat insomnia and depression. The offending batches of L-tryptophan contained impurities similar to the contaminants in toxic oil [12,13].

In environmental fibrotic disorders, as in idiopathic scleroderma, subpopulations of fibroblasts appear to be activated to synthesize excess collagen; this property is perpetuated by fibroblasts *in vitro*, indicating that the elevated collagen gene expression is independent of extracellular stimuli [11]. Cytokines appear to stimulate the proliferation of these abnormal clones of fibroblasts; thus, transforming growth factor-β (TGF-β) and platelet-derived growth factor (PDGF) are elevated in the eosinophilia–myalgia syndrome [14].

Numerous drugs have been reported to induce cutaneous sclerosis. Lesions resembling morphoea may follow injections of pentazocine [15], heparin [16] and vitamin K_1 (phytomenadione) [17–19]; in the case of vitamin K_1, the trigger may be a solvent rather than vitamin K_1 itself [20]. Morphoea-like plaques have also been reported in patients taking penicillamine [21] and valproate [22].

Diffuse scleroderma-like changes have been reported following bleomycin therapy [23]. A combination of L-5-hydroxytryptophan and carbidopa induced lesions resembling eosinophilia–myalgia syndrome [24]. Phenytoin and diltiazem both induce gingival hypertrophy [25,26]. A patient on phenytoin developed florid hypertrophic retro-auricular folds [27]. Thickened skin on the feet has been reported in a patient taking diltiazem [28].

Alcohol can provoke porphyria cutanea tarda, which can produce a sclerodermatous appearance (Fig. 46.37).

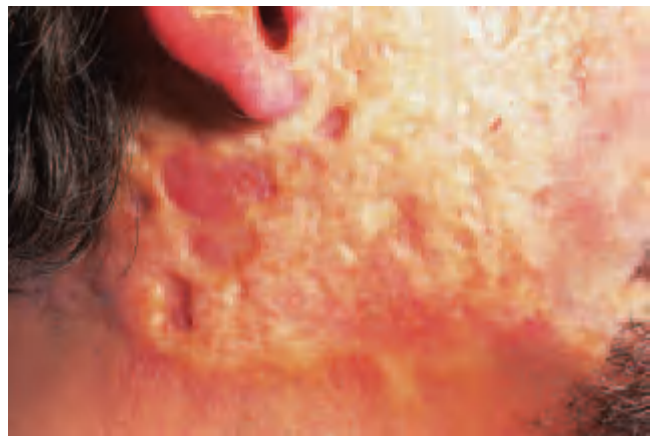

Fig. 46.37 Scleroderma and scarring of the face due to porphyria cutanea tarda. (Courtesy of Dr D.A. Burns, Leicester Royal Infirmary, Leicester, UK.)

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Nephrogenic fibrosing dermopathy

SYN. SCLEROMYXOEDEMA-LIKE ILLNESS OF RENAL DISEASE

Acute onset of skin thickening has been reported in patients with renal disease undergoing haemodialysis or renal transplant [1]. Irregular indurated plaques, with amoeba-like projections and islands of sparing, occur chiefly on the lower trunk and legs. Dermal mucin is detected with Alcian-blue staining and increased collagen is laid down in haphazard bundles; there are increased numbers of $CD68^+$ histiocytes, dermal dendrocytes and fibroblasts. Although initially described as 'scleromyxoedema-like', the lesions have a different distribution and morphology, and there is no associated paraproteinaemia or systemic involvement [2]. The cause is unknown. Although typically associated with haemodialysis, the condition preceded dialysis in one patient [3]. It may remit spontaneously, particularly with the correction of renal abnormalities. No treatment is of proven benefit, but thalidomide has been used empirically [4].

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GEMSS syndrome

This is an autosomal dominant condition, comprising *g*laucoma, lens *e*ctopia, *m*icrospherophakia (small, spherical lens), joint *s*tiffness and *s*hort stature [1]. Affected individuals have a stocky, 'pseudoathletic' build. Associated cutaneous sclerosis notably affects the upper back and limbs but spares the face. Skin histology is reminiscent of systemic sclerosis. Increased synthesis of collagen is reflected by markedly enhanced gene expression of TGF-β_1 [2].

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POEMS syndrome (see also Chapters 39 & 59)

SYN. CROW–FUKASE–TAKATSUKI SYNDROME

This acronym is derived from *p*olyneuropathy, *o*rganomegaly (of liver, spleen or lymph nodes), *e*ndocrinopathy (often diabetes mellitus), *M* protein (a monoclonal gammopathy) and *s*kin lesions. The skin features include hyperpigmentation, hyperhidrosis, hypertrichosis and diffuse thickening resembling scleroderma [1–3]. Rarer features include angiomas, white fingernails and alopecia [3].

The syndrome appears to be a rare variant of myelomatosis [4], although skeletal X-rays show single or multiple osteosclerotic lesions with areas of bony proliferation rather than the lytic lesions which are more typical of myeloma [5].

Overproduction of vascular endothelial growth factor (VEGF) may explain the microangiopathy, neovascularization and accelerated vasopermeability that occur in this syndrome [6].

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Keloids and hypertrophic scars

Both conditions represent an excessive connective tissue response to injury, which may be trivial. A keloid (cheloid, meaning 'crab claw') is a benign, well-demarcated area of fibrous tissue overgrowth that extends beyond the original defect. A hypertrophic scar is similar, but remains confined to the initial defect and tends to resolve with time [1].

Aetiology. The cause is unknown, although both local and constitutional factors are involved. A scar at any site has the potential to become hypertrophic or keloidal, although the earlobes, chin, neck, shoulders, upper trunk and lower legs are especially vulnerable. Burns or scalds and infected lesions predispose to hypertrophy. Another risk factor is the presence of foreign material, either exogenous (e.g. suture material) or endogenous (e.g. embedded hair). Some African tribes introduce foreign bodies into tribal marks to induce scar hypertrophy. Scarring acne, particularly on the trunk, may become keloid-like. Isotretinoin has been reported to delay wound healing and induce keloids in patients who received argon laser or dermabrasion for acne or rosacea [2,3].

Some races, notably Afro-Caribbeans, are more prone to develop keloids than others. A positive family history is obtained in 5–10% of Europeans with keloids, particularly severe lesions [4]. Family studies suggest an autosomal dominant inheritance with incomplete penetrance [5]. There is a genetic association with other 'fibromatoses' such as Dupuytren's contracture [6]. Keloids form readily in acromegalics, and after thyroidectomy in young patients. They have been reported in a boy with Dubowitz's syndrome [7]. Keloids are also recorded in association with EDS, pachydermoperiostosis and Rubinstein–Taybi syndrome [8]. Keloids are rare in infancy and old age, occurring chiefly between puberty and the age of 30 years. Women have a greater predisposition, and keloids may occur or enlarge during pregnancy [9].

Linear keloids have been reported to occur in athletes taking anabolic steroids [10].

Pathology [11–13]. Although the histology may be difficult to distinguish from normal wound healing in the early stages, hypertrophic scars and keloids typically exhibit increased cellularity. In keloids of recent onset, endothelial proliferation is surrounded by increased numbers of fibroblasts, which form large, irregular nodules or whorls of collagen with a peripheral capsule-like band [11]. Mast cells are increased in hypertrophic scars [12]. Mucinous material is deposited focally in keloids but not in hypertrophic scars. The epidermis is normal, or thinned by the underlying lesion.

On electron microscopy, the nodules contain stellate fibroblasts. It is uncertain whether these are [14] or are not [15] myofibroblasts. Scanning electron microscopy of keloids shows more haphazard organization of collagen bundles than in normal skin or mature scars. The collagen filaments are about half the diameter of those of normal skin.

Biochemical studies confirm that collagen and proteoglycan synthesis is increased in keloids and hypertrophic scars. Collagen degradation appears to be normal [16]. Synthesis of both types I and III collagen is increased [17], and hypertrophic scar collagen possesses the reducible keto cross-link, dehydrohydroxylysinonorleucine, normally associated with embryonic skin and granulation tissue [18]. Several growth factors have been studied using keloid fibroblasts *in vitro*. Keloid fibroblasts, unlike those from hypertrophic scar tissue, are hyperresponsive to both TGF-β, which is abundant in healing wounds [19], and PDGF [20].

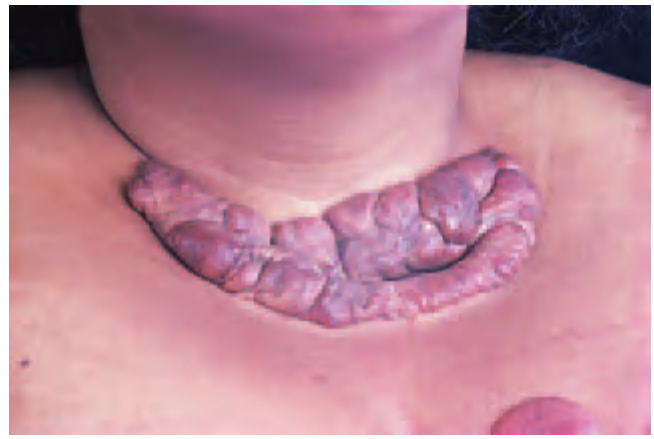

Fig. 46.38 Spontaneous keloids of the neck.

Keloid fibroblasts in culture secrete increased amounts of collagen and glycosaminoglycans for several passages in tissue culture [21]. It is unclear whether these cells represent a normal subgroup or have undergone transformation. Altered expression of proteoglycans in keloids may affect the three-dimensional organization of collagen fibres [22].

Immunohistochemical studies have shown that neuropeptide-containing nerves are present in hypertrophic scars but not in non-hypertrophic scars, and these may contribute to the symptoms of discomfort and itching in such scars [23].

Clinical features. Both hypertrophic scars and keloids become raised and thickened within 3–4 weeks of the provocative stimulus. The lesion becomes a firm, pink or red plaque, which may grow for months or years. Lesions often assume a 'dumb-bell' configuration, but sometimes become bizarre and irregular (Fig. 46.38). Usually, a hypertrophic scar shows signs of regression after a few months. The surface of a keloid becomes smoother and rounder, extending beyond the area of the original lesion. It is often irritable and hypersensitive, and sometimes exquisitely tender. Keloids tend to regress after several years; lesions on the beard area sometimes undergo central suppurative necrosis. Malignant degeneration has been reported [24], although a fibrosarcoma can mimic keloid clinically.

The diagnosis is usually simple if there is a history of trauma or an inflammatory skin lesion. Spontaneous keloids usually develop on the presternal region or upper

chest. Lesions which can cause diagnostic difficulty include sclerotic basal cell carcinoma, scar sarcoid or malignancy developing in a scar, and dermatofibrosarcoma. In endemic areas, blastomycosis and lobomycosis cause keloidal reactions.

Prophylaxis and treatment. Non-essential surgery should be avoided in the sites of predilection. If surgery is necessary, simple excision, aiming to minimize skin tension and secondary infection, is preferable to electrocoagulation or caustic chemicals. In an individual at risk, preoperative radiotherapy to the excision site may be useful.

Keloids usually recur following simple excision, although adjuvant therapy, such as radiation, local compression with a custom-made pressure garment [25], or intralesional steroids may reduce the risk of recurrence. Some lesions respond to pressure alone, or with occlusion with a hydrocolloid dressing. Small keloids can respond to silicone gel (e.g. Silastic) held in place with adhesive tape [26]. This treatment is also effective for hypertrophic scars [27,28].

Promising results have been obtained using a cream made of 20% silicone oil, applied under occlusion; this may be beneficial for sites where it is impracticable to apply gel-sheeting [29].

Radiotherapy, including superficial X-rays, electron-beam therapy or implantation with iridium-192 wires, may prevent recurrence following surgery [30], but electron-beam therapy offers no advantage over orthovoltage [31]. Intralesional triamcinolone (10 mg/mL) is useful, especially in early lesions. Several injections may be necessary at intervals of 3–6 weeks. Prior freezing with liquid nitrogen before the injection causes oedema, which allows the triamcinolone to be injected more readily. Acne keloids respond moderately well to either intralesional triamcinolone or cryotherapy, but the response to the latter is better in early vascular lesions [32].

Topical retinoic acid, applied daily, may be helpful [33,34], although systemic retinoids may enhance keloid formation [3]. Intralesional lathyrogens, such as β-aminoproprionitrile, have been used, but systemic penicillamine is ineffective [35]. Intralesional cytotoxic drugs may cause ulceration, but intralesional 5-fluorouracil and 585-nm flashlamp-pumped pulsed dye laser produced comparable improvement in one study [36]. Inhibitory cytokines, such as IFN-α and IFN-γ [37–39] and TGF-β analogues show promise. Interferons appear to reduce fibroblast collagen synthesis and increase collagenase activity by reducing the steady state levels of mRNA [39]. Different modes of laser treatment, e.g. the pulsed dye, Nd : YAG and carbon dioxide lasers, have a high recurrence rate.

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Premature ageing syndromes [1,2]

Increasing age appears to cause many anatomical and functional changes in human skin, but some of these may be the result of cumulative damage due to sun exposure, etc. To date, no disease has been found to cause a true acceleration of the rate of ageing in all tissues. More than 150 diseases manifest one or more features of apparent premature ageing, but there are discrepancies between this process and true ageing. All the premature ageing syndromes are probably inherited, although the defect may not be obvious in the first few years of life. Cutaneous changes which may be a sign of a premature ageing syndrome include atrophy, loss of cutaneous fat, wrinkling, canities, hair loss, nail dystrophy, defective pigmentation, poikiloderma, sclerosis and ulceration.

The conditions associated with cutaneous signs of premature ageing are shown below.

1 Classical inherited premature ageing syndromes:
  (a) pangeria (Werner's syndrome);
  (b) progeria (Hutchinson–Gilford syndrome);
  (c) acrogeria (Gottron's syndrome).
2 Other congenital progeroid syndromes:
  (a) trisomy 21 (Down's syndrome);
  (b) neonatal pseudohydrocephalic progeroid syndrome (Wiedemann–Rauchenstrauch);
  (c) osteodysplastic geroderma;
  (d) wrinkly skin syndrome;
  (e) familial mandibulo-acral dysplasia;
  (f) progeroid EDS.
3 Excessive exposure to irradiation (usually UV).
4 Photosensitivity, especially congenital, for example poikiloderma congenitale, xeroderma pigmentosum, Cockayne's syndrome.
5 Diseases causing elastolysis, for example cutis laxa.
6 Thickened immobile skin, for example diabetic cheiroarthropathy.
7 Fragile skin, for example prolidase deficiency.
8 Loss of subcutaneous fat, for example generalized lipodystrophy.

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Pangeria

SYN. WERNER'S SYNDROME; ADULT PREMATURE AGEING SYNDROME

Definition. An inherited disorder in which the ageing process is accelerated, starting after puberty. It is characterized by short stature, senile appearance, cataracts, joint contractures, early menopause, premature arteriosclerosis, various skin changes (including scleroderma-like features, premature canities, baldness and ulceration) and an increased risk of malignancy. Werner's syndrome is considered one of the genomic instability syndromes [1].

Aetiology. The syndrome is due to an autosomal recessive gene, with a calculated gene frequency of 1–5 per 1000 population [2].

Numerous abnormalities have been described in this syndrome, including chromosomal aberrations (most noticeably translocations, inversions and deletions), altered connective tissue metabolism, and abnormalities in the immune and endocrine systems [3–14].

Causal mutations have been identified in the RecQ type DNA helicase gene (*RECQL2*, *WRN* gene) [15]. It appears that the syndrome is the result of complete loss of the *WRN* gene product [16], but its exact role in preventing premature ageing has yet to be elucidated.

Pathology. Many tissues show premature ageing, but the changes are not uniform. Microsplanchnia and generalized atheroma are usually present. The epidermis is atrophic and some appendages are sparse. The dermis is thickened, with replacement of subcutaneous fat with hyalinized collagen, increased glycosaminoglycans, abnormal elastic fibres, disorganized nerves and vessel changes, which resemble those seen in diabetes mellitus. These abnormalities are more marked in the acral skin than on the trunk [3].

Clinical features [1]. The earliest manifestation of the syndrome is greying at the temples, which usually develops between the ages of 14 and 18 years but may rarely be present as early as 8 years. The greying rapidly becomes uniform and is sometimes associated with progressive alopecia. The first significant changes are usually noticed between 18 and 30 years but may begin earlier. The lower legs, feet, forearms and hands are most severely involved,

Table 46.4 Clinical features of the classical premature ageing syndromes.

	Pangeria (Werner's syndrome)	Progeria	Acrogeria
Stature	Small stature. Cessation of growth at 12 years	Small stature	Normal
Facies	Beaked nose; skin of ears atrophic and tightly bound down	Mid-facial cyanosis; bird-like facies; glyphic nasal tip; prominent frontal tuberosities and scalp veins; chin recessed	Micrognathia; atrophy of skin on tip of nose
Skin	Dry atrophic skin; mottled hyperpigmentation; telangiectasia	Dry, thin and wrinkled with mottled pigmentation; may present with scleroderma-like changes on limbs	Atrophic with telangiectasia and mottled hyperpigmentation on extremities
Scalp hair	Premature greying at 20 years; loss of hair at 20–25 years	Hair lost in first 2 years of life	Normal
Eyes	Bilateral juvenile cataracts (20–30 years); keratopathy; glaucoma	Prominent eyes; otherwise normal	Normal
Nails	Normal	Thin and brittle	Dystrophic or thickened
Limbs	Lower limb ulcers; hyperkeratosis over bony prominences; generalized loss of subcutaneous fat	Prominent joints; coxa valga; generalized subcutaneous fat loss; poorly developed muscular system; no acrosclerosis or Raynaud's phenomenon	Atrophy of skin most marked on extremities; no leg ulcers

the face and neck less so; atrophy of the skin and loss of subcutaneous fat results in a tense, shining and adherent appearance of the skin. Thin, spindly legs contrast with the normal or obese trunk, and there is a bird-like facies. The joints become fixed, and there may be sclerodactyly and acral gangrene. Mottled or diffuse pigmentation and telangiectasia are often conspicuous on the limbs, face and neck. Keratoses over pressure points on the feet and ankles separate to leave indolent ulcers. The voice may be high pitched and hoarse from thinning of the cords and fixation of the epiglottis. Intelligence is usually normal.

Most patients are of small stature and hypogonadal, with sparse or absent pubic and axillary hair, but some achieve normal stature and successful pregnancies. Other endocrine deficiencies are sometimes present; frank diabetes mellitus in at least 30% and abnormal glucose tolerance in many others. The diabetes is characterized by relatively low blood glucose levels and peripheral resistance to insulin [17,18].

Cataracts develop between the ages of 20 and 35 years in most cases and are usually posterior and subcapsular. Other ocular defects may occur [19].

The incidence of malignancy is high, especially fibrosarcomas, which occur in 10% of patients [20]. Carcinoma has developed in a chronic leg ulcer [21], but skin cancer is relatively rare. Generally, atheroma develops early. Abnormalities of metabolism are sometimes present but are not of uniform type. Death usually occurs in the fourth to sixth decade, due to myocardial infarction or malignancy [22].

The radiological changes [23] are often striking. There may be calcification of arteries, ligaments, tendons and subcutaneous tissues, with osteoporosis of the extremities, especially the legs.

Diagnosis. The prematurely aged appearance, the physical immaturity, the scleroderma-like changes and the cataracts, in combination, are unmistakable. In the Rothmund–Thomson syndrome, erythema, which is of early onset, is followed by poikilodermatous changes, and, although the facies may be superficially similar, there is no sclerosis. In systemic sclerosis, the hands are involved more than the feet and there is no premature ageing; in some advanced cases, confusion is possible but can be resolved by biopsy.

Huriez syndrome may require exclusion (Chapter 34). The differentiation from some of the other ageing syndromes is indicated in Table 46.4.

Mutational analysis of the *WRN* gene is now possible, although diagnosis by immunoblot analysis using a monoclonal antibody directed against the *WRN* gene product is also feasible [24].

Treatment. Only symptomatic measures are available. The management of the recurrent painful ulceration of the feet and legs is difficult, and amputation may be needed. Cataract surgery should be undertaken with special caution, for it is often complicated by severe degenerative changes of the cornea [19].

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Progeria

SYN. HUTCHINSON–GILFORD SYNDROME

Definition. This is a rare disorder characterized by retarded physical development and abnormal facies, skeletal abnormalities and the onset in early childhood of scleroderma. Although progressive senile degeneration occurs, many of the more common features of ageing, such as cataracts, presbyacusis and presbyopia, are not seen.

Aetiology. It has been recently reported to occur following *de novo* mutations of lamin A (LMNA) that encodes for a major constituent of the inner membrane lamina [1]. Affected families have a high risk of spontaneous abortion.

Various abnormalities of mesodermal tissue have been identified [2]. In tissue culture, progeria fibroblasts have a decreased survival time [3]. The fibroblasts show a threefold increase in the production of hyaluronic acid, and the urinary excretion of hyaluronic acid is increased [4–6]. Animal studies suggest that increased hyaluronic acid in the tissues might produce a reduction in vascularity [4,7]. Tropoelastin production is increased [8], and it has also been suggested that type IV collagen may accumulate due to an interaction between activated T lymphocytes and fibroblasts [9,10]. A preliminary study of cultured fibroblasts from two affected patients suggests mitotic instability [11]. A polymorphism in the galactosyltransferase gene (*B4GALT1*) has been identified in affected cell lines [12].

Fewer than 100 cases have been reported to date, and 97% of patients have been white [7].

Pathology [13]. The major changes are in the skin, bone and cardiovascular tissues.

The skin shows atrophy of epidermis and dermis. There may be progressive hyalinization of dermal collagen and loss of subcutaneous fat. Scanning electron microscopy of hairs from one patient showed unusual longitudinal depressions with minor cuticular defects [10].

The cardiovascular system shows extensive atheroma, and there may be extensive myocardial fibrosis, with extensive lipofuscin ('age pigment') deposition characteristic of elderly adults [14,15].

The bones show a variety of changes including osteolysis, osteoporosis, necrosis, dislocations and poorly healing fractures [16,17].

Clinical features [18]. Affected children usually appear normal at birth, and growth may be only slightly retarded in the first year, but during the second year there is profound growth failure, with reduced subcutaneous fat on the face and limbs [7]. The facial appearance is reminiscent of a fledgling bird, with a disproportionately large cranium with patent fontanelles and frontal bossing, prominent eyes and scalp veins, very sparse, downy scalp hair, sparse or absent eyebrows and eyelashes, centrofacial cyanosis, micrognathia, thin lips and a 'beaked' nose. By the second year, the skin has become thin, taut and shiny in some areas but lax and finely wrinkled in others. Eccrine sweating is decreased. The veins are prominent and there may be easy bruising. After several years, progressive mottled hyperpigmentation develops, most marked on exposed sites, but there is no photosensitivity. Thickened sclerotic areas may be present on the lower trunk or thighs, and in one case multiple keloids developed on the hands and arms [10]. The nails are usually small, thin and dystrophic, and koilonychia and onychogryphosis may occur. Generalized alopecia often begins in the first year of life and the few remaining hairs are pale, fine and 'fuzzy'. The nipples may be hypoplastic.

The dentition is abnormal and delayed, and there may be skeletal abnormalities such as dystrophic clavicles and coxa valga, with joint contractures and a 'horse-riding' stance. Progressive bone resorption may lead to frequent fractures [17]. Sexual maturation is absent but intelligence is normal.

Death usually occurs in the second decade as a result of severe generalized atheroma.

Diagnosis. The large, bald head with conspicuous veins, the bird-like facies and the well-proportioned little body are distinctive. Bird-headed dwarfism (Chapter 12) is distinguished by the absence of skin atrophy.

Cockayne's syndrome may cause confusion, but progeria is distinguished by the loss of hair, the lack of photosensitivity and ocular changes, and the absence of disproportionately large extremities.

In metageria, sexual maturation and skeletal growth are normal [19].

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Acrogeria [1–4]

SYN. GOTTRON'S SYNDROME

Definition. This disorder begins at birth or soon afterwards, and is characterized by cutaneous atrophy and loss of subcutaneous fat, particularly over the distal extremities, but with no tendency to atheroma, diabetes mellitus or decreased life expectancy. The term 'acrogeria' refers to premature ageing of the extremities.

Aetiology. Most cases occur without a family history, but presumed autosomal recessive as well as autosomal dominant inheritance has been reported [1,2]. Most patients have been female.

COL3A1 mutations cause variable phenotype, including Gottron-type acrogeria and vascular EDS [5,6].

Pathology. The subcutaneous fat is absent in the most severely affected regions. The dermis is atrophic, with sparse, thin collagen bundles, but there is abundant elastin, which appears clumped due to the deficiency of collagen.

Clinical features. The changes develop at or soon after birth. The skin becomes dry, thin, transparent and wrinkled, especially over the hands and feet, although the trunk and face may be affected to a lesser extent. The veins are prominent, and there may be easy bruising, poikiloderma and telangiectasia. The nails may be atrophic or thickened. The face appears 'pinched', with a hollow-cheeked 'owl-eyed' appearance, a beaked nose and thin lips. Micrognathism may be present. The lack of subcutaneous fat accentuates the appearance of premature senility. Some patients have low birth weight and persistent short stature, but the general health and life expectancy are normal. The hands and feet may be very small.

Diagnosis. The normal hair and eyes help to distinguish the condition from progeria and pangeria.

Cases are occasionally described which do not fit easily into any of the previously recognized categories and have been termed metageria and acrometageria [7,8]. It is not entirely clear whether these are separate entities.

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Laboratory studies [1–3]

Fibroblasts from normal human skin have a limited lifespan in culture, which is inversely proportional to the age of the donor, and it seems that the *in vitro* ageing of fibroblasts may serve as a model for the *in vivo* ageing

of the whole body. All the premature ageing syndromes studied to date have shown a marked reduction in fibroblast growth potential *in vitro*. These include Werner's syndrome, progeria, poikiloderma congenitale, trisomy 21 and diabetes mellitus. In addition, fibroblasts from progeria patients have shown a decrease in mitotic activity, rate of outgrowth from explants, DNA synthesis and cloning efficiency. Studies on fibroblasts from patients with progeria and Werner's syndrome have also shown enzyme changes consistent with an accelerated ageing process.

In the normal ageing process, there is a threefold increase in the affinity of surface insulin receptors for native insulin between the first and seventh decades. This accounts for the clinical finding of relative insulin resistance in the elderly. Patients with progeria also show increased insulin binding and relative insulin resistance.

Other cellular abnormalities in Werner's syndrome and progeria include a decrease in surface-membrane HLA antigens and a marked increase in the activity of a procoagulant, which may predispose to atheroma.

Post-irradiation DNA repair appears to be normal in progeria and pangeria, although the cultured fibroblasts may have reduced karyotype stability. A reduction in DNA stability might increase the rate of genomic deterioration, and this might accelerate cellular ageing.

The fact that the premature ageing syndromes have multiple features which are difficult to attribute to a single enzyme or protein defect suggests that they may result from a defect in the genetic coding for structural proteins or DNA repair enzymes [4].

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Other associated conditions

Premature ageing with short stature and pigmented naevi

SYN. MULVIHILL–SMITH SYNDROME

This rare syndrome [1] is characterized by low birth weight, short stature and moderate mental retardation, associated with multiple pigmented naevi and a distinctive bird-like facies. There is a small chin, with broad forehead, and the lack of facial subcutaneous fat gives an appearance of premature ageing. Other features include hypospadias, a high-pitched voice, irregular dentition, fine hair, hepatomegaly and low IgG. The clinical features tend to become more noticeable with increasing age.

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Neonatal pseudohydrocephalic progeroid syndrome of Wiedemann–Rautenstrauch [1–3]

This rare autosomal recessive condition is characterized by mental and physical retardation and frontal and lateral bossing of the skull, with small facial bones, a small, beak-shaped nose, low-set ears and small mouth with dysodontia. The scalp hair is long and sparse, the extremities are thin, and the hands are large with long fingers and atrophic nails. The subcutaneous fat is decreased, the skin is thin and wrinkled, and the veins are prominent.

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Gerodermia osteodysplastica [1]

Stunting of growth from early childhood is associated with senile changes in the skin, with normal scalp hair, generalized osteoporosis, multiple fractures, joint laxity and skeletal malformations, including wormian bones. The face appears sad, with drooping eyelids and jowls, malar hypoplasia and mandibular prognathism. Relatives presenting partial forms of the syndrome showed cutaneous ageing and osteodysplasia without dwarfism. Skin biopsy may show fragmented elastic fibres. Two consanguineous Arabian families showed features overlapping both gerodermia osteodysplastica and wrinkly skin syndrome, suggesting that they may represent variable manifestations of the same disorder [2].

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Wrinkly skin syndrome [1]

This rare familial condition is characterized by the appearance at birth of dry, wrinkled skin of the hands, feet and ventral surfaces of the trunk. The veins are unduly

prominent. There may also be mental retardation, ocular defects and poor muscle tone. The cause is unknown, and the dermal collagen and elastin appear normal on light microscopy. There appears to be phenotypic overlap with gerodermia osteodysplastica [2].

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Poikiloderma congenitale

SYN. ROTHMUND–THOMSON SYNDROME

This condition is fully described in Chapter 12. It may be considered as a premature ageing syndrome because of the atrophic hyperpigmented skin, the early onset of cataracts, and the premature greying and loss of hair. The striking poikiloderma is distinctive.

Cockayne's syndrome (Chapter 12)

The atrophic skin with mottled pigmentation and loss of subcutaneous fat on the face produce an appearance of premature senility, and the disease has often been confused with progeria.

Trisomy 21 (Chapter 12)

SYN. DOWN'S SYNDROME

This disorder shows more features of true ageing than the classical premature ageing syndromes [1]. These features include progressive dementia with the neurofibrillary tangle seen in senile dementia, amyloid and lipofuscin deposition in many organs, diabetes mellitus, cataracts, cardiovascular disease, increased incidence of autoimmune disease and malignancy, and a decreased life expectancy [2].

The cutaneous features include dry, lax skin, and premature greying and loss of hair [2].

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Familial mandibulo-acral dysplasia

SYN. CRANIOMANDIBULAR DERMATODYSOSTOSIS

The main features of this rare syndrome are mandibular hypoplasia, delayed cranial suture closure, dysplastic clavicles, abbreviated club-shaped terminal phalanges

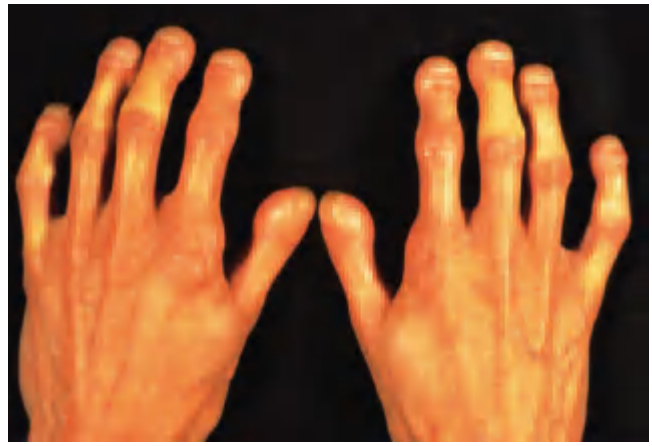

Fig. 46.39 Familial mandibulo-acral dysplasia, showing the short, club-shaped terminal phalanges, the so-called 'tree-frog' appearance. (Courtesy of Dr A.M. Zina, Turin University, Turin, Italy.)

associated with acro-osteolysis and atrophy of the skin over the hands and feet [1] (Fig. 46.39). Other characteristics may include short stature, multiple wormian bones, prominent eyes and a sharp nose [2,3]. In one family, the condition was also associated with the loss of the lower teeth and alopecia [4]. Partial lipodystophy may be present and associated with hyperinsulinaemia [5]. The condition is autosomal recessive and mutations have been identified in the gene encoding lamin A/C (*LMNA*) [6].

The cutaneous changes resemble those of a premature ageing syndrome, and some cases have been mistakenly diagnosed in the past as acrogeria or Werner's syndrome.

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Diabetic thick skin [1,2]

SYN. CHEIROARTHROPATHY

Diabetes may be classified as a premature ageing syndrome because of the predisposition to cataracts and atheroma and the reduced life expectancy [1,3].

Some patients with diabetes mellitus have thick, tight, waxy skin and limited joint mobility. This combination has been called *cheiroarthropathy* [4]. Affected patients are

unable to bring their palms completely together, and their fingers will not bend backwards. The 'prayer sign', in which the patient tries to oppose the two palms, provides an easy screening test [5]. Skin and tendon sheath thickness has also been measured by ultrasound [6,7].

Cheiroarthropathy is present in 30–40% of insulin-dependent diabetics, and in non-insulin-dependent diabetics the figures have varied widely, from 4% to 70%. The changes may even precede the diagnosis of diabetes [8]. The changes are important because affected patients have an increased risk of retinal and renal disease due to microvascular damage [9]. Patients with diabetic cheiroarthropathy also have an increased incidence of frozen shoulder and Dupuytren's contracture [10]. There is often associated thickening of the plantar fascia [11].

The biochemical change is not fully understood, but it seems likely that non-enzymatic glycosylation in diabetic subjects might alter collagen metabolism [1,3]. The lysines in collagen are slowly glycosylated with increasing age, and during this process the glucose attaches to the lysine and undergoes an Amadori rearrangement, thus making the process irreversible [12]. Enzymatic digestion of tendon collagen from young patients who died from diabetes showed that their collagen behaved as if it was from patients who were 50–65 years older than their actual age [13].

Studies of viscoelastic ratio and skin extensibility in patients with type 1 diabetes have shown subclinical stiffness and loss of skin elasticity [14].

The histology of the skin changes resembles systemic sclerosis, but there is a subtle difference, with a predominance of large collagen fibres, thickening of the capillary basement membrane and increased mucin [15].

In some diabetic patients with thick skin, the extensor surfaces of the fingers develop a characteristic, minutely pebbled appearance over or near the knuckles (Huntley's papules). On histology, this shows a papillated epidermal hyperplasia with hyperkeratosis [16].

Because biochemical studies suggest that collagen is 'aged' by increased binding with glucose, it is desirable to maintain tight control of blood glucose levels in diabetic patients [17].

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Leprechaunism

SYN. DONOHUE'S SYNDROME

Definition. Leprechaunism is a rare and poorly defined syndrome characterized by severe intrauterine and postnatal growth retardation, decreased subcutaneous tissue and muscle mass, and a characteristic facies [1]. Tissue resistance to insulin appears to be an important feature, as hyperinsulinaemia and pancreatic β-cell hyperplasia are frequently present [2,3].

Aetiology. The condition is inherited as an autosomal recessive trait. The basis for the insulin resistance is homozygous or compound heterozygous mutations in the extracellular domain of the insulin receptor, which leads to markedly impaired insulin binding [4]. Mutations that retain significant insulin binding activity cause the less severe phenotype of Rabson–Mendenhall syndrome.

The fibroblasts have a prolonged doubling time *in vitro*. They respond poorly to the metabolic actions of insulin, and to the actions of several other growth factors, such as epidermal growth factor.

Pathology [5]. In the skin, the elastic and collagen fibres are few and fragmented. On the extremities, the horny layer is markedly thickened. The muscles show a proliferation of abnormal connective tissue. In some cases, the ovaries are large and cystic, and there is β-cell hyperplasia of the pancreatic islets.

Clinical features [5–8]. The child is abnormal at birth, with low birth weight. The nose is broad, the ears low set and large, the eyes widely spaced. There is hypertrichosis of the forehead and cheeks. The skin appears too large for the body and is loosely folded at the flexures and may be corrugated with gyrate folds on the hands and feet, which may be disproportionately large. Muscle wasting, often

progressive, is usually present. The breasts and the penis or clitoris may be slightly hypertrophic. The bone age is retarded and there may be metaphyseal and epiphyseal dystrophy.

Growth is generally retarded, the nutritional status remains poor and susceptibility to infection is high. Death by the age of 1 year is usual.

Diagnosis. The cutaneous changes could be confused with cutis laxa, but in leprechaunism the skin, although folded, is thickened and not lax. The diagnosis is confirmed by the associated features and the finding of raised plasma insulin levels.

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Lipoatrophy

The absence of subcutaneous fat may give the appearance of premature ageing if the face is affected. Lipoatrophy is fully discussed in Chapter 55.

Perforating dermatoses

Many dermatoses occasionally exhibit the phenomenon of *TEE*, in which material from the dermis is extruded through the epidermis to the exterior with little or no disruption of the surrounding structures [1]. The extruded material may include inflammatory cells, red cells, microorganisms and extracellular substances, such as mucin or altered connective tissue components [2,3]. In most of these conditions, the TEE is secondary to some underlying disease, such as granuloma annulare or PXE, but there are four conditions that are regarded as *primary perforating disorders*, i.e. Kyrle's disease (Chapter 34), perforating folliculitis (Chapter 27), reactive perforating collagenosis and perforating serpiginous elastosis. It is possible that these primary perforating disorders might be due to defects in the epidermal keratinocytes, hair follicle, collagen and elastic fibres, respectively, with TEE being the final common pathway [2,3].

In acquired reactive perforating dermatosis (see below), the bulk of the coarse granular basophilic material which is extruded by TEE appears to derive from the nuclei of polymorphonuclear leukocytes [4]. It has been suggested that lysosomal enzymes derived from leukocytes might be responsible for the altered staining of collagen fibres, the degradation of elastic fibres and the impairment of keratinocyte adhesion, which allows TEE of dermal components [4].

Acquired reactive perforating dermatosis

Until recently, the four conditions mentioned above were thought to be unrelated, but there have now been numerous reports of these perforating dermatoses occurring in diabetes mellitus or in patients with chronic renal failure, many of whom were undergoing haemodialysis [2,5–9]. An incidence of 11% has been reported, with a particular association with long-standing diabetes [9]. The keratotic lesions in this condition develop on the trunk and limbs, and are usually pruritic, dome-shaped papules with central crusts (Fig. 46.40). They are not related to trauma.

The distinction between the four dermatoses has not always been clear-cut, and the presence or absence of the Koebner reaction, and the presence or absence of collagen fibres in the epidermis, are not reliable distinguishing features [2,3]. Both collagen and elastic fibres can be extruded in the same patient [7], and it seems likely that at least in the case of haemodialysis patients these conditions may overlap. The name *acquired reactive perforating dermatosis* has been suggested for this skin problem. These four conditions, however, appear to be separate entities when they occur outside the setting of renal failure or diabetes mellitus.

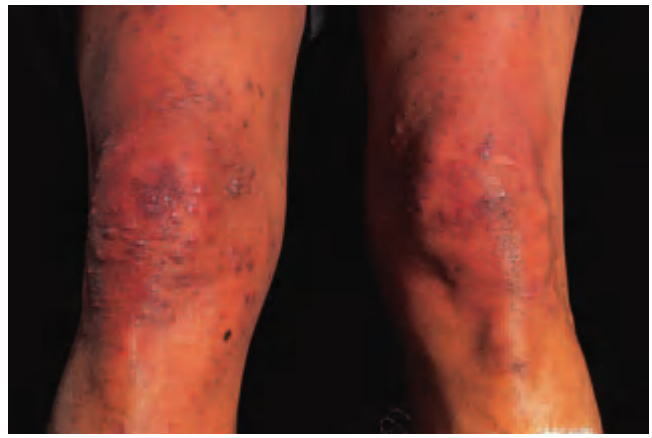

Fig. 46.40 Perforating dermatosis in a diabetic patient with renal failure. (Courtesy of Dr D.A. Burns, Leicester Royal Infirmary, Leicester, UK.)

Topical or intralesional steroids or topical retinoids may be helpful, but some patients improve spontaneously [9]. Other reported treatments include rifampicin and allopurinol [10].

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Perforating disease due to exogenous agents

Occasionally, a chemical which has been applied to the skin topically or by intradermal injection can be eliminated by the transepidermal route to produce a perforating disorder. Eight cases have been reported following occupational exposure to a caustic drilling fluid used in the petrochemical industry [1]. Each patient noted skin irritation following exposure to the fluid, and 1 or 2 days later developed tender papules with central umbilication, which ulcerated and crusted. Histological examination of the lesions revealed TEE of altered collagen and debris which stained for calcium.

It is possible that the lesions were due to follicular penetration by the calcium present in the drilling mud. The drilling fluids contain many additives, but calcium carbonate or calcium chloride are often present in high concentrations in the mud. Similar cases have been reported following the use of calcium-containing electroencephalography paste [2].

TEE of altered collagen has also been reported following the use of intradermal steroid injections [3,4].

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Reactive perforating collagenosis [1–4]

Definition. A rare inherited form of TEE in which collagen is extruded through the epidermis. It is usually precipitated by environmental cold or trauma. The commoner, acquired, form is often referred to as acquired perforating dermatosis (qv) which is typically associated with haemodialysis, although lesions have been recorded with internal neoplasia [4].

Aetiology. The cause is unknown, but the condition is often familial [5,6]. The basic defect seems to be a type of focal damage to collagen, which is then extruded as a result of necrolysis of the overlying epidermis [7].

Pathology [2,7,8]. The lesion originates in the papillary dermis, where collagen is surrounded and engulfed by focal epidermal proliferation. The collagen appears normal on electron microscopy, but gives an abnormal staining pattern with trichrome and phosphotungstic acid haematoxylin. The central crater which develops contains inflammatory cells and keratinous debris. Elastic tissue is typically absent, and the abnormal collagen is eliminated by transepithelial migration.

Clinical features [7]. The inherited form usually starts in early childhood as small papules on the extensor surface of the hands, the elbows and the knees following superficial trauma. Each skin-coloured papule increases to a size of about 6 mm over 3–5 weeks and then becomes umbilicated, with a keratinous plug. The lesions regress spontaneously in 6–8 weeks to leave a hypopigmented area or slight scar, but new lesions may appear. Lesions can be produced experimentally, and Koebner's phenomenon may be present, with linear lesions [9]. The papules can also be provoked by inflamed acne lesions, but deep incisions do not produce the lesions. The condition persists into adult life. In some cases, the disease is associated with intolerance to cold and improves in warm weather.

Diagnosis. The condition may be mistaken clinically for molluscum contagiosum, papular urticaria, perforating serpiginous elastoma, perforating folliculitis, perforating granuloma annulare and Kyrle's disease, but the histology is characteristic [6]. Verrucous perforating collagenoma must also be distinguished (see below).

The nosological relationship between reactive perforating collagenosis and the acquired reactive perforating dermatosis of renal failure remains uncertain (see above) [4].

Treatment. Topical retinoic acid may reduce the number of lesions. Other treatments which may help include oral isotretinoin, methotrexate, emollient creams, topical steroids under occlusion [3,4] and PUVA [10].

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Verrucous perforating collagenoma [1,2]

SYN. COLLAGENOME PERFORANT VERRUCIFORME

In this rare condition, severe (as opposed to superficial) trauma to the skin produces verrucous papules which show TEE of collagen. The eruption occurs as a single episode and is not familial.

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Elastosis perforans serpiginosa

SYN. PERFORATING ELASTOMA; ELASTOMA INTRAPAPILLARE PERFORANS

Definition. In this reactive perforating dermatosis, the material extruded through the epidermis is derived from elastic fibres in the upper dermis.

Aetiology. The cause is unknown, but a genetically determined defect of elastic tissue may be involved [1]. The altered elastin resembles that seen in experimental animals subjected to lathyrogens or copper deficiency.

It is probable that the primary abnormality is in the dermal elastin, which provokes a cellular response that ultimately leads to extrusion of the abnormal elastic tissue. It may be significant that the lesions are commonly seen in areas subjected to wear and tear. The lesions may follow an abrasion.

Some 40% of reported cases have been associated with connective tissue disorders, such as PXE, EDS, MFS, OI and acrogeria [2,3]. It has also been reported in otherwise healthy individuals and in mental deficiency, especially Down's syndrome [4–6].

It sometimes occurs in patients taking penicillamine, which is known to cause the production of abnormal elastin [7–10].

The relationship to perforating PXE and pseudo-PXE due to penicillamine is discussed on p. 46.25.

Pathology [4,11–13]. The earliest detectable change is the focal development of elastotic staining tissue and basophilic debris in the dermis. This is followed by a reaction of the overlying epidermis, which grows down to engulf the elastotic material. The epidermis surrounding the fully developed lesion is acanthotic and hyperkeratotic. The papule consists of a circumscribed area of epidermal hyperplasia traversed by a channel communicating directly with the dermis and containing a mass of tissue, which projects above the surface. This plug consists of horny material in its upper third and of amorphous debris derived from elastin in its lower two-thirds [11]. In the dermis beneath and around the lesion, there is a foreign-body giant cell reaction. The elastotic material is finally extruded, to leave irregular scarring and warty thickening. Electron microscopy shows an increase in elastic fibres, with fine filaments on the surface similar to those seen in normal embryos, and the hydroxylation of the dermis is similar to that of newborn skin [12].

Clinical features [14,15]. The age of onset ranges from 6 to 20 years. Small, horny or umbilicated papules are characteristically arranged in lines, circles or segments of circles in a serpiginous pattern. The individual papules may remain small or may enlarge slightly to assume a crateriform appearance with an elevated edge and a central plug, or further to leave an area of atrophic skin surrounded by smaller papules, each with a horny plug. The rings may reach a diameter of 15–20 cm but are usually smaller (Fig. 46.41). The back and sides of the neck are

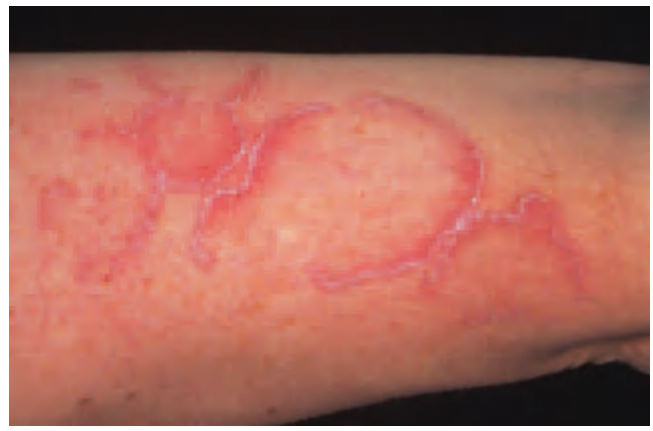

Fig. 46.41 Elastosis perforans serpiginosa in a patient with vascular Ehlers–Danlos syndrome.

most commonly affected, but the lesions may also occur on the cheeks or on the arms or thighs, and are sometimes bilaterally symmetrical. They may persist for several years, but eventually involute spontaneously to leave reticulate atrophic scars. Biopsy scars readily become keloidal.

Diagnosis. The annular or linear arrangements of the papules and their distribution suggest the diagnosis, which is confirmed by the characteristic histology. Conditions which may cause confusion include porokeratosis of Mibelli, reactive perforating collagenosis and perforating granuloma annulare.

A similar histological appearance can occur in the acquired reactive perforating dermatosis of renal failure (see above) [16].

Treatment. Careful removal of the nodules with a curette under local anaesthesia may give a reasonable cosmetic result. Freezing has been recommended [14,17]. Excision should be avoided, and dermabrasion may make the condition worse [4]. In a child with Down's syndrome and associated vitamin A deficiency, clinical improvement was observed with oral retinoid therapy, even though the treatment produced side effects [6]. Isotretinoin has been used successfully in a patient with penicillamine-induced disease [18]. There are reports of improvement following tazarotene [19], pulsed dye [20] and ultrapulsed carbon dioxide laser therapies [21].

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Miscellaneous disorders

Colloid milium

SYN. COLLOID PSEUDOMILIUM; COLLOID DEGENERATION OF THE SKIN; ELASTOSIS COLLOIDALIS CONGLOMERATA

Definition. Colloid milium is a degenerative change characterized clinically by the development of yellowish, translucent papules or plaques on light-exposed skin, and histologically by the presence of colloid in the dermal papillae.

Aetiology. The cause is uncertain, and the condition may not represent a single entity. The rare juvenile form [1,2], beginning before puberty and often familial, can be distinguished from a non-familial form occurring in later life. Although light appears to play little part in provoking the lesions in the juvenile form, it is certainly implicated in older patients, among whom the incidence is highest in fair-skinned, outdoor workers in sunny climates [1,3,4]. Cases among refinery workers in the tropics suggest that trauma and the photodynamic effects of phenols in oxide fuel (gas oil) may be contributory factors [5]. Cases have also been reported after the long-term application of strong hydroquinone bleaching creams. These patients also had ochronosis [5].

Pathology [6–11]. The earliest histological change is the appearance of colloid globules at the tips of the dermal papillae. Homogeneous fissured masses of colloid occupy the upper dermis, each surrounded by bands of collagen. The colloid is usually eosinophilic but may be basophilic. Within it, small blood vessels and the nuclei of fibroblasts are well preserved. In the larger, plaque-like lesions, the colloid change occurs diffusely throughout the dermis.

In the juvenile form, the colloid masses may also occur in the epidermis, and elastosis is not present, whereas in the adult form the colloid is separated from the epidermis by a band of elastin, and elastosis is present. In

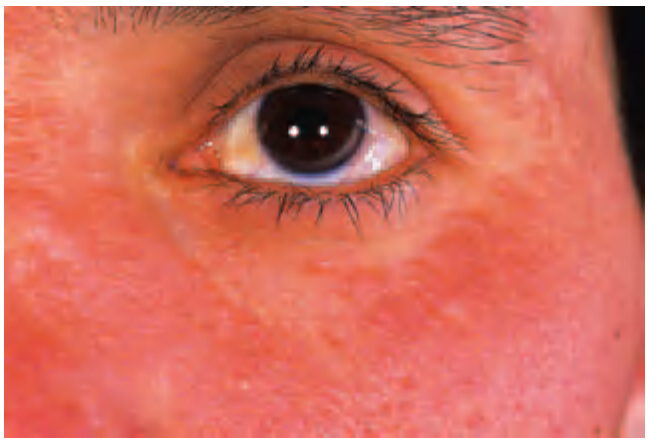

Fig. 46.42 Colloid milium of the infraorbital region. (Courtesy of Dr D.A. Burns, Leicester Royal Infirmary, Leicester, UK.)

the juvenile form, 'immature' Civatte bodies occur in the epidermis.

The source of the colloid material is uncertain. It could be a protein synthesized by fibroblasts or it could be derived from degraded elastic fibres [1,3,8].

The histological changes may be difficult to distinguish from those of amyloidosis, especially lichen amyloid. Electron microscopy may be needed for definitive diagnosis [6,8,11]. In adult colloid milium, the colloid is amorphous, with wavy, branching filaments. In the juvenile form, it is composed of closely packed filaments, which are often in parallel rows, forming whorled fascicles [1,11].

Clinical features. Small dermal papules 1–2 mm in diameter, yellowish brown and sometimes translucent, develop slowly and more or less symmetrically in irregular groups in areas exposed to sunlight (Fig. 46.42). They feel soft and may release their gelatinous contents when punctured. The most frequently involved sites are the face, especially around the orbits, the dorsa of the hands, the back and sides of the neck and the ears. There is some variation in the clinical features according to the age of onset. In young children, the lesions are often confined to the face, with diffuse infiltration surmounted by innumerable small papules, which may appear vesicular. In older patients, the papules are often fewer and larger, and their potential distribution is much wider, although often only one or two sites are involved in each individual. The changes induced by prolonged light exposure are associated to varying degrees. Although colloid milium may become more severe and more extensive over the years, most cases reach their maximum development within 3 years and then remain unchanged.

A nodular form has been described in which lesions may be 5–50 mm in size and may be single or multiple [10].

Diagnosis. The histological and clinical findings together are unmistakable, although the former alone may be difficult to differentiate from amyloidosis. Trichoepithelioma, tuberous sclerosis and hidrocystoma are distinguished by biopsy.

Treatment. Improvement has been reported following dermabrasion [12]. Destruction of the lesions with the diathermy or with cryotherapy has also been advocated, but the cosmetic result is seldom satisfactory.

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White fibrous papulosis of the neck

Asymptomatic, small, white, fibrous papules around the neck have been described in several Japanese [1,2], Iranian and European patients [3,4]. The number of papules ranges from 10 to 100; middle-aged to elderly men are predominantly affected. The papules are round to oval, clearly marginated and non-follicular (Fig. 46.43). Histology is unremarkable, showing bundles of thickened collagen fibres in the mid-papillary dermis. Although lesions clinically resemble disorders of elastic tissue, such as anetoderma and dermatofibrosis lenticularis disseminata, elastic fibres are morphologically normal on histology. Acquired connective tissue naevi could exhibit similar features, although the late age of onset makes this diagnosis unlikely. The condition appears to have no prognostic significance, and may be under-reported.

Recently, it has been suggested that there may be a relationship between fibrous papulosis of the neck and acquired elastolysis of the papillary dermis [5].

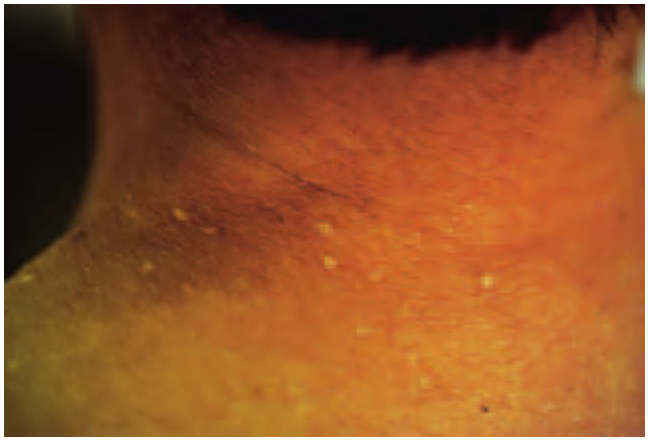

Fig. 46.43 White fibrous papulosis of the neck. (Courtesy of Professor H. Shimizu, Sapporo Hospital, Tokyo, Japan.)

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Papular elastorrhexis

This is a rare variant of connective tissue naevus. Adolescents or young adults present with non-follicular white or yellowish papules; dermal elastic fibres are decreased and fragmented on histology. Most case reports are sporadic, with no family history and no extracutaneous manifestations [1–3]. Similar lesions are seen in some patients with Buschke–Ollendorff syndrome (Chapter 15), in which osteopoikilosis is also a feature. To add to the confusion, abortive forms of Buschke–Ollendorff syndrome have been described, lacking osteopoikilosis [4]. A family has been described with this variant [5]. It is possible that papular elastorrhexis is not a separate entity. Intralesional triamcinolone may be beneficial [6].

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Progressive osseous heteroplasia [1,2]

This rare condition typically affects female infants and is characterized by ossification of skin and soft tissues. Ossification begins in the dermis, progressing to deeper tissues and to adjacent areas of skin. It is not associated with trauma or infection [3]. Skin lesions begin as groups of small, firm papules resembling rice grains; later, larger ossified nodules may develop. A skin biopsy should include subcutaneous fat. Cancellous and even mature intramembranous bone is found in the dermis and subcutis. The differential diagnosis includes plate-like osteoma cutis (in which the lesion is solitary) (Chapter 53), Albright hereditary osteodystrophy (which is associated with dysmorphic features, including brachydactyly and short stature, and less severe ossification) and fibrodysplasia ossificans progressiva, in which ossification initially affects muscle or fascia and the great toes are malformed. The disorder is caused by a paternally inherited inactivating *GNASI* mutation, the gene for guanine nucleotide-binding protein (G protein) alpha stimulating activity polypeptide 1. This is similar to the mutation identified in Albright hereditary osteodystrophy [4].

The condition is progressive, and the morbidity depends on the site and the severity of the ossification. There is no effective treatment to prevent the ossification, but lesions which disrupt function or impair movement can sometimes be removed surgically.

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Fascial hernias of the legs [1,2]

Small fascial hernias of the lower legs are not uncommon in athletes and heavy manual workers, and may present a problem in differential diagnosis. Herniation of muscle takes place through the hiatus in the deep fascia where it is perforated by communicating veins.

The hernias develop suddenly as nodules on the anterolateral aspect of the lower leg and are usually about 15 cm above the lateral malleolus. The nodules are soft,

compressible and 1.5–2.0 cm in diameter. If bilateral, they are strictly symmetrical. No treatment is required.

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Constricting bands of the extremities

SYN. AINHUM AND PSEUDO-AINHUM

Definition. This is a constricting band around a digit or limb. The band may be shallow, involving only the skin, or it may be deeper, involving fascia or bone, and in some cases amputation may result. The term *ainhum* (an African word meaning 'to saw' [1]) is applied to a specific type in which a painful constriction of the fifth toe occurs in adults, with eventual spontaneous amputation. *Pseudo-ainhum* is the term applied to other constricting bands which are congenital or secondary to another disease.

Ainhum

SYN. DACTYLOLYSIS SPONTANEA

Aetiology. The condition appears to be due to an abnormal blood supply to the foot in some patients, as arteriography has shown that in these patients the posterior tibial artery is attenuated at the ankle, and the plantar arch and its branches are absent [2]. Mechanical factors, including trauma from walking barefoot, may then precipitate the development of a groove in the ischaemic toe. Chronic fissuring in hyperkeratotic skin also seems to be an important factor. A family history is common, and the disease is more common in certain races. Ainhum is most common in black Africans, but many cases have been reported in black Americans, and it can also occur in other races.

Various tropical infections, including leprosy, tuberculosis and yaws have been suggested as possible contributory factors, but these conditions are probably coexistent rather than causative [2,3].

Pathology [4]. Fissuring and hyperkeratosis on the medial aspect of the digit is followed by fibrosis, distal degeneration and osteoporosis, ultimately leading to spontaneous amputation. There may be secondary infection and osteomyelitis.

Clinical features. The condition is most common between the ages of 30 and 50 years, but the earliest stages may be seen in childhood. The presenting symptom is usually a painful fissure. The toe is held dorsiflexed at the metatarsophalangeal joint, and gradually becomes clawed. Rest pain, coolness and cyanosis of the digit distal to the groove suggest that ischaemia is present. Once the constricting band has encircled the toe, the condition tends to progress rapidly. The toe becomes globular, hangs by a thread of fibrous tissue and is eventually shed (Fig. 46.44).

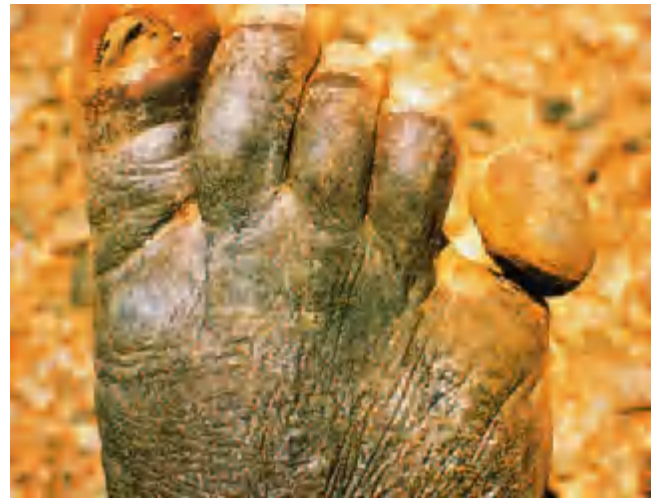

Fig. 46.44 Ainhum, just before shedding of the fifth digit. (Courtesy of Dr D. Burley, Princess Margaret Hospital, Swindon, UK.)

Diagnosis. The condition must be distinguished from pseudo-ainhum.

Treatment. Control of secondary infection and protection from trauma may prevent extension of the scarring process. If symptoms are severe, or the dangling digit is a disability, amputation is indicated.

Pseudo-ainhum

Congenital. Congenital pseudo-ainhum may involve a digit, a limb or even the trunk, and it ranges in severity from a superficial groove to amputation *in utero* [5–8]. The cause is unknown, but familial cases have been reported. Some cases of pseudo-ainhum may be due to amniotic bands [9] or adhesions *in utero*, which may arise as a result of tearing of the amnion some time after the 45th day of pregnancy [10]. Cases have occurred in EDS and after amniocentesis [10,11].

Histology of the affected digit or limb reveals broad, finger-like projections of collagen, and coarse elastic bundles that penetrate deep into the subcutaneous fat [8].

Congenital pseudo-ainhum must be distinguished from: *aplasia* of the limbs with rudimentary digits; *acromelia* (in which part of the limb does not develop); and *hypoplasia* (in which the parts, although formed, are poorly developed).

Acquired. Pseudo-ainhum may be acquired as a result of infection (particularly leprosy), trauma, cold injury, neuro-

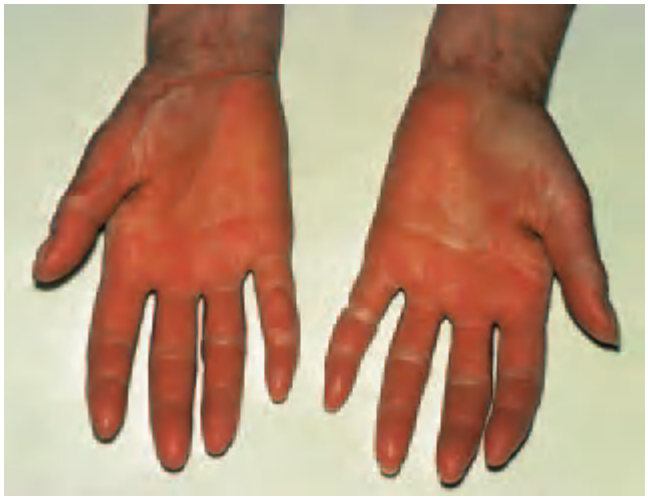

Fig. 46.45 Vohwinkel's disease with pseudo-ainhum of the fifth digit of the left hand. (Courtesy of Dr F.A. Ive, Dryburn Hospital, Durham, UK.)

pathy (especially congenital sensory neuropathy), systemic sclerosis, etc. [12], and it may occur in association with other hereditary diseases such as palmoplantar keratoderma (particularly Vohwinkel's disease) (Fig. 46.45), pachyonychia congenita, erythropoietic protoporphyria [13,14], and Olmsted's syndrome (Chapter 34). Factitial pseudo-ainhum has also been reported due to the self-application of a rubber tourniquet.

Multiple skin creases resembling constrictions may be seen in the Michelin baby syndrome (Chapter 15) and in 'multiple benign annular creases of the extremity' (Chapter 34).

Treatment. Staged Z-plasty sometimes gives an excellent result [15].

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Heberden's and Bouchard's nodes

Heberden's nodes [1] are posterolateral bony outgrowths affecting one or more *distal* interphalangeal joints. Similar changes, affecting the *proximal* interphalangeal joints, are termed Bouchard's nodes. Both Heberden's and Bouchard's nodes are associated with osteoarthritis, although they may be inherited independently as an autosomal dominant trait [2]. Characteristically, they are asymptomatic and of insidious onset, although tender nodes may develop acutely with a red, swollen joint. The association of multiple symmetrical nodes with distal interphalangeal joint arthritis has been termed 'primary generalized osteoarthritis'. Because this is associated with the tissue types HLA-A1 and B8 and shows a marked female preponderance, it has been postulated to be an autoimmune disorder; increased amounts of immune complexes can be detected in cartilage and synovium [3].

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Chapter 47

Urticaria and Mastocytosis

C.E.H. Grattan & A. Kobza Black

Urticaria

Introduction

Urticaria is common and embraces many different clinical entities. Dermatologists, allergists, general physicians and general practitioners see a quite different selection of cases, and this may cause confusion. The literature is large, and there are several monographs that can be consulted for a detailed bibliography [1–5].

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Definitions

The urticarias are characterized by short-lived swellings of the skin due to plasma leakage. Urticaria is often used to describe an eruption of weals, as distinct from angio-oedema—although this does lead to confusion with classification of the physical urticarias, and the term 'urticaria' is therefore better used as a collective term for weals and angio-oedema. Weals and angio-oedema often occur together and for practical purposes are similar processes. However, angio-oedema that is caused by C1 esterase inhibitor deficiency shows some differences clinically and in response to treatment.

Weals (syn. 'nettle rash', hives) is the descriptive term for transient, well-demarcated, superficial erythematous or pale swellings of the dermis, which are usually associated with itching.

Angio-oedema (syn. angioneurotic oedema, Quincke's oedema) swellings affect the deeper dermal, subcutaneous and submucosal tissues. They are usually painful rather than itchy, poorly defined, and pale or normal in colour.

Anaphylaxis, in the strict sense, is an acute life-threatening condition induced by an immunoglobulin E

(IgE)-mediated allergic reaction. It consists of a combination of symptoms and signs, including diffuse erythema, pruritus, urticaria and angio-oedema, hypotension and difficulty in breathing. A similar clinical picture from non-allergic causes is called an anaphylactoid reaction. However, 'anaphylaxis' is frequently used to describe the clinical picture whatever the cause (see Chapter 10).

Historical background

Urticaria has been recognized since the days of Hippocrates. The term dates back to the 18th century, when the stinging and burning was likened to the sting of a nettle (*Urtica dioica*). The changing opinions on the pathogenesis and management of urticaria provide a fascinating reflection of the changing fashions in medical thought [1,2].

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Classification

Urticaria is a heterogenous group of disorders that may be broadly classified by duration of disease and clinical features.

Urticaria is traditionally classified into acute and chronic, with a time division arbitrarily chosen between 6 weeks and 3 months. When urticaria is present daily or almost daily for less than 6 weeks, it can be termed acute in retrospect. If urticaria occurs on most days for longer than this, it can be categorized as chronic. This applies to all patterns of urticaria, but is most relevant to the ordinary presentation of urticaria, because physical urticarias and urticarial vasculitis nearly always have a chronic course, whereas contact urticaria usually presents with intermittent acute episodes. This classification by disease duration is of limited value, but an exogenous cause is more likely to be found in acute urticaria than in chronic urticaria. 'Episodic' is the best term used to classify the many cases of recurrent acute attacks.

A classification based on clinical features and trigger factors is convenient, but has inherent inconsistencies (Table 47.1). Several types of urticaria may coexist in the same person—for example, ordinary urticaria and various forms of physical urticarias, including delayed pressure urticaria. The term 'ordinary urticaria' can be used when predominantly physical, vasculitic and contact urticarias have been excluded. There is now strong evidence that up to 50% of patients previously diagnosed with chronic 'idiopathic' urticaria have an autoimmune basis for their disorder. It is therefore best to use the broader term chronic 'ordinary' instead of chronic 'idiopathic' urticaria for this group, so as to make no assumptions about aetiology. The criteria for 'idiopathic' will vary between clinicians depending on whether or not non-specific aggravating factors (such as aspirin and food additives) are regarded as causes [1]. Acute ordinary urticaria may be due to allergy, especially in atopics, but this does not account for chronic disease. It is convenient to separate angio-oedema without weals from angio-oedema with weals in the same patient, because some of these will be due to C1 esterase inhibitor deficiency and some to angiotensin-converting enzyme inhibitors (ACEIs) or non-steroidal anti-inflammatory drugs, but many will remain 'idiopathic' after full evaluation.

Table 47.1 Clinical classification of urticaria.

1 Ordinary urticaria
Acute
Chronic (often called 'idiopathic')
2 Physical and cholinergic urticarias
3 Urticarial vasculitis
4 Contact urticaria
5 Angio-oedema without weals
6 Other syndromes resembling urticaria or angio-oedema, or with urticaria as a component

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Associations

An association exists between chronic ordinary urticaria and autoimmune thyroid disease [1], and there is a higher frequency of autoimmune diseases in patients with autoimmune urticaria [2]. The older literature suggests that chronic 'idiopathic' urticaria may be associated with chronic infections, especially dental, and *Candida* infections of the bowel, but in the authors' experience this occurs rarely, if at all. A possible association between chronic 'idiopathic' urticaria and *Helicobacter pylori* infection remains to be proven with double-blind studies of eradication therapy. It has been proposed that *H. pylori* infection may play an indirect role in autoimmune chronic urticaria by molecular mimicry in genetically predisposed individuals [3]. Although there have been anecdotal reports of urticaria occurring with systemic malignancies, no association was found in a large epidemiological study [4].

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Prevalence

Urticaria is a common problem, with a point prevalence of 0.1% in one survey [1]. Estimates of the cumulative lifetime prevalence of chronic urticaria have varied from 0.05% to 23.6% in the general population, but a range of 1–5% seems more realistic [2]. In one British dermatology centre, of 2310 cases of urticaria seen over 32 years, ordinary urticaria made up 72% (excluding IgE-mediated allergic cases), physical and cholinergic urticarias 20%, allergic 3.4% (excluding stings and injected drugs), urticarial vasculitis 2.1% and hereditary angio-oedema 0.5% [3].

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Genetics

Hereditary C1 esterase deficiency angio-oedema, Muckle–Wells syndrome, familial cold urticaria and a few other rare physical urticarias are inherited as autosomal-dominant traits. Recent work has shown a highly significant linkage of human leukocyte antigen (HLA)-DR4 and its associated allele DQ8 in chronic ordinary urticaria patients with evidence of histamine-releasing autoantibodies [1].

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Histology

The histology of ordinary urticarial weals is usually non-specific, with vascular and lymphatic dilatation, oedema and a variable perivascular cellular dermal infiltrate consisting of lymphocytes, monocytes, neutrophils and eosinophils. On electron microscopy, dermal mast cells show signs of degranulation. In one study, dermal mast cells in weals of chronic urticaria were increased by 10 times [1] compared with non-urticated skin, but this increase was not confirmed in a recent study using tryptase as a marker [2]. In the majority of ordinary weals, there is a sparse perivascular infiltrate, predominantly of helper T lymphocytes [3,4] with a TH_0 cytokine profile expressing mRNA for interleukin (IL)-4, IL-5 and interferon-γ (IFN-γ) [5]. In a minority of weals, neutrophils are a conspicuous feature, within the vessel walls or scattered in the dermis [6]. Eosinophils may play a more important role than their sparse numbers seen on light microscopy would suggest, as extracellular eosinophil major basic protein is frequently deposited in spontaneous weals [7] and they stain for activation markers [8]. The spectrum of cellular changes may depend on the age of weals and their underlying cause. Biopsies are generally performed if individual weals are persistent, and they may show features of delayed pressure urticaria or urticarial vasculitis. In delayed pressure urticaria, the infiltrate is denser, with neutrophils often present in early weals, and eosinophils extending deep into the fat in early and late weals. These cellular changes correlated with moderate up-regulation of the vascular endothelial adhesion molecules E-selectin, intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) on perivascular cells [9]. Urticaria with histological evidence of vasculitis (venulitis) is defined as urticarial vasculitis.

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Pathophysiology [1–3]

Mast cell mediators and activation

Urticaria is due to a local increase in permeability of capillaries and venules. These changes are dependent on activation of cutaneous mast cells, which contain a range of pro-inflammatory mediators, but predominantly histamine. Increased concentrations of histamine have been recovered in tissue fluid from lesions of chronic idiopathic urticaria [4] and from venous effluent draining the urticated areas in most physical urticarias. The clinical improvement on treatment with H_1 antihistamines underlines the role of mast cell-derived histamine as a major

mediator in urticarias. Activation of H_1 receptors in the skin induces itching, flare, erythema and wealing. Activation of H_2 receptors contributes to erythema and wealing, but not itch or flare. So far, H_3 receptors—identified in the nervous system as inhibitory autoreceptors, in that their activation leads to reduced biosynthesis and release of histamine—have not been identified in human skin. Other vasoactive and chemoattractant mast cell-derived mediators, and secondary release of non-mast cell mediators from inflammatory cells, may amplify and prolong the weal. Little is known of the process of weal resolution.

Mast cell activation may be non-immunological or immunological. Non-immunological mast cell activation occurs with a variety of substances including neuropeptides, such as substance P; drugs, including opiate derivatives, such as morphine and codeine, vancomycin and polymyxin; some radiocontrast media; and some foods, such as strawberries. Neuropeptides elicit histamine but not prostaglandin D_2 (PGD_2) or leukotriene C_4 (LTC_4) release.

Immunological mast cell activation (see Chapter 9) occurs as a result of linkage of two adjacent α-subunits of high-affinity IgE receptors (FcεRIα) of a mast cell. Preformed histamine, proteases and newly generated mediators, including PGD_2 and cytokines—IL-3, -4, -5, -6, -8, -13 and tumour necrosis factor-α (TNF-α)—are released from mast cells. In classic immediate allergic reactions, receptor cross-linking occurs indirectly when an allergen (such as latex) reacts with two or more antigen-specific IgE antibodies, each bound to FcεRIα. Activation also occurs by cross-linking autoantibodies directed against IgE bound to FcεRIα or against the α-subunit of FcεRI itself. Complement C3a and C5a can release histamine directly and appear to be a necessary co-factor for some autoantibody-induced degranulation [5]. Basophils also express FcεRIα and release histamine, IL-4, IL-13 and LTC_4 on activation.

Compared with normal controls, the cutaneous mast cells from chronic urticaria also release more histamine spontaneously and in response to non-specific degranulating agents such as codeine and morphine [6]. There is no evidence for decreased skin histamine metabolism in the skin of chronic urticaria subjects. However, their cutaneous vasculature is more responsive to histamine than skin of normal controls [7].

Tryptase and chymase are released in conjunction with histamine. Potentially, they could play a part in the pathogenesis of urticaria, as chymase can induce mast cell degranulation and tryptase and chymase cleave C3 to C3a and C3b. C3a can activate mast cells, and C3b can activate the alternative complement pathway. The example of hereditary angio-oedema has encouraged a search for other inhibitor deficiencies as a cause for other types of urticaria. A decrease of α_1-antitrypsin has been reported in cold urticaria [8]. Low levels have only sometimes been found in other types of urticaria, including chronic 'idiopathic' urticaria [9]. Usually there is a poor correlation between the levels found and the clinical activity.

There is no convincing evidence that the low levels of vasoactive PGD_2 and LTC_4 released from cutaneous mast cells play a significant role in urticaria. While TNF-α up-regulates vascular endothelial adhesion molecules, IL-8 causes neutrophil leukocyte accumulation. IL-4 also influences T-lymphocyte differentiation towards a cytotoxic phenotype and immunoglobulin production by plasma cells. However, a direct role for these interleukins in urticaria has not been substantiated.

Histamine-releasing autoantibodies

Sera of approximately 60% of patients with chronic 'idiopathic' (ordinary) urticaria have been shown to cause a pink weal, probably due to histamine, when injected intradermally into the patient's own skin (the autologous serum skin test) [10]. Approximately half of these patients' sera (30% of total chronic 'idiopathic' urticaria patients) released histamine *in vitro* from basophils and skin slices obtained from healthy people in one series [11]. The proportion of chronic urticaria sera releasing histamine has been up to 50% in others [5]. This activity is due to functional IgG autoantibodies directed against the α-subunit of FcεRI or less frequently against receptor-bound IgE [12,13]. These functional autoantibodies are predominantly of IgG1 and 3 subclass [14]. Complement dependence of autoantibody-induced mast cell degranulation has been shown [15]. In a few patients with a positive skin test, there was evidence of an unidentified non-IgG factor reacting with mast cells but not basophils [16]. Autoantibodies, of predominantly IgG2 and 4 subclasses, against FcεRIα have been detected by Western blot and enzyme-linked immunoassay (ELISA) in the sera of patients with other conditions, such as systemic lupus erythematosus (SLE), dermatomyositis, bullous pemphigoid and pemphigus vulgaris [14], and even in healthy subjects [17], but appear to be non-functional and therefore unlikely to be of pathogenic importance.

Immune-modulating treatment of severely affected chronic urticaria patients with a positive skin test, using plasmapheresis [18] and intravenous immunoglobulin [19], was associated with clinical remission in some. Thus, in some patients, chronic urticaria appears to be a manifestation of a specific autoimmune disorder. In the remaining 50% of patients, no histamine-releasing factor can be identified *in vitro* or *in vivo*. The role for histamine-releasing factors in the clinical behaviour and therapeutic response of chronic urticaria is still under investigation.

Neuropeptides

Some nerve endings are positioned close to mast cells. Histamine can stimulate sensory afferent nerves to release

substance P. Neuropeptides appear to be responsible for the neurogenic axon flare after intradermal histamine injection [20], but there is no direct evidence for neuropeptide involvement in weal formation.

Kinins and complement

Plasma-derived kinins do not appear to have a significant role in chronic urticaria, but it is thought that production of bradykinin by the action of kallikrein on kininogen and kinin-like peptides derived from the early components of complement are important in the pathogenesis of angio-oedema associated with C1 esterase inhibitor deficiency. The angio-oedema seen with ACEI is believed to be due to inhibition of breakdown of bradykinin by ACE, which also acts as a kininase. Complement activation, with production of the anaphylatoxins C3a and C5a, occurs in urticarial vasculitis.

Cellular involvement

The dermal leukocyte cellular infiltrate in chronic ordinary urticaria, consisting of lymphocytes, neutrophils and eosinophils, releases a variety of cytokines with pro-inflammatory properties that may enhance and perpetuate the wealing response. Blood basophils may be involved in the pathogenesis of chronic ordinary urticaria, as their numbers are substantially reduced in the presence of histamine-releasing factors in serum [21], and they also release less histamine in response to anti-IgE stimulation [22]. Recent evidence indicates that they may contribute to prolongation of urticarial weals by active recruitment from the circulation [23]. The observation that the cellular infiltrates in weals of patients with chronic autoimmune and non-autoimmune ordinary urticaria are similar [24] suggests that the inflammatory response is determined by the event of mast cell degranulation rather than its stimulus.

In physical urticarias, there is no evidence for increased mast cell numbers. Infiltrates tend to be mild and mixed in dermographism [25]. In addition to histamine release, ill-defined eosinophil and neutrophil chemotactic factors have been demonstrated in venous effluent from cold, cholinergic and solar urticarial lesions. The mode of activation of mast cells in physical urticaria is poorly understood, but in some patients with dermographism, cold and solar urticaria, a transferable IgE-like factor has been identified. It has been speculated that the physical stimulus in these patients may induce a neo-antigen that could stimulate IgE production directed specifically against it. On rechallenge, this neo-antigen would react with its specific IgE bound to mast cells and activate mediator release. Increased substance P and vasoactive intestinal peptide (VIP) have been recovered from dermographic and cold urticarial lesions, while clinical lesions of cold and localized heat urticaria were diminished by prior application of topical capsaicin, a depletor of neuropeptides.

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Ordinary urticaria

Clinical features

Itching erythematous macules develop into weals consisting of pale to pink, oedematous, raised areas of the skin often with a surrounding red flare. They occur anywhere on the body, including scalp and palms and soles, in variable numbers and sizes, ranging from a few millimetres to lesions covering large areas and of varying shapes including rounded, annular, serpiginous and bizarre patterns due to confluence of adjacent lesions (Fig. 47.1). Occasionally, bullae may form in different types of urticaria. Weals generally last a few hours and resolve within 24 h, passing through a macular erythematous phase, but nearly always leaving the skin with a normal appearance. Weals are generally very itchy, especially superficial weals and particularly at night. Patients tend to rub rather than scratch, so excoriation marks are unusual, but occasionally bruising may result, which may be seen particularly on thighs. Weals may be more pronounced in the evenings or premenstrually.

In 50% of ordinary urticaria cases, there may be associated angio-oedema. These deep swellings, which may be the same colour as normal skin, occur most frequently on the face, affecting the eyelids and lips, but any other area of the body may be affected, such as ears, neck, hands, feet and genitalia. Mucosal swellings occur inside the oral cavity on the buccal mucosa, tongue, pharynx and larynx. Angio-oedema may be preceded by an itching or tingling sensation, but it is not always itchy and may be painful. The lesions may last for several days.

Urticaria may be preceded by vomiting [1] and be associated with systemic symptoms of malaise, loss of concentration, feeling hot and cold, headache, vomiting, abdominal pain, diarrhoea, arthralgia, dizziness and syncope and, in its most severe acute form, with anaphylaxis.

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Urticaria in childhood

The same multiplicity of factors is found as in the adult [1], with a tendency to more cases of acute disease. Cow's-milk allergy is the commonest cause of urticaria in infants under 6 months old [2]. In infants, there may be less itching and a greater tendency for weals to become purpuric. A not uncommon pattern is one of bizarrely shaped weals, not seen as frequently in adults. No specific aetiology or natural history has emerged in such cases. Neonatal haemorrhagic urticaria (purpura en cocarde) occurs in very young children and is borderline between urticaria and vasculitis (Fig. 47.2).

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Acute urticaria

Most acute urticaria is ordinary and some will become chronic. Serum sickness due to injection of therapeutic animal antisera (e.g. to snake venoms) is now rare. Physical urticarias will go through an acute phase but most will last more than 6 weeks. Contact urticaria does not usually present as acute urticaria because it tends to be intermittent and short-lived. The incidence in the community is not well defined. Many cases will not present to secondary care. Although some cases can be ascribed to allergy, non-allergic causes or infections, many will be idiopathic after evaluation.

Idiopathic

This form of acute urticaria, in which no cause can be identified, was present in more than 50% of patients with acute urticaria presenting to a city 'walk-in' dermatology centre [1]. In the others, the most common preceding event was an upper respiratory tract infection, followed by drug ingestion, but allergy or intolerance to food was rare [1,2].

Allergic

This is commoner in the community than in dermatological practice, where it is rare. Allergic urticaria is due to interaction of an allergen with specific IgE bound to the mast cell. It is commoner in people who are atopic and have elevated IgE levels. Although it is unusual to find an allergic cause for acute urticaria [1], any drug, food, foreign substance from blood transfusion, injection, implant, contactant and inhalant should be considered as a potential allergen (Table 47.2). In an IgE-mediated reaction, there will have been a previous exposure and the reaction may occur in minutes and no longer than 60 min. Patients will usually recognize this and avoid the offending substance. Acute urticarial reactions from drugs are common (Tables 47.2 and 47.3), usually occurring within 36 h of drug administration. It is unusual to develop urticaria from a drug taken continuously for months. Sometimes, it is uncertain if a drug-induced urticaria is allergic, and if it is, whether the reaction is IgE-mediated or IgG-mediated via immune complexes [3]. Antibiotics, especially penicillins and cephalosporins, are common causes. Increased risk factors include previous exposure and reaction to the drug or a chemically related drug, intermittent and multiple drug therapy, and a familial predisposition [4].

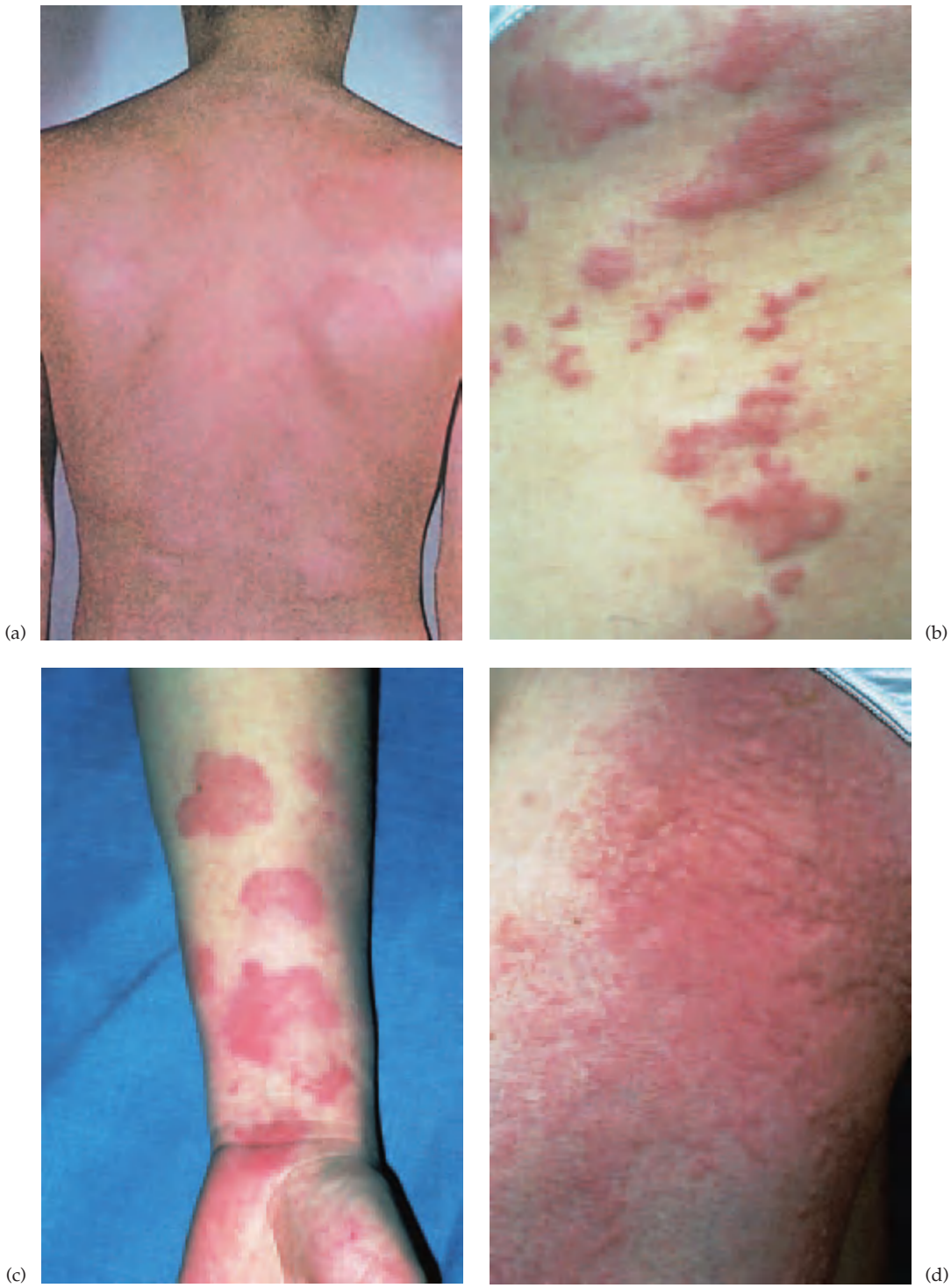

Fig. 47.1 Different morphology of urticarial weals. (Courtesy of Addenbrooke's Hospital, Cambridge, UK (a); courtesy of St John's Institute of Dermatology, London, UK (b–d).)

Acute urticarial reactions to food are believed to be common and many go unreported [5]. Urticarial reactions may not be to the basic nutrient but to other ingredients, such as seeds or spices. Reactions occur within minutes, but occasionally allergic urticaria develops many hours after food ingestion, probably due to slow absorption or metabolism of food. Rarely, allergic reactions to food occur only if intake is followed by exercise, with neither food nor exercise alone inducing weals (food-dependent exercise-induced anaphylaxis) [6]. Substances reported to cause this include wheat, hazelnuts and shellfish.

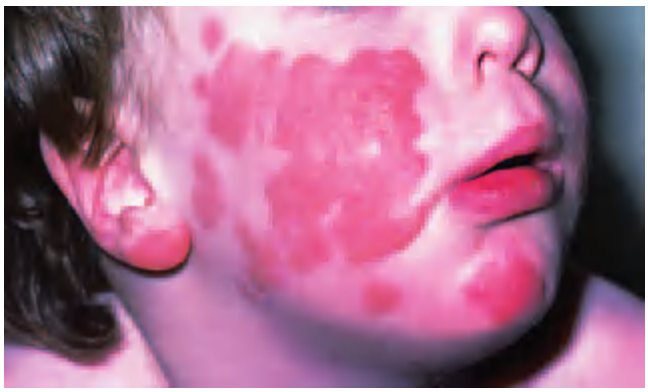

Fig. 47.2 Idiopathic haemorrhagic oedema or cocarde purpura of childhood. (Courtesy of Addenbrooke's Hospital, Cambridge, UK.)

Table 47.2 Some substances reported frequently to cause urticaria and anaphylaxis due to an immunoglobulin E-dependent mechanism, although other mechanisms may also be involved.

Latex
Hymenoptera (bee and wasp) stings
Penicillins
Cephalosporins
Insulin
Vaccines
Blood products
Crustaceans (lobsters, shrimp, crab)
Fish
Milk
Nuts, especially peanuts
Beans
Potatoes
Celery, parsley
Carrots
Spices
Rice
Bananas
Apples
Oranges

Table 47.3 Some substances implicated more frequently in causing non-immunological urticarial and anaphylactoid reactions.

Drugs
Acetylsalicylic acid (aspirin)
Other non-steroidal anti-inflammatory drugs
Polymyxin
Radiocontrast media
Plasma expanders
General anaesthetic agents

Stinging insects are members of the order Hymenoptera, and bees and wasps are representatives of its two major subgroups. Allergic reactions to injected sting venom are not uncommon and occasionally are fatal [7]. Development of bee-sting allergy usually requires multiple exposures, and is commonly seen in beekeepers. Development of allergy to wasp stings and the pattern of severity of reactions to any subsequent stings are unpredictable. Allergy to insect stings is not restricted to atopic individuals.

Reactions to some substances may be dramatically severe and may proceed rapidly to systemic anaphylaxis [8–10]. Here, prodromal symptoms include itching or tingling of the mouth, palms, soles and genital area. Subsequent signs include widespread erythema, urticaria, lacrimation, nasal stuffiness, bronchospasm, laryngeal oedema, nausea, diarrhoea, vomiting, hypotension or cardiac arrhythmias and can rarely lead to death. This is a medical emergency, and first-line treatment is with epinephrine (adrenaline) [10].

Some substances more readily evoking IgE-mediated anaphylactic reactions include penicillins, sesame seeds, peanuts, latex and Hymenoptera stings. The need to label food with individual constituents is increasingly recognized. In some patients, despite all efforts, no cause for anaphylactic symptoms can be identified [11].

Non-allergic

Acute urticarias from ingested substances may be non-allergic (see Table 47.3). They are then referred to as intolerance reactions. These may be due to direct histamine release from mast cells (histamine liberators) or due to other mechanisms (pseudoallergic). If they are very severe, resembling anaphylaxis, they are known as anaphylactoid [12].

Histamine liberators

Here, mast cell histamine release is not immunological and may occur after first exposure to a substance. Examples include morphine, codeine, tubocurarine and antibiotics, such as polymyxin, ciprofloxacin, rifampicin and vancomycin. Iodine-based radiocontrast dyes may cause anaphylactoid reactions. Exactly how radiocontrast media, low- and high-molecular dextran plasma expanders cause these reactions is not known. Complement activation is thought to play a role in serious dextran reactions.

Pseudoallergic reactions

The reaction is not substance-specific, and similar reactions may occur to unrelated compounds in the same individual. The severity of reaction is usually related to the dose of the offending substance. The mechanisms are unclear and may vary. Common offending substances include aspirin and other non-steroidal anti-inflammatory agents. These cause the reactions by pharmacological mechanisms thought to be related to their activity in inhibiting the cyclo-oxygenase pathway of arachidonic

acid metabolism, diverting it to pro-inflammatory lipoxygenase pathway products and by reducing PGE_2, which is inhibitory for immunological mast cell degranulation [13]. Although aspirin may exacerbate chronic urticaria, these reactions are usually not severe. While the exact role of food dyes and preservatives in exacerbating chronic urticaria is controversial, tartrazine and other dyes have been implicated in causing pseudoallergic reactions. Food preservatives are implicated less commonly.

Alcohol-induced urticaria is rare; the mechanism of causation is unknown, but appears not to be an allergic one [14]. Alcoholic beverages can aggravate urticaria non-specifically. White wines are often treated with sulphites, which have rarely been reported to cause urticaria and anaphylaxis [15,16]. Some red wines contain measurable concentrations of vasoactive amines including histamine [17] which could aggravate urticaria, but cutaneous symptoms relate poorly to histamine content [18].

Food may also contain vasoactive amines including histamine (such as cheese, fish, meat, tomatoes, pineapple and avocados) or histamine-releasing substances (such as in strawberries). Toxins in scombroid fish (under-processed tuna, mackerel) can cause acute urticaria by releasing histamine, and high levels of histamine can usually be found in affected fish [19].

Infections

Urticaria may follow non-specific infections [1,2], Epstein–Barr [20] or hepatitis B viral infections, anisakiasis (infection by a fish parasite) [21], streptococcal throat infections in children and, rarely, *Campylobacter jejuni* infections [22].

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Chronic urticaria

Chronic urticaria of at least 6 weeks' duration may be ordinary, physical or vasculitic.

Chronic ordinary urticaria

There does not appear to be an increased incidence of atopy. Up to 37% of patients with chronic urticaria have associated delayed pressure urticaria and occasionally other physical urticarias. Most were considered to be 'idiopathic' [1] before autoimmunity was recognized as a cause [2]. Even now, the cause can rarely be identified with certainty, since there are no routinely available tests for histamine-releasing autoantibodies, although provoking factors should always be sought.

Potential provoking factors

Drugs

Many drugs can induce urticaria, but this is frequently of the acute type. The relationship between penicillin and chronic urticaria is a complex one, but the amount present in dairy products seems unlikely to perpetuate chronic urticaria except in people with extreme penicillin sensitivity, or if penicillin is present in food above permitted levels [3].

Salicylates and other related non-steroidal anti-inflammatory drugs such as diclofenac can aggravate urticaria and asthma by non-allergic mechanisms. Patients usually react with either urticaria or asthma, but not both [4]. The percentage of patients whose urticaria is exacerbated by aspirin (acetylsalicylic acid) varied from 20% to 30% in different studies [5,6]. Many medicines and proprietary preparations contain aspirin, but the small amounts of salicylates present in food are unlikely to be significant [7].

ACEIs can provoke angio-oedema and may aggravate urticaria.

Foods and food additives

Numerous foods have been blamed as a cause of urticaria [8]. However, an allergic cause for ordinary urticarias was found in fewer than 3.5% of cases [1,9]. The general population blamed foods for their adverse clinical reactions, including urticaria, more often than could be reproduced on double-blind challenge [10].

There are many reports that food additives aggravate chronic urticaria, but the high incidence of 33% [11] has not been confirmed in some double-blind studies [12]. The discrepancies in incidence in different studies could arise from the differing populations and test methods used. Food and food additives are blamed more frequently in reports emanating from allergy departments. There are various reasons for this, not least a different selection of patients. Other variables during testing include antihistamine therapy, basic diet, hospitalization and whether testing was placebo-controlled and double-blind, with confirmation of positive results on retesting [13]. The exact percentage of reactions to additives is not known, but is considered to be important in fewer than 10% of patients with chronic ordinary urticaria. The most frequently implicated food additives are tartrazine (E102), other azo dyes including amaranth (E123) and sunset yellow (E110). Reactions to benzoate preservatives (E210–219) and antioxidants, such as butylated hydroxytoluene (E321) and butylated hydroxyanisole (E320), are reported less often. In our enthusiasm to remove unnecessary additives from our environment, it must not be forgotten that food preservatives help prevent infections transmitted by food, which are overall a much more important problem than food allergy or intolerance [14]. Sulphites (E223–228), monosodium glutamate (E621) and aspartate are very rare causes of urticaria, which is usually of the acute type. The sensitivity to additives gradually lessens as the urticaria resolves. Dyes and preservatives can be found in medicinal products, but usually in smaller doses than in food [15]. Skin tests may at times be helpful, but cannot be relied on [16]. Oral challenge testing may be performed if desired by physician or patient, but in the authors' urticaria clinics (see St John's challenge test, Table 47.4) we find fewer than 10% reacting. However, food additives may be a more important problem in other populations. Full labelling of food products with their food ingredients and additive constituents is increasingly regarded as important.

Table 47.4 Substances used in blind-challenge testing of food additives at St John's Institute of Dermatology.

Tartrazine 10 mg*
Sodium benzoate 500 mg*
4-hydroxybenzoic acid 200 mg
Yeast extract 0.6 g
Penicillin 0.5 mg†
Aspirin 100 mg
Aspirin 500 mg‡
New coccine 10 mg
Canthaxanthine 100 mg
Sunset yellow 10 mg*
Annatto 10 mg
Butylhydroxytoluene 50 mg
Butylhydroxyanisole 50 mg
Sorbic acid 600 mg
Sodium nitrite 100 mg
Sodium nitrate 100 mg
Quinoline yellow 10 mg
Sodium glutamate 200 mg

* One-tenth of the dose to be given if a child is under 10 years or if there is a history of asthma.
† Not to be given if there is a history of severe penicillin reaction.
‡ Not to be given if there is a history of asthma or severe aspirin reactions.

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Infections/infestations

Chronic urticaria is frequently flared by intercurrent viral infections. This may be a non-specific effect of circulating pro-inflammatory cytokines or chemokines, either acting on mast cells or leading to expression of adhesion molecules on endothelial cells.

The incidence of bacterial infections such as dental sepsis, sinusitis, urinary tract and gallbladder infections in chronic urticaria varies in different series. If present, treat-

ment of the infection usually does not improve urticaria [1] and, overall, infections are a rare cause of chronic urticaria. More recently, a possible role for *Helicobacter pylori* [2] has been suggested, but not confirmed by double-blind studies of eradication therapies. *Candida* infections, although described [3], are found extremely rarely to be a cause of urticaria. Intestinal parasites are a rare cause in developed and developing countries [4], but should be looked for if there is a blood eosinophilia or a history of recent travel to subtropical or tropical areas [5]. Rarely, protozoa or helminthic infection in the tissue may be a cause. Linear weals may follow migration of *Ancylostoma* and *Strongyloides* worms. Recently, *Toxocara canis* antibodies have been associated with chronic urticaria, but a causal relationship is not proven [6].

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Inhalants

Grass pollens, mould spores, animal danders, house dust [1] and even tobacco smoke have been implicated as triggers of acute or chronic urticaria, with or without respiratory symptoms, but this must be very rare. If pollen allergy is proven, desensitization may exceptionally be successful [2].

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Systemic disease

It is unusual to find a systemic cause that is not suggested in the history. Collagen vascular diseases, in particular lupus erythematosus and Sjögren's syndrome, have been described as possible causes of chronic ordinary urticaria, but these are usually associated with urticarial vasculitis. Chronic urticaria may be associated with IgM macroglobulinaemia (Schnitzler's syndrome).

Neither hypo- [1] nor hyperthyroidism [2] is commonly associated with chronic urticaria, but increased incidence of thyroid autoantibodies and disturbances of thyroid function have been reported [3]. Occasionally, appropriate treatment for an autoimmune thyroid disease [4] may help the urticaria but usually it has no influence.

Acquired C1 esterase inhibitor deficiency angio-oedema can be associated with collagen vascular disease and lymphoma. There is no convincing evidence of any association of chronic urticaria with malignancy [5].

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Menstrual cycle and pregnancy

Urticaria may occur in pregnancy, but it is difficult to evaluate any causal relationship. Pruritic urticated papules and plaques of pregnancy (PUPPP, syn. polymorphic eruption of pregnancy) is the most common specific dermatosis of pregnancy and occurs during the third trimester. Urticaria may worsen premenstrually, but if urticaria occurs predominantly or only premenstrually, it has been attributed to progesterone sensitivity [1] or more rarely oestrogen sensitivity [2], usually on an autoimmune basis. More recently, a non-immune mechanism has been suggested for 'autoimmune' progesterone urticaria [3].

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Implants

Urticaria has been linked anecdotally with a metal pin in the femur [1], a metal dental prosthesis [2] and with dental amalgams [3], but an apparent association in these cases may have been fortuitous.

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Psychological causes

Psychological factors appear to play a contributory role in a proportion of patients, and flare-ups of urticaria do occur at times of psychological stress [1]. Psychological factors are often wrongly thought to contribute to angio-oedema because of the old name 'angioneurotic oedema', which implied something very different when it was first introduced. The importance of psychological factors is difficult to evaluate scientifically and can be over-emphasized. Depression and anxiety were found more frequently in chronic urticaria in two studies [2,3], but not in another [4]; however, depression may reduce the threshold for pruritus [5], and the effect of chronic urticaria on quality of life should not be underestimated [6].

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Clinical history taking and diagnosis

The clinical diagnostic process is the same for all urticarias. A comprehensive history is essential for diagnosis and elucidation of any causative factors, as weals are often not present. Performing an extensive panel of investigations in addition to a standardized questionnaire added little to making a final diagnosis [1]. Information should be obtained regarding the onset, duration and course of the disease. The duration of individual weals and presence of purpura are important. Weals lasting more than 24–48 h, particularly if painful or tender, suggest the possibility of urticarial vasculitis or delayed pressure urticaria, but can occur in ordinary urticaria. Purpura, although rarely seen, suggests urticarial vasculitis, but can occur in ordinary urticaria. The location, numbers and shapes of weals vary and are usually not helpful in differentiating most urticarias, except for the typical small, monomorphic, short-lasting weals of cholinergic urticaria and the linear weals of dermographism. The presence of any angio-oedema, particularly if it has affected the oropharynx with difficulty in swallowing or breathing, should be noted. Enquiry should be made for systemic symptoms sometimes associated with cutaneous lesions, including malaise, headache, abdominal pain, arthralgia, wheezing and syncope. Possible precipitating or aggravating factors—including physical factors such as heat, cold, localized pressure on the skin, friction and sunlight—should be sought directly. It is important to enquire regarding any association with recent acute infection, drugs, non-prescription medicines and foods, although the latter are rarely a cause for chronic urticaria. A family history of atopy, autoimmunity or angio-oedema may be useful information.

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Differential diagnosis

The diagnosis of urticaria and angio-oedema is rarely a problem. They are distinguished by their evanescent nature and normal overlying epidermis. Papular urticaria, erythema multiforme and prebullous eruptions must be distinguished from urticaria. Acute contact dermatitis, lymphoedema and collagen vascular disease (such as dermatomyositis) may mimic angio-oedema, but these conditions last longer than 24–48 h. The part played by urticarial reactions in atopic dermatitis is discussed in Chapter 18.

Investigation

Acute urticaria

In patients with potentially life-threatening reactions to an allergen, confirmation by a semiquantitative radioallergosorbent test (RAST) or fluoroimmunoassay (CAP FEIA®, Pharmacia) that measures serum antigen-specific IgE antibody to the allergen may be possible, for example for peanuts. In most cases of acute urticaria in which no cause is suggested in the history, investigation rarely provides an answer. For moderately severe acute reactions, skin-prick testing with suspected allergens may be helpful, for example for *Hymenoptera* venom and some foods, if the reaction is not a delayed one. Prick testing is potentially dangerous if there is a background of anaphylaxis. Epinephrine administration for severe reactions may be less effective in patients on β-blocking drugs. The clinical relevance of the results of prick and RAST tests needs careful evaluation. Routine prick testing in chronic urticaria is not helpful [1].

Chronic urticaria

A thorough history of the rash and any associated systemic symptoms is essential. Attention should be paid to

medication, especially non-steroidal anti-inflammatory drugs. It is important to identify a physical urticaria, as delayed pressure urticaria may be associated in 37% of these patients. If weals persist and are painful, with presence of systemic symptoms, urticarial vasculitis should be considered, and a biopsy performed. Patients frequently suspect allergy to foods, but this is rarely found in chronic ordinary urticaria. A food diary may be helpful, especially in episodic urticaria, but it should be remembered that the time interval may vary from a few seconds with allergy to 24 h or more with dietary pseudoallergens, and the substance may have been consumed regularly for years. If the patients suspect food additives, or if they have improved substantially on elimination of this substance or on a diet free of food additives, challenge testing can be carried out on a placebo-controlled basis. This is performed when the patient is in relative remission, and antihistamine therapy need not be stopped, although this is desirable. Coded test substances (see Table 47.4) are given orally in a gelatine capsule on a daily basis, with additives alternating with placebo capsules, the method being based on that devised by Warin and Smith [2]. The most important test substances are tartrazine, aspirin, sodium benzoate and 4-hydroxybenzoate. The patient records any urticarial response, and if present the suspected substance and placebos are re-administered on at least one occasion for confirmation of the results. When the provocation tests are positive, a regionally appropriate tartrazine-free, salicylate-free or other appropriate diet can be suggested and is usually only necessary for a few months [3]. It is usually not necessary to carry out these elaborate and time-consuming provocation tests in patients who respond well symptomatically to antihistamine therapy. A low-pseudoallergen diet may be helpful for some patients [4], especially if antihistamines have failed or are not accepted.

Skin-prick or intradermal tests are even less helpful, and there were no relevant unsuspected positive tests in a group of urticaria patients [1]. In addition, a positive skin test is difficult to interpret, as an atopic patient with urticaria will show many irrelevant positive results, and false-negative results may also occur. Although a few patients with chronic urticaria and a positive intradermal test to *Candida albicans* were helped by an anti-*Candida*/antiyeast regimen (nystatin orally and vaginal pessaries, amphotericin lozenges and a yeast-free diet for 2–4 weeks) [5], this has not been our experience.

Other investigations are aimed at finding any associated disease, but it is uncommon for a cause of urticaria to be found in the absence of some lead from the general history. Only a total and differential full blood count and erythrocyte count is performed routinely. An elevated erythrocyte sedimentation rate (ESR) suggests the possibility of an underlying systemic disease (lupus erythematosus, urticarial vasculitis, macroglobulinaemia), and an eosinophilia would prompt a search for parasitic disease. Screening tests for thyroid autoantibodies may be worthwhile, as up to 14% of patients with chronic urticaria may have thyroid autoimmunity [6] and initial reports suggest that treatment with thyroxine to suppress thyroid activity may resolve the urticaria [7]. Further tests depend on history, and routine biochemistry, complement levels, serum proteins and electrophoresis, serum immunoglobulins, non-organ-specific and organ-specific autoantibodies, total IgE and RASTs, skin tests and fastidious searching for evidence of infection are not indicated [8]. There is currently no simple clinical test for serum histamine-releasing autoantibodies, which remains a research investigation, although the autologous serum skin test (ASST) appears to be a reasonably sensitive and specific marker for them [9]. If angio-oedema is a major component of the disease, screening tests for hereditary or acquired C1 esterase inhibitor deficiency should be performed by measuring plasma complement C4. It is reduced and rarely, if ever, reaches normal values even between attacks of C1 esterase deficiency angio-oedema. Reduction of functional C1 esterase inhibitor confirms the diagnosis.

A skin biopsy may be helpful if the weals persist for more than 48 h and do not respond to antihistamines. Urticarial vasculitis or delayed pressure urticaria is then suspected.

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Natural history

Acute attacks may last a few hours or days and be of great severity. There is no way of predicting the duration of an initial attack. Chronic cases where no diagnosis is established may last for weeks, months or even years. The severity is often greatest at the onset, with subsequent waning. New lesions appear daily or at irregular intervals, and there may be periodic exacerbations, sometimes

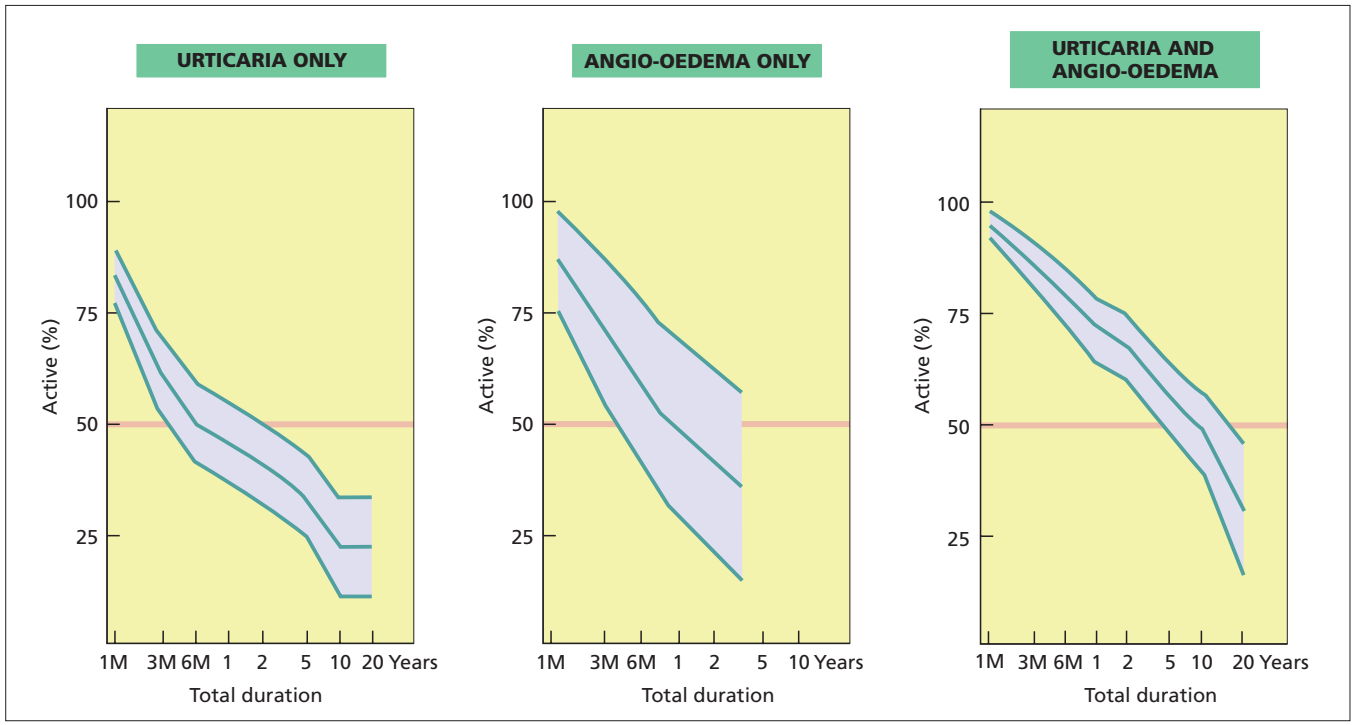

Fig. 47.3 The natural history of urticaria in 554 hospital patients. The expected percentage of patients with active urticaria, with 95% confidence limits, by the total duration of disease (log scale). M, months. (From Champion *et al*. [1].)

associated with intercurrent infections or non-steroidal anti-inflammatory drug intake. In general, spontaneous improvement occurs even in the absence of diagnosis or treatment. Fifty per cent of cases of those with weals alone attending a specialist clinic can be expected to clear within 6 months of onset, but 50% of those with associated angio-oedema can still be expected to have their condition 10 years later [1] (Fig. 47.3). A recent survey of the prognosis of patients attending a tertiary referral clinic in the Netherlands confirms the poor outlook for many patients with chronic urticaria, especially those with cold urticaria [2].

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Management

Explanation and non-specific measures may be helpful. Patients should minimize overheating, stress and alcohol. Aspirin and aspirin-containing compounds, and if possible other non-steroidal anti-inflammatory agents and also opiates, should be avoided. Paracetamol is usually a satisfactory alternative. If food additives, colourings or preservatives have been proven to be a problem, diets excluding these substances may be of value to a limited number of patients. Drug therapies can be first-, second-, or third-line, the choice of treatment depending upon the response to previous measures [1] and the impairment of quality of life for the patient.

First-line therapies

Histamine is the main mediator of urticaria, with H_1-receptor activation causing itch, wealing and flare, while H_2 activation plays a smaller role in weal formation. Thus, H_1 antihistamines are the first-line treatment of urticaria. They are usually modifications of the histamine molecule with which they compete and block the H_1 receptor. Generally H_1 antihistamines are rapidly absorbed, reaching peak serum concentrations in 2 h. However, many are metabolized in the liver, and some active metabolites have a longer half-life than the parent compound and determine the activity profile of the medication.

The use of traditional classic antihistamines has been limited by their side effects, including sedation, anticholinergic properties and paradoxical excitation in children. However, they are useful if night-time sedation is required. Hydroxyzine is the most potent of the classic antihistamines. Doxepin, a tricyclic antidepressant with potent antihistaminic activity, in a starting dose of 10–

30 mg, is useful for the anxious patient at night, but as it also reacts with α-adrenergic receptors it should not be taken with monoamine oxidase inhibitors.

The second generation of potent, specific, low-sedation H_1 antihistamines is now the treatment of choice [2], as well as their newly introduced derivatives, sometimes known as third-generation antihistamines. Their main advantage is low sedation at doses recommended by the manufacturer, and minimal anticholinergic side effects. They are at least as effective as hydroxyzine and generally as effective as each other. There is no clear evidence that tolerance occurs after continued use.

Terfenadine, the first available low-sedation antihistamine, is now little used due to concern about prolongation of the cardiac Q–Tc interval at normal doses, especially in circumstances where cytochrome P-450 is inhibited (liver disease, in conjunction with macrolide antibiotics, such as erythromycin, or imidazole antifungals, such as ketoconazole, itraconazole). Astemizole has been withdrawn for the same reason. Although this side effect is rare, serious irregular ventricular tachycardias with Q–Tc prolongation (*torsade de pointes*) have occurred, with fatalities. Recent elucidation of the *HERG1* gene encoding the major K^+ cardiac repolarization channels offers a molecular understanding of the cardiotoxic properties of terfenadine and astemizole, which block the channels at clinically relevant concentrations [3]. Mizolastine, which also undergoes limited conversion by hepatic CYP 3A4, is able to block *HERG1* channels to some degree. Its use with drugs that prolong the Q–Tc interval—such as amiodarone, quinidine and neuroleptic drugs and tricyclic antidepressants—and with electrolyte disturbance should be avoided. The classical antihistamines hydroxyzine and diphenhydramine also have the ability to induce Q–T prolongation [3], emphasizing that higher than recommended doses of these antihistamines should be used only with caution. The active metabolite of terfenadine, fexofenadine, appears to be ineffective at blocking K^+ channels.

Loratadine (adult dose 10 mg daily) is a derivative of azatadine. Although loratadine is also metabolized in the liver by cytochrome P-450 to some extent, the parent compound has not been reported to have an effect on the cardiac Q–Tc interval, and so far no clinically proven relevant drug interactions have been reported. It too has a recently launched metabolite, desloratadine, which has more potent antihistaminic properties than its parent compound. It is not yet clear whether it offers a clinical advantage in urticaria or any subsets of it.

Cetirizine (adult dose 10 mg/day) is poorly metabolized in the liver and is excreted, predominantly in the urine, unchanged. It is more sedative than placebo in some studies and is best taken at night. Cetirizine reduces dermal eosinophil cell accumulation *in vitro* and *in vivo*. However, the clinical importance of this effect in the treatment of delayed pressure urticaria and urticarial vasculitis, where eosinophils may be an important component of the inflammatory cell infiltrate, is uncertain. The active enantiomer, levocetirizine, has recently been launched.

Acrivastine (adult dose 8 mg three times a day) has a rapid onset and duration of action and is excreted predominantly in the urine.

Antihistamines cross the placenta. There is no reliable evidence that they are teratogenic, but they should be avoided in pregnancy and particularly in the first trimester if possible. If it is not possible, then chlorpheniramine appears to be the least risky to use.

Low-sedation antihistamines are used to reduce urticarial activity, with minimal side effects. Individual response is variable, but adequate dose and timing in relationship to maximal urticarial activity is important. Alternative low-sedation antihistamines can be tried, and sedating ones added at night. A combination of an H_1 antagonist with an H_2 antagonist may be more effective than H_1 antihistamines alone in an unpredictable subgroup of patients. Use of ranitidine (adults 150 mg twice a day) is preferable to cimetidine, which has more antiandrogenic side effects and drug interactions.

Second-line therapies

Oral systemic corticosteroids are effective in severe urticaria when given in higher doses such as 0.5–1.0 mg prednisolone/kg/day. Although short courses are useful for acute exacerbations, prolonged use should be avoided because of the risk of side effects. Oral corticosteroids are often required for disease control in severe delayed pressure urticaria and urticarial vasculitis, but every attempt should be made to minimize the dose and duration. In uncontrolled studies, anabolic steroids have been reported to benefit patients with refractory urticaria [4].

The emergency treatment for non-hereditary angio-oedema causing respiratory embarrassment from oropharyngeal–laryngeal angio-oedema is epinephrine. It acts rapidly by vasoconstriction and stabilizing mast cells through β-adrenoceptor stimulation. For moderately severe reactions it can be inhaled for its local effect, but for severe reactions particularly of the anaphylactic type, epinephrine must be injected intramuscularly or subcutaneously. Treatment should be repeated if there is no improvement after 10–15 min. Patients who have had a severe reaction should be shown how to self-administer epinephrine and should keep two unexpired ampoules or 'pens' available. Details of treatment of anaphylaxis can be obtained elsewhere.

The choice of other second-line therapies will be influenced by the clinical presentation. Perhaps the most promising new class of drugs is the leukotriene receptor antagonists, which have been shown to benefit aspirin-sensitive urticaria [5]. Mast cell stabilizers such as the

β-agonist terbutaline [6] and the calcium-channel antagonist nifedipine [7] also have been combined with H_1 antagonists in small numbers of patients, and any additional benefit remains to be confirmed. Narrow-band phototherapy may help some patients [8], although controlled studies are needed.

Third-line therapies

For patients with severe, unremitting urticaria not responding to conventional therapy, immunomodulatory strategies have been tested in small, uncontrolled trials. Plasmapheresis improved six out of eight such patients with autoimmune urticaria for 3–8 weeks only [8]. Intravenous immunoglobulin (IVIG) infusions, at 0.4 g/kg/day for 5 days, improved nine out of 10 patients, two of whom remained clear for 2 years [9]. Ciclosporin A at 2.5–3.5 mg/kg/day for 1–3 months improved or temporarily cleared the majority of patients with severe urticaria [10,11] and its efficacy has been confirmed in a randomized placebo-controlled study at 4 mg/kg/day for 4 weeks [12].

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Physical and cholinergic urticarias [1,2]

The physical urticarias are a distinct subgroup of urticarias in which a specific physical stimulus induces reproducible wealing (Table 47.5), and this feature is the basis of diagnosis. Cholinergic urticaria occurs in response to sweating caused by heat, so it is frequently included in the physical urticaria group, but it may also be triggered by emotional and gustatory sweating.

Table 47.5 A classification of physical urticarias and their prevalence.

	Prevalence
Due to mechanical force	
Dermographism	
Immediate symptomatic	+++
Red	+–
Cholinergic	+
Delayed	+–
Associated with mastocytosis	+
Delayed pressure urticaria	++
Vibratory angio-oedema	+–
Due to heat	
Generalized	
Cholinergic urticaria	++
Variants:	
Cholinergic pruritus	+
Persistent cholinergic erythema	+
Cholinergic dermographism	+
Exercise-induced anaphylaxis	+
Localized contact heat urticaria	+–
Due to cold	
Idiopathic	
Inherited	+–
Acquired	
Contact	
Cold erythema	+
Immediate cold contact	+++
Delayed cold contact	+–
Localized	+–
Systemic	
Generalized reflex cold urticaria	+–
Cold-dependent cholinergic urticaria	+–
Secondary to serum cryoproteins (cryoglobulins)	+
Solar urticaria	+
Aquagenic urticaria	+

Combinations of different types are common.
+–, rare; +, uncommon; ++, moderately common; +++, very common.

The frequency of physical urticarias in the general population is unknown, but they account for 19% of urticaria cases in a dermatology clinic [3], with dermographism making up 9% and cholinergic urticaria 4%. However, mixtures of various types of physical urticaria or of a physical urticaria with ordinary urticaria are common—for example, delayed pressure urticaria occurs in 37% of people with ordinary chronic urticaria.

Wealing caused by physical stimuli usually occurs in minutes at the site of contact with the skin and persists for less than 2 h (immediate contact type—for example, dermographism and most cold urticaria). However, sometimes a generalized stimulus affecting the whole body is

necessary (reflex type—for example, cooling body core temperature to induce reflex cold urticaria and a rise in core temperature to induce cholinergic urticaria). In a few forms of physical urticaria, a delay of several hours from the physical stimulus occurs before weals appear—for example, delayed dermographism, delayed pressure urticaria and the rare delayed cold urticarial reaction.

In many forms of physical urticaria, if the stimulus is sufficiently great or the patient is very sensitive, angioedema and systemic reactions may occur from mediator release.

Urticaria due to mechanical forces

Dermographism

Immediate symptomatic dermographism (factitious urticaria)

This involves the triple response which may arise from firm stroking of the skin [4]. This response consists of *local erythema* due to capillary vasodilatation, followed by *oedema* and a *surrounding flare* due to axon reflex-induced dilatation of arterioles. This reaction is normal, but in 5% of normal people this physiological response is sufficiently exaggerated to warrant the term dermographism [5,6]. In a minority of these people, it is accompanied by itching (symptomatic dermographism). Symptomatic dermographism may have an immunological basis. Dermographism has been successfully transferred when IgE (and occasionally IgM) in patients' sera has been injected into normal recipients [7,8]. It is postulated that mast cells sensitized with immunoglobulins (especially IgE) react to a neoantigen induced by mechanical stimulation of the skin and release their mediators. Neuropeptides may contribute to the reaction [9,10].

Symptomatic dermographism can occur at any age, but the greatest incidence is in young adults. Patients complain of wealing and itching at sites of trauma, friction with clothing, or scratching the skin. The itching is often disproportionately severe compared with wealing and is often most severe at night. The eliciting stimulus determines the shape of the weals (Fig. 47.4), but they are often linear from scratching or stroking (Fig. 47.5). Dermographism is not increased in chronic idiopathic urticaria, nor is there any correlation with systemic disease or food allergy [9]. Dermographism is usually idiopathic, but sometimes may follow a drug reaction—for example, penicillin reaction [10] or an infestation, including scabies. Dermographism may last for months or years, or be present intermittently.

Symptomatic dermographism is most easily diagnosed by using a calibrated instrument, the dermographometer [11], which has a spring-loaded stylus, the pressure of which can be adjusted to a predetermined setting.

Fig. 47.4 Dermographism, meaning 'skin writing'. (Courtesy of St John's Institute of Dermatology, London, UK.)

Fig. 47.5 Linear lesions of immediate dermographism induced by stroking back skin with a calibrated dermographometer. (Courtesy of St John's Institute of Dermatology, London, UK.)

Stroking the skin at a pressure on the skin of less than 36 g/mm^2 [9] induces a linear itching weal within 10 min.

Other forms of dermographism

Rarer forms of dermographism exist including *red dermographism*, where repeated rubbing is necessary to induce small, punctate weals [12]. *Cholinergic dermographism* is seen in some patients with cholinergic urticaria, whose dermographic response consists of an erythematous line

studded with punctate weals characteristic of cholinergic weals [13]. *Delayed dermographism* is rare. After a normal fading of the triple response or an immediate dermographic response, a weal returns in the same site, but is usually tender and persists up to 48 h [14]. The mechanism is unknown, but it is closely related to pressure urticaria [15], in which a delayed dermographic response is not unusual.

The presence of wealing following friction (Darier's sign) is characteristic of the lesions of urticaria pigmentosa and of systemic mastocytosis, in which the number of skin mast cells is increased.

Treatment of symptomatic immediate dermographism with low-sedating H_1 antihistamines is often effective, sometimes in low doses. For the more severely affected, there is no clinical benefit in combining H_2 antagonists with H_1 antagonists [16]. However, some improvement may be obtained with ultraviolet B (UVB) or psoralen and ultraviolet A (PUVA) therapy [17].

It should be noted that not all forms of dermographism are urticarial. *White dermographism* (due to capillary vasoconstriction following light stroking of the skin) occurs normally and is particularly pronounced in atopic subjects. *Black dermographism* is discoloration of the skin after pressure from a metallic object.

Delayed pressure urticaria

Delayed pressure urticaria [18–20] in its predominant form is uncommon (2% of urticarias) but it occurs to some degree in about a third of patients with chronic ordinary urticaria, although they may be unaware of this unless directly questioned [21]. Patients with predominantly delayed pressure urticaria nearly always have a component of chronic ordinary urticaria. Wealing occurs at sites of sustained pressure applied to the skin after a delay of 30 min to 9 h, but usually 4–8 h, and lasts 12–72 h [20].

The underlying mechanism for delayed pressure urticaria is unclear. On histological examination, there are decreased numbers of stainable mast cells [22], suggesting previous activation. Release of chemoattractant factors could account for the leukocyte infiltrate, which has been likened to a late-phase cutaneous reaction [23], but no allergen can usually be identified. Neutrophils are present in the majority of early lesions (less than 9 h) and the minority of late lesions (over 24 h). Eosinophils are found in early, and especially in late, weals (Fig. 47.6) with evidence of eosinophil major basic protein deposition [24]. These cellular changes correlated with up-regulation of vascular adhesion molecules, E-selectin and VCAM-1. IL-6 and fibrin present in lesions may amplify and perpetuate the process.

Weals occur frequently under tight clothing, on the hands after manual work, on the buttocks and lower back after sitting (Fig. 47.7) and on the feet after walking.

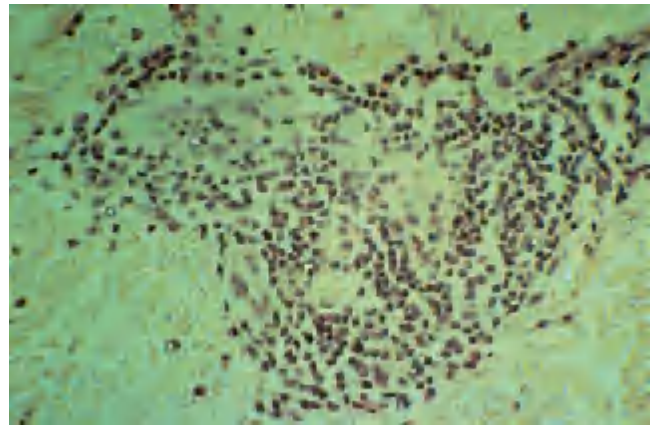

Fig. 47.6 Histology of 24-h lesion of delayed pressure urticaria, showing a profuse dermal inflammatory infiltrate of lymphocytes, neutrophils and eosinophils without vasculitis. (Courtesy of St John's Institute of Dermatology, London, UK.)

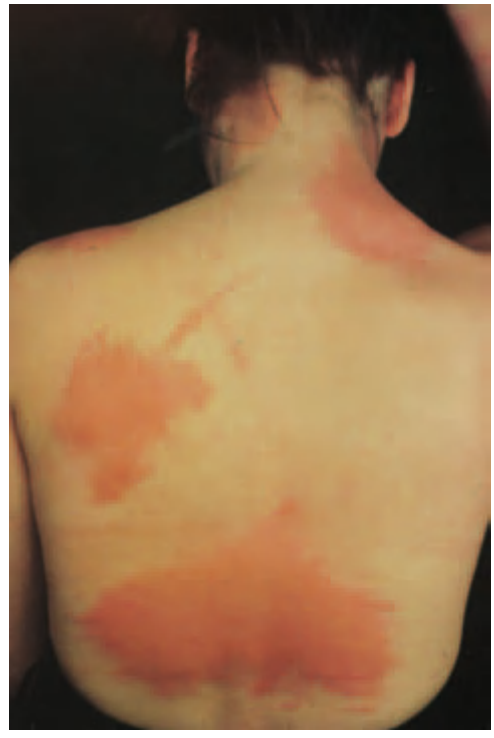

Fig. 47.7 Extensive delayed pressure urticaria over the back after sitting against a hard surface. Induced delayed dermographism is also seen on the upper back. (Courtesy of St John's Institute of Dermatology, London, UK.)

Lesions may be itchy, but are often tender or painful, particularly on the soles and scalp. The severity is variable, but it may be accompanied by systemic symptoms of malaise, flu-like symptoms, arthralgia, myalgia and leukocytosis. The condition may be mistaken for urticarial vasculitis.

The diagnosis can usually be made by careful questioning and confirmed by testing. Objective testing is performed by using a dermographometer set at 100 g/mm^2

pressed perpendicularly on the back for 70 s [25], or rods with a convex end diameter of 1.5 cm weighted with 2.5 kg for 20 min or 4.5 kg for 15 min on the back or thighs [21]. A positive response is when indurated lesions are present at test sites at 6 h. Weights (15 lb, 7 kg) applied for 15 min over the shoulder with a wide strap induce indurated lesions after a few hours [18,19]. Strapping a marble onto the forearm for 5 min has been described as an empirical test [26]. Areas of delayed pressure urticaria may be refractory to further pressure-induced lesions for up to 48 h [27].

Delayed pressure urticaria responds poorly to antihistamine therapy, which, however, may help the ordinary urticarial component. Cetirizine in high doses (10 mg three times a day) has been advocated as being more specific, as it also inhibits eosinophils. Although non-steroidal anti-inflammatory drugs may be helpful for the pressure-induced weals, they may exacerbate ordinary urticaria. Drugs that inhibit granulocyte infiltration such as montelukast, colchicine, dapsone and sulphasalazine have been tried, but are not of proven value.

Systemic steroids can provide symptomatic relief, but in doses that are usually unjustifiable for long-term therapy—although they can be used short term for exacerbations.

The prognosis is variable. The symptoms fluctuate in severity; they may show spontaneous improvement, or last for many years.

Vibratory angio-oedema

Vibratory urticaria is a very rare form of urticaria, which was first described in its familial form [28]. Any vibratory stimulus such as jogging, vigorous towelling or using lawnmowers induces a localized, red, itchy swelling within minutes and lasting less than a few hours, but if the stimulus is severe, generalized erythema and headache may occur. Avoidance of the precipitating stimuli enables patients to lead normal lives. Occasionally, vibratory angio-oedema may occur in an acquired form [29,30].

Temperature-dependent urticaria

Heat urticaria

Cholinergic urticaria

Cholinergic urticaria is a very distinctive type in which characteristic small weals appear in association with sweating. It accounts for about 5% of urticaria, and lesser degrees are common in adolescents. Wealing occurs on stimulation of sweating, whether induced by a rise in core temperature, emotion or gustatory stimuli.

The pathogenesis is still not clear. It is thought to be related to stimulation of the cholinergic postganglionic sympathetic nerve supply to the sweat glands. Increased histamine levels have been detected in the blood of patients with cholinergic urticaria. It was originally postulated that acetyl choline can release histamine, perhaps in an indirect way, but such a mechanism is conjectural [31]. Passive transfer tests with serum of affected individuals are sometimes positive, probably due to an immunoglobulin [32]. Such an antibody may prime the mast cell for activation. An allergy to sweat itself has been postulated [33]. Decreased levels of the protease inhibitor antichymotrypsin have been detected in the serum of some patients [34]. There is no generalized disturbance of autonomic function [35].

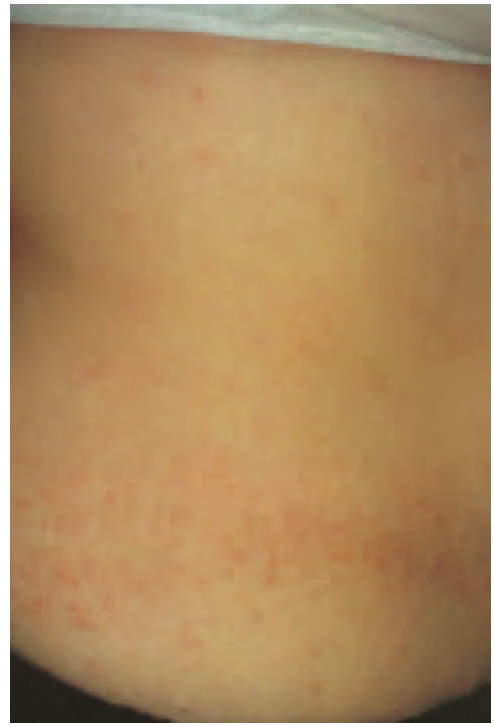

Fig. 47.8 Close-up of small monomorphic lesions of cholinergic urticaria on the trunk. (Courtesy of Norfolk and Norwich University Hospital, UK.)

The disease typically occurs in adolescents of either sex and may be worse in the winter months [36]. It has been reported to occur in families [37]. The patient complains of itching weals that appear within minutes of exertion, when hot, or after emotional disturbances or even eating spicy food. The weals characteristically are small, 1–3 mm across, with or without a well-marked flare (Fig. 47.8). Sometimes, the erythematous component is more pronounced, especially in the blush areas, and is confluent and studded with weals. Oblique lighting is helpful for observing the weals, especially in dark skin. The lesions persist for a few minutes to an hour or two. Ordinary urticaria not precipitated by heat may be associated with cholinergic urticaria in some patients. Although

micropapular weals resembling those of cholinergic urticaria can occur in ordinary urticaria, these usually last for hours. Cholinergic angio-oedema has been recorded [38,39]. In *persistent cholinergic erythema*, multiple small erythematous macules are distributed symmetrically on trunk and limbs, increasing in number after exercise. Individual macules are short-lived, but appear at different sites over a prolonged period, giving the overall impression of a persisting rash [40]. *Cholinergic itching* without weals has been described [41].

In some patients with cholinergic urticaria, systemic symptoms of flushing, faintness or asthma may occur [42,43]. Exercise-induced anaphylaxis may occur as part of the cholinergic urticaria spectrum after severe exercise [44]. However, exercise-induced anaphylaxis in others does not appear to be associated with cholinergic urticaria and often occurs in patients sporadically and unpredictably, and appears to be a distinct entity [45]. It is possible that some are examples of unrecognized food and exercise-induced anaphylaxis.

Rarely, a generalized eruption resembling cholinergic urticaria may be provoked by systemic chilling [46].

The diagnosis of cholinergic urticaria is best confirmed by provocation, with the appearance of typical weals after warming—for example in a hot bath at 42°C for 15 min, to raise the core temperature by 0.7–1°C—or exercise in a hot environment [47]. Intradermal injections of cholinergic drugs such as methacholine produce local axon reflex sweating and sometimes the appearance of satellite weals. However, this test is unreliable and not specific enough to be useful [47].

Some patients get partial relief from antihistamines used either regularly or before they forecast attacks, but most have to modify their lifestyle by reducing exercise. Ketotifen, which also has mast cell stabilizing properties, may be more helpful in some patients than conventional antihistamines [48] but is sedating. A few patients find that if they can bring on a severe attack by suitable exertion they can achieve freedom for up to 24 h afterwards. For selected severely affected patients not responding to antihistamines, the attenuated androgen danazol improved wealing [34]. Usefulness is limited by its side effects and, due to potential abuse in sport, restrictions in prescribing.

Localized heat urticaria [49,50]

This is one of the rarest forms of physical urticaria. Localized warming of skin at temperatures varying from 38 to 50°C for 2–5 min induces wealing at the test site lasting 1 h. The pathomechanism is variable, with histamine release being described in some reports [51] and complement activation in others [52]. Treatment with antihistamines or induction of tolerance by repeated heat exposure may be helpful [51,53,54].

Cold urticaria [55–57]

Cold urticaria encompasses a variety of syndromes in which cold induces urticaria (see Table 47.5).

Idiopathic cold contact urticaria is the most common, comprising 96% of a series of cold urticaria patients [57], while others are rare. In some patients with idiopathic cold contact urticaria, the serum can passively transfer the cold urticarial response to normal recipients. This autoantibody is usually IgE-like [58], but IgM has been recorded. *In vitro* histamine release occurred from skin challenged with cold [59]. The antigen may be either a protein produced normally by cold exposure or, less likely, an abnormal protein. Histamine is an important mediator [59–61]. The contribution of other mediators detected, such as PGD_2 [62], leukotrienes [63], platelet-activating factor [64] and TNF-α [65], remains to be elucidated.

It is important to warn against cold-water bathing due to the risk of anaphylaxis and drowning. Treatment with low-sedation antihistamine is helpful. Induction of tolerance by repeated graduated exposures to cold can be helpful for selected patients [60,66], but it is time-consuming and not always effective.

Idiopathic cold urticaria

Immediate cold contact urticaria

This is by far the commonest form, occurring at any age but most frequently in young adults. It may be preceded by non-specific upper respiratory viral infections, infectious mononucleosis or insect bites. Itching and wealing of the skin occur on cold exposure within minutes and last up to 1 h. Cold winds and cold rain are particularly effective stimuli. Sometimes, the mouth and pharynx may swell after drinking cold liquids. Systemic symptoms include flushing, palpitations, headache, wheezing and loss of consciousness, and drowning has occurred after cold-water bathing.

Dermographism and cholinergic urticaria are frequently associated. The average duration of cold urticaria was 6 years in one series [57], but it may persist for many years.

Diagnosis is made by application of an ice cube in a thin plastic bag for up to 20 min onto the skin, and wealing occurs within 15 min, usually during rewarming [57] (Fig. 47.9). Sometimes, a more extensive local challenge such as immersion of a forearm in iced cold water is necessary [57].

Delayed cold contact urticaria

This form, where wealing occurs after a delay of hours after cold contact, is very rare [67]. A familial form has been reported [68].

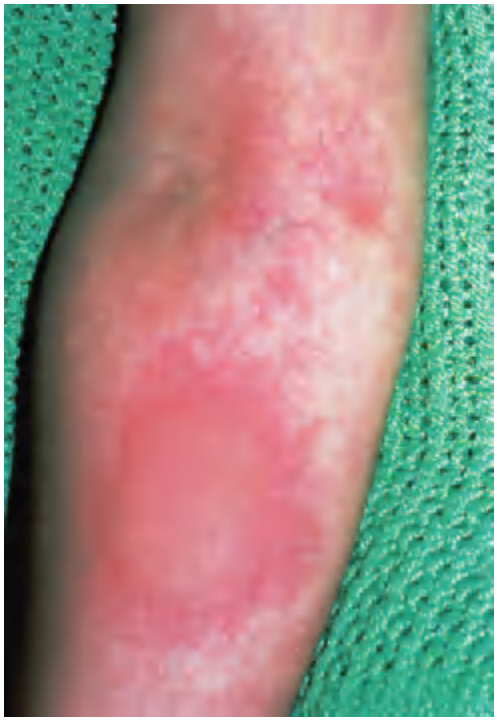

Fig. 47.9 Wealing following an ice-pack application for 20 min. (Courtesy of St John's Institute of Dermatology, London, UK.)

Localized cold contact urticaria

This is very rare [69].

Familial cold urticaria

This rare form is inherited as an autosomal-dominant trait and is now known to be caused by the same gene mutation as Muckle–Wells syndrome [70] (p. 47.29).

Acquired cold contact erythema

Painful erythema without wealing occurs in response to cold [71], but in other patients it may be a forme fruste of immediate cold contact urticaria.

Cold urticaria secondary to serum cryoproteins

This is rare and was found in only 1% of one series [57]. It is usually associated with other manifestations such as Raynaud's phenomenon, purpura or skin necrosis. Cryogobulinaemia may be idiopathic or occur in collagen vascular disease, chronic lymphatic leukaemia, myeloma and in infectious disease, including infectious mononucleosis. Cold urticaria is said to occur in only 3% of people with cryoglobulinaemia [72]. Blood samples for cryoprotein estimation must be kept warm until laboratory testing. Treatment is directed against the underlying condition. Cryofibrinogen occurred in the blood of 3.4% of a large hospital population [73], and in 3% of patients in cold urticaria [74]. Its significance in relationship to cold urticaria remains to be determined. Cold agglutinins are not usually associated with cold urticaria [75]. Cold haemolysins have not been detected in recent series.

Systemic cold urticaria

In generalized reflex cold urticaria, widespread wealing occurs in response to cooling of core body temperature, but a local ice-cube test is negative [76,77]. Testing is performed by placing the patient in a cold room at 4°C for 30 min in light clothes. In cold-induced cholinergic urticaria, additional exercise is necessary in the cold room to induce weals.

Solar urticaria [78]

Weals develop at the site of exposure within minutes of visible, long- or short-wave ultraviolet radiation [79] and usually fade within 2 h, in contrast to polymorphic light eruption, in which urticated lesions appear hours later and last days. The pathogenesis is discussed in Chapter 24.

Aquagenic urticaria [80–82]

Contact with water at any temperature induces an eruption resembling cholinergic urticaria, although the weals are few in number and are surrounded by a wide flare (Fig. 47.10). Other urticarias that can also be induced by water, such as cold urticaria, cholinergic urticaria and dermographism, must be excluded. It has been proposed that water carries an epidermal antigen to the sensitized mast cell [83]. This is a different entity from aquagenic pruritus, in which there is water-induced itching but no wealing [84,85].

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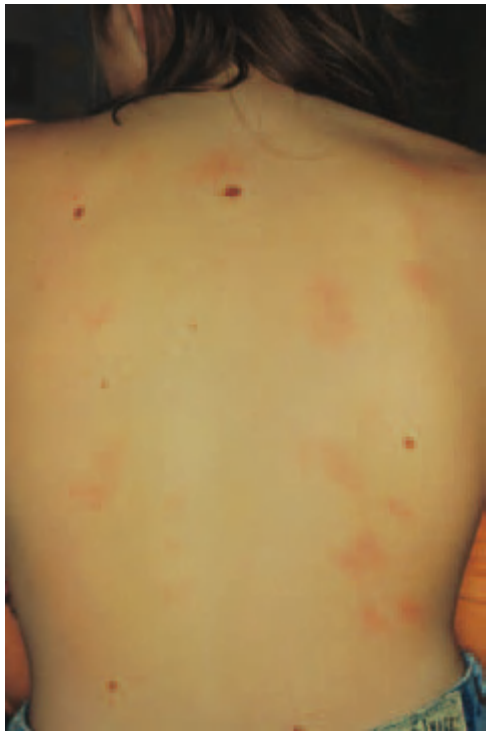

Fig. 47.10 Aquagenic urticaria on the back after swimming, showing a few small papular weals surrounded by wide flares. (Courtesy of Norfolk and Norwich University Hospital, UK.)

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Urticarial vasculitis [1–3]

Some urticarias are considered to be due to a type III hypersensitivity immune reaction, with deposition of immune complexes in blood vessels and other tissues and are often associated with systemic symptoms. The archetypal reaction is serum sickness. Some acute drug allergies give rise to a serum-sickness response.

Serum sickness [4]

Classically, serum sickness follows parenteral injections of therapeutic sera, the immune complexes consisting of antigen and IgG, usually with antigen excess (type III reaction). The immune complexes activate complement and are deposited in tissues including skin. It was a prevalent illness in the pre-antibiotic era—when heterologous antisera were used extensively to treat diphtheria, scarlet fever and pneumococcal pneumonia—but is now uncommon. Other causes of serum sickness-like syndrome include drugs, especially penicillin, radiocontrast media, hepatitis B infections and rarely foods. Onset is after 1–3 weeks, or more quickly if there has been previous exposure. Urticarial lesions are persistent, lasting a few days, and are sometimes tender or painful with bruising. Systemic features include fever, arthropathy, lymphadenopathy, cough, gastrointestinal disturbances and nephritis. The illness usually lasts for 5–28 days.

Urticarial vasculitis is essentially the same condition, but is frequently chronic, although it may be intermittent. The cutaneous lesions resemble urticaria in appearance, but histologically demonstrate vasculitis (venulitis). Characteristic histological changes include endothelial swelling, extravasation of red cells and a perivenular cellular infiltrate rich in neutrophils, with leukocytoclasis and fibrinoid deposits in and around blood vessels [5]. Occasionally, a lymphocytic infiltrate may be prominent. However, urticarial lesions demonstrate a gradation of histological changes from a sparse perivascular infiltrate, through an intermediate stage of a dense cellular infiltrate, to a frank vasculitis [6]. Thus, the distinction between ordinary urticaria and urticarial vasculitis may not be clear-cut. If the minimum criteria for vasculitis is evidence of vessel damage and/or leukocytoclasis, this histological change has been reported in 2–20% of chronic urticarial weals, but a realistic figure is about 5% [7].

That urticarial vasculitis can be considered as a type III hypersensitivity reaction was suggested by the presence of circulating immune complexes, deposition of immunoglobulin and complement in vessel walls, and consumption of complement in a significant proportion of cases. Serum hypocomplementaemia may be present in a minority of patients. When it is, serum $C1_q$ levels are reduced and $C1_q$ precipitins, which are IgG autoantibodies against the collagen-like region of $C1_q$, are increased. These anti-$C1_q$ autoantibodies are also present in SLE, suggesting a relationship between the two conditions. However, no cause can be found in most cases of urticarial vasculitis.

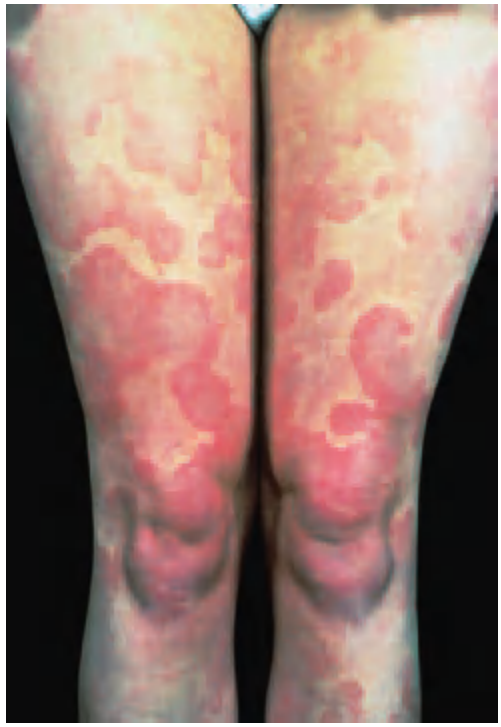

Fig. 47.11 Lesions of urticarial vasculitis which had been present for 2 days. (Courtesy of St John's Institute of Dermatology, London, UK.)

Only a minority are associated with infections (from hepatitis B and C, Epstein–Barr virus and *Borrelia burgdorferi*), serum sickness, collagen vascular disease (including lupus erythematosus and Sjögren's syndrome) or hypergammaglobulinaemia (including Schnitzler's syndrome, where IgM gammopathy is associated with fever and bone pain) [8]. Drugs such as cimetidine and diltiazem, haematological diseases [1] and cold and solar urticaria are very rare causes.

Compared with lesions of ordinary urticaria, lesions of urticarial vasculitis usually persist for more than 24 h and may burn as well as itch, be tender or painful and sometimes resolve with residual bruising or staining (Fig. 47.11). Rarely, bullae may occur. Angio-oedema is present in up to 40% [1] of cases. However, it is often not possible to distinguish urticarial vasculitis from urticaria by the clinical appearance of the lesions. Systemic involvement is common; the most frequent symptom, affecting more than 50% of cases, is arthralgia, which is usually flitting and migratory, but frank arthritis is rare. Gastrointestinal involvement, with abdominal pain, nausea and vomiting, occurs in approximately 20%. A similar percentage is affected with pulmonary disease, characteristically pulmonary obstructive disease found in smokers, especially in hypocomplementaemic urticarial vasculitis (HUVS). Microscopic proteinuria and haematuria occur in 5–10% of patients, but in the absence of connective tissue disease, progression to severe renal disease is unlikely. Rarer manifestations include Raynaud's phenomenon, lymphadenopathy and splenomegaly, conjunctivitis, episcleritis, uveitis, pseudotumour cerebri, myositis, pericardial and pleural involvement.

The diagnosis is established on lesional skin biopsy. Laboratory abnormalities are common, with a raised ESR being the most frequent. Hypocomplementaemia probably occurs in fewer than 50% of cases, but often correlates with the severity of systemic involvement. Other abnormalities sometimes found include circulating immune complexes, a positive antinuclear and rheumatoid factor (usually in low titre) and presence of cryoglobulins and $C1_q$ precipitins.

Investigations should include a search for the occasional associated disease, and for any systemic involvement. They should include a full blood count and ESR, urinalysis, renal and liver function, serum complement and immunoglobulins and chest radiograph. Further testing depends on other suspected clinical involvement.

Overall, the disease has a relatively benign course lasting an average of 3 years [1], although it can persist for many years.

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Contact urticaria [1]

Contact urticaria is quite common, but is not usually a cause of hospital referral unless there is an occupational problem, for instance latex allergy due to glove use. The term simply means urticaria resulting from skin or mucosal contact with the provoking substance. It may be allergic or non-allergic (also called immunological and non-immunological). The range of chemical, plant, animal and food exposures causing contact urticaria is very wide [2] (Table 47.6).

Allergic

Percutaneous or mucosal penetration of an allergen to which the individual has already developed specific IgE will result in a type I hypersensitivity response involving mast cell degranulation with histamine release. This may

Table 47.6 Some causes of contact urticaria.

Allergic (immunological)
Cow's milk
Cod
Kiwi fruit
Peanuts
Sesame seeds
Spices
Celery
Non-allergic (non-immunological)
Balsam of Peru
Cinnamic aldehyde
Methyl salicylate
Benzoic acid
Sorbic acid
Witch hazel
Jellyfish
Nettles

result in an immediate localized weal and flare resolving within 2 h, an acute episode of generalized urticaria, or even anaphylaxis if the individual is extremely hypersensitive. It is easily missed when it is responsible for exacerbations of a pre-existing eczema, for example in atopic children. Weals occur at sites of contact with the allergen, usually therefore on the hands and face. The commonest causes are foods (for example, nuts, fish, fruits) or latex. Diagnosis can be confirmed by RAST if there is a history of anaphylaxis, or by skin-prick testing. Management is largely directed at avoidance of the allergen, although taking an antihistamine prophylactically reduced the number of episodes of urticaria in atopic children [3].

Oral allergy syndrome

This is a form of allergic contact urticaria involving the mouth, characterized by immediate itching, swelling and burning after eating a wide range of fresh fruits and nuts, including apple, pears, cherries, plums and hazelnuts. Eating cooked fruit often does not cause symptoms. The wide range of cross-reactions is probably due to a natural panallergen in silver birch pollen [4]. Diagnosis is by skin-prick testing to the fresh fruit. RAST testing may be negative. Fortunately, the condition only rarely progresses to angio-oedema, and treatment with antihistamines is not usually necessary.

Non-allergic

This form of contact urticaria may be caused by direct injection of vasoactive chemicals by plants (e.g. nettles) or animals (e.g. caterpillars, jellyfish). A more common form, though, is from exposure to cosmetics (e.g. cinnamic aldehyde, balsam of Peru) or food additives (e.g. sorbic acid or benzoic acid). Occupational exposures include ammonium persulphate in hairdressers. The reaction may take up to 45 min to develop and is thought to be due to PGD_2 formation rather than histamine release, since it can be blocked by non-steroidal drugs. The relevant investigation is either a prick test or patch test, read at 15–45 min rather than 48 h.

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Angio-oedema (without weals) [1]

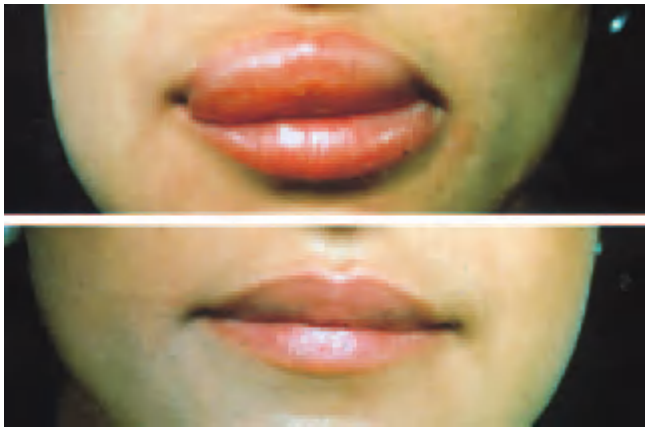
It is useful to separate angio-oedema without weals from angio-oedema with weals, as may occur in ordinary, physical and vasculitic urticarias since the aetiology, investigation and management may be different.

Ordinary angio-oedema

SYN. ANGIONEUROTIC OEDEMA; QUINCKE'S OEDEMA

This is a variant of urticaria in which the subcutaneous tissues, rather than the dermis, are mainly involved. The term 'angioneurotic oedema' is somewhat misleading. It was originally considered to be an abnormality of the nerve supply of the small blood vessels, without the implication of emotional disturbance that the word now suggests. The same multiple aetiology and frequent lack of precise diagnosis are found as in chronic ordinary urticaria [2,3]. However, both hereditary angio-oedema and the angio-oedema associated with ACEIs cause swellings without weals, suggesting that the mechanisms may not be identical for ordinary urticaria with angio-oedema and angio-oedema without weals. Almost any part of the body may be involved, but the commonest sites are the lips (Fig. 47.12), eyelids and genitalia. The tongue and pharynx may also be affected. Individual lesions may be single or multiple and may appear with dramatic suddenness. Itching is usually absent. The lesions last for a few hours, or occasionally persist for 2–3 days. Differential diagnosis includes eczema especially of the eyelids, cellulitis, lymphoedema, idiopathic oedema, idiopathic scrotal oedema and the Melkersson–Rosenthal syndrome.

The management of angio-oedema is essentially the same as that for acute urticaria, except that mucosal lesions may occur and cause great distress. Emergency treatment of mucosal lesions is discussed along with anaphylaxis in Chapter 71. However, in contrast to hereditary angio-oedema, described below, life-threatening



(a)

(b)

Fig. 47.12 Angio-oedema of the lip (a) during and (b) 3 days after an attack. (Courtesy of St John's Institute of Dermatology, London, UK.)

swellings are very rare. An association with epilepsy has been reported [4].

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ACEI-induced angio-oedema [1–4]

ACEIs have a special ability to cause angio-oedema, usually without associated urticaria [1]. The mechanism is thought to relate to the ability of ACEIs to prolong bradykinin survival and potentiate its effects by inhibiting kininase. Over 1000 cases had been reported by 1992 [2]. Most cases develop within 3 weeks of commencing treatment, but can occur at any time during treatment, even a year or two after starting. Angio-oedema affects the face and oral mucosa predominantly. Symptoms may be severe, and laryngeal involvement may be life-threatening. Intravenous antihistamines and corticosteroids are needed, sometimes repeatedly, and epinephrine injections should be given if swelling involves the airway [1]. Reactions are more likely to occur if the patient has had previous episodes of angio-oedema [3]. If such reactions do occur, it is not safe to change to one of the other ACEIs, which should be used with great care (or avoided) with angio-oedema of any cause.

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Hereditary angio-oedema [1–5]

This is a rare disorder, accounting for only 5% of all cases of angio-oedema without weals and only about 1% of all cases of angio-oedema. It is transmitted as an autosomal-dominant trait on chromosome 11. At a molecular level, several different mutations have been identified. A family history is usually but not invariably apparent. However, it must be remembered that a family history is not infrequent in the ordinary type of urticaria and angio-oedema. The clinical picture usually allows the diagnosis to be made before laboratory confirmation. Over 50% of cases present before puberty [3], but the onset may be delayed even into late adult life. There are recurrent swellings of the skin and mucous membranes throughout life, often associated with nausea, vomiting, colic and urinary symptoms. These attacks may occur regularly every few weeks, or may be less frequent. Between the attacks, the patient is well. Abdominal symptoms may occur in the absence of skin changes and cause great diagnostic difficulty. In one large series [3], 34% of patients had undergone abdominal surgery. Pharyngeal, laryngeal and even bronchial involvement are especially significant and dominate the prognosis. The skin and mucosal lesions are often solitary and may be painful. They seldom itch. They may appear spontaneously or after trauma, dental trauma, being especially hazardous. Ordinary urticaria does not occur, but there may be a rather distinctive reticulate erythema, perhaps with minimal oedema, which occurs prodromally [6] (Fig. 47.13). Some patients have a relatively minor disability and may improve over many years. In other families, before the advent of modern therapy, over 20% of cases used to die of respiratory obstruction before early middle age, and fatalities are still at risk of occurring.

The blood of these patients is deficient in a natural inhibitor of C1 esterase, which is made in the liver under genetic control [7]. It seems to require the activity of both alleles to maintain normal levels. The inhibitor is present either in reduced amounts (type I) or, in 15% of affected families, in an inactive form, although it can be detected in normal amounts immunologically (type II). A third type of hereditary angio-oedema has been proposed recently (type III), limited to women with a family history of recurrent angio-oedema, including swellings of the upper airway, but with normal levels of plasma C1 esterase inhibitor and C_4 [8], although this remains controversial. The protein is a natural inhibitor of the activated first component of complement and of kininogenase (kallikrein) and other enzymes. It may be that attacks are triggered off

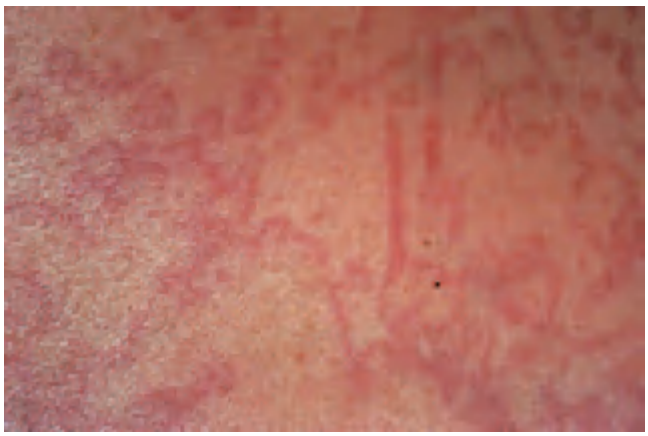

Fig. 47.13 The prodromal eruption of hereditary angio-oedema. 'Chicken-wire' reticulate erythema/urticaria, non-pruritic, on the trunk of a woman aged 38 years who had had numerous episodes over many years, each one lasting many hours or even days. Many attacks, but not all, were followed within 24 h by classical attacks of hereditary angio-oedema, confirmed by history and laboratory confirmation of C1 esterase deficiency. (Courtesy of Dr A.P. Warin, Royal Devon and Exeter Hospital, UK.)

by stimuli that normally activate Hageman factor and hence consume the deficient inhibitor. This C1 esterase inhibitor deficiency may be detected antigenically, but functional assays are necessary to detect type II hereditary angio-oedema. The components of complement (C_2, C_4 and CH50) are low during, after and to some extent even between attacks, or in symptomless carriers. Complement C_4 is nearly always low, and its measurement may be used as an initial screening test. There is no clear correlation between the clinical severity and laboratory abnormalities. There is a weak association with autoimmune diseases, including Sjögren's syndrome and SLE [9].

The response of hereditary angio-oedema to conventional treatment for urticaria is generally poor. Antihistamines, steroids and even epinephrine are said to be of little or no help. Not all patients need any treatment. Treatment may be considered as long-term prophylaxis, short-term prophylaxis and the emergency management of an established attack. Oestrogen therapies, such as the oral contraceptive pill, may induce or exacerbate hereditary angio-oedema and should be avoided if possible.

Androgens have been used prophylactically for many years with some success, but more recently the lives of many of these patients have been revolutionized by the use of attenuated androgen/anabolic drugs such as danazol and stanozolol. They stimulate the production of the deficient inhibitor. Long-term treatment is often required and may cause androgenic problems in women and children. The usual starting doses are danazol 200–600 mg daily or stanozolol 1.0–5.0 mg daily. However, considerably smaller doses given intermittently on several days of a week may suffice. The dose is assessed on the clinical response, rather than any changes in the laboratory tests, as improvement may occur even when the C1 esterase inhibitor levels remain low. Liver function tests should be monitored during long-term treatment, and benign hepatic adenomas have been reported. Such therapy may also be used for short-term prophylaxis, for example 6 days before and 3 days after dental surgery at the higher dose ranges [3]. Some, but not all, cases of the acquired variant of the disease (see below) also respond to this therapy. Epsilon amino caproic acid (not available in the UK), 12–18 g daily, or the related tranexamic acid 2.0–4.5 g daily, has been found to help some patients, but these drugs are contraindicated with thrombosis. They are less effective than danazol or stanozolol, but are useful where androgens are contraindicated, especially for short-term prophylaxis. Replacement therapy with fresh frozen plasma has been used for short-term prophylaxis. As well as providing the deficient inhibitor, it also provides more substrate; theoretically, therefore, it could worsen the angio-oedema, but in practice this does not seem to be a problem. However, a partly purified preparation of the inhibitor is now quite widely available. It is the treatment of choice for severe attacks, especially laryngeal oedema and abdominal colic, or it can be used for short-term prophylaxis [10] prior to procedures placing the patient at risk of laryngeal swelling, including dental extraction, endoscopy or intubation. Symptoms subside in 30–90 min [3].

Acquired C1 esterase inhibitor deficiency angio-oedema [11–15]

An acquired deficiency of the inhibitor may also give rise to a picture very similar to the hereditary form but with later onset. This may be associated with:

1 A B-cell lymphoma in which anti-idiotypic antibodies against the monoclonal antibody expressed on the surface of the abnormal cells allow complement activation and consumption of $C1_q$ and of the inhibitor.

2 SLE [16].

3 An antibody directed against the inhibitor, but without any evident lymphoma.

The laboratory changes are similar to those of hereditary angio-oedema, except that the C1 levels are also decreased. Danazol is helpful in some cases, but not the autoantibody type, which also fails to respond to replacement therapy but may be helped by corticosteroids.

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Episodic angio-oedema with eosinophilia [1]

Recurrent episodes of angio-oedema and urticaria associated with pyrexia, blood eosinophilia and infiltration of the dermis with eosinophils have been described. There is no evidence of systemic involvement or progression to a cardiomyopathy. Each episode resolves with prednisolone treatment. During an attack, elevated serum levels of IL-5 have been demonstrated in some cases [2], IL-6 in others [3] and a subsequent increase in TNF-α in others with a more transient variant [4].

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Other syndromes resembling urticaria or angio-oedema, or with urticaria as one component

Papular urticaria [1]

Injection of foreign protein by biting insects into skin of the most sensitive subjects may cause an immediate IgE-mediated reaction consisting of weals. A punctum is often visible on the weal, which may blister. This reaction sometimes evolves into a delayed hypersensitivity reaction leading to intensely itchy, indurated papules lasting weeks or months. It is most commonly seen on the legs of children after flea and mosquito bites.

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Cyclical oedema [1]

SYN. PERIODIC OEDEMA; PERIODIC DISEASE

These terms are used in different ways by different clinicians to describe several different entities. These include hereditary angio-oedema, some cases of familial Mediterranean fever, idiopathic oedema, the capillary leak syndrome and autoimmune progesterone urticaria. They are all characterized by oedema of the skin and perhaps other tissues, often with striking periodicity for which there may be no simple explanation.

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Idiopathic oedema [1–4]

This is known as the fluid-retention syndrome and is often described under the conditions listed above. The syndrome (or syndromes) is not a variant of angio-oedema, but can conveniently be considered in this chapter. It is quite separate from the premenstrual tension syndrome, which may also be associated with fluid retention. As the name implies, the aetiology of idiopathic oedema is obscure, but it involves an increase in capillary permeability. Other causes of oedema, such as cardiac, renal, hepatic, hypoproteinaemic, allergic, or those due to venous or lymphatic obstructions, are excluded by definition. Obesity is often a major factor, especially with recent weight gain; misuse of diuretics is common and other drugs may also contribute. Psychiatric disturbances are very often found.

The disease nearly always affects adult women, who are often overweight and labile in mood. The main changes are related to a periodic, often diurnal weight gain of more than 1.4 kg, sometimes more than 5 kg. This causes a bloated feeling in the abdomen, breasts, face and limbs. Pitting ankle oedema is not a feature. Symptoms suggestive of irritable bowel syndrome or frequency of micturition are common. Management includes sympathetic support, weight loss and only minimal use of diuretics. Psychotropic drugs are usually not needed.

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Systemic capillary leak syndrome [1–3]

SYN. CLARKSON'S SYNDROME

This is a rare syndrome in which there are dramatic recurrent attacks of exudation of fluid into various organs and may involve the skin. Attacks of angio-oedema have been reported. A severe shock-like state may ensue and the eventual mortality is high. There is an IgG paraproteinaemia. The response to treatment has been poor, although patients have been helped by a combination of aminophylline and terbutaline [4]. A similar syndrome may follow therapy for metastatic cancer with IL-2 [3].

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Schnitzler's syndrome [1–6]

SYN. URTICARIAL VASCULITIS WITH MONOCLONAL GAMMOPATHY

This syndrome was first reported in 1974 [1]. There is chronic urticaria, often with rather persistent non-itchy weals suggesting an urticarial vasculitis, which is sometimes confirmed by histology but more usually shows a neutrophilic urticaria [7]. Bone pains, with associated radiological bone changes, are present in half the cases. Malaise, fever and lymphadenopathy may occur. The characteristic finding is a monoclonal gammopathy—usually IgM, but perhaps IgG [5]. An IgG autoantibody against IL-1α was found in the sera of patients with Schnitzler's syndrome more frequently than controls [8], although the significance of this in the pathogenesis is not certain. The overall prognosis is often, but not always, benign. Long-term follow-up is required, because evolution to Waldenström's disease may occur [9]. Symptomatic treatment has included non-steroidal anti-inflammatory drugs, colchicine and dapsone, but sometimes prednisolone is required. IFN-α-2b was reported to relieve urticaria and bone pain in one patient [10].

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Periodic fever syndromes

Muckle–Wells/familial cold urticaria syndrome

These two rare autosomal-dominant periodic fever syndromes are due to mutations in a common gene called *CIAS1* on chromosome 1q.44, encoding a protein with a pyrin domain [1], but nevertheless have distinctive phenotypes.

Muckle–Wells syndrome [2–4]

During childhood and adolescence, patients with this rare disease suffer recurrent bouts of urticaria with chills, fever and malaise, each lasting 24–48 h. Nine separate families are known in the UK. The urticaria may start from birth and may occur daily throughout life. There may be actual weals or sometimes only macular erythema (Fig. 47.14). Conjunctival erythema may occur. Over the next two to four decades, sensory deafness appears, and in some cases progressive nephropathy due to amyloidosis. Amyloidosis is present in other parts of the body in the prereticulin pattern of deposition.

The condition, which is inherited as an autosomal-dominant trait, must be distinguished from familial Mediterranean fever, which has autosomal-recessive inheritance, and other forms of renal amyloidosis.

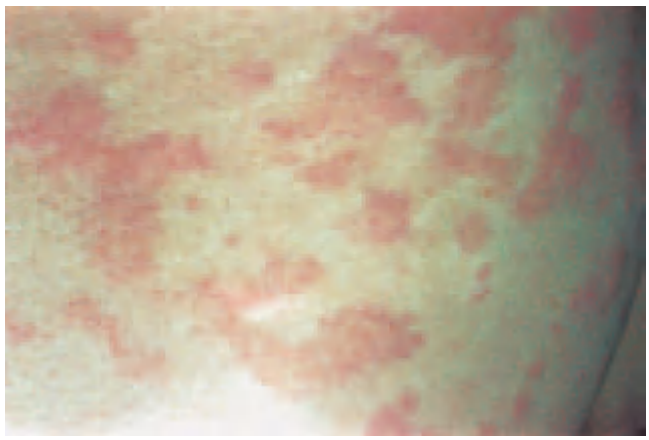

Fig. 47.14 Muckle–Wells syndrome. The characteristic, often rather faint, transient, sometimes erythematous, sometimes urticarial eruption. (Courtesy of Addenbrooke's Hospital, Cambridge, UK.)

Familial cold urticaria [5–7]

The onset is noted in infancy and persists for life. Weals, which are often painful, occur in response to a drop in body temperature and can persist for 48 h. Fever, headache and a leukocytosis may accompany the rash. An ice-cube test is negative. Treatment is difficult but there has been a good response to stanozolol in one family [8].

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Familial Mediterranean fever [1,2]

Familial Mediterranean fever usually has autosomal-recessive inheritance and a striking predilection for Sephardic Jews, Armenians and Arabs. The gene responsible is carried on the short arm of chromosome 16. Many patients present with recurrent self-limiting attacks of fever and a tendency to peritonitis, pleurisy and synovitis. Skin lesions include rather distinctive erysipelas-like lesions on the lower leg, but urticaria and vasculitic lesions may occur [3,4]. About one-quarter of patients develop or even present with renal amyloidosis, which is often fatal. Some symptoms are controlled by colchicine.

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Hyper-IgD syndrome [1–4]

A few cases have been recognized since its first description in 1984 [1]. It has some features in common with familial Mediterranean fever and Muckle–Wells syndrome, but appears to be a distinct entity. The clinical features include periodic fever and skin lesions, among which are erythematous macules, urticaria, annular erythema and nodules. Other findings include joint pains, abdominal pain, cervical lymphadenopathy, leukocytosis and raised ESR. The special finding is a raised IgD level in the blood, although it is uncertain how this is related to the other findings. There is no tendency to amyloid deposition. The response to treatment is unsatisfactory.

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TNF-receptor-associated periodic syndrome (TRAPS)
SYN. FAMILIAL HIBERNIAN FEVER [1,2]

This multisystem disorder comprises a recurrent migratory erythematous rash, fever, arthralgia, synovitis, conjunctivitis, pleurisy and amyloidosis of the kidneys and liver due to mutations in the TNF receptor I gene on chromosome 12. Levels of soluble TNF receptor are reduced in the blood during disease activity because the receptor is not shed from monocytes and neutrophils. Although the rash is typically migratory and macular rather than urticarial, oedematous plaques lasting up to 21 days may occur [2]. The condition should be considered in the differential diagnosis of the periodic fever syndromes.

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Mastocytosis

Introduction

Mastocytosis is a rare condition characterized by too many mast cells that are functionally normal, in contradistinction to urticaria, in which normal numbers of mast cells appear to be too releasable. It usually presents in the skin, but may affect other tissues, especially the bone marrow and gastrointestinal tract. The distinction between cutaneous mastocytosis and systemic mastocytosis (as defined by demonstrating excess mast cells outside the skin) will depend to an extent on how hard they are sought, and it is therefore of less value to the practising clinician than some classifications would suggest. The first description of mastocytosis was made by Nettleship and Tay in 1869 [1]. The term urticaria pigmentosa was used by Sangster to describe the skin lesions in 1878 [2], but it was not until 1939 that the term 'mastocytosis' was offered by Sézary to describe skin and systemic involvement occurring together [3].

There have been considerable gains in the understanding of its aetiopathogenesis and classification over the last decade, with the recognition of specific gene mutations in the proto-oncogene c-*kit*, which encodes a tyrosine kinase receptor on mast cells that is the binding site for stem cell factor (SCF, syn. Steel factor, mast cell growth factor, c-*kit* ligand). The relationship between mastocytosis presenting primarily in the skin and primarily as a haematological disorder continues to be clarified. Two recent in-depth reviews are recommended reading [4,5].

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Classification

A modification of the clinical classification embracing dermatological and haematological presentations of mastocytosis by Metcalfe [1] is shown in Table 47.7. It should be emphasized, though, that the great majority of cases presenting to dermatology clinics will have indolent (type I) mastocytosis (either cutaneous or systemic) and that progression to an associated haematological disorder (type II) is uncommon. Both type III (aggressive mastocytosis with lymphadenopathy) and type IV (mast cell leukaemia) are rare. Classifications based on aetiopathogenesis encompassing c-*kit* mutational analysis are currently of no practical value in the clinic, although it is possible that identifying subsets of disease using molecular genetics may lead to more accurate prognosis and better management in the future.

Table 47.7 Clinical classification of mastocytosis.

I	*Indolent mastocytosis*
	A Cutaneous
	Urticaria pigmentosa
	Mastocytoma
	Telangiectasia macularis eruptiva perstans (TMEP)
	Diffuse (erythrodermic) cutaneous mastocytosis
	B Systemic (extracutaneous mast cells in at least one organ)
II	*Mastocytosis with an associated haematological disorder*
	A Myeloproliferative disorders
	B Myelodysplastic disorders
III	*Aggressive mastocytosis with lymphadenopathy and eosinophilia*
IV	*Mast cell leukaemia*

Modified from Metcalfe's 1991 classification (Metcalfe DD. Classification and diagnosis of mastocytosis: current status. *J Invest Dermatol* 1991; **96**: 2S–4S).

REFERENCE

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Aetiopathogenesis

That the release of mast cell mediators causes symptoms of flushing, itching and gastrointestinal disturbance in mastocytosis is not in doubt, but the reason for mast cell accumulation in tissues in the first place is not yet clear. Interest has been focused on activating mutations of c-*kit* which were first found on a growth factor-independent mast cell line from a patient with mast cell leukaemia (HMC-1) and subsequently on adults with mastocytosis [1]. Two amino acid substitution mutations have been described in codons 816 and 560, leading to autoactivation of the receptor. However, the story is not straightforward, because the activating mutations have not been found in children with typical disease. Three of six children were found to have a novel dominant *in*activating mutation in codon 839 [2]. Furthermore, mutations in c-*kit* have not been identified in familial mastocytosis or in the germ line of affected adults, indicating that they are somatic. The *kit* receptor is also expressed on haemopoietic stem cells and melanocytes, which might be relevant to the occasional occurrence of myeloproliferative and myelodysplastic disorders in mastocytosis and the hyperpigmentation usually seen in urticaria pigmentosa lesions.

A report that soluble SCF was present in the epidermis of patients with cutaneous mastocytosis but not healthy individuals initially appeared to offer another potential mechanism for stimulation of *kit*, leading to hyperplasia of the skin mast cell population [3], but this has not been confirmed in later studies. Soluble SCF is not increased in the sera of patients with urticaria pigmentosa [4].

Clinical presentation

Nearly all mastocytosis with bone marrow abnormalities will show skin lesions, but few patients with skin lesions will have clinically significant haematological disease.

Prevalence

Mastocytosis is uncommon. Reliable population-based prevalence data are not available, but only two new patients were seen each year in one dermatology centre from a catchment population of 300 000 [5]. There is no sex difference or increase in atopy [6].

Genetics

Over 50 families with familial mastocytosis have been reported to date. Most of these had urticaria pigmentosa, but four cases of telangiectasia macularis eruptiva perstans (TMEP) occurred in three generations of one family, with an autosomal-dominant pattern of inheritance [7].

Cutaneous mastocytosis

Urticaria pigmentosa

This is the commonest pattern of cutaneous mastocytosis. Urticaria pigmentosa developed in the first year of life in 84% of 67 children [8]. The most common age of onset for adult urticaria pigmentosa is 20–40 years [9]. Numerous reddish-brown or pale, monomorphic maculopapules, plaques or nodules appear in a symmetrical distribution anywhere on the body except the face, head, palms and soles with the highest concentration usually being on the trunk (Fig. 47.15) and thighs (Fig. 47.16). The edges of the lesions are not completely sharp. They urticate within a few minutes of gentle rubbing (Darier's sign) (Fig. 47.17) causing localized itch, redness and wealing, which subsides within an hour. Stroking may also produce wealing in clinically unaffected skin. Darier's sign is not always demonstrable, especially in those with a long history of the disorder, and is not 100% specific for mastocytosis, since it has also been described rarely in juvenile xanthogranuloma [10] and acute lymphoblastic leukaemia of neonates [11]. Lesions may blister in infancy or childhood and may be the presenting feature, but heal without scarring.

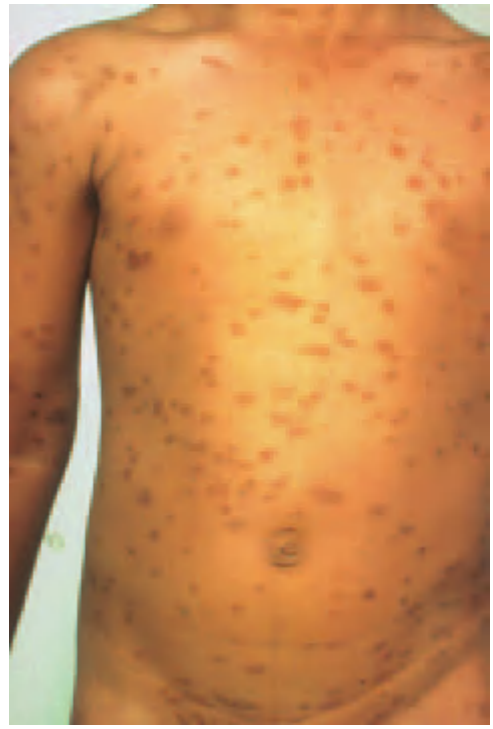

Fig. 47.15 Urticaria pigmentosa in a child, showing multiple pigmented lesions on the trunk. (Courtesy of St John's Institute of Dermatology, London, UK.)

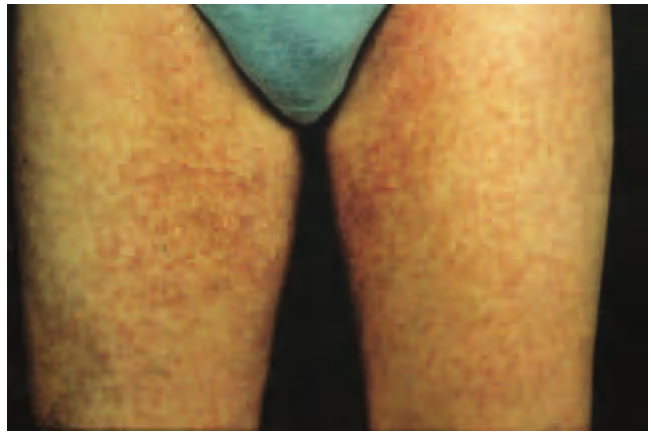

Fig. 47.16 Adult urticaria pigmentosa on the thighs, showing numerous reddish-brown lesions. (Courtesy of St John's Institute of Dermatology, London, UK.)

Flushing occurs in about 50% of patients, alcohol intolerance and pruritus in slightly less [4]. Other symptoms may include heat or cold intolerance, recurrent diarrhoea and headache. Wheezing is often quoted, but is extremely rare. Studies have shown that up to 60% of adult patients have bone marrow involvement [4,12,13], but there is no obvious relationship between finding this on biopsy and symptomatology or prognosis [4]. Clearance or fading

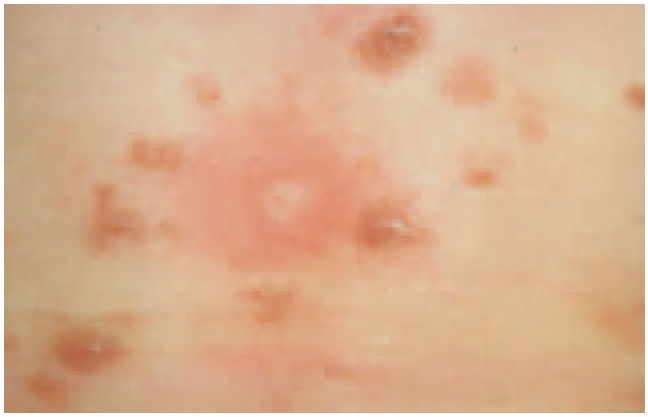

Fig. 47.17 Intense wealing and flare reaction (Darier's sign) induced by gentle rubbing of urticaria pigmentosa lesions on the back of an infant. (Courtesy of Norfolk and Norwich University Hospital, UK.)

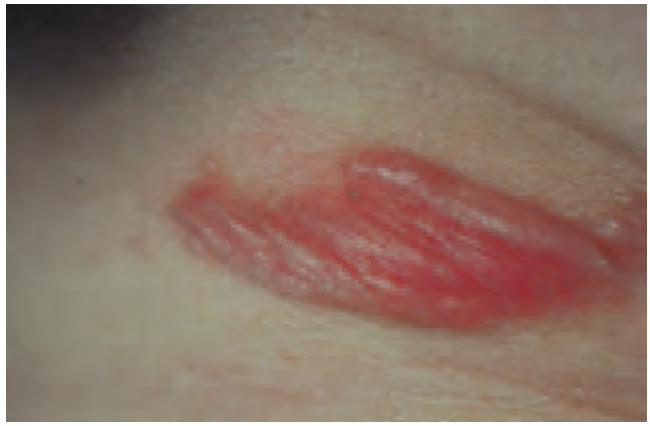

Fig. 47.18 Solitary mastocytoma, which urticates and blisters on rubbing. (Courtesy of St John's Institute of Dermatology, London, UK.)

of urticaria pigmentosa was observed in 12 of 106 adult patients with confirmed bone marrow involvement who were followed for 12–20 years, with a parallel overall improvement in the patients' well-being [14].

Mastocytoma

Cutaneous mastocytosis may present with red, pink or yellowish nodules or plaques in infancy or early childhood, measuring up to 3–4 cm in diameter (Fig. 47.18). They are usually solitary. About 15% of young children will present with localized lesions [15]. If multiple, the lesions can overlap in appearance with urticaria pigmentosa. They tend to blister if subject to friction, especially in the nappy area, and occasionally attacks of flushing can be induced by rubbing a solitary mastocytoma [16]. Nearly all mastocytomas involute over the first few years of childhood.

Telangiectasia macularis eruptiva perstans

Telangiectasia may rarely be the predominant clinical feature of cutaneous mastocytosis. Patients are usually adults presenting with red, telangiectatic macules, especially on the trunk, which tend not to urticate on rubbing (Fig. 47.19). Finding excess mast cells on skin biopsy will confirm the clinical suspicion, although they may not be numerous. TMEP tends to be very persistent and unresponsive to treatment.

Diffuse (erythrodermic) cutaneous mastocytosis

This is a very rare form of mastocytosis in which mast cells infiltrate the entire skin diffusely, and it usually presents in the neonatal period. The skin tends to be thickened and doughy in consistency, but may be smooth. Blistering is

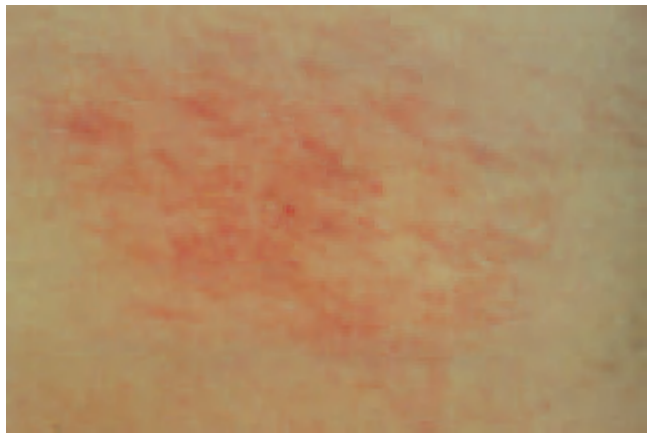

Fig. 47.19 Telangiectasia macularis eruptiva perstans after gentle rubbing on the thigh of an adult. (Courtesy of St John's Institute of Dermatology, London, UK.)

common (Fig. 47.20) and pruritus intense. Pigmentation is usually absent. Patients with this type of mastocytosis are at high risk of systemic disease and severe complications including anaphylaxis and diarrhoea [17], but it may resolve spontaneously, as in other types.

Systemic mastocytosis

Not all patients with proven bone marrow involvement will be symptomatic, but in those who are, nausea, vomiting, diarrhoea, palpitations, hypotension, syncope, headache, dyspnoea, wheezing and sometimes fatigue may feature as symptoms. This is partly due to cutaneous mast cell mediator release having distant effects and partly to direct local effects of infiltration in other tissues, such as the gastrointestinal tract. Bone pain, bone cysts, premature osteoporosis, osteopetrosis or spontaneous fractures should prompt further investigation.

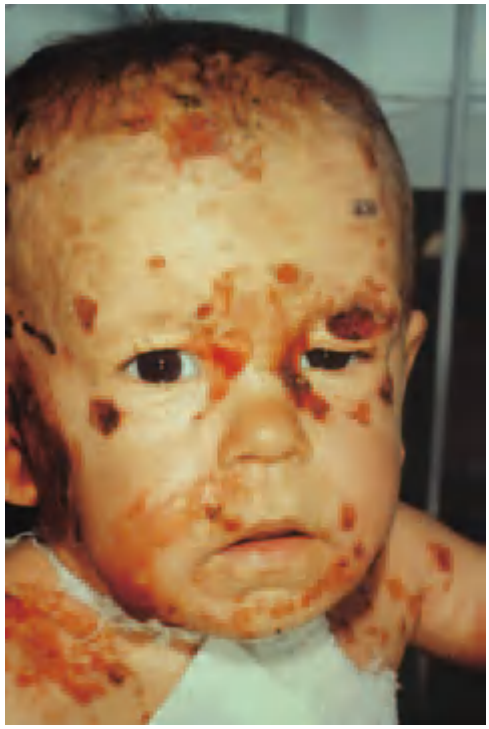

Fig. 47.20 Diffuse cutaneous mastocytosis in an infant, showing blistering and crusting on the face. (Courtesy of Dr C.T.C. Kennedy, Department of Dermatology, Bristol Royal Infirmary, Bristol, UK.)

As over half of adult patients investigated for urticaria pigmentosa will have bone marrow involvement and therefore, by definition, indolent systemic mastocytosis, making a distinction between them is more academic than practical. Preliminary evidence suggests that blood tryptase and urinary methylhistamine may be useful markers for bone marrow involvement [18]. Although there is a theoretical risk of progression of systemic indolent mastocytosis to type II disease (associated myeloproliferative or myelodysplastic disorders), the literature indicates that this is unusual and that there are no markers to identify subgroups of patients at greatest risk of this. The occasional presentation of type III disease (aggressive systemic mastocytosis with lymphadenopathy) or type IV disease (mast cell leukaemia) is more likely to be to a haematologist rather than to a dermatologist, with the patient showing changes in the peripheral blood against a background of being unwell.

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Histopathology

Skin

There are increased numbers of normal-appearing mast cells in the dermis of all types of indolent mastocytosis. The epidermis is normal apart from an increase in melanin. The mast cells are spindle-shaped and have granules that stain metachromatically with toluidine blue or Giemsa. Human skin mast cells are best demonstrated histochemically with Carnoy's fixative and staining with Alcian blue/safranin or conjugated avidin [1]. Mast cell infiltrates are predominantly found around blood vessels and skin appendages in the papillary dermis (Fig. 47.21). In urticaria pigmentosa, they are increased up to 15-fold above normal [2], but may be less numerous. Careful technique when taking the skin biopsy, to minimize traumatic degranulation, is important. Injecting local anaesthetic around the lesion to be sampled and avoiding epinephrine may yield a higher number of stainable mast cells. A small increase in numbers of mast cells has been found in non-lesional skin of urticaria pigmentosa [3]. Full-thickness infiltration of skin or a band-like involvement of the upper dermis are seen in mastocytomas and diffuse cutaneous mastocytosis. By contrast, mast cells are confined to superficial capillaries and dilated venules in TMEP.

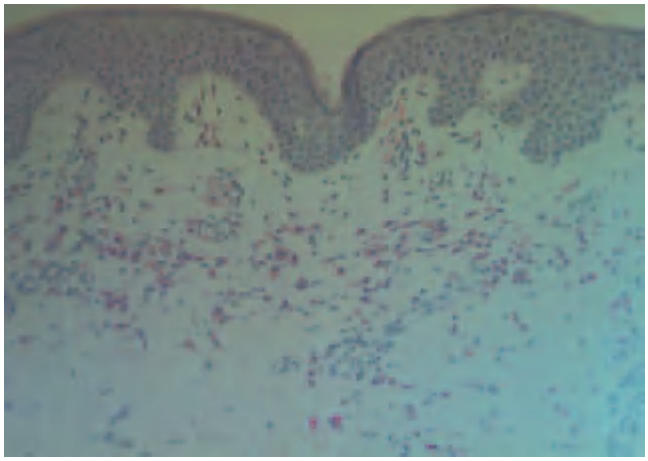

Fig. 47.21 Skin biopsy of urticaria pigmentosa, stained with chloroacetate esterase to show increased dermal mast cell numbers. (Courtesy of Dr A. Robson, St John's Institute of Dermatology, London, UK.)

Table 47.8 Protocol for diagnostic work-up and review.

Initial assessment
Skin biopsy
Full blood count (FBC)
If abnormal:
• Blood film + bone marrow biopsy if abnormal
• Any appropriate additional investigation, e.g. gastroscopy
Blood tryptase
If increased for:
• Abdominal ultrasound scan
• Bone densitometry for adults
• Consider bone scan for localized bone pain
Follow-up assessments
If initial assessments normal: none routinely
If probable systemic disease:
• At least yearly review with FBC, blood chemistry and blood tryptase
• Any appropriate additional investigation, e.g. gastroscopy

Bone marrow

Bone marrow involvement is usually seen as focal aggregates of mast cells on biopsy, although infiltration may be diffuse. Mast cell infiltration of the marrow is often accompanied by increased numbers of immature neutrophils, phagocytosing macrophages, eosinophils and lymphocytes and sometimes by fibrosis [4,5].

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Investigations

A skin biopsy is desirable to confirm a clinical diagnosis in most patients, although a policy of observation may be appropriate in young children, especially those with a mastocytoma, in whom natural resolution of their condition over childhood is likely. A full blood count should be performed at presentation and at yearly intervals when systemic disease is suspected or proven to detect the onset of significant bone marrow disease. Other investigations should be guided by the clinical presentation. Routine bone marrow examination is not required in the absence of other features, such as an anaemia, persistent leukocytosis, unexplained eosinophilia, bone pain, hepatosplenomegaly or lymphadenopathy. Blood tryptase levels may be a useful surrogate marker for bone marrow involvement [1] and could be done at initial diagnostic evaluation, although a raised result should not influence subsequent management or follow-up. An abdominal ultrasound scan may be helpful initially if there is a suspicion of systemic disease, and perhaps bone densitometry, especially if there is bone pain. A suggested protocol for the initial diagnostic work-up and review is summarized in Table 47.8.

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Management

Most patients presenting to dermatology clinics with cutaneous or indolent systemic mastocytosis will have an excellent prognosis, particularly children, so it is important to provide reassurance about the nature and outlook of the condition. Management hinges on avoidance of trigger factors for mast cell degranulation, symptomatic relief and detection of significant systemic disease. No cures are currently available, and there are no predictors for the onset of haematological complications or occurrence of familial disease.

Avoidance measures and management of anaphylactic emergencies

The flushing and itching experienced by many patients with cutaneous mastocytosis are due to release of mast

Table 47.9 Potential mast cell degranulating stimuli.

Physical triggers (especially rubbing)
Alcohol
Non-steroidal anti-inflammatory drugs (including aspirin, diclofenac)
Allergens (confirmed IgE-mediated reactions, e.g. latex allergy)
Insect and snake venoms (allergic and/or toxic effects)
Radiocontrast media (especially if iodinated)
Plasma expanders (especially dextran)
Opiates (including codeine and morphine)
General anaesthetic agents
• Non-depolarizing muscle relaxants (especially benzylisoquinolinium group, e.g. atracurium, gallamine)
• Anticholinergic drugs (e.g. hyoscine)

IgE, immunoglobulin E.

cell mediators. This can be exaggerated by physical stimuli, such as temperature extremes, towelling, massage or alcohol. Potential triggers of systemic mast cell degranulation include known allergens, non-steroidal anti-inflammatory drugs, opiates, Hymenoptera venoms (even in the absence of allergy), iodinated contrast media, dextrans and some muscle relaxants (Table 47.9).

Patients should be advised about the possibility of an anaphylactic emergency. Consideration should be given to carrying an epinephrine pen for self-administration, especially by those with a previous history of anaphylaxis. Oral antihistamines may be helpful for milder attacks not involving respiratory difficulty or hypotension. Venom immunotherapy for patients with anaphylaxis has been reported to reduce the risk of anaphylactoid reactions to Hymenoptera stings, even when there is no evidence of specific IgE [1], but this remains to be confirmed in larger studies. Fatal cardiovascular collapse during general anaesthesia has been reported [2]. Prophylactic administration of corticosteroids (e.g. 1 mg/kg prednisolone or equivalent) and antihistamines 30 min prior to general anaesthesia [3] is not necessarily protective.

Therapies

Antihistamines

Antihistamines are the mainstay of therapy, as for urticaria. Itching and flushing can be controlled by antihistamines in many patients, but can be refractory to treatment. Taking a classical sedating antihistamine at night, with or without a non-sedating antihistamine by day, may be beneficial, although there are no controlled studies of antihistamines in mastocytosis. It seems likely that the newer 'third-generation' antihistamines will be at least as effective as their parent drugs. Doxepin may also be used for its antihistaminic properties. H_2 antihistamines are used for gastrointestinal symptoms, including indigestion and diarrhoea.

Mast cell stabilizing and anti-inflammatory drugs

Abdominal pain, nausea and diarrhoea also respond to sodium cromoglycate which, however, has no value for other systemic symptoms because it is not absorbed from the gut [4]. Aspirin and other non-steroidal anti-inflammatory drugs have been reported to ameliorate prostaglandin-mediated flushing in some patients, but must be introduced with caution if there is any history of intolerance, under cover of antihistamines and with initial observation.

Photochemotherapy and phototherapy

Although oral PUVA may help itch and wealing and improve the appearance of urticaria pigmentosa [5], the benefits are only temporary, so the risks of long-term treatment need to be considered carefully. The mechanism for improvement is not certain, but probably involves a reduction of mast cell numbers in the papillary dermis only and total histamine content in lesional skin [6], with some cosmetic improvement due to tanning. Narrowband UVB therapy may be effective for pruritus when PUVA is not tolerated.

Corticosteroids

Use of potent or very potent topical steroids applied under polythene occlusion, or intralesional injection of individual mastocytomas, can lead to clearance of mast cells and reduction of pigmentation for at least a year [7], but steroid atrophy is an important limitation. Restriction of treatment to limited cosmetically sensitive areas, such as the forearms and lower legs, will minimize the risk of significant adrenocortical suppression.

Others

IFN-α-2a and -2b have been reported anecdotally to ameliorate some features of systemic mastocytosis [8,9], but not the number or appearance of skin lesions. Chemotherapies do not alter the course of the mast cell disease, but may benefit associated haematological disorders.

Prognosis

Most mastocytomas resolve in childhood. Around 50% of children with urticaria pigmentosa clear by adolescence. In a review of 67 paediatric cases, five resolved over 2 years of follow-up and 20 improved but did not clear over a mean period of 6 years [10] (Fig. 47.22). The outlook for paediatric cases that do not remit is the same as for adults with indolent disease. The prognosis for this group is difficult to ascertain due to the obvious limitations of not having information on lifelong follow-up, but it does

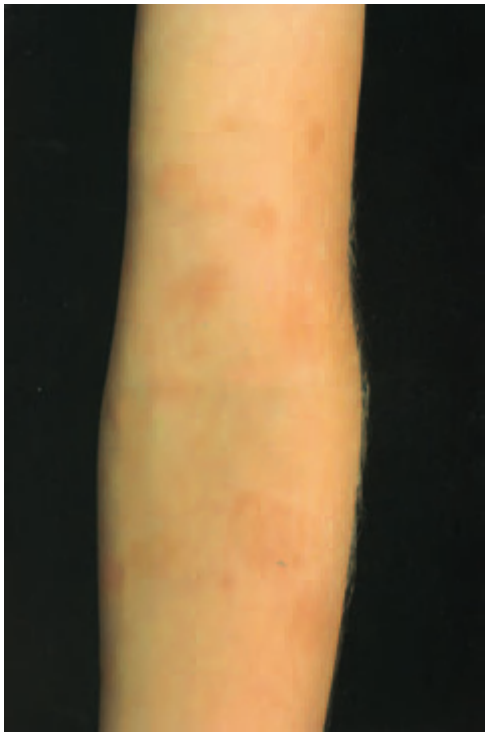

Fig. 47.22 Considerable improvement, but not complete resolution, of urticaria pigmentosa by the age of 5 years. (Courtesy of St John's Institute of Dermatology, London, UK.)

appear from the experiences of clinics with large numbers of patients under review that progression to significant haematological disorders is very rare, even with proven bone marrow involvement with mastocytosis [3,11]. Spontaneous resolution of cutaneous mastocytosis was observed in about 10% of adults [12]. The main problems likely to be experienced by patients relate to the risks of anaphylaxis and peptic ulceration. Prognosis of aggressive mastocytosis will relate to the associated haematological disorder, and management will be directed primarily towards this.

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Chapter 48

Purpura and Microvascular Occlusion

N.H. Cox & W.W. Piette

Introduction

Purpura, or bleeding into the skin, may occur as an isolated phenomenon or as part of a systemic disorder. It is the hallmark of vasculitis affecting the skin, and may be the dominant feature or a minor part of a systemic vasculitis (see Chapter 49). Purpura may occur as a result of other abnormalities of the blood vessel wall, and in numerous haematological conditions is due to platelet and coagulation disorders. Vasculitis itself may cause other cutaneous lesions, including urticarial lesions, nodules, ulcers, livedo and frank necrosis.

Patients with purpura may require management involving one or more of several disciplines, including haematology, general medicine, nephrology and rheumatology, as well as dermatology; multidisciplinary management is often appropriate as each specialty sees a different range of clinical manifestations and has different areas of expertise.

Classification of purpura is difficult, as no single approach is satisfactory. The same clinical pattern may arise from many different causes, both vasculitic and non-vasculitic, and the aetiology of either purpura or vasculitis may be impossible to determine. Classifications based on morphology or aetiology therefore have limitations. For example, clinically non-specific capillaritis may be idiopathic, drug-induced or a manifestation of cutaneous T-cell lymphoma. Furthermore, intravascular events such as microvascular occlusion may give rise to palpable lesions and inflammation as a secondary component, confusing both the clinical and histopathological picture. Despite these limitations, as a practical matter the initial approach

to a patient with purpura must typically start with a differential diagnosis based on morphology, since few patients present with a known aetiology of their lesions [1]. The importance of trying to differentiate between disorders causing primarily inflammatory or non-inflammatory lesions is clear [2].

This chapter addresses purpura that is not primarily of vasculitic causation; Chapter 49 deals with disorders in which a primary vasculitis is involved.

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Definition of purpura

Purpura is discoloration of the skin or mucous membranes due to extravasation of red blood cells. Petechiae are small purpuric lesions usually 1–2 mm (occasionally up to 4 mm) across, often occurring in crops. Ecchymoses or bruises are larger extravasations of blood. The many causes of petechiae and ecchymoses overlap, for example thrombocytopenia usually causes petechiae but more extensive bleeding may occur at lower levels of platelet count. In contrast, coagulation disorders usually cause ecchymoses rather than petechiae.

The sequence of colour changes in a bruise can help to identify it as such, should doubt exist, and can also help to establish its duration. Extravasated blood is broken down to various other pigments derived from haem, usually within 2 or 3 weeks. The characteristic colour changes [1,2] include red, blue and purple in the first 5 days (although these colours can occur at other times, particularly red), green after 5–7 days and yellow after 7–10 days (never less than 18 h). In smaller and more superficial purpuric lesions, orange or brown colours due to residual haemosiderin may predominate. Assessment of traumatic ecchymotic lesions is not a major part of routine dermatological practice, but may be important in suspected child abuse [3].

Unlike purpura, increased intravascular blood in the skin, whether as diffuse erythema or within telangiectatic vessels, can be blanched by pressure, typically using the technique of diascopy (see Chapter 5). However, not all telangiectatic lesions can be emptied in this way. Small angiomas (e.g. in angioma serpiginosum or the multiple minute variant of Campbell de Morgan spots) and angiokeratomas may cause particular confusion [4]. Sometimes, observation over several days is necessary. Capillary microscopy may also be helpful in determining whether blood is intravascular or extravascular.

Classification and investigation of purpura

An aetiological classification of purpura is provided in Table 48.1. However, for clinical purposes, correlations can be made between the clinical features and the mechanism of purpura. Purpura occurs as a result of one or more of the following main mechanisms in cutaneous vessels: simple haemorrhage, inflammatory haemorrhage or occlusion/ischaemia. Characteristics of lesions, including size, number, distribution pattern, and presence or absence of palpability and erythema, can be very useful in focusing on the most likely mechanisms of haemorrhage within these subsets.

In general, simple haemorrhage presents as macules without erythema (Table 48.2), though sufficient haemorrhage into subcutaneous tissue becomes palpable as a haematoma. The size of the macules has diagnostic importance. Inflammatory causes of haemorrhagic lesions usually evolve with increasing erythema in the first 24–36 h, along with increasing purpura. Such lesions are frequently, but not invariably, palpable. A subset of palpable purpura syndromes may uncommonly also produce lesions with retiform or stellate patterning, with accompanying early erythema and palpability (inflammatory retiform purpura). By 48 h, erythema and palpability begin fading in both types of lesions, although the purpura may persist for several days. In contrast, lesions of occlusion/ischaemia usually begin with minimal or no erythema, and may show minimal palpability unless eschar forms, but may develop erythema if sufficient necrosis occurs to induce a wound healing response. Occlusive syndromes tend to manifest retiform or branching patterns of purpura (non-inflammatory retiform purpura), sometimes with accompanying localized livedo reticularis, or as necrotic plaques with minimal erythema.

Non-inflammatory purpura is generally due to haematological causes and detailed discussion is outside the remit of this chapter; specialized haematology texts can be consulted [5–9].

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Table 48.1 Causes of purpura and ecchymosis.

Platelet disorders (see also Table 48.3)
Thrombocytopenia
Abnormal platelet function
Thrombocytosis

Coagulation disorders
Inherited, e.g. haemophilia or acquired factor deficiency or dysfunction (e.g. antibody inhibitor)
Drugs, e.g. anticoagulants
Localized, e.g. heparin injection sites, some insect bites
Metabolic, e.g. vitamin K deficiency, hepatic failure (decreased synthesis of clotting factors)
Thrombophilias, e.g. protein C deficiency, protein S deficiency
Disseminated intravascular coagulopathy and purpura fulminans

Other intravascular causes of purpura/microvascular occlusion
Dysproteinaemias, e.g. hypergammaglobulinaemic purpura (Waldenström), Sjögren's syndrome
Cryoproteinaemias
Emboli: crystal, fat, myxoma, infective

Mechanical vascular causes of purpura
Raised intravascular pressure
Coughing, vomiting, Valsalva manoeuvre, tourniquet
Stasis
Decreased support
Actinic ('senile') purpura
Corticosteroid purpura
Scurvy
Amyloidosis
Inherited disorders of connective tissue (pseudoxanthoma elasticum, Ehlers–Danlos syndrome)
Abnormal vasculature
Purpura around vascular lesions, e.g. targetoid haemosiderotic haemangioma, tufted angioma, aneurysmal fibrous histiocytoma

Purpura with inflammation
Non-thrombocytopenic toxin- and drug-induced purpura
Contact purpura
Purpura associated with infections
Capillaritis (pigmented purpuric dermatoses)
Idiopathic
Drug-induced
Pre-mycotic
Inflammatory purpura/vasculitis (see Chapter 49), e.g. Henoch–Schönlein purpura, acute haemorrhagic oedema
Associated with other inflammatory dermatoses that are not usually purpuric
Solar purpura

External and other causes of purpura or ecchymosis
Physical and artefactual causes
Multifactorial purpura associated with systemic diseases
Easy bruising syndrome and purpura simplex
Paroxysmal finger haematoma (Achenbach's syndrome)
Painful bruising (autoerythrocyte sensitization, Gardner–Diamond) syndrome
Stigmata

Table 48.2 Diagnosis of macular non-retiform haemorrhage/petechiae/ecchymosis by size.

Lesions < 4 mm
Thrombocytopenia
Immune thrombocytopenic purpura
Thrombotic thrombocytopenic purpura
Disseminated intravascular coagulation (DIC)
Other causes (see Table 48.3)

Abnormal platelet function
Congenital/hereditary
Acquired: drug, systemic disease
In myeloproliferative disease
Other causes (see Table 48.3)

With normal platelets
Raised intravascular pressure
Trauma
Scurvy (perifollicular pattern)
Hypergammaglobulinaemic purpura (Waldenström)

Intermediate-sized lesions
Hypergammaglobulinaemic purpura (Waldenström)
Infection in patients with thrombocytopenia or immune compromise
Early lesions of vasculitis (sometimes)

Lesions > 1 cm (all causes involve a degree of minor trauma)
Procoagulant defect
Anticoagulation
Liver failure
Vitamin K deficiency
DIC (some)

Poor dermal support
Actinic and corticosteroid purpura
Scurvy
Hereditary: Ehlers–Danlos syndrome
Amyloidosis

Platelet deficiency or functional defect

Other causes
Hypergammaglobulinaemic purpura (Waldenström)
Capillaritis
Easy bruising syndrome; purpura simplex
Physical and artefactual causes
Gardner–Diamond syndrome
Stigmata

Diagnosis and pathophysiology of simple macular haemorrhage [1–6]

Purpura due to simple haemorrhage is suggested by the presence of purpura that is macular (non-palpable) and that has no blanching component in newly developed lesions (Table 48.2). Palpable lesions, or a blanching component, suggest that there is associated inflammation (which may occur as a secondary effect, hence the emphasis that evaluation must concentrate on new lesions). The size of lesions, clinical patterns and body sites affected may all be diagnostically useful.

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Size of lesions

Petechiae are often defined as lesions of 2 mm or less in diameter, although non-palpable, non-blanching lesions up to 4 mm usually suggest the same process. There are four main mechanisms of simple haemorrhage: (i) severe thrombocytopenia (platelet count always $< 50 \times 10^9$/L, usually $< 10 \times 10^9$/L); (ii) platelet dysfunction (uncommon); (iii) regional or localized increased intravascular pressure; and (iv) many forms of capillaritis (pigmented purpura). Larger lesions may occasionally result from such syndromes, but petechial lesions will generally predominate.

In contrast, macular lesions of 1 cm or greater in diameter (ecchymoses) usually result from disorders of the cascade coagulation system (especially acquired), platelet dysfunction or poor dermal vascular support. Such lesions are usually provoked by minor trauma. This results in two important clinical clues. The first is that lesions tend to localize to areas prone to frequent minor trauma, such as the extensor forearm and dorsal hand, lateral thigh and anterior lower leg. The second finding is a linear or geometric shape of individual lesions, because such lesions typically result from a frictional injury or extension of blunt trauma. Finally, since photodamage of fair skin is a very common cause of poor dermal support, ecchymotic haemorrhage is very commonly found at areas with chronic exposure to both sun and trauma, for example the extensor forearm and dorsal hand.

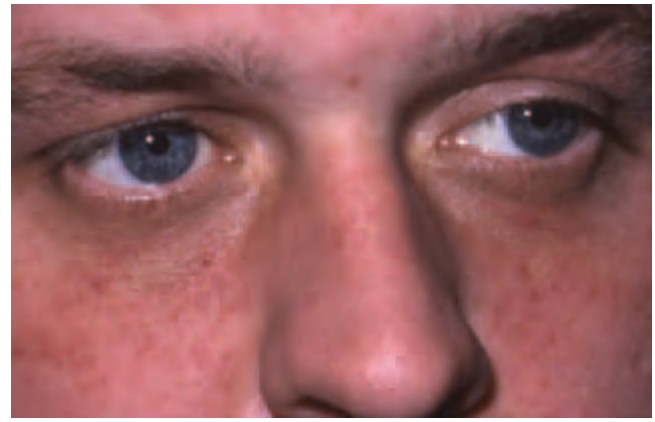

Fig. 48.1 Purpura on the face due to the raised intravascular pressure that occurs during vomiting. The lesions are small, non-palpable and all of the same age.

Clinical patterns of purpura

The clinical pattern may help to determine which patients require investigation, and may suggest the most likely major pathophysiological mechanisms. Tiny purpuric spots on the lower legs, for example, are not uncommon in the elderly, in patients taking antiplatelet drugs, or in the context of an inflammatory dermatosis; investigation of such lesions in these settings is seldom needed. Similarly, larger lesions that are macular, purple, stellate or blotchy, and confined to photo-aged skin on the dorsum of hands or forearms are generally diagnosed clinically as a consequence of actinic damage (although the same process on the face may produce smaller or more linear lesions, clinically resembling amyloidosis, and more widely distributed lesions of this morphology occur in Cushing's syndrome). Some degree of purpura is not uncommon in inflammatory skin disease of several types, but investigation is likely to be aimed at the disease process rather than the purpuric component *per se*.

Features that suggest a need for further investigation include:

- larger or variably sized lesions, particularly when not in sun-damaged skin;
- numerous or widespread lesions;
- lesions occurring in crops;
- palpable lesions;
- lesions forming reticulate patterns (livedo, retiform pattern);
- associated features such as pustules, necrosis, nodules, splinter haemorrhages, etc.;
- evidence of bleeding from other sites, e.g. haematuria;
- associated general symptoms, e.g. fever, malaise, arthralgia.

Diagnosis of purpura at various body sites

Gravitational change has a major influence on the distribution of purpuric lesions, as discussed elsewhere in this section. Other body sites of specific importance include the following.

- Eyelids: purpura due to coughing, vomiting, etc. (Fig. 48.1); purpura or ecchymosis in amyloidosis (panda sign); ecchymosis related to neuroblastoma.
- Ears: purpura due to cryoglobulinaemia and other hyperviscosity disorders; purpura due to some drugs, e.g. antineutrophil cytoplasmic antibody (ANCA)-positive propylthiouracil reaction, levamisole.
- Face, ears and acral: acute haemorrhagic oedema; cryoglobulinaemia.
- Acral: purpura due to cryoglobulinaemia and other hyperviscosity disorders; embolic causes of purpura; rickettsial infection.
- Friction sites: clothing contact purpura; some cases of capillaritis; Henoch–Schönlein purpura and other small-vessel vasculitis; ecchymosis of Ehlers–Danlos syndrome.
- Intraoral: thrombocytopenia; amyloidosis; myelomonocytic leukaemia; angina bullosa haemorrhagica.

Laboratory tests

Platelet count and function

This is the most important investigation in patients with non-palpable petechiae. The normal count is $150–400 \times 10^9$/L. It varies greatly from person to person, and from time to time in the same person. It may be affected by numerous exogenous factors such as infections, and by internal factors such as hormonal changes. Purpura due to thrombocytopenia seldom occurs with a platelet count above 50×10^9/L, and significant spontaneous bleeding is unlikely unless the count is less than 20×10^9/L. Thrombocytosis may also be a cause of bleeding. As well as variation in number, variation in function of platelets may need to be assessed by specialized *in vitro* tests. A full blood count should always be undertaken in the investigation of purpura.

Tests of occult bleeding

Simple tests to detect other sites of bleeding, whether in vasculitis or in haematological causes of purpura, include fundoscopy, urinalysis and faecal occult blood tests. Haematuria may occasionally occur in disorders which are felt to be essentially dermatological but non-vasculitic, such as drug-induced pigmented purpuric dermatoses [7].

Histology

Histological examination of non-palpable, non-blanching, small purpuric lesions is usually unhelpful; it is essential, however, to consider whether lesions are palpable or partially blanching. If there are palpable or partially blanching lesions, then vasculitis should be considered and biopsy is likely to be informative. If lesions are larger but not palpable, and platelet parameters are normal, then biopsy of the skin is appropriate, for example to assess disease of the vessel wall or surrounding tissues.

Capillary resistance and fragility [8–10]

If the pressure difference between the tissues and the capillaries is sufficiently increased, leakage of blood cells occurs. This is the basis of a variety of semi-quantitative tests for capillary fragility. However, the integrity of the capillary endothelium itself, and also the ability of platelets to fill any gaps which may arise in it, contribute to this type of bleeding. Abnormal results may therefore occur in conditions where there is thrombocytopenia, abnormal platelet function or intravascular coagulopathy, as well as in conditions where there is a vessel wall defect. Sometimes the capillary leakage is discovered accidentally due to development of a shower of purpura on the arm distal to a blood pressure cuff immediately after the pressure has been released (Rumpel–Leede sign).

The simplest clinical test, which essentially performs the same process, is the Hess test. A standardized increase in capillary pressure is produced by inflating a sphygmomanometer cuff around the upper arm to a constant pressure of 80 mmHg (or less if this approaches the systolic blood pressure) for 5 min. Petechiae develop over the next few minutes and can be counted in a measured area of 5 cm diameter just below the antecubital fossa; up to five may be considered normal. However, our experience is that the greatest density of purpura provoked by a Hess test is usually in the 'snuff-box' area over the space between the thumb and index finger metacarpals on the dorsum of the hand.

'Negative-pressure' tests require some simple apparatus to apply negative pressure to an area of skin usually 1–2 cm across. This technique is suitable for repeated tests in the same subject. The application of such a negative pressure at the rim of a cup may only be acting as a local venous tourniquet. Using these techniques capillary resistance is found to vary greatly, as does the platelet count, from individual to individual and with site and numerous other factors.

Bleeding time [4,11–14]

This is the time taken for bleeding to cease after a standardized tiny incision, usually in the skin of the forearm. This type of bleeding normally ceases because of contraction of the small vessels aided by production of a platelet plug. Techniques can be standardized in various ways, for example with a sphygmomanometer cuff at 40 mmHg the bleeding time is usually 4–10 min. The bleeding time is usually prolonged in thrombocytopenia where the platelet count is below 80×10^9/L and becomes progressively prolonged as the count falls, being 30 min at counts less than 10×10^9/L. It may be prolonged in von Willebrand's disease, other disorders of platelet function, severe anaemia, and in patients taking aspirin or receiving heparin. Although often stated to be normal in disorders of coagulation, it may be prolonged in severe haemophilia. It is a rather insensitive test whose wide range of normal values makes it of limited use, even as a screening test. The bleeding time does not accurately predict internal surgical bleeding [13], although it has been used to investigate the effect of aspirin and non-steroidal anti-inflammatory drugs (NSAIDs), which may be relevant as a cause of bleeding during skin surgery [14]. The PFA-100 is an *in vitro* technique to assess platelet function instead of the bleeding time. Although clinical experience with this technique is recent, this and similar methods are largely replacing the bleeding time in many clinical haematology laboratories.

Coagulation screen

Major coagulation defects can be excluded by a clotting screen including measurement of prothrombin time, kaolin cephalin clotting time, thrombin clotting time and fibrinogen levels. Clinical considerations and the results of the screening tests may suggest further laboratory tests, for example levels of individual clotting factors or antiphospholipid antibodies. Discussion of how these tests are performed is beyond the scope of this book.

Capillary microscopy

Direct microscopic examination of capillaries is disappointing in the elucidation of haemorrhagic and purpuric diseases. Purpura may at times be seen in the nail fold capillaries when not present elsewhere in the skin. Extravasation of blood may occur at the junction of the precapillary arteriole with the capillary, at the tip of the capillary or more usually at the venous end.

Summary

To avoid performing every type of investigation in all cases of purpura, the following broad generalizations may be made.

1 Purpura on the legs of the elderly, especially in association with other skin diseases, is common and seldom requires extensive investigation.

2 Coagulation defects usually present as large ecchymoses and external or internal bleeding but not as petechiae. Capillary fragility tests are normal unless there is severe deficiency of clotting factors.

3 Thrombocytopenia is often associated with petechiae but there may also be external or internal haemorrhages and bruising.

4 External bleeding and large ecchymoses are due to coagulation or platelet defects, or to diseases of connective tissue such as Ehlers–Danlos syndrome.

5 Petechiae are due to platelet defects or capillary changes.

6 Dysproteinaemias may cause lesions of simple haemorrhage, inflammatory haemorrhage or occlusion, depending on the properties of individual abnormal proteins.

7 Thrombophilias may present with livedoid change, retiform purpura or usually non-inflammatory cutaneous necrosis.

8 An initial retiform pattern without blanchable erythema or palpable lesions is generally indicative of microvascular occlusion.

9 Inflammatory lesions of the vessels are seldom the cause of external bleeding or ecchymoses, but are the most common cause of persistent and localized purpura. A blanchable erythematous inflammatory component is often present.

10 Inflammatory purpuric lesions are due to vascular changes rather than simple haemorrhage.

11 Splinter haemorrhages of the nails are due to purpura of the nail bed and are not diagnostic of any one condition (see Chapter 62).

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Purpura due to thrombocytopenia or platelet defects

Platelets are an essential component of the haemostatic process. Thrombocytopenia or abnormal platelet function from any cause may therefore produce purpura or a bleeding tendency [1,2].

Platelets exposed to damaged endothelium adhere to one another and to collagen and other subendothelial components. Numerous complex interactions occur, involving von Willebrand factor and its glycoprotein receptor, various integrin adhesion molecules, thrombospondin, fibronectin, laminin, phospholipases and ADP released from damaged cells, as well as collagen and platelets. Platelet activation causes release of serotonin and thromboxane A_2, both of which cause vasoconstriction, and increase platelet adhesiveness and aggregation leading to formation of a platelet plug. This process is aided further by the presence of plasma fibrinogen and by thrombin. Production of prostacyclin, a powerful vasodilator and inhibitor of platelet aggregation, is decreased as a result of endothelial damage. Developing platelet plugs are reinforced by fibrin strands formed as a result of activation of the plasma clotting system by platelet factor 3, when this is exposed by alterations in the surface characteristics of the aggregated platelets.

Purpura due to platelet defects can be divided into three groups:

- thrombocytopenia, i.e. decreased platelet numbers;
- abnormalities of platelet function;
- thrombocytosis, i.e. increased platelet numbers.

Thrombocytopenia

The platelet count at which purpura occurs is extremely variable. Purpura due to platelet deficiency usually occurs with a count below 20×10^9/L and is seldom observed with a count above 50×10^9/L. The main causes of thrombocytopenia are listed in Table 48.3.

Idiopathic (immune) thrombocytopenic purpura [1,3,4]

SYN. AUTOIMMUNE THROMBOCYTOPENIC PURPURA (ATP); WERLHOF'S DISEASE

Idiopathic immune thrombocytopenic purpura (ITP) results from immune destruction of platelets by autoantibodies that often show specificity for the platelet membrane glycoproteins IIb/IIIa and Ib/IX. Viral antigen–antibody reactions may be demonstrated in acute forms of the disease, usually in children following an acute viral illness. Vaccines to prevent viral illness have also been implicated, including recently the combined measles, mumps and rubella (MMR) vaccine. Some cases are drug-induced (see later) or are associated with systemic lupus erythematosus (SLE), agammaglobulinaemia, lymphoproliferative disease or myelodysplasia. Chronic ITP is usually autoimmune and apparently idiopathic.

The disease may occur at any age, but in two-thirds of cases it occurs before the age of 21 years. Either sex is affected in children but in adults there is a strong female predominance of at least 2 : 1. Antibodies may be transmitted from mother to fetus. The onset may be gradual or, especially in children, acute. The platelet count falls below 50×10^9/L and may even be zero. Megakaryocytes are present in normal or increased numbers in the bone marrow. Usually the only symptom is a tendency to bleed from gingivae after brushing teeth, or into the skin to produce crops of petechiae or larger haemorrhages. Bleeding may occur in any organ but joint involvement is unusual. The spleen may be slightly enlarged but gross splenomegaly should suggest an alternative diagnosis. Intracranial haemorrhage occurs in about 0.2% of children and is often fatal, but is very unlikely unless the platelet count is less than 10×10^9/L.

Lupus erythematosus develops in a small proportion of cases [5], although there are recently described differences in immunopathogenesis between the thrombocytopenia of SLE and that of ITP [6]. About 20% of adult patients with immune thrombocytopenia have associated features of the primary antiphospholipid antibody syndrome (APLS), with a prolonged activated partial thromboplastin time (aPTT), lupus anticoagulant and anticardiolipin antibodies. The immune thrombocytopenia associated with APLS is rarely severe [7].

The diagnosis is established by the clinical picture, low platelet count, exclusion of other causes of thrombocytopenia and the mainly negative bone marrow findings. Differential diagnosis includes especially SLE, drug-induced

Table 48.3 Platelet disorders causing purpura.

Thrombocytopenia
Defective platelet production
  Bone marrow abnormality
    Aplasia: toxic, immunological, idiopathic
    Neoplasia: leukaemia, myeloma, carcinomatosis
    Replacement: myelofibrosis, radiation damage, sarcoidosis
    Other impaired production: Wiskott–Aldrich syndrome, vitamin B_{12} or folate deficiency
  Metabolic: uraemia, alcohol, drugs
  Infections
Diminished platelet survival
  Platelet alloantibodies
    Neonatal
    Post-transfusion
    Antilymphocyte globulin
  Platelet autoantibodies
    Idiopathic (immune) thrombocytopenic purpura
    Marrow transplant
    Antiphospholipid antibodies
    Systemic lupus erythematosus
  Mechanical: prosthetic heart valves
Drugs and vaccines
Infections
Excessive platelet consumption
  Disseminated intravascular coagulation
  Haemangioma (Kasabach–Merritt)
  Haemolytic–uraemic syndrome
  Thrombotic thrombocytopenic purpura
Sequestration
  Splenomegaly
  Hypothermia

Abnormal platelet function
Inherited and congenital
  Von Willebrand's disease
  Storage pool disease and Hermansky–Pudlak syndrome (see Chapter 39)
  Bernard–Soulier disease (GpIb/IX deficiency)
  GpIa deficiency
  Glanzmann's thrombasthenia
Drug-induced
Uraemia
Cardiac bypass
Platelet antibodies
  Idiopathic (immune) thrombocytopenic purpura
  Systemic lupus erythematosus
Myeloproliferative disorders
Dysproteinaemias

Thrombocytosis
Essential thrombocythaemia
Other myeloproliferative syndromes
Other causes: blood loss, trauma, burns, post-splenectomy, malignant disease, tuberculosis, sarcoidosis

purpura, disseminated intravascular coagulation (DIC) and renal failure. Spontaneous remission often occurs in acute attacks (most children have spontaneous improvement within a month or two), but is rare in chronic cases of more than 3 months' duration, where a continuous or fluctuating course may occur. Corticosteroid therapy may be indicated; about 50% of adults treated with corticosteroids achieve complete remission. Splenectomy is beneficial in two-thirds of chronic cases and in acute cases in which a spontaneous or steroid-induced remission cannot be achieved. After splenectomy the platelet count tends to remain low but the purpura tends to cease. Immunosuppressive therapy is indicated in cases that fail to respond to splenectomy and steroids or where splenectomy is contraindicated. Other treatments that have been used in patients with refractory ITP include danazol, azathioprine, vincristine, interferon-α, ciclosporin (cyclosporin), Fc receptor blockade using intravenous immunoglobulin or intravenous anti-D antiserum, and various other monoclonal antibodies [3,4,8–11].

ITP may coexist with other haematological abnormalities, for example the combination of ATP and neutrophilia, which presents as mucosal bleeding with infections; the platelet deficiency tends to be chronic. Of greater dermatological importance is Evans' syndrome, which comprises Coombs-positive haemolytic anaemia with ITP; this is also associated with collagen vascular disorders, usually SLE or scleroderma but occasionally dermatomyositis [12,13].

Secondary or symptomatic thrombocytopenia

Drugs and toxins

Drug- or toxin-induced purpura may occur as a result of thrombocytopenia, altered platelet function or vascular damage. Each of these may be caused by many different mechanisms. The latter two are considered later. The main causes of drug- or toxin-induced thrombocytopenia are:

- direct bone marrow toxicity, e.g. benzol, nitrogen mustard;
- immunological bone marrow damage, e.g. chloramphenicol;
- destruction of formed platelets, via either immunological, e.g. apronalide (Sedormid), quinidine, quinine, sulphonamides, or non-immunological mechanisms.

It has been suggested that at least 200 drugs cause thrombocytopenia, the mechanisms often being uncertain. The most common are cytotoxic/chemotherapeutic drugs, quinine, quinidine, gold, heparin, sulphonamides, thiazides and furosemide (frusemide), indometacin (indomethacin) and other NSAIDs, thiouracils and carbimazole, bismuth, arsenicals, rifampicin and isoniazid, acetazolamide, acetylsalicylic acid, imipramine, interferon, phenytoin, carbamazepine and sodium valproate [2,14,15]. Immune-mediated platelet destruction is probably mainly due to binding of drug to platelets such that the platelet acts as a hapten and induces drug-dependent antibodies (type 3 drug-induced immune thrombocytopenia), which exert their effect while the drug is still present. However, the duration of thrombocytopenia after stopping the drug is too long to be explained on the basis of either drug clearance or platelet lifespan in some cases, particularly with quinidine or quinine, suggesting that true autoantibodies may be produced [16]. Heparin-induced thrombocytopenia type II [17–19] is important as it can be confused with post-transfusion purpura in early stages; also, it may be associated with arterial or venous thrombosis (heparin-associated thrombocytopenia and thrombosis syndrome) and can occur in conjunction with heparin-induced skin necrosis. It is due to formation of antibodies against an immunogenic complex involving heparin and platelet factor 4 (PF4), the antibody reaction causing platelet aggregation.

Other toxic causes of thrombocytopenia include alcohol, snake venoms and, rarely, foods and food additives.

Infections

Thrombocytopenia may be associated with a wide variety of infections, often with associated capillary damage as well. Infections that may be associated with thrombocytopenia include septicaemia of many aetiologies, typhoid, typhus, tuberculosis, smallpox, chickenpox, vaccinia, scarlet fever, influenza, measles, rubella, cat-scratch disease, infective hepatitis, subacute bacterial endocarditis, glandular fever, malaria, dengue, human immunodeficiency virus (HIV) and other virus infections.

Bone marrow diseases

Bone marrow diseases, for example leukaemia or aplastic anaemia, are the commonest causes of thrombocytopenia (see Table 48.3). In addition to the abnormal platelet production, there may be platelet antibodies formed in patients with lymphoma or leukaemia. Splenomegaly of many different aetiologies causes sequestration of platelets in the splenic sinuses but rarely produces a platelet count low enough to cause purpura. Purpura and ecchymosis are among the commoner cutaneous features of the haemophagocytic syndrome.

Platelet consumption, thrombotic thrombocytopenic purpura and haemolytic–uraemic syndrome

Thrombocytopenia may be associated with haemangiomas (Kasabach–Merritt syndrome, see Chapter 15). This is caused by ongoing chronic consumption and there is often compensated subacute or chronic DIC. Relevant haemangiomas are usually large and have undergone an

increase in size and become tender when the thrombocytopenia develops.

Thrombotic thrombocytopenic purpura (TTP, Moschowitz's syndrome) [20–25] in adults and haemolytic–uraemic syndrome (HUS) in children are rare forms of thrombotic microangiopathy in which thrombocytopenic purpura and bleeding are associated with fever, haemolytic anaemia and renal and neurological symptoms. HUS has recently been shown to involve a severe prothrombotic coagulation disturbance before onset of clinical features [26,27]. Schistocytes (fragmented erythrocytes) are seen on blood films. Microvascular injury and intraluminal platelet thrombosis occur; this, and platelet plugging in myeloproliferative disorders, are discussed later in this chapter.

Abnormalities of platelet function

Several haemorrhagic syndromes have become recognized in which platelet function is abnormal although the total count may be normal [1,2]. Such changes may be idiopathic or secondary to drugs or many other illnesses. These syndromes include thrombopathia, thrombasthenia, von Willebrand's disease, severe anaemia, chronic renal failure and fibrinogen defects. Hermansky–Pudlak syndrome consists of a bleeding disorder due to storage pool disorder, with oculocutaneous albinism and pigment-containing cells in the bone marrow (see Chapter 39).

Drugs that may cause abnormal platelet function with clinical bleeding include aspirin, diclofenac, some penicillin and lactam antibiotics, alteplase and other antifibrinolytic drugs, ticlopidine and some chemotherapeutic agents. Many other drugs may cause abnormal platelet aggregation *in vitro*, sometimes with abnormal bleeding time, but not necessarily with clinical bleeding [2].

Causes of abnormal platelet function may overlap with causes of thrombocytopenia. For example, both may occur in chronic renal failure (in which the abnormality of function is most important) or in myeloproliferative disorders (in which thrombocytopenia is usually paramount). Patients with IgM myeloma or Waldenström's macroglobulinaemia often have abnormal platelet function, less commonly those with IgA myeloma or benign monoclonal gammopathy, but bleeding in these conditions is usually due to hyperviscosity rather than to the platelet function defect.

Thrombocytosis

Abnormally high platelet counts may occur as a result of essential thrombocythaemia or other myeloproliferative disorders, or secondary to a variety of other disease processes (see Table 48.3). This may lead to a tendency to platelet plugging and thrombosis or, paradoxically, to a bleeding tendency (particularly when the platelet count exceeds 1000×10^9/L with a clonal platelet defect such as an acquired form of storage pool disease). Many cases of thrombocytosis do not achieve this high platelet count and are unlikely to cause purpura unless there are additional reasons related to the causative disorder (such as lymphoma or other malignant disease).

Dermatological manifestations and associations of thrombocythaemia include purpura with or without necrosis, livedo reticularis, acrocyanosis, purple (blue) toe syndrome, Raynaud's phenomenon, erythromelalgia, other vascular symptoms including gangrene, and associated disorders such as pyoderma gangrenosum [28–36]. The latter is relatively uncommon in pure thrombocythaemia [34] (this patient subsequently developed further myeloproliferative features; cited in [35]). In one large study, 22% of patients with essential thrombocythaemia had skin lesions; 41% of these had haematomas, ecchymosis, petechiae or purpura, and 26% had erythromelalgia [36]. Many of these presentations are also seen in other hyperviscosity and dysproteinaemic conditions.

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Pigmented purpuric dermatoses

SYN. CAPILLARITIS; PURPURA PROGRESSIVA PIGMENTOSA

Capillaritis is the generic term for a variety of chronic conditions that share certain histological features. The term 'purpura simplex' has also been applied to this group of disorders, on the basis of the common histological aspects. However, the same term has been applied to other mild and unexplained but morphologically different patterns of purpura such as easy bruising, and it is therefore potentially confusing. The term 'pigmented purpuric dermatoses' may be preferred, at least at present, as it conveys the message of a component beyond simple transient purpura.

The sometimes striking morphological patterns of the pigmented purpuric dermatoses have given rise to a wide range of descriptive and eponymous names [1–7]. Typical examples of the various eponymous diseases are sufficiently distinctive to warrant separate description but the clinical features may overlap, their aetiology is generally unknown and no clear distinction has been established between the different patterns other than on clinical morphological grounds. Gravity and increased venous pressure are important localizing factors in many cases. Exercise may be a provoking factor. Most are chronic but two-thirds may improve or clear eventually [5].

Pathologically, they are characterized by narrowing of the lumen and endothelial swelling of superficial small vessels, accompanied by perivascular T-lymphocytic infiltration, extravasation of erythrocytes and haemosiderin deposits in macrophages. The cellular infiltrate contains $CD4^+$ T cells in close contact with $CD1a^+$ Langerhans' cells [8,9], suggesting that a cell-mediated immune reaction is operative. Strong expression of endothelial cell adhesion receptors ICAM-1 and ELAM-1 may determine the pattern of the infiltrate [9]. Immune complex deposition has also been reported.

Capillaritis may on occasion be caused by drugs or food additives [10–12] (drugs caused 14% of cases in one large series [5]), may occur in rheumatoid disease [13], or may be a manifestation (sometimes the only manifestation) of mycosis fungoides [11,14–16]. Drugs reported to cause capillaritis resembling a pigmented purpuric dermatosis include calcium channel antagonists, β-blockers, angiotensin-converting enzyme inhibitors, nitrites, furosemide, antihistamines, antidepressants, chlordiazepoxide, analgesics such as paracetamol, glipizide, vitamin B_1 derivatives, tartrazine, interferon-α (in hepatitis C infection), polyvinyl pyrrolidone and topical 5-fluorouracil [10–12]. The apparently idiopathic variants, while much the commonest cause, are therefore a diagnosis made by exclusion. Stasis dermatitis, purpuric clothing dermatitis and hyperglobulinaemic purpura are also in the differential diagnosis.

Schamberg's disease [17,18]

SYN. PROGRESSIVE PIGMENTED PURPURIC DERMATOSIS

This uncommon eruption is most common in young adult males but may occur at any age including childhood. Familial incidence has been reported [19]. The lesions are most frequent on the lower limbs but may occur anywhere on the body, including the palms [20], and may be few in number or very extensive. They consist of irregular plaques of orange or brown pigmentation due to haemosiderin, with characteristic 'cayenne pepper' spots appearing within and at the edge of old lesions (Fig. 48.2). Slight changes in the epidermis may occur. There are usually no symptoms, although there may be some slight itching. The eruption is characteristically very chronic and may persist for many years. The pattern of the eruption changes, with slow extension and often some clearing of the original lesions. Spontaneous cure may occur eventually. Many patients have an eruption with features both of this disease and of the other pigmented purpuric dermatoses. An annular configuration may occur and there may be small lichenoid papules.

Itching purpura is a disorder that may be similar to

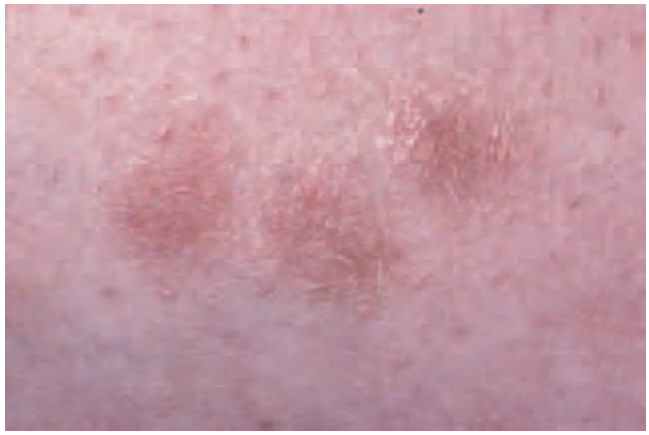

Fig. 48.2 Schamberg's disease.

Schamberg's disease, but the intensity of itch serves to distinguish the two.

Itching purpura [21–23]

SYN. ECZEMATIDE-LIKE PURPURA (OF DOUCAS AND KAPETANAKIS); DISSEMINATED PRURIGINOUS ANGIODERMATITIS

This condition has many similarities to Schamberg's disease but is generally more extensive, develops more rapidly and is characterized by persistent intense itch. It occurs most frequently in adult men and is of unknown aetiology. Purpuric lesions usually commence around the ankles and in a few weeks spread to involve the whole legs, sometimes the lower part of the body, and even elsewhere. They are more pronounced at sites of friction with clothing. The lesions consist of erythematous and purpuric macules that may become confluent. The eruption often has a rather characteristic orange colour. The dermal perivascular changes are those seen generally in the pigmented purpuric dermatoses and there are variable changes in the overlying epidermis, including spongiosis. Spontaneous improvement after a few months is usual, but recurrences may occur and a fluctuating but chronic course is frequent. The itching may respond to topical corticosteroids and oral antihistamines.

An almost identical picture occurs with carbromal sensitivity, and less commonly with other drugs such as meprobamate, carbamazepine and perhaps even some foods. Clothing or rubber dermatitis may produce a similar picture, and may explain many cases of itching purpura.

Pigmented purpuric lichenoid dermatosis of Gougerot and Blum [24]

This eruption occurs especially in men aged between 40 and 60 years. It usually affects the legs, but lesions may occur elsewhere. The characteristic clinical feature of the dermatosis is the presence of lichenoid papules in association with purpuric lesions similar to those of Schamberg's disease, and this may simply be a variation of the same disorder. This clinical pattern has been found in association with porphyria [25] and a similar pattern of eruption may occur in the oral mucosa [26].

Lichen aureus [27,28]

SYN. LICHEN PURPURICUS

This is a more localized, more intensely purpuric but often asymptomatic eruption that may have rather lichenoid morphology. Young adults and children are often affected, on body, limbs or even face. The lesions are often solitary and may be yellowish, golden, rust-coloured or purple. They may resemble a bruise, and hence must be distinguished from non-accidental injury in children, but may persist for a few years. Histologically, lichen aureus is distinguished from other pigmented purpuric dermatoses by a lack of epidermal component and in some cases a Grenz zone.

Purpura annularis telangiectodes [29,30]

SYN. MAJOCCHI'S DISEASE

This eruption occurs especially in adolescents and young adults of either sex but may occur at any age, and may be familial [31]. Exercise may have been a provoking factor in one case [32]. The clinical features are distinctive and described in its name. Lesions occur at any site, often in the absence of venous stasis, and may be few in number or very numerous. They consist of small plaques 1–3 cm across that are usually annular from their onset (Fig. 48.3). Lesions consist of telangiectases and haemosiderin staining of the skin. They may be purple, yellow or brown, and may contain 'cayenne pepper' spots. Individual lesions persist unchanged for many months or years, or there may be slow centrifugal extension with development of slight central atrophy. Sometimes the lesions disappear

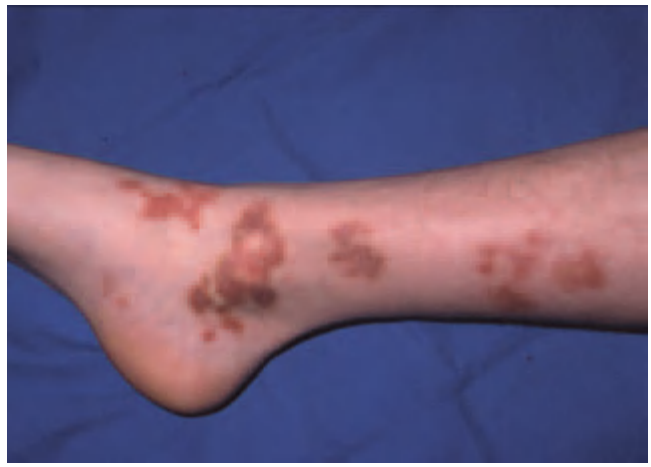

Fig. 48.3 Majocchi's purpura annularis telangiectodes.

and are replaced by similar lesions nearby. Treatment is usually ineffective. A variant termed *purpura telangiectatica arciformis (Touraine)* consists of fewer, larger and irregularly arciform lesions [33].

Granulomatous pigmented purpuric dermatosis

An uncommon variant of pigmented purpuric dermatosis has been reported in which there is granulomatous histology [34,35].

Familial pigmented purpuric eruption

There are rare reported instances of the familial occurrence of Schamberg's disease [18] and of purpura annularis telangiectodes [31]. A distinctive pigmented purpuric eruption has been observed in several members of a family in which it was probably determined by an autosomal dominant gene [36]. Discrete reddish-brown spots develop in childhood or adolescence. The individual macules are larger than in Schamberg's disease and are arranged in a mosaic pattern. The lesions gradually cover a larger area and involve new sites, mainly on the limbs and in the larger flexures, but there are no symptoms.

Linear and quadrantic pigmented purpuric dermatoses

Various morphological types of pigmented purpuric eruption may occur in a linear or zosteriform distribution [37–39], or less commonly may diffusely involve a single quadrant of the body [40]. Individual lesions usually resemble lichen aureus or Schamberg's disease.

Treatment of pigmented purpuric dermatoses

These disorders may persist for many years [5,6,28] and are very resistant to any form of therapy; explanation without active intervention, or simply support hosiery, is often the most appropriate approach. Topical steroids may be of some help, especially for itch, but very prolonged use is best avoided. Psoralen and UVA (PUVA) [9,41,42] has proven effective in treating capillaritis of Schamberg, Gougerot–Blum and lichen aureus patterns. Ciclosporin [43] and griseofulvin [44] have also been effective in individual reports.

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Non-thrombocytopenic vascular causes of purpura and syndromes of primarily ecchymotic haemorrhage

A number of disorders cause purpura or ecchymosis due to vascular fragility/poor dermal support, intravascular pressure increase, platelet dysfunction (see also earlier) or coagulation cascade defects. Minor trauma is often the precipitant of lesions.

Purpura due to raised intravascular pressure

Raised intravascular pressure may cause purpura in the absence of any other disease. Crops of petechiae after prolonged coughing or vomiting (see Fig. 48.1) occur especially on the relatively loose tissues of the face and neck. They are of no significance.

Gravity and venous stasis are the most important causes of purpura. Many purpuric eruptions are maximal on, or even restricted to, the lower leg. Likewise, many erythematous eruptions on the lower legs, especially in the elderly or those with leg oedema, show some degree of purpura that can usually be ignored. Bizarre patterns of purpura should always suggest the possibility of artefact.

Deaths from asphyxia are said to be associated with facial and conjunctival petechiae but the mechanism is probably due to vascular occlusion causing raised intravascular pressure rather than to hypoxia *per se* [1].

Purpura due to decreased support of blood vessels

Several disorders are associated with abnormal collagen, elastic or other dermal changes leading to poor support of the blood vessels. Conditions such as Ehlers–Danlos syndrome (collagen), pseudoxanthoma elasticum (elastic) and amyloidosis (abnormal protein) are discussed in more detail elsewhere. Facial or periorbital purpura occurs in 15% of patients with primary amyloidosis [2].

Scurvy is discussed in more detail in Chapter 57. Altered collagenous support for the blood vessels is manifest by either petechiae, especially on the legs, or by small or large bruises on the limbs following mild or inapparent trauma. Large deep bruises may lead to woody induration, usually of the legs. Perifollicular purpura is typical but is not diagnostic and is frequently absent. Diagnosis is established by the associated symptoms and signs (twisted 'corkscrew' hairs, gingival bleeding), dietary history, laboratory tests and therapeutic response.

Actinic purpura (*Bateman's purpura*, *'senile' purpura*) and *corticosteroid purpura* [3,4] are the commonest patterns of purpura due to lack of support of the blood vessels. They occur most commonly in skin altered by both age and solar radiation, but may occur in premature ageing syndromes. Corticosteroid purpura has the same pattern whether due to topical, oral, endogenous (Cushing's syndrome) or even inhaled [5] corticosteroids. The precipitating factor is a shearing stress. Patients who develop this type of purpura with ageing, in association with rheumatoid arthritis or with corticosteroids, are more liable to develop osteoporosis of the spine than patients without this sign [6]. The purpura occurs mainly in atrophic skin at exposed parts of the hands and forearms, or on the legs. Lesions appear after minor trauma or apparently spontaneously. They are usually asymptomatic and vary in size from a few millimetres to several centimetres across. They are often arranged linearly, and may show a linear or geometric shape. The appearance of the lesions is characteristic, with irregular areas, usually not palpable, that show little inflammatory reaction and which are usually dark purple rather than having the sequential colour changes of a normal bruise. They may persist for several weeks. Treatment is usually not necessary or possible.

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Easy bruising syndrome and purpura simplex

The term 'easy bruising syndrome' has been used in various ways, usually for a mild purpura for which no cause has been detected, especially on the thighs of women ('devil's pinches'). It has been used to include those cases of a mild bleeding tendency in which changes in the morphology of capillaries may be seen by capillary microscopy, and in some of which variable but slight changes in coagulation factors have also been found. There are significant limitations in deciding what constitutes

'abnormal' or excessive bleeding [1]. The term 'purpura simplex' has also been used for any inflammatory purpura without vasculitis including disorders with the morphology of the pigmented purpuric dermatoses [2,3] and this term is therefore also of uncertain value. Autosomal dominant inheritance of purpura simplex has been reported [4] and presumably represents a subtle haemostatic defect; in one family, purpura simplex was co-inherited with ptosis [5].

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Physical and artefactual causes of purpura

Bruising due to trauma seldom causes diagnostic problems, as there is usually a clear history, except when it occurs as an artefact or in child abuse. String vests may cause a distinctive reticular pattern of petechiae. Black heel (talon noire) is considered in Chapter 22. Bizarre patterns of purpura may be caused by suction, for example vacuum extractors in the neonate, electrocardiogram leads or around the mouth after sucking out the air from a glass [1]. Cultural remedies such as cupping, coin rubbing (Cao Gio) and spooning (Quat sha) may also produce unusual patterns of purpura that are usually obviously extrinsic in causation [2].

Paroxysmal finger haematoma [3–5]

SYN. ACHENBACH'S SYNDROME

In this syndrome there are recurrent episodes of painful bruising on the palms and palmar aspects of the fingers. It seems likely that it represents venous rupture, as frictional trauma may be reported, such as turning on a tap or twisting the top off a jar. It is probably more common than the number of reported cases would suggest. Its importance is that it may be confused with Raynaud's phenomenon or acute connective tissue diseases and investigated unnecessarily.

Autoerythrocyte sensitization syndrome [6–9]

SYN. PAINFUL BRUISING SYNDROME; GARDNER–DIAMOND SYNDROME

This is a distinctive but rare clinical entity apparently due, in many cases, to allergic sensitivity to red cells in the tissues. Minor extravasations of blood, for example those so common on the thighs of women, are followed by an intense inflammatory reaction. The disease occurs most frequently in young adult and middle-aged females, who are nearly always psychiatrically abnormal. They present with recurrent painful erythematous and purpuric lesions on the thighs and elsewhere. The diagnosis may be confirmed by intradermal injections of red cells or their washed stroma, or of phosphatidylcholine. This reaction occurs even in some subjects in whom a psychological cause is suspected and whose disease responds to psychological intervention [10,11].

Sensitivity to DNA [12,13] or to exogenous antigens attached to red cells [14] may present a similar picture. The condition is usually chronic, seldom disabling or associated with other abnormalities and is unresponsive to treatment. Plasmapheresis has been used successfully in isolated cases [15] and antimalarials are said to be effective in DNA sensitivity [16]. Dermatitis artefacta may produce a similar clinical picture, and is believed by some to account for all such cases [8,11,17].

Stigmata

In this very rare disorder there is exudation of apparently fresh blood through the unbroken skin of the hands, feet and side. The mechanism is obscure but, as with the previous syndrome, many if not all cases may have a traumatic origin [8,18].

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Purpura in other dermatoses

Many eruptions on the lower leg, especially in the elderly, tend to become purpuric due to a combination of gravitational changes with vascular damage caused by the dermatosis. Rapid development of lower leg oedema may cause an eczematous eruption in which purpura may be prominent [1].

Even without the gravitational component, many dermatoses may be sufficiently intense to cause purpura. Sometimes this is physically due to scratching, but some disorders such as lichen planus, lichen nitidus and Langerhans' cell histiocytosis are not infrequently purpuric. Purpuric erythema annulare centrifugum, dermatitis herpetiformis, pemphigoid, pityriasis rosea and eczemas (especially of discoid type) may all occur. Purpura may be present in lymphomas and lupus erythematosus, either because of platelet deficiency or, more commonly, because of vascular abnormalities.

Lichen sclerosus often has a haemorrhagic component due to loss of collagenous support for the vessels.

Some insect bite reactions have a purpuric centre due to inoculation of the skin with anticoagulant chemicals in the bite (purpura pulicosa, maculae ceruleae).

Purpura may also occur around localized lesions with a strong vascular component if there are fragile vessels, for example targetoid haemosiderotic haemangioma or aneurysmal fibrous histiocytoma.

A rather characteristic disorder of children under the age of 1 year has been termed the *persistent acrovasculopathy syndrome*. Lesions occur on the ears, cheeks and extremities and are scaly and erosive; they may be purpuric, and there may be local lipoatrophy and distal phalangeal osteopenia.

Most of these conditions are discussed in more detail in other chapters; two disorders are specifically described here.

Solar purpura [2–5]

This condition is distinct from the actinic purpura discussed previously which is a manifestation of cumulative sunlight-induced ageing of the skin. The term 'solar purpura' is used to describe rapid development of purpuric lesions after exposure to sunlight. The precise nature of this disorder is uncertain. Some view it as a variant of polymorphic light eruption. It is distinct from erythropoietic protoporhyria, although purpura clearly occurs in this dermatosis in some patients (Fig. 48.4). Some cases may simply be a variation of purpura in dermatoses that are not usually purpuric, but where profound inflammation has allowed purpura to develop.

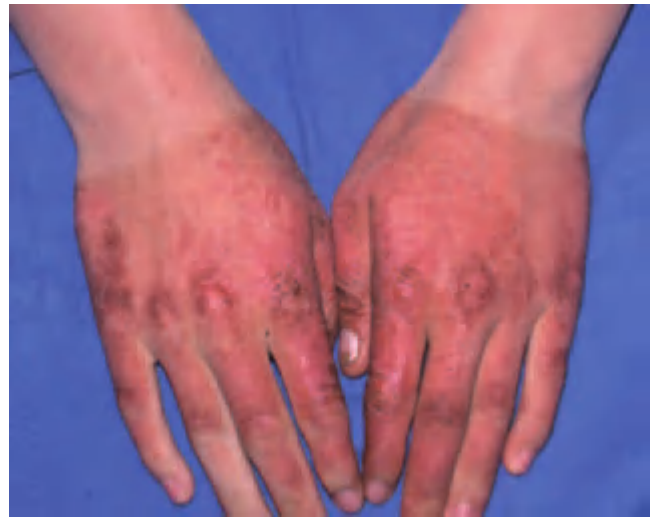

Fig. 48.4 Erythropoietic protoporphyria: marked purpura with sharp cut-off after sunlight exposure.

Acroangiodermatitis (of Mali) [6–8]

SYN. DERMITE OCRE OF FAVRE; GRAVITATIONAL PURPURA; PSEUDO-KAPOSI'S SARCOMA

This chronic dermatosis is associated with venous insufficiency or with vascular anomalies such as Klippel–Trenaunay syndrome [9], and there are several reports of it occurring as a stump dermatosis in amputees [10]. It has been reported in a patient with a thrombophilic prothrombin mutation [11]. It may mimic a pigmented purpuric dermatosis (see previously) but is discussed here as the purpura is due to abnormal vasculature rather than to capillaritis. It occurs more often in men than in women.

The lesions occur especially on the lower legs but may extend on to the dorsa of the feet and toes, and up the leg, especially over dilated varicosities. Individual lesions are minute purpuric macules that coalesce to form irregular plaques, which may be several centimetres in diameter. Follicular lesions may occur. The colour of the lesions is not usually the purple colour of fresh purpura but varying shades of yellow (ochre) and brown from haemosiderin and other breakdown products. The epidermis may be normal or show mild eczematous changes. Oedema, sclerosis, ulceration and other signs of venous insufficiency may be associated, but may be entirely absent even in cases of long duration. Differential diagnosis includes ordinary gravitational dermatitis, Schamberg's disease and Kaposi's sarcoma; the latter can be distinguished by the staining pattern with CD34 antigen, which stains perivascular spindle cells in Kaposi's sarcoma but only the endothelial cells in acroangiodermatitis [12]. Treatment is unsatisfactory but support hosiery seems logical.

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Dysproteinaemic purpura and Waldenström's hypergammaglobulinaemic purpura

Purpura may be the presenting and sometimes the only symptom of disturbances in plasma proteins. It may occur at exposed skin sites in cryoproteinaemia (see Chapter 23 and below) and may occur due to monoclonal hypergammaglobulinaemia in myeloma. In such instances there may be platelet dysfunction, but clinical bleeding is usually related to the hyperviscosity syndrome rather than to the altered platelet function. Cutaneous features of paraproteinaemia include various patterns of vasculitis and neutrophilic dermatosis (see Chapter 49), cryoglobulinaemia (see below), urticaria and systemic capillary leak syndrome, abnormalities of lipid metabolism (notably diffuse plane xanthomatosis), subcorneal pustular dermatosis, lichen myxoedematosus and scleromyxoedema, amyloidosis, and features due to hyperviscosity (purpura, mucous membrane bleeding, retinopathy and neurological disturbance) [1,2]. Haemorrhagic features are particularly seen in Waldenström's macroglobulinaemia.

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Waldenström's hypergammaglobulinaemic purpura is generally taken to imply an idiopathic phenomenon but in fact two of Waldenström's three cases had sicca symptoms, one with sarcoidosis [1]. Hypergammaglobulinaemic purpura is usually a polyclonal disorder most commonly linked with sarcoidosis, lupus erythematosus, Sjögren's syndrome, and other autoimmune conditions [2–8]. The majority of patients have positive antinuclear antibody and anti-SSA (Ro) or anti-SSB (La) antibodies [4–8]. Other features that have been associated include arthropathy (not uncommon), renal tubular acidosis, chest infections, lymphopenia and immune hypersensitivity pneumonitis. Most patients are female [9].

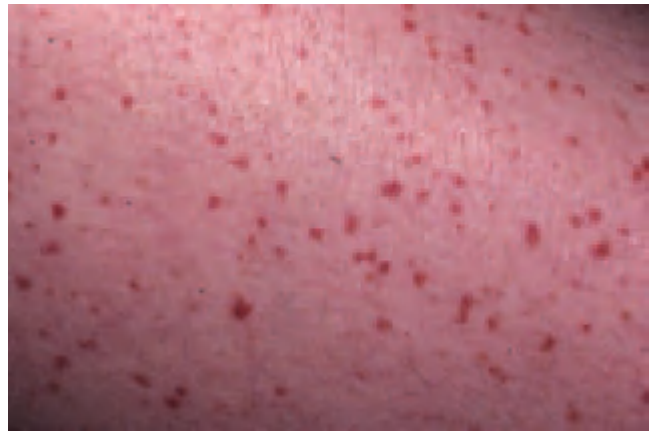

Fig. 48.5 Waldenström's hypergammaglobulinaemic purpura: lower leg lesions, in this patient usually provoked by prolonged standing or heat.

Clinically the pattern of purpura is often non-specific, usually consisting of crops of small erythematous macular or palpable purpuric spots on the lower leg (Fig. 48.5) [1–8], but unusual patterns with reticulate lesions may occur [10]. Prolonged walking, standing or sitting with the legs dependent, or other increase in venous pressure, may be an obvious provocative factor [7,8]. Itch or a burning sensation may occur. It is likely that this disorder is an immune complex vasculitis: immune complexes can be detected, histology may show vasculitic change, and direct immunofluorescence may show immunoglobulin in blood vessel walls [6,10,11]. Hyperviscosity leading to stasis and endothelial damage plays some part. There may be an abnormal ratio of IgG subclasses, with low IgG1/IgG2 ratio [12].

Lesions usually resolve in about a week but may become confluent and permanent. Treatment is often not required, although prednisolone, NSAIDs, hydroxychloroquine and etamsylate (ethamsylate) have been used.

A similar pattern has been reported in association with cystic fibrosis, due to either hypergammaglobulinaemia or cryoglobulinaemia [13,14]. It may appear suddenly, affects the lower legs mainly, and is exacerbated by prolonged standing or by tight garments or footwear. It is associated with severe lung disease and poor prognosis; a high antigenic load due to chronic lung infection may be the cause.

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Multifactorial purpura associated with systemic diseases

Non-thrombocytopenic purpura may be caused by a variety of systemic diseases. Many of these have already been discussed, but in some cases there may be mixed mechanisms of purpura or easy bruising. Of these, renal disease is perhaps the most important; petechiae, ecchymoses or mucosal bleeding are common in end-stage renal failure [1]. Platelet dysfunction is probably the major factor [2], but there may also be frank thrombocytopenia. Diabetes, severe anaemia, liver disease, haemochromatosis and carcinomatosis may also cause purpura.

In amyloidosis, with or without myelomatosis, purpura may be due to infiltration of the capillaries and perivascular tissue with amyloid, but platelet changes and liver disease may also contribute.

Purpura occurs in patients with malnutrition. It seems probable that changes in coagulation, platelets and capillaries all play their part. For example, in cystic fibrosis there may be dysproteinaemia, vasculitis and vitamin K deficiency.

Purpura has been associated with ovarian and other endocrine abnormalities [3], for example Cushing's disease, and may vary with the menstrual cycle.

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Inflammatory haemorrhage: anaphylactoid purpura and acute haemorrhagic oedema

Vessel damage with inflammation may lead to haemorrhage, typically manifest as palpable purpuric lesions. This is usually caused by one of the types of antigen–antibody reaction discussed in Chapter 10 but may be due to a direct toxic effect. The antigen in the allergic mechanism may be a component of the vessel itself or of surrounding tissues or, more commonly, an exogenous substance bound to the blood vessel or other tissues. Such substances include drugs, bacterial products and food additives; they may reach the blood vessel via the bloodstream or from the skin surface. The antigen–antibody reaction may occur on the surface of the endothelial cells or in adjacent tissues, or the vessels may be damaged by soluble complexes. The localization of many such lesions will be determined by local factors, for example changes due to gravity, cold and trauma. This inflammatory process is therefore a vasculitis, and is discussed in Chapter 49. Two conditions of this type are briefly discussed here, one because it carries the name purpura (Henoch–Schönlein purpura) and the other because it may present with striking haemorrhagic lesions (acute haemorrhagic oedema).

Henoch–Schönlein purpura is a vasculitic process due to immune complex deposition in the walls of arterioles and venules that gives rise to palpable inflammatory lesions; these are often purpuric as well as erythematous and may vary in size from 0.5 to 1 cm or more. However, minor lesions of anaphylactoid purpura may sometimes be confused clinically with other types of purpura.

Acute haemorrhagic oedema is now felt to be a variant of Henoch–Schönlein purpura. It has also been described as cocarde purpura, Seidlmayer's syndrome and Finkelstein's disease. Most cases have been reported from continental Europe [1,2] but English [3] and American [4] cases are also reported. It may be overtly haemorrhagic, but can present as arciform or annular brown lesions that are of acute onset but which have some morphological similarity to pigmented purpuric dermatoses.

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Disorders of cutaneous microvascular occlusion

Numerous conditions may cause microvascular occlusion (Table 48.4). This process may involve abnormal coagulation (e.g. DIC, APLS), platelet plugging (e.g. heparin necrosis), emboli or crystal deposition (e.g. cholesterol emboli), abnormal erythrocytes (e.g. sickle cell disease) or abnormal proteins (e.g. cryoproteinaemia). Many of these conditions may cause purpura as one of their manifestations; many cause an initial non-inflammatory purpuric process that can be diagnostically helpful in the differential from vasculitis.

Occlusion due to platelet plugs

Heparin-induced thrombocytopenia and heparin necrosis

Aetiology and pathogenesis. The syndrome of heparin-induced thrombocytopenia (HIT) is an uncommon paradoxical response to heparin, with some female predominance [1]. This syndrome can be defined as any clinical event best explained by PF4/heparin-reactive antibodies (HIT antibodies) in a patient who is receiving, or who has recently received, heparin [1]. While IgA and IgM class antibodies may play a role, IgG antibody is most closely associated with this syndrome [2]. The antibody that causes HIT is not simply an antiheparin antibody. Heparin and certain other polyanions, when bound to PF4, can induce conformational changes in tetrameric PF4, exposing new epitopes on PF4. This may trigger antibody production to these newly exposed regions. When antiheparin/PF4 antibody binds with heparin/PF4 complexes on the surface of platelets, platelet activation and aggregation results. Not all heparin/PF4 antibodies appear to be pathogenic, and some antibodies responsible for HIT do not bind to heparin/PF4 complexes but to chemokines or cytokines such as neutrophil activating peptide-2 (NAP-2) and interleukin-8, somehow activating platelets [1,2].

Unfractionated heparin is three times more likely to be associated with HIT following orthopaedic surgery compared with low-molecular-weight heparin [1]. HIT is more likely to be induced by bovine-derived unfractionated heparin than the porcine-derived variety, consistent with the hypothesis that longer and more flexible heparins bind to PF4 tetramers in ways that induce more conformational change and more exposure of neoepitopes. This may also explain the lower risk of HIT with low-

Table 48.4 Disorders of cutaneous microvascular occlusion: differential diagnosis by pathophysiological mechanism*.

Occlusion due to platelet plugs
Heparin-induced thrombocytopenia
Myeloproliferative disorders
Paroxysmal nocturnal haemoglobinuria
Thrombotic thrombocytopenic purpura (TTP)/haemolytic–uraemic syndrome (HUS)†
Occlusion due to cryogelling
Cryoglobulinaemia
Cryofibrinogenaemia
Cold-agglutinin-related occlusion
Occlusion due to vessel-invasive organisms
Ecythma gangrenosum
Lucio phenomenon
Vessel-invasive fungi
Disseminated strongyloidiasis
Occlusion due to embolus
Cholesterol embolus
Oxalate crystal embolus
Atrial myxoma
Cardiac sterile thrombi
Septic emboli
Fat emboli‡
Occlusion due to systemic coagulopathies with cutaneous manifestations
Protein C/S/thrombomodulin pathway abnormalies
Neonatal purpura fulminans
Coumadin necrosis
Sepsis-related purpura fulminans
Post-infectious purpura fulminans
Antiphospholipid antibody syndrome
Occlusion due to vascular coagulopathies§
Sneddon's syndrome
Livedoid vasculopathy/atrophie blanche
Malignant atrophic papulosis
Occlusion due to reticulocyte occlusion¶
Sickle cell disease
Other severe haemolytic anaemias
Occlusion due to unknown or controversial mechanisms
Cutaneous calciphylaxis
Some insect bites, especially Loxosceles (brown recluse spider)
Some snake bite syndromes**

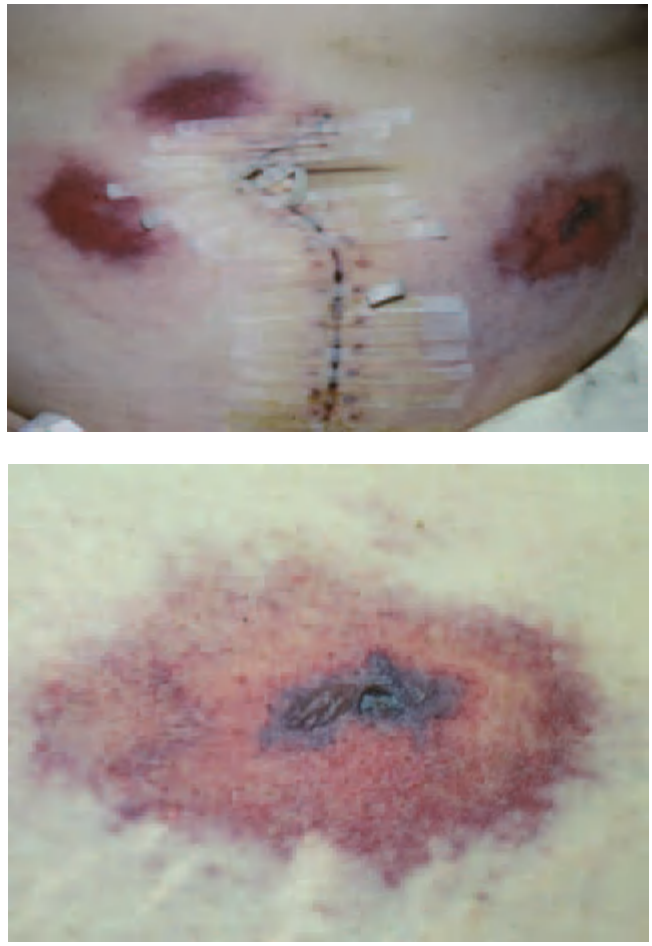
* Most of these disorders present with purpura or necrosis with minimal inflammation, and frequently show retiform (stellate, branching) morphologies.
† TTP/HUS is usually occlusive in visceral vessels, but skin lesions are most often non-palpable petechiae, and not due to occlusion.
‡ Fat emboli typically cause occlusion in viscera, especially lungs; cutaneous lesions are rare and typically petechial, due to minute fat particle occlusion.
§ Sneddon's syndrome typically presents with pathological livedo reticularis; livedoid vasculopathy may have retiform purpura morphologies, but atrophie blanche and malignant atrophic papulosis are often not purpuric, but heal with characteristic atrophic scar with surrounding telangiectasia.
¶ Syndromes involving reticulocyte occlusion often heal with lesions mimicking atrophie blanche, and are seldom purpuric or retiform.
** Most snake bites cause haemorrhage; if fulminant disseminated intravascular coagulation results, some lesions might be occlusive.

molecular-weight heparins. The risk of HIT is highest in post-surgical patients, less so in medical patients requiring heparin, and lowest in obstetric settings [1].

Clinical features. Patients with HIT usually develop absolute or relative thrombocytopenia (90%), often followed by evidence of venous or arterial thromboses or of heparin necrosis in the skin [1]. A proportional drop of over 50% in platelet number from the pretreatment count may be a better indication of early heparin-induced platelet aggregation than an absolute thrombocytopenia of 100–150 $\times 10^9$/L [1]. This may occur immediately after heparin administration if the patient has been previously sensitized and has received heparin within the past 100 days. In two-thirds of patients, the fall in platelet count begins between day 5 and 10 of heparin administration, though significant thrombocytopenia may take 7–14 days to develop [1,3,4]. Uncommonly, patients may develop HIT several days after stopping heparin (delayed-onset HIT); this is attributed to the presence of high-titre antibodies that can recognize PF4 neoepitopes even in the absence of heparin binding [1]. A history of HIT is not predictive of a second episode if the patient last received heparin more than 100 days previously.

Heparin administration commonly induces cutaneous findings of simple haemorrhage with ecchymoses, and occasionally triggers urticaria or infiltrated plaques [5–7]. Uncommonly, the syndrome of heparin necrosis results as a cutaneous microvascular occlusion subset of HIT. Purpuric, tender, sharply demarcated plaques develop; retiform extensions that sometimes develop at the lesional margins are characteristic of heparin necrosis. Erythema may sometimes accompany such lesions, and necrosis is frequent. Lesions are most common at subcutaneous injection sites but can occur elsewhere [8–10] (Fig. 48.6). Interestingly, as few as one-third of patients with skin lesions of heparin necrosis may develop absolute thrombocytopenia, even when HIT antibodies are detected [1]. Haemorrhagic adrenal infarction has been reported in such cases. Histological examination of lesions reveals 'white clots', representing platelet–fibrin thrombi, in the cutaneous microvasculature [4,11].

Treatment. Treatment of HIT and heparin necrosis continues to evolve. The correct diagnosis is important, since many patients on heparin develop thrombocytopenia for reasons other than the development of HIT antibodies; conversely, patients may develop the arterial or venous thromboses, or especially heparin necrosis, without manifesting thrombocytopenia [1]. While replacing heparin with coumadin was previously thought to be effective in treating HIT and heparin necrosis, coumadin substitution is not only ineffective but may in fact induce venous limb gangrene [1]. Although low-molecular-weight heparin is much less likely to cause HIT, it is contraindicated for treatment of patients with HIT due to other types of heparin. Surprisingly, heparin is the appropriate treatment for cardiac surgery patients with a previous history of HIT, but whose antibodies have disappeared (beyond 100 days). The anticoagulants currently used to treat patients with HIT are danaparoid (a heparinoid) and two thrombin inhibitors, lepirudin and argatroban [1]. Even with treatment with one of these agents, there is a 5–20% frequency of new thromboses. Major bleeding in HIT patients has occurred in 3.1% of those treated with argatroban, and in 5.9–14.4% of those treated with lepirudin.



(a)

(b)

Fig. 48.6 (a) Heparin necrosis at sites of subcutaneous heparin injection. (b) Close-up of a 15-cm lesion on left abdomen. Lesion is a non-palpable haemorrhage with retiform margins, minimal erythema and central retiform intense haemorrhage, early necrosis and bullae formation. (From Robson K, Piette W. The presentation and differential diagnosis of cutaneous vascular occlusion syndromes. *Adv Dermatol* 1999; **15**: 153–82, with permission from Mosby.)

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Myeloproliferative disorders

Cutaneous lesions are common in thrombocythaemia and other myeloproliferative disorders (see also Chapter 59). Paradoxically, patients with myeloproliferative thrombocytosis may both bleed and clot abnormally. Skin lesions were documented in 22% of 268 patients with essential thrombocythaemia [1], and included urticaria, livedo reticularis, petechiae, ecchymoses, haematomas, erythromelalgia, Raynaud's phenomenon, recurrent superficial thrombophlebitis, necrotizing vasculitis, leg ulceration and gangrene. Biopsy findings were variable, but some livedo reticularis and acral infarcts were associated with evidence of microvascular occlusion. Additionally, tender erythematous facial plaques and palmar violet macules and papules were reported as manifestations of platelet plugging in a patient with atypical chronic myeloproliferative disease and a history of Budd–Chiari syndrome, another known thrombotic complication of myeloproliferative disease [2]. This patient's cutaneous lesions were unresponsive to coumadin, but cleared within 24 h of aspirin administration following identification of platelet plugs as the cause of previously identified microvascular occlusion.

Essential thrombocytosis and polycythaemia vera, though rare, are the first and second most common causes of elevated platelet counts, with an increased frequency of thrombotic events and of erythromelalgia [3]. These diseases are more common at younger ages and in women. However, reactive or post-splenectomy thrombocytosis at any level is not associated with occlusion, suggesting that thrombosis in the setting of myeloproliferative disease is not a function of thrombocytosis alone. Platelet counts less than 1000×10^9/L are generally not considered sufficient to result in platelet-related vascular occlusion phenomena. The mechanisms for ischaemic or occlusive syndromes in myeloproliferative disease must therefore depend on more than platelet number alone; the following factors may be relevant. Acquired von Willebrand factors in myeloproliferative disease have been associated with both bleeding and thrombotic complications. Anticardiolipin antibodies, factor V Leiden mutations, abnormal endothelial cell function, and decreased levels of protein C and protein S may be synergistic for thrombosis in chronic myeloproliferative diseases [4,5]. In addition to high platelet counts, abnormal platelet function occurs in myeloproliferative or myelodysplastic disease, although whether this can lead to vascular occlusion at platelet counts less than 1000×10^9/L is controversial. Thrombotic events have been reported at platelet counts below 600×10^9/L in patients with essential thrombocytosis, including some events at normal platelet counts [6]. In a study of 56 consecutive patients with essential thrombocytosis, 46 developed complications mostly related to thrombosis [6]. In these 46 patients, severe complications occurred in 22% at platelet counts lower than 600×10^9/L, in 15% at counts lower than 500×10^9/L, and in 4% at counts lower than 400×10^9/L.

Erythromelalgia (erythralgia) can occur as a primary or secondary syndrome. This intensely uncomfortable burning associated with paroxysmal erythema of the distal extremities is frequently triggered by skin contact with a warm surface. While erythromelalgia has been seen in many different settings, the association of purpuric or necrotic areas on hands and feet with the dysaesthetic erythema is exclusively seen with myeloproliferative or myelodysplastic thrombocytosis [7]. Because of the platelet origin of occlusion and vascular symptoms in the myeloproliferative subset of erythromelalgia, aspirin administration is notably effective in clearing lesions and alleviating symptoms, whereas it is much less effective in primary and other secondary forms of erythromelalgia.

Splenomegaly may be seen in all forms of myeloproliferative syndromes. Ruddy cyanosis is characteristic of polycythaemia vera, as is elevation of haemoglobin, haematocrit and red cell mass. All syndromes may show elevations in white count, but this is most characteristic of chronic granulocytic leukaemia, especially in association with elevated eosinophil and basophil counts. Anaemia and altered red cell morphology can occur over time in all patients, and all these diseases have some risk of transition to dyspoiesis and severe anaemia, leukaemia or myelofibrosis.

Many therapies previously used for myeloproliferative thrombocytosis increase the risk of leukaemic transformation and of complications in fertility and pregnancy. Low-dose aspirin has been widely accepted as effective thrombosis prophylaxis, although definitive proof of its

efficacy is lacking. Its dramatic reversal of signs and symptoms in erythromelalgia provides some clinical evidence for its usefulness in thrombocythaemic complications. Anagrelide has become an important therapeutic agent, acting to both inhibit platelet activity and decrease the platelet count [8].

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Paroxysmal nocturnal haemoglobinuria

Paroxysmal nocturnal haemoglobinuria (PNH) is an acquired clonal blood disorder associated with deficient haematopoiesis, intravascular haemolysis and venous thrombosis [1,2]. Episodic haemoglobinuria is the characteristic result of nocturnal haemolysis, although it is the presenting feature in only 26% of patients [1,2]. The sleep-associated haemoglobinuria is secondary to an abnormally increased sensitivity of red blood cells to lysis by serum complement [1]. This increased sensitivity to complement lysis is related to abnormal regulation at two different points of the complement cascade, and this abnormal regulation is due in turn to the partial to complete deficiency of two membrane-associated inhibitors of the complement cascade, decay-accelerating factor (DAF) and membrane inhibitor of reactive lysis (MIRL, also known as CD59). DAF inhibits the activity of classic complement pathway C3 convertase and of alternative pathway C3 convertase, while MIRL/CD59 regulates the activity of the complement membrane attack complex on red cells. These two inhibitors are part of a group of roughly 20 red cell membrane proteins that share a common post-translational modification in the glycosylphosphatidylinositol (GPI) anchor. In PNH, a somatic mutation in the phosphatidylinositol glycan class A gene (*PIG-A*) on the X chromosome alters the ability of proteins sharing the GPI anchor to bind to the membrane [1–3].

This complex pathophysiology explains the haemolysis and haemoglobinuria in PNH, but does not yet completely explain other manifestations of this disease such as thrombosis. Thrombosis is a major morbidity; 40% of patients develop venous thrombosis [2]. At least some of the thrombotic tendency may be related to complement-mediated activation of platelets or to platelet–leukocyte complexes, which share the defect in GPI-anchored proteins. Budd–Chiari syndrome (hepatic vein thrombosis) is common, as are thromboses in unusual sites such as cerebral, dermal, hepatic and portal, mesenteric and splanchnic veins [1]. This unusual localization may also favour platelet activation as a pathogenic factor over typical plasma hypercoagulability. Anticoagulants, corticosteroids and thrombolytic therapy may be effective in treating thrombotic episodes; the role of antiplatelet therapy is unclear [4]. Clinical dermatological features of PNH include pyoderma gangrenosum, haemorrhagic bullae and DIC [5].

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Thrombotic thrombocytopenic purpura/haemolytic–uraemic syndrome

TTP was first recognized as recently as 1966 as a syndrome of thrombocytopenic purpura, microangiopathic haemolytic anaemia, renal dysfunction or failure, neurological abnormalities and fever, with a fatal outcome in 90% of patients [1]. Once plasma exchange proved at least sometimes effective in treating this disorder, criteria for diagnosis were pared to include only thrombocytopenia and microangiopathic haemolytic anaemia. HUS was originally described in children with acute renal failure, microangiopathic haemolytic anaemia and, usually, thrombocytopenia, but no purpura, neurological findings or fever. Current diagnostic criteria do not distinguish between TTP and HUS. However, childhood HUS is distinguished clinically because most cases are related to enteric infection with *Escherichia coli* O157:H7, HUS developing about 1 week after diarrhoea due to this agent; most children survive without plasma exchange [1]. Epidemic forms of HUS are most common, associated with

prodromal diarrhoea and with verotoxin (shigatoxin S1 or S2)-producing organisms, usually the *E. coli* strain mentioned previously, or enterococcus [2]. *Mycoplasma* can also provoke TTP. Pregnancy can induce TTP/HUS, as well as HELLP syndrome (haemolysis, elevated liver enzymes, low platelet count), as a complication of pre-eclampsia and eclampsia, and these may be difficult to distinguish [2]. TTP/HUS has been reported secondary to drugs (especially mitomycin C, ciclosporin, ticlopidine and quinine), after allogeneic bone marrow transplantation, and associated with autoimmune connective tissue disease (lupus erythematosus, scleroderma), vasculitis (polyarteritis nodosa), APLS [3], Sjögren's syndrome or metastatic carcinoma.

The molecular basis of TTP is a severe deficiency of a protease (ADAMTS13) that cleaves von Willebrand factor, resulting in persistence in plasma of ultra-large von Willebrand multimers secreted by endothelial cells [1,2]. Persistence of such large multimers in the circulation leads to formation of microvascular platelet thrombi. Congenital deficiency of ADAMTS13 leads to lifelong recurrent episodes of TTP; mechanisms for acquired ADAMTS13 are still unclear, but can include acquired autoantibody. Some regard ADAMTS13 deficiency as a diagnostic feature of TTP, whereas ADAMTS13 levels are reported to be normal in most patients with HUS [4,5]. Von Willebrand factor protease is deficient in hereditary, intermittent relapsing, intermittent acute, ticlodipine-induced and clopidogrel-induced TTP, but is normal in HUS and transplantation-related thrombotic micro-angiopathy. However, not all patients with deficient von Willebrand factor protease have active TTP.

Treatment options include plasma exchange with fresh frozen whole plasma or parts of plasma (e.g. cryoprecipitate-reduced plasma, high-molecular-weight fraction); corticosteroids, vincristine and antiplatelet drugs may also have a role. Outcome is usually good in childhood but less so in familial forms. As a practical matter, the response of patients to plasma exchange treatment in TTP or HUS is independent of whether they have deficient or normal levels of ADAMTS13 [6].

Microvascular platelet thrombi are characteristically seen in patients with TTP, especially in the renal and cerebral circulation [2]. Some have reported that HUS patients more often have fibrin-rich thrombi and more limited visceral vessel involvement [7]. Purpuric skin lesions are frequently mentioned in reports and reviews of TTP, but histological characterization of such cutaneous lesions is very sparse. Hyaline microthrombi composed of platelets and fibrin have been reported [8]. It seems likely from evaluation of lesional photographs that many, if not most, of the skin lesions in TTP are related to thrombocytopenia and simple haemorrhage rather than to microvascular platelet plugs as seen in the cerebral and renal vessels.

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Occlusion due to cryogelling

Common clinical features

Occlusion syndromes triggered by cold exposure are suggested by an acral distribution of lesions of necrosis or purpura, often with retiform features, and sometimes associated with acral livedo reticularis. An acral distribution must be distinguished from a dependent distribution of lesions. Both patterns may involve hands and feet, but with a dependent pattern there are typically many more lesions on the feet and legs than on the hands. A dependent distribution of lesions suggests immune complex-mediated disease, and usually presents as classical palpable purpura or occasionally as inflammatory retiform purpura, not as bland or non-inflammatory purpura or pauci-erythematous necrosis. An acral distribution of lesions is also characteristic of erythema multiforme. However, erythema multiforme presents with target lesions, atypical target lesions or classical palpable purpura, rather than non-inflammatory retiform purpura or necrosis, and it is not associated with livedo reticularis. In addition, the acral distribution of cryo-occlusion syndromes often includes the ears and nose, sites usually unaffected by erythema multiforme. While ill patients with immune complex vasculitis may develop dependent lesions on the posterior portions of the ears if supine due to their illness, their other lesions are typically in dependent areas as well, and there is usually no history of cold exposure as the precipitating factor. A biopsy of early lesions, before necrosis has had time to trigger a secondary vasculitic histology, should show non-inflammatory occlusion of dermal vessels with cryoprotein or agglutinated red cells.

Careful handling of serum and plasma is necessary to allow identification of cryogelling proteins, since those most likely to cause disease are those that gel at temperatures very close to normal body temperature. Likewise, identification of cryoproteins or cryoagglutinins does not prove a cryo-occlusion syndrome, since these may either gel at temperatures that are not relevant to typical cold exposure or may simply represent incidental findings. The latter is especially true of cryofibrinogens and cold agglutinins.

Cryoglobulins

Cryoglobulins, immunoglobulins that reversibly precipitate or gel in the cold, were first reported in 1933 and were named cryoglobulins in 1947 [1–4]. In 1974, Brouet *et al*. [2] proposed the now standard subset classification of cryoglobulins into types I, II and III. In the 1990s, a large proportion of cases were found to be associated with hepatitis C. While precipitation of cryoglobulins is primarily related to reversible cold-induced denaturation of protein, other factors such as cryoglobulin concentration in the microvascular environment, pH and non-covalent binding factors also influence the likelihood and intensity of precipitation.

Type I (single molecule) cryoglobulins are single monoclonal immunoglobulins, usually IgG or IgM, less commonly IgA, and rarely Bence-Jones protein. Accounting for 10–15% of cryoglobulins, they are often associated with an underlying lymphoproliferative disorder, especially multiple myeloma or Waldenström's macroglobulinaemia [5]. Since type I cryoglobulins are single proteins and are neither immune complexes nor proven to activate complement, then if they are to cause vascular injury or occlusion they can do so only by cryogelling and not by immune complex vasculitis.

Type II and III, termed mixed cryoglobulins, are multiple molecule proteins, typically immune complexes, that gel under laboratory conditions (2–4°C). Unless they gel at temperatures close to body temperature, they are much more likely to cause disease as immune complexes than as cryoproteins, but they can cause disease through either or both mechanisms in any given patient. Rheumatoid factor activity (defined by anti-Fc binding) is detectable in the sera of 87–100% of patients with mixed cryoglobulinaemia [3]. Type II cryoglobulins are composed of monoclonal proteins of IgM, IgG or occasionally IgA class that bind to an antigen present in the blood, most commonly the Fc portion of polyclonal IgG molecules. Those that bind immunoglobulin (usually IgG) by anti-Fc affinity are also, by definition, rheumatoid factors, though only the IgM/anti-IgG rheumatoid factors are recognized by standard rheumatoid factor testing. In up to 95% of type II cryoglobulins with IgM as the anti-rheumatoid factor immunoglobulin, the IgM contains a κ light chain, which would not be expected by chance alone [3,6]. Type III mixed cryoglobulins are also most commonly rheumatoid factors, but the IgM, IgG or IgA anti-Fc antibodies in this group are polyclonal rather than monoclonal. In patients with mixed type II or III cryoglobulins, complement levels are usually reduced, especially the C4 component.

Antibodies to hepatitis C virus (HCV) have been found in more than 50% (42–98%) of patients with type II and III cryoglobulins [2–4]. Conversely, 13–54% of patients with HCV have mixed cryoglobulins detected in the laboratory, and the majority of these are type III cryoglobulins (67–91%). Of HCV-infected individuals with cryoglobulins, only 27% had clinical signs consistent with the syndrome of cryoglobulinaemia [2]. The reasons why only a fraction of HCV-infected and cryoglobulin-positive patients develop symptomatic cryoglobulinaemia are unknown.

In a multicentre Italian cooperative study of 913 patients with cryoglobulinaemia, 8.9% of all patients with symptomatic cryoglobulinaemia had lymphoproliferative disease at diagnosis [2]. Of this subset of patients, 27% had type I, 68% had type II and 5% had type III cryoglobulins. Though type I cryoglobulinaemia is usually associated with lymphoproliferative disease, it is a much less common type than type II and III; the latter two types therefore accounted for the majority of cryoglobulinaemia-associated lymphoproliferative disease in this study from a region with a high endemic rate of HCV and mixed cryoglobulinaemia.

Other syndromes are also associated with cryoglobulins detectable in serum. Patients with connective tissue disease also have higher rates of cryoglobulinaemia: it occurs in up to 25% of patients with SLE, 12.5% of patients with systemic sclerosis, 46% of patients with active rheumatoid arthritis and 17–37% of patients with Sjögren's syndrome [2]. In addition to HCV, other chronic infections such as Lyme disease, subacute bacterial endocarditis (up to 90%), Q fever, hepatitis A and B, hantavirus, cytomegalovirus, human T-cell leukaemia virus I and HIV have been reported [2,7]. Chronic inflammatory disease, such as liver cirrhosis from any cause, is also associated with a higher than expected rate of detectable cryoglobulins. The presence of cryoglobulins in serum does not invariably predict disease; cryoglobulins were present at low titre in as high as 51% of normal individuals in one study [8]. In fact, despite detectable serum cryoglobulins in the patient groups mentioned, most will not develop symptomatic cryoglobulinaemia [2].

There are only two known ways in which cryoglobulins can result in disease. The first is by precipitation within the vascular lumen, typically cold-induced, with hyaline plug formation and minimal early phase inflammation. Typical clinical lesions would be minimally inflammatory cutaneous infarction with or without associated livedo reticularis, or non-inflammatory retiform purpura. Since

there is little evidence that cryogelling of monoclonal antibody induces complement activation, cryogelling is the only known mechanism for vascular lesions for type I cryoglobulins [5]. The second mechanism is that of immune complex vasculitis. Since nearly all type II and III cryoglobulins are immune complexes, they should all be capable of inducing an immune complex vasculitis, though many do not. If they cryoprecipitate near body temperature, they could also cause vascular injury by simple occlusion, although most appear to gel at temperatures well below 37°C.

The median age at diagnosis of cryoglobulinaemia is early to middle sixth decade, with a female to male ratio of 2 : 1 [2]. Recurrent showers of dependent palpable purpura, sometimes with burning or itching, frequently associated with arthritis or arthralgia, is the classic presentation of mixed (type II and III) cryoglobulinaemia (the combination of purpura, asthenia and arthralgia has been termed Meltzer's triad). Patients with symptomatic cryoglobulinaemia of any type most often present with cutaneous lesions, usually purpura (in 55–100%, especially if HCV-associated) [2–4,9]. Ulceration, haemorrhagic crusts or cutaneous infarction are seen in 10–25% of patients, most often with type I cryoglobulins. Cold-induced acrocyanosis of acral areas, and non-inflammatory retiform purpura are also more typical of type I cryoglobulinaemia. Other reported cutaneous findings include acral cyanosis, Raynaud's phenomenon, urticarial lesions, ulceration and livedo reticularis [4,10,11]. Histological demonstration of non-inflammatory hyaline thrombosis is more common in patients with type I cryoglobulinaemia, but some such patients have also been reported to have cutaneous vasculitis [9]. A prospective study of biopsies of only new lesions (duration < 48 h) of purpura in type I cryoglobulin patients has not been published. This leaves unresolved the issue of whether all reports of vasculitis in type I disease are those of vasculitis secondary to occlusive necrosis or ulceration. Non-cutaneous clinical findings most frequently include involvement of the joints (35–92%), peripheral nerves (17–56%), kidneys (21–29%) and liver [2–4].

Confirmation of cryoglobulins in sera requires careful handling of specimens to prevent cryoprecipitation before they can be detected. Collection of 10–20 mL of blood is suggested, and this must be kept warm and allowed to clot at 37°C for 30–60 min before centrifugation. The serum supernatant is left at 4°C for up to 7 days, with types I and II most likely to precipitate by 24 h [2,3,12]. A true cryoglobulin should once again be soluble if the sample is reheated to 37°C. Cryocrit measurements represent the percentage of the precipitate compared with the serum supernatant. Despite the presence of monoclonal protein, polyclonal gammopathy is the most frequent finding on serum protein electrophoresis of serum samples (not cryoprecipitate specimens) in patients with type II cryoglobulinaemia [2]. A more sensitive technique, such as immunofixation, is needed to identify the presence of a clonal protein.

Treatment of cryoglobulinaemia is often problematic, and prospective or controlled trials are rare [3,4]. If symptoms are mild, no treatment may be needed. If symptoms of acral lesions are precipitated by cold, then protection of affected areas may be sufficient. Measures to reduce the concentration of a type I cryoglobulin, such as plasmapheresis, plasma exchange or cytotoxic therapy, are occasionally effective, though unfortunately usually only in the short term. For immune complex-related disease, corticosteroids, cytotoxic agents or plasmapheresis may be effective, but relapse is typical once therapy is stopped. Interferon-α has been used to treat HCV-associated cryoglobulinaemia, with or without ribavarin [3,4,11]. Treatment with these agents has resulted in partial or complete remissions of vasculitic findings, but relapse often follows cessation of therapy. The therapy itself has occasionally been implicated in triggering the onset of vasculitis. In patients with mixed cryoglobulinaemia troubled primarily by recurrent cutaneous vasculitic lesions, colchicine or dapsone therapy may be of some help in reducing the frequency and severity of episodes.

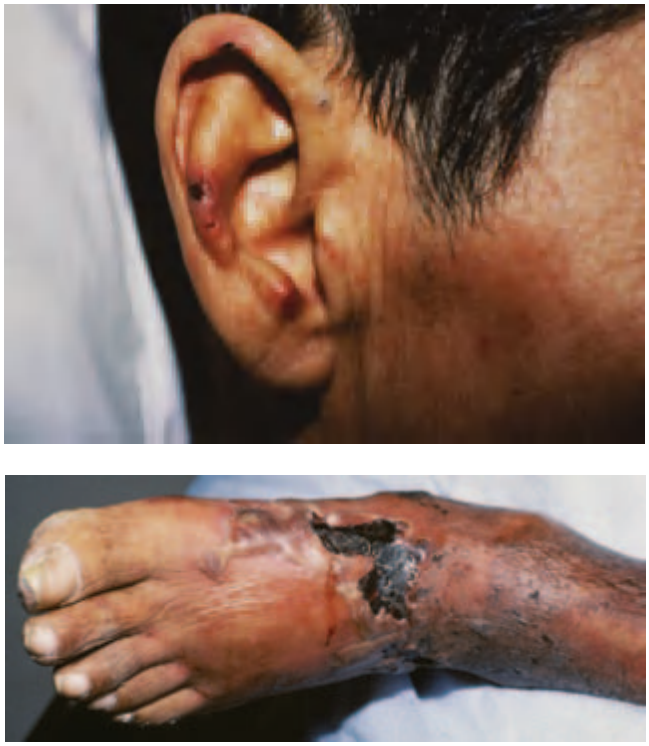
Cryofibrinogenaemia

Cryofibrinogen deposits consist of a complex of fibrinogen, fibrin and fibronectin that forms on cold exposure [13]. Since cryofibrinogens can be cleaved to form fibrin, plasma rather than serum must be tested to detect these cryogelling proteins. Cryoglobulins should be present in both plasma and sera [13,14].

Cryofibrinogenaemia is common as a laboratory abnormality but is a rare cause of symptomatic clinical disease. One study found an incidence of 3% in a random sample of hospital patients, usually as an incidental finding [15]. Therefore, clinicopathological correlation is important. Cryofibrinogenaemia may be idiopathic or can be associated with malignant disorders (especially haematological), thromboembolic disease, IgA nephropathy or various inflammatory, connective tissue or infectious syndromes [16,17].

Acquired dysfibrinogenaemia very rarely may mimic a cryofibrinogen syndrome by acral occlusion, including gangrene. Interestingly, this subset of dysfibrinogenaemia appears to act by greatly increasing red cell aggregation, mimicking occlusion-inducing cold agglutinins. Blood smear preparations show marked rouleaux formation.

The most common cutaneous findings are cold intolerance, purpura, necrosis, livedo reticularis, gangrene and ulceration (Fig. 48.7) [14,16,17]. The purpura or necrosis typically has a non-inflammatory retiform purpura morphology. Biopsy specimens from skin lesions typically show thrombi in small vessels with dermal necrosis [16].



(a)

(b)

Fig. 48.7 Cold-induced lesions due to cryofibrinogenaemia, (a) on the ear and (b) on the foot. Acral location is typical for cryogelling. Foot lesion shows minimal erythema, retiform bullae and haemorrhage with necrosis.

Leukocytoclastic vasculitis has been reported, but is probably due to ischaemic necrosis rather than being a cause [17]. Fibronectin may be a major component of vascular plugs in patients with cryofibrinogenaemia alone, whereas vascular occlusion in patients with both cryofibrinogens and cryoglobulins shows a predominance of cryoglobulin deposition [17]. Treatment of cryofibrinogenaemia should be aimed at the underlying disease, where possible, and at protecting areas from cold exposure [18]. Stanozolol, an androgenic steroid with fibrinolysis-enhancing effects, has also been used for treatment of cryofibrinogenaemia, as have other fibrinolytic agents [19].

Cold agglutinin-related cutaneous occlusion

Cold agglutinins are immunoglobulins that are able to agglutinate red blood cells below normal body temperatures. Since agglutination of red blood cells depends on binding of antibody to more than one cell at a time, pentavalent IgM is almost exclusively responsible for this phenomenon. Just as with cryoglobulins, there are both monoclonal and polyclonal cold agglutinins, usually directed at I, i or Pr antigens of erythrocytes [20,21]. Monoclonal cold agglutinins are idiopathic or secondary to malignant lymphoproliferative diseases. Polyclonal cold agglutinins are usually associated with infection, especially due to *Mycoplasma pneumoniae*, less often HCV, parvovirus B19 or leptospiral infections.

Just as with many cryoglobulins and most cryofibrinogens, cold agglutinins are most likely to be asymptomatic. When responsible for disease, reversible acrocyanosis secondary to cold-induced acral agglutination is most common. Livedo reticularis, Raynaud's phenomenon, cold urticaria and rarely cutaneous necrosis may occur. In addition to acral lesions on environmental cold exposure, cold intravenous infusions can also trigger localized cutaneous necrosis [20]. Cold agglutinins can induce complement activation after cold-induced binding to red blood cells, followed by lysis and haemolytic anaemia, independent of occlusive syndromes from agglutination.

Patients with cold-induced agglutination syndromes must avoid cold exposure. Therapies such as corticosteroids, cytotoxic agents, danazol, rituxan or interferon-α have been occasionally beneficial [21].

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Occlusion due to vessel-invasive organisms

Ecthyma gangrenosum

Ecthyma gangrenosum is a cutaneous syndrome characterized by usually painless, minimally erythematous macules or thin papules or plaques that typically progress to bullous lesions, followed by haemorrhage and necrosis, often with retiform extensions from lesional margins [1]. The anogenital area is a frequent site of involvement, but lesions can develop anywhere and at widespread cutaneous sites [2,3]. Patients are almost invariably immunocompromised, and the infectious agent is usually *Pseudomonas aeruginosa*.

In a small series of cases of ecythma gangrenosum, all eight patients had haematological disease and were receiving immunosuppressive medications [4]. All had positive blood cultures, seven of which were *Ps. aeruginosa*. Biopsies of ecthyma gangrenosum reveal minimal vascular neutrophilic infiltration despite necrotizing vessel injury, and special stains show extensive bacillary infiltration of the perivascular region, the adventitia and the media of larger subcutaneous arterioles, with sparing of the lumen and intima [3–5]. Other bacterial-induced vasculitides tend to show bacterial invasion of the vessel lumen and fibrin thrombi.

Prompt recognition of this syndrome is critical, since prognosis correlates partly with delay in instituting effective intravenous antipseudomonal therapy. Other factors correlating with poor prognosis include multiple lesions and neutropenia [4]. Other organisms that may induce ecthyma gangrenosum-like lesions include *Ps. cepacia* and *Ps. maltophilia*, *Serratia marcescens*, *Aeromonas hydrophila*, *Klebsiella pneumoniae*, *E. coli*, *Vibrio vulnificus*, *Morganella morganii*, *Staphylococcus aureus*, *Mucor*, *Aspergillus fumigatus*, *Fusarium*, *Scytalidium dimidiatum*, *Candida albicans* and *Moraxella* [6,7].

Lucio's phenomenon

Lucio's phenomenon (erythema necroticans) is a rare syndrome almost exclusively limited to leprosy patients from Mexico and Central America, but is rarely reported from Cuba, South America, the USA, India, Polynesia, South Africa and South-East Asia [8–10]. It is a type 2 reaction that may be fatal, despite being the presenting feature of leprosy for many patients who develop this reaction. Lesions may be recurrent and sometimes cyclical over periods of 2 months to 10 years, most often on the legs, but occasionally on the arms and trunk [9]. Lesions usually begin as painful purpuric macules or plaques or vesicles, often ulcerate and heal with atrophic scars. Unlike erythema nodosum leprosum, it is restricted to patients with diffuse non-nodular lepromatous leprosy, is not associated with fever, leukocytosis or tenderness, and fails to respond to thalidomide.

At least in some reports, some lesions appear to induce non-inflammatory retiform purpura, eschar or ulceration [8,9]. Ulceration of lesions is common. Histological findings include either leukocytoclastic vasculitis or endothelial proliferation and thrombus formation in dermal or subcutaneous vessels, with a sparse lymphocytic infiltrate [8–10]. How often vasculitic change is secondary to necrosis or ulceration is unclear, but at least in some cases an occlusive mechanism for purpura and necrosis seems likely. Aggregates of bacilli within proliferating cells are evident on acid-fast stain of biopsy material [9,10].

Treatment includes the standard multidrug therapy for lepromatous leprosy (rifampicin, clofazimine and dapsone). Control of infection and attention to fluid and electrolyte balance are important. Prednisone, thalidomide and clofazimine may all be required to control the reaction. Response to treatment is often reported as poor, with severe morbidity and frequent deaths, though numbers of reported cases are small.

Vessel-invasive fungi

As alluded to in the ecythema gangrenosum section, fungi may cause overwhelming infections in immunocompromised patients, often with cutaneous lesions, some of which may become purpuric or necrotic due to vessel-invasive organisms and thrombosis. *Aspergillus* and *Mucor* are two of the most commonly reported fungal groups to cause such vessel-invasive lesions.

Cutaneous lesions of *Aspergillus* may be either primary or secondary from haematogenous dissemination. Primary lesions typically occur at intravenous infusion sites, tubing sites secured by tape, or in skin in chronic contact with a colonized intravenous board [11,12]. Primary cutaneous aspergillosis can occur in immunocompetent patients, as well as in patients with burns or surgical wounds. Cutaneous lesions from systemic involvement have been divided into five categories: (i) a solitary necrotizing plaque; (ii) a subcutaneous abscess or granuloma; (iii) eruptive maculopapules with suppurative, vegetating or necrobiotic features; (iv) erythematous or exanthem-like reactions; and (v) progressive confluent granulomas [12,13]. Organisms in lesions appear as septate hyphae with acute-angle branching, invading blood vessels and surrounding tissues, often with minimal inflammation [13]. *Aspergillus fumigatus* is the most common cause of colonization and of disseminated infection by the *Aspergillus* group of fungi. *Fusarium* infections are increasing in frequency in patients with haematological malignancy; 72–91% of patients with this infection have skin lesions, which may be either metastatic or primary [14]. Metastatic skin lesions are described as either subcutaneous nodules, usually painful, or ecthyma gangrenosum-like.

The class Zygomycetes includes *Mucor*, *Absidia* and *Rhizopus* organisms, which can cause identical clinical manifestations (Fig. 48.8) [11]. Lesions may be either

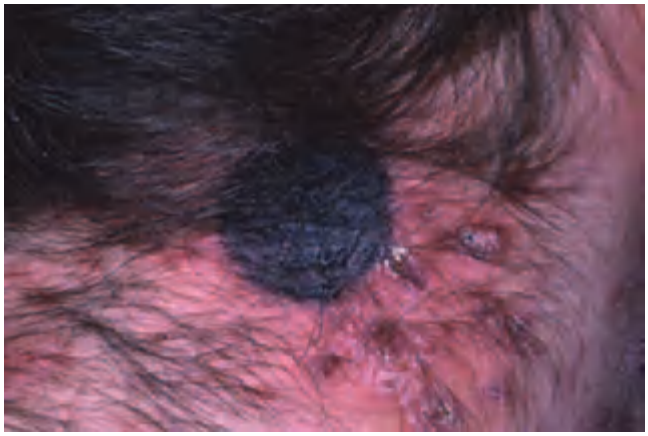

Fig. 48.8 Necrotic cutaneous lesion due to zygomycosis: invasion of vessel walls was apparent histologically.

primary or secondary to disseminated disease, and include superficial vesiculopustules, ulcerating gangrenous lesions, purpuric nodules, cellulitis and necrotic ulcers. These organisms easily invade the epidermis and spread rapidly in the dermis, with vessel invasion by very large and long non-septate hyphae, resulting in thrombosis and infarction [15].

Response to therapy in these types of infection is relatively refractory. With *Fusarium* infections, for example, response rates are 30–48% with current therapies and support measures [14].

Disseminated strongyloidiasis

Strongyloides stercoralis is the nematode responsible for the human parasitic infestation known as strongyloidiasis. Affecting 100 million people worldwide, it is endemic in tropical or subtropical soil that is contaminated by faeces, in some temperate-zone areas such as the rural south-east and Appalachia of the USA, or in closed communities such as immigrant populations, close-quartered military personnel or institutions [16]. Filiform larvae from contaminated soil penetrate the skin, enter the blood vessels, exit through the lungs and migrate to the glottis, where they are swallowed [16–18]. They mature and reproduce in the upper small bowel, with hatching of non-infective (rhabditiform) larvae. Transformation of these into infective larvae can lead to autoinfection through penetration of intestinal mucosa or perianal skin [18]. Skin lesions with simple infection include papules or erythematous serpiginous tracts, which can extend several centimetres per hour and represent cutaneous migration of the larvae (larva currens).

In immunocompromised patients, including those on corticosteroids, hyperinfection and dissemination of organisms can occur [16]. In this setting, the diagnosis is usually made through examination of stool samples, and skin lesions are uncommon. However, with such overwhelming infection, petechiae, purpura and reticulated purpuric skin lesions have been described [16,17,19,20]. These lesions may be widespread but may cluster, particularly in the periumbilical region where they are said to have a thumb-print appearance. Biopsy of purpuric lesions has shown larvae within capillaries and between collagen bundles in the dermis, with extravasated red cells [20].

Mortality in disseminated strongyloidiasis is high, up to 70–90% [16]. Treatment is with oral thiabendazole, and may need to be prolonged in immunocompromised patients [17,18].

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Occlusion due to embolus

Cholesterol embolus

Aetiology. The most commonly diagnosed cutaneous embolic syndrome is cholesterol embolus, which occurs

secondary to fragmentation of ulcerated arteriosclerotic plaques, with distal cutaneous and visceral vessel obstruction. Since it occurs secondary to atheromatous plaques, it is no surprise that cholesterol embolus is a syndrome reported primarily in men aged 50 years or older, and is associated with peripheral vascular disease and the known risk factors for atherosclerosis such as diabetes, hypertension and smoking [1,2]. While cholesterol embolus may be spontaneous, known triggers include angiography, angioplasty, vascular surgery, intra-aortic pump placement, cardiopulmonary resuscitation (all inducing traumatic rupture of plaques, usually within hours or days), thrombolytic therapy (acute clot lysis in plaque with release of friable plaque within hours or days) and anticoagulation (slow reduction of clot with release of plaque fragments, usually after at least 2 months of therapy) [2,3]. Blue toe syndrome associated with coumadin use is a syndrome of cholesterol embolus and not of coumadin necrosis.

Clinical features. There are two 'classic' clinical triads of cholesterol embolus. The first comprises leg or foot pain, livedo reticularis and preservation of good peripheral pulses [3]. The second comprises livedo reticularis, renal insufficiency and eosinophilia [4]. Cutaneous findings are frequent in patients recognized as experiencing episodes of cholesterol embolus. Reported in 35% of patients in one series, findings include livedo reticularis (49%), gangrene (35%), cyanosis (28%), ulceration (17%), nodules (10%) and purpura (9%) [1]. Additional clinical findings include fever, myalgia, altered mental status, sudden-onset arterial hypertension, gastrointestinal ulceration and renal insufficiency that may progress to renal failure [3,4].

The incidence of cholesterol embolization syndrome (CES) following vascular procedures has ranged from 0.15% to 30%, with large retrospective studies reporting figures of 0.6–0.9% [5–7]. Autopsy studies have shown cholesterol emboli in 77% of patients who underwent aortic aneurysm resection [6]. A prospective study of 1786 consecutive patients aged over 40 years who underwent left-heart catheterization found an incidence of cholesterol embolus of 1.4%, with nearly half having definite CES and the remainder having possible CES with primarily renal abnormalities [5]. Patients with cutaneous findings (livedo reticularis, blue toe syndrome or digital gangrene) were considered to have definite CES and comprised 48% of the total. In-hospital mortality was 16% and was associated with progressive renal dysfunction.

Investigation. Eosinophilia is a frequent finding in CES, occurring in up to 80% of patients, and may be related to generation of the C5 component of complement [5,8]. Preprocedure elevation in serum levels of C-reactive protein has been associated with an increased risk of post-procedure CES [5]. Additional laboratory findings may include leukocytosis, thrombocytopenia, pyuria, eosinophiluria, blood-positive urine or stool, elevated values of red cell sedimentation rate, creatinine, urea and amylase, and decreased serum levels of complement [1,2,8].

The traditional recommendation for cutaneous biopsy of livedo reticularis has been elliptical excisions centred on normal skin areas within rings of livedo reticularis, deep enough to include ample specimen from the fat layer of skin. However, our experience is that careful examination of the livedo reticularis reveals that many patients will have retiform purpura, and such areas are high-yield biopsy sites for demonstrating the diagnostic cholesterol crystals on histological examination. On histological examination, the arteriole involved in the skin is usually at the dermosubcutaneous junction, with elongated clefts within small-vessel lumina along with thrombi [9]. The clefts result from fixation-related dissolving of cholesterol crystals. In experimentally produced cholesterol embolus, a mixed inflammatory infiltrate may be seen in arterial walls within 24–48 h, followed by multinucleated histiocytes within 3–6 days, and subsequent occasional intimal fibrosis.

Treatment. Treatment of cholesterol emboli involves trying to minimize the risk of further embolization (removal of remaining plaque or perhaps stenting of an atheromatous segment of a major vessel), minimizing damage to end organs, and preventive therapies aimed at slowing progression of atheromatous disease. Statins, iloprost (prostacyclin analogue), pentoxifylline (oxpentifylline) and steroids have been reported as having limited success in therapeutic interventions to minimize organ damage [6,10]. Since anticoagulant use may precipitate cholesterol emboli, avoidance of these agents in patients with known CES seems prudent [3,7]. However, some types of cardiac surgery that may precipitate CES may also require postoperative anticoagulation, e.g. valvular prostheses [3,7].

Oxalate crystal embolus

Oxalate crystals are a rare cause of symptomatic emboli, but can mimic the cutaneous findings of cholesterol embolism. While primary hyperoxaluria is rare, it is the most common cause of oxalate crystal embolus. Two enzyme defects are associated with primary hyperoxaluria: type I hyperoxaluria (glycolic aciduria) is due to deficiency of the hepatic peroxisomal enzyme alanine : glyoxylate aminotransferase; type II hyperoxaluria (L-glyceric aciduria) is due to diminished activity of D-glyceric acid dehydrogenase [11,12]. Absorptive hyperoxaluria is also reported due to idiopathic intestinal hyperabsorption of oxalate. Secondary hyperoxaluria can be due to excessive intake of oxalate or its precursors (ethylene glycol, methoxyflurane anaesthesia, very high dose ascorbic

acid), pyridoxine deficiency, ileal resection, some intestinal diseases or long-term haemodialysis [11,13].

Type I hyperoxaluria is the most common and has three forms. The infantile form has no history of nephrolithiasis but has rapidly progressive renal failure. The juvenile form is the common type I subset. In this group, recurrent calcium oxalate nephrolithiasis precedes renal failure. Patients with the adult form typically present with renal failure and later develop complications of oxalate tissue deposition.

Cutaneous manifestations of primary hyperoxaluria are primarily those of oxalate crystal embolization: livedo reticularis, acrocyanosis, and peripheral gangrene, purpura or ulcerations [12,13]. Secondary hyperoxaluria, especially when due to long-term dialysis, is more likely to lead to extravascular cutaneous deposits of oxalate, producing calcified cutaneous nodules, or firm miliary papules that tend to form on the palmar aspect of the fingers [14].

Cardiac sources of embolization

Atrial myxomas, marantic endocarditis and septic endocarditis can be associated with cutaneous embolic phenomena. While rare, atrial myxomas are the most common benign cardiac tumour, with an estimated incidence of 0.03% [15] and onset usually between the third and sixth decades [16]. The left atrium is the most frequent tumour site. Symptoms may partly mimic those of infectious endocarditis, connective tissue disease, vasculitis or rheumatic fever, with constitutional symptoms such as fever, malaise, arthralgia or weight loss. Obstruction of intracardiac blood flow mimicking valvular disease or embolic phenomena may also occur. Lentigines may be a cutaneous finding in the hereditary NAME or LAMB syndrome, which is associated with cardiac myxomas. Cutaneous findings of myxomatous emboli include livedo reticularis, splinter haemorrhages, Raynaud's phenomenon, an acral papular eruption with claudication, serpiginous or annular purpuric lesions of the fingertips, red violet malar flush, petechiae of hands and feet, or toe necrosis [16–18]. Histology can confirm myxomatous emboli, but finding the emboli may require serial sectioning and multiple biopsies [16,19]. An echocardiogram is useful in evaluating patients with a history or physical examination compatible with emboli. Atrial myxomas require surgical treatment.

Marantic endocarditis results in the attachment of fibrin vegetations to heart valve leaflets, similar to those seen in acute rheumatic endocarditis and Libman–Sacks (APLS) valve disease, and these vegetations can embolize [19]. Infective endocarditis can also produce emboli from vegetations, but these are usually associated with acute bacterial endocarditis. Lesions in subacute bacterial endocarditis may be from either emboli or immune complex-related vasculitis. Idiopathic hypereosinophilic syndrome is associated with intracardiac mural thrombi, which can also produce emboli [20,21]. Documentation of cutaneous emboli is limited, with clinical lesions described as splinter haemorrhages, non-blanching livedoid discoloration, or necrotic, blistering or purpuric lesions [22–24].

Crystal globulin vasculopathy is a rare syndrome, usually associated with IgG or light-chain paraproteins, that can produce intravascular occlusion by spontaneous crystallization [25,26]. This syndrome results in rapidly progressive renal failure, polyarthropathy, peripheral neuropathy and skin lesions. Cutaneous lesions include ulcerations, petechiae and ecchymoses, with intravascular thrombus and crystalline deposits [27].

Other emboli

Petechiae, which may be few or very numerous, are an important sign of fat embolism [28,29]. They occur particularly on the upper part of the body 2–3 days after a major injury and are an important clue to this diagnosis. Minute fat emboli have been found within the vessels at the sites of the petechiae.

Emboli may also occur from tumours at sites other than the cardiac myxomas discussed above.

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Systemic coagulopathies with cutaneous predilection

There are several systemic coagulopathies that have a predilection for the cutaneous microvasculature. Cutaneous lesions may occasionally be a minor feature of a multiorgan syndrome, the most prominent findings of multiorgan involvement or sometimes the sole target of occlusion. The importance of recognizing these syndromes is critical in order to begin early, and sometimes syndrome-specific, therapy. There are two natural anticoagulant pathways that exist in humans. The most well known, the antithrombin III–heparin/heparan pathway, is important for primarily venous large-vessel thrombosis. The only cutaneous lesions related to antithrombin III disorders are stasis ulcers secondary to recurrent venous thrombosis with venous insufficiency. In contrast, disorders of the thrombomodulin–protein C/S anticoagulant pathway are important causes of severe cutaneous occlusion syndromes.

An understanding of this pathway is important in diagnosing and treating these syndromes. The end point of the coagulation cascade is conversion of prothrombin to thrombin, which rapidly catalyses the conversion of fibrinogen to fibrin and clot formation. The procoagulant role of thrombin is well known; less well known is its critical role in anticoagulation. When thrombin fails to bind to procoagulant sites on membranes and binds instead to the membrane protein receptor thrombomodulin, this powerful prothrombotic molecule undergoes a remarkable transformation. Bound to thrombomodulin, thrombin becomes ineffective at binding and activating clotting factors, and instead rapidly converts protein C in the plasma to activated protein C. Activated protein C, stabilized by certain phospholipids and by protein S, down-regulates clotting by cleaving circulating activated clotting factors, including factor VIIIa and most importantly factor Va. It thus exerts an anticoagulant effect; deficiency of protein C, or of its co-factor protein S, therefore creates a procoagulant tendency. The factor V Leiden mutation renders the factor V Leiden molecule much less sensitive to cleavage by activated protein C (APC resistance); about 5% of the UK and Caucasian North American population are heterozygous for this mutation (reported incidence is highest in Cyprus, Sweden and Turkey at 10–15%, and lowest incidence in Asia and Africa, and in populations of those ethnicities). This protection from cleavage means that activated factor V Leiden remains longer in the plasma and continues to enhance coagulation. It would be expected then that factor V Leiden mutation should be synergistic with deficiencies in the thrombomodulin–protein C pathway. In fact, in some kindreds of protein C-deficient families, the presence of the factor V Leiden mutation appears to be an important predictor for who will develop large-vessel thrombosis in individuals with similar levels of protein C deficiency.

Another major cluster of systemic coagulopathies with cutaneous microvascular occlusion are those related to lupus anticoagulant activity and APLS. The mechanisms for clotting in this group are less well understood, and will be addressed following discussion of protein C/S-related syndromes.

Protein C/protein S-related disease

Neonatal purpura fulminans: homozygous protein C or protein S deficiency

Protein C and S deficiencies can be inherited autosomally with variable penetrance. Patients who are heterozygous for deficiency may develop repeated venous thrombosis or pulmonary embolism early in adult life, or may be asymptomatic [1,2]. One variable affecting the likelihood of thrombosis in these individuals is known: the previously mentioned co-inheritance of homozygous or heterozygous factor V Leiden mutations [3,4]. The frequency of homozygous protein C deficiency is estimated at 1 in 250 000–500 000 births [1]. Homozygous deficiency of either protein C or protein S is associated with neonatal purpura fulminans as well as with cerebral and ophthalmic vessel thrombosis. Retiform (stellate) purpura and necrosis is the most typical cutaneous finding that results from thrombosis within the cutaneous microvasculature. Skin lesions typically begin within a few hours to 5 days after birth, and are most commonly distributed on the extremities, abdomen, buttocks and scalp; they may localize to sites of pressure or previous trauma [1,5,6]. Laboratory findings are consistent with DIC, with evidence of consumption of clotting factors (prolonged partial

thromboplastin time, PTT), clot lysis (elevated fibrin split products) and often thrombocytopenia. In the absence of appropriate therapy, lesions invariably progress to full-thickness cutaneous necrosis.

Traditional treatment included fresh frozen plasma to try to replace deficient protein C or S, or oral anticoagulants to reduce procoagulant factors. More recently, protein C and activated protein C concentrates have been used for treatment of both acute disease and as prophylaxis against subsequent episodes [7,8].

Coumadin (coumarin, warfarin) necrosis: severe acquired protein C dysfunction

Coumadin necrosis usually presents as the sudden onset of pain within affected areas 3–5 days after beginning coumadin therapy, followed by well-demarcated erythema progressing to haemorrhage, necrosis and often haemorrhagic bullae or eschar [9]. While coumadin necrosis may rarely involve acral areas, acral cutaneous purpura in patients on coumadin is more likely to be due to cholesterol embolus—so-called purple (blue) toe syndrome. The risk of coumadin necrosis is increased if loading doses (10 mg or more) of warfarin are used and if a second form of anticoagulation such as heparin therapy is not used to cover the initial phase of anticoagulant therapy [10,11]. Warfarin (coumadin) necrosis is more likely to occur in areas with abundant fatty subcutis, such as breast, hip, buttocks and thigh [9,10]. The peak incidence is between the sixth and seventh decades, and is four times higher in women.

The therapeutic effect of coumadin is due to inhibition of γ-carboxylation of the vitamin K-dependent coagulant factors II, VII, IX and X. While these factors are still produced and may be antigenically detected within the plasma, without γ-carboxylation they are dysfunctional. Importantly, protein C and protein S are also vitamin K-dependent plasma factors, and their inhibition can lead to a prothrombotic state. Protein C and factor VII, with half-lives of roughly 5 h, are particularly vulnerable to early inhibition, while protein S and the remaining procoagulant factors with much longer half-lives remain active for a considerably longer period [11,12]. There is thus a period, after the early inhibition phase, when the anticoagulant effect of protein C has been inhibited but there is an excess of uninhibited procoagulant clotting factors. Although up to one-third of patients with coumadin-induced skin necrosis may have partial protein C deficiency, the majority of cases appear unrelated to inherited deficiencies of protein C [10]. Since coumadin action mimics that of vitamin K deficiency, it would be expected that depletion of vitamin K should result in coumadin necrosis-like findings, though this has not been documented.

Restoration of protein C activity can be accomplished through protein C concentrates, and presumably also through the use of activated protein C. If these are not available, heparin therapy has been recommended.

Sepsis-related purpura fulminans (bland retiform purpura) with DIC: acquired severe protein C deficiency

The term 'purpura fulminans' is used by physicians for many different situations. It was originally coined in 1887 to describe a syndrome occurring days to a few weeks after some preceding infection, especially varicella zoster or streptococcal infections (now termed 'post-infectious purpura fulminans') [13]. The term 'purpura fulminans' has subsequently been used for widespread cutaneous haemorrhage in patients with sepsis, including infection with *Neisseria meningitidis*, *Staphylococcus aureus*, groups A and B β-haemolytic streptococci, *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Haemophilus aegyptius* [14]. However, haemorrhage in patients with DIC may be due to septic vasculitis, simple bleeding or microvascular thrombosis. The patterns of cutaneous haemorrhage for each of these different mechanisms are distinctive, and can be a guide to pathophysiology and therapy [15]. Cutaneous microvascular occlusion in sepsis with DIC presents clinically as non-inflammatory (bland) haemorrhage, usually with a retiform, stellate or branching configuration, with rapid transition to necrosis and eschar [16,17]. In a small study, early biopsy of retiform purpuric lesions showed microvascular occlusion with fibrin, and perivascular haemorrhage with minimal to no inflammation; these findings correlated with severe protein C deficiency [17]. This was not true of other forms of purpura in sepsis with DIC. The protein C pathway is increasingly recognized as critically important in bacterial sepsis, acting to inhibit both coagulation and inflammation [18]. The use of activated protein C concentrate in sepsis appears to be beneficial, especially in severe cases, though whether all patients with sepsis should receive this is not clear [19–22]. In patients with sepsis, DIC and retiform (occlusion) purpura, it seems reasonable to assume severe protein C deficiency in the acute setting and to treat appropriately. Protein C concentrates and plasma exchange have also been successfully used to replace protein C in purpura fulminans [23].

Post-infectious purpura fulminans: acquired severe protein S dysfunction

As mentioned previously, post-infectious purpura fulminans occurs primarily in children as rapidly progressive purpura a few days to weeks after a febrile illness [14,24,25]. The most common associated infections are varicella zoster and streptococci. This syndrome has been associated with lupus anticoagulant activity and with autoantibodies to protein S [14,25,26]. Replacement of protein S activity is difficult, presumably because this

Table 48.5 International consensus statement preliminary criteria for antiphospholipid antibody syndrome (definitive diagnosis requires at least one clinical and one laboratory criterion) [29].

Clinical criteria
Vascular thrombosis
One or more clinical episodes of arterial, venous or small-vessel thrombosis
Complications of pregnancy
One or more unexplained deaths of morphologically normal fetuses at or after 10 weeks of pregnancy *or*
One or more premature births or morphologically normal neonates at or before 34 weeks of gestation *or*
Three or more unexplained consecutive spontaneous abortions before 10 weeks of gestation
Laboratory criteria
Anticardiolipin antibodies, IgG or IgM, present at moderate or high levels on two or more occasions at least 6 weeks apart
Lupus anticoagulant antibodies on two or more occasions at least 6 weeks apart

condition is not due to simple clearing of protein S but rather to inhibition of protein S function by an antibody. Such antibody-mediated dysfunction is difficult to overcome by replacement of factor, and concentrated sources of protein S are unavailable.

Antiphospholipid antibody/lupus anticoagulant syndrome

From the original description as recurrent venous or arterial thrombosis, repeated fetal loss and thrombocytopenia to more recent consensus statement criteria, APLS continues to be redefined (Table 48.5) [27–29].

A variety of serological markers exist, usually detected as antibody against phospholipids (especially cardiolipin) in combination with antigens from a co-factor molecule (e.g. β_2-glycoprotein, prothrombin, annexin V), or as an inhibitor of an *in vitro* coagulation test, such as aPTT, dilute Russell viper venom time or, occasionally, prothrombin time. Detection of antiphospholipid antibodies is roughly five times more common than detection of lupus anticoagulant [30].

APLS may occur as a primary or secondary disorder. In one large study, primary APLS comprised 53% of cases, lupus-associated APLS 36%, lupus-like APLS 5% and other disease associations with APLS 6%, with catastrophic APLS occurring in 0.8% [31]. Compared with primary syndrome patients, lupus patients with APLS were more likely to have arthritis, livedo reticularis, thrombocytopenia or leukopenia. The mean age was 42 ± 14 years at study entry, onset of symptoms was most often in young to middle-aged patients (2.8% before age 15 years, 12.7% after age 50), and there was a strong female predominance (82%).

Mechanisms of coagulation in APLS are only partially understood. These antibodies were first detected in 1906 in patients with syphilis, and measured as false-positive serological tests for syphilis in 1952 [29]. However, today they are most often detected as lupus anticoagulants or antiphospholipid antibodies. The lupus anticoagulant activity is detected, often incidentally, by prolongation of PTT. While this would seem to predict a tendency towards bleeding, individuals with lupus anticoagulant activity are either normal or paradoxically predisposed to clot formation. Antiphospholipid antibody activity is detected by one of several antibody assays, the most common being screens for IgG or IgM antibody affinity for cardiolipin, a negatively charged phospholipid molecule found in mitochondrial membranes. The most important autoantigen appears to be β_2-glycoprotein I (apolipoprotein H), which binds anionic phospholipids as part of physiological disposal of apoptotic cells [32]. This binding of phospholipid to the glycoprotein induces a conformational change in both molecules, leading to exposure of neoantigens and, in some cases, to autoantibody formation. While anticardiolipin antibodies can be detected in the absence of binding to a co-factor such as β_2-glycoprotein I, such antibodies are almost never physiologically relevant in inducing thrombosis. Studies have shown that in patients with both lupus anticoagulant activity and anticardiolipin activity, there may be little or no cross-reaction between antibodies which bind to each. Both the lupus anticoagulant test and the various antiphospholipid antibody assays can be positive in a great many patients who never develop any thrombosis. Likewise, until the mechanisms responsible for thrombosis in patients with these antibodies are understood, it is highly probable that many patients with thrombosis may test negative with current assays, and yet ultimately be found to have disease mediated by antibodies interfering with physiological pathways responsible for clinical APLS.

Multiple pathways have been implicated by which these antibodies may promote thrombosis: promotion of procoagulant reactions (interfering with protective membrane proteins such as β_2-glycoprotein I or annexin V), interference with anticoagulant pathways (inhibition of protein C/S and antithrombin III pathways), activation of platelets by membrane binding, interference with prostacyclin production and release by endothelium, or interference with fibrinolytic pathways (inhibition of endothelial plasminogen activator or kallikrein activation) [29,33–35].

Clinically, APLS can present with a variety of cutaneous findings (Table 48.6). In one large study the frequency of these findings was livedo reticularis 24%, leg ulcers 5.5%, pseudovasculitis 3.9%, digital gangrene 3.3%, cutaneous necrosis 2.1% and splinter haemorrhages 0.7% [31]. Catastrophic APLS is an uncommon but disastrous variant in which patients typically present with widespread cutaneous necrosis and multiorgan failure, especially renal and pulmonary. Precipitating factors include infections, surgical procedures, drugs and discontinuation of anti-

Table 48.6 Cutaneous findings in antiphospholipid antibody syndrome.

Livedo reticularis, with or without retiform purpura
Sneddon's syndrome
Livedoid vasculopathy/atrophie blanche
Raynaud's phenomenon
Anetoderma-like lesions with thrombosis
Behçet's-like lesions
Nail fold ulcers
Widespread cutaneous necrosis (catastrophic antiphospholipid antibody syndrome)
Leg ulcers, secondary to recurrent thrombosis with stasis, or from conditions in this table
Cholesterol embolus-like proximal livedo reticularis, with or without distal retiform purpura
Acral livedo
Degos (malignant atrophic papulosis)-like lesions
Pseudo-Kaposi's sarcoma
Vasculitis-like lesions
Pyoderma gangrenosum-like ulcers
Splinter haemorrhages
Superficial thrombophlebitis migrans

coagulation. The most common extracutaneous manifestations of non-catastrophic APLS include deep vein thrombosis, pulmonary embolus and central nervous system abnormalities.

Specific therapy in APLS awaits an understanding of the mechanism by which thrombosis occurs in individual patients, and thus the capability to use tailored therapies to specifically oppose that pathway in that one individual. For now, treatment is empirical. Antiplatelet therapy is of uncertain benefit; most therapy depends on acute and often chronic anticoagulation, either with standard or low-molecular-weight heparin initially followed by coumadin [32]. Antimalarial therapy may be of some benefit for atrophie blanche-like or Degos-like syndromes in lupus patients; evidence suggests a protective effect in lupus patients against arterial or venous thromboses [29].

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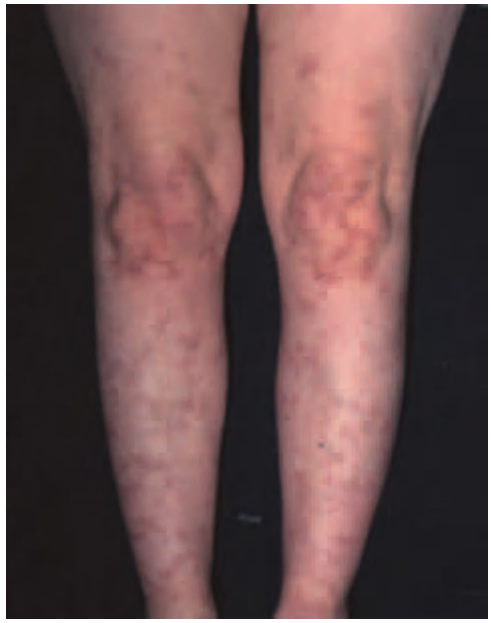

Fig. 48.9 Sneddon's syndrome showing a typical broad racemose livedo patterning.

Occlusion due to vascular coagulopathies

Sneddon's syndrome

Definition. This syndrome comprises generalized livedo racemosa or livedo reticularis with cerebrovascular lesions that cause focal neurological symptoms or signs [1–5].

Livedo racemosa is usually the first manifestation, initially affecting the lower trunk and proximal part of the legs but becoming more generalized. It typically has a broad network pattern (Fig. 48.9). Associated Raynaud's phenomenon or acrocyanosis may occur, and may be the presenting feature.

Incidence. This has been estimated as four cases per million population per year [5]. Sneddon's syndrome is twice as common in women as in men, and typically presents in the fourth or fifth decade of life. It is usually sporadic, although familial Sneddon's syndrome has been reported.

Pathogenesis. Several authors have reported the presence of antinuclear antibodies or of antiphospholipid antibodies/lupus anticoagulant (reviewed in [6]), but others would only accept the diagnosis of Sneddon's syndrome if these antibodies were absent. Differences have been documented between the clinical features of patients with Sneddon's syndrome depending on the presence or absence of antiphospholipid antibodies: those without antiphospholipid antibodies typically have a larger-sized livedo pattern, while those with antiphospholipid antibodies have a higher risk of seizures, mitral regurgitation and thrombocytopenia [7]. It is likely that there is a spectrum of disease from APLS to SLE that includes the preferential arteriolar pattern of Sneddon's syndrome. Antiprothrombin antibodies were demonstrated in 57% of 46 patients in one series [8], and there are reports of platelet activation in a patient with persistently elevated levels of circulating PF4 [9], of increased levels of antithrombin III [10], of factor V Leiden mutation [11] and of activated protein C resistance [12].

Histopathology. Biopsies may show an endarteritis of dermal arterioles. It has been demonstrated that the most informative biopsies are from the clinically normal centre of any network area rather than from the peripheral 'watershed' area of livedo, and that taking multiple biopsies increases the sensitivity [13]. Initial changes are endothelial swelling with a mixed inflammatory infiltrate, progressing to vascular plugging, subendothelial proliferation and eventual vascular occlusion, fibrosis and disappearance of the inflammatory component [14]. It is possible, if not likely, that the histological findings in patients with antiphospholipid antibodies, especially in association with lupus or lupus-like disease, would be more typical of non-inflammatory occlusion.

Clinical features. In addition to the cutaneous livedo, there may be non-specific neurological prodromal symptoms such as headache, migraine, dizziness or vertigo. Later neurological features include focal paresis or hemiparesis, focal sensory or hemisensory symptoms, fits and visual defects, and later cognitive changes. Transient ischaemic attacks are commoner than completed stroke [15]. Peripheral nerves may also be affected. Hypertension may be present and confers a worse prognosis if untreated; hypertension and the neurological aspects are sometimes aggravated by pregnancy or use of oral contraceptives. There may be renal or cardiac involvement, including valve defects such as mitral regurgitation, although internal organ involvement other than neurological is often asymptomatic [5]. Other features such as shortened digits have rarely been reported.

The differential diagnosis is wide, from both the cutaneous and the neurological perspective. In particular, other causes of livedo and microvascular occlusion syndromes discussed in this chapter need to be considered as well as vasculitic causes (e.g. polyarteritis nodosa). However, it should be noted that other patterns of livedo with anticardiolipin antibodies may be associated with evidence of cerebral microthrombosis, for example livedo with summer ulceration or livedo with pyoderma gangrenosum-like lesions [16].

Magnetic resonance imaging (MRI), electroencephalography and arteriography may help to confirm the neurological component; skin biopsy (as above) and exclusion of other causes of livedo are necessary. Patients with

positive antiphospholipid antibodies more commonly have infarcts in the distribution of the main cerebral arteries on MRI, whereas those with negative antibodies have small lacunar infarcts [17] and progressive leukoencephalopathy [15].

Treatment. There is generally no very effective treatment, reflecting the non-inflammatory nature of the disease. Corticosteroids may have some benefit but this is variable and often difficult to assess due to the intermittent nature of the neurological disease; other immunosuppressive agents are often disappointing. Avoidance of smoking and oral contraceptives, and treatment of hypertension and hyperlipidaemia (both of which are commonly present), are important. Thrombolytic agents and vasodilators have been used in the acute situation, and antiplatelet agents appear to be effective in the longer term [7]. In patients with antiphospholipid antibodies or lupus anticoagulants, maintenance of anticoagulation at an international normalized ratio (INR) of 2–3 seems warranted.

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Livedoid vasculopathy; atrophie blanche

SYN. LIVEDO RETICULARIS WITH SUMMER ULCERATION; SEGMENTAL HYALINIZING VASCULITIS

This syndrome is most common in young to middle-aged women as either an idiopathic or secondary syndrome [1]. One of the most commonly noted associations is with chronic venous hypertension and varicosities, though the atrophic scarring in this setting is not usually preceded by small painful ulcerations, nor with surrounding livedo reticularis. It would seem appropriate to separate venous stasis-related atrophie blanche from more typical forms of the syndrome.

Pathogenesis. The pathogenesis of livedoid vasculopathy is unknown. Clearly, APLS, with or without a lupus association, can produce this clinical syndrome [2]. Multiple pathophysiological abnormalities have been implicated, including platelet activation, factor V Leiden, altered fibrinolysis, antiphospholipid antibodies and hyperhomocystinaemia; however, definitive evidence is lacking [1–3].

Histology. The most characteristic histological findings in this syndrome are some thickening or hyaline changes in the walls of superficial dermal vessels, and luminal fibrin deposition [1,4]. Red cell extravasation and perivascular lymphocytic infiltrates are expected findings.

Clinical features. Persistent, very painful and often punched-out ulcerations of the legs, especially around the malleoli, in women are typical of atrophie blanche [4]. When accompanied by surrounding livedo reticularis, the term 'livedoid vasculitis' is more likely to be applied. Retiform or stellate purpura or ulcer extension can occur; healing results in a porcelain white scar frequently surrounded by telangiectasia. Besides venous hypertension and antiphospholipid antibody-related syndromes, sickle cell ulcers can show the same porcelain white scar of atrophie blanche.

Treatment. Antiplatelet, anticoagulant and fibrinolytic therapies have been reported to be helpful in this syndrome, as well as anabolic steroids such as danazol and stanozolol [2]. PUVA therapy has been reported as effective in some cases [5]. In patients with lupus and atrophie blanche-like lesions, antimalarial therapy may be effective.

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Malignant atrophic papulosis

SYN. DEGOS' DISEASE; KOHLMEIER–DEGOS' DISEASE; LETHAL CUTANEOUS AND GASTROINTESTINAL ARTERIOLAR THROMBOSIS

Definition. Malignant atrophic papulosis is a progressive vasculopathy causing occlusion of small and medium-sized arteries [1–6]. Originally reported separately by Kohlmeier [7] and Degos [8], it was also described as lethal cutaneous and gastrointestinal arteriolar thrombosis [9]. It is characterized by skin and gastrointestinal lesions, but neurological features are also frequent and post-mortem studies show widespread organ involvement. The skin lesions are usually the first feature, and may be the only manifestation over many years [2]; whether this represents a truly 'benign' variant is uncertain.

Incidence. It is rare: a review in 1995 suggested that about 120 cases had been reported [4]. It is mainly reported in whites, has a slight male predominance and is mainly a disease that presents in young adults, although it can affect any age group [3,5]. Familial cases have been reported [10].

Pathogenesis [3,5]. The pathogenesis probably involves abnormal coagulation, although the precise mechanism is uncertain. Platelet and fibrin thrombi are apparent in dermal, mesenteric and nervous system blood vessels, and both abnormal platelet aggregation and inhibition of fibrinolysis have been reported [3,5,11–14]. However, most patients have no clear evidence of a systemic coagulopathy, suggesting that the thrombotic tendency is at the microvascular level. Antiphospholipid antibodies have been documented in a small number of patients, usually in the context of SLE, although they may also occur even in the benign cutaneous variant [15].

There is also some support for a mechanism involving vascular inflammation. An autoimmune mechanism is suggested by the occurrence of lesions resembling malignant atrophic papulosis in some patients with SLE, rheumatoid arthritis, scleroderma or dermatomyositis [16–19]; antiendothelial antibodies have also been demonstrated but are probably not the cause of the disease [5]. Circulating immune complexes, or deposition of immune complexes or complement, are not usually demonstrated [2,20]. Although there can be a prominent lymphocytic infiltrate in later lesions, especially around venules, true arteritis and leukocytoclasis are not found [3,5,21].

Abnormal mucin deposits, which may be thrombogenic, occur even in early lesions although they tend to be more apparent in later lesions [3,5,21]. It is possible that they may be induced by activated T cells.

A viral aetiology was proposed on the basis of electron microscopic demonstration of interwoven tuboreticular structures resembling viral inclusions within endothelial cells [22], but these are seen in other disorders, including SLE, and can be induced by interferon [5]. Cases have been reported with HIV infection but a causal association is unproven.

Histopathology [2–6]. The histological picture in Degos' disease depends upon the duration of the lesion biopsied. Early lesions show a superficial and deep perivascular, perineural and peri-appendageal chronic inflammatory cell infiltrate [21]. Deep dermal vessels show endovascular inflammation, proliferation and thickening with thrombosis [23]. Mucin deposition is seen at all stages [2–4,21,24], and fibrin deposition may be demonstrated; fibrinoid necrosis of vessel walls may occur [23]. Immunofluorescence is occasionally positive for IgG or C3. Later lesions show a classical 'wedge-shaped' pattern of sclerotic change in the dermis, which is usually only sparsely cellular. Between these stages there is a phase with neutrophilic and eosinophilic infiltrate around adnexae and a dense perivascular lymphocytic infiltrate [21]. The epidermis, initially showing a mild vacuolar reaction, becomes atrophic with slight scaling, resembling that seen in lichen sclerosus and corresponding with the typical 'porcelain white' colour seen clinically. There may be some associated pigmentary incontinence.

Panniculitis resembling that seen in lupus profundus has recently been reported [25].

Similar changes occur in the intestinal wall, particularly the submucosa. The muscularis mucosae is intact. Blood vessels are thickened and disorganized, with fibrinoid degeneration; platelet–fibrin thrombi are more prominent than in skin biopsy material.

Microaneurysms of the bulbar conjunctival vessels have been described. Renal changes include thickening of the afferent glomerular arterioles and of the capillary basement membrane.

Clinical features [1–8]. Cutaneous lesions usually precede systemic manifestations by months to years. They develop as crops over a period of time and are usually asymptomatic, although they may be preceded by slight burning. Skin lesions affect any site, mainly the trunk and proximal limbs; the face, palms and soles are generally spared. Although they may evolve gradually, and the number of lesions may vary considerably, about 30–40 active lesions are usually present [4]. Oral mucosal lesions are rare but penile lesions may occur [26]; the bulbar conjunctiva

is often affected by lesions, which appear as sharply demarcated avascular areas [4]. Peristomal lesions have been reported.

Early skin lesions are pink or red, dome-shaped papules, usually 2–5 mm in size but sometimes up to about 15 mm. Papules soon become necrotic and umbilicated with central 'porcelain-white' pallor and scaling, and the pink oedematous border becomes telangiectatic. Most heal rather slowly to leave a small white scar, often surrounded by telangiectases as in atrophie blanche. Urticaria-like, ulceropustular and gumma-like nodules have been reported. New crops of lesions may continue for several years.

Similar lesions occur in many organs. Gastrointestinal lesions are the most important, as perforation of the gut is a cause of death. Neurological symptoms are also relatively common. The features in different systems include the following [4].

- Gastrointestinal: dyspepsia, abdominal pain or distension, bleeding, perforation, peritonitis, fistulae (enteroenteral or enterocutaneous), obstruction, pancreatitis.
- Neurological: cerebral infarction (causing headache, aphasia, dementia, focal epilepsy, hemiparesis, pseudobulbar palsy), cord infarction (paraplegia/quadriplegia, transverse myelopathy), peripheral nerve (cauda equina syndrome, mononeuritis multiplex), various sites (sensory disturbance).
- Ocular: ptosis, diplopia, nystagmus, ophthalmoplegia, optic neuritis, papilloedema, visual field loss, pupillary reaction defects, conjunctival avascular lesions, posterior subcapsular cataract.
- Cardiovascular: renal artery occlusion, pericardial effusion, constrictive pericarditis, ventricular wall defects.
- Pulmonary: pleuritis.

Differential diagnosis. There is sometimes a resemblance to atrophie blanche or to guttate lichen sclerosus, although the evolution of lesions is different. Identical lesions have been described in cases of various connective tissue diseases [16–19] and in a patient with Crohn's disease [27]. The characteristic features can scarcely be confused. A disorder termed 'cutaneous–intestinal syndrome with oropharyngeal ulceration' [28] included a combination of macular, blistering and crusting lesions of the skin, with oropharyngeal ulceration and death from perforation of one of many intestinal ulcers. This differed both clinically and histologically from Degos' disease. Patients in whom systemic disease precedes skin lesions may cause particular diagnostic problems.

Prognosis [4]. Although possibly overestimated by reporting bias, and acknowledging that there does appear to be a benign cutaneous ('skin-limited') variant, mortality of 50–60% within 2–5 years is anticipated. Prognosis in males appears to be worse than in females.

Treatment. There is no consistently effective treatment [2–4]. Steroids do not help, although some benefit in neurological symptoms has been suggested. Aspirin, antiplatelet agents, fibrinolytic agents and pentoxifylline, alone or in combination, may lead to remission and are perhaps most effective in the cutaneous disease [2–6,11,15,29–31]; phenylbutazone has been reported to be effective. Heparin may produce short-term benefit. There is one report of a good response to transdermal nicotine patches [32]. Warfarin, dextrans, chloroquine, immunosuppressive agents and plasma exchange have all been tried. Surgery to treat intestinal perforation may resolve the acute situation but is difficult as there are usually multiple lesions, and there is no long-term benefit from this approach.

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Occlusion due to reticulocytes

Patients with sickle cell anaemia may develop leg ulcers, which in tropical climates typically progress rapidly due to secondary bacterial infection [1]. However, in temperate climates the lesions are often perimalleolar, quite painful, and may heal with a porcelain-white scar often mimicking atrophie blanche. While this ulceration might be attributed solely to sickling of erythrocytes with microvascular occlusion, similar ulcers have been reported in other instances of severe chronic haemolytic anaemia, such as thalassaemia or antibody-mediated haemolysis, where sickling is not possible [2]. Multiple studies of possible occlusive mechanisms in sickle cell disease have shown that both young and old red cells in sickle patients also have abnormally sticky membranes. In addition, abnormal leukocyte adhesion may initiate occlusion episodes, followed by adhesion of erythrocytes to these leukocytes, with a drop in tissue perfusion, followed by hypoxia and sickling with propagation of occlusion [3]. A number of platelet, procoagulant, anticoagulant and fibrinolytic abnormalities have been noted in sickle cell disease [3–5]. Patients with sickle cell disease who are treated with hydroxycarbamide (hydroxyurea) appear to have a higher rate of ulcer development than other patients treated with hydroxycarbamide [6]. While the mechanism is unclear, macroerythrocytes may play a role in initiation of ulcers in this and also in syndromes of severe haemolytic anaemia with high reticulocyte count, very early reticulocytes, but with no sickling [2]. Whatever studies eventually prove, it seems that erythrocytes may play an active role in some occlusive syndromes.

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Occlusion due to unknown or controversial mechanisms

Cutaneous calciphylaxis

Cutaneous calciphylaxis (also termed 'calcific uraemic arteriolopathy') is a rare, but increasingly frequent, complication of renal failure and dialysis [1]. It may very rarely occur in other situations, such as alcoholic liver disease, and occasionally after chemotherapy, in patients with normal renal function. Obese middle-aged women appear to be most at risk.

Early lesions tend to present as painful plaques, often with a retiform or stellate pattern, and may show central necrosis. It may resemble hyperoxaluria. Woody induration with extending ulcer and eschar formation typically follows. Thrombosed vessels are seen occasionally; an expected finding is calcification in the medial layer of the wall of small subcutaneous vessels, with necrosis of overlying tissue [1,2]. Both vascular and extravascular calcification occur. The calcification of small-vessel walls extends more widely than the thrombotic change or the extravascular calcification. Most patients have secondary or tertiary hyperparathyroidism, although the occurrence of calciphylaxis in primary hyperparathyroidism is very rare.

The mechanism of this syndrome is unclear, as is the role of parathyroid hormone and calcium and phosphorus. An elevated calcium–phosphorus product is usual but is not always present.

Parathyroidectomy has been cited as effective, but there is clearly bias in patient selection for this procedure towards those who are most healthy. Reduction of the calcium–phosphorus product when elevated is recommended (using low calcium dialysis), as is good wound care and attention to possible accompanying infection. The prognosis is generally considered poor, with mortal-

ity of 50–80%, though occasional reports of a more benign course exist [1,3].

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Specific clinical presentations

This section briefly discusses clinical presentations that are common to a number of occlusive, embolic or vasculitis disorders, in order to allow an approach to the differential diagnosis.

Livedo [1,2]

Livedo describes a reticulate pattern of slow blood flow, with resultant desaturation of blood and bluish discoloration of the skin, which should be completely blanchable. Livedo has been divided into two patterns.

Livedo reticularis tends to develop as a tight net-like pattern of discoloration, often symmetrically distributed, and is more likely to be associated with general disturbances of blood flow such as cold-induced cutaneous vasoconstriction or vascular flow disturbances such as seen in polycythaemia or some cryogelling syndromes. Cutis marmorata in infancy is a perfect example of this pattern. Cutis marmorata telangiectatica congenita is a condition that causes a similar livid reticulate pattern because of telangiectasia.

Livedo racemosa typically has breaks in the tight net-like pattern, resulting in larger irregular rings than livedo reticularis. It is seldom symmetrical. Livedo racemosa may be more indicative of focal impairment of blood flow, such as with vasculitis, and seems most often the pattern of livedo described in European cases of Sneddon's syndrome. The distinction between livedo reticularis and racemosa may be important, but frequently the term 'livedo reticularis' is used to describe both patterns, so careful documentation of the clinical usefulness of this distinction is limited. Finally, lesions of a variety of vascular occlusion syndromes have sometimes been described as lesions of livedo (as discussed above). Although livedo reticularis or racemosa may accompany or surround lesions of retiform purpura, the presence of purpura provides a more specific finding to aid in diagnosis. Whether such conditions frequently present with livedo alone is clouded in the literature.

Conditions that may present as livedo are listed in Table 48.7.

Table 48.7 Acquired livedo reticularis, non-physiological.

Vascular disease associated
Vasculitis, especially microscopic polyangiitis, cutaneous periarteritis nodosa, rheumatic vasculitides, mixed cryoglobulinaemia, temporal arteritis, Sneddon's syndrome, livedoid vasculitis, arteriosclerosis
Rheumatic diseases
Lupus erythematosus, dermatomyositis, scleroderma, Sjögren's syndrome
Increased blood viscosity, decreased blood flow
Polycythaemia rubra vera, thrombocytosis, cryoglobulinaemia, cryofibrinogenaemia cold agglutinaemia
Embolic and hypercoaguable disorders
Cholesterol emboli, oxalate emboli, decompression sickness with nitrogen bubble embolization, ventilator gas embolization, antiphospholipid antibody syndrome
Infection
Some reports of livedo with infection may be secondary to emboli (e.g. endocarditis), angiitis (rickettsial) or purpura fulminans-related occlusion (meningococcal). Syphilis, tuberculosis and viral diseases are also important
Endocrine
Hyperparathyroidism, pseudohyperparathyroidism, hypothyroidism, Cushing's disease, carcinoid syndrome, phaeochromocytoma
Nutritional
Pellagra
Iatrogenic
Bismuth (intra-arterial), catecholamines, amantadine, quinidine (with drug-induced lupus syndrome), arsphenamine

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Cutaneous necrosis

Necrosis of the skin occurs in numerous diverse conditions and may present a diagnostic and therapeutic dilemma. Many of the conditions leading to skin necrosis are discussed elsewhere in this chapter or in Chapter 49; vasculitis and vascular occlusion disorders comprise a significant proportion of such cases, but other disorders are briefly considered here [1–9]. Table 48.8 lists some of the more important causes of cutaneous necrosis. It is not intended to be comprehensive, and the disorders listed are those that either commonly cause cutaneous necrosis or in which cutaneous necrosis is a significant risk. The table therefore lists the most important diagnoses to consider. Not uncommonly, more than one cause may be present, for example in patients with HIV treated for HCV infection with interferon, or use of anticoagulants or chemotherapy in patients subsequently found to have protein C deficiency. In some instances cutaneous necrosis may have predictive value, for example it has been

Table 48.8 Some causes of cutaneous necrosis.

Coagulation defects [1]
Purpura fulminans, disseminated intravascular coagulopathy
Protein C or S deficiency, antithrombin III deficiency

Vasculitis
Most vasculitides may cause skin necrosis, e.g. polyarteritis nodosa, Behçet's disease, Wegener's granulomatosis, Churg–Strauss disease, Henoch–Schönlein purpura (see Chapter 49)

Connective tissue disease (see Chapter 56)
Antiphospholipid syndrome/lupus anticoagulant, dermatomyositis [2], relapsing polychondritis, systemic lupus erythematosus, systemic sclerosis

Immunological
Shwartzmann reaction [3]

Hyperviscosity
Cryoglobinaemia, cryofibrinogenaemia, cold agglutinins, paraproteinaemia, POEMS syndrome

Embolic
Cholesterol emboli, cardiac myxoma, bacterial endocarditis, emboli from arterial aneurysms

Metabolic (see Chapter 57)
Diabetes, hyperhomocystinaemia, oxalosis, calciphylaxis [4], subcutaneous calcification

Arterial occlusion
Arteritis (e.g. temporal arteritis, Buerger's disease), Degos' disease, thrombosis, aneurysm, anastomosis, compartment syndrome

Infections (see Chapters 25–31)
Bacterial, e.g. necrotizing fasciitis, cellulitis, streptococci, clostridia, meningococcus, pseudomonas (ecthyma gangrenosum), leprosy (Lucio's reaction)
Viral, e.g. Rocky Mountain spotted fever, HIV, cytomegalovirus, hepatitis B or C, herpes zoster
Fungal, e.g. deep/disseminated fungal infection (especially *Aspergillus*, *Mucor*, *Rhizopus*)

Venoms
Snake bites, spider bites, stings (e.g. scorpion, stingray)

Drugs and toxins (see Chapter 73)
Systemic
- Anticoagulants, e.g. warfarin (coumadin), heparin
- Vasoactive drugs, e.g. vasopressin, norepinephrine, dopamine [5–8], metaraminol, β-blockers
- Chemotherapeutic drugs, e.g. methotrexate, bleomycin, cyclophosphamide, vincristine
- Cytokines and growth factors, e.g. tumour necrosis factor, interferons, interleukin-3, G-CSF, GM-CSF
- Antimicrobials, e.g. penicillins, sulphonamides, aciclovir, levamisole
- Antithyroid, e.g. thiouracils, carbimazole
- Toxins, e.g. carbon monoxide poisoning
- Miscellaneous, e.g. penicillamine, iodides, bromides, phenytoin

Topical
- Glutaraldehyde, cetrimide, calcium chloride, mustard gas, hydrofluoric acid

Injection sites
- Calcium salts, interferon, aminoglycosides, collagen, silicone, hydrocarbons, vaccines (DTP, BCG), iron dextran, chemotherapy extravasation, Depo-Provera, several illicit drugs, intra-arterial injections

Malignant disease
Leukaemia, lymphoma, mycosis fungoides, lymphomatoid granulomatosis, hypereosinophilic syndrome, myelodysplastic syndrome, Langerhans' cell histiocytosis
Phaeochromocytoma (localized or acral necrosis)
Paraneoplastic thrombosis, paraneoplastic acral vasculopathy

Physical damage
Burns, radiation, trauma, factitious ulcer, sclerotherapy, liposuction

Inflammatory dermatoses
Sarcoidosis, pityriasis lichenoides acuta, pyoderma gangrenosum and neutrophilic dermatoses, panniculitides

Miscellaneous
Intrauterine epidermal necrosis [9]

BCG, bacillus Calmette–Guèrin; DTP, diphtheria–tetanus–pertussis; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte–macrophage colony-stimulating factor; HIV, human immunodeficiency virus; POEMS, polyneuropathy, organomegaly, endocrinopathy, M protein, skin changes.

suggested to be linked with the presence of underlying malignancy in patients with dermatomyositis [2].

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Neonatal purpura [1]

The differential diagnosis of purpura or bleeding in neonates includes most of the causes of purpura. However, it is discussed as a separate entity due to the diagnostic dilemmas that may arise. The main causes are listed below.

- Deficiency of clotting factors and coagulation disorders (including purpura fulminans and vitamin K deficiency).
- Thrombocytopenia: congenital, maternal antibodies (ITP, SLE, others).
- Extramedullary erythropoiesis ('blueberry muffin' baby).
- Infections, e.g. TORCH syndrome, which comprises *t*oxoplasmosis, *o*ther infections (syphilis and viral), *r*ubella, *c*ytomegalovirus and *h*erpes simplex, may cause blueberry muffin baby; others infectious causes include HIV, parvovirus B19 and sepsis.
- Congenital/inherited conditions, e.g. Wiskott–Aldrich syndrome.
- Maternal antibody mediated: autoimmune (ITP, SLE, drug) or alloimmune (isoimmune) due to fetomaternal incompatibility.
- Associated with haemangiomas.
- Traumatic: caput succedaneum and facial petechiae (prolonged vertex delivery).
- Others, e.g. vascular purpura, non-accidental injury (both rare in this age group).

The three most important groups for dermatologists are purpura fulminans, blueberry muffin baby and infections [1]. Purpura fulminans in the neonate is an important manifestation of protein S or protein C deficiency (discussed above). Skin lesions in blueberry muffin baby are distinguished from purpura as they are palpably firm and elevated, but non-palpable purpura may coexist. The TORCH group of infections may cause this condition, but haemolysis (such as rhesus incompatibility), hereditary spherocytosis and twin transfusion syndrome may also be associated with extramedullary erythropoiesis.

Haemorrhagic disease of the newborn is due to accentuation of the normal fall of prothrombin within the first week of life but is now uncommon due to routine vitamin K prophylaxis. An early form within the first 24 h of life may occur if there is maternal intake of drugs that interfere with vitamin K (such as oral anticoagulants), and a late form (1–12 months) occurs in children with impaired gastrointestinal absorption and may cause deep nodular ecchymoses. Haemophilia and other coagulation factor deficiencies only rarely cause bleeding at this age.

The causes of purpura fulminans [2] have been classified as follows.

- Acute infectious: meningococcus, streptococcus, *Haemophilus* and other infections.
- Post-infectious: varicella, streptococcus and others.
- Congenital protein C or S deficiency; factor V Leiden mutation.
- Acquired protein C or S deficiency: coumarins, hepatic cholestasis, nephrotic syndrome, renal dialysis, marrow transplantation.
- Antiphospholipid antibody (termed 'catastrophic antiphospholipid syndrome'; may have associated SLE).
- Vasculitis: polyarteritis nodosa, Henoch–Schönlein purpura, others.
- Heparin-induced skin necrosis (most cases are related to local skin injection).
- Toxins and poisons: snake and spider bites (usually maximal purpura at the inoculation site).

However, the use of the term purpura fulminans as a broad term for widespread cutaneous purpura of any type is probably more confusing than helpful. It may be more helpful to restrict the term purpura fulminans to disorders in which cutaneous microvascular occlusion is the known cause of widespread cutaneous purpura.

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Miscellaneous causes of purpura

Non-thrombocytopenic toxin- and drug-induced purpura [1–6]

Many agents may lead to purpura by causing thrombocytopenia (discussed above). There are also many substances capable of causing capillary damage with or without any change in platelets, either by direct toxicity or

through an allergic reaction. The purpura varies in degree from a few petechiae to massive extravasation of blood. Sometimes there is obvious evidence of inflammatory lesions, as well as purpura, implying a frankly vasculitic process [7]. Exposure may be industrial, accidental or therapeutic. Some drugs may cause thrombocytopenia and either vascular purpura and/or frank vasculitis; the thrombocytopenia in such cases may be caused by a direct effect on platelets or by endothelial damage leading to platelet aggregation.

Substances capable of causing capillary damage include acetylsalicylic acid, allopurinol, *p*-aminosalicylic acid, arsenic, atropine, bismuth, barbiturates, carbimazole, carbromal, chloramphenicol, chlordiazepoxide, chlorothiazide, chlorpromazine, diethylstilbestrol, furosemide, gold, hair dye, indometacin, iodides, isoniazid, menthol, meprobamate, methyldopa, piperazine, quinidine, quinine, reserpine, snake venoms, sodium salicylate, sulphonamides, tartrazine and other food additives, thiouracil, tolbutamide and glyceryl trinitrate.

Carbromal is one of the few drugs that caused a rather distinctive pattern of purpura. The widespread areas of capillary leakage combined with erythema produced a picture which resembled itching purpura and Schamberg's disease. Drug-induced pigmented purpuric dermatoses are considered elsewhere.

Trimethoprim–sulfamethoxazole has been reported to cause an acral purpuric eruption, proven by rechallenge, that resembled the purpuric 'gloves and socks' syndrome more commonly caused by parvovirus B19 [8].

A diagnosis of toxin- and drug-induced purpura usually depends on circumstantial evidence. Unfortunately, laboratory tests are mainly unhelpful, although some drugs that cause purpuric reactions will produce a purpuric reaction when patch tested. Rechallenge may be dangerous; generally the diagnosis is made by careful history-taking.

Drug-induced vasculitis or livedo are also discussed in Chapter 73; drugs that cause skin necrosis are considered in Table 48.8.

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Contact purpura [1]

Purpura may occur as an irritant reaction to mechanical friction from abrasive agents such as woollen clothing or fibreglass. Some topical medications may rarely cause purpura that appears to be of irritant or toxic causation, such as clioquinol (at flexural sites), benzoyl peroxide or EMLA local anaesthetic [2,3]. Textile and rubber chemicals [4–6] are particular causes of contact purpura that may have little or no eczematous component, although itch or lichenoid morphology may be prominent in some instances. Such reactions may be widespread, the distribution corresponding only approximately with the distribution of contact, and may therefore be confused with idiopathic pigmented purpuras.

Purpura around the acrosyringium may occur at patch-test sites to cobalt, and purpuric patch tests to apronalide and quinidine have been reported in subjects with a purpuric rash after systemic administration of these agents.

The main groups of chemicals that have been reported to cause contact purpura are listed below.

- Dyes and textile agents: azo dyes, paraphenylenediamine, optical whiteners.
- Rubber antioxidants: IPPD, isopropylaminodiphenylamine.
- Resins: urea formaldehyde compounds, epoxy resin.
- Plants: *Rhus*, *Agave*.
- Others: topical medicaments, balsam of Peru, mercury.

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Purpura associated with infection

Purpuric skin lesions associated with infection [1] may be due to numerous mechanisms, more than one of which may be operative, including:

- thrombocytopenia (discussed above);
- localized or disseminated intravascular coagulation (discussed above);
- direct vascular damage (invasion or occlusion by organisms);

- vascular effects of toxins;
- immunological vascular damage (vasculitis, immune complex deposition);
- emboli.

Purpura is a characteristic feature of certain bacterial infections, for example meningococcal or other septicaemias and bacterial endocarditis, and of many viral and rickettsial infections, for example typhus, Rocky Mountain spotted fever and the viral haemorrhagic fevers (see Chapters 25 and 27) [2,3]. Acral purpuric lesions are typical of Rocky Mountain spotted fever; the histological features include a lymphohistiocytic capillaritis and venulitis with variable leukocytoclastic vasculitis, fibrin thrombi, capillary wall necrosis and immunofluorescent evidence of organisms within endothelial cells, suggesting that it is therefore a type of septic vasculitis. In typhus, however, acral sites are generally spared.

Skin lesions are the presenting feature in 70–90% of patients with meningococcaemia and are purpuric in 50%, often stellate in shape and tender. There may be a leukocytoclastic vasculitis with thrombi and meningococci within endothelial cells or leukocytes, typically resulting in a clinical lesion of classical palpable purpura, ranging in size from 2 to 8 mm in diameter. Lesions may progress to purpura fulminans due to microvascular occlusion, with lesions typically enlarging and often developing stellate or retiform features with minimal to no erythema (discussed above). In some cases of meningococcal septicaemia, organisms can be seen on blood smears taken from scraped skin lesions [4].

Various congenital infections may cause neonatal purpura (discussed above). Purpura may appear in the prodromal period of many infections, for example measles, in which case it is often a sign of a severe infection. When it occurs at the height of the infection it is of less serious importance. A large number of infections may cause purpuric lesions in children [5].

The petechial gloves and socks syndrome, or papular–purpuric gloves and socks syndrome, is a distinctive syndrome that has been attributed to parvovirus B19 infection [6,7] or to other viruses such as measles, hepatitis B, coxsackievirus B6 and cytomegalovirus [5,8] (see also Chapter 25). Purpura may also occur in the laterothoracic eruption, which may have an infectious aetiology.

Other infections may be associated with characteristic distributions of purpura, for example *Strongyloides* causes 'thumb-print' periumbilical purpuric lesions [9].

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Chapter 49

Vasculitis and Neutrophilic Vascular Reactions

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Vasculitis

Introduction

Vasculitis is a term applied to inflammation and necrosis of blood vessels, whether they be arteries, veins or both. Vasculitis may be local or systemic, and may be primary or secondary to another disease process. Small vessels (such as capillaries, arterioles and venules), medium-sized vessels (such as visceral vasculature, including renal, coronary or hepatic arteries) and large vessels (the aorta and its great vessels) may be affected. Many vasculitides have a cutaneous component. A dermatologist can provide invaluable assistance in the clinicopathological diagnosis of vasculitis and by guiding patient evaluation and treatment.

Because of the wide range of organ systems affected by vasculitis of blood vessels of various sizes, the clinical presentation of the many vasculitides is varied. However, classic cutaneous manifestations such as palpable purpura in dependent areas, typically the ankles and lower legs, characterizes smaller vessel involvement, whereas necrosing livedo reticularis or multiple sites of peripheral gangrene characterize larger vessel vasculitis. It is also important to note that vasculitides may be present without any cutaneous signs or symptoms.

Infiltration of inflammatory cells with subsequent destruction of blood vessel walls is classically demonstrated in nearly all vasculitides. However, specific histopathological features are dependent on the type and size of the affected blood vessel.

Many vasculitides are triggered by various antigenic agents, such as infection or medication, or are related to underlying disease such as connective tissue, vascular or inflammatory bowel disease, myelodysplastic or other malignancies. However, a single trigger may be associated with several distinct vasculitides, implying that different and more specific mechanisms of inflammation apply in different disorders. Pathogenetic factors in vasculitis are discussed below.

Classification

The classification of vasculitides has been a confusing and debate-provoking topic over the last half century. The first attempt at a classification was by Zeek in 1952 [1]. In this classification of necrotizing vasculitis, she incorporated a clinicopathological evaluation based on the size of the blood vessel involved in the inflammatory process. Zeek differentiated five types of necrotizing angiitis: periarteritis nodosa, hypersensitivity arteritis, rheumatic arteritis, allergic granulomatous angiitis and temporal arteritis [2].

Other factors that may be considered in the classification of vasculitis were discussed by Winkelmann [3]. He incorporated clinical classification, systemic versus cutaneous involvement, muscular vessel versus small vessel

Table 49.1 1990 American College of Rheumatology criteria for hypersensitivity vasculitis (traditional format) [5].*

1 Age at disease onset > 16 years
2 Medication at disease onset
3 Palpable purpura
4 Maculopapular rash
5 Biopsy including arteriole and venule with histological changes showing granulocytes in a perivascular or extravascular location

* At least three of the five criteria must be present. The presence of three criteria was associated with a specificity of 83.9% and a sensitivity of 71.0% [5].

Table 49.2 Chapel Hill Consensus Conference classification of vasculitis [6].

I *Large vessel vasculitis*
A Giant cell arteritis
B Takayasu's arteritis
II *Medium-sized vessel vasculitis*
A Classic polyarteritis nodosa
B Kawasaki disease
III *Small vessel vasculitis*
A Wegener's granulomatosis
B Churg–Strauss syndrome
C Microscopic polyangiitis (polyarteritis)
D Henoch–Schönlein purpura
E Essential cryoglobulinaemia
F Cutaneous leukocytoclastic vasculitis

Table 49.3 Proposed working classification of vasculitis.

Small vessel vasculitis
Cutaneous small vessel vasculitis—not further classified
Henoch–Schönlein purpura
Essential mixed cryoglobulinaemia (Chapter 48)
Waldenström's hypergammaglobulinaemic purpura (Chapter 48)
Associated with collagen vascular disease (Chapter 56)
Urticarial vasculitis
Erythema elevatum diutinum
Eosinophilic vasculitis
Rheumatoid nodules (Chapter 56)
Reactive leprosy (Chapter 29)
Septic vasculitis
Larger vessel vasculitis
Polyarteritis nodosa
• Microscopic polyarteritis
• Cutaneous form
• Systemic form
Granulomatous vasculitis
• Wegener's granulomatosis
• Allergic granulomatosis of Churg and Strauss
• Lymphomatoid granulomatosis (Chapter 54)
Giant cell arteritis
• Temporal arteritis
• Takayasu's arteritis
Larger vessel vasculitis with collagen vascular disease
Nodular vasculitis

disease, and histopathological features in his schema. He also discussed 'laboratory vasculitis', which reviewed the laboratory findings of patients with vasculitis as part of a classification scheme, as well as aetiological factors of various vasculitides [3].

In 1976, James Gilliam [4] proposed a classification of necrotizing vasculitis as part of Medical Grand Rounds at the University of Texas Southwestern Medical Center.

The American College of Rheumatology published classification criteria for vasculitis in 1990 [5]. However, several problems exist with this classification scheme, which is illustrated in Table 49.1. Particular problems with the criteria include an attempt to codify histological findings of small vessel ('hypersensitivity') vasculitis using 14 biopsy criteria. Furthermore, the use of such terms as 'maculopapular rash', 'medication at onset' and 'eosinophils on biopsy', as well as the separate classification of Henoch–Schönlein purpura, seem inappropriate to most dermatologists.

In 1994, the Chapel Hill Consensus Conference [6] proposed a new naming system for primary systemic vasculitides, which is depicted in Table 49.2. This system classifies the vasculitides into small, medium and large vessel types.

A further attempt to classify vasculitides based on an updated version of Gilliam's 1976 scheme is presented in Table 49.3.

Despite numerous attempts over 50 years, the development of a clinically relevant and easy-to-use classification system for vasculitis that incorporates clinical features, vessel size, histopathological and laboratory features, and aetiologies, is a goal that has not yet been fully achieved.

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Pathogenesis of vasculitis

The pathogenesis of vasculitis is a complex subject, not least because there are likely to be many different pathogeneses reflecting the many different causes and pathological entities. This brief overview describes some of the major mechanisms and systems involved, with emphasis on those that have clinical importance (such as the diagnostic potential of antineutrophil cytoplasm antibodies;

ANCA). More detailed recent reviews can be consulted [1–7].

Factors that play a part in the pathogenesis of vasculitis include antigen–antibody related mechanisms (including autoantibodies and immune complex diseases), inflammatory cells and their lysosomal content, complement, cytokines, chemokines, adhesion molecules, vascular and cellular growth factors, genetic influences and the fibrinolytic system, as well as direct vessel wall damage (e.g. by some infectious organisms). Local blood flow influences the development of the vasculitis lesion, as evidenced by lesions occurring at areas of constriction by tight clothing, and local release of histamine also has a role.

Antigens, immune complexes and complement

Antigenic triggers of immunological responses targeted at components of blood vessel walls elicit most vasculitides. The importance of circulating immune complexes has long been recognized in studies of serum sickness [8], and the deposition of immune complexes in blood vessel walls is the best characterized mechanism for the vascular injury associated with vasculitis [9]. It is this mechanism that may be particularly important in cutaneous small vessel vasculitis; potential antigens of relevance include bacteria, viruses, drugs and other chemicals. Most evidence for an immune complex-mediated pathogenesis is circumstantial (e.g. the demonstration of immunoglobulins in skin lesions) and is better documented for cutaneous small vessel vasculitis than for systemic vasculitides. It is generally accepted that immune complexes have a role in Henoch–Schönlein purpura (HSP), serum sickness, hepatitis B and C virus-induced vasculitis and in cryoglobulinaemic vasculitis.

A theory about the pathogenesis of cutaneous small vessel vasculitis is described below and depicted in Table 49.4 [6,7]. The circulating immune complexes mediating vasculitis interact with the complement system to generate C3a and C5a anaphylatoxins which degranulate mast cells. They stimulate the production of chemotactic factors and subsequent chemotaxis, the release of vasoactive amines (such as histamine) and the release of pro-inflammatory cytokines which induce the subsequent expression of adhesion molecules (such as P- and E-selectin in endothelial cells). Immune complexes with a sedimentation coefficient greater than 19S are deposited in vessel walls, a process that is strongly influenced by platelet-derived vasoactive amines. After vasoactive amine-induced endothelial cell retraction, the immune complex deposition leads to increased expression of selectins by endothelial cells. Neutrophils that are attracted to the site of immune complex deposition release lysosomal enzymes in a teleological attempt to engulf the deposited immune complexes, and are activated *in situ* through binding of the fragment crystallizable (Fc) portion of the antibody. This causes degranulation and destruction of the neutrophils (visible histologically as leukocytoclasis) with release of collagenase and elastase, and generation of reactive oxygen species, ultimately resulting in inflammation and 'bystander' fibrinoid necrosis of vessel walls. It is of practical importance to appreciate that neutrophils degrade immune complexes within 24–48 h after they are deposited [10], usually within 24 h; hence, direct immunofluorescence of vasculitis lesions older than 3–12 h will generally yield negative results [6,11]. Immune complexes may also activate endothelial cells to produce tissue plasminogen activator (t-PA) and thus alter local fibrinolysis and vascular permeability [6]. There are therefore many complex and dynamic changes that occur.

Table 49.4 Theory of pathogenesis of cutaneous small vessel vasculitis. (Modified from [7].)

Immune complexes interact with the complement system to generate C3a and C5a anaphylatoxins, which stimulate: • Production of chemotactic factors which initiate chemotaxis of neutrophils • Release of vasoactive amines (such as histamine), which cause endothelial cell retraction • Release of proinflammatory cytokines (e.g. IL-1, TNF-α), which induce the expression of adhesion molecules (P- and E-selectin) in endothelial cells
Immune complexes deposit in vascular walls after histamine-induced endothelial retraction which increases selectin expression in endothelial cells
Attracted neutrophils produce lysosomal enzymes in an attempt to engulf deposited immune complexes: • Neutrophils are activated through Fc binding and degranulate, and also produce reactive oxygen species • Ultimate inflammation and 'bystander' fibrinoid necrosis of blood vessel wall

Paraneoplastic vasculitis is thought to be caused by tumour antigens stimulating cell-mediated immunity or forming tumour antigen immune complexes, although direct vessel wall damage or occlusion can occur as a result of emboli. Haematological malignancies are the most common to be associated with vasculitis [12].

Antiphospholipid antibodies are important as a cause of microvascular thrombosis (Chapter 48). However, they also bind to endothelial cells and have numerous effects; they are pro-inflammatory, induce monocyte activation, stimulate cytokine and vascular adhesion factor expression, and result in a thrombophilic state [13]. In autoimmune conditions, binding requires plasma β_2-glycoprotein-I (β_2-GP-I), which itself binds to endothelial cells and complexes with phospholipids.

Superantigens have also been implicated in development of vasculitis, notably in Kawasaki syndrome, but this concept has been disputed [4].

Complement activation leads to the adherence of C3b to immune complexes, such that they remain soluble and are cleared by macrophages. Immune complexes that have

bound C3b also bind to erythrocytes via the complement receptor type 1 (CR1), leading to clearance from the reticuloendothelial system. Complement deposition is documented in skin lesions (e.g. in HSP) and genetic deficiency of complement is associated with immune complex diseases. However, IgA immune complexes in patients with HSP do not appear to activate the classical complement pathway, although activation of the alternative pathway by IgA1 (the main IgA subclass in HSP) may allow complexes to be made soluble.

Antiendothelial cell antibodies and other factors in vessel wall injury

Antiendothelial cell antibodies (AECA) are of uncertain importance in the pathogenesis of vasculitis [1,2,14]. They can be identified at high titre in most patients with Takayasu's arteritis or with active thromboangiitis obliterans, and are variably demonstrated in patients with Wegener's granulomatosis (WG), microscopic polyangiitis, Kawasaki disease, Behçet's syndrome and systemic lupus erythematosus (SLE) associated vasculitis. They are also found in several other connective tissue diseases and in haemolytic uraemic syndrome/thrombotic thrombocytopenic purpura, IgA nephropathy, ulcerative colitis and diabetes mellitus. Some studies correlate their titre with disease activity in medium or large vessel arteritis, but whether this reflects a pathogenic role or vascular damage is unclear. The fact that they bind preferentially to endothelium of mesenteric vessels supports the possibility of a pathogenic role in visceral arteritis [15]. AECA can cause endothelial damage by complement-mediated or complement-independent antibody-dependent cellular cytotoxicity.

AECA may also activate endothelial cells leading to up-regulation of adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and E-selectin [3,16]; this may be mediated by nuclear factor (NF)-κB [17]. Increased neutrophil cytotoxicity results. E-selectin is a promoter of endothelial cell activation and of leukocyte–endothelial cell interaction, being expressed on cytokine-activated endothelial cells, and might therefore have an active role in the pathogenesis of vasculitis; however, E-selectin levels in a variety of systemic vasculitides do not correlate with disease activity [18]. Von Willebrand factor, factor VIII and soluble thrombomodulin levels may all be increased in vasculitis, probably as a secondary effect resulting from vascular damage; the latter has been shown to be related to disease activity in WG [18]. However, soluble thrombomodulin is also increased in disseminated intravascular coagulopathy, thrombotic thrombocytopenic purpura, sepsis, malaria, diabetic microangiopathy and various other disorders in which there is damage to vessels. High levels of soluble VCAM-1 are found in Kawasaki disease but were even higher in febrile controls [3], and this finding is therefore presumably also a non-specific result of vascular injury.

Nitric oxide production is also increased in some vasculitides; neutrophil-derived nitric oxide is known to be damaging to endothelial cells [19].

Antineutrophil cytoplasm antibodies

By comparison with other pathogenetic factors, many of which are either not routinely measurable or are of uncertain relevance to pathogenesis, antineutrophil cytoplasm antibodies (ANCA) have diagnostic value as well as an important role in the pathogenesis of vasculitis [1–7,14,20–22].

ANCA are classified, according to their indirect immunofluorescence (IIF) pattern on ethanol-fixed neutrophils, into C-ANCA (granular cytoplasmic staining with accentuation between the nuclear lobes), P-ANCA (perinuclear and/or nuclear staining) and atypical ANCA (various patterns, including diffuse cytoplasmic and 'very perinuclear'; atypical ANCA are also termed X-ANCA or snowdrift-ANCA) [3,20]. These patterns correlate with varying degrees of specificity to specific neutrophil granule contents (Table 49.5). ANCA are usually of IgG type but may be IgM or IgA. In addition to systemic vasculitides, ANCA may be positive in various infections (malaria, human immunodeficiency virus infection; HIV), connective tissue disorders (SLE, rheumatoid arthritis) and gastrointestinal disease (inflammatory bowel disease, chronic autoimmune liver and biliary tract disease).

In most disorders other than vasculitides, the pattern is P-ANCA or atypical ANCA, and in most of these disorders there is no consistent ANCA specificity or correlation with disease activity. However, there are some exceptions, such as the association of cathepsin G-ANCA with malaria [23]. The presence of P-ANCA in SLE, although originally felt not to have any particular link with disease pattern [24], has been associated with serositis, livedo reticularis, venous thrombosis, anticardiolipin and anti-SSA/Ro positivity, and periodontal disease [25,26]; in particular, lactoferrin-ANCA is strongly linked with livedo reticularis [25]. Bactericidal/permeability increasing protein (BPI) ANCA and proteinase 3 (PR3) ANCA have also been linked with serositis in patients with SLE. Anti-dsDNA and anti-SSA/Ro antibodies may resemble P-ANCA, depending on fixation methods [27]. Human lysosome-associated membrane protein-2 (h-lamp-2) ANCA has been linked with pyoderma gangrenosum.

Generally, the P-ANCA pattern is relatively non-specific, having various (often undetermined) antigen specificities and often no link with disease activity. By contrast, the C-ANCA pattern almost always corresponds with antibodies against PR3, a 29-kDa neutral serine pro-

Table 49.5 Antigenic specificity and clinical correlates of antineutrophil cytoplasm antibodies.

Antigen	Usual ANCA pattern on IIF	Most commonly associated diseases
PR3	C-ANCA	WG, MPA, CSS, necrotizing and crescentic GN
MPO	P-ANCA	Idiopathic progressive GN, MPA, CSS, WG, SLE, ANCA-positive drug-induced systemic vasculitis, thromboangiitis obliterans
Cathepsin G	P-ANCA	IBD, especially ulcerative colitis, PSC, malaria
BPI (= CAP 57)	C-ANCA	Systemic vasculitis, SLE, IBD, PSC, cystic fibrosis, chronic airway infections
Azurocidin (= CAP 37)	P-ANCA or C-ANCA	Systemic vasculitis, drug-induced systemic vasculitis
Lactoferrin	P-ANCA or atypical ANCA	Rheumatoid arthritis, SLE especially with serositis or livedo reticularis, systemic vasculitis, ulcerative colitis, PSC, hydralazine-related vasculitis, thromboangiitis obliterans
Elastase	P-ANCA	WG, propylthiouracil-related systemic vasculitis, HIV infection
β-glucuronidase	P-ANCA	IBD
Lysozyme	P-ANCA	SLE, IBD, HIV infection
h-lamp-2	P-ANCA	Necrotizing and crescentic GN, pyoderma gangrenosum
Others (actin, catalase, α-enolase)	P-ANCA or atypical	Uncertain. Anti-actin may be present in autoimmune hepatitis

BPI, bactericidal/permeability increasing protein; C-ANCA, cytoplasmic antineutrophil cytoplasm antibody; CSS, Churg–Strauss syndrome; GN, glomerulonephritis; HIV, human immunodeficiency virus; h-lamp-2, human lysosome-associated membrane protein-2; IBD, inflammatory bowel disease; MPA, microscopic polyangiitis; MPO, myeloperoxidase; P-ANCA, perinuclear antineutrophil cytoplasm antibody; PBC, primary biliary cirrhosis; PR3, proteinase-3; PSC, primary sclerosing cholangitis; SLE, systemic lupus erythematosus; WG, Wegener's granulomatosis.

tease, and clinically with WG or other systemic vasculitis. In the context of systemic vasculitis, the important P-ANCA group are those with antibodies against myeloperoxidase (MPO). It is therefore important to confirm MPO or PR3 antibodies, usually by enzyme-linked immunosorbent assay (ELISA), in the context of a positive ANCA test identified by IIF screening, and to refer to the more specific result where possible (e.g. as PR3-ANCA) [20]. A positive C-ANCA has a sensitivity of 66% (91% if only considering active disease) and specificity of 98% for WG [28], but may be positive in about one-third of patients with microscopic polyangiitis or with necrotizing crescentic glomerulonephritis, and in about 20% with Churg–Strauss syndrome (CSS). Patients with WG who are negative for C-ANCA/anti-PR3 usually have positive P-ANCA/anti-MPO. In addition, anti-MPO are found in about 65% with progressive idiopathic glomerulonephritis, in about 50% with microscopic polyangiitis or CSS, and may be found in SLE or in ANCA-associated drug reactions (notably to propylthiouracil or hydralazine). If ANCA are present in drug-induced systemic vasculitis the pattern is usually P-ANCA or atypical ANCA.

Numerous studies suggest a pathogenetic role for at least anti-PR3 and anti-MPO antibodies in systemic vasculitides. In particular, the IgG3 subclass of PR3 is implicated, a rise in titres in WG being predictive of relapse [3]; this subclass is a particularly strong activator of neutrophils. The role of ANCA in the pathogenesis of vasculitis is multifactorial. ANCA cause activation of neutrophils primed by tumour necrosis factor-α (TNF-α), leading to production of reactive oxygen species, nitric oxide and cytokines such as interleukin-1 (IL-1) and IL-8 (a neutrophil chemoattractant). Neutrophils activated by ANCA up-regulate adhesion molecules, adhere to platelet monolayers or to TNF-activated endothelial cells *in vitro* rather than their usual behaviour of 'rolling', and develop pseudopodia [5]. ANCA also up-regulate expression of adhesion molecules and IL-6 production by endothelial cells, cause neutrophil degranulation with release of proteolytic enzymes, and stimulate monocytes to produce reactive oxygen species and to produce IL-8; monocyte activation may also be important in non-ANCA-associated vasculitides such as Behçet's disease [4].

Elastase is one of the main tissue-damaging enzymes released by neutrophil degranulation. It is potentially important that elastase stimulates release of tissue factor from cultured endothelial cells (human umbilical vein endothelial cells; HUVEC), as this may be relevant in development of microthrombi *in vivo* (PR3, but not MPO, also stimulates production of tissue factor from HUVEC) [29]. It is also of interest that autoantibodies to elastase enhance rather than decrease elastase activity, thus leading to tissue damage [30]; this might be a pathogenetic role for elastase-ANCA. It appears that the major role of ANCA in vasculitis is probably caused by their effects on the neutrophil, thus leading to endothelial cell damage.

Other cytokines and chemokines, and the cellular response [1,3,4]

Numerous cytokines have been implicated in vasculitis; some have already been discussed. Many are released as part of an acute phase response or because of up-regulation of production by peripheral blood neutrophils or monocytes, such as IL-1, IL-2, IL-6, IL-8, interferon (IFN) and TNF-α. These may therefore be non-specifically elevated in vasculitis, but may play a part in ongoing damage. TNF-α is important for priming endothelial cells

to express E- and P-selectin, ICAM-1 and 2, and VCAM-1 (see above), and also primes neutrophils to produce reactive oxygen species and to degranulate after exposure to ANCA. IL-8 is a potent neutrophil chemoattractant that is expressed by endothelial cells after stimulation by ANCA. IL-6 has been studied especially in giant cell arteritis and Takayasu's arteritis, in which it appears to reflect disease activity. Increased levels of soluble TNF receptor have been demonstrated in ANCA-positive vasculitides.

Other chemokines that have enhanced tissue expression in vasculitis include monocyte chemotactic protein-1 (MCP-1), macrophage inflammatory protein-1α and -1β and RANTES (regulated upon activation, normal T-cell expressed and secreted) [22]. Expression of MAC-1 by neutrophils is up-regulated by ANCA.

Based on a mouse model in which genetic deficiency of IL-1 receptor antagonist (IL-1Ra) is associated with arterial inflammation, it has been suggested that IL-1Ra has a significant role in vasculitis and that a recombinant IL-1Ra might be a useful treatment [31].

T cells, monocytes and macrophages play a part in vasculitis injury, in addition to the role of neutrophils discussed above. Both $CD4^+$ and $CD8^+$ T cells accumulate at the site of injury. In WG there is a Th1 cytokine profile, with increased IFN-γ, TNF and IL-12 but not IL-4, IL-5 or IL-10 [22], and CD28 expression; however, some studies have suggested a Th2 response in nasal mucosa, which may be of importance as nasal staphylococcal infection is associated with relapses in WG. Monocytes from patients with systemic necrotizing vasculitis produce more superoxide and MPO than monocytes from controls, and they can also be induced to express PR3 and to release IL-8 when exposed to ANCA [5]. However, monocyte activation also occurs in Behçet's disease, which is not ANCA-related. Defective macrophage apoptosis may lead to persistence and ongoing damage at the vasculitic site, as occurs with neutrophils [4].

Genetic factors

Familial clustering has been documented in some vasculitides such as WG, although this is uncommon [4,32]. Various explanations have been proposed, including the occurrence of TNF gene polymorphisms, genetic heterogeneity of ANCA antigens or their expression, and neutrophil Fcγ receptor polymorphisms. For example, expression of PR3 on resting neutrophils shows marked individual variation, the proportion of neutrophils expressing PR3 varying from approximately 10% to 80%, but being quite stable in any individual [4,33]; high expression has been associated with a higher risk of WG. Severe renal disease in WG has been linked with expression of the neutrophil receptor FcγRIIIb-NA1, although this is disputed [22,32]. The genetic region for elastase, azurocidin and PR3 is highly polymorphous, but no apparent associations with clinical disease have been identified [4].

α_1-Antitrypsin (α_1AT) is a natural inhibitor of PR3 and elastase (as is caeruloplasmin for MPO). Deficiency of α_1AT may be genetic or may be acquired by the formation of α_1AT–PR3 complexes by anti-PR3 ANCA. An association between the α_1AT-deficient PiZZ phenotype and ANCA-positive vasculitis has been described, and PiZ heterozygosity has been linked with poor prognosis in ANCA-positive systemic vasculitis [1,34]. However, a large study of PiZZ-deficient sera showed an association with antibodies against elastase but not against PR3, MPO or lactoferrin, and α_1AT deficiency is not in itself sufficient to induce ANCA-associated vasculitis [22,35]. An α_1 protease inhibitor has been used with dramatic response in the treatment of chronic vasculitis in a patient with α_1AT deficiency [36].

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Evaluation of the patient with suspected vasculitis

The evaluation of a patient with suspected vasculitis involves histopathological confirmation of the clinical diagnosis, an assessment of the extent of the disease and an attempt to establish an underlying aetiology. Clinical patterns that may suggest a vasculitis, other than the overtly vasculitic lesions discussed in this chapter, include cutaneous livedo, cutaneous necrosis, non-specific purpura and purple (blue) toe syndrome; these patterns can also occur in non-vasculitic microvascular occlusion disorders, and their significance and likely causes are discussed in Chapter 48.

Histopathological confirmation of suspected small vessel vasculitides is best performed by taking a punch biopsy of the lesions at the appropriate stage, recognizing that lesions represent various chronological stages of the disease process. Deeper elliptical incisional biopsies should be performed for suspected larger vessel vasculitides.

In attempting to assess the extent of the disease, it is important to consider where circulating immune complexes may deposit. Specifically, the following systems should be evaluated for immune complex-mediated pathology:

- *General*. Myalgia, arthralgia, fever
- *Renal*. Proteinuria, haematuria
- *Nervous system*. Central or peripheral, diffuse or localized findings
- *Musculoskeletal*. Non-erosive polyarthritis
- *Gastrointestinal*. Abdominal pain, gastrointestinal bleeding
- *Pulmonary*. Pleural effusion, pleuritis
- *Cardiac*. Pericardial effusion

It is helpful to work with a colleague in internal medicine or paediatrics when evaluating the patient.

Finally, an attempt should be made to determine the aetiology of the vasculitis. It may be helpful to screen for medications, infections or diseases associated with immune complexes (connective tissue vascular diseases, malignancy, inflammatory bowel disease, etc.). It is important to remember, however, that cutaneous small vessel vasculitis is idiopathic in up to 50% of cases.

The information in the following sections discusses the definition, history, aetiology, pathogenesis, histopathology, clinical features, diagnosis and treatment of various vasculitides affecting small, medium and large blood vessels.

Cutaneous small vessel vasculitis

SYN. CUTANEOUS LEUKOCYTOCLASTIC VASCULITIS; HYPERSENSITIVITY ANGIITIS/VASCULITIS VARIANTS CONFINED TO SKIN; CUTANEOUS NECROTIZING VENULITIS (NECROTIZING VARIANT INVOLVING PREDOMINANTLY VENULES)

Definition. Affecting mainly cutaneous post-capillary venules, cutaneous small vessel vasculitis (CSVV) is the most common type of vasculitis in dermatology. Features of CSVV include palpable purpura, urticaria or ulcers on the legs involving only small vessels. It affects both children and adults, and is seen primarily in women. Extracutaneous manifestations of CSVV are uncommon.

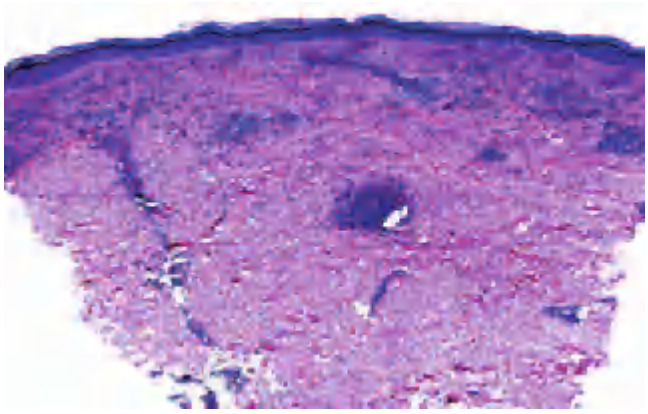

Fig. 49.1 Leukocytoclastic vasculitis. Low power photomicrograph showing perivascular infiltrates and fibrinoid deposits within the vessels of the upper dermis. (Courtesy of Dr Omar Sangueza, Wake Forest University School of Medicine, Winston-Salem, NC, USA.)

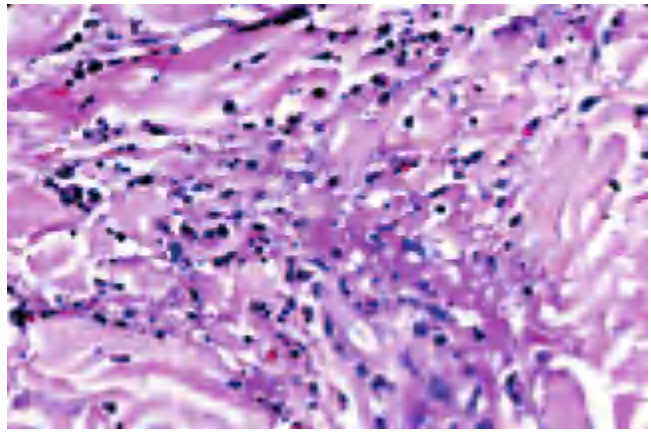

Fig. 49.2 Leukocytoclastic vasculitis. Higher magnification demonstrates nuclear dust, fibrinoid deposits, vascular alteration and collagen degeneration. (Courtesy of Dr Omar Sangueza, Wake Forest University School of Medicine, Winston-Salem, NC, USA.)

History and nomenclature. In the 1950s, Zeek described small vessel vasculitis related to drug exposure as a separate entity from large vessel vasculitis, and termed the small vessel vasculitis 'hypersensitivity angiitis'. Because of ambiguity, the term hypersensitivity angiitis was redefined by the Chapel Hill Consensus Conference in 1994 to describe patients with a small vessel vasculitis with primarily cutaneous involvement [1].

Aetiology and pathogenesis. A history of drug exposure or recent infection is frequently present in cases of CSVV. Circulating immune complexes can be identified in a large percentage of patients with CSVV.

Histopathology. Leukocytoclastic vasculitis with segmental inflammation in an angiocentric pattern, swelling of the endothelium, fibrinoid necrosis of vessel walls, extravasation of erythrocytes, and an infiltrate of neutrophils with karyorrhexis of nuclei (i.e. leukocytoclasia) are major features of CSVV (Figs 49.1 & 49.2). In superficial dermal papillary vessels, IgM or C3 perivascular deposits are often demonstrated in fresh lesions.

Clinical features. The skin lesions of CSVV typically arise as a simultaneous 'crop', resulting from the exposure to an inciting stimulus. They usually resolve within several weeks or a few months, although approximately 10% of patients will have recurrent disease at intervals up to years. The major cutaneous manifestation of CSVV is palpable purpura, ranging in size from 1 mm to several centimetres (Fig. 49.3). Sometimes macular in the early stages, such purpura may progress to a wide array of lesions including papules, nodules, vesicles, plaques, bullae or pustules, with secondary findings of ulceration, necrosis and post-inflammatory hyperpigmentation. Other cutaneous findings include livedo reticularis, oedema and urticaria. Lesions typically occur in areas prone to stasis, commonly including the ankles and lower legs [2–5], and typically sparing intertriginous regions. Although normally asymptomatic, pruritus, pain or burning may be experienced, as well as systemic symptoms including fever, arthralgia, myalgia and anorexia. The presence of symptoms affecting other organ systems should raise the suspicion of other vasculitides such as HSP, mixed cryoglobulinaemia, or CSVV associated with polyarteritis nodosa (PAN) or with WG. Renal involvement in patients with CSVV in one study led to reclassification as HSP, microscopic polyangiitis (MPA) or WG in 29 of 90 patients [6].

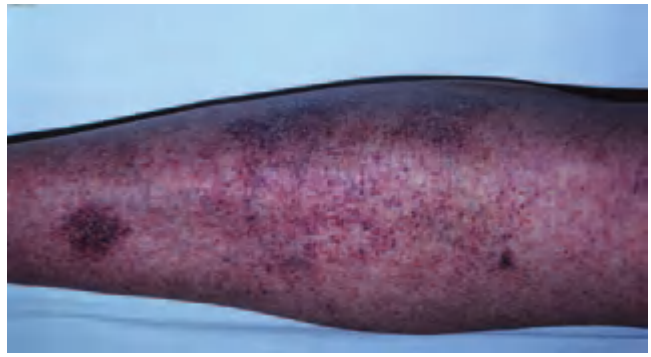

Fig. 49.3 Cutaneous small vessel vasculitis. Note the purpura on the anterior aspect of the leg.

Diagnosis. A thorough history and physical examination is essential for correct diagnosis of CSVV, with screening for infections, connective tissue disease, medication usage and cancer. Vasculitides with systemic manifestations must be ruled out, as CSVV is diagnosed by exclusion. Table 49.6 describes the evaluation of a patient with a suspected CSVV.

Table 49.6 Evaluation of a patient with suspected cutaneous small vessel vasculitis.

Confirm the clinical diagnosis histopathologically
Punch biopsy of lesion at the appropriate stage
Incisional biopsy for suspected larger vessel vasculitis

Assess the extent of the disease
General
- Myalgia
- Arthralgia
- Fever

Renal involvement
- Proteinuria
- Haematuria

Nervous system
- Central or peripheral
- Diffuse or local findings

Musculoskeletal involvement
- Non-erosive polyarthritis

Gastrointestinal system
- Abdominal pain
- Gastrointestinal bleeding

Pulmonary involvement
- Pleural effusion
- Pleuritis

Pericardial involvement
- Pericardial effusion

Attempt to establish the aetiology
Drugs
Infections
Diseases associated with immune complexes
- Connective tissue vascular diseases
- Malignancy
- Inflammatory bowel disease
- Chronic active hepatitis

Idiopathic (50%)

Treatment. Treatment of CSVV is typically unnecessary, as the disease is usually self-limiting. However, if any triggering agents are identified, such as a drug or infection, they should be removed or treated. Efforts to minimize stasis, such as use of compression hosiery and elevation of dependent areas, as well as the use of non-steroidal anti-inflammatory drugs (NSAIDs) and antihistamines, typically produce a decrease in symptoms [7]. Furthermore, oral corticosteroids at a dosage of 30–80 mg once daily, tapered over 2–3 weeks, often give effective symptom control, although no controlled trials have been carried out to evaluate the treatment of CSVV with oral corticosteroids. Corticosteroid use may be of particular benefit in cases with painful progressive cutaneous lesions. No data support the use of topical corticosteroids or antibiotics in CSVV, although such therapies are commonly used. Colchicine given at a dose of 0.6 mg twice daily has been shown to be of benefit by anecdotal evidence and open-label studies [8–10]. Similarly, the use of dapsone is based only on anecdotal or small case series, yet some believe that the use of dapsone along with colchicine may be advantageous in the treatment of CSVV [11–14]. In patients with disease refractory to the above therapies, cytotoxic agents may be considered. Such agents include azathioprine (typically at a dosage of 2 mg/kg/day; see also Chapter 72), methotrexate at a low dose of less than 25 mg/week, ciclosporin and cyclophosphamide [15–19]. Table 49.7 describes a therapeutic ladder for patients with CSVV.

Table 49.7 Therapeutic ladder for patients with cutaneous small vessel vasculitis.

Skin lesions alone
Supportive therapy (3)
Antihistamines (3)
Non-steroidal anti-inflammatory drugs (2)
Pentoxiphylline (3)
Colchicine (2)
Dapsone (2)

Ulcerative skin lesions alone
Thalidomide (3)
Low-dose weekly methotrexate (3)
Prednisone (2)

Systemic disease
Prednisone (2)
Azathioprine (2)
Cyclophosphamide (2)
Mycophenolate mofetil (3)
Ciclosporin (3)
Interferon-α (if hepatitis C-associated) (1)
Intravenous gammaglobulin (3)
Extracorporeal immunomodulation (3)

1, double-blind studies; 2, case series; 3, case reports.

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Drug-induced vasculitis

Definition. Vasculitis of various morphological types caused by drug ingestion. This is briefly discussed as a discrete topic as it is always important to consider medications and other ingested drugs as a possible cause of vasculitis. The clinical pattern is often that of a small vessel cutaneous vasculitis but other patterns occur. Drug-induced vasculitis is also considered in Chapter 73 with emphasis on causative agents.

Causes. Many drugs may cause vasculitis, and are listed in several reference sources [1–4]. A list of drugs that cause vasculitis is provided in (Chapter 73). Drugs that may cause skin necrosis and drug-induced purpura are discussed in Chapter 48. It is important to be aware that illicit drugs, drug excipients, vaccines and food additives can all cause vasculitis, as these may otherwise be overlooked as possible triggers. Cocaine in particular is recognized as a cause of systemic vasculitis.

Mechanisms. Most drug-induced vasculitis is of hypersensitivity type and presumed to be immune complex-mediated; it probably accounts for 10–20% of small vessel cutaneous vasculitis [4]. The evidence for this assumption is often indirect, although sulphonamide crystals have been observed in blood vessel walls [5]. This pattern occurs resulting from various antibiotics, diuretics, NSAIDs, anticonvulsants, antipsychotics, cardiac drugs such as diltiazem, and others [3,4]. Relatively recent drugs that can cause this pattern include zidovudine, various haemopoietic growth factors and etanercept.

The link between drugs and systemic vasculitis is often less clear. In some instances, such as leukotriene antagonists administered for asthma 'causing' CSS (Chapter 59), there is an argument that the asthma may simply have been an early feature of CSS and that the drug is not relevant. However, ANCA-positive (particularly MPO-positive) vasculitis has been convincingly linked with drugs such as hydralazine and thiouracils, and less commonly with penicillamine, allopurinol, minocycline and sulfasalazine [6–8]. Glomerulonephritis may occur related to propylthiouracil-induced ANCA-positive vasculitis. Hydralazine may also cause small vessel leukocytoclastic vasculitis.

Drug-induced lupus erythematosus is discussed in Chapter 56; drug-induced neutrophilic dermatoses are discussed later in this chapter.

Pathology. A small vessel vasculitis with a lymphocytic infiltrate and little leukocytoclasia, or the presence of some degree of tissue eosinophilia, are suggestive of the possibility of drug-induced vasculitis but are neither sensitive nor specific features. Serum complement levels are generally normal. ANCA may be positive (see above).

Clinical features. Drug-induced leukocytoclastic vasculitis presents with palpable purpura, petechiae, necrosis and urticarial lesions, indistinguishable from other causes of this pattern of vasculitis.

A serum sickness pattern of eruption, originally related to use of hyperimmune sera, is more commonly seen in relation to penicillins or sulphonamides, and less commonly with drugs such as thiouracil, phenytoin (hydantoin), phenylbutazone or streptokinase. The initial rash may be acral, with urticaria or purpura, followed by more generalized annular urticarial lesions. There may be fever, arthralgia, haematuria or proteinuria, lymphadenopathy and decreased complement levels.

Medium and large vessel vasculitides mimic the patterns described elsewhere in this chapter, although there may be atypical features such as eosinophilia or the fact that all lesions appear to be of similar duration. Some drug-induced cases resembling CSS have relatively minor respiratory symptoms compared with the idiopathic condition.

Treatment. Stopping any suspect drug is important and may be all that is required for cutaneous vasculitis. In cases with systemic disease, corticosteroids and even other immunosuppressive agents may be necessary. Supportive treatment such as compression hosiery may be required as in other forms of small vessel vasculitis. Renal function and urinalysis should be monitored.

In most instances, the causative drug should not be used again. It is also important to be aware of possible cross-reactions (notably between diuretics) when substituting a different drug.

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Henoch–Schönlein purpura

SYN. IGA IMMUNE COMPLEX VASCULITIS; ANAPHYLACTOID PURPURA; PURPURA RHEUMATOIDE

Definition. Originally described as a tetrad of palpable purpura, arthritis, gastrointestinal involvement and renal glomerular involvement [1,2], HSP is defined by the Chapel Hill Consensus Conference as a vasculitis affecting small vessels, involving deposition of IgA immune complexes, that characteristically involves the skin, gastrointestinal system and glomeruli with or without arthralgia or arthritis [3]. Unfortunately, many literature reports assume that all cutaneous small vessel vasculitis in children is HSP, rather than insisting on confirmed presence of IgA immune complexes, which causes great confusion. Although it can occur in adults, HSP is much more common in childhood; 75% of cases occur in children under 10 years old [4]. Furthermore, HSP occurs in various racial and ethnic groups [5,6].

History and nomenclature. Heberden first described HSP in 1801, in a young boy with abdominal pain, emesis, bloody stools, arthritis and a purpuric eruption. The eponymous term Henoch–Schönlein purpura was later applied after Johann Schönlein and Eduard Henoch described features of the vasculitis in the mid-19th century.

Aetiology and pathogenesis. Although some infections, such as those caused by group A β-haemolytic streptococci, were once thought to have a prominent role in the cause of HSP, no single pathogen has been linked as the major antigenic trigger [7]. However, IgA is thought to play a pivotal part in the pathogenesis of HSP, as increased levels of IgA in the serum, increased circulating immune complexes containing IgA, and increased deposition of IgA in blood vessel walls and in the renal mesangium are associated with HSP. In patients with HSP, IgA1 rather than IgA2 is the main IgA subclass deposited in the skin lesions [8]. Aberrant glycosylation of the hinge region of IgA1 may be an important factor in allowing the IgA to activate the alternative pathway of complement [9].

Histopathology. Biopsy specimens of the purpuric lesions demonstrate leukocytoclastic vasculitis. Direct immunofluorescence microscopy of lesional and perilesional skin reveals deposition of IgA, C3 and fibrin in dermal blood vessel walls.

Clinical features. Most commonly, HSP manifests at the outset with the classic findings of purpura, arthralgia and abdominal pain [7,9]. The cutaneous findings are typically erythematous urticarial papules, which may evolve within 24 h into palpable purpura with haemorrhage. Furthermore, urticaria, vesicles, bullae and necrotic ulcers may develop. Typically involving the extensor aspects of the limbs (especially elbows and knees) and buttocks in a symmetrical fashion, HSP may also affect the trunk and face. Usually fading within 5–7 days, crops of lesions can recur for a few weeks to several months. Although HSP is chronic in 5–10% of patients, the cutaneous involvement usually lasts between 6 and 16 weeks and then subsides. Rarely, gastrointestinal involvement and arthritis can occur in the absence of skin disease. Renal involvement with HSP is common, occurring in approximately 30–90% of patients. Most patients with renal involvement have mild disease, demonstrating only minimal proteinuria and haematuria. Only 1% of these patients progress to end-stage renal disease, although one-third to half of patients have renal abnormalities on long-term follow-up. Furthermore, gastrointestinal involvement is common, with gastrointestinal bleeding being demonstrated in 50–75% of patients with HSP. Arthritis is seen in about 75% of patients with HSP, most frequently affecting the knees and ankles.

Diagnosis. HSP is a clinical diagnosis, with confirmation by direct immunofluorescence and routine histology. Perivascular IgA deposits are characteristic of HSP and can help to distinguish it from other vasculitides including cutaneous small vessel vasculitis, WG, CSS and microscopic polyangiitis. IgA immune complexes are not specific to HSP, but can be seen in a variety of patients including those with SLE, endocarditis, dermatitis herpetiformis, alcoholism, IgA nephropathy, inflammatory bowel disease, ankylosing spondylitis, Sjögren's syndrome, rheumatoid arthritis, some cancers and in some drug hypersensitivity reactions [10–13]. No laboratory tests are specific for HSP, and although IgA ANCAs have been described in several adults with HSP, they are more typically negative [7].

Treatment. HSP is frequently self-limiting, the majority of patients fully recovering within several weeks or months, so treatment is mainly supportive. Although no data demonstrate the effectiveness of systemic corticosteroids in treating purpura, shortening the duration of HSP or decreasing the frequency of recurrences, they have been

shown in retrospective studies to be effective in the treatment of abdominal pain and arthritis. Dapsone (100 mg once daily) seems to shorten the duration of HSP as well as having a beneficial effect on the cutaneous lesions [7]. One trial proposed that factor XIII replacement may be useful in the treatment of abdominal pain and gastrointestinal bleeding associated with HSP, and another small trial demonstrated a decrease in the duration and severity of abdominal pain, as well as a decreased bleeding risk, with the use of ranitidine [14,15]. The presence of renal disease is the major factor determining the long-term morbidity and mortality associated with HSP [16]. Although no controlled trials have been conducted, data from several studies, as well as a case series, suggest a benefit from high-dose corticosteroids, either alone [17] or with cyclophosphamide and dipyridamole [18–20] in patients with progressive renal involvement associated with HSP. Furthermore, some case reports show that gastrointestinal involvement and cutaneous disease may be lessened, and rapidly progressive nephritis may be halted, by the use of intravenous immunoglobulin [21,22]. Patients with severe nephritis typically receive high-dose methylprednisolone at a dosage of 30 mg/kg once daily for 3 days followed by oral corticosteroids and an immunosuppressive drug such as azathioprine or cyclophosphamide [7]. NSAIDs have minimal, if any, benefit in the treatment of HSP, and should not be used in patients with renal involvement. The therapeutic ladder presented for cutaneous small vessel vasculitis is relevant for these patients as well.

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Urticarial vasculitis

SYN. CHRONIC URTICARIAL LESIONS AS A MANIFESTATION OF VENULITIS; UNUSUAL SYSTEMIC LUPUS ERYTHEMATOSUS-LIKE SYNDROME; HYPOCOMPLEMENTAEMIC VASCULITIS; HYPOCOMPLEMENTAEMIC–URTICARIA–VASCULITIS SYNDROME (HUVS)

Definition. Of patients with urticarial lesions, roughly 5–10% have urticarial vasculitis (UV) [1,2]. This is a chronic disease, which presents as urticarial lesions that most often occur on the trunk or proximal limbs, frequently with associated angioedema [3]. Lesions differ from those of simple urticaria in that individual lesions persist for greater than 24 h, often demonstrate purpura and post-inflammatory pigmentation, and cause symptoms of burning. Two types of UV have been described: UV associated with hypocomplementaemia, and UV without associated hypocomplementaemia (normocomplementaemic UV). Hypocomplementaemic UV is defined by the presence of anti-C1q precipitin and/or a decrease in the level of C1 [2,4]. Although all patients with hypocomplementaemic UV have these antibodies, this process must be distinguished from SLE, which can show similar laboratory findings [5,6]. Urticarial vasculitis may be described as a continuum starting with patients who have only skin lesions, progressing to patients with skin lesions and hypocomplementaemia, and finally to those who meet the criteria for SLE. UV without hypocomplementaemia has a slight female predominance, whereas hypocomplementaemic UV is seen almost exclusively in female patients.

History and nomenclature. Agnello *et al*. [7] first discussed UV, which was later described as a syndrome consisting of hypocomplementaemia, cutaneous vasculitis and arthritis by McDuffie *et al*. [8].

Aetiology and pathogenesis. UV is strongly associated with some connective tissue diseases, having a prevalence of 32% in patients with Sjögren's syndrome and 20% in patients with SLE [1]. Other associations include physical urticarias, hepatitis B or C, IgM or IgA gammopathies, serum sickness, colon cancer and drug ingestion. Some cases of UV have been reported in association with exercise or with exposure to ultraviolet light and cold. UV is thought to represent a type III hypersensitivity reaction, as circulating immune complexes may be demonstrated in up to 75% of patients [9]. Complement and immunoreactant deposition in vessel walls, with complement cascade activation in patients with UV [10], further supports this theory. Additionally, removal of immune complexes via plasmapheresis has been shown to briefly alleviate some symptoms of UV [11]. In hypocomplementaemic UV, autoantibodies are directed against the collagen-like region of C1q, resulting in a reduction of C1q in the serum with subsequent activation of the complement pathway [12].

Histopathology. Lesions of UV demonstrate leukocytoclastic vasculitis. Hypocomplementaemic UV shows a large number of interstitial neutrophils, rather than eosinophils, and may therefore be distinguished from normocomplementaemic UV [13,14].

Clinical features. Cutaneous lesions of both the hypocomplementaemic and normocomplementaemic forms of UV are erythematous indurated weals that may contain purpuric foci. Angio-oedema and macular erythema may also occur; livedo reticularis, nodules and bullae may be evident, and may also contain purpuric foci. Patients with the hypocomplementaemic form may have constitutional symptoms such as fever, malaise and myalgia, as well as other symptoms and signs including lymphadenopathy, hepatosplenomegaly, abdominal pain with or without nausea and/or diarrhoea, laryngeal oedema, dyspnoea, chronic obstructive pulmonary disease (COPD), glomerulonephritis, conjunctivitis, uveitis and episcleritis. Although hypocomplementaemic UV has features similar to SLE, signs such as ocular inflammation, angio-oedema and COPD distinguish the two processes.

Diagnosis. If urticarial lesions last for longer than 24 h (which can be determined by drawing around their margin), then by definition they are not ordinary urticaria and a skin biopsy should be performed. Pain rather than itch, or the presence of purpura, also suggest UV. History, physical examination and laboratory studies including C3, C4 and antinuclear antibody (ANA) should help to establish the extent of disease and to exclude underlying disease (e.g. hepatitis C), and to evaluate for SLE. Some patients may demonstrate an elevated erythrocyte sedimentation rate (ESR), hypocomplementaemia, a low-titre positive ANA and haematuria. A biopsy must be performed to confirm the diagnosis and to exclude other disorders such as atypical erythema multiforme.

Treatment. Although no single treatment is effective for all cases of UV, the majority of patients respond to systemic corticosteroids. However, other agents should be considered as steroid-sparing therapies [15–17]. Drugs that have been shown to be effective for the treatment of UV include dapsone (100–200 mg once daily), colchicine (0.6 mg twice to three times daily) and hydroxychloroquine (200 mg once to twice daily) [18–22]. Dapsone plus pentoxifylline (400 mg three times daily) has been used in one patient [23], and mycophenolate mofetil (2 g once daily) has been successfully tried as a maintenance therapy in two other patients [24]. Some patients require oral antihistamines for control of angio-oedema and urticaria-like lesions, in addition to the aforementioned therapies directed at the vasculitis.

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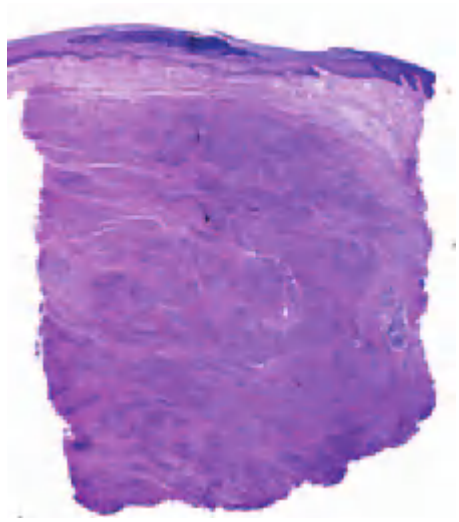

Fig. 49.4 Erythema elevatum diutinum. Low-power photomicrograph shows diffuse infiltrates throughout the entire dermis and areas of fibrosis. (Courtesy of Dr Omar Sangueza, Wake Forest University School of Medicine, Winston-Salem, NC, USA.)

Erythema elevatum diutinum

Definition. Erythema elevatum diutinum (EED) is a rare chronic cutaneous eruption that is most commonly seen in adults. It is characterized by fibrosing plaques with histological evidence of leukocytoclastic vasculitis.

History and nomenclature. The first patient with EED was described by Hutchinson and Bury in the 1880s. The condition was later named in 1894 by Radcliffe-Crocker and Williams.

Aetiology and pathogenesis. Although EED is thought to be related to immune complex deposition with subsequent inflammation, the exact aetiology is unknown. It has been associated with autoimmune diseases such as rheumatoid arthritis, coeliac disease, inflammatory bowel disease and type 1 diabetes mellitus. Associations with infections, including streptococcus, hepatitis and syphilis, have also been suggested [1–10]. Lesions characteristic of EED have been induced by injection of streptococcal antigen into the dermis [11–14]. EED has also been associated with HIV infection, as lesions of EED have responded to antiretroviral and dapsone treatment in HIV-positive patients [15–21]. In addition, EED has been associated with hypergammaglobulinaemia and IgA monoclonal gammopathies, as well as with myelodysplasia, pyoderma gangrenosum and relapsing polychondritis. The association with haematological disorders, such as multiple myeloma, is strong; however, EED may precede the haematological disease by several years [22].

Histopathology. Acute lesions of EED demonstrate leukocytoclastic vasculitis. Eosinophils may also be present in the upper and mid-dermis. Depending on the degree of oedema and infiltration into the dermis, unaffected collagen may be present just under the epidermis. Chronic lesions demonstrate fibrosis, capillary proliferation and infiltration of macrophages, plasma cells and lymphocytes. Cholesterol deposits in the intracellular and extracellular tissue may be present in older lesions. Figures 49.4 and 49.5 show the histopathology of EED.

Clinical features. Lesions of EED most commonly appear chronically in a symmetrical fashion over the dorsa of the hands, the knees, buttocks and Achilles tendons. They are red-violaceous, red-brown or yellowish papules, plaques or nodules. Occasionally, the face and ears are also affected by EED. Initially, the lesions are soft, but eventually they fibrose, and later leave atrophic scars. Although they are often asymptomatic, the lesions of EED may be painful. EED may last from 5 to 35 years, with crops of new lesions developing every few weeks to months.

Diagnosis. Although EED may be difficult to distinguish from cutaneous small vessel vasculitis histologically, the clinical presentation differs from that of other chronic small vessel vasculitis syndromes, allowing an accurate diagnosis. EED differs from Sweet's syndrome in the character of the lesions and their distribution, as well as in the histopathological features.

Treatment. Several medications have been used in the treatment of EED. Dapsone has a remarkable affect on EED [14], although discontinuation of dapsone is often

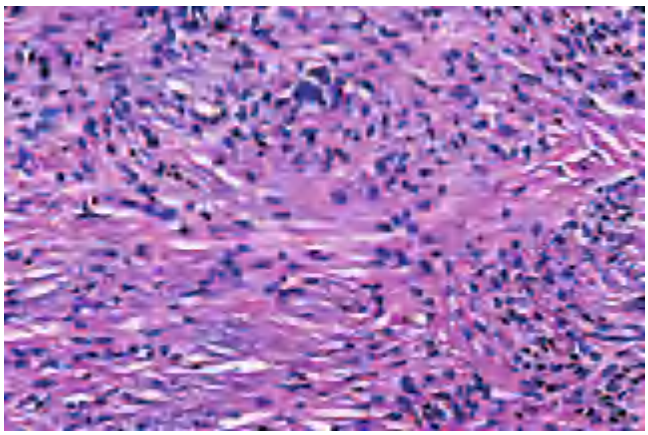

Fig. 49.5 Erythema elevatum diutinum. At higher magnification there is evidence of marked fibrosis and inflammatory infiltrates composed of lymphocytes, histiocytes, neutrophils and nuclear dust. (Courtesy of Dr Omar Sangueza, Wake Forest University School of Medicine, Winston-Salem, NC, USA.)

followed by swift return of the lesions. Niacinamide has also been used with good effect in EED [23]. High-potency topical or intralesional corticosteroids may minimize the size of lesions in patients with limited disease. Other therapies used for cutaneous small vessel vasculitis may also be effective in treating EED.

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Eosinophilic vasculitis

SYN. RECURRENT CUTANEOUS EOSINOPHILIC NECROTIZING VASCULITIS [1,2]

Definition. A relatively recently described and rare vasculitis consisting of a predominantly centripetal purpuric papular rash, angio-oedema, peripheral blood eosinophilia and an eosinophilic necrotizing vasculitis of small vessels.

History. This condition was recently distinguished from other eosinophilic vasculitides that affect medium to large vessels (CSS; see later in this chapter) and from eosinophilic disorders in which pruritic papules and/or angio-oedema may occur, such as hypereosinophilic syndrome, episodic angio-oedema with eosinophilia, dermatitis herpetiformis, Wells' syndrome, polymorphic eruption of pregnancy or drug eruptions. Association with connective tissue diseases and with rheumatoid arthritis has been reported [3,4].

Aetiology and pathogenesis. The cause is unknown. As in other strongly eosinophilic disorders, eosinophil cytokines such as IL-5, and toxic eosinophil granule proteins such as the major basic protein, have been demonstrated in serum and tissues, respectively, and presumably play a part in the tissue damage. Neutrophil elastase is prominent around vessels, and mast cell degranulation occurs. Eosinophilic vasculitis has also been reported in a patient with the hypereosinophilic syndrome; in this patient, CD40 (a glycoprotein of the TNF receptor family) was considered to be important in pathogenesis [5].

Histopathology. Shows fibrinoid deposition and necrosis of small dermal vessels with an infiltrate of eosinophils and absent or minimal leukocytoclasis. Small epidermal

vesicles containing eosinophils may be present. Immunoglobulin deposition is not a feature. This eosinophilic small vessel vasculitis is distinct from other vasculitides such as CSS, in which medium to large vessels are affected, and from most drug-induced vasculitis in which eosinophils are generally scanty.

Clinical features. Recurrent pruritic papules and urticarial lesions occur at any site, especially the head and neck, with angio-oedema of the face and extremities. Either sex and any age group may be affected. The course is long and recurrent but fever, arthralgia and visceral involvement are absent. Raynaud's phenomenon and digital gangrene were reported in a patient with cutaneous eosinophilic vasculitis associated with the hypereosinophilic syndrome [5], but they can also occur in the hypereosinophilic syndrome in the absence of cutaneous eosinophilic vasculitis [6].

Treatment. Oral corticosteroids, intermittently or as prolonged maintenance therapy depending on response, appear to be effective.

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Granuloma faciale

Definition. Granuloma faciale (GF) is an uncommon condition typified by asymptomatic cutaneous nodules occurring primarily on the face, with occasional extrafacial involvement. Granuloma faciale is limited to the skin, without any systemic manifestations. It is most common in males [1], typically in white people, although cases have been observed in populations of African or oriental ancestry [1,2].

History and nomenclature. Wigley [3] first described GF in 1945 as a type of eosinophilic granuloma, although it was distinguished from other eosinophilic granulomas by Lever and Leeper in 1950 [4]. Pinkus recommended the present name in 1952 [5].

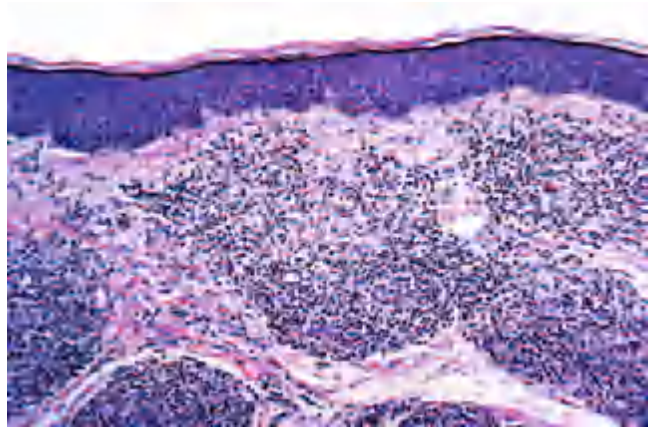

Fig. 49.6 Granuloma faciale. Low-power view shows perivascular nodular infiltrates within the dermis. (Courtesy of Dr Omar Sangueza, Wake Forest University School of Medicine, Winston-Salem, NC, USA.)

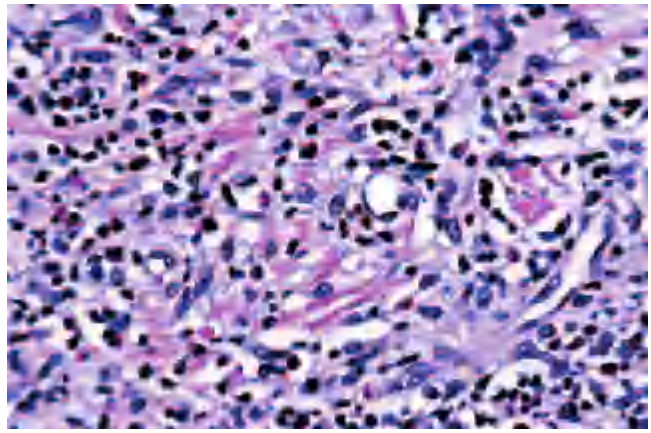

Fig. 49.7 Granuloma faciale. At higher magnification the infiltrate shows lymphocytes, eosinophils and a few neutrophils. (Courtesy of Dr Omar Sangueza, Wake Forest University School of Medicine, Winston-Salem, NC, USA.)

Aetiology and pathogenesis. Although the aetiology is somewhat unclear, GF is considered to be a histological variant of leukocytoclastic vasculitis with a prominent eosinophilic infiltrate, and confined to the skin [6]. Deposition of IgG in and around dermal vasculature has been demonstrated, lending some support to the idea that GF is immune complex-mediated [7].

Histopathology. GF is characterized by a mixed inflammatory infiltrate with a predominance of neutrophils and eosinophils, mainly in the upper half of the dermis but with occasional spread into the lower dermis and subcutaneous tissue (Figs 49.6 & 49.7). A band of normal collagen referred to as a 'Grenz' zone typically separates the inflammatory infiltrate from the epidermis and pilosebaceous appendages. Nuclear dust (fragmented neutrophil nuclei) may be observed near capillaries. Vasculitis, with

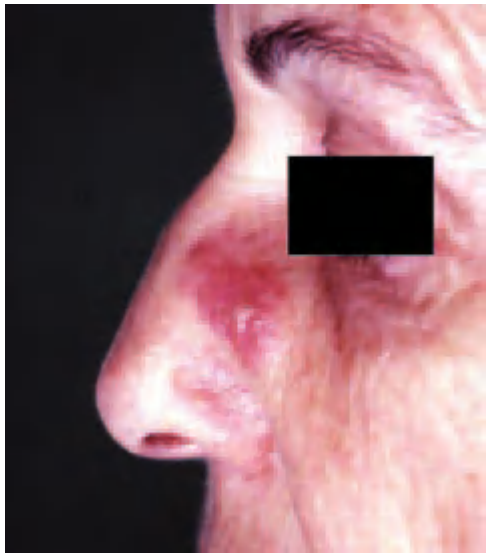

Fig. 49.8 Granuloma faciale. A reddish-brown plaque on the nose. (Courtesy of Dr G. Dawn, Cumberland Infirmary, Carlisle, UK.)

fibrinoid deposits near and within vessel walls, as well as haemorrhage, may be noted.

Clinical features. Lesions of GF are soft brown-red nodules or plaques that most commonly occur on the face (Fig. 49.8), although extrafacial involvement does rarely occur. The nodules or plaques are smooth, with prominent follicular orifices and telangiectatic surface changes or scaling. Lesions of GF never ulcerate. They are almost always asymptomatic, although some patients may describe itching, burning or pain associated with the lesions [8].

Diagnosis. A definitive diagnosis of GF requires clinically consistent lesions and a confirmatory biopsy. Although most laboratory studies are normal, mild peripheral blood eosinophilia may be present [9].

Treatment. A wide variety of treatment methods, both surgical and medical, have been used to treat GF. Examples include dermabrasion [10], laser treatments using both argon [11] and carbon dioxide (CO_2) lasers [10], electrosurgery [10], cryosurgery [12] and psoralen with ultraviolet A (PUVA) [13], as well as medical treatments with dapsone [14], clofazimine [15], antimalarial medications [16] and intralesional or systemic corticosteroids [9,16]. A therapeutic ladder for GF is depicted in Table 49.8.

Table 49.8 Therapeutic ladder for granuloma faciale.

Intralesional corticosteroids (3)
Cryosurgery ± intralesional corticosteroids (3)
Clofazimine (3)
Dapsone (3)
Surgery (3)
Laser (3)

1, double-blind studies; 2, case series; 3, case reports.

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Acute haemorrhagic oedema of childhood

SYN. HAEMORRHAGIC OEDEMA OF CHILDHOOD; ACUTE HAEMORRHAGIC OEDEMA OF INFANCY; FINKELSTEIN'S DISEASE; SEIDLMAYER'S SYNDROME; PURPURA EN COCARDE AVEC OEDEME; POST-INFECTIOUS COCKADE PURPURA

Definition. Acute haemorrhagic oedema of childhood (AHEC) is a rare disorder, which has almost exclusively cutaneous manifestations. It most commonly occurs in children under 2 years old. Patients with AHEC often have recently had an upper respiratory infection and/or have been treated with antibiotics. Clinical features include petechiae and ecchymoses of the head and distal extremities.

History and nomenclature. Snow first described AHEC in 1913.

Aetiology and pathogenesis. Infections, drugs or vaccines may trigger AHEC, which may be a variant of childhood cutaneous small vessel vasculitis [1,2].

Histopathology. Leukocytoclastic vasculitis is evident in lesions of AHEC.

Clinical features. Non-tender facial oedema may be the presenting sign of AHEC lesions, which are often asymmetrical. There is sudden development of tender oedematous petechiae and ecchymoses on the head and distal extremities, as well as large annular, coin-shaped or targetoid lesions that may later develop into bullae or necrotizing lesions. Lesions of AHEC start distally and spread proximally, sometimes involving the scrotum in males. Clinically, patients with AHEC are typically medically stable, although they may be febrile. Although AHEC may rarely involve joints, the gastrointestinal tract or the kidneys with vasculitic manifestations, the typical course of AHEC is a disorder that lasts 1–3 weeks with no persistent adverse effects following resolution [1,2].

Diagnosis. AHEC may be diagnosed only after meningococcaemia, erythema multiforme, UV, cutaneous small vessel vasculitis and Kawasaki disease have been ruled out.

Treatment. Wound care is the only treatment necessary for patients with AHEC.

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Nodular vasculitis

SYN. ERYTHEMA INDURATUM OF BAZIN AND OF WHITFIELD

Definition. Nodular vasculitis (NV) is a chronic relapsing lobular panniculitis with septal vasculitis. It is characterized by a vasculitis of subcutaneous arteries and veins, with subsequent ischaemia of subcutaneous tissue which results in clinical suppuration. The cause may be a hypersensitivity reaction to an antigenic trigger such as a bacterial infection. It occurs primarily in middle-aged women, and is manifest as tender nodules or plaques on the legs that may later progress to ulceration.

History and nomenclature. Erythema induratum of Bazin was initially described by Bazin in 1861 as indurated plaques on the legs of women of middle age [1]. In 1900, French dermatologists described an association between erythema induratum and tuberculosis [2], although British physicians reported similar patients without evidence of tuberculosis at approximately the same time, a pattern which was later designated 'Whitfield's erythema induratum' [3–5]. In the middle of the 20th century, American physicians suggested the term nodular vasculitis for Whitfield's erythema induratum, which was thought to be distinct from erythema induratum of Bazin [6]. Recently, there has been a move to consider erythema induratum of Bazin and nodular vasculitis as the same entity, regardless of aetiology [7–9].

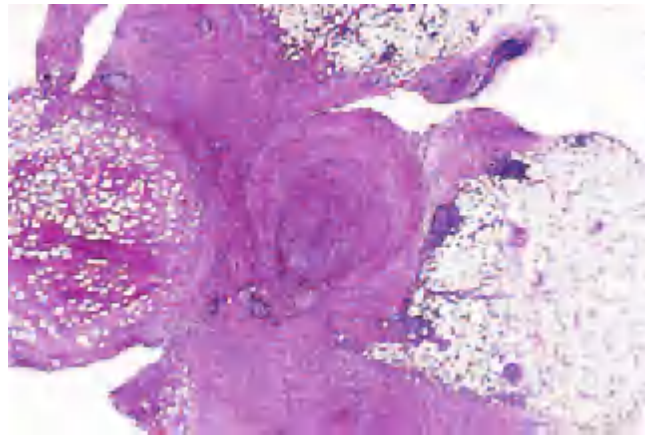

Fig. 49.9 Nodular vasculitis. Lobular panniculitis with prominent inflammation. Note the alteration of a vascular structure in the middle of the photograph. (Courtesy of Dr Omar Sangueza, Wake Forest University School of Medicine, Winston-Salem, NC, USA.)

Aetiology and pathogenesis. Several antigenic triggers have been implicated as the source for the hypersensitivity reactions with resultant subcutaneous vasculitis and lobular panniculitis in NV. These include bacterial infections, such as streptococcal or mycobacterial infections, and drugs. The pathogenesis may be similar to that of cutaneous small vessel vasculitis, but with septal vessels in the panniculus as the target.

Histopathology. Controversy exists as to whether arteries, veins or both are affected in NV. Regardless of the type of vessel involved, the early changes are of leukocytoclastic vasculitis of vessels in the subcutaneous tissue leading to ischaemic changes, followed by inflammation and injury to lipocytes [10]. The resulting occlusion leads to ischaemia and necrosis of fat lobules that may eventually involve the overlying dermis. Early in the disease process, the necrotic subcutaneous fat demonstrates fat cysts bordered by a finely granular eosinophilic substance with pyknotic nuclei. Later, foamy histiocytes encircle the necrotic areas (Figs 49.9 & 49.10).

Clinical features. NV is manifest as tender, dusky, often suppurative, nodules or plaques on the posterolateral aspect of the legs. It is typically seen in healthy, middle-aged, sometimes obese, women who may have venous stasis. Patients often have 'thick' calves with erythro-

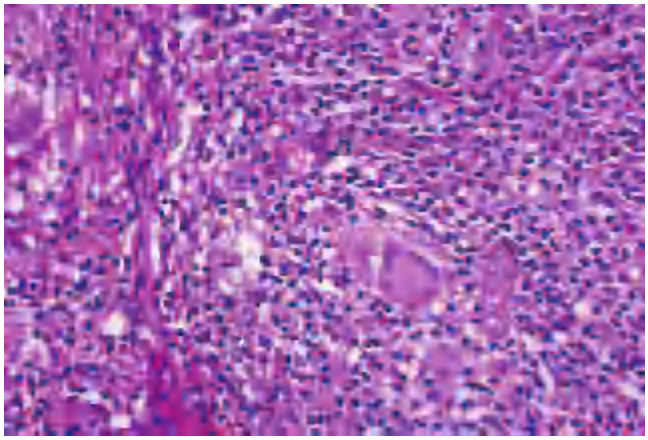

Fig. 49.10 Nodular vasculitis: the inflammatory infiltrate within the vessel wall is composed of lymphocytes and histiocytes, some of them multinucleated. (Courtesy of Dr Omar Sangueza, Wake Forest University School of Medicine, Winston-Salem, NC, USA.)

cyanosis and perifollicular erythema. Lesions may be unilateral, are often inflamed and may progress to ulceration. The lesions of NV heal slowly, sometimes leaving an atrophic scar. The course of NV is chronic, with relapses typically occurring over several years. Nodular vasculitis may sometimes be seen in men, with unilateral nodules or plaques involving the anterior aspect of the thighs and legs, and other locations.

Lesions that have previously been termed 'erythrocyanosis with nodules' may have been examples of NV, or alternatively a pattern of perniosis (Chapter 23). Equestrian panniculitis is a type of perniosis.

Diagnosis. NV is a clinicopathological diagnosis, which requires deep incisional biopsy of active lesions. In cases where a tuberculous aetiology is suspected, a tuberculin skin test and chest X-ray should be performed. Evaluation is otherwise similar to that for patients with cutaneous small vessel vasculitis.

Treatment. In patients in whom tuberculosis is demonstrated, at least a 9-month course of triple-agent antituberculosis therapy should be given (Chapter 28) [11,12]. In non-tubercular cases, supportive measures, such as compression hosiery, bed rest and NSAIDs are recommended. Systemic corticosteroids may also be considered, as well as potassium iodide, which has been reported as an effective treatment of NV [13,14]. Other treatments outlined for patients with small vessel vasculitis might also be appropriate for patients with NV. The treatment of NV is shown in Table 49.9.

Table 49.9 Treatment of nodular vasculitis.

Tuberculosis present
Triple-agent antituberculosis therapy for a minimum of 9 months
Tuberculosis not present
Palliative treatments
• Compression hosiery
• Bed rest
• Non-steroidal anti-inflammatory drugs
Systemic corticosteroids
Potassium iodide
Other treatments used to treat patients with small vessel vasculitis (Table 49.7)

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Polyarteritis nodosa

SYN. PERIARTERITIS NODOSA

Definition. A disease typically affecting medium-sized arteries, PAN is a segmental vasculitis. Affected patients may have several signs and symptoms involving multiple organ systems. Ischaemia, infarcts and haemorrhage result from the vasculitis and lead to end-organ damage in patients with PAN. The incidence of PAN is 4.6–9 per million per year [1], with men more commonly affected than women. PAN has been described in all racial groups [2–4].

History and nomenclature. Kussmaul and Maier [5] originally described 'periarteritis nodosa' in 1866. The disease was termed 'polyarteritis nodosa' in 1903 after Ferrari recognized its multivessel involvement as well as its transmural inflammation.

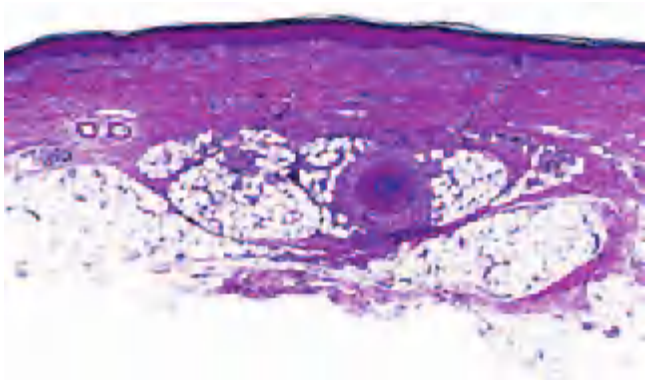

Fig. 49.11 Polyarteritis nodosa. Note the characteristic targetoid alteration of a vascular structure within the subcutaneous tissue. (Courtesy of Dr Omar Sangueza, Wake Forest University School of Medicine, Winston-Salem, NC, USA.)

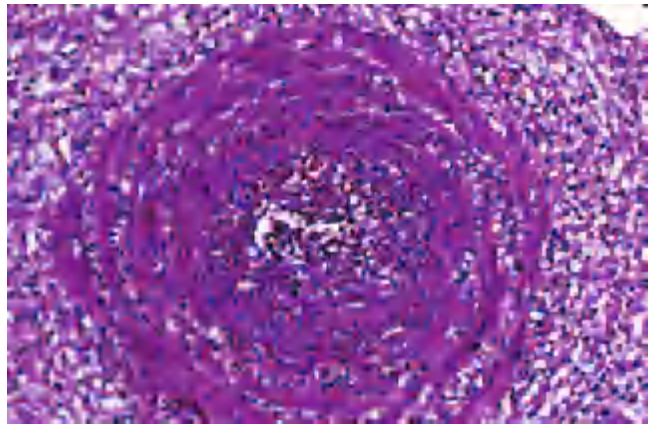

Fig. 49.12 Polyarteritis nodosa. Higher magnification demonstrates the partial destruction of the vascular wall and the inflammatory infiltrate composed of lymphocytes and neutrophils. (Courtesy of Dr Omar Sangueza, Wake Forest University School of Medicine, Winston-Salem, NC, USA.)

Aetiology and pathogenesis. Patients with PAN commonly have underlying infections caused by organisms such as streptococci, hepatitis B or C viruses. Approximately 5–7% of patients with PAN have associated hepatitis B virus infection, although incidences as high as 10–54% have been reported [1,6]. Other associations with PAN include SLE, inflammatory bowel disease, hairy cell leukaemia, familial Mediterranean fever and Cogan's syndrome. Although it has yet to be proven, one theory about the pathogenesis of PAN is that it may be related to the increased shear stress that occurs at arterial branch points, causing up-regulation of endothelial inflammatory factors [7–10]. There may also be a greater number of macrophages in the tunica intima at these stress points [11,12], adding to the susceptibility of endothelial cells at arterial branch points to inflammatory activity.

Histopathology. Biopsy material shows an inflammatory necrotizing obliterative arteritis affecting small and medium-sized arteries, with focal panniculitis. Aneurysms can form as blood vessel walls become weak and potentially necrotic secondary to nodose swellings caused by focal vasculitis. The most severely affected arterial branch points of vessels may rupture, leading to luminal thrombosis and obliteration, thus resulting in widespread distal tissue ischaemia and ultimately necrosis (Figs 49.11 & 49.12).

Clinical features. The distribution of vasculitic lesions of PAN is variable, accounting for the great variety of reported signs and symptoms. Constitutional symptoms are common, including fever, weight loss, arthralgia and malaise; more specific signs and symptoms occur relating to affected organ systems, such as congestive heart failure, hypertension, abdominal pain, orchitis and mononeuritis multiplex. Typically, there is no pulmonary involvement in PAN. Although not specific to PAN, arteriography may demonstrate multiple dilatations along medium-sized arteries in the renal, hepatic and visceral vasculature. Up to 60% of patients with PAN have cutaneous manifestations [13], usually a subcutaneous nodule or group of nodules along the course of a blood vessel. Typically seen around the knee, anterior lower leg and dorsum of the foot, these 5–10-mm nodules may be tender, pulsatile or secondarily ulcerated, with either normal or erythematous overlying skin. Other cutaneous findings include livedo reticularis with or without ulceration, digital gangrene and 'punched-out' ulcers. Cutaneous lesions in patients with PAN are depicted in Figs 49.13 and 49.14.

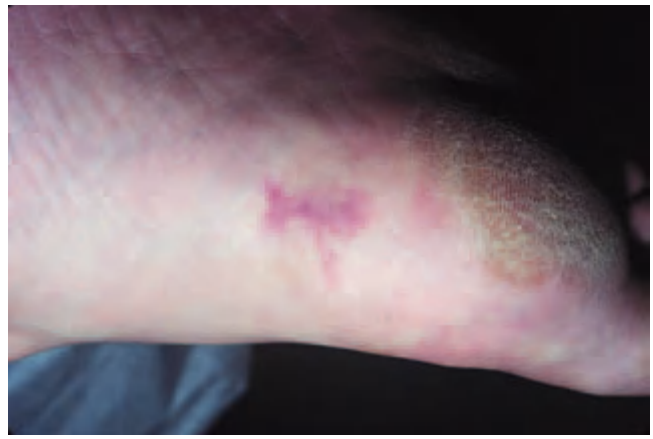

Fig. 49.13 Polyarteritis nodosa. Note the location of the lesion on the patient's foot.

Diagnosis. Although patients may have laboratory abnormalities such as leukocytosis with neutrophilia, thrombocytosis, normocytic anaemia, hypergammaglobulinaemia and cryoglobulinaemia, as well as haematuria,

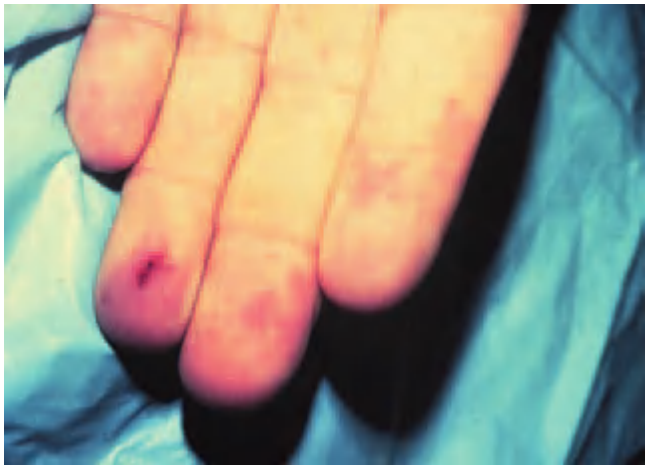

Fig. 49.14 Polyarteritis nodosa. Multiple lesions on the fingers.

proteinuria and the presence of casts in the urine, the diagnosis of PAN is best made from muscle or sural nerve biopsy. The sensitivities of the muscle and sural nerve biopsy specimens are 60% and 70%, respectively, in cases of symptomatic muscle involvement and nerve involvement demonstrated electrophysiologically [14,15]. Renal biopsy specimens (when urinalysis is abnormal) and angiography and/or aortography demonstrating pathognomonic aneurysmal dilatation of vessel walls may also be used to help establish a diagnosis of PAN. Although very sensitive, skin biopsy is not specific, and is not sufficient to establish the diagnosis of PAN. The P-ANCA is positive in 20% of cases of PAN, and is more commonly seen in MPA or CSS. A positive C-ANCA is typically associated with WG, CSS or MPA but not with PAN.

Treatment. Treatment with systemic corticosteroids remains the mainstay of therapy for systemic PAN. The use of corticosteroids has improved the 5-year survival in patients with PAN from 10–13% to 48–57% [1,4,16,17]. A regimen of 1–2 mg/kg/day of prednisone or prednisolone is typically used for patients with PAN with visceral involvement, and is eventually tapered to a maintenance regimen. The response to treatment may be evaluated by sequential measurement of the ESR. Although combination therapy of corticosteroids and cyclophosphamide may improve survival in patients with severe PAN [18], no controlled trials have demonstrated the level of absolute benefit necessary for cyclophosphamide to become the routine adjunct to corticosteroid therapy [19]. Plasma exchange combined with IFN-α_2 and/or vidarabine is an effective treatment for patients with PAN associated with hepatitis B infection. Some success has been reported with the use of these antiviral treatments without concomitant immunosuppression [20–22]. Corticosteroids should only be used initially on a short-term basis in patients with hepatitis B-associated PAN because of the possibility of viral replication [6,23].

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Microscopic polyangiitis

SYN. MICROSCOPIC POLYARTERITIS NODOSA; MICROSCOPIC POLYARTERITIS

Definition. MPA is a systemic vasculitis affecting blood vessels ranging in size from capillaries to medium-sized arteries. In some instances, there is only venous involvement with MPA. MPA is strongly associated with lung involvement (primarily alveolar haemorrhage) and crescentic glomerulonephritis [1]. The incidence of MPA is 6–8 per million per year [2].

History and nomenclature. Patients demonstrating signs of PAN without cutaneous nodules were first described by Wohlwill in 1923, and then by Arkin in 1930. In 1948, articles were published that distinguished MPA from PAN. In 1994, MPA was termed microscopic polyangiitis instead of microscopic polyarteritis by a consensus conference because of the lack of arterial involvement in some patients and the involvement of vessels other than arteries [1].

Aetiology and pathogenesis. The exact pathogenesis of MPA is poorly understood, although it is considered a pauci-immune vasculitis because of the relative absence of immunoglobulins or complement in affected vessel walls [3–7]. P-ANCA may have a role in the aetiology by activating neutrophils and monocytes via interactions with enzymes on the surface of or directly around endothelial cells [8], initially causing direct injury to the vessel endothelium. This is demonstrated in early findings of pauci-immune small vessel vasculitides in which there is fibrin accumulation in the subendothelium [7,9] as well as lysis of leukocytes within the vascular space [9] associated with endothelial injury. Products from neutrophils and monocytes (such as serine proteinases and metalloproteinases) may be inactivated at distant sites [10], accounting for the large degree of local tissue injury in lesions of MPA. Direct interactions between these cells and the endothelium may also explain the predilection of the disease for small rather than larger sized vessels. In some patients, there is a relationship between MPA and infection with either hepatitis B or C viruses [11,12].

Histopathology. Histological specimens from MPA lesions demonstrate segmental vascular necrosis. Neutrophils and monocytes permeate vessel walls, causing leukocytoclasia, accumulation of fibrin and haemorrhage. Biopsy specimens from lesions of palpable purpura demonstrate leukocytoclastic vasculitis.

Clinical features. Many patients with MPA initially experience constitutional symptoms, including fever, weight loss, myalgia and arthralgia. These may be present for several years before the onset of the pulmonary and renal disease that often occurs in patients with MPA. Between 79% and 90% of patients with MPA have necrotizing glomerulonephritis, and 25–50% have lung involvement, sometimes leading to pulmonary–renal syndrome [13], and leading to pulmonary haemorrhage in up to 29% of patients [14–16]. Symmetrical peripheral neuropathies or mononeuritis multiplex may occur in patients with MPA, but less commonly than in individuals with PAN. Although nearly half of patients have palpable purpura upon presentation [17], the presence of nodules should raise the suspicion of PAN, WG or CSS.

Diagnosis. MPA must be clinically distinguished from other vasculitides such as WG, CSS, CSVV or PAN. In patients with MPA, positive P-ANCA and rheumatoid factor tests are common, unlike in patients with PAN. About 50% have a positive MPO P-ANCA, and 30% a positive PR3 C-ANCA. Some authors claim that the presence of small vessel vasculitis in the skin can distinguish MPA from PAN, stating that cutaneous small vessel vasculitis lesions do not typically occur in patients with PAN, although this is controversial. When palpable purpuric lesions are present in the absence of constitutional symptoms, patients are more likely to have CSVV than MPA, although with constitutional symptoms the differential diagnosis can also include WG and CSS. Small vessel vasculitis and systemic symptoms in the absence of granulomatous inflammation or asthma suggests MPA instead of CSS or WG [1].

Treatment. Initially, patients with MPA should be treated with high-dose corticosteroids if renal and/or pulmonary disease is present. Cytotoxic agents (e.g. cyclophosphamide) are sometimes used as corticosteroid-sparing agents when treating patients with severe disease, although strong evidence-based support, such as that supporting their use in patients with WG, is lacking. The course of MPA is characterized by relapses, in contrast with that of PAN [18].

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Cutaneous polyarteritis nodosa

SYN. BENIGN CUTANEOUS PERIARTERITIS NODOSA; LIVEDO WITH NODULES

Definition. Cutaneous polyarteritis nodosa (C-PAN) is a variant of PAN that is limited primarily to the skin. Controversy exists over whether or not C-PAN simply represents an early or more limited form of PAN [1,2]. The course of C-PAN is typically benign and relapsing, despite the presence of moderate constitutional symptoms and mild nerve and muscle involvement in some patients [3,4].

History and nomenclature. C-PAN was first described by Lindberg in 1931 [5] as a more benign variant of systemic PAN that did not have visceral involvement.

Aetiology and pathogenesis. Infections such as *Streptococcus* (particularly in children), parvovirus B19, HIV and hepatitis B virus, as well as inflammatory bowel disease (IBD), have been associated with C-PAN [6], although the exact aetiology is unknown. Immunological mechanisms are thought by some authors to be involved only in the pathogenesis of systemic PAN, and not in the development of C-PAN [7].

Histopathology. Early in the course of C-PAN, there is a predominantly neutrophilic inflammatory infiltrate in the walls of medium-sized arteries and arterioles of septae in the upper portions of the subcutaneous fat. The involved vessels classically demonstrate a target-like appearance resulting from an eosinophilic ring of fibrinoid necrosis. Later in the disease process the infiltrate becomes less neutrophilic, consisting predominantly of lymphocytes and histiocytes. Complement and IgM deposits in vessel walls of lesions of C-PAN from some patients may be demonstrated by direct immunofluorescence [8]. Unlike those of systemic PAN, lesions of C-PAN do not typically involve arterial bifurcations.

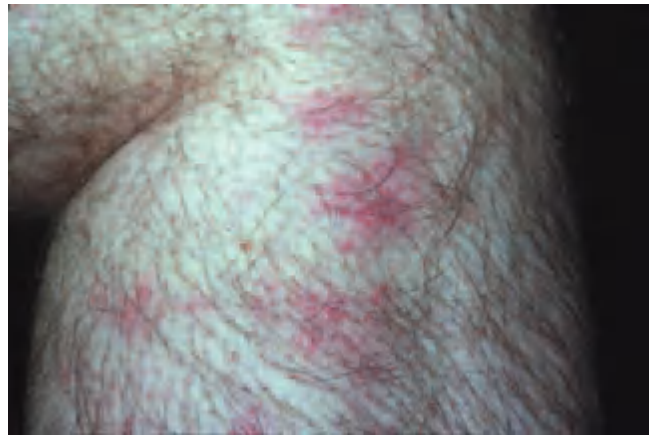

Fig. 49.15 Cutaneous polyarteritis nodosa. Erythematous lesions on the leg.

Clinical features. Although some patients with C-PAN may report constitutional symptoms as well as chronic mild involvement of both muscles and nerves [3,4], cutaneous manifestations are the most striking feature of the disease. Dermal or subcutaneous nodules are most commonly located on the lower legs near the ankles (Fig. 49.15) and may extend proximally to the thighs, buttocks, arms or hands. Patients may report tenderness associated with the nodules, which may ulcerate, or more commonly demonstrate livedo reticularis, which may be necrotizing. Gangrene of the digits can ultimately occur, most commonly in children with C-PAN [9,10].

Diagnosis. Patients with necrotizing lesions of livedo reticularis must be evaluated for vasculitis or vasculopathy (e.g. antiphospholipid antibody syndrome, cholesterol emboli or other factors that can produce non-vasculitic vessel occlusion; see Chapter 48). If nodules are present, they should be biopsied by incisional biopsy, as a panarteritis of muscular arteries would confirm a diagnosis of C-PAN. The distinction from systemic PAN requires patient evaluation by history, physical examination, screening laboratory tests and ongoing follow-up.

Treatment. Although no double-blind prospective trials have been performed, several reports suggest that NSAIDs and salicylates can be an effective treatment for symptoms of C-PAN [11]. High-dose corticosteroids, with the dose subsequently tapered off, may occasionally be necessary for some patients [12,13]. Although no controlled trials have been performed, penicillin is often

used for treatment and prophylaxis in children with C-PAN because of the strong association with streptococcal infection. Other treatments documented in anecdotal reports include dipyridamole, sulfapyridine, pentoxifylline and dapsone in patients with C-PAN. A low-dose weekly methotrexate regimen (7.5–20 mg/week) has been successful in some patients with skin lesions unresponsive to corticosteroids intralesionally and orally [14]. Anecdotally, a low-dose weekly methotrexate regimen and gradient support hosiery are adequate therapy for the majority of patients with C-PAN.

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Wegener's granulomatosis

Definition. WG is classically described as a triad consisting of systemic small vessel vasculitis, necrotizing granulomatous inflammation of both the upper and lower respiratory tracts, and glomerulonephritis. If not treated, WG can lead to end-organ damage and/or death. Affecting males and females equally, the incidence of WG is 5–10 per million per year, with the majority of cases occurring in white people [1–3]. The average age at onset is 40 years [4].

History and nomenclature. The first patient with WG was described in 1931 by Klinger, but the disease was later defined in 1936 by Wegener who described three patients.

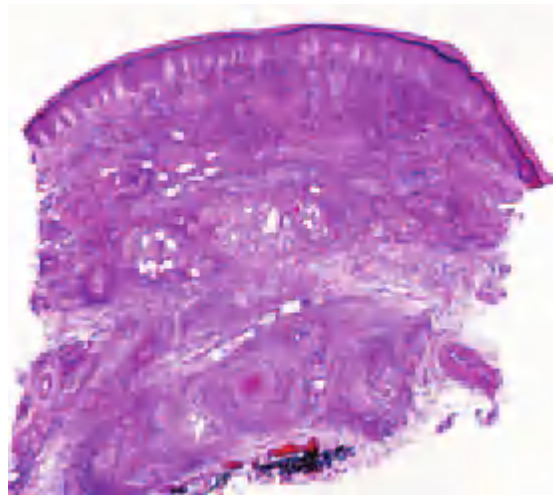

Fig. 49.16 Wegener's granulomatosis. There is extensive leukocytoclastic vasculitis involving the entire dermis. (Courtesy of Dr Omar Sangueza, Wake Forest University School of Medicine, Winston-Salem, NC, USA.)

Aetiology and pathogenesis. Although the pathogenesis of WG is not well understood, it is believed that it may involve an amplified immune response to an antigenic stimulus, such as an infection. One theory regarding the pathogenesis of WG is that neutrophils are activated via cytokines or apoptosis and degranulate, expressing cytosolic proteins on their surfaces and releasing harmful oxygen radicals as well as chemoattractants [5–8]. This enables ANCA to bind cytoplasmic antigens such as PR3, at which C-ANCA are directed, and MPO, at which P-ANCA are directed. Activated neutrophils then attract additional neutrophils and damage vascular endothelium by attaching to blood vessel walls [9–11]. Another theory about the role of ANCA in the pathogenesis of WG is that activated neutrophils located at damaged blood vessels release antigens, causing a secondary ANCA response [12].

Histopathology. Biopsy specimens of skin lesions usually show a perivascular lymphocytic infiltrate, but this is non-specific and may not be directly related to the pathogenesis of WG [13]. Leukocytoclastic vasculitis and/or granulomatous inflammation may be present in up to 50% of skin biopsy specimens (Figs 49.16 & 49.17), although granulomatous inflammation around vessels or palisading necrotizing granulomas are uncommonly demonstrated.

Clinical features. Features of the classic triad of WG are not always all present early in the course of the disease, which can make the diagnosis difficult. Furthermore, presentation without involvement of the classical sites can occur. However, in up to 80% of patients, symptoms involving the upper or lower respiratory tract are present

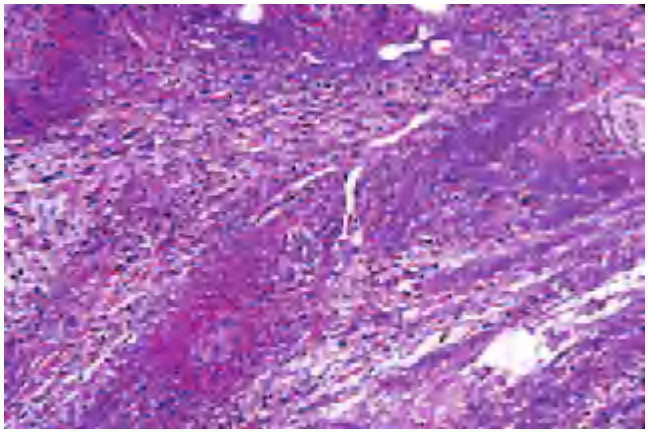

Fig. 49.17 Wegener's granulomatosis. Note the extensive area of collagen degeneration, destruction of vessels and mixed inflammatory infiltrate. (Courtesy of Dr Omar Sangueza, Wake Forest University School of Medicine, Winston-Salem, NC, USA.)

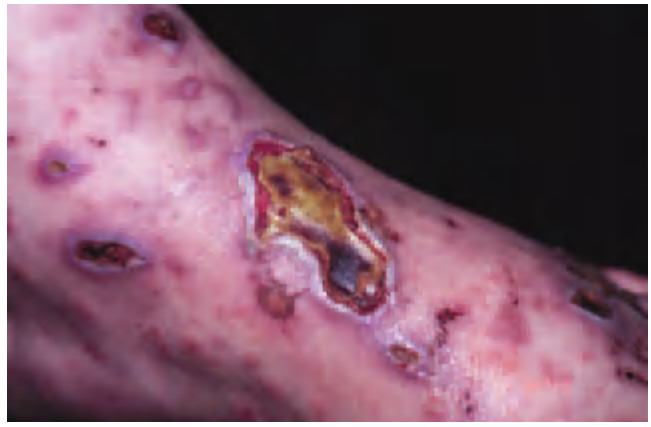

Fig. 49.18 Wegener's granulomatosis: ulcerated lesions.

[14], and at presentation approximately 73% of patients will have nasal, sinus, tracheal or ear involvement. Less than half of all patients with WG present with pulmonary infiltrates or nodules. Renal disease is initially present in only 18% of patients, although approximately 77% will eventually develop glomerulonephritis [15]. Although 40% of patients with WG will eventually manifest skin findings, cutaneous manifestations and oral ulcers are only found in 13% and 6% of patients at initial presentation, respectively [15]. The most common cutaneous manifestation of WG is palpable purpura, although others include tender subcutaneous nodules, papules, vesicles and petechiae, as well as pyoderma gangrenosum-like lesions. It is thought that patients previously diagnosed as having 'malignant pyoderma' may actually have had lesions secondary to WG. Papulonecrotic lesions, most commonly on the limbs but also occurring on the face and scalp, are ulcerated papules that may be mistaken for rheumatoid nodules. However, these non-specific lesions (also found in CSS, rheumatoid arthritis, SLE, IBD and some infectious states) differ from rheumatoid nodules in that they ulcerate and also that they are mobile within the dermis [16–18]. Oral ulcers are the second most common mucocutaneous sign of WG, and it has been suggested that 'strawberry' gingival hyperplasia is pathognomonic [19]. The upper respiratory tract is most commonly affected by WG, with otitis, epistaxis, rhinorrhoea and sinusitis as common presenting signs and symptoms. A saddle-nose deformity may result from necrotizing granulomas of the nasal mucosa. Lower respiratory signs and symptoms include cough, dyspnoea, chest pain and haemoptysis. An example of ulcerative lesions in a patient with WG is shown in Fig. 49.18.

Diagnosis. WG must be differentiated from CSS. Important differences between these two larger vessel vasculitides are the lack of upper respiratory involvement and of severe glomerulonephritis in CSS, and the presence of asthma and eosinophilia in CSS but not in WG. Laboratory findings in WG include elevated ESR and C-reactive protein, anaemia, leukocytosis and positive rheumatoid factor [2,3]. Although a small percentage of patients have a positive P-ANCA or no ANCA reactivity, up to 80% of patients have a positive C-ANCA (with anti-PR3 specificity) [20]. Those few patients with no ANCA reactivity may well have localized WG and a better prognosis when compared with those who are ANCA-positive [21,22]. Nodular densities from necrotizing granulomatous inflammation of lung tissue and pulmonary haemorrhage may be present on chest radiography; almost any change on chest radiography may represent WG, with the exception of hilar adenopathy [23].

Treatment. WG is most successfully treated using a combination of corticosteroids and cytotoxic agents, such as cyclophosphamide. This combination of therapy results in a significant resolution of symptoms in more than 90% of patients, with remission in 75%, and 87% surviving between 6 months and 24 years [15]. However, the median survival for untreated WG remains only 5 months, and this prognosis is not appreciably altered by treatment with corticosteroids given as a monotherapy. Long-term treatment with trimethoprim-sulfamethoxazole (co-trimoxazole) has been documented to reduce the incidence of relapses, although side effects are relatively common [24]. The benefit of this treatment may be because of a decrease in respiratory infections (it is known that nasal staphylococcal carriage increases the risk of relapse), although such infection was not a consistent factor in patients with relapses in this study.

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Churg–Strauss syndrome

SYN. ALLERGIC GRANULOMATOSIS; VASCULITIS OF CHURG AND STRAUSS

Definition. CSS is a rare vasculitis affecting multiple organ systems. The majority of patients demonstrate cutaneous findings while in the active phase of the disease. The disease is characterized by asthma, peripheral blood eosinophilia and necrotizing vasculitis with extravascular granulomas.

History and nomenclature. In 1939, the first patients with an allergic disease not classified as periarteritis nodosa were described by Rackermann and Greene. Churg and Strauss later described the syndrome and its histopathological characteristics in 1951.

Aetiology and pathogenesis. The aetiology of CSS is unknown, although vaccination, desensitization and rapid discontinuance of corticosteroids have been associated with the onset of symptoms [1]. Leukotriene antagonists have been associated with development of CSS (Chapter 59). The pathogenesis of CSS is not completely understood. Immune complex deposition was once thought to be the mechanism of vasculitis in CSS, although eosinophils, mediated by a Th2 response, are now thought to be the effector cells in the disease [2]. Serum levels of eosinophil cationic protein, which is a marker of eosinophil activation, often correspond with disease activity [3] and may be used to predict relapse [4]. Recent evidence based on detection of both eosinophil (major basic protein and neurotoxin) and neutrophil (elastase) enzymes, and of eosinophil-activating cytokines, suggested that both cell types are involved in the pathogenesis of CSS [5].

Histopathology. CSS is characterized by three key features: eosinophilic infiltration of tissue, formation of extravascular granulomas of the visceral and cutaneous tissue, and necrotizing vasculitis involving both arteries and veins. A biopsy specimen of a cutaneous lesion from a patient with CSS may demonstrate any or all of these features [6]. The granulomas of CSS contain necrotic polymorphonuclear leukocytes, eosinophils, severe fibrinoid and fibrillar collagen degeneration, and a proliferation of granulomatous tissue.

Clinical features. Three phases of CSS have been described. The first phase, which may continue for years, consists of allergic rhinitis, nasal polyps, asthma and peripheral blood eosinophilia. The asthma component of this phase typically begins in adulthood, in contrast with allergic asthma. The second phase of CSS is vasculitis; this phase is characterized by disease affecting almost all organ systems, including cardiac, pulmonary, nervous, gastrointestinal, renal, genitourinary and musculoskeletal systems. In this vasculitic phase, 70% of patients have skin lesions. The third stage of CSS is characterized by allergic rhinitis, asthma, hypertension resulting from damage to the kidneys that occurred in the second phase and peripheral neuropathies. There is typically complete resolution of damage to other organ systems. Nearly half of patients in all phases of the disease have cutaneous manifestations [1,6], with approximately 5% demonstrating cutaneous vasculitis [6]. Palpable purpura and infiltrated nodules (typically located on the scalp or limbs) [7] are the most common skin manifestations, but livedo reticularis,

migratory erythema, new-onset Raynaud's phenomenon, aseptic pustules or vesicles, and infiltrated papules may also be present.

Diagnosis. The manifestations of CSS may be easily confused with lesions of WG, although CSS is associated more strongly with both asthma and involvement of the gastrointestinal tract, spleen and heart, in contrast with the upper airway disease and strong association with renal disease in WG. The triad of asthma, eosinophilia and extravascular granulomas may also be used to distinguish CSS from other disease processes.

Treatment. Corticosteroids alone have been shown to be an effective treatment of CSS, with clinical remission achieved in over 90% of patients. However, the addition of cytotoxic agents may be useful in patients with recalcitrant disease, although no double-blind prospective trials have been performed to establish their use.

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Giant cell arteritis

SYN. TEMPORAL ARTERITIS; CRANIAL ARTERITIS

Definition. Considered a disease of persons over 50 years of age, giant cell arteritis is a granulomatous panarteritis associated with considerable morbidity, including blindness. It can affect any medium or large artery and typically demonstrates signs or symptoms including an elevated ESR, pain and morning stiffness often involving the neck, shoulders and pelvis [1]. It is three to four times more common in females than males, and the incidence is higher in persons of northern European descent than those from more southern regions. However, giant cell arteritis can occur in various races and ethnic groups [2].

History and nomenclature. Giant cell arteritis was described clinically by Hutchinson in 1890, who discussed an older man who displayed swelling of the temporal arteries. In 1931, giant cell arteritis was described both clinically and pathologically by Horton, Magath and Brown (cited in [2]).

Aetiology and pathogenesis. The aetiology of giant cell arteritis is unclear. The pathogenesis is thought to involve IFN-γ-producing T lymphocytes that are in the adventitia of inflamed arteries [3]. Multinucleated giant cells and macrophages located at the junction of the tunica media and tunica intima may be stimulated by IFN-γ [4,5] to produce platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF) [6], thus stimulating the production of myofibroblasts, which may proliferate and deposit extracellular matrix in the subendothelium of the artery, as well as angiogenesis (for support of the new hyperplastic intima). PDGF has been shown to play an important part in occluded arterial lumina [7]. Macrophages may also produce reactive oxygen species and matrix metalloproteinase-2 (MMP-2) [8], and may contribute to the dissolution of the elastic lamina with subsequent intimal hyperplasia [9] by creating a path for the myofibroblasts to migrate to the subendothelium, leading to intimal hyperplasia and subsequent occlusion of the arterial lumen.

Histopathology. Although it can extend anywhere from the tunica intima to the tunica adventitia, giant cell arteritis is a chronic granulomatous inflammatory disease that typically affects the tunica media of medium or large arteries. The non-specific infiltrate includes histiocytes, lymphocytes, monocytes, giant cells and sometimes eosinophils.

Clinical features. Cutaneous involvement is uncommon in giant cell arteritis; the most common skin finding is painful nodules over involved superficial arteries. The classic sign of giant cell arteritis is a tender, swollen, nodular, pulseless, indurated temporal artery, although it is uncommon to find all of these pathognomonic features in a single patient. Scalp ulcers occur rarely. Tongue involvement may be manifest as a swollen, cool, atrophied, cyanotic or tender tongue. Other extracutaneous symptoms include, most commonly, headache, jaw claudication, sore throat, vestibular symptoms, earache and the feared involvement of the retinal arteries causing unilateral blindness in up to 17% of patients, followed up to 7 days later by blindness in the second eye. Intracranial involvement, including transient ischaemic attacks (TIAs), infarcts or psychiatric conditions, is unusual but may also occur. Medium or large arteries other than those of the head and neck are affected by this granulomatous vasculitis in only 10–15% of cases. Many patients with giant cell arteritis also have features indicative of polymyalgia rheumatica, which includes at least 4 weeks of

aching and stiffness of the muscles of the neck, shoulders and pelvic girdle, an elevated ESR and rapid response to corticosteroids.

Diagnosis. A pathological diagnosis from a biopsy specimen of the temporal artery is the gold standard for the diagnosis of giant cell arteritis. However, in 90–100% of patients with giant cell arteritis, the ESR is greater than 40 mm/h, although the degree of elevation of the ESR does not parallel the severity of the disease.

Treatment. The first-line treatment for giant cell arteritis is systemic corticosteroids, as the disease is usually very corticosteroid responsive [10]. The dose of corticosteroids can be tapered after remission, although a regimen of 2.5–20 mg/day for at least 2 years is often required for maintenance. In one blinded controlled trial, methotrexate was useful as a corticosteroid-sparing treatment in patients with giant cell arteritis [11].

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Takayasu's arteritis

SYN. TAKAYASU'S DISEASE; TAKAYASU'S SYNDROME; AORTIC ARCH SYNDROME; PULSELESS DISEASE; OCCLUSIVE THROMBOARTERIOPATHY; AORTITIS SYNDROME

Definition. Most commonly seen in patients from Japan, Korea, China, South East Asia, India, Africa, Mexico or South America, Takayasu's arteritis is a rare chronic recurrent inflammatory vasculitis involving the aorta and the great vessels. Takayasu's arteritis is uncommon in males, the majority of cases occurring in women between the ages of 15 and 30 years. It can also be seen in children, in whom it has a more aggressive course than in adults.

History and nomenclature. Although Takayasu's arteritis was named after a Japanese ophthalmologist, the first descriptions of the disease were published in 1830 by Rokushu Yamamoto. Autopsy confirmation of the vasculitis was described in 1920 by Ohta [1].

Aetiology and pathogenesis. Infective, autoimmune and genetic factors have been implicated [2]. An association with connective tissue diseases such as rheumatoid arthritis supports the autoimmune theory, although no autoantigens have been identified as triggers for a potential autoimmune response. Tuberculosis infection has been associated with Takayasu's arteritis in some populations, suggesting a possible role for this infection in its pathogenesis [2–4]. Viral infections may also play a part in triggering the disease [5]. As suggested by Seko *et al*. [6], natural killer cells, $CD4^+$ and $CD8^+$ T lymphocytes may also have a role in the vasculitis, as aortic tissue in patients with Takayasu's arteritis expresses a heat shock protein to which $CD4^+$ T lymphocytes strongly react. A genetic component is suggested by human leukocyte antigen (HLA) associations; susceptibility seems to be linked to the *MICA* gene. However, the exact pathogenesis of Takayasu's arteritis is unknown.

Histopathology. During the prepulseless phase of Takayasu's arteritis, there is intermittent involvement of the blood vessel wall with granulomatous inflammation. Lymphocytes and plasma cells typically make up the infiltrate, which may also contain eosinophils and histiocytes. Medial smooth muscle-derived giant cells, as well as Langhans' foreign body-type giant cells, have been observed in the inflammatory infiltrate. Later, in the pulseless phase, there is little or no infiltrate but there is transmural sclerosis. The duration and severity of the disease correlates with the degree of intimal proliferation and adventitial fibrosis. Finally, there may be secondary thrombus formation [2,7]. The cutaneous lesions consist of a necrotizing vasculitis with polymorphonuclear leukocytes, fibrinoid necrosis within the vessel walls, a granulomatous vasculitis with polymorphonuclear leukocytes, eosinophils, giant cells and fibrinoid necrosis that may also be associated with lobular panniculitis with fat necrosis and septal panniculitis [8].

Clinical features [2]. Two phases of Takayasu's arteritis have been described. Early, in the prepulseless disease phase, patients may have constitutional symptoms such

as weight loss, fever, malaise, myalgia and arthralgia. Later, in the pulseless disease phase, they may present with bruits, blood pressure inequality between the arms or with actual loss of pulses. Some other signs and symptoms from ischaemia caused by the vessel inflammation include hypertension, TIAs, headaches, angina and seizures. Retinopathy is a notable feature, termed Takayasu's retinopathy [2]. Cutaneous manifestations are present in 15–20% of patients with Takayasu's arteritis. In the early phase, erythema nodosum-like nodules or lesions of erythema induratum are present, whereas in the late pulseless phase there are pyoderma gangrenosum-like lesions, or lesions related to necrotizing or granulomatous vasculitis [8].

Diagnosis. Clinical signs and symptoms are often the initial identifying factors for Takayasu's arteritis. However, vascular studies are necessary for diagnosis; angiography remains the gold standard. Other radiological studies, such as computed tomography (CT) or magnetic resonance imaging (MRI) and colour Doppler ultrasound, may be used in the future as non-invasive techniques for both diagnosis of Takayasu's arteritis and for monitoring of the response to therapy [2,9].

Treatment. Although corticosteroid treatment alone may control the inflammation associated with Takayasu's arteritis, cytotoxic agents such as cyclophosphamide are used to reduce the risk of relapse. Takayasu's arteritis should be treated during the acute phase; corticosteroids may be necessary for 6 months to 2 years to induce remission, which may be maintained with a prednisone dose of 7–10 mg once daily. Even during the acute phase, vascular occlusions may be relieved surgically by patch angioplasty or bypass grafting [2,7,10].

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Pityriasis lichenoides [1,2]

SYN. MUCHA–HABERMANN DISEASE

Definition and nomenclature. This disorder or group of disorders is difficult to classify. Clinically, pityriasis lichenoides is generally divided into two main forms [1–5]. *Pityriasis lichenoides chronica* (PLC) is the more common. It is largely a disease of young adults, with a male predominance of approximately 2 : 1. The more acute form, *pityriasis lichenoides et varioliformis acuta* (PLEVA, Mucha–Habermann disease), is less common, usually occurs in childhood and has an equal sex incidence. However, some patients may have simultaneous lesions of both types, or may have transitional lesions [1,2,4]. There is also a more recently described subset of PLEVA with a more aggressive course, known as *febrile ulcerative Mucha–Habermann disease* (FUMHD) [2,5]. All types are rare in infancy and old age, but PLEVA has been present at birth [6].

Nosologically, pityriasis lichenoides has been considered to be a variant of parapsoriasis (previous terms include parapsoriasis en gouttes and guttate parapsoriasis) and to overlap with lymphomatoid papulosis, and there are several reported cases with associated development of lymphoma. On the other hand, an overlap with vasculitis has been suggested—extravasation of erythrocytes is typical at a histological level, the acute form causes necrosis and may have vasculitic changes histologically, and the lymphomatous end of the spectrum is associated with an angiocentric destructive pattern of disease. In the absence of a clear aetiological or pathological classification, pityriasis lichenoides has been retained in this chapter, but the lymphomatous and lymphoma-associated end of the spectrum is discussed in more detail in Chapter 54. Recent evidence of clonality in most cases of PLEVA and some cases of PLC may mean that classification as a T-cell lymphoproliferative disease is more accurate [7–9]. However, to date, there is no evidence to support clonal development of PLC from PLEVA and most cases follow a prolonged but benign and apparently 'reactive' course.

Aetiology and pathogenesis. Pityriasis lichenoides has been reported mainly from Europe and America, but there is no specific geographical variation in incidence, and the cause is unknown.

The acute necrotic lesions of PLEVA bear some resemblance to allergic vasculitis [10,11], but recent reviews have found no evidence of a primary vascular injury [12]. One hypothesis is that the vascular injury is a hypersensitivity reaction to an infective organism, for which there are various lines of support. Cases have been reported in association with seroconversion against toxoplasmosis [13,14], cytomegalovirus [15], parvovirus [16], adenovirus and Epstein–Barr virus (EBV) [17] (although EBV could not be demonstrated immunohistochemically in one

series [18]). Bacteria such as *Streptococcus* have been implicated as a cause [19], and therapeutic response to tonsillectomy [20] and to antibiotics such as erythromycin [2,3] or tetracycline [21] can occur. Immune disturbance such as that caused by HIV infection or associated with common variable immunodeficiency have been reported with pityriasis lichenoides [22,23]. The occurrence of $CD8^+$ T-cell clonality, with IgM and C3 deposition in the vessels, suggests a form of chronic antigen stimulation with resulting immune complex deposition [1]. Paraneoplastic and drug-induced pityriasis lichenoides have also been reported; the association with lymphoma is discussed in Chapter 54.

Histopathology [1,2,7,24,25]. The histology varies with the stage, intensity and extent of the reaction; changes are more severe in PLEVA than in PLC. In the early lesions, an infiltrate of predominantly small lymphocytes surrounds and involves the walls of dilated dermal capillaries, which show endothelial proliferation. In PLEVA, the infiltrate may be deep, dense and wedge-shaped rather than predominantly perivascular. The epidermis is oedematous, with an interface dermatitis comprised mainly of $CD8^+$ lymphocytes; some necrotic keratinocytes are generally present, especially in PLEVA. Intraepidermal and perivascular extravasation of erythrocytes is typical. Later, over the centre of the lesion, a parakeratotic scale forms, containing lymphocytic pseudo-Munro abscesses. If the reaction is still more intense, as occurs in FUMHD, frank necrosis occurs and the lesion may not be histologically distinguishable from other forms of acute necrosis of the skin. In FUMHD there may be marked fibrinoid necrosis of deep vessels with luminal thrombi, partial necrosis of follicles and complete necrosis of eccrine glands [2].

Immunofluorescence studies commonly demonstrate IgM, C3 and fibrin in vessel walls of fresh lesions. Macrophages are increased in number and Langerhans' cells decreased. HLA-DR is expressed by the lymphocytic infiltrate and the overlying epidermis.

There is a histological resemblance to many other conditions, including common conditions such as psoriasis and resolving eczema. The most important is the distinction from parapsoriasis and particularly (as they may also be clinically similar) differentiation between PLEVA and lymphomatoid papulosis. The most useful distinction from lymphomatoid papulosis is that the latter has a predominant population of large $CD30^+$ cells, most of which are also $CD4^+$, whereas $CD30^+$ cells in pityriasis lichenoides are usually few and $CD8^+$ [26].

Clinical features [1–4]. The eruption is usually the first manifestation of the disease, and generally the only manifestation in PLC, but constitutional symptoms such as fever, headache, malaise and arthralgia may precede or accompany the onset of PLEVA.

PLEVA. The eruption develops in crops, and consequently appears polymorphic. The initial lesion is an oedematous pink papule that undergoes central vesiculation and haemorrhagic necrosis, which may be intense. In the vesicular forms [4], the vesicles may be small or so large that the eruption appears frankly bullous. The rate of progression of the individual lesions varies greatly, as do the frequency and extent of the crops of new lesions. New lesions may cause irritation or a burning sensation as they appear, but are often asymptomatic. The trunk, thighs and upper arms, especially the flexor aspects, are chiefly affected, but the eruption may be generalized. Lesions of the palms and soles are less common, and the face and scalp are often spared; erythematous or necrotic lesions of mucous membranes may be present. Lesions heal with scarring, which may be varioliform. PLEVA in pregnancy carries a potential risk of premature labour if there are mucosal lesions in the region of the cervical os [27].

FUMHD. In the acute ulceronecrotic form there is high fever and large necrotic lesions, with a fulminating course that may even be fatal [2,5,28,29]. About 50% of cases occur in children, and new crops of lesions may develop over many months. General malaise, weakness, myalgia, neuropsychiatric symptoms and lymphadenopathy occur, with non-specific serological markers of inflammation such as raised ESR and C-reactive protein; there may be serological evidence of associated viral infection [15].

PLC. The characteristic lesion of the chronic form is a small firm lichenoid papule 3–10 mm in diameter, and reddish brown in colour. An adherent mica-like scale can be detached by gentle scraping to reveal a shining brown surface—a distinctive diagnostic feature. Over the course of 3 or 4 weeks the papule flattens and the scale separates spontaneously to leave a pigmented macule which gradually fades. Post-inflammatory hypopigmentation may occur, and is occasionally persistent, but scarring is unusual in PLC. The body site distribution is the same as for PLEVA but an isolated acral form may occur [30,31]; segmental forms have been reported but at least some of these represent early lymphoma (Chapter 54).

The course of pityriasis lichenoides varies. If the onset is acute, new crops may cease to develop after a few weeks, and many cases are clear within 6 months. However, acute recurrences may occur over a period of years, or chronic lesions may supervene. In some cases, all lesions are of the chronic scaly type from the onset, and new crops of similar lesions may develop from time to time for years. Uncommonly, acute attacks occur after chronic lesions have been present for months or years. In general, the immediate prognosis is said to be better when the onset is acute and the lesions in successive crops are also of the acute type.

Differential diagnosis. The acute vesicular form must be distinguished from varicella; acute necrotic lesions may suggest necrotic skin infections, vasculitis or pyoderma gangrenosum. Lymphomatoid papulosis is a particularly difficult differential diagnosis in patients with necrotic lesions in view of its histological similarity, discussed above, although lesions of this disorder are usually less vesicular and more necrotic than those of PLEVA.

Pityriasis lichenoides chronica must be differentiated from guttate psoriasis or lichen planus. The acral form of PLC in particular may mimic psoriasis, and secondary syphilis may be mimicked, especially if the palms and soles are involved or if there are mucosal lesions. The single detachable mica-like scale on the red-brown papule is a characteristic sign of PLC. Gianotti–Crosti syndrome is less likely to be confused with pityriasis lichenoides, but insect bites and drug eruptions come into the differential diagnosis of any of the forms of the disease.

Treatment [1–4]. Treatment options include antibiotics such as tetracyclines [21] or erythromycin (preferred in young children because of dental pigmentation side effects of tetracycline) [2,3], and phototherapy of different types, including natural sunlight, UVB [32] and PUVA [33]. Topical corticosteroids may improve symptoms and healing of lesions but are not felt to alter the course of the disease [1]. In more aggressive disease of PLEVA or FUMHD pattern, and less commonly in PLC, additional therapeutic options include oral corticosteroids, methotrexate, dapsone, ciclosporin and intravenous immunoglobulin.

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Other vasculitides and mimics of vasculitis

Occlusion disorders

It is important in the differential diagnosis of vasculitis to be aware of disorders that may present with livedo or infarcted lesions, such as *cryoglobulinaemic vasculitis*, *cholesterol embolization*, *Sneddon's disease* and *malignant atrophic papulosis* (*Degos' disease*). The major pathology in these is either initially occlusive, or is probably mediated by antiphospholipid antibodies (in Sneddon's syndrome), so they are all discussed in the section on microvascular occlusion in Chapter 48. Other disorders associated with antiphospholipid antibodies are also discussed. In

calciphylaxis (Chapter 48), the earliest event is vessel wall calcification [1], therefore this also is discussed in the section on microvascular occlusion rather than as a primarily vasculitic disorder. *Hyperoxaluria* may cause acrocyanosis, gangrene and livedo reticularis. *Hyperhomocysteinaemia*, typically in homozygotes for methyl tetrahydrofolate reductase mutation C677T, also predisposes to endothelial damage and vasculopathy.

Thromboangiitis obliterans (*Buerger's disease*) [2] is a disorder of small or medium-sized arteries (less commonly veins) in which there is an inflammatory non-suppurative panarteritis or panphlebitis with thrombosis. Antiendothelial cell antibodies may be significantly elevated in active disease and have a role in monitoring the disease [3]. This disorder is discussed in more detail in Chapter 50.

Other arterial thrombotic disorders that may mimic vasculitis include hypothenar hammer syndrome (Chapter 22), thrombosis resulting from polyvinyl chloride haemodialysis tubing [4], vessel wall invasion by tumour or organisms and sickle cell anaemia. Amyloid infiltration of the vessel wall may cause occlusion. Drugs such as ergot, amphetamines or epinephrine (adrenaline) typically cause vasospasm but there may be histological evidence of vasculitis.

Other systemic diseases

Vasculitis is a feature of many *connective tissue diseases* (Chapter 56) and of disorders such as *sarcoidosis* (Chapter 58) in which there may be either a large vessel granulomatous vasculitis or an immune complex-associated small vessel cutaneous vasculitis [5].

Churg-Strauss granulomas, a histological feature known under several other names, are seen in some autoimmune disorders with circulating immune complexes in which small vessel leukocytoclastic vasculitis may also occur. These have been grouped together as 'palisaded neutrophilic and granulomatous dermatitis of immune complex diseases' [6]. A particular clinical entity that exhibits these occurs predominantly in women with rheumatoid arthritis or other autoimmune disease, and has been termed (amongst others) *interstitial granulomatous dermatitis with plaques*, *palisaded neutrophilic granulomatous dermatitis* and *interstitial granulomatous dermatitis with cutaneous cords and arthritis* [7–9]. Clinical features are: erythematous plaques, papular or nodular lesions, and firm linear subcutaneous cords or bands. It has been suggested that the lesions start as leukocytoclastic vasculitis but progress to form palisaded granulomas and dermal fibrosis [6].

Vasculitis can occur in *familial Mediterranean fever (FMF)*, *hyperimmunoglobulinaemia D* and the *periodic fevers* (Chapter 59). It is important to consider FMF as a cause of vasculitis in children with apparent HSP in areas where FMF is prevalent, as HSP is much more common in families with FMF compared with the general population [10]; diagnostic delay is common. Tests for faecal occult blood are often positive during acute attacks of FMF. Other vasculitic features in FMF include purpura, subcutaneous nodules and associated PAN (which occurs in about 1% of patients); in particular, perirenal haematoma is usually associated with PAN secondary to FMF [10]. Both circulating IgD immune complexes and IgD deposits on direct immunofluorescence of the skin have been identified in hyperimmunoglobulinaemia D [11].

Paraneoplastic vasculitis is particularly associated with haematological malignancies; mechanisms include vasculitis related to paraproteins, cryoglobulins or to the presence of antinuclear antibodies.

Vasculitis may also be a feature of *Wiskott–Aldrich syndrome* (Chapter 12), usually leukocytoclastic small vessel vasculitis but aortitis and mesenteric or renal arteritis may occur.

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Neutrophilic vascular reactions

Introduction

Neutrophilic vascular reactions are vessel-based dermatoses typified by neutrophilic infiltrates and changes in blood vessels within the dermis. The vessel damage responsible for these dermatoses is thought to be a result of immune complex deposition as well as to neutrophil-induced injury.

The following sections define and discuss the history, aetiology, pathogenesis, histopathology, clinical features,

Table 49.10 Dermatoses associated with neutrophilic vascular reactions.

Vasculitis
• Small vessel variants (cutaneous small vessel vasculitis and variants) (Table 49.3)
• Large vessel variants
Sweet's syndrome
Pustular vasculitis
• Behçet's disease
• Bowel-associated dermatosis–arthritis syndrome
Erythema nodosum
Other
• Familial Mediterranean fever
• Selected disseminated infections
Pyoderma gangrenosum

diagnosis and treatment of Sweet's syndrome, pyoderma gangrenosum, erythema nodosum, Behçet's disease and bowel-associated dermatosis–arthritis syndrome, with brief mention of rheumatoid neutrophilic dermatitis and neutrophilic eccrine hidradenitis.

Classification

Neutrophilic vascular reactions can be classified as vasculitis syndromes (see above), pustular vasculitides, Sweet's syndrome, erythema nodosum, pyoderma gangrenosum and miscellaneous forms (Table 49.10).

Sweet's syndrome

SYN. ACUTE FEBRILE NEUTROPHILIC DERMATOSIS

Definition. Sweet's syndrome is characterized by fever, peripheral neutrophil leukocytosis, acute onset of painful, erythematous papules, plaques or nodules and histological findings of a dense neutrophilic infiltrate without evidence of primary vasculitis [1]. Sweet's syndrome can be subdivided into three groups depending on the clinical setting: (i) classical or idiopathic; (ii) malignancy-associated; and (iii) drug-induced [2].

History and nomenclature. Sweet first described eight women with a 'distinctive and fairly severe illness' in 1964 [1].

Aetiology and pathogenesis. Sweet's syndrome is associated with underlying disease in approximately 50% of cases [3]. Classical or idiopathic Sweet's syndrome typically affects middle-aged women and has been associated with infection (streptococcal upper respiratory infections and yersinial gastrointestinal infections), IBD (ulcerative colitis and Crohn's disease) and pregnancy [3–6]. It is estimated that 20–25% of cases of Sweet's syndrome have an associated malignancy [7,8]; men and women are equally affected [9,10]. Most are haematological malignancies, especially acute myelogenous leukaemia. However, solid tumours, most commonly of genitourinary organs, breast and gastrointestinal tract, are present in about 15% [7,8]. The skin lesions of Sweet's syndrome may be the initial manifestation of malignancy or may precede the diagnosis by months to years, making close follow-up essential. In addition, recurrent episodes of Sweet's syndrome may be an indication of cancer recurrence [2,10]. Drug-induced Sweet's syndrome most commonly occurs in patients receiving granulocyte colony-stimulating factor (G-CSF) therapy [11–13]. Additional drugs implicated include all-*trans*-retinoic acid [14,15], minocycline [16,17], trimethoprim-sulfamethoxazole [18], carbamazepine [5], hydralazine [19] and oral contraceptives [20]. Other conditions reported in association with Sweet's syndrome include Behçet's disease [21], erythema nodosum [22], sarcoidosis [23–25], rheumatoid arthritis [4,26] and thyroid disease [27]; however, these reports may represent coincidental occurrences rather than true disease associations.

As with the other neutrophilic dermatoses, the pathogenesis of Sweet's syndrome is unknown, but it is thought to be related to altered immunological reactivity. A hypersensitivity reaction to bacterial, viral, drug or tumour antigens has been suggested as a possible aetiology [28,29]. This hypothesis is supported by the frequent association of Sweet's syndrome with infection, drugs or malignancy, along with the clinical improvement of symptoms and lesions with corticosteroid treatment [2]. Circulating autoantibodies [30], immune complexes [31] and cytokines [4,7] have also been proposed to play a part in the pathogenesis of Sweet's syndrome. ANCA have been found in a few cases of Sweet's syndrome but not in others [4,5,30]. Immunohistochemical studies to detect immune complex deposition in blood vessels have yielded inconsistent results. Some investigations have demonstrated evidence of immunoglobulins and complement within vessel walls [32–34] but this is not consistent [4,9]. Additional studies have found perivascular IgG, IgM, C3 and fibrin, thought to represent non-specific leakage from damaged vessels [35]. Cytokine dysregulation is currently a favoured theory in the pathogenesis of Sweet's syndrome. Potentially involved cytokines include IL-1, IL-3, IL-6, IL-8, G-CSF, granulocyte–macrophage colony-stimulating factor (GM-CSF) and IFN-γ [4,36–38]. As an example, drug-induced Sweet's syndrome is most commonly associated with G-CSF therapy [11–13]. Recently, an imbalance of cytokine secretion from helper T cells (Th) has been implicated. Th1 cytokines (IL-2 and IFN-γ) rather than Th2 cytokines (IL-4) are the proposed mediators, which in turn may stimulate the cytokine cascade leading to activation of neutrophils and release of toxic metabolites [39,40].

Histopathology. The diagnostic histopathological features of Sweet's syndrome include a dense, predominately

neutrophilic, infiltrate located in the superficial dermis, and prominent papillary dermal oedema which may occasionally lead to subepidermal vesiculation. The infiltrate may also contain lymphocytes, eosinophils and histiocytes [2]; an initial lymphocytic infiltrate has been reported. The infiltrate often occurs in a diffuse pattern, but may be perivascular or have an upper dermal band-like distribution [9]. Neutrophil karyorrhexis (fragmented neutrophil nuclei) is a common finding [3]. The epidermis is often normal but spongiosis may be present, and rarely neutrophils may extend into the epidermis to form subcorneal pustules [41]. Historically, the presence of vasculitis excluded the diagnosis of Sweet's syndrome; however, recent studies have reported histopathological features consistent with leukocytoclastic vasculitis. These findings include fibrinoid necrosis along with the presence of inflammatory cells within vessel walls. Additional evidence of vessel wall damage includes extravasated erythrocytes and intraluminal thrombi. However, multiple immunofluorescence studies have failed to demonstrate immune complex-mediated injury, further supporting the theory of secondary vessel damage rather than a primary vasculitis. It has been proposed that toxic metabolites released by activated neutrophils may have a role in the secondary vessel wall injury [4,9,42,43].

Clinical features. The clinical presentation of Sweet's syndrome is usually distinctive. The patient typically appears ill, with a persistent high fever, neutrophilia and an elevated ESR. The cutaneous manifestations consist of erythematous to violaceous tender papules or nodules that often coalesce to form irregular plaques (Figs 49.19 & 49.20) [44]. The lesions typically involve the arms, face and neck, but may occur anywhere [10,18]. The patient may present with a single lesion or multiple lesions. The distribution may be localized, particularly on the face [45,46], or widespread, as may occur in malignancy-associated cases [12]. Later lesions may appear pseudovesicular because of the prominent dermal oedema [29,47] and may be studded with tiny pustules resulting from neutrophil migration into the epidermis. The plaques may develop central yellowish discoloration, producing a targetoid appearance [4]. Healing usually occurs without scarring [2]. Oral lesions are uncommon but have been reported in patients with haematological disorders [7]. A variety of systemic manifestations can occur. Fever is the most common but may be absent, especially in malignancy-associated Sweet's syndrome [10]. Arthralgia, myalgia and arthritis are also frequent. The most common ocular manifestations include conjunctivitis and episcleritis. Neurological, pulmonary, renal and hepatic involvement have also been reported and are usually responsive to systemic corticosteroid therapy [3,4,48].

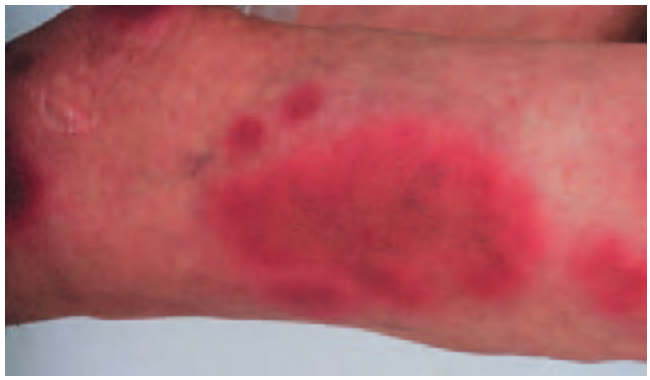

Fig. 49.19 Sweet's syndrome. Erythematous plaques on the leg of the patient.

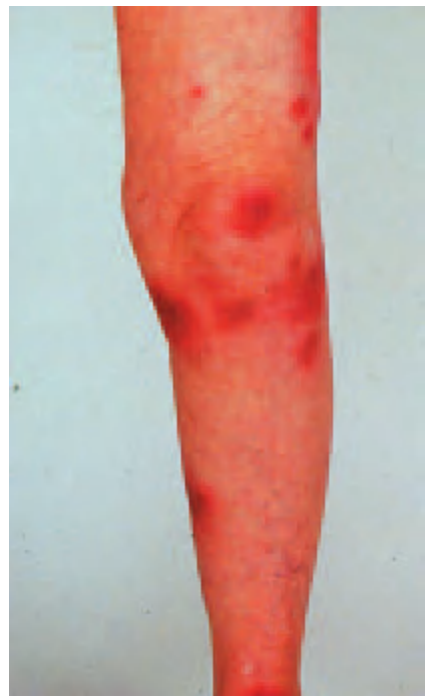

Fig. 49.20 Sweet's syndrome: large erythematous lesions.

Diagnosis. The proposed diagnostic criteria for Sweet's syndrome state that patients must meet both of the two major criteria and two of the four minor criteria for the diagnosis [40].

Major criteria:

1 Acute onset of typical skin lesions

2 Histopathological findings consistent with Sweet's syndrome

Minor criteria:

1 Fever > 38°C or general malaise

2 Association with malignancy, inflammatory disorder or pregnancy *or* antecedent respiratory or gastrointestinal infection

3 Excellent response to systemic corticosteroids or potassium iodide (KI)

Table 49.11 Treatment of Sweet's syndrome.

Corticosteroids
Systemic for 4–6 weeks
Adjuvant therapy for localized lesions
• Topical
• Intralesional
Corticosteroid-sparing agents
Potassium iodide
Colchicine
Indometacin
Clofazimine
Dapsone
Ciclosporin
Etretinate
Interferon-α

4 Abnormal laboratory values at presentation (three of four required: ESR > 20 mm; leukocytes > 8000; neutrophils > 70%; positive C-reactive protein)

For drug-induced Sweet's syndrome, both major criteria but only one minor criterion (fever > 38°C) are required, together with two proposed additional criteria: (i) a temporal relationship between drug administration and clinical presentation; and (ii) a temporal relationship between drug withdrawal and disease resolution [18].

Treatment. Systemic corticosteroids are a standard and effective therapy for Sweet's syndrome. A 4–6-week course of prednisone is generally sufficient to resolve cutaneous and systemic symptoms and signs, but occasionally prolonged low-dosage treatment may be required to prevent recurrences. In addition, topical and intralesional corticosteroids may be used alone or as adjuvant therapy for localized lesions [8,49,50]. Many corticosteroid-sparing agents have been reported to be effective in the treatment of Sweet's syndrome. Oral therapy with potassium iodide and colchicine has led to rapid regression of lesions and symptoms. These agents may be reasonable first-line therapy in patients with milder disease [51–55]. Indometacin and clofazimine have been used with success but appear to be less effective than corticosteroids, potassium iodide and colchicine [12,56–58]. Dapsone and ciclosporin have also been reported to be effective therapeutic agents, but require laboratory monitoring because of their potentially serious adverse effects [39,59–62]. Small studies have reported clinical improvement in Sweet's syndrome using etretinate or IFN-α [50,63,64]. Therapies for Sweet's syndrome are depicted in Table 49.11.

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Neutrophilic dermatosis (pustular vasculitis) of the dorsal hands

This is a disorder of uncertain nosology. An early case series described lesions that morphologically and histologically resembled Sweet's syndrome, but had additional histological features of vessel wall necrosis and deposition of fibrin around vessels, thereby constituting a vasculitis [1]. The presence of vasculitic change in this pattern of disease has varied in subsequent reports [2,3] and there remains controversy about whether this should be viewed as simply Sweet's syndrome, a specific subset of Sweet's syndrome or a vasculitic process in the spectrum of EED [4–6]. The fact that vasculitis has been documented as a feature in more classical Sweet's syndrome [7] supports the view that these clinical patterns are part of the same disease [4], as does the fact that some patients have lesions at other sites.

A link with myeloproliferative disease has been suggested [5], and it is possible that an earlier report of Sweet's disease confined to the dorsum of the hand in a patient with myeloproliferative disease may represent the same entity [8]. However, the number of cases reported is rather small for any conclusion about specific disease associations.

Treatment is as for Sweet's syndrome.

Pustules on the palms and soles have also been reported as a presentation of Sweet's syndrome [9].

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Pyoderma gangrenosum

Definition. Pyoderma gangrenosum (PG) is a rare non-infectious neutrophilic dermatosis commonly associated with underlying systemic disease. Diagnosis is based on typical clinical features and exclusion of other cutaneous ulcerating diseases [1]. Several clinical variants of PG have

been described including ulcerative, pustular, bullous and vegetative forms [2].

History and nomenclature. In 1916, Brocq first described PG [3]. It was later described in 1930 by Brunsting *et al*. [4]. The prevalence of PG in IBD was discussed by Greenstein *et al*. in 1976 [5].

Aetiology and pathogenesis. Although the pathogenesis of PG is not fully understood, an immune-mediated process is thought to have an important role. Approximately 50% of patients with PG have an associated systemic disease [6]. Common associations include IBD, arthritis, haematological malignancies and monoclonal gammopathies [7]. PG occurs in immunosuppressed patients secondary to accompanying disease, infection or therapy [8]. Both humoral and cell-mediated abnormalities have been associated with PG. Humoral defects reported include autoantibodies against skin and bowel, a dermonecrotic factor present in the serum that produces necrosis when injected into the subject's own skin, and a serum factor present in patients with PG that produces PG-like lesions when injected into guinea pigs [9,10]. Cell-mediated defects found include cutaneous anergy to *Candida*, streptokinase and purified protein derivative, as well as altered production of macrophage inhibition factor by lymphocytes [11]. Additional reports have described decreased neutrophil chemotaxis and impaired monocyte phagocytosis in association with PG [12]. These leukocyte abnormalities may contribute to the pathergic phenomenon that occurs in up to 50% of PG patients, whereby new lesions can be induced at sites of minor skin trauma including venipuncture, vaccination and surgical procedures [13–15]. Other studies have suggested the mechanism underlying PG is consistent with the Arthus and Schwartzmann reactions in which circulating immune complexes are deposited in vessels leading to activation of the classical and alternative complement pathways [9,16,17]. Direct immunofluorescence staining studies to detect immunoglobulins, complement and fibrin deposits in post-capillary venules have yielded inconsistent results [6,18].

Histopathology. Although the histopathological findings of PG are often variable and non-specific, they can be useful in excluding other possible aetiologies. Several variables must be considered when evaluating the histopathology, including the type of lesion, the site of the lesion from which the biopsy is obtained, the stage of evolution of the lesion, and therapy [2]. Typical findings include central necrosis and ulceration of the epidermis and dermis surrounded by an intense acute inflammatory cell infiltrate, with a more peripheral mixed to chronic inflammatory cell infiltrate [19]. Each clinical variant has additional more specific histopathological findings. In the ulcerative variant of PG, there is massive dermal–epidermal neutrophilic infiltrate with abscess formation; in pustular PG, a perifollicular neutrophilic infiltrate with subcorneal pustule formation; the bullous variant shows a neutrophilic infiltrate with intraepidermal vesicle formation; and in vegetative PG, there is a granulomatous reaction with peripheral palisading histiocytes and giant cells [20]. The presence of vascular involvement in PG is an area of debate. Many investigators have reported findings consistent with a neutrophilic vascular reaction or leukocytoclastic vasculitis, granulomatous vasculitis and lymphocytic vasculitis [21–23], although this is not supported by all studies [24].

Clinical features. PG can have a variety of clinical presentations. The classic presentation begins with small tender papules or pustules that evolve into painful ulcers with characteristic violaceous undermined edges [25]. There may be granulation tissue, necrosis or purulent exudate at the ulcer base. Lesions may be solitary or multiple. Healing usually occurs with an atrophic cribriform scar [26]. Associated symptoms include fever, malaise, myalgia and arthralgia [1]. Extracutaneous involvement has been reported, with sterile neutrophilic infiltrates and PG manifestations occurring in bone and lungs (Chapter 59) [27–30].

Clinical features of the four types of PG [2] are as follows.

The *ulcerative* variant is the classic type of PG, in which there is ulceration with an undermined border and surrounding erythema that may develop from an inflammatory pustule or nodule, or may be secondary to the pathergic phenomenon [2]. It typically begins on the legs or trunk but can occur at any site [31]. Frequent disease associations include IBD, arthritis and monoclonal gammopathy [2].

Pustular PG is a variant that often occurs during acute exacerbations of IBD. Discrete painful pustules, with a surrounding halo of erythema, develop on normal skin. These pustules commonly arise on the extensor aspects of the limbs and may evolve into the typical ulcerations of PG. The lesions often resolve with control of IBD [2].

Bullous or 'atypical' PG typically presents with rapidly arising superficial haemorrhagic bullae, often located on the arms [24]. It shares clinical and histopathological findings with Sweet's syndrome, but typically ulcerates and heals with scarring [26]. Bullous PG is often associated with myeloproliferative disorders [2].

Vegetative PG or superficial granulomatous pyoderma presents as a non-painful superficial ulcer with a non-purulent base and generally lacks the violaceous undermined border [2,32]. It is often a solitary, slowly progressing lesion that resolves with less aggressive treatment [33] and is not usually associated with any systemic disease [34].

Diagnosis. PG is often a diagnosis of exclusion as laboratory and histopathological findings are variable and nonspecific. Patient evaluation should include a detailed history, physical examination and skin biopsies for histopathology and culture, as well as appropriate laboratory tests to help rule out other possible aetiologies. Infectious ulcers may mimic PG. Histological stains and cultures of skin biopsies for bacteria, mycobacteria, fungi and occasionally viruses can aid in excluding these aetiologies. Syphilis serology and anticardiolipin antibody may be indicated because syphilitic gummatous ulcers and antiphospholipid syndrome can simulate ulcerative or vegetative PG [35]. Sweet's syndrome can often be distinguished by its rather sudden onset of non-ulcerating lesions that generally heal without scarring. Syndromes with vasculitis such as WG, Behçet's disease and SLE can also be confused with PG; however, leukocytoclastic vasculitis is not a feature of PG [2].

Treatment. Many effective treatment strategies have been reported. Choice of treatment generally depends on disease severity as well as on the presence of associated disease. For early or mild lesions, topical therapy may be sufficient [7]. This includes wet compresses, hydrophilic occlusive dressings, antimicrobial agents and topical corticosteroids. Topical tacrolimus has recently shown promising results for the treatment of early PG lesions [36], and intralesional corticosteroids are another therapeutic option of reported benefit [37]. For more severe disease or for PG resistant to topical therapy, oral corticosteroids have been the mainstay of therapy. Pulsed intravenous corticosteroid therapy has been reported to be effective in some cases refractory to oral corticosteroids; it is recommended in PG refractory to other forms of treatment [38]. Sulphones and other antimicrobials such as dapsone, clofazimine and minocycline have been found to be useful in treating PG. Their mode of action is likely related to their anti-inflammatory effects or their alteration of neutrophil function [39]. Immunosuppressant agents have been found to be useful as adjunctive or alternative therapy in corticosteroid-unresponsive PG or as corticosteroid-sparing agents. Because of the risk of severe adverse effects such as bone marrow suppression, these agents should be limited to severe or refractory PG. Azathioprine was among the first of these agents to be used [40] but ciclosporin may be the immunosuppressant of choice [41]. It is often effective at a dosage of less than 5 mg/kg/day, with a response time of 1–3 weeks [39]. Methotrexate may be useful in patients with underlying arthritis or IBD [24], and new biological TNF-α inhibitors such as infliximab and etanercept are now being used. Cyclophosphamide, melphalan and chlorambucil appear to be effective in the limited number of patients reported [35,42–44]. Several other effective treatments that have been reported in small studies include oral tacrolimus, plasmapheresis, intravenous immunoglobulin and thalidomide [45–50]. Aggressive surgical débridement is contraindicated because of possible exacerbation of PG by the pathergic response. However, split-skin grafts and cultured keratinocyte autografting have been demonstrated to be effective if performed while the pathergic response is minimized using prolonged courses of immunosuppressants [51–53]. Gradient support hosiery is also beneficial for leg lesions. Therapy decisions depend on an assessment of the degree of active inflammation as opposed to simple wound healing requirements in refractory ulcers. Treatment of PG is usually discontinued after complete healing of lesions. Recurrences may occur but are unpredictable and therefore do not justify prolonged maintenance therapy [2]. A therapeutic ladder for PG is depicted in Table 49.12.

Table 49.12 Therapeutic ladder for pyoderma gangrenosum.

Topical or intralesional corticosteroids (2)
Topical cromolyn sodium (3)
Topical tacrolimus (2)
Minocycline (3)
Clofazimine (3)
Colchicine (3)
Dapsone (2)
Sulfasalazine (2)
Thalidomide (3)
Methotrexate—weekly pulse (3)
Prednisone (2)
Ciclosporin* (2)
Azathioprine (3)
Cyclophosphamide (3)
Mycophenolate mofetil (3)
Intravenous gammaglobulin (3)
Etanercept (3)
Infliximab (3)
Granulocyte–monocyte colony-stimulating factor

* Pyoderma gangrenosum secondary to chronic underlying diseases (e.g. inflammatory bowel disease or rheumatoid arthritis) is best treated (in the opinion of the authors) with ongoing therapy of the underlying disease (e.g. methotrexate plus prednisone, or etanercept or infliximab) rather than with ciclosporin which can usually only be given for a number of months because of renal toxicity.
1, double-blind studies; 2, case series; 3, case reports.

Pyoderma gangrenosum associated with novel antineutrophil cytoplasmic antibodies to azurocidin

An unusual case of PG, polyarthritis and lung cysts associated with a novel ANCA to azurocidin was reported by Grattan *et al*. [54]. The patient initially presented with multiple skin lesions on the lower legs consistent with bullous and ulcerative PG. Subsequent analysis of this patient's sera revealed that azurocidin was the novel antigen for ANCA. The patient later developed a lesion on the

ankle resembling blastomycosis-like pyoderma that was associated with autoantibodies to BPI.

Azurocidin and BPI are antimicrobial components of neutrophil azurophilic granules. Azurocidin has been isolated from BPI and is distinct from other granule proteins such as PR3, MPO and cathepsin G. Antibodies to azurocidin and BPI may interfere with their antibacterial activity, thereby reducing innate immunity. Autoantibodies to azurocidin have also been associated with systemic and cutaneous vasculitis as well as with hydralazine-induced vasculitis [55].

Malignant pyoderma

Malignant pyoderma (MP) was first described by Perry *et al*. in 1968 [56] as a rapidly progressive ulcerative disease localized to the head, neck and upper trunk. Controversy exists as to whether MP represents a head and neck variant of PG or a cutaneous manifestation of WG. PG and WG may have similar clinical and histopathological findings, and both have been the reported cause of MP in some cases [57–61]. Interestingly, two of the original three reported cases of MP are now believed to represent WG. The presence of C-ANCA, which is highly specific for WG, may be useful in distinguishing PG from WG. However, some patients with WG may have negative C-ANCA test results, and thus close follow-up is warranted for possible pulmonary or renal lesions that may develop in WG [60–62]. Because of the uncertainty regarding the nosology of MP, it has been suggested that this term should not be used as a final diagnosis [60].

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Erythema nodosum

SYN. ERYTHEMA NODOSUM MIGRANS; SUBACUTE NODULAR MIGRATORY PANNICULITIS; CHRONIC ERYTHEMA NODOSUM

Definition. Erythema nodosum (EN) is characterized by painful erythematous, and sometimes ecchymotic, nodules on the anterior surface of the legs. The condition may be idiopathic or secondary to various internal diseases or treatments. The incidence of EN is 1–5 in 100 000 population per year, with women between the ages of 15 and 40 years being most commonly affected [1–5].

History and nomenclature. EN was initially described by Willan in 1798 [6]. The disorder was further discussed by Wilson in 1842, who believed it to be a type of erythema multiforme. In 1860, Hebra further described the clinical manifestations of the condition, and suggested 'dermatitis contusiformis' as a name for the disorder [7]. A more chronic variant was described as 'erythema nodosum migrans', 'chronic erythema nodosum' or 'subacute nodular migratory panniculitis' [8–10].

Table 49.13 Causes of erythema nodosum.

Infections
Group A β-haemolytic *Streptococcus*
Tuberculosis (uncommon) [3,5,8]
Coccidioidomycosis [9]
Histoplasmosis [10]
Blastomycosis [11]
Chlamydia [12–16]
Yersinia [17]
Bacterial gastroenteritis
• *Salmonella* [18–23]
• *Shigella* [24,25]
• *Campylobacter* [19–21]
Leprosy [22,23]
Dermatophytes [24,25]
Medications
Sulphonamides
Bromides
Oral contraceptive pill (uncommon)
Others
Sarcoidosis
Inflammatory bowel disease
Rheumatological and autoimmune disease
Malignancy
Pregnancy
Idiopathic

Aetiology and pathogenesis. EN is thought to be a hypersensitivity reaction that may be triggered by antigens usually associated with infections, typically group A β-haemolytic *Streptococcus*. Other infectious aetiologies are listed in Table 49.13 [3,5,11–28]. Sarcoidosis, rheumatological and autoimmune diseases, IBDs, medications, pregnancy and malignancies also have been cited as potential aetiological agents. In many patients with EN, the cause is unknown. Triggers of the chronic EN variant are generally unknown, although pregnancy and oral contraceptives have been implicated [29]. The exact pathogenesis of EN is not understood, although it is thought that it may be the result of deposition of immune complexes in the venules of the septae of subcutaneous fat.

Histopathology. Early lesions of EN demonstrate septal oedema and a lymphohistiocytic infiltrate, with an admixture of neutrophils and eosinophils [30]. The inflammation is typically concentrated at the periphery of

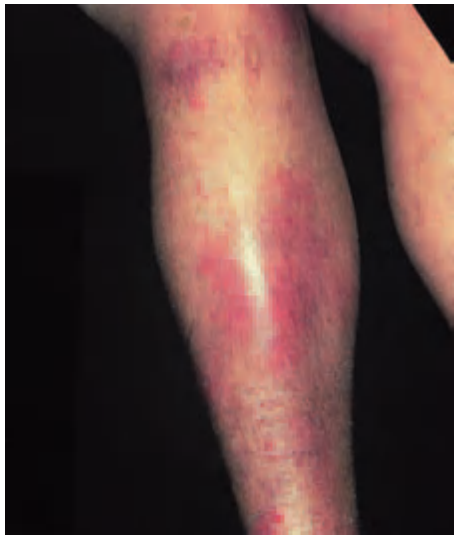

Fig. 49.21 Erythema nodosum. Note the location of the plaques on the anterior aspect of the lower leg.

the septae and spreads into surrounding fat lobules between adipocytes. Miescher's radial nodules, which are clusters of macrophages around small vessels or a slit-like space, are also seen in these lesions [31,32]. Finally, there may be oedema and lymphocytic infiltration of the walls of veins, although the amount of vascular involvement is variable [33,34]. Older lesions of EN demonstrate widened septae with peripheral fibrosis, and inflammation extending into peripheral regions of fat lobules. There are fewer vascular changes and a shift from a primarily neutrophilic infiltrate to one of primarily lipid-rich macrophages with a 'foam-cell' appearance. Macrophages without phagocytosed lipid surround multinucleated giant cells, forming granulomas. Histologically, chronic EN is similar to the later findings in acute EN. However, vascular proliferation is accompanied by endothelial thickening and extravasation of red blood cells [35], along with more marked formation of granulomas and lipogranulomas.

Clinical features. EN is typically manifest by the sudden onset of painful erythematous warm nodules and plaques on the shins, knees and ankles. These lesions are often more easily palpated than visualized, and are typically bilateral and symmetrical, ranging between 1 and 5 cm in diameter. The nodules may coalesce to form plaques (Fig. 49.21). After several days, the erythematous nodules often flatten and become ecchymotic in colour, finally taking on a yellow-green appearance (similar to an old ecchymosis), referred to as erythema contusiformis. This transformation is characteristic of EN, making retrospective diagnosis possible. Lesions of EN never ulcerate, atrophy or scar. Lesions erupt and are usually present for 3–6 weeks. In addition to cutaneous manifestations of EN, constitutional signs and symptoms may also be present. Fever, fatigue, malaise, gastrointestinal upset, headache and arthralgia may accompany the characteristic lesions of EN, as may ocular manifestations such as conjunctivitis.

In the chronic EN variant, lesions may be solitary or few, usually on the lateral part of the lower leg. They are initially nodular but become broader and flatter, vaguely circular or arciform in shape, and often last several months.

Table 49.14 Therapeutic ladder for erythema nodosum.

Non-steroidal anti-inflammatory drugs (3)
Potassium iodide (2)
Colchicine (3)
Hydroxychloroquine (3)
Dapsone (3)
Thalidomide (3)
Prednisone (3)

1, double-blind studies; 2, case series; 3, case reports.

Diagnosis. The diagnosis of EN is clinical, although histopathological evaluation may sometimes be necessary to support the diagnosis. In atypical cases of suspected EN (such as the absence of lesions on the legs, persistence or ulceration of the lesions), a deep elliptical biopsy of an active lesion should be performed. In some cases it may be necessary to search for an underlying cause of EN. A chest X-ray, tuberculin skin test and antistreptolysin (ASO) titre [5] may be obtained in such instances to exclude causes such as sarcoidosis, tuberculosis or streptococcal infection.

Treatment. EN typically resolves without treatment, therefore symptomatic support may be all that is necessary for the majority of patients. NSAIDs may also be used [36], as may potassium iodide at a dosage of 360–900 mg/day [37–40]. Systemic corticosteroids are infrequently required for the treatment of EN and may worsen underlying disease such as tubeculosis. A therapeutic ladder for EN is depicted in Table 49.14.

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Behçet's disease

Definition. Behçet's disease is a multisystem disease that is defined by the presence of oral aphthosis with at least two of the following: genital aphthae, synovitis, posterior uveitis, cutaneous pustular vasculitis or meningoencephalitis, in the absence of IBD or autoimmune diseases [1–3]. Children sometimes develop Behçet's disease, but it typically affects young adults [4]. It is uncommon in northern Europe and the USA, but is common in Middle Eastern and Japanese (i.e. 'silk route') populations [5].

History and nomenclature. Behçet's disease was named after the Turkish dermatologist who first described the multisystem disease.

Aetiology and pathogenesis. Although the exact cause of Behçet's disease is unknown, a genetic component of the disease is suggested by its association with HLA-B51 [2,6]. The possibility that infections may stimulate an abnormal immune response in persons susceptible to Behçet's disease is under consideration, although the idea that it may be the direct result of an infection is doubted.

Histopathology. Biopsy specimens of early aphthae or of lesions of pustular vasculitis demonstrate leukocytoclastic vasculitis or a neutrophilic vascular reaction [1,7–10], although late lesions are lymphocytic. Some case series even allow inclusion of follicular-based lesions, which the present authors discourage.

Clinical features. The clinical course of Behçet's disease is highly variable, although patients typically have oral aphthae with any combination of genital aphthae, cutaneous pustular vasculitis, ocular lesions or arthritis (Figs 49.22 & 49.23) [7,11,12]. Only pustular vasculitis and erythema nodosum-like nodules should be used to satisfy diagnostic criteria when considering Behçet's disease, although a wide range of cutaneous findings (especially Sweet's-like and pyoderma gangrenosum-like lesions) may be present in patients with the disease [2,8]. Posterior uveitis is the only ocular criterion for the diagnosis of Behçet's disease, yet there is an array of ophthalmological manifestations. The posterior uveitis observed in Behçet's disease is a consequence of retinal vasculitis and may result in blindness. Hence, loss of vision is a feared complication of Behçet's disease. Mimicking rheumatoid arthritis, the musculoskeletal involvement of Behçet's disease is an asymmetrical migratory non-erosive oligoarthritis [2,3,13]. Many neurological manifestations may be present in patients with Behçet's disease, although only meningoencephalitis is considered to be a diagnostic criterion [14]. Vascular involvement in Behçet's disease may affect arteries and veins, leading to aneurysms or occlusions that are

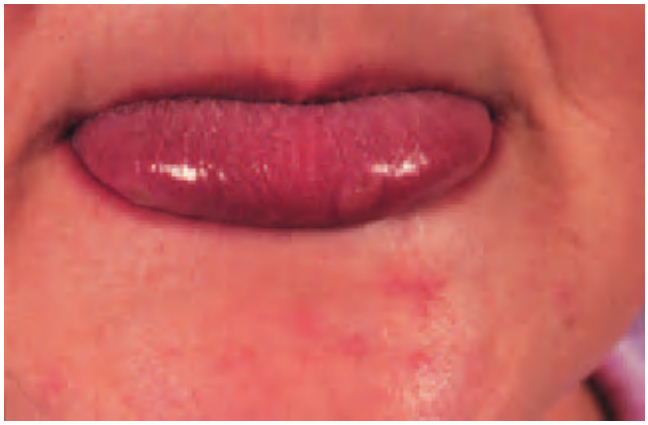

Fig. 49.22 Behçet's disease. This patient demonstrates oral aphthosis.

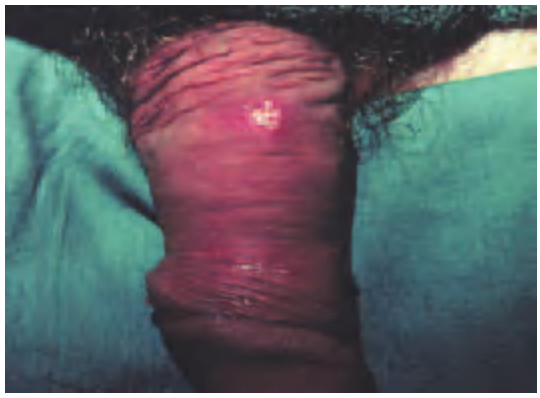

Fig. 49.23 Behçet's disease. An aphtha is present on the penis.

sometimes fatal [15,16]. Vascular complications should always be borne in mind in patients with known Behçet's disease, particularly pulmonary artery aneurysm as a cause of haemoptysis (the presence of haemoptysis and deep-vein thrombosis may erroneously suggest pulmonary emboli). However, these vascular complications are not a direct consequence of vasculitis and they typically do not respond to medical therapies.

Diagnosis. The diagnosis of Behçet's disease should be suspected in any patient with recurrent and extensive oral aphthosis. However, in these persons, other causes of aphthosis such as IBD, as well as lesions that mimic aphthae such as herpes simplex infection, must be excluded before a diagnosis of Behçet's disease can be made. The diagnosis should also be considered in young patients with deep-vein thrombosis, especially in the absence of other risk factors or thrombophilia. In addition, ophthalmology, neurology and rheumatology consultations may be beneficial when evaluating a patient with suspected Behçet's disease. A positive pathergy provocation test may further support the diagnosis [17]. The International Study Group criteria for the diagnosis of Behçet's disease [18] are depicted in Table 49.15.

Treatment. Aphthae may be treated palliatively with topical or intralesional corticosteroids, topical tacrolimus and/or with viscous lidocaine (lignocaine) applied topically to individual lesions. Colchicine (0.6 mg two to three times daily) may also be used to treat mucocutaneous manifestations, although this treatment option is limited by gastrointestinal intolerance and requires monitoring for neutropenia [1,19,20]. Dapsone in combination with colchicine has anecdotally been effective in treating Behçet's disease [21]. Behçet's disease that has manifestations other than mucocutaneous involvement may be treated with systemic corticosteroids, although such treatment may not control severe ocular, neurological or non-vasculitic vascular disease [2,3,7,11,13]. Immunosuppressive agents such as azathioprine, methotrexate or ciclosporin may be used in the treatment of patients with severe Behçet's disease [2,22]. Treatments for Behçet's disease are summarized in Table 49.16.

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Table 49.15 International Study Group criteria for the diagnosis of Behçet's disease [18] (applicable only in the absence of other explanations for the clinical findings).

Recurrent oral ulceration	Minor aphthous, major aphthous, or herpetiform ulceration observed by physician or patient that recurred at least 3 times in one 12-month period
Plus two of the following criteria:	
Recurrent genital ulceration	Aphthous ulceration or scarring observed by physician or patient
Eye lesions	Anterior uveitis, posterior uveitis, or cells in vitreous on slit-lamp examination; *or* retinal vasculitis observed by ophthalmologist
Skin lesions	Erythema nodosum observed by physician or patient, pseudofolliculitis or papulopustular lesions; *or* acneiform nodules observed by physician in post-adolescent patients not receiving corticosteroid treatment
Positive pathergy test	Read by physician at 24–48 h

Table 49.16 Treatments for Behçet's disease.

Palliative treatment of aphthae
Topical corticosteroids
Intralesional corticosteroids
Topical tacrolimus
Topical viscous lidocaine (lignocaine)
Mucocutaneous manifestations
Colchicine (0.6 mg two to three times daily)
Dapsone
Dapsone and colchicine
Systemic involvement
Systemic corticosteroids
Immunosuppressants for most severe disease
• Azathioprine
• Methotrexate
• Ciclosporin

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Bowel-associated dermatosis–arthritis syndrome (see also Chapter 59)

Definition. Bowel-associated dermatosis–arthritis syndrome (BADAS) is defined by the presence of pustular vasculitic lesions associated with blind loops of bowel, either from Billroth II or ileojejunal bypass surgery, or caused by IBD.

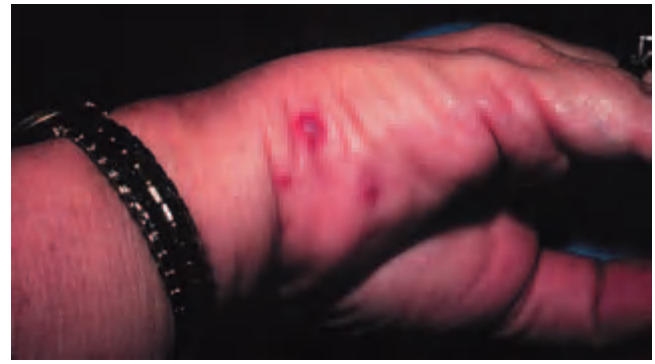

Fig. 49.24 Bowel-associated dermatosis–arthritis syndrome, showing a papule on an erythematous base.

History and nomenclature. BADAS was first described in 1971 as pustular vasculitis cutaneous lesions and serum sickness-like reactions in patients who had undergone jejunoileal bypass surgery for morbid obesity [1–4]. The term has now been extended to include the same syndrome in patients with IBD or in patients who have had creation of a blind loop following surgery for peptic ulcer disease [5].

Aetiology and pathogenesis. Blood vessel damage secondary to bowel flora antigen-associated circulating immune complexes is thought to be the pathogenesis of the cutaneous lesions. In these patients, peptidoglycans from gastrointestinal flora may be the antigenic trigger for immune complex-mediated vessel damage [4].

Histopathology. The changes noted in dermal blood vessels from early lesions of pustular vasculitis in patients with BADAS are similar to those in biopsies from patients with Sweet's syndrome [4–7] and Behçet's disease.

Clinical features. The cutaneous manifestations of BADAS begin as small macular lesions that progress into papules and later pustules on a purpuric base, most often on the arms and other areas of the upper body (Fig. 49.24). These pustules measure 0.5–1.5 cm in diameter and typically occur in crops, with each crop lasting up to 2 weeks, and recurring at intervals of several months [4,5,7–9]. Like Behçet's disease, pathergy seems to have a role in the distribution of the lesions. The cutaneous eruptions may be preceded by constitutional signs and symptoms such as fever, flu-like symptoms or myalgia, or by gastrointestinal upset. Arthralgia or non-erosive polyarthritis affecting hands, wrists and other peripheral joints have been described in patients affected by BADAS [1,3].

Table 49.17 Treatment of bowel-associated dermatosis–arthritis syndrome.

Secondary to previous bowel surgery
Surgical correction of bowel anatomy (may not eliminate symptoms if following blind loop)
Symptoms not secondary to or correctable by surgery
Systemic tetracycline
Systemic metronidazole
Systemic erythromycin
Treatments used to treat patients with cutaneous small vessel vasculitis (Table 49.7)
• Colchicine
• Dapsone
• Thalidomide

Diagnosis. It is important to distinguish between BADAS and Behçet's disease, as both may include oral aphthosis and lesions of pustular vasculitis. In order to distinguish between these two disease processes, an evaluation of the bowel, which may include barium studies as well as endoscopy, should follow a thorough patient history and physical examination. Clinicopathological evaluation of skin lesions is required but does not exclude lesions of Behçet's disease or early lesions of either PG or Sweet's syndrome.

Treatment. For patients with BADAS following bowel bypass surgery, surgical correction of bowel anatomy often eliminates the signs and symptoms. In other cases, such as patients with blind loops, surgical correction may be difficult and resolution of symptoms is therefore less likely. Manifestations of BADAS may be effectively controlled by the use of systemic tetracycline, metronidazole or erythromycin [4,5]. Systemic corticosteroids are typically unnecessary for the treatment of BADAS. Other treatments outlined for patients with cutaneous small vessel vasculitis, especially oral colchicine, dapsone or thalidomide have been used (Table 49.7). Treatments for BADAS are outlined in Table 49.17.

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Other neutrophilic dermatoses

Rheumatoid neutrophilic dermatosis [1,2]

Rheumatoid neutrophilic dermatosis was described by Ackerman in 1978 [3], and a number of cases have been described subsequently. It is thought likely to be immune complex-mediated, and tends to occur in patients with active rheumatoid disease and elevated rheumatoid factor. Lesions occur at any site, mainly the limbs and face, and may consist of papules, nodules or plaques, sometimes with an annular morphology. Urticated, vesicular and crusted lesions may all occur.

Histologically, there is a dense neutrophilic infiltrate that may extend into the epidermis or deeply into the subcutaneous fat; papillary microabscesses may be present [1,4]. Vasculitis is not seen but leukocytoclasis may occur. The picture is similar to that of Sweet's syndrome, but the latter usually has more prominent dermal oedema and less admixture with other cell types (some eosinophils, plasma cells and lymphocytes may be present in rheumatoid neutrophilic dermatosis).

Lesions may resolve spontaneously or as a result of treatment of the rheumatoid disease with immunosuppressive agents. Some plaques may be chronic over a period of months [5]. Topical or oral corticosteroids, dapsone and hydroxychloroquine have all been used with benefit.

A disorder termed 'neutrophilic lobular panniculitis associated with rheumatoid arthritis' is of uncertain aetiology, and has been classified as a lobular panniculitis with vasculitis. However, the few cases reported had perivascular neutrophilic infiltrate and leukocytoclasis without fibrinoid change or definite vasculitis, although one had associated leukocytoclastic vasculitis in the upper dermis [6].

Neutrophilic eccrine hidradenitis

Neutrophilic eccrine hidradenitis [1,7] is characterized by a neutrophilic infiltrate that is centred on and extends into the eccrine coils. Typically, the eccrine apparatus shows vacuolar degeneration or necrosis. Approximately 90% of cases have been in patients with malignancy, usually leukaemias, and there is a strong link with induction chemotherapy; most cases occur in the setting of neutropenia. Cytotoxicity of drugs on the eccrine coil is the most likely explanation for this dermatosis. Implicated drugs are discussed in Chapter 73.

Clinically, lesions may resemble those of Sweet's syndrome. They may affect predominantly the head

(especially the periorbital regions), neck and upper trunk, or may be limited to the limbs. Lesions may be plaques, papules or nodules, and may be grouped. They may resemble erythema multiforme, and sometimes occur as a pathergic phenomenon. Pustules and occasionally purpura may be present.

A paediatric variant of neutrophilic hidradenitis, variously termed 'idiopathic plantar hidradenitis' or 'recurrent palmoplantar hidradenitis' is discussed in Chapter 45. These disorders are not discussed further here as they are primarily neutrophilic eccrine rather than neutrophilic vascular reactions.

Subcorneal pustular dermatosis and neutrophilic bullous disorders

Subcorneal pustular dermatosis is a rare neutrophilic dermatosis that is associated with monoclonal gammopathy, multiple myeloma, lymphomas, PG, connective tissue disease and IBD [8]. Intraepidermal (neutrophilic) IgA pustulosis has some similarities, and has also been linked with monoclonal gammopathy (in 20% of cases) and with lymphomas. These disorders are bullous (Chapter 41) and are not discussed further here as they do not include a neutrophilic vascular reaction.

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Chapter 50

Diseases of the Veins and Arteries: Leg Ulcers

P.S. Mortimer & K.G. Burnand

Vasculogenesis, angiogenesis and arteriogenesis

Vasculogenesis is the first step in the development of the blood vessels and is the process whereby endothelial cells are generated from their mesenchymal precursors to form the primary vascular plexus of the embryo [1]. **Angiogenesis** is the process whereby existing vessels sprout, expand and remodel. Vasculogenesis precedes angiogenesis but the two processes continue in parallel during early development. The skin, being of ectodermal origin, is vascularized mainly by angiogenesis. A complex orchestration of molecular regulators is required for blood vessels to grow. First, extracellular matrix is degraded by local tissue proteases. This permits migration of budding endothelial cells under the influence of angiogeneic stimuli, particularly the family of vascular endothelial growth factors (vascular endothelial growth factors A, B, C and E plus placenta growth factor) and their receptors VEGFR-1 and VEGFR-2 [2]. Stabilization and maintenance of the newly formed vessels occurs mainly through the angiopoietins and the tie-receptors.

Differentiation into arteries, veins and capillaries is the responsibility of angiogenesis. **Arteriogenesis** produces rapid circumferential growth in the pre-existing collateral vessels, which are less perfused with blood under normal flow conditions [3]. It seems likely that endothelial stem cells from the bone marrow also contribute to the expansion of collateral vessels. While hypoxia is the main driving force for angiogenesis, inflammation mainly induces arteriogenesis.

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Arterial and peripheral ischaemic disorders

Arterial disease

Current concepts on aetiology of arterial disease, atherosclerosis and peripheral ischaemia. The mechanisms that initiate arterial disease are still poorly understood, but subtle endothelial injury is the likely final common pathway [1]. Evidence suggests that cardiovascular risk factors induce endothelial injury and endothelial dysfunction. Endothelial progenitor cells derived from circulating mononuclear cells may protect against cardiovascular disease [2] and perhaps against atherosclerosis. Atherosclerosis is a patchy accumulation of lipid, mostly in the form of cholesterol within the intima of the vessel wall. Such plaques eventually ulcerate through the endothelial lining, presenting a highly thrombogenic surface [3]. Platelets adhere to the ulcerated plaque and aggregates (platelet thrombi) may embolize distally or may initiate local thrombosis. Inadequate collaterals, or rapid occlusion by thrombosis or embolism, will lead to tissue infarction (e.g. peripheral gangrene). Atherosclerosis is responsible for more than

90% of all arterial disease in the Western world. It affects 5% of men over the age of 50 years, of which 10% may develop critical limb ischaemia; this increases to 20% if diabetic patients are included [4].

Atherosclerosis of the lower limb vessels. Many patients present initially with claudication (cramping pain on walking, which is usually experienced in the posterior calf muscles and which is relieved by rest). The presence of persistent pain in the foot at night indicates the onset of critical ischaemia, which will lead to gangrene or ulceration if left untreated.

In the past, arteriosclerosis (hardening of the arteries) has been classified as a disease, but most authorities would now regard this as a physiological response to ageing. Thickening of the arterial wall, with an increase in collagen and calcium deposition, causes loss of elasticity and increased tortuosity of the vessels in the elderly [3]. Similar changes are seen in the vessels of younger patients with hypertension.

Clinical features [3–6]

All aspects of the patient's history and lifestyle are relevant, with particular attention being paid to risk factors such as cigarette smoking, hypertension, diabetes, diet, hyperlipidaemia, lack of exercise, obesity, occupation, medication (including oral contraceptive pill in females and use of β-blockers [7]) and family history of cardiovascular disease.

Patients usually present with intermittent claudication, but ischaemic ulceration or infarction of the skin is the likely presenting feature to a dermatologist (Fig. 50.1). As the disease progresses, rest pain occurs. This is experienced predominantly in the foot or calf, usually at night. Altered skin colour (pallor or deep erythema) indicates ischaemia, and may be accompanied by other skin trophic changes such as dryness, scaling, loss of hair and thickened nails (Fig. 50.2).

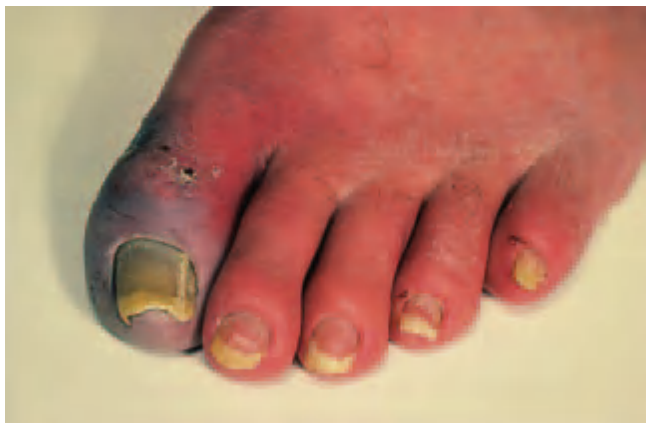

Fig. 50.1 An ischaemic hallux with pregangrene; the rest of the foot has an ischaemic erythema.

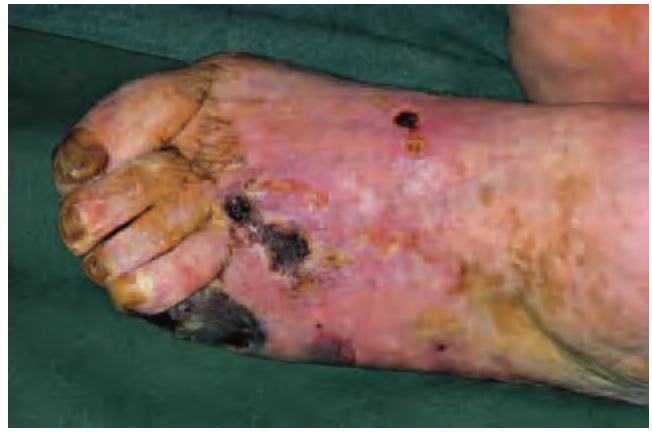

Fig. 50.2 An ischaemic foot showing patchy areas of gangrene and rubor. The skin is flaky and the nails are brittle.

A full general examination is essential. Particular attention should be paid to signs of anaemia, polycythaemia, xanthelasma and other xanthomatous deposits. Genetic disorders such as pseudoxanthoma elasticum and Marfan's syndrome should be considered. Cardiac examination should focus on dysrhythmias, particularly atrial fibrillation, murmurs and signs of heart failure. Abdominal examination should exclude the presence of any pulsatile mass, suggestive of an abdominal aortic aneurysm. The fundi should be examined for evidence of diabetic and hypertensive retinopathy. The blood pressure should be taken in both arms; a marked difference suggesting a stenosis or occlusion of the subclavian artery (although ischaemic disorders of the upper limbs are unusual).

The skin of the legs may have an erythematous or dusky mottled hue. If the ischaemia is marked, limb elevation causes pallor of the foot while dependency results in delayed but exaggerated hyperaemia, best observed on the dorsum of the foot (Buerger's sign) (Fig. 50.3) [8]. Inspection between the toes may reveal ulceration at sites of pressure (Fig. 50.4); small cracks may appear over the sole of the foot or heel (Fig. 50.5). Platelet emboli lodging in the plantar and digital vessels cause areas of discoloration, which are often present over many toes or on the sole. They often look like eccymoses initially and may be confused with vasculitis (Fig. 50.6). The aortic, femoral, popliteal, dorsalis pedis and posterior tibial pulses must be carefully palpated. Abnormally situated pulsations may indicate a collateral circulation or a congenital arteriovenous fistula. Auscultation over the course of the arteries may reveal the presence of a bruit indicative of turbulent flow. This is commonly caused by an up-stream stenosis or by an arteriovenous fistula (which usually causes a 'machinery' murmur, present throughout systole and diastole). Significant arterial disease demanding

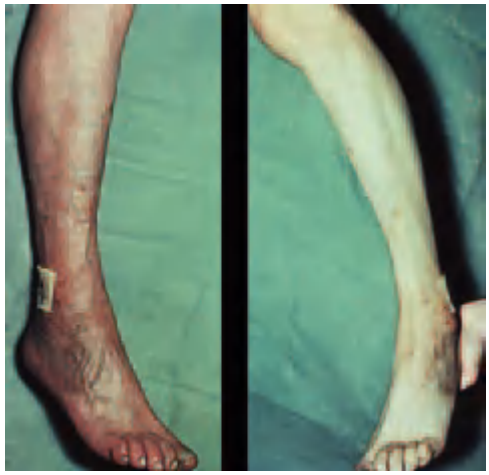

Fig. 50.3 Buerger's test showing postural colour change in an ischaemic foot—white when the foot is elevated (right) and red when lowered (left).

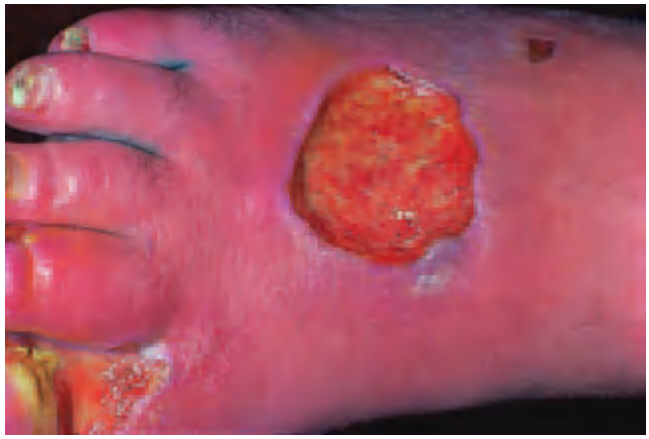

Fig. 50.4 An ischaemic ulcer on the dorsum of the foot with an ulcer arising in the first interdigital space. Pressure between the toes is a common consequence of tight bandages or footwear.

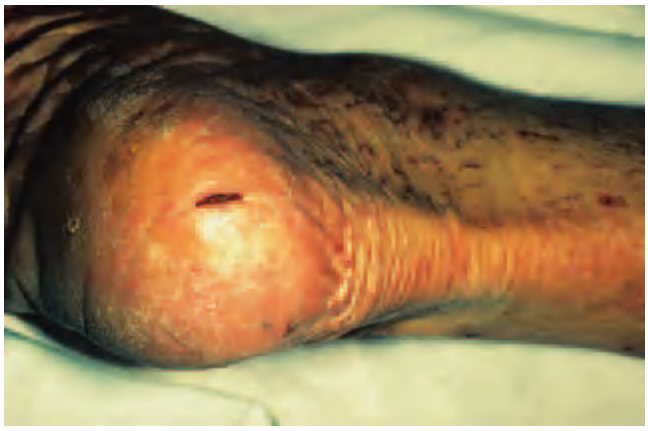

Fig. 50.5 An ischaemic 'crack' developing as a consequence of nutritional changes seen as hyperkeratosis and loss of suppleness of the skin of the heel.

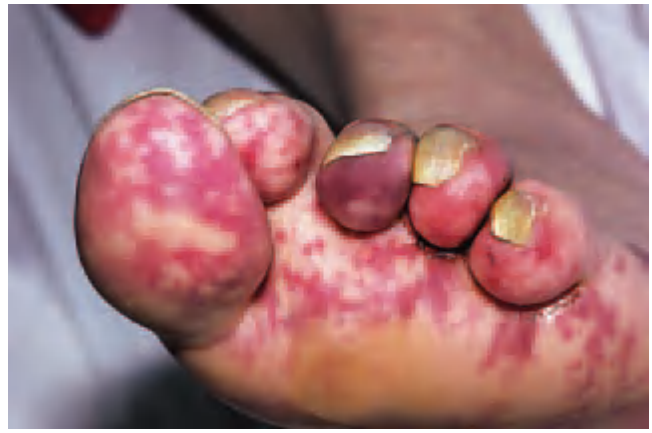

Fig. 50.6 Multiple platelet emboli into the skin of the foot.

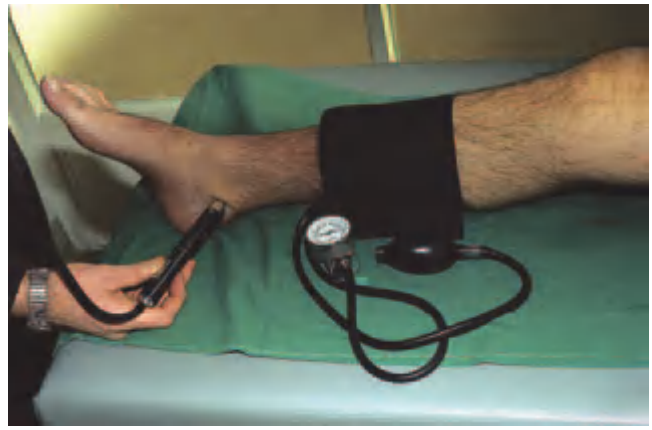

Fig. 50.7 Measurement of the ankle Doppler pressure using a sphygmomanometer cuff. The pressure at which the Doppler signal disappears in the leg is compared with the brachial pressure to give an index of blood supply.

further investigation is uncommon when the foot pulses are easily palpable.

Investigations. Confirmation of arterial disease can be obtained by measuring the ankle–brachial Doppler pressure index if a reduction or absence of pulsation is suspected or if a bruit is heard [9]. To perform this test, a sphygmomanometer cuff is placed around the limb above the ankle and inflated, after the Doppler ultrasound probe has been used to locate the dorsalis pedis or posterior tibial vessel (Fig. 50.7). The red cells flowing past the tip of the ultrasound probe deflect the beam, creating an audible noise. As the cuff is inflated above systolic pressure, flow in the artery ceases and the noise disappears. This pressure can be obtained for all vessels at the ankle and compared with the brachial artery pressure. This ankle–brachial systolic gradient is normally unity. A fall in the pressure of the ankle vessels results in a reduction of the pressure index. A ratio between 0.5 and 0.9 corresponds with claudication; less than 0.5 suggests arterial

ischaemia, and is associated with rest pain and gangrene. Falsely high indices may be obtained in some limbs if the vessels are very calcified and fail to compress at systolic pressure. This is especially true of diabetic limbs.

A more accurate means of assessment is to measure the Doppler pressures after exercise. This exaggerates the fall in the arterial pressure, allowing detection of minor reductions in blood flow; the degree of the post-exercise pressure fall is indicative of the severity of the ischaemia. Attenuation of the sound heard through the Doppler stethoscope when the limb is raised is another easily elicited sign of severe ischaemia. Other tests used to assess ischaemia include measurement of the transcutaneous Po_2 using a heated (Clark's) electrode applied to the skin of the lower limbs and compared with a reference site on the chest wall [10,11] (which may include a failure to increase with inhalation of oxygen), and isotope-washout studies (which estimate clearance of inert isotope from a tissue injection [12]).

Investigations in patients suspected of having peripheral arterial disease or critical leg ischaemia [4] should include: a full blood count to exclude anaemia or polycythaemia; electrolytes, urea and creatinine to monitor renal function; and an electrocardiogram (often repeated after exercise) to detect rhythm abnormalities or cardiac ischaemia. A chest radiograph allows the measurement of cardiac size and excludes a coincidental bronchogenic carcinoma, which is common in smokers. Diabetes should be excluded, and plasma cholesterol and fasting triglycerides should be measured.

When surgery is contemplated, a detailed assessment of the anatomy of the arterial tree is also required. Duplex Doppler scanning is often the initial investigation, especially as a screening test [13,14]. A duplex Doppler scan provides both a B-mode image of the artery and a measurement of blood velocity; these can be combined to provide a map of the stenoses and occlusions within the arterial tree from the aorta to the crural (calf) vessels. The greater the velocity, the tighter the stenosis. Most surgeons also obtain an arteriogram before angioplasty or bypass surgery is performed. Arteriography is performed by injection of non-ionic contrast media into the vascular tree, usually through a retrograde catheter inserted into the common femoral artery at the groin over a guide wire (Seldinger-type retrograde aortography), or from an intravenous or intra-arterial injection using digital subtraction equipment to enhance picture quality [15]. Each of these methods has its proponents, but retrograde aortography performed as an outpatient, or a combination of intravenous digital subtraction arteriography of the aorta, iliac and femoral vessels combined with femoral arteriography of the distal vessels, provide equivalent information.

The further management of arterial disease is discussed under the heading of the individual diseases, and usually requires referral to an appropriately experienced surgeon.

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Differential diagnosis. Thromboangiitis obliterans (Buerger's disease, p. 50.7) may be very difficult to distinguish from atherosclerosis. The preservation of the proximal femoral and popliteal pulses and the early age at first presentation usually indicate the possibility of this condition. Associated venous thromboses and characteristic histological changes on vessel biopsy make the diagnosis more secure.

In patients with acute ischaemia it is important to exclude the possibility of embolism, which may be suggested by a recent myocardial infarction or the presence of atrial fibrillation. Transoesophageal echocardiography can demonstrate small amounts of intracardiac thrombus and structural abnormalities, especially of the valves, with great accuracy [1].

Rarer causes of ischaemia include external arterial compression (popliteal entrapment or a cervical rib), dissecting or thrombosed aneurysms, ergot poisoning, intra-arterial injections of noxious substances, traumatic disruption of the arterial wall, coagulation disorders, particularly polycythaemia and thrombocytosis, and various forms of vasculitis. Diabetes must always be considered as a potentiating condition, even in patients with atherosclerotic disease.

Claudication pain may be mimicked by arthritic conditions of the hip, such as osteoarthritis or rheumatoid arthritis. Pain in the leg may also result from referred pain

arising in the lumbosacral spine, and spinal claudication is sometimes very difficult to differentiate from arterial claudication. Occasionally, venous claudication may be misdiagnosed. Ischaemic rest pain may have to be differentiated from other painful conditions of the feet and toes, such as gout, interdigital neuromas, glomangiomas, ingrowing toenails, flat feet, calcanial bursitis and plantar fasciitis. Other causes of gangrene may need to be excluded (e.g. clostridial infection, diabetes, other causes of vascular obstruction, vasculitis and coagulation disorders).

Prognosis. In addition to the surgical mortality discussed above, patients with atherosclerotic disease of the lower limb vessels usually have other arteries affected. The extent of the atheroma in the coronary and carotid arteries determines the life expectancy of the patient, although antiplatelet agents [2], lipid-lowering agents and bypass surgery may improve the prognosis as well as the symptoms of ischaemia. Silent myocardial infarction is present in about one-third of patients who have intermittent claudication.

Treatment. Treatment options differ for claudication, rest pain or gangrene and acute limb ischaemia.

Claudication. The indications for intervention in a patient with claudication are always relative and must be weighed against the risks of the procedure and the fact that the condition normally has a very benign course [3]. Only 5% of all patients with claudication progress each year to develop rest pain or gangrene; a far greater proportion die every year from other causes, such as myocardial infarction. Patients with intermittent claudication are therefore usually managed conservatively at first, as collateral vessels may develop with an associated improvement in the symptoms.

Patients should be advised to stop smoking, and encouraged to walk through the pain as this tends to stimulate development of collateral circulation, to recruit capillaries and to increase the claudication distance. There are a number of studies demonstrating that supervised exercise programmes are as effective as therapeutic intervention in alleviating claudication, although the benefits may not persist [4]. Antihypertensive treatment should not be instituted in the early stage of claudication in patients whose systolic pressure in the limb in the standing position is lower than 80 mmHg. An alternative medication such as an angiotensin-converting enzyme inhibitor should be considered if the patient is already taking a β-blocker, as withdrawal of the latter may improve the walking distance. Some drugs improve cardiac stroke volume and hence enhance peripheral perfusion. Many vasodilators have been tried but there are few reports that they are of benefit [5]. Similarly, anticoagulants, antiplatelet agents, haemorrheological drugs and prostaglandin analogues are mostly of little efficacy [6].

Further investigation is indicated if the claudication distance remains unacceptable when the patient has stopped smoking after a reasonable period of conservative treatment. Stenotic lesions confirmed by arteriography can be treated by balloon dilatation (angioplasty), using specially designed coaxial balloon catheters that are constructed to withstand high external pressures [7]. This technique is usually performed by radiologists under image-intensifier control, using a percutaneous femoral puncture to insert the balloon catheter in a prograde or antigrade direction. A specially slippery guide wire is used to cross the lesion and the balloon is then railroaded into the stenotic area and inflated [8]. As the balloon distends, the plaque is compressed outward and longitudinal fissures are produced. This technique works best on stenoses in large proximal vessels, and least well on long occlusions of the distal arterial tree. The results remain disappointing, with a 30% restenosis rate at 1 year. Most clinicians would, however, still try angioplasty as the first line of management for a single iliac stenosis causing moderate or severe claudication [9]. Potential complications include arterial rupture, aneurysm formation, thrombosis and dissection.

The technique of subintimal angioplasty has increased the scope of angioplasty to treat longer, more peripheral stenoses, although its long-term efficacy still remains to be assessed. Long-term follow-up data are not yet available but recurrent stenosis in and around the stents still seems to be a problem. Chemically treated slow-release stents may overcome 'restenosis' in the future. Angioplasty and stenting has become the standard method of treating stenoses and short occlusions of the iliac vessels. A number of endoarterial devices have been developed but have still not found widespread application. Most are based on a cutting or resecting principle and have similarities to transurethral resectoscopes.

Surgical endarterectomy or bypass remains the treatment of choice for extensive occlusions of the iliac or femoropopliteal segments. Aortofemoral bypass has an excellent 5-year patency (90–95%), but the operative mortality varies between 1 and 5% [8]. Femoropopliteal vein bypass grafting has a lower 5-year patency (60–70%) but a lower operative mortality (usually less than 1%) [10]. Distal bypass surgery (the lower anastomoses being below the popliteal artery into one of the three crural vessels) has no part to play in the treatment of claudication, although this procedure is of considerable value in patients with rest pain and early gangrene (see below) [11]. Operative or chemical lumbar sympathectomy does not help to relieve claudication [12].

Rest pain or gangrene. Once rest pain or early gangrene have developed the situation changes, for if this state is

left untreated amputation will be necessary to relieve pain and preserve life. Patients with rest pain or gangrene must be rapidly admitted and investigated, because successful revascularization can avert limb loss [4]. The position of the foot suffering from necrosis should be as low as possible without inducing oedema. Any anaemia or polycythaemia should be corrected, and if diabetes is found this should be brought under control by diet and hypoglycaemic agents. Dehydration and infection must be treated. The increasing use of more distal surgery with bypasses to the dorsalis pedis, posterior tibial, peroneal and even plantar vessels has saved many limbs that in the past would have certainly been amputated [11,13]. Angioplasty, stenting and surgery to the proximal vessels are, of course, still of value if these arteries are the main sites of disease. In patients without evidence of frank ischaemia, chemical sympathectomy may alleviate rest pain [14]. Prostacyclin, prostaglandin E and prostacyclin analogues, such as iloprost, are being tried in patients in whom a bypass cannot be constructed. There is now some evidence that these compounds can preserve a small proportion of threatened limbs [15]. Therapeutic angiogenesis with vascular endothelial growth factors has been tried experimentally but there is as yet no evidence of its efficacy.

The immediate amputation rate can be lowered from the 80% of a few years ago to 40% or less by a policy of aggressive reconstruction, but this improvement is probably at the cost of a few higher amputations and some increased loss of life when graft failure is associated with a further episode of ischaemia and consequent amputation [16].

Acute limb ischaemia. Patients presenting with acute limb ischaemia should be rapidly assessed and, unless there is unequivocal evidence of an embolus (suggested, for example, by normal vessels in the other limb, atrial fibrillation or recent myocardial infarction), the patient should have urgent catheter angiography to confirm the diagnosis and to assess the cause of the occlusion. This should be followed by infusion of a tissue plasminogen activator into the thrombus or embolus via the catheter unless the state of the limb demands urgent revascularization or amputation [17]. Repeat angiography, to confirm continuing or successful thrombolysis, is required at frequent intervals, and residual stenoses responsible for the thrombosis may require angioplasty, stenting or surgery. Patients whose vessels are opened up by thrombolysis must remain on anticoagulants.

Balloon-catheter embolectomy should be reserved for embolic occlusions. When platelet emboli are suspected, aspirin or dipyridamole may be prescribed before a definitive surgical or radiological intervention to remove the source of the emboli.

Amputation remains the final option in all types of ischaemic disease of the lower limbs where revascularization is impossible or ineffective. The value on subsequent mobility of preserving the knee joint is well recognized. The mortality of amputation stays stubbornly high (15–20%).

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Painful vascular disorders of the extremities

Small vessel calcification (calciphylaxis) [1,2]

Arterial calcification is a common and usually symptomless complication of chronic renal failure. More rarely, especially when associated with hyperparathyroidism, there is complete vascular occlusion and infarction of the skin (Fig. 50.8). There is usually extensive livedo reticularis and patchy subcutaneous thickening attributable to fat necrosis, which often underlies the infarcted skin, involving principally the inner aspects of the thighs [3]. The radiological appearances are characteristic with considerable small vessel calcification in addition to the involvement of large vessels. The pathogenesis is unexplained, but the term calciphylaxis is often used because of the similarity to changes occurring in rats in experiments that induced hypercalcaemia and metastatic calcification. Uraemia and hyperphosphataemia are often

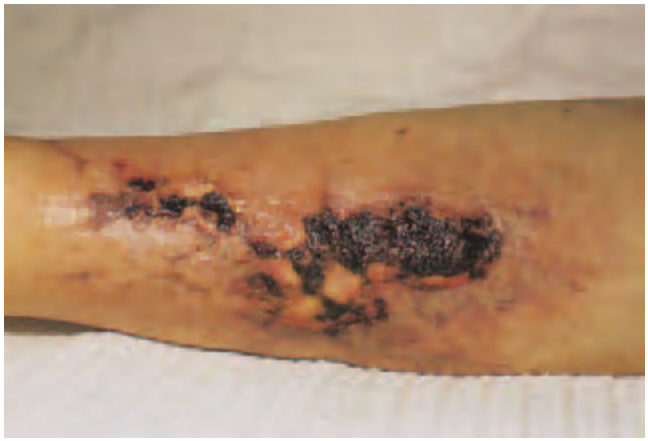

Fig. 50.8 Ulceration associated with calcification of arteries in secondary hyperparathyroidism.

more obvious than hypercalcaemia in the human. Women are most often affected. The exact role of hyperparathyroidism and, indeed, even its necessity for the diagnosis, is debated. Mehta *et al*. [4] identified a functional, although not quantitative, protein C deficiency in five patients: a hypercoagulable state has been inferred and the histology of the skin often reveals fibrin in the small vessels (Chapter 48). The prognosis is poor and treatment unsatisfactory. The management of uraemia, serum calcium and phosphorus is essential. Parathyroidectomy is only appropriate where there is definite evidence of hyperparathyroidism. The relevance of controlling a hypercoagulable state is unproven.

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Thromboangiitis obliterans [1,2]

SYN. BUERGER'S DISEASE [1]

This appears to be a distinct condition separate from other forms of vascular occlusion [2,3], with differences in the pathological appearance of the vessel wall, and in the affected population compared with other arterial diseases [2].

Definition. This condition was first recognized as an obliterative disorder of peripheral arteries of young males by Leo Buerger in New York in 1908 [1]. The affected young men were all heavy smokers and the disorder involved the small vessels of the upper limb much more commonly than in atherosclerosis. It is common in the Middle and Far East, and in the Indian subcontinent, but there is no evidence that Jews are particularly affected (Leo Buerger worked at Mount Sinai Hospital in New York where the clientele were almost exclusively Jewish). The accompanying veins and nerves are involved in the inflammatory process and there are often other signs of non-specific inflammation, such as erythema nodosum.

Aetiology [2]. The aetiology of the condition is unknown, although tobacco addiction is invariably a major contributing factor, and a failure to overcome this addiction is associated with progressive occlusion of the vessels. Autoantibodies have been found in the circulation within the blood [4] and there may be changes in the behaviour of complement and the release of endogenous vasodilators and anticoagulants. In particular, antiendothelial cell antibodies are present in high titre in active disease, may be used to monitor disease activity, and may have a pathogenic role [2] (Chapter 49).

Pathology [2,5]. The full thickness of the vessel wall is invaded by lymphocytes, eosinophils, plasma cells and monocytes, especially disrupting the internal elastic lamina, and there is occlusion as a result of highly cellular thrombosis. Accompanying nerves and veins may become involved in the inflammatory process. All changes are segmental or focal. At a later stage in the disease, fibrosis occurs, which spreads to involve surrounding structures.

Clinical features. The condition usually appears in men between the ages of 25 and 40 years; however, women may also be affected. Pain is the main presenting symptom and may be of several types: intermittent claudication; rest pain, more severe at night; pain associated with ischaemic neuropathy, ulceration or thrombophlebitis. Sensitivity to cold is a frequent complaint. Claudication of the foot is especially characteristic [2].

Ulceration or gangrene may develop early in the disease, particularly following trauma, and often starts around the sides of the nails or tips of the digits (Fig. 50.9). Trophic changes, thrombophlebitis and oedema are also often present. Red or cyanotic acral colour changes are often unilateral, asymmetrical or may affect isolated digits.

Recurrent venous thrombosis is a frequent problem and may take the form of superficial red streaks and cords of 0.5–3 cm [2] or deep-vein thrombosis presenting with pain and swelling. Erythema nodosum may also develop (Chapter 49).

Ischaemic areas are found on the tips of the fingers and toes and may initially present as chronic painful paronychia. The proximal pulses are usually present (the femoral, popliteal and brachial), while the distal pulses

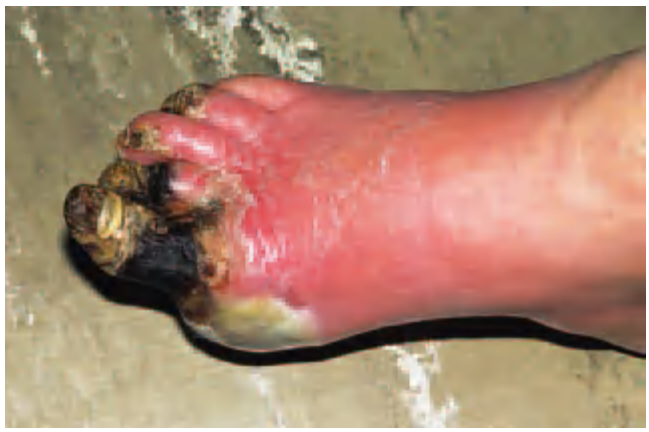

Fig. 50.9 Ischaemic toes in Buerger's disease.

Fig. 50.10 An arteriogram in a patient with Buerger's disease. No major vessels are seen, just multiple collateral arteries.

(dorsalis pedis, posterior tibial and radial) are lost at an early stage.

Investigations. The erythrocyte sedimentation rate (ESR) is often elevated, antiendothelial cell autoantibodies may be detected, and arteriography is often diagnostic (Fig. 50.10). The proximal vessels are usually entirely normal while the distal arteries are diffusely affected with multiple stenoses and occlusions. Many collaterals are often present and are typically described as 'corkscrew' collaterals. Arterial biopsy may show the histological changes described above.

Differential diagnosis. This includes atypical 'young onset' atherosclerosis, diabetic vasculopathy and rheumatoid arteritis. Collagen-vascular diseases, such as scleroderma and systemic lupus erythematosus, must also be considered in the differential diagnosis. Multiple emboli derived from a proximal source may pose real diagnostic difficulty, and ergotism must not be forgotten. In mild cases, acrocyanosis, livedo reticularis and erythromelalgia may be considered. Gout and osteoarthritis of the hip and knee may cause leg pain, and interdigital neuromas and metatarsalgia cause foot pain. Spinal cord compression and sciatica can also be responsible for pain in the lower limb.

Treatment and prognosis. The dermatologist may be faced with the problem of a patient referred for ulceration or erythema of the foot and toes. Once the diagnosis is established, the matter is best dealt with by the vascular surgeon, whose advice should be sought. Collateral anastomosis can be expected to occur during phases of inactivity of the disease. Warmth, bed rest and strict abstinence from smoking are the main facets of conservative treatment. There is little evidence that anticoagulants or corticosteroid therapy influence the outcome. Surgical or chemical sympathectomy is usually helpful; vasodilators (except alcohol and reflex warmth) are not [6]. In a double-blind study of a chemically stable prostacyclin analogue, 85% of patients treated showed ulcer healing or relief of pain compared with 17% of an aspirin-treated group [7].

Arterial reconstructive surgery has little part to play in the management of this condition because of the distal nature of the disease. After sympathectomy every effort should be made to avoid major amputations by the use of antibiotics and, when necessary, toe excisions. Below-knee amputation may eventually be required, particularly if gangrene extends to the foot. It should not be unreasonably delayed. The prognosis is poor in those patients who continue to smoke; hands as well as feet may be lost.

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Erythromelalgia [1]

Definition [2]. A condition of painful red extremities in which a sensation of burning is associated with a vasodilatation of the affected skin. The synonyms erythermalgia [3] and erythralgia are confusing and will not be used further. Essentially there are three types:
1 *Type 1*: Associated with thrombocythaemia and relieved by aspirin;
2 *Type 2*: Primary or idiopathic and usually congenital, provoked by exercise or exposure to warmth;
3 *Type 3*: Secondary to inflammatory or degenerative peripheral vascular disease.

Pathogenesis. Type 1 is the result of thrombocythaemia and is seen in polycythaemia and myelofibrosis. It may be unilateral or even affect one finger or toe [4–7]. It is not often relieved by cooling, and often progresses to ischaemic necrosis. There is fibromuscular intimal proliferation and occlusive thrombosis of digital arterioles and arteries [8].

Little is known of the primary pathology of type 2 [9]. It is confined to the lower legs and does not progress to ischaemia. It is often familial and the gene has recently been located to chromosome 2 [10]. Attenuation of vasomotor nerves, beginning in childhood, was observed in one case and caused diminished capacity to vasoconstrict, equivalent to a sympathectomy [11]. Other authors [12,13] have implicated a temperature-triggered release of chemical pain mediators and vasoactive substances, especially serotonin. Microvascular arteriovenous shunting has been proposed as the cause [14], symptoms being caused by tissue hypoxia induced by a maldistribution of skin blood flow. Dysfunction of autonomic nervous function has been demonstrated [15] as well as disturbances in the regulation of microvascular perfusion [16]. Post-ganglionic sympathetic dysfunction and denervation hypersensitivity may have a pathogenic role whereas local neurogenic and endothelial function appear to be unaffected [17].

Pain occurs in direct relationship to the temperature of the limb, occurring about a 'critical point', which normally lies between 32 and 36°C and which is constant for each individual [18,19]. Pain is not a direct result of vasodilatation itself and can be induced or maintained by warming the limb with its blood supply occluded by a cuff. Pain is worse with the limb dependent, irrespective of its temperature, and may be induced by obstructing venous return. Because such manoeuvres do not cause pain or distress in normal subjects, it must be assumed that those who suffer from erythromelalgia have an undue sensitivity to warmth in the skin of the extremities.

In considering secondary erythromelalgia [18,20], it must be understood that peripheral vascular disease is often characterized by high resting flows and vasodilatation of the microvascular bed. There is usually a failure to respond to a further increase in metabolic demand, such as reflex hyperaemia, or to the needs of tissue repair following injury and ischaemic necrosis.

Clinical features. Types 1 and 3 are rare in childhood, and most commonly affect those over middle age. The idiopathic type is more likely to be seen in younger subjects and is more often bilateral [19]. A dominant inheritance was noted in 19 out of 51 affected members of a family of five generations [21]. Females are more often affected [22]. In types 1 and 3, the hands and feet are usually involved but sometimes only a part of one extremity is affected. The principal feature of erythromelalgia of all types is that attacks are precipitated by exercise or heat, such as a warm bed, and are relieved by rapid cooling, such as immersion in iced water. The patient complains of intense burning associated with erythema and increased warmth of the extremity. Attacks last from a few minutes to several hours. A warm climate and fever may also increase the distress.

Ulceration and trophic changes, indicating a relative insufficiency of blood supply needed for tissue repair, may occur in all three types but are more likely to be a presenting sign in secondary erythromelalgia associated with arterial disease, or may result from cold immersion injury when relieving symptoms.

Differential diagnosis. The fully developed characteristics of the syndrome and the description given by the patient seldom leave doubt about the correct diagnosis. Complex regional pain syndrome (reflex sympathetic dystrophy) following trauma can produce a similar clinical pattern. The effect of dependency, and the bizarre measures usually taken by the patient to obtain relief, are also indicative of the diagnosis.

The relationship to temperature can be confirmed by reflex or direct heating to above the 'critical level'. Some young patients may complain of pain and colour change of the lower legs on prolonged standing. This presentation has been termed angiodyskinesia (p. 50.11).

Associations. Once the diagnosis is confirmed, the patient must be investigated for possible organic causes of the syndrome. These include hypertension, diabetes, rheumatoid arthritis, lupus erythematosus [23], thromboangiitis obliterans, gout and vasculitis [24]. The most important association of secondary erythromelalgia, however, is with myeloproliferative disorders, for example polycythaemia vera or thrombocythaemia, of which it may be a presenting and premonitory symptom, often by several years. Of 51 cases in one series [19], 30 were idiopathic and 10 of the remaining 21 had some form of myeloproliferative disease. Further cases of thrombocythaemia have been reported [7]. Vasoactive drugs, such as nicardipine, have been incriminated [25,26] as has mercury poisoning [27].

Prognosis. Although held to be poor—even fatal—in the past, this gloomy forecast was probably affected by the inclusion of cases of atherosclerosis and polycythaemia rubra vera. Nevertheless, there is a significant decrease in survival compared to the general population and most cases get worse over time [22].

Treatment. No treatment is consistently effective with a dearth of adequate studies. Management rests with avoiding exacerbating factors, and controlling secondary and underlying factors [28]. Thrombocythaemia, or causes of inflammatory vascular disease, must be treated where possible. Small doses of aspirin give considerable relief in some cases—presumably by preventing platelet aggregation and clopidogrel may be a more effective antiplatelet agent [5,29]. Patients with vasodilatation and warmth in their affected painful extremities prefer immersion in cold water. Elevation also provides some relief by decreasing oedema. Some have claimed relief of erythromelalgia with benoxybenzamine hydrochloride or propranolol [30]. Amitriptyline is often a useful first-line therapy. Pain has been totally controlled using epidural blocks for 3 weeks to obtain healing of ulceration. The response of one family to pizotifen has been reported as spectacular [31]. In a child with erythromelalgia and growth hormone deficiency, recombinant growth hormone therapy immediately relieved pain and healed cutaneous ulcers [32].

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Complex regional pain syndrome

SYN. COMPLEX REGIONAL PAIN SYNDROME TYPES I AND II; REFLEX SYMPATHETIC DYSTROPHY; CAUSALGIA; SUDECK'S ATROPHY

Complex regional pain syndrome (CRPS) is the name now given to a syndrome of chronic pain and hyperalgesia, associated with sensory, motor, autonomic and dystrophic disturbances, usually in a limb. Patients typically describe pain, swelling and difficulty with use of the affected limb. The pain has a burning or deep aching quality and is aggravated by movement, consequently there is a tendency not to use the limb. Similarly, hyperalgesia causes guarding of the limb to protect it. The skin takes on a deep red to blue colour, suggesting vasodilatation, and is initially warmer than the unaffected contralateral limb but becomes cooler in the later stages. Oedema may result from disuse and dependency, and atrophy develops (Sudeck's atrophy). Increased blood flow is an important diagnostic feature of early CRPS [1]. It is usually demonstrated objectively using a three-phase bone scan [2]; the delayed phase of this scan is very sensitive, and a segmental diffuse increase in uptake of radionuclide is very specific, but additional vascular scans may be helpful in some patients. Increased periarticular uptake is also typically seen.

The classic syndrome usually develops after a trivial injury or surgical operation (CRPS type II, causalgia) but the same syndrome can occur for no obvious reason and where peripheral nerves remain undamaged (CRPS type I, reflex sympathetic dystrophy) [3]. The mechanism for both types has been better clarified; there appears to be inhibition of cutaneous sympathetic vasocontrictor neurones, but in chronic CRPS the secondary effect of adrenergic supersensitivity overcompensates in response to this loss of sympathetic vasomotor control [4].

Treatments include physical therapy (first-line) with the addition of anticonvulsants, antidepressants and then opioid analgesia according to severity. Severe cases may require regional anaesthetic blockade [5]. In selected patients with severe and chronic pain, electrical stimulation of the spinal cord can reduce pain and improve quality of life [6].

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Angiodyskinesia

Paraesthesiae, painful burning sensations and redness or pallor of the legs after prolonged walking or dancing have been described in young people [1,2] and it has been suggested that these were a consequence of abnormal functioning of arteriovenous communications. The term 'angiodyskinesia' has been applied to this condition [3].

Under this title, Ryan and Wilkinson described a blotchy erythema of the legs in a 14-year-old boy [4]. His condition developed at the same time as osteochondritis dissecans. The erythematous areas were 2–3°C warmer than the adjoining skin, and disappeared when the patient was recumbent, reappearing and becoming uncomfortable when he was standing. These features suggest failure of the normal vasoconstriction that occurs when a limb is lowered. The condition was more marked in warmer conditions and after a bath.

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Restless legs syndrome

This syndrome characterizes a discomfort that forces those affected to fidget and to move their legs when at rest. Restless legs syndrome (RLS) is a disorder of motor activity with a circadian pattern, which occurs frequently in neurological disorders such as Parkinson's disease [1] but also in fibromyalgia and rheumatoid arthritis [2]. Dopaminergic agents and dopamine agonists are considered to be the treatment of choice [3]. Repeated blood donation and resulting iron deficiency can also be associated with RLS [4].

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Arteriovenous shunts and aneurysms

It is convenient to consider separately the following:
1 Arteriovenous shunts;
2 Arteriovenous aneurysms ('fistulae'):
(a) congenital;
(b) acquired.

Arteriovenous shunts

These form an alternative peripheral system of blood flow and are an integral part of a reserve or compensating mechanism at times of capillary stress and injury. They are called into play when the microcirculation is damaged and the superficial vessels congested, diverting blood away from the papillary capillary plexus [1]. Their presence can be demonstrated by finding a high oxygen saturation in venous blood and a reduced circulation time [2]. They are active in venous hypertension and varicosity [3] and in leg ulcers [4], in atherosclerosis [5] and perhaps with the hormonal changes of pregnancy [6]. They are also active in psoriasis, with neoplasia [7] and in skin flaps. They may be responsible for the postural changes seen in angiodyskinesia, and are a feature of arborizing telangiectasia.

Persistent arteriovenous shunts cause local venous hypertension, which may lead to ischaemia [1]. The

changes this produces in the vessels make the interpretation of biopsies difficult.

Arteriovenous fistulae

Arteriovenous fistulae [8] consist of direct connections between larger arteries and veins and are always pathological. Their various congenital and acquired forms have been given a large number of descriptive titles (cirsoid aneurysm, aneurysmal varix, pulsating angioma, etc.) but are best described here simply as congenital and acquired. Localized and pulsating, they may present as red nodules with overlying telangiectasia, like a giant spider naevus. While most common on acral sites, they also occur in the head and neck and on the trunk.

Congenital

These are discussed fully elsewhere (Chapter 15). They result from failure of embryological differentiation into artery and vein [8]. The many clinical varieties that affect the skin and visceral organs have been grouped together under the term congenital dysplastic angiopathy [6]. When such congenital fistulae involve the limb vessels they often give rise to distinctive physical signs which are described below.

Acquired

These are almost always traumatic; they are often large, and may therefore cause significant cardiovascular effects. Early diagnosis is important. Treatment is entirely within the province of the vascular surgeon, who should be consulted if there is suspicion of the existence of such a fistula. Treatment is by inserting a covered stent to close off the opening from 'within', or by open surgical closure.

Signs and effects of arteriovenous fistulae [9,10]

Traumatic fistulae following penetrating wounds, or occasionally operations, can occur anywhere in the body. They should be suspected whenever venous varicosity is unilateral or when signs of venous insufficiency develop unexpectedly after an injury. Increased warmth of a limb and the finding of a machinery-like constant murmur or palpable thrill establish the diagnosis. Arteriography confirms the site and indicates the size of the communication. Congenital fistulae commonly affect the limbs and are often multiple. They should be suspected when unilateral varices present early in life without a genetic background. The limb is warmer and may be larger than the contralateral limb. Slowing of the pulse produced by inflation of a proximal tourniquet at the root of the limb (Branham's sign) is indicative of a large arterial shunt.

The effects of arteriovenous aneurysms depend on their size and the volume of blood flow through the fistula, rather than its site. When small, no cardiovascular changes may be evident, although there will inevitably be some permanent diversion of blood from the capillary bed. Larger fistulae cause dilatation in the superficial veins distal to the site, with a varying degree of impairment of the arterial circulation. The cardiac output increases, often considerably; the heart is dilated and the diastolic blood pressure is reduced, increasing the pulse pressure.

In skilled hands, embolization under angiographic control is the most effective therapy. An alternative is to mobilize the vessel and ligate all the branches (skeletonization). It is now possible to insert a covered stent to block off a localized fistula and this is the treatment of choice in a traumatic fistula in an inaccessible location. Amputation may occasionally be necessary if congestive cardiac failure is a problem.

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Venous disorders

Anatomy, physiology and pathophysiology [1,2]

Anatomy

Although the general architecture of the veins is similar to that of the arteries, their walls are thinner, the middle (muscular) coat being particularly weak. Most veins are endowed with semilunar valves; these are usually in pairs, but sometimes only one, or sometimes three, are present. These valves are lined by endothelium and are found especially in the smaller veins and at the junction of these with larger branches. They prevent the reflux of blood and are particularly important in the leg, where their integrity, and that of the calf-muscle pump (the venous heart), must effectively counter the gravitational hydrostatic pressure. There are three systems: the deep veins; the superficial veins; and the communicating veins,

numerous and inconstant, connecting the other two systems. During muscular activity, blood is directed from the superficial to the deep system, from the foot to the thigh and up into the abdomen, such that venous blood returns towards the heart. Bicuspid valves are found in all three systems. The smallest veins containing valves lie at the dermal subcutaneous junctions [3] and are extremely variable. A complete avalvular state has been reported but, more often, valves are absent in just one of the three systems. Valves may become damaged, thickened or degenerate with age [4]. Thrombosis also causes vulvular destruction and a recanalized post-thrombotic vein is valveless, anatomically distorted and functionally inefficient [4]. There are approximately 80 potential communicating veins in the thigh and leg; the most important of these are considered to be the medial perforating veins (communicating veins) of the lower leg, the incompetence of which has been emphasized as a predominant factor in venous ulceration [4]. Many communicating veins link with a vein in the muscle before joining the deep veins, and are probably of little significance even when incompetent.

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Physiology

In health, venous return occurs as described above, the valves within the communicating veins preventing blood passing from the deep veins into the superficial veins of the legs. Factors affecting the normal venous return include the venous tone, the amount of muscular activity and the intrathoracic pressure. In the absence of muscular movement, an increase in the leg volume occurs without pitting oedema, and the tissue pressure rises considerably.

Little is known about the factors governing venous tone, but a loss of tone may be important in hypotensive or endotoxic shock, vasovagal syncope and in response to cooling [1,2]. Venous tone is reduced in pregnancy and it also changes during the menstrual cycle.

The efficient return of blood to the heart depends upon a functioning deep-vein system. In the erect posture, at rest, the pressure at the ankle is governed entirely by the individual's height (i.e. distance to the heart). Patients with venous disease were on average 1.4 cm taller in one study [3]. Venous pressure at the ankle is normally 70–100 mmHg (100–140 cmH_2O), dropping to 0–30 mmHg (0–40 cmH_2O) on exercise or recumbency, and remaining at about 55 mmHg (75 cmH_2O) while sitting [4]. The Western child spends 8–10 waking hours in a sitting posture, causing constantly high venous pressure [5]. There is also evidence that children in the developed world are no longer undertaking adequate physical activity [6].

Even apparently insignificant muscular movements of the lower leg cause a dramatic fall in venous pressure. This slowly returns to its original level after exercise ceases. A walking rate of only 40 paces/min is sufficient to empty the deep veins with a normal heel to toe gait. The venous network in the sole of the foot is emptied by compression from muscular contraction while standing and walking. This is known as the foot pump.

Physiology of small veins predisposing them to disease

The physiology of small veins is of particular importance. When venules and veins were first fully investigated [7–9] by electron microscopy [10], dye studies [11] and the identification of sites of increased permeability with radiolabelled carbon [12], it was appreciated that there was a gradient of permeability from arterioles to venules, with protein exchange occurring in the latter [12]. Endothelial contractility [12], leukocyte adherence and endothelial proliferation [13] all occur maximally at the venous end of the microvascular system. Manipulation of venous outflow compared with arterial inflow has a disproportionately greater effect on transcapillary exchange [7]. The blood enters the capillary bed under a reasonably constant head of pressure, and local shifts in capillary pressure are introduced by changes in the resistance presented by the effluent venules [8]. These venules are the most reactive of the microcirculatory components: they also have a larger surface area of endothelium than the capillaries [14].

Antigen–antibody complexes can be observed to injure the venules in experimental models such as the rabbit's ear chamber [11]. The Arthus and Schwartzmann phenomena occur in venules [15].

In this section, most of the pathology discussed relates to the legs, where venous hypertension and impaired flow readily occur and where cold further increases blood viscosity [13,16].

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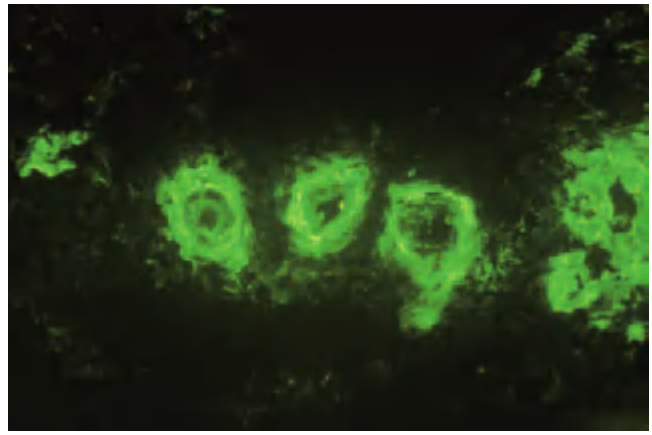

Fig. 50.11 Pericapillary fibrin cuffs. Immunofluorescence with antifibrinogen–fibrin antibodies on lipodermatosclerotic skin.

Pathophysiology

In patients in whom venous valves have become incompetent, blood is able to reflux back into the superficial veins, abolishing the normal pressure drop that occurs on exercise and causing a persistently elevated venous pressure during walking and other forms of erect exercise. This occurs when there is incompetence of the long or short saphenous veins, or of the communicating veins; incompetence of communicating veins may be especially important where the medial calf 'perforating' veins become incompetent such that the high pressure generated within the calf muscle pump (200 mmHg) is directly transmitted to the overlying dermal venous plexus beneath the skin. Incompetence of the perforating veins may occur as an extension of the varicose process but may also develop as a result of damage within the deep veins. Defective function of the deep veins is almost always the result of previous thrombosis, which can cause valvular damage or obliterate large segments of venous lumen. Subsequent perivenous fibrosis may prevent the veins from dilating and act as a 'functional' obstruction. For blood to return from the lower leg and bypass these obstructed segments, the valves in the perforating veins must cease to function, allowing blood to pass into the superficial channels which then become secondarily incompetent. The consequent raised venous pressure gives rise to abnormal microvascular responses, discussed below, with associated clinical features that are discussed later.

Microvascular response to raised venous pressure [1–3]

Persistently elevated venous pressure affects capillary function. The transmural and intraluminal pressures increase, particularly at the venous end of the capillary bed, encouraging more fluid and electrolytes to enter the tissues. This results in oedema. In addition, the individual capillary beds elongate and distend, allowing a larger surface area for transluminal migration [4–8], although there is also a reduction in the number of capillary loops supplying the epidermis [6]. As the capillaries distend, larger molecules and the cellular moieties of blood escape into the interstitial fluid. Normally, these cells and macromolecules are broken down and cleared by macrophages and the lymphatics, but if sufficiently large quantities enter the interstitial fluid, the normal homoeostatic mechanisms are swamped. This results in accumulation of solid particles in the interstitial space around the capillaries, particularly in the dermis where 'halos' have been found around the capillaries using cutaneous microscopy [1].

Fibrinogen is one of the largest molecules normally retained within the vascular compartment and when this escapes, becoming supersaturated within the tissues, it is capable of becoming cross-linked and forming insoluble fibrin. Pericapillary 'fibrin cuffs' have been found in the dermis of almost all patients with the pre-ulcerative changes of lipodermatosclerosis (pigmentation, induration and inflammation) [8]. They have also been found in limbs with chronic venous insufficiency (those with defective calf-pump function and post-thrombotic limbs) before the skin changes of lipodermatosclerosis are present [9]. An impaired hyperaemic response after 3 min of arterial occlusion in patients with venous ulcers was proposed to be caused by a mechanical barrier of fibrin or oedema around the small vessels [10]. Additionally, the number of capillaries with perivascular fibrin 'cuffing' (Fig. 50.11) was shown to correlate with the amount of oxygen crossing the dermis; the greater the number of capillaries with fibrin cuffs, the lower the transcutaneous Po_2 measured by a modified Clark electrode heated to 45°C [9]. However, *in vivo* diffusion studies in patients with lipodermatosclerosis [11] did not show a defect in xenon diffusion (xenon having similar diffusion char-

acteristics to oxygen), and modelling of oxygen diffusion suggests that fibrin cuffs would not act as a barrier [12]. It is therefore unlikely that the fibrin cuff theory could explain sufficient dermal hypoxia to cause ulceration. Theoretical models of fibrin cuffs [12] do not, however, take into account the thickened vessel walls and other constraints such as collagen, laminin and fibronectin found within the cuff.

Any fibrin that is formed should be broken down to soluble fragments (fibrin degradation products) by the action of plasminogen activators that convert plasminogen to the active enzyme plasmin. Investigation of the fibrinolytic capacity of patients with lipodermatosclerosis has shown diminished production of plasminogen activators and an increased level of inhibitors in both the blood and tissues, resulting in tissue inability to lyse fibrin clots artificially formed within the calf tissues. It is not known if the reduction in fibrinolytic ability is a primary tendency present from birth, or if it is an acquired abnormality as a result of exhaustion of fibrinolytic capability following extensive deep-vein thrombosis.

Homans [13] suggested that stagnation of venous blood as a result of defective venous return caused hypoxic tissue damage. Although there was initially some support for this hypothesis, the measurement of venous oxygen tensions failed to confirm hypoxia, and instead revealed that the oxygen tension of the venous blood from ulcerated limbs was high rather than low [14].

There is considerable controversy over what some believe to be the myth of 'venous stasis ulceration' [15,16]. 'Gravitational ulceration' is another unsatisfactory term that does not wholly explain the pathophysiology of ulcers. Nevertheless, the capillary venous bed in limbs with venous disease during sitting or standing may be composed of areas of impaired blood flow, at the same time as short circuits or preferential vascular pathways open up [6].

The finding of increased oxygen tension in the veins led to the hypothesis that arteriovenous shunts may have opened up in response to the raised venous pressure [14]. The presence of increased numbers of arteriovenous shunts has not been a consistent finding [17], and functional studies using isotopically labelled macroaggregates gave no indication of a physiologically important shunt [18,19]. High resting flows as a consequence of both persistent arteriolar dilatation and loss of vasoconstrictor response to changes in posture are suggested by laser Doppler studies [20].

Positron emission tomography (PET scanning) confirmed that patients with lipodermatosclerosis or venous ulceration had an increased calf blood flow in the ulcer-bearing region and a decreased oxygen uptake by these tissues [18]. Such findings obviously fit with the diffusion (fibrin) block hypothesis and do not exclude the presence of arteriovenous fistulae. It is also possible that high resting flows cannot increase further to meet the demands of wound healing following injury, a concept that is currently popular in diabetology and is based on vessel-wall stiffness caused by fibrin and collagen [21].

Dependency of normal limbs causes white cells to disappear from the venous effluent draining the dependent limb [22]. This observation was extended by Thomas *et al*. [23], who showed that dependency caused even more white cells to disappear in limbs with venous hypertension and chronic venous insufficiency.

Coleridge-Smith *et al*. [24] found that dependency appeared to reduce the number of capillary tufts seen on cutaneous microscopy and assumed that the 'disappearing' white cells were lodging in the capillary bed and occluding flow through the cutaneous capillaries [25]. These two sets of observations led to the development of the theory that white-cell plugging impairs perfusion and this could be exacerbated by vessel narrowing or stiffening caused by the fibrin cuff. It is sometimes forgotten that the capillary bed is a network in which preferential or low-resistance pathways can virtually act as shunts while less preferred channels are slow-flowing or static. While whole-skin blood flow is enhanced, the nutritional bed can experience ischaemia.

Histological studies have failed to show white cells blocking capillaries but have shown a greater number of leukocytes within the tissues [26]. This suggests that white cells migrate in the same way as fibrin. Another histological study [27] shows that the 'fibrin cuff' contains many more proteins than just fibrin; for example collagen and often proteins like laminin are important constituents. The expression of specific adhesion molecules on both leukocytes and endothelial cells is influenced by a number of cytokines, some of which may even be trapped in the 'fibrin cuff' surrounding the venules. Such adhesion molecules are discussed in Chapter 10. The relationship between the release of the endogenous vasodilator endothelial-derived nitric oxide and the control of the adhesion molecule P-selectin is but one of many discussed in a review of this topic [28]. There does appear to be an increase in adhesion molecules and activated neutrophils both locally and in the circulation [29,30] in venous hypertension, but the cause of this remains to be elucidated. Vascular cell adhesion molecule 1 (VCAM-1) seems to be the most significant factor in this process [26].

Falanga and Eaglstein [5] have suggested that the pericapillary cuffs block epidermal growth factor migration and this leads to inadequate tissue repair, which eventually causes ulceration. Other theories on venous ulcer causation include reperfusion injury from ischaemia and reperfusion caused by the venous hypertension associated with changes in posture [29]. More recently it has again been suggested that the whole mechanism is a purely mechanical problem [31]. No current theory fits all

the circumstances that are known to be associated with venous ulceration.

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Venous thrombosis

Deep-vein thrombosis (DVT)

Incidence. Prevalence studies have relied on a clinical history in population surveys and hospital records of clinically diagnosed thrombosis. Autopsy studies are also available. Studies of selected populations by phlebography or by clinical symptoms and signs do not correlate well with subsequent clinical behaviour [1]. It seems likely that improved post-operative management and the use of anticoagulants has reduced the incidence of DVT. On the other hand, the ageing population and sedentary lifestyle may increase the prevalence of both venous and arterial thrombosis.

Pathogenesis. This involves coagulation, platelet aggregation and injury to venous endothelium. The maintenance of the fluidity and circulation of the blood and its ability to thrombose are essential for the maintenance of life and are governed by extremely complex homoeostatic mechanisms. The mechanisms of thrombosis, a protective device to prevent loss of blood and to seal off a damaged blood vessel, and of fibrinolysis, which counteracts or stabilizes the effects of thrombosis, depend upon systems of consecutive enzyme activity with activators and inhibitors finely balanced at every stage.

Thrombosis is discussed in Chapter 48. Alterations in the blood coagulability, platelet population and agglutinating power, with changes in blood flow and endothelial damage, are the precursors of intravenous thrombosis. Of these, the loss of normal function of the vascular endothelium is probably of primary importance [1]. Anticardiolipin antibody is also now recognized as an important cause of thrombosis [2,3]. A number of other hereditary and acquired conditions that predispose to thrombosis (the thrombophilias) have now been recognized. These include protein C and S deficiency, antithrombin deficiency and activated protein C resistance (which is usually associated with a factor V genetic abnormality [4]). Screening for these 'thrombophilias', and for anticardiolipin antibody, should be performed in patients having sporadic or recurrent thrombosis [5]. Surgical operations and pregnancy remain important triggers, and prolonged immobility as in aeroplane flights, or hormonal influences, such as the contraceptive pill, are also well-documented risk factors.

Any agent that causes inflammation or damage of the vein wall is a potential cause of thrombophlebitis. In some

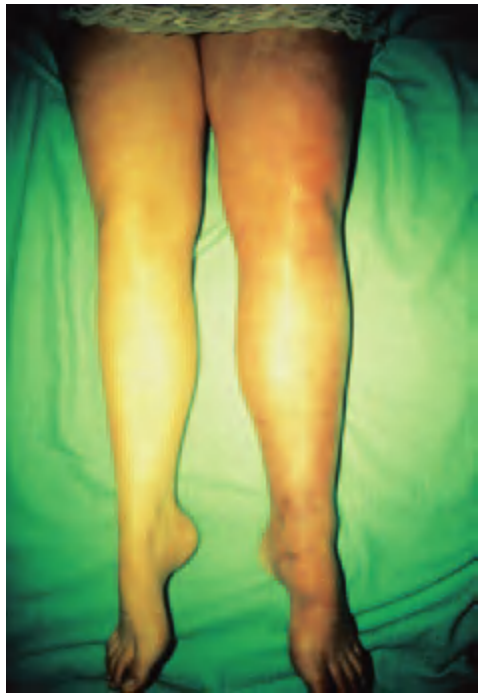
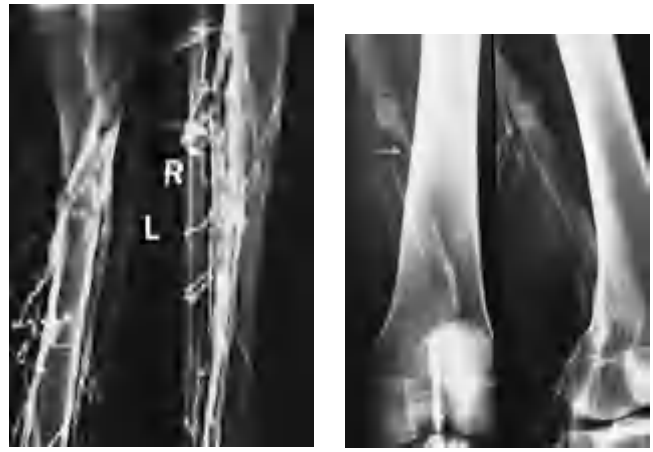


Fig. 50.12 An iliofemoral venous thrombosis causing swelling and erythema of the whole left limb.

cases, this agent is obvious: sclerosing agents, intravenous infusions, chemotherapy lines, ionizing radiation or neighbouring inflammatory processes. Injuries, especially tibial fractures, are a common cause of thrombosis [6]. Venous thrombosis may be an important and presenting sign of thromboangiitis obliterans (p. 50.7). Thrombophlebitis also occurs in malignant disease, in conditions such as Behçet's syndrome, and in infective fevers such as typhoid.

Clinical features. The onset of a thrombosis is often 'silent' and may remain so. It commonly occurs at or about day 7–10 after a surgical operation, parturition or the onset of an acute infection, concomitant with a rise in the platelet count and an increase in young 'sticky' platelets. Between one-third and two-thirds of patients complain of some swelling and pain in the leg, usually in the calf [1]. An iliac thrombosis should be suspected (Fig. 50.12) if the whole leg is swollen and dusky. Direct pressure on the calf muscles or over the course of the deep veins usually elicits direct tenderness; but the foot dorsiflexion test (Homan's sign) [5] should be abandoned as it is inaccurate. There may be a cyanotic hue to the leg and superficial venous dilatation. The temperature of the leg may be raised, and oedema of one ankle is an important physical sign. However, chest pain or cardiac arrest from pulmonary embolism are often the first indications of a DVT. Pulmonary hypertension may follow repeated small emboli, and is associated with the development of progressive dyspnoea.



(a) (b)

Fig. 50.13 (a) Thrombus in all the calf veins with localized thrombus in the popliteal veins. (b) Massive fresh thrombus extending up the common femoral and profunda femoris veins occluding the external iliac vein.

Pain and tenderness in the calf and popliteal fossa may occur resulting from other conditions such as a ruptured Baker's cyst or a torn plantaris tendon [7], and it is important to make a definitive diagnosis of thrombosis before anticoagulating the patient unnecessarily for 3–6 months.

Diagnosis. Compression ultrasonography has become the preferred first-line investigation; venography and/or phlebography is only performed where clinical doubt remains. However, bipedal ascending phlebography using non-ionic contrast media remains the most accurate method of confirming the diagnosis and of determining the best method of treatment (Fig. 50.13) [1,8]. Duplex Doppler scanning can detect thrombus in the iliac, femoral (Fig. 50.14) and popliteal veins with considerable accuracy (98–99% compared with phlebography) but is far less successful at detecting thrombi in the calf veins (approximately 70% concordance) [8]. Measurement of circulating D-dimer concentration (a by-product of fibrin production) is a useful adjunct to ultrasonography as it has a high negative predictive valve (i.e. low values strongly exclude thrombosis) [9].

Complications. Pulmonary embolism, post-thrombotic syndrome and recurrent thrombosis are the main complications of DVT. Post-thrombotic syndrome develops as the result of high venous pressure from valvular damage and venous obstruction.

Prevention. Dermatologists should be aware of risk factors for DVT, particularly in elderly bedridden in-patients with widespread skin disease and infection (Table 50.1). Prolonged sitting is as harmful as lying. Active exercise and early mobilization is desirable when possible. The

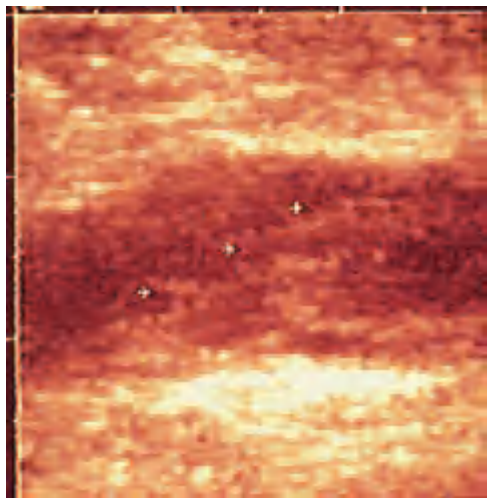


Fig. 50.14 A duplex scan showing non-compressible thrombus seen as a filling defect within the vein lumen. The proximal surface is outlined with markers.

Table 50.1 Risk factors for deep-vein thrombosis.

Obesity
Varicose veins
Paralysis or immobility
Surgical procedure lasting more than 30 min
Personal or family history of thromboembolism
Active cancer
Hormonal influences (pregnancy, oral contraceptive pill, hormone replacement therapy, tamoxifen)
Serious illness
Hypercoaguable states (protein C and S deficiency, activated protein C resistance, antiphospholipid syndrome, antithrombin III deficiency)

incidence of thrombosis is reduced from approximately 30% to 10% by graduated compression stockings [10]. Below-knee stockings appear to be as effective as thigh-length hosiery. Pneumatic compression therapy has been proved effective but is probably only realistic in post-operative circumstances.

Antiplatelet drugs such as aspirin provide some protection. Low-molecular-weight heparin given by daily subcutaneous injection provides effective prophylaxis with little increase in the risk of serious bleeding [11].

Treatment. The diagnosis should be confirmed as soon as possible by compression ultrasonography if a DVT is suspected. Initial treatment with a low-molecular-weight heparin given subcutaneously once a day should be based on a clinical suspected diagnosis plus an assessment of the patient's risk and a raised result on D-dimer testing. On confirmation of the diagnosis, once daily tinzaparin should be continued for up to 72 h. Warfarin treatment should be started after 24–48 h, unless contraindicated. When the activated partial thromboplastin time (APPT) is above 2, heparin may be discontinued. Warfarin should be maintained for 3–6 months, depending on the site and extent of the thrombosis. Warfarin is usually given in a dosage of 10 mg, 10 mg and 5 mg on the first 3 days. Elevation of the leg is recommended, particularly if oedema is present.

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Superficial thrombophlebitis

In the absence of an obvious vein injury, thrombosis in the superficial veins usually develops because of slow flow within a varicose vein, and may occur in isolation. Nevertheless, coexistence of a silent DVT should be considered [1]. Thrombophlebitis occurring in apparently normal superficial veins should alert the clinician to the possibility of an underlying malignancy or thrombophilia.

Superficial thrombophlebitis of a varicose vein. This is the most common presentation of superficial thrombophlebitis. Pain, heat and tenderness overlying a palpable subcutaneous nodule or cord makes the diagnosis straightforward. Cellulitis may extend for some distance into surrounding tissue making distinction from infection sometimes difficult. There is no lymphadenitis or peripheral limb oedema unless accompanied by a DVT. Local oedema may be profound. Duplex ultrasound should be performed if the diagnosis is in doubt or if a DVT is suspected.

Superficial thrombophlebitis in non-varicose veins. Superficial thrombophlebitis may occur after an intravenous injection or insertion of an intravenous cannula with or without infection (septic thrombophlebitis). Damage to the

venous endothelium from needle trauma or an irritating substance (e.g. a chemotherapeutic agent) may induce both phlebitis and local thrombosis; extravasation of injected material into the perivenular tissues may have the same effect. When recurrent or widespread, consideration should be given to the possibility of a systemic cause such as cancer, a hypercoaguable state (protein C or protein S deficiency, antiphospholipid syndrome) or other diseases such as Behçet's syndrome or Buerger's disease.

Treatment. Superficial thrombophlebitis, unless accompanied by a DVT, is harmless but may be exquisitely painful. Spontaneous resolution usually occurs and only symptomatic treatment required. Oral non-steroidal anti-inflammatory agents may be helpful. Anticoagulation is not necessary, unless there is extension to the saphenofemoral or saphenopopliteal junction or an associated DVT. In some instances, post-inflammatory hyperpigmentation remains for some time along the course of the inflamed segment of vein. Elastic hosiery support is very valuable once the acute tenderness has eased, and exercise is essential.

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Post-thrombotic syndrome [1]

SYN. POST-PHLEBITIC SYNDROME

Post-thrombotic syndrome (PTS) causes venous hypertension as a consequence of thrombotic damage to valves. It complicates 50–75% of deep-vein thromboses [2–6]. The more proximal the DVT, then the greater the risk of PTS. Elastic hosiery worn after a DVT will halve this risk.

Recanalization of the vein after thrombosis is variable. The walls of the vein are damaged and the lumen irregular. The valves are incompetent or missing. Even though not directly affected, the valves upstream may become incompetent with time as the proximal pressure progresses. Occasionally the vein does not recanalize and may fibrose or calcify. Any increase in venous outflow resistance further enhances venous hypertension.

Consequences of post-thrombotic damage include further DVT, superficial thrombophlebitis, oedema, skin changes from venous hypertension and eventually ulceration. Lipodermatosclerosis with prominent perforating veins are characteristic. Subcutaneous calcification can occur and calcium may be extruded through the skin, leading to ulceration.

The main differential diagnosis is primary varicose veins with deep-vein incompetence, or primary superficial venous incompetence which eventually leads to a decompensated deep-vein system as well. Consideration should also be given to other venous disorders (e.g. Klippel–Trenaunay syndrome, Parkes Weber syndrome, venous aneurysms, Ehlers–Danlos syndrome, arteriovenous fistulae and chronic deep-vein obstruction).

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Chronic deep-vein obstruction [1]

The most common cause of deep-vein obstruction is DVT. Non-thrombotic causes include malignant disease or other pelvic masses compressing the iliac veins. Increased intra-abdominal pressure from obesity can result in venous hypertension and venous ulcers. In one report gastric bypass treated all but three of 37 venous ulcers [2]. Retroperitoneal fibrosis can obstruct the iliac veins and the inferior vena cava. The iliac compression syndrome (Cockett's or May–Thurner syndrome) is present when the left common iliac vein is compressed by the right common iliac artery crossing its path (Fig. 50.15) [3]. Flow alterations do not usually cause problems unless thrombosis supervenes. Large tumours (e.g. soft-tissue sarcomas) or aneurysms in the thigh may compress the deep femoral vein. In the popliteal fossa an aneurysm or a Baker's cyst can compress the popliteal vein. Primary tumours of the vein wall (leiomyosarcoma) are rare but are found more often in the lower limb. Ligation of deep veins may be unavoidable when removing malignancy or when repairing damage from accidental trauma.

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Mondor's disease

Mondor's disease is diagnosed when palpable tender cords develop around the breast and chest wall [1].

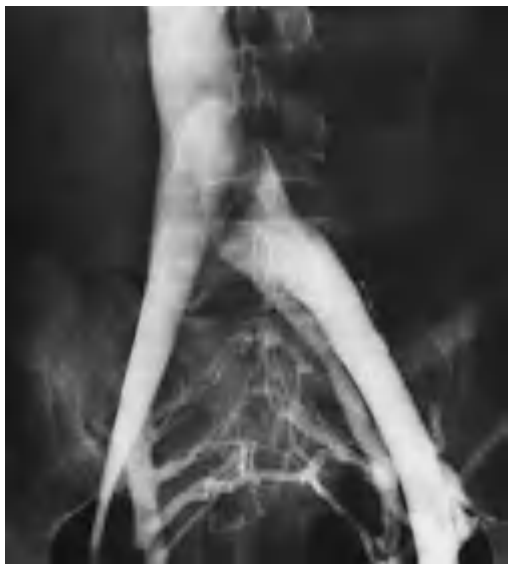

Fig. 50.15 Iliac vein compression syndrome. There is a filling defect where the left common iliac vein is compressed by the right common iliac artery. Collateral veins confirm the presence of venous obstruction.

Occasionally they can 'bowstring' across the axilla and even extend down the upper limb as far as the hand. Doubt exists if this disorder is truly a phlebitis and it may be the result of a lymphangiothrombosis or even perineural inflammation. Thrombo-occlusive lymphangitis can also occur in the lower leg [2] or in the penis [3].

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Thrombophlebitis migrans [1–4]

Recurrent migratory thrombophlebitis is an uncommon form of thrombophlebitis that affects large and small veins throughout the body. The condition may last months or years. The superficial veins of the lower extremities, abdominal wall, flank, arms or elsewhere undergo segmental thrombosis, causing crops of tender, linear or oval subcutaneous lumps or streaks. This is the pattern in Behçet's disease [5,6].

Much of the literature regarding migratory thrombophlebitis is concerned with the link with underlying malignancy, termed Trousseau's syndrome. This association was carefully reviewed by Sack *et al*. [7] and by Samlaska *et al*. [8], who suggested that migratory thrombophlebitis is chronic disseminated intravascular coagulation disorder.

The identification of many new factors contributing to coagulation has shed light on these syndromes. They include deficiencies of factor XII, antithrombin III, protein C, protein S, as well as abnormal plasminogen activators, lupus anticoagulant and anticardiolipin antibody syndrome, and activated protein C resistance. Clues to a primary hypercoaguable state include a family history, recurrent thrombosis, unusual anatomical site, early age of onset and resistance to conventional anticoagulation. Secondary hypercoaguable states are a consequence of malignancy, infection, pregnancy, the contraceptive pill, nephritis or liver disease [3,4,8]. A follow-up study of 4399 patients who had venography for suspected DVT recorded that 150 of 1383 with proven DVT and 182 of 2412 without thrombosis developed cancer; although the overall difference was not significant, there were significantly more cancers in the DVT group (66 cancers) than in the non-DVT group (37 cancers) in the first 6 months after the venography [9]. A more severe type of thrombophlebitis is associated with malignant disease. In 1500 cases of thrombophlebitis, 31 of 77 occurring with malignancy were of a migratory type [2]. The lung and pancreas were the most common sites of malignant tumours, although the breast, colon and stomach were also responsible. The cause of the thrombosis is unknown: a blood-borne neoplastic cell embolus seems unlikely; a coagulation factor associated with carcinomatous tissue has been postulated [4] but has not yet been isolated. A fibrinolytic defect has been found in some patients; often this is the result of an increase in inhibitors and may be associated with high levels of plasma triglycerides.

Treatment. Malignancy must be carefully excluded in patients with migratory thrombophlebitis. It may be difficult to locate, especially pancreatic carcinomas. Computed tomography (CT) scanning, ultrasound and magnetic resonance imaging (MRI) and even PET scans of the abdomen may be necessary to detect cancers in the pancreas and other organs. Treatment is otherwise conservative. Lowering triglycerides may be advisable; exercise is good prophylaxis. Stockings or bandage support for the legs are helpful. Stripping of the saphenous system has been advocated [1]. Earlier observations on the good effects of oral fibrinolytic agents [10,11] in Behçet's disease have not been substantiated by some later case reports [12].

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Varicose veins and venous reflux

Varicose veins [1]

SYN. VENOUS VARICOSITY

The term should be reserved for visible tortuous elongation and dilatation of the larger superficial venous trunks and their tributaries. Leg varicosities seldom develop before adolescence in women [2]. Nevertheless, other types of venous dilatation are often incorrectly included within the category of varicose veins. Capillary telangiectasias (diameter 0.1–0.4 mm) are predominantly red and intradermal. The colour of telangiectasias depends upon the calibre of the dilated venule; large dilatations are dark blue and often palpable (although still less than 1 mm in diameter) [3–5]. Reticular varicose veins are subcutaneous (2–4 mm in diameter) and arise from a blue leash of small veins.

Aetiology. It has long been recognized that varicose veins of the leg are inherited [6,7]. They are about three times more common in women than in men; the influence of pregnancy, and possibly of other hormonal factors, is probably important. They often present for the first time in pregnancy, 8–20% of women being affected. An increased blood volume and cardiac output, a rise in vena caval pressure and a direct effect of hormones on the smooth muscle of the vein wall may particularly affect those with a genetic predisposition. Persistence may be the result of simple superficial valvular incompetence, or the result of an unsuspected antepartum, postpartum or postoperative thrombosis.

Two main theories have been put forward to explain the nature of the inherited defect responsible for varicose veins: an inherent weakness of the vein wall or a congenital absence of the valves [8]. Each theory is justified by some experimental evidence. Most of the evidence is now in favour of an inherited structural defect of the vein walls, which have been shown to contain altered amounts of mucopolysaccharide and collagen when compared with control normal vessels [9–12]. Congenital valvular aplasia is extremely rare.

The most common cause of secondary varicose veins is PTS. Varicose veins can also complicate Parkes Weber syndrome (congenital arteriovenous fistulae) and Klippel–Trenaunay syndrome, but these are also rare conditions.

Incidence and prevalence [1,13]. A number of surveys have shown that the prevalence of varicose veins is high in the developed world. A community study in London in 1992 concluded that the prevalence of varicose veins in men and women aged 35–70 was 17% and 31%, respectively [14]. A study in Edinburgh found the prevalence to be 40% in men and 32% in women [15]. Varicose veins may, however, be underestimated in the developing world.

Clinical features. Varicose veins may be a purely cosmetic problem but many patients also complain of aching pain, which tends to be worse on prolonged standing at the end of the day. Patients with varicose veins may also complain of itching and ankle swelling, and many ultimately develop lipodermatosclerosis with ulceration, although some authorities believe that this only occurs if there is associated incompetence of the calf perforator veins [16].

Legs must be carefully examined with the patient standing erect, with the leg exposed from the foot to the groin. The distribution of the varices may indicate long saphenous incompetence (Fig. 50.16) (over the anteromedial aspect of the lower limb) or short saphenous incompetence (over the posterior aspect of the calf), but this may occasionally give a totally false impression as varices on the back of the calf may connect to the long saphenous vein. Short saphenous incompetence is invariably present if a large venous channel can be palpated crossing the popliteal fossa (which should be examined when the patient is standing erect with the knees slightly bent to relax the popliteal fascia). Tourniquet tests are used to confirm the clinical suspicion of the sites of venous incompetence (Fig. 50.17).

Complications of varicose veins, such as haemorrhage and thrombophlebitis, result from the varicose veins themselves; oedema, haemosiderin pigmentation, varicose eczema, atrophie blanche, lipodermatosclerosis and venous ulceration result from venous hypertension.

Investigations. Reflux at the saphenofemoral junction, saphenopopliteal junction and within the deep venous system can be confirmed with the hand-held Doppler. Colour duplex Doppler ultrasound scanning is increasingly being used to investigate all patients with varicose veins, and is the investigation of choice for detecting deep-vein reflux. Duplex scanning is also essential to investigate patients with skin changes attributed to

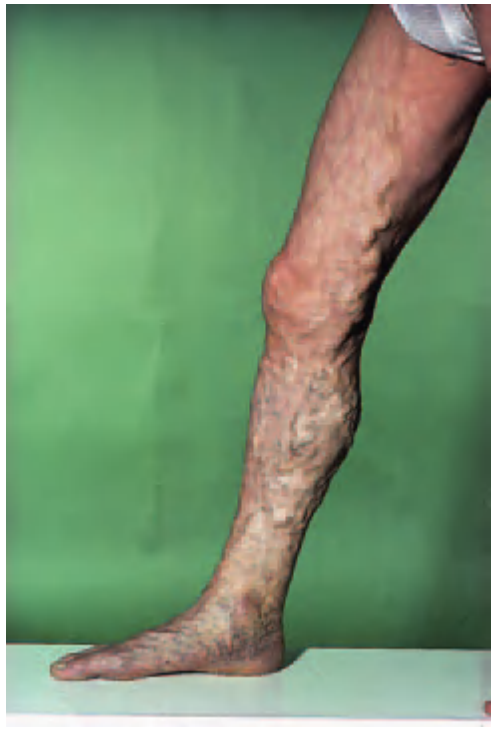
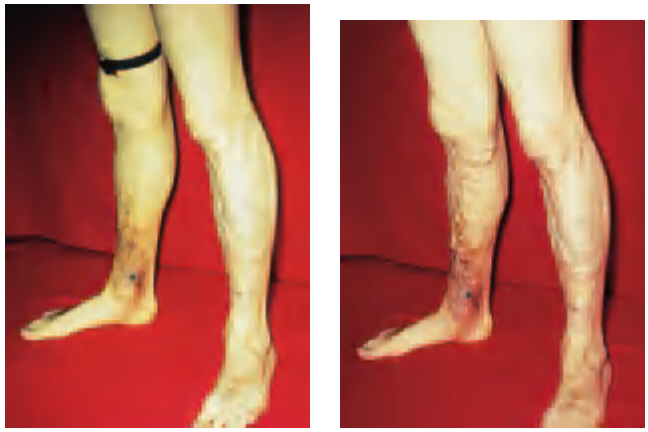


Fig. 50.16 Tortuous dilated long saphenous vein tributaries.



(a) (b)

Fig. 50.17 The Brodie–Trendelenburg tourniquet test. (a) An above-knee tourniquet controls the varicose veins indicating long saphenous incompetence. (b) When the tourniquet is released, the varicosities fill from above downwards.

venous hypertension. Ascending phlebography, while delineating the veins more clearly, is better at detecting post-thrombotic changes and incompetent communicating veins (Fig. 50.18) [17]. Other methods such as light reflective rheography and foot volumetry are primarily used in research.

Management. The recognition of skin changes associated with varicose veins is important because of the likely

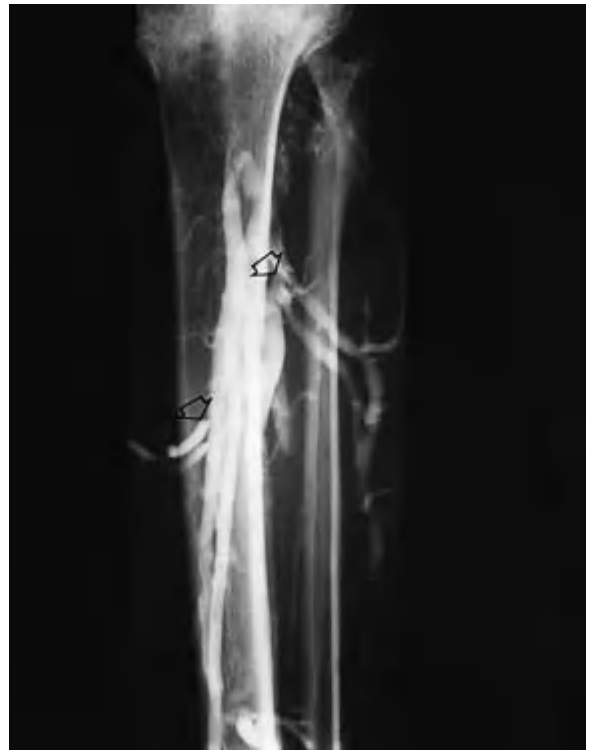


Fig. 50.18 Incompetent communicating veins shown by ascending phlebography (arrowed).

risk of progression to venous ulceration. Causes of secondary varicose veins should be sought, including DVT and intra-abdominal pathology. Approximately one-third of patients presenting with varicose veins have symptoms unrelated to their varicose veins, and only require explanation and reassurance. Patients whose main symptom is discomfort may benefit from compression hosiery [18].

Venous surgery is potentially curative for refluxing superficial veins when the deep veins are competent. Conversely, surgery should be avoided in patients in whom the superficial veins may be acting as collaterals, which are the major route for venous return, in a severely post-thrombotic limb.

Surgery for saphenofemoral incompetence consists of high saphenous ligation (saphenofemoral ligation) with stripping of the long saphenous vein, to the level of the knee, combined with multiple avulsions of the tributaries [19]. Short saphenous incompetence and varicosities are treated by saphenopopliteal ligation, short saphenous stripping and avulsion of prominent tributaries. Subfascial endoscopic perforator surgery ligation (SEPS) is performed by inserting an endoscope through the deep fascia via a small incision in the upper calf [20]. This operation has never been tested in a prospective randomized trial and is ineffective in patients with post-thrombotic limbs.

Surgical reconstruction of the post-thrombotic limb remains a controversial topic, with anecdotal reports of good results for valve transplantation, valve reconstruction, vein transposition and bypass grafts. There is no evidence from any randomized studies that this type of surgery prevents recurrent or future ulceration. The long-term use of good graduated below-knee compression stockings is, however, of proven value [18]. Injection sclerotherapy is now used to treat minor branch vein varicosities but not truncal varices because the recurrence rate was very high in the presence of major saphenous incompetence. Patients with reticular veins and capillary telangiectasia can be treated by microinjection sclerotherapy, laser or application of high intensity light.

Venoactive drugs (e.g. coumarin, rutin) have been shown to relieve 'aching' pain and oedema, but their value is still disputed [21].

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Clinical features of chronic venous disease

It is not varicose veins *per se* but the mechanical failure of venous return, and the sustained periods of raised venous pressure, that lead to the characteristic skin changes of chronic venous disease [1–3]. Trophic skin changes are more likely to be seen in the post-thrombotic syndrome (post-phlebitic leg) but can arise from a superficial venous reflux that occurs in primary varicose veins. Thrombosis may be silent in up to half of those patients in whom it occurs [4]. Conversely, even after a definite major thrombosis, the development of post-phlebitic sequelae is both variable and unpredictable.

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Varicose veins

The widening, elongation and tortuosity of the venular end of the upper dermal capillary (capillary telangiectasia) (Fig. 50.19), the venules in the subpapillary plexus (blue

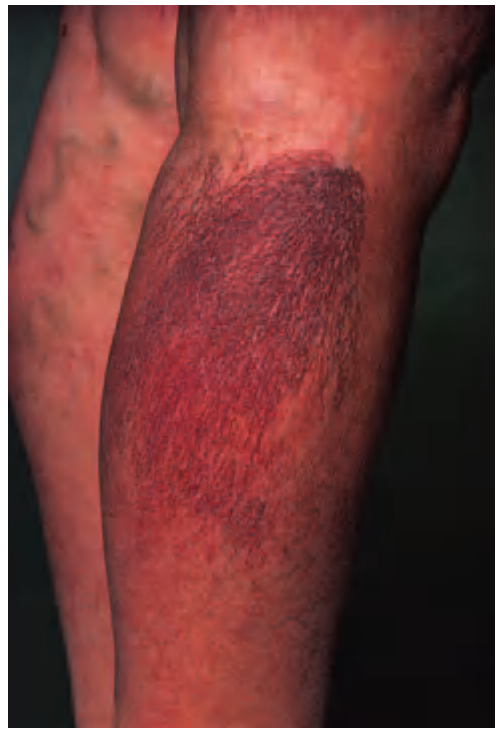

Fig. 50.19 Surface telangiectases.

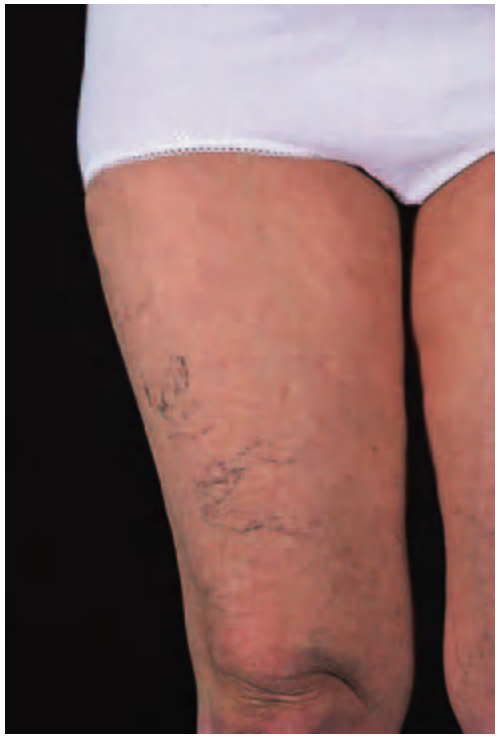

Fig. 50.20 'Sunburst veins'.

'venous' telangiectasia, 'venectasia') and truncal varicose veins are usually associated with venous hypertension. Telangiectasias are fed by blood refluxing from a venule or varicose vein. The term corona phlebectatica paraplantaris is used to describe the dilated venules behind and below the medial malleolus, a finding invariably associated with venous hypertension.

Reticular varicose veins of small calibre (2–3 mm) (Fig. 50.20), frequently seen around the popliteal fossa, are less likely to be associated with venous reflux.

Haemosiderin pigmentation and erythrocyte extravasation

Raised capillary pressure and vessel wall changes resulting from raised venous pressure permit red cell extravasation into the dermis. At first this takes the form of petechiae or purpura and occurs in the distal part of the lower limb (the foot or gaiter region) where pressures are highest. As red cells degenerate so haemosiderin remains and a brown pigmentation develops. Sometimes this may be an isolated finding. Only by examining the patient standing will an underlying varicose vein be identified as the cause.

Gravitational purpura (dermite ocre, Favre pigmented and purpuric angiodermatitis) is very common on the anteromedial part of the lower leg. Distinction from forms of capillaritis and from post-inflammatory hyperpigmentation (e.g. in lichen planus) may be difficult. Biopsy may risk a leg ulcer if venous hypertension is severe.

Acroangiodermatitis of Mali (pseudo-Kaposi's sarcoma)

A pigmented purpuric eruption occurring around the malleolae and in the skin of the dorsal forefoot (particularly the base of the second toe) suggests acroangiodermatitis. Brown to plum-red papules coalescing into plaques resemble Kaposi's sarcoma clinically. The term acroangiodermatitis was introduced by Mali *et al*. in 1965 [1]. In 1967, Stewart [2] and Bluefarb and Adams [3] independently described similar lesions on the legs of patients with arteriovenous malformations; in these cases the findings are usually unilateral and a palpable thrill may be noted. The condition can lead to ulceration of the toes and forefoot, in which case an arteriovenous (AV) shunt is the more likely underlying cause.

Histologically, there is marked capillary proliferation, plump endothelium and red cell extravasation.

Rashkovsky *et al*. [4] described five possible causes:

1 Chronic venous hypertension
2 Arteriovenous malformations
3 Iatrogenic AV shunts in haemodialysis patients
4 Paralysed limbs
5 Amputation stumps

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Oedema

Increased capillary filtration is a direct result of raised capillary pressure, and in turn of raised venous pressure. Pericapillary oedema occurs at an early stage in venous disease [1]. Pitting oedema does not occur until the interstitial fluid volume has doubled. Any oedema is the result of an imbalance between capillary filtration and lymph drainage. Therefore oedema should be avoided if the lymph drainage is compensating properly for increased filtration. The term 'venous' oedema fails to consider the contribution of local lymph drainage (Chapter 51).

Venous disease may not be the only cause of oedema. Raised venous pressure from right-sided heart failure or inferior vena caval or iliac vein obstruction should be considered, as should hypoalbuminaemia. It is important to examine the internal jugular vein, and to ask the patient to stand up to look for collateral veins over the abdomen.

The oedema resides mainly in the subcutis but there is a significant increase in the papillary dermis [2]. Oedema affects the nutrition of the epidermis and reduces com-

pliance of the skin, making it more susceptible to injury. Oedema also seems to increase the likelihood of eczema, particularly of asteototic pattern, presumably through its effect on the epidermis and particularly on the stratum corneum. This is typically a chronic effect but can occur acutely, usually a result of oedema of cardiac causation [3].

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Eczema ('varicose' eczema, 'stasis' dermatitis)

The mechanism for 'varicose' eczema is unknown. Any eczema affecting the leg or foot should prompt a search for underlying venous disease. The presentation may vary from an acute exudative diffuse or discoid eczema to a more chronic lichenified form. Mention has already been made of an asteototic type (eczéma craquelé), particularly if oedema is present. The presence of any inflammation of the lower leg, particularly eczema, may contribute to oedema through increased vascular permeability and so set up a vicious cycle of more oedema and worse dermatitis. Autosensitization (secondary generalization of eczema) occurs frequently with 'varicose' eczema and may be the presenting feature, so it is important to examine the lower legs, if necessary removing any bandage or elastic stocking in such cases.

Lower leg eczematous dermatitis may also occur with venous disease because of the contact irritant effect of any skin exudation. Contact dermatitis from medicaments may also occur and may be through irritant or allergic mechanisms. Patch tests should be carried out in all patients with persistent 'varicose' eczema.

Any break in the skin integrity, not least oozing eczema, increases the risk of infection. Impetiginization of varicose eczema is common. The use of topical steroids in an ointment base increase the risk of staphylococcal folliculitis, particularly with occlusion and maceration from wet dressings and bandages.

Cellulitis and the red leg [1]

The risk of cellulitis is increased in the presence of oedema or lymphatic insufficiency. Typical lower leg cellulitis is characterized by redness, pain, swelling and systemic upset (fever, flu-like symptoms, vomiting, rigors). Blistering and necrosis may occur if the oedema is marked.

The differential diagnosis includes DVT, superficial thrombophlebitis, acute venous obstruction, acute dermatitis and acute lipodermatosclerosis. Suspected bilateral cellulitis is a diagnostic pitfall but is rare. Much more likely is lipodermatosclerosis or eczematous dermatitis, both of which are often bilateral.

Necrotizing fasciitis needs to be distinguished from necrotizing cellulitis. Blistering and necrosis occur in both. Marked local tenderness and increasing 'crescendo' pain, early neutrophilia and hypotension from associated shock are common in fasciitis.

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Lipodermatosclerosis

Lipodermatosclerosis was a term coined by Browse and Burnand [1] to describe the progressive induration, inflammation and pigmentation, associated with excessive fibrosis of the skin and subcutaneous tissues, that is induced by chronic venous hypertension (Fig. 50.21). It appears in two forms—acute and chronic. The acute variety is painful (often burning in quality) and disabling, and is characterized by plum-red skin which is oedematous and very tender. A firm mass can be palpated in the subcutis, with a distinct edge, usually in the lower third or 'gaiter' region of the lower leg. This involvement of the subcutis has led to other descriptive terms such as sclerosing panniculitis and fat necrosis. Thrombophlebitis within the superficial truncal veins almost certainly coexists. Often misdiagnosed as 'chronic' cellulitis, acute lipodermatosclerosis does not cause fever, leukocytosis or lymphadenitis. It is frequently bilateral. Antibiotics have no effect but elevation and a reduction in venous pressure often alleviate the symptoms.

Chronic lipodermatosclerosis may result from progression of acute lipodermatosclerosis or develop spontaneously and insidiously. The skin is thickened and tight with fixed to hard, indurated fibrosing subcutaneous tissues. Progressive subcutaneous fibrosis gives the leg an

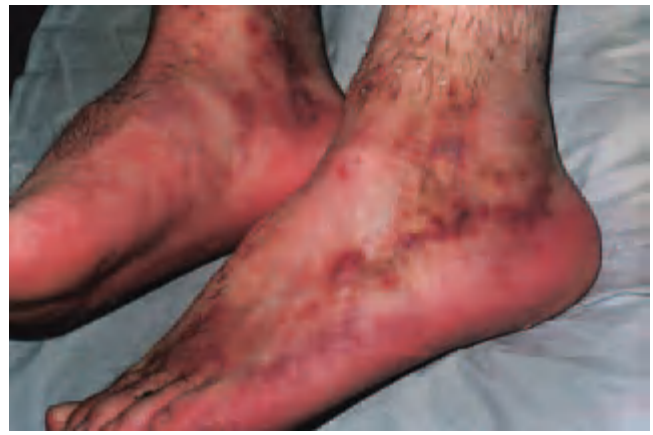

Fig. 50.21 Lipodermatosclerosis and ankle flare.

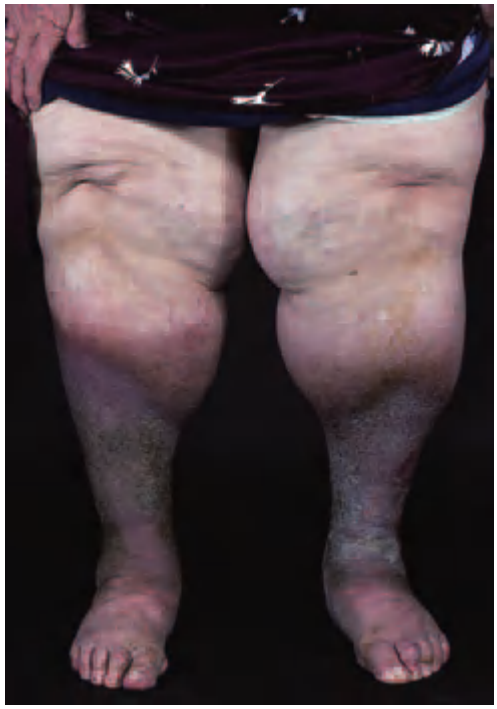

Fig. 50.22 'Champagne bottle' legs.

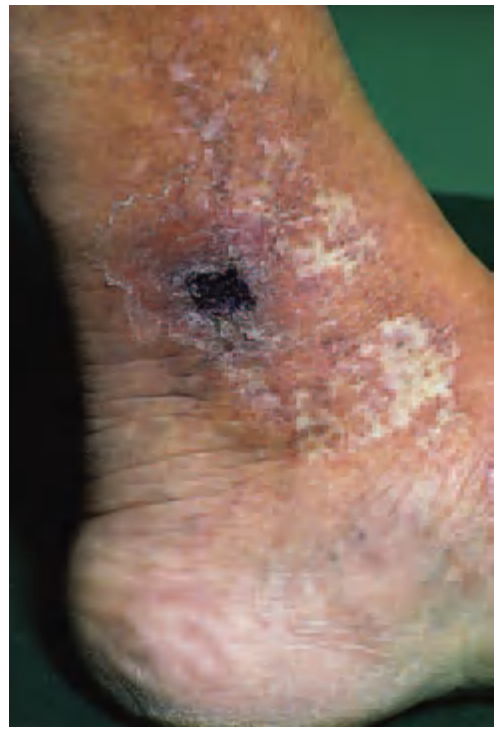

Fig. 50.23 Atrophie blanche: white scars with a central ischaemic ulcer and telangiectasia at the edge of the white areas.

inverted 'champagne bottle' shape (Fig. 50.22). The skin is not usually red by this stage but pigmented brown. Pitting oedema is invariably found in the calf above the affected area.

Lipodermatosclerosis has also been described in association with lymphoedema [2], suggesting that oedema or 'chronic congestion' within a leg from venous or lymph hypertension is the main cause. In the absence of any venous or lymphatic abnormality, the diagnosis of lipodermatosclerosis cannot be sustained, and other conditions such as panniculitis must be considered. Biopsy may then be indicated.

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Atrophie blanche [1–4]

SYN. MILIAN'S WHITE ATROPHY

Definition. A smooth ivory-white plaque of sclerosis stippled with pinpoint telangiectasia (grossly enlarged tortuous capillaries seen end on) and often surrounded by haemosiderin pigmentation. The condition occurs chiefly but not exclusively on the lower leg or foot, particularly in women (Fig. 50.23). Rarely, lesions occur on the dorsum of the hand or elsewhere on the limbs. Blister formation and crusting may precede ulceration. In the absence of ulceration the condition is often symptomless. Ulceration occurs in about one-third of cases and takes two forms: a small, exquisitely painful ulcer may form within a patch of atrophie blanche, or a larger crusted superficial ulcer may develop. Both forms are notoriously slow to heal.

Aetiology. The most common cause is chronic venous insufficiency. Twenty-one of 81 patients attending a surgical clinic with venous insufficiency were observed to have this condition [5]. Capillary hypertension is probably the major aetiological factor. In patients with atrophie blanche, 35 of 41 cases were found to have varicose veins [1]. Each telangiectatic vessel is greatly elongated and coiled, resembling a renal glomerulus when viewed with an ophthalmoscope. The telangiectasias may thrombose, which presumably undermines local skin viability leading to scarred (white atrophy) areas and ulceration.

Atrophie blanche can be associated with naevus flammeus, thalassaemia minor [6], cryoglobulinaemia, systemic lupus erythematosus and scleroderma [7]. It may also coexist with livedoid vasculitis (livedo vasculitis), but neither condition represents a true 'inflammatory' vasculitis [8].

Histopathology [1]. The epidermis is atrophic with scleroderma-like changes in the dermis, with little or no

evidence of inflammation. There is new vessel formation in the subpapillary layer with capillary tufting and increased vessel diameter. Thrombosis of small vessels and proliferative endothelial changes may be present. A striking fibrinoid change has been noted.

Differential diagnosis. Around the ankle, the only condition likely to be confused is the scar of a healed venous or arterial ulcer. However, lesions elsewhere on the body may be confused with discoid lupus erythematosus, lichen sclerosus or malignant atrophic papulosis [4].

Treatment. The patient should be instructed to protect the area from all knocks, abrasions, known allergens or ill-fitting shoes. Only in this way will ulceration be avoided. Rest and compressive therapy are seldom successful, although warmth and reflex vasodilatation may offer benefit, provided they are combined with elevation [7]. Intralesional injections of lidocaine (lignocaine) and triamcinolone may relieve pain dramatically, and thus allow conventional pressure therapy to be applied. Nicotinic acid has been advocated [8]. Low-molecular-weight dextran is sometimes useful in providing immediate relief of pain. A satisfactory response to phenformin and ethinylestradiol, or now more commonly stanozolol 5 mg twice daily, has been reported [9]. Others have favoured 5000 i.u. heparin subcutaneously twice weekly, or use of drugs that inhibit platelet aggregation [10].

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Livedoid vasculopathy [1]

SYN. LIVEDO VASCULITIS; SEGMENTAL HYALINIZING VASCULITIS

The mechanism may be identical to atrophie blanche as it usually occurs in the same location (foot and gaiter regions) and is associated with chronic venous disease. The distorted leaky vessels are fibrinolytically exhausted and easily thrombose. Ischaemic necrosis of the overlying epidermis is a consequence. It would appear to be a thrombotic disorder of small dermal blood vessels rather than a true vasculitis, as suggested by its association with factor V mutation [2] and antiphospholipid syndrome (Chapter 48) [3]. Suggestions for treatment are anecdotal but include intravenous immunoglobulins [4].

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Congenital venous abnormalities

Klippel–Trenaunay syndrome (KTS; MIM 149000)

The combination of varicose veins, port-wine stain and increased bone length form the major features of this syndrome. First described in 1900 [1], the condition almost certainly represents a post-zygotic genetic fault (somatic mutation) in mesodermal development. Presentation is usually soon after birth. The naevus is usually first to appear; 95% of KTS patients exhibit a cutaneous haemangioma (port-wine stain) usually involving only the affected limb but sometimes beyond [2]. Limb hypertrophy develops later in childhood; venous abnormalities may not be evident until adolescence. Lymphatic abnormalities frequently coexist, and affected children may present with a swollen limb. Veins are large and extensive with an abnormal distribution. A characteristic feature is a large ectatic 'primitive' vein in the lateral thigh. Varicosities may extend into the pelvis as well as down the leg. Superficial thrombophlebitis is not uncommon in children. The bones may overgrow, resulting in increased leg length. Soft-tissue hypertrophy often occurs but may be difficult to distinguish from swelling caused by oedema or engorged veins.

Skin changes other than the vascular naevus occur because of venous or lymphatic hypertension. Other abnormalities described with the syndrome include lymphangiectasia (cutaneous vesicles that leak lymph) and consumptive coagulopathy (Kasabach–Merritt syndrome) [3].

The diagnosis is largely clinical, supported by venous duplex Doppler scanning or by ascending phlebography to demonstrate the abnormal venous anatomy. The differential diagnosis includes multiple arteriovenous fistulae (Parkes Weber syndrome), phlebectasia, gigantism and PTS.

Treatment includes epiphyseal stapling for excessive longitudinal bone growth, and compression hosiery to control venous hypertension. Superficial veins should not be removed unless the deep veins are competent. As the vascular naevus improves with time, treatment is not necessary.

Parkes Weber syndrome [4]

This syndrome is caused by multiple arteriovenous fistulae, but can manifest with varicose veins and limb overgrowth as in KTS. Whereas in KTS leg length disparity rarely increases after the age of 10 years, overgrowth gets progressively worse in Parkes Weber syndrome. An obvious pulsatile swelling may be present with discoloration of the overlying skin and large veins radiating from it. Duplex ultrasound will demonstrate high blood flow and abnormal enlargement of the arteries; cardiac enlargement and failure may occur.

Diffuse phlebectasia

SYN. BOCKENHEIMER'S SYNDROME

Phlebectasia is the term used to describe enlarged and irregular superficial and deep veins. Histology of the phlebectasia shows a decrease in elastin in the wall of the ectatic veins. Thrombus and calcification are often present [5]. **Phlebangiomatosis** involves cavernous angiomas, which manifest with cutaneous angiomas that extend into deeper layers including bone. Both conditions resemble KTS and Parkes Weber syndrome but without bone overgrowth.

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Leg ulceration

Ulceration of the lower limb affects 1% of the adult population and 3.6% of people older than 65 years [1]. The main causes are venous hypertension, arterial disease and diabetes, but many factors may contribute (Table 50.2). Venous disease is the single most common cause, but gravitational and venous influences may be contributory to inducing other pathologies in the lower leg (e.g. vasculitis).

Table 50.2 Causes of lower limb ulceration.

Venous hypertension	Varicose veins, deep-vein thrombosis, venous obstruction, congenital vascular malformations, Klippel–Trenaunay syndrome
Arterial disease	Atherosclerosis, diabetes, hypertension, embolism, arteriovenous fistula, calciphylaxis
Skin cancer	Basal and squamous cell carcinoma, melanoma, Kaposi's sarcoma, malignant fibrous histiocytoma
Vasculitis	Connective tissue disease (systemic lupus erythematosus, rheumatoid disease, systemic sclerosis)
	Livedoid vasculopathy
Haematological disorders	Coagulation states/protein S or C deficiency, sickle cell disease, thalassaemia, spherocytosis, lymphoproliferative disorders (myeloma, cryoglobulinaemia), myeloproliferative disorders (polycythaemia), cholesterol and platelet emboli
Peripheral neuropathy	Leprosy, diabetes
Infections	Diabetes, osteomyelitis, Buruli ulcer, fungal infections, syphilis, mycobacteria, Leishmaniasis, leprosy, acute 'desert' sore, necrotizing fasciitis and cellulitis
Trauma	Physical, chemical or thermal
	Self-harm
	Intravenous drug use
Drugs/therapy	Radiation
	Hydroxyurea
	Iododerma
Skin conditions	Pyoderma gangrenosum
	Necrobiosis lipoidica
	Scleroderma
	Graft-versus-host disease
	Blistering disorders (e.g. pemphigoid), insect, snake and scorpion bites
Genetic	Prolidase deficiency
	Klinefelter's syndrome
Cold injury	Perniosis
	Immersion injury

Venous ulceration of the leg [2]

Definition. Ulceration of the lower leg is the result of persistently elevated venous pressure and its secondary effects on the microvascular system. Nearly half of all venous ulcers are associated with deep-vein valvular incompetence or post-thrombotic damage while the remainder result from incompetence of the superficial or communicating veins. Venous ulceration of the leg is an age-related disease with a maximal prevalence in middle-aged or elderly women. It has a chronic or relapsing course and is often exacerbated or originated by external injury.

Epidemiology [3–5]. Community surveys suggest an overall incidence of about 0.2% [4]. It is clearly an age-related disease, mainly affecting older women; 2% of all those over the age of 80 years suffer from the problem. The aetiological groups are difficult to define, and patients with leg ulcers present at different clinics. Sixty per cent of patients receive no specialist opinion.

Venous ulceration is a common disease of all civilized communities. It appears to be associated with a sedentary and physiologically unnatural mode of life and is comparatively rare in African people [6,7], although the incidence may be underrated [8].

A study of 4422 healthy working adults in Basle found 'chronic venous insufficiency' in 19% of men and in 25% of women [9]. Ulceration was present in 1.1 and 1.4%, respectively. Figures from other areas are similar. It has been emphasized that up to one-third of ulcers in elderly people have coexisting arterial insufficiency as one factor contributing to their failure to heal. A family history of leg ulcers is found in over half of those affected [10]; this applies about equally to those who have suffered a known thrombosis and to those who have not. The significance of this is not known, although inheritance of coagulation defects may be one factor.

Over the last 10 years, the incidence of DVT has decreased significantly, whereas arterial insufficiency is becoming more common. The incidence of venous ulcers is influenced by the recurrence rate, and this is influenced by the effectiveness of both treatment and regular supervision in the healed state. Once treated, up to 72% of patients can suffer recurrence.

Venous disease accounts for 1–2% of the health care budgets of European countries [11].

Pathogenesis. Venous ulcers are the end result of superficial venous insufficiency or PTS described above. The consequent alterations in the microvasculature and interstitium make the skin more liable to break down, or to fail to repair, following minor degrees of trauma. The fundamental fault is a sustained capillary hypertension resulting from persistently raised venous pressure. A failure to reduce venous pressure satisfactorily when the lower limb is dependent is a combination of haemodynamic failures, mainly consequent upon a failure of venous valves (allowing reflux) and poor calf muscle pump function. The skin changes resulting from venous hypertension often, but not always, culminate in ulceration. The lack of skin viability must reflect local hypoxia but the exact mechanism is not understood. The pathogenesis of microvascular damage is discussed on p. 50.14.

A history of deep leg-vein thrombosis is obtained from a significant proportion of patients. In Anning's carefully documented series [10], a story of prior thrombosis was obtained in 75% of the patients. Leg injuries, particularly fractures, are frequently followed by thrombosis [12]. Other relatively common causes include hip replacements, pelvic and lower abdominal operations, medical illnesses and prolonged recumbency from any cause. In one study, 12 of 46 patients admitted to hospital with leg ulcers demonstrated resistance to activated protein C [13], a finding that has been observed in 20–40% of patients known to have had a previous DVT. Patients with chronic venous ulcers have a 41% prevalence rate of thrombophilia which is 30 times higher than the general population. Interestingly, thrombophilia does not necessarily appear to be related to past DVT [14].

Recent studies have shown that up to 60% of patients with venous ulcers have isolated superficial vein incompetence with normal deep veins [15]. The concept of a primary defect in collagen or elastic tissue [9] has been revised by the recognition of ulceration consequent on prolidase deficiency (p. 50.39). Congenital absence of venous valves as a cause of leg ulcers is probably rare [16].

Clinical features. The ulcer may be preceded by patchy erythema or discoloration of an intense bluish red colour, in which ischaemia of the skin finally leads to necrosis, often following a minor episode of trauma. This intense bluish colour can be seen by capillary microscopy to be caused by capillary congestion [17].

The ulcer is characteristically situated on the medial lower aspect of the leg, the 'gaiter' region, which is drained on the medial side by three large pairs of perforating veins (Fig. 50.24). Venous ulcers do not usually develop initially below the level of the malleoli or in the foot unless complicated by livedoid vasculitis or arterial disease.

Two events may lead to a break in the continuity of surface epithelium. The first is capillary thrombosis, when the complete outline of the capillary can be seen to be filled with broken-up thrombus, which does not disperse on pressure. The second is a small bleed from the peak of the capillary; this separates the epidermis from its blood supply. These changes in the capillaries supplying the epidermis are frequently induced by small knocks, scratching or epidermal pathology such as dermatitis. The

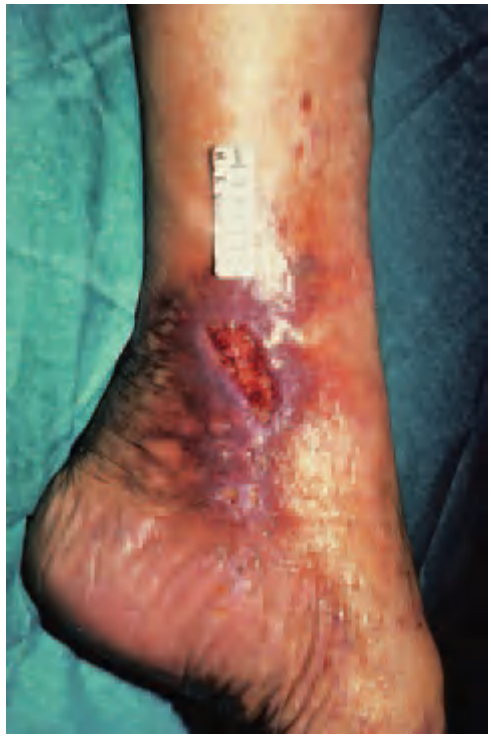

Fig. 50.24 A venous ulcer on the medial side of the leg surrounded by pigmented sclerotic skin (lipodermatosclerosis).

skin around an ulcer is frequently irritated by exudate, and inflamed varicose or medicament dermatitis may contribute. Other signs of venous hypertension are usually present, for example lipodermatosclerosis, varicose veins (corona phlebectasia), varicose eczema or oedema; sometimes a nearby perforator vein may be evident by a palpable depression in the subcutaneous fat. Venous ulcers can develop as a result of ulceration of atrophie blanche.

Ulcers often show pseudoepitheliomatous hyperplasia at their edge, which may be mistaken for a squamous cell carcinoma. The ulcer bed is oedematous, with abundant newly formed capillaries lying in a granulation tissue covered by serous exudate or slough. Such ulcers most frequently occur within a few years of a thrombosis. Neglect and attempts at self-treatment may cause delay in seeking proper advice. By then, one or more infected ulcers are present, sometimes completely encircling the leg.

Healing ulcers have a shallow sloping edge with healthy granulation in their base and little slough. Epithelial islands may become scattered over the surface of a well-vascularized bed, and quickly enlarge (Fig. 50.25). The pink lip of the epithelium at the edge of an ulcer is uniform and supplied by relatively uncongested capillaries. The overall appearance is like a normal nail fold and cuticle. By contrast, a non-healing ulcer resembles severe paronychia, being boggy, undermined and congested.

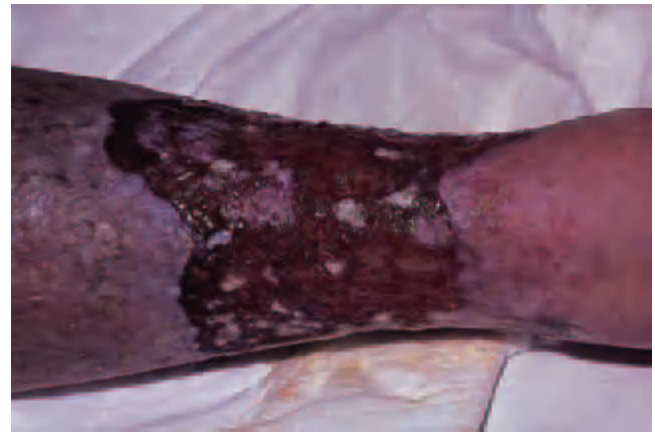

Fig. 50.25 A healing venous ulcer. There are multiple islands of reforming epithelium spreading over healthy granulation tissue.

The coexistence of arterial disease can contribute to the progression of a venous ulcer so symptoms and signs of peripheral ischaemia should be sought in all patients with leg ulceration. Rest pain can occur in the absence of arterial disease. Patients develop typical ischaemic pain on elevation of the ulcerated leg, which is oedematous. To relieve pain, the patient keeps the leg in a dependent position, especially at night; this exacerbates the underlying pathogenesis. After excluding arterial disease, a period of enforced elevation, necessitating strong analgesia, results in disappearance of the oedema with subsequent relief of pain. Occasionally, venous ulceration occurs at other sites in the limb, but other aetiologies should be suspected in such instances, especially if ulcers are present over the foot or just below the knee. Hyperkeratosis and papillomatosis around an ulcerated area or along the border of the foot, particularly below the malleoli, is a result of impaired local lymphatic drainage.

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Associations and complications of venous leg ulcers

The main conditions associated with venous ulceration are anaemia and malnutrition (especially in elderly people living alone), and these must be assessed and corrected as far as possible.

General disease [1–3]. Coincidental obesity and hypertension are common. The relationship of these to the presence of the ulcer is uncertain, but they are undoubtedly perpetuating causes. Increased intra-abdominal pressure increases cardiac filling pressures, femoral venous pressures, renal vein pressure, systemic blood pressure and vascular resistance [4]. Cardiovascular disease is common and heart failure can be a major contributor to venous ulceration through its effect on: (i) further raising venous pressure; (ii) creating peripheral oedema; and (iii) encouraging long periods of sitting. Joint disease, peripheral arterial disease and neurological disease can obviously impair the already precarious nutrition of the skin and the action of the muscle pump. Severe rheumatoid disease or long-standing poliomyelitis also reduce the effectiveness of the muscle pump and encourage recurrence. They also discourage healing.

Anaemia and hypoproteinaemia. Sickle cell anaemia [5], iron-deficiency anaemia and thalassaemia can cause ulceration, and the presence of marked anaemia may prevent other ulcers from healing by reducing peripheral oxygenation. Repeated infection or chronic inflammation arising from the ulcer may itself cause a normochronic normocytic anaemia. A poor diet, combined with continuous seepage of protein and blood from an untreated ulcer, relatively commonly leads to anaemia and hypoalbuminaemia.

Diabetes. Diabetes is common, and will compound any venous ulcer through arterial disease, infection and neuropathy.

Personal attitudes and habits: sociology [6]. It is common, in patients with long-standing ulcers, to find a number of complications that stem from the personality, domestic and social situation of the patient. Walking has long been abandoned and substituted by more damaging motionless sitting. The ankle becomes fixed in equinus and the foot inverted. The leg becomes transformed into a useless and deformed peg and the calf muscles atrophy. An attitude of apathetic acceptance, often associated with depression, is frequent. The patient retires to the fireside chair, beslippered, ill-nourished, useless to the family but, nevertheless, the object of much attention and sympathy. Many such patients never go to bed but sit motionless in the chair all night. In a few cases, it is clear that any real attempt to cure the ulcer will be resisted unless this can be accompanied by a vigorous social and psychological rehabilitation. Lonely patients may find that an ulcer is their only means of obtaining a visitor, be it district nurse or doctor.

Zinc depletion. This has received considerable attention [7–14], following the observation that zinc deficiency in rats impairs wound healing. Low plasma zinc levels have been found in patients with venous ulceration, and accelerated healing of such ulcers after oral zinc sulphate therapy has been reported. However, it is the tissue levels of zinc that are of most importance to ulcer healing, and these have never been shown to be low in patients with leg ulcers. Analysis of six randomized trials indicates that oral zinc does not aid healing of leg ulcers, except possibly in patients with low serum zinc [15].

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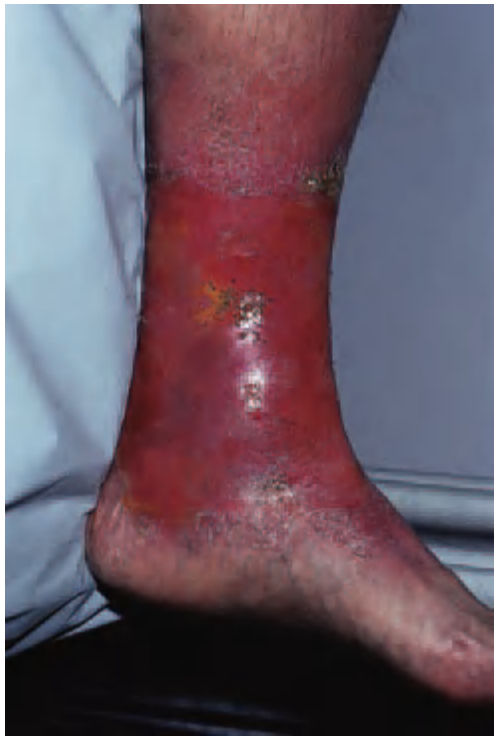

Fig. 50.26 Redness caused by exudate localized to the site of an overlying absorbent dressing, often confused with a contact allergy to the dressing.

Table 50.3 Leg ulcer allergens.

Ointment bases and preservatives
Wool alcohols (lanolins)
Parabens
Propylene glycol
Chlorocresol
Ethylenediamine
Cetostearyl alcohols
Additives in bandages
Ester gum resin
Azo disperse (dyes)
Colophony (adhesives)
Additives that prevent rubber and elastic from perishing
Antibacterial agents
Sodium fusidate
Gentamicin sulphate
Neomycin
Framycetin
Quinoline mix (Vioform, Chinoform)
Self-medication
Caine mix (local anaesthetics)
Antihistamine creams
Chlorxylenol (Dettol)
Germolene

Infection [1]. The role of antisepsis in the healing of leg ulcers is much debated [2–4]. Pathogenic organisms are commonly found in leg ulcers of all types [3]. The bacterial flora is often profuse and usually mixed, but *Staphylococcus aureus* predominates. There is still insufficient evidence to determine to what extent such a flora influences the rate of healing, but quantitative bacteriology has indicated that fewer than 100 000 organisms per square centimetre of surface area or per gram of tissue does not delay repair [5]. However, certain pathogens are traditionally taken seriously; for example, the group A β-haemolytic *Streptococcus* or a heavy growth of *Pseudomonas*. Unimpeded resolution of uncomplicated leg ulcers under occlusive compressive bandaging is frequently accompanied by considerable pus formation, but healing is not necessarily impaired. Sometimes lakes of pus develop in an atrophic skin that readily breaks down. Referred to as erosive pustular dermatosis of the leg, the pus is sterile and the condition responds to intermittent use of potent topical steroids [6].

Fusiform bacilli and spirochaetes are found in the phagedenic anaerobic or 'tropical' ulcer of hot humid regions [7]. Fungi vary in extent and importance. Some authors have found *Candida albicans* only rarely [8], but it can be a common commensal organism, perhaps because of the widespread use of specific antibiotics. Ointment-impregnated bandages without preservatives were blamed for candidal overgrowth in one study [9]. Moist wound healing using contemporary occlusive dressings seems not to encourage infection [10].

Penicillin- and tetracycline-resistant staphylococci, and *Pseudomonas aeruginosa*, are very common in hospital-treated patients, and cross-contamination is the rule in leg ulcer clinics [11]. *Proteus vulgaris* and other Gram-negative organisms are probably of little importance. The importance of non-clostridial anaerobic organisms such as *Bacteroides* spp. has probably been underestimated. As with other types of infection, large controlled trials are required to measure healing after the ulcer surface has been sterilized. This information is not currently available to provide advice on the value of infection control. Venous ulcers are less likely to develop infection than arterial or diabetic ulcers [12].

Contact dermatitis. The skin around an ulcer frequently becomes red and sore, caused predominantly by the irritant effect of exudate (Fig. 50.26). Small pustules and superficial ulcers may develop, especially in the presence of β-haemolytic streptococci. Eczema may be responsible for further compromising skin viability, and so increasing the size of an ulcer. In most cases, the eczema is the result of local treatment (Table 50.3) and sensitivity can be demonstrated by patch testing. Patients with venous ulcers appear to become sensitized easily (Fig. 50.27) [13], often to several medicaments including lanolin and rubber [14–16]. The components of paste bandages may be responsible [17]. True medicament sensitivity is a frequent complication of therapy (Fig. 50.28).

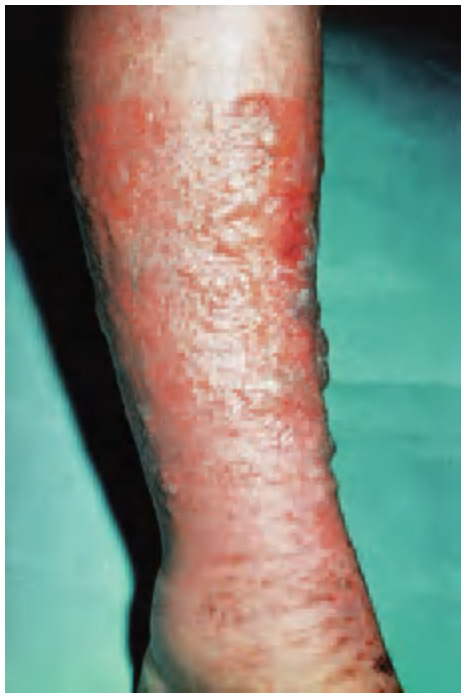

Fig. 50.27 A sensitivity reaction to strapping showing blistering.

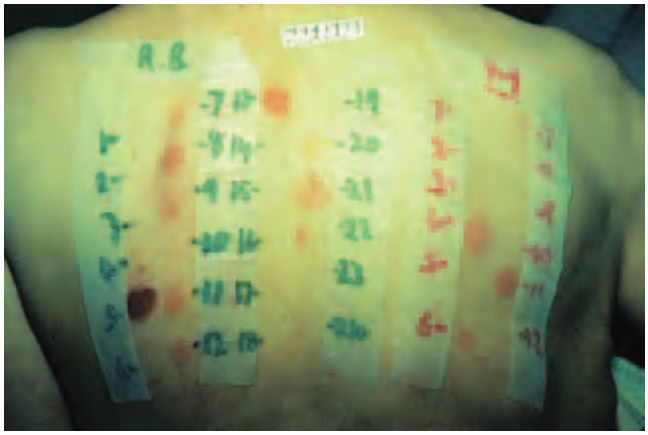

Fig. 50.28 Patch testing: 72-h reading showing multiple sensitivities, typical of patients with a long history of ulcer therapy.

It is unfortunately not widely appreciated that the effect of potent topical corticosteroids on leg ulcers may inhibit healing for several weeks by producing an indolent 'arterial-type' ulcer with a deep adherent slough, 'steroid ulcer' (p. 50.37).

Haemorrhage [18,19]. Spontaneous haemorrhage occasionally occurs, especially from large ulcers [19]. This may be severe and can cause death if the patient faints and is held in the vertical position. First-aid measures include immediately lying the patient on the floor and elevating the limb while applying firm direct pressure to the bleeding point in the base of the ulcer. Occasionally, a suture will be required, but a tight bandage and elevation usually prevents further bleeding.

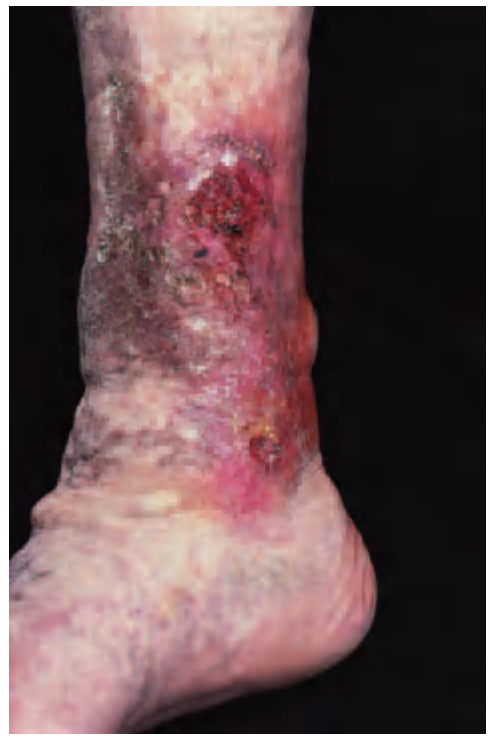

Fig. 50.29 Heaped-up squamous epithelioma.

Lymphoedema (Chapter 51). The superficial lymphatics are absent in and around ulcers and their distortion or obliteration contributes to hyperkeratosis, papillomatosis, dermal fibrosis and oedema. An inadequacy of the lymphatic drainage predisposes to attacks of cellulitis [20], and with each episode of infection damage is compounded and chronic lymphoedema delays ulcer healing.

Malignant change [21]. Primary malignancies of the leg presenting as ulcers are increasingly common in an ageing population or those with sun exposure or transplantation-associated immunosuppression. Malignant change in an established ulcer is much rarer but carries a worse prognosis. Squamous epitheliomas may be difficult to distinguish from pseudoepitheliomatous hyperplasia, but if missed because of a failed diagnosis will often metastasize [22]. Biopsy should be considered if the diagnosis is in doubt [23]; multiple biopsies have been recommended as features may vary throughout the ulcer-associated tumour [24]. The edge becomes progressively heaped up (Fig. 50.29), vegetating and cauliflower-like and does not flatten with compressive therapy. Basal cell carcinomas may remain quite flat and undetected (Fig. 50.30).

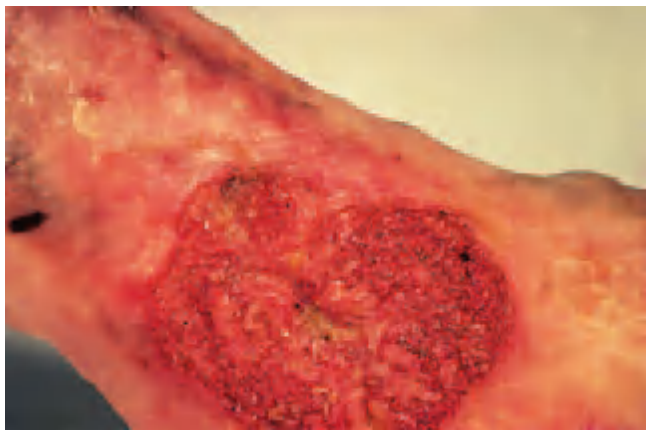

Fig. 50.30 A flat basal cell carcinoma complicating lipodermatosclerosis.

Suspicion may be aroused when the ulcer fails to respond to compression therapy. A distinction should be made between the rarity of malignant change in a chronic ulcer associated with disorders of the venous system, and the common primary malignancy occurring in the skin of legs that have had prolonged exposure to sunlight.

Subcutaneous calcification (post-phlebitis subcutaneous calcinosis) [25]. This is often widespread. It occurs in up to 10% of patients with chronic venous insufficiency [25]. It may cause non-healing of an ulcer or be found incidentally. The calcification, which is sometimes osteoid, occurs around areas of fat necrosis and fibrosis [26]. Radiography reveals a coarse network of calcification, the edges of individual plaques impinging on the dermis. Other causes of calcification include phleboliths, atherosclerotic calcification, cysticercosis and a ligamentous form of dystrophic calcification (in which the serum calcium and phosphorus levels are normal). Calcium deposits act as a foreign body nidus for organisms and delay healing.

Bone changes. Periostitis is commonly seen beneath a chronic ulcer. Osteoporosis is often present in the later stages as the result of disuse atrophy. Osteoarthritis is a common concomitant condition in the affected or unaffected leg, especially the knee. Fibrous ankylosis occurs in the ankle of neglected cases. Old tibial fractures are common in patients with post-thrombotic ulceration.

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Diagnosis of venous ulceration

This is essentially clinical, based on ulceration in the gaiter area and the presence of signs of venous hypertension (p. 50.23). Arterial disease must be excluded and the ulcer should respond to compression therapy. A past history of venous thrombosis, treatment for varicose veins or a family history of venous disease is supportive evidence.

An ankle–brachial pressure index should be performed if foot pulses are not easily palpable, although the diagnosis of arterial disease does not exclude the possibility of an ulcer predominantly caused by venous disease (mixed origin). Arterial duplex Doppler scanning or arteriography should be undertaken if doubts remain regarding the presence of arterial ischaemia. Colour duplex Doppler ultrasound should be performed, not just for confirmation of venous reflux but also to see if superficial venous incompetence is responsible, in which case venous

surgery may be an option if the deep veins are competent [1].

A skin biopsy may not heal in the presence of venous hypertension but is indicated if alternative causes such as skin malignancy [2] or vasculitis are possibilities. The preference is to wait for ulceration to heal before fully assessing the venous system, although some may wish to carry out photoplethysmography and duplex scanning at an early stage. Signs of a peripheral neuropathy should be excluded and the range of hip, knee and particularly ankle movement should be tested.

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Other causes of leg ulceration

The main causes of leg ulceration are listed in Table 50.2.

Arterial ulceration

Death of the skin automatically follows occlusion of its arterial blood supply unless this occurs slowly enough to allow a collateral circulation to be established. Arterial or arteriolar occlusion, if present, also complicates the treatment and prognosis of ulcers that are primarily venous in origin. A study of 600 leg ulcer patients in the Lothian and Forth Valley, Scotland, revealed evidence of arterial disease in slightly less than one-quarter [1].

Atheroma of the abdominal and limb vessels is the single most common cause of ischaemic ulceration likely to be seen by the dermatologist involved in the care of patients with leg ulcers. Many other pathological states may, however, cause arterial occlusion, and not all can be defined with accuracy on clinical grounds. A useful empirical approach to the diagnosis of clinically ischaemic ulcers is to consider the causes in three main groups:

1 Extramural 'strangulation'
2 Mural thickening or accretion
3 Intramural restriction of blood flow

There is often considerable overlap, and the exact pathology cannot always be well defined.

Extramural. Scar tissue and radiodermatitis cause a fibrotic strangulation of the arterioles and may give rise to small but persistent ulcers. Ulceration occurs in a number of diseases associated with dermal sclerosis, including scleroderma and progeria (Werner's syndrome; Chapter 12). Such ulceration is often located over the medial malleolus, and is associated with atrophie blanche. Compression by tumours may also obstruct arterial flow; tumours may also require an increased blood supply that cannot be provided by existing vessels.

Mural. Ulceration depends on the speed with which changes take place in the vessel wall. In vasculitis this is often sudden, but in hypertension it is slower and is preceded by pain, erythema and tenderness. In atherosclerosis the accretion of intimal plaques may proceed with a reduced flow until thrombosis, embolism or infection precipitate complete closure.

Intramural. Microvascular occlusion caused by changes in blood viscosity and clotting mechanisms is discussed in Chapter 48.

Clinical features [2]. The general symptoms and signs shown by the patient with advancing ischaemic disease of the limbs have already been described (p. 50.2).

Arterial ulcers frequently arise in the pretibial area or on the toes, whereas venous ulcers favour the gaiter region. Severe pain is usual, but is not a reliable discriminator from venous ulceration, which can also be very painful. Pain is as marked in small ischaemic ulcers as in large ulcers. The edges of the ulcers are sharply defined and the ulcer itself is often punched out.

There is often no pigmentation or lipodermatosclerosis in the surrounding skin, unlike the changes around venous ulcers, but the two can coexist. Usually, exudation from arterial ulcers is minimal. The base is often pale and covered with a slough (Fig. 50.31), which may have bare tendons in its base. When smaller arteries and arterioles are occluded, the ulceration may have an irregular outline with strands of infarction extending along a vascular pattern in the skin. The condition is often indolent, healing only when the blood supply is improved and the ulcer base is excised and grafted.

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Vasculitis

Most acute forms of vasculitis, and some subacute and chronic forms, are likely to cause ulceration. Vasculitic lesions are usually but not always multiple. Palpable purpura is characteristic but vasculitis may be polymorphous, even pustular. Raynaud's disease, scleroderma and lupus erythematosus typically affect the fingertips rather than the leg, but lupus should be considered in any abnormal form of leg or foot ulceration.

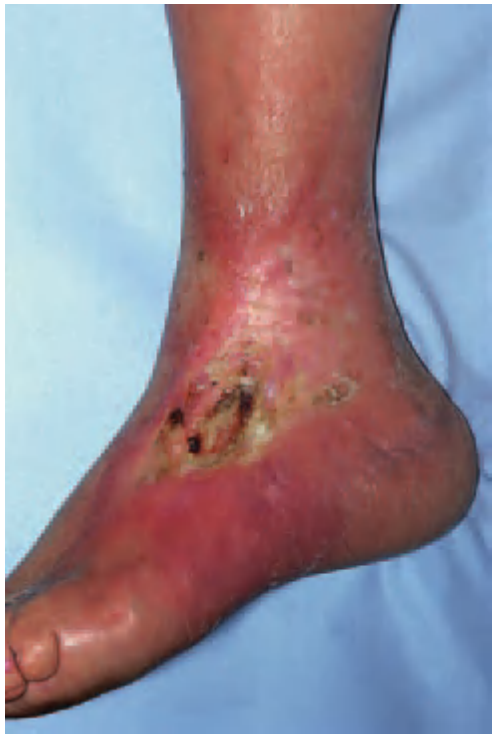

Fig. 50.31 An ischaemic ulcer with slough and exposed tendons.

Rheumatoid disease [1]. Leg ulceration in rheumatoid arthritis is common and the causes can be multifactorial. Poor joint movement impairs the calf muscle pump and immobility increases the risk of DVT. True 'rheumatoid ulcers' occur as a manifestation of rheumatoid arteritis. Ulcers are often situated in the gaiter region and have a sloughy base with poor granulation. The absence of surrounding lipodermatosclerosis or of other signs of venous disease, the presence of a positive rheumatoid factor (particularly if at high titre) and demonstration of normal Doppler pressures and venous duplex studies suggest that the ulcer is truly 'rheumatoid'. Biopsy may be helpful but is not always confirmatory and the site may not heal. Ulceration of rheumatoid nodules is uncommon except at pressure sites in bedridden patients. Thin skin because of long-term corticosteroid treatment, and the use of methotrexate, also increase the risk of ulceration. Healing can be very impaired, particularly in the presence of muscle atrophy, immobility and oedema.

Other autoimmune disease. Leg ulceration in patients with lupus erythematosus is well recognized [2]. In Felty's syndrome and Still's disease, multiple painful ulcers occur on the legs and feet and are difficult to heal. Ulcers also occur in polyostotic fibrous dysplasia (Jaffe–Lichtenstein disease), in which a diffuse mesenchymal abnormality is present. Ulceration occurs over large areas of subcutaneous or muscular calcinosis, especially around the knee.

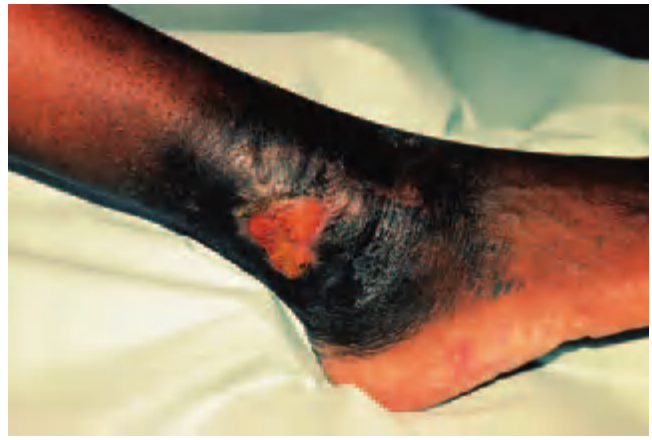

Fig. 50.32 Sickle cell ulcer.

Livedo reticularis. Livedo reticularis, a fixed but broken pattern of mottling, may result from vasculitis but also occurs with intravascular thrombosis caused by cryoproteinaemias [3], antiphospholipid and Sneddon's syndrome (Chapter 48).

Livedoid vasculopathy (livedo vasculitis) is a more specific form of occlusive vasculopathy limited to the gaiter skin and often extending onto the dorsum of the foot. Ulcers are small, painful and heal with ivory white scars (atrophie blanche).

Livedo with summer ulceration is a variant of the same condition (see p. 50.27).

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Haematological disorders

Indolent non-healing ulcers on the leg are a feature of sickle cell anaemia (Fig. 50.32), hereditary spherocytosis and other haemolytic anaemias. In thalassaemia [1], the skin is shiny and pigmented [2]. Myelo- and lymphoproliferative disorders may contribute to leg ulceration if cell size compromises capillary perfusion or if thrombosis develops. Leg ulceration is common in sickle cell disease, occurring in 43% of patients in one series; venous disease is a major contributing factor [3]. Other haemolytic anaemias also predispose to leg ulceration [4].

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Traumatic, decubitus and neuropathic ulceration

This is common on the shins and ankles and may accompany or follow fractures. Arteriovenous aneurysm formation or arterial insufficiency should be suspected if the ulcer persists. Pressure sores occur easily and with little warning on the heels and ankles of elderly people, especially in those who are comatose or paralysed. Ill-fitting calipers or pressure bandages may cause ulceration in those with 'polio legs' or in limbs with a diminished blood supply. Accidental burns usually occur in a domestic setting, but may also occur from hot-water bottles used to warm an unconscious or anaesthetized patient. Chemical burns are unusual unless factitious, but extravascular leakage from intravenous injections, especially in those having sclerotherapy for varicose veins, may cause local sloughing. In all cases where ulceration is protracted in the absence of venous, arterial or trophic disease, artefacts must be considered; interference with ulcers already present may also occur, even through bandages. Drug addicts develop ulcers at sites of injection into superficial veins, and also at extravascular sites when extravasation occurs.

Neuropathic ulcers are most common in diabetic subjects (Fig. 50.33). About 70% of diabetic foot ulcers are caused by neuropathy with adequate vasculature. Infection frequently coexists and osteomyelitis must always be considered [1].

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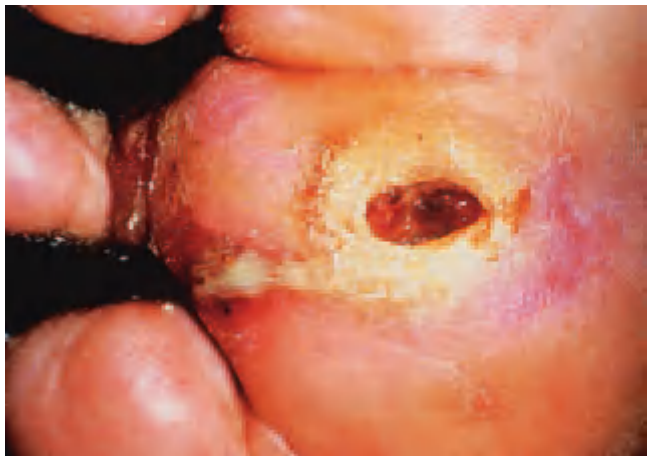

Fig. 50.33 Neuropathic–ischaemic ulcers over the base of the foot (diabetic).

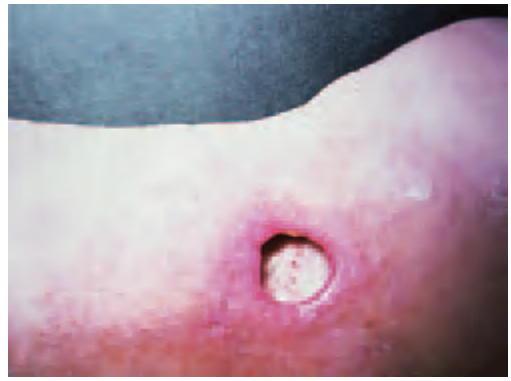

Fig. 50.34 'Steroid ulcer' with totally suppressed granulation tissue.

'Steroid ulcers'

Intralesional steroid injections, especially if made in areas with an already impoverished blood supply, may cause an indolent ulcer with a characteristic greyish slough (Fig. 50.34) [1]. This condition is most commonly seen when strong topical corticosteroids are applied to venous or other ulcers of the lower leg and ankle.

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Infection

Infection may lead to ulceration, which is often slow to heal because of associated oedema, cellulitis, thrombophlebitis, diabetes or underlying vascular disease. Primary uncomplicated pyococcal ulceration is rare; ecthyma is an example. Meleney's ulcer (bacterial synergistic gangrene) extends rapidly and has a burrowing, bluish, undermined and painful edge (Fig. 50.35).

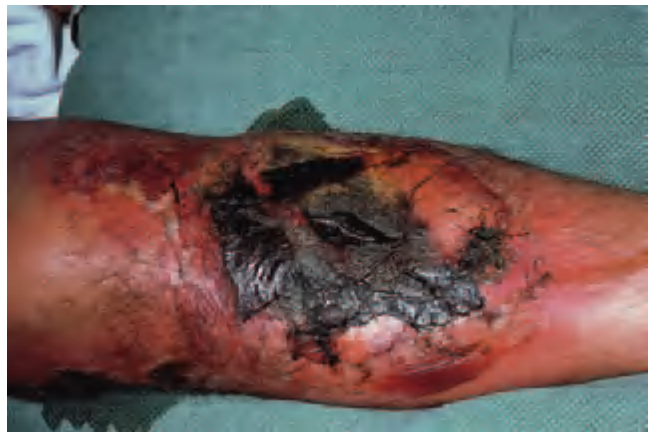

Fig. 50.35 Meleney's spreading gangrene.

Tuberculous ulcers occur in erythema induratum (Bazin's disease) and are chronic, often on the back of the calves. They usually have undermined edges and considerable surrounding inflammation (Chapter 28). Occasionally, an unusually extensive tuberculous ulceration occurs and often remains misdiagnosed. Other mycobacterial infections may be more common than suspected (Chapter 28). Ulcers in leprosy are usually on the foot, especially the dorsum, and on the proximal phalanx of the great toe, but can occur occasionally on the leg. The 'classical' appearances of the ulceronodular form of tertiary syphilis are well known, but this is extremely rare today. Multiple tissue-paper scars on the legs occur typically in yaws (Chapter 29). The so-called 'desert' or 'veldt' sore is shallow and crusted: the role of *Corynebacterium diphtheriae* is uncertain. The 'tropical' ulcer is a variety of phagedenic ulcer with a mixed symbiotic infection and rapid spread. Other phagedenic ulcers are seen rarely, only occurring in the seriously ill or undernourished. Leishmaniasis, relatively uncommon on the legs, should be remembered as a possible cause of an indolent granulomatous ulcer. Among other uncommon infective causes of ulceration are glanders, tularaemia, brucellosis and cat scratch fever.

Pyoderma gangrenosum (Chapter 49)

This causes rapidly spreading and often bizarre and extensive ulceration, which may mimic an artefact, particularly when it precedes obvious ulcerative colitis. Two-thirds of cases are associated with inflammatory bowel disease, rheumatoid arthritis or haematological malignancies [1].

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Necrobiosis lipoidica and granulomatous diseases

Necrobiosis lipoidica may ulcerate following trauma, is extremely indolent, and should be regarded as ischaemic. Similarly, any granulomatous lesion may ulcerate if its blood supply is inadequate or if the vessels are involved in the granulomatous process, as may occur in sarcoidosis.

Hypertensive ulcer

SYN. MARTORELL'S ULCER

This ulcer was first described by Martorell [1] and there have been several other reports subsequently [2].

Pathogenesis. Hypertension may arise spontaneously in elderly people in association with a gradual reduction in the density of the capillary bed. The density of the capillary bed in the middle and deep dermis of the shin, particularly on its lateral aspect, is much reduced even in healthy persons [3], and this may predispose them to ischaemic necrosis when the somewhat sparse arterioles are subjected to severe hypertension. Hypertensive ulceration is more common in women and tends to be bilateral. It produces superficial ulceration because the affected vascular bed is near the surface; the peripheral pulses are always present, distinguishing the condition from atherosclerosis. The ulcer characteristically has a reddish or yellowish edge with livedo patterning at its periphery. It is often initiated by trauma, and the ischaemia may be a consequence of a failure to meet the demands for repair.

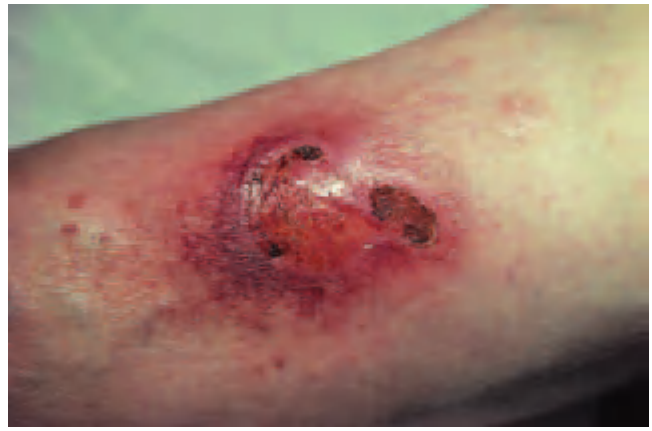

Fig. 50.36 A Martorell ulcer. High blood pressure causes vessel wall hypertrophy or vasospasm. Pain and ulceration with a livid reticulate edge but no lipodermatosclerosis is diagnostic. It is usually more proximal than a venous ulcer.

Histology. There is increased thickening of the arteriolar walls with luminal narrowing by subendothelial hyalin degeneration. Smooth-muscle hyperplasia is most marked in the media and is most easily recognized by an increase in the number of smooth-muscle nuclei. It is later replaced by collagen fibres. Whether it truly represents a specific disease has been questioned [4].

Clinical features. The ulcer is initially preceded by a small macular cyanotic lesion present on the anterior external aspect of the leg at a point between the middle and lower thirds of the limb. It is usually extremely painful, and this may be alleviated by holding the leg in the dependent position. The livid edge is a characteristic feature (Fig. 50.36).

Treatment. The blood pressure should be controlled, and the leg should be placed in a position to prevent oedema but not so high as to promote further ischaemia. A firm non-elastic support bandage, without compression, is the most helpful dressing. At this site on the leg, the blood supply is difficult to re-establish, and several weeks may

pass before the ischaemic necrotic tissue separates and granulation tissue begins to form. Smoking should be stopped and β-blockers avoided. Excision of the ulcerated area with grafting has been advised.

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Prolidase deficiency

Prolidase deficiency is transmitted as an autosomal recessive condition. It is a rare cause of recurrent ulceration of the skin, especially in young people, often beginning in childhood [1–5]. Fragility of the skin, resulting in breakdown at the site of injury, is often preceded by purpura or bruising (Fig. 50.37). Fine scarring and telangiectasia may be a feature. The facies are characteristic, consisting of hypertelorism with a saddle nose. Other associations, not present in all cases, are dental caries, splenomegaly, hyperextensibility of ligaments, osteoporosis, respiratory infections, corneal opacities, amblyopia and optic atrophy. The skin may have a doughy consistency as in other collagen disease. The diagnosis is ascertained by iminopeptiduria greater than 5 mmol/24 h. The predominant peptide is glycylproline. A characteristic feature of the disorder is absolute resistance to all forms of treatment including rejection of skin grafts. It is thus a highly disabling affliction. Because co-factors of prolidase are ascorbic acid and manganese, these have been recommended therapy, as has diphenylhydantoin [6]. Japanese investigators recommend an ointment containing 5% glycine and 5% proline [7], and this was confirmed to be effective by Jemec and Moe [6]. Apheresis exchange was successful in two patients [8].

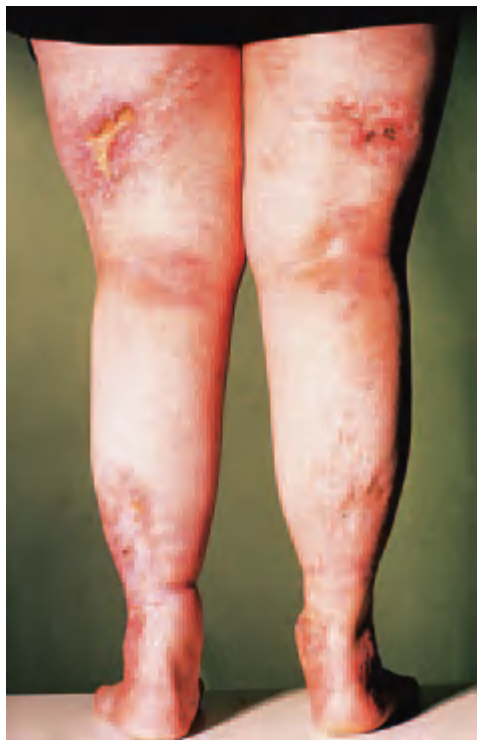

Fig. 50.37 Multiple ulcers with unusual distribution associated with prolidase deficiency.

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Hydroxyurea therapy

Painful leg ulcers associated with hydroxyurea have been reported several times. The ulcers healed after the drug was withdrawn [1].

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Ulcers of the foot [1]

In industrialized societies, shoe wearing protects the tissues from the effects of the gravitational thrust when the leg veins are incompetent. It is unusual therefore to see ulcers of purely venous origin below the line of the edge of shoes, although atrophie blanche or livedoid vasculopathy are not uncommon on the dorsum of the foot or on the relatively unsupported region at the base of the first and second toes. Nevertheless, in one study of all ulcers of the leg, 30% were of the foot; men developed them earlier than women [2].

Vasoconstriction operates more powerfully in the feet than in the legs, and it is here that the earliest effects of arterial insufficiency or of peripheral neuropathy are

found. A reduction in the capillary blood supply is present even in healthy subjects and may predispose to delayed healing at an affected site [3]. The foot is subject to almost constant pressure at several points. When a diminished vascular supply or prolonged recumbency intensifies the pressure on the heel or edge of the toes, ulceration quickly develops (gravitational or decubitus ulcers). This is the most frequent cause of ulceration seen in dermatological practice, especially in elderly people, and may be avoided by good nursing care, padding and polo rings to prevent excessive pressure developing. Atherosclerotic ulcers may occur in the distribution of a single artery or extend widely when a larger, more proximal vessel is affected. Foot ulceration between the toes has recently been described in patients who have received tight compression bandaging to treat their venous ulcers [4].

In impoverished populations who do not wear fitted shoes, the foot is also prone to infection and infestation.

Diabetic foot ulcers [5]

Apart from conventional arterial disease there are two major causes of foot ulcers in diabetes: neuropathy and infection. Lack of sensation makes the patient unaware of any ulceration or progressive damage from footwear or bandage, so underlying osteomyelitis or deep soft-tissue infection may pass unnoticed.

Trophic ulcers

The term is an unsatisfactory one. Some occur as the result of pressure (decubitus) and friction on areas that have become anaesthetic as a result of a neurological disease (Fig. 50.33), but others are associated with underlying vascular abnormalities (gravitational). Most commonly there is a reduced arterial supply, as in diabetes, but sometimes there is an increased resting blood flow to the skin. This is a consequence of arteriovenous shunting. It also occurs in patients with features of 'acropathie ulcéromutilante', originally described in male alcoholics in France [6,7], in which dilated stiff-walled microvasculature is unable to respond to injury by the further vasodilatation necessary for repair. It may obviously complicate other neuropathies. Such shunts have been demonstrated by non-pictorial tracer techniques and arteriography [6]. Some therapeutic success has been claimed by tying off the feeding artery or by 'skeletonizing' all its branches [7]. This may allow the ulcer to heal and thus may arrest progression of the destructive bony changes.

Neuropathic ulceration of the foot benefits from protection from shearing forces [8] by the use of a plaster cast or 'Scotchcast boot'. If this fails to achieve healing, the pressure must be taken off the foot and the base of the ulcer excised before being grafted. Split skin, rotation flaps or pedicle flaps may be used to cure the defect. It may be simpler to excise the toe and most of the first metatarsal to achieve rapid healing if the ulcer is situated over the ball of the foot. Patient education is of prime importance to avoid recurrent inadvertent self-trauma.

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Management of venous ulcers [1–4]

Many venous ulcers are cared for in the community by appropriately trained nurses and general practitioners. The diagnosis of venous ulceration is essentially clinical. The ankle–brachial pressure index (ABPI) should be measured unless peripheral pulses can be easily felt. Sensory testing is always important in diabetic patients and in any patient with foot ulceration. While in an ideal world every healed venous ulcer should have a colour Doppler duplex ultrasound performed to exclude a surgically correctable superficial venous incompetence, resources and logistics do not always permit this [5]. The presence of venous reflux on duplex scanning does not necessarily confirm a venous cause; basal cell carcinomas, for example, can develop in a limb with varicose veins.

General management

First-line therapy for venous ulcers is compression bandaging. The concept is to reduce venous pressure, particularly during walking, by improving calf muscle pump function and by opposing gravitational venous reflux. Exercise and movement are to be encouraged, while long periods spent sitting and standing are discouraged. When resting, the legs should be elevated, ideally with the ulcer just above the level of the heart to ensure the maximum reduction in venous pressure. Thus, lying is always preferable to sitting with the leg elevated. Patients should always be instructed to sleep in a bed; this might sound obvious but it is remarkable how many patients with venous ulcers fall asleep and remain in chairs with

dependent legs both day and night, so exacerbating venous ulcers (despite bandaging).

Obesity is often a problem that becomes worse with immobility, boredom and social isolation. Weight control is therefore essential, but malnourishment with anaemia and poor protein intake can coexist with obesity.

The contribution of other medical conditions, particularly heart and chest problems, needs to be considered. Heart failure exacerbates venous hypertension, while the need to sit upright in bed or in a chair to alleviate dyspnoea will further compound the situation.

Compression therapy [6]. Graduated multilayer high compression bandage regimens capable of sustaining compression for a week at a time should be the first line of treatment for uncomplicated venous ulcers with an ABPI ≥ 0.8. Randomized controlled trials (RCTs) have shown that compression provided by Unna's boot [7], two-layer [8], four-layer [9] or short-stretch bandages [10] improved healing rates compared to treatments using no compression.

Three RCTs compared elastic high compression (Tensopress® or Setopress®) with low compression (Elastocrepe®) [11]. More patients were healed at 12–15 weeks with high compression.

Multilayer high compression systems have been compared with single-layer systems. Four-layer bandaging was superior to a single-layer adhesive bandage [12,13]. However, no differences were found in healing rates when four-layer compression bandaging was compared with short-stretch bandaging and with Unna's boot, although the studies were small [14,15]. A recent study has shown that a rigid three-layer paste regimen produced healing rates as good as four-layer compression [16]. When leg ulcer clinics have promoted high compression treatment, healing rates have generally improved when compared with usual care given by community nurses [9,17]. Enthusiasm by professionals and a defined strategy, however, may explain the improvement.

In the UK, elastic (long-stretch) bandages are mainly used, whereas in Europe short-stretch bandages are preferred. Elastic bandages sustain compression for longer, whereas short-stretch bandages produce high 'venous' pumping pressures during exercise but lower resting pressures [18]. Multilayer bandaging (e.g. the Charing Cross four-layer bandage) has gained popularity owing to the high healing rate success reported in one study [19]. Unfortunately, all large ulcers were excluded and grafted in this study, and other surgeons have had difficulty in producing equivalent results. Nevertheless, multilayers provide good conforming properties for distribution of pressures as well as good sustainability of pressures.

Adequate training is essential for good results [20]. Incorrectly applied bandages can be harmful.

Dermatological assessment. The condition of the ulcer and of the surrounding skin influences treatment outcome. If eczema is present, exudation and scratching will jeopardize the integrity of the surrounding skin. Consideration must be given to the underlying cause of the eczema which may be: (i) varicose; (ii) contact allergy, or; (iii) contact irritant (e.g. caused by maceration from soaked dressings). A topical steroid is indicated to treat eczema, whereas emollients alone are sufficient for non-inflamed skin. Fragile oedematous skin needs careful application of compression bandages (but not necessarily less compression).

Cleansing and débridement. Management of the leg ulcer itself is important but should only be addressed once the patient's general health and venous hypertension have been considered. Cleansing of the ulcer should be kept simple [21,22]. Irrigation of the ulcer with warmed tap water or sterile saline is usually sufficient [23].

Any dressing technique should be clean and aimed at preventing cross-infection. Strict antisepsis is unnecessary. It is customary to remove sloughy or necrotic tissue from the ulcer bed by débridement, as this improves wound healing [24]. Maggots are used in some clinics for débridement but have never been compared with surgical débridement [25].

Dressings and topical therapies [26]**.** Dressings should be simple, low adherent, inexpensive and safe. There is no evidence that any particular dressing or dressing type is more effective in healing venous leg ulcers. 'It's not what you do with the ulcer that is important, it is what you do with the leg' is a good axiom, reflecting the fact that the most important aspect of treatment is reversing the venous hypertension, not the choice of wound dressing. Nevertheless, an absorptive dressing may be valuable in a highly exuding wound; more frequent dressings are an alternative option.

Ideally, a dressing should be left undisturbed for as long as possible so the ulcer can get on with the job of healing. Changes of dressing only disrupt new fragile epithelium. Conversely, a wet soaked dressing and bandage tends to produce maceration of surrounding skin and encourage infection. 'Strike-through' of exudate to the outside of a bandage is usually an indication for a dressing change. Patients can develop allergies after using a product for some time. Patch testing should be considered if dermatitis develops or is difficult to control.

Tissue-engineered skin equivalent (e.g. Apligraf®) has been shown to aid healing over and above that achieved by compression [27] and was found to be particularly effective in therapy-resistant ulcers. Granulocyte–macrophage colony-stimulating factor appears to promote healing of venous ulcers, but further research is required [28].

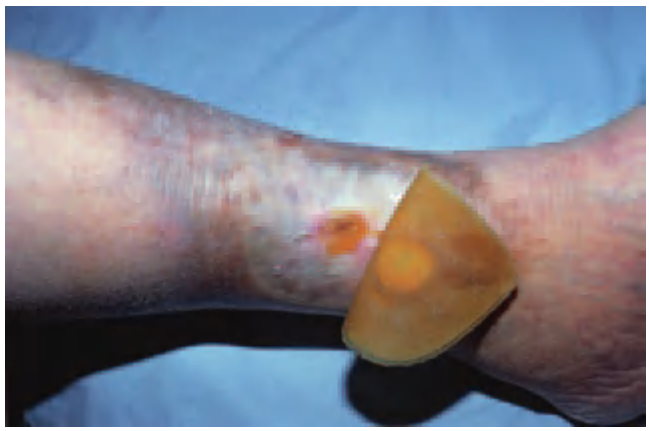
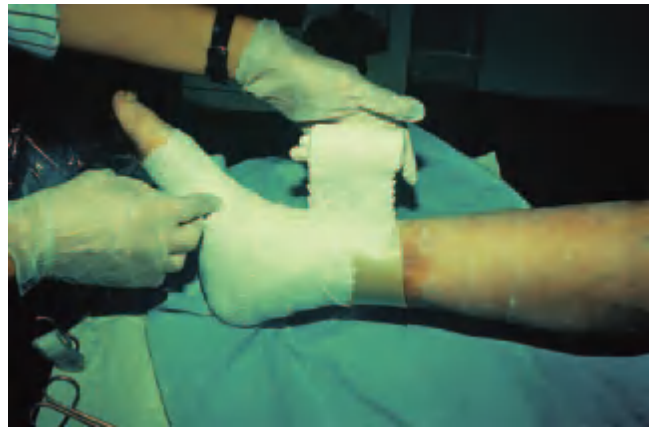


Fig. 50.38 A hydrocolloid dressing applied to an ulcer provides comfort and stimulus to healing. The centre of the dressing dissolves and contributes to odour and exudate on removal.

(a)



(b)

Fig. 50.39 Applying a paste bandage to an ulcer, avoiding a tourniquet effect by frequent: (a) cutting; (b) folding.

First-line primary dressings [29] include a knitted viscose primary dressing (e.g. N-A Dressing®) with a superimposed absorbent pad (secondary dressing). Tulle dressings impregnated with paraffin (e.g. Jelonet®) can increase maceration; medicated tulle dressings are not generally recommended unless infection is likely [30]. Foam dressings are helpful in exuding wounds. Hydrocolloid dressings can be helpful in dry sloughy wounds to reduce pain but are not recommended if there is much exudate (Fig. 50.38). Alginate dressings are highly absorbent and are suitable for exuding wounds. Zinc paste bandages (e.g. Steripaste®) can be applied directly to the wound base and to the intact skin from the base of toes to knee, with a covering compression bandage in one or two layers (Fig. 50.39).

Microbiology. Chronic leg ulcers are usually colonized by microorganisms but whether this affects healing is debatable [31,32]. Routine wound swabs for bacteriology are unnecessary unless there is evidence of clinical infection such as: (a) surrounding inflammation, redness or cellulitis; (b) increased pain; (c) purulent exudate; (d) a rapid deterioration of the ulcer; or (e) fever. The discovery of group A haemolytic *Streptococcus* should prompt use of a course of penicillin, but otherwise antibiotics should not be used too readily.

Pain relief. Most patients with venous ulcers suffer moderate to severe pain [33]. Pain can result in reduced mobility, particularly of the range of joint movement, leading to a poor calf muscle pump. Pain may also indicate other pathology such as arterial insufficiency, malignancy or infection. Analgesia is recommended if compression fails to resolve pain from a venous ulcer. Opioids may be necessary in some cases. Some deep pain is mediated by the autonomic nervous system and may be helped by amitriptyline or a guanethidine block [34]. Quinine is a useful therapy for night cramp [35].

Measurement [8]. It is unwise to recommend any agent for the healing of ulcers that has not been subjected to a properly controlled trial. The only measurement that matters is the time taken for total healing of a large number of ulcers, which would, if possible, be stratified by initial ulcer size. The size influences the time taken for total healing to occur [36]. Large ulcers generally take significantly longer to heal than small ones. The healing rate is a poor measure; however, it is of value in monitoring the progress of individual ulcers (Fig. 50.40).

Systemic therapy. Systemic antibiotics have not been shown to improve the healing rates of venous ulcers and should be reserved for ulcers with clear evidence of infection [37].

The effectiveness of pentoxifylline in healing venous leg ulcers may be because of its fibrinolytic action and a reduction in leukocyte adhesion. Although randomized

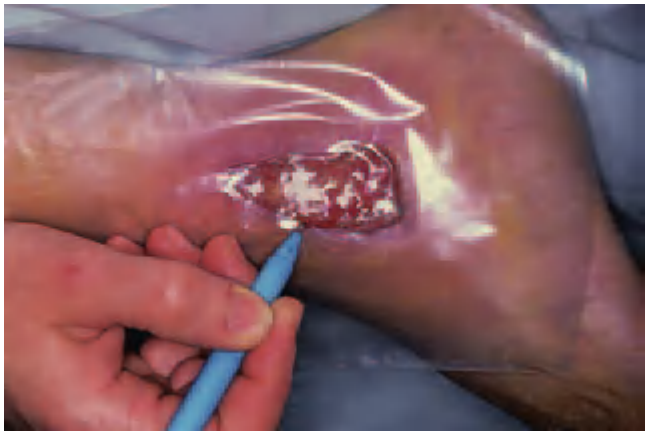


Fig. 50.40 Tracing around the margins of an ulcer to ensure that healing is occurring.

trials have reported both positive and negative results, a systematic review was positive [38]. A dose of 800 mg three times daily may be better than 400 mg three times daily as conventionally used.

An increased rate of venous ulcer healing with the use of oral enteric-coated aspirin (300 mg) daily was reported in one randomized trial [39]. Mixtures of flavanoid drugs (e.g. oxerutins) are licensed for use in venous disease. Daflon 500 accelerated healing of small ulcers in a randomized trial [40].

Stanozolol, an androgenic steroid with fibrinolytic properties, is helpful in lipodermatosclerosis [41] but no studies have demonstrated improved ulcer healing.

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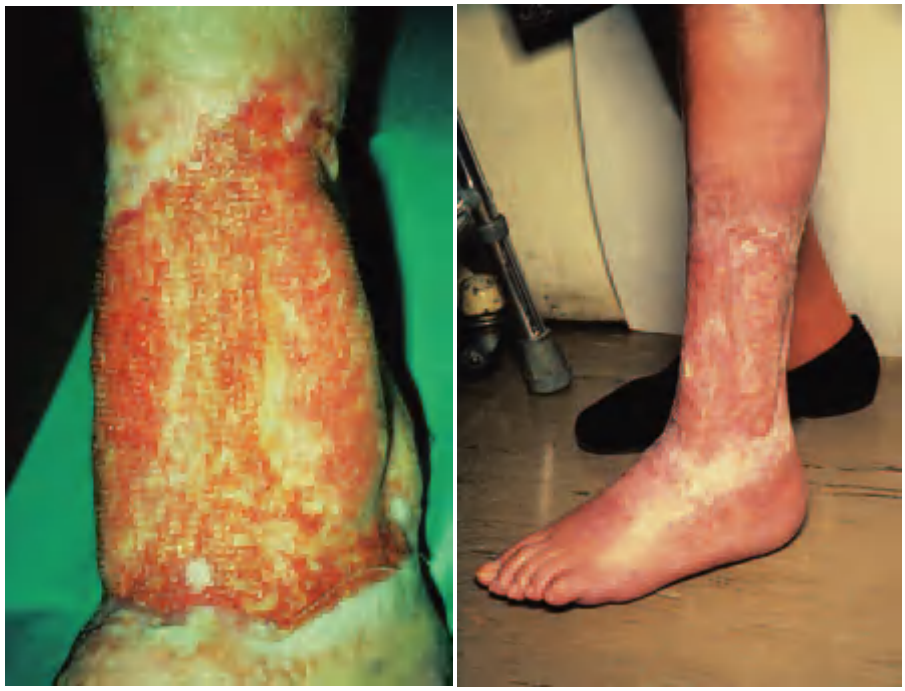

(a) (b)

Fig. 50.41 A large ulcer (a) before and (b) after skin grafting.

Surgical treatment [1]

The exact role of surgical treatment is a matter of considerable dispute. Recurrence rates of 30–50% after different surgical manoeuvres have been reported within 5 years [2–4]. Ligation and stripping of the saphenous veins and compressive sclerotherapy are the procedures most frequently undertaken. Complete extirpation of the communicating veins 'feeding' the ulcer is a logical approach but other communicating veins are easily missed [3].

It would appear that surgical eradication of superficial incompetent veins is effective in preventing recurrence but it is of little or no value in preventing recurrent ulceration in patients with damage to the deep venous system [5]. The newer procedures of deep-vein bypass, valvuloplasty and brachial valve transplant have still not been subjected to rigorous assessment by independent centres concerned with treating large numbers of patients with post-thrombotic limbs and venous ulcers. The value of these techniques in preventing ulcer recurrence in post-thrombotic limbs is therefore unknown. Elastic stockings must be worn for life and renewed at 6-monthly intervals if recurrence is to be prevented, and even these are not totally effective [6].

Shave therapy, a method of excision of ulcer and surrounding lipodermatosclerosis followed by meshed split-skin graft, healed 88% of ulcers in 18 patients [7].

Skin grafting. Skin grafting on the lower legs is a means of considerably reducing the time taken for the ulcers to heal. It is usually performed on in-patients but can be carried out as an outpatient ambulatory procedure [8]. Pinch grafting provides small quantities of dermis as well as epidermis but leaves unsightly donor sites; large ulcers usually require split-skin grafts, which must be placed on surgically débrided beds. The application of mesh grafts has proved very effective when combined with ulcer excision (Fig. 50.41) [9]. Recurrence rates depend on patient selection. Those with many underlying medical or social problems are likely to have ulcer recurrence within a few weeks or months of grafting. Many studies of skin grown *in vitro* have indicated that keratinocytes will stimulate healing with the repopulation of host tissues even though the grafts may not themselves survive. Mechanisms underlying growth stimulation by cytokines have led to a growth-factor industry [10]. However, no cytokine can be relied upon to promote healing unless most of the above-mentioned management factors are first attended to. If the underlying causes of ulceration are well managed, healing rates are excellent and added cytokines are not necessary [11].

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Recurrent ulcers

Once their ulcer is healed, patients should be transferred from a bandage regimen to compression hosiery [1,2]. There are three categories of compression hosiery [3]:

1 *Class I*: Ankle pressure 14–17 mmHg
2 *Class II*: Ankle pressure 18–24 mmHg
3 *Class III*: Ankle pressure 25–35 mmHg

Class II or III should be chosen, depending on the severity of the venous hypertension. It is of the utmost importance that stockings are carefully fitted and that patients are instructed about how to put them on and take them off. An applicator may need to be purchased. Hosiery should not be worn overnight. At least two pairs should be provided, to allow for daily changing and washing. Washing is necessary to retain the elastic property of Lycra-containing hosiery. Two stockings per leg should last 6 months before compression is lost and replacements are required.

Many recurrences are the result of poor follow-up and inadequate or worn-out elastic stockings. Indeed, the 50% overall recurrence rate over 5–7 years has been shown to be higher in those prescribed stockings and is an indication of poor supervision [4]. Some recurrences are the result of superimposed arterial disease causing tissue ischaemia and skin necrosis. Many ulcers are precipitated by minor trauma, in which case a foam or felt pad should be worn over or under the stocking over vulnerable areas. Despite this, a considerable proportion of well-treated formerly ulcerated limbs develop recurrences from time to time, often for no obvious reason. These recurrences are more likely in post-thrombotic limbs. Obsessional attention to detail in stocking use, avoidance of minor trauma and early vigorous treatment of any breakdown should reduce the period of re-ulceration to a minimum. Surgical ligation of the saphenous veins and of incompetent communicating veins appears no better than stanozolol and stockings in preventing ulcer breakdown.

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Telangiectases

Telangiectases (Latin: Tel, end + Greek: Angos, vessel + ectasis from Greek: ektasis, expansion) are chronically dilated capillaries or small venules. They appear on the skin and mucous membranes as small, dull red, linear, stellate or punctate markings. Telangiectases (telangiectasias) represent dilatations (expansion, stretching) of pre-existing vessels without any apparently new vessel growth (angiogenesis) occurring. As such, telangiectases can be bracketed with spider angioma (spider naevi) and capillary aneurysm-venous lake, whereas vascular malformations represent anomalies of embryological development (disturbances in vasculogenesis or angiogenesis). Hamartomas include proliferation of other tissue elements, e.g. melanocytic, eccrine and are not solely vascular [1].

Development of telangiectasia [2]

The common telangiectases can be explained by abnormalities in the organization and ultrastructure of the small vessels rather than by neovascularization (angiogenesis) or random anastomoses. The *macular telangiectases* seen in scleroderma, generalized essential telangiectasia and naevus flammeus are produced by dilatation of postcapillary venules of the upper horizontal (subpapillary) plexus (Fig. 50.42). *Cherry angiomas* are produced by spherical and tubular dilatations of capillary loops in dermal papillae with tortuous cross-connections between individual loops. *Angiokeratomas* of Fabry and Fordyce have the ultrastructure of collecting venules that contain valves and appear to represent the ectopic development or placement of small valve-containing collecting veins. The cutaneous lesions of hereditary haemorrhagic telangiectasia (HHT) represent microvascular arteriovenous anastomoses.

The development of telangiectases is nevertheless a complex dynamic process where different mechanisms may be at play. In HHT, for example, where arteriovenous anastomoses cause focal dilatations of postcapillary venules, mutations in Endoglin (ENG) HHT-1 or activin receptor-like kinase I (ALK-1 or ACVRL1) HHT-21, are responsible. Mutations in ALK-1 interfere with an integral membrane protein on vascular endothelial cells responsible for binding transforming growth factor-β (TGF-β). TGF-β signalling mediates vascular remodelling through effects on extracellular matrix production [3]. Disruption of this latter maturation phase of angiogenesis seems to be important in the development of HHT [4].

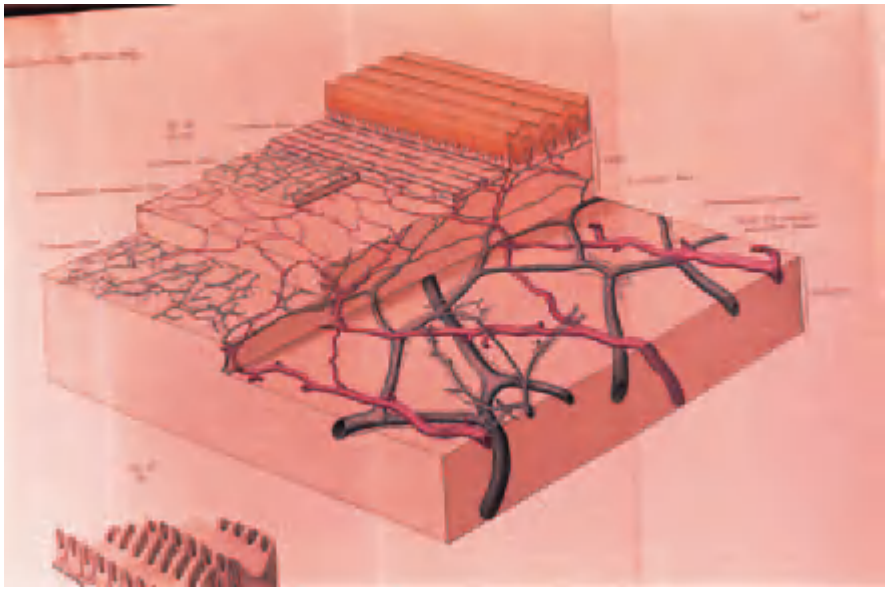

Fig. 50.42 Diagrammatic representation of the blood vessels of the skin. (From Jadassohn J ed., *Handbuch der Haut und Geschlechtskrankheiten 1*, 1927, p. 379. With permission from Springer-Verlag.)

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Secondary telangiectasia and dilatation of pre-existing vessels

Telangiectases commonly represent the effect of wear and tear on the skin, and are particularly frequent on ageing, light-exposed skin, or following trauma or X-irradiation. In fact, they are found in most processes which cause atrophy of the skin whatever the aetiology, for example poikiloderma. Smoking and UV radiation are known to have a detrimental effect on human skin characterized by elastosis and telangiectasia. The association between increasing age, sun exposure and amount of telangiectasia is strong among men but less apparent among women; similarly smoking is associated with elastosis in both sexes but only with telangiectasia in men [1].

Prolonged vasodilatation may be followed by permanent telangiectases, for example, in rosacea. Varicose veins are frequently the cause of telangiectases on the legs, where they may produce a type of arborescent telangiectasia. Telangiectasia associated with chronic venous disease are assumed to be due to rise in venous pressure so stretching the vulnerable venous end of the capillary or draining venule [2]. The significance of telangiectasia of the lower limbs must not be underestimated. Considered a 'cosmetic' problem, their presence is often indicative of early or established abnormalities of the main leg veins. Telangiectases may be present individually, in sheets or as an arborizing appearance. The colour of the telangiectasia depends on the calibre of the dilated venule. Large dilatations (< 1 mm) are dark blue and often palpable. The smallest (0.1 mm), most superficial, telangiectases are red and barely empty when the leg is raised. The term *corona phlebectatica paraplantans* is used to describe perimalleolar and paraplantar venous telangiectasia which is always associated with venous hypertension.

Telangiectases around the lower border of the ribs are virtually physiological in older age groups.

Telangiectases may be an important diagnostic sign in certain systemic disorders, especially lupus erythematosus, dermatomyositis and scleroderma, or in association with Raynaud's phenomenon. Capillary microscopy of nail-fold telangiectases in such patients may help in the differential diagnosis (Figs 50.43–50.45). Usually, the distribution and associated abnormalities leave little doubt about the diagnosis, but on occasion telangiectases may be the presenting or only sign, or may be the end result of an otherwise burnt-out process. Thus, patients with scleroderma, especially of the so-called Thibierge–Weissenbach or CREST type, may present with telangiectases that closely mimic HHT, and even cause severe bleeding; patients with dermatomyositis may have telangiectases on the eyelids, hands or elsewhere; and localized areas of telangiectases on the face may be a manifestation of discoid lupus erythematosus. Telangiectases of the face and also of the mucous membranes are a common feature of Raynaud's phenomenon without other evidence of scleroderma. Telangiectases may be a manifestation of neonatal lupus erythematosus, with or without any other eruption [3].

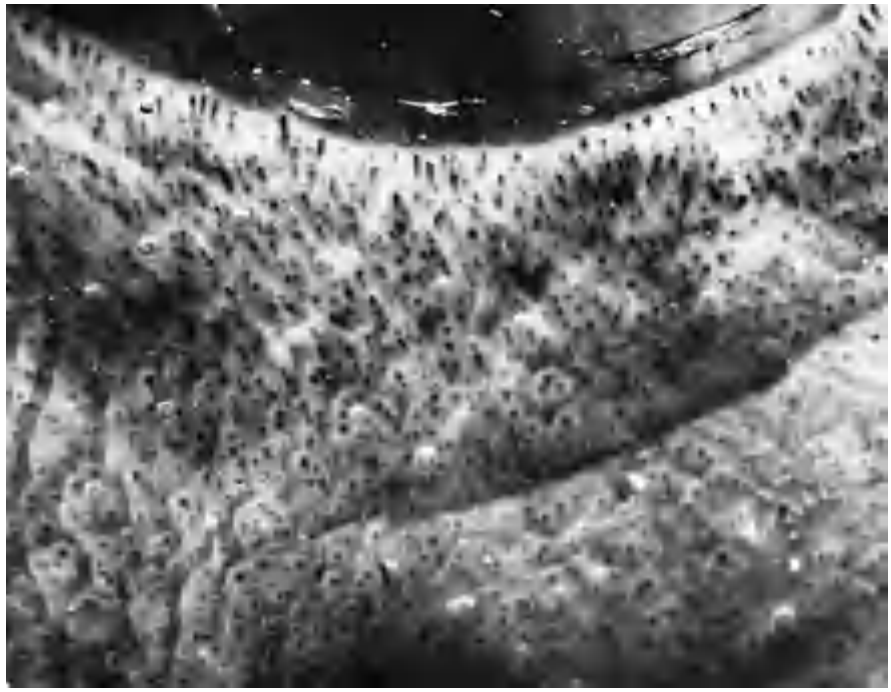

Fig. 50.43 Normal nail-fold capillaries. (Courtesy of Dr H.R. Maricq, Lyons, NJ, USA.)

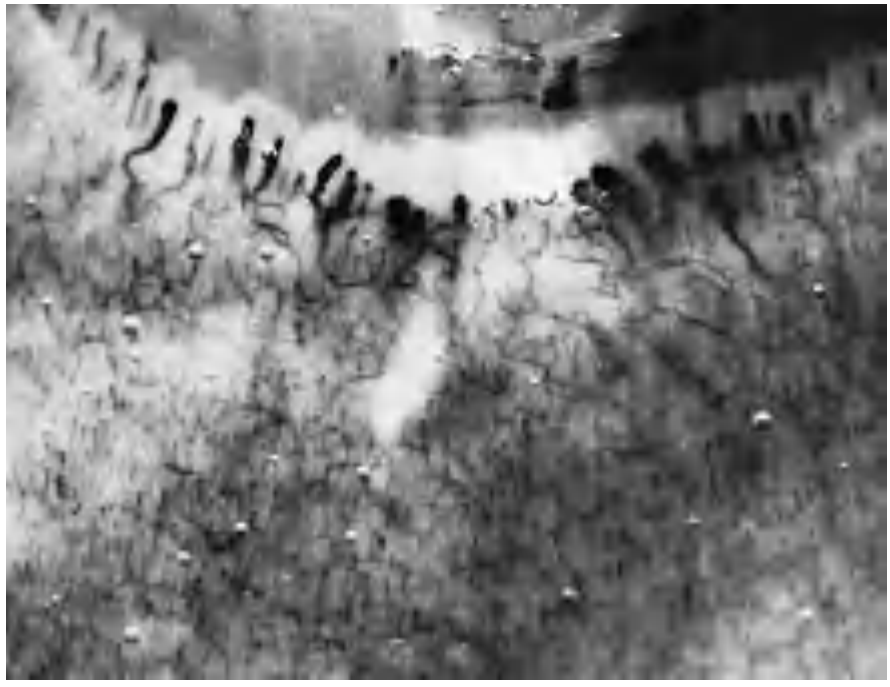

Fig. 50.44 Nail-fold capillaries in scleroderma. (Courtesy of Dr H.R. Maricq, Lyons, NJ, USA.)

Unusual mat-like telangiectases, especially on the upper back, have been reported in men working in an aluminium plant [4]. Telangiectases on the chest wall [5] and other sites [6] have been reported in patients with AIDS.

Telangiectasia are also described secondary to other conditions including cutaneous mastocytosis (telangiectasia macularis eruptiva perstans) and angiotropic (intravascular) lymphoma [7].

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Fig. 50.45 Capillary microscopy of a haemorrhage in a nail bed reveals that it is in the shape of a capillary loop and there is intravascular microthrombosis. (Courtesy of Professor T.J. Ryan, Oxford Radcliffe Hospital, Oxford, UK.)

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Spider telangiectases

SYN. ARTERIAL SPIDER; SPIDER NAEVUS; NAEVUS ARANEUS; SPIDER ANGIOMA

Aetiology and pathology. Spider telangiectases occur in up to 15% of completely normal persons, and more frequently in children [1,2]. They occur in large numbers during pregnancy—one or more spiders are found in two-thirds of all pregnant women [1]. They may appear in the first few months, but tend to increase in number until term: they usually disappear within 6 weeks of delivery but may persist or recur in the same sites in subsequent pregnancies. They are also characteristically found in liver disease, of which they may be a presenting sign [3]. A relationship to oestrogens has been suggested on this clinical evidence. Palmar erythema may be associated with spiders, with or without liver disease or pregnancy.

The main vessel of the spider is an arteriole. The blood flows from this to the periphery, and then passes into a capillary network [4]. The lesion is not therefore a true arteriovenous anastomosis, although glomus cells may be associated with the lesions.

Clinical features. Spiders vary in size and shape, and may be up to 1.5 cm across. The central body may be raised, and is usually pulsatile on diascopy. The radiating vessels are just visible to the naked eye (Fig. 50.46). They occur on the upper half of the body, especially the face, neck and hands. They are frequently solitary, but may be multiple, even in health. Liver disease is seldom found, but should be suspected at any age when lesions are numerous. They

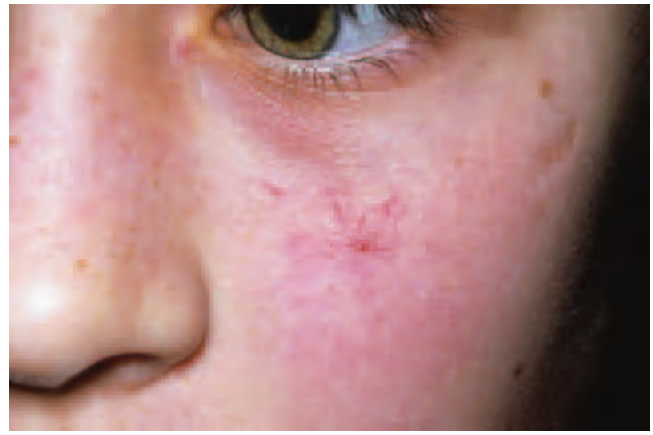

Fig. 50.46 Spider telangiectasis.

may develop at sites of trauma and may be unilateral [5]. Similar lesions occur on the mucous membranes of the lips and nose. Here, the typical morphology is less apparent and differentiation from HHT may be difficult.

Natural history. The majority of lesions which occur in pregnancy disappear spontaneously, but some may persist. Lesions appearing in otherwise healthy children tend to persist indefinitely, but a small proportion regress spontaneously.

Diagnosis. The typical morphology, with a central pulsating vessel, does not occur in other conditions. In HHT, the telangiectases are macular, punctate or linear; when they are stellate they do not pulsate.

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Cherry angiomas (Campbell de Morgan spots)

These are particularly common on the trunk of middle-aged or elderly people. They disappear in extreme old age. Increased numbers have been recorded in diabetics [1], but this may not be significant. Ultrastructural examination has shown that they have reduplicated basement membranes and fenestrations of the endothelium [2].

When fully developed they are readily recognized. Tiny lesions, which may be very numerous, can resemble either petechiae or other types of telangiectases. They cannot

always be made to blanch with pressure, and may need to be observed repeatedly to distinguish them from petechiae.

Angiokeratomas

Angiokeratomas are probably not vascular neoplasms but acquired telangiectases of pre-existing blood vessels of the papillary dermis, although some types of venular malformation cannot be excluded. They possess the ultrastructure of collecting venules with valves [3].

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Telangiectasia with calcium channel blocking drugs

There have been increasing numbers of reports associating telangiectasia with calcium channel blockers [1–3], particularly in sun-exposed sites. In a study of renal transplant recipients the grade of photodamage was strongly associated with the use of calcium channel blockers [4].

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Venous lakes [1]

A form of senile angioma occurring on the face, lips and ears of elderly patients. Histologically, they consist of greatly dilated, thin-walled venules without the proliferation of vascular tissue of the true angioma. There is degeneration of the supporting connective tissue [2].

Palmar varices. Small varicosities of the palms and fingers, particularly on the palmar phalangeal creases, are common in elderly people [3].

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Treatment of telangiectasia [1,2]

The central vessel of a spider naevus can be destroyed with electrolysis or pin-point hyfrecation without anaesthetic. A significant proportion of such lesions recur. Larger isolated angiomas can quite readily be sealed off by diathermy or cautery. Treatment of extensive small lesions is unsatisfactory. Various types of laser have been recommended [3]. Cryotherapy is somewhat disappointing. Injection with sclerosants for venous telangiectasia [1–4] is helpful. Cosmetic camouflage certainly has its uses.

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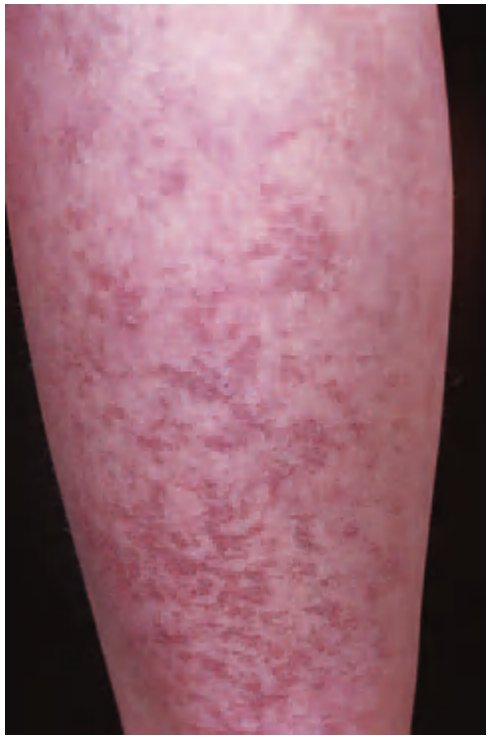
Primary telangiectasia

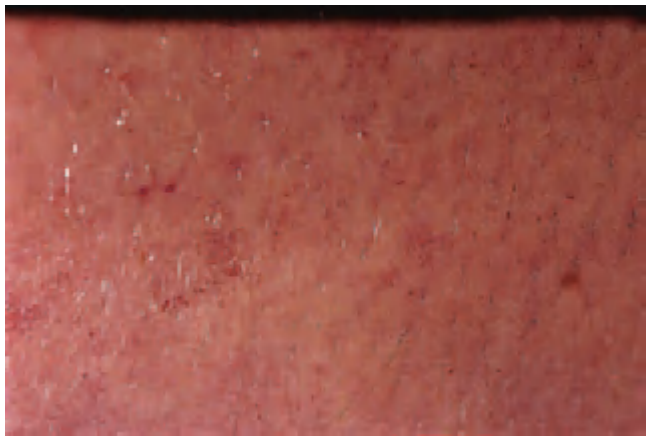
Angioma serpiginosum [1–4]

Angioma serpiginosum is a rare naevoid disorder affecting the small vessels of the upper dermis. Histology shows that the affected papillae are distended by a large, single, ectatic capillary lined by flattened endothelial cells of normal appearance. Inflammatory changes are not usually present.

The disease occurs predominantly in females (90%), and usually starts in childhood. Most cases are sporadic, but a family history suggesting dominant inheritance has been reported [5]. The common sites are the lower limbs and buttocks, but it may be more widespread. It is often unilateral initially. Characteristically, there are red or purple puncta up to 1 mm in diameter (Fig. 50.47). These are grouped in areas a few centimetres across, or sometimes form large sheets. Irregular lesions may arise, and commonly there is livedoid patterning of the puncta. Frequently, there is a background of more diffuse erythema. The lesions may not blanch completely on pressure, but nevertheless true purpura does not occur, and angioma serpiginosum should not be classified among the purpuric dermatoses. The dilated capillaries are easy to see under the capillary microscope. The background erythema is due to dilatation of the subpapillary venous plexus. The condition starts as one or more small lesions, and characteristically extends over a period of months or years. After this period further extension usually ceases, but may recommence in adult life. Individual puncta often disappear spontaneously, and complete regression of the eruption



(a)



(b)

Fig. 50.47 Angioma serpiginosum.

may occur, or traces may persist indefinitely. There are no symptoms, and no other changes in the skin, although slight atrophy has been reported. A single case associated with retinal and spinal nerve-root angiomas has been reported [6]. Histologically dilated and tortuous capillaries are observed in the papillary dermis but without any inflammation or red cell extravasation. Epiluminescence microscopy can be helpful in diagnosis by demonstrating 'red lagoons' [7].

Differential diagnosis includes angiokeratoma corporis diffusum (Chapter 57), angiokeratoma circumscriptum naeviforme (Chapter 15) and forms of capillaritis. Treatment, if necessary, with pulsed dye laser improves the disorder [8].

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Hereditary haemorrhagic telangiectasia [1]

SYN. OSLER–RENDU–WEBER DISEASE

Hereditary haemorrhagic telangiectasia (HHT) is an autosomal dominant disorder characterized by epistaxis, cutaneous telangiectasia and visceral arteriovenous malformations (AVMs). HHT is more prevalent than previously estimated [1]. Clinical diagnosis is made on the basis of: (i) epistaxis—spontaneous, recurrent nose bleeds; (ii) telangiectases—multiple, at characteristic sites (lips, oral cavity, fingers, nose); (iii) visceral lesions—such as gastrointestinal telangiectasia (with or without bleeding), pulmonary AVMs, hepatic AVMs, cerebral AVMs, spinal AVMs; and (iv) family history—a first-degree relative with HHT. Three criteria indicate a definite diagnosis of the disorder; two a possible or suspected case [2].

Aetiology and pathogenesis. Mutations in at least two genes are associated with HHT. Endoglin (ENG) on chromosome 9 is the gene responsible for HHT-1, while activin receptor-like kinase 1 (ACVRL-1 or ALK) on chromosome 12 is responsible for HHT-2. HHT-1 families have a higher prevalence of pulmonary AVMs than HHT-2 families who generally have a milder phenotype and later onset [3]. ENG and ALK both encode a homodimeric integral membrane glycoprotein which is the surface receptor for TGF-β. Both genes have been reported to be essential for angiogenesis. Mice lacking the ENG or ALK genes develop age-dependent vascular lesions of the skin, extremities, oral cavity and internal organs in a phenotype very similar to the human condition [4].

Clinical features (Fig. 50.48). Recurrent epistaxis is usually the presenting symptom. It may begin in childhood or even in infancy, but far more commonly begins at puberty or in early adult life. Telangiectasia of the skin is not often seen before puberty, and usually appears in the third or fourth decade, but it may be extensive in early childhood. The individual lesions are punctate or linear. On the rare occasions when they are spider naevus-like,

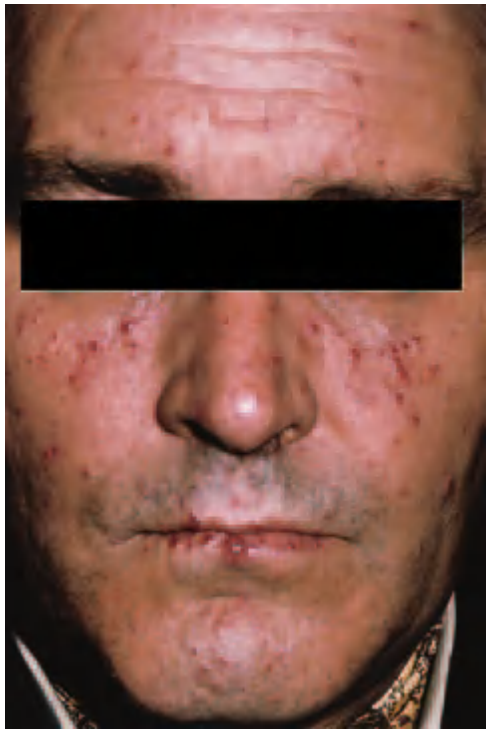

Fig. 50.48 Hereditary haemorrhagic telangiectasia.

Table 50.4 Some causes of telangiectasia.

Secondary telangiectasia
Prolonged vasodilatation (rosacea, varicose veins)
Prolonged exposure to sunlight, tar, etc.
Post-traumatic
Radiodermatitis
Xeroderma pigmentosum
Atrophy, e.g. poikiloderma, topical corticosteroids
Raynaud's disease
Lupus erythematosus
Dermatomyositis
Systemic sclerosis
Morphoea
Mastocytosis (telangiectasia macularis eruptiva perstans)
Acquired immune deficiency syndrome
Primary telangiectasia
Vascular naevi
Angiomas and angiokeratomas
Angioma serpiginosum
Hereditary haemorrhagic telangiectasia
Ataxia–telangiectasia
Generalized essential telangiectasia
Unilateral naevoid telangiectasia syndrome
Hereditary benign telangiectasia
Spider telangiectases
Bloom's syndrome
Morquio's syndrome
Angiotropic lymphoma
Mycosis fungoides
Naevus anaemicus with telangiectatic vessels
Cutis marmorata telangiectatica
Solitary plaque-like telangiectatic glomangioma

they do not pulsate. Nodular lesions may be present but are sparse in comparison with the smaller lesions which may be very numerous. Lesions may occur anywhere, but especially on the upper half of the body—face, lips, ears, conjunctiva, trunk, forearms, hands and fingers. They are often conspicuous in the nail beds. The soles and toes may also be affected. The skin lesions seldom bleed.

The mucous membranes are almost invariably involved. Lesions occur on the nasal septum, in the mouth, nasopharynx, and throughout the gastrointestinal tract [5,6], where they may be demonstrated by endoscopy or arteriography but not by barium studies. They may also be found in many other organs, including the retina. The lesions on the tongue have a characteristic and perhaps diagnostic appearance on capillary microscopy. Within a fungiform papilla there is a single, much-dilated vessel, which may cause the papilla to be expanded [7]. Haemorrhages may occur from any site, and their severity and frequency determine the clinical manifestations and course. Pulmonary arteriovenous fistulae are present in some cases, and occur particularly in some families [8,9]. They reveal their presence by dyspnoea, cyanosis and clubbing of the fingers in adolescence, and can be demonstrated radiologically. Paradoxical embolization to the systemic circulation may occur. This disease is the commonest cause of pulmonary arteriovenous anastomoses. Hepatic arteriovenous anastomoses have been reported, and liver enlargement and cirrhosis also occur [8]. Aneurysms of other vessels, the aortic arch and splenic artery [5], have occurred. Lesions of the eye [10] and CNS are uncommon.

Diagnosis. The history and morphology of the individual lesions are usually sufficient to establish the diagnosis. The lesions do not have the characteristic morphology of the arterial spider. Other causes of telangiectasia (Table 50.4) have to be excluded. Capillary microscopy may be helpful. Phlebectasia of the lips may be familial [11].

Treatment. In mild cases, no treatment is needed. Individual lesions may be destroyed with the cautery, diathermy or laser. In some severe cases, where nasal bleeding is causing severe anaemia, more extensive surgery may be required, replacing the nasal mucous membrane with a split-skin graft, an operation not without hazard. Usually, however, treatment is limited to the control of secondary anaemia. Iron replacement is necessary in all but mild cases. In some cases of severe recurrent epistaxes, oestrogens seem to be helpful, perhaps by inducing keratinization of the mucous membrane rather

than by any direct effect on the blood vessels themselves [12]. The smaller dosage of oestrogens in contraceptive pills may aggravate the condition [13,14]. Antifibrinolytic therapy with ε-aminocaproic acid may be helpful [15]. The disease does not usually shorten life. The mortality rate is less than 10%.

Pulmonary and other systemic arteriovenous malformations may be amenable to resection, ligation or embolization.

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Ataxia–telangiectasia

SYN. LOUIS–BAR SYNDROME

Ataxia–telangiectasia syndrome [1] is a rare recessive disease with pleiotropic involvement of the nervous and lymphoid systems, caused by homozygous mutations in the ataxia telangiectasia mutated (*ATM*) gene. Defective excision repair of DNA damaged by UV light, gamma or X-rays is therefore responsible.

The syndrome manifests with telangiectases, progressive cerebellar ataxia, combined immunodeficiency and a marked susceptibility to cancer. A diminished level of, or absent, IgA is especially characteristic but there may be a reduction in other immunoglobulins. Defects of T and B cell function may also be present.

Affected children, who are usually small, are apparently normal until the second year of life when they are noticed to be clumsy, and the ataxia becomes progressive, so that by the age of 12 years they are unable to walk without assistance. Other signs of cerebellar disease occur, such as nystagmus and slurred speech, and mental deterioration may be observed. Neurological symptoms may not commence before the age of 6 years. Telangiectases may be present as early as the second year, but usually develop between the ages of 3 and 5 years. They first appear on the bulbar conjunctiva, and subsequently involve the ears (Fig. 50.49), eyelids, butterfly area of the cheeks and limbs. Not all sites are affected in every case. Bleeding is very uncommon. There may be some associated atrophy, the skin may be dry, and the hair prematurely grey. Disturbances of pigmentation and eczematous lesions may also occur [2], as may granulomas [3]. Recurrent sinus and pulmonary infections are frequent, and may dominate the clinical picture; they are not infrequently fatal. Ovarian agenesis is not uncommon. Treatment has until recently been directed only at control of secondary infection, but the use of gammaglobulin has given rise to some more hopeful reports.

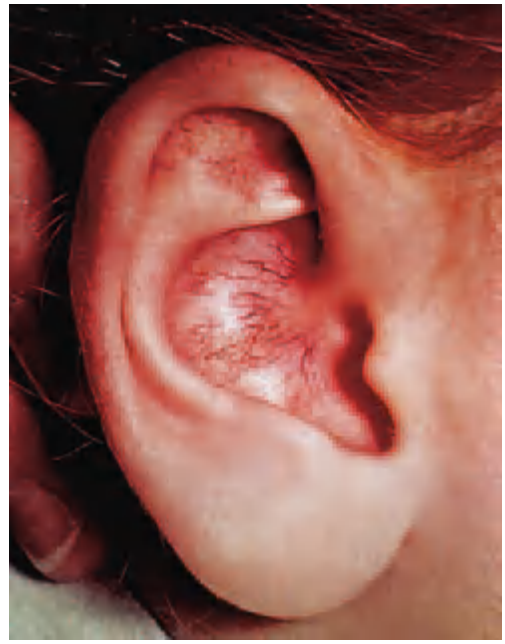

Fig. 50.49 Ataxia–telangiectasia. (Courtesy of Dr P.W.M. Copeman.)

These patients should have as few X-ray investigations as possible.

The laboratory diagnosis currently relies on measurement of serum alphafetoprotein (AFP) and cellular sensitivity to ionizing radiation. Improved diagnostic testing by immunoblotting of nuclear lysates from lymphoid cell lines for ATM has recently been described [4].

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Generalized essential telangiectasia

Generalized essential telangiectasia [1–3] is a condition which is not as rare as the paucity of reported cases suggests. Many cases may be misdiagnosed as atypical HHT. The heading 'essential telangiectasia' probably includes more than one disease.

The condition occurs more frequently in females, and commonly commences in late childhood or early adult life. Extensive sheets of telangiectases, unassociated with other changes in the skin, occur on the limbs or body (Fig. 50.50). The telangiectases are usually linear, but small angiomas may be present. Recurrent haemorrhages from the skin and mucous membranes or into the eye may produce incapacity, but in the majority of cases, the disease is of cosmetic importance only.

Differential diagnosis is from other causes of telangiectasia. HHT is distinguished clinically by the distribution of the lesions, their presence in large and sometimes asymmetrical sheets, and by the usual lack of haemorrhages in generalized essential telangiectasia. Laser treatment may be helpful but lesions tend to relapse [4].

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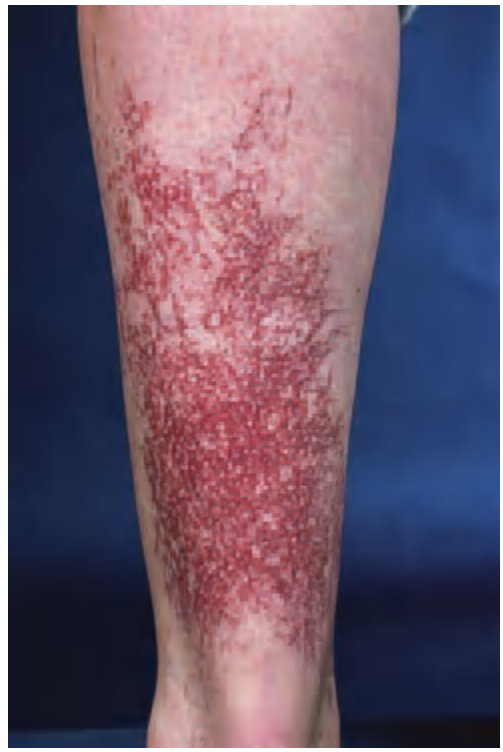
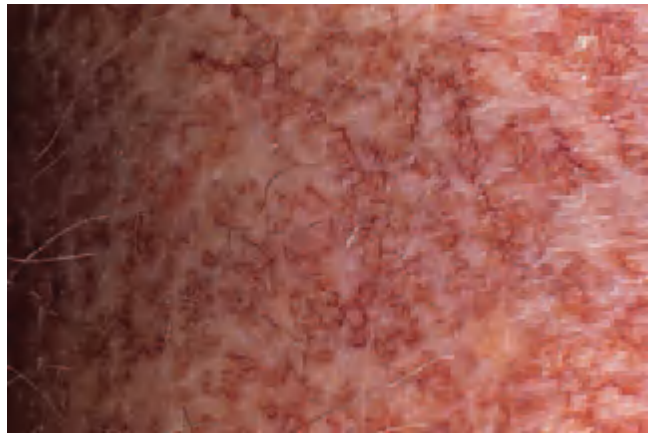
Unilateral naevoid telangiectasia syndrome [1,2]

Unilateral naevoid telangiectasia can be congenital or acquired. There have been reports to suggest an increase in skin oestrogen and progesterone receptors. When acquired, it arises almost exclusively during periods of relatively increased oestrogen levels such as pregnancy or puberty or in association with alcoholic cirrhosis or hepatitis C infection [1]. Polymorphic light eruption has been described confined to an area of acquired naevoid telangiectasia [2].



(a)



(b)

Fig. 50.50 Essential telangiectasia.

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Hereditary benign telangiectasia

This disorder probably has a dominant inheritance [1] and is characterized by the presence of sometimes extensive telangiectases resembling generalized essential telangiectasia, starting in childhood and without other systemic lesions [2,3]. Less commonly, they may be present at birth [4]. They tend to occur more in light-exposed skin. Histology and electron microscopy have been used to distinguish this condition from HHT [5]. Distinction from HHT is dependent on the lack of bleeding, although lesions do appear related to arteriovenous anastomoses as in HHT [6].

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Naevus anaemicus with telangiectatic vessels [1]

Following dermabrasion of the epidermis overlying a naevus anaemicus, enlarged telangiectatic vessels were observed within the previously pale area. The area was transplanted with thin epidermal grafts but 1 year later the naevus looked the same as before grafting. The explanation proposed for a naevus anaemicus and port-wine stain coexisting was vascular twin spotting, but the primary abnormality could be telangiectasia with surrounding skin blanched through a 'steal' effect of blood flow.

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Solitary plaque-like telangiectatic glomangioma [1]

A painful solitary telangiectactic plaque revealed ectatic vascular lumens in the upper dermis surrounded by glomus cells on biopsy.

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Chapter 51

Disorders of Lymphatic Vessels

P.S. Mortimer

Introduction

The lymphatic system comprises the lymph, lymphatic vessels, lymph nodes and other organs containing lymphoid tissue, especially the spleen and bone marrow. Although not a true circulation like the blood vascular system, the lymphatic vessels do provide an important 'limb' to the microcirculation, particularly in the skin, and, with the blood vessels, cater for the constant recirculation of protein and cells. This is done in partnership with the macrophage system. Through its own specialist cell, the lymphocyte, a close relationship exists between peripheral lymphatics, the blood circulation and the spleen and liver. Therefore, while lymph drainage serves a predominantly 'plumbing' role, the lymphatic system does possess important immunological responsibilities. The lymphatic vessels are essential for the continual drainage from the tissues of the body of both plasma proteins and lymph-borne cells. If this drainage ceases death will ensue [1].

While technology has advanced our knowledge of human biology at the cellular and molecular level, our understanding of whole-body physiology lags behind. There is no better example than the importance of lymphatics to disease processes, where the theoretical basis for a causal relationship may be strong but the evidence is often limited, usually because of a lack of reliable and sensitive investigatory methods.

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Lymphangiogenesis

The embryonic origin of the lymphatic system has long been uncertain, but its close development with the venous system is not in doubt. Sabin proposed that early in fetal development, isolated primitive lymph sacs originate by endothelial cell budding from embryonic veins [1,2] and that the skin lymphatics develop by endothelial sprouting from these primary lymph sacs (centrifugal

development). Alternatively, it has been suggested that initial lymph sacs develop from precursor cells, 'lymphangioblasts', in the mesenchyme (centripetal development) [3].

VEGFR-3

In 1995, the first specific growth factor receptor of lymphatic vessels was identified and termed FLT-4 [4]. It is now termed vascular endothelial growth factor receptor-3 (VEGFR-3). The family of vascular endothelial growth factor receptors and their ligands are central to the development of blood and lymph vessels [5]. In embryos, VEGFR-3 is initially expressed in all vasculature, but during development its expression in blood vessels (veins not arteries) becomes restricted to the developing lymphatic vessels. In embryos, therefore, VEGFR-3 is important for cardiovascular development, but in adults it is responsible for the regulation of the lymphatic vessels [6].

Signalling via VEGFR-3 has been shown to be critical for growth, migration and survival of isolated lymphatic endothelial cells in culture [7]. VEGFR-3-positive lymphatic vessels have been observed to sprout from preexisting lymphatics and to grow into the granulation tissue in healing skin wounds [8].

VEGF C/D

Blood vessel development depends upon the vascular endothelial growth factor (VEGF) family of proteins. This family consists of VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E and placenta growth factor (PLGF). A paracrine expression pattern is seen between VEGF-C and VEGFR-3 at sites where the first lymphatic sprouts occur [9]. VEGF-C and VEGF-D are the main ligands for VEGFR-3 and therefore for lymphangiogenesis. Overexpression of VEGF-C in skin keratinocytes leads to dermal lymphatic hyperplasia [10]. VEGF-D is also lymphangiogenic when overexpressed in skin keratinocytes.

Prox-1

Prox-1 is a homeobox-containing transcription factor involved in the growth and elongation of the lymphatic vessel sprouts during development [11].

Angiopoietins and Tie-2

A second family of receptor tyrosine kinases known as Tie-1 and Tie-2 are important for vessel (including lymphatic) stabilization and maintenance during development. The ligands for Tie-2 are angiopoietin-1 and angiopoietin-2 (Ang-2). Ang-2 knock-out mice develop lymphatic abnormalities including chylous ascites and a disorganized and leaky lymphatic vasculature [6].

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Anatomy

In the skin, lymphatic vessels form two horizontally running networks, a narrow-meshed superficial network lying subepidermally and a deeper wide-meshed network. The networks are connected to each other through obliquely running vessels (Fig. 51.1). Although fewer in number than blood vessels, lymphatics are potentially larger at capillary level. Lymphatics are essentially of two types:

1 Smaller, non-contractile, initial lymphatics (these used to be called terminal lymphatics), which commence or 'initiate' the drainage process within the tissues.

2 Larger, contractile, lymphatic collectors or trunks, into which the initial lymphatics drain [1].

Afferent collectors drain to lymph nodes and efferent collectors drain from lymph nodes. Lymphatic capillaries originate as blind-ending endothelial lined tubes in the subpapillary region and are rarely seen within dermal papillae except in certain disease states—for example, psoriasis [2,3]. From the superficial lymphatic plexus in the upper dermis, lymph drains through a series of enlarging precollectors into the contractile collecting trunks close to the dermosubcutaneous junction [1]. The lobules of adipose tissue have lymphatics only in their periphery, and clearance of lymph from the centre of the lobule is slow [4].

Initial lymphatics in the skin are arranged in loosely constructed polygonal meshes (Fig. 51.2) high in the dermis [1,5]. Territories of skin are drained by these meshes into the vertically draining precollectors. A series of

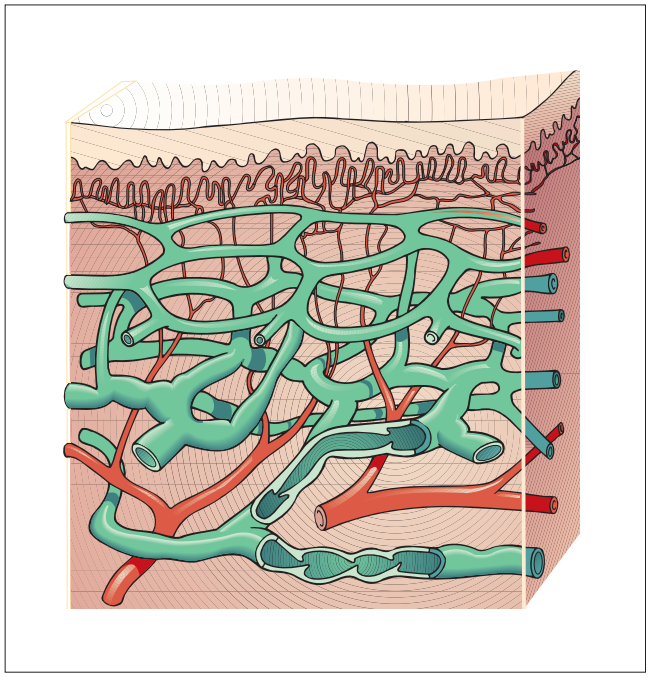

Fig. 51.1 Diagram of superficial and deep initial lymphatic vessels in the skin. Lymph vessels are coloured green, blood vessels are coloured red. (From Kubik and Manestar [1], with permission.)

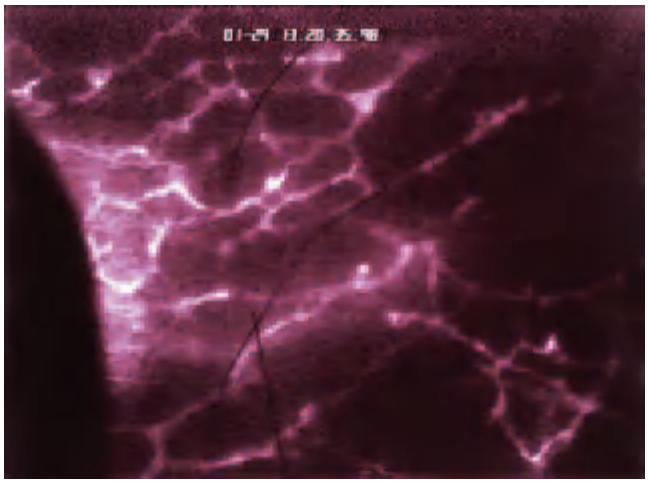

Fig. 51.2 Superficial network of dermal lymphatic vessels as viewed *in vivo* using fluorescence microlymphography.

valves ensure that flow is unidirectional. Such is the capacity of initial lymphatics for dilatation that the valves can become incompetent. Obstruction to deeper lymphatic routes leads to re-routing of lymph and results in 'dermal backflow', as witnessed both on conventional X-ray lymphography and lymphoscintigraphy. In this way, the initial lymphatic network of the skin provides collateralization by which lymph can escape to other (more) normally draining areas [6].

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Structure

The lymphatic capillary is lined by a fine endothelium which is more attenuated than that of blood capillaries (Fig. 51.3). Potentially larger than blood capillaries, lymphatics are frequently not visualized in histological sections, because they are collapsed. A distended lymphatic exhibits characteristically thin attenuated walls with nuclei bulging into the lumen. On electron microscopy, the gaps between overlapping endothelial cells are much larger than in the blood capillary. These 'open junctions' act as flap valves and clearly serve as the entry point for macromolecules [1]. Lymphatics have little in the way of a basement membrane or pericytes [2]. The lymphatic endothelium contains very few pinocytotic vesicles and lacks Weibel–Palade bodies and fenestrae [3]. Attached to the outside of the endothelium is a network of reticulin and elastic fibres which act as anchoring filaments [4]. The elastic fibres form a partial envelope around the dermal lymphatics [5]. In addition to the flap valves in the lymphatic wall are bileaflet intralymphatic valves [6].

Contractile lymphatics are endowed with smooth muscle, are innervated and respond to vasoactive mediators

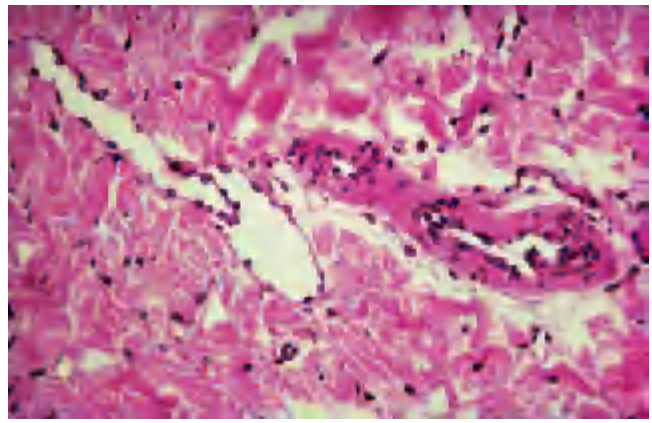

Fig. 51.3 Mid-dermal vessels showing the typical appearance of a mid-dermal blood capillary with plump endothelium compared with adjacent lymphatic vessels with attenuated endothelium and a valve. Such valves are not present in blood vessels high in the dermis.

including nitric oxide [7]. The contractile lymphatics contain a regularly spaced chain of intralymphatic valves that prevent retrograde flow even at high pressures.

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Identification of skin lymphatics—specific lymphatic markers

The recent discovery of specific markers for lymphatic endothelium has contributed greatly to the identification of skin lymphatics in tissue sections. Previously, the only certain way of distinguishing a lymphatic from a blood vessel was by electron microscopy. Flap valves or wide open junctions between overlapping endothelial cells are pathognomonic of skin lymphatic vessels [1]. If large skin biopsies are fixed in an expanded condition by stretching the specimen in different directions, lymphatic vessels become visible for both light and transmission electron microscopy [2]. In normal skin, demonstration of the elastic fibre envelope can help distinguish upper dermal lymphatics from nearby capillaries [3], but elastin readily disappears with photo-ageing and inflammation.

A number of markers are available for labelling endothelial cells, but the majority stain both blood and lymph vessels (e.g. factor VIII-related antigen, CD31 (PECAM-1), ulex europaeus agglutinin 1 and EN4). Because initial lymphatics lack a continuous basement membrane, immunocytochemistry for the extracellular matrix components type IV collagen and laminin has been used to distinguish them from blood capillaries [4]. Pal-E monoclonal antibody is consistently negative in lymphatic vessels but positive in venules and small veins, the vessels most likely to be mistaken for lymphatics [5].

Of the newer molecular markers, VEGFR-3 was the first to be documented to be expressed in lymphatic endothelium, but it can also be found in a subset of blood vessels and in angiogenic vessels in certain pathological conditions. The most robust marker for skin lymphatics is LYVE-1 [6]. This is a receptor for extracellular matrix/lymphatic fluid glycosaminoglycans in lymphatic endothelial cells (Fig. 51.4). Podoplanin is a glomerular podocyte membrane mucoprotein which serves as a specific marker for the isolation of lymphatic endothelial cells

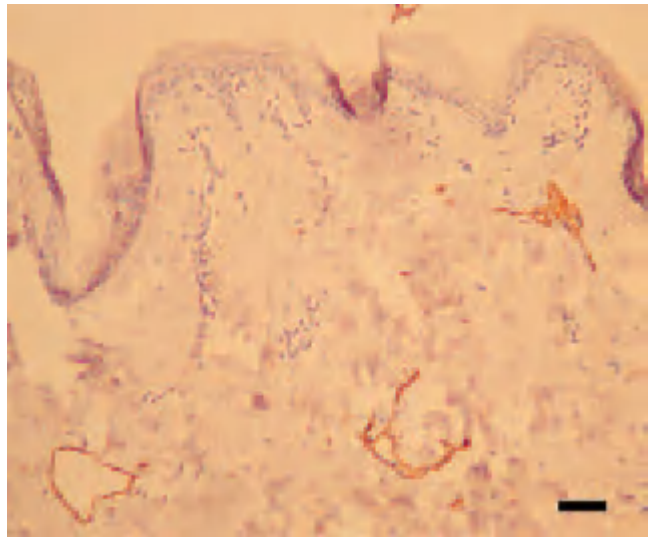

Fig. 51.4 LYVE-1 antibody marker for lymphatic endothelium. (Courtesy of Dr D.G. Jackson.)

[7]. It is present in small lymphatics, but not in the larger contractile lymphatics.

Other markers reported to be positive in lymphatics, but not in blood vessels, include Prox-1 [8] and a β-chemokine receptor, D6 [9], the latter only being positive on a subset of lymphatic vessels and therefore suggesting functional heterogeneity. These markers are summarized in Table 51.1 [10]. It is unlikely that any one marker will be totally specific, particularly in disease states, and the use of several markers is recommended.

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Table 51.1 Markers for lymphatic vessels.

Molecule	Protein class	Biological effect
VEGFR-3	Receptor tyrosine kinase on endothelial cell	Lymphangiogenesis survival of LEC
LYVE-1	Receptor for extracellular matrix glycosaminoglycan	Transport of HA from tissues to lymph nodes
Prox-1	Transcription factor	Developmental lymphangiogenesis
Podoplanin	Integral membrane protein	Unknown
Desmoplakin	Component of intercellular adhering junction in LECs	Adhesion of LECs

HA, hyaluronan; LEC, lymphatic endothelial cell; LYVE-1, lymphatic vessel endothelial HA receptor; VEGFR-3, vascular endothelial growth factor receptor-3.

Purpose of lymphatics

Lymphatics are primarily concerned with draining, from the tissue spaces, materials which cannot directly return to the bloodstream. Colloids, and particularly protein, fall into this category as do many cells—extravasated erythrocytes, macrophages, lymphocytes and, of course, malignant cells. Lymphatics carry material that has penetrated the dermis, including microorganisms, injected vaccines, solvents of skin cosmetics, inorganic material such as silica and stains from tattoos [1]. Under normal circumstances, water is acting predominantly as a vehicle for the colloids, cells and particulate matter which can only be drained via the lymph route. Nevertheless, lymphatics also serve as an 'overflow pipe' in order to drain excess interstitial fluid. It is important to understand this role of the lymphatic acting as a 'safety valve' or buffer against fluid overload, because it incriminates the lymphatic to some degree in every form of oedema.

Bacterial and other microorganisms are channelled through lymphatics as a protective mechanism to prevent noxious agents from directly entering the bloodstream. Presumably this failure to 'police' infection is the reason why cellulitis/erysipelas can be such a recurrent problem with lymphoedema. Similarly, immobilization slows lymph flow—for example, causing venom to remain contained within the lymphatics following a snake bite [2].

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Lymph transport

After filtration from the microvasculature, interstitial fluid enters a series of passive initial lymphatics and is then propelled within the collecting trunks through a series of intervalvular pumping segments (lymph hearts) to the lymph nodes before eventually returning to the venous system at the thoracic duct. Transport of fluid and other materials (prelymph) across the interstitial space towards initial lymphatics is a passive process dependent upon changes in local pressures (convective flow) [1,2]. Deformation or movement of the dermis by surface pressure and underlying muscle contractions and by dermal components, such as arterioles, causes expansion or compression of the initial lymphatics. The process of expansion is likely to result from pulling of the anchoring filaments on the abluminal surface of the lymphatic [3]. These probably act to prevent lymphatic collapse when interstitial pressure is high, as in oedema [4]. Negative fluid pressure inside the initial lymphatics serves to open the interendothelial junctions (flap valves) and to permit inflow of interstitial fluid. After filling and equilibration of pressure the flap valves close. Pressure on the skin surface, e.g. massage, or from below, e.g. muscle contractions, compresses the filled lymphatic. Lymph then moves downstream, i.e. towards bigger lymphatics; the valves within the lymphatic vessels ensure that flow is in one direction. Recoil of the lymphatic occurs when the compression wave (squeezing) of the lymphatic ceases and the cycle repeats itself. Cardiac arrest leads to cessation of lymph flow, but lymph flow can be maintained with active skin motion even after the arrest of the heart.

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Immune functions

The lymphatic vessels form part of the immune system. Lymphocytes and mononuclear phagocytes constantly patrol the skin, leaving via the afferent lymphatic vessels for the lymph nodes. Langerhans' cells of the epidermis, and dermal dendritic cells, screen the skin for invading antigens. They migrate from skin to regional nodes where a primary immune response is initiated [1]. Dendritic cells enter dermal lymphatics by transmigration through

intercellular spaces of adjacent endothelial cells, frequently carrying material such as melanosomes and apoptotic bodies [2]. Receptors on lymphatic endothelial cells facilitate migration of proteins and cells to and within lymphatics. LYVE-1 [3] is related to the CD44 receptor for hyaluronan and is involved in its uptake from the dermis and transport in the lymph. When dendritic cells are activated by a variety of inflammatory stimuli, e.g. bacterial lipopolysaccharide or cytokines such as tumour necrosis factor-α or secondary lymphoid tissue chemokine (SLC/CCL21), the cell surface expression of CC chemokine receptor 7 (CCR-7) on lymphatics is increased [4]. CCL21 is a chemokine that is produced constitutively by lymphatic endothelial cells in the skin [5]. Disruption of the CCR7 gene which prevents expression of CCL21 prevents migration of dendritic cells from tissue to regional nodes.

Bacteria, viruses, fungi and toxins which penetrate the skin are absorbed by lymphatics and not by blood capillaries [6,7]. Virulent haemolytic streptococci, tubercle bacilli and many types of soluble or particulate antigens injected intradermally readily reach the regional lymph node [8].

Without intact lymphatics a primary immune response cannot develop. In the case of allogeneic skin grafts, removal of the lymph drainage channels causes cessation of the cellular reactions in the lymph nodes until lymphatic pathways are re-established [9]. Rejection is delayed in grafted skin sites where all draining lymphatics are severed [10]. Lymphatic vessels draining skin appear to play an important role in immunosurveillance. Studies in lymphoedema following curative breast cancer treatment demonstrated an impaired response to dinitrochlorobenzene testing in the swollen limb but not in the contralateral control limb [11]. Similar results were reported in lymphoedema associated with Kaposi's sarcoma [12].

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Oedema

Oedema is an excess of interstitial fluid. Interstitial fluid volume must increase by over 100% before oedema is clinically detectable. Dermal oedema manifests as 'peau d'orange' due to expansion of the interfollicular dermis, whereas subcutaneous oedema gives rise to pitting.

Any oedema, whatever the cause, is due to capillary filtration overwhelming the lymph drainage for a sufficient period of time [1]. Interstitial fluid is reabsorbed almost entirely by the lymphatics. Contrary to popular belief, venous reabsorption of interstitial fluid cannot be maintained for any length of time except in certain vascular beds, e.g. that of the kidney [1]. The causes of oedema formation are listed in Table 51.2. Most oedemas arise from increased capillary filtration overwhelming lymph drainage. To some extent, therefore, any oedema incriminates the lymphatic through its failure to keep up with demand. Lymphoedema, however, is oedema arising principally from a failure in lymph drainage.

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Lymphoedema

Definition: swelling due to the excess accumulation of lymph in the tissues caused by inadequate lymph drainage. Lymphoedema differs clinically from other forms of chronic oedema by its altered skin texture and the brawny quality of the subcutaneous tissues, which limit pitting. There may be no distinguishing features, particularly in the early stages of swelling. A more precise definition would be 'a swelling of soft tissues which is the result of accumulation of protein-rich interstitial fluid caused by a low output failure of lymph' [1].

Epidemiology

Lymphoedema *per se* is perceived as uncommon, yet lymphatic insufficiency is a major contributing cause in chronic ankle oedema, which is considered common (particularly in the elderly) [2]. Because lymphoedema can be a difficult diagnosis, particularly if mild or in the early stages, it is frequently underdiagnosed. A recent epidemiological survey, which determined the problem

Table 51.2 Causes of oedema.

Increased capillary filtration
Increased capillary pressure
- Increased venous pressure, e.g. right heart failure, DVT, obstructing malignancy, overtransfusion
- Increased blood flow, e.g. inflammation, arteriovenous fistula

Reduced plasma proteins
- Increased loss, e.g. nephrotic syndrome, protein-losing enteropathy
- Reduced synthesis, e.g. cirrhosis, advanced cancer
- Malabsorption, malnutrition

Increased capillary permeability
- Inflammation, e.g. varicose eczema, psoriasis, urticaria and angioedema

Reduced lymph drainage
Primary lymphatic insufficiency
- Familial
  Milroy's disease (onset at or soon after birth)
  Lymphoedema, distichiasis (postpubertal)
  Meige's disease (postpubertal)
- Sporadic

Secondary lymphatic insufficiency
- Surgery, e.g. lymph-node dissection
- Radiotherapy for cancer
- Recurrent cancer
- Infection, e.g. filariasis, cellulitis
- Accidental trauma

Dysfunctional lymphatics
- Dependency syndrome
- Loss of mobility
- High output failure in venous disease

DVT, deep vein thrombosis.

of chronic oedema in the community, ascertained 823 patients in a catchment area of 619 000 in south-west London. This estimated the overall prevalence of chronic oedema as 1.33/1000 population; the prevalence increased with age and was 5.4/1000 in subjects aged over 65 years. In only a quarter did the oedema arise from cancer treatment. Twenty-nine per cent had experienced at least one attack of cellulitis over the previous year. Ten per cent of subjects had lost, or had had to change, employment as a result of their chronic oedema. Chronic oedema that was likely to be lymphatic in origin is common in the community and often goes unrecognized [3].

Primary types of lymphoedema tend to affect females more frequently (70–80% of patients are female). In less than 10% of cases is swelling present at birth; most cases present at or soon after puberty. It is estimated that 80% will present before the age of 35 years (lymphoedema praecox) and 10% after the age of 35 years (lymphoedema tarda) [4]. Data on prevalence of lymphoedema are few, and a figure for overall prevalence of primary lymphoedema is not available. However, a recent study of 1000 young adults showed that 8% of women demonstrated signs of lymphoedema in the lower limb [5], and the cumulative prevalence of swelling following breast cancer treatment in women is 28% [6]. Similar prevalence studies for the lower limb following cancer treatment are lacking, but lymphoedema was noted in 11 of 58 patients undergoing radical vulvectomy with bilateral inguinal lymphadenectomy for vulval carcinoma [7].

Pathophysiology

Lymphatics may fail for a number of reasons. First, there may be an intrinsic abnormality of the lymph-conducting pathways. Such cases are referred to as *primary lymphoedemas*: in practice, this simply means that no identifiable extrinsic cause can be found. *Secondary lymphoedemas* are those due to some factor originating from outside the lymph system, such as surgical removal of lymph nodes, radiotherapy or a severe infection. Physiologically, there are only a limited number of ways lymphatics may fail. They may be reduced in number, obliterated, obstructed or simply fail to function. A lack of sensitive methods for investigation makes it difficult to distinguish between these mechanisms (Table 51.3).

A reduction in lymphatics may be due to total *aplasia*, such as the absence of skin lymphatics in Milroy's disease, or, more commonly, to partial *hypoplasia*. In the commonest form of primary lymphoedema, that presenting at or soon after puberty with distal leg swelling, lymphangiograms usually demonstrate a reduction in the size and number of peripheral leg lymphatic collectors. It is often assumed that the lymphatics have been abnormal since birth but it is always possible that the lymph vessels have undergone an accelerated atrophy or ageing process. The congenitally determined abnormality may not therefore be an underdevelopment of lymphatics from birth, but

Table 51.3 Possible causes of lymph drainage failure.

Mechanism	Causes
Reduced lymph-conducting pathways	Aplasia, hypoplasia of whole vessel
	Acquired obliteration of lymphatic lumen (e.g. lymphangiothrombosis, lymphangitis)
Poorly functioning lymphatics	Pump (contractility) failure
Obstructed lymphatics	'Scarring' from lymphadenectomy, radiotherapy or infection
Grossly incompetent lymphatics with reflux	Megalymphatics, lymph vessel hyperplasia

rather a failure of growth/regeneration following damage or injury. This would explain the latent period before swelling manifests, particularly in those forms presenting later in life (lymphoedema tarda). In truth, we do not know and these possibilities are speculative.

An *obliterative process*, where there is permanent obliteration of the lymphatic lumen and consequently of the vessel itself, probably develops through lymphangiothrombosis or lymphangitis in the same way as for veins. Lymph, like blood, will clot, but not so readily. Unfortunately, there is no clinical investigation for lymph thrombosis.

Pathology. Decreased transport of lymph from the skin leads to an increase in protein-rich interstitial fluid. In circumstances other than where dermal lymphatics are congenitally absent (for example, Milroy's disease) or are destroyed (for example, post-erysipelas), interstitial pressure consequently rises and lymphatics dilate. Temporal changes observed in experimental lymphoedema indicate that the collagen fibres initially become swollen and separated [8]. Mononuclear cells are seen around the lymphatic and blood vessels [9]. Lymphatic walls thicken and fibrose. The muscular elements of the collecting trunks atrophy and new collagen is deposited underneath the intima. Macrophages, fibroblasts and lymphocytes accumulate perivascularly. Overgrowth of the interstitial connective tissue gradually transforms the soft stage of lymphoedema into the hard late-stage form [10]. The simple excess of protein seems to be the cause of the fibrosis [11,12]. The number of blood vessels greatly increases.

In human skin, the epidermis overlying an area of lymphoedema becomes acanthotic, with reduplication of the epidermo-dermal basement membrane. In the dermis, there is an increase in collagen, but the elastic fibres, including anchoring filaments, disappear. Ultrastructurally, the basal lamina of the dermal lymphatics thickens, but remains discontinuous, connective tissue microfilaments are increased, myofibroblasts appear and the connective tissue ground substance becomes hyalinized [13]. Inflammatory cells are conspicuous in the dermis. In the infiltrate, mast cells, macrophages, plasma cells and lymphocytes can be observed. Extravasated erythrocytes are often seen and large amounts of fibrin become deposited. Well-characterized morphological changes develop in the blood vessels (lymphostatic vasculopathy). In the upper dermis, numerous newly formed vessels can be seen. Angiogenesis results in a highly vascularized dermis.

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Aetiology and classification

Lymphoedema may be primary (Table 51.4), secondary (Table 51.5), dysfunctional, or cancer-related.

Primary lymphoedema

Lymphoedema arising from an intrinsic abnormality of the lymph-conducting pathways is referred to as primary lymphoedema [1]. A simple classification by age of onset without reference to aetiology or other clinical features is into the following subdivisions: congenital (present at or very soon after birth), praecox (presenting before age 35 years) and tarda (presenting after age 35 years). The development of lymphangiography in the 1950s resulted in a radiological classification: aplasia (no formed lymph pathways found), hypoplasia (lymphatics smaller or fewer than normal) and hyperplasia (lymphatics larger and more numerous). Aplasia, hypoplasia and hyperplasia refer to abnormalities in the main (leg) conducting lymph vessels as opacified on lymphangiography, and not to initial lymphatics, which are not imaged with this method. Further investigation revealed types of lymphoedema where few, if any, lymph conducting vessels could be identified in the foot, but vessels were found to be normal further up the limb [2].

The last 5 years have seen an increasing understanding of the genetic abnormalities causing lymphoedema.

Inherited forms of lymphoedema where the gene is known

1 *Milroy's disease* (primary congenital lymphoedema, hereditary lymphoedema type 1; MIM 153100). In 1892, Milroy published a large pedigree with lymphoedema beginning at or soon after birth [3]. Although the same

Table 51.4 Causes of primary lymphoedema.

Congenital onset		Postpubertal onset	
Familial	Sporadic	Familial	Sporadic
• Milroy's disease: below knee and bilateral	• Turner's syndrome, Noonan's syndrome: can be transient; other phenotype abnormalities • Neurofibromatosis, Proteus syndrome • Pure or mixed vascular lymphatic malformations, lymphangiomatosis, Klippel–Trenaunay syndrome, Maffucci's syndrome: usually unilateral • Amniotic bands: associated with autoamputation	• Distichiasis–lymphoedema, Meige's disease: below knee and bilateral	• Distal hypoplasia, lymph reflux: bilateral foot and lower leg swelling • Ilio-inguinal node sclerosis: whole limb and unilateral • Yellow nail syndrome: bilateral, widespread oedema

condition was described earlier by Nonne [4], it was Milroy who gave the most complete description, and the eponym 'Milroy's disease' is universally accepted. Milroy's disease is often considered synonymous with primary lymphoedema, but the term should be restricted to cases of familial lymphoedema where the onset is at birth. Linkage studies in families with Milroy's disease showed mapping to chromosome 5q35.3 [5,6] and were subsequently localized to the VEGFR-3 locus. Therefore, a failure of lymphangiogenesis due to inactivation of VEGFR-3 appears to be responsible for the autosomal dominant inheritance of Milroy's disease [7]. Genotype–phenotype correlation demonstrates swelling which is confined to below the knee, and which is often brawny in the extreme with little pitting. Hydrocoele can be an additional feature but, much as Milroy described, there appear to be no other manifestations.

2 *Lymphoedema–distichiasis syndrome* (LDS; MIM 153400). Distichiasis is a congenital anomaly in which accessory eyelashes occur along the posterior border of the lid margins in the position of the Meibomian glands. It causes symptoms of corneal irritation, conjunctivitis and photophobia and occurs from birth. Lymphoedema, however, does not develop before puberty and may be delayed in onset until the fifth decade. Other features of this syndrome include ptosis, congenital heart defects and varicose veins [8]. The lymphatic abnormality appears to be lymph reflux with an increased number of lower limb lymph vessels [9].

LDS shows an autosomal-dominant pattern of inheritance with variable expression and has been mapped to 16q24.3 [10]. Subsequently, mutations in FOXC2 (MFH-1), a forkhead family transcription factor, have been found to be responsible for this condition [11].

3 *Incontentia pigmenti* (MIM 308300). Incontentia pigmenti (IP) is not usually associated with lymphoedema in surviving females. The second liveborn male to be reported recently led to the identification of a NEMO (MF-kappa β essential modulator) stop codon mutation in the affected child and in his mother, who had classical IP [12]. He had features of hypohidrotic ectodermal dysplasia with immune deficiency, recurrent infections and lower limb lymphoedema which developed at a few weeks of age. A lymphoscintigram showed severe lymphatic obstruction. MRI suggested a lymphangiomatous malformation. Cutaneous capillary angiomas and possible mixed vascular/lymphatic malformations coexisted in the gut [13].

Other genetic forms of lymphoedema

1 *Meige's disease* (Kinmonth's lymphoedema praecox, hereditary lymphoedema type II; MIM #153200). In 1898, Meige described the pedigree of a family with a distinct history of lymphoedema appearing at puberty [14]. The eponym Meige's disease has therefore come to be associated with this, the commonest variety of primary lymphoedema, which predominantly affects adolescent females. Swelling is usually mild, rarely extends above the knee and is generally bilateral. Lymphography demonstrates a reduced number of distal lymphatics (hypoplasia) with proximal collectors remaining patent. The term Meige's disease should be reserved for familial lymphoedema developing at or soon after puberty in which there are no associated abnormalities, e.g. distichiasis.

2 *Turner's syndrome*. This well-known abnormality is due to the absence of one X chromosome. Early spontaneous abortion occurs in over 95% of fetuses. Severely affected fetuses who survive to the second trimester can be detected on ultrasonography, which may reveal cystic hygroma, chylothorax, ascites and hydrops fetalis. The diagnosis may be suggested in the newborn by redundant neck skin and peripheral oedema. Surviving children have webbed necks and may exhibit peripheral oedema which often diminishes with age. Conversely oedema may present later in life. Chromosomal testing should always be

Table 51.5 Causes of secondary lymphoedema.

Cancer
Treatment
Surgery
Radiotherapy
Tumour
Kaposi's sarcoma
Infiltrative cancer
Lymphoma
Relapsed tumour
Infection
Filariasis
Lymphangitis, lymphadenitis
Cellulitis
Tuberculosis
Lymphogranuloma inguinale
Lice
Inflammation
Lymphatic occlusion
Podoconiosis
Pretibial myxoedema
Dermatitis, e.g. hand eczema
Rheumatoid arthritis
Psoriasis
Rosacea/acne
Granulomatous disease
Orofacial granulomatosis
Crohn's disease
Sarcoidosis
Vascular
Venous disease
Post-thrombotic syndrome
Venous leg ulcers
Trauma
Surgery
Lymphadenectomy
Vein harvesting
Femoropopliteal bypass
Self-harm
Tourniquet application
Intravenous drug abuse
Accident
Degloving injury
Burns

undertaken in neonates or young children with primary lymphoedema.

3 *Noonan's syndrome* (MIM #163950). Noonan's syndrome is a multiple congenital anomaly syndrome for which a gene has recently been discovered [15]. Lymphoedema is usually present at birth but the age of onset may vary from prenatal period to adulthood. Phenotypic characteristics include short stature, ptosis, low-set ears and posterior hairline, neck webbing and congenital cardiac anomalies (typically pulmonary stenosis).

4 *Hennekam lymphangiectasia–lymphoedema syndrome* (MIM *235510). A syndrome of intestinal lymphangiectasia with severe lymphoedema of the limbs, genitalia and face, with mental retardation [16]. The intestinal lymphangiectasia causes hypoproteinaemia, hypogammaglobulinaemia and lymphopenia. Facial anomalies are characteristic and look somewhat oriental, with flat face, flat nasal bridge, epicanthic folds, hypertelorism, tooth abnormalities and small ears. Onset of lymphoedema is between birth and 12 years, with probable autosomal-recessive inheritance.

5 *Cholestasis–lymphoedema syndrome (Aagenaes syndrome)* (MIM *214900). Jaundice becomes evident soon after birth and recurs throughout life. Oedema of the leg, due to hypoplasia of the lymph vessels, begins at school age and progresses [17].

6 *Proteus syndrome* (MIM 176920). This very rare syndrome causes many varied (protean) manifestations. Characteristic features are asymmetrical overgrowth of almost any part of the body, macrodactyly, and rugose or cerebriform overgrowth of the palmar and plantar soft tissue. Verrucous epidermal naevi, angiomas and lymphangiomatous swelling also occur. Germ-line mutations in P10 have been proposed [18].

7 *Microcephaly lymphoedema–chorioretinal dysplasia* (MIM *152950). An autosomal-dominant syndrome [19] in which microcephaly and lymphoedema are linked to chorioretinopathy.

8 *Pes cavus and lymphoedema* Lymphangiography revealed hypoplasia of leg lymphatics [20].

9 *Yellow nail syndrome* (MIM #153300) (YNS). The evidence that YNS is inherited is unsubstantiated, only one report describing YNS with familial primary hypoplasia of leg lymphatics [21].

Congenital non-hereditary forms of lymphoedema

A number of sporadic forms of lymphoedema occur, usually presenting at birth or during childhood. The defect in such cases is likely to be due to a somatic rather than a germ-line mutation. The most common type is Klippel–Trenaunay syndrome (MIM 149000), in which lymphoedema may be the presenting abnormality. Subsequently, more characteristic features such as limb overgrowth, cutaneous angiomas and venous disease may develop. Another poorly understood form of congenital lymphoedema is that associated with amniotic bands. These bands, which allegedly wrap around digits or limbs, cause circumferential fibrosis and scarring. This can lead to amputation of digits or lymphoedema distal to the band [22].

Maffucci's syndrome (dyschondroplasia with haemangioma, MIM #166000) usually manifests with venous cavernous malformations in infancy, but cavernous lymphangiomas are also often seen, and may be the sole manifestation, giving rise to limb swelling. Hard nodules arise from the bones, especially of the fingers and toes; these are pathologically enchondromas and are radiologically translucent. The malignant potential of the syndrome is high [23].

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Clinical patterns of primary lymphoedema

1 Distal hypoplasia. The most common presentation, contributing about 80% of all cases of primary lymphoedema, is that of mild oedema of both feet and ankles. Patients are usually female with onset at puberty. The swelling is often asymmetrical and deteriorates slowly. Extension above the knee is uncommon and mild (Fig. 51.5). The cause is a paucity of distal lymph vessels.

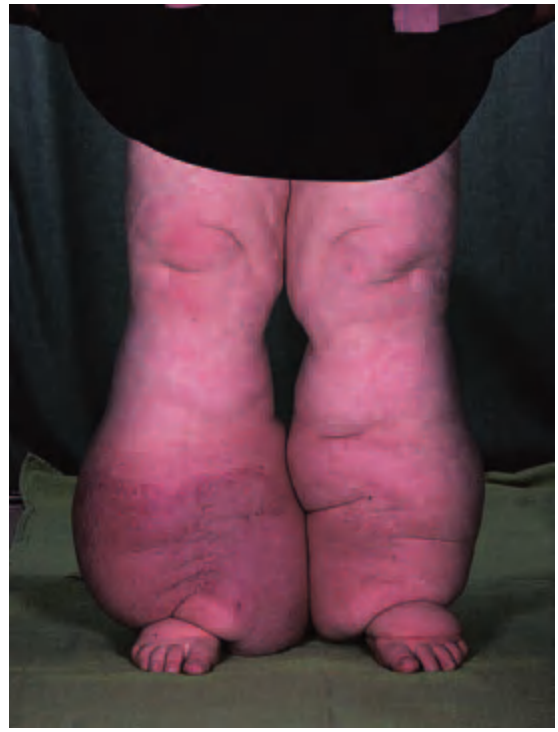

Fig. 51.5 The commonest form of primary lymphoedema: distal hypoplasia of peripheral lymphatic vessels presenting with asymmetrical but usually bilateral swelling of feet and lower legs.

2 Proximal obstruction. This variety is unilateral in 85% of cases. It usually involves the whole limb and develops rapidly. There is no family history. It is of paramount importance to exclude pelvic causes of venous or lymphatic obstruction—for example, tumour or thrombosis. The cause in primary lymphoedema is fibrosis within ilioinguinal lymph nodes or obliteration of proximal lymph vessels [1].

3 Bilateral whole-limb swelling. Reflux of lymph due to gravitational forces and gross incompetence of valves leads to huge dilatation of lymphatic collectors (megalymphatics) in a manner similar to venous reflux and varicose veins. Chylous reflux may coexist.

Progressive distal failure of lymphatic collectors, the so-called 'die-back' phenomenon, occurs with time as a result of proximal obstruction or reflux [2].

Secondary lymphoedema

Secondary lymphoedema refers to those forms of lymphoedema resulting from acquired obstruction or obliteration of lymph-conducting pathways due to some identifiable pathological process arising extrinsic to the lymphatic system. These processes include infection, inflammation, trauma (including surgery and radiation) and malignant disease. No form of lymphoedema is mutually exclusive, and frequently a number of factors

combine to produce swelling. For example, lymphoedema may become clinically obvious only when the lymphatic load is increased because of increased blood flow.

Lymphoedema associated with infection. Infection may cause progressive damage to lymph drainage routes by intraluminal obliteration of lymphatic vessels through processes such as lymphangitis and lymphangiothrombosis.

In recurrent cellulitis or erysipelas, the damage to lymphatics may ultimately lead to formation of lymphoedema, which itself predisposes to further episodes of infection, so exacerbating the lymphoedema [3].

Lymphatic filariasis is concentrated in the tropics and subtropics and is the most common cause of lymphoedema worldwide, with an estimated 90 million people affected [4]. Infection is transmitted by mosquitoes, which introduce microfilariae into the skin. These larvae migrate to the lymphatics, where they mature into adult worms. Progressive and permanent damage to the infested lymphatics causes lymphoedema. It has been established in animal studies that, within days of infection, vigorous movement by adult worms directly impacts on the endothelial lining of the lymphatic trunks and indirectly distorts the local lymph-node architecture. Dilated lymphatics with thickened walls and valves, thrombus formation and perilymphangitis result [5].

Lymphogranuloma inguinale and tuberculous node infection can cause lower limb lymphoedema [6]. Lymphoedema of the ear lobe has been described following head lice infestation [7].

Lymphoedema associated with inflammation. Circumstances exist in which chronic inflammation without evidence of infection is associated with the development of lymphoedema. It is assumed that the inflammation progressively damages lymph drainage routes.

Facial lymphoedema may result from rosacea or even acne vulgaris. Skin or subcutaneous initial lymphatics fail rather than main regional collecting trunks. The forehead, cheeks or periocular regions are usually affected and swelling is often asymmetrical.

Upper limb swelling may occur following chronic hand dermatitis, with or without documented episodes of lymphangitis [8]. Like other forms of lymphoedema, once established it tends to be permanent irrespective of remission of the skin disease.

Podoconiosis (non-filarial elephantiasis) is a form of lymphoedema caused by particles of silica dust, present in certain soils, which penetrate the skin of the foot during barefoot walking. The microparticles are taken up by the lymphatics, causing damage. Soils rich in these substances determine the geographical distribution of the condition [9].

Studies with quantitative lymphoscintigraphy and fluorescence microlymphography have confirmed functional and structural changes to lymph drainage in pretibial myxoedema. It is likely that mucin deposition in the dermis impairs initial lymphatic function, resulting in the clinical appearance which resembles lymphoedema [10].

A small number of patients with rheumatoid arthritis develop lymphoedema, predominantly of the upper limbs. A study in rheumatoid arthritis found impaired lymph drainage only in patients with lymphoedema [11]. This suggested that inflammatory arthritis alone does not directly impair lymphatic drainage. Similar findings have been described in psoriatic arthritis [12].

Granulomatous diseases such as Crohn's disease, sarcoidosis and orofacial granulomatosis cause inflammatory changes in local skin and subcutaneous lymphatics, leading to lymphoedematous swelling.

Panniculitis that is extensive enough to cause severe fibrosis may produce lymphoedema. This has been described following idiopathic retroperitoneal fibrosis [13].

Lymphoedema secondary to trauma. Trauma to lymphatics, either from elective surgery or by accident, usually needs to be extensive to induce lymphoedema. Indeed, the experimental production of lymphoedema is extremely difficult to achieve owing to the excellent regenerative powers of lymphatics [14]. It is probably the failure of lymphatics to regenerate and re-anastomose satisfactorily through scarred or irradiated tissue which is responsible for lymphoedema following cancer treatment. Surgical excision of axillary or ilioinguinal lymph nodes will not uncommonly produce limb lymphoedema. The puzzles are why such intervention in animal models rarely produces chronic swelling and why there can be such a delay—up to 20 years—before lymphoedema manifests [15]. Radiotherapy to lymph nodes can be as much a risk factor towards lymphoedema as surgery [16]. The incidence of lymphoedema following varicose vein surgery is estimated to be 0.5% [17].

Accidental trauma, such as a degloving injury to a limb, will produce lymphoedema distal to the injury if widespread circumferential scarring occurs.

Self-inflicted injury, such as the repeated application of a tourniquet, will eventually cause permanent lymphatic damage and chronic swelling (Secrétan's syndrome) [18]. The abrupt termination of the swelling often coincides with a depression due to subcutaneous atrophy caused by a tight constricting band. Skin pigmentation may also coexist at the site.

Intravenous drug abuse may cause lymphoedema due to a combination of infection and associated venous damage.

Lymphoedema and venous disease. Oedema is a common complication of venous insufficiency. It is assumed that venous oedema is the sole consequence of increased

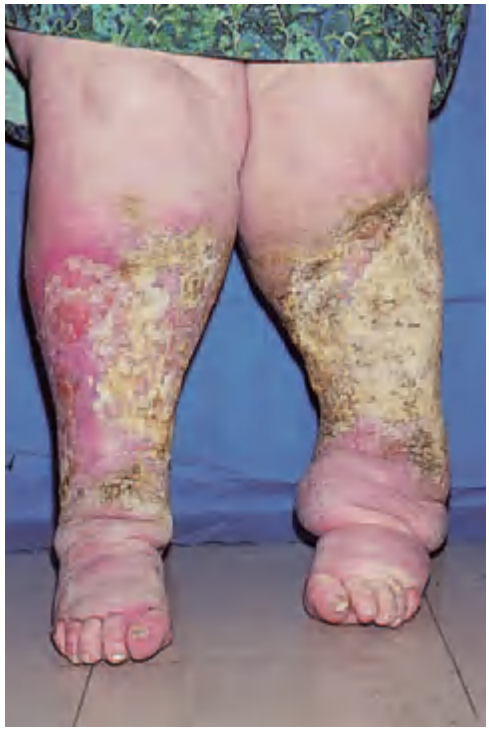

Fig. 51.6 Lymphoedema associated with chronic venous disease.

capillary filtration from venous hypertension. As lymph drainage is the main buffer against oedema, it is in fact the failure of local lymphatics to compensate for the increased lymph load from filtration that leads to oedema. Thrombosis of the major veins and deep vein incompetence does not generally affect the main collecting lymphatics but the small initial and precollecting lymphatics of the skin and subcutaneous tissues of the lower leg are damaged by prolonged venous hypertension. Lymphoedema develops with chronic lipodermatosclerosis, with or without venous ulceration. Lymphoscintigraphy has shown impaired limb lymph drainage [19] while fluorescence microlymphography has revealed damaged skin lymphatics [20]. Lymphoedema associated with venous disease can give rise to the most gross swelling and skin changes owing to the combined effect of impaired lymph drainage in the face of increased lymph load (capillary filtration) (Fig. 51.6).

Malignancy-related lymphoedema. Lymph flow is maintained remarkably well through malignant nodes, therefore cancer does not usually present with swelling. The few exceptions to this general rule are lymphophilic tumours, such as malignant eccrine poroma or Kaposi's sarcoma, as well as advanced cancers where other factors such as venous obstruction and hypoproteinaemia will contribute to oedema formation. Recurrent cancer, however, should always be considered as a cause of limb swelling, particularly if associated with pain. Full staging investigations should always be undertaken in such circumstances. Therefore, in general, malignancy-related lymphoedema usually results from cancer therapy, i.e. surgery, radiotherapy or a combination of the two, or from recurrent tumour directly infiltrating collateral drainage routes.

Kaposi's sarcoma may present with lymphoedema, sometimes years before tumour is evident. The association with lymphoedema [21] supports the view that Kaposi's sarcoma arises from lymphatic endothelium [22].

Lymphoedema arising from dysfunctional lymphatics. Lymph drainage, unlike blood flow, requires intermittent changes in local tissue pressure generated by movement and exercise in order to produce initial lymphatic transport. Consequently, immobility tends to encourage swelling, particularly if gravitational forces (dependency syndrome) encourage ongoing fluid filtration. A common scenario is 'armchair legs', a term coined by Sneddon and Church [23], where patients sit in a chair day and night with their legs dependent. No premorbid abnormalities of lymphatics exist, but the immobility results in minimal lymph drainage and a functional lymphoedema due to a lack of movement or exercise to stimulate normal lymph drainage. Dependency of the limb compounds the problem by increasing capillary filtration. Armchair legs is otherwise known as elephantiasis verrucosis nostras because of the severe lymphoedema skin changes that ensue. The syndrome is not confined to the legs, but can affect any chronically dependent and immobile part, as demonstrated in the pendulous abdomen [24]. With time, pathological changes within the failing lymphatics occur and an irreversible lymphoedema develops.

Clinical features and diagnosis

Lymphoedema most commonly affects the extremities. This predilection for the limbs is due, at least in part, to the limited collateral drainage available at the root of a limb. Careful examination often reveals extension of the swelling to the associated quadrant of the trunk because the lymph drainage routes are shared with the limb.

The major clinical changes of lymphoedema take place in the skin and subcutaneous tissues; such changes are of value in diagnosis. Lymphoedema differs from all other oedemas (in which increased capillary filtration is the major factor) in that cells, proteins, lipids and debris accumulate in addition to water. This results in a 'solid' as well as a 'fluid' component to the swelling, so giving rise to the brawny nature of the oedema which does not readily pit [25]. The lack of pitting is an unreliable sign in lymphoedema, however, because easy displacement of tissue fluid on pressure can often be demonstrated particularly in the early stages.

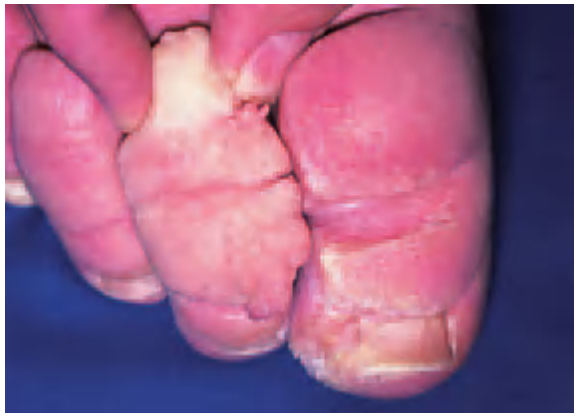

Fig. 51.7 The Kaposi–Stemmer sign: a failure to pinch or pick up a fold of skin at the base of the second toe indicates lymphoedema.

A reticulate pattern on a background of lymphoedema has been associated with thermal injury on the lower legs [26].

Lymphoedema does not usually respond to elevation or diuretics, except in the early stages or when it is compounded by increased capillary filtration. Chronic oedema that does not reduce significantly after overnight elevation is likely to be lymphatic in origin. The symptoms accompanying uncomplicated lymphoedema are few. Swelling frequently develops rapidly, for example, overnight. In the distal hypoplastic type one ankle may swell. Pain may feature initially, prompting diagnoses including deep vein thrombosis or soft-tissue injury. Oedema is often intermittent before becoming permanent, and is often painless although discomfort, aching and tightness are commonly reported symptoms. Eventually both legs swell. In proximal obstructive lymphoedema, swelling usually develops in the thigh and progresses distally.

Disfigurement from lymphoedema can lead to significant psychological morbidity in terms of depression and adjustment to psycho-social issues in areas such as the workplace, home and personal relationships [27]. Pain, in particular chronic aching, occurs commonly with lymphoedema and may require regular analgesia [28]. Although swelling occurs most in the subcutaneous layer, the skin exhibits most changes. It becomes thicker, as demonstrated by the Kaposi–Stemmer sign (a failure to pick or pinch a fold of skin at the base of the second toe) (Fig. 51.7) [29]. Skin creases become enhanced and hyperkeratosis develops. Dilatation of upper dermal lymphatics with consequent organization and fibrosis gives rise to papillomatosis. As dermal lymph stasis progresses these skin changes become more marked and are referred to as elephantiasis. Occasionally the tissue fibrosis and thickening may become so marked in the later stages of lymphoedema that pitting is absent.

Complications

Complications of lymphoedema are mainly due to swelling and infection.

Swelling. Limb swelling leads to discomfort, limb heaviness, reduced mobility and, on occasions, impaired function. The size and weight of affected limbs can result in secondary musculoskeletal complications such as back pain and joint problems. Thickening of the skin causes pseudoscleroderma and consequently impairs small-joint mobility. The difficulty in finding clothes or shoes to fit creates social problems. Poor footwear will further compound the swelling by discouraging a normal gait or enough exercise.

Leakage of lymph through the skin (lymphorrhoea) may occur from engorged dermal lymphatics (lymphangiectasia).

Infection. Episodes of secondary infection are a characteristic feature of lymphoedema. It is probable that patients with lymphoedema from any cause are liable to these attacks and this presumably reflects a failure of immune surveillance. Recurrent cellulitis or erysipelas is a particular problem. Constitutional symptoms such as fever, rigors, headache or vomiting can be profound and sudden in onset. Within 24 h, redness and pain appear within the lymphoedematous area. Recurrent episodes may be frequent and further impair lymph drainage so exacerbating the lymphoedema. Thus, a vicious cycle is established. Haemolytic streptococci of group A, B or G have been demonstrated [30] although the bacterial aetiology has been brought into question [31]. Indeed, it is not unusual for patients to comment that attacks of cellulitis can be induced by strenuous exercise or long car journeys. This suggests a mechanism not dissimilar to herpes simplex where the microorganism is always present but becomes reactivated.

Fungal infections, particularly tinea pedis, are difficult to avoid because of web-space skin maceration from swollen toes. Local immune deficiency may also be a contributing factor as illustrated by a case of cryptococcosis complicating congenital lymphoedema [32].

Malignancy. A rare but important complication of chronic lymphoedema is the development of cutaneous malignancy. Although the most well-known association is lymphangiosarcoma [33], other tumours have been recorded and include basal cell carcinoma [34], squamous cell carcinoma, lymphoma [35–38], melanoma [39,40], malignant fibrous histiocytoma [41] and Kaposi's sarcoma [42]. The Stewart–Treves syndrome describes lymphangiosarcoma developing from well-established postmastectomy oedema. However, lymphangiosarcoma is now described as occurring with lymphoedema of any cause. The

favoured theory for these associations is altered immune surveillance in the lymphoedematous region [43].

Miscellaneous conditions. A range of other cutaneous conditions have been reported as occurring preferentially at sites of lymphoedematous involvement. These include xanthomatous deposits [44], atypical pemphigoid [45], toxic epidermal necrolysis [46], atypical neutrophilic dermatosis [47] and severe necrotizing fasciitis [48].

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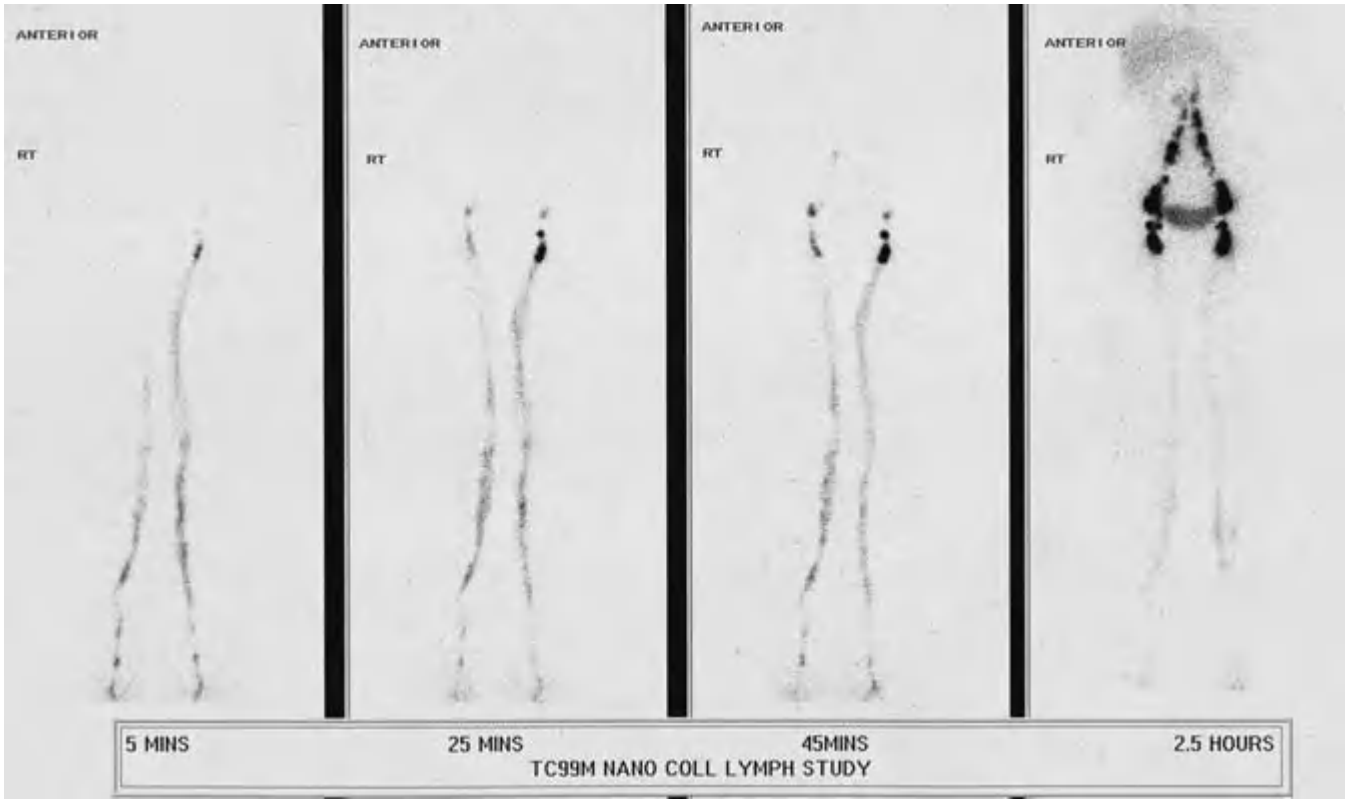
Investigations

Swollen limb

There are limited methods available which permit reliable investigation of lymphatics. Lymphoscintigraphy (isotope lymphography) involves the interstitial (dermis or subcutis) injection of a radiolabelled protein or colloid. Radioactivity, measured using a wide field-of-view γ-camera, is determined over the injection site depot and at regions of interest over vessels or nodes. Measurement of transit times and time activity curves permit quantitative analysis of lymph drainage [1]. Measurement of tracer uptake within axillary or inguinofemoral lymph nodes at a specified time following a standardized exercise routine will discriminate lymphoedema from oedema of non-lymphatic origin [2] (Fig. 51.8).

(a)



(b)

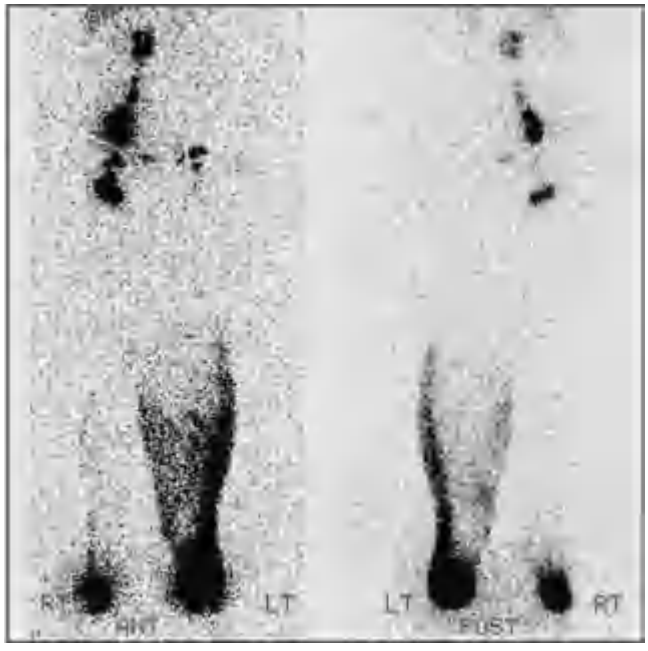


Fig. 51.8 (a) Normal lymphoscintigraphy. Images show patent lymph routes draining tracer from feet to ilio-inguinal nodes. (Courtesy of Professor A.M. Peters.) (b) Obstruction of lymph drainage at the groin leads to re-routing of tracer through skin collaterals (dermal backflow).

Computed tomography (CT) of lymphoedematous limbs has demonstrated a characteristic 'honeycomb' pattern in the subcutaneous compartment which other oedemas do not show [3]. CT not only provides information through cross-sectional area of volume change to a limb, but will also identify the compartment in which that change takes place. Whereas in post-thrombotic syndrome the muscle compartment deep to the fascia is enlarged, in lymphoedema it is unchanged or may even show some reduction in size. Thickening of the skin is also a characteristic feature of lymphoedema, although not specific. Magnetic resonance imaging (MRI) is poten-

tially better than CT for distinguishing types of oedema [4].

X-ray contrast lymphography remains the gold standard for demonstrating lymphatic collecting trunks and nodes [5]. The technique is invasive and difficult to perform in the presence of oedema. It involves first of all the interstitial subcutaneous injection of a vital dye—for example, patent blue—to visualize the lymphatic for cannulation. The oily contrast medium Lipiodol is then administered directly into the peripheral lymphatic identified, usually on the dorsum of the foot. The failure to opacify subcutaneous collectors with the vital dye and its persistence in the tissues for days afterwards are sufficient evidence for a diagnosis of lymphoedema. If there is lymphatic obstruction, the dye will often flow retrogradely into the dermal network—so-called 'dermal backflow'. Lymphography has been used less often to confirm lymphoedema since the advent of lymphoscintigraphy.

Initial lymphatics in the skin

In vivo visualization of lymphatic vessels (lymphangiography) was first achieved using vital dyes—for example, patent blue—to delineate intradermal and subcutaneous lymphatics. Some classic studies were undertaken in this way [6]. Fluorescence microlymphangiography enables the superficial lymphatic network of the skin to be seen under the vital microscope by means of fluorescing molecules (FITC-Dextran, Sigma) which, when injected subepidermally, are taken up by the initial lymphatics. Information regarding the morphology of initial lymphatics and the extent of tracer propagation within the dermal lymphatic network can be recorded on video for analysis [7].

Indirect lymphography involves the intracutaneous injection of a water-soluble contrast medium. Using an infusion pump, the contrast medium is administered over 10 min to create a depot of approximately 3 mL. Intradermal and subcutaneous lymphatics can be opacified by X-ray using the mammography film method, sometimes as far as the first lymph node [8,9]. The advantages over conventional lymphography are the convenience of the interstitial injection without recourse to direct access into the lymphatics, and the ease of application to multiple sites.

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Differential diagnosis of the swollen limb (Table 51.6)

Swelling of a limb may be caused by oedema, in which case pitting should be evident to some degree, or it may be caused by an increase in volume of other tissue elements, e.g. bone, muscle or fat. MRI scanning is useful in circumstances where the nature of the swelling is uncertain. One must remember also that a patient may perceive one leg to be swollen when in fact the other leg has become smaller, e.g. through atrophy of muscle or fat.

Obvious lymphoedema with characteristic skin changes is not usually a difficult diagnosis but such cases are relatively uncommon. Milder cases frequently go unrecognized. Chronic non-inflammatory, and in particular asymmetrical, limb oedema should always suggest lymphoedema. In such cases lymphoscintigraphy is the investigation of choice.

Systemic causes of oedema including cardiac disease, renal disease or hypoproteinaemia should always be considered, particularly if bilateral leg swelling is present. Calcium channel blocking agents cause peripheral oedema in 50% of cases.

A condition frequently misdiagnosed as lymphoedema is lipoedema (lipidosis, lipodystrophy) in which a 'fatty' non-pitting swelling is confined to the legs, thighs and hips [1]. Lipoedema is peculiar to females and is usually dismissed as a variant of normality in women with chunky legs and a 'bottom-heavy' weight distribution. Features of importance in recognition include onset at or after puberty, bilateral and symmetrical involvement of the legs, sparing of the feet resulting in an 'inverse shouldering' effect at the malleoli (Fig. 51.9), tenderness, easy bruising, absence of pitting and lack of benefit from elevation. Dieting tends to result in weight loss from body sites other than those affected by lipoedema. Lymph drainage within main leg lymphatics is relatively normal [2] until the later stages when foot oedema develops—the so-called lipoedema–lymphoedema syndrome.

Limb hypertrophy may also simulate lymphoedema. Occasionally, lymphoedema coexists with complete hemihypertrophy, Klippel–Trenaunay syndrome, Parkes–Weber syndrome (multiple arteriovenous anastomoses) or Proteus syndrome. Elephantiasis neurofibromatosa is a diffuse neurofibromatosis of nerve trunks with overgrowth of the subcutaneous tissue and of the skin, producing considerable enlargement of that region.

Table 51.6 Causes of a swollen limb.

Congenitally determined
Vascular
Haemangioma
Diffuse phlebectasia
Klippel–Trenaunay syndrome
Parkes-Weber syndrome
Maffucci's syndrome
Lymphatic
Lymphoedema
Lymphangioma
Other
Fat hypertrophy
Lipoedema
Plexiform neurofibroma
Proteus syndrome
Muscle hamartoma
Gigantism
Hemihypertrophy
Acquired
Vascular
Deep venous thrombosis
Post-thrombotic syndrome
Chronic venous reflux
Venous outflow obstruction
Thrombophlebitis
Venous injury, e.g. intravenous drug abuse
Idiopathic oedema of women
Acute arterial ischaemia
Reflex sympathetic dystrophy
Lymphatic
Lymphoedema
Armchair legs
Trauma
Reconstructive surgery
Femoropopliteal bypass
Vein harvesting
Factitial (tourniquet)
Pretibial myxoedema
Inflammatory
Cellulitis
Varicose eczema
Asteatotic eczema
Psoriasis
Musculoskeletal
Rheumatoid arthritis
Joint effusion
Ruptured Baker's cyst
Haematoma
Torn muscle
Pathological fracture
Achilles tendonitis
Myositis ossificans
Paget's disease
Tumours
Lymphoma
Sarcoma
Metastases

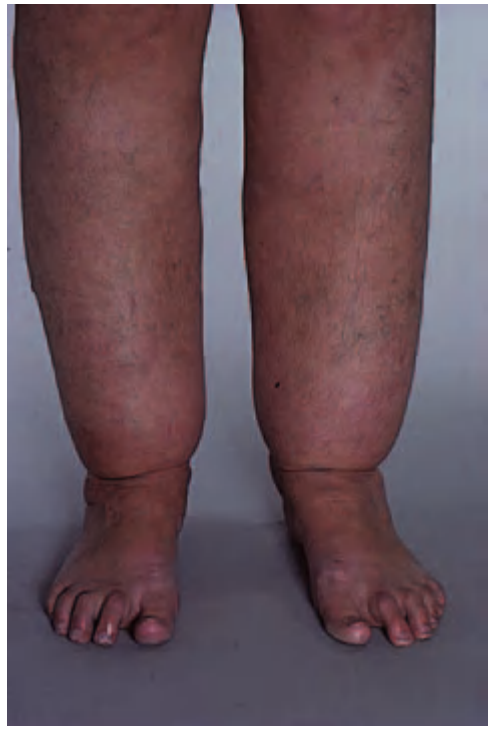

Fig. 51.9 Lipoedema.

YNS is associated with peripheral oedema, but the clinical features rarely resemble classical lymphoedema. Lymphangiogram abnormalities have been described [3], although a lymphoscintigraphic study demonstrated that a primary lymphatic abnormality is unlikely [4].

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Management of lymphoedema

Lymphoedema represents end-stage failure of lymph drainage and is essentially irreversible and incurable; treatment is difficult because of the presence of the 'solid' component in the swelling. In addition, most of the underlying causes are irreversible. As a non-fatal condition, and considering the shortcomings and difficulties of treatment, most patients are told to learn to live with it. This is neither necessary nor acceptable. While incurable, much can be done to improve quality of life. Indeed, improvements in the strategy for lymphoedema care and the development of dedicated lymphoedema clinics have provided fresh impetus for treatment.

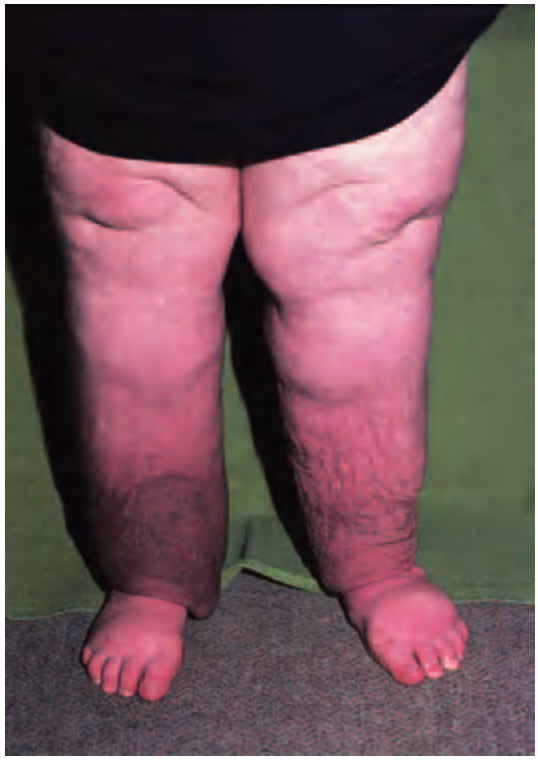

Fig. 51.10 Reduction of swelling in lymphoedema following 3 weeks' intensive therapy with multilayer bandaging and an exercise programme. (The same patient as in Fig. 51.5.)

The management of lymphoedema varies greatly around the world. In developed countries, the emphasis is more on physical forms of therapy involving compression, whereas in poorer, hotter countries where hosiery and appropriate bandages are too costly, surgery may be the mainstay of treatment. There is therefore a need to consider treatment based on the underlying cause(s), the problems created for the patient and the circumstances of that patient.

Two particular problems need to be overcome with lymphoedema: the swelling and the predisposition to infections, particularly recurrent cellulitis.

Physical (decongestive lymphatic) therapy

Physical methods of treating lymphoedema have been practised in Europe for many years [1]. Therapy essentially aims to control lymph formation (capillary filtration), including treatment of inflammatory causes or of venous hypertension, and to improve lymph drainage through existing lymphatics and collateral routes by applying normal physiological procedures that stimulate lymph flow. Physical treatment can, in the majority of cases, improve quality of life considerably (Fig. 51.10). Central to management is getting patients to understand their condition and know what they can do for themselves [2]. Only then can a high level of motivation and compliance with treatment be generated.

It is important to explain to patients that, unlike the blood, which is propelled by the heart, lymph drainage relies on local changes in tissue pressure generated by exercise and movement. Physical treatment exploits these principles, enhancing lymph flow as much as possible within the limits of a compromised drainage. It should be appreciated that lymph flow still exists in lymphoedema, otherwise swelling would be a relentlessly progressive process.

1 *Exercise* is crucial to lymph drainage [3,4]. Dynamic muscle contractions (isotonic exercises) encourage both passive (movement of lymph along tissue planes or through non-contractile lymphatics) and active (increased contractility and therefore propulsion of lymph within contractile lymphatics) phases of lymph drainage. Overexertion and excessive static (isometric, e.g. gripping) exercise increase blood flow, which therefore tends to increase oedema.

2 *External compression (hosiery or bandage)* complements the exercise programme. Such compression is not intended to 'squeeze' oedema, but to limit capillary filtration by opposing capillary pressure and to act as a counterforce to striated muscle contractions which act as the most powerful stimulus to lymph drainage. Without exercise, the emphasis for which should be movement not vigour, external compression is much less effective. Breathing and posture are also important particularly for clearance of lymph flow from the thorax and abdomen; without the dispersal of truncal lymph, more peripheral oedema will persist. Elevation *per se* does nothing to improve lymph drainage, but lowering venous pressure (and therefore filtration) can help to reduce swelling. Rest and elevation alone, however, are not the correct treatment for lymphoedema! Hosiery (below-knee or full-length stockings, half or full tights, sleeves) usually requires high compression and double hoses may occasionally be required. Most garments last no more than 6 months. Two garments (or pairs) should be provided, one to wear and one for the wash. Washing is necessary to maintain the compression properties of the garment.

3 *Massage* is a contentious treatment, despite being accepted as a necessary component of lymphoedema therapy in continental Europe [1]. The problem is that there are different forms of massage, used mostly for increasing blood flow and therefore of vigorous nature. Tissue movement, if gentle, is a stimulus to lymph flow without increasing blood flow [5]. Indeed, in the absence of lymphatic contractility, massaging of filled lymphatics by muscle exercise or surface massage may be the major stimulus to lymph flow, just as it is with blood flow during cardiac arrest [4]. The skin lymphatic network is the likely route for collateral drainage to areas which have normal lymph drainage [6]. The practice that encourages such

flow, referred to as manual lymphatic drainage therapy (MLD), is directed at normally draining lymph node regions; this 'siphons' or 'milks' lymph away from congested lymphoedematous areas, so complementing attempts to improve drainage 'upstream' by exercise and external compression [7].

Multilayer bandaging can be used for limb reduction, but also has the advantage of restoring limb shape so that containment hosiery is more effective at controlling swelling [8]. Bandaging may be the only method suitable for huge limbs and for controlling lymphorrhoea. Layers of strong non-elastic (short-stretch) bandages are applied to generate a high pressure during muscular contractions but low pressure at rest. The use of foam or soft padding helps to distribute pressure more evenly and to protect the skin. The digits are also bandaged to control swelling of fingers and toes. The strategic positioning of rubber pads 'irons out' pockets of swelling and deep skin folds. Multilayer bandaging is a skill which takes time to learn and should not be undertaken by any professional without appropriate training.

Pneumatic compression therapy (intermittent/sequential pneumatic compression) is employed widely [9]. An inflatable boot, legging or sleeve is connected to a motor-driven pump and lymph is displaced towards the root of the limb. If hosiery is not fitted immediately following compression therapy, the swelling readily recurs. Pneumatic compression softens the tissues and reduces limb volume during treatment, but it is doubtful that any long-term benefit is gained over hosiery and exercise alone.

Microwave heat therapy has been popular in China [10]. Possibly it activates macrophage clearance of macromolecules and reduces fibrosis by stimulating collagenase or by altering the viscosity and stiffness of the tissues.

Evidence of efficacy

While decongestive lymphatic therapy has become accepted first-line therapy, evidence for best treatment is weak. Using limb volume change as the main outcome measure, bandaging plus hosiery was significantly more effective at 6 months than hosiery alone [8]; hosiery was more effective than no hosiery [11]; MLD and hosiery were no more effective than hosiery alone [12]; and pneumatic compression therapy was no better than no treatment [13].

Care of the skin and prevention of infection. Elephantiasis skin changes are not only unsightly, but lead to problems including infection, odour, lymphorrhoea, restricted movement (pseudoscleroderma) and possibly poor wound healing. Such problems can be particularly troublesome where scarring and fibrosis have become excessive—for example, after trauma or surgery. Tinea pedis is almost invariable because of the closely apposed swollen toes, circumstances not improved by elastic hosiery. Modern antifungal creams unfortunately macerate skin further and therefore it is preferable to apply half-strength Whitfield's ointment prophylactically each night. For deep cracks and crevices which bacteria may readily colonize, regular toilet is necessary followed by an antiseptic drying agent, for example eosin, Brilliant Green or Castellani's paint applied with a cotton bud. Areas which constantly seep lymph should respond to sustained compression, but at sites where this is not possible, simple cautery or carbon dioxide laser therapy will often discourage leakage, even if only for a period of time. Hyperkeratosis can often be improved through the regular application of 5% salicylic acid ointment, but the best treatment to reverse elephantiasis skin changes is long-term compression.

Prevention of infection, particularly lymphangitis/cellulitis, is crucial to the control of lymphoedema. Care of the skin, good hygiene, control of tinea pedis and good antisepsis following abrasions and minor wounds are important. Administration of antibiotics at the time of an attack of cellulitis must be prompt, otherwise they do not significantly influence the course of the illness. Therefore, patients need to carry a supply of antibiotics—for example, co-amoxiclav or amoxicillin—with them at all times. For attacks recurring more than once a year, prophylactic antibiotics are the only effective treatment [14]. Phenoxymethyl penicillin 500 mg daily is as effective as any broad-spectrum antibiotic. Long-term prophylaxis is often necessary. Control of the oedema and diabetic type skin care may help reduce antibiotic requirements.

The only trials investigating prophylaxis against infection were undertaken in filarial lymphoedema and compared the efficacy of diethylcarbamazine (DEC), ivermectin and skin care in preventing lymphangitis/adenitis [15]. The authors concluded that a foot care programme alone can drastically reduce the number of attacks of acute adenolymphangitis. In a second study [16], the same group compared oral penicillin, diethylcarbamazine and antibiotic cream. Both the penicillin group and the DEC group had significantly reduced frequency of attacks of lymphangitis compared with patients treated with placebo. The authors concluded that antifilarial drugs do not have a role in reducing acute inflammatory attacks (lymphangitis, cellulitis), but that penicillin does contribute significantly to a reduction in attacks when combined with foot care.

Drug therapy

Drug therapy is generally disappointing. Diuretics remain the most commonly used treatment because most doctors consider oedema to be an indication for such drugs. Diuretics alone have little benefit in lymphoedema

because their main mode of action is to limit capillary filtration by reducing circulating blood volume. Improvement with diuretics suggests that the predominant cause of the oedema is not lymphatic.

The benzopyrone group of drugs have been advocated as treatment for lymphoedema, but their clinical effect seems to be small. In the UK, the only available or prescription medication in this class (although only actually licensed for venous disease) is oxerutins (Paroven). Three randomized and placebo-controlled trials have been published, all demonstrating a marginal significant effect on limb volume but of little clinical benefit [17]. Other benzopyrone drugs investigated include Daflon and coumarin (5,6-benzo-α-pyrone) and, while most trials claim significant volume reduction, the poor reporting means a meta-analysis is not possible. One robust trial concluded that there was no difference in effect between coumarin and placebo, and reported serious liver toxicity from coumarin [18].

Surgery

Surgery has a specific role in the management of lymphoedema. It is of value in a few patients in whom, even after conservative treatment, the size and weight of a limb inhibit its use or interfere with mobility. Surgery involves either removing excessive tissue or bypassing local lymphatic defects. Lifelong non-surgical measures—for example, hosiery—must be continued postoperatively.

Reduction (excisional) operations remove a longitudinal ellipse of skin and the underlying abnormal subcutaneous tissue down to the deep fascia. Undercutting of the skin allows removal of additional tissue. This procedure is preferred to circumferential excision and skin grafting or to the addition of in-rolling of one of the skin flaps (which can be followed by troublesome dermal sinuses). Two or three ellipses may be required for each circumference; the operations are separated by 3–6 months. Procedures involving surgery both above and below the knee or the elbow are usually undertaken one region at a time, because blood loss can be extensive.

Bypass operations involve either bridging an area of defective lymphatics with tissue containing lymphatics or with a vessel graft. If the lymphoedema results from excision of, or damage to, a local group of lymph nodes (e.g. in the axilla or groin) the area can be bridged with omentum or with an isolated and opened-out segment of gut. Lymph node-to-venous and direct lymph vessel-to-venous shunts have been undertaken but long-term patency is doubtful [19]. Lymph vessel transplantation, where autologous lymphatics are removed from an unaffected part of the body and anastomosed end-to-end with other unaffected collectors proximal and distal to the obstruction, has been shown to improve lymph transport [20].

Provision of care

The best results are obtained with an interdisciplinary approach to care, ideally delivered from a dedicated lymphoedema clinic. Improvement will be gained by implementing all measures known to improve lymph drainage and to control capillary filtration. The philosophy of care is to transfer the responsibility for treatment to the patient. Enabling patients to understand their condition and know what they should, and should not, do for themselves is central to care; only then can a high level of motivation and compliance with treatment be generated. Many patients with lymphoedema are overweight, because of morbid obesity as well as fluid retention. Excessive weight gain is likely to impair lymph drainage in the same way as it impairs venous drainage, and obesity reduces mobility (and therefore exercise). Control of weight in combination with physical treatment may be sufficient to resolve oedema completely in some patients.

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Midline lymphoedema

Lymphoedema localized to central regions such as the head and neck, trunk or external genitalia is uncommon, presumably because bilateral drainage routes operate and cross-flow from one region to another prevents swelling. Midline lymphoedema therefore usually develops when the lymphatics of the skin or subcutaneous tissue rather than the regional lymphatics fail. A course of MLD therapy may be helpful for any form of midline lymphoedema, but remains unproven in clinical trials.

1 *Facial swelling* can coexist with obvious primary lymphoedema of one or more limbs, suggesting that there is widespread congenitally determined lymphatic insufficiency. More commonly, the problem occurs later in life secondary to a variety of inflammatory or traumatic mechanisms. Rosacea, and less commonly acne [1,2], are the commonest causes of facial lymphoedema. Swelling affects the central forehead, periocular skin and cheeks where it may be surprisingly asymmetrical. In rosacea, erythema is always present, but inflammatory pustules and papules may be conspicuous by their absence. Treatment should start with attempting to control the rosacea but the erythema and swelling are notoriously resistant. General measures which can be helpful include raising the head of the bed to help prevent overnight reaccumulation of oedema, and perhaps even wearing a custom-made pressure garment. Avoidance of overheating is important.

2 *Chronic oedema of the eyelids* is common and may be quite simply due to acquired lax skin from photo-ageing and other processes which have undermined tissue compliance. Medical conditions to be considered with periocular oedema are dermatomyositis, thyroid or renal disease, and even YNS. Recurrent inflammatory processes, for example contact allergy or angio-oedema, may slowly compromise lymphatic function. Equally, one severe attack of facial erysipelas or cellulitis may damage lymphatics sufficiently to cause lymphoedema. Once underlying conditions have been excluded or treated, plastic surgery to the eyelids may be the treatment of choice.

3 *Oedema of the upper or lower lip* (or both) may start with intermittent bouts of swelling resembling angio-oedema, but with time the condition may become persistent. Extension of oedema within the mouth is common and is the reason for the rugose changes on buccal mucosal and tongue (scrotal tongue). Biopsy may or may not reveal the presence of granulomas. If present, a diagnosis of orofacial granulomatosis (granulomatous cheilitis, Melkersson–Rosenthal syndrome) is made, but it remains unclear if the granulomas are cause or effect despite the occasional documentation of Crohn's disease or sarcoid elsewhere [3]. Treatment remains difficult. Once simple emollient, antiseptic measures and prophylactic antibiotics have been tried, a therapeutic trial of oral or intralesional steroids is worth considering [4].

4 *Genital lymphoedema* is more common in the male and may develop from lymphatic obstruction due to advanced pelvic/abdominal cancer or its treatment. In an otherwise healthy patient with oedema confined to the scrotum or mons pubis, the cause is usually a primary abnormality of local lymphatics. Recurrent cellulitis is frequently associated and may antedate the swelling. Genital swelling may be precipitated by compression therapy to one or both lymphoedematous legs by forcing fluid into the adjoining trunk. Treatment rests with prevention of infection and if necessary prophylactic antibiotics. Good support is essential if the scrotum is very enlarged and pendulous. Plastic surgery may be the only way to reduce scrotal size. Penile oedema may respond to night-time application of tubular finger-sized bandages in layers.

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Congenital lymphatic malformations

Like the venous system, the lymphatic system is subject to many minor aberrations. Surgeons are only too well aware of the individual differences in position and number of regional lymph nodes, and of the territories drained, a significant problem in cancer management. Because of the similar ontology of veins and lymphatics, it is hardly surprising that malformations of each can coexist. It is also not unusual to find blood within a pure lymphatic malformation such as lymphangioma circumscriptum.

Generally speaking, lymphatics may be absent (aplasia), reduced (hypoplasia) or increased (hyperplasia). Congenital hyperplasia of lymph vessels may occur in isolation without other anomalies being present—for

example, circumscribed hyperplasia of lymph vessels of extremities may be found fortuitously by lymphography or at post-mortem.

Lymphangioma/lymphangiectasia (lymphangiectasis)

Simple sustained dilatation of otherwise normal lymphatic vessels is referred to as lymphangiectasia, but when lymphatics are distended due to structural abnormalities of a tumour-like nature the term lymphangioma is best used. Lymphangiectasia can be seen as translucent flat areas in the skin, which may ooze lymph spontaneously or after trauma. They may also be a consequence of defective collagen or elastin as documented in a report of penicillamine dermopathy [1]. Congenital lymphangiomas, like angiomas, are best classified as hamartomatous malformations. The most important feature of all congenital lymphangiomas is that they are not part of the normal lymph conducting system. Lymphangiomas may appear localized to the skin (lymphangioma circumscriptum) but there is frequently communication with a more extensive malformation arising from the main lymphatic vessels of the region, particularly at the root of a limb. The vesicles on the skin surface are very small and the surface can be so warty that the diagnosis may be missed. Lymphangiomas consist of dilated lymph channels of various sizes lined by normal lymphatic endothelium. The majority of lymphatic malformations arise in infancy but some may not manifest clinically until later in life. Familial cases do not seem to occur.

Lymphangioma circumscriptum

Lymphangioma circumscriptum is a term best reserved for a lymphatic malformation which is localized to an area of skin, subcutaneous tissue and sometimes muscle [2]. Clinically the condition manifests with fluid-filled vesicles which bulge on the skin surface (Fig. 51.11). The vesicles may be well defined and discrete, or may be grouped into structures resembling frogspawn. The lymphangiomas may be translucent when the overlying epidermis is very thin, or they may vary in colour from red to blue-black when they contain blood, a frequent finding. Alternatively, the surface of the lymphangiomas may appear extremely warty and the lesions may be mistaken for viral warts. There may or may not be swelling of the underlying tissues, depending on the presence and size of enlarged anastomosing lymphatic channels beneath the skin. The term 'circumscriptum' may in many cases be misleading, because there may be an extensive deeper component to the malformation which is not clinically apparent [3]. Indeed, simple surgical excision of the visible lymphangioma will frequently result in further development of surface vesicles, indicating a more widespread

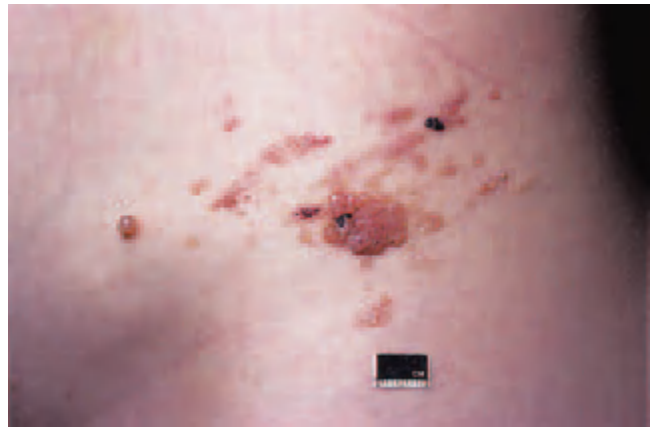

Fig. 51.11 Lymphangioma circumscriptum: fluid-filled vesicles resembling frogspawn. At times the vesicles can contain blood, weep clear fluid (lymphorrhoea) or become warty.

subcutaneous malformation. It has been postulated that the original malformation arises from deep contractile lymphatics which are malformed and not in continuity with the normal lymph-conducting pathways [4]. Tissue drainage into these abnormal lymphatics results in their gradual dilatation into lymphatic cisterns, contraction of which results in retrograde flow into the skin initial lymphatics. Only by identifying the limits of the subcutaneous cisterns prior to wide excision will there be any chance of cure.

Lymphangioma circumscriptum may present at any age but is usually noted at birth or appears during childhood. The commonest sites are the axillary folds, shoulders, flanks, proximal parts of the limbs and perineum. Frequently the vesicles are filled with fresh or altered blood but how the blood gets there is a mystery. The presence of limb swelling suggests an extensive underlying lymphatic abnormality. Lymph weeping (lymphorrhoea) from one or more surface vesicles is common and is likely to increase the risk of infection. Squamous cell carcinoma is described arising within lymphangioma circumscriptum [5]. The treatment of choice for lymphangioma circumscriptum is radical surgery. If this is not possible or is inappropriate, then intralesional administration of a sclerosant—for example, doxycycline [6] or picibanil (OK-432) [7]—can be helpful. Simple electrocautery and vaporization with carbon dioxide laser can be of palliative benefit, and superficial X-rays have been successfully used [8].

Diffuse lymphangioma (deep cavernous lymphangioma)

There is no clear distinction between lymphangioma circumscriptum and diffuse lymphangioma. The difference depends solely on the extent of the malformation. MRI can provide excellent evaluation of the extent of lymphangioma [9]. Diffuse lymphangioma usually gives rise to

ill-defined swelling, sometimes involving large areas of a limb. The swelling may be due either to lymphoedema (tissue oedema) or to gross dilatation of abnormal lymphatic channels (lymphangioma) or both [10]. Surface pressure with a digit will result in an indentation but a cavernous lymphangioma will rapidly refill, unlike the situation in pitting oedema where it takes many seconds for the interstitial fluid to redistribute when the pressure is released (like a sponge). Surface lymphangiomas are the result of dermal backflow. In diffuse lymphangiomas, the vesicles are more widely distributed, indicating the more extensive nature of the underlying malformation. Diffuse lymphangioma may not necessarily have any surface vesicles.

Diffuse lymphangiomas, although present from birth, may go unnoticed for many years and only manifest when disturbed by accidental injury, surgery or infection. Bleeding into a lymphangioma may be a cause of sudden pain. Swelling may or may not be apparent and the diagnosis can understandably be missed.

Cystic hygroma (cystic lymphangioma)

Lymphangiomas with few but large cyst-like cavities containing clear lymph are called cystic hygromas (hygroma = moist or watery tumour). Most occur in the neck, but they frequently extend into the upper mediastinum. Cystic hygromas are to all intents and purposes no different from cavernous lymphangiomas, but in structure hygromas have larger cystic spaces. The term tends to be reserved for those congenital lymph malformations which appear at birth or in infancy. In the neck, they presumably arise from an embryonic jugular lymph sac, whereas lymphangiomas derive from more peripheral lymph vessels [11]. Exceptionally, a cystic hygroma occurs in the groin, presumably from an embryonic iliac lymph sac. Fetal cystic hygroma can give rise to severe abnormalities, leading to fetal death [12].

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Acquired lymphatic abnormalities

Lymphangitis

In theory, the lymphatic system has evolved in humans as a host defence mechanism. Noxious agents and predators such as bacteria, if not dealt with at the point of entry to the host, access the lymphatic system. Lymphatic vessels, together with adjoining lymph nodes, effectively act as the second line of defence, hopefully preventing further onward spread and so limiting systemic involvement. In some circumstances, the inflammatory response may be profound, perhaps due to a heavy infection load, and either an overt lymphangitis or lymphadenitis, or both, arise. Lymphangitis represents inflammation of the lymphatic collectors and is clinically seen as tender red streaks up the limb corresponding to the inflamed vessels. In the lower limb, oedema is so often an accompanying feature that red streaks, such as are seen with lymphangitis of the arm, are rarely seen. A more diffuse erythema is seen extending up the medial side of the leg and thigh. Distinction from an ascending cellulitis becomes difficult.

Infection is usually limited by the lymph nodes, and in the lower limb lymphadenitis may give rise to painful swelling in the groin. Occasionally, infection bypasses a group of lymph nodes and affects those at a higher level. Constitutional upset can be severe and is greater the more proximally the infection has extended.

Lymphangitis may occur without any demonstrable inflammation or may be recurrent, e.g. following relapsing herpes simplex infection. Permanent obliteration of lymphatic collectors may follow severe or recurrent lymphangitis. In such cases, if reserve lymphatic capacity is limited, permanent swelling (lymphoedema) can result.

Recurrent acute inflammatory episodes

SYN. RECURRENT CELLULITIS, ERYSIPELAS OR LYMPHANGITIS

Where lymphatic insufficiency exists and the local lymphoid tissue/lymphatic system fails in its host defence duty, recurrent infection can occur. Clinically, this manifests as recurrent cellulitis/erysipelas. Indeed, any patient who presents with recurrent attacks of cellulitis in one leg almost certainly has a compromised lymph drainage in that leg, whether overt lymphoedema is present or not. In most cases, however, subtle signs of lymphoedema are evident particularly in the skin over the toes and forefoot. Because there is no localization of infection by the

lymphatics, the first sign of illness will be constitutional upset with fever, rigors or vomiting. Only later may redness and tenderness appear in the leg and the diagnosis become clear.

Lymphangitis, as witnessed by red streaks up the leg, is generally not seen, presumably because the infection, uncontrolled by the lymphatic system, has spread through tissue planes (cellulitis) with rapid dissemination into the circulation. However, inflammation following the line of lymphatic channels can sometimes be apparent at the proximal border of a cellulitic area in patients with lymphoedema [1].

Treatment for recurrent cellulitis should first of all address predisposing factors such as tinea pedis, foot dermatitis, leg ulcers, etc. If no portal of entry or cause can be identified, then long-term prophylactic antibiotics may be necessary if the debilitating attacks are to be controlled.

Carcinoma erysipeloides

SYN. CARCINOMA TELANGIECTATICA

Carcinoma erysipeloides manifests clinically with a fixed erythematous patch or plaque resembling cellulitis/erysipelas, but without fever [2]. The inflamed area may show a distinct raised periphery and oedema secondary to lymphatic obstruction. Histology reveals plugging of superficial and deep dermal lymphatics by adenocarcinoma, usually carcinoma of the breast, but the condition has been described with melanoma, lung, ovarian, colonic and pancreatic tumours. The redness appears to be a consequence of the dermal lymphatic plugging with tumour, presumably through the release of cytokines. The term carcinoma telangiectatica refers to the presence of purpuric plaques, papules and vesicles where only the more superficial lymphatics are involved. 'Inflammatory breast carcinoma' has been suggested as an alternative term to 'carcinoma erysipeloides', but oncologists already classify inflammatory breast carcinoma as a subtype of cancer within the breast.

Lymphangiothrombosis

Lymph is capable of clotting, but the circumstances in which this happens and what pathological effect lymph thrombosis has are totally unknown. Extrapolating from venous thrombosis would suggest that lymph thrombosis is likely to impair the function of lymphatic valves and the contractility of lymph-collecting vessels.

Mondor's disease is alleged to be a superficial thrombophlebitis of the breast and chest wall [3] (see Chapter 50). A similar process, whereby cords or threads like violin strings extend down the inner arm, is frequently seen following axillary lymphadenectomy. The manner in which the cords 'bowstring' across the axilla with the arm abducted, their diameter and the fact that the cords can snap between finger and thumb suggests that lymph thrombosis may be a more likely explanation than phlebothrombosis/thrombophlebitis. An equivalent condition may well exist in the lower limb but be mistaken for thrombophlebitis.

'Seroma'

SYN. LYMPHOCOELE; LYMPHOCYST

Following lymphadenectomy, it is not unusual for a localized swelling containing clear fluid to develop. Often referred to as a 'seroma', the fluid is not serum, but lymph which has drained from the cut ends of the lymphatic collectors, so filling the space originally occupied by the nodes. The wall of lymphocoeles is 'false', in that no endothelial lining exists and instead a dense network of fibrin with lymphocytes is present [4]. Aspirated fluid is indistinguishable from lymph. Repeat aspiration is often necessary until a collateral lymph drainage forms. A 'seroma', particularly if infected, may herald the onset of lymphoedema if alternative drainage routes are not established.

Acquired lymphangiomas

SYN. LYMPHANGIECTASIA

Acquired or secondary lymphangiomas arise following damage to previously normal deep lymphatic vessels [5]. The mechanism by which they form is identical to congenitally determined lymphangiomas, i.e. obstruction to drainage leads to back-pressure and dermal backflow, with subsequent dilatation of upper dermal lymphatics. Acquired lymphangiomas are not true neoplasms or hamartomas, but represent simple dilatation (lymphangiectasia) of surface lymphatics. Lower-limb lesions usually arise in association with lymphoedema following either ilioinguinal block dissection or pelvic surgery and radiotherapy for gynaecological cancer. Acquired lymphangiomas have been described in association with scarring processes including recurrent infections, radiotherapy, scrofuloderma, scleroderma, keloid, tumour, tuberculosis and repeated trauma [6].

The clinical appearance of acquired lymphangiomas may vary greatly, ranging from clear fluid-filled blisters to smooth flesh-coloured nodules. Histologically, the latter show oedematous polypoid nodules within which are dilated lymphatics. Lesions may be solitary but scattered throughout a lymphoedematous limb, or they may be grouped, as seen in lymphangioma circumscriptum.

Lymphangiomas of the vulva are described following cancer treatment, tuberculous inguinal lymphadenitis and genital involvement with Crohn's disease. Clinically, the most common pattern is that of circumscribed groups of tense, thin-walled vesicles. However, a hyperkeratotic appearance may make distinction from viral warts difficult

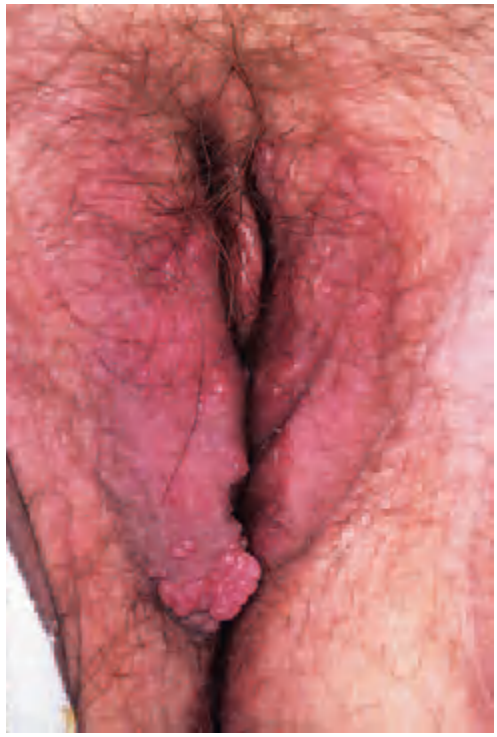

Fig. 51.12 Acquired lymphangiomas (lymphangiectasias) following cervical cancer treatment. The lymphangiomas were mistaken for genital warts.

[7] (Fig. 51.12). Recognition and appropriate treatment of vulval lymphangiomas is important primarily because the lesions may act as portals of entry for infection. In addition, persistent leakage of lymphatic fluid may be mistaken for urinary incontinence.

Treatment of acquired lymphangiomas is essentially the reduction of underlying lymphoedema and control of infection. This may be relatively straightforward on the leg, but is not so easy on the genitalia, where compression is not possible. Simple excision may prove successful at this site, particularly as tightening of the labial skin will discourage recurrence.

Acquired lymphangiomas may be widespread and problematic in palliative circumstances where advanced cancer produces profound oedema of lower limbs, genitalia and lower trunk. In these circumstances, widespread lymphangiomas weep copious lymph. Opposing intralymphatic pressure with equivalent surface compression is the only way of controlling the lymphorrhoea unless the lymphatic obstruction can be relieved.

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Lymphatic tumours

Acquired progressive lymphangioma

SYN. BENIGN LYMPHANGIOENDOTHELIOMA

This benign tumour differs from simple acquired lymphangioma by its clinical behaviour and histopathology [1,2]. Acquired progressive lymphangioma presents as reddish or bruise-like plaques which are usually located on the abdominal wall, thigh or calf. Typically the condition affects young adolescents but may also arise in adults. It is usually localized, flat and grows slowly. Considered to originate from lymphatic endothelium, the histopathological appearance can mimic a low-grade sarcoma or Kaposi's sarcoma. Anastomosing dilated channels, with a tendency to dissect the collagen bundles, are lined by swollen endothelial cells but without cellular atypia. It usually runs a long and benign course.

Lymphangiomatosis

A deep cavernous or diffuse lymphangioma that slowly progresses due to an intrinsic proliferative process, as opposed to extension due solely to raised hydraulic pressure, is termed lymphangiomatosis. Typically, it presents in children and in a significant proportion of cases is confined to one limb with or without bone involvement [3].

Involvement of visceral organs, as opposed to soft tissues and bone, is associated with a poor prognosis [4]. Cases in soft tissue present as diffuse, fluctuant swellings which may have surface lymphangiomas. Histologically, it can be impossible to distinguish from simple lymphangioma, but it shows dissection of collagen reminiscent of angiosarcoma and the lymphatic channels are far more extensive. Haemosiderin may be present in the interstitium. The diagnosis is based on the slow progression and infiltration of surrounding structures including bone.

Maffucci's syndrome consists of diffuse haemolymphangiomatosis accompanied by severe widespread deformities of bone and cartilage, notably enchondromas of digits [5]. The lymphangiomas do not appear on lymphography to communicate with the main lymphatic pathways and often possess both blood vascular and lymphatic elements. Bony deformity may be gross and slowly uniting pathological fractures are common. The disease has high malignant potential including lymphangiosarcoma.

Lymphangiomyomatosis

SYN. LYMPHANGIOPERICYTOMA

This condition, exclusive to females, presents with central lymphatic problems, namely progressive dyspnoea associated with chylous effusions and a chest X-ray which reveals honeycombing of the lungs [6]. Masses of spindle cells proliferate in and around the walls of lymph vessels in a hamartomatous manner, particularly in retroperitoneal tissues and mediastinum. Lymphoedema of one or both legs can coexist.

Lymphangiosarcoma

This is a rare but well-recognized complication of any chronic lymphoedema, irrespective of cause. Red–brown or purple discoloration, like a bruise, appears in the skin of the lymphoedematous limb. Nodules or raised plaques may appear later. As the tumours proliferate, the oedema may increase and older lesions may ulcerate. The tumour metastasizes early and has a poor prognosis.

The tumour is best described in the upper limb following breast cancer treatment (Stewart–Treves syndrome) [7], but it is well reported in the lower limb in association with lymphoedema, usually of many years duration [8]. Radical amputation, if performed early enough, may offer hope of cure.

Kaposi's sarcoma

There is increasing evidence that Kaposi's sarcoma (KS) may arise from lymphatic rather than vascular endothelium, although its origins may lie with a primitive cell capable of either differentiation [9]. Histologically the earliest stages of the disease show jagged proliferations of capillaries extending out from the normal capillaries in the mid-dermis. As the lesion develops a network of spindle cells and large vascular spaces will be seen with characteristic thin-walled 'back-to-back' capillaries.

The classical form of the disease, as described by Kaposi, presents with dark-blue or purple lesions, usually on the feet. Initially, lesions may be flat; when they become tumid, diascopy may produce partial blanching to reveal a brown tinge from extravasated blood. Individual tumours enlarge to a diameter of 10–30 mm and stop growing, whereupon adjacent areas fuse to form a plaque or tumour. New lesions appear proximally alongside a superficial vessel. Unlike the situation in patients with lymphangiosarcoma, lymphoedema is rarely evident at the time the first lesions appear, but otherwise the morphology is similar. KS, however, is characteristically multifocal and, in time, symmetrical, affecting both lower limbs. In prolonged venous hypertension of the lower legs, nodules with a close resemblance to KS may develop (termed acroangiodermatitis or pseudo-Kaposi's sarcoma; see Chapter 48); they differ, however, in lack of progression, and spindle cell proliferation is not seen histopathologically in acroangiodermatitis.

Brawny oedema resembling lymphoedema develops with advanced KS. In the African and Mediterranean types of KS, oedema is often the first sign with lymph nodes as the main tissue involved.

KS associated with immunodeficiency, whether HIV-induced or not, produces subtle lesions which are often widely scattered and quite dissimilar from the classical type.

Where a small area is involved, excision or radiotherapy can be used. Superficial radiotherapy is rapid and effective, and is the treatment of choice for the majority of patients with nodular disease of the extremities.

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Chylous reflux

Chyle is a 'milky lymph' which flows from the lacteals of the gut through the cisterna chyli and even through the thoracic duct. Incompetence of valves within megalymphatics, i.e. large varicose main lymphatic trunks, results in gross reflux of chyle to the skin below the waist [1]. The most common sites to be affected are the perineum and thigh. Lymphoedema may be present, but the characteristic symptom is oozing of milky fluid through the skin, usually from visibly dilated chylous vesicles (chylous lymphangioma). Rupture of such vesicles may result in a spurt of chyle under pressure, or chronic leakage may give rise to warty plaques of a cream-yellow colour.

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Chapter 52

Histiocytoses

A.C. Chu

The histiocytoses are a heterogeneous group of diseases that are characterized by the accumulation of reactive or neoplastic histiocytes in various tissues. Many of the signs and symptoms of the histiocytoses may be the result of the functional activity of these cells, and abnormal or altered regulation of histiocyte activity may be important in the pathogenesis of these diseases (Fig. 52.1).

Ontogeny of the histiocyte

SYN. TISSUE MACROPHAGE

Histiocytes are derived from circulating monocytes and thus share a common bone marrow progenitor cell, the *neutrophil/macrophage colony-forming unit* (NM-CFU) (Fig. 52.2). Promonocytes are actively dividing cells and their replication is controlled by a series of stimulatory glycoprotein hormones, colony-stimulating factor (CSF) and inhibitory prostaglandins. CSF has a molecular mass of 20–50 kDa. Its main source is cells of the monocyte/macrophage lineage [1] but activated T cells [2], keratinocytes [3] and neoplastic monocytes and macrophages [4] are also capable of secreting CSF. Cell division is limited by a negative feedback mechanism involving the E prostaglandins, which are released by macrophages after stimulation by CSF.

Other factors have been shown to influence the maturation of monocyte precursors, including 1,25-dihydroxyvitamin D_3 [5], retinoic acid [6], interferon-γ (IFN-γ) [7] and phorbol esters [8]. The promonocyte matures into a monocyte, which is released into the circulation where it represents a replacement pool for tissue macrophages or histiocytes. The half-life of a circulating monocyte is about 71 h [9], after which the cells migrate into various tissues where they differentiate into histiocytes without further division. Most histiocytes do not actively divide, although in some tissues, such as the lung, they are capable of replication [10]. The trophic factors that induce migration of precursor cells into certain tissues and induce their maturation into phenotypically recognizable cells are unknown.

The *Langerhans' cell* is a histiocytic cell that represents a resident immigrant population in the epidermis. As with all histiocytic cells, Langerhans' cells are of bone marrow origin [11] and it is assumed that the $CD34^+$ NM-CFU is the most likely precursor cell. The intermediate stages of Langerhans' cell development are unknown, but a possible intermediate cell in the bone marrow has been identified, which, in common with the Langerhans' cell, expresses the CD1 complex [12]. In the blood of healthy individuals, $CD1a^+$ cells are found in very low numbers, but in cord blood [13] and blood from burns patients [14] high levels of $CD1a^+$ cells are observed. It is speculated that these represent immature Langerhans' cells.

The factors that control the migration and development of Langerhans' cells in the skin are still poorly understood

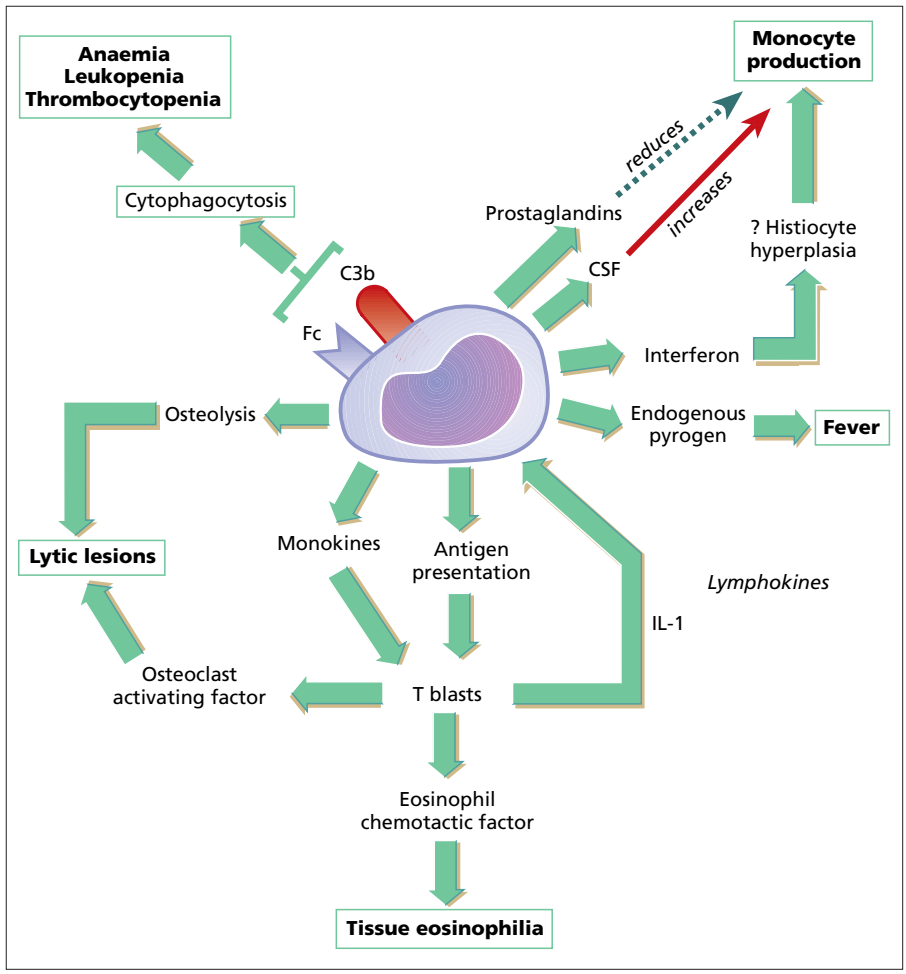

Fig. 52.1 Alteration in histiocyte function causing symptoms of the histiocytoses. CSF, colony-stimulating factor; C3b, complement 3b; Fc, heavy chain fragment of immunoglobulin; IL-1, interleukin-1; T blasts, thymus-derived lymphoblasts.

but granulocyte/macrophage CSF (GM-CSF), interleukin-3 (IL-3) and tumour necrosis factor-α (TNF-α) all induce $CD34^+$ cells to develop the phenotypic features of Langerhans' cells. Caux *et al.* [15] generated $CD1a^+$ cells from $CD34^+$ bone marrow cells using GM-CSF and TNF-α. The cells demonstrated potent antigen-presenting function. However, further research has shown that the whole field of Langerhans' cells ontogeny is more complex. Studies have now shown that GM-CSF will induce CD1a, CD1b and CD1c on blood monocytes [16]. It thus appears that although *in vivo* CD1a is a very specific marker for Langerhans' cells, this antigen can be induced on a variety of cells by cytokines such as GM-CSF. The interpretation of *in vitro* studies must therefore be cautious. A possible immediate precursor of the Langerhans' cell in the epidermis is the *indeterminate cell* [17], which bears the Langerhans' cell surface phenotype but lacks the characteristic Birbeck granule (see Chapter 3 and section on phenotype of Langerhans' cell below).

The fate of Langerhans' cells after their development in the skin is speculative. Some authors maintain that Langerhans' cells migrate from the skin in the efferent lymphatics as *veiled cells* and eventually develop into *interdigitating reticulum cells* in the paracortical zone of the regional lymph nodes. If Langerhans' cells are cultured, they lose their characteristic phenotype and adopt an interdigitating reticulum cell phenotype [18]; this phenomenon has been proposed as evidence for the extra-epidermal differentiation of Langerhans' cells. However, the *in vitro* culture conditions are very unphysiological, and it is more probable that the Langerhans' cell, veil cell and interdigitating cell are related but differentiate separately from an early common progenitor cell series.

The dermal dendrocyte, first described by Headington in 1986 [19], is an interstitial cell of the dermis that is highly dendritic. These cells are distributed throughout the papillary and reticular dermis. They are positive for adenosine triphosphatase (ATPase), α-napthylbutyrate esterase, β-glucuronidase and acid phosphatase, indicating that they are cells of the monocyte/macrophage lineage. They are also phagocytic *in vivo*, showing melanin and haemosiderin phagocytosis. Dermal dendrocytes are of bone marrow origin and are thought to have a possible role in phagocytosis, antigen presentation or in homeostasis of macromolecules of the dermis [20]. Elegant computer-assisted three-dimensional reconstruction of

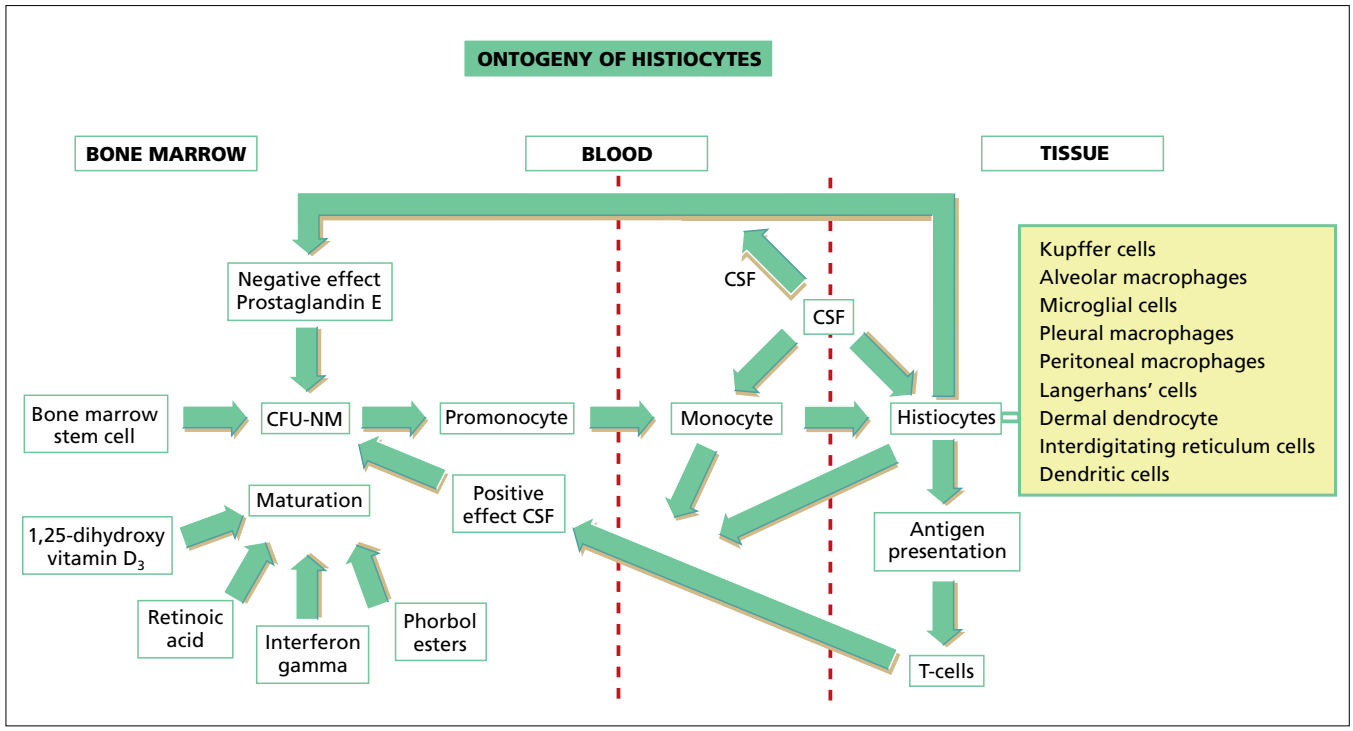

Fig. 52.2 Ontogeny of histiocytes showing factors that can influence the division and maturation of the cells. CFU-NM, neutrophil/macrophage colony-forming unit; CSF, colony-stimulating factor.

dermal dendrocytes in adult human skin has shown that in those associated with superficial blood vessels, the dendrites are thin membrane-bound flaps that enshroud the vessel wall. In subepidermal dermal dendrocytes, the flap-like dendrites are parallel to the dermal–epidermal junction. Between 20 and 40% of perivascular dermal dendrocytes and some subepidermal dermal dendrocytes are closely associated with mast cells, their membrane flaps enshrouding 50–90% of the surface of the mast cell [21].

Phenotype of Langerhans' cells

For many years after the original description of Langerhans' cells [22], this epidermal clear cell was considered to be an effete melanocyte. Major interest in this cell was generated by the finding that Langerhans' cells expressed a number of surface molecules, which suggested immunological importance. These molecules include major histocompatibility complex (MHC) class II molecules (which are constitutively expressed by Langerhans' cells), FcIgG receptors and C3b receptor. Langerhans' cells also express the chemokine receptors CCR5 and CCR6. A full list of the phenotypic markers of Langerhans' cells is given in Table 52.1.

A major advance was the finding that epidermal Langerhans' cells expressed the CD1 complex [23], previously considered to be restricted to cortical thymocytes. CD1 is a group of non-polymorphic membrane glycoproteins that non-covalently bind to β_2-microglobulin. Five genes have been identified and cloned [24]. Four

Table 52.1 Surface markers of Langerhans' cell (LC), activated LC and LC histiocytosis (LCH) cells.

Marker	LC	Activated LC	LCH cells
Surface ATPase	+	+	+
MHC II	+	+	+
MHC I	±	±	±
FcIgG receptor	+	+	+
FcIgE receptor	+	+	?
C3bi receptor	+	+	+
CD1a and CD1c	+	+	+
CD4	±	+	+
CD45	+	+	+
CD14	+	+	?
CDw29	+	+	?
IL-2 receptor	–	+	+
B7	–	+ (cultured)	+
CD11b and CD11c	+	+	+
S100	+	+	+
Placental alkaline phosphatase	–	+ (transient)	+
Peanut agglutinin	–	–	+
IFN-γ receptor	–	–	+
Neurone-specific enolase	+	+	+
Birbeck granule	+	±	+

ATPase, adenosine triphosphatase; IFN, interferon; IL, interleukin; MHC, major histocompatibility complex.

molecules have been described: CD1a, CD1b, CD1c and CD1d [25]. CD1a and CD1c have been shown to be expressed by Langerhans' cells and may play a role in presenting antigen to γ/δ T cells [26]. Langerhans' cells have since been shown to express other molecules, identified by CD4 and CD25 antibodies, which were initially thought to be specific for lymphocytes.

The unique phenotypic feature of Langerhans' cells is the trilaminate cytoplasmic organelle, the *Birbeck granule* [27]. This organelle is only observed in Langerhans' cells, Langerhans' cell histiocytosis (LCH) cells (which are abnormal Langerhans' cells) and some hairy cell leukaemia cells. The granules are rod-shaped structures with a central lamella. They are of uniform width (33 nm) and of variable length (200–360 nm). The granules often have terminal vesicular dilations, giving rise to the characteristic 'tennis racket' appearance. The Birbeck granule was initially thought to originate from the Golgi apparatus, but studies now suggest that it arises from the cytoplasmic membrane by receptor-specific endocytosis [28]. The exact function of the Birbeck granule remains unknown and the factors that induce its appearance in Langerhans' cells remain speculative.

The phenotype of the Langerhans' cell changes with activation or with culture *in vitro*. Activation involves up-regulation of human leukocyte antigen (HLA)-DR and expression of CD4 and the co-stimulatory molecules CD80 and CD86 [29]. At the same time, Birbeck granules become sparser and CD1a is down-regulated (see Table 52.1).

Phenotype of the dermal dendrocyte

In addition to showing the enzyme histochemical features of the monocyte/macrophage lineage, a characteristic feature of dermal dendrocytes is expression of factor XIIIa. The cells are always negative for CD1a, which differentiates them from Langerhans' cells, and express HLA-DR, HLA-DQ, CD36, CD68, CD34, CD11a and CD11b but not CD15, CD54 and CD2. Thus they show the immunophenotype of monocyte/macrophages and antigen-presenting cells, with no features of granulocytes or T cells [30]. Following IFN-γ stimulation, expression of HLA-DR increases and dermal dendrocytes express CD54. In atopic dermatitis and psoriasis, cells positive for factor XIIIa, HLA-DR and CD54 are observed in the upper dermis and foci of factor XIIIa-positive cells are seen in the epidermis [30].

In recent studies, dermal dendrocytes have been shown to express S100A6 [31] and type XVI collagen [32]. $CD14^+$ peripheral blood monocytes stimulated with GM-CSF and IL-4 express factor XIIIa [33] and collagen XVI [32]. It is postulated that type XVI collagen forms an intermolecular cross-link through its non-collagenous domain, contributing to the integrity of factor XIIIa.

Dermal dendrocytes also express the von Willebrand factor receptor GPIbα. Expression of this factor *in vitro* is up-regulated by mast cell degranulation [34]. Expression of GPIbα on dermal dendrocytes suggests that these cells may have a role in skin remodelling and repair.

The fate of dermal dendrocytes is unknown. The factors that influence maturation of these cells include mast cell products, although *in vitro* studies using TNF-α have failed to demonstrate up-regulation of GPIbα on factor XIIIa-positive cells [35]. When skin is maintained in organ culture, dermal dendrocytes lose their dendritic morphology and become more rounded. This change is accentuated by mast cell degranulation, regardless of stimulus. These non-dendritic cells express variable amounts of factor XIIIa, CD34 and CD68.

Function of the histiocyte

Histiocytes can be broadly divided into two functionally separate cell populations: the 'professional' phagocyte and the antigen-presenting cell.

Phagocytes include the majority of resident tissue macrophages and immature macrophages. Immature macrophages are cells that have migrated, as monocytes, from the blood but remain responsive to chemotactic stimuli and are attracted to sites of inflammation where they become inflammatory macrophages. Phagocytes take up foreign or altered material and digest it using a number of lysosomal enzymes. Phagocytes recognize material to be taken up by a variety of different surface receptors. Important in this are the carbohydrate and lectin receptors, which are involved in the phagocytosis of bacteria and possibly tumour cells. The cells also express the specific complement component receptors CR1 and CR3, which bind to C3b and C3bi respectively, and FcIgG receptors, which bind to the Fc fragment of IgG. These receptors are important in the phagocytosis of material that has bound IgG and complement, which act as opsonins and augment phagocytosis.

Phagocytosis is important in the removal of particulate matter and destruction of bacteria and parasites. The phagocytosed particles are internalized and destroyed in phagolysosomes. Partially degraded antigen may subsequently become associated with MHC class II antigens and be re-expressed on the surface of the macrophage, where it can be presented to T-helper cells.

Phagocytes also possess some antigen-presenting capacity, although this is limited—cells express class II MHC molecules and can process and re-express antigen on their surface in association with these specific molecules, but only elicit responses in specific responder T-cell populations. In general, phagocytes present antigen to sensitized T cells but not to naive or 'memory' T cells.

Antigen-presenting cells are histiocytic cells, or in some instances other cell types, that have specialized functional

activity in presenting antigen to T cells. These cells are represented in humans by the blood dendritic cell, epidermal Langerhans' cell, interdigitating reticulum cell of the lymph node paracortex and veil cell of the efferent lymph. These cells have no phagocytic activity and, unlike professional phagocytes, are unable to adhere to surfaces. They are able to internalize antigen by endocytosis, process it by lysosomal digestion and re-express the antigen on their surface in association with MHC class II molecules. In addition these cells are potent antigen-presenting cells and are able to present antigen not only to sensitized T cells but also to memory and naive T cells, and are also able to present self antigen to allogeneic T cells to elicit an allogeneic or mixed-cell reaction [36].

Langerhans' cells are central to the sensitization and elicitation phases of contact allergic dermatitis, are responsible for cutaneous immune surveillance and are the target for skin graft rejection [37]. Intraepidermal Langerhans' cells are immature but, following stimulation, they migrate from epidermis to lymphatics and thus to the regional lymph nodes, and during this process undergo maturation. The signals that initiate and regulate the directed movement of Langerhans' cells from the skin to regional lymph nodes include chemokines and cytokines. In cutaneous sensitization, TNF-α, GM-CSF, IL-1β and IL-18 are required, while IL-4 and IL-10 antagonize this process [38,39]. Maturation of Langerhans' cells is accompanied by specific phenotypic changes, with up-regulation of HLA-DR, down-regulation of CD1a, and expression of CD4 and CD25. There is a switch in chemokine receptor expression from CCR5 and CCR6 to CCR7 and CXCR4, which enables Langerhans' cells to exit the epidermis and follow a gradient of chemokines (CCL19, CCL21 and CXCL12) to the paracortical zone of the lymph nodes [40]. Langerhans' cells also express other activation markers, including CD83 and CD40 and the T-cell co-stimulatory molecules CD80 and CD86 [41].

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Classification of the histiocytoses

Understanding of the histiocytoses has been severely hampered by the lack of a universally accepted classification of these diseases and the widespread use of eponyms to describe them. For these reasons, the Histiocyte Society published their classification of the histiocytoses for use as a standard in both diagnosis and management [1]. This classification has been generally accepted and is now widely used. In this chapter I have modified the original classification in the light of new insights into reactive histiocytoses of dermal dendrocyte phenotype. The histiocytoses are separated into four classes according to our current understanding of the biology of these diseases.

Class I: Langerhans' cell histiocytosis

Class I histiocytoses are a diverse group of clinical diseases that are all reactive histiocytoses in which the predominant histiocyte is of Langerhans' cell phenotype. Patients with LCH can be further subdivided on the basis of the clinical organ involvement present. Bone disease and lung disease in adults appear to be significantly different in their biology from other single-system involvement and it is valid to separate them. The significance of organ involvement is discussed further in the section on LCH.

Class IIa: histiocytoses involving cells of the dermal dendrocyte lineage

Class IIa histiocytoses are reactive diseases in which cells with the phenotype of the dermal dendrocyte (positive for CD68 and factor XIIIa) accumulate in the skin and other tissues causing tissue damage. The typical histological change is a xanthogranulomatous reaction, although the histological changes reflect the cell type present. Juvenile xanthogranuloma is typical of this group of diseases, and some of the conditions described may not be specific disease entities but clinical variants of a single disease. These diseases are reactive with no clinical evidence of malignancy.

Class IIb: histiocytoses involving cells other than Langerhans' cells and dermal dendrocytes

Class IIb histiocytoses are reactive diseases in which histiocytes other than those bearing the Langerhans' cell or dermal dendrocyte phenotype accumulate in various tissues and may cause tissue damage. Within this heterogeneous group of diseases are included a number of rare and often poorly understood disorders. The major features of all these histiocytoses are that they are reactive, with no clinical or laboratory evidence of malignancy, and that Langerhans' cells and related cells are not involved.

Class III: malignant histiocytic disorders

Class III histiocytoses include all the malignant histiocytic diseases. These include monocytic leukaemias, malignant histiocytosis, which may be of the mononuclear phagocyte, dendritic cell or Langerhans' cell type, and the true histiocytic lymphoma, which once again may be of the mononuclear phagocyte, dendritic or Langerhans' cell type.

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Class I histiocytosis: Langerhans' cell histiocytosis

SYN. HISTIOCYTOSIS X; EOSINOPHILIC GRANULOMA; LETTERER–SIWE DISEASE; HAND–SCHÜLLER–CHRISTIAN SYNDROME; HASHIMOTO–PRITZKER SYNDROME; SELF-HEALING HISTIOCYTOSIS; PURE CUTANEOUS HISTIOCYTOSIS; LANGERHANS' CELL GRANULOMATOSIS; TYPE II HISTIOCYTOSIS; NON-LIPID RETICULOENDOTHELIOSIS

Definition. LCH is a reactive condition in which a clonal population of cells with the phenotype of the Langerhans' cell accumulate in various tissues and cause damage. Tissue damage appears to be due, in part, to cytokine production.

Aetiology. The aetiology of LCH is unknown but over the last century several possibilities have been considered, including tuberculosis [1] and a lipid abnormality [2,3]. The discovery of Birbeck granules in the cytoplasm of lesional cells using electron microscopy [4] led to the suggestion that these cytoplasmic bodies could be viral inclusion bodies and that LCH could be a virally mediated disease [5]. However, a large retrospective study on the fulminant form of LCH showed a random geographical distribution and little month-to-month variation in the

incidence of the disease, which argued against it being due to a conventional virus [6]. A study of 56 LCH samples using *in situ* hybridization and polymerase chain reaction (PCR) analysis failed to show any consistent evidence of adenovirus, cytomegalovirus, herpesvirus, parvovirus, human T-cell virus or human immunodeficiency virus infection [7].

The possibility of an immunological aetiology for LCH has been suggested by the occurrence of a number of immunological abnormalities in this disease. The fact that the lesional cell bears the phenotype of the Langerhans' cell, which is a key cell in the immune system, also suggests that the immune system is in some way involved in its pathogenesis. However, none of the immunological abnormalities have been a consistent feature, and most authors now consider them to be epiphenomena.

Serum immunoglobulins may be increased or decreased. The most common finding is that of reduced IgG and IgA levels, with normal IgM and IgE levels. In some reported cases, IgM and IgE levels were elevated [8].

In some patients, particularly those with aggressive disease, cutaneous anergy has been found on cutaneous testing, and *in vitro* studies have shown reduced T-cell responses to mitogens, recall antigens and alloantigens [9]. A reasonably consistent feature in three reported series of LCH [10–12] is a reduction of the $CD8^+$ T-cell subpopulation in the blood, with an associated normal or reduced total T-cell number. In one report [12], this reduction in the number of $CD8^+$ cells was associated with reduced suppressor T-cell activity *in vitro*.

Considering that Langerhans' cells are members of the monocyte/macrophage series of cells, very few abnormalities of this group of cells have been reported. Reduced monocyte-mediated, antibody-dependent cytotoxicity occurred in six patients with LCH, all of whom were in clinical remission [13]. This certainly warrants further study. LCH cells are unable to provide accessory cell function in a mitogen-driven T-cell response, and were inhibitory to T-cell proliferative responses [14]. Only one study has investigated the functional activity of LCH cells in depth [15]. In this report, LCH cells were shown to be functionally deficient in presenting alloantigen to T cells. It is possible that the defect in functional activity may be linked with the apparent arrest of these cells in an early stage of activation, leaving the cells immature so that they do not have the functional capacity of a normal Langerhans' cell.

Historically, LCH has been considered a malignant disease, and care of children with the disease has been in the hands of paediatric oncologists. The main reason for this is the clinical course and high mortality associated with the more fulminant forms of LCH. Flow cytometric studies have in general failed to identify aneuploidy in LCH [16,17]. In one report of an adult case with clinical and histologically confirmed LCH involving the skin, flow cytometry revealed an aneuploid peak [18]. Many features of this case were unusual and it is possible that the patient had the rare form of malignant histiocytosis of Langerhans' cell type.

Recent studies have demonstrated that lesional $CD1a^+$ cells in LCH are clonal. Clonality studies in LCH have been difficult to perform because of the lack of cell-specific markers. Unlike the T-cell receptor in T cells and immunoglobulins in B cells, histiocytic cells have no markers that can be employed in such studies. The study of genes carried on the X chromosome have now allowed such studies in female patients with this disease. Of the gene loci examined, the human androgen receptor (*HUMARA*) is the most informative as there is a high degree of heterogeneity for this locus in the population. The underlying theory behind the assay is that the two alleles for *HUMARA* are acquired from maternal and paternal genes, each of which is a different size because of the presence of tandem repeats. Only one allele is activated, the other being inactivated by methylation, and the use of methylation-sensitive restriction enzymes in PCR allows the inactivated allele to be expanded and identified. In a normal population of cells, activation of the alleles is random so that 50% are derived from maternal and 50% from paternal genes, giving two bands on gel electrophoresis. In a clonal population of cells, all cells are derived from a single cell and therefore all these cells will have an inactivated allele, which is either maternal or paternal, giving a single band on gel electrophoresis. In a study of four female patients with LCH, purified lesional $CD1a^+$ cells were shown to be clonal using this assay system [19]. Studies by Willman *et al.* [20] have confirmed these studies and shown that lesional cells are clonal regardless of the extent or severity of the disease. In isolated pulmonary LCH in adults, a recent study using X chromosome inactivation at the *HUMARA* locus has shown that 29% were clonal and 71% non-clonal. Discrete lung nodules from the same patient showed different allele inactivation [21]. Pulmonary LCH in adults is often an isolated disease that may remain restricted to the lungs and thus behaves in a different way biologically than other forms of LCH. It is possible that primary lung disease is a separate entity and only when it progresses to involve other organs does it become a clonal disease.

What clonality in LCH means is difficult to interpret. It certainly identifies the LCH cell as the primary cell in this disease but this does not mean that LCH is a malignancy. Many reactive diseases, for example lymphomatoid papulosis, have been shown to be clonal. Although of major interest, such studies have thus not altered our management of patients with this disease, nor have they identified the disease as malignant.

Pathology. The histological picture of LCH depends on the age of the lesion biopsied and the organ involved. The

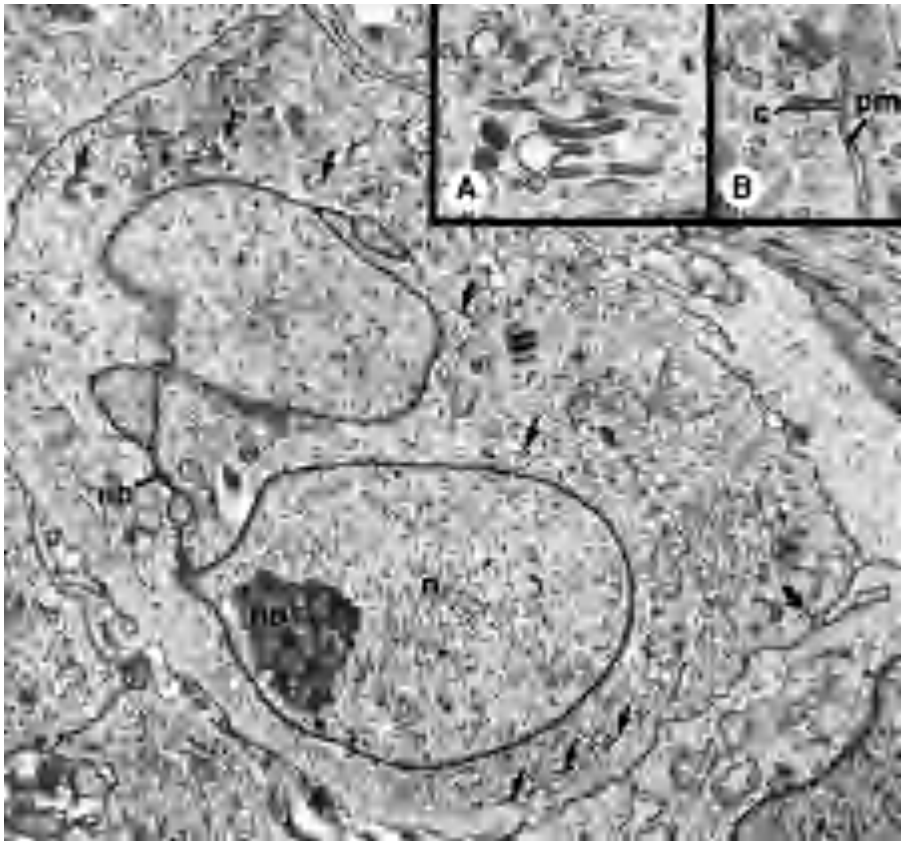

Fig. 52.3 Electron micrograph of a Langerhans' cell histiocytosis (LCH) cell in the epidermis of a patient with multisystem LCH. The cell shows a lobulated nucleus (n) with a prominent nucleolus (no) and attenuated nuclear bridge (nb). Numerous Birbeck granules (straight arrows) are evident in the cytoplasm. One granule (curved arrow) is seen projecting from the plasma membrane (× 13 000). (A) Birbeck granule in the cytoplasm. Some show characteristic vesiculation of the end, forming typical tennis-racket bodies. (B) Birbeck granules appear to be budding from the plasma membrane (pm) (× 39 000). (Courtesy of Professor R.A.J. Eady, St John's Dermatology Centre, London, UK.)

pathology of LCH was reviewed by the Histiocyte Society in 1987 [22], who recommended three levels of diagnostic confidence. A presumptive diagnosis is made when the histological appearance of the biopsy is consistent with the diagnosis of LCH. Diagnostic confidence increases if marker studies are performed and lesional cells are found to be positive for S100 protein, peanut agglutinin or α-D-mannosidase. If lesional cells are found to express the CD1 complex or to exhibit Birbeck granules on electron microscopy (Fig. 52.3), this constitutes a definitive diagnosis.

The characteristic histological appearance of LCH in the skin is of an upper dermal and junctional accumulation of large histiocytic cells with homogeneous pink cytoplasm. These cells have lobulated, bean-shaped or boat-shaped nuclei (Fig. 52.4). There is a variable lymphocytic infiltrate, deep to the aggregates of LCH cells. In some patients with LCH, large numbers of γ/δ T cells have been identified in the lymphocytic infiltrate [23]. Eosinophils are present in variable numbers, being rare in the more fulminant forms of LCH but present in high numbers in the less aggressive spectrum of LCH. Within the epidermis, LCH cells are often observed either singly or forming Pautrier-like microabscesses (Fig. 52.5).

With time, the histological picture changes, with fewer LCH cells present and the emergence of a more xanthomatous pattern, which is eventually followed by fibrosis. Several studies have shown no correlation between

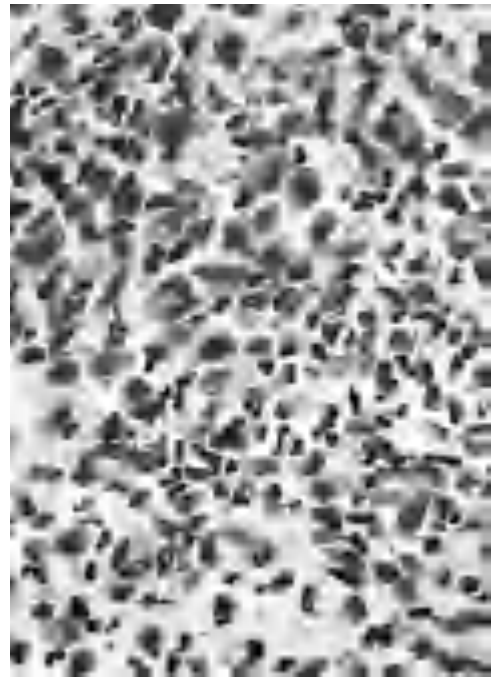

Fig. 52.4 Langerhans' cell histiocytosis cells in the dermis intermingled with polymorphs and eosinophils (H&E × 250). (Courtesy of Professor E. Wilson Jones, St John's Dermatology Centre, London, UK.)

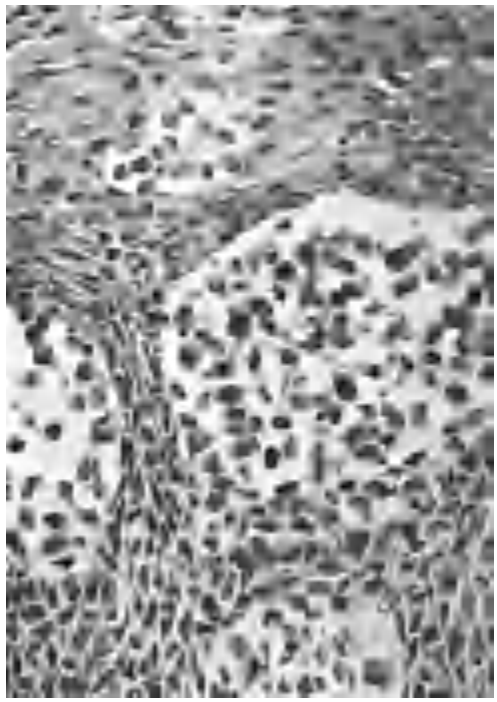

Fig. 52.5 Langerhans' cell histiocytosis (LCH). Details of a papillary tip containing LCH cells, with a small intraepidermal abscess overlying it (H&E × 250). (Courtesy of Professor E. Wilson Jones, St John's Dermatology Centre, London, UK.)

histology and extent of disease, morbidity or mortality [24–27].

In one clinical variant of LCH, described by Hashimoto and Pritzker [28], in which the disease is restricted to the skin and regresses spontaneously over a period of several months, the pathology in the skin is sufficiently different to warrant separate description. In this variant, the infiltrate is deep within the dermis, with sparing of papillary dermis and epidermis. Lesional cells are large histiocytic cells with copious glassy eosinophilic cytoplasm. Multinucleate giant cells are often observed. Up to 25% of these histiocytes contain Birbeck granules.

Immunocytochemistry. Immunohistochemical studies have demonstrated that LCH cells show many of the characteristics of the epidermal Langerhans' cell, particularly in its activated state (see Table 52.1) [29–31]. The labelling pattern with certain markers (C3b and C3bi receptors, CDW14, Ki-M1 and Ki-M6) has been shown to be variable. This does not correlate with the clinical course of the disease but probably reflects different phenotypic 'ages' of the Langerhans' cell [30].

Three markers have now been shown to be expressed by LCH cells but not by normal epidermal Langerhans' cells. These are peanut agglutinin, an epitope shared with IFN-γ [32,33] and placental alkaline phosphatase [34]. Placental alkaline phosphatase is negative in normal

Table 52.2 Diagnostic markers for Langerhans' cell histiocytosis (LCH) cell.

Marker	Tissue needed
S100	Paraffin-embedded
Peanut agglutinin	Paraffin-embedded
Placental alkaline phosphatase	Paraffin-embedded
α-D-Mannosidase	Fresh
CD1a	Fresh-frozen (paraffin-embedded with 010 monoclonal antibody)
Birbeck granules	Electron microscopy prepared

Langerhans' cells and is not observed in reactive dermatoses where Langerhans' cells are present in the dermal infiltrate. However, *in vitro* studies have shown that placental alkaline phosphatase expression is an early and transient activation marker of Langerhans' cells [35]. These observations are of particular interest, as they show that LCH cells are not merely reactive Langerhans' cells but are Langerhans' cells arrested at a particular stage of their ontogeny.

Immunohistochemistry is important in confirming the diagnosis of LCH. For retrospective studies where only formalin-fixed and paraffin-embedded tissue is available (Table 52.2), three markers are of value: S100 protein, peanut agglutinin and placental alkaline phosphatase. S100 protein staining is a consistent feature of LCH cells but is also present in normal Langerhans' cells and a variety of other skin cells and structures, including nerve tissue, melanocytes and naevus cells. In a study by Rowden *et al.* [36], the histiocytic cells and giant cells in juvenile xanthogranuloma, necrobiotic xanthogranuloma, papular xanthoma, eruptive histiocytoma and reticulohistiocytosis were all negative for S100 protein, but all LCH specimens were positive.

Peanut agglutinin shows characteristic labelling of LCH cells, with paranuclear and cell-surface deposition of reaction products. Peanut agglutinin labels other cell types in the same way, including interdigitating reticulum cells [37], but normal Langerhans' cells and other histiocytic cells show diffuse cytoplasmic labelling with this marker [32].

Placental alkaline phosphatase is normally found in placental tissue and in the female reproductive tract. It is also expressed in malignancies of the ovary and testis. In normal skin, placental alkaline phosphatase is negative and cells expressing this enzyme are absent in reactive disorders. It is perhaps the most informative marker that can be used in archival LCH material, where only the LCH cells express this enzyme [34].

A recently described marker for dendritic cells is now being used by some histopathologists to differentiate LCH from other histiocytoses. Fascin is a 55-kDa actin bundling protein that is highly selective for dendritic

cells of lymphoid tissue and blood. It is involved in the formation of dendritic processes in maturing epidermal Langerhans' cells. In a study of 34 samples of LCH from skin, bone, lymph node, thyroid, orbit and extradural cranial tissue, all samples stained positive for fascin, CD1a and S100. Normal epidermal Langerhans' cells were consistently negative for fascin [38].

To establish a definitive diagnosis by the criteria of the Histiocyte Society, the involved tissue must be examined for anti-CD1a staining or for the presence of Birbeck granules (which requires fixation and processing for electron microscopy). Until recently, staining with anti-CD1a antibodies required fresh frozen tissue. A new monoclonal antibody, 010, has now been described that works in paraffin-embedded tissue [39].

Incidence. The incidence of LCH is unknown because of the heterogeneity of clinical expression of the disease. In many patients, the disease is undiagnosed, with mild skin involvement being attributed to seborrhoeic dermatitis and isolated bone disease remaining undetected. Also, the diverse clinical presentation of the disease means that patients may be under the care of orthopaedic surgeons, ear, nose and throat surgeons, paediatricians, paediatric oncologists or dermatologists. In the UK, 15–20 cases are reported to the UK Children's Cancer Study Group Register each year. These represent only the more severe paediatric cases, and the real incidence in the general population is more likely to be at least four to six per million, with 50–70 new cases presenting annually.

Clinical features. LCH can affect many different organs and may cause fever, malaise and, in children, failure to thrive.

Of 58 patients with LCH seen at the Hospital for Sick Children, London, over a 7-year period, 14 had single-system disease (13 bone and one skin) and 44 had multisystem disease, of whom 50% had vital organ dysfunction [40]. At the Children's Hospital in Philadelphia, 64 patients were seen over a 14-year period of whom 33 had single-organ involvement in bone (27 patients) or skin (six patients), 22 had multifocal single-organ disease affecting bone (17 patients) or soft non-osseous tissue (five patients), and nine patients had disseminated disease with dysfunction of liver or lungs [41].

In a large series of 124 patients [42], bone, lymph node and skin lesions were the most frequently seen, but 50% of patients showed liver disease and 23% lung disease with frequent haematological changes.

Skin. The most characteristic presentation is with scalp involvement. The scalp is erythematous with greasy scales, looking very like seborrhoeic dermatitis (Fig. 52.6). On the trunk, the lesions are discrete, yellow-brown, scaly papules, often showing areas of purpura (Figs 52.7 & 52.8). Lesions may become nodular and crusted or eroded. Ulceration of the flexures, groin or perianal or vulval region is a common presentation in adult patients (Fig. 52.9).

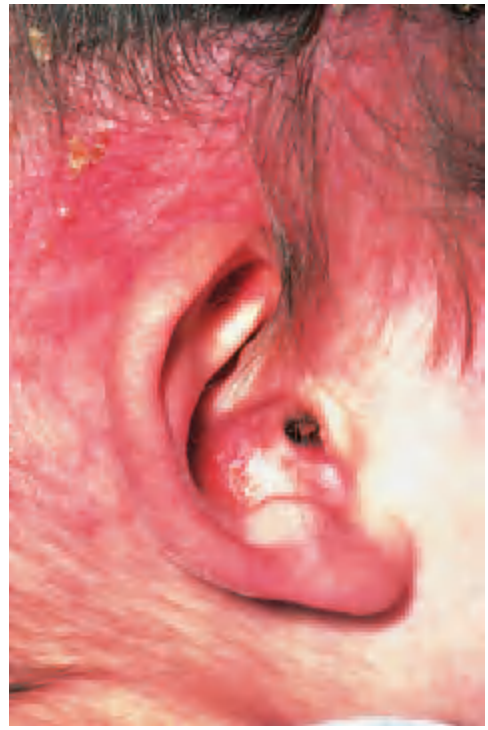

Fig. 52.6 Langerhans' cell histiocytosis of the scalp and ear of a child showing the characteristic seborrhoeic dermatitis-like eruption.

In the Hashimoto–Pritzker variant of LCH, the eruption starts in the neonatal period with nodular lesions that resemble healing chickenpox. The eruption may involve any skin surface, including palms and soles, and is self-limiting over a few weeks. In a recent report of four cases of Hashimoto–Pritzker LCH, follow-up showed recurrence of disease in two children, with cutaneous relapse in one at 3 months of age and bony relapse requiring systemic therapy at 6 months in the other child. Follow-up of such children is therefore necessary [43].

In patients with peripheral lymph node involvement, chronic draining sinuses may develop over involved sites (Fig. 52.10).

Juvenile xanthogranuloma has been associated with LCH. In a report of three children with multisystem LCH, juvenile xanthogranulomas appeared 3–6 years after the initial presentation with LCH [44]. It is possible that the juvenile xanthogranulomas developed as a reaction to the inflammatory reaction in LCH.

Nails. Nail involvement in LCH is rare. Changes include paronychia, nail fold destruction, onycholysis and subungual expansion with nail plate loss (Fig. 52.11) [45].

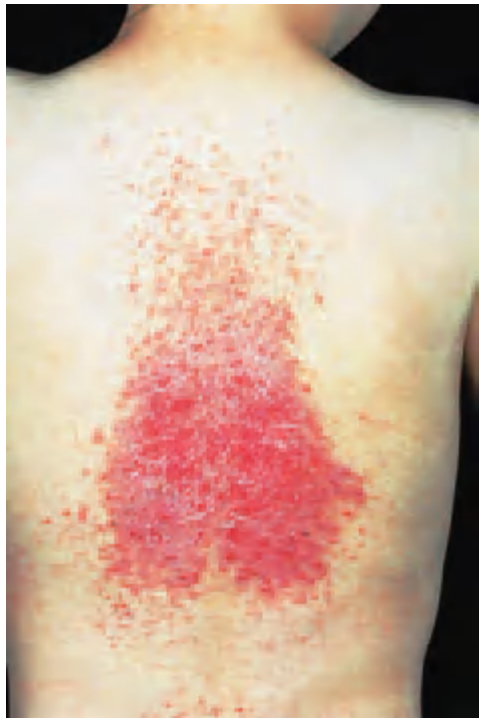

Fig. 52.7 Langerhans' cell histiocytosis in a child. Scaly maculopapular eruption on the back with mild purpura.

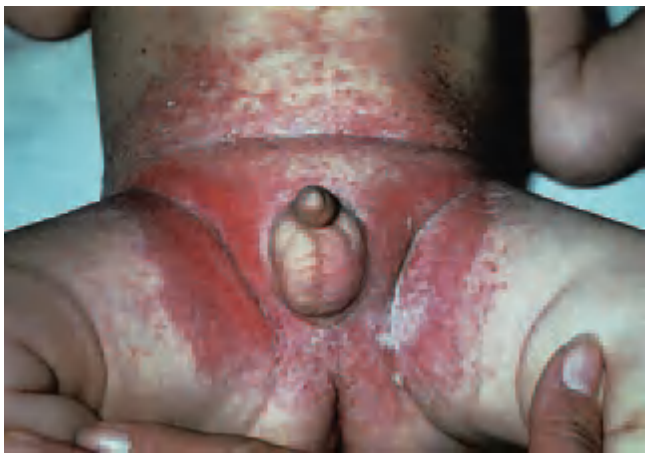

Fig. 52.8 Langerhans' cell histiocytosis in an infant showing typical eruption on the abdomen and groins mimicking seborrhoeic dermatitis and napkin eruption.

Ears. Disease of the ears is common [46], with involvement of external and middle ear and mastoid. This may present with persistent aural discharge due to skin involvement or polypoid involvement of the external auditory canal. If the middle ear or mastoid is involved, deafness is common.

Oral. The commonest presentation in the mouth is with periodontal involvement, affecting particularly the lower molar areas [47]. There may be destruction of the alveolar ridge with infiltration of the gums with LCH cells resulting in the teeth floating free from their sockets (Fig. 52.12). Premature eruption of the teeth may be a presenting sign [48]. Mandible involvement is frequently observed in adults, with a palpable tender mass over the affected area. This is usually associated with oral involvement.

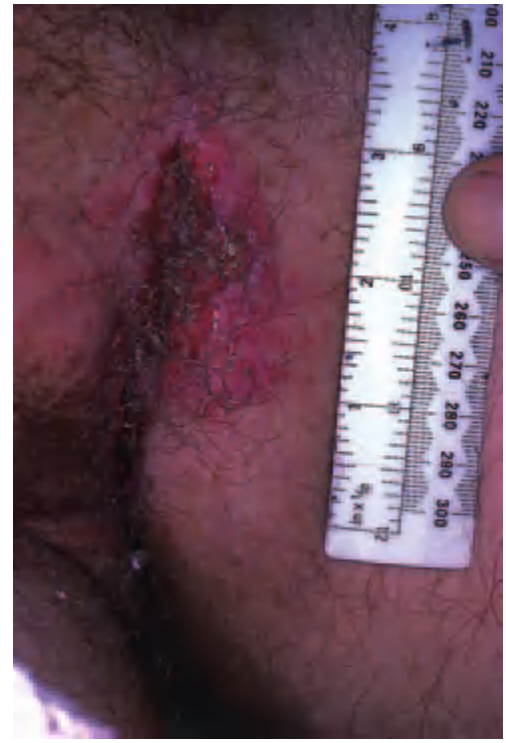

Fig. 52.9 Langerhans' cell histiocytosis in an adult showing a characteristic erosive lesion in the groin.

Bone marrow. Involvement may be occult or there may be pancytopenia. When bone marrow involvement is severe, splenomegaly is generally present.

Lungs. Primary pulmonary LCH is rare and is usually seen in young or middle-aged adults. In adult patients, smoking is invariably associated with lung involvement, and in any adult smoker with LCH the lung should be examined for possible involvement. Computed tomography is usually more informative in such patients as it identifies lung disease at an earlier stage than chest X-ray. Diagnosis is established by lung biopsy or bronchial lavage, as LCH of the lungs may be impossible to differentiate from other chronic interstitial lung diseases on clinical and radiographic findings.

Pulmonary signs and symptoms are non-specific and are rarely observed until there is frank dysfunction, with dyspnoea, tachypnoea and subcostal recession. Pain and sudden dyspnoea may indicate a pneumothorax due to rupture of a peripheral bulla. Pneumothoraces are common [49], but up to 23% may be asymptomatic.

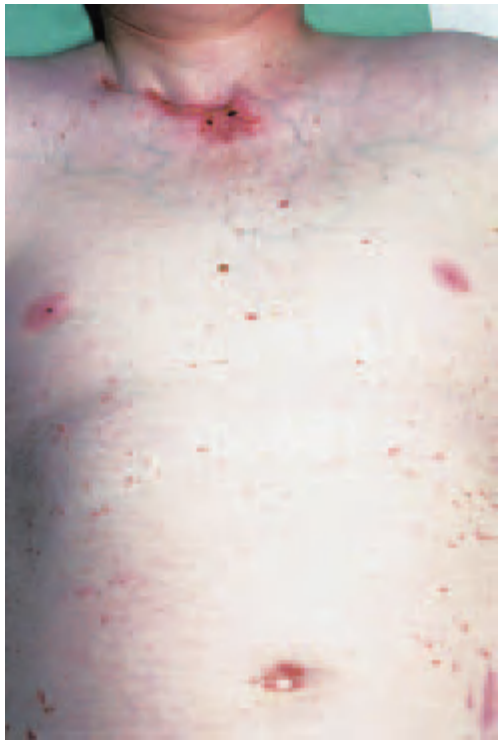

Fig. 52.10 Langerhans' cell histiocytosis in an adult with multisystem involvement. Scarring is present at sites of previous fistulae from underlying involved lymph nodes. Active skin lesions are scattered over the chest. These are scaly, erythematous, maculopapular lesions. Marked striae are the result of high-dose steroids used in therapy.

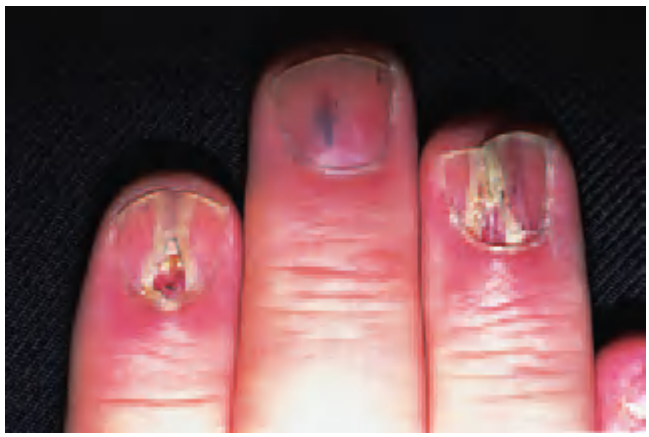

Fig. 52.11 Langerhans' cell histiocytosis: involvement of nails in an adult patient showing nail fold destruction. (Courtesy of Dr D.A.R. de Berker, Bristol Royal Infirmary, Bristol, UK.)

Gastrointestinal tract. Liver involvement is very common as part of multisystem LCH, producing hepatomegaly or ascites. Cholestatic jaundice may be a late feature due to fibrotic obstruction of the biliary tree. Diarrhoea may be the result of infiltration of the lamina propria by LCH cells or may be caused by abnormal bile acid metabolism or

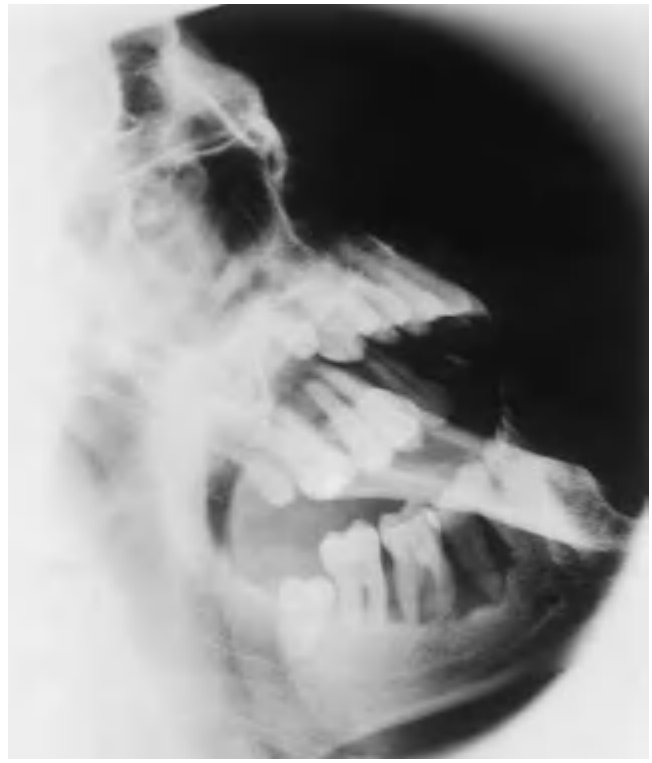

Fig. 52.12 Radiograph of the jaw of an adult with oral involvement in Langerhans' cell histiocytosis. The alveolar bone shows marked reabsorption and the teeth have become detached and appear to be floating.

infection within the gastrointestinal tract. In children, even mild involvement of the gastrointestinal tract, which produces no overt symptoms of diarrhoea, may still cause failure to thrive due to mild malabsorption.

Central nervous system. Diabetes insipidus may be the presenting feature of LCH. Other focal lesions may occur, commonly affecting the cerebellum, temporal lobe and occipital lobe. Intracerebral disease is more frequently seen with bone involvement of the skull. A cerebellar syndrome with ataxia, dysarthria and choreoathetoid movements may be a late sequela of LCH. This is caused by progressive cerebellar atrophy. Biopsies of the cerebellum have so far failed to show infiltration with LCH cells but only gliosis.

Bone. Solitary bone involvement with LCH is common but occasionally goes undiagnosed. The commonest sites are the bones of the calvarium, but femur, scapula, rib, mandible and vertebra are often affected [50]. Lesions may be asymptomatic or may present with swelling over the affected bone, pain or pathological fracture. Radiography is better than radionucleotide studies in detecting bone involvement in LCH [51]. Lesions appear as osteolytic areas that are sharply demarcated and may have a

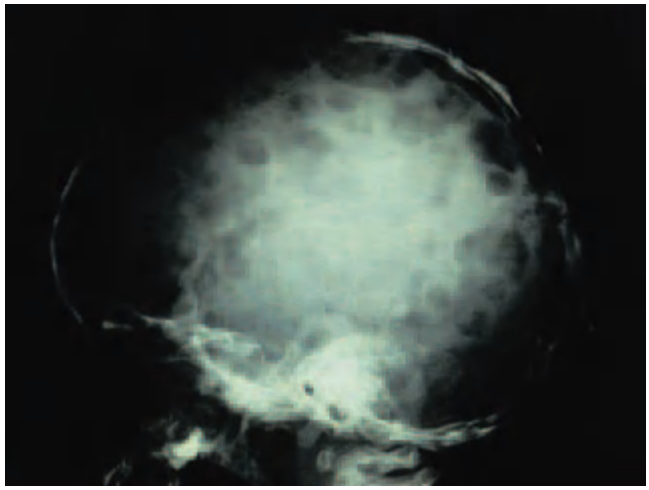

Fig. 52.13 Multiple osteolytic lesions in the skull of an infant with Langerhans' cell histiocytosis.

scalloped border (Fig. 52.13) [52]. When vertebrae are affected, the structural bone is lost and the vertebra may collapse. Spinal cord compression resulting from vertebral collapse has been reported with LCH [24]. Healing of bone lesions is usually seen as peripheral sclerosis of the lytic lesion. Radiographic changes may still be evident for long periods after the disease has been adequately treated or has undergone spontaneous remission.

Endocrine system. Diabetes insipidus is the commonest endocrine problem, the incidence in children with multisystem disease ranging from 22 to 50% [53–55]. Diabetes insipidus may result from pituitary involvement or hypothalamic involvement. Magnetic resonance imaging may show thickening of the pituitary stalk with recent-onset disease.

Short stature in children with LCH has been associated with growth hormone deficiency, which may be secondary to hypothalamic involvement [56]. Some of these children respond to treatment with growth hormone [54,56]. Hypogonadism with delayed puberty and thyroid involvement have also been reported [57,58].

Prognosis. Three important, independent, prognostic indices in LCH are the age of the patient, the extent of the disease and the presence of vital organ failure.

Children under the age of 2 years with multisystem disease have a much poorer prognosis than older children. In a study by Komp *et al.* [58], the mortality in children under the age of 2 years with disseminated LCH was 37% compared with 16% in the group aged over 2 years.

Lahey [59] found a positive relationship between increased mortality rate and widespread organ involvement, but Greenberger *et al.* [60] found that organ failure was a better prognostic indicator than organ involvement. Both Lahey and Greenberger *et al.* [59,60] looked at prognosis in relation to mortality, but since LCH is a reactive rather than a malignant disease, prognosis should consider morbidity as well as mortality. The long-term sequelae of LCH can be related to both disease and treatment. Morbidity caused by the disease itself may be minor (e.g. skin lesions) or there may be major consequences if organs such as the liver, lungs and brain are damaged. Treatment with cytotoxic reagents may result in sterility and may cause leukaemias and other secondary malignancies.

Diagnosis. Pathological diagnosis is most important as many diseases can clinically mimic LCH, and S100 staining or even CD1a staining is insufficient to establish a diagnosis of LCH if the histological picture is not consistent. The differential diagnosis in cutaneous LCH includes seborrhoeic dermatitis, juvenile xanthogranuloma, xanthoma disseminatum and benign cephalic histiocytosis. In disseminated LCH there may be diagnostic problems with familial haemophagocytic lymphohistiocytosis, sinus histiocytosis with massive lymphadenopathy (SHML) and virus-associated haemophagocytic syndrome. Histological examination of tissue biopsy with specific marker studies is usually sufficient to differentiate LCH from these other conditions.

Treatment. Treatment depends on the extent and severity of disease. Patients with single-system bone or skin disease have a good prognosis and often require no or only limited treatment. In one study, McLelland *et al.* [40] showed that in 14 patients with single-system disease, eight required no treatment. In isolated bone disease, curettage to establish the diagnosis may be curative. In weight-bearing bones that are symptomatic, intralesional steroid injections are effective [9]. If vital structures are compromised, such as the optic nerve or spinal cord, low-dose radiotherapy (700–1000 cGy) can be given.

In single-system skin disease, topical treatment with 20% nitrogen mustard is effective [61]. Psoralen and UVA (PUVA) therapy may be useful for those patients who do not tolerate topical nitrogen mustard or fail to respond adequately. Recent reports have shown a good response of isolated skin disease to thalidomide [62].

In multisystem LCH where there is evidence of organ dysfunction, systemic chemotherapy is indicated. Treatment in children should initially be with prednisolone 2 mg/kg for a short course of about 2 months, with dose being adjusted to disease response [40]. Adults tend not to respond to systemic steroids and often suffer severe side effects from their use. In unresponsive disease, disease in adults or more aggressive disease, a number of chemotherapeutic agents have been tried, mainly the vinca alkaloids, especially vinblastine, but also methotrexate and 6-mercaptopurine in combination with prednisolone. Response rates of about 50–70% can be achieved using

these agents. Evidence suggests that the epipodophyllotoxin etoposide as a single drug is better than other drugs tested [63], and ciclosporin and IFN-α have also been beneficial [64]. 2-Chlorodeoxyadenosine, a purine analogue with antiproliferative effects on histiocytes and lymphocytes, has been used in recurrent or high-risk LCH. Treatment is with 5–7 mg/m^2 daily for 5 days every 21–28 days. In a recent study of six children with LCH, five patients remained in clinical remission with a follow-up of 15 months [65].

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Class IIa histiocytosis: histiocytoses involving cells of the dermal dendrocyte lineage

Class IIa histiocytoses are non-malignant diseases in which mononuclear phagocytic cells with the dermal dendrocyte phenotype accumulate in various tissues where they may or may not cause symptoms.

In many of these diseases the histological features are of a xanthogranulomatous reaction in the skin. This pattern is seen in juvenile xanthogranuloma, benign cephalic histiocytosis, generalized eruptive histiocytosis, xanthoma disseminatum and necrobiotic xanthogranuloma. In reticulohistiocytosis, the histological features are dominated by the presence of eosinophilic histiocytes with finely granular cytoplasm giving a ground-glass appearance. In some, such as progressive nodular histiocytosis, the cells have a more spindle-shaped appearance in a storiform pattern, particularly as the lesions progress.

Recent histopathological studies have suggested that benign cephalic histiocytosis represents a clinical variant of a xanthogranulomatous reaction rather than being a distinct entity in its own right. In one study [1], biopsies from benign cephalic histiocytosis, generalized eruptive histiocytosis, papular xanthoma and juvenile xanthogranuloma were examined in an observer blinded fashion. In all specimens examined, three distinct patterns of histiocyte proliferation were observed—papillary dermal, lichenoid and diffuse. Benign cephalic histiocytosis, generalized eruptive histiocytosis and early non-xanthomatous juvenile xanthogranuloma could not be specifically differentiated on histopathological grounds. This study certainly suggests that benign cephalic histiocytosis may be a localized form of generalized eruptive histiocytosis or an aborted phase of juvenile xanthogranuloma. In a further study, sequential biopsies were taken from a patient with solitary giant xanthogranuloma and from a patient with benign cephalic histiocytosis. In both cases, early stages of the disease showed infiltration with histiocytes positive for Ki-M1p, HAM56 and factor XIIIa. This was followed by a polymorphic infiltrate of mononuclear and multinuclear histiocytes, which were CD68 positive. This study suggests that both entities are variants of a xanthogranulomatous reaction [2]. In one case report, a 2-year-old girl with clinical, histopathological and ultrastructural benign cephalic histiocytosis developed a varicella-zoster infection with evolution of her skin disease both clinically and histologically to juvenile xanthogranuloma [3]. In a further report of a child with generalized eruptive histiocytosis, where the diagnosis was made on clinical, histological and ultrastructural grounds, the disease progressed with the growth of yellowish confluent papules and the development of diabetes insipidus. At this stage the diagnosis was changed to xanthoma disseminatum [4].

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Dermatofibroma

This benign, nodular, dermal lesion is discussed in Chapter 53.

Juvenile xanthogranuloma

SYN. NAEVOXANTHOENDOTHELIOMA; XANTHOMA MULTIPLEX; JUVENILE XANTHOMA; MULTIPLE ERUPTIVE XANTHOMA IN INFANCY; CONGENITAL XANTHOMA TUBEROSUM; XANTHOMA NAEVIFORME; JUVENILE GIANT CELL GRANULOMA

Definition. Juvenile xanthogranulomas are benign tumours of histiocytic cells that occur predominantly in infancy and early childhood and spontaneously regress.

Aetiology. The aetiology of juvenile xanthogranuloma is unknown. The tumours represent accumulations of

differentiated histiocytes. These cells express the phenotype of the dermal dendrocyte, although a recent study has suggested that the cell of origin could be the plasmacytoid monocyte [1]. The appearance of giant cells and foamy lipid-laden histiocytes occurs late, and they are almost certainly secondary events, possibly in response to cytokine production by the lesional histiocyte. Serum lipid levels are normal. Conflicting reports have suggested that juvenile xanthogranuloma can be associated with cytomegalovirus infection. A recent study by Vasconcelos *et al.* [2] has demonstrated early and late cytomegalovirus antigens in some histiocytes in a case of oral juvenile xanthogranuloma.

Pathology. An established lesion shows a mixed cellular dermal infiltrate with histiocytes, lymphocytes, eosinophils and occasional neutrophils and plasma cells. This extends from the epidermis into the subcutaneous fat but epidermal involvement is rare. A typical feature is the presence of giant cells with a wreath-like arrangement of nuclei (Touton giant cells).

In very early lesions, only spindle-shaped fibrohistiocytic cells are seen. In older lesions, foamy lipid-laden histiocytes appear, and resolution is marked by gradual replacement by fibrous tissue. A spindle cell variant of juvenile xanthogranuloma has been described [3].

Immunocytochemical examination in most cases shows that lesional cells are positive for lysozyme, α_1-antichymotrypsin, CD68, fascin, factor XIIIa and may express HLA-DR and CD4, but are negative for S100 protein [4]. However, Tahan *et al.* [5] found a small population of S100 dendritic cells in juvenile xanthogranuloma, which they felt were important in pathogenesis, and Kraus *et al.* [1] have shown reactivity to polyclonal S100 in six of eight specimens they examined. Cells are always CD1a negative.

At the ultrastructural level, the lesional histiocytes do not exhibit Birbeck granules but do show complex interdigitation of the cytoplasmic membrane [6].

Incidence. Half of the cases of juvenile xanthogranuloma have been reported in infants less than 6 months of age. Lesions may occur in children over 3 years of age and cases have been reported in adults [7]. There is no sex association and no familial tendency. Juvenile xanthogranuloma is 10 times more frequent in white than in black people.

Clinical features. The characteristic clinical features of juvenile xanthogranuloma are its onset in infancy, sudden appearance of lesions and spontaneous regression. Most patients develop single lesions, but in others several lesions may develop and occasionally hundreds of lesions may be present. In one case report, a generalized lichenoid variant of xanthogranuloma was described. The eruption consisted of small, flat, shiny papules, which resolved spontaneously [8]. The lesions most commonly occur on the upper part of the body, particularly affecting the face, neck, scalp and upper trunk (Fig. 52.14). Lesions may occur in the oral mucosa with or without skin involvement [9]. They generally start as reddish-yellow papules, which may enlarge up to 1 cm in diameter and evolve into yellow–brown plaques and macules. The lesions are firm and rubbery and can develop surface telangiectasia. Larger lesions, up to 2–3 cm in size, have been reported [10] and ulceration and satellite lesions have been described [11]. Resolution occurs spontaneously over a period of months or years, leaving small atrophic scars. There are no subjective symptoms.

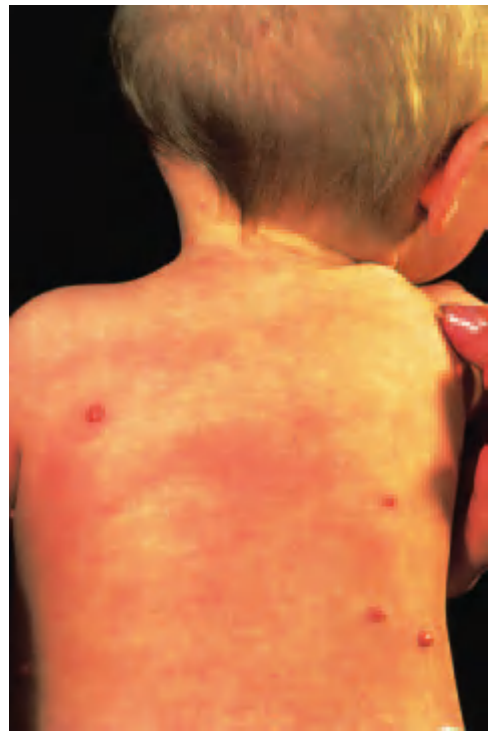

Fig. 52.14 Juvenile xanthogranuloma in an infant with typical lesions on the back.

Visceral involvement may occur in lung, liver, spleen, testes [12], pericardium, gastrointestinal tract, kidney [13], deeper soft tissues [14] and central nervous system. Eye involvement occurs in up to 10% of cases [15] and may lead to secondary glaucoma or may be mistaken for a malignant tumour, such as melanoma or neuroblastoma. The iris is most commonly affected, producing haemorrhage into the anterior chamber, which may result in secondary glaucoma. Infiltration of the orbit, iris, ciliary body and episclera may occur, with unilateral glaucoma, recurrent hyphaema, uveitis, heterochromia, iritis or severe and sudden proptosis [16]. Eye lesions may precede the appearance of skin lesions. Central nervous system involvement is rare but several reports have recently been

published. Lesions may present as isolated or multiple tumours of the brain involving the cortex and cerebellum [17,18], and extensive involvement of cranial nerves has been reported [19]. Central nervous system involvement may occur with or without cutaneous involvement.

Juvenile xanthogranuloma has been associated with neurofibromatosis [20], Niemann–Pick disease [21], myelogenous leukaemia [22], lymphocytic leukaemia [23], urticaria pigmentosa [24] and LCH [25].

Prognosis. Juvenile xanthogranuloma is a self-healing tumour and lesions resolve in 1–5 years.

Diagnosis. Juvenile xanthogranuloma can be differentiated from xanthomas by the distribution of the lesions and the absence of lipid abnormalities. Papular urticaria can be distinguished by the symptomatic nature of the lesions and histology. The major difficulty in clinical diagnosis is with the nodular forms of LCH. Histology and immunocytochemistry will easily differentiate the two disorders.

Treatment. No treatment is necessary for the cutaneous lesions as they are self-healing. Where treatment is indicated in ocular and central nervous system lesions, surgery or radiotherapy gives good results [26]. In patients with symptomatic visceral involvement, chemotherapy with vinca alkaloids has been used successfully [27].

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Multicentric reticulohistiocytosis

SYN. RETICULOHISTIOCYTIC GRANULOMA; LIPOID DERMATOARTHRITIS; GIANT CELL HISTIOCYTOMA; RETICULOHISTIOCYTOMA CUTIS; MULTICENTRIC GIANT CELL RETICULOHISTIOCYTOSIS

Definition. This is a rare histiocytic proliferative disease in which joints, skin and mucous membranes are affected [1]. The arthropathy usually precedes nodular skin involvement and mucosal infiltration. Other organs may be involved and 20% of patients have an associated internal malignancy. This must be differentiated from solitary or multiple reticulohistiocytomas that are restricted to skin with neither associated arthropathy nor internal malignancy.

Aetiology. Pathogenesis is unknown. The cells involved are phagocytic histiocytes, and the disease is considered to be a reactive histiocytosis. No infective agent has been implicated but there is evidence of exposure to tuberculosis in some patients. In one study, 33% of patients had evidence of exposure to tuberculosis and 5% of patients had active tuberculosis on clinical examination [2]. There is no recorded genetic link. Those cases with internal malignancy have no clinical or pathological differences from those without associated malignancy.

Pathology. The characteristic pathological picture in the skin and mucous membranes is of infiltration by

mononucleated and multinucleated giant cells with voluminous ground-glass cytoplasm. In early lesions, the predominant infiltrating cells are histiocytes, lymphocytes and eosinophils, with few giant cells, but the giant cell infiltrate quickly follows. The giant cells are large (100 μm) with 1–20 nuclei. The cells are periodic acid–Schiff (PAS) positive and contain variable amounts of lipid and free or esterified cholesterol. In older lesions, fibrosis usually signals regression of the lesions, with a reduction in the inflammatory cell infiltrate.

Recent electron microscopic studies have shown type IV collagen inclusions in multicentric reticulohistiocytosis. These inclusions were both intracytoplasmic and extracytoplasmic. Such inclusions are usually found in lymphohistiocytic neoplasms, suggesting that multicentric reticulohistiocytosis is a proliferative rather than an inflammatory disorder [3].

Immunocytochemical studies show a histiocytic phenotype of the cells, which are positive for acid phosphatase, ATPase, lysozyme, α_1-antitrypsin [4] and factor XIIIa. The cells are also positive for vimentin, CD68 and CD45, but negative for CD1, S100 and CD34 [5]. Cells contain TNF-α, IL-1β and IL-12 [6]. Electron microscopic studies have shown that the cells contain dense bodies, coated vesicles, fat droplets in limiting membranes and myeloid bodies [7].

Clinical features. The disease typically affects women, with a male to female ratio of 1 : 3 [8]. It is a disease of middle age, and rarely affects children [9] and adolescents. Some 60% of patients present with polyarthritis, which typically affects the hands. The interphalangeal joints are affected with symmetrical, erythematous, deforming polyarthritis, which ultimately results in shortening of the fingers and mutilation (Fig. 52.15). Other joints may be involved, including the knees, shoulders, wrists, hips, ankles, feet, elbows, spine and temporomandibular joints. Radiography of the affected joints shows destruction of the articular surfaces, with bone resorption and eventually secondary osteoarthritis [10].

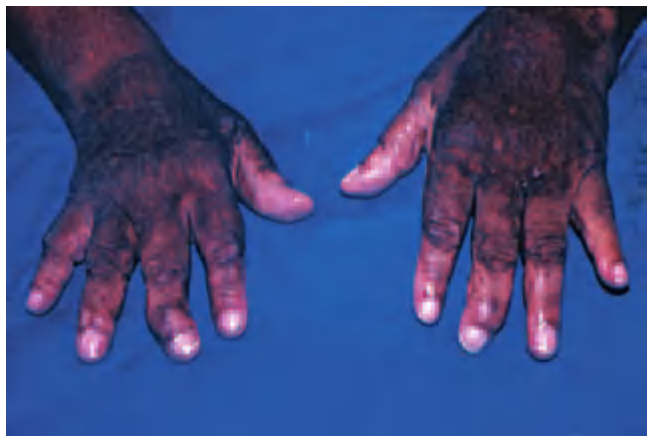

Fig. 52.15 Multicentric reticulohistiocytosis showing the characteristic skin changes, with multiple firm papular lesions on the sides of the fingers and obvious destructive arthropathy. (Courtesy of Professor N. Saxe, Groote Schuur Hospital, Cape Town, South Africa.)

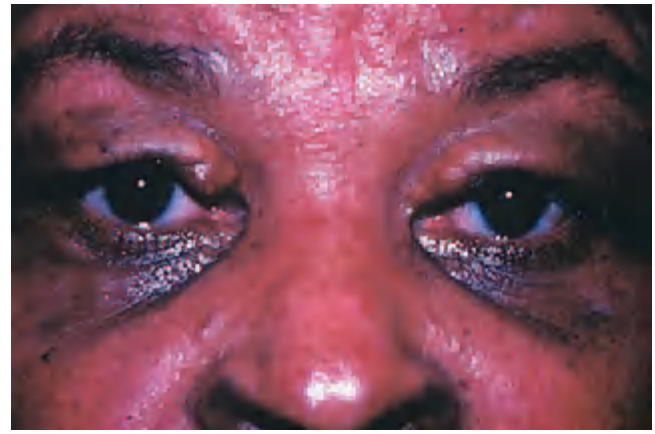

Fig. 52.16 Multicentric reticulohistiocytoma with characteristic lesions around the eyes. (Courtesy of Professor N. Saxe, Groote Schuur Hospital, Cape Town, South Africa.)

The classical skin lesions are firm brown or yellow papules and plaques, which predominantly affect extensor surfaces, particularly on the hands and forearms. The face (Fig. 52.16), scalp, hands and ears are often affected but involvement of the lower trunk and legs is rare. Coral bead-like lesions may occur around the nail folds, which may result in nail dystrophy. Skin lesions are of variable size and rarely ulcerate. Large nodular lesions in proximity to affected joints and cystic swellings of tendon sheaths may occur. About 25% of patients complain of pruritus associated with skin lesions. Diffuse cutaneous reticulohistiocytosis without arthropathy [9] and isolated reticulohistiocytomas [11] have been described. The cutaneous lesions have the same histology as lesions in multicentric reticulohistiocytosis but are not associated with joint problems or neoplasms.

More than 50% of patients have mucosal involvement affecting the mouth, gingiva, pharynx, larynx and sclera. Characteristically, the lips and tongue are involved [12], and 30% of patients have abnormalities of serum lipids. Laboratory findings are normal with a negative rheumatoid factor. Even in the most active stages of the disease, the erythrocyte sedimentation rate is only marginally elevated.

Constitutional symptoms of pyrexia and weight loss may occur. Involvement of bone marrow, skeletal muscle, lymph nodes, heart, pericardium, lungs, pleura, bones, liver, duodenal mesentery and kidney have been reported. Deaths have occurred with cardiac involvement [13]. Multicentric reticulohistiocytosis has been reported in association with Sjögren's syndrome [14] and thyroid involvement [15].

Around 20% of patients have been found to have an associated internal malignancy. The commonest tumours are gastric, ovarian, breast and uterine carcinomas, myeloma [16], melanoma [17] and lymphomas. Rare case reports have described Ki-1 lymphoma occurring in association with multicentric reticulohistiocytosis [18]. Myelodysplastic syndrome has been reported in one patient with multicentric reticulohistiocytosis, although this patient had been treated with cytotoxic drugs for many years and the myelodysplasia may have been drug related [19]. The diagnosis of multicentric reticulohistiocytosis precedes that of the neoplasm in most cases, and the disease may relapse with recurrence of the neoplasm [20].

Prognosis. The prognosis is good if there is no systemic malignancy, the disease becoming quiescent in 7–8 years. Fatal cardiac involvement may occur with widespread systemic involvement [13]. It does, however, leave considerable morbidity, with a crippling arthropathy and scarred skin.

Diagnosis. Biopsy of skin nodules helps to differentiate multicentric reticulohistiocytosis from eruptive xanthomas and juvenile xanthogranulomas. The disease can usually be clinically differentiated from other disorders involving cutaneous nodules and arthritis (e.g. rheumatoid arthritis, sarcoidosis, gout and xanthomatosis).

Treatment. No treatment is of consistent value in this disease. Systemic steroids may be successful for brief periods but their long-term value is uncertain. Combination of systemic steroids with azathiopine has been used with success [21]. Non-steroidal anti-inflammatory agents have no effect on the arthropathy. Immunosuppressive drugs give variable results. Cyclophosphamide is reported to give high success rates [22], and ciclosporin has been reported to give good results [23].

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Benign cephalic histiocytosis

SYN. PAPULAR HISTIOCYTOSIS OF THE HEAD

This is a rare self-limiting histiocytosis that typically starts at the end of the first year of life [1]. Erythematous papules, nodules and macules develop on the cheeks and spread to the forehead, earlobes and neck. The lesions, which are asymptomatic, gradually become reddish-brown and may spread onto the trunk, upper limbs and rarely the buttocks. Mucous membrane involvement has not been described.

No sex predisposition has been reported. The disease is self-limiting, and in 13 cases the mean age at resolution was 9 years [2]. In one case report, a 5-year-old girl developed diabetes insipidus 1 year after presenting with typical benign cephalic histiocytosis. Imaging demonstrated infiltration of the pituitary stalk [3]. Histologically, the epidermis is thinned over a well-circumscribed histiocytic infiltrate in the superficial and mid-dermis. In older lesions, a few giant cells may be present. The cells are S100 negative [4]. Electron microscopy shows that 5–30% of the infiltrating cells have cytoplasm rich in comma-shaped bodies and coated vesicles [2]. Dense bodies may be present and worm-like bodies have been described [5]. Since the condition is self-limiting, no therapy is indicated.

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Erdheim–Chester disease

SYN. UBER LIPOIDGRANULOMATOSE

This is a rare lipoid granulomatosis characterized by infiltration of viscera, bones, retroperitoneum and skin. It was first described by William Chester while working in the laboratory of Jakob Erdheim in 1930 [1] and the eponym was first used by Jaffe in 1972 [2].

Veyssier-Belot *et al.* [3] reviewed the literature on Erdheim–Chester disease in a comprehensive study of 59 patients. The age range was 7–84 years with a mean of 53 ± 14 years, and there was a male to female ratio of 33 : 26. The most common presentation is with chronic mild bone pain, particularly of the lower limbs. Radiography shows symmetrical sclerosis, typically affecting the long bones, with involvement of the diaphyseal and metaphyseal regions; 86% of reported cases have involvement of the long bones [4], with the distal femur, proximal tibia and fibula being most commonly affected [5]. Up to 30% of patients show lytic lesions of flat bones, which can cause problems in differentiating this disease from LCH.

Half of patients have extraosseous involvement involving the retroperitoneal space, lungs, heart, kidneys, liver, pituitary, central nervous system, orbit and skin. Approximately 30% of patients have exophthalmos, diabetes insipidus or retroperitoneal involvement. Retroperitoneal disease is often asymptomatic and may develop over many years. It may present with dysuria, abdominal pain, obstructive renal damage or renal artery stenosis [6]. Skin involvement is seen in about 20% of patients, usually presenting with xanthoma-like lesions, usually on the eyelids but occasionally on the trunk and submammary area. Two patients have been reported with cutaneous masses. Lung disease is seen in 35% of patients, with accumulation of histiocytes and fibrosis in a perilymphatic and subpleural pattern. It is generally asymptomatic and found on chest X-ray with diffuse interstitial fibrosis or infiltration. Advanced pulmonary involvement is associated with extensive fibrosis, which may result in cardiopulmonary failure. Prognosis tends to be poor despite treatment [7]. Pericardial involvement is uncommon and myocardial involvement has not been described, but three reported cases died of heart failure. Central nervous system involvement is seen in 15% of patients, presenting with ataxia, paraparesis, hemiparesis or change in mental state. Imaging has shown thickening of the dura, with infiltration extending into the cerebellum. More rarely, intracerebral masses have been described. A case of slowly progressive cerebellar syndrome, similar to that seen in LCH, has been reported in a 50-year-old patient with Erdheim–Chester disease associated with unilateral exophthalmos, secondary hypogonadism and skin lesions [8].

Histological examination shows a xanthogranulomatous infiltration by lipid-laden histiocytes within a mesh and surrounded by fibrosis. Touton giant cells and eosinophils may be prominent. Cells are positive for CD68 and factor XIIIa [6] but negative for CD1a and S100 [9]. In one study of a 35-year-old woman with Erdheim–Chester disease, clonality studies based on the *HUMARA* assay in paraffin-embedded tissue showed only random distribution of allele activation and thus no evidence of clonality [10].

A variety of treatments have been used in Erdheim–Chester disease, including IFN-α [11], corticosteroids, radiotherapy, vinblastine, vincristine, cyclophosphamide [3] and 2-chlorodeoxyadenosine [12], with variable responses. There is no clear consensus as to the best therapeutic regimen. Overall mortality is 57%, with death resulting from pulmonary, cardiac or renal failure [3].

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Fat-storing hamartoma of dermal dendrocytes

A single case report has described this entity [1]. The patient was a 30-year-old man who had a very large, circumscribed, red-brown plaque in the lumbosacral area. The plaque was composed of firm papules and nodules and was asymptomatic. The lesion had been present since birth and had slowly grown since that time.

Histology showed a slightly acanthotic epidermis and a Grenz zone, below which was a dense infiltrate of foamy histiocytes, which extended deep into the dermis. Occasional Touton giant cells were present. Lesional cells stained for factor XIIIa and vimentin and 40% of the cells labelled with Mac-387, a monoclonal antibody directed against monocyte-derived macrophages. S100 and CD1a staining were negative. Electron microscopy showed large histiocytic cells with convoluted nuclei filled with lipid droplets.

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Generalized eruptive histiocytoma

This is a rare cutaneous histiocytosis that mainly affects adults [1], although children with the disease have been reported [2,3]. Clinically, the disease presents as multiple symmetrical papules that occur on the face, trunk and proximal extremities. The papules are skin coloured, brownish or blue-red and tend to come up in crops, although they are not grouped. The number of lesions is variable but may reach hundreds. Mucosal lesions are rare. The lesions are asymptomatic and resolve spontaneously to leave a macular area of hyperpigmentation.

Histology shows a proliferation of monomorphic histiocytic cells in the upper and mid dermis. No giant cells or foam cells are present. Scattered lymphocytes may be present. Ultrastructural studies have shown that the histiocytic cells lack Birbeck granules but do have cytoplasmic laminated bodies [4]. These bodies are often clustered in the cytoplasm of the cells and each measure about 1.5 μm. They are not restricted to generalized histiocytoma but have been reported in congenital self-healing histiocytosis [5].

In one case report of a 4-year-old boy with generalized eruptive histiocytoma, diagnosed using clinical, histological and ultrastructural studies, the patient subsequently developed a new eruption of yellowish confluent papules with associated diabetes insipidus. Histology of the lesions and ultrastructure confirmed the diagnosis of xanthoma disseminatum. The authors suggest that generalized eruptive histiocytoma and xanthoma disseminatum are variants of a continuous spectrum of histiocytoses [3].

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Papular xanthoma

This is a rare histiocytic disorder that was first described in adults [1] and subsequently reported in children [2]. Whether it represents a separate clinicopathological entity or a variant of other xanthogranulomatous conditions is open to debate. Clinically it can resemble juvenile xanthogranuloma but has not been associated with systemic involvement or café-au-lait spots, and may resemble xanthoma disseminatum but papules do not coalesce and there is no predilection for flexures.

Clinically, papular xanthoma is characterized by 2–15 mm yellow or reddish-yellow papules affecting both skin and mucous membranes. The back and head are most commonly affected. There are marked clinical differences between papular xanthoma occurring in adults and children. Mucous membranes are affected in adults but this has not been reported in children. In adults progessive disease has been reported [3] but in children spontaneous resolution is the norm, with involution starting after weeks or months and being complete in 1–5 years, often leaving anetoderma-like scarring [4].

Histologically, there is an upper- and mid-dermal infiltrate of foamy histiocytes and giant cells. Few inflammatory cells are present. Histiocytic cells are positive for CD68 and factor XIIIa and negative for S100 and CD1a [2]. One case report in a 13-month-old boy demonstrated that the cells were CD68 positive but factor XIIIa negative. In such a rare condition, further studies are needed to confirm the dermal dendrocyte origin of lesional cells [5]. Electron microscopy shows similar changes to those seen in mature juvenile xanthogranuloma, with myeloid bodies filling the cytoplasm of the histiocytes with associated lysosomal inclusions, laminate bodies and lipid droplets.

No treatment is needed in children while none is effective in adults.

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Progressive nodular histiocytosis

SYN. PROGRESSIVE NODULAR HISTIOCYTOMA; SPINDLE CELL XANTHOGRANULOMA

This is a rare histiocytosis first described by Taunton *et al.* [1] in 1978. The eruption consists of two different types of lesions, superficial papules and deep nodules, both of which may number into hundreds [2,3]. Papules are 2–10 mm and yellow-orange (Fig. 52.17). Nodules are 1–5 cm and may be skin coloured or reddish-orange. Distribution is random with no predilection for the flexures. Lesions may occur in the oral cavity, larynx and conjunctival mucosa.

Over the years new lesions may develop and although patients remain in good general health, the eruption may be very disfiguring causing a marked reduction in quality of life.

Histologically, this is a dermal disease with neither epidermal involvement nor epidermotropism. Early lesions show an accumulation of xanthomatized and scalloped histiocytes with some infiltrating lymphocytes. In older lesions the histiocytes are spindle shaped and arranged in a storiform pattern. Occasional giant cells may be present. Cells are positive for CD68 and factor XIIIa and negative for S100 and CD1a [4].

Progressive nodular histiocytosis is not generally associated with systemic involvement or other disorders. In one case report, a 57-year-old man had suffered from progesssive nodular histiocytosis for 26 years and during that time had developed chronic myeloid leukaemia, hepatosplenomegaly, hypothyroidism, hyperuricaemia and hypocholesterolaemia, although the relationship between progressive nodular histiocytosis and the systemic disorders remains unclear [5].

Progressive nodular histiocytosis is a benign disease and no treatment has yet been shown to be effective in reducing the size of skin lesions or in inducing remission.

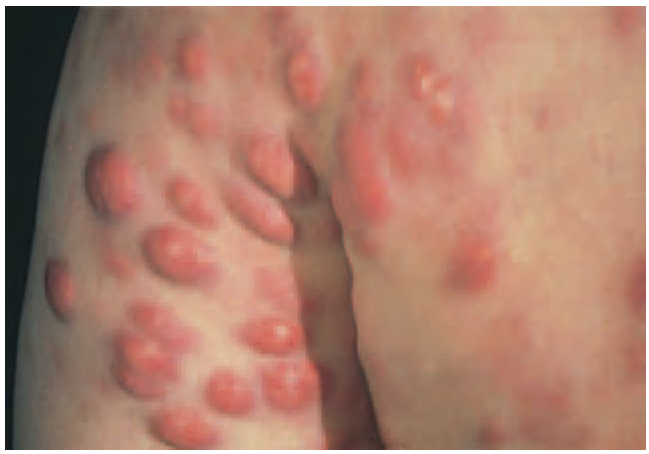

Fig. 52.17 Progressive nodular histiocytosis in a 48-year-old man with nodular lesions in the posterior axillary fold. (Courtesy of Professor J.M. Naeyaert, University Hospital, Gent, Belgium.)

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Xanthoma disseminatum

SYN. DISSEMINATED XANTHOSIDEROHISTIOCYTOSIS; MONTGOMERY'S DISEASE

This is a rare non-familial disease, characterized by proliferation of histiocytic cells in which lipid deposition is a secondary event. The disease predominantly affects male children and young adults, with involvement of the skin, mucous membranes of eyes and upper respiratory tract, the meninges and rarely other organs including liver, spleen and bone marrow [1–4].

The clinical lesions of xanthoma disseminatum are erythematous, yellow-brown papules and nodules, which are symmetrically distributed on the trunk, face and proximal extremities (Fig. 52.18). The lesions become confluent, especially in flexures, to form xanthomatous plaques, which may become verrucous (Fig. 52.19). In 30% of patients, the mucous membranes are affected, with particular involvement of the lips, pharynx, larynx, conjunctivae and bronchus. Respiratory tract involvement has been fatal in one reported case of a 61-year-old woman with involvement of large and medium-sized bronchi who died of acute respiratory failure [5]. Meningeal involvement is common, with infiltration at the base of the brain leading to diabetes insipidus in up to 40% of cases. Other manifestations of meningeal involvement are seizures and growth retardation. Intracranial involvement presenting as a discrete mass simulating glioma has been reported [6]. Progressive bone disease has been reported in xanthoma disseminatum [7,8], but this is a rare complication of the disease. One case report demonstrated hepatic involvement on computed tomographic

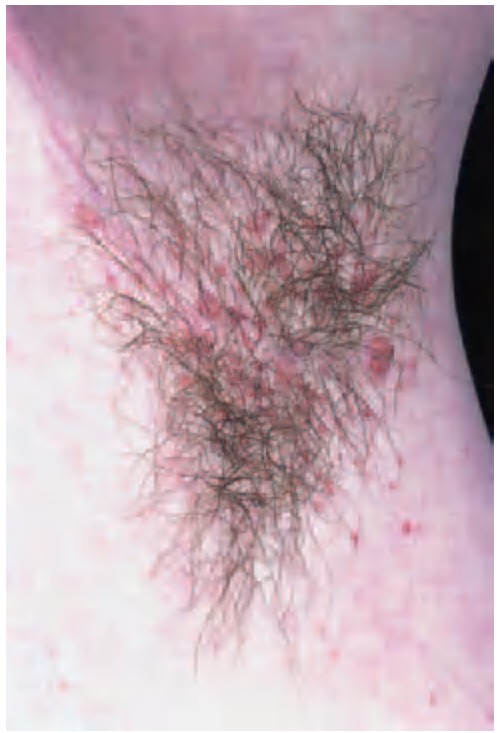

Fig. 52.18 Xanthoma disseminatum. (Courtesy of Dr R. Cerio, St John's Dermatology Centre, London, UK.)

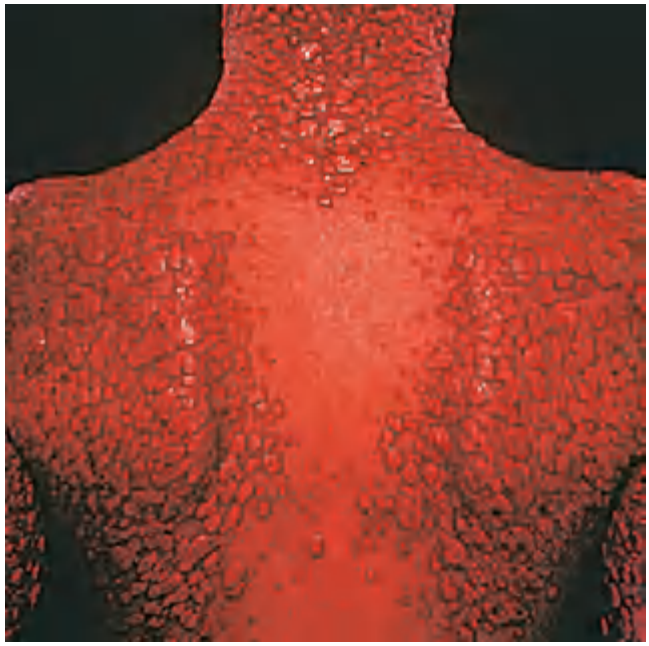

Fig. 52.19 Xanthoma disseminatum with verrucous lesions over the back of a 10-year-old boy.

examination [9]. Lytic bone lesions have been reported in a patient with xanthoma disseminatum, although the clinical features of the patient were atypical for this diagnosis [10].

A clinical variant of this disease was described by Halprin and Lorincz [11] under the name xanthosiderohistiocytosis. In this variant, there is diffuse infiltration of the skin, subcutaneous tissue and muscle, giving rise to sclerodermatous changes in the skin and muscle wasting. The foamy histiocytes that are involved contain significant amounts of iron, which gives the skin a greenish-brown colour.

Histologically, xanthoma disseminatum is a dermal disease, characterized by early infiltration of the dermis with spindle-shaped mononuclear cells, foamy histiocytes, giant cells, lymphocytes, polymorphs and eosinophils. Lesional cells in xanthoma disseminatum have irregular scalloped borders with extensive cytoplasm and ovoid vesicular nuclei. Cells label strongly with factor XIIIa and KP1 [12]. Iron and lipid can be detected in the histiocytes. In older lesions, more foamy histiocytes are evident and Touton giant cells may be observed. At the ultrastructural level, histiocytic cells contain myeloid bodies and membrane-bound fat droplets.

Xanthoma disseminatum is a self-limiting disease but may persist for years. Lesions are only mildly radiosensitive. Skin lesions of xanthoma disseminatum are disfiguring and patients often request treatment. The carbon dioxide laser has been used with good results [13]. Conjunctival involvement can be treated with surgery.

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Class IIb histiocytosis: histiocytoses involving cells other than Langerhans' cells and dermal dendrocytes

Diffuse plane xanthomatosis

SYN. ATYPICAL XANTHOMA DISSEMINATUM; DIFFUSE NORMOLIPAEMIC PLANE XANTHOMATOSIS

This is a rare non-lipaemic disease in which xanthomatous lesions develop in the skin in association with paraproteinaemia. Patients present with large, flat, plaque-like, xanthomatous skin lesions involving the eyelids, neck, upper trunk, buttocks and flexures [1,2]. Serum lipids are usually normal. About 50% of patients have a myeloproliferative disorder with multiple myeloma, granulocytic or lymphocytic leukaemia [3]. The majority of patients have a circulating paraprotein and have some abnormalities of serum complement [4,5].

The histological features include both xanthomatous and inflammatory elements. Accumulations of foamy macrophages infiltrate the dermis, with a distinct perivascular accentuation, and are associated to a variable degree with a mixed inflammatory cell reaction.

The condition arises as a result of perivascular deposition of lipoprotein–immunoglobulin complexes. Antilipoprotein antibodies are formed in association with paraproteinaemia [5]. Although serum lipid levels are usually normal, they may be raised, possibly due to reduced clearance of lipoprotein–antibody complexes. Treatment of this condition is that of the underlying myeloproliferative disease or paraprotein. Theoretically, plasma exchange should be of value but its use has not yet been reported.

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Familial haemophagocytic lymphohistiocytosis

SYN. FAMILIAL HAEMOPHAGOCYTIC RETICULOSIS; GENERALIZED LYMPHOHISTIOCYTIC INFILTRATION; FAMILIAL ERYTHROPHAGOCYTIC LYMPHOHISTIOCYTOSIS; FAMILIAL HISTIOCYTIC RETICULOSIS; FAMILIAL LYMPHOHISTIOCYTOSIS; FARQUHAR'S DISEASE

This is a rare reactive histiocytosis in which there is widespread infiltration of multiple organs by lymphocytes and mature histiocytes showing prominent cytophagocytosis. It is rapidly fatal in most patients. The incidence is 1.2 per million children [1], with a slight preponderance in boys. Three-quarters of cases are familial, and it is generally considered to be an autosomal recessive disease [2].

The gene responsible is unknown, but in one patient a constitutional inversion 9 (p23;q31) was observed in cells from bone marrow, lymphocytes and fibroblasts [3]. Studies have now identified mutations of the perforin gene on chromosome 9 in 10% of cases [4].

Fever is usually the first sign, with symptoms of an upper respiratory or gastrointestinal tract infection in 30%. Pallor, anorexia, vomiting and irritability are often noted. Hepatosplenomegaly is usually present at presentation and is progressive. Moderate lymphadenopathy is common. Around 50% of patients develop a transient, non-specific, maculopapular rash, which is often seen at times of high fever, but no persistent skin infiltration is seen. About 20% of patients have neurological symptoms, due to meningeal involvement, usually with convulsions but also with other signs of meningeal irritation.

Laboratory tests show anaemia, thrombocytopenia and raised liver enzymes and hyperbilirubin. Hyperlipidaemia (with elevation of triglycerides and very low-density lipoproteins) and hypofibrinogenaemia are common.

Immunological testing shows abnormalities of both the humoral and cellular limbs of the immune system. Natural antibody titres are low, antibody titres after previous immunization are low and there is an impaired response to primary immunization. All T-cell responses to mitogens, antigens and alloantigens are reduced. There is also a T-cell-suppressor factor, probably related to triglycerides, in the plasma of the patients [5]. Cytotoxic T-cell and natural killer cell activity is markedly reduced or absent in affected patients. Recent studies have shown mutations in a lytic granule constituent, perforin, in a number of individuals with familial haemophagocytic lymphohistiocytosis. A study of 34 families and linkage studies of a subset of consanguineous families indicates that perforin mutations account for 20–40% of cases of familial haemophagocytic lymphohistiocytosis and that the familial haemophagocytic lymphohistiocytosis I locus on chromosome 9 accounts for approximately 10% of cases [4]. The mutation in the perforin gene occurs at position 374, resulting in a premature stop codon. Other mutations include nonsense and missense mutations and deletions of amino acids [6].

A number of studies have now demonstrated hypercytokinaemia in this disease, with elevated circulating IFN-γ, TNF-α and IL-6 during active disease [7]. Serum levels of IL-6 have been shown to be of no prognostic importance [8]. Soluble CD8 has also been shown to be elevated, suggesting a role for cytotoxic T cells in the pathogenesis of this disease.

Histologically, the involved tissue shows a diffuse infiltrate with lymphocytes and mature histiocytes. The histiocytes exhibit active phagocytosis, especially of erythrocytes but also of leukocytes and occasionally platelets. The histiocytes stain positively for acid phosphatase, non-specific esterase, lysozyme and α_1-antichymotrypsin. A striking histological finding is lymphocyte depletion of lymph nodes, spleen and thymus.

Prognosis is poor, with median survival of 2–3 months [9] from diagnosis and 96% dying within 12 months. Central nervous system disease and persistently low natural killer cell activity are associated with poorer prognosis [10]. Long-term survivors have been reported after chemotherapy, but maintenance therapy is always required.

Initial treatment regimens used splenectomy, exchange transfusion [11] and chemotherapy [12], including vinblastine and intrathecal methotrexate. Recently, Henter *et al.* [13] reported a more successful regimen using etoposide and teniposide with prednisolone and intrathecal methotrexate until remission is achieved, followed by maintenance therapy with teniposide or etoposide.

Bone marrow transplantation and haemopoietic stem cell transplantation are now regarded as being the most effective treatments for this disease. Results are much better when HLA-identical siblings are used as donors. Studies have now shown that even partial engraftment is compatible with long-term remission [10,14].

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Familial sea-blue histiocytosis

This is a rare inherited abnormality of lipid metabolism [1] in which characteristic histiocytic cells are found in the bone marrow and other tissues. The histiocytes are identified by the May–Gruenwald stain, which colours the cytoplasmic granules a deep azure blue, hence the name 'sea-blue histiocytosis'.

Familial sea-blue histiocytosis in an autosomal recessive trait [2]. It usually presents in young adulthood with hepatosplenomegaly and thrombocytopenia, although the age at presentation ranges from 1 to 83 years. The skin, lungs, gastrointestinal tract, eye and nervous system may be involved. In the skin, patchy and irregular brownish-grey pigmentation of the face, upper chest and shoulders has been reported. In one case [3], skin involvement, with eyelid swelling and facial nodules, was confirmed histologically. In the eye, white stippled deposits may be observed at the margins of the fovea or macula, with discoloration of the macular region. Neurological symptoms occur early, with ataxia, epilepsy and dementia.

Sea-blue histiocytosis is not malignant, but it may disseminate and lead to death from liver or lung involvement. The biological abnormality is poorly understood, but the condition probably represents a storage disease in which glycolipid, phospholipid or both accumulate in histiocytic cells in various organs. Sea-blue histiocytes have also been described in chronic myelogenous leukaemia [4,5], adult Niemann–Pick disease [6], following the prolonged use of intravenous fat emulsions in children [7] and in partial sphingomyelinase deficiency [8].

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Hereditary progressive mucinous histiocytosis

This is a rare autosomal dominant genodermatosis, which was first described in 1988. Skin lesions appear in the first decade of life and gradually increase throughout life. Lesions consist of skin-coloured to red-brown papules that characteristically affect the nose, hands, forearms and thighs. Two sets of case reports have described mothers and daughters who have both presented with the disease [1,2]. Histologically, the epidermis is normal but within the dermis there are small collections of epithelioid histiocytes with telangiectatic vessels in the upper dermis in early lesions. As tumours develop, the infiltrate changes to nodular mid-dermal aggregates of tightly packed, spindle-shaped cells. In both early and established lesions, there is moderate to extensive mucin production by the epithelioid histiocytes and spindle-shaped cells. On electron microscopy, the spindle-shaped cells are shown to be dendritic histiocytes with abundant lysosomal storage organelles, myelin bodies and zebra bodies.

Immunohistochemically, these cells stain with CD68 and MS1 [3]. The condition is progressive, with gradual increase in numbers of tumours throughout life. These patients show no evidence of spontaneous resolution. No systemic involvement has been described and no treatment seems to have any impact on the disease [4].

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Malakoplakia

Malakoplakia is an immunodeficiency disease in which macrophages fail to phagocytose and digest bacteria adequately. The term 'malakoplakia', which means soft plaque, was adopted as a descriptive term [1].

Malakoplakia can affect many organs but most commonly affects the urinary and gastrointestinal tracts [2]. Cutaneous lesions are rare, non-specific and variable. Draining abscesses, sinuses, ulcers, fluctuant masses, isolated tender nodules and grouped papules have been reported. Mucous membranes may be affected, including the tongue [3] and cervix [4]. The disease generally runs a benign self-limiting course, but fatal cases have been reported [5].

Histologically, sheets of large histiocytic cells with abundant cytoplasm are present in the skin, affecting any level from epidermis to subcutaneous fat. The cells have fine eosinophilic granules in their cytoplasm and are referred to as Hansemann cells. They also contain one or more round basophilic inclusion bodies (Michaelis–Gutmann bodies). Michaelis–Gutmann bodies are 5–15 μm and stain positively with PAS, von Kossa stain (for calcium) and Perls ferrocyanide reaction (for ferric iron). They are considered pathognomonic for this disease and are thought to represent abnormal degradation of bacteria, with calcium and iron deposited on the remaining glycolipid.

The commonest bacterium found in this disease is *Escherichia coli* [6–8], although *Staphylococcus aureus* has also been cultured [9]. Recently, mycobacteria have been identified in two cases of cutaneous malakoplakia using polyclonal anti-*Mycobacteria bovis* antibodies [10]. In some patients, the disease is related to drug-induced immunosuppression [11]. In one patient [6], intracellular cyclic guanosine monophosphate (cGMP) levels were found to be low, and *in vivo* and *in vitro* treatment of the cells with bethanechol chloride, a cholinergic agonist, increased cGMP and restored their bactericidal activity.

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Necrobiotic xanthogranuloma

The syndrome of necrobiosis with xanthomatous granulomas and an associated paraprotein has been recognized since 1966 [1–3], but it was not until 1980 that it was recognized as a distinct dermatosis [4].

The characteristic clinical lesions are periorbital nodular and ulcerative lesions, which have the reddish-yellow colour of xanthomas (Fig. 52.20). On the trunk and limbs,

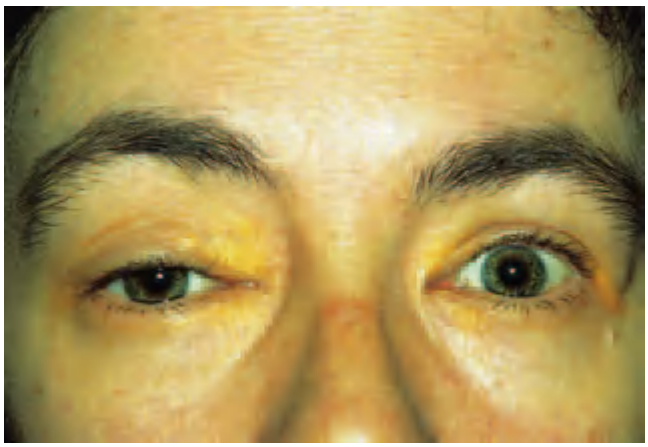

Fig. 52.20 Early lesions of necrobiotic xanthogranuloma with characteristic distribution in the periorbital area. (Courtesy of Dr A. Layton, Leeds General Infirmary, Leeds, UK.)

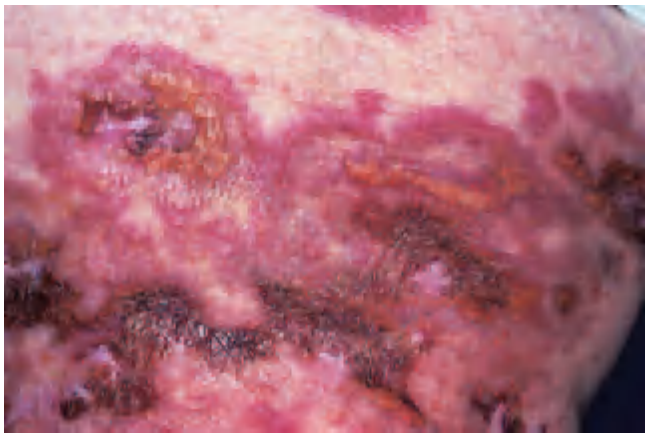

Fig. 52.21 Established lesions of necrobiotic xanthogranuloma on the abdomen showing xanthomatous plaques and atrophy. (Courtesy of Dr P. Holt, University Hospital, Cardiff, UK.)

subcutaneous nodules and xanthomatous plaques are present with atrophy and ulceration (Fig. 52.21). The eyes are often affected with conjunctivitis, keratitis, uveitis, iritis and proptosis. Blindness has been reported in two affected patients [4]. Systemic symptoms have been reported, including nausea, vomiting, fatigue, epistaxis, back pain and Raynaud's phenomenon. Atypical forms of necrobiotic xanthogranuloma have been reported, including solitary tumours of the skin [5].

The majority of cases have an associated paraprotein, usually an IgG κ or λ monoclonal protein. In a series of 22 patients, 16 had IgG monoclonal protein, three had multiple myeloma, three had cryoglobulinaemia and one had normal serum protein electrophoresis [6].

Decreased levels of C1 inhibitor have been reported in some patients with necrobiotic xanthogranuloma, occasionally associated with angio-oedema. Immune complex formation resulting from autoantibodies against the paraproteins have been implicated in the depletion of C1 inactivator [7].

Histologically, confluent granulomatous masses are present as either sheets or nodules, replacing much of the dermis and extending into the subcutaneous tissue [8]. Hyaline areas of necrobiosis separate individual nodules. Numerous giant cells are present, with Touton cells and bizarre angulated giant cells. Cholesterol clefts, lymphoid nodules (some of which develop germinal centres) and perivascular aggregates of plasma cells are frequent features. Less common, but characteristic when present, are palisading cholesterol cleft granulomas and xanthogranulomatous panniculitis. Granulomatous invasion of blood vessels with thrombosis has been described.

The pathogenesis of necrobiotic xanthogranuloma is unknown. Bullock *et al.* [9] suggested that the abnormal paraprotein becomes complexed with lipid and deposited in the skin, where it produces a foreign-body granulomatous reaction.

Treatment is generally directed to the associated paraproteinaemia. Alkylating agents such as melphalan, with or without prednisolone, have resulted in temporary clearing of the skin [10]. In one patient where cytotoxic drugs had failed, plasmapheresis reduced the level of the circulating monoclonal IgG and resulted in clearing of the skin [11]. Successful treatment with chlorambucil 2 mg/day for 7 months has been reported in a 51-year-old man with necrobiotic xanthogranuloma and associated paraproteinaemia [12]. Radiotherapy was successful in one case involving the eye [13].

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Sinus histiocytosis with massive lymphadenopathy

SYN. ROSAI–DORFMAN DISEASE

SHML is a rare histiocytic proliferative disorder that is defined by its histopathological features [1,2]. A registry of this disease now contains information on 423 patients [3].

SHML is currently considered to be a reactive rather than a malignant histiocytosis. An infectious cause has been suggested by the occurrence of fever and pharyngitis, which often precede the onset of SHML. However, the search for a possible infectious agent has been inconclusive. Some patients show evidence of Epstein–Barr virus infection while others have demonstrable infection with *Klebsiella rhinoscleroma* and *Brucella*, but these are not consistent findings. A recent study failed to show evidence of human herpesvirus 6 and 8 in skin lesions [4].

The onset of SHML is usually in young adults, with a range from birth to 74 years. The sex incidence is equal. Clinical presentation is usually with painless lymph node enlargement, which may reach massive proportions. About 90% of patients present with cervical adenopathy, the rest presenting with axillary, inguinal or mediastinal node enlargement. Fever, weight loss, malaise and night sweats have been reported, usually at presentation.

Extranodal involvement is common, with 43% of patients having at least one extranodal site of involvement. Skin is the most common extranodal site and may be involved without nodal disease. Pure cutaneous SHML may remain localized to the skin with no systemic involvement even with long-term follow-up [5]. Skin lesions are normally yellow, but may be violaceous or purple. Macular erythema, papules, nodules or infiltrated plaques have been reported. Scaling is often present and telangiectasia may be observed. Skin lesions may occur at any site [6]. Of patients with skin SHML, 50% have evidence of one or more additional extranodal sites, particularly involving the nasal cavity, with polyps and paranasal sinuses.

Other organs involved in SHML include bone, salivary gland, central nervous system, genitourinary system, lower respiratory tract, liver, gastrointestinal tract, heart and thyroid gland. Isolated central nervous system involvement in SHML is well recognized. In a report of 11 cases, seven were male and four female, with an age range of 22–64 years. Presentation was with headaches, seizures, numbness or paraplegia. Eight cases involved the cranial area and three the spinal cord. Most lesions were dura based and only one case involved the brain parenchyma [7]. Treatment of these patients was surgical, with one patient dying of surgical complications and nine showing no evidence of disease progression after a mean of 15 months follow-up.

Laboratory investigations usually show a mild normochromic normocytic anaemia or hypochromic microcytic anaemia with elevation of erythrocyte sedimentation rate. Serum proteins are often abnormal, with a low serum albumin and polyclonal gammopathy. Serum lipids are normal.

Histology of involved nodes reveals the pathognomonic features of SHML. The sinuses are expanded by large pale histiocytes. The histiocytes have abundant pale-pink cytoplasm and indistinct margins or may have glassy eosinophilic cytoplasm and well-defined cytoplasmic membrane. Nuclei are round or oval, usually with a single small nucleolus. Occasionally, multinucleate cells or cells showing nuclear atypia are present but mitoses are rare. Lymphophagocytosis or emperipolesis (phagocytosis of leukocytes, particularly lymphocytes) is always present, and less frequently intracytoplasmic plasma cells, neutrophils and red blood cells may be seen. Between the expanded sinuses, lymphocytes and plasma cells are present and reactive germinal centres are occasionally seen. Rarely, neutrophils are observed scattered throughout the involved node. Electron microscopy shows numerous lipid vacuoles and moderate numbers of lysosomes in the cytoplasm of the histiocytes. The surface of the cells is often thrown into complex convoluted villous processes.

In extranodal SHML, the histological picture is strikingly similar to that seen with nodal disease, with what appears to be abnormal lymph node architecture, dilated sinuses and reactive germinal centres in the extranodal site. Extranodal SHML usually shows more fibrosis and lymphophagocytosis.

On immunophenotypic analysis, SHML cells show pan-macrophage markers (EBM11, HAM56 and Leu M3, FcIgG and C3 receptors), monocyte markers (OKM5 and Leu M1), activation antigens (Ki-1, transferrin receptor and CD25) and lysosomal enzymes (lysozyme and α_1-antichymotrypsin) [8]. Surprisingly, however, these cells also display factor XIIIa, a marker of dermal dendrocytes [9], and the S100 antigen that is usually present on dendritic cells; and of two frozen samples tested, both were positive for NA1/34, one for OKT6 but neither for Leu 6. These three monoclonal antibodies react with different epitopes on CD1a, which is characteristic for Langerhans' cells. The exact cell lineage is therefore still uncertain.

The prognosis in SHML is reasonably good. In 238 patients followed for more than a year [6], 49 were well and clear of the disease, 126 had persistent disease, three had progressive disease and 21 patients died, although four deaths were unrelated to SHML. Poor prognostic features in this disease are immunological abnormalities and multiple extranodal sites of disease.

Many treatments have been tried, including the vinca alkaloids, etoposide, ciclosporin and X-rays but no ideal treatment has been identified and the response is poor [10]. A recent review of the literature showed that 32 of 40 patients received no treatment and underwent spontaneous regression. Radiotherapy gave complete remission in

three of nine patients. Surgical debulking was successful in eight of nine patients, resulting in complete remission. Chemotherapy was generally unsuccessful [11].

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Virus-associated haemophagocytic syndrome

SYN. VIRUS-INDUCED HISTIOCYTOSIS WITH ERYTHROPHAGOCYTOSIS; VIRUS-INDUCED HISTIOCYTIC MEDULLARY RETICULOSIS

Virus-associated haemophagocytic syndrome is a rare reactive histiocytosis in patients with an active viral infection. Patients can be divided into two groups: group 1 have no evidence of underlying disease; group 2 are receiving immunosuppressive therapy for underlying disease [1–3]. The disease results from a cytokine storm derived from an inappropriate immune reaction caused by proliferating or activated T cells or natural killer cells associated with macrophage activation or inadequate apoptosis of immunoresponsive cells.

Any age group can be affected and, although children and neonates are often affected, many adult cases have been reported. The syndrome presents suddenly with fever, constitutional symptoms, hepatosplenomegaly, lymphadenopathy, pancytopenia, coagulopathies with thrombocytopenia and hypofibrinogenaemia, raised liver enzymes and bilirubin, pulmonary involvement and skin rashes. Non-specific, generalized, macular eruptions occur fairly frequently.

The viruses implicated include adenovirus, herpesvirus [4], human herpesvirus 6 [5], Epstein–Barr virus and measles virus [6]. In the bone marrow, lymph nodes and other involved tissue, there is infiltration by histiocytes showing erythrophagocytosis. These cells are banal-looking histiocytes with no cytological evidence of malignancy.

The differential diagnosis includes familial haemophagocytic lymphohistiocytosis, malignant histiocytosis and LCH. In the past, many patients with virus-associated haemophagocytic syndrome have been misdiagnosed as malignant histiocytosis and given inappropriate treatment with cytotoxic drugs. It is important to differentiate between these two entities, as the administration of cytotoxic drugs in a viral disease such as virus-associated haemophagocytic syndrome can precipitate a fulminant fatal infection.

The prognosis is variable. In a series of 19 patients [7], 30% died in the acute stages of the disease. The other patients recovered completely in 1–8 weeks with no recurrence in a follow-up period of 32 months. Prognosis is related to prompt introduction of immunosuppressive therapy to control the cytokine storm; ciclosporin or systemic steroids are used in low-risk groups and etoposide-containing regimens in high-risk groups [8].

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Class III histiocytosis: malignant histiocytoses

Class III histiocytoses are malignancies of the monocyte/macrophage series of cells. These diseases are separated into monocytic leukaemia, malignant histiocytosis and true histiocytic lymphoma on clinical criteria, but there is an enormous overlap and it may not always be possible to differentiate them.

In monocytic leukaemia, the malignancy primarily affects the bone marrow and blood but extramedullary

involvement is common. In malignant histiocytosis, the histiocytes retain their ability to migrate through the body, which results in widespread involvement of the reticuloendothelial system. In true histiocytic lymphoma, the cells are derived from fixed tissue histiocytes and the tumours are localized, although they may disseminate.

In a recent study by the International Lymphoma Study Group [1], tumours of histiocytes were phenotypically assessed using a panel of markers. Four groups were identified:

1 Histiocytic sacrcoma: CD68 and lysozyme positive, CD1a and CD21/35 negative, with 33% showing S100 reactivity. This tumour was predominantly extranodal and associated with a high mortality.

2 Langerhans' cell sarcoma: CD68, lysozyme, CD1a and S100 positive but CD21/35 negative. This tumour was predominantly extranodal, with a 50% mortality rate.

3 Follicular dendritic cell sarcoma: CD21/35 positive. This tumour was localized to lymph nodes and associated with a low mortality.

4 Interdigitating dendritic cell sarcoma: S100 positive, 50% CD68 positive, CD1a and CD21/35 negative.

Most of these tumours were localized to lymph nodes and associated with a low mortality.

This is a useful phenotypic aid for recognizing tumours of histiocytic origin. In the Histiocyte Society classification, malignant histiocytosis and true histiocytic lymphoma can be subdivided into tumours of these four phenotypes.

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Monocytic leukaemia

Definition. Monocytic leukaemia may be acute or chronic. The acute myelogenous leukaemias have been classified in the Franco-American–British classification according to the characteristics of the cells involved. Acute myelomonocytic leukaemia is classified as M5. The chronic myelomonocytic/monocytic leukaemias usually transform into acute forms of the leukaemia in a matter of months.

The monocytic leukaemias typically exhibit increased extramedullary disease and organomegaly, and are associated with reduced remission rates and a poorer prognosis.

Aetiology. The aetiology of monocytic leukaemias is unknown. A characteristic karyotype has been reported in M5 leukaemias, translocation t(9;11)(p22;q23).

Pathology. Leukaemic cells in monocytic leukaemia show varying degrees of monocyte differentiation. In acute forms of the disease, the cells stain positively for peroxidase, Sudan black B and non-specific esterase. The cells also contain granules that stain for α-naphthylbutyrate esterase [1]. The cells demonstrate CD13 and CD33, with 30% of cells exhibiting HLA-DR. Monocyte-associated membrane antigen (CD14) expression is variable [2].

Ultrastructurally, the cells have irregular nuclei with nuclear blebs, numerous pinocytic vesicles and perinuclear fibrillar bodies [3].

Skin infiltration favours the lower dermis and subcutaneous fat, with prominent involvement of adnexal structures, nerves and vessels of the superficial and deep plexus. Cellular atypia may be prominent and mitotic figures are common. Differentiation from other forms of leukaemia depends on examination of the blood and bone marrow and special stains in skin sections. The best marker for monocytic leukaemia is non-specific esterase.

Clinical features. Skin lesions in monocytic leukaemia may be specific, for example leukaemia cutis, or non-specific, related to anaemia, thrombocytopenia, infection or drugs. Leukaemia cutis occurs in about 20% of patients with acute monocytic leukaemia [2,4]. Specific skin lesions are light-red, brown or violaceous macules and nodules [1]. These are firm and generally asymptomatic. Skin lesions may undergo rapid cycles of development and spontaneous regression. Skin involvement is not related to the circulating white cell count. Gum involvement occurs in 25–50% of patients.

The prognosis in acute monocytic leukaemia is not related to skin involvement, and leukaemia cutis may spontaneously regress. The prognosis depends on the age of the patient, presence of renal failure and serum β_2-microglobulin levels. Aggressive chemotherapy is associated with complete remission in 60% of patients.

Diagnosis. Diagnosis is made on clinicopathological features of the disease. Differentiation from other forms of leukaemia cutis demands examination of the blood or bone marrow and the use of special stains. M4 and M5 leukaemias are associated with elevated serum lysozyme levels [1].

Treatment. Treatment of leukaemia cutis is that of the underlying leukaemia. Leukaemia cutis in monocytic leukaemia has a tendency to spontaneous regression, but large lesions or ulcerating lesions may be treated with local radiotherapy. Acute monocytic leukaemia is resistant to the chemotherapeutic regimens used in acute myeloid leukaemias but the epipodophyllotoxin drugs are achieving good results [5].

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Malignant histiocytosis

SYN. MALIGNANT RETICULOHISTIOCYTOSIS; MALIGNANT RETICULOSIS; HISTIOCYTIC MEDULLARY RETICULOSIS; SINUSOIDAL HAEMATOLYMPHOID MALIGNANCY; MALIGNANT ASTROCYTOSIS; ALEUKAEMIC RETICULOSIS; HISTIOCYTIC RETICULOSIS

Definition. Malignant histiocytosis is a widespread neoplastic proliferation of histiocytic cells that typically involves liver, spleen, lymph nodes and bone marrow. The cells usually arise from sinusoidal histiocytes, although very rare cases of malignant histiocytosis of Langerhans' cell phenotype have been reported.

Aetiology. Malignant histiocytosis is a neoplastic proliferation of cells of the mononuclear phagocyte system. There is no evidence of a viral aetiology in this disease and no reported familial incidence. There have been reports of a characteristic chromosomal translocation t(5;6)(q35;p21) in malignant histiocytosis [1,2]. The major problem with these reports is that the large cell anaplastic lymphoma (Ki-1-positive lymphoma) is often grouped with malignant histiocytosis, but these are T-cell lymphomas. However, the 5q35 break-point does appear to be specific for malignant histiocytosis [3].

Incidence. Malignant histiocytosis is a rare disease with a male to female ratio of 3.5 : 1. It has been reported in all age groups, with a median age of 35 years [4]. Childhood disease is uncommon with few reported series [5]. The disease tends to occur earlier in women (second to third decades) than in men (third to fourth decades) [6]. Reports have suggested an increased incidence of this disease in parts of tropical Africa, with reports from Malawi [7] and Uganda [8].

Pathology. The histological picture in skin and lymph nodes is similar and the diagnosis can be established in either site. Characteristically, there is an infiltrate of histiocytic cells showing varying degrees of atypia that are typically non-cohesive. Cells are large (up to 50 μm in diameter) with abundant cytoplasm and distinct cytoplasmic membranes.

The histiocytic cells are heterogeneous. Some show more marked histiocytic differentiation, with pale cytoplasm, prominent vacuolation or even foamy cytoplasm, and exhibit phagocytosis of erythrocytes, leukocytes and cellular debris. Other cells are more 'primitive', with deeply eosinophilic or amorphous cytoplasm. Nuclei are usually lobulated, with finely granular or reticulated chromatin and prominent or bizarre nucleoli. Nuclear membranes tend to be thickened. Mitoses are common.

Cytochemical and immunohistochemical studies have shown that the cells in malignant histiocytosis are negative for chloracetate esterase, Sudan black B, alkaline phosphatase and β-glucuronidase [9]. Presence of non-specific esterase, acid phosphatase and lysozyme is variable, with the better differentiated cells showing these enzymes [10]. The more differentiated phagocytosing cells usually stain for factor XIIIa and the antimonocyte monoclonal antibody MOI [11]. In some cases, EMA, HLA-DR, CD25, CD30, CD68 and CD71 have been detected. In rare cases CD1a or CD21/35 may be found. In lymph nodes, the architecture is disarranged but not effaced by the malignant cells.

In the skin, there is extensive perivascular and periappendageal infiltration of the dermis, with extension into subcutaneous fat. In advanced lesions, fat necrosis may occur. The epidermis and papillary dermis are characteristically spared but in the more tumid lesions epidermal ulceration may be present.

Clinical features. Malignant histiocytosis is usually of acute onset, with fever, sweats, wasting, generalized painful lymphoadenopathy and hepatosplenomegaly. As the disease progresses, jaundice, purpura, anaemia and leukopenia occur. In 50% of patients, extranodal extension of the disease is seen, most commonly affecting the skin, bone and gastrointestinal tract.

In the skin, single or multiple lesions may be present [12,13], ranging from skin coloured to violaceous. Large lesions may ulcerate. A widespread papulonodular eruption similar to that in acute monocytic leukaemia may also be seen.

In bone, the lesions are focal, destructive, lytic and may become widespread with associated hypercalcaemia. Gastrointestinal involvement is usually observed late in the disease. Small and large bowel may be involved, with infiltration of the lamina propria and local intraluminal masses. This presents with obstruction or haemorrhage or both. A rare presentation with multiple lesions is with malabsorption.

In the past, this disease has been associated with a poor prognosis. However, with aggressive management (radiotherapy or radiotherapy and chemotherapy) complete remission has been reported in up to 50% of cases, with a mean duration of complete remission of over 12 months [4]. Microscopic evidence of vascular invasion carries a poor prognosis.

Diagnosis. The major differential diagnosis is with large cell anaplastic lymphomas, in which the clinical and

histological features may be similar. Other diseases that may be confused with malignant histiocytosis are familial haemophagocytic lymphohistiocytosis, virus-associated haemophagocytic syndrome, Hodgkin's disease and SHML. Diagnosis can usually be established on clinicopathological features of the disease, although special stains may be needed to exclude large cell anaplastic lymphoma.

Treatment. Malignant histiocytosis is sensitive to both radiotherapy and chemotherapy but treatment must be started early, as many patients die before therapy can be started [5]. Chemotherapy is usually with a combination regimen, which includes Adriamycin and radiotherapy. In one series, complete remission was achieved in seven of nine patients treated [4]. In a study of 27 children with malignant histiocytosis, complete remission was achieved in 22 children using a regimen of vincristine, cyclophosphamide, doxorubicin and prednisolone, with a 5-year survival of 81% [14]. In patients who relapse after conventional chemotherapy, autologous bone marrow transplantation has successfully achieved long-term remission [15]. Large skin tumours or ulcerated tumours can be treated with local radiotherapy. A review of the treatment of malignant histiocytosis has recently been published [16]. Conventional chemotherapy and radiotherapy are still the mainstay of treatment.

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True histiocytic lymphoma

SYN. RETICULUM CELL SARCOMA; HISTIOSARCOMA; MONOCYTIC SARCOMA

Definition. A malignant histiocytic neoplasm that may disseminate.

Aetiology. The aetiology is unknown. The disease represents malignant proliferation of non-Langerhans' cell histiocytes or more rarely of Langerhans' cells. Differentiation from malignant histiocytosis may be difficult.

Pathology. True histiocytic lymphoma exhibits many of the features described in malignant histiocytosis, infiltrating cells being predominantly dermal and non-cohesive. Nemes and Thomazy [1] suggest that the cells in true histiocytic lymphoma are more differentiated than those in malignant histiocytosis and that the cell population is more homogeneous, showing phagocytosis and labelling for factor XIIIa. These cells stain with macrophage markers CD11c and CD68 and are negative for T- and B-cell markers [2].

Clinical features. This is a localized tumour of malignant histiocytes that may be nodal or extranodal. In 40% of patients, presentation is with the painless enlargement of one or more groups of superficial lymph nodes. Constitutional symptoms of malaise, anorexia, sweating and fever may be present.

Extranodal presentation may be with bone, gastrointestinal tract or skin lesions. Bone and gastrointestinal tract lesions are as described in malignant histiocytosis. Skin lesions are localized bluish-red tumours that can attain a large size. An isolated skin tumour of true histiocytic lymphoma in a 79-year-old patient has been described that reached 20 cm in diameter at presentation [3]. In one case report from Japan, an isolated dark-red skin tumour developed on the leg of a 49-year-old woman. Histology showed a monomorphous infiltrate of large cells, with erosion of the overlying epidermis. These cells were CD1a positive and on electron microscopy contained multiple Birbeck granules. This Langerhans' cell, true histiocytic lymphoma disseminated to regional lymph nodes, liver, lungs, kidneys, bone marrow and skin and the patient died 3 years after diagnosis [4]. Hepato-

splenomegaly occurs in only a minority of patients with true histiocytic lymphoma, and peripheral blood involvement is rare. In one case report, a 44-year-old man with true histiocytic lymphoma was treated with autologous bone marrow transplantation and subsequently developed histiocytic leukaemia classified as M5c monocytic leukaemia [5].

Prognosis. True histiocytic lymphoma is treatable, and the prognosis is probably better than in malignant histiocytosis.

Treatment. True histiocytic lymphoma is both radiosensitive and chemosensitive. Complete remission has been achieved in localized skin disease using electron-beam therapy [3]. Reports of therapeutic responses are difficult to evaluate because of doubt over the diagnosis in older series.

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Chapter 53

Soft-Tissue Tumours and Tumour-like Conditions

E. Calonje & R.M. MacKie

Introduction

For many clinical dermatologists, soft-tissue tumours arising in the dermis, subcutis or deeper soft tissues are a confusing group of lesions. This is probably partly explained by the fact there is a very long list of soft-tissue tumours, and a large majority can arise in the skin or affect it secondarily. Most of these tumours have no characteristic clinical appearance, and present as non-specific, dermal, or deep-seated nodules. However, it is necessary for all clinical dermatologists to have an understanding of the range of tumours that may arise in the dermis, and also

of the likely biological behaviour of individual lesions. Although cutaneous malignant soft-tissue tumours are rare, many benign lesions may be histologically confused with a malignancy. Furthermore, there is a group of soft-tissue tumours that have low-grade malignant potential with frequent local recurrences but little or no potential for metastatic spread (e.g. dermatofibrosarcoma protuberans). These tumours may cause important morbidity, and their recognition is therefore essential for the planning of treatment and follow-up. Recognizing a wide range of soft-tissue tumours is also important as a number of these lesions—particularly when multiple—may be markers of genetic syndromes (for example, multiple neurofibromas and plexiform neurofibroma in neurofibromatosis type I).

A broad division can be made between tumours according to the morphological lines of differentiation. The latter include fibroblastic, myofibroblastic, neural, vascular, muscular and adipocytic types. In a number of tumours, the line of differentiation is not clear, as a normal cell of origin cannot be identified (e.g. epithelioid sarcoma). In a still larger group of tumours, their origin is descriptively ascribed to fibrohistiocytic cells, but with mounting evidence that many of these lesions have fibroblast and/or myofibroblastic differentiation and almost none display true histiocytic differentiation. The list of tumours discussed in this chapter is not all-inclusive. For a full account of the very wide range of these tumours, the reader is referred to the standard major work in this field [1]. True histiocytic tumours are discussed in Chapter 52, and keloids and hypertrophic scars in Chapter 46. Metastatic malignant tumours are covered in Chapter 59.

The most useful biological triage is into totally benign lesions; lesions that may recur locally and never or almost never metastasize; and those that are truly malignant and may metastasize. The great majority of dermal or superficial soft-tissue tumours come into the first two categories, whilst truly malignant soft-tissue tumours arise much more frequently below the deep fascia. In the case of these rare malignant tumours, there is a relationship between bulk and prognosis, smaller lesions carrying a better prognosis. More superficially situated lesions tend to carry a better prognosis than those deeply situated. Mitoses (particularly abnormal mitotic figures) and necrosis both tend to be associated with malignant rather than benign lesions.

The usual clinical presentation of many of the tumours described in this chapter is of a non-specific lump or nodule. An incisional biopsy should be arranged, and it must be adequately deep so that the nature of the lesion at its deepest margin can be determined. Once the pathologist has established the nature of the tumour, appropriate definitive surgery can be planned. Prior consultation with the pathologist is strongly recommended, as samples may be needed for cytogenetics, electron microscopy or immunohistochemistry. All of these may be of supportive value in arriving at an accurate diagnosis.

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Fibrous and myofibroblastic tumours

Fibrous papule of the face [1]

SYN. FIBROUS PAPULE OF THE NOSE

Definition and incidence. A small facial papule with a distinctive fibrovascular component on histological examination. The condition is relatively common, and several large series have been reported [2–4].

Clinical features [2–4]. The lesions usually occur singly on the nose. Occasionally, they may occur on the forehead, cheeks, chin or neck, and there may be several lesions. The lesion usually presents in middle life, and both sexes are equally affected. Similar papules may present on the fingers or oral mucosa, where they have been described as reactive nodular hyperplasia or giant cell fibroma [5,6].

The papule develops slowly as a dome-shaped, skin-coloured or slightly red or pigmented lesion, which is usually sessile. Most are asymptomatic, but about one-third bleed on minor trauma.

Pathology [2–4]. The epidermis appears normal, although there may be an increased number of clear cells overlying the lesion. In the dermis there are broad bands of connective tissue orientated vertically to the surface. These are interspersed with multinucleate, somewhat bizarre cells, often with a few cells resembling melanocytic naevus cells. There are prominent dilated capillaries, but relatively few elastic fibres.

It has been suggested that the condition may be a variant of a melanocytic naevus [2,4], but others disagree [3]. S100 protein, which is an immunohistochemical marker of neuroepithelial elements, is present neither in the stellate cells in the papillary dermis nor in the mesenchymal 'naevus' cells [7].

Treatment. The lesion is benign, but it may easily be excised or surgically pared for cosmetic reasons.

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Storiform collagenoma [1,2]

SYN. SCLEROTIC FIBROMA

Definition. Storiform collagenoma is a fibrous hypocellular cutaneous lesion which, when multiple, may be associated with Cowden's disease (multiple hamartoma and neoplasia syndrome; see Chapter 59) [3].

Clinical features. It usually presents as a small solitary asymptomatic papule in adults of either sex, with wide anatomical distribution.

Pathology. It typically consists of a fairly well-circumscribed dermal nodule with prominent hypocellular hyalinized collagen bundles in a storiform pattern. Bland spindle-shaped cells are rare. A similar histological pattern may be seen in the late stages of lesions as diverse as fibrous histiocytoma (FH) and myofibroma.

Treatment. Simple excision is curative.

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Pleomorphic fibroma

Definition [1]. Pleomorphic fibroma is a relatively rare lesion with features very similar to those of a fibroepithelial polyp (skin tag), but characterized histologically by bizarre mono- or multinucleated stromal cells.

Clinical features. Lesions present in adults as a polyp, with no sex predilection and a wide anatomical distribution.

Pathology. Normal or mildly acanthotic epidermis surrounds a collagenous and vascular stroma containing scattered bizarre mono- or multinucleated cells with hyperchromatic and pleomorphic nuclei. Mitotic figures are rare.

Treatment. Simple excision is curative, and there is no tendency for local recurrence.

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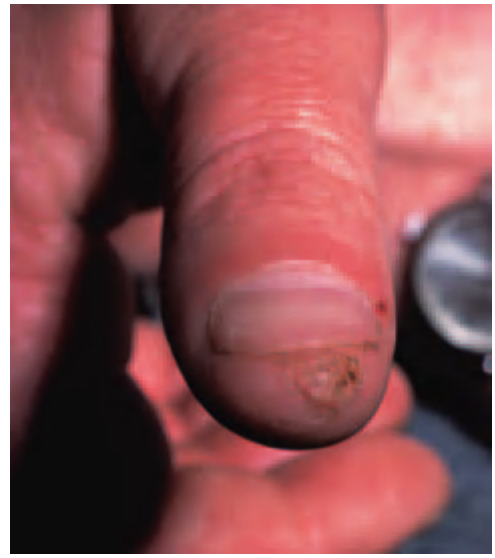

Fig. 53.1 Clinical appearance of an acquired digital fibrokeratoma.

Acquired digital fibrokeratoma [1]

Definition. A benign lesion, possibly a reaction to trauma, which occurs on the fingers and toes [2] (Fig. 53.1), although the palms and the soles have occasionally been involved.

Clinical features. The lesion usually occurs in adults as a solitary dome-shaped lesion, with a collarette of slightly raised skin at its base. Occasionally, it may be elongated or pedunculated. The surface may appear to be slightly warty.

There is a wide clinical differential diagnosis, which includes dermatofibroma, viral wart, supernumerary digit and cutaneous horn. Histologically, the lesion is extremely similar to the Koenen tumour [3], the periungual fibrous papule that arises from the nail fold in tuberous sclerosis.

Pathology. The histology shows thick collagen bundles, thin elastic fibres and increased vascularity. Occasionally, there is an obvious increase in fibroblasts, and rarely the collagen bundles may be separated by oedema [4]. The epidermis is relatively normal, but acanthosis and hyperkeratosis may occur.

Treatment. Acquired digital fibrokeratoma is cured by simple excision.

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Nodular fasciitis [1–4]

SYN. SUBCUTANEOUS PSEUDOSARCOMATOUS FIBROMATOSIS

Definition. A rapidly enlarging subcutaneous nodule, which is due to a benign proliferation of myofibroblasts and fibroblasts and has a superficial resemblance to a sarcoma.

Incidence and aetiology. A number of quite large series have been published in the last 10 years, suggesting that the condition is not uncommon. It is most frequent in young adults, but has been reported in patients from 5 months to 75 years. There is no predilection for either sex. It is not associated with other diseases. There is no evidence that trauma initiates the lesions.

Clinical features [4–7]. The majority of tumours appear as tender, rapidly growing masses beneath the skin. The average size is 1–3 cm in diameter. The commonest situation is the upper extremities, particularly the forearm, but the lesion can occur anywhere, including the orbit and the mouth. Lesions on the head and neck often present in children. In nearly half the patients, the tumour has been noticed for only 2 weeks or less when they come for advice. Prolonged follow-up has shown that the condition is benign.

Pathology [1–4]. These lesions may look extremely worrying in view of the high mitotic rate and rapid growth (see below). The tumour is only focally circumscribed and it is composed of bundles of fairly uniform fibroblasts and myofibroblasts with pink cytoplasm, vesicular nuclei and a single small nucleolus. Myxoid change and mucin deposition is often prominent, resulting in a typical tissue culture-like appearance (Fig. 53.2). In the background, there are numerous small, delicate blood vessels, extravasated red blood cells and scattered mononuclear inflammatory cells. Multinucleated giant cells may be seen, and they resemble osteoclasts. Mitoses are usually numerous, but there are no abnormal forms. Hyalinized collagen bundles are often present and may display a keloidal appearance. At the periphery, compact bundles of fibroblasts and capillaries probe the fascial planes and may infiltrate fat or skeletal muscle. It is not surprising that this histological picture is relatively often confused with that of a malignant tumour. Variants of nodular fasciitis include those with metaplastic bone (ossifying fasciitis); a variant that involves the periosteum (periosteal fasciitis); a variant that involves the scalp and tends to occur in children (cranial fasciitis); and a variant within the lumen of a blood vessel (intravascular fasciitis) [5]. A rare variant of intradermal nodular fasciitis has also been described [5]. Tumour cells are variably positive for smooth muscle actin.

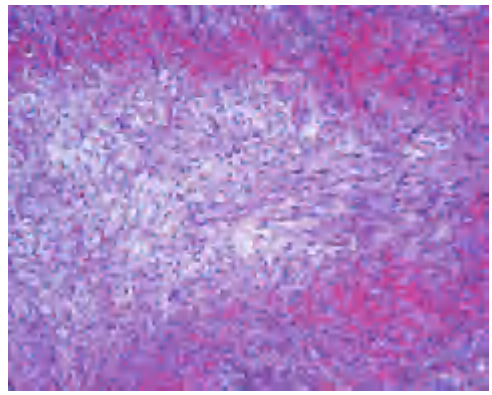

Fig. 53.2 Typical tissue culture-like appearance of nodular fasciitis with prominent myxoid background.

Treatment. Resolution usually follows incomplete surgical removal. Simple excision is therefore an adequate treatment. Local recurrence is exceptional.

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Fibro-osseous pseudotumour [1,2]

SYN. FLORID REACTIVE PERIOSTITIS

Definition. This is a reactive myofibroblastic proliferation with bone formation, which occurs exclusively on the digits.

Clinical features. It presents predominantly in young adults, with predilection for females. The fingers are more commonly affected than the toes. The lesion grows rapidly and it is not attached to bone.

Pathology. The tumour is ill-defined and is very similar to nodular fasciitis, except for the fact that there is formation of osteoid and mature bone.

Treatment. Local recurrence is rare, and excision is the treatment of choice.

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Ischaemic fasciitis [1–3]

SYN. ATYPICAL DECUBITUS FIBROPLASIA

Definition. Ischaemic fasciitis is a reactive fibroblastic/myofibroblastic proliferation that simulates malignancy and occurs as a result of alterations in local circulation and sustained pressure.

Clinical features. Most patients are elderly and immobilized, and there is a slight predilection for females. The lesion presents as an asymptomatic subcutaneous mass, predominantly over bony prominences, that may extend to deeper soft tissues and to the overlying dermis.

Pathology. The lesion is poorly circumscribed and contains areas of fibrosis, vascular proliferation, necrosis and focal myxoid change. Thrombosed blood vessels with recanalization and areas of fibrinoid necrosis, focal haemorrhage and mononuclear inflammatory cells are additional features. In the background, there are variable numbers of spindle-shaped myofibroblasts/fibroblasts with vesicular or hyperchromatic nuclei and a prominent nucleolus. Mitotic figures may be seen, but are not prominent.

Treatment. Excision of the lesion is an adequate treatment.

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Fibrous hamartoma of infancy [1–4]

Definition. This is a benign fibroblastic/myofibroblastic deep dermal and subcutaneous tumour presenting in children and characterized by three distinctive pathological components, as described below.

Incidence and aetiology. This is a rare tumour, often considered to be a hamartoma, but probably neoplastic in nature.

Clinical features. Most cases present in children under 2 years as an asymptomatic solitary lesion only a few centimetres in diameter. A quarter of the cases present at birth. Males are more affected than females. The tumour grows rapidly and has a predilection for the axillae, arm and shoulder girdle [1–3]. A familial association has not been reported.

Pathology. The tumour is composed of three components:
1 Bundles of interlacing, elongated, bland, wavy spindle-shaped cells in a variable collagenous background.
2 Nests of more immature round cells with focal myxoid change.
3 Mature adipose tissue.

A focal resemblance to a neurofibroma may be seen when the first component predominates, but tumour cells are actin-positive and S100-negative [5].

Treatment. Simple excision is the treatment of choice; recurrences are exceptional.

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Calcifying fibrous tumour/pseudotumour [1,2]

Definition. This is a rare benign hypocellular tumour characterized by dense collagen bundles, areas of calcification and a patchy mononuclear cell infiltrate.

Clinical features. Most lesions occur in children, and less commonly in young adults, as a fairly large subcutaneous or deeper asymptomatic mass with a wide anatomical distribution.

Pathology. The tumour typically consists of haphazardly arranged collagen bundles with scattered bland fibroblasts, focal small calcifications and focal aggregates of lymphocytes and plasma cells.

Treatment. Local recurrence is rare, and the treatment of choice is simple excision.

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Calcifying aponeurotic fibroma [1,2]

Definition. This is a rare fibroblastic tumour characterized by a nodular proliferation of bland spindle-shaped cells surrounding nodules at different stages of calcification. Cartilage and, less commonly, bone formation may be seen.

Clinical features [1]. Most cases present in children, with a predilection for the hands and, less commonly, the feet. Occurrence at other sites is very rare [2]. Tumours are small, slowly growing and usually asymptomatic.

Pathology. The growth pattern is multinodular. Tumour cells are elongated, with scanty pink cytoplasm, vesicular nuclei and very rare mitotic figures. Tumour nodules frequently contain areas of calcification, which are surrounded by tumour cells in a pattern reminiscent of palisading.

Treatment. Local recurrence is observed in up to 50% of the cases, but malignant transformation is exceptional [3] and conservative treatment is therefore indicated.

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Dermatomyofibroma

SYN. DERMAL PLAQUE-LIKE FIBROMATOSIS

Definition [1–4]. A benign dermal and superficial subcutaneous myofibroblastic proliferation microscopically mimicking a fibromatosis. The tumour, however, has no potential for local recurrence and lacks an infiltrative growth pattern.

Clinical features. It presents as a solitary, asymptomatic, skin-coloured or hypopigmented plaque measuring less than 4 cm in diameter. Most lesions occur on the trunk, and there is a predilection for young adults, particularly females. Children are only exceptionally affected.

Pathology. Low-power examination reveals a plaque-like proliferation of fascicles of myofibroblast-like cells with an almost parallel orientation to the epidermis. Tumour cells are bland, and mitotic figures are very rare. The tumour does not destroy adnexal structures, but may extend focally into the subcutaneous tissue.

Treatment. Simple excision is curative.

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Elastofibroma [1–3]

Definition. Elastofibroma is a reactive, probably degenerative, process of the elastic fibres of deep soft tissues that occurs almost exclusively around the shoulder.

Clinical features. It presents as an asymptomatic, slowly growing mass on the posterior upper trunk of middle-aged individuals. Lesions in other locations including internal organs are exceptional.

Pathology. The mass is poorly circumscribed, and the appearances are characteristic. Abundant hypocellular hyalinized collagen containing numerous large, thick eosinophilic elastic fibres is the most distinctive feature. Sometimes the fibres are beaded and fragmented. Staining for elastic tissue nicely highlights the changes.

Treatment. Simple excision is all that is necessary, as the tumours do not have a tendency to recur.

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Infantile myofibromatosis and adult myofibroma [1–6]

SYN. CONGENITAL GENERALIZED FIBROMATOSIS; INFANTILE HAEMANGIOPERICYTOMA

Definition. This tumour is composed of cells showing differentiation towards perivascular contractile cells, and has been described in the past as infantile haemangiopericytoma [7]. Infantile myofibromatosis and adult myofibroma are part of the spectrum of lesions recently described as myopericytomas [8].

Clinical features [1–3]. Most cases of infantile myofibromatosis present before the age of 2 years, with slight male predominance. Congenital tumours occur in up to a third of the cases. Multiple lesions are present in 25% of

patients. The preferred sites are the head and neck, followed by the trunk. Familial cases are rare. Involvement of other organs, including the gastrointestinal tract, lungs and bone, is seen in some cases. Multicentric involvement may be associated with mortality. Multiple lesions in the skin and soft tissues behave in a benign fashion and may regress spontaneously. Solitary myofibroma tends to occur in adults, with the same anatomical distribution as that of cutaneous and soft-tissue lesions presenting in infantile myofibromatosis [4,5]; multiple superficial tumours are rarely seen in adults.

Pathology [1,2,5,6]. Tumours have a distinctive biphasic growth pattern:
1 Areas composed of bundles of mature, spindle-shaped myofibroblasts with pink cytoplasm and vesicular nuclei.
2 Areas composed of immature round cells, with scanty cytoplasm arranged around small blood vessels, often displaying a haemangiopericytoma-like pattern ('staghorn-like').

Protrusion of tumour cells into vascular lumina is frequent, often mimicking vascular invasion. Old lesions often undergo hyalinization of the more mature areas. Mitotic figures and necrosis are relatively common. Tumour cells, particularly in the mature areas, are focally positive for actin.

Treatment. Lesions tend to regress spontaneously, but it is important to remember that patients with visceral tumours may die from the disease. Solitary lesions are treated by simple excision and do not tend to recur locally.

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Inclusion body (digital) fibromatosis [1–3]

SYN. INFANTILE DIGITAL FIBROMATOSIS

Definition. Inclusion body fibromatosis is a fibro/myofibroblastic proliferation that almost only occurs on the fingers and toes. It is characterized by bright round intracytoplasmic eosinophilic inclusions.

Clinical features. Most lesions present either at birth or during the first year of life as small multiple nodules with predilection for the third, fourth and fifth digits. Involvement of the first digits (thumb and hallux) does not occur. New lesions often develop over a long period of time. Only rare cases have been described at other sites or in adults [4,5]. Spontaneous regression is sometimes seen. Aggressive behaviour has not been described.

Pathology. Monomorphic bundles of bland, myofibroblast-like cells are seen in the dermis and often the subcutis. Tumour cells have vesicular nuclei, an inconspicuous nucleolus and pink cytoplasm. Some mitotic figures may be seen. A distinctive feature is the presence of variable numbers of small round eosinophilic intracytoplasmic inclusions in tumour cells. These are periodic acid–Schiff (PAS)–negative, but stain red with Masson's trichrome. They also stain for actin.

Treatment. Simple excision may be required for lesions that interfere with function, but simple observation of histologically confirmed lesions may be all that is necessary.

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Fibroma of tendon sheath [1,2]

Definition. This is a distinctive, well-circumscribed fibroblastic tumour, presenting almost exclusively on the distal extremities.

Clinical features [1,2]. It is a small, slowly growing asymptomatic tumour, presenting in young to middle-aged adults and with a marked predilection for the distal upper limb, particularly the hand and fingers. Lesions on the foot are much less common.

Pathology [1,2]. The neoplasm is multilobular and well-circumscribed and consists of cellular or poorly cellular areas on a background of variably hyalinized stroma. Stromal clefting is usually prominent. Tumour cells are

spindle-shaped, with scanty cytoplasm and vesicular nuclei. Cytological atypia tends to be absent, and the mitotic count is low.

Treatment. About 25% of cases recur locally, but the growth is not destructive.

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Collagenous fibroma [1,2]

SYN. DESMOPLASTIC FIBROBLASTOMA

Definition. Collagenous fibroma represents a distinctive, subcutaneous fibroblastic tumour consisting of a prominent collagenous stroma.

Clinical features. It is relatively common and presents in adults as an asymptomatic nodule less than 4 cm in diameter, at any body site.

Pathology. This is a well-circumscribed tumour composed of bland elongated or stellate cells, with a background collagenous stroma and focal myxoid change. Mitotic figures are very rare.

Treatment. Simple excision is the treatment of choice, as there is no tendency for local recurrence.

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Nuchal fibroma [1,2]

Definition. Nuchal fibroma is a dermal or subcutaneous tumour consisting of hypocellular dense collagen.

Clinical features. Tumours are rare and occur in adult males. Patients often have diabetes. The great majority of cases present on the nape of the neck. Coexistence with scleroedema is possible, probably reflecting the association with diabetes, and this lesion is now recognized to occur in Gardner's syndrome (Chapter 59).

Pathology. Dense aggregates of collagen with very few cells and entrapment of adipose tissue.

Treatment. Simple excision is the treatment of choice but local recurrence is possible.

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Palmar and plantar fibromatosis (superficial fibromatoses) [1,2]

SYN. PLANTAR FIBROMATOSIS: LEDDERHOSE'S DISEASE; SYN. PALMAR FIBROMATOSIS: DUPUYTREN'S DISEASE, DUPUYTREN'S CONTRACTURE

Definition. Palmar and plantar fibromatoses are superficial neoplastic proliferations of fibroblasts and myofibroblasts that have a tendency for local recurrence, but do not metastasize.

Incidence and aetiology. Palmar fibromatosis is more common than plantar fibromatosis. Both lesions are more common in men, but the sex difference is more marked in palmar lesions. Both conditions affect middle-aged to elderly patients and are exceptional in younger individuals. Affected patients are mainly of Northern European origin; non-whites are rarely affected. Coexistence between the two variants of fibromatoses and desmoid tumours, penile fibromatosis (Peyronie's disease) and knuckle pads may be seen. Genetic predisposition as well as trauma are thought to play an important role in the pathogenesis of these conditions. Associations with diabetes, alcoholic liver disease and epilepsy have also been described.

Clinical features. Palmar fibromatosis presents as indurated nodules or as an ill-defined area of thickening, bilateral in about 50% of cases, that may result in contracture. Plantar fibromatosis usually consists of a single nodule. Functional limitation is common.

Pathology. Early lesions are fairly cellular and consist of bundles of bland fibroblasts with some collagen deposition. The latter increases considerably in older lesions.

Treatment. Complete excision is desirable, as there is otherwise a risk of local recurrence.

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Penile fibromatosis [1–3]

SYN. PEYRONIE'S DISEASE

Definition. Although usually regarded as a variant of

superficial fibromatosis, it is more likely that this disease represents a reactive fibrotic disorder of unknown aetiology.

Clinical features. It presents as a solitary nodule or multiple nodules close to the corpus cavernosum on the dorsal surface of the shaft. Most patients are middle-aged, and in most the lesion is small. Pain and curvature of the penis on erection are frequent complaints.

Pathology. In early lesions, there is a patchy chronic mononuclear inflammatory cell infiltrate and focal vasculitic changes. These changes lead to dense bands of hyalinized collagen in late stages.

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Dermatofibrosarcoma protuberans [1–3]

Definition. Dermatofibrosarcoma protuberans (DFSP) is a locally invasive tumour arising in the dermis and likely to show fibroblastic differentiation.

Incidence and aetiology [1–3]. DFSP is uncommon, with equal frequency in males and females. Most patients present in the third and fourth decades of life. Some cases develop at the site of previous trauma.

Clinical features. The tumour is more often situated on the trunk (up to half of the cases), particularly in the flexural regions, than on the extremities or the head [1,2]. Involvement of the limbs is usually proximal. It may begin in early adult life with one or more small, firm, painless, flesh-coloured or red dermal nodules (Fig. 53.3). There are rare examples of DFSP occurring in infancy [4–6], and congenital cases have been described [6].

The tumour starts as a plaque, which may occasionally be atrophic [5,7]. Progression is usually slow, and may occur over many years. Eventually, nodules develop, coalesce and extend, becoming redder or bluish as they enlarge to form irregular, protuberant swellings. At this stage, the base of the lesion is a hard, indurated plaque of irregular outline. In the later stages, a proportion of lesions become painful and there may be rapid growth, ulceration and discharge.

Local recurrence of ordinary DFSP is reported to vary from 15% to up to 60% [3,8,9], and that of the fibrosarcomatous variant is as high as 75% [10–13]. Metastases to lymph nodes and internal organs tend to be extremely rare in pure DFSP [10,14,15] but occur in up to 20% of cases with fibrosarcomatous transformation [11–13].

Pathology [1–3,8]. The tumour is usually a solitary multinodular mass. The dermis and subcutaneous tissue are replaced by bundles of uniform spindle-shaped cells with little cytoplasm and elongated hyperchromatic, but not pleomorphic, nuclei. Usually there is little mitotic activity. Deeper involvement may be seen in some cases. Laterally, the tumour cells infiltrate widely between collagen bundles of the deeper dermis and blend into the normal dermis, forming quite definite bands, which interweave or radiate like spokes of a wheel; this is described as a 'storiform' pattern (Fig. 53.4). The interstitial tissue contains collagen fibres, except in the most cellular parts of the tumour. The subcutaneous tissue is extensively infiltrated and replaced in a typical lace-like pattern. Myxoid change may be focal or, rarely, prominent; in the latter setting, the histological diagnosis is difficult. Some tumours are colonized by scattered, deeply pigmented melanocytes, a variant known as pigmented

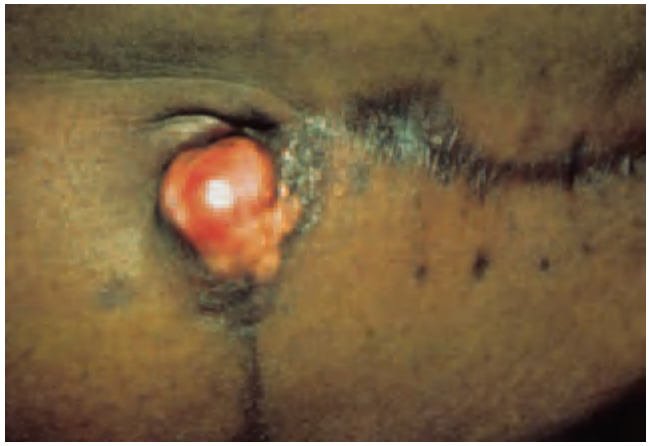

Fig. 53.3 Recurrent abdominal dermatofibrosarcoma protuberans.

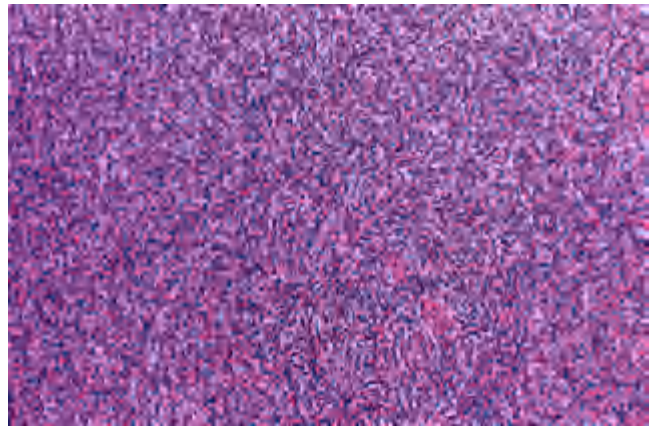

Fig. 53.4 Pathological appearance of dermatofibrosarcoma protuberans, showing the storiform or 'cartwheel' distribution of the fairly uniform spindle-shaped tumour cells.

DFSP (Bednar tumour) [16,17]. A further variant consists of myoid nodules and is thought to represent myofibroblastic differentiation [18]. Rare cases show focal granular cell change.

Fibrosarcomatous DFSP [11–13] is an important variant of this tumour, which is recognized by the focal presence of areas with long sweeping fascicles of tumour cells intersecting at acute angles in a typical 'herring-bone' pattern, almost identical to that seen in fibrosarcoma. In these areas, mitoses are increased and there is more nuclear hyperchromatism. Identification of this pattern and its quantity is very important, as it seems to be related to metastatic potential. Fibrosarcomatous areas are more common in recurrent tumours.

DFSP may show areas of giant cell fibroblastoma (see below) and either tumour may recur, displaying features of the other tumour [19].

The majority of the lesions are positive on staining with the antibody CD34, although this is not specific for DFSP [8]. Fibrosarcomatous areas often show decreased staining with CD34 [13].

Cytogenetic studies are helpful, as ring chromosomes indicative of a 17:22 translocation are invariably found [19]. The same cytogenetic abnormality is found in giant cell fibroblastoma, confirming that both tumours are part of the same spectrum.

Diagnosis. In the early stages, it may be impossible to distinguish this tumour from a histiocytoma or a keloid. Some lesions may also be confused with morphoea profunda. The slow progression, deep red or bluish-red colour, and the characteristic irregular contour and extended plaque-like base, are strongly suggestive of DFSP.

Treatment. The tumour should be excised completely, with a generous margin of healthy tissue. Local recurrence invariably follows inadequate removal; the clearance necessary to cure the tumour is often underestimated [20]. A margin of between 2 and 4 cm has been recommended [9,21]. Mohs surgery has been reported as effective in reducing the rate of local recurrence [22,23]. If this type of treatment is used it should be performed using formalin-fixed paraffin-embedded sections rather than frozen sections, and evaluation should be by an experienced pathologist.

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Giant cell fibroblastoma [1–3]

Definition. This is a locally recurrent fibroblastic tumour, closely related to DFSP. It is characterized by spindle-shaped, oval or stellate, mono- or multinucleated cells in a fibromyxoid stroma with irregular pseudovascular spaces lined by tumour cells.

Clinical features [1–3]. The large majority of cases present as a subcutaneous ill-defined mass in the first few years of life. It is rare in adults. The trunk is much more commonly involved than the proximal limbs. Tumours measure a few centimetres in diameter, have a predilection for males and tend to be asymptomatic.

Pathology. Solid fibromyxoid areas with variable collagen deposition contain stellate and spindle-shaped mono- and multinucleated tumour cells with hyperchromatic nuclei. Dilated, irregularly branching pseudovascular spaces are commonly seen scattered throughout the lesion. These spaces are lined by tumour cells, which often appear multinucleated. Mitotic figures are exceptional. Focal areas identical to DFSP may be seen and can occupy a substantial part of the tumour. Excised lesions can recur as a pure giant cell fibroblastoma, as a tumour with focal DFSP, or as pure DFSP [4–6]. Tumour cells are focally positive for CD34 and only very focally positive for actin. Ring chromosomes with sequences of chromosomes 17 and 22 identical to those found in DFSP have been described in this tumour, confirming their close histogenetic relationship [7].

Treatment. Recurrence may be seen in about half of the cases, but metastasis has not been reported.

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Fibrohistiocytic tumours

Giant cell tumour of tendon sheath [1,2]

SYN. BENIGN SYNOVIOMA

Definition. This is a benign tumour that in its localized variant occurs mainly on the hands, and consists of a nodular proliferation of histiocyte-like cells with scattered multinucleated giant cells and variable numbers of mononuclear inflammatory cells. The diffuse variant of this tumour that involves joints is not discussed further in this chapter.

Clinical features. Tumours present mainly on the hands with predilection for the fingers. They are typically between 1 and 3 cm in diameter and asymptomatic, although they may interfere with function. There is a predilection for young females.

Pathology. It is a multinodular lesion composed of sheets of histiocyte-like cells with bland vesicular nuclei, intermixed with multinucleated giant cells, foamy cells, siderophages and scattered mononuclear inflammatory cells. Hyalinization, haemosiderin deposition and cholesterol clefts are often seen.

Treatment. Excision is the treatment of choice; the rate of local recurrence is around 30%.

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Fibrous histiocytoma [1–4]

SYN. DERMATOFIBROMA, HISTIOCYTOMA CUTIS; SUBEPIDERMAL NODULAR FIBROSIS; SCLEROSING ANGIOMA

Definition. Fibrous histiocytoma (FH) is a benign dermal and often superficial subcutaneous proliferation of oval cells resembling histiocytes, and spindle-shaped cells resembling fibroblasts and myofibroblasts. Their line of differentiation remains uncertain, but these lesions are descriptively classified as fibrohistiocytic tumours because of the microscopic appearance of the tumour cells. The aetiology of FH is unknown, but recent cytogenetic studies demonstrating clonality favour these lesions being neoplastic [5,6]. The neoplastic nature of FH is also suggested by their clinical persistence and by the frequency of local recurrence of some variants (cellular, aneurysmal and atypical; see below). The previous theory that they are a dermal response to injury, such as insect bite, has been challenged [7].

Clinical features. FH is commonest on the limbs and appears as a firm papule, which is frequently yellow-brown in colour and slightly scaly (Fig. 53.5). If the overlying epidermis is squeezed, the 'dimple sign' will be seen, indicating tethering of the overlying epidermis to the underlying lesion. Giant lesions (>5 cm in diameter) are occasionally seen [8]. A number of clinicopathological variants of FH have been described, which should be recognized by clinicians and pathologists in order to avoid a misdiagnosis of malignancy. These variants include: cellular FH [9,10], aneurysmal FH [11,12], atypical FH (pseudosarcomatous FH, dermatofibroma with monster cells) [13,14] and epithelioid FH [15,16]. A further variant, described as 'atrophic', does not usually pose a problem in differential diagnosis.

Cellular FH represents less than 5% of all FHs [9]. Like

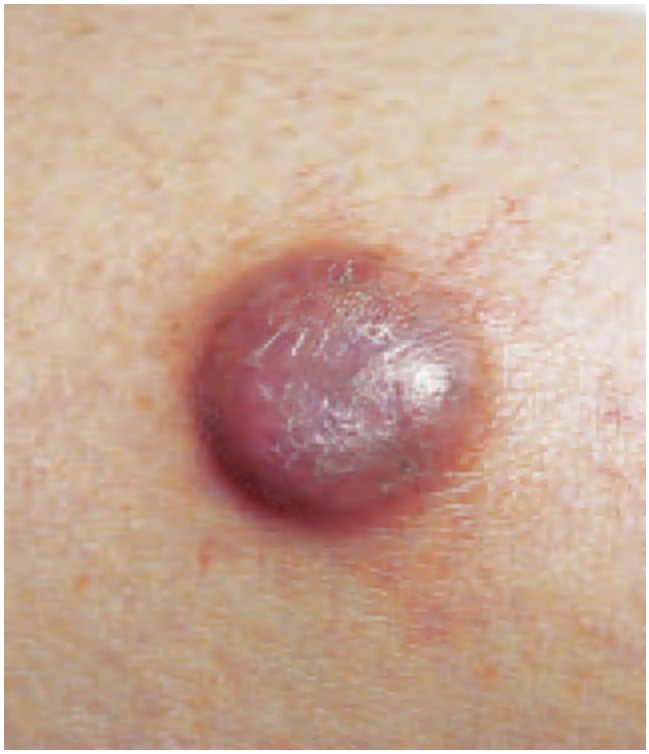

Fig. 53.5 Clinical appearance of a fibrous histiocytoma or dermatofibroma.

ordinary FH, it has a predilection for the limbs of young adults, but it tends to occur more commonly in males. However, the distribution of age and site is wide; cellular FH is not infrequent in children, and on sites such as the head, neck, fingers and toes. The size of these lesions is also larger than that of ordinary FH. Most cellular FHs are less than 2 cm in diameter, but lesions measuring more than 5 cm may occur. Recognition of this variant is important, because it has a local recurrence rate of 25%, and metastases have been reported anecdotally [10].

Aneurysmal FH has the same age and sex distribution as ordinary FH [11,12]. Tumours are usually rapidly growing and may attain a very large size. They clinically mimic a vascular tumour. The rate of local recurrence is 19% [12].

Atypical FH presents mainly in young adults, with a predilection for the lower limbs [13,14]. It is commoner in males than in females. The clinical presentation is that of a papule, nodule or plaque, usually less than 1.5 cm in diameter. The rate of local recurrence is around 14%, and exceptional metastases have been reported [14].

Epithelioid FH [15,16] presents on the limbs of young patients, with a predilection for females [15,16]. The typical clinical appearance is that of a polypoid, often vascular, lesion resembling a non-ulcerated pyogenic granuloma.

Pathology. The overlying epidermis frequently shows a degree of epidermal hyperplasia [17] (Fig. 53.6). Occasionally, the epidermal proliferation is associated with immature follicular structures, which are often confused with a basal cell carcinoma. In the dermis, there is a localized proliferation of histiocyte-like cells and fibroblast-like cells, associated with variable numbers of mononuclear inflammatory cells. Foamy macrophages, siderophages and multinucleated giant cells are also variably present. A focal storiform pattern is often seen. The tumour blends with the surrounding dermis. Collagen bundles at the periphery of the lesion are surrounded by scattered tumour cells and appear somewhat hyalinized. As variable expression of factor XIIIa antigen is often seen, it has been suggested that this tumour shows differentiation towards dermal dendrocytes [18]. Focal myofibroblastic differentiation is often suggested, particularly in the cellular variant. Older lesions show focal proliferation of small blood vessels in association with haemosiderin deposition and fibrosis, hence the older name of 'sclerosing haemangioma'.

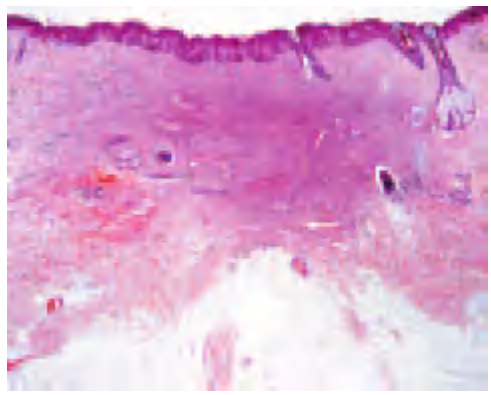

Fig. 53.6 Histological appearance of dermatofibroma, showing epidermal hyperplasia overlying the dermal sclerotic component.

Cellular FH [9] also shows epidermal hyperplasia, but the lesions are more cellular, less polymorphic and consist of bundles of spindle-shaped cells with pink cytoplasm and a focal storiform pattern (Fig. 53.7). The mitotic rate varies, and necrosis may be found in up to 12% of cases. Extension into the subcutaneous tissue is more prominent than that seen in ordinary FH. However, the pattern of infiltration is mainly along the septae, and only focally into the subcutaneous lobule in a lace-like pattern. The cellularity and growth pattern often make distinction from DFSP difficult, particularly in small biopsies. DFSP is, however, more monomorphic, tends to infiltrate the subcutaneous tissue diffusely and is generally uniformly positive for CD34 [18]. Cellular FH may be focally positive for CD34, but this is predominantly seen at the periphery of the tumour. Staining for FXIIIa is positive in FH and negative in DFSP. Furthermore, cellular FH is often focally positive for smooth muscle actin, whereas this marker is negative in DFSP.

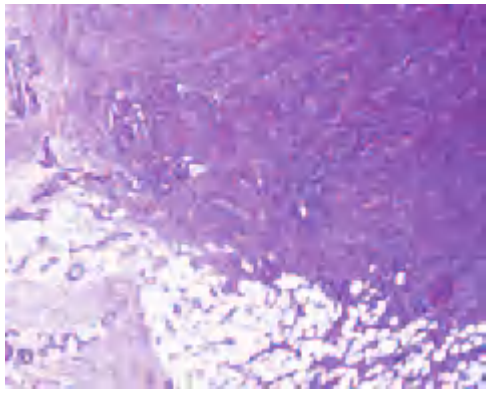

Fig. 53.7 Cellular fibrous histiocytoma. Note the increased cellularity, fascicular appearance and focal extension into the subcutis.

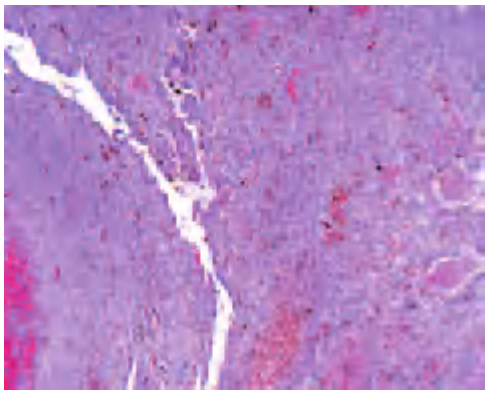

Fig. 53.8 Aneurysmal fibrous histiocytoma. Prominent haemorrhage and cavernous-like spaces obscure the typical background of a fibrous histiocytoma.

Aneurysmal FH [11,12] shows extensive haemorrhage, with prominent cavernous-like pseudovascular spaces (Fig. 53.8) which are not lined by endothelial cells. The mitotic rate varies, but may be prominent. The background is that of an ordinary FH.

Atypical FH [13,14] shows variable numbers of mono- or multinucleated, pleomorphic, spindle-shaped or histiocyte-like cells on a background of an ordinary FH. These cells may be very prominent, making the histological diagnosis difficult. Mitotic figures, including atypical forms, may be seen. These lesions used to be classified as 'atypical fibroxanthoma occurring in non-sun-exposed skin of young patients'.

Epithelioid FH [15,16] contains a predominant population of cells with abundant pink cytoplasm and vesicular nuclei, and there is often myxoid change and a prominent vascular component. Distinction from a Spitz naevus may be difficult, but in epithelioid FH there is no junctional component, tumour cells are not nested and they are negative for S100.

Many histological variants of FH have been described; recognizing these variants is important to avoid misdiagnosis. They include lesions with palisading, granular cell change [19], lipid [20] and prominent clear cell change [21].

Treatment. Most FHs are no more than a cosmetic nuisance, and no treatment is necessary. However, cellular, aneurysmal and atypical variants should be completely removed, because of the risk of local recurrence and the occurrence of occasional distant metastases.

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Angiomatoid fibrous histiocytoma [1–3]

SYN. ANGIOMATOID MALIGNANT FIBROUS HISTIOCYTOMA

Definition. Angiomatoid FH was initially described as a variant of malignant FH [1]. It has recently been

reclassified as a neoplasm with low-grade malignant behaviour, unrelated to malignant FH. Although it is considered to be 'fibrohistiocytic' due to the cytological resemblance of tumour cells to histiocytes, focal positivity of these cells to desmin raises the possibility of muscular differentiation.

Clinical features. It presents in children and young adults, with no sex predilection, as an asymptomatic blue or skin-coloured subcutaneous or deeper mass. Most cases occur on the limbs and patients may present with systemic symptoms including fever, anaemia and weight loss. Generalized lymphadenopathy may also be seen.

Pathology [1–3]. Low-power examination reveals haemorrhagic, pseudovascular, cavernous-like, cystic spaces filled with red blood cells. Mononuclear inflammatory cells are prominent and germinal centres are present in some cases. Tumour cells are arranged in sheets and consist of short spindle-shaped and round cells with pink cytoplasm and vesicular nuclei. Cytological atypia is sometimes present, and the mitotic count tends to be low. Tumour cells are focally positive in some cases to desmin [3], muscle-specific actin and CD68, but not for smooth muscle actin.

Prognosis and management. Most cases are cured after adequate excision, but local recurrence is observed in about 15% of patients and, exceptionally, metastasis to neighbouring soft tissues or regional lymph nodes may occur. Complete excision and follow-up are therefore indicated. Local recurrence is more likely with deep tumours, those with an infiltrative growth pattern and those that are incompletely removed [2].

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Plexiform fibrous histiocytoma [1–3]

SYN. PLEXIFORM FIBROHISTIOCYTIC TUMOUR

Definition. Plexiform FH is a distinctive, predominantly subcutaneous tumour with two distinctive components:
1 A fibro/myofibroblastic fascicular component.
2 A nodular histiocytic-like component, which also includes giant cells.

Despite its new name, it does not represent a plexiform variant of an ordinary FH (dermatofibroma).

Clinical features [1,3]. It mainly occurs in children and young adults, most commonly in females, and has a predilection for the upper limbs. The tumour is solitary, measures no more than a few centimetres in diameter and is asymptomatic.

Pathology [1–3]. Low-power examination reveals a predominantly subcutaneous tumour, with focal involvement of the dermis and a distinctive plexiform growth pattern. Purely dermal lesions are occasionally seen. Two components are usually identified and consist of fascicles of bland spindle-shaped fibro/myofibroblast-like cells and nodules of histiocyte-like cells with scattered giant cells, focal haemorrhage and haemosiderin deposition. In some tumours, one of the components may predominate. The spindle-shaped cells stain focally for smooth muscle actin, and the cells in the nodules are focally positive for CD68.

Prognosis and treatment. Local recurrences are observed in up to 30% of cases. Metastases to regional lymph nodes or to the lungs have been reported [1,3,4]. Complete surgical excision and follow-up are therefore indicated. The histological features do not predict aggressive behaviour.

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Atypical fibroxanthoma [1–3]

Definition. Atypical fibroxanthoma (AFX), by definition, arises in sun-damaged skin of elderly people. Recently, ultraviolet radiation-induced *p53* mutations have been observed in these lesions, confirming the association with sun-damaged skin [4]. Tumours described in younger patients in non-sun-damaged skin represent examples of atypical FH.

Clinical features. The lesions occur most frequently on the ears, bald scalp and cheeks of elderly males (Fig. 53.9). Females are much less frequently affected. The lesions are often ulcerated and have a red, fleshy appearance; they rarely exceed 30 mm in diameter, and are usually of less than 6 months' duration. Many cases of AFX have been misdiagnosed clinically as granuloma telangiectaticum and—treated by curettage and cauterization—have been cured. Local recurrence has occasionally been seen, and

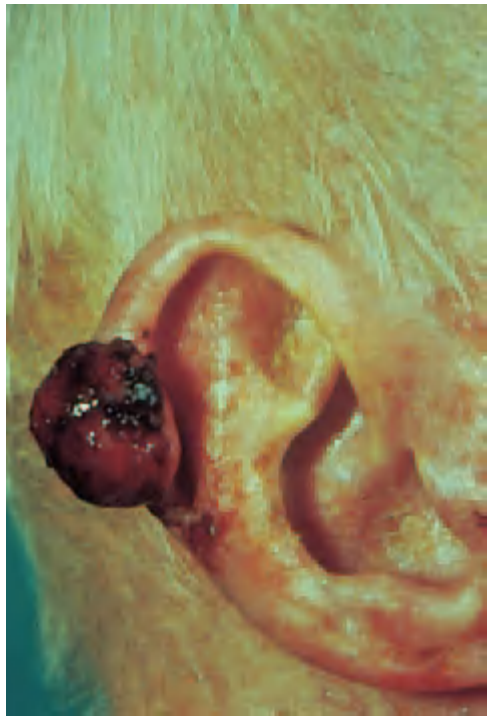

Fig. 53.9 Typical clinical appearance of an atypical fibroxanthoma with a polypoid architecture.

spread to lymph nodes is reported. However, since the advent of immunohistochemistry, reports of metastatic tumours have been very rare. This suggests that many lesions reported in the past as metastatic AFX, which were diagnosed by examination of haematoxylin and eosin stained slides alone, probably represented other tumours, such as spindle cell melanomas or sarcomatoid squamous cell carcinoma.

Pathology. The tumours are exophytic, fairly well-circumscribed and surrounded by an epidermal collarette. The remarkable and paradoxical feature of AFX is its histological resemblance to a highly malignant soft-tissue sarcoma (Fig. 53.10) [5–8]. It arises in the dermis and may extend into the fat, but the edge is pushing rather than infiltrative. It is composed of large spindle-shaped and histiocyte-like pleomorphic cells, many of which appear multinucleated. The cells are arranged in a haphazard fashion and mitotic figures, including atypical forms, are frequent. The histiocytic cells may contain lipid or haemosiderin [9,10]. There is current controversy as to whether the very atypical giant cells are aneuploid [11] or diploid [12]. A small series of a less pleomorphic spindle cell variant, which may cause considerable problems in differential diagnosis, has recently been described [13]. The diagnosis of AFX is a diagnosis of exclusion. An immunohistochemical panel to rule out melanoma (S100), sarcomatoid squamous cell carcinoma (pan-keratin) and

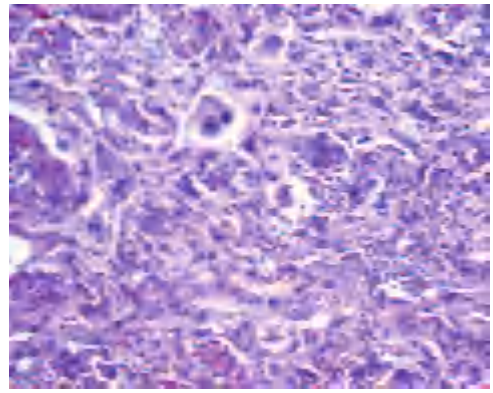

Fig. 53.10 Prominent cellular pleomorphism in a case of atypical fibroxanthoma.

even leiomyosarcoma (desmin) should be performed in all cases.

Treatment. The benign behaviour of the tumour enables it to be treated by limited local removal. Radiotherapy is not recommended.

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Malignant fibrous histiocytoma [1–4]

Definition. 'Malignant FH' is an umbrella term encompassing a heterogeneous group of neoplasms that initially included five different clinicopathologic subtypes: pleomorphic, myxoid, giant cell, inflammatory and

angiomatoid. There is little relation between the different subtypes; the angiomatoid variant has recently been reclassified in the group of fibrohistiocytic tumours and the name changed to 'angiomatoid FH'. The concept of pleomorphic malignant FH has been challenged as not representing a distinct group of neoplasms but a heterogeneous category, including pleomorphic poorly differentiated sarcomas. If cases classified as such are extensively studied with ancillary studies including immunohistochemistry and electron microscopy, a large percentage may be reclassified as pleomorphic variants of other soft-tissue tumours, including liposarcoma, rhabdomyosarcoma and leiomyosarcoma [5]. The myxoid variant of malignant FH is now known as 'myxofibrosarcoma', and it is likely to show fibroblastic differentiation; this tumour often involves the skin because of its frequent origin in the subcutis, and it will therefore be discussed in more detail below. Angiomatoid FH has been described under fibrohistiocytic tumours. The inflammatory and giant cell variants of malignant FH hardly ever involve the skin and will not be discussed further.

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Myxofibrosarcoma [1–4]

SYN. MYXOID MALIGNANT FIBROUS HISTIOCYTOMA

Definition. Myxofibrosarcoma is a neoplasm of the subcutis and deeper soft tissues with variable cellularity, myxoid change and cells with pleomorphic nuclei. The cellular end of the spectrum is identical to a pleomorphic malignant FH, and the diagnosis is made based on the presence of myxoid areas with less cellularity and a lobular pattern. The myxoid change should be seen in 10% or more of the tumour before a lesion is classified as myxofibrosarcoma.

Clinical features. This tumour mainly presents in middle-aged to old adults, with a slight predilection for females and for involvement of the extremities or trunk [4]. Typically, an asymptomatic mass, measuring several centimetres in diameter, is found in the subcutis or deeper soft tissues. This is one of the sarcomas that more often involves the dermis as a result of extension from the subcutis or deeper soft tissues, rather than having a dermal origin.

Pathology [4]. These tumours have a lobular growth pattern. They are classified according to the degree of cellularity and pleomorphism into low, medium and high grade. Low-grade tumours are paucicellular and consist of round or elongated bland and pleomorphic cells in a prominent myxoid stroma. The atypical cells have irregular hyperchromatic nuclei, and mitotic figures are relatively frequent. In the background, a fairly prominent number of thin-walled vascular channels with a typical curvilinear pattern are seen. Vacuolated Alcian blue-positive cells, focally mimicking lipoblasts, are relatively frequent. In some tumours, hypocellular areas blend with more cellular areas containing cells with increased pleomorphism; such tumours are classified as intermediate-grade. Tumours with high cellularity (high-grade) are indistinguishable from the so-called pleomorphic malignant FH and may have necrosis. Grading of lesions is important, because the rate of local recurrence and metastasis varies (see below). Tumour cells are positive for vimentin and only rarely display very focal positivity for actin.

Prognosis and treatment [4]. Excision with clear margins is essential. High-grade lesions have a higher tendency for local recurrence and for metastatic spread to regional lymph nodes. The overall 5-year survival is around 60%.

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Vascular tumours

Reviews of vascular tumours may be found in [1,2]. The vascular ectasias, verrucous haemangioma, tufted angioma and cavernous and capillary haemangiomas are described in Chapter 15.

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Intravascular papillary endothelial hyperplasia [1–4]

SYN. MASSON'S PSEUDOANGIOSARCOMA; MASSON'S VEGETANT INTRAVASCULAR HAEMANGIOENDOTHELIOMA

Definition. Intravascular papillary endothelial hyperplasia is regarded as a form of organizing thrombus in which endothelial cells line hyalinized papillae.

Incidence and aetiology. This is a relatively common lesion, which usually presents as a primary phenomenon within a thrombosed blood vessel, usually a vein [2–4]. The secondary variant is commonly seen as an incidental finding within other vascular tumours, or in lesions such as haemorrhoids. Exceptionally, the same phenomenon is seen within a haematoma [4]. The primary form presents in young adults, with a slight predilection for females.

Clinical features. The primary form presents as a slowly-growing single asymptomatic or slightly painful bluish nodule less than 20 mm in diameter. The site of predilection is the head and neck, followed by the hand (particularly the fingers). Multiple lesions are exceptional [5].

Pathology. The pathology is that of a widely dilated vascular channel in the dermis or subcutis, containing an organizing thrombus and prominent papillary projections with a hyalinized collagenous core. The papillae are lined by a single layer of usually bland endothelial cells with few mitotic figures. The presence of hyalinized collagen lined by endothelial cells produces an appearance similar to the 'dissection of collagen bundles' described in angiosarcoma. Distinction from angiosarcoma, however, is easy, as the latter is only exceptionally purely intravascular; it also displays cytological atypia, multilayering and mitotic figures. In secondary forms of Masson's tumour, the changes are seen within one or several vascular channels of a vascular tumour, usually a cavernous haemangioma or a vascular malformation.

Diagnosis. The clinical diagnosis suggested usually is that of a vascular tumour.

Treatment. Simple excision is usually curative and there is no tendency for local recurrence.

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Reactive angioendotheliomatosis [1–3]

Definition. A reactive vascular proliferation, which is usually multifocal and which is associated with a number of systemic diseases. In the past, it was divided into a reactive and a malignant form. With the advent of immunohistochemistry, it became apparent that the malignant form is a variant of aggressive intravascular lymphoma (see Chapter 54).

Incidence and aetiology. This condition is rare and involves adults, with a wide age range and no sex predilection. Most cases present with cutaneous involvement only and are idiopathic. It has been described in association with systemic diseases, including bacterial endocarditis, peripheral vascular atherosclerotic disease, cryoglobulinaemia [2], liver and renal disease, antiphospholipid syndrome [4] and amyloidosis [5]. It is not clear how systemic diseases induce this vascular proliferation.

Clinical features. Most patients present with multiple erythematous and/or haemorrhagic macules, papules and plaques on the trunk and limbs. Patients with fewer, more localized, lesions may also be seen. In the latter cases, the association with systemic disease is not usually present. In patients with antiphospholipid syndrome or cryoglobulinaemia, ulcerated lesions may be present.

Pathology [6]. The dermis and, in some cases, the subcutis show a multifocal proliferation of clusters of capillaries lined by plump endothelial cells with little or no cytological atypia. A layer of pericytes surrounds each capillary. In some areas, dilated capillaries appear to contain smaller vascular channels within their lumina. Patients with cryoglobulinaemia show thrombosis of capillaries by hyaline eosinophilic globules.

Treatment. There is no treatment available, but the condition is usually self-limited and resolves spontaneously within a few weeks.

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Glomeruloid haemangioma [1,2]

Definition. This is a distinctive multifocal vascular proliferation that occurs in association with POEMS syndrome (*p*olyneuropathy, *o*rganomegaly, *e*ndocrinopathy, *M* protein and *s*kin changes) or with multicentric Castleman's disease. This condition is best considered as a form of reactive angioendotheliomatosis in the setting of POEMS syndrome.

Incidence and aetiology. This is a rare disease that presents exclusively in the context of POEMS syndrome and multicentric Castleman's disease. It presents in adults, with no sex predilection.

Clinical features. Patients present with multiple vascular papules on the trunk and limbs. Only a minority of these vascular lesions have the histological appearance of glomeruloid haemangioma; most have the histological appearance of cherry angiomas, or overlap with other vascular lesions, including cirsoid aneurysm (p. 53.19).

Pathology. The histological appearances in a typical case are striking, consisting of a multifocal dermal proliferation of clusters of closely packed dilated capillaries with a striking similarity to renal glomeruli. A layer of pericytes surrounds each capillary. Vacuolated cells are focally present and, in some cases, there are eosinophilic hyaline globules within the lumina of capillaries. These globules represent deposits of protein.

Treatment. The lesions do not tend to regress spontaneously. Individual lesions can be removed surgically, but because of their numbers this is not generally a practical option.

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Pyogenic granuloma [1,2]

SYN. LOBULAR CAPILLARY HAEMANGIOMA; GRANULOMA TELANGIECTATICUM

Definition. A vascular nodule that develops rapidly, often at the site of a recent injury, and which is composed of a lobular proliferation of capillaries in a loose stroma.

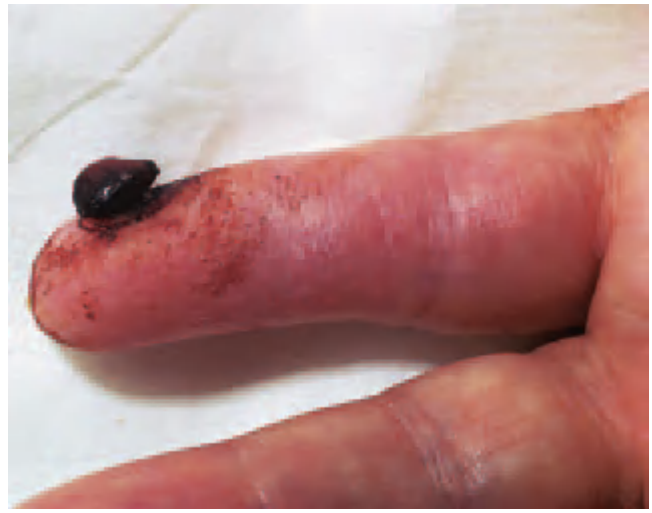

Fig. 53.11 Clinical appearance of a pyogenic granuloma on a typical site at the tip of the finger.

Incidence and aetiology. This is a common lesion affecting both sexes with a predilection for females. It may occur at any age, and is seen quite often in children and young adults but is unusual in the elderly [3]. In a minority of cases, a minor injury, usually of a penetrating kind, has occurred a few weeks before the nodule appears. In other cases, no injury can be recollected, but this is likely on the basis of the patient's occupation or the body site affected. The balance of evidence indicates a reactive lesion.

Granuloma gravidarum is a variant of pyogenic granuloma that presents in the oral cavity during pregnancy.

Clinical features. The tumour is vascular, bright red to brownish-red or blue-black in colour. It is partially compressible, but cannot be completely blanched and does not show pulsation. The surface of early bright-red lesions is usually thin, intact epidermis. Older and darker lesions are frequently eroded and crusted, and may bleed very easily. Occasionally, the surface is raspberry-like or even verrucous. The size is commonly between 5 and 10 mm, but may reach 50 mm. The outline is rounded. The base is often pedunculated and surrounded by a collar of acanthotic epidermis; the lesion may be sessile. The common sites are the hands, especially the fingers (Fig. 53.11), the feet, lips, head and upper trunk, and the mucosal surfaces of the mouth and perianal area. The initial evolution is rapid, but growth ceases after a few weeks. Spontaneous disappearance is rare. Lesions are not painful; patients mainly complain of the appearance or of recurrent bleeding. There is a recent report of multiple pyogenic granulomas developing after exfoliative dermatitis [4]. Eruptive forms of this tumour have rarely been described [5]. In this setting, distinction from bacillary angiomatosis is crucial, as the latter often presents with multiple lesions that can be clinically and histologically difficult to distinguish

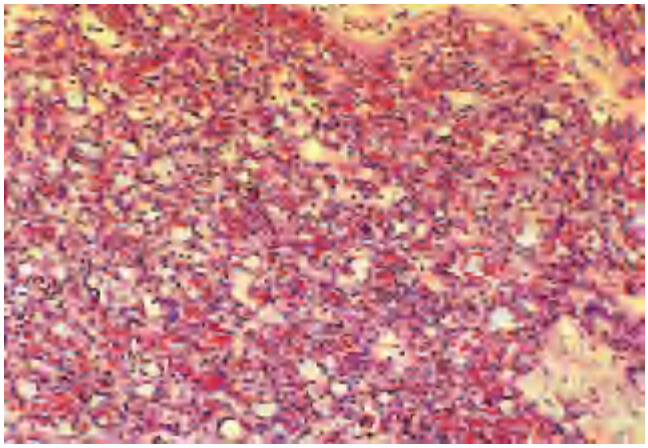

Fig. 53.12 Typical lobules of capillaries in a myxoid background, in a case of pyogenic granuloma.

from pyogenic granuloma. Multiple lesions closely resembling pyogenic granulomas have been reported after systemic [6] and topical [7] treatment with retinoids. Subcutaneous [8] and intravascular [9] variants are rarely seen and do not have distinctive clinical features.

Pathology. There is a lobular proliferation of small blood vessels, which erupt through a breach in the epidermis to produce a globular pedunculated tumour. The epidermis forms a collarette at the base of the lesion and covers part, or all, of the tumour in a thin layer. The proliferating vessels are set in a myxoid stroma, lacking in collagen in the earlier stages and relatively rich in mucin. The endothelial cells are plump, as in new granulation tissue, lining the vessels in a single layer. They are surrounded by a mixed cell population of fibroblasts, mast cells, lymphocytes, plasma cells and, where the surface is eroded, polymorphonuclear leukocytes (Fig. 53.12). Mitotic figures may be prominent. Older lesions tend to organize and partly fibrose. Late lesions can display focal degenerative atypia, raising the possibility of malignancy. In rare instances, particularly in children, and sometimes following treatment, satellite lesions which have a similar pathology to the primary lesion may develop around a pyogenic granuloma. These respond to simple destructive measures, thus ruling out malignancy [10]. Bacillary angiomatosis shows an almost identical histology to that of pyogenic granuloma [11]. However, in bacillary angiomatosis, pale epithelioid endothelial cells are prominent, neutrophils and nuclear dust are seen throughout the lesion and violaceous amorphous aggregates of bacilli which are positive with either Giemsa or Warthin–Starry stains are easily identified.

Diagnosis. In most cases, the history and clinical appearance leave little doubt about the diagnosis, and microscopic confirmation is straightforward. In 38% of one case series, the clinical diagnosis of pyogenic granuloma proved to be wrong [12]. The errors included keratoacanthoma and other epithelial neoplasms, inflamed seborrhoeic keratoses, melanocytic naevi, juvenile and malignant melanoma, virus warts, molluscum contagiosum, angioma, glomus tumour, eccrine poroma, Kaposi's sarcoma and metastatic carcinoma.

Treatment. The pedunculated lesions are easy to treat by curettage with cauterization or diathermy coagulation of the base. A considerable proportion of pyogenic granulomas recur after such treatment, because the proliferating vessels in the base extend in a conical manner into the deeper dermis. In some areas—for instance in the nail fold or on the palmar aspect of a finger—it may be reasonable to carry out curettage and hope for the best. Wherever possible, it is desirable to excise a narrow, but deep, ellipse of skin beneath the lesion and close the wound with sutures.

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Cirsoid aneurysm [1–3]

SYN. CUTANEOUS ARTERIOVENOUS HAEMANGIOMA; ACRAL ARTERIOVENOUS TUMOUR

Definition. Cirsoid aneurysm is a small vascular proliferation characterized by small to medium-sized channels with features of arteries and veins. As opposed to deeper tumours showing similar features, shunting is absent.

Clinical features. Most lesions present on the head and neck region of young adults, with no sex predilection, as a small blue/red asymptomatic papule.

Pathology. The dermis contains a mixture of scattered blood vessels with thick walls and features of veins and arteries.

Treatment. As there is no associated shunting or deep component, simple excision is the treatment of choice.

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Epithelioid haemangioma [1,2]

SYN. ANGIOLYMPHOID HYPERPLASIA WITH EOSINOPHILIA; PSEUDOPYOGENIC GRANULOMA; HISTIOCYTOID HAEMANGIOMA

Definition. A benign, locally proliferating lesion composed of vascular channels lined by endothelial cells with abundant pink cytoplasm and vesicular nuclei. Kimura's disease is distinct from angiolymphoid hyperplasia with eosinophils. In Kimura's disease, the lesions occur in younger patients, are deeper-seated, are associated with lymphadenopathy, have no initial overlying skin lesions and do not contain epithelioid endothelial cells [3,4]. Furthermore, peripheral blood eosinophilia is much more common in Kimura's disease.

Incidence and aetiology. These lesions have now been reported from many parts of the world. The cause is unknown, but most studies suggest a reactive process [5].

Clinical features [6–10] (Fig. 53.13). Affected individuals are commonly young adults who present with a cluster of small, translucent nodules on the head and neck, particularly around the ear or the hairline. The lesions may also involve the oral mucosa [11]. Less frequently, lesions can involve the trunk and extremities. Involvement of deeper soft tissues and internal organs, including bone, can be seen. Both sexes are equally affected. Individual nodules rarely exceed 2–3 cm in diameter, but occasionally deeper extension and larger subcutaneous lesions occur. Spontaneous regression is seen in the majority of cases after a variable period of time. Peripheral blood eosinophilia may be present but only in less than 10% of patients.

Pathology [2,12]. A poorly circumscribed lobular lesion is seen. It is composed of clusters of proliferating capillaries and, often, thicker blood vessels lined by plump, epithelioid endothelial cells with little cytological atypia and rare mitotic figures. Around the blood vessels there is a cellular inflammatory infiltrate composed mainly of lymphocytes and large numbers of eosinophils. However, only less than half of cases contain a prominent infiltrate. Older lesions show sclerosis of the stroma and the endothelial cells become more prominent. A frequent finding, particularly in larger lesions, is the involvement of larger blood vessels. Rare cases are entirely intravascular [13]. The endothelial cells stain for vascular markers including CD34, von Willebrand factor and CD31. In cutaneous cases, endothelial cells are negative for pan-keratin.

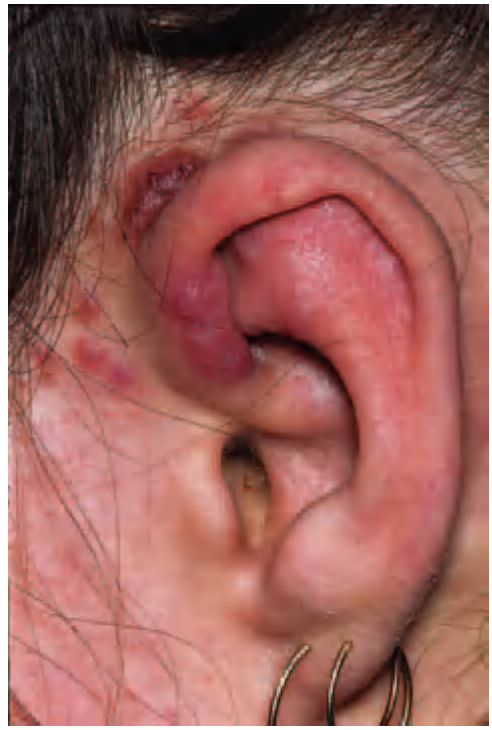

Fig. 53.13 Epithelioid haemangioma, or angiolymphoid hyperplasia with eosinophilia. (Courtesy of Dr R.H. Champion, Addenbrooke's Hospital, Cambridge, UK.)

Treatment. The natural history of the lesion is such that if a confident diagnosis is made on a small lesion, it is reasonable to observe the lesion for 3–6 months and await spontaneous regression. Both surgery and radiotherapy are effective, but local recurrences are common.

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Hobnail haemangioma [1–4]

SYN. TARGETOID HAEMOSIDEROTIC HAEMANGIOMA

Definition. This is a benign vascular dermal proliferation characterized by small channels lined by endothelial cells with little cytoplasm and a prominent dark nucleus (hobnail cells). Formation of small papillae is also often seen. The original name proposed for this condition was based on a distinctive targetoid clinical appearance produced by bleeding and haemosiderin deposition. However, only a minority of lesions present with this typical appearance and therefore, the alternative name of hobnail haemangioma has been proposed.

Incidence and aetiology. It is relatively uncommon and occurs mainly in young to middle-aged adults with a slight predilection for males. Trauma may play a part in its pathogenesis [4].

Clinical features. This entity presents as a rapidly developing, asymptomatic, solitary red or brown lesion, which in some cases has a central raised violaceous papule and is surrounded by a paler brown halo (targetoid appearance) [1]. Any body site may be affected, but it has predilection for the lower limbs and trunk. The oral mucosa may also be affected [3].

Pathology. Pathological examination shows dilated vascular channels in the papillary and high reticular dermis, with a single layer of endothelial cells lining intraluminal papillary projections. These cells give a hobnail ('matchstick') appearance. They may occasionally be more numerous and appear to fill the lumen of the vessel. The vascular channels tend to disappear in the mid and lower reticular dermis, and the endothelial cells become less prominent and loose the hobnail appearance. Haemosiderin deposition is prominent and can be highlighted with a Perl's stain. The pathological appearance may resemble Kaposi's sarcoma, but this differential diagnosis can usually be resolved by clinicopathological correlation, as hobnail haemangioma is a solitary entity, whereas Kaposi's sarcoma is usually composed of multiple lesions. Histological distinction can be made if attention is paid to the symmetry of the lesion, the presence of hobnail endothelial cells with papillary projections and the absence of inflammation in hobnail haemangioma.

Diagnosis. It is usually suspected clinically if lesions have a targetoid appearance. The diagnosis is otherwise made histologically.

Treatment. Simple surgical excision is the treatment of choice; there is no tendency for recurrence.

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Microvenular haemangioma [1–3]

Definition. This is a benign dermal vascular lesion characterized by proliferation of small vascular channels with features suggestive of venules.

Incidence and aetiology. It is relatively rare and presents mainly in young adults, with no sex predilection. Presentation in children is very rare [4]. Although the histological appearances suggest a venular differentiation, this has not been proven.

Clinical features. It presents as a solitary red/brown or bluish papule, nodule or plaque with predilection for the limbs. Most lesions are less than 10 mm in diameter.

Pathology. There is a superficial and deep dermal proliferation of angulated, thin-walled, vascular channels, all of which are surrounded by a single layer of pericytes. These channels are lined by flat, bland, endothelial cells and are surrounded by somewhat hyalinized collagen. A frequent finding is the infiltration of arrector pili muscles by vascular channels. Inflammation is not usually a feature.

Treatment. Simple surgical excision is the treatment of choice; there is no tendency for local recurrence.

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Sinusoidal haemangioma [1]

Definition. This is a benign dermal and/or subcutaneous variant of cavernous haemangioma composed of thin-walled dilated vascular spaces in a typical sieve-like distribution.

Incidence and aetiology. Lesions are rare and present in adults, with a slight predilection for females.

Clinical features. Sinusoidal haemangioma presents as a solitary blue asymptomatic nodule, particularly on the trunk or upper limbs. The dermis and subcutaneous tissue overlying the breast is not uncommonly involved and may suggest a diagnosis of angiosarcoma (see below).

Pathology. The lesion is usually well circumscribed, but several lobules of subcutaneous tissue may be focally affected by the tumour. A striking feature is the presence of back-to-back dilated and congested thin-walled vascular channels. These channels are interconnected, and transverse sectioning is in part responsible for the distinctive sinusoidal appearance. Pseudopapillary projections are focally present and thrombosis with dystrophic calcification may also be seen. Focal cytological atypia secondary to degenerative changes may be seen. Distinction from angiosarcoma, particularly in tumours presenting in the breast, is based on the fact that the latter occurs in the breast parenchyma and only invades the dermis and subcutis secondarily. Tumour cells in angiosarcoma also display cytological atypia, multilayering and mitotic figures.

Treatment. Simple surgical excision is the treatment of choice, and there is no tendency for local recurrence.

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Spindle cell haemangioma [1–5]

SYN. SPINDLE CELL HAEMANGIOENDOTHELIOMA

Definition. This is a benign vascular tumour, initially described as a low-grade malignant lesion with high tendency for local recurrence and minimal potential for metastasis. Further studies, however, demonstrated that it is a benign multifocal process often associated with a vascular malformation [3–5]. Confirmation of its benign nature has led to the change of the name 'haemangioendothelioma' for 'haemangioma' as the former implies low-grade malignant potential [6].

Incidence and aetiology. Spindle cell haemangioma is relatively rare. Males and females are affected equally, and the age range is wide. Often, lesions present in childhood or early adulthood and tend to be long-standing. The process appears to be reactive, and it is often associated with lymphoedema, Maffucci's syndrome (multiple enchondromas) [7], early onset varicose veins or Klippel–Trenaunay syndrome.

Clinical features. The majority of cases present in the distal limbs, particularly the hands and feet, as multiple cutaneous or subcutaneous red or bluish nodules. Deeper tumours are rare. Lesions continue to appear over many years, indicating multifocality rather than true recurrences. Most nodules are less than a few centimetres in diameter; they may occasionally be painful.

Pathology. Low-power magnification reveals single or multiple, fairly well-circumscribed, haemorrhagic nodules. Origin from a pre-existing blood vessel is often seen, and individual lesions may be entirely intravascular. Dilated, thin-walled, congested, cavernous-like vascular spaces are intermixed with more cellular areas composed of bland, short, spindle-shaped cells, with formation of slit-like spaces. Scattered more epithelioid cells, with pink cytoplasm and prominent vacuolation, are also seen. The spindle-shaped cells are a mixture of endothelial cells, pericytes and fibroblasts. Focal degenerative cytological atypia may be present. Immunohistochemistry reveals staining for CD31 and CD34 and focal staining for smooth muscle actin.

Diagnosis. The clinical appearances usually suggest a vascular process, but the final diagnosis usually requires histological confirmation.

Treatment. Single lesions are easily treated with simple excision. Treatment is more difficult in the presence of multiple lesions, as new lesions are more likely to appear over time.

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Kaposiform haemangioendothelioma [1–5]

SYN. KAPOSI-LIKE INFANTILE HAEMANGIOENDOTHELIOMA

Definition. Kaposiform haemangioendothelioma is a locally aggressive vascular neoplasm, which occurs mainly in the abdominal cavity [1] but can affect primarily the skin or deeper soft tissues.

Incidence and aetiology. This tumour is rare and presents mainly in young children under the age of 2 years, with no sex predilection. Some lesions are congenital [6]. Rare cases occur in older children and adults. In 20% of cases, there is an association with lymphangiomatosis [3]. It appears clear that this lesion is truly neoplastic. Although it is not malignant, it causes morbidity and mortality due to its location and the frequent occurrence of Kasabach–Merritt syndrome.

Clinical features. The most common presentation by far is that of a large retroperitoneal infiltrative mass. Involvement of neighbouring organs and the very common association with consumption coagulopathy (Kasabach–Merritt syndrome) may lead to death. This complication is less common in more superficial tumours, particularly those located in the dermis and subcutaneous tissue [5,7,8].

Pathology. The growth pattern is lobular and infiltrative. Multiple nodules with haemorrhage and surrounding fibrosis are seen. Tumour lobules are composed of bland spindle-shaped cells with poorly defined pink cytoplasm. Cleft-like spaces are often seen between spindle-shaped cells, and a resemblance to Kaposi's sarcoma can be striking. However, numerous capillaries, often associated with microthrombi, are also present in tumour lobules. Epithelioid endothelial cells with focal vacuolation are also present. These features, along with the striking lobular architecture of the tumour, allow distinction from Kaposi's sarcoma.

Treatment. Complete excision is desirable as local recurrence is frequent, but this may be difficult to achieve when involvement is extensive. Spontaneous regression does not occur.

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Atypical vascular proliferation after radiotherapy [1–3]

These lesions usually present a few years or months after radiotherapy for breast cancer (by comparison, post-irradiation angiosarcomas tend to present many years after radiotherapy) [1–3]. The clinical lesions are not distinctive and vary from macules to papules. Occasional cases may mimic lymphangioma circumscriptum. Irregular lymphatic-like vascular channels, lined by a single layer of endothelial cells, are seen in the dermis. The endothelial cells can have a hobnail appearance, and papillary projections can also be found. Careful examination of multiple sections is recommended to make sure that there are no mitotic figures or cytological atypia, as distinction from a well-differentiated angiosarcoma can be very difficult.

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Giant cell angioblastoma [1,2]

This is a very rare distinctive congenital vascular tumour of which only a few cases have been reported, situated on the hand, the palate and the scalp. The tumour is diffusely infiltrative and slowly growing. Two of the reported cases showed no progression after incomplete excision. The

tumour is composed of infiltrative vascular channels lined by a single layer of bland endothelial cells and intermixed with solid nodules composed of spindle-shaped cells, histiocyte-like cells and osteoclasts. A plexiform growth pattern is often seen.

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Retiform haemangioendothelioma [1–3]

SYN. HOBNAIL HAEMANGIOENDOTHELIOMA

Definition. Retiform haemangioendothelioma is a rare variant of low-grade angiosarcoma with a tendency for local aggressive behaviour. It is characterized by arborizing vascular channels lined by endothelial cells with a hobnail morphology.

Clinical features [1–3]. Retiform haemangioendothelioma presents mainly in young adults, with no sex predilection, as a slowly growing, asymptomatic, dermal and subcutaneous plaque or nodule. Exceptional cases present with multiple lesions [4]. Rarely there is an association with lymphoedema or radiotherapy. Local recurrence occurs in up to 60% of cases. So far, only one tumour has metastasized to a regional lymph node, and a further lesion has spread to locally to soft tissues [5]. No tumour-related deaths have been reported.

Pathology. Scanning magnification is distinctive and reveals arborizing, thin-walled narrow vascular channels with a striking resemblance to the rete testis. The growth pattern is infiltrative, and the vascular spaces are lined by bland hobnail endothelial cells with prominent nuclei and scanty cytoplasm. Intravascular papillae with collagenous cores, similar to those seen in papillary endolymphatic angioendothelioma, are sometimes seen. The surrounding stroma often appears hyalinized; a prominent mononuclear inflammatory cell infiltrate is common. The endothelial cells stain for vascular markers. There is no relationship to human herpesvirus 8 (HHV8).

Treatment. Wide local excision is the treatment of choice.

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Papillary intralymphatic angioendothelioma [1]

SYN. ENDOVASCULAR LYMPHATIC ANGIOENDOTHELIOMA; DABSKA'S TUMOUR

Definition. Defining this entity is difficult because, since its original description in 1969, few further convincing cases have been described [1–4]. Furthermore, the original series included some examples of what it is now known as retiform haemangioendothelioma. Recently, the tumour has been better characterized under the preferred name of 'papillary endolymphatic angioendothelioma' [5]. It belongs to the family of tumours with hobnail endothelial cells, and it is characterized by dilated, cavernous-like lymphatic spaces with frequent papillary projections.

Clinical features. It presents mainly in infants and children, with 25% of the cases occurring in adults. There is no sex predilection. Presentation is as a slowly growing asymptomatic plaque or nodule with a predilection for the limbs. Although in the original series of six cases, a tendency for local recurrence and metastasis to regional lymph nodes was reported [1], in a recent series of 12 cases, none of the eight cases with follow-up recurred locally or metastasized [5]. It therefore seems likely that the behaviour of this tumour is benign.

Pathology. This tumour is composed of dilated, thin-walled channels simulating a cavernous lymphangioma. These channels are lined by bland hobnail endothelial cells with very rare mitotic figures. A striking feature is the formation of intraluminal papillary tufts with hyaline cores. Aggregates of mononuclear inflammatory cells may be seen around the vascular channels.

Treatment. Until the issue regarding the biological behaviour of this tumour is resolved, complete excision is recommended.

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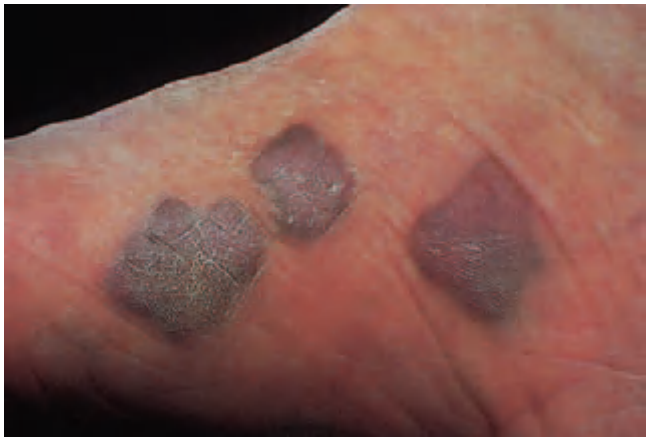

Fig. 53.14 Classic Kaposi's sarcoma arising on the feet of a male patient of Mediterranean origin.

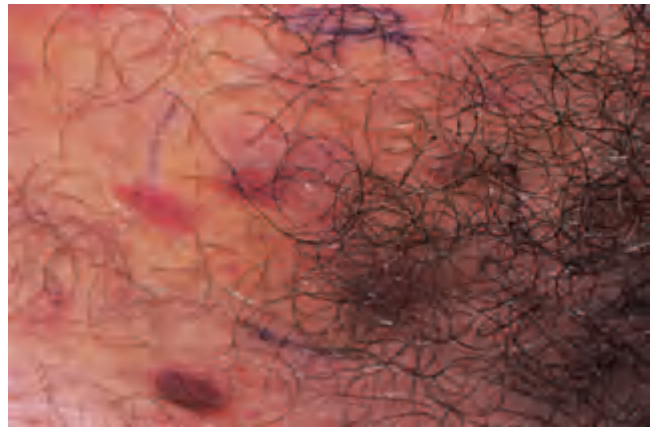

Fig. 53.15 Patch-stage Kaposi's sarcoma in an HIV-positive patient.

Kaposi's sarcoma [1–3]

SYN. KAPOSI'S DISEASE; GRANULOMA MULTIPLEX HAEMORRHAGICUM; IDIOPATHIC MULTIPLE PIGMENTED SARCOMA

Definition. A multifocal endothelial proliferation predominantly involving the skin and other organs and associated with formation of vascular channels and proliferation of spindle-shaped cells. It is not clear whether Kaposi's sarcoma is a reactive vascular proliferation or a neoplastic process. The recent demonstration of clonality tends to favour a neoplastic process [4].

At present, there are four recognized clinical subsets of Kaposi's sarcoma. These are:

1 Classic
2 Endemic
3 Iatrogenic
4 Human immunodeficiency virus (HIV)-related (Chapter 26).

Recent work has clearly identified a new type of herpesvirus, HHV8, in all Kaposi's sarcoma patients, both those with and those without additional HIV infection [5–7]; additionally, seroconversion to positivity against Kaposi's sarcoma-associated herpesvirus nuclear antigens has been observed [8]. This gives further support to the belief that this virus, along with genetic, immunological and environmental factors, is closely involved in the pathogenesis of Kaposi's sarcoma [9].

Classic Kaposi's sarcoma [10–12] is as described originally by Kaposi. It is found mainly in elderly males, particularly from Southern Europe or Jews of Eastern European origin. The lesions begin slowly and insidiously around the ankle and slowly spread up the leg (Fig. 53.14). Lymphoedema can occur as a complication. Lesions in other locations, including the oral mucosa, are very rare. Involvement of internal organs is not usually seen. The disease is very rarely responsible for the death of the patient. An association with haemopoietic malignancies may be seen.

Endemic Kaposi's sarcoma [13,14] is found in equatorial Africa, mainly in Zaire, Uganda [15,16] and Rwanda. In adults, males predominate, but this form is also seen in children. Crops of cutaneous vascular lesions develop, and may be associated with gross oedema. Visceral lesions may also occur; the prognosis is poor if there is extracutaneous involvement. The condition responds to chemotherapy.

Iatrogenic Kaposi's sarcoma [10,17,18]. This is seen in transplant patients and after cytotoxic chemotherapy for lymphomas. In transplant patients, it is 150 times more common than expected, and affected patients may be younger than those with other types of Kaposi's sarcoma (excepting those with HIV infection). Both systemic and cutaneous involvement may occur, and the progress of the disease may be aggressive, causing the death of the patient. If it is possible to remove the immunosuppression, the lesions will regress.

Kaposi's sarcoma associated with HIV infection [19–21]. This variant was first recognized in 1979 [22–24] when an epidemic of Kaposi's sarcoma was identified in the homosexual community in New York. Since that time, it has become firmly associated with the later stages of HIV infection [25–28]. However, it is much commoner in homosexuals than in others at risk, such as drug abusers or haemophiliacs. Kaposi's sarcoma usually develops in the later stages of the disease and is rarely a presenting feature of HIV infection. However, because of an awareness of the association between Kaposi's and HIV infection, both clinicians and pathologists may be called on to diagnose, or more often to exclude, Kaposi's sarcoma in its very early stages in 'at-risk' individuals. At this stage, only one or two flat macules may be present (Fig. 53.15). In the later stages, however, the lesions may occur anywhere on the body, develop with explosive rapidity and become

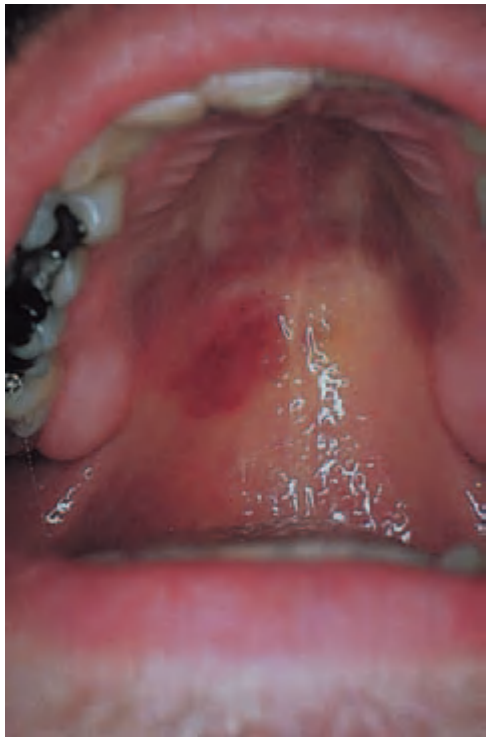

Fig. 53.16 Early lesion of Kaposi's sarcoma in an HIV-positive patient.

large nodules. The face and mucous membranes such as the soft palate are relatively frequently involved (Fig. 53.16). Involvement of lymph nodes, lungs and gastrointestinal tract is common. While both radiotherapy and chemotherapy may offer worthwhile temporary benefit, the prognosis is poor.

Clinical features [2,29–31]. Kaposi's sarcoma tends to occur in males. The lesions have a dark-blue or purplish colour. Initially, they may be almost macular and when they become tumid, pressure may produce partial blanching to reveal a brown tinge. The process usually begins on the extremities, most commonly on the feet and occasionally on the hands, ears or nose. Individual tumours enlarge to a diameter of 10–30 mm and stop growing. The process is multifocal, and adjacent areas may fuse to form a plaque or tumour. Oedema of the limb may follow, or at times precede, the appearance of the tumour. There are few subjective symptoms; pain may be felt in nodules on pressure areas. The lesions may involute to leave pigmented scars, or may become eroded, ulcerated or fungating. New lesions may appear along the course of superficial veins, and in time most patients have more or less symmetrical lesions. The rate of spread is remarkably variable. It tends to be slow in Europeans and more rapid in Africans, where oedema is often the first sign. Lymph nodes, mucosal surfaces and internal organs, particularly the small intestine, may all be involved as the disease

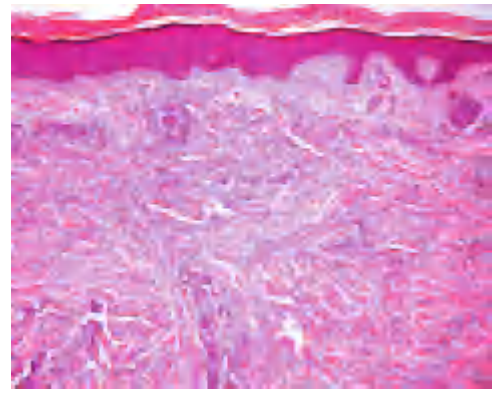

Fig. 53.17 Patch-stage Kaposi's sarcoma. Note the dermal proliferation of small, thin-walled, irregular lymphatic-like channels around pre-existing normal blood vessels and adnexal structures.

progresses. Kaposi's sarcoma may at times start in other organs and run its course without skin manifestation. Visceral involvement is the common pattern in African children, with lymph nodes as the main tissue involved.

Patients presenting with Kaposi's sarcoma associated with severe immunodepression have subtle lesions, which may well be missed by the unwary [2]. They may have only one or two lesions scattered over the body, and these may resemble slight areas of trauma or a simple bruise. The lesions are therefore quite dissimilar from the classic florid lesions developing on the lower limbs of the older patients from central Europe.

Pathology [31–35]. The cutaneous lesions of Kaposi's sarcoma can generally be divided into patch, plaque and nodular stages. These stages often overlap clinically and histologically. In the patch stage of the disease, there is a proliferation of jagged, irregular, lymphatic-like vascular channels lined by a single layer of bland endothelial cells, surrounding pre-existing blood vessels and adnexal structures (Fig. 53.17). Normal pre-existing capillaries and even adnexal structures seem to be floating within the newly formed channels, the so-called 'promontory sign' (Fig. 53.18). From the early stages a patchy, variably prominent, mononuclear inflammatory cell infiltrate containing plasma cells is seen. This is associated with extravasation of red blood cells and haemosiderin deposition. In some cases, numerous irregular, widely dilated, lymphatic-like channels impart a prominent lymphangiomatous appearance (lymphangiomatous Kaposi's sarcoma) [36].

The plaque stage is an exaggeration of the patch stage (Fig. 53.19). The vascular channels increase in number, and a network of bland spindle-shaped cells with pink cytoplasm develops. Dilated vascular channels in a back-to-back pattern may also be seen. Intra- or extracellular hyaline PAS-positive eosinophilic globules are common, and probably represent degenerate red blood cells [36].

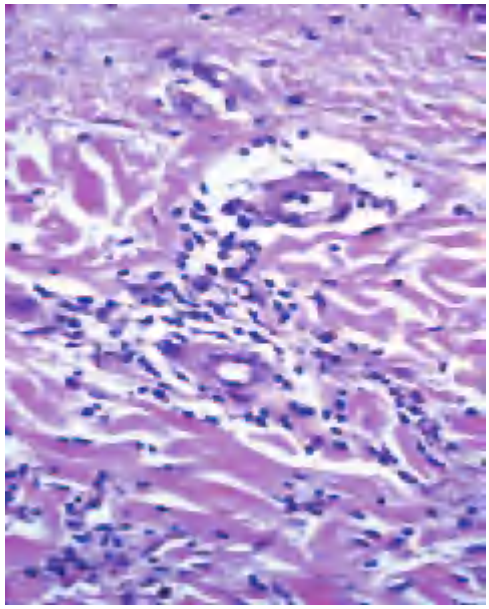

Fig. 53.18 Patch-stage Kaposi's sarcoma. Small irregular vascular channels lined by bland endothelial cells. Note the promontory sign, in which a normal pre-existing capillary seems to be floating in a newly formed channel.

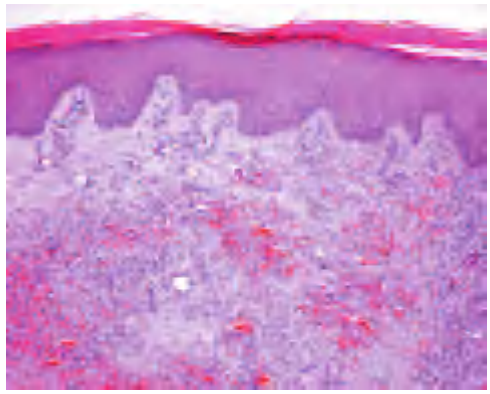

Fig. 53.19 Plaque-stage Kaposi's sarcoma. More diffuse proliferation of vascular channels with prominent haemorrhage.

Involvement of the whole dermis and superficial subcutis is frequent.

In the nodular stage, there are fairly well-circumscribed nodules of generally bland, spindle-shaped cells forming frequent cleft-like spaces that impart a typical sieve-like appearance (Fig. 53.20). Extravasated red blood cells are plentiful, as are hyaline globules. Mitotic figures are common. The periphery of the nodules may display a more angiomatous appearance.

Very rare examples of Kaposi's sarcoma display a high degree of cytological atypia and behave in an aggressive fashion.

A useful aid in the histological diagnosis of Kaposi's sarcoma is a newly developed monoclonal antibody against HHV8, which stains tumour cells in all cases of the disease. *In-situ* hybridization may also be used to demonstrate the virus, but this more expensive and time-consuming technique is not widely available.

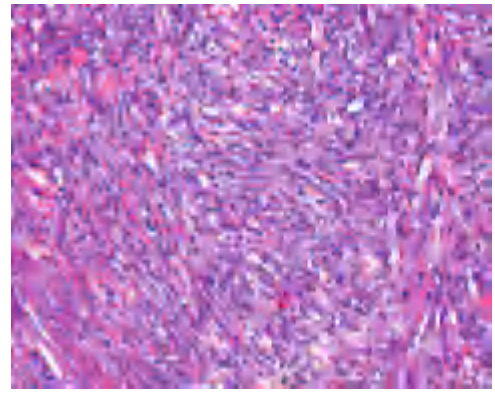

Fig. 53.20 Nodular Kaposi's sarcoma. Note the typical sieve-like appearance, with blood cells between the cleft-like spaces.

The pathological differential diagnosis includes many benign vascular tumours or reactive proliferations, including spindle cell haemangioma, tufted angioma, microvenular haemangioma, hobnail haemangioma, progressive lymphangioma and, on the lower legs, a 'venous' dermatitis (acroangiodermatitis). Angiosarcoma is also often considered in the differential diagnosis, but in the latter there is clear evidence of cytological atypia and multilayering.

Diagnosis [28]. The early lesion is most likely to be confused with a wide variety of benign vascular proliferations (see above) [31,34,35]. It must also be distinguished from histiocytoma or from other types of sarcoma. Its evolution from a macular lesion and its characteristic colour, slow development and multifocal distribution make the diagnosis likely in most instances. Cases in which the tumour is preceded by oedema may cause difficulty, as lymphangiosarcoma may arise in chronic lymphoedema. In prolonged venous hypertension of the lower legs, or in association with underlying vascular malformations, nodules with a close resemblance to Kaposi's sarcoma may develop (acroangiodermatitis, pseudo-Kaposi's sarcoma); they differ, however, in lack of progression, and a spindle cell proliferation is not seen in the histological sections.

Treatment [30,31]. Where a small area is involved, excision or radiotherapy can be used. Superficial radiotherapy is rapid and effective, and is the treatment of choice for the majority of patients with nodular disease of the extremities. Extensive disease can be treated by cytotoxic drugs such as chlorambucil [38], cyclophosphamide, vinblastine or actinomycin [39]. Cases related to acquired immune

deficiency syndrome (AIDS) may respond to intralesional vinblastine or vincristine, interleukin-2 or interferon [40] (Chapter 26).

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Angiosarcoma [1–4]

SYN. MALIGNANT HAEMANGIOENDOTHELIOMA; HAEMANGIOSARCOMA; LYMPHANGIOSARCOMA

Definition. A malignant vascular tumour, arising from both vascular and lymphatic endothelium. Except for the pure epithelioid variant of angiosarcoma (see below), cutaneous angiosarcoma almost exclusively occurs in three settings: idiopathic angiosarcoma of the face, scalp and neck [2–4], angiosarcoma associated with chronic lymphoedema (Stewart–Treves syndrome) [5–9] and postirradiation angiosarcoma [10–12]. In this chapter, the terms 'angiosarcoma' and 'lymphangiosarcoma' are used interchangeably.

Incidence. This is a rare tumour in any form.

Stewart–Treves syndrome occurs in 0.5% of patients who survive mastectomy for more than 5 years. The mean age at appearance of the angiosarcoma is 62 years, and the mean interval between mastectomy and the appearance of the tumour is 10.5 years [9]. Two cases have been reported in men following mastectomy [13]. Not all patients have received radiotherapy in association with the mastectomy, and not all have had axillary nodes removed. Lymphoedema is not invariably present, or it may be late in appearing and antedate the tumour by only a short time. The incidence and cause of postmastectomy lymphoedema have been reviewed [14]. In the majority of cases, the clinical course and autopsy findings have shown that the treatment of the breast carcinoma was successful and that patients have had less frequent involvement of the axillary nodes than usual [9]. A small number of cases have arisen in lymphoedema of the lower limb, or in the upper limb without breast cancer and mastectomy [15]. Most of these patients were women.

Multiple primary malignancies have occurred in 8% of cases of Stewart–Treves syndrome [6] and a systemically acting carcinogen has been suggested [8,9]. There is no evidence to support this.

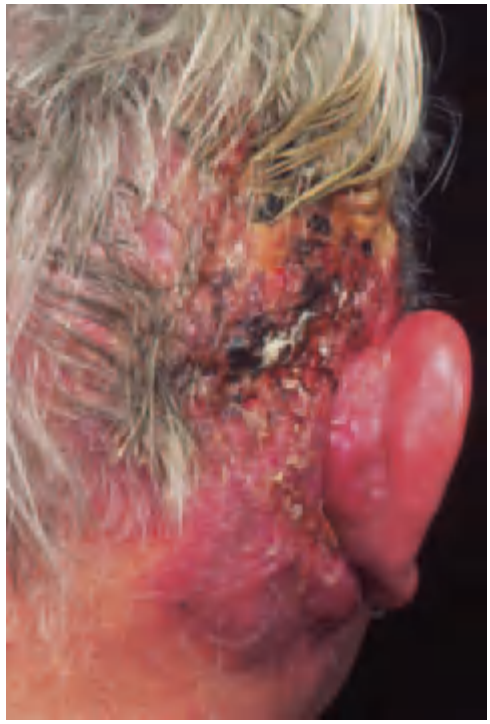

Fig. 53.21 Typical haemorrhagic appearance of an angiosarcoma.

Clinical features [3,4,16,17]. In all types of angiosarcoma, the first sign may be an area of bruising, often thought by the patient to be traumatic (Fig. 53.21). Dusky blue or red nodules develop and grow rapidly, and fresh discrete nodules appear nearby. In some cases, haemorrhagic blisters are a prominent feature. As the tumours grow, the oedema may increase and older lesions may ulcerate. Multifocality is a very frequent finding; this makes surgical excision very difficult, particularly in those cases occurring on the face and scalp. Dissemination occurs early, with the first visceral deposits usually being in the lung and pleural cavity.

Angiosarcoma in children is exceptional and mainly occurs in deep soft tissues. Several cases have arisen in vascular naevi some years after treatment [21].

Most studies reporting outcome have confined their attention to idiopathic angiosarcoma of the face, neck and scalp, in which the reported 5-year survival is low, at between 12% and 33% [3,22]. A recent study combining angiosarcomas of the face and scalp with those in soft tissue reported a 5-year survival of 24% [1]. Angiosarcomas arising in the setting of chronic lymphoedema and after radiotherapy appear to be equally aggressive.

Pathology [4,19–21]. In the well-differentiated tumour, vascular channels infiltrate the normal structures in a disorganized fashion, as if trying to line every available tissue space with a layer of endothelial cells. The collagen is characteristically lined by tumour cells in a pattern that has been described as 'dissection of collagen' (Fig. 53.22). Tumour cells may be plumper than normal, double-layered in places and form solid intravascular buds. The pattern of growth is more suggestive of lymphatic vessels than blood vessels, but both are probably involved. Haemorrhage is often prominent. Less well-differentiated tumours show more atypical pleomorphic endothelial cells, often with a spindle cell morphology, which may be heaped into several layers or become syncytial. Advancing malignancy may be associated with loss of vascular pattern and proliferation of cell masses.

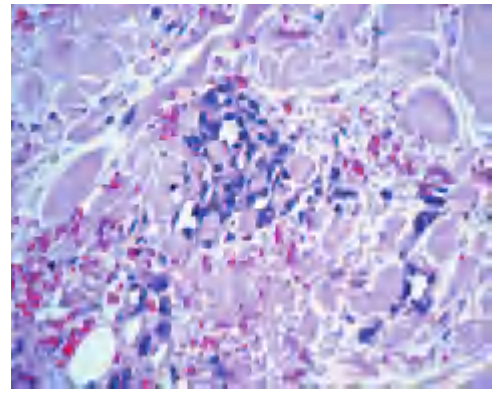

Fig. 53.22 Well-differentiated angiosarcoma, with thin-walled irregular vascular channels lined by atypical endothelial cells. Note the dissection of collagen pattern.

Immunohistochemical studies have indicated that the antibodies to CD31 are the most reliable markers for routine use, compared with antibodies against factor VIII and CD34 [7]. However, a panel of antibodies including the three markers is recommended in difficult cases as positivity to the various markers varies.

Treatment [3]. All angiosarcomas, regardless of the setting in which they occur, have a bad prognosis. In the less malignant types, wide excision and grafting has controlled some cases. The response to radiotherapy is disappointing and is usually only palliative. In the early stages of angiosarcoma of a limb, radical amputation may offer a hope of cure. It has been suggested that a high mitotic count correlates with poor prognosis and that a heavy mononuclear inflammatory cell infiltrate correlates with good prognosis [3,5,16]. In our experience, however, histological features do not seem to correlate with prognosis. Tumour size and completeness of excision appear to be more reliable factors to predict outcome [16].

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Epithelioid haemangioendothelioma [1–3]

Definition. Epithelioid haemangioendothelioma is a distinctive tumour characterized by epithelioid endothelial cells arranged in strands or individual units in a myxoid or hyalinized stroma. It was initially described as a low-grade malignant tumour, but it has recently been proposed that it should be classified as a fully malignant neoplasm, in view of the associated morbidity and mortality [3].

Clinical features [1–3]. This tumour may occur in many internal organs, and it is more commonly seen in deeper soft tissues. Involvement of the skin may occur primarily or as a result of direct extension from a deep-seated primary. Less than 10% of cases occur primarily in the skin. Tumours present in middle-aged adults, with an equal sex incidence. Cutaneous tumours are usually small, but deeper lesions are often several centimetres in diameter. Pain is a frequent complaint, probably due to angiocentricity. Involvement of other organs, including the lung, liver and bone may be seen in some cases, and it is not clear whether this represents multicentricity or metastatic spread.

Pathology [1–3]. The neoplasm is infiltrative and is composed of strands, cords and nests of endothelial cells in a hyaline or myxoid stroma. Dermal lesions often consist of a fairly well-defined nodule. The tumour cells have epithelioid morphology and consist of pink cytoplasm, vesicular nuclei and inconspicuous nucleoli. Angiocentricity is commonly seen. Formation of vascular channels is not readily apparent but a common finding is the presence of intracytoplasmic vacuoles with or without red blood cells. A small number of cases display cytological atypia, which may be prominent, and a high mitotic count. There is no clear correlation between cytological grade and behaviour. Occasional tumours overlap with epithelioid angiosarcoma. Staining for endothelial cell markers, especially factor VIII-related antigen and CD31, is usually positive, and 20% of cases are focally positive for keratin [3,4].

Prognosis and treatment. Purely cutaneous tumours appear to have a benign behaviour, but there is some tendency for local recurrence. Deeper tumours have a recurrence rate of up to 15% and a mortality rate of 20%. Complete excision with clear margins is therefore necessary.

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Epithelioid angiosarcoma [1–3]

Definition. A distinctive variant of angiosarcoma composed almost exclusively of endothelial cells with an epithelioid morphology, often mimicking a carcinoma. This tumour represents the malignant end of the spectrum of tumours with epithelioid cell morphology.

Incidence. This is a rare tumour that mainly occurs in deep soft tissue, but may present primarily in the skin or other organs.

Clinical features [1–3]. Cutaneous tumours present in young to middle-aged adults, mainly in males, with a predilection for the extremities. The typical presentation is that of solitary, or more rarely multiple, asymptomatic papules or nodules which are often haemorrhagic. It is not

clear whether multiple lesions represent multifocality or metastatic disease. Occasional cases have been reported in association with a foreign body [4], radiotherapy [1] or an arteriovenous fistula [5].

Pathology [1–3]. Sheets of atypical epithelioid cells with abundant pink cytoplasm, vesicular nuclei and a single eosinophilic nucleolus occupy the dermis and/or subcutis. Haemorrhage and haemosiderin deposition is often seen. Formation of vascular channels is not readily apparent, and the main feature is the presence of intracytoplasmic vacuoles with or without red blood cells in variable numbers of tumour cells. Mitotic figures are common. Tumour cells are variably positive for vascular markers including CD31, CD34 and von Willebrand factor. In 50% of cases, there is positivity for cytokeratin. Focal positivity for epithelial membrane antigen is also seen in some cases.

Prognosis and treatment. Although it was initially suggested that cutaneous epithelioid angiosarcoma has a relatively good prognosis, this was based on only very few cases with limited follow-up [2]. The behaviour of these tumours appears to be aggressive, and complete excision and close follow-up are therefore indicated.

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Lymphatic tumours

Cavernous lymphangioma, cystic hygroma and lymphangioma circumscriptum are described in Chapter 51.

Progressive lymphangioma

SYN. BENIGN LYMPHANGIOENDOTHELIOMA

Definition. This is a benign dermal tumour composed of irregular lymphatic channels dissecting between collagen bundles.

Clinical features [1–4]. Most cases present in middle-aged adults, but the age range is wide and children may be affected. The tumour presents as a slowly enlarging red macule, usually several centimetres in diameter with predilection for the limbs. Males are slightly more affected than females. Multiple lesions are exceptional [3].

Pathology [1–4]. Low-power examination reveals an ill-defined, often pan-dermal, proliferation of irregular thin-walled lymphatic channels dissecting between collagen bundles. These channels tend to be orientated parallel to the epidermis and are lined by a single layer of bland endothelial cells. Involvement of the subcutaneous tissue is rare. Distinction from the lymphangiomatous variant of Kaposi's sarcoma is often very difficult, but in the former there are aggregates of inflammatory cells including plasma cells, and the cells lining the vascular channels are usually positive for HHV8. Distinction from a well-differentiated angiosarcoma is based on the absence of cytological atypia and mitotic figures.

Treatment. Excision is all that is required; there is no tendency for local recurrence.

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Tumours of perivascular cells

Glomus tumour [1–3]

SYN. GLOMANGIOMA; GLOMANGIOMYOMA

Definition. A tumour of the myoarterial glomus composed of vascular channels surrounded by proliferating glomus cells. The tumours have variable quantities of glomus cells, blood vessels and smooth muscle. According to this finding, they are classified as solid glomus tumour, glomangioma and glomangiomyoma.

Incidence and aetiology. Glomus tumours are comparatively uncommon. Some are present at birth; they rarely appear during infancy, but from the age of 7 years onwards the incidence increases gradually. Multiple tumours are 10 times more frequent in children than in adults [3,4]. The occurrence of familial cases with autosomal-dominant inheritance [1,5,6], and the association of multiple tumours with malformation of the same limb, suggest that genetic factors may be involved [7]. There may be a history of trauma preceding the tumour.

Clinical features. A solitary glomus tumour is a pink or purple nodule varying in size from 1 to 20 mm; it is conspicuously painful (Fig. 53.23). Pain may be provoked by direct pressure or a change in skin temperature, or may be

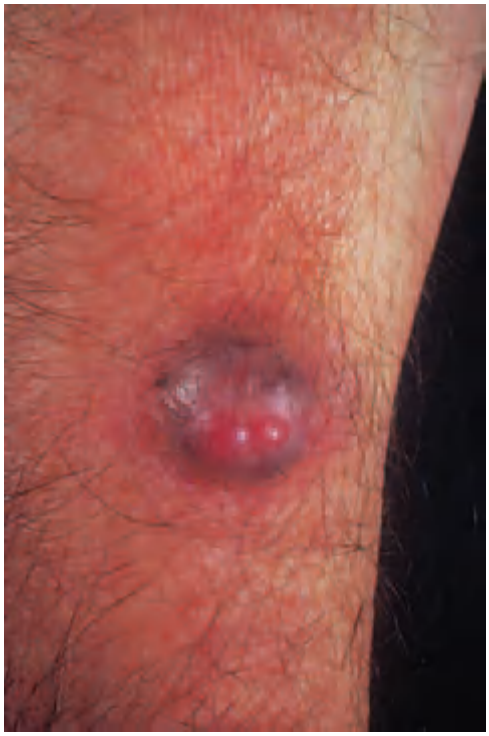

Fig. 53.23 Clinical appearance of a glomus tumour.

spontaneous. There is an equal sex incidence; adults present mainly during the third or fourth decades of life. The commonest site is the hands, particularly the fingers, followed by other sites on the extremities including the head, neck and penis. Tumours beneath the nail are particularly painful, and patients present for treatment while the lesions are still very small. The affected nail has a bluish-red flush. Glomus tumours may also involve internal organs.

Multiple glomus tumours are larger and usually dark blue in colour, and are situated deep in the dermis. They are less restricted to the extremities, may be widely scattered and are not usually painful [8–11]. In some cases, grouped multiple tumours may be painful, and pain, intermittent discoloration and sweating of a limb may precede the development of a palpable tumour.

Pathology. The tumour is round, well-circumscribed and situated in the dermis. The proportion of glomus cells to vascular spaces varies. The smaller, painful lesions tend to be mainly cellular. The larger, multiple and often painless lesions are angiomatous, with only a band of cells around the dilated vascular channels. The glomus cell is cuboidal, with a well-marked cell membrane and a round central nucleus. The cells align themselves in rows around the single layer of endothelial cells of the vascular spaces and in a somewhat less orderly fashion further out. Numerous non-myelinated nerve fibres course through the cellular masses. More than 50% of tumours can be classified as glomangiomas, and a minority (less than 15%) are classified as glomangiomyomas. Electron microscopy [12–14] suggests that glomus cells are transversely cut smooth muscle cells and that there are many mast cells around the tumour, but that nerve fibres are not associated with the glomus cells. Tumour cells are universally positive for smooth muscle actin and are usually negative for desmin. An oncocytic variant has been described [15], and also variants developing within a cutaneous nerve [16] and within a vein [17]. Malignant glomus tumour (glomangiosarcoma) is exceedingly rare. Even tumours that are histologically malignant rarely metastasize, but they have a potential for local recurrence [18,19].

Diagnosis. The solitary tumour is to be distinguished from other painful tumours such as leiomyoma and eccrine spiradenoma. Distinction is usually only possible on histological examination. The multiple glomangioma may be indistinguishable clinically from a cavernous haemangioma, and is possibly identical to 'blue rubber bleb' naevus [5].

Treatment. Surgical excision is usually curative. Local recurrence is very rare and occurs mainly after incomplete excision. Most recurrences are seen in deeper lesions with an infiltrative growth pattern. These lesions have been described as infiltrating glomus tumours [18].

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Peripheral neuroectodermal tumours

Reviews of neural tumours may be found in [1–5].

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Neuromuscular hamartoma [1,2]

SYN. TRITON TUMOUR

Definition. These lesions appear to be combined hamartomas of both muscular and neural tissue.

Clinical features. The clinical appearance is of a subcutaneous mass.

Pathology. Multinodular masses of skeletal muscle are mixed with both myelinated and unmyelinated nerve fibres. Malignant triton tumours, composed of a mixture of schwannoma-like material and rhabdomyosarcoma, are very much commoner than the benign variety of triton tumour.

Management. Surgical excision is required.

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Multiple mucosal neuromas [1]

SYN. SIPPLE'S SYNDROME

In Sipple's syndrome, multiple neuromas of the oral mucosa may be associated with phaeochromocytoma, parafollicular thyroid cysts secreting calcitonin, medullary thyroid carcinoma and opaque nerve fibres on the cornea (Chapters 12 and 59).

REFERENCE

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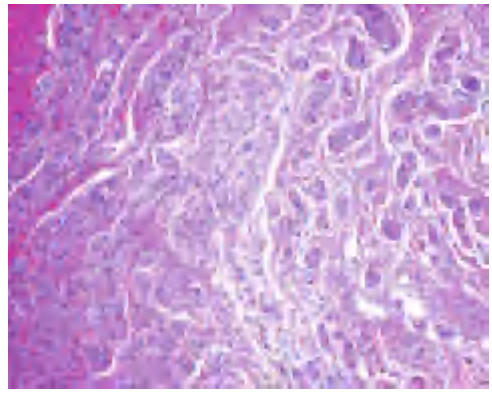

Fig. 53.24 Histological appearance of an amputation neuroma. Small nerves proliferate in the dermis in a background of fibrosis.

Amputation stump neuroma [1]

SYN. TRAUMATIC NEUROMA

Definition. This is a benign response of nerve tissue to injury.

Clinical features. A small, tender nodule is found in a scar site.

Pathology. Foci of proliferating nerve tissue surrounded by scar tissue are typically seen (Fig. 53.24). Accessory digits may show a very similar pattern of tissue involvement.

Management. Surgical excision is usually required. The problem can be prevented by apposing ends of nerves at sites of injury.

REFERENCE

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Morton's neuroma [1,2]

SYN. MORTON'S METATARSALGIA

Definition. This is the result of damage to the plantar digital nerve, followed by fibrosis. The condition has been associated with the use of high-heeled footwear.

Clinical features. It is most common in women, who complain of severe pain, usually between the third and fourth metatarsals, especially when walking.

Pathology. On pathological examination, there is very prominent perineurial, endoneurial and epineurial fibrosis. Perivascular fibrosis and intimal thickening are also seen.

Management. Excision is the recommended therapy and is curative.

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Solitary circumscribed neuroma

SYN. PALISADED ENCAPSULATED NEUROMA

Definition. This is a distinctive variant of cutaneous neuroma composed of variable proportions of the normal components of nerve tissue.

Clinical features [1–3]. It is fairly common and presents mainly on the face of adults as a small asymptomatic papule, which may resemble a naevus. There is an equal sex incidence.

Pathology [1–3]. Examination reveals a well-circumscribed, partially encapsulated dermal nodule, often associated with a nerve in the deep dermis. It is composed of uniform cells with pink cytoplasm in a collagenous background and with artifactual clefting between bundles. The capsule displays epithelial membrane antigen-positive perineurial cells. Most of the cells within the nodule are S100-positive, and special stains may demonstrate axons.

Treatment. Simple excision is curative.

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Schwannoma

SYN. NEURILEMMOMA

Definition. A tumour of nerve sheaths composed of Schwann cells.

Incidence. The tumour is relatively uncommon. It arises most frequently from the acoustic nerve. Bilateral acoustic schwannomas are characteristic of neurofibromatosis type 2. There is no association with neurofibromatosis type 1. In the peripheral nervous system, it is usually found in association with one of the main nerves of the limbs, usually on the flexor aspect near the elbow, wrist or knee, the hands or the head and neck [1]. It may be seen on the tongue. Other sites include the wall of the gastrointestinal tract and the posterior mediastinum. It may occur at any age, but is most common in the fourth and fifth decades. Females are affected more often than males [2].

Clinical features [3]. They are rounded or ovoid, circumscribed nodules varying in size up to 5 cm, usually firm (but sometimes soft and cystic) in consistency, and sometimes painful. The colour is pink-grey or yellowish. Small lesions may be intradermal, but larger ones are subcutaneous. They usually grow slowly. Malignant transformation of a schwannoma is exceedingly rare and may contain areas of epithelioid angiosarcoma [4,5].

Pathology [1,6]. The tumour is rounded, circumscribed and encapsulated. It is situated in the course of a nerve, usually in the subcutaneous fat. The cells are spindle shaped with poorly defined cytoplasm and elongated wavy basophilic nuclei. Variable amounts of collagen are seen in the background. Cells are arranged in bands, which stream and interweave. The nuclei display palisading and are arranged in parallel rows with intervening eosinophilic cytoplasm in a typical appearance known as Verocay bodies. Cellular areas known as Antoni A are intermixed with areas showing prominent myxoid change known as Antoni B [7]. The latter areas are likely to be the result of degeneration. In some tumours, there is mucous secretion, producing a vacuolated stroma. Scattered mononuclear inflammatory cells are often seen. In some cases, the nerve of origin may be found associated with the capsule. Electron microscopy shows that tumour cells have typical features of Schwann cells [8]. There is no proliferation of nerve fibrils. S100 protein staining is strong and uniform [9].

There are several variants of schwannoma, which may be confused histologically with other benign or malignant tumours.

Ancient schwannoma [10] often occurs in a deep location and is characterized by prominent degenerative changes, which often result in cytological atypia. There is loss of Antoni A areas, which makes histological diagnosis difficult.

Cellular schwannoma [11] also tends to have a predilection for deep soft tissues. It is characterized by high cellularity, with almost complete absence of Antoni B areas. This, coupled with the presence of mitotic figures, often leads to a misdiagnosis of malignancy.

Plexiform schwannoma [12,13] tends to occur in younger patients, may be painful and has a predilection for the dermis. Multiple cellular nodules composed of bland Schwann cells are seen in the dermis. Distinction from plexiform neurofibroma is important, as these tumours are not usually associated with neurofibromatosis type 1.

Melanotic schwannoma [14] only exceptionally occurs in the skin; it has a predilection for spinal nerve roots. Tumour cells are epithelioid and melanin pigment is prominent. The importance of this variant is that they are

capable of malignant behaviour and may be a marker of Carney complex (Chapter 59).

Pacinian schwannoma is a rare variant composed of structures closely resembling the Pacinian corpuscles.

Glandular schwannoma [15] represents in most cases an ordinary schwannoma with entrapment of normal sweat glands.

Diagnosis. Of the various nodular dermal and hypodermal tumours, schwannoma is most likely to be mistaken for a glomus tumour when painful, and for a lipoma, epidermoid cyst, synovial ganglion, juxta-articular node or neurofibroma when asymptomatic. The diagnosis can be suspected when it is in the course of a nerve; otherwise, histological examination is necessary.

Treatment. Simple excision is curative.

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Solitary neurofibroma [1–4]

Definition. An isolated lesion probably arising from the endoneurium and composed of a mixture of Schwann cells, fibroblasts and perineurial fibroblasts. It is not related to neurofibromatosis type 1. Although it appears to be hamartomatous in nature, the demonstration of clonality suggests a neoplastic origin [5].

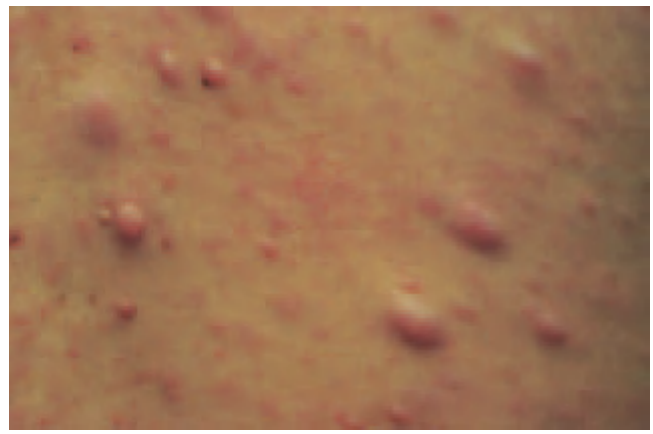

Fig. 53.25 Multiple soft papules, typical of neurofibroma in a patient with neurofibromatosis type 1.

Clinical features. Both sexes and any body site may be affected. It usually appears during the third decade as a slow-growing, small polypoid lesion. Multiple neurofibromas are rare outside the setting of neurofibromatosis type 1 (Fig. 53.25).

Simple excision is curative. Malignant change is said not to occur outside the setting of neurofibromatosis type 1.

Pathology. These lesions differ from neurilemmomas in that they do not have a capsule, they are only focally positive for S100 protein, and they do not usually have well-defined Antoni A and Antoni B areas. Instead, they are composed of bland spindle-shaped cells with wavy nuclei in a myxoid or collagenous stroma. Mast cells are usually prominent. Degenerative changes are sometimes seen but mitotic activity is absent. Less than 50% of the cells in these lesions are S100-positive. There is also focal positivity for CD34 and epithelial membrane antigen.

Several histological variants of neurofibroma have been described, including epithelioid neurofibroma and granular cell neurofibroma [3].

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Plexiform neurofibroma

This tumour is considered to be pathognomonic of neurofibromatosis type 1 (see Chapter 12). It presents in

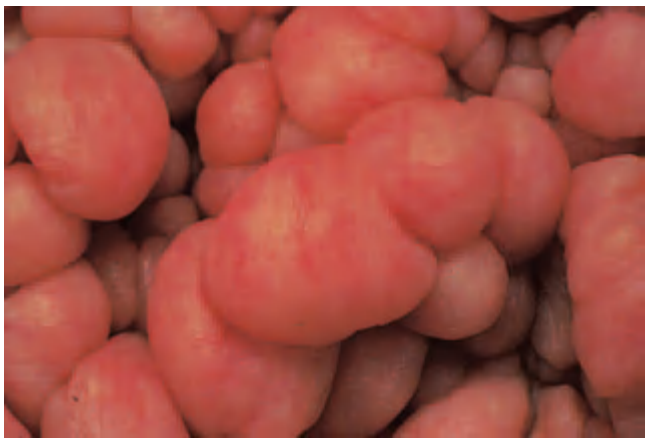

Fig. 53.26 Clinical appearance of a plexiform neurofibroma.

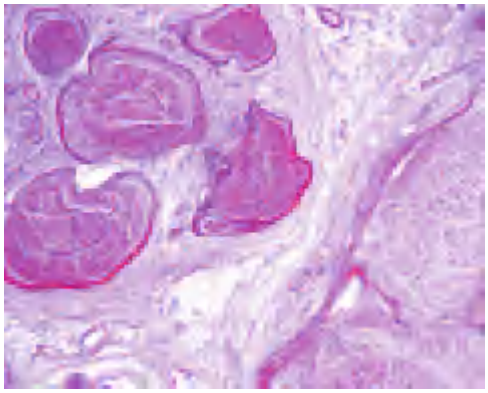

Fig. 53.27 Irregular, poorly formed nerves in a plexiform neurofibroma.

children and young adults of either sex, with predilection for the lower limbs and the head and neck. Tumours are large and located in the dermis, subcutis and even deeper soft tissues (Fig. 53.26). The overlying skin is folded and hyperpigmented and the lesion is described as having an appearance like a 'bag of worms'. This reflects the typical histological appearance of nerve trunks of different size randomly distributed throughout the involved tissues (Fig. 53.27). Careful histological examination of these lesions is necessary because the presence of any mitotic activity usually indicates malignant transformation.

Surgical removal of these lesions is usually very difficult because of the extensive involvement. When planning the surgical removal of these tumours, surgeons should remember that there is a tendency for haemorrhage within the tumour that may lead to morbidity or mortality.

Diffuse neurofibroma

This lesion presents as a diffuse, poorly-defined induration of the skin and subcutaneous tissue in children or young adults, with a predilection for the trunk and head and neck area. Only a minority of cases are associated with neurofibromatosis type 1. The histological features are identical to those of a solitary neurofibroma except for the fact that there is diffuse replacement of involved tissue by the tumour.

Perineurioma [1–3]

SYN. STORIFORM PERINEURAL FIBROMA

Definition. Perineurioma is a tumour originally described in soft tissues. It is relatively common in the skin and it is composed of cells showing differentiation towards perineural fibroblasts.

Clinical features. The lesion has predilection for the lower limbs of young females. Tumours are small and asymptomatic. A distinctive sclerosing variant affecting, almost exclusively, the hands has been described recently [3].

Pathology. Tumours are well-circumscribed and composed of bipolar and slender bland, thin, spindle-shaped cells with scanty cytoplasm and wavy nuclei. They are often arranged in a storiform pattern. Cellularity varies and is low in the sclerosing variant where hyalinized collagen predominates. Tumour cells are distinctively positive for epithelial membrane antigen. Focal positivity for factor XIIIa and CD34 may also be seen.

Treatment. Lesions are entirely benign, and simple excision is the treatment of choice.

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Dermal nerve sheath myxoma [1–3]

SYN. NEUROTHEKEOMA

Definition. This is a myxoid tumour that is thought to display nerve sheath differentiation.

Clinical features [1,2]. It presents most commonly on the upper limbs or face of young individuals, with a predilection for females. Lesions are small, skin-coloured and asymptomatic.

Pathology [1–3]. The dermis shows a well-defined tumour composed of lobules that vary in size and shape and separated by fibrocollagenous stroma. Each lobule is composed of slender stellate or spindle-shaped cells

with bland nuclei and indistinct cytoplasm margins in the background of prominent myxoid change. Mitotic figures are very rare. Occasional cases display more cellular areas [4]. Tumour cells are uniformly positive for S100.

Treatment. Simple excision is curative. There is no tendency for local recurrence.

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Cellular neurothekeoma [1–4]

Definition. Despite its name, this tumour is not likely to be related to dermal nerve sheath myxoma, and its line of differentiation has not been established. It should not be confused with ordinary nerve sheath myxomas showing focal cellular areas [1–3].

Clinical features. The tumour presents as a small, asymptomatic papule in children and young adults, with a predilection for the trunk and face and neck [4].

Pathology. In the dermis, there is an ill-defined tumour composed of nests and fascicles of epithelioid or spindle-shaped cells with vesicular nuclei and a single small eosinophilic nucleolus. Mitotic figures are relatively common and scattered multinucleated cells may be seen. Tumour cells resemble melanocytes, and this often leads to the lesion being confused with a melanoma. However, there is no junctional activity, and cells are negative for S100. Some tumours have larger size, more cytological atypia and increased mitotic count, and these tumours have been classified as atypical cellular neurothekeoma. However, this does not seem to be related to a more aggressive behaviour. Tumour cells are often positive for smooth muscle actin, NKI-C3, neurone-specific enolase and PGP 9.5.

Treatment. Simple excision is curative, and there is no tendency for local recurrence.

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Granular cell tumour [1–4]

SYN. ABRIKOSSOFF'S TUMOUR

Definition. A tumour composed of cells with characteristic granular cytoplasm. The histogenesis of the classic granular cell tumour seems to be neuroectodermal. However, it is worth remembering that many tumours of different histogenesis may show granular cell change, due to the cytoplasmic accumulation of secondary lysosomes.

Incidence. This is a rare tumour, occurring in the tongue as well as in the skin, and also in a variety of deeper locations including internal organs. Females are slightly more affected than males, and it is common in the third to fifth decade of life. It can occur in childhood [5,6].

Clinical features. The tumour is usually solitary, situated in the skin, the gingiva [7], or beneath the epithelium of the tongue. It is firm and rounded but with rather indefinite margins, sessile or pedunculated, and between 5 and 20 mm in diameter, although larger tumours may be seen. The colour may vary from flesh colour to pink or greyish-brown. It is most common in the tongue, where the epithelium over it may be thickened. On the skin surface, the epithelium covering the tumour is usually normal, although it may thicken or at times ulcerate. There is no particular site of predilection. Multiple tumours may occur, and several have been reported in children, one of whom also had axillary freckling [5]. The tumour grows slowly.

A malignant type of granular cell myoblastoma that metastasizes has been reported [8,9].

Among the internal sites reported are muscle, lip, jaws, parotid gland, pharynx, larynx, trachea, bronchus, lung, chest wall, breast, lacrimal sac, orbit, heart, oesophagus, common bile duct, urinary bladder, spermatic cord, male urethra, perineum, anal region, vulva and ovary [6,10].

Pathology [11,12]. Large polyhedral cells arranged in sheets, which infiltrate the dermal connective tissue and subcutaneous fat, form the tumour. The cytoplasm is pale and contains brightly acidophilic granules. The nuclei are relatively small and round, and tend to be vesicular. The epithelium over the area may show pseudoepitheliomatous hyperplasia. The original suggestion that the cells are myoblasts probably arose from examination of tumours of the tongue in which infiltration between the striated muscle bundles gave the impression of origin from the muscle. The general belief now is that the cells are of neural or nerve sheath origin [13–18].

Diagnosis. Histological examination is usually necessary to separate this tumour from other tumours of the deeper dermis.

Treatment. Local recurrence, mainly due to incomplete excision, is uncommon, and simple excision is therefore the treatment of choice.

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Meningothelial heterotopias [1–8]

SYN. CUTANEOUS MENINGIOMA

Lesions with meningothelial elements presenting in the skin and soft tissue were divided into three groups by Lopez *et al*. [4]. The first two groups of lesions represent meningothelial heterotopias or hamartomas. The main differences between both groups reside in the fact that affected patients are children in the first group and adults in the second group. The third group consists of intracranial meningiomas that extend secondarily into the skin or soft tissues. This group will not be discussed in more detail here.

A small number of cases of meningothelial heterotopias have been associated with von Recklinghausen's disease [1]. The tumour occurs over the scalp or in the paraspinous region of the trunk of children and young adults. Occasionally it appears to be familial [6]. The lesions resemble 'soft naevi'. On the scalp, the area may be bald. The skin is adherent to the mass, which is dermal or subcutaneous, and there may be a central depression with epidermal atrophy or ulceration. A connection with the cranial cavity is not usually demonstrated. The size ranges from 2 to 10 cm.

Pathology [6–8]. Low-power examination often reveals a lesion with a striking resemblance to a lymphangioma. Irregular dilated spaces are seen dissecting between collagen bundles. The spaces are partially lined by plump epithelioid cells, which are also seen in clusters in the surrounding stroma. Focal formation of psammoma bodies may be present. The dermal collagen and blood vessels also appear to be increased. Some lesions contain more solid areas. The presence of meningothelial cells can be demonstrated by positive staining for epithelial membrane antigen.

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Glial heterotopic nodules [1,2]

SYN. NASAL GLIOMA

Definition. This represents the presence of heterotopic mature glial tissue in the dermis or subcutis, predominantly on the central face. It may be considered to be a developmental defect in the closure of the neural tube. However, rare cases occur away from the midline, suggesting a different unexplained mechanism for its occurrence [3].

Clinical features. Most lesions present in infants or children as a subcutaneous mass on the bridge of the nose. Presentation in adults is exceptional. Communication with the cranial cavity is present in up to 20% of cases.

Pathology. Nodules of astrocytes in a neurofibrillar background are characteristic. Less commonly, oligodendrocytes are seen; neuronal elements are exceptional.

Treatment. Excision is curative, but it is very important to make sure that an underlying communication with the cranial cavity is ruled out, as failure to do so may result in complications such as meningitis or cerebrospinal fluid leakage.

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Pigmented neuroectodermal tumour of infancy [1]

SYN. MELANOTIC PROGONOMA; RETINAL ANLAGE TUMOUR

For many years, there has been a debate as to whether this tumour is of neural or melanocytic origin [2–4]. Recent evidence seems to indicate that this tumour recapitulates the early stages of development of the retinal epithelium [5].

Clinical features. This tumour occurs most frequently in the anterior part of the maxilla, usually in infants less than 6 months old, and often presents as a pigmented oral mass [6]. It has been reported also in the anterior fontanelle, the shoulder, epididymis and mediastinum. There is a slight predilection for males. It may cause a high urinary excretion of vanillylmandelic acid [2]. This benign tumour has been mistaken in the past for malignant melanoma, and could also be confused with a cellular blue naevus.

The clinical appearance is that of a rapidly expanding nodule in the jaw, which may affect dentition. Although classified as benign, the lesions may cause considerable local destruction, and around 5% of cases may metastasize and prove fatal [7].

Pathology [8,9]. A mass of irregular alveolar spaces surrounded by fibrous stroma is seen. Two types of cells are easily recognized: small round blue cells with scanty cytoplasm in a fibrillary matrix, and large epithelioid cells with pink cytoplasm and vesicular nuclei. These cells often contain melanin. Both types of tumour cells stain for synaptophysin and neurone-specific enolase, and are negative for S100. The large cells are positive for cytokeratin and HMB45.

Treatment. Complete surgical excision is the treatment of choice.

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Malignant peripheral nerve sheath tumour [1,2]

SYN. NEUROFIBROSARCOMA; MALIGNANT SCHWANNOMA

Definition. A malignant tumour arising from the nerve sheath.

Aetiology. Cutaneous tumours usually arise in patients with neurofibromatosis type 1 from a plexiform neurofibroma [3]. Deep-seated lesions arise *de novo* or in association with neurofibromatosis type 1. Patients with this disease develop malignancy in 30–50% of cases.

Incidence. It is an uncommon tumour. It occurs in young adults, or even children, when it complicates multiple neurofibromatosis. Sporadic cases occur in older individuals.

Clinical features [4]. The diagnosis should be suspected when a previously static tumour in a patient with neurofibromatosis begins to enlarge or becomes painful. The pain may become radicular as the lesion progresses but the tumours are not always associated with nerve trunks. The commoner sites are the flexor aspects of the limbs. A minority of cases occur as a complication of radiotherapy.

Pathology. The basic pattern is that of fascicles of tumour cells, often with a herringbone pattern and resembling a fibrosarcoma. Tumour cells tend to concentrate around blood vessels and myxoid change is common. The degree of pleomorphism and the number of mitotic figures varies.

Treatment. Wide local excision or amputation is necessary because of the aggressive behaviour of the tumour, and even then the prognosis is not good. Systemic metastases particularly to the lungs are common. The prognosis is

worse in cases associated with radiotherapy. The tumour is not radiosensitive.

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Clear cell sarcoma [1–4]

Definition. Clear cell sarcoma is a distinctive malignant soft-tissue tumour that displays melanocytic differentiation.

Clinical features. Most cases occur on the lower limbs, with a predilection for the foot. The upper limb is affected in about 25% of cases. There is a predilection for females. Tumours tend to grow around tendons, are usually less than 3 cm in diameter and are often painful.

Pathology. The lesion has a lobular growth pattern. Tumour cells are fairly homogeneous and contain clear or pale pink cytoplasm and a prominent eosinophilic nucleolus. Mitotic figures are not prominent, but multinucleated giant cells with a wreath-like arrangement of the nuclei are often identified. Loose thin bands of collagen surround tumour cells. Secondary involvement of the dermis is relatively common. Necrosis is sometimes seen. Melanin is sometimes identified, and S100, HMB45 and melan A are usually positive. Electron-microscopic examination of tumour cells reveals the presence of melanosomes.

Cytogenetic analysis often reveals a translocation between chromosomes 12 and 22; this translocation is not found in melanoma [5].

Prognosis and treatment [1–4]. About 50% of patients develop metastatic disease, often many years after the initial diagnosis. Wide excision is the treatment of choice. Chemotherapy does not seem to be effective in the treatment of disseminated disease.

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Peripheral primitive neuroectodermal tumour [1,2]

SYN. PERIPHERAL NEUROEPITHELIOMA; EXTRAOSSEOUS EWING'S SARCOMA

Primary cutaneous or subcutaneous peripheral primitive neuroectodermal tumour is extremely rare, and only a handful of cases have been reported in the literature. The tumour presents in children and has no distinctive clinical features, although it is often confused with a vascular tumour. It has been suggested that superficial tumours have a better prognosis than those presenting in deeper soft tissues, but the number of cases reported and their follow-up is too limited for this to be certain. The histological diagnosis includes tumours composed of small blue round cells and immunohistochemistry plays an important role in diagnosis. Tumour cells are diffusely positive for CD99. This tumour usually presents a reciprocal chromosome translocation t(11;22)(q24;q12) that is an important aid in diagnosis.

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Tumours of muscle

Congenital smooth muscle hamartoma

This lesion is described in Chapter 15.

Leiomyoma [1–3]

Definition. A benign tumour of smooth muscle derived from the arrector pili muscle, from the media of blood vessels, or from smooth muscle of the scrotum, labia majora or nipples (genital leiomyoma) [4,5].

Incidence. The tumour occurs in three main types, all of which are relatively uncommon.

Pilar leiomyoma (leiomyoma cutis) originates in the pilomotor muscle and is the most frequent. It can occur at any age from birth onwards, but appears usually in early adult life. It has been reported in identical twins, in siblings and in several generations of a family [6–8]. The cases with a familial background have all had multiple tumours. The sexes are affected equally.

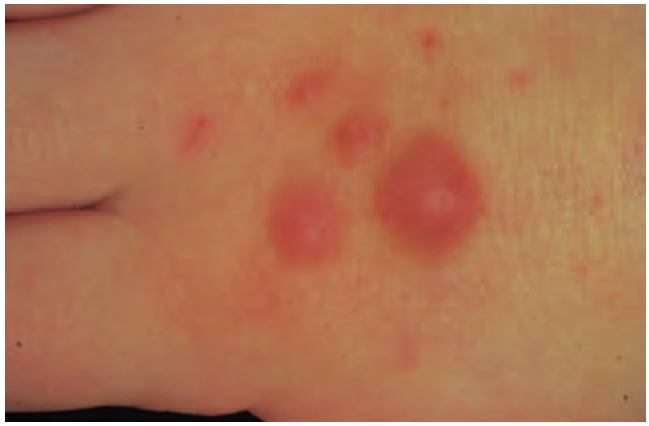

Fig. 53.28 Clinical appearance of multiple leiomyomas.

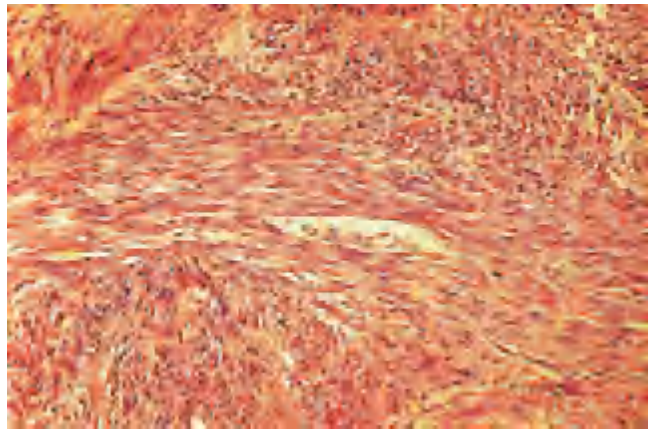

Fig. 53.29 Pathology of leiomyoma, showing large, spindle-shaped cells with eosinophilic cytoplasm.

Genital leiomyoma (dartoic myoma) arises in the smooth muscle of the genitalia and areola of the nipple [9,10]. It can occur at any age. The cutaneous variety is about six times more frequent than the genital type [11].

Angioleiomyoma arises from the muscular coat of veins, and is seen mainly in middle age or later as a solitary nodule on a limb. It is rather more prevalent than glomus tumour in published series [6,12,13]. Females are more commonly affected than males.

Clinical features [6,14]. Pilar leiomyoma generally presents as a collection of pink, red or dusky brown, firm dermal nodules of varying size but usually less than 15 mm diameter (Fig. 53.28). The nodules are often subject to episodes of pain and may be tender. The pain can be provoked by touching or chilling the skin, or by emotional disturbance. It is often worse in winter. Some lesions contract and become paler when painful [12,15]. The condition usually begins with the appearance of one small nodule, which gradually increases in size, and further similar lesions appear nearby or at some other area. Adjacent tumours may coalesce to form a plaque. The areas most commonly affected are the extremities, with the proximal and extensor aspects somewhat favoured. The trunk is involved more often than the head and neck. Multiple lesions may be regional and unilateral, or more than one region can be affected. Solitary lesions may occur, apart from the dartoic type. The gene that predisposes to multiple pilar leiomyomas has been mapped to chromosome 1q 42.3-q43 [16].

Genital leiomyoma is a solitary dermal nodule occurring most commonly in the scrotum, but also appearing on the penis, labia majora and nipple area. Scrotal tumours are often large. Pain is less frequent than with leiomyoma cutis. Contraction in response to stimulation by touch or cold can occur.

Angioleiomyoma is usually a solitary, flesh-coloured, rounded, subcutaneous or deep dermal tumour up to 40 mm in diameter. It is more frequent on the lower limb than the upper and may appear on the trunk or face. About half the reported cases have been painful [6,12]. Lesions are long-standing and present between the fourth and sixth decades of life. Pain may be triggered by changes in temperature, pregnancy or menses.

Pathology [12,14,17,18]. The smooth muscle cells proliferate to produce interweaving bundles of spindle-shaped cells, which are strongly eosinophilic (Fig. 53.29). The nuclei are long and thin, and the general appearance of the mass in ordinary sections may suggest a hypertrophic fibrous reaction. The smooth muscle cells can be distinguished from collagen by their different reaction with trichrome stains, and by the presence of myofibrils, which stain with phosphotungstic acid haematoxylin, and by their blunt-ended nuclei. Tumour cells are positive for actin and desmin.

The tumour of pilomotor origin (leiomyoma cutis, multiple cutaneous leiomyomas) is usually composed of numerous dermal nodules with vague margins where the cells penetrate the surrounding collagen bundles, and an upper border that approaches the papillary body. Associated epidermal hyperplasia is common. Focal nuclear atypia likely to be degenerative in origin and very low mitotic activity (up to one per 10 high-power fields) may be seen without this being indicative of malignant degeneration [19]. Genital leiomyomas are nodular tumours with a similar appearance. Scrotal tumours are less circumscribed and more cellular than those developing in the vulva. The angiomyomas are related to veins in the subcutaneous tissue, and are rounded and well-circumscribed [20]. Vessels of variable thickness are intermixed with bundles of mature smooth muscle. Focal degenerative cytological atypia may be seen, but mitotic figures are absent. Calcification, hyalinization and thrombosis of vessels are often seen.

Diagnosis. The multiple type should cause little difficulty, and even without pain it is fairly distinctive. The solitary painful lesion may be mistaken for a glomus tumour or an eccrine spiradenoma, and a history of contraction is helpful. In practice the diagnosis can be elusive.

Treatment. Surgical excision cures the solitary tumour. The severity of the pain may make the patient demand treatment, and extensive lesions require plastic surgery. Excision of an area containing multiple tumours is often followed by their appearance in the neighbourhood of the treated area. Medical treatments that may relieve pain include calcium-channel blockers and gabapentin.

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Leiomyosarcoma [1–3]

Definition. A malignant tumour displaying smooth muscle differentiation. Tumours are divided into those occurring in the subcutaneous tissue and those arising in the dermis. Pure dermal lesions have a very different behaviour from those arising in the subcutis and it is therefore important to separate them (see below).

Incidence. This is a rare tumour. Dermal leiomyosarcoma presents predominantly on the lower limbs of young adults, with a predilection for males. Subcutaneous leiomyosarcoma affects middle-aged to elderly patients with slight predilection for males.

Clinical features [4,5]. The tumour may be situated in the dermis, when it is reddish in colour and may bleed on trauma. It is usually larger than a leiomyoma and dermal lesions may be painful. The majority of tumours have, however, arisen in the subcutaneous or deeper tissues as nodular tumours, ulcerated plaques [6] or diffuse swellings [7]. It may invade underlying muscle fascia. It is most common on the thigh, followed by the head and neck, arm and trunk, and may arise from the penis [8] or vulva. It is unlikely to be diagnosed clinically. Dermal leiomyosarcomas have a 40% recurrence rate, but they almost never metastasize [9]. Subcutaneous tumours metastasize in up to 50% of cases and they are associated with a mortality of about 30%.

Pathology [3,9–13]. The lesion is distinguished from other dermal malignant tumours composed of spindle-shaped cells by the presence of fascicles of eosinophilic spindle-shaped with vesicular cigar-shaped nuclei. The degree of differentiation varies and necrosis tends to be present in deeper tumours, but not in those arising primarily in the dermis. Most tumours are actin- and desmin-positive, but staining for the later may be lost in poorly differentiated variants. About 30% of leiomyosarcomas are positive for keratin, but this is less commonly seen in cutaneous examples.

Treatment. Wide surgical excision is necessary, as local recurrence follows inadequate excision.

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Skeletal muscle tumours

Rhabdomyosarcomatous congenital hamartoma

This lesion is described in Chapter 15.

Rhabdomyoma

Rhabdomyomas are divided into adult, fetal and genital types. They mainly occur in soft tissues, vulva or vagina, upper respiratory tract and internal organs. Presentation in the skin is almost never seen, and they will not be discussed further in this chapter.

Cutaneous rhabdomyosarcoma

Malignant tumours with skeletal-muscle differentiation are classified into two large groups, namely embryonal and alveolar types. Although rhabdomyosarcomas represent up to 8% of tumours in children, primary involvement of the skin by this tumour is very rare. Much more common is involvement of the skin by direct extension from deeper soft tissues. Only 16 cases of primary cutaneous rhabdomyosarcoma have been reported in the literature so far, and only five of these have occurred in adults [1,2]. The most common subtype occurring in the skin is the alveolar variant. The majority of cases have presented on the face. The prognosis is difficult to estimate because of the rarity of these cases and the limited follow-up available.

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Tumours of uncertain histogenesis

Superficial angiomyxoma [1,2]

Definition. Superficial angiomyxoma is a dermal or subcutaneous tumour composed of a mixture of small blood vessels and sparse spindle-shaped cells in a prominent myxoid stroma.

Clinical features [1,2]. Most cases occur in adults as an asymptomatic solitary papule or nodule with equal sex incidence. Lesions are usually less than 3 cm and have a wide anatomical distribution with a predilection for the trunk, head and neck and genital skin. In patients with multiple lesions, the possibility of Carney complex should be considered (see Chapter 59) [3].

Pathology. Tumours are multilobulated, with copious myxoid stroma, numerous delicate small blood vessels and spindle-shaped or stellated bland cells probably representing fibroblasts. Aggregates of inflammatory cells, mainly neutrophils, are frequent. In up to 30% of cases epithelial structures, probably representing hyperplastic trapped adnexal structures (particularly hair follicles), are identified.

Treatment. Local recurrence is seen in up to 30% of cases [3], but the behaviour is benign and therefore excision is the treatment of choice.

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Digital myxoma [1]

SYN. CUTANEOUS MYXOID CYST

Digital myxoma is relatively rare and presents mainly on the fingers as a small, solitary painful nodule. Females are much more commonly affected than males and there is a tendency for local recurrence. Lesions are poorly circumscribed and consist of abundant myxoid stroma with only scattered bland spindle-shaped cells.

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'Aggressive' angiomyxoma [1,2]

Definition. 'Aggressive' angiomyxoma is a distinctive tumour occurring in the genital region and pelvis predominantly of females. It is characterized by bland

spindle-shaped cells in the background of a prominent myxoid stroma and frequent thick-walled blood vessels.

Clinical features. This tumour occurs almost exclusively in females of reproductive age, but rare lesions have been described in males [3]. Tumours are slowly growing and by the time of presentation they are large and ill-defined, often measuring 10 cm or more. The most commonly affected sites are the vulva and perineum. Extension into deeper soft tissues is often found.

Pathology. The lesion is infiltrative and is composed of spindle or stellate-shaped, bland, cells with scanty cytoplasm, surrounded by prominent myxoid stroma. Small to medium-sized thick-walled blood vessels are seen throughout the tumour. Mitotic figures are very rare. Interestingly, tumour cells are positive for actin and desmin.

Prognosis and treatment. Local recurrence is observed in up to a third of cases, and complete surgical excision is usually difficult because of the infiltration of surrounding tissue. However, recurrences are not usually destructive, and radical surgical procedures are therefore not indicated.

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Epithelioid sarcoma [1,2]

Definition. A distinctive malignant soft-tissue tumour composed of cells with epithelial differentiation. It is not clear whether this tumour represents a primary soft-tissue carcinoma or a sarcoma with epithelial differentiation.

Incidence. It is an uncommon tumour, affecting males more often than females and tending to begin in early adult life.

Clinical features [3,4]. The presenting sign can be a dermal nodule that grows outwards and may ulcerate early, a nodule or lobular subcutaneous tumour that is painless and grows slowly, or a tumour attached to deeper structures that is rather poorly defined and causes pain, paraesthesiae or muscular wasting when growing along a large trunk nerve. As a result of prominent perineurial and perivascular extension of tumour cells, multiple nodules in a sporotrichoid distribution may be seen. The distal extremities are the usual situation for the tumour, particularly the flexor aspect of the finger and the palm. It may grow at a deceptively slow rate.

A distinctive variant of epithelioid sarcoma previously described as 'extrarenal rhabdoid tumour' has been reported in older patients who present with a large mass on the proximal limbs, genitalia, buttocks, trunk or head and neck [5]. This variant is known as 'proximal-type epithelioid sarcoma'.

Pathology [6,7]. The tumour is composed of firm nodules 5–50 mm or larger in diameter surrounded by fibrous tissue and fat. It is often closely associated with fascia, periosteum, tendon or nerve sheaths. The cut surface is greyish-white and flecked or mottled with yellow or brown, reflecting the presence of areas of necrosis. Microscopically, there are masses of large, round, polygonal or spindle cells with acidophilic cytoplasm. Spindle cells are often present and may predominate. The larger nodules have necrotic centres and show so-called 'geographical necrosis', which may be mistaken on scanning power microscopy for a granuloma. Mitotic figures are common, and binucleate cells occur. Variable cytological atypia is always present and may be prominent. Intercellular hyalinized collagen increases the acidophilia, while calcification, with osteoid or bone formation, may take place in the necrotic areas. The tumour spreads along dense fibrous structures and may ulcerate in areas with little subcutaneous fat. Local recurrence after excision is common, and metastasis, principally to lymph nodes, lung and pleura, may occur. Tumour cells show clear histological, ultrastructural and immunohistochemical evidence of epithelial differentiation.

The proximal type of epithelioid sarcoma shows a similar multinodular growth pattern but tumour cells are larger and with a more rhabdoid appearance consisting of abundant cytoplasm and large nuclei with or without a prominent eosinophilic nucleolus.

Immunohistochemically, tumour cells in both variants of epithelioid sarcoma have the same profile. They are positive for keratin and epithelial membrane antigen. They also express vimentin, and in 50% of the cases they are positive for CD34 [8].

Diagnosis. Superficial lesions can easily be mistaken for an ulcerating squamous cell carcinoma, deeper ones are usually regarded as inflammatory in nature. Histological diagnoses have varied, with granulomatous inflammation and synovial sarcoma being the commonest benign and malignant diagnoses, respectively.

Prognosis and treatment. Complete removal by surgical excision is essential if local recurrence and eventual metastasis are to be avoided, and the earlier this is done the less likely is the process to spread along fascial planes. Surgical excision followed by radiotherapy is often

recommended. Involvement of regional lymph nodes is associated with distant metastasis and death [9]. Local recurrence and metastasis may occur years after the original diagnosis. The survival rate has been estimated at between 65% and 70% [6,9]. Features associated with poorer prognosis include male sex, older age at diagnosis, proximal location, tumour size, mitotic rate, necrosis, vascular invasion and local recurrence and lymph node metastasis [6,7,9].

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Tumours of fat cells

Lipoma, angiolipoma and hibernoma

These lesions are described in Chapter 55.

Lipoblastoma and lipoblastomatosis

Definition. Lipoblastoma is a tumour that occurs almost exclusively in infants and children. It is characterized by a proliferation of immature fat cells in a myxoid stroma and intermixed with mature adipocytes [1]. Lipoblastoma is a well-circumscribed subcutaneous tumour; lipoblastomatosis refers to a deeper lesion or those that have an infiltrative growth pattern.

Clinical features [1–3]. Most cases present during the first few years of life, with a predilection for males. The majority of tumours occur on the limbs as an asymptomatic mass no more than a few centimetres in diameter. Lipoblastoma is much more common than lipoblastomatosis.

Pathology [1–3]. Tumours have a characteristic lobular appearance. Each tumour lobule is separated by fibrous septae and consists of a mixture of small univacuolated signet-ring cells, spindle-shaped or stellate cells and scattered mature adipocytes. In the background, there are prominent myxoid changes and numerous small vessels in a typical 'crow's-feet' distribution, mimicking a myxoid liposarcoma. Distinction from the latter may be very difficult, especially in small biopsies. The clinical information is therefore crucial, as myxoid liposarcoma is vanishingly rare in children and almost never occurs before the age of 10 years [4]. Furthermore, lipoblastoma tends to be less cellular than myxoid liposarcoma and has a lobular architecture. Over time, maturation occurs, and in some cases most of the tumour is composed of mature fat cells.

Cytogenetic studies in lipoblastoma have shown rearrangements on chromosome 8q [5].

Treatment. The tumour is benign, and simple excision is the treatment of choice. Deeper lesions have some tendency for local recurrence.

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Spindle cell and pleomorphic lipoma [1–5]

Definition. Spindle cell lipoma is composed of mature adipocytes and variable numbers of short bland spindle-shaped cells with indistinct cytoplasm. Pleomorphic lipoma is composed of mature adipocytes, cells with hyperchromatic nuclei and frequent multinucleation, and collagen bundles. Both types of tumour may overlap, and they are therefore considered to be part of the same spectrum.

Clinical features [1,2,4,5]. Spindle cell lipoma usually presents as a small subcutaneous nodule on the upper back and nape of the neck of middle-aged to old patients, with marked predilection for males. Occasional purely dermal examples may be seen. Multiple lesions, and familial cases, occur rarely [3]. Pleomorphic lipoma has a similar clinical presentation.

Pathology [1,2,4]. Spindle cell lipoma presents as a well-circumscribed tumour composed of mature adipocytes intermixed with short spindle-shaped cells with wavy nuclei. Hyalinized collagen bundles and focal myxoid change are prominent. Pseudovascular spaces are

prominent in some cases. The spindle-shaped cells stain for CD34 and the adipocytes are positive for S100. Pleomorphic lipoma is also well-circumscribed and composed of mature adipocytes intermixed with uninucleated or multinucleated cells with hyperchromatic nuclei. The nuclei in the multinucleated cells are often arranged in a circle (floret cell).

Cytogenetic studies of both tumours have shown variable abnormalities, most commonly in chromosome 16q and rarely in chromosomes 13q and 6p [6,7].

Treatment. There is little tendency for local recurrence, and simple excision is therefore the treatment of choice.

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Atypical lipomatous tumour [1–4]

SYN. WELL-DIFFERENTIATED LIPOSARCOMA

Definition. This is a lesion composed of lobules of mature adipose cells, with scattered larger cells with variation in nuclear size and hyperchromatism. The term 'atypical lipomatous tumour' is usually used for neoplasms occurring in the subcutis or within skeletal muscle. Similar tumours occurring in the abdominal cavity are regarded as well-differentiated liposarcomas, in view of the fact that they have a potential to cause death as a result of extensive growth. Only subcutaneous lesions will be discussed here.

Clinical features [1–3]. Subcutaneous atypical lipomatous tumours occur in middle-aged to old adults with predilection for the lower limbs. Tumours may be large, are asymptomatic and have the same clinical appearance as a lipoma.

Pathology. Typically, lobules of mature adipose tissue, with or without fibrous tissue and myxoid change, are seen. Focal variation in the size and shape of adipocytes is seen and this is associated with nuclear enlargement and hyperchromatism. Vacuolated cells may also be found. Atypical cells are often present in the fibrous tissue.

Cytogenetic studies of these neoplasms have found chromosomal abnormalities in most cases. About a third of the cases show supernumerary ring chromosomes affecting chromosome 12q 13–15 [4].

Prognosis and treatment. There is a tendency for local recurrence, but metastases are not seen unless the tumour undergoes dedifferentiation [5]. Complete surgical excision is indicated.

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Liposarcoma [1]

Myxoid and round cell liposarcoma and pleomorphic liposarcoma are vanishingly rare in the skin. Only a few cases of primary cutaneous liposarcoma have been described. Follow-up is limited, but the behaviour seems to be better than that of their deeper counterparts, probably reflecting early detection and treatment and the easy accessibility to the skin. Liposarcoma will not be discussed further in this chapter.

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Ossifying lesions in the dermis [1]

A wide range of subcutaneous lesions may occasionally show partial ossification. The most common are pilomatricomas and melanocytic naevi. Other soft-tissue lesions, such as soft-tissue chondromas and fibromyxoid tumours, may show metaplastic bone formation.

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Osteoma cutis [1]

Definition. A true bony new growth arising within the skin from bone-forming tissue and showing no tendency to invade.

Incidence and aetiology. Osteoma cutis is a rare tumour. Most osseous nodules in the skin are not true neoplasms, but result from metaplastic ossification, which usually occurs in a focus of calcification; the initiating lesion is frequently an inflammatory granuloma or scar. The majority of these lesions are best classified as dystrophic ossification rather than as osteomas. Dystrophic ossification has been reported in scleroderma, in old acne cysts and at sites of puncture of the skin or of haematomas. They may be found in melanocytic naevus, pilomatricoma, histiocytoma and chondroid syringoma, and may be secondary to basal cell carcinoma [2,3]. Another cause is Albright's hereditary osteodystrophy, in which cutaneous ossification has recently been recognized with increasing frequency [4–6]. Rarely, multiple miliary osteomas of the skin can occur after acne [7,8], sometimes with neurotic excoriations or after dermabrasion [9]. There remain a minority of reported cases that appear to be primary osteomas, the majority of which are multiple and on the face or scalp [9–11].

There is no point in trying to estimate the age and sex incidence for a group as heterogeneous as individuals with dystrophic calcification of the skin. It seems likely that primary osteomas will become even more rare if hereditary osteodystrophy and other causes are sought.

Clinical features. Metaplastic osteomas are frequently small and clinically undetectable in the primary lesion. They are usually situated deep in the dermis or subcutaneous tissue. They may be seen when radiographs of the area are taken, but are most commonly first noticed by the histology technician as a hard body that damages the knife edge. The distinguishing feature, if the tumour is found clinically, is the stone-hard texture on palpation, similar to pilomatricoma. A case of osteoma cutis associated with diaphyseal aclasis has been reported [12].

Pathology [3]. Whether metaplastic or primary, the microscopic picture is of a small circumscribed nodule of osseous tissue with trabeculae enclosing fat and, occasionally, marrow cells.

Treatment. If required, simple excision is curative.

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Cutaneous calculus [1,2]

SYN. SUBEPIDERMAL CALCIFIED NODULE

This small tumour, which is not very uncommon, has a characteristic yellowish white colour and is situated in the subepidermal tissue. It is seen most commonly on the face in children; it varies in size up to 10 mm or so, but may occasionally be larger and plaque-like, and it has a hard consistency. The epidermis over it may be verrucose. Episodes of inflammation and shedding of a portion of the lesion may occur. Microscopic examination shows calcareous bodies in the superficial part of the dermis. A histiocytic or foreign-body reaction often surrounds some of the calcified bodies. The exact histogenesis is uncertain. Calcification of naevus cells has been suggested. The lesion can be removed easily by curettage.

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Progressive osseous heteroplasia

This is discussed in Chapter 46.

Chapter 54

Cutaneous Lymphomas and Lymphocytic Infiltrates

S.J. Whittaker & R.M. MacKie

Introduction

For many years, the terms cutaneous reticulosis and mycosis fungoides (MF) were the only two used to describe a wide range of clinical and histological presentations of malignant cutaneous lymphocytic infiltrates, many of which appeared to have a very unpredictable prognosis. Over the past 20 years, advances in the classification of lymphoid cells have greatly improved our understanding of the cutaneous lymphomas. Various node-based classifications of lymphomas, including the Kiel classification first introduced in 1980 and updated in 1988 [1], were of relatively little value for cutaneous lymphoma as they were based purely on detailed pathological assessment of nodes with no clinical correlation. Current classifications are based on clinical, pathological, immunopathological, molecular and cytogenetic findings [2,3], and the classification of cutaneous lymphomas in turn has a critical influence on the therapeutic approach.

In 1975, it was demonstrated that the great majority of lymphoid infiltrates associated with the skin were of T-cell type and Edelson introduced the term cutaneous T-cell lymphoma (CTCL) [4]. In Europe, the work of the Dutch Cutaneous Lymphoma Working Party (DCLWP) clearly identified different subsets both of CTCL and of primary cutaneous B-cell lymphomas [5]. MF is the most common of the CTCL subsets, but other subsets with clearly identifiable clinicopathological features and varying prognoses have also been described. These data formed the basis for the European Organization for Research on Treatment of Cancer (EORTC) classification of cutaneous lymphomas in 1997 [2]. In contrast, human T-lymphotropic virus type 1 (HTLV-1)-associated cutaneous lymphoma [6] is relatively rare in Europe but much more common in Japan and usually occurs as secondary cutaneous involvement. At the present time, there is no clear evidence that other CTCLs are directly associated with HTLV or other related viruses. A critical observation has been the realization that lymphomas with a similar pathology arising in different organs carry very different prognoses. Nodal CD30+ lymphoma can be associated with a poor prognosis, whereas primary cutaneous CD30+ lymphomas are generally associated with a good prognosis [7]. It is also now clear that primary cutaneous B-cell

lymphoma is not as rare as was previously believed [5]. Extensive studies from the DCLWP suggest that primary cutaneous B-cell lymphomas are about one-third as common as primary CTCLs, and that the majority of these B-cell lymphomas have a good prognosis. This is in contrast to earlier reports, many of which concerned B-cell lymphomas arising in other body sites and only involving the skin at a late stage. The recent World Health Organization (WHO) classification has encompased most of the EORTC primary cutaneous lymphoma categories with the exception of distinct cutaneous B-cell lymphomas, although the WHO classification does acknowledge the presence of a primary cutaneous follicle centre cell lymphoma which is pathogenetically distinct from primary nodal follicular lymphoma [3].

The concept of a subset of circulating lymphocytes with a special avidity or affinity for the skin has been supported by the identification of T cells expressing the cutaneous lymphocyte antigen, CLA (HECA 452), which binds to its ligand, E-selectin, on dermal endothelial cells [8]. These subsets of T cells are thought to traffic through the skin comprising skin-associated lymphoid tissue (SALT), and contribute to the skin immune system (SIS), in a similar manner to other mucosal sites such as the gut mucosa-associated lymphoid tissue (MALT). The expression of the chemokine receptor CXCR3 by tumour cells may also contribute to epidermotropism in CTCL [9]. In early stage disease, the identification of T-cell clones in skin using T-cell receptor (TCR) gene analysis has critically established both the neoplastic nature and lineage of a wide variety of cutaneous lymphoproliferative entities during the last decade, and both TCR and immunoglobulin gene analysis are now a standard part of the assessment of cutaneous lymphoid infiltrates [10]. The presence of a T-cell clone is not synonymous with malignancy and the significance of T-cell clones in benign cutaneous lymphoid infiltrates is unclear at present. It is unclear whether these techniques will also provide prognostic information but they do complement existing staging approaches, particularly for analysis of lymph node and peripheral blood in MF and Sézary syndrome. The underlying molecular pathogenesis of CTCL is still unknown but various abnormalities have been identified including a high frequency of tumour-suppressor gene inactivation involving particularly genes controlling the cell cycle such as the *p53* and *p15/16* genes [11,12]. These abnormalities appear to be associated with disease progression and may contribute to treatment resistance. In addition, several novel molecular cytogenetic techniques have detected a consistent pattern of chromosomal abnormalities indicating the location of putative genes that may have a fundamental role in the pathogenesis of CTCL [13,14].

Several novel therapies have been developed specifically for CTCL: a retinoid, bexarotene, that binds to the RXR receptor and a diphtheria interleukin-2 (IL-2) fusion toxin, Denileukin Diftitox (Onzar; Ontak) [15–17]. Both have been assessed in rigorous clinical trials and offer promising alternatives to existing therapies.

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Primary cutaneous T-cell lymphomas

Mycosis fungoides

Definition. The most common variant of primary CTCL, generally associated with an indolent clinical course and characterized by well-defined clinicopathological features.

Aetiology. The aetiology of MF is not yet established. The HTLV-1 retrovirus was first isolated from a patient with CTCL and subsequently it was appreciated that this

patient had adult T-cell leukaemia–lymphoma (ATLL). Because of clinical and pathological similarities to cutaneous involvement in ATLL, there has been an intensive search for HTLV-1 and related viruses in MF. However, although an association with HTLV-1 has been suggested, subsequent extensive investigations have failed to identify conclusively any of the currently recognized HTLV-associated viruses in MF [1–5]. For over 20 years, one of the theories associated with the development of MF has been that this is a disease of antigen persistence associated with chronic lymphocyte stimulation and eventual transformation of benign lymphocytes to a low-grade malignant T-cell lymphoma [6]. This is a plausible and attractive theory, but as yet the antigen or antigens responsible for this transformation have not been identified.

A number of case–control studies have investigated the possibility of environmental agents precipitating or aggravating early CTCL. One study from the east coast of North America [7] recorded a significantly higher incidence of allergies and of fungal and viral infections in patients who developed CTCL compared with healthy controls, and also reported that a higher proportion of CTCL patients had worked in the petrochemical, textile, machine and metal industries. A study from the UK did not confirm these observations but did record a significantly higher incidence of atopic disease in MF patients and there have been subsequent reports of CTCL developing in patients with severe atopic dermatitis [8]. A more recent study from North America has failed to confirm any clear occupational or environmental exposure but has observed a higher than expected prevalence of other malignancies including non-lymphoma cutaneous malignancies in patients with MF [9]. Further reports have also suggested that there is a possible increased incidence of non-melanoma skin cancer, melanoma and also lung cancer in MF but whether or not this is related to prior therapy remains to be clarified [10].

Clinical features. Classical MF is characterized by typical cutaneous stages of disease consisting of patches and plaques involving less than 10% of the body surface area (stage T1/IA), more than 10% of the body surface area (stage T2/IB), tumours (stage T3/IIB) and erythrodermic disease (stage T3/III). Patients may progress from having limited patches and plaques to extensive plaques or tumours and even erythroderma [11]. However, many patients do not show any evidence of progression. Patch stage MF is characterized by subtle fine scaly and often slightly atrophic erythematous patches on the trunk (Fig. 54.1), usually involving the limb girdle areas and breast and particularly the buttocks. There may be mild pruritus but patients are often asymptomatic. At this stage, the clinical differential diagnosis includes pityriasis rosea, fungal infection, mild dermatitis or even a rather atypical form of psoriasis. Plaques are more obvious persistent polymorphic erythematous lesions with a similar distribution but, with the development of stage T2/IB, there is usually involvement of the head, neck and limbs as well as the trunk (Figs 54.2 & 54.3). Individual plaques may become very large, and there may be some degree of regression, giving rise to unusual arcuate and horseshoe-shaped lesions that can show considerable variation in colour, degree of scaling and border definition. Striking psoariasiform scaling can sometimes be a feature. There is some evidence that the overall thickness of plaques in stage T2/IB may have prognostic significance [12]. Once again patients may complain of pruritus or be asymptomatic. Rarely, individual plaques may become eroded or ulcerated and painful, which is often associated with secondary bacterial infection and such patients may have a very poor quality of life and high morbidity despite having an early stage of disease. Tumours can show considerable variation in size (Fig. 54.4), and if there are only a few small tumours it may be difficult to decide if this is truly stage T3/IIB disease. Many patients with early

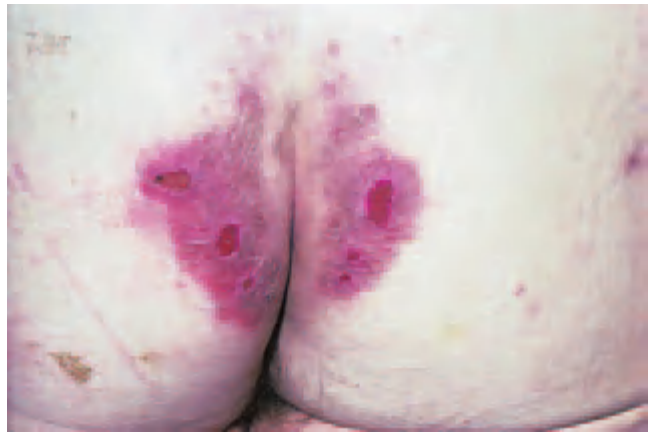

Fig. 54.1 Early mycosis fungoides showing plaques in the buttock area.

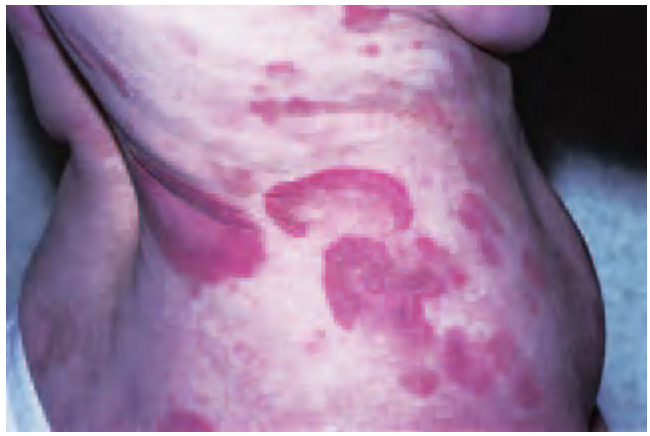

Fig. 54.2 More advanced mycosis fungoides showing typical polycyclic plaques.

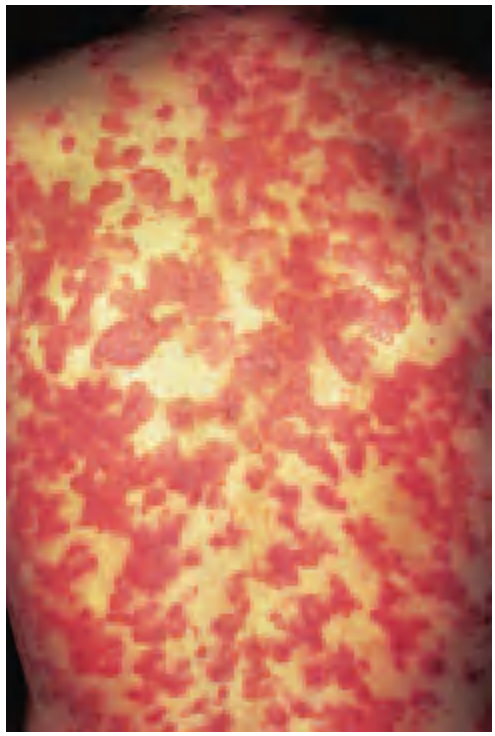

Fig. 54.3 Further stage of mycosis fungoides showing plaques involving more than 10% of the body surface.

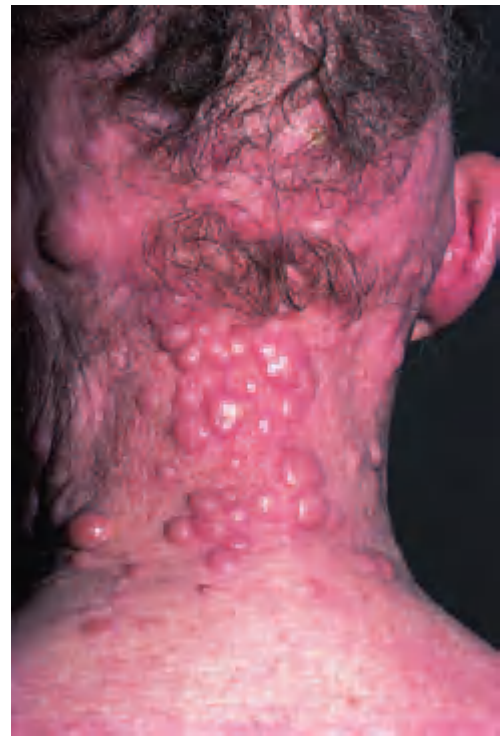

Fig. 54.4 Nodular mycosis fungoides showing striking nodules on the back of the neck. Similar lesions were present on all four limbs.

stages (T1/IA–T2/IB) of disease do not progress but rarely patients may gradually develop an *erythroderma* (stage T3/III), which is usually associated with severe pruritus. A *tumeur d'emblée* form of MF, in which patients rapidly develop large nodules and tumours without the prior presence of patches and plaques, has been described in the past [13], but many of these patients have other CTCL variants, which should be excluded on the basis of a critical assessment of the histological and immunophenotypical features. Patients may also rarely present with erythrodermic stages of disease and the differential diagnosis for these patients includes inflammatory dermatoses and Sézary syndrome.

The development of peripheral lymphadenopathy in MF alters the staging regardless of the cutaneous stage of disease [14]. Although the great majority of patients with early stage disease do not develop overt clinical involvement of lymph nodes or other organs (see prognosis), a small proportion do eventually show generalized systemic spread and may exhibit typical 'B' symptoms with fever and weight loss. Histological involvement of lymph nodes and other organs is a very poor prognostic sign. Any systemic organ can be involved but apart from liver, spleen and bone marrow, pulmonary, skeletal and central nervous system (CNS) involvement is well documented.

There are a large number of clinical variants of MF. Some plaques have a rather verrucous [15] or hyperkeratotic appearance, and bullae may rarely develop in the course of progression of individual plaques [16]. Rare icthyosiform variants have been described. An important subset of patients have MF that appears to be associated with pilosebaceous follicles, giving rise to a follicular clinical pattern often with alopecia (pilotropic or folliculotropic MF; see below) and there is some recent evidence that these patients may be resistant to treatment and have a poorer prognosis independent of their stage of disease. Rarely, younger patients present with a purpuric eruption not unlike the pigmented purpuric dermatosis associated with capillaritis but with histological features of MF [17]. Non-white younger adult patients may also present with a hypopigmented variant of MF [18,19], characterized by striking hypopigmented scaly patches often involving the trunk and especially the pelvic girdle area rather than the limbs. Histologically, these lesions tend to show marked epidermotropism, in contrast to the subtle clinical features. In *poikilodermatous* MF, patients develop clinical lesions characterized by either widespread or isolated poikiloderma, which may or may not be associated with typical patches and plaques of MF. The trunk is usually involved and the breasts and pelvic girdle area may also be affected (Fig. 54.5). The poikiloderma is typically characterized by atrophy, pigmentation and telangiectasia and must be distinguished from poikiloderma resulting from other disorders by appropriate histology. Rarely, patients may have extensive poikiloderma as a feature

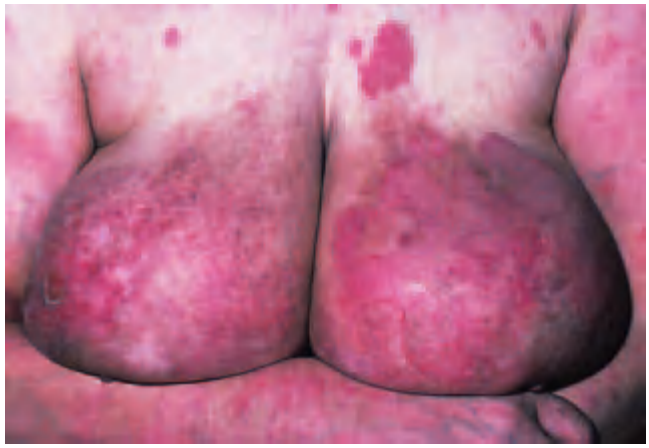

Fig. 54.5 Poikilodermatous mycosis fungoides showing involvement of both breasts.

of erythrodermic disease. These clinical variants do not have any prognostic significance with the exception of pilotropic MF.

Clinical differential diagnosis. In the early stages of MF, the clinical differential diagnosis may include such diverse conditions as allergic contact dermatitis, atopic dermatitis, psoriasis and fungal infection. Any patient with persistent polymorphic plaques, particularly involving the pelvic girdle area, should have a skin biopsy and histological confirmation of the disease. Multiple biopsies may be required to confirm a clinical suspicion of MF in early stages of disease.

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Staging. There are two staging systems in current use that have prognostic significance [1–3]. The TNM classification and the staging system suggested by the North American MF Cooperative Group are given in Tables 54.1 and 54.2. All patients should have a defined stage so that appropriate advice can be given regarding prognosis and treatment.

All patients with MF should have a full clinical examination and adequate diagnostic biopsies for histology and immunophenotypic and preferably molecular studies as, even for stage IA disease, studies suggest that patients with a detectable T-cell clone have a shorter duration of response and a higher rate of failure to respond [4]. Occasionally, multiple skin biopsies and the opinion of experienced dermatopathologists are required to make a diagnosis. Peripheral blood samples should be taken for routine haematology, biochemistry, serum lactate dehydrogenase (LDH), Sézary cells, lymphocyte subsets, CD4 : CD8 ratio, HTLV-1 serology and, ideally, TCR gene analysis of peripheral blood mononuclear cells. These tests are necessary to distinguish patients with ATLL and those patients with peripheral blood T-cell clones who may have a poor prognosis. Any palpable and bulky peripheral nodes should be biopsied but the practice of 'blind' lymph node biopsy of non-palpable nodes is not essential, although histological evidence of lymphoma can very rarely be detected in the absence of palpable lymphadenopathy. Chest X-ray should be performed [5]. Staging CT scans of the chest, abdomen and pelvis are indicated in all those patients with stage IIA, IIB, III and IV MF, but not in those with stage IA or IB MF [4]. Bone marrow aspirate and trephine biopsies may be indicated in patients with stage IIB, III and IV MF and patients with peripheral blood involvement, as indicated by the presence of Sézary cell counts representing more than 5% of the total leukocyte count, although the overall positive yield will be low [6,7].

Table 54.1 TNM classification of mycosis fungoides (MF).

Cutaneous involvement (T)	
T_0	Lesions clinically and/or histologically suspicious but not diagnostic
T_1	Plaques involving less than 10% of skin
T_2	Plaques involving more than 10% of skin
T_3	Tumours present
T_4	Erythroderma
Lymph nodes (N)	
N_0	Clinically and pathologically normal
N_1	Palpable; pathologically not involved
N_2	Clinically non-palpable; pathologically MF
N_3	Clinically enlarged; pathologically MF
Viscera (M)	
M_0	No visceral spread
M_1	Visceral spread present
Peripheral blood (B)	
B_0	No atypical circulating cells
B_1	Atypical circulating cells present

Table 54.2 A staging system for mycosis fungoides related to TNM classification.

Stage	T	N	M
IA	T_1	N_0	M_0
IB	T_2	N_0	M_0
IIA	$T_{1–2}$	N_1	M_0
IIB	T_3	$N_{0–1}$	M_0
III	T_4	$N_{0–1}$	M_0
IVA	$T_{1–4}$	$N_{2–3}$	M_0
IVB	$T_{1–4}$	$N_{0–3}$	M_1

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Prognosis (Table 54.3). Multivariate analysis has established that age at onset (over 60 years), skin stage and the presence of nodal (IVA) or visceral (IVB) disease are independent prognostic factors in MF [1–5]. Recent findings have confirmed that a patient's life expectancy is not adversely affected in stage IA disease [6]. Patients with stage IB–IIA disease have a 73–86% or 49–73% overall 5-year survival, respectively, while patients with stage IIB disease have a 40–65% 5-year survival [7–9]. The 5-year survival of patients with erythrodermic stage III disease is 45–57%, for those with stage IVA 15–40% and for stage IVB disease 0–15% [7,10,11]. The presence of a peripheral blood T-cell clone may indicate which patients with early stage disease are likely to develop disease progression [12]. The development of lymph node disease has a significant impact on prognosis [13]. Sézary syndrome patients by definition are staged as T4 N1–3 M0 B1 and have a poor prognosis, with an overall median survival of 32 months from diagnosis [14]. Recent studies of erythrodermic CTCL have shown that the presence of peripheral nodal disease is the most important prognostic factor in a multivariate analysis, although the peripheral blood tumour burden is also very close to significance [15]. In addition, prognostic data on a large series of patients have suggested that patients with thick plaques may have a worse prognosis than those with thin or patch stage disease and this has formed the basis for a suggested modification of the staging system, although the reproducibility of this histological assessment has not been confirmed [16].

A high incidence of second malignancies in MF patients, notably non-melanoma skin cancer and pulmonary small cell lung cancer, and also of malignancies in relatives of patients, mainly lymphomas and leukaemias, have been reported [17,18]. Other types of lymphoma–leukaemia and Hodgkin's lymphoma have also been described in association with MF and Sézary syndrome [19–21].

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Table 54.3 Published prognostic data in mycosis fungoides.

	IA (%)	IB (%)	IIA (%)	IIB (%)	III (%)	IVA (%)	IVB (%)	Overall (%)	Reference	Nos.	Median FU (years)
OS at 5 years	99	86	49	65		40	0	80	Doorn *et al*. [7]	309	5.2
	100	84		52	57				Zackheim *et al*. [9]	489	4.7
	96	(78)		(40)	(40)				Kim *et al*. [6]	122	9.8
		73	73*						Kim *et al*. [8]	176	8
					45	17			Kim *et al*. [11]	106	10.5
						15	15		Coninck *et al*. [10]	112	
OS at 10 years	84	61	49	27		20	0	57	Doorn *et al*. [7]	309	5.2
	100	67		39	41				Zackheim *et al*. [9]	489	4.7
	88	(60)		(20)	(20)				Kim *et al*. [6]	122	9.8
		58	45*						Kim *et al*. [8]	176	8
						5	5		Coninck *et al*. [10]	112	
DSS at 5 years	100	96 (81)	68	80		40	0	89	Doorn *et al*. [7]	309	5.2
DSS at 10 years	97	83 (36)	68	42		20	0	75	Doorn *et al*. [7]	309	5.2
	98								Kim *et al*. [6]	122	9.8
Median survival	NR	12.1 years		2.9 years	3.6 years				Kim *et al*. [6]	556	9.8
		12.8 years	10.0 years						Kim *et al*. [8]	176	8
					4.6 years	13 months			Kim *et al*. [11]	106	10.5
						13 months	13 months		Coninck *et al*. [10]	546	
Disease progression at 5 years	4	21	65	32		70	100		Doorn *et al*. [7]	309	5.2
Disease progression at 10 years	10	39	65	60		70	100		Doorn *et al*. [7]	309	5.2
Disease progression at 20 years	0	10		36	41				Coninck *et al*. [10]	546	
Overall disease progression	9								Kim *et al*. [6]	122	9.8
		20	34*						Kim *et al*. [8]	176	8
FFR at 5 years	50								Kim *et al*. [6]	122	9.8
		36	9						Kim *et al*. [8]	176	8
FFR at 10 years	25(50)								Kim *et al*. [6]	122	9.8
		31	3						Kim *et al*. [8]	176	8

DSS, disease-specific survival; FFR, freedom from relapse; FU, follow up; NR, not reached; OS, overall survival.
* Some cases assumed to be dermatopathic.
Comments:
(1) All actuarial survival curves calculated according to method of Kaplan-Meier and based on stage at diagnosis.
(2) In the study by Doorn *et al*. [7] (and in a subsequent publication: van Doorn *et al*. *Arch Dermatol* 2002; **138**: 191–8), the presence of follicular mucinosis was an independent poor prognostic feature possibly related to depth of infiltrate in patients with stage IB disease (DSS of 81% and 36% and OS of 75% and 21% at 5 and 10 years respectively). A lack of a complete response to initial therapy was also associated with a poor outcome ($P<0.001$) in a multivariate analysis as well as increasing clinical stage and the presence of extracutaneous disease. A different staging system was used in this study (based on Hamminga *et al*. [2]) but for the purposes of this table the staging has been altered to be consistent. This study is the only one to provide comprehensive DSS data for different stages of mycosis fungoides. Only 3 patients had stage IVB disease and only 18 patients each had stage IIA and IVA disease. Therefore the results for these stages must be interpreted cautiously.
(3) In the study by Zackheim *et al*. [9], black patients had a relatively more advanced stage of disease than white patients. The TNM classification was used in this study. Lymph node stage had an unfavourable impact on survival but this trend did not reach significance for each individual T stage because of a lack of sufficient power (an estimated 1700 subjects required) and IIA/IVA patients were not designated separately. Similar considerations apply to peripheral blood involvement. Similar outcomes for patients with stage IIB (T3) and III (T4) disease is consistent with other studies but this might reflect a lack of lymph node staging data included in this study.
(4) The study by Kim *et al*. [6] primarily included data on 122 patients with stage IA disease but survival data on 556 patients with all stages was also included to give the figures in brackets. The FFR data at 5 and 10 years is confusing because the text states that the FFR at 10 years was 25% but the figure indicates that it remains at approximately 50% as for FFR at 5 years. The median survival for stage IA patients was not reached at 32.5 years.
(5) In the study by Kim *et al*. [8], overall survival at 20 years for stage IB and IIA patients was 27%. DSS was better for patients <58 years of age ($P<0.03$). In 23 of the 56 patients with palpable lymphadenopathy, no histological assessment was made and these patients were assumed to have reactive/dermatopathic nodes (IIA). This might account for the lack of difference in OS at 5 years* between stage IB and IIA patients, although there appears to be an apparent difference in OS at 10 years*.
(6) In the study by Kim *et al*. [11], the overall and median survival data was calculated from the date of initial treatment which was usually within 3 months of diagnosis. This study also stratified patients into 3 groups according to the presence of none, one or two to three poor prognostic parameters, namely age at presentation (>65 years), the presence of clinical adenopathy and B1 stage producing varied median survivals of 10.2 years (0 factors), 3.7 years (1 factor) and 1.5 years (2/3 factors), $P<0.005$.
(7) The study by Coninck *et al*. [10] included 112 patients with extracutaneous disease at presentation or with progression and 434 patients with only cutaneous disease giving the 546 patients listed in the table for median survival and disease progression.

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Pathology [1–3]. The features of MF vary according to the clinical stage. The earliest pathological features of MF are the presence of a moderate, predominantly lymphocytic infiltrate in the papillary dermis. Many of the small lymphoid cells may be hyperchromatic and show a tendency to 'line up' just below the dermal–epidermal junction. Even at this early stage, the affinity of these T lymphocytes for the epidermis and papillary dermis is apparent, as there is rarely significant involvement in the underlying reticular dermis. As the disease progresses with the development of thicker plaques, prominent epidermotropism (Fig. 54.6) is seen. This describes the selective colonization of the epidermis by these atypical T cells and is characterized by single-cell colonization often along the basal layer, or by clusters of atypical lymphocytes in the epidermis—

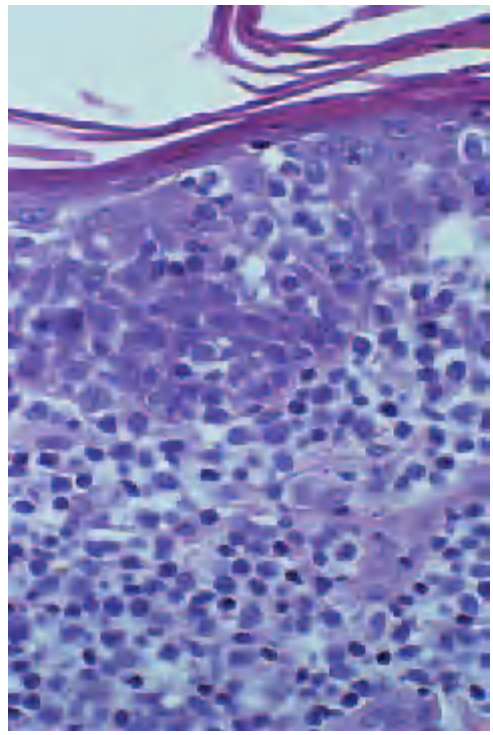

Fig. 54.6 Histology of mycosis fungoides showing striking epidermotropism with the presence in the epidermis of cytologically atypical small dark cells proven on marker studies to be $CD4^+$ helper T lymphocytes.

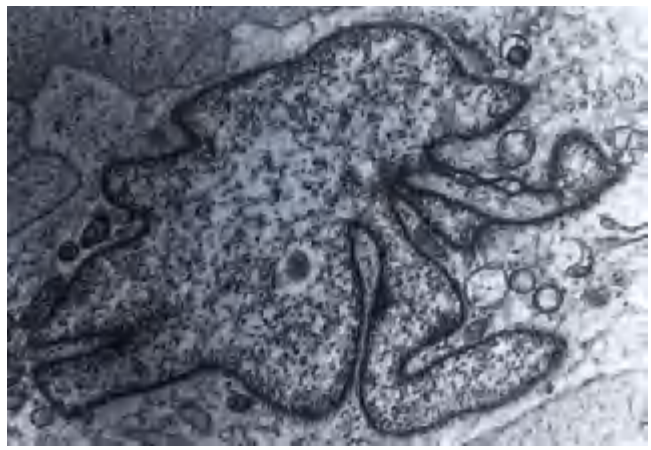

Fig. 54.7 Electron micrograph of T cell infiltrating the epidermis in mycosis fungoides, showing the striking cellular contours of the typical cell of Lutzner with a typical high nuclear contour index.

so-called *Pautrier microabscesses*. The lymphocytes in the epidermis are often strikingly cerebriform (Fig. 54.7), with a very irregular nuclear outline and heavy nuclear staining. If these cells are examined either under high power or with thin sections, the cerebriform and irregular nature of the nuclei can be better appreciated in three dimensions. In early MF, the T-cell lymphocytic infiltrate may be associated with a number of other cell types including

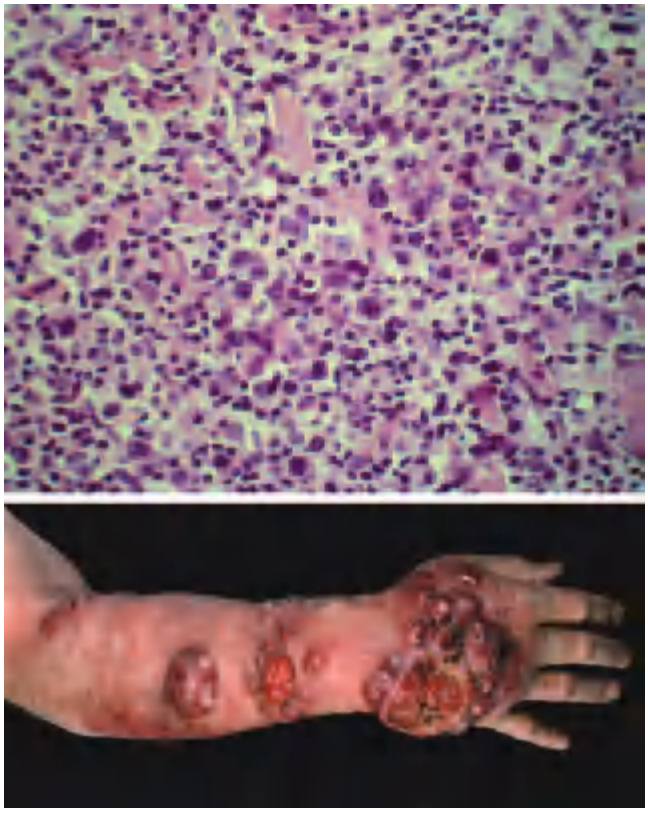

Fig. 54.8 High-power view (a) of large cell transformation in mycosis fungoides (b).

small numbers of plasma cells or eosinophils, but as the infiltrate becomes more intense and more epidermotropic, the infiltrate becomes monotonous and monomorphic. Granulomatous features may be rarely present and a prominent histiocytic infiltrate can be seen [4].

In more advanced stages of disease (IIB–IVB), the striking epidermotropic quality of the lymphocytic infiltrate may be lost, with scattered larger tumour cells showing marked cellular atypia. Large cell transformation may also occur and is a poor prognostic feature on univariate analysis, although this does not appear to be independent of age and stage of disease on multivariate analysis [5]. An earlier study showed no difference in survival for stage IIB patients showing histological features of large cell transformation compared to those without, but there was a significant difference in survival from diagnosis [6]. Large cell transformation (Fig. 54.8) is defined as the presence of more than 25–50% of large cells (either CD30 positive or negative) within the dermal infiltrate or the development of microscopic dermal nodules consisting of larger cells with pleomorphic and occasionally anaplastic morphology [5]. It is important to distinguish large histiocytic cells from large $CD30^+$ tumour cells and occasionally the presence of reactive germinal centres in MF can also cause histological confusion.

A further problem is the differentiation between large cell transformation in MF and the association with a primary cutaneous $CD30^+$ lymphoproliferative disorder such as lymphomatoid papulosis or anaplastic large cell lymphoma, which have a good prognosis. The development of large tumours on patches or plaques of MF would suggest large cell transformation if the histological criteria were fulfilled. In contrast, the presence of very large numbers (more than 75%) of $CD30^+$ large cells in only one or a few isolated tumours developing at sites distant from patches and plaques can present a very difficult diagnostic problem.

Immunopathology. The tumour cells in MF are $CD3^+$, $CD4^+$, $CD45RO^+$ and usually $CD7^-$ T cells. This is the phenotype of a mature helper T cell of memory type [7]. The tumour cells are CLA^+, consistent with a skin homing T cell [8]. In rare cases, the tumour cells are $CD3^+$ and $CD8^+$ and these cases may be hyperpigmented [9]. $CD8^+$ MF must be distinguished from an epidermotropic cytotoxic variant of CTCL with a poor prognosis (see below). Occasionally, there is a very prominent infiltrate of reactive tumour infiltrating $CD8^+$ T cells expressing cytotoxic proteins, which may indicate a good prognosis [10,11]. The dermal infiltrate often consists of a prominent population of $CD1a^+$ dendritic cells and $CD68^+$ histiocytic cells. In advanced disease, tumour cells may express an aberrant phenotype with either loss of T-cell surface antigens 'null-cell phenotype' or expression of the CD30 antigen either by scattered larger tumour cells or by prominent dermal nodules consisting of large pleomorphic or anaplastic tumour cells [5,7]. The latter feature may be associated with large cell transformation but CD30 expression does not appear to have any prognostic significance [5]. The tumour cells usually express the αβ T-cell receptor [12] and only rarely express cytotoxic proteins with disease progression [13].

Pathological differential diagnosis. In early MF, the main differential diagnosis includes a dermatitis reaction. The epidermotropic quality of the T-cell infiltrate in MF may be helpful, as may the cytology of the individual T cells, as in MF these intraepidermal lymphocytes tend to be larger than surrounding keratinocytes and have intensely stained nuclei with a very irregular outline. Spongiosis, if present in association with epidermotropic T cells or Pautrier microabscesses, is minimal, whereas this tends to be more striking in dermatitis reactions. A useful clue may be the characteristic basal layer colonization and the larger size of the intraepidermal T cells compared to the dermal mononuclear cells.

The pathological diagnosis of early MF can still, however, be extremely subjective and is best made in full collaboration with the clinician and only after careful correlation with the clinical features. It is often wise to take several biopsies from separate lesions, and if necessary to

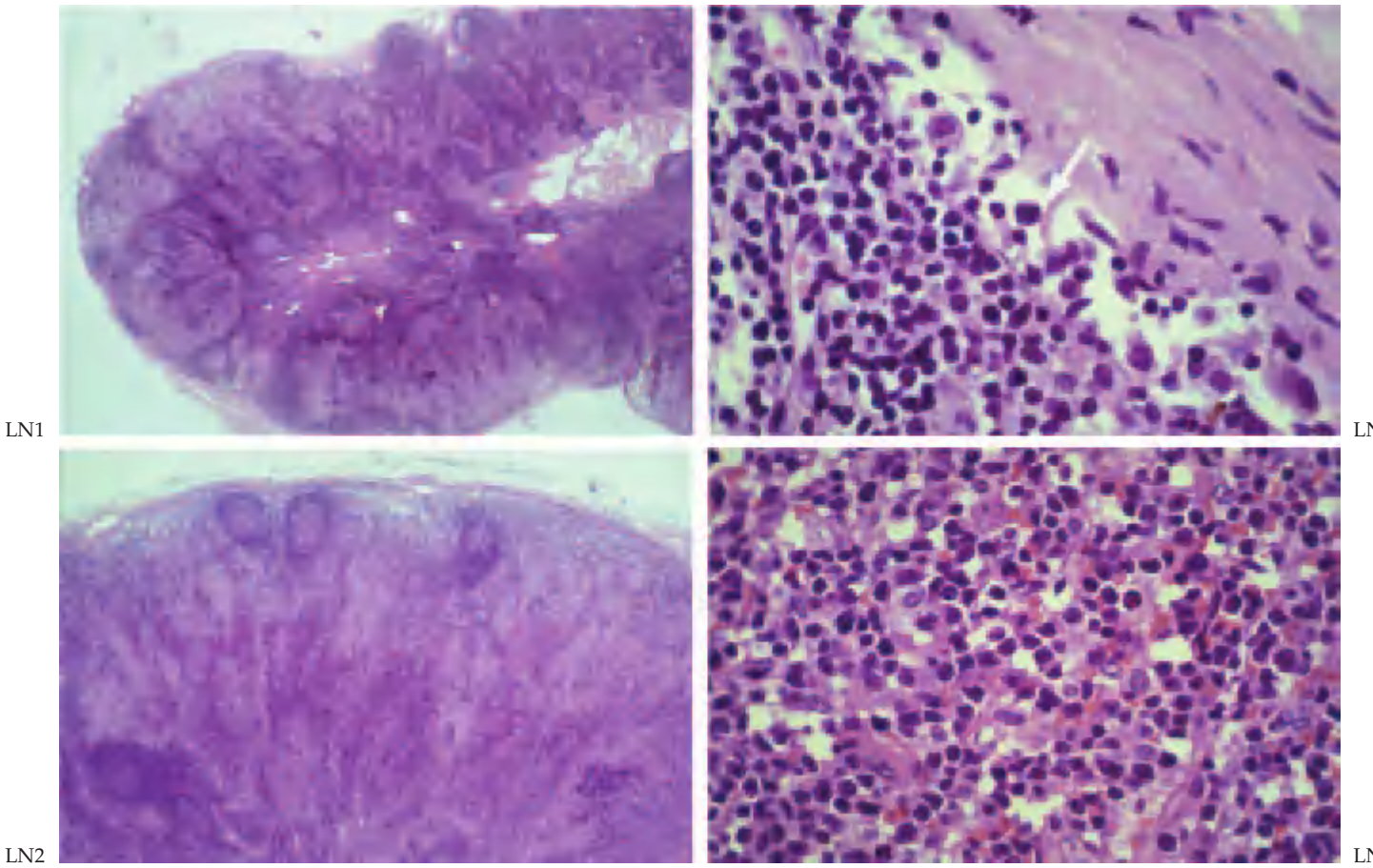

Fig. 54.9 Composite photomicrograph showing features of dermatopathic lymphadenopathy. LN1 is characterized by dermatopathic changes with melanin deposition and occasional atypical lymphocytes. LN2 with paracortical expansion of T-cell areas. LN4 showing a high-power view of lymph node effacement by small and medium sized atypical convoluted cells.

arrange for repeat biopsies to be carried out as the clinical picture evolves over a period of months or even years.

Immunophenotypic studies are usually of minimal value in differentiating early MF from other cutaneous lymphocytic infiltrates, as the majority of these cells will also be $CD3^+$, $CD4^+$ although a predominance of larger $CD4^+$ cells within the epidermis compared to the mixed population of smaller cells within the dermis can sometimes be helpful [12].

The differential diagnosis of early MF from conditions such as arthropod bites and lymphomatous drug eruptions can also be difficult, and good clinicopathological correlation is essential. In general, reactions to arthropod bites tend to show a higher proportion of eosinophils, and the disposition of the infiltrate in lymphomatous drug reactions will be perivascular rather than epidermotropic. In a proportion of cases, however, the diagnosis is suspected on clinical grounds but cannot confidently be made with certainty on histological examination. In these cases, sequential biopsies at 3–6-month intervals may be needed.

Pathology of extracutaneous disease. The usual pattern of extracutaneous spread is from the skin to the draining peripheral lymph nodes and thereafter to other organs such as the liver and spleen, but pulmonary, skeletal and CNS involvement have been documented. The histological assessment of peripheral nodes is based on the study by Scheffer *et al*. [14]. Those biopsies with no abnormalities are recorded as LN0 while those with dermatopathic changes are designated LN1 (*dermatopathic lymphadenopathy*), which is characterized by enlargement of the paracortical area of the lymph node because of the presence of large numbers of macrophages and pale dendritic (interdigitating reticulum) cells. The macrophages contain aggregates both of melanin and lipid material, giving rise to the older term 'lipomelanic reticulosis'. Histological evidence of possible involvement (LN2) is characterized by the additional presence of small clusters of larger atypical mononuclear cells within the expanded paracortical areas (Fig. 54.9). In contrast, partial (LN3) or complete effacement (LN4) of the lymph node architecture is consistent with definite lymphomatous involvement (Fig. 54.9).

An NCI classification system was proposed in 1985 that, although similar, has subtle differences [15]. In this system, lymph node architecture is preserved in LN1–3 in which dermatopathic changes may predominate. LN1 is characterized by single infrequent atypical cells, LN2 shows small clusters of atypical lymphocytes and LN3 shows larger clusters of atypical cells in paracortical areas. LN4 is characterized by partial or complete effacement by atypical cells [15].

A comparison of these systems has shown that both have a poor prognosis for partial or totally effaced nodes with non-effaced nodes showing no difference in survival [16]. In the recent WHO classification system, a modification of these classifications has been proposed whereby LN1 and LN2 have been grouped together as grade I (no histological involvement), with LN3 as grade II and LN4 as grade III, both representing definite histological involvement, although this system has not yet been validated [17]. However, there is a subtle difference in this system because in the WHO proposal grade I can be characterized by scattered but not clusters of atypical cerebriform cells, whereas nodes showing clusters of atypical cerebriform cells are graded as II (LN3).

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T-cell receptor gene analysis. TCR gene analysis consists of analysis of DNA from tissue samples for the detection of clonal rearrangements of the TCR genes as a marker of a monoclonal T-cell population. A similar approach can be used to identify a B-cell clone using analysis of immunoglobulin genes. A clonal lymphoid population is usually synonymous with a neoplastic proliferation but this does not signify malignancy. In contrast, the malignant potential of a lymphoid clone is related to the underlying molecular abnormalities. Analysis of TCR genes in MF is now a standard approach that has diagnostic, prognostic and therapeutic implications. Originally, Southern blot analysis of the β TCR gene was employed but this approach is time-consuming, requires large amounts of high-quality DNA and is relatively insensitive [1,2]. Consequently, most studies are now based on more sensitive PCR techniques and several different methods are employed including denaturing gradient gel electrophoresis (DGGE), temperature gradient gel electrophoresis (TGGE), single-strand conformational gel electrophoresis (SSCP) and gene scan methods for analysis of the γ TCR gene [3–8]. Although MF tumour cells usually express an αβ TCR, the γ TCR gene is rearranged in lymphocytes expressing both a γδ and an αβ TCR and this gene is much easier to analyse comprehensively than the β TCR gene. These different approaches have not been compared adequately but most results are broadly consistent.

T-cell clones can be detected in a proportion (approximately 70% overall) of patients with early stage disease and are almost invariable in patients with later stages of disease [5,6]. The lack of T-cell clones in all patients with early stages of disease almost certainly reflects a lack of sensitivity of the technique, although studies have shown that those early stage patients without a T-cell clone achieve a higher complete remission rate with skin-directed therapy than those with a T-cell clone [9]. This suggests that the proportion of non-tumour cells in the infiltrate, possibly reflecting the host immune response, may also be critical. Identical T-cell clones can be detected in peripheral blood of patients with all stages of disease and this may have independent prognostic significance [7,10]. In contrast, non-identical peripheral blood T-cell clones can also be detected and may not be pathological, emphasizing that results from all samples must be carefully compared [11]. In patients with both MF and lymphomatoid papulosis or $CD30^+$ large cell anaplastic lymphoma, identical T-cell clones can be found, suggesting a common pathogenesis [1,2,12]. T-cell clones identical to those in the skin can be detected in dermatopathic lymph nodes (LN1–LN2) but whether this has any pro-

gnostic significance is unclear at present [13–16]. Because of the sensitivity of these PCR-based techniques, T-cell clones have rarely been detected in non-neoplastic inflammatory disorders and therefore it is critical that the presence or absence of a clonal TCR gene rearrangement must always be interpreted in conjunction with the clinical and pathological features. Recent PCR-based studies have also detected T-cell clonal proliferations in some cases of pityriasis lichenoides acuta, small and large plaque parapsoriasis and pityriasis lichenoides chronica [17–21]. The clinical significance of these findings is unclear at present. Although these results would appear to support clinical impressions that large plaque parapsoriasis probably represents early stage MF, small plaque parapsoriasis has been thought to be a separate inflammatory condition that is not related to MF. The findings in pityriasis lichenoides acuta support previous suggestions that this represents part of a spectrum with lymphomatoid papulosis and, intriguingly, lesions resembling pityriasis lichenoides chronica can be associated with MF.

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Molecular features. The underlying molecular pathogenesis of MF is currently unknown. No disease-specific translocations have been identified [1], but various abnormalities of tumour-suppressor genes have been detected including overexpression and mutation of *p53* in advanced stages of disease [2–5]. In one study, UVB-type *p53* mutations were found, although this has not yet been confirmed in other studies [4]. *p53* abnormalities are not found in early stages of disease, suggesting that inactivation of *p53* is related to disease progression, similar to findings in other nodal and extranodal lymphomas. At present, it is unclear if *p53* abnormalities are associated with treatment resistance and a poor prognosis as seen in other non-Hodgkin's lymphomas.

Inactivation of both *p15* and *p16* genes has also been detected in MF [6–8]. Unlike *p53*, this is usually a result of hypermethylation of promoter sequences rather than mutation, but it is unclear whether this is restricted to late-stage disease [8]. Frequent allelic losses on 10q have been detected predominantly in late stages of disease, suggesting that this region harbours a gene that is involved in the pathogenesis of MF [9]. In this study, a tumour-suppressor gene on 10q, *PTEN*, was homozygously deleted in a proportion of patients [9]. Recent studies have identified loss of Fas protein expression in later stages of disease and infrequent mutations of the *Fas* gene on 10q have also been detected in early stages of disease, providing a further mechanism by which tumour cells in MF may escape apoptosis [10]. Therefore, it is possible that biallelic inactivation of the *Fas* gene may be a consequence of mutation and deletion on 10q in MF. A specific pattern of chromosomal losses and gains has also been found in MF using allelotyping and comparative genomic hybridization [11–13]. Deletions on chromosomes 1p, 13, 19, 17p and 10q and gains of 4 and 17q are characteristic, with an identical pattern seen in Sézary syndrome suggesting a similar pathogenesis. 17p loss may be associated with biallelic inactivation of *p53* through a combination of deletion and point mutation. These results suggest that

abnormalities of genes in these chromosomal regions are critical to the pathogenesis of MF.

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Follicular mucinosis [1–4]

SYN. ALOPECIA MUCINOSA

Definition. Boggy cutaneous plaques showing follicular prominence and histological evidence of mucinous degeneration of hair follicles that is often associated with an atypical pilotropic T-cell infiltrate and clinical features of MF (pilotropic or folliculotropic MF).

Clinical features. There appear to be two distinct forms of follicular mucinosis, one associated with MF and an entirely separate benign inflammatory form of follicular mucinosis, which is not associated with the development of MF. The clinical features of these two types of follicular mucinosis are identical: follicular papules and plaques often associated with severe pruritus and with a predilection for the face and scalp but the trunk and limbs can be affected and the classic patches and plaques of MF may also be present. A younger age group is affected by inflammatory forms but there are no satisfactory criteria for distinguishing this from MF-associated follicular mucinosis, suggesting that both may represent forms of MF. Prominent giant comedones are often a feature with acneiform lesions (Fig. 54.10), and significant alopecia may be present, rarely with mucinorrhoea [5].

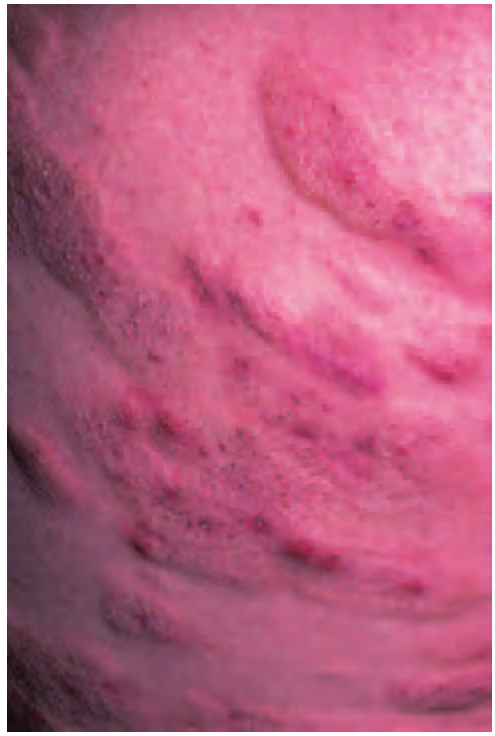

Fig. 54.10 Clinical appearance of follicular mucinosis showing boggy mucin-secreting plaques on the trunk.

Pathology. There is degeneration of involved hair follicles, associated in MF with a prominent pilotropic atypical T-cell infiltrate. In MF there may also be associated interfollicular epidermotropism. Although these histological features distinguish follicular mucinosis from pilotropic MF, both conditions may simply represent points on a spectrum [5]. Mucin stains such as alcian blue show the presence of large quantities of mucin (Fig. 54.11). In MF, a pilotropic or folliculotropic infiltrate may also occur without mucinosis. In contrast, the inflammatory form of follicular mucinosis does not show a prominent atypical pilotropic T-cell infiltrate, although repeated biopsies may be required to fully exclude MF and it may be impossible to distinguish these two forms with confidence [6]. Follicular mucinosis can also occur as an incidental histological feature in the context of a variety of inflammatory dermatoses [7].

Immunophenotype. The tumour cells in both follicular mucinosis and folliculotropic/pilotropic MF are usually $CD3^+$, $CD4^+$ and $CD8^-$. Prominent $CD30^{+/-}$ blast cells may be associated with a poor prognosis [5,6]. TCR clonal gene rearrangements can be detected in both MF-associated follicular mucinosis and so-called benign forms of

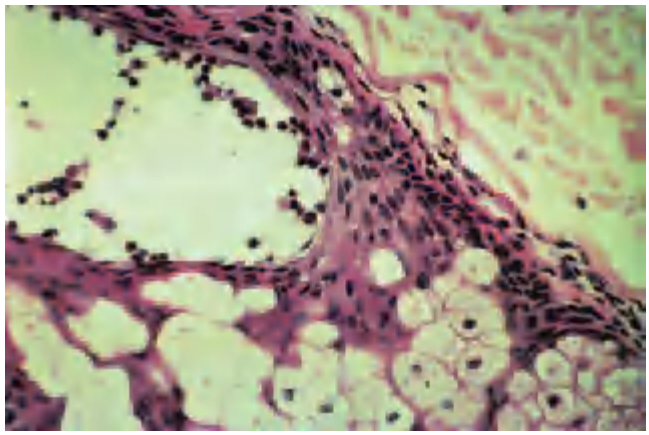

Fig. 54.11 Histology of lesion illustrated in Fig. 54.10 showing degeneration of the hair follicle.

inflammatory follicular mucinosis, consistent with suggestions that both may represent MF variants [6,8].

Pathogenesis. It is likely that follicular mucinosis represents a follicular (pilotropic) variant of MF with mucinous degeneration of the hair follicle, although the reason for mucin deposition is not currently known. This is supported by the presence of this clinical and histological pattern in patients with typical features of MF. The poor prognosis of folliculotropic variants may relate to the poorer efficacy of skin-directed therapies because of the depth of the associated T-cell infiltrate or a currently unknown pathogenetic difference.

Treatment. There is emerging evidence that follicular variants of MF have a worse prognosis, with disease-specific survival rates of 81% at 5 years and 36% at 10 years [5]. MF associated with follicular mucinosis is treated with skin-directed therapy as for early stages of MF, but patients may also require systemic treatment with IFN-α or retinoids. Total skin electron beam therapy may be appropriate for resistant cases. Dapsone can be effective for inflammatory forms of follicular mucinosis. However, if the hair follicles have been destroyed, scarring alopecia will be present and the hair loss permanent.

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Pagetoid reticulosis

SYN. WORINGER–KOLOPP DISEASE

Definition. A localized solitary variant of CTCL, which histologically shows intense epidermotropism.

Clinical features. This entity was first described in 1939 [1] and is rare but appears to affect younger adults [2]. It is characterized by an isolated persistent scaly plaque, commonly involving an acral site (Fig. 54.12). The lesion may be asymptomatic and slowly expands, but no further plaques develop on other body sites. A more generalized variant with multiple plaques at other sites has also been described (*Kettron Goodman*), but it is likely that this represents an epidermotropic variant of MF or the more recently described $CD8^+$ epidermotropic CTCL variant [3; and see below].

Pathology. Biopsies show very striking colonization of an acanthotic epidermis [4,5] by atypical large pale mononuclear cells, which usually either fail to express lymphoid markers or express an aberrant T-cell phenotype. Originally there was controversy over whether these cells were derived from histiocytes, Langerhans' cells or Merkel cells. However, the detection of an aberrant T-cell phenotype in some cases and clonal TCR gene rearrangements has clearly established that this entity represents a CTCL variant [6–8].

Pathogenesis. This entity may either represent a localized epidermotropic variant of either MF [9] or the more

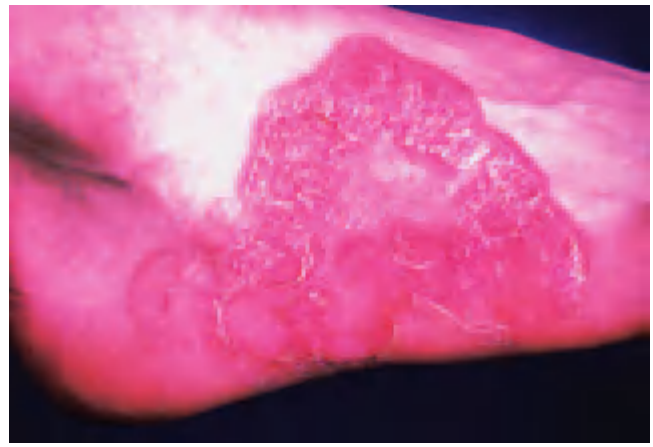

Fig. 54.12 Pagetoid reticulosis. Striking solitary scaling lesion on the side of the foot of a young male.

recently described $CD8^+$ epidermotropic CTCL [3]. However, the underlying pathogenesis will not be understood fully until the fundamental biology of MF has been clarified.

Treatment. The natural history of this lesion is of very slow local extension with an excellent prognosis. Successful remission and probable cure has been reported with both surgical excision and low-dose superficial radiotherapy.

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Granulomatous slack-skin disease

Definition. A rare disease characterized clinically by the slow development of pendulous folds of lax erythematous skin and histologically by dermal granulomas and elastolysis.

Clinical features. The lesions develop slowly, usually in middle-aged adults, and then progress over several years, [1]. They are typically flexural in distribution. This condition appears to be caused by cutaneous elastolysis provoked by an underlying lymphoma. Several patients have died of Hodgkin's disease or non-Hodgkin's lymphoma [2–4] and the otherwise unaltered epidermis may show lymphocytic epidermotropism, similar to that seen in MF. The condition must be distinguished from other forms of cutis laxa.

Pathology. Histology reveals a dense granulomatous dermal infiltrate with destruction of dermal elastic tissue (elastolysis) [5–7]. The destruction appears to be mediated by histiocytic giant cells [8]. Similar granulomas may occasionally be found in the spleen and lymph nodes [4]. The lymphocytic infiltrate in the dermis has an aberrant T-cell phenotype, which is suggestive of a lymphomatous proliferation. TCR gene analysis has confirmed that there is a T-cell clone present suggesting CTCL, but whether this condition represents a variant of MF or a different type of CTCL is currently unclear [9].

Treatment. No effective therapy has yet been identified.

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Sézary syndrome [1–4]

Definition. The presence of a clinical triad consisting of erythroderma, peripheral lymphadenopathy and atypical mononuclear cells (Sézary cells) comprising 5% or more of peripheral blood lymphocytes on a buffy coat smear (B1), or more than 20% of total lymphocyte count or a total Sézary count of more than 1000×10^9/L (B2). The presence of a peripheral blood T-cell clone as indicated either by a CD4 : CD8 ratio greater than 10, aberrant expression of pan T-cell antigens, cytogenetics or TCR gene analysis is now also required to confirm that the patient has a malignant disease, Sézary T-cell lymphoma–leukaemia [5].

Clinical features. The majority of patients are elderly males and may develop the syndrome either *ab initio* or as progression from classical MF. Many patients describe a prolonged history of 'dermatitis'. Patients present with a generalized exfoliative erythroderma, and may have systemic problems because of shunting of blood through grossly dilated cutaneous vasculature, and resulting high-output cardiac failure. There may be associated ectropion, scalp alopecia, palmoplantar hyperkeratoses and fissuring and the nails often show gross subungual hyperkeratoses (Fig. 54.13). Peripheral lymphadenopathy is often

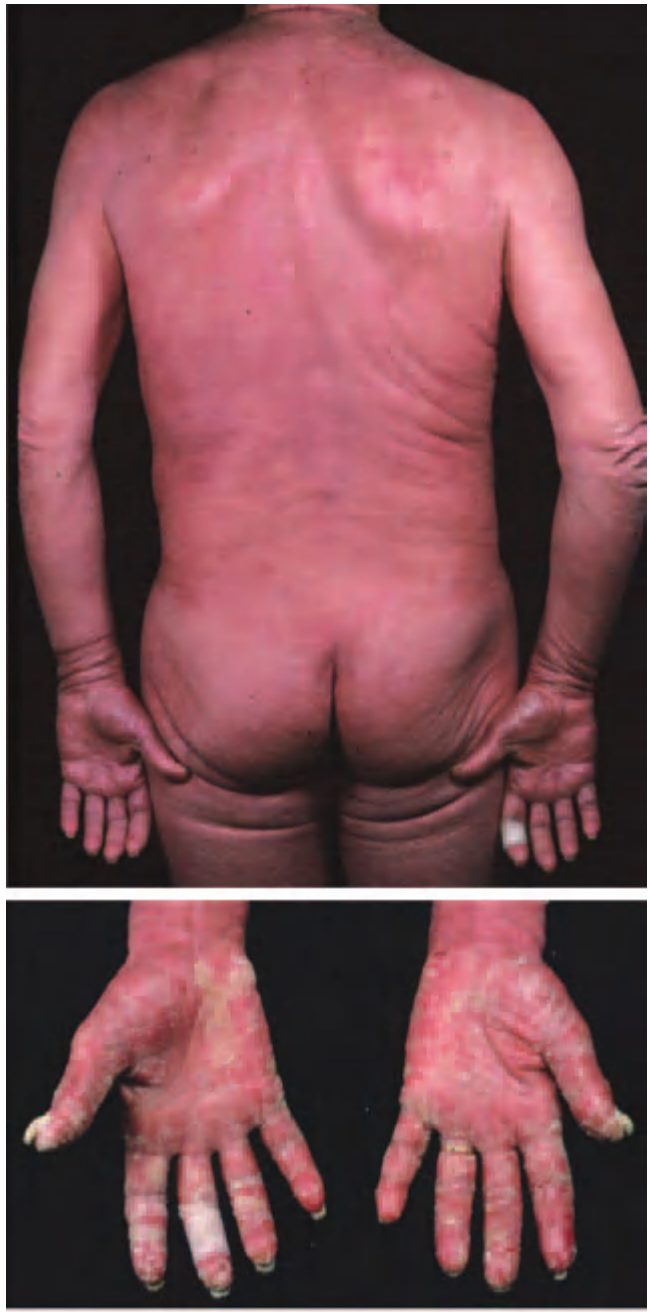

Fig. 54.13 Sézary syndrome showing erythroderma with palmoplantar hyperkeratoses and prominent nail dystrophy.

present. The distinction from erythrodermic MF (T4 N0–3 M0/stage III–IVA) is based on the degree of peripheral blood involvement (more than 5% Sézary cells per 100 lymphocytes (T4 N0–3 M0B1/stage III–IVA) as suggested in the original National Cancer Institute (NCI) staging system) [6]. However, there has been a debate about the diagnostic and prognostic relevance of the proportion of peripheral blood Sézary cells. In 1988, the NCI originally published a revised staging system, with over 20% Sézary cell count (per 100 lymphocyes) as the B1 rating [7], based on previous studies showing that this figure had prognostic significance in Sézary syndrome [8,9]. However, this has been shown to include some patients with benign disorders and may also actually represent a larger tumour burden (B2). An absolute Sézary cell count of over 1000/mm^3 has recently been proposed as a criterion for the diagnosis of Sézary syndrome, which most closely represents the B2 rating for peripheral blood involvement, but this figure may exclude those patients with a lower tumour burden (more than 5% per 100 lymphocytes; B1), who nevertheless have a neoplastic form of Sézary syndrome [5,10]. A recent study suggests that the presence of lymph node disease in Sézary syndrome is an independent prognostic factor while the degree of peripheral blood involvement also has some prognostic significance [11]. The prognosis for patients with Sézary syndrome is poor, with a median survival of 35 months from diagnosis. Most die of opportunistic infection. However, with improved earlier diagnosis the prognosis may now be better.

Immunopathology. Skin biopsies can show large numbers of atypical mononuclear cells in the dermis with epidermotropism, but it has been shown that non-diagnostic and lymphomatoid histology is frequently seen in proven cases of Sézary syndrome [12]. The presence of atypical (Sézary-like) peripheral blood cerebriform mononuclear cells has also been reported in a variety of inflammatory conditions including actinic reticuloid, erythroderma associated with dermatitis and psoriasis, and severe drug reactions, but in general the percentage of atypical cells in such conditions is fewer than in the Sézary syndrome (Fig. 54.14) [13,14]. In addition, T cells with the morphological and ultrastructural features of Sézary cells can be identified in the peripheral blood of normal healthy individuals [15,16]. However, it is important to realize that the total lymphocyte count does not have to be raised for the diagnosis to be made, and the presence of a normal total white cell count without careful morphological examination of the 'tail' of a blood smear or of a buffy coat preparation may mask this diagnosis. Consequently, it can be difficult to conclusively distinguish cases of T-cell leukaemia–lymphoma from inflammatory dermatoses. Large Sézary cell variants (over 16 μm diameter) are easier to recognize but small Sézary cell variants (12–14 μm) are more common and are more difficult to distinguish from activated lymphocytes [4]. Sézary cells are usually CD3$^+$, CD4$^+$, CD7$^-$, CD26$^-$ T cells but CD7$^+$ and CD8$^+$ variants have been reported [17–21]. Absolute CD4 counts and CD4 : CD8 ratios are elevated. A CD4 : CD8 ratio greater than 10 distinguishes most cases of T-cell leukaemia–lymphoma from inflammatory dermatosis associated with Sézary cells but is not pathognomonic. A consensus has now been agreed that diagnostic criteria should include the clinical triad of features plus the presence of a peripheral blood T-cell clone detected either by expression

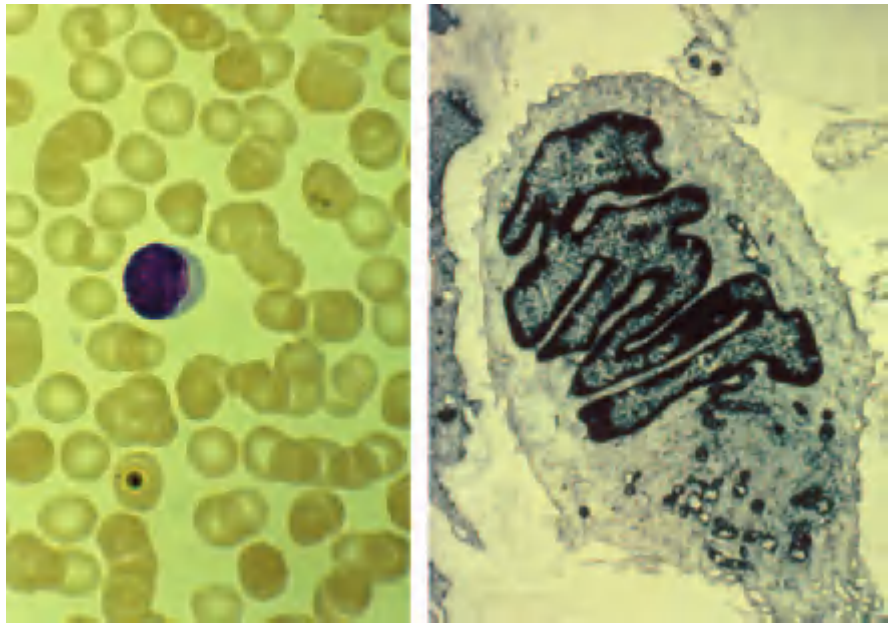

Fig. 54.14 High-power view of Sézary cells in peripheral blood showing large cell with very large nucleus and minimal cytoplasm, and ultrastructural features of a typical cerebriform nucleus.

of aberrant pan T-cell antigens, cytogenetics or TCR gene analysis [5]. Those patients without evidence of a T-cell clone may have a benign inflammatory dermatosis with an excellent prognosis [22]. Sézary syndrome should also be distinguished from other T-cell malignancies such as T-prolymphocytic leukaemia, which can present with cutaneous involvement including rarely erythroderma, although this is usually apparent on the basis of clinicopathological and immunophenotypic features [23].

Molecular features. Conventional G-banded karyotypes reveal multiple, often clonal, complex chromosomal abnormalities consisting of numerical and structural changes in approximately 50% of cases of Sézary syndrome and an abnormal karyotype is a poor prognostic factor [24,25]. No disease-specific recurrent translocations have been detected as yet, despite intensive studies with multicolour fluorescent in-situ hybridization (M-FISH) [26]. Extensive comparative genomic hybridization (CGH) studies have revealed similar chromosomal gains and losses to MF, suggesting a similar pathogenesis [27].

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Epidermotropic $CD8^+$ cytotoxic lymphoma

Definition. A primary cutaneous $CD8^+$ T-cell lymphoma that expresses cytotoxic proteins and shows a prominent epidermotropic infiltrate [1]. Although there are currently few reports of this entity, the distinctive pathological and immunophenotypic features and poor prognosis suggest that it represents a distinct subtype of CTCL [1,2].

Clinical features. These patients rapidly develop generalized papules, plaques, nodules and/or tumours which may show ulceration and necrosis [1]. Mucosal involvement may occur. The characteristic distribution of MF, namely involvement of the limb girdle areas, is usually not a feature. The prognosis is very poor, with a 5-year survival of 0%.

Pathology. These lymphomas show a prominent epidermotropic band-like infiltrate with nodular infiltrates of large or small- to medium-sized atypical T cells. These cutaneous lymphomas must be distinguished from MF, $CD30^-$ small to medium pleomorphic and $CD30^-$ large T-cell lymphomas.

Immunophenotype. The tumour cells are $CD8^+$ and usually $CD45RA^+$ and $CD3^+$ [1,2]. The tumour cells also express cytotoxic proteins such as T-cell intracellular antigen-I (TIA-I), granzyme B and perforin. Epstein–Barr virus (EBV) is not detected, in contrast to nasal-type natural killer (NK)/T-cell lymphomas [3].

Pathogenesis. Although the number of cases reported is small, many of these cases express the γδ TCR and show clonal rearrangements of the γ TCR gene with the β TCR gene in a germline configuration, consistent with an origin from a cutaneous γδ T cell [4]. These lymphomas may previously have represented disseminated pagetoid reticuloses (Ketron Goodman). In the EORTC classification this subtype is defined as either $CD30^-$ small to medium pleomorphic or large T-cell lymphomas, while in the WHO classification these lymphomas are defined in the peripheral T-cell lymphoma category.

Treatment. These patients have a very poor prognosis and responses to radiotherapy and chemotherapy are limited.

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Large cell $CD30^-$ cutaneous lymphoma (peripheral T-cell lymphoma—unclassified)

Definition. In the EORTC classification a separate category of primary cutaneous $CD30^-$ large cell lymphoma is defined on the basis of a lack of prior or concurrent clinicopathological features of MF and the presence of $CD30^-$ large pleomorphic or immunoblastic cells [1,2].

Clinical features. The characteristic presentation is the sudden appearance of solitary or multiple nodules or tumours on the skin with no preceding plaques or patches of typical MF. In the past, this subgroup of T-cell lymphomas may have been called tumeur d'emblée type of MF. The lesions can be localized or generalized. Patients are HTLV-1 negative. The prognosis is poor, with a 5-year survival of 15% reported [1].

Pathology. Prominent nodular or diffuse infiltrates are characteristic with medium to large pleomorphic T cells and immunoblasts. This CTCL variant must be distinguished from $CD30^-$ small to medium pleomorphic CTCL. Epidermotropism is usually absent. Although an angiocentric pattern was originally reported [1], it is likely that $CD30^-$ cutaneous angiocentric lymphomas represent extranodal NK/T-cell lymphomas (nasal type).

Immunophenotype. The tumour cells usually express T-cell antigens such as CD4 but the pattern may be aberrant with loss of most pan T-cell antigens. By definition, these cells are $CD30^-$ and $CD56^-$. Clonal TCR gene rearrangements are usually present. Epidermotropic cytotoxic $CD8^+$ variants almost certainly represent a separate entity (see above). Similarly, $CD56^+$ cases represent either extranodal NK/T-cell lymphomas (nasal type) or blastic NK-cell lymphomas (see below).

Pathogenesis. This CTCL variant must also be distinguished from transformed MF, HTLV-1 positive ATLL, cytotoxic $CD8^+$ epidermotropic CTCL and blastic NK-cell or extranodal NK/T-cell lymphomas (nasal type). The remaining group of $CD30^-$ CTCL, which are classified as peripheral T-cell lymphoma in the WHO classification, require further study to clarify the pathogenesis.

Treatment. Superficial radiotherapy and multiagent chemotherapy are usually required but the overall prognosis is poor.

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Pleomorphic (small to medium) $CD30^-$ cutaneous lymphoma (peripheral T-cell lymphoma—unclassified)

Definition. This subtype of CTCL defined by the EORTC classification must be distinguished clinically from MF and is characterized by small to medium pleomorphic tumour cells [1]. In the WHO classification these lymphomas are classified as peripheral T-cell lymphomas.

Clinical features. Several erythematous or purple nodules or tumours without typical patches or plaques of MF. Patients are HTLV-1 negative. The estimated 5-year survival is 62–80%, but this is only based on small series [1–3]. Systemic involvement is unusual.

Pathology. There are dense nodular or diffuse infiltrates of small to medium pleomorphic T cells within the dermis, often extending into the subcutis [1–3]. This subtype can be distinguished from large cell $CD30^-$ CTCL because in the latter more than 30% of the tumour cells are large pleomorphic cells. Epidermotropism may be present.

Immunophenotype. The tumour cells are usually $CD4^+$ and $CD3^+$ but loss of some T-cell antigens is common [1–3]. It is now appreciated that cases with a $CD8^+$ phenotype and marked epidermotropism represent a different entity, namely cytotoxic epidermotropic $CD8^+$ CTCL (see above), which has a worse prognosis. Clonal TCR gene rearrangements are present.

Pathogenesis. Currently, little is known about the underlying aetiology and pathogenesis of this rare group of primary cutaneous lymphomas. Cases must be distinguished from MF and pseudo T-cell lymphomas. In the WHO classification these lymphomas are classified as peripheral T-cell lymphoma and further studies are required to characterize this group in more detail.

Treatment. In view of the excellent prognosis, superficial radiotherapy is appropriate for solitary lesions. Single-agent chemotherapy and IFN-α have been reported to be effective [3].

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Treatment of mycosis fungoides and Sézary syndrome

Current therapy of MF and Sézary syndrome includes:

1 Topical steroids
2 Topical chemotherapy—mechlorethamine (nitrogen mustard) and carmustine (BCNU)
3 Phototherapy—both UVB and psoralen with UVA (PUVA) and UVA-1
4 Radiotherapy, including total skin electron beam therapy (TSEB)
5 Immunotherapy (IFN-α, IFN-γ and IL-12)
6 Retinoids
7 Combination therapies
8 Systemic single and multiagent chemotherapy
9 Photopheresis
10 Toxin therapies
11 Monoclonal antibodies.

The choice of initial treatment for the MF patient will depend on the stage of the disease as well as the general condition and age of the patient (performance status). At present, there are very few published studies that could form the basis for evidence-based therapy, mainly because of the rarity of the condition and also because of the variation between individual patients in disease pattern and progress. A large proportion of patients with MF are frail, elderly and likely to succumb either to other general medical problems or to the side effects of overenthusiastic therapy. These points and the patient's quality of life should always be considered when selecting a treatment regimen. One of the few randomized trials of treatment of MF reported on 103 patients who received either TSEB (3000 cGy total skin electron beam) together with cyclophosphamide, daunorubicin, etoposide and vincristine (a rigorous 'treat to cure' regimen) or sequential topical therapy consisting of topical nitrogen mustard, superficial radiotherapy and TSEB, progressing to PUVA

if required (a 'gentle palliative' regimen). After a median follow-up time of 75 months, there was no difference in disease-free or overall survival between the 52 patients who received TSEB plus chemotherapy and the 51 who received sequential palliative topical therapy [1]. This study established a consensus that therapy in MF should be based on stage of disease and aimed at disease palliation rather than an aggressive intent to cure. The role of novel therapeutic approaches, such as photodynamic therapy, remains to be established.

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Topical steroids

For patients with limited early stage MF, life expectancy may not be adversely affected and it is acceptable to simply use emollients with or without moderate potency topical steroids. Potent topical corticosteroids can produce a clinical response, although this is usually short-lived [1].

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Topical chemotherapy—nitrogen mustard (mechlorethamine) and carmustine (BCNU)

Topical mechlorethamine (nitrogen mustard) 0.01% or 0.02%, either as an aqueous solution (normal saline) or ointment base (emulsifying ointment), is effective for superficial disease with response rates of 51–80% for IA, 26–68% for IB and 61% for IIA disease [1–4]. The aqueous solution is relatively unstable, and the ointment base—more commonly than the aqueous solution—can cause irritancy or an allergic dermatitis in sensitized individuals (35–58%), but efficacy is similar. This product must not be used in pregnancy and there are rare reports of non-melanoma skin cancer in patients treated with topical mechlorethamine. There is no consensus as to whether mechorethamine should be applied to individual lesions or the whole skin, daily or twice weekly, or about the duration of topical therapy after a clinical remission has been produced; responses can be sustained for prolonged periods.

Topical carmustine (BCNU) is an alternative topical chemotherapeutic agent in MF, with similar efficacy to mechlorethamine as indicated by response rates of 86% in stage IA, 47% in stage IB and 55% in stage IIA patients [5]. Alternate day or daily treatment with 10 mg BCNU in 60 mL dilute alcohol (95%) or 20–40% BCNU ointment can be used. Hypersensitivity reactions occur less often (5–10%) than with mechlorethamine. All patients treated topically with carmustine should have regular monitoring of their full blood counts and treatment is normally given for only 2–4 weeks to avoid myelosuppression; maintenance therapy is contraindicated.

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Topical retinoids

Recently, a novel retinoid, 1% Targretin (bexarotene) gel, has been approved by the Food and Drug Administration (FDA) for topical therapy in stage I MF in patients who are resistant or intolerant of other topical therapies [1]. In open uncontrolled studies, response rates of 63% with 21% complete response rates have been reported in 67 patients with early stage (IA–IIA) disease. Median time to and duration of response were 20 and 99 weeks, respectively.

Other topical therapies

There has only been one randomized placebo-controlled trial of topical therapy in MF. Topical peldesine cream (BCX-34—an inhibitor of the purine nucleoside phosphorylase enzyme) showed no benefit, compared to vehicle, with complete responses of 28% and 24%, respectively, emphasizing the difficulties in interpretation of uncontrolled studies of topical therapy in early stages of MF [2].

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Phototherapy and photochemotherapy

The clinical benefit of PUVA (photochemotherapy) was noted over 20 years ago and response rates of 79–88% in

stage IA and 52–59% in stage IB disease have been reported [1–5]. Flexural sites ('sanctuary sites') often fail to respond completely and the duration of response varies. There is no significant response in tumour (IIB) stage disease. Maintenance therapy is rarely effective at preventing relapse and therefore should be avoided if possible so as to limit the total cumulative dose, as patients will often require repeated courses over many years. One study has shown that 56% of stage IA and 39% of stage IB complete PUVA responders had no recurrence of disease after 44 months follow-up without maintenance therapy [6]. PUVA is an ideal therapy for patients with stage IB–IIA disease who are intolerant of or fail to respond to topical therapies such as mechlorethamine, although both therapies can be complementary for some patients. Treatment regimens have varied in reported studies of PUVA in CTCL with twice to four times weekly and different protocols for incremental dosage, but usually 2–3 times weekly treatment is acceptable until disease clearance or best partial response. Many patients will inevitably have a high total cumulative UVA dosage and the risks of non-melanoma and melanoma skin cancer are consequently increased for these patients. Efforts should be made to restrict the total PUVA dosage to less than 200 treatment sessions or a total cumulative dose of 1200 J/cm^2. In some circumstances patients may receive a greater total dosage if clinically justified and with the consent of the patient. PUVA remains one of the most effective therapies for patients with early stage disease but there are surprisingly no data to establish if PUVA can improve overall survival. PUVA therapy is rarely tolerated in erythrodermic (stage III) disease but occasional patients will respond repeatedly.

Broad- and narrow-band UVB and high-dose UVA-1 phototherapy have also been used in MF with success [7–9]. There have been no adequate comparative studies of different phototherapy regimens in CTCL.

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Radiotherapy and electron beam therapy

MF and other CTCL variants are very radiosensitive malignancies and individual thick plaques, eroded plaques or tumours can be treated successfully with low-dose superficial orthovoltage radiotherapy often administered in several fractions (e.g. two or three fractions of 400 cGy at 80–120 kV). Large tumours may require a different energy source. Radiotherapy is often used with other therapeutic modalities such as PUVA, and closely adjacent and overlapping fields can often be re-treated because of the low doses used [1].

Whole body TSEB therapy has been evaluated extensively in CTCL [2,3]. Different field arrangements have been used in an attempt to treat the whole skin uniformly to a depth of 1 cm with various total dosage administered and additional radiotherapy to shielded areas. A meta-analysis of open uncontrolled and mostly retrospective studies of TSEB as monotherapy in 952 patients with CTCL has established that responses are stage-dependent, with complete responses of 96% in stage IA, IB and IIA disease but disease relapse rates are very high, indicating that this approach is not curative even in early stage disease [4]. In stage IIB disease, complete responses are less common (36%), but erythrodermic (stage III) disease shows complete responses of 60%. Greater skin surface dose (32–36 Gy) and higher energy (4–6 MeV electrons) are associated with a higher rate of complete response and 5-year relapse-free survivals of 10–23% were noted [4]. A retrospective study of erythrodermic disease has also shown 60% complete responses with 26% progression-free at 5 years [5]. In this study, the overall median survival was 3.4 years with a median dose of 32 Gy given as five weekly fractions over 6–9 weeks. Patients with stage III disease did best compared to those with significant nodal or haematological (IVA–B) disease. The duration of response was also longer for those who received more than 20 Gy using 4–9 MeV [5].

A comparative study of TSEB versus topical mechlorethamine in early stage MF showed similar response rates and duration of response, suggesting that TSEB therapy should be reserved for those who fail first- and second-line therapies [6]. Adverse effects of TSEB include temporary alopecia, telangiectasia and skin malignancies, and the treatment is only available in a limited number of centres [7]. Although TSEB is usually only given once in a lifetime, several reports have documented patients who have received two or three courses, although the total dosage tolerated and duration of response have been lower with subsequent courses [8,9].

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Immunotherapy

Different forms of immunotherapy have been evaluated in CTCL, with the intention of enhancing antitumour host immune responses by promoting the generation of cytotoxic T cells and Th1 cytokine responses. Studies of IFN-α have shown overall response rates of 45–74%, with complete responses of 10–27% [1–3]. Various regimens have been employed (from 3 MU three times weekly to 36 MU/day) and it appears that response rates are higher for larger dosage regimens (overall responses of 78% compared to 37% for the lower dosage regimen) [2]. Overall response rates are also higher in early (IB–IIA 88%) compared to late (III–IV 63%) stages of disease [2].

Other small pilot studies have shown that both IL-12 and IFN-γ can produce clinical responses in CTCL but their therapeutic value remains to be established [4,5]. Ciclosporin has been used in CTCL, particularly in erythrodermic variants, to relieve severe pruritus but there is some evidence that treatment may actually cause rapid disease progression and its use in CTCL is not recommended [6].

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Retinoids

Oral retinoid therapy has been used both as a single agent and in combination with interferons and PUVA in the management of MF (see below). A non-randomized study comparing acitretin and isotretinoin in MF and Sézary syndrome has shown no obvious differences, with complete responses of 21% in both groups [1].

Phase II and III studies of a novel synthetic retinoid in CTCL have recently been published [2,3]. Bexarotene (Targretin) is the only retinoid that selectively binds and activates the RXR receptor. Bexarotene has been shown to promote apoptosis and inhibit cell proliferation. It is relatively selective and therefore should have little effect on the RAR receptor involved in cell differentiation. In phase II and III studies of 152 patients with CTCL, response rates from 20% to 67% have been reported [2,3]. The most effective tolerated oral dosage is 300 mg/m^2/day, although responses improve with higher dosage. Side effects are transient and generally mild but most patients while on therapy require treatment for hyperlipidaemia and central (hypothalamic) hypothyroidism. At a dosage of 300 mg/m^2/day in early stage disease (IA, IB, IIA), response rates of 54% have been noted [2], while advanced MF patients (stage IIB–IVB) have shown response rates of 45% with a notable reduction in pruritus in stage III disease [3].

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Combination therapy

Combined IFN-α and retinoids produce similar response rates to IFN alone and are not recommended [1]. Studies comparing PUVA and IFN-α with IFN-α and acitretin in early stage disease have shown complete response rates of 70% and 38%, respectively, but there are no data on duration of response [2]. Uncontrolled studies of combined PUVA and IFN-α (maximum tolerated dosage 12 MU/m^2 three times weekly) in MF and Sézary syndrome have shown overall responses rates of 100%, with 62% complete response rates [3]. This combination may also be useful in patients with resistant early stage disease such as those with thick plaques and folliculotropic disease. Open studies comparing PUVA with combined PUVA and acitretin have shown a similar complete response rate (73 and 72%, respectively), although the cumulative dose to

best response was lower in patients receiving the combination therapy [4]. Current randomized controlled studies are comparing: (i) PUVA versus PUVA and IFN-α in early stage MF; (ii) the role of maintenance IFN-α after induction of a complete response with PUVA and IFN; and (iii) PUVA alone compared to PUVA combined with bexarotene. At present there are few data on the impact on disease-free and overall survival.

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Systemic chemotherapy

MF and Sézary syndrome are relatively chemoresistant and responses are usually short-lived [1]. This may partly reflect the low proliferative rate of tumour cells and a high prevalence of inactivating *p53* mutations, which produce a relative resistance to tumour cell apoptosis. A systematic review of published data on different regimens has shown complete response rates of 33% in 526 patients treated with single-agent chemotherapy with a median duration of 3–22 months [2]. Combination chemotherapy in 331 patients produced complete response rates of 38%, with a median duration of 5–41 months [2]. CTCL patients are prone to infection and septicaemia is a common preterminal event.

Chemotherapy should not be used in patients with early stage IA, IB or IIA disease. However, treatment of stage IIB and IVA disease remains problematic. Individual tumours and effaced peripheral lymph nodes will respond to superficial radiotherapy and additional chemotherapy should be considered in patients with a good performance status (WHO 0–2). However, responses are likely to be short-lived and patients should be entered into ongoing clinical trials. Single-agent chemotherapy that has been shown to produce a clinical response in stage IIB–IVB disease includes oral chlorambucil (4–6 cycles of 0.15–0.2 mg/kg/day for 2 weeks every 28 days), methotrexate and etoposide, and the intravenous use of the purine analogues 2-deoxycoformycin, 2-chlorodeoxyadenosine and fludarabine [2]. Open studies of 2-deoxycoformycin in MF and Sézary syndrome have reported response rates of 35–71%, with complete response rates of 10–33% [3,4]. Methotrexate has been reported to produce a complete response rate of 41% in 29 patients with erythrodermic (stage III/T4) disease, with a median survival of 8.4 years with single weekly doses of 5–125 mg. However, this study was uncontrolled and it is unclear if the patients included represented an usually good prognostic group [5]. Recently, liposomal doxorubicin and gemcitabine have been used in CTCL [6,7].

Recent pilot studies assessing the use of TSEB and/or total body irradiation (TBI) combined with high-dose conditioning chemotherapy prior to autologous stem cell transplantation in patients with stage IIB–IVA disease have shown good clinical responses [8,9] but high relapse rates and there are no data available at present to indicate if this approach affects disease-free or overall survival. Allogeneic stem cell or bone marrow transplantation has only been used in a few patients with encouraging results [10,11], but the associated mortality suggests that this approach is difficult to justify. However, a graft-versus-lymphoma effect may be therapeutically important and in the future non-myeloablative miniallografts may have a role for selected CTCL patients.

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Photopheresis

Extracorporeal photopheresis (ECP) involves administration of oral psoralen, followed by *ex vivo* collection of an

enriched buffy coat preparation using a cell separator. These leukocytes are then passed through thin polythene tubing with exposure to UVA and the cells thereafter returned to the patient. This regimen is repeated on 2 successive days and the 2-day cycle repeated monthly or fortnightly in an accelerated regimen. A specially designed photopheresis apparatus is required for this technique. The underlying theory is that a proportion of the UVA-exposed leukocytes, including some tumour lymphocytes, undergo apoptosis and that dendritic cells are activated during the *ex vivo* circulation with induction of a host antitumour immune response after the treated cells are returned to the patient. Different models of autoimmune disease support this suggestion [1,2] and recent evidence has also shown activation of dendritic cells during an expanded period of *ex vivo* incubation overnight (transimmunization) [3].

ECP is licensed by the FDA for the treatment of CTCL but there are no randomized studies to clarify whether ECP has any impact on overall survival. The original open study of ECP in 29 patients with erythrodermic CTCL reported a response rate of 73% but response rates in patients with earlier stages of MF were much lower (38%) [4]. Subsequently, a median survival of 62 months was reported in the original cohort of 29 erythrodermic patients, which compares favourably with historical controls (30 months) [5]. A study of 33 patients with Sézary syndrome treated with ECP reported a median survival of 39 months, which was similar to historical controls from the same institution [6]. Other studies have shown more prolonged median survival data [7]. An accelerated regimen consisting of nine collections rather than six for each cycle and an increase to treatment every 2 weeks has shown overall response rates of 50%, with 18% complete responses in erythrodermic disease [8]. A systematic review of response rates in erythrodermic disease (stage III–IVA) with ECP has shown overall responses of 35–71%, with complete responses of 14–26% [9]. Other studies are more difficult to interpret because they have either involved small numbers, patients with earlier stages of disease and in most studies many of the patients have been on other concurrent therapies [10,11]. Preliminary non-randomized studies suggest that the combination of IFN-α and ECP is more effective than ECP alone but this has yet to be confirmed in randomized studies [12,13]. There are isolated case reports of combined ECP and IFN-α that have induced complete clinical and molecular responses [14,15].

Randomized controlled trials of ECP are required to establish an effect on disease-free and overall survival. There have been claims that the CD8 count is critical in predicting whether patients will respond to ECP [5], although others have provided evidence that the total baseline Sézary count is the only predictor of response [16].

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Toxin therapies

Recently, Denileukin Diftitox, a DAB_{389}–IL-2 fusion toxin (Ontak USA/Onzar Europe), has completed phase I–II studies and has received provisional FDA approval for the treatment of resistant or recurrent CTCL. Onzar is a recombinant fusion protein consisting of peptide sequences for the enzymatically active domain (389) of diphtheria toxin and the membrane translocation domain of IL-2 that is capable of inhibiting protein synthesis in tumour cells expressing high levels of the IL-2 receptor resulting in cell death. Phase III studies of 71 heavily pretreated patients with stage IB–IVA, and more than 20% $CD25^+$ lymphocytes, showed an overall response rate of 30%, including 10% with complete responses [1]. Patients

were assessed with a rigorous skin scoring system and documented responses were defined as lasting at least 6 weeks. The median duration of response was 6.9 months (range 2.7–46.1 months). The optimally tolerated intravenous regimen is 18 μg/kg/day for 5 days, repeated every 21 days for 4–8 cycles. Adverse effects include fever, chills, myalgia, nausea and vomiting, and a mild increase in transaminase levels. Acute hypersensitivity reactions occurred in 60%, invariably within 24 h and during the initial infusion. A vascular leak syndrome characterized by hypotension, hypoalbuminaemia and oedema was defined retrospectively within the first 14 days of a given dose in 25% of patients. Myelosuppression is rare. Five per cent of adverse effects are severe or life-threatening. The clinical relevance of antibody responses to Denileukin Diftitox is unclear. The duration of clinical response has not yet been established and current studies are comparing different regimens of Onzar and are also assessing the use of this therapy in $CD25^-$ tumours. This therapy is not likely to be appropriate for early stage disease but may be useful in advanced disease.

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Monoclonal antibody therapy

A humanized chimeric anti-CD4 monoclonal antibody has been used to treat eight patients with CTCL of whom seven showed a clinical response but this was of short duration [1]. A radiolabelled anti-CD5 antibody has also been used in MF with some objective results [2] and CAMPATH (anti-CD52/alemtuzumab) has also been administered to CTCL patients (stage III) with demonstrable but short-lived clinical responses [3].

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CD30+ cutaneous lymphoproliferative disorders

In the skin, $CD30^+$ lymphoproliferative disorders are invariably of T-cell origin although nodal $CD30^+$ lymphomas can be derived from B, T or null cells. By definition, primary cutaneous $CD30^+$ disorders do not have any systemic or nodal involvement [1–3]. CD30 positivity was originally identified on Reed–Sternberg cells in Hodgkin's disease, but has since been found on a proportion of activated T and B lymphocytes. In general, cutaneous lymphomas that are $CD30^+$ *ab initio* are associated with a good prognosis, in contrast to $CD30^+$ lymphomas in other anatomical sites such as the lymph nodes where CD30 positivity is more commonly associated with a poor prognosis. In the skin, the situation in which tumour cells acquire CD30 expression, during the course of disease, is associated with a poor prognosis [4].

Molecular studies show the presence of the Epstein–Barr genome in a proportion of $CD30^+$ infiltrates in Hodgkin's disease, but this has not to date been found in patients with lymphomatoid papulosis [5]. Recent work indicates that CD30 is a cell-surface receptor for tumour necrosis factor-α and -α-like cytokines [6], and it has been demonstrated that CD30 expression can be up-regulated by EBV.

Specific disease entities described in this section include:

- Lymphomatoid papulosis
- Primary cutaneous $CD30^+$ (anaplastic) large T-cell lymphoma
- CD30 large T-cell lymphoma with regional nodal involvement
- Regressing atypical histiocytosis
- Secondary cutaneous $CD30^+$ large T-cell lymphoma.

However, it should be remembered that there is overlap between these conditions and that one may transform into another during disease progression.

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Lymphomatoid papulosis

Definition. This term was first used in 1968 by Macaulay to describe a 'self-healing rhythmical paradoxical papular eruption, histologically malignant but clinically benign' [1–6].

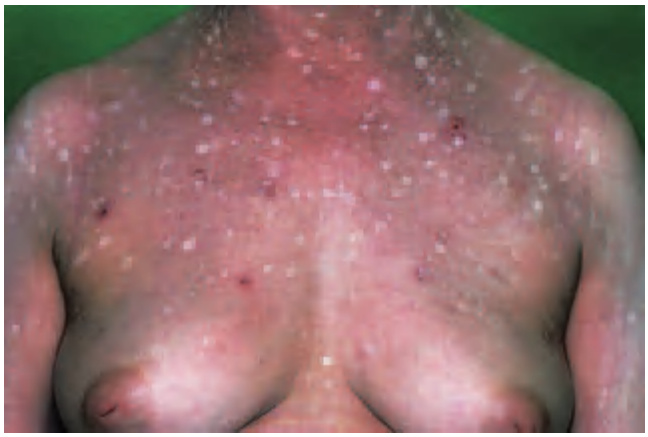

Fig. 54.15 Lymphomatoid papulosis. Note multiple scars on the upper chest area of this patient, with a small number of fresh papular lesions.

Clinical features. Affected patients have recurrent crops of papular lesions predominantly affecting the trunk, although any body site can be involved and regional localized patterns may occur (Fig. 54.15) [7]. These lesions grow rapidly over a few days and develop ulcerated necrotic centres. Healing occurs slowly, with fine atrophic circular or varioliform scars, but the cycle recurs every few months, with no obvious initiating factor. The lesions generally occur first in adult life and may recur in crops for up to 40 years. Over time, every individual skin lesion will resolve and there may eventually be a persistent remission. A small number of cases have been reported in children [8,9].

The original description of lymphomatoid papulosis suggested a benign and non-progressive chronic pattern of the disease, but there are well-documented cases both of patients with lymphomatoid papulosis developing $CD30^+$ large cell anaplastic T-cell lymphoma or MF, and of patients with pre-existing MF developing lesions indistinguishable from those of lymphomatoid papulosis [10,11]. A follicular variant of the condition has also been described [12]. A proportion of patients also go on to develop Hodgkin's disease, or develop lymphomatoid papulosis-like lesions in the course of established Hodgkin's disease [13–15].

Pathology. The histological features of the papules are a relative lack of epidermotropism and Pautrier abscesses, but the presence in the dermis of a mixed infiltrate composed of atypical lymphocytes with large nuclei and frequent abnormal mitoses, eosinophils, neutrophils, free red cells and large histiocytic cells [16]. Some of these cells may show gross cytological atypia (Fig. 54.16). The epidermis may be ulcerated and the infiltrate may extend deeply into the reticular dermis. True vasculitis is rarely seen.

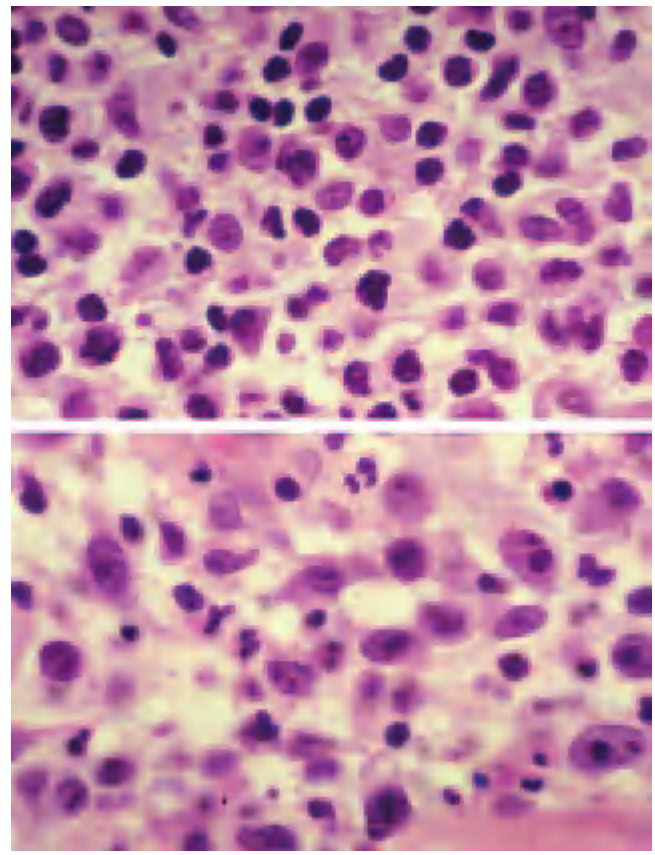

Fig. 54.16 Composite high-power view of atypical cerebriform cells in type B lymphomatoid papulosis (top) and large 'Reed–Sternberg-like' ($CD30^+$) cells in type A histology (bottom).

Lymphomatoid papulosis can be divided on histological grounds into types A, B and C subgroups [17]. In the A subgroup there appears to be a predominance of large, strikingly atypical $CD30^+$ cells similar to those seen in Hodgkin's disease [18]. In the B subgroup, smaller atypical T lymphocytes with convoluted nuclei similar to those seen in MF predominate. Group C lesions have large clusters of $CD30^+$ cells and an overall pattern suggestive of an anaplastic $CD30^+$ large cell lymphoma. Many cases, however, have all types of lesions coexisting simultaneously or a mixed pattern of A and B. Some patients with clinical lesions resembling pityriasis lichenoides acuta (PLEVA) show a lymphomatoid histology and this probably represents a form of lymphomatoid papulosis (type B) [19,20].

Clonal TCR gene rearrangements can be identified and are identical in different lesions from the same patient, but some biopsies may not show a clonal pattern either because of an inability to detect a small clonal T-cell population as a result of a lack of sensitivity, or because of a non-T-cell lineage in type A lesions [4,21]. Identical T-cell clones can be detected in patients with both MF and lymphomatoid papulosis [21].

Treatment. There is no current treatment that alters the natural history of the disease but some therapies appear to accelerate healing and may reduce or prevent the frequency and severity of new crops of lesions for a short time. There is absolutely no evidence that intensive combination chemotherapy alters beneficially the course of lymphomatoid papulosis, and indeed there are individual case reports suggesting that high-dose intensive chemotherapy may cause transition to a more virulent CD30+ lymphoproliferative disorder. Topical or intralesional steroids and topical nitrogen mustard applied to developing lesions may accelerate clearance, but have little effect on well-developed lesions. Narrow-band UVB therapy and PUVA both appear to benefit individual patients for short periods of time. Low-dose oral methotrexate appears to be the most useful systemic therapy, and there are reports of a beneficial effect with oral dapsone [22,23].

Long-term follow-up is necessary in all cases because of the risk of progression to a more aggressive lymphoma such as CD30+ anaplastic large T-cell cutaneous lymphoma, MF or Hodgkin's disease in less than 5% of cases. The prognosis in patients with both MF and lymphomatoid papulosis appears to be excellent [10]. There appear to be no currently available clinical or pathological prognostic markers to indicate whether such progression is likely.

An excellent recent review of 118 patients with lymphomatoid papulosis followed for many years suggests that approximately 4% will develop extracutaneous disease within 10 years [24].

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Primary cutaneous (anaplastic) CD30+ large cell lymphoma

Definition. A rare anaplastic large T-cell CD30+ lymphoma originating in and confined to the skin.

Clinical features. These lymphomas are usually seen in adults and present as large solitary or multiple and often ulcerated nodules, most often on the trunk (Fig. 54.17) [1]. There are no patches or plaques of MF elsewhere, and some individual lesions may regress spontaneously, although new lesions will also develop. Some individuals develop disease localized to a limb. Progression to extracutaneous sites is rare but has been recorded in approximately 10% [1,2]. Careful staging consisting of bone marrow and CT scans are required. Disease-related 5-year survival rates of 90% have been reported [1].

Pathology. Biopsy shows a dense lymphocytic infiltrate of large atypical cells with an anaplastic morphology and mitoses, but usually no epidermotropism as seen in MF (Figs 54.18 & 54.19). The tumour cells variably express T-cell antigens and the vast majority will be CD30+. Some tumour cells show a very lymphomatoid-like morphology, while others are more anaplastic [3–5]. Clonal TCR gene rearrangements are detected in almost all cases consistent with a T-cell origin.

Treatment. Both excision and localized radiotherapy are acceptable methods of treating isolated lesions. The recurrence rate on the treated site is very low, but new lesions may develop over time elsewhere on the skin. Spontaneous clearance of even quite large lesions is recorded, and

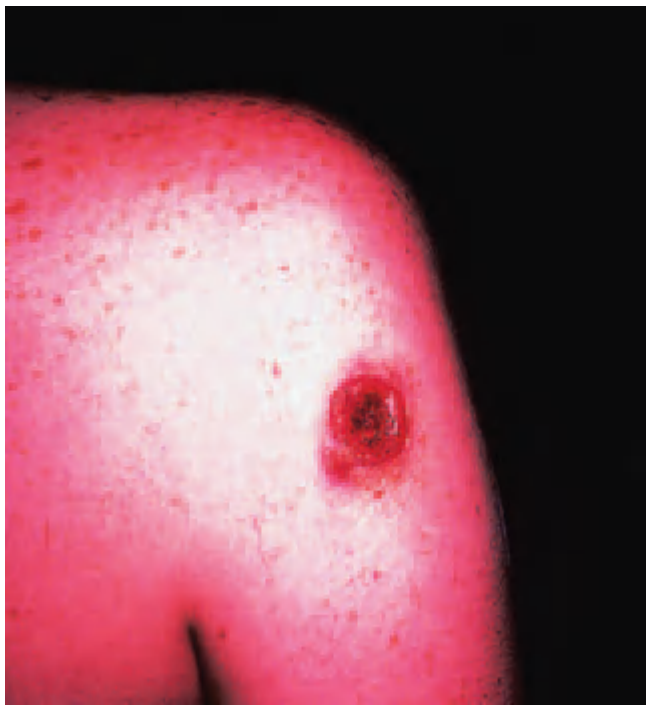

Fig. 54.17 CD30$^+$ cutaneous lymphoma showing typical ulcerated lesion on shoulder.

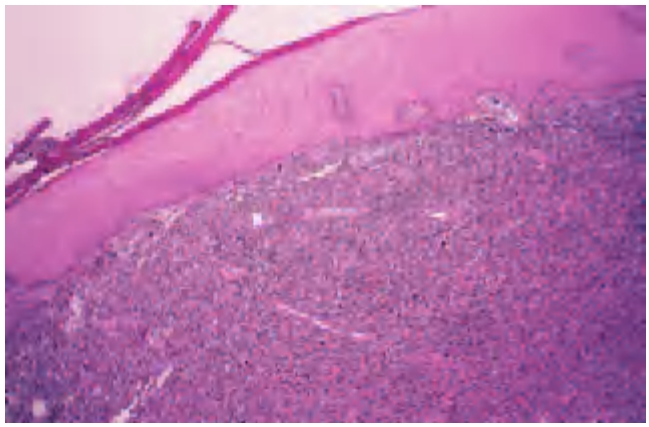

Fig. 54.18 Low-power view of CD30$^+$ infiltrate showing lack of epidermotropism but dense infiltrate in the underlying dermis.

therefore a short period of observation after the diagnosis is made is also acceptable [6]. Systemic chemotherapy including CHOP may be effective but cutaneous recurrence is likely, and chemotherapy is therefore not the treatment of choice for disease confined to the skin. Low-dose methotrexate may also be effective.

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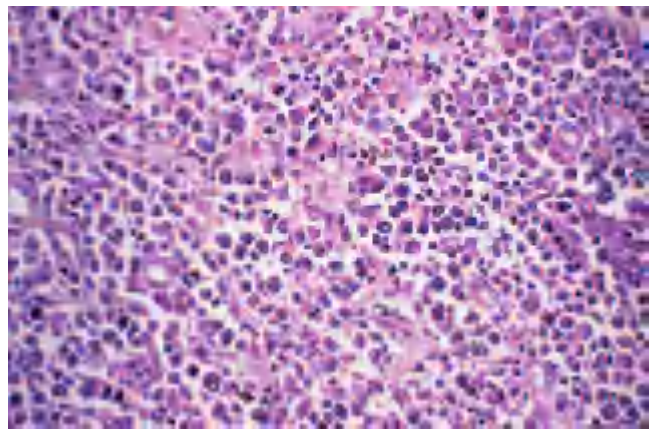

Fig. 54.19 CD30$^+$ lymphocytic infiltrate showing striking large atypical cells.

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CD30$^+$ large cell cutaneous lymphoma with regional nodal involvement

Clinical features. This is a relatively rare variant described by the Dutch Lymphoma Group, who identified 11 cases with either solitary or multiple ulcerated cutaneous tumours, involving one anatomical site and associated with palpable and pathologically involved regional lymph nodes, but no evidence of lymphoma beyond the regional nodal basin [1]. The limited evidence to date on treatment and prognosis suggests that this lymphoma is similar if not identical to primary cutaneous CD30$^+$ large cell lymphoma, with a 5-year survival of over 90%.

Pathology. This is identical to that found in primary cutaneous CD30$^+$ anaplastic large cell lymphoma.

Treatment. If a patient has biopsy proven CD30$^+$ large cell lymphoma in both skin and local nodes, full staging including CT scan and bone marrow aspirate should be carried out. If these investigations show no spread beyond the local draining nodes, then local radiotherapy to the skin lesions is a useful first-line treatment. Low-dose methotrexate may also be helpful. Use of either of these modalities may coincide with resolution of the draining

nodes. It is suggested that treatment should be based on the extent and severity of the cutaneous lesions, as patients treated with chemotherapy including CHOP show good initial clearance of lesions but relatively rapid cutaneous relapse.

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Regressing CD30$^+$ large cell cutaneous lymphoma (regressing atypical histiocytosis)

Definition. A rare primary cutaneous CD30$^+$ T-cell lymphoma associated with nodulo-ulcerative lesions of the skin. This entity was first described in 1982 by Flynn *et al*. [1] who considered it to be 'a cutaneous proliferation of atypical neoplastic histiocytes with unexpectedly indolent biologic behaviour'. However, it has now been identified as being of T-cell derivation rather than histiocytic [2].

Clinical features. The clinical features are of large, rapidly developing, ulcerative nodules, often on the thighs and buttocks (see Fig. 54.15). The lesions may be solitary or multiple and the patient is not generally unwell. If untreated, a proportion of these lesions will heal spontaneously. There is thus a striking clinical and pathological similarity to lymphomatoid papulosis [3], although individual lesions are larger, and this entity almost certainly represents a variant of primary cutaneous CD30$^+$ anaplastic large T-cell lymphoma.

Pathology. The pathology is that of a confluent dermal infiltrate that is not angiocentric and has overlying epidermal ulceration in virtually all cases. Large and strikingly atypical mononuclear cells are present with associated inflammatory cells including eosinophils and neutrophils. Focal tumour cell necrosis and perilesional fibrosis are both common. T-cell antigen expression is variable but the tumour cells are CD30$^+$. A recent report has detected the presence of clonal rearrangements of the TCR gene, confirming the T-cell origin [4].

Treatment. As the majority of these lesions regress spontaneously, treatment should be expectant and conservative. Low-dose radiotherapy may accelerate shrinkage of lesions. Methotrexate may be effective.

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Secondary cutaneous CD30$^+$ anaplastic large cell lymphoma

Definition. A systemic CD30$^+$ anaplastic large T-cell proliferation in which there is secondary cutaneous involvement. These rare patients generally have a known CD30$^+$ anaplastic large cell lymphoma (ALCL) involving multiple lymph node basins, liver, spleen and other organs. In the course of their disease they may also develop cutaneous papules, nodules and ulcerated lesions.

Clinical features. Patients with CD30$^+$ systemic ALCL are usually systemically unwell with weight loss and other symptoms. Cutaneous lesions may develop at a relatively late stage in disease progression. Crops of large painful ulcerated lesions may develop rapidly, and there is usually palpable lymphadenopathy and hepatosplenomegaly.

Pathology. The histology is usually indistinguishable from primary cutaneous CD30$^+$ ALCL.

Treatment. These patients have a poor outlook. A small series of 11 patients reported by the Dutch Lymphoma Group reported a temporary complete remission in two of seven patients given systemic chemotherapy, but subsequently six patients died within 13 months. Combined chemotherapy and radiotherapy are appropriate [1].

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Secondary cutaneous lymphomas

Subcutaneous panniculitis-like T-cell lymphoma

Definition. This is a rare cytotoxic lymphoma, representing less than 1% of all non-Hodgkin's lymphomas, which usually affects younger adults with an equal sex incidence [1].

Clinical features. Patients present with indolent, slowly expanding, subcutaneous nodules usually involving the limbs, which may initially be misdiagnosed as panniculitis (Fig. 54.20) [2–5]. Occasional cases present with more diffuse erythematous induration mimicking a cellulitis, and necrotic lesions can develop. Lymphadenopathy is usually absent at presentation. Systemic symptoms may occur, particularly in those patients who develop a haemophagocytic syndrome consisting of fever, pancytopenia and hepatosplenomegaly [3,6]. The prognosis is

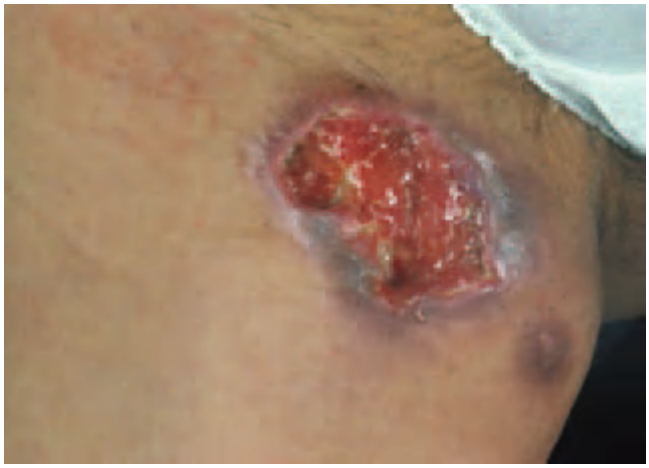

Fig. 54.20 Subcutaneous panniculitis-like T-cell lymphoma: indurated and eroded deep plaque on the thigh.

poor, although there is often a prolonged indolent phase before the diagnosis is established [7].

Pathology. There is a diffuse infiltrate extending throughout the subcutis without epidermotropism [3,7,8]. The degree of cellular atypia can be minimal but large hyperchromatic cells are usually present (Fig. 54.21). Rimming of the tumour cells around fat cells is a useful diagnostic feature. A prominent reactive histiocytic infiltrate is common and the tumour cells may show vascular invasion with angiocentricity. In patients with the haemophagocytic syndrome, erythro- and lymphophagocytosis may be present. Indolent cases were previously diagnosed as benign cytophagic histiocytosis (Weber–Christian disease) [9,10].

Immunophenotype. Tumour cells have a mature T-cell phenotype and are usually $CD8^+$ [8,11]. They express cytotoxic molecules including granzyme B, perforin and TIA-I. Clonal rearrangements of the TCR genes are present and most express an αβ TCR. However, in 25% of cases, tumour cells express a γδ TCR and are $CD4^-$, $CD8^-$ and $CD56^+$, with a possible worse prognosis [8,11,12].

Pathogenesis. There is no evidence for an association with EBV, and the underlying molecular pathogenesis remains to be established.

Treatment. Superficial radiotherapy and combination chemotherapy can be associated with successful clinical responses and resolution of haemophagocytic syndrome, although these remissions are usually short-lived and the overall prognosis is poor.

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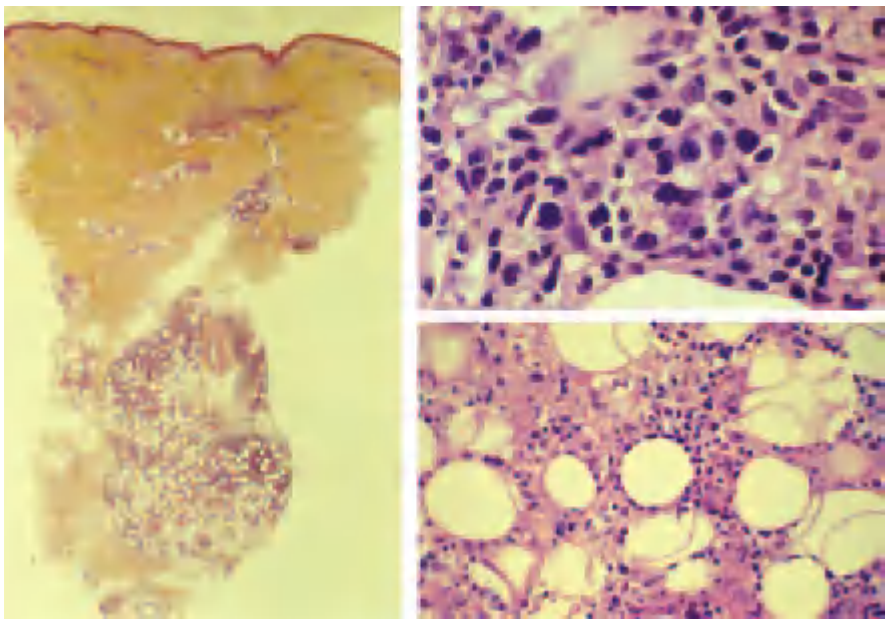

Fig. 54.21 Low-power view of subcutaneous infiltrate with high-power view showing rimming of fat cells by atypical mononuclear cells and medium/large pleomorphic tumour cells seen in subcutaneous panniculitis-like T-cell lymphoma.

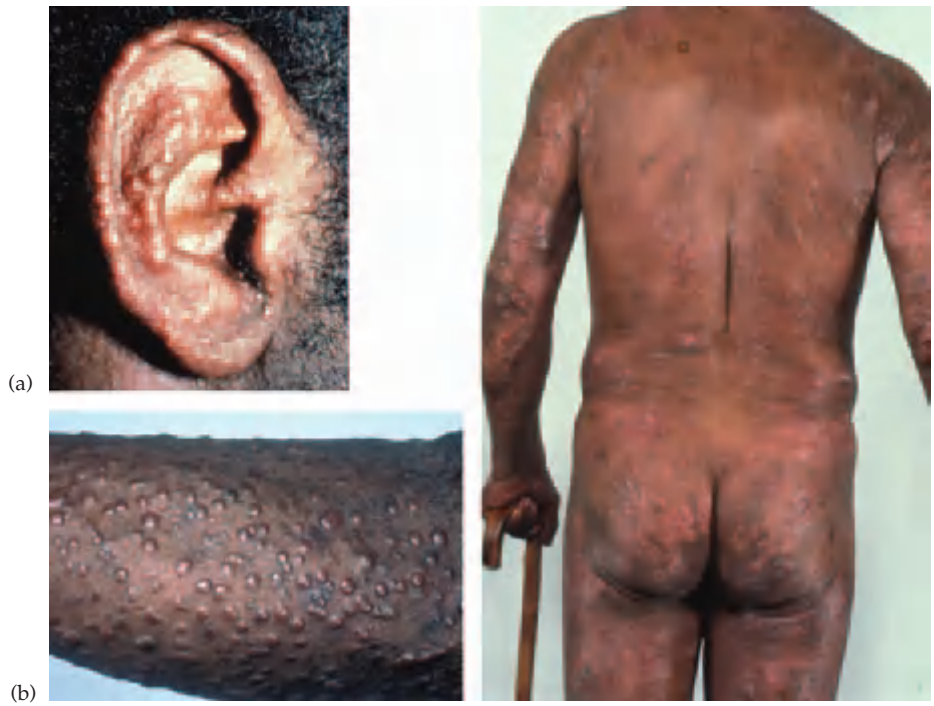

Fig. 54.22 Three clinical presentations of cutaneous adult T-cell leukaemia–lymphoma, namely (a) a pruritic papular eruption confined to the auricle, (b) an extensive nodular eruption on the forearm, and (c) superficial patches and plaques involving the limb girdle area similar to mycosis fungoides.

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Adult T-cell leukaemia–lymphoma (HTLV-1-associated)

Definition. ATLL is a pleomorphic peripheral T-cell leukaemia–lymphoma caused by the human retrovirus HTLV-1. HTLV-1 infection is prevalent in certain parts of the world, including Japan, central Africa, the Caribbean and south-eastern states of the USA, and consequently ATLL is endemic in these regions. Sporadic cases are found throughout the world. The disease has a long latency and the incidence of ATLL among HTLV-1 carriers has been estimated to be 2.5% [1]. The virus can be transmitted in breast milk and in blood products. There is a slight male predominance and the median age of onset is 55 years [1].

Clinical features. Patients with ATLL often have extensive lymph node and peripheral blood involvement but the skin is the most common extranodal site of disease and primary cutaneous disease can occur [2]. Other extranodal sites of disease include bone, lung, liver, gastrointestinal tract and CNS. Cutaneous involvement is characterized by widespread or solitary papules, nodules, tumours or erythroderma often associated with intense pruritus (Fig. 54.22) [3,4]. Patients may present with patches and plaques that are clinically indistinguishable from MF [5]. Several clinical variants have been defined [6]: an acute variant is characterized by a leukaemic phase with generalized lymphadenopathy and hepatosplenomegaly often associated with cutaneous involvement and hypercalcaemia with lytic bone lesions. Opportunistic infections are common because of a relative T-cell immunodeficiency. A lymphomatous variant is similar but with the absence of peripheral blood involvement. A chronic variant is typically characterized by cutaneous disease and a peripheral blood lymphocytosis without hypercalcaemia. The smouldering variant is also characterized by prominent cutaneous disease without overt peripheral blood involvement. Pulmonary lesions may occur. Progression from the chronic and smouldering variants to acute disease occurs in at least 25% of cases but often only after a long duration [5]. HTLV-1 serology is invariably positive [6].

Pathology. In the skin, a prominent epidermotropic infiltrate consisting of medium to large cells with a pleomorphic nuclear morphology is usually found, particularly in the acute and lymphomatous variants (Fig. 54.23) [4–6]. Blast-like cells may be present. Pautrier-like microabscesses and a cerebriform nuclear morphology can be

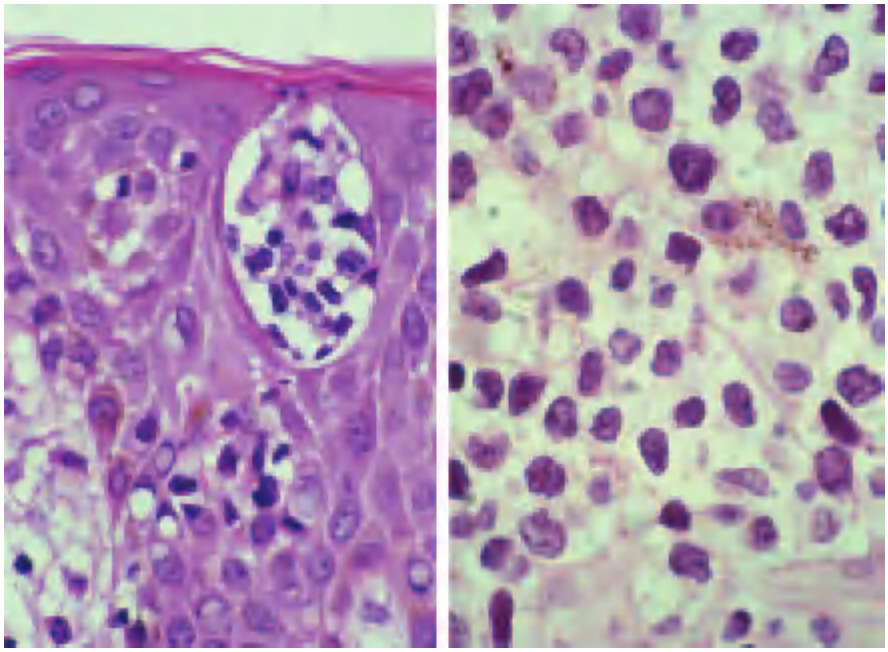

Fig. 54.23 Adult T-cell leukaemia–lymphoma: prominent atypical cells forming a Pautrier micro-abscess and large pleomorphic cells within the dermis.

seen simulating MF. However, the degree of cellular atypia may also be mild, causing diagnostic difficulties. Eosinophilia is often present. Granulomatous features have been rarely described [5]. In the peripheral blood, the tumour cells are polylobulated ('flower cells'). Lymph nodes usually show a leukaemic pattern of infiltration, with preservation and dilation of lymph node sinuses containing tumour cells. Rarely, Hodgkin-like features are present within an expanded lymph node paracortex containing a diffuse infiltrate of small, mildly atypical lymphocytes and scattered $CD30^+$, $CD15^+$ Reed–Sternberg-like EBV-positive cells resulting from expansion of EBV-positive cells as a consequence of a relative T-cell immunodeficiency [7].

Immunophenotype. Tumour cells are $CD2^+$, $CD3^+$, $CD5^+$ and $CD7^-$. Most cells are $CD4^+$, although $CD8^+$ and $CD4^-$, $CD8^-$ variants also occur [8]. CD25 expression is almost universal. Large blast-like cells can be $CD30^+$ but are ALK^-. Cytotoxic proteins are not expressed. Analysis of TCR genes shows clonal gene rearrangement.

Pathogenesis. HTLV-1 is the underlying cause of ATLL. The virus is randomly integrated into the host genome following expression of viral reverse transcriptase, and the viral tax protein is a potent transactivation factor that induces expression of numerous host genes. Additional molecular abnormalities produce a malignant phenotype. The HTLV-1 provirus is clonally integrated, confirming a pathogenetic role for the virus in individual cases [8].

Treatment. Cutaneous disease can respond to skin-directed therapy but patients with the acute and lymphomatous variants have a poor prognosis (less than 10% 5-year survival) and require combination chemotherapy. In contrast, patients with the chronic (30% 5-year survival) and smouldering (65% 5-year survival) variants can have a prolonged course although disease transformation eventually occurs for most patients [6].

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Blastic NK-cell lymphoma

Definition. This is a rare lymphoma, which is derived from NK cells and shows a predilection for extranodal sites and particularly the skin [1]. There is no racial pre-

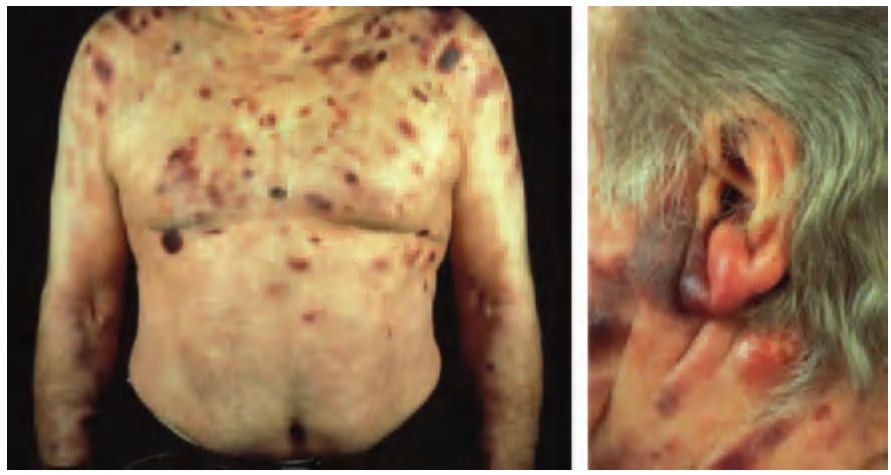

Fig. 54.24 Typical clinical presentations of blastic lymphoma in the skin with large mauvish and pigmented dermal plaques involving the head/neck and trunk.

disposition. Elderly patients are mostly affected and the prognosis is poor.

Clinical features. Patients usually present with multiple and rarely solitary large dusky mauve dermal tumours, which can become ulcerated (Fig. 54.24). There is no specific site predilection. Primary cutaneous disease is common but lymphadenopathy and systemic dissemination is likely during the course of disease [2–5].

Pathology. A dense monomorphic infiltrate of medium-sized tumour cells with a fine chromatin resembling lymphoblasts is seen throughout the dermis with a well-defined grenz zone (Fig. 54.25) [4,5]. Occasionally, tumour cells show a rosette pattern. Necrosis and angiocentricity are usually absent.

Immunophenotype. Tumour cells are $CD56^+$ with variable expression of CD4, and CD43 but do not express surface CD3. CD2, CD7 and cytoplasmic CD3ε are usually negative [3–5]. Cytotoxic proteins may be rarely expressed. Rare cases are $CD34^+$ and TdT^+ and, because of a morphological resemblance to myeloblastic and precursor T-lymphoblastic leukaemia which also express CD56, it is important to confirm that the tumour cells are negative for surface CD3 and myeloperoxidase. TCR gene analysis reveals a germline pattern for all TCR genes consistent with an NK-cell origin [4–6]. Markers of myelomonocytic lineage are usually negative but, intriguingly, a recent study suggests that these tumours may actually be derived from very rare peripheral blood $CD68^+$, $CD123^+$ plasmacytoid monocytes rather than NK cells [7].

Pathogenesis. EBV has not been detected in tumour cells and no disease-specific cytogenetic abnormality has been detected [5,6].

Treatment. Combination chemotherapy and radiotherapy can produce a partial remission, which is invariably short-lived, and the prognosis is very poor. Patients with localized cutaneous disease may have a better prognosis.

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Extranodal NK/NK-like T-cell lymphoma (nasal type)

Definition. This rare type of extranodal EBV-positive angiocentric lymphoma preferentially involves the nasal cavity and nasopharynx but also shows a predilection for the skin and used to be referred to as polymorphic reticuloses or angiocentric immunoproliferative lesion [1–4]. The disease is more prevalent in Asia and Central and South America. Most cases are derived from NK cells but rare cases have a cytotoxic T-cell phenotype.

Clinical features. Involvement of the nasal cavity, nasopharynx, paranasal sinuses, orbit and oropharynx is associated with tissue destruction ('lethal midline granuloma'). Secondary involvement of other extranodal sites

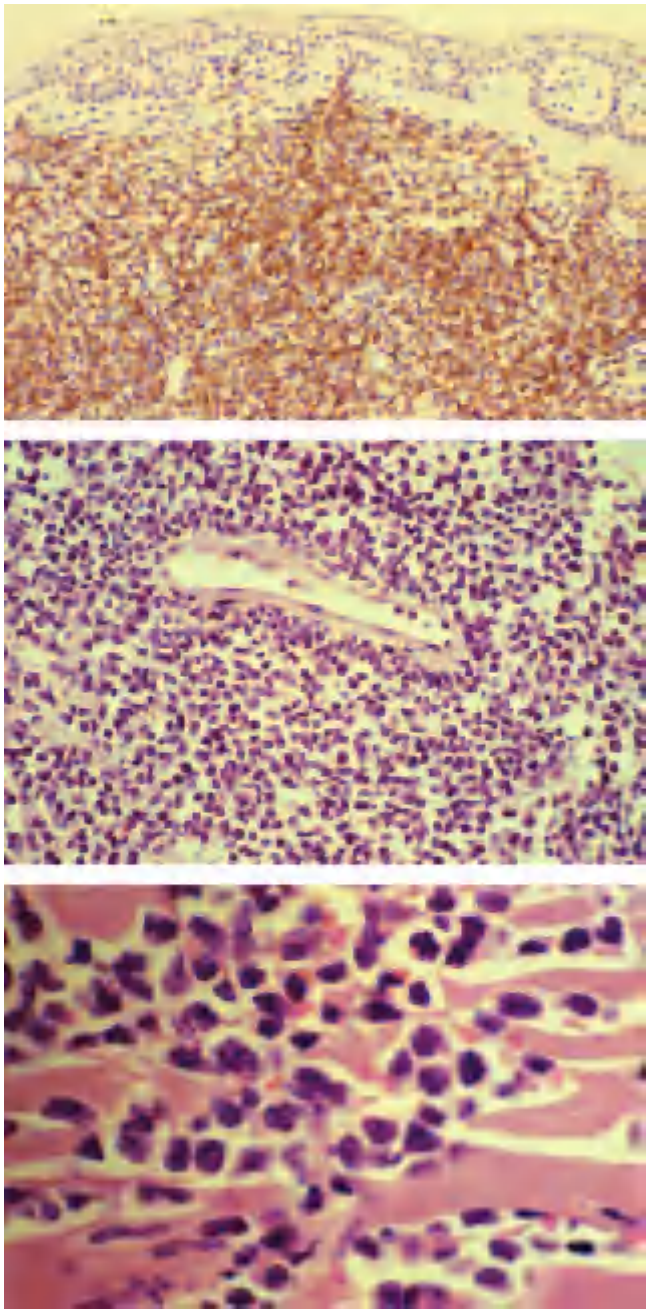

Fig. 54.25 Blastic NK-like lymphoma in the skin: CD56 positivity; rosetting of blood vessels; large atypical mononuclear cells.

including the skin and gastrointestinal tract occurs but primary cutaneous disease is rare. Cutaneous nodules and tumours may ulcerate and become necrotic. Purpura, bullous lesions and diffuse maculopapular rashes have been described [5–8]. A haemophagocytic syndrome can develop rarely and systemic symptoms are common. Bone marrow and peripheral blood involvement is rare but such cases can be indistinguishable from aggresive NK-cell leukaemia–lymphoma.

Pathology. There is a diffuse infiltrate that is angiocentric and angiodestructive [1–4,6]. Extensive necrosis is common. Tumour cells can show a variable morphology with small, medium and large anaplastic cells described. An associated heavy mixed inflammatory infiltrate is common and pseudoepitheliomatous hyperplasia may be found, which can lead to diagnostic confusion.

Immunophenotype. Tumour cells are $CD56^+$, $CD2^+$, surface $CD3^-$, cytoplasmic $CD3\varepsilon^+$. Most cases express cytotoxic proteins, namely granzyme B, perforin and TIA-I [1–4,6]. Rare cases are $CD30^+$ and this may confer a more favourable prognosis [6]. TCR genes are in a germline configuration consistent with an NK-cell origin. However, rare cases of extranodal NK/T-cell lymphomas have a $CD56^-$, $CD3\varepsilon^+$ cytotoxic phenotype and show a clonal TCR gene rearrangement consistent with a cytotoxic T cell [4,7].

Pathogenesis. EBV is present in almost all cases of extranodal NK/T-cell lymphoma, whether $CD56^+$ or $CD56^-$ [3]. EBV is present in clonal episomal form, suggesting that the virus has a critical pathogenetic role. No disease-specific cytogenetic abnormality has been identified but deletions of 6q and isochromosome 6q are common [9].

Treatment. The prognosis is poor despite aggressive chemotherapy, particularly for those patients with disease outside the nasal cavity [4]. The multidrug resistance phenotype is often expressed in cutaneous cases and the median survival for patients presenting with cutaneous disease is 15 months [6].

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Primary cutaneous B-cell lymphomas

Primary cutaneous B-cell lymphomas constitute approximately one-quarter of all primary cutaneous lymphomas [1]. There is still controversy about the precise classification of cutaneous B-cell lymphomas, illustrated by the differences between the EORTC classification which is an organ-specific system, and the recent WHO classification which only recognizes that primary cutaneous follicular lymphomas may occur rarely [2,3]. Full staging investigations are essential for all patients with a cutaneous B-cell lymphoma because most primary cutaneous B-cell lymphomas are indolent with an excellent long-term prognosis [4]. Other types of systemic B-cell non-Hodgkin's lymphomas such as small cell lymphocytic lymphoma and mantle cell lymphomas are only found within skin as secondary cutaneous involvement associated with underlying nodal disease [5–7], although very rarely mantle cell lymphomas can be restricted to skin [7,8].

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Follicle centre cell lymphoma

SYN. CROSTI'S LYMPHOMA

Definition. An indolent primary cutaneous B-cell lymphoma derived from follicle centre cells (PCFCCL) consisting of a mixture of centrocytes and centroblasts.

Clinical features. Patients present with clinically non-specific solitary or grouped papules, nodules or tumours, most commonly on the head and neck or trunk [1–3], although any body site may be involved (Figs 54.26–54.28). A gradual increase in size of pre-existing lesions and the appearance of new nodules over a period of years is likely without treatment [1–3]. Staging investigations including CT scans of the chest, abdomen and pelvis, and bone marrow aspirate and trephine biopsies are negative

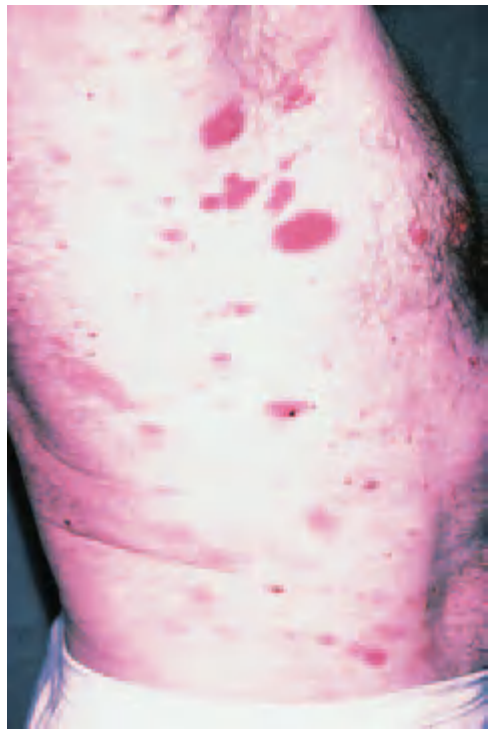

Fig. 54.26 Primary cutaneous follicle centre cell lymphoma. Extensive erythematous plaque and nodular lesions on the lower back.

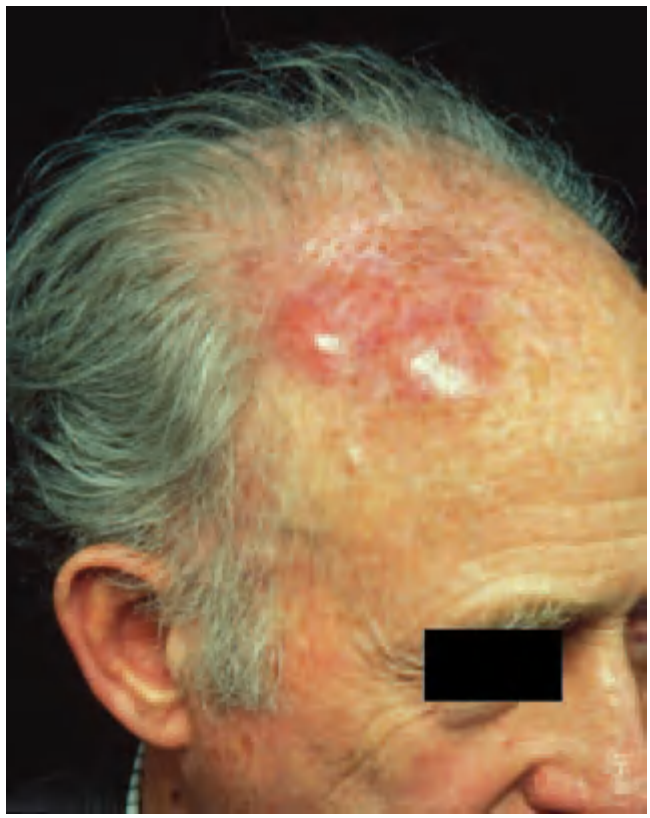

Fig. 54.27 Typical clinical presentation of primary cutaneous follicle centre cell lymphoma on the scalp.

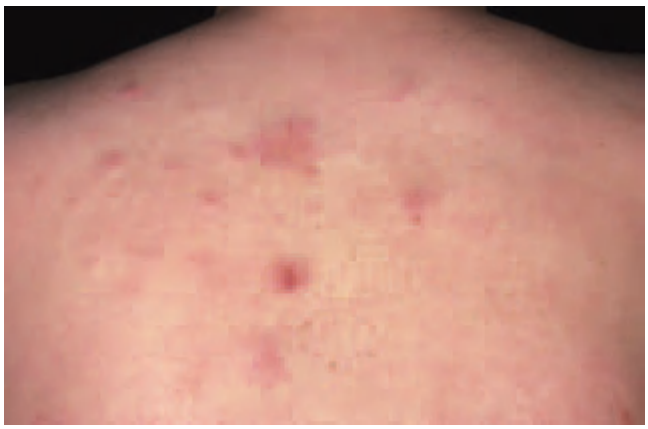

Fig. 54.28 Primary cutaneous follicle centre cell lymphoma. Cutaneous presentation of a systemic follicular t(14;18) lymphoma on the trunk with subtle dermal papules and plaques.

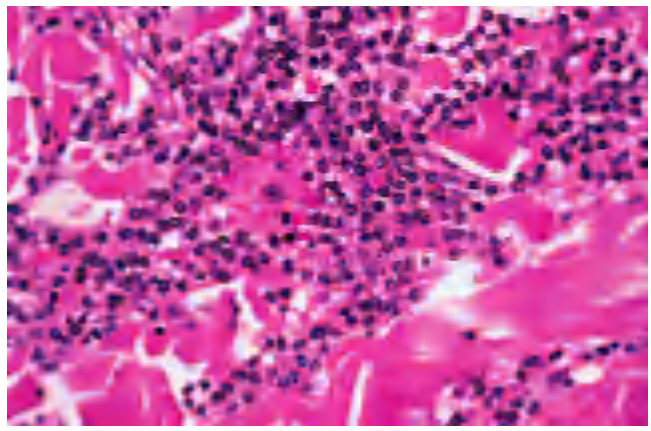

Fig. 54.29 Primary cutaneous follicle centre cell lymphoma, pathology. B-cell lymphoma. H&E section showing characteristic lymphoid infiltrate.

at the time of diagnosis. The estimated 5-year survival of PCFCCL is 94–97% [3].

Pathology. The histology of PCFCCL is variable but the infiltrate shows no epidermotropism and there is a clear grenz zone in the papillary dermis. In the reticular dermis and subcutaneous fat, there is a 'bottom-heavy' lymphocytic infiltrate composed of a mixture of centrocytes, centroblasts and a prominent infiltrate of reactive T cells with the remnants of poorly formed germinal centres [1–3]. This pathology has to be distinguished from marginal zone lymphomas with follicular colonization of reactive germinal centres. Prominent larger tumours tend to show a diffuse infiltrate of larger centrocytes, centroblasts and immunoblasts with fewer reactive T cells and no evidence of follicular structures [3]. Individual patients may show both histological patterns in biopsies from the same group of lesions. A subset of PCFCCL shows neoplastic follicular structures with an expansile growth pattern, a thin poorly formed mantle zone and an absence of tingible body (starry sky) macrophages similar to nodal follicular lymphoma although the phenotypic and molecular features are distinct [4]. In the WHO classification, the diffuse pattern of PCFCCL would be classified as a diffuse large B-cell lymphoma (DLBCL; Figs 54.29–54.31).

Immunophenotype. The tumour cells express B-cell-associated markers such as CD19, CD20, CD22 and CD79a but are $CD5^-$ [3,5,6]. CD10 and both cytoplasmic and surface immunoglobulin is variably expressed by the neoplastic cells [7]. Follicular structures can be more clearly defined by identifying networks of $CD21^+$ and $CD23^+$ follicular dendritic cells. The tumour cells are also mostly Bcl-2 negative, in contrast to systemic follicular lymphoma and DLBCL in which a significant proportion of the tumour cells are $CD10^+$ and Bcl-2 positive [5]. In contrast, Bcl-6 is usually expressed by tumour cells with

Fig. 54.30 Primary cutaneous follicle centre cell lymphoma, pathology. B-cell lymphoma stained with L26 (B-cell marker) showing striking positive staining.

evidence of somatic mutation as also seen in follicular lymphoma and DLBCL consistent with lymphomas derived from germinal centre cells [8]. Clonal immunoglobulin gene rearrangements are present in most cases. False-negative cases are common, caused by somatic hypermutation affecting the primer binding for PCR immunoglobulin gene analysis [9]. Extensive somatic mutation of variable region genes has been identified, which is also consistent with an origin from germinal centre cells [10,11].

Pathogenesis. The relationship between PCFCCL and both systemic follicular lymphoma and DLBCL remains unclear. While there are morphological similarities, PCFCCL follows an indolent clinical course, the immunophenotypic features (CD10 and Bcl-2 often negative) are usually distinct and the t(14;18), which is characteristic of systemic follicular lymphoma and a significant proportion of DLBCLs, has not been consistently detected in

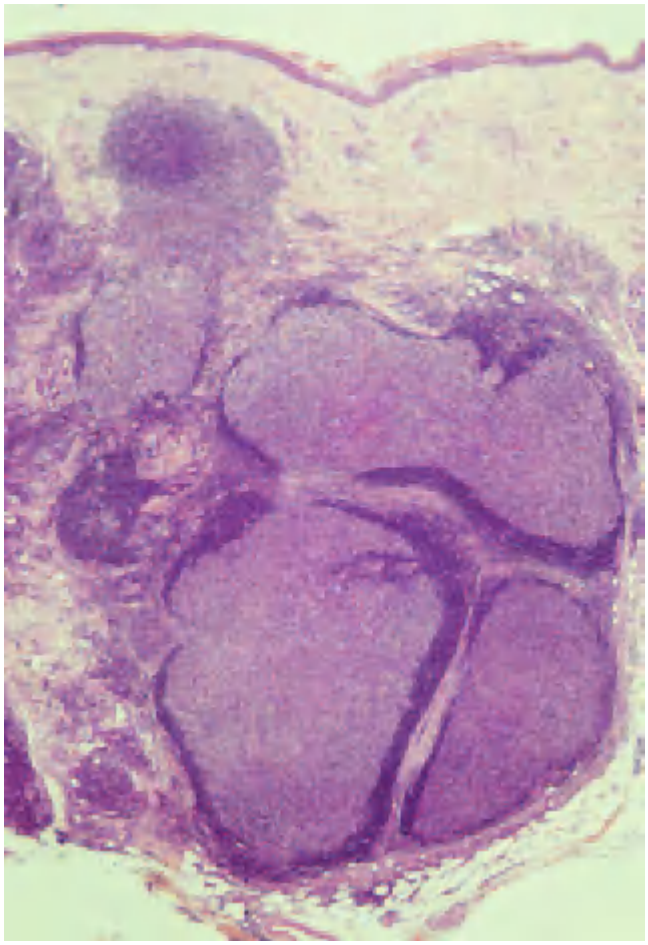

Fig. 54.31 Primary cutaneous follicle centre cell lymphoma.

most European studies of PCFCCL [6,12,13]. Cases with a diffuse pattern are classified as a diffuse large B-cell lymphoma in the WHO classification. In addition, rare PCFCCL cases with a distinctive follicular growth pattern show $CD10^+$ and Bcl-6 positive tumour cells. Microdissection of tumour cells has confirmed the follicular origin of these tumour cells, which are usually Bcl-2 negative and do not show evidence of the t(14;18) translocation, suggesting a different pathogenesis to nodal follicular lymphoma [4]. However, studies from the USA have detected the t(14;18) in a high proportion of $CD10^+$ and Bcl-2 positive PCFCCL with a follicular growth pattern, suggesting that there might be some unexplained geographical distinction although there are no obvious prognostic differences [14,15]. Inactivation of both the cyclin-dependent kinase inhibitors, namely the *p15* and *p16* genes, by promoter hypermethylation has been detected in a proportion of cases but the clinical significance is not yet clear [16]. CGH studies have also identified a consistent pattern of chromosomal gains and losses associated with specific oncogene abnormalities in PCFCCL [17]. However, a detailed characterization of the molecular abnormalities in PCFCCL is required to clarify the pathogenetic relationship between PCFCCL and systemic follicular and DLBCLs.

Treatment. Superficial radiotherapy is the treatment of choice for solitary, recurrent and multifocal cutaneous disease, except in rare cases with very extensive cutaneous disease or systemic involvement when single-agent treatment with chlorambucil or combination chemotherapy may be indicated. Solitary lesions may be excised, although subsequent radiotherapy is probably advisable to reduce the risk of local recurrence [18–20].

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Marginal zone lymphoma (immunocytoma)

Definition. An indolent cutaneous B-cell lymphoma derived from post-germinal centre cells and characterized by a proliferation of small lymphocytes, lymphoplasmacytoid cells and plasma cells with monotypic cytoplasmic immunoglobulin.

Clinical features. These lymphomas present as asymptomatic solitary or multiple dermal papules, plaques or nodules on any body site, although the trunk is most often involved (Fig. 54.32) [1–4]. Full staging investigations are indicated. Benign monoclonal paraproteinaemia may be present. There is a slight male predominance. Anetoderma associated with individual lesions has been described [5]. The estimated 5-year survival is 98–100% [4,6,7].

Pathology. The histology is characterized by nodular or diffuse dermal infiltrates of small- to medium-sized lymphocytes, lymphoplasmacytoid cells and plasma cells, often with a reactive T-cell infiltrate [2–4]. There is no epidermotropism. Reactive follicular structures are often present and tumour cells present within expanded marginal zones and interfollicular areas may colonize these follicular structures (Fig. 54.33). This pattern has to be distinguished immunophenotypically from rare follicular patterns of PCFCCL [4]. Occasional scattered centrocytes, centroblasts and immunoblasts may be present. The tumour cells, characterized by monotypic κ or λ expressing larger paler lymphoplasmacytoid cells, are concentrated at the periphery of the cellular aggregates or residual follicular structures. PAS-positive intranuclear or intracytoplasmic inclusions may be present [2–4].

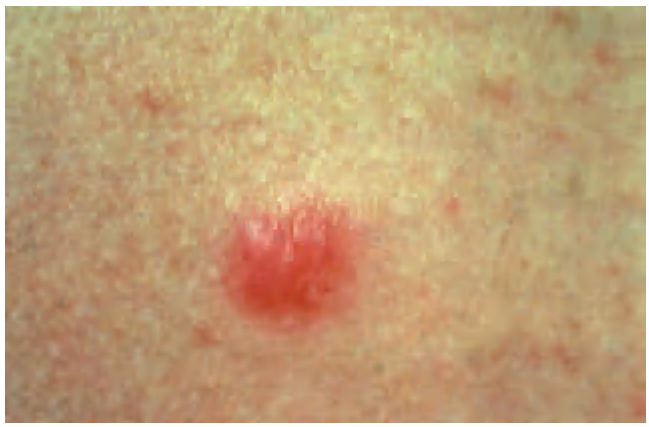

Fig. 54.32 Marginal zone primary cutaneous B-cell lymphoma: typical urticated dermal erythematous papules and plaques predominantly situated on the trunk.

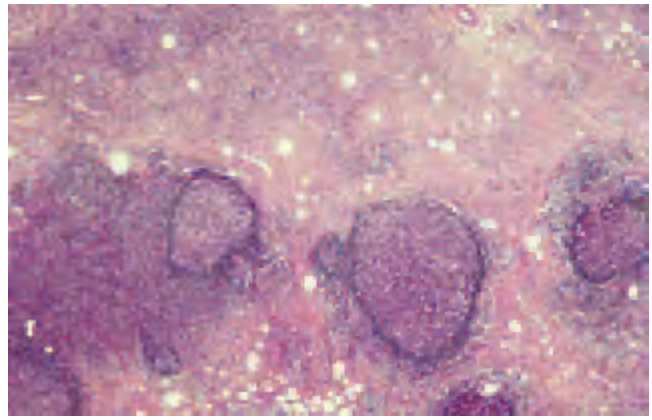

Fig. 54.33 Marginal zone primary cutaneous B-cell lymphoma: reactive germinal centres with a non-epidermotropic monomorphic infiltrate of lymphoplasmacytoid cells and mature plasma cells.

Immunophenotype. The tumour cells show either κ or λ light chain restriction (although this can often be difficult to detect in cutaneous sections because of non-specific staining of collagen) and express CD20 and CD79a but are Bcl-6, CD5 and CD10 negative [4]. The tumour cells are Bcl-2 positive but the t(14;18) is not present [3,4]. Marginal zone lymphomas of the skin should be distinguished from cutaneous infiltrates of B-chronic lymphocytic leukaemia, which are $CD5^+$. Clonal immunoglobulin gene rearrangements are detected in most cases. There is a high false-negative rate because of somatic hypermutation, which interferes with primer annealing in the analysis of immunoglobulin genes as for follicle centre cell lymphomas [8].

Pathogenesis. Marginal zone lymphoma was first described in the stomach (MALT lymphoma) and has since been described in the thyroid, salivary gland, orbit and lung as well as the skin. Although not recognized as a distinct entity in the EORTC classification, primary cutaneous marginal zone lymphomas have since become more clearly defined. At present it is not clear if these primary cutaneous lymphomas have a similar pathogenesis to other extranodal marginal zone lymphomas. The demonstration of light chain restriction and/or a clonal immunoglobulin gene rearrangement represents a critical technique for distinguishing these low-grade cutaneous lymphomas from reactive B-cell infiltrates. The distinction between primary cutaneous marginal zone B-cell lymphoma and immunocytoma is based on the predominance of a monomorphic plasma cell infiltration in immunocytoma but, in view of similar clinical behaviour, the two subtypes are grouped together. In the WHO classification, immunocytoma is recognized in the skin only with sec-

ondary cutaneous involvement. There are no disease-specific cytogenetic abnormalities in cutaneous cases, although a consistent pattern of chromosomal gains and losses have been identified using CGH techniques [9]. In extranodal marginal zone B-cell lymphoma of MALT, trisomy 3 (involving up-regulation of the Bcl-6 gene) and t(11;18) are present in most cases [10]. The t(11;18) produces a fusion protein involving the *AP12* gene and the *MALT-1* gene. In addition, a t(14;18) involving the *IgH* gene locus and the *MALT-1* gene has also been recently identified in a subset of MALT lymphomas including some cutaneous marginal zone lymphomas [11]. Other subsets show a t(1;14) involving the Bcl-10 gene on 1q [12].

Development of immunocytomas has been reported in areas of acrodermatitis chronica atrophicans and has led to speculation about the role of *Borrelia burgdorferi* producing chronic antigen stimulation leading to neoplastic transformation (see below). The detection of *Borrelia* DNA in some cutaneous lesions of immunocytomas and marginal zone B-cell lymphomas using PCR has provided support for this role, but the frequency of positivity varies considerably in different geographical regions with positive results in central Europe and Scotland [13,14] but no evidence of an association in the USA [15].

Treatment. Radiotherapy is appropriate and some patients may simply be observed in view of the excellent long-term prognosis [16]. The role of IFN-α has not been established but it may be effective either systemically or intralesionally [17]. In cases associated with *Borrelia burgdorferi* antibiotic therapy is appropriate [16,17].

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Large B-cell lymphoma

Definition. Large B-cell lymphoma (LBCL) is characterized by a diffuse proliferation of large B cells consisting of centroblasts and immunoblasts. This (i.e. diffuse LBCL) is the most common form of non-Hodgkin's lymphoma, derived from germinal and post-germinal centre cells, which usually develops as a primary nodal lymphoma but rarely may present as an aggressive primary cutaneous B-cell lymphoma. Common extranodal sites include the gastrointestinal tract.

Clinical features. As primary cutaneous lymphomas these tumours affect an elderly population with a female predominance. These lymphomas tend to develop on the lower limbs, predominantly as large dermal nodules or tumours, which are either solitary or multifocal (Fig. 54.34) [1]. This has led to the EORTC classification of these lymphomas as LBCL of the leg, although primary cutaneous LBCL can also rarely occur at other sites [2]. The prognosis of primary cutaneous LBCL is poor, with a 5-year survival of 52–58% [1,3]. Full staging investigations are critical to exclude systemic involvement.

Pathology. There is a diffuse non-epidermotropic infiltrate of large cells with morphological similarity to centroblasts and immunoblasts (Fig. 54.35). There are relatively few associated inflammatory cells but a reactive T-cell infiltrate may be present. Germinal centres are not apparent and mitoses are prominent. Several morphological variants have been defined in nodal disease including an anaplastic variant [4]. Morphological variants in cutaneous disease have also been recognized including cleaved and round cell types but the reproducibility of this distinction may be poor [3]. However, the presence of a round cell morphology has been shown to be an

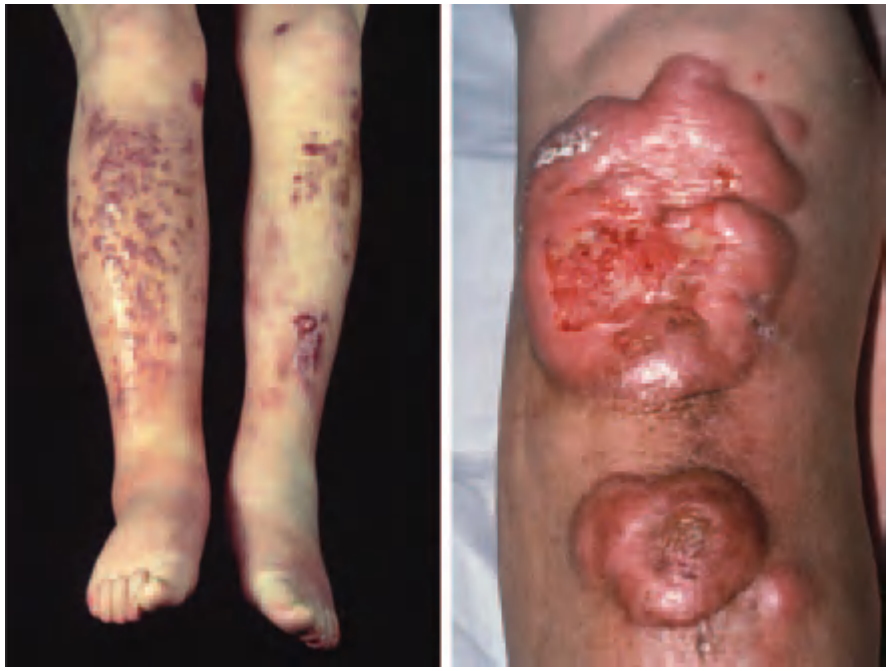

Fig. 54.34 Clinical presentation of primary cutaneous large B-cell lymphoma on the legs.

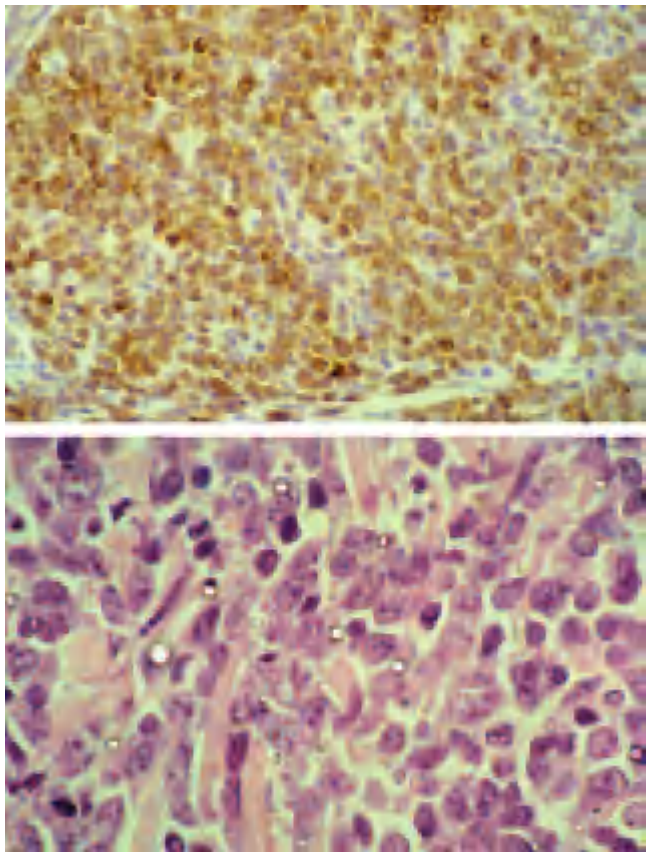

Fig. 54.35 Primary cutaneous large B-cell lymphoma showing a diffuse pattern of large mononuclear cells and strong Bcl-2 positivity.

independent adverse prognostic feature in multivariate analysis [3]. The cleaved cell type showing a predominance of large centrocytes and multilobated cells with few exceptions represent diffuse PCFCCL (Crosti's lymphoma).

Immunophenotype. The tumour cells are CD19, CD20, CD22 and CD79a positive with monotypic expression of surface and/or cytoplasmic immunoglobulin in some cases [5]. Tumour cells are usually strongly Bcl-2 positive [5], except for cases involving sites other than the leg, although most of these cases have a predominance of large cleaved cells [6], and Bcl-6 is also expressed by most cases with evidence of Bcl-6 gene mutations [5,7]. CD30 can be expressed in nodal cases with an anaplastic morphology but this has not been described in primary cutaneous cases. In nodal cases, CD5 (cyclin D1 negative) and CD10 have only rarely been detected and CD10 expression can also be rarely detected in primary cutaneous disease [5].

Pathogenesis. Although LBCLs usually arise *de novo* in the skin, they may also occur resulting from high-grade transformation of a low-grade primary cutaneous B-cell lymphoma such as PCFCCL [8]. These lymphomas are derived from germinal or post-germinal centre B cells. At present it is unclear whether primary cutaneous LBCL has the same pathogenesis as the more common primary nodal DLBCL, although this would seem likely. The EORTC classification of cutaneous cases as large B-cell lymphoma of the leg has caused controversy although there are a number of examples of site-specific lymphomas. However, the disease can rarely occur at sites

other than the leg. It may be difficult to distinguish this type of lymphoma from diffuse forms of PCFCCL, but the excellent prognosis of the latter suggests that this distinction is clinically relevant [8]. In addition, cases with a predominance of large cleaved (centrocyte) and multilobated cells invariably represent diffuse forms of PCFCCL.

Clonal rearrangements of immunoglobulin genes are present in most cases with false-negative results resulting from somatic hypermutation [9]. No disease-specific cytogenetic abnormalities have been identified. The t(14;18) translocation has not been identified in Bcl-2 positive cutaneous cases although this is a common feature of nodal DLBCL [5,6,10]. Chromosomal amplification of the *bcl-2* gene may account for bcl-2 overexpression in some cutaneous cases and, unlike PCFCCL and primary cutaneous marginal zone lymphoma (PCMZL), 6q loss and 18q gain are characteristic CGH findings [11]. In addition, inactivation of *p15* and *p16* genes by promotor hypermethylation has been detected and array CGH studies have identified specific oncogene abnormalities [11,12]. Recent studies in nodal DLBCL using microarray technology have detected at least three distinct expression profiles: one characteristic of germinal centre cells; one with an expression profile consistent with activated peripheral blood B cells; and one with an indeterminate profile [13]. Moreover, these patterns have prognostic and therapeutic significance [14]. As yet there are no data on cutaneous cases.

Prognosis. The prognosis for primary cutaneous LBCL, excluding cases of diffuse PCFCCL, is poor, with a 58% 5-year survival, but this is generally better than for nodal DLBCL [1]. Studies have previously suggested that Bcl-2 expression is site-related (lower limbs and multifocal lesions are more frequently bcl-2 positive) and possibly associated with a worse prognosis [3,6], although other studies have disputed the prognostic significance of bcl-2 expression [15]. A recent study of 145 cases has shown that multifocal disease, location on the leg and a round cell morphology are associated with a worse prognosis in a multivariate analysis (5-year survival of 52% vs 94%) [3]. However, this study included a significant number of cases with a diffuse pattern of large cleaved cells representing diffuse forms of PCFCCL. Unfortunately, tumour Bcl-2 expression was not included in this analysis and the possibility that Bcl-2 expression is a poor prognostic feature requires further study.

Treatment. In elderly patients with solitary tumours, radiotherapy may be appropriate but multiagent chemotherapy is usually required, especially for multifocal disease [16,17]. The role of rituximab (a chimeric mouse/human anti-CD20 antibody which induces antibody-dependent cytotoxicity) in cutaneous disease has yet to be determined [18,19], but this has proved effective in relapsed nodal DLBCL with or without chemotherapy. Intralesional rituximab may prove to be effective [20].

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Cutaneous plasmacytoma [1–3]

Definition. Plasmacytomas are clonal proliferations of plasma cells without evidence of multiple myeloma. These

are usually localized tumours either in bone (osseous) or extramedullary sites. A variety of sites may be affected including the skin (4% of all extramedullary plasmacytomas). Extraosseous lesions in association with multiple myeloma are not uncommon, and the skin is infiltrated in approximately 10% of cases [4]. However, primary involvement of the skin without evidence of bone involvement is extremely rare, with less than 30 cases recorded to date in the world literature.

Clinical features. Patients usually present with solitary or multiple, slowly growing violaceous dermal or subcutaneous nodules with no specific site predilection. Full staging investigations and skeletal surveys are required to exclude underlying myeloma, although a proportion of patients may have a benign monoclonal gammopathy. The prognosis is excellent, although patients may rarely develop myeloma.

Pathology. Nodular or diffuse dermal infiltrates consisting of mature plasma cells with some abnormal forms and occasional multinucleated forms. Occasionally, it can be difficult to distinguish plasmacytoma from immunocytoma (marginal zone B-cell lymphoma).

Immunophenotype. Tumour cells are $CD38^+$ (usually $CD19^-$ and $CD20^-$) and show κ or λ light chain restriction with clonal immunoglobulin gene rearrangements. These findings help to distinguish plasmacytoma from benign reactive plasma cell infiltrates (plasmacytosis).

Pathogenesis. There are few studies in cutaneous plasmacytoma in view of the rarity of the disease, but the underlying pathogenesis of extramedullary and osseous plasmacytoma is related to plasma cell myeloma.

Treatment. There are excellent responses to excision and/or radiotherapy.

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Borrelia burgdorferi-associated lymphomas

In 1982, Burgdorf *et al*. suggested that Lyme disease was caused by the tick *Ixodes ricinus*, and since that time the spirochete *Borrelia burgdorferi* has been recognized as being the vehicle responsible for carrying infection from the tick to human [1]. Cutaneous manifestations of Lyme disease are fully described in Chapter 27, but prior to the publication by Burgdorf *et al*. it was recognized in the German literature that patients with acrodermatitis chronica atrophicans, now recognized as part of the spectrum of Lyme disease, could develop cutaneous B-cell lymphomas [2–4].

There have recently been descriptions of a number of patients with low-grade primary cutaneous B-cell lymphoma in association with chronic *Borrelia burgdorferi* infection [5]. These patients developed multiple plaques and nodules superimposed on lesions of acrodermatitis chronica atrophicans. In a small number of reported cases, the lesions of acrodermatitis chronica atrophicans clear with antibiotic therapy, but the nodules of B-cell lymphoma may or may not persist. In contrast, the role of *Borrelia* in the pathogenesis of primary cutaneous B-cell lymphoma without clinical evidence of acrodermatitis is more controversial, with some studies detecting positive *Borrelia* serology and the presence of *Borrelia* in tumour DNA using PCR [6,7] while others have consistently shown negative results [8–10].

These lesions show a lymphoid proliferation characterized by an absence of epidermotropism, a grenz layer, and a fairly dense dermal and subcutaneous lymphocytic infiltrate. The cells express B-cell antigen and are monoclonal for either κ or λ light chains. To date, most cases reported have been κ-chain-positive. Immunoglobulin gene analysis can confirm the presence of a B-cell clonal proliferation. Extensive investigations have revealed no evidence of systemic involvement in most cases. The recognition of this entity suggests that chronic antigenic stimulation, in this case caused by the presence of *Borrelia burgdorferi* infection, may rarely encourage emergence of a neoplastic B-cell clone from a previously benign reactive proliferation of B lymphocytes [11].

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Secondary cutaneous B-cell lymphomas

Intravascular large B-cell lymphoma [1–8]

SYN. MALIGNANT ANGIOENDOTHELIOMATOSIS; ANGIOTROPHIC LYMPHOMA

Definition. A rare extranodal B-cell lymphoma characterized by accumulation of large B cells within small blood vessels. This tumour usually involves multiple extranodal sites including the CNS and skin, which may be the presenting feature.

Clinical features. Patients present with diffuse, tender, hard, infiltrated plaques, commonly on the thigh (Fig. 54.36), and the clinical appearance may suggest a sclerotic connective tissue disorder or panniculitis. A variety of clinical features may occur as a consequence of occlusion of internal small vessels. The prognosis is poor, although rare cases with disease confined to the skin may have a better outlook.

Pathology. The tumour cells are large and show striking atypia with an occasional anaplastic morphology. These cells are situated entirely within vessel lumina (Fig. 54.37). Fibrin thrombi may be present.

Immunophenotype. The tumour cells are positive for B-cell-associated antigens consistent with origin from a peripheral post-germinal centre B cell. Clonal immunoglobulin gene rearrangements are present. Rare cases are derived from T cells and show a clonal TCR gene rearrangement. Rarely, factor VIII, an endothelial cell-related antigen, may be positive but this is thought to be caused by absorption of antigen by tumour cells rather than indicating an endothelial cell origin.

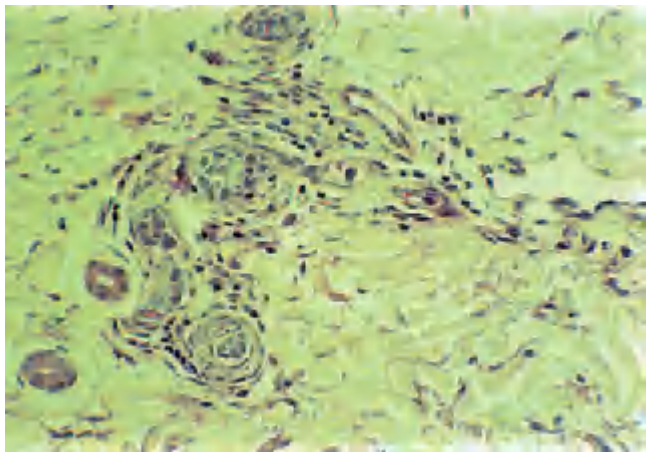

Fig. 54.36 Histology of angiocentric B-cell lymphoma showing B cells within small vascular channels in the dermis. These are stained with membrane markers for B cells, not with membrane markers for endothelial cells.

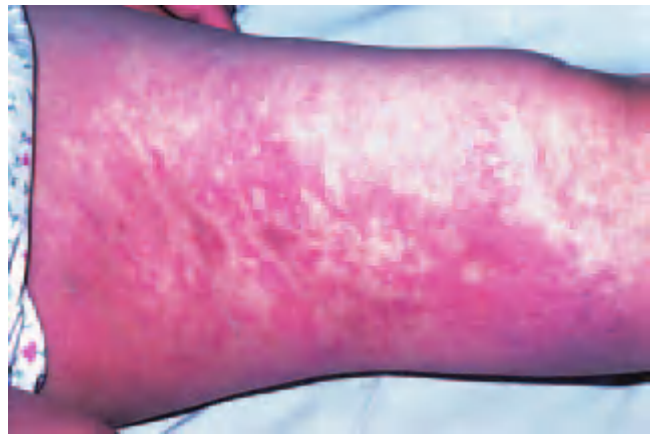

Fig. 54.37 Clinical illustration of patient illustrated in Fig. 54.36. Note marbled appearance of inner thigh which was woody hard on palpation. B-cell lymphoma showing lack of epidermotropism and clear grenz zone in the papillary dermis. (Courtesy of R.S. Lever, Western Infirmary, Glasgow, UK.)

Treatment. There are some reports of partial response to chemotherapy, but the disease has a poor prognosis and is usually fatal.

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Lymphomatoid granulomatosis

Definition. An angiocentric and angiodestructive extranodal EBV-positive B-cell lymphoma, which invariably involves the lungs and may involve the skin [1–3].

Clinical features. Patients most frequently present with pulmonary symptoms associated with systemic malaise,

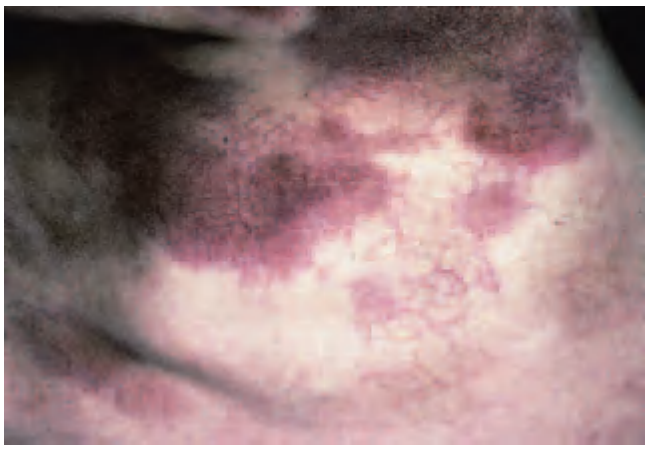

Fig. 54.38 Clinical features of lymphomatoid granulomatosis showing extensive purpuric, bruise-like lesions on the trunk.

arthralgias, weight loss and fever. The skin (50% of cases), CNS and kidneys are also often directly involved. The cutaneous lesions described are diverse but include subcutaneous nodules and plaques, more superficial plaques and a diffuse erythematous maculopapular eruption (Fig. 54.38) with epidermal atrophy and purpura [4–6]. Necrosis and ulceration may also occur [4]. Some patients have a fluctuating course with spontaneous remissions but eventually progressive disease develops.

Pathology. The striking feature is the angiocentricity of the infiltrate and the gross vessel destruction sometimes accompanied by fibrinoid necrosis (angiodestruction) [7]. The infiltrate is polymorphous and contains both lymphocytes and histiocytes with pleomorphic or immunoblastic tumour cells and often a prominent reactive T-cell infiltrate. Multinucleated cells may be present although well-formed granulomas are rare. The presence of large transformed cells is associated with a worse prognosis.

Immunophenotype. The tumour cells are EBV-positive, express CD20 and are variably CD79a$^+$. CD30 may be expressed but the cells are CD15$^-$. The reactive T cells are CD3$^+$ and CD4$^+$. Clonal immunoglobulin gene rearrangements can be detected in most cases and Southern blot analysis usually confirms the presence of clonal episomal EBV [8].

Pathogenesis. Lymphomatoid granulomatosis is an EBV-driven lymphoproliferative disorder that can be associated with immunodeficiency states. This lymphoma should be distinguished from extranodal NK/T-cell lymphoma (nasal type), which is also EBV-positive and characterized by an angiodestructive histology [8].

Treatment. Although some patients have spontaneous remissions, the development of high-grade disease is associated with a median survival of less than 2 years. Short-lived remissions with high-dose chemotherapy have been described. There are reports of responses to cyclophosphamide and IFN-α, particularly for patients with low-grade disease [9].

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Pseudolymphomas

Definition. Benign but persistent lymphoid proliferations in the dermis, which may very rarely transform to true lymphoma in some cases [1–3]. The term cutaneous lymphoid hyperplasia has been suggested and both terms are more commonly used to describe a pathological than a clinical appearance. Confusion between pseudolymphoma and true lymphoma can easily arise if a biopsy is submitted to the pathologist without an adequate history of recent events such as drug ingestion or scabies infestation.

Aetiology. T-cell pseudolymphomas may arise as a form of adverse drug reaction. The range of drugs causing T-cell pseudolymphomas is wide but includes anticonvulsants, angiotensin-converting enzyme inhibitors, β-blockers, cytotoxics, antirheumatics, antibiotics, antidepressants and many others [4–8]. Persistent contact dermatitis may also produce a T-cell pseudolymphoma pathological picture [9]. Persistent nodular scabies and arthropod bites may also cause a T-cell pseudolymphomatous histology [10], possibly caused by retained foreign material stimulating a persistent antigenic reaction [11,12]. There are three reports in the literature of putative CTCL arising in association with silicone breast implants, which may be examples of this phenomenon [13].

Actinic reticuloid (see below) may resemble a T-cell lymphoma histologically, and in very rare cases may actually progress to true lymphoma. Jessner's lymphocytic infiltrate (see below) can also be classified as a T-cell pseu-

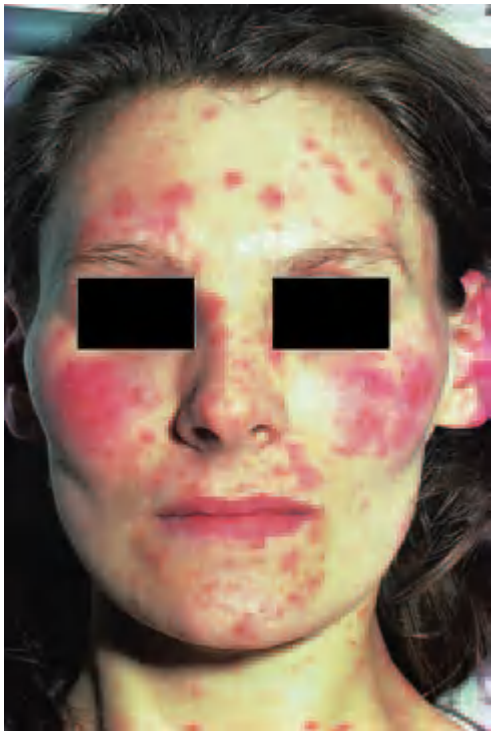

Fig. 54.39 Clinical appearance of a persistent photosensitive drug eruption induced by co-trimoxazole (Septrin).

dolymphoma, although there is a view that it is a variant of cutaneous lupus erythematosus.

B-cell pseudolymphomas may arise in the course of Lyme disease with *Borrelia burgdorferi* infection [14], in tattoos as a reaction to certain pigments [15,16], after vaccination and trauma [17], acupuncture [18] and within scars after herpes zoster infection [19]. The classic entity of lymphocytoma cutis also histologically resembles a B-cell pseudolymphoma, and is at present of unknown aetiology.

It is generally wise to be guarded in the diagnosis of pseudolymphoma, as in a number of cases clear progression from apparent pseudolymphoma to true lymphoma has been recorded. This appears to confirm the concept that chronic, initially benign, reactive inflammatory conditions may very rarely progress to frank lymphoma.

Clinical features. Both T- and B-cell pseudolymphomas may present as multiple cutaneous nodules (Fig. 54.39) as in persistent nodular scabies or lymphocytoma cutis. T-cell pseudolymphomas may also present as persistent erythema sometimes developing into an exfoliative erythroderma [20]. This is characteristic of T-cell pseudolymphomas caused by drug reactions or contact dermatitis. B-cell pseudolymphomas may also be associated with palpable lymphadenopathy, adding to diagnostic confusion.

Pathology [21–26]. It is vital to give the pathologist a good clinical history if the distinction between true lymphoma and pseudolymphoma is to be made, as the pathological, phenotypic and molecular differentiation is not absolute. The salient feature of a pseudolymphoma is the presence of T- or B-cell lymphoid proliferations. A few mitotic figures may be present, and there may also be subtle nuclear atypia. T-cell pseudolymphomas may be band-like or nodular in distribution, whereas B-cell pseudolymphomas are usually nodular. Germinal centre formation is usually absent in B-cell pseudolymphomas. Rarely, the lymphoid cells may be very bizarre and resemble mitogen-stimulated lymphocytes seen *in vitro* during the lymphocyte-transformation test [27]. In general, T-cell pseudolymphomas do not show epidermotropism or the presence of Pautrier's microabscesses.

Immunophenotypic studies show a normal T-cell phenotype and a mixed κ/λ expression. When germinal centres are present, Bcl-2 is not expressed in B-cell pseudolymphomas [28]. TCR and immunoglobulin gene analysis usually show evidence of a polyclonal proliferation, but rarely a monoclonal pattern has been detected, suggesting a neoplastic proliferation, but the significance of this finding is unclear at present [29–33].

Management. If the diagnosis of pseudolymphoma is considered likely, the presumed cause should be removed if possible. This is probably easiest in the case of an adverse drug reaction, but it may take weeks or even months for the cutaneous reaction to subside. In the cases of persistent nodular scabies or other pseudolymphomas that cause symptomatic itch, application of topical steroids will accelerate clearance.

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Parapsoriasis

This term has caused confusion since its introduction in 1902 because of a lack of a universally agreed definition of the clinical entities to be included. For this reason, many dermatologists prefer not to use the term at all, and to substitute one of the many synonyms for clinical conditions that might be included in one of the parapsoriasis groups. There is unresolved controversy as to whether or not two of the parapsoriasis variants are either precursors to cutaneous lymphoma in the form of MF (so-called *premycotic eruptions*) or established but early MF from the outset. There is a broad division of parapsoriasis into small and large plaque variants, each with a number of synonyms. The evidence that the majority of cases of small plaque parapsoriasis are a chronic benign condition is reasonable.

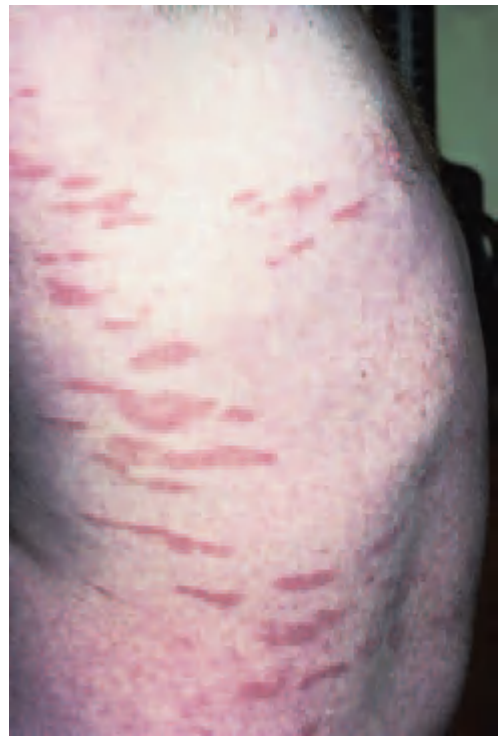

Fig. 54.40 Typical chronic superficial scaly dermatitis showing linear plaques on the trunk that change little over time.

In the case of large plaque parapsoriasis, there is more evidence that, at least in some cases, from the outset it is a form of MF. Unfortunately, TCR gene rearrangement studies have not been conclusive, although the proportion of cases with evidence of monoclonality is lower in small plaque parapsoriasis. Future long-term follow-up of these cases is now required.

Small-plaque parapsoriasis [1,2]

SYN. CHRONIC SUPERFICIAL SCALY DERMATITIS; PERSISTENT SUPERFICIAL DERMATITIS; DIGITATE DERMATOSIS; XANTHOERYTHRODERMA PERSTANS

Definition. A chronic asymptomatic condition, characterized by the presence of persistent small scaly plaques, mainly on the trunk.

Clinical features. The lesions usually appear insidiously and asymptomatically on the trunk and, to a lesser extent, on the limbs of young adults. Individual lesions are monomorphic round or oval erythematous patches, 2.5–5 cm in diameter, with slight scaling (Fig. 54.40). Some have a slightly yellow, waxy tinge. The lesions persist for years or even decades, and may be more obvious in the winter months. There is sparing of the pelvic girdle area and the striking polymorphic appearance of individual patches in MF is lacking.

Pathology. This is non-specific. There are small focal areas of hyperkeratosis and parakeratosis, and in the underlying dermis there are small aggregates of morphologically normal $CD4^+$ T cells, mainly around the vasculature. There is no epidermotropism, and no Pautrier's microabscesses.

Immunophenotypic studies reveal a normal mature T-cell phenotype. One report has identified a 'dominant T-cell clone' in two out of five cases of small-plaque parapsoriasis, using PCR analysis [3]. The significance of this observation in terms of relationship to MF and disease progression is not yet clear. There is also a report of a higher frequency of clonal T cells in the peripheral blood of patients with small-plaque parapsoriasis [4] with no evidence of clonality in the skin, although the significance of this finding is now questionable because non-pathological T-cell clones can rarely be found in the peripheral blood of normal healthy volunteers.

Treatment. Often little treatment is needed. Emollients may help control the scaling, and a course of UVB phototherapy may result in temporary clearance of the lesions, but recurrence is invariable [5].

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Large-plaque parapsoriasis

SYN. PARAKERATOSIS VARIEGATA; RETIFORM PARAPSORIASIS; ATROPHIC PARAPSORIASIS; POIKILODERMATOUS PARAPSORIASIS

Definition. A chronic condition characterized by the presence of fixed large atrophic erythematous plaques, usually on the trunk and occasionally on the limbs.

Clinical features. Patients present with persistent large yellow-orange atrophic patches and thin plaques on the trunk and limbs. Involvement of covered skin on the breast and buttock areas may suggest MF and in these cases patches and plaques may show striking polymorphism and poikiloderma with slow progression. Large series (129 cases followed for several years) have recorded the development of definite MF in 11% of cases [1].

Pathology [2,3]. There is frequently epidermal atrophy, and a lichenoid or interface reaction may also be seen at the dermal–epidermal junction. There is a band-like lymphocytic infiltrate in the papillary dermis, and there may also be free red cells present. The histology is not diagnostic for MF and most biopsies only show a mild dermatitis.

Immunophenotypic studies reveal a normal T-cell phenotype. TCR gene rearrangement studies have shown a clonal T-cell population in the skin in six of 12 patients, but progression to overt CTCL was only noted in one of the 12 patients [4].

Treatment. Topical emollients, UVB and PUVA are all helpful in offering symptomatic relief. Topical steroids should be used with caution because of the atrophic nature of the condition.

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Actinic reticuloid [1,2]

Definition. This condition was first described by Ive *et al*. in 1969 [3]. The original description was of a group of elderly, exclusively male patients who developed a severe and very disabling photosensitivity involving reaction to light throughout the UVB, UVA and visible part of the spectrum. A number of these patients had a past history of contact dermatitis and a milder form of photosensitivity ('persistent light reactors'), but the true relationship between contact dermatitis, particularly to plants of the Compositae family [4], persistent light reactors (chronic actinic dermatitis) and actinic reticuloid is not yet established. The photosensitivity is very severe.

Clinical features. The clinical features are the symptoms of severe and persistent photosensitivity with erythema, oedema and striking 'leonine' thickening of the light-exposed skin of the face, neck and hands (Fig. 54.41) [5].

Patients with atopic dermatitis may be more likely to develop actinic reticuloid, and this should be considered in those with chronic atopic dermatitis who develop photosensitivity [6].

Pathology. The histological picture is that of an intense, superficial and deep lymphocytic infiltrate extending from the papillary dermis deep into the reticular dermis. Signs of actinic damage to collagen are present and some

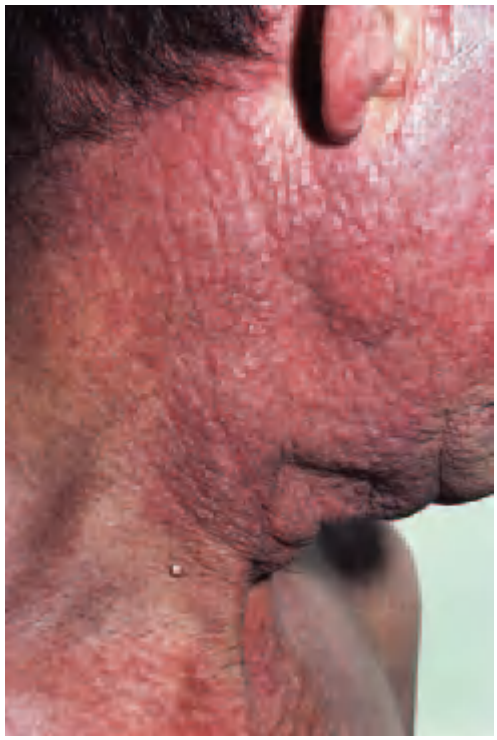

Fig. 54.41 Actinic reticuloid showing marked infiltration of light-exposed skin of the face, with a striking change in skin texture at the collar area and normal skin on the area usually covered by clothing.

of the lymphocytic cells are large and atypical, hence the term 'reticuloid'. The majority of the lymphoid infiltrate consists of $CD8^+$ T cells.

TCR gene analysis does not show a clonal T-cell population [7], but the development of a T-cell clone has been reported in a single patient with a photosensitive dermatosis who developed MF [8]. One case has been reported of neutrophilic eccrine hidradenitis in actinic reticuloid [9].

Treatment. Treatment is based on light avoidance and the use of both the titanium dioxide-containing physical light barrier creams and the newer, more effective chemical UVA and UVB blockers. Low-dose systemic steroid therapy, ciclosporin, hydroxyurea [10] and azathioprine [11] may be effective in some patients.

The prognosis for recovery is poor and the majority of patients tend to have severe photosensitivity for the remainder of their lives.

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Lymphocytoma cutis

SYN. SPIEGLER–FENDT SARCOID; LYMPHADENOSIS BENIGNA CUTIS OF BAFVERSTEDT

Definition. Lymphocytoma cutis is a benign cutaneous B-cell lymphoproliferative condition. It presents as nodules or plaques usually on the head and neck and pursues a chronic course [1–3].

Aetiology. This is at present unknown.

Clinical features. More cases are reported in females than males. Most patients show solitary or grouped asymptomatic erythematous or violaceous nodules or plaques, on the head, especially the ear lobes, and rarely the trunk or limbs (Fig. 54.42). Occasionally, they may have a translucent appearance. They are asymptomatic and not tender, painful or itchy. Lesions are often multiple and may be in all stages of development. They enlarge slowly and may reach a diameter of 3–5 cm. Associated sunlight sensitivity has been reported in some patients. Bafverstedt [4] has described an unusual form of lymphocytoma that presented as a solitary tumour of scrotal skin. Disseminated or miliary lymphocytoma cutis is also rare [5], and occurs in older patients on any body site.

Pathology [6,7]. The epidermis is usually unaffected and is often separated by a relatively acellular grenz zone from the dermis, which is replaced by a nodular dense infiltrate extending through the full thickness of the dermis. In classic cases, lymphocytes and histiocytes form a follicular arrangement resembling the appearance of a lymph node (Fig. 54.43). Mitotic figures may be visible in the cells of the follicles and occasional eosinophils may also be present. Appendages and blood vessels are spared. In some instances, there is no tendency for lymphoid follicle formation, although the histological appearance with normal

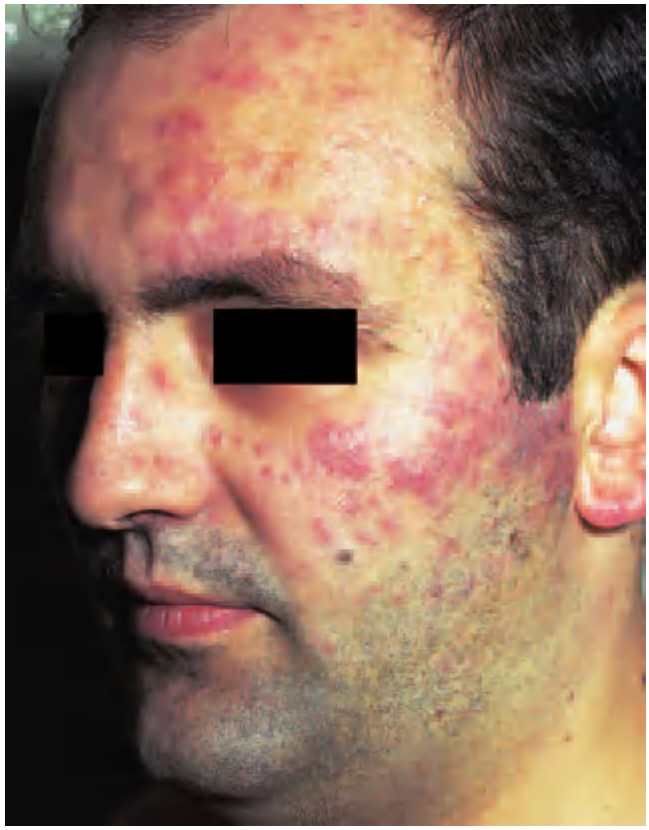

Fig. 54.42 Clinical presentation of a patient with lymphocytoma cutis.

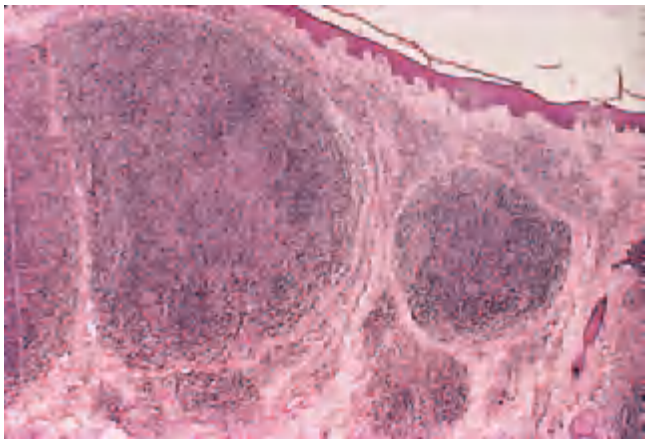

Fig. 54.43 Histology of Spiegler–Fendt sarcoid showing striking lymphoid follicles.

lymphocytes and histiocytes is otherwise similar. The histological differential diagnosis includes primary cutaneous lymphoma, particularly of marginal zone origin.

Immunopathology. The majority of lymphocytes in the dermis are B cells. Germinal centres are frequently seen in lymphocytoma cutis, and appropriate markers will confirm the morphological similarity of these structures to the germinal centres of lymph nodes. A cuff of reactive T cells may be seen around the periphery of the main B-cell aggregate.

Differential diagnosis. Histological examination should distinguish lymphocytoma cutis from granulomatous disorders including sarcoidosis, granuloma faciale and rosacea. Distinction from primary cutaneous B-cell marginal zone lymphoma (MZL) lymphoma is difficult, although the presence of atypical lymphoid cells would suggest a cutaneous MZL lymphoma. Insect bite reactions may also be impossible to distinguish with any confidence from lymphocytoma cutis.

Jessner's benign lymphocytic infiltration, tumid discoid lupus erythematosus (LE) and polymorphic light eruption can also cause difficulties. However, in Jessner's lymphocytic infiltrate, which characteristically waxes and wanes in severity, the dermal lymphocytic infiltrate is dominated by T cells. The presence of basal cell liquefaction degeneration and positive direct immunofluorescence helps distinguish LE.

Treatment. There is no treatment of proven value for lymphocytoma cutis. Penicillin and radiotherapy have been advocated in the past without adequate clinical trials. Intralesional steroids have also been advocated. Miliary lesions may partially respond to topical steroids. Hydroxycloroquine has also been effective.

Prognosis. Lymphocytoma cutis is a benign disorder in both localized and disseminated forms, although often running a very protracted course. Long-term follow-up of these patients suggests that a small proportion progress to cutaneous B-cell lymphoma and therefore the prognosis must be guarded [8–11].

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Jessner's lymphocytic infiltrate [1]

Definition. A chronic benign T-cell lymphoproliferative disorder, usually of exposed skin.

Clinical features. Females are more often affected than males [2]. Both children [3,4] and familial cases [5,6] have been recorded. Benign lymphocytic infiltration of Jessner is characterized by the presence of red tumid nodules, usually on facial skin (Fig. 54.44). The lesions may involute spontaneously, but more commonly are persistent, and new lesions develop over time. There is variation in seasonal activity of the lesions, with winter exacerbations. The individual lesions are smooth raised non-scaling erythematous nodules or plaques and are commonly asymptomatic, although some patients complain of burning or pruritus.

Pathology [7–11]. Biopsies reveal a lymphocytic infiltrate predominantly in the lower dermis and concentrated tightly around blood vessels (Fig. 54.45). The epidermis and papillary dermis are relatively normal, and within the lymphocytic infiltrate there is no evidence of germinal centre or follicle formation. The great majority of these cells are $CD4^+$ T cells.

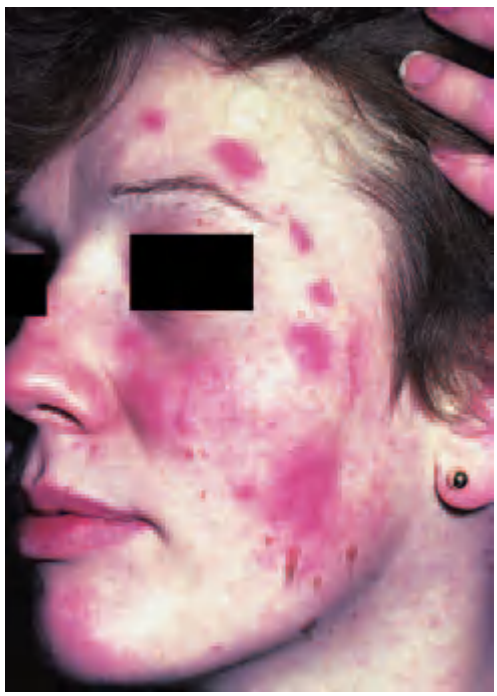

Fig. 54.44 Clinical appearance of a young woman with Jessner's lymphocytic infiltrate.

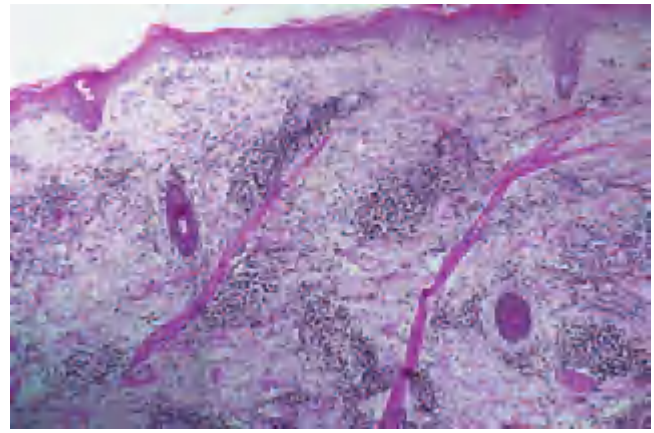

Fig. 54.45 Pathological pattern of Jessner's lymphocytic infiltrate. Note perivascular distribution and absence of epidermotropism.

Differential diagnosis. The clinical differential diagnosis includes a fixed drug eruption and cutaneous discoid LE. The lesions are usually more numerous than would be associated with a fixed drug eruption, although the histology is very similar. The individual lesions of Jessner's lymphocytic infiltrate are smooth and non-scarring, in contrast to the scaling atrophic scarring associated with chronic discoid LE. In addition, Jessner's lymphocytic infiltrate does not demonstrate a lupus band as seen at the dermal–epidermal junction in chronic discoid LE. However, there is a view that Jessner's lymphocytic infiltrate is a variant of LE.

Treatment. This is unsatisfactory, and lesions tend both to persist and to increase in numbers. There are individual case reports of successful therapy with topical steroids, systemic steroids, PUVA, radiotherapy, dapsone, hydroxychloroquine and gold [12].

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Leukaemia cutis [1–3]

Diagnosis. The diagnosis of the specific type of leukaemia depends on detailed examination of the blood and bone marrow. The cutaneous infiltrate rarely indicates the type of leukaemia involved.

Specific cutaneous lesions occur more often in myelomonocytic leukaemia and T-cell prolymphocytic leukaemia than in other forms [4]. Specific lesions in the other forms of leukaemia are unusual as a presenting feature, and usually appear after the diagnosis has been established. There are a few cases where the diagnosis of leukaemia has been established first by analysis of the skin lesions [5]. These lesions usually consist of small reddish papules or nodules which may be fleeting or persistent. Clinically, they may resemble lesions of Sweet's syndrome, sarcoidosis, panniculitis, other granulomas or cutaneous lymphoma (Fig. 54.46). Ulceration, especially around the ankles, simulating gravitational ulceration, is seen most often in chronic lymphatic leukaemia and may represent the development of a leukaemic deposit in an area of low resistance.

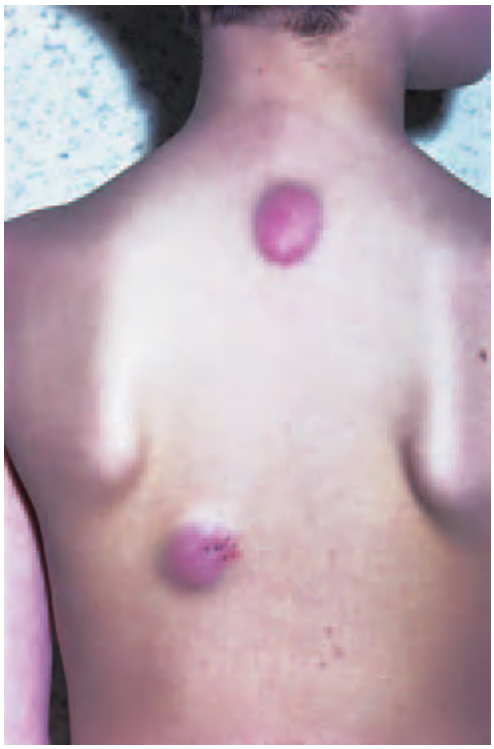

Fig. 54.46 Specific deposits in a child with leukaemia. Note two large nodular lesions on the back.

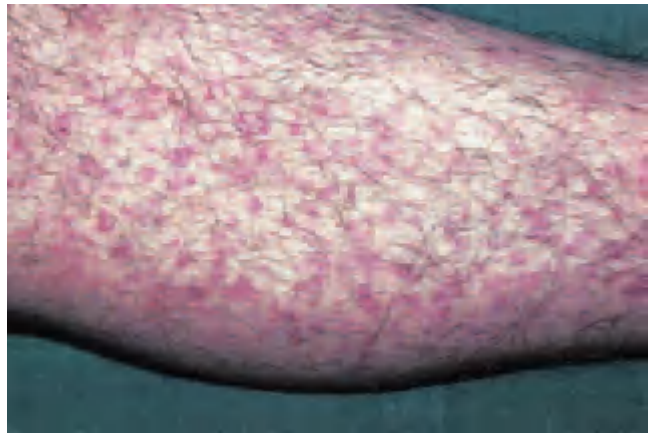

Fig. 54.47 Purpuric lesions in an adult patient with myelocytic leukaemia.

Although 'non-specific' lesions are said to be common, they are rarely reported by dermatologists. Generalized pruritus may be a presenting symptom and prurigo-like papules develop in some cases. Erythroderma has been recorded in association with an underlying T-cell leukaemia such as T-cell prolymphocytic leukaemia which must be distinguished from Sézary syndrome. There is usually marked exfoliation and the skin may be markedly thickened, especially over the face. The histological features in the skin may or may not be diagnostic.

Disseminated or unusually severe herpes zoster is common in association with all types of malignant disease. Specific infiltrations into herpetic scars may occur and bullous lesions have been recorded [6]. In multiple myeloma, both generalized and local amyloidosis is common. Anhidrosis has been recorded. Patients with myelomatosis may subsequently develop variants of acute myelogenous leukaemia [7,8] and it has been suggested that this complication is the result of treating the underlying disease with irradiation or alkylating agents [9].

Three cases of a perniotic syndrome associated with monocytosis and neutropenia have been described as a possible association with a preleukaemic state [10]. Sweet's disease and bullous pyoderma have also been associated with leukaemia (see Chapter 61).

Thrombocytopenic purpura is a characteristic symptom of the acute leukaemias and may occur on skin or mucous membranes, often as the presenting symptom (Fig. 54.47).

Beek [9] recorded 289 cases of lymphatic leukaemia with skin lesions and, in these, tumours were present in 50%, the head being the most common site. Erythroderma was present in 25%, herpes zoster in 26%, prurigo-like papules in 21%, bullae in 10%, varicelliform eruptions and urticaria in 3%. Haemorrhagic gangrene of the skin has also been recorded. The usual age at presentation of patients with lymphatic leukaemia is 45–54 years, but those

with cutaneous lesions tend to be older. Skin lesions in myelogenous leukaemia are much less frequent, with only 72 recorded cases. When the skin is involved the prognosis is poor.

A relatively specific picture is observed in a number of patients with chronic T-cell lymphatic leukaemia [6]. These patients are frequently elderly males and may present with diffuse generalized erythroderma, splenomegaly and lymphadenopathy. This may be caused by lymphokine release by the malignant T cells during their passage through the dermal vasculature, as skin biopsy of these lesions does not reveal a specific cutaneous infiltrate, or epidermotropism characteristic of MF.

Diagnosis. Diagnosis of all these conditions is based on pathological examination of material from blood, bone marrow, lymph nodes and skin [8,11–13].

Treatment. The treatment for leukaemia cutis is management of the underlying disease, with symptomatic measures for the skin lesions when required. Superficial radiotherapy may be useful, giving rapid symptomatic relief, and regression of specific cutaneous deposits.

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Cutaneous Hodgkin's disease

The existence of a variant of Hodgkin's disease that begins in the skin is still debated, and it can be difficult if not impossible to differentiate from Hodgkin's disease beginning in the nodes, which spreads at an early stage to the skin [1–5]. Invariably, cutaneous Hodgkin's disease only occurs as direct extension from an underlying involved regional lymph node. Thus, careful clinical examination, followed if appropriate by node biopsy and CT scans, should be performed before a diagnosis of primary cutaneous Hodgkin's disease is made. In view of the cytological similarity between the cells of lymphomatoid papulosis and those of Hodgkin's disease, this differential diagnosis must be carefully considered and positively excluded.

Clinical features. One review of 1810 cases of Hodgkin's disease reports only nine (0.5%) with specific cutaneous lesions [6] but a more recent study records involvement in 16 of 465 cases (3.4%) [7]. They usually consist of small nodules, but ulcerative lesions have been recorded and rarely are the presenting symptom. There have been a number of reports of the first lesions appearing on the scalp.

Pathology [1,2,8]. To consider the diagnosis of Hodgkin's disease either involving the skin as a secondary process, or originating in the skin, the cutaneous infiltrate should consist of nodules of atypical lymphoid and histiocytic cells, including the presence of Reed–Sternberg cells that are $CD30^+$ and lymphoid cells that are $CD15^+$ [9–11]. CD15 positivity is not seen in lymphomatoid papulosis.

Cutaneous signs associated with Hodgkin's disease [5,12] are as follows:

Non-specific lesions. These are very common and occur in 3–50% of cases. These include pigmentation, pruritus, prurigo, atrophy, alopecia, exfoliative dermatitis and herpes zoster.

Pigmentation. This is melanin pigmentation and is very common. It resembles the pigmentation of Addison's disease, being most marked in areas that normally show some darkening such as the axillae, groins and around the nipples. Less often it is more widespread, and occasionally a bizarre pigmentation occurs. The mucous membranes are usually spared.

Pruritus. This often occurs together with pigmentation. Pruritus is not infrequently the presenting feature of the disease, and may precede the presence of palpable nodes by months or years. It tends to start on the legs. It is especially severe in patients who show other general symptoms such as fever and weight loss. Both pigmentation and pruritus occur in association with enlarged mediastinal or retroperitoneal glands, the presence of which should always be suspected when itching is severe.

Prurigo. This is a development from pruritus. In addition

to the widespread irritation, there are excessively itchy papules, which are scratched until the skin surface is removed and is replaced by a blood crust. The papules and crusts are usually found on the trunk. When present in association with enlarged superficial glands, this forms a very characteristic picture, often called *Hodgkin's prurigo*.

Ichthyosiform atrophy. An acquired ichthyosis occurring in the course of a chronic wasting disease is fairly common. Hodgkin's disease is probably the most common condition to be associated with this change. It usually starts on the legs and may remain restricted, but in severe cases progresses until it becomes universal. It resembles ichthyosis vulgaris, with thin, dry and rather firmly attached scales. It is not static and may regress for a time, only to return later. Red streaks are often visible between the scales. The patient is usually wasted and severely ill. Malabsorption from the gut may occur in some cases and contribute to this problem.

Alopecia. Hair loss is common in Hodgkin's disease. It can be caused by rubbing or scratching to relieve itching. It may also be part of the ichthyosiform atrophy or be caused by endocrine dysfunction, when specific infiltration occurs in organs such as the pituitary or adrenal. Rarely, it may be brought about by specific infiltration in the scalp.

Exfoliative dermatitis. Erythroderma and exfoliative dermatitis have been recorded as occurring in Hodgkin's disease on many occasions [4]. Most recorded cases would probably be more correctly included under ichthyosiform atrophy.

Herpes zoster. Herpes zoster is common in the course of Hodgkin's disease, but disseminated zoster is much less likely to occur in Hodgkin's disease than in chronic lymphatic leukaemia.

Miscellaneous conditions. Many other non-specific skin lesions have been described in association with Hodgkin's disease, but they are probably incidental. Erythema nodosum is seen occasionally and is apparently caused by the disease itself; in these cases, differentiation from sarcoidosis may be difficult, but the Kveim test or node biopsy should establish the diagnosis.

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Lennert's lymphoma

Definition. A rare variant of systemic lymphoma with a characteristic histology, first described in 1968 as a variant of Hodgkin's disease [1].

Clinical features. Most patients have lymphadenopathy, fever, fatigue and weight loss. The skin is involved very rarely as a secondary event and this usually consists of clinically non-specific papules or nodules [2]. One patient presented with chronic cutaneous infection and pyoderma [3], and another simulating atypical granuloma annulare [4].

Pathology. The characteristic pattern is an infiltrate with a high content of epithelioid histiocytes, admixed with $CD4^+$ cells. If the skin is involved, there may be a subcutaneous infiltrate consisting of epithelioid histiocytes and T cells. Reed–Sternberg cells are rare [2,3].

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Chapter 55

Subcutaneous Fat

M.M. Black & W.J. Cunliffe

Introduction

Subcutaneous fat (subcutis) occurs almost universally over the body surface between the skin and the deep fascia, but it is absent from the eyelids and the male genitalia. It varies in thickness with the race, age, sex, endocrine and nutritional status of the individual.

Subcutaneous fat acts as an insulating layer and a protective cushion, and also has an important role in thermogenesis, and as a store of readily available energy. In a normal person, fat constitutes about 10% of body weight, and provides about 40 days' reserve energy [1]. Brown fat has a very important thermoregulatory role and acts by increasing the basal metabolic rate [2]. This is particularly important in infancy, and heat production in response to cold exposure is maximal in neonates, who have large quantities of brown fat.

Fat also provides support and has a cosmetic function, for example in the contours of the face. It also has great social importance. Fat children may be bullied or ostracized at school [3], fat adults may find it harder to get certain jobs, and the contribution of fat to the shape of the breasts and buttocks as a secondary sexual development in the female has been known to influence social behaviour.

Embryology. The first fat-containing cell, the lipoblast, appears in the mesenchyme around the 14th week of fetal life. This cell matures to form the large unilocular lipocyte, the characteristic cell of adult fat. The primitive mesenchymal cell that forms the lipoblast is also capable of maturing to form a fibrocyte, a myocyte, a chondrocyte or an osteoblast. The distinction between adipocytes and fibroblasts is not always clear, and 'pre-adipocytes', which do not contain enough fat to be counted as fat cells by standard techniques, have been described [4].

Brown fat is a special type of granular fat that differs from white fat in its distribution, histology and function. It is multilocular and is metabolically very active, with many mitochondria, so that it is capable of producing heat. It is most prominent in the neck and upper thorax of the fetus, and it may be homologous to the hibernating gland fat found in some animals [5]. Brown fat is now known to persist into adult life [6], and it may have a role in preventing obesity [6]. Warm patches develop in the skin 1 h after taking ephedrine orally, and these warm patches may indicate the site of thermogenic brown fat.

Histology. The fat cells (lipocytes) form a specialized part of the reticuloendothelial system, which is capable of fat synthesis as well as fat storage. They are the largest connective tissue cells in the body, with a diameter of up to 100 μm. The mature fat cell has a characteristic signet-ring appearance, because the flat oval nucleus is displaced to the side by a single large intracellular vacuole, which contains fat. Groups of lipocytes are arranged in lobules, which are separated by interlobular septa composed of collagen and reticulin fibres. Fat tissue has an abundant blood supply, each individual lobule being supplied by an arteriole that runs along the septa, before breaking up to form capillaries which come into close apposition with the individual fat cells. The subcutaneous fat also contains a

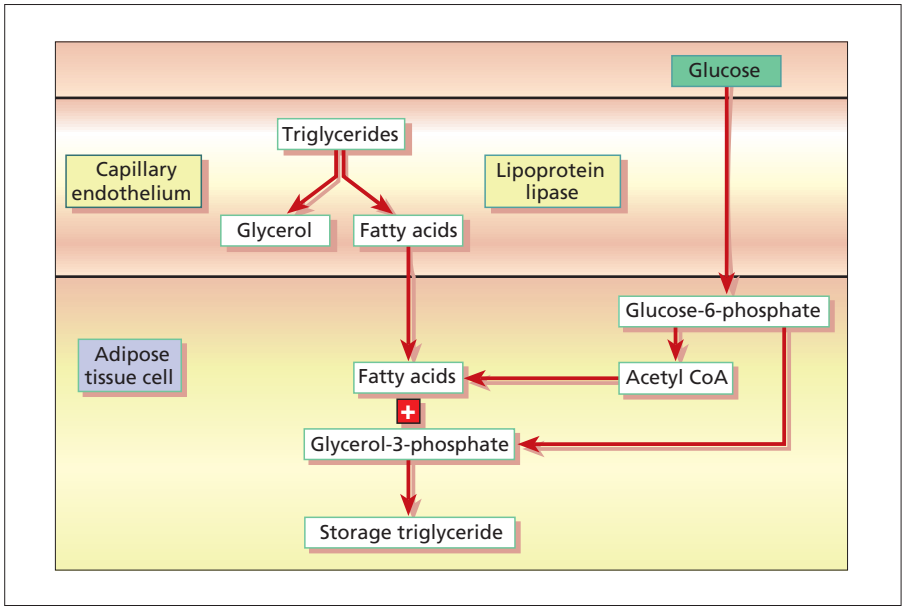

Fig. 55.1 The metabolic pathways related to adipose tissue.

rich lymphatic plexus, which receives vessels from the dermis. These lymph vessels traverse the subcutaneous layer parallel to the skin surface for some distance, before eventually penetrating the deep fascia and draining into the regional lymph nodes.

The nature of the lipocyte and its relationship to blood vessels and lymphatics has been reviewed in detail by Ryan and Curri [7].

The fat tissue and the fat organ. The fat tissue is composed of lobules of fat cells with their supporting connective tissue, blood and lymph vessels, and reticuloendothelial cells. In addition to forming subcutaneous fat, fat tissue occurs in the mediastinal and retroperitoneal tissues, the mesentery and the bone marrow. This tissue, although it is widely scattered throughout the body, forms a true organ as regards both structure and function [1]. The thickest subcutaneous fat deposits are found over large muscles such as the gluteal muscles, and the blood supply in these areas comes mainly from the underlying muscle.

Physiology [8,9]. The synthesis and catabolism of fat in the subcutaneous depot depends on many factors, including nourishment, endocrine and nervous activity. The role of the autonomic nervous system in regulating fat metabolism is now well established [10].

Hormones that may affect the metabolism of fat cells include insulin, cortisol, norepinephrine (noradrenaline) and several pituitary hormones, including somatotrophin, adrenocorticotrophic hormone (ACTH) thyrotrophin and lipotrophin.

The fats contained within the lipocytes are predominantly triglycerides, especially those of palmitic and stearic acids and the unsaturated oleic acid. All the fatty acids have an even number of carbon atoms, predominantly C16 and C18, with a few C14 and C12. Adipose tissue contains 10–30% of water with a small proportion of lipochromes, and less than 2% cholesterol. Fat-soluble substances are also present in varying amounts. These include fat-soluble vitamins and traces of chlorinated hydrocarbons (e.g. aldrin, dieldrin) ingested with the diet, as well as drugs such as acitretin. Adipose tissue *in vitro* has a metabolic rate similar to that of kidney tissue, and approximately half that of liver. Approximately half the triglyceride in the adipose tissue of rats and mice is catabolized and reconstituted in the course of a week or so.

The fat for storage enters the lipocyte as fatty acids, which combine with coenzyme A, using the energy of adenosine triphosphate (ATP), to form the corresponding acyl coenzyme A compounds. Some of these are then oxidized to provide energy for the regeneration of ATP, but most are converted to triglyceride by combination with glycerol-3-phosphate derived from glucose. Figure 55.1 shows the metabolic pathways related to adipose cells. When triglyceride is to be oxidized in the body for the provision of energy, it is converted to non-esterified fatty acids (NEFA) and conveyed in the blood to tissues such as liver and muscle, in which fatty acid oxidation readily takes place. In both tissues, the essential part of the process consists of the oxidation in the mitochondria of the long-chain fatty acids. The glycerol of the triglyceride molecule reacts with ATP to form glycerol phosphate, which is oxidized to glyceraldehyde-3-phosphate. This in turn may either be converted to glycogen by reversal of glycolysis, or it may be converted to pyruvate. Skeletal muscle readily oxidizes fatty acids but glucose, if available, is preferentially used. In cardiac muscle, fatty acids are a major source of energy.

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Obesity

Obesity is a condition in which there is excessive fat in the body. It is a disease that is often neglected—indeed, frequently it is not even thought of as a disease but more as a self-inflicted condition, easily prevented and cured by self-control and determination. Unfortunately, this is not just the opinion of lay people but also of doctors. In truth, obesity is a worldwide epidemic. Obesity is given low priority as a medical illness. One reason for some negative attitudes is that, although a positive energy balance, which is the pathogenesis of obesity, should be easy to correct, in practice it is not. Most physicians know this from their own clinical experience—so why spend time and energy? Yet to be obese, or even slightly overweight, is these days totally unfashionable, especially among young women, and obese people may be insulted and bullied [1].

Obesity has been defined as a body mass index (BMI: body weight in kilograms divided by height in metres) above 30 kg/m^2. For example, to be considered as obese, a man whose height is 180 cm must weigh more than 100 kg and a woman of 160 cm more than 75 kg. With this cut-off, the prevalence of obesity in much of Europe is 15–20% of the middle-aged population. This means that countries such as the UK, France and Germany each have 5–10 million inhabitants who are obese and need treatment. A medical problem of this size is probably beyond the capacity of even the best health care system [1]. There has been a dramatic increase in obesity between the 1980s and 1990s in contrast to between the 1960s and early 1980s when the prevalence of obesity changed but little [2].

Obesity is accompanied by complications such as hypertension, non-insulin-dependent diabetes mellitus and atherosclerosis, which in turn cause ischaemic heart disease, stroke and premature death [2–4]. Other complications include certain malignancies such as prostate cancer, sleep apnoea, osteoarthritis and depression.

The alarming increase in diabetes is most probably a consequence of the current rapid rise in the prevalence of obesity. For example, in the UK, average body weight has risen by about 1 kg during the past decade.

Developing countries in other parts of the world are now seeing serious increases in obesity, for example in the Caribbean, South America and South-East Asia [5,6], while in Australian Aborigines and Polynesia figures approaching 80% have been recorded.

Obesity in children is of a special significance, because many obese children remain obese as adults. Observations indicate that the prevalence of childhood obesity is high where adult obesity is common [7,8].

Although precise methods for measuring the distribution of body fat, such as computed tomography (CT) and magnetic resonance imaging (MRI), are available, simpler measurements are required for clinical practice. Waist circumference divided by hip circumference (WHR) can be used for this purpose. The waist is measured, after an overnight fast, halfway between the lower costal margin and the iliac crest, and hip circumference is measured over the widest part of the gluteal region [9]. WHR should not exceed 1.0 in men and 0.85 in women—cut-offs based on Scandinavian data [10]. Waist circumference is another reasonable way of assessing obesity. Circumference values that indicate a significant increased relative risk are more than 88 cm for women and more than 102 cm for men [10].

Measurement of skinfold thickness with callipers is another alternative technique, but there are possible variations in the distribution of fat between subcutaneous areas and deep body fat. The typical female fat distribution (gynoid or 'pear-shape') over the hips, thighs and buttocks is related to energy needs during lactation, and is more healthy than the excess fat that accumulates over the upper trunk and abdomen in the male or android distribution [11–13].

Aetiology. Obesity is the result of genetic, behavioural, environmental, physiological, social and cultural factors that cause energy imbalance and promote excessive fat deposition. Although genes have an important role in the regulation of body weight, the World Health Organization consultation on obesity [6] concluded that behavioural and environmental factors, such as sedentary lifestyles combined with excessive energy intake, are primarily responsible for the dramatic increase in obesity in the last 10–20 years. The precise underlying mechanisms behind imbalance in energy intake and energy expenditure that lead to obesity are still controversial. Obesity is the result of a positive energy balance input that exceeds output. In most populations, obesity is more common among women than men and is a multifactorial phenotype, which may result from a complex network of

genetic and non-genetic factors. The relative importance of genetic factors for obesity is under debate [6,14]. Genome searches, using polymorphic markers in inbred mice with phenotypes that result in extreme obesity, and studies of human candidate genes, are being performed in an attempt to identify genes that contribute to obesity [15,16]. There is evidence that body weight is physiologically regulated [6,17,18], and it has been postulated that the storage of fat may provide signals to the brain that the body is obese, which in turn may make the subject eat less and burn more fuel [19]. One of the molecules that may be involved in such signalling is the obese (*ob*) gene product—leptin [20,21]. Mutations in *ob* result in profound obesity and type II diabetes in mice. The mouse *ob* gene and its human homologue have been cloned and sequenced [22]. The gene is expressed in adipose tissue and the product has features of a secreted protein.

Plasma leptin was found to be highly correlated with BMI [22] in rodents and in 87 lean and obese humans. In humans, there was variability in plasma leptin at each BMI, suggesting that there are differences in its secretion rate from fat. Weight loss because of food restriction was associated with a decrease in plasma leptin in samples from mice and obese humans.

One of the main effects of leptin may be to inhibit synthesis and release of the hypothalamic neuropeptide Y, which increases food intake, decreases thermogenesis and increases levels of insulin and corticosteroid in the plasma [23]. A particularly important effect may be to suppress ingestion of fat without affecting carbohydrate ingestion [23].

In aggregate, these data are consistent with the hypothesis that the size of the adipose tissue mass is in part regulated by a negative-feedback loop in which the level of leptin is a sensed parameter (Fig. 55.2) [24,25].

However, a word of caution on the *ob* gene story is necessary. The investigation of large numbers of obese individuals for abnormalities in the genes for both leptin production [26] and leptin receptors suggests that a genetically faulty system is rare. The raised concentrations of circulating leptin found in obesity are probably a consequence of an enlargement of the producing tissue, adipose tissue. Leptin may therefore be of limited interest for the pathogenesis of obesity in humans, and this may turn out to be true for other genes that are important for obesity in genetically obese animal models. This should not, however, diminish the importance of these discoveries for our understanding of the physiological regulation of energy balance, and they might even open up the study of the regulatory events that occur as a consequence of the leptin signal to the hypothalamus [1].

Genotype–environmental interreactions also have been implicated in the development of obesity [27]. Bouchard *et al*. [28] demonstrated that the amount of body weight and fat gained, as well as the distribution of fat gained in response to overfeeding, had greater similarity within identical twin pairs, further supporting the heritability of the tendency to become overweight or obese.

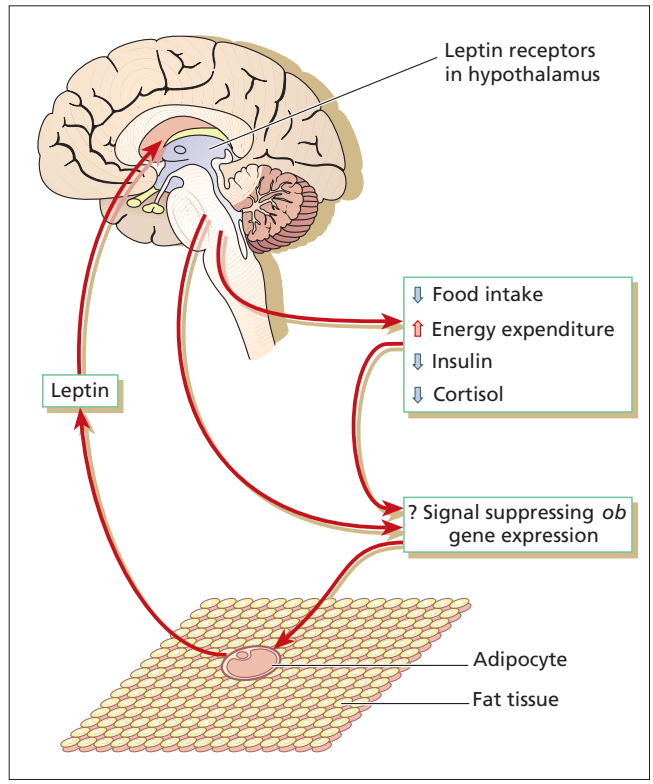

Fig. 55.2 Neurohormonal control of adipose tissue.

In accordance with the first law of thermodynamics (energy cannot be created or destroyed), excess energy is stored as tricyglcerols in adipose tissue. The primary functions of adipocytes are to store energy when calories are in excess, and to mobilize energy from this fatty source when energy needs exceed intake [29]. Weight gain during adulthood is characterized predominantly by adipocyte hypertrophy, a process by which adipocytes can increase their volume some several thousand-fold to accommodate large increases in fat.

Prevention and treatment. The aim of obesity treatment is to achieve and then maintain clinically meaningful weight loss, with the ultimate aim of reducing the risk for or severity of obesity-related diseases. Measures directed at improving public health awareness should be given high priority in national efforts; they include information campaigns, making exercise-sparing devices such as escalators less readily available, and establishing bicycle and walking lanes in cities. Despite an increased focus on nutrition, an increased awareness of the energy and fat content of foods, and the availability of various reduced-fat, fat-free and sugar-free food and beverages, obesity continues to increase [30].

Effective therapeutic regimens for treating obesity should incorporate multiple approaches to encourage behavioural change or modification and create strategies to facilitate consistent and long-term follow-through [30]. Numerous options are available [31,32], including reduced-energy diets, physical activity and exercise, behavioural modification, pharmacotherapy and surgery.

The principle for treatment, self-evidently, is to induce a negative energy balance. Short-term weight loss is easy, but long-term weight maintenance after that is unusual [30,33]. Powerful but insufficiently understood regulatory factors strive to induce regain of the weight lost. The body weight itself is often not the most important problem, unless it is affecting mobility. It is the morbidity associated with the metabolic complications that is of major concern, and this can improve rapidly even after a limited loss of weight. A normal body weight is not necessary, and is often unrealistic in the long term.

Reduced energy intake must be individually tailored to allow normal activities. A deficit of 500–600 kcal (0.210–0.251 mJ) per day is usually well tolerated. Emphasis should be placed on fat intake and on the energy density of food. Involvement of family is important [34]. A combination of exercise and diet is more effective than either alone [33], and long-term low-intensity exercise such as walking is as effective as high-intensity activities [35]. This is important because most obese patients are unaccustomed to sporting activities and will drop out of vigorous regimens.

Behaviour modification is an important component of all weight loss programmes [36,37]. Frequently, behavioural strategies are targeted toward identifying stimuli that signal unhealthy behaviours such as binge eating, learning about the role of readiness in initiating or continuing positive behaviours [38], and recognizing barriers that may compromise healthy pursuits.

Pharmacological agents may be used in conjunction with diet, exercise and behavioural strategies when non-pharmacological approaches have failed to produce a success. Several appetite-suppressant drugs are approved for weight loss and the reader is referred to authoritative sources on the subject [30].

Surgery is reserved for cases of extreme obesity (BMI over 40 kg/m^2). One of the most common procedures is gastric bypass surgery.

An excellent review on the aetiology prevalence and treatment of obesity is by Racette *et al*. [30].

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Cellulite

Cellulite is an alteration of the topography of the skin that occurs mainly in women in the pelvic region, the limbs and abdomen. It is characterized by a padded or orange peel appearance.

Many authors confuse cellulite with obesity. However this is incorrect; in obesity only adipocyte hypertrophy and hyperplasia occurs [1], whereas in cellulite there are several structural alterations in the dermis, in the local microcirculation and within the adipocytes. These may result in further morphological, histochemical and biochemical modifications [2–5].

Cellulite may be classified in at least two ways. One classification divides cellulite into four stages according to the histopathological and clinical changes [1].

Grade 1. The patient has no symptoms and there are no clinical alterations. Histologically, there may be an increased thickness of the areolar layer, increased capillary permeability and microhaemorrhages.

Grade 2. There are no obvious changes in the skin at rest, but after skin compression or muscular contraction small dimples, local pallor, decreased temperature and decreased elasticity may be evident.

Grade 3. A padded skin or an orange peel appearance is evident at rest, and there is a slight feeling of granularity in the deeper parts of the skin on palpation, which may be associated with some pain. At this stage, there is the beginning histologically of fatty tissue destruction and the formation of micronodules.

Grade 4. This stage is characterized by changes seen in grade 3 but with more visible palpable and painful nodules and an obvious wavy appearance of the skin surface. Histopathologically, the lobular structure of the fatty tissue has disappeared and some nodules are encapsulated by dense connective tissue and there may be much fibrosis.

Cellulite may also be classified by the consistency of the skin—being hard, flaccid, oedematous or mixed [6]. Hard cellulite is observed in young women who perform regular physical activity. The appearance is of compact firm tissues and is not changed according to position. Flaccid cellulite is characteristically found in inactive women, especially if they have suddenly lost weight. In contrast, oedematous cellulite presents as an increased volume of the entire affected limb, and is associated with depression of the tissue to fingertip palpation, which persists when the finger is removed.

Aetiology. Just what precisely triggers the histopathological and clinical changes of cellulite is poorly understood. Hormonal factors may play a predisposing or aggravating part. Oestrogen is probably the most important hormone. Evidence for oestrogen involvement includes the fact that cellulite predominantly occurs in females, the onset of the disease after puberty, aggravation of the condition during pregnancy, menstruation and with oestrogen therapy [7].

A genetic predisposition may also be important. White women tend to be more prone to cellulite than Asian or black women and Latin women develop cellulite on the hips while Anglo-Saxon women develop cellulite on the abdomen.

Sedentary lifestyle contributes to the aggravation of cellulite as a consequence of a decrease in muscle mass, and the consequent decreased muscular pumping mechanism in the lower limbs inhibiting venous return. Obesity contributes to the problem by increasing the fatty mass. Factors that act as a mechanical barrier to the venous return are also likely to be important: tight clothes and pregnancy may be important in this context.

Treatment. Because of the multifactorial pathogenesis of cellulite, there are numerous therapeutic approaches—especially because many of the treatments are much less than optimal in their success. Treatments include reduction in aggravating factors, the use of physical and mechanical methods, and pharmacological agents.

Attempts to reduce weight, regular exercise and the use of non-hormonal contraceptives need to be encouraged. Physical therapies include ultrasound, thermotherapy, pressotherapy and lymphatic drainage. Several pharmacological agents have been tried, but adequate double-blind placebo-controlled studies are relatively lacking. The reader is referred to specialized texts on this topic [7]. A number of products for systemic and topical use have been developed but most have little scientific basis.

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General pathology of adipose tissue: panniculitis [1–11]

Inflammatory disorders of the subcutaneous fat present an important diagnostic challenge to the dermatologist, because the lesions often develop as subcutaneous nodules or plaques. An adequate diagnostic biopsy is essential as a prerequisite to accurate diagnosis in almost all instances. A larger scalpel incisional biopsy is preferred, which obviously should extend deeply through the subcutis. Conventional punch biopsies (4 mm or smaller) are totally inadequate, as the tissue tapers down to leave little, if any, subcutaneous tissue. However, trephine punches are adequate and provide acceptable cosmetic results [10]. The pathologist may well need to cut serial sections, as some of the panniculitides are characterized by rather focal or even scattered pathological changes, and to look for evidence of damage to larger blood vessels.

Most panniculitides are persistent, lasting for weeks or months. For diagnostic purposes, the biopsy should be taken from an active earlier lesion: erythematous, indurated and usually tender. Although subcutaneous tissue has a rich capillary blood supply closely applied to fat cells, there are no lymphatics and very little intervening connective tissue [11]. Furthermore, the vasculature in the subcutis area is slow flowing. This renders the subcutaneous fat vulnerable to a variety of noxious insults [9]; for example, cold injury or enzymatic damage.

The sequence of cellular events following injury to the subcutis may take weeks or months to fully evolve, and is usually as follows [1,2]:

Neutrophils (eosinophils)
↓
Lymphocytes
↓
Histiocytes (granulomatous 'foamy macrophages')
↓
Fibroblasts (fibrosis)

The histological changes of the granulomatous stage are not necessarily diagnostic. When fat cells are damaged, the liberated lipid undergoes hydrolysis to glycerol and fatty acids, which usually provoke a foreign-body-type granulomatous reaction. Macrophages are attracted and foam cells are produced. After the phase of reaction to released lipocyte products, there is a period of reconstitution, the ease of repair depending on the extent of the initial lipocyte damage and the efficiency of the local circulation.

Atrophy of subcutaneous tissue (lipoatrophy) is a consequence of some types of inflammation in the fat lobules. In other instances, extensive fibrosis is inevitable after damage to subcutis, resulting in the formation of chronic subcutaneous fibrotic nodules.

In certain types of panniculitis, an ongoing slow chain reaction is set up, in which small foci of fat necrosis provoke a peripheral inflammatory reaction, which in itself leads to further peripheral fat necrosis, thus allowing the lesion to spread centrifugally. It is therefore clear that the histological findings will differ, depending on the age of the lesion biopsied.

In difficult cases of panniculitis, the author (MMB) recommends that it may well be helpful to submit more than one biopsy from lesions at different stages of their clinical evolution. Polarization of sections should be routinely performed to look for crystalline material, and in certain clinical situations extra tissue should be submitted for bacterial or fungal culture.

Classification of panniculitis [1–4]

1 Septal panniculitis:
- (a) erythema nodosum (see Chapter 49)
- (b) erythema nodosum migrans (see Chapter 49); (subacute nodular migratory paniniculitis)
- (c) eosinophilic panniculitis (this condition may overlap with lobular or mixed panniculitis)

2 Lobular panniculitis:
- (a) relapsing febrile nodular panniculitis (Weber–Christian syndrome)
- (b) idiopathic nodular panniculitis
- (c) lipoatrophic panniculitis (formerly Rothman–Makai syndrome)
- (d) panniculitis associated with crystal deposition—sclerema neonatorum (see Chapter 14), subcutaneous fat necrosis of newborn (see Chapter 14), gout or factitial panniculitis, poststeroid panniculitis
- (e) enzymic (pancreatic) panniculitis
- (f) α_1-antitrypsin deficiency panniculitis
- (g) fat necrosis—cold injury, nodular cystic fat necrosis, lipomembranous
- (h) lymphomatous panniculitis
- (i) cytophagic histiocytic panniculitis

3 Mixed panniculitis:
- (a) lupus erythematous profundus
- (b) scleroderma (fasciitis with eosinophilia)
- (c) connective-tissue panniculitis (overlaps with lipoatrophic panniculitis)
- (d) subcutaneous sarcoidosis (see Chapter 58)
- (e) subcutaneous granuloma annulare (see Chapter 57)
- (f) necrobiosis lipoidica (see Chapter 57)
- (g) infective panniculitis (e.g. opportunistic bacterial or fungal infections)
- (h) physical and factitious panniculitis (e.g. sclerosing lipogranuloma, oil granuloma)
- (i) sclerosing panniculitis (lipodermatosclerosis)
- (j) fasciitis—panniculitis syndrome

4 Panniculitis with vasculitis (see Chapter 49):
- (a) small-vessel vasculitis—leukocytoclastic vasculitis
- (b) large-vessel vasculitis—polyarteritis nodosa, thrombophlebitis, nodular vasculitis (erythema induratum)

(c) neutrophilic panniculitis
(d) oedematous scarring vasculitic panniculitis.

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Inflammatory disorders of subcutaneous fat

Septal panniculitis

Erythema nodosum (see Chapter 49)

Although erythema nodosum is the prototype of a septal panniculitis, the inflammatory changes always involve the overlying dermis. In acute lesions, there is oedema of the septae with transudation of neutrophils, and sometimes eosinophils, into the septae and adjacent margin of fat lobules. In older lesions, the infiltrate becomes lymphohistiocytic and finally granulomatous, before the septae became thickened and finally fibrotic. Radial granulomas (Miescher) are often found in the interlobular septae in erythema nodosum [1]. There is still some debate as to whether *erythema nodosum migrans* (subacute nodular migratory panniculitis) [2–4] and the chronic and granulomatous forms of erythema nodosum [5] are variants of the same pathological process. Erythema nodosum migrans tends to be characterized by markedly thickened and fibrotic septae, marked capillary proliferation and a massive granulomatous reaction (with giant cells) along the borders of the widened septae [6].

Eosinophilic panniculitis

Eosinophilic panniculitis is characterized by a prominent infiltration of subcutaneous fat with eosinophils, and has been identified in patients presenting with a variety of associated clinical conditions [7–14].

The inflammatory infiltrate, including eosinophils, occurs principally within the septae but can involve the lobules. The overlying dermis is often involved, closely resembling eosinophilic cellulitis (Wells' syndrome) [9]. Fragmented eosinophilic granules (flame figures) are occasionally seen (Fig. 55.3). The current view of eosinophilic panniculitis is that it is not a disease entity, but it can be principally considered as a reactive process, often associated with a systemic condition [8].

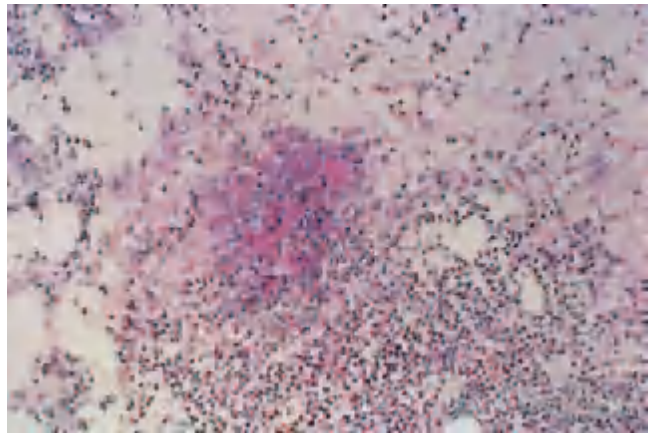

Fig. 55.3 Eosinophilic panniculitis. H&E, × 40.

More common causes of eosinophilic panniculitis include arthropod bites, atopic eczema, erythema nodosum, infectious causes (*Gnathostoma*, *Streptococcus*, *Toxocara*) and leukocytoclastic vasculitis [8]. The condition has also been associated with chronic recurrent parotitis [11], lupus panniculitis, morphoea profundus [12] and fasciola hepatica infection [13]. Fortunately, only very rarely is eosinophilic panniculitis associated with malignancy, either leukaemia [14] or a solid tumour [9].

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Lobular panniculitis

Relapsing febrile nodular panniculitis

SYN. WEBER–CHRISTIAN SYNDROME

Relapsing febrile nodular panniculitis was first described by Pfeifer in 1892 [1]. The term Weber–Christian syndrome came to be used following the cases reported by Weber [2] and Christian [3]. Weber–Christian syndrome encompasses a febrile disease, characterized by the recurrent formation of single or multiple crops of tender inflammatory nodules in the subcutaneous fat. Because the range of clinical features differed, and the extent of systemic involvement varied, the concept of Weber–Christian syndrome never became popular and the view was put forward that it should not be considered to be a distinct entity [4–6]. The term nodular panniculitis was preferred [5]. Nodular panniculitis is essentially a lobular panniculitis in which fat necrosis develops in the absence of overt vasculitis.

Macrophages ingest fat released from damaged lipocytes, thus producing a characteristic foamy appearance. In some cases, liquefactive nodules appear, which ulcerate and discharge an oily yellow liquid [7]. In others, there is more systemic involvement, which may affect visceral fat or even the myocardium [8].

Nodular panniculitis can affect both adults and children, when it can occur in early infancy [9,10]. However, it must be stressed that nodular panniculitis or Weber–Christian syndrome may not be a distinct disease entity. On further investigation, many cases of nodular panniculitis can be subsequently reclassified depending on their cause; for example, pancreatic panniculitis, α_1-antitrypsin deficiency or cytophagic panniculitis. However, there are undoubtedly some cases of nodular panniculitis, in both children and adults, in which the aetiology remains to be determined.

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Idiopathic nodular panniculitis

An idiopathic condition characterized by recurrent crops of nodular panniculitis. Some cases are accompanied by fever, malaise, abdominal pain and arthritis. As indicated, the term Weber–Christian syndrome is best avoided. Many cases of nodular panniculitis can now be attributed to specific causes (see below).

Pathology. The histological changes are non-specific but the panniculitis is mainly lobular [1] (Fig. 55.4). In the early stages, the fat lobules are infiltrated with acute inflammatory cells, producing a pseudopyogenic reaction. Later, lymphocytes and macrophages appear to ingest the fat released from damaged lipocytes. These lipophages develop a characteristic foamy cytoplasm, producing the typical appearance of a lipophagic granuloma (Fig. 55.5). Healing is by fibrosis, the fibrocytes invading the lobules from the fibrous septae and ultimately producing complete lobular fibrosis.

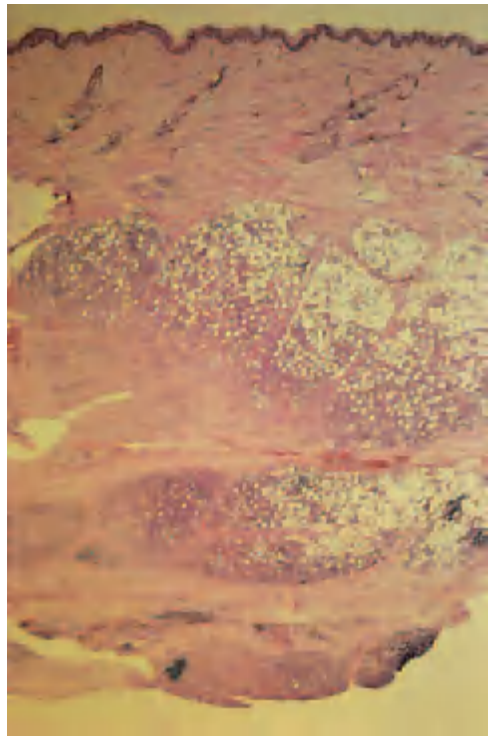

Fig. 55.4 Idiopathic nodular panniculitis. Low-power view showing lobular pattern of panniculitis. H&E, × 2.5.

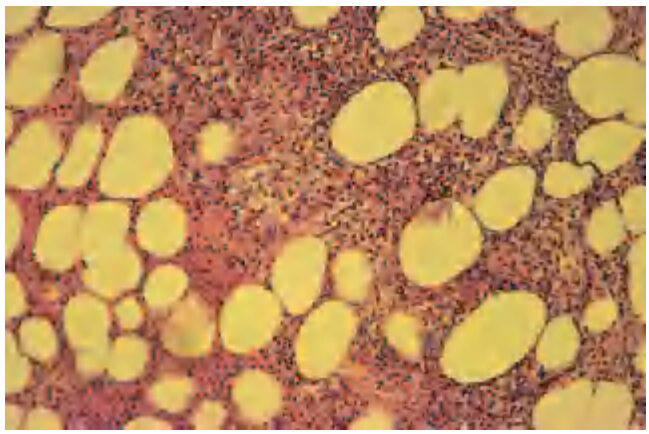

Fig. 55.5 Idiopathic nodular panniculitis: typical appearances of a lipophagic granuloma. H&E, × 40.

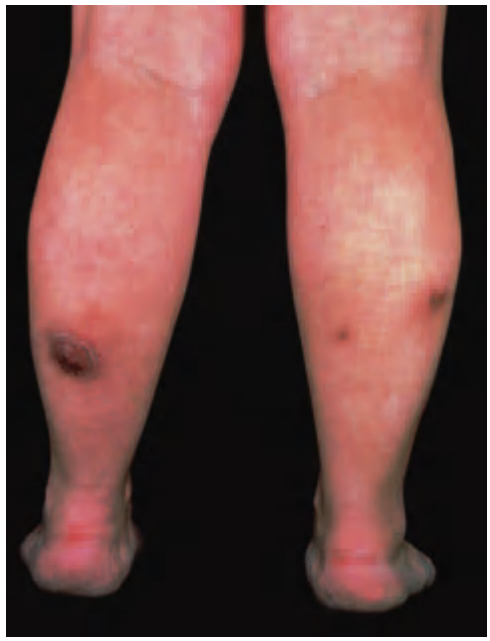

Fig. 55.6 Idiopathic nodular panniculitis.

Clinical features. Approximately 50% of cases of nodular panniculitis are idiopathic [2]. All ages may be affected, but the condition is very rare in childhood [3,4]. The majority of cases are young adult females who develop crops of dull-red tender subcutaneous nodules, usually about 1–2 cm in diameter. The lesions tend to be maximal on the lower limbs (Fig. 55.6), although the trunk and face can be affected.

Systemic features including fever, malaise, myalgia, arthralgia and weight loss are often present when there are multiple lesions. Many of the nodules eventually resolve, leaving a pigmented area or an atrophic depression. In a few cases, there may be overlying necrosis with drainage of oily brownish serous fluid (Fig. 55.7), eventually leading to scarring. Rarely, there may be involvement of visceral fat, including the heart, lungs, liver and kidneys, which may lead to death [5].

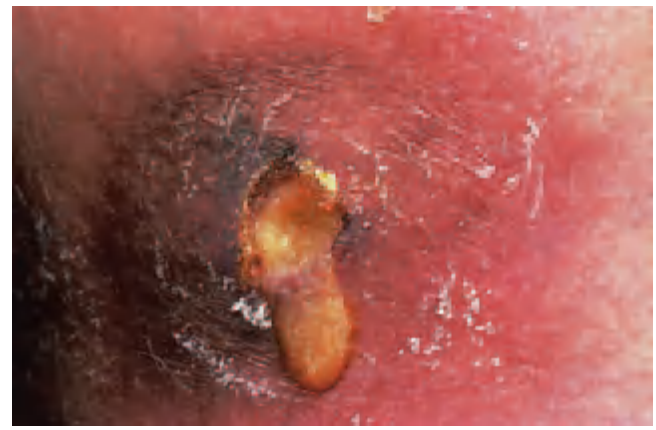

Fig. 55.7 Idiopathic nodular panniculitis: drainage of serous fluid.

The laboratory features are non-specific, but there may be anaemia, leukocytosis or leukopenia, thrombocytopenia and a raised erythrocyte sedimentation rate.

Diagnosis. Idiopathic nodular panniculitis has to be distinguished from other forms of panniculitis (see below). It is important to perform repeated laboratory tests for pancreatic disease, autoimmune disease, complement deficiency, α_1-antitrypsin deficiency, and to exclude cytophagic histiocytic panniculitis. The possibility of factitial or infective panniculitis must also be considered.

Prognosis. When only subcutaneous fat is involved, the prognosis is good [2]. Some cases recover after a few months, and permanent remission within 2–5 years is usual. Rarely, recurrences may continue for 10 years or longer, but without serious deterioration of the general condition. Exceptionally, the condition can be fatal if there is visceral involvement [5].

Treatment. Once the possibility of systemic disease has been excluded, the treatment is mainly symptomatic. Analgesics may be needed to alleviate pain, and ulceration may need bland aseptic dressings. In severe cases, systemic corticosteroids may be effective, provided adequate dosage (up to 80 mg/day prednisolone) is used for 7–10 days. The dosage should then be slowly tapered over a period of 4–6 weeks. Other treatments that have helped in some cases include antimalarials [6] and thalidomide [7].

Unusual causes of lobular panniculitis resembling idiopathic nodular panniculitis

Increasing numbers of case reports, usually isolated, are appearing that link nodular panniculitis to other illnesses

or events. Autoimmune diseases such as Sjögren's syndrome have been linked to a lobular plasma cell panniculitis [8], and ulcerative colitis and myopathy with nodular panniculitis [9].

Infections, for example hepatitis A [10] and *Borrelia burgdorferi* [11,12], have also been implicated in the causation of nodular panniculitis. Granulomatous panniculitis has been associated with crescentic glomerulonephritis [13]. Lobular panniculitis has been reported to develop at the site of interleukin-2 injections for treatment of metastatic carcinoma, and to be exacerbated by intravenous use of the same treatment [14]. Oral administration of the low-calorie artificial sweetener aspartame (NutraSweet®) has been implicated in the causation of lobular panniculitis [15].

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Lipoatrophic panniculitis

SYN. CONNECTIVE TISSUE PANNICULITIS; AUTOIMMUNE PANNICULITIS

As the name implies, lipoatrophic panniculitis denotes the findings of prominent lipoatrophy. However, the development of lipoatrophy should be considered to be an 'end-stage' process, which is preceded by inflammation in the fat lobules and sometimes the fibrous septae. In the earlier literature, many cases of lipoatrophic panniculitis were considered to have Weber–Christian syndrome or Rothman–Makai syndrome [1]. As the aetiology of lipoatrophic panniculitis is unknown, it is perhaps not surprising that the nomenclature remains confused, and almost certainly there is considerable overlap in these clinical entities. 'Primary' lipophagic panniculitis has been described in adults (Fig. 55.8) [2] and children [3,4], either as an acute benign condition or as a chronic recurrent disabling disease. In children, a granulomatous histopathology can be seen prior to the development of lipoatrophy, for which the term lipophagic panniculitis is used [4]. Connective tissue panniculitis is a rare form of panniculitis, affecting septae and lobules, and leading to prominent lipoatrophy [5] (Fig. 55.9). The condition has been described in female adults and children [6]. Episodes of intense lymphocytic panniculitis lead to lipoatrophy. At various times in the illness, a circulating antinuclear antibody and/or SSB (La) antibodies may be detected [5,6]. A recent report has strengthened the view that the clinical spectrum of lipoatrophic panniculitis encompasses connective tissue panniculitis [7]. Histologically, in connective tissue panniculitis there is no evidence of hyalinization of fat and collagen, which is typical of lupus erythematosus profundus [8]. Various other autoimmune diseases have been reported in association with lipoatrophic panniculitis, including diabetes mellitus, rheumatoid arthritis and Hashimoto's thyroiditis [3]. Lipoatrophic

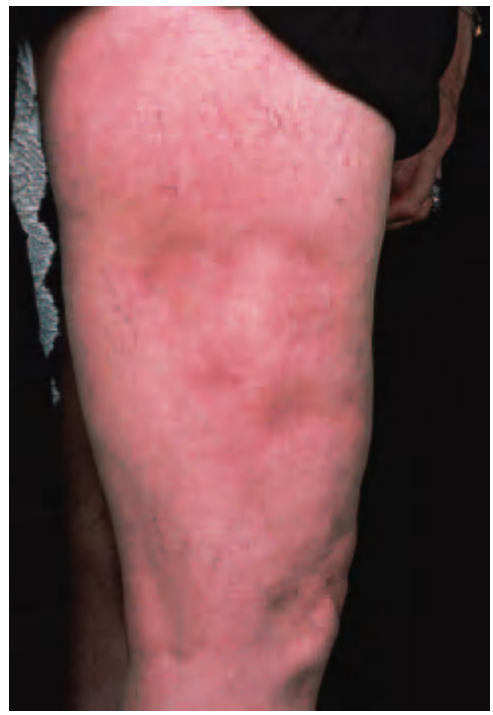

Fig. 55.8 Lipoatrophic panniculitis: recurrent episodes of panniculitis have resolved to leave prominent lipoatrophy on the outer thigh. (Courtesy of St John's Institute of Dermatology, London, UK.)

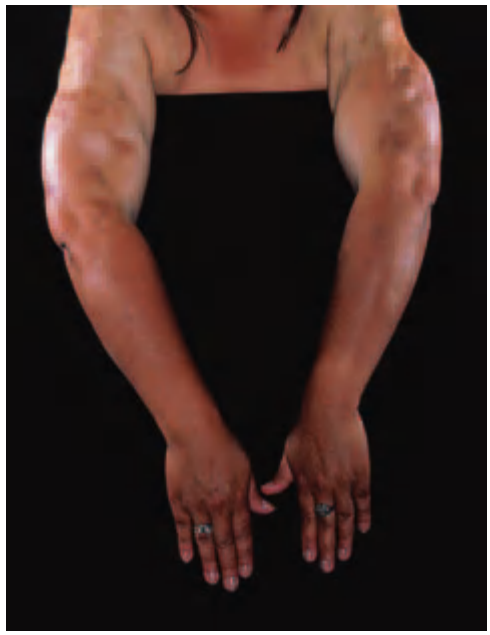

Fig. 55.9 Lipoatrophic (connective tissue) panniculitis: note the dimpled atrophic fat of the upper arms. (Courtesy of Dr M.R. Pittelkow, Mayo Clinic, Rochester, MN, USA.)

panniculitis has been reported in a very young child with a chromosomal abnormality on chromosone 10q26 [9].

Treatment. Systemic corticosteroids are effective, but usually only in higher doses. Antimalarial therapy, hydroxychloroquine or chloroquine, is the most effective acceptable treatment [10], but may not be sufficient alone [5,7]. Reconstructive surgery, in the form of vascular pedicles or alloplastic implants, has been successfully used in severe cases of lipoatrophic panniculitis [7].

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Panniculitis associated with crystal deposition

Polarization of skin histology is important in the assessment of any inflammatory or granulomatous type of panniculitis, as it may be the only way to identify crystals readily [1].

Lipid-containing crystals are dissolved out during formalin fixation, but usually leave cleft-like spaces, which often produce a characteristic histology. Needle-shaped clefts are characteristically seen in subcutaneous fat necrosis of the newborn (see Chapter 14), sclerema neonatorum (see Chapter 14) and post-steroid panniculitis. Cholesterol crystals may cause panniculitis, but the crystals are only found in the lumen of smaller blood vessels.

Post-steroid panniculitis [2–5]

Post-steroid panniculitis is now undoubtedly very rare. All the reported cases have been in children, in whom subcutaneous nodules developed 1–13 days after stopping high doses of systemic corticosteroids quickly. The nodules vary in size from 0.5 to 4 cm, and tend to localize in those areas where there is the greatest accumulation of fat from steroid therapy. Although the nodules appear after the rapid discontinuation of steroids, they are not associated with systemic manifestations of the steroid-withdrawal syndrome. Resolution of the nodules is gradual, occurring over several weeks or months. There is no effective treatment.

The histology of post-steroid panniculitis is very similar to that of subcutaneous fat necrosis of the newborn, in that needle-shaped crystals may be found within lipocytes and histiocytes.

Calcifying panniculitis with renal failure [6]

In patients with chronic renal failure, a chronic alteration of calcium and phosphate metabolism often exists, and secondarily causes hyperparathyroidism. High parathyroid hormone levels lead to the processes of calciphylaxis and metastatic calcification [7,8]. The calcification is principally present within smaller and medium-sized arteries. Trauma to the subcutis can initiate a process of fat necrosis with sometimes distressing consequences. The process begins with erythematous tender nodules or plaques that progress to violaceous livedo-like areas, usually located on the thighs, abdomen or buttocks. These lesions tend to increase rapidly in size, progressing to large necrotic ulcers. Cutaneous necrosis mimicking calciphylaxis in renal failure has been reported resulting from oxalate crystal deposition [9]. Treatment should be aimed at preventing the hyperparathyroidism and secondary infection, but usually the disease has a high mortality.

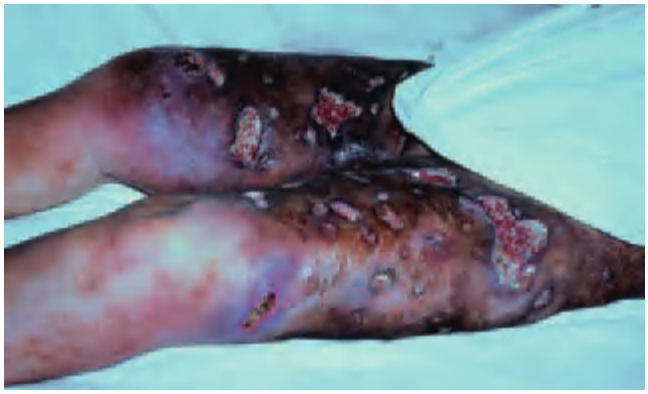

Fig. 55.10 Ulceration of the thighs secondary to panniculitis caused by injections of pentazocine. (Courtesy of Dr R.F. Palestine, Mayo Clinic, Rochester, MN, USA.)

Gout

Urate crystals are inflammatory, and occasionally lobular panniculitis can be caused by deposition of crystals secondary to hyperuricaemia [10,11]. Urate crystals can be distinguished by their fine needle-like shape and tendency to form sheaves.

Drugs

Lobular panniculitis with crystals can occur following injection of drugs such as meperidine and pentazocine (Fig. 55.10) [12,13].

Crystal-storing histiocytosis

Crystal-storing histiocytosis is a rare condition in which tumorous deposits of histiocytes containing crystalline immunoglobulins are deposited in soft tissue. The condition has been reported to cause panniculitis of Weber–Christian type in a patient with lymphoblastic lymphoma [14].

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Enzymic panniculitis

SYN. PANCREATIC PANNICULITIS [1]

Clinically, enzymic panniculitis overlaps closely with nodular panniculitis (Weber–Christian type) and leads to foci of subcutaneous fat necrosis. Systemic features are quite common, including arthritis, pleural effusions and ascites. The erythematous subcutaneous nodules tend to be present in the distal part of the extremities (often around periarticular areas). In milder cases, the nodule(s) can be single and resolve without ulcerating [2], but usually they evolve into sterile necrotic abscesses, which spontaneously ulcerate and exude a thick brown oily material, which represents adipose tissue that has undergone liquefaction necrosis (Fig. 55.11).

Subcutaneous fat necrosis affects 2–3% of all patients with diseases of the pancreas [3]. It appears that all three pancreatic enzymes (lipase, trypsin and amylase) are needed to induce fat necrosis [4]. In 40% of cases associated with pancreatic-induced subcutaneous fat necrosis, the skin lesions were the presenting feature [5]. Monoarticular or oligoarticular arthritic symptoms are common, and may also precede diagnosis of pancreatic disease [6]. The nature of the pancreatic pathology can vary widely. Surgical correction of an anatomical ductal

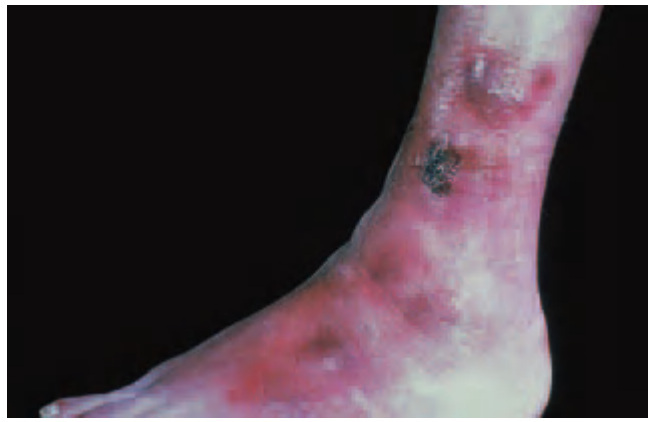

Fig. 55.11 Enzymic (pancreatic) panniculitis: suppurative nodules occurring around the ankles in a patient with pancreatic carcinoma. (Courtesy of Dr D.H. McGibbon, St John's Institute of Dermatology, London, UK.)

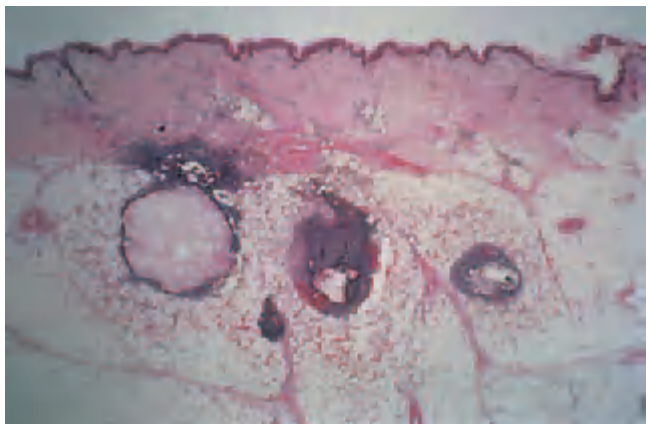

Fig. 55.12 Enzymic (pancreatic) panniculitis: low-power view showing foci of fat necrosis in lobules. H&E, × 4.

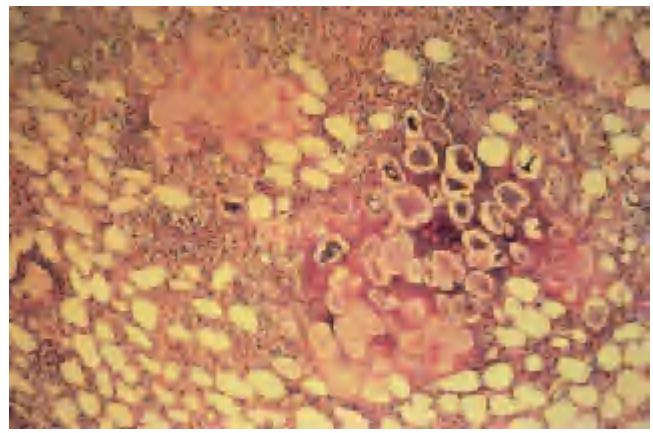

Fig. 55.13 Enzymic (pancreatic) panniculitis: coagulative necrosis of lipocytes, associated with ghosts of lipocytes and focal calcification. H&E, × 40.

anomaly [7] or pancreatic pseudocyst [8] can result in complete resolution of panniculitis.

The syndrome has been described in post-traumatic pancreatitis [9], acute and chronic pancreatitis [10] and pancreatic carcinoma [1]. CT can be useful in delineating the pancreatic lesion, as well as outlining areas of subcutaneous fat necrosis [11]. Rarely, acute panniculitis can be associated with a high urinary amylase excretion in the absence of overt pancreatic disease [12]. The association of subcutaneous fat necrosis with pancreatic disease has been reported in systemic lupus erythematosus [13].

Pancreatic panniculitis has recently been reported in association with primary human immunodeficiency virus (HIV) infection and a haemophagocytic syndrome [14].

The histological changes of pancreatic panniculitis are unique but rarely encountered. Focal fat necrosis in the lobules occurs, which is probably initiated by circulating enzymes (Fig. 55.12). A characteristic coagulative necrosis of lipocytes ensues, which leads to ghosts of lipocytes and varying degrees of calcification [1]. In older lesions, fat necrosis and 'ghost' lipocytes become less prominent, and are replaced by a granulomatous infiltrate with Langhans' giant cells [1] (Fig. 55.13). In the very early stages of pancreatic panniculitis, a septal pattern of inflammatory involvement has been described [15].

The treatment of pancreatic panniculitis is primarily supportive and dependent on the underlying pancreatic pathology. Occasionally, complete resolution of symptoms occurs when gallstones are removed [16] or when an anatomical ductal anomaly has been divided [7]. Usually, the prognosis is gloomy. In a review of 27 patients with pancreatic panniculitis, all eight cases with pancreatic carcinoma and 42% of the 19 patients with pancreatitis died of their disease [17].

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α_1-Antitrypsin-deficiency panniculitis

Subcutaneous panniculitis simulating Weber–Christian syndrome may be associated with deficiency of α_1-protease inhibitor (α_1-antitrypsin) [1].

Aetiology. Severe deficiency of this important inhibitor in the blood is inherited as the ZZ phenotype, which

occurs in about 1 in 2500 people [2]. Severe deficiencies of α_1-antitrypsin can be associated with emphysema, hepatitis, cirrhosis, vasculitis, urticaria, angio-oedema and panniculitis.

Homozygous deficiency with phenotype ZZ is the most commonly associated with panniculitis, although heterozygous deficiency with phenotype MZ has also been implicated [2,3].

α_1-Antitrypsin inhibits trypsin activity, but it is also active against neutrophil elastase, pancreatic elastase, serine proteases, collagenase, factor VIII and kallikrein [4].

The exact pathogenesis of the panniculitis is obscure, but deficiency of α_1-antitrypsin could accelerate the activation of lymphocytes and phagocytes, thus producing severe inflammation as well as tissue necrosis secondary to protease action.

Pathology. Characteristically, the panniculitis is severely necrotic and suppurative, involving lobules and septae. Vasculitis, haemorrhage or phlebothrombosis can occur in areas of severe inflammation. The end result can be extensive liquefactive necrosis of the dermis and fibrous septae in the subcutis, leading to transepidermal elimination of necrotic material. Even so, large areas of normal fat can be found adjacent to necrotic lobular and septal areas, which contain abundant polymorphonuclear leukocytes and macrophages [5]. In the earliest stage of inflammation, splaying of neutrophils between collagen bundles in the reticular dermis has been noted [6].

Clinical features. The age of onset of the panniculitis ranges from infancy to old age. Early lesions may resemble a cellulitis, as has been described in Marshall's syndrome (Sweet's syndrome leading to acquired cutis laxa), which has been reported to be associated with α_1-antitrypsin deficiency, and may represent part of the disease spectrum [7]. A clue to the diagnosis of α_1-antitrypsin deficiency is that the ulcerative lesions occur predominantly on the trunk and proximal extremities [2] (Fig. 55.14). The clinical findings of ulcerative panniculitis, combined with the histological findings of acute inflammation, necrosis and haemorrhage, certainly justify investigation of α_1-antitrypsin blood levels. Some of the lesions may be precipitated by trauma, and can be exacerbated by surgical débridement [5]. Even cryosurgery has been implicated [8].

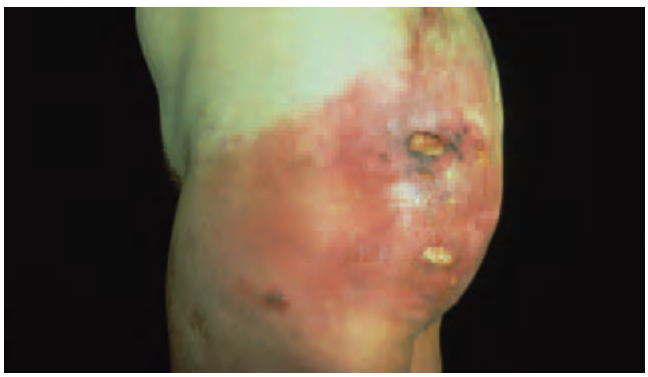

Fig. 55.14 Severe suppurative panniculitis secondary to deficiency of α_1-antitrypsin. (Courtesy of Dr M.R. Pittelkow, Mayo Clinic, Rochester, MN, USA.)

Treatment. Dapsone [9] or doxycycline [10] can be very effective in controlling panniculitis [2,9] while systemic steroids, antimalarials and immunosuppressive drugs often give an inconsistent response. For patients with more severe manifestations of disease (e.g. emphysema, lung fibrosis and liver failure), replacement with α_1-antitrypsin offers a valuable treatment. Each patient requires approximately 10 g/month; the treatment is expensive. The creation of transgenic sheep to produce sufficient α_1-antitrypsin is being explored [11].

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Fat necrosis

Fat necrosis is often an important accompanying feature in panniculitis, and can be prominent enough and sufficiently distinctive to merit separate description. Insults to the fat, including cold injury [1] or trauma [2], are well known to cause fat necrosis, often when there is accompanying venous insufficiency in the lower legs.

Cold panniculitis

SYN. ADIPONECROSIS E FRIGORE (HAXTHAUSEN) [1]

Cold panniculitis is a form of localized panniculitis that results from cold injury to subcutaneous fat.

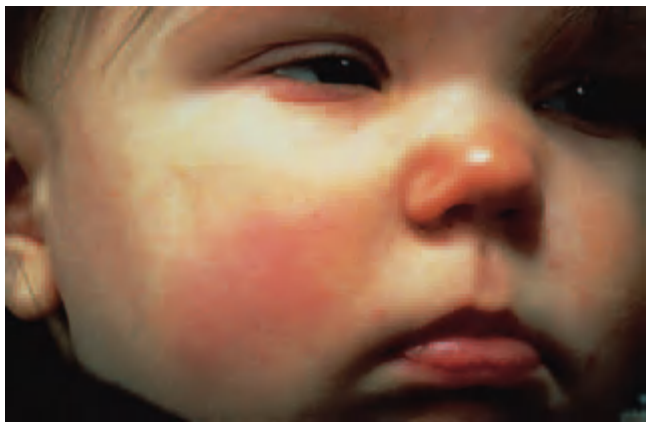

Fig. 55.15 Cold panniculitis: erythematous nodular area on the malar region of a 6-month-old infant which developed after exposure to a very cold wind. (Courtesy of Dr D.J. Atherton, St John's Institute of Dermatology, London, UK.)

Clinical features. The condition has been reported in neonates [3], children [1,4] and adults, notably as a consequence to ice cubes [5], ice packs [3] or exposure to freezing air temperatures, particularly in adults with a chilblain-type of circulation [6].

Some 48–72 h after cold exposure, the affected areas become indurated with an ill-defined margin. The skin may be red or bluish and the area is usually cold to the touch (Fig. 55.15). The subject may complain of a cold sensation or a dull ache. If the area is kept warm, the subcutaneous plaques slowly soften and resolve over weeks without scarring. Cold panniculitis of the thighs or buttocks may occur in skiers or horse riders who wear inadequate clothing [6], although in this situation perniosis is more common than true panniculitis [7]. Children sucking ice lollies (popsicles) can induce cold panniculitis in the facial subcutaneous tissues [8].

Differential diagnosis. The clinical appearances may resemble other forms of panniculitis (especially erythema induratum) but can usually be distinguished by the location and history of prior cold exposure.

Treatment. Cold panniculitis resolves spontaneously if further exposure to cold injury is avoided. In horse riders, tight jeans should be replaced by several layers of looser and thicker clothing. If the limb becomes thoroughly chilled, rapid rewarming should be avoided. Vasodilators tend not to be helpful [9].

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Nodular cystic fat necrosis [1]

SYN. ENCAPSULATED FAT NECROSIS [2]

The term denotes a characteristic form of encapsulated subcutaneous fat necrosis that presents as solitary or multiple subcutaneous nodules.

Aetiology. Early lesions begin as lobules of adipose tissue, which, because of compromised blood supply, often following trauma, become separated from the surrounding tissue [3]. These lobules subsequently become surrounded by thin fibrous tissue, and remain as encapsulated necrotic tissue or later undergo dystrophic calcification.

Clinical features. The painless lesions occur often on the lower legs of healthy adolescent boys or middle-aged women. The lesions can be solitary or multiple, often mobile, and varying from 2 to 35 mm in diameter. Preceding trauma is present in about 30% of cases. The nodules may be present for several weeks to years before excision. During surgical removal, a smooth-walled cyst within the subcutaneous fat containing solitary or multiple free-floating or attached nodules is usually found. Nodular cystic fat necrosis is probably not uncommon, but not readily recognized. Similar changes in the fat have been reported within the abdominal cavity [4] or within the abdominal wall [5]. Some authors take the view that encapsulated angiolipomas and encapsulated lipomas are variants of nodular cystic fat necrosis, with a variable degree of vascularity [2,6].

Histopathology. The lesions are totally or nearly totally encapsulated, showing massive fat necrosis with preservation of the outlines of non-nucleated adipocytes, usually with little in the way of inflammatory changes. Fibrous septae within the lesion, and dystrophic calcification, tend to be seen in older lesions. Focal lipomembranous changes may coexist [7].

Differential diagnosis. This includes lipoma, angiolipoma, pancreatic fat necrosis and membranous fat necrosis.

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Lipomembranous fat necrosis [1]

SYN. MEMBRANOCYSTIC FAT NECROSIS

Lipomembranous fat necrosis is a striking and distinctive alteration in adipose tissue that was first described in Nasu–Hakola disease, a genetic disorder characterized by profound membranocystic degeneration of long bones and systemic adipose tissue, with associated progressive sudanophilic leukodystrophy of the brain [2]. Cystic areas of fat necrosis are lined by wavy hyaline acidophilic membranes (Fig. 55.16). Convoluted projections and arabesques of the membranes into the interior of the cysts are prominent [3]. The membranous structures stain brightly with periodic acid–Schiff but are resistant to diastase. Ultrastructurally, the membranes consist of two layers [4].

Changes of lipomembranous fat necrosis can occur as a non-specific reaction pattern in a wide range of autoimmune diseases including lupus erythematosus [3], diabetes mellitus [3], morphoea [5] and dermatomyositis [6]. In a clinical and pathological correlation of 1806 biopsies of panniculitis, lipomembranous fat necrosis was only identified in 13 cases [3]. It is now clear that venous stasis and ischaemia are important co-factors [1,3,7,8] in the development of lipomembranous fat necrosis. Most cases are seen in middle-aged obese women who develop venous stasis-associated chronic sclerotic plaques on the lower legs and ankles [1]. The condition therefore overlaps with or is a part of sclerosing panniculitis [9], lipodermatosclerosis; some consider it to be a non-specific finding [10].

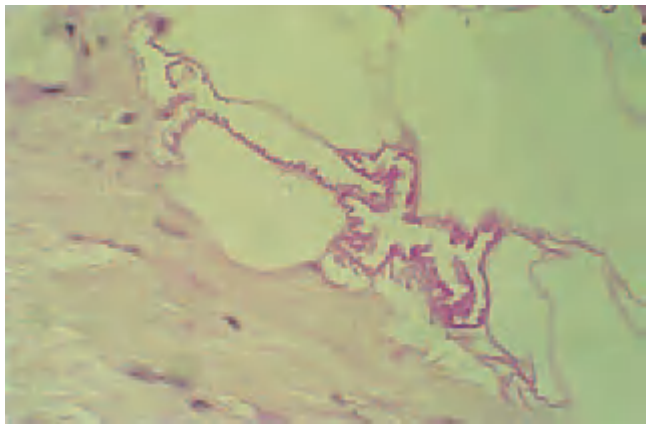

Fig. 55.16 Lipomembranous fat necrosis: the cystic areas are lined by wavy hyaline membranes. Periodic acid–Schiff (PAS) stain, × 25.

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Panniculitis caused by cellular proliferative disease

Subcutaneous T-cell lymphoma is a rare type of peripheral T-cell lymphoma, which clinically and histologically may mimic benign forms of panniculitis [1]. Erythematous subcutaneous nodules localized to the extremities appear in crops, often accompanied by fever and malaise [1,2]. The lymphoma may behave indolently for months to years, but in most cases it enters an acute aggressive phase in which the majority of patients develop fatal haemophagocytic syndrome [3] or sometimes acute leukaemia [4].

Although low-power histological appearances may resemble benign panniculitis, high-power examination reveals cytological atypia of the malignant lymphoid cells, and immunochemistry studies confirm the T-cell lineage [5]. Angiocentric lymphoma can also cause lobular granulomatous panniculitis [6,7].

Cytophagic histiocytic panniculitis [1,2]

Cytophagic histiocytic panniculitis is the term commonly used to refer to the specific cutaneous manifestation of haemophagocytic syndrome (HPS) [3].

In HPS, there is a histiocytic proliferation throughout the reticuloendothelial system. The proliferation and phagocytic activity of histiocytes in HPS is associated with a proliferation of lymphocytes [3]. Indeed, the primary abnormality in cytophagic histiocytic panniculitis may be a clonal T-cell proliferation [8].

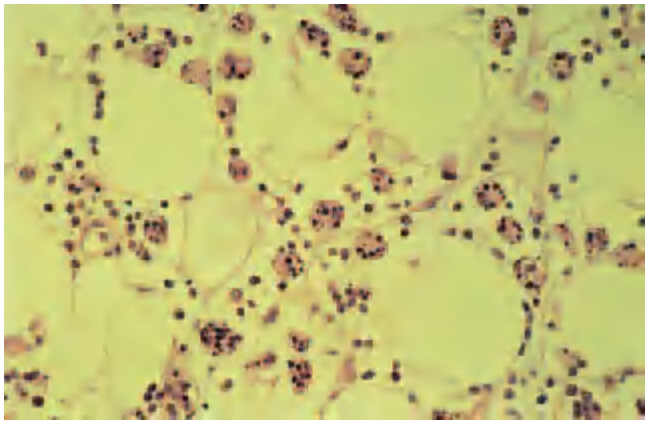

Fig. 55.17 Cytophagic histiocytic panniculitis: many histiocytes are present in the fat lobule, showing the characteristic 'bean-bag' appearance. H&E, × 25.

Aetiology. The proliferation of lymphocytes and histiocytes in HPS may be secondary to viral infections (e.g. Epstein–Barr virus [9], cytomegalovirus) or may be neoplastic in origin [2]. HPS has a higher rate of mortality when it is associated with a state of known immunosuppression, and has been reported in HIV-1 infections [2]. Indeed, lymphoma and infection may act as co-factors in the development of HPS. It has been postulated that in HPS cytokine production by the proliferating lymphocytes is important as a stimulus to activate macrophages [2].

Pathology [10]. Cytophagic histiocytic panniculitis may begin as a type of regional histiocytosis that primarily involves the subcutis [10]. In most cases, the condition spreads to involve the bone marrow, lymph nodes and reticuloendothelial system. The affected tissues are gradually replaced by a syncytium of histiocytic cells with associated T lymphocytes and plasma cells. The histiocytes are actively cytophagic, so that they become stuffed with white blood cells, red cells, nuclear fragments and platelets, thus giving them a characteristic 'bean-bag' appearance (Fig. 55.17).

The histiocytic proliferation is accompanied by lobular panniculitis with areas of fat necrosis, together with massive hyaline necrosis, oedema and haemorrhage [10]. Immunohistochemical studies tend to show that the histiocytic population is benign, whereas the lymphoid element, whether benign or malignant, is composed primarily of T cells [2].

Clinical features. This is a rare condition, which in the past has probably been labelled as systemic nodular panniculitis (Weber–Christian syndrome) [11,12]. The condition begins with crops of red tender nodules, associated with fever (Fig. 55.18). The nodules often develop a purpuric or bruised appearance (Fig. 55.19). The condition

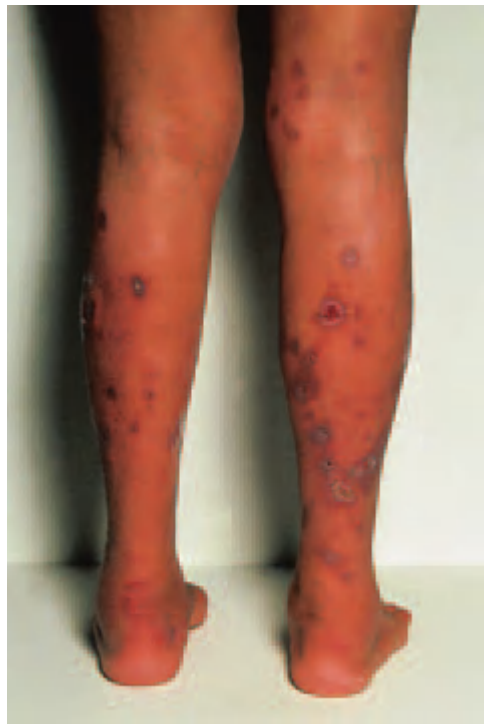

Fig. 55.18 Cytophagic histiocytic panniculitis: early stage with recurrent crops of lesions. (Courtesy of the Mayo Clinic, Rochester, MN, USA.)

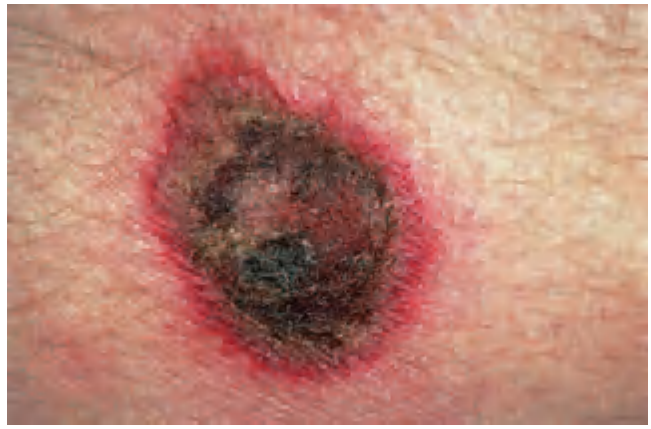

Fig. 55.19 Cytophagic histiocytic panniculitis: note the haemorrhagic nature of this early lesion on the thigh. (Courtesy of St John's Institute of Dermatology, London, UK.)

can be acute, or chronic with a febrile course associated with anaemia and pancytopenia. More severe cases tend to display weight loss, thrombocytopenia, raised liver enzymes, serosal effusions and hepatosplenomegaly [11–13].

Most patients have a progressive form of the disease, which is ultimately fatal. The fatal progression is usually determined by the development of severe anaemia, thrombocytopenia, coagulation defects, hypocalcaemia and liver failure [12,13]. At this stage, the development

of terminal T-cell lymphoma [14,15], B-cell lymphoma [16,17], histiocytic lymphomas [18] or sinus histiocytosis with massive lymphadenopathy (Rosai–Dorfman) [19] may also be evident. The complex coagulation defects are not fully understood. There may be a combination of thrombocytopenia or thrombocytosis, decreased factor VIII and fibrinogen levels, and an increase in excretion of fibrin degradation products.

It has been suggested that these abnormalities in coagulation may be caused by a circulating proteolytic enzyme other than thrombin, which may originate from proliferating lymphocytes [20]. The occurrence of cytophagic histiocytic panniculitis has been reported as a late complication of allogeneic bone marrow transplantation [21]. However, prolonged survival after combination-type chemotherapy has been reported, even in cases where the clinical features indicate a poor prognosis [22,23]. Monitoring of phagocytic activity may be of value in assessing disease activity [22].

Treatment. Many cases are ultimately fatal, and for the progressive forms combination cytotoxic chemotherapy should be tried [9,13]. Prolonged survival or even complete remission have been reported with this type of treatment schedule [23,24]. Ciclosporin has been reported to be effective in cytophagic histiocytic panniculitis [25], presumably by suppression of the abnormal T-cell activation and proliferation. Combinations of systemic corticosteroids and azathioprine have been reported to be effective [26], as has the use of intravenous immunoglobulins [27].

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Mixed (septal and lobular) panniculitis

Lupus panniculitis

SYN. LE PROFUNDUS

Lupus panniculitis is a rare condition in which the inflammatory changes primarily affect the deep dermis and subcutaneous fat. The overlying skin may be associated with discoid lupus erythematosus (LE) in 20% of cases [1,2]. The serum antinuclear antibody is usually positive in approximately 70% of cases, but only 25–50% fulfil the American Rheumatism Association criteria for systemic LE [1,2]. However, there are a significant number of cases of lupus panniculitis that never meet the criteria for systemic LE, and some have no extracutaneous manifestations [3]. Many patients with lupus panniculitis tend to have a relatively mild but usually chronic disease course [3].

Clinical features. The lesions begin with subcutaneous nodules or plaques, where the overlying skin may appear normal, erythematous or may show changes characteristic

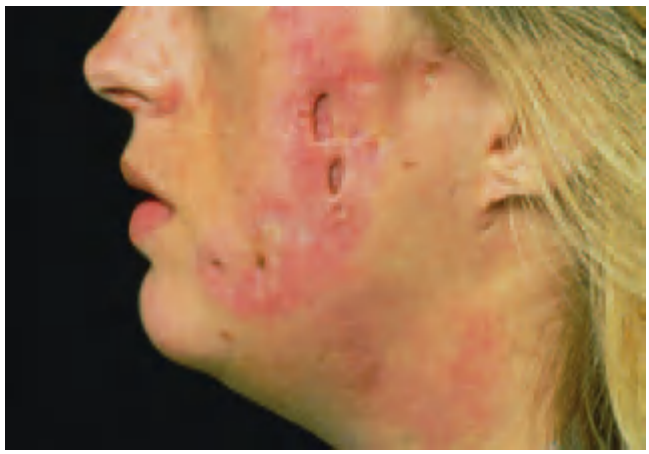

Fig. 55.20 Lupus panniculitis. (Courtesy of St John's Institute of Dermatology, London, UK.)

of discoid LE [2]. The lesions can be painful and may ulcerate, leading to atrophy and scarring after healing [4].

Common sites for nodules include thighs, buttocks, arms, breasts and face (Fig. 55.20). When breast tissue is involved (lupus mastitis), there may be difficulty in distinguishing lupus mastitis from breast carcinoma, even on mammography [5]. Indeed, lupus mastitis may account for 10% of all patients with lupus panniculitis [6]. Many cases of lupus panniculitis may have only mild extracutaneous features, but the coexistence of photosensitivity, arthritis, pericarditis, renal involvement [3] and even neuropsychiatric manifestations has been reported [6].

Perhaps not surprisingly, lupus panniculitis can overlap with morphoea-like lesions [7] or other forms of connective tissue panniculitis [4]. LE panniculitis is rare in childhood [8] but a linear variant has been described [9].

Pathology. The major histological criteria needed for a diagnosis of lupus panniculitis include hyaline necrosis of fat, lymphocytic aggregates or lymphoid follicle formation, periseptal or lobular lymphocytic panniculitis, and calcification [1] (Fig. 55.21). Minor changes (not necessary for diagnosis) include overlying changes of discoid LE, hyalinization of the subepidermal zone, mucin deposition, lymphocytic vascular inflammation and collections of plasma cells and eosinophils [10].

Treatment. Treatment can be difficult in chronic forms of lupus panniculitis. Local treatment in the form of potent corticosteroids under hydrocolloid dressings [11] or intralesional triamcinolone can be of benefit. Dapsone [12], oral hydroxychloroquine [8] and corticosteroids [5] can be effective in the management of lupus panniculitis. Low-dose thalidomide can be effective for antimalarial drug-resistant cases of discoid LE and LE profundus [13].

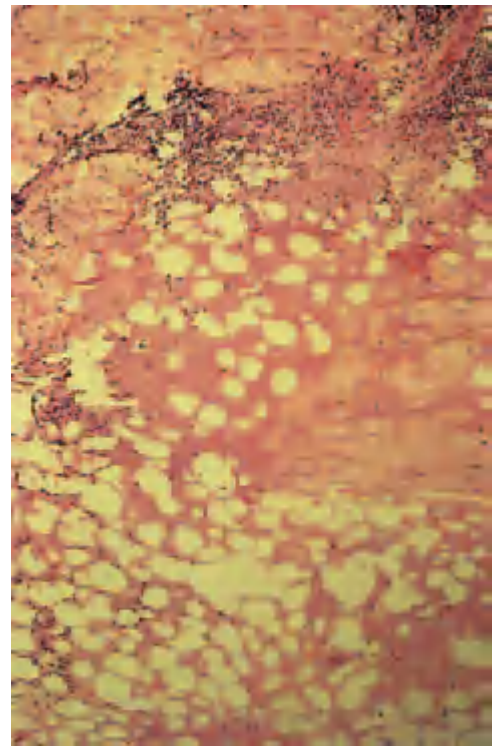

Fig. 55.21 Lupus panniculitis: extensive hyaline necrosis of fat with overlying lymphocytic aggregates are shown. H&E, × 4.

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Panniculitis with complement deficiency

Although complement deficiencies are perhaps better known for their association with partial lipoatrophy syn-

dromes [1], they have also been reported in lobular panniculitis. The association of an immunoglobulin E (IgE) paraproteinaemia and severe acquired depletion of C1-esterase inhibitor with episodes of nodular panniculitis and hepatitis has been reported [2]. Nodular panniculitis has also been associated with a low serum complement, together with a systemic LE-like disease and circulating IgM immune complexes [3].

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Infective panniculitis

Infective panniculitis (either through direct inoculation or as a manifestation of sepsis) is becoming an increasingly important cause of panniculitis [1]. This is particularly so for any immunocompromised patient, either as a result of steroid or immunosuppressive therapy [2] or brought about by HIV infection [3]. An association of acquired immune deficiency syndrome (AIDS) with cutaneous aspergillosis is developing, and some patients present with subcutaneous nodules [4].

Granulomatous panniculitis on the legs caused by *Candida albicans* has been reported in a diabetic who had not received immunosuppressive treatment [5]. Other occasional cases with infective panniculitis are not overtly immunosuppressed [1].

Clinical features [1]. Most cases of infectious panniculitis appear as inflamed subcutaneous nodules, plaques or ulcers [4] on the lower extremities. Other sites include the shoulders, arms, fingers, abdominal wall and gluteal region. The differential diagnosis includes erythema nodosum, abscess or other type of panniculitis.

A wide variety of organisms have been identified in infective panniculitis. These particularly include Gram-negative [3] and Gram-positive [1] bacteria, *Histoplasma* [2,6], *Mycobacterium tuberculosis* [7], atypical mycobacteria [8,9], *Actinomyces* and *Nocardia* species [1], *Candida* [4] and various fungi [1].

Histology. Classically, in infective panniculitis there is a mixed pattern of septal and lobular involvement. Neutrophilic involvement of the fibrous septae can occur [1], a feature that can rarely overlap with acute erythema nodosum [10]. Indeed, neutrophilic involvement in infective panniculitis can also overlap with other neutrophilic dermatoses (neutrophilic vasculitis and panniculitis) [11]. Certain morphological changes are found in infective panniculitis, whatever the identity of the infective organism. Epidermal involvement is common, as is papillary dermal oedema with diffuse neutrophilic infiltrate, vascular proliferation and haemorrhage [1]. Focal necrosis of sweat glands and discrete microabscess formation may be noted [1].

It is important to stress that infection should be suspected in virtually any case of panniculitis when it is known that the patient is immunocompromised. Extra biopsy material submitted for tissue culture is highly desirable, if not essential [3], as special stains may fail to demonstrate the organisms [1].

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Factitial panniculitis [1]

Factitial panniculitis is a rare condition in which the panniculitis is self-inflicted. Its importance lies in the fact that some cases may masquerade as systemic disease or idiopathic Weber–Christian syndrome. The causes and clinical features of factitial panniculitis may vary widely depending on the type of insult to the subcutaneous fat. Factitial panniculitis may result from blunt trauma to the skin, usually on the forearm and hand (l'oedème bleu) [2]. Histologically, such cases may show an organizing haematoma in the fat, together with haemosiderin and amorphous polysaccharide masses [2]. Cupping and acupuncture techniques for relief of pain may rarely lead to factitial panniculitis on the limbs [3]. More commonly, however, factitial panniculitis is induced by injected materials (e.g. drugs and silicone materials). Injected drugs such as morphine, pentazocine, meperidine or tetanus toxoid can all cause chronic ulcerative panniculitis

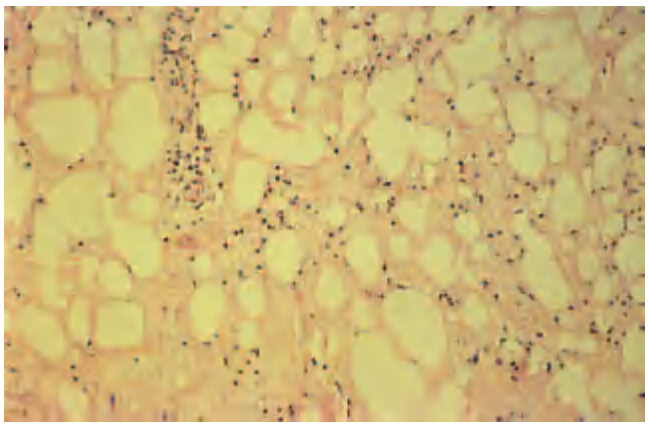

Fig. 55.22 Paraffinoma: showing typical 'Swiss-cheese'-like pseudocystic spaces. H&E, × 25.

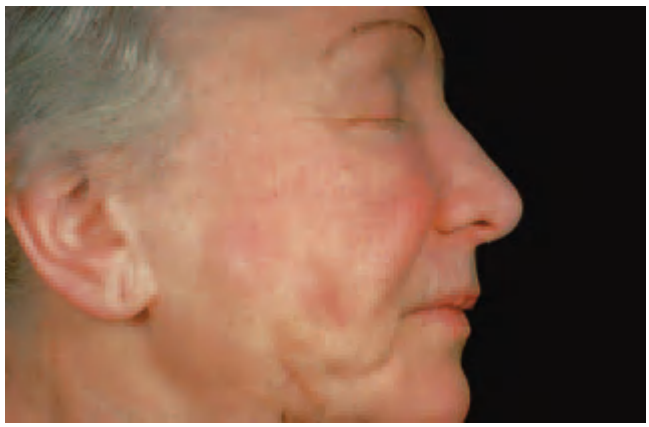

Fig. 55.23 Paraffinoma: firm indurated areas present on the malar areas, following paraffin oil injections many years before for cosmetic purposes. (Courtesy of St John's Institute of Dermatology, London, UK.)

on the thighs and buttocks, associated with 'woody-hard' fibrotic induration (see Fig. 55.10) [4,5]. Silicone injections (used by some patients to augment the size of breasts or genitalia) can cause panniculitis [6], as can the accidental injection of various oily vehicles for therapeutic agents. Povidine, a synthetic polymer used as a dispersing or suspending agent for drugs, has also been reported to cause panniculitis associated with fever [7]. The injection of mineral oil into tissues may induce a granulomatous foreign body reaction (sclerosing lipogranuloma) or 'paraffinoma' [8]. Histologically, paraffinomas show multiple 'Swiss-cheese-like' pseudocystic spaces (Fig. 55.22), which are surrounded by fibrosis and inflammation. Most paraffinomas occur on the head and neck area in women who have the injections for cosmetic reasons [9] (Fig. 55.23).

Rarely, however, paraffinomas are not factitial in origin. The development of orbital and palpebral paraffinoma has been reported to ensue after ethmoidectomy for chronic sinusitis, when the nasal cavity was packed with gauze containing a petrolatum-based antibiotic ointment [10]. Mentally disturbed patients have been known to inject milk or faeces, which produces a severe cellulitis or suppurative panniculitis.

Factitial panniculitis simulating pyoderma gangrenosum has also been reported in Münchausen syndrome [11].

Histology. The histology will obviously vary according to the type of noxious injury to the fat. Blunt trauma tends to produce deeper haematomas [2]. Polarization is essential to reveal the possibility of injected crystals [4,5]. The presence of vacuoles or pseudocystic spaces favours the injection of silicone [6] or paraffin [9,10].

The use of scanning electron microscopy or energy-dispersive spectroscopy techniques can aid in the identification of injected materials [6]. In general, factitial panniculitis is a mixed septal and lobular panniculitis that is associated with a prominent degree of inflammatory or granulomatous infiltrate, with fibrosis ensuing.

Differential diagnosis. The diagnosis may be suggested by the personality of the patient, the chronic and recurrent nature of the panniculitis and by its focal or bizarre site. In some cases, there may be fever or systemic symptoms and the condition may then be mistaken for systemic nodular panniculitis (Weber–Christian syndrome).

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Oil granuloma

SYN. OLEOGRANULOMA; OLEOMA; PARAFFINOMA; SCLEROSING LIPOGRANULOMA

Definition. A granulomatous reaction to the injection of a relatively bulky oily fluid into the tissues. In many cases the condition overlaps with that of factitial panniculitis, but in some cases it may represent an industrial injury.

Aetiology. Many years ago, mineral oils, particularly liquid paraffin and soft paraffin, were in vogue for improving the contour of the body (breasts, face, genitalia) [1]. Oil granulomas are now less common since the development of less toxic silicones and bovine collagen for tissue replacement, or the use of liposuction techniques.

Grease-gun injuries can cause sclerosing lipogranulomas [2].

Histology. A massive injection of oil tends to provoke an initial acute inflammatory response, but some mineral oils will remain in the tissue for a considerable time without producing any marked inflammatory reaction. Larger oil droplets become encysted by fibrosis ('onion-skin cysts'). The classical 'paraffinoma' shows multiple small cystic areas ('Swiss-cheese effect') associated with very little inflammatory change but a prominent degree of fibrosis. Certain animal fats produce a tuberculoid granuloma, whereas vegetable oils, by virtue of irritant substances liberated by hydrolysis, often provoke inflammatory changes and lipophagic granuloma.

Differential diagnosis of a mineral oil granuloma from idiopathic sclerosing lipogranuloma may be very difficult, although the use of scanning electron microscopy and energy-dispersive spectroscopy techniques can be of help [3].

Clinical features. The nodules or plaques usually appear several months after injection, but their onset can be delayed for up to 42 years [4]. Once initiated, the lesions tend to persist indefinitely. Firm non-tender nodules or plaques form, which may be fixed to both skin and deeper fascia. Ulceration occasionally occurs. The common sites following cosmetic procedures are the face and breasts of women. Nodules on the thighs and buttocks are the result of injections of therapeutic agents in oily vehicles. It is not rare for some patients to strenuously deny any history of earlier injections for cosmetic or therapeutic purposes.

The grease-gun injury characteristically affects the dorsum of the left hand and appears as a nodule, plaque or sinus [2,5]. The onset is more rapid, the patient usually being unaware of the injury, but there may be an anaesthetic period before the gradual onset of swelling, pain and ischaemia. Rapid referral to a plastic surgeon or hand specialist is necessary. Perianal oil granulomas have been reported to follow injections for haemorrhoids [6]. Factitial panniculitis (dermatitis artefacta) can be caused by self-injection of mineral oils or silicones. An analysis of the lipid content in 23 cases of sclerosing lipogranuloma of the male genitalia demonstrated the presence of paraffin hydrocarbons in all specimens [7].

Prognosis. In chronic cases, the lesions remain essentially unchanged almost indefinitely, although the coexistence of sarcoma has been reported [8]. With acute grease-gun injuries, ischaemic changes may rapidly develop.

Treatment. Xeroradiology can be helpful, as is a knowledge of the offending material. Decompression and clearing of the affected area are needed in grease-gun injuries [2]. Tetanus toxoid may be needed along with high-dose systemic steroids if there has been a delay in diagnosis of grease-gun injuries [2]. If there is any doubt about the diagnosis of chronic oil granuloma, a deep surgical biopsy should be performed. No effective treatment exists other than complete excision.

Idiopathic sclerosing lipogranuloma

An idiopathic form of sclerosing lipogranuloma has also been reported [9], but the lack of recent reports may indicate that it really represents an oil granuloma in which the history is concealed [6,7].

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Sclerosing panniculitis [1–4]

SYN. LIPODERMATOSCLEROSIS [3]; HYPODERMATITIS SCLERODERMAFORMIS [3]

There is growing evidence that the term sclerosing panniculitis encompasses both lipodermatosclerosis and hypodermatitis sclerodermaformis, perhaps appearing in different stages [2]. The patients, usually women, gradually develop well-circumscribed indurated inflammatory plaques around the lower extremities, which lead to hyperpigmentation. Histologically, there is a combination of fat necrosis, sclerosis and a lobular panniculitis. Lipomembranous changes can coexist [5]. Not all cases are overtly associated with chronic venous stasis, although the condition may show some gradual response to elastic compression stockings [2]. It has been postulated that there may be overlap in the pathogenesis between lipodermatosclerosis and eosinophilic fasciitis [6].

Infective cellulitis may also have a role in exacerbating lipodermatosclerosis and the fasciitis–panniculitis

syndrome [7]. It is likely that the pathogenesis of lipodermatosclerosis is multifactorial [8]. The condition may be initiated by venous stasis, which may lead to leukocyte plugging and endothelial injury to the microcirculation. Perivascular cuffing by fibrin deposits may activate fibroblasts, endothelial cells and mastocytes, which ultimately lead to fibrous thickening of the fascia and fibrous septae in the subcutis [5]. Elevated matrix turnover has also been implicated in lipodermatosclerosis [9].

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Fasciitis–panniculitis syndromes [1]

In eosinophilic fasciitis and related syndromes, the inflammation often extends to involve the fibrous septae and fat lobules [1]. It has become increasingly recognized that a histological picture similar to eosinophilic fasciitis, involving the subcutaneous fat, can occur in a variety of diseases, including morphoea profunda [1], lupus panniculitis [1], toxic oil syndrome [2], L-tryptophan-induced eosinophilia–myalgia syndrome [3], graft-versus-host reaction [4], post-irradiation injury [5], infections [6] and cancer-related (paraneoplastic) syndromes [7,8].

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Panniculitis in other connective tissue diseases

As already indicated, panniculitis in connective tissue diseases may overlap with lupus panniculitis [1] and also lipoatrophic panniculitis [2]. Deep morphoea (morphoea profunda) may show lipoatrophy, scleroderma-like lesions and deeper subcutaneous nodules or plaques. They may also share some histological features, notably lymphocytic panniculitis, lymphoid nodular areas in the fat, widening of the fibrous septae and lymphocytic vasculitis [3–5]. The association of panniculitis with dermatomyositis is very rare but well documented [6–8]. The parallel course of panniculitis and muscular involvement, and their response to treatment, suggest that panniculitis may be an inherent part of dermatomyositis [6–8].

Subcutaneous nodules or plaques develop on the arms, buttocks, thighs and abdomen, or features of multifocal lipoatrophy may be present [9].

Partial lipoatrophy may also coexist with dermatomyositis [10,11]. The association of panniculitis and dermatomyositis has been reported to respond to a combination of low-dose methotrexate and prednisolone [9], or high-dose intravenous immunoglobulins [12].

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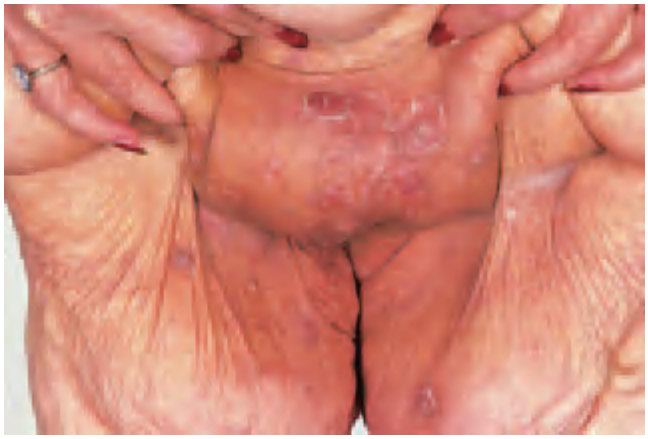

Fig. 55.24 Scarring of lower abdominal folds secondary to panniculitis and/or vasculitis following jejuno-ileal bypass for gross obesity.

Panniculitis with vasculitis

Because the vasculature of the subcutis is 'housed' in the fibrous septae that divide up fat lobules, it is obvious that most deep vasculitis syndromes (particularly large-vessel vasculitis) begin as a septal panniculitis and involve the fat lobules later.

Nearly all cases of leukocytoclastic vasculitis in the subcutis zone also affect the overlying dermis. Nodular forms of vasculitis affecting the fat are primarily dealt with in Chapter 49, together with larger vessel vasculitis syndromes (e.g. polyarteritis nodosa).

This section covers a series of miscellaneous entities that may overlap with vasculitis, or may in some way be associated with them.

Panniculitis has rarely been reported in association with relapsing polychondritis, and histologically was characterized by septal and lobular involvement with vasculitis [1,2]. The association of granulomatous lipophagic panniculitis with temporal arteritis and chronic active hepatitis has been reported, and perhaps represents three-organ manifestations of an underlying aberration of the immune defence mechanism [3].

Unusual forms of vasculitis-associated panniculitis include that resulting from the complications of jejuno-ileal bypass surgery for obesity (Fig. 55.24) [4,5].

Neutrophilic panniculitis

Subcutaneous neutrophilic infiltrates are a rare accompaniment in atypical Sweet's syndrome and bullous pyoderma gangrenosum [6]. Recent case reports have highlighted the association of neutrophilic panniculitis with myelodysplastic syndromes [7,8]. The neutrophilic infiltrates spread out from the septa to the lobules, without evidence of necrotizing panniculitis. It has been postulated that neutrophilic panniculitis belongs to the spectrum of atypical neutrophilic dermatoses associated with myelodysplastic syndromes [7]. Septal forms of neutrophilic panniculitis can occur in classical Sweet's syndrome, and may present as erythema nodosum-like eruptions [9].

A pustular neutrophilic form of panniculitis has been associated with rheumatoid arthritis [10]. Clearly, in all forms of neutrophilic panniculitis it is necessary to exclude an infective organism, particularly in an immunocompromised patient [11].

Oedematous scarring vasculitic panniculitis

A condition termed oedematous scarring vasculitic panniculitis has been identified in children, which is described as a novel multisystemic disease with a mortality rate of 35.7% [12]. The cutaneous lesions may intially resemble hydroa vacciniforme, but later disfiguring involvement affects both covered and sun-exposed areas. The lesions develop as oedematous vesicles, which progress to deep ulcerations and varicelliform scars. Histologically, panniculitis and vasculitis coexist with a heavy nodular lymphohistiocytic infiltrate. In cases with systemic involvement, malaise, fever, failure to thrive, leukopenia, thrombocytopenia, hepatosplenomegaly and increased levels of serum C3 have been frequently observed [12]. Several of the patients ultimately developed cutaneous lymphoma, after an interval of 5–8 years [12]. Other patients with 'hydroa vacciniforme' have also been reported to develop malignant lymphoma [13–15]. Currently, it is not clear whether oedematous scarring vasculitic panniculitis is a disease entity, whether it is in any way related to hydroa vacciniforme or whether it represents an evolutionary process in the development of malignant lymphoma in children.

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Wells' syndrome [1–4]

SYN. EOSINOPHILIC CELLULITIS; RECURRENT GRANULOMATOUS DERMATITIS WITH EOSINOPHILIA

Definition. This is a syndrome with an impressive and distinctive clinical picture resembling cellulitis, and with a typical histology characterized by tissue eosinophilia, oedema and 'flame' figures.

Aetiology. A good example of this is the association of eosinophilic cellulitis with idiopathic hypereosinophilic syndrome [5]. Eosinophilic cellulitis has also been reported with herpes simplex virus type 2 infections, in which antiviral therapy led to a complete remission of the eosinophilic cellulitis [6]. Some cases may be associated with malignancy [7].

Pathology. Early on, there is an infiltrate of polymorphs and especially of eosinophils, with considerable oedema. Flame figures are noteworthy—clusters of eosinophils and histiocytes around a core of collagen and eosinophilic debris. The flame figures may disappear after the acute stage. Blood eosinophilia is usual but not invariable.

Clinical features. Wells' syndrome is rare. It can affect either sex, usually in adult life, but some congenital [8], neonatal [9] or childhood cases [10] have occurred. Any site may be involved, with single or multiple lesions. The disease evolves over a few weeks, and recurrences are common. Initially, the lesions are itchy erythematous plaques with features resembling both urticaria and cellulitis. Unusual nodular variants [11] and lesions that followed the lines of Blaschko [12] have been described. After a week or two they become flatter, and sometimes go through a greenish colour change before resolving without scarring. The general health is usually unimpaired, but fever has been reported.

Differential diagnosis. Clinically, cellulitis and urticaria are the main differential diagnoses. *Toxocara* infections may be similar, both clinically and histologically. Flame figures can be found in many other diseases, including insect-bite reactions, dermatophyte ide eruptions and pemphigoid. There may also be features resembling the Churg–Strauss syndrome [13].

Treatment. Often no specific treatment is needed. Low-dose systemic steroids can provide symptomatic relief in severe cases [14].

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Lipodystrophy

The terms lipoatrophy and lipodystrophy are sometimes used interchangeably and without precise definition. Perhaps it is best to define lipodystrophy as an abnormality of fat that is usually associated with atrophy (lipoatrophy), or infrequently hypertrophy of the adipose tissue. Lipoatrophy refers specifically to loss of fat. However, the lipoatrophy may be part of a local panatrophy affecting all mesodermal layers [1]. Lipodystrophies are a rare and heterogeneous group of the disorders characterized by selective and variable reduction in and, more often, loss of adipose tissue from different parts of the body; in all but the more very localized varieties they are often associated with metabolic complications of insulin resistance, in particular insulin-resistant diabetes mellitus [2]. Over the last 5 years, there has been a much better understanding of the aetiology of these disorders. The loss of adipose tissue can have a genetic, immunological, infectious or drug-associated aetiology [3]. The age of onset may also determine the nomenclature of the disease. Some patients may develop the disease very early on in life—such patients are

then sometimes referred to as having congenital lipodystrophy. In other patients, the disease occurs later on in life—so-called acquired lipodystrophy. The lipodystrophies can also be classified according to the extent of the disease into three major clinical entities: localized, partial body and whole body distribution. The atrophy may be localized (e.g. to the thighs); it can be widespread, involving the upper part of the trunk (partial lipodystrophy); or it may affect the whole body (generalized lipodystrophy).

Nevertheless, the aetiology and clinical presentation are not always clear-cut. For example, cases of partial lipoatrophy have been reported that have evolved into generalized lipoatrophy, suggesting some common link between these uncommon disorders.

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Localized lipoatrophy

Localized atrophy may be seen in insulin-dependent diabetics, induced by insulin; following certain inflammatory conditions, such as panniculitis and morphoea; or as primary idiopathic lipoatrophy. Failure to perform a biopsy in the early phases of the atrophy may explain why some of the cases are labelled as idiopathic in origin. It has been suggested that many cases may be preceded by an inflammatory reaction in the fat (see also lipoatrophic panniculitis) [1].

Insulin lipodystrophies

This is a cosmetically distressing complication of insulin administration. Both atrophy and hypertrophy of the fat tissue can occur. It occurs in various degrees in up to 37% of insulin-dependent diabetics [2].

Aetiology. Insulin lipoatrophy is usually seen in women and children, rarely in men. The mechanism remains speculative but local changes induced by insulin or impurities are probably important [3] as are antibodies to insulin [4]. Most cases are associated with high levels of insulin requirement and/or an increased insulin-binding capacity.

Cross-reaction of insulin antibodies with cells thus changed could result in further damage [5]. It was thought that the introduction of highly purified insulin would make a significant impact in reducing the frequency of this disorder. There is evidence to support this view because the subcutaneous damage is reduced if highly purified insulins are used, resulting in clinical improvement and a reduction in insulin requirements and insulin-binding capacity [5–7]. However, localized lipodystrophies in insulin-requiring patients are still very common, affecting up to 40% of patients.

A recent publication investigated a cross-sectional study of 112 children and adolescents with type 1 diabetes mellitus and related the presence of insulin antibodies to the clinical features of insulin lipodystrophies [4]. The antibodies against insulin increased significantly after diabetes manifestations and initiation of insulin treatment, while β-cell-specific antibodies did not. Severe lipohypertrophy was seen in four children, severe lipohypertrophy in 18 and moderate lipohypertrophy in 27 children. Among clinical and immunological parameters investigated, insulin antibodies were significantly associated with hypertrophy or atrophy of injection sites. It was concluded that lipodystrophies in diabetics are significantly associated with insulin antibodies, and that these may have a role in the development of the disease.

Histopathology. There is a loss of fat tissue and inflammatory changes are conspicuously absent. In lipohypertrophy, there may be replacement of mid-dermal collagen by hypertrophic fat cells.

Clinical features. Although both features can occur in the same patient, recent publications suggest that insulin fat hypertrophy is more common than atrophic changes [4]. Most cases present 6 months to 2 years after the start of insulin administration. Lesions may vary from only a small dimple to an extensive disfiguring area with much local loss of fat or firm fatty induration. The changes are usually found only at the sites of injection, but loss of fat may occur elsewhere. There is a definite tendency to spontaneous recovery at the involved site when the site of injection is changed.

Treatment. A change to a purified insulin, particularly the new human insulin, is not necessarily curative [8]. Prevention is either by constant alteration of the site of injection, so that no two injections are given in exactly the same area more frequently than once a month, or by the use of the more purified insulins [5,9]. Liposuction may help the hypertrophic variety [10]. In one very resistant case of progressive lipoatrophy, continuous subcutaneous infusion with human insulin was required to control the atrophy [9].

Localized lipohypertrophy has also been reported in a 51-year-old female patient with panhypopituitism during growth hormone replacement therapy [11].

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Localized 'idiopathic' lipoatrophy

This group of disorders predominantly affects the thighs, ankles or abdomen, and all cases may possibly be variants of the same process.

Histopathology. Two histological subsets exist: involutional and inflammatory [1]. Sixty per cent can be termed involutional; the adipocytes are small and embedded in hyaline connective tissue with many capillaries. Such patients usually have a single lesion and only one-third show immunoreactants. Forty per cent can be classed as inflammatory [2]; the lipocytes are normal and there is a sparse infiltrate of lymphocytes, histiocytes and plasma cells; all show immunoreactants [1]. The epidermis is normal. The appearance should not be confused with the striking lipomembranous (membranocystic) changes seen occasionally in morphoea, panniculitis and other inflammatory dermatoses.

Clinical features. Two clinical groups, based on the localization of the atrophy, have been described.

Lipoatrophia semicircularis [3–5]. These patients show lesions on the anterolateral aspects of the thighs, characterized by a band-like circular depression, 2–4 cm in width. Patients have also been described with lipoatrophy of the ankles which can extend up the legs (Fig. 55.25) [6]. The overlying skin is normal. An association with osteodystrophy of the hands and feet has also been reported [7].

The loss of fat develops rapidly within several weeks, usually without associated symptoms, although rheumatic-like pains within the involved areas were reported by two women. Trauma is a possible triggering mechanism—a series of seven cases has been reported in individuals working in the same office. The exact position of the indentations corresponding to the height of the desks strongly supports the hypothesis that in some patients this condition is caused by repetitive trauma to the upper thighs [8].

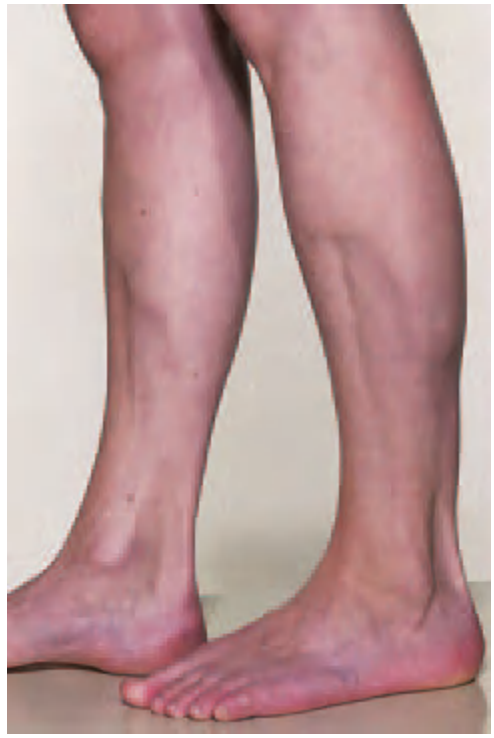

Fig. 55.25 Extensive lipoatrophy of the legs.

Primary inflammatory vascular changes in the subcutaneous tissue have been demonstrated in these patients, and also during the early period of other lipoatrophies [9]. There is no treatment, but considerable improvement may occur after the activity of the disease settles.

Centrifugal lipodystrophy. Lipodystrophia centrifugalis abdominalis infantalis is rare and has been seen predominantly in Japanese children [10–14], affecting the subcutaneous fat, usually of the abdomen and upper groin. Patients of Chinese and English ancestry have been reported [15]. The condition spreads in a centrifugal fashion with a central large bluish depressed area and slight erythema of the edge. Further experience has shown that the original name is inappropriate, because the condition may affect other areas and may occur outside infancy and not affecting the abdomen [16,17]. The condition may be strikingly unilateral [18,19]. One case is reported to have lasted over 40 years, and was associated with angioblastoma, which occurred at the same site at the age of 46 years [11]. Regional lymphadenopathy may occur [13]. A 10-year-old boy with a centrifugal lipodystrophy also developed serpiginous erythema of the scalp with

scarring alopecia [20]. Ulceration may also be a complication [21].

Histology shows a decrease in the subcutaneous fat with an inflammatory infiltrate in the lower dermis and subcutis. Immunocytochemistry has more recently suggested the possible involvement of apoptosis as a factor responsible for fatty tissue degeneration [22]. A patient has been reported who showed characteristics of both centrifugal and progressive lipodystrophy [17].

Treatment. Treatment is disappointing, although after the disease activity has ceased there seems to be regrowth of fat in 75% of cases. Some improvement has been reported in most cases treated with oral and topical corticosteroids [10].

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Partial or generalized lipoatrophies [1–4]

In these rare syndromes there is extensive absence or progressive loss of subcutaneous fat. Several syndromes are described: congenital generalized lipodystrophy, acquired generalized lipodystrophy, partial (cephalothoracic) lipodystrophy and partial face-sparing lipodystrophy [5]. Genetic explanations for the disease are increasingly being reported.

Congenital generalized lipodystrophy

SYN. LIPOATROPHIC DIABETES; LAWRENCE–SEIP SYNDROME; BERARDINELLI–SEIP SYNDROME

A rare congenital generalized lipoatrophy, sometimes familial, with loss of the subcutaneous and visceral fat, hepatomegaly, increased bone growth, hyperlipaemia and, later, diabetes mellitus [1,6,7].

Aetiology. The inheritance is probably autosomal recessive, and it is suggested that patients with the full syndrome are homozygous; heterozygous subjects manifest hyperlipaemia only. Gene alterations on chromosome 11q13 have been reported [8,9]. The pathogenesis is unknown, but a defect in the diencephalon or hypothalamus has been suggested [10], because some patients have an increased level of hypothalamic releasing factors. A defect in the insulin receptor gene has been reported [11].

Histopathology. There is complete loss of subcutaneous and visceral fat.

Clinical features. There is complete loss of subcutaneous and other fat, noticeable at birth or before the age of 2 years. Detailed metabolic and radiological studies have shown poor metabolically active adipose tissue, whereas mechanical adipose tissue is well preserved [12]. Hepatomegaly (occasionally with splenomegaly), hyperlipaemia and sometimes cutaneous xanthomas, hypertrichosis, hypermetabolism and excessive bone growth are characteristic. Younger patients show glycosuria only when given large amounts of glucose. Hyperglycaemia with excessive thirst and polyuria usually develop only after the age of 10 years. The diabetes is insulin resistant. Although there is complete loss of fat, the skin retains its elasticity. The loss of fat is usually quite widespread, but can be localized to the legs [13]. There is often generalized hypertrichosis, even at birth, and the scalp hair becomes abundant and often curly with the onset of disease. The scalp hair is frequently luxuriant, almost reaching the eyebrows. There is precocious enlargement of the genitalia, and in females marked enlargement of the clitoris.

As a result of increased bone growth, the children are tall for their age; the somatic musculature is increased and the abdomen markedly protuberant, often with an

umbilical hernia. All patients have a remarkably similar facial appearance, most have a dolichocephalic skull. The loss of facial fat gives a very characteristic gaunt appearance. The joints, particularly of the hands and feet, are enlarged. Widespread pigmentation, particularly of the axillary and inguinal folds, may be associated with linear epidermal thickenings, giving the appearance of acanthosis nigricans [1,7].

A proportion of congenital cases have progressive hypertrophic cardiomegaly [14], renal anomalies such as nephrotic syndrome, nephromegaly, medullary hyperechogenicity [15] and neurological disorders (including mental deficiency and hemiplegia). Pregnancy in such patients is most unusual, but can be associated with a successful outcome.

Some patients may have increased plasma levels of corticotrophin-releasing factor, follicle-stimulating hormone-releasing factor and melanocyte-stimulating hormone-releasing factor, presumably caused by neurological dysfunction [10].

X-rays show focal bone lesions, which on MRI can be shown to be caused by absence of marrow fat.

Acquired generalized lipodystrophy

When the onset is in the adult, excessive height is not a feature, muscularity is less obvious and abdominal protuberance not so marked. However, acromegaloid features with enlargement of the skin, hands and feet may precede the diabetes. The acquired type is frequently heralded by a febrile illness. Death from hepatic failure or haematemesis is usual.

Differential diagnosis. In congenital cases, differentiation from de Lange's disease may be difficult, especially if neurological features are present. In adult cases, the differential diagnosis is from acromegaly and thyrotoxicosis.

Insulin lipoatrophy in diabetics is focal, and usually confined to the sites of insulin injection.

Treatment. The response to treatment is poor. Pimozide, a selective dopaminergic blocker, may be helpful in restoring the fat and decreasing the levels of hypothalamic-releasing factors [10]. A diabetic diet may control glucose levels, and lipid-lowering agents and plasmapheresis may improve the hyperlipidaemia [16]. Specific anatomical defects can be improved, such as the repair of severe buttock deformities with bilateral gluteus maximus muscle flap advancements [17].

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Partial lipoatrophy [1,2]

SYN. PARTIAL LIPODYSTROPHY; BARRAQUER–SIMONS DISEASE; PROGRESSIVE LIPODYSTROPHY

This rare lipoatrophy occurs either in childhood or in young adults as an incidental part of a widespread mesodermal atrophy. The partial lipodystrophy locus has been mapped to chromosome 1q with no evidence of genetic heterogeneity [3].

Aetiology. Most patients are children or young adults when the disorder begins, but onset in the first year and in middle age is reported. Females are affected four or five times more frequently than males [4], and the condition is sometimes familial. It may follow an acute specific fever such as measles, but the common occurrence of non-specific fevers makes proof of this observation difficult. Facial hemiatrophy associated with loss of subcutaneous fat in borreliosis has been reported [5]. Partial lipodystrophy has followed damage to the region of the mid-brain or diencephalon [6]. The association of lipodystrophy with immunologically related renal disease [4,7–10], systemic sclerosis [11], systemic lupus erythematosus [12] and high titres of thyroid antibodies supports the view of lipodystrophy being an immunological disorder in some patients [13], but one that requires more investigation.

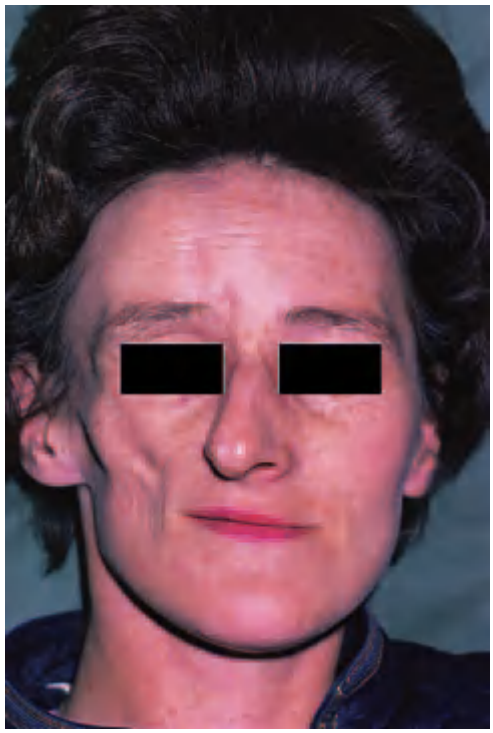

Fig. 55.26 The typical cadaveric facies of a patient with partial lipodystrophy. She also has melasma.

It is difficult to explain the abnormal distribution of adipose tissue in partial lipodystrophy. Fatty tissue autotransplanted to an atrophic site lost fat, while atrophic tissue autotransplanted to a fatty site accumulated it, suggesting that local factors determine the distributions of fat [14]. The local factor may be neuronally mediated, as suggested by observations that there may be symmetrical segmental loss of fat, and the line demarcating dystrophic and normal tissue in partial lipodystrophy may correspond to a dermatome. Jensen [15] described increased adrenergic activity in a patient with partial lipodystrophy, and proposed that this was of significance, as adipocytes in the upper body are sensitive to the lipolytic effects of epinephrine (adrenaline) and those in the lower body are not.

Histopathology. There is usually complete loss of adipose tissue over the affected areas.

Clinical features. The disease is characterized by the relatively slow symmetrical disappearance of the facial fat, producing a cadaverous appearance (Fig. 55.26) and complete loss of the subcutaneous fat in the upper half of the body (Weir–Mitchell type). In some cases, there is a coincidental hypertrophy of the subcutaneous fat of the lower part of the body (Laignel-Lavastine and Viard type) [3]. Ten per cent may have 'hemilipodystrophy' involving half of the face or body. Up to 90% can develop progressive membranous mesangiocapillary glomerulonephritis [3,16,17] and this can be precipitated by the contraceptive pill, pregnancy (especially in the third trimester) or the use of ergot derivatives [4]. A successful outcome in pregnancy is uncommon [18]. Thus, such patients should be observed by a renal physician during pregnancy, and oral contraceptives are prohibited.

The association of hypocomplementaemia and mesangiocapillary glomerulonephritis is now well established [7,8]. Approximately half of the patients with this form of glomerulonephritis have a persistently low plasma concentration of the third component of complement (C3), while the concentration of the fourth component (C4) is normal. This is accompanied by the presence of a factor in serum that is capable of activating C3 without activation of the earlier components. This material has been termed 'C3 nephritic factor' or C3NeF [6]. Lupus, C3 nephritic factor and partial lipodystrophy are perhaps not as rare as previously thought [19,20]. Juvenile dermatomyositis is also a rare association [21].

The relationship between C3NeF, persistently low C3 and mesangiocapillary glomerulonephritis is not clear. It has been suggested that the C3NeF predisposes the glomerulus to the development of mesangiocapillary glomerulonephritis in response to some other agent. In a series of 12 patients, four died from renal failure 10–25 years after the onset of the partial lipoatrophy [4]. Transplantation in one case resulted in normalization of C3 and the disappearance of C3NeF [16].

Insulin-dependent diabetes mellitus develops in one-third of patients with partial lipodystrophy. Retinitis pigmentosa, acanthosis nigricans and hepatomegaly are rare associated features [2]. Chronic purpura resulting from leukocytoclastic vasculitis has been reported [22]. This patient had extensive and moderate hypertrophy of the subcutaneous fatty tissue, macroglossia, polyarthralgia and mononeuritis. Myopathy associated with muscle weakness has rarely been reported, and is caused by fat droplets between the myofibrils [23]. Mammography in patients with partial lipodystrophy reveals unusually dense breasts with homogeneous opacities and ectopic fat depositions. These changes are possibly diagnostic, but confusing to the ill-informed radiologist [24].

Treatment. There is little effective treatment, other than the prevention and treatment of kidney disease. New plastic surgical techniques, including free radial forearm adipofascial flaps, can markedly improve the facial appearance [25,26].

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Partial face-sparing lipodystrophy

SYN. KOBBERLING–DUNNIGAN SYNDROME

This even rarer form is a genetically heterogeneous set of disorders characterized by a widespread but partial absence of subcutaneous fat usually sparing the face and neck; it can be easily missed because of the normal facial appearance [1]. Insulin-resistant diabetes, hypertriglyceridaemia and pancreatitis may coexist, but renal disease as yet has not surfaced. An autosomal dominant inheritance has been reported in some patients with the so-called Dunnigan subtype, who have a chromosomal abnormality on 1q21-22 [2,3]. As new reports appear, more types of lipodystrophy are likely to be reported, as is evidenced by a report of a patient with mental retardation, generalized lipodystrophy, diabetes and dysmorphic traits [4,5]. These patients do not at all fit into previously reported lipodystrophies.

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Lipodystrophy associated with protease inhibitors

Lipodystrophy has been reported in HIV-infected patients taking protease inhibitors, which have been recommended since 1996 as standard therapy for such patients in combination with nucleoside analogues. In these cases, lipodystrophy consists of an association of peripheral lipoatrophy with central adiposity [1]. The incidence of such lipodystrophy, lipodystrophy with subcutaneous lipoatrophy, and lipodystrophy with central obesity were 11.7 in 100 patient-years. An increased risk for any lipodystrophy is found among women as compared with men, heterosexuals and homosexuals as compared with intravenous drug users, with increasing age, and with the duration of exposure to antiretroviral therapy but not with any individual antiretroviral agent [2]. Reversion of the lipodystrophy does not occur after withdrawal of protease inhibitors [3].

In a further study on 614 patients, 20 months after initiation of protease inhibitor therapy, a cross-sectional study demonstrated that 23% of patients had abnormal glucose metabolism, 20% had hypertriglyceridaemia and 57% hypercholesterolaemia [4]. Cardiovascular problems in such patients not surprisingly occur with significant frequency.

This syndrome associated with protease inhibitors also occurs in children but less so if they received a lower dose of the protease inhibitor [5].

Treatment simplification approaches in which protease inhibitors are replaced by nevirapine have been shown to improve the lipid profile of these patients [6]. Treatment with dehydroepiandrosterone and indometacin can improve the lipid abnormalities, the abnormalities of glucose metabolism and the lipodystrophy. The mechanism of action of this combination may relate to the underlying peroxisome dysregulation induced by protease inhibitors.

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Summary of the metabolic abnormalities in lipodystrophies

It has been suggested that reduced synthesis and secretion of adipose-specific proteins may relate to the metabolic complications of lipodystrophies [1]. The authors measured fasting serum concentrations of adiponectin and leptin in patients with a variety of lipodystrophies. Patients with congenital generalized lipodystrophy and acquired generalized lipodystrophy had markedly reduced serum adiponectin levels compared to those with familial partial lipodystrophy. The same trend was noted for serum leptin levels. Serum adiponectin levels correlated negatively with fasting serum triglycerides and insulin levels, and positively with serum high-density lipoprotein cholesterol levels. These results indicated that adiponectin and leptin levels are extremely low in patients with generalized lipodystrophies, and may be related to the severe insulin resistance and its metabolic complications in such patients.

Further support for this link comes from the fact that chronic leptin treatment (recombinant mathionyl human leptin) improves insulin-stimulated hepatic and peripheral glucose metabolism in severely insulin-resistant lipodystrophic patients [2,3]. This therapy also influences, directly or indirectly, menstrual regularity. Of five patients so treated, only one female was cycling normally before therapy; all had normal menses by the fourth month of leptin therapy [4].

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Lipomas

Lipomas are benign tumours composed of mature fat cells. They are found in the subcutaneous tissue and less commonly in internal organs.

Aetiology. The metabolic changes associated with benign tumours are varied but include fundamental defects responsible for the altered growth properties of the tumour. It has been demonstrated that loss of negative-feedback control regulatory enzymes (by citrate or phosphofructokinase) may be an early feature in the development of lipoma [1].

Histopathology. Fat cells in groups slightly larger than the normal lobule are typically enclosed within a capsule of connective tissue, but the capsule may be deficient and the tumour then appears locally invasive. Relatively large blood vessels are seen traversing the connective tissue septa. Primitive fat cells may be found in clinically benign lipomas in children [2]. Xanthomatous and mucinous changes appear in many lipomas. Lipomas exhibit, like many other solid tumours, distinctive cytogenic abnormalities (karyotypic aberrations affecting mainly 12q,6p,13q). Such distinctive changes may be of help in histologically borderline or difficult cases [3]. There are also a variety of rare lipomatous-like tumours; the reader is referred to specialized texts [4].

Clinical features. A lipoma is a subcutaneous nodule, often lobulated, with a characteristic soft putty-like consistency. The overlying skin is normal and moves freely over the tumour, and feels cooler than the surrounding skin. The tumour grows very slowly to reach a diameter that is usually between 2 and 10 cm but may be considerably greater. The most common sites are the neck, shoulders and upper arms, back and thighs. There are rarely any subjective symptoms, but pain from pressure on the nerves is sometimes experienced. Another rare event is infiltration of adjacent tissues in a particular muscle [5]. In these patients, there is a high recurrence rate after surgical intervention because of its diffuse infiltration; thus complete surgical excision is often impossible [6]. Fat necrosis may cause enlargement, pain and tenderness. A large lipoma on the exposed skin of the lower legs is susceptible to nodular perniosis.

There may be only one lipoma, or large numbers [7] may develop at intervals over a period of years. Seven per cent of patients with lipoma have multiple lesions [8,9]. Such lipomas may be randomly distributed, or more or less confined to one region of the body. In most patients,

the presence of multiple lipomas appears to have no special significance [2]. They may, however, be associated with neurofibromatosis, or with visceral lipomas in the respiratory, alimentary or genito-urinary tract. Tendon sheath lipomas are rare but usually associated with a mild disomfort [10]. They are an inconstant feature of Gardner's syndrome, in which they are associated with multiple sebaceous cysts, osteomas and polyposis of the colon.

Atypical lipomatous tumours are uncommon and occur predominantly in middle-aged patients; they often present as slow-growing masses in the extremity. Fifty-two per cent had a recurrence at an average of 4.7 years after resection, of which 39% required additional surgical procedures [11]. Occurrence of a deep lesion and positive margins at the time of the initial surgery correlated closely with the rate of recurrence and the need for additional surgical treatment. The differentiation into a high-grade liposarcoma developed in 13% of such patients [11]; such a malignant change is very rare.

Diagnosis. The diagnosis is usually easy, but in cases of doubt a biopsy should be performed. Angiolipomas are morphologically similar to lipomas, but are intermittently painful. Lipofascial herniae in the natal or perianal region simulate lipomas. Excision and suture are required to prevent recurrence. Mobile encapsulated lipomas are literally very mobile and can be moved from side to side over a range of up to 8 cm [12].

An epidermoid cyst can mimic a lipoma. However, the presence of the central punctum gives a clue to the correct diagnosis. The possibility of hibernoma should be considered when tumours appear in the neck and scapular region.

Treatment. This usually depends on the patient's desire for the lipoma to be surgically removed. Lipoma of the lumbar region may be associated with underlying spina bifida occulta, and removal of the tumour is dangerous without simultaneous exploration of the cauda equina. An MRI scan is essential in such patients; the spinal cord involvement is more frequent in girls than in boys, as is significantly associated with bladder dysfunction [13].

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Angiolipoma

Angiolipomas are benign encapsulated lobulated tumours differing histologically from a lipoma in the excessive degree of vascular (capillary) proliferation. Fibrin thrombi are common. Approximately 10% of all lipomatous lesions examined pathologically are angiolipomas [1]. The age of onset is relatively young, and in one series of 288 patients averaged 17 years. Clinically, the lesions are from 0.5 to 5 cm in diameter and closely resemble lipomas. They are usually painful and tender and are sometimes bluish in colour [2]. The degree of pain varies with the degree of vascularization. They occur most frequently on the arms, legs and abdomen and are often multiple [3].

Angiolipomas are categorized into two groups: infiltrating and non-infiltrating [3]. The non-infiltrating angiolipoma is typically a soft well-encapsulated subcutaneous nodule. The non-infiltrating type occurs in younger individuals and is usually painful. Compression of nerve fibres that accompany the vascular channels may cause pain, which is usually dull. The infiltrating type, which is the less common type of angiolipoma, has a more aggressive behaviour, and can infiltrate osseous, muscular, neural and fibrocollagenous tissues. It may cause signs and symptoms that can simulate malignant neoplasms. The infiltrating type has the propensity to recur following local surgical excision; therefore the treatment for infiltrating angiolipoma is wide excision to include normal tissue surrounding the tumour. Associated features are rare; the association of multiple angiolipomas, multiple cerebral aneurysms and multiple meningomas has been reported [4].

Three cases of HIV-1 infected patients have been described who developed symptomatic angiolipomatous shortly after starting antiretroviral therapy, including protease inhibitors [5].

Painful lesions can be excised if single. Conventional analgesics usually do not help. Multiple lesions have been shown to respond to β-blockade with atenolol (50 mg/day). Pain relief was evident after 24 h. Therapy should be continued for a pain-free period of 2–3 months [6]. A double-blind study proved the benefit of intravenous

lidocaine (lignocaine) (5 mg/kg) in saline given over 45 min. The pain disappeared after 1–2 days but reappeared 3 weeks later [7]. Infiltrating angiolipomas need wide excision [8]. Liposuction has been successfully used in one patient [9].

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Frontalis-associated lipoma [1,2]

This is a deeply placed lipoma of the forehead, which deserves special mention because it is often mistaken for an epidermoid cyst. The lipoma presents a smooth doughy dome-shaped mass, which appears relatively immobile and the skin glides over it. It arises either within the frontalis muscle or between the undersurface of the muscle and its deep fascia, and its removal requires greater surgical skill than is required for removing an epidermoid cyst or lipoma. A layered closure is essential to repair the severed frontalis muscle, and a pressure dressing is advisable to close the 'dead space'.

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Fat-storing hamartoma of dermal dendrocytes

One patient has been described with a congenital reddish brown plaque over the lumbosacral area, which was composed of dermal dendrocytes that had phagocytosed lipid droplets [1]. There were no fat cells in the lesion and no associated metabolic abnormalities.

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Hibernoma [1–3]

SYN. GRANULAR CELL LIPOMA

A rare benign tumour, which consists of primitive fetal brown fat. The histology is characteristic, showing masses of distinctive cells with fine granules and a solitary central nucleus [1–3]. The tumour is encapsulated and multilobular. It occurs in adults of either sex and presents as a firm non-tender nodule, with vascular dilatation of the overlying skin. The sites of predilection are the cervical, axillary and interscapular regions. Surgical excision is the only treatment. Local recurrence at excision is unusual [4].

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Lipomatosis

Several different types of lipomatosis have been described.
1 Multiple symmetrical lipomatosis, characterized by a symmetric formation of fatty tumours, associated with signs of mediastinal location and neuropathy.
2 Pelvic lipomatosis, characterized by fat accumulation in the pelvic cavity with vesical and ureteral displacement, compression and occlusion.
3 Mediastino-abdominal lipomatosis, characterized by intrathoracic and intra-abdominal accumulation of fat, mimicking respiratory disease or ascites.
4 Mediastinal lipomatosis, frequently associated with long-term oral steroid exposure.
5 Renal sinus and perirenal lipomatosis, characterized by a tumour-like accumulation of fat in the renal and perirenal space inside the renal capsule.
6 Adiposis dolorosa, or Dercum's disease, a disease affecting women, characterized by the formation of painful para-articular lipomatous masses.

The cutaneous lipomatoses [1,2] are well-defined but rare syndromes of which two major types are identified: the symmetrical and non-symmetrical varieties. Both produce marked disfigurement. Except in the rare cases when they compress a vital structure, they usually present no physical threat to the patient. Both are benign and non-encapsulated, and represent progressive growth and extension of mature adipose tissue far beyond its normal proportions. The fat accumulation is caused by an increase in cell number rather than cell size by a zonal differentiation of adipoblasts into mature adipocytes [3].

Non-symmetrical lipomatosis

The most common albeit rare form of localized lipomatosis is the non-symmetrical subcutaneous lipomatosis. It is a benign entity and normally has no clinical significance except for the cosmetic disability. A localized form affecting the shoulder girdle [4,5] may infiltrate the deeper structures and produce distal symptoms. A case has been reported with tuberous sclerosis, but the association may be fortuitous [6]. It is not usually the result of any metabolic disturbance, and is not usually associated with abnormalities of lipid metabolism; in one case there was familial hyperlipidaemia [7]. It is familial and the mode of inheritance suggests an autosomal dominant trait [7]. Other associations include ipsilateral cranial and facial asymmetry, cranial and ocular manifestations, alopecia, spasticity and mental retardation. These associations occur with what is called encephalocraniocutaneous lipomatosis—a very rare syndrome [8,9]. It has been suggested that this syndrome is a variety of Proteus syndrome, in which such patients have hyperostoses of the skull, cutaneous lipomas outside the skull and visceral lipomatoses [10].

Multiple symmetrical lipomatosis

By contrast, multiple symmetrical lipomatosis (Fig. 55.27) is characterized by large symmetrical masses of fat, mainly in the neck and shoulder region in a horse-collar distribution. MRI can be used to characterize the nature and extent of disease [11,12]. It may be associated with hypertriglyceridaemia, elevated high-density lipoprotein cholesterol [13], hyperuricaemia, impaired glucose tolerance and renal tubular acidosis. The lipomatous tissue in these patients has been shown to have enhanced lipoprotein lipase activity [14], a possible explanation for the elevated high-density lipoprotein cholesterol levels displayed by these patients. The inheritance in this type is autosomal dominant. Specific chromosomal abnormalities have been reported [15]. Mitochondrial dysfunction is common in multiple symmetrical lipomatosis and may be based on identifiable defects in the mitochondrial genome [16].

These patients may also have severe peripheral and autonomic neuropathy [17], often alcoholism and mediastinal lipomas producing space-occupying symptoms [18]. Sebaceous naevus of Jadassohn has been reported in association with mediastinal lipomatoses [19]. Fifty per cent have alcohol-induced problems [2]. An unusual patient had benign symmetrical lipomatoses and giant rhinophyma producing a grotesque appearance [20]. Madelung's neck, probably the same condition, is a diffuse multilobular lipomatosis involving the back of the neck and the shoulders in a cape-like distribution. It classically afflicts wine porters and brewery workers. The disease may infrequently be sited in the upper thighs and lower abdomen [21]. Localization to the soles has been reported [22]. Localization of the symmetrical lipomatoses to the tongue results in macroglossia. Therapy is partial glossectomy [23].

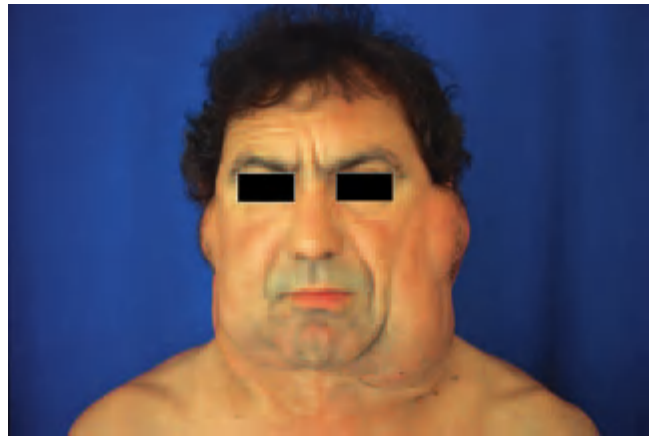

Fig. 55.27 Multiple symmetrical lipomatosis. (Courtesy of M.C. Rodrîguez-Cerdeira, R. Trillo and X.C. Brana, Meixoerio Hospital, Vigo, Spain.)

The prominent fat deposits over the buttocks that constitute the steatopyga of the Bushmen and Hottentots may be regarded as a racial form of physiological lipomatosis. A distal form of acquired symmetrical lipomatosis of the hands has been reported in a chronic alcoholic Bantu male [24].

Treatment of lipomatosis is difficult. It includes classical lipectomy [25,26] but recurrence is common. Liposuction [27–29] has been reported to help considerably.

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Congenital diffuse lipomatosis [1–4]

This has been infrequently recorded. Several syndromes that may involve a neuroectodermal defect have been described, in conjunction with various types of haemangioma or lymphangioma. Congenital lipomatosis may be associated with angiomatosis and macroencephalia (Bannayan's syndrome) [5]. The Proteus syndrome is very rare; the clinical features include hemihypertrophy, macrodactyly, exostoses, epidermal naevi, characteristic cerebriform masses involving the plantar or palmar surfaces, a variety of subcutaneous masses and scoliosis [6]. Histological examination of the subcutaneous masses has identified a variety of lipomatous and angiomatous tumours and hamartomas.

Treatment. Treatment is difficult but liposuction may help.

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Dercum's disease

SYN. ADIPOSIS DOLOROSA

Dercum's disease is a rare progressive disease characterized by localized overgrowth of fat with painful subcutaneous plaques and ecchymoses.

Aetiology. The mechanism of Dercum's disease is not known. It most commonly affects menopausal women; they are usually obese at the time of onset of the disorder and severe emotional disturbance is common. In some families there is a dominant inheritance [1].

Histopathology. The changes are non-specific; there is a combination of fat cell necrosis and interstitial tissue proliferation.

Clinical features [2,3]. Dercum [4] coined the term 'adiposis dolorosa' to describe three cases of a syndrome characterized by painful deposits of adipose tissue occurring over multiple areas of the body (Figs 55.28 & 55.29). Adiposis dolorosa occurs predominantly in postmenopausal women (female : male ratio of up to 30 : 1) and is associated with weakness, fatigue and, frequently, emotional disturbances. Obesity is almost always present initially, but patients may lose weight and become asthenic as the syndrome progresses. The painful areas of fat may occur as subcutaneous 'lumps', which feel like a 'bag of worms' on palpation, or may be diffuse in a localized or generalized pattern. The juxta-articular areas are the most commonly involved site, but painful areas have been described over virtually all areas of the body. The pain occurs with palpation of the involved fat, but may also occur spontaneously. The disease usually begins gradually with only mild discomfort, but may progress to exquisite pain, particularly with movement, so that the patient is effectively immobilized. The pain tends to be cyclical with constant mild to moderate discomfort punctuated by episodes of severe pain, which is unresponsive to many or all analgesic agents.

Psychic disturbances are frequently observed, ranging from mild irritability to dementia. Depression, failure of memory and hypochondriacal complaints are quite common.

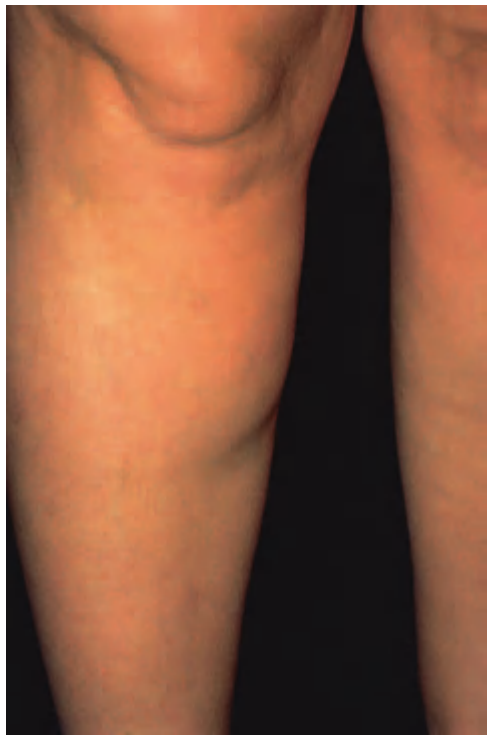

Fig. 55.28 Dercum's disease. (Courtesy of Dr R. Motley, University of Wales College of Medicine, Cardiff, UK.)

Diagnosis. This is not difficult when the classical triad is present: painful plaques, ecchymoses and obesity, appearing in women with amenorrhoea and neurotic symptoms.

Cushing's disease with diffuse deposition of fat, plethora and hirsutes must be distinguished from Dercum's disease. Amenorrhoea and ecchymoses are common to both disorders.

Treatment. Weight reduction and surgical excision of individual tumours may be helpful [5]. The pain is usually unresponsive to conventional therapy but several cases have been shown to respond to intravenous lidocaine [2,6–10]. Two studies were placebo controlled. The pain relief was from 3 to 52 weeks, and repeat therapy was associated with increasing duration of benefit [2,9]. The lidocaine effect is very specific, as other types of pain

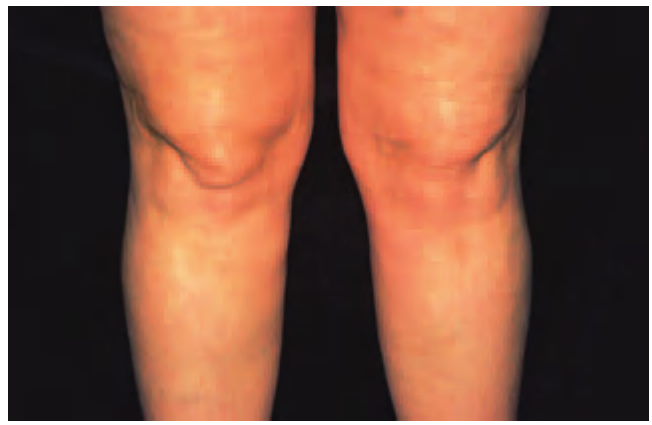

Fig. 55.29 Dercum's disease showing much improvement after liposuction. (Courtesy of Dr R. Motley, University of Wales College of Medicine, Cardiff, UK.)

(e.g. headaches) continued; the mechanism of action is unknown. Some response to mexiletine 150–750 mg orally has been reported [11].

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Chapter 56

The 'Connective Tissue Diseases'

M.J.D. Goodfield, S.K. Jones & D.J. Veale

Introduction

Many single diseases can produce pathology in one or multiple organ systems. However, not all of the conditions that can affect multiple organ systems are related to each other, so what is it that determines the classification of diseases as 'connective tissue diseases'? We recognize that there are certain features common to all of them—the existence of autoimmunity in the form of autoantibody production or disordered cell-mediated immunity, vascular abnormalities characterized by Raynaud's phenomenon, occlusive vascular disease and vasculitis (although the pathology is not entirely a result of vascular inflammation), arthritis or arthralgia, and skin disease. However, dependence on clinical patterning is unreliable because similar patterns of disease may be seen with widely different pathologies. For instance, the primary vasculitides such as Wegener's granulomatosis or polyarteritis nodosa may share many systemic features of the connective tissue disorders, but so may sarcoidosis with a granulomatous pathology but without autoantibody production.

Despite this problem, it is still true that those disorders contained within the umbrella of the 'connective tissue diseases' share many clinical and pathological features. Indeed, it was this pathological similarity that first suggested that abnormalities of the connective tissue might be the common factor linking these conditions. In 1933, Klinge [1] was the first to propose that rheumatic fever and rheumatoid arthritis were disorders of the entire connective tissue. The changes in the intercellular components of the connective tissue, the presence of fibrinoid necrosis in collagenous tissue and the myxomatous swelling of ground substance were similar to those seen in experimental animals made hypersensitive to foreign protein, and for these reasons he concluded that the rheumatic diseases were caused by hypersensitivity. He included other conditions in which fibrinoid necrosis was a feature, such as polyarteritis nodosa, dermatomyositis and malignant hypertension. The presence of widespread fibrinoid change in the vessels led to the inclusion of systemic sclerosis by Masugi and Yä-Shu [2], and also of systemic lupus erythematosus. However, Klemperer *et al.* [3], with whose work the term 'collagen disease' is associated, struck a note of caution by pointing out that fibrinoid necrosis could be seen in the absence of hypersensitivity mechanisms, for example, in the base of peptic ulcers. It has been stated [4] that the presence of fibrinoid degeneration does not warrant the grouping of the conditions showing this change, nor does it imply an allergic mechanism. It is now recognized that there are various types of fibrinoid with somewhat similar staining properties. They have a multiple origin from the degeneration of collagen, from the ground substance, muscle and fibrin and other plasma proteins.

In 1950, Klemperer [5] stated: 'The term diffuse collagen disease was originally applied to acute and chronic maladies which are characterized anatomically by generalized alterations of the connective tissue, particularly by abnormalities of its extracellular components. In this case the term can include rheumatic fever, rheumatoid arthritis,

polyarteritis nodosa, acute lupus erythematosus, generalized scleroderma and dermatomyositis.' Klemperer emphasized his dissention from the widespread indiscriminate use of the term 'collagen disease' for disorders with unusual clinical or pathological features. He confirmed that his sole intention was to put forward the concept that, 'in certain diseases anatomical investigations reveal conspicuous alterations in the intermediary substances of the connective tissue in a systemic manner'. It is now realized that the connective tissue is not the only tissue involved in these disorders.

It has been customary to consider that systemic and discoid lupus erythematosus (SLE and DLE), systemic sclerosis, localized and generalized morphoea, dermatomyositis, rheumatoid arthritis and Sjögren's syndrome should be grouped together, and this has been supported by evidence of clinical, pathological and immunological overlap. The primary vasculitides, such as polyarteritis nodosa, Wegener's granulomatosis and giant cell arteritis, are sufficiently distinct to be considered separately, although there is much clinical overlap with these diseases too. However, these groupings may not be justified and may even hamper our understanding of these diseases. On the other hand, certain patients with evidence of clinical overlap can be distinguished by characteristic immunological abnormalities, associated with differences in outcome and response to therapy. With the passage of time, other conditions, sometimes newly described, such as eosinophilic fasciitis [6], may have to be added to the group.

There is an urgent need for precise and universally acceptable criteria for diagnosis. When adequate criteria and modern investigative techniques are used, it is apparent that each disorder can usually be distinguished as a separate entity. For example, evidence has been produced that DLE is a separate disorder and not a benign variant of SLE [7–9]. Often, subsets can be distinguished clinically, pathologically or immunologically. Immunological subgroupings are becoming more numerous and complex with the identification of new antigens and the reacting autoantibodies. Specific antibodies may be strongly associated with particular disease patterns, such as the antibody to extractable nuclear antigen found in mixed connective disease or anti-Ro or anti-La antibodies in a clinically distinctive type of lupus erythematosus called subacute cutaneous lupus erythematosus (SCLE; see p. 56.24). Moreover, certain diseases that appear clinically homogeneous may be genetically heterogeneous. The separate genotypes in DLE related to age of onset [8,9], the clinical subsets in SLE and the severity of disease in systemic sclerosis related to HLA-B8 [10] are good examples.

Despite these improvements in investigational techniques, diagnosis of these disorders is sometimes far from easy. Results have to be interpreted in the context of the clinical presentation. Patients are not helped by a diagnosis of 'collagen vascular disease' or 'collagenosis' when suffering from an illness with obscure symptoms and signs, possibly associated with an elevated plasma viscosity, and a weakly positive antinuclear antibody. It is the resort of the intellectually destitute and must be avoided. It is usually ultimately possible to make a precise diagnosis. This is very important for the patient and critical for research, both epidemiological and therapeutic. It is more than an academic exercise as, in the future, specific therapy may well depend on the precision of diagnosis.

Accurate naming of diseases is important for patients, but is also relevant to this chapter. Is the term 'the connective tissue diseases' [11] the most appropriate title for this contribution? We believe that it is because there seems to be no better alternative. Some authorities prefer the older term, 'collagen disease'; others [12] apply it to all inherited or acquired disorders of the connective tissue system. 'Collagen disease' is incorrect because there is no evidence that collagen is primarily at fault. 'Collagen vascular disease' conveys a little more detail, but is still incorrect. The increasing emphasis on immunological abnormalities in these conditions has brought the terms 'autoimmune disease' [13] and 'immunological disease' [14] some popularity, but both are overinclusive. To avoid the premature coining of a confusing new term we have preferred to continue to refer to 'connective tissue disease' wherever the use of a collective term is unavoidable.

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Lupus erythematosus [1,2]

Lupus erythematosus (LE) is usually divided into two main types: DLE and SLE (defined on pp. 56.5 and 56.28

Table 56.1 Comparison of data on a series of patients with discoid and systemic lupus erythematosus seen by the authors.

	Discoid lupus erythematosus (n = 120) (%)	Systemic lupus erythematosus (n = 40) (%)
Rash	100	80
Joint pains	23	70
Fever	0	40
Raynaud's phenomenon	14	35
Chilblains	22	22
Poor peripheral circulation	26	32
ESR > 20 mm/h	20	85
Serum globulin > 3 g (%)	29	76
LE cells	1.7	83
Antinuclear factor(s)	35	87
Homogeneous	24	74
Speckled	11	26
Nucleolar	0	5.4
Precipitating autoantibodies	4	42
WR positive	5	22
Rheumatoid factor positive	15	37
Direct Coombs' test positive	2.5	15
Leukopenia	12.5	37
Thrombocytopenia	5	21

ESR, erythrocyte sedimentation rate; LE, lupus erythematosus; WR, Wassermann reaction.

respectively). Although some authors [3] would prefer the term cutaneous LE to DLE, we are continuing to use the term DLE in view of the long usage and to avoid confusion with SCLE. Others [4] suggest classifying LE into three groups—cutaneous LE, intermediate LE and SLE, but this is still controversial. DLE can be subdivided into a localized form in which lesions are confined to the face above the chin, the scalp and the ears, and a disseminated form in which lesions also occur elsewhere on the body [5,6]. Although haematological and serological abnormalities occur slightly more frequently in the disseminated form, the natural history of the two subgroups is similar, and it is likely that they are subsets of the same disorder. SCLE has been described as a subset intermediate between DLE and SLE [7].

The more controversial point is whether DLE and SLE are variants of the same disease. The evidence in favour of this may be summarized as follows:

1 The cutaneous lesions of SLE and DLE may be clinically and histologically indistinguishable.

2 Certain clinical features are found in both conditions (Table 56.1).

3 Similar haematological, biochemical and immunohistochemical abnormalities can be demonstrated in both conditions (Table 56.1), although the incidence of abnormalities is lower in DLE.

4 Patients with DLE occasionally develop evidence of overt SLE.

5 Patients with SLE may develop typical lesions of DLE when the active phase subsides [8].

6 Conditions such as lupus panniculitis, a recognizable clinical and pathological entity, occur in both DLE and SLE.

This seems to be formidable evidence, but the following observations require explanation.

1 The risk of a patient with DLE developing overt SLE is small. It varies from 1.3% [9] to about 6.5% [2,10–12]. The risk is higher in patients with disseminated DLE (22%) than in DLE confined to the head and neck (1.2%) [12]. In some series [13–15], such conversion was not encountered despite follow-up for nearly 30 years. A retrospective study [16] of 127 patients with SLE showed that eight patients had had discoid lesions from 2 to 29 years.

2 The presence of laboratory abnormalities in DLE does not in itself appear to predispose to the development of SLE [17], although they are common in disseminated DLE [12,18]. Haematological abnormalities were still present in 50% of 77 patients with DLE 5 years after initial assessment, yet none had developed SLE in the same period [14]. The same prognosis was found in a subgroup intermediate between discoid and SLE as in patients with uncomplicated LE [15].

3 Immunoglobulins and complement are present in uninvolved skin of patients with SLE and absent in patients with DLE [19].

4 Most patients with DLE exposed to UV radiation, stress, trauma, etc., do not develop the systemic disease.

5 The age and sex distribution of SLE [20,21] is strikingly different from that of DLE [15,22].

It has been proposed [2,21–24] that both SLE and DLE are initiated by the occurrence of somatic mutations in lymphocytic stem cells of predisposed individuals, and that they are genetically distinct. There are at least three genotypes related to age of onset in DLE [24] and the female/male ratios found in each disease suggest that

there is only one X-linked allele involved in genotype 2 and two in genotype 3. On the simplest interpretation, three 'forbidden clones' [25] of lymphocytes synthesizing cellular autoantibodies develop in SLE, whereas only one 'forbidden clone' is involved in DLE. Autosomal predisposing alleles are probably also present in all the genotypes in both SLE and DLE. The nature of these somatic mutations and the predisposing alleles remain unkown, but almost certainly include polymorphisms of genes determining the production of inflammatory cytokines [26].

6 Further evidence that DLE and SLE are genetically different disorders is now available from studies of histocompatibility antigens in the two diseases [27]. There is a significant difference in the incidence of HLA-B8 in female patients developing each disease between the ages of 15 and 39 years. It is considered that patients may have the predisposition to SLE, DLE or both. Those patients who 'convert' from DLE to SLE, and those patients with SLE who have discoid skin lesions, must be genetically predisposed to both conditions. Those patients with only a genotype for DLE will never convert, even when subjected to environmental factors, such as drugs, bacterial or viral infections, UV radiation and stress. More recent molecular genetic data give further support to this concept [28].

At present it is not possible to determine the genetic pattern of individual patients or to predict accurately the small proportion of patients with DLE-like lesions who will develop SLE, although the link with HLA-B8 has already been discussed [27]. Humoral autoantibodies are not the primary pathogen in these diseases [29], but they probably reflect the underlying cell-bound autoimmunity that causes the disease. Nevertheless, they may enhance tissue damage [30], and specific antibodies may be responsible for certain features such as the risk of neonatal LE (anti-Ro) and for thrombosis (the lupus anticoagulant). The ability to synthesize particular antinuclear antibodies may depend on additional genetic factors, and this could account for the absence of such antibodies in certain patients with active disease. If the possession of a serological abnormality in DLE implies a predisposition to transformation into systemic disease, we would expect the sex ratio of this group to be similar to that for SLE. This is not the case [11]. The sex ratio in patients with DLE and laboratory abnormalities is not significantly different from the sex ratio in patients without abnormalities.

From consideration of the clinical features, the natural history, the age and sex distribution, and studies of histocompatibility antigens, it is concluded that patients with DLE and haematological and serological abnormalities are not cases of SLE in disguise, but are cases of DLE, which is a separate entity from SLE, and has a different genetic background. Each of these entities, however, consists of several subsets, also genetically determined.

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Discoid lupus erythematosus

SYN. CUTANEOUS LUPUS ERYTHEMATOSUS; CHRONIC DISCOID LUPUS ERYTHEMATOSUS

Definition. DLE is a benign disorder of the skin, most frequently involving the face, and characterized by well-defined red scaly patches of variable size, which heal with atrophy, scarring and pigmentary changes. The histology is characteristic. There are haematological and serological changes in approximately half of patients, and these changes, with other evidence, suggest an autoimmune aetiology.

Aetiology. This disorder has a characteristic age and sex pattern. The disease affects twice as many females as males, with a peak age of onset in the fourth decade in females and slightly later in males, although it can occur at any age. In a series of 1045 cases, 3% began under 15 years of age and 2.5% at over 70 years [1].

Genetic factors. Differences in the incidence of histocompatibility antigens [2–4] have supported the concept of multiple genotypes. Positive associations with HLA-B7, -B8, -Cw7, -DR2, -DR3 and -DQw1 are reported [5,6], but not always confirmed. The relative risk is increased with certain combinations of antigens—HLA-Cw7, -DR3 and -DQw1 and for HLA-B7, -Cw7 and -DR3. The extended haplotype—HLA*01, B*08, DRB1*0301—is associated with both SCLE and DLE, and the A*03, B*07, DRB1*15 haplotype has been associated with DLE alone [5]. Patients of both sexes developing lesions between the ages of 15 and 39 years have an increased incidence of HLA-B7, and females over the age of 40 years of HLA-B8, compared with controls [3]. Familial cases do occur [6]. A family history was found in 4% of one series [7]. Steagall *et al.* [8] reported the condition in identical twin sisters, and listed 25 families with two or more members who had DLE or SLE. Recent studies also indicated a striking relationship between polymorphic light eruption and DLE, first in twins [9] and then in a large cohort of patients and their relatives, suggesting a common genetic background for these disorders [10]. DLE has been noted in three consecutive generations [11].

It has been proposed that genetic factors, including somatic mutations, are implicated in the pathogenesis of the disease [11–13]. In a mathematical model based on the age of onset of the disease, there are at least three genotypes and probably a fourth corresponding to those 'transitory' cases [14] in which immunoglobulins are present at the dermal–epidermal junction of uninvolved skin. The relative size of these subgroups may differ between countries, because of differences in the frequency of the predisposing genes. The initiation of the disease may result from the occurrence of random events, either related to somatic mutation or to environmental factors. The model suggests that: (i) three mutations affecting autosomal genes; (ii) four mutations (one of which affects an X-linked gene); or (iii) five mutations (one involving an X-linked gene) could explain the three genotypes. As a result of the mutations, control of lymphocytes is lost and, after a latent period of approximately 4 years in females and 2 years in males, clinical signs of the disease become manifest. Normally, an endogenous defence mechanism appears to be directed against the uncontrolled lymphocytes. Environmental factors, by interfering with this defence mechanism, can precipitate or exacerbate the disease. Supporting this view, DLE-like lesions have occurred after allogeneic bone marrow transplantation [15].

Environmental factors. The onset of lesions may be precipitated by a variety of factors. At Leeds, lesions started with trauma in 11%, with mental stress in 12%, sunburn in 5%, infection in 3%, exposure to cold in 2% and pregnancy in 1%. The types of trauma included splashing with hot fat, a scratch on the nose and various types of wounds and scars. In the remainder (approximately two-thirds), lesions started apparently spontaneously. Once lesions had developed, exacerbations occurred particularly with exposure to sunlight and trauma.

Lodin [16] noted a lower incidence of trauma (2.2%) and included exposure to X-rays, diathermy and chemical burns, and lesions in scars of herpes zoster. DLE has developed in an old smallpox vaccination scar [17] and precisely in the field of radiation given for bronchogenic carcinoma [18]. DLE may have followed gas tungsten arc welding [19], psoralen and UVA (PUVA) therapy [20] and laser therapy [21]. Occasionally, drugs (e.g. isoniazid [22], penicillamine [23], griseofulvin [24] and dapsone [25]) may precipitate lesions of DLE. Patients with the primary antiphospholipid antibody syndrome may also develop DLE [26].

The finding of antibodies to reovirus RNA in 42% of patients suggests that viruses may have a role in DLE [27]. The significance of the finding of tubular structures, approximately 20 nm in diameter and similar to paramyxoviruses, in endothelial cells, perivascular histiocytes or fibroblasts [28,29], particularly of new lesions, is not yet known. They are found in the lesions of DLE but only occasionally in uninvolved skin [30]. A decrease in the frequency and size of these structures has been observed after chloroquine therapy [31]. It is possible that they are of viral origin.

Once lesions have developed, exacerbations may be associated with a variety of factors. In 120 patients at Leeds, a history of exacerbations with sunlight was found in 68%, but others have disagreed [32]. In those with photo-aggravated disease, both wavelengths shorter than 329 nm [33] and the whole range through UVB, UVA and visible light can produce lesions under experimental

conditions [34]. Skin lesions clinically and histologically compatible with lupus erythematosus (LE) were induced by UVB and UVA radiation in 42% of patients with DLE, 64% of patients with SCLE and 25% of patients with SLE [35]. Seventeen per cent of patients notice an exacerbation with cold, but more than half of patients note that the condition worsens in the summer, whereas 10% are worse in winter. Approximately 13% of patients notice a premenstrual deterioration. The effect of pregnancy is variable [36], as is the response to hormone replacement therapy [37].

There is no doubt that worry and anxiety play a part, and 16% of patients have noticed lesions deteriorating at such times.

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Pathology [1]. The various clinical types of LE show an essentially similar histological picture (Figs 56.1 & 56.2) [2], and the subsets of LE cannot be distinguished histologically [3]. The salient features are as follow:

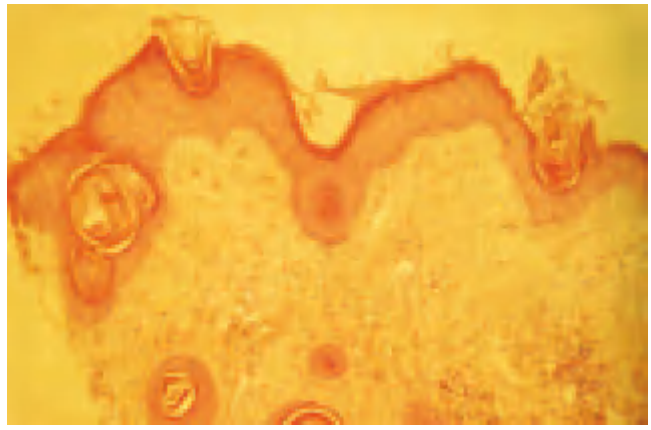

Fig. 56.1 Discoid lupus erythematosus: there is atrophy of the epidermis, keratotic plugging, liquefaction degeneration of the basal layer, oedema and hyalinization of the connective tissue below the epidermis and a marked inflammatory infiltrate.

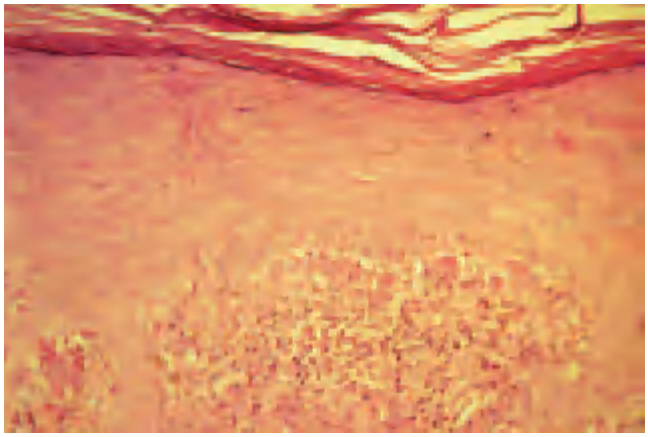

Fig. 56.2 Discoid lupus erythematosus: the degeneration of the basal layer and predominantly lymphocytic infiltration are well shown.

1 Liquefaction degeneration of the basal cell layer of the epidermis
2 Degenerative changes in the connective tissue, consisting of hyalinization, oedema and fibrinoid change, most marked immediately below the epidermis
3 A patchy dermal lymphocytic infiltrate with a few plasma cells and histiocytes, particularly around the appendages, which may be atrophic.

The presence of at least two of these is essential to the histological diagnosis of LE. The majority of infiltrating lymphocytes are T lymphocytes [4] and express Ia-like antigens, as well as the γ/δ T-cell receptor [5]. The following changes may also be found, but are less important:
1 Thinning and pallor of the epidermis with relative hyperkeratosis and plugging of the follicular mouths
2 Thickening of the basement membrane of the epidermis and sometimes of small vessels
3 Premature elastotic degeneration of collagen in light-exposed areas.
In tumid lesions the dermal infiltrate can be very dense, and sometimes almost granulomatous. Dermal deposits of mucin occur [6], which may be diffuse or localized, and form nodular lesions. Deposits may be very gross [7]. Occasionally, irregular hyperplasia of the epidermis occurs, and there may be clefts, or even bullae, between the dermis and epidermis. Although keratotic plugs are usually found in the openings of the hair follicles, they may also block the sweat ducts or occur independently of either structure. Sometimes, the hair follicles contain concentric layers of keratin instead of hairs. Pilosebaceous atrophy is a characteristic feature of DLE [8]. Atrophy of the prickle cell layer occurs to a variable extent, and sometimes there may be acanthosis. Melanin may be found in the upper dermis as the result of pigmentary incontinence. Blood vessels are dilated and the upper dermis is oedematous. Sections stained with the periodic acid–Schiff (PAS) technique show thickening of the basement membrane.

Table 56.2 Diseases associated with the presence of immunoreactants at the dermal–epidermal junction that may be confused with lupus erythematosus.

Mixed connective tissue disease
Systemic sclerosis
Dermatomyositis
Sjögren' syndrome
Myasthenia gravis
Porphyrias
Granuloma annulare
Necrobiosis lipoidica
Amyloidosis
Graft-versus-host disease
Psoriasis
Pyoderma gangrenosum
Sarcoidosis
Leprosy
Erythema multiforme
Pityriasis lichenoides acuta
Granuloma faciale
Keratoacanthoma
Scabies
Facial telangiectases
Bullous pemphigoid

Immunopathology. Immunohistology [9,10] shows the presence of immunoglobulins IgG, IgA, IgM and complement at the dermal–epidermal junction, in skin lesions present for 6 weeks or more, in approximately 80% of patients [11,12]. Homogeneous, granular or thready patterns occur, but the deposition is usually homogeneous in older lesions. They are more frequent on the face and in untreated lesions, but are rare on the trunk [13], and decrease after treatment with topical corticosteroids. They do not occur in uninvolved skin, unlike the majority of cases of SLE. For the diagnosis of DLE lesions, light microscopy is most valuable and should be carried out before direct immunofluorescence [14]. Immunoreactants are also found in oral mucosa and the conjunctiva [15]. C1q deposits are found in 29% of patients with immunofluorescent-positive DLE, compared with 90% in SLE, and the presence of such deposits implies an increased risk of eventual systemic disease [16]. Deposits at the dermal–epidermal junction are not specific to LE and have been found in many other circumstances (Table 56.2). However, in these diseases the deposits are less prominent at the dermal–epidermal junction and are more striking in the blood vessel walls. In LE, the deposits are heavy and contain several immunoglobulin classes, whereas in the other diseases only a single immunoglobulin class is usually present. In scarring alopecia caused by LE, the deposits occur around hair follicles, a feature not seen in other types of scarring alopecia [17].

Properdin has been demonstrated at the dermal–epidermal junction in 70% of lesions, usually in association with deposition of immunoglobulin, C3 and C4 [18]. It may also be found in non-lesional skin. Serum

properdin levels are raised compared with controls, as they are in patients with clinically active SLE [18]. In more acute forms there is less hyperkeratosis and dermal infiltration, but more dermal oedema, liquefaction necrosis and atrophy. Disruption of the elastic lamina and, rarely, endothelial proliferation and thrombosis of the deeper vessels of the dermis have been reported [19]. Biopsy material from lesions on the palms stained for alkaline phosphatase activity shows irregular capillary loops with branching, 'dead end' spurs and coiling [20]. In SLE, similar changes are found in involved and uninvolved skin.

Chronic DLE must be differentiated from five other conditions in which lymphocytic infiltrations of the dermis occur.

1 In Jessner's lymphocytic infiltration [21], the dermis shows large circumscribed aggregations of lymphocytes, often concentrated round the dermal appendages and blood vessels, with a normal epidermis. Sometimes, the infiltrate may extend into the fat of the subcutaneous tissues. Immunohistochemical studies show that the cells are predominantly T lymphocytes [22], as they are in DLE and SLE [23]. Monoclonal antibody studies show an increase in natural killer (NK) cells and activated cytotoxic T lymphocytes in Jessner's lymphocytic infiltration [24].

2 In polymorphic light eruption (PLE), the infiltrate is less prominent and more likely to occur around blood vessels than cutaneous appendages. Liquefaction degeneration is infrequent but, if present, it may be difficult to distinguish from that of DLE. There may be spongiotic changes in the epidermis and parakeratosis (the histology has some features of eczema, but the dermal infiltrate is usually denser). Lever and Schaumburg-Lever [25] believe that most cases of Jessner's lymphocytic infiltration and the plaque-type of PLE represent variants of chronic DLE, but immunoglobulin does not occur at the dermal–epidermal junction in either of the first two conditions [26,27].

3 Scattered patches of lymphocytes occur in the dermis in lymphocytic lymphoma, but there are no epidermal changes.

4 The infiltrate in lymphocytoma cutis (Spiegler–Fendt sarcoid; see Chapter 54) is usually separated from the normal epidermis by a band of normal collagen, and consists of lymphocytes and a few histiocytes. Sometimes, a follicular arrangement is present, with lymphocytes surrounding islands of histiocytes resembling lymph node follicles.

5 In benign lymphocytic infiltration, polyclonal T and B cells form aggregates in the dermis.

Sometimes, patients show clinical, histopathological and immunofluorescence overlap between DLE and lichen planus [28,29]. In such cases, a definite diagnosis cannot always be made, and it is likely that such patients have both diseases [30]. A major immunohistological finding is the presence of fluorescent ovoid bodies at the dermal–epidermal junction and in the dermis [29], which may be associated with a linear band of immunoglobulins, complement or fibrinogen.

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Incidence. Because the condition is persistent, DLE appears to be more common than it really is. The incidence among new patients in the Department of Dermatology at Leeds is approximately 4 or 5 in 1000. It is said that it is only half as frequent in black people [1], although the distribution is worldwide.

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Clinical features

Symptoms. The patient usually presents with a rash, but on questioning a history of Raynaud's phenomenon, chilblains or poor peripheral circulation is often obtained. In 120 patients at Leeds, 14% had Raynaud's phenomenon and 22% had chilblains; a poor peripheral circulation, without a definite story of Raynaud's phenomenon, was noted in a further 26% of patients. Joint pains are complained of by approximately one-quarter of patients, but this is similar to the incidence in controls [1]. Most patients have no symptoms of systemic upset, even with widespread cutaneous disease.

Most patients have disease limited to the head and neck (localized DLE), but a few have much more extensive disease, potentially affecting any area of the skin (disseminated DLE).

Localized disease. The face is most commonly affected, and the scalp, ears, nose, arms, legs and trunk to a lesser extent. The circumscribed or discoid type is the most frequent (Fig. 56.3), and occurs particularly on the cheeks, the bridge of the nose, the ears, the side of the neck and the scalp. Lesions may be bilateral, although not necessarily symmetrical, or unilateral. Alopecia occurs in the scalp lesions in approximately one-third of patients [2], and is usually permanent (Fig. 56.4). The eyebrows may be sparse, with erythema of the eyebrow skin. Usually, lesions occur as well-defined erythematous patches, varying in size from a few millimetres to 10–15 cm. There is adherent scale in many cases, and when this is removed its undersurface shows horny plugs which have occupied dilated pilosebaceous canals. This so-called 'tin-tack' sign can sometimes also be seen in localized pemphigus foliaceus [3]. When not obscured by scaling, these horny plugs can be seen on direct examination. The surface may present a dirty brownish yellow appearance that is rough to the touch, because of the follicular plugging. If hyperkeratosis is marked, a warty lesion with a red, slightly raised edge results. This warty type of LE is most commonly seen on the nose, temples, ears and scalp, but may also occur on the palms and soles and cause difficulty with walking (Fig. 56.5) [4].

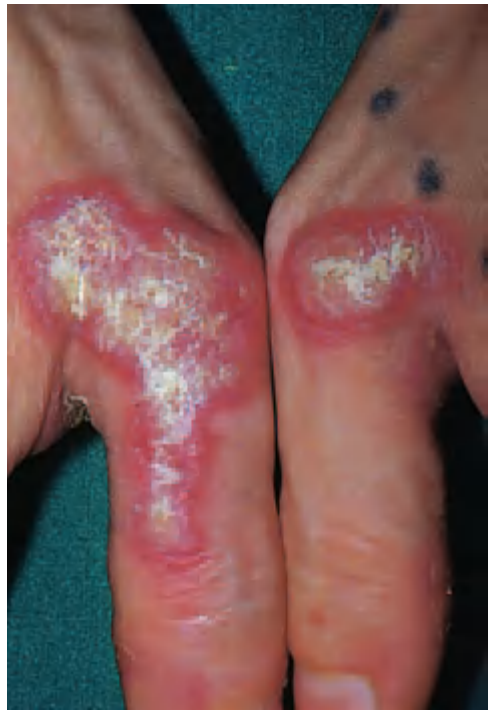

Fig. 56.3 Discoid lupus erythematosus: the typical scaling is well shown.

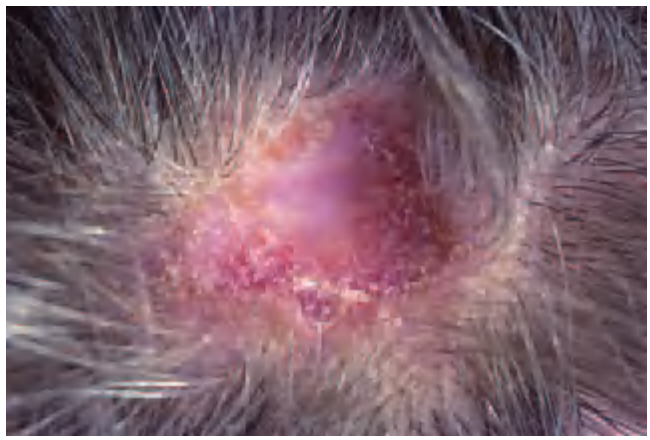

Fig. 56.4 Discoid lupus erythematosus of the scalp: note the follicular plugging.

Non-itching hyperkeratotic papulonodular lesions on the arms and hands, resembling keratoacanthoma, hypertrophic lichen planus or nodular prurigo, also occur [5]. Sometimes, the appearance resembles psoriasis. In other cases, there may be very little hyperkeratosis. Lesions

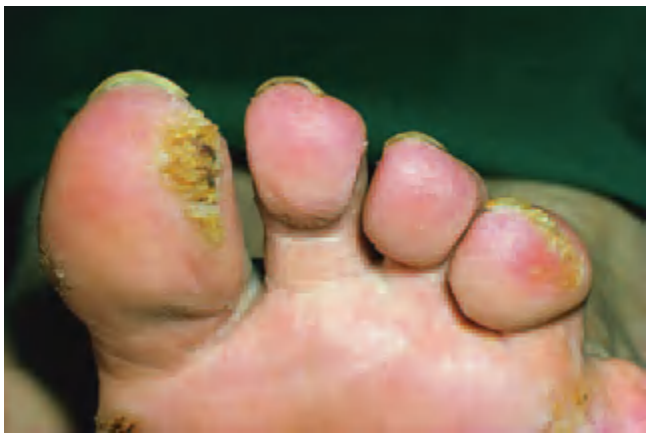

Fig. 56.5 Warty lesions of the feet in chronic lupus erythematosus.

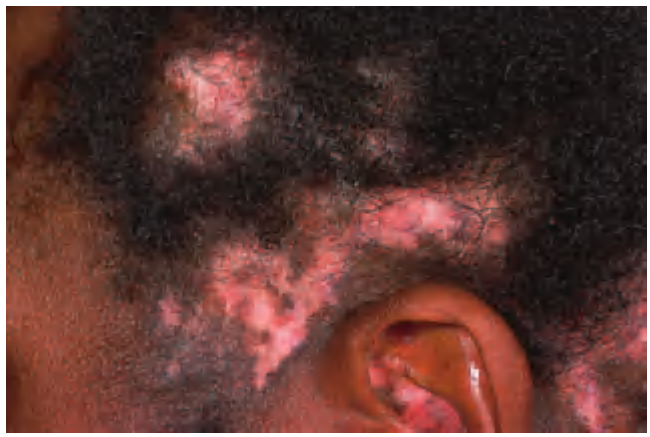

Fig. 56.7 Discoid lupus erythematosus in a black person.

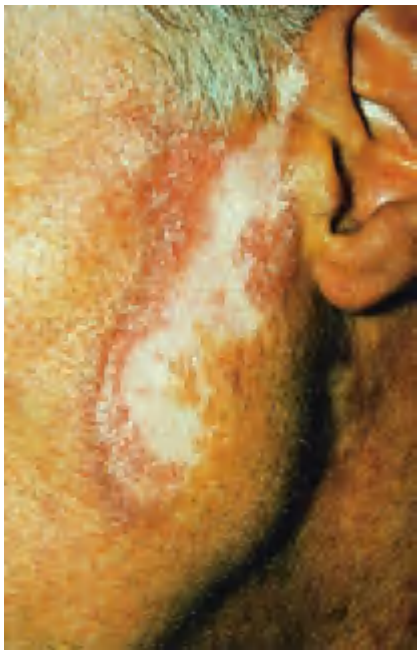

Fig. 56.6 Discoid lupus erythematosus: the pre-auricular type with pigmentation around the scarred area.

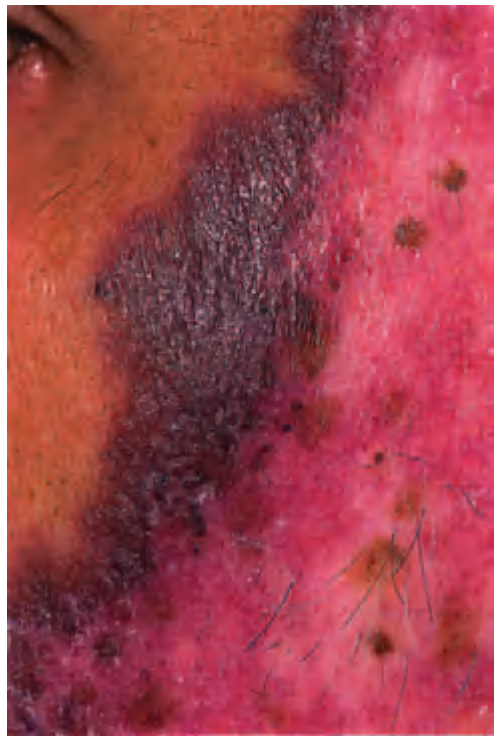

Fig. 56.8 Discoid lupus erythematosus in an Asian patient, showing marked hyperpigmentation at the border of the affected area.

then present as reddish, well-defined, almost smooth plaques with little or no scaling. Sometimes, these plaques may show prominent flattening in the centre, giving rise to annular lesions. Over the course of some months, particularly if treated, lesions flatten and may clear completely without much scarring. More frequently, a thin white scarred area, often with a slightly raised, red border or zone of hyperpigmentation, remains (Fig. 56.6). Localized cribriform scarring occurs, particularly on the face. Pigmentary disturbances are common, especially in dark-skinned people, and there is some evidence that DLE is more severe in black people (Figs 56.7 & 56.8) [6]. Patches of leukoderma may be interspersed with hyperpigmented areas. If relapse occurs, it usually starts in the reddish zone surrounding the scar. Calcification may occur in the plaques [7]. Lesions on the ear lead to considerable atrophy and scarring (Fig. 56.9). Wide follicular pits, sometimes containing scale or blackheads, occur mainly in the concha or triangular fossa of the ear (Fig. 56.10). They occur in up to one-third of cases [8] of DLE but they also occur in SLE. A pruritic chronic discrete umbilicated papular eruption may occur on the back, and results in acneiform hypertrophic follicular scars [9]. In approximately 7.5% of patients, the lesions on the face resemble rosacea, and differentiation can be difficult, particularly as in approximately 15% of cases patients with

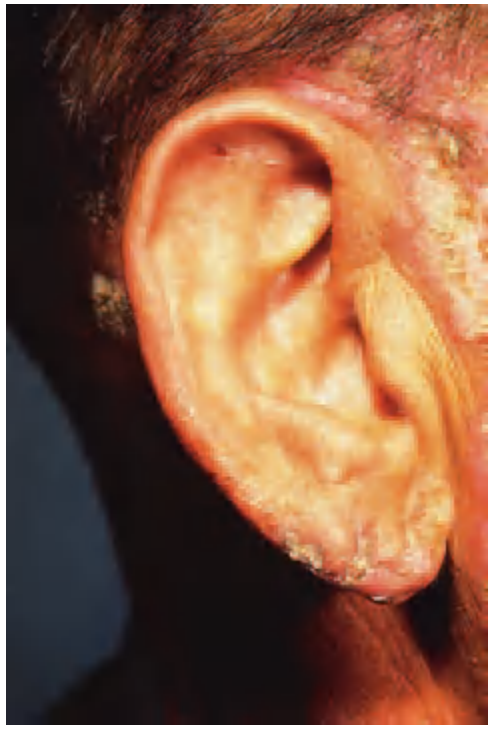

Fig. 56.9 Discoid lupus erythematosus of the ear with scarring and atrophy.

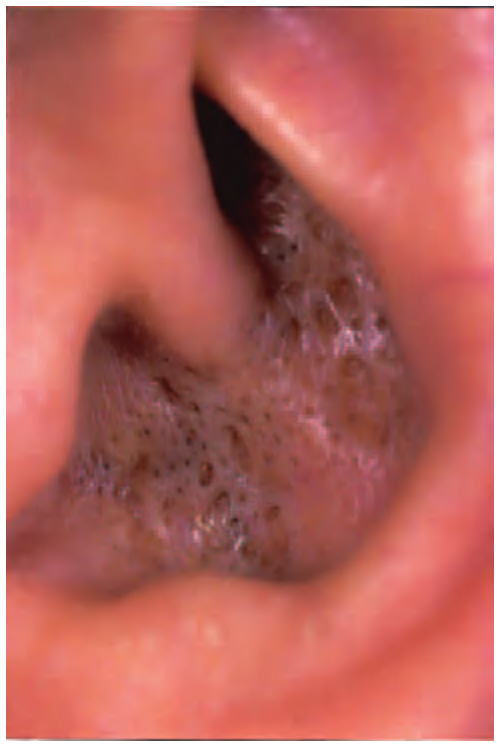

Fig. 56.10 Discoid lupus erythematosus: characteristic pits in the ear.

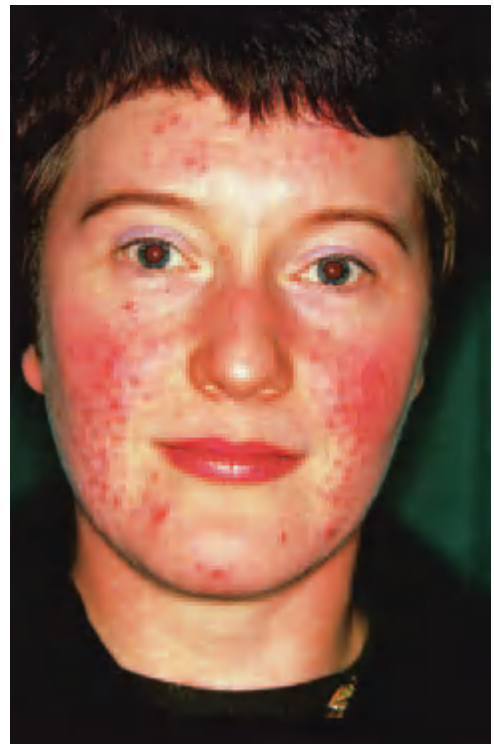

Fig. 56.11 Discoid lupus erythematosus: a rosaceous pattern seen in 7.5% of patients.

true rosacea show exacerbation by sunlight. LE of this type presents with reddish nodular lesions on the nose, cheeks, forehead and sometimes chin, and is associated with a diffuse erythema of the face and easy flushing. Usually, there are no pustules as in true rosacea (Fig. 56.11) [10]. Low-titre antinuclear antibody in rosacea can be ignored [10]. Biopsy may be required to distinguish between LE and rosacea. Tumid lesions may occur, in which the tissues are swollen, brawny, warm and tense (Fig. 56.12). The surface shows a reddish, mottled appearance resulting from scarring. This type of lesion may be many centimetres in diameter and involve the whole of one cheek, or even the whole of a limb. Another clinical type of DLE results in annular atrophic plaques [11] on the face, neck and behind the ears. The centre of the plaques is depressed and sclerotic, and the lesions resemble morphoea, lichen sclerosus or 'annular atrophic plaques' [12]. Early lesions show IgG and complement at the dermal–epidermal junction [11], but repeated biopsies may be necessary to confirm the diagnosis.

Disseminated DLE (DDLE). Characteristic lesions of DLE may occur in a widespread pattern on the trunk and limbs, or may be localized to other body sites. This occurs almost always in women, and they are usually cigarette smokers. The appearance may be indistinguishable from the papulosquamous type of SCLE (see p. 56.24), but

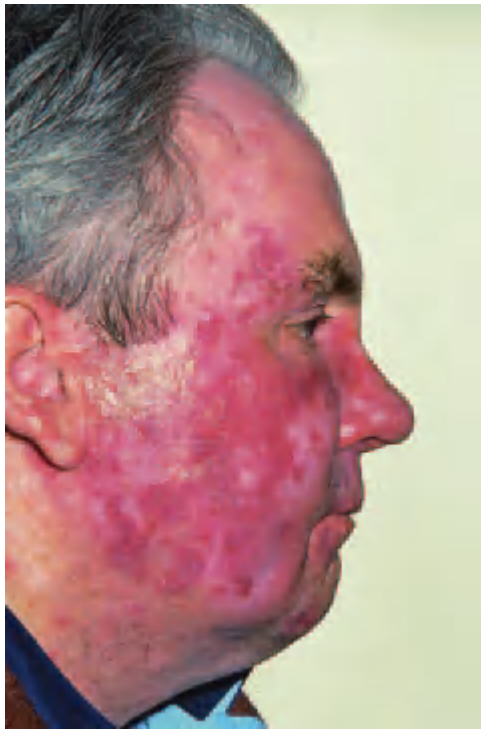

Fig. 56.12 Discoid lupus erythematosus: tumid lesions of the face.

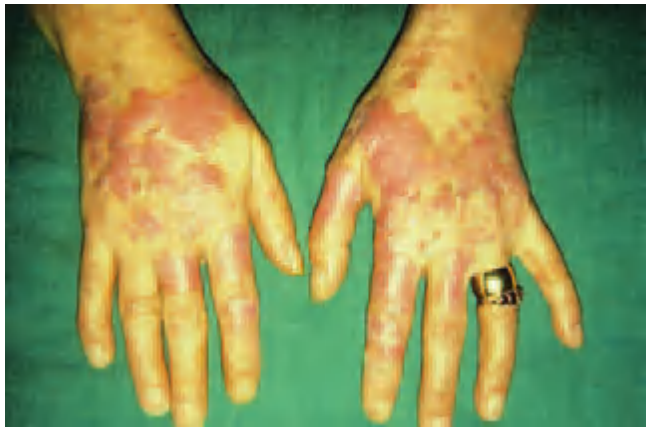

Fig. 56.13 Discoid lupus erythematosus: plaques on the back of the hands.

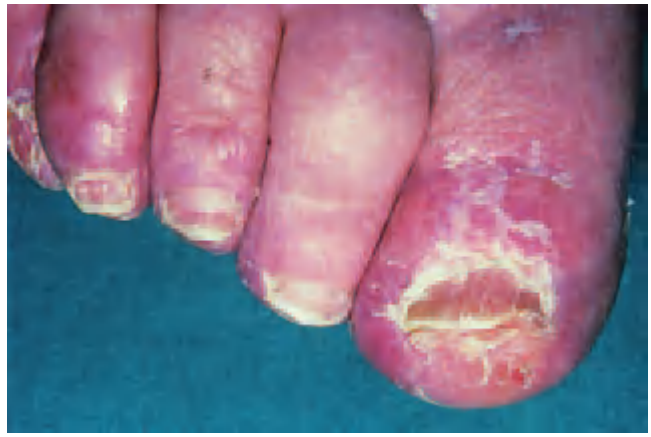

Fig. 56.14 Discoid lupus erythematosus: characteristic redness and scaling of the toes.

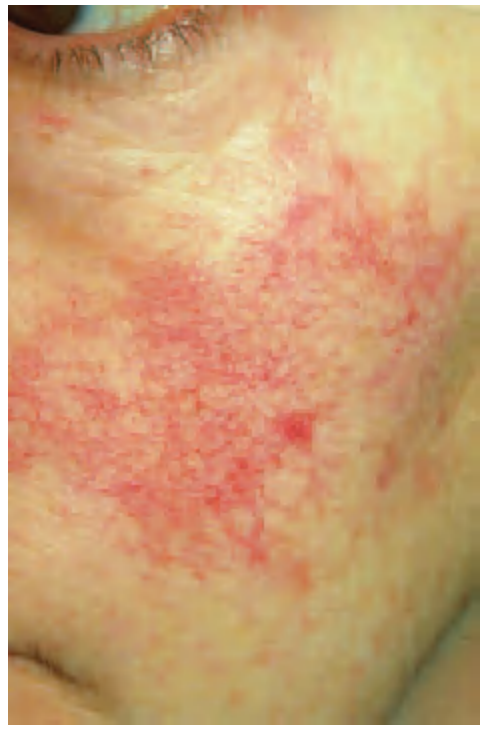

Fig. 56.15 Telangiectatic lupus erythematosus of the cheek.

scarring occurs in most patients. This variety tends to be persistent, resistant to therapy and associated with severe psychological upset. Lesions on the dorsa of the hands (Fig. 56.13), palms [4] or toes (Fig. 56.14) [13] occurred in 6% of patients at Leeds. Purplish plaques may occur on the front of the knees and on the back of the heels. Another disseminated variety results in a reticulate telangiectasia, usually seen on the arms, legs and the back of the calves. This type of telangiectasia is probably similar to 'lupus erythematosus telangiectoides', first described by Crocker [14]. Behçet [15] reviewed this clinical variant, which occurs in SLE as well as in DLE. The appearances are characterized by a persistent blotchy reticulate telangiectasia, which occurs on the face, neck, ears, dorsa of the hands, breasts, heels and on the sides of the feet (Fig. 56.15). Healing occurs with punctate atrophic scarring. The histology of this type of lesion shows an atrophic epidermis, with dilatation of the superficial vessels of the skin and slight infiltration of the papillary part of the corium. A further, more annular variant has been called 'lupus erythematosus gyratus repens' and consists of a migratory gyrate annular erythema with the histological features of LE, although the lupus band test is negative [16]. There may be an underlying carcinoma.

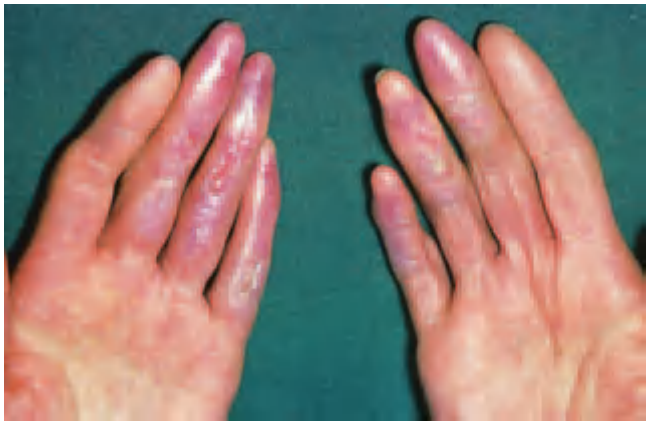

Fig. 56.16 Unusual spindling of the fingers and hyperextension of the distal phalanges in discoid lupus erythematosus.

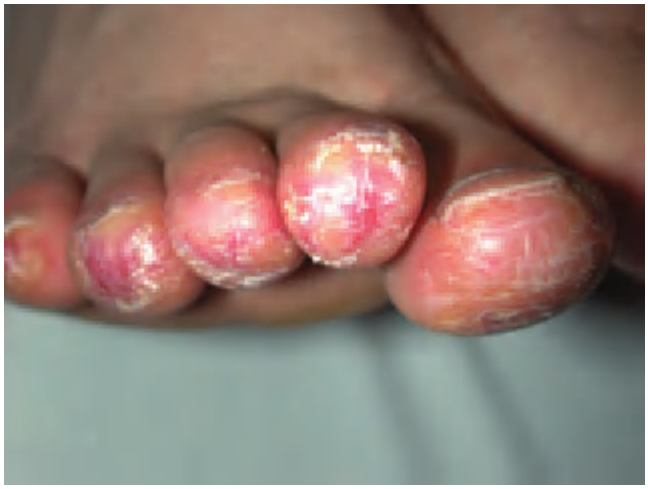

Fig. 56.17 'Chilblain' lesions in a patient with Ro-positive systemic lupus erythematosus.

Occasionally, one or more fingers may show a curious atrophic spindling, sometimes with hyperextension of the terminal phalanges and dystrophy of the nails (Fig. 56.16). The fingers and toes may become markedly atrophic, with patchy erythema and tuft resorption on X-ray. Rarely, bullous lesions [17] may occur. Arteritic lesions resembling those of Degos' syndrome or disseminated atrophie blanche occasionally occur, and linear lesions following Blaschko's lines have been reported [18].

'Chilblain lupus' (Fig. 56.17) [19]. Approximately 6% of patients, predominantly female, develop chilblain-like lesions chiefly on the toes and fingers, but also on the heels, calves, knees, knuckles, elbows, nose and ears. Usually, but not always, the chilblain lesions occur some years after the development of discoid lesions on the face. It can be precipitated by pregnancy [20]. When the discoid lesions remit with treatment, the chilblains persist. Less commonly, discoid and perniotic lesions start simultaneously, and sometimes perniotic lesions occur alone. Histology and immunohistology is that of DLE, and the non-lesional skin gives a negative fluorescent band test. Some patients may have cryofibrinogenaemia or cold agglutinins. Patients are usually Ro antibody-positive [21]. They are also either smokers, or have markedly abnormal peripheral circulation with low resting blood flow [22]. Approximately 15% of patients develop SLE, and this occurs more frequently in those who develop both forms of cutaneous LE simultaneously and in those with the erythema multiforme syndrome.

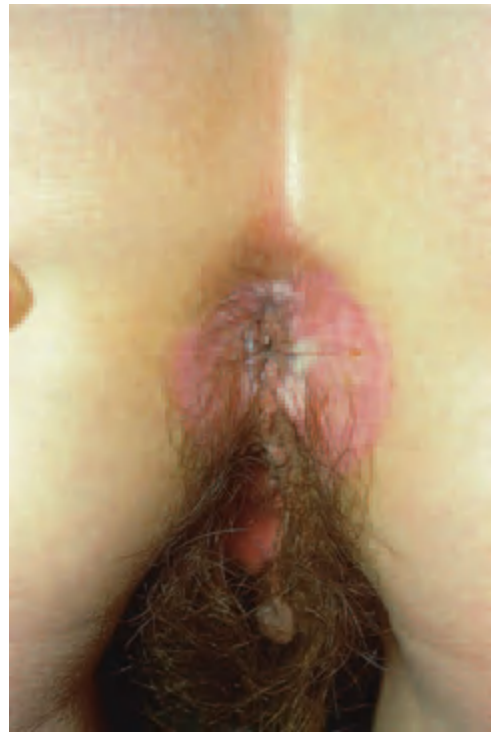

Fig. 56.18 Discoid lupus erythematosus of the perianal area.

Nail changes. Subungual hyperkeratosis is more common than the red-blue colouring of the nail plate with longitudinal striae and crumbling away of the nail [22]. The changes may respond to chloroquine.

Mucous membranes [23]. These are involved in approximately 24% of patients. Nasal mucosal lesions occur in 9% and hyperkeratotic lichen planus-like plaques on the buccal mucosa and palate in a similar number. The lips show slight thickening and roughness and redness, sometimes with superficial ulceration and crusting. Healing occurs with some scarring. Erythematous patches with a depressed centre and superficial ulceration occur on the inner cheeks, tongue and on the palate. Oral lesions may resemble leukoplakia [24]. Erythematous lesions occur on the vulva in 5% [23], or around the anus (Fig. 56.18) [25].

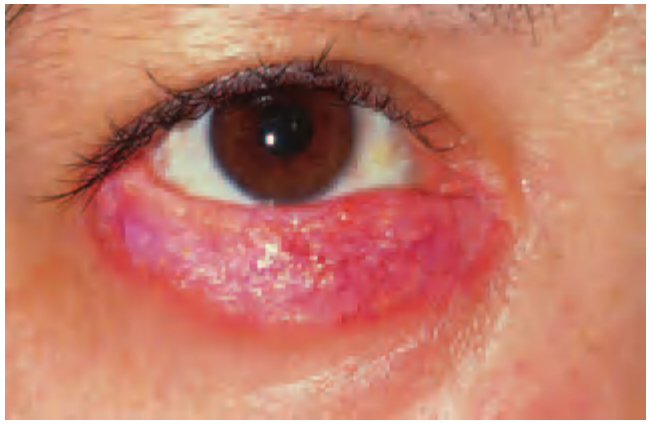

Fig. 56.19 Discoid lupus erythematosus of the lower eyelid.

Eye lesions. Velvety oedema and marked redness of the conjunctiva may occur. Palpebral lesions have been reported without lesions elsewhere on the face [26]. The eyelids are red, especially peripherally, and are slightly infiltrated and always scaly. The horny spikes of follicular plugging are seen on removal of the scale. They are most common on the lower eyelids, especially on the outer third. The free edge is rarely completely involved. Erythematous plaques on the lower eyelids occur in 6%, and may be associated with conjunctival scarring (Fig. 56.19), and symblepharon [27]. The lesions may itch, and are exacerbated by trauma and sunlight. Corneal involvement is rare. Superficial punctate keratopathy and stromal keratitis have been reported [28]. Acute mucinosis of the eyelids and periorbital skin can occur [29].

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Lupus erythematosus and erythema multiforme-like syndrome (syn. Rowell's syndrome) [1–4]. The distinctive syndrome of cutaneous LE, either discoid or systemic, occurring with lesions resembling erythema multiforme on the face, neck, hands, chest and in the mouth (Fig. 56.20) was first

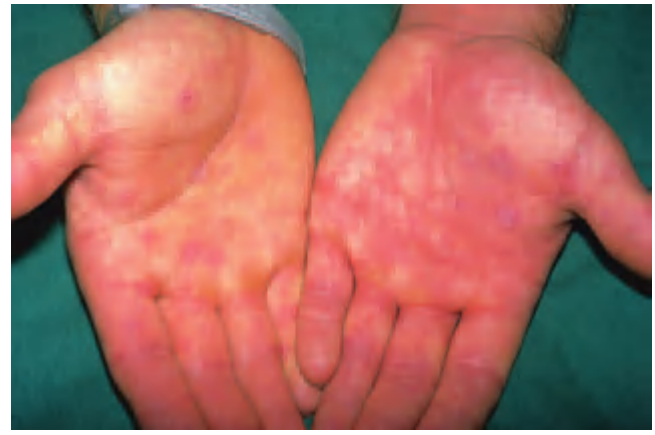

Fig. 56.20 Annular lesions of discoid lupus erythematosus resembling erythema multiforme and associated with characteristic immunological abnormalities (Rowell's syndrome).

described by Rowell in 1963 in patients with discoid LE, but may be seen in both subacute and systemic disease. Characteristically, it lasts from a few days to over a month, but episodes may occur at intervals over a period of 20 years. No precipitating factor can be elicited. The lesions are at first papular, but later a ring forms and the edge becomes vesicular. Bullae, necrosis and ulceration may develop if the reaction is intense, although sometimes healing occurs without scarring. Patients with this syndrome also frequently have perniotic lesions [5]. They show a characteristic pattern of serological abnormality, in that the speckled type of antinuclear factor is associated with rheumatoid factor and the same precipitating antibody to saline extract of human tissues (anti-SjT). Anti-SjT is now thought to be identical to anti-La (SS-B). The syndrome has been reported in identical twin sisters, one of whom had DLE and the other SLE [3]. In patients with SLE, the homogeneous type of antinuclear antibody may also be present in the serum. When the syndrome occurs in DLE, the dermal–epidermal band test is positive in the discoid lesions and negative in the erythema multiforme lesions. If the LE is systemic, the bullous lesions show positive findings comparable with those seen in the uninvolved skin of patients with SLE [2]. The syndrome may be confused with patients showing coincidental LE and erythema multiforme [6]. In one case, anti-SS-B antibody and rheumatoid factor only developed after the erythema multiforme-like lesions appeared, suggesting that these factors are not just incidental findings but may have a role in the clinical presentation [7]. A maintenance regimen of prednisolone may keep patients with SLE clear of lesions [8].

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Childhood DLE [1]. DLE is uncommon in childhood. There appears to be no female preponderance, there is less photosensitivity and the frequency of progression to systemic disease is higher. The other clinical features are similar to those in adults.

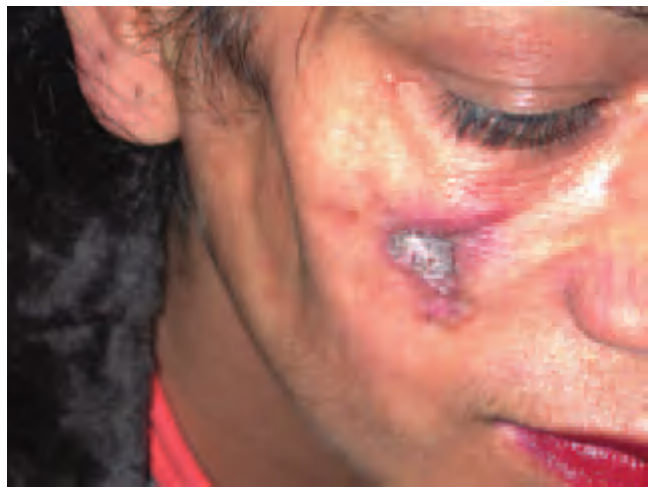

Fig. 56.21 Lupus erythematosus profundus.

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Lupus erythematosus profundus (panniculitis) (Fig. 56.21) [1]. This is an unusual clinical variety of LE in which the cutaneous infiltrate occurs primarily (but not always exclusively) in deeper portions of the corium, with only microscopic epidermal changes, giving rise to firm, sharply defined nodules from one to several centimetres in diameter, lying beneath clinically normal skin [2]. The histopathology is sufficiently characteristic to make the diagnosis in the absence of other cutaneous or systemic lesions of LE [3]. LE profundus occurred in six out of 228 patients with DLE [4,5], and in four out of 86 in another series [6]. It can occur at any age and has been described in childhood [7]. The age and sex distribution of published cases is similar to that of DLE [8]. The earliest age reported is 3 months [9]. Familial cases have been reported [4]. One patient had four first-degree relatives with LE, and the condition also occurred in two sisters. It has been seen in three generations of one family [10].

Kaposi first described subcutaneous nodules in LE in 1883 [11], but Irgang [12] first used the term 'lupus erythematosus profundus' in 1940. Some authors [13] have considered the lesions to be sarcoid, but it is now usually accepted as a variant of LE [14], related more to DLE than SLE [15]. Although Arnold [2] considered that it was different from 'lupus erythematosus hypertrophicus et profundus' described by Behçet [16], this seems unlikely. In the latter, the overlying skin is abnormal, with raised scaly plaques, whereas in LE profundus it is usually normal. Subcutaneous nodules also occur in SLE [17], and sometimes antinuclear antibody and other immunological abnormalities can be demonstrated in LE profundus. Deep dermal and subcutaneous lymphocytic infiltrates

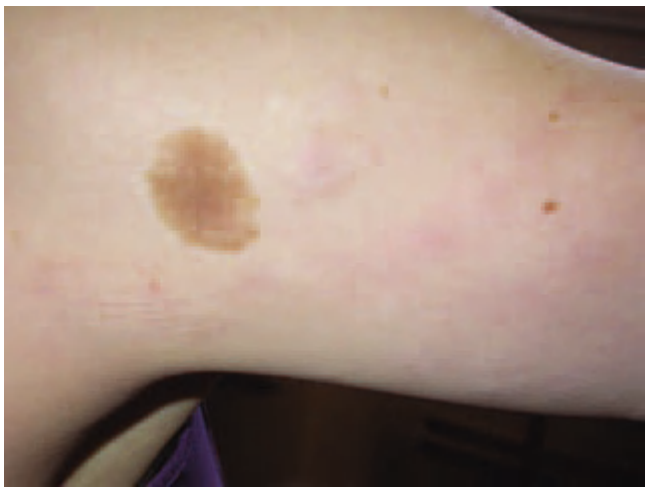

Fig. 56.22 Anetoderma secondary to lupus erythematosus profundus.

were found in 28 out of 100 histological sections of DLE, and in eight of these the infiltrate was extensive enough to be considered as LE profundus [14].

Histopathology. Microscopically [15], there may be epidermal atrophy, hydropic degeneration of the basal layer, follicular plugging and necrosis of the dermal collagen, suggesting LE. Collections of lymphocytes may occur around skin appendages and vessels in the mid-dermis. There is a striking lower dermal and subcutaneous necrobiosis, with some vasculitis and little cellular response. The collagen fibres in the lower dermis, in the septa and between the fat cells are swollen and poorly stained, and in some areas homogeneous masses and amorphous eosinophilic material replace the collagen. Immunofluorescence microscopy frequently shows linear staining at the basement-membrane zone [18]. Immune complexes can be demonstrated by direct fluorescence in small deep vessels in the dermis [19].

Clinical features. The nodular lesions are of varying size, but are usually one to several centimetres in diameter. They are usually firm, rubbery, sharply defined and persistent. The overlying skin usually appears normal, although histologically there are changes at the dermal–epidermal junction in 61% [20]. Typical lesions of DLE may be found elsewhere, most frequently on the cheeks, but they can occur on the face, arms, hands, breasts, buttocks, trunk or legs. Healing usually leads to the development of depressed areas, and rarely to soft, slightly pink areas of anetoderma (Fig. 56.22) up to 4 cm in diameter. Cutis laxa followed one case [21]. Lupus profundus confined to the breast has been called lupus mastitis and may herald SLE. It may be confused with carcinoma [22]. LE profundus may affect the periorbital tissues and cause severe localized oedema [23,24]. It may occur with eyelid plaques [25]. Wherever it occurs, the nodules are persistent, and lesions in the cheeks may lead to marked disfigurement.

LE hypertrophicus et profundus starts as a violaceous scaly tender lesion, which rapidly enlarges, developing a warty hypertrophic surface with coarse adherent scales, which form a hard brown-black tar-like plaque [19]. Patients with LE hypertrophicus et profundus may have extensive serological abnormalities [19], and antibodies to extractable nuclear antigen (ENA) may sometimes be present [26]. In the legs, it may initially resemble thrombophlebitis [27]. No characteristic immunological or genetic markers have been demonstrated in this subset [27]. Calcification can occur, and may be extensive, with the extrusion of thick, yellowish white material through ulcerated areas.

Associated diseases. LE profundus followed thrombocytopenic purpura in one case [13]. Lesions can occur after trauma or surgical biopsy [19], and have been precipitated by electromyography [28]. Monoclonal gammopathy has been reported in LE profundus [29].

Treatment. Clobetasol propionate cream (Dermovate) under a hydrocolloid occlusive dressing (Granuflex) is worth trying [30]. Antimalarial drugs are helpful [2,4,8], including in children [31]. Intralesional injections of triamcinolone (5 mg/mL) may be helpful [32]. Oral thalidomide has resolved resistant lesions, and this has been confirmed in a patient with associated partial C4 deficiency [33].

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Associated features. Small telangiectases on the face occur in approximately 20% of patients. These dilated vessels may sometimes resemble spider naevi, but are usually small capillaries of irregular size and distribution, particularly on the cheeks. Dilated nail fold capillaries, similar to those seen in SLE and dermatomyositis, may be visible with the naked eye in 3%, and sometimes there may be erythema of the pulps of the fingers. More than half of patients state that they have a dry skin. Very occasionally, mild diffuse alopecia may occur, similar to that found in SLE, and alopecia areata has occurred in 10% of one series of DLE and mild SLE [1].

Bilateral enlargement of the parotids has been reported [2,3]. Histologically, there is lymphocytic infiltration of the parotid, which is said to be like that of LE profundus [3]. The parotid swelling may increase with exposure to sunlight and decrease during treatment with antimalarials and corticosteroids [3].

Livedo reticularis on the legs has been reported in DLE, and in one case cryoglobulins were intermittently demonstrated in the serum [4].

Porphyria cutanea tarda and, less commonly, variegate porphyria or acute intermittent porphyria may occur in patients with LE, including those showing discoid lesions [5,6]. Porphyria cutanea tarda may be precipitated by antimalarial therapy [7]. Erythropoietic protoporphyria may also occur [8]. The relation to pemphigus, myasthenia gravis and thymoma has been discussed [9].

DLE has also been associated with chronic lymphatic leukaemia, macroglobulinaemia [10], polychondritis [11], autoimmune thyroiditis [12], carpal tunnel syndrome [13], PLE [14], Sheehan's syndrome [15] and erysipelas [16]. Two siblings showing an autosomal form of chronic granulomatous disease with DLE-like lesions have been reported [17]. An illness resembling LE, especially of the discoid type, occurs in mothers of boys with X-linked chronic granulomatous disease. In these maternal carriers, a population of defective leukocytes can be demonstrated. Photosensitivity, chilblain LE of the fingers and toes, rosaceous lesions on the face, LE profundus and Jessner's lymphocytic infiltration-like lesions and stomatitis occur [18–20].

Hereditary C2 deficiency occurs in association with skin lesions resembling the discoid lesion of SLE [21]. Homozygous C2 deficiency in females is the most common association, but DLE has also been reported in heterozygous C2 deficiency [22]. Low levels of C4 have been demonstrated in two sisters [23]. Hereditary deficiency of the third [24] and of the fifth component of complement has also been associated with a lupus-like syndrome [25]. DLE has also occurred with C1q deficiency [26]. Identical twin boys have been reported with DLE skin lesions, immunological abnormalities of SLE and hereditary angio-oedema with low C1 inhibitor and C4 [27]. DLE is associated with classical hereditary angio-oedema with reduced levels of C1-esterase inhibitor [28]. Approximately 2% of patients with hereditary angio-oedema have LE-like disease [29]. A classic case of DLE with the less common variant form of hereditary angio-oedema has been reported [30], in which normal levels of C1-esterase inhibitor were present but activity was decreased.

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Laboratory abnormalities in DLE. The incidence of laboratory abnormalities in 120 patients is shown in Table 56.1 [1]. Abnormalities were found in 55% of patients. Anaemia, leukopenia or thrombocytopenia can be found in approximately one-third of patients, and the erythrocyte sedimentation rate (ESR) is raised in 20%. The serum globulin is raised in 29% of patients, elevation of gammaglobulin being the most common abnormality. Higher mean IgG levels are associated with scarring [2]. Benign monoclonal gammopathy and multiple myeloma occasionally occur [3]. Chronic lymphatic leukaemia with macroglobulinaemia has been reported [4]. Occasionally, the Coombs' test may be positive, and cryoglobulins [5,6] and cold agglutinins may be detected in the serum. False-positive reactions for syphilis have been reported in 26% of cases [7]. Anticardiolipin antibodies (mainly IgM) in low titre occur in approximately 15% and are associated with antinuclear antibody, but do not seem to indicate an increased thrombotic tendency [8], although a case associated with the anticardiolipin syndrome has been reported [9]. Anticardiolipin antibody has also been reported in chilblain lupus [10]. Sometimes, the LE cell test may be positive (1.7%). Rheumatoid factor is present in approximately 17% of patients.

Antinuclear antibodies are found in 35%, the 'homogeneous' type of antinuclear factor being twice as frequent as the 'speckled' type. Antinuclear antibodies (ANA) are more common in older patients, in those who have had the disease for a long time and when there is extensive skin involvement. They are also more common in patients with chilblains, Raynaud's phenomenon and joint pains [11]. The incidence of antinuclear antibodies varies between series—5% [12], 13% [13,14], 50% [15] and 60% [16]—but such differences may be a result of the selection of patients or the sensitivity of the laboratory techniques. The incidence of anti-DNA antibodies varies from 0% [12,17] to 27% [18]. In the latter series, patients did not show any evidence of systemic involvement, and follow-up 3 years later showed no evidence of SLE [19], but it is possible that patients with DNA antibodies are more likely to develop SLE [20]. Antibodies to single-stranded DNA occur in nearly one-fifth and may indicate widespread and progressive disease [21]. DNA antibody titres fall with chloroquine therapy. One-fifth of patients have IgM antibodies to single-stranded DNA [17]. Antibodies to RNA occur in 42% [22]. Low-titre anti-Ro antibodies are found in 10% of patients with DLE, but are not related to photosensitivity and do not imply an increased risk of developing SCLE [23]. Serum complement levels are occasionally reduced [12]. DLE occurs with low levels of complement components [24–26], but there is no specific complement profile [27]. Antibody to extractable nuclear antigen is not found, but lymphocytotoxic antibodies have been demonstrated in 23% of patients in one series [28] but not found in another [12]. Precipitating autoantibodies are found in approximately 4% of patients. The SjT type of antibody (anti-La [SS-B]) is associated with 'speckled' antinuclear factor and rheumatoid factor in those patients with DLE and erythema multiforme [29]. Soluble interleukin 2 (IL-2) receptors may be found [30].

Antibodies to saline extracts of liver, blood vessels, skin, kidney, heart, spleen, leukocytes, gammaglobulin and deoxyribonucleoprotein have been detected by complement utilization [31]. The highest titres occur in the mildest non-scarring forms of the disease and the lowest

in the scarring type. It has been suggested that these antibodies may have a protective function [31].

A high incidence of antithyroid antibodies has been found in DLE, particularly in females [15]. Gastric parietal cell cytoplasmic antibodies occur in 13% of patients [15], but this incidence may not be higher than in controls.

Intradermal tests with autologous leukocytes [32] were positive in one-third of cases, but this test is not specific and the results do not differ from controls [33].

T-cell counts are significantly lower than in controls, although B cells are not reduced [34]. Kidney biopsy has shown silent lupus nephritis in patients with hypocomplementaemia [35].

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Differential diagnosis. The relationship of DLE to SLE has been discussed elsewhere (see p. 56.2). The cutaneous lesions may be very similar, although patients with DLE of the face usually show more scaling, pigmentary disturbances, atrophy and scarring. In those with extensive DDLE, positive antibodies and mild systemic symptoms, it can be difficult to fit the patient into a precise diagnostic category. The annular atrophic plaque variety of DLE may resemble morphoea or lichen sclerosus [1]. Jessner's lymphocytic infiltration may be confused with the more acute localized oedematous lesions of LE, but the marked histological lymphocytic infiltration in the former should help to distinguish it from the latter, and immunoglobulin deposition does not occur at the dermal–epidermal junction in Jessner's infiltration [2]. Jessner's infiltration is rare in childhood [3] and has been reported in three members of one family [4], as well as in a mother and son, and father and daughter. Evidence has been produced from a study of 100 patients that Jessner's lymphocytic infiltration is a distinct entity, which does not seem to proceed to DLE, PLE or lymphoma [5], and studies of lymphoid infiltrates using the monoclonal antibody Leu-8 tend to confirm the difference between DLE and Jessner's lymphocytic infiltrate [6]; however, there is still disagreement on this point. Benign lymphocytic infiltration of the skin may be a further form of cutaneous LE as indicated by phototesting [7]. The distinction from PLE may be difficult, but the absence of antinuclear factor from the

serum [8] and of dermal–epidermal immunoglobulin deposits [9] in PLE may be helpful. PLE and DLE may coexist, or PLE may precede DLE by many years [10]. PLE is more common in the relatives of patients with LE; as many as 65% of patients with cutaneous LE have symptoms indistinguishable from those of PLE [11]. There may be an actinic factor in the reticular erythematous mucinosis (REM) syndrome (see Chapter 57), which can show clinical and histological features similar to DLE. The history and the presence of lesions elsewhere should exclude contact eczema, seborrhoeic eczema and psoriasis. Lupus vulgaris may resemble DLE, but the lesions of the former usually occur at an early age, are rarely symmetrical, may be ulcerated and usually show characteristic 'apple-jelly nodules'. Necrobiosis lipoidica can give facial lesions like DLE. The rosaceous type of LE can usually be differentiated from true rosacea by the absence of pustules.

Chronic DLE has been found in 12% of patients diagnosed as having scarring alopecia of the pseudopelade type [12]. Lesions on the lips, tongue and buccal mucosa may be confused with lichen planus, and the skin of some patients may show clinical, histological and immunological features of both diseases [13,14]. Overlap cases, in addition to LE-like lesions, have lichenoid papules, verrucous lesions, anonychia, and oral and vulval lesions resembling lichen planus. Patients with lichen planus do not have features of LE immunopathologically or by HLA typing [15]. Overlap cases either have both diseases or are variants of LE. In favour of the latter, the verrucous lesions show immunofluorescent findings of LE, and electron microscopy reveals tubuloreticular inclusions in endothelial cells of dermal blood vessels—which are found in LE but not in lichen planus [16].

LE of the legs and feet may resemble chilblains. Plaques of sarcoidosis and lesions of eosinophilic granuloma may cause diagnostic difficulties that can only be resolved histologically. Occasionally, lesions resembling DLE are caused by dermatophytes [17].

Infants may show sharply marginated, erythematous, finely scaling plaques on the cheeks and bridge of the nose, sometimes exacerbated by the sun [18], or a transitory rash with telangiectases on the face, particularly around the eyes, which clinically and histologically resembles LE [19]. These rashes probably are part of so-called neonatal LE (see p. 56.53). The annular erythemas of infancy have been reviewed [20].

An LE-like rash on the face with sun sensitivity occurs in Bloom's syndrome (see Chapter 12), which is thought to be caused by an autosomal recessive gene. A congenital telangiectatic erythema occurs in well-proportioned dwarfs, who look alike because of their bird-like facial appearance. The skin changes occur in infancy and may be associated with ectodermal and mesodermal defects.

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Prognosis [1]. The untreated skin lesions of DLE tend to be persistent. With treatment, the more tumid lesions with little scaling may clear completely in the course of a month or two. Lesions of longer standing with much scaling and some scarring are slower to remit. Ultimately, scarring is found in 57%, with scarring alopecia in 35%; 35% also have pigmentary abnormalities [2]. Areas of activity at the edge of such scars may take years to settle. Twenty per cent of female patients notice a premenstrual flare, but there is no evidence of a deterioration of the condition on hormone replacement therapy [3]. Complete remission in the course of years can be expected in over 50% [1]. Long duration and lack of remission are related to Raynaud's phenomenon, scalp involvement and chilblain-like lesions

[4]. Relapses occurring with sunlight, cold, trauma or mental stress after months or years of remission are not infrequent. In spite of the chronic and relapsing nature of the condition, the patient usually remains in good health.

Despite the fact that over half of patients have haematological and serological abnormalities, the risk of developing overt SLE is only approximately 6.5% [4,5]. The risk is higher in patients with disseminated DLE (22%) than in DLE confined to the head and neck (1.2%). Females developing DLE before the age of 40 years, with HLA-B8 in their histocompatibility type, have an increased risk of 'converting' to SLE [6]. There is little clinical difference between those cases with or without abnormalities. Neither immunological nor biochemical abnormalities appear to alter the patient's progress [5,7]. Patients with active discoid skin lesions rarely have severe renal disease [8]. Patients with DLE showing signs of nephropathy, arthralgia and ANA titres of 1 : 320 or more should be carefully monitored [9].

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Neoplastic change in DLE. Squamous cell and, less commonly, basal cell carcinomas occasionally occur in the scars of DLE, particularly on the scalp, ears, lips and nose. An incidence of 3.3% has been noted in a series of 120 white patients with DLE [1]. They are said to be more common in middle-aged males [2], but in either sex occur only in cases of 20 years' duration or more. Black people with DLE may also develop carcinoma [3,4], especially of the lip. Death may occur from multiple metastases [1,5]. Keratoacanthoma [6], malignant fibrous histiocytoma [7] and atypical fibroxanthoma [8] in lesions have been reported.

Although carcinoma has been considered more common in patients who have had radiotherapy for DLE, 65 out of 100 cases had not had such treatment [9].

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Treatment. It is important to carry out a complete medical survey of the patient at the first attendance. Such a survey establishes a baseline by which later progress may be judged. General measures play a large part in successful management. Overwork, mental stress and fatigue are often factors in deteriorating disease, and patients with facial scarring often suffer severe psychological upset and depression [1]. Effective forms of camouflage by covering creams are available and help morale. Patients should be warned against excessive exposure to sunlight, especially those who have noticed exacerbation of lesions by UV light. They should be advised to wear a broad-brimmed hat, and avoid short-sleeved shirts and shorts. A sunscreen cream or lotion should be prescribed. These vary in their degree of protection [2]. A preparation with a UVB protection factor of at least 15 is required, but UVA protection is at least as important. Application should be frequent—probably every 2–3 h in bright sunlight. There are many suitable preparations, and patient acceptability is an important element in the choice of agent. It is important that patients understand the preventative action of these preparations.

Topical therapy can frequently control and sometimes clear lesions without systemic treatment. In one series [3], 43 out of 59 patients could be controlled by applications of 0.025% fluocinolone cream. In another, 0.1% betamethasone 17-valerate cream alone was effective in 68 out of 78 patients, and in a 5-year trial steroid-induced atrophy of the epidermis was not observed [4]. Applications are usually required twice a day. Similar results are given by 0.1% triamcinolone acetonide cream. Unfortunately, the effect is usually only suppressive. The efficacy in resistant cases may be enhanced by applications of the above steroid creams under plastic occlusion, using a self-adherent plastic dressing (e.g. Tegaderm [5]), or by 0.2% fluocinolone or 0.05% clobetasol propionate cream without occlusion.

Topical fludroxycortide (flurandrenolone) cream under a moulded plastic prosthesis has helped persistent painful lesions on the ears [6]. Flurandrenolone (Haelan) tape, in which the topical steroid is on the tacky side of polythene tape, can be cut to size and stuck on individual lesions. Satisfactory results have been obtained by changing the tape weekly. The tape is best for localized lesions on non-hairy and moisture-free areas not subject to excessive movement.

Intralesional corticosteroid injections are helpful in resistant cases [7–9], even on lips, mouth and ears. Triamcinolone acetonide 5–10 mg/mL is injected as superficially as possible into each lesion. Large lesions may require injections at several sites. Injections are usually given at 6-weekly intervals, and from one to 10 may be required. Reversible, and occasionally irreversible, atrophy may result. Intralesional therapy is sometimes surprisingly effective in lesions on the nose and ears and it may also help resistant lesions on the palms and soles [10]. The scalp is usually unresponsive. The Dermojet can be used to deliver intralesional steroid. Intralesional injections of antimalarials, including chloroquine [11], have been tried, but the results were not as good as with corticosteroids and there can be considerable local pain and inflammation. Interferon-α (IFN-α) has also been used intralesionally with success [12]. Among other local measures, cryotherapy, surgical excision [13], painting small lesions with trichloracetic acid and local laser therapy may be helpful. The carbon dioxide laser, and both the pulsed-dye and argon lasers may be valuable for telangiectatic LE [14].

Oral therapy. Most patients referred to hospital will need oral therapy. However, it is always important to reiterate the general measures described above. In addition, vasodilator drugs, particularly calcium-channel blockers such as nifedipine are helpful in those with Raynaud's phenomenon and chilblain lesions, and intravenous prostacyclin may be very helpful in winter, and used before intensive oral therapy in these patients.

For patients with severe, extensive or scarring disease, particularly affecting the scalp, oral prednisolone is often the most helpful initial treatment. A dosage of 0.5 mg/kg, rapidly tapered over 6 weeks is quickly effective, minimizes scarring, and allows the slower acting agents such as antimalarials to work. Long-term therapy with oral steroids is best avoided because of side effects, and there is little doubt that in most cases first-line oral treatment should be with one of the antimalarials (see Chapter 72). Most would start therapy with hydroxychloroquine, initially at 200 mg twice daily, reducing to 200 mg/day once a response is achieved. Chloroquine sulphate is equally effective, usually at a dosage of 200 mg twice daily, but hydroxychloroquine is used first by most prescribers because side effects, particularly eye toxicity, are less likely provided that the dosage limitations of 6.5 mg/kg lean body weight are adhered to [15]. The comparable safe daily dosage for chloroquine is unclear, but is probably around 2.5 mg/kg/day of chloroquine base [15]. Cumulative toxicity is rarely a problem with hydroxychloroquine, although it can occur with chloroquine [16]. For this reason, courses of treatment lasting approximately 6 months are preferred, but this may not be possible in the most severely affected patients who will require on-going therapy. Mepacrine is also useful, and is safe from an ophthalmological point of view [15], but it is often reserved for later use (because of skin pigmentation). It may be used alone, or as part of a combination of antimalarials, which may be more effective than the equivalent amount of each drug given individually [17].

The response to therapy varies: usually, the more tumid lesions with slight scaling respond more rapidly than chronic, atrophic and scarring lesions. Most patients who are going to respond to antimalarials usually do so within 6 weeks. There are few data indicating superiority of one agent over another, but some authors find chloroquine more effective. The milder side effects consist of nausea and vomiting, and patients with such symptoms should be given an alternative antimalarial because some patients can tolerate hydroxychloroquine better than chloroquine, and vice versa. The most serious side effects of antimalarials [18] include corneal deposits, retinopathy, pigmentation of the palate, nails and legs, bleaching of the hair and moustache, exfoliative dermatitis, lichenoid rashes, myasthenia, myopathy, extrapyramidal involuntary movements, neuropathy and mental disturbances, but these are uncommon. Taking an ophthalmological history and arranging for an examination by an optician before treatment in any patient with symptoms not corrected by spectacles may help in avoidance of the ocular manifestations. Monitoring during therapy should include taking an ophthalmic history, and testing reading ability with appropriate charts [15]. More elaborate tests, such as the electro-oculogram and electroretinogram, are no longer believed to be helpful [15].

Approximately 60–75% of all patients are helped by antimalarials. Cigarette smoking reduces the efficacy of treatment with antimalarials, probably by modifying metabolism [19]. Of those who respond, approximately 50% relapse within 6 months, and repeated courses of therapy are usually required. Some patients keep their lesions under control by taking an antimalarial for only a few days at a time. Nevertheless, over the course of several years, most cases treated with intermittent oral antimalarials and topical corticosteroids tend to improve, and some clear completely. Subsequent relapses are often, but not always, less severe than the original lesions. There is no evidence that the continuation of antimalarials after clearance prevents relapses. Hydroxychloroquine appears to be safe in pregnancy [20].

Oral auranofin has helped 50% of patients with long-

standing lesions, particularly on the face and trunk [21]. Some patients may clear completely. A daily dose of 6–9 mg may be needed for up to 1 year. Mild diarrhoea not requiring discontinuation of treatment is the most common side effect, but pruritus, transitory rashes and stomatitis also occur. Liver and renal function must be monitored regularly during treatment. Acitretin [22,23] also appears to be as effective as hydroxychloroquine if given as first-line oral therapy, but tends to be slower in onset and associated with more side effects. Consequently, it is used later, in patients who are unable to tolerate antimalarials or in whom they are ineffective. Unfortunately, when used in these circumstances, neither agent produces response rates much higher than 20% [24]. The same appears to be true of the majority of other agents described as useful in DLE. Etretinate [25] (1 mg/kg/day), preferably combined with chloroquine, has helped patients with chronic hyperkeratotic lesions [26]. Isotretinoin 20–80 mg/day [27] has helped resistant cases, particularly in those with hypertrophic lesions [28]. Dapsone 100 mg/day may help some patients [29,30]. In our experience, ciclosporin is usually unsuccessful in DLE, and others have confirmed this [31,32], possibly because of the resistance to ciclosporin of some circulating suppressor T cells [33]. Oral methotrexate may be useful in patients unresponsive to antimalarials [34].

For cases not responding to topical steroids, antimalarials and sunscreens, oral thalidomide has proved remarkably effective in suppressing lesions [35,36], and also in the treatment of chilblain LE. With an initial dosage of 400 mg/day and a maintenance dosage of 50–100 mg/day, 90% of patients had complete or marked regression of the disease [37]. More recently, lower dosage (100 mg/day) has also been shown to be successful. If used as initial therapy, response rates of 80–90% may be achieved, but when used as second-line treatment the response rate is nearer 50% [24,38]. When treatment was stopped, 71% relapsed, but further courses were effective. Mild side effects were common and 25% had slight to moderate polyneuritic symptoms, which in some patients were persistent. Polyneuropathy was not noticed in a series treated with lower doses [39], although the therapeutic results were not quite as good, and neuropathy can occur with a total dose as low as 3 g [39]. It would seem that 100–200 mg/day, initially for 4–6 weeks, followed by a lower maintenance dosage, should be recommended, with gradual reduction until discontinued. Fertile women should start therapy immediately after menstruation, and must use very strict contraceptive measures because of the teratogenicity of the drug. Patients should be advised not to drive and to avoid alcohol, and the drug must be stopped immediately if polyneuropathy is suspected. Mild side effects of sleepiness, dizziness, constipation, amenorrhoea, dry mouth and dry scaly skin remit on stopping therapy. Impotence may occur.

A number of agents have been reported to help individual cases. Clofazimine (Lamprene) possesses antimalarial activity and suppresses the lesions of DLE in two-thirds of patients. The optimum daily dose is 100 mg. Pink discoloration of the skin is a side effect that is not too disturbing to patients [40]. Danazol may be useful in the treatment of premenstrual exacerbation of DLE [41]. Sulfasalazine (0.5 g three times daily) has been reported to help [42], and phenytoin (100 mg sodium diphenylhydantoin three times daily) may be useful, but 8% have side effects requiring discontinuation of therapy [43]. Beta-carotene is also reported to help some cases [44].

When all of the above have failed in patients with severe and persistent disease, other forms of systemic treatment may be used. Pulsed methylprednisolone 500–1000 mg/day for 2 or 3 days may help resistant lesions, particularly of the scalp. Cyclophosphamide 50–200 mg/day has helped patients with DLE not responding to oral antimalarials or to oral or topical corticosteroids [45]. Intravenous pulses of this drug are also used, usually at a dosage of 10 mg/kg, at 3–4 weekly intervals. It is usually given in combination with intravenous methylprednislone. Azathioprine has helped discoid lesions, even those occurring on hands and feet [46,47]. Undoubtedly, gold by intramuscular injection can be useful [48], but is often very toxic.

IFN-α2a is reported as producing transient improvement [49], and excision of oral lesions also may be practicable [50]. The carbon dioxide (CO_2) [51] and argon lasers [52] may produce improvement of disfiguring LE, although the latter may precipitate DLE [53]. Dermabrasion may help cribriform scarring of the face [54], as may CO_2 laserbrasion. Excision without grafting was successful in a case of verrucous LE following a burn [55].

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Subacute cutaneous lupus erythematosus

Definition. Subacute cutaneous lupus erythematosus (SCLE) is a specific 'subset' of lupus first described by Sontheimer *et al*. in 1979 [1]. Patients exhibit mainly cutaneous disease and usually have a good prognosis. Antibodies to the Ro/SS-A antigen are closely associated with this subgroup.

Aetiology. Antibodies to the Ro/SS-A antigen are an almost universal finding in this subset of lupus. That these antibodies may be pathogenic was first suggested by LeFeber *et al*. [2], who demonstrated that sublethal doses of ultraviolet light (UVL) induced the synthesis of Ro/SS-A antigen by cultured human keratinocytes. In addition, they also showed that UVL promoted the expression of Ro/SS-A antigens on the surface of cultured human keratinocytes where they might bind antibodies. In 1988, Ro/SS-A antigen was identified in both adult and neonatal epidermis *in vivo* [3], and subsequent studies have confirmed that UVL increases Ro/SS-A antigen expression on the surface of keratinocytes [2,4,5] and that this is increased by oestrogen [6–8]. Thus, it has been postulated that in photosensitive lupus, UVL exposure leads to increased synthesis and subsequent expression of Ro/SS-A antigen on the surface of keratinocytes where it binds antibody and initiates disease [9]. Further support for this

hypothesis comes from a recent study, which showed that photosensitivity and the titre of Ro/SS-A antibodies correlated with the expression of Ro/SS-A in skin specimens of patients with LE [10].

Although attractive, this hypothesis does not explain why other patients with Ro/SS-A antibodies (e.g. patients with Sjögren's syndrome) do not exhibit photosensitivity and why in the clinical setting Ro/SS-A titres rarely reflect disease activity [11].

HLA antigen status may have a role in disease susceptibility. The most common haplotype in SCLE is HLA-DR3 with HLA-B8, -DR3 being most commonly associated with the annular phenotype and the expression of Ro/SS-A antibodies [12]. HLA-DR2 has been associated with an older age of disease onset and papulosquamous lesions [13]. Recently, two studies [14,15] have reported an association of SCLE with the tumour necrosis factor-α (TNF-α) 308A polymorphism, which may be pathogenic or act as a marker for the HLA A*01, B*08, DRB1*0301 haplotype associated with other autoimmune conditions. Studies of Ro60 exons to see whether sequence alterations might be associated with SCLE have not shown differences between patients with SCLE, DLE or controls [16].

Autoantibody status. SCLE was originally labelled ANA-negative lupus, as these patients often exhibited negative autoantibody screens. This was probably because of the use of test substrates that did not contain suitable antigens for the antibodies found in this group of patients. Using human cell lines as substrates, homogeneous antinuclear antibodies are found in approximately 60% and anti-Ro/SS-A antibodies in approximately 80% of patients [1], rising to higher levels in females [17]. Anticardiolipin antibodies occur in 16% [18].

Histopathology. Histopathologically, SCLE can be differentiated from DLE by the presence of more epidermal atrophy and less hyperkeratosis, basement-membrane thickening, follicular plugging and inflammatory infiltration [19,20]. Colloid bodies and epidermal necrosis are present in more than 50%, especially in those with Ro/SS-A antibodies [21]. Dust-like particles of inter- and intracellular IgG in the basement layers of the epidermis may be a specific feature [22]. It has been suggested that pilosebaceous atrophy is the only significant predictor of DLE versus SCLE [21,23]. Lesional subepidermal immunoglobulin is found in approximately 60%, and is more frequent in papulosquamous (88%) than annular lesions (29%) [1].

Clinical features. This subset [1,24,25], which comprises approximately 10% of patients with LE, have either non-scarring papulosquamous (two-thirds) (Fig. 56.23) or annular polycyclic (one-third) lesions. The disease predominantly affects adults, although SCLE has been reported in a child [26]. Lesions usually occur above the

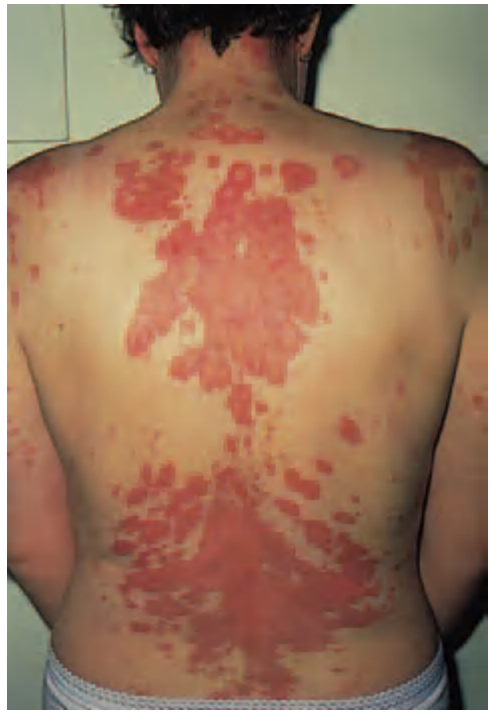

Fig. 56.23 Subacute cutaneous lupus erythematosus.

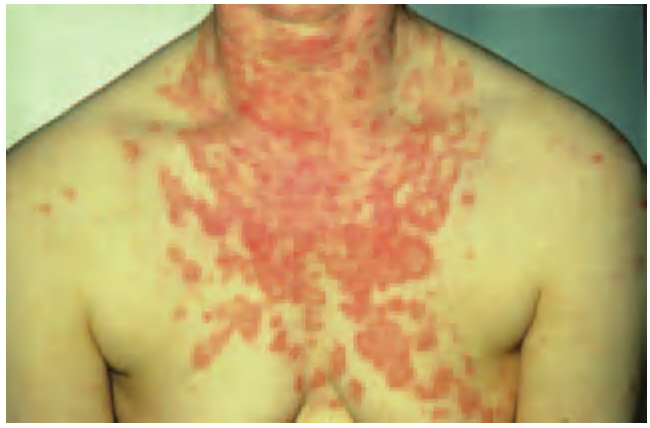

Fig. 56.24 Subacute cutaneous lupus erythematosus showing annular polycyclic lesions.

waist and particularly around the neck, on the trunk and on the outer aspects of the arms (Fig. 56.24). The borders may show vesiculation and crusting. Follicular plugging and hyperkeratosis are not prominent, and the lesions resolve leaving grey-white hypopigmentation and telangiectases. The pigmentary changes usually resolve completely. Diffuse non-scarring alopecia and photosensitivity occur in approximately half of patients, and other features include mouth ulceration (especially of the palate), reticular livedo, periungual telangiectasia and Raynaud's phenomenon. Presentation with pityriasiform lesions [2], erythroderma [27] and generalized poikiloderma [28] has

been described. Morphoea [29] and dystrophic calcinosis cutis [30] have followed SCLE.

Approximately half of patients fulfil the criteria for SLE of the American Rheumatism Association (ARA) [31], with arthritis the most frequent feature. Fever, malaise and central nervous system involvement occur, but renal disease is mild and infrequent, although a recent study suggested that the latter may occur in up to 16% of patients [32]. Chronic interstitial pneumonitis has been reported [33] as has hypokalaemic tetraparesis [34]. Occasionally, the annular lesions may resemble the lesions of Rowell's syndrome or the gyrate erythema secondary to occult malignancy [35]. Some patients also have Sjögren's syndrome [36], rheumatoid arthritis, deficiency of the second [37], third [38] and fourth [39] components of complement, Sweet's syndrome [40], Crohn's disease [41], lichen planus [42], hereditary angio-oedema [43,44], porphyria cutanea tarda [45], gluten-sensitive enteropathy [46], toxic epidermal necrolysis [47], inclusion body myositis [48] or calcifying lupus panniculitis [49]. A number of drugs have been reported to precipitate or exacerbate SCLE, including thiazide diuretics [2], griseofulvin [50], terbinafine [51,52], cinnarizine [53], calcium-channel blockers [54] and etanercept [55]. SCLE may occur in the course of PUVA treatment of psoriasis [56], radiation therapy [57] and IFN-β1a therapy [58]. There have been occasional reports of associations with cancer, namely breast carcinoma [59], meningioma [60], hepatocellular carcinoma [61], Hodgkin's disease [62] and lung cancer [63]. Occasional patients develop overt SLE with severe visceral disease [64].

Treatment. The condition in most patients is controlled by sunscreens [65] and topical or intralesional corticosteroids [66]. In those not responding to these agents, antimalarial drugs are often helpful. These can be used as either hydroxychloroquine or chloroquine base, although the former is safer from the ophthalmological point of view and requires less ophthalmological monitoring [67]. The antimalarial mepacrine (quinacrine) does not have ocular side effects but does induce yellow discoloration of the skin. There is evidence that a combination of antimalarials may be more effective than either alone [68] and that they are less effective in smokers [69]. Patients not responding to antimalarials may respond to oral corticosteroids or methylprednisolone [70], etretinate [71], acitretin [72], isotretinoin [73,74], dapsone [75], methotrexate [76,77], thalidomide [78–80], UVA [81], IFN-α [82], long-term cefuroxime axetil [83] or mycophenolate mofetil [84].

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Systemic lupus erythematosus [1,2]

Definition. A systemic disease characterized by multisystem organ inflammation, most commonly the skin, joints and vasculature, and associated immunological abnormalities. The main clinical features include fever, rashes and arthritis, but renal, pulmonary, cardiac and neurological involvement may occur, with increased mortality. For any individual patient, the ARA criteria may be used as an aid to diagnosis (Table 56.3).

Incidence. SLE is an uncommon disease [3–9], with incidence estimated at 1–12.5 in 100 000 per year at Leeds General Infirmary; for every case of SLE there are six cases of pernicious anaemia and 10 of leukaemia. The condition is universal, but is three times more common in black people than in white people [3]. Younger black American females are particularly predisposed to the disease [4], although it is rare in native Africans. It is also common in the Chinese and in New Zealand Polynesians [5]. The pattern of disease appears to be different in such ethnic subgroups, with black Americans and Hispanics having the highest rate of internal organ damage [6]. A study in Hawaii gave similar racial variation, with the prevalence in those of Chinese origin being 24.1 in 100 000, whereas that in whites was 5.8 in 100 000 [7]. The incidence of newly diagnosed cases in New York is 10–14 per million population [8]. The prevalence varies from less than 1 in 1000 for black females in New York [9] to approximately 1 in 2000 white females in San Francisco, and recent figures for England and Wales suggest a prevalence of 12.5 in 100 000 women, although this is an underestimate [10]. The observed annual incidence increased from 25 per million in 1955 to 50 per million in 1959 [11]. In Hong Kong, in 1987, the incidence was 2.4 in 100 000 [11], and in Baltimore, in 1985, it was 4.6 in 100 000, a twofold increase over the preceding 15 years. Self-reported physician-diagnosed SLE occurred in 124 in 100 000 in the USA [12]. This suggests that the disorder may be more common than it used to be, but it may also represent better awareness and earlier diagnosis. An epidemiological survey in New York showed that morbidity and mortality rates were highest among black people, followed in descending order by Puerto Ricans and then other white people. Racial differences were independent of housing, overcrowding and migration, but were associated with racial variation in normal gammaglobulin levels, which were higher in black people [6]. A more recent study from England confirms the increased risk of SLE in Afro-Caribbeans and Asians, irrespective of their place of birth [13]. Familial cases occur in approximately 10% [14,15]; relatives of patients with SLE also have an increased incidence of SLE and DLE, rheumatoid arthritis, rheumatic fever, polyarteritis nodosa, dermatomyositis and poikiloderma atrophicans vasculare [16].

The condition tends to occur in early adult life, and the peak age of onset of the first symptom or sign in females is approximately 38 years (35.5 in black women, and 40.7 in white women); it is 44.2 in men [17]. The incidence of the disease is the same in all age ranges, although serositis and Sjögren's syndrome are more common disease manifestations in the elderly [18]. Most authors agree that females outnumber males by a ratio of approximately 8 : 1, but the features in males are the same as in females [19].

Table 56.3 American Rheumatism Association criteria for diagnosis of systemic lupus erythematosus.

1	Malar rash
2	Discoid rash
3	Photosensitivity
4	Oral ulcers
5	Non-erosive arthritis
6	Serositis—pleurisy or pericarditis
7	Renal disorder—persistent proteinuria (> 0.5 g/day) or cellular casts
8	Neurological disorder—seizures or psychosis
9	Haematological disorder—haemolytic anaemia or leukopenia (< 4000/mm) or lymphopenia (< 1500/mm) or thrombocytopenia (< 100 000/mm)
10	Immunological disorder—LE cells or anti-DNA antibody or anti-Sm antibody or false-positive serology for syphilis (longer than 6 months)
11	Antinuclear antibodies

LE, lupus erythematosus.

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Aetiology. The aetiology of SLE remains unknown. Aetiological theories must account for the known variations in the incidence of the disease, the marked immune dysfunction, known precipitating factors and the clear familial predisposition.

Genetic factors. There is considerable evidence to suggest that genetic factors play a part in the pathogenesis [1]. The condition has been reported in identical twins [2,3], with a concordance rate of 65% [2]. Of all cases, 4% are familial [4], with marked concordance of disease expression between parents and offspring. The onset of SLE in identical twins occurred within 2 years, compared with an interval of 9 years between siblings and 20 years between parents and offspring [5]. However, the onset of disease in siblings is temporally rather than age-related, indicating a possible environmental factor [6]. Occasionally, identical twins may be discordant for SLE. In this case, the non-affected twin does not have abnormalities of helper and suppressor T-cell numbers and activity, and has different cellular immune responses [7,8]. The incidence of SLE is probably higher in XXY males with Klinefelter's syndrome [9]. Relatives of patients with SLE have a higher incidence of connective tissue disease, hyperglobulinaemia and antinuclear factor than the relatives of matched controls [10,11]. They may also show increased incidence of anti-RNA and lymphocytotoxic antibodies, specific anti-DNA antibody idiotypes [12], anticardiolipin antibodies [13] and impaired suppressor T-lymphocyte function [14], although these are not related to disease expression [15].

Studies of histocompatibility antigens further support a genetic predisposition. White people with SLE have increased frequencies of HLA-B8 [16], -DR3, -A1 and -DR2 [17]. Similar associations have been confirmed in black people [18,19], as has an association with immunoglobulin allotypes Gm 1 and 17 [20]. HLA-DQ antigens may be even more closely related to the risk of developing the disease, and different alleles may be implicated in the risk of developing the disease from those that influence its expression [21]. There is evidence of linkage disequilibrium between B8-DR3 and alleles at the DQ locus, which is prevalent in patients who express anti-Ro antibodies [22].

Eighty per cent of patients (compared with 40% of controls) have null complement alleles [23], mainly at the C4A or B locus [24]. HLA-DR2 and the C4A null allele are independent and additive risk factors in SLE [25]. Deficiency of complement factors C5–9 is relatively common in familial cases of SLE. Genetic factors other than HLA and complement component deficiencies may also be involved [26]. The results of genome scanning of family pedigrees multiplex for SLE, including over 400 sib pairs and 175 affected relatives, suggest an epistatic interaction between chromosome 14p16-15.2 and chromosome 5p15 in European American families [27].

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Autoantibodies [1,2]. Non-organ-specific humoral autoantibodies are the hallmark of SLE. A range of autoantibodies may be present in the disease, although some are more disease-specific (anti-double-stranded DNA and anti-Sm antibodies), and some are much more commonly found (antinuclear anti-Ro antibodies). The disease could be produced by the development of such antibodies against tissue antigens to which tolerance has been lost by failure of homeostatic immunological mechanisms. This could occur either because of polyclonal B-cell activation or specific antigenic drive. There is evidence for both mechanisms of production of autoantibodies [3]. There is also considerable evidence that such non-organ-specific autoantibodies are not the primary pathogens: they are not specific to any disease, they are not present in all cases, their titres are independent of the activity of the disease, they are transmitted across the placenta without apparently harming the fetus [4] and they can be transfused into human volunteers without causing any apparent disease. In animal models, however, antinuclear antibodies can intensify experimental inflammatory lesions [5]; there is also evidence for involvement of immune complexes containing antinuclear antibody (either deposited or formed *in situ*) in the renal lesion of SLE as well as in tissue damage in other sites [6]. Recent evidence suggests that these antibodies may be formed against DNA-containing debris which is packaged into a vesicle after cells have undergone apoptosis, so-called 'apoptotic bodies' [7,8]. Anti-DNA antibodies bind the DNA receptor on white blood cells and block the binding and sequestration of free DNA by mononuclear cells [9]. These antibodies also produce the release of IFN-γ from mononuclear cells, enhancing immunological and inflammatory reactions [10]. Anti-Ro or closely related antibodies are implicated in the development of the rash and heart block found in neonatal LE (see p. 56.54), and possibly in other childhood SLE. The antiphospholipid antibodies, including the so-called lupus anticoagulant, are linked to thrombosis and abortion in patients with SLE (see p. 56.69). Conversely, neurofilament autoantibodies occur in 21% of patients with SLE, but do not correlate with neurological involvement [11]. Antiribosomal P proteins are highly specific for lupus psychosis [12]. Recent evidence suggests that there is switching of antibody types between the active and quiescent stages of the disease, with low-affinity IgM antibodies present when the disease is controlled, and high-affinity IgG, often directed against endothelial cells, being present when the disease is active [13]. Antiendothelial cell antibodies are associated with renal and vascular complications [14].

Idiotypes and anti-idiotypes [15]. Idiotypes are the antigenic determinants of immunoglobulin molecules and are found in the variable region of these molecules and the T-cell receptor. Antibodies to these antigens develop (anti-idiotype antibodies), and are themselves capable of stimulating anti-anti-idiotype antibodies. Thus, complicated networks of antibodies develop, which are involved in the mechanisms of autoimmunity and self-recognition. Anti-idiotype antibodies may have some of the capabilities of the original antigen, and may also cross-react with other self-antigens, interfering with the development of tolerance produced by the removal of self-reactive T cells. This interference would allow the development of the 'forbidden clones' originally predicted by Burch and Rowell [16]. Cross-reaction between self-antigens and those derived from extraneous sources such as infection or other environmental agents may provide the original source of anti-idiotype antibodies [17].

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Other immune factors. Impaired cell-mediated immunity in SLE has been demonstrated by a variety of techniques. Decreased leukocyte migration inhibition [1], lymphocyte transformation responses to common antigens [2] and decreased skin-test responses to purified protein derivative, candidin and streptokinase-dornase [3] are related to disease activity [4]. T-cell counts are diminished [5] and null cells are increased [6] in active disease. It would appear that there is an imbalance between T and B lymphocytes in the disease, with depressed cellular immunity and an overactive humoral antibody response, possibly related to a relative lack of suppressor and/or inducer T cells [7], although all T-cell types are reduced, and their function is impaired [8]. IL-2 production by peripheral blood leukocytes is impaired, reducing the inhibitory effects of T cells on activated B cells [9].

There is a reduction in activated B cells, but hyperactive B cells are increased in SLE [10], and their differentiation abnormally stimulated by monocytes [11]. Autologous serum has been found to modify leukocyte migration inhibition to liver antigens in SLE [12] and this blocking of cell-mediated immunity, if active *in vivo*, might be a factor in the waxing and waning of clinical activity. There is some evidence that in remission there is a return of immunological suppressor function despite a persisting impairment of T-lymphocyte reactivity [13]. Antibody-dependent cellular cytotoxicity may be another pathogenic factor, and antibodies directed against lymphocyte membranes are found in SLE. Serum-induced cytotoxicity occurs to both T cells [14] and human target cells [15], and immune complexes may be implicated [16]. Circulating immune complexes occur in approximately half of patients, especially those with active and extensive disease [17]. Lymphocytotoxins can be demonstrated in approximately one-third of cases [18]. Killer cell activity is increased [19]. Complement activation occurs, and the anaphylatoxins C3a and C5a are increased during disease exacerbations, possibly contributing to the pathogenesis of the vascular lesions [20].

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UV radiation. This may precipitate the onset or exacerbate the course of SLE in up to 60% of patients [1,2]. Phototesting to UVB [3] and UVA [4] shows reduced minimal erythema doses and the development of skin lesions in patients with LE. The mechanism of action of UV radiation in SLE remains unknown, although antibodies to UV radiation-denatured DNA can be demonstrated. There is no defect of DNA repair in SLE [5], and the antibodies to denatured DNA have no clinical or immunological correlations [6]. The expression of Ro antibody can be induced on cultured keratinocytes by UV radiation [7], and this antibody is commonly found in photosensitive patients. However, there is no relationship between absolute levels of Ro and disease activity [8]. Fibroblasts and lymphocytes

from patients with SLE are abnormally sensitive to UVA and UVB exposure [9].

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Environmental factors. Lupus-like disorders have been reported in association with a variety of environmental factors [1]. Although early reports suggested that silicone breast implants are more frequently associated with connective tissue diseases including lupus-like syndromes, scleroderma, fibrositis, inflammatory myopathy and autoimmune thyroid disease [2], recent studies show that the incidence is no higher than in control populations [3]. Haemolytic anaemia with high titres of antinuclear and anti-dsDNA antibodies has followed the ingestion of sprouts, seeds and dietary supplements of alfalfa, which contains the amino acid L-canavanine [4]. Heavy metals including cadmium, mercury and gold have also been associated with autoimmunity [5]. Other industrial factors include silica [6,7] and trichlorethylene [8].

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Infections, stress, hormonal factors. Other factors may precipitate the onset of SLE, and these include bacterial infection and mental or physical stress. A role for antigens derived from infecting organisms in the generation of anti-idiotype antigens [1] has been suggested, and microbial superantigens may stimulate abnormal T- and B-cell interactions, resulting in the state of autoimmunity found in SLE [2]. Infection is more common in SLE than in those not affected, and depressed generation of serum chemotactic factors may contribute to this increase [3]. Initial phagocytosis by polymorphonuclear neutrophils and macrophages is reduced [4].

As markedly more females than males are affected in early adult life, it has been suggested that endocrine factors may be involved [5]. In addition, 20% of female patients have premenstrual flares of skin disease, and a small number present after initiation of oestrogen-containing contraceptive therapy [6]. Levels of circulating androgens are reduced in women with SLE compared with normal controls [7], and men with SLE have reduced testosterone levels [8], indeed hypogonadism from whatever cause may be an aetiological factor in SLE [9]. Prolactin is an immunoregulator, and is secreted by immunologically active cells, suggesting an autocrine effect [10]. Normal humoral and cellular immune responses are greater in females than in males, but this may be a result of the influence of oestrogen on gene expression, rather than on immune responses [11]. A late menarche is associated with an increased risk of SLE in Japanese patients [12]. There is some evidence that neuroendocrine factors play a part in immunity, which could to some extent explain the influence of stress factors in the disease [13].

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Viruses. An infective cause for SLE has long been postulated. Myxovirus-like tubular structures have been found in the endothelium of arterioles, venules and capillaries of the subpapillary plexus and in the cells of the dermal infiltrate in both involved and uninvolved skin [1], as well as in the endothelial cells of glomeruli in patients with renal involvement resulting from SLE. They are also present in approximately one-quarter of patients with various types of renal disease, but not in normal subjects [2]. They have not been confirmed as viruses [3], and indeed can be induced by the action of IFN [4], suggesting an immunological rather than viral origin. Equally, they could represent cellular material phagocytosed by endothelial cells. If they are genuine virus particles, they could act as a precipitating factor in predisposed subjects. The high incidence of antibodies to reovirus double-stranded RNA (70%) [5] and raised titres of antibody to measles and rubella antigens [6], suggest potential viral involvement, but this may be only an expression of T-cell suppression in this disease. There is no evidence of retrovirus infection in SLE [7], but endogenous retroviral DNA sequences are found [8]. Recently, a number of cases of SLE have been reported following acute parvovirus infection [9]. Warts are more frequent than expected, especially in elderly patients, although the incidence of wart virus antibodies is decreased [10], implying a defective immune mechanism. There is an inverse relationship between the occurrence of warts and rheumatoid factor.

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Drugs. The precipitation of SLE by drugs [1–3], especially the antihypertensive hydralazine, is well known. However, there are features to suggest that drug-induced SLE differs from the spontaneous disease: it is uncommon in black people, it occurs in an older age group, renal and central nervous system involvement are infrequent, antihistone antibodies are frequent, anti-DNA antibodies are absent and serum complement is normal. Hydralazine is known to inhibit binding of complement component C4, and this action, with subsequent lack of control of complement activity, may explain the development of lupus-like syndromes.

Cutaneous involvement in drug-induced SLE may be vasculitic [4], bullous [5], erythema multiforme-like [6] or resemble pyoderma gangrenosum [7]. Cases have been reported of hydralazine-induced lupus with Sweet's syndrome [8]. It was thought that the clinical manifestations of drug-induced lupus resolved when the drug was withdrawn, but this is not necessarily so, and patients with hydralazine-induced syndromes may have hyperglobulinaemia and other abnormalities before the administration of hydralazine [4,9]. Patients who develop antinuclear antibodies during treatment with hydralazine need not have the drug stopped unless they have features of the lupus syndrome [10], which occurs in 6.7% of patients after 3 years' treatment with hydralazine [11]. It is dose-dependent, occurring in 5.4% on 100 mg/day and 10.4% on 200 mg/day, but not at all on 50 mg/day. The incidence is much higher in women (11.6%) than in men (2.8%). Some authors suggest that hydralazine can be safely used in SLE in conjunction with immunosuppression [12]. Twenty-four cases of lupus induced by minocycline [13] have been reported. It usually occurs after 2 years of therapy. Patients who require more than 1 year's therapy should have ANA and liver function tests monitored. Other drugs, particularly certain anticonvulsants and procainamide, are known to precipitate SLE-like syndromes (Table 56.4). Drugs recently associated with lupus syndromes have been reviewed [1].

Drugs have been implicated in precipitating or activating SLE in 3–12% of cases [14]. There is an increased incidence of HLA-DR4 in drug-induced SLE [15] and the ratio of females to males is 4 : 1, indicating a possible genetic predisposition. It appears that individuals who are slow acetylators are more likely to develop drug-induced LE or LE-like syndromes [16]. The determination of acetylator type and DR typing may enable susceptible patients to be identified. In spontaneous SLE, however, there appears to be a preponderance of slow acetylators [17], although this

Table 56.4 Drugs inducing systemic lupus erythematosus-like syndromes.

Acebutolol	Oral contraceptives, including:
Allopurinol	Chlormadinone
Aminoglutethimide	Ethinylestradiol
p-Aminosalicylic acid	Etynodiol diacetate
Atenolol	Medroxyprogesterone
Captopril	Mestranol
Carbamazepine	Norethindrone
Chlorpromazine	Norethisterone
Clobazam	Norethynodrel
Clofibrate	Oxprenolol
Co-trimoxazole	Oxyphenisatin
Diphenylhydantoin	Penicillamine
Ethosuximide	Penicillin
Gold salts	Phenylbutazone
Griseofulvin	Phenothiazine
Guanoxan	Phenytoin
Hydralazine	Pindolol
Hydrochlorothiazide	Piroxicam
Hydroxyurea (hydroxycarbamide)	Practolol
Ibuprofen	Primidone
Interferon	Procainamide
Isonicotinic acid hydrazide	Propranolol
Isoquinazepon	Propylthiouracil
Labetalol	Quinine
Leuprolide acetate	Recombinant interferon
Lithium carbonate	Streptomycin
Methyldopa	Sulfasalazine
Methylphenylethylhydantoin	Sulphonamides
Methylthiouracil	Tertalol
Methysergide	Tetracycline
Minocycline	Timolol eye drops
Minoxidil	Trimethadione
Nitrofurantoin	Valproate
	Venocuran
	Vostatin/simvastatin

is disputed [18]. There does not appear to be a correlation between acetylator phenotype and clinical manifestations, antinuclear factor or activity of the disease [19].

Antihistone antibodies are not drug-specific, although different drugs do induce antibodies to different histone epitopes, and the antibodies are often present well before clinical manifestations occur [20]. Indeed, 50% of procainamide-treated patients develop immunological abnormalities, whereas only 20% develop clinical disease [21]. Of patients with drug-induced lupus syndromes, 82% have antihistone antibodies, compared with 32% of those with serological changes only [20].

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Relationship of genetic and environmental factors and autoimmunity. The relationship of genetic factors, possible virus infection and depression of cell-mediated immunity has led to the suggestion that genetic factors might allow virus replication in the thymus and in T cells, inducing damage to these cells and hence defective cellular immunity. The age pattern of the disease and its female predominance suggest that these abnormalities appear to affect only a specific susceptible genotype, involving three dominant X-linked alleles. Phenotypic expression then depends on accumulated randomly occurring changes in lymphoid stem cells, with three 'forbidden' clones of lymphocytes developing [1–4], and with hyperglobulinaemia and autoantibody formation from hyperactive B cells and the lack of T-cell suppression following. Normal defence mechanisms, which are more effective in females, prevent these changes persisting, but may be impaired by infections, drugs, UV radiation and stress, thus precipitating the disease. Organ involvement is determined by genetically controlled antigenic expression in target tissues. Such a concept would explain the sex differences, the occurrence

of clinical and subclinical autoimmune disease and antibodies in the relatives of patients, the apparent spontaneous onset in many cases, and the precipitation and exacerbation of clinical manifestations by factors impairing the defence mechanisms.

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Pathology (Table 56.5). The pathological changes of SLE have been well described. The primary lesions of SLE are fibrinoid necrosis, collagen sclerosis, necrosis and basophilic body formation, and vascular endothelial thickening. The basophilic (haematoxylin) bodies are aggregates of homogeneous material staining blue with haematoxylin and staining positively for DNA by the Feulgen technique. This material is similar to that of the homogeneous nuclear material of the LE cell.

Macroscopic appearances. Despite the widespread clinical manifestations and fatal outcome, it is often disappointing to find no macroscopic changes at autopsy. Sometimes, terminal changes and infection obscure the picture. Frequent macroscopic findings include pleurisy with adhesions and effusion, and pericarditis, especially if the patient has died with uraemia. The verrucose vegetations of Libman–Sacks endocarditis are diagnostic (Fig. 56.25) [1]. These are small firm warty deposits, up to 0.5 cm in diameter, adherent to the valves of both sides of the heart and adjacent endocardium of the ventricles, chordae tendinae and on the papillary muscles. Sometimes, lesions of subacute bacterial endocarditis may be superimposed on the warty lesions.

Table 56.5 Pathological features of systemic lupus erythematosus.

Macroscopic
Pleurisy
Pericarditis
Libman–Sacks endocarditis
Lymphadenopathy
Splenomegaly
May be none
Microscopic
Immunoglobulins and complement at the dermal–epidermal junction in skin lesions (90%) and uninvolved skin (60%)
Haematoxylin bodies in the endocardium, renal glomuruli and elsewhere
Periarterial fibrosis of the spleen. Wire loop lesions in the kidneys

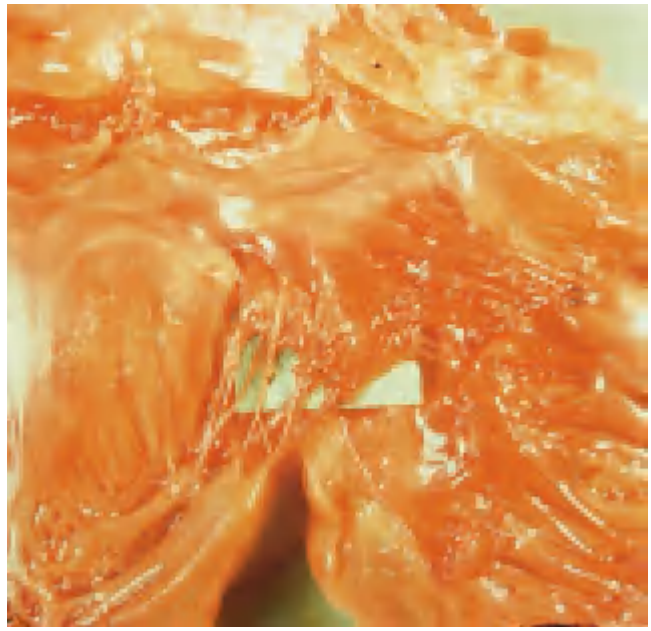

Fig. 56.25 Libman–Sacks endocarditis. Note the warty vegetations on the heart valves.

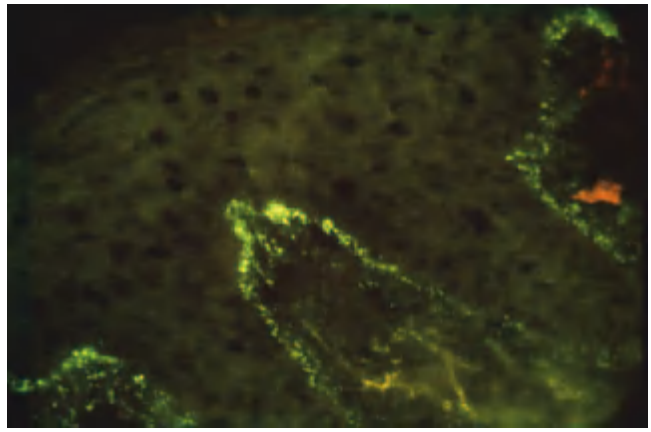

Fig. 56.26 Immunoglobulin at the dermal–epidermal junction in systemic lupus erythematosus.

Microscopic appearances. Usually, pathological diagnosis requires histology, but in some cases histological changes can be demonstrated only by immunohistological techniques (Fig. 56.26) [2]. Immunohistology is also useful in diagnosing SLE in patients with a rash.

Skin. There is no single diagnostic pathological feature in the skin, but a combination of features aids diagnosis [3]. Some changes, such as hyperkeratosis without parakeratosis, and keratotic plugging of the hair follicles and glandular orifices, are similar to those found in chronic DLE. There may also be some atrophy or acanthosis of the prickle cell layer. Liquefaction degeneration of the basal cell layer is common. Epidermal necrolysis has been

reported [4]. The dermal tissues may be oedematous, and sometimes vesicle formation occurs at the dermal–epidermal junction, with dilatation of the superficial vessels and perivascular lymphocytic infiltration. Occasionally, dermal mucinosis occurs, especially in papular lesions [5] and in areas of alopecia [6]. Pigment-containing chromatophores may occur in the infiltrate. Sometimes, the infiltrate is widely distributed in the upper portion of the dermis, being most pronounced in the more chronic type of lesions. Using monoclonal antibodies, the infiltrate is shown to consist of abundant T cells and Ia-positive cells, with rather fewer B cells and macrophages. Helper or inducer T cells and suppressor or cytotoxic T cells occur in equal numbers [7]. Fragmentation, splintering and oedema of the elastic tissue occur. Changes in the walls of blood vessels are relatively infrequent, but hyaline changes and fibrinoid degeneration occur.

Immunohistology [8,9]. Immunoglobulins, predominantly IgG, but less frequently IgM and IgA, together with complement (C1, C3) can be demonstrated at the dermal–epidermal junction by immunofluorescence techniques [10,11]. They occur in more than 80% of skin lesions of DLE and SLE, and may be preceded by basement-membrane abnormalities in erythematous and purpuric lesions [12]. Deposits occur more frequently in light-exposed areas and are invariably present in acute lesions, although in early and late stages the test may be negative. If IgG, IgM and IgA are all present, the diagnosis of SLE is likely, and the more common combination of IgG and IgM is also suggestive. Single immunoglobulins favour another diagnosis (see DLE). The basement-membrane phenomenon can also be demonstrated in the uninvolved skin in three-quarters of active cases of SLE if the biopsy specimens are taken from the exposed skin, preferably from the dorsum of the wrist or forearm. Biopsy specimens from the unexposed skin are positive in only approximately 50% of cases, which may or may not have more severe renal disease and decreased long-term survival [13,14]. Variability in the presence of immunoglobulins and complement in adjacent sites of both light-exposed and light-protected areas probably accounts for differences between series. Biopsy specimens taken from oedematous areas may be negative. The presence of IgG in unexposed normal skin rarely occurs without SLE, and indicates a poorer prognosis than the presence of IgM or the absence of deposits. An IgM band may be found in other diseases, and without other evidence is not sufficient to make a diagnosis of LE [15]. IgM can be found in 80% of lesion-free sun-exposed skin in patients with actinic keratoses [16]. Deposits also occur in patients without rashes or may be present before other features of LE develop. Positive tests may come and go depending on activity, and decrease after treatment or in remission. Deposits in uninvolved skin may occasionally occur in systemic sclerosis, mixed connective tissue disease, dermatomyositis, anaphylactoid purpura, hypocomplementaemic vasculitis, rheumatoid arthritis, pemphigoid and dermatitis herpetiformis. This basement-membrane phenomenon can also be demonstrated in the uninvolved skin in patients with the so-called transitory type of DLE [17]. This is a subgroup of DLE, described by Baart de la Faille-Kuyper [18], with cutaneous lesions of DLE and immunoglobulins at the dermal–epidermal junction in uninvolved skin, as in SLE, but no definite clinical or serological evidence of the latter. The basement-membrane phenomenon is negative in uninvolved skin in other cases of DLE. The staining may be homogeneous or granular, or there may be larger aggregates under the dermal–epidermal zone [19]. Burnham and Fine describe homogeneous, thready and stippled patterns [20], which are different from the 'tubular' band of bullous pemphigoid [21]. The stippled band occurs in uninvolved skin, thready bands in new lesions and homogeneous bands in older chronic lesions. The band type depends on the type of skin lesion and does not distinguish between DLE and SLE. The presence of complement at the dermal–epidermal junction in patients with widespread SLE without renal disease may be associated with a lowering of the serum complement [22]. Both fibrin and properdin have been demonstrated in the lesions of SLE [23]. Properdin deposition in normal skin appears to correlate with disease activity [24]. The presence of properdin suggests that the alternative pathway of complement activation is involved, but nevertheless the classical pathway is the primary complement pathway involved in SLE. In drug-induced SLE, deposits of IgG, IgM and C3 at the dermal–epidermal junction may disappear when clinical symptoms regress [25].

Epidermal nuclear deposits, usually giving a speckled IgG pattern, occur in the basal epidermal nuclei and cells of the lower epidermis in nearly one-third of patients [26]. Immunoglobulin (IgG, IgA and IgM), with or without complement, can be found in the walls of blood vessels in skin lesions and uninvolved skin. There may be homogeneous fluorescence of the subendothelial part of the vessel wall, or intramural or perivascular granular fluorescence, and these changes are present in discoid, transitory and systemic LE. Homogeneous staining occurs in the uninvolved skin of 20% of patients with DLE and over 80% of patients with transitory or systemic LE. Electron microscopy of involved and uninvolved skin has shown deposits of proteins on the dermal side of the dermal–epidermal junction and in small blood vessels, resembling morphologically those present in 'wire-loop' lesions in the kidney [27].

Internal organs. The characteristic microscopic features in the internal organs include haematoxylin bodies in the heart valves and elsewhere, periarterial fibrosis of the spleen, and the so-called 'wire-loop' lesions in the kidneys.

In the heart, microscopic changes, including fibrinoid necrosis, may occur in normal-looking valves. The vegetations of Libman–Sacks endocarditis [1] occur in 50% of cases coming to autopsy [28], and arise from proliferation of ground substance and connective tissue cells [29], which raise the endothelium. Focal necrosis occurs in these areas, and basophilic bodies are frequently seen. Later, infiltration with inflammatory cells occurs, together with fibrosis. Focal atrophy and fibrosis occur in the myocardium, but myocarditis is unusual.

The lungs frequently show pulmonary oedema and infective changes, but specific abnormalities are uncommon. Pulmonary parenchymal lesions or pleuritis occurred in 18% of one series [30], and other findings included interstitial fibrosis, pulmonary vasculitis, haematoxylin bodies and pneumonitis. A mucinous basophilic oedema of the alveolar walls occurs, with a hyaline alveolar lining membrane similar to hyaline membrane disease of the newborn. Alveolar wall thickening and vascular changes similar to those of Hamman–Rich syndrome may be found.

The liver may show infiltration of the portal tracts with lymphocytes, histiocytes and plasma cells. The so-called 'onion skin' appearance in the spleen is caused by concentric periarterial fibrosis around central and penicilliary arteries.

The lymph-node enlargement is usually associated with retention of normal architecture, but sometimes necrosis and haematoxylin bodies may be found.

The so-called 'wire-loop' appearance in the kidneys is caused by thickening and hyalinization of the capillary basement membrane of the glomerular tufts. Although this change may be seen in other diseases such as systemic sclerosis, chronic glomerulonephritis and malignant nephrosclerosis, the changes in SLE are more likely to be localized to one part of the glomerulus. Thickening of the glomerular capillary basement membrane and alterations in reticular tissue in the media of arterioles are associated with deposits of IgG and C3 [31]. Lupus nephritis has been divided into three types [32]: focal proliferative (lupus glomerulitis) and membranous, which are relatively benign, and diffuse proliferative (lupus) glomerulonephritis, which has a poor prognosis. In focal proliferative nephritis, a mild proliferation is confined to parts of some of the glomeruli and electron microscopy shows no electron-dense material. In membranous lupus nephropathy, there is irregular thickening of the glomerular basement membrane with epimembranous deposition of electron-dense material. The most common renal disorder is diffuse proliferative nephritis, in which there is irregular endothelial cell proliferation, fibrinoid necrosis, hyaline thrombi and interstitial inflammatory changes. Electron-dense deposits are seen on electron microscopy in subendothelial, subepithelial and mesangial areas. Heavy proteinuria with large numbers of red and white cells and casts in the urine suggests glomerulonephritis [33]. Although most cases of the nephrotic syndrome and renal vein thrombosis show membranous glomerulonephritis, focal proliferative glomerulonephritis has also been reported [34].

Germinal centres in the thymus are frequently increased [35]. Abnormal epithelial hyperplasia in the thymus is said to occur in all cases of SLE, but the change is not specific [36].

There may be evidence of widespread vasculitis in other organs and in the central nervous system. Although the vasculitis in the nervous system is usually mild, it can be florid [37]. Gammaglobulin deposits and complement have been found in the choroid plexus when immunohistology of the cerebrum, cerebellum and brainstem has shown no abnormality [38]. This, together with the finding of low cerebrospinal fluid complement levels [39], suggests an immune-complex pathogenesis for the involvement of the central nervous system.

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Clinical features. See Table 56.6 for an analysis of the clinical features of several series.

Table 56.6 Clinical features of systemic lupus erythematosus.

Clinical feature	Percentage
Fever	90
Arthritis and arthralgia	90
Skin lesions	80
Renal involvement	67
Lymphadenopathy	50
Pleurisy	40
Raynaud's phenomenon	35
Pericarditis	25
Hepatomegaly	25
Central nervous system involvement	25
Abdominal symptoms	20
Splenomegaly	15

Presenting symptoms. The disease may affect many systems of the body, and the presentation and course are by no means uniform. Large series of cases have been reported [1–8] including one from the Far East [9]. The subject has been reviewed [8,10]. Despite the female sex predominance, clinical gender differences are not found, although men may be more liable to fits and renal failure [11].

The initial manifestations vary. In one series of 200 cases, the first changes were articular in 58% and cutaneous in 13.5% [12]. Presentation with renal abnormalities, psychiatric disturbances, pericarditis, pleurisy, abdominal pain and pyrexia of uncertain origin are less common.

In fulminating cases, there is usually marked constitutional disturbance, with fever, loss of weight, anorexia, malaise and joint pains; the skin may be involved later, if at all. On the other hand, the evolution can be gradual, starting with localized skin lesions and systemic involvement developing later. Fatigue is a prominent symptom, both at presentation and subsequently [13]. The diagnosis in many cases is made only by considering the condition in a patient with an obscure illness. As most cases are females, sex is an important diagnostic point. Although weight loss is a feature in nearly 50% of the cases, some patients may gain weight, and 18% actually did so in the Leeds series, which included several patients with long histories. Menstruation is irregular in 18% and absent in 75%. The onset in 15% of females is after the menopause. Sometimes, there is a previous history of sensitivity to drugs such as penicillin, gold or sulphonamides. Raynaud's phenomenon occurs in the course of the illness in approximately 35% of patients, and others frequently have chilblains and a poor peripheral circulation. Approximately 2% of patients with Raynaud's phenomenon eventually develop SLE. Sometimes, there may be other apparent precipitating factors, such as exposure to the sun, stress, trauma and infection. Rarely, hypothermia may occur, often precipitated by therapy [14].

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Skin. Approximately 80% of cases have a rash at some stage, and in up to 25% it is the presenting sign [1]. The prevalence varies between series. Findings from a typical UK population are shown in Table 56.7 [2].

The cutaneous changes may be broadly divided between: (i) those specific for LE, and showing the characteristic histopathological appearances of LE; and (ii) those that are less specific in their origin and not showing LE histological changes. Many of these are also seen in the other connective tissue diseases.

Specific changes. Cutaneous erythema is the most common feature, particularly on light-exposed areas (Fig. 56.27). A butterfly blush or discrete maculopapular eruption with fine scaling on the butterfly area of the cheeks or elsewhere is also frequently found (Fig. 56.28). Photoaggravation brought about by increased sensitivity to sunlight occurs in approximately 33% of patients at Leeds, but up to 73% has been reported from America [3]. This may relate to the amount of sunlight. UV radiation such as that found in discos [4], fluorescent lighting [5] and UVA from photocopiers [6] may also cause exacerbations. Oedema, especially of the face, may resemble contact dermatitis, seborrhoeic eczema, dermatomyositis or erysipelas, and

Table 56.7 Cutaneous features of systemic lupus erythematosus in 73 patients. (From Yell *et al*. [2].)

Cutaneous feature	Percentage
Butterfly rash	51
Facial oedema	4
Subacute cutaneous LE	7
Chronic discoid LE	25
Scarring DLE alopecia	14
Non-scarring alopecia	40
Chilblain lupus	20
Mouth ulceration	31
Bullous eruptions	8
Photosensitivity	63
Raynaud's phenomenon	60
Chronic urticaria (> 36 h)	44
Cutaneous vasculitis	11
Livedo reticularis	4
Episcleritis	4
Cheilitis	4

DLE, discoid lupus erythematosus; LE, lupus erythematosus.

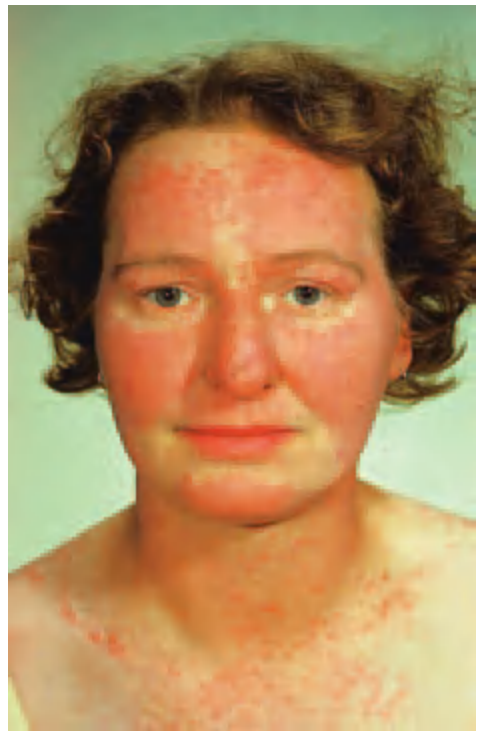

Fig. 56.27 Systemic lupus erythematosus: typical symmetrical slightly scaling erythema of the face and neck.

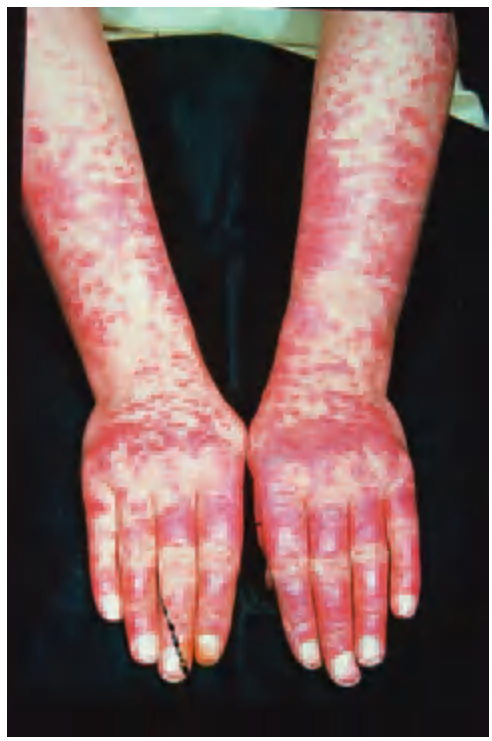

Fig. 56.28 Systemic lupus erythematosus of the dorsa of hands and forearms. Identical changes may occur in discoid lupus erythematosus. Note the chloroquine pigmentation of the distal part of the nails.

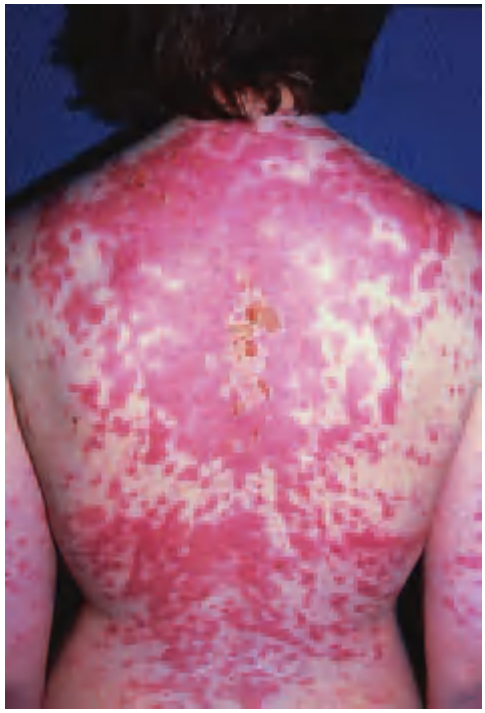

Fig. 56.29 Systemic lupus erythematosus: gross involvement of the back.

can follow tooth extraction [7]. Occasionally, more acute lesions with bullae may follow exposure to the sun (Fig. 56.29), and bullae may be haemorrhagic [8,9].

Epidermal necrosis may give an appearance resembling toxic epidermal necrolysis [10]. In other cases, lesions are like those of erythema multiforme (Rowell's syndrome; see p. 56.14). Very rarely, the skin may show centrifugal annular erythema like that of SCLE. Lesions resembling chronic discoid lesions are initial manifestations in approximately 10% of patients and occur in the course of the disease in approximately 33%. Discoid lesions may be more common in men [11]. Discoid lesions may also be found as the acute phase of SLE settles [12].

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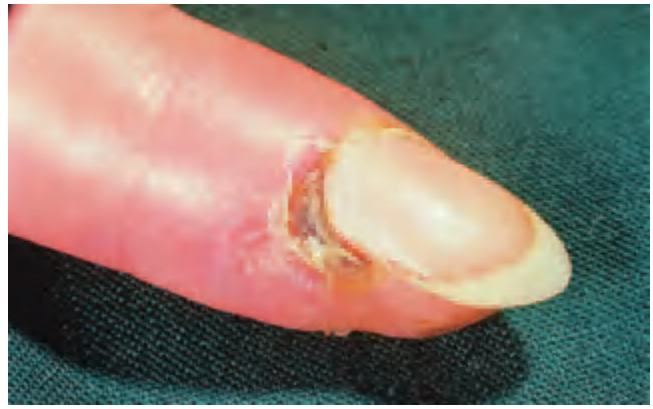

Fig. 56.30 Necrosis of the nail fold in systemic lupus erythematosus.

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Non-specific changes. Sometimes, lesions may be minimal. This is particularly so in the case of the reticulate telangiectatic erythema seen on the thenar and hypothenar eminences of the palms, on the pulps and dorsum of the fingers and, to a lesser extent, on the toes and over the lateral borders of the feet and heels. The lesions on the palms may be confused with the palmar erythema of liver disease. They are bluish red and may show small whitish areas of scarring. The changes occur particularly on the dorsa of the distal phalanges and between the joints, but sometimes there may be small vascular necroses on the tips of the fingers and alongside the nails (Fig. 56.30). The nail folds may show hyperkeratotic and ragged cuticles (Fig. 56.31). Splinter haemorrhages may sometimes be seen in the nails [1], and other changes include pitting, ridging, onycholysis, striate leukonychia [2] and red lunulae [3]. Nail changes occur in approximately 25% of patients [4]. Recurrent Osler's nodes may occur in the absence of infective endocarditis [5]. Clubbing has been reported [6]. Dilatation of the nail fold capillaries also occurs, but this is seen in other conditions. Biopsies from the nails and from areas of palmar erythema show marked dilatation of superficial capillaries [7].

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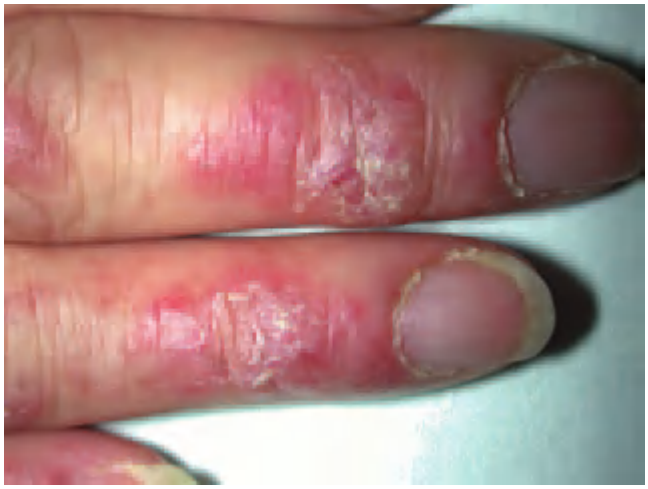

Fig. 56.31 White nail and ragged cuticle in systemic lupus erythematosus.

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Hair changes. Alopecia occurs in over 50% of patients, especially in the active phase of the disease. This takes the form of diffuse loss of hair with a reddish scalp or, less frequently, permanent scarring alopecia, similar to that found in DLE. The hair is usually coarse, dry and fragile, especially on the frontal margin. This leads to an unruly appearance with short, broken-off hair, the so-called 'lupus hair' (Fig. 56.32) [1]. This occurs in 30% of patients, predominantly females [2]. The hair recovers as the disease becomes inactive, but 'lupus hair' usually persists longer than alopecia. The shortened hairs are unbroken and are probably brought about by slowed anagen growth.

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Urticarial lesions and vasculitis. Persistent non-itching urticaria-like weals are common, and may respond to dapsone if associated with C1q deficiency. Urticarial lesions occurred in 7% of one series, but in 20% of patients at Leeds, and were considered to be brought about by immune-complex deposition [1]. SLE may present as hypocomplementaemic urticarial vasculitis [2]. Widespread

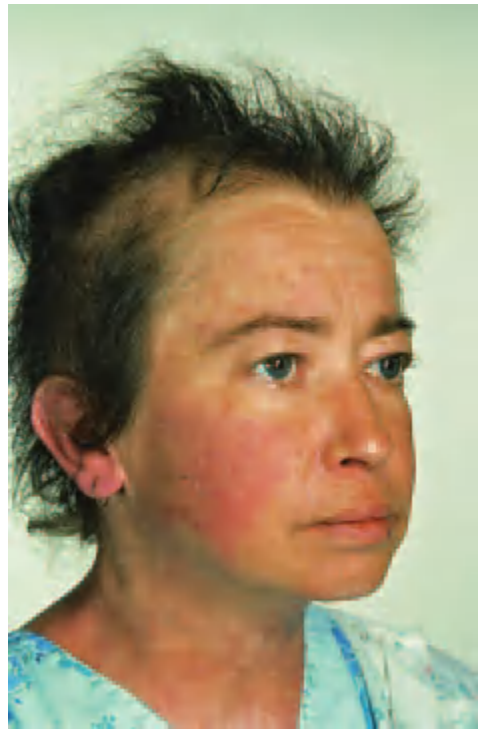

Fig. 56.32 Unruly 'lupus hair' with diffuse alopecia.

purpura, resulting from thrombocytopenia or cutaneous vasculitis, is a common finding. Leukocytoclastic vasculitis may lead to purpuric macules, up to 1 cm in diameter, and in certain cases purpuric urticarial lesions may be found. Purpura can also be a result of corticosteroid therapy. Livedo reticularis, a mottled or bluish red discoloration, which blanches on pressure and is not affected by temperature changes, may develop, especially on the outer aspects of the arms. It occurs most frequently in patients who later develop central nervous system lupus [3]. The appearance of livedo reticularis in association with flares of cerebral vasculitis has been noted [4]. Superficial ulceration can occur in areas of livedo. Atrophie blanche [5] and lesions similar to those of malignant atrophic papulosis (Degos' disease) [6] are other features of vasculitis. Patients with the perniotic lesions of 'chilblain lupus' (see p. 56.13) may go on to develop SLE. These lesions may ulcerate, as may the hyperkeratotic keratodermatous skin sometimes found. A subset has been described in which perniotic lesions on the dorsum of the knuckles and toes, fingers and the pulps and palmar and plantar surfaces is associated with anti-Ro antibody [7]. Chronic pyoderma gangrenosum occurs, and has been the presenting feature of hydralazine-induced SLE [8]. Follicular pyoderma resulting from infection has also been described [9]. Large areas of acute gangrene (e.g. of the buttocks) may separate during systemic corticosteroid therapy, and require grafting.

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Large vessel disease. Gangrene of the tips of the fingers and toes [1] may develop insidiously. At first the digits become blue and cold and may be painful. Radiography of the fingers in cases with peripheral ischaemia shows absorption of the distal part of the terminal phalanges, as in systemic sclerosis. Later, the phalanges may become exposed, and spontaneous separation of the tips of the fingers may occur. Amputation of digits may be required. Occlusion of large- and medium-sized arteries can occur suddenly and result in gangrene requiring amputation of a limb [2,3]. This may be the result of vasculitis or thrombosis. Patients with thrombosis frequently have antiphospholipid antibodies [3]. Major vessel occlusion can occur in childhood [4]. Leg ulcers (Fig. 56.33) occur in approximately 10% of patients, usually near the malleoli but sometimes on the feet and elsewhere, from breakdown in reticular livedo and in areas of cutaneous vasculitis. Erythromelalgia (pain in the feet aggravated by heat and dependence and relieved by cooling and elevation) may be a presenting feature [5].

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Mucinosis. Although mucin deposition is a common and often prominent histological feature of cutaneous lupus, specific clinical patterns of mucinosis also occur. Papular or nodular lesions resulting from mucinous deposits in the dermis without microscopic features of LE have been reported [1], and form a distinct entity which may be the presenting feature of LE [2]. Multiple firm non-tender dermal papules and nodules, between 5 and 15 mm in diameter, occur on the upper part of the body and extremities [3–6]. The overlying epidermis appeared normal. Hyperpigmented acral papular mucinosis has also occurred in one patient with total alopecia [6].

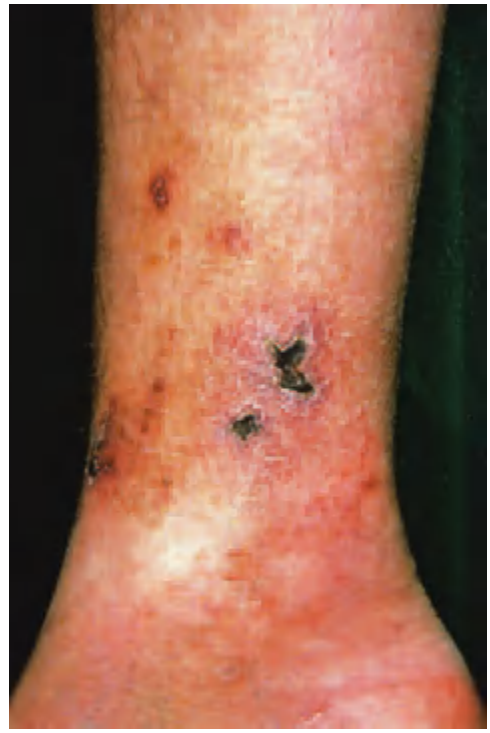

Fig. 56.33 Necrotic crusted leg ulcers in systemic lupus erythematosus.

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Connective tissue changes. Hardening, binding-down and pigmentation of the skin of the face and limbs may resemble systemic sclerosis, although the typical mat-like telangiectases of the latter are usually absent. Calcinosis is rare [1], but occasionally widespread and large palpable deposits may develop [2] or be found radiologically [3]. Subcuta-

neous nodules occur in approximately 5% of patients [4]. They resemble rheumatoid nodules, although there may be no evidence of arthritis. They occur mainly over the backs of the proximal phalangeal joints and wrists, but are also found on the elbows, knees, occiput and the flexor aspects of the fingers. They may respond to hydroxychloroquine [5]. Some are histologically identical with classic rheumatoid nodules [6], others are probably caused by vasculitis and thrombosis [7]. Panniculitis, similar to LE profundus, can occur in the course of the disease or can be the presenting sign [8–10]. Lesions may break down, resolve with oral corticosteroids or require surgery and grafting. Relapsing nasal and auricular chondritis have been described [11]. The nose and ears are tender, warm, swollen and red, but cartilage collapse does not occur as in polychondritis. Treatment with corticosteroids is effective.

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Pigmentary changes. Pigmentary disturbances are not uncommon. Whole areas can show hypopigmentation. A bluish black pigmentation of the skin results from antimalarial therapy [1].

Other cutaneous changes. In the Chinese, hyperkeratotic follicular erythematous papules, sometimes becoming pigmented or confluent, occur on the trunk and limbs. Psoriasiform lesions and hyperkeratosis of the palms and soles are found [2,3]. Widespread ichthyosis and warty excrescences on knees and elbows may occur [4]. Eruptive dermatofibromas have been reported [5]. Acanthosis nigricans has been reported in lupoid hepatitis [6]. Herpes zoster is more frequent than expected in SLE [7], and scabies is more severe and may be of the crusted type [8].

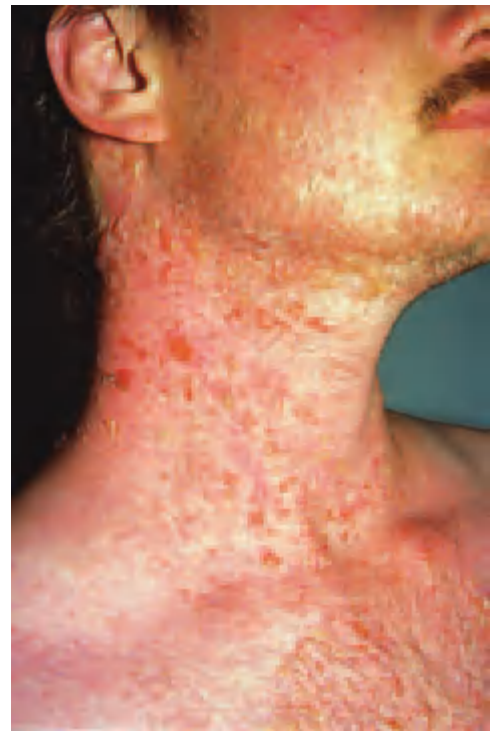

Fig. 56.34 Bullous lupus erythematosus of the face and neck.

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Bullous SLE (Fig. 56.34) [1]. Blistering is uncommon in SLE. In the classic disease, separation of the epidermis and dermis occurs as a result of severe liquefaction degeneration of the basal layer and dermal oedema. A separate subset called bullous SLE has been defined, with distinct clinical and histopathological features, the latter resembling dermatitis herpetiformis [2]. Subepidermal vesicles contain neutrophils with microabscesses, and nuclear 'dust' and fibrin at the tips of dermal papillae. Immunohistology, however, shows linear deposition of IgA, IgG and IgM and, to a lesser extent, C3 at the basement membrane, resembling bullous pemphigoid and unlike the IgA seen in the dermal papillae in dermatitis herpetiformis.

Electron microscopy shows the immunoreactants to be in the sublamina densa [3] and not in the lamina lucida as in pemphigoid, although the immunopathological changes are variable and may indicate that a number of basement-membrane antigens can act as targets [4]. This has subsequently been confirmed [5]. In particular, a form resembling epidermolysis bullosa acquisita (EBA) has been described [6]. The target antigen in some patients is type VII collagen, but other antigens may be involved in bulla formation [7].

Clinically, the bullous lesions are predominantly on the face, neck and upper trunk, but may be more widespread, and may heal with milia formation. One-third have mouth lesions. Photosensitivity may occur. The patient may initially present with lesions resembling erythema multiforme [8]. Glomerulonephritis is common, and associated with hypocomplementaemia and anti-DNA antibodies. Circulating antibasement-zone antibodies have many features of EBA antibodies. The demonstration of such antibodies may precede the development of SLE by many years [9]. It is not yet established whether patients with EBA antibodies are a unique subset of bullous LE or whether they represent the coexistence of two separate diseases, although it has been suggested that the spectrum of bullous LE should include all cases of bullous disease occurring in patients with SLE [1]. Rarely, drugs, including hydralazine [10] and IFN-α [11], may precipitate bullous SLE. Dapsone alone or in combination with prednisone is the treatment of choice. It is not always successful and may even exacerbate the disease [7]. The authors have used thalidomide successfully in these resistant cases.

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Pemphigus erythematosus [1]. Erythematous, scaly, hyperkeratotic or crusted lesions, sometimes adversely affected by the sun, occur in a butterfly distribution on the cheeks and in a seborrhoeic distribution on the trunk of patients with Senear–Usher syndrome (see Chapter 41). This combines the immunological features of pemphigus and LE. Direct immunofluorescence shows immunoglobulin and complement in the intercellular substance and at the dermal–epidermal junction of perilesional and, to a lesser extent, of light-exposed and non-exposed skin. Circulating pemphigus-like antibodies and antinuclear factor occur in 80–100%, but anti-DNA and ENA antibodies are not found. Recently, antidesmoglein antibodies have been demonstrated [2]. The condition occurs spontaneously, but has been induced by penicillamine, propranolol, captopril, pyritinolol and thiopronine. Topical steroids alone may control the condition, but systemic steroids, immunosuppressives or dapsone may be required.

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Mucous membrane lesions [1–3]. Mucous membrane lesions occur in 26% of cases, usually on the palate (82%) (Fig. 56.35), buccal mucosa or gums, in active phases of the disease [3]. Lesions start as small erythematous or purpuric areas, which break down to form shallow and sometimes painful ulcers, with a dirty yellow base and surrounding reddish halo. There may be difficulty in swallowing. Histology and immunohistology show changes similar to

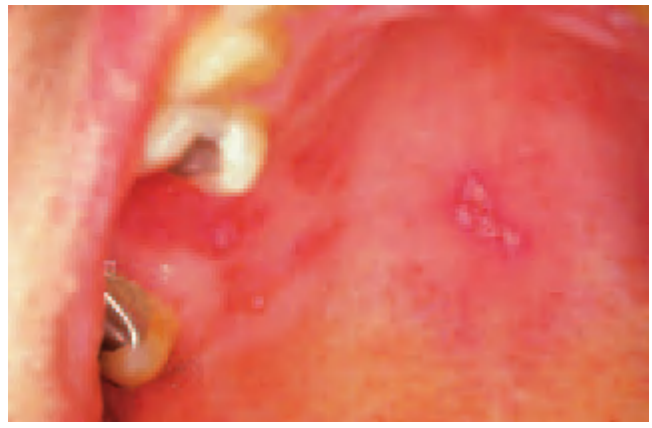

Fig. 56.35 Systemic lupus erythematosus involving the palate.

those in the skin. Light microscopy can usually distinguish between LE and lichen planus [4]. Immunofluorescence is usually positive [5]. Repeated sore throats and oral ulceration may be presenting features [6]. The appearances can resemble a *Candida* infection, and sometimes *Candida* is present as a secondary infection. The lips may become cracked, oedematous and crusted in acute cases. Infarction of the tongue, with anticardiolipin antibodies, was the presenting feature in one case [7]. Cheilitis occurs in approximately 6%, the lips having a silvery appearance, with erythema, scaling and blurring of the vermilion border [1]. The larynx is occasionally involved. Ulceration of the mucosa of the nasal septum occurs in approximately 5%. Perforation of the nasal septum is a complication of exacerbations and presents with epistaxis [8]. Erythema of the vulva and perianal area occurs and vulval ulceration may develop, but is less common than oral ulcers. Patients may present with vulval and vaginal ulceration. Orogenital ulceration has been reported with hydralazine-induced lupus [9].

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Arthritis [1]. Involvement of the joints occurs at some time in approximately 90% of patients, arthralgia being more common than arthritis. A rheumatoid-like deformity is present in approximately 25% of cases, with marked soft-tissue swelling, especially of the dorsa of the fingers, hands and wrists, although joint erosions on X-ray are not a feature. The deformity is usually less, but the soft-tissue swelling is more marked than in rheumatoid arthritis [2]. Jaccoud's syndrome, severe deformity of the hands with ulnar deviation and swan-neck configuration, often with little pain and good function, occurred in 13% and fixed flexion contractures of the elbows in 11% in one series [3]. Arthritis mutilans of the distal interphalangeal joints of the hands can occur [4]. The elbows, shoulders, knees and feet may also be involved and soft-tissue nodules may occur, usually indicating calcinosis. Temporomandibular joint involvement may be indicated by locking or dislocation, tenderness and pain on mastication [5]. Features distinguishing SLE from rheumatoid arthritis are shown in Table 56.8. Migratory polyarthritis with inflammation, effusion and erythema occur less frequently. Sacroiliitis occurs in male patients [6]. SLE may rarely present with polymyalgia rheumatica [7]. *Salmonella* infections occur in patients with SLE, and may be associated with septic arthritis [8,9].

Table 56.8 Features distinguishing systemic lupus erythematosus (SLE) from rheumatoid arthritis (RA).

Distinguishing feature	SLE (%)	RA (%)
Deforming arthritis	25	Common
Subcutaneous nodules	5	25
Radiological erosions	Rare	Common
Involvement of kidneys	Common	Rare
Positive LE cell test	80	15
Positive ANA test	90	20
Rheumatoid factor present	40	80

ANA, antinuclear antibody; LE, lupus erythematosus.

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Heart. Cardiac involvement in SLE is common, and increases with the duration of the disease [1]. Pericarditis is the most frequent cardiac manifestation, but the incidence of 87% in one review [2] must have been the result of selection. Fibrinous pericarditis is frequently found, but sometimes a large effusion may occur and reabsorb on adequate corticosteroid therapy. Rarely, a large effusion can develop within hours, giving rise to cardiac tamponade [3] and requiring aspiration. The incidence of classic endocardial lesions (Libman–Sacks endocarditis) is difficult to estimate, but the diagnosis is rarely made clinically. Lesions were found at autopsy in only four out of 30 patients in one series [4] and in 50% of patients in another [5]. The valves on the left side of the heart are commonly

involved. Both systolic and diastolic murmurs may be found depending upon the site of the lesion, and bacterial endocarditis can occur on the damaged heart valves. Aortic incompetence may occur without involvement of the mitral valve [6] at an early stage of the disease before steroids are used, or when the condition is well controlled. Tricuspid regurgitation has been reported [7]. Echocardiography is helpful in diagnosis [8], and valve replacement has been successful [9].

Coronary arteritis results in myocardial infarction [10]. Infarction may also result from atherosclerosis in young patients [11]. Antiphospholipid antibodies may be demonstrated in such patients [12]. The myocardium may also be affected and results in cardiac failure [13]. The diagnosis can be confirmed by endomyocardial biopsy [14]. Alterations in rhythm include atrial fibrillation and heart block of all types. This may be associated with both Ro and U_1-RNP antibodies [15].

Hypertension occurs in approximately 35% of patients. Alterations in the electrocardiogram (ECG) in the course of the illness may be helpful in diagnosing or in confirming the presence of cardiac involvement. There is some evidence that treatment with corticosteroids increases the incidence and degree of hypertension, coronary atherosclerosis and heart failure [5]. Reduced exercise tolerance occurs and may be caused by abnormal myocardial dynamics on exercise [16].

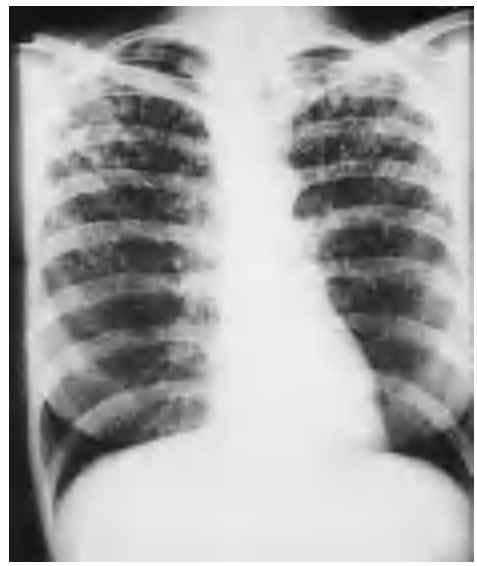

Fig. 56.36 Pulmonary infiltration in systemic lupus erythematosus. This cleared in approximately 2 years on treatment with corticosteroids.

Lungs [1]. The incidence of involvement of the pulmonary system varies between series, and the radiological changes [2,3] depend on the stage of the disease. Transient pleurisy is the most common feature, and in approximately two-thirds of these cases some fluid develops, occasionally haemorrhagic. Pleural effusions can be massive and used to be treated by pleural powder poudrage [4] or pleurectomy [5], but this is now uncommon. Pleural thickening can be shown radiographically. Involvement of the lungs is less frequent, and is shown mainly as transient infiltration, sometimes with mottling and reticulation (Fig. 56.36) [6]. Acute pneumonitis with severe dyspnoea and fever may be a presenting manifestation of SLE [7], and cases have been reported with disseminated intravascular coagulation [8]. There is a high incidence of anti-Ro antibodies in pneumonitis [9]. Diffuse fibrosis, like that occurring in systemic sclerosis, is not found [10]. Shrinking lung syndrome is probably caused by diaphragmatic fibrosis [11]. Pulmonary hypertension occurs [12], and pulmonary haemorrhage can be dangerous [13]. When dyspnoea, pleuritic pain and fever occur with linear shadows on radiography, recurrent pulmonary infarction may be simulated. Fibrosing alveolitis has been reported, as well as haemopneumothorax [14]. Hilar lymphadenopathy may cause confusion with other diseases [15]. Unlike those of systemic sclerosis, the pulmonary changes may resolve with steroid therapy. Pulmonary function tests may be abnormal, even in those showing no radiological abnormality. Impairment of pulmonary diffusion (trans-

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fer factor) occurred in 42–80% [16,17], and is more common than reduction in lung volumes [18]. Such reduction in pulmonary function persists but is rarely progressive [19]. Function of the diaphragm may also be deficient [17], and bilateral elevation of the diaphragm with linear shadows over the lower zones is characteristic of SLE. Death may occur from overwhelming pneumococcal infection [20]. *Pneumocystis carinii* infections should be considered in all steroid-treated patients who present with respiratory distress and pulmonary infiltration [21]. The diagnosis is confirmed by biopsy. Nocardial infection with lung abscesses [22,23] and Legionnaires' disease [24] have been reported. Tuberculosis occurred in 5% in one series, and may be missed [25]. Laryngeal involvement is rare and indicated by stridor and hoarseness, and may be life-threatening. It can occur in inactive disease [23], and may be complicated by nocardiosis [26].

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Renal changes. The renal changes [1] in SLE are very important in assessing the prognosis (see p. 56.64). Most patients will have renal involvement, as histological evidence of nephritis may occur without proteinuria or microscopic urinary abnormality [2] and with normal renal function [3]. Sometimes, proteinuria and casts may occur transiently with febrile exacerbations. Renal disease in lupus accounts for 3% of end-stage renal failure, and is an important cause of mortality in SLE [4]. The need for regular screening by urinalysis, blood pressure monitoring, assessment of renal function and early renal biopsy is critical [5]. Impaired renal tubular potassium secretion can lead to persistent hyperkalaemia [6]. Usually, renal exacerbations are associated with high titres of antinuclear factor, elevated DNA binding and low serum complement, but occasionally these features may revert to normal in severe relapse [7].

The course is variable, and albuminuria and casts may persist for years without marked deterioration in renal function. Kidney damage, if this is going to develop, usually appears early (within the first 3 years) [5] and is more frequent and severe in younger patients [8]. However, renal involvement may appear as long as 34 years after diagnosis of SLE [9]. A relatively benign course is associated with membranous lupus nephropathy [10]. This occurs in approximately 8% of patients with SLE. Clinically, proteinuria and microscopic haematuria occur some years after other evidence of the disease. Prednisone treatment does not seem to influence proteinuria or renal function in this type.

Some cases develop typical signs of the nephrotic syndrome, and renal vein thrombosis has been reported [11,12]. The development of pleuritic pain in a patient with SLE and the nephrotic syndrome should alert the clinician to the possibility of renal vein thrombosis and pulmonary emboli [13]. Massive ascites as the major manifestation of SLE has been reported [14]. The mean survival time of these patients is 8 months [8], although those with normal serum cholesterol levels have a better prognosis. A normochromic normocytic anaemia, unresponsive to iron, is common. Although the serum gammaglobulin is frequently raised, it can be normal or low in association with severe renal involvement. Some patients, after minimal signs of renal involvement for years, die with symptoms of malignant hypertension.

Cystitis with reduction of bladder capacity and thickening of the bladder wall may be a primary manifestation of SLE [15]. Pulmonary haemorrhage may occur more frequently in these patients [16]. A strong correlation between lupus cystitis and gastrointestinal involvement has been noted [17].

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Gastrointestinal tract [1]. Anorexia, nausea and vomiting sometimes occur, and impairment of oesophageal motility has been reported [2], especially in patients with Raynaud's phenomenon. Motility studies show absent or impaired contractions in one-third of patients [3]. Abnormalities may occur in any part of the oesophagus but particularly in the upper third, and such dysfunction is not related to activity of the disease. Fewer patients complain of dysphagia or show radiological abnormalities. Pain, vomiting, diarrhoea, malabsorption [4,5], gluten-sensitive enteropathy [6] and protein-losing enteropathy [7], or evidence of obstruction or bleeding, result from intestinal involvement. Pneumatosis cystoides intestinalis and spontaneous pneumoperitoneum are rare [8], but have been reported in a patient with antinuclear-negative SLE [9]. Patients with arteritis may present as an acute surgical emergency, and this complication may be fatal [10]. Small intestinal ulceration occurs in patients with antiphospholipid antibodies [11]. Mesenteric arteriography may be helpful in showing irregularities of the small intestinal arteries [12]. Pancreatitis [13,14] occurs in both children and adults and is often fatal. It can be associated with subcutaneous fat necrosis and calcinosis cutis [15]. Ulcerative colitis [16] and colonic perforation [17] also occur. Mesenteric lymphadenopathy may be associated with hilar lymphadenopathy [18].

Lymphangiographical changes can resemble those seen in early malignant lymphoma [19]. Painless ascites, in the absence of the nephrotic syndrome, congestive heart failure or hepatic cirrhosis, may be the presenting feature [20,21]. It is presumably a result of peritoneal serositis. Infarction of the tongue can be another presentation [22].

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Hepatic lesions [1]. These may be more common than previously recognized [2]. Liver disease is present in approximately one-third of patients, but it is usually mild and often asymptomatic. Histology usually shows steatosis or mild hepatitis. Lesions include granulomatous hepatitis, chronic active hepatitis, cirrhosis, death from liver failure and hepatic infarction. Nodular regenerative hyperplasia occurs [3], and hepatic veno-occlusive disease has been reported [4]. Subclinical liver disease indicated by mild transaminase elevation occurs in approximately 8% [5]. LE cells are sometimes found in hepatitis. The condition, inappropriately named 'lupoid hepatitis', involves mainly young females who have a benign cirrhosis and evidence of adrenal overactivity such as acne, hirsutism, pigmentation, amenorrhoea and abdominal striae. Other features include febrile upsets, polyarthritis, hyperglobulinaemia and other protein abnormalities. Smooth muscle and mitochondrial antibodies may be demonstrated. Patients with chronic active hepatitis may show extensive purplish telangiectasia [6].

Thyroid disease. Both hyperthyroidism and hypothyroidism occur in SLE [7–9], and there is a high frequency of abnormal thyroid function tests and thyroid autoantibodies in patients without diagnosed thyroid disease [10,11].

Nervous system [12–15]. Approximately 50% develop neuropsychiatric features from the disease itself [16]. There is no direct correlation between neurological and psychiatric disease and clinical or laboratory indices of disease activity [14]. Livedoid vasculitis of the skin may be an important prodromal sign of central nervous system (CNS) lupus [17]. Anticardiolipin antibodies may or may not be present. Migraine can be a feature [18,19]. Epilepsy, resulting from small thromboses in cerebral vessels affected by vasculitis, can be the presenting manifestation of SLE, particularly in patients with high titres of anticardiolipin antibodies. The incidence of epilepsy is difficult to evaluate, owing to selection of cases in series from special clinics. Peripheral sensorimotor [20] and autonomic neuropathy occurs [21,22], brought about by vasculitis in the vasa nervorum. It is important to distinguish this from the neuropathy induced by chloroquine [23]. Trigeminal neuropathy, with numbness and pain in the face [24], deafness [25], transverse myelitis [26,27], which may occur in pregnancy [28], optic neuritis [29], aseptic meningitis [30], Guillain–Barré syndrome, and a case presenting as disseminated encephalomyelitis, have been reported [31]. Patients may present with clinical features of multiple sclerosis, and in this variant there is a high incidence of chronic biological false-positive Wassermann reactions and mitochondrial antibodies [32]. Occasionally, a single cranial nerve may be involved. Sometimes, signs simulate an intracranial mass [33], and pseudotumour cerebri because of raised intracranial pressure occurs [34]. Subarachnoid haemorrhage [35] and massive spontaneous subdural haematoma have been reported [36]. Parkinsonism is rare [37]. The association of chorea with SLE has been reviewed [38]: two cases of chorea were reported in a series of 175 patients with SLE [39], and the authors have seen this association in two girls aged 3 and 16 years. Chorea gravidarum also occurs [40]. SLE may also cause psychiatric symptoms, including anxiety, hypomania, emotional lability, memory defects and depression. Psychiatric symptoms [41,42] are found in approximately 20–30%. Patients may respond to the disease with hypochondriasis, depression and hysteria [43]. Pseudocyesis has been reported [44].

Dislike of a patient by the physician may be a clue to serious psychiatric impairment resulting from SLE in that patient [45]. The electroencephalogram (EEG) [46], conventional brain scanning [47] and oxygen-15 brain scanning [48] may be helpful in the diagnosis of cerebral LE, and abnormalities are related to clinical progress [47]. Cranial computed tomography (CT) may show focal areas of infarction and cerebral atrophy [49]. The latter may be caused by steroid therapy rather than the disease [50]. Calcification occurs in cerebral LE. Magnetic resonance imaging (MRI) may be helpful [51] and show abnormalities not found on CT, but its use is limited [52]. Autoantibodies to neuronal antigens can be demonstrated in approximately 20% of patients with SLE [53], especially in those with neuropsychiatric features [54]. Antiribosomal P protein antibodies seem to be associated with psychosis [55]. Patients with multiple strokes followed by dementia are likely to have antiphospholipid antibodies [56]. Depressed levels of C4 in the cerebrospinal fluid (CSF) are found in patients with CNS involvement, but not in patients with active SLE without CNS manifestations [57].

Toxoplasmosis of the brain may occur as an opportunistic infection in patients with SLE and the manifestations resemble cerebral lupus [58].

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Involvement of the eyes. The eye changes in SLE have been reviewed [1]. They include lid oedema, conjunctivitis and subconjunctival haemorrhages, lacrimal hyposecretion, episcleritis, scleritis, anterior and posterior uveitis, retinal cytoid bodies, retinal haemorrhages and branch- and main-trunk arterial and venous occlusions. All the changes can occur without hypertension. Optic neuritis is uncommon [2] but may be the presenting feature, causing confusion with multiple sclerosis [2]. The retinal cytoid bodies—oval, whitish areas alongside arteries and veins—are not specific to SLE, and are thought to be brought

about by damage to the endothelium of capillaries, which allows the passage of plasma and red cells into the nerve fibre layer. Depigmentation of the retina may be present. Retinal lesions rarely cause visual impairment, but blindness can occur [3]. Lupus retinopathy was found in approximately 8% in one large series and was associated with active disease and lupus cerebritis, and was a marker for poor prognosis [4]. Retinal changes can be demonstrated in nearly one-third of patients by fluorescein angiography, and are associated with active disease [5]. Visual impairment may be the presenting symptom of SLE [6]. Symptoms of corneal involvement occur in more than half of patients, and 88% have corneal staining with fluorescein [7].

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Involvement of the ears. Sudden bilateral loss of hearing, presumably because of vasculitis of the arteries of the cochlea, may be dramatic and permanent. One patient's hearing responded to plasma exchange [1].

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Muscle changes. Muscle pain occurs in approximately 50% of patients, and this may be confused with the pain of arthritis. Muscle weakness is a less common feature. Electromyographic abnormalities correlate better with weakness than myalgia. The serum aldolase level is frequently raised but the serum creatine phosphokinase is usually normal [1]. A vacuolar myopathy is considered to be specific [2]. Calcinosis may occasionally occur [3,4]. Very rarely, there may be a myasthenic reaction and SLE can follow, or be associated with myasthenia gravis [5,6]. Lupus with muscle disease may follow thymectomy for myasthenia gravis [5]. A thymoma may sometimes be found [7].

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Involvement of tendons [1,2]. Tendon rupture is rare, and involves particularly the weight-bearing tendons such as the patellar, quadriceps and Achilles tendons, but it may also occur in the tendons of the hands [3] or biceps [4]. Tendinous laxity may precede rupture and be partly attributable to hyperparathyroidism secondary to chronic renal failure [5]. It may be bilateral. Usually, the patient has been on corticosteroids for a long time. Surgical suture can be successful. Abnormalities of the feet with clawing of the toes and flexion contractures have been designated 'lupus foot' [6,7].

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Calcification. Calcification may occasionally occur. Nine patients in one series of 130 cases had calcification [1]. This is more frequent in the legs, and may be bilateral and diffuse in the skin or deeper soft tissues, or be unilateral and localized. Sometimes, there are large deposits or nodules in the subcutaneous tissues [2]. It can occur without preceding local inflammation or ulceration, and may antedate other manifestations of SLE by as long as 7 years [3]. Periarticular calcification in the hand has been reported [1]. Calcification of the arteries of the legs may occur in early adult life. The myopathy of SLE may result in calcification [4]. A case of SLE with hypercalcaemia has been reported [5]. The serum calcium returned to normal when the patient had responded to treatment with corticosteroids and intravenous pulse cyclophosphamide.

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Bone changes. Avascular bone necrosis [1] occurs in 5–7% or more of patients and is considered to be part of the disease, although it may be exacerbated by corticosteroid treatment [2,3], especially in high doses. It may be more frequent in patients with the lupus anticoagulant [4]. It occurs in relatively mild cases of SLE [5]. The risk is increased in patients with Raynaud's phenomenon [6]. The femoral head or condyle is most frequently involved [7], but the condition also may involve the knees, ankles, humerus, metatarsals and the carpal bones causing wrist pain [8]. It is commonly bilateral, with involvement of multiple joints. It is rarely crippling, although it may proceed to destruction of the joint. X-rays may be normal, but the diagnosis is often clear on MRI [9]. Symptomatic improvement may occur from local or systemic corticosteroids [10]. The condition is thought to be associated with increased pressure in the bone marrow because of altered venous drainage, and core decompression may be successful [11] clinically but not radiologically [12]. Total hip replacement may be required if it fails, or in the late stages [3]. There may be patchy sclerosis and cystic changes in the bones of the hands and feet, and metacarpophalangeal and metatarsophalangeal joints may rarely show subcondylar erosions and adjacent sclerosis [13]. Osteonecrosis, possibly resulting from infarction, has been found in as many as 13 joints during corticosteroid treatment [14].

Other manifestations of systemic involvement include lymphadenopathy, which occurs in more than 50% of cases, and splenomegaly. Swelling of the parotid, submaxillary and lacrimal glands sometimes develops. Classic Sjögren's syndrome occurred in 1.4% in one series [10], but some features of Sjögren's syndrome have been found in practically all cases of SLE on detailed investigation [15].

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SLE in childhood [1]. The clinical picture, course and treatment are similar to the disorder in adults, but on the whole children have more severe disease [2]. The earliest age of onset reported is 3 months [3]. Bullous SLE may resemble chronic bullous disease of childhood [4]. In one series [5], 30% had CNS involvement and 87% had renal disease (diffuse proliferative lupus nephritis, 34%). Overall survival was 85% at 10 years and 77% at 15 years after onset. Children with CNS lupus did no worse than other patients, and this has been noted by others [6]. The prognosis of patients with renal disease is now better than earlier reports suggested. Enlargement of the liver, spleen and lymph nodes is more common in childhood cases. Pancreatitis associated with cutaneous panniculitis and calcinosis has been reported [7]. Prolonged therapy with high-dose steroids may increase disease-related damage; this may be avoided by judicious use of immunosuppressives [8]. Autologous stem cell transplantation has been used successfully [9].

SLE in the elderly [10]. The onset of disease over 60 years occurs in nearly 20% of patients and is often insidious. There is an increased incidence of lung disease and Sjögren's syndrome, and a lower incidence of renal disease and mesenteric vasculitis [11], and antibodies to Ro and La are frequent. There appears to be an association with HLA-DR3.

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SLE in pregnancy [1,2]. Fertility is normal if renal function is good [3]. Worsening of SLE is uncommon in pregnancy [4], especially in those on immunosuppressive therapy [5]. Clinical remission for 6 months before conception should indicate an uncomplicated pregnancy and a live birth [6]. Inactive disease is not associated with disease recurrence [7]. The outcome with renal involvement is comparable with those whose kidneys are not affected [8]. Permanent deterioration in renal function occurs in less than 10% [3]. There is a higher risk of premature delivery, fetal loss and perinatal mortality in all patients. Abortion occurred in 8% and perinatal mortality was 13% in one series [9]. The increased risk of fetal death may be because of immune complex deposition on the trophoblast basement membrane [10], or the transplacental passage of antiphospholipid antibodies. Anticardiolipin antibodies, especially of the IgG isotype [11] or the lupus anticoagulant, are associated with a markedly increased fetal loss in all stages of pregnancy, but the presence of these antibodies without a previous history of fetal loss or thrombosis is not an indication for treatment [1]. With a history of recurrent fetal loss, treatment with prednisone and aspirin may be effective [12]. With good obstetric care, close follow-up, and treatment with low-dose aspirin if antiphospholipid antibody is present, a success rate of 71% has been reported [13]. The authors have seen successful pregnancies following *in vitro* fertilization in patients with SLE and the lupus anticoagulant.

Therapeutic abortion is not indicated and only causes added stress, nor is caesarean section required. It is important to avoid excessive trauma, haemorrhage or shock. The dosage of corticosteroids should be temporarily increased at the time of delivery and postpartum. Corticosteroids do not appear to cause impairment of growth or malformation in the fetus, but high-dose steroids during early pregnancy can cause cleft palate. Babies of mothers with untreated SLE are usually smaller than expected, and corticosteroids may assist growth of the fetus *in utero* [8]. If the patient is on azathioprine, this should be continued [9]. There is no evidence of an increase in the malformation rate [14].

Oestrogen-containing contraceptives, even at low dosage, should be avoided in women with SLE. If mechanical methods of contraception or intrauterine devices are not possible, pure progestogens may be an alternative [15]. Breastfeeding is probably safe if the patient is on aspirin or low-dose steroids, but should probably be avoided if other immunosuppressives are used.

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Neonatal lupus erythematosus

Definition. Neonatal lupus erythematosus (NLE) is a disorder thought to be caused by the transplacental passage of maternal antibodies. The most frequent clinical manifestations are cutaneous lesions and congenital heart block (CHB).

Aetiology. Aylward [1] was the first to report CHB in the siblings of a mother with Mikulicz's disease (Sjögren's syndrome) in 1928. McCuiston and Schoch [2], however, were the first to suggest that the association of NLE and maternal systemic lupus may be related to the transplacental transfer of 'a transmittable aetiological agent' (maternal antibodies). This suggestion subsequently gained credence from the fact that the NLE skin lesions resolve as maternal antibodies are cleared from the infant's serum [3].

The first associated antibody described [4] and the serological marker most commonly associated with NLE is the Ro/SS-A antibody. This has been reported to be present in between 82% of infants and 92% of mothers [5] and 100% of NLE patients [6–8]. Two main Ro/SS-A proteins exist (52 and 60 kDa), and studies have suggested that the former is more frequently found in CHB [9,10] while the latter is more frequently associated with cutaneous disease [11], although this is by no means a universal finding. La/SS-B antibodies are less frequently found, one study detecting these in approximately 50% of NLE infants and 60% of mothers (usually in association with Ro/SS-A antibodies) [5]. U_1-RNP antibodies are much less frequently found but have been reported as the only antibody in some patients with cutaneous NLE [12,13]. In this and subsequent reports, U_1-RNP antibodies have not been associated with CHB.

Evidence that these antibodies may be pathogenic comes from the studies of Lee *et al.* [14] who showed that purified Ro antibody bound to human skin grafted onto nude mice, in a pattern similar to that found in typical LE lesions. In addition, Ro/SS-A antigen is present in neonatal skin [15]. These antibodies have also been shown to bind to Ro/SS-A and La/SS-B antigen in human fetal cardiac conducting tissue [16–18] where they can cause conduction abnormalities [19,20].

It is unlikely that these antibodies represent the whole story, however, as they are non-specific for NLE, occurring in Sjögren's syndrome and SCLE. They are also found in approximately 0.5–2% of the normal population when assessed by immunodiffusion and in 5–11% when assessed by enzyme-linked immunoabsorbent assay (ELISA) [5]. Some studies have suggested that disease expression may be related to HLA status, the HLA-DR3 haplotype (especially when associated with DQA1 and DQB1), having been associated with the immune response to Ro/SS-A [21,22]. These, and a previous study [8], suggest that the HLA haplotype is important for antigen production in the mother but not necessarily relevant in the infants. Other workers argue that these antibodies are only indirectly related to disease, the disease process being caused by either: (i) the 52 kDa Ro/SS-A showing homology with the 5-HT_4 serotoninergic receptor, binding to which then mediates cardiac damage [10]; or (ii) the presence of antibodies to a completely separate 57 kDa protein [23].

Clinical features

Cutaneous. Approximately half of NLE infants manifest skin lesions [5], which may be present at birth or occur in the first few weeks of life. The most common finding is an erythematous, slightly scaly eruption on the face and periorbital skin (raccoon sign/owl-eye/eye mask) (Fig. 56.37), with the scalp, trunk, extremities, neck and intertriginous areas involved in decreasing order of frequency [24]. The eruption can be exacerbated by UV exposure and there are reports of the rash being precipitated by phototherapy for neonatal jaundice [25,26], although the rash is sometimes present at birth, which would make it difficult to implicate UV exposure in the aetiology [27]. Other manifestations include a vitiligo-like eruption in a black infant [28] and morphoea-like lesions [29].

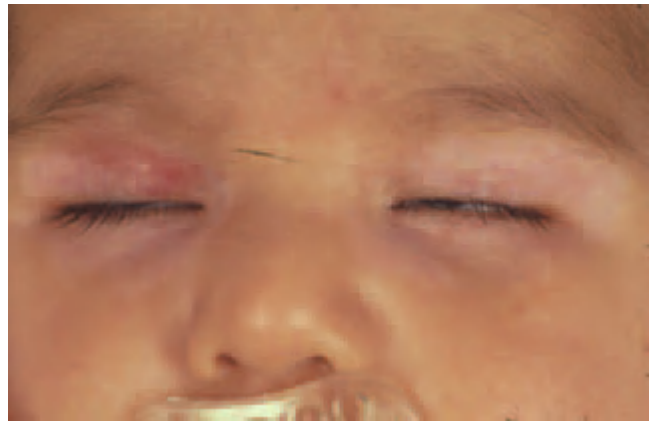

Fig. 56.37 Typical 'raccoon' eyelid lesions in neonatal lupus erythematosus.

The rash improves over the first few months of life and has usually resolved without scarring by 12 months of age. Occasional patients exhibit residual telangiectasiae [30], dyspigmentation or atrophy [24].

Cardiac. Complete heart block occurs in approximately 60% of white patients [5], although it may be less common in Japanese patients [31]. Associated features may also include pericardial effusions, pleural effusions, ascites, intrauterine growth retardation and hydrops fetalis [32]. Up to 50% will require pacing in the neonatal period and others will require a pacemaker at a later date [33]. Dilated cardiomyopathy occurs in up to 20%, and has a significant mortality in the first year of life [33].

Haematological. Thrombocytopenia may occur in up to 20% of cases [30,34], is transient and does not usually require treatment, although it has been associated with petechial and purpuric lesions. Neutropenia, haemolytic anaemia and aplastic anaemia have also been reported [35,36].

Hepatic. Hepatomegaly and splenomegaly have been reported in NLE [37], with histological changes of 'neonatal hepatitis' and, on occasions, fibrosis. Cholestasis has also been reported [37,38]. A recent study showed hepatobiliary disease in 19 of 219 patients with NLE, and in three this was the only finding [39].

Miscellaneous. Case reports have associated NLE with pneumonitis [6], haemochromatosis [40], aseptic meningitis [41], myelopathy [42], transient myasthenia gravis

[43], hydrocephalus [44], spastic paraparesis [30,45] and chondrodysplasia punctata [46].

Treatment

Cutaneous lesions. Skin disease is often mild and requires no treatment. Sun avoidance should be advised and low-potency topical steroids may be of benefit [5,33]. Persistant telangiectasiae have been reported to respond to the tunable dye laser [47].

Cardiac. Up to 50% may require pacing in the newborn period, and others may require pacemaker insertion at a later date [32]. There is little information with regard to whether CHB and its consequences can be prevented or treated *in utero*. One study reviewed outcomes in pregnancies of mothers with Ro antibodies who had received systemic steroids during pregnancy [48]. When steroids had been given during the first 16 weeks of pregnancy, no conduction defects occurred, suggesting that they may have possibly suppressed disease initiation during this period of gestation. Corticosteroids administered after the first 16 weeks, however, were not beneficial and did not reverse established complete heart block. Another study compared outcome in fetuses whose mothers were treated with oral corticosteroids at various stages during pregnancy. Although there was no improvement in established complete heart block, the treated group showed less progression from first- to second-degree block to complete block and some improvement in pleural effusions, ascites and hydrops [31]. Anecdotally, a mother with the HLA-DR3 phenotype, high titres of Ro/SS-A and La/SS-B antibodies and an existing child with neonatal lupus, delivered a healthy infant after plasmaphoresis three times weekly and systemic steroids during gestation [41].

Haematological. Most resolve spontaneously without treatment.

Hepatic. Most resolve spontaneously without treatment.

Pregnancy. A pregnant patient who is known to have Ro/SS-A or La/SS-B antibodies should be made aware of the possible problems, and their obstetrician alerted. The risk of NLE in a Ro/SS-A positive mother without connective tissue disease or a previous history of NLE is probably low [33,49]. The risk rises, however, with the presence of maternal lupus and the presence of the HLA-DR3 haplotype in the mother [8], and one study has suggested a risk of 1 : 60 for a woman with lupus and 1 : 20 if Ro/SS-A antibodies are also present [50]. However, another study suggests the risk of non-cardiac NLE in these groups to be 3% in the former and up to as high as 32% in the latter [51], although the risk is lower (and non-quantifiable) for CHB. The risk of NLE in a pregnancy in a mother who has already had a child with NLE has been reported as 25% [52] or 50% [5].

Prognosis

Infant. Although follow-up data are limited, some children have gone on to develop SLE in later life [3,53,54] and one child developed a CNS vasculopathy at the age of 17 years [55]. Follow-up is therefore advised.

Mother. Although mothers are often asymptomatic at the time of the birth, some may go on to develop an autoimmune disease, usually SLE or Sjögren's syndrome, and follow-up is therefore advised [52].

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Laboratory investigations [1]. Laboratory investigations are frequently necessary to confirm the diagnosis, although even after extensive investigations it may be impossible to be entirely dogmatic, in view of the overlap of the manifestations of connective tissue diseases. Anaemia, of some degree, is found in approximately 75% of patients and is brought about by deficiency of iron, haemolysis or renal failure. The serum iron is usually low and may rise after corticosteroid therapy [2]. A positive Coombs' test can occur in the absence of haemolytic anaemia, and was present in 15% in a series of cases seen by the authors. Pure red cell aplasia has been reported [3]. Although leukopenia, specifically a lymphopenia, is a characteristic feature of the condition, and a white cell count of below 5000/mm^2 occurs in more than 33% of patients, leukocytosis may occasionally be found. The platelet count is reduced in approximately 20% of cases and is usually below 40 000/mm^2 in patients presenting with thrombocytopenic purpura. Thrombocytopenia may appear only during exacerbations or be a mild persisting feature [4]. Hyposplenism may occur [5]. The ESR is raised at some time in nearly 90% of patients; the C-reactive protein (CRP) is usually normal in the absence of infection, but some patients have a normal ESR throughout. The plasma viscosity may be raised, although initially thought unreliable, a more consistent assay is now being more widely used as an indicator of activity [6]. Serum globulins are frequently raised, with a rise in the gammaglobulin usually, although α_2-globulin may be elevated and the albumin decreased. IgE antibodies may be raised [7,8], particularly in patients with arthritis. False-positive serological tests for syphilis are found in approximately 25% of patients [9] and an atypical 'beaded' pattern of fluorescence of the *Treponema pallidum* antigen occurs when sera from certain patients are tested in the fluorescent treponemal antibody absorption (FTA-ABS) test [10]. Rheumatoid factor occurs in approximately 40%. Thrombosis occurs with the lupus anticoagulant (see p. 56.69), but occasionally haemorrhage results from other haematological abnormalities [11]. The lupus anticoagulant is one of a number of antiphospholipid antibodies that may be found in up to 50% of patients with SLE. As well as thrombosis, CNS disease is strongly related to the presence of these antibodies [12].

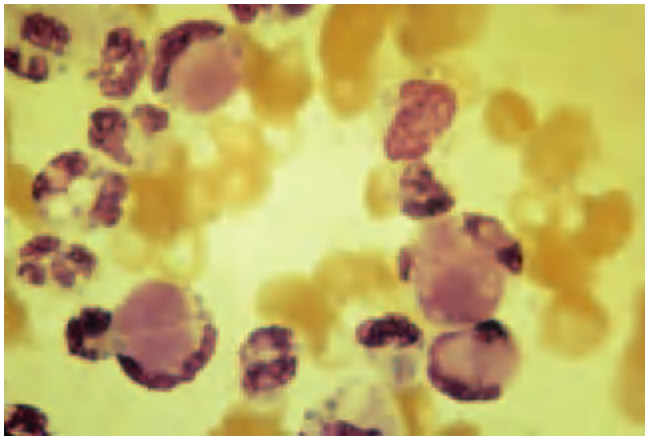

Fig. 56.38 Lupus erythematosus cells: the phagocytosed nuclear material is homogeneous and displaces the polymorph nucleus to one side.

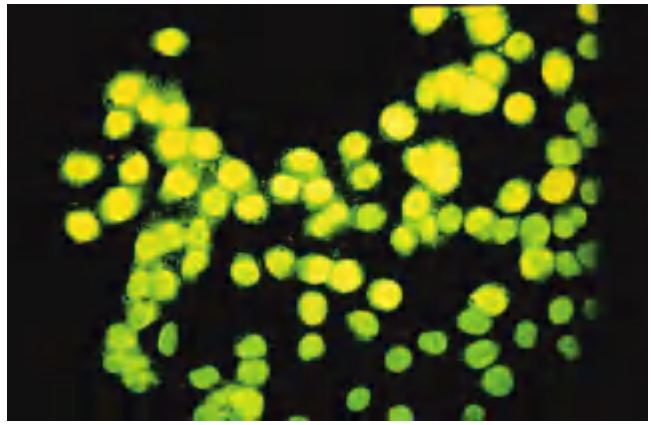

Fig. 56.39 Homogeneous type of antinuclear factor demonstrated on Hep-2 cells.

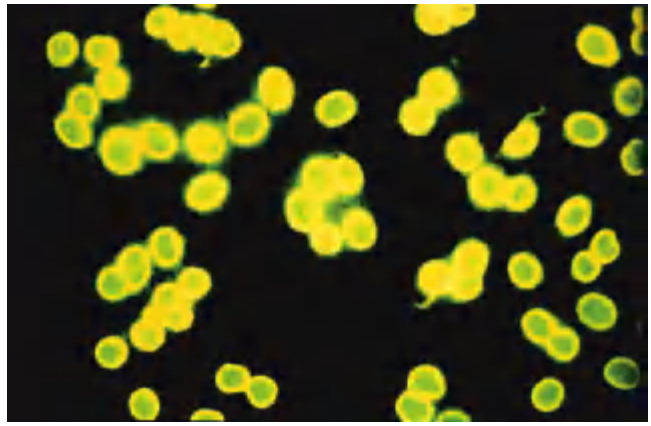

Fig. 56.40 Peripheral type of antinuclear factor demonstrated on Hep-2 cells.

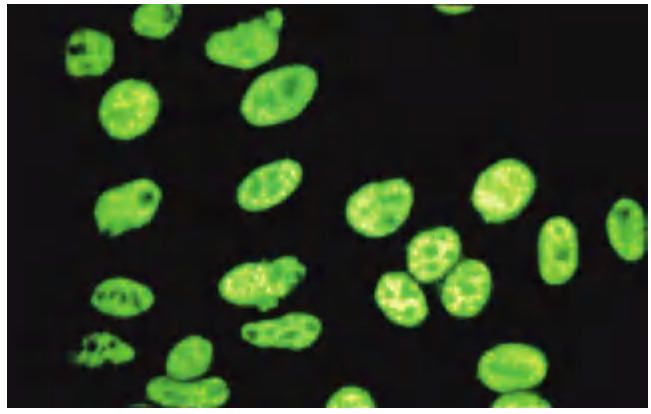

Fig. 56.41 Speckled type of antinuclear factor demonstrated on Hep-2 cells.

The LE cell phenomenon, first described by Hargraves *et al*. [13], is the basis for the LE cell test, which is positive in over 80% of patients. LE cells are polymorphonuclear leukocytes which have ingested nuclear material from degenerative white cells, in the presence of an antibody to deoxyribonucleoprotein (the LE cell factor) (Fig. 56.38). Sometimes, large masses of nuclear material are found extracellularly and, with surrounding leukocytes, form rosettes. LE cells, if present in large numbers, are highly suggestive of SLE, but the occasional LE cell is sometimes demonstrated in other conditions, including chronic DLE, systemic sclerosis and rheumatoid arthritis [14]. A positive LE cell test is a feature of drug-induced LE; LE cells were demonstrated in 60 out of 66 patients with procainamide-induced lupus [15]. The LE cell test has now been superseded by tests for antinuclear factors and anti-DNA antibodies.

One or more antinuclear antibodies can be detected by fluorescent antibody techniques in over 80% of cases. The incidence depends on the substrate used. Most British laboratories now use human cell lines for antibody testing, particularly Hep-2 cells derived from a human laryngeal cell line. This produces a reduction in the proportion of patients said to be antinuclear factor negative. Previously, the standard substrate was rat or mouse liver. Using rat liver, four staining patterns can be demonstrated [16], representing four systems of antinuclear antibodies (Figs 56.39–56.42).

1 In the *homogeneous pattern*, produced by antinucleohistone, the nuclei are stained all over

2 The *speckled pattern* shows minute points of fluorescence scattered all over the nucleus, the antigens being saline-soluble proteins

3 The *nucleolar pattern* shows uniform staining of each nucleolus

4 Sera containing anti-DNA antibody give rise to the fourth *peripheral or membranous pattern* [16,17], in which staining occurs at the periphery of the nucleus.

These staining patterns are produced by separate antibodies, but more than one antibody may be present in

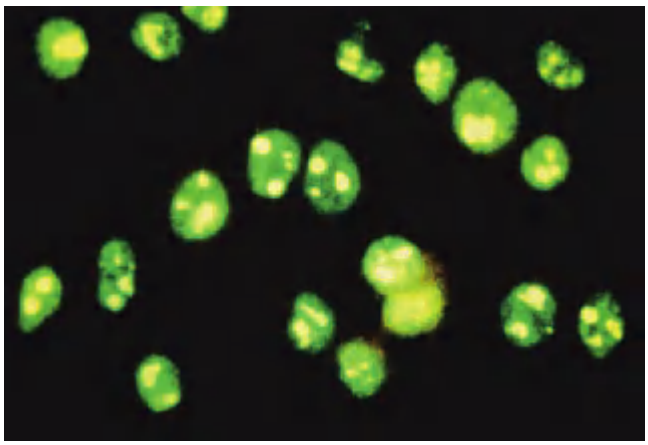

Fig. 56.42 Nucleolar type of antinuclear factor demonstrated on Hep-2 cells.

a single serum, usually in different titres. No particular antibody is specific for any disease. Discrepancies in the incidence between series probably depend on differences in techniques and the substrate used.

Homogeneous antinuclear factor (which is the same factor as the LE cell factor, although the fluorescent antibody test is more sensitive than the LE cell test) is more than twice as common as the speckled factor, but antinucleolar antibody is only occasionally found. The peripheral factor is present in high titre in more than 50% in the active phase of the disease [18], and is infrequent in other diseases. The so-called shrunken peripheral pattern is thought to be associated with a poor prognosis and a high incidence of renal disease [19]. It may appear 10–15 days before an exacerbation of the disease and be associated with a fall in serum complement [20]. In a series of 63 cases of SLE seen by the authors, one or more antinuclear factors were demonstrated in 55 patients (87%). Homogeneous staining was present in 46 cases, speckled staining in 18 and nucleolar staining in five. Titres up to 1 : 32 000 occur, but the titre frequently bears no relation to the activity, progress or duration of the disease. A high titre (over 1 : 64) of antinuclear factor(s), in a patient with symptoms and signs of a multiple system disorder, suggests the possibility of SLE or systemic sclerosis, and almost certainly excludes polyarteritis nodosa or cutaneous vasculitis. Any person in apparently good health found to have a high titre of antinuclear factor should be followed-up for years, as there is a considerable likelihood of developing LE or systemic sclerosis. A low titre (less than 1 : 16), in the absence of clinical symptoms and signs, can be ignored [21].

When Hep-2 cells are used as substrate, as well as being more sensitive to the presence of antinuclear antibody, further patterns can be identified [22]. These include centromere staining (see p. 56.109) associated with the CREST syndrome and in 6% of patients with SLE, homogeneous, peripheral (specific to SLE), fine and coarse speckles and a ground-glass appearance produced by Scl-70 antibody (see p. 56.109) found in systemic sclerosis. There are also several patterns of nucleolar staining: homogeneous, speckled and clumpy. The full clinical association of these antibodies has not been determined.

Circulating antibodies to DNA are almost always present in active disease [23,14] and may occur in the absence of antinuclear factors [24], although this is very uncommon using Hep-2 cells. Their demonstration by the Farr technique is the most specific aid to diagnosis, and levels often correlate with disease activity, although DNA antibodies should not be the only criterion [25]. Radiolabelled DNA is incubated with the test serum and any DNA–anti-DNA complexes formed are precipitated by 50% ammonium sulphate. Comparison of the radioactivity in the supernatant and precipitate gives the so-called DNA-binding activity. Values above 30% are abnormal. The level was raised in 83% of patients with SLE and in 100% of those with active disease. A rise in the index may precede an exacerbation of the disease, and levels fall with remission [26]. Normal values are found in drug-induced LE and in other disorders in which antinuclear antibodies occur. A high binding capacity is associated with poor prognosis and renal disorder [16]. The peripheral staining pattern of antinuclear antibody does not correlate with anti-DNA antibodies or with disease activity [27].

Several other antibodies occur in patients with SLE. Patients with antihistone antibodies have a lower incidence of renal and CNS disease, alopecia, anaemia and decreased complement [28]. Antibodies to soluble cellular antigens include anti-Sm antibody, which is found in 15–25% of patients and appears to be specific for the disease, occurring particularly in patients with renal disease, CNS disease and vasculitis. Anti-RNP antibodies occur in 25% of patients [29], but are characteristic of mixed connective tissue disease (see p. 56.116). It has been reported that titres correlate with disease activity [30].

Anti-Ro [31] antibody occurs in 30% of patients who have an increased tendency to photosensitivity [32,33], renal disease, Sjögren's syndrome and rheumatoid factor, as well as being a marker for neonatal lupus (see p. 56.53). It is also found in SCLE (see p. 56.24). Anti-Ro is an antibody to an RNP derived from RNA polymerase III-transcribed hY RNAs with a protein component that appears to be the main target. Two different proteins, one of 60 kDa and another of 52 kDa, react with most positive sera. The 60-kDa protein predominates in SLE, the 52-kDa in Sjögren's syndrome [34]. Patients with anti-Ro antibodies are more likely to have HLA-B8 and -DRw3 [35]. Anti-La, an antibody to another RNP product of RNA polymerase III, is present in 10–15% of patients, often with Sjögren's syndrome and with anti-Ro antibody. Although several different antibodies occur in the same patient, they fluctuate independently, and the antibody profile may

alter over the years. The only characteristic pattern of antibody appears to occur in the LE–erythema multiforme syndrome [36], in which there is speckled type of antinuclear factor, a specific precipitating antibody (originally designated SjT but now thought to be anti-La) and rheumatoid factor. This syndrome is occasionally found in cases of systemic as well as DLE, in which it was originally described (see p. 56.14). In cases associated with SLE, homogeneous antinuclear factor is also usually present.

Cryoglobulins may be found in 11% of patients. Cryoglobulinaemia may precede the manifestations of SLE by many years [37]. Cold agglutinins occur in 6%. Serum complement is frequently low [38], especially in patients with active nephritis. A decrease in levels may precede clinical evidence of an exacerbation of disease, and return to normal with remission but, in general, estimations of CH50, C3, C4 and circulating immune complexes are rarely helpful in assessing disease activity [39]. Other possible indicators of disease activity include β_2-macroglobulin [40] and serum IFN [41]. Increased levels of plasma anaphylatoxins (C3a) may predict exacerbations [42]. The intracutaneous injection of DNA solution, which has been advocated as a skin test [43], is not specific. Occasionally, circulating anticoagulants may be demonstrated [44,45]. Factor II may be absent and return with steroid therapy [46].

Inherited deficiencies of the major complement components occur with SLE [47], usually as autosomal recessive traits [48]. These include C1 [49], C2 [50] and C4 [51], as well as C5–C9. The most common is homozygous C2 deficiency in which SLE occurs in one-third of patients. Clinically, the lupus-like syndrome in C2 deficiency shows a low incidence of renal disease, low incidence and low titres of anti-DNA antibodies, infrequent occurrence of immunoglobulin and complement deposits in the skin, and frequent anti-Ro antibodies [46]. Isolated C1q deficiency has also been reported [52], and there is an association between C1-esterase inhibitor deficiency and SLE [53]. Patients may be helped by danazol [54]. Hereditary angio-oedema and SLE were found in the mother of twin boys who had DLE and angio-oedema, and this was associated with low C1 inhibitor and C4 levels [55]. Antibodies to Australia antigen can be demonstrated in 25% of cases [56]. Serum CRP levels are usually normal or only slightly elevated. A level higher than 60 mg/L suggests the presence of superimposed infection [57]. A number of soluble cytokines or their receptors may be found in serum of patients with SLE, and may correlate with disease activity: intercellular adhesion molecule-1 (ICAM-1) [58], TNF receptor [59] and IL-10 [60]. There is differential overexpression of heat-shock proteins in patients with differing patterns of systemic involvement [61]. Urinary levels of neopterin [62], or of IL-6 [63], may also be useful to monitor disease activity.

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Antinuclear antibody-negative SLE [1,2]. Patients originally described under this title have many similarities with patients suffering from SCLE (see p. 56.24). Because the cutaneous involvement is usually the predominant feature, many patients present initially to dermatologists. Clinically, a non-scarring malar flush, oral ulceration and photosensitivity, with papulosquamous or annular lesions on the face, trunk and arms, are prominent, but arthritis, serositis, renal disease and haematological involvement are less frequent than expected in SLE. In approximately 5–10% of patients with SLE, antinuclear factor cannot be demonstrated using standard substrates such as rat or mouse liver. This is a problem in less than 1% if Hep-2 cells are used. These patients frequently have anticytoplasmic antibodies. Over 60% of patients have anti-Ro antibodies and approximately one-third have anti-La antibody (anti-La rarely occurs without anti-Ro). Twenty-five per cent have antibodies to single-stranded DNA. There is no difference in the histology of the skin between antinuclear-negative and -positive cases. Immunoglobulins and complement are found at the dermal–epidermal junction in 70% of patients, but are rare in the non-light-exposed uninvolved skin. Topical steroid therapy may be helpful, but oral antimalarials and steroids may be required. Approximately 10% of patients eventually become antinuclear factor-positive, although the pattern of anticytoplasmic antibodies does not alter.

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Assessment of disease activity. A number of attempts have been made to devise definitions of disease activity, accompanied by scoring systems using combinations of clinical and laboratory parameters to allow comparative and longitudinal studies. Global measures such as European Community Lupus Activity Measure (ECLAM) [1], Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) [2] and the more detailed British Isles Lupus Activity Grading (BILAG) [3] are useful in the context of clinical trials in patients with active systemic disease. However, none is specifically designed for the assessment of patients who most concern dermatologists, and do not grade skin disease in any meaningful way.

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Association with other diseases. SLE can occur concurrently with rheumatoid arthritis [1], and may present with polymyalgia in elderly patients [2]. Systemic sclerosis and SLE may occur in the same patient [3], and the demonstration of immunoglobulins at the dermal–epidermal junction may be helpful in confirming the presence of both diseases [4]. SLE occurs with lichen sclerosus and with 'en coup de sabre' morphoea [5], and linear and plaque morphoea [6]. Sjögren's syndrome and SLE occur together [7–9] but the former is usually mild, and is unlike secondary Sjögren's syndrome occurring with rheumatoid arthritis. Patients with hyperglobulinaemic purpura may have antinuclear factor; this condition may, in certain cases, have features of SLE [10]. The finding of LE cells in young females with liver disease has already been mentioned. SLE can follow primary biliary cirrhosis [11], and may occasionally occur in association with necrotizing angiitis [12] and giant cell arteritis [13]. Patients who have LE and psoriasis often have anti-Ro antibodies [14].

Myasthenia gravis may follow SLE [15], and SLE may follow thymectomy for myasthenia gravis [16] or be associated with a thymoma [17]. Myasthenia gravis, thymoma and pemphigus may occur together in patients with SLE [18], and heterozygous C2 deficiency associated with angio-oedema, myasthenia gravis and SLE also occurs [19]. Angio-oedema resulting from C1-esterase deficiency can be associated with SLE [20], and protein S deficiency can occur in these patients [21].

SLE has been reported with Hashimoto's thyroiditis and pernicious anaemia [22]. It was associated with seminoma of the ovary in one case. Removal of the tumour led to an apparent permanent cure of the LE [23]. Lymphatic leukaemia or Hodgkin's disease has followed SLE [24], and lymphoma has been reported [25]. Amyloidosis [26] can develop in SLE, and in one case this led to adrenal insufficiency and was followed by malignant lymphoma [27]. The presentation with haemolytic anaemia [28] or thrombocytopenic purpura [29] is well documented, and overt SLE may appear after splenectomy for 'idiopathic thrombocytopenic purpura'. If this occurs, it is likely that the thrombocytopenia is an early manifestation of SLE. It may also occur in association with thrombotic thrombocytopenic purpura [30], pernicious anaemia [31], von Willebrand's disease [32], myelofibrosis [33,34], selective IgA deficiency [35], erythroleukaemia [36], red cell aplasia [37], monoclonal gammopathy and multiple myeloma [38], biclonal gammopathy [39], myelofibrosis [39], hyperviscosity syndrome [40], Whipple's disease [41] and ulcerative colitis [42]. SLE also occurs with pemphigoid [43] and cicatricial pemphigoid [44], pemphigus [45], dermatitis herpetiformis [46], linear IgA disease [47], epidermolysis bullosa dystrophica [48], porphyria cutanea tarda [49] (although the association has not been confirmed) [50], and occasionally with porphyria variegata or acute intermittent porphyria [51–53]. The disease has been reported in patients with Sweet's syndrome [54], Klinefelter's syndrome [55], hypoparathyroidism [56], partial lipodystrophy [57], relapsing polychondritis [58], pyoderma gangrenosum [59] and Kikuchi's disease [60]. In one case it has been associated with retroperitoneal fibrosis [61], and in another with eosinophilic fasciitis and retroperitoneal fibrosis [62]. It uncommonly occurs with gout [63] and sarcoidosis [64]. An unusual syndrome of breast hypertrophy, erythema annulare centrifugum, generalized melanoderma and immunodeficiency to viral warts has been associated with SLE [65]. Twelve per cent of patients with SLE have warts, which is a higher incidence than in a control population [66]. Senear–Usher syndrome (pemphigus and LE) has been associated with internal malignancy [67], but an overall increased incidence of malignancy in SLE is debatable. Malignancy occurred in 4.7% in one series [68]. Epidermodysplasia verruciformis occurs presumably as a result of immunodeficiency or prolonged treatment with corticosteroids [69]. Among other rare associations are Kaposi's sarcoma [70] and Kawasaki disease [71].

The relationship to DLE is discussed on p. 56.2. Patients with persistent false-positive serological tests for syphilis [72] may later develop SLE.

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Kikuchi's disease and SLE. Histiocytic necrotizing lymphadenitis was first described independently by Kikuchi

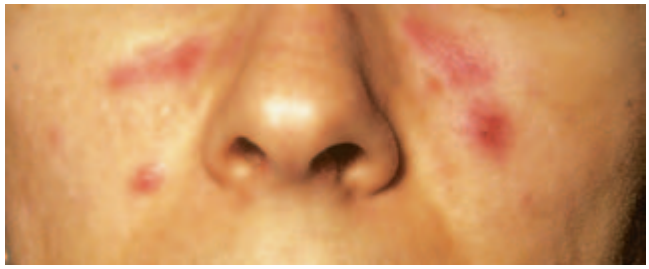

Fig. 56.43 Erythematous facial plaques in Kikuchi's disease.

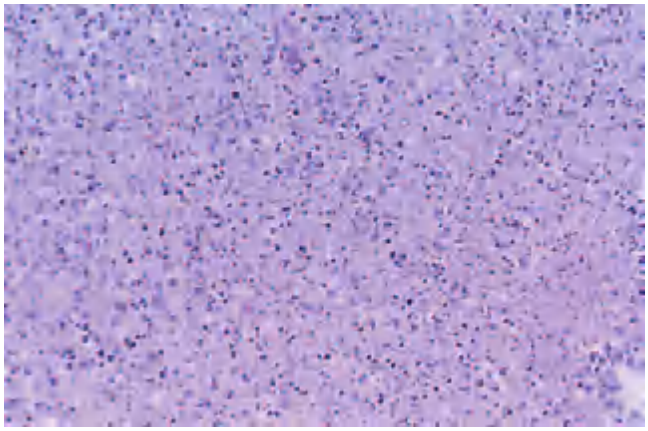

Fig. 56.44 Histiocytic necrotizing lymphadenitis (Kikuchi's disease). Lymph node. (Courtesy of Dr W. Merchant, Leeds General Infirmary, Leeds, UK.)

[1] and Fujimoto *et al.* [2] from Japan in 1972. Cases are predominantly female, but it can occur in males, and can occur at all ages. Usually, patients present with lymphadenopathy, frequently cervical, although other nodes can be involved. Fever, weight loss and night sweats are found in the more severely affected cases. There may be leukopenia and elevation of the ESR. Skin changes occur in 30% of patients [3]. They are all non-specific and include multiple indurated red papules on the back and arms [4], erythematous plaques resembling lymphoma, erythema and acneiform eruptions on the face (Fig. 56.43), and morbilliform, urticarial and rubella-like eruptions elsewhere. The oropharynx may be red or ulcerated.

Histology of the skin shows oedema of the papillary dermis, with a patchy perivascular infiltrate in the dermis and subcutaneous fat. The infiltrate consists of histiocytes containing nuclear debris and small lymphocytes. The nuclei of the histiocytes may be deformed. The lymph nodes show focal or complete loss of follicular architecture, with necrosis of cortical and paracortical areas (Fig. 56.44). The extensive infiltrate consists of small lymphocytes, immunoblasts, macrophages and so-called plasmacytoid T cells [5]. Neutrophils are rarely seen, a feature that may help to distinguish this condition from SLE. The natural history is for spontaneous healing in a few months but it can be fatal as a result of heart failure brought about by microscopic myocardial necrosis [6]. There was a 3.3% recurrence rate in one series [7]. In most cases, no treatment is required, but a course of prednisolone may speed resolution. Various triggers have been incriminated, including the human herpesvirus 6 [8], parvovirus B19 [9], Epstein–Barr virus [5], dengue virus [10] and infection by *Yersinia enterocolitica*, *Toxoplasma*, cytomegalovirus and human immunodeficiency virus (HIV) [11], and rupture of a silicone breast implant [12]. The condition is occasionally associated with SLE. It may precede SLE [13], may be the presenting feature of SLE [14] and, rarely, SLE may precede it [15]. The association was found in two of 108 patients with Kikuchi's disease studied by Dorfman [16], and two of eight patients studied by El-Ramaki *et al.* [17]. It has occurred with DLE in a case encountered by the authors, and may be associated with other cutaneous manifestations of lupus [18]. Other associated conditions include Still's disease [19,20] and Sweet's syndrome [21]. In addition to SLE, the disorder can occur with lymphoma, tuberculous lymphadenitis, viral lymphadenitis, infectious mononucleosis and drug eruptions.

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Differential diagnosis. The conditions mentioned in the above section must be differentiated from LE. Many patients suspected of having a connective tissue disease may, even after investigation, present problems of categorization. The criteria for SLE of the ARA (1982) are shown in Table 56.3 [1]. The presence of four or more of the 11 manifestations, serially or simultaneously, is compatible with SLE (96% sensitive, 96% specific).

Other features, such as cutaneous LE lesions of any type, diffuse alopecia, involvement of the scalp or mucous membranes, preferably confirmed by histopathology, or direct immunofluorescence, may be helpful.

Several practical points are important. The ESR need not be elevated. In patients at Leeds, 15% followed up for at least 5 years have never had an ESR above 20 mm in the first hour. Several of these have had high titres of antinuclear factor, raised levels of anti-DNA antibodies and lowered serum complement. Diagnosis thus depends upon the association of features rather than on any specific abnormality. The demonstration of a high titre of antinuclear factor is important. In the acute phase, the membranous types of antinuclear factor may be present as well as a raised level of anti-DNA antibody, anti-Sm antibody and a reduction in the serum complement. In the authors' experience, the presence of antinuclear factor in high titre almost certainly excludes polyarteritis nodosa and other arteritic disorders. When a raised ESR, raised serum globulin, leukopenia and evidence of renal disease are added, the diagnosis becomes highly probable. It is important to remember that antinuclear factor is not always present in SLE, and in such cases alopecia, Raynaud's phenomenon and oral ulceration commonly occur [2]. The demonstration of immunoglobulins in the dermal–epidermal junction of uninvolved as well as involved skin may be very helpful (see p. 56.34). The combination of IgG and IgM at the dermal–epidermal junction of involved and uninvolved skin, raised DNA binding, antinuclear antibody in a titre of more than 1 : 64 and decreased C3 or C4 is highly suggestive of SLE [3]. In drug-induced LE, anti-DNA antibodies are absent, serum complement is normal and globulin is not found in the uninvolved skin. Acute febrile neutrophilic dermatosis (Sweet's syndrome) may mimic SLE when a 'butterfly rash' is associated with fever, myalgia, arthralgia, hepatosplenomegaly, renal disease and hyperglobulinaemia [4].

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Prognosis [1]. The course of SLE is very variable [2]. Acute fulminating cases are much less common than subacute cases, which smoulder on for many years. Mortality rates have declined in both England and Wales in the 10-year period 1974–83 [3] and in the USA [4]. Although, in pre-steroid days, 52% of patients in one series [5] died within 2 years, in another series 54% of patients survived 11 years [6], compared with controls, of whom 97% survived a similar time. In 1977, an overall 5-year survival of 91% was reported [7], and 98% in another series in 1978 [8], although a 5-year survival of only 88% was reported from a rheumatological clinic in 1990 [9]. Approximately three-quarters will now survive 15 years [10]. Survival is related to organ involvement and to frequency of exacerbations [11]. Of those without renal involvement, 84% survive 15 years, compared with 57% whose kidneys are affected [10]. Spontaneous remissions, sometimes lasting 10–20 years, occurred in 35% of Dubois and Tuffanelli's [12] patients, the longest being 26 years. Serological as well as clinical remission occurred in 4% of 305 patients [13]. Exacerbations are more frequent in the first 5 years of the disease [14]. Pregnancy does not affect long-term survival. Prolonged survival is associated with an increased risk of atherosclerosis, avascular necrosis and neuropsychiatric dysfunction [15]. In elderly people the presentation is insidious and the clinical course is relatively benign. Renal disease and serological abnormalities are less frequent, and arthritis, with subcutaneous nodules, and pleuropericarditis are more prominent in elderly people [16].

The better prognosis of the more recent series is a result, not only of the administration of corticosteroids, but also of earlier diagnosis, the avoidance of stress and drugs such as sulphonamides, and the control of infections by antibiotics. The cause of death is frequently progressive renal failure, occasionally with anuria. Secondary infection, particularly bronchopneumonia, was a much more common cause of death in the pre-antibiotic era, although infection may still be more important than renal failure.

The high infection rate is not caused solely by steroid [17] or antimetabolite therapy. Spontaneous peritonitis caused by Gram-positive bacteria is a complication of lupus nephritis treated with corticosteroids [18]. Unusual infections such as pneumococcal epiglottitis have been reported [19]. There is an increased risk of *Salmonella* bacteraemia [20] and rapidly fatal pneumococcal septicaemia [21]. Repeated skin infections may be a presenting feature. Cellulitis of the periorbital area caused by *Staphylococcus aureus* and group A haemolytic streptococci has been reported [22,23]. Neisserial infections may also occur [24]. Death may result from vasculitis of the CNS in patients presenting with convulsions, psychoses and paralysis. Patients with CNS lesions and psychosis have a poor prognosis. Deaths from CNS involvement become more important in the later stages of the disease [25]. Others may die from heart failure or the side effects of therapy [26].

A bimodal pattern of mortality has been described [27], but not confirmed, in black patients [28]. Patients who die early in the disease die from active LE, including renal involvement, receive large doses of steroids and have a high incidence of infection. Those who die later have relatively inactive disease, long duration of steroid therapy and a high incidence of atherosclerotic heart disease and myocardial infarction [11]. Nevertheless, it is the authors' experience that death from infection is common, even in long-standing cases. The maximum disease activity occurs early, and patients rarely develop new organ involvement after the first few years [8,14]. Late reactivation of SLE can occur [29].

Although the disease is much more common in females, the prognosis is worse in males [30–33]. Males are more likely to develop renal failure [34]. Although race and ethnic origin have been claimed not to influence prognosis [35], increased mortality has been noted in Asians [36] and black people [37], probably in part because of socioeconomic conditions. The degree of renal involvement is probably the most important factor in prognosis. Patients with nephrotic syndrome at the onset of nephritis do badly and may die within a few months, but development later in the disease does not have an adverse effect. Patients with albuminuria may survive on small doses of steroids for many years, and the overall prognosis of patients with renal involvement is not as bad as early studies suggested. Patients with cutaneous lesions of DLE and laboratory abnormalities have the same prognosis as uncomplicated cases of DLE [38]. Patients with arteritis, antiphospholipid syndrome, thrombocytopenia, haemolytic anaemia and CNS involvement have a poorer prognosis than those whose illness mainly involves the joints. There appears to be no increased risk of malignancy [39], although earlier reports suggested this might be so [40,41].

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Genetic counselling. The clinical genetics of lupus has been reviewed [1]. Approximately 5% of first-degree relatives of patients may have or may develop lupus. The risk is doubled if there are two affected first-degree relatives, and this risk is even greater if further family members are affected. The risk for female relatives is greater than for males and may also be increased for those with hyperglobulinaemia or antinuclear antibodies. Mothers with anti-Ro and anti-La antibodies may have children with neonatal lupus and heart block. When a child has neonatal lupus or CHB, the risk of a subsequent child having heart block is approximately 25%.

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Treatment [1–3]. The aim is to try to maintain optimal function with the minimum of therapy. SLE is an episodic disease, and treatment must be tailored to the patient's requirements. Morale must be maintained. In acute cases, and during severe exacerbations, bed rest is required. Undue exposure to the sun should be avoided and patients should be advised to wear broad-brimmed hats, to cover the 'V' of the neck and the arms, and to use a sunscreen preparation. Mental stress, physical overexertion and secondary infection should be avoided. There seem to be few problems with menopausal women on hormone replacement therapy [4]. Drugs may be required for symptomatic treatment but should be kept to a minimum. However, the danger from infection is great, and antibiotics should not be withheld for fear of causing an exacerbation. Death can occur from *Salmonella* infection [5]. Estimation of CRP may be helpful; if raised it suggests infection. Dapsone may be helpful for urticarial lesions [6], bullous eruptions [7] and for thrombocytopenia [8].

Hypertension must be treated, and while it is generally agreed that hydralazine can be used safely in most patients with SLE [9], there are now better modern alternatives including angiotensin-converting enzyme inhibitors and α-blockers. Diuretics may be required for the nephrotic syndrome or cardiac failure, and anticonvulsants for epilepsy. Chlorpromazine is a good sedative for psychosis. Aspirin may be very useful, particularly in patients with joint manifestations. There is an increased risk of aspirin hepatoxicity in SLE [10]. Indometacin may also be of benefit in cases with arthritis. Ischaemic necrosis of bone may be best treated early by core decompression [11].

Corticosteroids are required in acute cases, and should be given in adequate regimens. Prednisolone 60 mg/day is the steroid of choice initially. It is rare for higher dosage to be needed. Once the condition appears to be under control, the dosage may be reduced gradually, until a maintenance dosage of approximately 5–15 mg/day is reached. A single dose daily, given in the morning [12], produces fewer side effects and does not impair the therapeutic response.

Not all patients require steroids, especially if there is no internal organ involvement [2]. It is important to assess the patient's progress by their general well-being and relief of symptoms, rather than by strict attention to laboratory abnormalities [13]. The ESR and DNA antibodies are no guide to the adequacy of therapy; the titre of antinuclear antibodies often persists unchanged despite clinical remission. Anti-DNA antibody and serum complement levels may be helpful in predicting exacerbations [14]. Low C3 often indicates severe renal disease. There is some evidence that a return of serological abnormalities to normal is followed by a prolonged remission [15], but exceptions indicate that serological data alone cannot be used as a basis of therapy.

Some fulminating cases have been treated with massive doses of steroids but the advantages of such therapy rarely outweigh the risks. There is no evidence that a very high dosage of corticosteroids is beneficial in CNS disease [16]. Steroid-induced psychosis is less common than cerebral lupus, but both can occur in the same patient [16]. Prolonged high dosage of corticosteroids (e.g. prednisolone 60 mg/day for 6 months) is said to improve renal lesions more than small suppressive doses [17,18]. This improvement of survival is not seen in patients with raised blood urea before the onset of therapy. There is no evidence that steroids are prophylactic and that prolonged therapy will prevent the development of new features. No single test can reliably indicate the degree of activity [19]. Steroid myopathy can occur with high doses: serum enzymes are usually normal but urinary creatine is increased [20]. Myopathy may take up to 4 months to improve on reducing therapy.

In mild cases, the administration of chloroquine or hydroxychloroquine may allow the dosage of steroids to

be reduced, but the reduction may not be clinically meaningful [21]. Antimalarials are less useful than in DLE, and may be dangerous for long-term therapy. They may have a place in patients with photosensitivity. Pregnancy is not contraindicated, as healthy live babies have been delivered by women on antimalarial therapy throughout pregnancy [22].

Immunosuppressive drugs have been used for patients not responding to corticosteroids or to act as steroid-sparing agents [23]. It has been concluded that azathioprine adds nothing to high-dose prednisolone treatment in mild or moderate renal disease [24]. Another controlled trial, comparing azathioprine plus prednisolone with prednisolone alone, did not show any significant difference in the number of deaths, renal or extrarenal manifestations, serum complement levels, DNA antibodies, LE cells, antinuclear antibody titres, or Coombs' antibodies, or any evidence of a steroid-sparing effect [25]. Sudden withdrawal may be followed by relapse [26]. Cyclophosphamide may be a more effective immunosuppressant, but it is more toxic than azathioprine. Most but not all trials have suggested that it may be useful in SLE [27–30], although not all support routine use. Nevertheless, pulsed therapy with cyclophosphamide may be useful for renal disease and is as effective as pulsed methylprednisolone [31]. Triple therapy with prednisolone plus azathioprine and cyclophosphamide had no therapeutic advantage over prednisolone and azathioprine [32].

Chlorambucil has been found to be helpful by some [33,34], but not by others [35]. An extensive trial [23] involving 53 patients has shown excellent results with a combination of prednisolone and chlorambucil in the treatment of diffuse lupus glomerulonephritis when compared with 110 patients treated with prednisolone alone, prednisolone and azathioprine, or prednisolone and cyclophosphamide. There are still some reservations about this combined therapy.

Methotrexate 7.5 mg/week has improved steroid-resistant patients [36], and patients without renal or CNS involvement [37], and 10–20 mg/week is useful for mucocutaneous lesions [38].

The long-term risk of malignancy must be considered whenever immunosuppressive drugs are used. Cyclophosphamide has been associated with bladder cancer [39], acute non-lymphocytic leukaemia and solid tumours. Mesna may reduce urotoxic side effects, but 50% of patients develop rashes which may be confused with an exacerbation of SLE [40]. Reticulum cell sarcoma [41] and non-Hodgkin's lymphoma [42] are hazards of azathioprine therapy.

Ciclosporin has been used in resistant cases in a dosage of 3–5 mg/kg, but four of 16 patients had a flare during treatment and three discontinued treatment because of side effects [43]. Pulse therapy with methylprednisolone 1 g given intravenously in 500 ml normal saline over 4 h on 3 successive days to in-patients may be helpful in individuals who are not controlled by oral prednisolone and immunosuppressives [44]. Double-blind trials have indicated that any initial improvement may not be maintained [45]. Given monthly it may prevent deterioration in renal function in patients with nephritis [46].

Plasmapheresis of 2 L/day for 3–4 days each week over a period of 2–3 weeks may be helpful in a small number of patients with a high level of immune complexes, whose condition is deteriorating despite other therapy, but controlled trials have not been convincing [47], and plasmapheresis may even be detrimental [48]. Any benefit lasts only approximately 2–3 weeks. Plasmapheresis may be useful in managing life-threatening complications such as fulminating vasculitis or CNS disease [49]. Intravenous gammaglobulin 1 g/kg/day for 3 days improved four out of five patients. The effect lasts 4–6 weeks [50]. Provisional studies of extracorporeal photochemotherapy have shown improvement in a few patients, and treatment was not associated with any side effects [51]. Anticoagulants may be required for patients with lupus anticoagulant or anticardiolipin antibodies who have thrombotic episodes. Danazol 400–600 mg/day may help patients with premenstrual exacerbations [52], and sometimes has a marked effect on thrombocytopenia [53]. Oral levamisole, in a dosage of 150 mg three times daily has been found helpful by some [54], but not by others [55]. Antilymphocyte and antithymocyte antisera may help patients with nephritis not responding to either corticosteroids or azathioprine [56]. Although thymectomy has been carried out for SLE, this cannot be advocated as a satisfactory method of treatment, and in some patients SLE has actually followed thymectomy and myasthenia gravis. Acute anuric renal failure may respond to dialysis, corticosteroids and heparin [57]. SLE remains clinically inactive in patients undergoing dialysis for chronic renal failure [58]. Renal transplantation should be considered for terminal lupus nephritis. Disease activity and exacerbations decrease [59]. There may be no recurrent lupus nephritis in the allograft [60]. The risk of failure of allograft function is increased when there is serological evidence of disease activity [61].

A new and surprising therapeutic approach is that although UV light, especially UVB, can exacerbate SLE, it has been found in a controlled trial that exposure to UVA-1 (340–400 mm) at a dosage of 60 kJ/m^2 three times weekly reduced disease activity, reduced the need for medication and decreased antibody levels [62]. A low-fat, high marine oil diet (eicosapentaenoic acid: max EPA 20 g/day) modified disease activity in 27 patients in a placebo-controlled trial over 3 months [63].

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The lupus anticoagulant, anticardiolipin antibodies and the antiphospholipid antibody syndrome [1,2]

The lupus anticoagulant was first described in SLE [3], but it also occurs in drug-induced SLE, other connective tissue diseases, polymyalgia rheumatica/giant cell arteritis (where 40–50% of patients may have antibodies [4]) and carcinoma and lymphoma [5]. It may be induced by infection, including that caused by Epstein–Barr virus [6] and varicella [7]. It also occurs as the causative abnormality of the primary antiphospholipid (Hughes') syndrome [8,9], although a small proportion of those classified as having the primary syndrome will progress to lupus or a lupus-like syndrome [10].

The lupus anticoagulant is only one of several antiphospholipid antibodies, which include the anticardiolipin antibody demonstrated by ELISA. IgG anticardiolipin antibody has been found in 23% of patients with SLE [11], and is associated with similar clinical features to those seen with the lupus anticoagulant [12–15]. The presence and titre seem to depend on disease activity and decrease with treatment, particularly when of IgM type. In a study of healthy blood donors, anticardiolipin antibodies and the lupus anticoagulant were found in 4–6% of 499 donors, mainly young females [16].

The features associated with the lupus anticoagulant are caused by an acquired immunoglobulin (IgG or IgM), identified by prolonged activated partial thromboplastin and kaolin clotting times, which cannot be corrected by normal plasma. There may also be IgA antiphospholipid antibodies [17]. There are now a number of methods for detecting the abnormalities. These have been reviewed [18], and include assessment of the extrinsic pathway of coagulation [19]. These antibodies are directed against a range of phospholipids, including cardiolipin. The route by which thrombosis is induced remains unclear, but some antiphospholipid antibodies interact with a complex of phospholipid and β_2-glycoprotein-I to inhibit factor XII activation, platelet activation and prothrombinase activity [20]. The antibodies are found in 14% of patients with SLE, half of whom have thrombotic episodes [21] in leg, renal, hepatic [22], cerebral or pulmonary vessels. The lupus anticoagulant has been associated with Libman–Sacks endocarditis [23], chorea [24], labile hypertension, epilepsy, myelitis, myocardial infarction, valvular heart disease, haemolytic anaemia, retinopathy [25] and Addison's disease [26]. The presence of a lupus anticoagulant may also be related to avascular necrosis of bone [27]. Rarely, patients develop vascular occlusions in multiple organs [28]. This catastrophic variety may be fatal. There is also a syndrome in which a severe reduction in clotting occurs because of a different set of antiphospholipid antibodies—the haemorrhagic lupus anticoagulant syndrome [29].

Cutaneous lesions [30] include thrombophlebitis, purpura and ecchymoses, livedo reticularis, leg ulcers, cutaneous necrosis [31], gangrene and subungual splinter haemorrhages [32]. Histologically, non-inflammatory thrombosis of small dermal blood vessels can be demonstrated, but necrotizing vasculitis is not a feature [33]. Thromboses in the placenta lead to fetal death, and may recur in subsequent pregnancies. Thrombocytopenia also occurs. All women with SLE who have recurrent abortions and thrombotic episodes, or who are biological false-positive reactors, should be screened for the lupus anticoagulant, as treatment with prednisone 40–80 mg/day and aspirin 75 mg/day may result in successful pregnancy [34]. One patient with repeated fetal loss was successfully treated with intravenous human gammaglobulin [35]. Full anticoagulation (international normalized ratio (INR) greater than 3), with or without aspirin, appears to be the most effective therapy in the non-pregnant patient [36]. The presence of the antibodies without clinical features is not an indication for either steroid therapy or anticoagulation.

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Scleroderma [1]

Sclerosis of the skin occurs in a variety of conditions, such as dermatomyositis and LE, and invariably occurs as part of the cutaneous manifestations of systemic sclerosis, which is described elsewhere. However, the term 'scleroderma' should strictly be confined to sclerosis of the skin, either localized or generalized, occurring in patients as the only or prominent feature. In such circumstances it is better to use the term 'morphoea'. There has been much discussion and confusion about the relationship of morphoea to systemic sclerosis (see below), but the two conditions, despite certain similarities, are best considered as distinct entities.

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Localized morphoea

SYN. LOCALIZED SCLERODERMA; CIRCUMSCRIBED SCLERODERMA

Definition. A disorder of unknown cause in which there is localized sclerosis of the skin. The condition may be subdivided clinically into the following types [1–3]:

1 Circumscribed plaques
2 Morphoea profundus/subcutaneous (deep)
3 Bullous morphoea
4 Linear morphoea
5 Frontoparietal lesions (en coup de sabre), with or without hemiatrophy of the face.

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Aetiology. The cause of morphoea is unknown. A number of studies, however, have shown *in vitro* abnormalities in fibroblasts from patients with morphoea. These include fibroblast promotion of migration of mononuclear leukocytes across endothelial cell monolayers [1], increased platelet-derived growth factor and receptor expression [2] and increased transforming growth factor-β (TGF-β) receptor expression [3], which may lead to increased connective tissue growth factor (CTGF) gene expression and ultimately fibrosis [4,5]. That morphoea is an immunologically mediated disease also gains support from studies that have found increased levels of circulating cytokines in patients with morphoea. These include IL-2 receptor [6,7], IL-6 receptor [8], soluble CD4 and CD8 [9], CD23 [10], CD30 [11], TNF-α [12], soluble vascular cell adhesion molecule-1 (VCAM-1) and E-selectin [13], antiendothelial cell antibodies [14] and antibodies to fibrillin 1 [15]. That they may be involved in disease activity is supported by some studies, which have found increased levels of, for instance, soluble IL-2 receptor in active but not inactive disease [6,7], although such findings are by no means uni-

versal. Additional support for an autoimmune aetiology is the occurrence of scleroderma-like lesions in chronic graft-versus-host disease, and an association with idiopathic thrombocytopenic purpura [16].

Experimental exchange of Thiersch grafts between normal and affected sites resulted in rapid transformation of the normal graft to morphoea and vice versa [17]. Trauma may be a triggering factor [18,19] and may precede the onset by many months. Immobilization has also been reported as a cause [20]. Morphoea has also occurred after bacillus Calmette–Guérin (BCG) vaccination [21], following varicella [22], injections of vitamin K [23] and after antitetanus vaccination [24]. There are several reports of morphoea occurring at the site of previous radiotherapy [25,26]. Recently, surgical trauma has been reported as a stimulus for the development of lesions after arteriovenous fistula formation [27] and rhinoplasty [28]. Hormonal factors may influence the disease: morphoea may develop during, or be exacerbated by, pregnancy, but the influence of the menopause is less clear.

Infection with borrelial organisms has been implicated in the aetiology of morphoea, some central European studies suggesting a relationship between morphoea and acrodermatitis chronica atrophicans, a disease induced by infection with *Borrelia burgdorferi* [29–31]. These studies found raised levels of antibodies against this organism in patients with morphoea compared with controls, and described the presence of viable organisms in biopsies from morphoeic lesions. In addition, using the polymerase chain reaction, *Borrelia* DNA has been found in skin biopsies from patients with morphoea [32]. However, other studies [33–37] have shown no evidence of *Borrelia* antibodies or DNA in morphoea of patients from Scandinavia, Germany, Spain or America. A recent review [38] has suggested that the reason for these contradictory findings is that either *Borrelia* infection is not the cause of morphoea or that a subset of morphoea is caused by a special species of *Borrelia* present in some parts of Europe and Asia but not in the USA and other parts of Europe.

The genetic influence on morphoea is unclear. A familial incidence has been noticed [39], and localized and systemic scleroderma has been noted in monozygotic twins [40]. Some cases of the frontal type appear to have a genetic basis [41], but there are no significant HLA associations [42]. There is an increase in the incidence of organ-specific autoantibodies in patients and relatives [43]. Morphoea has been associated with phenylketonuria, and improvement has occurred with a low-phenylalanine diet, but excretion of phenylalanine and *o*-hydroxyphenylacetic acid in nine children with morphoea was normal [44].

Morphoea has been reported after therapy with a number of drugs. Morphoea-like plaques occurred in a patient on penicillamine therapy and remitted within a year of stopping treatment [45]. Cutaneous lesions have also been reported after therapy with bromocriptine [46], hydroxytryptophan and carbidopa [47,48], pentazocine [49,50], docetaxel [51], bleomycin [52,53] and after melphalan limb perfusion [54]. These localized lesions are in contrast with the systemic sclerosis-like reactions reported later in this chapter.

Although the clinical picture of morphoea is usually distinctive, and different from systemic sclerosis, the histology and histochemistry [55–57] of the skin are similar, and X-ray diffraction, historadiographical and electron microscope investigations [44,58–60] show no differences. Electron microscopy may show changes in the underlying muscle fibres in both conditions, but only in systemic sclerosis are endothelial changes found in the muscle capillaries [61]. Skin collagen may be increased in morphoeic plaques [62], possibly because of clonal overactivity of fibroblasts [63], but is decreased in the involved skin in systemic sclerosis [64]. The two disorders rarely occur together. Nail fold capillaroscopy may reveal abnormal capillaries in such patients [65].

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Pathology (Fig. 56.45). The epidermis may be normal, or flattened and atrophic with loss of the rete ridges. At first the dermis is oedematous, with swelling and degeneration of the collagen fibrils, which become homogeneous and eosinophilic. There may be a scanty perivascular lymphocytic infiltrate. Cellular infiltrates of lymphocytes, plasma cells and macrophages, either perivascular or diffuse, occurred in 84% in one series, and there is some evidence that the infiltrate may precede fibrosis [1,2]. Later, the dermis is markedly thickened, with dense collagen and relatively few recognizable fibroblasts. The elastic tissue is reduced. The dermal appendages and dermal and subcutaneous fat are progressively lost. Some sweat glands may

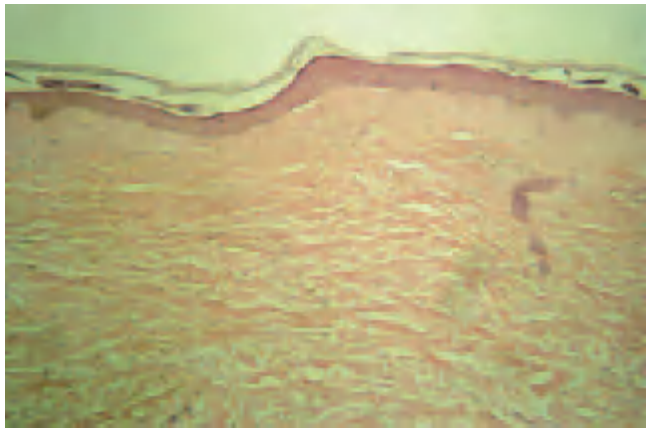

Fig. 56.45 Morphoea: slight atrophy of the epidermis with loss of dermal appendages and degeneration of dermal collagen.

survive, deep in the dense sclerotic mass. Small dermal blood vessels may show intimal thickening.

Immunohistochemistry shows that the main changes in morphoea consist of foci of intercollagenous staining for connective tissue antigens in the reticular layer of the dermis [3]. IgM and C3 are found at the basement membrane and in dermal blood vessels, particularly in more extensive and deeper lesions, but there is no relation to systemic disease [4]. The histological features are similar to those seen in generalized morphoea and in the skin in systemic sclerosis.

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Incidence. All ages are affected, the peak incidence occurring between 20 and 40 years of age, although 15% begin below the age of 10 years [1,2], in which age group the linear lesions predominate. The female to male ratio is around 3 : 1 in most studies. Most linear lesions (75%) occur before the age of 40 years, whereas 75% of localized plaques arise between the ages of 20 and 40 years [2]. In one series, localized plaques occurred in 60 patients, with linear lesions in 33 and guttate in 13 [3], but in another series [2] there were more patients with linear lesions than with plaques. The condition is said to be rare in black people [3]. A recent epidemiological study of morphoea in the USA has found a female to male ratio of 2.5 : 1, an incidence of 2.7 in 10 000 and a prevalence at 80 years of age of 1 in 500 [4].

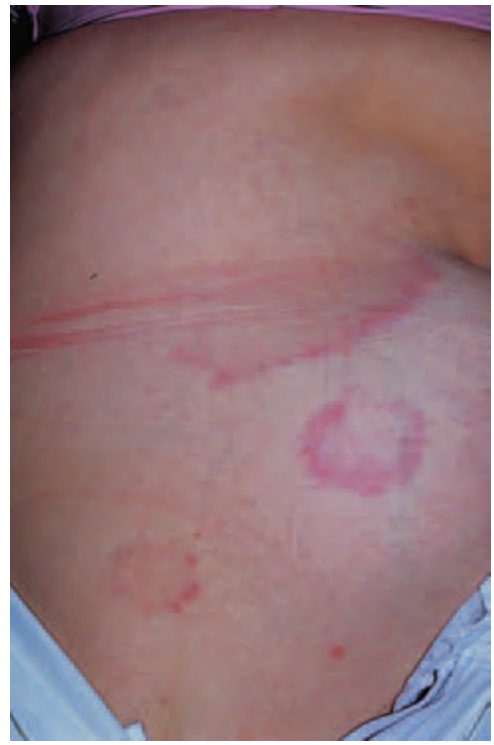

Fig. 56.46 Localized morphoea: plaque-like lesions on the abdomen.

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Clinical features

Plaque lesions. These occur as indurated areas of skin, which at first are faintly purplish or mauve in colour. After some weeks or months they lose their colour (Fig. 56.46), especially in the centre, and appear as thickened waxy areas, which are ivory in colour, with a characteristic lilac-coloured edge (Fig. 56.47). The surface is usually smooth and shiny but may be nodular [1]. The hairs are absent, and usually the area ceases to sweat. Vesicles, bullae [2] and haemorrhages may occasionally occur, and sometimes telangiectases may be seen. The plaque is attached to the deeper tissues and, if thick, may be hypoaesthetic. The lesions are round or oval, sometimes irregular, and vary in size from approximately 2 to 15 cm or more in diameter. They are usually multiple, and often bilateral, but asymmetrical. They occur on the trunk and limbs, face

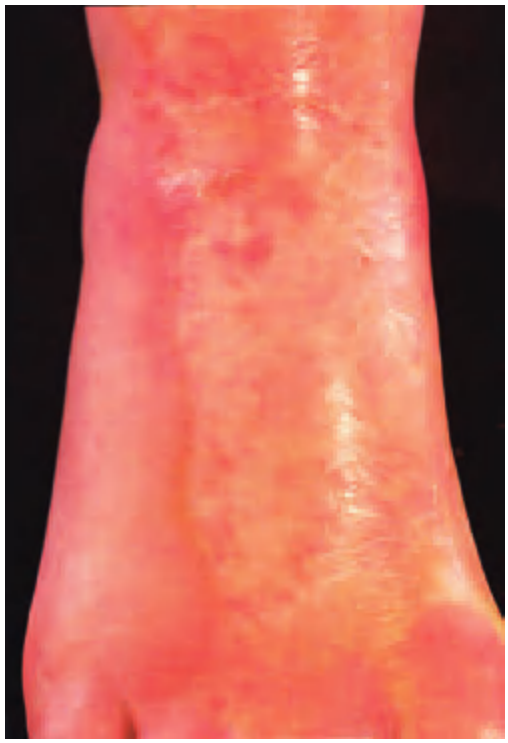

Fig. 56.47 Localized morphoea on the foot: late stage but still showing lilac border.

Fig. 56.48 Localized morphoea: pigmentation usually occurs as the lesion resolves but may occur at the onset.

and genitalia. They are less commonly found in the axillae and perineum and around the nipples. Sometimes, plaques accompany linear lesions.

Although the onset of lesions is usually insidious, they can occasionally occur rapidly, with erythema and oedema. Sometimes they may be preceded by pigmentation (Fig. 56.48). In subcutaneous morphoea, induration is indistinct and the lilac ring is absent. Deep involvement of underlying structures in morphoea of the trunk is unusual, but occurs occasionally and may be followed by deep atrophy [3]. Obscure abdominal pain and migraine were features in approximately 15% of patients in one series [4], but usually any pain is limited to the skin lesions. One study detected abnormalities of the vertebral column in 47% of those X-rayed, with spina bifida occulta occuring in 20 patients. These findings were most common in those with linear lesions, occurring in 26 of these 108 patients [4]. Other studies have not, however, reported such findings.

It has been suggested that atrophoderma of Pasini and Pierini is a primary abortive form of morphoea [5] in which induration fails to occur.

Guttate lesions. In true guttate morphoea, the lesions are similar to, but smaller and more numerous than plaque lesions. Some cases may represent lichen sclerosus et atrophicus (white spot disease) rather than true morphoea. It has been suggested that these two diseases may have a similar pathogenesis [6] or coexist [7,8].

Bullous lesions. Peterson's classification [9], describes bullous morphoea as a distinct entity. However, blisters have been described in all types of morphoea and have been thought to result from lymphatic dilatation along with the release of major basic protein from eosinophils [10]. Others have suggested that, at least in some cases, the blisters represent the development of associated lichen sclerosus [11].

Subcutaneous morphoea/deep morphoea/morphoea profundus. Nodular [1], keloidal [12] or subcutaneous morphoea are variants of morphoea that exhibit differing amounts and depths of inflammatory changes and sclerosis. The term morphoea profundus was first suggested by Whittaker *et al.* [13], in 1989, to describe a solitary fibrotic plaque on the shoulder, back, neck or paraspinal area, which histologically showed fibrosis, hyalinization of collagen fibres and a deep dermal and subcutaneous inflammatory infiltrate. The overlying skin may be pigmented or hypopigmented. Osteoma cutis can develop within such lesions [14] and contracture of the flexor muscles of the finger has been reported in subcutaneous morphoea [15].

Linear lesions (Fig. 56.49) [16]. The essential features are similar to the plaque lesions, but the lilac ring is inconspicuous or only present at the advancing border. They are usually single and unilateral, although occasionally bilateral lesions occur. They can follow the lines of Blaschko [17]. The limbs are frequently affected, the legs more than the arms. They may also occur on the anterior aspect of the thorax, and sometimes the abdomen or buttocks are affected. Lesions involving one arm and one leg are usually homolateral. Rarely, half of the body (face, arm, trunk and leg) is involved [18]. Occasionally, a linear lesion on the leg is preceded by oedema of the limb. Lesions take the form of linear areas of induration, similar to those found

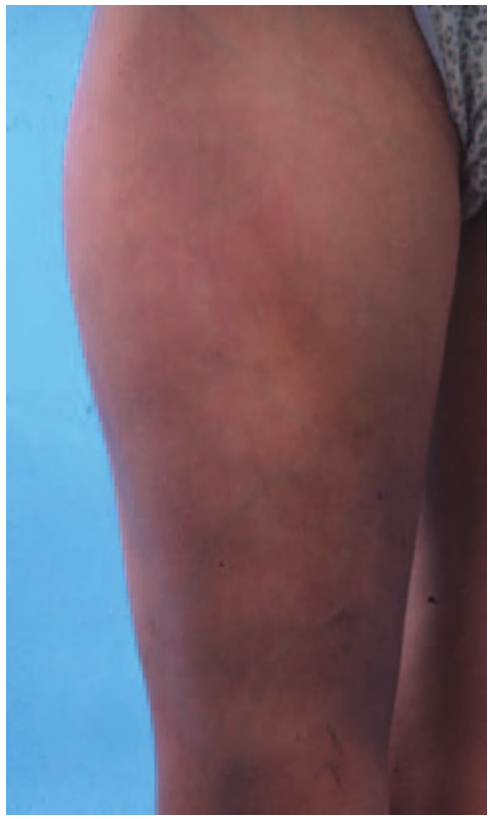

Fig. 56.49 Linear morphoea.

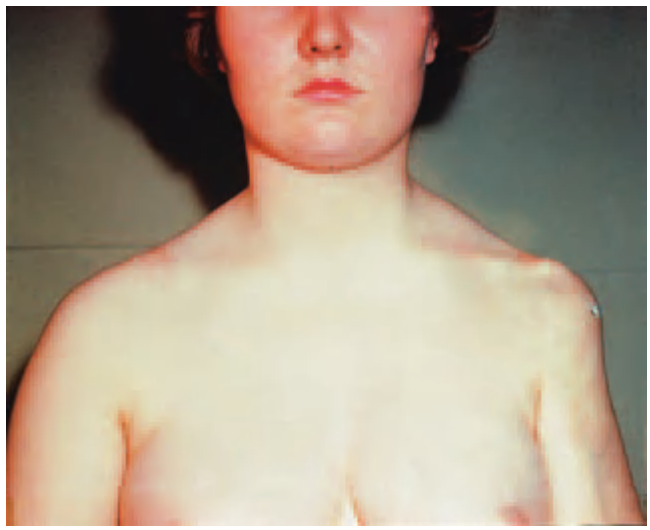

Fig. 56.50 Localized morphoea of the arm showing growth retardation.

in the plaques, but sometimes the condition may extend to involve the underlying muscles, or even bone, with resulting disturbances in growth in approximately 20% (Fig. 56.50) [19] and possibly severe flexion deformity [20,21]. The surface may show patchy hyperkeratosis. Usually, lesions occur along the length of the limb or around the trunk, but sometimes a band surrounds a limb

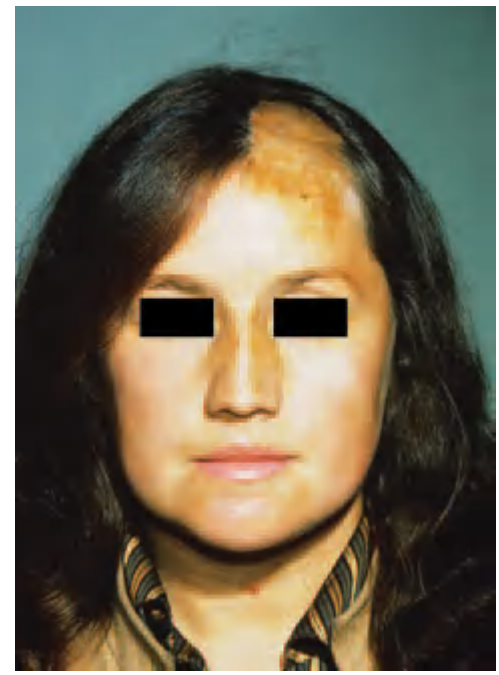

Fig. 56.51 Frontoparietal morphoea ('en coup de sabre').

or a finger, resembling ainhum [22,23]. The tissues distal to such a band may be oedematous and depigmented [19]. The fibrosis may spare areas within an otherwise linear lesion, producing 'skip' lesions.

Linear scleroderma has been associated with hypertrichosis [24], melorheostosis [25–27], and ulcerated dystrophic calcinosis cutis [28]. Nodular morphoea has been reported in a linear pattern [29].

Frontoparietal lesions (Fig. 56.51) *'en coup de sabre' (from its resemblance to a sabre cut), with or without hemiatrophy.* These lesions usually start with contraction and firmness of the skin over the affected area. Subsequently, an ivory irregular sclerotic plaque develops, sometimes with telangiectatic vessels coursing over it, together with hyperpigmentation at the edge. Eventually, a linear depressed groove appears on the frontoparietal region, extending into the scalp, producing a linear zone of alopecia, which may be preceded by bleaching of the hair. The groove may extend downwards into the cheek, nose and upper lip, and involve the mouth and gum. In severe cases, it extends as far as the chin and neck. The condition may affect the gingivae [30] and the jaw may also be involved, with alteration of the spacing and direction of the teeth [31]. The corresponding side of the tongue may be atrophic, although sometimes the lesion is in the midline of the tongue. Not infrequently, there is atrophy of the corresponding part of the face and cheek, with facial asymmetry, and this usually occurs within a year. The Parry–Romberg syndrome of hemifacial atrophy looks very similar, but there should be no cutaneous sclerosis at

any stage [32]. Rarely, frontoparietal lesions may be bilateral [33,34] or trilinear [35] and may follow Blaschko's lines [36]. Sometimes, there may be morphoeic plaques elsewhere on the body or evidence of linear morphoea on the extremities and trunk. Facial atrophy without frontoparietal morphoea can be associated with morphoea elsewhere. Ipsilateral wasting of the upper limb occurs in less than 10% of cases [37]. Total hemiatrophy of one side of the body can occur.

Contralateral or bilateral atrophy is rare. The bones of the skull can be involved and the EEG may show evidence of dysrhythmia, maximal over the affected area. Neurological abnormalities have been reported [38–40]. A variety of ocular lesions occur [41], including enophthalmos, involvement of the lids, oculomotor muscles, iris and fundus, and myopathy of the external eye muscles [42]. Atrophy of the nasal part of the iris and loss of cilia on the upper eyelid followed exactly the line of the skin lesions in one case [43]. Heterochromia of the iris also occurs [44]. 'En coup de sabre' morphoea has presented as unilateral eyelid oedema [45]. Ossification occasionally occurs [46].

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Scleroderma in childhood [1–3]. Childhood onset occurs in 2–3% of all cases of scleroderma. Most present with morphoea-type lesions (particularly linear) although systemic sclerosis does occur. The clinical features are similar to adult cases but localized trauma a few months before

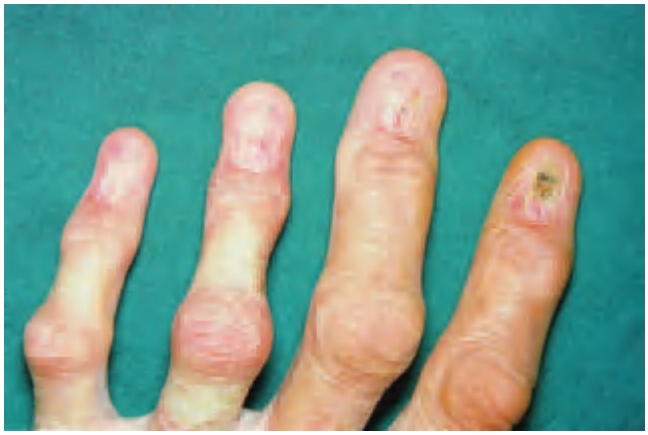

Fig. 56.52 Disabling pansclerotic morphoea of the fingers.

onset of morphoeic lesions occurs in one-quarter of childhood patients. Children are less likely to show serological abnormalities than adults, with antinuclear antibodies being found in only approximately one-third of those with localized disease. Scl-70 antibodies are found in children with systemic sclerosis, although much less frequently than in adults.

Disabling pansclerotic morphoea of children [4]. This is a rare severe mutilating form of morphoea involving the dermis, fat, fascia, muscle and even bone, usually starting before the age of 14 years. It may develop from linear morphoea. Superficial and deep cutaneous sclerosis involve the trunk and extremities, scalp and face, with sparing of the fingertips and toes (Fig. 56.52). There may be a claw deformity of the hands, and patients may walk on tiptoe because of contracture of the Achilles tendons (Fig. 56.53). Arthralgia and stiffness occur at the onset, and intense pain may be a problem, presumably because of involvement of cutaneous nerves [5]. Raynaud's phenomenon is not found, but a few cases have had oesophageal, pulmonary and periodontal changes. Flexion contractures, osteoporosis and other bone changes are frequent. The electromyogram and histology of muscle may be abnormal, but creatine phosphokinase is normal. Elevation of ESR, hypergammaglobulinaemia and eosinophilia are frequent. Treatment with PUVA [6], low-dosage UVA-1 [7] and ciclosporin [8] has been reported. The reponse is often poor, however, and in most patients the condition is progressive [9] and occasionally fatal [4].

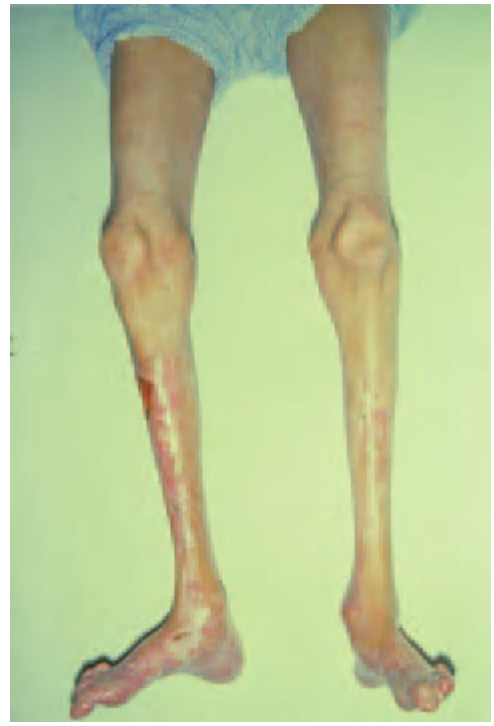

Fig. 56.53 Disabling pansclerotic morphoea of the legs.

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Associated lesions. Arthralgia, sometimes localized to the sclerodermatous extremity, unilateral Raynaud's phenomenon, a history of migraine and intermittent recurrent colicky abdominal pain are sometimes found [1]. Abnormal radiological appearances of the spine occurred in 47% of patients in one series, [1] particularly those with linear scleroderma. Spina bifida was found in 20 patients and was most common in patients with linear morphoea of the legs, lower abdomen and buttocks. Other abnormalities included sacralization of lumbar segments, the presence of six lumbar vertebrae, prolongation of transverse arches, scoliosis and kyphosis. Pain in the lumbar region, like that of a protruded lumbar intervertebral disc, was sometimes a feature. Rib abnormalities such as rudimentary or cervical ribs, torticollis, atrophic clavicle, absent pectoralis muscle, contracted pelvis, shortened ulna and deformities of the feet and toes have been reported [1], but other studies have not reported similar findings. Associated cutaneous abnormalities include warty, vascular or pigmented naevi, usually with linear morphoea on the same

side, café-au-lait spots, alopecia areata, vitiligo, generalized ichthyosis or pigmentation, dystrophy of the nails and hirsutism. Localized morphoea occurred in a pigmented area of Becker's melanosis [2]. Children may be intellectually precocious [1]. A variant occurring later in life, in which morphoea confined to the face and anterior part of the scalp is associated with tissue calcification, hair loss and beaking of the nose, has been reported [3]. Sclerotic panatrophy, disseminated granuloma annulare and morphoea have occurred in the same patient [4].

Occasionally, morphoeic lesions may occur in association with lesions of lichen sclerosus et atrophicus. Localized patches of morphoea may occur in patients with systemic sclerosis [5] and occasionally patients with localized patches of morphoea may later develop systemic sclerosis [1,6]. Although no systemic abnormalities were found in 27 autopsies on patients with localized morphoea [7], changes in the oesophagus, muscles and joints may occur in as many as 27% of cases [8]. The diagnosis of systemic sclerosis was confirmed at autopsy in a 71-year-old woman with two patches of localized morphoea on the front of the chest, who subsequently developed cardiac enlargement, pulmonary fibrosis and a dilated aperistaltic oesophagus [9]. Typical morphoeic patches on the skin and gastrointestinal radiological changes typical of systemic sclerosis were found in another patient [10].

Morphoea has occurred with DLE [11], mixed connective tissue disease [12] and eosinophilic fasciitis [13], and frontoparietal morphoea has been associated with SLE [14]. Morphoea has followed SCLE [15] and may also occur with dermatomyositis [16], carpal tunnel syndrome [17], nephritis [18], vitiligo [19], pemphigus [20], primary biliary cirrhosis [21] and myasthenia gravis [22]. The coexistence of morphoea, localized bullous pemphigoid and subcorneal pustulosis has been reported [23]. Elastosis perforans serpiginosa has also occurred with morphoea [24]. Localized scleroderma can follow augmentation mammoplasty [25] and linear oedema, nodularity and scarring, with hidebound skin, has been attributed to leaking of silicone into an arm [26].

There is no relationship between localized morphoea and internal malignancy [27], although systemic sclerosis has been associated with carcinoma of the lung, skin and liver [27,28]. The morphoea-like changes found in patients with carcinoid syndrome are thought to occur as a result of serotonin release by the tumour [28]. Squamous cell carcinoma has been reported in patients with long-standing pansclerotic morphoea [29] and in localized scleroderma in a patient treated with azathioprine [30].

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Laboratory abnormalities. ESR and serum protein assays are usually normal, but eosinophilia may occur [1]. Anti-single-stranded DNA antibodies are more frequent in generalized morphoea (75%) and linear morphoea (53.3%) than in localized morphoea (27.3%) [2]. Antihistone antibodies have been detected in 32% of patients with linear morphoea and in 25% with localized morphoea [3]. They

do not correlate with the clinical features [4]. In children, a higher incidence of rheumatoid factor, compared with controls, has been found [5]. Hereditary deficiency of complement factor C2 is reported [6]. Organ-specific autoantibodies are more commonly found than in controls [7]. Thrombocytopenia responding to corticosteroid therapy has been reported in two patients [8]. Approximately 40% of patients with linear morphoea have positive antinuclear antibodies, and the presence of these antibodies (with homogeneous and nucleolar patterns), antibodies to single-stranded DNA and the presence of eosinophilia may indicate disease activity [9] and the late development of systemic complications [10]. Serum procollagen type 1 carboxy-terminal propeptide has been reported to be raised in 30% of patients with localized morphoea, correlating with the number of lesions. Levels are lower than in generalized morphoea and may be a useful indicator of disease activity [11]. Type 3 procollagen propeptide has also been reported to be raised [12]. However, others have not found these markers as useful. Ultrasound scanning has been reported as being helpful in monitoring the course of localized morphoea [13].

Prognosis. Plaque-like lesions tend to improve with time. The induration lessens and the lesions blend in with the rest of the skin, leaving a brownish stain, which may persist for a long time. The duration of activity is usually between 3 and 5 years, but some lesions last up to 25 years. It is common to find fresh lesions developing on new sites as other lesions resolve. Residual pigmentation persists for a long time in approximately one-third of patients. Linear lesions tend to persist for longer than plaque lesions, but on the whole improve with time. Calcinosis occasionally occurs in linear lesions, and sometimes requires surgical removal. Contractures may limit movement of joints and give rise to clawing of the hand. Unilateral atrophy of one or more limbs may occur. Facial hemiatrophy is usually persistent, but frontoparietal scleroderma may clear, and may be accompanied by regrowth of hair. In 63 of 88 children with morphoea, lesions resolved with minimal cosmetic disability [14]. Very rarely, patients with localized morphoea may subsequently develop classical systemic sclerosis [14,15]. It has been suggested that the presence of anti-Ku antibody may be a prognostic indicator of such progression [15].

Differential diagnosis. The diagnosis is usually not difficult, the insidious development of indurated plaques and bands in the skin, with or without hemiatrophy, being unlikely to occur in other conditions. If there is a lilac-coloured border diagnosis is easier. Reticulate lilac lesions with minimal induration can resemble cutaneous polyarteritis nodosa. Morphoeic lesions occur in sarcoidosis [16]. Lesions can start as a vascular blush, and may be mistaken for a macular vascular naevus. In the acute phase, the condition must be distinguished from scleroedema of Buschke, but in this condition the onset is much more acute, and the lesions may follow an infectious episode. Fading pigmented lesions are sometimes very difficult to diagnose, but the previous history of some induration in the area is usually helpful. Atrophic pigmented lesions resembling lesions of the atrophy of Pierini and Pasini (see Chapter 46) [17], occurred in 47% of the patients in one series [18]. Abdominal lesions may be confused with so-called lipodystrophia centrifugalis abdominalis infantilis (see Chapter 55) [19,20]. Atrophic morphoeic plaques can result from intramuscular injections of vitamin K [21] or subcutaneous corticosteroid injections [22]. Conditions producing pseudoscleroderma (see p. 56.83) may have to be considered. *Melorheostosis* is a rare condition presenting in adults with painful abnormalities of the skeleton and adjacent soft tissues, usually limited to a single limb. Linear endosteal bony densities of the long bones are seen on radiography, and resemble candle wax flowing along the affected bone. In children, the usual presentation is with asymmetrical contractures of a limb, occurring in association with thickening of the overlying skin and fascia, and distal vascular problems exacerbated by attempted surgical correction of the orthopaedic problem, including angiomas and arteriovenous malformations [23]. It is suggested that the distribution of these lesions represents the sclerotome, or the areas of the body supplied by a spinal sensory nerve, and that skin and muscle involvement occur in the relevant dermatome and myotome [24]. The cutaneous lesions are almost certainly a part of the developmental abnormality, rather than coexisting linear morphoea [25].

Treatment. As the expected natural history is towards spontaneous resolution, the condition may be allowed to take its natural course, if uncomplicated. If intervention is required, localized treatment with topical or intralesional steroids may be helpful [26]. More recently, calcipotriol has been shown to inhibit the growth of morphoea fibroblasts *in vitro* [27], and has proved beneficial when used topically *in vivo*, both alone [28] and in combination with UVA-1 in children [29].

Numerous systemic agents have been reported to be helpful in morphoea (on the basis of case reports or small open studies), including phenytoin [30], *p*-aminobenzoate [31], griseofulvin [32], etretinate [33], vitamin E [34], chloroquine and hydroxychloroquine [35]. Tranilast was reported as helpful in a boy with linear morphoea and contractures [36], and plasmapheresis was helpful (in combination with systemic corticosteroids) in three patients with localized scleroderma and antinuclear antibodies [37]. Topical photodynamic therapy was been reported as being helpful in five patients with localized disease [38].

Systemic corticosteroids have been found to be helpful in an open trial [39], although they are probably only

beneficial in the inflammatory stage of the disease [26]. D-penicillamine has been reported as helpful in open trials [40–42] in regimens of 2–5 mg/kg/day, with or without pyridoxine 20 mg/day. However, there is a risk of renal damage [40]. Ciclosporin was found to be helpful in open studies in localized morphoea [43,44]. Oral calcitriol, in regimens of 0.5–0.75 μg/day, has been reported as helpful in a small study [45], but a recent double-blind placebo controlled trial did not confirm this [46]. In recent years, UVA irradiation, both alone at low [47–50], medium [51] and high doses [52], as bath or oral photochemotherapy [53–56], and in combination with calcipotriol [29], has been reported as helpful. None of these studies, however, was a randomized double-blind controlled trial. Low-dose methotrexate has proved useful in widespread morphoea [57,58] and in localized morphoea in children when used in combination with systemic corticosteroids [59].

Physical therapy in the form of physiotherapy may be helpful in preventing joint deformities and contractures and in maintaining joint movement and muscle strength. It may also help to prevent sclerosis secondary to lymphoedema in the limbs of patients with linear morphoea [26]. Surgical intervention for the relief of contractures [60], the lengthening of limbs and the correction of deformities may have to be carried out in certain cases. Various plastic surgery techniques can help patients with 'en coup de sabre' morphoea [61–65] and those with ossification [66]. For those patients in whom the sclerotic processes have extended into the jaw to involve the teeth, dental treatment may be required.

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Generalized morphoea

SYN. GENERALIZED SCLERODERMA

Definition. A rare condition in which idiopathic sclerosis of the skin occurs in a widespread manner. It usually starts on the trunk and is not associated with systemic disturbances.

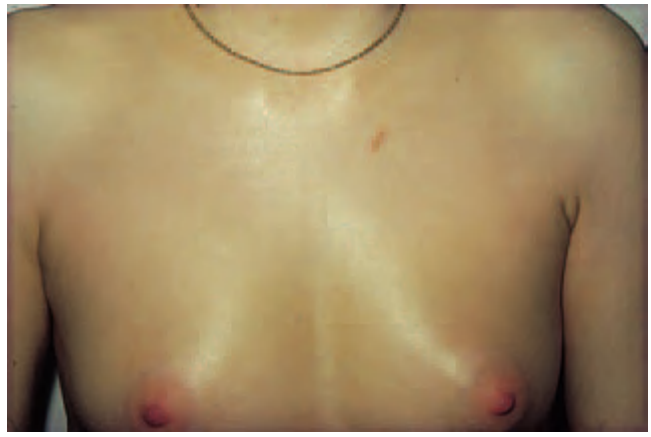

Fig. 56.54 Generalized morphoea showing diffuse tightness of the skin of the chest.

Aetiology. The aetiology is unknown. The most frequent age of onset is between 30 and 40 years, and lesions start between the ages of 11 and 50 years in 80% of patients [1]. Approximately three females are affected for every male. The occurrence of generalized morphoea and localized morphoea in two sisters has been reported [2].

Pathology. This is identical to that of localized morphoea. It has been suggested that in the early stages an inflammatory infiltrate of lymphocytes, histiocytes and plasma cells is found, primarily in the subcutaneous tissue. Later, the subcutaneous tissue is replaced by hyalinized connective tissue and this is responsible for the induration of the skin. Direct immunofluorescence shows changes in approximately one-third of cases, with IgM in the basement membrane and IgM and C3 in the dermal blood vessels being the most frequent findings. Similar changes may occur less frequently in linear morphoea.

Clinical features (Fig. 56.54). The onset is usually insidious, and the patient notices the development of plaques resembling those of localized morphoea. A lilac-coloured border surrounding the indurated ivory-white shiny lesions is usually seen in the early stages. The plaques are commonly much larger than those seen in localized morphoea, being many centimetres in diameter. Usually, plaques start on the trunk and gradually increase in size, with the development of new plaques over the first year or two. The main areas involved are the upper trunk, breasts, abdomen and upper thighs. The arms may also be involved, and in some cases the hands resemble those seen in the tumid phase of systemic sclerosis, with spindling of the fingers, binding of the skin to the underlying tissues and semiflexion of the hands and fingers. The legs, face, neck and scalp may also be involved. Scarring alopecia can result from involvement of the scalp. In some cases, the whole of the body may be involved from the top of the

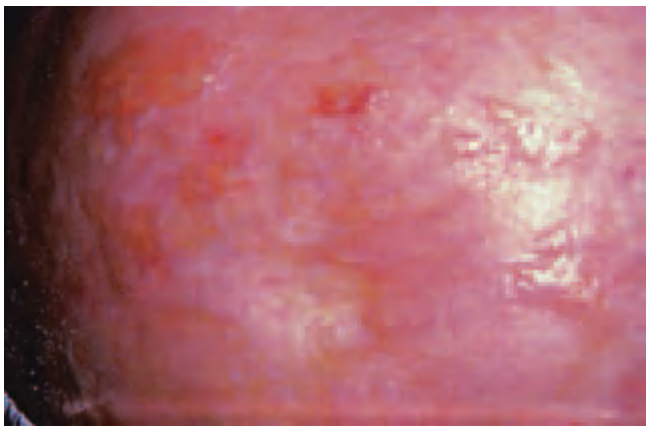

Fig. 56.55 Bullous lesions in generalized morphoea.

head to the feet, although this occurred in only one out of 44 cases in one series [1]. If the chest wall is markedly involved there may be difficulty in breathing because of constriction of the thorax. The intercostal muscles may also be involved, and death may result from respiratory failure [3]. The face is expressionless, the skin being shiny, often brown, and indurated. Telangiectasia of the face is not a feature, and although mouth opening may be restricted, the radial furrowing of systemic sclerosis is not seen. Raynaud's phenomenon occurs occasionally but is not a characteristic feature. Sometimes, especially after trauma, the hands may develop whitlows, but there is no atrophy as seen in systemic sclerosis. The tissues of the trunk and limbs sometimes show a brawny non-pitting oedema. Bullae may develop in localized areas, particularly on the abdomen (Fig. 56.55). Nodular lesions may also occur [4], and multiple keloids may be the first manifestation of the disease [5]. Acral myofibromas have been reported [6]. If the condition is generalized, it may be impossible to see any area showing a lilac border. Pigmentation is common, and in some patients may be generalized. Keratoses and calcinosis can occur.

Contractures occur in limbs, which become thin and hard. Some patients complain of considerable soreness in the acute phase, especially of the trunk and breasts. Joint pains occur in approximately 50% of patients, particularly in the fingers, wrists, elbows and knees. Definite rheumatoid arthritis may be found. Very occasionally, severe contractures, atrophy and infection may be associated with intractable pain in the limbs, and amputation may be required. Squamous cell carcinoma may develop in lesions of over 20 years' duration [7,8].

Sometimes generalized morphoea may develop as an extension of localized morphoea or be associated with lesions of lichen sclerosus et atrophicus [9]. Subcutaneous morphoea [10] seems to be more inflammatory than generalized morphoea of the dermis, and may respond to anti-inflammatory agents. Such cases may be more likely to develop mild systemic involvement and have eosinophilia. Generalized morphoea has been associated with polymyositis and the sick sinus syndrome [11] and necrotizing vasculitis [12].

Laboratory investigations. Investigation for systemic disease is usually negative. Eosinophilia, elevated ESR and hypocomplementaemia occasionally occur. Anti-single-stranded DNA antibody occurs, but anti-double-stranded DNA antibody is rare. Serum procollagen type 1 carboxy-terminal propeptide may be a useful index of activity. Levels are higher than in localized morphoea [13]. Scl-70 antibodies are rarely found.

Differential diagnosis. The following points help to distinguish morphoea from systemic sclerosis. Raynaud's phenomenon is uncommon in generalized morphoea and is almost universal in systemic sclerosis. The distribution of the lesions also differs. In generalized morphoea, the trunk is more frequently involved, whereas the face, hands and, to a lesser extent, the feet, are most commonly involved in systemic sclerosis. Generalized morphoea usually slowly improves over the years. Scleroedema of Buschke is usually a more acute and less widespread disorder. Morphoea must also be distinguished from the various conditions described below under 'pseudoscleroderma'. Generalized morphoea may have to be distinguished from eosinophilic fasciitis (see p. 56.90).

Prognosis. Some improvement is usually seen in the course of 3–5 years, but the disease may last for many years and one patient still showed changes 33 years after diagnosis [1]. In most cases, the skin slowly softens and the pigmentation decreases. With time, the tendency to ulceration, with trauma and blistering, decreases. Although some patients may be severely disabled by the immobility associated with the sclerotic changes and contractures, others with widespread sclerosis may remain surprisingly active. Patients usually remain in good health.

Treatment. The general measures outlined previously for the treatment of localized disease are just as important for patients with generalized disease.

A number of the systemic agents may also help generalized disease including systemic steroids, penicillamine, antimalarials and low-dose methotrexate. In addition, individual case reports suggest a role for agents such as sulfasalazine [14], salazopyrin [15], grenz ray treatment [16] and extracorporeal photochemotherapy [17]. Initial reports suggested a role for oral calcitriol but a recent double-blind study has not confirmed this.

An increasing body of literature suggests that ciclosporin may be helpful for generalized morphoea [18,19], although controlled studies are lacking. It must be used with care, as side effects are common. Severe renal disease

may result, although the latter is perhaps more likely in patients with active systemic disease [20,21]. As for localized disease, perhaps the modality with the greatest body of literature supporting its use is UVA phototherapy and photochemotherapy, although it must be stressed that none of these studies was controlled.

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Pseudoscleroderma

Sclerosis of the skin may be seen in several conditions other than morphoea or systemic sclerosis [1]. Scleroedema of Buschke is usually triggered by a febrile illness and comprises non-pitting induration of the face, neck, shoulders, arms and sometimes trunk. Scleromyxoedema also presents with thickening and tethering of the skin and is usually associated with a circulating paraprotein.

Scleroderma-like changes are sometimes seen in porphyria cutanea tarda [2,3] and in phenylketonuria [4,5], when they usually appear in the first year of life. Irregular indurations appear first in the muscles and subcutis of the thighs and buttocks, and later the changes extend to the trunk and proximal parts of the limbs. Contractures, especially of the legs, are characteristic. Histology shows proliferation of histiocytes and fibroblasts in the connective tissue stroma, atrophy of the skin appendages and an inflammatory infiltrate. Improvement in the skin lesions occurs with exclusion of phenylalanine from the diet. In older children, the lesions and histology resemble morphoea. Two mentally retarded siblings with phenylketonuria had morphoea and atrophoderma of Pasini and Pierini, respectively [6], suggesting that these conditions may be related.

Scleroderma-like lesions have been observed in cases of muscle glycogenosis with an undetermined enzyme defect [7]. Induration and atrophy occur in the skin and muscles in the first few months of life. The proximal parts of the limbs are involved early and contractures occur, particularly in the legs, giving a characteristic bent-knee gait. Mental retardation may be a feature.

The scleroderma-like lesions of primary systemic amyloidosis, with or without multiple myeloma, may be difficult to distinguish if not accompanied by nodular and papular lesions, particularly about the shoulders and neck, and by macroglossia. Primary localized cutaneous amyloidosis occurs in systemic sclerosis [8]. Pseudoscleroderma also occurs in multiple myeloma [9] and paraproteinaemia [10].

Acrodermatitis atrophicans, a disease found in central and eastern Europe, resembles localized morphoea (see Chapter 46).

Sclerosis of the legs is found in patients with the carcinoid syndrome [1,11,12] and atrophy of the acral parts in Werner's syndrome [1], but these disorders should be distinguished by their other manifestations. Progeria, acrogeria and poikilodermatous epidermolysis bullosa [13] are other rare conditions in which scleroderma-like lesions occur. Sclerosis of the skin occurs in the GEMSS syndrome (*g*laucoma, lens *e*ctopia, *m*icrospherophakia, *s*tiffness of the joints and *s*hortness due to increased production of normal collagen [14]) and in Moore–Federman syndrome (short stature, stiffness of joints, characteristic facies).

The skin is oedematous and indurated in hypothyroidism, and atrophic changes in the skin in postpartum hypopituitarism may resemble scleroderma [1]. Pseudosclerodermatous changes may also be seen in rheumatoid arthritis [15], and in patients with long-standing diabetes mellitus in which limited joint mobility, termed cheiroarthropathy, is associated with thickening of the skin. The changes are most marked in the hands [16].

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Occupational scleroderma

Vinyl chloride disease [1–4]

One to six per cent of polyvinyl chloride (PVC) workers, particularly reactor cleaners, develop coldness, stiffness, numbness, burning pain and discoloration of the fingers and hands, and to a lesser extent the feet, on exposure to cold. Other symptoms include loss of energy, loss of libido, impotence, dyspnoea and feeling light-headed, with irrational laughter and whistling. The skin of the hands, forearms, face and trunk may be thickened. The hands show mottled pink, purple or white areas. The terminal phalanges are shortened and bulbous, and the nails are curved. Telangiectases occur on the face, resembling those of systemic sclerosis, and there may be difficulty in opening the mouth, although radial furrowing and pigmentation are not features. Usually, it is possible to distinguish between classic systemic sclerosis and vinyl chloride disease [5]. Parotitis [6], hepatomegaly and splenomegaly occur. X-rays show erosion of the tufts of the terminal phalanges and thinning of the other phalanges of the fingers and toes. Erosions also occur in the metatarsals, pelvic bones, clavicles and bones of the arms and legs. Nail fold capillaroscopy shows changes similar to those seen in systemic sclerosis. Narrowing of digital arteries and hypervascularity of the digital tufts are seen on arteriography.

Histologically, there is thickening and separation of collagen fibres and fragmentation of elastic fibres in the dermis. Immunohistology reveals an immune-complex vasculitis with deposits of IgG, complement and fibrin in the media of small- and medium-sized arterioles [7]. Other immunological features include low levels of non-organ-specific autoantibodies, polyclonal hyperglobulinaemia, cryoglobulinaemia, cryofibrinogenaemia, *in vivo* complement activation and conversion, reduced T cells and moderate B-cell proliferation. Anticentromere or anti-Scl-70 antibodies cannot usually be demonstrated [8], although a patient who presented with 'pneumoconiosis' and systemic sclerosis features 10 years after exposure did have a positive ANA and Scl-70 antibodies [9]. Thrombocytopenia, abnormal platelet aggregation, abnormal liver function tests, raised serum creatine phosphokinase indicating muscle involvement, patchy defects of pulmonary ventilation and perfusion, hepatic fibrosis and oesophageal varices also occur.

The prognosis is unknown, and many men have not improved after removal from exposure. There is no effective treatment. Angiosarcoma of the liver is a serious complication. If the level of exposure to vinyl chloride monomer in PVC manufacturing plants is kept below five parts per million, further cases of vinyl chloride disease should not occur. A genetic susceptibility is shown by an increase in HLA-DR5 in all patients and of -B8 and -DR3 in those severely affected [8]. Acro-osteolysis has also been reported in a worker not exposed to vinyl chloride [10].

Scleroderma-like lesions resulting from perchlorethylene, trichlorethylene and organic solvents

A disorder, resembling vinyl chloride disease, has been reported after exposure to perchlorethylene, a solvent used in dry cleaning of clothes [11,12]. Acrocyanosis and acrosclerosis were associated with polymyopathy and hepatic damage. Some of the features, including the presence of speckled antinuclear factor and favourable response to prednisone, were suggestive of 'mixed connective tissue disease'. Exposure to trichlorethylene may be associated with scleroderma [13–16], possibly after even a single prolonged exposure. Of patients with systemic sclerosis in an eastern European series, 28% had suffered significant exposure to organic solvents [17]. Similarly, an Italian study has confirmed an aetiological role of exposure to solvents in scleroderma [18]. A man who used trichlorethylene for cleaning metal also had peripheral neuropathy, Raynaud's phenomenon, impotence, gynaecomastia, hepatomegaly, lymphadenopathy and pigmentation [16]. He was probably a case of

Crow–Fukase (POEMS) syndrome. In a Japanese series, generalized morphoeic lesions, similar to those found in occupational scleroderma, were found in nine of 115 patients with systemic sclerosis. Seven had been exposed to organic solvents before the onset of Raynaud's phenomenon. Some had visceral changes of systemic sclerosis [19]. The same authors induced sclerotic skin changes in mice by the intraperitoneal injection of napththa, *n*-hexane and hexachlorethane. A sclerodermatous syndrome consisting of cold sensitivity, restrictive lung defect, peripheral neuropathy, oesophageal dysfunction, labile hypertension and monoclonal paraproteinaemia has been reported in a man who had worked with many solvents. These included benzene, toluenes, toluidines, xylenes, xylidenes, aniline compounds, and ethanolamine and its derivatives [20]. Solvents recorded in other reports include isopropylalcohol, ethyl acetate, naphthalene, trimethylbenzene and turpene derivatives [21]. Systemic sclerosis occurred in two workers handling *meta*-phenylenediamine [22].

Scleroderma-like lesions resulting from pesticides

Sclerodermatous changes can occur in workers handling pesticides. Substances possibly incriminated include chlordane, heptochlor, malathion, parathion, DDT, sodium dinitro-orthocresolate and 7-chlorocyclohexane [2,23,24]. Raynaud's phenomenon occurs, but there is no evidence of involvement of internal organs. Hyperkeratosis of palms and soles with sclerodactyly of the fingers and toes has been reported in a weed sprayer with chloracne [25].

Scleroderma-like lesions resulting from epoxy resin

Six Japanese men exposed to the vapour of epoxy resins in the production of transformers for television sets developed scleroderma-like skin changes and erythema, with fatigue, loss of weight, myalgia and arthralgia [26]. The histological changes were those of scleroderma, but there was no definite evidence of systemic involvement. A hardener—1,1′-*bis*(3-methyl)-4-amino(cyclohexyl)methane—was thought to be the cause. Improvement occurred when the men stopped work, and the disorder resolved completely within 5 years without any internal organ involvement developing [27]. One patient developed systemic sclerosis sine scleroderma after exposure to epoxy resin [28].

Silicosis and scleroderma

The association of silicosis and scleroderma has been reported in Italy [18], in South African coal mines [29] and in coal mines in other countries where silica is present [30–33]. Men in other occupations, such as sandblasters and quarrymen, may be affected. Because of the occupational risk, the condition occurs predominantly in men, particularly those suffering from silicosis. In East Germany, 93 of 120 male patients with systemic sclerosis had suffered long-term silica exposure, and 49 had coexisting silicosis [34]. The lung changes frequently precede the scleroderma. Visceral manifestations resembling those of systemic sclerosis occur in approximately half of cases, and antinuclear factor can be demonstrated in one-third. In these cases, the clinical and immunological changes are indistinguishable from those found in systemic sclerosis without any environmental exposure [35]. Systemic sclerosis-like syndromes may follow exposure to urea formaldehyde foam insulation [36].

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Iatrogenic scleroderma

Scleroderma-like changes resulting from bleomycin [1,2]

Cutaneous fibrosis with acrocyanosis, acrosclerosis, pigmentation, hair loss, flexion contractures and ulceration occurs in patients treated with the antitumour agent bleomycin. Pulmonary fibrosis is a prominent feature. Remission occurs some months after withdrawal of the drug. Cisplatin can cause similar changes.

Scleroderma resulting from other drugs

Carbidopa [3], pentazocine [4], cocaine [5] and appetite suppressants [6] have all been implicated in the development of sclerodermatous disease.

Scleroderma induced by silicone or paraffin implants (human adjuvant disease) [7]

Skin sclerosis, sometimes resembling morphoea, occurs at the site of injection of silicone for cosmetic breast surgery. It may act by the release of silica. Sometimes, more widespread connective tissue disease resembling systemic sclerosis [8], mixed connective tissue disease, SLE, rheumatoid arthritis, primary biliary cirrhosis, Sjögren's syndrome [9] or eosinophilic fasciitis [10] occurs. Paraffin injections may be a more important factor than silica in causing systemic sclerosis-like disease [11]. A causal link between silicone breast implants and autoimmune diseases seems to have been discounted [12].

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'Toxic oil' epidemic syndrome [1,2]

In 1981, in certain areas of Spain, the ingestion of rapeseed oil denatured with aniline caused a multisystem disease affecting 18 000 people. The most prominent pathological feature was a widespread non-necrotizing intimal vasculitis in practically every organ [3]. The early phase, lasting 2–3 months, consisted of atypical pneumonia, gastrointestinal and neurological symptoms and a pruritic rash. The rash involved the limbs, abdomen and trunk, and resembled a viral exanthem lasting approximately 5–20 days. Occasionally, palpable purpura or erythema multiforme occurred. Eosinophilia was always present, antinuclear antibodies were frequently found, and elevation of IgE and abnormal liver function tests could be demonstrated in one-third of cases. Histology showed dilatation of blood vessels, and an inflammatory exudate including eosinophils in the dermis. Three to four months after the onset, 10% of patients developed a transitory eruption consisting of multiple yellowish or brownish papules of all areas except palms and soles. Five to six months after the onset, patients, mainly women, developed a neuromyopathy, and either localized or gen-

eralized morphoea or a disorder resembling systemic sclerosis, with dysphagia, oesophageal changes and occasionally renal involvement. Sicca syndrome and pulmonary hypertension were prominent features in some cases. Histology of the skin showed dermal infiltration and sclerosis with interfibrillar mucin deposits, but immunology was negative.

Most patients recovered to some extent, although 50% had persistent symptoms when reviewed in 1984 [4]. The cause is unknown. An immune reaction to an unknown antigen seems likely. HLA typing showed an increased incidence of HLA-DR3 and -DR4 in females with chronic disease [5].

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Graft-versus-host disease [1–5]

Definition. Graft-versus-host disease (GVHD) occurs when immunocompetent cells from a donor recognize and react against 'foreign' tissue antigens in an immunocompromised host. Originally reported following bone marrow transplantation (regularly used in the management of leukaemias, lymphoma, immunodeficiency and inborn errors of metabolism), GVHD is now recognized to occur following transfusion of non-irradiated blood, after maternofetal transfer of lymphoid cells, and following peripheral blood stem cell transfer [6]. Post-transfusion-related GVHD is an uncommon but potentially fatal complication of transfusing blood between immunologically related individuals. It appears that transfused white blood cells are not recognized as foreign, and react against host tissue. The reaction seems to depend on heterozygosity of class I antigens. The two recognized forms of the disease are acute and chronic.

Incidence. Even using prophylactic therapy to prevent its occurrence, GVHD occurs in approximately 50% of patients receiving successful marrow allografts for various disorders, including immunodeficiency diseases, aplastic anaemia, acute leukaemia and radiation exposure, despite careful histocompatibility matching [7]. The frequency is the same in those receiving peripheral blood stem cell grafts [8]. It has recently become clear that the typical acute form of the syndrome can also occur after syngeneic (identical twin) or autologous bone marrow grafting, in which genetically identical material is transplanted, and may occur in approximately 10% of such cases [8].

Aetiology [4,9]. Billingham described the original criteria for the development of a graft-versus-host reaction in 1966:

1 Genetically determined histocompatibility differences between donor and recipient

2 Immunocompetent cells in the grafted tissue able to recognize foreign histocompatibility antigens in the host and to react against them

3 Inability of the host to recognize and react against the grafted tissue.

It is clear from animal experiments [10,11], as well as the occurrence of typical GVHD in human syngeneic transplants, that criterion **1** is no longer an essential prerequisite for the development of the acute form of the syndrome. GVHD in this situation occurs because of MHC class II differences. It usually only occurs after the withdrawal of immunosuppression [12].

A similar syndrome occurs in recipients of IL-2 and lymphocytes activated by this stimulating lymphokine given as treatment for widespread malignancy. Cells activated by this technique are non-specifically cytotoxic, capable of self-reactivity and may have the features of NK cells. In animal models, and in humans, HLA-DR-bearing Langerhans' cells are reduced in the acute form of the disease, and T cells directed against these cells are found. In addition, IFN production by activated T cells induces HLA-DR expression on keratinocytes, making them targets for a similar reaction [13,14]. The risk of developing GVHD may be related to cytokine gene polymorphisms [15].

A possible hypothesis is suggested by Ferrara [16]; immunologically competent donor T lymphocytes are not destroyed in the host because they are not recognized as foreign. Activated T cells release IL-2, IFN and probably other lymphokines. IL-2 activates cytotoxic cells (probably NK cells), and HLA-DR-bearing epidermal cells and Langerhans' cells may be specifically attacked, giving rise to acute GVHD. The same, or similar, cells recognize any persisting malignant cells in the host, and it is suggested that graft-versus-leukaemia reactions explain the lowered incidence of recurrence of the original malignancy in patients with GVHD. However, there are some criticisms of the theory of T-cell-mediated cutaneous pathogenesis, mainly that early graft-versus-host reactions do not show T-cell infiltration of the skin [17]. In addition, successful treatment of GVHD is accompanied by the induction of apoptosis in T cells and some epidermal cells. This suggests that a failure of programmed cell death may be a feature of pathogenesis [18]. Nevertheless, the use of T-cell-depleted marrow for grafting reduces the incidence of GVHD and prevents HLA-DR expression on keratinocytes,

but unfortunately the failure rate of the transplant is markedly increased.

Pathology [19]. For acute GVHD, the cutaneous histological changes have been graded for severity.

Grade I Basal cell vacuolation with or without mononuclear cell infiltration

Grade II Solitary epidermal cell necrosis, surrounded by mononuclear cells

Grade III Regional epidermal cell necrosis with bullae

Grade IV Toxic epidermal necrolysis

Less severe histological grades may be impossible to differentiate from drug-induced reactions. At an immunocytochemical level, the earliest (preclinical) changes are an increase in dermal macrophages expressing α_1-antichymotrypsin. In grade I disease, there is keratinocyte HLA-DR and ICAM-1 expression, and in the later stages, $CD25^+$ T cells, L1 antigen-positive keratinocytes, and VCAM-1^+ macrophages are increased [20].

In chronic GVHD, histological changes are lichenoid, or resemble scleroderma. IgM may occur at the dermal–epidermal junction, with granular deposits of IgM, IgA and C3 in the walls of dermal vessels. There is associated microvascular disease mediated by cytotoxic T cells [21].

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Clinical features [1,2]. Acute GVHD usually occurs within 60 days of a bone marrow transplant, and most often after 7–12 days. Mild fever is followed by a faint red maculopapular rash on the hands, feet, face and forehead. This spreads to the trunk and limbs, becoming deeper in colour. Desquamation or even toxic epidermal necrolysis follows. Bullous and ulcerated forms are described [3], and a follicular pattern may indicate more severe disease [4]. Hepatitis (indicated by raised bilirubin and alkaline phosphatase) and bloody diarrhoea resulting from enteritis are other features and, in severe cases, death occurs by the 21st day. In the original cases, it was rare to have liver and gut involvement without cutaneous pathology, and skin biopsy was the simplest reliable test for diagnosis. However, the introduction of T-cell depletion as a prophylactic measure has changed the pattern of disease so that skin disease may be mild, while liver and bowel disease may be severe. Thus, the value of skin biopsy has been questioned [5]. Clinical stagings for each organ system, and grading for the overall clinical picture, have been proposed [6].

Chronic GVHD may be localized (Fig. 56.56) or generalized, and principally involves the skin and the liver. The former occurs in 10% of patients as hyperpigmented nodular areas, which may be guttate, and eventually soften and atrophy. The early phase of generalized GVHD generally appears up to the 100th post-transplant day and usually, but not always, follows acute GVHD. Initially, a slowly progressive erythematous rash on the face, palms and soles becomes lichenoid, with changes resembling lichen planus in the oral mucosa [7]. Lichenoid changes may be limited to the nails [8]. Later, scleroderma-like changes occur, which are sometimes widespread and disabling. The condition resembles systemic sclerosis, with tightening of the skin of the face, hands and feet. Autoantibody changes similar to those found in systemic sclerosis may occur [9]. Disease may be localized to the extremities and associated with a polyneuropathy [10].

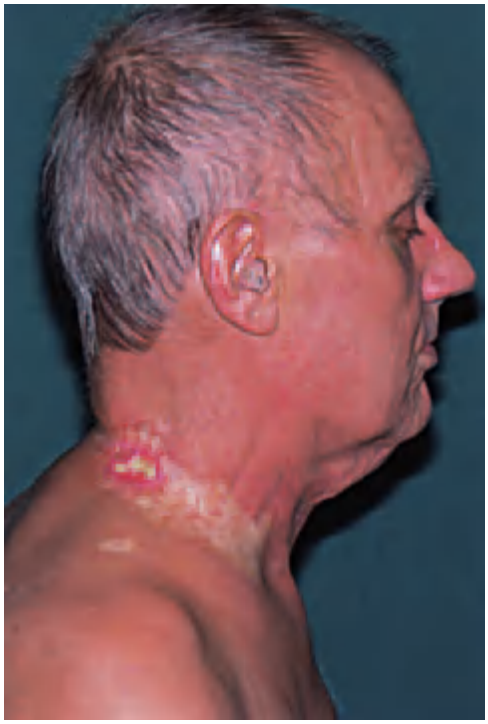

Fig. 56.56 Localized eroded sclerotic graft-versus-host disease.

Oesophageal changes and subcutaneous calcification may occur. Morphoea-like changes have been reported [11]. Eruptive violaceous vascular tumours on the legs may occur [12]. Reticulate patchy hyperpigmentation and, less commonly, hypopigmentation, poikiloderma, vitiligo (which may be total [13]), erythema, atrophy, alopecia, multiple follicular papules, deep ulcerations of the buttocks and legs, and dystrophic nail changes are other features [14]. Panniculitis may occur [15]. Gastrointestinal symptoms, a Sjögren-like syndrome [16], polymyositis [3], abnormal liver function tests, primary biliary cirrhosis [17] and other organ changes occur [3].

That there may be some interaction between viral infections and minor histocompatibility differences in the pathogenesis of chronic GVHD is suggested by the development of scleroderma-like skin changes in areas affected by measles in a patient 8 months after bone marrow transplantation [18]. Similarly, pathogen-free transplanted animals do not develop GVHD until given bacteria or endotoxin, and patients nursed in laminar flow isolation remain disease-free until they are removed from this environment [19].

Treatment. Prophylactic use of ciclosporin [20,21], methotrexate and prednisolone [22] and, in particular, combinations of these agents [23], has reduced the incidence of acute GVHD. None of these regimens has produced a definite reduction in the incidence of chronic GVHD, and recent studies indicate no benefit in 24-month rather than 6-month ciclosporin therapy in this situation [24]. T-cell depletion by using anti-T-cell receptor antibodies is successful in reducing the frequency of acute GVHD when used with post-transplant ciclosporin [25]. Combination therapy appears to be better at preventing GVHD than monotherapy, but overall survival is unchanged in younger patients because of higher leukaemic relapse. Older patients survive longer on combination therapy (methotrexate with ciclosporin or T-cell depletion) [26]. Intravenous IgG may help to prevent GVHD, but its value is unconfirmed [27]. Granulocyte colony-stimulating factor, used to enhance engraftment may reduce the incidence of GVHD [28].

Once the disease is established, treatment with high-dose corticosteroids or ciclosporin is of value symptomatically, and antilymphocyte globulin may be of additional benefit [29], particularly if combined with tacrolimus [30]. Treatment with prednisone and azathioprine for at least 9–12 months helps generalized chronic GVHD in one-third of patients [31], but complications are common, and survival may be reduced by the addition of azathioprine. Thalidomide, used in both low dosage (100 mg/day) and high dosage (400 mg/day) has been of value, but may result in severe cutaneous ulceration [32,33]. PUVA therapy [34], UVB [35], UVA-1 [36] and extracorporeal photophoresis [37] may be of benefit, even in severe disease [38,39]. Most recently, infliximab, the monoclonal anti-TNF therapy, has been used successfully [40].

Prognosis. Forty to fifty per cent of patients with chronic GVHD are dead within 10 years of developing the disease. Mortality is caused both by the disease itself, and by severe superinfection, related, at least in part, to the immunosuppressive effects of treatment. Recurrence of the original disease is also a problem. Patients who develop chronic GVHD after the acute form, those with the lichenoid type of eruption, and those with significant liver disease have a worse prognosis, with 80% mortality at 10 years [41]. Persistent thrombocytopenia is also an adverse sign [23].

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Eosinophilic fasciitis [1–8]

SYN. SHULMAN'S SYNDROME

This scleroderma-like syndrome appears to be a distinct entity, although some have suggested that it is an early variant of systemic sclerosis [2,9] or linear scleroderma [10], or that it may occur in conjunction with other connective tissue disease [11]. It occurs in children and adults, more commonly in males than females. The clinical features are the acute onset of pain, swelling and tenderness of the distal part of the limbs, which become indurated. There is limitation of movement of the feet and hands. Occasionally, the face or abdomen can be affected, and there may be superficial blistering and haemorrhage. A relationship to strenuous exertion or trauma has been suggested. Twenty-nine per cent of 52 patients showed lesions of localized morphoea at some stage [12]. Raynaud's phenomenon is rare, there is limited evidence of involvement of internal organs such as occurs in systemic sclerosis, and no history of a previous infection to suggest scleroedema. Blood eosinophilia up to 30% is a striking feature, occurring in approximately 70% of cases [13]; it is associated with elevation of the ESR and hyperglobulinaemia, but these are not present in all cases. Rarely, aplastic anaemia and thrombocytopenia occur [7]. Antinuclear antibodies cannot be demonstrated and serum complement levels are normal. Cytokine production by mononuclear cells is enhanced but the pattern is of mixed Th1 and Th2 [14]. Histologically, there is dermal sclerosis, with inflammation and fibrosis of the fat and deep fascia. The fascia is thickened and infiltrated with lymphocytes, plasma cells, histiocytes and eosinophils. IgG and C3 deposits can be demonstrated in the deep fascia. Clinical improvement and disappearance of eosinophilia follows corticosteroid therapy, but spontaneous remission has been reported. Methotrexate may be useful [15].

An eosinophilic fasciitis-like syndrome occurs after recent ingestion of L-tryptophan [16,17]. In addition to the usual features of fasciitis, there is muscle weakness and elevated muscle enzyme levels. Enhanced type I procollagen gene expression in the skin has been demonstrated [17]. Myalgia, eosinophilia, dyspnoea, oedema, arthralgia, neuropathy and rashes occur in the eosinophilia–myalgia syndrome [18,19] which can also be precipitated by tryptophan [9]. Cutaneous manifestations include localized and generalized morphoeic lesions and urticarial and papular lesions [20].

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Connective tissue panniculitis (see Chapter 55)

This term has been used [1] for focal nodular or atrophic linear or plaque-like lesions on the face, upper trunk or extremities, which histologically show lymphocytic panniculitis with caseation necrosis. The lesions may respond to chloroquine.

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Relapsing eosinophilic perimyositis [1]

This rare disorder is in the spectrum of eosinophilic myositis, and is characterized by inflammation within the perimysium (and often epimysium) without necrosis, as opposed to polymyositis and eosinophilic myositis in which necrosis and inflammation occur in the endomysium.

Clinically, patients may present with episodic swelling of the muscles, fatigue and fever. Skin lesions include blotchy erythema over the swollen muscles and erythematous papular lesions of the palms. There is peripheral blood eosinophilia and hyperglobulinaemia, but the muscle enzyme levels are normal or only slightly elevated. Histologically, there are perimysial eosinophilic infiltrates.

The aetiology is unknown. The prognosis is good, although the patient should be followed up in case of the development of lymphoproliferative disease. Most patients respond to moderate doses of steroids or indometacin.

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Systemic sclerosis [1,2]

SYN. PROGRESSIVE SYSTEMIC SCLEROSIS; SYSTEMIC SCLERODERMA; ACROSCLEROSIS

Definition. Systemic sclerosis is a multisystem disorder characterized by the association of vascular abnormalities, connective tissue sclerosis and atrophy, and autoantibodies (see p. 56.95 for diagnostic criteria) [2].

The name progressive systemic sclerosis was coined by Goetz in 1945. In most cases, the disease is not 'progressive' and this term is now omitted by most authors [2–5].

Incidence. Systemic sclerosis is a rare disorder, with an incidence between 2.3 and 10 per million population [6–8]. The prevalence rates in a British study were 13 per million males and 48 per million females, although these are probably minimum figures [9], and there may be considerable regional variations, possibly as a result of environmental factors [10]. Figures from South Carolina are much higher (67–265 in 100 000) [11]. The ratio of females to males is between 3 and 6 : 1 [8,9,12]. The peak onset is in the fourth decade in females and usually later in males;

however, overall, 85% of patients present between the ages of 20 and 60 years [8]. In men, the condition appears to be more common among coal miners and those who work in dusty trades, and it has been suggested that silicosis may be a predisposing factor [13]. It occurs in all races, but seems to be less frequent in Asians [14]. There is evidence that black women with systemic sclerosis are more likely to develop diffuse disease at a younger age and have decreased survival compared with white women [15].

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Aetiology [1]. The aetiology of systemic sclerosis is unknown. The presence of vascular symptoms in virtually all patients, the fact that these may predate the development of classic fibrotic change, and the presence of markers of vascular damage (e.g. elevated von Willebrand factor antigen levels [2,3]), suggest that the vasculature, in particular the endothelial cell, is the initial target in this disease. Vascular abnormalities are not limited to the clinically abnormal skin [4]. Damage to the endothelial cell may initiate the fibrotic process, either through the effects of ischaemia or via growth-modulating mediators released from platelets and inflammatory cells. However, the pathological changes in the internal organs do not always seem to be directly related to changes in the small blood vessels of the same area.

There is clear evidence of endothelial injury and death [5], and the primary pathology in vascular endothelium appears to be a fibromucinous change [6]. Serum from patients with the disease is cytotoxic to endothelial cells, either directly [7] or by antibody-dependent cellular cytotoxicity [8], but patients' serum has no effect on unstimulated release of prostacyclin [9], although stimulated release may be impaired [10]. The influence of sera from affected patients on angiogenesis varies with the phase and type of disease, being stimulatory in early limited disease, but inhibitory in chronic diffuse disease [11]. Damage to endothelium is followed by vascular occlusion resulting from thrombus formation, and tissue ischaemia follows. Abnormalities in various blood components contribute to this tissue anoxia: red cell deformability is reduced [12], platelet aggregation to collagen may be specifically enhanced [13] and *in vivo* markers of platelet activation are increased [14]. Levels of fibrinogen, von Willebrand factor antigen (possibly indicating the degree of vascular damage) [15] and other plasma proteins are also raised, contributing to increased plasma viscosity, further reducing microvascular blood flow. Anticardiolipin antibodies are present in more severely affected subjects, and may cause endothelial cell damage [16].

The associated fibrosis in systemic sclerosis is caused by the increased accumulation of collagen. Scleroderma fibroblasts synthesize more collagen than those from normal controls [17,18], and collagenase activity is normal [19]. The deposited collagen is similar in composition to that deposited in other fibrotic disorders, with a normal ratio of type I to type III collagen [19]. The cause of this excessive production is unknown: both intrinsic overactivity and excessive stimulation of fibroblasts may occur. Fibroblast function is modified by endothelial cell products released in a cell culture system [20]. Small collagen fibres are increased, and the response of systemic sclerosis fibroblasts to most mitogens is normal, or reduced, indicating overstimulation [21]. Raised levels of growth factors, both platelet-derived [22] and non-platelet-derived [23], support this suggestion. In addition, glycosaminoglycan synthesis is increased in fibroblasts from patients with the disease, and is stimulated by a mononuclear cell product (possibly IL-1) [24], although other mononuclear cell products can inhibit collagen overproduction [25]. Other connective tissue proteins, including tenascin, are increased [26]. However, there is evidence for an expanded clone of overactive fibroblasts in systemic sclerosis [27], possibly derived from fibroblasts from the deeper dermis [28,29]. There is also an excessive response of fibroblasts to TGF-β [30], to platelet growth factors [31] and to serum from patients with the disease [32]. TGF-β may have a role both in fibroblast stimulation and in endothelial inhibition [21]. There is a failure of the inhibitory feedback of the amino-propeptide of type I collagen on the fibroblasts [33]. Soluble cytokine receptors [34]

and serum levels of adhesion molecules [35] are raised, and reflect disease activity. Circulating anticollagen antibodies to collagen types I and IV occur in patients with systemic sclerosis [36], but these appear to be inversely related to the severity of the disease. They occur in approximately half of British patients and in at least one relative in over 80% of their families. It has been suggested that serotonin hypersensitivity may be a factor in both the vascular and fibrous changes of the disease [37]. Abnormal metabolism of, and responses to, serotonin and tryptophan may contribute to both fibrosis and vascular abnormalities [38]. Raised numbers of mast cells in affected skin may similarly contribute.

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Autoimmunity. It is not clear whether autoimmunity, indicated by the presence of antinuclear and other antibodies, is a primary abnormality or occurs because of cellular damage. A role for immune factors in endothelial injury is suggested by the presence of antiendothelial cell antibodies in 30% of patients [1,2], the ability of endothelial cells to act as a modulator of immune responses [3] and the finding of an IgM vasculopathy in acute-onset systemic sclerosis. Furthermore, circulating immune complexes occur in over 50% of cases [4], but their significance is unknown.

There is also evidence of abnormal cellular immunity. Patients with systemic sclerosis show leukocyte migration inhibition to a variety of autologous, homologous and heterologous antigens [5]. However, the development of delayed cutaneous hypersensitivity is normal [6]. Patients have a deficiency of circulating T lymphocytes [7]

and impaired lymphocyte transformation in response to phytohaemagglutinin (PHA) [8]. Both these features are related to the severity of the disease and the degree of visceral involvement, and also to an increased incidence of HLA-B8 [9]. The haplotype B8/DR3 is associated with decreased cellular immunity [10]. Helper cells [11], T cells possibly activated by raised levels of IL-2 [12] and NK cells are increased [13], and suppressor cells decreased [14]. These T-cell changes are more marked in later stage generalized disease. Patients with extensive disease have reduced antibody-dependent cytotoxicity, PHA-induced T-cell cytotoxicity [15] and NK-cell cytotoxicity to Chang liver cells [16], although others have found enhanced NK activity [17]. Some patients with systemic sclerosis develop a delayed cutaneous reaction to autologous leukocytes [18]. Sclerodermatous changes may occur after allogeneic bone marrow transplantation (see p. 56.87).

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Genetic factors. Despite the rarity of familial cases of systemic sclerosis [1–4], abnormalities of the serum immunoglobulins [5] and the high incidence of antinuclear factor in first-degree relatives of patients with systemic sclerosis [6], together with an increased incidence of HLA-B8 in the more severe cases [7], suggest that genetic factors play a part in the aetiology. Clinical and immunological subsets may be genetically determined, but to date there appears to be no clear relationship between HLA, autoantibodies and clinical manifestations [8]. Chromosomal abnormalities have been described in patients with the disease [9,10] and in their relatives, and a serum factor may be responsible for this abnormality. HLA-DR typing shows an increase in DR2, DR3 and DR5 [11]. There is an association between the B8-DR3-DR52-DQB2 haplotype and the development of pulmonary fibrosis [12]. Patients with mild disease have raised DR2 and DR5 and anticentromere antibodies. No relationship between HLA type and Scl-70 antibodies has yet been demonstrated. In identical twins discordant for the disease, autoantibodies [13], T-cell abnormalities and abnormal fibroblast response to mononuclear cell stimulation were found only in the affected twin [14].

A recent intriguing hypothesis suggests that transfer of fetal cells to the mother or vice versa during pregnancy may result in microchimerism, which has been demonstrated in higher frequency in systemic sclerosis [15]; this may then stimulate a unique immune response.

The age distribution of the disease suggests that the susceptible genotype is probably characterized by a single inherited dominant allele on the X chromosome, explaining the female predominance, together with autosomal factors. Initiation would depend on the occurrence of specific random events believed to be somatic mutations in lymphoid stem cells [16], producing 'forbidden' clones of lymphocytes. These synthesize cellular autoantibodies that are pathogenic, damaging endothelial cells. After a variable latent period, damage to tissue occurs. Antinuclear factors are the result of the disease. Normal defence mechanisms (more efficient in females) may be inhibited by precipitating factors such as silica or other environmental hazards. The pattern of organ involvement may be related to particular forbidden clones that are active, or to local tissue differences.

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Other factors. There is no evidence of a chemical cause, although cocaine has been suggested as a trigger in some cases [1]. The role of silicone gel prostheses used for breast augmentation has been much discussed, but there is now agreement that there is no relationship between this procedure and the development of systemic sclerosis [2,3]. Physical trauma appears to precipitate the disease in genetically predisposed individuals [4], who may have the allele HLA-DR52 [5]. Virus-like particles have been observed by electron microscopy in striated muscle [6], and acid-fast bacilli, closely allied to mycobacteria, have been found in skin biopsies [7] in systemic sclerosis, but their significance is not known. Glucose-tolerance curves may suggest latent diabetes [8]. A prolongation of sensory chronaxia has been found in both normal and abnormal skin [9], and it has been suggested that the condition is a primary abnormality of the central autonomic nervous system. Reciprocal skin grafting has shown that if sclerodermatous skin is placed in a normal bed, it remains sclerodermatous, and if clinically normal skin is placed in a sclerodermatous area it becomes sclerodermatous [10]. Thus, in systemic sclerosis, the skin involvement is generalized or irreversible, in contrast with morphoea, in which the disorder is localized and reversible.

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Diagnosis. The criteria for diagnosis have been established by the Subcommittee for Scleroderma Criteria of the ARA [1] and are generally accepted. Patients should have either:

1 Scleroderma proximal to the digits, affecting limbs, face, neck or trunk—this is the single major criterion; or
2 At least two minor criteria, consisting of:
(a) sclerodactyly
(b) digital pitted scarring
(c) bilateral basal pulmonary fibrosis.

These criteria have 97% sensitivity and 98% specificity, and difficulty arises principally in males who have a sclerodermatous condition brought about by occupational exposure to, for example, silica or vinyl chloride. These patients often fulfil two minor criteria, and indeed share many characteristics, both clinical and immunological, with true systemic sclerosis [2].

Classification of systemic sclerosis. There have been many attempts to classify the disease [3–6]. Most recently, a simplified classification has been proposed [7]. In this system, patients are classified as having diffuse cutaneous systemic sclerosis (dSSc), or limited cutaneous systemic sclerosis (lSSc). The distinction is made principally on the basis of the extent of cutaneous involvement, but also includes certain other clinical and immunological features (Table 56.9). This system appears satisfactory because systemic involvement, which determines the prognosis of the disease, is less frequent in patients with limited cutaneous disease.

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Table 56.9 Classification of systemic sclerosis.

Diffuse cutaneous systemic sclerosis
Short interval (< 1 year) between the onset of Raynaud's phenomenon and the development of skin changes
Truncal and peripheral skin involvement
Tendon friction rubs
Pulmonary fibrosis, renal failure, gastrointestinal disease, myocardial involvement
Capillary drop-out visible in nail folds
Scl-70 antibody-positive
Anticentromere antibody-negative
Limited cutaneous systemic sclerosis
Long history of Raynaud's phenomenon
Limited skin involvement (peripheral only)
Calcification, telangiectasia, late onset of pulmonary hypertension
Capillary dilatation visible in nail folds
Anticentromere antibody-positive

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Pathology [1]. It is important to realize that this widespread disease does not involve all organs in any patient: in certain cases it may be limited to one or two organs. Even when changes are present in an organ, the distribution of these changes is by no means uniform. Although a striking abnormality in systemic sclerosis is the sclerotic change in tissues such as the heart, lungs, submucosa and muscularis of the gastrointestinal tract, widespread vascular lesions may be a prominent feature of certain cases. The digital arteries may be severely involved, and changes of endarteritis may be seen in the lungs, heart, gastrointestinal tract, muscle and kidney. Infiltrations of inflammatory cells, particularly lymphocytes, may occur in the joints, mucosa and submucosa of the gastrointestinal tract, and in striated muscle.

In the skin, the dermis shows hyalinization of the collagen, often with associated abnormalities of elastic tissue and reticulin. The changes may be slight and difficult to detect unless the histological technique is excellent. In particular, standard fixatives must be used if hyalinization of the collagen is to be assessed. In severely involved skin, the epidermis and its appendages are usually atrophic, with loss of the rete ridges. Sometimes, there is hyperkeratosis, and the dermis shows variable degrees of homogenization of the collagen, and occasionally a light dermal lymphocytic infiltrate. In the tumid or 'inflammatory' phase in the fingers, the dermis may show a striking infiltrate, with lymphocytes predominating. Cellular infiltrates of lymphocytes, plasma cells, fibroblastic-type cells and macrophages, either perivascular or diffuse, occurred in 49% of patients of one series [2], but there was no correlation with serum serological abnormalities. Electron microscopy has shown that both T and B lymphocytes are present in the infiltrates [3], although most are activated helper T cells. Hyalinization and intimal thickening of the blood vessels may occur, but fibrinoid change is uncommon. Evidence from electron microscopy [4] and the normal distribution of cutaneous enzymes, acid mucopolysaccharides and other ground substances, together with the absence of any abnormal gammaglobulin, fibrinogen or albumin, using fluorescent antibody techniques, suggests that the alterations in dermal collagen are the result of a simple increase in the number of fibrils. Quantitatively increased fibrillogenesis, with an increased proportion of thin fibrils of type III collagen [5] in the dermis, has led some authors [6] to conclude that qualitative and quantitative disturbances in mesenchymal ground substances may play an important part in the increased formation of qualitatively normal collagen fibrils in scleroderma [7]. Further evidence that the ground substance is the tissue mainly involved has been provided by the finding of a normal concentration of water and hydroxyproline in the dermis [8]. Some authors believe that the main alterations in the skin in systemic sclerosis take place in the subcutaneous tissue and not in the dermis [9]. It is suggested that the replacement of subcutaneous tissue by connective tissue is the cause of the induration of the skin.

Histology, histochemistry, immunopathology and electron microscopy of depigmented areas of skin show changes similar to those found in vitiligo [10]. The digital vessels frequently show intimal and medial thickening, which may be so gross as to almost occlude the vessel (Fig. 56.57); this accounts in certain cases for gangrene of the fingers. Occasionally, fresh thromboses may be seen. Similar but less marked changes are found in the digital arteries of the toes, and the vessels of the leg may also show intimal thickening, which results in ischaemia and gangrene. The intimal thickening is very similar to that seen in the peripheral vascular obstruction that occurs in rheumatoid arthritis. Thromboses of major arteries can also occur [11], and reduction of local tissue fibrinolytic activity can be demonstrated in the involved vessels. Giant cell granulomatous necrosis of the intima of vessels and fat in nodular lesions of the skin has been described [12].

Immunoglobulins and complement may be demonstrated by fluorescent antibody techniques at the dermal–epidermal junction in telangiectases, but not in the indurated skin without telangiectasia [13]. Biopsies should not be taken from telangiectatic areas. The main immunohistological changes in the skin in systemic sclerosis consist of foci of intercollagenous staining for connective tissue antigens in the reticular layer of the dermis [14]. The absence of immunoglobulin and complement from the dermal–epidermal junction may be useful in distinguishing systemic sclerosis from SLE, in which the major changes are at the dermal–epidermal junction. Patients who have both systemic sclerosis and SLE have

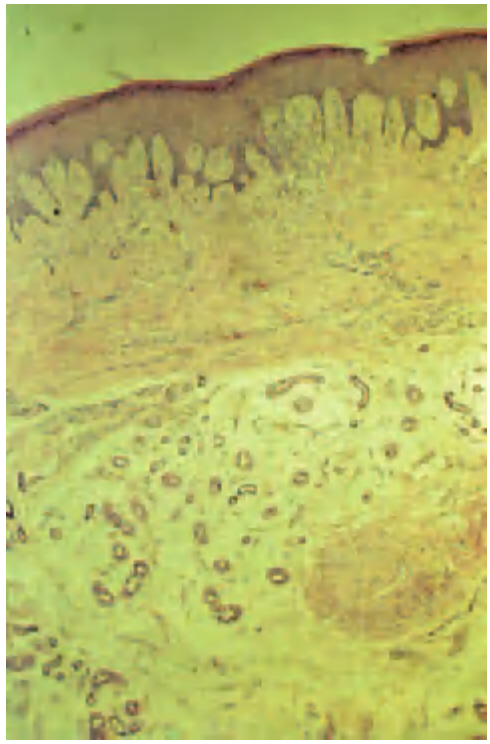

Fig. 56.57 Systemic sclerosis: section of finger showing thickened dermis with hyalinization of the collagen and almost complete occlusion of a digital vessel.

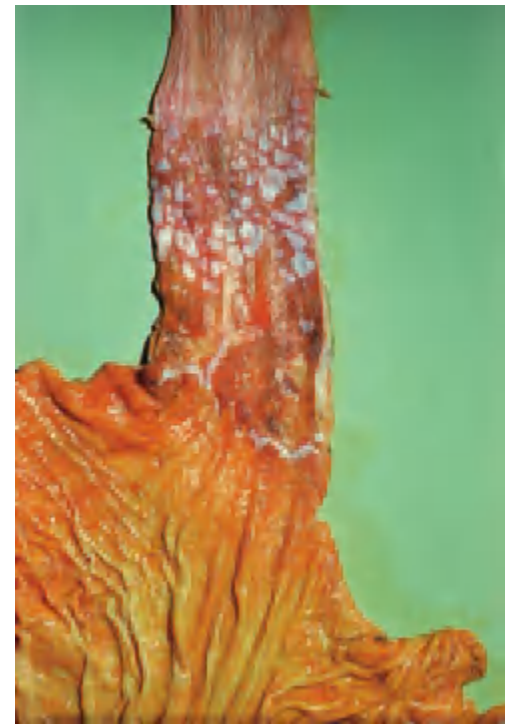

Fig. 56.58 Pearly white plaques in the oesophagus in systemic sclerosis, giving a cobblestone appearance.

deposits of immunoglobulin and complement at the dermal–epidermal junction in involved and uninvolved skin as well as changes in the dermal collagen. Patients with scleroderma as part of 'mixed connective tissue disease' have positive immunofluorescence at the dermal–epidermal junction [15].

The gastrointestinal tract is frequently involved. The oesophagus may show areas of epithelium looking like pearly white plaques, giving a cobblestone appearance (Fig. 56.58). Microscopically, subepithelial fibrosis is the most common finding, but fibrosis may also occur in areas of muscular atrophy. The smaller arteries may show endarteritis, and some cellular infiltration also occurs. In the duodenum, jejunum, ileum and colon there is a patchy disappearance of muscle, especially of the circular layer, with replacement by fibrous tissue. The subserosal and submucosal tissues may also be thickened and fibrosed. Vessels in these areas may show sclerosis and intimal fibrosis.

Pathological changes in the lungs may be seen, even in the absence of symptoms or radiological signs of pulmonary involvement and even in the presence of normal pulmonary function. Progressive diffuse alveolar fibrosis occurs with obliteration of capillaries and alveolar spaces, but is preceded by an inflammatory alveolitis [16,17]. In other cases, hyaline degeneration and fibrosis of alveolar walls result in the disappearance of the alveolar parenchyma and of the capillaries. Rupture of the thinned alveolar walls gives rise to cysts that are lined by cuboidal or columnar epithelium, which may be ciliated. Electron microscopy [18] may show thickening of the alveolar–capillary basement membrane. Arterial lesions in the lungs take the form of concentric thickening of the intima by loose myxomatous tissue and, later, sclerosis. In certain cases, the vessels may be almost completely occluded. Neoplastic change is a rare complication of the pulmonary abnormalities in systemic sclerosis. Various types of neoplasm have been reported [19,20], including malignant pulmonary adenomatosis, alveolar cell carcinoma, adenocarcinoma, oat cell carcinoma and squamous cell carcinoma.

The heart may show no change macroscopically, although showing widespread histological changes. The major coronary arteries are usually patent. Pericarditis, sometimes with effusion, is not uncommon, and sometimes the myocardium shows considerable streaky or focal fibrosis. Occasionally, the mitral or tricuspid valve is involved [21], and Libman–Sacks type of non-bacterial endocarditis has been reported [22]. Histologically, the myocardium may show focal or diffuse fibrosis, associated with degeneration or atrophy of some of the muscle fibres. Occasionally, smaller arteries and arterioles show thickening of the walls. Sometimes, an aneurysm of the myocardial wall develops, and the aorta may show

adventitial fibrosis with a focal necrotizing panaortitis and valvulitis.

Involvement of the kidneys used to be the most common cause of serious morbidity and mortality, but this is now uncommon, probably because of the early and improved control of hypertension. In one of the first pathological studies, renal lesions were found in 74% of patients at autopsy [23], and in 90% in another series [24]. It has been suggested [25] that a triad of intimal proliferation of the small intralobular arteries and arterioles, fibrinoid necrosis of the walls of the afferent arterioles and sometimes the glomerular loops, together with cortical infarction characterizes renal lesions in systemic sclerosis. Vascular luminal occlusion may occur, particularly in patients with renal crisis [26]. These changes are not always found, and there are probably no absolutely specific features. Other changes include a mucoid appearance of the intimal thickening of the proximal part of the intralobular arteries. Hypercellularity of the glomeruli and fibrinoid necrosis of the basement membrane of the glomerular tufts may be found. The tubules may be atrophic and surrounded by increased connective tissue, or be dilated and full of hyaline eosinophilic material. A hyaline droplet nephrosis may occur. In the more chronic cases, glomerular hyalinization and interstitial fibrosis predominate. Immunohistological techniques [27] show thickening of the glomerular capillary basement membrane and alteration in the reticular tissue of arterioles associated with deposits of fibrin and very occasionally with the presence of IgG and C3.

The liver is usually normal in systemic sclerosis, although mild fibrosis of the portal tracts and around the bile ducts can occur. The gall bladder may be fibrosed. The spleen may show fibrinoid necrosis of arterioles and endarteritis obliterans, and endarteritis is also found in the adrenals, mammary glands, pancreas, uterus and ovaries.

Histological changes in the muscles are similar to, if not identical with those of dermatomyositis. Muscle fibres show varying degrees of degeneration, such as loss of cross-striations, hyalinization of bundles, vacuolation and splitting, with interstitial and focal infiltration of lymphocytes. Later, sclerosis develops and the vessel walls may be thickened. There may also be some thickening of the endomysium and perimysium. The thyroid [28] and parathyroid [29] glands may be involved in the fibrotic process, and the thymus may show cortical atrophy [30].

Widening of, and vascular changes in the periodontal membrane of the teeth occur.

The CNS is rarely involved, but occasionally there may be thickening of the walls of vessels in the white matter, and meningeal lymphocytic or granulomatous infiltrates. Peripheral neurological involvement is characterized by increased collagen deposition in the epi- and perineuria, and intimal thickening of the vasa nervorum [31].

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Natural history. In the majority of patients, the onset is with Raynaud's phenomenon, although this may have been present for many years, and the cutaneous changes occur after an interval. This is much shorter in males—in whom it is usually under a year—than in females, in whom it is usually approximately 5 years, but may be as long as 30 years [1]. Occasionally, Raynaud's phenomenon and cutaneous sclerosis are noticed at the same time, and sometimes Raynaud's phenomenon may follow the onset of cutaneous or other manifestations, or be absent. The risk of anyone with Raynaud's phenomenon developing systemic sclerosis is relatively small, although it seems to be greater in males than in females [2]. Sclerodactyly may be found in approximately 10% of patients with Raynaud's disease, but systemic sclerosis occurs in approximately 4% of patients with this combination [3]. The differentiation between severe Raynaud's disease and early systemic sclerosis is difficult, but may be aided by nail fold capillaroscopy and the presence or absence of autoantibody [2]. The main cause of mortality used to be renal disease, but recent studies show a preponderance of cardiovascular problems, with coronary and cerebrovascular events [4]. In addition to the microvascular changes described, it is now apparent that large vessel changes similar to atherosclerosis are also increased in systemic sclerosis [5].

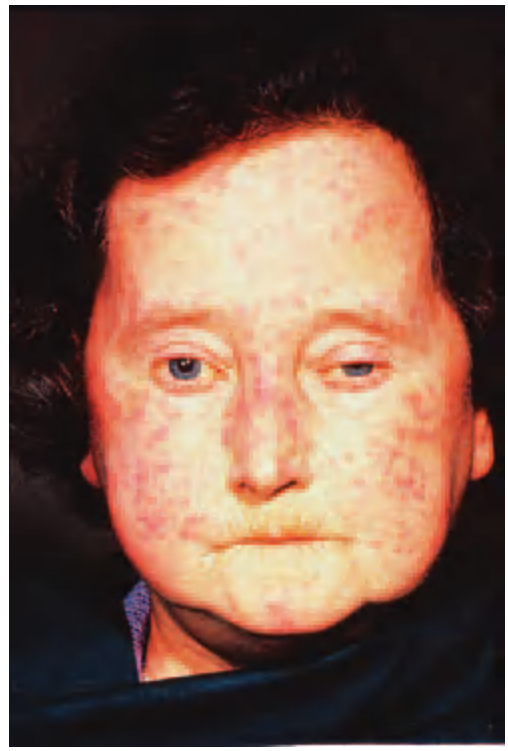

Fig. 56.59 Systemic sclerosis: typical beaked nose, telangiectasia and radial furrowing round the mouth.

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Clinical features. The earliest feature is usually, but not invariably, Raynaud's phenomenon. Other early presenting symptoms and signs include swelling of the hands in approximately 15% of patients, swelling of joints, ulceration of the fingers, whitlows and even gangrene. Occasionally, the diagnosis may be made in a patient presenting with leg ulcers or calcinosis cutis. With the increased availability of laser treatments, some patients' first presentation is for treatment of telangiectasia. Less common early symptoms include gastro-oesophageal reflux and dysphagia; constipation, diarrhoea and abdominal pain are usually late features.

Cutaneous changes. The hands and face are the most frequently involved, but the changes may extend proximally to involve the forearms and upper arms, usually but not always in a continuous fashion. The fingers may be oedematous and swollen, and the skin feels tight and has a shiny appearance. With increasing severity, the skin becomes immovable or hidebound. The clinical impression of thickness and toughness of the skin is enhanced because of binding down of the skin to deeper structures. The collagen content is decreased but the density is normal [1]. Sometimes, the chest becomes tight, shiny and pigmented. The facial appearance in a well-developed case is characteristic. The forehead is smooth and shiny, the skin is bound down and hard, the lines of expression are smoothed out and the nose becomes small and pinched (Fig. 56.59). The mouth opening is constricted and radial furrows appear, giving a pursed appearance (Fig. 56.60). The lower eyelids cannot be depressed by the fingers to show the conjunctivae, because of atrophy of the tissues. Very rarely, periorbital oedema can occur [2]. Small matlike telangiectases are frequently found on the face. Sometimes, the changes on the face are minimal and detected only by an astute observer after the diagnosis has been suspected because of other changes. Mandibular atrophy can occur (Fig. 56.61). Chondrodermatitis nodularis helicis was found in three of 21 patients with limited cutaneous disease [3].

Just as the face may be involved to a greater or lesser extent, the hands may also show great variability in their appearance (Fig. 56.62). Sometimes, in the early stages, only a little atrophy can be seen. Occasionally, the fingers and hands are swollen and rather tumid, and there is

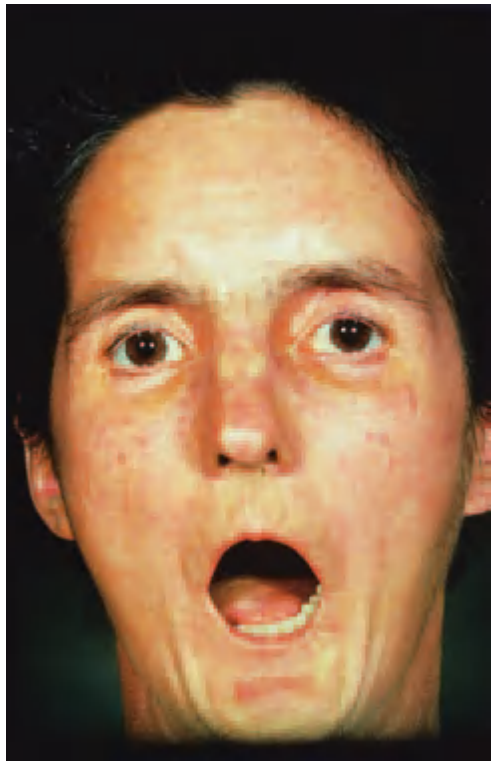

Fig. 56.60 Systemic sclerosis: restricted mouth opening.

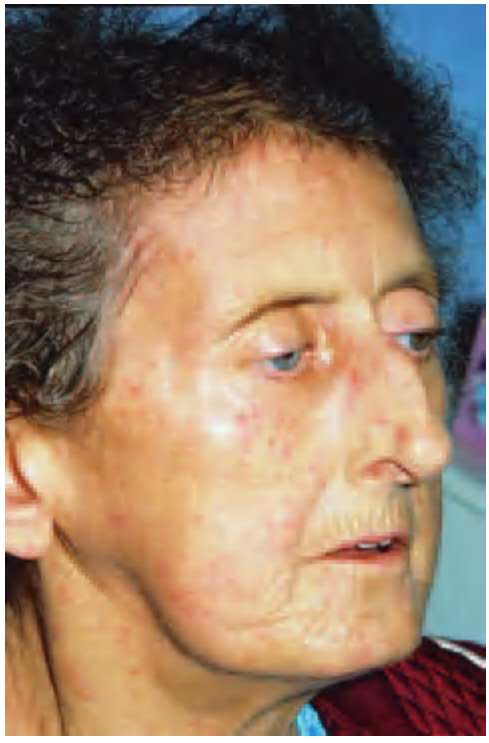

Fig. 56.61 Systemic sclerosis: mandibular atrophy. (Courtesy of Dr J. Cotterill, Leeds, UK.)

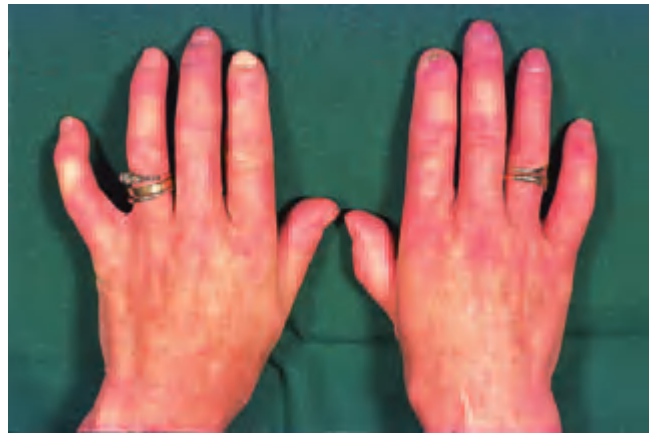

Fig. 56.62 The hands in systemic sclerosis: oedematous phase.

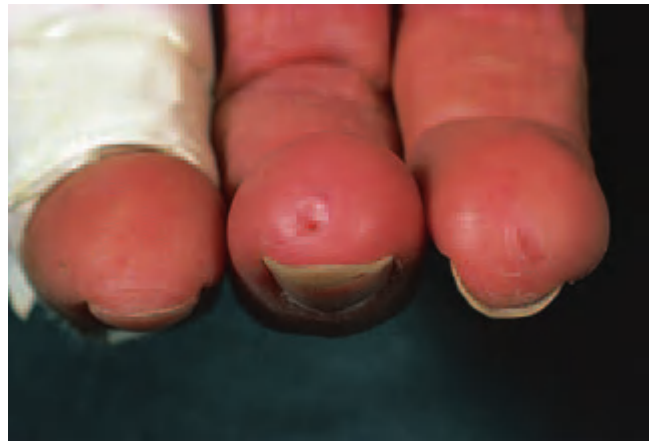

Fig. 56.63 Systemic sclerosis: healed ulceration of the fingertips.

difficulty obtaining full extension. The terminal phalanges may be bulbous. Later, however, the changes are easily recognized. Atrophy occurs first in the pulps of the fingers, and small painful ulcers are formed, which heal leaving depressed scars (Fig. 56.63). Pitted scars occur in over one-third of patients, not only on the tips of the fingers but also in a linear distribution on the ulnar border of the thumb and radial borders of the index and middle fingers, as well as the dorsa of the fingers over the joints [4]. Later, sclerosis of the overlying skin of the fingers develops, giving the fingers a smooth shiny tapered appearance, with the nails curving over the atrophic phalanges. Later still, the nails become very small and the whole of the distal part of the finger atrophies. The nail folds may show ragged cuticles. Pterygium inversum unguis-like changes are sometimes found [5]. Slow-healing whitlows and paronychia are common, and ulcers may also occur over the knuckles. Later, the atrophy and sclerosis extends to involve the whole hand, which is held in semi-flexion, full extension of the fingers and metacarpal joints being impossible. Gangrene of the fingers is not uncommon, and

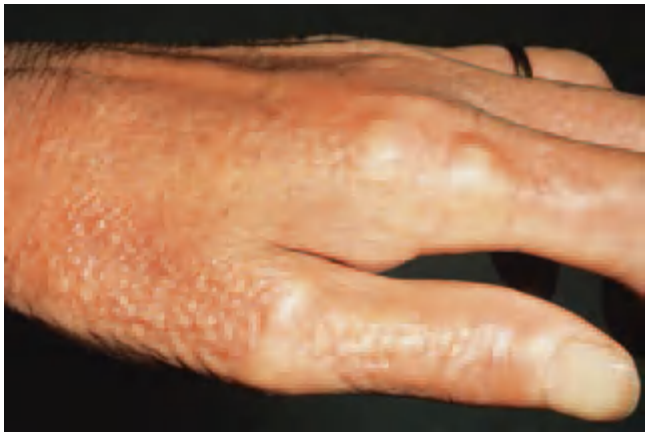

Fig. 56.64 Systemic sclerosis: 'cobblestone' appearance on the dorsum of the hand.

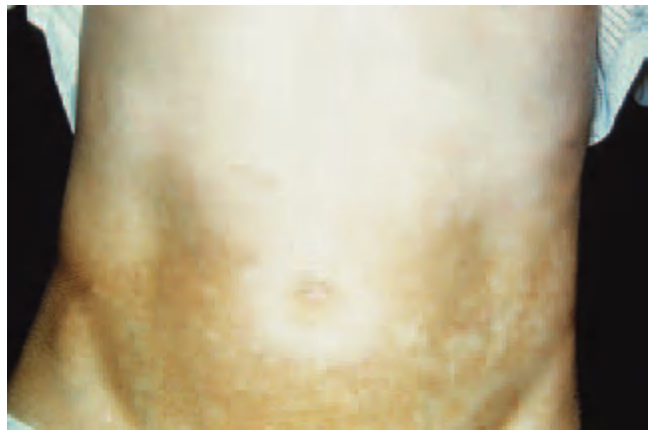

Fig. 56.65 Systemic sclerosis: pigmentation of the abdomen.

may occur surprisingly early in the disease. It does not necessarily indicate a poor prognosis. Digital arteriography confirms narrowing of the digital arteries [6].

Telangiectases are often found on the palms and on the rest of the hands. Calcium deposits occur in the skin of the fingers and hands, and may break down to discharge chalky material. Calcinosis may also be found around the elbow, where the olecranon bursa may be involved. Erythema may be seen on the thenar and hypothenar eminences. Hyperkeratotic plaques over the phalanges may indicate amyloid material deposited in the dermal papillae [7]. Multiple small papules of lymphangiectasia may occur in 'hidebound' skin because of obstruction of lymphatic channels by the sclerosing process (Fig. 56.64) [8]. Ivory-coloured subcutaneous nodules 3–20 mm in diameter occur rarely on the trunk and limbs. Histology shows fibromatous changes [9] or fibrinoid necrosis [10].

Similar, although less severe changes occur on the feet, and not infrequently the tips of the toes become black with incipient gangrene. The feet become encased in tight firm skin with mottled patches of pigmentation and atrophy. These changes may extend up the legs and be present on the thighs.

In a series of patients at Leeds, changes on the hands occurred in 95% of cases, on the face in 90%, beneath the clavicles in 30% and on the feet in 15%. The changes on the face, hands and feet tend to be progressive, but changes on the trunk have been seen to regress over the years. Dilated nail fold capillaries visible without a lens occur in approximately 10% of patients and, occasionally, heliotrope cyanosis around the eye suggests a diagnosis of dermatomyositis. There is some evidence that the degree of nail fold capillary dilatation correlates with the severity of organ involvement [11], but this has not been confirmed [12]. Nail fold capillary abnormalities have been correlated with Raynaud's phenomenon, digital pitted scars and low finger temperature [13]. Using wide-field microscopy, the capillaries are enlarged and distorted. There is loss of capillaries with disruption of the capillary bed in approximately 90% of patients. These features may indicate those patients with Raynaud's phenomenon who will go on to develop systemic sclerosis [14,15], but do not distinguish between different connective tissue diseases [16]. Transient nodules resembling erythema nodosum occasionally occur; the histology of these shows panniculitis and endarteritis.

Telangiectases varying from 2 to 20 mm in diameter, blanching on pressure and refilling from several different foci, occur in 75% of patients. They are found mainly on the face, lips, mouth, upper trunk and hands, but may extend as far as the upper thighs. These mat-like telangiectases are not absolutely diagnostic of systemic sclerosis. Pigmentation occurs in approximately 50% of the patients, most frequently on the face, and to a lesser extent on the legs, thighs, lower abdomen (Fig. 56.65), axillary folds and dorsa of the hands. Occasionally, the pigmentation is so gross as to lead to a suspicion of Addison's disease [17], and sometimes gives a mottled appearances. Dense warty pigmentation in the axillae can resemble acanthosis nigricans [18]. Leg ulcers occur in 40% of patients and are difficult to heal. Livedo reticularis [19] and small white areas of atrophie blanche develop around the ankles, even without ulceration. These features can occur in patients without hypertension. A case has been reported of large soft cystic lesions over the interphalangeal joints of both hands. Aspiration revealed mucoid material, and the histology suggested focal mucinosis [20]. Rarely, papular and nodular mucinosis may occur and may be a presenting feature [21]. Lesions resembling acrokeratoelastoidosis have been described [22].

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Systemic sclerosis without skin involvement [1–4]. Although skin lesions and Raynaud's phenomenon usually precede systemic changes, there is no doubt that occasionally the situation is reversed. In these cases, diagnosis may be difficult until the disease has progressed further to give characteristic changes in other organs.

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Calcinosis. Weber [1] described calcinosis in scleroderma long before Thibierge and Weissenbach [2], whose names are usually associated with the syndrome. Calcification in systemic sclerosis occurs most commonly (25%) in the fingers, especially on the palmar aspects of the terminal phalanges. It is less common than absorption of the phalanges, but sometimes occurs in the absence of any radiological bone change. Digital calcification is approximately 10 times as common in females as in males. Calcification also occurs in the soft tissues around the iliac crests, alongside the spine between the vertebrae, around the knees, on the dorsa of the feet and around the elbows. Occasionally, ulceration of superficial nodules occurs, with discharge of chalky material. Deposits tend to be of considerable size and less diffuse than the calcification seen in the muscles of healed dermatomyositis. Calcification may occur in the internal organs. A suggestion that warfarin may inhibit and reverse calcification requires confirmation [3].

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Bone changes. Absorption of the terminal phalanges is a feature of both systemic sclerosis and Raynaud's phenomenon, but systemic sclerosis is the only condition in which phalangeal absorption is associated with calcinosis (Fig. 56.66) [1]. Approximately 70% of patients show absorption, which may be minimal and only involve one terminal phalanx, or be gross and involve several phalanges, including the middle or even proximal phalanges. An erosive arthropathy, with 'pestle and mortar' deformity of the distal interphalangeal joints, resembles that seen

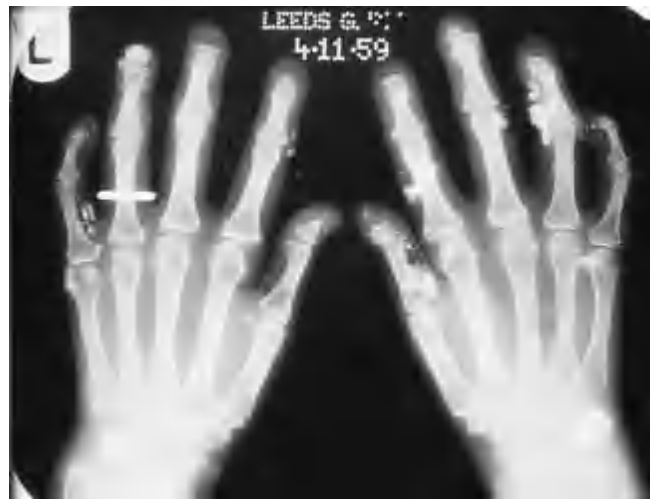

Fig. 56.66 Systemic sclerosis: terminal absorption of the phalanges and calcinosis.

in psoriatic arthropathy [2]. It must also be distinguished from gouty arthritis [3]. Pain in the temporomandibular area and a grinding sensation on chewing may be associated with bone resorption of the angle of the mandible [4] and zygomatic arches [5]. Other bone changes in systemic sclerosis include an increased intraosseous deposition of calcium [6,7] and osteopoikilosis, a rare condition in which multiple small islands of dense bone occur at the epiphyses and metaphyses [8–10]. Osteolysis also occurs in the distal end of the radius and ulna, humerus [11], acromioclavicular joint, ribs and cervical spine [12]. Avascular necrosis of the head of the femur, presumably resulting from vasculitis, has been described [13,14].

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Pulmonary involvement. Lung involvment predominantly represents diffuse pulmonary fibrosis associated with diffuse disease or pulmonary hypertension, which is more associated with limited disease or CREST syndrome [1]. Symptoms may develop only some time after the lung disease, so they are a poor predictor of lung involvment. Dyspnoea on exertion is usually the first symptom, and this may progress until the patient is distressed even at rest. Cough, usually without sputum, is also a common symptom, and may be troublesome at night, suggesting aspiration; haemoptysis is rare. Cyanosis and occasionally finger clubbing may occur in patients with severe involvement, and these signs may indicate cor pulmonale. Recurrent episodes of pneumothorax, pleurisy, pulmonary effusion and pneumonia are less common features. Considerable loss of weight may also be a prominent feature at this stage. The earliest change consists of diffuse reticular shadowing extending from the cardiac borders to the peripheral and basal parts of the lungs, usually in the lower lung fields. Sometimes, nodular changes are seen, and occasionally the apices are involved (Fig. 56.67). Cystic changes are frequent. The cysts are usually small, but if extensive the appearances are those of 'honeycomb lung'. Pneumothorax may occur [2]. Pulmonary calcification has rarely been reported [3,4], as has telangiectasia [5].

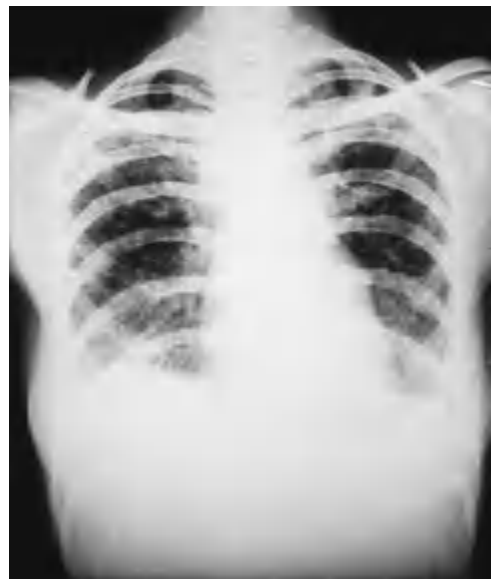

Fig. 56.67 Pulmonary involvement in systemic sclerosis: nodules are prominent, particularly in the upper zones, and there is some reticulation in the lower zones.

Pulmonary function is frequently abnormal when radiology shows no abnormality [6]. A sensitive test of pulmonary function is the estimation of diffusing capacity (transfer factor); this test is impaired in 75% of patients. The DL_{co} may give an indication of survival, if it is less than 40% there is a 10% 5-year survival, compared with 75% if it is greater than 40%. Pulmonary involvement is more frequent in more severe and rapidly progressing disease, especially in males [7], but occurs in the CREST syndrome [8], and may precede cutaneous changes [9]. The presence of antihistone and antitopoisomerase (Scl-70) are associated with pulmonary fibrosis [10]. Small-airway disease may precede measurable impairment of gas diffusion [11]. In severely affected cases, the vital capacity and maximum breathing capacity are both abnormal. Serial observations of pulmonary function may be helpful [12]. Pulmonary hypertension, sometimes severe, can occur, and does not necessarily correlate with tests of pulmonary function [1]. It is not yet possible to say whether impairment of pulmonary diffusion is caused by vascular changes or thickening of the alveolar wall and interstitial tissue. Pulmonary hypertension tends to be progressive and fatal, although new therapeutic options are available.

Lung radiography may be normal in the face of symptoms and abnormal lung function, so the investigation of choice for pulmonary fibrosis is high-resolution CT scan, which is non-invasive. One series showed that high-resolution CT was 24% more accurate than radiography in demonstrating minimal evidence of fibrosing alveolitis [13]. The role of bronchoalveolar lavage is still debatable, but in expert centres it may provide additional information.

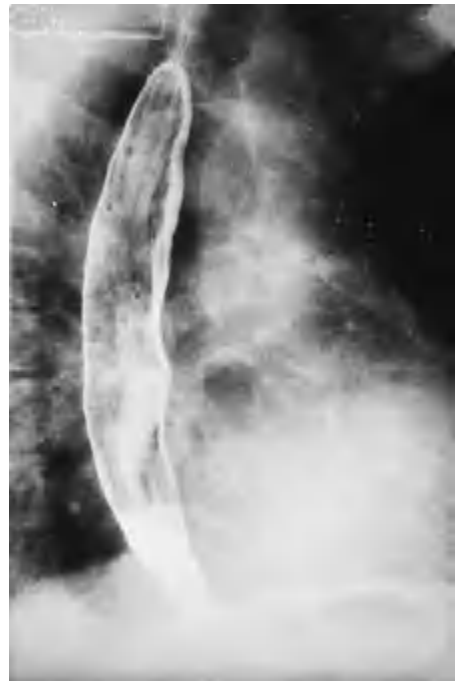

Fig. 56.68 The typical atonic dilated air-containing oesophagus in systemic sclerosis.

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Involvement of the gastrointestinal tract. Macroglossia has been reported [1]. The oesophagus is involved in approximately 75% of all patients and is the most frequent part of the gastrointestinal tract to be affected. Oesophageal manometry and radionuclide transit are better than radiography for showing motor abnormalities [2,3], although the changes are non-specific [4]. Although dysphagia is usually regarded as being the predominant symptom, this is not correct, as symptoms of oesophageal reflux are twice as common. The typical radiological appearance is that of an atonic dilated oesophagus, which contains air in the resting state (Fig. 56.68). Oesophageal dilatation and abnormal peristalsis do not necessarily occur together. Stricture of the lower end of the oesophagus occurs in just over 10% of patients, is not necessarily related to gastro-oesophageal reflux or hernia, and can occur without any symptoms of dysphagia. Dysphagia is much more commonly the result of loss of propulsive activity in the oesophagus, and may occasionally be related to candidal overgrowth [5]. Hiatus hernia occurs in approximately 25% of patients. It is important to remember that approximately four out of every 10 patients with radiological changes have no symptoms. Carcinoma of the oesophagus has been reported [6,7]. Occasionally, dysphagia may be localized to the neck because of thickening of the pharyngo-oesophageal muscles [8].

Oesophageal aperistalsis has been reported in SLE and Raynaud's syndrome [9,10], but whenever aperistalsis is found systemic sclerosis must be suspected. Diffuse spasm may be detected by oesophageal manometry in approximately 5% of patients with systemic sclerosis [11].

The stomach shows dilatation and lack of peristalsis in approximately 6% of cases. Involvement of the stomach may be more common in Asians [12]. Carcinoma of the stomach has been reported [13]. Bleeding can occur from telangiectasia in all parts of the gastrointestinal tract, especially the stomach [14]. Systemic sclerosis is one cause of gastric antral vascular ectasia—the so-called watermelon stomach, because of the striped appearance on endoscopy. Gastric bleeding may occur at any time and may precede other signs of systemic sclerosis [15].

The duodenum shows changes of dilatation and lack of peristalsis in approximately one-third of patients. This does not appear to be a result of excess collagen deposition [16]. The changes are most pronounced in the second and third parts. Duodenal ulceration has been reported, but is probably not significant in comparison with its incidence in the normal population.

Intestinal involvement is infrequently noted in patients who have no relevant symptoms, but colicky abdominal pain and abdominal distension, with a pattern of distended loops visible through the abdominal wall, together with diarrhoea or, alternatively, constipation, may lead to a clinical diagnosis of obstruction, and death may follow from paralytic ileus. Volvulus of the small intestine may occur [17]. There may be bleeding from telangiectases. Radiological changes consist of dilated loops of bowel, with impairment of peristalsis and segments of normal or narrowed intestine. Strictures are rare. Jejunal sacculation has been reported [18,19]. Radiological changes occurred in approximately 10% of patients in the Leeds series, but others [20] found changes in 57%. Intestinal motility studies may be useful in determining changes in the small bowel [21]. If the abdomen is opened, distended loops of bowel may be seen showing a blue-grey serosal surface with numerous dilated lacteals. Small intestine involvement, determined by jejunal biopsy, small bowel radiology and tests for bacterial overgrowth and malabsorption, occurs in 55% of patients [18].

Steatorrhoea, malabsorption of glucose, calcium, vitamin B_{12} and folic acid may occasionally occur. It is important to remember that malabsorption of one or more of these substances may occur in the presence of normal fat absorption. Osteomalacia or skin changes have not been seen as the result of malabsorption. Excessive enteric loss of protein is sometimes a feature [22]. There is evidence [18] that bacterial overgrowth in the intestinal lumen as a result of stagnation because of abnormal peristalsis is a major cause of malabsorption in systemic sclerosis, and this may be corrected by therapy with tetracycline. Intestinal permeability is normal [23]. Pancreatic function is abnormal in 15% of cases [24], and death may occur from pancreatic necrosis [25].

Pneumatosis cystoides intestinalis may complicate small intestine involvement [26]. Patients present with recurrent acute or subacute intestinal obstruction [27] and rupture of cysts can cause pneumoperitoneum [28]. Treatment with respiration of high concentrations of oxygen has been successful [29].

The colon is frequently involved. In the Leeds series it occurred in 43% of cases. The patients may complain of constipation or diarrhoea. The most striking radiological change is the presence of wide-mouthed diverticula, best demonstrated on post-evacuation roentgenograms (Fig. 56.69). They usually occur on the inferior surface of the transverse colon and in the descending colon, which may be dilated and atonic; occasionally, the appearance may resemble that of ulcerative colitis [30]. Perforation of colonic diverticula [31] may result in death from peritonitis. Volvulus has been reported [32]. Colonic telangiectasia with consequent iron-deficiency anaemia may occur [33]. The mucosa of the colon has been described as being pale, dry and rather rigid on sigmoidoscopy [34], but this must be very uncommon. Anorectal pressure measurements show abnormal motility in 74% of patients [35]; symptoms are very much less common. Rectal prolapse and faecal incontinence may result. Primary exudative ascites has been reported [36].

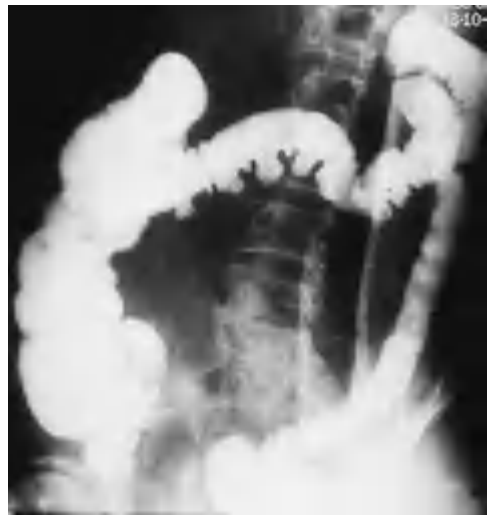

Fig. 56.69 Wide-mouthed diverticula of the colon in systemic sclerosis.

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Hepatic involvement. The liver is usually normal in systemic sclerosis, although cirrhosis and portal hypertension are occasionally found. It is by no means substantiated that such fibrosis is caused by systemic sclerosis. Bleeding from oesophageal varices may occur [1]. Systemic sclerosis has been reported in 17% of patients with primary biliary cirrhosis [2,3]. Ascites can occur without liver disease [4].

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Cardiac involvement [1,2]. The resting ECG is abnormal in approximately 50% of cases, and cold-induced changes also occur [3]; however, the changes may be the result of other causes. Abnormalities of rhythm occur and these include paroxysmal atrial tachycardia, atrial fibrillation and flutter. Partial or complete heart block is not uncommon. In addition to abnormalities of rhythm, ECG may show bifid P waves and T-wave changes, indicating atrial or ventricular myocardial involvement. The conduction system seems to be relatively spared in systemic sclerosis and the high incidence of conduction disturbances may be the consequence of damage to the working myocardium [4]. Dyspnoea may be present but pain in the chest is not a prominent feature. Pericardial involvement occurs and is usually asymptomatic [5]. Mitral valve prolapse occurs more frequently in a number of connective tissue diseases, including systemic sclerosis, than in normal controls [6]. Other valvular abnormalities are rare [7]. Coronary reserve is reduced [8]. General enlargement of the heart, left-ventricular hypertrophy or a triangular outline are the most frequent radiological abnormalities. Radionuclide scanning [9], echocardiography [10], and 24-h ECG monitoring [11] are useful in the detection of abnormalities of the myocardium.

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Renal involvement. Pathological changes in the kidney used to lead frequently to serious clinical problems, but the management of hypertension, and in particular the introduction of modern drugs such as inhibitors of angiotensin-converting enzyme (ACE), have revolutionized this aspect of the disease. Slight proteinuria is considered to be the most common clinical feature, often early in the disease. Proteinuria occurred in 36%, hypertension in 24%, azotaemia in 19% and malignant hypertension in 7% of one series [1]. One or more markers were found in 45% of patients. Approximately 40% of patients show dis-

turbances of creatinine clearance. Nephrotic syndrome is increasingly rare [2]. Approximately 8% of patients with renal involvement develop malignant hypertension [3]. This may develop rapidly in the course of a few weeks, with headaches, nausea, vomiting and deterioration of vision in a patient whose renal function has previously been normal. Prior to 1971, survival beyond 1 year was unusual, the usual survival being 1–3 months. The prognosis, even with renal crisis, has improved dramatically since the introduction of ACE inhibitors (see p. 56.114). Although renal involvement has an adverse effect on survival in systemic sclerosis, patients with mild impairment of renal function may live for years.

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Muscle involvement [1,2]. Muscle weakness may occur, and differentiation from dermatomyositis may be difficult, especially if there is a heliotrope appearance and oedema of the eyelids, and dilatation of the nail fold capillaries. In one series [3], the two diseases could not be distinguished in 36 of 727 patients. Muscles of the forearms and hands are affected as well as the proximal muscles. Creatine phosphokinase elevation and excessive creatinuria correlate well with muscle weakness. Electromyography is abnormal in 50% of patients early in the disease and in 93% in late stages [4], and histological changes are present in approximately 40%. MRI and spectroscopy can be useful non-invasive monitors of disease activity [5]. There does not appear to be any evidence that systemic sclerosis occurs as a cutaneous marker of internal malignancy, although carcinoma of the lung may develop in patients with pulmonary involvement [6].

Tendon involvement. Leathery, palpable and audible friction rubs occur over the limbs and tendons [7] in approximately 25% of cases. Rupture of the extensor tendons of the hand has been reported [8]. The tendon was infiltrated with amyloid.

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Joint involvement [1–3]. Arthritic pain is not uncommon in the early stages of systemic sclerosis, and sometimes rheumatoid arthritis is the initial diagnosis made. Radiological changes indistinguishable from rheumatoid arthritis occur, especially in the hands, but there are no specific changes ascribable to systemic sclerosis. They include periarticular osteoporosis, joint-space narrowing, erosions and, rarely, avascular necrosis [4], erosions of long bones [5], bone ankylosis [6] and erosive osteoarthritis.

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Dental changes (see Chapter 66) [1]. Widening of the periodontal membrane because of fibrosis, with thickening of the vessel walls, occurs in approximately 30% of cases (Fig. 56.70). Usually the whole root is involved. Anterior

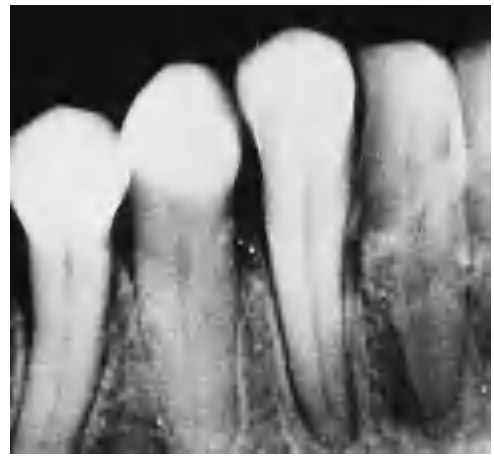

Fig. 56.70 Widening of the periodontal membrane in systemic sclerosis.

as well as posterior teeth are affected, and the lamina dura may or may not be abnormal. Thickening of the periodontal membrane is not related to the duration of Raynaud's phenomenon, calcinosis, involvement of internal organs, antinuclear factor or prognosis. Thickening of the periodontal membrane is not diagnostic of systemic sclerosis and is also found in periapical infection. Widening of the periodontal membrane in only one tooth is usually a result of such infection.

Osteolysis of the mandibular angle and coronoid process occurs with equal frequency [2], and these osteolytic areas may fracture [3]. A patient who had multiple external and internal root resorptions for which all the teeth were removed was successfully treated with osseointegrated implants [4].

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Central nervous system [1,2]. The nervous system is involved in fewer than 10% of cases [3], although asymptomatic involvement may be more common [4], and others have found involvement in 40% of patients, which can be associated with ulceration of the skin [5]. Neuropathy has been reported [6,7]: autonomic neuropathy may not be uncommon [8,9]; trigeminal neuropathy presents with numbness and pain in the face [10], and occurs in 4% of patients [11]. Of 22 cases with chronic trigeminal sensory neuropathy, nine had systemic sclerosis [12]. It is unilateral at first but later becomes bilateral. Other cranial nerves may be involved [13]. Carpal tunnel syndrome and meralgia paraesthetica may occur. Local anaesthetics may have an abnormally prolonged action [1]. Subacute combined degeneration is the result of vitamin B_{12} deficiency caused by malabsorption secondary to involvement of the small intestine by systemic sclerosis [14]. Spinal cord compression may occur because of soft-tissue calcification [15]. The EEG is not specific. Sensory chronaxia is prolonged in both abnormal and normal skin. Such prolongation in normal skin does not occur in any other condition apart from tabes dorsalis [16]. Impotence has been reported as an initial manifestation of the disease [17,18].

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Eye changes. Tightness of the lids, diminished tear secretion, keratoconjunctivitis sicca and shallow fornices are specific ophthalmic changes [1]. Sjögren's syndrome occurs in 15% of cases. Retinopathy, with haemorrhages, exudates and cytoid bodies may occur with a relatively low blood pressure, and has been attributed to direct vascular involvement by systemic sclerosis [2]. Fluorescein angiography shows vascular abnormalities in the choroid in 50% and in the retina in 10% of patients [3]. Central retinal vein occlusion has been reported [4].

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Laboratory investigations. Anaemia may be found in patients with renal failure, gastrointestinal bleeding or malabsorption. The ESR is raised in approximately half of patients, as is the serum globulin level. Elevation of gammaglobulin occurs more frequently than elevation of α_2-globulin. Other acute-phase reactants are usually normal, although there are defects in the acute-phase response

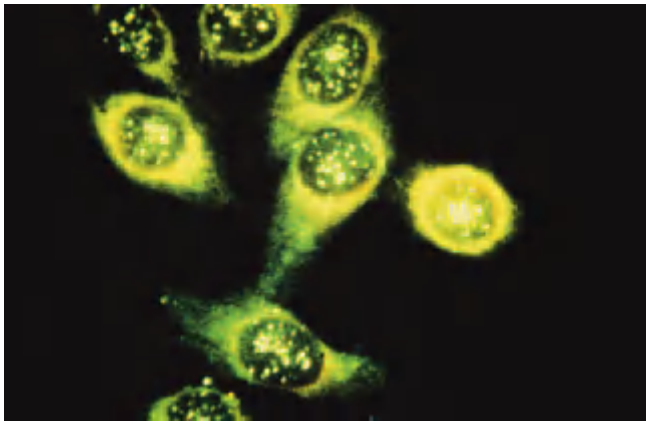

Fig. 56.71 Anticentromere antibody demonstrated on Hep-2 cells.

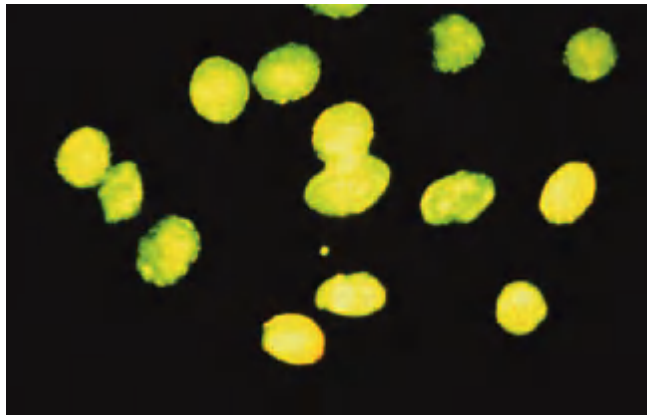

Fig. 56.72 Scl-70 antibody demonstrated on Hep-2 cells.

to some stimuli [1]. False-positive serology occurs in approximately 5%. Cold agglutinins may be found in 25% of cases. The Coombs' test is usually negative, although Coombs'-positive haemolytic anaemia and pancytopenia have been reported [2]. Circulating anticoagulant has been demonstrated in one case [3], but was not found in 24 patients at Leeds [4]. Anticardiolipin antibodies are found in 25% of cases overall, and occur more frequently in those severely affected [5]. Cryoglobulins are only rarely detected. Cryofibrinogenaemia has been held responsible for ulceration and gangrene of the fingers in some cases. Rheumatoid factor is present in approximately 30% of patients. Serum complement levels are usually normal. LE cells may be demonstrated in 8% of patients. Sometimes, SLE may occur in association with systemic sclerosis [6,7], but the presence of LE cells in systemic sclerosis does not necessarily imply coexistent SLE. Antinuclear antibodies have been demonstrated in 78% of patients using rat liver [8], and in 97% using Hep-2 cells [9] as substrate. Using Hep-2 cells, both speckled and homogeneous types occur, and nucleolar patterns—speckled, homogeneous and clumpy—are demonstrated more frequently than in other diseases. Centromere staining, resulting from an antibody that reacts with the kinetocore of metaphase chromosomes, occurs in 40–70% of milder (or CREST) cases [9,10] who have longer duration of disease and little renal involvement (Fig. 56.71). Anticentromere antibodies may be present in patients with Raynaud's phenomenon before the clinical features of systemic sclerosis appear. They seem to be indicative of a favourable prognosis [11]. They also occur in 6% of patients with SLE (including drug-induced lupus) [12], 6% of patients with mixed connective tissue disease, 17% of patients with primary biliary cirrhosis and systemic sclerosis [13], 11% of patients with primary biliary cirrhosis alone and 5% of patients with morphoea [14]. A diffuse 'frosted glass' staining of nuclei of Hep-2 cells is caused by Scl-70 antibody, a precipitating antibody to topoisomerase I, which is unique to systemic sclerosis and occurs in approximately 20% of patients, particularly those with lung involvement (Fig. 56.72) [10,15]. Higher frequencies are described, even in patients with acrosclerosis alone [16]. Scl-70 and anticentromere antibody occur together in 5% of cases [17], but when occurring alone may define separate subsets of the disease. There is no relationship between Scl-70 and disease survival [18]. Scl-86 is a related antigen [19]. Other antibodies occur, presumably indicating immunological subsets, and include antibody to centriole [20,21], anti-Jo-1 [22] and anti-Ro/SS-A [23]. More intensive investigation of autoantibodies may reveal additional subsets of the disease [24]. Several patterns of nucleolar staining have been described [25]. A homogeneous pattern was associated with polymyositis/scleroderma overlap, a clumpy pattern with diffuse cutaneous systemic sclerosis and a speckled pattern with localized cutaneous systemic sclerosis. Anti-DNA antibodies are not found [26]. Anti-IgE antibodies occur [27]. Other precipitating antibodies to saline extracts of human tissue [8] may be found in 15% of patients. Anti-smooth-muscle and antiendothelial antibodies have been reported [28,29]. Antineutrophil cytoplasmic antibodies occur in 9% [30] and antihistone antibodies in 42% [31]. The latter was more frequent in patients with cardiac and renal involvement. Serum type III procollagen peptide concentrations are raised and reflect disease activity [32,33]. Urinary excretion of 5-hydroxyindole-acetic acid is normal, as is thyroid function.

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Variations. Patients with calcinosis, Raynaud's phenomenon, sclerodactyly and telangiectasia may form a separate entity known as CRST syndrome [1], or CREST syndrome if oesophageal (esophageal) involvement is included. This is unlikely to be a separate syndrome, distinct from systemic sclerosis [2]. The variability of expression and course of the authors' series of patients with systemic sclerosis suggests that this type of case is only a subgroup of systemic sclerosis. This has been confirmed by other workers [3,4]. However, the delineation of this group of patients emphasizes that the diagnosis of systemic sclerosis does not always imply such a poor prognosis as has hitherto been considered.

The suggestion that 'systemic scleroderma' should be divided into two groups—diffuse scleroderma and acrosclerosis—remains to be confirmed [5]. The former, a relatively small group, can be distinguished from acrosclerosis in that the sex distribution is equal, the age of onset is later, Raynaud's phenomenon is absent, cutaneous sclerosis is the usual presenting feature, the sclerosis of the skin is usually generalized rather than acral, and the course is more rapid and fulminating, with death in a few years. However, both types show similar visceral involvement and laboratory abnormalities, and some patients with acrosclerosis have a short course, and Raynaud's phenomenon is not invariable. Occasionally, acute diffuse scleroderma may be much more benign than expected [6]. These two groups are probably clinical variants of systemic sclerosis. A more recent attempt at subdivision of the disease into diffuse and localized forms has met with more agreement (see p. 56.95) [7].

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Systemic sclerosis in childhood. Systemic sclerosis occurs in childhood, and the clinical features resemble those seen in adult cases. Raynaud's phenomenon is less frequent and renal disease is rare [1]. The course of systemic sclerosis in childhood is said to be slower, and the disability and visceral involvement less severe than in adults [2], but fatal cases have been reported [3]. The problem has been reviewed in depth [4].

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Involvement of the genital tract [1]. Vaginal dryness, ulcerations and dyspareunia are significantly more frequent in patients with systemic sclerosis when compared with controls. Frequency of sexual intercourse and sexual satisfaction is decreased, and the menopause may be early.

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Pregnancy [1]. Systemic sclerosis usually remains unchanged during pregnancy, but postpartum renal failure and peripheral gangrene have been described [2]. Severe renal, pulmonary or cardiac disease in the mother may be an indication for termination of the pregnancy [3], and such complications may occur late in pregnancy. ACE inhibitors may be of value for hypertension in pregnancy, although there are potential risks to the fetus [4]. There is conflicting evidence regarding the incidence of abortion and stillbirth [5,6]. Fertility may be impaired.

In some cases, pregnancy seems to precipitate the disease.

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Associations. Sometimes, systemic sclerosis occurs in association with other conditions, particularly those considered to have some autoimmune features. Usually, it is possible to differentiate between the diseases, but occasionally there is clinical and immunological overlap. The relationship to SLE and dermatomyositis has already been mentioned. Immunohistology of involved and uninvolved skin is of value. Sjögren's syndrome, the most common features of which are dryness and atrophy of the conjunctiva, cornea and buccal mucosa, together with arthritis, occurs with systemic sclerosis in approximately 17–20% of patients [1,2], and resembles the primary form of Sjögren's syndrome [3]. Extensive investigation reveals at least one abnormal test of the sicca syndrome in all cases [4]. Salivary flow is normal, but deficient in IgA [5]. Antibodies to Ro and La are useful markers of the presence of Sjögren's syndrome in systemic sclerosis [6], occurring in 60% of cases [7]. Other muscle disorders that have been reported in association with systemic sclerosis include polymyositis [8], myasthenia gravis [9] and muscular dystrophy [10]. Pathological features of systemic sclerosis are sometimes found in patients with polyarteritis nodosa [11–13], but there is not the same clinical or immunological overlap as seen with SLE. Temporal arteritis has been reported [14,15], and the condition has also occurred with malignant atrophic papulosis (Degos' syndrome) [16], thrombophlebitis and cryofibrinogenaemia. The association with Hashimoto's thyroiditis is rare. Unsuspected hypothyroidism may occur [17]. Systemic sclerosis is one of the disorders that are sometimes associated with congenital agammaglobulinaemia and IgA deficiency [18]. It may occur with autoimmune haemolytic anaemia [19], autoimmune neutropenia [20], thrombocytopenic purpura [21], microangiopathic haemolytic anaemia [22], urticaria pigmentosa [23], pemphigus vulgaris [24], monoclonal gammopathy [25], primary biliary cirrhosis [26,27], nodular hyperplasia of the liver [28], coeliac disease [29], pseudoxanthoma elasticum [30], elastosis perforans serpiginosa [31], lymphoma [32] and multiple sclerosis [33]. Reversible myasthenia gravis may occur on treatment with penicillamine [34].

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Differential diagnosis. Well-developed cases of systemic sclerosis presenting with Raynaud's phenomenon and typical cutaneous changes on the face and hands are easy to recognize. Generalized morphoea may sometimes cause confusion. However, Raynaud's phenomenon is less common in the latter, and the distribution of the skin changes is different in so far as generalized morphoea involves the trunk, as well as the limbs. Systemic involvement is unusual, although not unknown, and the course is usually towards improvement over the years.

Localized morphoea should present little difficulty, although occasionally morphoeic patches may be seen in systemic sclerosis, and systemic lesions may occasionally be found in morphoea [1–3]. Sometimes, patients with localized morphoea may later develop systemic sclerosis. Morphoeic lesions were seen in 6.7% of Japanese patients with systemic sclerosis [4]. Patients with atrophoderma of Pasini and Pierini may progress to systemic sclerosis [5]. Acrosclerotic skin changes occasionally occur in SLE and dermatomyositis. Cold blue hands with inability to extend the fingers has been reported in bisalbuminaemia [6]. The pigmentation of systemic sclerosis may be confused with Addison's disease [7,8]. Cutaneous changes resembling systemic sclerosis have been reported in an unusual type of porphyria with features of erythropoietic protoporphyria and hepatic cutaneous porphyria [9]. A case of primary amyloidosis presenting as scleroderma has been described [10]. There is no Raynaud's phenomenon in familial sclerodactyly [11].

The stiff-skin syndrome [12] or congenital fascial dystrophy [13] is a rare condition presenting in childhood, in which stone-hard indurations of the fascia and dermal collagen occur. There is no systemic involvement, and the resulting disability is permanent. Patients with sclero-myxoedema—a variant of lichen myxoedematosus—may resemble systemic sclerosis but there is no Raynaud's phenomenon or systemic involvement apart from the characteristic slow paraprotein in the serum. The POEMS (*p*olyneuropathy, *o*rganomegaly, *e*ndocrinopathy, *M* protein, *s*kin changes) or Crow–Fukase syndrome also shows a monoclonal paraprotein among a large number of potential features, including diffuse hyperpigmentation, scleroderma, hypertrichosis and lymphadenopathy, as well as the features indicated by its acronym. Of these patients, 50% have multiple myeloma [14]. Differentiation from systemic sclerosis relies on the presence of neuropathy and gammopathy [15,16].

Raynaud's phenomenon, firmness of the skin of the fingers, radiological absorption of the terminal phalanges and thickening of the walls of dermal arteries occur in workers engaged in the polymerization of vinyl chloride (see p. 56.82). The cutaneous changes of systemic sclerosis may resemble acrogeria (see Chapter 46), but the latter dates from birth. The condition may have to be distinguished from leprosy if a peripheral neuropathy is present [17]. Up to 40% of insulin-dependent juvenile diabetics have contractures at the proximal interphalangeal joints, with thickening of the skin of the fingers (diabetic cheiroarthropathy) [18,19].

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Prognosis [1–3]. The prognosis for this disorder is variable. Some patients die within a year or two and others live for many years, even those whose course may initially have been rapid with gangrene of the extremities. Males have a poorer prognosis than females [2,3], although in a recent series [4] the reverse was true. Overall, there is a fourfold increase in mortality in patients with systemic sclerosis. Patients with extensive skin and visceral involvement have a poorer prognosis [5], as do approximately 20% with rapidly progressive disease [6]. Pulmonary involvement is permanent; patients with 60% or greater reduction in pulmonary diffusing capacity have a 5-year survival of less than 10% [7]. Renal involvement is also an adverse factor, although some patients live for years. Patients with telangiectases and calcinosis have the same prognosis as other patients. Those with changes confined to the hands have a good prognosis [8]. Five-year survival varies between series from 34 to 80%, the difference probably depending on the proportion of females. Cumulative survival rate in one series [9] was 80% at 2 years, 50% at 8.5 years and 30% at 12 years. There is no relation to the presence or type of antinuclear factor. Patients with depression of T cells and decreased cell-mediated immunity [10], and with histocompatibility type HLA-B8, appear to have extensive disease and a poor prognosis [11]. The usual causes of death are from intercurrent infection, respiratory failure, cardiac failure, renal failure sometimes with malignant hypertension, and perforation of the gastrointestinal tract. Occasionally, patients with pulmonary involvement develop carcinoma of the lung [12], but the association of isolated cases of carcinoma of the thyroid, ovary, cervix, brain, oesophagus, stomach, breast [13], lymphoma and leukaemia with systemic sclerosis may be fortuitous [14]. Occasionally, the two diseases occur simultaneously and a rare improvement of systemic sclerosis with treatment of the malignancy has been observed [15]. Localized radiotherapy for solid malignant tumours in patients with systemic sclerosis has been noted to exaggerate the cutaneous and internal fibrotic reaction in the irradiated areas [16].

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Treatment. Symptomatic management of the patient is very important. There is no specific treatment, and no therapy is known to alter the course of the disease. Corticosteroids in low dosage may give a feeling of increased well-being and reduction of articular symptoms, and in these cases maintenance on a low dosage of prednisolone, such as 5 mg once or twice daily, is justified. Larger dosage will be required for patients with associated LE. There is no evidence that corticosteroids retard the progress of the disease in any way, nor is there any real evidence that corticosteroids induce the onset of renal failure. Dexamethasone pulse therapy has been claimed to improve some patients [1]. It is important to advise the patient to keep as warm as possible, particularly in the winter months, and suitable work may have to be found

to allow this. A light job in a warm atmosphere is ideal, and it is important to avoid even minor trauma of the hands. Electrically heated gloves are helpful [2], except in patients with incipient gangrene. Smoking should be discouraged [3]. There is no specific therapy for the skin, but applications of 0.025–0.05% tretinoin (Retin-A) have decreased perioral and facial tightening and creases [4]. Areas affected by calcium deposits may break down and heal with difficulty. Occasionally, deposits may have to be excised [5]. These techniques may be superseded by treatment with the carbon dioxide laser [6]. Treatment of digital calcinosis was successful in approximately two-thirds of cases. The average healing time was 6 weeks. Reconstructive surgery for sclerodactyly has sometimes given satisfactory results [7].

Vasodilators, such as oral reserpine [8], guanethidine [9], and particularly nifedipine 10–20 mg four times daily [10,11] and diltiazem [12], may improve the blood flow in the fingers. Ketanserin 20 mg twice daily to 40 mg three times daily may [13] or may not [14] be useful. Nifedipine may worsen oesophageal symptoms [15]. Prazosin 1 mg orally three times daily reduces the frequency and severity of vasospasm [16]. Simply warming the hands in hot water for 5–10 min produces considerable improvement in peripheral blood flow [17], and regular use of such a technique reduces the number and severity of attacks of Raynaud's phenomenon [18]. Intra-arterial reserpine is ineffective, and may have serious side effects [19]. Prostacyclin [20,21] and the synthetic prostacyclin analogue iloprost [22] are potent vasodilators and inhibitors of platelet aggregation, and have been found to be effective in decreasing the frequency, duration and severity of Raynaud's phenomenon, warming the hands, relieving pain and healing ischaemic ulcers. Earlier reports of the effect of prostaglandin E_1 have not been confirmed [23]. Infusion of prostacyclin via a central venous catheter over 72 h at a rate of 2.5–10 ng/kg/min produces improvement for approximately 8 weeks. Side effects include hypertension, headache, facial flushing, abdominal colic, nausea, vomiting and diarrhoea, and pain at the angle of the jaw at the beginning of mastication, disappearing within minutes. Similar results have been obtained by 5-h intravenous infusions given weekly for 3 weeks through a peripheral vein [24], a procedure that can be carried out on outpatients. Iloprost is useful in cases of incipient gangrene and digital ulcers [25]. Transdermal applications of these agents may be beneficial [26].

The use of intravenous low-molecular-weight dextran (Rheomacrodex) has been advocated [27], but controlled trials [28] have shown no consistent benefit, although in occasional patients there is healing of ulcerated fingertips. Renal failure and oliguria have followed this treatment [29]. Intravenous pentoxifylline may be of benefit in acute ischaemic lesions [30]. Cervical or lumbar sympathectomy may produce some improvement in the cutaneous circulation for a year or two, but there is no lasting benefit.

Penicillamine in regimens of from 500 to 1500 mg/day (mean 750 mg) given over approximately 2 years may decrease skin thickness, reduce the rate of further visceral involvement and improve the prognosis of patients if given early in their disease [31,32], particularly those with pulmonary involvement [33]. Other authors have found no benefit or no improvement in vascular or systemic complications, even if there is limited skin improvement [34]. In particular, progression of oesophageal disease continues [35]. Penicillamine therapy is associated with troublesome side effects [36]. In one study [37], the skin of 32% of patients improved but deterioration occurred in the same percentage. In patients known to be sensitive to penicillin, the risk of an immediate allergic reaction is low [38]. Colchicine (1 mg/day or higher for 6 days per week) has also been advocated [39], but found to be ineffective [33]. Isotretinoin in a dosage of 1 mg/kg may help cutaneous sclerosis [40], as may factor XIII given intravenously [41]. Plasmapheresis [42] and plasma exchange [43] combined with prednisone and cyclophosphamide have been used for patients with severe systemic sclerosis [42], with some clinical improvement and reduction of endothelial cell cytotoxicity. Extracorporeal photochemotherapy is encouraging but expensive. It has been shown to be more effective than penicillamine in decreasing clinical skin involvement and also safer in patients with disease of less than 4 years' duration [44]. Patients were treated for two consecutive days every 4 weeks for 6 months. It may be insufficient to control severe progressive disease with systemic involvement [45] and its use is controversial [46]. Azathioprine in a dosage of 150 mg/day has been subjectively helpful in approximately one-third of cases. Chlorambucil by mouth does not halt the progression of systemic sclerosis [47,48]. Intravenous 5-fluorouracil, given intermittently for 6 months, improved cutaneous and systemic features in an uncontrolled trial [49].

Ciclosporin may be of benefit [50,51]. It may improve skin induration but not visceral manifestations; adverse reactions, particularly nephrototoxicity, are frequent [52]. IFN-γ influences fibroblast behaviour *in vitro* [53]. It has reduced the skin score and improved blood gas analyses without any adverse effects over 12 months' therapy, but other systemic involvement was unchanged [54]. Others have noticed no alteration in skin score or improvement in visceral involvement [55]. IFN-α2a has also failed to improve visceral involvement [56]. Antithymocyte globulin is ineffective [57].

Symptomatic treatment for cardiac, renal and gastrointestinal symptoms may be required. Antihypertensive drugs, including minoxidil, reduce the blood pressure in malignant hypertension [58,59], and captopril, an oral ACE inhibitor, is a considerable advance in its treatment [60,61], as in most cases there is elevation of plasma renin

activity. It controls blood pressure in most, if not all patients and relieves encephalopathy. It can improve renal function and, if given early, prevents renal failure and death. Improvement in renal function over 2 years has been reported [62], but is not uniform [63]. There is little evidence for a more general improvement in the disease resulting from these agents [64]. Benefit must be weighed against side effects. Haemodialysis and renal transplantation have helped patients with renal failure, with surprising improvement in the renal function and cutaneous manifestations [65]. Recovery of renal function can occur after months of dialysis. In one case, renal biopsy 14 months after transplant showed no evidence of the original disease [66]. Cimetidine or ranitidine are worth trying for the symptoms of oesophageal reflux. Gastrostomy may be required for short-term feeding difficulties if dysphagia is severe [67]. Stricture of the oesophagus may benefit from surgical intervention [68]. Although the diffusion defect in the lungs cannot be altered, patients benefit from breathing exercises, and chest infections must be treated energetically with antibiotics. Pulmonary hypertension is a serious complication that may be treated with bosentan [69].

Many other preparations, including relaxin, Salazopyrin, 3-hydroxy-2-phenylcinchoninic acid (HPC), antihistamines, dihydrotachysterol and nicotinic acid, potassium *p*-aminobenzoate [70,71], intravenous disodium edetate, topical dimethyl sulfoxide [72], the combination of phenformin and ethylestrenol [73], and antiplatelet therapy [74] have not proved of benefit. Hyperbaric oxygen may occasionally produce some improvement [75]. Calcitriol 1.75 μg/day may be helpful [76]. Dietary essential fatty acids such as γ-linolenic acid do not improve the vascular or other features [77].

Migraine sometimes occurs with systemic sclerosis [78], and methysergide or drugs containing ergot should not be given to such patients.

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Mixed connective tissue disease [1]

Overlap syndromes occur in the connective tissue diseases, and have recently been reviewed [1]. A number of attempts at defining diagnostic criteria, along the lines of those used for SLE, have been made with varying degrees of success [2]. Some associations are more frequent than others. For example, systemic sclerosis combined with dermatomyositis is more frequent than systemic sclerosis combined with SLE [3]. Some of these patients may have so-called 'mixed connective tissue disease', an entity associated with a specific antibody to U_1-RNP, an ENA first described by Sharp and colleagues in 1972 [4]. These patients, predominantly female, show features of SLE, systemic sclerosis, dermatomyositis and polymyositis. Raynaud's phenomenon, arthritis and arthralgia, sausage-shaped fingers and swelling of the dorsa of the hands, abnormal oesophageal motility, impaired pulmonary diffusing capacity and myositis are frequent. More than half have the abnormal nail fold capillaries seen in systemic sclerosis. Angiography shows obstruction of small blood vessels in almost 90% of cases [5]. Occasionally, vascular disturbances may be severe, with peripheral gangrene (Fig. 56.73) [6]. The incidence of clinical renal disease is only approximately 5% [7], but renal histology is abnormal in 20% [8]. Aseptic meningitis, trigeminal neuropathy, transverse myelitis and psychosis are prominent neurological features. Neuropsychiatric manifestations were noted in 15% of one series [9]. Rarely reported features include orogenital ulceration [10], pneumatosis intestinalis [11], protein-losing enteropathy [12] and autonomic neuropathy [13]. Enlarged nodes of Kikuchi's disease were the presenting feature in one case [14].

The response to treatment with corticosteroids is good [15], and this includes both skin and pulmonary involvement that may be severe [16]. The characteristic antibody may be suppressed by treatment, and disappears in patients in remission [17].

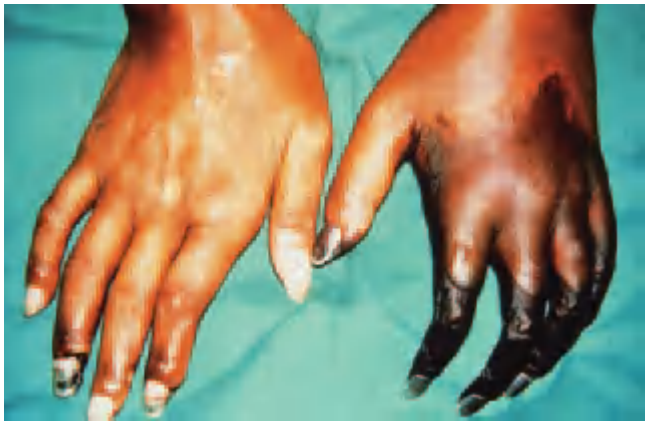

Fig. 56.73 Gangrene of the hands in mixed connective tissue disease.

Mixed connective tissue disease may be more severe in children, in whom cardiac and renal disease and arthritis are common, and thrombocytopenia may be marked [18], although the overall prognosis may be quite good [19]. Thrombocytopenia is also occasionally found in adult cases [20], and may occur with thrombotic thrombocytopenic purpura [21]. Statistically there is an increased risk of mixed connective tissue disease after silicone breast implants [22], but others have not found any association between breast implants and connective tissue disease [23]. Livedoid vasculitis [24], ankylosing spondylitis [25] and anti-neutrophil cytoplasmic antibody (ANCA)-related glomerulonephritis [26] are reported to occur with mixed connective tissue disease .

Immunology. All patients have the speckled type of antinuclear antibody together with a high titre of antibody to ENA, which is sensitive to digestion with ribonuclease (RNase), unlike the ENA antibodies often found in patients with SLE. Different molecular forms of U_1-RNP may be associated with different clinical variants [27]. Ro and La antibodies are also frequently found, usually in association with sicca symptoms [28,29]. Precipitating antibodies designated PM-1 [30] and Ku [31] occur in polymyositis/systemic sclerosis overlap, and SL-Ki in patients with SLE, scleroderma and the sicca syndrome [32]. Immune complexes occur in 90% of patients, and T cells are decreased. Complement levels are normal. Sometimes, anti-DNA antibody occurs in low titre, but this usually disappears with steroid therapy. There may be local, rather than generalized antibody production (e.g. in the pericardium in cases of pericarditis [33]). Antiendothelial antibodies occur in approximately 50% of cases, and are associated with abnormal pulmonary, neurological and cardiac function. They are also related significantly to spontaneous abortion in female patients [34]. HLA-DR4 is found more commonly in patients with arthritis than in normal controls, and is associated with a young age of onset of the condition [35]. There are also reports of familial cases [36]. Differences in HLA antigens between patients with mixed connective tissue disease and SLE indicate that they are genetically separate disorders [37].

Immunohistology may be helpful in distinguishing this condition from uncomplicated systemic sclerosis [38]. Immunoglobulin, particularly IgM or IgG, is present at the basement membrane of uninvolved skin [39], and this is in contrast with systemic sclerosis in which there is no basement-membrane immunofluorescence of lesional or non-lesional skin. However, the fluorescent band test cannot distinguish mixed connective tissue disease from SLE.

Direct immunofluorescence study of apparently normal skin reveals particulate ('speckled') epidermal nuclear staining, and this correlates with high titres of anti-RNP. Occasionally, epidermal nucleolar staining occurs. Clinically, patients with these features [40] show a high incidence of persistent, diffuse, non-scarring and focal alopecia, hyper- and hypopigmentation with follicular retention of pigment, swollen hands with sclerodactyly, and lesions of DLE.

Although the presence of anti-RNP is usually associated with a good prognosis, death occurs in approximately 4% from pulmonary hypertension, brought about by vascular changes similar to those seen in primary pulmonary hypertension [41], nephritis, myocarditis or widespread vasculitis. Other authors [42] noted that 25% developed into systemic sclerosis, 25% into SLE and a few patients with HLA-DR4 developed rheumatoid arthritis. In patients whose disease differentiated into systemic sclerosis, there was an association with HLA-DR5. These authors suggest that mixed connective tissue disease is frequently only an intermediate stage in a genetically determined progression. Those whose disease continues unchanged may be a distinct subset. Patients with a high titre of anti-RNP appear to have an increased risk of developing mixed connective tissue disease [43]. The relatively good prognosis has been confirmed recently [44].

With time, more variants of the overlap syndromes are being described, both with and without U_1-RNP antibody. Hence, some authors now regard mixed connective tissue disease as one among many 'undifferentiated connective tissue diseases' or 'overlap syndromes'. Doubts about the concept of mixed connective tissue disease have been expressed, particularly in children [45]; nevertheless, it is important to recognize this group of patients because of the good prognosis and the response to steroid therapy. There may be an increased risk of malignancy, with cancer developing in 10% of cases [46].

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Cold, flexed fingers (Fig. 56.74)

Several female patients have been seen with cold, flexed fingers, but no evidence of systemic abnormality, despite extensive investigations including pulmonary function

Fig. 56.74 Cold flexed fingers: note the inability to extend the fingers fully.

tests. The presenting feature of inability to extend the fingers fully starts in the second to fourth decades. There may be difficulty in flexion of the fingers and in making a fist. All have thin, cold fingers, but there is no evidence of acrosclerosis, and Raynaud's phenomenon is not invariable. The condition remains unchanged for years and is not influenced by vasodilators or systemic corticosteroids.

Some patients may be early cases of systemic sclerosis. One patient has developed rheumatoid arthritis, with deformities of the hands.

The condition was first described in the first edition of this textbook in 1968 [1]. It appears to be similar to what has been termed 'bowed fingers' [2]. Some patients with bowed fingers had features of systemic sclerosis or mixed connective tissue disease.

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Lichen sclerosus [1,2]

SYN. LICHEN SCLEROSUS ET ATROPHICUS; GUTTATE MORPHOEA; GUTTATE SCLERODERMA; WHITE-SPOT DISEASE

Definition. An uncommon disease of unknown aetiology in which characteristic, easily recognized, small, white, sclerotic areas occur at any site on the skin. This frequently involves the perineal skin in the female, and the penis and foreskin in the male. It may occur in genital and non-genital skin separately or together. Hallopeau [3] first described the condition in 1887, and Darier [4] reported the histological changes in 1892. They considered the disorder to be a type of lichen planus; others thought that the condition was related to circumscribed scleroderma. Most people now regard lichen sclerosus as a separate entity, because of the distinct clinical signs and pathological changes, but this point remains unclear. The term 'white-spot disease' is sometimes applied to the skin lesions on the trunk and limbs, although some authors refer to these lesions as 'guttate scleroderma'. It may be closely related to morphoea, as the two conditions can occur together and, rarely, morphoea can produce similar genital lesions [5]. White-spot disease has been reported with systemic sclerosis [6].

Incidence. The condition is an uncommon one. Females predominate; one series [7] consisted of 38 females and five males. In Wallace's [8] series of 359 patients, females outnumbered males by 10 : 1. Wallace and Whimster [1] found that in the vulva, lichen sclerosus was as common as leukoplakia and slightly more frequent than primary atrophy. With modern terminology, these figures are difficult to interpret. Approximately 20% of their patients with lichen sclerosus of the vulva had lesions on the trunk. Certainly, involvement of the vulva, perineum and perianal skin in females is more common than balanitis xerotica obliterans, which is the corresponding lesion in the adult male. The condition occurs particularly around and after the menopause, but also occurs in girls between the ages of approximately 1 and 13 years. The disease is not uncommon in boys with phimosis [9], and the incidence is probably underestimated. The mean age of onset in one series of cases [7] was 50 for females and 43 for males. The condition has been seen in mother and daughter, mother and son, brother and sister, and sisters and brothers, but not in father and son. It has occurred in monozygotic female twins [10] and in non-identical female twins [11]. It is uncommon in Bantu and in black people.

Aetiology. The aetiology is unknown, lesions usually appearing spontaneously without any precipitating factor. The predominance of females, the frequent onset around the menopause and the spontaneous improvement in girls after puberty suggest a hormonal factor, but no convincing causative factors have been identified. The increased prevalence of organ-specific antibodies and of associated autoimmune diseases in both female patients and relatives suggest an autoimmune cause, but there is no difference in the natural history of those with or without antibodies [12]. The incidence of other autoimmune diseases in patients is highest when the onset is between the ages of 41 and 60 years, but is not related to the site or duration of lesions. Once the diagnosis of lichen sclerosus has been established, patients do not seem to be at continued excessive risk of developing autoimmune diseases [13]. Approximately 50% of female patients will have a personal or family history of autoimmune disease [14]. Male patients also have an increased prevalence of autoimmune disorders and autoantibodies [15]. An increase in HLA-B40 in females has been reported [16] but not confirmed [17]. More recently, HLA-A29 and -B44 were found to occur more frequently, both separately and together [18], and the class II antigens DQ7, 8 or 9 were found to be present in 78% of patients [14]. In this last study, no HLA class I associations were found, although HLA-A2 was only found in patients with localized anogenital disease. In men, HLA-DR11, -DR12 and -DQ7 were found to be positively associated with the development of the disease, and the association with autoimmune disease is less marked [19].

A history of preceding vaginitis and, in the male, the limitation of genital involvement to the uncircumcised or very recently circumcised, who often give a history of chronic balanitis, suggests that infection may play a provocative or localizing part. Borrelial DNA has been found in skin biopsies, although there is no confirmed role for the organism in this disease [20]. There may be

geographical differences in the occurrence of *Borrelia*, with evidence of infection found in Germany and Japan but not in the USA [21]. The subject has been reviewed [22]. Vulval lesions are not related to parity. Trauma can also act as a precipitating factor, and lichen sclerosus has been reported in a vaccination site [23], in the area of radiotherapy following mastectomy [24], after severe sunburn [25], in an old burn scar [26], as a result of welding sparks [27] and at the site of a strawberry naevus [28].

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Pathology. The striking histological change in lichen sclerosus is a band of hyalinization of the dermal collagen below the epidermis. The hyalinized tissue appears structureless and oedematous, and contains sparse cells, but may show dilated capillaries. The epidermis shows variable thickening, hyperkeratosis and follicular plugging. Later, the epidermis becomes thinned. A band of lymphocytic infiltration may also be seen below the hyalinized area: in older lesions this may be more scanty and focal. The subepidermal elastic tissue tends to be depressed and separated from the epidermis by oedema. The infiltrate contains lymphocytes staining with CD3, CD4 and CD8, as well as the macrophage marker CD68 [1], and HLA-DR^+ activated T cells associated with Langerhans' cells, which are increased in number [2]. There may be an expansion of specific T-cell clones in the skin, suggesting a specific antigen stimulus [3]. Many of the lymphocytes are $CD57^+$ [4]. Staining with HLA-DR can also be demonstrated on the surface of keratinocytes and around blood vessels. A decreased CD44 expression on epidermal cells may be related to hyaluronate deposition [5]. Androgen receptors are reduced [6]. Fibrillin, collagens I and III and elastin are all abnormal [7], and the distributions of tenascin, fibronectin and fibrinogen are abnormal [8].

In vulval lesions, secondary infection and superficial erosion are common, and may mask the primary changes. In lesions with sclerotic change, the epidermis shows marked thickening, irregularity and hyperkeratosis. The dermal oedema tends to regress and sclerosis and dense chronic inflammation occupy the subepidermal zone. These changes are seen in over half of all biopsies of vulval lichen sclerosus, and in two-thirds when there is itching [9]. They may occur in small areas, only a few millimetres in diameter, and be easily missed.

The condition must be distinguished from lichenification, in which the dermal papillae are prolonged and oedematous, with corresponding lengthening of the rete pegs. There is usually dermal oedema and epidermal spongiosis and parakeratosis. In primary atrophy of the vulva, the epidermis is thinned, the lower border is flattened and keratinization is normal or reduced. There is also a reduction in the elastic tissue, particularly in the superficial zone, but the collagen is unaltered. Immediately beneath the epidermis there is a band of chronic inflammatory cells. In leukoplakia, there is some degree of hyperplasia of the epidermis, with considerable irregularity in the outline of the deeper border, together with some hyperkeratosis. An inflammatory infiltrate occurs near

the deeper border of the epidermis. The collagen of the superficial part of the dermis shows hyaline changes and the elastic tissue is lost.

Electron microscopy has revealed striking changes in dermal collagen fibres and increased amounts of elastin [10]. Immunoglobulins (IgG, IgM, IgA), complement and fibrin may be demonstrated in the damaged skin. Immunohistology in balanitis xerotica obliterans is normal.

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Clinical features. Lesions may occur in the following areas.

Non-genital lesions. The lesions on the skin are symptomless and occur on the trunk, particularly on the upper part and around the umbilicus, around the neck, in the axillae, on the flexor surfaces of the wrists (Fig. 56.75), around the eye and, very rarely, on the scalp, palms and soles [1]; they may be confined to the latter. They have also been described confined to the skin around the areolae [2]. Lesions can occur at sites of pressure (e.g. underneath bra straps or belts). The lesions are small, ivory or porcelain-white, shiny, round macules or papules, a few millimetres in diameter. Occasionally, they are semi-translucent and resemble mother-of-pearl. They may be very extensive, involving most of the trunk. Lesions may follow Blaschko's lines [3]. They are slightly raised, or level with the surface of the skin, and typically their surface shows prominent dilated pilosebaceous or sweat duct orifices, which often contain yellow or brown horny plugs. If the plugging is marked, the surface may be rather warty. Lichenification may occur as a result of rubbing. Occasionally, bullae, which may be very extensive [4], telangiectases and purpura may occur. In the later stages, atrophy occurs, and the surface of the lesions becomes wrinkled, and may actually be depressed. Usually, lesions are aggregated into plaques, but the individual lesions can nearly always still be identified. Plaques may resemble those of morphoea, but histology will distinguish between the two conditions. The degree of pigmentation is variable in coloured skin. Bullous lesions may resolve with the formation of a large number of milia [5]. Scarring alopecia may occur. Involvement of the tendon sheath of the superior oblique muscle of the eye can give rise to diplopia [6]. Nail disease is reported [7].

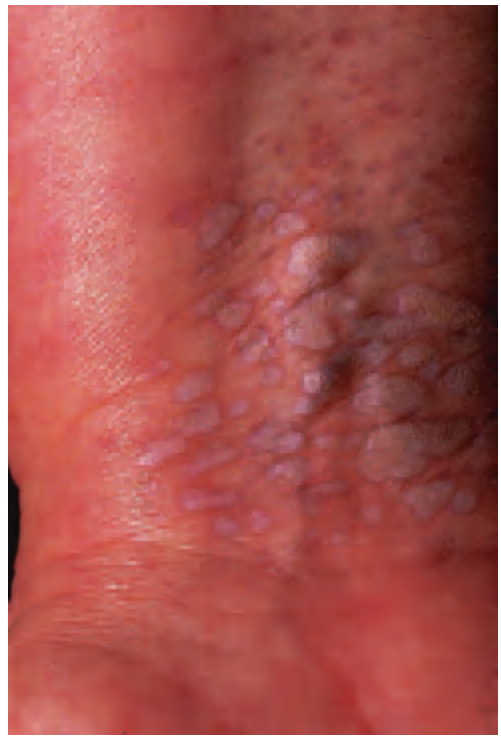

Fig. 56.75 Lichen sclerosus of the front of the wrist.

Anogenital lesions in women (see Chapter 68) [8,9]. The condition most commonly starts between 45 and 60 years of age but is not uncommon in childhood. Lesions occur on the vulva and around the anus, and may extend to the skin of the inner side of the thighs. The ivory-coloured atrophic papules with follicular hyperkeratosis and plugging can often be identified on the vulva but, owing to friction and moisture, the lesions frequently break down to form a red raw surface, resembling macerated intertrigo (Fig. 56.76). Vesicles and bullae, sometimes haemorrhagic, may occur. In other sites, the tops of the papules become smooth and the area becomes flat and glistening. Small telangiectases and purpuric lesions sometimes occur, probably as a result of injury to the atrophic skin. Irritation may be marked, although sometimes—particularly in children—the condition is symptomless (Fig. 56.77). Patients often complain

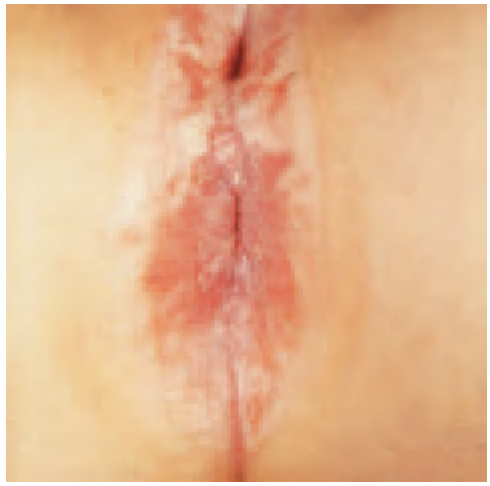

Fig. 56.76 Lichen sclerosus of the vulva and adjacent skin. (Courtesy of Professor J.L. Burton, Bristol, UK.)

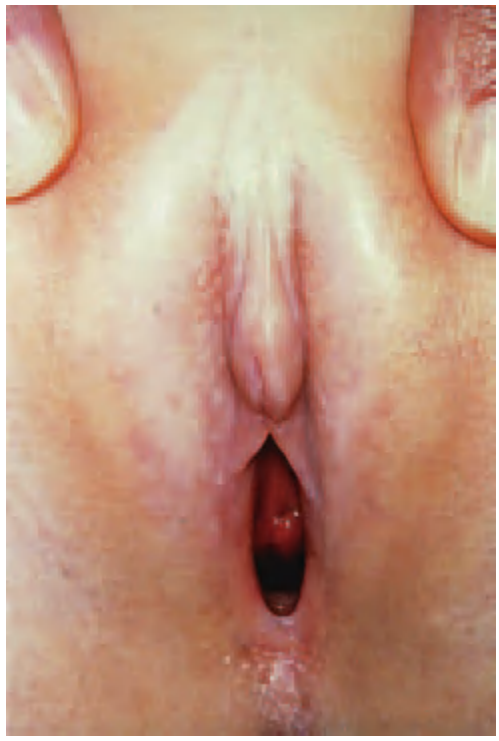

Fig. 56.77 Lichen sclerosus of the vulva in a young girl.

of soreness rather than pruritus, and dyspareunia may be considerable. Atrophy is a feature, and there may be gross shrinkage of the vulva, especially of the clitoris and labia minora. Labial fusion, clitoral burial and labial resorption can all occur. The vaginal introitus may become as small as 1 cm in diameter. Despite this, pregnancy and delivery are uninfluenced [10].

Mouth lesions. Occasionally, lesions are found in the mouth. They consist of bluish white plaques, usually on the inner surface of the cheek or on the palate. There may be superficial ulceration. Sometimes, a reticulate appearance occurs and is difficult to distinguish clinically from the lesions of lichen planus [11]. The tongue can be involved. The presence of lesions of lichen sclerosus elsewhere is helpful, as biopsies from the mouth are sometimes difficult to interpret.

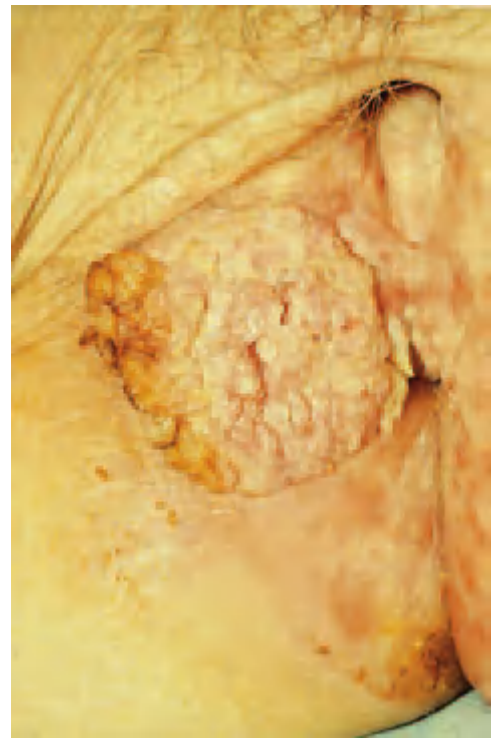

Fig. 56.78 Squamous carcinoma in an area of lichen sclerosus of the vulva.

Malignancy in lichen sclerosus. Premalignant and frankly malignant changes can occur in patients with lichen sclerosus, with as many as 50% of patients ultimately showing changes. These changes can occur in childhood [12]. Squamous cell carcinoma of the vulva occurred in 12 of 290 patients (4.4%) [13], although the true incidence may be greater than this. It usually arises in a sclerotic area, especially on the anterior part of the vulva (Fig. 56.78).

In a review of 83 cases of squamous cell carcinoma of the vulva [14], two patients with lichen sclerosus were found. Paget's disease may rarely occur in cases of lichen sclerosus of the vulva.

Lichen sclerosus in the male (balanitis xerotica obliterans) (Fig. 56.79) (see Chapter 68). Acquired phimosis or recurrent balanitis are the presenting features [15], together with itching and soreness, and erection may be painful. The prepuce becomes sclerotic and cannot be retracted. Ulceration of the foreskin can occur. The glans and undersurface of the prepuce are shining and bluish white,

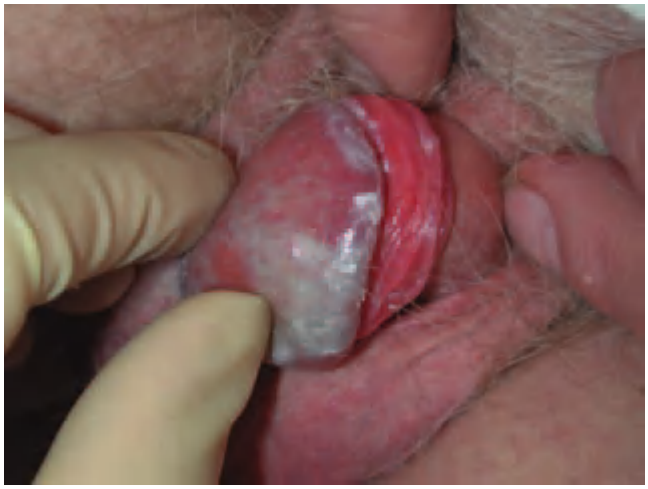

Fig. 56.79 Lichen sclerosus of the penis.

and there can be considerable telangiectasia. There may be back pressure affecting the urinary tract, demonstrated by urography, as a result of meatal closure. This may require surgical correction [16]. The shaft of the penis is only occasionally involved. The condition is most common between the ages of 15 and 50 years. It can be overlooked in boys unless the prepuce is examined histologically in cases of circumcision for acquired phimosis. It was found in 22% of sections from boys aged 5–11 years, and less than 3% in boys under 5 years [17]. In one series, the condition only occurred in patients not circumcised early in life [18]. The scrotum and perianal area are not involved. Carcinoma may develop, and the condition may be associated with morphoea and vitiligo.

Very rarely, classical macular and papular lesions of lichen sclerosus occur on the glans and shaft of the penis and on the scrotum. The skin remains quite soft compared with the usual sclerotic skin of balanitis xerotica obliterans. Occasionally, classical lesions occur on the trunk.

Lichen sclerosus et atrophicus in female children [19]. The disorder is much less common in children than in adults. Published series show from 2% [20] to 15% [21] of cases begin before the age of 13 years. The earliest reported age of onset was at 6 months [10]. In Wallace's series [13], 28 of 50 started between the ages of 3 and 6 years. In this group, HLA associations are seen more frequently, although these may vary [22].

General health remains normal, and often the condition is symptomless. A vaginal discharge may precede the vulval lesions in approximately 20%, and pruritus vulvae occurs in approximately half of cases. Other presentations include pain on defaecation and dysuria, resulting in constipation, nocturia and nocturnal enuresis as well as rectorrhagia [22]. Lesions have followed trauma (e.g. in operation scars and in scratch marks). The individual lesions are identical to those seen in the adult [17]. The vulva and anal region may be encircled in a figure-of-eight pattern, and shrinking of the labia and stenosis of the introitus may be marked. Follicular plugging and delling are usually absent from areas of the vulva with few or no hair follicles. Vesicles and excoriations occur. The condition may be misdiagnosed as sexual abuse [23], causing much anxiety [24], but there are suggestions that sexual abuse may precipitate the condition as a Koebner phenomenon [25]. Abnormal hirsutism may be seen on the inner side of the labia majora, disappearing with resolution of the lichen sclerosus [13]. In approximately 5% of cases, the lesions are solely outside the anogenital region, and in just over 10% lesions are found both in the anogenital region and elsewhere.

The prognosis in childhood has been studied by Wallace [13]. Extragenital lesions usually clear before the menarche. In approximately two-thirds, anogenital lichen sclerosus involutes before or around the menarche. In the remaining one-third, the condition persists, sometimes with considerable atrophy. Premalignant changes and squamous cell carcinoma may develop. There appears to be an increased incidence of recurrent urinary infections and congenital abnormalities of the genitourinary tract [17].

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Laboratory investigations. Approximately three-quarters of female patients have one or more organ-specific autoantibodies [1,2], usually to thyroid microsomes, thyroglobulin, gastric parietal cells or intrinsic factor. The prevalence in males is approximately half that in females, and the antibodies are mainly to smooth muscle and gastric parietal cells.

Differential diagnosis. Lichen sclerosus of the trunk must be distinguished from plaques of morphoea, but this is rarely difficult in the presence of characteristic papules with follicular plugging. Lichen planus is distinguished by its raised itchy violaceous papules. The atrophic form of lichen planus may simulate lichen sclerosus quite closely [3]. Lesions of lichen sclerosus may sometimes occur in association with patches of morphoea and, in some patients, typical plaque morphoea may resolve to leave the white sclerotic features of lichen sclerosus. In patients with vulval lesions, a search should be made for lesions elsewhere on the trunk, but even if none is present, the margins of the affected area of the vulva or the perianal area usually show a few typical papules, sometimes forming a well-defined edge. The differential diagnosis of the genital lesions is discussed in Chapter 68. Vulval cicatricial pemphigoid may mimic lichen sclerosus [4]. The annular atrophic plaque type of DLE on the face may resemble lesions of lichen sclerosus [5].

Associations. Morphoea was found in 13 and vitiligo in 10 of 380 cases [6], and these frequencies are greater than would be expected by chance. Vitiligo and alopecia areata are more common than expected in males [7], and pernicious anaemia is more common in females [1]. Rarely, it may be associated with SLE or limited cutaneous systemic sclerosis [8]. It may coexist with lichen planus [3] and primary biliary cirrhosis.

Prognosis. Lichen sclerosus is a chronic condition, but signs and symptoms may wax and wane. It is usually permanent but, occasionally, spontaneous resolution occurs. This is particularly likely in girls around the menarche [6,9–11]. Resolution of cases appearing after puberty is uncommon, and is probably restricted to extragenital lesions arising before the age of 30 years.

Treatment. There is no confirmed effective treatment for extragenital lesions. Calcipotriol may be helpful [12], and low-dose UVA-1 [13] has been reported to be of benefit. Mycophenolate mofetil was dramatically effective in one severe case seen by the authors.

For genital lesions, there is increasing evidence that the use of potent topical steroid preparations gives both symptomatic relief and prevents scarring, and may induce complete resolution of the problem, both histologically and immunohistologically [14]. Oestrogen [15] or testosterone [16] -containing creams have given symptomatic benefit, but there has not been a trial comparing their use with topical steroids, and no report suggests histological resolution with their use. Adrenocorticotrophic hormone (ACTH) injections helped a severe case with haemorrhagic bullae [17]. Potassium *p*-aminobenzoate, 12 g/day in divided doses, is claimed to have helped symptoms and haemorrhagic bullae, and softened the skin in some cases [18]. Topical ciclosporin is ineffective. Etretinate may have helped both adult [19] and juvenile cases [20]. Sulfasalazine has helped a solitary case [21]. Tangential excision produced a good result in one patient with bullous lesions [22]. Creams containing local anaesthetic preparations should not be prescribed because of the risk of sensitization. Superficial radiation or painting with thorium X are no longer used, and are potentially dangerous.

Vulvectomy is contraindicated for uncomplicated vulval lichen sclerosus, as recurrence occurs in approximately 80% of patients. Dysplastic change should at first be treated conservatively and observed regularly. Applications of liquid nitrogen may be useful, but treatment with a nitrous oxide cryoprobe has been found to be more satisfactory [23]. The carbon dioxide laser is also effective for genital lesions in both males and females [24]. Photodynamic therapy has been used to treat vulval disease [25]. Radical surgery is obviously required if a carcinoma develops. Surgery may also be required for severe narrowing of the introitus.

Topical corticosteroids, sometimes for short periods under a condom, or intralesional injections of triamcinolone may soften the sclerotic lesions of balanitis xerotica obliterans and reduce the phimosis. Circumcision may be helpful or even curative if the condition involves only the foreskin [26]. Meatal instillation of corticosteroid may help meatal narrowing. Attention to local hygiene and treatment of balanitis may be required.

Patients with genital lesions should be seen at intervals of 6–12 months to facilitate the early detection of carcinoma. Repeated biopsies may be required.

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Scleroedema

SYN. SCLEROEDEMA ADULTORUM; SCLEROEDEMA OF BUSCHKE

Although the name of Buschke [1] is usually associated with this condition, it was originally described by Piffard in 1876. The older term, 'scleroedema adultorum' is incorrect, as the condition can occur in childhood [2]: 29% of cases start before the age of 10 years, and a further 22% between the ages of 10 and 20 years [3].

Definition. A rare disorder of unknown cause in which areas of induration appear in the skin, frequently after an infection but also in diabetes, and spontaneously clear in months or years. There is an excess of acid mucopolysaccharides in the dermis.

Aetiology. The aetiology is unknown. Suggestions that have been considered include obstruction to lymphatic channels by inflammation, streptococcal hypersensitivity and disorders of the peripheral nervous system or pituitary function. Sera from patients with paraproteinaemia stimulate collagen production in dermal fibroblast cultures [4]. Some persistent cases are associated with moderate to severe diabetes mellitus [5–8], and neither the skin nor the diabetes respond to antidiabetic treatment with insulin, chlorpropamide or phenformin. This persistent type, with no preceding infection and a strong association with diabetes, has been called scleroedema diutinum [9]. Scleroedema has been reported with malignant insulinoma [10], paraproteinaemia and multiple myeloma [11], Waldenstrom's macroglobulinaemia [12], rheumatoid arthritis and Sjögren's syndrome [13], primary hyperparathyroidism [14] and anaphylactoid purpura [15].

Histology. The epidermis is normal. The dermis may be three times its normal thickness. There is swelling and splitting of the dermal collagen bundles by an increase in ground substance. Clear unstained spaces, or fenestrations, occur between the bundles in severe cases. This process extends into the subcutaneous tissues, the fat of which is replaced by coarse collagen fibres. The ground substance stains metachromatically with cresyl violet or toluidine blue. Metachromasia in scleroedema is caused by the presence of hyaluronic acid [16], and is poorly seen in formalin-fixed sections as the hyaluronic acid is removed by the fixative, and in tissues treated by hyaluronidase. There is an excess of acid mucopolysaccharides, but neutral polysaccharides are normal. Mast cells may be increased [17]. Electron microscopy [18] shows an excess of interfibrillary material, and this is associated with clumping of the collagen fibrils. The voluntary muscle and heart may be affected. Deposition of IgG, IgM and C3 at the dermal–epidermal junction has been reported.

Clinical features. The condition is uncommon [19]. Occasional familial cases have been reported [3,20–22]. Females are more frequently affected than males in patients without diabetes, but scleroedema associated with diabetes occurs predominantly in males [21].

Although the condition may apparently start spontaneously, there is a history of an infectious episode, from a few days to 6 weeks prior to onset, in 65–90% [4] of cases. It is usually influenza, tonsillitis, pharyngitis, measles, mumps, scarlet fever, impetigo or cellulitis; prior

streptococcal infections appear to be particularly common. Sometimes, there is a history of trauma. Prodromal symptoms of slight fever, malaise, muscle and joint pains occasionally occur between the infectious episode and the onset of induration. The latter is usually symmetrical and often starts on the back and sides of the neck or on the face. This loses its expression, and the patient notices difficulty in wrinkling the forehead and in smiling. There may be difficulty in opening the mouth. The tongue and pharynx may be involved, with difficulty in swallowing. Later, the shoulders, arms, hands and upper trunk become involved, but less frequently the abdomen and legs may be affected. The condition can be limited to the thighs [23]. The induration is non-pitting and hard, and there is no sharp demarcation between normal and abnormal skin. Wrinkling occurs when the skin is compressed between the thumb and index finger, indicating that the epidermis is spared. Brownish pigmentation can be widespread in the indurated areas [24]. The onset is more insidious in diabetics, and the skin induration may be preceded by erythema or pustules [8]. Sometimes, there is stiffness and restriction of movement of joints. Pleural and pericardial effusions sometimes occur, and the skeletal and cardiac muscles can be affected. Occasionally, there are ocular manifestations. The parotid glands may be involved [25].

Laboratory investigations. The ESR may be moderately elevated, and the serum proteins usually show mild non-specific abnormalities. IgG [26,27] and IgA paraproteinaemia [28] have been reported. The paraproteins of scleroedema are most commonly IgGκ [29]. Hyperlipoproteinaemia has been reported [30]. The antistreptolysin-O titre may be raised, especially in children.

Prognosis. The condition may completely disappear in the course of some months, but many cases last approximately 2 years and a few may persist for many years. One case [17] still had changes 38 years after the onset. A fatal case occurred following the development of IgA myeloma [30].

Differential diagnosis. The condition is usually easy to diagnose in view of the rapidity of the onset, especially if there has been a history of preceding infection. Localized and generalized morphoea are usually of much slower onset, and the ivory sclerotic areas, with a well-defined and, frequently, lilac-coloured border, are characteristic. Systemic sclerosis is usually preceded by Raynaud's phenomenon. Dermatomyositis may present more difficulty, as cutaneous oedema is a feature of both conditions. However, the presence of heliotrope cyanosis, particularly around the eyes, dilatation of nail fold capillaries and muscle weakness should distinguish the condition. Pseudoscleroderma (induration of the legs as a result of chronic oedema) and localized myxoedema should rarely cause confusion. Trichinosis may have to be considered. In the newborn, sclerema and subcutaneous fat necrosis differ in their mode of onset and course.

Treatment. No effective remedy is known, although multiple therapies have been tried, including systemic and intralesional corticosteroids. In a case associated with multiple myeloma, the skin softened with intravenous pulses of cyclophosphamide and oral prednisolone [31]. Improvement with ciclosporin [32] and electron beam therapy [33] have been reported. PUVA using psoralen cream [34], extracorporeal photophoresis [35] and low-dose methotrexate are more recent suggestions [36].

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Dermatomyositis [1]

Definition. A disorder mainly of skin, muscle and blood vessels in which characteristic erythematous and oedematous changes in the skin are associated with muscle weakness and inflammation. Calcinosis is frequent, especially in childhood, and is usually associated with a more favourable prognosis for life, but functional disability may be severe. In adults, the disease is commonly associated with an underlying carcinoma or lymphoma.

Incidence. Dermatomyositis is rarer than SLE, polyarteritis nodosa or systemic sclerosis. It occurs at least twice as frequently in females as in males. The incidence in children under 16 years was recently estimated as 1.9 per million, with the median age at onset of 6.8 years, and occurring much more frequently in girls (ratio 5 : 1) [2]. The onset in childhood cases is usually before the age of 10 years, and in adult cases is predominantly between the ages of 40 and 60 years. The mean age of onset is later in men than in women [3]. It may occur in infancy [4,5]. It appears to be approximately 10 times more common in the Bantu than in the white population of the Transvaal [6].

Aetiology. The cause is not known, but there is increasing evidence of early blood vessel damage, probably humorally mediated [7]. There may be significant titres of antiendothelial cell antibodies, particularly in those patients with pulmonary involvement [8]. The disorder is not consistently caused by infection, vaccination, immunization or drugs, nor is it associated with trauma, but occasional cases seem to follow such events [9]. Preceding heavy muscular exertion and stress have been suggested as triggering factors [7]. Polymyositis and dermatomyositis can occur with penicillamine therapy, and may be fatal as a result of cardiac involvement [10]. A possible relationship to tamoxifen therapy for carcinoma of the breast has been reported [11]. One patient developed dermatomyositis after taking oral progesterone for dysmenorrhoea. A very high frequency of IgM immunofluorescent antibodies to *Toxoplasma gondii* in patients with polymyositis/dermatomyositis suggests a possible association with recent infection with *Toxoplasma* [12], and treatment of such infection may produce remission of dermatomyositis [13]. In a patient who developed dermatomyositis in association with staphylococcal osteomyelitis, the former resolved after the infection had been treated, and onset of the disease has been reported after staphylococcal arthritis [14]. There is also a degree of homology between streptococcal type 5 protein and skeletal myosin, and flares of disease were associated with a rise in antistreptococcal antibodies, suggesting another role for infection in disease pathogenesis [15]. There are also suggestions that parvovirus B19 may have a causative role, at least in adult disease [16], and coxsackie B virus infection has been linked to childhood disease [17]. Tubular inclusions, possibly related to viral infection, have been reported [18].

Dermatomyositis affects all races and there is no obvious geographical variation. It very rarely occurs in relatives, but has been found in identical twins [19] and in first cousins: only three other familial cases are known [20]. A genetic factor is suggested by the increased incidence of HLA-B8 in childhood dermatomyositis in white people but not in black people [21], and -DR3 [22] and -B14 in adult patients [23]. Other HLA haplotypes may be associated with pulmonary disease [24]. It has been reported in a patient with absence of the second component of complement (C2) inherited as an autosomal recessive trait [25]. There are rare familial cases [26] and antinuclear antibodies occur in a significant percentage of first-degree relatives of patients with dermatomyositis and polymyositis [27].

Immunological abnormalities. It seems likely that immunological mechanisms are concerned in the development of dermatomyositis. There is some evidence of an increased incidence of hyperglobulinaemia in relatives [20], and the relation of the disease to malignancy in adults suggests that there may be an abnormal immunological response to the neoplasm. A patient with carcinoma of the breast showed skin sensitivity to an extract of her own breast tumour when it was injected intradermally [28]. Tests using an extract of normal skin, subcutaneous tissue and muscle were negative. In another female patient, with metastatic adenocarcinoma of the lung and dermatomyositis, positive intradermal reactions were found to injections of aqueous extracts of the tumour [29]. The immediate skin reaction and passive transfer tests established the humoral nature of the antibodies involved. Granular deposits of IgG, IgM and C3, alone or in combination, have been described in the walls of skeletal muscle

blood vessels, especially in childhood dermatomyositis [30]. Globulin has been demonstrated in plasma cells around hair follicles and sebaceous glands in a case of dermatomyositis associated with carcinoma of the breast [31]. In some patients, myopathy seems to have been mediated by an IgGκ paraprotein with antimuscle specificity [32]. It is not clear whether paraneoplastic dermatomyositis is the same entity as the condition occurring without an associated cancer.

Several precipitating autoantibodies have been demonstrated [33], including PM-1, Jo-1, PL-12 and, in Japanese patients, KU. Jo-1 and PL-12 antibodies are directed against tRNA synthetase enzymes and are associated with interstitial pulmonary fibrosis, and the antibody may be detected before the appearance of the lung disease [34]. It has been suggested that Jo-1 production may be linked to HLA-DR3 [22]. Patients with Jo-1 antibodies tend to have an onset of symptoms between February and July; this is not the case for the other serological subgroups of the disease [35]. Humoral antimuscle antibodies have not been demonstrated. The serum of patients may contain complement-fixing antibodies to their own tumour [36].

Circulating immune complexes have been demonstrated in 70% of patients [37]. There is evidence that polymyositis may be caused by lymphocyte-mediated hypersensitivity [38]. Large numbers of T lymphocytes can be demonstrated in the infiltrates in the muscle [39], and there is marked decrease of suppressor/cytotoxic cells in the blood [40]. Lymphocytes from patients with dermatomyositis and polymyositis have shown an increased response to muscle antigen in lymphocyte-stimulation tests, and the index of response showed some correlation with clinical activity. Lymphocytes from patients with dermatomyositis were cytotoxic to muscle cultures, and this cytotoxic action could be prevented by antilymphocyte serum [41]. Soluble CD30 levels are increased, indicating activation of T lymphocytes [42], and soluble TNF receptors are found [43]. An increased frequency of the more inflammatory polymorphisms of the TNF-α gene is found [44]. Soluble IL-2 receptor is elevated in juvenile disease [45].

Relationship to malignancy. Several possible mechanisms to account for the relationship with malignancy can be envisaged, but these are mainly speculative at present. Tumours are known to differ antigenically from the tissues from which they are derived. New antigens are produced, probably as the result of somatic mutation, and are regarded by the body as 'foreign' and lead to an immune response. If such tumour antigens share common antigenic determinants with skin and muscle, the immune response will be directed against these tissues. On the other hand, dermatomyositis might result from the damaging action of cellular autoantibodies synthesized by forbidden mutant clones of immunologically competent cells such as lymphocytes. If such was the mechanism, neoplasia could act as a precipitating factor by competing with a defence mechanism against the development of such forbidden clones. Removal of the tumour would then allow the defence mechanism to suppress the activity of the forbidden clones and a clinical remission of the dermatomyositis would result. There is no evidence to suggest that dermatomyositis results from a direct toxic effect of a chemical substance released by tumour cells.

The primary tumour most commonly occurs in the lung, breast, female genital tract [46], stomach, rectum, kidney or testis. In the Chinese, nasopharyngeal carcinoma accounted for 75% of malignant disease [47]. The association with a range of tumours has been reviewed [48]. Dermatomyositis precedes the neoplasm in 40%, both conditions may occur together (26%) or the neoplasm may occur first (34%) [49]. It is difficult to assess the incidence of carcinoma in association with dermatomyositis. Figures vary from 15 to 34% [50]. Using strict criteria, 26% of adult patients with dermatomyositis were found to have a malignancy [51]. Patients with dermatomyositis are more likely to have a malignancy than those with polymyositis, and usually do not fare so well. The incidence of neoplasia seems to be higher in males than in females with dermatomyositis [52], although this has not been noted by others [53]. The overall incidence in one series was 29% [54], but this rose to 40% in patients over 40 years and to 66% in males over 40 years. Neoplasia is not associated with childhood cases. Usually, dermatomyositis worsens in parallel with the progress of the neoplasm, but it may improve when the latter is treated. Neoplasia may be missed because of failure to reinvestigate relapse of previously stable dermatomyositis [53].

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Pathology [1]. Dermatomyositis mainly involves the skin and muscles, although occasionally other organs are affected. The histological appearance of the skin depends on the stage of the disease. In acute dermatomyositis, the changes resemble those of subacute LE, although the dermal oedema may be more extensive and involve all layers of the dermis. There is usually some lymphocytic infiltrate, either perivascular or in clumps. The majority of the cells are $CD4^+$ T cells and HLA-DR-expressing macrophages. B lymphocytes are absent [2]. The infiltrate may also include histiocytes, plasma cells and, occasionally, eosinophils. Mucin deposits commonly occur in the dermis, and mucin in an otherwise non-specific skin biopsy, although not diagnostic, is suggestive of dermatomyositis [1]. Hyperkeratosis, acanthosis and mild papillomatosis are features seen in Gottron's papules [3]. In the later stages, the collagen of the dermis may show thickening, homogenization and sclerosis, with thickening of the walls of cutaneous blood vessels. The epidermis becomes atrophic, with flattening of the rete ridges, and the basal layer may show an increase in pigment. At this stage, the appearance can be similar to that of scleroderma [4,5]. On direct immunofluorescence, IgM, IgG and C3 may be found at the dermal–epidermal junction in 50% of cases. Those with IgM may also have cytoid bodies [6]. The subcutaneous fat may show mucoid degeneration and lymphocytic infiltration, or sclerosis and calcification, sometimes with membranocystic changes [7].

The most frequently involved muscles are those of the limb girdles, the proximal parts of the limbs, the pharynx and the tongue. The muscle involvement [8] is not uniform. It is important to remember this, because histological examination of biopsy material may be negative. It

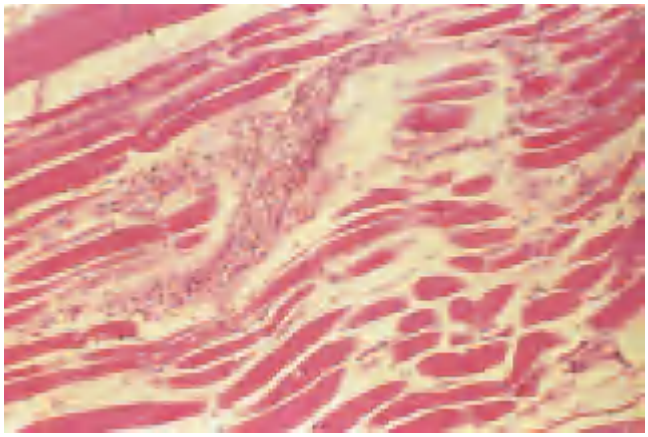

Fig. 56.80 Dermatomyositis: variable degeneration of the muscle bundles with oedema and inflammatory cells.

is better to try to obtain a specimen from a muscle that is clinically weak. The affected muscles may be pale, soft and flabby, or firm and fibrotic, depending on the stage of the disease. In patients with fibrosis, there may be calcification in the muscles and soft tissues. Histologically, in the early stages, the muscle fibres show loss of transverse striation, hyalinization of the sarcoplasm and an increase in sarcolemmal nuclei (Fig. 56.80). Later, the fibres fragment and show granular and vacuolar degeneration, and basophilic staining with histiocytic phagocytosis. There is variable cellular infiltration, mainly of lymphocytes, but also occasional plasma cells and macrophages. The blood vessels in the muscles may show eosinophilic intimal thickening, resembling the changes seen in malignant hypertension. Later still, the affected muscle fibres become atrophied and sclerosed, and resemble the changes seen in the muscles of systemic sclerosis. No significant morphological differences have been found in the muscles in any of the diagnostic subgroups of polymyositis and dermatomyositis, and no consistent relationship between pathological changes in serial biopsies and clinical improvement in individual patients [9].

Intimal proliferation and thrombosis of arteries and arterioles of the skin, fat and alimentary tract [10] are sometimes seen, and the latter accounts for the gastrointestinal ulceration and haemorrhage that occasionally occur [11]. Changes resembling those seen in systemic sclerosis occur in the lungs or in the kidneys. The heart muscle may show changes similar to, but milder than those in the voluntary muscles. Vasculitis of the cerebral and meningeal vessels has been reported, and in one case resulted in subarachnoid haemorrhage [12].

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Clinical features. The clinical picture is variable. Some patients with typical features of muscle involvement show little or no evidence of skin involvement, and the condition is then known as polymyositis [1,2]. Sometimes, the rash occurs alone [3,4], a condition that has been called amyopathic dermatomyositis, and this appears to imply a good prognosis [5]. Severe calcinosis may occur even in this variety [6]. In one series, the rash preceded muscle weakness in 56% of patients [7]. Usually, the patient first notices aching and weakness of the muscles, which may be painful and tender, and later show some atrophy. Typical histories include difficulty in going up stairs or rising from a chair, or difficulty in raising the arms high enough to comb the hair. Occasionally, patients may present with, or have nasal speech and regurgitation. Usually, there is a feeling of malaise, and fever may occur. Raynaud's phenomenon occurs in approximately 10% of adults, but is very rare in children. Obliteration of digital arteries may be revealed by arteriography [8]. Recurrent bursitis of shoulders and hips may precede myositis, and joint effusions occur [9,10].

The rash in well-developed cases is diagnostic. A purplish red heliotrope erythema occurs on the face, especially involving the eyelids, the upper cheeks, forehead and temples (Fig. 56.81). Oedema of the eyelids and periorbital tissues is not uncommon [11]. The distribution may resemble that of seborrhoeic dermatitis [12]. Oedema of the hands and arms and sometimes of much of the body may also be found, and this is usually associated with erythema of the backs of the forearms, the upper back and, sometimes, elsewhere. Small erythematous or violaceous, flat papules (Gottron's papules [13]) and small plaques occur over the knuckles, on the dorsa of the finger joints and around the nail folds (Fig. 56.82). They also occur on the dorsa of the toes, on the front of the knees and on the backs of the elbows. Frequently, the rash of dermatomyositis on the dorsa of the hands occurs as linear streaking over the extensor tendon sheaths (Fig. 56.83). These may be hyperpigmented as the only cutaneous

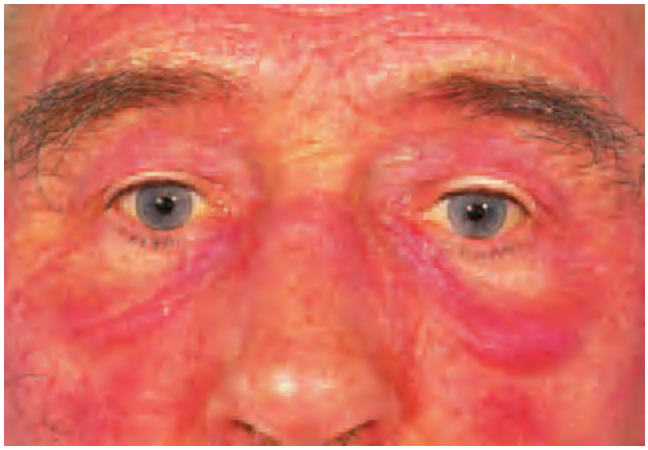

Fig. 56.81 Dermatomyositis: note the erythema and oedema of the eyelids.

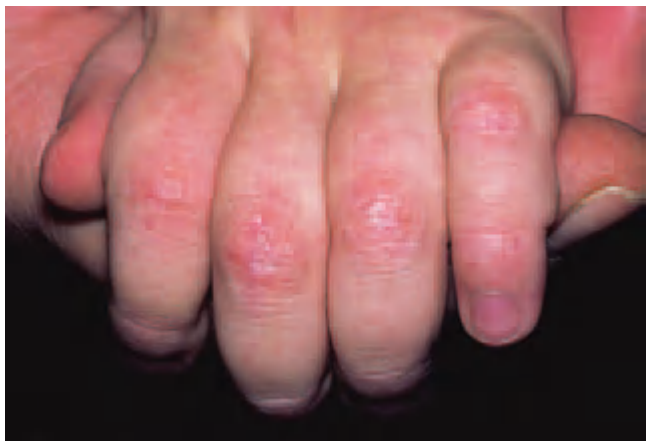

Fig. 56.82 Violaceous lesions on the dorsa of the finger joints in childhood dermatomyositis.

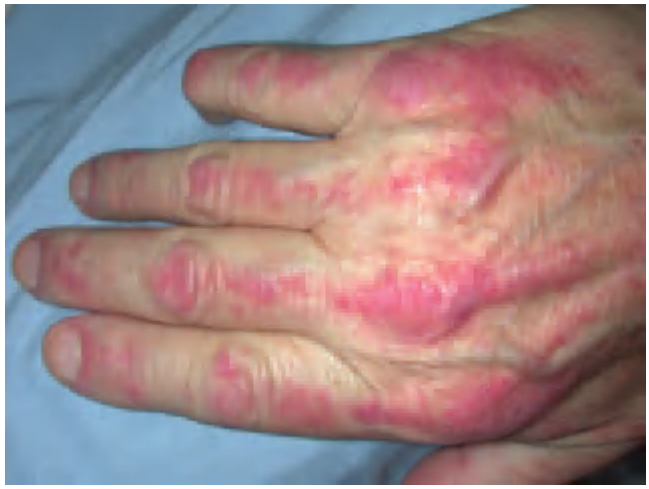

Fig. 56.83 The hands in dermatomyositis: note the linear erythema on the dorsa of the fingers.

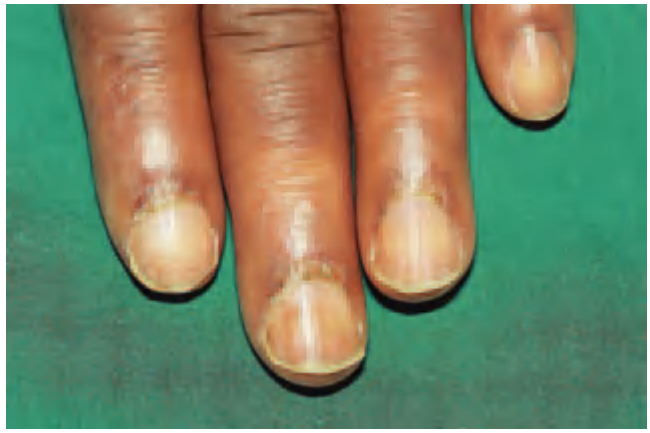

Fig. 56.84 Hyperpigmented nail fold lesions in an Afro-Caribbean patient with dermatomyositis.

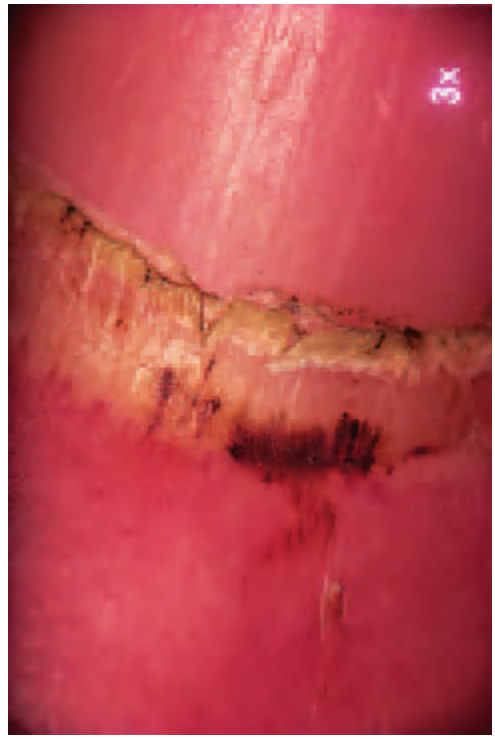

Fig. 56.85 Dermatomyositis: dilated nail fold capillaries and hypertrophic ragged cuticle.

sign in Afro-Caribbeans (Fig. 56.84) [14]. As well as diffuse redness and shininess of the nail folds, the capillary loops of the nail folds may be dilated, irregular and tortuous, and easily visible with or without a lens, or by capillaroscopy. The capillary changes are more marked in patients with Raynaud's phenomenon, arthritis and pulmonary involvement, but are not related to active myositis or malignancy (Fig. 56.85) [15]. Thickening, roughness, hyperkeratosis and irregularity of the cuticles, with minimal or no redness or inflammation [16], is frequent. Ragged cuticles are also found in other connective tissue diseases

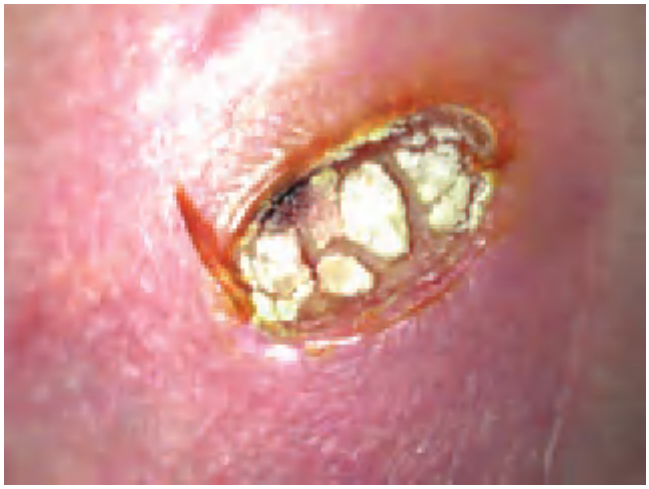

Fig. 56.86 Panniculitis with calcinosis in the thigh in dermatomyositis.

such as systemic sclerosis and LE. When healing occurs, reticulate telangiectatic erythema may be seen, with areas of atrophy and scarring, and sometimes pigmentation and depigmentation. At this stage, the appearances may resemble radiodermatitis.

Some cases show less specific changes, spreading erythema of the face and neck or of the limbs, and fleeting or more persistent oedema of the face and limbs. A wide variety of lesions has occasionally been reported: dermographism, bullous lesions [17], urticarial lesions [18], photosensitivity [19], erythema nodosum, erythema multiforme, follicular keratosis, hypertrichosis [20], hyperhidrosis, psoriasiform eruptions and pitting of the fingernails. Gingival telangiectasia appears to be common in childhood disease [21]. Linear, violaceous, itchy and oedematous streaks, mainly on the trunk and lasting a few weeks, have been likened to the pattern of zebra skin and called flagellate erythema [22]. Rarely, exfoliative dermatitis may occur. Hyperpigmentation occurs in the later stages. Erythema of the scalp, with diffuse alopecia, may develop. Livedo reticularis may occasionally be seen, and sometimes the skin breaks down to form ulcers up to 3 cm in diameter, containing pale green sloughs. In other patients, red firm tender areas of panniculitis develop (Fig. 56.86), and these may ulcerate or break down to form sinuses [23,24]. In the Chinese, hyperkeratotic follicular erythematous papules occur on the face, back of the neck, trunk, dorsa of the hands and feet, and palms and soles. On the dorsa of the hands and feet, the lesions occur in a linear fashion [25]. Patients with antisynthetase antibodies may have 'mechanics hands'—hyperkeratosis, fissuring and linear hyperpigmentation of radial and palmar surfaces of the fingers [26]. Histology shows hyperkeratosis, acanthosis, a mononuclear dermal infiltrate and liquefaction necrosis of the basal layer [27].

In addition to the weakness of the limb muscles, which is mainly proximal, there may be difficulty with speech and swallowing (because of involvement of the muscles of the tongue, the pharynx and the upper third or distal part [28] of the oesophagus), diverticular out-pouching of the oesophagus [29], impaired muscular activity of the small intestine, pneumatosis intestinalis [30], sometimes with pneumoperitoneum [31], wide-mouthed diverticula of the colon, weakness of the ocular muscles and respiratory difficulty from involvement of the intercostal muscles and diaphragm. The cause of death is usually respiratory infection or heart failure. Interstitial pneumonitis [32], with non-productive cough, dyspnoea and hypoxaemia and radiological infiltrates or pulmonary fibrosis, may be the presenting manifestations or may occur in the course of the disease [33]. Pulmonary hypertension, with cor pulmonale [34] and fibrosing alveolitis [35], has been reported. Interstitial lung disease may be more frequent than suspected [33]. Myocarditis, myocardial fibrosis, disorders of conduction and cardiac failure occur in approximately one-third of cases [36]. Renal lesions are uncommon [37]. Retinitis produces fluffy exudates around the papilla and along the veins; permanent visual loss occurs rarely [38]. A case of myoglobinuric acute renal failure has been reported [39]. Calcification [40] occurs in the muscles of more than half of childhood cases, and approximately 15% of adults. The muscles mainly involved are those of the shoulder and pelvic girdles, and to a lesser extent those of the trunk and the limbs, especially around the elbows and hands. In adults, the distribution is less markedly around the pelvic and shoulder girdles than in childhood. Calcinosis increases over the course of months or years and, if extensive, can cause severe functional disability. Calcification also occurs in the subcutaneous tissues. Extrusion of calcium through the skin is associated with ulceration and cellulitis. Calcinosis is a good sign for survival, but functional recovery is less likely. Sometimes, patients present with widespread calcification and apparently have not had a preceding myositic illness. In these cases, it is presumed—but not proved—that calcinosis is the result of old dermatomyositis. Sometimes, calcinosis developing in childhood decreases in adolescence; rarely, hypercalcaemia may occur [41]. A mild inflammatory arthritis may occur; erosive arthritis is rare. Patients with arthritis frequently have pulmonary involvement [42]. Trigeminal neuropathy has been reported [43].

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Dermatomyositis in childhood. This has been well described [1,2]. It is possible that microchimerism may be an aetiological factor [3]. The condition resembles that seen in adults, but malignancy is rarely associated with it and it is usually much more severe than in adults. The prognosis is variable. Calcification occurs more frequently than in adults and contractures develop in under 5%. Widespread vasculitis affecting small arteries, capillaries and veins of the skin, muscle, subcutaneous tissue and gastrointestinal tract is a prominent feature of the so-called Banker type [4,5]. It may take many years for the disease to burn out. Occasionally, a child recovers without any residual disability. Late recurrences are rare. Psychological difficulties occur more frequently than might be expected [6]. A rare feature is hypertrichosis (Fig. 56.87) [7,8]. Juvenile dermatomyositis can be associated with partial lipodystrophy [9].

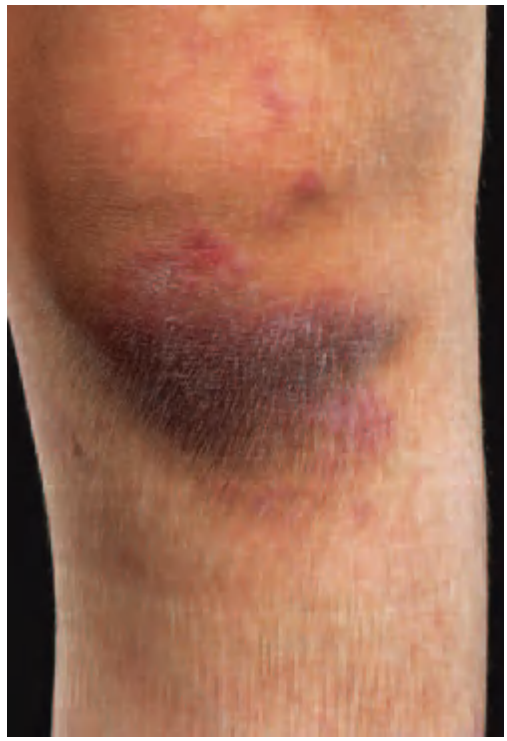

Fig. 56.87 Hypertrichosis in an area of erythema on the knee in childhood dermatomyositis.

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Sclerodermatomyositis in childhood. This is an overlap syndrome in which cutaneous changes of systemic sclerosis and dermatomyositis are associated with myositis and the homogeneous nucleolar pattern of antinuclear antibody (anti-PM/Scl antibody). Serum muscle enzymes are normal or only slightly raised. The features of dermatomyositis are usually transient and respond to non-steroidal anti-inflammatory drugs or corticosteroids, and aggressive treatment is not usually required. The systemic sclerosis features such as Raynaud's phenomenon, calcinosis and arthritis tend to grumble on over years, but visceral involvement is not marked. One case with 'mechanic's hands'—hyperkeratosis and fissuring on the tips and sides of the fingers resembling a labourer's dirty hands—has been reported [1].

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Dermatomyositis in pregnancy [1,2]. Pregnancy exacerbates the disease in approximately 50% and is associated with remission in 20%. Dermatomyositis can start in pregnancy. The overall fetal loss is over 50%, and half of pregnancies end prematurely. Fertility is decreased [3]. Pregnancy should be planned at a time of remission and the patient monitored at least every month. If possible, treatment should be confined to oral steroids.

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Association with other disorders. The association with carcinoma in adults has already been mentioned. Dermatomyositis has been reported in association with thymoma [1] and hyperthyroidism [2], and complicating penicillamine therapy [3]. A dermatomyositis-like eruption has been reported in association with hydroxyurea therapy, where ulceration of the legs may occur [4]. Calcinosis universalis, involving the central portion of the trunk, probably results from old dermatomyositis. Presentation with aplastic anaemia [5] and haemolytic anaemia [6], and in association with agammaglobulinaemia [7], cystinuria [8], Hashimoto's disease and ovarian carcinoma [9], generalized amyloidosis [10], multiple myeloma [11], lichen myxoedematosus [12], dermatitis herpetiformis [13], as well as coeliac disease [14], bullous pemphigoid [15], porphyria cutanea tarda [16], fibrosing alveolitis [17], cutaneous vasculitis [18], Sjögren's syndrome [19] and Hughes' syndrome [20] have been described. Linear morphoea of the back of the thigh in a child of 7 years with dermatomyositis and calcinosis has been seen. Polymyositis has been reported with periorbital fasciitis [21]. Multiple asymmetrical lesions of lipoatrophy have been reported in a patient with juvenile dermatomyositis [22], and partial lipodystrophy has also occurred with phaeochromocytoma and urticarial vasculitis [23].

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Differential diagnosis. The diagnosis depends upon the association of a typical rash with muscle weakness, and is confirmed by muscle biopsy, electromyography and certain laboratory investigations. The serum creatine phosphokinase (CPK), glutamic oxalacetic transaminase (SGOT) or aldolase are frequently, but not invariably raised [1,2], and in certain cases may reflect the activity of the disease and be helpful in regulating the dosage of steroids [3,4]. However, some patients continue to show considerable activity in the presence of normal serum enzymes, so serial estimations of the 24-h urinary creatine are helpful, if available [5]. Skin and muscle biopsy are helpful, but histological changes may be absent or minimal. Radiology of the muscles in the later stages may show calcinosis, a feature that may differentiate the condition from SLE [6]. In dermatomyositis, the calcium deposits are widely scattered throughout the muscles and soft tissues, whereas in systemic sclerosis the calcium deposits are found mainly in the hands and around the elbows and knees. Moreover, in the latter, the tips of the terminal phalanges often show some bone resorption. MRI scanning [7] and ultrasound give useful information for longitudinal studies and are non-invasive [8]. In patients with little or no rash, muscular dystrophies may be closely simulated [9]; dermatomyositis is of more rapid onset and remissions are frequent.

Electromyography [10] is helpful in distinguishing myopathy from neuropathy. The ESR is moderately elevated in some, but not all patients in the active phase, and there may be some elevation of the serum globulin. It has been claimed that an elevated ESR and cutaneous necrosis are potential markers of malignancy [11]. Antinuclear factor, raised DNA binding and anti-RNP may occur, especially in overlap syndromes [12]. Antibodies to aminoacyl-tRNA synthetase are antibodies to soluble nuclear antigens and are associated with myositis [13]. Anti-Jo-1 antibody, an autoantibody directed at the cellular enzyme histidyl-tRNA synthetase, is found in 25% of patients with myositis, especially in those with cryptogenic fibrosing alveolitis, Raynaud's phenomenon, sicca syndrome and mild arthritis [14]. Anti-Ku antibody is associated with dermatomyositis–systemic sclerosis overlap syndromes, which have a good prognosis [15], and anti-KJ with polymyositis and interstitial lung disease [16]. KL6 may also be a marker for interstitial lung disease [17]. Antibodies to cytoplasmic antigens such as anti-SRP (signal recognition particle) occur, and antibodies to the nuclear antigen Mi-2 are strongly associated with dermatomyositis [18]. Occasionally, rheumatoid factor is found. The Wassermann reaction is negative. Anticardiolipin antibodies were found in three out of 14 patients with juvenile dermatomyositis, two of whom had vascular complications [19]. In all adult cases, a determined effort to exclude internal malignancy should be carried out [20], but most of the neoplasms can be diagnosed by physical examination (including the breasts, pelvis and rectum), blood count, radiography of the chest, examination of the stools for occult blood and, in men, acid phosphatase estimation.

Dermatomyositis can be confused with systemic sclerosis, and the two conditions can occur together. The muscle changes may be identical in the two disorders, but visceral changes are much more common in systemic sclerosis. Antinuclear factor can commonly be demonstrated in the serum in systemic sclerosis, but is frequently absent in dermatomyositis. From the clinical point of view, differentiation between the two diseases may be difficult, particularly in those cases showing sclerosis in the healing phase. Occasionally, patients with systemic sclerosis show heliotrope cyanosis of the eyelids, and dilatation of the nail fold capillaries. Sometimes, patients with dermatomyositis resemble patients with SLE but, in the latter, antinuclear factors and anti-DNA antibodies can usually be demonstrated. Myositis is a feature of so-called mixed connective tissue disease (see p. 56.116). Neuropathy is distinguished by the electromyographic changes and the presence of a raised CPK and urinary creatine excretion. The atrophic changes of the skin in the later stages may resemble morphoea, but the history should lead to the correct diagnosis. Polymyositis [21,22] is more common than dermatomyositis. It is usually found in adults in the third to the fifth decades. Females are three times more likely to develop the disease than males. Occasionally, scleroedema may cause difficulty. It is important to exclude metabolic disorders in those patients with only muscle disease [23].

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Prognosis [1–4]. The course is variable. The prognosis is said to be better in dermatomyositis than in polymyositis; however, some have found the reverse to be true [5]. Patients without muscle involvement have a better prognosis and may not require steroids [6]. Doubts have been cast about the dosage of steroids required. No alteration in survival was shown when low-dose therapy was compared with high-dose therapy [7]. Combined therapy with azathioprine produces better results than steroids alone [8]. Approximately 50% of patients seem to be responsive to therapy; the remainder appear to be relatively resistant. The overall mortality is approximately one-quarter [9], and two-thirds of deaths result from carcinoma [1]. Adverse factors include acute pulmonary infiltrations, dysphagia, cutaneous necrosis and increasing age. Fulminating cases may deteriorate rapidly despite therapy, and some 20% die within the first year. After an acute phase lasting some months, most cases settle slowly and burn out in time, usually over several years. Sometimes, patients complain of vague aching in the limbs when there does not appear to be any residual activity. One patient had three separate episodes over 33 years [10]. Some are left with minimal cutaneous change and no residual weakness. Others, particularly children, have gross disability, with contractures of the limbs and calcinosis. Of the children followed up for 5–16 years, 75% survived [11]. Removal of an underlying carcinoma in adults can lead to regression of the dermatomyositis [12].

Calcinosis is a good prognostic feature. Out of 75 adults without calcification, 26 died, usually in approximately 2 years, whereas of 12 adults with calcinosis none died [13]. Seven out of 14 children without, and only one of 17 with calcinosis died in a mean time of approximately 16 months. Calcification can decrease without treatment.

Death usually occurs from respiratory infection, cardiac failure, malnutrition, weakness or debility because of difficulty in swallowing, carcinoma, or from the side effects of steroid therapy.

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Treatment [1]. Rest is essential in the acute phase. In adults it is important to exclude an underlying carcinoma. Treatment with corticosteroids is required in almost all cases, the dosage depending upon the degree of activity. Initial dosage of as much as 60–120 mg/day prednisolone may be required. This dosage should be gradually reduced as the patient clinically improves and the biochemical markers improve. However, a maintenance dosage of between 5 and 15 mg/day may be required for many months, or even years, and it is important to balance the maximum therapeutic effect against the presence of side effects. If the clinical signs and serum CPK level are not improving sufficiently quickly, bolus infusions of methylprednisolone (1 g on three successive days) may be tried. Alternatively, an antimetabolite should be added. Oral azathioprine (1.5–3 mg/kg/day in divided doses) as a steroid-sparing agent, or oral methotrexate in a small

weekly dosage (7.5–15 mg) may be used. This may only suppress disease activity [2], and treatment may have to be stopped because of side effects [3]. Intravenous methotrexate (0.5–0.8 mg/kg at weekly intervals, after a test dose) has been advocated [4]. Patients not responding to prednisolone and immunosuppressives may be helped by the addition of ciclosporin 5 mg/kg/day [5]. Ciclosporin is also effective in childhood in a dosage of 2.5–7.5 mg/kg [6]. It has also been used alone in childhood as an initial treatment [7]. A number of studies have indicated a successful role for intravenous immunoglobulin in a regimen of 1 mg/kg for 2 days each month over 4–6 months [8,9]. Lower dosage may also be successful, and it may be combined with ciclosporin [10]. Cyclophosphamide 100 mg/day [11], or as pulsed intravenous therapy, is used for pulmonary interstitial fibrosis.

Children with minimal myopathy may remit with indometacin without steroids [12], and antimalarials may help the rash of dermatomyositis, which may persist when muscle activity settles [13]. Topical steroid or a topical calcineurin inhibitor may be of value [14]. Levamisole (100 mg/week) [15] or plasma exchange [16,17] may help patients with severe disease not responding to steroids or immunosuppressives. Improvement may occur within 48 h of plasmapheresis [18]. Extracorporeal photochemotherapy may be useful in combination with other therapies [19]. Methandienone (30 mg/day) [20], dapsone [21] and pentoxifylline [22] have all produced apparent improvement in patients unresponsive to corticosteroids. Whole-body radiation produced dramatic improvement in a patient with polymyositis [23]. Antiplatelet agents—aspirin (650 mg/day), dipyridamole (400 mg/day) and sulfinpyrazone (400 mg/day)—helped one patient with *in vivo* platelet thrombi formation causing digital and vascular ischaemia [24].

Therapy, with either prednisolone alone or in combination with an antimetabolite, may be required for some years, and the dosage is reduced very gradually until the disease is burnt out. Any recrudescence is treated with an increase in dosage. Early treatment with low-dose steroids in children is associated with fewer relapses and lower morbidity [25]. Occasionally, weakness may arise from corticosteroid myopathy, and may be difficult to distinguish from an exacerbation of the disease. Serum enzymes are normal, but the 24-h urinary creatine excretion is raised [26]. Recovery on reduction of dosage takes up to 4 months. Weakness in dermatomyositis may occur because of hypokalaemia, the result of corticosteroid therapy. Regular electrolyte estimations are required and potassium supplements should be given.

Gastrointestinal haemorrhage may occur as a result of the disease or corticosteroid therapy. Constipation can be a feature, and octreotide may increase gastrointestinal motility. Osteoporosis is a considerable risk because of immobility and corticosteroid therapy, and prophylactic treatment should be given to both female and male patients. Backache may be caused by corticosteroid osteoporosis, although it is also a common symptom of the disease itself.

Treatment of calcinosis is usually ineffective, although spontaneous improvement can occur after the disease burns out. Warfarin (1 mg/day) [27] or probenecid 2 g/day [28] may be worth trying. The results of the administration of chelating agents have been disappointing [29]. Aluminium oxide, by producing insoluble aluminium phosphate, decreases the intestinal absorption of phosphate and has been successfully used in calcinosis in a child. Aludrox 15 mL four times daily (2.4 g/day aluminium oxide) was given by mouth [30]. Diltiazem has also been used succesfully [31].

Physiotherapy plays a considerable part in preventing the development of contractures, and careful splinting may also be required. Artificial ventilation may be required in reversible transitory ventilatory failure [32], as may intravenous feeding in patients with severe oesophageal involvement. If there is definite serological evidence of recent infection with *Toxoplasma gondii*, treatment with pyrimethamine and/or sulfadiazine may be indicated [33].

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Dermatological manifestations of rheumatoid disease

Dermatologists may be concerned with the diagnosis and management of several skin lesions that may occur in association with rheumatoid arthritis, although most patients will probably be under the care of a rheumatologist. Others present primarily as dermatological problems, and the presence of rheumatoid arthritis is detected on general examination of the patient. The occurrence of rheumatoid nodules and vasculitis in rheumatoid disease is well recognized, but more recently other abnormalities, such as transparent skin and linear subcutaneous bands, have been described in detail [1]. Localized areas of atrophy and liver palms also occur.

Sometimes, there may be difficulty in deciding between rheumatoid disease and SLE. In the skin of the former, fluorescence of the dermal–epidermal junction is not found [2], even in cases with a high titre of antinuclear factor [3].

Pseudosclerodermatous changes, particularly of the hands, occur in rheumatoid arthritis, and arthralgia, tenderness and swelling of the joints are presenting features of some patients with systemic sclerosis. Systemic sclerosis and rheumatoid arthritis may also coexist [4].

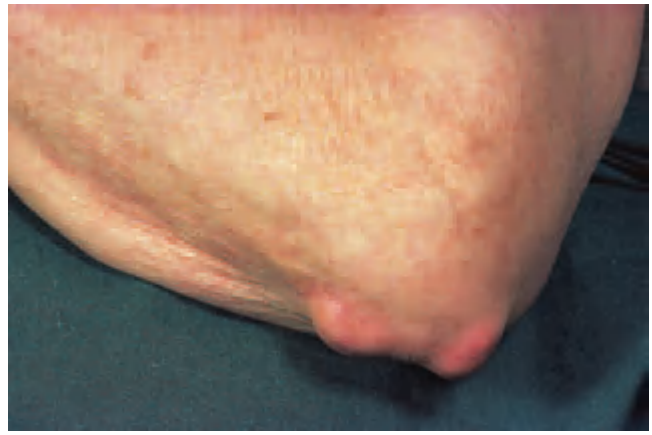

Fig. 56.88 Rheumatoid nodules on the elbow.

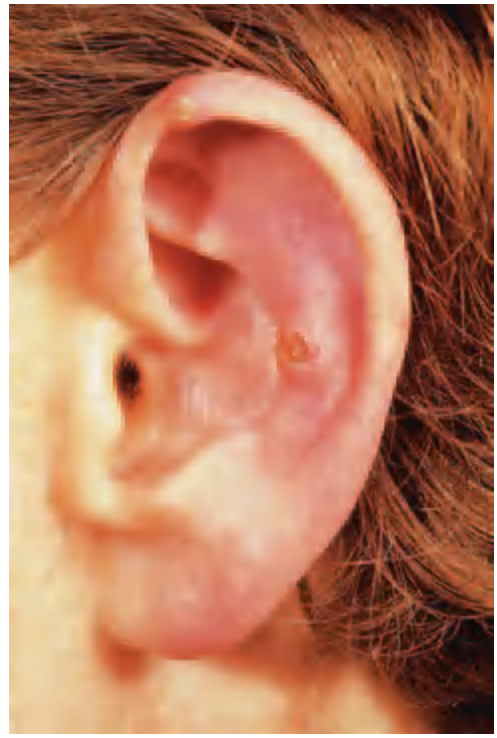

Fig. 56.89 Ulcerated rheumatoid nodule on the ear.

Rheumatoid nodules (Fig. 56.88)

Palpable subcutaneous nodules occur in approximately 20% of patients with rheumatoid arthritis. The most common site is on the ulnar border of the forearm. Less commonly, they occur on the dorsa of the hands, on the knees, on the ears, over the scapulae and occasionally in other areas, especially those subject to pressure, such as the sacrum, buttocks or heels. They vary in size up to several centimetres in diameter, are firm in consistency and tend to ulcerate with trauma (Fig. 56.89). This is particularly important on the sacrum, where ulceration may be missed [5]. Secondary infection with staphylococci can result

in staphylococcal septicaemia and septic arthritis. Subcutaneous nodules can erode the underlying bone [6]. Sometimes, there are numerous violaceous papules with centripetal scaling. A variant of rheumatoid disease, termed 'rheumatoid nodulosis' [7], has been described in which nodules occurred with palindromic rheumatism and little evidence of synovitis. Nodules are multiple and small, and recur mainly on the hands and feet. Rheumatoid nodulosis may, after many years, turn into rheumatoid disease with joint involvement.

Nodules are almost invariably associated with more severe forms of the disease, and rheumatoid factor and antinuclear factors are frequently found in the serum. Occasionally, nodules may occur in mild rheumatoid arthritis and in anarthritic rheumatoid disease [8]. Sometimes, they may precede rheumatoid arthritis by some years [9]. Rheumatoid nodules may rarely occur in the sclera (scleromalacia). The sclera becomes atrophic and may perforate (scleromalacia perforans), leading to complete blindness.

Histologically, rheumatoid nodules consist of fibrous tissue in which foci of fibrinoid necrosis are scattered, surrounded by a palisade of cells, mainly fibroblasts and histiocytes. A peripheral zone of lymphocytes and plasma cells occurs. Within the necrotic area are thin reticulum fibres, similar to those seen in young granulation tissue, amorphous material and some nuclear debris. Vasculitis can occur in rheumatoid nodules and papules. The histology has features in common with those of granuloma annulare (see Chapter 57).

The subcutaneous nodules of rheumatic fever [10] can be distinguished histologically from those of rheumatoid arthritis. There is much fibrinoid material, considerable oedema of the collagen, but relatively little infiltration with fibroblasts, histiocytes or lymphocytes. There is little attempt at zoning and fibrosis is minimal or absent. Large mononuclear cells, like those seen in Aschoff's nodes in the myocardium, may be found. Nodules from patients with Still's disease (juvenile rheumatoid arthritis) [10] resemble those seen in rheumatic fever.

Linear subcutaneous bands [11]

Elongated subcutaneous bands, 3–5 mm wide and 10 cm or more in length, have been described in patients with rheumatoid arthritis with nodules.

Histologically, the bands show changes similar to the nodules. The bands, which are firm and non-tender, are adherent to the skin. They have so far been observed in the axilla, and extending from the axilla to the iliac crest.

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Vascular lesions in rheumatoid arthritis [1–5]

The presence of vascular lesions in rheumatoid arthritis has been increasingly recognized in recent years. Raynaud's phenomenon is uncommon; it occurred in only 2.7% of one series [6].

The most characteristic lesions of arteritis in rheumatoid patients are small infarcts around the nails, sometimes at the apex of small cutaneous nodules. These are best seen with a magnifying glass and a bright light. The lesions are usually transitory and may last only 2 or 3 days. Because they are usually painless, patients rarely complain about or even notice the lesions. Usually, a small brown spot persists a little longer, and sometimes scarring may occur. Occasionally, infarcts of the nail fold may result in grooving of the nail. Such lesions occurred in 34% of males and 18% of females in 157 consecutive cases of rheumatoid arthritis [3]. This sex incidence is similar to that found in other forms of arteritis in rheumatoid arthritis. Of these patients, 50% were on long-term corticosteroids, whereas of those without arteritic changes only 38% were on steroids. It is difficult to be certain whether patients are more likely to develop arteritis on steroids, although there is some evidence that this may be so [7]. Certainly, arteritic lesions seem to occur when steroids are stopped suddenly or the dosage is changed, or when the patient is under physical stress. In addition to arteritic lesions in the skin, a sensory or motor neuropathy may occur at these times. The lesions may also be confused with those caused by occupational trauma. Tailor's cutters are particularly liable to show small black marks on the nail folds, which are the result of trauma from needles [3], and similar-looking lesions have been reported in a woodworker whose nail folds had been hit by a hammer [3]. The occurrence of digital necroses is closely correlated with the presence of rheumatoid factor and rheumatoid nodules [2]. Anticardiolipin antibodies can sometimes be demonstrated in patients with vasculitis, and are statistically significantly related to rheumatoid nodules but not

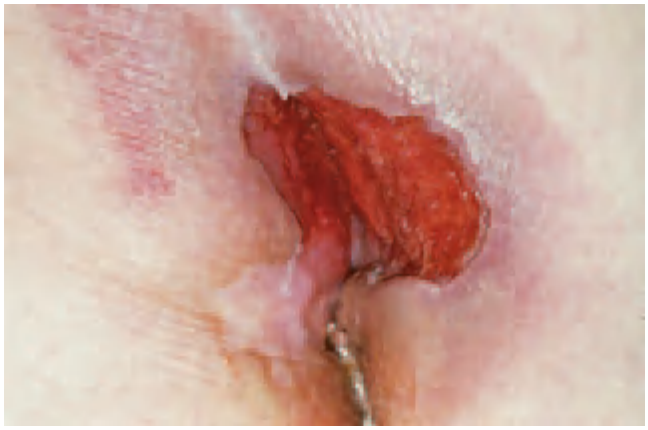

Fig. 56.90 Felty's syndrome: pyoderma gangrenosum of the perianal area.

to thrombotic events [8]. In 13 out of 24 patients antinuclear factor could be demonstrated, sometimes transiently, but these were not regarded as cases of SLE. In addition to the infarcts around the nail folds, the pulps of the fingers may show small painful purpuric nodules (Bywaters' lesions). Histologically, these show leukocytoclastic vasculitis [9]. Palmar erythema is common.

In addition, the skin may show purpuric and necrotic arteritic lesions, which can be painful. The haemorrhagic areas appear without preceding trauma, and vary in size from small petechiae to areas of bruising and necrosis several centimetres in diameter. Sometimes, these areas develop black crusting, which may break down and ulcerate. The ulcers are well defined, with a surrounding bluish red halo. Some of the ulcers are related to rheumatoid nodules. Healing occurs with scarring and may be slow. Arteritis occurs widely in rheumatoid disease, and involvement of the gastrointestinal tract [10] gives rise to abdominal pain, which may result from multiple ischaemic ulcers, gangrene of the bowel, intraperitoneal haemorrhage or splenic infarction.

Gangrene may result from changes in the digital vessels, and sometimes this may extend to involve a large part of the foot or hand, occasionally within a few days. Extensive pustular panniculitis, particularly on the legs, may occur as the result of breakdown of red painful nodular lesions. Treatment can be very difficult [11].

Leg ulcers are not uncommon in the rheumatoid population. Although vasculitis is an important cause, it was only considered to be a factor in 18% of rheumatoid patients in a recent series [12]. Venous insufficiency, complicated by immobility and postural factors, occurs in nearly half of cases, and trauma, pressure or arterial insufficiency are also major factors. Leg ulcers [13] may also be pyodermatous (Fig. 56.90). Arteritic ulcers are more common in males, particularly those with subcutaneous nodules and positive tests for rheumatoid factor. They are usually deep, punched out and slow healing. There is little discoloration of the legs and usually no sclerosis. Some of the ulcers may start as frankly purpuric or nodular lesions. Secondary infection is common, especially with *Staphylococcus aureus*. Response to treatment is slow and relapse frequent. Ten of 27 cases [13] were associated with other clinical evidence of arteritis. Although six patients with leg ulcers and rheumatoid arthritis were described as cases of SLE [14], mainly because of the demonstration of LE cells in four of them, there seems little doubt that they had rheumatoid arthritis. Leg ulcers are said to be more common in Felty's syndrome, in which arthritis is associated with splenomegaly and leukopenia.

Sometimes, bullae of the finger- and toetips may occur in the arteritic lesions of rheumatoid arthritis and occasionally spread to involve a large part of the body [3]. Livedo reticularis [15] also occurs in rheumatoid arthritis, as does delayed pressure-induced vasculitis.

Peripheral sensory or motor neuropathy [16–18] is often associated with clinical evidence of arteritis elsewhere, and is caused by occlusion of the vasa nervorum by the arteritic process. These patients also have a high incidence of rheumatoid factor and nodule formation.

A rash identical to that found in Still's disease (juvenile rheumatoid arthritis; see p. 56.142) occurs in adult rheumatoid arthritis, but is rare. It was found in only seven out of more than 500 patients [19].

Rheumatoid neutrophilic dermatosis. This may occur [20,21] in patients with severe arthritis as symmetrical erythematous nodules and 'urticaria-like' plaques on the dorsa of the hands and arms, extensor aspects of the joints, and the back of the neck and scalp and trunk. They are sometimes tender. Vertical symmetrical infiltrated linear cords on the median axillary line have been reported [22]. Ulceration and vesiculation may occur. Histologically, there is a dense diffuse infiltrate of neutrophils in the dermis, papillary microabscesses and leukocytoclasia, but no vasculitis. The lunulae may be red [23]. Pyoderma gangrenosum may occur in association with neutrophilic dermatosis [24]. Dapsone, either alone or combined with colchicine, may help rheumatoid vasculitis and neutrophilic dermatosis [25]. Another possible cause of nodulosis is the coexistence of erythema elevatum diutinum [26].

Many patients with rheumatoid arthritis who have been treated with steroids show the typical purple discoloration of corticosteroid therapy. This is mainly found on the posterior aspect of the forearms, although it may occur on the legs and elsewhere, and is caused by shearing of the blood vessels in the dermis as the result of degeneration of the dermal collagen.

Associations with other disorders. These have been comprehensively reviewed [27]. They include bullous pemphigoid, pemphigus vulgaris, pemphigus foliaceus, dermatitis herpetiformis, subcorneal pustular dermatosis [28], epidermolysis bullosa acquisita, yellow-nail syn-

drome, acquired cutis laxa [29] and angioendotheliomatosis [30].

Erosive pustular dermatosis of the scalp has been reported [31].

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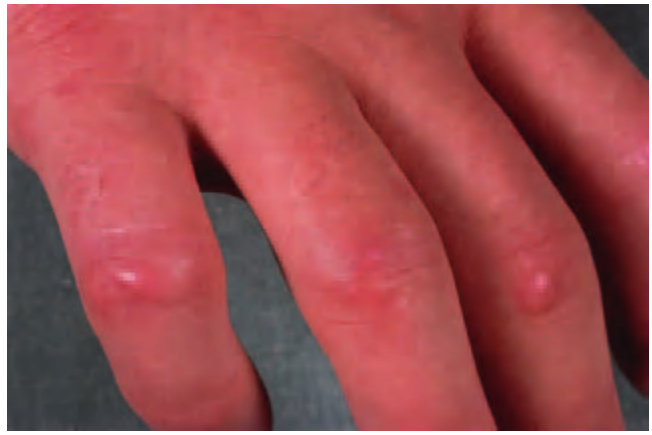

Fig. 56.91 Nodules on the dorsa of the interphalangeal joints in fibroblastic rheumatism. (Courtesy of Dr M.H.A. Rustin, The Royal Free Hospital, London, UK.)

Fibroblastic rheumatism

This entity was originally described by Chaouat *et al*. [1] in 1980, and since then further cases have been described, mainly in France [2]. It occurs at all ages and affects both sexes equally. Clinically, it starts suddenly with symmetrical polyarthritis and cutaneous nodules. These are between 5 and 20 cm in diameter, and can occur before the onset of arthritis. Raynaud's phenomenon, sclerodactyly with inability to join palms, joint effusions and stiffness are frequent. The nodules occur on both surfaces of the hands, usually over the joints, and on the elbows, knees, ears and neck (Fig. 56.91). They are smooth, firm and usually skin-coloured. They resolve in 6 months to a few years. Histology shows a marked proliferation of spindle cells and dermal fibrosis. The hyperplastic cells have the phenotypic features of muscle, suggesting myofibroblastic differentiation [3]. There is a reduction of collagen and non-collagen protein synthesis by the fibroblasts from involved skin, which contrasts markedly with the increase in collagen synthesis in scleroderma.

Systemic involvement does not usually occur—all laboratory tests are negative.

Spontaneous resolution of the nodules may be expected. Joint erosions may develop and changes tend to persist. It is impossible to say whether treatment with aspirin, corticosteroids, colchicine, penicillamine and other anti-inflammatory agents influences the outcome.

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Still's disease

SYN. JUVENILE RHEUMATOID ARTHRITIS

The characteristic rash [1] is seen in approximately 25% of patients with Still's disease. It occurs in boys (36%) more frequently than in girls (22%), the incidence decreasing with age. It consists of small non-pruritic macules or papules up to 3 mm in diameter, with a slightly irregular margin. Larger lesions up to 5 cm show central pallor. The colour is bright salmon pink, often surrounded by a zone of pallor. The rash occurs most frequently on the limbs and trunk, but may occur on the face and neck, and lasts only a few hours, characteristically appearing at midday or in the evening with increased temperature of the patient or environment. It is more common in patients with fever, splenomegaly, lymphadenopathy and a raised ESR. It usually appears in the first 2 weeks of the disease but may precede other manifestations by up to 9 years. The rash may occur intermittently for many years and has no prognostic value [2].

Histologically, there is a scanty infiltrate, sometimes of neutrophils if the rash is marked, in the dermis. The rash fades as the disease settles; corticosteroids do not have a specific effect.

The rash can be distinguished from erythema marginatum by the smaller size of the lesions, their occurrence on the face and the fact that lesions are at their greatest size at the onset.

Subcutaneous nodules occur in Still's disease. The histology resembles that seen in the nodules of rheumatic fever rather than in those of rheumatoid arthritis [3]. Still's disease has been associated with Kikuchi's disease (see p. 56.62) [4,5].

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Adult Still's disease [1]

In 1971, Bywaters [2] described 14 adults with arthritis and clinical features similar to those of juvenile rheumatoid arthritis. Features include a high spiking fever, sore throat, joint pain and arthritis, a transitory maculopapular rash, lymphadenopathy, hepatosplenomegaly and serositis. The white cell count is raised, and rheumatoid and antinuclear factors are usually absent. Both sexes are equally affected, and the onset is usually in the mid-twenties. The salmon pink maculopapular rash is transitory. It usually occurs in the evening, with fever in over 80% of patients, on the proximal limbs, trunk and face. Alopecia is another feature. Histologically, there is a perivascular dermal infiltrate of lymphocytes and histiocytes. Immunofluorescence is negative. The rash is an adverse prognostic indicator. Approximately one-third remit and another third become chronic; the remainder have an intermittent course. Aspirin and other non-steroidal anti-inflammatory drugs are the first line of treatment, but systemic steroids may be required. In the more chronic cases, intramuscular or oral gold may be helpful. Methotrexate has been of benefit in refractory cases [3].

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Sjögren's syndrome [1,2]

SYN. GOUGEROT–HOUWER–SJÖGREN SYNDROME

In 1933, Sjögren [3] drew attention to the syndrome that now bears his name. The first case was described in 1888, although earlier authors had noted several of the manifestations. The most common features of the condition are dryness and atrophy of the conjunctiva and cornea (keratoconjunctivitis sicca), a dry mouth (xerostomia) and rheumatoid arthritis. Two of these three components, particularly the first two, are considered sufficient for diagnosis. The nasal mucosa, the throat and vagina may show similar dryness and atrophy, and there may be diminished gastric secretion. Swelling of the lacrimal and salivary glands may also occur. The diagnosis of keratoconjunctivitis sicca is confirmed by Schirmer's test, which measures tear secretion, staining the cornea and conjunctiva in the region of the palpebral fissure with rose bengal solution, and slit-lamp microscopy, which shows filiform keratitis. The syndrome has been divided into primary Sjögren's syndrome (sicca syndrome), which is not associated with any other connective tissue disease, and secondary Sjögren's syndrome, in which it is associated with rheumatoid arthritis, SLE or systemic sclerosis. The 'sicca' components alone occurred in 35% of one series [4]. Malignant lymphoma is associated with the primary form [5].

Aetiology. The onset occurs most frequently in the fourth, fifth and sixth decades, and 95% of the patients are women. A genetic predisposition is indicated by the finding of an increased incidence of HLA-B8 and -DR3 in patients with Sjögren's syndrome. Associations with the

complement allele C4AQO [6] and HLA-DRw52 [7] in Japanese patients have been reported. That genetic subsets occur is shown by the increased frequency of DR2 in primary Sjögren's syndrome associated with rheumatoid arthritis [8]. There is also an increase in DR4 in patients with primary Sjögren's syndrome and Raynaud's phenomenon [9]. Antibodies to Ro occur in excess in relatives of patients with Sjögren's syndrome, especially in association with DR2 and DR3 [10]. The presence of hypergammaglobulinaemia, antinuclear factors and precipitating antibodies in the serum [11], together with the female predominance and age distribution, and the occurrence of a Sjögren-type syndrome after allogeneic bone marrow transplantation [12], suggest an autoimmune aetiology. Further evidence is provided by the infiltration of the tissues by lymphocytes and plasma cells, and the experimental production of sialoadenitis in guinea pigs [13]. Over 90% show reactivity to parotid extract antigen in the leukocyte migration test [14]. Tubuloreticular structures possibly related to viral infection have been found in labial salivary glands [15]. Raised levels of IgG antibody to cytomegalovirus have been reported [16] and there have been recent suggestions of a link to hepatitis infection [17].

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Pathology [1]. The changes in the salivary glands are strikingly similar to the thyroid changes in Hashimoto's disease. Infiltration with lymphocytes and plasma cells, and connective tissue proliferation, are followed by fibrosis. Histological examination of skin may show absence of sebaceous glands and a decrease in the number of sweat glands [2]. Cellular infiltration round the sweat glands has been reported [3,4]. Focal lymphocytic infiltration has been observed in the mucous membranes, and reduced secretory activity of the submucous glands of the respiratory and upper alimentary tracts and of the vagina accompanies progressive atrophy. Degenerative changes are also reported in apocrine glands and in the external root sheath of hair follicles [5].

The mucocutaneous lesions are largely the result of diminished exocrine gland activity, but the ocular changes may not be entirely attributable to reduced secretion of tears. The conjunctiva is at first oedematous but is later very thin. In the subepithelial tissue there is early destruction of elastic tissue, hyalinization of collagen and infiltration with plasma cells.

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Clinical features [1–6]. The clinical picture is extremely variable. The consequences of reduced exocrine gland activity may be a minor manifestation of a serious systemic illness, or the presenting, and for many years the only features. In a prospective study of patients presenting with dry eyes, 43% were found to have keratoconjunctivitis sicca with xerostomia, and 23% had associated connective tissue disease, particularly rheumatoid arthritis [7]. Oral symptoms may precede ocular, or both may occur late in the disease. Some cases present with generalized or anogenital pruritus, or with diffuse alopecia. Reduction in the appreciation of taste and smell has been observed [8]. Infections, including pneumonia, oral candidosis and bacterial conjunctivitis, are frequent.

Skin manifestations. Dryness of the skin occurs in approximately 50% of patients, and scaling occurs in approximately

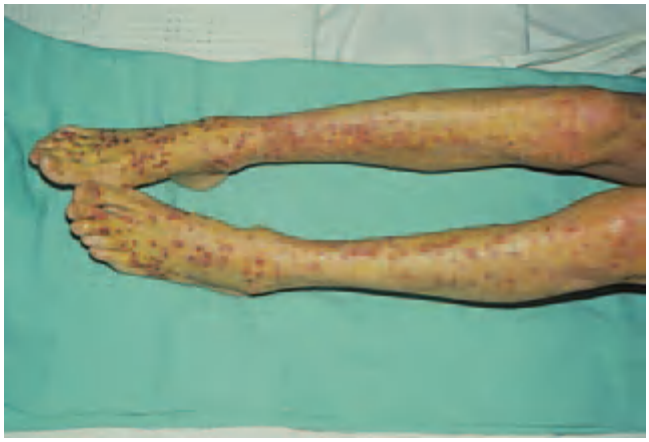

Fig. 56.92 Hyperglobulinaemic purpura in Sjögren's syndrome.

25% of these. The skin may be irritable, and secondary lichenification can develop. Annular erythematous lesions, considered to be a variant of SLE [9], have been reported, but other patients have had no histological evidence of LE [10,11]. Annular erythema in Japanese patients may differ from others. In Japan, annular erythema has been subdivided into three types clinically: Sweet's disease-like annular erythema with an elevated border; SCLE-like marginally scaled erythema; and papular erythema [12]. Annular erythema of Asian patients is the counterpart of SCLE in white people, and may occur in patients with LE, Sjögren's syndrome or both diseases [13]. Lesions are recurrent and often occur on the face and trunk; they clear without pigmentation. They are not photosensitive in origin. Ro antibody-positive patients tend to develop annular polycyclic lesions of SCLE as well as neuropsychiatric and pulmonary disease, and have a guarded prognosis [14]. Partial or complete loss of sweating may be noted. Vascular responsiveness may also be impaired [15], and nail fold capillary abnormalities are found [16]. The hair may be dry, sparse and brittle, and diffuse alopecia may involve the scalp, limbs, axillae and pubis. Erythema of the nose and cheeks has been reported [5].

Non-thrombocytopenic purpura may occur as recurrent crops of round pink lesions in dependent areas (Fig. 56.92). The lesions resolve in a few days, leaving brown pigmented stains, but crops occur over many years. Biopsy shows perivascular mononuclear infiltration. Hypergammaglobulinaemia is a feature of patients with purpura. Other vascular lesions occur, including an arteritis like that seen in rheumatoid arthritis, lesions indistinguishable from polyarteritis nodosa and nail fold infarcts, splinter haemorrhages and gangrene of the fingers [17]. Raynaud's phenomenon occurs in 25% of cases.

Mouth. The saliva is at first thick and mucoid, but later salivary volume decreases. The tongue is red, smooth and dry, and in severe cases there may be difficulty in swallowing dry food. Parotid duct narrowing and web formation may develop [18]. Dental caries is often severe and progressive. The lips are red, dry and scaly. There are frequently cracks at the corners of the mouth. Chronic oral candidiasis is frequent. Recurrent episodes of swelling of one or both parotid glands or, less often, the submaxillary and sublingual glands, may be accompanied by fever.

Other mucous membranes. Atrophic changes in the mucous membranes of the upper respiratory tract lead to nasal crusting and dryness, recurrent episodes of infection, hoarseness or aphonia. Pulmonary infiltration, atelectasis or fibrosis may occur. Atrophic rhinitis can occur, and the sense of smell may be reduced. Digestive symptoms are attributable to atrophy of the gastric mucous membrane with achlorhydria. Similar changes in the vulva and vagina give rise to pruritus and vaginitis, and dryness of the anal and rectal mucous membrane leads to dyschezia and pruritus.

Other manifestations. In patients without associated connective tissue disease, mild articular symptoms occur in 83%, with mild synovitis. They respond to non-steroidal anti-inflammatory drugs [19]. Cervical or generalized lymphadenopathy and enlargement of the liver and spleen, which is sometimes considerable, may be found. Features of Sjögren's syndrome can be demonstrated in patients with primary biliary cirrhosis [20]. Splenomegaly occurred in approximately 20% of one series [1]. Oesophageal dysfunction has been reported in one-third of patients [21]. The pancreas may be involved. Pulmonary abnormalities occur in 9–29% of cases, and appear to be similar in patients with primary or secondary Sjögren's syndrome [22]. They include pulmonary fibrosis, pulmonary hypertension [23], recurrent chest infections, granulomatous infiltration and fibrosing alveolitis. The most common functional disorders are a restrictive ventilatory defect and impaired gas transfer. Speckled antinuclear factor is frequent. Neurological abnormalities are generally mild [6], but peripheral and trigeminal neuropathy (probably resulting from vasculitis of the vasa nervorum), cerebral manifestations, both focal and diffuse, and spinal cord disease are associated with the presence of anti-Ro antibodies [24]. Migraine is more frequent than expected and is associated with Raynaud's phenomenon [25]. Myopathy and myasthenia [26] have been reported. Interstitial nephritis [27], renal tubular acidosis, impaired renal concentrating ability and generalized aminoaciduria [28] are the main renal lesions. Impaired renal function can occur without clinical manifestations [29]. A high prevalence of fetal loss has been

recorded, but there was no correlation with anticardiolipin or anti-Ro antibodies [30].

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Sjögren's syndrome in childhood. Primary Sjögren's syndrome is rare in childhood. Recurrent annular erythema similar to that seen in adults has been reported on the face, trunk and limbs [1]. Episodes, with or without fever and parotid swelling, occur over years and last a few months. Anti-Ro antibodies are positive but there is no evidence of SLE. Histology of the lesions shows a dermal lymphocytic infiltration but no vasculitis, and immunohistology reveals no immunoglobulins or complement at the dermal–epidermal junction or around blood vessels. The condition responds to oral steroids.

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Laboratory abnormalities. Hypergammaglobulinaemia and rheumatoid factor are frequently demonstrated in the serum, even in patients without arthritis. There may be increased serum viscosity [1,2]. Antinuclear antibodies are present in more than 50% of patients (homogeneous factor is more frequent than speckled, and nucleolar factor is only occasionally found). Anti-DNA antibody can occasionally be demonstrated, but anti-Sm and anti-RNP antibodies are never found in the sicca syndrome alone. Precipitating antibodies reacting with saline extracts of human tissues were demonstrated 30 years ago [3]. Similar, or identical, antibodies have been designated anti-Ro (also called SS-A) and anti-La (SS-B).

Antibodies to Ro/La were found in 53% of patients with Sjögren's syndrome [4]. Facial rashes, photosensitivity and serositis in patients with Sjögren's syndrome were associated with SLE. Initially, anti-La was thought to be highly specific for the sicca complex but this is not correct. Anti-Ro antibodies are particularly associated with vasculitis, purpura, lymphadenopathy, and haematological and serological abnormalities [5]. Precipitating antibodies to extracts of lacrimal and salivary glands have been reported in three cases [6]. Antibody to salivary duct epithelium can be demonstrated in approximately 50% but is also found in uncomplicated rheumatoid arthritis [7]. Thyroglobulin antibodies are present in 25% of cases [8]. Leukopenia and eosinophilia are not infrequent. Immune complexes occur in 60%, but are not related to disease activity [9]. Recurrent annular erythema is associated with anti-La antibodies in Sjögren's syndrome [10,11] but not all anti-La-positive patients have a rash, and no disease-specific epitope has been demonstrated [12]. The epitope of anti-Ro antibody is similar in the annular erythema of Sjögren's syndrome and SCLE [13].

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Associations [1]. Sjögren's syndrome occurs in association with systemic sclerosis [2,3], DLE [4,5], SLE [6,7], polyarteritis nodosa [8] and polymyositis and dermatomyositis [9]. Of 122 patients with Sjögren's syndrome, 26% had rheumatoid arthritis, 22% had systemic sclerosis, 22% had sicca syndrome and 20% had primary biliary cirrhosis [10]. Sjögren's syndrome occurred in 69% of patients with systemic sclerosis in this series but in only 20% of another [11]. Three patients had anti-DNA antibodies in the absence of any evidence of SLE [1]. Sjögren's syndrome has also been associated with SCLE and Sweet's syndrome [12]. A range of lymphoproliferative disorders occurs, including B-cell [13] and T-cell [14] lymphomas. Drug allergy, especially to penicillin [15], is more common than expected. The 'sicca complex' [16] is common in patients with active chronic hepatitis, primary biliary cirrhosis and cryptogenic cirrhosis [17]. Sjögren's syndrome may be associated with complete or partial lipodystrophy [18], and has been reported with granulomatous panniculitis [19]. Features indistinguishable from Sjögren's syndrome have been found in a case of Behçet's disease [20]. It has occurred with coeliac disease and autoimmune thyroiditis [21], hypoparathyroidism [22], myasthenia gravis [23], idiopathic haemochromatosis [24], autoimmune haemolytic anaemia [25], dermatitis herpetiformis [26], Darier's disease [27], multicentric histiocytosis [28], ulcerative colitis, sarcoidosis [29] and Waldenstrom's hypergammaglobulinaemic purpura [30].

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Diagnosis. So variable is the clinical picture that the diagnosis is easily overlooked, except in the more obvious cases presenting with ocular or oral symptoms.

It should also be suspected in the presence of anogenital pruritus in association with ocular and oral changes or with rheumatoid disease, and should be confirmed by specialist ophthalmological examination. Biopsy of labial salivary glands [1] or nasal mucosa [2] is useful, and the value of lip biopsy has been stressed, but a negative biopsy does not exclude the diagnosis [3]. The demonstration of antisalivary duct antibody may be helpful. Contrast sialography is useful [4], and sequential salivary scintigraphy [5] gives objective and sensitive estimation of salivary gland function. Every case requires detailed investigation to determine the extent and nature of the associated abnormalities. The demonstration of anti-Ro (SS-A) and anti-La (SS-B) antibodies may be helpful in diagnosis. Anti-La may antedate clinical evidence of Sjögren's syndrome by months or even years [6].

Treatment. Symptomatic treatment for the dryness of the eyes is best accomplished by lubricating agents, such as 0.5% methylcellulose eye drops instilled into the eyes four or five times daily. Bromhexine (Bisolvon R) 16 mg three times daily has been found to increase the lacrimal secretion [4], but has no effect on salivary flow [7]. However, it does change the salivary composition towards normal [8]. Artificial saliva can be prescribed, and steam inhalations or an air humidifier may help dryness of the respiratory tract. Patients with Sjögren's syndrome associated with SLE seem to improve more than those with primary Sjögren's syndrome. Systemic corticosteroids are effective in reducing parotid swelling, but rarely increase parotid or lacrimal secretion. The immunological abnormalities in the serum are not markedly altered by corticosteroids, although patients remain in good health. Chloroquine or hydroxychloroquine sulphate by mouth have been found useful by some authors [9] but not by others [10]. Ciclosporin improved subjective xerostomia and seemed to retard the histopathological lesion [11], but its use is probably not justified. Nifedipine may help pulmonary Raynaud's phenomenon [12]. A patient with associated polymyositis improved with monthly intravenous pulse cyclophosphamide therapy [13]. The annular erythema in Japanese patients may be controlled by prednisolone 10–20 mg/day or by dapsone.

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Rheumatic fever

Erythema marginatum is the characteristic rash of rheumatic fever, and occurs in 25% of cases [1]. It appears as evanescent asymptomatic pinkish superficial semicircles and rings, which disappear without scaling or pigmentation in a few days. Histologically, there is a perivascular infiltration of neutrophils in the papillary dermis, and biopsy may help in the early diagnosis of rheumatic fever when the rash precedes arthritis and carditis [2]. Erythema multiforme, petechiae and urticaria may sometimes be seen in rheumatic fever. Livedo reticularis has been reported [3]. The overall clinical picture must be distinguished from post-streptococcal reactive arthritis [4].

Subcutaneous nodules occur particularly on the occiput, wrist and the backs of the forearms, and are smaller and more transient than those seen in rheumatoid arthritis, from which they can be distinguished histologically [5–7]. Generalized eruptive histiocytomas have also occurred [8].

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Chapter 57

Metabolic and Nutritional Disorders

R.P.E. Sarkany, S.M. Breathnach, C.A. Seymour, K. Weismann & D.A. Burns

The cutaneous porphyrias

[R.P.E. Sarkany, pp. 57.1–57.23]

Introduction

The porphyrias are a group of disorders caused by defects in the biosynthesis of haem. Their relevance to the skin arises from the phototoxic properties of the porphyrins, which accumulate in most porphyrias and cause photosensitivity.

The majority of the porphyrias are inherited. Many of them affect other organs as well as the skin. The recognition and management of both the genetic and internal consequences of porphyrias presenting in the skin are a key challenge for the dermatologist.

Clinical management in these disorders is made easier when the clinician understands their theoretical basis. Thus, this section is divided into two halves. The first provides a theoretical basis for understanding the porphyrias, the general principles of clinical management and a clinician's guide to laboratory testing. The second half covers each individual disease in detail.

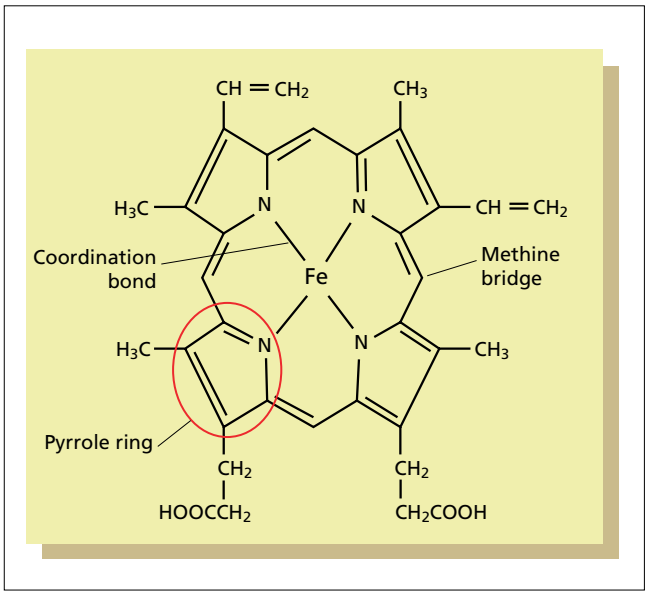

Fig. 57.1 The haem molecule and its key structural features. The alternation of single and double bonds around the tetrapyrrole ring indicates the aromaticity of the molecule, central to its chemical characteristics. The four coordination bonds between iron and nitrogen atoms are shown. The two remaining bonds between the iron and either molecular oxygen or amino acid residues lie perpendicular to the page.

General considerations: theoretical basis, clinical features and laboratory testing in porphyria

A theoretical basis for understanding the porphyrias

The phototoxicity of porphyrins

The phototoxic properties of porphyrins are responsible for the cutaneous features of the porphyrias. Porphyrins are intermediates in the biosynthesis of haem, and consideration of the chemical features of the haem and porphyrin molecules is necessary to understand the cause of porphyrin phototoxicity.

The chemistry of porphyrins and haem [1]. A pyrrole is a ring composed of four carbon atoms and one nitrogen atom. Four pyrroles linked into a ring create a tetrapyrrole, a remarkable and biologically critical molecular structure found in chlorophyll, haem and vitamin B_{12}. A porphyrin is a special type of tetrapyrrole in which four pyrrole rings are linked by methine bridges into a large ring structure.

Haem is the molecule created by the insertion of ferrous iron into the centre of the porphyrin molecule, protoporphyrin IX (Fig. 57.1). Essentially, incorporation of iron into the porphyrin molecule enables it to become biologically useful. Iron's capacity to bind to molecular oxygen, and to transfer electrons (by moving between the 2+ and 3+ oxidation states) makes it potentially useful in biological systems, but free iron precipitates in the presence of water. For iron to be useful, it has to be kept soluble by protecting its binding sites against water. In addition, subtle modification of the electronic structure of the iron atom can optimize its ability to transfer electrons and reversibly bind molecular oxygen. Binding of iron to the porphyrin molecule solubilizes iron and also optimizes its electronic structure. The porphyrin's central cavity is the right size to fit an iron atom, and its four central nitrogen atoms occupy four of the iron's coordination binding sites leaving only two free. A key feature of the porphyrin structure is that (see Fig. 57.1) each double bond is adjacent to a single bond, so it is 'aromatic' with 18 of its electrons being delocalized and free to move around the molecule. This electron current results in the central nitrogen atoms tending to donate electrons to the iron atom, as well as other subtler electronic interactions involving transient changes in the porphyrin's electronic state [2]. Haem can bind to a variety of proteins, and the nature of this interaction reflects the protein's function. In proteins with electron transport functions, such as respiratory cytochromes, amino acids bind to both remaining coordination binding sites on the iron so that haem can transfer electrons through alterations in the iron's oxidation state. In proteins with oxygen-binding functions, such as haemoglobin, an amino acid binds to one of the iron's remaining coordination binding sites, leaving the sixth site free to bind to oxygen. In summary, the aromatic porphyrin structure is well suited to complexing with iron to form haem, rendering the iron useful for electron transfer (respiratory cytochromes), reversible oxygen binding (haemoglobin and myoglobin), and oxidation and reduction reactions (cytochrome P450, catalase), with fine tuning of the iron's functionality being determined by the apoprotein which binds to the haem.

Photochemistry of the porphyrins [3,4]. The complex electronic structure of the large aromatic porphyrin molecule results in its 18 delocalized electrons having unusual excitation characteristics. These electrons are excited by relatively long wavelength light. The main absorption peak is at 408 nm ('Soret band') [3], and this long wavelength of exciting light predisposes to phototoxic behaviour by the porphyrin; these photons have insufficient energy to chemically alter the porphyrin structure, so that alternative fates for the energy, particularly fluorescence and phosphorescence, become more likely [4]. Thus, following excitation by light around the 408 nm peak, electrons either return to the non-excited ground state by releasing the energy as the characteristic red fluorescence, or the porphyrin's excited singlet state transforms (by intersystem crossing) to the longer-lived excited triplet state.

Transfer of energy from this excited triplet state to neighbouring molecules leads to the phototoxicity responsible for the clinical features of the cutaneous porphyrias. Thus cutaneous disease in the porphyrias can be thought of as a by-product of the unusual porphyrin structure which enables haem-proteins to fulfil their biological functions.

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Enzyme deficiencies and the porphyrias

The porphyrias all result from a partial deficiency of one of the enzymes required for the biosynthesis of haem. Such a partial deficiency causes the accumulation of the enzyme's substrate. The toxicity profile of the accumulated molecule determines the clinical features of the resulting porphyria. Thus, a basic understanding of the biosynthetic pathway enables the clinician to interpret laboratory results and to predict the clinical features of each porphyria on the basis of each porphyrin's properties.

The biosynthesis of haem [1,2] (Fig. 57.2). Haem is synthesized from simple biochemicals (glycine and succinyl CoA) via an eight-step pathway, each step being catalysed by an enzyme. Synthesis of the pyrrole ring (porphobilinogen (PBG)) is followed by assembly of the tetrapyrrole structure (hydroxymethylbilane). One of the pyrrole rings (the 'D' ring) is 'flipped' around to create the III isomer (the alternative I isomer forms in the absence of the cosynthase enzyme). Next, the carboxylic acid side-chains of uroporphyrinogen III are progressively decarboxylated via coproporphyrinogen III to protoporphyrinogen, which is then oxidized to protoporphyrin IX. It is likely that the progressive decarboxylation to remove six of the eight electron-withdrawing carboxylate groups increases the flux of electrons onto the molecule's central nitrogens to facilitate coordination with iron. Finally, ferrous iron is chelated into the protoporphyrin's central cavity to form haem. Around 80% of haem is synthesized in erythroid cell precursors in the bone marrow (for haemoglobin production). The decarboxylation of uroporphyrinogen to coproporphyrinogen, and thence to protoporphyrinogen, decreases water solubility, so that uroporphyrinogen is only excreted via the kidneys whereas hydrophobic protoporphyrinogen and protoporphyrin are exclusively excreted into the bile. Coproporphyrinogen is excreted by both routes. Physiological concentrations of porphyrins stay low because of the high efficiency of haem synthesis.

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Clinical features of the porphyrias: general considerations

Porphyrias present with either skin disease or acute attacks or both.

The classification of the porphyrias [1,2]

In any porphyria, a partial enzyme deficiency causes the accumulation of porphyrins. The enzyme deficiency associated with each disorder is shown in Fig. 57.3. The porphyrias have previously been classified, according to the predominant site of porphyrin accumulation, into the erythropoietic group (congenital erythropoietic porphyria and erythropoietic protoporphyria) and the hepatic group (all the others). This division is not of value clinically. For the clinician, the key division is between porphyrias that cause acute attacks and those that cause skin disease. In this chapter the following classification is used for the six common porphyrias:

1 Cutaneous disease only:
Porphyria cutanea tarda (PCT)
Congenital erythropoietic porphyria (CEP)
Erythropoietic protoporphyria (EPP).
2 Cutaneous disease and acute attacks:
Hereditary coproporphyria (HC)
Variegate porphyria (VP).
3 Acute attacks only:
Acute intermittent porphyria (AIP)

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Porphyria and the skin

The cutaneous porphyrias share many features. Consideration of these underlying similarities is necessary for a logical approach to clinical management of patients.

All the cutaneous porphyrias, except EPP, present with fragility and blistering in light-exposed skin, and can appear so similar that they can only be reliably differentiated by biochemical analysis. The term 'bullous porphyrias' is often used for this group of diseases. Also, the

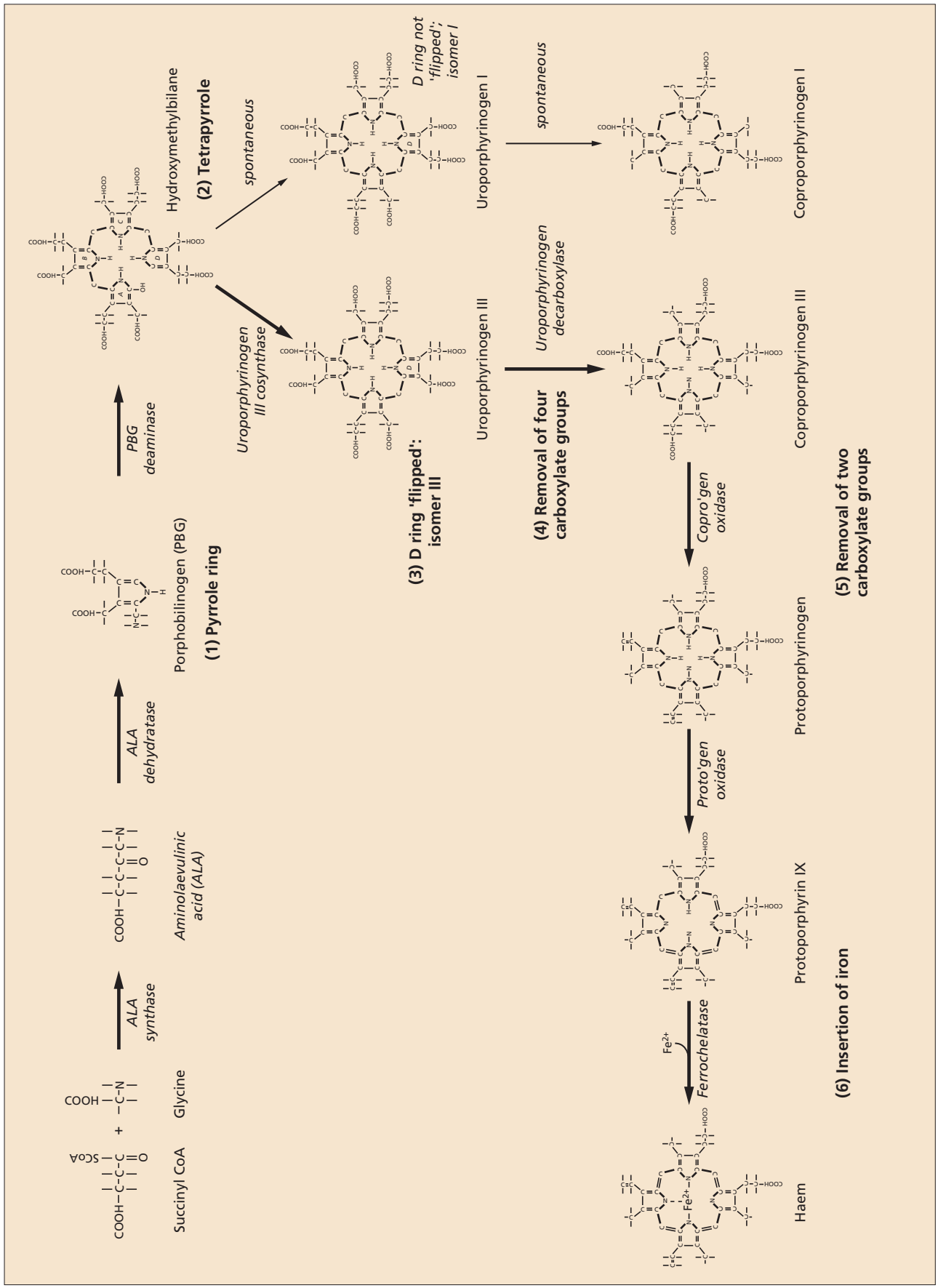

Fig. 57.2 The pathway of haem biosynthesis showing the six key structural changes.

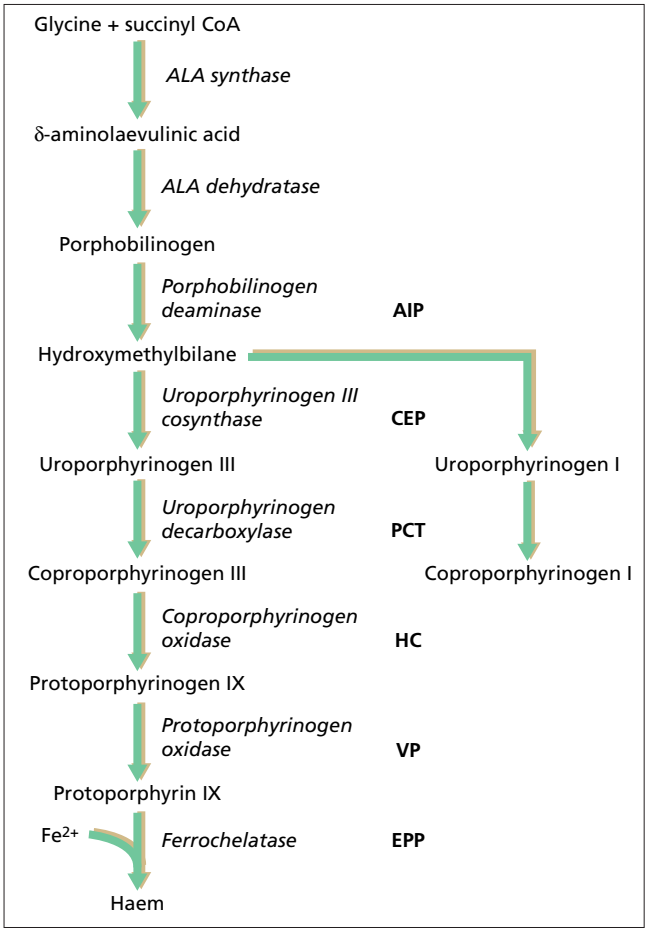

Fig. 57.3 The pathway of haem biosynthesis showing the enzyme deficiency associated with each porphyria. (The abbreviations of disease names are defined in the text relating to classification of the porphyrias.)

mechanism underlying the skin disease in all cutaneous porphyrias is a local porphyrin phototoxicity reaction, and this common pathogenetic mechanism results in similar histopathological appearances. Finally, Soret wavelength light (408 nm) causes the skin disease in all these disorders, so the same strategy for photoprotection applies to them all, as detailed below.

The pathogenesis of skin disease in porphyria (Fig. 57.4) [1,2]. Photons of violet light, with a wavelength peak at 408 nm, transform the porphyrin molecule into an excited singlet state. This may revert to the unexcited ground state by emission of the characteristic red porphyrin fluorescence, but intersystem crossing can convert it to the excited triplet state, long-lived enough to interact with other molecules, particularly molecular oxygen, converting it to excited singlet oxygen in the process. The singlet oxygen damages tissue directly, and also indirectly by stimulating complement activation [3], mast cell degranulation [4] and matrix metalloproteinase activity [5]. The site of this phototoxic reaction in the skin determines the clinical characteristics of the porphyria. In EPP, lipophilic protoporphyrin tends to localize to membranes including endothelial cell membranes, and to remain within erythrocytes, and the phototoxic reaction involves upper dermal blood vessels causing pain. In PCT, the water-soluble uroporphyrin diffuses easily into surrounding tissues and the phototoxic reaction occurs in the upper dermis, causing lysis of cells in the superficial dermis with the formation of membrane-limited vacuoles which merge to produce a blister under the basal lamina, producing the characteristic clinical presentation [6]. In VP, copro- and protoporphyrin accumulate (Fig. 57.3), but patients suffer from PCT-like upper dermal blisters rather than EPP-like acute pain. This is likely to be because, although hydrophobic porphyrins predominate in plasma in VP, hydrophilic porphyrins, particularly uroporphyrin, predominate in the skin, probably due to secondary local photoinactivation of uroporphyrinogen decarboxylase (UROD) in the skin by coproporphyrin [2]. In addition, the protoporphyrin in VP is conjugated to a peptide which may reduce its phototoxicity.

There is no simple correlation between the plasma porphyrin concentration and the severity of cutaneous disease in porphyria because of the large number of local variables which can alter the extent of the phototoxic reaction in the skin, and an increased plasma porphyrin concentration is not always associated with cutaneous disease [7].

Histopathology of the skin in porphyria [8,9]. In all the cutaneous porphyrias, homogeneous material is seen within vessel walls of the upper dermal and papillary vascular plexus. It is periodic acid–Schiff (PAS)-positive and diastase resistant, and contains a protein polysaccharide complex, lipids and tryptophan. Immunofluorescence reveals immunoglobulins (mainly IgG) in a similar vascular distribution, and IgG at the dermal–epidermal basement membrane zone, in involved skin. Electron microscopy shows reduplication of the vascular basal lamina and the presence of masses of fine fibrillar material, mainly around these blood vessels and often also at the dermal–epidermal junction. In EPP the vessel wall changes are more pronounced, whereas the basement membrane zone changes predominate in affected skin in PCT and VP. In the bullous porphyrias, bullae are subepidermal with the split occurring in the lamina lucida [10] (Fig. 57.5) leaving the dermal papilla protruding into the blister cavity, an appearance called 'festooning' [9]. The findings in bullous porphyrias are indistinguishable from those of pseudoporphyria. In EPP in the acute phase there is visible endothelial damage in superficial dermal vessels [11]. Electron microscopy shows the 'amorphous' material seen in vessel walls on light microscopy in light-exposed skin to be a replicated, layered and fragmented

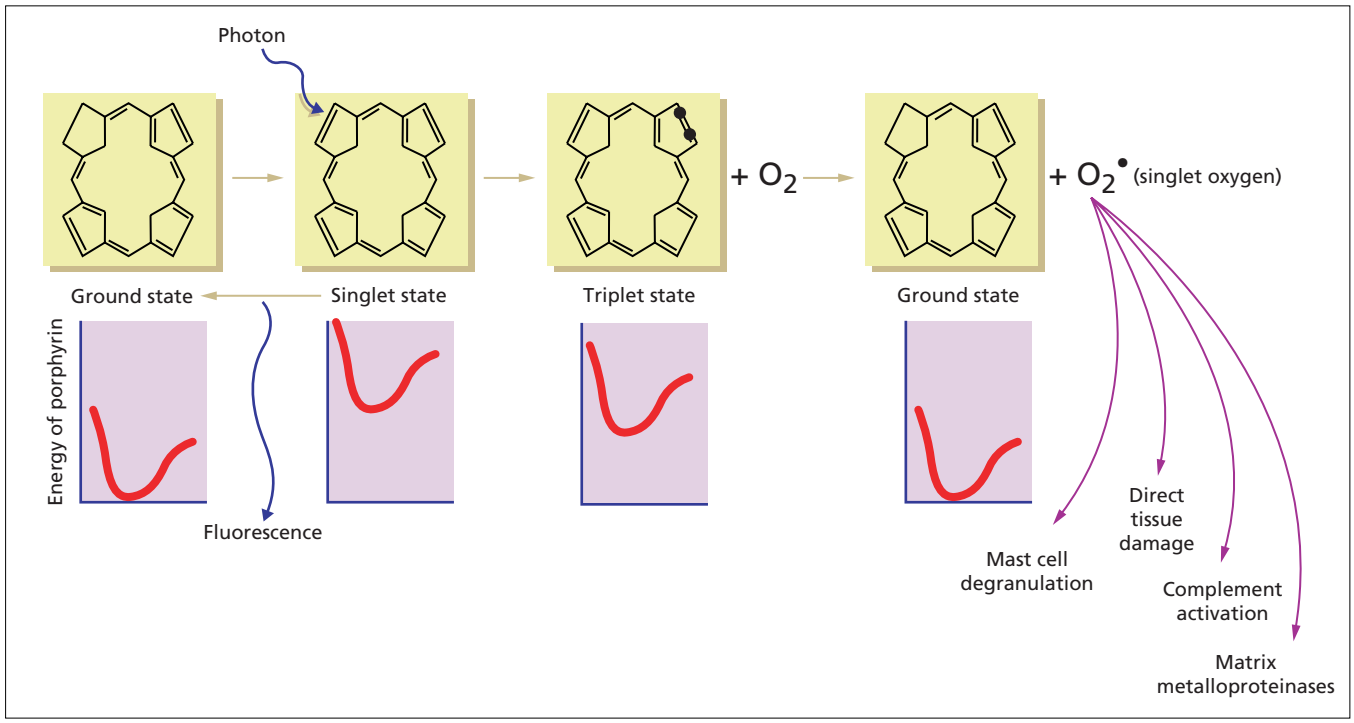

Fig. 57.4 The pathogenesis of skin disease in porphyria.

basement membrane, with fine fibrillar material permeating the capillary connective tissue sheath and extending beyond the vessel walls, caused by the repeated episodes of damage [12,13].

General considerations in the management of skin disease in porphyria. Apart from PCT, and to some extent CEP, where effective specific treatments exist, the management of the skin in the other cutaneous porphyrias is based on preventing violet (Soret wavelength) light penetrating the epidermis. The connection between sun exposure and symptoms is obvious in EPP, but is not obvious to patients with the bullous porphyrias where fragility and blistering are not related to individual episodes of sun exposure. It can therefore be difficult to convince these patients of the importance of photoprotection. Basic measures include sun avoidance behaviour, sun-protective clothing and hats. Most sunscreens, including UV-absorbent chemical 'total sunblocks', do not protect against the visible violet Soret wavelength [14]; any sunscreen providing significant visible light protection will be opaque rather than transparent. Sunscreens containing reflectant particles, particularly large particle size titanium dioxide (pigmentary grade), zinc oxide and iron oxide, can effectively protect against violet light [15], and cosmetically acceptable sunscreens with reasonable protection up to 430 nm are available commercially, e.g. Dundee sunscreen, Tayside Pharmaceuticals, Dundee, UK [14,15]. Dihydroxyacetone paint induces formation of a light-absorbing brown pigment in the stratum corneum, and has been used in some patients with EPP [16]. Some reasonably clear window films can absorb some violet light, and are useful on car or home windows, particularly in EPP and CEP [17]. This author generally uses two films which are clear and provide reasonable, though not complete, protection against Soret wavelength light (Dermagard film, Bonwyke, Hants, UK; CLS200XSR film, Madico, USA). Clearly, films applied to car windows must comply with local legislation, which varies considerably in different parts of the world.

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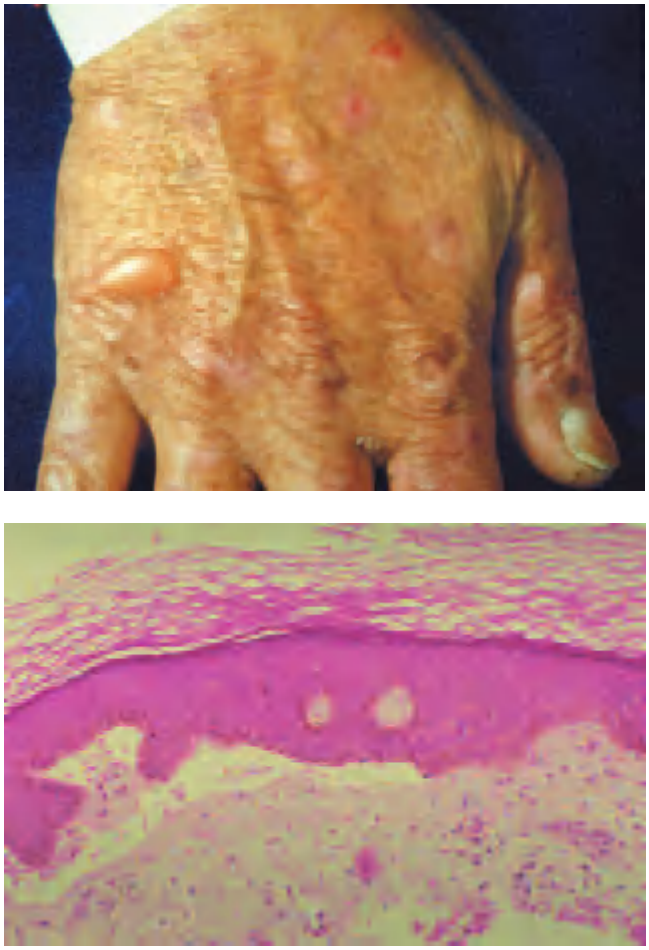

(a)

(b)

Fig. 57.5 Typical subepidermal bulla in a bullous porphyria: (a) clinical appearance, (b) histological appearance.

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Acute attacks of porphyria [1,2]

AIP, HC and VP can all cause acute attacks, and HC and VP may also cause cutaneous disease. (A rare autosomal recessive acute porphyria, aminolaevulinic acid (ALA) dehydratase porphyria, which does not cause skin disease has also been reported and will not be discussed further.)

Definition. An acute and potentially fatal illness, frequently triggered by drugs and hormones which are metabolized by cytochrome P450. It is characterized by an acute neurotoxic reaction in many tissues.

Prevalence. The commonest acute porphyria is AIP, followed by VP. HC is rare. The prevalence of clinically overt acute porphyria in Europe is 1–2/100 000 inhabitants, but over 90% of individuals possessing AIP or VP gene defects are asymptomatic, so the enzyme deficiencies are common; PBG deaminase deficiency, which causes AIP, is present in 0.2% of all blood donors [3].

Aetiology [4]. Impaired activity of PBG deaminase is associated with acute attacks. The deficiency can be primary (as in AIP) or secondary, the latter being due to inhibition of the enzyme by accumulated coproporphyrinogen and protoporphyrinogen (as in HC and VP) [5]. In the liver, haem is mostly incorporated into cytochrome P450 proteins, whose production is induced by many of the drugs and hormones metabolized by the P450 system. When a drug or hormone induces cytochrome P450, and hence acutely increases the hepatic requirement for haem, the inability of the pathway to respond adequately because of the PBG deaminase deficiency is exposed. This acute hepatic haem deficiency in turn causes secondary accumulation of ALA and increased ALA synthase activity due to loss of end-product negative feedback. The symptoms of the acute attack result from neuronal dysfunction, the pathogenesis of which is not fully understood though postulated mechanisms include disturbed metabolism of neurotransmitters (due to reduced activity of haem-containing hepatic trytophan dioxygenase), direct neurotoxicity of accumulated ALA (which structurally resembles the neurotransmitter γ-aminobutyric acid (GABA)) and acute haem deficiency within neurones.

Factors that may precipitate an acute attack [1]. The most common precipitants are drugs and the menstrual cycle, with recurrent attacks often occurring in the late luteal phase. Alcohol, cannabis, fasting, stress and infection may also trigger attacks. It is not possible to predict whether a specific drug will provoke an attack in an individual. Drugs should be prescribed only after reference to a drug list (Table 57.1), but such recommendations are not absolute and do not substitute for clinical judgement. The risk of a drug provoking an attack is obviously highest where

Table 57.1 Drugs considered to be safe in patients with acute porphyria. This list was compiled in 2002. It is regularly updated and the most up-to-date version is available on the Internet [http://www.uwcm.ac.uk/study/medicine/medical_biochem/porphyria/porphyria3.htm (2002)]. (Courtesy of Cardiff Porphyria Unit and Welsh Medicines Information Centre [6].)

Anti-emetics
Cyclizine
Domperidone
Meclozine
Prochlorperazine
Promazine

Antihistamines
Alimemazine (trimeprazine)
Chlorphenamine (chlorpheniramine)
Diphenhydramine
Ketotifen
Mequitazine
Promethazine

Antibacterial agents
Aminoglycosides
Co-amoxiclav
Ethambutol
Flucloxacillin*
Penicillins
Pentamidine
Sodium fusidate
Streptomycin
Vancomycin

Lipid-lowering agents
Bezafibrate
Colestyramine (cholestyramine)
Clofibrate
Colestipol
Fenofibrate
Gemfibrozil
Probucol

Local anaesthetics
Bupivacaine
Lidocaine (lignocaine)†
Prilocaine
Procaine
Tetracaine (amethocaine)

Immunizations
Immunoglobulins
Vaccines

Antidepressants
Amitriptyline
Fluoxetine
Lofepramine
Mianserin

Antipsychotics
Chlorpromazine
Fluphenazine
Haloperidol
Pipotiazine (pipothiazine)
Trifluoperazine

Antivirals/antifungals
Aciclovir
Amphotericin
Famciclovir

Antivirals/antifungals cont.
Flucytosine
Ganciclovir
Valaciclovir
Zalcitabine

Cardiovascular agents
Amiloride
β-Blockers
Bumetanide
Chlorothiazide
Cyclopenthiazide
Dalteparin
Diazoxide
Digoxin
Dipyridamole
Dobutamine
Dopamine
Enalapril
Enoxaparin
Glyceryl trinitrate
Guanethidine
Heparin
Hydrochlorothiazide
Lisinopril§
Naftidrofuryl
Prazosin
Procainamide
Quinidine
Streptokinase
Tinzaparin
Triamterene
Urokinase

Anticonvulsants
Clobazam
Clonazepam
Gabapentin
Sodium valproate‡
Valproate‡
Vigabatrin

Drugs used in anaesthesia
Atropine
Cyclopropane
Epinephrine (adrenaline)
Ether
Isoflurane
Neostigmine
Nitrous oxide
Pancuronium
Phentolamine
Propofol
Suxamethonium

Analgesics
Alfentanil
Aspirin
Buprenorphine
Co-codamol
Codeine phosphate
Co-dydramol
Dextromethorphan

Analgesics cont.
Dextromoramide
Dextropropoxyphene
Diamorphine
Diflunisal
Dihydrocodeine
Fenbufen
Fentanyl
Flurbiprofen
Ibuprofen
Indometacin (indomethacin)
Ketoprofen
Methadone
Morphine
Nalbuphine
Naproxen
Paracetamol
Pethidine
Sulindac
Tiaprofenic acid

Malaria prophylaxis
Chloroquine
Mefloquine
Proguanil

Miscellaneous
Acetazolamide
Acetylcysteine
Allopurinol
Alpha-tocopheryl
Aluminium salts
Amantadine
Ascorbic acid
Azathioprine
Beclometasone (beclomethasone)
Bismuth
Bromazepam
Buserelin
Calcitonin
Calcium carbonate
Carbimazole
Chloral hydrate
Cisplatin
Clomifene (clomiphene)
Colchicine
Corticosteroids
Corticotropin (corticotrophin)
Dantron (danthron)
Desferrioxamine
Dextran
Dextrose
Dicycloverine (dicyclomine)
Dimercaprol
Dimeticone (dimethicone)
Diphenoxylate
Distigmine
Doxorubicin
Droperidol
Flumazenil
Fructose
FSH
Glipizide

Miscellaneous cont.
Glucagon
Glucose
Glycopyrronium
Gonadorelin
Goserelin
Hetastarch
Hydrocortisone
Insulin
Iron
Ispaghula
Lactulose
Leuprorelin
Levomepromazine (methotrimeprazine)
Levothyroxine
LHRH
Lithium
Loperamide
Lorazepam
Magnesium sulphate
Melphalan
Mesalazine
Metformin
Methylphenidate
Methylprednisolone
Midazolam
Naloxone
Octreotide
Omeprazole
Oxybuprocaine
Oxytocin
Paraldehyde
Penicillamine
Phytomenadione
Pirenzepine
Prednisolone
Primaquine
Propantheline
Propylthiouracil
Proxymetacaine
Pseudoephedrine
Pyridoxine
Pyrimethamine
Quinine
Resorcinol
Salbutamol
Senna
Sodium acid phos
Sodium bicarbonate
Sorbitol
Sucralfate
Temazepam
Thiamine
Thyroxine
Tranexamic acid
Triazolam
Vitamins
Warfarin
Zinc preparations

Names in brackets are old BAN name before modification to accord with rINN.
FSH, follicle-stimulating hormone; LHRH, luteinizing hormone-releasing hormone.
* Large intravenous doses may be associated with acute attacks (unproven as causative agent).
† Intravenous doses should be avoided.
‡ Sodium valproate should only be used where other safe antiepileptics are ineffective or inappropriate.
§ Safety under review.

that drug has previously caused an attack in that patient, and in any patients who have previously had symptoms suggestive of an acute attack.

Clinical presentation [1,2]. Acute attacks are five times more common in females, and most frequently occur between the ages of 10 and 40 years. They are rare before puberty. The severity of acute attacks varies from mild abdominal pain, sometimes accompanied by vomiting and constipation, through to very severe attacks with bulbar palsy and respiratory paralysis. Severe, constant abdominal pain occurs in almost all acute attacks. It can be in any quadrant or even in the back, buttocks and thighs, and may require large amounts of opiate analgesia. There may be guarding but no true peritonism. Vomiting and constipation (due to partial ileus) occur in at least half of attacks. The pulse rate and blood pressure are often moderately raised, dehydration is common and hyponatraemia (probably caused by inappropriate secretion of vasopressin) may be severe enough to cause convulsions. The pain, tachycardia, hypertension and partial ileus are all caused by an acute autonomic neuropathy. Sensory or sympathetic involvement with severe dysaesthesia or causalgia are rarer. A motor neuropathy occurs in 5–10% of cases, usually heralded by aching pains in the limbs and sometimes by disappearance of the abdominal pain. It may cause a severe acute Guillain–Barré-type syndrome. The motor neuropathy usually occurs when porphyrinogenic drugs have been adminstered inadvertently during the developing acute attack. Respiratory paralysis is the commonest cause of death. Confusion, abnormal behaviour, agitation and hallucinations occur in up to 50% of attacks. Porphyria is not related to any chronic psychiatric disease, except generalized anxiety.

Biochemical diagnosis of an acute attack [7,8]. The diagnostic finding is of increased urinary PBG excretion. Although qualitative screening tests may be useful in an emergency, their low sensitivity makes it essential to also carry out a quantitative assay. Commercially available kits can provide a rapid and reasonably sensitive semi-quantitative assay, after which a specific quantitative assay should be carried out (reliable quantitative assay kits are commercially available). A normal urinary PBG concentration excludes an acute porphyric attack (except in ALA dehydratase porphyria). An increased PBG concentration does not necessarily mean that an acute attack is occurring since urinary PBG falls between attacks but does not always return to normal, particularly in AIP. The higher the PBG concentration, the more likely an acute attack, but, in the presence of an increased urinary PBG, an acute attack can only be diagnosed on clinical grounds. Urinary ALA is also increased during an acute attack but to a lesser extent than PBG and is not as useful diagnostically (the only exception being ALA dehydratase porphyria in which only ALA is increased and urinary PBG is normal).

Long-term management of patients with acute porphyria [1,2]. The dermatologist may diagnose VP (or less commonly HC) on the basis of cutaneous disease before any acute attack has occurred. Once an acute porphyria has been diagnosed, the patient should be given a list of drugs with information about their safety in acute porphyria. Many lists exist both of 'safe' drugs and 'unsafe' drugs. It is obviously vital for clinicians and patients to be clear about whether they are dealing with a list of 'safe' or of 'unsafe' drugs, and there are advantages to using a 'safe' list. A widely recognized list of safe drugs is shown in Table 57.1 [6]. A standard list of unsafe drugs is also widely available [9]. It is important to recognize that a list of safe drugs is a guide, and that no drug can be guaranteed to be safe in an individual patient. Conversely, drugs which do not appear on a 'safe' list should not be withheld in patients who need them to treat a serious or life-threatening illness; in that situation expert advice should be sought from a specialist centre.

The patient should also be advised to abstain from alcohol, cannabis and from prolonged calorie-restricted diets, and to wear an emergency identification bracelet (e.g. MedicAlert) so that medical staff are aware of the diagnosis if the patient is ever found in an unconscious or confused state. Screening of relatives is essential to identify those with clinically latent disease, who are also at risk of acute attacks. The choice of test and interpretation of results can be complex and details are covered in the 'laboratory testing' section and under each individual disorder in this chapter. Such testing is ideally carried out in a specialist centre. Relatives diagnosed with an acute porphyria need the same advice as the index case. Conversely, patients with PCT, EPP and CEP can be reassured that acute attacks are not part of their disease.

Treatment of the acute attack [1,2]. The key to managing an acute attack is early diagnosis. Once the diagnosis has been made, avoidance of acute attack-inducing drugs is essential to prevent exacerbation. Supportive treatment includes analgesia, sedatives and antiemetics (with drugs known to be safe in acute porphyria) and careful management of fluid balance with rehydration and correction of hyponatraemia. The specific treatments are intravenous haematin or haem arginate (Normosang, Orphan Pharmaceuticals), which have now replaced carbohydrate as the treatment of choice. These drugs suppress hepatic ALA synthase activity and so reduce ALA and PBG accumulation. Haem arginate is more effective when given earlier during an attack, increasing the importance of early diagnosis. Advice from a specialist centre should be sought when treating an acute attack.

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A clinician's guide to laboratory testing in porphyria [1–3]

Although clinical features may raise the possibility of a porphyria, the cutaneous presentations of several porphyrias are very similar. Precise diagnosis is essential in porphyria because of the great differences in clinical management between porphyrias which can be clinically indistinguishable. An accurate diagnosis can only be made on the basis of porphyrin analyses carried out in an experienced laboratory. The clinician's role is to suspect the diagnosis of cutaneous porphyria, and then to use laboratory testing to confirm whether this is the diagnosis, and if so to precisely identify the porphyria. For any porphyria characterized by acute attacks, testing for latent porphyria in relatives will then be necessary.

What samples to send. In an adult with suspected bullous porphyria, it is generally sufficient to analyse urine and either plasma (where fluorimetry is available) or faeces (where it is not). However, urine, plasma and faeces need to be analysed in children, because of the increased complexity of the differential diagnosis. Faecal analysis is also necessary in instances when urine and plasma results do not differentiate HC from CEP, and in renal failure, where urine may be unavailable and plasma analysis unhelpful because renal failure increases plasma porphyrins. In suspected EPP, red cells and either plasma or faeces should be analysed.

Handling of samples. Laboratory testing of body fluids measures porphyrins, since porphyrinogens are spontaneously oxidized to their respective porphyrins outside the body. PBG has a tendency to polymerize to other molecules but porphyrins are reasonably stable when protected from light and oxidants. Thus, all specimens should be kept at room temperature or at 4°C in the dark and ideally should be analysed within 48 h of collection.

For urine and faecal analysis, fresh random specimens (10–20 mL urine or 5–10 g dry weight faeces) are preferable to 24 h collections. Random specimens yield equally useful results, and 24 h collections delay samples reaching the laboratory. Very dilute urine (creatinine < 4 mmol/L) is unsuitable.

Laboratory analysis of porphyrins. Old-fashioned qualitative screening methods for detecting porphyrins in specimens (often involving a Wood's light) are insensitive, and negative results from such tests are not of value. In urine, faeces and red cells or whole blood, quantitative screening using spectrophotometric or fluorimetric techniques is necessary and yields results as a total porphyrin concentration. Whole blood or red cell porphyrin testing measures both the total and free protoporphyrin concentrations. Plasma is analysed by fluorimetric scanning, a diagnostically powerful and simple qualitative technique. In urine and faeces, the finding of an increased porphyrin concentration will lead on to high-performance liquid chromatography (HPLC) which can be used to rapidly identify the accumulated porphyrins (Fig. 57.6). For PBG measurement in urine, qualitative tests are insensitive,

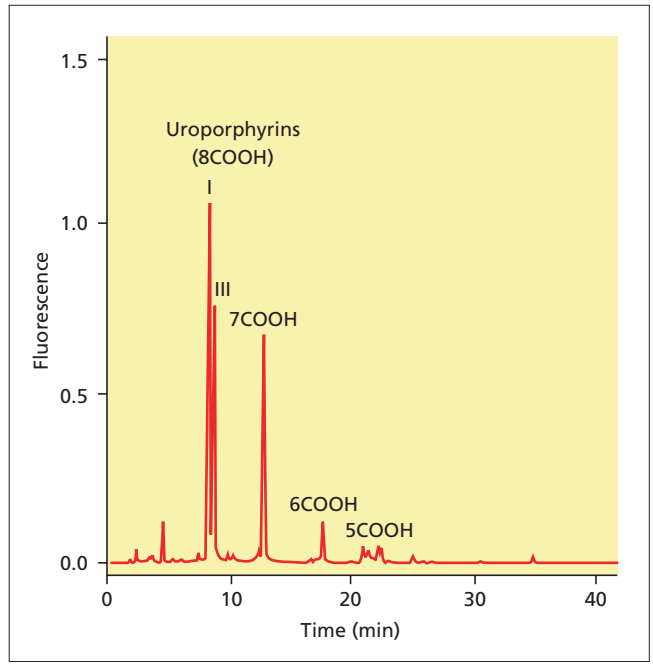

Fig. 57.6 High-performance liquid chromatography (HPLC) analysis: the more carboxylate groups it possesses, the faster a porphyrin molecule passes through the column. After passing through the column, porphyrins are detected by fluorimetry. This HPLC trace of urine shows the porphyrin profile typical of porphyria cutanea tarda (PCT). (Courtesy of Dr A. Deacon, King's College Hospital, London, UK.)

Table 57.2 The major biochemical findings in the cutaneous porphyrias. (Adapted from Deacon and Elder [4].)

	Urine	Faeces	Red cell	Plasma fluorimetry
Congenital erythropoietic porphyria	Uroporphyrin I; coproporphyrin I	Coproporphyrin I	Zinc- and free protoporphyrin; uroporphyrin I; coproporphyrin I	Peak at 615–620 nm
Porphyria cutanea tarda	Uroporphyrin III; heptacarboxy-porphyrin	Isocoproporphyrin; heptacarboxy-porphyrin	Normal	Peak at 615–620 nm
Hereditary coproporphyria	Coproporphyrin III	Coproporphyrin III	Normal	Peak at 615–620 nm
Variegate porphyria	Coproporphyrin III	Protoporphyrin; coproporphyrin III; X-porphyrin	Normal	Peak at 624–627 nm
Erythropoietic protoporphyria	Normal	Protoporphyrin (not diagnostically helpful)	Free protoporphyrin	Peak at 626–634 nm

and quantitative measurement, usually using a kit, is required, with semi-quantitative test kits being useful in emergencies where a result is needed quickly.

Interpretation of results [4] (Table 57.2). In cutaneous porphyrias, the accumulated porphyrin can usually be detected in plasma as an emission peak on spectrofluorimetry. Uro- and coproporphyrin are excreted into the urine and copro- and protoporphyrin into the faeces. Protoporphyrin accumulates in red cells in EPP.

(i) Plasma spectrofluorimetry. In plasma spectrofluorimetry, the sample is excited by 410 nm light, and fluorescent emissions detected. An emission peak at 615–620 nm indicates the presence of uro- or coproporphyrin and suggests a diagnosis of PCT, HC, CEP or HEP (urine analysis will differentiate PCT and HEP from the other two conditions). A peak at 624–626 nm indicates the presence of a porphyrin-peptide conjugate diagnostic of VP. This 624–626 nm peak is a sensitive indicator of VP and may even persist during periods of clinical remission when faecal excretion becomes normal. It is also positive in most cases of latent VP (in relatives) [5,6]. A peak around 633 nm (it can lie between 626 and 634 nm) is caused by protoporphyrin and suggests EPP, and EPP is an unlikely diagnosis in the absence of this peak. Plasma porphyrin concentrations, particularly uroporphyrin, increase in renal failure and can be as high as those found in patients with PCT.

(ii) Whole blood/red cell. An increased free protoporphyrin concentration is the diagnostic finding in EPP. The total protoporphyrin concentration includes both free and zinc-protoporphyrin. Zinc-protoporphyrin is also increased in iron deficiency, lead poisoning and certain anaemias. In a child with plasma, urine and faecal results typical of PCT, red cell UROD activity needs to be measured to exclude hepatoerythropoietic porphyria (HEP).

(iii) Urinary and faecal analysis. An increased total porphyrin concentration suggests a diagnosis of cutaneous porphyria. The total urinary porphyrin concentration is used to monitor disease activity in PCT. HPLC analysis is used to identify the porphyrins once an increased concentration has been found.
(a) In urine. An increase in uroporphyrin (and other highly carboxylated porphyrins especially heptacarboxyporphyrin) is typical of PCT though this does not exclude VP. Plasma spectrofluorimetry differentiates these two conditions and faecal analysis is required where this is unavailable. When PCT goes into remission and the total urinary porphyrin concentration returns to normal, it may still be possible to diagnose PCT from the characteristic urinary HPLC pattern. Coproporphyrinuria, in the presence of normal faecal porphyrin levels, does not indicate porphyria and can be caused by certain drugs, lead toxicity and hepatobiliary disease.
(b) In urine and faeces. Increased coproporphyrin suggests VP, but does not exclude HC. Isomer III to isomer I ratios are increased in every porphyria except CEP (where they are decreased). In CEP, excess type I isomers of uro- and coproporphyrin are present in urine and type I coproporphyrin in faeces.
(c) In faeces. In the presence of a plasma spectrofluorimetry peak at 615–20 nm, if urine HPLC does not show the PCT pattern, faecal analysis is required to differentiate HC (increased coproporphyrin III concentration) from CEP (increased coproporphyrin I concentration). Increased faecal isocoproporphyrin is characteristic of PCT. In renal failure, faecal analysis is vital, since urine may be unavailable and plasma porphyrins are increased in renal failure (PCT is the porphyria most commonly associated with renal failure). Increased faecal protoporphyrin is suggestive but not diagnostic of EPP, since it can also derive from bacterial degradation of haem in the gut and may indicate gastrointestinal haemorrhage when porphyrin concentrations are normal elsewhere.

Biochemical diagnosis of an acute attack of porphyria [3,4]. This is discussed above (Acute attacks of porphyria, p. 57.7). A definitive diagnosis of VP or HC can usually be

made on the basis of detailed porphyrin analysis. A definitive diagnosis of AIP requires enzyme or genetic tests.

Screening of relatives. In VP and HC, porphyrin levels are normal before puberty. Over the age of 15 years, a plasma fluorimetry scan is a reasonably sensitive biochemical test for latent VP in asymptomatic relatives of patients, picking up most cases. A positive scan is diagnostic of latent VP but a negative result is uninformative [5,6]. Faecal analysis, to measure the ratio of coproporphyrin isomers, will pick up some cases of latent HC after puberty [7]. In VP and HC, a negative porphyrin screening test in a relative needs to be followed by DNA analysis before latent disease can be excluded. The lack of any common mutations in porphyria (apart from South African VP) means that the causative mutation usually has to be identified for each family.

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The individual porphyrias

Porphyrias which cause cutaneous disease but do not cause acute attacks

Congenital erythropoietic porphyria (Günther's disease)

Definition. A severe and rare childhood porphyria causing lifelong mutilating photosensitivity and haematological disease.

Aetiology. Congenital erythropoietic porphyria (CEP) is caused by an autosomal recessive inherited deficiency of the uroporphyrinogen III cosynthase enzyme. Since this enzyme is required to form the biologically useful type III porphyrin isomers, its absence results in non-enzymatic reactions producing large amounts of type I isomer porphyrins which cannot participate in haem formation, and which massively accumulate in erythroid cells and then gradually leak into the plasma. The incidence in the UK is 2 per 3 million live births and less than 100 cases have ever been reported worldwide.

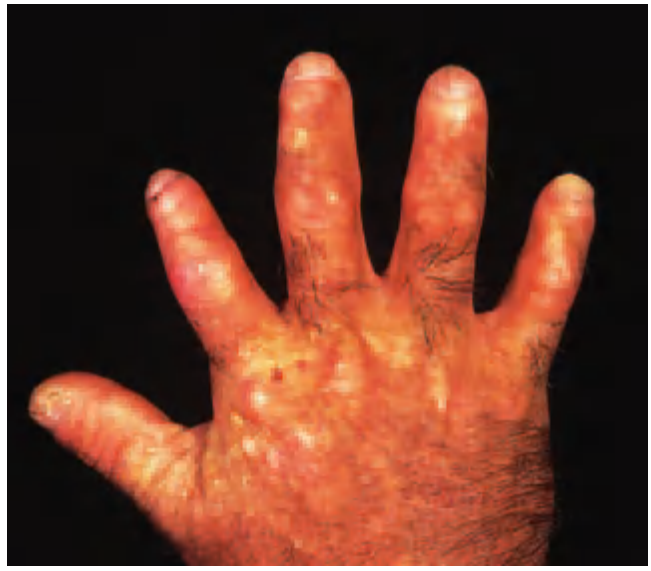

Fig. 57.7 Congenital erythropoietic porphyria (CEP): scarring of skin with resorption of terminal phalanges. (Courtesy of Dr A. du Vivier, King's College Hospital, London, UK.)

Clinical features [1–3]. CEP has a wide spectrum of presentation, from hydrops fetalis through to severe disease starting in infancy and also mild forms presenting later in life. The first sign of CEP is often the child's mother noting brown discoloration of amniotic fluid at the onset of labour, or observing pink or brown porphyrin staining of nappies (which fluoresce red-orange under Wood's light).

(i) The skin in CEP [1,3]. Severe photosensitivity begins in infancy, often in the neonatal period, with blisters developing in light-exposed skin on minimal light exposure. Phototherapy for neonatal jaundice may trigger lesions. Most children are so sensitive to the light that they have problems throughout the year. Exposed (and sometimes non-exposed) skin is fragile. The repeated bouts of inflammation with vesicles and bullae, often complicated by secondary infection, cause mutilating scarring particularly of the face and hands (Fig. 57.7). This photomutilation is associated with erosion of the terminal phalanges, onycholysis and destructive changes affecting the pinnae and nose. A diffuse pseudoscleroderma-tous thickening of exposed skin often gradually develops, with microstomia and sclerodactyly-like changes [3]. Hypertrichosis is found in most patients, particularly on the upper arms, temples and malar region. Patchy hypo- and hyperpigmentation occur even in minimally exposed areas.

A milder late onset form, presenting at any age from the third decade onward, has been described; this presents in a manner similar to PCT or VP, but may also cause thrombocytopenia secondary to hypersplenism [4]. Although clinically much less severe, enzyme activities in late onset CEP are often as low as in the childhood form [1].

(ii) Involvement of eyes and internal organs [3]*:*
(a) Eyes. Keratoconjunctivitis, blepharitis, cataracts, corneal ulcers, scars, cicatricial ectropion and scarring alopecia of eyelashes and eyebrows may all occur. Scleromalacia, pterygium formation, optic atrophy and retinal haemorrhage are less common.
(b) Bones and teeth. When teeth emerge, they are almost always stained brown (and fluoresce under Wood's light). Decreased bone density, osteopenia and osteolytic lesions secondary to erosion by hyperplastic bone marrow are seen on X-ray and are associated with vertebral compression and collapse, and with pathological fractures. In the hands there is resorption of terminal phalanges with acroosteolysis and cortical bone rarefaction. Occasionally, strict avoidance of the sun may impair vitamin D metabolism.
(c) Haematology [1,3]. The high concentrations of porphyrins in red cells cause haemolytic anaemia, severe enough to induce marrow hyperplasia often with visible expansion of the maxillary bones in the face. Hypersplenism is common. The haemolysis can be fully compensated or may cause a severe anaemia, and is occasionally so severe that some patients become transfusion dependent. The severity of the anaemia often fluctuates strikingly over time. Very severe haemolytic anaemia may even cause hydrops fetalis. Bone marrow examination reveals normoblastic hyperplasia, and under violet illumination most normoblasts have persistent red fluorescence localized to their nuclei, with haem-containing inclusion bodies being seen in the nuclei of these fluorescent cells.

Differential diagnosis. The photosensitivity differentiates CEP from other scarring blistering disorders of childhood, including epidermolysis bullosa dystrophica. The cutaneous changes may resemble HEP (the homozygous form of familial PCT) or homozygous VP. The cutaneous disease in late onset CEP is clinically indistinguishable from PCT or VP.

Biochemical findings [1]. The uroporphyrinogen III cosynthase enzyme deficiency results in the massive accumulation in all tissues of type I isomers of porphyrins, mainly uroporphyrin, along with coproporphyrin and smaller amounts of 7-, 6- and 5-carboxylic acid porphyrins. Red cells and urine contain large amounts of uro- and coproporphyrin (mainly type I) and faeces contains increased concentrations of coproporphyrin (mainly type I). A plasma spectrofluorimetry peak is seen at 615–620 nm. The absence of isocoproporphyrins and the normal level of 5-carboxylic porphyrin excretion in faeces distinguish CEP from HEP.

Prognosis. In the past most patients died by the age of 40 years but improvements in supportive care (particularly use of antibiotics) have improved the prognosis, though the haematological complications may be fatal. Long-term hypertransfusion causes significant problems with iron overload as patients reach adulthood, even when iron chelation has been used. Bone marrow transplantation now holds out the promise of cure for these patients (see below).

Treatment [5]. The photosensitivity is so severe that photoprotection is crucial. Sun avoidance and use of sun protective clothing and hats are essential. Opaque sunscreens containing pigmentary grade titanium dioxide or zinc oxide, possibly with added iron oxide, may be of limited value [6,7], and amber window films on home or car windows can reduce exposure to Soret wavelength light (TA81SXR, Madico, USA) [8], though more opaque films may be necessary (which are obviously not allowed on car windows). Prompt treatment of secondary infection is important.

β-Carotene may help cutaneous disease in some patients [1].

Many therapies reduce the porphyrin concentrations by suppressing erythropoiesis. Hypertransfusion with regular blood transfusions to maintain a polycythaemia inhibits endogenous haemoglobin production and decreases porphyrin formation, and may reduce haemolysis and cutaneous symptoms in moderately affected patients. However, splenomegaly may increase transfusion requirements and the value of hypertransfusion often decreases at puberty [5]. Hypertransfusion is frequently complicated by iron overload, even when desferrioxamine has been used, and blood-borne infections can be a complication. Hydroxyurea has been used with hypertransfusion and may be useful in transfusion-dependent CEP [9]. Intravenous haematin has been tried in late onset disease [10]. Haemolysis worsens the porphyria by causing anaemia and usually necessitates blood transfusion. Splenectomy may reduce haemolysis though the improvement may be temporary [5]. Lights during surgical procedures may cause phototoxic reactions and, at the least, clear filters should be used over the operation lights during any unavoidable surgery.

Since 1991, allogeneic bone marrow transplantation (bone marrow or umbilical cord blood stem cells) from a human leukocyte antigen (HLA)-compatible sibling has emerged as the treatment of choice in severe CEP. It provides a long-term cure [11] though the difficulties of finding a tissue-matched donor, and the dangers of marrow

transplantation, mean that it should be reserved for the most severely affected patients. Gene therapy has been successfully used '*in vitro*', but no '*in vivo*' studies have been carried out yet [12].

Genetic counselling. Since CEP is autosomal recessive, parents will be unaware of the risk until an affected child has been born, and the risk of disease is in further offspring rather than subsequent generations. For parents of an affected child, the chance of each future offspring suffering from the disease is 25%. The diagnosis may be made before birth by measuring the uroporphyrin I concentration in amniotic fluid, which is increased as early as 16 weeks *in utero* [13]. If the mutations in the index case have been identified, or the fetus is homozygous for the common C73R mutation, prenatal diagnosis from chorionic villous biopsy is possible [13].

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Porphyria cutanea tarda [1,2]

Definition. Porphyria cutanea tarda (PCT) is the commonest of all the porphyrias. It is characterized by fragility and blistering of exposed skin. It is usually acquired and is often associated with liver disease. It does not cause acute attacks.

Aetiology and classification. PCT results from deficiency of UROD [3]. This causes accumulation of uroporphyrin and other highly carboxylated porphyrins. Seventy-five per cent of patients have the *type I* (*sporadic*) form in which the enzyme deficiency is acquired and restricted to hepatocytes, due to inhibition of a normal UROD enzyme [3]. Twenty-five per cent have *type II* (*familial*) disease where the enzyme deficiency is hereditary, present in all tissues and associated with a UROD gene mutation. The penetrance of this autosomal dominant inherited form is so low that a family history is present in under 7% of cases, and since at least a 75% reduction in enzyme activity is required for clinical expression, some enzyme inhibition in the liver also occurs in familial PCT. Thus, UROD mutations are increasingly thought of as a risk factor for the development of PCT, rather than as representing a completely separate familial form of the disease. *Type III* disease is rare and characterized by an hereditary enzyme deficiency localized to the liver. *Toxic porphyria*, in which halogenated aromatic hydrocarbons inhibit the enzyme, is rare and mainly affects workers making herbicides [4]. A major epidemic of toxic porphyria in the 1950s in Turkey was caused by hexachlorobenzene added as a fungicide to seed wheat [5].

In PCT, the UROD enzyme is inactivated by an inhibitor which binds to its catalytic site. The inhibitor is generated in the liver by reactive oxygen species in the presence of iron (Fig. 57.8) [6]. The accumulated uroporphyrin diffuses from the plasma into surrounding tissues, causing a phototoxic reaction in the upper dermis in sun-exposed skin. This leads to lysis of cells in the superficial dermis with the formation of membrane-limited vacuoles which merge to produce a blister cavity under the basal lamina [7].

Histopathology [8]. The bullae in PCT are subepidermal with a sparse inflammatory infiltrate and 'festooning' of dermal papillae into the bullae. There is deposition of PAS-positive diastase-resistant fibrillar glycoprotein material in and around upper dermal blood vessel walls, and reduplication of the basement membrane. Immunofluorescence reveals IgG, a little IgM, fibrinogen and complement at the epidermodermal junction. Morphoea-like lesions in PCT are histologically indistinguishable from other forms of morphoea.

Clinical features (Fig. 57.9) [9]. Sporadic PCT usually presents in middle age whilst the familial form can occur at a younger age. Almost all patients notice increased fragility on light-exposed skin, particularly the backs of the hands and forearms, with minor trauma shearing the skin away to leave sharply marginated erosions. Most patients suffer from bullae, which can be over 1 cm in diameter and may be painful. They crust and resolve over a few weeks, leaving atrophic scars, milia and often mottled hyper- or

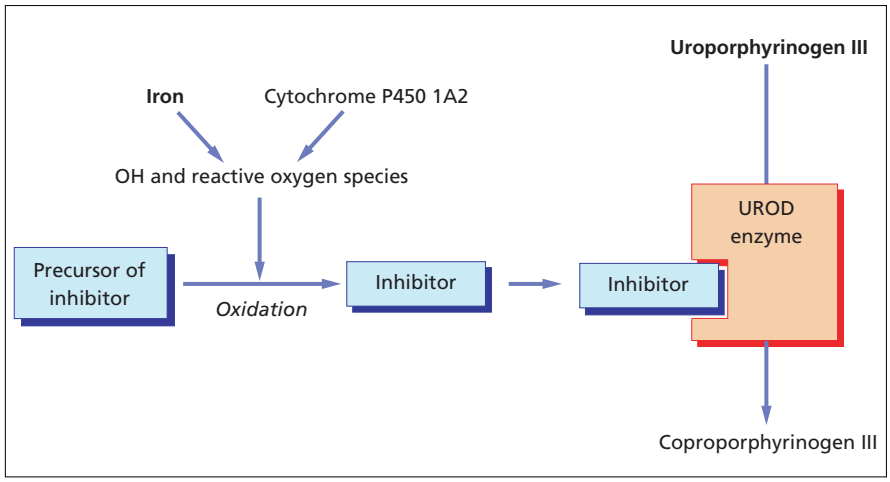

Fig. 57.8 Porphyria cutanea tarda (PCT) is caused by production of an inhibitor of uroporphyrinogen decarboxylase (UROD) in the liver, in the presence of iron. (Adapted from Elder [2].)

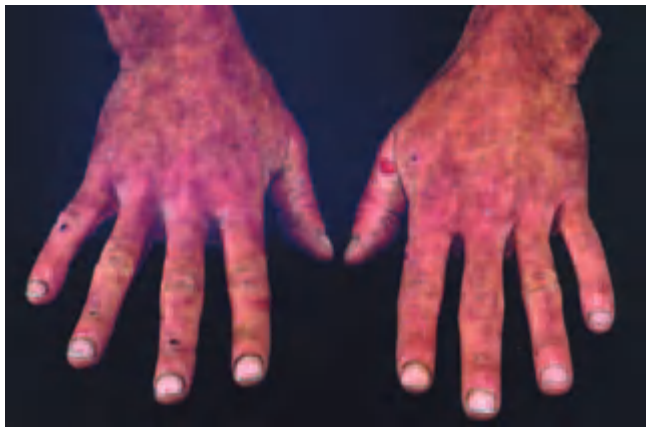

Fig. 57.9 Porphyria cutanea tarda (PCT): erosions, blisters, pigmentary changes and scarring.

hypopigmentation. Patients rarely associate development of new lesions with sun exposure, but symptoms are generally worse in the summer. Other common features are: patches of scarring alopecia following resolution of bullae on the scalp; hypertrichosis, usually on the upper face and forehead, sometimes on the ears or arms [10] and occasionally affecting the whole body; hyperpigmentation in a melasma-like pattern on the cheeks and around the eyes, or in a diffuse pattern on light-exposed skin, or occasionally in a reticulate distribution [9,10]. Photo-induced onycholysis [11] and accelerated solar elastosis [10] may also occur. Morphoea-like plaques may develop, particularly on the head and upper trunk. They are histologically indistinguishable from true scleroderma and mainly occur in longstanding untreated disease. It has been postulated that they arise as a result of the induction of collagen synthesis by uroporphyrin I [12]. These plaques may calcify, and may require excision and grafting if they ulcerate [9]. On the scalp, the morphoea-like change may cause a slowly expanding scarring alopecia starting in the frontoparietal and occipital areas [9,10,13], and even sclerodactyly or the facial changes of systemic sclerosis have been reported.

Hepatoerythropoietic porphyria [10,14]. The homozygous form of familial PCT, hepatoerythropoietic porphyria (HEP), is associated with over 90% reduction in UROD activity. It usually causes a severe disease clinically similar to CEP, with photosensitivity during infancy causing immediate pain on sun exposure, blisters on sun-exposed skin, and mutilating scarring of face and fingers. Prominent hypertrichosis, fluorescent teeth, eye involvement and shortened distal phalanges also occur. Haemolysis is milder than in CEP, and life expectancy is normal. HEP can occasionally present with a milder disease similar to PCT. Since the mutated alleles in HEP have to be associated with some residual enzyme activity to be compatible with life, the UROD gene mutations in HEP patients are different to those found in type II PCT [15].

Differential diagnosis. PCT can be clinically indistiguishable from VP, drug-induced pseudoporphyria, renal pseudoporphyria, HC, late onset Günther's disease or mild HEP. Biochemical analysis is necessary to diagnose PCT and it is particularly important to exclude VP and HC among the differential diagnoses, since they can cause acute attacks.

Biochemical findings [2]. In PCT, the urinary porphyrin concentration is increased, consisting mainly of uroporphyrin, some heptacarboxylic acid porphyrin, and sometimes also hexa- and pentacarboxylic acid porphyrins. A plasma spectrofluorimetry peak is seen at 615–620 nm. Isocoproporphyrin accumulates in the faeces. Urine analysis alone is insufficient to diagnose PCT, since a few patients with VP have the PCT urine pattern ('dual porphyria') [16]. In patients with renal failure, faecal analysis is essential, since plasma porphyrins are increased by

haemodialysis and urine collection may not be possible. The biochemical marker of disease activity and response to treatment is quantitative urinary porphyrin excretion measured in a random urine sample.

In HEP, the findings are as in PCT, but with the additional finding of a raised red cell zinc-protoporphyrin, and lower red cell UROD activity than occurs in type II PCT.

The investigation of the patient with PCT. PCT is essentially a liver disorder with secondary effects in the skin. It is crucial to investigate patients thoroughly both regarding other systemic diseases predisposing to the development of PCT, and in order to assess the severity of any liver disease.

(a) Risk factors for the development of PCT [17]. The major risk factors for developing PCT are subclinical genetic haemochromatosis, hepatitis C infection, alcohol and oestrogens. They all predispose to the inhibition of the UROD enzyme in the liver. Since some inhibition of the hepatic enzyme is also required for clinical expression of familial PCT, the same risk factors apply to sporadic and familial PCT. Since most of the risk factors have significant implications both for treatment and for the patient's general health, it is essential to investigate for risk factors in all patients diagnosed with PCT.

(i) Haemochromatosis. As expected in a disorder where hepatic iron plays a key role, almost all patients have increased stainable iron in the liver, and total body iron stores are increased in at least 60% of patients [2,17,18]. In the USA and Northern Europe, around 20% of PCT patients have true hereditary haemochromatosis [17,19] with homozygosity for the Cys282Tyr haemochromatosis mutation. Homozygosity for this mutation increases the risk of developing PCT 60-fold [17]. The clinical relevance of heterozygosity for the mutation is unclear. In Southern Europe, haemochromatosis is a less important risk factor. The iron overload found in PCT patients who do not have haemochromatosis is milder, and its cause obscure.

(ii) Hepatitis C infection. In Southern Europe, 70–90% of all PCT patients are infected with the hepatitis C virus [20,21], compared with around 60% of patients in the USA [17] and 7–12% in Northern Europe [22,23].

(iii) Alcohol. Between 30% and 90% of PCT patients consume over 40 g of alcohol daily, and 2% of all alcoholics with cirrhosis develop PCT [6].

(iv) Oestrogens. Ingested oestrogens, in the oral contraceptive pill or in hormone replacement therapy, are the sole risk factor in over a quarter of female patients [17]. Stopping the hormone may be sufficient to induce remission if the duration of therapy has been short [24]. If it is not possible to stop the hormone therapy, transdermal drug delivery is a safer alternative than the oral route [25].

There are other less common risk factors for developing PCT: haemodialysis predisposes to PCT [10], though PCT is less common in renal failure than pseudoporphyria —faecal porphyrin analysis differentiates these disorders. Human immune deficiency virus (HIV) infection predisposes to PCT [26], an association which may be due to coinfection with the hepatitis C virus [27]. Non-insulin dependent diabetes mellitus, systemic lupus erythematosus, dermatomyositis, hepatitis A and B infection, haematological malignancy, sideroblastic anaemia and thalassaemia have all been reported to be associated with PCT [2,9,28].

Most patients possess more than one risk factor for developing PCT, with hepatitis C infection and alcohol being strongly linked in men.

(b) Liver disease in PCT [18]. Since PCT is primarily a liver disorder with secondary effects in the skin, liver disease is a major concern. In almost all cases, liver biopsy reveals increased stainable iron, fatty change and intracellular porphyrin crystals. Fifty per cent of patients have more severe changes (lobular necrosis or inflamed fibrotic portal tracts), and cirrhosis occurs in 15% [18]. As one would expect, the most severe liver disease tends to occur in patients who have alcoholism, hepatitis C infection and iron overload [17]. The accumulated porphyrins are carcinogenic to the liver, and so PCT confers an additional risk for developing hepatocellular carcinoma on top of the risk conferred by the hepatitis C infection present in many patients [29]. In Southern Europe around 15% of PCT patients develop hepatocellular carcinoma during the decade after presentation, the main risk factors being a symptomatic period longer than 10 years prior to treatment, severe changes on hepatic histology at presentation, male sex and age over 50 years at presentation [30,31]. The incidence of hepatic malignancy is probably not as high in countries with lower hepatitis C infection rates. The converse situation, where a primary hepatic tumour secretes porphyrins to cause a PCT-like skin disease, is rare [32]. Hepatic function must be assessed at presentation in all PCT patients, and patients at high risk of hepatic malignancy require regular ultrasounds and serum α-fetoprotein measurement to detect carcinoma at a treatable stage [30]. PCT should be managed as a liver disorder, and the threshold for referral to a hepatologist should be low.

Treatment

Photoprotection. Visible light sunscreens containing pigmentary grade titanium dioxide or zinc oxide, sometimes with added iron oxide [33,34], and filter films for car and home windows, play an important role in controlling symptoms during the period of several months before specific therapies take effect.

Elimination of risk factors. Stopping oestrogen therapy [24], if it has not been used for more than 2 years, can induce

remission. However, elimination of the underlying cause by abstaining from alcohol, or by treating hepatitis C with interferon-α [35], usually does not induce remission. All patients should be advised to abstain from alcohol or oestrogen therapy to prevent exacerbation of the disease.

Specific treatments. Definitive treatment with venesection or low-dose antimalarials is required in almost all cases. Venesection depletes iron stores and eliminates hepatic iron overload, thus restoring normal enzyme activity. Around 500 mL of blood is removed every week or every 2 weeks, aiming to decrease transferrin saturation to 15%, haemoglobin to 11–12 g/dL and plasma ferritin to below 25 µg/L [36,37]. Blistering usually resolves within 2–3 months, skin fragility within 6–9 months [38], and porphyrin concentrations generally normalize within 13 months or so [9], at which point treatment should be stopped. Hypertrichosis [9] and sclerodermoid lesions [13] respond more slowly during the years after treatment has stopped. Excision and grafting may be needed for ulcerated sclerodermoid lesions [9]. Desferrioxamine leads to earlier remission than venesection [39] because it rapidly chelates hepatic iron, but it is expensive and requires use of a subcutaneous pump at night. Erythropoietin mobilizes hepatic iron into haemoglobin and is the treatment of choice for PCT in renal failure where patients are too anaemic for venesection and cannot excrete chloroquine [40]. Low-dose antimalarials are a very effective treatment for PCT. They work by complexing with uroporphyrin and promoting its excretion into the bile [41]. Daily doses of chloroquine cause a potentially dangerous acute hepatitis but chloroquine at the low dose of 125 mg [42,43] or 250 mg [44,45] taken twice a week is safe and effective. It leads to clinical remission within 6 months or so and biochemical remission after 6–15 months, at which point treatment is stopped [42–45]. Retinopathy does not seem to occur with such low doses of chloroquine [44]. Hydroxychloroquine (200 mg twice weekly) can be used but duration of remission is shorter than with chloroquine [46,47].

Low-dose chloroquine is the treatment of choice except in the following situations, in which venesection is preferable: (i) patients who do not respond to chloroquine; (ii) patients with a pathologically high serum ferritin concentration or homozygous for the Cys282Tyr mutation (if genetic analysis is available), who require iron depletion to protect internal organs; and (iii) patients with significant hepatitis C liver disease, who require iron depletion since hepatic siderosis increases their virally induced liver damage [48] and reduces the effectiveness of interferon [49]. However, chloroquine is not contraindicated in these situations, and may be needed when venesection is not possible, particularly in patients with hepatitis C liver disease where venous access is impaired by previous intravenous drug abuse. In renal failure, erythropoietin is the treatment of choice [40].

Remission with low-dose chloroquine generally lasts 17–24 months [43,44]. With venesection, relapse generally occurs around 2.5 years after the end of treatment [9,42]. Long-term follow-up is necessary for all patients to monitor for relapse (by measuring urinary porphyrin excretion), and for the management of coexisting liver disease.

Genetic counselling [50]. Familial and sporadic PCT can be differentiated by measuring red cell UROD activity. Since additional inhibition of the hepatic enzyme is required for clinical expression of disease in familial PCT, UROD mutations can be considered as a risk factor for developing the disease rather than as a different form of PCT. In view of the identical management of sporadic and familial PCT, the lack of evidence that identifying latent PCT in relatives alters outcomes, and the very low penetrance of familial PCT, it is difficult to justify family screening in familial PCT. It is therefore of little value to measure red cell UROD activity unless one is trying to differentiate HEP from PCT.

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Erythropoietic protoporphyria

Definition. EPP is an hereditary porphyria characterized by painful lifelong photosensitivity and occasionally liver disease.

Incidence and aetiology. The prevalence of EPP is around 1/100 000. EPP results from deficient activity of ferrochelatase, the final enzyme of haem biosynthesis. This causes the accumulation of protoporphyrin predominantly in cells of the erythroid series, which causes a phototoxic reaction as the porphyrin-laden cells pass through small upper dermal blood vessels and are exposed to the Soret wavelength in sunlight. The photoactivated porphyrin from red cells and plasma causes an acute injury to the endothelium mediated by singlet oxygen [1]. Many ferrochelatase gene mutations have been identified in EPP patients and none are particularly common [2]. A few adult onset cases have been reported which are associated with haematological malignancy and may be associated with chromosomal deletions involving the ferrochelatase gene [3].

Histopathology [4,5]. In the acute phase there is visible endothelial damage in superficial dermal vessels [6]. In the chronic phase, in exposed areas of skin, the repeated episodes of damage to small vessels in the upper dermis cause deposition of PAS-positive diastase-resistant hyaline material in the walls of blood vessels of the upper dermal and papillary vascular plexuses. Immunofluorescence shows immunoglobulins (mainly IgG) in a similar distribution. On electron microscopy the hyaline material can be seen to be a greatly replicated, layered and fragmented basement membrane, with fine fibrillar material permeating the capillary connective tissue sheath and extending beyond the vessel walls [4,7].

Clinical features [8,9]. Unlike the other cutaneous porphyrias, EPP causes immediate pain on exposure to bright sunlight. It presents most commonly between the ages of 3 and 5 years, and also quite often in babies who usually present with crying in their prams in sunny weather, or crying for no obvious reason at night in the summer. Onset later in childhood does occur but onset in adulthood is rare. In spring and summer, after anything from a

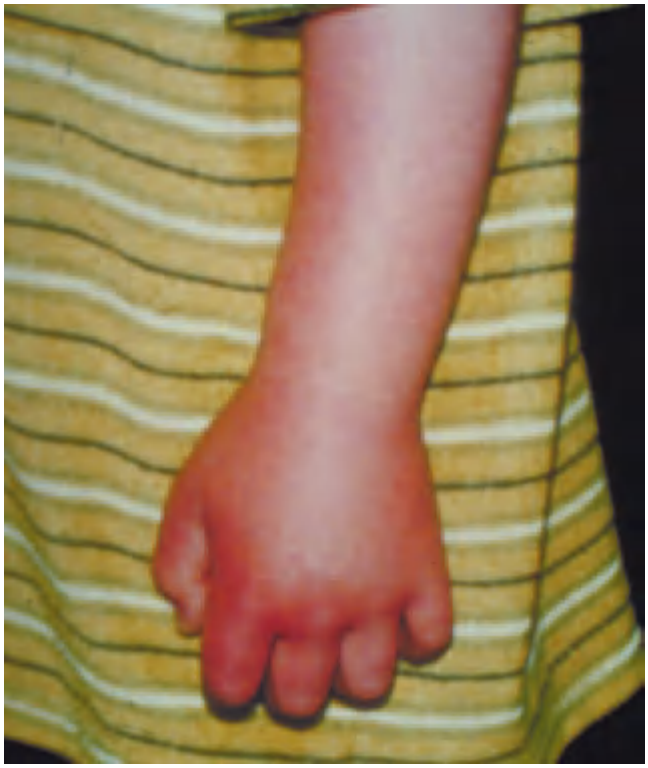

Fig. 57.10 Oedema during an acute painful attack in a child with erythropoietic protoporphyria (EPP).

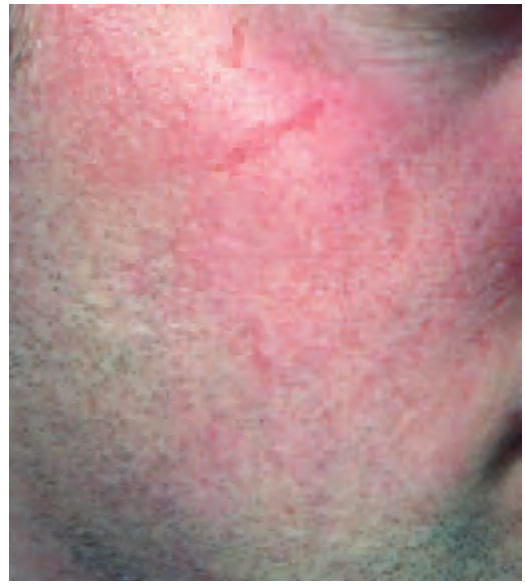

Fig. 57.11 Typical scars on the cheeks in erythropoietic protoporphyria (EPP).

few minutes to an hour or two of sun exposure, patients describe discomfort, tingling or itching in exposed skin, particularly the dorsae of the hands and the face. If exposure continues, severe burning pain follows which can last anything between an hour and several days. Children often find partial relief with cold water and wet cloths, and this feature may be diagnostically useful. Usually the only physical sign during an attack is oedema which may be subtle (Fig. 57.10). Erythema is less common. The lack of physical signs often leads to delay in diagnosis, with some patients initially being labelled as malingerers. Many patients experience a 'priming phenomenon' in which sunlight tolerance is reduced on the day after significant sun exposure [10]. In severe attacks, purpuric lesions and crusted erosions or vesicles may occur; these take a week or two to resolve after the attack settles down, and the pain may be severe enough to require hospital admission. Rare cases of EPP with prominent purpura and histological changes resembling a leucocytoclastic vasculitis [11], acute photo-onycholysis [12] or erythematous plaques [13] have been described. Physical signs may develop during childhood, with slight thickening of skin over the metacarpophalangeal and interphalangeal joints, superficial vermicular waxy scarring on the nose, shallow linear, punctate or small circular scars on cheeks and forehead and radial scars around the lips (Fig. 57.11). The skin over the nose, cheeks and forehead can become roughened and 'pebbly' in texture. However, most patients have no physical signs at all [8]. Children with EPP suffer from social isolation due to difficulty joining friends to play outside, and sensitivity to psychosocial issues is important for clinicians. Although EPP is lifelong, childhood and adolescence are frequently the most difficult times because it is easier for adults to organize their lives to reduce sun exposure. Symptoms usually improve and porphyrin levels fall during pregnancy [14]. Patients may develop a mild hypochromic microcytic or normocytic anaemia which can be associated with decreased serum iron levels and increased serum iron binding capacity [8]. With the exception of patients with EPP liver failure, operating theatre lights do not necessarily cause severe photosensitivity after surgery, though photosensitive reactions can occur [15]. It would seem reasonable to advise patients to avoid sun exposure for 48 h prior to elective surgery (to avoid priming), and to use clear filter films (e.g. Dermagard film, Bonwyke, Hants, UK; CLS200XSR film, Madico, USA) if available, over operating theatre lights, particularly for long procedures. Anaesthetists can be reassured that acute attacks do not occur in EPP. In contrast, operating theatre lights can cause a devastating and potentially fatal phototoxic reaction in patients undergoing liver transplantation for protoporphyric liver failure.

Biochemical investigation [16]. The diagnostic finding is of an increased red cell free protoporphyrin concentration. Protoporphyrin is seen as a peak at 633 nm on plasma fluorimetric scanning. Sixty per cent of EPP patients have an increased faecal protoporphyrin concentration though this is not very useful diagnostically because

of its lack of specificity. Urinary porphyrins are normal except in biliary impairment, when coproporphyrinuria develops.

Treatment [9]. No therapy has ever been proven to be effective in EPP mainly because of the lack of an objective test for disease activity in EPP, and high placebo rates make useful clinical trials difficult. This author's experience is that results with the specific therapies are generally fairly disappointing, and that attention to sunlight protection is the key to management.

Photoprotection. Basic measures include sun avoidance behaviour, sun-protective clothing and hats. Most sunscreens do not protect against the Soret wavelength including the UV-absorbent chemical sunscreens often misleadingly called 'total sunblocks' [17,18]. Some sunscreens containing reflectant particles can effectively protect against violet light, particularly large particle size titanium dioxide (pigmentary grade) or zinc oxide sometimes with added iron oxide [18]. Reasonably cosmetically acceptable sunscreens which protect against light up to 430 nm wavelength are available commercially (Dundee sunscreen, Tayside Pharmaceuticals, Dundee, UK) [17,18]. Dihydroxyacetone paint, which induces formation of a violet light absorbing brown pigment in the stratum corneum, has also been used in some patients with EPP [19]. Some relatively transparent window films, which absorb violet light, can be useful for car or home windows, particularly in severely affected patients. This author recommends two films to patients which are slightly yellowish grey but clear and provide partial protection against Soret wavelength light (Dermagard film, Bonwyke, Hants, UK; CLS200XSR film, Madico, USA). Regulations concerning films applied to car windows vary widely between countries.

The acute reaction. For the acute reaction, complete sun avoidance (even through windows) leads to earlier resolution, and fans and cold water provide some pain relief. Antihistamines and most analgesics are of little value. For severe attacks, hospital admission may be necessary, for light avoidance and analgesia (usually opiate).

Specific therapies. Oral β-carotene is the most widely used treatment, usually at a dose around 180 mg daily in adults (90 mg daily in children) taken throughout the spring and summer. It is postulated to scavenge free radicals involved in the acute phototoxic reaction. Although many patients report that it reduces symptoms, others do not, and proof of efficacy from controlled trials is lacking. Patients may need to take it for several months before any effect is observed. The most common adverse effect is reversible skin discoloration. A controlled trial of *N*-acetyl cysteine has shown no benefit [20]. Short courses of a few weeks of psoralen and long-wave UV radiation (PUVA) [21] and narrow-band UVB [22] used in the early spring may be valuable, particularly in milder cases, and probably increase photoprotection by inducing epidermal thickening and pigmentation. Unlike PUVA, narrow-band UVB does not overlap with the EPP action spectrum and so cannot trigger attacks of pain. Many other systemic treatments with antioxidant or free radical scavenging properties have been used in EPP in an uncontrolled way on small numbers of patients, with conflicting and generally unconvincing results.

Genetic counselling. Although rare cases of autosomal recessive inheritance have been reported [23], EPP is generally an autosomal dominant disorder with incomplete penetrance, the disease resulting from co-inheritance of a gene mutation on one ferrochelatase allele with a low expression variant on the other allele. This low expression variant is present in around 10% of the Caucasian population and is associated with reduced ferrochelatase mRNA levels resulting from the presence of the polymorphic variant IVS-48C [24]. Overall, the probability of each offspring of an EPP patient suffering from the disease is under 10% [25], but testing for the IVS-48C polymorphism in a patient's partner is now available and can indicate more precisely whether there is a significant probability of future offspring being affected. This is useful for patients who would not consider having children if there were a significant likelihood of them having the disease. For a disorder which is rarely life-threatening, termination of pregnancy and thus antenatal diagnosis are not relevant.

Liver disease in EPP [23]. Protoporphyrin is excreted exclusively into the bile. It precipitates to form gallstones in around 12% of patients [8]. It is also hepatotoxic, particularly to bile canaliculi, and severe liver damage occurs in around 1% of patients. EPP liver failure is most common in the teens and twenties. Usually a patient develops jaundice, worsening photosensitivity and often upper abdominal pain over a period of weeks or months. Investigation shows severe or total cholestasis, and a dramatically high red cell protoporphyrin concentration (due to its impaired excretion), which causes the worsening photosensitivity. Liver histology reveals deposition of protoporphyrin in vacuoles within bile canaliculi and hepatocytes, which may be accompanied by cirrhosis (Fig. 57.12). Although such acute episodes may resolve spontaneously, the porphyrin-induced cholestasis may become increasingly severe and itself further increase the protoporphyrin concentration in a vicious cycle, in which case the patient will die unless a liver transplant can be performed. Under operating theatre lights during the transplant surgery, the very high protoporphyrin concentration may cause a severe phototoxic reaction with

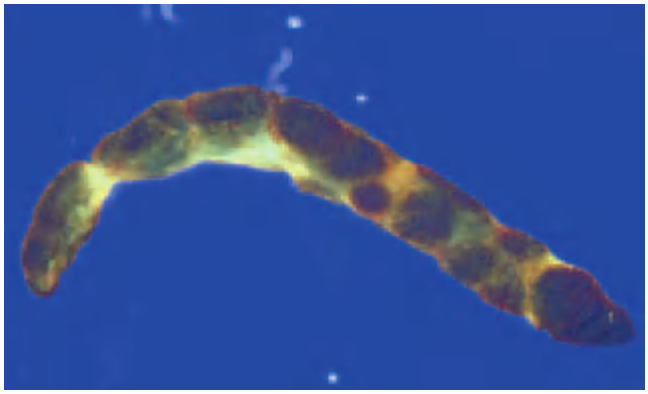

Fig. 57.12 Liver biopsy in protoporphyric liver disease, showing nodules of cirrhosis and black staining by deposits of protoporphyrin.

postoperative burns, massive haemolysis and a severe neuropathy, so clear filters protective against violet light need to be used over operating theatre lights [23]. If these immediate postoperative complications are avoided, the prognosis after liver transplantation is good. Protoporphyric liver disease may recur in the graft over several years, although severe recurrent liver disease has been reported in only one case [26].

It is vital to recognize impending protoporphyric liver failure early enough that arrangements can be made for a liver transplant if it should become necessary. Thus, all EPP patients should have liver function tests and red cell protoporphyrin concentration checked at least once a year. The appearance of coproporphyrin in the urine is a sensitive indicator of significant liver disease in EPP [27]. Worsening photosensitivity may be the only clinical indication of the development of severe liver disease. Although protoporphyric liver failure is rare, mild abnormalities of liver function tests are common in EPP [27]. Since the significance of these abnormalities is unclear, it is advisable to monitor closely in these patients, and to refer the patient to a hepatologist if the abnormality is persistent or deteriorating. In such patients, an ion exchange resin such as cholestyramine may protect the liver against further porphyrin toxicity. The major difficulty for the dermatologist is the lack of any means of identifying those EPP patients at risk of liver failure. Since several cases have been described in siblings, patients with a relative who has suffered protoporphyric liver failure should be treated as being at increased risk of developing it themselves. Recessive inheritance of EPP may increase the risk of severe hepatic disease, though it is not clear how significant an association this is [28].

Iron deficiency anaemia may trigger or exacerbate hepatic disease by increasing porphyrin accumulation [23], and subsequent iron replacement may make the situation temporarily worse by acutely stimulating haem biosynthesis.

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Porphyrias which cause cutaneous disease and acute attacks

Hereditary coproporphyria

The skin is not affected in most patients suffering from this rare acute porphyria. Like VP, the disease presents from puberty onwards and only around 10–20% [1] of patients have cutaneous involvement with fragility and blistering in sun-exposed areas, that is indistinguishable from PCT or VP. The skin disease may be triggered or exacerbated by intercurrent liver disease [2]. HC is caused by an autosomal dominant inherited deficiency of coproporphyrinogen oxidase. The biochemical findings are of a 615–620 nm peak on plasma spectrofluorimetry, increased uro- and coproporphyrin concentrations in urine, and increased coproporphyrin in faeces. Predominance of the type III isomer in faeces is a sensitive indicator of HC [1]. Rare variants include a homozygous form characterized by short stature, acute attacks and skin changes with prominent hypertrichosis and pigmentation [3], and harderoporphyria which causes haemolysis in the neonate or bullae.

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Variegate porphyria

Definition. A rare inherited disease usually characterized by photo-induced skin fragility and blistering, which may cause acute attacks.

Aetiology and incidence. VP is caused by an autosomal dominant inherited deficiency of protoporphyrinogen oxidase. In addition to causing photosensitization, accumulated coproporphyrinogen and protoporphyrinogen also inhibit PBG deaminase, the probable mechanism for acute attacks in VP [1]. In South Africa, VP is common (due to a founder effect) with a prevalence in whites and Afrikaner-descended non-whites of 1/200. Elsewhere the prevalence is around 1/100 000 [2]. At least 80% of South African carriers of a pathogenic VP mutation are completely asymptomatic [3].

Pathogenesis of skin lesions in VP. It is perhaps unexpected that the accumulated copro- and protoporphyrin should cause PCT-like upper dermal blistering rather than EPP-like acute pain. This is likely to be because, although hydrophobic porphyrins predominate in plasma, hydrophilic porphyrins, especially uroporphyrin, predominate in the skin. This local accumulation is thought to result from secondary local photo-inactivation of UROD in the skin by coproporphyrin [3]. In addition, the protoporphyrin in VP is conjugated to a peptide which may reduce its phototoxicity.

Clinical features [2–4]
Skin. Of those patients with symptomatic VP, around 70% of patients have cutaneous involvement, and only around 17% of these patients will ever suffer an acute attack [5]. VP only very rarely presents before puberty, and usually the skin disease begins in adolescence or young adulthood. Patients describe skin fragility, usually fairly mild, affecting sun-exposed skin particularly on the backs of the hands [2,3]. The skin disease is generally indistinguishable from PCT, with painful tense bullae occurring in sun-exposed skin, as well as scarring, pigmentary abnormalities, sometimes pseudosclerodermatous changes of the hands and fingers, and occasionally photo-onycholysis. However, a significant number of patients do not describe worsening in the summer, and the patients who do describe seasonal variation often have their worst problems in late summer and autumn. In addition, around half of patients with VP describe mild transient light-related eruptions in the early summer. The examination findings of scarring, patches of hypo- and hyperpigmentation at sites of blisters, milia and mild hypertrichosis particularly around the eyes, are indistinguishable from PCT. Intercurrent biliary obstruction exacerbates the cutaneous disease since the accumulated porphyrins are excreted into the bile. Acute photosensitivity can occur in patients with disturbed liver function. Hormonally induced hepatic dysfunction may explain the exacerbations of skin disease seen in females taking oral contraceptives and during pregnancy. VP sometimes goes into clinical and biochemical remission in old age.

Acute attacks [2,3,5]. As in other acute porphyrias, women are three times as frequently affected as men, and 70% of acute attacks occur between the ages of 20 and 40 years. Around 17% of patients with cutaneous VP ever suffer an acute attack: the number has declined recently due to improved use of prophylactic measures. The severity of acute attacks varies from mild abdominal pain, sometimes accompanied by vomiting and constipation, through to very severe attacks with bulbar palsy and respiratory paralysis. The presentation, diagnosis and management of acute attacks is covered in the section on acute attacks of porphyria, p. 57.7.

Homozygous VP [6]. In this disease, a mutation on both protoporphyrinogen oxidase alleles results in an enzyme activity less than 20% of normal, compared to the 50% in

other VP patients. In homozygous VP, fragility, bullae and often hypertrichosis develop in exposed (and sometimes non-exposed) skin in neonates or infants and the skin disease may be severe. Delayed development, epilepsy, sensory neuropathy, nystagmus, various hand deformities and growth retardation also commonly occur. Acute attacks do not occur in these patients. The biochemical findings are the same as in VP, except for the lower enzyme activity.

Differential diagnosis. VP cutaneous disease is easily distinguished from non-photosensitive blistering disorders. It can be clinically very similar to PCT, late-onset CEP, HC and pseudoporphyria. Biochemical analysis is required to diagnose VP.

Biochemical findings. A plasma spectrofluorimetry peak around 626 nm (caused by a porphyrin–protein complex) is diagnostic of VP in the absence of a raised free red cell protoporphyrin level, and is present in virtually all symptomatic cases of VP. It may persist during periods of clinical remission when faecal excretion becomes normal. The urine contains increased levels of coproporphyrin, and increased concentrations of copro- and protoporphyrin are found in faeces. In a few patients, the urine shows the typical PCT pattern of uroporphyrin accompanied by hepta- and sometimes hexa- and pentacarboxylic acid porphyrins, a situation known as 'dual porphyria' [7]. Thus, urinary analysis alone can result in the misdiagnosis of VP as PCT, with potentially disastrous consequences. During acute attacks, urinary PBG (and ALA) are raised. The urinary PBG usually falls to normal within weeks of the attack resolving, but may stay a little increased outside the context of an acute attack [8].

Treatment. The key to successful management of the skin disease is photoprotection with sun avoidance using clothes, hats and gloves. Opaque sunscreens, containing pigmentary grade titanium dioxide or zinc oxide sometimes with the addition of iron oxide, are protective against Soret wavelength light [9,10]. The skin disease is rarely severe enough to require filter films for car and home windows. Since the relationship between sun exposure and skin lesions is not obvious, the role of light in producing the skin lesions should be explained to the patient. β-Carotene and canthaxanthin have also been claimed to provide limited protection in some patients, and narrow band UVB phototherapy may also be of value [3]. If liver function tests indicate biliary obstruction, relief of this will reduce cutaneous symptoms. The risk of acute attacks is the key issue for safe management of patients and their families. Patients should be given a list of drugs to avoid, including those which can induce attacks (see Table 57.1), those known to induce cholestasis, and cannabis; they should also be advised to wear an emergency identification bracelet, to avoid low calorie diets, and to become teetotal.

Genetic counselling. It is important to identify relatives who have latent VP because of the risk of acute attacks. The plasma 624–626 nm peak is found in the majority of cases of latent VP but only from teenage onwards. A positive plasma fluorimetry result is diagnostic of latent VP but a negative result is uninformative [11,12]. The only completely reliable way to identify those carrying the VP gene defect if the plasma scan is negative is to identify the protoporphyrinogen oxidase gene mutation in the index case and then assess its presence or absence in relatives. This is labour intensive because, outside South Africa, most families have their own private mutation. Relatives found to have the gene defect are at a low risk (roughly 5–10%) of acute attacks and should take all the precautions taken by any patient diagnosed with an acute porphyria. The risk of a patient passing the mutated gene on to each offspring is 50%, and around 20% of those carrying the mutation will eventually develop symptoms of some sort.

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Mucinoses [1–5]

[S.M. Breathnach, pp. 57.23–57.36]

Mucins are jelly-like acid glycosaminoglycans (formerly known as mucopolysaccharides) of the ground substances and probably play a part in the extravascular exchange of

metabolites. Mucin is normally produced in small quantities by fibroblasts. Acid glycosaminoglycans, such as hyaluronic acid and heparin, stain with toluidine blue, colloidal iron, or with alcian blue at pH 2.5, the coloration depending on the number and nature of the acid groups [6]. PAS stains heparin, but not hyaluronic acid. In general, acid glycosaminoglycans stain much brighter in frozen fixed tissue, or in 1% cetylpyridinium chloride solution [7], rather than in formalin-fixed biopsies [8].

Neutral glycosaminoglycans are glycoproteins in which the hexosamine sugar polymer is incorporated in a protein chain. Hale and alcian blue stains are negative but PAS stain is positive. The mucins in the skin and their histochemistry have been well reviewed [9]. Histopathological examination of many cutaneous mucinoses reveals that collagen fibres are fragmented [10].

Classification of the cutaneous mucinoses [1–5]

Mucinous infiltration of the skin is found in many widely differing disorders, some affecting the skin only, others related to systemic disease [1–5,11]. The association of HIV infection with lichen myxoedematosus seems to be more than coincidental [12]. They can be classified as shown in Table 57.3.

Table 57.3 Classification of the cutaneous mucinoses.

Primary

Diffuse (degenerative-inflammatory mucinoses):
Generalized myxoedema (Chapter 59)
Pretibial myxoedema (Chapter 59)
Lichen myxoedematosus (papular mucinosis, scleromyxoedema)
Reticular erythematous mucinosis (plaque-like mucinosis)
Scleroedema (Chapter 56)
Self-healing juvenile cutaneous mucinosis
Cutaneous mucinosis of infancy
Papular and nodular mucinosis associated with lupus erythematosus
Papular mucinosis of the toxic oil syndrome

Focal (neoplastic-hamartomatous mucinoses):
Cutaneous focal mucinosis
Mucous (myxoid) cyst
Acral persistent papular mucinosis
Mucinous naevus

Follicular forms:
Follicular mucinosis (alopecia mucinosa)
Urticaria-like follicular mucinosis

Secondary

Collagen vascular diseases (especially dermatomyositis, lupus erythematosus)
Malignant atrophic papulosis (Degos' syndrome) [13]
Hereditary progressive mucinous histiocytosis
Papular mucinosis in L-tryptophan-induced eosinophilia–myalgia syndrome
Mucinosis accompanying mesenchymal and neural tumours

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Lichen myxoedematosus

SYN. PAPULAR MUCINOSIS; LICHEN FIBROMUCINODOSIS; SCLEROMYXOEDEMA

Lichen myxoedematosus is a cutaneous myxoedematous state characterized by the formation of numerous lichenoid papules which coalesce together to form generalized plaques, causing extensive thickening and hardening of the skin [1,2] (Fig. 57.13). It is a rare disorder characterized by proliferation of fibroblasts with fibrosis and excessive deposition of acid glycosaminoglycans in the skin, and is distinct from scleroderma [3]. Montgomery and Underwood [2] divided it into four types:

1 a generalized lichenoid papular eruption (scleromyxoedema);
2 a discrete papular form;
3 a localized to generalized lichenoid plaque form; and
4 an urticarial plaque form.

However, a recent review of this area suggests that there are really only two main divisions of lichen myxoedematosus, a generalized papular and sclerodermoid form (scleromyxoedema) and a localized papular form [1]. Some atypical variants have also been suggested.

Scleromyxoedema is usually associated with a monoclonal gammopathy. Serum from patients with lichen myxoedematosus, even after elution of the IgG paraprotein, can stimulate synthesis of DNA and cell proliferation in cultured fibroblasts [4]. Localized forms of lichen myxoedematosus, without a demonstrable paraprotein, are recognized, and include a discrete papular form involving

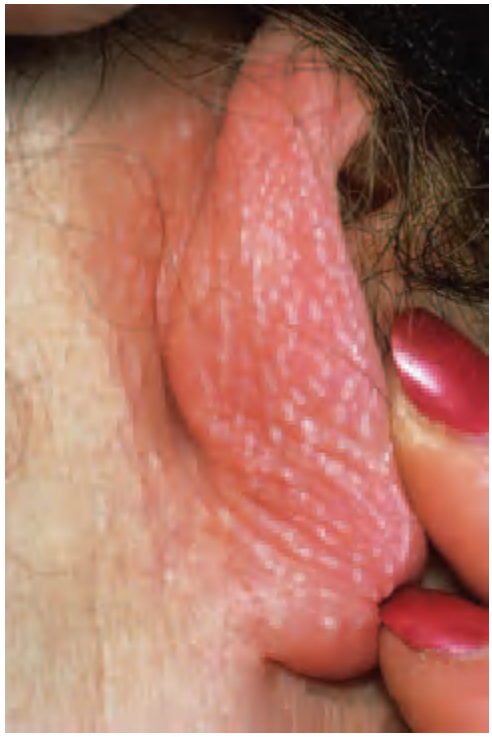

Fig. 57.13 Lichen myxoedematosus. Close up of micropapules behind earlobe. (Courtesy of St Thomas' Hospital, London, UK.)

any site; acral persistent papular mucinosis involving only the extensor surface of the hands and wrists; self-healing papular mucinosis, of juvenile and adult types; papular mucinosis of infancy, a paediatric variant of the discrete form or of acral persistent papular mucinosis; and a nodular form [1,5,6].

Histopathology [2,7–9]. Mucinous deposits occur in the middle and deeper layers of the dermis, where they displace collagen fibres, but do not involve the dermal papillae or accumulate around blood vessels. Histochemically, the mucinous deposits are heterogenous mixtures of acid glycosaminoglycans, which stain positively with alcian blue and toluidine blue. Large, stellate, elongated fibroblasts are present within the mucinous stroma [10]. Mucin deposition in the media and adventitia of vessels and in many organs including the myocardium is reported, and the skeletal muscles may be infiltrated with lymphocytes [11].

Clinical features [1,12]. In scleromyxoedema (the Arndt–Gottron syndrome) the pattern of lichen myxoedematosus is confluent, papular and sclerotic. Diffuse thickening of the skin underlies the papules. The facial features may be distorted by exaggeration of the facial ridges (Fig. 57.14), and flexion of the fingers may be limited. Multiple periorbital myxomas may progress to scleromyxoedema [13]. The involvement of the hands may simulate the sclerodactyly of scleroderma (Fig. 57.15), but the clinical appearance of numerous small papules of more or less uniform size, often in linear patterns on an erythematous and palpably thickened background, is very distinctive.

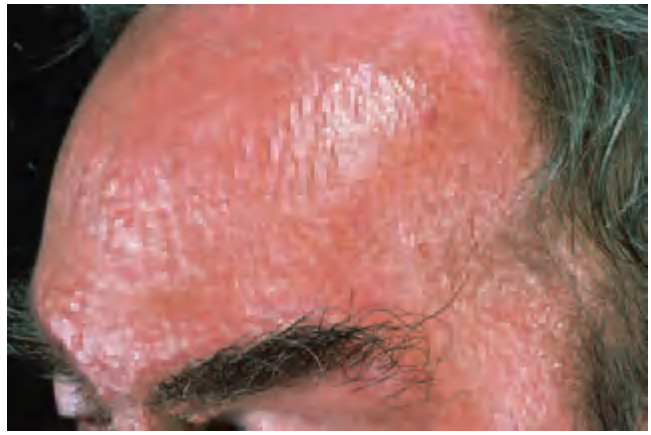

Fig. 57.14 Scleromyxoedema. View of forehead showing sclerodermoid appearance and linear papulation. (Courtesy of St Thomas' Hospital, London, UK.)

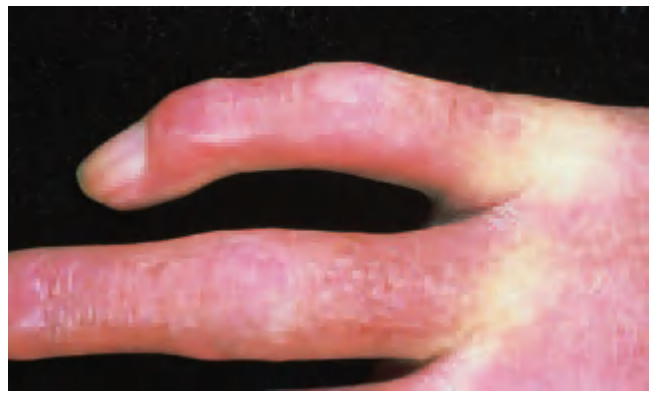

Fig. 57.15 Scleromyxoedema. Sclerodermoid appearance of finger. Same patient as shown in Fig. 57.14. (Courtesy of St Thomas' Hospital, London, UK.)

No endocrine abnormalities have been demonstrated, but cardiovascular abnormalities may occur in 10% of cases [7], whereas others may complain of extreme muscular weakness and lassitude due to myopathic or neurological involvement [13,14]. Occasionally, systemic involvement may occur in other internal organs; this has recently been reviewed [11,15].

An IgG class paraproteinaemia is almost always found on serum electrophoresis, although total serum protein values are usually normal [1,16]. Bone marrow studies may show a mild plasmacytic infiltration. Radiological survey of the skeletal system is normal. In one case, acid glycosaminoglycan levels in the serum were elevated [17].

Localized lichen myxoedematosus is characterized by small, firm, waxy papules of limited distribution [1], although a rare nodular form has larger lesions.

Diagnosis. Infiltrates appearing in and around old scars may simulate 'scar sarcoidosis'. Papules on the dorsa of the hands and ears may cause confusion with granuloma annulare. Systemic scleroderma may show many features simulating scleromyxoedema. However, in scleroderma the skin is thickened and bound-down, whereas in scleromyxoedema it is also thickened but moveable over the subcutis. Papules are absent in scleroedema and scleroderma, but common in scleromyxoedema.

Prognosis. The prognosis of scleromyxoedema is poor despite the introduction of treatment with cyclophosphamide and melphalan [11]. Death may result from non-specific complications such as bronchopneumonia, coronary occlusion or from haematological malignancies [11].

Treatment. The potential for spontaneous long-term regression renders treatment of severe lichen myxoedematosus or scleromyxoedema difficult to assess [18]. Systemic steroids alone are usually ineffective. Treatment with melphalan is probably the treatment of choice, although potentially toxic; long-term low-dose melphalan therapy resulted in the gradual resolution of skin lesions, with noticeable softening of sclerosis within 3 months [19]. However, the effect on the reversion of the monoclonal protein tended to be variable. Oral aromatic retinoids produce inconsistent but occasionally successful results [20,21]. Plasmapheresis can be beneficial if combined with pulsed corticosteroid and/or immunosuppressive therapy [22,23]. Other therapies reported to be successful in isolated cases of scleromyxoedema include topical betamethasone and dimethyl sulfoxide (DMSO) [24], extracorporeal photochemotherapy [25,26], intravenous immunoglobulin [27,28] and electron-beam therapy [29]. Aggressive surgical intervention for palliation of severe aesthetic and functional disability may be indicated [30].

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Reticular erythematous mucinosis [1]

SYN. REM SYNDROME, PLAQUE-LIKE CUTANEOUS MUCINOSIS [2]

This syndrome comprises areas of reticular erythema on the trunk with a mucinous and round cell infiltrate in the dermis, and is frequently called the REM syndrome. Plaque-like cutaneous mucinosis is essentially the same disease process [3].

Aetiology. The aetiology is unknown, but there is some clinical and also experimental evidence that light is a factor in the pathogenesis of this disorder [4,5]. REM syndrome can be associated with the production of a monoclonal paraprotein, suggesting that the disease may

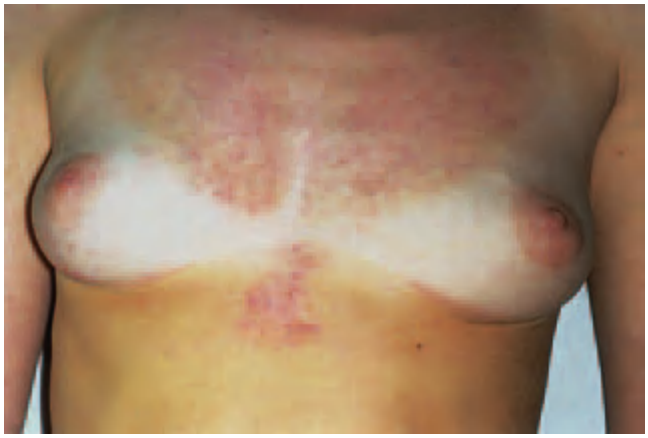

Fig. 57.16 Reticular erythematous mucinosis syndrome. View of anterior chest to show erythematous rash in photodistributed location.

involve disturbance of immune mechanisms [6]. Immunophenotypic studies have suggested a potential overlap between REM syndrome and Jessner's lymphocytic infiltration [7]. An hormonal influence may be operative [8].

Pathology. The epidermis appears normal. In the papillary and upper reticular dermis there is a perivascular, and occasionally perifollicular, infiltrate largely composed of small mononuclear cells and populations of FXIIIa+/ hyaluronan synthase 2+ dermal dendrocytes, which have been postulated to be responsible for accumulation of hyaluronan, rather than this being derived from fibroblasts [9]. There is separation of collagen bundles and fragmentation of elastic fibres. Histochemical stains show an increase in dermal mucin with a profile consistent with hyaluronic acid [4]. Direct immunofluorescence is usually negative for immunoglobulins, fibrin and complement [4], although granular basement-membrane deposits of IgM, IgA and C3 have been described in isolated cases [5,10].

Clinical features. Most affected patients are female [1,3,4,11] and usually middle aged, but the condition has been reported in children [12]. Areas of pink, reticulate or sheet-like erythema are present on the central part of the chest and back, particularly over the sternum and on the upper back (Fig. 57.16). There is usually no pruritus, although sometimes the areas become itchy following sun exposure, and the erythema may be then more apparent. The areas become infiltrated and then slowly increase in size. Coexisting disorders reported in association with occasional cases of REM syndrome include hyperthyroidism, hypothyroidism, discoid lupus erythematosus, carcinoma and thrombocytopenic purpura [13]. Evolution of REM syndrome to systemic lupus erythematosus has been reported [14].

Treatment. Topical steroids are ineffective, but fortunately antimalarials are almost invariably effective in controlling the eruption [1,4,11]. Ciclosporin appears to be of no value in treating REM syndrome [15]. UVB radiation combined with steroid impregnated tape [16], and use of the pulsed dye laser [17], have been beneficial.

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Self-healing juvenile cutaneous mucinosis [1–4]

Self-healing juvenile cutaneous mucinosis is a rare disorder characterized by an early age of onset accompanied by inflammatory phenomena and spontaneous resolution over a few months. The condition has also been reported in a child undergoing chemotherapy for nephroblastoma [5], and in two brothers [6]. Clinically, there are papules, nodules or plaques with a predilection for the head and trunk rather than the extremities. Histologically, there is

dermal mucinosis and a mild increase in fibroblasts and mast cells. It is postulated that a temporary alteration of fibroblast synthetic function occurs, possibly as a result of a viral infection [3]. Rare cases of self-healing cutaneous mucinosis have been reported in adults [7,8].

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Cutaneous mucinosis of infancy [1–4]

In this rare condition, opalescent papules may be noted at birth [2] or develop a few months later [1,3]. The papules are scattered on the dorsa of the hands or around the elbows, and may have a linear distribution [2]. Focal mucinous material is deposited in the papillary dermis without overt fibroblast proliferation. It is not clear what the long-term outlook of cutaneous mucinosis of infancy is, but some cases appear to progress [3]. Thus, certain cases of cutaneous mucinosis of infancy are in fact the infantile presentation of lichen myxoedematosus [5].

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Papulonodular mucinosis associated with systemic lupus erythematosus [1–5]

Papulonodular mucinosis is a distinct but rare cutaneous manifestation occurring in patients with systemic lupus erythematosus or chronic cutaneous lupus erythematosus [6]. It presents as indolent, flesh-coloured papulonodules or plaques [7] on the neck, trunk and upper limbs due to diffuse mucinosis in the dermis. It differs from the diffuse mucinosis that may be found in lesional skin of lupus erythematosus in that it occurs in areas free of specific lupus erythematosus lesions. Clinical recognition is important because in one-third of cases it precedes both clinical and serological evidence of systemic lupus erythematosus, sometimes by several years. Cutaneous mucin deposition in papulonodular lupus erythematosus is associated with increased glycosaminoglycan production by dermal fibroblasts, which appears to be due to an unidentified serum factor [8].

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Cutaneous mucinosis in the toxic oil syndrome [1]

Toxic oil syndrome occurred in Spain in 1981 related to the ingestion of adulterated oil. During the late recovery stages, an asymptomatic papular eruption developed on the arms, thighs and legs due to dermal mucin deposition. The papular eruption gradually resolved but sometimes led to sclerodermoid changes.

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Cutaneous focal mucinosis [1–3]

Cutaneous focal mucinosis has been accepted as a distinct entity, although recently it has been classified as a superficial angiomyxoma [4,5] (see also Chapter 53). Clinically, it is characterized by a solitary, asymptomatic, flesh-coloured papule or nodule that can occur on the face, trunk or extremities. Histologically, there is localized accumulation of mucin in the dermis with an increased number of fibroblasts. The fibroblasts appear to function as mucoblasts with many large condensing vacuoles or secretory granules in their cytoplasm [2]. It is suggested

that cutaneous focal mucinosis arises as a result of a dysfunction of the fibroblasts in a localized area only. If treatment is required, local excision is satisfactory, since recurrence is unusual. The condition may show some overlap with other mucinoses, for example REM syndrome and scleromyxoedema [6].

Focal cutaneous mucinosis forms part of the Birt–Hogg–Dubé syndrome, where it is associated with multiple fibrofolliculomas and a predisposition to renal cancer [7].

Oral focal mucinosis of the tongue, causing a clinically elevated mass, is an uncommon clinicopathological entity which is considered to be the oral counterpart of cutaneous focal mucinosis [8].

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Acral persistent papular mucinosis

Acral persistent papular mucinosis has been proposed as a distinct form of cutaneous mucinosis [1–3]. The characteristic findings include discrete papules or annular lesions on the extensor surfaces of the hands and wrists, mucinous deposits within the dermis, persisting for several years, and usually an absence of systemic abnormalities. Familial occurrence has been reported in two sisters [4]. The accumulation of lysosomal structures in acral persistent papular mucinosis may be a distinctive feature of the disorder [5]. However, it is still debatable whether acral persistent papular mucinosis is a distinct entity [6] or whether it is a variant of the discrete papular form of lichen myxoedematosus [1]. A case resembling acral persistent papular mucinosis has been described in which transient carpal tunnel syndrome appeared, suggesting that extracutaneous involvement might occur [7].

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Mucinous naevus

The association of dermal mucinosis in association with a congenital plaque-like lesion in the interscapular area was first reported in a 16-year-old female [1]. In the absence of an overt connective tissue naevus and associated systemic disease, it was felt the lesion represented a congenital cutaneous mucinosis (mucinous naevus). Analysis of further cases suggests that these lesions may be a connective tissue naevus of proteoglycan type, and the only type to contain hyaluronic acid [2].

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Follicular mucinosis [1]

SYN. ALOPECIA MUCINOSA

Definition and nomenclature. Follicular mucinosis is an inflammatory disorder characterized clinically by infiltrated plaques with scaling and loss of hair, and histologically by the accumulation of acid glycosaminoglycans in the sebaceous gland and the outer root sheath of the hair follicles. The condition was first described by Pinkus in 1957 [2] under the name alopecia mucinosa, but alopecia is not always evident, especially when only vellus follicles are involved.

Aetiology [3–6]. The cause of follicular mucinosis is unknown, but cell-mediated immune mechanisms may play a role in its pathogenesis [7]. Follicular mucinosis may be subclassified into three groups. The first and largest group consists of patients with solitary or only a few lesions, clearing spontaneously in 2 months to 2 years. In a second group are patients in whom the lesions persist, or new lesions continue to develop over many years. In the third group (about 15% of cases [3]) the mucinosis is associated with a lymphoma [5,6]; in such cases, histological evidence of the lymphoma is present from the onset, but it may be overlooked until the sections are later re-examined with hindsight.

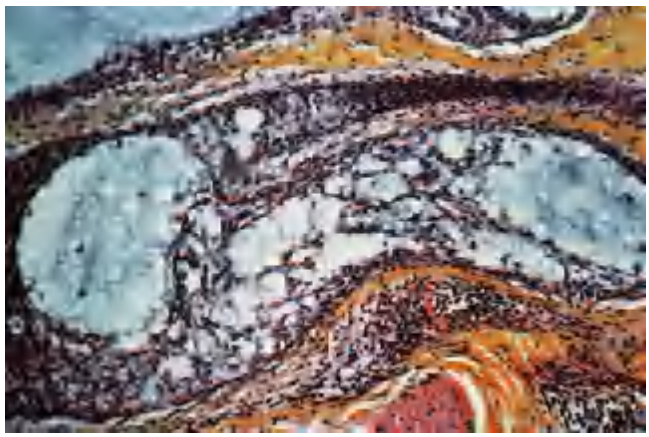

Fig. 57.17 Follicular mucinosis. Marked spongiosis and mucinous degeneration of outer root sheath of a follicle. Alcian blue, H&E, × 50. (Courtesy of St John's Institute of Dermatology, London, UK.)

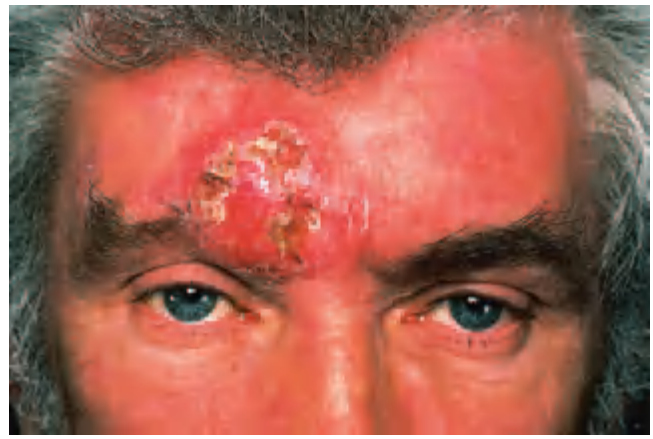

Fig. 57.18 Follicular mucinosis. 'Boggy' erythematous plaque on forehead. (Courtesy of St John's Institute of Dermatology, London, UK.)

Patients with lymphoma-associated follicular mucinosis tend to be older (age 20–70 years; average 45 years) than those with benign disease (age 2–75 years; peak between 20 and 40 years), but there is no absolute distinction in age incidence [3,8,9].

Some authorities regard follicular mucinosis as a non-specific follicular reaction [4], as similar changes have been observed in association with lupus erythematosus [10], angiolymphoid hyperplasia [11], Hodgkin's disease [12] and alopecia areata [13].

Pathology [3,4,14]. The earliest change appears to be oedema of the outer root sheath and sebaceous gland, with formation of cystic spaces in which mucin accumulates. The entire depth of the follicle may be involved, but the degree of damage to the hair matrix is variable. Later, the sebaceous glands may appear to be absent, or the whole follicle may be converted into a cystic cavity containing mucin and degenerate root-sheath cells (Fig. 57.17). Dermal inflammatory changes are variable, and may become granulomatous. Electron-microscopic studies [15,16] have shown changes in the keratinocytes of the follicular epithelium. Autoradiographic studies [17] have failed to show increased synthesis of glycosaminoglycans in affected follicles.

Histopathological findings may not allow clear-cut differentiation between idiopathic and lymphoma-associated follicular mucinosis [5]. In general, the presence of large numbers of eosinophils in the inflammatory infiltrate and marked mucinous changes in the follicular epithelium favour a benign form, whereas lymphocytic epidermotropism and a dense perifollicular infiltrate with atypical cells suggests an associated lymphoma. Similarly, monoclonal rearrangement of the T-cell receptor (TCR) gamma gene on polymerase chain reaction analysis does not reliably differentiate the benign and lymphoma-associated forms. In one study, TCR gene rearrangements were found in about 50% of tested cases from both idiopathic primary and lymphoma-associated groups of patients [5], whilst a study of patients with primary follicular mucinosis found no evidence of progression to cutaneous T-cell lymphoma despite the presence of a clonal TCR gene rearrangement [18]. When a lymphoma is demonstrated, this is usually of T-cell type [19–21], although B-cell lymphoma has been reported [22]. A follicular variant of mycosis fungoides is being increasingly recognized, although overt mucinous spongiosis is not necessarily present [6,23]. Syringolymphoid hyperplasia with alopecia and anhidrosis is a syringotropic variant of follicular mucinosis and should be viewed as a facultative precursor lesion of mycosis fungoides [24].

Clinical features [3,25]. In the acute benign form, the earliest changes are grouped, skin-coloured papules or erythematous plaques, with some scale, and with prominent follicles. Each plaque, commonly 2–5 cm in diameter but sometimes larger, changes little in appearance. Multiple lesions may be present from the onset or may develop within a period of a few weeks. The face, scalp, neck and shoulders are commonly affected. The hairs are shed from the affected follicles, so that alopecia may therefore be the presenting symptom when the scalp or eyebrow region is involved. Spontaneous recovery usually takes place within a few months, but may be delayed for a year or more.

In the chronic form, the lesions are often more numerous and more widely distributed and their morphology tends to be more variable. There may be elevated, flat or domed plaques or nodules, some of which may ulcerate. The plaques and nodules are often of soft, gelatinous consistency; sometimes mucin can be squeezed out of affected follicles (Fig. 57.18). Non-infiltrated, red, scaly plaques, patchy scaling, alopecia (Fig. 57.19) and indurated plaques

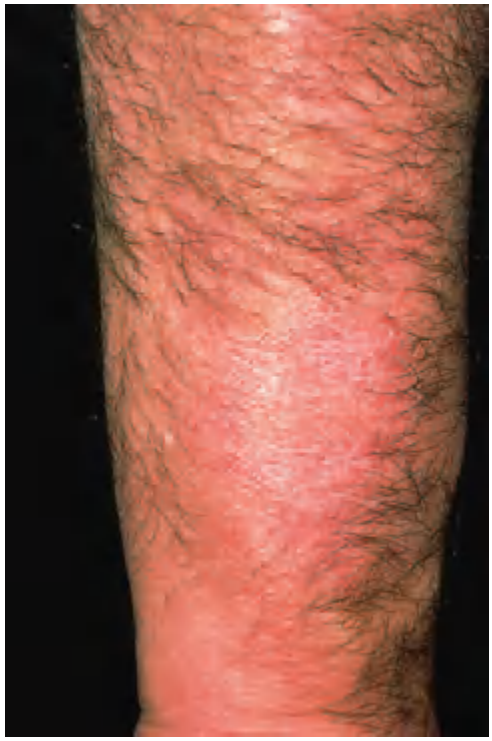

Fig. 57.19 Follicular mucinosis. Circumscribed patch of hair loss associated with erythematous plaque on forearm. (Courtesy of St John's Institute of Dermatology, UK.)

may all be present. In some cases, leprosy may be simulated [26]. Presentation with an unusual acneiform eruption has been recorded [27].

Rarely, follicular papules may be generalized without obvious grouping. Irritation may be troublesome and persistent. Destruction of follicles may give rise to patches of permanent alopecia, which may be studded with horny plugs. This chronic form may persist for many years without any evidence of associated disease. An unusual case associated with erythroderma and boggy plaques on the scalp and face, associated with alopecia and purulent paronychia and nail loss, has been described [28].

Unfortunately, no single clinical feature distinguishes lymphoma-associated cases from the chronic benign form. Extensive cystic changes have been recorded in the lymphoma-associated type [29]. Contrary to earlier opinion [3,7] lymphoma-associated follicular mucinosis has been reported where the lesions occurred on the head and neck [19,30]. The temporal relationship between lymphoma and follicular mucinosis is very variable. Gross manifestations of the lymphoma may have been present for some time before the mucinosis develops; in other cases, the first indication of the lymphoma is uncovered by histology.

Diagnosis. The loss of hair in plaques with prominent follicles but minimal inflammatory changes should suggest the diagnosis. Sometimes, mucin can be expressed from the follicle. Eczema, seborrhoeic dermatitis, lichen simplex, pityriasis rosea, traumatic alopecia and tinea capitis can all be closely simulated. Biopsy and serial sectioning of the tissue should confirm the diagnosis.

Treatment. There are no clear guidelines for treating follicular mucinosis. Some improve spontaneously, while treatment with topical and intralesional steroids has been claimed to be of benefit. Superficial radiotherapy may be beneficial in some of the lymphoma-associated cases [19,30], but some cases fail to respond [31]. A case of follicular mucinosis responding to dapsone has been reported [32]. Low dose systemic steroids may benefit widespread pruritic follicular mucinosis [28] and interferon therapy, with or without acitretin, has also proved successful [33,34].

Urticaria-like follicular mucinosis

Urticaria-like follicular mucinosis appears to be a variant of follicular mucinosis, largely confined to middle-aged men, in which urticarial pruritic papules or plaques appear on the head and neck on an erythematous 'seborrhoeic' background [35]. The lesions tend to fade but recur for months to years leaving neither follicular plugging or alopecia. Sun exposure may temporarily clear the eruption. The histopathological features are identical to follicular mucinosis but the prognosis is good with a long benign course.

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Secondary mucinoses [1]

The number of diseases in which dermal mucinosis may be associated to a greater or lesser extent with histopathological features otherwise typical of the disease in question continues to grow [1]. In some, the mucinous deposition may be so striking as to suggest the diagnosis, e.g. Degos' disease [2].

Collagen vascular diseases

Dermal mucinosis in lupus erythematosus and dermatomyositis has been linked in some patients to parvovirus B19 infection [3]. Marked periorbital oedema from massive mucinosis has been reported in a patient with discoid lupus erythematosus [4]. Infiltrated erythematous plaques on the back progressing to erythematous and elastic soft tumorous masses over 20 cm in diameter were recorded in a patient with systemic lupus erythematosus [5]. Dermatomyositis may present as plaque-like mucinosis [6,7]. Papular and nodular mucinosis has been recorded as a presenting sign of progressive systemic sclerosis [8], and development of multiple large soft skin lesions over the interphalangeal joints of both hands, resembling cutaneous focal mucinosis, has also been reported [9]. Lesions typical of papular mucinosis without evidence of paraproteinaemia occurred in a patient with generalized morphoea [10]. Dermal mucinosis has been associated with severe chronic cutaneous graft-vs-host disease of the sclerodermoid variety [11].

Hereditary progressive mucinous histiocytosis [12]

Hereditary progressive mucinous histiocytosis (MIM 142630) is a rare, probably autosomal dominant, disease in which small skin-coloured papules or nodules begin to appear anywhere in the first decade of life. In contrast to other benign histiocytic skin diseases there is no spontaneous resolution, so that a steadily increasing number of papules is noted. To date the disease has been confined to females. Histologically, the disease is associated with a progressive proliferation of histiocytes (non-X type) and dermal mucinosis but there is no evidence of any known lysosomal storage disease.

Papular mucinosis in L-tryptophan-induced eosinophilia–myalgia syndrome [13]

The L-tryptophan-related eosinophilia–myalgia syndrome, due to ingestion of contaminants of L-tryptophan, was first recognized in 1989 [4]. The skin lesions include a diffuse morbilliform eruption, urticaria and angio-oedema, dermographism, alopecia and cutaneous induration. Papular mucinosis may coexist for a while, although the lesions slowly regress after cessation of L-tryptophan ingestion [13]. There is associated weakness, fatigue, arthralgias and pneumonitis.

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Mucopolysaccharidoses [1,2]

The mucopolysaccharidoses (MPS) are a group of genetically determined lysosomal storage diseases that are associated with deficiencies of lysosomal enzymes required for the normal sequential degradation of glycosaminoglycans (formerly known as mucopolysaccharides; mainly dermatan sulphate, heparan sulphate and keratan sulphate). The accumulation of glycosaminoglycans in a wide variety of tissues results in a complex and progressive disease leading to death in the first or second decade in most patients [3]. Multiple different enzymes known to degrade glycosaminoglycans have been implicated, resulting in a number of clinical syndromes of variable severity, which may share certain clinical features. Apart from the characteristic facies, the hypertrichosis and some thickening of the skin, dermatological changes are not prominent.

All are inherited as autosomal recessive traits except for Hunter's syndrome, which is sex linked. Mucopolysaccharidosis type I (MPS I) is caused by a deficiency of the lysosomal enzyme α-L-iduronidase. MPS I covers a broad spectrum of clinical severity ranging from severe Hurler's syndrome characterized by skeletal abnormalities, hepatosplenomegaly and severe mental retardation, through intermediate Hurler–Scheie syndrome to mild Scheie's syndrome, where there is aortic valve disease, corneal clouding, limited skeletal problems, but no mental retardation. There is molecular heterogeneity in mutations in MPS I [4–6]. MPS II (Hunter's syndrome) is caused by deficiency of the enzyme iduronate-2-sulphatase [7]. MPS III (Sanfilippo's syndrome) is characterized by progressive nervous system involvement with mental retardation, behavioural problems and seizures, associated with deficiency in one of the four enzymes involved in the degradation of heparan sulphate [8–11]. Details of these enzymes, and the deficient enzymes and clinical features of the other MPS [12–15], are listed in Table 57.4 [1].

Clinical features. The main types are summarized in Table 57.4. In some syndromes, the emphasis is on mental retardation with little somatic change; in others, mental development may be normal but somatic changes predominate. Children are generally born normal, and the changes develop over the first 2 or 3 years. There may be an early phase of increased growth, followed by growth retardation. Mental retardation occurs progressively, with hyperactivity and loss of skills. There may be severe mental retardation later, with almost complete paralysis and marked contractures. Bony changes (dysostosis multiplex) are pronounced in some syndromes, including pectus carinatum, thoracic kyphoscoliosis and hip dysplasia [16]; joint changes also occur. The head is large, the facies characteristically coarse and the tongue large. Umbilical and inguinal hernias are frequent and the abdomen protuberant. Corneal clouding is found in some syndromes and may lead to loss of vision, and deafness may also occur. Cardiac involvement, with or without aortic valve lesions, is one of the commoner causes of death, which usually comes before the age of 20 years. Respiratory infections are also common. The simultaneous occurrence of glycosaminoglycan type II (Hunter's) disease and systemic lupus erythematosus has been reported [17].

Skin lesions. Luxuriant hair or generalized hypertrichosis are found in several of the syndromes, and may be one of the very earliest clinical signs. Ivory-white nodules or ridges may occupy symmetrical areas between the angles of the scapulae and posterior axillary lines [18–23]. Individual nodules range from 1 to 10 mm in size and are especially found in Hurler's and Hunter's diseases, but also in Hurler–Scheie syndrome [24]. In some cases, they have also been found on the upper arms, forearms, pectoral regions and outer thighs. Thickening of the digits may simulate acrosclerosis [25]. Telangiectases have been found in Morquio's syndrome. Cases of extensive mongolian spots in infants with Hurler's and with Hunter's syndromes have been reported [26,27].

Histology [28–30]. There may be distinctive changes even in the absence of any clinical skin abnormalities. The occasional Malpighian cell in the epidermis develops a pale distended cytoplasm, which may displace the nucleus to one side. Large, vacuolated cells (gargoyle cells) are prominent just below the epidermis and in sweat glands [12,31] and, to a lesser extent, in the external root sheaths of hair follicles. Fragmentation and hyalinization of collagen, and increased tissue mucin, have been demonstrated in biopsies of scleroderma-like skin. Pooling of metachromatic material between the collagen bundles of the lower reticular dermis is sometimes especially marked [21,28].

Ultrastructurally, the presence of membrane-limited cytoplasmic vacuoles containing fibrillogranular material in dermal connective tissue and Schwann's cells has been demonstrated in all varieties of the MPS syndrome [12,28,29,31].

Table 57.4 Classification of the mucopolysaccharidoses (MPS). (Data from Neufeld and Muenzer [1].)

Number (& MIM no.)	Eponym	Clinical manifestations	Enzyme deficiency	Glycosaminoglycan affected
MPS I H (*252800)	Hurler	Corneal clouding, dysostosis, multiplex, organomegaly, heart disease, mental retardation, death in childhood	α-L-iduronidase	Dermatan sulphate, heparan sulphate
MPS I S (*252800)	Scheie	Corneal clouding, stiff joints, normal intelligence and life span	α-L-iduronidase	Dermatan sulphate, heparan sulphate
MPS I H/S (*252800)	Hurler–Scheie	Phenotype intermediate between I H and I S	α-L-iduronidase	Dermatan sulphate, heparan sulphate
MPS II (*309900)	Hunter (severe)	Dysostosis multiplex, organomegaly, no corneal clouding, mental retardation, death before 15 years	Iduronate sulphatase	Dermatan sulphate, heparan sulphate
	Hunter (mild)	Normal intelligence, short stature, survival to 20s to 60s	Iduronate sulphatase	Dermatan sulphate, heparan sulphate
MPS III A (*252900)	Sanfilippo A	Profound mental deterioration, hyperactivity, relatively mild somatic manifestations	Sulphamidase	Heparan sulphate
MPS III B (*252920)	Sanfilippo B	Phenotype similar to III A	α-*N*-acetyl-glucosaminidase	Heparan sulphate
MPS III C (*252930)	Sanfilippo C	Phenotype similar to III	Acetyl-CoA: α-glucosaminide acetyl-transferase	Heparan sulphate
MPS III D (*252940)	Sanfilippo D	Phenotype similar to III A	*N*-acetyl-glucosamine 6-sulphatase	Heparan sulphate
MPS IV A (*253000)	Morquio A	Distinctive skeletal abnormalities, corneal clouding, odontoid hypoplasia; milder forms known to exist	Galactose 6-sulphatase 6-sulphate	Keratan sulphate, chondroitin
MPS IV B (#253010)	Morquio B	Spectrum of severity as in IV A	β-galactosidase	Keratan sulphate
MPS V	No longer used	—	—	—
MPS VI (*253200)	Maroteaux–Lamy	Dysostosis multiplex, corneal clouding, normal intelligence; survival to teens in severe form; milder forms known to exist	*N*-acetyl-galactosamine 4-sulphatase	Dermatan sulphate
MPS VII (*253220)	Sly	Dysostosis multiplex, hepatosplenomegaly; wide spectrum of severity	β-glucoronidase	Dermatan sulphate, heparan sulphate, chondroitin 4-, 6-sulphates
MPS VIII	No longer used	—	—	—

Diagnosis. The diagnosis is usually suspected clinically, but the onset may be insidious and can readily be missed at an early stage. It can be confirmed and the exact syndrome clarified by finding the abnormal glycosaminoglycan in the urine, although this is not always easy biochemically at an early stage. The enzyme defect may be demonstrable in fibroblasts, white blood cells or serum. X-rays of bones may be helpful. Prenatal diagnosis is available for several of the diseases.

Treatment. Symptomatic treatment for the many symptoms can be very valuable but there is no effective cure. Clinical studies of enzyme replacement therapy are currently underway for MPS I, II and VI [3,32,33]. Bone marrow transplants, with all their hazards, can stabilize and to some degree reverse the pathological features [34–36], and currently remain the only hope for a long-term remission. Gene therapy offers hope for the future; lentiviral vector may prove useful for the delivery and expression of the α-L-iduronidase gene to cells *in vivo* for treatment of MPS I [37].

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Mucolipidoses

The term mucolipidoses refers to a number of Hurler-like syndromes in which there is no accompanying mucopolysacchariduria but in which both polysaccharides and sphingomyelin and related lipids are stored. Dense cytoplasmic inclusions arise in cultured fibroblasts [1] and skin biopsy may reveal several types of lysosomal residual bodies, membrane-bound vacuoles, cytoplasmic bodies, and a diverse spectrum of lipopigments [2]. Mucolipidosis III (MIM *252600) has been reported in association with a large connective tissue naevus [3].

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Leroy's syndrome

This is a rare lipoglycosaminoglycan disorder showing skin thickening and bone changes. The X-ray appearances mimic Hurler's disease. No corneal opacities are seen and fibroblast cultures show nuclear inclusions [1].

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Amyloid and the amyloidoses of the skin

[S.M. Breathnach, pp. 57.36–57.51]

Amyloidosis is a generic term, originally coined by Rudolf Virchow in 1854, which denotes extracellular deposition of a proteinaceous substance composed of one of a family of biochemically unrelated proteins, depending on the underlying condition, and which is usually associated with considerable tissue dysfunction [1–6]. A classification based on the biochemical nature of amyloid fibril proteins is shown in Tables 57.5 and 57.6. Amyloidosis now tends to be classified on the basis of characterization of the fibril proteins rather than according to clinicopathological features [7]. Fibrils in primary and myeloma-associated systemic amyloidosis are composed of immunoglobulin protein AL, whereas in secondary systemic amyloidosis they are composed of a non-immunoglobulin protein termed protein AA.

Amyloid proteins, regardless of biochemical constitution, share certain characteristic physicochemical properties, tinctorial properties (Congophilia and green birefringence under polarized light) and a fibrillar ultrastructure. Paired, 7.5–10.0 nm, rigid, linear, non-branching, aggregated, hollow fibrils of indefinite length constitute the bulk of amyloid deposits, regardless of clinicopathological type or the tissue involved, and are arranged in a loose meshwork. Amyloid fibrils have been shown by X-ray diffraction crystallography and infrared spectroscopy to have, at least in part, a beta-pleated sheet configuration; this probably accounts for their ability to bind Congo red and for the low solubility and resistance to proteolytic digestion of amyloid.

Non-fibrillar amyloid proteins

All types of amyloid contain small amounts of a protein termed amyloid P component (AP) derived from and identical to serum amyloid P component (SAP), present in the blood of all normal individuals [1]. SAP prevents proteolysis of the amyloid fibrils of Alzheimer's disease, of AA amyloidosis and of AL amyloidosis, and may contribute to persistence of amyloid *in vivo* [8]. AP is constantly associated with the microfibrillar sheath of elastic fibres throughout the body in normal adults [9]. AP binds to isolated amyloid fibrils *in vitro* in a calcium-dependent manner, which may account for the frequent observation of amyloid deposition in the vicinity of elastic fibres [10]. Amyloid deposits also contain extracellular

Table 57.5 Biochemical nature of fibril proteins in systemic amyloidosis.

Clinical type of amyloidosis	Amyloid fibril protein	Precursor substance
Primary (immunocyte dyscrasia)	AL	Monoclonal immunoglobulin light chains
Myeloma-associated	AL	Monoclonal immunoglobulin light chains
Secondary (chronic active disease)	AA	Serum amyloid A protein (SAA)
Haemodialysis-associated (periarticular, bony and renal)	β_2-microglobulin	
Heredofamilial		
Predominantly nephropathic		
Familial Mediterranean fever	AA	SAA
Muckle–Wells syndrome	AA	SAA
Predominantly neuropathic		
Familial amyloid polyneuropathy	Transthyretin variant or Apoliprotein A1 or Gelsolin	
Non-neuropathic forms (Ostertag)	Apoliprotein A1 or Lysozyme or Fibrinogen α chain	
Predominantly cardiomyopathic	Transthyretin variant	
Cardiomyopathy with persistent atrial standstill	Unknown	
Senile systemic	Transthyretin from plasma	

Table 57.6 Biochemical nature of fibril proteins in organ-limited (localized) amyloidosis.

Nodular (skin, lung, genitourinary)	AL
Primary localized cutaneous	
Nodular	AL
Macular amyloid and lichen amyloidosus	?Altered keratin
Secondary localized cutaneous amyloidosis	?Altered keratin
Hereditary syndromes	
Hereditary cerebral haemorrhage with amyloidosis	
Icelandic type	Cystatin C
Dutch type	β-protein
Cerebral amyloid angiopathy and cortical plaques (Alzheimer's disease, senile dementia, Down's syndrome)	β-protein
Sporadic Creutzfeld–Jakob disease, kuru	Prion protein
Focal senile amyloidosis	
Heart atria	Atrial natriuretic peptide
Joints	Unknown
Seminal vesicles	Seminal vesicle exocrine protein
Prostate	β_2-microglobulin
Ocular deposits (corneal, conjunctival)	Unknown
Endocrine amyloidosis (APUD organs, APUDomas)	
Elderly non-insulin-dependent diabetics, benign insulinomas of the pancreas, normal aged pancreas	Islet amyloid polypeptide (homology with calcitonin gene-related peptide)
Medullary carcinoma of the thyroid	Precalcitonin-related

APUD, amine precursor uptake and decarboxylation.

matrix components, including glycosaminoglycans and proteoglycans, which may be involved in the pathogenesis [2,4,11].

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Staining reactions [1–3]

Special stains for amyloid include the triphenyl-methane dyes methyl and cresyl violet for the demonstration of metachromasia, the PAS method, the substantive cotton dyes Congo red and Sirius red with or without fluorescence [4] or polarized light microscopy (Fig. 57.20), and fluorescence with thiazole dyes such as thioflavine T (Fig. 57.21). Immunohistochemical staining with anti-SAP has also been advocated [5].

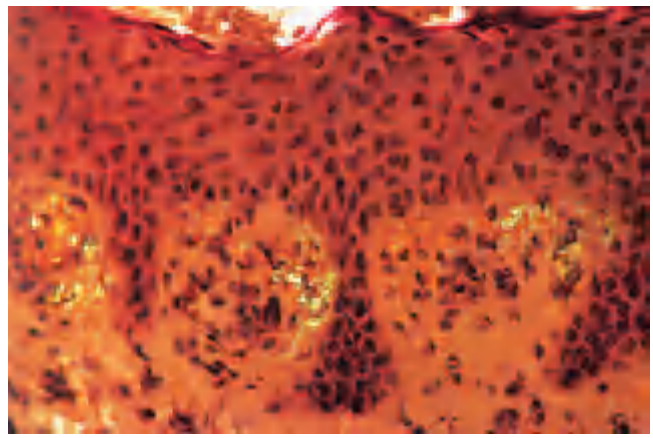

Fig. 57.20 Lichen amyloidosus. Alkaline Congo red, × 100. View under polarized light to show specific green fluorescence in amyloid deposits in papillary dermis.

The staining properties depend to some extent upon the duration of fixation in formalin and tend to be far brighter on frozen fixed material. Congophilia is the most specific. Unfortunately, methyl violet and Congo red staining may be equivocal and inadequate for detecting small deposits of amyloid; false positive results occur in colloid milium and lipoid proteinosis. False positive staining with thioflavine

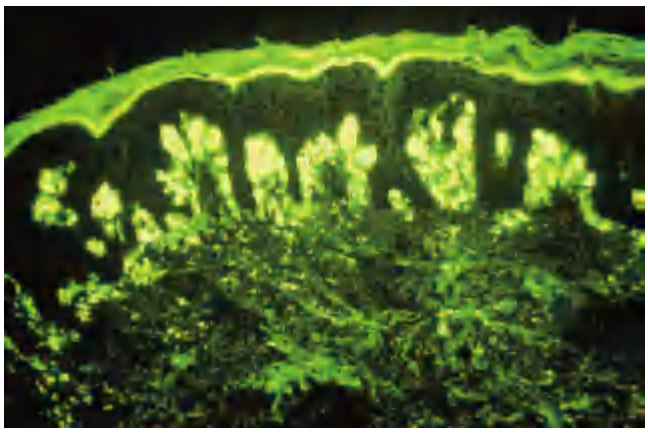

Fig. 57.21 Cutaneous amyloidosis. Thioflavine T, × 50. Viewed under fluorescence microscopy to show bright-yellow staining of amyloid deposits.

T is seen with stromal hyaline deposits, collagen fibres and colloid bodies in lichen planus: anti-SAP also stains colloid bodies and elastotic elastic fibres. Use of a battery of stains is therefore recommended. In some cases it may be necessary to resort to electron microscopy to look for the characteristic ultrastructure of the fibrils. *In vivo* scintigraphy techniques using ^{123}I-labelled human SAP component can be used to delineate amyloid deposits in systemic amyloidosis and to monitor the effects of therapy [6].

AL type amyloid, unlike AA type amyloid, retains its affinity for Congo red and its typical polarization characteristics after exposure to potassium permanganate [7]. Immunohistochemical staining with specific antisera [8,9], or either amino acid sequencing or mass spectroscopy of material extracted from fibrillar deposits (using sections of formalin-fixed, paraffin-embedded biopsy specimens) [10], are used to differentiate between the various types of fibril protein in amyloid deposits. Immunohistochemical staining with antikeratin antibody EAB-903 using formalin-fixed tissue appears to be a useful method in the differential diagnosis of primary localized cutaneous amyloidosis [11].

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Primary localized cutaneous amyloidosis

In primary localized cutaneous amyloidosis (PLCA) there is deposition of amyloid in previously apparently normal skin, with no evidence of deposits occurring in internal organs. Various subtypes of PLCA are recognized, including the more common macular and papular (lichen amyloidosus) types and the rare nodular (tumefactive) form. Both macular and papular lesions can occur in the same patient.

Aetiology. Nodular PLCA may be regarded as a form of extramedullary plasmacytoma, since the fibrils are of immunoglobulin AL type, and are thought to arise as a result of local aberrant light chain material production by clonally expanded plasma cells [1,2].

The aetiology of other forms of PLCA remains unknown. Lichen amyloidosus is commoner among the Chinese [3]. Macular amyloidosis is rare in Europe and North America, but is much more common in Central and South America, the Middle East and Asia, suggesting the importance of genetic factors [3–8]. The occurrence of rare familial cases reinforces this view [8–15]. Primary cutaneous amyloidosis has been described in identical twins who also had numerous congenital abnormalities [16]. A review of the current literature has revealed no instance of systemic deposition of amyloid.

Fibrils in lichen amyloidosus and macular amyloidosis do not bind antibodies to protein AA or prealbumin [17], and although immunoglobulins, κ and λ light chains, and complement are frequently observed in deposits of macular and papular PLCA [18], they are not thought to be integral constituents of the fibrils, since they are readily eluted. The close proximity of the amyloid deposits to the lower epidermis in macular amyloidosis and in lichen amyloidosus suggests that the epidermis plays a role in its pathogenesis [19,20]. It has been proposed that focal epidermal damage and filamentous degeneration of keratinocytes is followed by apoptosis and conversion of filamentous masses (colloid bodies) into amyloid material in the papillary dermis [21,22]. There may be a contribution from the dermal–epidermal junction [23]. In support of this

theory is the fact that dermal amyloid deposits in these forms of PLCA react immunohistochemically with anti-human keratin antibody [24,25]. It is not clear why colloid (keratin) bodies produced in other dermatoses such as lichen planus are not transformed into amyloid. It has been proposed that in lichen amyloidosus specific immunological tolerance to the presence of colloid bodies in the papillary dermis favours their transformation into amyloid by macrophages or fibroblasts, whereas in lichen planus a brisk inflammatory response ensures their removal [26].

PLCA is associated with chronic friction, perhaps causing epidermal damage, as in the so-called friction amyloidosis seen especially in the Japanese as a result of rubbing the skin vigorously with a nylon towel or brush, bath sponge, towel, plant sticks or leaves [27–30], and in nodular prurigo and lichen simplex chronicus [31]. The association of macular amyloidosis with notalgia paraesthetica strengthens the role of chronic pruritus [32,33]. In the dyschromic forms of primary cutaneous amyloidosis, hypersensitivity to UVB with a possible DNA-repair defect may be significant [34]. The association of maculopapular amyloidosis with chronic active Epstein–Barr viral infection has recently been reported [35]. The patient's skin improved after treatment with aciclovir and interferon-α, suggesting that the viral infection may have played a role in inciting the keratinocytes to produce amyloid.

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Pathology. In papular and macular forms of PLCA, the amyloid deposits are confined to the papillary dermis, and do not involve blood vessels or adnexal structures [1,2]. In macular amyloidosis, the deposits of amyloid are composed of small multifaceted amorphous globules, similar in size to the hyaline bodies found in lichen planus. They may be so sparse that more than one biopsy is necessary to confirm the diagnosis, and are easily missed without the use of special stains. The epidermis is usually of normal thickness but pigmentary incontinence with melanophages is a notable feature. In papular lichen amyloidosus, focal deposits of amyloid are often large enough to expand the dermal papillae and displace the elongated rete ridges laterally (Fig. 57.22). The overlying epidermis shows considerable irregular acanthosis and hyperkeratosis. The amyloid deposits are in close apposition to the

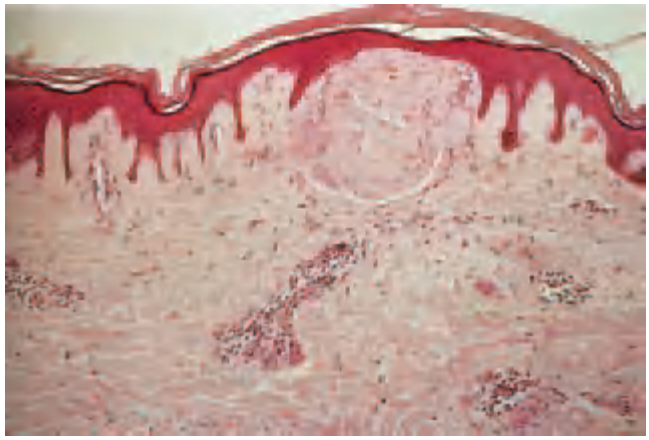

Fig. 57.22 Lichen amyloidosis. H&E, × 4. Amorphous globular hyaline amyloid deposition widening the rete ridges.

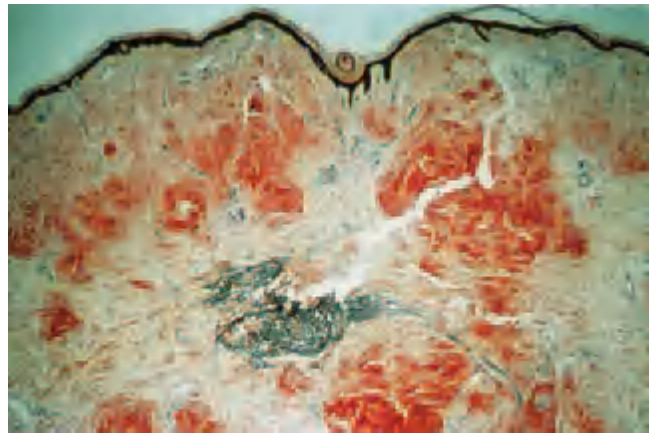

Fig. 57.23 Nodular or tumefactive cutaneous amyloidosis. Congo red, × 4. Amorphous masses of amyloid are present in the entire dermis with focal collections of plasma cells.

basal layer of the epidermis and contain a few melanophages. Near the amyloid deposits, there is usually a sparse lymphohistiocytic perivascular infiltrate.

By contrast, in the nodular or tumefactive forms of PLCA the dermis, subcutis and blood vessel walls are diffusely infiltrated with amyloid as seen in primary systemic amyloidosis (Fig. 57.23). However, there is usually a perivascular infiltrate of plasma cells [3–5].

Table 57.7 Clinical classification of primary localized amyloidosis.

Papular or lichen amyloidosus
Macular amyloidosus
Maculopapular amyloidosis
Nodular or tumefactive
Familial (dyschromic)

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Clinical features [1–5]. Several distinctive clinical forms of PLCA have been described (Table 57.7). Because macular amyloid and lichen amyloidosus may coexist in an affected individual (biphasic amyloidosis), they are regarded as variants of a single pathological process [6].

The papular form (lichen amyloidosus) is perhaps the best known. It usually presents as a pruritic eruption of multiple discrete hyperkeratotic papules, scaly and often hyperpigmented, distributed principally on the shins (Figs 57.24 & 57.25). The calves, ankles, dorsa of the feet and thighs, and the extensor aspects of the arms and abdominal or chest wall, may also be involved. Papules may coalesce to form thickened plaques, closely simulating hypertrophic lichen planus or lichen simplex chronicus. The condition usually persists for many years with localized pruritus as the prominent symptom.

The predominant sign in macular amyloidosis is clusters of small, pigmented macules, about 2 or 3 mm in diameter, which may coalesce to produce macular hyperpigmented areas. A reticulate or 'rippled' pattern of pigmentation is a characteristic diagnostic feature in many cases (Figs 57.26 & 57.27). The lesions tend to be associated with mild to moderate pruritus, but pruritus may be absent in 18% of cases. The lesions may be confined to the interscapular area (Fig. 57.26), but more commonly are extensively distributed over the back or chest [7,8]. Macular amyloidosis on the back has been reported to follow prolonged chronic friction (see above). Lesions may also occur on the extensor aspect of extremities, and occasionally on the chest and buttocks. Hypopigmented areas may produce a 'poikilodermatous' appearance. The condition usually presents in early adult life and persists for many years; both sexes are equally affected. Macular amyloidosis can be misdiagnosed as post-inflammatory pigmentation, resolving lichen planus or neurodermatitis, or as the reticulate hyperpigmentation of the neck ('dirty neck') that has been described in association with atopic eczema [9–11]. Amyloid-like material has been demonstrated by electron microscopy, but not at light microscope level, in the atopic dirty neck [12].

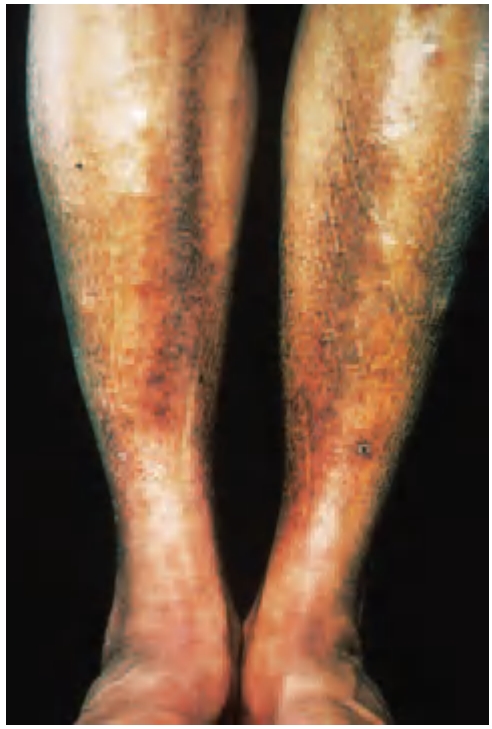

Fig. 57.24 Lichen amyloidosus (papular form). Typical appearance of pigmented pruritic papular eruption on shin in an Asian male. (Courtesy of St John's Institute of Dermatology, UK.)

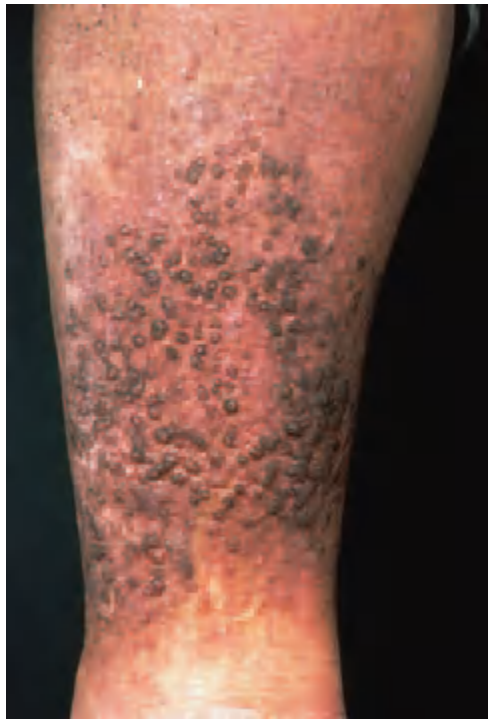

Fig. 57.25 Lichen amyloidosus (papular form). Close-up of small hyperkeratotic papules on shin. (Courtesy of St John's Institute of Dermatology, London, UK.)

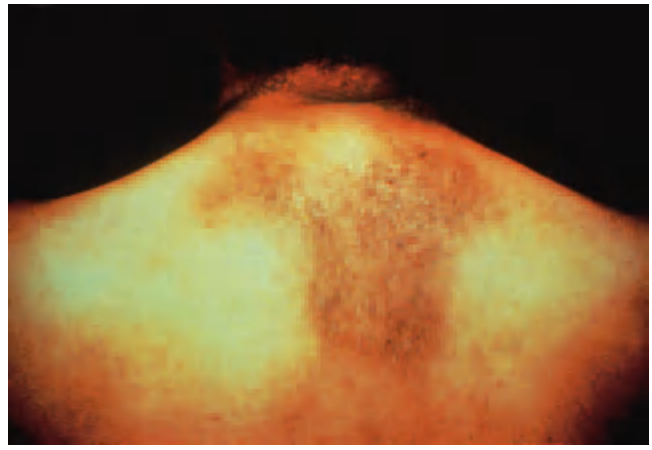

Fig. 57.26 Macular amyloidosis. Confluent pigmentation in an interscapular area in an Asian male. (Courtesy of St John's Institute of Dermatology, London, UK.)

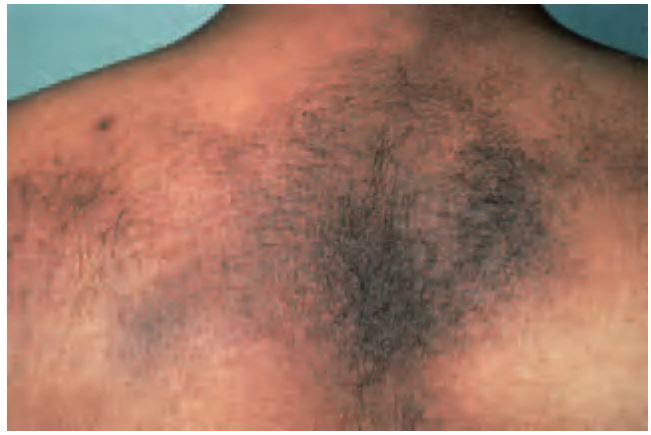

Fig. 57.27 Macular amyloidosis. Close up to show characteristic reticular or 'rippled' pigmentation over deltoid region. (Courtesy of St John's Institute of Dermatology, London, UK.)

Unusual variants of PLCA include: macular forms with widespread diffuse hyperpigmentation without papules but with poikiloderma-like facial involvement [13]; causing periocular hyperpigmentation [14]; simulating naevoid hyperpigmentation [15]; following Blaschko's lines [16]; resembling incontinentia pigmenti [17]; and a poikiloderma-like form [18,19]. Amyloidosis cutis dyschromica is assumed to be a congenital disorder with hypersensitivity to UVB radiation, with possible DNA repair defects; hyperpigmented and hypopigmented xerotic lesions with deposits of amyloid in the papillary dermis occur in sun-exposed skin [20]. Primary cutaneous amyloidosis of the auricular concha, in which small papules are grouped on the concha of the ear, is also believed to be a variant of PLCA, and may coexist with lichen amyloidosus [21,22].

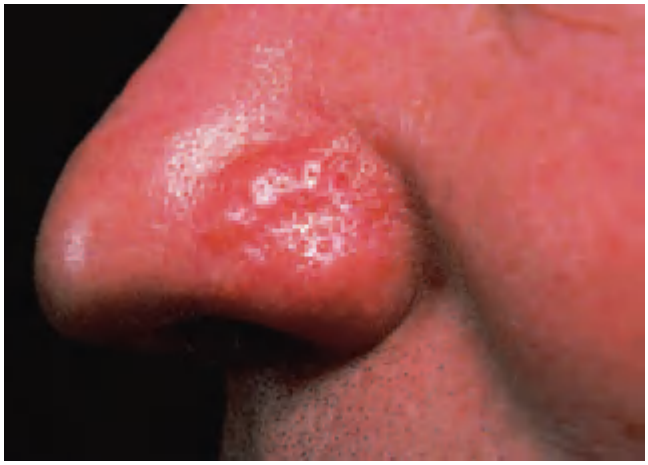

Fig. 57.28 Nodular or tumefactive cutaneous amyloidosis. Close up of tumour on side of nose. (Courtesy of St John's Institute of Dermatology, London, UK.)

Associations of PLCA in a few kindreds with pachyonychia congenita [23], dyskeratosis congenita [24], familial palmar–plantar keratoderma [25] and multiple endocrine neoplasia type 2a have been described; in the latter, lichen amyloidosus is confined to the interscapular region [26,27]. Cases of PLCA have also been described in association with a variety of connective tissue disorders: systemic lupus erythematosus [28], systemic sclerosis [29], dermatomyositis [30], primary biliary cirrhosis and scleroderma [3,31], and Raynaud's phenomenon with livedo reticularis [32].

Anosacral cutaneous amyloidosis is a rare syndrome described in Japanese and Chinese males, in which pigmented macules and glossy hyperkeratotic lesions radiate out from the anus [33]. Fifty per cent of patients present below the age of 60 years, and the disease may be misdiagnosed as lichen simplex chronicus, post-inflammatory hyperpigmentation or tinea cruris.

The nodular or tumefactive form is a rare variant of PLCA (Fig. 57.28). Most reported patients have been females. Single or more commonly multiple nodules or plaques, indistinguishable from those associated with plasma cell dyscrasia-related systemic amyloidosis, may occur on the face, trunk, limbs or genitalia [1,3,5,34–41]. They vary in size from a few millimeters to several centimetres. The overlying skin is often atrophic, and there may be petechial haemorrhages within the nodules. The condition may follow a prolonged benign course over many years [38]; however, some patients later develop paraproteinaemia and overt systemic amyloidosis [1,3]. Some cases are associated with diabetes mellitus and Sjögren's syndrome [37]. Rare familial cases of nodular cutaneous amyloidosis have been reported [42].

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Treatment. In general, the treatment of PLCA is disappointing. Milder cases can be helped by using potent topical corticosteroids with or without occlusive dressings, but usually in the short term only. Calcipotriol or phototherapy are similarly of limited use [1,2]. There have been reports of response to topical DMSO therapy in some [3–7] but not all [8] cases. Etretinate or acitretin therapy has been beneficial in a proportion of [9–12] but not all [13] patients; the condition soon relapses after the etretinate is stopped [14]. A trial of long-term cyclophosphamide 50 mg daily in lichen amyloidosus found that itching was markedly decreased within 4 months [15]. Ciclosporin given to treat atopic eczema coincidentally improved lichen amyloidosus [16]. Dermabrasion may have a long-term beneficial effect on papular lichen amyloidosus of the shins [17].

Nodular PLCA shows a good response to shave removal [18], curettage and cautery [19], cryotherapy, dermabrasion [20] or the carbon dioxide or pulsed dye laser [21–23], but subsequent recurrence is likely.

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Secondary localized cutaneous amyloidosis [1–3]

Microscopic deposits of amyloid material have been described in association with a variety of cutaneous tumours, including intradermal melanocytic naevus [4], sweat gland tumours, pilomatrixoma, dermatofibroma, seborrhoeic wart, photosensitive annular elastolytic giant cell granuloma [5], solar keratosis, porokeratosis of Mibelli [6,7], Bowen's disease [8,9], basal cell carcinoma [10,11] and trichoepithelioma [12,13]. The amount of amyloid material in tumours is usually clinically insignificant but massive deposits may occur and cause diagnostic difficulty [14]. A similar phenomenon has been noted following PUVA therapy [15,16].

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Systemic amyloidosis

Systemic types of amyloidosis include those associated with plasma cell dyscrasia, either overt as in multiple myeloma, or occult as in 'primary' systemic amyloidosis, amyloidosis secondary to a variety of chronic diseases, and in the heredofamilial amyloidoses. Clinically evident involvement of the skin is frequent in 'primary' systemic and myeloma-associated systemic amyloidosis, but occurs only rarely, if at all, in secondary systemic amyloidosis. Although there is a degree of overlap, primary and myeloma-associated systemic amyloidosis typically involve the tongue, heart, gastrointestinal tract, skeletal and smooth muscle, carpal ligaments, nerves and skin, whereas secondary systemic amyloidosis affects the liver, spleen, kidneys and adrenals [1]. Skin manifestations are associated with a number of systemic heredofamilial syndromes of amyloid deposition including familial Mediterranean fever [2], the Muckle–Wells syndrome [3] and heredofamilial amyloid polyneuropathy [4].

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Primary and myeloma-associated cutaneous amyloidosis

Aetiology. In primary and myeloma-associated amyloidosis, the fibrils are composed of 'protein AL' (amyloid L-chain protein) and appear to be a consequence of plasma cell dyscrasia, although bone marrow aspiration may not reveal any abnormality. Amino acid sequence analysis has demonstrated that protein AL consists of fragments of immunoglobulin polypeptide light chain, particularly the variable (amino-terminal) region, or of an intact immunoglobulin light chain, or of both [1–4], and is usually associated with a similar abnormal immunoglobulin light chain in the serum, commonly of λ class. Abnormal light chain material is almost always present in the serum or urine, even in so-called primary systemic amyloidosis, and can be demonstrated on tissue culture of bone marrow cells from affected patients. Only a proportion of Bence-Jones proteins produce amyloid fibrils on digestion [5], which may account for the fact that amyloidosis develops in only about 15% of patients with myelomatosis. Amyloidogenic immunoglobulin AL monoclonal proteins appear to be preferentially of λ type, of lower molecular weight, and of lower isoelectric point [6]. Domains may be destabilized by specific amino acid residue changes due to point mutation, rendering them susceptible to the formation of ordered, fibril-like aggregates *in vitro* [7]. The organ tropism (i.e. whether there is predominant renal, cardiac or hepatic involvement) in AL amyloidosis may reflect germ-line gene use and plasma cell burden [8].

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Histopathology [1–5]. In primary and myeloma-associated amyloidosis, deposits of amyloid are usually superficially placed in the papillary dermis as amorphous, faintly eosinophilic, often fissured masses, with associated thinning or obliteration of the rete ridges, accounting for the papules seen clinically. Amyloid deposits in the deep

reticular dermis and subcutis give rise to the clinical appearance of nodules and tumefactions, and infiltration of blood vessel walls correlates with the clinical finding of purpura. Marked thickening of blood vessel walls due to amyloid infiltration has been described [6]. Usually, there is little in the way of any inflammatory infiltrate, unlike nodular PLCA in which infiltration of plasma cells is a significant feature [3,4]. In areas of alopecia, amyloid deposits may surround and compress pilosebaceous units with resultant atrophy and loss of hair from the shafts. Amyloid may also be deposited in arrector pili muscles, the lamina propria of sweat glands and ducts, and around individual fat cells in the subcutis as characteristic 'amyloid rings'. Amyloid deposition in the nail fold and bed of dystrophic nails has been reported [7]. An affinity for amyloid to coat elastic fibres has been noted [8].

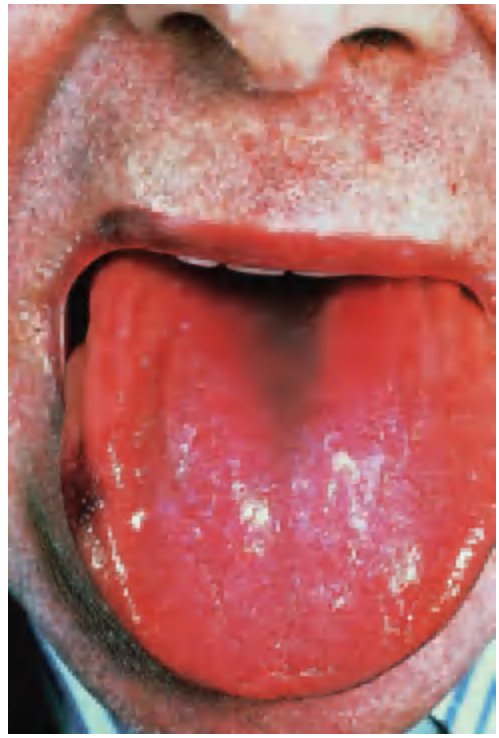

Fig. 57.29 Primary systemic amyloidosis. Macroglossia. (Courtesy of St John's Institute of Dermatology, London, UK.)

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Clinical features [1–8]. The mean age of onset of primary amyloidosis is about 65 years, and there is a slight male preponderance. Presenting symptoms may be rather nonspecific, and include fatigue, weight loss, paresthesiae, hoarseness, oedema, dyspnoea, and syncope secondary to orthostatic hypotension. These features may predate the histological diagnosis by up to 2 years. The classical presentation with symptoms of carpal tunnel syndrome, macroglossia, specific mucocutaneous lesions which occur in up to 40% of cases, hepatomegaly and oedema should always alert the clinician to the presence of an underlying plasma cell dyscrasia.

Amyloidosis is the commonest cause of macroglossia in adults [9], and occurs in about 10% of cases. The tongue is usually diffusely enlarged and firm (Fig. 57.29), but it may also be fissured, with haemorrhagic papules, nodules, plaques or even bullae on its surface. There may be permanent tooth indentations along its lateral borders. Macroglossia may be so extensive as to cause dysphagia.

The commonest skin lesions are those related to intracutaneous haemorrhage due to infiltration of blood vessel walls by amyloid deposits (Table 57.8). Petechiae, purpura and ecchymoses may occur spontaneously or after minor trauma on normal or clinically involved skin, especially in the body folds, for example eyelids, sides of neck, axillae, umbilicus, oral and anogenital regions. Purpuric

Table 57.8 Cutaneous lesions in primary and myeloma-associated systemic amyloidosis.

Common	Less common
Petechiae, purpura, ecchymoses	Pigmentary changes
Waxy, translucent or purpuric papules	Scleroderma-like infiltration
Nodules	Bullous lesions
Plaques	Alopecia
Tumefactive lesions	Cord-like blood vessel thickening
	Nail dystrophy
	Cutis laxa; localized redundant skin folds and depressions

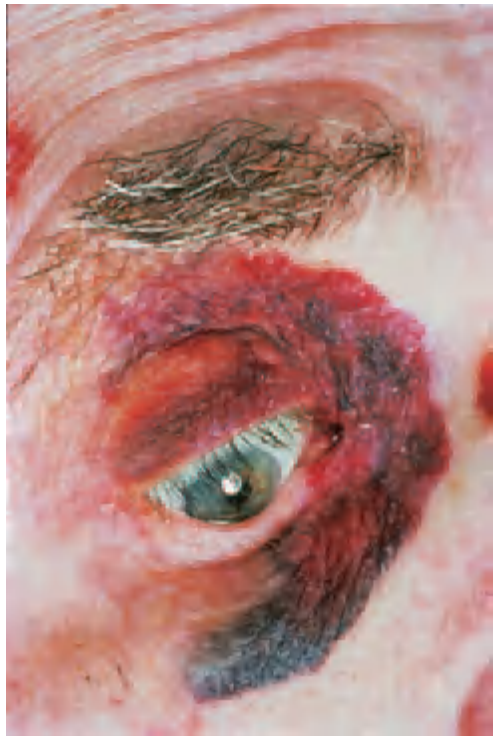

Fig. 57.30 Primary systemic amyloidosis. Prominent eyelid purpura following coughing. (Courtesy of St John's Institute of Dermatology, London, UK.)

haloes may occur around long-standing Campbell de Morgan spots [10]. Eyelid purpura after pinching, and periorbital purpura after proctoscopy ('post-proctoscopic palpebral purpura'), coughing (Fig. 57.30), vomiting or the Valsalva manoeuvre, are characteristic. Pigmentary changes include jaundice due to hepatic disease, cardiac failure or severe haemorrhage, pallor due to anaemia and hyperpigmentation due to haemorrhage.

Smooth, shiny, waxy papules or plaques, often with a haemorrhagic component, may also be found (Fig. 57.31). Translucent areas may resemble vesicles. Flexural areas are sites of predilection, including the eyelids, retroauricular region, neck, axillae, umbilicus, inguinal and anogenital regions. Lesions may also be found on the central face, lips, tongue and buccal mucosa. Widespread nodules may occur, coalescing to form large tumefactions. They may resemble condylomata lata on perianal and vulval skin [11,12], and when widespread may appear like xanthomas [13]. Diffuse infiltration of large areas, especially on the face, hands and feet, may simulate scleroderma [14,15], or on the face produce a myxoedema-like appearance. Alopecia may be patchy or widespread [16], and the scalp skin may be thrown into longitudinal folds resembling cutis verticis gyrata. Nail involvement due to infiltration of the nail matrix by amyloid may produce longitudinal striation (Fig. 57.32), crumbling, brittleness and partial anonychia, and may be a presenting sign [17–19]. Chronic paronychia with palmodigital erythema has also been described [20]. Signs which occur rarely include bullae of the skin or mucous membranes as a result of shearing within dermal amyloid deposits, resulting in changes resembling porphyria cutanea tarda or epidermolysis bullosa acquisita (Fig. 57.33) [21–25]. Extensive amyloid infiltration may lead to cord-like thickening of superficial blood vessels [26]. Amyloid elastosis is an unusual, recently recognized, syndrome in which papulo-

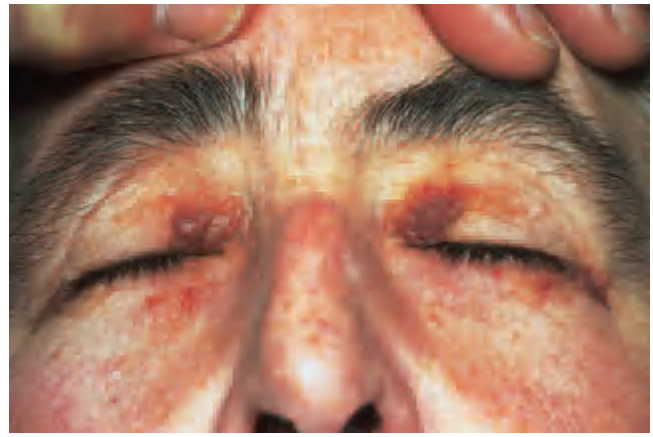

Fig. 57.31 Primary systemic amyloidosis. Purpuric plaques situated on upper eyelids. (Courtesy of St John's Institute of Dermatology, London, UK.)

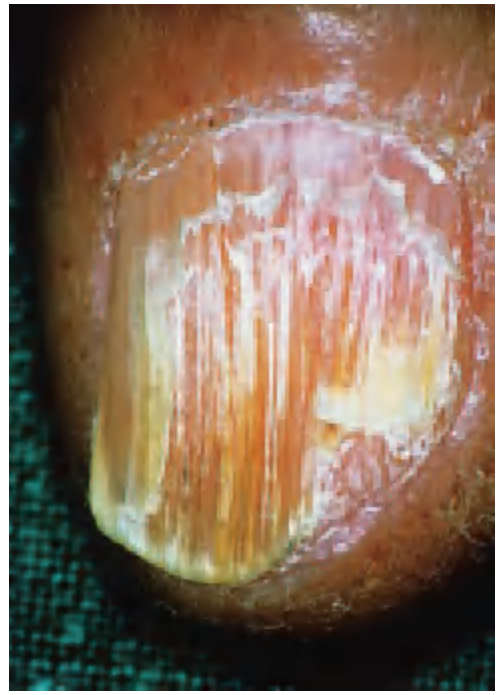

Fig. 57.32 Primary systemic amyloidosis. Close up of thumbnail showing longitudinal ridging and splitting. A nail biopsy in this case confirmed amyloid deposition. (Courtesy of St John's Institute of Dermatology, London, UK.)

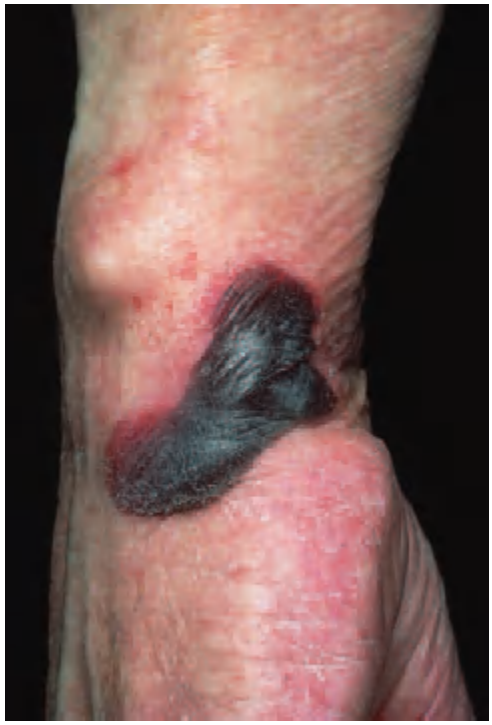

Fig. 57.33 Primary systemic amyloidosis. Haemorrhagic bulla on side of wrist. (Courtesy of St John's Institute of Dermatology, London, UK.)

nodular cutaneous lesions are associated with widespread amyloid infiltration of visceral and cutaneous blood vessels, particularly in relation to elastic fibres [27,28]. Acquired cutis laxa has also been reported [29,30]. Localized elastolytic cutaneous lesions may present as soft, loose folds or indentations on the fingertips [31]. Other cases of cutis laxa may reveal fibrillar extracellular deposits, which are different from amyloid fibrils [32].

Hepatomegaly occurs in about 50%, and splenomegaly in about 10% of patients. The nephrotic syndrome or congestive cardiac failure (both of which occur in about 30% of cases), and rarely protein-losing enteropathy from amyloid involvement of the small bowel, may cause pitting oedema. Ascites may develop. Cardiac infiltration results in angina, infarction, congestive cardiac failure, orthostatic hypotension or arrhythmias [33]; it accounts for death in about 40% of cases of AL type systemic amyloidosis. Pulmonary involvement is common but usually asymptomatic. Amyloid infiltration of blood vessels may lead to claudication of the legs or jaw. Gastrointestinal tract involvement may simulate inflammatory bowel disease with haemorrhage; malabsorption is found in 5% of cases. The carpal tunnel syndrome [34] has been reported in up to 25% of patients with 'primary' systemic amyloidosis. Peripheral neuropathy [35], initially of the lower extremities, tends to pursue a chronic course; there may be superimposed autonomic neuropathy leading to orthostatic hypotension, diarrhoea, loss of bladder control or impotence. Muscle weakness may be caused by neuropathy, or by amyloid infiltration of muscle or its vascular supply; infiltration between muscle fibres leading to pseudohypertrophy is reported. Lymphadenopathy occurs in about 10% of patients [36]. Sjögren's syndrome or sicca syndrome due to amyloid infiltration of lacrimal and parotid glands [37] are occasional presenting features. Amyloid deposition in joints may mimic rheumatoid arthritis, and deposition around the shoulders may cause extensive soft-tissue enlargement (the shoulder-pad sign) [38]. Giant cell arteritis and polymalgia rheumatica are recorded [39], as are isolated factor X deficiency [40], disseminated intravascular coagulation and fibrinolysis with severe bleeding.

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Diagnosis. The diagnosis should always be considered when a patient presents with the triad of carpal tunnel syndrome, macroglossia and mucocutaneous skin lesions [1,2]. Biopsy of classical mucocutaneous lesions should be the procedure of first choice. Biopsy of even clinically normal forearm skin has been reported positive in up to 50% of cases of primary and myeloma-associated disease. Fine-needle biopsies of the subcutaneous fat from clinically normal abdominal skin have a high positive yield in AL- and AA-type amyloidosis as well as in heredofamilial amyloidoses [3–5]. Rectal biopsy is positive in up to 80% of cases of AL or AA amyloidosis, jejunal biopsy in about two thirds, but gingival biopsy in only 19%. Gastric biopsy may produce a higher yield than rectal biopsy. Ninety-six per cent of hepatic, and 90% of renal and of splenic percutaneous needle biopsies, as well as carpal tunnel tissue biopsies at the time of decompression, are positive. Bone marrow aspiration may be positive in up to 45% of cases. Electrocardiography, echocardiography, angiocardiography, technetium scanning and endomyocardial biopsy are useful in the diagnosis of amyloid heart disease [6,7]. Computed tomography, ultrasound examination, and Doppler analysis of blood flow may be useful in renal amyloidosis. Sural nerve biopsy in patients with peripheral neuropathy [8], and synovial fluid analysis in patients with arthropathy, may be helpful. Scanning with ^{123}I-labelled SAP component enables specific localization and imaging of amyloid deposits *in vivo* [9,10].

Immunoelectrophoresis of both serum and concentrated urine is essential if the clinical presentation suggests the presence of a plasma cell dyscrasia, as conventional urine heat tests and simple electrophoresis of serum and urine may not detect small amounts of paraprotein or Bence-Jones protein. Protein electrophoresis of serum shows a spike pattern in just under half of patients with primary AL, and in about two thirds of those with myeloma. Immunoelectrophoresis of serum reveals a monoclonal protein in two thirds of patients with AL amyloidosis; only 45% have a monoclonal heavy chain, while 20% have free monoclonal light chains (Bence-Jones proteinemia). Immunoelectrophoresis of concentrated urine reveals a monoclonal light chain in about two thirds of cases (λ to κ ratio 2 : 1). When screening of both serum and urine is performed, the frequency of patients with an identifiable monoclonal protein rises to about 86%. A combination of immunofixation on agarose gel electrophoresis and bone marrow plasma cell light chain κ to λ ratio analysis improves diagnostic sensitivity [11]. Nevertheless, in some cases with the clinical features of AL amyloidosis it is not possible to demonstrate a paraprotein, even after prolonged follow-up for as long as 24 years [12].

Skeletal survey may be useful, as 50% of patients with myeloma-associated amyloidosis have radiological abnormalities, compared with only 6% of those with primary amyloidosis. Most myeloma cases, but no primary systemic amyloidosis cases, have more than 15% plasma cells in the marrow. In general, myeloma is not present if a patient has no lytic bone lesions, hypercalcaemia or anaemia, has only a small serum or urine monoclonal component, and has less than 25% bone marrow plasma cells.

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Prognosis. Prognosis in primary systemic and myeloma-associated amyloidosis is poor, the major causes of death being cardiac and renal failure, and is linked to degree of plasma cell clonality and marrow infiltration [1]. The median survival of patients with myeloma-associated amyloidosis is only 5 months. The median survival of 859 patients with primary systemic amyloidosis seen at the Mayo Clinic from 1982 to 1992 was 2.1 years [2]; actuarial survival for 810 patients seen from 1966 to 1987 was 51% at 1 year, 16% at 5 years and 4.7% at 10 years [3]. Prognosis also depends on response to therapy and the extent of disease: the median survival of patients with primary amyloidosis with response to chemotherapy was 18–29 months, compared to 8.5 months in those receiving colchicine alone [4,5]. Cardiac involvement indicates a very poor prognosis, with a median survival of 1.08 years from diagnosis and 9 months from onset of heart failure [6–8]; cardiac transplantation improves survival to 60% at 2 years and 30% at 5 years [7,8]. Occasional patients surviving longer than 10 years have been recorded [3,9–11]. Patients presenting with amyloid neuropathy without associated cardiac, renal or hepatic involvement have a significantly better prognosis (median survival 40–50 months; 5 years survival 31.6%) [12]. Survival for more than 10 years has been recorded in a patient with primary systemic amyloidosis with sensorimotor polyneuropathy only [13].

Treatment. Most patients receive a trial of chemotherapy, most often using melphalan, prednisone and/or colchicine, with or without autologous bone marrow transplantation [14–19]. There is a relatively high risk of development of leukaemia or a dysmyelopoietic syndrome [20]. Cardiac [6–8] or renal transplantation can prolong survival; renal amyloidosis is not an absolute contraindication to transplantation, although amyloid may re-accumulate in the transplanted kidney. A recently developed competitive inhibitor of SAP binding to amyloid fibrils, *R*-1-[6-[*R*-2-carboxy-pyrrolidin-1-yl]-6-oxo-hexanoyl]pyrrolidine-2-carboxylic acid, also cross-links and dimerizes SAP molecules, leading to their very rapid clearance by the liver and marked depletion of circulating human SAP. This mechanism of drug action potently removes SAP from human amyloid deposits in the tissues and may provide a new therapeutic approach to both systemic amyloidosis and diseases associated with local amyloid [21].

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Secondary systemic amyloidosis

In secondary systemic amyloidosis, the fibrils are composed of a non-immunoglobulin protein designated protein AA [1,2]. A precursor of protein AA, known as serum

amyloid A protein (protein SAA), is present in the serum of normal individuals as an apolipoprotein of high-density lipoprotein, and behaves as an acute phase reactant.

Secondary amyloidosis occurs as a complication of many chronic inflammatory diseases in which the immune system is stimulated [3,4]. These include acute recurrent and chronic infections, rheumatoid arthritis [5], juvenile chronic arthritis, ankylosing spondylitis [6], Reiter's syndrome, Behçet's syndrome, Sjögren's syndrome, dermatomyositis, scleroderma, systemic lupus erythematosus (very rarely) [7], inflammatory bowel disease [8], Hodgkin's disease and some solid non-lymphoid tumours, as well as Castleman's disease [9] and Rosai–Dorfman disease [10]. Secondary systemic amyloidosis may also arise as a complication of a number of dermatoses [11], such as venous ulceration [12], generalized psoriasis and psoriatic arthritis [13–15], pustular psoriasis [16], lepromatous leprosy [17], hidradenitis suppurativa, chronically infected burns, chronic skin infection in drug addicts [18,19], nodular non-suppurative panniculitis [20], giant, ulcerated or metastatic basal cell carcinoma [21], acne conglobata [22], epidermolysis bullosa of dystrophic [23–25] and aquisita types, and X-linked anhidrotic ectodermal dysplasia.

Secondary systemic amyloidosis rarely produces specific skin lesions, but commonly involves the kidneys (causing the nephrotic syndrome), spleen, alimentary tract and adrenals; the diagnosis should be confirmed by rectal or renal biopsy. Needle aspirates of abdominal wall subcutis may yield positive histological identification of amyloid [26]. Small or minute amyloid deposits are most often found around the adnexae, sometimes in small blood vessels and in the subcutis around fat cells: 'amyloid rings'.

There is no specific treatment, and many die from progressive renal failure. Treatment of the primary disease may arrest progression of the amyloidosis; estimated survival at 10 years was 90% in patients whose median protein SAA level was under 10 mg/L, and only 40% among those whose median SAA level exceeded this in one study [27]. Renal disease has responded to colchicine therapy or cyclophosphamide [5,28]. Renal transplantation is certainly worthy of consideration.

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Dialysis-related amyloidosis

In systemic amyloidosis related to haemodialysis, the major constituent protein of amyloid firbrils is β_2-microglobulin. Most of the clinical findings are related to amyloid deposition in osseo-articular tissues [1,2]. Extensive tissue deposition of β_2-microglobulin may rarely present as masses in the buttocks [3], or as lichenoid lesions [4].

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Inherited systemic amyloidosis

Several distinct genetic types of amyloidosis are recognized, which may be associated with mutations in a number of plasma proteins including transthyretin (MIM *176300), apolipoprotein AI (MIM *107680), fibrinogen A α chain (MIM *134820), lysozyme (MIM *153450), gelsolin (MIM *137350) and the 55-kDa tumour necrosis factor (TNF) receptor [1–3]. The kidney, peripheral nerves and spinal ganglia, or the heart are predominantly affected. Skin manifestations are associated with a number of systemic heredofamilial syndromes of amyloid deposition, including familial Mediterranean fever [4], the Muckle–Wells syndrome [5] and heredofamilial amyloid polyneuropathy [6]. Familial Mediterranean fever, inherited as an autosomal recessive disorder, may involve erysipelas-like lesions on the lower legs, urticaria, Henoch–Schönlein purpura and vasculitic nodules [4]. Associated features are intermittent fevers with abdominal pain and joint effusions, and a tendency to peritonitis, pleurisy, synovitis and renal amyloidosis. The Muckle–Wells syndrome, which has autosomal dominant inheritance, is characterized by periodic attacks of urticaria, fever and limb pains, associated with progressive perceptive nerve deafness and renal amyloidosis [5]. Trophic skin changes may develop in heredofamilial amyloid polyneuropathy [6]. The Finnish type of heredofamilial neuropathic amyloidosis, a gelsolin-related systemic amyloidosis characterized by cranial neuropathy and corneal lattice dystrophy, may be associated with cutis laxa, blepharochalasis and lichen amyloidosus [7].

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Angiokeratoma corporis diffusum

[S.M. Breathnach, pp. 57.51–57.56]

Angiokeratoma corporis diffusum is the dermatological hallmark of several rare inherited lysosomal disorders, which include the following:
1 Anderson–Fabry disease (deficient α-galactosidase A; MIM 301500) [1];
2 fucosidosis (deficient α-L-fucosidase; MIM *230000) [2,3];
3 deficient lysosomal α-*N*-acetyl-galactosidase activity with glycopeptiduria (Kanzaki's disease; MIM *104170) [3–6];
4 aspartylglycosaminuria (deficient glycosylasparaginase; MIM *208400) [7];
5 adult-onset GM1 gangliosidosis (deficient β-galactosidase; MIM *230500) [8];
6 galactosialidosis (combined β-galactosidase and sialidase (neuraminidase) deficiency; MIM *256540) [9];
7 cases with no specific enzyme deficiency.
In each of these disorders, the skin lesions slowly develop as clusters of individual telangiectases or small angiomas. The larger and older lesions may become hyperkeratotic. The characteristic cutaneous eruption is often accompanied by a varied degree of vasomotor disturbances, neurological features, cardiovascular episodes and, sometimes, renal failure. Glycoproteinoses (fucosidosis, α-*N*-acetylgalactosaminidase deficiency and aspartylglycosaminuria) belong to the lysosomal storage disorders group, the common feature of which is deficiency of a lysosomal protein enzyme that hydrolyses glycoprotein (glycan) carbohydrate chains by stepwise removal of terminal monosaccharides. Deficiency of a single enzyme causes blockage of the entire pathway, and induces storage of incompletely degraded substances inside the lysosome. Different mutations may be observed in a single disease [3].

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Anderson–Fabry disease (MIM *301500) [1–3]

Aetiology. Angiokeratoma corporis diffusum is an X-linked disorder, in which deficiency of lysosomal hydrolase α-galactosidase A results in the progressive deposition of uncleaved, neutral glycosphingolipids—predominantly α-galactosyl-lactosyl-ceramide (trihexosylceramide, globotriaosylceramide)—within the lysosomes of endothelial, perithelial and smooth muscle cells, leading to severe painful neuropathy with progressive renal, cardiovascular and cerebrovascular dysfunction and early death. Physical stigmata, such as angiokeratomas in skin and mucous membranes and characteristic benign corneal abnormalities, facilitate identification of Fabry's disease. Men are predominantly affected; most women who are carriers are symptomless, but they may have clinical evidence of the disease, and in a few this may be as severe as in men including increased risk of stroke [1,4]. The gene responsible for expressing α-galactosidase A has been localized to the middle of the long arm of the X chromosome [5,6], but the mutations involved are heterogeneous [7–10].

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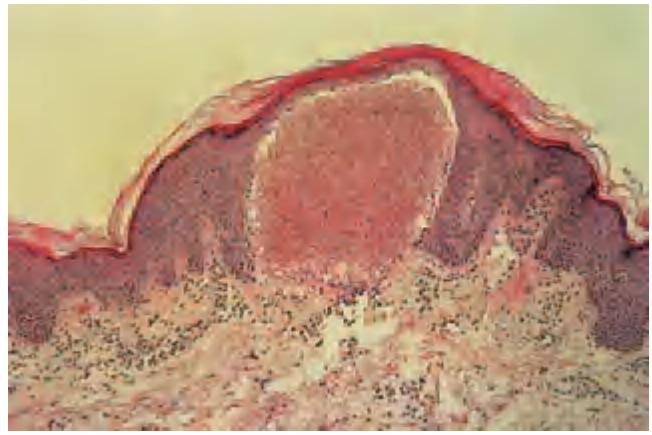

Fig. 57.34 Angiokeratoma corporis diffusum: H&E, × 4. Dilated blood-filled vessels in papillary dermis.

Histopathology [1]. Light microscopy of cutaneous lesions of angiokeratoma corporis diffusum shows dilated blood-filled vessels in the upper dermis lying beneath a thinned epidermis (Fig. 57.34), with or without hyperkeratosis. Detection of lipid in the skin necessitates the use of special fixation and lipid-staining techniques. The characteristic and diagnostic feature of the disease is the presence of vacuolated cells in the walls of capillaries, arterioles and venules. Glycolipid material can be demonstrated by polarized light as a double refractile substance in frozen sections, in the media and intima of smaller skin blood vessels. The diagnosis can be made more easily with the electron microscope than by light microscopy [2]. Electron-dense cytoplasmic inclusion bodies with a lamellar internal organization, consisting of alternating electron-opaque and electron-light regions with a periodicity of 4–6 nm are found in endothelial (Fig. 57.35) and muscle cells of blood vessels, perithelial and perineural cells, arrectores pilorum muscles and dermal macrophages. They may represent lipid deposits within lysosomes [3,4]. Inclusion bodies have been reported in the skin of adult patients even in the absence of clinically evident angiectases [5,6], and have also been found in 'normal' skin from an infant with the disease [7]. Characteristic cytoplasmic inclusions were observed in eccrine sweat glands and in their associated unmyelinated nerve fibres in a patient with hypohidrosis [8]. Ultrastructural study of kidney biopsies reveals typical concentric lamellation bodies in the cytoplasm of all types of renal cell [9].

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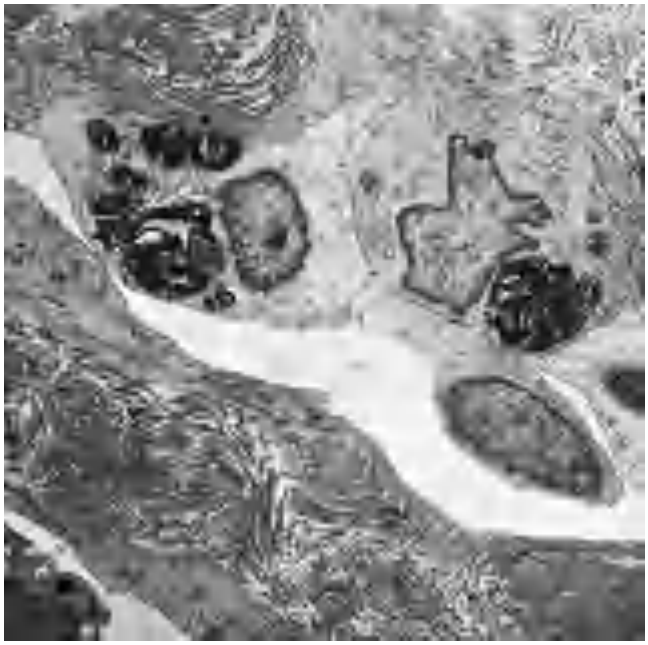

Fig. 57.35 Angiokeratoma corporis diffusum. Electron-dense cytoplasmic inclusion bodies are present within endothelial cells. (Courtesy of Dr P.H. McKee, King's College, London, UK.)

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Clinical features [1–5]. Cutaneous involvement [6–8] usually first appears shortly before puberty. The initial lesion is a dark-red or black telangiectatic macule or papule up to 4 mm across, remaining unchanged on diascopic pressure; overlying hyperkeratosis is not always obvious. Occasionally, skin lesions may be minimal or even absent. Grouping tends to occur, and in mild cases telangiectatic spots may be seen only on the thighs, scrotum or around the umbilicus (periumbilical rosette). In severe cases, widespread lesions are present, particularly on the limbs, hips, buttocks (Fig. 57.36), lower trunk and shaft of the penis. The association of Anderson–Fabry disease with perioral telangiectases has been noted [9]. The skin is often dry, lax, hypohidrotic or even anhidrotic [10,11].

A symptomless superficial corneal dystrophy (cornea verticillata) is a frequent ophthalmic finding, and is of diagnostic importance, since it can only be mimicked by chloroquine keratopathy [6]. It is often present in carrier females. Dilatation and tortuosity of the conjunctival and retinal vessels are common and may be present in childhood. The upper eyelids may be oedematous. A variety of oral and craniofacial abnormalities are described, including an increased prevalence of cysts/pseudocysts of the maxillary sinuses and the presence of maxillary prognathism [12].

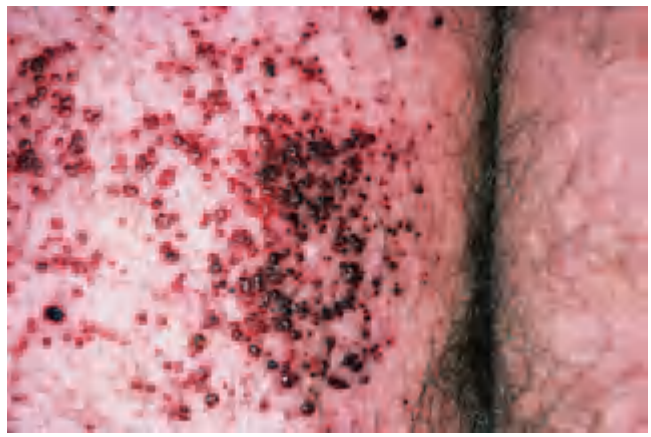

Fig. 57.36 Angiokeratoma corporis diffusum. Clusters of telangiectatic spots. Micropapules are present on the buttocks. (Courtesy of St John's Institute of Dermatology, London, UK.)

Episodic attacks of pain [13,14] mainly in the skin of the fingers and toes (acroparaesthesia), often of an excruciating and apparently unique character, and usually beginning between the ages of 5 and 15 years, occur in 90% of males and in fewer than 10% of females. High-frequency sensorineural deafness may be present [3]. Vasomotor disturbances appear later, probably as a result of involvement of the autonomic nervous system. The hands may be blue or blanched, or there may be flushing of the extremities. Mild arthritis of the terminal phalanges is frequent.

Patients with angiokeratoma corporis diffusum are often mildly hypertensive, and liable to coronary artery disease and other cardiac abnormalities, including disturbances in conduction, valvular disorders and hypertrophic cardiomyopathy [15,16]. Varicose veins and stasis oedema are fairly common. Cerebrovascular disease and strokes are an important cause of premature death [2–5,17]. Renal dysfunction is a major complication; end-stage renal failure, requiring dialysis or transplantation, usually occurs between 40 and 50 years of age, but may occur much earlier [2,3,18,19]. Gastrointestinal involvement, including achalasia of the oesophagus, is common. Other reported presenting features include fever and generalized lymphadenopathy [20].

The full syndrome occurs predominantly in men. In women, there may be only corneal opacities, retinal vessel tortuosity and urinary signs of renal involvement, but sometimes the disease is as severe as in men [5].

Prognosis. The median cumulative survival was reduced to 50 years due to cerebrovascular or renal disease in one series, and attendance at school, sports and social activity were significantly affected, with only 57% of patients being employed [3]. Cerebral lesions did not appear until 23 years of age in another series, but were present in all patients by 55 years of age; the peak onset of proteinuria occurred in the fourth decade, and the peak onset of end-stage renal disease occurred in the fifth decade [2]. Prolonged survival without impairment of renal function is, however, possible.

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Diagnosis. A skin biopsy may confirm the clinical diagnosis. Albuminuria, haematuria and specific lipophages may be seen in the urine as a result of lipid infiltration of the glomerular vessels; PAS-positive, 'mulberry-like' cells in urinary sediment can be used as a diagnostic aid [1]. The finding of a decreased level of α-galactosidase A in plasma, leukocytes and cultured skin fibroblasts is diagnostic. Slit-lamp examination of the cornea and renal biopsy should be performed in doubtful cases. The differential diagnosis includes purpura, angioma serpiginosum and other types of angiokeratoma: circumscriptum, scrotal (Fordyce type) and Mibelli type.

Treatment. Males with Anderson–Fabry disease recorded significantly lower health-related quality-of-life scores compared with males in the general population and individuals with severe haemophilia; the scope for improvement in quality of life as a result of treatment with an appropriate agent is therefore large [2]. Management has been largely symptomatic. Laser therapy may be helpful for the angiokeratomas [3]. Painful crises may respond to phenytoin or carbamazepine, either alone or in combination [4,5]. Early use of antiplatelet agents, for example aspirin, may mitigate embolic or thrombotic cerebrovascular events due to platelet activation caused by deposition of sphingolipid in vascular endothelium. Renal or cardiac transplantation have been undertaken for end-stage disease [6,7], but there is a tendency for reaccumulation of ceramide in transplanted organs. Enzyme replacement therapy using human recombinant α-galactosidase A has resulted in symptomatic improvement, as well as documented lessening of globotriaosylceramide deposits, and improvement in renal, cardiac and cerebrovascular function [8–14]. However, the future lies with gene therapy [15–17].

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Glycoprotein lysosomal storage disorders

Glycoprotein lysosomal storage disorders that may have cutaneous features include fucosidosis, glycopeptiduria due to deficient lysosomal α-*N*-acetyl-galactosaminidase activity, and aspartylglycosaminuria.

Fucosidosis (MIM *230000)

Fucosidosis is an autosomal recessively inherited lysosomal storage disease caused by a deficiency of α-L-fucosidase, leading to accumulation of fucose-containing glycolipids and glycoproteins in various tissues. It is extremely rare; less than 100 patients have been reported worldwide, although the disease occurs at a higher rate in Italy, in the Hispanic-American population of New Mexico and Colorado, and in Cuba [1]. Fucosidosis is characterized by progressive psychomotor deterioration, angiokeratoma and growth retardation [1–4]. Other clinical features include coarse facies, recurrent infections, visceromegaly and epilepsy. The clinical spectrum varies between a rapidly progressive infantile type (type I) and a less severe adolescent or adult type (type II). The angiokeratomas are more frequent in the less severe type and possibly imply a better prognosis. The angiokeratomas may also occur on the tongue and be associated with increased vascular markings on the palms and soles [2]. The genetic mutations causing fucosidosis are heterogeneous [1,5]. Bone marrow transplantation has been recorded as an effective treatment [6,7].

Ultrastructure of melanocytes, endothelial cells, sweat glands and fibroblasts reveals numerous empty storage vacuoles, which enables ready differentiation from Anderson–Fabry disease [8].

Glycopeptiduria due to deficient lysosomal α-*N*-acetyl-galactosaminidase activity (MIM *104170) [9–12]

SYN. KANZAKI'S DISEASE

This very rare type of angiokeratoma corporis diffusum was first delineated in 1989 in a Japanese woman [10]. The disease overlaps with infantile neuroxomal dystrophy [11] so that infantile and adult-onset subtypes have now been identified [9]. The angiokeratoma lesions may be very diffuse and slowly spread to involve the face and extremities. The lesions tend to be most dense on the axillae, breasts, lower abdomen, groins and buttocks. Telangiectases have been noted on the lips, inside the oral cavity and on endoscopy in the gastric mucosa [9]. Dilated, corkscrew-like, tortuous, vessels occur in the ocular fundi [9]. In adults, the disease can be associated with impairment of intellect and features compatible with peripheral neuroaxonal degeneration [9].

Aspartylglycosaminuria (MIM *208400)

SYN. DEFICIENT ASPARTYLGLYCOSAMINIDASE

The main symptom is progressive mental retardation. Facial angiofibromas and oedema of the buccal mucosa (leukoedema) with gingival overgrowths have been described [13].

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Angiokeratoma corporis diffusum with no overt enzyme deficiencies

Isolated cases of angiokeratoma corporis diffusum without overt enzyme deficiencies continue to be reported

rarely [1–4]. The association of angiokeratoma corporis diffusum with normal enzyme activities and Turner's syndrome has been observed [5]. It is unclear at the present time whether such cases may ultimately be proved to have other enzymatic deficiencies that have yet to be identified.

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Lipoid proteinosis (MIM #247100)

SYN. URBACH-WIETHE DISEASE [1–3];
HYALINOSIS CUTIS ET MUCOSAE [4];
LIPOGLYCOPROTEINOSIS [5]
[S.M. Breathnach, pp. 57.56–57.57]

Lipoid proteinosis [6,7] is a very rare, autosomal recessive, genetic disorder characterized by infiltration of hyaline material into the skin, oral cavity, larynx and internal organs. It usually presents in infancy with hoarseness. The sexes are equally affected. Large kindreds of lipoid proteinosis have been reported in South Africa, where most of the cases can be traced back to a German immigrant [8,9].

Aetiology. Very recently, the disorder has been mapped to chromosome 1q21 and has been shown to be caused by mutations in the extracellular matrix protein 1 gene [10]. The exact nature of the hyaline material is still unknown.

Histopathology [2,11,12]. Epidermal hyperkeratosis and irregular acanthosis overlies a considerably thickened dermis. The upper dermis contains extracellular hyaline material, at first deposited along the course of capillaries and concentrically around sweat coils, and in older lesions tends to be orientated vertically in broad bands. The hyaline material stains strongly with PAS, implying the presence of glycoproteins. Mucosubstances can usually be demonstrated but the histochemical characteristics of the hyaline deposits may vary from site to site and with time [11]. Around the blood vessels and appendages, accumulations of type IV and V collagen occur [12]. Elsewhere, type III collagen is abnormally distributed and there is a reduction in type I collagen.

Ultrastructurally [13–15], hyaline material with a granular appearance is interspaced between collagen bundles.

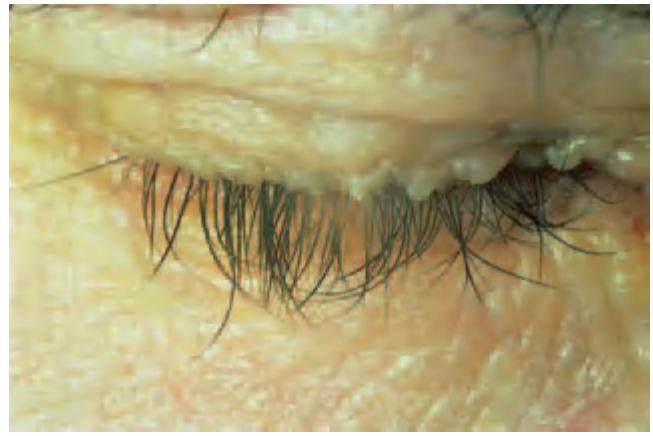

Fig. 57.37 Lipoid proteinosis. Typical 'beaded' papules present along the margins of the upper eyelids. (Courtesy of Dr R.C.D. Staughton, Chelsea and Westminster Hospital, London, UK.)

Immediately surrounding blood vessels, there is reduplication of basal laminae in an 'onion skin' arrangement.

Clinical features [16–21]. Lipoid proteinosis develops early in life. Scarring from mild skin inflammation and injury is marked. Hoarseness develops in infancy; it becomes prominent within the first few years of life, and can progress to complete aphonia but fortunately usually without breathing difficulties [6]. The mucosae of the pharynx, tongue and lips soon develop firm yellow-white infiltrates; the lingual frenulum may be short. The soft palate, pillars of the tonsils, uvula and under-surface of the tongue show extensive yellow irregular infiltrations. The tonsils are covered with a hard, white mass. The larynx is involved to a severe degree, with nodules in the epiglottis and vocal cords [22]. The tongue is enlarged and feels firm on palpation; its range of movement is decreased, so that the patient is usually unable to protrude it beyond the margins of the lips. Occasionally, there is similar involvement of the mucosa of the labia and vagina.

Skin changes frequently become prominent in early life with the development of yellow-brown nodules appearing on the face and lips. Involvement of the scalp leads to loss of hair. Very typical 'beaded' papules are present along the margins of the upper and lower eyelids (syn. moniliform blepharosis) (Fig. 57.37) and there may be total loss of eyelashes. Scattered, atrophic, pock-like scars are often seen on the face [16]. Nodular lesions on the elbows resemble xanthomas. Deposits may appear in the skin and mucous membranes after trauma. Later, the colour of the skin darkens and the lesions become hyperkeratotic or warty. Small nodules are sometimes present on the finger joints, in the axillae and on the knees and scrotum. Dental abnormalities [23], intracranial (e.g. bilateral temporal) calcification [20] and epilepsy are often associated with lipoid proteinosis, and recurrent parotitis

can occur. Widespread visceral involvement is described, and indeed virtually every organ in the body can be involved [24].

Diagnosis. A combination of hoarseness from early childhood, thickening and stiffening of the tongue and characteristic cutaneous nodules makes the diagnosis relatively easy. In erythropoietic protoporphyria, which causes waxy papules and depressed scars, there is solar sensitivity and the scarred areas are confined to exposed skin; on histology, the hyaline material is not so extensively deposited, is never found around sweat coils, and fine droplets of lipid can be demonstrated. Xanthomatosis and amyloidosis can also be excluded by the histological appearances. In adult life, differential diagnosis from lichen myxoedematosus, and myxoedema with hoarseness, have to be considered.

Prognosis. Lipoid proteinosis is progressive until early adult life, but in general the prognosis is good [24]. Involvement of the larynx only occasionally leads to respiratory difficulties in childhood, resulting in tracheotomy.

Treatment. Microlaryngoscopy and dissection of the vocal cords can be successful. Dermabrasion [25], chemical skin peeling, blepharoplasty and carbon dioxide laser therapy [26] may be helpful. Remarkable clearance of skin and laryngeal lesions was reported in a single case of lipoid proteinosis after 3 years of continuous oral dimethyl sulfoxide therapy [27]. However, no improvement was demonstrated in a further three patients [28]. Beneficial effects of etretinate [29,30] and of penicillamine [31] have also been reported.

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Neutral lipid storage disease (MIM 275630)

SYN. DORFMAN–CHANARIN SYNDROME

[S.M. Breathnach, pp. 57.57–57.58]

This rare autosomal recessive genetic lipid disorder is briefly mentioned because it may be associated with congenital ichthyotic erythroderma [1–4]. Lipid-filled vacuoles may be identified in neutrophils and basal keratinocytes, fibroblasts, Schwann's cells, smooth muscle cells and sweat glands [5]. The prognosis depends on the pattern and degree of systemic involvement. Etretinate may help the ichthyosis [2].

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Farber's disease [1] (MIM *228000)

SYN. DISSEMINATED LIPOGRANULOMATOSIS

[S.M. Breathnach, p. 57.58]

Farber's disease is a rare and fatal lipid-storage disease of infants, probably inherited in an autosomal recessive fashion, in which there is deficiency of lysosomal acid ceramidase and an accumulation of ceramide [2]. Most cases have been sporadic.

Histopathology. In the skin and subcutaneous tissue, dense areas of mixed granulomatous infiltration are found among a fibrovascular stroma. Groups of large, foamy histiocytes are found towards the centre of the granulomas. At systemic sites (especially the brain) the presence of vacuolated cells is similar to the pathology encountered in other metabolic storage diseases.

Histochemical studies indicate that the deposited material is an acid glycolipid [3] of which ceramide is probably the most important [2]. It has been suggested that estimation of acid ceramidase in cultured fibroblasts or amniotic fluid cells may provide a means of early diagnosis [4]. Ultrastructurally, curvilinear bodies (Farber's bodies) have been described in the cytoplasm of fibroblasts [5,6].

Clinical features. Involvement of the laryngeal joints and the adjoining tissue produces dysphonia, laryngeal stridor, hoarse cry and noisy respiration. Erythematous papules and nodules appear close to joints and tendons of the hands and feet, leading to painful and progressively deformed joints. The ears, the occipital region and the trunk are other sites of predilection with infiltrated papules, plaques and nodules predominating. Gross mental and motor retardation are features of the disease. Cherry-red spots may be noted at the macula [3]. The lungs, heart and lymph nodes may also be affected.

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Gaucher's disease (MIM *606463)

[S.M. Breathnach, pp. 57.58–57.59]

Definition. A rare inborn error of metabolism characterized by the accumulation of complex lipid substances in macrophages (Gaucher's cells) within liver, spleen and bones.

Aetiology [1,2]. This congenital and familial disorder of lipid metabolism is transmitted as an autosomal recessive disorder, and is due to a deficiency of the lysosomal hydrolase, acid-β-glucosidase (glucocerebrosidase) [3–5]. The abnormal lipid that results, kerasin, accumulates in the cells of the reticuloendothelial system leading to enlargement of the spleen, liver and lymph nodes. This condition may also be associated with a thrombocytopenia and coagulation defect [6,7]. Even patients and siblings with the same mutation, including monozygotic twins, may exhibit marked variability in disease expression and severity, illustrating our lack of understanding of the phenotype–genotype relationship in the sphingolipidoses [4].

Pathology. The classical feature of the disease is the presence of numerous characteristic histiocytes (Gaucher's cells) which infiltrate the pulp of the spleen, the liver and bone marrow, lymph nodes, sinuses and sometimes other organs. Gaucher's cells are large cells with a small nucleus and a voluminous pale-staining cytoplasm, which differ from other lipid-containing cells because of the delicate, striated, tissue-paper appearance, best seen in thicker sections (10 μm). Ultrastructurally, Gaucher's cells contain elongated residual bodies containing tubular structures composed of twisted microfibrillar elements [1,8]. These structures probably represent aggregated glucocerebroside molecules within distended lysosomes, and contain acid phosphatase [9]. In the juvenile neuropathic form, the brain shows loss of neurones and some perivascular accumulation of PAS-positive cells, but typical Gaucher's cells are few or absent.

Clinical features. The adult type (type I) is the most common form and shows an insidious onset with only slow progression. In the adult, the initial complaint is usually that of weakness or perhaps of minor bleeding tendencies [7]. Dull pain in the bones is another early feature. Common cutaneous features include diffuse pigmentation, which may be due to haemosiderosis or to deposition of melanin, easy tanning and pigmented macules [10,11]. Telangiectasia may be noted when there is marked liver

involvement [11]. Anaemia as part of a pancytopenia is an almost constant finding. Generalized osteoporosis of bones due to infiltration by Gaucher's cells leads to gross deformity of the skeleton with collapse of thoracic and lumbar vertebrae. The finding of Gaucher's cells in sternal marrow is important diagnostically [12].

The infantile type (type II), comprising 10% of all cases of Gaucher's disease, begins during the first 6 months of life and ends fatally before the second year [13]. The symptoms of the acute infantile form are predominantly neurological, and include neck rigidity, increased muscle tone, catatonia and laryngeal spasm. The infant dies of acute respiratory infection complicated by laryngospasm, cyanosis and cachexia. Splenomegaly and hepatomegaly are prominent, but there are no specific skin lesions. Some cases are capable of more prolonged survival and this has been referred to as the juvenile form (type III). A rare association between type II Gaucher's disease and congenital ichthyosis presenting as the collodion baby phenotype has been noted [14–16].

Prognosis. This depends very largely on the age of onset. If the symptoms appear in the first decade of life, the prognosis is poor. If in the third or later decades of life, the progress of the disease is much slower, and survival to old age is not unusual.

Treatment. There is no specific treatment. Splenectomy is indicated as a palliative measure to reduce abdominal distension and on occasions to try and relieve anaemia and thrombocytopenia. However, the benefits of splenectomy are rather variable and depend on the extent of marrow destruction by Gaucher's cells. X-ray therapy to the bones may relieve pain. Little can be done for the infantile or juvenile form of Gaucher's disease. Liver transplantation can disperse tissue glucocerebroside deposition and this effect has been explained by the mechanism of microchimerism (migration of cells from the allograft) [17]. Enzyme replacement therapy has been the most successful therapeutic approach for lysosomal storage disorders, and reverses systemic manifestations of Gaucher's disease but does not effectively treat the neurological complications [18,19]. Bone marrow transplantation continues to be effective in Gaucher's disease, but it has high morbidity and mortality that limits its use. Drugs that slow the rate of formation of accumulating glycolipids are being developed and one of them, OGT-918 (*N*-butyldeoxynojirimycin), is showing promise in Gaucher's disease [18]. Gene therapy requires much more development before clinical efficacy trials.

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Niemann–Pick disease (MIM *257200) [1,2]

[S.M. Breathnach, pp. 57.59–57.60]

Definition. Niemann–Pick disease refers to a group of congenital lipidoses (sphingolipidoses) bearing a wide spectrum of clinical symptoms. It is usually fatal in early childhood and is characterized by emaciation, hepatomegaly and splenomegaly.

Aetiology. Niemann–Pick disease is inherited as an autosomal recessive lack of sphingomyelinase [3]. Six types of Niemann–Pick disease have been described, of which only types B and E are consistently free of neurological manifestations [4]. They are characterized by the accumulation of enormous quantities of sphingomyelin in histiocytes, macrophages and reticulum cells of all organs. The sex incidence is approximately equal, and the condition is said to be more common in Jewish infants. At least 96% of all Niemann–Pick disease type C patients link to *NPC1*, which encodes for a lysosomally targeted protein [5].

Pathology. There is massive enlargement of the liver, spleen, lymph nodes and infiltrations in lungs and bone marrow. Niemann–Pick cells are readily demonstrated in all organs including the skin [6]. In the brain and central nervous system, a variety of degenerative features similar to those of Tay–Sachs disease have been described. The Niemann–Pick cell is usually mononucleate, large, pale and foamy, but accompanied by neither granulomatous nor inflammatory cells. In cryostat sections, they stain readily with Sudan stains and contain doubly refractile material. PAS positivity is less marked as compared with Gaucher's cells. Circulating lymphocytes frequently also show lipid inclusions [7]. Ultrastructurally, the Niemann–Pick cell is similar to a histiocyte, with cytoplasm containing variably sized lipid cytosomes, many with concentrically arranged whorled features [8]. The diagnosis can also be confirmed by finding a very low level of sphingomyelinase activity in the leukocytes [9].

Clinical features. An apparently normal infant begins to lose weight about the second or third month of life. The abdomen becomes protruberant from massive enlargement of liver and spleen. Lymph nodes are increased in size. The infant becomes progressively more emaciated and apathetic, and the face appears mongoloid. Muscle weakness increases, the child is unable to sit or raise the head, and all muscle tone is lost. Deafness and blindness are common features. Death takes place usually before the age of 2 years and often earlier. Older survival has been recorded [10] in the absence of severe liver involvement.

The skin involvement in Niemann–Pick disease has been described as waxy induration with transient xanthomas overlying enlarged cervical nodes [10,11]. Other skin lesions described include papular [12], papulonodular [13] or suppurative lesions on the face, associated with foamy cell infiltration, indurated discoloured patches on cheeks [6], purpuric lesions, café-au-lait spots and dark-bluish mongolian spots on skin and oral mucosa [8].

Treatment. Allogenic bone marrow transplantation has been tried in Niemann–Pick disease type B [14].

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Xanthomas and abnormalities of lipid metabolism and storage

[C.A. Seymour, pp. 57.60–57.77]

Classification of lipid disorders can be based on clinical assessment, including family history, levels of fasting plasma lipids and lipoproteins. The World Health Organization (WHO) classification of lipoprotein phenotypes has been superseded by a more useful classification, which now provides a basis for indicating which lipoproteins are in excess in patients, but does not specifically indicate genetic forms of the disease. The Fredrickson classification of hyperlipidaemia (Table 57.9) is based on plasma lipoprotein patterns associated with increased concentration of cholesterol and/or triglyceride (TG; triacylglycerol), and provides a useful basis for characterizing which specific lipoprotein is increased in patients. Such a classification is not diagnostic and does not include a high-density lipoprotein (HDL) cholesterol category. HDL is an important lipoprotein, since low levels of HDL are associated with an increased risk of cardiovascular disease. This risk is increased if the low HDL is associated with increased total cholesterol and/or TG. Recent advances in our knowledge of lipoprotein metabolism have resulted in a more functional classification, which recognizes that dyslipidaemias are more often polygenic and multifactorial in origin. This classification is not an aetiological one and does not specifically differentiate primary (genetic) from polygenic and secondary hyperlipidaemias. Establishing a lipoprotein phenotype does not substitute for making a diagnosis of the underlying cause. About 60% of the variation in plasma lipids is genetically determined, most being polygenic with interaction with environmental factors. Familial forms of hyperlipidaemia, where the family history is important in the clinical assessment, may have monogenic influences

Table 57.9 Classification of hyperlipidaemia.

Primary hyperlipidaemia (new terminology)	Frederickson lipoprotein phenotype (WHO classification)	Lipid changes				
		Plasma cholesterol	LDL cholesterol	Plasma TG	Lipoprotein changes	Secondary causes
Hypercholesterolaemia		Raised or normal	Raised	Normal	Excess LDL	Hypothyroidism
Familial hypercholesterolaemia	IIa, IIb					Primary biliary cirrhosis
Polygenic hypercholesterolaemia	IIa					
Combined hypercholesterolaemia		Raised	Raised	Raised	Excess LDL	Acute intermittent porphyria
Familial combined (mixed) hyperlipidaemia	IIa, IIb (IV)				Excess VLDL	Anorexia nervosa Cushing's syndrome Diabetes Hepatoma Nephrotic syndrome
Remnant particle disease (dysbetalipidaemia)	III	Raised	Low or normal	Raised	Excess CM remnants Excess IDL	Diabetes Hypothyroidism Monoclonal gammopathy Obesity
Hypertriglyceridaemia		Raised or normal	Normal	Raised	Excess VLDL	Alcoholism Chronic renal disease Diabetes Lipodystrophies Monoclonal gammopathy Uraemia
Familial hypertriglyceridaemia	IV					
Familial combined hypertriglyceridaemia	V	Raised	Normal	Raised	Excess CM Excess VLDL	Alcohol Diabetes Drugs: β-blockers Diuretics Oral contraceptives Retinoids
Chylomicronaemia syndrome	I	Raised	Low/normal or raised	Raised	Excess CM	SLE (rarely)
Lipoprotein lipase deficiency						
Apoprotein CII deficiency						
HDL abnormalities not classified						Androgenic steroids
Hypoalphalipoproteinaemia						
Hyperalphalipoproteinaemia						

C, cholesterol; CM, chylomicrons; HDL, high-density lipoproteins; IDL, intermediate-density lipoproteins; LDL, low-density lipoproteins; N, normal; TG, triglycerides; VLDL, very-low-density lipoproteins.

that are variably expressed; for example, familial hypercholesterolaemia (FH), which is expressed independently of environmental factors, and familial dysbetalipoproteinaemia (type III), where the gene defect may only be expressed by interaction with the environment.

Primary hyperlipidaemias

Clinical classification of hyperlipidaemia and hyperlipoproteinaemia (lipoprotein phenotypes) is based on measurement of levels of non-fasting total cholesterol, fasting TG, low-density lipoprotein (LDL) and HDL cholesterols, the ultracentrifugation pattern of plasma lipoproteins and, increasingly, the measurement of apolipoproteins, particularly apo-A1 (in HDL), apo-B (in LDL) and apo-C (in VLDL). The classification is still divided into six categories [1–4], but most usefully in terms of treatment into pure or combined hypercholesterolaemia, or pure or combined hypertriglyceridaemia (Table 57.9).

Secondary hyperlipidaemias [1,2]

There are a variety of disorders that may produce or exacerbate a pre-existing hyperlipidaemia (Table 57.10) and of these diabetes mellitus, alcoholism and ingestion of oestrogens are the most commonly encountered. Where hyperlipidaemia occurs in association with certain acquired systemic diseases, treatment of the systemic disorder results in normalization of the circulating lipoprotein profile, unless the hyperlipidaemia is also due

Table 57.10 Secondary hyperlipidaemia.

	Cholesterol ↑	Cholesterol ↑ LDL ↑	Triglyceride ↑ VLDL ↑	Triglycerides HDL ↑	LDL↑ VLDL ↑
Common	Primary biliary cirrhosis Biliary cirrhosis	Nephrotic syndrome (IIA/IIB) Hypothyroidism (IIA or IIB) Drugs: Thiazide diuretics Ciclosporin	Chronic renal failure (IV) Maturity onset Diabetes mellitus (IV) Juvenile onset (less commonly (V)) Alcoholism (IV)	Oral contraceptives Pregnancy Oestrogens Prostatic carcinoma (treated) Drugs: β-blockers Epanutin Retinoids (IV) Cimetidine (V, I)	Sex hormones (exogenous) Myeloma (III)
Rare		Hepatoma (IIA) Acute intermittent porphyria (IIA) Cushing's syndrome (IIB) Anorexia nervosa (IIA)	Monoclonal gammopathy (IV) Lipodystrophy (all forms, IV or V) Gout (V) Obesity Occasional alcohol Polycythaemia (V) SLE (I)	Gaucher's disease Glycogen storage disease Regular/heavy alcohol	

HDL, high-density lipoproteins; LDL, low-density lipoproteins; SLE, systemic lupus erythematosus; VLDL, very-low-density lipoproteins.

to a coincident primary hyperlipidaemia, when the increase is more marked. The abnormal lipoprotein pattern in secondary hyperlipidaemia may not be clearly diagnostic although it can mimic a primary lipoprotein disorder. For example, the hyperlipidaemia of uncontrolled diabetes mellitus and that of lipoprotein lipase deficiency may appear similar (Table 57.9); this may be because of similarities in underlying mechanisms. However, there are others, for example the hyperlipidaemias associated with chronic biliary obstruction and monoclonal gammopathy, which have unique patterns (i.e. pure hypercholesterolaemia). In chronic renal disease, varying lipoprotein profiles may occur that mimic all types of primary hyperlipidaemia. In addition, a number of systemic disorders may modify primary hyperlipidaemia, for example diabetes mellitus and familial hypertriglyceridaemia.

While any hyperlipidaemia may be a major risk factor for coronary artery disease (CAD), a number of other factors may be equally important. These include increased risk of thrombosis due to increased fibrinogen, elevated plasma lipoprotein (a) (Lp(a)) and, in patients with insulin resistance, diabetes mellitus and microalbuminuria.

Other risk factors that can complicate and exacerbate an underlying lipoprotein abnormality are obesity, smoking and hypertension. It is also recognized that some factors are associated with an increased risk of atherogenesis, and some with an increased risk of thrombogenesis (such as Lp(a), factor VII and plasminogen activator inhibitor 1 (PAI-1)). Some of these are also independent risk factors for CAD. In addition to lifestyle factors, common causes of secondary hyperlipidaemia are shown in Table 57.9. Some drugs such as those used in the treatment of psoriasis (retinoids) may precipitate a combined hyperlipidaemia picture. More recently treatment of HIV with protease inhibitors may produce a marked hypertriglyceridaemia (increase in VLDL).

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Lipid metabolism [1–10]

In the last two decades there has been an improvement in knowledge of the component parts of lipid metabolism and a more integrated understanding of the pathophysiology of lipid transport. It is well established that lipoproteins are derived from an *exogenous* pathway, where diet will have a large influence, and an *endogenous* pathway, which will involve lipoprotein production, processing and catabolism.

Lipids are essential as energy stores and respiratory substrates, and are structural components of cell walls. Lipids are transported in the blood and extravascular body fluids in combination with proteins, usually apoproteins. Lipoprotein particles are globular and vary in

composition, but contain an outer polar component of phospholipid and free cholesterol enclosing the core of hydrophobic lipids (cholesterol esters and TGs, also termed triacylglycerols). In addition, apoproteins, also enclosed in the core but with charged groups (polar regions) exposed to the surface, have a role both in the lipoprotein structure and in regulation.

Exogenous transport in chylomicrons (chylomicron pathway) [5,6,9,10]

The exogenous pathway transports the products of fat digestion from the gut and liver to peripheral tissues. Triglyceride-rich chylomicrons (CMs) from the gut and VLDL from the liver are processed in similar ways. The major difference is that, in the gut, CMs contain an edited form of apolipoprotein B (apo-B48), while the liver secretes the full apo-B100 in VLDL. Absorbed dietary TG (absorbed as free fatty acids and monoglycerides), free cholesterol and phospholipids are packaged within the enterocyte with intestinal apo-B48 to form CMs. Nascent CMs are secreted from intestinal villi to lymph (chyle) and enter lacteals, reaching the blood through the thoracic duct. In the circulation, CMs (which carry dietary fat and cholesterol) acquire further apolipoproteins, mainly apo-C, and apo-E from HDL. The apo-CII component of these particles activates the enzyme lipoprotein lipase found on the capillary endothelium of skeletal and cardiac muscle (providing energy) and adipose tissue (where it is stored). This leads to the rapid hydrolysis of the core of TG and entry of the resultant fatty acids and glycerol to peripheral tissues. Thus CMs become remodelled and smaller; VLDLs share this common catabolic pathway, and produce CM 'remnants'. The CM 'remnant' (rich in cholesterol ester containing both apo-B48 and apo-E) re-enters the circulation (reverse cholesterol transport) and is taken up by the liver via specific apo-E receptors (which, unlike the LDL receptor, are not affected by entry of free cholesterol into the hepatocyte) and catabolized in lysosomes. This transport system is efficient and as a result dietary cholesterol remains in the plasma for only a few minutes and can enter hepatic metabolic pathways, including excretion to bile.

Endogenous transport from the liver (VLDL–LDL pathway) [7–10]

Triglyceride-rich lipoproteins (VLDLs) are produced continuously in large amounts by the liver in a similar way to CMs in the enterocyte, with the exception that in humans the liver synthesizes and secretes the full-length apolipoprotein, apo-B100, rather than the truncated enterocyte form, apo-B48. The VLDL particles are secreted to provide tissues with VLDL in the absence of CMs (e.g. in the fasting state) and to prevent hepatic steatosis. Nascent VLDL particles (containing both TG, surplus fatty acid, cholesteryl esters and apolipoproteins B, CII and E) compete with CMs for lipolytic sites on endothelial cells, but have a lower affinity for the enzyme (lipoprotein lipase) than CMs. Again, as with CMs, hydrolysis occurs outside the liver by lipoprotein lipase to yield 'remnant' particles. The apo-B-containing lipoproteins (VLDL, intermediate-density lipoprotein (IDL) and LDL) are all involved in a process of delipidation, mediated in larger particles by lipoprotein lipase and in the smaller particles by hepatic lipase (IDL, dense LDL). Delipidation of large VLDL with cofactor apo-CII results in remnant particles $VLDL_2$, IDL and LDL, and direct catabolism of these particles occurs through uptake by apo-B and apo-E receptors on cells. The LDL receptor facilitates endocytic uptake of VLDL, IDL and LDL. Hepatocyte LDL receptors recognize apo-E on VLDL 'remnants' and allow some endocytosis and uptake into the cell, while some 'remnant' particles are processed by surface lipase to LDL, which can then be taken up by the apo-B100 receptors on hepatocytes. 'Remnant' particles, unlike LDL particles, have a short half-life in circulation [9].

LDL particles consist mainly of a core of cholesterol, cholesteryl esters and apolipoproteins B100 and E (about two thirds of the plasma cholesterol is in the LDL form). These lipoproteins bind to receptors that recognize apo-E and apo-B100, enter the liver and are metabolized, providing cholesterol for membrane and steroid hormone synthesis. LDL particles are metabolized slowly over a matter of days. The uptake of LDL regulates both the circulating levels of this lipoprotein and the synthesis of cholesterol. The number of cell receptors and rate of cholesterol synthesis are regulated by the cholesterol concentration in the cell. Cells also take up LDL via unregulated processes, such as through the scavenger pathway involving macrophages, which is dependent on the extracellular LDL concentration. These become more important when the circulating level of LDL is increased by the presence of dense LDL particles.

In normal and hyperlipidaemic individuals, LDL particles are heterogeneous, existing in three distinct forms (I, II, III). Pattern A, on a gel electrophoresis, is associated with low TG and larger LDL-I and -II, whereas pattern B has higher levels of TG and small, dense LDL (III) [9]. LDL-I and -II are converted to LDL-III by the action of cholesteryl ester transfer protein (CETP), which allows exchange of cholesteryl ester in LDL for TG in TG-rich lipoproteins. Subsequently LDL-III is hydrolysed by hepatic lipase to produce dense LDL, which are not metabolized through the usual LDL receptors.

LDL catabolism in the cell occurs in lysosomes after internalization, cell surface receptors recognizing lipoproteins with apo-B and apo-E. These LDL particles undergo lipolysis to cholesteryl esters, free cholesterol, apo-B and amino acids. Free cholesterol can regulate expression of

more cell surface LDL receptors (except in FH) and also regulates intracellular cholesterol synthesis via 3-hydroxy-3-methylglutaryl coenzyme A—the HMG-CoA reductase pathway. Subsequently activity of another enzyme (cholesterol-*O*-acyl transferase) resynthesizes cholesteryl ester from free cholesterol for storage within the cell. LDL can also enter cells in a non-receptor-mediated pathway, which is more important in atherosclerosis. At low concentrations of plasma LDL, this would be insignificant but is increased with increasing plasma LDL concentrations (important in individuals taking a high fat diet) and with lack of HDL, which can competitively inhibit non-receptor LDL (i.e. dense LDL uptake). This predisposes to atheroma in the FH patient (with reduced LDL-receptor uptake), in the high-fat-intake individual (with increased plasma LDL concentration) and where plasma HDL concentrations are low (lack of competition for the non-receptor pathway). Monocyte uptake of LDL, oxidized LDL and dense LDL (LDL-III) may also occur, which also predisposes to an increased risk of atheroma.

High-density lipoprotein and transport of cholesterol from tissues to liver (reverse cholesterol transport) [11]

Apolipoproteins AI and AII are the main protein components of plasma HDL, which also consists of cholesteryl esters and a phospholipid bilayer. They are secreted from the intestine as part of the nascent CMs. Some nascent HDL is also derived from hepatocytes. The core of cholesteryl esters is derived from the esterification of cholesterol from lipoproteins with a fatty acyl residue to form lecithin (phosphatidyl choline), catalysed by the liver enzyme lecithin cholesterol acyltransferase (LCAT). The conversion of polar cholesterol to non-polar cholesteryl esters creates a gradient that allows cholesterol to be continually transferred to HDL. HDL particles increase in size with increased lipolysis, reflecting transfer of surface components from TG-rich lipoproteins to HDL and stimulation of cholesterol esterification (the reverse process to delipidation of other lipoproteins during lipolysis). HDL particles are constantly exchanging components with other larger lipoproteins (VLDL, LDL) through lipolysis mechanisms and action of the enzyme LCAT.

The main role of HDL is to accept cholesterol and remove excess from cell surfaces and transport it as cholesteryl ester. Clearance of HDL is partly through reverse cholesterol transport through uptake by the liver, either as HDL or via transfer of cholesteryl ester from HDL to VLDL through CETP transfer to apo-B-containing particles, which are then taken up by the liver and possibly through a smaller HDL cleared through the liver. Thus HDL is not catabolized as a whole particle, and its components are redistributed continuously.

HDL plays an important role in preventing the accumulation of cholesterol in the body. It should be noted that high concentrations of HDL may contribute to an increase in total plasma cholesterol producing a mild hypercholesterolaemia and is not associated with an increased risk of CAD. Thus specific measurement of HDL should be undertaken to indicate whether it is an independent risk factor for CAD (i.e. low HDL concentrations).

Apoproteins [1,5,8,10]

These are lipid-free protein components of plasma lipoproteins. They form amphipathic helical structures, which allow the formation of stable structures with polar phospholipids at the surface of the plasma lipoproteins and so solubilize cholesterol esters and TG for transport (Table 57.11). The role of these proteins as components of lipoproteins and in lipid metabolism is now better understood (Table 57.11).

Table 57.11 Apolipoproteins.

Class	Origin	Function (where known)
Apo-AI	Liver, intestine	LCAT activator
Apo-AII	Liver, intestine	?
Apo-AIV	Liver, intestine	
Apo-B48	Intestine	CM production
Apo-B100	Liver	Receptor-mediated catabolism of LDL
Apo-CI	Liver	LCAT activator
Apo-CII	Liver	LpL activator
Apo-CIII	Liver	Inhibits catabolism of TG-rich Lp
Apo-D	?	?
Apo-EII	Liver	Receptor-mediated catabolism of apo-E-containing Lp
Apo-EIII	Liver	
Apo-EIV	Liver	

CM, chylomicrons; LCAT, lecithin cholesterol acyltransferase; LDL, low-density lipoproteins; LpL, lipoprotein lipase; TG, triglycerides.

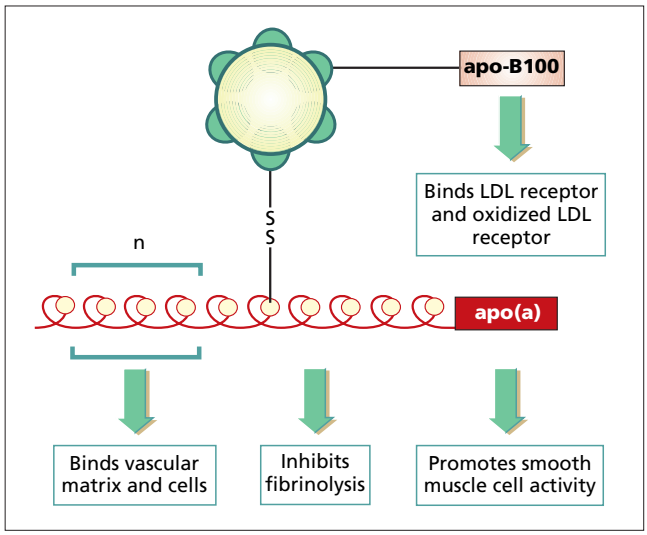

Fig. 57.38 The role of lipoprotein (a). (Redrawn from Sterling [15].)

Lipoprotein (a) (Lp(a)) [12–15]

This lipoprotein varies in concentration, and its physiological function has only recently been determined. It is larger and more dense than LDL but has a similar lipid composition. It is thought to come from the liver but not via the VLDL pathway. It seems to correlate well with atheroma [7] as does apo-B and LDL, but also to have a wider role in thrombogenesis. It consists of an LDL-like particle with apo-B100 enclosing a lipid core but with an additional side chain of a highly glycosylated protein, apolipoprotein (a) (apo(a)). The latter is linked to apo-B by a disulphide bridge (Fig. 57.38). Apolipoprotein (a) has homology with the fibrinolytic system protein precursor, plasminogen, in the presence of kringle structures; one of which is increased in apo(a). The molecular weight of Lp(a) varies due to the variation in the number of kringle repeats (usually four) within apo(a). The gene locus for apo(a) is encoded on chromosome 6 near that for plasminogen. The concentration of circulating Lp(a) varies in different populations largely due to differences in expression of the apo(a) gene and apo(a) isoforms [14]. The latter vary inversely with plasma Lp(a), and small, fast-moving isoforms are associated with higher Lp(a) concentrations. Circulating Lp(a) particles are regulated more by synthesis than by catabolism, which appears to occur only in the liver.

Lipoprotein (a) has a role in atherogenesis because of its LDL (apo-B) content, and because it does not bind as well as LDL to receptors—it therefore becomes oxidized (ox-Lp(a)) and can be taken up by the scavenger macrophage pathway. It also has a role in thrombogenesis by virtue of the homology with plasminogen. In the apo(a) structure, specific areas are identified that bind with the vascular matrix and cells, inhibit fibrinolysis and promote smooth muscle activity [13]. Family studies indicate that Lp(a) may also be affected by inherited factors independent of apo-B (FH) and apo(a) gene size. There is still controversy as to its precise importance in predicting CAD risk, but increased Lp(a) concentrations occur with increase in acute phase proteins, in renal disease. High Lp(a) concentrations have also been found in CHD, early myocardial infarction, stroke and peripheral vascular disease.

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Xanthoma

Xanthomas are a common presentation of disorders of lipid metabolism usually associated with abnormalities of cholesterol metabolism, for example FH (type IIa), combined hyperlipidaemias (both combined hypercholesterolaemia type IIb, III) and combined hypertriglyceridaemia (type V); and may be associated with increased risk of arteriosclerotic vascular disease (type II) and occasionally with pancreatitis (type V). Discrete xanthomas affecting tendons are typical of FH, whereas eruptive xanthomas affecting the skin are typical of type V. However, it is the skin manifestations that will bring the patient to the

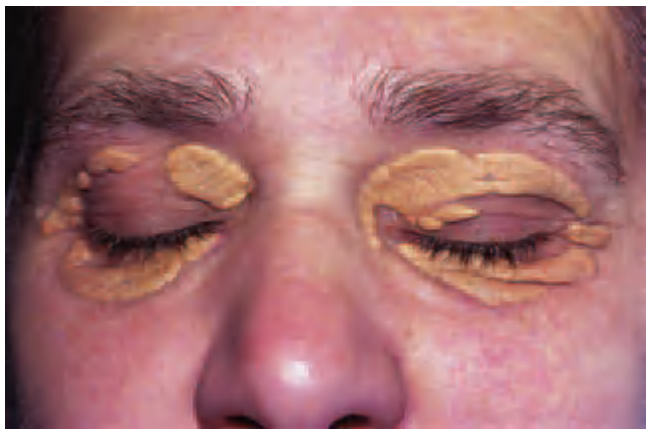

Fig. 57.39 Extensive xanthelasmas palpebrarum. (Courtesy of Addenbrooke's Hospital, Cambridge, UK.)

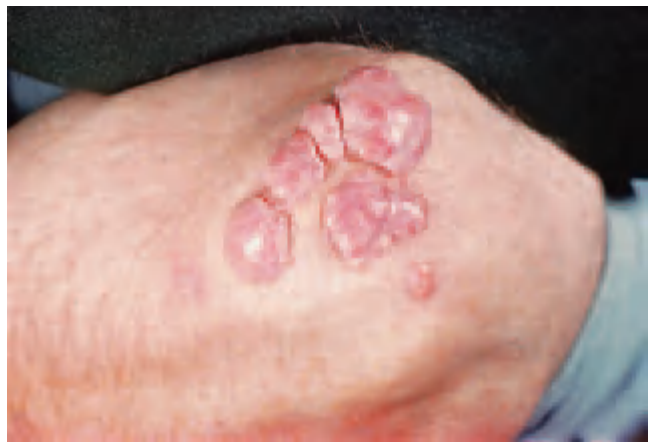

Fig. 57.40 Tuberous xanthomas. (Courtesy of Addenbrooke's Hospital, Cambridge, UK.)

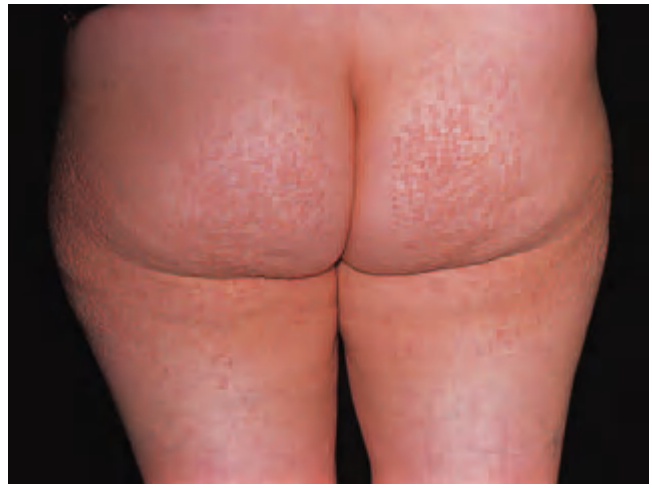

Fig. 57.41 Eruptive xanthomas. (Courtesy of Addenbrooke's Hospital, Cambridge, UK.)

dermatology clinic and therefore these are dealt with separately [1–3].

Xanthelasma palpebrarum. These usually appear as bilateral and symmetrical, soft, velvety papules and plaques arranged around the eyelids. The upper eyelid and the region around the medial canthus are the most common sites of involvement, although in severe hypercholesterolaemic conditions (e.g. FH) they may occur circumferentially or on the outer aspects of the eye (Fig. 57.39). They may represent a localized cutaneous phenomenon, but they may more usually signify a systemic hyperlipidaemia and are then associated with elevation of LDL as in pure hypercholesterolaemia (such as FH) or type III hyperlipoproteinaemia. They may also be associated with mixed hyperlipidaemia (type IIb or IV) or as an isolated finding in certain apo-E phenotypes, particularly E2/E2 [3], or in chronic biliary obstruction (e.g. primary biliary cirrhosis) [4,5]. Generalized plane xanthomas may be seen in normolipidaemic patients.

Tuberous xanthoma (Fig. 57.40). These lesions vary in size and shape, from small papules 0.5 cm in diameter to lobulated tumours 2.5 cm or more across. These are firm and yellow or orange in colour, often with an erythematous halo. Usually they are painless but larger lesions may be tender on direct pressure. They develop slowly and are seen on pressure areas, such as the extensor aspect of the limbs, particularly over knees, elbows and buttocks. These xanthomas are commonly seen with hypercholesterolaemia and increased levels of LDL (e.g. FH [3,4]) and familial dysbetalipoproteinaemia (type III) as well as in secondary hyperlipidaemias (e.g. those associated with hypothyroidism, chronic biliary disease, and very rarely in association with a monoclonal gammopathy [6,7]).

Tendinous xanthoma. These appear as slowly enlarging subcutaneous nodules attached to tendons, ligaments, fascia and periosteum. They are symptomless and the overlying skin appears normal. Although any tendon may be involved, most frequently the xanthomas are on the extensor tendons of hands and feet and the Achilles tendon. The latter often present to the orthopaedic surgeon, and may even be diagnosed on ultrasound as a fatty nodule. The subperiosteal lesions may involve bony prominences such as the malleoli and elbows but do not calcify. They are found in association with severe hypercholesterolaemia and elevated levels of LDL, typical of pure hypercholesterolaemia and FH (type II). Tendinous xanthomas may also be found but less frequently in secondary hypercholesterolaemia associated with prolonged cholestasis.

Eruptive xanthoma (Fig. 57.41). Eruptive xanthomas may occur at any site but are most commonly seen over the buttocks, shoulders and extensor surfaces of extremities.

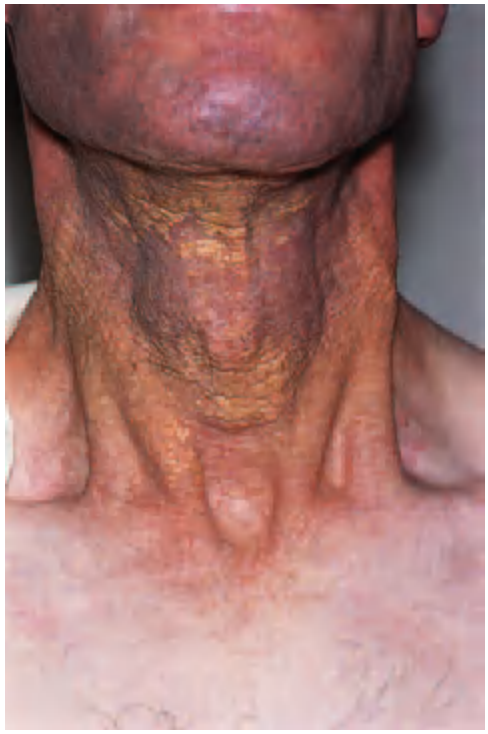

Fig. 57.42 Plane xanthomatosis. (Courtesy of Addenbrooke's Hospital, Cambridge, UK.)

The oral mucosa and face are very occasionally affected. They appear as pinhead or larger yellow papules with a reddish base; they may be fleeting in nature and occur in crops. They may cause pruritus. Occasionally, these papules may coalesce and overlie a tuberous xanthoma and are then called *tuberoeruptive xanthomas*.

These xanthomas are associated with pure or mixed hypertriglyceridaemia and a high concentration of VLDL or CMs (i.e. pure or combined hypertriglyceridaemia) in the modern classification (and Fredrickson types I, V and, less commonly, type IV hyperlipoproteinaemias (Table 57.9)). They may also be seen in secondary hyperlipidaemia, usually in association with diabetes [8].

Plane xanthoma (Fig. 57.42) [6,7,9,10]. Plane xanthomas appear as yellow or orange macules or slightly palpable plaques. They involve almost any site, but when plane xanthomas occur in palmar creases (xanthoma palmaris) they are pathognomonic of type III/familial dysbetalipoproteinaemia. Plane xanthomas may also be seen in the secondary hyperlipidaemias associated with conditions of chronic biliary obstruction or prolonged cholestasis such as primary biliary cirrhosis and, rarely, monoclonal gammopathy.

Generalized plane xanthoma. These plane xanthomas cover large areas of the face, neck and thorax, and also involve flexures and palms. Many patients with these diffuse plane xanthomas develop a monoclonal gammopathy [6,7] associated with either myeloma (with a type III pattern [3]), macroglobulinaemia or lymphoma, and even with normal plasma lipid levels. The latter are associated with a particular apo-E phenotype and are not associated with an increased risk of vascular disease [5]. Lipid metabolism may be disturbed, and approximately 50% of patients with IgA myeloma have hypolipidaemia with low plasma total and LDL cholesterol concentrations. Less commonly, endogenous hypertriglyceridaemia may be present and the lipoproteins may be in the density range of VLDL, LDL [9] or intermediate forms and CMs. It is not known how these monoclonal antibodies produce the lipid abnormalities, but at least some combine with the lipoproteins or interfere with receptor-mediated catabolism [7,10–12].

Pathology. Ultrasound of xanthomas indicates the presence of lipid, and histology of skin biopsies may show intracellular sudanophilic material in abnormal quantities, particularly around capillaries. Differential staining of this material often shows a characteristic reaction for cholesterol and polariscopic examination of frozen sections may show doubly refractile (anisotropic) droplets.

Treatment. Most xanthomas respond well to dietary control and/or to appropriate medical treatment for the underlying condition with lowering of LDL concentrations (details are given in the following sections). However, they may need to be removed surgically. Xanthomas are likely to recur unless dietary and other cholesterol-lowering measures are continued. If it is an isolated finding, xanthelasma palpebrarum may be destroyed with cautery, trichloroacetic acid or can be excised, but they are likely to recur over a period of years. Probucol, a recognized antioxidant, is associated with specific regression of xanthelasma [13,14], but this has recently been withdrawn from the market. Other antioxidants such as vitamin E may be effective in the long term.

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Xanthomas in lymphoedema [1–4]

Xanthomas in association with lymphoedema are reported. Lymph stasis with intraluminar and periluminar retention of lipoproteins and ingestion by local histiocytes seems a likely explanation. Scattered, firm, yellowish papules are seen within lymphoedematous areas. Chylous exudation may be spontaneous or follow abrasion. Histologically, the epidermis shows irregular acanthosis and hyperkeratosis. Intralymphatic and perilymphatic collections of foam cells are characteristic. Alleviation of the lymph stasis by surgery or pressure bandaging is sometimes effective.

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Xanthoma cells in inflammatory and neoplastic disease

Cholesterol deposition is not infrequent in inflammatory disorders, where it appears to result from the liberation of lipids in the tissues. These lipids are ingested by histiocytes producing the characteristic foam cell seen in histological sections. In some instances, there may be an abnormal production of cholesterol *in situ*.

Diffuse xanthoma may appear in previously inflamed skin [1,2]. Similar secondary xanthomatous infiltration is also seen in certain localized inflammatory and neoplastic disorders. The diseases in which xanthoma cells may be encountered are listed below.

1 Inflammatory disease:
  (a) histiocytoma;
  (b) juvenile xanthogranuloma.
2 Neoplastic disease:
  (a) multicentric reticulohistiocytosis;
  (b) eosinophilic granulomas [3];
  (c) Letterer–Siwe disease, Hand–Schuller–Christian disease;
  (d) mycosis fungoides.

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Genetic primary hyperlipidaemia

There is no doubt that CAD is strongly associated with high concentrations of cholesterol and/or TG, although the circulating levels and incidence of CAD vary from country to country, with higher CAD incidence in northern Europe and lowest in Japan and rural Africa. An inverse relationship exists between HDL and CAD. Most causes of a high cholesterol and/or TG are due to a number of interrelating factors (risk factors) but some are due to a combination or solely to individual susceptibility involving either one or a number of genes [1–4]. Although monogenic hyperlipidaemias are rare in the general population as compared with polygenic hyperlipidaemias, they do enable an application of 'Garrod's legacy', to allow a useful classification on the basis of a well-defined clinical disease, which is helpful in deciding treatment. Large clinical trials (Scandinavian 4S Study [5], West of Scotland Coronary Prevention Study [WOSCOPS] [6,7] and many other studies [8]) have clearly established that reduction of cholesterol levels is effective in both primary and secondary prevention of ischaemic heart disease. Similar studies have claimed secondary prevention with the lowering of combined or pure hypertriglyceridaemia [9].

Evidence of the hereditary basis of these diseases is often presumptive, and detailed investigation of first-degree relatives can reveal partial metabolic defects suggestive of recessive inheritance [4].

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Primary hypercholesterolaemia

Familial hypercholesterolaemia (FH) (MIM #143890) [1]

SYN. ESSENTIAL FAMILIAL HYPERCHOLESTEROLAEMIA

This is a common autosomal dominant disorder affecting approximately one per 500 of the European and American populations. It is characterized by an increase in the levels of LDL (and apo-B), and is the commonest cause of tendon xanthomas and xanthelasma.

Aetiology. The primary defect is a reduction in LDL catabolism because of an abnormality in the LDL receptor [2], leading to increased plasma LDL concentrations. The molecular defect was first described by Goldstein and Brown [3]. The gene for the LDL receptor is found on chromosome 19. Heterozygotes express half the number of LDL receptors, and homozygotes have between 0% and 25% of receptors found in normal individuals. Cultured fibroblasts have shown four mutant alleles at the LDL receptor locus [4]. The most common of these results in a non-functional gene product, and therefore reduces LDL receptor expression; the next most frequent results in a defective gene product that interferes with transport and binding of LDL; and the rarest produces a receptor that binds LDL normally but fails to transport cholesterol into the cells by preventing internalization after LDL binding, because of a mutation affecting the cytoplasmic domain of the receptor [3,4]. To date, some 200 or so mutations have been described. More recently, 3% of patients presenting with features of FH have a mutated apo-B due to a glutamine substitution for arginine at a position that affects LDL binding. This is known as *familial defective apo-B* [1,5], which presents in childhood with hypercholesterolaemia; tendon xanthomas appear in the 30s; and by the age of 80 years all heterozygotes have xanthomas.

In FH, homozygotes have two of these mutant alleles and therefore are unable to clear LDL from the plasma. They present in childhood with cutaneous xanthelasma and xanthomas. Heterozygotes have one normal allele and can remove about half of the plasma LDL.

Levels of plasma cholesterol correlate directly with the severity of LDL receptor deficit [1,6]. Polygenic hypercholesterolaemia is the commonest form. FH accounts for less than 3% of males dying from CAD under the age of 60 years [7].

The defect in *common polygenic hypercholesterolaemia* is usually due to overproduction of VLDL by the liver. There is rapid conversion to LDL, which initiates up-regulation of the LDL receptor, and an increase in dense LDL; the latter results in non-receptor-mediated uptake via macrophages to produce foam cells and an increase in atheroma. This is most commonly caused by excessive dietary intake and obesity.

Clinical features. Heterozygotes usually present in the third to fourth decades with premature onset of CAD, at least 20 years earlier in FH than the normal population. This can be avoided by cholesterol screening of children/siblings of an affected individual. Tendon xanthomas are a very common hallmark of the disease, and incidence increases with the age of the patient. The very rare homozygous condition usually presents in the first year of life with cutaneous planar or tuberose xanthomas, often at the site of trauma and on the palms of the hands. Tendinous and tuberous xanthomas, xanthelasma and corneal arcus are all commonly present [8]. CAD may become manifest before the age of 20 years due to atheromatous narrowing of the aortic root and coronary ostia. In addition, cholesterol deposits may give rise to supravalvular aortic stenosis.

Investigation. Plasma total cholesterol is elevated with a normal TG level. Lipoprotein ultracentrifugation shows a type IIA pattern with increased LDL cholesterol (increased apo-B) in the top five percentile cut-off for the control population, taking into account age and sex variations. Most patients with type IIA (pure hypercholesterolaemia), however, do not have FH but common polygenic hypercholesterolaemia (see above). The presence of tendinous xanthomas and family members with elevated plasma total LDL cholesterol help to establish the diagnosis. A few patients with FH have a combined but predominant cholesterol (type IIB pattern) with mildly raised TG levels (see also familial combined hypercholesterolaemia [FCH]). Again the presence of tendon xanthomas and family studies should help to separate these patients from 'multiple-type' hyperlipidaemia. A few centres can assay LDL apo-B receptors directly in both heterozygous and homozygous patients. DNA analysis is unlikely to be helpful on a routine basis since so many mutations have been described.

Familial combined hypercholesterolaemia (MIM #144250)

This was originally termed type IIb in the Fredrickson classification (Table 57.9) and initially described by Goldstein *et al*. [1]. It is a common phenotype associated with a combined hyperlipidaemia but predominant hypercholesterolaemia (increased cholesterol and slightly

increased TGs). However, the diagnosis cannot be made in a subject whose family members are not available, since the term FCH implies multiple-type hyperlipidaemia occurring in one family. Family studies show 50% of relatives of an affected individual to have either hypercholesterolaemia (type IIa), hypertriglyceridaemia (type IV or V) or both abnormalities (type IIb) [1,9] It is probably inherited as an autosomal recessive trait in which patients show variable increased plasma cholesterol, TGs and lipoprotein patterns. Thus individuals within a family could be type II, IV or even V, or a type IV patient when treated could appear to have a type II lipid profile. There are also non-genetic and polygenic causes of these lipid profiles; the latter exacerbated by environmental factors and lifestyle.

Metabolic abnormalities in these patients can allow a subclassification. They may have postprandial hyperlipidaemia, most have an increase in apo-B100, and genetic lipoprotein lipase deficiency can be demonstrated in some families. The metabolic and genetic basis of FCH is not entirely understood, and family studies of individuals presenting with a high cholesterol or high TG picture are important. Fasting hypertriglyceridaemia is frequently seen in an FCH subject with delayed clearance of the apo-B particle (atherogenic) and delay in postprandial clearance of CMs and CM remnants, also found to be associated with insulin resistance. The latter is termed Reaven's syndrome and is associated with a fasting hyperinsulinaemia, increased body mass index, systolic hypertension and dyslipidaemia (reduced HDL, increased fasting plasma VLDL and TG), with impaired free fatty acid metabolism. Increased plasma apo-B levels frequently coincide with small, dense LDL particles (subclass pattern B (see p. 57.63)), which has an increased risk of myocardial infarction. No clear pathogenic association has been established with the apo-B gene, lipoprotein lipase gene, apo-AI -CII -CIV gene cluster, or with the apo-E gene on chromosome 19 [10,11].

Aetiology. In FCH, increased cholesterol and/or TG reflect increases in LDL and/or VLDL particles due to increased production (mainly VLDL), decreased catabolism or a combination of these. It has been suggested that some heterozygotes could have deficiency of lipoprotein lipase or of the cofactor apo-C II (therefore causing reduction in VLDL lipolysis), and that FHC is a dominant disorder with onset in the third decade but the precise inheritance is unclear [10,11].

Clinical features. These will depend on the predominant lipid; thus, hypercholesterolaemia will produce a picture similar to FH and hypertriglyceridaemia will be similar to the pure familial hypertriglyceridaemias. Xanthelasma and xanthomas, for example, may be much less prominent and only evident in patients over the age of 30–40 years.

The diagnosis is, however, of great importance, since mixed hyperlipidaemia is the most commonly found lipid abnormality in survivors of myocardial infarction. Premature death and non-fatal myocardial infarction are also prevalent in FCH. Once the diagnosis is made within a family, an individual diagnosis can be made from a high TG, high LDL and low HDL level, or a combination of these lipoproteins.

Investigation. FCH is associated with an increase in TG and/or LDL/IDL within many family members.

Treatment of pure or combined hypercholesterolaemia [12–21]

In any patient with pure (familial, type IIa) or combined predominant hypercholesterolaemia (type IIb) the aim of treatment is to reduce the level of LDL to within the normal range. In all patients, attention should be paid to the diet, which should be low in saturated fats and high in poly- and mono-unsaturated fats [12]. Treatment of homozygous and heterozygous FH involves drug therapy, and starts in childhood. Cholestyramine or colestipol, non-absorbable anion exchange resins, may be most suitable in children, in young women of child-bearing age, during pregnancy and while breast feeding, and may lower the cholesterol by up to 25% [13,14]. Compliance is a problem with all resins. This medication has in all other patients been superseded by the now well-established HMG-CoA reductase inhibitors or 'statins' (e.g. lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin or rosuvastatin), which have greatly improved management. Results of large double-blind trials have shown the safety, efficacy and cost-effectiveness of the statins in lowering cholesterol [12–19]. The statins may be used alone or in conjunction with other agents such as cholestyramine [1,15] and more rarely fibrates. The net result is a dose-dependent reduction in cholesterol, but, more importantly, even when the cholesterol has normalized there is an overall reduction in CAD, mortality and morbidity with continued statin use [13–19]. It is recognized that there are many other beneficial effects (pleiotrophic) of statins on the microcosm of the arterial wall in reducing smooth muscle migration, fibrosis, increasing collagen formation and effects on endothelin-1 and nitric oxide [22]. These drugs work best in heterozygotes, who have a partial LDL-receptor deficiency. Homozygotes are less responsive to standard therapy.

For homozygotes, plasma exchange or LDL apheresis [19] is helpful in homozygous FH or familial defective apo-B, but treatment needs to be repeated at weekly intervals. Portocaval shunt has been used in cholesterol lowering therapy but liver transplantation in carefully selected homozygotes may be a more effective way to correct the hepatic deficiency of LDL receptors and normalize choles-

terol levels [19] until gene therapy becomes feasible. In the past, ileal bypass was thought to be helpful in severely affected patients, but has been superseded by the advent of the statins [21].

Treatment of FCH is the same as for pure or familial hypercholesterolaemia, and where TG is equally elevated, treatment will be as for familial hypertriglyceridaemia with fibrates (see p. 57.73).

Prognosis

This depends on the severity of the defect. Untreated homozygotes (FH) often die from heart disease by the age of 30 years, while many untreated heterozygotes (FH) have had a myocardial infarction by the age of 55 years.

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Mixed hyperlipoproteinaemia

Familial dysbetalipoproteinaemia (MIM *107741)

SYN. FAMILIAL TYPE III HYPERLIPIDAEMIA; REMNANT PARTICLE DISEASE

This is a rare inherited disorder in which plasma cholesterol and TG are elevated (often to a similar degree) because of increased remnants of CMs and IDL (β-VLDL), which fail to be cleared by hepatic remnant (or apo-E) receptors [1].

Aetiology. The defect involves a polymorphic genetic locus for apo-E (apo-E3) [2]. Particles containing apo-E2 show no binding to the apo-B/E receptor. Most patients are homozygous for this form of apo-E2 but some are heterozygous with apo-E2/E3 or apo-E3/E4 phenotypes [1,3]. Patients with complete deficiency of apo-E4 have also been described. The presence of an E4/E4 phenotype has now been associated with other diseases (such as Alzheimer's disease). Apo-E3, a component of remnant lipoprotein derived from CMs and VLDL, is essential for uptake of these CM 'remnants' by the liver. All patients with this disorder are homozygotes (1% of the population for Ed allele, where d = deficient). Heterozygotes are common in the population (apo-E2/E2 phenotype, one per 100) but most individuals can compensate in some way for the abnormal apo-E, and it is only those who cannot do so that express the disease. Expression of the disease therefore depends on other genetic or metabolic factors, such as the inheritance of multiple type hyperlipidaemia, FH, insulin-dependent diabetes mellitus, hypothyroidism and obesity [1,4]. It rarely presents in premenopausal females or in childhood.

Clinical features [5]. Onset of symptoms is delayed to the second or third decade, although presentation may be later in women because of the effect of oestrogens on hepatic uptake of remnant particles. Xanthomas are a

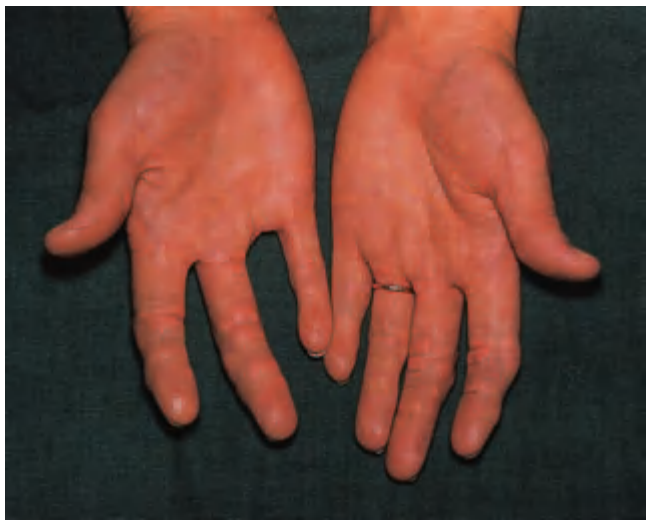

Fig. 57.43 Xanthomatosis and yellow palmar creases. (Courtesy of Addenbrooke's Hospital, Cambridge, UK.)

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common presentation, and patients may have tuberous, tuberoeruptive or plane xanthomas involving the palmar and digital creases (xanthoma palmaris) (Fig. 57.43) [6], as well as typical eruptive lesions over elbows, knees and wrists often surrounded by satellite lesions. Xanthelasma may also occur. Premature severe coronary, cerebral and peripheral vascular disease occurs and patients may in addition have hypothyroidism, central obesity or diabetes [7].

Investigation. Plasma cholesterol and TG levels are elevated to almost the same degree (i.e. cholesterol greater than 7.0 mmol/L and TG greater than 4.0 mmol/L). Lipoprotein electrophoresis shows type III pattern with a broad pre-β-band, and the IDL fraction obtained by ultracentrifugation shows a high cholesterol content. These changes are not diagnostic. The demonstration of the Ed allele on isoelectric focusing is diagnostic for familial dysbetalipoproteinaemia [2,8]. The diagnosis should also be confirmed by apo-E phenotyping, particularly of E2. Genotype testing is now available in some centres.

Treatment. Appropriate treatment will resolve the xanthoma lesions, which eventually disappear. Treatment of any other metabolic disease, such as obesity, diabetes mellitus or hypothyroidism, will contribute to lowering of the lipid levels. Most patients will respond to therapy with fibric acid derivatives (such as bezafibrate or gemfibrozil), either alone or in combination with nicotinic acid. Clofibrate is no longer used in the management of this disorder. HMG-CoA reductase inhibitors may be useful, particularly for double homozygotes (type III and FH) [1,7,9].

Primary hypertriglyceridaemias

Under this title will be considered patients presenting with a predominant increase in TG due to increases in fasting plasma CMs or VLDL, or both (type I, IV or V phenotypes).

Familial hypertriglyceridaemia (MIM *145750) [1,2]

SYN. ENDOGENOUS HYPERTRIGLYCERIDAEMIA

This category is usually subdivided according to whether the phenotype of individuals is type IV or V.

Familial pure hypertriglyceridaemia (type IV). This is a common autosomal dominant disorder with delayed penetrance, which gives rise to moderate hypertriglyceridaemia due to increased levels of VLDL and normal levels of LDL [3]. The frequency of this disorder in the population is of the order of 0.2–0.3% [3] and it is expressed in childhood [3]. The underlying mechanism for VLDL TG overproduction is not certain, but VLDL TG synthesis is increased more than VLDL apo-B synthesis and the catabolic rate of both VLDL components is decreased [4]. The pathogenesis of the condition is not clearly understood. Obesity, diabetes mellitus and alcohol are commonly exacerbating causes in the non-familial form but are not a part of familial hypertriglyceridaemia. They may exacerbate the condition by increasing VLDL production [1] and by insulin resistance [5].

Clinical features [1,6]. Typically, patients are obese, with glucose intolerance, hypertension and hyperuricaemia [6,7]. Severe exacerbations can be precipitated either by ingestion of oestrogen-containing oral contraceptives [6],

poorly controlled diabetes [6,7] or excessive alcohol intake [8], and under these circumstances CMs appear in the plasma and the patient develops a 'mixed hyperlipidaemia'. During such an exacerbation, patients occasionally develop eruptive xanthomas over buttocks or arms, but xanthomas are not normally a feature of the condition. The increase in TGs increases the risk of any associated increase in cholesterol, and, if the clinician assesses the risk of CAD to be high, treatment for lowering the TG should be started [9,10].

Investigation. A moderate increase in plasma TG (between 2.0 and 10 mmol/L) with normal cholesterol and type IV pattern ultracentrifugation should suggest the diagnosis, although these findings are found in other genetic and acquired hyperlipidaemias [1,11].

Occasionally patients may have severe triglyceridaemia with increased levels of CMs and VLDL [5,10]. Plasma LDL levels may appear within the normal range as are the LDL-apo B levels but TG levels in excess of 5.0 mmol/L interfere with LDL measurements. There are no other specific tests for familial hypertriglyceridaemia but study of the adult members of a family may show that 50% of them have increased TGs.

Treatment. Adherence to a modified low fat diet to achieve ideal body weight is essential, and the patient's weight, diabetes mellitus and thyroid disease (if present) should all be treated appropriately. Sucrose, alcohol and oral contraceptives should be avoided, and the diet should be low in total and saturated fats. If these dietary measures do not succeed, drug therapy with fibrates (bezafibrate, fenofibrate or gemfibrosil) or more rarely nicotinic acid can be effective in controlling this hyperlipidaemia. Use of a fish-oil preparation (ω-3 fatty acid), such as Maxepa® or Omacor®, can result in a rise of LDL and should be avoided [12].

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Familial type V hyperlipidaemia (MIM 238400) [1–3]

Within some families there are individuals who in late adult life show mixed hyperlipidaemia. This is a disorder with features of both type IV and type I hyperlipoproteinaemias, due to increases in VLDL and CMs and where serum TG are in excess of 11 mmol/L. The condition is rare, approximately one in 1000 adults. Severe hypertriglyceridaemia occurs when CMs and VLDL compete for the same lipoprotein lipase and when there is an increase in hepatic VLDL synthesis. This can be genetic or exacerbated by alcohol, obesity, diabetes or oestrogen administration. Reduced VLDL clearance and reduced lipoprotein lipase activity, as in diabetes, will increase fasting plasma TG and absorbed CMs will be also cleared from the blood more slowly after a meal.

Clinical features. These patients present with eruptive xanthomas, abdominal pain and occasionally acute pancreatitis associated with a marked or severe increase in TG, even in the fasted state (TGs in excess of 11 mmol/L). Patients may often have other clinical features, such as hepatosplenomegaly due to fatty change or fatty infiltration of the liver; lipaemia retinalis (a white appearance of retinal arteries and veins) may also occur and is characteristic of the condition. Pseudohyponatraemia can occur in association with increased TGs. There is a risk of atheroma due to increased dense LDL secondary to increased VLDL (insulin resistance), which predisposes to CAD and peripheral vascular disease.

Investigation. Fasting TG concentrations will be excess of 11 mmol/L and the serum will appear cloudy due to the presence of CMs even when fasting.

Treatment. Treatment is essentially towards weight reduction by reducing carbohydrate and total fat intake but may be difficult because a low fat diet (less than 50 g/day) can increase VLDL synthesis. Use of medium chain TGs can be useful, as these are not incorporated into CMs. Use of heparin to stimulate lipoprotein lipase activity may be useful in the management of patients with acute pancreatitis due to increase in TGs. Gestational pancreatitis should be managed with intravenous carbohydrates and fat restriction to 10 g/day [3]. Lipolysis can be increased by oxandrolone in males and norethisterone in females,

and by nicotinic acid or by fish oils containing ω-3 fatty acids (Maxepa® or Omacor®) to reduce TG synthesis.

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Familial lipoprotein lipase deficiency (MIM *238600) [1–5]

SYN. FAMILIAL TYPE I HYPERLIPOPROTEINAEMIA; FAT-INDUCED LIPOPROTEINAEMIA; BURGER–GRUTZ TYPE

This is a rare autosomal recessive disorder, which results in deficiency of extrahepatic lipoprotein lipase, the rate-limiting enzyme for hydrolysis and removal of CMs and VLDL TG from circulation, which results in accumulation of CMs in the plasma. Lipolysis initiates the cascade of conversion of lipoprotein particles, which results in reduction in circulating LDL and remodelling of HDL. Lipoprotein lipase facilitates binding of non-HDL lipoprotein to extracellular matrix and uptake of the lipoprotein by cell-specific receptors through mechanisms independent of lipolysis.

Clinical features. This condition presents in childhood with recurrent attacks of abdominal pain or acute relapsing pancreatitis and eruptive/tuboeruptive xanthomas (often occurring over the buttocks). Hepatosplenomegaly and retinopathy (lipaemia retinalis) are frequent findings. More rarely neurological abnormalities have been described: memory loss, dementia and peripheral neuropathy. The major threat to health in these patients appears to be acute pancreatitis.

Investigation. Lipaemic plasma in young individuals after a 12-h fast should suggest the diagnosis, and if the sample is left in the refrigerator (at 4°C) overnight a creamy layer collects at the top of the tube, while the infranatant remains relatively clear. The plasma TG level is markedly elevated in the region of 50–100 mmol/L [5] with plasma TG to cholesterol mass ratio often exceeding 9 : 1. VLDL levels are normal or decreased, and LDL and HDL levels are markedly reduced. As in other hypertriglyceridaemias, some blood tests may be inaccurate (pseudohyponatraemia, low plasma amylase and increased aspartate/alanine transaminases). Measurement of the lipoprotein lipase level [6] or apo-CII may occasionally be necessary to establish the diagnosis [6].

Treatment. Restriction of dietary fat to 20–30 g/day by decreasing the intake of long-chain TGs usually results in loss of the symptoms and signs of the hyperlipidaemia. Medium-chain TGs are not normally incorporated in CMs and therefore may be given in unrestricted amounts. In addition to dietary measures, use of fibrates, fish oils or nicotinic acid/acipimox can further lower TG concentrations. The risk of acute pancreatitis is significantly diminished if plasma TG concentrations are kept below 10 mmol/L.

Prognosis. Until recently, the risk of acute pancreatitis was thought to be most important, and early reports suggested that lipoprotein lipase deficiency did not predispose patients to accelerated atherosclerosis. The concept that atherosclerosis was not a feature of the genetic disorder was accepted because CMs were considered to be too large to penetrate the endothelial barrier. A recent case report has thrown this into doubt [3]. In addition, a low level of circulating LDL can be apparent because of difficulty in measuring cholesterol in the face of increased CMs.

Familial apo-CII deficiency (MIM *207750) [1,7–9]

This is a very rare autosomal recessive disease [7,8], which in the homozygous state (due to recessively inherited mutant genes) results in an absence of normal apo-CII [7], an essential cofactor for lipoprotein lipase. As a consequence of this defect, there is a functional lipoprotein lipase deficiency, since lipoprotein lipase cannot hydrolyse CMs or VLDL in the absence of normal apo-CII. This defect in lipolysis causes a rise in both CMs and VLDL.

Clinical features. These might be expected to be the same as for lipoprotein lipase deficiency, but patients usually present in adult life and do not show hepatosplenomegaly or eruptive xanthomas. Abdominal pain due to pancreatitis, however, remains a major threat to health [9].

Investigation. Plasma TG levels are markedly elevated in the range 17–107 mmol/L. By strict criteria, the lipoprotein ultracentrifugation pattern is type V, but many patients have an intermediate pattern between types I and V [10]. It also manifests in decreased post-heparin lipase activity, which normalizes with addition of apo-CII [10]. Deficiency of apo-CII can be measured by isoelectric focusing of de-lipidated VLDL.

Treatment. This is either by fat restriction, as in lipoprotein lipase deficient patients, or by replacement of the apo-CII by transfusion with normal plasma [10]. Synthetic apo-CII may become more widely available for treatment [1,7,11].

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Sporadic hypertriglyceridaemia [1]

SYN. COMMON 'POLYGENIC' HYPERTRIGLYCERIDAEMIA

This heterogeneous group of patients have elevated plasma TG with or without increased levels of CMs. They differ from those with familial hypertriglyceridaemia and familial multiple type hyperlipidaemia in that their first-degree relatives are unaffected [2].

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Lipid storage diseases

Two very rare lipid storage diseases are important to dermatologists in spite of their rarity, because these disorders characteristically present with xanthomas. Tangier disease is included but the skin involvement is usually minor.

Cerebrotendinous xanthomatosis (MIM #213700) [1,2]

SYN. CHOLESTANOLOSIS

This rare autosomal recessive condition is characterized by widespread tissue deposition of cholestanol and cholesterol, resulting in progressive neurological defects and premature death from arteriosclerosis [3,4].

Aetiology. The primary biochemical defect is due to a deficiency of hepatic mitochondrial enzymes catalysing the hydroxylation of cholestanol (27-hydroxylase deficiency). This deficiency affects bile acid synthesis by reducing feedback inhibition on cholesterol 7α-hydroxylase (a rate-limiting enzyme). This allows synthesis and accumulation of cholestanol [5]. The resulting deficiency of primary bile acids (chenodeoxycholic and cholic acids) probably leads to increased cholesterol and cholestanol synthesis by the liver [6,7].

Clinical features. Patients present in childhood or early adult life and sterol deposits are found throughout the body. Tendon xanthomas, especially in the Achilles tendon, are an early characteristic of the disorder and clinically are similar to those seen in FH. Xanthelasma and tuberous xanthomas may also be present. Central nervous system abnormalities occur early in childhood, and mental retardation and progressive spasticity develop. Patients often have a myopathic facies with open mouth and protruberant tongue. Neuropathological studies suggest that the enzyme defect leads to an accumulation of brain metabolites that are neurotoxic, causing axonopathy and non-specific lipid deposition in the injured tracts [8]. Thus neurological signs develop from extensive myelin destruction within the cerebellum, brainstem and peripheral neuropathy. Patients also develop juvenile cataracts (as early as 5 years old) due to deposition of cholestanol and cholesterol in the lens. Osteoporosis and bone fractures are common. They are also at risk from premature arteriovascular disease [1,4].

Investigation. Key biochemical findings are that cholestanol levels are diagonostically elevated in the plasma, tissues and bile. Xanthomas occur in association with low or normal plasma cholesterol levels. Also because of defective bile acid synthesis, reduced levels of cholic and chenodeoxycholic acids are found in bile.

Treatment. This is based on the concept that plasma cholestanol increases because of a block in bile acid synthesis. Use of chenodeoxycholic acid/ursodeoxycholic acid may be useful in lowering plasma cholestanol by suppression of endogenous bile acid synthesis. Correction of the bile acid deficiency with chenodeoxycholic acid produces a reduction in plasma cholestanol levels and improvement in the neurological signs [1]. This is a

life-long treatment. HMG-CoA reductase inhibitors have also been tried with some success in reducing cholesterol and cholestanol concentrations but with no deterrent effect on disease progression [9–11].

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Sitosterol storage disease (sitosterolaemia) and xanthomatosis (MIM #210250)

This very rare condition inherited as an autosomal recessive trait is characterized by xanthomas in childhood or early adult life with tendon and subcutaneous xanthomas due to accumulation of plant sterols within the tissues [1–3].

Aetiology. The biochemical defect has not been clearly established but it has been suggested that absorption of plant sterols, β-sitosterol, campestanol and stigmasterol are increased. These are all related to cholesterol and may be converted to bile acids. However in homozygotes, intestinal absorption of sitosterol is increased two- to threefold over controls, and cholesterol synthesis was reduced due to markedly reduced HMG CoA reductase activity. Furthermore LDL-receptor expression was increased in the sitosterolaemic hepatocyte resulting in increased LDL uptake.

Clinical features. Tendinous xanthomas, particularly over the Achilles tendon and extensor tendons of the hand, have been present in all cases reported to date, and usually appear in early childhood. Less commonly, tuberous xanthomas and xanthelasma may be present. Haemolysis due to abnormal spherocytes as well as abnormal platelets are associated with an enlarged spleen. Arthritis and arthropathy also occur. Premature arteriovascular disease affecting coronary arteries and aorta has been noted particularly in young males.

Investigation. The diagnosis is made by the demonstration of increased amounts of these plant sterols by gas–liquid chromatography of plasma or xanthomas. These patients also have hypercholesterolaemia. Heterozygotes are clinically and biochemically normal although some may have slightly increased plasma sitosterol concentrations.

Treatment. This usually involves exclusion of plant and shellfish sterols from the diet and this, combined with bile acid sequestering agents (cholestyramine or colestipol) to reduce absorption from the gastrointestinal tract, results in reduction of sitosterolaemia and improvement in the clinical signs. Use of statins to reduce cholesterol levels is not effective in treating these patients. In fact a diagnosis of sitosterolaemia should be considered and excluded in patients with hypercholesterolaemia unresponsive to statins.

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Tangier disease (MIM #205400)

SYN. FAMILIAL HDL DEFICIENCY; B-LIPOPROTEIN DEFICIENCY DISEASE

This is a very rare autosomal recessive disorder characterized by a deficiency or absence of normal HDL in the plasma [1–4].

Aetiology. Tangier disease is caused by mutations in the gene of the ATP-binding cassette transporter 1 (*ABC1*) located on the long arm of chromosome 9 (9q31) [5,6]. The primary biochemical defect is not known, but *ABC1* plays a role in the secretion of mature HDL and secretion of cellular lipids. Defective maturation underlies increased catabolism of apo-A1 and apo-AII and, as a result, HDL is

markedly reduced and of abnormal composition (apolipoproteins AI and C are present in only trace amounts [2–4]). This reduction in HDL results in the production of abnormal CM remnants and the accumulation of cholesteryl esters in many tissues [6].

Clinical features. Twenty-six patients have been reported to date [3]. Orange-yellow tonsils and adenoids are characteristic but hepatosplenomegaly and peripheral neuropathy are common features. Cholesteryl esters are found in the skin within foamy histiocytes [7–9]. Slit-lamp examination of the eye shows corneal infiltration in most patients as they age.

Investigation. The combination of a very low level of cholesterol and elevated plasma TG is almost diagnostic. Ultracentrifugation shows HDL to be absent or present in only trace amounts, and lipoprotein electrophoresis shows no α_2-protein. Plasma apolipoprotein A (apo-A1) is very low (less than 3% of controls).

Treatment [2,3]. There is no specific treatment for this disease as yet, although reduction in fat content of the diet may be logical, since remnants of TG-rich lipoproteins appear to accumulate in the plasma with normal fat intake.

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Disorders of amino-acid metabolism

[C.A. Seymour, pp. 57.77–57.85]

The disorders of amino-acid metabolism are of growing importance. As well as abnormalities of skin, patients may show mental retardation, abnormalities of hair and impaired general body growth. These disorders are the result of inherited defects of enzymes that mediate the metabolism or transport of amino acids.

Hyperphenylalaninaemia syndromes

These syndromes are characterized by defects in hydroxylation of phenylalanine to tyrosine, or defects in the generation of tetrahydrobiopterin (BH_4), a coenzyme for hydroxylation, resulting in increased fasting plasma phenylalanine concentrations (normal range 40–80 mmol/L).

Phenylketonuria (MIM *261600)

SYN. HYPERPHENYLALANINAEMIA TYPE I; FOLLING'S DISEASE; PHENYLPYRUVIC OLIGOPHRENIA

Phenylketonuria (PKU) is a rare inherited disease in which a deficiency of the enzyme phenylalanine hydroxylase (PAH) leads to an accumulation of phenylalanine in the plasma (normal range: less than 2 mg/dL, 120 µmol/L: in PKU, plasma levels are greater than 1000 µmol/L) and to the excretion of phenylpyruvic (about 1 g is excreted daily) and phenylacetic acids in the urine. Known forms include primary deficiency of PAH (PKU and non-PKU phenylalaninaemia), and impaired synthesis of BH_4, guanosine triphosphate (GTP) cyclohydrolase or 6-pyruvoyl tetrahydropterin synthase (6-PTS; MIM *261640), or dihydropteridine reductases (DHPR; PKU2, MIM *261630). PKU is the commonest of these hyperphenylalaninaemias; however, not all are PKU, nor is it always due to PAH deficiency.

Aetiology [1,2]. PKU is inherited as an autosomal recessive disorder with overall incidence of one in 8000–12 000 live births. It accounts for 0.04–1.00% of residents in institutions for the mentally disabled. One in 50 individuals carries the mutant gene. It is a heterogeneous genotype, PAH deficiency being caused by over 400 mutations at the PAH locus on chromosome 12q22–q24.1 [1]. Other phenylalaninaemias include BH_4 deficiency caused by alleles at three other loci: one on chromosome 4 and the others unmapped to date [3,4]. The *DHPR* gene has been localized to chromosome 4 band 15.1p16.1 [1,3]. The clinical condition arises in the presence of the mutation alone (if due to deficient BH_4) or in combination with exposure to phenylalanine (in PKU and non-PKU PAH deficiency). The near complete deficiency of PAH impairs conversion of phenylalanine into tyrosine, leading to the accumulation and excretion of abnormal compounds. Heterozygotes have a high fasting serum phenylalanine level and some 'dilution' of hair colour. The usual gene dose effects are seen in heterozygotes.

In PKU, there are only abnormal concentrations of normal metabolites, and no abnormal metabolites. The metabolic block in the conversion of phenylalanine to tyrosine, carbon dioxide and water, which is the rate-limiting step, leads to the accumulation of phenylalanine,

phenylpyruvic acid and related metabolites. Phenylalanine has ketogenic (acetoacetate) and gluconeogenic (fumarate) intermediates that contribute to the glucose pool, which could play a role in normal brain development and function. The oxidation rate in the brain is probably diminished but, although degenerative changes have been described in the cortex and basal ganglia and in the liver, they are inconstant [5–7]. The reduction of melanin formation in the hair is probably due to the inhibition of tyrosine–tyrosinase reaction by phenylalanine, as the hair will darken if large amounts of tyrosine are ingested.

Clinical features [1,5–7]. The clinical phenotype of PKU is largely of historical interest, because with early diagnosis and treatment the damaging features of the disease can be reduced or prevented. In addition, genotype–phenotype expression can now be examined (with complementary DNA expression *in vitro*). The metabolic phenotype (hyperphenylalaninaemia with or without neurotransmitter deficiency) is the link between the gene and the disease. Affected infants are of average height and weight at birth, but thereafter show wide variation in the ages at which the developmental stages are passed. Unless diagnosis is made early, they present with psychomotor delay in early childhood due to an effect on brain development and function. Recent studies have suggested that the clinical features previously associated with PKU may not be linked. However, these patients almost invariably have fair skin and hair (due to the impairment of melanin synthesis), although in darker races the resultant skin pigmentation may be darker than in the average white person. If untreated in early life, there is nearly always mental retardation, and most of these patients will require special care. About 50% have epilepsy, and often extrapyramidal manifestations, such as athetosis and exaggerated tendon reflexes, may be found. The excreted amino acids can exude a musty odour. The electroencephalogram is abnormal in 80% of patients and correlates with the metabolic phenotype. Magnetic resonance imaging has demonstrated changes consistent with disturbance in the water content of the white matter. It is not clear whether these are of clinical significance [8], although brain phenylalanine concentrations may be lower than expected and are then associated with less effect on the IQ.

The fair and sensitive skin readily develops eczema. This may be of the atopic variety or of less distinctive type. Although clinical light sensitivity has been reported, the ability to tan and the erythematous response to UV radiation are normal [9]. The incidence of pyogenic infections is increased. Scleroderma-like lesions with involvement of the muscles have been described [10]. Eye abnormalities associated with hypopigmentation may occur [1,11]. Impaired physical growth affects the head circumference and height (abnormality in metaphyseal endplate of long bones) in the untreated condition [7,11].

There is some evidence that in mothers with PKU, phenylalanine crosses the placental barrier (along a concentration gradient) and may cause an embryopathy/fetopathy affecting growth, congenital malformations, microcephaly, epilepsy or mental deficiency in the fetus [6]. This diagnosis should therefore be considered in fair-skinned, light-sensitive individuals, especially in mothers of mentally retarded children.

Diagnosis. Newborn screening is the established way to determine hyperphenylalaninaemia (HPA). Although the urine may contain phenylpyruvic acid at birth, the urine test may be negative in the first months of life (ferric chloride test). The blood phenylalanine, however, is raised from an early date, and therefore it is recommended that screening is performed on blood samples during the first week of life [12]. This is now an established neonatal screening programme in the UK [13].

The most widely used method of screening is based on the Guthrie test [13]. The test is performed on a dried capillary blood sample collected on filter paper and analysed by microbiological inhibition assay (Guthrie) or by chromatography, fluorimetry or tandem mass spectrometry. The latter test has few false negatives. A method is described for differentiating the hyperphenylalaninaemias based on the response to phenylalanine content in the diet [4]. Some patients with hyperphenylalaninaemia do not have PKU (see also hyperphenylalaninaemia types II to V). Some patients with persistent HPA have impairment in synthesis or recycling of BH_4, which must also be screened for.

Prenatal diagnosis. Indications for this are uncertain, as treatment is experimental. Families at risk can have prenatal diagnosis by a combination of DNA analysis, enzyme activity, or amniocyte or chorion villus sample metabolite levels [1,3,12]. There are advantages to gene testing by DNA analysis, if alleles have been identified in an affected family member.

Treatment [5–19]. The aim of treatment is to normalize phenylalanine levels as early as possible and for as long as possible (i.e. throughout life) and particularly during pregnancy. It is of prime importance that the diagnosis is made early so that a low phenylalanine diet can be instituted as soon as possible, in order to avoid cerebral damage (assessed by IQ) produced by high blood phenylalanine levels. Blood phenylalanine levels are routinely measured to assess the effects of any treatment. The diet is selectively restricted in phenylalanine to about 250–550 mg/day to keep the plasma phenylalanine level below the toxic range [20]. The patient's diet may need supplementation with tyrosine/tryptophan. The aim is to keep the plasma level to less than 480 μmoL/L. Repeated monitoring of the blood phenylalanine levels (by the Guthrie

test) is required during treatment. Phenylalanine is monitored twice a week in the neonate, weekly in infants, 2–3 weekly in toddlers and ideally monthly thereafter even during adult life. During pregnancy, dietary measures should be adhered to as early as possible and preferably even before conception, but definitely from the fifth and sixth week of pregnancy. This is likely to reduce the risk of damage to brain development but is unlikely to avert congenital heart disease [21–23], which is only prevented by adhering to a strict diet before conception. Twice weekly sampling blood tests are ideal to maintain levels of 100–250 μmol/L. There is evidence that reduction in maternal phenylalanine levels during pregnancy results in neonates with a higher birth weight [24].

The diet is based on a synthetic substitute for most of the dietary protein and should be continued not only until the child has passed the main period of brain development but also during adult life, as it has now been established that neurological sequelae (long tract signs) can develop in the untreated affected adult [21]. The diet is often relaxed at about 8 years of age but some limitation of diet is still essential, otherwise there is a risk of relapse or of failing to develop the full IQ potential. Thus, contrary to previous practice, tight control of circulating phenylalanine is not only essential during pregnancy, but more recently has been shown to be advisable if not essential to continue throughout adult life [1,22,24,25]. Unfortunately, the response to dietary treatment is variable despite early and careful control, and the effectiveness of treatment varies with individual patients. The amount of phenylalanine supplied in the diet should be low enough to prevent its accumulation in the blood, but high enough to allow protein synthesis and growth. Foods are given on an exchange basis using tables to indicate food with 1 g protein (equivalent 50 mg phenylalanine). Enzyme therapy with phenylalanine ammonia lyase (PAL) can be given in enteric-coated capsules and has a beneficial effect on plasma phenylalanine levels. However enzyme replacement therapy can only be achieved at present with heterologous liver transplant. Enzyme substitution, using PAL, can lower blood phenylalanine if given orally but the effect is too short lived to be therapeutic.

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Non-PKU hyperphenylalaninaemia (types II and III)

Not all infants with hyperphenylalaninaemia have PKU [1]. Types II and III represent a continuum, from those difficult to separate from typical PKU to those who are mildly affected. There is a general correlation between PAH activity and blood levels of phenylalanine [2]. Accurate classification usually requires testing with phenylalanine loading and measurement of metabolites [3,4]. Treatment needs to be modified according to the severity of the enzyme deficiency, but essentially is as for PKU.

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Hyperphenylalaninaemia (types IV and V)

Types IV and V are due to deficiencies in the coenzymes DHPR [1] and dihydrobiopterin synthetase [1–5], respectively. The chromosomal locus encoding DHPR is assigned to human chromosome 4. Patients lacking DHPR are deficient in neurotransmitters whose synthesis is dependent on normal DHPR-tyrosine and tryptophan hydroxylase activities. They have low urinary and cerebrospinal fluid vanilyl mandelic acid and 5-hydroxyindole acetic acid. Other rarer forms, resulting in BH_4 synthesis disorders —GTP cyclohydrolase deficiency [6,7] and 6-PTS [5,8] deficiency—can be more easily detected by loading tests. These infants represent only 1.3% of all patients with hyperphenylalaninaemia but need accurate diagnosis, as their treatment is very different from that of typical PKU [1,6]. Treatment of DHPR deficiency needs dietary restriction of phenylalanine and restoration of the neurotransmitter levodopa (about 12 mg/kg/day) and 5-hydroxytryptophan (about 10 mg/kg/day), together with carbidopa to reduce peripheral breakdown of levodopa. Folate replacement or folinic acid treatment is also necessary, as DHPR plays a role in tetrahydrofolate homeostasis.

Prenatal diagnosis. It is now possible to measure DHPR in amniocytes and to detect the condition by DNA analysis by restriction length fragment polymorphism (RFLP) in informative families [5].

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Tyrosinaemia

There are a number of inherited conditions that cause hypertyrosinaemia. These include inborn errors of metabolism (e.g. oculocutaneous and hepatorenal tyrosinaemia) and secondary causes (e.g. severe hepatocellular dysfunction, transient tyrosinaemia of the newborn and other diseases, for example hyperthyroidism). Tyrosine comes either from dietary intake or from hydroxylation of phenylalanine. It is degraded in the hepatocytes by the rate-limiting enzyme, tyrosine aminotransferase (TAT).

Tyrosinaemia I (hepatorenal) (MIM *276700) [1–3]

This is a rare but well-documented autosomal recessive disorder due to a deficiency in fumarylacetoacetoic hydroxylase (FAH). This enzyme has been located to chromosone 15. It can present as an acute or chronic form, and principally affects the liver, kidney and peripheral nerves.

The *acute form* presents in the first few weeks of life with failure to thrive, vomiting, diarrhoea and a cabbage-like odour. Hepatomegaly and a bleeding diathesis are common features and untreated patients die of hepatic failure.

The *chronic form* is characterized by chronic liver and renal disease (Fanconi-like syndrome) with death within the first decade. Some patients may develop hypertension, and hypertrophic cardiomyopathy and porphyria-like neurological crises (due to δ-aminolaevulinic acid (ALA)). Hepatoma is a late complication. Plasma tyrosine and methionine are elevated diagnostically and there is a global increase in urine amino acids, with particular increase in ALA [3].

Secondary deficiency of hepatic 4-hydroxyphenylpyruvate dioxygenase (HPDD) may occur and is important to note. Some patients develop hypermethioninaemia, the importance of which is uncertain, although it is also increased in cirrhosis and hepatoma. The episodes of porphyria-like peripheral neuropathy are thought to be due to succinylacetone, which inhibits the porphyrin synthetic enzyme, ALA dehydratase [3].

Prenatal diagnosis. This is either by direct determination of the FAH enzyme activity or detection of succinylacetone directly or from its inhibitory activity in amniocytes or chorionic villus samples [2,4]. Neonatal screening is aimed at detecting increased levels of tyrosine, methionine or succinylacetone from blood spots on filter paper, and more recently these have also been used for screening ALA dehydratase. Several different mutations have been reported, and where the mutation is known, molecular analysis should be carried out.

Treatment. This is with a low tyrosine and phenylalanine diet, which may reduce the succinylacetone excretion and

reduce the effects on the kidneys. Liver transplantation has been successful and is the treatment of choice [5–7] and gene therapy may be possible [8]. Treatment is with NTBC (2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione), which inhibits key enzymes in the degradation pathway reducing production of toxic metabolites [6,7].

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Tyrosinaemia II (MIM *276710) [1–3]

SYN. RICHNER–HANHART OCULOCUTANEOUS SYNDROME [4]

This is a very rare disorder, inherited as an autosomal recessive trait, due to a deficiency of cytoplasmic TAT, now mapped to chromosome 16q22–q24, the rate-limiting enzyme for tyrosine catabolism [5]. Males and females are equally affected. The deficiency leads to tyrosinaemia, unique tyrosinuria and an increase in the urinary tyrosine metabolites. The eyes, skin and nervous system are the only organs affected. Mild but painful corneal herpetiform erosions and dendritic ulcers develop within the first few months of life and may lead to photophobia, corneal scarring [6,7] and glaucoma. Ulceration also has occurred on corneal transplants [7]. Skin lesions usually occur after eye lesions have developed, although in some families the skin lesions may exist without eye lesions [1,2]. Painful erosions may develop on palms and soles, especially the tips of digits, thenar and hypothenar eminences. Later, these areas become hyperkeratotic [4]. The skin biopsy, although showing hyperkeratosis and acanthosis, is not diagnostic, but electron microscopy shows intracellular granules and filaments, probably caused by tyrosine crystal-induced inflammation. Hyperkeratosis of the tongue has been reported [8]. In the original description of this disease [4], mental retardation occurred in fewer than 50% of patients. Disturbance of fine coordination and self-mutilation also occur [1,2].

Diagnosis. This is made by detection of increased blood tyrosine levels, normal phenylalanine and increased urinary metabolites of 4-hydroxyphenylacetic acid, *N*-acetyltyrosine and 4-tyramine.

Treatment. Most patients respond to dietary restriction of tyrosine and phenylalanine [2,9] by reducing protein to 2–3 g/kg/day, with the aim of reducing blood levels to less than 600 µmol/L, although the precise reduction in tyrosine required to control the skin and eye features is unknown.

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Alkaptonuria (MIM #203500) [1,2]

This is a rare metabolic disorder first described by Garrod in 1902 [1], which results from a single gene defect. It is characterized by a discrete biochemical lesion, with deposition of oxidized homogentisic acid pigment throughout the body, particularly in fibrous and cartilaginous tissues. Dark urine (homogentisic aciduria), distinctive cutaneous pigmentation (ochronosis) and arthritis are characteristic. Generally, it is considered a benign degenerative disorder with normal life expectancy [2].

Aetiology [1–3]. It is inherited as an autosomal recessive condition. Its incidence in the population is one in 200 000. It is characterized by a constitutional deficiency of homogentisic oxidase (homogentisic 1,2-dioxygenase activity). This leads to an accumulation of homogentisic acid, an intermediate metabolite of phenylalanine and tyrosine catabolism. The enzyme is normally found in the liver and the kidney.

Ochronosis [4,5] describes the deposition of a melanin-like brownish-black pigment, derived from the oxidized product of homogentisic acid (benzoquinone acetic acid), in connective tissues and cartilage. The enzyme homogentisic acid oxidase contains an essential sulph-hydryl group, which is inhibited by certain chemicals. These include various drugs such as phenol, resorcin, mepacrine and perhaps other antimalarials that may cause acquired ochronosis. An exogenous ochronosis can also occur from hydroquinone-containing skin-bleaching creams [4].

Genetics. Alkaptonuria is an autosomal recessive condition. The gene locus (*AKU*) has been assigned to chromosome 3q by consanguinity and by comparative mapping. The gene has been cloned to 3q21–q23 with demonstration that the human 1890 gene harbours missense mutations and cosegregates with the disease [3]. The incidence is one in 200 000 but in areas of consanguinity it is higher [6].

Histopathology. There is deposition of black pigment in the cartilage, fibrous tissue, tendons and atheromatous areas. The intervertebral discs, larynx, tracheal rings and articular cartilages are jet-black as if 'dipped in Indian ink'. Differentiation of the ochronotic pigment from melanin is difficult, and stains do not consistently differentiate between the two pigments.

Clinical features [2,7]. Cardinal features are due to homogentisic acid in urine, and pigmentation of cartilage, connective tissue and joints. The patient with the hereditary type is symptom-free until adult life. The only manifestations in childhood are discoloration of the urine and 'spotting or staining' of the napkins or clothing due to alkaline pH. The clinical sequence of events is alkaptonuria, then ochronosis and lastly ochronotic arthropathy (fifth decade). The cutaneous manifestations appear in the fourth decade. One of the earliest signs is thickening of the ear cartilage, associated with blue-black or grey-blue discoloration. The pinna feels noticeably thickened and flexible, and in later stages there may be gross calcification. Cerumen is often brown or jet black. Scleral pigmentation is noted as early as the third decade; it appears as brown or grey deposits midway between the corneal margin and the medial canthus. The skin of the eyelids and forehead is also pigmented and the tarsal plates often appear blue on transillumination. All the tendons are similarly discoloured; the dark discoloration over the extensor tendons on the knuckles is best seen when the patient makes a fist. Widespread dusky cutaneous pigmentation may be noted, but this feature is particularly marked over the cheeks, forehead, axillae and genital regions. The buccal mucosa and larynx are also affected and the nails are sometimes distinctly coloured brown. Ochronotic changes affecting the ear drum and ossicles may produce deafness; prostatic concretions and black renal calculi, as well as calcific aortic disease, have been recorded. The urine is of normal colour but darkens on exposure to air or within seconds of adding an alkaline solution. Patients sometimes observe that both their sweat and urine discolour clothing.

Ochronotic arthropathy follows a fairly consistent clinical pattern. There is low back pain with stiffness early in the fourth decade; during the next 10 years the knees become involved and, later, the shoulders and hips. The friable articular cartilages lead to prolapsed intervertebral discs or a ruptured nucleus pulposus with accompanying acute pain. Spondylosis spreads to the thoracic spine; patients then assume a stooping posture and can lose up to 15 cm in height. Limitation of expansion of the chest provokes dyspnoea. The spinal X-ray appearances are diagnostic.

Marked atherosclerosis is common in the older age groups as well as valvulitis and calcification of aortic and mitral valves. In spite of their marked disability, many patients reach old age.

Diagnosis. The diagnosis is by demonstration on gas–liquid chromatography of homogentisic acid in the urine (by its reducing ability), or with specific enzyme tests [8].

Differential diagnosis. An incorrect diagnosis of glycosuria or diabetes can be made if the urine is tested with Fehling's solution (but this is rarely used now). The pigmentation of acquired ochronosis from exogenous foreign chemicals or drugs is identical to the genetic disorder, but is unaccompanied by homogentisic acid in the urine or by arthropathy.

The overall clinical picture and the localization of pigment thus distinguish the genetic disease from other pigmentation disorders such as Addison's disease, haemochromatosis, argyria, chronic photosensitivity pigmentation, cutaneous porphyria and pellagra. The ferric chloride urine test gives variable results; other phenolic compounds give similar colour reactions and thus, when the test is positive, the urine should be examined by chromatography.

Treatment [2]. Since the major damage induced by the metabolic defect is pigmentation and joint changes, treatment is directed towards reducing connective tissue damage by ascorbic acid (acting as an antioxidant), and by analgesics and physiotherapy for the arthropathy. A low protein diet limiting the amount of phenylalanine and tyrosine is not practicable as a long-term measure, although it could be used intermittently. Use of vitamins (B_{12}, C) may be helpful (for example ascorbic acid in reducing homogentisic acid oxidation).

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Homocysteinurias [1–5]

SYN. HOMOCYSTINURIAS

Homocystinurias are a group of rare, inborn errors of amino-acid metabolism first reported in 1962 [4]. They also encompass hypermethioninaemia and cystathioninuria. The defects arise when there is abnormality in transfer of the sulphur of methionine to serine in the synthesis of cysteine.

Aetiology. Initially homocysteinuria was thought to be due to deficiency of cystathionine-β synthase (CBS; MIM *236200), but it is now apparent that homocysteine accumulation may also result from inherited (MIM #236250) or acquired blocks in the 5-methyltetrahydrofolate–homocysteine methyltransferase reaction [1,3,6]. The enzyme deficiency is involved in homocysteine to cystathione conversion or in homocysteine to methionine conversion, which is dependent on 5-methyltetrahydrofolate and leads to an increase in homocysteine in the blood and in the urine. These can be distinguished because there is an increase in urine methionine in the CBS deficiency, and methionine is low in the secondary form. Secondary forms of homocystinuria can occur in vegetarians with vitamin B_{12} deficiency, or with treatment with isonicotinic acid.

Clinical features. CBS deficiency is inherited as an autosomal recessive trait, with a world prevalence of one in 344 000 and detection of one in 58 000–100 000, depending on the country [1]. Four major organs are affected: the eye, skeletal system, central nervous system and the vascular system. The underlying cause of tissue changes is because accumulated homocysteine interferes with collagen cross-links. The newborn infant may appear clinically normal, but lens dislocation, mental deficiency, growth disorder and cutaneous signs develop slowly over the next few years. Other clinical features include epilepsy, genu valgum and growth changes resembling Marfan's syndrome. There is often an abnormal glucose tolerance test and increased growth hormone levels. The hair is fine, sparse and brittle, and the malar area flushed. In some cases, hair examination shows no fluorescence with acridine orange, indicating abnormality of disulphide bonds. The cysteine content is normal. Livedo reticularis of the legs and tissue-paper scars on the hands may be present.

Osteoporosis of the spine is common and predisposes to scoliosis. Other features include hepatomegaly (secondary to fatty change) and myopathy. Psychiatric abnormalities occur in about 50% of such patients, with episodic depression (10%), and chronic behavioural disorders (17%) [7]; chronic obsessive–compulsive disorders (5%); personality disorders (19%), usually with an IQ of less than 79. Some children develop spontaneous venous and arterial thrombosis due to increased platelet stickiness [6,8]. In the vascular system, thrombosis with embolic abnormalities is a frequent cause of mortality. This affects any vessel and patients are at an increased risk of post-operative thromboembolism. More recently this association of homocysteine with vascular disease has been more clearly recognized [9,10].

Differential diagnosis. Marfan's syndrome, an hereditary mesodermal dysplasia, exhibits visceral manifestations without mental deficiency. The hair is normal and homocysteine is absent from the urine.

Diagnosis. This is by detection of urinary homocysteine by a positive urinary cyanide–nitroprusside reaction. Recently, plasma homocysteine measurement (with increases of 50–200 μmol/L), confirmed by changes after methionine loading, is regarded as a more accurate assessment. Heterozygotes can be detected by assaying for the enzyme in the liver, phytohaemagglutinin-stimulated lymphocytes and in cultured fibroblasts. In addition, the presence of abnormal sulphur-containing metabolites can be detected in the urine after an oral load of L-methionine. CBS deficiency can be diagnosed by hypermethioninaemia or by detection of increased homocysteine in urine or blood. Methods for detecting heterozygotes rest on enzyme assays, metabolite measurements or a combination using liver tissue, cultured fibroblasts or phytohaemagglutinin-stimulated lymphocytes. Newer techniques include tandem mass spectrometry [11].

Treatment [1,12]. There are two aims of treatment: (i) control/elimination of the biochemical abnormality; and (ii) treatment of complications. Patients are usually divided into pyridoxine-responsive or non-responsive individuals, detected after the newborn period. For the newborn, diets restricting methionine and supplemented with cysteine have been used with encouraging results when started early in life. Large doses of vitamin B_6 (pyridoxine) in the form of pyridoxine hydrochloride 150–300 mg/day produce complete reversal of the biochemical abnormality in some cases. Some may become folate deficient; administration of vitamin B_{12} and folic acid improves

clinical symptoms. For the non-pyridoxine responsive patients, a low protein diet with methionine-free amino acid supplements and exchanges, and minerals and vitamins may be helpful. In non-responsive patients diagnosed after birth (non-responsive after a trial of 500–1000 mg/day for several weeks), the use of betaine as a methyl donor agent to lower homocysteine levels could be a useful adjunct in combination with a low-methionine diet.

Prognosis. Prognosis is more favourable than might be thought, with recent surveys showing that fewer than 5% die by the age of 20 years [1–3].

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Hartnup disease (MIM *2345000) [1–3]

This is a very rare hereditary recessive metabolic disorder of neutral amino-acid transport, which is characterized by a pellagrous eruption, a temporary and intermittent cerebellar ataxia, and a characteristic renal amino-aciduria with excessive indicanuria [1].

Aetiology [1,4]. The defect is due to a failure of the transport of tryptophan and is limited to the small intestine and kidney [5–7]. The defect is believed to be caused by a genetic defect in the specific system for transport of neutral amino acids across the brush border epithelium of the intestine and kidney, leading to hyperamino-aciduria and urinary indolic compounds due to bacterial action on the unabsorbed tryptophan. It is likely that Hartnup disorder is a monogenic defect which interacts with polygenic and environmental factors giving a wide clinical spectrum [8]. The failure of absorption of tryptophan results in a deficiency in the synthesis of nicotinamide causing a pellagra-like syndrome.

Clinical features. The onset is usually in childhood between 3 and 9 years, but the first signs are occasionally encountered as early as 10 days after birth. The cutaneous signs precede the neurological manifestations. The rash is dry, scaly and well marginated, affecting the light-exposed areas, notably the forehead, cheeks, periorbital regions, the uncovered areas of the arms and the dorsal surface of the hands. After exposure to sunlight, the skin reddens and an exudate may occur.

Cerebellar ataxia is the most commonly encountered neurological feature. It usually follows the skin lesions. Other signs of cerebellar origin include nystagmus and diplopia, and occasionally tremor of the hands and tongue. Early reports suggested mental retardation, but this has not been the case with most patients. Minor cognitive defects have been reported. Less commonly, there are associated psychiatric disturbances such as depression, delusions and hallucinations. Exacerbations are most frequently seen in the spring or early summer [2], cutaneous manifestations being accompanied by transient ataxia. Rarely, the attacks are provoked by febrile illness. Other somatic abnormalities include oedema and hypoproteinaemia with fatty change in the liver [2], fever, diarrhoea and atrophic glossitis.

Intravenous tryptophan is metabolized normally and the serum amino acids are normal. The urine contains increased amounts of amino acids of the monoamine monocarboxylic groups [5], and it is the pattern of the amino-acid excretion that confirms the diagnosis.

Differential diagnosis. The eruption in mild cases closely simulates infantile atopic eczema, seborrhoeic eczema or pityriasis alba; in Hartnup disease the covered areas are usually spared. Florid cases closely mimic nutritional pellagra.

The congenital poikilodermas, particularly the light-sensitive hereditary disorders such as Cockayne's syndrome, may present diagnostic difficulties.

Treatment [2,3]. The rationale for the treatment is to replace the defect by giving nicotinamide (50–300 mg/day) orally. Treatment usually results in amelioration of the rash and may improve ataxia and psychotic behaviour. A high-protein diet may be a useful adjunct. Intravenous nutrition may be necessary in severely affected patients.

Prognosis. Symptoms become milder with increasing age.

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Gout

[C.A. Seymour, pp. 57.85–57.86]

This heterogeneous group of purine metabolism abnormalities is characterized by hyperuricaemia, and recurrent attacks of acute arthritis in some cases, with the deposition of monosodium urates in the articular cartilage and urate deposits in the skin (tophi) (Fig. 57.44). Arthritis may be progressive and nephropathy is common. Nephrolithiasis due to uric acid may precede arthritis.

Aetiology [1–4]. Uric acid is the degradative product of purine metabolism in humans. Increased circulating levels of uric acid arise because of overproduction or underexcretion of uric acid. Primary gout has long been recognized as a heterogeneous disorder with up to 40% of patients in whom pedigree analysis suggests an inherited cause [4]. Population studies suggest that the disorder is multifactorial and attributable to a combination of genetic and non-genetic factors [1]. There are two very rare specific enzyme deficiencies associated with gout, which have X-linked inheritance. These are partial deficiency of hypoxanthine–guanine phosphoribosyl transferase (HGPRT; HPRT-related gout, MIM #300323) and increased activity of phosphoribosyl-pyrophosphate (PRPP) synthetase. Most patients with primary gout appear to have reduced excretion of uric acid [5,6] but the metabolic abnormalities are poorly understood. Fewer than 10% of patients with primary gout have an increase in the rate of purine biosynthesis [7]. A number of defects have been suggested but only partial deficiency of HGPRT and increased PRPP synthetase activity are of importance [8].

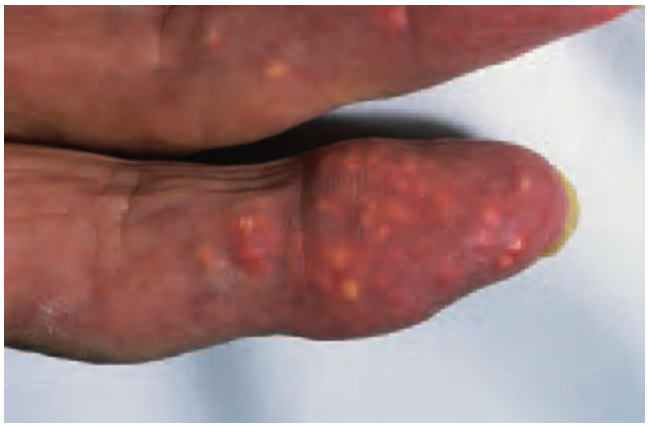

Fig. 57.44 Gouty tophi. (Courtesy of Dr R.H. Champion, West Suffolk Hospital, Bury St Edmunds, UK.)

Secondary gout may result from decreased excretion of uric acid. The most important cause of this is diuretic therapy but it may also occur in a number of disease states, especially renal disease. Increased uric acid production is commonly secondary to increased turnover of nucleic acid in conditions such as polycythaemia rubra vera, lymphoma, myeloma and in patients with leukaemia receiving active chemotherapy. A number of other disorders may not uncommonly occur with increased uric acid and gout. Eighty-two per cent of patients with pure or combined hypertriglyceridaemia have increased uric acid levels, and conversely 74% of patients with gout have raised lipoproteins (TG, VLDL [8,9] and Lp(a) [10]); it may be associated with combined hypertriglyceridaemia (types IIb, and IV hyperlipidaemia) and with insulin-resistance (hyperinsulinaemia and glucose intolerance). Although associated with coronary heart disease, the role of uric acid is controversial [9]. Hypertension, obesity, diabetes mellitus and ethanol consumption in susceptible persons may also be associated with gout [11].

Histopathology. Sodium urate crystals may be found in joint fluid. The crystals can be identified by microscopic examination and by their ability to polarize light strongly. In the dermis and medulla of the kidney, the urate crystals provoke a giant cell reaction [11,12].

Clinical features [1,3,4,6]. Hyperuricaemia appears at about the age of puberty in males and later in females, often after the menopause. Patients remain asymptomatic until the fourth to sixth decades when the first attack of acute gouty arthritis occurs. Recurrent, self-limiting attacks usually follow after a period of about 6 months to 2 years. Initially single joints, and classically the great toe, are involved, but later the condition may become polyarticular and then usually involves the joints of the lower extremities. Later in the disease, a chronic tophus state develops with deposits in cartilage, synovial membranes, tendons and soft tissues. The classical localization for tophi is in the helix and antihelix of the ear, and on the index fingers (Fig. 57.44). Criteria for clinical diagnosis of acute gout have been reported [3,13].

Acute uric acid nephropathy results from precipitation of uric acid crystals in the collecting ducts of the kidney and is most commonly seen in patients with leukaemia

undergoing aggressive chemotherapy. Renal stones develop in up to one-quarter of patients [12] and renal colic may be a presenting manifestation of gout. Chronic urate nephropathy is a common manifestation [6,14] and contributes significantly to the morbidity and mortality of gout [14]. Uric acid has been suggested as a risk factor for CAD [15].

Differential diagnosis. Pseudogout [2,16] (calcium pyrophosphate deposition disease) shows close similarities to gout (particularly the acute attacks), familial incidence and later chronic arthropathy, pseudotophi and precipitation by surgical operations and diuretic therapy. The serum uric acid is normal, calcium pyrophosphate is found in synovial fluid and X-rays show articular calcification [2].

Multicentric reticulohistiocytosis frequently shows papules and nodules on the ears and fingers with an associated arthropathy.

Rheumatoid arthritis with necrobiotic nodules is usually sufficiently characteristic to avoid confusion with gout. Psoriatic arthropathy may cause diagnostic difficulties.

Treatment [1,3,14,17,18]. All patients with gout or a raised uric acid level should be investigated for its cause. Acute attacks are treated by rest of the affected joint and with regular anti-inflammatory treatment, such as indometacin. Colchicine (0.5 mg 6-hourly until symptoms subside, or maximum oral dose of 6 mg has been reached) may also be useful in acute episodes. Side effects of diarrhoea, renal and hepatic damage need to be carefully monitored. It is a matter of clinical judgement whether to treat asymptomatic gout with anything other than antiuricaemic therapy.

Antiuricaemic therapy using allopurinol, a xanthine oxidase inhibitor, is effective after the acute event and in prophylaxis. Drugs such as probenecid and sulfinpyrazone may be used to increase uric acid excretion, but are usually less effective prophylaxis. The newer, non-steroidal anti-inflammatory agents may be used. Treatment must be tailored to the needs of individual patients [7,19].

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Lesch–Nyhan syndrome (MIM #300322) [1–6]

[C.A. Seymour, pp. 57.86–57.87]

This syndrome is probably determined by a sex-linked recessive gene. The underlying metabolic defect is a complete lack of the purine salvage enzyme HGPRT resulting from mutations in the gene. HGPRT is coded for by a single gene on the X chromosome (Xq26–q27), and is expressed in all tissues. Eighty-five per cent of mutations are point mutations or small deletions rather than major gene changes. This enzyme catalyses the salvage of hypoxanthine and guanine to inosine monophosphate (IMP) and guanosine monophosphate (GMP). It is characterized by choreoathetosis, spasticity, mental retardation and self-mutilation, particularly biting of the lower lip in childhood. Patients are normal at birth, but by 6 months developmental abnormalities are apparent. Choreiform movements occur within the first year. There may also be a macrocytic/megaloblastic anaemia. Increased levels of HGPRT causing neurotransmitter imbalance are found in the basal ganglia, but their relevance to the clinical disease is uncertain. HGPRT-deficient mice do not show abnormal neurological behaviour. The origin of the neurological abnormality in humans is still unknown but is likely to be due to accumulation of purine metabolites rather than deficiency of purine nucleotides, which in some way interfere with brainstem neurotransmitter function. Secondary changes in terminal arborization of dopaminergic neurones have been suggested because of reduced concentrations of dopamine homovanillic acid, dopa and tyrosine decarboxylase in dopaminergic neurones in the putamen. Blood uric acid levels are high and, although there are no reports of gouty arthritis, renal function is impaired by deposit of urates. Patients with partial

deficiency of HGPRT may develop gouty arthritis and/or uric acid calculi without the neurological and behavioural features.

Prenatal diagnosis. HGPRT analysis can be carried out on amniocyte or chorionic villus samples in the ninth week of pregnancy. Affected male heterozygotes can be identified by HGPRT assay on red cell lysates. Carrier females can be identified by $HGRPT^+$ and $HGRPT^-$ mosaicism in hair roots; mosaicism can also be identified in cultured fibroblasts [7].

Treatment. Allopurinol, in appropriate dosage, can reduce plasma urate and urinary uric acid to reduce occurence of gouty arthritis, urate nephropathy and renal calculi. There is no effective treatment of the neurological features. However, padded wheelchairs and physical restraints may reduce spinal injury and self-mutilation. Dental extraction may also assist in preventing the latter [5,7].

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Nutrition and the skin

[K. Weismann, pp. 57.87–57.106]

Lack of essential nutrients is most commonly due to insufficient intake of food, malabsorption (see below), vomiting or decreased passage time of food due to diarrhoea or fistulae. Some medications may interfere with utilization of nutrients. An increased metabolic requirement of nutrients may occur during periods of sudden weight gain, such as growth and convalescence. This may lead to relative deficiencies, as seen in patients receiving long-term parenteral nutrition who may become deficient in zinc or selenium.

In most cases, the cutaneous changes of inadequate nutrition are varied, reflecting combined deficiencies. Hence, when there is an apparently isolated deficiency, an underlying genetic or enzymatic defect should be suspected.

Table 57.12 Various causes of malabsorption.

Chelating substances in the gut
Phytates
Insufficient digestive enzyme activity
Pancreatic diseases (pancreatitis, mucoviscidosis)
Defective micelle formation
Obstructive jaundice, liver cirrhosis
Contaminated small bowel syndrome (i.e. presence of an abnormal bacterial flora in the small bowel)
Gastric resection (lack of hydrochloric acid production)
Stagnant loop syndrome (strictures, surgical blind loops, scleroderma, diabetic enteropathy)
Colonic reflux (intestinal fistula, extensive small bowel resection)
Agammaglobulinaemia
Defective enzyme activity or carrier function in the intestinal mucosa
Disaccharidase deficiency
Coeliac disease
Acrodermatitis enteropathica (zinc deficiency)
Hartnup disease (pellagra)
Loss of absorption capacity
Intestinal resection and bypass operation
Crohn's disease
Pernicious anaemia
Interference with intestinal lymphatics
Lymphangiectasis
Tuberculous mesenteric adenitis
Hodgkin's disease
Inadequate transport mechanisms in the blood
Abetalipoproteinaemia
Miscellaneous
Polyarteritis nodosa
Lupus erythematosus
Amyloidosis
Mastocytosis
Diabetes mellitus
Zollinger–Ellison syndrome
Protein-losing enteropathy
Hyperthyroidism
Hypothyroidism
Cronkhite–Canada syndrome
Dermatogenic enteropathy

Malabsorption

Malabsorption is a condition characterized by a decreased intestinal uptake of nutrients associated with an increased faecal excretion of fat (steatorrhoea). This may lead to various degrees of lack of proteins, minerals, trace elements, fat-soluble vitamins, carbohydrates and water. Some causes of malabsorption are listed in Table 57.12.

Non-specific cutaneous symptoms [1,2]. Non-specific symptoms may be observed in patients who have lost weight due to malabsorption or malignant disease. The skin changes reflect general illness rather than specific disease.

Itching and acquired ichthyosis. Itch is mostly caused by dry skin. Elderly patients are especially prone to developing dry skin, which easily becomes eczematized. Patients with cancer, chronic liver and kidney diseases and

lymphoma may develop an itchy atrophic ichthyosis [3]. Hypoferraemia may cause itch, which disappears after initiation of iron therapy. Serum ferritin is a sensitive indicator of the state [4].

Melanosis. Malnutrition due to malabsorption may cause symmetrical melanin hyperpigmentation of the skin, although melanocyte-stimulating hormone (MSH) levels are seldom increased. Other skin colour changes associated with malnutrition are those due to wasting and atrophy, and pallor due to anaemia.

Skin appendages. Brittle nails and hair loss are frequent findings in poorly nourished patients. In some cases, lack of zinc, iron and vitamins is the main cause. In the majority of patients the aetiology is probably multifactorial.

Specific cutaneous effects [1]. Vitamin deficiencies occur due to malabsorption. Lack of fat-soluble vitamins, in particular, may cause skin changes including follicular hyperkeratosis (lack of vitamin A), ecchymoses and haematuria (lack of vitamin K), and cheilitis, glossitis, neuritis and dermatitis (lack of vitamin B complex). Zinc deficiency-related skin changes may be seen.

Investigations. Patients presenting with skin changes suggestive of malabsorption should have a thorough medical examination and laboratory tests to determine both the causes and the consequences of malabsorption. Relevant tests include serum calcium, zinc, folate and albumin levels, faecal fat excretion and X-ray examination of the small intestine.

Treatment. The cause of malabsorption should be treated where possible, and dietary measures instituted to ensure adequate supply of all essential nutrients from a wide variety of foods [2].

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Specific syndromes with malabsorption

Cronkhite–Canada syndrome [1]

See Chapter 59.

Whipple's disease

This is a rare disease of uncertain aetiology involving the gastrointestinal tract, skin, joints, heart and lymph nodes (Chapter 59). There is diffuse hyperpigmentation of the skin, and leg nodules or erythema nodosum may occur. The involvement of the heart includes inflammatory changes of the pericardium, myocardium and endocardium and may lead to valvular insufficiency [2].

Dermatitis herpetiformis (Chapter 41)

Enteropathy is present in at least two-thirds of all patients and may respond to a gluten-free diet. Patients may be managed on a gluten-free diet alone, and it at least enables most patients to reduce their requirement for dapsone [3].

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Mucoviscidosis

SYN. FIBROCYSTIC DISEASE; CYSTIC FIBROSIS OF THE PANCREAS

Mucoviscidosis is an inherited disorder characterized by three major components: chronic lung disease, exocrine pancreatic insufficiency and an abnormally high sodium concentration of the sweat.

Aetiology. The mode of genetic transmission is autosomal recessive. The basic metabolic defect is unknown. The mucous secretion has an increased viscosity resulting in obstruction of the small bronchial branches, the excretory ducts of the pancreas and the bile ducts of the liver. This eventually leads to respiratory disease, pancreatic insufficiency and hepatic failure. The high sodium concentration in sweat is due to a lowered reabsorption of sodium in the sweat glands [1] (Chapter 45).

Histopathology. The exocrine sweat glands and pancreas show electron-dense bodies, and there are fewer than normal secretory vacuoles in the 'dark cells' of the sweat coils [2].

Clinical features. The main presenting features are chronic pulmonary disease, exocrine pancreatic insufficiency with malabsorption, retarded growth and hepatic disease. Skin changes in the form of acrodermatitis enteropathica-like lesions due to essential fatty acid and zinc deficiency have been seen [3,4]. Several studies have indicated that atopy is more common in patients with cystic fibrosis than in the general population [5], although the

prevalence of urticaria is not increased [6]. A purpuric rash may occur in patients with cystic fibrosis (Chapter 49).

Diagnosis. The diagnosis is established by finding of high sodium concentration in the sweat, absence of pancreatic enzymes in the duodenum, chronic respiratory disease, retarded growth and a family history of the disease.

Treatment. Respiratory infection is controlled by prolonged antibiotic therapy according to bacterial cultures. Pancreatic insufficiency is treated by pancreatic enzyme preparations orally and a diet low in fat. The liver disease and the sweat abnormality are not amenable to treatment at present.

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Vitamins [1]

Vitamins are biologically active organic compounds, which are indispensable for the normal functions of the body. They have no direct function as an energy source or as structural tissue components, but in most cases act as coenzymes in various enzyme systems.

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Vitamin A

Vitamin A (retinol) is a cyclic polyene alcohol present in yellow and green vegetables, egg yolk, butter, liver and fish oils [1]. β-Carotene occurs in fruits, carrots and green vegetables, and is absorbed and converted to vitamin A in the body. The recommended daily allowance is 5000 i.u. (equivalent to 6000–12 000 i.u. β-carotene). The plasma level in normal adults is about 600 ng/mL [2]. Vitamin A is mobilized from liver stores and transported in plasma, in which it is bound to retinol-binding protein [3].

Vitamin A is essential for the reproductive system, bone formation, vision and epithelial tissues [4]. *In vitro* studies on human keratinocytes have shown that vitamin A affects their growth and differentiation [5]. In human volunteers, 150 000 i.u. daily of vitamin A produced demonstrable retardation of keratinocyte maturation [6]. Skin disorders with abnormal keratinization, such as ichthyosis, pityriasis rubra pilaris and Darier's disease, have been treated with high doses of oral vitamin A. There is a risk of intoxication by such treatment and stereoisomers of retinoic acid are now used instead [1,7].

Vitamin A deficiency

Vitamin A deficiency is seldom seen in the Western world today. It is observed mainly in diseases causing malabsorption and is often associated with deficiency of other fat-soluble vitamins.

Clinical features. Classical manifestations of vitamin A deficiency include xerophthalmia, follicular hyperkeratosis and generalized xerosis [8]. Follicular papules are seen especially on the dorsal and lateral areas of the extremities, so-called phrynoderma. Histologically, there is lamellated hyperkeratosis around the hair follicles with keratinous plugs and atrophy of the sebaceous glands [9]. Diagnosis is confirmed by the finding of a low vitamin A level in blood and a positive response to vitamin A supplementation.

Zinc deficiency may lead to vitamin A deficiency as zinc acts on the retinol-binding protein, which is the transport protein for vitamin A and which is indispensable for mobilization of the vitamin from the liver. Furthermore, zinc acts on the oxidation–reduction interconversion of vitamin A (alcohol dehydrogenase is a zinc metalloenzyme). Lack of zinc may provoke symptoms of vitamin A deficiency [10], for example night blindness in alcoholics may be due to a combined lack of vitamin A and zinc [11].

Vitamin A intoxication

Aetiology. Chronic hypervitaminosis A may be observed in young children if they are persistently overdosed with strong vitamin preparations. Most reported adult cases have ingested more than 100 000 i.u. daily for several months. There is probably a risk of toxic effects if more than 50 000 i.u. daily are ingested for long periods [1].

Clinical features. There is lethargy, anorexia, weight loss and diffuse alopecia. The skin becomes pruritic, rough and dry with desquamation. The lips are dry and cracked. Follicular keratosis, patchy erythema and purpura may occur in hypervitaminosis A or due to administration of synthetic retinoids [2]. In young children, painful swellings of the limbs due to bone changes are conspicuous.

Diagnosis. Vitamin A intoxication is diagnosed by consistent clinical findings associated with an increased vitamin

A level in the blood. Radiology may demonstrate bone changes in young children and in some adults.

Treatment. No treatment is needed except immediate discontinuation of the vitamin A.

Carotenoderma

β-Carotene is the natural provitamin of vitamin A (retinol). A high intake of food containing carotene, especially carrots, causes carotenaemia (increased carotene in plasma) and may induce carotenoderma due to excess carotenes in the sweat. The condition is characterized by orange discoloration of the stratum corneum, especially on palms, soles and in areas where sebaceous glands predominate. The condition is quite harmless and subsides gradually when the dietary habits are regulated. It may occur in pregnancy as a 'pica'.

Carotenaemia is also seen in patients with hyperlipidaemia (diabetes mellitus, myxoedema) and occurs in subjects unable to convert ingested β-carotene into vitamin A [12].

β-Carotene traps free radicals and has been studied together with vitamin E and selenium as a possible dietary factor that may inhibit cancers [13], although this hypothesis remains unproven [14].

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Vitamin D [1,2]

Vitamin D is a group of antirachitic steroid derivatives with similar biochemical activity. It is synthesized in the body as vitamin D_3 (cholecalciferol), and is present in the diet from some animal sources (as vitamin D_3) or from plant sources as vitamin D_2 (ergocalciferol). There is little vitamin D_3 in the diet although it is present in cod-liver oil, butter, eggs and liver. Vitamin D is synthesized in the skin from 7-dehydrocholesterol, which is present in abundance, by the action of 290–320-nm UV irradiation (to previtamin D) followed by a temperature-dependent conversion stage. Vitamin D_2 is synthesized from its inactive provitamin, ergosterol, in plants, also by the action of UV irradiation. With adequate exposure to sunlight, dietary vitamin D is unnecessary [1]. Cholecalciferol is hydroxylated in the liver to form hydroxycholecalciferol, and further hydroxylation takes place in the kidney to form the biologically active 1,25-dihydroxycholecalciferol [1,2]. Vitamin D_2 follows the same hydroxylation pathway, and is equipotent to vitamin D_3. 1α-Hydroxyvitamin D_3 is a synthetic, highly potent vitamin D analogue used in the management of hypoparathyroidism, vitamin-D-resistant rickets and osteomalacia.

Vitamin D regulates calcium and phosphorus absorption and deposition, and influences the level of serum alkaline phosphatase. The skin is of unique importance in the synthesis, storage and release of vitamin D into the circulation [2]. Lack of vitamin D in children results in tetany and rickets (rachitis), and osteomalacia in adults. Elderly people produce less vitamin D_3. In children, limited exposure to sunshine may play an aetiological role; the same applies to some Asian women in the UK in whom there may be a combination of dietary deficiency and little sunlight exposure. Regular use of sunscreens may also lead to inadequate synthesis of vitamin D_3 [3]. It is remarkable how exposure to sunlight a few times a week can reduce the risk of osteoporosis, osteomalacia, muscle weakness and fractures [1]. The daily need for calciferol is about 400 i.u.

Vitamin D intoxication (long-continued administration of more than 100 000 i.u. daily) causes anorexia, vomiting, headache, diarrhoea, hypercalcaemia and hypercalciuria with osteoporosis, resembling the action of parathyroid hormone. Treatment consists of withdrawal of vitamin D, a low-calcium diet and systemic corticosteroids.

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Vitamin E [1,2]

SYN. α-TOCOPHEROL

Tocopherols are present in oils of vegetables, seeds, corn,

whole wheat flour, nuts and some meats; D-α-tocopherol is the most biologically active form. The main physiological activity of tocopherol is antioxidation. Whether the vitamin is essential to humans is still a matter of debate. In rats, guinea pigs and rabbits, a true vitamin effect has been demonstrated. Various dermatological diseases and conditions have been claimed to respond to vitamin E [1–3]. So far, no true benefit has been definitely documented. Fat-soluble vitamin E is located in the stratum corneum and seems to play a role in protecting this layer from damage [2]. An inhibitory effect on hyaluronidase and a protective effect on cellular membranes and on vitamin A oxidation have been suggested, but the clinical relevance is doubtful. Neurological function in children with chronic cholestasis was improved following large doses of vitamin E [4]. Large doses of vitamin E in a controlled trial have been shown to reduce the risk of myocardial infarction [5]. Vitamin E has also been used in dermatology to reduce dapsone-induced haemolysis [6] and headache [7].

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Vitamin B complex

The vitamins of the B complex are of great clinical significance. Isolated deficiencies of certain B vitamins are uncommon. Mostly combined deficiencies of the vitamins belonging to the group are involved, often occurring as a result of insufficient supply of protein and other essential nutrients (zinc, essential fatty acids).

The group includes:

1 aneurin (thiamine) (vitamin B_1);
2 riboflavine (vitamin B_2);
3 niacin (nicotinic acid) (B_3);
4 pyridoxine (vitamin B_6);
5 cyanocobalamin (vitamin B_{12});
6 folic acid;
7 pantothenic acid;
8 biotin (vitamin H).

Aneurin

SYN. VITAMIN B_1; THIAMINE

Aneurin is present in yeast, cereals, liver, meat, eggs and vegetables. It functions as cocarboxylase in carbohydrate metabolism and numerous other enzyme systems. It is involved in growth processes and in the function of the nervous system. Deficiency results in accumulation of pyruvic and lactic acids. Dietary deficiency may be a consequence of consuming polished rice as the staple food or, more commonly, of insufficient nutrition associated with chronic alcoholism (although beer drinkers have a reduced risk of developing B vitamin deficiency due to the presence of the vitamins in beer). Additionally, hypovitaminosis B_1 may be associated with pregnancy, lactation, diabetes mellitus, ulcerative colitis, coeliac disease, achlorhydria or myxoedema [1].

Clinical features [1]. The classical form of vitamin B_1 deficiency is beriberi, characterized by anorexia, weakness, constipation, symmetrical progressive polyneuritis, cardiac insufficiency with oedema and wasting of musculature. The diagnosis is based on the history and a low urinary aneurin excretion following an injection of 1.0 mg of aneurin. Excretion of less than 50 µg indicates a deficiency state.

Treatment. Aneurin 2–3 mg is given three times daily in mild cases. With severe cardiac and gastrointestinal involvement, or severe polyneuritis and muscular paresis, 20 mg twice a day given parenterally is indicated.

Riboflavine

SYN. VITAMIN B_2, LACTOFLAVINE

Riboflavine is a D-ribitol isoalloxazine derivative which is widely distributed in plant and animal tissues. It plays a part in intracellular redox reactions. Nutritional sources are milk and the same sources as those of vitamin B_1 [1]. The human requirement is 1–2 mg daily.

Clinical features. Deficiency becomes clinically manifest after several months of deprivation due to chronic illness and malnutrition, especially in elderly women who suffer from achlorhydria, or in malnourished children with malabsorption.

Ariboflavinosis may occur in alcoholic liver cirrhosis, and an association with other deficiencies, such as pellagra, is frequent. Clinically, there is photophobia due to conjunctivitis, sometimes with corneal vascularization, angular stomatitis (perlèche) and sore lips, tongue and mouth [1]. The tongue is purplish red and smooth. A scaly seborrhoeic dermatitis-like eruption may be seen around the nose, eyes, ears and genital area (oro–oculo–genital syndrome). An association with zinc deficiency is to be

expected, as the content of the two nutrients in foodstuffs is correlated [2].

Treatment. Treatment consists of 5–15 mg riboflavine two to three times daily for 2 weeks and correction of dietary errors.

Pyridoxine

SYN. VITAMIN B_6, PYRIDOXAL

Pyridoxine is a pyridine derivative, participating as a coenzyme in transaminase and decarboxylase reactions and in the metabolism of cystein, tryptophan and essential fatty acids. It is present in many foods including yeast, eggs and various grains. The recommended daily allowance is about 2 mg.

Although much is known about experimental deficiency in many species, the manifestations in humans are not well defined. Convulsions, anaemia and acrodynia may develop in infants [3]. Dermatitis has occurred and is attributed to disturbed metabolism of unsaturated fatty acids. Pyridoxine deficiency may follow therapy with isoniazid, hydralazine and penicillamine [4].

Vitamin B_{12}

SYN. CYANOCOBALAMIN; CYCOBEMINE

Vitamin B_{12} is involved in nucleic acid synthesis and erythrocyte production. Deficiency may occur in vegetarians, as plants do not contain the vitamin. More frequently it is due to lack of 'intrinsic factor' in pernicious anaemia. Hyperpigmentation, especially in dark-skinned races, may occur (Chapter 39). It is most pronounced in skin flexures, such as finger and palm creases, and on the knuckles. Pigmented streaks of the nails may be seen. An enlarged, red tongue is a characteristic finding [5].

Folic acid

Folic acid is a compound consisting of pteridine, *p*-aminobenzoic acid and glutamic acid. It is present in liver, meat, green leaves and milk. In the organism, folic acid is converted to folinic acid, which is the biologically active form. The conversion requires the presence of vitamin C. Folinic acid is needed for the transport of one-carbon units and therefore plays a role in growth and erythrocyte production. The daily requirement is estimated to be about 0.4 mg.

Although no consistent or specific cutaneous changes are related to folate deficiency, greyish brown pigmentation on light-exposed parts has been described [5,6]. Cheilitis, glossitis and mucosal erosions are common. Pigmentation similar to that of vitamin B_{12} deficiency has been associated with folate deficiency in pregnancy and lactation. Spotty pigmentation of palms and soles and pigmented palmar creases have been described. Folate deficiency is estimated by serum and erythrocyte folate levels. Subclinical deficiency may be present in patients with extensive skin disease.

Niacin

SYN. NICOTINIC ACID; VITAMIN B_3

Niacin is an essential component of two coenzymes, coenzyme I (nicotinamide adenine dinucleotide, NAD) and coenzyme II (NAD phosphate, NADP), which either donate or accept hydrogen in a wide range of biochemical reactions. Tryptophan, an essential amino acid, can be transformed to niacin, which is converted to the amide in the body. Niacin is involved in the biosynthesis of ceramides as well as of other stratum corneum lipids which improve the epidermal permeability layer [7].

Pellagra [8]. Cellular deficiency of niacin, resulting from an inadequate dietary supply of niacin and tryptophan, is termed pellagra. In Western Europe and North America pellagra is only rarely encountered now, mostly in subjects living on an unbalanced diet, such as chronic alcoholics, and in patients with gastrointestinal diseases or severe psychiatric disturbances. Rare causes are functioning carcinoid tumours (Chapter 44) and Hartnup disease (p. 57.84). Therapy with isoniazid (which competes biochemically with niacin owing to a close structural resemblance), 6-mercaptopurine or 5-fluorouracil may provoke pellagra [8,9].

The classical triad of clinical features (Fig. 57.45) is *dermatitis*, *diarrhoea* and *dementia*, not invariably appearing in this order. Redness and superficial scaling appear on areas exposed to sunlight, heat, friction or pressure (Fig. 57.46). The changes resemble sunburn and subside leaving a dusky, brown-red coloration, but this occurs more slowly than typical in sunburn [2] and exacerbation follows re-exposure to sunlight. On the face, a symmetrical 'butterfly' eruption is frequently observed and there is often a characteristic well-marginated eruption on the front of the neck ('Casal's necklace'). Asymmetrical lesions may appear at sites of old injury or stasis [10]. Gastrointestinal symptoms include pain, diarrhoea and achlorhydria in 50% of cases. In mild instances, the mental disturbance may pass unnoticed, patients perhaps being slightly depressed or apathetic. Sometimes, there may be frank disorientation, restlessness or other severe central nervous system symptoms [11]. Peripheral neuritis and myelitis are occasionally encountered.

Histological examination shows hyper- and parakeratosis, acanthosis and multiple melanin granules throughout the epidermis. Such changes are suggestive, but not diagnostic, of pellagra.

Drug eruptions, various forms of porphyria, photodermatitis, lupus erythematosus and actinic reticuloid may

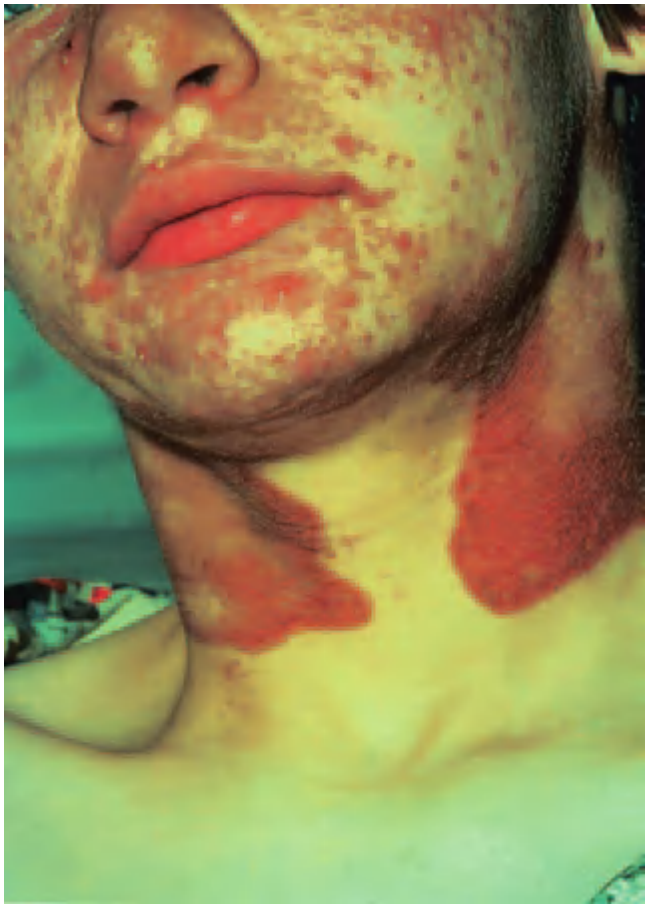

Fig. 57.45 Pellagra. Erythema, scaling and hypermelanosis of the neck (Casal's necklace). (Courtesy of Dr J. Jörgensen, Copenhagen, Denmark.)

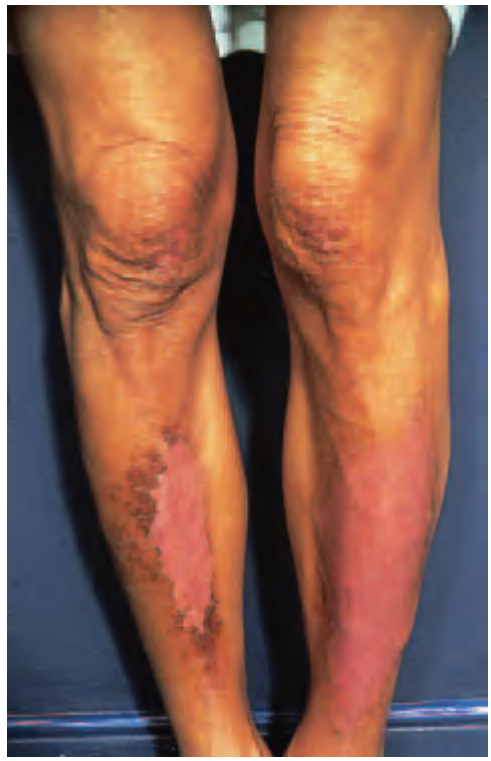

Fig. 57.46 Pellagra on the lower legs. (Courtesy of the Department of Dermatology, Gentofte Hospital, Hellerup, Denmark.)

cause diagnostic difficulty. The so-called pellagrous vulvitis, vaginitis and scrotal dermatitis may be attributed to accompanying ariboflavinosis and other deficiencies of the vitamin B group and of zinc.

In severe cases, intravenous niacin is required in doses of 50–100 mg once or twice a day. Otherwise, divided doses of oral niacin amide in a total dose of 0.5 g/day should be given. The amide is to be preferred, as it does not precipitate flushing, itching and burning as is seen following ingestion of niacin in large doses. Improvement can be expected within a day or two.

Kava dermopathy. Kava, a psychoactive intoxicating beverage used ceremonially and socially by Pacific Islanders [12], may produce a pellagra-like ichthyosiform dermopathy with widespread acquired ichthyosis [13]. Kava is produced by infusing dried roots of *Piper methysticum* with water or coconut milk. The cause of the skin disease has not been established; interference with tryptophan or niacin as previously suggested [13] is not likely. Interference with cholesterol metabolism akin to changes associated with lipid-lowering agents is a possibility. Kava dermopathy is curable with abstinence.

Biotin

SYN. VITAMIN H

Biotin is a water-soluble, sulphur-containing, heterocyclic carboxylic acid involved in bacterial metabolism and possibly functioning as a coenzyme in decarboxylation and other enzymatic processes. Deficiency can be induced by feeding raw egg-white containing avidin; this binds biotin and makes it poorly absorbable [14]. Short bowel syndrome in association with parenteral nutrition may cause biotin deficiency [15]. Symptoms include alopecia, conjunctivitis, eczema around the nose and mouth, hyperaesthesia, paraesthesia, depression and muscle pain. A multivitamin preparation supplying 60 µg of biotin daily cured an adult patient within 3 weeks [16]. Biotin seems to possess some antiseborrhoeic actions and has been used in high doses for therapy of Leiner's disease in infants (Chapter 14) [17].

Inborn errors of biotin metabolism [18]. The genetically determined disorders of biotin metabolism consist of two separate diseases: holocarboxylase synthetase deficiency and biotinidase deficiency. Both are transmitted as an autosomal recessive trait. Patients with holocarboxylase

deficiency present in the neonatal period with severe symptoms of organic acidaemia. The patients may have shown recurrent episodes of vomiting from birth and rapid respiration as a sign of severe metabolic acidosis. There are seizures, hypo- as well as hypertonia, electroencephalogram abnormalities, and the disease progresses to death unless diagnosis and effective therapy supervene. An erythematous, scaly rash is prominent over most of the body in the patients who survive the first days of life. The skin lesions may resemble ichthyosis and seborrhoeic dermatitis. The pattern of excretion of organic acids is characteristic, especially 3-hydroxyisovaleric acid and 3-methylcrotonylglycine in urine being increased. Lactic acidaemia is striking. The molecular defect is in the enzyme holocarboxylase synthetase.

Biotinidase deficiency. Biotinidase deficiency usually presents after 3 months of age. The cutaneous lesions may resemble those of acrodermatitis enteropathica, i.e. severe zinc deficiency. The hair is sparse, and there may be total alopecia. Neurological symptoms are prominent with myoclonic seizures and ataxia as common features. There are low levels of biotin in blood and urine. The fundamental defect is in biotinidase, which normally acts on biocytin, a biotin–lysine complex, thereby separating biotin from lysine [18].

Biotin treatment. Both of the biotin-related disorders discussed above are treated with an oral dose of biotin, usually 10 mg/day but some patients need less and some have required as much as 40 mg/day.

It has been reported that *uncombable hair syndrome* (Chapter 63) responded to oral biotin 0.3 mg three times a day [19].

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Vitamin C [1,2]

SYN. ASCORBIC ACID

Vitamin C is a relatively strong organic acid, chemically related to the carbohydrates. Only the laevo form is biologically active. Ascorbic acid is a strong reducing agent, easily oxidized to dehydroascorbic acid, with which it constitutes a reversible redox system. Vitamin C plays a central role in collagen and ground-substance formation [3], metabolism of aromatic amino acids (phenylalanine, tyrosine), reduction of folic acid to folinic acid and a broad range of biochemical redox reactions, including the preservation of sulphur-containing enzymes in a reduced form. It occurs naturally in cabbage, potatoes, green vegetables and fruits. The recommended daily dose is 30–80 mg; a daily intake of 10 mg prevents scurvy.

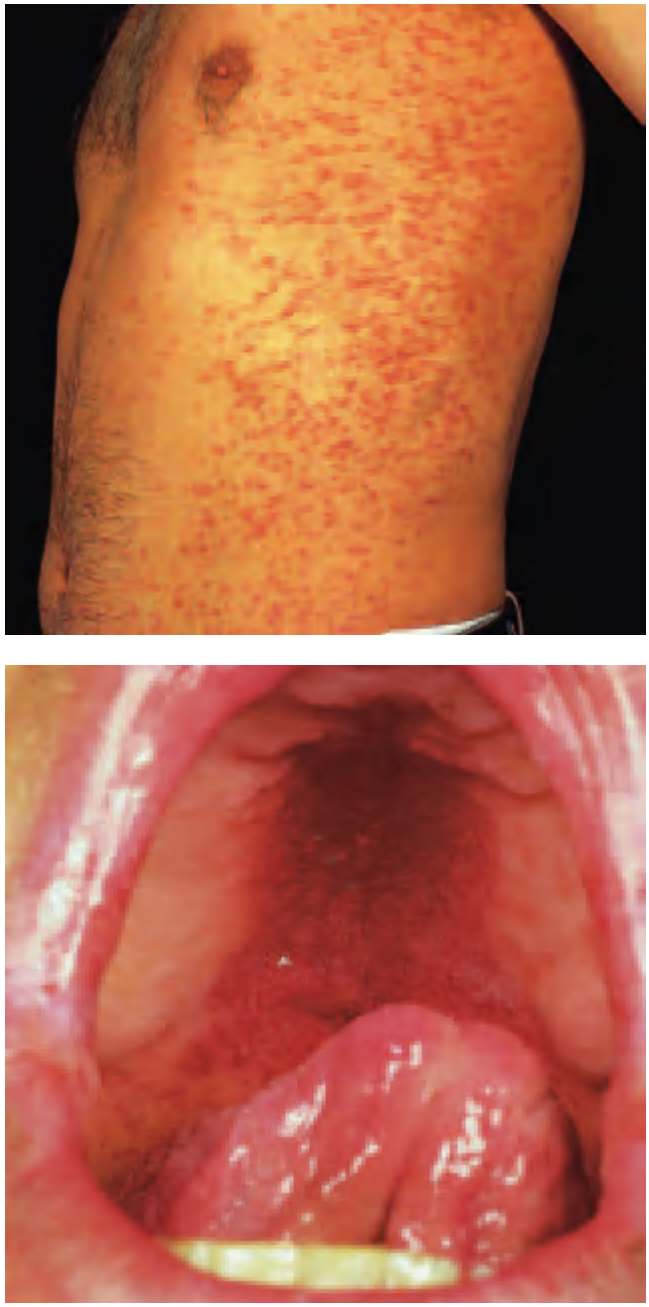
Vitamin C deficiency

SYN. SCURVY; SCORBUTUS; HYPOVITAMINOSIS C

Unlike most other animals, humans and guinea pigs are unable to synthesize ascorbic acid due to lack of the enzymatic pathways for synthesis of L-ascorbic acid from D-glucuronic acid.

In the deficiency state, collagen and ground-substance synthesis are depressed, which leads to a multiplicity of symptoms involving bones, mucous membranes and skin.

Aetiology. Lack of vitamin C is still a serious problem in many parts of the world where access to fruit and vegetables is limited and where general malnutrition prevails. By contrast, most cases in developed countries are a consequence of food faddism, ignorance or alcoholism [4,5]. Danish beer no longer contains vitamin C as an antioxidant, and can therefore no longer prevent scurvy in alcoholics [6]. Malnourished children with scurvy (Barlow's disease) may still be a paediatric problem as reported from Australia [7] and vitamin C deficiency has been observed in teenagers living on processed food devoid of fresh fruit and vegetables [8]. In patients with chronic gas-



(a)

(b)

Fig. 57.47 Scurvy. (a) Purpuric rash on the trunk and lower extremities; (b) purpura on the hard palate.

trointestinal disturbances, subclinical scurvy may be present [9]. Elderly men living alone, who rarely get fresh fruit or vegetables and who may abuse alcohol, are particularly at risk [10].

Clinical feature [4]. (Fig. 57.47). The initial skin change is follicular keratosis with coiled hairs on the upper arms, back, buttocks and lower extremities. Later, perifollicular haemorrhage with blood pigment discoloration especially on the legs, swollen bleeding gums, stomatitis and epistaxis occur. Large skin haemorrhages may be seen. Anaemia is usually present, and the patient appears resentful and mentally depressed. In the infant, dental development is impaired and oral changes may be severe. Tender subperiostal haematomas may develop and dominate the picture. Chronic hypovitaminosis C with 'woody' oedema and discoloration of the legs as the presenting feature has been described [11]. Subnormal serum levels of vitamin C are present (normal range about 17–94 μmol/L). The significance of low values without clinical symptoms is doubtful [7].

Treatment. The scorbutic patient should be treated with oral vitamin C 100 mg three times daily in addition to protein-rich food [4]. The response is dramatic. It is advisable to continue the therapy for several weeks to ensure repletion of the emptied body stores.

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Kwashiorkor and marasmus [1,2]

Kwashiorkor is a nutritional syndrome with characteristic cutaneous changes due to severe protein malnutrition with relative carbohydrate excess. In children, there is retardation of skeletal and mental development, muscular wasting, fatty infiltration of the liver and oedema. Marasmus is the result of prolonged starvation, a wasting syndrome, resulting in 40–50% reduction in body weight but with no peripheral oedema.

Kwashiorkor

Aetiology [2]. Protein–energy deficiency is one of the commonest and most widespread nutritional disorders in developing countries. The majority of kwashiorkor cases are found in countries where the diet consists of corn, rice or beans. Kwashiorkor is more common in children than in adults and is a major paediatric problem in certain parts of the world. The onset in infancy is during the weaning and postweaning period. In Europe and North America,

Table 57.13 Some features distinguishing kwashiorkor from pellagra.

Kwashiorkor	Pellagra
Children more than adults	Adults more than children
Dermatitis with systemic signs of apathy and oedema	Dermatitis precedes gastrointestinal and neuropsychiatric symptoms in most cases
Eruption generalized; pale, ill-defined; 'crackled skin'	Exposed areas only; red, thickened, well-defined; later, dry, branny scales
Hair light, 'pepper and salt' appearance, thin	Normal
Nails sometimes soft and thin	Normal
High mortality if untreated	Low mortality

occasional cases are seen in patients suffering from malabsorption or eating a diet that includes an inadequate amount of protein. Milder forms are probably not uncommon, particularly in the elderly.

Kwashiorkor refers to the 'deposed child' who is no longer suckled. It is a multiple deficiency syndrome. The cause is related to lack of essential amino acids, vitamins and trace elements, particularly zinc. The skin manifestations, hair changes and failure to thrive may mimic those seen in acrodermatitis enteropathica. Serum zinc is low, but this may be attributable partly to hypoalbuminaemia. Hospitalized children may show persistent hypozincaemia after clinical cure has occurred, indicating a need for zinc supplementation together with vitamins and protein-rich nutrition [3,4].

Clinical features [1,2,5]. The symptoms of kwashiorkor usually first develop between the age of 6 months and 5 years. The most important feature in the child is a failure to thrive, with inhibition of growth and mental development; oedema and muscle wasting are also found.

The skin lesions are initially erythematous and later purple or reddish brown in colour with marked exfoliation. In milder cases a lacquered 'flaky paint' ('enamel paint') or 'cracked skin' appearance is present. The hair is dry and lustreless and may become light red-brown in colour. In more severe cases it may be prematurely grey or show a 'pepper and salt' appearance, and become sparse, fine and brittle.

The skin often shows dyschromia with hypopigmentation, perhaps the result of phenylalanine deficiency, and patchy post-inflammatory hyperpigmentation. In severe cases pigmentary changes are particularly striking. Mucosal lesions, such as cheilosis, xerophthalmia and vulvovaginitis, are found.

Mental disturbances are variable and may appear either as apathy or irritability. The child does not smile; when it does, it is a sign of recovery.

Oedema is the result of hypoalbuminaemia (less than 2.5 g/100 mL). The α- and β-globulins are low, while an increase in gammaglobulin is usual.

Hypoglycaemia with hypothermia, coma and severe bacterial or parasitic disease are rare, but often fatal, complications [6].

Mild cases of kwashiorkor appearing in the elderly show as a 'cracked skin' appearance on the front of the legs and lower abdomen. They have been reported under the title of geriatric nutritional eczema.

Prognosis. The short-term prognosis of mild cases which are given full dietary treatment is good, but mortality is high in severe and relapsing cases.

Diagnosis. Diagnostic difficulties occur in mild cases. The dietary history, 'cracked skin' and oedema, particularly when associated with pigmentary changes, should lead to the suspicion of protein deficiency. Acrodermatitis enteropathica may be mistaken for kwashiorkor.

The features distinguishing kwashiorkor from pellagra are shown in Table 57.13.

Prevention and treatment. Prevention of kwashiorkor depends on increasing the supply of animal proteins, and on education and social welfare in poor areas.

In an established case, a complete and balanced diet should be given as soon as possible. Skimmed milk is the most useful treatment, presumably through its amino-acid content. Appropriate measures should be taken to correct any electrolyte disturbance.

Marasmus [1]

Aetiology. Marasmus is derived from the Greek *marasmos*, which means wasting. It is a result of severe protein and calorie deprivation for a prolonged period. Worldwide, marasmus is more frequent than kwashiorkor and is especially seen in developing countries where food is absent or scarce. Severely ill, hospitalized patients may show signs of marasmus. Low zinc levels are a predominant feature.

Clinical features. Patients have a wrinkled, loose, dry skin. There is a substantial loss of subcutaneous fat tissue, and the facial expression is described as 'monkey facies' due to loss of the buccal adipose tissue. Follicular hyperkeratosis may be prominent in adults. The hair is thin and sparse and readily lost and the nails are fissured. Skin ulceration occurs.

Diagnosis. The combined finding of a severely reduced body weight, loss of subcutaneous fat, poor hair and nail growth and a loose, wrinkled, dry skin that appears too large is diagnostic. There is no peripheral oedema.

Prevention and treatment. This is as for kwashiorkor. Skin ulceration may respond to topical zinc paste or oral zinc supplementation in addition to a protein-rich nutritional supply.

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Calcification and ossification of the skin [1–3]

Calcification or calcinosis cutis is the result of deposition of calcium and phosphate in organic matrices of the tissues. The process occurs in a wide range of different conditions. The mineral phase may be arranged in the manner seen in normal bone formation, *ossification*. If the deposition is not organized, the condition is termed *calcification*. The organic matrix consists largely of collagen or elastic tissue. All organic matrices of calcified or ossified tissues contain protein-bound phosphorus. In pathological ectopic calcification, the matrix is altered and contains acid proteins. In pseudoxanthoma elasticum, γ-carboxyglutamic acid, an amino acid present in calcium-binding proteins, has been found in high concentrations in the dermis. The solid phase of calcified tissue is made up of hydroxyapatite and amorphous calcium phosphate. Once formed, the focus increases in size by growth and may result in disorganized masses of pasta-like material.

Aberrant calcium deposition in the skin may be divided into three main groups:

- associated with localized or widespread tissue changes or damage (dystrophic calcification);
- unassociated with tissue damage or demonstrable metabolic disorder (idiopathic calcification);
- associated with an abnormal calcium and phosphorus metabolism (metastatic calcification) (Table 57.14).

Table 57.14 Various forms of calcinosis cutis.

Dystrophic calcification
Calcification usually associated with localized injury
Congenital
Fibrodysplasia ossificans
Traumatic
Foreign-body, haematoma, fat cell necrosis
Inflammatory
Acne, varicose veins, tuberculous granuloma, postoperative inflammation in scars
Degenerative infarcts (arterial, venous), venous stasis, parasitic cysts (e.g. echinococcal cysts)
Neoplastic
Benign: sebaceous cysts, lipomas, angiomas, calcifying epithelioma of Malherbe
Malignant: some liposarcomas
Calcification associated with widespread tissue injury
Dermatomyositis
Generalized scleroderma (Thibierge–Weissenbach or CREST syndrome)
Systemic lupus erythematosus
Acrodermatitis atrophicans
Pseudoxanthoma elasticum
Ehlers–Danlos syndrome
Idiopathic calcification
Calcinosis universalis; calcinosis circumscripta
Solitary nodular calcification of the skin ('cutaneous calculus')
Pinnal calcification
Tumoral calcinosis
Metastatic calcification
Hypercalcaemic
Hyperparathyroidism
Sarcoidosis
Vitamin D excess
Milk–alkali syndrome
Destructive bone disease
Metastatic carcinoma, lymphoma, multiple myeloma, leukaemia
Paget's disease
Normocalcaemic
Chronic renal failure
Pseudohypoparathyroidism

Dystrophic calcification [4]

The calcinosis is confined to the dermis or subcutaneous tissue and related to local connective tissue or fatty tissue damage, in the absence of any detectable abnormality of calcium metabolism. The calcification appears a variable time after the injury; for example, in dermatomyositis it occurs after a few years and in generalized scleroderma usually after 10 or more years. Dystrophic calcification may also occur in systemic lupus erythematosus [5,6].

Electrical injuries may be particularly likely to result in dystrophic calcification. An accumulation of calcium salts on dermal collagen fibres of pig skin was observed in scars following electrical injury [7]. Deposition of calcium salts in high concentration on a damaged skin surface may induce dermal calcification, as observed following electroencephalography in children [8]. In these cases, the skin was abraded prior to application of an electrode paste containing calcium chloride; lesions developed shortly after electroencephalography and disappeared in 2–6

months without therapy. An intact stratum corneum is protective.

Idiopathic calcification

Calcinosis universalis

The deposition of calcium in the dermis, subcutis and muscles is unrelated to any recognizable tissue injury or metabolic disorder. Many cases reported in the literature under the diagnosis were probably suffering from undetected dermatomyositis, systemic lupus erythematosus or scleroderma, but there remain a number of instances in which no underlying disease is demonstrable [2].

Histopathology. Initially, calcium particles gather around fat cells. Electron microscopy of early lesions has shown apatite crystals lying parallel to the collagen fibres [9].

Clinical features. Nodules or plaques 0.5–5.0 cm in size are symmetrically distributed over the extremities and, less commonly, the trunk. The lesions may become tender and ulcerate, discharging chalk-like creamy material consisting mainly of calcium phosphate with a small amount of calcium carbonate. After ulceration, a slowly healing sinus remains. Fingertip lesions are often painful, while in other sites there may be limitation of movement due to stiffening of the skin. The disease is eventually fatal.

X-ray examination is valuable for localizing the deeper deposits. Biochemical investigations are normal.

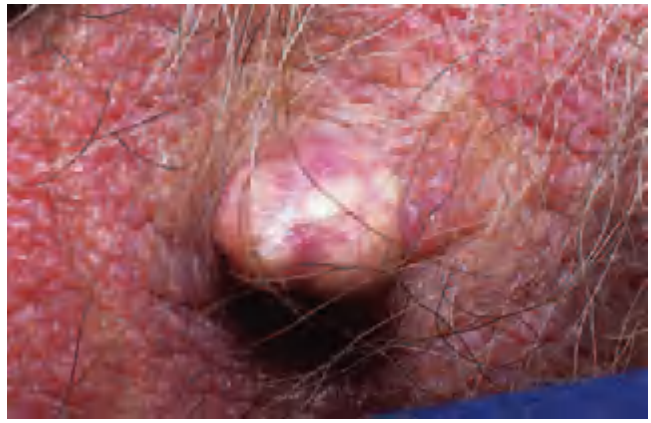
Treatment. Surgical removal of painful deposits may give temporary relief. In some instances, corticosteroids may be considered, although the response is variable. Cellulose phosphate combined with a low-calcium diet should be considered as therapy [10].

Calcinosis circumscripta

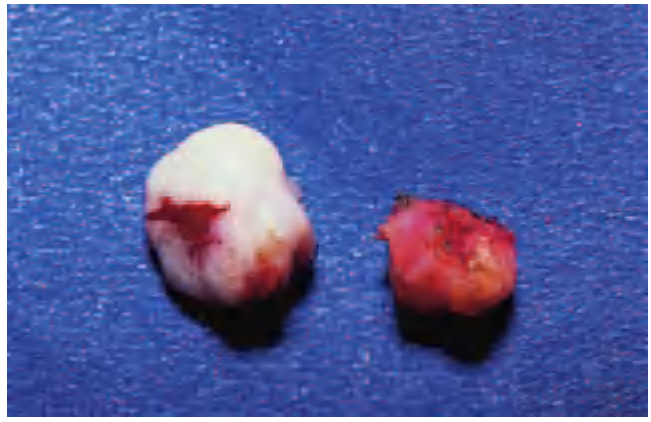
There may be only a few calcium deposits in the skin. Most cases of calcinosis circumscripta are found in generalized scleroderma or dermatomyositis but rarely it may occur as an idiopathic disorder [3]. Keloid formation with calcification has been described [11].

Idiopathic calcinosis of the scrotum [11,12]

Calcinosis scrotalis (Fig. 57.48) is a rare benign disorder consisting of multiple asymtomatic firm nodules 0.2–1.0 cm in diameter. It is often misdiagnosed as scrotal cysts. Dystrophic calcification in the penis has been reported following trauma, Peyronie's disease and cytostatic therapy.



(a)



(b)

Fig. 57.48 (a) Calcinosis scrotalis. (b) Shows solitary nodules after removal.

Calcifying epithelioma of Malberbe

This is described in Chapter 37.

Tumoral calcinosis [2,13,14]

Tumoral calcinosis occurs most commonly in the native population of Africa, particularly among younger age groups. Clinically, the lesions present as swellings around the large joints (hip, elbow, ankle and scapula), but there is no actual involvement of the joint. Extrusion of calcified material, which has been likened to a suspension of procaine–penicillin, may take place. Histologically, there is initially collagen necrobiosis, which results in cyst formation and a foreign-body response. The calcification is first granular; later, dense deposits are seen [13]. The aetiology is unknown, but it is probably a form of dystrophic calcification caused by mechanical injury.

Pinnal calcification [2]

Calcified ear cartilage has been observed in several conditions such as Addison's disease, ochronosis, acromegaly,

diabetes mellitus, hyperthyroidism, systemic chondromalacia (von Meyenburg's disease), familial cold hypersensitivity and frostbite.

Metastatic calcification [3,15]

In metastatic calcification, calcinosis occurs as a precipitation of calcium salts in normal skin, subcutaneous tissue, muscles and internal organs.

Aetiology. In all cases, there is an increase in the serum levels of calcium or phosphate. Hypercalcaemia may be due to hyperparathyroidism, vitamin D intoxication, milk–alkali syndrome or destructive bone disease with excessive osteoclastic activity. Metastatic carcinoma, multiple myeloma, leukaemia and Paget's disease of bone may all be associated with metastatic calcification. Calciphylaxis (Chapters 49 and 59) is a potentially fatal syndrome due to a raised serum calcium phosphate product, which is the result of chronic renal insufficiency in patients undergoing long-term renal dialysis, in whom there has been development of secondary or tertiary hyperparathyroidism [16].

Clinical features. The cutaneous manifestations are similar to those of calcinosis universalis. Additional clinical features reflect the primary disease.

Treatment. Only in hypervitaminosis D and the milk–alkali syndrome can improvement be expected by regulation of dietary habits and withdrawal of vitamin D and milk intake. In cases of renal insufficiency, restriction of dietary phosphate and oral administration of an aluminium hydroxide gel may be useful.

Ossification of the skin

SYN. OSTEOMATOSIS; OSTEOMA CUTIS

Osteomatosis represents cutaneous calcification with *de novo* bone formation in the skin [17]. It has been noted in suprapubic prostatectomy scars and in otherwise normal postoperative scars [18]. It may also occur in collagen vascular disease (lupus erythematosus, scleroderma and dermatomyositis) [19]. Cutaneous ossification without any known causative factor (also known as osteomatosis cutis, primary osteoma cutis or osteosis cutis) has been reported [17].

Post-acne osteoma cutis

This is a rare complication of long-standing acne vulgaris. It has been reported to occur as pigmented osteomas during tetracycline or minocycline therapy. The osteomas that represent metaplastic bone formation are located in mid or reticular dermis and consist of concentric lamellae with lacunae, Haversian canals and marrow cavities. With the use of tetracycline, more patients develop bluish, 1–2-mm, moveable papules on the face. Treatment consists of surgery or local 0.5% tretinoin cream with resultant transepidermal elimination of the lesions [20].

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Iron metabolism [1]

The total iron content of an adult man is 4–5 g, 60–70% of which is blood haemoglobin iron. Small amounts of ferritin iron are present in erythrocytes, plasma and leukocytes [1]. Iron is stored in the liver, spleen and bone marrow as ferritin and haemosiderin. It is released readily from these sites according to the body's needs. Serum ferritin levels vary with the iron status of the individual and with certain diseases. The body has a limited ability

to excrete iron, and homeostasis is therefore regulated mainly by adjusting iron absorption. Iron compounds need to be reduced to the ferrous form (Fe^{2+}) to be absorbed. Ascorbic acid, which can reduce and chelate iron, enhances iron absorption.

The mechanism of iron absorption is not completely understood. Recent evidence points to an iron-transport system involving the binding of iron to the plasma membrane of mucosal cells and the interaction of transferrin in plasma with these sites.

Total iron in faeces varies between 6 and 16 mg/day depending on the amount ingested. Most of it is unabsorbed food iron.

Iron deficiency

General symptoms include fatigue, palpitations on exertion, sore tongue with atrophic filiform papillae, angular cheilitis (perlèche), dysphagia and koilonychia (Chapter 62). Generalized itch may be present [2] and hair loss with or without morphological changes of the hair shaft [3,4]. In infants and children, anorexia, retarded growth and decreased resistance to infections are the outstanding features. The recommended daily allowance is 10 mg in infants, 10–15 mg in children, 18 mg in young males and females, and 10 mg in both sexes above 20 years of age [5]. Pregnant women should receive supplemental iron, as the increased need for iron can barely be met by ordinary diets [6].

The diagnosis of iron deficiency is based on low serum iron levels, clinical symptoms and improvement following iron therapy. Serum ferritin is significantly correlated to bone marrow haemosiderin iron and provides a convenient method for assessing marrow iron stores in normal subjects [7].

Iron intoxication

Daily ingestion of 50–75 mg iron has been reported as safe [1], and even higher intakes in some individuals turn out to be harmless. Chronic iron intoxication has been reported among Bantus consuming beer that is brewed in iron utensils. The iron is in a soluble form and may supply a substantial net supply of iron. Iron-contaminated cereals do not induce siderosis because iron is present in a less available form.

Haemochromatosis [1,8]

Haemochromatosis is a syndrome characterized by the triad of hyperpigmentation, diabetes mellitus and cirrhosis of the liver, associated with increased iron deposition in the internal organs. Hypogonadism is frequently present. The female/male ratio is 1 : 10. Onset of symptoms is gradual, usually between 40 and 60 years.

Aetiology. Haemochromatosis can be found in the following conditions: idiopathic or primary haemochromatosis; chronic iron intoxication (e.g. Bantu haemochromatosis); chronic liver disease and iron overload (alcoholic haemochromatosis); hepatic haemosiderosis in anaemic patients with an ineffective erythropoiesis; and congenital transferrin deficiency. The cause of primary haemochromatosis is basically unknown, but a defective control of iron absorption is involved. The abnormality is inherited as an autosomal recessive trait (Chapter 59). Erythrocyte ferritin is increased 60-fold in idiopathic haemochromatosis, which allows a distinction between this disorder and alcoholic liver disease with iron overload [9]. In alcoholic haemochromatosis, alcohol consumption, particularly red wine and iron-containing beverages, plays an aetiological role. Whether the acquired form is seen in patients heterozygous for the trait is not known.

Histopathology. Liver biopsy in primary haemochromatosis shows marked iron deposits in the parenchymal cells and to a lesser degree in the Kupffer's cells. The hyperpigmentation of the skin is due to increased epidermal melanin and upper dermal melanophages, but iron deposits can be identified in the deeper dermis.

Clinical features. The skin shows a distinctive grey-brown pigmentation, especially on the face, flexural creases and exposed parts. This may precede other signs by many years but can appear late in the course. Sometimes, the buccal mucosa is involved as in Addison's disease but adrenal insufficiency is not present. The various skin changes were studied in 100 patients [10]. There was almost 100% frequency of hyperpigmentation, 75% had hair loss (including axillary and pubic hair), about 50% had koilonychia and 45% had ichthyosis-like, atrophic dry skin. Less frequent signs included palmar erythema, striate onychia, leukonychia and spider angiomas (findings that may be seen in cirrhosis of any cause). Hepatomegaly, diabetes, testicular atrophy, heart disease and weight loss are additional findings. Arthropathy, present in 25–50% of the patients, resembles rheumatoid arthritis, but serology is negative.

Diagnosis. The diagnosis should be suspected in a patient with diabetes mellitus, liver cirrhosis and hyperpigmentation. Liver biopsy is usually diagnostic.

Routine laboratory tests may reveal evidence of chronic hepatic disease or of diabetes mellitus. Total serum iron is increased to the range 180–300 mg/100 mL [1], serum transferrin saturation is above 80% [10] and the transferrin level and the total iron binding capacity (TIBC) may be reduced [8]. Serum and erythrocyte ferritin is high, reflecting the increased iron stores [9]. HLA-typing has revealed an increased frequency of HLA-A3, and -B14 [11] but has largely been superseded by genotyping for the commoner haemochromatosis genes (Chapter 59).

Treatment. An iron liver concentration above 100 μmol/g weight is an indication for therapy [6]. Organ damage may be reversed by reducing the excessive iron stores by repeated venesection for 1–2 years. Serum iron and serum transferrin and transferrin saturation remain unchanged until excess iron has been removed. Serum or erythrocyte ferritin should be monitored as a guide to the efficacy of treatment. Family members should have their serum iron estimated and, if found to have iron overload, should be treated with prophylactic venesection.

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Sulphur metabolism [1]

Sulphur is a vital element for the normal function of the human body. It is an essential component of the amino acids methionine and cysteine and of chondroitin sulphate, which are involved in keratinization and formation of dermal collagen, respectively. Dietary thionine and cysteine are the main precursors for the synthesis of sulphur-containing components in the body. In homocystinuria there is a metabolic block in the pathway; clinical features include tissue-paper scars on the hands and sparse, fair hair due to impaired keratin formation. When the supply of sulphur-containing amino acids is inadequate, less sulphur is available to nail and hair growth, but the keratin produced seems to be normal [2]. The liver plays a central role in degradation of sulphur-containing amino acids. In chronic liver disease, low urinary levels of inorganic sulphate are present [1].

In exfoliative psoriasis with increased epidermopoiesis, relative sulphur depletion is found and the urinary excretion of inorganic sulphate is decreased. Hair loss in chronic exfoliative dermatoses may be related to diversion of sulphur-containing amino acids to synthesis of skin protein instead of hair keratin formation [2]. Mucopolysaccharide synthesis in the dermis is influenced by certain hormonal factors. Thyrotrophin (thyroid-stimulating hormone, TSH) has a stimulant action on connective tissue and the pituitary somatrophic hormone (growth hormone, GH) stimulates chondroitin sulphate formation.

Trichothiodystrophy [3,4]

Trichothiodystrophy is a sulphur-deficient brittle hair syndrome associated with ectodermal dysplasias. The hair is short and brittle with a characteristic microscopy in polarized light showing alternating light and dark bands (Chapter 63) [4]. There is a 50% decrease or more in the cysteine and sulphur of hair. The disease is inherited as an autosomal recessive trait.

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Zinc metabolism [1,2]

Zinc belongs to the group of essential trace elements that comprises zinc, iron, copper, manganese, nickel, cobalt, molybdenum, selenium, chromium, iodine, fluorine, tin, silicon, vanadium and arsenic [3]. High concentrations of zinc are present in shellfish, legumes, nuts, whole grain and green leafy vegetables, whereas fruits usually contain insignificant levels [4]. Wine, beer and spirits contain very low concentrations of zinc. The zinc supply depends largely on the protein content of the food, and protein undernourishment will lead to an insufficient zinc supply.

Recommended dietary allowance of zinc [5]. The daily oral intake of zinc should average 3 mg in infants less than 6 months, 5 mg in infants 0.5–1.0 years old, 10 mg in children 1–7 years old and 16 mg from 11 years old onwards. Pregnant and lactating women should receive 20–25 mg zinc daily.

Biological functions. Zinc is indispensable to the normal function of all cells, cellular systems, tissues and organs in the human body. The essentiality is related mainly to its function as the metal moiety of important enzymes, such as alkaline phosphatase, alcohol dehydrogenase and several different dehydrogenases, and digestive enzymes [6]. Zinc also regulates DNA and RNA polymerases,

thymidine kinase and ribonuclease, and plays an important role in immunological functions.

Zinc deficiency

Zinc deficiency may be caused by a specific absorptive defect, as occurs in acrodermatitis enteropathica, by insufficient dietary intake, or due to diseases of the gastrointestinal tract causing diarrhoea and malabsorption (conditioned or acquired zinc deficiency).

Acrodermatitis enteropathica

Acrodermatitis enteropathica was first recognized in 1936 by Thore Brandt [7] and further investigated by Danbolt and Closs [8]. It is a rare disease believed to be transmitted as an autosomal recessive trait. In Denmark, the prevalence is about 1/500 000 inhabitants. *Adema disease* in black-pied cattle of Dutch descent represents a true parallel of the human disease.

Aetiology. Zinc absorption in young patients with acrodermatitis enteropathica is low, about 2–3% compared with 27–65% in normal adults. The cause of the specific zinc malabsorption is not known but can be overcome by an oral zinc load. Without zinc therapy, serum zinc levels are consistently low [9].

Clinical features. The disease typically starts after weaning or earlier if the infant is not given breast milk. The child turns peevish, withdrawn and photophobic, and develops a vesicobullous dermatitis on hands, feet and periorificial areas. The scalp hair is lost. Diarrhoea is often present. Growth is stunted and there is a decreased resistance to infections. Wound healing is poor and skin lesions do not heal [10].

Prognosis. Without proper management, the prognosis is poor and in the past a lethal outcome within 4–5 years was the rule.

Treatment. Halogenated 8-hydroxyquinolines (e.g. diodoquin) were formerly used for therapy on an empirical basis. Experimental animal studies have shown that iodochlorohydroxyquinoline, a commonly used antibacterial agent, increases ^{65}Zn absorption [9,10]. Zinc sulphate for acrodermatitis enteropathica was introduced in 1973–74 [11–13]. Oral zinc in a dose of about 2 mg/kg/day was found to cure all clinical manifestations. Prolonged therapy at least up to adult age is necessary.

Endemic nutritional zinc deficiency

Endemic zinc deficiency presenting with dwarfism and hypogonadism as the main symptoms has been reported from rural districts in Iran, Egypt and Turkey. The chronic zinc deficiency is attributed to the diet, which consists mainly of unleavened whole grain bread with a high fibre and phytate content. Zinc deficiency has been described in severely malnourished children in Jamaica [4], Egypt and various parts of Africa.

Acquired zinc deficiency

Zinc depletion syndrome. Where there is disturbed bowel function, the zinc loss is increased; if combined with decreased absorption and low dietary zinc intake, zinc depletion will develop. Zinc depletion syndrome was originally identified in patients who received prolonged total parenteral nutrition [13,14], most of whom had undergone extensive intestinal resections. The serum zinc level is decreased, often below 20 µg/100 mL (normal range 70–125 µg/100 mg, equivalent to 10–19 µmol/L).

Zinc deficiency in breastfed infants. Premature infants receiving mother's milk are at risk of developing zinc deficiency due to an insufficient zinc content in the milk to ensure rapid growth [15]. Premature infants have an extra need for zinc and zinc absorption is less than in mature infants.

Diseases of liver and pancreas. Chronic zinc deficiency may develop in patients suffering from malabsorption–malnutrition associated with alcoholic liver cirrhosis and alcoholic pancreatitis [13]. A defective exocrine pancreatic function and elevated urinary zinc excretion associated with liver cirrhosis [16] add to a negative zinc balance (Chapter 59).

Cancer chemotherapy. Cancer chemotherapy for leukaemia in children may provoke zinc deficiency [17].

Zinc deficiency and skin changes [18]

Acute zinc deficiency. General symptoms include septicaemia, photophobia and mental depression. Skin changes consist of eczematous eruptions on hands, feet, in the anogenital regions and around the body orifices. The finger flexural creases and the palms show characteristic flat, greyish, bullous lesions surrounded by red-brown erythema (Fig. 57.49). Oozing lesions may be seen on the heels of bedridden patients. Some lesions are black and necrotic, and burn-like skin changes may be seen. There is angular stomatitis with perioral lesions sparing the vermilion border.

Chronic zinc deficiency. The patient is often listless and mentally depressed. Skin lesions are typically seen on areas subject to repeated pressure and trauma, such as elbows, knees, knuckles and malleolar regions of the

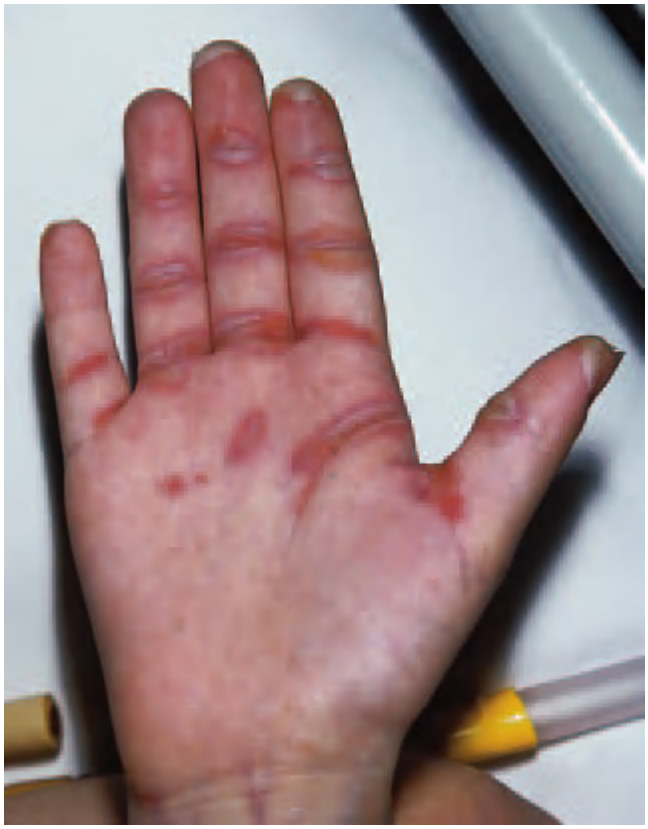

Fig. 57.49 Zinc depletion syndrome with flat bullae on flexural finger creases.

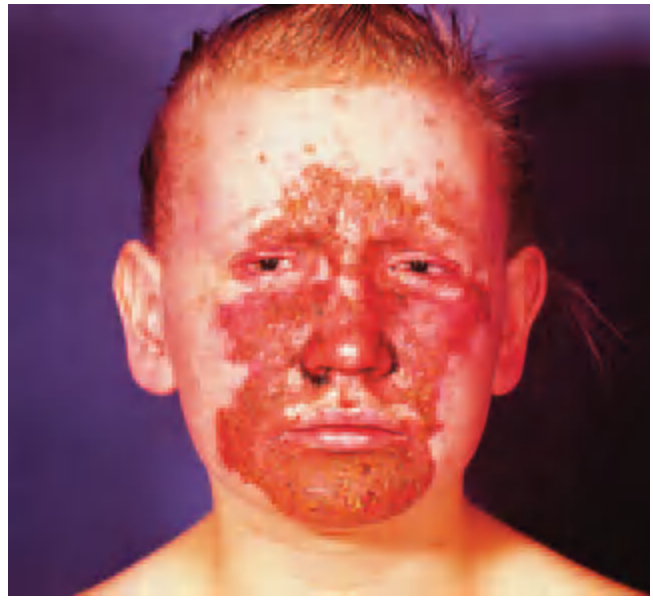

Fig. 57.50 Acrodermatitis enteropathica with chronic zinc deficiency symptoms. Typical periorificial chronic skin lesions with necrotic areas around the nose. The vermilion area is always spared. The hair growth is poor.

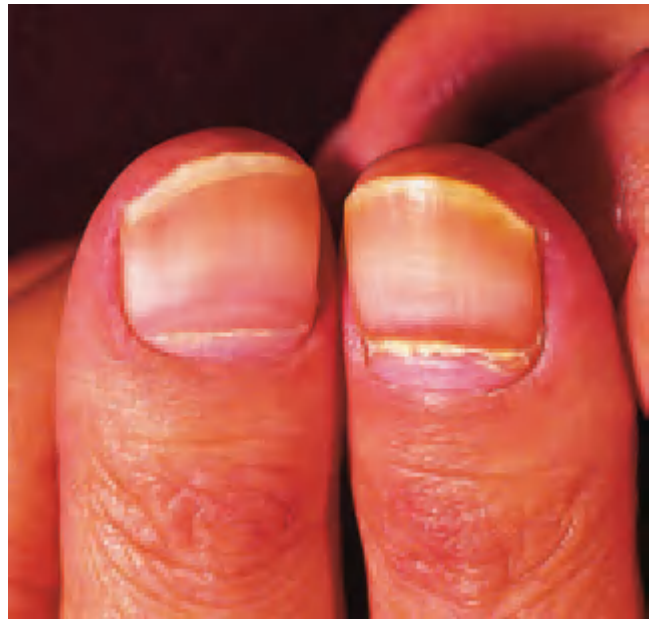

Fig. 57.51 Beau's lines on thumbnails in a case of zinc depletion syndrome treated with zinc sulphate.

ankles. The lesions are brownish (Fig. 57.50). Seborrhoeic dermatitis-like changes may be seen on the face and acne vulgaris may flare.

A non-itchy, scaly dermatitis on the trunk has been described in chronic zinc deficiency of alcoholics.

Hair and nail changes. In zinc deficiency, hair growth ceases, and diffuse thinning of the scalp hair becomes progressive and eventually leads to total alopecia after weeks. Structural changes of the hair may be observed, such as broken spearhead-like endings, transverse striation of the shaft, pseudomonilethrix, longitudinal splits and bayonet hairs. Severe zinc deficiency usually causes temporary arrest of nail growth, which is manifest as transverse depressions (Beau's lines) on the fingernails which become visible 3–4 weeks after the start of zinc supplementation as the normal nail growth recommences from the nail matrix (Fig. 57.51) [19].

Pathology. In the acute stage, light microscopy reveals spongiosis, sometimes with formation of suprabasal cysts and clefts (Fig. 57.52). The horny layer is often separated or lost, and necrosis of the outer epidermal cells may be seen. In chronic zinc deficiency, there are more or less psoriasis-like changes of the epidermis (Fig. 57.53).

Electron microscopy of acute lesions shows degenerate basal cells with slender cytoplasmic protrusions and an intact basal lamina with multiple invaginations.

Diagnosis. Severe zinc deficiency is usually suspected from the clinical findings. The serum zinc and alkaline phosphatase levels are low and rise during zinc therapy

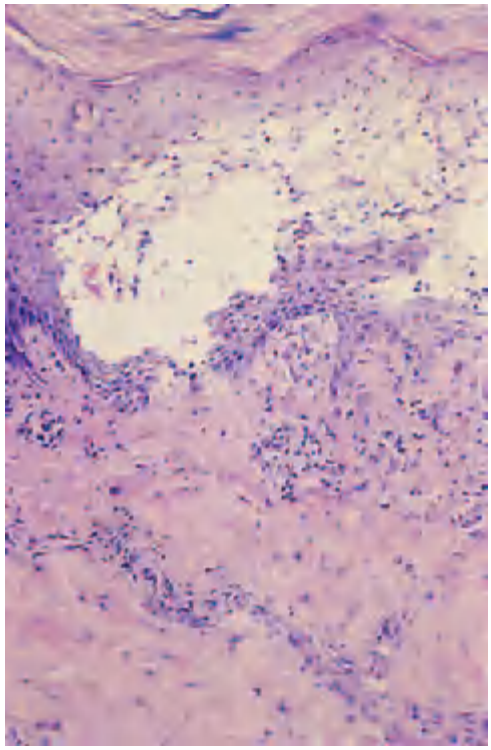

Fig. 57.52 Acute zinc deficiency with bullous dermatitis (same patient as in Fig. 57.49). Spongiosis, bulla and cleft formation is prominent. The basal cell layer is degenerate.

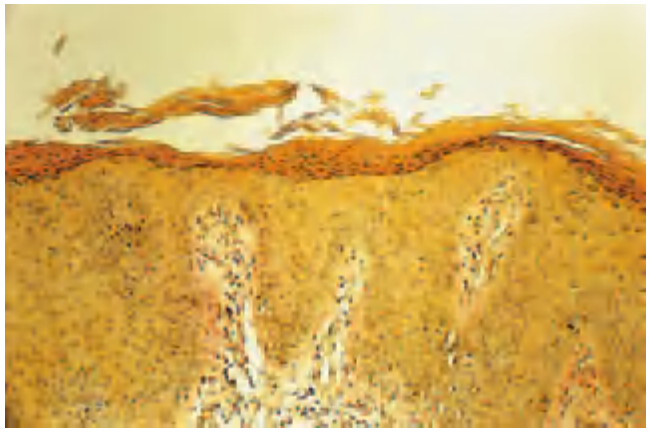

Fig. 57.53 Chronic zinc deficiency with parakeratosis, acanthosis and slight spongiosis.

[18]. It is important to consider the level of plasma albumin that binds 60–70% of circulating zinc. Hypoalbuminaemia is associated with lowered serum zinc values, which do not necessarily reflect a zinc deficiency.

In suspect cases, a therapeutic trial with oral or parenteral zinc should be undertaken. If no clinical improvement occurs within 4–5 days and the serum alkaline phosphatase remains unaltered, the patient is probably not zinc deficient.

Treatment with zinc. In adult patients, oral zinc sulphate ($Zn_2SO_4 \cdot 7H_2O$) tablets of 0.2 g are given two to three times a day (about 2 mg zinc/kg). Similar doses on a kilogram basis are given to children. Parenterally, 0.2–0.3 mg zinc/kg/day (about 10–20 mg/day in adult patients) is sufficient. For prophylactic purposes, total parenteral nutrition should supply no less than 70–80 µg zinc/kg/day. Infants and premature babies on parenteral nutrition should receive a prophylactic dose of 0.1–0.3 mg/kg/day [20].

There is no evidence of benefit from the general use of zinc sulphate in patients with chronic leg ulcers [21] or for the use of zinc to treat the common cold [22].

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Copper metabolism

The normal adult body has been estimated to contain about 80 mg of total copper.

Copper in plasma occurs in two forms: about 90% is firmly bound as the blue copper protein coeruloplasmin, the remainder is loosely bound to plasma proteins, primarily albumin. Copper competes with the albumin-binding sites for zinc, so fluctuations in concentration of one of these metals are reflected by a change in concentration of the other. Coeruloplasmin is an oxidase involved in iron utilization. It does not play a role in copper transport to the tissue; this is done by albumin, which is the true transport protein. Copper is part of superoxide dismutase, catalysing superoxide anion radicals into hydrogen peroxide and oxygen.

Copper-induced green hair

Green hair is usually caused by deposition of copper from exogenous sources. Usually, the patient has blond or reddish hair that has been exposed to physical or chemical damage (sun damage or bleaching) whereby high-sulphur matrix proteins (mainly cysteine) are exposed, and are therefore available to bind copper ions. A high copper concentration may occur in swimming-pool water due to copper-containing algicides and in household tapwater due to copper piping [1,2]. A hair shampoo with an added copper chelating agent such as dimethylcystein (penicillamine) can remove the discoloration.

Copper deficiency

Copper deficiency has been reported to occur in infants receiving milk low in copper and in malnourished children given high-calorie nutrition with an insufficient copper supply. The symptoms include anaemia, neutropenia and failure to thrive.

Menkes' kinky hair syndrome. This is an X-linked defect in copper absorption, resulting in low copper levels in blood, liver and hair. There is progressive mental deterioration, metaphyseal lesions, degenerative aortic elastin and defective keratinization of hair (Chapter 63). There is no effective treatment [3].

Wilson's disease (hepatolenticular degeneration syndrome). This is a rare inborn error of copper metabolism, inherited as an autosomal recessive trait [4]. It is characterized by cirrhosis of the liver and degenerative changes in the brain, particularly the basal ganglia. Deposition of copper takes place primarily in the liver, brain, kidneys and cornea (Kayser–Fleischer ring). The patients have low coeruloplasmin and plasma copper levels.

Treatment consists of cupriuretic agents such as penicillamine or by inhibiting intestinal copper absorption by oral zinc sulphate [4].

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Selenium metabolism [1]

Selenium is an essential element of the enzyme glutathione peroxidase. It plays a role against oxidative damage by endogenous peroxides. Selenium deficiency has long been known in several animal species. Selenium-deficient rats grow slowly, develop cataracts, lose their hair and show aspermogenesis. In humans, selenium deficiency has been reported in children, causing hypopigmented skin lesions and various other symptoms. Treatment consists of supplementation of selenium in low doses of 2 mg/kg/day [2]. Patients with psoriasis, atopic dermatitis, dermatitis herpetiformis and acne vulgaris have a lower glutathione peroxidase activity than normal controls [3]. The significance of this remains to be further studied. In a study on malignant melanoma, significantly lower serum selenium levels were demonstrated as compared with controls [4]. Serum selenium levels have been shown to be of a prognostic value in the follow-up of malignant melanoma and cutaneous T-cell lymphoma [5]. However, there is no apparent protective effect of selenium supplementation against the development of non-melanoma skin cancer [6,7].

Selenium is incorporated as the sulphide into shampoos for the treatment of seborrhoeic dermatitis. Selenium sulphide is water insoluble and possesses a very low toxicity. A possible protective role of selenium on cancer, cardiovascular diseases and rheumatic diseases has attracted much attention. There is no proven reason to recommend selenium supplementation.

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Skin disorders in diabetes mellitus

[K. Weismann, pp. 57.106–57.109]

Diabetes mellitus [1,2]. Diabetes mellitus is a metabolic disorder characterized by elevated fasting and postprandial blood glucose levels and a variety of multisystem complications, mainly in the blood vessels, eye, kidney, nervous system and integument. Three main types can be distinguished. Type 1, also known as insulin-dependent diabetes mellitus or juvenile-onset diabetes, is characterized by abrupt onset of symptoms, insulinopenia, dependence on insulin injections, proneness to ketoacidosis and lack of ability to produce C peptide. Type 2, non-insulin-dependent diabetes mellitus or adult-onset diabetes, is characterized by lack of ketoacidosis except under stressful circumstances, ability to produce C peptide, a tendency to obesity and improvement following loss of weight. Type 3, secondary diabetes, is an additional type of diabetes, which occurs as a complication of pancreatic, hormonal or genetic disease or following ingestion of certain drugs or chemical compounds.

There are several reviews of skin disorders associated with diabetes mellitus [2–7].

Skin symptoms due to diabetic vascular abnormalities [3–5]

Diabetic microangiopathy. Both small and large blood vessels are affected in diabetes mellitus. In diabetic microangiopathy, there is proliferation of endothelial cells and deposits of PAS-positive material in the basement membrane of arterioles, capillaries and venules with resulting decreased luminal area [8]. Basement-membrane thickening is a characteristic finding in diabetic and prediabetic patients, but it is neither absolute nor pathognomonic for the disease [9]. The diabetic microangiopathy precedes manifest abnormalities of the disease, and it is possible that vascular changes are the primary expression of the disease. Microangiopathy is responsible for the retinopathy, nephropathy and possibly also neuropathy and dermopathy associated with diabetes.

Erysipelas-like erythema [9]. Well-demarcated, red areas occur on the legs or feet of elderly diabetics. Some of the patients have an underlying destructive bone disease caused by a small vessel insufficiency. It is seen mostly in elderly patients with an average duration of diabetes mellitus of 5 years. Cardiac decompensation may be involved.

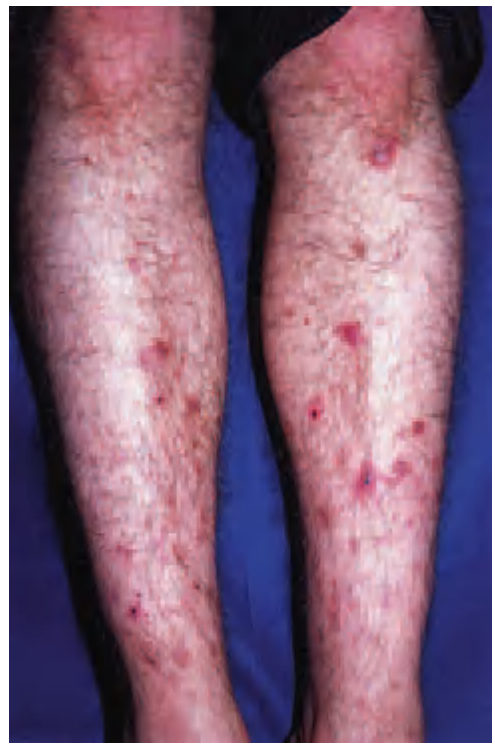

Fig. 57.54 Diabetic dermopathy.

Wet gangrene of the foot. This is a late manifestation of diabetic microangiopathy. Non-diabetic atherosclerotics tend to develop a dry form as a result of large vessel insufficiency.

Diabetic rubeosis [10]. A peculiar rosy reddening of the face, and sometimes of the hands and feet, may be seen in long-standing diabetes. The changes have been attributed to decreased vascular tone or diabetic microangiopathy. Rubeosis may have some practical diagnostic significance, especially in fair-skinned patients.

Diabetic dermopathy (diabetic shin spots) (Fig. 57.54). This is the most common dermatosis associated with diabetes mellitus. Microangiopathy and possibly neuropathy are involved [11]. Lesions are predominantly situated on the shins, forearms, thighs and over bony prominences. About half of patients show such lesions, more frequently men than women. The initial lesion is an oval, dull-red papule 0.5–1 cm in diameter. It evolves slowly, producing a superficial scale, leaving an atrophic brownish scar. The colour is due to haemosiderin in histiocytes near the vessels [12]. Microscopically, a combination of vascular disease with PAS-positive thickening of the vessel wall and minor collagen changes is found. Although not confirmed in all studies, recent research suggests that there is a significant correlation between the presence of these lesions and other complications of diabetes, such as retinopathy, nephropathy and neuropathy [13].

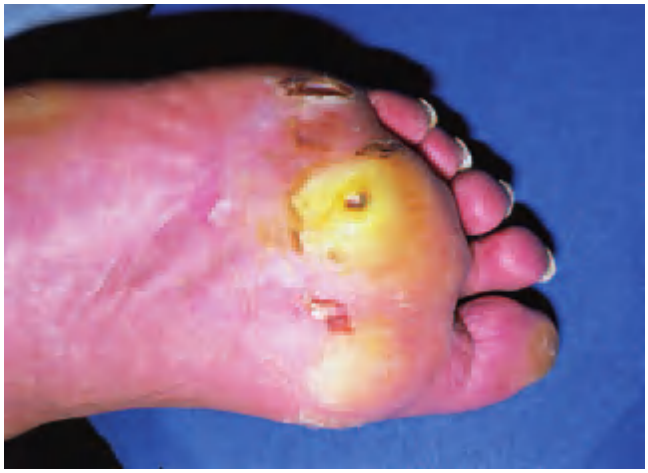

Fig. 57.55 Diabetic foot with neurotrophic ulceration.

Large vessel disease [4]. Atherosclerosis is the second form of vascular disease frequently associated with diabetes mellitus. The patient shows intermittent claudication with pallid and cool skin distally on the extremities. The postural test discloses delayed filling of the veins. Common clinical sequelae are myocardial infarction, cerebral thrombosis, nephrosclerosis and ischaemic gangrenous lesions of the legs and feet. Microangiopathy is usually present together with large vessel involvement.

Diabetic neuropathy

Elderly patients with an insidious onset of the disease are especially at risk. Commonly, there is a distal symmetrical polyneuropathy with mixed motor and sensory nerve involvement. The motor neuropathy of the foot is characterized by dorsally subluxed digits, distally displaced plantar fat pads, depressed metatarsal heads, hammer toes and pes cavus [3]. Proper foot care is essential to prevent formation of indolent perforating ulcers ('mal perforans'). A painless and slowly penetrating ulcer of the sole and of other pressure sites is suggestive of diabetic neuropathy. The ulcer is circular and punched out in shape, occurring in the middle of a callosity (Fig. 57.55). An initial subepidermal haemorrhagic bulla may give rise to discoloration of the surrounding skin [4]. Loss of temperature and pain sensation and absence of the ankle reflex (an early sign of diabetic neuropathy) indicate a neuropathic origin. Sensory abnormalities of the lower extremities include numbness, tingling, aching and burning. Burning feet and restless legs are common complaints, which intensify at night while lying down. Autonomic neuropathy may cause decreased or absent sweating of the lower extremities with compensatory sweating in other skin areas. Damage to autonomic nerves of the skin in chronic advanced cases is manifested by oedema, erythema and atrophy [3].

The *diabetic foot* requires special attention. There is a multifactorial aetiology [6]. Peripheral neuropathy causes ulcers, loss of ankle jerks and vibration sensation. The foot has accentuated plantar arches and hammer toes, there is interdigital maceration leading to bacterial and fungal infection. Diabetic angiopathy leads to ulceration, which may be complicated by necrosis, gangrene and osteomyelitis [14].

Cutaneous infections in diabetes mellitus

Skin infections due to *Staphylococcus aureus* and group A *Streptococcus haemolyticus* are common in diabetic patients [15]. Before insulin and antibiotics were available, infections causing severe furuncles, carbuncles and styes were frequent among diabetic individuals. In malignant external otitis, invasive *Pseudomonas* infection can progress through cellulitis and osteitis to cranial nerve damage and meningitis with a high mortality rate, so-called malignant otitis externa (Chapter 65) [16].

Non-clostridial gas gangrene. This complication develops in the soft tissues near a gangrenous focus. It was diagnosed in 17% of diabetics who were admitted to hospital because of gangrene or ulceration [17]. The commonest pathogens are *Escherichia coli*, *Klebsiella*, *Pseudomonas* and *Bacteroides* spp. in various combinations. The outcome is generally good.

Candida albicans. Candida albicans infections of mouth, nail folds, genitals and intertriginous skin areas are frequent in diabetics. Candidiasis may be the presenting feature of diabetes, and is frequently seen in diabetic patients whose disease is not well controlled [3]. A high glucose level of the saliva seems to account for the oral infection [18]. Phimosis is a common complaint of diabetic men, and recurring candidal infection is usually the cause. Dermatophyte infections are not more frequent in diabetic than in non-diabetic individuals [19].

Insulin resistance and acanthosis nigricans [20–22]

Tissue resistance to insulin is a major feature underlying the development of acanthosis nigricans in many diseases (e.g. Cushing's syndrome, acromegaly, Laurence–Moon–Bardet–Biedel syndrome, Prader–Willi syndrome and congenital lipodystrophy). There are two syndromes of insulin resistance. The type A syndrome has been reported in hyperandrogenetic women with clinical signs of virilization or accelerated growth (the acronym HAIRAN has been proposed: HA, hyperandrogenism; IR, insulin resistance; AN, acanthosis nigricans). A genetic defect at the insulin receptor or in a post-receptor pathway has been postulated. The type B syndrome has been reported in older women with signs of immunological

dysfunction. High plasma levels of insulin are thought to contribute to the development of acanthosis nigricans.

Various skin disorders associated with diabetes mellitus [23]

Necrobiosis lipoidica (pp. 57.119–57.124) [2–7]. Necrobiosis lipoidica is frequently associated with diabetes mellitus. Frequencies of diabetes between 42% and 62% have been reported in patients with necrobiosis lipoidica, although necrobiosis lipoidica is uncommon (0.3%) among diabetic patients [3].

Disseminated granuloma annulare (pp. 57.109–57.119). This is rarely seen in diabetic patients; the evidence that granuloma annulare is associated with diabetes mellitus is inconclusive [24].

Diabetic bullae. Various forms of diabetic bullae have been described. They occur as spontaneous atraumatic lesions mostly on feet and hands. A typical blister arises on a non-inflamed base, measures from a few millimetres to 3–5 cm in size, and heals without scarring in 2–5 weeks. Histological examination shows intra- or subepidermal separation without acantholysis [5,25,26].

Pruritus. Pruritus was once considered a typical symptom of diabetes mellitus. The frequency of generalized pruritus in diabetic patients is unknown. Anogenital pruritus may be caused by candidiasis or haemolytic streptococci.

Stiff joints and waxy skin. Waxy tight skin on the backs of the hands and limited joint mobility may be seen in patients with insulin-dependent diabetes [5,6,27].

Scleredema of diabetes mellitus. Whether post-infectious scleredema and diabetic scleredema are identical diseases, with a more severe course in the diabetes-associated form due to altered host response, is still a matter of debate [23]. The condition is seen mainly in overweight adults with non-insulin-dependent diabetes, is essentially permanent, causes little morbidity, and there is no specific treatment although penicillin, methotrexate, ciclosporin, low-density lipoprotein apheresis and PUVA have all been used with benefit in scleredema adultorum.

Vitiligo (Chapter 39). Vitiligo occurs more frequently in diabetic individuals. In late-onset diabetes, a 4.5% frequency has been reported [28].

Lichen planus (Chapter 42). An increased incidence of abnormal glucose tolerance tests in patients with lichen planus, especially oral lichen planus, has been reported [29]. However, the overall support for a true association is limited [6].

Haemochromatosis (Chapter 59). The main symptoms are liver disease, hyperpigmentation, joint disease, hypogonadism and, eventually, diabetes.

Eruptive xanthomas of the skin. Eruptive xanthomas of the skin may develop in diabetic patients with hyperlipidaemia. The lesions slowly resolve when the diabetes is properly managed.

Finger pebbles. Among 60 patients with diabetes mellitus, 45 (75%) had a pebbly appearance of the knuckle and distal finger skin. Similar changes were observed in 21% of control subjects [30]. The changes may be of external origin (trauma) or internal (acanthosis nigricans).

Skin tags. Skin tags are small, soft, pedunculated lesions occurring on eyelids, neck and axillae. They are often associated with obesity. Among 216 patients with skin tags, 57 (26%) had diabetes of the non-insulin-dependent type, of whom only about one-quarter were classified as obese [31].

Local insulin reactions [6,32]. Insulin may cause immediate local reactions, starting as erythema, which turn urticarial within 30 min and subside within an hour; these are probably IgE mediated. Serious generalized immediate reactions are rare.

The most common reactions are delayed, starting about 2 weeks after onset of insulin therapy. An itchy nodule develops at the site of injection. It lasts for days and heals with hyperpigmentation and perhaps a scar. Delayed hypersensitivity is involved.

Insulin lipodystrophy. Insulin lipodystrophy is rare. Patients present with atrophic plaques at the sites of insulin injection. There is atrophy of the subcutaneous fat. The lesions seldom show complete spontaneous resolution. The mechanism is not known.

Reactive perforating collagenosis (folliculitis). There have been reports of perforating collagenosis in patients with diabetes with and without renal insufficiency. The cause is attributed to diabetic microangiopathy and injury by scratching [33].

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Granuloma annulare

[D.A. Burns, pp. 57.109–57.119]

Introduction. Granuloma annulare was first described by Colcott Fox in 1895 [1], and established as a specific entity by Radcliffe Crocker in 1902 [2]. It is a disease in which, in typical cases, the skin and/or subcutis are involved in a process characterized by foci of alteration of collagen (necrobiosis) surrounded by histiocytes and lymphocytes. Clinical variants include localized, generalized, perforating and subcutaneous patterns [3,4].

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Aetiology [1–3]. Although the aetiology and pathogenesis of granuloma annulare are unclear, it appears likely that it represents a reaction pattern to a variety of triggering factors. Reported triggering factors have included insect bites [4], a cat bite [5], waxing-induced pseudofolliculitis [6], tuberculin tests [7], bacille Calmette-Guérin (BCG) vaccination [8,9], hepatitis B vaccination [10], a possible relation to antitetanus vaccination [11], and occupational pressure on the fingers in a milkman [12]. In the past, its occurrence with tuberculosis was noted in a number of reports, and cases may still be encountered in which there appears to be an association between these two disorders [13]. Other infectious agents that have been implicated in the causation of lesions of granuloma annulare include human papilloma virus [14], varicella/zoster virus [15–20] (although persistence of viral DNA does not appear to be related to granuloma formation [18,21]), Epstein–Barr virus [22,23] (but Epstein–Barr virus could not be demonstrated in lesions occurring in HIV-positive patients [24]), parvovirus B19 [25], hepatitis C virus [26] and HIV [24,27–35]. Although there has been evidence implicating *Borrelia burgdorferi* in some cases [36,37], it was absent in others [38]. Examination of several biopsy specimens using polymerase chain reaction amplification did not reveal any evidence of *Bartonella* infection [39].

Seasonally recurrent granuloma annulare has been described [40,41], and sun exposure may have acted as a precipitating factor in one of these cases [41]. Sun exposure is thought to have provoked or contributed to localization of lesions in a number of cases [42–45]. Disseminated granuloma annulare has occurred in a patient undergoing PUVA therapy [46]. Whether actinic granuloma is a distinct entity, or represents granuloma annulare on sun-exposed skin has been discussed recently [47–49], and has been the subject of debate in the past [50–55].

A report of granuloma annulare occurring in the red areas of tattoos [56] prompted description of a similar case and the suggestion that both were examples of a perforating collagenosis [57].

There is a report of disseminated granuloma annulare occurring in the same sites as lesions of erythema multiforme minor [58].

Some cases of granuloma annulare-like lesions attributed to drugs may have been examples of drug-induced interstitial granulomatous reactions [59].

It has been suggested that an immunoglobulin-mediated vasculitis is the cause of the necrobiotic granulomas [2,60], but evidence from immunofluorescence studies is conflicting—some authors have demonstrated immunoreactants in vessel walls [60], whereas others have not [61,62]. An alternative view is that the pathogenetic mechanism is a delayed-type hypersensitivity response [2,62–66].

An increased prevalence of HLA-Bw35, compared with controls and those with localized lesions, has been demonstrated in individuals with generalized granuloma annulare [67].

The relationship between diabetes mellitus and granuloma annulare is discussed below, as are apparent associations with several other disorders.

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Histopathology [1–5] (Figs 57.56 & 57.57). The most characteristic histological lesion in granuloma annulare is the necrobiotic granuloma, but there are three histological patterns that may occur: necrobiotic palisading granulomas, an interstitial form, and granulomas of sarcoidal or tuberculoid type [1]. Umbert and Winkelmann [3] found that the commonest histological pattern was the interstitial type, as did Friedmann-Birnbaum *et al*. [4]. The latter authors compared the histopathological features of localized and generalized granuloma annulare, and noted that the interstitial pattern was more frequent in localized than in generalized disease; the prevalence of the palisading granuloma pattern was almost equal in both clinical types. Dabski and Winkelmann [5] also found that the interstitial pattern was common in both these types of granuloma annulare, and in many cases it occurred alone, without palisading granulomas. However, they noted a prominent palisading pattern more frequently in localized disease than in the generalized variety. Observer variation and the existence of more than one pattern in the same section may have contributed to differences in the findings in these series.

Necrobiotic granulomas are characterized by foci of necrobiosis surrounded by histiocytes and lymphocytes,

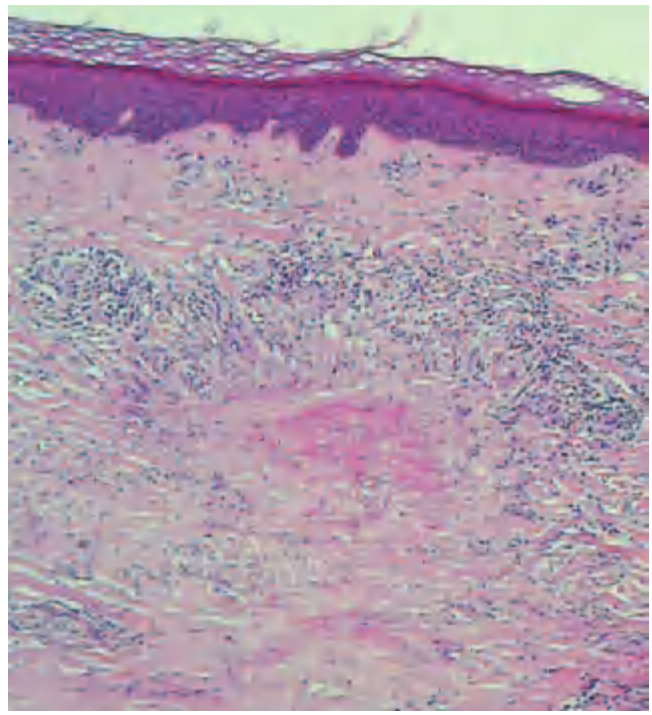

Fig. 57.56 Granuloma annulare. Nodule in upper dermis. H&E stain. (Courtesy of Dr M. Bamford, Department of Pathology, Leicester Royal Infirmary, Leicester, UK.)

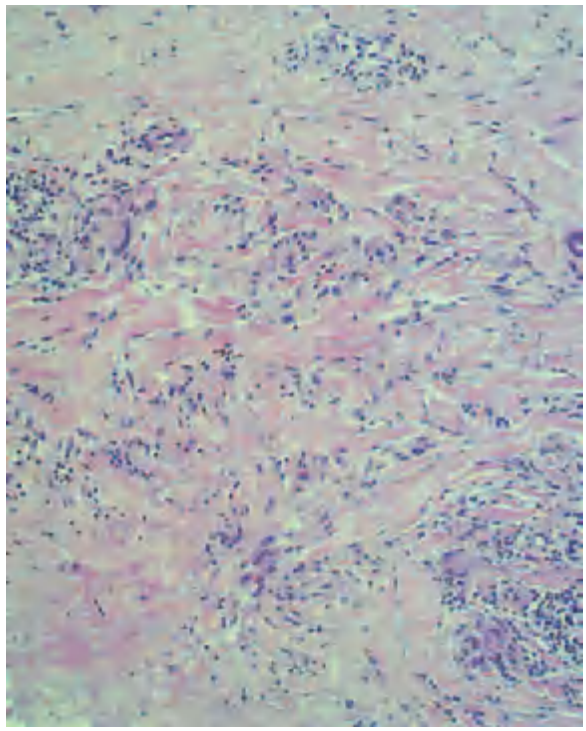

Fig. 57.57 Granuloma annulare. Nodule—well circumscribed with good palisade of histiocytes and central necrobiosis. H&E stain. (Courtesy of Dr M. Bamford, Department of Pathology, Leicester Royal Infirmary, Leicester, UK.)

with the histiocytes commonly forming a palisaded pattern. There are varying numbers of multinucleate giant cells in this peripheral zone. T cells in the lymphocytic infiltrate are of the helper/inducer phenotype ($CD4^+$) [6–8], but in two cases associated with HIV infection a predominantly T-suppressor ($CD8^+$) infiltrate was demonstrated [9,10]. Analysis of the T-cell repertoire and cytokine pattern has shown a T-cell response characterized by a combination of a few skin-specific clones together with many non-specific T cells, and abundant production of interleukin-2 (IL-2) [8]. The high local production of IL-2 could be responsible for the non-specific attraction of T cells to the granulomas.

Mucin is present within the foci of necrobiosis, and can be seen more readily by staining with alcian blue or colloidal iron. Small deposits of lipid material may also be present in these areas. Some form of collagen alteration, most commonly fragmentation of collagen bundles, was observed in 79% of cases of localized and 53% of cases of generalized granuloma annulare by Dabski and Winkelmann [5]. There is a marked reduction in, or absence of, elastic fibres [11,12]. Metalloproteinases are probably involved in the damage to collagen and elastic fibres [13,14].

The granulomas are situated in the superficial and middermis and, in contrast with necrobiosis lipoidica, areas between them are relatively normal.

In the interstitial pattern there are no formed areas of necrobiosis, histiocytes and lymphocytes are present around blood vessels and between collagen bundles, and collagen fibres are separated by mucin.

The sarcoidal or tuberculoid pattern is uncommon, and may cause problems in diagnosis. The presence of mucin and eosinophils can help to distinguish granuloma annulare from sarcoidosis.

There is a perivascular infiltrate of lymphocytes and histiocytes. Eosinophils are variably present [15]. In one study [16], the presence of eosinophils was strongly associated with a palisaded architectural pattern and the presence of necrobiosis. Plasma cells are rare. A vasculitis has been described in or near foci of necrobiosis [17].

Histiocytes express the marker PG-M1 [18]. They may show an increased mitotic rate, recognition of which is important, in particular in differentiating granuloma annulare from epithelioid sarcoma [19–22].

Epidermal changes are inconspicuous except in perforating granuloma annulare. In this variant there is a superficial area of necrobiosis surrounded by palisading histiocytes, situated beneath a perforation in the epidermis [1,2,23]. The necrobiotic material is extruded via the perforation. At the margins of the perforation there are varying degrees of epidermal hyperplasia.

The lesions of subcutaneous granuloma annulare often contain large areas of necrobiosis, and they are similar to rheumatoid nodules both clinically and histologically. Patterson [24] found that alcian blue staining of mucin in lesions of granuloma annulare was the most helpful distinguishing feature.

Other disorders with similar histological features include granulomatous mycosis fungoides [25–27], interstitial granulomatous dermatitis (interstitial granulomatous dermatitis with arthritis; interstitial granulomatous dermatitis with plaques; palisaded neutrophilic granulomatous dermatitis) [28–34] and the interstitial granulomatous drug reaction [35,36].

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Clinical features [1,2]. Granuloma annulare can occur at almost any age—in one series the youngest patient was 1 year old and the oldest was 76 years old [3]—but the majority of affected individuals are under 30 years of age [3]. It is twice as common in women as in men. There are a few reports of familial cases [3–8]. Clinical variants include localized, generalized, perforating and subcutaneous.

Localized granuloma annulare is the commonest form, and typically presents as a ring of small, smooth, flesh-coloured or erythematous papules (Fig. 57.58). Stretching the skin enables the papules to be seen more readily. The surface of the skin over the papules is intact and there is usually no scaling. Annular lesions tend to enlarge centrifugally. They may be solitary or multiple, and may occur anywhere on the skin, although the dorsa of the hands (Figs 57.59 & 57.60) and feet, and the fingers (Fig. 57.61) are the commonest sites. Lesions are usually symptomless, although some may be tender to touch.

The other patterns of granuloma annulare may occur alone or in association with the annular lesions. In the generalized or disseminated pattern, there are numerous skin-coloured or erythematous papules, which may have an annular configuration or consist of myriad symmetrically distributed, often coalescing lesions, on the trunk and limbs [9–11] (Fig. 57.62). The area enclosed by annular papules is often violaceous in colour. Pruritus may be a prominent complaint in generalized lesions [11]. Although generalized granuloma annulare may occur in children, the mean age at onset is later than in the localized variety, and in the series of Dabski and Winkelmann [11] it was 51.7 years. The exact incidence of the generalized pattern is unknown, but 8.9% of all patients with

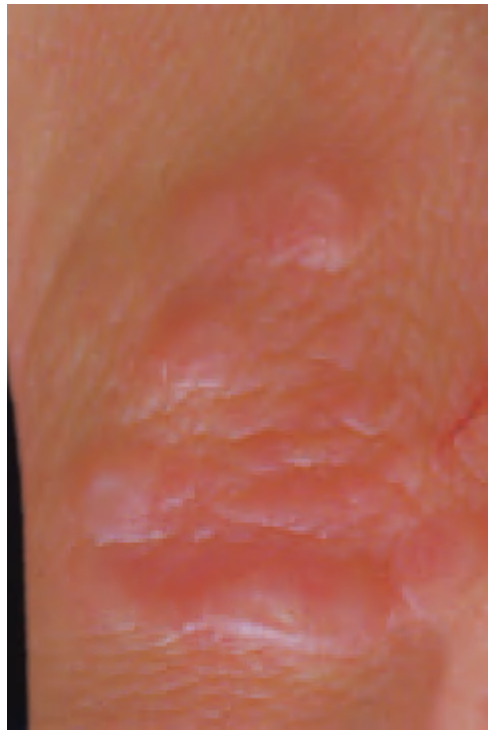

Fig. 57.58 Typical papules of granuloma annulare.

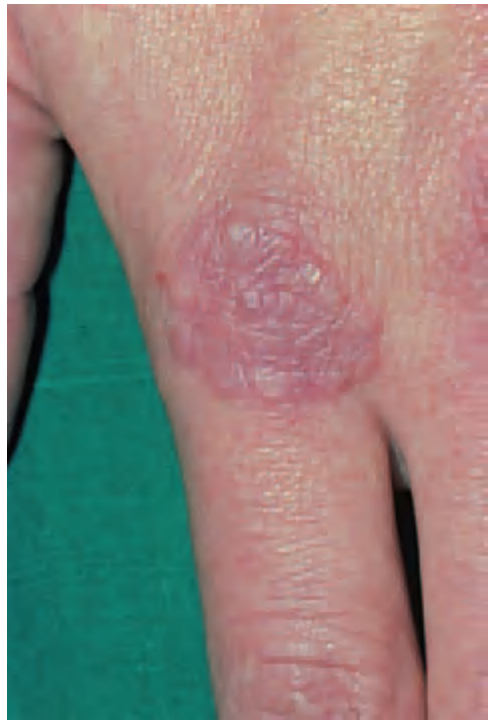

Fig. 57.59 Granuloma annulare on the dorsum of the hand—a typical site.

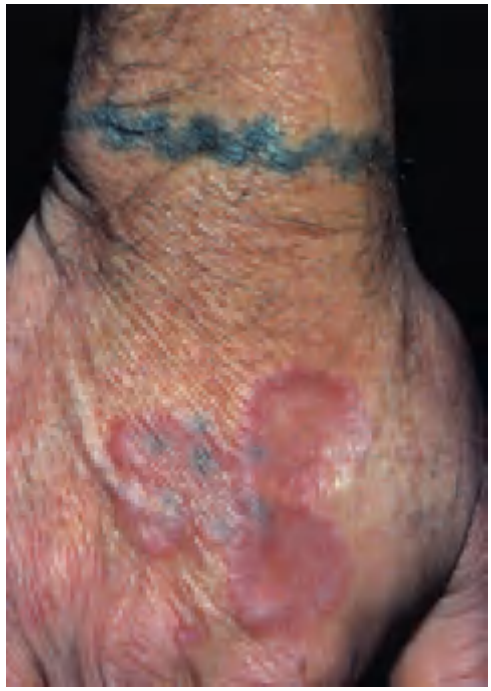

Fig. 57.60 Granuloma annulare on the dorsum of the hand. Altered pigmentation and atrophy in the centre of the lesions.

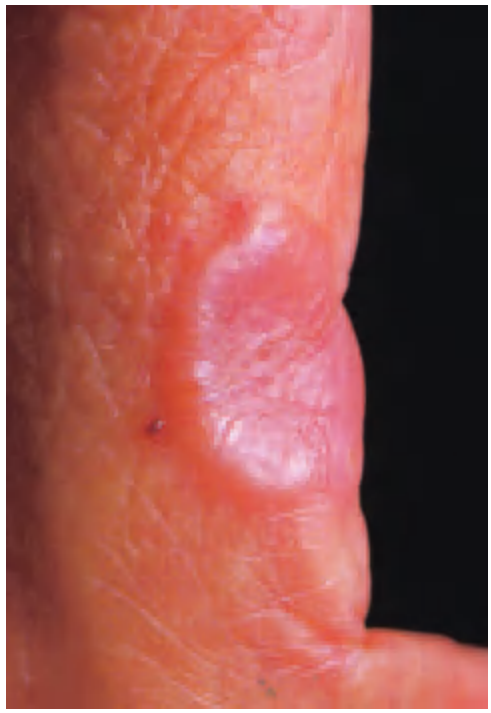

Fig. 57.61 Granuloma annulare on the side of a finger.

granuloma annulare seen at the Mayo clinic had a generalized or disseminated pattern [11]. As in the localized form, twice as many females are affected as males. Although in immunocompetent individuals localized disease is more

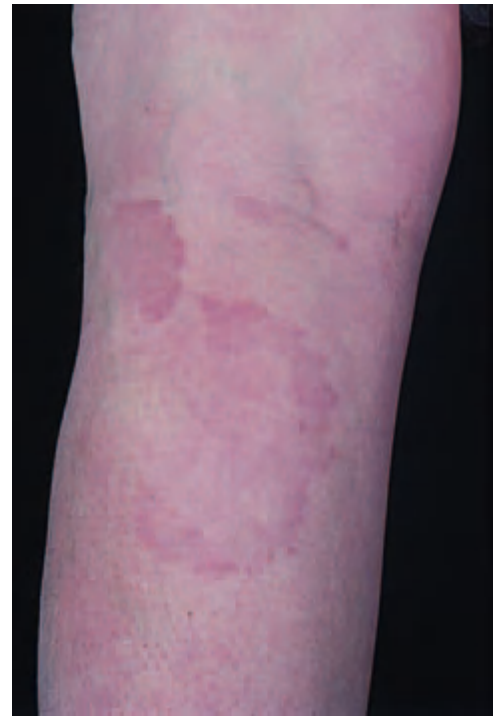

Fig. 57.62 These annular lesions were part of an extensive eruption on the limbs in a patient with generalized granuloma annulare.

common than generalized granuloma annulare, in HIV-infected patients the generalized pattern predominates [12–16]. The sparing of vaccination sites in a case of generalized granuloma annulare is an interesting phenomenon [17].

Perforating granuloma annulare was named by Owens and Freeman in 1971 [18]. In this uncommon variety, some of the papules develop yellowish centres and discharge a little clear, viscous fluid. This dries to form a crust, which eventually separates, and may leave a hypo- or hyperpigmented scar. Lesions may be localized or generalized [19–22]. A high incidence of perforating granuloma annulare has been reported in the Hawaiian Islands [20,21]. Perforating lesions have been present in some of the reported HIV-positive individuals with granuloma annulare.

Subcutaneous granuloma annulare is also uncommon. It occurs predominantly in children, and has been given a variety of names, including benign rheumatoid nodules [23], pseudo-rheumatoid nodules [24], deep granuloma annulare [25,26], subcutaneous palisading granuloma [27], isolated subcutaneous granuloma and subcutaneous necrobiotic granuloma [28]. Lesions are nodular and occur predominantly on the scalp and legs, particularly in a pretibial location [4,28–30]. Magnetic resonance imaging features are diagnostically helpful [31,32].

Other reported variants of granuloma annulare include a papular umbilicated form on the dorsa of the hands in children [33], a case of 'follicular pustulous' granuloma

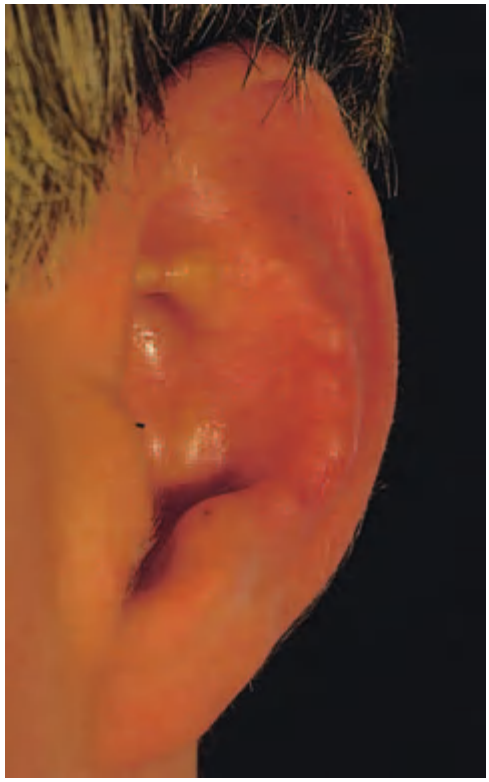

Fig. 57.63 Granuloma annulare on the ear.

annulare, in which palisading necrobiotic granulomas occurred in a perifollicular distribution [34], linear granuloma annulare [35,36] and 'patch' granuloma annulare, in which erythematous patches occur on the trunk and limbs [37]. It must be remembered that in interstitial granulomatous dermatitis there are linear lesions on the chest wall, producing the so-called 'rope sign', and erythematous patches occur in the interstitial granulomatous drug reaction.

Uncommon sites for lesions are the ears (Fig. 57.63), where the perforating variety is particularly unusual [38], penis [39–44], palms [45] and periocular regions [46–51].

Mucous membranes are spared, although there is a report of involvement of the oral mucosa in a patient with HIV infection [52].

A destructive form has been described [53,54].

The postal questionnaire survey carried out by Wells and Smith [3] revealed that in about 50% of patients the lesions resolved within 2 years. However, about 40% of those whose lesions cleared had a recurrence, in the majority of cases at the same sites as the original lesions. In this study, there did not appear to be any difference in prognosis between individuals with single lesions and those with multiple lesions, and although there is an impression that spontaneous resolution is less likely to occur with generalized granuloma annulare there does not appear to be any documented confirmation of this.

There are reports of anetoderma secondary to generalized lesions [55], and of mid-dermal elastolysis occurring with granuloma annulare [56] or subsequent to lesions resembling granuloma annulare [57].

Levin *et al.* [58] have discussed resolution of lesions following biopsy, and noted the paucity of information relating to this phenomenon in the literature. There appears to be anecdotal evidence of its occurrence, but little documentation. However, it is of interest, in this context, that scarification is one form of physical treatment which has been advocated in the past [59–61].

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Differential diagnosis. When the typical annular arrangement of papules is present, the diagnosis is usually straightforward. However, granuloma annulare may be mistaken for tinea corporis, although the latter is more inflammatory, and the annular margin is scaly. Other annular lesions and granulomatous conditions may cause diagnostic confusion, including annular lichen planus, erythema annulare centrifugum, erythema multiforme, erythema migrans of Lyme disease and tertiary syphilis [1].

With regard to subcutaneous granuloma annulare, the differential diagnosis of subcutaneous nodules of the scalp and legs in children is extensive, and includes trauma, infection and tumours; a diagnostic biopsy will usually be necessary. In adults, nodular lesions have to be distinguished from sarcoidosis and rheumatoid nodules.

The differential diagnosis of perforating granuloma annulare includes molluscum contagiosum, transepithelial elimination disorders such as perforating collagenosis and acquired perforating dermatosis, sarcoidosis and papulonecrotic tuberculide [2,3]. As mentioned above, epithelioid sarcoma may masquerade as perforating granuloma annulare.

Mycobacterium marinum infection has histologically simulated interstitial granuloma annulare [4]; other histological differential diagnoses include granulomatous mycosis fungoides, interstitial granulomatous dermatitis and interstitial granulomatous drug reaction, as mentioned above.

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Associations. There has been much discussion of whether there is an association between granuloma annulare and diabetes mellitus. A number of studies have not demonstrated any relationship, whereas several others have found a significant association [1–3]. In those whose results suggest a possible relationship, some have favoured an association with generalized granuloma annulare [4–6] whilst others have shown an association with localized disease [3,7], and possibly with localized nodular granuloma annulare [8]. It is of interest to note that in three reports [3,7,8] the majority of diabetics were insulin-dependent (type 1). A recent study, employing a case–control design, did not show any association between granuloma annulare and type 2 diabetes [9]. The patient population studied did not include anyone with type 1

diabetes. In order to clarify the situation further, large-scale studies are required, in which the pattern of granuloma annulare and the type of diabetes are recorded.

Thomas *et al.* [10] reported a man with granuloma annulare of the skin and intra-abdominal lesions, insulin-dependent diabetes and polyendocrine disease, in whom there appeared to be a relation between diabetic control and the granuloma annulare.

Granuloma annulare has been described in a child with Mauriac's syndrome (juvenile diabetes, stunted growth and hepatomegaly) [11].

There are a number of reports of the coexistence of both localized and generalized granuloma annulare and autoimmune thyroiditis in women [12–17], and results of a recent case–control study indicated an association between localized granuloma annulare and autoimmune thyroiditis [18]. In one case with generalized granuloma annulare, the skin lesions improved in concert with disappearance of antithyroid antibodies and restoration of the euthyroid state [13]. Generalized granuloma annulare has also been reported in a patient with a toxic adenoma of the thyroid (Plummer's disease) [19].

Recent reports suggest the possibility of an association between uveitis and granuloma annulare [20,21].

Li *et al.* [22] have summarized and analysed reports addressing a possible relationship between granuloma annulare and malignant neoplasms. In the cases reviewed, skin lesions which had histological features of granuloma annulare, but were often atypical clinically (for example, painful lesions on the palms and soles), occurred in patients with a neoplasm (in 56% of cases this was a lymphoma). They concluded that there was no definite relationship between granuloma annulare and malignant neoplasms.

There are isolated reports of the occurrence of temporal arteritis in a patient with generalized granuloma annulare [23] and of the coexistence of granuloma annulare and morphoea [24].

There are a number of reports of the occurrence of granuloma annulare and necrobiosis lipoidica in the same patient [25–28], and of the association of granuloma annulare and sarcoidosis [29–32].

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Treatment. The tendency of granuloma annulare to remit spontaneously complicates accurate assessment of the efficacy of any treatment. In some patients explanation that this is the natural course of the disease is all that is required, and certainly in children it is preferable to await spontaneous resolution rather than subjecting them to the

discomfort of some of the treatment methods. Potent topical steroids, with or without occlusion, are used by many dermatologists, but often with little benefit. Intralesional steroids, given either by needle injection or jet injector [1], appear to be more effective in the management of localized lesions. Cryosurgery also appears to be an effective treatment for localized disease. In a study of 31 patients, in which nitrous oxide and liquid nitrogen were employed, resolution was achieved in all following a single freeze–thaw cycle in the majority [2]. The cosmetic result obtained by cryosurgery with nitrous oxide was independent of the size of the lesion, whereas in individuals treated with liquid nitrogen a better cosmetic result was obtained with smaller lesions. Because of this, the authors of the report proposed that use of nitrous oxide as refrigerant was preferable to liquid nitrogen.

Localized granuloma annulare has also been treated with local injections of low-dose recombinant interferon-γ [3]. Complete resolution of lesions occurred in the three treated patients, with no recurrence during 12 months of follow-up.

Although some reports have indicated a beneficial effect of oral potassium iodide in the treatment of disseminated granuloma annulare [4,5], a double-blind, placebo-controlled, crossover study showed that it had no advantage over placebo [6].

PUVA therapy appears to be an effective treatment for generalized granuloma annulare, and good results have been reported using both oral and topical psoralens [7–13]. In many cases, however, maintenance therapy is required to sustain the benefit. Cream PUVA therapy has also been shown to clear localized lesions [14]. Ultraviolet A-1 phototherapy has also been reported as effective in the treatment of generalized granuloma annulare [15].

Etretinate [16,17] and isotretinoin [18–20] have both been of benefit in disseminated disease. Isotretinoin has also improved localized [21] and perforating granuloma annulare [22].

There are a few reports of the use of ciclosporin in generalized granuloma annulare [23–25], with good results in most cases. Other treatments which have been used with apparent benefit in isolated cases or in small numbers of patients with disseminated granuloma annulare include low-dose chlorambucil [26–30], dapsone [31], antimalarials [32–34], niacinamide [35], pentoxifylline [36], tranilast [37], fumaric acid ester [38], clofazimine [39], topical vitamin E [40], and a combination of vitamin E and a 5-lipoxygenase inhibitor [41].

Recent reports suggest that imiquimod [42] and topical tacrolimus [43] may be helpful.

Most of the treatments mentioned above have been employed in patients with perforating lesions, with varying degrees of success [44].

Lesions of subcutaneous granuloma annulare should be left to resolve spontaneously once the diagnosis has been confirmed [45].

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Necrobiosis lipoidica

[D.A. Burns, pp. 57.119–57.124]

Introduction. Necrobiosis lipoidica was first described by Oppenheim in 1930 [1], and was subsequently named necrobiosis lipoidica diabeticorum by Urbach in 1932 [2]. Because it is not peculiar to diabetes, it is now usually called necrobiosis lipoidica. It is similar in histological appearance to granuloma annulare, but has a distinctive clinical appearance characterized by sharply demarcated plaques of atrophic yellowish skin, which may ulcerate.

Aetiology [3]. This condition was originally regarded as a complication of diabetes mellitus, but it was soon realized that some patients with necrobiosis lipoidica did not have overt diabetes. The precise relationship of the diabetic state to necrobiosis lipoidica is still not clear, although they are undoubtedly associated. The association is discussed below.

Some authors have considered vascular changes to be important in the pathogenesis of necrobiosis lipoidica, but in Muller and Winkelmann's histopathological study vascular involvement was very mild in about a third of the cases [4]. An altered plasma protein profile [5], elevated factor VIII-related antigen [6] and fibronectin [7] may contribute to the vascular changes.

The possible role of an antibody-mediated vasculitis as an initiating event in necrobiosis lipoidica has provoked debate, as results of immunofluorescence studies differ. Laukkanen *et al*. [8] did not demonstrate immunoreactants in lesional skin, but others have shown immunoreactants, principally IgM, C3 and fibrin, in vessel walls in the involved skin, and IgM, C3 and fibrinogen at the dermal–epidermal junction [9,10]. Dahl [11] has discussed immunofluorescence findings in necrobiosis lipoidica.

Whatever the mechanism, there is evidence of impaired microcirculation in non-diabetic individuals with necrobiosis lipoidica compared with controls, as measured by laser-Doppler flowmetry [12].

Although vascular factors may play a role, the precise pathogenesis of necrobiosis lipoidica remains unknown.

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Histopathology [1–3] (Figs 57.64 & 57.65). The histological appearances are similar to those of granuloma annulare, but some features differ. The epidermis is normal or atrophic, and absent if there is ulceration. The dermal changes involve its full thickness, and often extend into the subcutaneous fat. Early lesions show a perivascular and interstitial mixed inflammatory cell infiltrate. Areas of necrobiosis are usually more extensive and less well defined than in granuloma annulare. There is degeneration of collagen and elastin within lesions [4]. Histiocytes border the areas of necrobiosis. There are variable numbers of Langhans' or foreign-body giant cells.

A perivascular inflammatory infiltrate includes occasional eosinophils and, in contrast with granuloma annulare, plasma cells.

Lymphoid nodules, containing germinal centres, may be present in the deep dermis or subcutaneous fat [5].

Lipid can be demonstrated in the necrobiotic areas, and cholesterol clefts may be present [6]. Mucin may be present in the dermis, but it is not as prominent as in granuloma annulare.

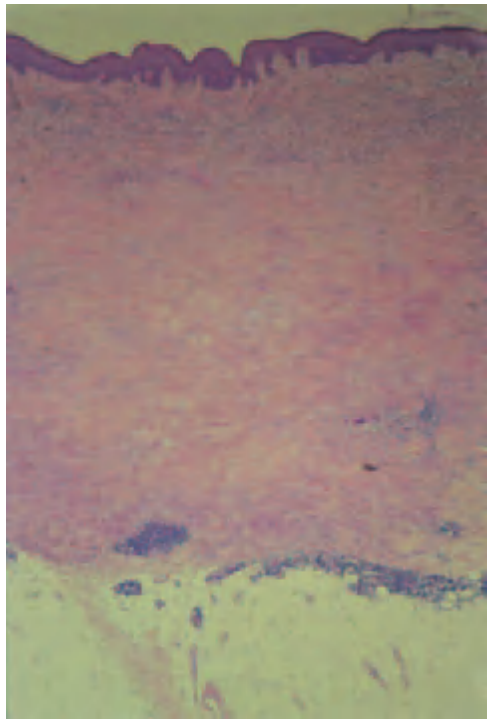

Fig. 57.64 Necrobiosis lipoidica. Extensive necrobiosis in the dermis. H&E stain. (Courtesy of Dr M. Bamford, Department of Pathology, Leicester Royal Infirmary, Leicester, UK.)

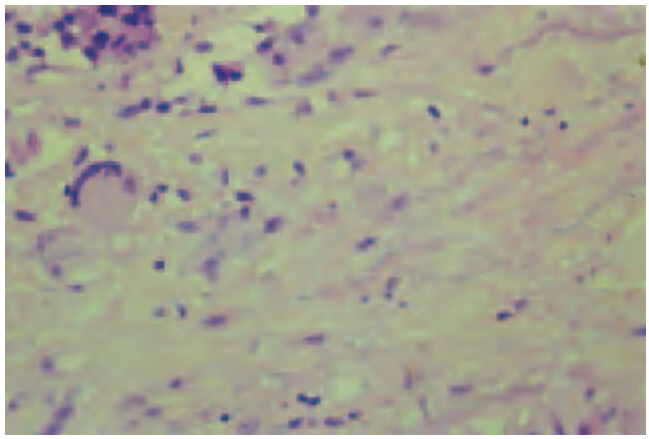

Fig. 57.65 Necrobiosis lipoidica. Giant cell adjacent to area of necrobiosis. H&E stain. (Courtesy of Dr M. Bamford, Department of Pathology, Leicester Royal Infirmary, Leicester, UK.)

Small, superficial blood vessels are increased in number and telangiectatic. Deeper dermal blood vessels often show thickening of their walls and proliferation of endothelial cells. The walls are often infiltrated with PAS-positive, diastase-negative material.

Histologically, comedo-like plugs at the periphery of lesions represent elimination of necrotic material through hair follicles [7].

Anaesthesia in the lesions appears to be related to a decreased number of nerves within them [8].

In old, atrophic lesions there is considerable fibrosis in the dermis and subcutis.

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Clinical features [1–3]. Necrobiosis lipoidica may occur at any age, but usually develops in young adults and in early middle age. In those with insulin-dependent diabetes, the age of onset is earlier than in non-insulin-dependent and non-diabetic individuals [4]. It is rare in childhood [5,6]. The female : male ratio is 3 : 1. Familial occurrence is rare [7,8].

Typical lesions occur on the pretibial skin, and begin as a firm, dull-red papule or plaque, which enlarges radially to become a yellowish, atrophic plaque with an erythematous edge (Figs 57.66 & 57.67). The surface is often glazed in appearance, and telangiectatic vessels may be prominent (Fig. 57.68). Lesions are usually symptomless. Anaesthesia and hypohidrosis are features of the affected skin [2,9,10]. Comedo-like plugs may occur at the periphery of lesions [11] (see above). In most cases, lesions are bilateral, and they are similar in appearance whether occurring in diabetic or non-diabetic individuals [1].

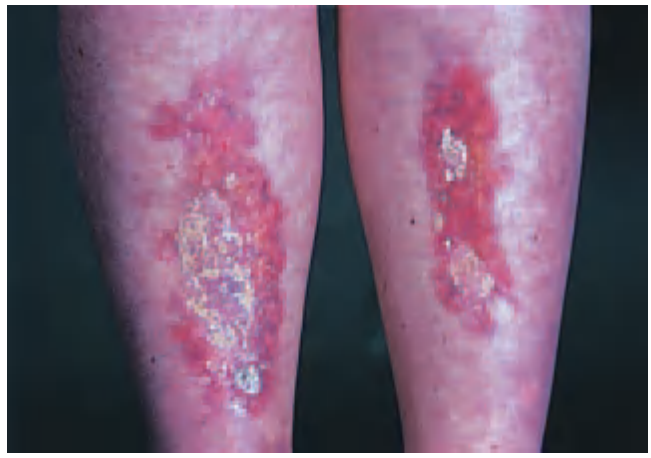

Fig. 57.66 Necrobiosis lipoidica. Lesions on both shins.

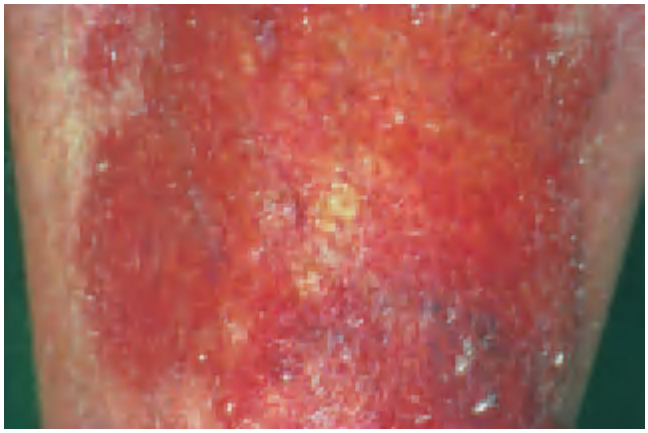

Fig. 57.67 Area of necrobiosis lipoidica showing yellowish colour, atrophy and prominent vessels.

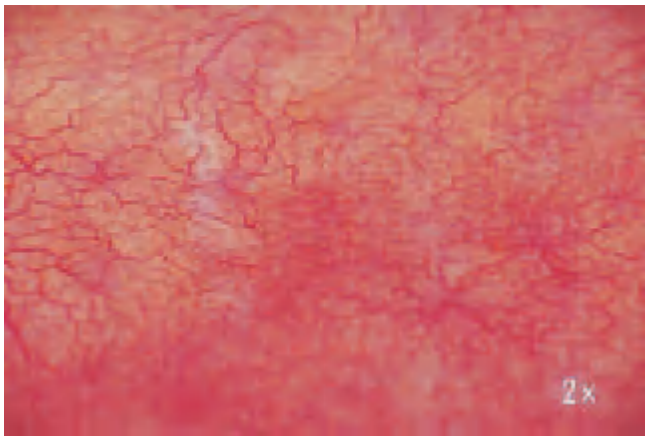

Fig. 57.68 Prominent telangiectasia in an area of necrobiosis lipoidica.

They tend to be persistent, and some may ulcerate [12] (Fig. 57.69). In one study [4], ulceration correlated with sensory impairment. Squamous cell carcinoma may develop in long-standing lesions [13–16].

Lesions can also occur on other parts of the body, including the trunk [17] and penis [18,19], and rarely may be diffuse [20]. They may also occur in surgical scars [21–23].

The number of lesions and their rate of progress are very variable. Slow extension over many years is usual, but long periods of quiescence, or resolution with variable atrophy and scarring (Fig. 57.70), may occur.

Wilson Jones [24] described an 'atypical annular form' of necrobiosis lipoidica affecting the upper face and scalp margins. The majority of affected individuals were female, and some developed lesions of necrobiosis lipoidica elsewhere. Since then, other authors have described similar annular lesions occurring predominantly on the exposed skin of the head, neck and arms, and these have been named Miescher's granuloma [25] and actinic

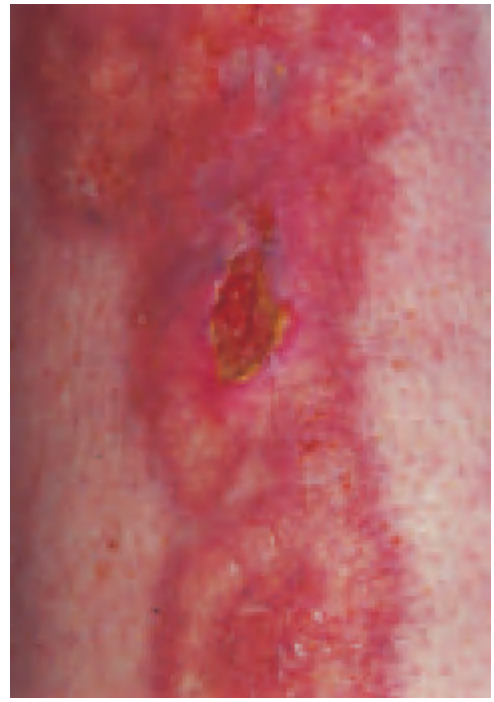

Fig. 57.69 Ulcerated necrobiosis lipoidica.

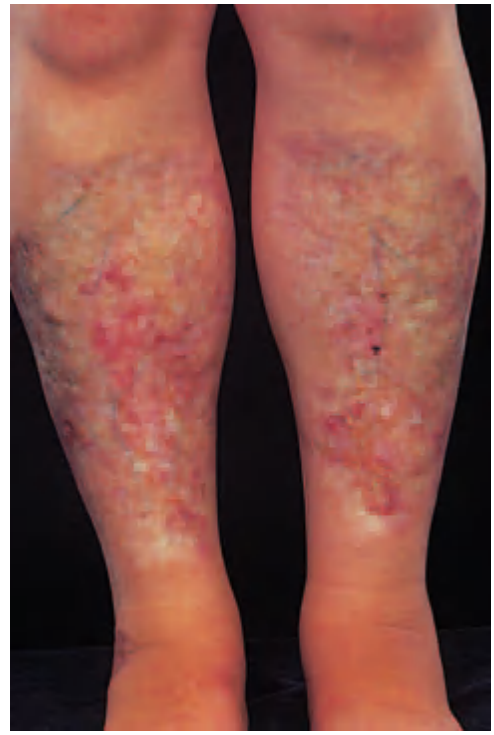

Fig. 57.70 'Burnt out' necrobiosis lipoidica—marked atrophy is evident.

granuloma [26]. Hanke *et al.* [27] proposed the term 'annular elastolytic giant cell granuloma' for these lesions. A similarity to granuloma multiforme (p. 57.124) is also apparent. The relationship of these disorders to each other

and to the necrobiotic granulomas has provoked debate [3,28].

Differential diagnosis. Lesions with marked fatty infiltration, particularly when not on the legs, may be mistaken for xanthomas. Necrobiotic xanthogranuloma is a rare destructive xanthogranuloma, in which red-orange or yellowish indurated plaques most frequently involve the periorbital regions and trunk [29,30]. It is associated with systemic lesions and a monoclonal gammopathy (Chapter 52).

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Associations. Although it is accepted that there is a relationship between necrobiosis lipoidica and diabetes mellitus, there is some disagreement about the closeness of this association. In Muller and Winkelmann's large series of cases, 111 of 171 patients with necrobiosis lipoidica (65%) had diabetes, and several of the non-diabetic patients subsequently had abnormal glucose tolerance tests [1]. Whereas, in a study from Ireland [2], of 65 individuals with necrobiosis lipoidica only seven (11%) were known to have diabetes at the time of presentation. Necrobiosis lipoidica is relatively uncommon in diabetic patients, with reported prevalences of 0.3% [1] and 1.2% [3], and appears to be rare (0.06%) in childhood diabetes [4].

It is most commonly seen in patients with type 1 diabetes [3,5], but also occurs in type 2 diabetes, and in recent years has been reported in children and adolescents with type 2 diabetes [6,7], including Prader–Willi-associated diabetes [8]. A recent survey of the records of 178 patients fitting the clinical criteria for maturity-onset diabetes of the young (MODY), which is a subtype of non-insulin-dependent diabetes, showed a prevalence of necrobiosis lipoidica of 2.8% [9].

There is some evidence that diabetic patients who have necrobiosis lipoidica are at higher risk of retinopathy and nephropathy than diabetics who do not [5,10,11].

In the past, it was noted that good control of diabetes did not appear to have a significant effect on the course of necrobiosis lipoidica [1], but it would be of interest to reassess this aspect of the disease in the context of advances in diabetes care in recent years.

Necrobiosis lipoidica has also been reported as occurring in association with ulcerative colitis [12] and Crohn's disease [13], ataxia-telangiectasia [14] and after jejunal bypass surgery [15]. Reports of its occurrence with granuloma annulare have been mentioned previously (p. 57.117). It has also been reported in association with sarcoidosis [16,17].

Magro *et al.* [18] have demonstrated histopathological evidence of an 'active vasculopathy' in the majority of a series of cases of necrobiosis lipoidica associated with systemic disease.

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Treatment. Potent topical corticosteroids, particularly if applied beneath an occlusive dressing and changed weekly, may help [1]. Locally injected triamcinolone, delivered by needle or jet injector [2], can improve the appearance, but atrophy usually remains. As there is evidence of extension of the inflammatory infiltrate into apparently normal skin surrounding active lesions, injection of steroids into perilesional areas might help to limit progression [3]. The use of oral steroids may be of benefit [4,5]. Petzelbauer *et al*. [5] employed short-course steroid therapy which resulted in cessation of disease activity in six patients, and no recurrence in a mean follow-up period of 7 months.

There are several reports of benefit from topical PUVA therapy [6–10].

Other treatments which have been employed in the past, with varying degrees of success, include fibrinolytic agents [11], high-dose nicotinamide [12], clofazimine [13], pentoxifylline [14–16], tretinoin (0.05%) [17], prostaglandin E_1 [18,19] and aspirin or an aspirin/dipyridamole combination [20–22]. Aspirin alone was subsequently shown to be ineffective [23,24], and in a randomized, double-blind comparison with placebo, patients treated with an aspirin/dipyridamole combination did not show any significant improvement [25].

Pulsed dye laser has been employed, and may improve the telangiectatic and erythematous components [26] but skin breakdown can occur [27].

Ulcerated necrobiosis lipoidica has been treated by excision and grafting [28–30], although recurrence tends to occur unless the excision is deep [30]. Other treatments that have been used for ulcerated necrobiosis lipoidica include oral steroid [31], ciclosporin [32,33], mycophenolate mofetil [34], topical granulocyte–macrophage colony-stimulating factor [35,36], infliximab [37], hyperbaric oxygen [38,39], topically applied bovine collagen [40] and grafting with bioengineered dermal tissue [41,42].

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Granuloma multiforme

[D.A. Burns]

Definition. A chronic granulomatous skin condition, which is characterized clinically by firm papules aggregated into plaques or forming the edges of annular lesions and histologically by focal necrobiosis and histiocytic granulomas. It has been reported from Africa, Indonesia and India [1–7]. Leiker and coworkers [1–3] first described granuloma multiforme and distinguished it from tuberculoid leprosy. Leiker called it Mkar disease, after the town where it was first studied. The condition is endemic in certain villages in eastern Nigeria, where the local inhabitants refer to it in the Ibo tongue as 'Ununo Enyi' (elephant ringworm) [4,7].

The disease appears to occur predominantly in females over the age of 40 years [4,7,8].

Aetiology. The morphology and histological features of lesions, and their distribution predominantly on exposed parts of the body indicate that this disorder may be granuloma annulare on light-exposed areas. It has been suggested that the primary event may be sun-induced damage to dermal connective tissue [8].

Pathology [4,9]. There are focal areas of necrobiosis, with loss of elastic tissue, surrounded by histiocytes. Multinucleated giant cells are usually a prominent feature. There is a perivascular lymphocytic infiltrate with variable numbers of plasma cells and eosinophils.

Clinical features. The upper, uncovered parts of the body are predominantly affected. The initial lesions are small, flesh-coloured papules which become aggregated into plaques or form the elevated rims of annular lesions. In larger annular lesions the central area is often hypopigmented. Pruritus may be prominent. The condition lasts for many months or years, and may persist indefinitely.

Differential diagnosis. Leprosy is endemic in the same regions where granuloma multiforme is found, and can look very similar. However, there is no loss of sensation or sweating, or other evidence of neural involvement in granuloma multiforme. In addition, the histological changes are different.

Treatment. None is known to be effective.

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Chapter 58

Sarcoidosis

D.J. Gawkrodger

Definition

There is no universally accepted definition of sarcoidosis. Many attempts have been made, but as long as its cause is unknown, definitions must be empirical and may also be inaccurate. Current definitions still have to avoid aetiological implications and the illogicalities that may result from them.

Scadding and Mitchell [1], after a full discussion of the difficulties, suggested the following: 'Sarcoidosis is a disease characterized by the formation in all or several affected organs or tissues of epithelioid cell tubercles, without caseation, although fibrinoid necrosis may be present at the centre of a few, proceeding either to resolution or to conversion of the epithelioid cell tubercles into hyaline fibrous tissue.'

The characteristic histology should be present in all affected tissue and similar in all parts of it. This excludes the sarcoid-like histology found in tuberculosis, brucellosis or leprosy. It is characterized by non-caseating epithelioid granulomas.

Main features

The most important features of sarcoidosis are as follows.

1 The disease process is usually generalized. The term is seldom applicable to a localized granulomatous reaction even though it may have similar histological findings.

2 The clinical manifestations are protean; the disease process is usually widespread; the course is protracted and usually benign, though sometimes with dangerous and disabling sequelae and complications.

3 The disease may affect any organ of the body (the adrenal gland possibly excluded). The lymph nodes, lungs, liver, spleen, skin, eyes, small bones of hands and feet, and salivary glands are most frequently affected.

4 All affected organs conform to a similar histological pattern.

5 Other changes present to a varying and inconstant degree include suppression or weakening of tuberculin and other intradermal responses, an increase in the serum gammaglobulins and a raised serum calcium level.

6 The Kveim reaction is positive in most active cases. This test is no longer available.

History [2–4]

The earliest description of a case which would now be categorized as sarcoidosis was probably Besnier's report in 1889 [5] of an association between reddish-blue lesions of the face and nose with swellings of the fingers [4]; the name 'lupus pernio' reflected his view that this might be a variant of lupus vulgaris. Tenneson in 1892 added the histological description [6]. In 1898 Hutchinson described two more cases of a skin eruption, probably sarcoidosis, to which he gave the name of 'Mortimer's malady' after one of his patients [7]. Boeck in 1899 [8] recorded his 'multiple benign sarkoid of the skin', and the current term 'sarcoidosis' stems from his misinterpretation of the histological changes. However, it was Boeck who first developed

the concept of a disease involving both the skin and internal organs—a concept taken further by Schaumann [9], who again emphasized the generalized nature of the disease and showed that skin changes were not a necessary feature of it. The disease was further expanded by the inclusion of 'osteitis tuberculosa multiplex cystica' [10], uveoparotid fever [11], pulmonary and other manifestations [12,13]. The introduction of mass radiography led to the recognition of hilar lymphadenopathy, with or without erythema nodosum, as an early benign form [14,15] and this has altered the whole concept of the disease, which is now seen more often by chest and general physicians than by dermatologists.

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Epidemiology [1]

The apparent increase in sarcoidosis over the last 40 years has been due partly to better detection, especially by mass radiography. However, even in countries with compulsory notification of the disease, there are bound to be many cases in an early, asymptomatic stage that remain undetected. For this reason, prevalence and incidence figures have to be interpreted with caution, though it is now clear that the disease has a worldwide distribution.

Sarcoidosis seems to be most prevalent (more than 10 per 100 000 population) in developed countries, but 'each succeeding world congress brings to the fore yet another country which has achieved manhood by joining in the world recognition of sarcoidosis' [2].

The danger of drawing inferences from unrepresentative collections of patients is well known [3], but certain groups do seem to be especially prone to sarcoidosis. It is, for example, more common in Afro-Caribbeans than in white inhabitants of the same area [4,5]. Other especially vulnerable groups include Puerto Ricans in New York and Irish immigrants to England. A useful study of 401 consecutive patients presenting to a district general hospital in the UK [6] gives a view of ethnic representation: Irish and Afro-Caribbean patients were disproportionately common in the material, but no attempt was made to assess incidence or prevalence in the population covered. Erythema nodosum was particularly common in the British and Irish; other skin manifestations occurred in 30 patients, 80% of whom were under 45 years of age.

Overall, sarcoidosis may be slightly more common in women than in men, and usually presents between the ages of 20 and 40 years. It is rare in young children [7]. The fact remains, however, that despite the voluminous data available, the factors influencing the prevalence and incidence of sarcoidosis remain obscure. Occupational, socioeconomic and climatic factors may be more important than have been recognized so far.

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Aetiology

Despite intensive investigation, the cause of sarcoidosis remains unknown; it is not even clear whether the condition has only one or many causes. Most of the earlier theories have been discarded; others remain unproven. Evidence from genetic and environmental sources has been inconclusive, and immunological studies have, perhaps, raised more questions than they have solved. Speculations now lie in two main areas: infectious causes and genetic factors. Both may be interlinked.

Infectious agents

Many infectious agents have been put forward as the cause of sarcoidosis, but cultures are always negative and responses to treatment have not supported these beliefs. However, it remains possible that the disease represents an unusual host reaction to one or more infective agents—

as yet unknown. Diagnostic confusion with tuberculosis led to speculation that *Mycobacterium tuberculosis*, perhaps in some transmuted form, might be responsible for the symptom complex of sarcoidosis. Recent evidence has lent some support for this. Serological studies have shown that patients with sarcoidosis have raised levels of antibodies to *M. paratuberculosis*, similar to those seen with Crohn's disease [1]. A polymerase chain reaction study revealed the presence of various subtypes of mycobacterial DNA (including *M. avium–intracellulare*) in 16 of 20 cases of cutaneous sarcoidosis [2]. In addition, it was recently reported that acid-fast cell-wall-deficient forms of *M. tuberculosis* have been grown from the blood of patients with active sarcoidosis [3]. The significance of these findings is unclear at present, and the contribution of any mycobacteria to the pathogenesis of sarcoidosis is unknown. The onset of cutaneous sarcoidosis has been described following *M. marinum* infection [4].

Histoplasmosis and other fungi, which can produce granulomas exactly mimicking sarcoidosis, also have been suspected as possible causes, but their geographical limitations rule them out. Finally, it is always tempting to consider a viral cause for an obscure disease, but there is still no evidence to take this beyond mere speculation.

Genetic and familial factors

Familial sarcoidosis is well recognized and occurs more commonly than chance would predict. In ethnic groups known to have a high prevalence of sarcoidosis, the probability that an index case will have a sibling with sarcoidosis is about 10% [5]. In one study of 645 cases of sarcoidosis, 26 came from 12 families [6]. A literature search [7] found 182 affected sibling pairs; the excess of like-sex pairs was thought to reflect the effects of environmental exposure which they are more likely to share than unlike-sex pairs. Far fewer examples of husband/wife sarcoidosis have been recorded [8] and this suggests that family aggregates occur either on a mainly genetic basis, or require a common environmental exposure during childhood. No consistent mode of inheritance has been found, although a recessive pattern may be more common [9].

Studies of human leukocyte antigens (HLA) have not clarified the matter [10]. Differences between black and white subjects exist. Among black patients in the USA, sarcoidosis occurred significantly more frequently in individuals with BW15—but so did tuberculosis [11]. In London, white people with HLA-B8 were especially likely to have arthritis or erythema nodosum [12]. A recent Japanese study of 63 patients with sarcoidosis suggested that susceptibility for the disease may reside in the HLA-DRB1 locus, with resistance being conferred by the HLA-DRB1*1302 locus [13].

It seems likely that the HLA type can influence the pattern of the disease, rather than determine its occurrence.

Interferon-alpha (IFN-α) therapy

In more than 20 case reports [14–18], sarcoidosis has developed 15 days to 30 months after commencing IFN-α treatment. Some patients [14–16] had chronic myelogenous leukaemia and cutaneous lymphoma, conditions known to be associated with sarcoidosis on occasions. Others have had chronic hepatitis C [17,18]. Fifty per cent of cases have skin signs [18]. It is suggested that IFN-α might stimulate Th1 immune responses that are thought to be involved in sarcoidosis.

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Histopathology

The histological changes are similar in all organs affected and are remarkably constant. The essential feature is a monotonous repetition of aggregates of epithelioid cells with pale-staining nuclei, which form the characteristic discrete sarcoidal granulomas (Fig. 58.1). Multinucleate giant cells are usually, but not invariably, present. An inconstant and variable rim of lymphoid cells surrounds the granuloma but this is never well developed—hence the

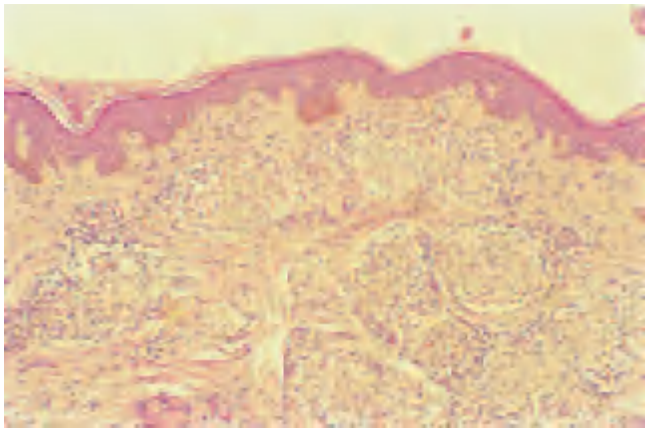


Fig. 58.1 Sarcoidosis. The epidermis is normal, while the superficial and mid-dermis contain numerous small granulomas without caseous necrosis. (Courtesy of Dr T.J. Stephenson, Royal Hallamshire Hospital, Sheffield, UK.)

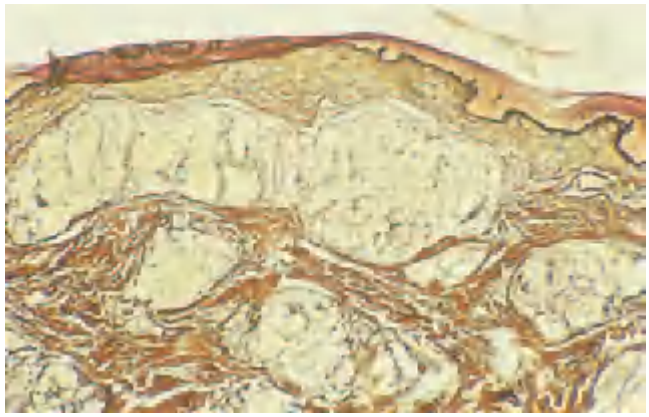
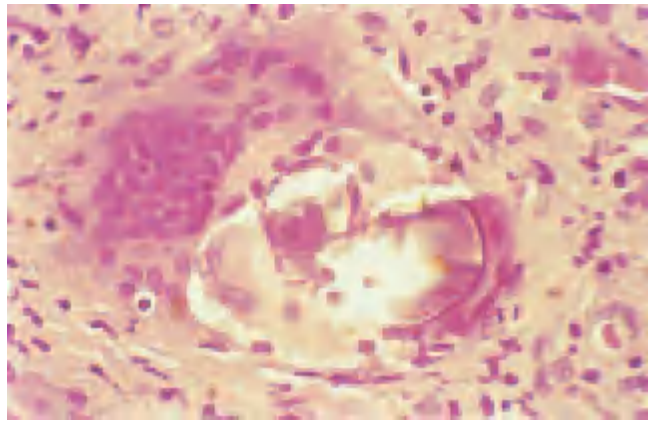
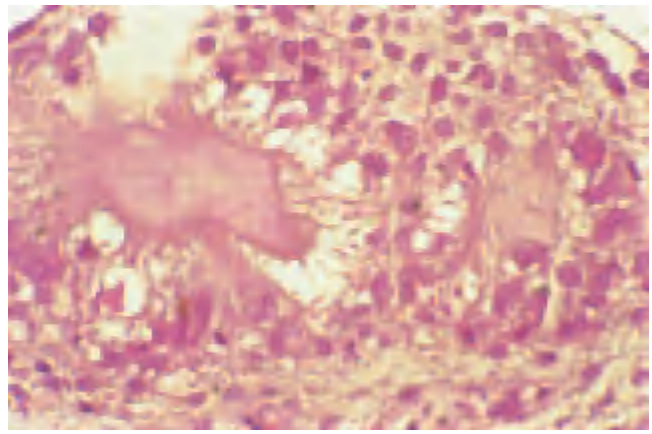


Fig. 58.2 Sarcoidosis. Reticulin stain of the section shown in Fig. 58.1, showing that the granulomas contain strands of staining reticulin, indicating that they lack caseous necrosis. (Courtesy of Dr T.J. Stephenson, Royal Hallamshire Hospital, Sheffield, UK.)



(a)



(b)

Fig. 58.3 (a) A Schaumann or conchoid body. These laminated calcospherites tend to fracture and to cause score marks. They stain basophilically. They are thought to arise from dystrophic calcification and it is suggested that they indicate chronicity. (b) High-power view of a granuloma in sarcoidosis showing an asteroid body within a giant cell. (Courtesy of Dr T.J. Stephenson, Royal Hallamshire Hospital, Sheffield, UK.)

term 'naked tubercle'. Caseation is absent, although an inconspicuous focus of fibrinoid necrosis or coagulation may occur within the granuloma. A fine reticulin network encircles the granuloma and may penetrate it (Fig. 58.2). The infiltrate tends to occur lower in the dermis than that of lupus vulgaris, and in erythrodermic sarcoidosis the granulomas are looser and less well defined. Epidermal changes can include hyperkeratosis, parakeratosis, acanthosis, atrophy and spongiosis: occasionally a lichenoid reaction is seen [1].

During the development of the granuloma, the loosely packed epithelioid cells of the early stage become more numerous and compact (their development is stimulated by IFN-γ produced by Th1 lymphocytes), and giant cells appear by their fusion. Reticulum appears and hyalinization becomes progressively more apparent as fibrosis gradually obliterates the characteristic features of the granulomas. This is the cause of the irreversible tissue scarring of the late stage of the disease. Polarizable foreign bodies were found in 12 of 50 cases of cutaneous sarcoidosis (all of whom also had systemic granulomatous disease), suggesting that in some patients, a foreign body may be an inciting stimulus for granuloma formation [2].

Inclusion bodies

These are often found in the giant cells in sarcoidosis and other sarcoidal granulomas, but are not specific. Their numbers increase as lesions age. The following types are recognized.

1 *Schaumann (conchoid) bodies* (Fig. 58.3a) are basophilic concentric lamellar structures, 100 μm in diameter, composed of lipomucoglycoproteins impregnated with calcium and iron, and they show central birefringent crystals.

2 *Asteroid (stellate) bodies* (Fig. 58.3b) are between 10 and

Table 58.1 Main histological features of sarcoidosis and tuberculosis.

Feature	Sarcoidosis	Tuberculosis
General structure	Monomorphic tubercles	Caseating tubercles
Form	Discrete, sharply defined 'naked tubercles'	Confluent, diffuse
Epithelioid cells	Large, grouped, predominant	Massed, irregular or at margin of caseation less than 50%
Giant cells	Large, usually sparse Langhans' and foreign body	More numerous, Langhans' predominate
Lymphocytes	Sparse cuffing	More numerous and scattered
Inclusion bodies	Frequent	Occasional
Blood vessels	Usually normal or dilated	May show fibrinoid changes
Reticulin	Fine and abundant around tubercles	Destroyed
Caseation	No	Yes (but not lupus vulgaris)
Fibrinoid	Sometimes at centre of tubercle	Vascular and perivascular (late)
Healing process	Progressive hyalinization from periphery; gradual dissolution	Dense collagen mesh. Retraction, fibrosis, calcification

15 μm in size; their central core is surrounded by radiating spicules (the 'open umbrella frame' [3]). They consist of collagen [4].

Development of the granuloma [5]

Several strands of research have combined to increase our understanding of the complex cascade of cellular and mediator interactions involved in granuloma formation:

1 The technique of bronchoalveolar lavage, allowing easy harvesting of cells involved in the inflammatory process within the lungs.

2 Studies of evolving Kveim antigen-induced granulomas.

3 The study of immune deposits in cutaneous sarcoidosis.

4 The use of monoclonal antibodies to characterize the cells found within the sarcoidal lesions.

The architecture of a cutaneous sarcoid granuloma follows a pattern in which the centre consists of activated macrophages and epithelioid cells, surrounded by dendritic cells. Many activated $CD4^+$ helper/inducer T lymphocytes are present at the centre of the granuloma with a smaller population of $CD8^+$ suppressor/cytotoxic T lymphocytes at the periphery [6]. The antigen in sarcoidosis remains unknown, but the arrangements within the granuloma suggest an active immunological process. In addition, most workers have been able to demonstrate immune deposits within cutaneous granulomas, presumably as a consequence of the presence of circulating immune complexes known to occur in some patients with sarcoidosis. The most usual finding has been of immunoglobulin M (IgM) in the walls of dermal blood vessels or at the dermo-epidermal junction.

In the lung, an alveolitis precedes granuloma formation. Circulating blood monocytes appear in the lung, presumably in response to local chemotactic factors, and these aggregate into epithelioid cell granulomas. Pulmonary macrophages are induced by an unknown trigger mechanism to secrete interleukin-1 (IL-1), which is responsible for the migration of T lymphocytes to the site of disease activity. IL-1 also activates T cells and stimulates T-cell release of IL-2, which further amplifies local inflammatory activity. Activated T cells secrete chemotactic factors for monocytes and migration inhibitory factors. Fibrosis is enhanced by fibronectin and growth factors derived from alveolar macrophages.

Differential diagnosis

Typical tuberculosis is usually distinguishable by the histological features listed in Table 58.1. Sarcoidosis may be particularly hard to separate from lupus vulgaris if lymphocytes are more abundant than usual. In tuberculoid leprosy, epithelioid cells surround and are associated with the nerves, and there is more central necrosis.

However, the histology of true sarcoidosis cannot always be distinguished from that of sarcoidal granulomas due to other causes—the key to the diagnosis of sarcoidosis lies in the uniformity of the histological changes in all affected organs.

Lupoid leishmaniasis, granulomatosis disciformis, rosacea and Crohn's disease may pose difficulties. Plasma cells and coagulation necrosis are features of syphilis. The granulomas of cat scratch fever are said to be larger than those of sarcoidosis. When sarcoid-like reactions occur in a scar, the possibility of a foreign-body reaction must be considered. Talc may be recognized by its refractile nature.

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Immunological aspects [1,2]

Important advances have been made in our understanding of the immunology of sarcoidosis in recent years; yet the paradox of the disease remains. How is it that granulomas can evolve, presumably as a consequence of a local T-cell-mediated immune response to antigenic insult (e.g. a superantigen or a particulate antigen ingested by macrophages), in a condition apparently characterized by reduced cell-mediated immunity? Even if the cutaneous anergy of sarcoidosis is partly explained by a movement of activated helper T cells to sites of disease activity, leaving in the circulation an excess of anergic suppressor cells, then it still has to be accepted that Kveim-induced granulomas, at least, can develop during a state of depressed immune responsiveness.

Cell-mediated immunity

Depression of cell-mediated immunity is the hallmark of sarcoidosis; indeed, the first immunological defect to be demonstrated was lack of reactivity to tuberculin. Sensitivity to tuberculin is depressed to a variable degree and becomes negative in about two-thirds of patients [3]. However, there is no absolute correlation between reactivity and the state of the disease, and some failure of immunological response may persist despite apparent clinical resolution.

Later, this anergy was shown to extend to other intradermal allergens such as *Candida*, pertussis, trichophyton and mumps antigens. The combination of a depressed reaction to mumps antigen with normal circulating antibody responses is characteristic of, but not specific for, sarcoidosis. The response to dinitrochlorobenzene (DNCB) is also defective [4].

The levels of circulating T lymphocytes expressing the γ/δ T-cell marker are increased in sarcoidosis, and correlate with the defect in cellular immunity [5]. T-cell receptor gene studies from blood and sarcoid lesions are consistent with an oligoclonal expansion of T cells from an antigen-driven response [6]. The formation of sarcoid granulomas, like tuberculoid, is characterized by the expression of a Th1 cytokine profile, i.e. the T-lymphocytes secrete IL-2, IFN-γ, and tumour necrosis factor-α (TNF-α) [7]; there is inactivation of Th2 lymphocytes. Th2-type granulomas have a prevalence of eosinophils and are seen, for example, in schistosomiasis.

Humoral immunity

All classes of serum immunoglobulins are increased. Activated T lymphocytes release B-cell growth factor and a B-cell differentiation factor, which together increase immunoglobulin production at the sites of disease [8]. Significantly raised levels of circulating antibodies may be found to rubella, measles, herpes simplex, the Epstein–Barr virus and cytomegalovirus [9]. The prevalence of asthma, eczema and hay fever is unaltered in patients with sarcoidosis [10].

Immune complexes are present in more than 50% of patients with sarcoidosis [11] and are manifested clinically by erythema nodosum, polyarthritis and uveitis.

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General manifestations of sarcoidosis [1–3]

There is no disease with more varied manifestations. Its course is unpredictable. Several years may separate one manifestation from another, and any organ of the body may be involved. Symptoms result from invasion and replacement, pressure, anaemia, hypercalcaemia and fibrosis.

A full history must include details of race, area of residence, previous tuberculin testing and bacille Calmette–Guérin (BCG) vaccination, industrial exposure to beryllium and any previous disease, such as erythema nodosum, that may be related, even distantly.

Staging of the disease

Pulmonary sarcoidosis is classically divided into four stages on the basis of the chest radiograph:
Stage 0: 5–10% of patients with sarcoidosis have a normal chest radiograph.
Stage I: bilateral hilar lymphadenopathy alone—seen on the presenting radiograph of 35–45% of patients (Fig. 58.4).
Stage II: bilateral hilar lymphadenopathy with parenchymal lung involvement of fine 'fluffy' or coarse type.

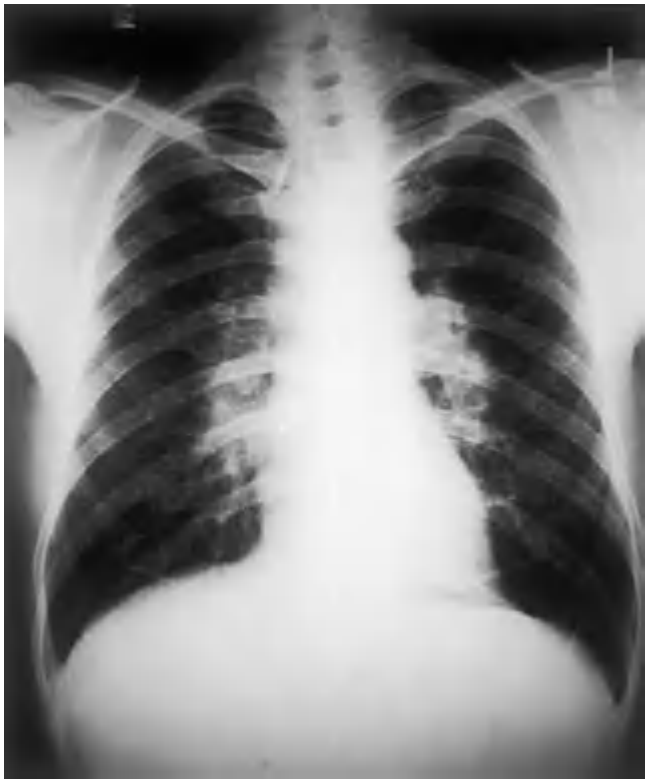

Fig. 58.4 Chest radiograph showing bilateral hilar lymphadenopathy typical of sarcoidosis.

Stage III: late stage of pulmonary infiltration with fibrosis and pulmonary insufficiency.

Extrapulmonary manifestations of sarcoidosis cannot be staged in this way, although some generalizations are possible. Erythema nodosum is, *par excellence*, an early feature, occurring with stage I pulmonary disease, and carrying a good prognosis. Iridocyclitis and anterior uveitis are usually associated with the later stages and more persistent forms of the disease. An attempt can be made to classify sarcoidosis on the basis of the degree of internal involvement, and on the type of skin lesions, as 'early' (e.g. erythema nodosum and bilateral hilar lymphadenopathy), 'intermediate' (e.g. papular and nodular forms) and 'late' (e.g. plaque, subcutaneous or lupus pernio). However, this may be unreliable, as the prognosis mostly depends upon the extent of internal disease, and this may not become apparent until treatment is too late to be effective. Of this disease, it has been aptly said: 'One of its most singular details . . . is the frequency of its clinical silence'.

Systemic features

General symptoms

The onset is often marked by lethargy, loss of weight and general malaise, but may be symptomless. A dry cough, dyspnoea and chest pain are present in half the patients.

Bone and joint changes

An acute polyarthralgia may accompany erythema nodosum. A more chronic polyarthritis may appear later in the disease, chiefly in Afro-Caribbeans. Bone changes, often asymptomatic, were found in 8% of 260 patients routinely examined radiologically [4]. Classically, they involve the small bones of the hands and feet in middle-aged females with lupus pernio. The most common change is lysis with bone cysts. The nasal bones, and occasionally the calvarium, may be involved in a way which mimics metastatic deposits [5].

Cardiac involvement [6,7]

Granulomatous infiltration of the conducting system may lead to heart block, papillary muscle dysfunction, congestive cardiac failure, pericarditis, chest pain, arrhythmias or even sudden death. The patients are often young, and the condition may be revealed only at post-mortem. Cardiac involvement is more common than was once believed, being found in 20–50% of autopsies on patients with sarcoid [6]. An abnormal electrocardiogram (ECG) was found in 14% of 401 patients examined routinely [4]. A careful cardiac examination should be routine procedure in all cases of established sarcoidosis.

Muscle involvement

Polymyositis and myopathy occur rarely, and even muscle weakness and tenderness are uncommon despite the fact that random muscle biopsies in patients with sarcoidosis are positive in 50–80%.

Nervous system involvement [8,9]

About 5% of patients with sarcoidosis have nervous system involvement and a wide variety of syndromes may result, including optic nerve lesions, cranial nerve palsies, meningoencephalitis, multiple sclerosis-like changes, peripheral neuropathy, mononeuritis multiplex and psychiatric changes. The facial nerve is frequently affected, with or without Heerfordt's syndrome (see below). Involvement of the hypothalamus or brainstem is rare but important. Sarcoidosis may also present as diabetes insipidus, hypopituitarism or endocrine abnormalities. The cerebrospinal fluid can show elevated protein and/or cells. Magnetic resonance imaging (MRI) may reveal abnormalities. Peripheral neuropathies often settle, but central nervous system manifestations seldom do so.

Ocular involvement [10]

The eyes are involved at some time in 25–50% of patients

with sarcoidosis; eye disease is the first feature of sarcoidosis in about 10% of patients. The main types of ocular involvement are as follows:

1 *Uveitis*. Anterior and posterior uveitis are the most important and serious manifestations. Acute and chronic forms occur. The onset is usually insidious and 'mutton-fat' precipitates are found on the corneal epithelium. Iridocyclitis may be severe and recurrent. Complications include glaucoma, cataract and iris synechiae.

2 *Iris nodules*. These represent granulomatous infiltration of the stroma of the iris.

3 *Retinochoroiditis*. This usually occurs with chronic uveitis.

4 *Conjunctivitis*. Conjunctival nodules are common and are opaque, grey, slightly elevated lesions. 'Millet-seed' nodules may involve the eyelid margins. Biopsy will help to confirm the diagnosis of sarcoidosis; even 'blind' biopsies may reveal the disease.

5 *Lacrimal gland involvement*. Decreased lacrimal gland secretion is not uncommon (keratoconjunctivitis sicca is a presenting feature in about 10% of cases). Sarcoidosis is one cause of Mikulicz's syndrome (bilateral swelling of the lacrimal and salivary glands). Sjögren's syndrome can coexist with sarcoidosis and poses particular diagnostic problems.

6 *Optic nerves*. These may be involved as part of a widespread involvement of the central nervous system or as unilateral retrobulbar disease. Papilloedema, retrobulbar neuritis and optic atrophy may result.

7 *Orbital involvement*. This may cause unilateral proptosis.

8 *Other ocular syndromes*.

(a) Lofgren's syndrome (erythema nodosum, bilateral hilar lymphadenopathy and acute iridocyclitis) is usually self-limiting.

(b) Heerfordt's syndrome includes uveitis, parotid gland enlargement, fever and cranial nerve palsies, usually of the facial nerve.

(c) Keratoconjunctivitis sicca with parotid and lacrimal gland enlargement.

(d) Lupus pernio, chronic iridocyclitis, bone cysts and pulmonary fibrosis.

Pulmonary and upper respiratory changes [11]

Pulmonary changes dominate the later stages of the disease, and progressive diminution of respiratory function is the most common cause of incapacity. All patients with clinical or radiographic evidence of pulmonary involvement should be referred to a chest physician, who will decide on the need for and timing of treatment.

Upper respiratory involvement is often associated with chronic pulmonary disease and may be asymptomatic. Nasal stuffiness or blockage, with crusting and a nasal discharge, are common [12]. Cartilage or bone may be destroyed.

Renal involvement [13]

Symptoms are rare, but scattered granulomas can be found at autopsy in up to 40% of patients. Renal failure may be secondary to granulomatous invasion or to hypercalcaemia.

Reticuloendothelial system involvement

Lymph nodes are enlarged in about 50% of patients and may provide a convenient site for biopsy. An enlarged spleen can be felt in about 15% of cases [14]; hypersplenism may cause thrombocytopenia [15].

Involvement of the liver and other organs

It is evident that no organ is exempt from the occasional deposit of sarcoidal granuloma, and the dermatologist, as much as the general physician, should attempt to delineate the full extent of the disease in all patients. In no disease is it more important to look repeatedly 'under the skin' for other signs. Liver granulomas are found in 63–87% of patients with sarcoidosis and mild elevation of the serum alkaline phosphatase or bilirubin is seen in up to 80% of cases [16] although the liver is only palpable in about 20% of patients.

Hypercalcaemia and hypercalciuria [17]

The frequency of hypercalcaemia varies greatly (from 2% to 40% in different series), but it is less common than hypercalciuria. In one series, 11% of 1760 sarcoid patients had hypercalcaemia, while 40% had hypercalciuria [18]. Persistent hypercalcaemia is manifest clinically as polyuria, nocturia or polydipsia in the absence of hypertension. It can cause nephrocalcinosis and renal failure. The details of the abnormal calcium metabolism in sarcoidosis are still debated: sarcoid granulomas can themselves produce 1,25-dihydroxyvitamin D [19], which may increase calcium absorption via the gut. Persistent hypercalcaemia is one indication for systemic steroid therapy.

Sarcoidosis and pregnancy

The condition may improve during pregnancy, only to relapse thereafter. Miscarriages and congenital abnormalities are not especially common [20].

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Sarcoidosis of the skin

Between 20% and 35% of patients with systemic sarcoidosis have skin lesions [1], but cutaneous sarcoidosis can also occur without systemic disease. Significant pulmonary disease may be silent [2]. In six of 13 patients with cutaneous sarcoidosis, but without a past history of sarcoidosis, no other systemic signs of the disease were detected during prolonged follow-up [3]; in another series of 188 patients with cutaneous sarcoid, 50 had no systemic involvement [4]. Finally, the extent of any cutaneous lesions does not correlate with the extent of systemic disease.

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Classification. This has been made more difficult by the use of eponyms which are no longer appropriate and which should now be discarded. A simple morphological classification is shown in Table 58.2, but more than one type of lesion may exist at the same time. The differences between the main patterns lie in the manner and extent of the involvement of the skin or subcutaneous tissues.

Table 58.2 Classification of sarcoidosis of the skin.

Type of cutaneous lesions	Stage of disease
Erythema nodosum	Acute ('benign')
Erythematous and erythematopapular	Acute and subacute
'Scar sarcoidosis'	Acute and subacute
Papular ('small nodular')	Acute and subacute
(Boeck) lichenoid variety	
Erythrodermic (Schaumann)	Subacute and chronic
Nodular	Subacute and chronic
Annular (or circinate)	
Angiolupoid (Brocq–Pautrier)	
Subcutaneous	
Plaque	Chronic
Lupus pernio	
Miscellaneous	Usually chronic
Ulcerative, psoriasiform, palmoplantar, ungual, mucosal	
Sarcoidosis of black Africans	

The specific lesions of sarcoidosis take the form of granulomatous infiltrates: erythema nodosum stands out from these as a non-specific accompaniment of early sarcoidosis without the characteristic sarcoidal granulomas.

Clinical features. The features of the specific cutaneous lesions arise from a dense accumulation of epithelioid cell granulomas in the dermis. In the deep nodular and infiltrative types, the subcutaneous tissue is involved by extension. The lesions of sarcoidosis are generally recognizable as nodules or plaques with a greater degree of infiltration than would be expected from their surface appearance. Their colour ranges from yellow ochre to the livid violaceous hue which is most marked in lupus pernio. On diascopy, a pale yellowish-grey colour remains; sometimes, individual nodules are apparent. There is a tendency to form annular lesions. The epidermis is rarely affected, except for a light scaling, but some degree of vascular dilatation is frequent, especially in angiolupoid sarcoid. Scarring is unusual except in the papular and annular forms.

There is no characteristic distribution, though the small nodular type tends to involve the extensor aspects of the limbs, and rarely the trunk, while the large nodular type affects predominantly the face, hands and trunk. The manifestations of the disease vary from country to country: mucosal involvement, for instance, is rare in France but common in Scandinavia.

Classical forms

Angiolupoid form

A rare but characteristic variety. It affects women predominantly, almost always occurring at the side of the bridge of the nose towards the corner of the eye, below the

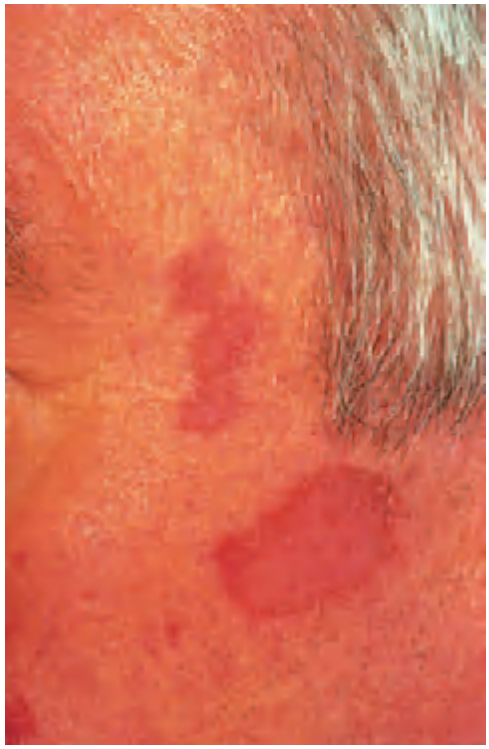


Fig. 58.5 Annular sarcoidosis of the face.

inner edge of the eyebrow, or on the adjacent area of cheek. There are seldom more than two tumours. They are soft and hemispherical, with a well-marked orange-red or reddish-brown colour and of a more livid hue than other forms. This is due to the marked telangiectatic component, which alters the normal grey-yellow appearance on diascopy. There is little tendency to spontaneous resolution.

Annular forms (Fig. 58.5)

Annular lesions were seen in 32 of 188 white subjects with cutaneous sarcoid lesions [1] and occurred mainly in the chronic stage. They are formed by peripheral evolution and central clearing. They occur particularly on the forehead, face and neck. The central area may become depigmented and scarred. Ulceration is rare. The lesions may resemble annular necrobiosis of the scalp [2], but can be differentiated histologically. Diffuse papular forms may also show an annular configuration.

Erythema nodosum

Sarcoidosis is but one of the many causes of erythema nodosum—a subject dealt with in detail in Chapter 49. It occurs most often in the spring, in young women, and signals an early and usually 'benign' variety of sarcoidosis, with bilateral hilar lymphadenopathy and a tendency to involute spontaneously. Most cases resolve completely within 2 years.

The frequency with which erythema nodosum is reported in sarcoidosis varies from series to series, no doubt depending upon the selection of material. This was well shown in a worldwide survey of sarcoidosis [3] in which erythema nodosum pinpointed the onset of the disease in 600 (17%) of 3676 patients. The distribution was uneven between the countries studied, the condition affecting one-third of British patients and being less evident elsewhere. In a Danish series [1], 25 out of 188 patients with cutaneous sarcoidosis had erythema nodosum which tended to affect younger patients (mean age 30 years) than did infiltrative sarcoidal lesions (mean age 48 years).

Lupus pernio [4]

This is a relatively common skin manifestation of sarcoidosis. In a Danish series of 188 patients with cutaneous sarcoidosis, 22 had lupus pernio [1]; a British series of 147 patients with various skin lesions included 35 with lupus pernio [4]. It tended to affect older patients, was twice as common in women as in men, and was more common in Afro-Caribbeans than in their white counterparts.

Large bluish-red and dusky violaceous infiltrated nodules and plaques occur more or less symmetrically on the nose (Fig. 58.6), cheeks, ears, fingers, hands and toes (Fig. 58.7). The lesions may feel soft, doughy or

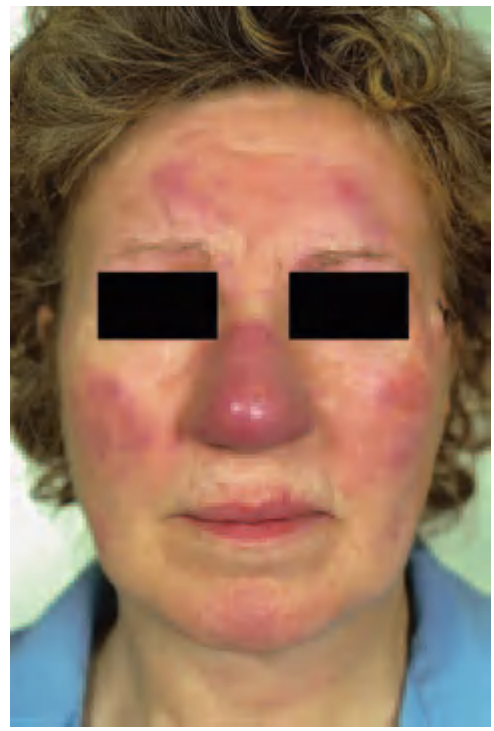
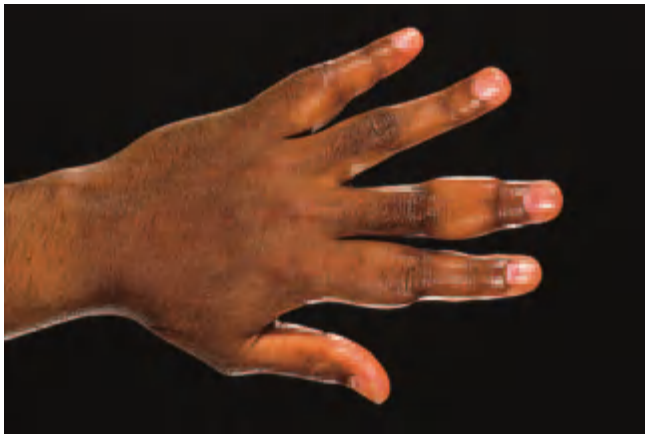


Fig. 58.6 Lupus pernio. (Courtesy of Dr F.A. Ive, Dryburn Hospital, Durham, UK.)



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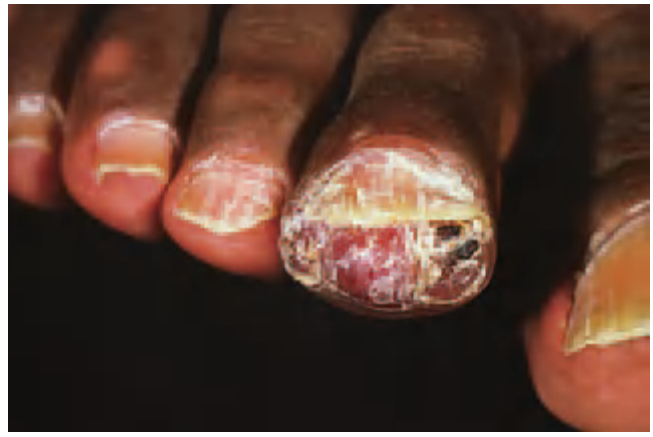

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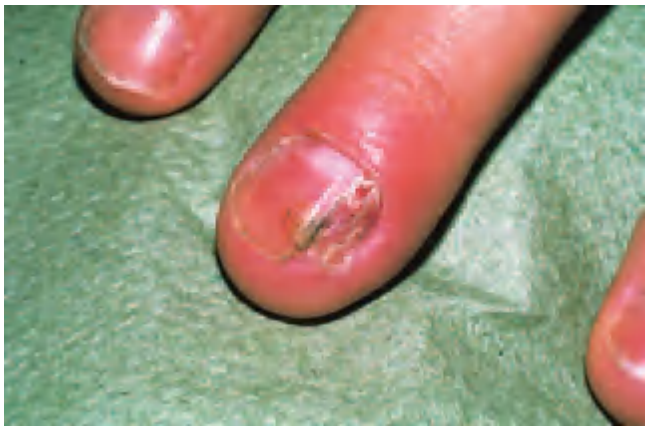

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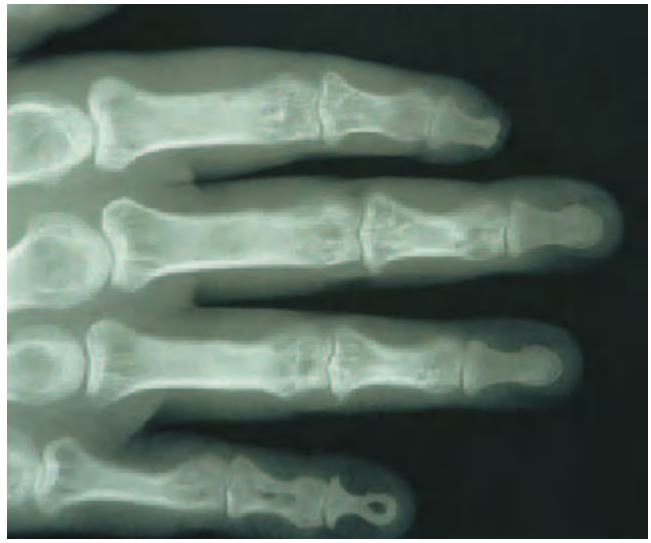


(d)

Fig. 58.7 (a) Typical fusiform appearance of the fingers from bone involvement. (Courtesy of Dr F.A. Ive, Dryburn Hospital, Durham, UK.) (b) Sarcoidosis of the terminal phalanx of the toe. (Courtesy of Dr F.A. Ive, Dryburn Hospital, Durham, UK.) (c) Sarcoidosis of the terminal phalanx involving the nail. (d) Radiograph of the hand in a patient with finger involvement by sarcoidosis, showing lucent areas in the bones of the phalanges.

indurated. Discrete nodules with a typical appearance on diascopy may be found at the edge sometimes. The surface is often glistening, and the epidermis stretched, with large pilosebaceous follicles. Ulceration rarely occurs in the skin; gross mutilation, as in lupus vulgaris, never. Involved ear-lobes may become massive ('turkey ears'). Other chronic skin lesions, including plaques and subcutaneous nodules, may accompany lupus pernio. Scarring alopecia may occur on the scalp.

Nasal involvement is associated with swelling, ulceration or crusting of the nasal vestibule, and patients may present with difficulty in breathing. Submucous resection carries the risk of nasal septal perforation and collapse of the nose.

Lupus pernio tends to be associated particularly with other forms of chronic fibrotic sarcoidosis, including upper respiratory tract sarcoidosis, bone cysts, lacrimal gland and renal sarcoidosis, and with hyperglobulinaemia and hypercalcaemia.

Lupus pernio tends to persist: lesions of more than 2 years standing seldom resolve. The facial disfigurement it causes may lead to emotional scarring, which may justify aggressive lines of therapy including plastic surgery [5]. Topical camouflage is an important adjunct to this therapy.

Maculopapular and erythematous forms (Fig. 58.8)

This is separate from the papular form (see below). Transient 'prodromal' maculopapular eruptions were noted in the early stages of sarcoidosis in no less than eight of 33 patients who showed cutaneous signs of the disease [6] and are apparently seen most commonly by chest and general physicians. Diffuse forms of papular sarcoidosis do occur but are uncommon. Even less common are ill-defined patches of a lavender colour, sometimes slightly

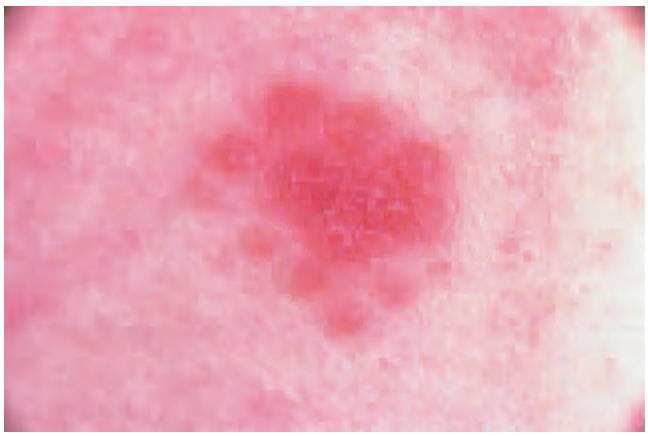


Fig. 58.8 Confluent scaly macules of the trunk due to sarcoidosis. (Courtesy of Dr R.H. Champion, Addenbrooke's Hospital, Cambridge, UK.)

scaly or lightly infiltrated. On the face, these simulate rosacea. Sand-like lupoid grains are sometimes seen on diascopy, but more frequently there is a yellow discoloration. Transient parotid swellings and hepatosplenomegaly may be seen [7]. Such cases pursue a long course, fluctuating in severity. Pruritic maculopapular lesions have been described [8].

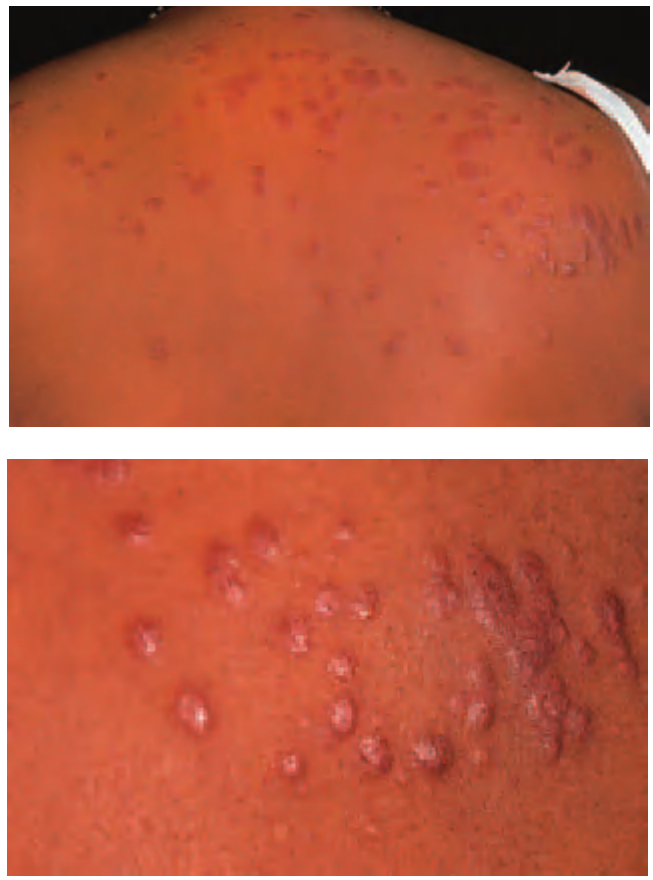
Nodular forms (Fig. 58.9)

Here the lesions are larger than 5 mm, usually single or relatively few, and remain circumscribed. Red or yellowish-red at first, becoming violaceous or purplish-brown later, they are soft or firm, round and most often affect the proximal parts of the limbs, the trunk and the face. Dilated vessels may be seen on the surface of the lesions which are extremely indolent. As they involute, the centre may become depressed, and the lesions are eventually replaced by brownish telangiectatic marks, or yellowish-white atrophic and fibrotic patches.

Papular (small nodular type) (Figs 58.10 & 58.11)

The papules are hemispherical and vary in size from 1 to 5 mm. Orange or yellowish-brown at first, they later become brownish-red or violaceous, painless and torpid. Only a few lesions or several hundred may appear, arising in crops but eventually becoming stationary. They particularly affect the face (especially in Afro-Caribbeans) and extensor aspects of the limbs, but rarely the trunk or mucous membranes.

On diascopy, the lupoid grains are of a more opaque appearance and colour than those of lupus vulgaris, resembling grains of sand. If probed with a needle they feel firm. When lesions disappear they often leave a pale, yellowish-white or telangiectatic scar. Occasionally they become confluent, merging into an erythematous plaque



(a) (b)

Fig. 58.9 (a) Nodular sarcoidosis on the upper back; (b) close-up of the same patient, showing the grouped nodules. (Courtesy of Dr D.A. Burns, Leicester, UK.)

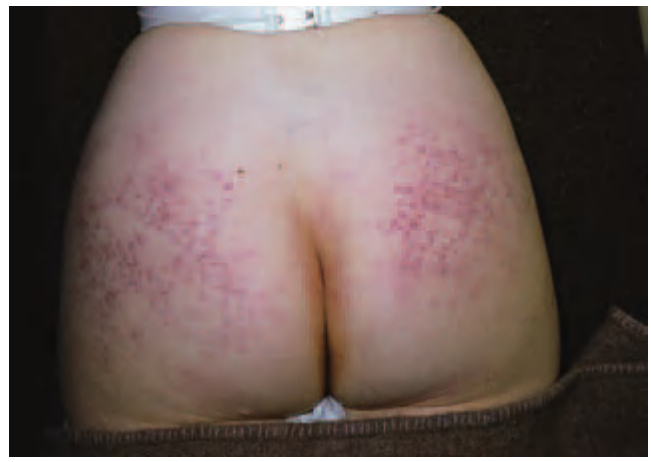


Fig. 58.10 Papular sarcoid of the buttocks. (Courtesy of Professor J.A.A. Hunter, Royal Infirmary, Edinburgh, UK.)

(Fig. 58.12). A ringed nummular configuration was present in the second of Schaumann's four cases [9].

Widely disseminated, hard, shotty, subcutaneous papules can appear with the granulomas lying in the deep subcutaneous tissues and fascial planes. A lichenoid variety is discussed separately on p. 58.15.

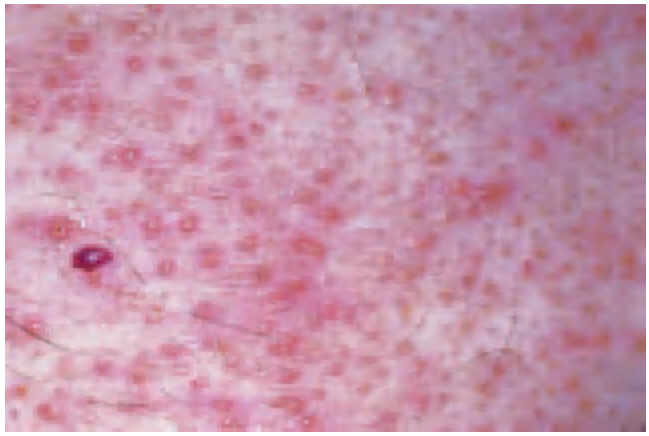


Fig. 58.11 Micropapular sarcoidosis. (Courtesy of Dr R.H. Champion, Addenbrooke's Hospital, Cambridge, UK.)

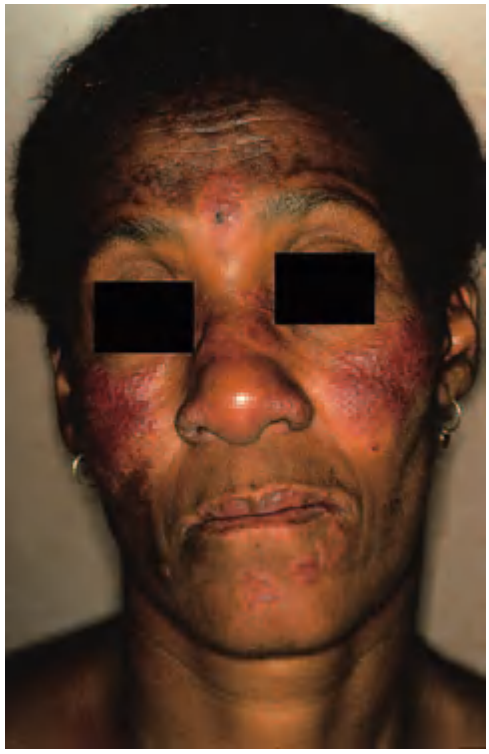


Fig. 58.12 Plaque-type sarcoidosis affecting the face in a black African. (Courtesy of Dr J.E. Bothwell, Barnsley District General Hospital, Barnsley, UK.)

In general, the papular type carries a more favourable prognosis than do other types of infiltration. Confirmatory biopsy of other organs should be carried out, although this form may occur without other manifestations of the disease.

Histopathology. The infiltrate is in the high and mid-dermis. It may be hard to distinguish from acne agminata in which, however, caseation can be seen.

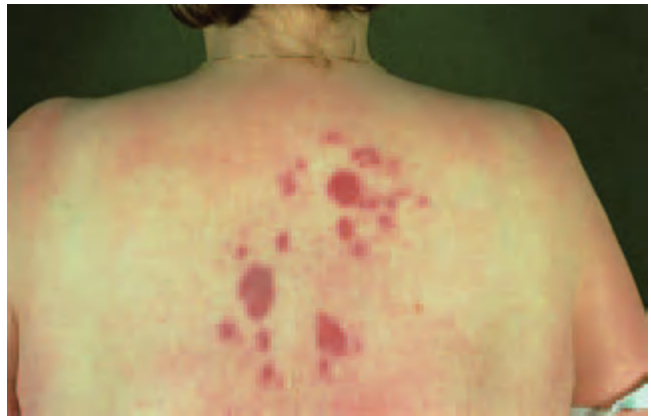


Fig. 58.13 Sarcoidosis. Lesions of the plaque type are present on the upper back. (Reproduced with permission from Harcourt Publishers, Ltd.)

Differential diagnosis. Lupus erythematosus can be mimicked. Papular forms of secondary syphilis are distinguished by the course and associated features of this disease. Occasionally, acne agminata (Chapter 43) presents difficulties.

Plaque form (Fig. 58.13)

It is convenient to keep this form distinct. It involves chiefly the limbs, shoulders, buttocks and thighs. The lesions are characteristically diffuse, and extend further than is apparent on the surface. They may form placards of an irregular shape with more superficial nodules superimposed, sometimes having a crescentic or serpiginous outline resembling tertiary syphilis. On the legs, they may closely resemble necrobiosis lipoidica (Fig. 58.14). They are very persistent.

Scar sarcoidosis (Fig. 58.15)

Sarcoidosis appearing in a scar may be the only cutaneous sign of the disease, and is therefore of diagnostic importance. Scar involvement was seen in 26 of 188 white patients with sarcoidosis [1], and may represent a form of Koebner phenomenon. Long-standing scars, often on the knees, become inflamed and infiltrated, giving rise to typical purplish-red lesions which turn brown as they fade. There is some resemblance to a keloid, but the lesions do not itch. This form of sarcoidosis is as common in men as in women [10].

Scar sarcoidosis occurs in three situations:

1 In the acute eruptive phase, following erythema nodosum, or in the scars of biopsies taken at that time.

2 At any later stage of the disease, sometimes moving in parallel with pulmonary changes and slightly in advance of iritis [6]. Exacerbation of the systemic disease may be preceded by this warning sign.

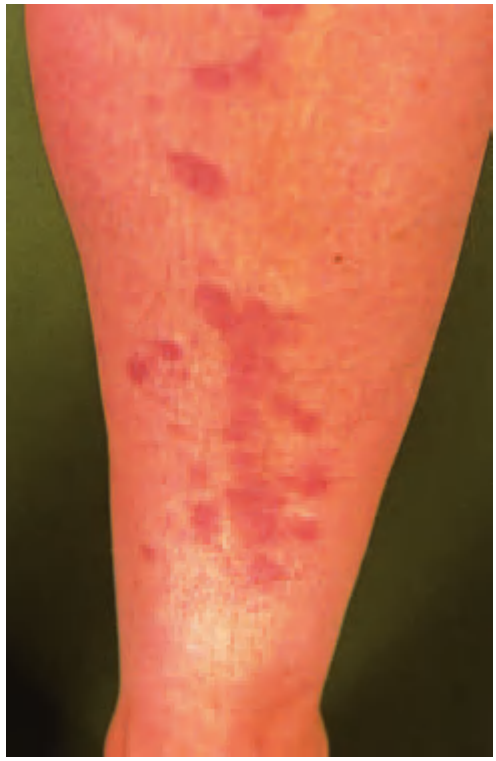


Fig. 58.14 Sarcoidosis of the plaque type on the shins, resembling necrobiosis lipoidica.

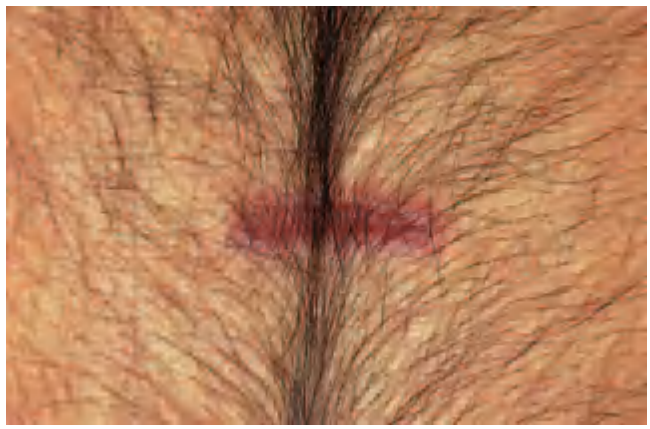


Fig. 58.15 Scar sarcoidosis on the presternal area. (Courtesy of Dr D.A. Burns, Leicester, UK.)

3 At inoculation sites—for example, after venepuncture [11], BCG or tuberculin tests. The involvement of tribal scarification marks is the commonest presentation of sarcoidosis in Nigeria [12,13].

The histology is typical. Confirmatory evidence of sarcoidosis should be sought (by chest radiography, and biopsy from other organs), as local sarcoidal reactions may occur in scars contaminated with silica. A silica granuloma in a scar may, rarely, progress into scar sarcoidosis [14]. Tattoos may also show sarcoidal reactions.

Subcutaneous sarcoidosis [15]

It seems likely that the first case report of subcutaneous sarcoidosis was indeed that of Darier and Roussy in 1904 [16], although they considered that their patient had tuberculosis. However, the term 'sarcoid of Darier–Roussy' has been used so often for granulomatous conditions other than sarcoidosis that it has become devalued and should be discarded.

Nevertheless, subcutaneous sarcoidosis does exist, although it is rare, especially in white people [17]. It takes the form of tender or painless persistent nodules, most often on the extremities of middle-aged patients. Systemic involvement is usually present, sometimes as hilar lymphadenopathy [18].

Histopathology. The infiltrate is naturally greater in nodular lesions but remains circumscribed. In the subcutaneous form, the sarcoid process may at first be located in the septa and at the periphery of the fat lobules, eventually replacing the lobules with granulomatous nodules. In the angio-lupoid form, vascular dilatation is prominent.

Differential diagnosis. Lymphocytoma cutis can be separated by its histology. Four other diseases cause particular difficulty, and serial sectioning and cultures of biopsy material may be necessary. They are as follows:

1 *Tuberculoid leprosy*. Distinguished by loss of thermal appreciation and of the histamine flare, a positive Mitsuda test and invasion of nerves.

2 *Lupus vulgaris*. In its exuberant form, this can scarcely be distinguished, although vitropression is said to reveal more translucent nodules of an 'apple jelly' rather than a greyish-yellow colour. Ulceration and scarring ultimately occur. Histology helps, but does not decide: a therapeutic test with antituberculous drugs does.

3 *Lupoid leishmaniasis*. The same difficulties exist clinically and histologically. Leishman–Donovan bodies are rarely found. The Kveim test is negative.

4 *Local sarcoid reaction*. By definition, this is confined to local areas or sites of trauma. There are no other signs of sarcoidosis, and the Kveim test is negative.

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Unusual and atypical forms

In addition to the 'classical' forms of the disease described above, a wide variety of unusual forms have been recorded, particularly in Afro-Caribbeans.

Alopecia

Alopecia of the scalp due to sarcoidosis is well recognized [1,2]. Alopecia of the shin has been a presenting sign of the disease [3]. Sarcoidal granulomas were found on histology, and the Kveim test was positive.

Atrophic forms

The rare atrophic types of cutaneous sarcoidosis may be localized to the legs [4] or generalized [5–7]. It is usually accompanied by ulceration.

Erythrodermic sarcoidosis

This is extremely rare. Red scaling patches extend and merge into infiltrated brownish-red sheets. Lymphadenopathy is usually pronounced. During resolution, typical papules and nodules may separate from the plaque, which gradually loses its infiltration and disappears. A reticulate yellowish stippling may be seen as it resolves. One unique case was associated with periarteritis and ulceration [8]; in another patient, a 6-year-old boy, the eruption resembled pityriasis rubra pilaris [9].

Hypopigmentation

Macular hypopigmentation or hypopigmented areas around a central indurated lesion were first recorded in eight of 145 patients (mostly Afro-Caribbeans) with sarcoidosis [10]. There have been several subsequent reports [11–13]. Lesions vary from 0.2 to 1 cm in diameter and occur mainly on the limbs [13]. They may be tender, but are not anaesthetic, and may be the first sign of the disease [14].

Histologically, epithelioid cell granulomas are usually present in the dermis; occasionally the changes are non-specific [11,14]. The melanocytes show degenerative changes but electron-microscopy studies have not been helpful [11]. The differential diagnosis includes leprosy, post-inflammatory hypopigmentation, idiopathic guttate hypomelanosis and pityriasis lichenoides chronica [15]. The condition does not respond to corticosteroids [11], but may repigment after prolonged psoralen and UVA (PUVA) therapy [14].

Ichthyosiform sarcoidosis [16–18]

More than 19 cases of ichthyosiform sarcoidosis are reported [18]. It usually occurs on the lower legs as large, thick, polygonal adherent scales that may or may not overlie dark red papules and nodules. Biopsy reveals epidermal changes consistent with ichthyosis vulgaris, as well as non-caseating epithelioid granulomas in the dermis, even in the absence of clinically detectable dermal abnormality. Almost all patients with ichthyosiform sarcoidosis have systemic involvement. In patients with acquired ichthyosis, biopsy may be worthwhile to exclude occult sarcoidosis.

Lichenoid forms

The lichenoid variety of sarcoidosis consists of pinhead-sized papules, skin-coloured, erythematous or yellowish in hue, that can be follicular or closely grouped in round or oval clusters and show slight scaling [18]. It constitutes 1–2% of skin sarcoidosis and may pose difficulties in diagnosis [19]. Although the lichenoid form resembles lichen planus or lichen scrofulosorum, the tuberculin test is negative, the course is indolent and the histology characteristic. Arguments have, however, been adduced in favour in a mycobacterial cause, because of atypical features which are sometimes present [20].

Miscellaneous forms

Many have been described, including the following: pseudotumoral [21], psoriasiform [22,23] and pruriginous varieties [24]; lupus erythematosus-like and lupoid forms; a bizarre polymorphous light eruption type; perifollicular pustules and papules widely scattered over the body; keratotic lesions of the palms simulating psoriasis or syphilis [25], thrombophlebitis [26]; vulval disease [27]; and breast mass [28,29]. Hyperpigmentation may occur, particularly in Afro-Caribbeans [10]. Oedema of the lower leg, usually

unilateral, is an uncommon manifestation of sarcoidosis [30]. It may occur due to vascular or lymphatic compression from enlarged inguinal or parailiac lymph nodes, or from direct granulomatous infiltration of the skin. Calcinosis with subcutaneous plaques was present in one unusual patient [31]. Pain after alcohol or showering has also been described.

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Mucosal involvement

Buccal lesions or tongue involvement are occasionally found when sought [1]. The nasal mucosa is often affected in lupus pernio [2,3] and is a convenient site for biopsy. Difficulty in breathing, or a purulent catarrh, may be the presenting symptom. Yellowish-brown nodules or a diffuse infiltration with crusting occur [4]. The nasal bones may be involved; or the nasal cartilage may collapse [5]. Nodules with a hyperpigmented halo, diffuse pale-yellow plaques, or ulceration may be found on the buccal mucosa, palate, larynx or tongue.

Nail involvement [6]

This is rare, affecting only one in 400 patients with sarcoidosis in one series [7]. Changes recorded have included the following: thickening, opacity, fragility, layering, convexity, longitudinal ridging, pitting, atrophy, nail loss, pterygium and red or brown discoloration of the nail beds. Surrounding skin changes may be minimal, but in almost every case the nail abnormalities will be accompanied by cysts in the bone of the underlying terminal phalanx and a chronic disease course, often with lupus pernio.

Sarcoidosis in black Africans and African Americans (Fig. 58.16)

The lesions are often exuberant and bizarre, and the skin is especially affected, although erythema nodosum is uncommon [8,9]. Psoriasiform or lupus erythematosus-like

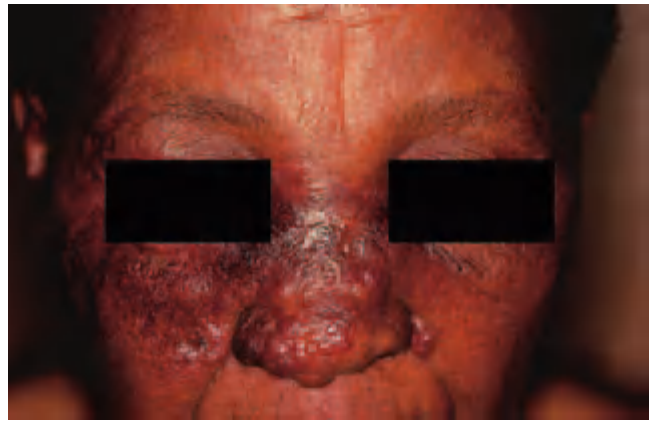

Fig. 58.16 Sarcoidosis in a black African, showing typical verrucous changes. (Courtesy of Dr J.E. Bothwell, Barnsley District General Hospital, Barnsley, UK.)

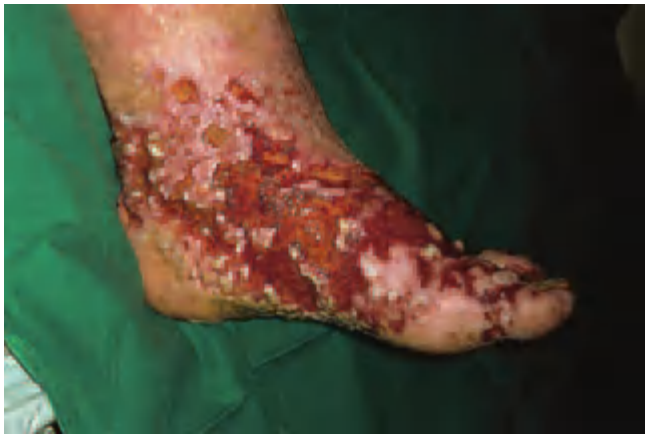

Fig. 58.17 Extensive ulceration of the foot and ankle due to sarcoidosis. (Courtesy of Dr R.H. Champion, Addenbrooke's Hospital, Cambridge, UK.)

lesions [10], verrucous and keloid-like forms [11,12], 'atypical' plaques or nodules [13], ulcerative lesions resembling papulonecrotic tuberculides [11], giant nodular forms and other atypical lesions occur, with more typical manifestations elsewhere. Shiny, waxy papules are a particular presentation [8]. The histological features may be equivocal and tuberculosis is a common cause of death. When the lesions are annular, histoplasmosis must be excluded [14].

Small ulcerating nodules, sometimes associated with deep, softer non-ulcerative lesions, have been described [10]. The histology is that of sarcoidosis but the infiltrate is diffuse, fibroblasts are numerous and the vessel walls in the subcutis are thickened.

Skin lesions in children [15]

Sarcoidosis in children is uncommon; a presentation with erythema nodosum is especially so. In one series of 28 children [16], nine had skin lesions and three developed serious eye or joint symptoms. Though papular forms of skin sarcoidosis are seen in older children, younger ones may present with uveitis or keratitis, progressive joint disease and skin lesions consisting of maculopapules, reddish-brown confluent plaques or eczema-like lesions [17–19]. Other reported cases have shown unusual features: follicular [20], miliary [21] or erythrodermic lesions with keratotic pitting [22]. The chest radiograph is often normal [17]. The severity of eye or joint involvement may justify corticosteroid therapy, often for several years, despite the risks at this early stage.

Ulcerated sarcoidosis [23] (Fig. 58.17)

This is a rare presentation: more than 35 cases have now been described, most of which were reported individually [24,25]. It usually occurs in women and black people. Ulcers develop most often on the legs [26] and may be punched-out and apparently appearing *de novo*, or arising on existing nodules and plaques, or, rarely, on extensive atrophic areas [27]. The possibility of necrobiosis lipoidica should be kept in mind, particularly in patients with diabetes [25]. The distribution of the ulcers may be unusual: a flexural distribution in one patient resembled that of metastatic Crohn's disease [28]. The granuloma may be of necrotizing type, with caseation or minimal fibrinoid necrosis [29]. True primary vasculitic changes are usually absent.

Verrucose forms [30]

Papular lesions may progress to crusted verrucose and sometimes ulcerative lesions [31] which may mimic halogen eruptions, fungal infections or tuberculosis.

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Associated diseases

Some associated diseases are understandable against the background of depressed immunological responses; some are due to a simple blocking of the activity of an organ by granulomatous infiltration, and others are uncommon and poorly understood associations. In a disease as common as sarcoidosis, coincidental associations can be expected from time to time.

Infections

A critical review of previous reports of invasive fungal infections such as cryptococcosis [1] has suggested that in many of these the entire cause of the granulomatous illness was infection, rather than sarcoidosis complicated by infection. In the series which accompanied the review, 122 patients with sarcoidosis were, in fact, found to be remarkably free of infections: three had *Aspergillus* mycetomas in cystic areas in the lung and another also had pulmonary tuberculosis, but the only extrathoracic manifestation was one case of disseminated zoster. Patients with sarcoidosis, however, are prone to extensive and stubborn wart virus infections, despite an unusually high prevalence of circulating antibodies to wart antigen [2].

Immunologically mediated conditions

In a series of 190 female patients with sarcoidosis, four had hyperthyroidism and four had Hashimoto's thyroiditis with antibodies [3]. Another patient in the same series had myxoedema and Addison's disease. Chronic urticaria may occur more frequently than would be expected by chance [4]. At least 14 cases of associated sarcoidosis and connective tissue disorders have been described [5].

Effects of infiltration

Granulomas, especially in the pituitary or thyroid, may cause endocrine disease. Invasion of the thyroid may be without effect or, if massive, can cause hypothyroidism [6]. Cushing's syndrome and diabetes insipidus, secondary to involvement of the pituitary, have been reported. The list of such cases may be extended to cover most endocrine diseases.

Vasculitis with sarcoidosis

There are occasional but well-authenticated reports of cutaneous vasculitis occurring in the course of sarcoidosis, usually early in the disease. In a series of six patients, five of them children, the vasculitis was associated with systemic illness including fever, lymphadenopathy, musculoskeletal and eye disease, and systemic steroids were given [7]. Three of these patients, all African Americans, had large-vessel disease on angiography. Erythema nodosum itself may be regarded as a form of vasculitis. Skin biopsy may show foci of epithelioid cell granulomas centred on damaged vessels [8]. An apparently unique case of leukocytoclastic vasculitis with epithelioid cell granulomas has been described [9] and annular forms documented [10]. The occurrence of vasculitis fits with the presence of circulating immune complexes in the early stages of sarcoidosis.

Malignancy

An analysis of 131 cases of coincident sarcoidosis and malignancy suggests an increased risk of developing lymphoproliferative disease [11]. The relationship between sarcoidosis and solid tumours was less clear-cut, but most marked with carcinoma of the lung. Sarcoidosis may precede the development of a lymphoma (the 'sarcoidosis–lymphoma syndrome') by 18 months to 28 years [12]. All types of lymphoma may develop [12]. Another study [13] found an increased incidence of thyroid cancer and leukaemia. Five patients with sarcoidosis developed multiple myeloma (four several years later and one at the time of diagnosis of the sarcoidosis) [14].

Necrobiosis lipoidica and granuloma annulare

There have been several reports of patients with sarcoidosis and necrobiosis lipoidica [15,16], and with sarcoidosis and granuloma annulare [17]. To complete the circle of association, patients with both necrobiosis lipoidica and granuloma annulare have also been described. In one African American woman with pulmonary sarcoid, fresh lesions of histologically typical granuloma annulare were adjacent to histologically classic sarcoid papules, suggesting that the former progressed to the later [18].

These associations may be fortuitous, but histological overlap between sarcoidosis and necrobiosis may occasionally be seen [19]. Granuloma annulare is important in the differential diagnosis of sarcoidosis, as is necrobiosis, particularly of the scalp and face. Granuloma annulare shares some aspects of collagen metabolism with sar-

coidosis [20], but in granuloma annulare the Kveim test is negative [21,22].

Other associations

Associations with psoriasis and gout [23], pyoderma gangrenosum [24,25] and secondary syphilis [26] have been reported, but seem likely to have been coincidental. Two Kveim-positive patients were found to have primary biliary cirrhosis [27], and a sarcoidal plaque on the face has been described in a woman with primary biliary cirrhosis [28]. Two cases of porphyria cutanea tarda have also been reported [29,30].

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Course and prognosis [1]

The prognosis of sarcoidosis is difficult to assess because of its frequent 'clinical silence' and the uncertainty of its onset. Several attempts have been made to list favourable and unfavourable factors [2–4], most of which have been mentioned elsewhere in this chapter. Table 58.3 is an attempt to summarize the course of sarcoidosis. The prognosis is generally better in females, in those with less severe pulmonary disease at the onset and in patients with a positive tuberculin test and normal globulin levels [4]. HLA-B8 may be associated with a tendency to spontaneous resolution [5]. In the African American, the course may be fulminant.

Table 58.3 The course of sarcoidosis.

Prognosis	Stage	Cardinal features*	Unfavourable events
? Abortive cases, or may be absent	Prodromal	Malaise, fatigue, fever, depression, polyarthralgia	–
60% subside in 6–18 months	Acute	*Erythema nodosum*, *scar sarcoidosis*, *erythematopapular rashes*, polyarthralgia, iridocyclitis, lymphadenopathy	? Sudden cardiac death
	Subacute	*Papular*, *nodular* or *scar*, pulmonary changes, lymphadenopathy, recurrent iritis, parotitis, spleen, liver	May be cardiac death
Prolonged intermission or resolution	Intermittent Chronic		
Gradual, often slow	Progressive	*Lupus pernio*, *erythrodermic*, bone cysts, cataracts, hypersplenism	Blindness
Irreversible but often extremely slow and patient survives, though disabled	Fibrotic regression	Progressive pulmonary fibrosis, nephritis, nephrosis, cataracts, glaucoma	Blindness, death
	Functional failure	Emphysema, cor pulmonale, nephrolithiasis, renal failure, tuberculosis	Death

* Skin signs are in *italics*.

About 60% of patients with stage I pulmonary disease will have recovered within 2 years [6,7]. The presence of erythema nodosum does not alter the prognosis. In the classic forms of the disease, the prognosis is quite different: only a small proportion of those in pulmonary stage II and beyond resolve spontaneously [7]. Morbidity from blindness, pulmonary disease, renal failure and the cosmetic and social effects of a disfiguring skin lesion are the not inconsiderable burdens of a disease that follows a relentless course of smouldering activity [8]. Despite corticosteroid therapy, half the patients continue to have abnormal respiratory function.

Most types of cutaneous sarcoidosis occur in the subacute and chronic stages, and their course is usually prolonged. Many papules and nodules tend to resolve within months or years, but plaques are even more resistant. Lupus pernio is especially persistent and is often accompanied by the involvement of other organs, further modifying the prognosis.

Mortality in sarcoidosis [9] has been estimated at 3–6% [4,7]. However, this may ignore undiagnosed deaths from cardiac involvement. Renal involvement is also a potential cause of death as, rarely, is progressive pulmonary disease.

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Investigations

The most important single criterion for the diagnosis of sarcoidosis is the finding of typical granulomas histologically [1], but the need for histological support varies with the pattern of clinical features. For example, in the UK, patients with erythema nodosum and bilateral hilar gland enlargement may not require biopsy, although this is necessary in other forms of the disease. Other investigations may add weight to the diagnosis, and may be useful in monitoring the activity of the disease.

Biopsy

The involvement of several organs will allow the clinician to select the biopsy site best suited to the individual patient. The dermatologist has the advantage of dealing with a site easily accessible for biopsy, but it may still be necessary to confirm the presence of sarcoidosis as opposed to a sarcoidal reaction, and biopsies from other organs are then needed. In one series [2] involving 292 biopsies from 10 sites, 87% were positive, but biopsies from the skin proved less reliable than those from lymph nodes, parotid gland or nasal mucosa. Scars that become infiltrated provide acceptable histological evidence of sarcoidosis. A mucosal biopsy is an alternative to skin biopsy in lupus pernio. A conjunctival biopsy should be considered, and may be positive even if no obvious lesions can be seen [3], as may a biopsy of the lower lip [4].

A range of techniques is now available to obtain biopsy material from other areas. These include the removal of epitrochlear or scalene lymph nodes, mediastinoscopy with mediastinal node biopsy, liver biopsy, gastrocnemius muscle biopsy (even when there are no muscle symptoms) [5], and transbronchial lung biopsy or mediastinal node biopsy through a flexible fibrescope [6]. The latter may be the most helpful and least disturbing for patients with suspected systemic sarcoidosis and intrathoracic manifestations, but carries some risk of pneumothorax. Bronchoalveolar lavage in patients with active pulmonary involvement shows an increase in the number of helper T lymphocytes present, but this is not specific for sarcoidosis.

Kveim test [7,8]

Fifty years after Kveim described it, the test which bears his name is still something of an immunological puzzle. Until recently, it was a simple and useful way of supporting a diagnosis of sarcoidosis. The Kveim test is no longer available due to the infective risk of injecting human tissue, but nevertheless details of the test are of interest and will be outlined.

The test depends upon the ability of sarcoidal tissue, usually from the spleen of an affected individual, to evoke epithelioid cell granulomas like those of sarcoidosis when injected intradermally into a patient with sarcoidosis. Positive results were found in a high proportion of patients with active early disease, but became less common in chronic disease.

The technique used is important. An easily relocated site, usually on the forearms, was injected intradermally with 0.1–0.2 mL of shaken antigen using a 1-mL tuberculin syringe and a narrow-gauge needle. In a positive reaction, a papule usually appeared within 2–3 weeks and slowly increased in size. It was best excised at 6 weeks for histology.

A positive result was the unequivocal presence of an epithelioid granuloma, exactly mimicking the natural disease, though usually less profuse. Histological interpretation was difficult in 10–20% of responses; epithelioid

cells may be diffusely scattered in the dermis or granulomatous aggregates of histiocytes may not be arranged in the usual circumscribed foci of an epithelioid granuloma. The occasional presence of birefringent particles can make interpretation more complicated. False-positive foreign body-type reactions had to be disregarded.

An adequate Kveim antigen had to be sensitive enough to detect at least 60% of cases of active sarcoidosis and specific enough to exclude all but 2–3% of non-sarcoid cases [9]. To achieve this, the antigen had to be validated by extensive tests on normal subjects and on patients with other conditions, such as Crohn's disease, in which false-positive reactions are known to occur [10]. The safety of the Kveim test with regard to it being free from infective agents, e.g. human immunodeficiency virus, cannot be guaranteed and hence it is not available at the present time. The active principle in Kveim material was heat-stable, and also stable on storage, though some loss of sensitivity was observed over a period of years [11]. The active material is particulate and probably lies within the membrane-containing elements of the sarcoidal tissue [12], although its exact constitution has not been established. It is not known whether the active ingredient is an antigen derived from the aetiological agent of sarcoidosis or whether a positive Kveim response is a manifestation of host predisposition to form granulomas on antigenic stimulation. These two hypotheses are not mutually exclusive.

Other investigations

A chest radiograph should be taken in all cases, no matter what the clinical presentation. Hand radiographs show cystic changes only in chronic disease, and usually only when there are clinical abnormalities in the fingers. Sputum should be examined and cultured for acid-fast bacilli, and a weak or negative tuberculin response may add weight to the diagnosis of sarcoidosis. An ECG is needed to exclude cardiac involvement. Pulmonary function tests may also be indicated. High-resolution computed tomography of the chest is helpful to define lung field involvement.

The erythrocyte sedimentation rate (ESR) is usually raised in active phases, and a rise in the ESR 6–8 weeks after the onset of erythema nodosum may indicate lung involvement [13]. Slight anaemia, neutropenia or lymphopenia are often noted, but these changes, and the hypergammaglobulinaemia which occurs in over half the chronic cases, are not of proven diagnostic or prognostic significance. Serum calcium should be checked, as an increase may lead to chronic renal failure.

Angiotensin-converting enzyme (ACE) [14] is produced by sarcoidal granulomas. Raised serum levels are found in some 60% of patients with sarcoidosis, but are also present in other conditions such as diabetes and alcoholic liver disease. This limits the value of the test as a diagnostic aid, although it remains a useful monitor of disease activity.

Other markers of disease activity [15] vary in their usefulness in sarcoidosis. They include lysozyme, β_2-microglobulin, neopterin, collagenase and fibronectin levels. The serum level of soluble intercellular adhesion molecule 1 (ICAM-1), which is shed from cell surfaces and is a measure of the inflammatory response, mirrors disease activity in active sarcoidosis [16]. Hydroxyprolinuria may indicate disease activity. Radioactive gallium-67 uptake occurs in some pulmonary infections and neoplasms as well as sarcoidosis, but if these can be excluded it provides a way of separating active from fibrotic pulmonary disease.

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Treatment [1,2]

The chance of spontaneous remission favours a conservative approach to systemic therapy, which will usually carry the hazards of long-term immunosuppression, such as opportunistic mycobacterial infection [3] or a gross proliferation of viral warts [4]. At any time the pattern of the disease may change, but an expectant policy is often best if the course is not progressive and if vital structures are not involved.

Johns *et al*. [1] list the most frequent indications for systemic treatment:

1 Symptomatic pulmonary disease
2 Progressive or persistent parenchymal lung disease after 2 years
3 Posterior ocular disease or anterior disease not responding to local steroids
4 Persistent fever or weight loss
5 Liver disease with significant dysfunction or hepatosplenomegaly
6 Disfiguring skin disease or lymphadenopathy
7 Nervous system disease
8 Hypercalcaemia
9 Myocardial disease
10 Myopathy or myositis
11 Thrombocytopenia
12 Other significant organ involvement—for example, kidneys.

A major determinant is the degree to which a patient's normal life is disrupted by the disease, but objective measurements, such as pulmonary function tests, may be a more valuable way of monitoring therapy than symptoms alone.

A few patients with severe cardiac or pulmonary disease have come to transplantation; the sarcoidosis does not necessarily recur in the graft, perhaps due to the use of potent immunosuppressive agents [5].

In the skin clinic any decisions about the use of systemic therapy must take into account the seriousness of the accompanying internal involvement and the natural history of the particular type of skin lesion. Papular lesions, for example, are likely to fade without treatment, whereas lupus pernio is not.

Topical therapy

High-potency topical corticosteroids may sometimes prove helpful, as may intralesional triamcinolone injections. Tacrolimus, which inhibits hapten-induced production of Th1 cytokines and TNF-α by T cells, was recently reported to be beneficial when used topically in cutaneous sarcoidosis [6]. Cryotherapy and radiotherapy have occasionally been used [2]. PUVA therapy has been successful in hypopigmented sarcoidosis [7] and in erythrodermic sarcoidosis [2]. In certain types of cutaneous sarcoidosis, e.g. lupus pernio, cosmetic camouflage advice is helpful.

Systemic therapy

Corticosteroids are usually the most effective treatment, given at first in a relatively high dose, possibly 30 or 40 mg prednisolone daily, and then tapered over a period of several weeks to a lower maintenance dose of possibly 15 mg on alternate days. The length of the course of treatment will vary from case to case but is usually at least 6 months. Intravenous 'pulse' methylprednisolone, for example 1 g/week for 8 weeks, may be effective in those with the most severe neurological disease [5].

Cytostatic drugs may be tried if corticosteroids are contra-indicated or have been ineffective. Methotrexate has been used with some success [8] and has been recommended for use with corticosteroids for lupus pernio [9]. Chlorambucil [10] has its advocates, and azathioprine may be used for its steroid-sparing effect.

Other drugs which have been tried with some success include allopurinol [11,12] and antimalarials [13]. Minocycline, 200 mg daily for 12 months, produced complete resolution in eight and partial improvement in two out of 12 patients with cutaneous sarcoidosis [14]. Levamisole is not recommended [15]. The response to ciclosporin has been variable [5]. Isotretinoin and thalidomide have induced complete resolution in one case each of cutaneous sarcoidosis [16,17].

Laser and ultraviolet radiation

Lupus pernio has been improved using a flashlamp pulsed-dye laser [18], and UVA1 (340–440 nm) has been effective for forehead plaque sarcoid [19].

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Other sarcoidal reactions

A number of infections and chemicals may cause sarcoid-like granulomas, although their features are seldom as clear-cut histologically [1,2]. Such reactions differ from sarcoidosis in several important respects:

1 They involve only those organs normally affected by the disease in question, or on the route of absorption or deposition of the chemical.

2 The Kveim test when performed has been negative.

3 The tuberculin reaction is usually not depressed.

The following text describes reactions which should be borne in mind in the differential diagnosis of sarcoidosis.

Infections

The problem of differentiating tuberculosis and leprosy from sarcoidosis has been dealt with on p. 58.5. Syphilis, brucellosis, fungus infections and some bacterial or viral diseases may produce a sarcoidal type of tissue response but any clinical resemblance is usually superficial.

Foreign materials

Silicates occur in many common materials—for example, in talc, kaolin, quartz and as a constituent of slate, brick, gravel and coal. Silicosis from the inhalation of silica dust is an important industrial hazard, but wounds containing crystals of silica normally remain unchanged indefinitely. Talc has been the cause of granulomas in surgical wounds when used as a glove powder. The long delay between the implantation of silica and the appearance of the granuloma suggests that the silica may not be the immediate cause of the reaction. In one case, a silica granuloma has progressed to scar sarcoidosis [3]. It is wise to examine all sarcoidal reactions under polarized light: silica particles are doubly refractile and differ from Schaumann bodies in that the crystalline material is spiculated but not laminated.

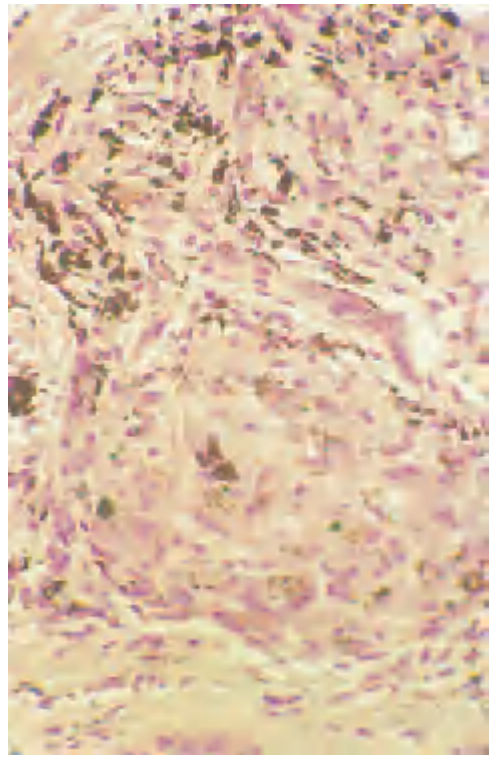
Beryllium reactions [2] are rarely seen now that beryllium is no longer used in the manufacture of fluorescent lights. The cutaneous lesions of systemic berylliosis are indistinguishable histologically from those of sarcoidosis, whilst the granulomas due to local beryllium implantation show marked central necrosis.

Zirconium granulomas may form in the axillae as a delayed hypersensitivity reaction to the zirconium content of deodorants [1,4].

Sea-urchin spines may induce foreign-body or sarcoidal granulomas [5]. The exact cause of the reaction is unknown. Intralesional triamcinolone may help speed resolution if excision is not practicable [6].

Foreign-body reactions to lipids (fat granulomas, epidermal cysts) and reactions to other lipid and non-lipid extraneous matter are variable and often show many giant cells.

(a)



(b)

Fig. 58.18 (a) Sarcoidal reaction to pigment in a tattoo. (Courtesy of Dr P. Collins, St Vincent's Hospital, Dublin, Eire.) (b) Histology of a sarcoidal reaction to two varieties of tattoo pigment, one opaque and one green. (Courtesy of Dr T.J. Stephenson, Royal Hallamshire Hospital, Sheffield, UK.)

Thesaurosis [7] is a pulmonary infiltration occurring in those heavily exposed to polyvinyl–pyrrolidine hair sprays in hairdressing procedures.

Sarcoidal reactions in tattoos (Fig. 58.18). A granulomatous dermal infiltrate may accompany sensitization reactions to any pigment of the tattoo, or may occur alone. Less commonly, a pure sarcoidal reaction is present as an indolent lump within a tattooed area. Regional lymph nodes may also show a sarcoidal reaction [8]. Such lesions may be accompanied by other signs of sarcoidosis or a

positive Kveim test [9,10] and are occasionally the only skin manifestation of the disease [11]. The pulmonary disease may be silent [12]. The association of a sarcoidal reaction in a cobalt tattoo with uveitis in three cases and with erythema nodosum in one [13] emphasizes the need for a thorough investigation of all cases showing a sarcoidal type of infiltrate.

Other reactions. A sarcoid-like reaction has been reported from exposure to acrylic or nylon fibres, either as dust or from walking on acrylic carpets [14]. The significance of a sarcoidal reaction to ear piercing [15] was not clear in the presence of a positive Kveim test.

Crohn's disease

The similarity between the histological and immunological features of Crohn's disease and sarcoidosis led to speculation about a common aetiology. However, the rarity of sarcoidosis of the intestine makes this unlikely, and earlier reports of positive Kveim tests in patients with Crohn's disease have not been fully substantiated [16].

Whipple's disease

Sarcoid-like changes have been recorded in the skin and lymphatic glands [17]. Diarrhoea is an important distinguishing clinical feature and jejunal biopsy will confirm the correct diagnosis (Chapter 59).

Farmer's lung [18]

This is caused by the inhalation of mouldy hay containing fungal spores: sarcoid-type granulomas sometimes develop slowly around the air passages and the condition then runs a course not unlike pulmonary sarcoidosis.

Other conditions

Sarcoid-like granulomas can occur in the skin and lymph nodes of patients with lymphoma: most commonly in Hodgkin's disease [19], but also in non-Hodgkin's lymphoma [20,21]. Sarcoid reaction is described with other malignancies, e.g. papillary thyroid carcinoma [22].

Epithelioid cell granulomas may also be a feature of rosacea [23]. In one unusual case [24], rosacea-like facial lesions, with a sarcoidal histology, were seen in a patient with a poorly differentiated lymphoma.

An epithelioid cell granuloma histology is found in granulomatous cheilitis and the Melkersson–Rosenthal syndrome, sometimes in necrobiosis lipoidica [25] and in granulomatosis disciformis, and has been reported in giant cell and other forms of arteritis [26].

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Chapter 59

Systemic Disease and the Skin

R.M. Graham & N.H. Cox

Introduction

The systemic associations of skin diseases have been stressed throughout this book. In this chapter, many of these associations are listed again, along with some other important conditions. They are grouped so as to be helpful to the general physician or internist. It is hoped that such a presentation will also be useful to the dermatologist who is asked to help in the diagnosis of obscure internal disease. Many further references may be found by turning to the chapter in which the relevant dermatosis is considered in detail. The texts listed below [1–4] provide much more information than it is possible to give here, and are also a source of additional references.

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Endocrine disorders

The physiological effects of hormones on pigmentation, hair growth, sebaceous glands and connective tissue have been described in other chapters. This section is limited to discussion of specific endocrine pathology with cutaneous features. Greater detail is provided in several general references [1–5].

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Pituitary syndromes

Hyperpituitarism [1–3]

Excessive secretion of growth hormone (GH, somatotrophin) causes an increase in plasma insulin-like growth factor-1 (IGF-1). These hormones stimulate synthesis of collagen and glycosaminoglycan in the skin and skeleton, leading to insidious hypertrophy of skin, subcutaneous tissues and viscera, and to periosteal bone growth. This causes acromegaly in the adult (most cases), and gigantism in children whose bony epiphyses have not yet closed.

Acromegaly (MIM *102200) and gigantism

Aetiology. The usual cause (over 95%) is a benign adenoma or hyperplasia of the eosinophilic cells of the adenohypophysis, producing GH and often prolactin. Other tumours, such as bronchial carcinoma, may occasionally cause acromegaly, usually by ectopic secretion of GH-releasing hormone (GH-RH). Individual, viable epidermal cells are larger than normal, and epidermal cell turnover is increased [4].

Clinical features. Periosteal new bone formation of the facial bones and skin causes the characteristic facies. Features are prognathism, frontal bossing, widely spaced teeth and acral hypertrophy, which causes elongated, blunt and thickened fingers. Dermatological features include a protruding, thickened lower lip, oedematous thick eyelids, a large and furrowed tongue (Fig. 59.1), triangular large ears, numerous skin tags ('fibroma molluscum'), widened skin pores, wet and oily skin due to hyperhidrosis and increased sebum production, acne and cutis gyrata of the scalp (Chapters 12 and 63) in more extreme cases. Hyperpigmentation develops in about half of the affected individuals due to increased levels of melanocyte-stimulating hormone (MSH), and acanthosis nigricans may occur. The scalp hair is initially coarse and there may be hirsutism, but later in the disease there is a decrease in gonadotrophin production, which causes the hair to become finer, with loss of secondary sexual hair. The nails are flat and wide and grow fast. Pachydermoperiostosis (Chapter 12) is an important differential diagnosis. In this disease, there is no macroglossia or prognathism, and the fingers are characteristically clubbed.

Non-cutaneous features include macroglossia, heart failure and hypertension due to left ventricular hypertrophy, visual field defect and headache due to the neoplasm, arthropathy, carpal tunnel syndrome and proximal myopathy.

Fig. 59.1 Acromegalic macroglossia.

Diagnosis. The clinical picture is in most cases suggestive of the diagnosis. Serum GH and prolactin levels are generally elevated, but vary considerably; plasma IGF-1 is a more reliable test of chronically elevated GH levels [5]. Failure of GH levels to suppress during glucose challenge, and GH-RH stimulation tests, help to confirm the diagnosis. Magnetic resonance imaging (MRI) confirms the site of the tumour in most cases.

Treatment. Neurosurgical removal of the tumour is the preferred treatment. Patients in whom this fails to achieve a cure may be treated with somatostatin analogues such as octreotide, or with bromocriptine [1–3,5,6].

Pituitary insufficiency [1–3,7]

Insufficiency of the adenohypophysis (anterior pituitary) may involve individual or multiple hormones. In classical hypopituitarism, all endocrine cell functions of the pituitary gland are involved to a varying degree. However, the clinical picture is influenced by the cause of hypopituitarism; for example, adenomas may produce GH or prolactin, but may also cause compression atrophy of cells producing gonadotrophins. Concurrent loss of function of the posterior pituitary may occur if there is a hypothalamic lesion, such as Langerhans' cell histiocytosis.

Aetiology. Over 95% of cases of hypopituitarism are due to pituitary cell destruction [6]. Familial hypopituitarism has a genetic basis due to mutations in Pit-1 or its precursor Prop-1, resulting in deficient production of GH, prolactin and thyrotrophin. Insufficiency of the adenohypophysis may occur due to:

- Neoplasia—adenomas (most), craniopharyngioma, metastases
- Infection—tuberculosis, abscess
- Trauma, surgical, iatrogenic
- Congenital—familial, 'empty sella syndrome'
- Vascular—Sheehan's syndrome (postpartum) and other infarction, bleeding, diabetes mellitus, vasculitis, antiphospholipid syndrome
- Idiopathic
- Hypothalamic—due to hypothalamic tumours, trauma, infiltration (Langerhans' cell histiocytosis, sarcoidosis), congenital causes of hypothalamic failure.

Clinical features. The various endocrine dysfunctions are typically insidious and less impressive than those seen in the primary glandular disorders. Pallor of the skin due to decreased MSH secretion results in generalized hypopigmentation, most apparent in the skin of the nipple areola and genitalia; in contrast with anaemia, the mucous membranes retain their normal colour. There is an increased sunburn tendency and lack of tanning, and there may be a degree of carotenaemia due to hypothyroidism. Loss of terminal hair due to decreased gonadotrophin secretion is observed in all patients, first in the axillae and later, but not invariably, in the pubic area. Fine wrinkling and dryness of the skin simulates advanced age. The face appears expressionless due to diminution of the facial skinfolds. The activity of sebaceous and sweat glands is reduced. Onycholysis, longitudinal ridging and brownish discoloration of the nail plate may be seen.

Pituitary dwarfism is characterized by proportionate retardation of somatic growth in conjunction with normal mental development. The cutaneous changes of old age may develop prematurely from the third decade onwards.

Diagnosis and treatment. Measurement of hormone levels—prolactin, IGF-1, thyroid-stimulating hormone (TSH) and thyroxine (T_4), cortisol, gonadotrophins—is required to detect subnormal levels; prolactin or IGF-1 may be elevated if the cause of hypopituitarism is a pituitary tumour. Posterior pituitary function should also be assessed, and visual field testing and MRI should be performed. Treatment is of the primary cause, together with hormone replacement [6,7].

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Adrenal syndromes

Cushing's disease and syndrome [1–3]

Chronic glucocorticoid excess may occur due to increased secretion of adrenocorticotrophic hormone (ACTH, corticotrophin), usually from the pituitary (MIM *219090), due to glucocorticoid hypersecretion of adrenal origin (ACTH-independent, MIM *219080) or due to exogenous administration of glucocorticoids.

Aetiology. The commonest ACTH-dependent cause is that due to a pituitary adenoma (Cushing's disease or pituitary-dependent Cushing's syndrome), which accounts for about 70% of spontaneous cases; pituitary overproduction of ACTH leads to adrenal hyperplasia and thus to glucocorticoid excess. Other ACTH-dependent causes include the ectopic ACTH syndrome (for example, from small cell lung cancer or bronchial carcinoids) and, rarely, ectopic corticotrophin-releasing hormone (CRH) syndrome. ACTH-independent causes include cortisol-producing adrenocortical adenomas and carcinomas, various types of bilateral adrenal hyperplasia (including the Carney complex), and commonly iatrogenic causes such as long-term administration of systemic glucocorticoids. The glucocorticoid hormones, among other effects, impair synthesis of collagen and mucopolysaccharides and thus lead to atrophy and vascular fragility of the skin.

Clinical features. The cutaneous manifestations are quite similar whether caused by endogenous or iatrogenic hypercorticism, although there are additional effects mediated by androgens in patients with adrenal disease. Truncal obesity (classically deposits of fat over the clavicles and back of the neck, the 'buffalo hump') and facial fullness and plethora ('moon facies') are most frequent, and contrast with the slender limbs. Other frequent cutaneous features are skin atrophy and fragility, poor healing, telangiectasia, bruising, striae (typically wide and red), hirsuties and acneiform lesions. In contrast with acne vulgaris, the lesions are uniform, and comedones and cysts are absent. Clitoral hypertrophy and male-pattern baldness may occur in women. Dermatophyte and yeast infections occur. In iatrogenic hypercorticism, hypertrichosis is limited and usually confined to the cheeks in the form of lanugo hair. About 6–10% of patients with pituitary Cushing's disease have Addisonian-like pigmentation [1], as oversecretion of the common precursor

pro-opiomelanocortin causes overproduction of both ACTH and MSH.

Diagnosis. Twenty-four-hour urinary cortisol (95–100% sensitivity and 94–98% specificity) and/or a 1-mg overnight dexamethasone suppression test (98–100% sensitivity, lower specificity, using a cut-off of plasma cortisol below 50 nmol/L) are generally considered to be satisfactory screening tests. A midnight plasma cortisol level (100% specific if over 50 nmol/L) or a 2-day low-dose dexamethasone suppression test may resolve equivocal results. Additional tests may be required [2].

Treatment. Trans-sphenoidal selective adenomectomy is the treatment of choice for Cushing's disease in adults, with radiotherapy as second choice; radiotherapy is more effective in children. Bilateral adrenalectomy is the third-choice definitive cure for pituitary Cushing's syndrome, and is the treatment of choice when the disease is caused by bilateral adrenal hypersecretion; lifelong replacement therapy with glucocorticoids and mineralocorticoids is required. A substantial number of such patients eventually develop a pituitary adenoma and cutaneous hyperpigmentation (Nelson's syndrome); this is best treated by pituitary surgery [3]. Unilateral adrenal disease (adenoma or carcinoma) is treated by unilateral adrenalectomy. Medical treatments may act at hypothalamic–pituitary level (serotonin antagonists, dopamine or GABA agonists, somatostatin analogues), at corticosteroid receptors (mifepristone, a relatively new treatment) or on adrenal glands (metyrapone, aminoglutethimide and others). Most of these agents have significant potential side effects.

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Adrenal insufficiency [1–6]

SYN. ADDISON'S DISEASE; HYPOCORTICISM; HYPOADRENALISM

This condition is due to insufficient secretion or supply of adrenocortical hormones or hormonal compounds—mainly cortisol and mineralocorticoids.

Aetiology. Most cases of adrenal insufficiency occur due to prolonged supraphysiological glucocorticoid therapy for a variety of inflammatory and other diseases; this suppresses ACTH production, so abrupt discontinuation of treatment may cause acute adrenal insufficiency.

Primary adrenal insufficiency (Addison's disease) in developed countries is most commonly due to autoimmune adrenalitis. Most such patients show circulating antibody to the cortex cells; about 40% of adults and virtually all children with Addison's disease have other autoimmune-related disorders as part of a polyglandular syndrome [2,4–6]. Other causes of primary adrenal damage include infections (tuberculosis is the commonest cause, others include histoplasmosis and viral infections), metastatic malignant disease or (rarely) haemorrhage. The latter is of some dermatological importance, as it may rarely occur due to sepsis (Waterhouse–Friderichsen syndrome); this is classically described as a consequence of meningococcaemia, but in a study of paediatric deaths due to sepsis with bilateral adrenal haemorrhage the commonest cause was *Pseudomonas* infection.

Secondary adrenal insufficiency may occur due to hypothalamic or pituitary disease, leading to insufficient secretion of ACTH; patients with pituitary hyposecretion of ACTH lack the pigmentary changes that are characteristic of primary adrenal insufficiency, and mineralocorticoid production is generally maintained.

Clinical features [1–6]. General symptoms include wasting, fatigue, orthostatic hypotension, dizziness, anorexia, abdominal pain and amenorrhoea. Hyperpigmentation of the skin, due to increased secretion of pituitary MSH and ACTH as a response to low adrenal corticosteroid levels, is the cardinal dermatological feature. This develops insidiously and is often not recognized as abnormal by the patient. It is most pronounced in the following main distributions:

1 Light-exposed areas—face, dorsa of hands
2 Areas subject to friction—elbows, knees, waistline, under bra straps
3 Areas of high pigmentation normally—genital, perineum, axillae, areolae, umbilicus
4 Palmar creases
5 Tongue and mucous membranes
6 In scars
7 Hair and nails—longitudinal melanonychia.

There may be speckled skin pigmentation, and darkening of existing pigmented lesions. Mucous membrane lesions are usually spots or patches rather than diffuse pigmentation, and the oral pigmentation may persist after glucocorticoid replacement therapy. Scar pigmentation only occurs in scars acquired during adrenal insufficiency and is permanent—scars that precede the disorder or occur during therapy are unaffected [6]. In women, in whom the adrenal gland is the main source of androgens, there may be loss of axillary and pubic hair and improvement in acne. Features of associated autoimmune disease may be present, notably vitiligo in 15% of patients with autoimmune causation. Calcification of the pinna has been described [7], but may occur in other endocrine conditions and is more commonly the result of frostbite or injury.

Similar pigmentation may be seen in Nelson's syndrome and in tumours causing ectopic ACTH secretion; in the latter case, cortisol production is increased, so the clinical picture and electrolyte changes may be those of Cushing's syndrome.

Nelson's syndrome is due to development of an ACTH-producing pituitary tumour in patients who have previously undergone bilateral adrenalectomy to treat Cushing's syndrome.

Diagnosis. Anaemia, lymphocytosis, hyponatraemia, hyperkalaemia and hypoglycaemia are expected. A short Synacthen test demonstrates impaired cortisol secretion in response to corticotrophin, and ACTH and cortisol production are subnormal in response to an insulin stress test. Adrenal calcification may be present in autoimmune or tuberculous disease. Primary adrenal failure can be identified by demonstrating elevated ACTH levels, presence of adrenal autoantibodies, and by stimulation tests such as the metyrapone test or CRH test.

Treatment. Primary adrenal failure requires glucocorticoid and mineralocorticoid replacement [5,6]. In secondary cases related to pituitary insufficiency, usually only cortisol is required [3]. During stress, such as when undergoing major surgery and in severe systemic infections, the need for cortisol is increased. The hyperpigmentation may start to regress within days, but generally takes weeks to months to fully resolve—the process is slower in hair and nails, and pigmented scars remain pigmented [6].

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Thyroid diseases

General reviews of thyroid disease and the skin can be found in the following references [1–3].

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Hyperthyroidism [1–4]

SYN. THYROTOXICOSIS

This is a hypermetabolic state that results from excessive production or administration of thyroid hormones—thyroxine (T_4) and triiodothyronine (T_3). It is most common in women.

Aetiology. Hyperthyroidism is usually due to Graves' disease (diffuse toxic goitre, Basedow's disease), but 10–15% of cases are due to other causes, including toxic multinodular goitre, adenoma, thyroiditis, and iatrogenic or factitious ingestion of T_4 or iodine. Secondary hyperthyroidism may occur due to production of TSH or thyrotrophin-releasing hormone (TRH) from the pituitary or from tumours at other sites. Graves' disease is an autoimmune disorder in which there is a high incidence of antithyroid antibodies and of other autoimmune diseases. Thyroid-stimulating immunoglobulins (TSIs) such as long-acting thyroid stimulator (LATS, a 7S immunoglobulin) are typically present in Graves' disease. These bind to TSH receptors, acting as thyroid gland agonists.

Clinical features. Most of the features of hyperthyroidism (Table 59.1) are not specific to the cause. Increased sympathetic nervous system activity causes vasodilatation, leading to warm skin, flushing, palmar erythema and increased sweating (especially of palms and soles). Hair is fine, with diffuse alopecia in about a third of patients.

Table 59.1 Cutaneous features of hyperthyroidism.

Skin
Soft, smooth, velvety
Increased skin temperature
Palmar erythema, facial flushing
Increased sweating
Pruritus
Hyperpigmentation
Pretibial myxoedema*
Vitiligo*
Others—urticaria, palmoplantar pustulosis*
Nails
Fast nail growth
Soft nails, koilonychia
Distal onycholysis
Thyroid acropachy*
Hair
Fine thin hair, diffuse alopecia
Alopecia areata*

* Associated with autoimmune thyroid disease; not a feature of hyperthyroidism *per se*.

Nails may be thin, with koilonychia and onycholysis (Plummer's nails); the onycholysis typically commences on the fourth digit of the hands [5]. Hyperpigmentation, similar to that of Addison's disease, may occur due to increased corticotrophin (ACTH) levels, and may be diffuse or localized to scars, but usually spares the buccal mucosa. Hyperpigmented eyelids have been described (Jellinek's sign).

Pretibial myxoedema, thyroid acropachy (both discussed separately below) and exophthalmos are features of Graves' disease (collectively known as Diamond's triad), although pretibial myxoedema can also occur in Hashimoto's thyroiditis. The combination of *e*xophthalmos, pretibial *m*yxoedema and hypertrophic *o*steoarthropathy has also been termed the EMO syndrome. In addition to these linked conditions, cutaneous features of associated autoimmune disease may be present, especially vitiligo.

The associations between thyroid diseases and other dermatoses are considered separately below.

Diagnosis [6]. In most instances, negative feedback mechanisms cause suppressed serum TSH levels before T_4 or T_3 levels are elevated. The exception is when hyperthyroidism is of secondary type, due to increased TRH or TSH levels. Thyroid antibodies are less helpful, as they are common in euthyroid individuals, and TSI levels are not usually measured. Isotope scanning can confirm the cause (diffuse goitre, adenoma, etc.).

Treatment. Beta-blockers may be used in the initial phase of therapy to suppress the increased sympathetic activity. The hyperthyroid state can be reversed by surgery, radioactive iodine or therapy with antithyroid drugs (propylthiouracil and carbimazole). However, changes that are unrelated to the hormone production tend to persist. Ophthalmopathy is not influenced by a return to euthyroidism, and the prognosis in severe cases is doubtful.

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Pretibial myxoedema

SYN. LOCALIZED MYXOEDEMA

Localized oedematous and thickened pretibial plaque formation occurs in 1–10% of patients with hyperthyroidism. It is usually a late feature, occurring after ophthalmopathy and diagnosis of hyperthyroidism (sometimes only becoming evident after antithyroid treatment has been initiated), but it can occasionally precede other features [1,2]. Almost all patients with pretibial myxoedema have ophthalmopathy [1]. The same process often occurs on the dorsum of the hallux, and may affect other sites, including the lower abdomen, arms, shoulders, neck and pinnae [3].

Aetiology. It is unclear whether circulating or local factors are the main determinant of pretibial myxoedema. It was demonstrated over two decades ago that serum of pretibial myxoedema patients caused a two- to threefold increase in hyaluronic acid production by cultured fibroblasts from the pretibial area of patients and normal subjects, but had no effect on those from the shoulder or prepuce [4]. Most patients with pretibial myxoedema, whether thyrotoxic or not, have elevated levels of LATS in their serum, so this specific antibody does not seem to be causally involved [5]. A role for TSI was proposed, as fibroblasts from the pretibial and orbital regions have TSH receptors; TSIs have agonist effects on TSH receptors. Ribonucleic acid sequences encoding parts of the TSH receptor, and TSH receptor-like immunoreactivity, have been demonstrated in fibroblasts from these sites in affected patients [6]. There is, however, no obvious association between the clinical manifestations and the presence of TSH receptor autoantibodies. Recent research demonstrated that patients with pretibial myxoedema, but not control subjects, have circulating immunoglobulin A2 (IgA2) fibroblast antibodies capable of binding to a 54-kDa antigen of dermal fibroblast cell lines [7]. IGF-1 has also been suggested to have a role in the pathogenesis [8]. However, the occurrence of pretibial myxoedema in both the donor and recipient site in a patient who had excision of pretibial myxoedema, with normal skin grafted into the area, suggests that there are local factors operative which are not explained by site-specific properties of the dermal fibroblasts [9].

Pretibial myxoedema also occurs in other situations, especially in chronic stasis dermatitis [10].

Histopathology. The dermis is thickened, especially in the mid-dermis and deeper part, by extensive deposits of acid mucopolysaccharides, which may cause separation of the collagen fibres. Stellate, mucin-producing fibroblasts may be prominent.

Clinical features. In many instances, the lesions first appear on the anterolateral aspect of the lower limbs and

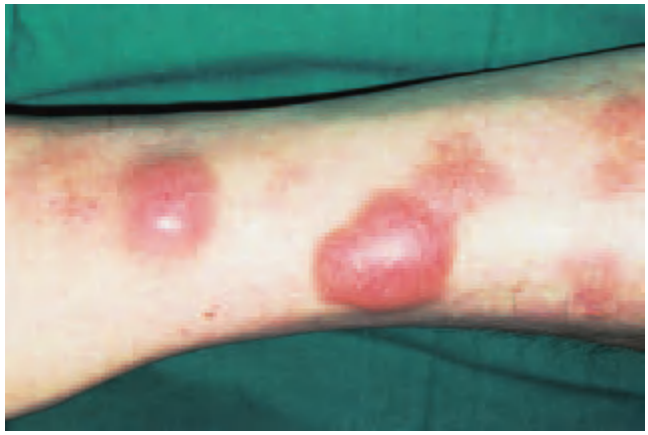

Fig. 59.2 Pretibial myxoedema. (Courtesy of Dr S.O.B. Roberts, Addenbrooke's Hospital, Cambridge, UK.)

only later extend to the back of the legs, and feet (Fig. 59.2). The nodules are pink or skin-coloured, sometimes yellow and waxy, with prominent hair follicles giving a 'peau d'orange' appearance. They may occur in old or recent scars [9,11,12]; localized hypertrichosis over the lesions may be a feature, and localized hyperhidrosis has also been reported [13,14]. Three clinical types are recognized:
1 Sharply circumscribed, in which both nodular and tuberous lesions appear on the shins and toes.
2 Diffuse, producing solid non-pitting oedema of the shins and feet.
3 Elephantiasic, in which there is both oedema and nodule formation.

Treatment. Topical glucocorticoids, with or without occlusive dressings, or intralesional glucocorticoid injections, may be useful [1,15]. The long-term benefits of surgery vary, although debulking procedures may be of benefit (for example, for lesions on the toes) [16]. Octreotide [17,18], plasmapheresis (perhaps acting by removal of TSIs, although not all patients respond) [19], photochemotherapy, intravenous immunoglobulin [20] and gradient pneumatic compression [21] have all been used.

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Thyroid acropachy [1,2]

Clubbing of the fingers and toes in Graves' disease, associated with soft-tissue swelling of hands and feet and with periosteal new bone formation, is termed thyroid acropachy. It occurs in less than 1% of thyrotoxic patients, and is usually associated with exophthalmos and pretibial myxoedema (Diamond's triad), occurring in about 5% of patients with these other features. Acropachy usually appears some time after the other components of the syndrome, usually after treatment of Graves' disease. Pathologically, there is periosteal new bone formation involving the phalanges and other distal long bones, which is manifest radiologically as a feathery pattern of lamellar new bone parallel to the diaphyses, sometimes with perpendicularly orientated new bone spicules, and which can be demonstrated as osteoblastic activity using a bone scan [2]. The proximal phalanges and first or second metacarpals are most commonly affected. Most patients have minimal or no symptoms, but in those with symptoms, stiffness is the most frequent; by comparison with hypertrophic pulmonary osteoarthropathy, pain and heat are absent. Pachydermoperiostosis (Chapter 12) shows some resemblance to acropachy, but other features of the syndrome are absent.

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Hypothyroidism [1–3]

SYN. MYXOEDEMA; HYPOTHYREOSIS

In hypothyroidism, there is a slowed metabolic rate involving all organs. It is caused by a decreased concentration of free thyroid hormone in the blood, or target cell resistance to thyroid hormone.

Aetiology. The most common cause is idiopathic (primary) hypothyroidism, which is an autoimmune disease, usually affecting women from the fourth decade. A high percentage of patients with Hashimoto's thyroiditis (who may initially be thyrotoxic) eventually develop hypothyroidism, and iatrogenic hypothyroidism may occur as a late effect of radio-iodine treatment of thyrotoxicosis. Secondary hypothyroidism due to pituitary disease is uncommon, TSH production being relatively spared compared to sex hormone and ACTH production, but pituitary infarction, haemorrhage or neoplasm may lead to hypothyroidism in some cases. Severe iodine deficiency, or drugs such as lithium, may cause hypothyroidism. Congenital hypothyroidism (cretinism), usually due to absence of the thyroid, is rare. Tertiary hypothyroidism is due to hypothalamic failure of TRH production.

Clinical features. Cutaneous changes of hypothyroidism (Table 59.2) [1–7] were well known in the latter part of the 19th century [4]. The most prominent manifestation of hypothyroidism is related to dermal accumulation of mucopolysaccharides, in particular chondroitin sulphate and hyaluronic acid, which bind water in the tissue and lead to puffiness of the skin. Whilst characteristic, the features may be insidious in development, and some are of low specificity. For example, loss of the outer third of the eyebrow (madarosis, Hertog's sign) is common in many euthyroid elderly individuals. The yellowish skin colour is due to a combination of alterations in connective tissue of the dermis, carotenaemia and vasoconstriction (due to the slowed metabolic rate). The connective tissue changes also cause loss of support of dermal vessels and, along with decreased levels of clotting factors, predispose to purpuric lesions or bruising. Asteatotic eczema [5] and keratoderma of palms and soles [6] may occur, sometimes as the presenting feature. Features of previous autoimmune thyrotoxicosis, or of associated autoimmune diseases, may also be present.

In congenital hypothyroidism ('cretinism'), coarseness of features, lethargy, periorbital puffiness, swelling of hands and feet, macroglossia, cold and dry skin with livedo, umbilical hernia and poor muscle tone are pathognomic, but may not be apparent until a few months of age. Cutis marmorata occurs due to vasoconstriction. Without treatment, physical and mental development is retarded. The scalp hair is coarse, and the eyebrows may be confluent.

In juvenile hypothyroidism, abnormal physical and mental development is the principal manifestation of the disease. Some children develop hypertrichosis of the upper back and shoulders. The waxy, yellowish skin changes may be prominent, but the puffiness may be less apparent than in older individuals. Rarely, juvenile hypothyroidism is associated with sexual precocity; the penis and scrotum enlarge in males, or menstruation and galactorrhoea occur in females, but axillary and pubic hair do not develop.

Table 59.2 Cutaneous and oral features of hypothyroidism.

Skin
Pale, cold, scaly and wrinkled skin
Xerosis, asteatotic eczema, itch
Palmoplantar keratoderma
Absence of sweating
Ivory-yellow skin colour
Puffy oedema of hands, face and eyelids
Purpura and ecchymoses
Punctate telangiectases on arms and fingertips
Delayed wound healing
Xanthomatosis (secondary to hyperlipidaemia)
Nails
Brittle and striated nails
Slow nail growth
Hair
Coarse sparse scalp hair
Loss of pubic, axillary and facial hair
Loss of lateral eyebrows (madarosis)
Oral
Large tongue
Gingival swelling (in congenital hypothyroidism)
Oral candidosis

Diagnosis. Protein-bound iodine, T_4 and T_3 levels are low. In primary hypothyroidism, the TSH level is elevated; in pituitary failure, it is low or undetectable. The histological changes in the dermis may be helpful in difficult cases [8]. Recognition of hypothyroidism in the elderly may be difficult. Symptoms and signs develop insidiously and may easily be taken as evidence of arteriosclerotic disease. Serum TSH is recommended as the primary investigation for screening of elderly patients.

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Thyroid disease and other dermatoses

Thyroglossal cysts are in the differential diagnosis of other congenital cysts in the neck, such as branchial cysts or ectopic bronchial mucosa.

Thyroid cancer may give rise to cutaneous metastases, or to thyroxine-producing metastases which therefore cause features of thyrotoxicosis. Thyroid cancer is also a feature of syndromes such as Cowden's disease and multiple endocrine neoplasia (MEN) type 2, discussed elsewhere in this chapter.

There are associations between either the presence of antithyroid antibodies, or of overt thyroid dysfunction or thyroiditis, with a number of other skin diseases and disorders with cutaneous manifestations (Table 59.3) [1–13]. Some of these associations are based on small studies, but associations with disorders such as dermatitis herpetiformis and chronic urticaria are strongly supported by the available literature. About 20% of children with alopecia areata have thyroid antibodies, although clinical thyroid dysfunction is rare [13]. It is debatable to what extent management is altered by routinely testing for thyroid antibodies or thyroid dysfunction in the absence of other clinical symptoms, although there are reported instances where chronic urticaria, for example, has resolved after treatment of associated thyrotoxicosis; it has also been recommended that T_4 treatment should be considered in euthyroid patients with chronic urticaria if they have evidence of thyroid autoimmunity [7].

Table 59.3 Some skin disorders and other diseases with prominent cutaneous manifestations that have been associated with thyroid dysfunction or with the presence of antithyroid antibodies.

Bullous diseases
Dermatitis herpetiformis
Bullous pemphigoid
Pemphigus
Pemphigoid gestationis
Endocrine diseases
Pernicious anaemia
Diabetes mellitus
Addison's disease
Acanthosis nigricans with insulin resistance
Autoimmune polyglandular syndromes I–III
Other autoimmune conditions
Alopecia areata
Vitiligo
Connective tissue diseases
Lupus erythematosus
Scleroderma
Dermatomyositis
Sjögren's syndrome
Others
Chronic urticaria
Palmoplantar pustulosis
Psoriasis
Atopic dermatitis
Sweet's syndrome
Sarcoidosis
POEMS syndrome
Granuloma annulare
Pseudoxanthoma elasticum
Polyostotic fibrous dysplasia
Melasma
Lichen sclerosus
Xanthelasma

POEMS, polyneuropathy, organomegaly, endocrinopathy, M protein and skin changes (syndrome).

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Parathyroid disease

Skin changes are not a particular feature of hyperparathyroidism, although subcutaneous calcification may occur (especially in hyperparathyroidism secondary to renal failure; see below) [1–4].

Itch is occasionally felt to be related to hyperparathyroidism [5], although this is poorly documented [6] and some of the documentation is inferred (from resolution in some instances of renal itch after parathyroidectomy, or paraneoplastic itch after resection of parathormone (PTH)-producing bronchial tumours). Hyperparathyroidism has also been linked to cutaneous T-cell lymphoma [7].

Hypoparathyroidism may cause skin changes somewhat similar to those of hypothyroidism—the skin may be dry, keratotic and puffy, with sparse, coarse hair. Nails are brittle and ridged, with cracking at the free margin, or crumbling of the distal nail plate. Chloasma or pellagra-like pigmentary disturbance is less common [1,3,8].

Chronic mucocutaneous candidiasis, especially of the nails and oral mucosa, may occur in conjunction with hypoparathyroidism when this occurs as part of the polyglandular autoimmune syndrome (see below) or in association with immunological defects such as Di George's syndrome [1], but it is not a feature of post-thyroidectomy, iatrogenic hypoparathyroidism.

Subcutaneous ossification is a feature of Albright's hereditary osteodystrophy, which encompasses both pseudohypoparathyroidism type Ia and pseudopseudohypoparathyroidism [1,9–11]. The somatic features include obesity, short stature and short metacarpals—Albright's sign is dimpling over the knuckle of the typically affected fourth metacarpal. The dominant condition occurs due to a heterozygous functional defect of the α-subunit of the stimulatory G protein (G_s α protein) of adenylate cyclase, with which PTH interacts at the cell surface. This is encoded by the *GNAS1* gene on chromosome 20q13.3, but there are tissue-specific differences in expression of G_s α and other *GNAS1* transcripts that are different for the maternal and paternal alleles [10]. It is now known that pseudopseudohypoparathyroidism is the same disorder as pseudohypoparathyroidism type Ia, but with the genetic defect inherited from the father; patients have the somatic features of pseudohypoparathyroidism, but with normal hormone responses [11].

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Multiple endocrinopathy syndromes

It is common that autoimmune conditions may occur simultaneously—due to, for example, human leukocyte antigen (HLA) linkage. Some of these produce an overlap between endocrine disease and:

- Other autoimmune conditions, e.g. polyglandular autoimmune syndrome (see below), various combinations of Sjögren's syndrome and sarcoidosis with endocrine autoimmune conditions [1,2].
- Infections, such as in autoimmune polyglandular syndrome type I (see below).
- Ectodermal changes, e.g. alopecia areata (commonly), ANOTHER syndrome (*a*lopecia, *n*ail dystrophy, *o*phthalmic complications, *t*hyroid dysfunction, *h*ypohidrosis, *e*phelides and enteropathy, *r*espiratory tract infections) [3].
- Gastrointestinal disease, e.g. the triple A syndrome (Allgrove's syndrome) of achalasia, addisonianism and alacrima (MIM #231550).
- Pigmentary change, e.g. vitiligo (commonly), Carney complex (see cardiac disease, below), POEMS syndrome (see cardiac disease, below).
- Bone disease, e.g. McCune–Albright syndrome (MIM #174800). G protein mutations cause dysregulation of cyclic adenosine monophosphate (cAMP), leading to growth and hyperfunction of many organs—features include hypophosphataemic osteodystrophy, hyperparathyroidism, hyperthyroidism, large irregularly shaped café-au-lait macules, Cushing's syndrome, acromegaly and hyperprolactinaemia.
- Cerebral disease, e.g. triple H syndrome—*h*ippocampus (anterograde memory loss), *h*air follicle (alopecia areata), *h*ypothalamic–pituitary–adrenal axis (isolated ACTH deficiency) [4].

Autoimmune polyglandular syndromes [5–9]

Three types of autoimmune polyglandular syndrome (APS) are described—types 1–3. The most important example dermatologically is APS type 1 (MIM *240300), which is usually due to the R257X mutation of the *AIRE* gene on chromosome 21q22.3 [9]. It is also termed

mucocutaneous candidiasis–endocrinopathy syndrome, multiple endocrinopathy syndrome, autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy (APECED) syndrome, or Whitaker's syndrome. It is defined by the presence of two or more of the three major features, which are chronic mucocutaneous candidiasis (usually by age 5 years, present in about 80%), chronic hypoparathyroidism (usually by age 10 years, present in about 90%) and autoimmune adrenal insufficiency (usually by age 15 years, present in about 70%). Other features are hypergonadotrophic hypogonadism (45%), diabetes mellitus, and thyroid antibodies or overt thyroid dysfunction. Alopecia areata (25%) and vitiligo (10%) are both relatively common. An interesting feature of vitiligo in this condition, which does not occur in isolated vitiligo or in other autoimmune combinations, is the presence of complement-fixing melanocyte autoantibodies [9]. Most patients also have adrenal cortex autoantibodies, and those with gonadal failure have steroid-producing cell antibodies. Nail dystrophy and tooth enamel defects comprise the ectodermal dystrophy component. Epidermolysis bullosa acquisita has also been reported in type 1 syndrome [10].

Patients with APS types 2 and type 3 more commonly have diabetes, but less commonly have alopecia or vitiligo, and do not have chronic mucocutaneous candidiasis. Addison's disease is present in all patients with APS type 2 and may occur with autoimmune thyroid disease (Schmidt's syndrome) and/or with immune-mediated diabetes (Carpenter's syndrome). It is not a feature of APS type 3, which is defined as co-occurrence of autoimmune thyroid disease with two other autoimmune disorders in the absence of Addison's disease [11]. APS type 2 is due to defects in the *HLA* region on 6p21 or in *CTLA4* on 2q33.

The MEN syndromes are discussed later in this chapter.

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Cutaneous markers of internal malignancy [1–9]

The different types of skin change associated with internal malignancy are so numerous that to report all documented associations here is impracticable. The above references serve as more detailed compendia. Various criteria may be used to group changes [5,6]. It is, however, convenient to classify into several broad categories:

1 Direct tumour spread/cutaneous metastasis.
2 Genetically determined syndromes with cutaneous manifestations, where there is a recognized predisposition to internal malignancy.
3 Cutaneous markers of exposure to carcinogens, those affected being at higher risk of internal malignancy.
4 Paraneoplastic syndromes—a medley of cutaneous reaction patterns that have a statistical association with neoplasia involving various internal organ systems.

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Direct tumour spread/cutaneous metastasis [1–3]

Other than primary skin neoplasms, the skin may be involved by tumour as a result of cutaneous metastases from an internal tumour, or by direct involvement in continuity with an adjacent organ (as occurs in Paget's disease [4], discussed in Chapter 36). Local and in-transit metastases from primary epidermal tumours are discussed in relevant chapters; melanoma is the most important tumour to behave in this fashion.

Direct invasion of the skin manifests itself by tumid

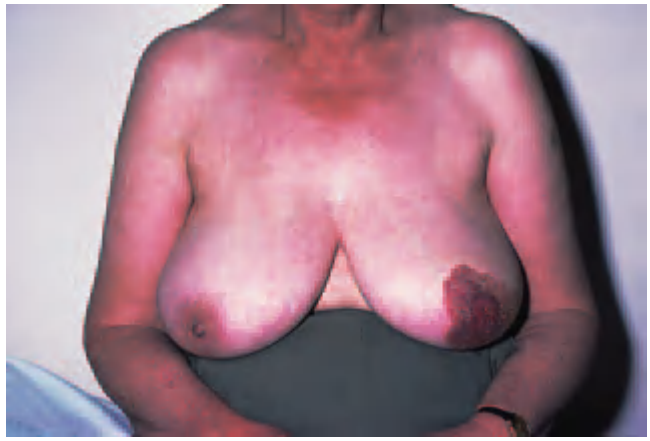

Fig. 59.3 Paget's disease of the breast with underlying ductal carcinoma. (Courtesy of Dr R. Emmerson, Royal Berkshire Hospital, Reading, UK.)

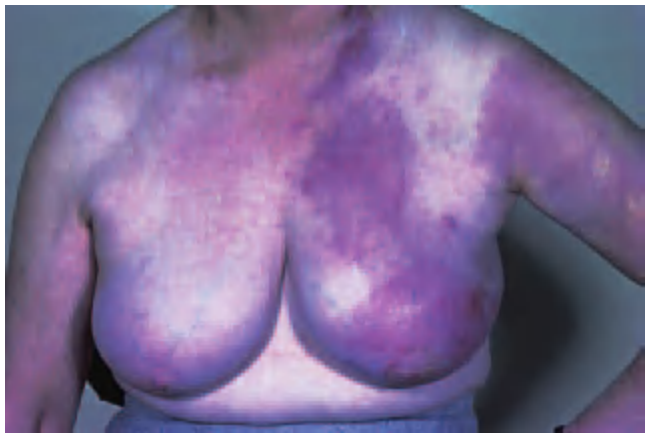

Fig. 59.4 Carcinoma erysipeloides. (Courtesy of Dr R. Emmerson, Royal Berkshire Hospital, Reading, UK.)

ulceration or inflammation. The most frequent cause is carcinoma of the breast, which may present as skin ulceration, scaly plaques of Paget's disease (Fig. 59.3), or more rarely as carcinoma erysipeloides (Fig. 59.4), carcinoma telangiectoides or as peau d'orange-like carcinoma en cuirasse. The next commonest cause is carcinoma of the oral cavity, usually squamous cell carcinoma (SCC) ulcerating onto the face [5]. Direct cutaneous metastasis may also occur after therapeutic manoeuvres, such as draining a malignant pleural effusion.

Paget's disease of the breast presents with scaling and erythema on or around the nipple, which can mimic eczema. It is an epidermal manifestation of an underlying adenocarcinoma, usually ductal in origin; early recognition may allow curative intervention. Extramammary Paget's occurs in apocrine gland-bearing areas such as anogenital and axillary sites. It may be a marker of underlying neoplasia [6], and, whilst this is not mandatory [7], it does warrant investigation of adjacent tracts.

Specific cutaneous infiltrations of the skin may occur with myeloproliferative disorders; this is commonly recognized with lymphoma, but can occur with leukaemia [8].

Cutaneous metastasis from tumours affecting other organs [1,2]

The skin is a relatively uncommon site for distant metastatic deposits, compared with organs such as liver, lung and bone. Autopsy studies suggest a higher frequency of skin metastasis than may be apparent from clinical studies [5,9–11]; up to 9% of patients with internal cancer may have skin metastasis (3–4% is probably a representative figure) and in about 0.5–1% it is the presenting feature [1,2]. The most common sources of cutaneous metastases are breast, lung, colon, stomach, upper aerodigestive tract, uterus and kidney.

Cutaneous metastases generally present as solitary or multiple painless, firm to hard nodules, which may be skin-coloured, blue-brown or reddish-purple. Other patterns include a morphoea-like sclerotic pattern. Although they may occur on skin in the vicinity of the affected organ (for example, prostatic tumour metastases are often on the lower abdomen), the head, neck and upper trunk are disproportionately commonly affected [11]. Other sites that are notable as sites for skin metastasis include the umbilicus (Sister Mary Joseph's nodule) [12,13] and recent operative scars (often for the primary tumour). Breast tumour metastasis to skin typically affects the chest wall, with patterns as discussed above. Metastases to the scalp may give rise to focal alopecia, with breast, lung and kidney being the commonest sources. Renal and thyroid skin deposits have a reputation for being vascular in appearance, both clinically and pathologically [14], and are occasionally misdiagnosed as benign haemangiomas or pyogenic granuloma; hypernephroma metastases may even be pulsatile. Generally, cutaneous metastases may be mistaken for cysts or inflammatory lesions.

Metastasis to the skin occurs as a result of lymphatic or haematogenous dissemination of tumour. This may give rise to showers of metastases in some patients. The tumour cells may be identifiable as having a specific organ of origin, or may be highly anaplastic. In general, they resemble the cells of the primary tumour. Immunohistochemistry is generally of little value in determining the diagnosis of the primary tumour, except in the case of prostatic metastases (prostate-specific antigen) or thyroid metastases (thyroglobulin). In some instances, there may be marked oedema or dilated lymphatic vessels, which may make diagnosis difficult. In some specific tumours such as hypernephroma, or in some clinical patterns such as carcinoma telangiectoides, the tumour cells may either be scanty or the vascular proliferation may dominate the histopathological appearance. The lymphatic spread of

tumour cells may lead to an 'Indian filing' appearance in some cases, sometimes with fibrosis.

Cutaneous metastases are usually indicative of disseminated disease and a correspondingly poor prognosis; survival is typically only about 3 months in patients with disseminated skin metastases [10]. Patients with solitary metastases without other evidence of dissemination may have a better survival [15]. Infrequent cases of tumour regression after primary tumour removal are documented [16]. It is noteworthy that cutaneous metastases do not necessarily relate to a prior, documented tumour; the histological pattern, localization and temporal relationship may occasionally point to a second primary [17]. Treatment options, depending on the primary tumour, may include excision or other destructive therapy (e.g. laser destruction, radiotherapy, photodynamic therapy) for limited numbers of lesions, and chemotherapy or other systemic treatment for disseminated lesions.

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The genetic group

Most cutaneous signs of neoplasia do not involve direct spread of tumour to the skin but are paraneoplastic. Genodermatoses account for a significant minority of paraneoplastic skin lesions [1–6].

Gardner's syndrome (MIM *175100) (Chapter 12) [7,8] is an autosomal-dominant condition of multiple cutaneous epidermoid cysts, fibromas and pilomatrixomas associated with a high incidence of early malignant change in intestinal adenomatous polyposis to adenocarcinoma. Oldfield's syndrome [9] represents the same condition. Other malignancies include papillary and follicular thyroid cancer, adrenal adenomas and adenocarcinoma, hepatoblastoma and duodenal carcinoma around the ampulla of Vater. These are also discussed in the section on gastrointestinal polyposis; linkage with the familial cancer syndrome of familial adenomatous polyposis (FAP), via the adenomatous polyposis coli (APC) gene mutation, seems likely [10].

Familial cases of simple epidermal cysts are more common and do not have a recognized correlation with malignancy.

Peutz–Jeghers syndrome (PJS; MIM #175200) (Chapter 39) is an autosomal-dominant condition comprising the complex of mucocutaneous pigmentation, particularly in the peri- and intraoral regions, and gastrointestinal polyposis, predominantly hamartomatous involvement of the small intestine, but with increase in cancer frequency [11]. Pigmentation can also occur on the palms, fingertips and soles; cutaneous changes fade with age. As well as an increased risk of gastrointestinal malignancy, there is also a substantive increase in non-gastrointestinal malignancy. The PJS gene, localized on chromosome 19p13.3, has been termed *STK11* (*LKB1*), mutations in which interfere with the protein regulatory function of a group of enzymes—serine/threonine protein kinase—that may act to suppress cell growth [10]. There is a fuller discussion in the section on gastrointestinal polyposis.

Palmoplantar keratoderma (Howel-Evans syndrome) (Chapter 34) is the association of autosomal-dominantly inherited keratoderma of the palms and soles (tylosis) with the eventual development of oesophageal carcinoma in most cases [12]. Since the original description, other families linked with inherited tylosis and carcinoma of the oesophagus have been described [13,14]. However, in diffuse palmoplantar keratoderma starting in infancy, there is no genetic susceptibility to neoplasia. Acquired palmar hyperkeratosis may also occur as a cutaneous paraneoplastic phenomenon, or as a marker of carcinogen ingestion (pp. 59.18–59.19), principally arsenic. The relationship with arsenical keratoses, punctate keratoderma and internal malignancy is a matter of conjecture. A possible familial association has been described with gastrointestinal malignancy [15]. Palmoplantar punctate keratoses are linked with internal malignancy via Cowden's disease

(Chapter 12). Punctate porokeratotic keratoderma has been tentatively associated with internal neoplasia [16]. Palmar hyperkeratosis is linked with malignancy via the paraneoplastic condition, acrokeratosis of Bazex (Chapters 34 & 62).

Basal cell naevus syndrome (BCNS; Gorlin's syndrome, MIM #109400) (Chapter 36) [17–19]. In this autosomal-dominant trait of multiple basal cell carcinomas (BCC), mandibular keratocysts, skeletal anomalies, abnormal calcification and dyskeratotic pits of palms and soles, the most common reported malignancies are medulloblastoma [20] and ovarian tumours, but astrocytomas, meningiomas, craniopharyngiomas, fibrosarcomas and ameloblastomas have occasionally been reported [18]. It is important to note that individuals may have only the family history, without themselves having developed BCC; neoplasia may also commence early in life, with a median age of onset of BCC by 20 years. The BCCs may present as small brown papules on the face, neck, back, chest and upper limbs. They may become more aggressive as the patient ages, and metastases are rarely possible. The gene for BCNS has been mapped to chromosome 9q22.1–q31, with a high percentage of germ-line mutations in the *PTCH* gene [10].

Familial melanoma syndrome (B-K mole syndrome, dysplastic naevus syndrome, MIM 155600) (Chapter 38). This is a variable group of disorders, linking multiple melanomas, on a background of multiple atypical melanocytic naevi and a familial history, with probably polygenic inheritance. Large multiple and irregular naevi are the norm, with an early onset of melanoma, potentially multiple primaries and in some groups an increase in non-cutaneous malignancies such as pancreatic, gastrointestinal, lung, breast and laryngeal sites, as well as ocular melanoma and cutaneous SCC of the head and neck. The *CDKN2A* germline mutation in the 9p21 gene region has been implicated in a high percentage of cases [10].

Xeroderma pigmentosum (XP; MIM 194400, 278700–278800) [21]. A complex of disorders that is autosomal-recessive in inheritance, it is dealt with in more detail in Chapter 12. XP characteristically presents at an early age with severe photosensitivity, marked reduction in threshold for sunburn and myriads of lentigines, principally in a sun-exposed distribution. Early onset of photoageing is found in infants, followed by sun-induced dysplasias, BCC, SCC and malignant melanomas, commencing in the first decade of life. There is significant resultant surgical scarring from multiple excisions, and reduced life expectation. A marked increased incidence of internal malignancy is also found, in part related to ocular and intraocular non-melanoma and cutaneous melanoma skin malignancy, but associations with other tumours such as central nervous system (CNS) sarcomas, leukaemia, lung and gastric cancers. The mutations causing XP cause abnormal fibroblast sensitivity to ultraviolet radiation, resulting from a defective DNA repair process; different mutations are classified as complementation groups A to G. Inactivation of tumour suppressors and activation of oncogenes due to these mutations results in development of multiple tumours [10].

Werner's syndrome (adult progeria; MIM #277700) [22]. An autosomal-recessive condition of premature ageing, with onset in the second to third decade of life. It is due to mutation of the *WRN* gene on chromosome 8p12. The Werner's syndrome gene product is a DNA helicase belonging to the RecQ family; it unwinds double-stranded DNA and is able to resolve aberrant DNA structures, so that aberrations occurring during repair, recombination and replication are made good, together with those that result from direct DNA damage [23]. Neoplasms develop in about 10% of cases, although the commonest cause of death is arteriosclerosis. Sarcomas, melanomas, leukaemia and a variety of epithelial-derived carcinomas have been reported [24,25]. Meningiomas are a recognized association, and an astrocytoma has been documented [26]. Werner's syndrome is a chromosome-instability syndrome and, as with XP, ataxia–telangiectasia, Bloom's syndrome and Fanconi's anaemia, is likely to be associated with a high incidence of neoplasia [2,10].

Von Hippel–Lindau syndrome (VHL; MIM *193300). A rare, autosomal-dominantly inherited condition characterized by benign and malignant tumours of various systems, particularly haemangioblastomas of the CNS, angiomatosis of the retinae, phaeochromocytoma [27], renal [28] and pancreatic adenoma, carcinoma and cysts [29]. The non-specific cutaneous manifestations include haemangiomas and café-au-lait spots [3]. The VHL gene has been located on chromosome 3p25; although different mutations have been found to be causative, the gene is a tumour-suppressor gene following the Knudson 2-hit model. Families may be characterized by the presence (type 2, missense mutations) or absence (type 1, deletions/protein-truncating mutations) of phaeochromocytoma. Type 2b has, in addition to an association with phaeochromocytoma, a high incidence of renal cell carcinoma and haemangioblastomas, whereas in type 2a there is a lower incidence of renal cell carcinoma and in type 2c an exclusive association with phaeochromocytoma [30].

Neurofibromatosis types 1 and 2 (NF1, von Recklinghausen's disease, MIM *162200; NF2, MIM *101000) (Chapter 12). There are two main forms of neurofibromatosis, type 1 (NF1) and type 2 (NF2). Both have an autosomal-dominant trait with a high incidence of new mutation, which—as a result of abnormal neural crest cell function—

produces multiple peripheral neurofibromas, as well as CNS tumours and café-au-lait macules [31]. NF1 is the commonest form of neurofibromatosis, with a prevalence of approximately one in 4000, with NF2 at around one in 200 000. There are several different clinical presentations, depending on the localization of the lesions. Clinical overlap between NF1 and NF2 occurs particularly in children, who may have café-au-lait macules and peripheral nerve tumours; flexural freckling is indicative of NF1. The associations with benign tumours, malignancy and systemic manifestations are varied [2]. Lisch nodules (pigmented iris hamartomas) are found with slit-lamp analysis in 90% of adult patients with NF1. Around 80% of patients with NF2 have posterior subcapsular cataracts. In general, NF2 patients have fewer skin lesions than in those with NF1, but more severe disease in NF2 is linked with greater prevalence of skin tumours [10].

NF2 patients develop vestibular and peripheral nerve schwannomas, together with CNS tumours such as meningiomas, astrocytomas and ependymomas. Perhaps the commonest neoplasia developing in patients with neurofibromatosis is a malignant neurofibrosarcoma [32,33]. Most superficial neurofibromas have a low malignant potential, change occurring more often in the deep plexiform neurofibromas and those more in continuity with nerves, designated schwannomas. Benign tumours such as acoustic neuromas, dumb-bell tumours and optic gliomas can result in disastrous sequelae when occurring in confined, pressure-sensitive sites. The commonest CNS malignancy is an astrocytoma. Other malignancies include nephroblastoma (Wilms' tumour), fibrosarcoma, rhabdomyosarcoma and leukaemia, especially in children [34–36]. Ocular melanoma has also been reported [37] and there is an increased frequency of phaeochromocytomas. The *NF1* gene, located on chromosome 17q, has a role as a tumour-suppressor gene, and although 50% of cases are inherited, 50% come through new mutation of the *NF1* gene. A genotype–phenotype association is the early onset of cutaneous neurofibromas and abnormal facial features, with a complete deletion of one copy of the *NF1* locus. These patients appear to have a higher incidence of malignant neurofibrosarcoma. It appears that transformation of benign neurofibromas to malignant peripheral nerve sheath tumours involves the loss of other tumour-suppressor genes such as p53 and p16. The gene product in *NF1* is called neurofibromin, and in its non-mutated role inhibits oncogenic activity of *ras* proteins [10,38].

The *NF2* gene locus appears to be that of a tumour suppressor on chromosome 22. The product of this gene, termed merlin, has an uncertain effect on tumour suppression [10].

Tuberous sclerosis complex (TSC; Bourneville's disease; TSC1, MIM #191100 and TSC2, MIM *191092) (Chapter 12). An autosomal-dominant condition of angiokeratomas, epilepsy and mental retardation. It may be associated with multisystem tumour involvement, mostly hamartomatous. The CNS, renal and cardiopulmonary systems are most significantly affected [2]. Malignant, sarcomatous change can occur, particularly with angiomyolipomas and rhabdomyomas, although this development and subsequent metastases are uncommon [3]. Renal cell carcinoma is a recognized, infrequent complication [39]. There are two known causative genes—*TSC1* on chromosome 9q34, encoding hamartin, and *TSC2* on chromosome 16p13, encoding tuberin. There are large numbers of different mutations, but in familial cases about half of the families show linkage to *TSC1* and the other half to *TSC2*. Attempts to identify a specific phenotype associated with mutations in either specific *TSC* gene have so far proved unrewarding, although there does seem to be a higher prevalence of mental retardation for *TSC2* mutation carriers [38].

Multiple endocrine neoplasia syndrome (multiple endocrine adenomatosis, MEA). This is now divided in to MEN1, MEN2A and MEN2B.

Multiple endocrine neoplasia type 1 (MEN1; Wermer syndrome; MIM *131100) is an autosomal-dominant familial cancer syndrome, with parathyroid, pancreatic islet cell and pituitary gland tumours, as well as cutaneous findings. It is caused by mutations in the *MEN1* gene, located on chromosome 11, which codes for the production of a protein named menin. The cutaneous findings in MEN1 are mostly multiple facial angiofibromas and collagenomas. Café-au-lait macules and lipomas are also encountered [40,41].

MEN1 is, at least in part, a tumour-suppressor gene. MEN1 is characterized by tumours of the parathyroid, anterior pituitary, pancreatic islet cells, neuroendocrine origin, foregut carcinoid and adrenal cortex. It is associated with 20–25% of cases of Zollinger–Ellison syndrome (ZES). In MEN1, 80–100% of cases have pancreatic endocrine tumours (pancreatic polypeptidomas or non-functional 80–100%, ZES 54%, insulinoma 21%, glucagonoma 3% and vasoactive intestinal peptide (VIP)oma 1%). Associated endocrine disease consists of parathyroid hyperplasia > 95%, anterior pituitary adenomas around 60% (range 14–100%), adrenal adenomas about 30%, lung carcinoids 7% and gastric carcinoids 13–30%. The pituitary adenomas are prolactinomas in 14–76% and cause acromegaly in 11–33% and Cushing's syndrome in 5–19%. The commonest tumours in MEN1 secrete PTH or gastrin. Secondary dissemination from malignant neuroendocrine tumours (carcinoid) may be one of the commonest causes of mortality in MEN1; most of these, unlike non-MEN1 cases, arise from the foregut (bronchi, thyroid, stomach, duodenum and pancreas) [10,42,43].

Multiple endocrine neoplasia type 2A (MEN2A, Sipple's syndrome; MIM #171400—mucosal neuromas, medullary

thyroid carcinoma and phaeochromocytoma; MEN type 2B or 3, MIM #162300) [2,4]. This can be divided into type 2A (Sipple's syndrome) and type 2B (formerly type 3). MEN2A and 2B affect principally the thyroid, parathyroid glands and the adrenal medulla and are linked with familial medullary thyroid carcinoma (FMTC) [44,45]. They are caused by mutations of the *RET* oncogene. Type 2A can present with pruritus, prior to recognition of the syndrome. Symmetrical, bilateral skin lesions overlying the scapular area have been described, with hyperpigmentation and hyperkeratosis in the intervening skin. Cutaneous deposits of amyloid have also been reported [10,43].

Type 2B patients tend to have a characteristic facial appearance. The lips and eyelids are thickened and bumpy, with multiple mucosal neuromas, causing blubbery, protuberant lips; other mucosal surfaces, such as buccal, gingival and pharyngeal surfaces may occasionally be affected, as can corneas and conjunctivae. Neuromas manifest as flesh-coloured papules or nodules. Prognathism can be evident, and patients often have a marfanoid appearance; muscle weakness and musculoskeletal anomalies may also be present [45].

Type 2B is additionally associated with medullary thyroid carcinoma (MTC) and phaeochromocytoma. The MTC in type 2B presents earlier and more aggressively than MTC in type 2A. It is often multicentric and bilateral, starting in those as young as 3 years, and early lymphatic spread may occur. Parathyroid hyperplasia or adenomatosis is seen more in MEN types 1 and 2A than in type 2B. Intestinal ganglioneuromatosis is more common in type 2B than 2A. Mucosal neuromas and a marfanoid appearance are not apparent in type 2A. Type 2A is linked to a mutation of the *RET* oncogene, located on chromosome 10, compared to a sporadic *RET* oncogene in 2B; both are autosomal-dominant in inheritance. Phaeochromocytomas, often bilateral, occur in many cases. Cutaneous café-au-lait spots occur and, rarely, a progressive striated pigmentary change of hyperplastic dermal nerves on the trunk [46]. The risk of medullary carcinoma is high, and this is the major cause of mortality; in MEN2, the mortality is greater from MTC than phaeochromocytoma. *RET* testing has replaced calcitonin screening to diagnose *MEN2* carrier status. The specific *RET* codon mutation will delineate the course of the disease and degree of aggression [2,10,42,47]. Prophylactic thyroidectomy may be indicated.

Carney complex (CNC; Carney's syndrome; NAME syndrome; LAMB syndrome; type I MIM #160980, type II MIM *605244). A group of disorders associated with cutaneous pigmented lesions, cutaneous, subcutaneous and internal myxomas, at various sites with endocrinopathy, principally endocrine tumours. NAME syndrome consists of *n*aevi (congenital melanocytic), *a*trial myxomas, *m*yxoid neurofibromas and *e*phelides. LAMB syndrome consists of *l*entigines, *a*trial myxomas, *m*ucocutaneous myxomas and *b*lue naevi. Cardiac myxomas are the most important internal myxomas, due to the causation of cardiac symptoms and potentially life-threatening effects (see also the section on cardiac disease later in this chapter). Likewise with endocrine involvement, adrenal-linked Cushing's syndrome can have critical, life-threatening effects. Gonadal hormone-secreting tumours, together with pituitary tumours producing GH, may produce their expected clinical effects; both benign and malignant thyroid tumours also occur [43,47].

Carney's complex, which often affects the adrenal cortex, thyroid and pituitary glands and gonads, is due in over half the patients to mutations in genes coding for a regulatory subunit type 1A of protein kinase A. CNC is clinically and probably genetically heterogeneous. At least two gene locations have been proposed, one on chromosome 2p16 and another on 17q2 [10,47].

Multiple hamartoma and neoplasia syndrome (Cowden's disease, CD; MIM #158350) [48–54]. This is a rare, cancer-associated genodermatosis, which is inherited as an autosomal-dominant trait with incomplete penetrance. It is due to mutations in the *PTEN* (*MMAC1*) gene on chromosome 10q23.3. It has been proposed that *PTEN* mutations produce their effects in Cowden's disease and allied hamartomatous disorders due to a failure to regulate cell death [10,55,56].

Multiple hamartomatous lesions of ectodermal, endodermal and mesodermal origin are associated with a predisposition to neoplasia; this can involve nearly all internal malignancies, but particularly the breast [54], colon and thyroid. The eponymous family was first described by Lloyd and Dennis [49].

The disease is most readily recognized by its characteristic mucocutaneous appearances, which are a consistent finding. The clinical picture is of warty, 'cobblestone' hyperplasia of the mucosal surfaces (Fig. 59.5), particularly the tongue and buccal mucosa, periorificial facial papules, acral warty keratoses and palmoplantar semitranslucent, punctate keratoses. The lesions, which are grouped especially around the mouth, nose and ears, have a hyperkeratotic, flat-topped, wart-like appearance, as do many lesions elsewhere; these are mostly trichilemmomas or related benign tumours of the follicular infundibulum [48,52]. Other inconstant cutaneous lesions include ganglioneuromas, lipomas, angiomas, angiolipomas, epidermoid cysts and a variety of pigmentary changes. Craniomegaly commonly occurs. Other occasional findings include an adenoid facies, kyphoscoliosis and a high-arched palate.

Benign internal anomalies are legion. The commonest internal organ affected is the thyroid; goitres and adenomas are the expected finding, although carcinomas

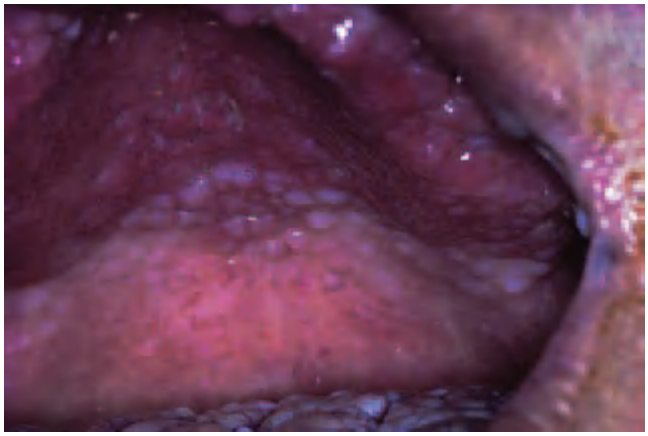

Fig. 59.5 Warty papillomatosis of the hard palate in Cowden's disease. (Courtesy of Dr R. Emmerson, Royal Berkshire Hospital, Reading, UK.)

also occur [53]. Gastrointestinal polyposis and cysts or polyps of the female genitourinary system also frequently occur. Less often, in these tracts, malignant change has been recorded in both male and female patients. The association with meningioma does appear real, although it is difficult to be certain with more varied and possibly secondary phenomena such as seizures and mental retardation.

The most important association of Cowden's disease is with breast pathology. The majority of women have severe fibrocystic disease of the breasts, and around 50% develop malignant change in the form of adenocarcinoma. These changes may have an early onset, and screening of at-risk family members is therefore recommended. Even prophylactic mastectomy has been suggested [54]. Benign gynaecomastia has been reported in the male, but malignancy of the breast or thyroid is exceptional. The disorder therefore appears more sinister in the female. It has been linked with several other hamartomatous disorders; Lhermitte–Duclos disease, in which hamartomatous outgrowths of the cerebellum occur, is now viewed as part of CD. Criteria for this disease have been established by the International Cowden Disease Consortium [10].

Bannayan–Zonana syndrome (BZS) has many hamartomatous findings in common with Cowden's disease, but lacks the extent of the malignant degeneration seen in Cowden's disease. BZS is characterized by microcephaly, vascular anomalies, lipomas, thyroid disease, gastrointestinal polyposis and speckled genital pigmentation [10].

Sebaceous tumours, keratoacanthomas and visceral malignancy (Muir–Torre syndrome, MTS, Torre's syndrome; MIM 158320) [3,57–59]. This is a cancer-associated genodermatosis in which there is an association between sebaceous lesions and, to a lesser extent, keratoacanthomas and internal malignancy. Inheritance is probably autosomal-dominant. It is thought that this may represent a variant of the 'cancer family syndrome' [3,60], as internal malignancy may be equally common in members of some of these families who do not exhibit pilosebaceous cutaneous lesions. Similarities exist between MTS and hereditary non-polyposis colon cancer (HNPCC) syndrome; analysis has demonstrated overlap on chromosome 2p and correlation with *MSH2* gene mutations, the product of which involves DNA mismatch repair enzymes. Defects result in varying lengths of repetitive DNA sequences, a finding in HNPCC which has also been commented on in MTS's keratoacanthomas and sebaceous tumours [10].

Sebaceous tumours are usually multiple, but occasionally solitary. Although sebaceous adenoma is the commonest, sebaceous carcinoma and epithelioma frequently occur, and within the same patient a variety of different pilosebaceous-derived skin lesions including keratoacanthomas may arise. Multiple or solitary keratoacanthomas associated with SCC of the larynx and lower gastrointestinal tract [61,62] probably represent a variant of MTS in which expression of sebaceous tumours and adenocarcinomas is not exhibited. The cutaneous manifestations of MTS have been reported to be exacerbated by immunosuppression. The world literature, reviewed by Serleth *et al*., contained 162 reported cases with 316 internal malignancies [63]. Colorectal and urogenital malignancies predominated, and nearly half of the patients had two or more internal malignancies. Many such tumours have an early onset—around 10 years earlier than in the normal population—but despite this, the survival is often quite good (the 50% survival time is about 12 years [59]) and the incidence of metastases relatively low. Tumours may also arise in a variety of other sites; there is also an association with non-Hodgkin's lymphoma [64].

Wiskott–Aldrich syndrome (MIM #301000) (Chapter 14) [65,66]. A sex-linked, recessive condition of immunodeficiency, associated with the development of malignancy, usually of the lymphoreticular system, such as lymphoma (especially large cell or immunoblastic) and leukaemia. The small intestine is a particular site for lymphomatous involvement. Astrocytoma and leiomyosarcoma have also been reported [67]. The incidence of malignancy is probably high, but the statistics are modified by the frequent childhood mortality [68].

Chediak–Higashi syndrome (MIM #214500) (Chapter 14) [69]. A fatal autosomal-recessive illness, with features of partial albinism, photophobia, neurological abnormalities and severe, recurrent bacterial infections. In the terminal accelerated phase, patients develop fever, jaundice, hepatosplenomegaly, lymphadenopathy, pancytopenia and a deterioration of neurological changes. Death may result from bleeding due to thrombocytopenia, or from

infection. Although strongly suggestive of lymphoma, the infiltrate of affected organs is reported to be of a reactive, diffuse, mononuclear cell type, rather than neoplastic [69].

Ataxia–telangiectasia syndrome (AT; Louis-Bar syndrome; MIM *208900) (Chapter 14) [70]. A condition of autosomal-recessive inheritance, characterized by progressive cerebellar ataxia and oculocutaneous telangiectasia. There is a variable but progressive immune deficiency of both the cell-mediated and humoral types, which results in frequent infections and a reduction in immune surveillance [70]. As a result, there is a high incidence of neoplasia, approximately 10%, usually in or before the teenage years [71,72]. The majority of tumours are lymphoproliferative or leukaemic, although carcinomas of various sites also occur [2]. T-cell leukaemia occurs in younger patients and an aggressive prolymphocytic leukaemia in older cases, although B-cell leukaemias are also encountered. A higher risk of breast malignancy in females who are heterozygotes for AT has been reported, but may not manifest with early onset [10]. The *ATM* gene has been associated with chromosome 11q22; a large gene has been described in this region. There may be many different germ-line mutations that alter the product, ATM protein, which is involved in the handling of chromosome strand breaks and activation of the p53 oncogene [10].

Bloom's syndrome (MIM *210900) (Chapter 14) [73]. An autosomal-recessive disorder that affects principally the Ashkenazi Jewish ethnic group. It is characterized by small stature and slight build, a sun-sensitive telangiectatic rash and café-au-lait macules. Minor anatomical abnormalities and congenital anomalies commonly occur. Levels of IgA and IgM are low and bacterial infections frequent. The occurrence of lymphoproliferative neoplasia and epithelial tissue cancers, particularly gastrointestinal, is high [71,74]. Mutations of the gene designated *BLM* on chromosome 15q26 lead to inhibition of the function of the protein product, a DNA helicase enzyme. There is a predisposition to malignancy through mutations in other target genes [10].

Rothmund–Thomson syndrome (RTS; poikiloderma congenitale; MIM #268400) (Chapter 12). RTS is a rare autosomal-recessive genetic disease, characterized by developmental abnormalities in the skin and skeletal systems, including photosensitivity, poikiloderma, small stature and juvenile cataracts. Premature ageing and a predisposition to certain malignancies occur; malignancies include an approximate 30% incidence of osteosarcoma, whilst fibrosarcoma, myelodysplasia and non-melanoma skin cancer also occur. A mutation of genes for RecQ helicase is thought to be responsible for at least some, if not all, cases of RTS. Two other human RecQ helicase gene mutations are recognized in the recessive conditions Bloom and Werner syndromes—all three conditions predispose to abnormal growth, premature ageing and increased incidence of site-specific malignancies [75–77].

Dyskeratosis congenita (Zinsser–Engman–Cole syndrome; MIM #305000) (Chapter 14) [78]. An X-linked recessive genodermatosis delineated by atrophy and pigmentation of the skin, nail dystrophy and mucous membrane changes. The latter change, termed mucosal leukokeratosis, is prone to develop carcinoma; there is also a raised incidence of malignancy, particularly gastrointestinal, including pancreatic adenocarcinoma and severe haematological disorders, similar to those found in Fanconi's anaemia and Hodgkin's disease, which may evolve into leukaemia [71,79]. Data exist to suggest that there is a defect in cell-mediated immunity involving suppressor T cells, which may be linked to the premature ageing sometimes associated with this syndrome [80].

Follicular atrophoderma (Bazex–Dupré–Christol syndrome; MIM *301845) [81]. A rare, X-linked, dominant condition of follicular atrophoderma, milia, epidermoid cysts, hypotrichosis, basal cell epitheliomas and occasional generalized or localized hypohidrosis, which appears to have an association with leukaemia. The characteristic perioral, pigmented cutaneous manifestations may assist early recognition [82].

In many of the above conditions, it has been presumed that defective immunosurveillance is responsible for the raised incidence of neoplasia. However, exact mechanisms have often been uncertain and/or multifactorial; increasingly, the expansion of our understanding of the human genome is elucidating the mechanisms underlying these syndromes. Clearly, chromosome instability and failure of DNA-repair mechanisms have been thought to be and are now shown to be partially responsible in some groups. The need for identification, screening and early detection of neoplasia in all at-risk cases should be emphasized.

Exposure to carcinogens [83]

Nicotine staining of the fingers is one of the commonest signs that a patient may be predisposed to bronchial carcinoma, together with other tobacco-linked neoplasia.

X-ray damage to the skin may indicate that underlying tissues are at increased risk of neoplasia; this is particularly relevant for neck and thyroid carcinoma. X-ray damage and/or multiple basal cell carcinomas over the spine following radiotherapy for ankylosing spondylitis may indicate the patient is predisposed to leukaemia.

Arsenic-induced pigmentation (Fig. 59.6; Chapter 73), keratoses (Chapter 36), Bowen's disease, superficial BCCs and multiple sebaceous tumours can be linked to an increased risk of internal neoplasia (especially bronchial).

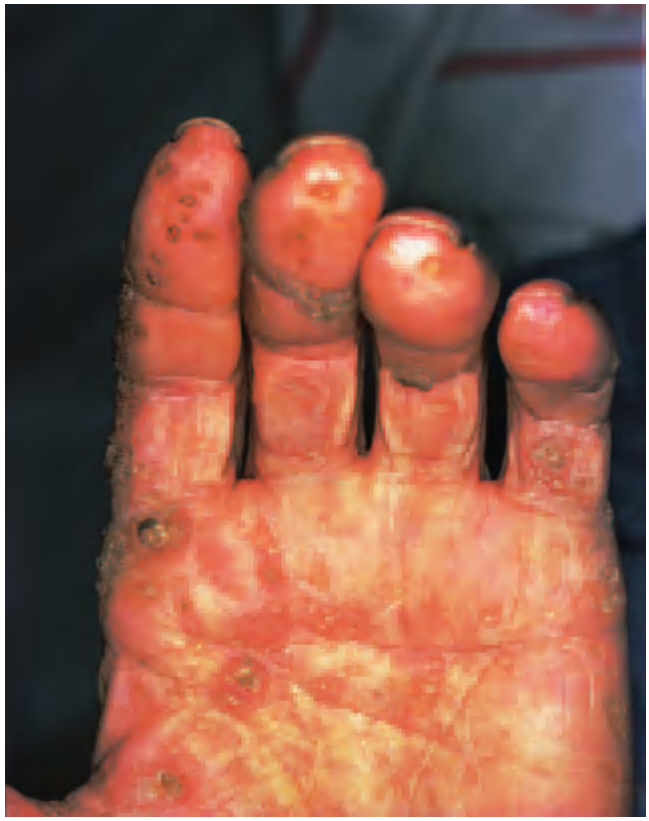

Fig. 59.6 Arsenical keratoses on the hand. (Courtesy of Dr P. Dufton, Clatterbridge Hospital, Wirral, UK.)

The relationship between Bowen's disease of non-sun-exposed skin and an increased risk of internal neoplasia has been a long-standing controversy [84]. If the link with arsenic is excluded, the association appears unsubstantiated [85,86].

Vinyl chloride-related acrosclerosis, acro-osteolysis and papular skin changes are variable markers of heavy industrial exposure in polyvinyl chloride manufacture. An occasional link with angiosarcoma of the liver has been noted [87].

Paraneoplastic syndromes [83]

Acanthosis nigricans (Chapter 34) [88,89] may be divided into two important categories: benign and malignant. Schwartz [89] describes eight types of acanthosis nigricans: benign, obesity-associated, syndromic, malignant, acral, unilateral, medication-induced and mixed types. When its onset is in adult life and is not associated with a predisposing cause such as positive family history, obesity, various endocrinopathies (particularly insulin-resistant types [90]) or drug ingestion (especially nicotinic acid), then there is a high correlation with internal malignancy. Malignancy-associated acanthosis nigricans is much less common than the non-malignancy-associated types. It may have a rapid onset and spread [89]. Paediatric occurrence does not necessarily, however, imply a benign form. Whilst it has been associated with a number of different malignancies, the most common site of underlying neoplasm is the gastrointestinal tract (90%), especially gastric adenocarcinoma [2]. Rarely, an association with lymphoma has been recorded [91]. The prognosis with malignant acanthosis nigricans is generally poor, which at least in part is related to the low survival rate from the neoplasia concerned. However, the changes may resolve with eradication of the cancer [92]. The clinical dilemma is often to exclude malignancy, especially as acanthosis nigricans can be a presenting sign; an algorithm for evaluation is therefore useful [93]. Malignancy-associated acanthosis nigricans may occur in association with the sign of Leser–Trélat, florid cutaneous papillomatosis and acanthosis palmaris. More rarely associated paraneoplastic phenomena include pachydermoperiostosis, paraneoplastic pemphigus and acquired hypertrichosis lanuginosa [1–6,94].

Acanthosis palmaris (tripe palms, pachydermatoglyphy) [95]. This consists of thickened palms and/or occasionally soles with an enhanced dermatoglyphic change, which gives rise to a velvety or honeycombed pattern of the hand. Acanthosis palmaris usually occurs in association with neoplasia; it can occur in isolation without neoplasia, or as a reflection of exfoliative psoriasis [96]. Coexistence with acanthosis nigricans is recognized. Acanthosis palmaris occurring alone was more often associated with bronchial carcinoma (53%) compared with combined acanthosis nigricans and acanthosis palmaris, in which 35% had gastric carcinoma and only 11% bronchial neoplasia [97]. Resolution of the palmar changes has been described with resection of the tumour [97]. As the condition can frequently be the presenting sign of neoplasia, it requires appropriate evaluation and investigation.

Dermatomyositis (Chapter 56) [98]. Both dermatomyositis and polymyositis in adults may be associated with internal malignancy. The frequency of the link varies between 6% [99] and 50% [100], depending on the age range of the series reported and the numbers involved. The association with neoplasia is much stronger for dermatomyositis than for polymyositis or dermatomyositis/autoimmune disease overlap conditions. Conventional teaching has been to implicate a malignancy association with dermatomyositis in the over-40 age group, and this is normally the case; however, paediatric cases with neoplasia are reported [101]. As there is a lower incidence of malignancy in the younger age group, it is difficult to judge the association without age-matched comparative studies against a control population [98]; until these data are available, no absolute judgement in this respect should be made on the basis of age alone.

The validity of the temporal association of polymyositis–dermatomyositis with neoplasia is still questioned by some workers, but even so the important 2-year initial period has a four to five times increased incidence of malignancy [102]. Accounts of specific malignant associations seem subject to bias by rare-case reporting. In reality, the malignancies seem to some extent to reflect tumour prevalence in the general population; lung cancer in men, breast and gynaecological tumours, particularly ovarian, in women [103,104]. The value of extensive screening for neoplasia in dermatomyositis is questionable. Emphasis should be attached to thorough clinical evaluation, simple investigations and then specific investigations as indicated [104]. Exceptions to this are if previous neoplasia has been present, when the therapeutic response is poor, and perhaps a recognition of the possibility of hidden tumours in the female genitourinary tract.

Digital ischaemia [105]. Persistent, painful digital ischaemia, often progressing to gangrene and having an unusual Raynaud's syndrome-type appearance, has been linked to a variety of solid tumour and reticuloendothelial neoplasia [105,106]. The process may have a vasculitic element [107]. Often, however, the aetiology is uncertain, but clearly there may be a merging of malignancy-associated systemic sclerosis [108] or dermatomyositis with mixed connective tissue disease overlap. Hyperviscosity syndromes such as polycythaemia rubra vera or myeloma-linked cryoglobulinaemia may give rise to cutaneous ischaemia and phlebitis by a more direct vascular sludging effect.

Vasculitis and malignancy [107]. There appears to be an association of cutaneous vasculitis with neoplasia, particularly in myeloproliferative disorders [109], although clearly there is overlap with digital ischaemia. The dermatological manifestations include palpable purpura, maculopapular, urticarial and petechial lesions; these presumably reflect a small-vessel vasculitis or even, when ulceration occurs, a necrotizing vasculitis [107]. The changes often appear to antedate bone marrow involvement, as opposed to the more predictable purpura due to thrombocythaemia, which reflects bone marrow infiltration by myeloproliferative disease or carcinoma. Leukocytoclastic vasculitis has been variably associated with infections, cryoglobulinaemia and drug reactions, but a paraneoplastic aetiology is specifically recognized, including a rare presentation of multiple myeloma [110].

Migratory erythemas

There are three main variants, which may be associated with internal neoplasia to a very variable extent.

Erythema gyratum repens (p. 59.71). This is a rare, bizarre cutaneous eruption consisting of mobile concentric, often palpable, erythematous, wave-like bands, which give a 'wood-grain' appearance to the skin (Fig. 59.7). A peripheral scale or collarette may be present. The complete torso is frequently affected. There is a substantial association with internal malignancy, but this is not absolute [111]. It is, however, mandatory to investigate for this possibility. Perhaps the commonest underlying neoplasm is lung cancer [112], but many solid cancers have been implicated and some myeloproliferative disorders. Resection of the tumour can result in resolution of the eruption.

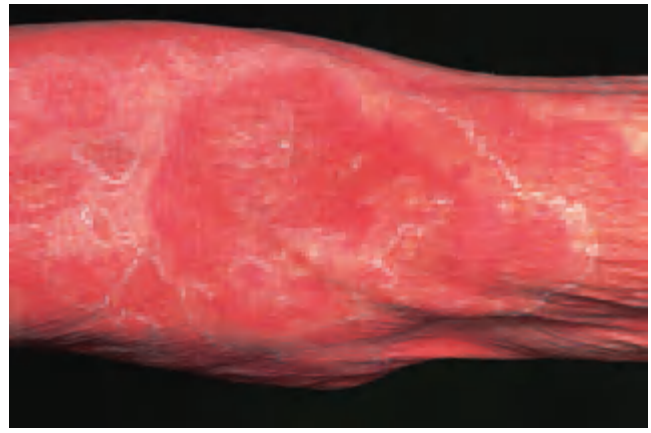

Fig. 59.7 Erythema gyratum repens of the arm secondary to carcinoma of the bronchus. (Courtesy of Dr A.W. McKenzie, Norfolk and Norwich Hospital, Norwich, UK.)

Necrolytic migratory erythema (glucagonoma syndrome) [113–115]. This is the characteristic eruption associated with an α-cell tumour of the pancreas. It is discussed in the section on pancreatic disease later in this chapter.

Erythema annulare centrifugum [116,117]. Most annular erythemas of this type are not associated with neoplasia (p. 59.72). Rarely this can occur, particularly with myeloproliferative disorders [117]. Clinical examination and routine screening tests are the only investigation required, rather than an exhaustive search for malignancy, unless there are additional clinical pointers.

Multicentric reticulohistiocytosis (lipoid dermatoarthritis; reticulocytoma cutis) [118,119]. In this rare condition, approximately 28% of cases are associated with internal neoplasia, virtually always solid tumours such as those of the breast, ovary or cervix [118,119], although haematological malignancies have been reported [120]. Tumours may coexist at the presentation of the disorder, usually in adult life. The characteristic papulonodular lesions occur most often on fingers or other extremities, and mucous membranes. A severe polyarthritis is frequently associated [121].

Paraneoplastic acrokeratosis (Bazex's syndrome) [122–128]. This is a rare condition, associated particularly with SCC of the upper respiratory or gastrointestinal tracts, particularly when there are metastases in the cervical lymph nodes. Rare associations such as metastatic adenocarcinoma of the prostate and transitional cell carcinoma of the bladder have been reported [125,126]. It is much commoner in males than females [127,128]. The cutaneous changes develop gradually, often in several phases, initially with violaceous erythema and scaling on the peripheries, especially ears, nose, hands and feet. The eruption then becomes more hyperkeratotic, with a keratoderma on hands and feet. Subsequently, the eruption may become more generalized. Nail dystrophy and paronychia are often present. Changes on the face may appear more eczematous or lupus erythematosus-like, whereas acral changes are often psoriasiform. The differential diagnosis can include dermatitis, especially seborrhoeic or contact-allergic types. Alternatively, acral psoriasis with the possibility of Reiter's syndrome may be considered. The course mostly parallels the underlying neoplasm; resolution may occur with successful tumour resection, and recurrence may develop on relapse of malignancy. When resection is felt inappropriate or impracticable, systemic retinoids may improve the cutaneous changes [124]. The histological changes are non-diagnostic, but essentially reflect the clinical appearance with hyperkeratosis, parakeratosis, focal spongiosis and a mixed, inflammatory cell infiltrate [127].

Acquired ichthyosis [129,130]. Sudden onset of ichthyosis similar to the pattern of ichthyosis vulgaris in adult life does appear to be associated with internal malignancy, particularly lymphoreticular tumours. However, cases linked with solid tumours are also well documented [130]. The acquired change should not be confused with asteatosis, which of course is a common problem in elderly people. Acquired ichthyosiform changes can be a manifestation of other systemic disorders, including nutritional deficiencies, sarcoidosis, leprosy, hypothyroidism, lupus erythematosus and drug reactions. Again, in such reports it is important to distinguish ichthyosis from dry-skin changes. Pityriasis rotunda—a fixed, annular, scaling, dry-skin change more often seen in the African and Asian races—has been associated with neoplasia, particularly hepatocellular carcinoma. However, it may also be seen in other systemic diseases and in leprosy [131].

Pruritus [132]. Haematological disorders and lymphoma may cause generalized pruritus; in particular, itch may be a severe problem in patients with Hodgkin's disease and may indicate a poorer prognosis [133]. Sézary syndrome, mycosis fungoides, myelomatosis and leukaemia may also cause generalized pruritus [132]; the mechanisms in these conditions are poorly understood. In polycythaemia rubra vera (PRV), the initiating factor appears to be rapid cooling of the skin, as encountered after bathing. This is thought to be due to the release of pruritogens by degranulated mast cells [134]. However, patients with PRV can also develop intractable itching unrelated to bathing.

Internal carcinoma is a non-specific, rare, but important cause of pruritus. Clearly, this can occur through secondary metabolic effects such as uraemia or cholestasis. Alternatively, changes such as iron-deficiency anaemia, acquired ichthyosis or xerosis may be involved. Even excluding these mechanisms, virtually any of the visceral carcinomas can cause pruritus; again, the mechanisms are frequently poorly understood. Brain tumours can be an uncommon cause of pruritus. If itching or paraesthesiae are localized to the nostrils, a tumour invading the floor of the fourth ventricle may be the cause, but sometimes generalized itching can occur with intracranial neoplasia [17]. Unfortunately, senile pruritus and asteatosis are not uncommonly encountered in elderly patients, a group who are more at risk from malignancy. It is therefore difficult to dissociate chance from real occurrence, which can lead to difficulties in deciding whether screening is indicated on a cost-effective basis [135]. In a 6-year study of 125 patients with generalized pruritus, Paul *et al*. [135] found no significant increase in malignancy, although of the eight patients with malignancy detected, two had lymphoma—a higher than expected incidence.

Bullous eruptions. Bullous pemphigoid has, in isolated reports, been associated with underlying neoplasia [136–138]. However, when large series have been examined, the results indicate that there is not a significant association with malignant disease [139,140]. Despite this, the issue remains controversial, and more selective studies have shown there may be a correlation when immunofluorescent findings are negative and mucosal involvement is present [139,141]. Some cases may also reflect the difficulty in diagnosing or excluding epidermolysis bullosa acquisita, in which saline–split skin immunofluorescence, immunoelectron microscopy or immunoblotting may be required [142]. Malignancies have been reported from breast, lung, thyroid, larynx, skin, soft tissue, stomach, colon, lymphoreticular system, prostate, cervix, bladder, kidney and uterus [143]; in a Japanese population, there was an association with gastric carcinoma [144]. Clearly, in a disorder that principally affects elderly people, who are more prone to internal neoplasia, a reported association with choriocarcinoma is interesting, as this tumour usually occurs in a younger age group [145]. It is likely that this association is with pemphigoid gestationis (herpes gestationis); nevertheless, in such circumstances it is also a paraneoplastic phenomenon. Perhaps particular consideration should also be given to an association with malignancy in the young and those who respond poorly

to therapy. The debate will continue—hopefully supported by carefully controlled studies—as to whether there is a definite association in onset, course and resolution. This may be particularly true of squamous tumours of the genitourinary tract [143], where SCC-related, cross-reacting antigen could be a factor. However, an exhaustive search for internal neoplasia is not generally warranted; rather, the emphasis should be on thorough clinical examination, evaluation and routine screening tests.

Pemphigus and paraneoplastic pemphigus (PNP). Historically, pemphigus has been linked with various tumours; some of these, such as thymoma [146] and Castleman's pseudolymphoma [147] are rare and the association therefore seemed likely to be real. Pemphigus foliaceus has been associated with acanthosis nigricans-like lesions and hepatocellular carcinoma [148], and pemphigus in Japanese subjects has been associated with lung cancer [144]. The concurrence of internal malignancy and pemphigus, as with bullous pemphigoid, may be a true association [149], although critical reviewers suggest this to be coincidence [150].

A specific condition, now termed PNP, has been delineated [151–154]. This may represent one manifestation of a heterogeneous, multiorgan, autoimmune syndrome in which patients may display a spectrum of five different mucocutaneous manifestations including pemphigus-like, pemphigoid-like, erythema multiforme-like, graft-versus-host disease-like and lichen planus-like; in addition, there is an association with small-airways occlusion [152] and deposition of autoantibody complexes in different organs. The mucosal disease is often severe and progressive. Associated neoplasms in one large review series were mainly B-cell proliferations and thymoma or thymoma-like neoplasms; specific neoplasms included Hodgkin's lymphoma (42%), chronic lymphocytic leukaemia (29%), Castleman's tumour (10%), thymoma (6%), spindle cell neoplasms (6%) and Waldenström's macroglobulinaemia (6%) [151]. PNP is distinguished from pemphigus by its clinical features and by the presence of serum autoantibodies to a range of antigens of 250, 230, 210, 190 and 170 kDa (which include bullous pemphigoid antigen, desmosomal and hemidesmosomal proteins); high sensitivity and specificity for this differential diagnosis has recently been reported by taking account of the association with a lymphoproliferative disorder, indirect immunofluorescence of rat bladder, and recognition of envoplakin and/or periplakin bands on immunoblotting [154].

Linear IgA disease appears to have a higher-than-predicted association with lymphoproliferative malignancy. However, it is uncertain whether this is due to a common aetiological factor or represents a true paraneoplastic phenomenon [155]. Lymphoma is known to occur with increased frequency in gluten-sensitive enteropathy, and a questionable raised incidence of lymphoma has been reported in dermatitis herpetiformis [156]; but again, there is considerable doubt whether this should be regarded as a cutaneous paraneoplastic manifestation.

Transient acantholytic dermatosis has been linked with internal malignancy, particularly with myelogenous leukaemia and carcinoma of the genitourinary tract. However, this may be linked in part with therapy [157].

Porphyria cutanea tarda, acute intermittent and variegate porphyrias have been associated with hepatocellular carcinoma [158]. Myeloma and visceral carcinoma have also been reported [159]. Acquired epidermolysis bullosa has been reported to occur in association with neoplasia, particularly myeloma and lymphoma; problems may arise in distinguishing the condition from porphyria cutanea tarda, as well as from bullous pemphigoid.

Erythema multiforme, erythema nodosum and subcutaneous fat necrosis. With erythema multiforme and erythema nodosum, any association is hard to evaluate, as both may be reactions to drugs, radiotherapy or infections—all of which are likely scenarios in patients with neoplasia. Erythema multiforme-like eruptions do occur with carcinomas, lymphomas and leukaemias [2], particularly myelomonocytic types. However, histological analysis of the latter lesions sometimes demonstrates the presence of abnormal cells. In acinar cell carcinoma of the pancreas, a syndrome of panniculitis, polyarthritis and eosinophilia can occur [1]. This form of subcutaneous fat necrosis is similar to the changes in Weber–Christian disease (Chapter 55). It seldom occurs with islet cell tumours.

Migratory thrombophlebitis (Trousseau's sign) [2]. Unlike superficial thrombophlebitis of the lower limbs, this recurrent and migratory type is often associated with neoplasia, particularly carcinoma of the pancreas, stomach and lung. A variety of sites, especially the upper extremities and trunk, can be involved. Deep veins, particularly on the lower limbs, are rarely affected; lesions are usually multiple. The mechanism is thought to be an intravascular, low-grade hypercoagulation, which responds poorly to anticoagulant therapy. Skin manifestations may be the only presenting sign and may point to a highly malignant and often metastatic malignancy of correspondingly poor prognosis [1].

Pyoderma gangrenosum and neutrophilic dermatoses. These are discussed in greater depth in Chapter 49. Pyoderma gangrenosum, particularly in a superficial and bullous (Fig. 59.8) form, has been associated with myeloproliferative diseases, including acute and chronic mye-

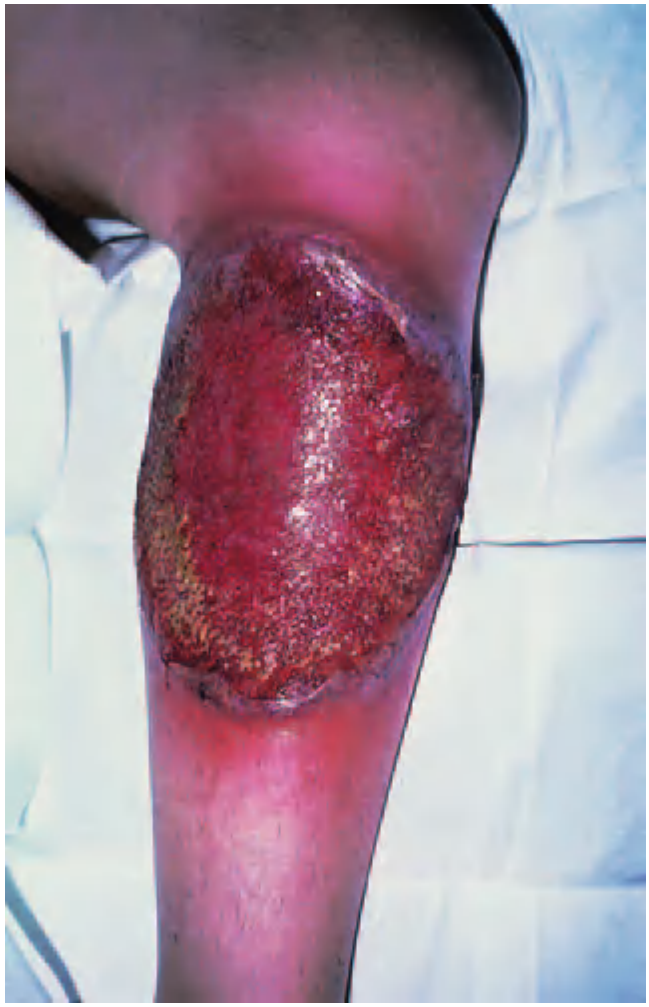

Fig. 59.8 Bullous pyoderma gangrenosum of the leg. (Courtesy of Dr P. Dufton, Clatterbridge Hospital, Wirral, UK.)

loid leukaemia, acute lymphocytic leukaemia, myeloid metaplasia, PRV, multiple myeloma, lymphoma and myelofibrosis [160,161]. The association of pyoderma gangrenosum with monoclonal gammopathy is uncertain, but it does occur at a frequency higher than expected in the general population and is usually of IgA type, whereas IgG gammopathy is the commonest type overall [110]. Solid tumours reported include carcinoid, colon, bladder, prostate, breast, bronchus, ovary and adrenocortical carcinoma [161].

Sweet's syndrome has likewise been associated with several malignancies, especially haemopoietic.

Erythroderma (Chapter 17). Whilst this may be an expression of mycosis fungoides and its leukaemic variant, Sézary syndrome, there is still a small number of patients who have neither condition, but present with erythroderma and eventually develop lymphoma or leukaemia. The incidence is uncertain and rare; a report in an Asian population failed to demonstrate one association in 80 patients [162]. Immunophenotypic studies do not appear to help distinguish benign from malignant cases. Ofuji papuloerythroderma has also been associated with peripheral T-cell non-epidermotrophic cutaneous lymphoma [163]. Correlations with solid tumours such as lung, colon, stomach, prostate, liver, pancreas and thyroid have been infrequently recorded, often in late-stage disease [164].

Leser–Trélat sign [165,166]. Internal malignancy associated with the sudden development of numerous seborrhoeic keratoses, in an eruptive fashion with or without pruritus, is generally accepted as the sign of Leser–Trélat. Unfortunately, multiple seborrhoeic keratoses are such a common occurrence, especially in elderly people, that caution should be exerted when attempting to make this diagnosis. Even the most positive pointer of multiple, rapidly erupting seborrhoeic keratoses is an unreliable guide. Care should also be taken when interpreting multiple eruptive seborrhoeic keratoses in association with a generalized dermatosis, as this is a recognized occurrence with certain primary dermatoses, rather than necessarily being linked to internal malignancy [167].

A closer association is found between internal malignancy and the seborrhoeic keratosis-like lesions of acanthosis nigricans. Of the cases reported, the most frequent link is with adenocarcinoma, especially of the gastrointestinal tract and breast. However, this in part may just reflect the incidence of these tumours in an age group at risk of seborrhoeic keratoses. Rare associations have been documented with a variety of other neoplasms, including those of the reticuloendothelial system [168], malignant haemangiopericytoma [169], malignant melanoma [170] and transitional cell carcinoma of the bladder [171].

The inclusion of the sign of Leser–Trélat as a paraneoplastic phenomenon can at best be regarded as tenuous, but the sign may have clinical relevance when associated with acanthosis nigricans and/or an appropriate eruptive history. Weakened subepithelial matrix from the effects of neoplasm on the extracellular matrix of the host has been postulated as a possible cause for the changes seen in Leser–Trélat and acanthosis nigricans [172].

A variety of other eruptive lesions have been reported rarely as paraneoplastic phenomena, including keratoacanthomas in MTS (p. 59.17), angiomatous lesions [173] and telangiectasia. Campbell de Morgan angiomas are a common normal finding with age, but unusually rapid onset may be an important feature [2].

Seed-like keratoses of the palms and soles [174]. Acquired punctate keratoses of the palms and soles may be associated with internal malignancy. They are a common

normal finding in healthy subjects (36%) over 50 years old, but are apparently more common in individuals with carcinoma of the bladder (87%) and bronchus (71%) [174]. There are, however, problems with differentiation from keratosis punctata et plantaris occurring as an inherited condition and associated with adenocarcinoma of the colon [175]. Punctate keratoderma occurring in Cowden's syndrome (Chapter 12) and seed-like keratoses with arsenic ingestion may also be associated with internal malignancy.

Flushing is a normal physiological response and may be a problematic menopausal symptom. However, it may also suggest a diagnosis of carcinoid syndrome. The gastrointestinal system is the most commonly affected site, especially the appendix and ileum. Flushing and other symptoms such as diarrhoea, abdominal pain and breathing difficulties do not usually occur until liver metastases have developed. Ovaries and bronchi may be alternative primary sites. Flushing is the commonest feature of carcinoid syndrome, often affecting the face or upper extremities, and at least initially is transient in nature. Skin manifestations can therefore be the presenting symptoms and may also include a persistent erythema with or without telangiectasia, scleroderma-like change, pigmentary anomalies and a pellagra-like dermatitis [1].

Confusion can occur between the plethoric appearance seen in PRV and the facial suffusion found in superior vena caval obstruction.

Unilateral lymphoedema. Acquired unilateral lymphoedema of reasonably rapid onset, especially over the age of 40 years, suggests regional lymphatic obstruction proximally, which may be explained by malignant deposits or compression by an expanding tumour.

Clubbing and hypertrophic osteoarthropathy of the airways. Clubbing and secondary hypertrophic osteoarthropathy of the airways (HOA) have been documented with many neoplasms, the commonest being carcinoma of the bronchus. A high incidence of HOA occurs particularly with mesothelioma; but it may also occur with malignancies of the pulmonary, cardiovascular, gastrointestinal and hepatobiliary systems [176].

Cutis verticis gyrata. In its secondary form, this may on occasion occur as a paraneoplastic phenomenon [177].

Scleroderma-like skin changes may be a cutaneous manifestation of carcinoid syndrome, but without Raynaud's phenomenon [1]. However, in scleroderma there does appear to be an association with malignant disease [108], at least on a temporal basis. Some cases do seem to be linked with management of the malignant disease, in particular when radiotherapy has been employed [178].

Herpes zoster occurs more severely, with higher incidence and wider dissemination, in patients with reticuloendothelial or myeloproliferative neoplasia [179]. However, the uncomplicated form is common in elderly people and does not demand intensive investigation.

Infections. A variety of viral, bacterial and fungal infections may occur with internal malignancy, particularly when the patient has a severely compromised immune response, either as a result of the malignant process or therapy.

Urticaria. With the exception of cold urticaria and peripheral gangrene as a result of circulating cryoglobulins, where there is a possible, but uncommon, link with myeloma and lymphoma [180], associations of urticaria and neoplasia are difficult to evaluate. Certainly it cannot be regarded as an established paraneoplastic phenomenon, other than in Schnitzler's syndrome (a distinct disorder of chronic urticaria, bone pain, hyperostosis, high erythrocyte sedimentation rate and monoclonal IgM gammopathy). IgM κ is the commonest paraprotein found; the urticaria under histological analysis is described as neutrophilic inflammation within dermal venules with some perivascular involvement, but can rarely extend to a leukocytoclastic vasculitis. Although the overall prognosis is reasonable, around 10–15% of patients develop lymphoplasmacytic lymphoma [110].

Acquired hypertrichosis lanuginosa (Chapter 63). An exceedingly rare condition, for which, once drug-induced causes such as diazoxide and minoxidil have been excluded, there is a reliable link with internal malignancy.

Generalized hyperhidrosis. A rare occurrence, which may be associated with malignant disease.

Lichen planus may rarely be induced by neoplasia [181]. There is also an increased risk, particularly in males, of oral squamous carcinoma; this may be due to a combined direct effect and co-factors such as smoking [182].

Conclusion

Potential cutaneous markers of internal malignancy vary in their reliability for predicting underlying neoplasia. A clinical decision on the extent of investigation and screening, if any, must therefore be made. No absolute directive can be given. A good history, careful clinical examination and simple investigations such as chest radiography, full blood count, urine analysis and stool examination for occult blood are often sufficient. The identification of genes linked with a high incidence of malignant disease, where appropriate, will assist with diagnosis and therapy.

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The gastrointestinal tract

Skin changes related to nutritional defects, a consequence of many gastrointestinal diseases, are discussed in Chapter 57, and oral disease in Chapter 66. This section concentrates on bowel, hepatic and pancreatic diseases in which skin manifestations are prominent [1–4]. Links between skin disorders and abdominal pain are not specifically considered, but many of the disorders in this section may cause this symptom; less overt causes of skin eruption with abdominal pain include disorders such as hereditary angio-oedema (Chapter 47), vasculitides (Chapter 49), porphyrias (Chapter 57), and periodic fevers (see the section on bone and joint disease). Cutaneous metastases and paraneoplastic eruptions due to gastrointestinal

malignancy are discussed in the preceding section of this chapter.

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Oesophagus and stomach

Bleeding from the oesophagus or stomach may be associated with skin and nail changes of iron deficiency, such as koilonychia, smooth tongue and angular cheilitis (Chapter 57). Iron deficiency is associated with dysphagia and development of a postcricoid web as in the Paterson–Brown–Kelly (Plummer–Vinson) syndrome. Skin disorders that are associated with gastrointestinal bleeding, or with polyps, are discussed later. Cutaneous metastases may occur from tumours of the oesophagus or stomach. Paraneoplastic eruptions linked to the upper gastrointestinal tract, such as tylosis with oesophageal carcinoma (Howell–Evans syndrome), acrodermatitis and nail dystrophy with upper gastrointestinal carcinoma (Bazex's syndrome), or acanthosis nigricans with gastric carcinoma, are discussed earlier in this chapter.

Bullous diseases may affect the pharynx, oesophagus, or stomach. Epidermolysis bullosa (EB) is of particular relevance; dystrophic EB may cause oesophageal scarring [1], with a risk of SCC, and gastric outflow is affected in junctional EB, resulting in pyloric atresia [2,3]. Cicatricial pemphigoid may cause oesophageal scarring and stenosis. Lichen planus may also occur in the oesophagus [4,5].

Sclerodermatous processes also affect the oesophagus, in particular CREST (*c*alcinosis, *R*aynaud's phenomenon, o*e*sophagus, *s*clerodactyly, *t*elangiectasia). This disorder is discussed more fully in Chapter 56. The oesophageal abnormality consists of decreased and disordered peristalsis. Scleroderma is also associated with decreased peristalsis throughout the bowel, leading to malabsorption, constipation and diverticulae. Sjögren's syndrome may also cause dysphagia, as may dermatomyositis in cases in which there is involvement of the pharyngeal musculature.

Helicobacter pylori has been implicated as an aetiological factor in some cases of urticaria, rosacea, vasculitis, Sweet's syndrome, erythema multiforme, alopecia areata, chronic itch and prurigo nodularis, and atopic and nummular dermatitis [6–8]. Although there are some individuals in whom eradication therapy coincides with resolution of a dermatosis, most larger studies in which there is adequate control for confounding factors such as age and social class have failed to demonstrate either a higher prevalence of *H. pylori* infection, higher titres on ^{13}C urea breath test, or a higher rate of response to eradication therapy in infected individuals compared with controls [9–12].

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Crohn's disease (regional ileitis)

Skin lesions are frequently seen in Crohn's disease [1–4]. These include:

- Crohn's disease occurring as direct extension from the bowel
- Cutaneous lesions of Crohn's disease at other skin sites
- Reactive lesions that are associated with Crohn's disease, but which do not have granulomatous histology
- Skin lesions related to malabsorption (Chapter 57)
- Skin lesions related to treatment: drug reactions, stoma dermatoses, etc.
- Other associated dermatoses.

Direct skin and mucosal involvement in continuity with the bowel

Cutaneous Crohn's disease may occur at sites in continuity with the bowel, such as the lip, stoma sites [5] or, commonly, the perineal skin. Orofacial granulomatosis and the overlap with Crohn's disease is discussed in Chapter 66. The umbilicus, a site connected to the bowel by a vestigial tract, may also be involved [6].

Perineal abscesses and multiple fissures and fistulae occur in about a quarter of patients ('watering-can peri-

neum'). This is more frequent in individuals with colonic disease [7] and may affect about 60% of patients, although symptoms may be absent. By contrast, such lesions are rare in ulcerative colitis. Anal tags, which may be oedematous or have granulomatous histology, are common.

Oral Crohn's disease is manifest as a thickened, corrugated appearance of the oral mucosa and lips. Granulomatous cheilitis may precede other features of Crohn's disease (Chapter 66).

Cutaneous Crohn's disease at other sites ('metastatic Crohn's disease')

Cutaneous Crohn's disease may also occur at sites separated from the bowel by normal tissues—a situation that is termed 'metastatic Crohn's disease', although not technically correctly [8–11]. Lesions may parallel gastrointestinal disease activity, or may occur with a totally separate temporal pattern.

Lesions of cutaneous Crohn's disease may be solitary or multiple, and may have varied morphology, including intact or eroded plaques and nodules, or sinus formation. The lower legs are involved in half of the cases, with lesions sometimes mimicking erythema nodosum, but cutaneous Crohn's disease may affect the abdominal wall, groin and inframammary flexures, face and other sites. Genital involvement may be a presenting feature, affecting the perineum [11], vulva [12], scrotum or penis [4,13]. Unusual patterns include perifollicular papules [14], erysipelas-like lesions [15] and necrobiotic lesions [16]. In any of these morphological variants, there is a granulomatous histology in the dermis and subcutis.

Treatments for both contiguous and 'metastatic' Crohn's disease include topical and intralesional corticosteroids, agents used to treat the bowel disease (oral corticosteroids, sulphasalazine and split products such as mesalamine, immunosuppressive agents), oral metronidazole, hyperbaric oxygen and recently antitumour necrosis factor-α monoclonal antibodies.

Reactive dermatoses associated with Crohn's disease

These include oral aphthae, erythema nodosum and a variety of neutrophilic dermatoses. As most of the reactive processes can occur with either type of inflammatory bowel disease, but most are more commonly associated with ulcerative colitis than with Crohn's disease, they are discussed later in this section.

Other dermatoses that have been associated with Crohn's disease

Epidermolysis bullosa acquisita (EBA) has been associated with both Crohn's disease and ulcerative colitis, mainly the former [17] (see also Chapter 41). In most instances, Crohn's disease had been established for several years prior to development of EBA, although EBA may precede diagnosis of the bowel disease [18]. This condition may be very refractory to treatment; drugs that may improve both the bowel disease and the cutaneous lesions of EBA include corticosteroids, azathioprine and ciclosporin.

Other bullous disorders that have been linked with Crohn's disease include *oral intraepidermal IgA pustulosis* [19] and *subcorneal pustular dermatosis* [20]; it has been suggested that the latter eruption was actually pustular pyoderma gangrenosum [21].

Polyarteritis nodosa (PAN) has been associated with Crohn's disease, but not specifically with ulcerative colitis [22,23]. It may be difficult to distinguish PAN from 'metastatic' Crohn's disease in patients with both disorders, as the histological features include a granulomatous component with the arteritis [24]; PAN may also resemble erythema nodosum or early pyoderma gangrenosum. The presence of livedo may suggest the diagnosis, but this can also occur due to cryoglobulinaemia. Other patterns of vasculitis associated with inflammatory bowel disease are discussed in the section on ulcerative colitis.

Psoriasis has been associated with Crohn's disease in several epidemiological studies [25], and vitiligo may also be associated.

In patients with Crohn's disease, apparently unrelated skin disorders may develop granulomas, for example hidradenitis suppurativa [26]. The presence of granulomas within predominantly neutrophilic infiltrates may cause diagnostic difficulty [27].

Disorders of keratinization that have been linked to Crohn's disease include *porokeratosis* [28] and *parakeratotic horns* [29].

Acrodermatitis enteropathica due to secondary zinc deficiency is a well-documented consequence of Crohn's disease [30] (Chapter 57).

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Ulcerative colitis [1–4]

Skin lesions occur in up to a third of patients with ulcerative colitis [2], although usually in the region of 10–15%. As with Crohn's disease, these fall into several categories:

- Reactive lesions (a similar spectrum, but commoner in ulcerative colitis than in Crohn's disease)
- Direct involvement contiguous with the bowel (fissures and fistulae; rare)
- Skin lesions related to malabsorption (Chapter 57)
- Skin lesions related to treatment: drug reactions, stoma dermatoses, etc.
- Other associated dermatoses.

Reactive lesions associated with ulcerative colitis and Crohn's disease

A variety of non-specific eruptions may occur with either ulcerative colitis or Crohn's disease, usually paralleling the activity of inflammatory bowel disease [5]. However, all of these may occur for other reasons or in isolation. They include:

- Erythema nodosum—this occurs in about 5% of patients with ulcerative colitis and in about 2% with Crohn's disease, and is the predominant pattern of reactive skin lesions in children [6].
- Aphthous ulceration [1]—this occurs in about 5–8% of patients with ulcerative colitis and a rather smaller proportion with Crohn's disease. In some instances, the mechanism may be malabsorption, leading to iron and vitamin deficiency. Oral aphthae also occur in isolation, in association with numerous medications and in other medical disorders (including other bowel disorders, such as coeliac disease).
- Erythema multiforme [7,8]—this may occur in either disorder, usually associated with active disease (or as a side effect of treatment).
- Urticaria and angio-oedema.
- Neutrophilic dermatoses—these also occur in association with other disorders, but pyoderma gangrenosum and pyostomatitis vegetans in particular are strongly associated with inflammatory bowel disease. These disorders are discussed in more detail below.
- Vasculitis and intravascular coagulation disorders—these also occur as a consequence of inflammatory bowel disease, most commonly active ulcerative colitis, and are discussed separately below.

Neutrophilic dermatoses

Pyoderma gangrenosum [9–12]. Pyoderma gangrenosum occurs as a complication of inflammatory bowel disease, haematological disorders, inflammatory arthritides and other medical conditions [10] (it is discussed more fully in Chapter 49). It is estimated to occur in about 2–5% of patients with ulcerative colitis, this disorder being the single commonest cause of pyoderma gangrenosum; it is three to five times commoner in patients with ulcerative colitis than in those with Crohn's disease. The ulcerative and pustular variants in particular are associated with inflammatory bowel disease. It may also occur in other bowel diseases, such as the bowel-associated dermatosis–arthritis syndrome (see below) and diverticular disease [13], as a peristomal dermatosis [14] and in patients with hepatitis. The characteristic lesions are rapidly progressive necrotic skin ulcers with a bluish-coloured undermined border, but nodular and pustular lesions may occur, especially in early disease. Trauma is sometimes a predisposing factor. Pyoderma gangrenosum generally parallels the activity of the colitis [1–4], but may precede the diagnosis [15] or occur many years after complete removal of the diseased bowel [16]. Treatments for pyoderma gangrenosum include corticosteroids (topical, oral, intralesional), dapsone, azathioprine, ciclosporin, mycophenolate mofetil, tacrolimus, chlorambucil, intravenous immunoglobulin,

and antitumour necrosis factor-α monoclonal antibodies [17–19].

Pyodermatitis–pyostomatitis vegetans [20,21] is a rare disorder of the oral mucosa and skin; the skin lesions were previously termed *pyodermite végétante*. The oral lesions consist of multiple pustules, plaques and erosions, which may have a 'snail's-track' appearance. The skin lesions are crusted papules and plaques, which coalesce into annular lesions, mainly affecting the major flexures and the scalp. There are similarities to pemphigus vegetans, but this is associated with strongly positive direct immunofluorescence of lesional skin, which is either negative or weak in pyodermatitis–pyostomatitis vegetans. Oral and skin lesions show the same histological features, having intraepidermal and superficial dermal microabscesses containing neutrophil and eosinophil polymorphs, and a more mixed deeper dermal inflammatory infiltrate. Acanthosis, acantholysis and pseudoepitheliomatous hyperplasia occur especially in the oral lesions. Most cases of pyodermatitis–pyostomatitis vegetans are associated with inflammatory bowel disease, usually ulcerative colitis, although the condition has also been reported with sclerosing cholangitis and in isolation. It is difficult to control; high-dose, systemic corticosteroids are the first-line therapy, but dapsone or azathioprine may be of benefit. Remission may occur following colectomy.

Acute febrile neutrophilic dermatosis (Sweet's syndrome) has been associated with inflammatory bowel disease, especially ulcerative colitis [22–25]. It may coexist with pyoderma gangrenosum [22,24], and may also occur after colectomy in patients with inflammatory bowel disease. It is discussed more fully in Chapter 49. Treatment options include corticosteroids, dapsone, non-steroidal anti-inflammatory drugs, colchicine, tetracyclines, ciclosporin and other immunosuppressive agents and, in the context of inflammatory bowel disease, metronidazole [25]. A neutrophilic colitis in a patient with Sweet's syndrome and acute myeloid leukaemia, and with previous Crohn's disease, was felt to be histologically distinct from Crohn's disease or ulcerative colitis [26].

Vesicopustular eruption and other neutrophilic dermatoses. A vesicopustular eruption may occur in ulcerative colitis [1,2,27,28], or less commonly in Crohn's disease [29]. The lesions consist of a dense neutrophilic infiltrate similar to that of pyoderma gangrenosum or Sweet's syndrome, and may be a variation of these [2,9]. In practice, many of the group of neutrophilic dermatoses may overlap, coexist or evolve from smaller papular or pustular lesions. Morphologically similar lesions in the bowel-associated dermatosis–arthritis syndrome may have vasculitic histology; features of this syndrome may also occur in patients with inflammatory bowel disease [30]. Treatment is similar to that of the other neutrophilic dermatoses.

Erythema elevatum diutinum has been reported with both Crohn's disease and with ulcerative colitis [31,32], as has oral intraepidermal IgA pustulosis [33,34].

Vasculitis and intravascular coagulation disorders

Vasculitis and purpura [1,2,35–37] may occur in either ulcerative colitis or Crohn's disease, most commonly in ulcerative colitis. The clinical picture is of a leukocytoclastic vasculitis with palpable purpura, typically affecting the lower legs and sometimes causing nodules or ulceration. Pustular lesions may have vasculitic histology. Joint pain and malaise may be prominent. Polyarteritis nodosa in Crohn's disease is discussed above.

Antineutrophil cytoplasm antibodies (ANCA) are present in 60–70% of patients with ulcerative colitis and 5–10% with Crohn's disease [38].

Cutaneous gangrene and focal thrombosis [39] is a rare complication. Patients with ulcerative colitis have significant coagulation defects; in one large early series, this was sufficient to complicate the clinical course in more than 1% of patients [40]. Abnormalities underlying this tendency include thrombocythaemia, elevated levels of fibrinogen, factor VIII and factor V, and decreased levels of antithrombin III. Microvascular thrombosis of the skin may result in cutaneous gangrene. High-dose systemic steroids have no effect on the thrombotic complications, which should be treated with anticoagulant therapy. Similar features have been reported due to cryoglobulinaemia associated with inflammatory bowel disease.

Other cutaneous disorders associated with ulcerative colitis

Linear IgA disease. Linear IgA disease may be relatively common in patients with ulcerative colitis, which usually precedes the dermatosis by several years [41]. Linear IgA disease may resolve after colectomy has been performed [42]. Whether these patients actually have ulcerative colitis or a specific colitis associated with linear IgA disease is uncertain; two recent patients with preceding bowel symptoms developed oral ulceration and were found to have linear IgA deposition in mouth and colon. The bowel histology was that of a lymphocytic colitis or Crohn's disease [43]. Linear IgA disease has also been associated with Crohn's disease [44].

Hermansky–Pudlak syndrome (MIM #203300) (Chapter 39) may be associated with inflammatory colitis that resembles ulcerative colitis but has a granulomatous infiltrate pathologically; this appears to be distinct from either ulcerative colitis or Crohn's disease [1,45].

Ulcerative colitis has been linked with a variety of autoimmune disorders and with sarcoidosis [46,47], although the strength of this association is not clear. Finger clubbing

may be associated with inflammatory bowel disease, particularly ulcerative colitis [48], as well as with several other gastrointestinal diseases, including tumours, chronic infections, protein-losing enteropathy and laxative abuse [49]. Acne fulminans has also been reported in association with inflammatory bowel disease [50].

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Bowel-associated dermatosis–arthritis syndrome [1–6]

SYN. BLIND LOOP SYNDROME; BOWEL BYPASS SYNDROME; INTESTINAL BYPASS ARTHRITIS–DERMATITIS SYNDROME

This is a serum sickness-like illness which is related to bacterial overgrowth in the bowel. Bacterial antigens in the form of peptidoglycans are probably released from the

intestinal flora, particularly *Escherichia coli* [2]. Circulating immune complexes can be demonstrated in most patients actively developing skin lesions [3].

It was originally linked with bowel bypass surgery for obesity [1–4], which created a 'blind loop' of bowel. Most cases now are related to other causes of a blind loop, or simply to areas of stasis, and the condition has attracted the name 'bowel bypass syndrome without bowel bypass' [6]. Causes include achalasia [7], strictures and inflammatory bowel disease [5], as well as surgical procedures. Pyoderma gangrenosum secondary to diverticular disease [8] is probably in the same spectrum of disease.

The characteristic skin lesions are crops of erythematous papules, sterile vesicopustules similar to those associated with ulcerative colitis, or overtly indurated or necrotic vasculitic lesions. Erythema nodosum-like and panniculitis-like lesions may occur. Associated constitutional symptoms include fever, polyarthritis, tenosynovitis, myalgia and nephritis. Raynaud's phenomenon has been described, as has Sweet's syndrome. The joint involvement is variable and similar to the type of arthritis recognized in regional ileitis and ulcerative colitis. The bypass enteropathy may manifest itself as acute massive abdominal distension resembling intestinal obstruction, but milder and chronic forms have been described.

Histological examination shows dilated dermal venules and capillaries with a marked perivascular neutrophilic infiltrate. This is most pronounced in vesicopustular lesions, in which the resulting dermal oedema may lead to dermal–epidermal separation. Epidermal necrosis may be found. Treatments include oral corticosteroids, antibiotics such as metronidazole, a variety of immunosuppressive medications and restorative surgery.

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Skin complications of stomas [1,2]

Dermatoses associated with a stoma include those related to the function of the stoma (irritation from faecal leakage, infections, contact dermatitis), Koebner reaction of existing or new dermatoses (psoriasis, lichen sclerosus) and disorders related to bowel disease (peristomal pyoderma gangrenosum, cutaneous Crohn's disease) [1,2].

The skin around a gastrointestinal or urinary tract stoma is liable to irritation from the effluent, the wafer and pouch, and substances applied as barriers, adhesives and cleaners. The collection pouch is either attached to a wafer or directly to the skin; a barrier/sealant may be applied before adhesion. This is either a gelatin–pectin formulation, karaya (a hygroscopic partially acetylated polysaccharide), or a flexible plastic, applied in liquid form. The adhesives are usually acrylic, silicone or latex. Ideally, the wafer should adhere perfectly to the skin, with a rim of skin 1–2 mm between the stoma and the appliance. If this rim is too narrow, chafing against the stomal mucosa will occur, and if it is too wide there is a higher risk of dermatitis. Any surface irregularities beneath the attachment surface will allow effluent to track beneath. This may occur if there are changes in body weight, or if there is incorrect or unavoidable siting of the stoma in body folds or adjacent to scars.

Enzyme-degradation dermatitis, caused by proteolytic enzymes in an alkaline fluid medium, is commonest with ileostomies [3], and presents with maceration, erythema and erosions. Because of the tracking of the fluid downwards, the pattern of dermatitis depends on the patient's predominant position. Diversion of the urinary stream also causes problems because of stagnation and ammonia production.

Treatment. Most peristomal skin disease is irritant and is treated by judicious use of topical corticosteroids together with soothing and barrier preparations. Infections such as *Candida* or pyogenic bacterial infection should be treated with an appropriate specific antimicrobial agent. Many types of protective wafer and protective powders are available. These contain gelatin, pectin, polyisobutylene and sodium carboxy-methylcellulose. They adhere to moist skin and allow healing to take place if they are left for about 3 days. Creases and crevices around a stoma or fistula can be filled using pastes, which generally consist of gelatine, sodium carboxy-methylcellulose, triacetin, fixin and ethanol. They are applied in layers, moulded into the creases with a moist finger and built up to the required level. If the drainage application can then remain in position for several days, this will usually allow the damaged skin to heal. Other topical treatments for irritant peristomal dermatoses include soothing compresses (for example, saline or 1 : 40 aluminium acetate), karaya and sucralfate [3].

Allergic contact dermatitis can occur to the adhesive [4], the barrier or any part of the appliance. Epoxy resins have been a problem in pouch materials, even though they are often present in small amounts only [5]. It has been suggested that patch testing should be carried out on the symmetrically opposite part of the abdomen [1]. It

is usually possible to provide substitutes for materials causing the allergic reaction.

Urostomy encrustations and acanthotic chronic papillomatous dermatitis (pseudoverrucous lesions). The encrustations are crystals of phosphates and sometimes uric acid that form on the stoma and can damage the mucosa and even the bag. Pseudoverrucous lesions are grey or reddish-brown, warty papules at the mucocutaneous junction. They are more common around urostomies than around gastrointestinal stomas, occurring in about 20% of urostomy patients. There may be a non-specific erythematous and erosive change [6]. Stagnation and urinary infection are important in the aetiology of both encrustations and pseudoverrucous lesions and, as well as treating infection, acidification of the urine is helpful—for example, with cranberry juice or vitamin C in large doses [1]. Peristomal viral warts are a particular differential-diagnostic problem.

Parastomal fistulae and ulcers [7] are particularly associated with ileostomy for Crohn's disease and may represent or herald recurrent disease. Fistulae are often preceded by abscesses, and may be multiple. The parastomal ulcer is defined as a defect in the surface 1.5 cm or more across. It is typically accompanied by severe burning pain and erythema, and often associated with induration and erythema of the stoma [8]. Low-grade infection should be considered as a possible cause in parastomal ulcers that occur early after formation of the stoma, but in late-appearing ulcers, recurrent Crohn's disease is probably the most important underlying cause. Treatment of both parastomal ulcers and fistulae is usually surgical.

Dermatoses. Psoriasis and pemphigus have been described as a result of the Koebner reaction around 'ostomies' [9], and pyoderma gangrenosum can localize to the peristomal skin after colectomy for inflammatory bowel disease [10,11], and much less commonly in relation to urostomies. A papular, erythematous condition similar to granuloma inguinale infantum has been described following intensive use of a potent fluorinated steroid around a colostomy site [12].

Neoplasms. BCC has been described as a long-term complication of colostomy [13]. Metastatic carcinoma at the stoma site, sometimes invading the surrounding skin, has been reported following ureterosigmoidostomy [14] and in patients who have had colectomy for ulcerative colitis [15–18].

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Coeliac disease

Coeliac disease usually presents due to malabsorption and diarrhoea. There may be cutaneous features of malabsorption of nutrients (Chapter 57). The association with dermatitis herpetiformis (DH) is of specific dermatological relevance and is discussed in detail in Chapter 41; some degree of abnormality of small-bowel mucosa is present, even if minimal and asymptomatic, in all patients with DH. A significant increase in the frequency of coeliac disease in patients with inflammatory bowel disease has been suggested recently.

Diagnosis of coeliac disease can be made by serological tests for IgA antiendomysial antibodies—sensitivity is reported as 85–98% and specificity as 97–100% [1]. These antibodies recognize tissue transglutaminase, which acts as an autoantigen—it deaminates gliadin to create negatively charged glutamic acid residues that activate T cells. IgA antigliadin antibodies are less specific. Antigliadin, antiendomysial and tissue transglutaminase antibody levels all become undetectable after a period of 3–6 months on a strict gluten-free diet (GFD). Other tests include documentation of malabsorption and small-bowel biopsy. Darkening of previously white hair has been reported after starting GFD to treat coeliac disease [2]. Coeliac disease occurs in association with other autoimmune disorders, notably Addison's disease [3], and has been

reported following interferon treatment for hepatitis C and other disorders [4].

Improvement of psoriasis in a small number of patients who were treated with GFD suggested the possibility that coeliac disease and psoriasis might be associated. Patients with psoriasis have a high frequency of positive IgA antigliadin antibodies, which correlate with lymphocytic infiltration of the duodenal mucosa but do not have an increased incidence of coeliac disease, and there is no increase in antireticulin or antiendomysial antibodies [5,6].

There is an association between DH and internal malignancies, the most important being lymphoma of the small bowel (enteropathy-associated lymphoma) [7,8]. GFD exerts a protective effect [8].

Vasculitis, sometimes with cryoglobulinaemia, may occur in association with coeliac disease [9].

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Whipple's disease

This disorder is another cause of malabsorption and diarrhoea, which may be accompanied by skin manifestations. Diffuse pigmentation is frequent, and may resemble Addison's disease, but buccal pigmentation is not a feature. Subcutaneous nodules may occur, resembling rheumatoid nodules or sarcoidosis [1–3]. The disorder usually presents with arthralgia and general malaise; abdominal features (pain, diarrhoea and malabsorption leading to weight loss) occur in most individuals with more advanced disease. Cardiac, pleural, ophthalmological or neurological symptoms also occur, and there may be generalized lymphadenopathy. The diagnosis has historically been confirmed by demonstration of periodic acid–Schiff-positive particles in biopsies from infected tissue (usually bowel mucosa). The diagnosis can now be made using polymerase chain reaction (PCR) amplification of sequences from the causative organism *Tropheryma whippelii* in infected tissue [4].

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Skin disorders associated with gastrointestinal bleeding

These are listed in Table 59.4. Most are discussed elsewhere in this section, or in other chapters. In addition, gastrointestinal tumours may metastasize to skin (see earlier in this chapter), some tumours may affect the skin and gastrointestinal tract (e.g. Kaposi's sarcoma), and skin tumours may rarely metastasize to the gastrointestinal tract (e.g. melanoma).

Several patterns of cutaneous vasculitis or collagen vascular disease may be associated with mesenteric vasculitis and/or thrombosis, leading to bleeding or ulceration. Various radiological signs of mesenteric vasculitis seen on computed tomography (CT) have been reviewed in relation to systemic lupus erythematosus, and include a palisade and comb-like pattern of vessels, peritoneal enhancement of ascitic fluid, thickening of the bowel wall, and a 'double-halo' or 'target sign' [1,2].

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Intestinal polyposis [1,2]

A number of, usually inherited, gastrointestinal polyposis disorders also have cutaneous features. The most important are:

- Peutz–Jeghers syndrome
- Gardner's syndrome
- Cowden's disease (multiple hamartoma syndrome)
- Bannayan–Riley–Ruvalcaba syndrome (Ruvalcaba–Myhre–Smith syndrome, Bannayan–Zonana syndrome)
- Cronkhite–Canada syndrome
- Birt–Hogg–Dubé syndrome
- Naevoid BCC syndrome [3]
- Neurofibromatosis (Chapter 12).

Additionally, ganglioneuromas of the gastrointestinal tract and oral mucosal neuromas may be associated with Hirschsprung's disease and colonic diverticula as features of MEN type 2B syndrome.

Table 59.4 Skin lesions associated with gastrointestinal disorders that may present with bleeding.

Disease	Gastrointestinal lesion	Skin symptom
Vascular defects and inherited		
Osler–Weber–Rendu disease (Chapter 50)	Telangiectasia	Telangiectasia
Blue rubber bleb naevus (Chapter 15)	Haemangiomas	Haemangiomas
Pseudoxanthoma elasticum (Chapter 46)	Involvement of visceral arteries	Yellowish papules and plaques
Ehlers–Danlos syndrome (type IV) (Chapter 46)	Fragility of visceral arteries	Hyperelasticity of skin and joints
Polyposis (see text in this chapter)		
Neurofibromatosis (von Recklinghausen)	Neurofibromas	Café-au-lait spots, neurofibromas
Cronkhite–Canada syndrome	Gastrointestinal polyposis	Diffuse hyperpigmentation, alopecia, nail defects
Gardner's syndrome	Polyposis of colon (cancer)	Lipomas, epidermoid cysts
Peutz–Jeghers syndrome	Polyposis, especially small intestine	Hyperpigmentation on lips, circumoral area and fingertips
Cowden's disease	Polyposis	Papules, lipomas, angiomas
Inflammatory bowel disease		
Crohn's disease, ulcerative colitis	Inflammatory changes of the intestinal wall	Erythema nodosum Aphthous stomatitis Pyoderma gangrenosum, other neutrophilic dermatoses Necrotizing vasculitis Acquired epidermolysis bullosa Erythema multiforme
Vasculitis and systemic disease		
Henoch–Schönlein purpura and other vasculitides (Chapter 49)	Mesenteric vasculitis, gastric ulcers (polyarteritis nodosa)	Purpura, livedo, nodules, necrosis
Cholesterol emboli (Chapter 48)	Intestinal arterial occlusion	Vasculitis, necrosis, livedo
Degos' disease (Chapter 48)	Intestinal perforation	White atrophic lesions
Amyloidosis (Chapter 57)	Vascular fragility	Purpuric lesions
Neoplasia		
Primary gastrointestinal cancers	Neoplasm	Metastases, paraneoplastic eruptions, features of polyposis syndromes
Kaposi's sarcoma (Chapter 26)	Kaposi's sarcoma of bowel	Kaposi's sarcoma of skin

Peutz–Jeghers syndrome (MIM #175200) [4]. This is an autosomal-dominant or sporadic condition due to mutations in the *STK11* (*LKB1*) gene on chromosome 19p13.3 [5–7]. Polyps occur mainly in the small intestine, but also in the stomach and colon. The usual presentation is with intussusception or melaena. Polyps can also be found in the genitourinary and respiratory tracts, and occasionally in the gallbladder.

The cutaneous feature is lentiginosis, with a predominantly perioral, periorbital and intraoral distribution; perianal and acral lentiginosis (occasionally causing longitudinal melanonychia) also occurs. The pigmented macules appear in early childhood and may fade with increasing age, although the mucosal lesions persist [4].

Cancers may occur in the gastrointestinal tract, but the frequency is relatively low, as the polyps are hamartomatous. However, there is an increased risk of non-gastrointestinal cancers, with an overall risk estimated at 18-fold greater than that of the general population [8]. Other associated neoplasias include pancreatic adenocarcinoma (100-fold more common than expected [8]), and less commonly breast and pulmonary adenocarcinoma. Multiple myeloma may occur more frequently than expected. Precocious puberty may occur in either sex, and a variety of genital cancers have been associated with PJS, including Sertoli cell tumours; there is a particular link with multifocal sex-cord tumours and an aggressive variant of adenocarcinoma of the cervix [1]. Finger clubbing may occur in conjunction with the ovarian sex-cord tumours.

Gardner's syndrome (MIM *175100) [6,7,9]. This is the association of adenomatous colonic polyposis with large numbers of subcutaneous fibromas, epidermoid cysts (both mainly on the upper trunk and head), desmoid tumours (mainly abdominal wall), retinal pigmentary changes, osteomas (especially of the facial bones), odontomas and other dental abnormalities, including supernumerary teeth [9]. The onset of cysts is generally prepubertal. Multiple pilomatricomas, or pilomatricoma-like areas within the epidermoid cysts, have also been recorded. The occurrence of fibromas may involve a general tendency to fibromatosis, including desmoid tumours, mesenteric and retroperitoneal fibrosis. Nuchal-type fibromas [10], especially if multiple or at unusual sites [11], may be an early sign of the syndrome. Leiomyomas, lipomas, neurofibromas and BCCs may also occur [9].

It is an autosomal-dominant condition with variable

expression, and is caused by mutations in the same APC gene on chromosome 5q21 that also causes familial polyposis coli without associated cutaneous abnormalities [1,6,7]. The phenotype is not simply determined by different mutations of the gene, as exactly the same mutation may on occasions give rise to a phenotype with or without skin lesions—suggesting that other genes influence the disease expression. There are also subsets of this condition in which skin lesions may be limited in type; for example, epidermoid cysts and colonic polyposis without the other features has been termed Oldfield's syndrome [12]. Skin lesions are usually the earliest manifestation of this group of diseases, although the retinal pigmented lesions (hypertrophy of the pigment epithelium) occur in 90% and are probably congenital. The latter are dark, roughly oval-shaped lesions, at the periphery of the retina; they are generally multiple, bilateral, and also occur in first-degree relatives [13].

The bowel polyps are premalignant, and virtually all untreated cases will eventually develop colonic cancer, even in childhood occasionally, so regular colonoscopy and early colectomy is advised for affected individuals. The colon and rectum are the main cancer sites, but gastric and small-bowel polyps may occur. There is also an increased incidence of other neoplasia, which may be gastrointestinal (especially duodenal), bony (osteosarcoma and chondrosarcoma), hepatic (hepatoblastoma), neurological (medulloblastoma), endocrine (thyroid and adrenal) or soft tissue (liposarcoma) [8]. The diagnosis is usually suspected from the family history, can be supported by funduscopy and dental radiological studies and is confirmed by genetic testing.

Cowden's disease (multiple hamartoma syndrome; MIM #158350) [1,2,14–17]. Gastrointestinal polyposis and less commonly malignant change occur. However, the main neoplastic condition in Cowden's disease is breast cancer; this condition is therefore discussed in more detail in the section on paraneoplastic dermatoses earlier in this chapter.

Bannayan–Riley–Ruvalcaba syndrome (Ruvalcaba–Myhre–Smith syndrome; Bannayan–Zonana syndrome MIM *153480). This multiply named syndrome comprises gastrointestinal polyposis with vascular malformations, lipomas, penile pigmentation, macrocephaly and thyroid disease. There is considerable overlap with Cowden's disease, and recent studies have demonstrated mutations that suggest a common genetic background [18,19].

Birt–Hogg–Dubé syndrome (Hornstein–Knickenberg syndrome; MIM #135150) [20–22]. These two conditions probably represent the same entity, in which there is autosomal-dominant inheritance. Birt–Hogg–Dubé syndrome consists of multiple fibrofolliculomas, trichodiscomas and acrochordons; several cases have also had intestinal polyposis. Hornstein–Knickenberg syndrome is the association of perifollicular fibromas with intestinal polyposis. Lipomas, angiolipomas, parathyroid adenomas, renal tumours, lung cysts and flecked choroidoretinopathy have also been linked with these conditions.

Cronkhite–Canada syndrome (MIM 175500) [23–25]. This rare syndrome is characterized by skin pigmentation, alopecia, nail-plate defects and polyposis of the gastrointestinal tract, from oesophagus to anus. The cause is unknown, and only sporadic cases have been reported. Affected patients are middle-aged or elderly, with a male/female incidence ratio of 3 : 2.

Chronic diarrhoea due to protein-losing enteropathy associated with the intestinal polyposis is the usual presenting feature, leading to hypoalbuminaemia, hypokalaemia and hypocalcaemia. There is diffuse macular pigmentation of the skin (but not intraorally) with accentuation over the face, neck and extremities; histologically, there is an increased number of melanin granules in keratinocytes and an increased number of melanosomes in melanocytes, with marked hyperkeratosis and a perivascular inflammatory infiltrate in the dermis. The palms and volar aspects of the fingers are also involved. The scalp hair becomes thin and sparse, initially resembling alopecia areata; later, total loss of hair occurs. All fingernails and toenails are dystrophic, undergoing onycholysis, onychoschizia and onychomadesis with a peculiar, triangular, residual nail plate. The course is usually slowly progressive; therapy is symptomatic and non-specific.

Acrochordons (fibroepithelial polyps, 'skin tags'). Several studies have suggested a link between acrochordons and colonic polyposis [1,2]. However, most of these studies were either small or examined only a population who were being investigated for bowel disease. A meta-analysis that divided patients into those with colonic symptoms and those who were asymptomatic demonstrated that the association was only sustained in the former group, and that this was therefore an artefact of patient selection [26].

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Liver disease

Hepatobiliary diseases are frequently associated with abnormalities of the skin, nails and hair. However, most are non-specific, as they may be present in other diseases and absent even in patients with advanced liver dysfunction—jaundice, for example, may occur due to haemolysis rather than due to liver damage. Additionally, many diseases may share the same cutaneous features (for example, most causes of cirrhosis cause the same clinical signs), and there is no clear correlation between the degree of the skin changes and the severity of liver dysfunction. However, there may be constellations of features that suggest specific diagnoses (e.g. pigmentation, jaundice and xanthomas in primary biliary cirrhosis). The overall picture of the patient may therefore be as useful as the presence of particular cutaneous signs.

This section will discuss some of the main groups of hepatobiliary disease, followed by some of the more important symptoms and signs.

Hepatitis and acute liver disease

Acute hepatic damage is most often due to viral hepatitis, alcohol or other drugs. Cutaneous features may be absent, or there may be jaundice. Other features may occur, depending on the cause. Most of the cutaneous features of alcohol excess are related to chronic abuse and are considered later; flushing and, uncommonly, urticaria may occur as short-term effects. This section considers the dermatological associations of infective hepatitis [1–10].

Hepatitis A virus infection is usually asymptomatic and transient. Dermatological features, if present, are jaundice, urticaria (less than 2%) and exanthem. Chronic liver disease is not a feature, but a relapsing variant has been described in which itch, purpura and urticarial lesions occur [2]. Histology in such cases demonstrates a small-vessel vasculitis. More severe vasculitis or panniculitis is rare.

Hepatitis B virus (HBV) infection [1,3,4] is of major relevance to health care workers, as it may be transmitted parenterally. It is also transmitted sexually, and HBV infection may be associated with other sexually transmitted diseases. HBV screening and vaccination are recommended for all health care workers; routine HBV screening may be recommended for patients attending genitourinary medicine clinics, but at present is usually targeted to high-risk groups (human immunodeficiency virus (HIV)-positive individuals and parenteral drug abusers). Vaccination is not without dermatological side effects—provocation of granuloma annulare, lichen planus, Gianotti–Crosti syndrome, urticaria and contact reactions to excipients have all been reported [11–14].

Dermatological features of acute HBV infection include:

- Urticaria, non-specific erythema or a serum sickness-like picture (generalized malaise, fever and arthralgia)—this occurs in 20–30% of patients with hepatitis [3]. Angioedema, erythema multiforme or erythema nodosum-like lesions may occur. Circulating immune complexes are probably involved [4], and skin biopsy shows small-vessel vasculitis with positive direct immunofluorescence for IgG, IgM, complement C3 and hepatitis B surface antigen (HB_sAg). This eruption may precede other features of infection, or may occur as recurrent urticaria after infection.
- Gianotti–Crosti syndrome (papular acrodermatitis of childhood, papulovesicular acrolocated syndrome)—this eruption was originally linked with HBV infection, although accumulated knowledge documents that it is a

feature of numerous viral infections. Lesions consist of small, umbilicated papules, often affecting the knees, buttocks, cheeks and extremities; the lesions usually last about 6–8 weeks and are associated with non-specific malaise in the early phase.

- Polyarteritis nodosa (PAN)—about 20% of patients with PAN may have positive HBV serology, but the frequency has decreased considerably over the last 20 years, some units that previously expected HBV positivity in 30–50% of cases only finding this in 10% now. PAN is discussed in Chapter 49.
- Cryoglobulinaemic vasculitis—about 15% of patients with HBV have detectable cryoglobulins, although most have no symptoms. The association is more important in hepatitis C.
- Other skin lesions—pyoderma gangrenosum, lichen planus and dermatomyositis have been reported with HBV infection.

Hepatitis C virus (HCV) infection (previously termed non-A, non-B hepatitis) is usually transmitted parenterally. Acute HCV infection is usually only mildly symptomatic; chronic hepatitis occurs in about 75%, but progression varies considerably [6–8]. The main dermatological features [1,6–9] are:

- Mixed cryoglobulinaemia, usually type II (polyclonal IgG and monoclonal IgM rheumatoid factor) and less commonly type III (polyclonal IgG and polyclonal IgM rheumatoid factor). About 70% of type II cryoglobulinaemia is HCV-associated; the major idiotype in the monoclonal rheumatoid factor is different from that in rheumatoid arthritis, but commonly present in primary Sjögren's syndrome. Features of the cryoglobulinaemic vasculitis include small-vessel vasculitis (mainly on the legs), livedo reticularis, acrocyanosis, arthralgia, glomerulonephritis, peripheral neuropathy, hepatosplenomegaly and hypocomplementaemia. Other patterns of vasculitis may also occur.
- PAN—in patients with 'classic' PAN in whom hepatitis virus is of relevance, the association is usually with HBV rather than HCV infection, but preceding HCV infection has been reported in up to 30% of patients with the cutaneous variant of PAN [15]. Hypocomplementaemia seems to be more common in patients with cutaneous PAN who also have HCV infection, but the numbers of patients studied is small.
- Porphyria cutanea tarda (PCT) is most commonly associated with alcoholic liver disease and with hereditary haemochromatosis. However, in countries where there is a low prevalence of haemochromatosis, serological evidence of chronic HCV infection can often be demonstrated in patients with PCT; the prevalence of positive HCV serology in PCT varies from about 10% to 90%, depending on geography [16]. HCV has also been linked to variegate porphyria. A case–control study in the USA found that 16 of 17 patients with PCT were HCV-positive (94%), compared with 0.17% of nearly 150 000 volunteer blood donors (although these may not be fully representative of the general population) [16], and HCV positivity is now viewed as an important risk factor in development of PCT [17,18]. However, PCT appears to be uncommon as a manifestation of HCV positivity. A large study of patients with HCV or HIV infection, or both, only found one of 177 patients to have a PCT porphyrin excretion pattern and did not support a direct role of HCV in provoking PCT. However, the mean coproporphyrin level was significantly raised in HCV-positive patients and especially in those who were also HIV-positive [19].
- Autoimmune disorders. There are associations between HCV infection and lichen planus, autoimmune thrombocytopenic purpura, Behçet's disease, vitiligo and a Sjögren's syndrome-like sialadenitis.
- Other dermatological symptoms. Pruritus may be a presenting symptom of HCV infection, and persistent itch may occur [9]. Urticaria, erythema multiforme and erythema nodosum have been reported, but are not a specific feature. Necrolytic acral erythema is a recently described and apparently specific, if rare, feature of acute HCV infection [10].

Treatment of HCV infection and associated cryoglobulinaemia is with antiviral agents, typically interferon with ribavirin.

Hepatitis D causes cutaneous features similar to those of HBV. Hepatitis E is generally mild, but may cause disseminated intravascular coagulation [1]. Hepatitis F is disputed, and hepatitis G is usually transmitted parenterally [20].

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Cirrhosis of the liver

Cutaneous features of chronic liver disease are listed in Table 59.5 [1,2]. Causes include chronic hepatitis (above), alcohol abuse and others—some of the idiopathic causes are discussed below, as each has some specific features in addition to those that occur in liver failure of any cause.

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Haemochromatosis [1–8]

Hereditary (idiopathic or HLA-linked) haemochromatosis (bronze diabetes) is an autosomal-recessive disorder that is usually associated with mutations C282Y (cysteine 282 tyrosine) or H63D (histidine 63 asparagine) of the *HFE* gene [4,5]. Other genes in which mutations cause haemochromatosis include the gene for ferroportin (*SCL11A3*) [6]. Haemochromatosis usually presents in males over the age of 40 years. An acquired form also occurs, secondary to haemosiderosis or alcohol abuse. There is increased iron absorption leading to iron deposition in various organs, including the liver, pancreas, heart, pituitary and endocrine organs. Skin pigmentation, diabetes, hepatic cirrhosis and cardiac failure are prominent features [2,3,7]. Dryness of the skin and koilonychia may have been underestimated in the past [8]; stigmata of chronic hepatic failure may also be present. Deposition of iron in the skin has been used as a surrogate for deposition in other organs [9,10]; in idiopathic haemochromatosis, iron deposition includes deposition in eccrine sweat glands [8]. However, the pigmentation of haemochromatosis is due to melanin rather than to haemosiderin [2,3,7]. It typically has a grey hue, and is most prominent on exposed skin, similar to Addisonian pigmentation. Keratin cysts with a black colour have also been reported [11].

There is a 200-fold increase in the risk of hepatocellular carcinoma compared with the general population [3].

PCT has been linked with haemochromatosis for some years [7,12,13]. It has subsequently been shown that homozygosity for the C282Y mutation and seropositivity for HCV are the greatest risk factors for expression of PCT [14] and that they appear to act as independent co-factors [15]. In patients with mutations in uroporphyrinogen decarboxylase, which leads to PCT, coinheritance of C282Y homozygosity is associated with earlier age of onset of PCT [16].

Table 59.5 Skin lesions associated with chronic liver disease.

Spider angiomas, telangiectasia
Palmar erythema
Dilated abdominal/chest veins (including periumbilical caput medusae)
Jaundice
Increased melanin pigmentation
Thin 'paper-money' skin, striae
Excoriations
Loss of secondary sexual hair in males
Bruising, purpura
Nail changes: clubbing, pallor, Muehrcke's bands, Terry's nail
Features of malnutrition (see Chapter 57)
Associated lesions
Xanthomas (primary biliary cirrhosis)
Porphyria cutanea tarda (alcoholic liver disease)
Vasculitis/capillaritis/pyoderma gangrenosum (chronic active hepatitis)
Lichen planus (primary biliary cirrhosis)

Primary biliary cirrhosis and biliary tract disease

From the dermatological standpoint, primary biliary cirrhosis (PBC) is the most important biliary tract disease. The cutaneous features of significance are marked itch (discussed in more detail below), excoriation, hyperpigmentation and various xanthomatous lesions due to secondary hyperlipidaemia [17,18]. Xanthelasma, palmar crease, tuberous and tendinous xanthomas may all occur. PBC occurs mainly in middle-aged women as an autoimmune disease, is strongly associated with the presence of antimitochondrial antibodies (AMA), and has been associated with numerous other autoimmune conditions, including CREST, morphoea and other scleroderma spectrum disorders, lichen planus and lichen sclerosus [17–23]. The constellation of CREST with PBC is also known as Reynolds' syndrome, and is usually associated with M2 antibodies. Sarcoidosis [24] and other patterns of granulomatous disease such as granuloma annulare are also reported. There is a strong link with Sjögren's syndrome—about 10% of patients with Sjögren's syndrome have AMA, sometimes with abnormal liver function tests

or liver histology, and over half of patients with PBC have some evidence of Sjögren's syndrome [25]. Itch is often the first symptom of PBC, so serology to detect AMA is a useful screening test in women with unexplained pruritus; AMA-negative PBC causes particular diagnostic difficulty.

Cholestasis and bile stones may cause acute or chronic jaundice and other features of liver disease. Pigment bile stones may occur due to erythropoietic protoporphyria.

Congenital biliary tract hypoplasia is a feature of Alagille's syndrome (MIM #118450) [26], a dominantly inherited disorder due to a gene mutation on chromosome 20p12. Affected individuals have a characteristic facies, jaundice, pruritus and retardation of growth and mental development. Various skeletal, ocular and vascular defects are associated.

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Drugs and the liver

Drug-related links between the skin and the liver include the following:

- Drugs used to treat the skin, whose hepatic metabolism is altered by liver disease or by other drugs that are also metabolized in the liver, e.g. ciclosporin.
- Drugs used to treat skin disease that may cause hepatitis or other liver damage, e.g. azathioprine, methotrexate.
- Drugs used to treat liver disease that may have cutaneous side effects, e.g. local reactions to vitamin K (Texier's syndrome), elastosis perforans serpiginosa due to penicillamine for Wilson's disease.
- Drugs used to prevent liver disease that may have cutaneous side effects, e.g. local reactions due to thimerosal or other preservatives in hepatitis vaccines.
- Drugs that cause liver changes with secondary cutaneous signs, e.g. oestrogens leading to PCT.
- Drugs that may cause concurrent hepatitis and rash, e.g. phenytoin and other anticonvulsants.

Systemic diseases and the liver

A large number of systemic diseases may affect the liver, many with cutaneous features. Most are discussed in other chapters. For example, sarcoidosis is associated with subclinical hepatic involvement in over 50% of patients, but may cause overt hepatomegaly or abnormalities of liver function in conjunction with skin lesions.

Porphyrias, especially PCT, may occur as a consequence of liver disease (see Chapter 57 and the discussion of PCT below); severe liver disease is also a feature in some patients with erythropoietic protoporphyria.

Dermatological features and dermatoses associated with liver disease

Pruritus

Pruritus is the most common skin symptom associated with liver disease. It may precede the onset of jaundice of

any cause, and may be a feature of hepatitis, as discussed above. Liver diseases in which itch is most prominent are PBC, sclerosing cholangitis and any other biliary tract obstruction, and disorders causing cholestasis; itch is less prominent in haemochromatosis, alcoholic cirrhosis and autoimmune chronic active hepatitis [1]. The symptoms are generally most severe at acral sites and areas of tight clothing, and are more prominent nocturnally. Disappearance of pruritus may accompany severe deterioration in hepatic function [2].

The precise mechanism of itch in obstructive liver disease remains unclear. It was believed to be due to the presence of bile salts in the skin [3,4], but the intensity of itch does not reliably correlate with bilirubin or bile acid levels in chronic liver failure, and this theory is not supported by more recent research [1,5]. Other proposed mediators of cholestatic itch include alternative liver metabolites, histamine or other mast cell mediators, and endogenous opiates. Although patients with cholestasis may have elevated plasma histamine levels, the therapeutic response to antihistamines is limited, and it is unlikely that release of histamine plays an important role in the pathogenesis of hepatobiliary itch [1]. Improvement in hepatic itch after administration of drugs that block the action of opiates suggests that endogenous opiates may be important in the mechanism of this type of itch [6–8].

Treatment where possible is for the underlying cause—for example, drug withdrawal in drug-induced cholestasis, surgery for mechanical biliary obstruction, interferon and ribavirin for chronic HCV infection, etc. Less specific options include ursodeoxycholic acid, cholestyramine, phenobarbital, anabolic steroids such as stanozolol, rifampicin, antihistamines and dietary manipulation to supplement polyunsaturated fatty acids [1,9,10]. Phototherapy of various types—daylight, ultraviolet A (UVA), ultraviolet B (UVB), photoirradiation of plasma and extracorporeal photophoresis—can be effective, but ongoing treatment is generally required [1,11,12]. Other treatments that have been used with success include haemoperfusion or plasma perfusion through charcoal-coated beads (which can produce benefit lasting several weeks), plasmapheresis, infusions of albumin (benefit for a few days) and slow injection of intravenous lidocaine (lignocaine) (which produces short-term benefit only). On the basis that endogenous opiates play a role in this symptom, and that these have a circadian rhythm regulated by light, bright-light therapy to the eyes was studied and found to reduce cholestatic itch in a short-term study [13].

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Skin pigment changes in liver disease [1–3]

Jaundice (icterus) is first visible as a yellowish hue of the sclerae and soft palate before it becomes generalized. It is due to hyperbilirubinaemia. Carotenaemia may have a similar appearance but does not affect sclerae; skin discoloration following mepacrine and busulphan therapy may simulate jaundice, but these usually also cause subungual pigmented bands.

Green-coloured sweat [4] and green discoloration of the gingivae may occur due to jaundice.

A muddy-grey coloured hyperpigmentation occurs in chronic liver disease of any cause. It is due to hypermelanosis with normal numbers of melanocytes, but the precise mechanism is uncertain. There may be a yellowish tinge due to associated jaundice. Usually, pigmentation is more prominent in sun-exposed areas. It may be blotchy or diffuse, may be exaggerated in the perioral and periorbicular areas (resembling chloasma), may resemble freckling and may localize to palmar creases. Males frequently show increased pigmentation of the areola in association with gynaecomastia and testicular atrophy.

Spotty hypomelanosis may occur on the back, buttocks and thighs, often in relation to spider angiomas.

Associated dietary deficiency may cause the pigmentary changes of pellagra (Chapter 57).

Vascular changes

Spider angiomas are a characteristic feature in patients with severe chronic liver disease (Fig. 59.9). Contributory factors [5] include decreased hepatic metabolism of oestrogen leading to hyperoestrogenaemia (which also

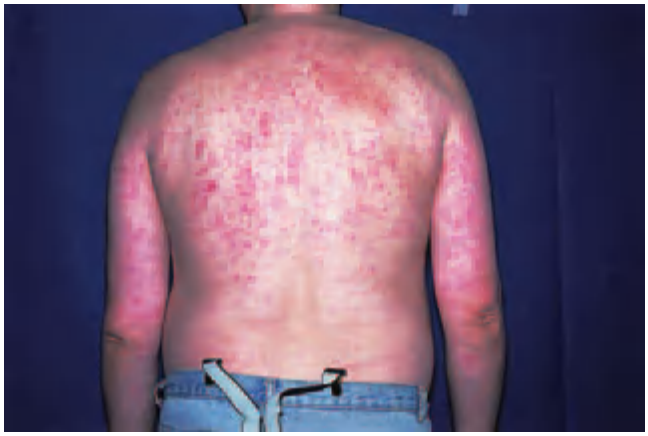

Fig. 59.9 Telangiectasia in alcoholic liver cirrhosis.

accounts for loss of secondary male-pattern hair, gynaecomastia and testicular atrophy); alcohol-induced vasodilatation and altered central vasomotor control may also be involved. The same factors lead to palmar erythema ('liver palms'), which is most pronounced on the thenar and hypothenar regions and may also affect the soles of the feet, and also to facial plethora. None of these vascular features are specific for liver disease. Diffusely scattered tiny telangiectatic vessels are referred to as 'paper money skin'. Increased peripheral blood flow with dilatation of digital pulp arteriovenous anastomoses is thought to be the cause of finger clubbing, which occurs in about 15% of patients with hepatic cirrhosis.

Purpuric lesions including scurvy may occur as a result of poor nutrition, especially in alcoholic liver disease (see Chapter 57). Altered production of prothrombin and deficiency of vitamin K may lead to frank ecchymoses.

In progressive liver disease with portal hypertension, collateral blood flow creates visible coiled varicose veins on the abdominal wall. When these are in a pattern radiating from the umbilicus, the appearance is termed 'caput Medusae'.

Hair, nail and collagen changes [1–3]

The body hair is often thinned or partially lost, and males tend to develop a female pubic-hair pattern. There is both increased production and decreased metabolism of oestrogens, as well as decreased production and increased metabolism of testosterone. When there is severe loss of scalp hair, zinc deficiency should be suspected (Chapter 57).

Nail colour changes include diffuse white colour with an invisible lunula, proximal white colour with distal pink colour (Terry's nails) and white bands (Muehrke's bands [6]). Altered digital blood flow, soft-tissue overgrowth and hypoalbuminaemia may all contribute. Lunulae may be red in patients with hepatic cirrhosis, and occasionally an azure-blue colour in hepatolenticular degeneration (Wilson's disease). Nail-plate changes include clubbing (see above) and its milder variant, the 'watch-glass' deformity; flattened nails or koilonychia may occur if there is poor nutrition or altered iron metabolism (e.g. haemochromatosis).

Striae occur in both sexes, especially on the lower abdomen, thighs and buttocks. Chronic alcoholism also alters metabolism of corticosteroids, leading to 'pseudo-Cushing's syndrome'.

Porphyria cutanea tarda

Chronic liver disease is involved in the skin changes of porphyria cutanea tarda. Lesions consist of bullae, scarring and hyperpigmentation of sun-exposed skin areas and hypertrichosis of the face. This is discussed in more detail in Chapter 57.

Other cutaneous lesions associated with liver disease

Lichen planus has been reported in a number of diseases with abnormal immune function. The association of erosive oral lesions in PBC [7] and chronic active hepatitis [8] may be related to a common immunological pathogenesis. Most reported patients have received penicillamine therapy which is believed by some to trigger the eruption [9–11]. HCV infection is associated with lichen planus [12].

In chronic active hepatitis (juvenile cirrhosis, lupoid hepatitis) and in PBC, firm reddish papules resembling pityriasis lichenoides chronica or lymphomatoid papulosis have been reported [8,13]. The lesions erupt on the trunk and extremities and may heal leaving slightly depressed atrophic scars. Histological examination reveals a capillaritis of the skin. Pityriasis lichenoides has also been reported in association with HCV seropositivity.

Pyoderma gangrenosum has also been reported in chronic active hepatitis [14]. The Gianotti–Crosti syndrome has been discussed in relation to hepatitis. Skin changes simulating classical glucagonoma syndrome have been reported in cirrhosis and termed the 'pseudoglucagonoma syndrome' [15].

Acquired zinc deficiency (Fig. 59.10) may occur in chronic alcoholic liver disease due to increased loss of urinary zinc in cirrhosis and poor nutrition [16,17]. Clinical features are a crackled and reticulate eczema on the trunk and extensor aspects of the limbs, erosive crusted changes in the perianal and genital areas, cheilitis, hair loss and multiple Beau's lines on the nails. Increased hair growth, often with a deeper pigmentation, may occur. Beer, wine and spirits are practically free of zinc, but most beer brands contain vitamin B in significant amounts and the typical zinc-deficient beer-drinker does not show additional clinical signs of vitamin B depletion [17].

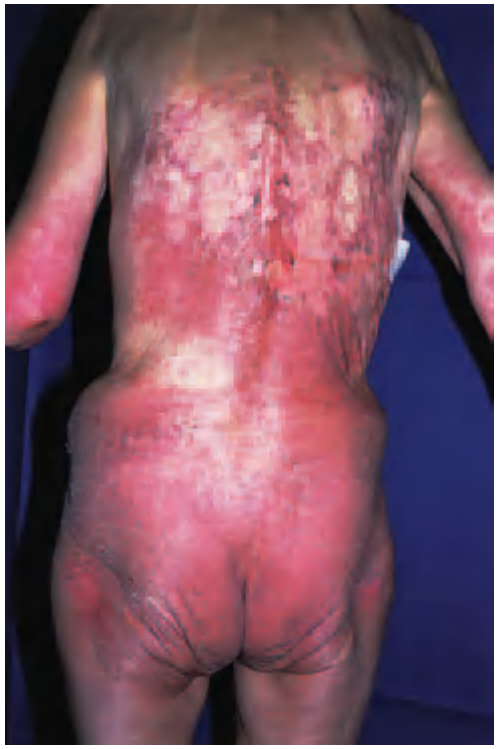

Fig. 59.10 Chronic zinc deficiency in alcoholic liver cirrhosis. Widespread eczema craquelé on the trunk.

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Pancreatic disease

Apart from jaundice and panniculitis, skin changes associated with pancreatic disease are uncommon. As with other causes of chronic, localized pain, erythema ab igne has been described in the skin overlying the pancreas in cases of chronic pancreatitis. The glucagonoma syndrome is a rare but highly characteristic skin disorder, which is discussed below. The pancreas is often involved in haemochromatosis (see the section on liver disease, above). Skin disorders associated with diabetes mellitus are discussed in Chapter 57.

Acute pancreatitis [1–3]

Jaundice and fat necrosis (see below) may both be prominent. Purpura or bruising of the left flank (Grey Turner sign) or of the periumbilical area (Cullen's sign) may occur in about 5% of patients with acute pancreatitis. Features of causative factors may also be present, such as signs of alcohol abuse or hepatic cirrhosis, or xanthomas due to hypertriglyceridaemia.

Subcutaneous fat necrosis [1–7]

SYN. NODULAR PANNICULITIS

Systemic nodular fat necrosis is a rare condition that affects 2–3% of patients with pancreatic disease [6]. It may be associated with acute or chronic pancreatitis, post-traumatic pancreatitis or pancreatic carcinoma [1–3]. Pancreatitis accounts for about two-thirds, and carcinoma one-third, of reported cases [4]. Most of the reported pancreatic neoplasms are acinous adenocarcinoma, which is rare. Subcutaneous fat necrosis associated with acute pancreatitis in a newborn has been reported [5].

The mechanism of fat necrosis is not fully understood, but the condition is probably due to the effect of enzymes released from the damaged pancreatic tissue. However, the condition does not simply relate to release of amylase or lipase from the pancreas. Not only is fat necrosis relatively uncommon in pancreatitis, but the eruption does not correlate with enzyme levels—it may occur in patients with normal lipase levels, or fail to occur in subjects with grossly elevated levels. Furthermore, incubation of skin with lipase or with patient's serum *in vitro* fails to demonstrate fat necrosis [4]. Thus, other enzymes are presumably involved.

Clinical features. Pancreatic nodular fat necrosis is accompanied by fever, abdominal pain (less common in those with underlying carcinoma), blood eosinophilia and synovitis of the small joints. Either the nodules or the

arthralgia may predominate. Nodular lesions are usually 1–3 cm in diameter and tender or symptomless. The areas of predilection are the trunk and the lower extremities, especially the anterior shins, but lesions may occur anywhere. They persist for 2–3 weeks and usually heal without scar formation, leaving slightly depressed hyperpigmented spots. More severe changes due to periarticular fat necrosis may occur. Polyserositis may be part of the syndrome [7]. Increased serum amylase or lipase levels can be demonstrated in most cases, but may be normal in cases due to carcinoma.

Histopathology. There are foci of subcutaneous fat necrosis, with ghost cells and a surrounding inflammatory infiltrate of neutrophils and eosinophils. At the periphery of the lesion histiocytes, foam cells and foreign-body giant cells are seen. Secondary calcification may be observed in necrotic areas.

Migratory thrombophlebitis [1–3,8–11]

Pancreatic cancer is one of the classical associations with Trousseau's sign, in which multiple migratory superficial thromboses occur. Recent studies indicate that lung cancer is the most common associated neoplasm in men aged over 40 years, but pancreatic cancer is still an important cause; historically, pancreatic cancer accounts for about 25–30% of cases of migratory thrombophlebitis. Cancers elsewhere in the gastrointestinal tract may also cause this condition. The usual interval to diagnosis is about 4 months from onset, but pancreatic neoplasia may present later than this [9]. The phlebitis is distributed on the trunk, neck and extremities and is usually limited to a short segment of the vein. A significantly increased frequency of deep venous thrombosis is also found. The cause is unknown, but probably related to increased levels of clotting factors and disordered fibrinolysis, a form of disseminated intravascular coagulopathy. The combination of thrombotic change with haemorrhage (purpura fulminans) may also occur as a paraneoplastic phenomenon. Thrombotic change may coexist with other paraneoplastic features; it was demonstrated in the skin of a patient with malignancy-associated fasciitis due to a pancreatic carcinoma [11]. Other signs of pancreatic carcinoma include cutaneous metastasis; about 10% of cases of Sister Mary Joseph's nodule (metastasis to the umbilicus) are due to pancreatic carcinoma [2].

Other dermatological features of pancreatitis

The main dermatological features of acute and chronic pancreatitis have been described above, or are the result of malabsorption in the chronic disease (Chapter 57). Livedo reticularis has also been described in both acute and chronic pancreatitis as 'Walzel's sign' [12,13].

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Necrolytic migratory erythema, pancreatic islet cell tumours and glucagonoma syndrome [1–6]

Necrolytic migratory erythema

Aetiology. Necrolytic migratory erythema is a cutaneous reaction that occurs in the context of hyperglucagonaemia. The syndrome was described in 1941 [1] and there have been several subsequent reviews [2–6]. The same condition occurs in dogs and other animals. It is usually due to a glucagonoma, an α-cell tumour, which is usually in the tail of the pancreas [4,7]. However, it may also occur due to other causes such as pancreatic insufficiency [8], intestinal causes of malabsorption [6,8,9], hepatic cirrhosis [10,11], and aberrant glucagon-secreting tumours such as bronchial or nasopharyngeal carcinoma [12,13]. It has also been documented as an iatrogenic condition after administration of glucagon [6] and in a heroin abuser [14]. MEN (discussed below) is associated with glucagonoma, which occurs in about 3% of cases and accounts for about 20% of glucagonomas.

Hyperglucagonaemia also causes diabetes; the 'diabetico-dermatogenic syndrome' occurs in almost 60% of patients with glucagonoma [4], but when only some of the features are present this may lead to delay in diagnosis.

The pathogenetic mechanism of the skin eruption is not certain, but the condition is probably due to hypoaminoacidaemia caused by high glucagon levels [5]. There may be a contributory role of essential fatty acid and zinc

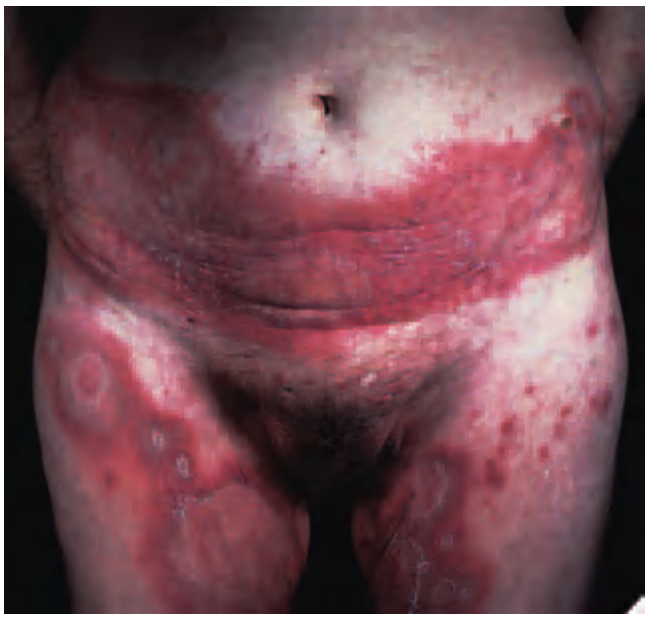

Fig. 59.11 Glucagonoma syndrome. (Courtesy of Dr Kristian Thomsen, Finsen Institute, Copenhagen, Denmark.)

deficiencies, but abnormal zinc levels or response to zinc supplementation are not consistent, and correction of amino acid levels does not reliably lead to resolution of the skin eruption [14]. It is characteristic that all skin changes disappear after complete surgical removal of the tumour in cases in which this is the cause [15].

Clinical features. The typical patient with glucagonoma is a woman of 45–65 years. The usual features are weight loss (67%), anaemia (one-third), glucose intolerance (56%) and necrolytic migratory erythema (72%) [7]. The rash is itchy or burning and particularly affects flexural sites on the lower abdomen, groin, buttocks and thighs (Fig. 59.11). It is initially macular, extending to form superficially eroding areas of erythema that progress to fragile vesicle and bullae formation. Irregular centrifugal extension of the annular lesions causes a marginated, often crusted, polycyclic or geographical pattern. It has a prolonged, fluctuating course or cyclical pattern; the central part heals over 7–14 days, leaving postinflammatory pigmentation, while the erythematous periphery becomes crusted. Perianal and genital lesions are common. Angular cheilitis and a painful beefy-coloured glossitis occur in about one-third of patients with glucagonoma [7].

The clinical spectrum also includes diarrhoea (20%), weakness, venous thromboses (10%) and psychiatric disturbances. The plasma glucagon level is generally elevated several-fold above the upper limit of the normal range, but may show only minor elevation. The systemic features, such as weight loss, anaemia and hypoaminoacidaemia, are all more frequent in patients with glucagonoma with the diabetico-dermatogenic syndrome than in those without [4]. The same pattern of eruption has been described due to zinc deficiency with normal glucagon levels, usually in the context of liver disease.

Histopathology [2,3]. Biopsy should be taken from the edge of early lesions. The characteristic histological feature is well-demarcated necrolysis of the outer cell layers in the Malpighian stratum. Early lesions may present as a dyskeratotic dermatitis with superficial perivascular inflammation in the dermis, and minor spongiosis and dyskeratotic epidermal cells [3,16]. Clefts and separation occur, associated with necrotic keratinocytes and cellular debris surrounding the cleft. In the dermis, a mild perivascular lymphocytic and histiocytic infiltrate is seen. Older lesions show various degrees of dyskeratosis, acanthosis and a lymphocytic infiltrate in the dermis. The histological changes are similar to those observed in acute zinc deficiency, in which cell degeneration and the formation of clefts and vesicles are predominant at the level of the basal cells.

Diagnosis. Pancreatic and hepatic scans and arteriography are helpful in locating a primary pancreatic tumour and its metastases if present. Serum amino acid, glucose, zinc and plasma glucagon levels should be determined. In cases with an elevated plasma glucagon level and a clinical and histological picture suggestive of the disease, surgical exploration should be performed.

Treatment. Where there is a glucagonoma, surgical resection is indicated, with embolization of hepatic metastases, which are present in the majority at the time of diagnosis. Various forms of chemotherapy have been used [2,5,17–19], such as streptozocin (a nitrosourea compound used for the ablation of β-cell adenoma) with 5-fluorouracil. Octreotide, a somatostatin analogue, rapidly improves symptoms, especially the rash, by altering glucagon metabolism, but it does not influence tumour growth [7,18]; dacarbazine is also useful [19]. Parenteral amino-acid infusions and correction of any essential fatty acid deficiency may be helpful [17], although the benefit of amino-acid infusions does not appear to be sustained long term [15]. In the rare cases related to malabsorption, correction of this (for example, GFD in coeliac disease) is usually effective [4,9].

Other non-insulin-secreting pancreatic endocrine tumours

Although glucagonoma is more important dermatologically, the most common islet cell tumours are insulinoma of β-cells and gastrinoma of δ-cells (Zollinger Ellison syndrome, ZES). These do not have specific skin changes, but they may occur together with other tumours that secrete ACTH, MSH and serotonin; severe diarrhoea in ZES may

cause secondary hypovitaminosis and other nutritional deficiencies, giving rise to skin and hair changes. Both of these tumours occur sporadically or as part of the autosomal-dominant MEN type 1 syndrome (Wermer syndrome, MIM *131100), which is due to a mutation in the *MEN1* gene on chromosome 11q13. In this condition, as well as the endocrine tumours, other cutaneous features include angiofibromas, collagenomas, café-au-lait macules, lipomas and gingival macules [20]. MEN1 was associated with 13% of glucagonomas in one large series [4], and glucagonoma has also been reported in MEN2.

Tumours that produce vasoactive intestinal polypeptide (VIPomas) cause flushing (discussed in Chapter 44) with watery diarrhoea, hypokalaemia and achlorhydria [21]. A macular rash that resolved after tumour resection was reported in a patient with a pancreatic polypeptide-producing tumour of the pancreas (PPoma) [22].

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Renal disease [1–4]

The skin and renal system may be affected not uncommonly by the same disease processes. The more important of these renocutaneous syndromes are listed in Table 59.6.

Angiokeratoma corporis diffusum (Fabry's disease; MIM *301500) (Chapter 57). Affected individuals often show proteinuria, microscopic haematuria and lipiduria. Renal disease eventually develops in most male patients, and as lipid deposition in the form of glycosphingolipids occurs, renal function deteriorates. The premature mortality in the condition is often a result of renal failure. Renal transplantation can supply a source of the deficient enzyme lysosomal hydrolase, α-galactosidase A, and results in an improvement in the condition; commercial preparations of this enzyme are also now available. Other enzyme defects may give rise to the same clinical phenotype.

Table 59.6 Renocutaneous syndromes.

Hereditary syndromes
Angiokeratoma corporis diffusum
Neurofibromatosis
Tuberous sclerosis
Nail–patella syndrome
Birt–Hogge–Dubé syndrome
Sickle cell disease
Pseudoxanthoma elasticum
Oral-facial-digital syndrome
von Hippel–Lindau disease
Hereditary haemorrhagic telangiectasia
Metabolic disorders
Primary systemic amyloidosis
Calcinosis
Collagen disease and vasculitis
Allergic vasculitis
Systemic lupus erythematosus
Polyarteritis nodosa
Scleroderma
Nephrogenic fibrosing dermopathy
Wegener's granulomatosis
Erythema multiforme
Anaphylactoid purpura
Drug-induced toxic epidermal necrolysis

Neurofibromatosis (NF1, MIM *162200; NF2, MIM *101000; von Recklinghausen's disease) (Chapter 12). Urinary outflow obstruction may develop secondary to an impinging neurofibroma. Vascular lesions can result in renal artery thrombosis and subsequent hypertension. In patients with hypertension, normal plasma and urine catecholamine levels—especially those under the age of 20 years—renal artery stenosis should be suspected [5]. Raised blood pressure may also develop as a result of an associated phaeochromocytoma. Causes of hypertension in neurofibromatosis should be fully investigated [5]. Nephroblastoma is a recognized association in neurofibromatosis [6] and renal polycystic disease.

Tuberous sclerosis complex (TSC1, MIM #191100; TSC2, MIM *191092; Bourneville's disease) (Chapter 12). An increased incidence of rhabdomyomas and carcinoma may occur in this condition [7]. Malignant renal tumours may include renal cell carcinoma, malignant angiomyolipoma and Wilms' tumour [8] The classical renal lesion associated with tuberous sclerosis is an angiomyolipoma. Renal cysts also occur in conjunction with these, or as isolated findings [9].

Nail–patella syndrome (Fong's syndrome; hereditary osteo-onychodysplasia; MIM #161200) (Chapters 12, 62). Renal dysplasia presenting as chronic glomerulonephritis occurs in some cases, and electron-microscopic evidence of glomerular abnormalities in all cases, of nail–patella syndrome. Renal lesions are asymptomatic; patients show proteinuria, haematuria and reduced creatinine clearance. Although there is often a progressive course to renal failure, many patients with the complication do surprisingly well [10]. Helpful diagnostic signs include small, defective nails that do not reach the free nail border, triangular lunulae, the thumbnails being the most frequently and severely affected nails and the severity of the affect reducing from the index to little finger nails. The patellae are less well developed, potentially giving stability problems for the knee; other indicators include (radiologically) posterior iliac horns and (ophthalmically) irregular hyperpigmented pupillary borders. The defective gene is located on the long arm of chromosome 9 (9q34.1); this gene regulates type IV and VI collagen expression, which in turn affects skeletal and basement membrane structure and function [11].

Birt–Hogge–Dubé syndrome (BHD; Hornstein–Knickenberg syndrome; MIM #135150). Hereditary renal cell cancer syndromes include BHD, VHL, as well as hereditary papillary renal cell carcinoma, familial oncocytoma and hereditary clear cell renal cell carcinoma [12].

BHD has recognized cutaneous manifestations, which are described elsewhere in this chapter. Understanding the genetic basis of renal cell carcinoma, in which an imbalance of positive and negative genetic signals favours unregulated cellular growth and carcinogenesis, can help explain why the associated epithelial hamartomas (BHD) and other organ manifestations (VHL and BHD) occur [12].

Multiple cutaneous leiomyomas, which have an inherited predisposition, are linked to uterine leiomyoma and also appear to be associated with an increased incidence of renal cell carcinoma [12].

Multiple hamartoma and neoplasia syndrome (Cowden's disease; MIM #158350) is associated with an increased incidence of renal cell carcinoma, liposarcoma and transitional cell carcinoma of the bladder [8].

Linear IgA disease has been reported with renal cell carcinoma. Palliative treatment of the metastatic renal cell carcinoma with interferon-α replaced the need for conventional therapy for linear IgA disease [13].

Partial lipodystrophy. Renal disorders occur frequently in this condition, usually as a membranoproliferative glomerulonephritis; subsequent renal failure is common at an early age. There is a circulating C3 nephritic factor and reduced levels of complement (C3) [14]. An association with hereditary angio-oedema (C1 inhibitor deficiency) has been reported [15].

Familial Mediterranean fever with urticaria (FMFU) and Muckle–Wells syndrome (MWS) [16] (Chapter 47). In MWS, there is an association with urticarial eruptions, fever, arthralgia and deafness. Both FMFU and MWS are associated with a significant risk of renal failure secondary to amyloidosis, frequently resulting in premature death.

Primary and myeloma-associated systemic amyloidosis. Up to 40% of patients have waxy, purpuric cutaneous or mucosal changes [17], which may be diagnostically useful. Typically, patients may also have macroglossia, hepatomegaly, oedema and carpal tunnel syndrome. Cutis laxa-like clinical changes have also been reported [18]. Without dialysis, renal failure is often fulminant and fatal; peritoneal dialysis may be the most appropriate approach. Although renal amyloid may recur after transplantation, this is not completely contraindicated [17]. Primary cutaneous amyloid does not appear to have renal associations. Nodular or tumid amyloidosis often represents an early phase of systemic amyloid [19].

Sarcoidosis. This may explain polyuria and nocturia, through secondary effects such as hypercalcaemia; patients are therefore at risk of renal impairment. Nephrolithiasis and nephrocalcinosis occur in patients with sarcoidosis with a 20% higher frequency than in the

normal population. Renal sarcoidosis can give rise to diffuse interstitial nephritis, but it is seldom that there are identifiable granulomas or direct renal involvement. Rarely, cases of outflow obstruction from retroperitoneal sarcoidal masses and sarcoid of the urethra have been reported [20].

Oral–facial–digital syndrome. Polycystic disease of the kidneys and liver occurs commonly in this condition [21].

Von Hippel–Lindau syndrome (VHL; MIM *193300) (see earlier in this chapter, also Chapter 15). Renal lesions in VHL are either simple cysts or adenocarcinomas; usually they are a late manifestation [22]. Renal carcinoma may present with cutaneous metastases several years in advance of the systemic malignancy; alternatively, cutaneous deposits may indicate a recurrence of previously treated neoplasia [23]. VHL represents one of the hereditary kidney cancer syndromes in which a two-hit model of tumour genesis occurs, explaining the often late development of this complication [12,24].

The other tumours linked to VHL are dealt with in Chapter 15, but phaeochromocytomas and pancreatic tumours can occur with increased frequency in close anatomical association with each other.

Vasculitis (Chapter 49). Renal involvement commonly occurs in various types of vasculitis that present with cutaneous changes and is the main cause of mortality in many of these syndromes. This should be considered particularly in classical Henoch–Schönlein purpura (anaphylactoid purpura) (especially adult forms), where IgA nephropathy has become recognized as a fairly common form of glomerulonephritis. An association between anaphylactoid purpura and familial IgA nephropathy has also been described [25]. Patients labelled as having allergic vasculitis and arteritis with livedo reticularis [26] should also be regarded as being at risk of kidney damage. It can also occur in cases of erythema multiforme and drug-related toxic epidermal necrolysis [27,28].

Renal failure is a recognized, but rare complication of Behçet's syndrome, usually with immune-complex deposition [29]. Concomitant or delayed renal involvement is common in Wegener's granulomatosis, usually as a focal necrotizing glomerulitis. Deposits of IgM and IgG are present in renal vessels and circulating immune complexes are also frequently detected [30]. Renal changes that occur in these conditions and in collagen vascular disorders such as polyarteritis nodosa, systemic lupus erythematosus and scleroderma are considered in Chapter 56.

Bullous pemphigoid. Renal disease—including membranous glomerulopathy, diffuse proliferative and mesangioproliferative glomerulonephritis—has been infrequently reported in patients with pemphigoid [31].

Streptococcal impetigo. An acknowledged cause of acute glomerulonephritis, but most cases of acute nephritis are not the sequel of streptococcal infection [30].

Secondary syphilis. A rare cause of the nephrotic syndrome.

Herpes zoster. If affecting the appropriate dermatomes, this may cause neurogenic bladder dysfunction and pain [32], leading to acute urinary retention.

Signs of renal failure and dialysis

Cutaneous signs of renal failure are present only in fairly advanced cases, in which the findings are of limited diagnostic value. Urea frosting, in which crystalline urea is deposited on the skin, is rarely seen.

Uraemic patients tend to have a dry skin, sometimes with fine scaling. A reduction in the size of eccrine sweat glands in uraemia may contribute to this effect [33], although high-dose diuretic regimens are a co-factor [34].

Pigmentation. Anaemia presenting as pallor is an early and common sign in renal failure resulting from reduced erythropoiesis and increased haemolysis.

A muddy brown hyperpigmentation develops in many cases, attributed to retention of chromogens and deposition of melanin, possibly due to impaired renal processing of MSH [35]. Increased nail pigmentation usually confined to the distal aspect occurs in a proportion of patients [36]. This distal brown or more normal red colour, combined with a proximal white appearance gives rise to the 'half-and-half' nails, a distinctive pattern seen in about 10% of renal failure cases [37].

Purpura due to a mild thrombocytopenia or more marked platelet dysfunction is common and may be partly corrected by dialysis [38]. Wound healing is prolonged and patients may be more susceptible to pressure sores.

Pruritus. Generalized, severe pruritus occurs in about one-third of renal failure cases, less troublesome involvement in many more. Unfortunately, haemodialysis can initiate the symptom as well as improve it. Up to 85% of patients on haemodialysis suffered from itching in one study [39], one-third before dialysis, the others after; 12% had reduced pruritus after 6 months' dialysis. There seems to be an association with predialysis blood urea levels, and a less assured correlation with dry skin and secondary hyperparathyroidism [28]. Subtotal parathyroidectomy may be very helpful [40], but the problem can subsequently recur, and many cases are not related to secondary hyperparathyroidism. Moreover, many patients with this finding do not itch. A complete explanation for pruritus in renal failure is obscure, as pruritus is unusual in acute renal failure and a reduction in uraemia often does not improve the symptom. Slowly accumulated or

deposited pruritogen(s), of as yet uncertain nature, are the likely cause. In dialysis, lowering the magnesium concentration of the dialysate has been reported as helpful [41]. In intractable itching, UVB radiation is an effective therapy [42], benefit being associated with a reduction of skin phosphorus to normal values. UVA (without psoralen) has been reported nearly as effective [43]; oral cholestyramine and activated charcoal are alternatives [44,45]. Erythropoietin therapy can alleviate pruritus in some cases of renal failure.

Calcification and calciphylaxis. Calcifying panniculitis has been reported occasionally in renal failure, caused by a mechanism known as calciphylaxis [46,47]. It is usually, but not invariably, associated with a high serum calcium phosphate product. Metastatic skin calcification is a rare phenomenon in uraemic patients; it usually presents as papular or nodular cutaneous lesions around large joints or flexural sites. Non-cutaneous metastatic calcification is by comparison much commoner [48]. Metastatic calcification in blood vessel walls associated with hyperparathyroidism and renal failure may lead to cutaneous necrosis or gangrene, as a result of thrombosed vessels; however, calcification does not always need to be present, and vascular damage may be triggering a premature haemostatic cascade [49].

Perforating disorders. A perforating disorder variously described as perforating collagenosis, Kyrle's disease or perforating folliculitis occurs in renal failure; often there is diabetes, diabetic nephropathy and/or retinopathy. Pruritus is nearly always present, and up to 10% of dialysis patients may be affected. The condition seems to have a higher incidence in Afro-Caribbeans. The cutaneous lesions consist of hyperpigmented papules up to 1 cm in diameter with a central keratinous plug. The extensor surfaces of the limbs are more commonly affected but the trunk and face may be involved. The pathogenesis is uncertain, but there is some histological evidence that it is a perforating collagenosis [50].

Other cutaneous features. Uraemic neuropathy affects some 60% of patients with renal failure or on long-term haemodialysis. This appears to be a predominantly sensorimotor neuropathy [51].

Up to 40% of patients with renal failure may develop gynaecomastia while receiving dialysis [52]. It may be reversed by a low phosphorus diet and aluminium hydroxide gel [53].

Features related to treatment. Premature ageing of the skin and actinic keratoses have been described [54], a reason for avoiding excessive ultraviolet therapy for pruritus. This should be distinguished from the numerous viral, dysplastic and frankly malignant skin lesions which may develop in immunosuppressed, renal allograft recipients. In such circumstances there is also a raised incidence of Kaposi's sarcoma [55]. These aspects are dealt with under cutaneous manifestations of immunosuppressive therapy (Chapter 14).

Cutaneous complications affecting the limb of patients in which their haemodialysis arteriovenous shunt is situated include infection, phlebitis and haematoma. However, both irritant and allergic contact eczema may also develop [56]. Vascular complications of arteriovenous fistula construction are relatively uncommon, but include digital ischaemia and aneurysm formation. The venous hypertension syndrome with or without ulceration, together with pseudo-Kaposi's sarcoma, are rare developments [57].

The diagnosis of the porphyria cutanea tarda-like bullous eruption that may develop in dialysis patients appears to be dependent on the sophistication of biochemical analysis for porphyrins; the importance of accurate assays is emphasized [58–60].

A recently described condition termed nephrogenic fibrosing dermopathy or scleromyxoedema-like illness of renal disease was initially linked with haemodialysis but occurs in other patients with renal failure [61–63]. Clinical features include indurated plaques, sometimes with finger-like projections, that may be erythematous, yellowish or skin coloured. Nodules and contractures occur in more advanced disease. Scleral plaques may also occur, although the face is usually spared (by contrast with scleromyxoedema). There is no associated plasma cell dyscrasia as seen in most patients with scleromyxoedema. Histology shows increased spindle cells and compact collagen bundles, with increased mucin deposition.

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Cardiac disease

There are several diseases in which both cardiac and skin involvement may be found (Table 59.7). Most of these are part of a syndrome or are systemic disorders affecting other organs as well [1,2]; most are discussed in other chapters, but some are briefly described below. Disorders of blood vessels are not included here. The effects of skin disease on the heart (e.g. cardiac failure due to erythroderma) and indirect effects, such as anaemia due to immunosuppressive agents used to treat the skin, are not discussed. Numerous infections may occasionally cause myocardial disease and may have an exanthem, but these are not discussed individually. Drug reactions due to cardiac medications are described in Chapter 73.

Consequences of cardiac disease

Dermatological consequences of cardiac disease include skin colour changes such as cyanosis, erythema due to secondary polycythaemia, and a combination of the two that may occur in congenital heart disease (and which has been termed erythremia). Finger clubbing is a consequence of congenital cyanotic heart disease, but occurs in other

Table 59.7 Conditions that affect the heart and skin.

Disease	Main cardiac feature, or comment
Congenital / inherited	
Ehlers–Danlos syndrome	Dilated main vessels, mitral or tricuspid insufficiency
Cutis laxa	Early CAD, aortic aneurysm, mitral valve prolapse
Marfan syndrome	Aortic aneurysm, aortic regurgitation, mitral valve prolapse or regurgitation
Pseudoxanthoma elasticum	Arterial calcification, CAD, mitral valve prolapse
Werner's disease	Early CAD
Progeria	Early CAD
Cockayne's syndrome	Early CAD
Cornelia de Lange's syndrome	Septal defects, persistent ductus arteriosus, pulmonary stenosis
Fabry's disease	Conduction defects, arrhythmias, hypertension, left ventricular hypertrophy, mitral valve prolapse
Noonan's syndrome	Pulmonary stenosis, septal defects, hypertrophic cardiomyopathy, aortic abnormalities, others
Rubinstein–Taybi syndrome	Aortic coarctation, persistent ductus arteriosus, pulmonary stenosis, septal defects
LEOPARD syndrome	E, ECG abnormalities (various forms of heart block); P, pulmonary stenosis. Also subaortic stenosis and hypertrophic cardiomyopathy
Tuberous sclerosis	Cardiac rhabdomyomas
Neurofibromatosis	Hypertension (renovascular or phaeochromocytoma)
Incontinentia pigmenti	Patent ductus arteriosus, tricuspid insufficiency
Alagille's syndrome	Pulmonary artery hypoplasia/stenosis
Di George's syndrome	Tetralogy of Fallot, aortic arch defects
Lymphoedema–distichiasis syndrome	Tetralogy of Fallot, patent ductus arteriosus
Naxos disease	Arrhythmogenic right ventricular cardiomyopathy
Chromosomal syndromes	Various—includes Down's syndrome, Turner's syndrome, trisomy 13, trisomy 18
Inflammatory diseases, connective tissue disease, vasculitis	
Systemic lupus erythematosus	Vegetations (especially mitral, Libman–Sacks endocarditis), pericarditis, myocarditis, aortic/mitral regurgitation
Neonatal lupus erythematosus	Neonatal heart block (various patterns), septal defects, persistent ductus arteriosus, tricuspid/mitral insufficiency
Systemic sclerosis	Pericarditis and effusion, conduction defects, myocardial fibrosis, cardiomyopathy, cor pulmonale
Polyarteritis nodosa	Coronary artery vasculitis, ECG abnormalities, hypertension
Behçet's disease	Pericarditis, pulmonary and coronary artery aneurysm
Antiphospholipid syndrome	Vegetations, coronary artery thrombosis, pericardial effusion
Degos's disease	Pericarditis, pericardial effusion
Churg–Strauss disease	Pericarditis, cardiac fibrosis, pericardial effusion
Wegener's granulomatosis	Cardiomyopathy
Cholesterol emboli	Coronary artery occlusion
Other vasculitides	Coronary artery vasculitis
Dermatomyositis	Conduction defects, arrhythmias, cardiomyopathy, CCF
Relapsing polychondritis	Mitral or aortic insufficiency, dissecting aortic aneurysm, pericarditis, myocardial ischaemia, heart block
Rheumatic fever	Mitral and aortic valve disease
Kawasaki disease	Conduction defects, coronary artery aneurysms, pericardial effusion, cardiomegaly
Multicentric reticulohistiocytosis	Pericarditis, cardiomegaly, CAD, CCF
Hypereosinophilic syndrome	Eosinophilic endomyocarditis, valvular scarring, CCF, restrictive cardiomyopathy
Sarcoidosis	Conduction defects, arrhythmias, CCF
Reiter's disease	Conduction defects, aortic regurgitation
Deposition, metabolic and endocrine disorders	
Amyloidosis	Conduction defects, cardiomegaly, CCF
Haemochromatosis	Arrhythmias, cardiomyopathy, CCF
Wilson's disease	Arrhythmias, cardiomyopathy
Mucinoses: scleromyxoedema	Cardiomyopathy, CCF
Atrial myxoma syndromes	See text
Hyperlipidaemias	CAD
Diabetes mellitus	CAD, cardiomyopathy
Hyperthyroidism	Tachycardia, atrial fibrillation, mitral regurgitation
Hypothyroidism	Bradycardia, CAD, pericardial effusion
Acromegaly	Left ventricular hypertrophy, CCF
Carcinoid syndrome	Tricuspid or pulmonary stenosis, right heart failure
Phaeochromocytoma	Variable heart rate, hypertension/hypotension
Mastocytosis	Tachycardia, hypotension, arrhythmia, angina
Homocystinuria	Atherosclerosis

(*cont'd*)

Table 59.7 (*cont'd*)

Disease	Main cardiac feature, or comment
Embolic diseases	
Subacute bacterial endocarditis	Vegetations, valvular incompetence
Cholesterol emboli	Usually from proximal arteries rather than cardiac
Atrial myxomas	See text
Infections	
Lyme disease	Myocarditis, heart block
Syphilis	Aortitis, aortic aneurysm, aortic and mitral regurgitation, obstructed coronary arteries
Varicella	Myocarditis
Septicaemia	Pustules, infarcts, disseminated intravascular coagulopathy
Congenital rubella	Pulmonary artery and valve stenosis, patent ductus arteriosus
Whipple's disease	Pericarditis, myocarditis, valve deformity (especially mitral valve endocarditis)
Drugs	
Used in cardiology, causing rash	e.g. amiodarone (photosensitivity, pigmentation)
Cardiotoxic and cause skin eruptions	e.g. doxorubicin (cardiotoxic, anagen effluvium, pigmentation)
Used for skin disease, cardiovascular side effects	e.g. ciclosporin (hypertension)
Teratogenic, causing both skin and cardiac defects	e.g. alcohol, phenytoin, retinoids
Miscellaneous	
Earlobe crease	CAD
POEMS syndrome	Cardiac failure
Mycosis fungoides, Sézary syndrome	Heart is infiltrated in advanced disease
Kaposi's sarcoma	Heart is commonly involved
Diffuse neonatal haemangiomatosis	High output cardiac failure
Erythroderma, any cause	High output cardiac failure
Pacemaker reactions	Infection, contact dermatitis, mechanical issues
Clubbing of nails	Cyanotic congenital heart defects
Red lunulae	Occur in CCF

CAD, coronary artery disease; CCF, congestive cardiac failure; ECG, electrocardiogram; LEOPARD, lentigines, ECG abnormalities, ocular hypertelorism, pulmonary stenosis, abnormalities of genitalia, retardation of growth, and deafness (syndrome); POEMS, polyneuropathy, organomegaly, endocrinopathy, M protein, skin changes (syndrome).

situations as well. Applying pressure on the tip of the nail in subjects with aortic regurgitation reveals visible flushing of the nail bed in time with the pulse, due to the wide pulse pressure in this disorder (Quincke pulsation) [2].

Congenital and inherited disorders

Cardiac involvement occurs in several congenital and inherited conditions, such as the LEOPARD syndrome, Anderson–Fabry disease, Alagille's syndrome and the cardiofaciocutaneous and Noonan's syndromes [1–8], as well as in chromosomal abnormalities such as Turner's syndrome and trisomy 13 or 18 [1]. The lymphoedema–distichiasis syndrome, due to mutations in *FOXC2* (*MFH-1*) on chromosome 16q24.3, has been linked to cardiac anomalies such as tetralogy of Fallot and patent ductus arteriosus [9,10]; spinal arachnoid cysts also occur. Cardiac rhabdomyomas occur in about 50% of patients with tuberous sclerosis (see Chapter 12).

In the LEOPARD syndrome (multiple lentigines syndrome; MIM *151100) [3] there are widespread *l*entigines, *e*lectrocardiographic abnormalities, *o*cular hypertelorism, *p*ulmonary stenosis, *a*bnormal genitals, *r*etardation of growth and *d*eafness. The cardiac involvement includes left-axis deviation on the electrocardiogram (ECG), ventricular hypertrophy and arrhythmia.

In angiokeratoma corporis diffusum (Anderson–Fabry disease; MIM *301500) [4], cardiac involvement may be manifest as arrhythmias, an abnormal P–R interval on ECG and left-ventricular hypertrophy. ECG abnormalities may also be found in heterozygotes. Manufactured α-galactosidase is now available to treat this condition [4] and appears to be more beneficial for the renal and cardiac lesions than for the cutaneous angiokeratomas, although accumulated globotriaosylceramide in the skin decreases during treatment.

Coronary artery disease

Coronary artery disease and ischaemic heart disease may occur in premature ageing syndromes such as progeria and Werner's syndrome, and premature myocardial ischaemia has also been reported in pseudoxanthoma elasticum, although it seems to be less common than the presence of a calcifying vascular pathology might suggest [2,11]. Coronary artery disease may be associated with

xanthelasma or xanthomas due to hyperlipidaemia [2]. Both all-cause and cardiac-specific morbidity and mortality have been linked with the presence of a unilateral or bilateral diagonal earlobe skin crease [12,13], although others suggest that the association is with older age rather than with coronary artery disease *per se*. Both antinuclear [14] and high-titre anticardiolipin antibodies [15] have been demonstrated in a high proportion of patients with coronary artery disease; the significance of these is uncertain.

Connective tissue and systemic diseases

Cardiac involvement is common in systemic disorders such as sarcoidosis [16], connective tissue diseases [17–19], vasculitides [20,21] (Chapter 49), dermatomyositis (Chapter 56), relapsing polychondritis (Chapter 65) [22] and the hypereosinophilic syndrome [23,24], although it may be underestimated if symptoms are absent. Sudden death due to conduction defects and ventricular arrhythmias is the most important complication, and is particularly well recognized in sarcoidosis [16]. The major vasculitides that affect the heart are Wegener's granulomatosis, polyarteritis nodosa, Churg–Strauss syndrome, temporal arteritis and Takayasu arteritis. Cardiac involvement is commoner in Churg–Strauss syndrome than in Wegener's granulomatosis, but has low discriminatory value—this is discussed in more detail in Chapter 49 and in the section on respiratory disease and the skin, below.

A number of cardiac complications occur in systemic lupus erythematosus (LE), especially pericarditis, which may be present in 60–80% of patients at autopsy (Chapter 56) [2,25]. Neonatal LE is a particularly important entity, as about two-thirds of affected children have congenital heart block, although the frequency of this manifestation varies between countries [18,19]. Mothers of affected children generally express the 52-kDa and 60-kDa anti-SS-A (Ro) antibodies, even if they have no other features of LE. This antibody group is particularly associated with subacute cutaneous LE, but also with systemic LE. Mothers of children with neonatal LE with heart block tend to have higher titres of anti-SS-A but lower titres of anti-SS-B (La) antibody than mothers of children with neonatal LE rash alone [19].

Cardiac involvement occurs in 80% of patients with systemic sclerosis, but is not always clinically apparent; pericarditis, pericardial effusion, myocardial fibrosis, endothelial damage to coronary arteries and heart failure due to pulmonary arterial hypertension all occur [2,26,27]. Symptoms include heart failure, palpitations and myocardial infarction. Vasospasm may occur due to Raynaud's phenomenon.

In the antiphospholipid syndrome [28], about 50% of patients have valvular heart disease, either vegetations or thickening. The mitral valve is most frequently affected. About 5% require cardiac valve surgery, but many have no symptoms. There is also an increased incidence of coronary artery disease. Intracardiac thrombus is a rare complication.

Cardiac involvement is frequent in primary and in familial amyloidosis [29], causing features of cardiomyopathy such as congestive heart failure, low voltage on the ECG and conduction disturbances. Cardiomegaly is present in about one-third of the patients. Cutaneous signs, macroglossia and demonstration of amyloid deposition on skin histology support the diagnosis.

Kawasaki disease (mucocutaneous lymph-node syndrome) is an acute febrile disease of unknown aetiology, with accepted diagnostic criteria [30]. Coronary artery aneurysms may develop in up to 25% of patients, more commonly in children; conduction defects, pericardial effusion and cardiomegaly also occur. Symptoms and signs may include murmurs, gallop rhythm, angina and myocardial infarction [25,30]. Echocardiography and ECG are indicated. Treatment consists of acetylsalicylates and high doses of intravenous gammaglobulin.

Infections

Subacute bacterial endocarditis (SBE) [31–33] typically occurs in patients with a past history of heart disease (rheumatic fever, congenital heart disease, heart valve operation) or of parenteral drug addiction. About 75–80% of cases are caused by *Staphylococcus aureus* or streptococcal species, predominantly *Streptococcus viridans*. Cutaneous lesions may represent either septic emboli or immune complex disease due to the bacterial focus [31]; organisms can occasionally be cultured from skin lesions [32]. The skin lesions may be purpuric, pustular or erythematous, and various patterns are described. A non-specific small-vessel vasculitis with splinter haemorrhages of the nail fold or nail bed occurs in about half of affected individuals. Similar small haemorrhages occur on the conjunctivae and retina (Roth spots). Osler's nodes are small, tender red papules situated mainly on the distal finger and toe pads; Janeway lesions are faint red macular lesions on the thenar and hypothenar eminences. Both rheumatoid factor and cANCA can be demonstrated in some patients with SBE; these are of uncertain significance, but may erroneously suggest that the diagnosis is of systemic ANCA-associated vasculitis rather than of infective aetiology [33].

Rheumatic fever is a complication of streptococcal infection [34]. It causes arthritis, carditis, neuromuscular disease (Sydenham's chorea, dysphagia, dysarthria, distal weakness) and cutaneous lesions. The latter include erythema marginatum and papular lesions on the extensor surface of the extremities, particularly near the joints—both of these manifestations are usually transient, typically

resolving after a few weeks. Erythema marginatum is a transitory gyrate erythema situated mainly on the trunk and proximal parts of the extremities. Urticaria, erythema nodosum and purpura are described in about 2% of patients. Cardiac features include valvular disease, pericarditis, myocarditis and congestive cardiac failure.

Cardiac myxoma syndromes

Carney complex (type I, MIM #160980; type II, MIM *605244). A number of atrial myxoma syndromes have been described, with various eponyms and acronyms and overlapping features [35–39]. These include LAMB syndrome, NAME syndrome, Danoff syndrome and the Carney complex. LAMB is an acronym for *l*entigines, *a*trial myxoma, *m*ucocutaneous myxoma and *b*lue naevi. The NAME syndrome indicates blue *n*aevi, *a*trial myxoma, *m*yxoid neurofibromas and *e*phelides. The inheritance is autosomal-dominant. In the Danoff syndrome there are, apart from atrial myxomas, adrenocortical dysplasia, lentigines and spindle cell tumours.

About 50% of cases of bilateral, pigmented, micronodular adrenal hyperplasia—a rare cause of ACTH-independent Cushing's syndrome—are associated with the Carney complex; anti-ACTH receptor antibodies are present and stimulate adrenal growth and secretion. Other features include cardiac myxomas (in one-third of patients), skin myxomas (two-thirds), skin pigmentation (96%), myxoid fibroadenomas of the breast (in one-third of women, uncommon in men), GH-secreting pituitary tumours (acromegaly occurs in 8% of patients), Sertoli cell (in 10%) and Leydig cell testicular tumours (which cause male precocious puberty), thyroid cysts, hyperplasia and tumours (10%), and ovarian cysts and tumours (which are felt to be underestimated in frequency) [37–39]. Psammomatous melanotic schwannoma is rare, but is usually part of this syndrome when it occurs [40].

The genetic background of these disorders has been extensively investigated. Carney complex type 1 (CNC1) is linked to a susceptibility gene for the protein kinase A type 1α regulatory subunit gene (*PRKAR1A*) and has loci on chromosomes 2p16 and 17q23–24, whilst CNC2 links to a currently unknown gene on chromosome 2p. Genetic evaluation has demonstrated that this disorder is related to PJS. Any patient with multiple melanocytic and myxomatous tumours of the skin and mucosa (including vulval melanotic macules) should have a cardiac evaluation.

From a dermatological aspect, atrial myxomas may present due to embolic infarction of the skin. They may mechanically interfere with cardiac function and can also lead to pericarditis. Systemic malaise, pleurisy, Raynaud's phenomenon and the occasional occurrence of ANCA [41] may suggest other forms of vasculitis as the cause of skin lesions.

Miscellaneous

Cardiac pacemaker and implantable defibrillator dermatoses. Cutaneous reactions over the site of implanted cardiac pacemakers have been reported [42–45]. Most of these are either infections or mechanical issues (erosions, extrusions, capsular contracture, exposed generator or electrodes, bronchopleural cutaneous fistulae) and may respond to antibiotics or altered positioning of the pacemaker [42,43]. However, contact dermatitis to epoxy resins, nickel or chromium may occur, in which event removal of the implanted material and use of titanium pacemaker casings may be appropriate [44,45]. A reticular telangiectatic pattern of erythema overlying pacemaker or defibrillator sites may occur [46,47]. Cardiac pacemakers also have dermatological surgical relevance, as they may malfunction during the use of electrosurgery [48].

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Respiratory system

Pulmonary disease rarely occurs as a direct consequence of a primary skin disease, except for instances such as metastasis from a primary skin tumour (e.g. melanoma).

Similarly, there are relatively few instances in which skin abnormalities occur as a direct consequence of respiratory pathology. Examples include cyanosis due to severe pulmonary disease or intrapulmonary right-to-left shunts, and finger clubbing due to chronic cyanotic lung disease or neoplasm. Dermatomyositis may occur as a paraneoplastic phenomenon due to lung cancer (but, as discussed below, lung disease also occurs as a consequence of dermatomyositis). Amyloidosis may occur secondary to chronic respiratory diseases such as bronchiectasis or cystic fibrosis, but cutaneous signs in secondary amyloidosis are generally few, even though aspiration of subcutaneous fat for histological examination can be diagnostic. Tumours may cause direct nerve damage and abnormalities of sweating [1,2].

However, in most instances in which the skin and respiratory tract exhibit the same disease process, this is as part of a multisystem disorder. This section concentrates on this diverse group of disorders (Table 59.8).

Congenital and inherited disorders

Examples are listed in Table 59.8. NF1 (Chapter 12) is not uncommonly associated with the development of restrictive lung disease if there is severe scoliosis. Intrathoracic, intra-abdominal or retroperitoneal diffuse plexiform neurofibromas can also compromise pulmonary function [3]. Fibrosis is found in around 10% of patients with NF1, mainly in the lower lobes, and bullous changes may occur in the upper lobes [4]. Pleural effusions have been reported in tuberous sclerosis [5] (Chapter 12). Pulmonary involvement is uncommon but, especially in adult female patients, there may be numerous small cysts which represent lymphangioleiomyomatosis [6]. These may be mistaken for tuberculosis or sarcoidosis radiologically. Diffuse lower lobe fibrosis and laryngeal involvement has been reported in Darier's disease [7] (Chapter 34). α_1-Antitrypsin deficiency, particularly the ZZ genotype, links cutaneous panniculitis with emphysema and hepatic cirrhosis [8]. In familial dysautonomia (Riley–Day syndrome), there are acute episodes of bronchopneumonia, with profuse mucous secretion causing dyspnoea. Skin changes include multiple excoriations, and erythematous mottling associated with fever and sweating [9]. Radiological features of lung disease [10] may be accompanied by abdominal distension as the 'chest–abdomen' sign [11]. Ataxia–telangiectasia (Louis-Bar syndrome) may be associated with pulmonary problems, including recurrent pneumonia, bronchiectasis and pulmonary fibrosis [12].

Table 59.8 Conditions that affect the skin and respiratory system.

Disease	Respiratory tract features or comment
Congenital / inherited	
Atopic disease	Asthma, hay fever
Cutis laxa	Emphysema, cor pulmonale
Tuberous sclerosis	Rhabdomyomas
Neurofibromatosis	Kyphoscoliosis, intrathoracic neuromas, lung fibrosis, bullae
Ataxia–telangiectasia	Pneumonia, bronchiectasis, pulmonary fibrosis
Hereditary haemorrhagic telangiectasia	Haemoptysis, dyspnoea, cyanosis due to arteriovenous shunting
α_1-antitrypsin deficiency	Emphysema
Darier's disease	Lower lobe fibrosis, laryngeal involvement
Lipoid proteinosis	Laryngeal involvement
Riley–Day syndrome	Lung infiltrate
Birt–Hogg–Dubé syndrome	Lung cysts, pneumothorax
Infections and infestations	
Tuberculosis	Specific skin lesions, erythema nodosum
Mycobacterium avium–intracellulare infection	May disseminate to skin (usually in HIV infection)
Leprosy	Laryngeal involvement
Mycoplasma infection	Causes erythema multiforme (often mucosal)
Dissemination of pulmonary fungal infections	Blastomycosis, coccidioidomycosis, cryptococcosis, aspergillosis, histoplasmosis, melioidosis
Scrub typhus	Pneumonia (common)
Varicella	Pneumonia
Measles	Pneumonia
Larva migrans	Asthma/bronchitis with eosinophilia
Chronic mucocutaneous candidiasis	Bronchiectasis
Whipple's disease	Cough, pleural effusion, pulmonary infiltrate, hilar lymphadenopathy
Infiltrations and metabolic	
Histiocytoses (Langerhans' cell histiocytosis, Rosai–Dorfman disease, haematophagocytic syndrome, necrobiotic xanthogranuloma, sea-blue histiocytosis, others)	Pulmonary nodules and fibrosis, upper respiratory tract infiltration disease, xanthoma disseminatum
Amyloidosis	Cutaneous amyloid deposition secondary to chronic lung disease, lung infiltration in primary amyloidosis
POEMS	Pleural effusion, bronchospasm
Carcinoid syndrome	Bronchospasm
Hypothyroidism	Laryngeal involvement
Myxoma	Pleurisy
Inflammatory	
Sarcoidosis	Pulmonary fibrosis, hilar lymphadenopathy, laryngeal involvement
Pulmonary vasculitides	See text (this section)
Systemic sclerosis	Interstitial fibrosis, pneumothorax, pulmonary hypertension
Sjögren's syndrome	Decreased secretions, sinusitis, bronchoalveolitis, interstitial lung disease
Lupus erythematosus	Pleurisy
Mixed connective tissue disease	Fibrosing alveolitis (especially U_1 ribonucleoprotein antibody-positive)
Antiphospholipid syndrome	Pulmonary embolism, infarction, thrombosis, haemorrhage
Dermatomyositis	Muscular weakness, pharyngeal dysfunction (aspiration pneumonia), interstitial lung disease, bronchiolitis obliterans
Relapsing polychondritis	Tracheal collapse
Multicentric reticulohistiocytosis	May be associated with bronchial neoplasia, also lung infiltration, pleural effusion
Bullous diseases (epidermolysis bullosa, pemphigus, erythema multiforme/Stevens–Johnson syndrome/ toxic epidermal necrolysis)	Upper respiratory tract involvement; paraneoplastic pemphigus is associated with intrathoracic disease, especially Castleman's disease, thymoma
Graft-versus-host disease	Restrictive defect, fibrosis
Pyoderma gangrenosum	Neutrophilic nodules in lung, tracheal pyoderma
Familial Mediterranean fever	Pleuritis
Drugs	
Used in respiratory disease, causing rash	e.g. co-trimoxazole (drug rash)
May cause skin eruptions and respiratory tract disease	e.g. antibiotic-induced toxic epidermal necrolysis, cisplatin (bronchospasm, pigmentation)
Used for skin disease, respiratory side effects	e.g. isotretinoin (bronchospasm)
Miscellaneous	
Angio-oedema	Upper airway obstruction
Anaphylaxis	Bronchospasm
Pancreatitis	May cause basal pleural reaction, and cutaneous fat necrosis
Yellow nail syndrome	Pleural effusion, bronchiectasis
Mastocytosis	Rhinorrhoea, laryngeal oedema, bronchospasm
Tumours	Metastatic disease, Kaposi's sarcoma, lymphomatoid granulomatosis, extensive mycosis fungoides/Sézary syndrome, others

HIV, human immunodeficiency virus; POEMS, polyneuropathy, organomegaly, endocrinopathy, M protein, skin changes (syndrome).

Infections

Numerous infections may be associated with both respiratory and skin disease, and only a selection of these have been listed. Many viral infections, for example, may cause upper and sometimes lower respiratory tract symptoms in association with either a non-specific exanthem or with erythema multiforme. *Mycoplasma infection* is particularly associated with erythema multiforme with mucosal involvement (Stevens–Johnson syndrome). *Psittacosis (ornithosis)* may be accompanied by erythema nodosum and erythema multiforme (Bateman's syndrome).

Associations between *tuberculosis* and the skin include non-specific reactions such as erythema nodosum or erythema multiforme, as well as several patterns of specific skin lesion such as lichen scrofulosorum, Bazin's disease or papulonecrotic tuberculide (Chapter 28). Several *systemic mycoses* are caused by inhalation but may subsequently cause skin lesions (Table 59.8)—either non-specific reactions such as erythema multiforme or erythema nodosum, or specific lesions caused by haematogenous dissemination. Other mycoses may have primary cutaneous lesions with occasional spread to internal organs, including the lung (e.g. sporotrichosis). *Pulmonary melioidosis* may run a subacute course and last for one to several weeks. It may be contracted by inhalation, causing early pneumonic symptoms, or via skin defects, in which case abscess formation precedes the septic stage. Urticaria may occur in chronic melioidosis [13].

Connective tissue diseases

This group of disorders have a variety of respiratory features.

Respiratory disease is frequent in the various forms of *scleroderma* [14,15]. Systemic sclerosis is associated with fibrosing alveolitis and interstitial fibrosis, causing a restrictive defect. This occurs in at least 50% of patients. Symptoms (exertional dyspnoea and cough) may be relatively late in presenting—pulmonary function tests including transfer factor should be measured. Pneumothorax, pleural effusion, respiratory muscle involvement and 'splinting' of the chest by sclerotic skin may all occur. Pulmonary vascular disease leading to pulmonary hypertension is a particular concern in CREST syndrome.

Over 50% of anti-U1RNP-positive patients with *systemic lupus erythematosus* (SLE) and about a quarter of those with *mixed connective tissue disease* may have pleurisy [16]. These conditions are discussed in more detail in Chapter 56. Pulmonary embolism, haemorrhage, infarction and hypertension may occur in patients with the *antiphospholipid syndrome* [17].

Relapsing polychondritis [18] is due to autoantibodies against type II collagen, and is a potentially fatal disease. Dyspnoea and inspiratory stridor occur due to swelling of the respiratory tract, and collapse of cartilages of the larynx and trachea, in over 50%. Costal cartilage is involved in one-third of cases. Inflamed nasal and auricular cartilages are present in most patients, with nasal obstruction, arthropathy and high erythrocyte sedimentation rate (ESR). The disorder may therefore mimic one of the vasculitides, such as Wegener's granulomatosis. The non-cartilaginous lobe of the ear is classically spared in relapsing polychondritis.

In *dermatomyositis*, there are three main mechanisms that provide a link with respiratory disease [19–21]. Firstly, dermatomyositis may occur as a consequence of bronchial carcinoma, the commonest malignancy associated with dermatomyositis in males [19]. Muscular weakness due to myositis may affect the intercostal and thoracic musculature, or may affect the larynx and pharynx—the latter may lead to aspiration pneumonia as a complication. Finally, interstitial lung disease or bronchiolitis obliterans may occur due to dermatomyositis. The lung disease is typically associated with the presence of antiaminoacyl-tRNA synthetase antibodies, notably anti-Jo-1, and with anti-tRNA antibodies such as anti-$tRNA^{his}$. Patients with these antibodies only comprise 15–20% of individuals with dermatomyositis, but most patients with lung disease have one of these antibodies. The antisynthetase syndrome consists of dermatomyositis (or polymyositis) with interstitial lung disease, arthritis and Raynaud's phenomenon [21]. Presence of antisynthetase antibodies is also associated with the clinical entity of 'mechanic's hands' in dermatomyositis, but they are not usually a feature of paraneoplastic dermatomyositis. Dermatomyositis may also indirectly be associated with lung disease as a consequence of treatment—either infection due to immunosuppression, or rarely drug-induced pneumonitis (methotrexate).

In *Sjögren's syndrome*, alveolitis can be demonstrated in about 50% of patients, but is often asymptomatic. Inspissated secretions may predispose to pneumonia; obstructive and interstitial lung disease may occur [22].

Vasculitis and neutrophilic dermatoses

(see also Chapter 49)

Vasculitis of many types may affect the lung. The major pulmonary vasculitides are Wegener's granulomatosis, Churg–Strauss disease, polyarteritis nodosa and Behçet's disease [23].

Behçet's disease. The frequency of lung involvement in Behçet's disease may be as high as 19%, although 5–10% is a more frequent estimate. Pleurisy or perihilar radiological opacities may be found [23], and pulmonary arterial aneurysm is an important feature, which can be fatal [24]. About 90% of patients with Behçet's disease complicated by pulmonary artery aneurysm also have thrombophlebitis.

Small-vessel vasculitis. Any form of small-vessel vasculitis can also affect the lung, even urticarial vasculitis. In one large series, over 20% of patients with urticarial vasculitis had pulmonary disease, either chronic obstructive pulmonary disease or asthma. Although it is not clear that these were always causally related to the vasculitis, obstructive pulmonary disease was more frequent in the group of patients with hypocomplementaemia [25], and lung vasculitis or serological evidence of LE was demonstrated in over 50% of patients with lung disease.

Wegener's granulomatosis [26,27]. This is a rare disease. The 'classic' syndrome is characterized by necrotizing granulomatous vasculitis of the upper and lower respiratory tracts, necrotizing glomerulonephritis and disseminated vasculitis of various organs. Skin lesions are frequent, including vasculitis with purpura, subcutaneous nodules and ulcers (see also Chapter 49). Upper airway disease causes nasal discharge, ulceration and bleeding, and oral ulceration. Pulmonary changes are typical with bilateral infiltrate, nodules or cavities. Subglottic or tracheobronchostenosis may also occur. There is no hilar or mediastinal lymphadenopathy. Prognosis is poor in patients with lung or renal disease; chronic nasal staphylococcal carriage is also associated with a poorer prognosis. Treatment consists of immunosuppressive agents (cyclophosphamide, azathioprine, chlorambucil and methotrexate). Trimethoprim-sulfamethoxazole (co-trimoxazole) also appears to be of benefit in induction of remission [28]. Diffuse alveolar haemorrhage, due to extensive pulmonary capillaritis, is a life-threatening complication of Wegener's granulomatosis—it also occurs in microscopic polyangiitis, and more rarely in SLE, antiphospholipid syndrome, Behçet's disease and secondary to drugs such as D-penicillamine [29].

Churg–Strauss syndrome (allergic granulomatous angiitis) [26,27]. This rare condition comprises rhinitis, asthma, pneumonitis, fever, malaise, eosinophilia (usually over 10%) and widespread vasculitis, which may cause skin lesions, neuropathy and cardiac or less commonly renal disease. Cutaneous lesions include palpable purpura and nodular lesions. Distinction from Wegener's granulomatosis or microscopic polyangiitis may be difficult in the early stages—peripheral eosinophilia is the most useful discriminatory feature [30], but eosinophils in inflammatory infiltrates may occur in all three disorders (also in SLE and Sjögren's syndrome), as may mononeuritis multiplex. Cardiac disease is more frequent in Churg–Strauss syndrome than in Wegener's granulomatosis, but is not specific; a history of asthma and other allergies with the other features suggest Churg–Strauss syndrome [23,26]. There is some concern that leukotriene receptor antagonists may provoke Churg–Strauss syndrome in patients with asthma, although an alternative explanation is simply that disease progression or altered corticosteroid therapy allowed additional clinical features to become apparent [31,32]. Therapy consists of high-dose corticosteroids, if necessary with other immunosuppressive agents such as cyclophosphamide, azathioprine or chlorambucil.

PAN and microscopic polyangiitis (microscopic polyarteritis) [26]. These conditions are distinguished by the size of vessels affected and by the usual absence of antineutrophil cytoplasm antibodies against myeloperoxidase (MPO-ANCA) in 'classic' PAN. The term 'polyangiitis' is preferred to polyarteritis for the microscopic disease, as arterioles, venules and capillaries may all be affected. Lung disease is not a particular feature of classic PAN, although bronchial arteries can be affected. By contrast, microscopic polyangiitis has many similarities to Wegener's granulomatosis, including nasopharyngeal involvement, renal vasculitis and tendency to cause alveolar haemorrhage [26,29]. However, the presence of granulomas and proteinase 3-ANCA (which suggest the diagnosis of Wegener's granulomatosis) help to distinguish these disorders.

Neutrophilic dermatoses. Pulmonary and major airway involvement have been described with pyoderma gangrenosum and neutrophilic dermatoses [33–37], usually comprising focal, dense neutrophilic infiltrates with scattered radiological opacities. Tracheal lesions may occur. Endobronchial involvement may also occur in eosinophilic states such as the hypereosinophilic syndrome, although cardiac disease is more important in this condition.

Other systemic diseases

Sarcoidosis [38] is discussed in Chapter 58. Hilar lymphadenopathy occurs with erythema nodosum in acute sarcoidosis. Pulmonary involvement is the major feature in chronic sarcoidosis, about 30% of such patients also having skin lesions.

Multicentric reticulohistiocytosis is associated with pleural effusion and hilar lymphadenopathy [39]; it may also occur as a paraneoplastic phenomenon.

Scleromyxoedema has been associated with lung disease, causing dyspnoea, in a sixth of reported cases [40]. Pulmonary hypertension has been reported.

Amyloidosis (Chapter 57). Involvement of the respiratory tract is common in primary amyloidosis; it may cause dyspnoea, but is often asymptomatic.

Lymphomatoid granulomatosis [41,42] is a rare disease which primarily affects the lung; radiology shows multiple,

small nodules that predominantly affect the periphery of the lower lung fields. Cutaneous lesions are present in about 50% of cases, typically on the face, and consist of infiltrated flat or nodular lesions that may become necrotic and ulcerated. Histologically, there are necrotizing angiocentric lesions of various organs, with an infiltrate of atypical lymphocytes. Epstein–Barr virus infection has been demonstrated [43]. The condition behaves as a lymphoma with poor prognosis; corticosteroids and cyclophosphamide may help in some cases.

Miscellaneous

Yellow nail syndrome (MIM #153300). Associated respiratory features include recurrent pleural effusion, bronchiectasis and chronic infections such as empyema [44,45].

Hoarseness as a sign of systemic disease [46]. Hoarseness from laryngeal or tracheal involvement is an important audible sign of certain systemic diseases with skin involvement. Examples are pachyonychia congenita, de Lange's syndrome, Farber's disease, erythema multiforme, sarcoidosis, secondary syphilis, epidemic typhus, LE and dermatomyositis. Voice changes are of major diagnostic value for the recognition of lipoid proteinosis, pemphigus vulgaris, relapsing polychondritis and hypothyroidism. Carcinoma of the larynx may complicate some of these chronic conditions.

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Haematology [1]

Anaemia. The mucocutaneous signs of iron-deficient or hypochromic anaemia—pallor, koilonychia (Fig. 59.12), brittle and ridged nails, angular cheilitis and atrophic glossitis—are recognized, but unreliable indicators of anaemia, especially compared with the ease of a blood-haemoglobin estimation. Pallor is usually only discernible if the haemoglobin level is below 9.0 g/dL, and this in turn is often dependent on temperature and skin blood flow. When anaemia is acute and extreme, retinal haemorrhages may be present [1].

Syndromes associated with gastrointestinal haemorrhage may point to iron deficiency and anaemia; perhaps hereditary haemorrhagic telangiectasia (Osler–Rendu–Weber disease, Chapter 50) and blue rubber-bleb naevus syndrome (Chapter 15) are the most noteworthy. Occasionally, iron deficiency is linked with generalized pruritus [2], but this association remains controversial.

There are no specific cutaneous markers of megaloblastic anaemias, but in pernicious anaemia (PA) the deep-red cobblestone appearance of the tongue is an archetypal, but late manifestation. A lemon tinge of jaundice due to excess production of unconjugated bilirubin subsequent to defective erythropoiesis is characteristic. Premature greying of the hair (canities) is a recognized occurrence, as is melanin pigmentation of the skin. Other autoimmune associations such as vitiligo, thyroid disorders and Addison's disease may occur, the latter sometimes producing its own pigmentary changes, especially in the skin creases and mucosal surfaces. Late onset of vitiligo may be of particular significance as an indicator of PA.

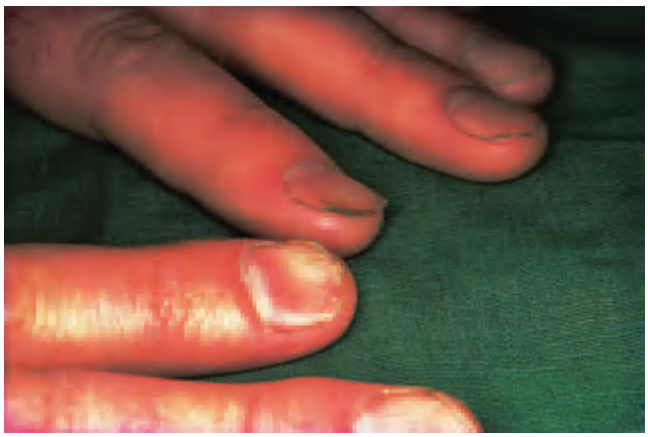

Fig. 59.12 Koilonychia. (Courtesy of Dr P. Dufton, Clatterbridge Hospital, Wirral, UK.)

Sickle cell anaemia may be suggested by the occurrence of leg ulcers, particularly when occurring at an early age. Unequal growth of the digits as a result of dactylitis in childhood may result in hand–foot syndrome [1]. Haemosiderosis and melanosis of the legs may also occur [3]. In dermatitis herpetiformis, anaemia is often due to dapsone-induced haemolysis [4], but malabsorption from gluten enteropathy may result in folate deficiency. This reduction in folate may also occur in extensive skin disease and occasionally causes a macrocytic anaemia. Anaemia not uncommonly occurs in patients with erythroderma [5], but this in part may be explained by a haemodilution effect. In dermatoses in which there is an increased turnover of skin, such as psoriasis, iron may be lost; this may be aggravated by a relative malabsorption of iron from a dermatogenic enteropathy [6]. However, defective handling rather than real deficiency may more often explain the hypoferraemia.

Leukocytosis is common with infection, but may frequently occur in erythroderma, without coexistent sepsis [5]. Leukocytosis also occurs in pustular psoriasis, pustular miliaria, erythema multiforme and as a result of corticosteroid therapy.

A neutrophil leukocytosis usually occurs in acute febrile neutrophilic dermatosis (Sweet's syndrome) (Chapter 49). Approximately 10–15% of published cases of Sweet's syndrome are associated with malignancy, the commonest being acute myeloid leukaemia; but correlation with other myelo- and lymphoproliferative disorders is well documented [7,8], including a small number of cases of non-Hodgkin lymphoma [9]. Both typical Sweet's syndrome and a variant termed disseminated pustular dermatosis have been described in polycythaemia rubra vera [10,11].

Several cases have been reported in which a polycyclic dermatosis, possibly representing an allergic reaction to exogenous factors, has been associated with a blood eosinophilia [12]. Sézary cell counts may be raised in an erythrodermic variant of mycosis fungoides (Sézary syndrome) or a pre-Sézary syndrome state, but may also occur in exfoliative erythroderma with a non-specific dermatitis as its aetiology [13].

Down's syndrome in infants is associated with increased risk of haematological abnormalities, including a vesiculopustular eruption with a myeloproliferative disorder that may be self-limiting. It is important to differentiate this and other benign or transient conditions from potentially life-threatening infections or conditions that may progress to leukaemia [14].

Platelets. Purpura may arise from intravascular, vascular or extravascular mechanisms (Chapter 48). Whilst decreased platelet formation as in Wiskott–Aldrich syndrome or

increased platelet consumption as in Kasabach–Merritt syndrome are obvious, intravascular causes of purpura, excessive platelet production or thrombocythaemia, as found in some myeloproliferative disorders, can also give rise to it [15]. Thrombocythaemia may also give rise to cutaneous manifestations, which are often present at the time of primary diagnosis in essential thrombocythaemia; these can include haematoma, bruising, purpura, erythromelalgia, livedo reticularis, recurrent superficial thrombophlebitis, ischaemic limbs and leg ulcers [16].

Disseminated intravascular coagulation (DIC) resulting from severe sepsis and giving rise to purpura fulminans is a more dramatic and fulminant presentation of thrombocytopenia than idiopathic thrombocytopenic purpura. Purpura fulminans can also represent a marker of protein C deficiency [17]. A diffuse angioma-like change has been rarely associated with chronic DIC, possibly as a result of vasculitis [18].

Vascular purpura (Chapters 48 and 49), with or without evidence of vasculitis, is probably the largest group causing purpura. This includes hypersensitivity vasculitis, of which Henoch–Schönlein purpura is the best recognized cause of palpable purpura. Cases of mixed cryoglobulinaemia often develop palpable purpura on the lower limbs and can also exhibit livedo reticularis, cold-induced urticaria and frank ulceration or gangrene. Purpuric vasculitis can also be found in most of the connective tissue diseases, urticarial vasculitis and occasionally with malignancy. More rarely, purpura can occur with larger vessel necrotizing vasculitis, including PAN, giant cell arteritis and granulomatous vasculitis. Urticaria, livedo and necrotic ulceration are also cutaneous manifestations of these large-vessel vasculitides.

Between the inflammatory and non-inflammatory purpuras are the pigmented purpuric eruptions, in which the inflammatory changes are much less severe. The non-inflammatory causes include plasma cell dyscrasias, amyloidosis and embolic phenomenon with cholesterol or fat [15].

Livedo and erythromelalgia may be causally linked with thrombocythaemia and PRV. Classically, the latter may present with pruritus, especially on cooling of the skin, often after bathing, although iron deficiency may be a co-factor [19].

Antiphospholipid syndrome. Cutaneous manifestations may occur with antiphospholipid syndrome, including livedo reticularis with or without cerebrovascular disease, leg ulcers, necrotizing purpura, distal cutaneous ischaemia, peripheral gangrene, thrombophlebitis and haemorrhage [20]. An examination for antiphospholipid antibodies may be worthwhile in all patients with thrombotic cutaneous signs [20].

Haemorrhagic cellulitis, a syndrome presenting with painful erythema, followed by dermal haemorrhage, sloughing of overlying epidermis, associated with a non-cutaneous Gram-positive or -negative infection and underlying systemic disease, has been linked with the presence of tumour necrosis factor-α [21].

ESR is non-specifically raised in many inflammatory dermatoses, particularly erythroderma, when it is often associated with a raised gammaglobulin [5].

Lymphoma. After the gastrointestinal tract, the skin is the extralymphatic organ most frequently affected by malignant lymphomas. Most are cutaneous T-cell lymphomas, which are dealt with elsewhere (Chapter 54), but cutaneous involvement with B-cell tumours is not that uncommon and may represent up to one-third of such primary neoplasms [22]. Specific skin involvement in Hodgkin's disease is rare, but does occur in around 0.5% of cases [23]. Approximately 50% of patients with lymphomatoid granulomatosis have cutaneous involvement, mostly scattered nodules, but other changes include eroded and crusted lesions, facial oedema, papules and a folliculitis-like eruption [24].

Leukaemia. Specific cutaneous leukaemic infiltrates can occur in all types of leukaemia, but are more common in monocytic forms [25,26]. Very rarely, a long latent period can occur from cutaneous presentation to clinical illness [27]. Urticaria is documented as being an uncommon manifestation of acute basophilic leukaemia [28]. A pemphigus foliaceus-like dermatosis has been described in chronic lymphocytic leukaemia [29]. Paraneoplastic pemphigus in association with chronic B-cell lymphocytic leukaemia has been reported, and its more aggressive clinical behaviour was noted by comparison with the less aggressive course associated with neoplasms such as thymomas and Castleman's disease [30]. The leukaemias are discussed in more detail elsewhere (Chapter 54).

Pyoderma gangrenosum (PG) (Chapter 49) is perhaps a better-known cutaneous presentation of myeloproliferative diseases, including leukaemias [31]. PG and subcorneal pustular dermatosis may be associated with paraproteinaemia with or without multiple myeloma [32]. PG can occur in allogeneic bone marrow transplant recipients [33], but is more commonly a manifestation of inflammatory bowel disease and rheumatoid arthritis.

Disseminated cutaneous granulomatous eruptions have been reported with myelodysplastic syndrome and acute myeloid leukaemia [34].

Miscellaneous. Blood dyscrasias are common in dyskeratosis congenita (DC) (Chapter 12) and in Fanconi's anaemia

(FA). In the latter, olive-brown skin pigmentation is a common finding. Both DC and FA represent familial forms of aplastic anaemia [35]. DC is a rare multisystem disease with a whorled hyperpigmentation of the skin, in which there is an 80% incidence of bone marrow failure; pulmonary manifestations have infrequently been reported, and immune dysfunction and consequent infection contribute to the morbidity and mortality of the disorder. The X-linked form of DC has been identified on Xq28 and designated as *DKC1* [36]. RTS (Chapter 12), a rare autosomal-recessive condition caused by a DNA repair defect, has been associated with myelodysplasia. Early onset of skin changes of poikiloderma, photosensitivity, scaling, hyperkeratosis and disordered hair growth are characteristic together with ocular and skeletal abnormalities [37].

Raynaud's phenomenon, scleroderma and oedema are features of the plasma cell dyscrasia found in the POEMS syndrome [38,39]. This multisystem disease is characterized by the presence of polyneuropathy, organomegaly, various endocrine disorders and the aforementioned skin changes; these features are thought to be secondary to the plasma cell dyscrasia and in most cases the production of IgM [40]. Thrombocytosis has been noted in many cases, less commonly polycythaemia [40]. The differentiation of POEMS from osteosclerotic myeloma with peripheral neuropathy does not appear to serve any clinical function [41]. Skin angiomas have been reported in many of the cases and a patient with angio-endotheliomatosis associated with Castleman's lymphoma and POEMS syndrome has been reported [39].

Bullous pemphigoid has also been reported, as well as the more commonly associated paraneoplastic pemphigus in Castleman disease [42].

Erythematous papules, nodules and urticarial weals may develop in the hypereosinophilic syndrome [43]; pruritus is a frequent finding [44]. Eosinophilic pustular folliculitis, apart from an association with human immunodeficiency syndrome, has haematological associations with myelodysplastic syndrome, bone marrow transplantation, leukaemia and lymphoma [45].

A papulonodular, pruritic, therapeutically resistant eruption occurring in patients with blood dyscrasias has been termed the eosinophilic dermatosis of myeloproliferative disease [46].

Concurrent polycythaemia and mastocytosis have been reported [47]. Cold agglutinins may manifest with Raynaud's syndrome, acrocyanosis or gangrene. Cold haemolysins may give rise to cold urticaria or Raynaud's syndrome.

Rarely, cutaneous extramedullary haemopoiesis may develop in myelofibrosis [48]; multicentric reticulohistiocytosis may also occur with this disorder [49]. PG in PRV may herald deterioration to myelofibrosis or myeloid leukaemia [50].

The histiocytic syndromes represent a rare group of disorders resulting from proliferation of the monocyte–macrophage cell line (Chapter 52). They can be divided into self-healing (non-X) or progressive (X) types. The histiocytosis X group includes Letterer–Siwe disease, in which cutaneous changes can take on a seborrhoeic dermatitis-like or purpuric appearance, although semi-translucent red-yellow papules are more typical skin changes. Hepatosplenomegaly is common, but lymphadenopathy is a rarer manifestation. Eosinophilic granuloma rarely shows cutaneous manifestations, and only about one-third of cases of Hand–Schüller–Christian disease do. Non-histiocytoses include self-healing reticulohistiocytosis, benign cephalic histiocytosis, sinus histiocytosis with massive lymphadenopathy and multicentric reticulohistiocytosis, amongst others [51].

Scleromyxoedema is associated with a paraproteinaemia, almost always IgG [52].

Scleroedema of Buschke may be associated with multiple myeloma as well as benign monoclonal gammopathies [53].

Necrobiotic xanthogranuloma is usually associated with paraproteinaemia [54], but not invariably [55].

Occasionally, von Willebrand's disease may show albinism; in the Hermansky–Pudlak syndrome, oculocutaneous albinism is associated with platelet dysfunction, as it is a similar disorder with the additional feature of pulmonary fibrosis [56,57].

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Bone and joint diseases

There are several diseases in which bone or joint abnormalities occur together with skin changes (Tables 59.9 and 59.10) [1,2]. In some instances, as occurs in several inflammatory diseases, these may be symptomatic; in other conditions they may be asymptomatic but demonstrated radiologically. For example, more than half of adults with *mastocytosis* may have diffuse bone disease detected radiologically [3], and the osteopoikilosis of *Buschke–Ollendorf syndrome* (Fig. 59.13) is asymptomatic and usually only demonstrated as an incidental finding or if the patient presents due to cutaneous elastomas. Bony changes may be an important factor in diagnosis in several *genodermatoses* [4,5] and *congenital lesions* (especially midline lesions, such as faun tail and facial or scalp nodules and pits) [6,7]. The genetic and metabolic basis for some of these are now well understood—for example, the role of G proteins in *McCune–Albright syndrome* [5].

Soft-tissue calcification, and less commonly ossification, occurs in numerous disorders [8]. It is particularly prominent in *childhood dermatomyositis* and is discussed in more detail in Chapter 56. *Progressive systemic sclerosis* and *CREST* (Chapter 56) are characterized by atrophy and dystrophic calcifications in the soft tissues, ultimately leading to joint deformities and resorption of the terminal tufts of the phalanges. Resorption of bone occurs at other sites as well, and marginal erosions may develop in the metacarpophalangeal and interphalangeal joints of the hands [9].

Table 59.9 Skin disorders that are commonly associated with bony abnormalities.

Disorder	Skin lesions	Bony change
Congenital/inherited		
Ectodermal dysplasias and keratodermas	Various	Chapter 34
Conradi–Hunermann syndrome	Chapter 34	Chondrodysplasia punctata
Neurofibromatosis	Neurofibromas, café-au-lait patches	Kyphoscoliosis, vertebral erosions, partial absence of sphenoid bone, cystic lesions, pseudarthroses
Tuberous sclerosis	Angiofibromas, ash leaf macules, collagenomas	Intracerebral calcification, bony sclerosis (especially skull), cortical thickening, bone cysts (especially phalanges)
Klippel–Trenaunay syndrome	Port-wine stains, other vascular lesions, lymphangioma	Bony hypertrophy, macrocephaly, polydactyly/syndactyly
Proteus syndrome	Soft-tissue overgrowth, epidermal naevi	Partial gigantism (usually hand/foot), scoliosis and vertebral abnormalities, exostoses, osteochondromas
Maffucci's syndrome	Haemangiomas, lymphangiomas	Enchondromas (especially hands), chondrosarcoma
Sturge–Weber syndrome	Port-wine stain	Calcification of meningeal vessels, hemiatrophy
Gorham's syndrome (osteovascular dysplasia)	Vascular malformations	Lytic lesions, 'disappearing bones'—usually unilateral
Gardner's syndrome	Cysts, lipomas, fibromas	Osteomas, exostoses
Ehlers–Danlos syndrome	Skin laxity, atrophic scars, molluscoid pseudotumours	Kyphoscoliosis (especially type IV), abnormalities of long bones, short clavicles, occipital exostoses (all in type IX)
Osteogenesis imperfecta	Atrophic skin	Brittle bones, otosclerosis
Marfan syndrome	Arachnodactyly	Increased limb length, arachnodactyly, chest deformities, joint laxity
Focal dermal hypoplasia (Goltz's syndrome)	Dermal atrophy, telangiectasia, fatty herniation	Syndactyly, scoliosis, skeletal asymmetry, osteopathia striata, bony tumours, dental abnormalities
Rothmund–Thomson syndrome	Poikiloderma	Hypoplasia of thumbs or forearm bones, dental abnormalities, osteosarcoma
Linear naevus sebaceus syndrome	Sebaceous naevi (often facial or widespread)	Asymmetry (especially skull), spinal abnormalities, hypophosphataemic rickets
Linear epidermal naevus syndrome	Epidermal naevi	Asymmetry, kyphoscoliosis, bone cysts, equinovarus deformity
Incontinentia pigmenti	Atrophic streaks, fatty herniations	Dental abnormalities (conical teeth), spina bifida occulta, skeletal asymmetry, vertebral/rib abnormalities, phalangeal lytic lesions
Hypomelanosis of Ito	Pale, whorled streaks	Kyphoscoliosis, spina bifida occulta, skeletal asymmetry, various digital anomalies
Buschke–Ollendorf syndrome	Elastomas	Osteopoikilosis
McCune–Albright syndrome	Pigmented macules	Fibrous dysplasia, asymmetry, scoliosis, sclerosis of base of skull, fractures, rickets, osteomas
Lipoid proteinosis	Confluent waxy papules, alopecia	Intracranial calcification
Disseminated lipogranulomatosis	Nodules on digits	Destructive arthropathy
Pseudoxanthoma elasticum	'Plucked chicken' appearance of neck, flexures	Calcification of soft tissues, falx cerebri, dura, choroid plexus
Nail–patella syndrome	Hypoplastic nails	Absent or small patellae, iliac horns, scoliosis, hypoplasia of first rib, absent fibulae
Fabry's disease	Angiokeratomas	Necrosis of femoral head, arthritis of distal interphalangeal joints
Werner's syndrome	Premature ageing	Osteoporosis, sclerodactyly, joint contractures, sarcomas
Progeria	Aged appearance	Skeletal dysplasia, osteolysis, osteoporosis, dislocation or avascular necrosis of hip, non-union of fractures
Gaucher disease	Pigmentation	Bone pain, fractures, cortical destruction
Naevus of Ota	Facial naevus	Posterior cranial fossa defects
Midline lesions	Various, includes scalp nodules/cysts, nasal gliomas, pits and sinuses, faun tail	Various; connections between skin and CNS may be associated with bony defects, e.g. spina bifida

(*continued*)

Table 59.9 (*cont'd*)

Disorder	Skin lesions	Bony change
Infection		
Local		
Dental sinus	Localized nodule, may discharge	Usually periapical abscess, may be retained root, cyst
Chronic ulcer	Skin ulcer	Underlying osteomyelitis
Systemic		
Syphilis	Various; see Chapter 30	Periostitis, osteitis, focal osteolysis or sclerosis
Cryptococcosis	Skin nodules	Osteolytic lesions
Blastomycosis	Skin nodules	Osteomyelitis
Inflammatory and systemic diseases		
Psoriasis and Reiter's syndrome	See Chapter 35	Erosive arthritis, sacroiliitis
Palmoplantar pustulosis	Palm and sole pustules	See text (this section)
Sarcoidosis	See Chapter 58	Honeycomb change and bone cysts (especially hands), acrosclerosis
Scleroderma	See Chapter 56	Resorption of terminal phalanges (acronecrosis), soft-tissue calcification, erosive arthritis Linear scleroderma may show underlying linear hyperostosis Acro-osteolysis is typical of vinyl chloride disease
Scleromyxoedema	Mucinosis	Arthralgia, carpal tunnel syndrome, acro-osteolysis
Acne fulminans/conglobata	See Chapter 43	Lytic lesions, especially clavicles; clavicular hyperostosis
Neutrophilic dermatoses	See Chapter 49	Periosteal reaction adjacent to pyoderma gangrenosum, osteomyelitis-like lesions (chronic recurrent multifocal osteomyelitis)
Gout	Tophi	Erosive arthritis
Multicentric reticulohistiocytosis	Skin and subcutaneous nodules	Destructive polyarthritis, especially terminal interphalangeal joints (similar to rheumatoid disease), atlantoaxial disease
POEMS syndrome	Pigmentation, sclerosis, hypertrichosis	Sclerotic lesions, may have central lucency
Neoplastic		
Naevoid basal cell carcinoma syndrome (Gorlin's syndrome)	Basal cell carcinomas	Cysts of jaw and other bones, frontal bossing, calcification of falx cerebri, bifid ribs, spina bifida and other spinal abnormalities, polydactyly/syndactyly, shortened metacarpals
Histiocytoses (Langerhans' cell histiocytosis, Rosai-Dorfman disease, Erdheim–Chester disease, juvenile xanthogranuloma, others)	See Chapter 52	Lytic lesions, defects of skull and mandible, vertebral lesions
Mastocytosis	See Chapter 47	Diffuse or focal osteoporosis or sclerosis
Fibromatoses	See Chapter 53	Various; most characteristic are cystic lesions of skull and long bones in infantile myofibromatosis
Other		
Subungual exostosis	Hard subungual nodule	Underlying exostosis
Osteoma cutis	Hard plaque(s)	Focal bone formation, possibly primary or within a preceding lesion
Becker's naevus	Pigmented hairy lesion	Scoliosis, spina bifida
Thyroid acropachy	Finger clubbing	Expanded distal phalangeal tuft
Acromegaly	See p. 59.2	Increased periosteal bone growth
Fat embolism	Petechial rash on anterior trunk	Causative fracture(s)

POEMS, polyneuropathy, organomegaly, endocrinopathy, M protein, skin changes (syndrome).

Table 59.10 Some inflammatory and metabolic disorders that affect skin and joints.

Psoriasis, Reiter's syndrome, palmoplantar pustulosis
Connective tissue diseases
Lupus erythematosus (especially systemic and subacute cutaneous)
Mixed connective tissue disease
Sclerodermas
Still's disease
Rheumatic fever
Rheumatoid disease
Gout
Behçet's disease and related disorders
Sarcoidosis
Interstitial granulomatous dermatitis with plaques and cords
Vasculitis (any; see Chapter 49)
Neutrophilic dermatoses
Bowel-associated dermatosis–arthritis syndrome
Acne fulminans and conglobata
Relapsing polychondritis
Periodic fevers, e.g. familial Mediterranean fever
Whipple's disease
Pancreatic panniculitis
Amyloidosis
Multicentric reticulohistiocytosis
Scleromyxoedema, cardiac myxoma
Ochronosis
Acromegaly
Fabry's disease

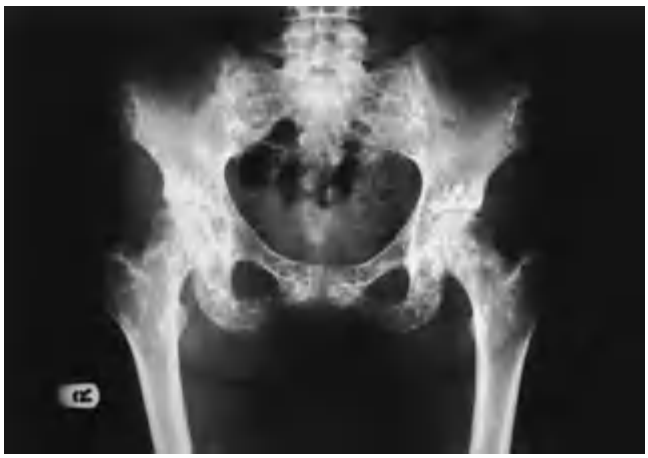

Fig. 59.13 Osteopoikilosis in Buschke–Ollendorf syndrome (Courtesy of Dr C. Blasdale, Newcastle upon Tyne, UK.)

Skin lesions may also occur as a consequence of bone injury. *Fat embolism*, particularly with fractures of the long bones, may present cutaneously with petechiae, usually 2 or 3 days after trauma; other symptoms may include respiratory distress and cerebral impairment. The intensity of the petechiae may indicate the severity of other organ involvement. Fat globules may be observed histologically in affected tissue, including the skin, when suitably processed. The distribution of skin petechiae is principally on the anterior trunk; they are seldom found on the back or face [10].

Inflammatory conditions

Arthralgia and/or arthritis is frequent in a number of inflammatory and metabolic conditions which also affect the skin, such as psoriasis and sarcoidosis (Table 59.10). Most of these are discussed in more detail elsewhere, but some of the multisystem disorders are briefly described here.

Vasculitides and connective tissue disease. These are discussed in Chapters 49 and 56. Arthralgia or arthritis is a common feature of many disorders in this spectrum, occurring for example in about 90% of patients with systemic lupus erythematosus, two-thirds of those with Henoch–Schönlein purpura and about 40% of those with Behçet's disease.

Relapsing polychondritis (Chapter 65). Migratory arthritis of small and large joints, usually sparing the hands, is a frequent feature [11]. It probably occurs in about two-thirds of patients. Chondritis affecting spinal vertebra may cause chronic back pain.

Multicentric reticulohistiocytosis (Chapter 52). Polyarthritis, especially affecting the interphalangeal joints of the hands, occurs as the first manifestation of the disorder in half to two-thirds of patients. It is typically rapidly progressive, and all of the synovium-lined joints may become affected, with arthritis mutilans the end result in one-third to half of cases. The erosions are strikingly symmetrical and well circumscribed, and accompanying osteoporosis is disproportionately mild. The arthritis may burn out, but residual hypertrophic osteoarthropathy may persist [9,12]. A disorder reported as familial histiocytic dermatoarthritis [13] has been described in which there is early onset of a papulonodular eruption, a symmetrical destructive arthritis and ocular lesions such as cataract and glaucoma. Subsequent cases and electron microscopy studies [14] suggest that this may be part of the spectrum of multicentric reticulohistiocytosis, but this remains uncertain.

Palmoplantar pustulosis (Chapter 35). A group of overlapping joint diseases occur in conjunction with palmoplantar pustulosis, and less frequently with psoriasis, acne and non-dermatological conditions such as inflammatory bowel disease. The various patterns have been brought together under the acronym SAPHO (*s*ynovitis, *a*cne, *p*ustulosis, *h*yperostosis and *o*steitis). Individual components include predominant sternoclavicular disease (variously termed intersternocostoclavicular osteitis, sternoclavicular pustulotic osteitis, sternocostoclavicular hyperostosis, pustulotic arthro-osteitis or anterior chest wall syndrome, Fig. 59.14) and a more widespread non-purulent chronic recurrent multifocal osteomyelitis [15–17]. Diagnostically, scintigraphy is more sensitive than radiographic

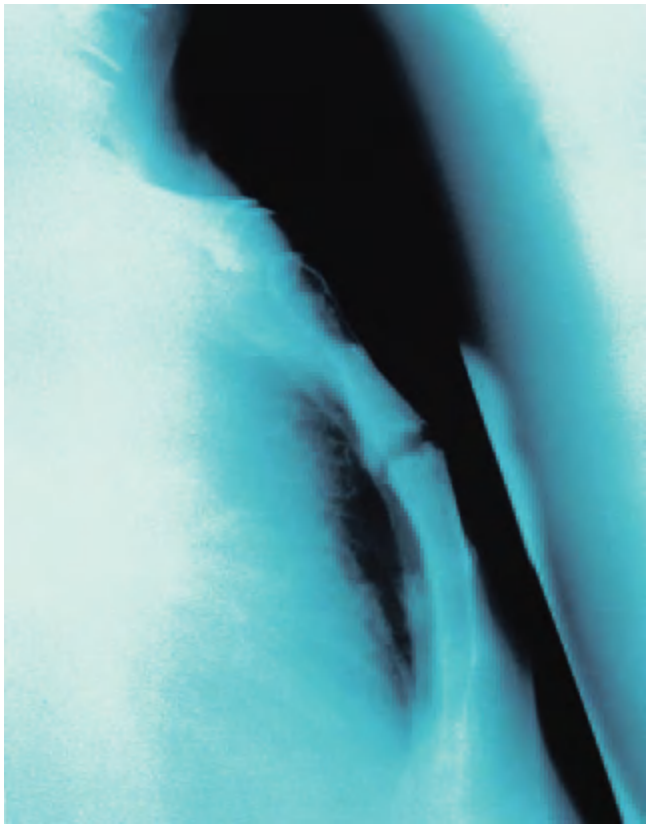

Fig. 59.14 Tomogram showing inflammatory changes of the sternal synchondrosis with widening and 'woolly' appearance in a patient with palmoplantar pustulosis.

examination. Therapeutic options include non-steroidal anti-inflammatory drugs, doxycycline, methotrexate and intra-articular corticosteroid injections.

Acne. In addition to the SAPHO pattern described above, arthritis of larger joints occurs in about a third of patients with acne fulminans—most have arthralgia. This is associated with fever, systemic malaise and weight loss, and can usually be controlled with short-term oral corticosteroids. Other skeletal manifestations linked to acne are those secondary to therapeutic agents (skeletal hyperostosis due to isotretinoin, usually only if given long term, and arthralgia in the lupus-like syndrome caused by minocycline); infectious arthritis due to *Propionibacterium acnes* may also occur [18].

Periodic fevers. The most important are familial Mediterranean fever (FMF; MIM *249100), FMF with amyloidosis (MIM *134610), Hibernian fever—now redesignated as *t*umour necrosis factor (TNF) *r*eceptor–*a*ssociated *p*eriodic *s*yndrome, TRAPS, MIM #142680—and the hyperimmunoglobulin D and periodic fever syndrome (HIDS; MIM #260920). All are characterized by recurrent fever with serositis (peritonitis-like abdominal pain, pleurisy, pericarditis), headache and arthralgia or arthritis [19–23]. In FMF, there may be urticarial lesions, subcutaneous nodules, purpura, leukocytoclastic vasculitis (described, probably incorrectly, as Henoch–Schönlein purpura), or transient cellulitis-like erythematous plaques [19–22]. Like the articular symptoms [22], the erysipelas-like lesions are predominantly on the lower leg [20]. Erythematous macules and nodules, but not the erysipelas-like lesions, may occur in HIDS [19]. In TRAPS, the cutaneous features include migratory patches, oedematous plaques and periorbital oedema [23]. FMF is due to a variety of mutations in the *MEFV* gene [24]; classic-type HIDS is due to mutations in the *MVK* gene leading to deficient activity of mevalonate kinase [25,26]; and TRAPS is due to mutations in *TNFRSF1A,* which codes for the 55-kDa TNF receptor [23].

Neutrophilic dermatoses. This group of disorders is discussed in relation to gastrointestinal and haematological disease in this chapter, and in more detail in Chapter 49. Sweet's syndrome may be associated with arthralgia, with a frequency of around one-third to over 60% in some series [27,28]. Multifocal osteomyelitis (usually in children), which may be chronic or recurrent, or localized osteitis may occur in association with PG [29,30].

Interstitial granulomatous dermatitis. This histological pattern may occur in many situations including infections (such as borreliosis or hepatitis C infection), lymphoreticular malignancies, drug eruptions and autoimmune disease. Various skin lesions have been described in *palisading neutrophilic and granulomatous dermatitis (PNGD) of immune complex disease,* including papulonodules, urticaria, vasculitis and granuloma annulare-like lesions. Arthralgia may occur due to systemic vasculitis, and PNGD may occur in rheumatoid arthritis [31]. There are also several reports of a related disorder in which arthritis occurs together with cutaneous lesions that may be plaques or subcutaneous cords, which are linear or arciform and typically on the trunk or proximal limbs; this disorder is usually termed *interstitial granulomatous dermatitis with plaques* [32,33].

Metabolic conditions

Gout may present to dermatologists due to tophi, but is generally diagnosed due to acute arthropathy or chronic erosive joint disease. Recent developments from the rheumatological perspective are use of CT or MRI to detect tophi within the carpal tunnel, and a suggestion that ciclosporin in patients with renal transplant may predispose to gout. Intermittent excessive alcohol consumption remains the major aetiological factor [34].

Haemochromatosis. Arthropathy is a frequent complication, probably due to abnormal accumulation of metal ions [35,36]; other aspects are discussed elsewhere in this chapter.

Ochronosis is discussed in Chapter 65. Calcium crystal deposition accompanies the cartilage degradation characteristic of this disease [36].

Amyloidosis (Chapter 57) is closely linked to joint disease, as rheumatoid arthritis is the commonest cause of secondary amyloidosis [37]. Amyloid A has cytokine-like properties and may be actively involved in inflammatory processes.

Scleromyxoedema causes arthralgia or arthritis in 10% of patients, and is also associated with rheumatoid arthritis and sicca syndrome. Carpal tunnel syndrome and acroosteolysis may also occur [38].

Other metabolic disorders that may have skin and bony or joint symptoms include Fabry's disease, Gaucher's disease and Farber's disease [36]. Bone symptoms are an important part of *Gaucher's disease* [36,39]. Bone crises may be related in part to haemorrhage; they may be treated with prednisolone, bisphosphonates or with prophylactic enzyme replacement therapy. Avascular necrosis, pathological fractures and cortical destruction of bones with extraosseous extension also occur.

Infections

Numerous infective conditions may affect both the skin and joints. Arthralgia is associated with the exanthem of viral infections such as parvovirus, hepatitis B or rubella. *Reiter's syndrome* may be provoked by genital infections such as *Chlamydia*, or by various enteritic organisms such as *Yersinia*, *Shigella* or *Campylobacter*. Arthralgia is frequent, with constitutional symptoms and a non-specific exanthem, in brucellosis. Other bacterial causes of arthritis with pustular or vasculitis skin lesions include disseminated *gonococcal infection* and *chronic meningococcal septicaemia*. Arthralgia may be prominent in spirochaetal diseases such as *Lyme disease* or *secondary syphilis*. In the latter, the flat bones of the skull are frequently involved, causing headache. Osteomyelitis is a feature of tertiary syphilis. Arthralgia is the presenting feature in two-thirds of patients in the early stage of *Whipple's disease* [40,41].

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Annular and figurate reactive erythemas

Numerous dermatoses produce annular lesions, many of which occur in conjunction with other lesional morphology (for example, in psoriasis) or lead to a specific diagnosis (for example, tinea corporis or granuloma annulare). However, there are a group of often chronic, annular and figurate eruptions that do not easily lead to a specific diagnosis. This group, and some of the important differential diagnoses, may have systemic causes and may pose diagnostic and therapeutic problems. The nomenclature of this group of disorders has been discussed in detail elsewhere [1] but most of the descriptive and eponymous terms that are applied do not help greatly in management of the patient. Equally, although the pathological features can be divided into those cases with superficial or deep perivascular lymphohistiocytic infiltrate ('superficial or deep gyrate erythema' [2], clinically corresponding to annular erythema with scaling or with smooth surface respectively), the clinical relevance of this is not clear.

For the purposes of this section, the following will be discussed:

1 erythema (chronicum) migrans
2 erythema marginatum (rheumaticum)
3 erythema gyratum repens
4 erythema annulare centrifugum
5 annular erythema of infancy
6 annular erythema associated with extractable nuclear antigens.

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Erythema migrans (Chapter 27)

SYN. ERYTHEMA CHRONICUM MIGRANS

Erythema migrans is the term applied to skin lesions of Lyme borreliosis. It is caused by infection with *Borrelia burgdorferi sensu lato*, *B. afzelli* or *B. garinii*, which are spirochaetes transmitted by bites from *Ixodes* ticks [1]. The primary lesion of erythema migrans at the site of a tick bite is usually solitary and usually macular but may be urticated or haemorrhagic (lesions of *B. burgdorferi* are usually more inflammatory and more rapid in evolution than those caused by the other species). Malaise, flu-like symptoms and lymphadenopathy are common at this stage. The lesion expands slowly over a period of weeks to a median size of about 15 cm with central clearing (the early-localized stage) [2–6]. The term 'chronicum' is something of a misnomer. In the early disseminated stage, which occurs within a few weeks, multiple similar annular plaques may develop in up to half of patients and may be multiple. These may have a polycyclic pattern that resembles erythema annulare centrifugum or an annular erythema multiforme-like appearance.

Histology shows a deep and superficial perivascular lymphocytic infiltrate, which may contain plasma cells.

Treatment is usually with tetracyclines (generally doxycycline 100 mg b.d. for 2–3 weeks) or ampicillin; third-generation cephalosporins are the alternative. Vaccination is also now available.

Other skin lesions that may occur include nodular lymphocytomas (early disseminated stage) and acrodermatitis chronica atrophicans (late stage). Associated systemic manifestations include arthralgia and arthritis, myalgia, cardiac involvement (especially atrioventricular block or pericarditis) and a variety of neurological manifestations (cranial nerve palsies, peripheral neuropathy, meningitis, encephalitis).

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Erythema marginatum (rheumaticum)

SYN. ERYTHEMA ANNULARE RHEUMATICUM

Rashes of various morphologies can occur in rheumatic fever and Still's disease, erythema marginatum being the most classical and distinctive, but now rare, pattern. Along with carditis, migratory polyarthritis, chorea and

subcutaneous nodules, it is one of the Duckett Jones major criteria for the diagnosis of rheumatic fever, and is probably specific for this diagnosis (two major, or one major and two minor, criteria are strictly required for the diagnosis but newer echocardiography techniques and Doppler colour flow mapping may extend the diagnostic criteria). However, erythema marginatum may be subtle, and only occurs in about 10% of patients (especially in children) with active rheumatic fever [1–3]; one study of 126 children (80 first attacks and 46 recurrences) did not identify any with erythema marginatum [4].

The eruption consists of rings or segments of rings, pale or dull red in colour, flat or palpably thickened. The rings may be discrete, or may enlarge and merge to produce a polycyclic or reticular pattern.

Characteristically, the lesions fade in a few hours or at most in 2–3 days, and tend to be more prominent in the afternoon. Recurrent crops, often in different sites, may appear at intervals for many weeks. The lesions occur most frequently on the trunk, especially on the abdomen, but are occasionally seen on the limbs. They are asymptomatic.

Histologically, an infiltrate of polymorphs can help to distinguish this disease from other annular erythemas [5], but is not always found.

A similar eruption has been reported with psittacosis [6], and erythema marginatum has been reported preceding attacks of hereditary angioneurotic oedema [7,8].

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Erythema gyratum repens

The first description of this condition in 1953 is attributed to Gammel, who reported a case associated with breast carcinoma [1]. It is exceptionally rare but clinically distinctive (Fig. 59.7) [2–5].

Clinical features [2,4,6,7]. Regular waves of erythema spread over the body to produce a series of concentric figurate bands in a pattern resembling the grain of wood. The characteristic feature is the way rings, swirls or waves appear within existing lesions to form a concentric pattern of sequential eruptions, with day-to-day migration of the leading edge by about 1 cm. Scaling, usually at the trailing edge, and itch are usually prominent. This is by contrast to the more common 'annular erythemas' of erythema annulare centrifugum pattern, in which each lesion is usually a distinct ring or arc with variable but usually not prominent scale, and no concentric arrangement. Hyperkeratosis of palms occurs in about 10% and has been reported in both paraneoplastic and idiopathic cases.

Aetiology. This eruption has been briefly discussed earlier (p. 59.20) as a paraneoplastic eruption; about 80% of reported cases are associated with an internal tumour [4,6–8], most commonly of the lung. Other tumour sites include bowel, urogenital tract, pancreas and haematological neoplasia.

However, not all cases are paraneoplastic. Since the report of a case associated with tuberculosis [9], several cases have been reported in apparently well patients or associated with other disorders such as CREST syndrome (reviewed in [4,6]). Drug hypersensitivity has also been implicated. Some of these non-paraneoplastic cases are questionable in the absence of photographic documentation, but some cases appear very convincing, such as a patient with recurrent pregnancy-associated episodes [10]. An infant was reported in whom lesions were controlled by long-term systemic ketoconazole [11].

Pathology [12]. There is a superficial, and occasionally deep, perivascular lymphocytic infiltrate associated with acanthosis, spongiosis and parakeratosis. Deposition of C3 or IgG in the sub-lamina densa region supports the concept that the eruption is immunologically mediated, possibly by immune complex deposition [5,13].

Investigation. Biopsy should be performed to exclude other causes such as unusual morphologies of vasculitis. Fungal infection should be excluded, especially tinea imbricata in relevant populations. The paramount issue is a detailed search for underlying malignancy. Skin biopsy is important as a similar gyrate eruption may be a prodromal manifestation of pemphigoid [14], and similar but rather localized lesions have been reported due to vasculitis in lupus erythematosus [15]; a morphologically similar disorder termed lupus erythematosus gyratus repens has been reported [16]. Necrolytic migratory erythema (p. 59.45) and erythrokeratoderma variabilis (Chapter 34) may produce very similar lesions, as may the subacute annular (Lapière) variant of psoriasis, although none of these typically have multiple concentric lesions. Cases of apparent idiopathic erythema gyratum repens have also been suggested to represent a stage in the evolution of pityriasis rubra pilaris [17,18].

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Erythema annulare centrifugum (EAC)

This term was originally used by Darier [1], who delineated EAC from a more scaly and itchy eruption described earlier by Colcott Fox as erythema gyratum perstans. The term EAC is conveniently applied to the annular erythemas that do not obviously fall into one of the more specific categories discussed previously, although EAC probably constitutes a mixed group of disorders with similar histological features. Annular erythema of infancy is discussed separately, as it can be defined by the age group, and annular erythemas associated with anti-SSA (anti-Ro) and anti-SSB (anti-La) antibodies can now be separated and discussed as a group.

Clinical features. EAC has been reviewed by several authors [2–6]. It is commonest in young and middle-aged adults, although onset may occur in infancy (discussed separately below). Some authors suggest a female preponderance [5]. A small, pink, infiltrated papule slowly enlarges and forms a ring, as the central area flattens and fades (Fig. 59.15). The rate of extension is variable; although a diameter of 6–8 cm may be achieved in less than 2 weeks, extension is usually much slower (typically 2–3 mm/day), especially in the cases with epidermal involvement. Extension may be irregular, to leave arciform segments. Lesions may be solitary or, more often, multiple. The edge may be quite flat or easily palpable with a superficial cord-like quality, and lesions may be smooth or show slight scaling behind the advancing edge. Rarely, vesiculation occurs. Itching is variable, but seldom intense. The commonest sites are the buttocks, thighs and upper arms, but any areas may be involved. Sometimes lesions are mainly on the extremities, but the face is seldom affected.

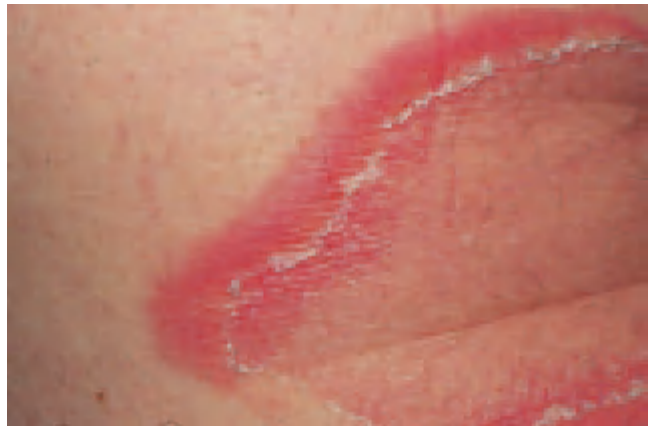

Fig. 59.15 Erythema annulare centrifugum; an expanding lesion with central clearing and scaling at the 'trailing edge'. This case was seasonally recurrent.

Individual lesions last for a few days, more often a few weeks, or slowly extend for a few months. Further lesions usually occur, and the disease is usually chronic with periodic fluctuations over many years. Purpura and pigmentation may rarely occur within the lesions [7].

Pathology. The characteristic feature in EAC is a perivascular 'sleeve-like' lymphohistiocytic infiltrate, referred to as a 'gyrate erythema', which may be mainly superficial, mainly deep, or mixed. The pathological changes may be entirely within the dermis, whereas in other cases there is much more obvious epidermal change (spongiosis and parakeratosis) [8,9]. There is dispute about whether these represent two separate diseases or a continuous range. Eosinophils may occasionally be seen around superficial vessels. Significant peripheral eosinophilia raises the possibility of parasitic infection as the underlying cause.

A very rare eruption that has clinical features of EAC but with a frankly eosinophilic infiltrate has been described under the name 'eosinophilic annular erythema' [10,11].

Aetiology. A broad range of associations have been described as causes of EAC (Table 59.11) [12–26]; some 'associations' that have been described may be coincid-

Table 59.11 Possible causes and associations of erythema annulare centrifugum.

Category	Examples
Idiopathic	Including annually recurrent forms [12]
Familial	Dominant inheritance [13], twins [14]
Infantile onset	(see p. 59.74)
Fungi	Cutaneous tinea [5], intestinal *Candida* [15,16], ingested fungi (cheese) [15]
Other infections [2–6]	Molluscum contagiosum , Epstein–Barr virus, genital herpes, Q fever, recurrent appendicitis, *E. coli* urinary tract infection, tuberculosis, *Ascaris* infection, trypanosomiasis
Drugs [2–6]	Aldactone, amitryptiline, ampicillin, cimetidine, etizolam, granulocyte colony-stimulating factor, gold, hydrochlorthiazide, hydroxychloroquine, penicillin, piroxicam, salicylates, thiacetazone, vitamin K
Endocrine	Hyperthyroidism [17], Hashimoto's thyroiditis, autoimmune progesterone dermatitis, polyglandular autoimmune syndrome type I (the latter possibly mediated by *Candida* infection)
Haematological disorders	Lymphomas (various) [4,5,18,19], leukaemias [20], thrombocythaemia [21], polycythaemia rubra vera, myelodysplastic syndrome, hypereosinophilic syndrome [22], myeloma, dysproteinaemia, cryoglobulinaemia
Other neoplastic conditions [4,5,23]	Carcinomas of bronchus, prostate, nasopharynx, ovary, rectum and liver; carcinoid tumour
Immunological	Relapsing polychondritis [24,25], sarcoidosis [26]
Miscellaneous	Liver disease, following biliary surgery, localized at pacemaker site

ental, and some may be more properly categorized as unusual presentations mimicking EAC. In the large majority of cases the aetiology remains obscure, even after prolonged observation and investigation.

One study of 66 cases identified cutaneous fungal infection as the most important aetiological factor (in 72%), other causes being internal neoplasm in 13%, other skin diseases in 18% and other internal diseases in 21% [5]. However, a causal association could not always be proven, and the high frequency of fungal infection may have been influenced by the geographical location of the study in Korea.

Investigations. These are aimed at excluding alternative diagnoses, and search for an underlying cause (see section on Aetiology, above).

Fungal infections should be excluded by microscopy and culture of skin scrapings in all cases where scaling occurs. Granuloma annulare can usually be distinguished on clinical and/or histological features, and has slower evolution of individual lesions, but can cause diagnostic difficulty in some cases. Lymphomas, especially mycosis fungoides, may produce annular lesions very similar to those of annular erythemas; these usually have a broader edge, but a very EAC-like appearance over 10 years prior to diagnosis has been reported [19]. Pseudolymphomas also pose a diagnostic dilemma, as they may be both clinically and histologically similar to EAC—especially a disorder termed palpable migratory arciform erythema of Clark, which may be a variant of Jessner's lymphocytic infiltrate [27]. Genodermatoses such as erythrokeratoderma variabilis and erythrokeratoderma en cocardes should be considered in children, and similar lesions may be seen in carriers of chronic granulomatous disease. Several immunobullous diseases have been reported to have EAC-like lesions, especially in the prodromal phase, including bullous pemphigoid, pemphigus, dermatitis herpetiformis and linear IgA disease. Sarcoidosis, Still's disease, necrolytic migratory erythema, subacute annular psoriasis, pityriasiform seborrhoeic dermatitis, neutrophilic dermatoses, vasculitides, acute haemorrhagic oedema of childhood, leprosy, leishmaniasis and trypanosomiasis may all cause clinical confusion at times, but should be identifiable by histology and evolution of the eruption. Cases of pityriasis rosea in which there are few and large lesions may cause confusion but are self-limiting. Lupus erythematosus and Sjögren's syndrome need to be excluded, particularly cases with a dermatosis mediated by extractable nuclear antigens (see below).

Otherwise, it is seldom possible to establish an underlying cause. A search for a neoplasm should be made, especially in those with older age of onset, but exhaustive investigations are not recommended in the absence of other clues. Tinea pedis, *Candida* infection of the gut and other underlying infections are always worth excluding.

Treatment. Discovery and elimination of the cause are seldom possible. Numerous other treatments have been used including antihistamines, oral or topical corticosteroids, various types of allergen avoidance, and systemic immunosuppressive therapies. In cases where there is a marked epidermal component, topical steroids or calcipotriol [28] may be helpful, but most treatments appear to be relatively unsuccessful. The eosinophilic variant of annular erythema has been reported to respond to chloroquine [11].

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Annular erythema of infancy

This term was first applied by Peterson and Jarratt [1] although infantile onset of a similar eruption had been reported previously [2]; numerous cases have been reported subsequently [3–8]. Although the age group does not define a category that can be distinguished from other cases of EAC, and probably also represents a range of disorders, the implications for investigation are somewhat different. For example, cutaneous fungal infection and malignant diseases are unlikely causes, whereas other infections and lupus erythematosus-related antibodies (see below) are important to exclude. However, the fact that some cases started in teenage years and others in infancy in a family with autosomal dominantly inherited annular erythema [9] argues against there being a specific infantile variant.

Clinical features. The clinical morphology of lesions is generally as described for EAC.

Pathology. Histological appearances are typically the same as in cases of EAC. However, some authors have reported eosinophils to be prominent [7,8] and they may be the predominant cell type and associated with peripheral eosinophilia [10]. A neutrophilic variant has also been reported [11].

Aetiology. As in EAC, no cause can be identified in many patients, often despite extensive investigation. Some childhood cases may be discovered to have lupus erythematosus or have had transplacental transfer of maternal antibodies against extractable nuclear antigens, as discussed below; a clinical pattern described as erythema gyratum atrophicans transiens neonatale is now felt to be a variant of neonatal lupus erythematosus [12]. Heavy intestinal colonization with *Candida albicans* has been documented as a cause [13], and concurrent Epstein–Barr virus infection has been reported in an infant [14]. *Pityrosporum* infection in an infant has been reported as a mimic of EAC [15]; other differential diagnoses that may apply in children are listed previously.

Treatment. Any associated infection should be treated as discussed in the section on aetiology. Responses to sodium cromoglycate and to IFN-α have been reported, but in many cases new lesions continue to erupt over many years.

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Annular erythema associated with extractable nuclear antigens

It has been recognized for many years that annular lesions in neonatal lupus erythematosus are related to maternal antibodies against SSA(Ro) [1]. Neonatal lupus erythematosus with annular lesions but without anti-SSA antibodies may be explained by the demonstration that some patients have anti-U1RNP antibodies instead [2].

More recently, it has been recognized that annular lesions may occur in anti-SSA(Ro)-positive patients with Sjögren's syndrome, lupus erythematosus (or both together), and less commonly in otherwise well patients who do not fit criteria for either of these diagnoses [3–6]. A role for anti-SSB(La) antibodies has also been proposed in patients with a rather more tumid-appearing pattern of annular erythema [7]. Further investigation has shown that patients with Sjögren's syndrome and/or lupus erythematosus who have anti-tRNA antibodies as well as anti-SSA or anti-SSB antibodies are more likely to have recurrent papulosquamous annular erythema than are those with anti-SSA or anti-SSB alone [8]. Conversely, anti-alpha-fodrin antibodies (which are most common in primary Sjögren's syndrome) do not appear to be linked with annular erythema [9].

Affected patients are usually young adults, although childhood onset occurs [10], and they are usually female; individuals of Japanese origin seem to be particularly likely to develop annular lesions. Although the edge of the lesions is often broader than in many cases of EAC, and the distribution is often photosensitive and limited to the face, it is likely that some cases previously classified as EAC may be explained by this mechanism.

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Chapter 60

The Skin and the Nervous System

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Introduction

The relationship between the nervous system and the skin is complex, and the aim of this chapter is to outline the physiology and pathophysiology of the interactions. Nervous system disorders may be divided broadly into those associated with sensory abnormalities and those associated with autonomic abnormalities, although there is overlap between these two groups. Skin manifestations may occur when the pathology is predominantly located either in the central nervous system (CNS), such as the spinal cord, or in the peripheral nervous system.

The sensory innervation of the skin allows the detection of a number of stimuli from the surrounding environment and the transmission of this information to the CNS (Chapter 4).

Groups of disorders affecting the skin and nervous system simultaneously might include genetic conditions (e.g. neurofibromatosis and tuberous sclerosis, Chapter 12), metabolic abnormalities (e.g. the mucopolysaccharidoses and Tangier disease, Chapter 57), Refsum's disease (Chapter 34), vitamin deficiency states (e.g. pellagra, Chapter 57) and exposure to toxins (e.g. arsenic poisoning) or infective agents (e.g. *Meningococcus*).

Skin innervation

The skin is innervated by a dense three-dimensional network of highly specialized afferent sensory and efferent autonomic nerve branches. The sensory system contains receptors for touch, temperature, pain, itch and various other physical and chemical stimuli [1,2]. The autonomic system comprises post-ganglionic cholinergic parasympathetic nerves and adrenergic and cholinergic sympathetic nerves. It plays a crucial role in maintaining cutaneous homeostasis by regulating vasomotor function, pilomotor activity and eccrine gland secretion. As many as 1000 such afferent neurones may innervate 1 cm^2 of skin. The afferent sensory neurones are unipolar and branch off with a single axon travelling towards the skin. The autonomic nerves innervate the skin in a different pattern. Post-ganglionic fibres originate in the sympathetic chain and are co-distributed with the sensory neurones until they arborize into plexuses around sweat glands, blood vessels and arrector pili muscles [1,2]. Skin nerves may contain myelinated and/or unmyelinated fibres: subgroups of sensory neurones are myelinated A fibres, whereas unmyelinated C fibres contain sensory and autonomic fibres. The sensory myelinated fibres can be further subdivided, on the basis of diameter, into rapidly conducting Aα and slowly conducting Aδ nerves, which transmit tactile sensitivity or temperature, noxious sensation and itch, respectively [2–4]. In the upper dermis, small myelinated nerves lose their nerve sheaths and, together with the unmyelinated nerves, end in either free nerve endings or in association with receptors, such as Merkel cells or nerve ending organs [2,3].

Sensory innervation

Sensory innervation follows well-defined dermatomes with some overlap between adjacent dermatomes. Sensory nerves not only function as an afferent system to conduct stimuli back from the skin to the CNS, but also act in an efferent neurosecretory fashion, releasing neuropeptides with important visceromotor, inflammatory and trophic effects on skin (see below). Unmyelinated type C fibres terminate as either free nerve receptor endings or in association with receptors such as the pacinian or Meissner's corpuscles. Pacinian corpuscles, innervated by a single myelinated sensory axon, are most densely located on the palms and soles, where they act as mechanoreceptors. Meissner's corpuscles also occur in greatest density on the palms and soles; being innervated by one or more sensory nerve endings, they also act as mechanoreceptors, and in addition transmit touch sensation. Merkel cells, which occur at low density generally, with an increased density around hair follicles and at the palms, nail beds and lips, are innervated by synaptic nerve endings. Merkel cells produce and contain a wide range of neuropeptides, which may be important in the local regulation of inflammation [2].

Afferent sensory nerves, either unmyelinated C fibres or myelinated Aδ fibres, derive from the dorsal root ganglion and are capable of the release of a variety of neuropeptides in response to noxious stimuli [2–4]. Sensory impulses are conducted in the peripheral and central axon of the spinal ganglion cell in the dorsal root ganglion, and pass via the lateral spinothalamic tract and the lemniscus spinalis to the thalamus [4]. From the thalamus the information reaches consciousness via the thalamic radiation to the post-central gyrus of the parietal lobe.

C and Aδ fibres not only conduct nociceptive information to the dorsal root ganglion but also have an important efferent function, in that they stimulate target tissues by releasing a range of neuropeptides in response to noxious stimuli, such as chemical, electrical, thermal and mechanical injury, or UV radiation. Neuropeptides with an important neurotransmitter function contained in primary sensory neurones include the tachykinins, substance P, neurokinin A and calcitonin gene-related peptide (CGRP) [5]. These three neuropeptides most frequently coexist in the same subpopulation of primary sensory neurones, the Aδ and C fibres, and are involved in the nerve transmission of impulses initiated by noxious stimuli. They usually occur in free nerve endings in the upper dermis (Fig. 60.1) and epidermis throughout the body, but are at greatest density on the palms and soles, where some end in a plexus around Meissner's corpuscles (Fig. 60.2) [5].

Release of neuropeptides often leads to neurogenic inflammation. The key components of neurogenic inflammation are precapilliary vasodilation, plasma protein extravasation and leukocyte infiltration, which follow antidromic stimulation of peripheral nerves. Neuropeptides can regulate both acute and chronic inflammation by influencing vascular motility and cellular trafficking. After release, neuropeptides are metabolized by membrane-bound endopeptidases that occur on target structures such as blood vessels and eccrine sweat glands in skin [6].

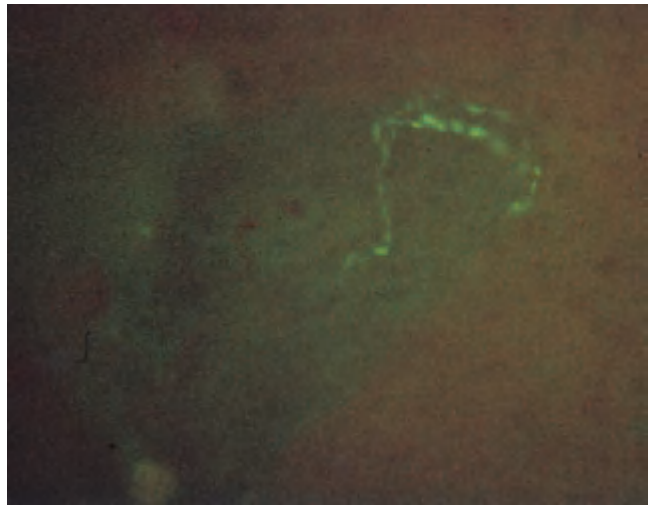

Fig. 60.1 Substance P immunoreactive nerve endings in the epidermis of human skin.

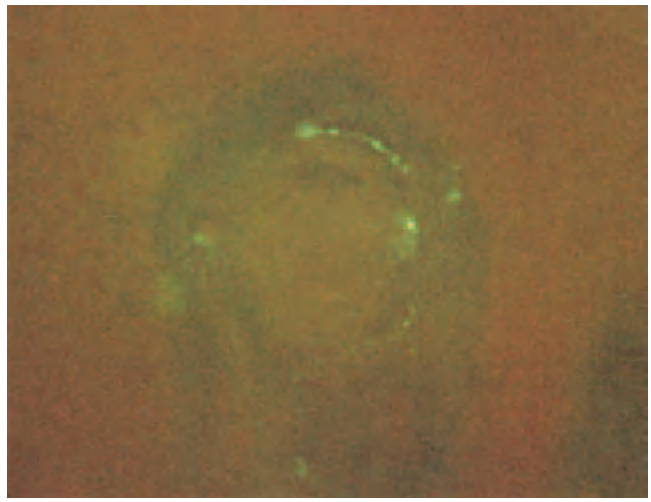

Fig. 60.2 Substance P fibres ending in Meissner's corpuscles of skin.

Autonomic nervous system

The autonomic nervous system innervates the skin through post-ganglionic fibres originating in sympathetic ganglia, and terminating in autonomic plexuses that supply sweat glands, blood vessels and arrector pili muscles [1]. Histochemically there are two main groups of post-

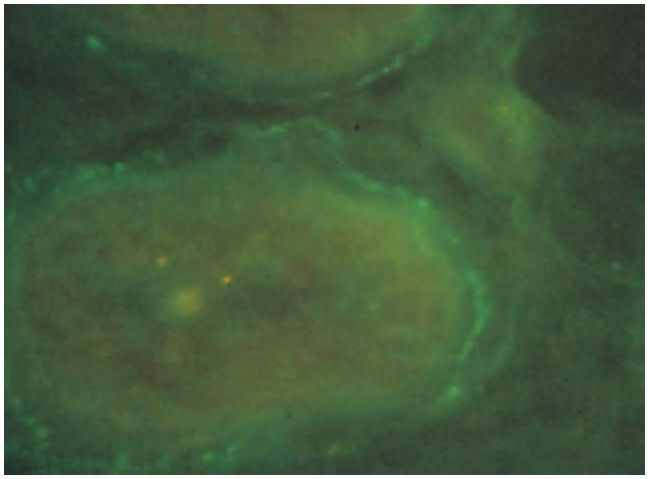

Fig. 60.3 Vasoactive intestinal peptide immunoreactive fibres surround secretory cells of eccrine sweat gland.

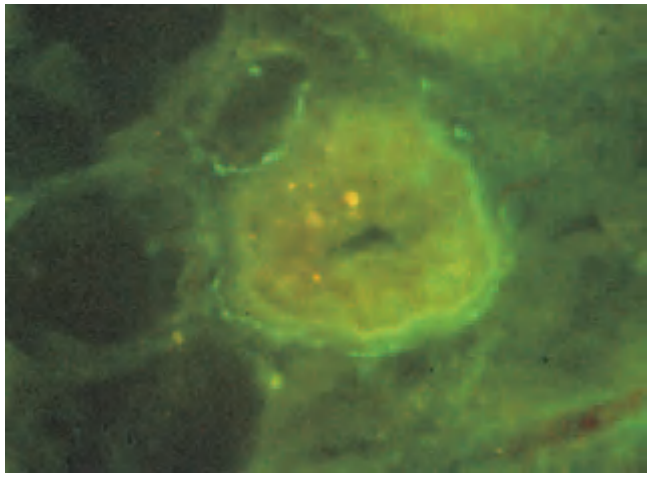

Fig. 60.4 Peptide histidine methionine immunoreactive fibres surround eccrine sweat glands.

ganglionic nerve fibre in the skin. Firstly, adrenergic fibres synthesize and store catecholamines and norepinephrine (noradrenaline). The second major group consists of the cholinergic fibres containing acetylcholine. Co-localizing with acetylcholine are 'secretory' neuropeptides such as vasoactive intestinal peptide (VIP) and peptide histidine methionine (PHM). Nerves containing these should be regarded, at least physiologically, as parasympathetic [5]. The secretory portion of the eccrine sweat glands, myoepithelial cells and nearby blood vessels are innervated by a basket-weave pattern of nerves containing predominantly acetylcholine but also significant numbers of fibres containing 'secretory neuropeptides' including VIP (Fig. 60.3), PHM (Fig. 60.4), neuropeptide Y (NPY), CGRP, galanin, atrial natriuretic peptide (ANP) and norepinephrine. Secretory neuropeptides, mainly VIP and ANP, together with norepinephrine, are not as effective as acetylcholine at sweat production, and probably synergistically amplify acetylcholine-induced adenosine 3',5'-cyclic monophosphate (cAMP) accumulation, which is the most important secondary messenger in sweat production. ANP may be responsible, at least in part, for regulation of sodium and other electrolytes being released in sweat [5]. NPY has been identified in the periarteriolar nerve fibres of the deep and superficial vascular plexus, and in eccrine sweat glands, and is likely to play a role in regulation of skin blood flow and eccrine sweating [5].

Blood vessels in the skin are innervated by adrenergic fibres which are vasoconstrictor, while acetylcholine and neuropeptides, such as VIP and PHM, act as vasodilators and increase vascular permeability [5,7]. Thus, by increasing release of acetylcholine and secretory neuropeptide, the body has a mechanism of increasing blood flow to the skin and increasing sweating, both of which act to reduce body temperature. If body temperature falls, this is detected in the preoptic region of the hypothalamus, which activates the sympathetic nervous system, which in turn reduces skin blood flow and sweating. Conversely, if warmer blood is detected in the hypothalamus, inhibition of sympathetic response allows skin sweating and blood flow to increase, thereby reducing core temperature [8,9].

Adrenergic fibres mediate strong vasoconstriction and arrector pili muscle activity, thus diverting blood from the skin, and pulling hairs into the upright position, in the classical 'fight or flight' reaction [1].

The digital nerves in patients with Raynaud's phenomenon and with systemic sclerosis are deficient in CGRP fibres [10], and intravenous infusions of CGRP increase digital blood flow in such patients. A similar depletion of CGRP fibres has been described in digital nerves of patients with vibration white finger, and this may be responsible for both the vasoconstriction and sensory abnormalities characteristic of this condition [11].

Wound healing and trophic effects

Impaired wound healing is often found in patients suffering from peripheral neuropathies, spinal cord lesions or after peripheral nerve trauma. Depletion of neuropeptides in animal models using capsaicin, and *in vitro* studies demonstrating that certain neuropeptides such as substance P, neurokinin A, CGRP and VIP stimulate DNA synthesis in fibroblasts, keratinocytes, melanocytes and endothelial cells, suggest that they are likely to act as mitogens stimulating proliferation of tissue cells, thereby aiding the healing process [5,11–14]. The sprouting of sensory nerve endings, containing large amounts of substance P, occurs in wounds during the first 3 weeks, and is probably important in wound healing. Substance P has also been shown to up-regulate the synthesis of interleukin-1 (IL-1), IL-6 and transforming growth factor-α (TGF-α) in keratinocytes [14]. Nerve growth factor (NGF)

is a neurotrophic factor released from sensory neurones, as well as fibroblast mast cells, lymphocytes and keratinocytes, which may act as a major controller of cutaneous wound healing and inflammation [14].

CGRP has a trophic effect in the regeneration of UV-damaged skin, and synthesis of CGRP increases after nerve injury, suggesting that this peptide may have a role in nerve regeneration [15].

Neuroimmunology

There is significant evidence of a close interaction between the nervous system and the immune system. Substance P, neurokinin A and CGRP predominantly function as pro-inflammatory mediators, whereas VIP, somatostatin and α-melanocyte-stimulating hormone (α-MSH) largely have anti-inflammatory properties [16].

Substance P *in vivo* and *in vitro* enhances proliferation and function of B and T cells and induces cytokine secretion from monocytes, including IL-1, IL-6, tumour necrosis factor-α (TNF-α) and interferon-γ (IFN-γ) [17]. Substance P influences inflammatory responses by enhancing macrophage and leukocyte activity, and acts to release histamine, prostaglandin and leukotriene from mast cells [18]. Furthermore, it activates human dermal microvascular endothelial cells to express vascular adhesion molecule 1 [19].

While VIP is a potent releaser of histamine for mast cells, a mechanism that is independent of IgE activation, it also has anti-inflammatory effects, suppressing delayed hypersensitivity *in vitro* and inhibiting phospholipase A2 [20]. VIP inhibits natural killer cell activity and may have an inhibitory effect in inflammatory processes, such as contact dermatitis, an effect which may be mediated through an increased production of IFN-γ in peripheral blood monocytes [20].

Neuropeptides can activate a number of target cells including keratinocytes, Langerhans' cells, mast cells, epithelial cells, granulocytes, eosinophils, macrophages and lymphocytes, all of which have been shown to have receptors for neuropeptides. Recent evidence shows that many of these cells may also synthesize these neuropeptides. In addition cytokines, including IL-1, TNF-α and NGF are potent stimulators of neuropeptide production [16]. The release of substance P, CGRP and other neuropeptides may ultimately hold the link between psychological stress and the flaring of inflammatory skin diseases [21,22]. Substance P, neurokinin A and CGRP are all up-regulated by UV light exposure of human skin, and may contribute to the inflammation of acute UV exposure, while in the longer term CGRP inhibits Langerhans' cell activity, thus leading to immunosuppression as a result of UV exposure [23]. Similarly, α-MSH is produced in the skin as a result of UV irradiation, which has been shown to induce the production of IL-10 and inhibit the production of IL-1 and IL-12, thereby inhibiting the chemokine-mediated migration of antigen-presenting cells [24].

In addition to their role as neurotransmitters, neuropeptides can modulate immune responses, leading to the concept of the neuro–immuno–cutaneous system, representing an interrelationship between the nervous system, immunity and skin. This may explain the link between the flare up of inflammatory diseases, such as atopic dermatitis [25] and psoriasis [21,22,26], during periods of emotional stress.

Neurophysiological testing for skin innervation

Sympathetic skin response

Sympathetic skin response (SSR) is a safe, simple and non-invasive electrophysiological test used to evaluate sudomotor function in a variety of clinical settings [27,28]. It can be used to assess autonomic function in patients with suspected sympathetic nerve dysfunction. The SSR is a polysynaptic reflex associated with the activation of sweat glands. It is usually performed by electrical stimulation of the median, ulnar, peroneal or sural nerves and measuring the change in galvanic resistance on glabrous skin brought about by sweating using a conventional electromyograph apparatus. The afferent component may be activated by non-specific sensory stimuli or repeated electrical stimulation; the efferent component depends on the functioning of the sympathetic-cholinergic fibres from the sympathetic chain to the sweat glands. In autonomic failure the SSR cannot be elicited.

Cold-induced vasodilation

Hand cooling is a cold pressor test, in which an extremity is placed in cold water leading to a rapid decrease in skin temperature, accompanied by initial strong vasoconstriction aimed at limiting heat transfer to the environment [29–33]. After a few minutes, skin temperature starts increasing as a consequence of cold-induced vasodilation. The precise mechanism of this reflex is unknown, but it is thought to be mediated through an increase in sympathetic stimulation, although factors independent of the sympathetic nervous system may also play a role. Exposure of the human body to cold stress elicits generalized cutaneous vasoconstriction. This is a response mediated by a sympathetic control process, triggered partly by stimulation of cutaneous cold receptors and partly by cold blood returning to the general circulation and stimulating the temperature-regulating centre in the hypothalamus. The tone of cutaneous vessels is controlled mainly by vasoconstrictor skin sympathetic nerve activity. A reduction in this response has been reported in diabetic and

neuropathic patients, and in the immature and elderly, probably resulting from reduced skin sympathetic nerve vasoconstriction [32,33].

Triple response of Lewis

Lewis described the capacity of the cutaneous microcirculation to vasodilate in response to direct stimulation with a firm mechanical stroke or with a dermographometer (the axon reflex) [33–35]. The amount of vasodilatation can be measured by Doppler flow meter. The axon reflex, known as 'antidromic vasodilation', does not occur in chronically denervated skin or skin in which neuropeptides have been depleted by capsaicin. The antidromic vasodilatation and plasma extravasation, which occurs in the skin following stimulation of the dorsal nerve roots or peripheral sensory nerves, can be mimicked by intra-arterial infusion of substance P.

Histamine is known to be a principal mediator of the triple response of Lewis, and to act via H_1 and H_2 receptors to produce vasodilatation and increased vascular permeability. However, it is known that substance P, neurokinin A and CGRP from primary sensory fibres are also mediators in the skin flares of the triple response of Lewis [36,37].

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Post-herpetic neuralgia

Herpes zoster (Chapter 25) is itself painful, and is sometimes followed by neuralgia. The risk of developing post-herpetic neuralgia rises with age, which influences both the duration and the severity of the neuralgia once it appears [1]. Post-herpetic neuralgia, defined as pain persisting beyond 4 weeks, occurred in 16% of patients

younger than 60 years but in 47% of those older than 60 years [2]. Only about one-quarter of those with pain 4 weeks after the vesicles have healed still have pain a year later, but this pain, which is chronic and debilitating, especially in the elderly, can be so severe that it interferes with sleep, and causes depression or even suicidal tendencies.

Patients may report a variety of painful sensations with different components, including spontaneous and continuous deep aching and throbbing pain, burning, lancinating pain, or paroxysms of burning pain, sometimes provoked by non-noxious stimuli, such as contact with clothing or changes in temperature [3]. The pain is accompanied by autonomic instability and its intensity is exacerbated by physical and emotional stress and alleviated by relaxation. Some patients with post-herpetic neuralgia have profound sensory loss in the area of maximum pain (anaesthesia dolorosa), while others have pronounced allodynia with minimal sensory loss. Another group of patients have areas of sensory loss surrounded by a 'transition zone', within which a noxious stimulus can elicit a particularly unpleasant pain that radiates widely [3]. The patient may go to extraordinary lengths to protect the area from innocuous stimuli, while firm compression of the skin may actually produce pain relief.

Why some patients develop post-herpetic neuralgia is incompletely understood. There is, for example, no consistent relationship between this type of pain and a loss of large fibres in the damaged nerves, but *in vitro* studies [4] suggest that the virus itself may cause normally silent neurones to produce spontaneous action potentials.

Pathophysiology of pain

Post-herpetic neuralgia may be caused by neurological lesions at all levels of the nervous system including peripheral, central and autonomic components.

In pain associated with peripheral damage in the dorsal root ganglion, spinal cord and afferent neurones, ectopic impulse generation may occur at the site of damage, and these impulses can be evoked by mechanical or thermal stimuli in the local environment (tactile allodynia) [3]. For this type of disorder, membrane-stabilizing drugs are likely to work best. There is also some evidence that nociceptors in painful skin of post-herpetic neuralgia patients have enhanced adrenergic sensitivity [3].

When sensory deficits are present, suggesting destruction of dorsal root ganglion cells, the pain is primarily sustained by processes in the CNS, resulting in what is known as 'deafferentation pain' [3].

With the realization that several pain mechanisms may be operating in any one individual, it is unrealistic to expect any one drug to completely alleviate the pain in all neuropathic pain disorders, or to significantly reduce the pain in all patients suffering from the same neuropathic condition.

Prevention of post-herpetic neuralgia

Two controlled studies [5,6] suggested that the use of systemic corticosteroids during the acute episode of herpes zoster might reduce the risk of developing post-herpetic neuralgia, and in neither was generalized herpes zoster a problem. However, a recent systematic review [7] concluded steroids not to be of proven efficacy, and this was borne out in a recent randomized open trial [8]. Given its immunosuppressive effects, and potential for serious complications, systemic corticosteroids are not recommended.

In older adults with localized herpes zoster, oral aciclovir (800 mg five times daily for 7 days) reduces acute pain and healing times if treatment is initiated within 72 h of the onset of the eruption [9]. A reduction in ocular complications, particularly keratitis and anterior uveitis, occurs with treatment of herpes zoster ophthalmicus [10]. A recent systematic review of four placebo-controlled trials of oral aciclovir showed only marginal evidence for pain reduction after herpes zoster. Famciclovir and valaciclovir significantly reduced the duration but not the incidence of post-herpetic neuralgia, in one placebo-controlled trial for each agent. Famciclovir (500 mg three times daily for 7 days) or valaciclovir (1000 mg three times daily for 7 days) may provide more prompt relief of zoster-associated pain than aciclovir in acute herpes zoster in older adults (over 50 years of age) [11].

In immunocompromised patients with herpes zoster, intravenous aciclovir (500 mg/m^2/8 h for 7 days) reduces viral shedding, healing times, the risks of cutaneous dissemination and visceral complications, as well as the length of hospital stay in disseminated zoster [12].

Management of established post-herpetic neuralgia [13]

In mild and moderate cases of established post-herpetic neuralgia, simple analgesics help, but in severe cases they may have little effect. Opioids should probably be prescribed for resistant pain not coming under control with other drugs (below). Controlled-release oxycodone at a dose of 10–30 mg 12-hourly was shown to be effective in a randomized placebo-controlled study for steady-state, paroxysmal spontaneous pain and allodynia [14]. Tramadol, a centrally acting analgesic with both opioid and non-opioid activities, seemed to work well in a pilot study up to a maximum dose of 600 mg daily [15].

The most effective drugs include antidepressants and anticonvulsants (membrane-stabilizing drugs). In a placebo-controlled trial, amitriptyline was shown to be superior to placebo, with about 60% of patients experiencing a good response to the active drug [16]. Pain relief was achieved with a relatively low dose. At a dose of around 70 mg/day, some 60% of patients experienced a good

result with reduction of pain from severe to mild, and 14% had no pain. Most patients complained of side effects including dry mouth, drowsiness, constipation or urinary hesitancy. Other antidepressants recommended for post-herpetic neuralgia include desipramine, nortriptyline and maprotiline. Of these, nortriptyline [17] and desipramine [18] were shown to be effective in randomized controlled trials, whereas a controlled trial showed no advantage of maprotiline over amitriptyline [19]. While anticonvulsants such as sodium valproate, phenytoin, carbamazepine and clonazepam are frequently advocated for shooting or lancinating pain, others have claimed that these drugs are unproven and relatively ineffective [20]. The new anticonvulsant drug, gabapentin, has been shown in a randomized, double-blind placebo-controlled trial to reduce post-herpetic neuralgia pain [20]. The mechanism of action of gabapentin is unknown, but it does not interact with any known neurotransmitter receptors and specifically it is not a γ-aminobutyric acid (GABA) agonist, unlike its close relative, baclofen. To date, there are no studies directly comparing gabapentin with antidepressants, but it is considered as least as effective and safe as the antidepressants but with fewer side effects [3]. The results of these studies support the use of gabapentin as a first-line medication in the treatment of chronic neuropathic pain syndromes such as post-herpetic neuralgia. Other drugs reported to be of help are clonidine and lamotrigine, although, as yet, no controlled trials have been carried out on these drugs [3]. Randomized controlled trials of capsaicin, at either 0.025 or 0.077% applied 3–4 times per day, have been shown to be effective [21]. The use of topical 5% lidocaine (lignocaine) patches either worn for around 12 h/day [22], or applied up to four times per day [23], has been shown to be efficacious, well tolerated and associated with low systemic absorption. Other treatments that have been reported to produce benefit in some patients include baclofen [24] and weekly lumbar intrathecal injections of methylprednisolone and lidocaine [25].

Surgical treatments have been tried in the past, including division of the dorsal root or tractotomy, or ablation by injection of the ganglion or sensory root, but these are not advocated due to limited efficacy and the high rate of morbidity [3]. Spinal cord stimulators have been used with variable results and transcutaneous stimulation (TENS) may be helpful, but proper trials seem lacking [26]. There seems to be no good evidence to support a role for acupuncture in treating post-herpetic neuralgia [27].

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Neuropathic ulcers

Neuropathic ulcer is a form of chronic ulceration, also known as 'perforating ulcer', which develops in anaesthetic skin. Characteristically neuropathic ulcers are painless, persistent and uninflamed, appearing on areas subject to trauma or pressure.

Aetiology. While a number of neurological disorders may cause neurotrophic ulcers, the vast majority occur in

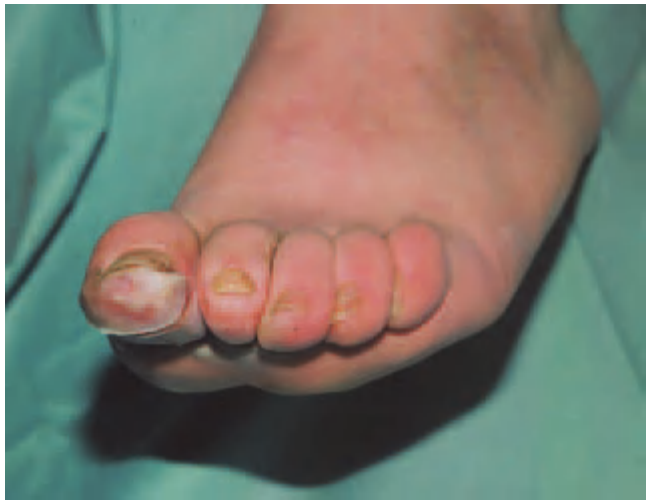


Fig. 60.5 Clawing of feet occurring in neuropathic foot with painless damage to skin on great toe.

patients with type II diabetes [1,2]. Other causes include leprosy, peripheral neuropathy, alcoholism, vitamin deficiencies, pernicious anaemia, syringomyelia, tabes dorsalis, spinal dysraphism, spinal cord injury and hereditary sensory and autonomic neuropathies [3,4].

Neuropathic ulcers result from a distal polyneuropathy encompassing motor, sensory and autonomic components.

Motor involvement leads to weakness of the intrinsic muscles of the feet and an imbalance between the long flexor and extensor tendons, leading to a typical cavus or high arched foot along with clawing of the toes (Fig. 60.5) [5]. This combined with arch collapse, leads to the 'rocker-bottom foot', which is prone to tissue break down and ulceration. The plantar aspect of the foot is protected by fat pads, which anticipate weight-bearing forces in all directions. Increased pressure under the metatarsal heads and heel, the sites of around 90% of such ulcers, results in high pressure with initial callosity leading to ulceration. In the majority of patients, a palpable pulse in the affected foot is an indication of good vascular supply. However, the presence of rest pain, diminished or absent pulses, pallor on elevation and sluggish refilling of toe capillaries, together with trophic signs in the skin, are highly indicative of ischaemic ulcers. The associated sensory neuropathy allows the patient to injure the foot, either suddenly by standing on sharp objects such as pins or glass, or gradually, for example from pressure within a poorly fitting shoe, without the patient being aware of the damage. Autonomic neuropathy leads to a foot with loss of sweating, leading to dryness with fissuring and cracking and changes in the normal microcirculation autoregulation. Such cracks or fissures allow a portal of entry of infection. In the diabetic foot there is an impairment of the neurogenic vasodilator response, or flare, which correlates with the clinical diminution in pain sensation. It is likely that loss of both components of the nociceptive C-fibre function, both neurological inflammation and pain sensation, is an important factor in the development of foot complications in diabetes. Diabetics have been demonstrated as having a defect of unmyelinated nociceptive C fibres on the soles of their feet, leading to loss of nociceptive function and the development of both neuropathic plantar ulcers and neuroarthropathy. As sympathetic tone is lost, increased peripheral blood flow leads to arterial venous shunting, with blood bypassing the capillary bed, thereby reducing nutritive skin blood flow [6].

Clinical features. Primary neuropathic limbs tend to be warm, insensitive and prone to ulceration on the sole of the foot, while neuroischaemic limbs are usually cool, discoloured and prone to ulceration on the foot margins [2]. Neuropathic ulcers typically occur under the metatarsal heads or heel, surrounded by thick, hyperkeratosis, and have a pink punched out base that bleeds easily and is painless (Figs 60.6 & 60.7). The foot is warm with palpable

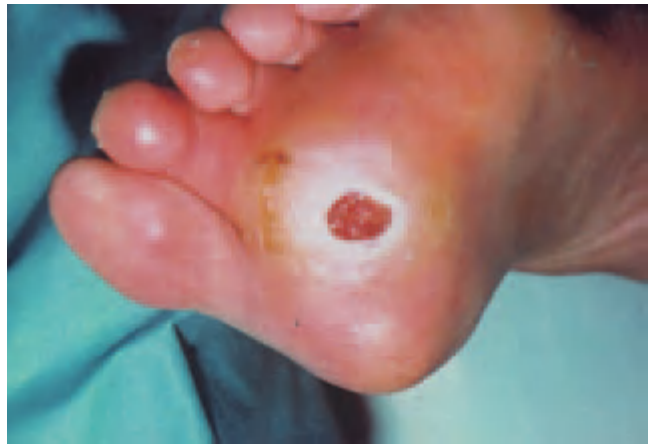


Fig. 60.6 Typical neuropathic ulcers with surrounding hyperkeratosis under metatarsal heads.

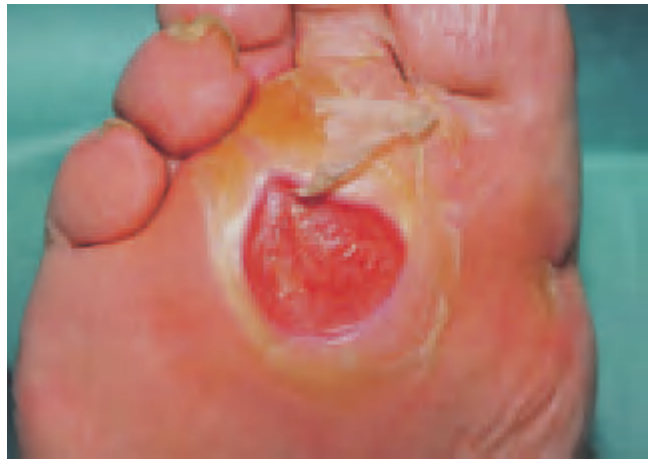


Fig. 60.7 Neuropathic ulcer with hyperkeratosis removed.

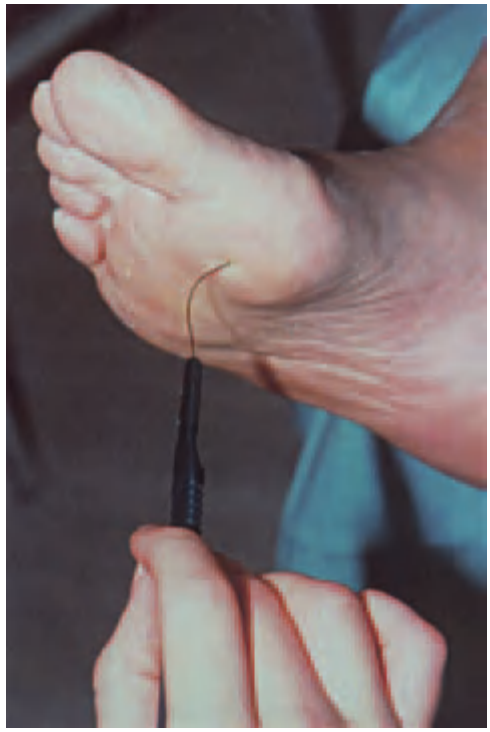
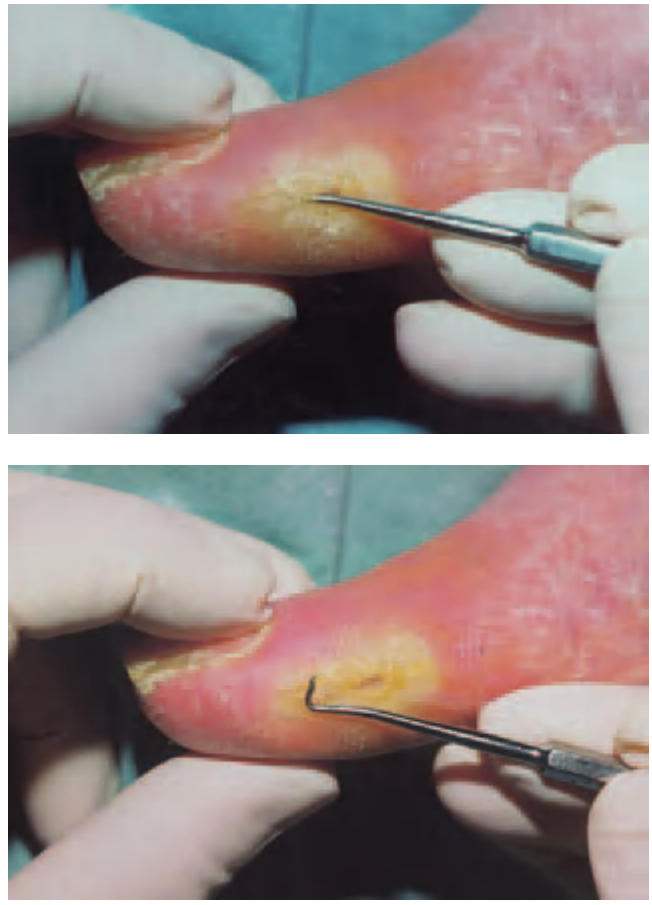


Fig. 60.8 Bailey® nylon monofilament assessing sensory loss on neuropathic foot.

pulses and the changes include pes cavus, warm, dry and insensitive foot with dilated veins, clawed toes and hyperkeratosis under the forefoot and heel [2]. In diabetic patients, there may be a complex interplay of neuropathy and ischaemia, and when the latter is present, the foot may be cold with absent pulses, hyperkeratosis and a dark fibrotic base that does not bleed easily and is painful to touch. In the neuropathic ulcer, the sensations of light touch and vibration and sharp–blunt discrimination are reduced, which can be demonstrated using a Bailey® nylon monofilament (Fig. 60.8), which buckles in response to 10 g force, neurotheissometer and Neurotip® [7], respectively. Absent pulses suggest ischaemia. Falsely high ankle–brachial pressure indices may occur, especially in diabetics, as a result of non-compressible calcified vessels.

A frequent complication is the presence of cellulitis or deep infection with abscess formation or osteomyelitis. One study found that Gram-positive aerobic bacterial colonization predominates (84%), with *Staphylococcus aureus* being the commonest organism (79%). Methicillin-resistant *S. aureus* (MRSA) was isolated in 30% of patients, which was almost double the proportion of MRSA-infected patients 3 years previously [8]. Bacterial colonization of the ulcer does not necessarily indicate infection. By contrast, infection may be present, especially in diabetics, without a very apparent pyrexia; leukocytosis, elevation of erythrocyte sedimentation rate and local signs may be less than expected. Cellulitis should alert one to the possibility of underlying osteomyelitis; plain X-rays may exhibit periosteal reactions or osteolysis. Probing a wound to find palpable bone at the base of an ulcer is an excellent predictor of osteomyelitis [9] (Fig. 60.9). A plain X-ray of the foot should be done to check for foreign bodies, tissue gas or bony abnormalities. A sinogram may be required to show communication of the sinus with a joint or a subfascial plantar abscess. A radioisotope bone scan, or magnetic resonance imaging (MRI) scan, may help to establish the diagnosis [10].



(a)

(b)

Fig. 60.9 Probing a neuropathic wound. (a) Probe in position. (b) With probe removed.

Treatment. The prevention of ulceration in neuropathic patients is of the utmost importance [10]. Persons at risk should receive instruction on basic foot care, preferably from a podiatrist, with education on regular self-inspection of feet and correct nail-cutting techniques. Shoes should accommodate any deformity, have broad rounded or square toes, adequate toe depth and a low heel to avoid excessive pressure on the forefoot [11,12]. They should fasten securely to prevent movement within the shoe. Orthotic devices such as cushioned insoles may also be beneficial in preventing ulceration. Patients should be discouraged from removing callus themselves; this

Fig. 60.10 Aircast Walkers® boot.

should be done by a podiatrist. Control of hypertension, cessation of smoking, prescription of aspirin in patients with atherosclerosis and meticulous control of hyperglycaemia can slow or even reverse the signs of peripheral neuropathy [13].

In the treatment of a neuropathic foot ulcer, a multidisciplinary approach is most effective, and has been shown to significantly reduce amputation [14]. Typically, the ulcer is debrided surgically or treated using a hydrogel followed by the application of a hydrocolloid dressing. Randomized controlled trials have shown benefit from the use of the platelet-derived growth factor becaplermin [15], cultured dermis (Dermograft®) [16] and hyaluronic acid dressings (Hyalofill®) [16,17] in promoting wound healing in clean wounds.

An essential part of treatment is the offloading of areas of abnormal pressure on the foot [14]. Contact casting is useful for healing ulceration over metatarsal heads but requires expertise in application and should not be used in patients whose ulcers are infected, or where there is a significant ischaemic component [14]. An example of such a casting is the Aircast Walkers® foam boot (Fig. 60.10). A modified non-weight-bearing boot made out of layers of adhesive foam padding may achieve complete removal of pressure points [18]. Boots made of Plaster of Paris (with a rocker base) seems popular in some centres, especially with orthopaedic practitioners. The plaster boot is applied, initially weekly, and every 3 weeks, until ulceration is healed [19].

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Peripheral neuropathy

Peripheral neuropathy may be sensory, motor or mixed [1]. In most types of peripheral neuropathy, the involvement is symmetrical and symptoms begin in the extremities with sensory loss in a glove and stocking distribution. In contrast to this, is the patchy involvement of peripheral nerves in mononeuritis multiplex seen, for example, in polyarteriitis nodosa, or sarcoidosis (Chapter 58). The causes of peripheral neuropathy are numerous and include diabetes mellitus, carcinomatous neuropathy, vitamin B group deficiency and drugs or chemicals (Table 60.1).

The typical picture of polyneuropathy occurs with acquired, toxic or metabolic neuropathic states, and it is these that will usually be seen by a dermatologist. The first symptoms tend to be sensory, consisting of tingling, prickling, burning or band-like dysaesthesia in the balls of the feet or tips of the toes, or in a general distribution over the soles. Symptoms and findings are usually symmetrical and graded distally. If the polyneuropathy remains mild,

Table 60.1 List of causes of peripheral neuropathy.

Metabolic	Diabetes mellitus, alcohol, porphyria, myxoedema, acromegaly, uraemia, POEMS syndrome, hypoglycaemia
Neoplastic	Paraneoplastic neuropathy, lymphoma, Hodgkin's disease, multiple myeloma
Nutritional	Deficiencies of vitamins B_1, B_{12} or E and malabsorption syndromes including coeliac disease
Toxic	Alcohol, heavy metals (e.g. lead, mercury, gold, thallium), drugs (e.g. amiodarone, cisplatin, hydralazine isoniazid, dapsone, nitrofurantoin, disulfiram, phenytoin, vincristine, metronidazole, antiretroviral nucleoside analogues), other toxic agents (e.g. organophosphates, diphtheria, acrylamide)
Trauma	Pressure neuropathy, ischaemia, pressure from tumours, electrical shock
Infective	Diphtheria, leprosy, mumps, Guillain–Barré syndrome, HIV infection, Lyme disease
Inflammatory	Rheumatoid arthritis, polyarteritis nodosa, sarcoidosis, systemic lupus erythematosus, primary biliary cirrhosis, primary systemic amyloidosis, chronic obstructive airways disease, Churg–Strauss syndrome, critical illness
Genetic	Charcot–Marie–Tooth disease, Refsum's disease, HSANs, Fabry's disease, Roussy–Levy syndrome, metachromatic leukodystrophy

HIV, human immunodeficiency virus; HSANs, hereditary sensory autonomic neuropathies; POEMS, polyneuropathy, organomegaly, endocrinopathy, M-protein, skin changes.

Table 60.2 Investigation of peripheral neuropathy [1].

Urine	Glucose, protein, Bence Jones protein
Haematology	Full blood count, erythrocyte sedimentation rate, vitamin B_{12} and folate
Biochemistry	Fasting blood glucose, renal function, liver function, thyroid function, glucose tolerance test, serum protein electrophoresis, serum angiotensin-converting enzyme, prostate-specific antigen
Radiology	Chest X-ray, abdominal or pelvic ultrasound, chest and abdominal computed tomography, mammography, PET
Immunology	Antinuclear factor, antibodies to extractable nuclear antigen (Ro, La), neutrophilic cytoplasmic antigen, HIV, gliadin, neuronal (Hu, Yo)
Neurophysiology	Proximal and distal nerve conduction studies
Cerebrospinal fluid	Cells, protein, immunoglobulin oligoclonal bands

HIV, human immunodeficiency virus; PET, positron emission tomography.

objective motor or sensory signs may not be detectable. With progression, the dysaesthesia spreads up the legs, pan-sensory loss is found over the feet and the ankle reflexes are lost. Sensory loss moves centripetally in a graded 'stocking' fashion. The patient may complain that the feet have a numb or 'wooden' feeling. Neuropathy is usually less severe in the arms, and spreads in a centripetal, symmetrically graded manner with palmar sensory loss and areflexia. Overall, nerve fibres are affected according to axon length, without regard to the root or nerve trunk distribution, giving rise to the term 'stocking and glove' distribution to describe the pattern of the sensory deficit. Mononeuritis multiplex refers to sequential involvement of individual non-contiguous nerve trunks. This leads to a patchy multifocal neurological defect, and is often caused by an immunological or toxin-mediated disease process. Lightning pains may be a feature of tabes dorsalis and angiokeratoma corporis diffusum (Fabry's disease).

Autonomic neuropathies can be a manifestation of a more generalized polyneuropathy, but may also occur in isolation, when structural changes in the pre- and post-ganglionic neurones occur. Autonomic neuropathy is characterized by symptoms of postural hypotension, anhidrosis, hypothermia, bladder atonia, constipation, dry mouth and eyes, failure of salivary and lacrimal glands to secrete, blurring of vision from lack of pupillary and ciliary regulation, and sexual impotence in males [1].

Carpal tunnel syndrome is caused by an entrapment mononeuropathy of the median nerve at the wrist. It may be secondary to excessive use of the wrist, tenosynovitis, or local infiltration with connective tissue such as in acromegaly, amyloid or mucopolysaccharidosis. The main symptoms are nocturnal paraesthesiae of the thumb, index and middle fingers.

Investigations. The investigations appropriate in peripheral neuropathy are shown in Table 60.2 [1].

Treatment. Treatment of neuropathic pain and neuropathic foot, sexual dysfunction and bowel or bladder control are dealt with in the relevant sections in this chapter.

Human immunodeficiency (HIV) neuropathy

With the effectiveness of antiretroviral treatment and the decline in opportunistic infections and HIV-induced dementia, HIV-associated neuropathies have become the most common neurological disorder associated with acquired immune deficiency syndrome (AIDS). They present as acute or chronic demyelinating neuropathies, mononeuritis multiplex, cytomegalovirus (CMV)-related

polyradiculoneuropathy, autonomic neuropathy or distal painful sensory neuropathy [2–4]. They are multifactorial in aetiology, occurring in all stages of the illness, and take a variety of courses. Early in the course of HIV infection, acute inflammatory demyelinating polyneuropathy resembles Guillan–Barré syndrome. In other patients, a progressive or relapsing inflammatory neuropathy, resembling chronic inflammatory demyelinating polyneuropathy and mononeuritis multiplex, occurs. The most common peripheral neuropathy in patients with HIV infection is distal sensory polyneuropathy (DSP), which may be either a direct consequence of HIV infection, or a side effect of antiretroviral therapy, antiretroviral toxic neuropathy (ATN), or both [2,4].

Aetiology. DSP is characterized by axonal degeneration of long nerves in the extremities. The virus, which is not found within ganglionic neurones or Schwann cells but only within the endoneurial macrophages, may generate a tissue-specific autoimmune attack by secretion of cytokines that promote trafficking of activated T cells and macrophages within the endoneurial parenchyma [5–7].

Studies of skin biopsies of patients with HIV-associated sensory neuropathy, developing during treatment with didanosine or zalcitabine, have shown a reduction in the density of epidermal fibres in distal lower extremities, with an inverse correlation between reduced nerve density and neuropathic pain [7,8]. Mononeuritis multiplex in AIDS may be due to immune complex necrotizing vasculitis, resulting from associated hepatitis B or C infection or cryoglobulinaemia [9,10]. In patients with opportunistic infection and AIDS, extension of CMV cytopathic effects may involve endothelial cells and Schwann cells in the nerve roots, dorsal root ganglia or spinal cord [2].

Clinical features. Distal sensory neuropathy and ATN lead to sensory loss and neuropathic pain in the extremities. Presenting symptoms are usually painful burning sensations in the feet and lower extremities. When due to antiretroviral therapy, patients may complain of a sensation that they are walking on ice. Findings on examination would include a stocking type sensory loss of pin prick, temperature and touch sensation and loss of ankle reflexes. Patients may develop a progressive weakness in the distal muscle groups in limbs [2–4]. Two-thirds of patients with AIDS may have electrophysiological studies showing some evidence of peripheral nerve disease. Progressive, relapsing inflammatory neuropathy, mononeuritis multiplex and CMV-related neuronal damage give rise to sensorimotor neuropathies. Xerosis is common in HIV infection, occurring in around 20% of seropositive patients. This may be related to a decrease in immunoreactive substance P and CGRP fibres occurring around the tubules of the eccrine sweat glands [11].

Treatment. In the acute stage of demyelination, plasma exchange or intravenous immunoglobulins may have been tried with variable success. Gabapentin [12], carbamazepine [13], tricyclic antidepressants or analgesics may be effective for dysaesthesia [2–4].

A multicentre placebo-controlled randomized trial has been carried out using recombinant human NGF, which is trophic for small sensory neurones and stimulates the regeneration of damaged nerve fibres [14,15]. The treatment was shown to be efficacious in reduction of neuropathic pain and increase in pin prick sensitivity. Side effects of treatment included pain at the site of injection and transient myalgic pain.

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Trigeminal trophic syndrome

This is an uncommon disorder in which trophic ulceration follows minor, repetitive trauma to anaesthetic skin within the trigeminal area. Neurotrophic changes in the trigeminal area may follow the destruction of fibres conveying pain and temperature sensation [1]. Causes of this disorder include central sensory neuronal damage (post-encephalitic parkinsonism, syringobulbia, posterior fossa tumour or occlusion of the posterior inferior cerebellar

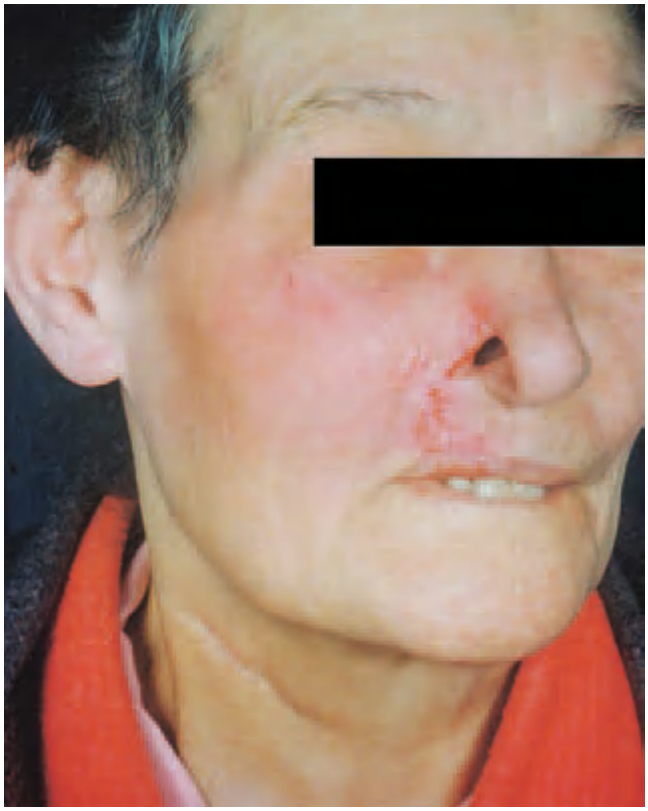

Fig. 60.11 Trigeminal trophic syndrome resembling basal cell carcinoma of the right ala nasi.

artery [2,3], leprous neuritis and brain stem infarcts [4]) or damage to the trigeminal nerve by attempts to relieve intractable trigeminal neuralgia (by surgery or alcohol injections into the gasserian ganglion [5]) or herpes zoster [6] or simplex-related neuritis [7]. Trigeminal trophic syndrome is usually a disease of adults, although recently a case has been described in a 14-year-old child secondary to herpes simplex trigeminal neuritis [8].

Clinical features. The patient complains of paraesthesiae or a sensation of itch on the ala nasi. This is then picked, rubbed or scratched and, because the trauma is painless, the erosion increases in size and may extend to destroy the nasal cartilage [1,9]. The patients freely admit to traumatizing the area in an attempt to relieve the uncomfortable sensation. A clinical similarity to a basal cell carcinoma may be striking, often requiring a biopsy, which in trigeminal trophic syndrome simply shows inflammatory reaction [9] (Fig. 60.11). The pattern of ulceration may be sufficiently bizarre to suggest dermatitis artefacta. The ulcer spreads towards the cheek and the upper lip and, apart from the problems of control of secondary infection, subsequent scar formation in the area of the ala can result in the elevation of the lip resulting in a disfiguring sneer [9]. Characteristically, the alar rim is involved and the tip of the nose spared. Sites less frequently involved include the forehead, scalp and cheeks. Neurological examination should reveal decreased perception of light touch and pain over the area, and sometimes an absent corneal reflex on the same side [9].

Treatment. Surgical approaches in the past have included cervical sympathectomy [10], transcutaneous electrical stimulation [11] and grafting or the use of innervated transposition flaps [12], although these can fail if trauma to the area continues. Protection through occlusive dressings and wearing gloves can be of some help, but the ulceration commonly persists, particularly in the elderly or in confused patients who compulsively pick at the skin. Treatments which have resulted in improvement have included amitriptyline [5], diazepam [5], chlorpromazine [1] and pimozide, presumably through influencing the paraesthesiae and behavioural factors involved in the syndrome. Carbamazepine was found to be very effective in one reported case [9], although less so in others [1].

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Peripheral nerve injury

Lesions of the peripheral nerve may cause permanent denervation with paralysis and disability, and represent a challenging problem in neurosurgery. The slow rate of nerve regeneration conspires together with atrophy and degeneration of the denervated organs to increase the risk of permanent disability after peripheral nerve injury, emphasizing the importance of rapid and timely intervention [1,2]. Neurotrophic factors are secreted polypeptides that control the survival, differentiation and maintenance of neurones. Sectioning of peripheral nerves results in the almost total loss of immunoreactivity for both low

(p75) and high affinity (TrkA-like) receptors for NGF [3]. Meissner's and pacinian corpuscles, after nerve section, lose immunohistochemical antigens such as S100 protein, epithelial membrane antigen and vimentin, strongly suggesting that the structure and integrity of the nerve axis is essential in maintaining some immunohistochemical characteristics of the human sensory corpuscles [4].

Section or severe contusion of a peripheral nerve has been held responsible for a variety of cutaneous changes. Skin manifestations are found in some 20% of patients with the carpal tunnel syndrome [5], and include a reddish discoloration of the fingers with bullae, small foci of necrosis and nail dystrophy [6]. Nail dystrophy and other trophic changes are also sometimes caused by a cervical rib [7]. In one report, injury to the lateral femoral cutaneous nerve during appendicectomy [8] was followed 6 days later by the development of bullae on the outer aspect of the right lower leg, with subsequent ulceration and scarring.

Cooling also affects conduction in peripheral nerves. Loss of sensation in the feet has been reported after prolonged immersion in cold seawater [9]. Areas of skin looking like partial thickness burns and blistering were found on the feet of 25 out of 160 participants in a barefoot run: a temporary cold-induced neuropathy of the feet had allowed subjects to continue running despite these injuries [10]. Neuropathy may be induced by cryotherapy, and in one series of 183 lesions treated in this way, some subsequent sensory loss was demonstrated in 28%. This was usually mild and transient, although rarely long lasting [11].

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Syringomyelia

This is a rare disorder characterized by a longitudinal cyst in the cervical cord and/or medulla (syringobulbia) immediately anterior to the central canal, which spreads, usually asymmetrically, to each side. The majority of lesions occur in association with type 1 Chiari's syndrome where there is a congenital extension of the cerebellar tonsils below the foramen magnum [1]. Other causes include trauma and tumours [1]. MRI scanning of the hindbrain and upper spinal cord is best for delineation of the syrinx [1–3]. An association with other abnormalities, such as a short neck and a low hairline, suggests a developmental origin. Symptoms usually appear in young adults and the disease is generally slowly progressive over 20–30 years, although limited resolution of symptoms has occurred in adults [1] and children [2,3].

Early involvement of pain and temperature fibres, where they cross the midline anteriorly, leads to a characteristic dissociated sensory loss, in which pain and temperature sensation is lost early in the upper limbs, while other sensory modalities carried in the posterior columns (e.g. touch, vibration and position sense) may remain relatively intact. These changes are responsible for the earliest manifestation of the disease, a tendency to sustain painless burns and cuts on the hands and forearms. Later, upper motor neurone signs in the legs may accompany weakness, wasting and loss of reflexes in the arms. Occasionally a combination of progressive pain loss, resultant skin ulceration, loss of soft tissue, resorption of the phalanges and muscular atrophy (Morvan's syndrome) occurs.

Body asymmetry or hemi-hypertrophy is known to occur in syringomyelia and can occur on the head and face. Hypertrophy of the hands and feet, together with hypertrophy of the bones and muscles in the same limb (especially in the upper limbs), has been described with syringomyelia [4].

Many of the skin changes accompanying syringomyelia are the result of repeated burns or other injuries, particularly of the hands, where the skin over the fingers and knuckles may become thickened, swollen, cyanotic and keratotic. Analgesia renders the patient liable to minor injuries, which heal slowly. Gangrene rarely occurs, but damage to, or loss of, terminal phalanges or nails is not uncommon. The French term '*la main succulente*' refers to the swollen and oedematous hands of syringomyelia sufferers. Syringomyelia is responsible for dyshidrosis with hyperhidrosis or hypohidrosis, this being more common than previously recognized, with one series showing dyshidrosis in 60% of patients [5]. The dyshidrosis, usually occurring over the face and upper arms, may be spontaneous or occur reflexly, when the patient consumes hot or highly seasoned food. Its distribution, which can be studied by thermography, correlates with the location

of the syrinx and other neurological manifestations [5]. Hyperhidrosis is probably caused by stimulation of the sympathetic preganglionic neurones and, as the disease progresses, hyperreactivity gradually decreases and is replaced by hypoactivity. This may be important, as focal hyperhidrosis can be regarded as a hallmark of a relatively intact, even though slightly damaged, spinal cord [5]. Asymmetry of scalp hair can also occur in syringomyelia, with the denervated areas having less abundant hair, which grows more slowly [6].

Extension of the syrinx into the medulla may disrupt the vestibular pathways, the descending root of the trigeminal nerve, the sympathetic and taste pathways, and the hypoglossal nerve. The symptoms and signs may then include vertigo with nystagmus, dissociated sensory loss over the face, loss of taste, a wasted tongue, Horner's syndrome and sometimes paralysis of the vocal cords. Facial oedema confined to areas of sensory loss has been described [7].

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Tabes dorsalis

This is still the most common form of neurosyphilis and is the one with the longest incubation period (usually 10–20 years: range 5–50 years), affecting men more often than women. The main symptoms are due to degeneration of the afferent fibres of the dorsal roots. It is characterized by a triad of symptoms (lightning pains, dysuria and ataxia) and a triad of signs (Argyll Robertson pupils, areflexia and loss of proprioceptive sense) [1].

Usually, sensory symptoms precede ataxia by months or years. Lightning pains are the most characteristic early symptom, and occur in 90% of cases at some stage, most often affecting the legs. Pain sensibility is also impaired early, the deep tissues becoming insensitive before the skin does. This may be demonstrated by squeezing the Achilles tendon. Argyll Robertson pupils, miotic pupils that fail to react to direct light, are found in about half of the patients. Originally associated with tabes dorsalis, the sign is now recognized as being common to a number of conditions causing lesions in the area of the nucleus of Edinger–Westphal. Thus, MRI studies have localized lesions to this region in patients with sarcoidosis and multiple sclerosis [2]. With the declining incidence of neurosyphilis, the sign is increasingly likely to indicate another cause, although an assiduous search for syphilis should also be undertaken.

Later features may include ataxia, with a wide-based gait, made worse by the elimination of visual clues, dribbling overflow incontinence, visceral crises, optic atrophy and a painless distortion of the hips, knees or ankles (Charcot's joints).

The commonest trophic change in the skin is a neuropathic ulcer. Symptomatic herpes zoster may occur, as in other conditions affecting dorsal roots.

The clinical features and laboratory findings may be modified by the widespread use of antibiotics and corticosteroids for treating unrelated diseases [3]. This sometimes leads to difficulty in deciding whether tabes dorsalis is active or 'burned-out', with a neurological deficit due to fixed structural damage. Penicillin treatment will arrest the course of the disease, but residual lightning pains, gastric crises and urinary incontinence are likely to persist.

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Spinal dysraphism

Spinal cord development occurs between weeks 2 and 6 of embryonic life. A raphe is a line of junction between symmetrical embryological structures: dysraphism is a failure of this type of fusion [1]. Spinal dysraphism leads to malformations of midline dorsal structures [2]. Defects in the early embryonic stages produce spinal dysraphisms, which can be categorized clinically into two subsets. Open spinal dysraphisms are exposed to the environment (e.g. spina bifida, myelomeningocoele), while closed spinal dysraphisms are covered by intact skin.

A review of 200 published cases of spinal dysraphism [3] included 102 with cutaneous abnormalities, often in combination. A dermatologist may be the first physician to see such patients, and should be aware of possible associations with underlying neurological abnormalities.

Patients with giant congenital melanocytic naevi overlying the scalp or dorsal spine can, on MRI, have abnormalities of the leptomeninges, the amygdala, cerebellum and pons [4].

Many skin abnormalities overlying the lumbosacral region have been reported to be associated with spinal dysraphism and cord tethering, including lipomas [5], port-wine stains, haemangiomas [6], 'faun tail' (hypertrichosis)

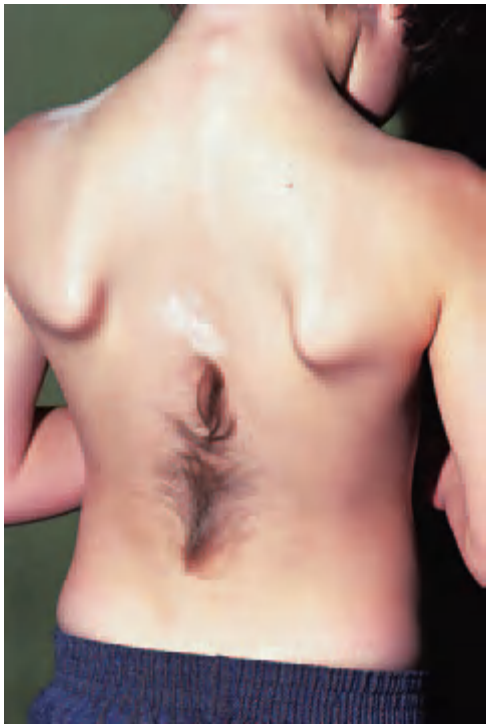

Fig. 60.12 Tuft of hair in association with spina bifida.

[7], pigmented macules and pits or dimples. Because tethered spinal cord is a treatable condition and, if left untreated, can lead to progressive neurological degeneration, spinal MRI scanning of infants with giant melanocytic naevi involving the lumbosacral area is advocated [8,9]. Approximately 20% of patients with large congenital naevi in this region will have associated neurological or developmental abnormalities on MRI scanning [10].

Spina bifida

Several varieties of spina bifida are described, differing in the nature and severity of the spinal defect. In the severe form, a sac protrudes through the vertebral opening and transmits an impulse on crying or coughing. In the least severe cases (spina bifida occulta) there is no such protrusion, but a defect in the vertebral lamina may be felt as a depression, and is sometimes covered by a tuft of hair or a dimple (Fig. 60.12). Spina bifida occulta may give rise to no symptoms, and be a chance finding in the course of a routine examination. However, lesions preventing the ascent of the spinal cord, which occurs during normal growth, can lead to undue traction on the lower end of the cord and cauda equina.

The neurological changes will then be those of a chronic lesion of the cauda equina. Such patients may have been slow to learn to walk. Sensation may be impaired over the areas innervated by the lowest sacral segments, leading to a characteristic saddle-shaped area of analgesia over the buttocks and dorsa of the thighs. Trophic changes are conspicuous in some cases, and are rarely lacking altogether. In milder cases, the feet are usually cold and cyanosed: cutaneous injuries are slow to heal and tend to ulcerate, not only on the feet but also in the analgesic skin of the buttocks and thighs. The most severe neurological abnormality is a flaccid paraparesis with sphincter paralysis.

The diagnosis is confirmed by radiography, showing defective fusion of the laminae in the affected region, usually the first sacral and fifth lumbar vertebrae. An MRI scan or myelography may be helpful. Estimation of α-fetoprotein in the amniotic fluid or in the maternal serum may successfully identify a fetus with a severe malformation of the CNS such as spina bifida cystica or anencephaly.

Patients with spina bifida are at risk of latex sensitivity [11] due to exposure to latex products, both at the time of surgery and also with indwelling catheters, etc. Such patients should be assessed using latex-specific serum IgE, radioallergosorbent test (RAST), skin prick testing to latex suspension and latex glove usage test [12,13]. Patients allergic to latex may display urticaria, conjunctivitis, angio-oedema, rhinitis and bronchial asthma. They are at risk of anaphylaxis during procedures when health care workers are using latex gloves during bladder catheterization and, because of cross-sensitivity to food allergens, can be allergic to fresh foods including kiwi, pear, orange, pineapple, tomato and banana.

The treatment of spina bifida lies in the domain of the paediatrician or neurologist, but the dermatologist may be asked for advice on the trophic ulcers.

Congenital dermal sinuses

These lie close to the midline and may be no more than 1 or 2 mm in diameter [1]. Hairs may protrude from the opening, but these sinuses differ from pilonidal sinuses in that they connect directly to the contents of the spinal canal and so serve as a portal of entry for infection. Probing is therefore unwise. Such sinuses may expand into cysts deeply, and these may press on the spinal cord.

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Spinal cord injury

The spinal cord may be injured directly by penetrating wounds or, more frequently, it suffers indirectly as a result of dislocations or fracture dislocations of the vertebral column. Damage may not necessarily be as a result of direct trauma but because of surrounding tissue damage, causing the spinal cord to swell and occupy the entire diameter of the spinal cord at the level of the injury. Causes include motor vehicle accidents (36–48%), violence (5–29%), falls (17–21%) and recreational activities (7–16%) [1]. Conventional radiography on its own should not be depended on to define the damage, and dynamic views in flexion–extension movement may provide additional information; where these are not deemed safe, MRI is necessary [1]. Rare dermatological causes of spinal cord injury have included a neglected basal cell carcinoma on the back [2], an adenocystic carcinoma in overlying skin [3] and multiple myeloma in a man presenting with primary cutaneous plasmacytomas, resulting in spinal cord compression [4].

Seborrhoea and seborrhoeic dermatitis have been reported in quadriplegia patients [5,6]. In one study [6] of 20 patients with spinal injury but no seborrhoeic dermatitis on admission, 13 developed the condition on the face and trunk within a few weeks. Nummular eczema may also occur below the level of the lesion [5]. Twenty-one patients with complete paralysis below levels varying from C5 to T12 were investigated for sebum excretion rate, skin temperature and the presence of acne [7]. An increased incidence of acne was found on the back and buttocks, often occurring for the first time after the onset of paralysis. Sebum excretion on the forehead did not differ from that of normal, but was significantly increased below the neurological lesion. This could not be explained by changes in skin temperature.

The changes in eccrine sweating after spinal cord injuries are complex [8]. Episodes of profuse sweating on the face, neck and upper trunk in patients with lesions at or above T6 may occur as an exaggerated response to stimuli such as bowel or bladder distension (autonomic dysreflexia). Facial flushing and headache may be associated with these episodes. Other patients develop sweating of the face and arms after dizziness due to postural hypotension. Finally, post-traumatic syringomyelia can lead to hyperhidrosis [9]. Dryness of the skin, particularly noticeable on the soles, is an effect of anhidrosis.

Chronic decubitus ulceration can be a problem, and local osteomyelitis rarely leads to secondary amyloidosis. Excellent nursing, prevention of pressure and attention to the patient's general health are essential. There should be frequent review of pressure ulcer prevention and management strategies, and patients should be supplied with aids such as ripple mattresses to help reduce localized pressure. Pressure sore closure is frequently a reconstructive challenge and in itself can be deforming. The use of an inferiorly based vertical rectus abdominis myocutaneous flap for both recalcitrant ischial and trochanteric pressure sores has been shown to be useful [10].

Early decompression and high-dose methylprednisolone may reduce further spinal cord damage following injury. Small gains in neurological regeneration can lead to a disproportionate gain in function, since, for example, fewer than 10% functional long-tract connections are needed to enable good locomotor action. Adequate rehabilitation will prevent many complications and improve outcome [1]. Tendon transfer can improve hand grip and transcutaneous electrical stimulation can help muscles, including the diaphragm, facilitate erection and ejaculation and control pain. Bladder and bowel control may be helped with implantable electrical stimulators or botulinum toxin [11]. Sexual dysfunction can be treated by mechanical (vacuum pumps, penile implants, electrical stimulation) or pharmacological interventions (sildenafil, intracavernosus injection) [1,12], the latter depending on the sparing of either the sacral (S2–S4) or thoraco–lumbar (T10–L2) spinal segments. Exciting new treatment opportunities emerged through the use of NGFs, creation of neuronal 'bridges' using peripheral nerves and the use of stem cells [1], and future development is likely through collaboration between scientists and clinical specialists [1].

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Disorders associated with autonomic abnormalities

Hereditary sensory autonomic neuropathies (HSANs)

The classification of HSAN was modified by Dyck [1] into five main groups of syndromes with common clinical, pathophysiological and genetic phenotypes.

Hereditary sensory autonomic neuropathy type I (HSAN I)

HSAN type I differs from all other HSANs in that its symptoms appear late, rather than congenitally. It is an autosomal dominant disorder, mapping to chromosome 9q22.1–q22.3 [2,3]. It is the most common HSAN, resulting in progressive degeneration of sensory dorsal root ganglia, with loss of both small myelinated and unmyelinated nerves leading to a distal sensory and motor loss, particularly in the lower limbs [2,4]. HSAN type I presents in late childhood or adolescence with progressive loss of all modalities of sensation in the lower extremities, particularly pain and temperature. This often results in chronic trophic ulceration on weight-bearing areas of the feet, associated osteomyelitis and mutilating deformity [4,5]. Later manifestations include muscle wasting, weakness and lancinating pain in the lower limbs and extension of sensory symptoms to the upper limbs. Neural deafness is frequent, and congenital cataracts and mental retardation have been reported [4].

Treatment is supportive, with good fitting shoes and alleviation of weight bearing if ulcers form [5].

Hereditary sensory autonomic neuropathy type II (HSAN II)

HSAN type II is an autosomal recessive disorder with a congenital or early onset, with marked loss of sensory, motor and autonomic motor neurones and marked loss of unmyelinated nerves [1,6–8]. No chromosomal linkage has been identified. A high urinary excretion of sphingomyelin and lecithin suggest that the primary mechanism may be a disorder of phospholipid metabolism [7].

Infantile hypotonia is common. Unlike HSAN I, which primarily affects the feet, HSAN II results in loss of sensation equally in hands and feet, leading to ulceration at sites such as the forehead, trunk, tongue and lips as a result of repeated injury. Fingers can show ainhum-like constriction bands and spontaneous amputations. Loss of deep sensation results in deep ulceration, osteomyelitis, stress fractures and injury to long bones [6–8]. Tendon reflexes and anhidrosis occur in areas of decreased sensation, although anhidrosis is less prominent than in HSAN IV.

Associated features include mental retardation, neural deafness, impaired taste and smell, retinitis pigmentosa and cataracts.

Hereditary sensory autonomic neuropathy type III (HSAN III) (familial dysautonomia)

HSAN type III (previously familial dysautonomia; Riley–Day syndrome) is the most common of the sensory and autonomic neuropathies [9–13]. The disorder is transmitted as an autosomal recessive trait, mapping to 9q31–q33 [14–16], and is prevalent in Ashkenazi Jews, in whom the frequency is 1 : 10 000. Scattered cases in non-Jewish patients have been reported. Prenatal diagnosis is now possible [15].

Onset is congenital, and hypotonia, sucking difficulties, a poor cry and vomiting are present at birth. Autonomic features are prominent, with impaired production of tears, unstable temperature control, postural hypotension and excessive sweating, especially during infection, all being major features. Impaired oesophageal motility, with resultant pneumonia, together with bouts of apnoea, are causes of death in childhood. Blotchy erythema occurs during overheating, and erythematous macules 2–5 cm in diameter may occur on the trunk and limbs in response to emotional upsets [13].

A diagnosis is sometimes made in infancy because the child cries without producing tears. Other diagnostic criteria include absent fungiform papillae on the tongue, absent tendon and corneal reflexes, lack of axon flare after intradermal histamine, and miosis following instillation of methacholine. Later, the child may show delayed growth and invariably displays postural hypotension. Intelligence remains normal, but emotional lability is common. Progressive abnormalities of cutaneous temperature discrimination and nociception are found in most patients [11]. Mortality rates remain high but have improved with better supportive measures, and 50% of patients now survive to adulthood [17]. Death may follow inhalation during attacks of vomiting, and hypotension and cardiac arrest are risks with a general anaesthetic [18].

Treatment is symptomatic. Attention to feeding must be meticulous and gastrostomy may be required. Diazepam and chlorpromazine can be used to treat acute autonomic crises and intranasal midazolam can be used for patients at home [19].

Hereditary sensory autonomic neuropathy type IV (HSAN IV)

HSAN type IV probably comprises a heterogeneous group of patients and is transmitted by autosomal dominant inheritance [20]. Defects in the human *TRKA* (*NTRKI*) gene located on chromosome 1 (1q21–q22) which encodes a receptor tyrosine kinase (RTK) have been shown [21].

Clinically, the boundary between HSAN II and IV can be difficult to delineate. HSAN IV is an autosomal recessive disorder characterized by recurrent episodic fevers, anhidrosis, absence of reaction to noxious stimuli, self-mutilating behaviour and mental retardation [20,21]. Infants are hypotonic and areflexic. High fever related to an inability to sweat, especially in the summer, can be associated with seizures [20–22]. Insensitivity to pain with self-inflicted injury results in multiple scars and bone fractures, autoextraction of teeth and ulceration of tongue, lips and buccal mucosal [23].

The anomalous pain and temperature sensation and anhidrosis in HSAN V are due to the absence of afferent neurones activated by tissue-damaging stimuli and a loss of innervation of eccrine sweat glands, respectively [22]. These patients have recently been shown to have a decrease in skin nerve fibres positive for PGP 9.5, CGRP, substance P, NPY, nitric oxide and VIP [22,23], and innervation is almost completely absent around eccrine sweat glands [22].

Treatment is limited; oral shields may prevent damage to the oral tissues [24].

Hereditary sensory autonomic neuropathy type V (HSAN V)

SYN. CONGENITAL INSENSITIVITY TO PAIN

HSAN type V is a rare autosomal recessive hereditary sensory autonomic neuropathy characterized by insensitivity to pain, self-mutilating behaviour, anhidrosis with recurrent hyperpyrexia and mental retardation [25,26].

This autosomal recessive condition results in a defect in the development of sensory and autonomic peripheral nerves [26]. It is caused by mutations of the human *TRKA* (*NTRK1*) gene located on chromosome 1q21–q22, which codes for the receptor for NGF and tyrosine kinase [27–30]. Nociceptive and sympathetic Aδ-fibre and C-fibre nerve activity is reduced or absent in the skin, S100 protein and neurone-specific enolase are reduced or absent in the vicinity of eccrine sweat glands, and substance P receptors are absent from nerve fibres and the epidermis [31]. This is consistent with the loss of unmyelinated and small myelinated fibres, as seen in sural nerve biopsies [32].

Patients present in early childhood when they start to crawl; they fail to learn the consequences of injury and do not cry with soft-tissue injury. There is associated heat intolerance due to anhidrosis, with episodes of hyperpyrexia. Death from hyperpyrexia has been recorded in up to 10% of patients in the first 3 years of life. Sunburn and frostbite may occur. There is a striking absence of the SSR. Congenital insensitivity to pain with anhidrosis is characterized by multisystem involvement. Skin ulcerations on the fingers and toes are common from self-biting, and neurological examination often reveals complete analgesia, although tactile discrimination, sensation of cold, head and vibration may be normal. Corneal reflexes are usually present but deep tendon reflexes are abolished. Neonatal hypotonia and psychomotor retardation are common, as are slow healing fractures, joint deformities, osteomyelitis, avascular necrosis and acro-osteolysis of fingers [33].

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Sympathetic nerve injury [1]

When the sympathetic supply of the skin is interrupted, loss of vasoconstrictor impulses leads to erythema. There is passive vasodilatation and the denervated area is anhidrotic. The skin may become noticeably dry with scaliness and fine fissures. The affected area heals only slowly following minor trauma, and some patients complain that it is hyperaesthetic. It has been shown that after sympathetic ganglionectomy there can be dissociation of sudomotor and pilomotor activity [2]. In the denervated areas, there is no loss of cutaneous sensation, and the phenomenon may be due to the regeneration of post-ganglionic cholinergic fibres. In general, the areas of vasodilatation correspond to the areas of anhidrosis, suggesting a close correspondence of sudomotor and vasoconstrictor fibres [3]. Measurements of sweating and vasomotor responses can help to determine the extent of autonomic denervation.

As discussed earlier in this chapter, when sympathetic denervation is combined with a loss of somatic sensation, as, for instance, in peripheral nerve injury or severe peripheral neuropathy, neurotrophic ulcers may be encountered. These result from local minor trauma and are characteristically painless and slow to heal. Sympathetic denervation may also slow or prevent the normal greying of hair that takes place with increasing age [4,5], and in one case it seemed to cause hyperpigmentation of the skin in the affected area [6].

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Complex regional pain syndrome (CRPS)

Complex regional pain syndrome (previously known as reflex sympathetic dystrophy or causalgia) is a heterogeneous group of conditions resulting in neuropathic pain that is characterized by pain and dysfunction of the sympathetic nervous system [1–3]. It has been recommended that the diagnostic criteria include at least one event from each of four groups: (i) a syndrome that develops after a noxious event; (ii) spontaneous pain or allodynia/hyperalgesia not limited to the territory of a single nerve and disproportionate to the initiating stimulus; (iii) past or present oedema, abnormal skin blood flow or sudomotor activity; and (iv) absence of conditions that might otherwise account for pain and dysfunction [1,2].

Aetiology. Complex regional pain syndrome commonly develops after trauma, with at least 50% of cases involving a fracture (most often a Colles' fracture), but it can be induced by sprains, contusion or lacerations. It usually involves a distal limb site. Other antecedent factors have included injury to the central or peripheral nervous system, stroke, myocardial infarction, tuberculosis and

Table 60.3 Dermatologically associated causes of complex regional pain syndrome (CRPS) [1,4–7].

Acrodermatitis continua of Hallopeau
Chronic venous ulceration
Dupuytren's contracture
Epithelioid haemangioendothelioma
Herpes zoster
Human parvovirus B19
Minor surgery (nail, skin biopsy)
Osteogenesis imperfecta
Psoriatic arthritis
Systemic lupus erythematosus
Vasculitis
Weber–Christian panniculitis

Table 60.4 Dermatological manifestations of complex regional pain syndrome (CRPS) [1].

Oedema
Erythema and warmth
Pallor or cyanosis
Hypertrichosis or hypotrichosis
Hypohydrosis or hyperhydrosis
Beau's lines or nail notching, leukonychia, onychodystrophy
Factitious ulcers
Bullae

certain drugs [1]. Dermatologically associated causes of CRPS are listed in Table 60.3 [1,4–7].

The pathogenesis of CRPS is not well understood, and hypotheses include neuropeptide release causing pain and vasodilation, enhanced α-adrenergic receptor activity, and up-regulation of afferent nocioreceptors in response to norepinephrine release from sympathetic efferents. Other theories suggest excessive inflammation at the site of injury and involvement of the immune system or the CNS [1].

Symptoms. It is common to divide the symptoms of CRPS into three stages [1].

The first stage begins several days or weeks after the injury and lasts about a month. During this first stage, the symptoms are those of spontaneous burning and stinging pain, or shooting pain precipitated by mechanical stimuli such as bathing, clothing resting on the skin or drafts blowing on a limb [2].

The second stage occurs from 1 to 7 months after injury and lasts 3–6 months. The symptoms relate to sympathetic hyperactivity and include cool, oedematous skin, hyperhydrosis and cyanosis or livedo-like changes. Hair may show decreased growth and nails become brittle. Pain is variable and the neuralgia may either spread or decrease.

In the third stage, starting some 8 months after injury there is progressive tissue damage, which can become permanent. The skin becomes shiny, atrophic and dry and fingertips may diminish in size. When pain is made worse by a variety of stimuli, the patient may protect the limb, leading to trophic changes of thin, shiny skin with muscle wasting and bone demineralization (Sudeck's atrophy).

Dermatological manifestations of CRPS are listed in Table 60.4 [1].

Diagnosis. Diagnostic tests include: pain relief on α_1-adrenergic blockade with intravenous phentolamine; pain exacerbation on α_2 stimulation by clonidine; and elicitation of severe pain on cold stimulation, induced by evaporation of a drop of acetone or ethyl chloride on the skin.

Treatment. Interdisciplinary pain management techniques should include the use of occupational therapy and physiotherapy to aid active movement and allow graded increase in activity. Early mobilization of 'at risk' extremities or joints, for example the wrist after Colles' fracture or surgery, can be preventative. This can be accomplished by a series of exercises using devices; for example, in the case of Colles' fracture a rubber ball progressing to spring grip strengtheners and mat exercises [2,8]. Desensitization techniques such as rubbing the skin with silk, then cotton, then towelling, or baths of contrasting temperature, can be particularly useful [2,8].

Drug treatment may include tricyclic antidepressants, or newer antidepressants such as venlafaxine and mirtazapine, especially in the setting of associated depression [2]. Gabapentin [9], lamotrigine and carbamazepine have proved useful, although randomized control trials in CRPS are lacking [2]. Both α- (phentolamine) and β- (propranolol) blockers have been found useful in some patients [1]. An eutectic mixture of local anaesthetics (EMLA) or capsaicin creams have not generally proved beneficial [2,10]. Where inflammation is considered to have an aetiological role, ketoprofen or even a short course of oral steroids may be of help [2]. Interestingly, calcitonin is one of the best-studied drugs in the management of CRPS and produced significant pain relief in almost 60% of patients in a randomized clinical trial [11].

There has been a recent report of resolution of CRPS with thalidomide therapy [12]. Although sympathectomy has been a traditional first line of treatment in CRPS, there is little evidence to support its use, and it does not seem to have a long-term effect [13,14]. Intravenous regional sympathetic blockade using guanethidine [2] or bretylium [2,15], use of a spinal cord stimulator [16] and subcutaneous lidocaine infusions [17] may be helpful.

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Horner's syndrome [1]

This follows partial or complete interruption of the sympathetic pathways of the face. It is characterized by ptosis, miosis and anhidrosis.

Aetiology. The fibres responsible for the sympathetic nerve supply to the skin of the face travel from the hypothalamus via the spinal cord, to relay at the level of the first and second thoracic segments in the lateral column of the spinal grey matter. The preganglionic fibres emerge from the cord in the anterior rami of the first and second thoracic spinal nerves, and pass up the cervical sympathetic chain to relay in the superior cervical ganglion. From here, post-ganglionic fibres pass to supply the eye and the skin of a small central area of the face via the internal carotid sympathetic plexus. Other fibres pass along the external carotid artery and its branches to innervate the greater part of the facial skin with vasomotor and sudomotor fibres.

This pathway can be interrupted centrally in the spinal cord; for example, by medullary infarction, syringomyelia, multiple sclerosis or intraspinal tumours. The peripheral fibres can be damaged by an aortic aneurysm, cervical lymphadenopathy, surgery, regional anaesthetic procedures or tumours. Horner's syndrome may follow sympathectomy for the treatment of palmar and axillary hyperhidrosis, and occurs in up to 40% of patients having cervical sympathectomy by conventional open surgery and in up to 8% of those having transthoracic endoscopic sympathectomy [2]. In such cases, there may be resolution of long-standing pompholyx-type hand eczema on the ipsilateral side, suggesting a neurological pathogenesis for endogenous pompholyx in some patients [3,4].

Clinical features. An irritative phase is described, but rarely seen, in which there is transient unilateral hyperhidrosis and vasoconstriction. The paralytic phase is characterized by drooping of the eyelid (ptosis) with narrowing of the palpebral fissure. The pupil is small, but shows normal reflex constriction to light and accommodation, and sweating is absent on the ipsilateral side of the face. There may be slight retraction of the globe of the eye into the orbit (enophthalmos). Cases of bilateral Horner's syndrome are rarely encountered. Sweat glands on the medial and lateral parts of the forehead are innervated separately, with the medial forehead being supplied by nerve fibres from the sympathetic plexus of the internal carotid artery, while the lateral forehead derives its sympathetic nerve supply from the plexus surrounding the external carotid artery [5]. This accounts for the findings in Raeder's syndrome, where damage involving the perivascular plexus of the internal carotid artery leads to anhidrosis medially but not laterally on the forehead [6].

Treatment. This should be directed to the underlying cause; usually, however, this is not amenable to therapy.

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Gustatory hyperhidrosis

The autonomic nervous system has a propensity for regrowth [1]. Damage to adjacent preganglionic parasympathetic fibres and post-ganglionic sympathetic fibres

may be followed by parasympathetic fibres regrowing into the sympathetic nerves, thereby directly controlling sweat gland function. In the neck, for example, following damage to the sympathetic cervical trunk and the vagus (parasympathetic) at the time of thyroidectomy or after trauma, such reinnervation may result in gustatory hyperhidrosis even after eating bland foods [2]. A similar event may occur on the cheeks or chin following surgery to the parotid or submandibular glands—the so-called auriculotemporal syndrome (Frey's syndrome) [3]. Secretory sweating is now more frequently seen after endoscopic trans-thoracic sympathectomy [4,5].

Treatment. Fortunately, topical preparations such as those containing aluminium chloride hexahydrate often control these symptoms well, but may themselves produce an irritant dermatitis. Botulinum toxin has been shown to be effective and safe in gustatory sweating [6]. A further option is the use of a 0.5% aqueous solution of glycopyrronium bromide topically, which has been shown to be effective, safe, well tolerated and convenient in diabetes-associated gustatory sweating [7].

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Chronic skin pain

The diagnosis of dysmorphophobia or dermatological non-disease [1,2] should always be considered when patients present with chronic skin pain, especially when areas important to body image are involved. These include the burning vulva syndrome (vulvodynia) and the burning scrotum syndrome (Chapter 68) as well as orodynia (Chapter 66). However, one should keep an open mind about other entities including notalgia paraesthetica, brachioradial pruritus (BRP) and skin–ache syndrome. Post-herpetic neuralgia is discussed earlier in this chapter.

Notalgia paraesthetica

Notalgia paraesthetica was first described in 1934 by Astwazaturow [3]. It is characterized by episodes of itch and skin pain, usually close to the medial border of the scapula, corresponding to the posterior primary rami of the thoracic nerves T2–T6. The condition may be caused by entrapment of the posterior rami of these spinal nerves as they pass through muscle, and may be predisposed to by back injury or back trauma from prolonged sitting [4]. Patients present with localized discomfort or pruritus on the back; the condition runs a chronic course, and is probably more frequent than previously thought. Examination often reveals a speckled or uniform area of pigmentation, which may be associated with lichenification. There may be hypoaesthesia or hyperaesthesia to pin prick, often localized to the centre of the area [5]. Histopathology characteristically shows intraepithelial necrotic keratinocytes with melanin and macrophages in the papillary dermis [6]. One study found increased substance P immunoreactive fibres in the skin [7].

The relationship of this condition to primary localized cutaneous amyloidosis of macular type [5] is unclear; but in most cases amyloid has been found to be absent, although it may have been missed because deposits were sparse [3,8]. Cases with classical features of notalgia paraesthetica have been reported in which macular amyloid was present on skin biopsy [3]. It is well known that prolonged scratching and rubbing can give rise to friction-related amyloid deposits (Chapter 57); the intractable pruritus characteristic of notalgia paraesthetica may thus explain the association with localized cutaneous amyloidosis.

In one study, 70% of patients treated with topical capsaicin, and 30% of patients receiving vehicle, reported some degree of improvement, but it was difficult to maintain the double-blind design of the study because of the symptoms produced by capsaicin itself [9]. In a series of three patients, all patients were reported as improved by application of topical EMLA (2.5% lidocaine and 2.5% prilocaine) [6].

Brachioradial pruritus

BRP is a localized itch in a dermatomal distribution, which usually occurs on the lateral aspect of the arm and elbow, or less commonly on the shoulders, neck or upper thorax [10]. It was originally described in patients from Florida, USA, and the Transvaal, South Africa. A strong seasonal variation, with symptoms being worse in summer months, improvement with photoprotection and the fact that case reports have come mainly from tropical areas, have all been cited as evidence that BRP is a photodermatosis [10–14]. In other cases, cervical root damage (C5–C8) from degenerative arthropathy, cervical rib or spinal tumours may have been important aetiological factors [15]. It is likely that both cervical spine disease and sunlight-induced damage to cutaneous nerve endings are important underlying contributors and triggering factors [13]. Dermal pin prick hyperaesthesia may be present in a

cervical nerve distribution [14]. MRI scanning should be performed to define cervical nerve-root compression [16].

Unlike normal itch, which tends to be relieved by scratching, in BRP scratching seems to potentiate the sensation of itch transmitted by the C fibres [10,17]. BRP is often refractory to topical or oral steroids and antihistamines [15]. Reports of response to topical capsaicin have been variable [9,17,18]. Gabapentin may be useful for BRP [19].

Skin-ache syndrome

Bassoe [20] suggested the term 'skin-ache syndrome' for a situation in which patients experience pain of unknown aetiology characterized by cutaneous trigger points, although this is not widely used. Relief of symptoms was reported after injection of lidocaine or surgical removal of the skin trigger point. This is in contrast to fibromyalgia, from which it must be distinguished, and where pain is more refractory.

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Restless leg syndrome (RLS)

RLS is a common sleep and movement disorder with a population prevalence of around 2–5% [1]. RLS is a clinically pleomorphic syndrome, probably reflecting multiple genetic and acquired factors. A significant linkage was established to chromosome 12q [2], and it has long been felt that it represented a subclinical sensory neuropathy [3]. Others have related it to a dopamine imbalance, due to the presence of dyskinetic movements and response to levodopa [4]. Studies of the basal ganglia using positron emission tomography (PET) scanning techniques have shown a decreased binding of dopamine to its receptor [1]. Up to 30% of patients have iron deficiency, with consequent reduced levels in brain tissue and cerebrospinal fluid [1]. RLS is a common disorder in haemodialysis patients [5].

Clinical features. Two subtypes are recognized. The first, with an early onset, accounts for some 25% of cases, is more commonly familial and is associated with a history of 'growing pains' in childhood [6]. Those with a late on-set (idiopathic RLS) have less painful paraesthesiae or dysesthesias, insomnia and lack a family history of the condition. RLS is characterized by leg paraesthesiae, associated with an irresistible urge, occurring at rest, to move the legs, which is relieved by movement [3,7,8]. These symptoms are worse at night and often lead to disruption of life and chronic sleep deprivation. Sensory symptoms include painful legs and arms, and pain at 'internal' sites. Many patients will have a previous diagnosis of a musculoskeletal disorder, such as joint and back pains, and there is a significant association with depression and other neuropsychiatric symptoms [6,7]. Headache on awakening and daytime headache occurs frequently, while in men, hypertension and heart problems have been reported [8].

Treatment. Some believe the first choice of treatment for RLS should be dopaminergic agents such as levodopa [3] or the longer acting cabergoline [3]. Other dopaminergic drugs that show promising results are pramipexole and ropinirole, although double-blind trials are not available, and the associated daytime somnolence probably makes these a second-line treatment [9]. In recent randomized, double-blind studies of gabapentin, significant improvement occurred in both idiopathic RLS [10] and haemodialysis patients [5]. Ferrous sulphate, which had been felt to be effective as an empirical treatment, was not shown to have an effect in a randomized double-blind placebo-controlled trial [11].

Burning feet syndrome (BFS)

BFS is a poorly recognized and often underdiagnosed condition [12,13]. It may occur as a result of diabetic neuro-

pathy, but in most cases it is idiopathic. Families with an autosomal dominant inheritance for BFS have been described [14]. A kindred of 21 patients with familial BFS has been described; BFS was often associated with minor foot abnormalities such as high arches or reduced toe fanning [14]. Loss of small fibre sensory nerves has been found in both in type 2 diabetics [12] and idiopathic cases. Tests on the autonomic system have shown predominantly cholinergic defects, unlike other autonomic neuropathies. There is a close correlation between quantitative abnormalities in the sudomotor axon reflex test and the loss of small nerve fibres in the skin [12].

Clinical features. The main clinical features are of a burning sensation on the feet with accentuation by heat or cold. Other autonomic associated features may include dry skin, eyes and mouth, vasomotor symptoms with peripheral coldness, burning or flushing, hypertension and impotence. Orthostatic hypotension does not appear to be an association [12,13].

Treatment. Treatment options for BFS appear less defined than for RLS, but treatments efficacious for the latter would probably also help in the BFS.

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Chapter 61

Psychocutaneous Disorders

L.G. Millard & J.A. Cotterill

Introduction

An essential component of dermatological illness is the relationship that somatic dermatology has with the psychological status of the patient at the time. The influence that these psychological, psychosocial and sometimes psychiatric factors have can be conveniently assessed as:

1 Multifactorial dermatological disorders that can be substantially influenced by psychological factors (e.g. psoriasis)

2 Dermatological disorders as a result of psychiatric illness (e.g. factitious dermatoses, body dysmorphic disorder)

3 Psychiatric illness developing as a result of skin disease (e.g. reactive depression, adjustment disorder)

4 Comorbidity with other psychiatric disorder (e.g. alcoholism).

In large centres, this work can be refined and developed in specific clinics for psychosomatic dermatology [1]. Ideally, liaison psychiatry should be available together with help from clinical psychologists and social workers [2]. Research and dissemination of further knowledge in psychosomatic dermatology is supported in Europe by the European Society for Dermatology and Psychiatry (ESDaP) and in North America by the Association for Psychodermatological Medicine of North America (APMNA).

The dermatological consultation is substantially different from the psychiatric one. However, for those who feel intimidated, the consultation process and descriptive psychopathology of psychological medicine is well described for non-psychiatrists [3,4].

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Emotional factors in diseases of the skin [1–4]

The narrative of clinical anecdote and experience held for a long time that emotional stress could be counted as an integral cause of skin disease or at least an exacerbating factor leading to increased disease morbidity [1].

It has been estimated that the effective management of at least one-third of patients attending skin departments depends upon the recognition and treatment of emotional factors [5]. While in disease such as dermatitis artefacta this influence is primary and pathogenic, the relationships between the mind and the skin are usually more complex than this. This intricate interaction may reveal that chronic insult hand dermatitis is the result of the hand-washing rituals of those with obsessive compulsive disorders [6], or that the intractability of atopic dermatitis is a response to an impaired parent–child relationship [7]. The narrative has been supported by an increasing evidence base showing, for example, that stressed patients with psoriasis have more prolonged disease and that simple counselling support can be an effective way of reducing disease severity [3].

The burgeoning science of psychoneuroimmunology has contributed enormously to an understanding of altered immune mechanisms in depression and anxiety. This knowledge might help to explain why pemphigus might be triggered by stress [8] or viral skin infections prolonged [9]. The concepts of the relationship between mind and body and mind and skin may have seemed rather nebulous in the past but measurement and analysis of these interconnections is established. Although the intricacies of the neuro-immuno-cutaneous–endocrine (NICE) network [10] remains rudimentary and science lags behind practice, practical applications in dermatology are effective using hypnosis or biofeedback [11]. Similarly, work on the relationship between mental activity and peripheral blood flow [12] may shed light on the exacerbation of some inflammatory dermatoses by stress, and perhaps on the effect of stress on itching. The influence of psyche upon the skin implies that there are chemical mediators that translate an emotion to a cutaneous lesion. These mediators are neurotransmitters and hormones that can be produced directly in skin by nerve fibres or by other cells such as keratinocytes, Langerhans' cells and perhaps Merkel cells [13]. Neuropeptides, substance P (SP), substance Y, vasoactive intestinal peptide (VIP), calcitonin gene-related peptide (CGRP), and melanocyte stimulating hormone (MSH) all bind to cell surface receptors.

Nevertheless, many of the conditions mentioned in this chapter form obvious groups, shading from one into another. One such spectrum ranges from natural anxiety over disfiguring skin lesions, through disproportionate worry over minor blemishes, to disturbances of body image that lead patients to become obsessed with their skin in the absence of any abnormality, and, finally, to psychotic delusions about their skin (e.g. of parasitosis), which may occasionally be caused by organic brain pathology [14]. These are dealt with in more detail on p. 61.8.

In any patient-centred medical specialty, physical symptoms often present as a manifestation of emotional distress. Somatization is defined as physical symptoms suggesting physical disorder for which there are no demonstrable organic findings and for which there are positive evidence that symptoms are linked to psychological factors or conflicts (Diagnostic and Statistical Manual of Mental Disorders, fourth edition; DSM-IV). In primary care practice, an emotionally distressed patient is more likely to present with physical symptoms than to complain about psychological or social problems [15]. Many studies confirm that this type of patient, with unrecognized psychiatric morbidity, is often passed on to medical and surgical clinics [16]. Surgeons see patients with somatic abdominal pain, physicians those with chest pain and breathlessness, and neurologists those with somatic or 'functional' headache. Dermatologists see a spectrum of those who, for example, may have symptoms as varied as psychogenic itch to those with intractable burning genitalia. Indeed, dermatology in-patients are known to have a higher prevalence of psychiatric disorders than general medical in-patients and dermatology outpatients a higher prevalence than the general population [17].

Somatizing patients may recognize psychological symptoms as part of their illness, but these are overshadowed by intense physical complaints that allow those reluctant to accept the stigma of mental illness still to occupy the 'sick role' [18]. Depression and anxiety are the most common underlying psychological disorders but their mood disturbance and characteristic patterns of thinking are not volunteered. Some somatic symptoms are amplifications of normal physiological sensations (e.g. itching), which tend to worsen under stress [19]; others relate to the physiological accompaniments of anxiety, such as excessive sweating. This type of behaviour merges imperceptibly with hypochondriasis. In some patients, this amplification of physical symptoms with symptom hyperbole is an enduring personality trait [20].

Those areas of overlap between psychiatry and dermatology are important, and a competent dermatologist should be able to pick up any emotional and psychological clues and cues that may be advanced by the patient during consultation. All patients are individual but individual patient personality styles present with recognizable distinctive verbal and body language [21].

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Psychological importance of the skin [1–3]

Some cutaneous stimulation is a basic need. Newborn mammals require the stimulus of licking and stroking, and caressing favours emotional development. Massaged babies gain weight as much as 50% faster than unmassaged babies. The functions of swaddling clothes provide an environment of warmth, touch and decreased stress as demonstrated by reduced heart rate, better feeding and longer sleep patterns. Children who live in emotionally destructive homes may show growth arrest as a response to the withdrawal of love and touch. As an organ of touch, temperature and pain sensation, and as an erogenous zone, the skin has great psychological importance at all ages. Many of the alternative medical therapies such as aromatherapy and kinesthesiology show clinical effects related to the the measureable effects of touch. Furthermore, patients who are regularly touched by their carers show quicker improvement than those who do not [3] and this effect is measureable at all ages and intelligences [4]. It is an organ of emotional expression and a site for the discharge of anxiety. Its texture and colour have meaning socially and politically, and its disorders carry with them a disproportionately heavy psychological punishment [5].

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Body image [1,2]

Body image can be conceptualized by individuals in many different ways. There are a multiplicity of definitions, but the simplest is that of Critchley [3] who defined body image as 'the physical properties of a person carried into the imagery of himself'. It is important to remember that body image is completely abstract in conceptualization, depending on many factors, including memory, intellect, perception and early life experiences.

Body image may be conceptualized as the internal subjective representation of physical appearance and bodily experience [2]. This develops early, by the age of 3–4 years, with the drawing of the first recognizable figures by children [4]. Body image represents a view of ourselves not only physical but also has always had vital psychological and sociological importance [5]. There is a very significant cutaneous component, the most important areas of which include the face, scalp, hair, breasts in females and genital areas. A child's first recognizable body drawings are 'tadpole' figures, which emphasize the head with spindly legs and an absent body [4]. The nose, which is the central part of the face, is also focal to body-image conceptualization and it is not surprising therefore that skin disease manifesting itself even as a tiny spot on the nose, may produce disparate cosmetic distress, while a much larger lesion on an adjacent cheek may be completely ignored. As the face is both visible and in a very important body-image area, skin disease in this area can produce major distress and lowering of self-esteem. It has been shown that individuals with severe acne, particularly female, have a significant depression of their body image and self-esteem, which was reversible with successful treatment [6]. In addition, individuals with acne are less successful at gaining employment [7]. It may be that potential employers perceive individuals with acne as unattractive,

but also the interviewees themselves may reflect their lower self-esteem and confidence at interviews. Eczema and psoriasis are both likely to produce the same sort of effects, particularly at times of life when the individual would normally be beginning to socialize [8]. Adolescence can be particularly difficult for the teenager with acne, facial psoriasis or eczema. This self-recognition also appears early in child drawings of their disfigurement. The stigmatization induced by a port-wine stain may also deter individuals, particularly males, from making any sort of contact with the opposite sex [9]. The older that patients were before treatment, the higher negative scores for most psychosocial parameters such as self-esteem, supporting the argument for early treatment on psychological grounds [10].

It is important to recognize that individuals with skin problems in important body-image areas may be manifestly depressed. These individuals can be helped both by effective treatment and also by an empathetic medical practitioner. In some instances, a clinical psychologist may help a person to come to terms with his or her problems while, in a minority, depression is severe enough to merit treatment with antidepressants and the help of a psychiatrist. A liaison clinic is particularly helpful in managing this type of patient, where at times there may be a definite risk of suicide or parasuicide [11].

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Psychoneuroimmunology [1–3]

The immune system and its relationship to cutaneous reponses is now established as part of the NICE system [1,2]. None of these processes can be be regarded as autonomous because immunoregulatory processes are part of an integrated system of defence [1]. Psychoneuroimmunology is the study of this integrated system and of behavioural–neuroendocrine–immune system interactions in particular.

The brain and immune system are linked by the autonomic nervous system and the neuroendocrine outflow via the hypothalamus and the pituitary gland. Communication between the immune system and the brain is bidirectional and probably largely mediated by neuropeptides [2]. More than 50 neuropeptides have now been identified, the smallest ones containing only two amino acids while the larger peptides contain 40 or more amino acids. Neuropeptides act not only as neurotransmitters, but also as neuromodulators.

Lymphoid tissue is innervated by noradrenergic postganglionic sympathetic nerve fibres, and peptidergic nerve fibres have also been identified in lymph nodes, thymus, spleen and bone marrow [3]. These nerve fibres form close neuroeffective junctions with lymphocytes and macrophages, which also possess receptors for neuropeptides [1].

Neuropeptides in the skin [2] are found not only in cutaneous nerves but also in most skin cells including keratinocytes, fibroblasts and Langerhans' cells. The role of vasoactive petides such as calcitonin gene-related peptide (CGRP), nocioceptive neurotransmitter SP, VIP, neuropeptide Y, and the newer pituitary adenylcyclate-activating peptide are increasingly evident in cutaneous inflammatory disease [3]; SP receptors found on mast cells, neutrophils and macrophages suggest a link between neurogenic stimuli and infiltration of the skin by inflammatory cells. CGRP has crucial immunomodulating effects on disease expression, perhaps by inhibition of antigen presentation by Langerhans' cells.

Moreover, lymphocytes have receptors for corticotrophin-releasing hormone (CRH), adrenocorticotrophic hormone (ACTH) and endogenous opioids, and both endorphins and enkephalins are known to directly influence antigen-specific and non-specific *in vivo* and *in vitro* responses [1].

Mind–body efferent immune interactions

Dermatologists have long recognized the relationship between stress and exacerbations of skin disease. With further knowledge of the psychoneuroimmunology of depression [4] and the further reviews of these effects in psychosomatic medicine [5], the efferent pathway from stress to disease is becoming clearer. Exposure to either naturally occurring or experimentally induced stress affect both humoral and cell-mediated immune responses. Bereavement is often associated with depression and many changes in immune function have been shown in depressed patients. Depression is associated with an increased number of circulating neutrophils, a decreased number of natural killer (NK) cells, T and B lymphocytes, and helper and suppressor cytotoxic T cells [6]. There are

also alterations in B-cell function, manifest by increased antibody titres to herpes simplex and cytomegalovirus [1]. Changes in both humoral and cell-mediated immunity have been found following marital separation and divorce [7] and alterations in immune function may occur during examinations [2]. Slowing of human wound healing has also been shown to be associated with stress, possibly mediated by depression of local production of the cytokine interleukin 1B [8].

Raychaudhuri and Farber [9] have proposed a psychoneuroimmunological basis for psoriasis. Thus, psoriatic skin has been shown to have a significant increase in SP-containing nerves. Psoriatic lesions are rich in neuropeptides such as SP and VIP. Proliferation of keratinocytes, a central feature of psoriasis, could be triggered by release of both SP and VIP, while SP could also induce localized lymphocytic proliferation. Moreover, the initiation and maintenance of the lymphocytic infiltrate characteristic of psoriasis could be in part related to SP, CGRP and VIP; indeed, SP can induce the expression of E-selectin on endothelium. For patients with atopic eczema, both SP and VIP have been demonstrated in lesional skin [10]. Moreover, NPY, a very potent vasoconstrictor, has been detected in the Langerhans' cells of patients with atopic eczema, but not in normal control subjects.

Body–mind afferent immune reactions

The bidirectional communication between the central nervous system (CNS) and the immune system provides the basis not only for behaviourally induced alterations in immune function, but also for immunologically based changes in behaviour [1]. Those patients who present with diseases causing intense afferent stimuli such as scratching, rubbing or traction are probably in a NICE loop where the inflammatory reaction stimulates an immune response which in turn releases cytokines to activate CNS neurotransmitters. Endorphins, for example, modify not only the perception of pain, but also other sensory perceptions [11] such as beauty. The compulsive and irresistible nature of scratching, excoriating and picking may relate to the pleasureable release of endorphins. These pathways may explain how emotional stress influences a wide range of disorders.

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Emotional reactions to skin disease [1,2]

Skin disease causes physical problems and distress. The anthropological importance of the skin as an organ of communication both tactile and visual by touch and expression is well recorded [1]. With either real or imagined disfigurement comes shame and reclusiveness. These emotions are part of the arcane folk beliefs that most cutaneous disease is the result of infection with significant imputations of uncleanliness and self-neglect, even in Western cultures. The religious significance of leprosy in many cultures continues to exert an influence where the psychosocial stigma of depigmented skin in vitiligo may operate even in non-endemic populations. A poor self-image and low self-esteem is easily demonstrated by appropriate questionnaires [3]. Patients with psoriasis are aware that other people stare at them, particularly in socially revealing situations such as swimming, and experience much social distress [1,2]. Patients with vitiligo adjust better to their disorder than do those with psoriasis, but also tend to have low self-esteem [4]. There may be a hidden and unbroached difficulty with sexual expression and confidence [5], as skin disease frequently has a negative impact on sexual relationships [6], independent of extent but significantly related to site. The impaired self-image and psychological distress of patients with acne improve with successful treatment of the skin lesions [7].

One of the consistent correlates of the social isolation and low self-esteem is heavy alcohol consumption, which in male psoriatics correlates with both the physical severity of their skin disease and its duration [8]. Ten per cent of patients with psoriasis reported a death wish and 6% reported active suicidal ideation in one study [9]. Acne scarring can lead to profound depression and suicide [10].

Genital skin disease, particularly herpes and chronic candidosis, produces initial shock and emotional numbing at diagnosis followed by a frantic search for a cause, and later by a sense of loneliness and isolation. Some 10–15% of patients with genital herpes never adjust satisfactorily and continue to experience difficulties in all areas of their lives, which become increasingly reclusive and monastic [11].

The concept of stigma [12] is important in this context. It can be defined as a biological or social mark that sets a person apart from others, is discrediting and disrupts interactions with others [13]. In a study of adults with psoriasis, those who were older at the onset of the disease seemed less likely to anticipate rejection, and to be less sensitive to the opinions of others and to feelings of guilt, shame and secrecy [13]. Further, the perceptions of stigmatization were found to be related to psychological distress and degree of disability but not to clinical severity of involvement or anatomical area [14,15].

Atopic dermatitis in children is associated with high levels of psychological morbidity [13]. The disturbance was best predicted by the distribution of the eczema rather than its extent, with facial involvement in children showing particularly high levels of psychological distress. The additional effect of brief, simple, psychotherapy was sufficient to help those patients with high anxiety levels achieve normal remission [16].

With the approach of puberty, a disfiguring skin disease becomes an increasing anxiety to many children and may handicap them in developing easy relationships with the opposite sex [17]. Some children become increasingly introspective and solitary, while others become aggressive and uncooperative. The consultation process in these circumstances is most demanding. The best results are achieved by defusing the anger, which is usually the result of frustration and disappointment, by adopting a planned therapeutic and supportive role. This may be difficult but an organized programme with cooperation from parents, teachers and physicians can maintain optimism through established coping strategies [18]. With sensible and affectionate parents and intelligent teachers, children with disfiguring skin lesions will often adjust extremely well, form satisfactory sexual relationships and establish themselves in successful careers.

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Disability and quality of life [1,2]

This aspect of dermatology is covered in more detail in Chapter 71.

Quality of life is defined as an individual's perception of their position in life in the context of the culture and value system in which they live and in relation to their goals, expectations, standards and concerns. It is a broad-ranging concept affected in a complex way by the person's physical heath, psychological state, level of independence, social relationships and relationship to salient features of their environment.

Established dermatological medicine describes skin disorders in relatively enclosed diagnostic terms, which takes little account of the effect of a particular skin disease on the individual patient. The patient with disease needs to be understood not only in terms of mechanistic outcomes of the kind usually assessed in clinical practice but also those composed of the psychosocial (hermaneutic) constructs that are assessed from the patient's self-reports. It is important to try to determine these disparate degrees of disability that a particular skin disease confers because their recognition leads to greater patient compliance and a more positive response [1–3].

The concept of skin failure is just as valid as that of renal, heart or respiratory failure [2]. The effect on quality of life induced by psoriasis, eczema and acne have been assessed using disability indices that are readily accessible [4]. These scales can also be used to quantify reduction in disability before and after treatment. The newer indices of disability have successfully combined the physical and psychological measures to produce a more holistic assessment of disease as exemplified by the Salford Psoriasis Index [3,5]. For instance, the presence of relatively trivial amounts of psoriasis on an individual's face may induce disparate depression. There are other instruments available for atopic eczema [6], acne in adolescence [7] and hair loss [8], which continue this development.

Quality of life assessments are not related to health but to disease and are usually specific to a particular diagnosis. This is very different from the non-medical

connotation of the meaning of the phrase, which is accepted to relate to a well state of contentedness of 'having a good time'. It has been proposed that in future the quality of life of ill people may need to take account of this difference because the patient's pathology involving release of cytokines and other mediators may affect their psychological state and thus response to questionnaires [9].

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Classification [1,2]

There are two main internationally recognized classifications of psychiatric disorders. The first is produced by the American Psychiatric Association with disorders defined by diagnostic criteria describing their essential features. The DSM is modified regularly, the current revision dating from 2000 [1]. The current international classification and nomenclature system for medical and psychiatric disorder is published by the World Health Organization [2] and in many respects is similar to DSM. These classifications are part of the essential practice of psychiatry where the language and symptoms of disease and thus its subsequent treatment is to identify, for example, organic syndromes, schizophrenia, bipolar disorders, somatic and personality disorders. This may not be user friendly enough for clinical dermatologists in everyday practice. However, whatever the presenting features to dermatologists, it is signally important to remember that the symptoms are not a diagnosis and therefore should not be assumed to be amenable to the same treatment. For example, dermatitis artefacta may be a symptom of depression, personality disorder or an abnormal psychosocial situation; each requires different treatment. Various other classifications have their merits [3–5] but as our knowledge increases, overlap and clarification make changes inevitable. This classification is therefore pragmatic with an emphasis on usefulness for dermatologists.

Conditions that are primarily psychiatric but which commonly present to dermatologists

Delusional beliefs of skin
(i) Parasitosis (Ekbom's disease)
(ii) Smell
(iii) Impregnation and contamination
(iv) Folie à deux
Disorders of body image
(i) Body dysmorphic disorder (BDD) (syn. dysmorphophobia, dermatological non-disease)
(ii) Atypical pain disorders such as glossodynia and essential vulvodynia
(iii) Dermatological hypochondriasis
(iv) Cyberchondria
(v) Anorexia nervosa
(vi) Bigorexia
(vii) Tanorexia
Phobic states
(i) Venereophobia and acquired immune deficiency syndrome (AIDS) phobia
(ii) Mole phobia
(iii) Wart phobia
(iv) Erythrophobia
(v) Age phobia and botoxophilia
(vi) Ateroidphobia
Obsessive compulsive hand washing

Group and mass population reactions

Sick building syndrome
Epidemic hysteria

Dermatoses primarily factitious in origin

Dermatitis artefacta
Artefact by proxy
Witchcraft syndrome
Dermatological pathomimicry
Dermatitis simulata
Malingering
Compensation neurosis
Munchausen's syndrome
Munchausen's syndrome by proxy
Deliberate self-cutting
Self-mutilation
Religious stigmata and psychogenic purpura

Dermatoses aggravated by harmful habits and compulsions

Lichen simplex
Neurotic excoriations
Prurigo nodularis
Acne excoriée

Hair plucking
Trichotillomania
Trichophagia
Nail destruction
Onychotillomania
Lip-licking cheilitis
Knuckle biting
Disorders of neglect of self-care (syn. Diogenes syndrome)

Dermatoses caused by accentuated physiological responses

Hyperhidrosis
Blushing

Dermatoses in which emotional precipitating or perpetuating factors may be important

Vesicular eczema of the palms and soles
Atopic dermatitis in the adult
Seborrhoeic dermatitis
Psoriasis
Some cases of localized or generalized pruritus
Alopecia areata
Aphthosis
Rosacea
Chronic urticaria

This last group produces most debate and significant continuing research. Different views are held by dermatologists but while the early work relating skin disease to stress [6] was greeted with scepticism, the evolving body of evidence (see above) is a significant development to support the link.

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Dermatological delusional symptoms [1,2]

A delusion is a disorder of the content of thinking. Delusions are beliefs that are false or not true to fact, cannot be corrected by an appeal to reason of the individual and are out of harmony with his or her educational and cultural background. Furthermore, the delusion can be further subclassified into [1,2]: (a) primary, where the delusion is the only psychological symptom; rather than (b) secondary functional, in which there is an underlying psychiatric condition such as depression; or (c) secondary organic, where there is physical illness such as dementia [3].

The dermatologist is most likely to see patients with delusions of parasitosis, which in itself is rare, rather than other cutaneous delusions. These are delusions of smell [2], of impregnation or of ocular or oral infestation, all of which are exceedingly uncommon. Equally so are patients who have a belief that they are ageing rapidly, the so-called Dorian Gray syndrome.

Delusions of parasitosis [4–6]

Definition. The patient with delusions of parasitosis (DP) has an unshakeable conviction that his or her skin is infested by parasites (this must be differentiated from parasitophobia—the *fear* of becoming infested).

Aetiology. Most patients with DP have a primary disorder defined as a monosymptomatic hypochondriacal psychosis being characterized by a single delusional system, relatively distinct from the remainder of the personality. The term monosymptomatic hypochondriacal psychosis may be applied to patients with a single, fixed, hypochondriacal delusion that is apparently not secondary to another psychiatric disorder [7]. Occasionally, there are associated visual hallucinations.

Secondary DP has been recorded as a feature of depression, bipolar disorder, paranoid states and schizophreniform illnesses [4–7]. It is therefore essential to define the full psychiatric spectrum in each patient. Those seen by psychiatrists are more likely to be labelled schizophrenic or depressed, or both. Such patients are often intelligent, and the professions are well represented, including doctors and even psychiatrists, but they are often rather solitary people and sometimes thought to be eccentric individuals. Lyell [4] has commented that it is hard to know where eccentricity ends and psychiatric illness begins. Moreover, some patients have a rather obsessional premorbid personality. Table 61.1 summarizes the secondary organic causes of DP [5]. Delusions of perception may follow disease in the non-dominant hemisphere, and so DP is sometimes seen in patients after a cerebrovascular accident involving that side of the brain. Similarly, DP may be part of the picture of dementia and should be considered when examining the elderly patient [8]. DP has also been described in pellagra, vitamin B_{12} deficiency, following coronary bypass surgery, as a side effect of phenelzine and in severe renal disease. DP in a young adult suggest illicit exposure to recreational drugs, in particular amphetamine or cocaine [9].

It is particularly important to exclude the possibility of

Table 61.1 Organic medical disorders associated with delusional parasitosis.

Neurological
Cerebrovascular disease
Dementia
Parkinson's disease
CNS tumours
Cardiovascular disorders
Arrhythmias
Heart failure
Coronary artery bypass
Endocrine disease
Diabetes mellitus
Hyperthyroidism
Hypoparathyroidism
Acromegaly
Nutritional disorders
Pellagra
Vitamin B_{12} deficiency
Anorexia nervosa
Infectious diseases
Syphilis
AIDS
Tuberculosis (pulmonary)
Leprosy
Malignancy
Breast cancer
Lung cancer
Lymphoma
Chronic lymphatic leukaemia
Substance abuse
Amphetamines
Cocaine
Medicines
Corticosteroids
Phenelzine pargyline

a real infestation. In 6% of one series, patients developed DP following real infestation [4] and 12% had a delusion shared with another member of the family (folie à deux; see below).

Incidence. Patients with DP are rare but the true prevalence is unknown. The condition affects both sexes equally below the age of 50 years, but after that age three times as many women are affected as men [3,10]. Although patients with DP are relatively easily recognized, it is possible to spend a lifetime as a dermatologist and never see such a patient. The young patient with DP should be regarded with the utmost concern for they may be drug abusers or the symptom may be the early signs of a major psychotic illness [9].

Clinical features. The presenting features of DP may be extremely variable. It can be as dramatic as an appeal from the primary care practitioner to see urgently a patient with an established delusion of infestation because they are disrupting everyone's life with constant demands, to an apparently benign, ill-defined, persistent itching with no immediate obvious delusional thoughts.

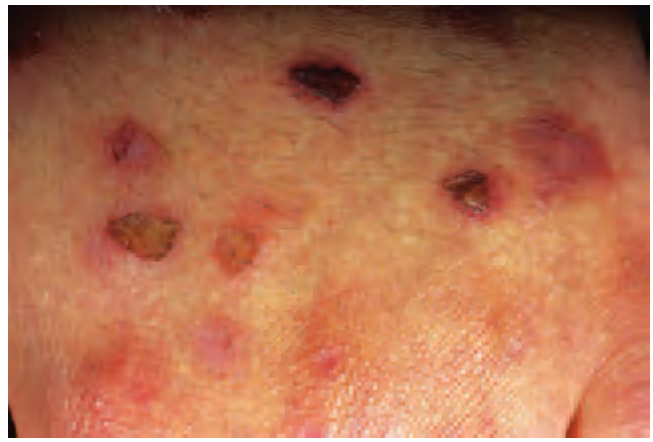

Fig. 61.1 Neurotic exoriations.

In the most established case, the patient may have consulted a series of specialist services to eradicate the imagined infestation. The family doctor is consulted repeatedly for even 'stronger' medicines to treat the 'bugs', the public health authorities called on many occasions to disinfest the home and the veterinary services recruited to scrutinize and treat pets. Eminent university personnel may have been consulted, both medical in infectious disease departments or scientific in zoology specialties. Specimens are sent to international institutions such as the British Museum for the ultimate examination. By the time the patient reaches the clinic there is always an inevitable degree of frustration, anger and impatience which makes the first consultation both difficult and vital.

The presenting symptoms may often be surprisingly ill-defined. Some speak of a sensation in their skin as though an insect or worm is crawling around, followed by a prolonged and elaborate description of the pathway the organism is taking. This agent may not be confined to the skin but also involve the genital, oral [11] or ocular [12] areas. They may describe and draw the insect or worm concerned but not uncommonly describe the infestation as invisible or dissolved in orificial secretions.

No obvious skin disease may be present, but excoriations are common and can be both extensive and very destructive (Fig. 61.1). These follow attempts by the patient to extract the 'parasites' and are therefore not artefactual lesions but produced in an apparently legitimate attempt at cure. Usually, the patient will bring samples to the clinic. Commonly, they proffer a small container, such as a matchbox or pill container, enclosing their 'insects' (Fig. 61.2). Some samples may be described as 'seeds', a guarded interpretation particularly in the patient who is

Fig. 61.2 Container of imaginary insects—from a patient with delusional parasitosis.

now cautious after seeing many doctors. Other samples that have been brought are collections of sweat, sellotape strippings of skin, folded elastoplast impregnated with debris and liquid samples collected from orifices. On microscopy these offerings are usually found to be fragments of skin and hair, samples of fabric and coagulated elements of serum, dust and detritus. The samples may include actual organisms such as ants, flies and sundry isolated fleas. The purification rituals that rapidly become established compel the patients to cleanse the skin and their environment with ever-increasing zeal. Their skin may smell of organic solvents such as benzyl benzoate or horticultural insecticide spray, the hands of bleach and disinfectant. A secondary general or localized chemically induced dermatitis is a feature. This irritant dermatitis is a further reinforcement of the delusional belief.

In 12% of cases, delusions are shared [2,7,13,14]: so-called folie à deux. This is defined in DSM-IV as a delusion developing in an individual in the context of a close relationship with another person, who has an established delusion. Once again this phenomenon is reported more often in women [14] and therefore the relationship between subjects is more often between sisters (34%), wife and husband (20%) and mother and child (20%). This contrasts with that reported between brothers (9%) and fathers and sons (2%). Rarely, the disorder can involve whole families [14].

Diagnosis. Although it is unlikely, the first task is to be certain there is no infestation; primarily scabies, rarely onchocerciasis. In most cases, the history, clinic behaviour, physical examination and presentation of specimens makes the diagnosis of DP obvious. It is also important to rule out underlying secondary organic disease, although this is rare. However, presentations in patients with secondary delusions as part of a depression or dementia may present in a more subtle fashion. The nature of depression may make the patient less communicative and more guilt-ridden. There may be a need to enquire actively about beliefs of infestation in a patient who complains of itching alone. Clinically, there may be a distinction between a true delusion and an overvalued idea [15]. The latter is an acceptable comprehensible idea carried on beyond the bounds of reason. It becomes so dominant that all other ideas are secondary. The patient's life becomes to revolve around this one idea. For example, a depressed bereaved widow who suddenly becomes a social isolate may come to believe that her itching is caused by insects. The nature of depression with feelings of unworthiness and guilt is part of this psychopathology.

Management. Musalek *et al.* [3] have emphasized the importance of establishing a psychiatric diagnosis before instituting treatment. Some patients with DP are depressed, and have been treated with conventional tricyclic antidepressants or serotonin reuptake inhibitors (SSRIs), often with pimozide. It should be remembered that suicide is an ever-attendant risk in these patients [1,4]. The management of patients with DP is always difficult. The basis of the consultation is to change the agenda from one of dermatological infestation as seen by the patient to one of psychiatric intervention. It is therefore essential to maintain a cohesive doctor–patient relationship. The full consultation process should be pursued, with adequate time given for the history, and proper care taken in the physical examination. All samples should be examined at the time and under the microscope. If you are perfunctory about this the patient will be less likely to continue with the same cooperation. Neither should you collude with the patient; it is better to say, 'I can't see any of the parasites today' than to tell the patient that you will treat 'them just in case' to get them out of the room. Neither is it helpful to say directly on the first visit that he or she has a mental problem. Sometimes, patients can be persuaded to accept the medication if told that it has helped previous patients with similar problems. Initially, it is often best to admit the patient to hospital. This reduces pressure at home on other family members and ensures compliance with medication. A psychiatric colleague can more easily be asked to see the patient in the dermatology ward. The further management is ideally a joint consultation with liaison psychiatry but the inevitable difficulty is to convince the patient that this is a psychiatric problem [16].

The response to pimozide is often good in these patients and the initial dose (2 mg) is increased weekly by 2-mg increments as necessary to a maximum of 12 mg/day [16,17]. On higher doses, patients may develop extrapyramidal symptoms which require addition of benzatropine 1–2 mg up to four times daily. With higher doses of pimozide there is a definite risk of ventricular arrhythmias and other electrocardiogram (ECG) abnormalities such as prolongation of the Q–T interval and T-wave changes. An ECG should be performed before pimozide therapy, and the drug should not be given to patients with a prolonged Q–T interval or to patients with a history of cardiac arrhythmia. Patients taking long-term pimozide should have a regular ECG at least once a year and if the Q–T interval is prolonged, treatment should be reviewed or withdrawn [10]. Moreover, concurrent treatment with other antipsychotics, tricyclic antidepressants and other drugs that prolong the Q–T interval, such as the antihistamines terfenadine and astemizole, antimalarials or drugs such as diuretics that alter the electrolyte status, should be avoided [17]. Hypokalaemia may predispose to the cardiotoxic effects of pimozide and care should be taken in patients with hepatic or renal dysfunction [16]. For most patients, pimozide is slightly stimulant so is best given in the morning. However, some find it hypnotic and this minority should take the drug in the evening.

Alternative effective therapy with a better side effect profile includes sulpiride 200–400 mg/day [18]. While this too may produce extrapyramidal side effects, there is no risk of arrhythmias. More recently, the antipsychotic risperidone has proved of use at a dosage of 4–8 mg/day [18,19]. When compliance is a problem, depot neuroleptics may be used [18].

Patients frequently defect from follow-up clinics with the risk of relapse and therefore strenuous efforts should be made to maintain contact either via the general practitioner or community psychiatric services.

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Delusions of smell [1,2]

In these cases, there is no actual olfactory hallucination but the patient 'knows' that they are emitting a foul odour. This is because they believe that other people avoid them and talk about them with evident disgust [1]. They believe that the origin of the smell is usually flatus and may see a gastroenterologist, or possibly foul sweat usually produced in excess from body folds and orifices. A subgroup complain of unbearable halitosis and seek dental advice. This delusion is commonly related to a chronic avoidant paranoid personality trait [2].

Two organic syndromes should be noted. First, delusions of smell have been associated with cerebral tumours and, secondly, the fish odour syndrome [3] where patients have suffered social exclusion because of the pungent smell. Occasionally, people who sweat excessively are made to feel unwanted, particularly if they are in an enclosed work environment. This form of social phobia may precipitate a more paranoid response.

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Body dysmorphic disorder [1–4]

SYN. DERMATOLOGICAL NON-DISEASE; DYSMORPHOPHOBIA

The terms 'dysmorphophobia'and more recently 'dermatological non-disease' have been in use for over a century to describe patients who are rich in symptoms (especially in areas important in the body image) but poor in signs of

organic skin disease [1]. All dermatology clinics contain these distressed patients whose chronic attendance is a reflection of their impaired family, social and occupational functioning. This somatoform disorder is defined in DSM-IV as body dysmorphic disorder (BDD), a preoccupation with an imagined defect in appearance; if a slight defect is present the person's concern is markedly excessive. Although BDD is classified as a somatoform disorder, there is a delusional variant which is recognized as a psychotic disorder.

Prevalence. This condition was originally thought to be uncommon, but screening research over the last decade has revealed a prevalence of 12% [2]. A point prevalence study of a community sample of women in the USA showed a frequency of 0.75% [5], while a study of German students revealed a prevalence of 5.3% [6]. Patients who present for plastic surgery show rates of up to 15% [7]. Subclinical BDD (patients who keep their beliefs covert) are found in approximately one-fifth of patients presenting to aesthetic medicine; there is an equal gender frequency [8].

Aetiology. The aetiology is unknown. Some patients may be examples of monosymptomatic hypochondriacal psychosis [9] in that they have an isolated delusion. Affected individuals are often solitary, unmarried or divorced. As a whole, they socialize poorly and do not like contact with other people [2,10]. Their symptoms may appear after severe emotional, especially marital, problems and perineal symptoms in men may follow imagined or real sexual exposure. The disorder most often comorbid with BDD is major depression; rates of 60% and a lifetime rate of up to 80% have been reported [2,11]. The depressive symptoms may be subclinical but is revealed on direct questioning. An obsessional premorbid personality is not unusual [10] and comorbidity with obsessional compulsive disorder may be found in 30% [10,12]. Dysmorphophobic symptoms in a teenager or adult may be the presentation of schizophrenia, while in an elderly patient dementia should be considered. Comorbid psychiatric conditions have also included social phobia, trichotillomania, substance abuse and avoidant personality disorder [12,13]. In a study of patients with anorexia nervosa, 39% were diagnosed with comorbid BDD unrelated to weight concerns. These individuals had higher levels of delusionality and lower levels of social functioning than those with eating disorders alone [14]. There is usually no evidence of any underlying organic disease.

Clinical features. Most patients are in their third decade although reported ages are from 5 to 80 years. In one study, the average age of onset was 15 years and the average duration of symptoms was 18 years [12]. Opinions differ whether BDD is more common in men or women [2,10], although referral sources may affect the statistics. Many patients are unmarried and unemployed [15]. Dermatological non-disease presents with symptoms particularly in the face and head including the mouth and scalp. Facial symptoms include complaints of excessive redness, blushing, a burning feeling, scarring, large pores, excessive facial hair and facial greasiness. Patients with orodynia or glossodynia fit into this group with their defect in pain perception involving the mouth. Scalp symptoms include a feeling of intense burning, unremitting by day or night, and excessive hair loss. Those patients with facial and scalp problems are more often female, but those with perineal symptoms are more likely to be male. Perineal symptoms in males include complaints of an excessively red scrotum, discomfort in the genital area, often spreading on to the anterior thighs and making the wearing of clothes uncomfortable, described rather cumbersomely as the dysthaesic peno-scrotal syndrome [16]. The female equivalent, vulvodynia (the burning vulva syndrome) consists of several different clinical entities, including vulval dermatosis, cyclic vulvitis, vulval papillomatosis, the vulva vestibular syndrome and essential vulvodynia [17]. In essential vulvodynia, the discomfort may be so severe that the patient will neither sit down nor go to bed, and this drives every other member of the family to distraction. Women with essential vulvodynia are more distressed than patients with an identified physical cause of vulval pain [18] (see also Chapter 68).

A consultation with a patient with dermatological non-disease always takes much longer than one with a patient with organic disease. The same ground has to be gone over repeatedly and the patient never appreciates normal non-verbal communication emanating from the doctor. The content of the consultation is dominated by complaints of ugliness, unattractiveness and irreconcilable deformity. Any body part may be involved, although a minority may worry about more than one area. Their thoughts are dominated by the abnormality for up to 8 h daily, the distress is intense, self-esteem poor and insight minimal. They admit to compulsive behaviours with excessive grooming, clothes changes and mirror gazing [2]. Patients are driven by the desire to know what they look like, a desire that is made worse if they resist the urge. BDD patients invariably feel worse after mirror watching but cannot resist looking in other reflective surfaces such as shop windows, cutlery and shiny compact discs. The function of mirror watching may be to practise showing the best face to the public [19]. Other activities and behaviour may be stimulated by these beliefs with diet regimes, the purchase of enormous quantities of beauty products and the seeking of unending aesthetic treatments. Muscle dysmorphia describes the men who use illicit anabolic steroids and obsessive weight training to develop their bodies, so-called 'bigorexia'.

Patients with dermatological non-disease are 'doctor shoppers' and will have often seen many doctors over the years about their many problems. An individual patient is likely to return to the clinic within a few minutes of being seen and may repeatedly telephone the doctor asking questions that have already been answered many times in the immediate past. Uncommonly, the delusional type of BDD gives rise to familial BDD where the parent imposes a delusional idea upon the child who in turn develops BDD [20] or, even more rarely, the patient believes that their child has a bodily defect, BDD by proxy [21].

There is a definite risk of suicide in patients with dermatological non-disease [1,2,22,23] and in a large series of 30 patients with BDD, 29% had made a suicide attempt [24].

Dermatological and plastic-surgical treatment. Most patients with dysmorphophobia perceive the solution to their problems in dermatological or plastic-surgical terms and so come to haunt dermatologists and plastic surgeons rather than psychiatrists. It is interesting that a significant proportion of patients presenting with dysmorphophobia have previously received plastic surgery, most commonly to change the shape of their nose. However, occasionally plastic surgery in carefully selected cases may be helpful, but there is always a risk that the patients themselves may then move to a preoccupation with another part of the body. In a series of 30 patients, it was found that 30% of patients had received previous cosmetic surgery, with a mean of 2.0 ± 1.3 procedures and as many as six procedures had occurred in individual patients [24]. Furthermore, 81% of patients with BDD were either dissatisfied or very dissatisfied with their consultation and results of surgery [12]; therefore, if plastic surgery is planned in this group of patients it is very important to have careful preoperative psychiatric assessment. Those contemplating surgery should remember that some patients with BDD are angry and go to litigation relatively easily. A perfect cosmetic result may be perceived by a depressed dysmorphophobic patient as worse than the situation before surgery. Photography before and after surgery is important to refute such claims objectively.

Diagnosis [2,3]. It may be surprising that BDD is often diagnosed late because patients are reluctant to disclose their distress, shame and embarrassment. The clinical clue may be a persistent return to the clinic for a harmless small lesion. BDD should be asked about and stringent questionnaires are available to expose BDD-related thoughts and behaviours [2,3].

Management. The management of patients with dermatological delusional disease is always difficult. There are two treatments that are shown to be successful; first, pharmacotherapy with SSRIs and latterly with cognitive–behavioural therapy.

Treatment with SSRIs. Early studies showed that nearly 50% of patients may respond completely or partially to fluoxetine or clomipramine, whereas there was only a 5% response to all other medications [24]. Systematic review of trials [25] confirmed that over 60% of patients have significant improvement in symptoms. It is important that the medication be continued long term as discontinuation precipitates relapse in 80%. All SSRIs are equally effective and the choice depends on tolerability. In many patients there is a significant improvement in the social prognosis evidenced by an ability to return to school or work. This is accompanied by a reduction in ritualistic behaviour, such as mirror checking and skin picking. Phillips *et al*. [24] observed that only a small proportion of patients responding to SSRIs experience any change in insight.

It is important to note that the effective dosage of SSRIs is usually higher than the dosage conventionally used to treat depression (e.g. the dosage of fluoxetine and fluvoxamine are 50 and 260 mg/day, respectively). In short, the dosage of SSRI needs to be high and the duration of treatment is long term, with response taking on average 2–4 months. The duration of treatment is usually at least 1 year.

There are several pharmacological options for patients who fail to respond to this type of regimen, and the addition of low-dose clomipramine, buspirone 30–60 mg/day or other antipsychotics have been used by psychiatrists. Venlafaxine 37.5 mg/day can be substituted for the SSRI. The help of liaison psychiatry services can be very helpful at this stage.

Patients with somatic pain (e.g. vulvodynia and scrotodynia) may benefit from tricyclic antidepressants such as amitriptyline 50–150 mg/day or alternatively gabapentin 900–1500 mg/day.

Cognitive–behavioural therapy [2,26]. Simple behavioural treatment, such as encouraging patients to avoid ritualistic behaviour and mirror checking, and urging them to give up unnecessary cosmetic camouflage, while gradually exposing them to the most feared social situations, can be helpful, especially if combined with a cognitive approach involving self-esteem building and modification of distorted thinking, coupled with coping strategies. All these techniques are more likely to be effective when combined with SSRI treatment, and initially some patients may be too ill to benefit from a cognitive–behavioural approach. This needs the help of a skilled clinical psychologist but has the advantage that it is often more acceptable to the patient. Up to 77% response can be measured in stress and symptom reduction [26].

Supportive psychotherapy can be helpful in those patients with overvalued ideas who are not truly deluded, but it is very time-consuming and emotionally demanding. As a generalization, patients with BDD are poor communicators and difficulty with interpersonal relationships

may be one of the central crucial and earliest features of this disorder. The physician therefore undertaking supportive psychotherapy has to be patient and very tolerant. Dysmorphophobic patients are poor attenders at clinics, but the consultation may, in some cases, be the only opportunity that they have to talk to another human being, a reflection of the isolated life these patients often lead.

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Habituation to dressings

Liddell and Cotterill [1] described a group of patients who became habituated to occlusive bandages, which had been initially applied many years before as treatment for either gravitational ulcers or eczema of the legs. Although the skin in all patients had returned to complete normality, it was impossible to persuade the patients to abandon their occlusive therapy. The patients tended to be elderly, single, lonely and inadequate, and most were male.

It was thought that the behaviour in this group may be regarded as 'attention seeking' in that they derive some sympathy from others because of their problem. Avoidance of work may have been successfully accomplished by some of these patients.

Some patients seem to enjoy the social contact that regular attendance at the clinic brings and are reluctant to be discharged. Thus, it appears that occlusive dressings may support not only the legs, but in a minority of patients, the psyche too.

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Cutaneous phobias

A phobic disorder is said to exist when anxiety, often amounting to panic, is evoked only or predominantly in well-defined situations. Patients who are subject to obsessional and ruminative thoughts about contamination and infestation may formalize these specifically into phobias about warts, infestation, dirt or bodily secretions. Patients are afraid to touch anything in the consulting room; indeed, in the hospital occasionally. Such patients will wear gloves when shopping or filling their car with petrol, and even the sight of a wart on another person can induce acute panic. Wart-phobic patients will bring other family members to dermatologists, and attempts will be made to make the dermatologist collude with the phobia and treat a wide variety of minute skin lesions in both the patient and his or her immediate relatives. A sterile pack may be produced so that there is no question of the patient's bare feet coming in contact with anything in the consulting room. Tights and socks are abandoned on the consulting room floor because they are regarded as contaminated by the patient. While relatively few patients with obsessive–compulsive disorder present directly to psychiatrists, it has been claimed that up to 14% of anxious, itchy, dermatological patients have this psychiatric disorder [1]. The typical patient realizes that these persistent ideas are inappropriate, but they continue to engender much distress and anxiety. Attempts are made to ameliorate the anxiety resulting from the obsession by compulsive acts and rituals, which vary from rubbing, lip licking or touching the skin, to more complex rituals involving washing, cleaning, hair pulling, skin excoriation and other cutaneous damaging behaviour.

Patients' phobias about dirt and bacteria may present as hand eczema induced by repeated hand washing. This psychiatric diagnosis should be considered in all patients with refractory hand eczema. The obsessional ideas become heightened during periods of emotional stress.

Mole phobia has also become more common since the recent publicity campaigns about the early diagnosis of malignant melanoma. Affected individuals consult dermatologists repeatedly, along with their unwilling family members. This is often a response to an actual tragic death from malignant melanoma in family, friends or neighbours. Despite reassurances they present repeatedly at clinics [2] and often demand that all the moles are removed and if refused will find a private surgeon to do this [3]. Regularly timed appointments with responsibility given to the physician can be a simple way to defuse panic attacks.

Patients with an overvalued idea about the possibility of venereal disease, including AIDS and herpes simplex, may be anxious or depressed, and a rather obsessional personality trait is not unusual in this group of patients [4].

Although blushing itself is normal under certain circumstances, blushing that is grossly excessive in both frequency and extent is particularly seen in women and may be the cause of considerable embarrassment. The fear of easy and excessive blushing gives rise to erythrophobia [5], which has two components: first, the fear of blushing and, secondly, excessive reactive flushing. Patients with erythrophobia show abnormal autonomic regulation under mental stress [5]. It has also been shown that task training can reduce the phobic behaviour independent of facial coloration [6]. These patients frequently suffer emotional difficulties and inhibitions and can sometimes be helped by a sympathetic clinical psychologist. Flushing may be a manifestation of hyperthyroidism and the distinctive flushing of the carcinoid syndrome must also be excluded (see Chapter 44).

A patient presenting with 'multiple allergies' may have a fear of allergic reactions [7]. All minor skin complaints are misinterpreted by the phobic patient as allergies and the consequent avoidant behaviour may become socially destructive.

An unreasonable fear of topical steroids amounting to an overvalued negative idea prompts patients and parents to refuse treatment. This was based first on real fears of skin thinning but, secondly, in one-quarter of those questioned, on a belief that non-specifically there will be long-term bad effects [8]. Treatment compliance is greatly improved by close surveillance and reassurance.

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Anorexia nervosa and bulimia [1–3]

Anorexia nervosa can be looked upon as a phobia about body weight. In the definition of anorexia nervosa in the International Statistical Classification of Diseases 10 (ICD-10), body image distortion is one of the essential features. There is a dread of fatness as an intrusive overvalued idea. There are associations with other psychodermatoses, BDD and self-injurious behaviours. Hair pulling, self-cutting, excoriations and bruising occurred in 44% of 134 female patients [4].

The nutritional consequences of anorexia nervosa are frequent and many dermatological sequelae have been described. The most frequent skin manifestation is xerosis (58%), with a particular form of branny scaling developing on the extensor surfaces of the limbs and flexures. Hair effluvium occurred in 50%, with nail deformities in 45% and cheilitis in 40%. Diffuse hypertrichosis, carotenoderma, poor wound healing and striae distensae were more common in the restrictive type of anorexia as opposed to the bulimic type where hair and nail changes and generalized pruritus were more prominent [3]. Severe perniosis is also seen in individuals with anorexia nervosa [5]. Drenching night sweats during weight recovery, possibly brought about by secondary changes in thermoregulation, which occur with rapid refeeding, have also recently been described in patients with eating disorders [6] as has acne [2].

A minority may develop melasma and seborrhoeic dermatitis. Brittle nails, dry skin and calluses on the fingers are produced by repetitive self-induced vomiting. In the mouth, there may be dental enamel erosion and gingivitis and some patients develop a Sjögren-like syndrome. Other cutaneous features may result from the use of laxatives, such as phenolphthalein, producing a fixed drug reaction, and thiazide diuretics, producing photosensitivity, while the use of the emetic ipecacuanha can be associated with a dermatomyositis-like syndrome [7]. Compulsive hand washing and trichotillomania may result from accompanying psychiatric illness.

The alert dermatologist should suspect anorexia nervosa when presented with these suggestive signs, particularly hair loss and xerosis in an underweight girl. A simple screening questionnaire (SCOFF) [8] is helpful for detecting eating disoders. The patient should be referred to the psychiatrist for specialized care.

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Group and mass population reactions [1]

Epidemic hysteria syndrome and occupational mass psychogenic illness

The modern nomenclature for hysteria is conversion or dissociation disorder. The implications of this classification are that the symptoms are psychogenic, that the causation is unconscious, and that symptoms may carry some advantage, either primary such as debilitating symptoms or secondary by being exempted from community responsibility or gaining public attention. Conversion implies the behaviour of physical illness without evidence of organic pathology, the patient being unaware of the psychopathology. The prime examples of this group response are epidemics occurring in the closed communities of workplace and school.

In 1978 there were two separate outbreaks of skin disorders among factory workers in a small town in northern England. In each outbreak, a central female figure with non-industrial dermatological problems fuelled an epidemic of what was thought to be dermatitis among several employees in a ceramics factory and a second epidemic in a textile factory. In the first outbreak 10 employees were affected and 17 in the second. No significant dermatological pathology of industrial origin was found [2]. A similar outbreak occurred in a warehouse, triggered by two severe cases of non-occupational eczema, combined with the idea that incoming aircraft parts to the warehouse from foreign countries might be 'dirty' in some way. This caused a heightened perception of the risk of skin disease, with increased frequency of hand washing. Overfrequent hand washing in a few employees resulted in precisely what the warehouse staff had been trying to avoid [3]. An outbreak in the pottery industry that began as isolated gum arabic sensitivity developed into a more widespread epidemic described as 'epidemic hysteria dermatologica' in eight female workers [4]. There was also a female preponderance in the outbreak at a textile factory where the skin problems were common dermatoses unrelated to work [5]. Most of these mass reactions involve female workers and to try to explain this it has been postulated that in stressful situations in boring, low-paid, repetitive jobs women are more likely to externalize their discontent as a conversion symptom than a direct complaint that may jeopardize their job [1].

Surveys of occupational mass psychogenic illness (OMPI) episodes stress that many outbreaks occur in dehumanizing jobs with poor management communication. Secondary compensation neurosis may follow to prolong the epidemic from those who feel particularly injured. It is clearly important, if possible, to visit a factory very early and examine all the complainants in an outbreak of alleged 'epidemic' industrial dermatitis.

In the other common closed community, schools, epidemic complaints of itch dry skin and transient rash were predominant [6–8]. These outbreaks involved 50–100 children aged 7–12 years. The symptoms lasted 2 weeks and no cause was found. Girls outnumbered boys by 3 to 1. It has been suggested that the precipitating factors may be illness in a favourite teacher or student, rigid teaching regimens and parental pressure for academic success.

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Sick building syndrome [1,2]

The concept of building-related illness (BRI) [1] has grown from the rather vague and controversial grouping of symptoms that appear to be caused by a range of supposed allergic, toxic, irritative and possibly infectious causes, to a subject where objective evidence is beginning to define the multifactorial aetiology of this contemporary phenomenon. Both sick building syndrome (SBS) and BRI refer to illnesses related particularly to non-industrial premises such as large blocks of apartments or offices where people spend considerable periods of time in close association. These syndromes consist of a series of heterogeneous complaints such as irritable dry skin, dryness and cracking of mucous membranes of mouth, nose and eyes, recurrent sore throat, headache, fatigue and loss of concentration. In over half of patients the symptoms are

dermatological but the lack of demonstrable biological correlates together with vague aetiological attributes makes precise definition of the problem difficult [2]. Patch testing is negative.

Much of the debate has centred on dampness, smell and ventilation in buildings. In a large review [2], symptoms were significantly associated with signs of dampness, condensation, water leakage, high humidity and mouldy odour. Furthermore, the symptomatology could be related more to mechanical ventilation systems and internal air conditioning than in buildings where there was efficient natural ventilation [3,4]. In addition, changing from artificial ventilation to a natural one reduced skin symptoms by one-third [5].

Workers may feel ill when exposed to odours from xenobiotic sources (cacosmia) [6]. The presence of a strange smell at work may precipitate symptoms in a significant number of previously healthy individuals. Subsequent exposure sets up a classical conditionary loop with somatic amplification of symptoms. Patients develop headache, itchy eyes, transient rash and congested nose or throat followed by sweating, faintness and tachycardia. In most cases, the odour is chemically harmless. A significant psychological component has been postulated, as was the case when 24 workers reported sensitivity to electricity in the workplace, causing itchy whealing of face and limbs [7]. The patients reported increased symptoms not only when they were exposed to an experimental electromagnetic field but also when they believed they were exposed, even though the field was turned off.

Not surprisingly therefore, work stress, manifested by role conflict, work overload, managerial difficulties and workplace building renovations have all been significantly associated with perceptions of poor workplace air quality and increased dermatological symptoms of SBS [8].

Symptoms were more common in those lower down the office hierarchy than in managers, and women had more symptoms than men, irrespective of their status [2].

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Self-inflicted and simulated skin disease

It is important to differentiate the dermatological diseases provoked by voluntary, admitted, self-traumatizing behaviour from those induced by covert deception to give the appearance of disease. The former group may range from a normal stress-related activity such as nail biting to a more disease-classifiable problem (e.g. trichotillomania or compulsive hair plucking). At no time is there an intention to falsify the origin of the skin-related damage or to actively obscure the part the patient plays in its production. This does not mean that the shame and self-reproach associated with these activities are not occasionally responsible for a reluctance to primarily volunteer the patient's part. However, this behaviour is significantly different from that of a true factitious disorder, which exhibits the essential elements of the intentional production or feigning of physical or psychological signs or symptoms and the continued denial of the disease origin to the physician. The motivation for this behaviour is assumed to be the sick role and an essential difference from malingering is that there is no external incentive for the behaviour such as economic, legal or employment advantage.

There are normal behaviour habits associated with the skin that appear repetitively at times of stress and anxiety. Picking, plucking, sucking, rubbing, biting and pulling behaviour on skin, nails and hair are stress-relieving activities, which may be reinforced by the release of endorphin-like substances as a neuroendocrine response.

Each of these behaviours is physically brief or spasmodic and, on most occasions, a conscious activity that does not intrude on normal skin function. However, when these habits become entrenched as a repetitive almost compulsive daily routine, or progress beyond the stage where they are an incidental stress-relieving activity, then they are recognizable as a number of dermatological disorders. Nail biting (onychophagia) has been recorded from the age of 15 months [1] but is more common after the age of 3 years and is present in over one-third of children between the ages of 7 and 10 years [2]. Up to half of adolescents continue to bite their nails, and 13.7% of older students and young adults [3,4] show continued body-focused repetitive behaviours (BFRBs), of which nail biting was the most frequent. In addition, those patients who continue with BFRBs also exhibit frequent somatizing activity in other illness. Obsessive onychophagia is well recorded [5]. Studies of college students [5,6] showed 1.5% of males and 3.4% of females continued hair pulling, but only 0.5% satisfied the DSM-IV-R criteria for trichotillomania.

Scratching and rubbing behaviour may progress to lichen simplex or nodular prurigo. Destructive picking activity may develop into neurotic excoriations or acne excoriée. Nose picking (rhinotillexomania) greater than

20 times per day may persist in 8% of adolescents [7] and while this may be a culture-bound syndrome, it is associated with multiple BFRBs in approximately 15% of individuals, usually men. In extreme cases, trigeminal trophic syndrome may follow herpes zoster in the nasal area. Persistent pluckers most commonly abuse their hair and can present with trichotillomania. Perioral dermatitis can be a consequence of chronic lip-licking behaviour and chronic cheilitis the result of lip biting (see Chapter 66). Chronic nail disease such as paronychia follows from nail biting and onychophagia (see Chapter 62).

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Lichen simplex and neurodermatitis

(see Chapter 17)

Lichenification describes the characteristic pattern of response of the predisposed skin to repeated rubbing. In some instances, a minor initiating event, such as trauma, infection or insect bite, precipitates episodic insistent scratching and rubbing. Irresistable itching is the major complaint, scratching the chronic accompaniment. This behaviour takes the form of rubbing with either the hands, back of nails or knuckles and in extreme cases sometimes with the use of a convenient instrument such as a hairbrush, a pen or some other domestic implement. The actions may be subconscious and proceed without continuous conscious control. However, in some cases patients subject themselves to frenetic prolonged spasms of uncontrollable self-damage, which proceeds with increasing rapidity until the pruritus is replaced by soreness and pain. The change from itch to pain is quite sudden and this abrupt cessation has been described as orgasm cutanée. Lichen simplex and neurodermatitis are much less common in the elderly.

Regular rubbing and pressure on the skin produces the characteristic thickened, coarsely grained nodules on the skin with hyperpigmentation. The classic sites of involvement are within easy reach, particularly on the nape and sides of the neck, elbows, thighs, knees and ankles. It is unknown why these areas remain so discrete. These areas may be in varying stages of evolution, from early small violaceous papules with surface excoriations to chronic areas that present as hyperkeratotic plaques with pigment changes, described as 'dermatological worry beads'. Localized patches of lichen simplex presenting as pruritus ani and vulvae are described in Chapters 17 and 68. These lesions are more often found in females and occur predominantly after puberty. They are found, very rarely, as isolated phenomena in children, even in atopics. They are more often seen in Afro-Caribbean patients.

Most authors have commented on the relationship of emotional tension to bouts of scratching [1]. Patients are usually described as stable but anxious individuals, whose reactions to stress are relieved by ritualized behaviour such as rubbing [2]. Aggression and hostility related to anxiety [3] caused by emotional disturbance may lead to itching. This maladaptive response has been treated successfully with behaviour therapy [3] to break the itch–scratch cycle.

Treatment with antihistamines is helpful, but antidepressants, particularly tricyclic compounds such as doxepin in dosage as low as 25–50 mg/day, have been shown to be more effective [4]. Non-psychotropic medication is also sometimes effective using thalidomide 50–100 mg/day for up to 2 months at a time.

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Psychogenic excoriations

SYN. NEUROTIC EXCORIATIONS; COMPULSIVE SKIN PICKING; DERMATILLOMANIA; ACNE EXCORIÉE [1,2]

The most common of the self-inflicted dermatoses are neurotic excoriations and acne excoriée. The differences between the two are more a matter of distribution than degree of severity of the lesions. The lesions differ from other artefactual disorders as those who suffer readily admit to an urge to pick and gouge at their skin. Both of these clinical syndromes are characterized by the preponderance of females, the destructive scarring nature of the lesions and the relationship to psychological stress. Some patients show features of both conditions and one condition may merge into the other.

Destructive excoriations are seen most frequently in middle-aged women, the average age of onset being between 30 and 50 years of age [1,4], but significantly the average duration of disease before presentation can be up to 10 years. This group make up the most severe cases, where the problem tends to be persistent and unremitting.

The picking and excoriation proceeds in bouts that exceed the bounds of simple habit. These patients are described as rather rigid and obsessional individuals with repressed emotions [3,5]. They have difficulty in verbalizing their problems and are aggressive but also insecure [4]. Depression was a very common feature in one series [2]. These patients describe picking, scratching, gouging and using implements on their skin, producing bleeding and pain during periods of low mood and self-esteem. There is a compulsive quality about the need to continue until pain is produced. The duration of these bouts may last for some hours and can be ritualized to a set time and place. Psychosocial stresses have been reported to precede exacerbations of excoriations in 30–90% of patients [1,4]. Immediately following such behaviour, patients are characteristically unhappy and guilty about the disfigurement.

Patients with psychogenic excoriations frequently have co-morbid disorders in the compulsivity–impulsivity spectrum, including BDD, substance abuse, eating disorders and trichotillomania [2]. The Skin Picking Impact Scale (SPIS) is a self-report instrument developed to assess the psychosocial consequences of repetitive skin picking. SPIS scores were significantly higher for those with self-injurious behaviour than those with reactive scratching from itchy dermatoses and correlated with anxiety and depression inventories [6].

Clinical features. Lesions can be seen in all stages of development. Clinically, the lesions are polymorphic, the newer lesions are angular crusted excoriated erosions with a serosanguinous crust, found predominantly on the sides of the neck, chin, upper chest shoulders and upper arms. The healing lesions are erythematous and depigmented, eventually with chronicity becoming white and atrophic centrally and commonly hyperpigmented at the periphery. They may be quite deep, extending into dermis, and are distributed symmetrically within reach of the hands. Older lesions show pink or red scars, some of which may be hypertrophic. Chronic lesions may also show atrophic scars, which merge and are eventually seen as linear coalescent areas. Lesions appear at all stages of development and may number from a few to several hundred (Fig. 61.1).

Differential diagnosis. It is important to exclude excoriations caused by generalized pruritus, bullous disorders such as pemphigus, and linear excoriated lesions, which may be the presenting signs of lichen planus or lupus erythematosus.

Treatment. Simple, empathic, supportive psychotherapy can produce significant improvement, whereas insight-orientated analysis may exacerbate symptoms [7]. Cognitive–behavioural therapy has improved some patients, although the management of underlying personality difficulties may require the specific skills of a psychotherapist [8,9]. Habit reversal programmes may also help [2]. The compulsive nature of this disorder responds well to antidepressants and in particular to SSRIs, such as fluoxetine, fluvoxamine and citalopram [2,6]. Clomipramine [10] and doxepin [11] have been reported to work well. While the condition eventually resolves, the most difficult cases are middle-aged women with established patterns of excoriation, which may have been present continuing for decades. It may be necessary to continue antidepressants in these patients for some years.

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Acne excoriée (see Chapter 43) [1,2]

There is not one patient with acne who can resist squeezing and pinching of lesions. Brocq [3] in 1891 described acne excoriée particularly in adolescent girls under emotional stress who picked and squeezed acne spots. The condition should be considered to be a variant of psychogenic (neurotic) excoriation [2] with the lesions largely confined to the face. Acne excoriée is more common in women [1–4] and seen in an older age group than acne vulgaris, with a mean age of approximately 30 years [1,2,4]. Psychological studies have shown no diagnosable DSM-IV-R disorder [4,5], although associated phobic states [1] and depressive and delusional disorders [6,7] have been described.

The clinical lesions resemble those of excoriations. They are found predominantly around the hairline, forehead, pre-auricular cheek and chin areas. Extension to the neck and occipital hairline is common and with even more extensive lesions producing an overlap clinically with psychogenic pruritus. Chronic lesions characteristically show white atrophic scarring with peripheral hyperpigmentation.

A strong association with atopy has been suggested with resemblances to prurigo mitis.

Although patients with acne excoriée sometimes respond to simple topical acne therapy, most require systemic antibiotics and isotretinoin. The tetracyclines, in particular doxycycline, are better than the other antibiotics [1] and topically the patients prefer antibiotic roll-on preparations to the benzoyl peroxide creams, which are too irritant. While this may arrest the development of new lesions and scarring, the physical course of the disease is poor without psychological support [1]. These patients tend to be psychologically dependent, and the benefits of simple supportive consultation and psychotherapy should not be underestimated [8]. Compulsive behaviour that leads to further scarring may respond to cognitive and habit-reversal therapy [9].

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Psychogenic pruritus [1,2]

This subgroup of the psychopruritic disorders represents those with intractable or persistent itch for which no pruritic physical illness or dermatological illness can be found [1]. Musaph [2] pointed out that one mechanism for relieving everyday irritations is to scratch a little. The motorist stopped at a red traffic light almost invariably scratches some accessible site such as the neck and most of us develop a small itch from time to time during the day that is relieved by slight scratching. He called this the 'traffic-light phenomenon' and its function is a common way of relieving minor frustrations. Individuals who develop localized or generalized neurodermatitis may begin in this way, but their itch–scratch cycle gets out of hand. In some individuals, intense scratching can induce an ultimate feeling of pleasure and this may be related to the release of opioids centrally.

Enkephalins and endorphins are important as neurotransmitters in the CNS in mediating the sensation of itch because it has been recognized for many years that, although morphine may alleviate pain, it may aggravate itch. As itch and pain are thought to share common neurological pathways, the central elicitation of itch by morphine may result from binding to opioid receptors and this binding may mimic normal physiological binding of endorphins and enkephalins at these receptor sites [3]. Moreover, naloxone, an opioid antagonist, has been found to reduce or abolish histamine-provoked itch. It has been shown that naloxone can relieve itching experienced by patients with intrahepatic cholestasis and may also be effective in patients with generalized pruritus caused by chronic liver disease. This drug, however, did not produce a uniform reduction in itching in all patients. Patients with generalized pruritus who had responded well to placebo reported greater itching after naloxone, probably because of the abolition of the placebo response. Conversely, the placebo non-responders reported less itch after naloxone than the placebo responders, suggesting that naloxone may be competing with an endorphin system, thus modulating the individual's perception of itch [3,4].

There are more intricate relationships between allergic disease and neural mechanisms, which identify further mechanisms that produce central itch [5] including those selectively responsive to histamine [6].

The psychopruritic disorders have some common features that help to differentiate them from physical diseases. Pruritic episodes may be bizarre in onset and presentation with abrupt and sudden termination. This itching may occur commonly during relaxation or sometimes after nighttime waking [7]. Furthermore, localized itching may lead to generalized body itch within a short time. The episodes are chronic and relapsing and last variable lengths of time from hours to days.

Patients with psychogenic itch tend to be introverted and there may be a history of recent major psychological stress [8]. A psychiatric and psychodynamic investigation of patients with prurigo nodularis demonstrated an extraordinary propensity for these patients to suffer from psychological trauma, and a distinct correlation was claimed between the outbreak of the disease and the preceding loss of a human relationship detrimental to self-esteem [9]. A significant proportion of patients with generalized pruritus may be suffering from depression. Using the Beck depression inventory, significantly more patients with generalized pruritus (32.4%) had depressive symptomatology than controls [10].

Treatment with antihistamines is disappointing, although those that have phenothiazine activity, such as hydroxyzine 50–75 mg/day, may produce more relief. Doxepin used in dosage up to 125 mg/day is more effective, probably because of the combined effect of both antipruritic and antidepressant actions. SSRIs can also afford relief: typical dosage is paroxetine 20–40 mg/day, fluvoximine 100–200 mg/day or citalopram 20–40 mg/day [11].

Behaviour-orientated therapy may give some benefit but relies upon a receptive patient, and success will be limited and disappointing in those with significant mood shift or personality disorder [12].

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Trichotillomania [1–3]

Definition. Trichotillomania is defined as the irresistable urge to pull out hair, accompanied by a sense of relief after the hair has been plucked. The term was firstly used by Hallopeau in 1889 and literally means a morbid craving to pull out hair. Originally, DSM-IV [4] listed trichotillomania under impulse–control disorders in company with compulsive gambling and kleptomania, but the broad spectrum of psychopathologies [1] prompted modifications to the definition. The revised DSM-IV-R [5] diagnostic criteria for trichotillomania are:

1 Recurrent pulling out of one's own hair resulting in hair loss

2 An increasing sense of tension immediately before pulling out the hair or when attempting to resist the behaviour

3 Pleasure, gratification or relief when pulling out the hair

4 The disturbance is not better accounted for by another mental disorder

5 The disturbance provokes clinically marked distress and/or impairment in occupational, social or other areas of functioning.

The ICD-10 definition [6] is consistent with this but does not mention distress or loss of functioning.

Aetiology and pathogenesis [1,2]. The epidemiology of this complaint is not absolutely clear, probably for the reason that this physical sign and response is a product of various psychopathologies. Studies of frequency show a wide variation. In an unselected population the incidence has been reported as below 1 in 1000 to as high as 1 in 200 by the age of 18 years [6]. However, there appear to be two distinct populations: those who present in childhood [2,7] and who probably represent the bulk of cases [6,8]; and fewer but more chronic cases who present as adults, who have continued hair-pulling activity from adolescence or developed the disorder in early adult life [2]. There is an estimated lifetime prevalence of 0.6% in college students [9], with equal sex incidence. If the criteria are based on ICD-10 then the prevalence increased to 3.4% in females and 1.5% in men. The number of affected children may be seven times that of adults [10] and preschool children are more likely to be boys (62%) although after this older boys and adolescents are 30% of the group [7]. This early-onset group, usually between the ages of 2 and 10 years, show benign self-limiting behaviour and most are probably suffering from a habit disorder, perhaps as an extension of hair twirling activity and childhood stress [11]. The association with nail biting and thumb sucking, skin picking, nose picking, lip biting and cheek chewing is well documented [12,13]. In children, there is an association with anxiety and dysthymia [12], learning disability and iron deficiency [8]. Emotional problems in the pre-adolescent group tend to be less severe, more a reflection of a stressful life event rather than serious psychopathology [13].

The adolescent age group, more likely to be girls, have more psychopathology related to parent relationships, school difficulties commonly bullying, body image changes and infrequently sexual abuse. It is more likely that there is an accompanying anxiety disorder although depression in children may be missed because the features are of somatic complaints and irritability [14].

The adult age groups are associated with greater psychopathology and show distinct female preponderance [1,2,7,], usually 4 : 1, but 15 : 1 being most evident in the oldest group [15]. This remains true for different racial groups [16–18]. The adult patients show more diverse psychopathology with depression, anxiety disorder, obsessive–compulsive disorder (OCD) and panic attacks prominent. Depression was present in 14% and anxiety in 15% [19]. Substance abuse (6%) and eating disorders may also be evident [2,3]. There is a significant debate about the relationship of trichotillomania to OCD [1]. While it has been proposed that adult chronic trichotillomania is a variant of OCD, with positive correlation in family studies [20], this definition is too narrow for many patients [2] and has not been supported by psychometric testing [21]. OCD compulsions are performed to avoid increased anxiety, are not pleasureable and are performed in full awareness. Patients with OCD have an explanation for their responses, whereas those with trichotillomania rarely justify their actions. In addition, the activity relieves stress

for those with trichotillomania, although a small subset may have the typical disabling compulsive conscious behaviours [22]. A family history is present in 5–8%, which may represent either a genetic predisposition or, more likely, a continuing family psychosocial response [20].

Clinical features [1]. The hair pulling activity is usually not as a response to any skin symptoms but is either a conscious deliberate act or, more often, a subconscious act, in some children being part of a hypnogogic (dream-like) state. Most adult patients describe an increased sense of tension before hair pulling or a sense of relief after the act. Some patients may have incomplete awareness until the pattern has been established [23].

Hair pulling and plucking is most common from the scalp but only occasionally as a response to scalp symptoms. Most pull hair from the vertex, but temporal, occipital and frontal hair loss in children may be more obvious on the side of manual dominance. The hair loss may be minimal, commonly a solitary patch, but visible hair thinning may progress to virtual total depilation, significantly so in adult women. Typically, the hairs are short, irregular, broken and distorted. The hair feels like stubble because of the fractured hair shafts, in contrast to alopecia areata which is much smoother. The patterns of plucking activity are centrifugal from a single starting point or linear, in wave-like activity. In extreme cases, the centrifugal pattern removes all hair except the most difficult to access, namely the occiput. This shows as a 'tonsure pattern' [24] or 'Friar Tuck' [25] distribution. The eyelashes, eyebrows, facial and pubic hair may also be primarily affected. Children will pluck the eyebrows and eyelashes but adults almost exclusively pluck hair on the torso. Two-thirds of adults pulled hair from two or more sites and one-third from three areas [2,3]. Body and pubic hair plucking is more common in males and may become a ritualized activity, either alone or as a conjugal activity.

Younger patients will tend to pick and pluck the hair at times of leisure, when alone or when tired and in the evening. Adults have a more conscious structured activity, initially seeking thicker or distorted hair and then progressing to larger areas, taking longer and longer over the activity. This may become more like a compulsion with elaboration of the rituals using instruments. The more frequent the plucking episodes, the greater the body image dissatisfaction and the more likely the patient will have depression and anxiety.

Patients present in the clinic with bald patches but associated features are the use of wigs, false eyelashes and semi-permanent use of hats and scarves. Occasionally, the psychosocial effects of hair loss (e.g. reluctance to swim, date and do sports) may precipitate referral to clinical psychologists or psychiatrists. Chronic folliculitis of the neck, chin, chest, pubic areas or thighs as a result of plucking activity may also be the presenting complaint.

One of the secretive activities in many patients with trichotillomania is some degree of hair licking, chewing and eating (trichophagia). Children may pluck the hair, stroke or suck the hair root before chewing and swallowing the remainder. Occasionally, hair may be seen stuck between the teeth. Patients may swallow longer strands of hair and a small percentage develop gastrointestinal bezoars. There should be a high index of suspicion in children with trichotillomania who present with abdominal pain, weight loss, nausea, vomiting, anorexia and foul breath [7,8]. Gastric trichobezoars may cause intestinal bleeding, pancreatitis or obstructive jaundice [1,17]. If the hair bolus extends down the small intestine (Rapunzel syndrome), life-threatening intestinal obstruction necessitates a laparotomy [26]. It has been reported in over 10% of adults, who usually report no abdominal symptoms, and patients with learning disability [27].

Investigations. Scalp biopsy has been shown to be most useful [7,10]. The most important findings include multiple catagen hairs, pigment casts and traumatized hair bulbs.

Gastrointestinal bezoars have been investigated by conventional radiography, sonography, and computed tomography (CT) scanning. CT scan diagnosed all cases in both stomach and small intestine, while ultrasound was almost as accurate [28]. Conventional X-ray of bezoar was least helpful.

Differential diagnosis. See Chapter 63.

Treatment. Clinical assessment scales are helpful in the fuller evaluation of treatments but remain largely research tools [29]. For many adolescents and children, identification of stressful episodes with accompanying support and parent education is usually all that is necessary. It is essential to present the harmful habit in an atmosphere of non-blame or fault but to change the agenda to a positive one to negotiate change. Habit reversal [29] is effective as is behaviour therapy. This was effective in children [1,22,30] and reduced symptoms by 90% in 19 adults [29]. It is time consuming and needs expert clinical psychology support to maintain progress.

One study showed that tricyclic antidepressants were effective agents and further that clomipramine was more effective than desipramine [16], although relapse may be common unless treatment is continued for at least 1 year. SSRIs have been of benefit in open studies. In two further studies [31,32], fluoxetine in dosage of up to 80 mg/day decreased severity by 60%. In a double-blind study, citalopram reduced severity by 30% by week 12 [33]. Low-dose pimozide has been shown to augment this response [34] as has risperidone because relapse is common after 1 year if SSRIs are used as monotherapy [35].

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Onychotillomania and onychophagia

(see Chapter 62) [1,2]

The compulsive habits of nail picking and nail biting have been shown to be common in children and adolescents [2,3]. The aetiologies suggested include stress, imitation of family members and a transference from the thumb sucking habit. Nail biting is usually confined to the fingernails, but nail picking, especially in adults, may involve all digits. Damage to cuticles and nails causes paronychia, nail dystrophy and longitudinal melanonychia [4]. In chronic cases, there is an association with trichotillomania [1]. Compulsive biting, tearing or picking with instruments such as scissors, knives or razorblades may lead to permanent destruction [5].

Onychotillomania is often denied by the patient but some admit to the habit. Of these, the most common problem is a compulsive action, not always at times of stress. Self-induced anonychia of the toenails was produced by one man who plucked out the nails with pliers rather than suffer recurrent paronychia of previously crushed toes [6]. DP may provoke self-destruction of the nails [7] as can a folie à deux in the confused elderly [8]. Successful response to treatment has been shown with clomipramine [9] and pimozide [8].

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Psychogenic purpuras [1,2]

This group of disorders is incompletely understood. The common features are the presence of purpura, bruising or frank bleeding in patients who show severe emotional

disturbance. The patients are predominantly female. For clarification it is helpful to consider the following separate categories, although some overlap is apparent:

1 Autoerythrocyte sensitization syndrome (Gardner–Diamond syndrome) [3]
2 Psychogenic purpura without autoerythrocyte sensitization but with other abnormalities [4,5]
3 Psychogenic purpura with no measurable abnormality [6,7]
4 Purpura factitia [8–10]
5 Religious stigmata [2].

Autoerythrocyte sensitization syndrome [3]

SYN. GARDNER–DIAMOND SYNDROME

In this rare but well-recognized condition (see Chapter 48), exquisitely tender bruises arise after minimal trauma with or without a history of emotional disorders. In the original cases, it was noted there was a preceding history of an injury involving extensive bruising or major surgery. These bizarre tender lesions are most commonly located on the arms and legs [11,12]. Bruising is heralded by a burning or stinging sensation followed after a few hours by oedema and erythema. The bruising appears a day or so later [12]. Abdominal pain, bleeding from internal organs and neurological symptoms may occur [1]. Psychiatric symptoms were present in 21 of 30 cases reported [13]. Severe emotional disturbances are a constant feature and the relationship to religious stigmatization has been discussed [1,2,14]. The possible relationship of stress to altered fibrinolysis is conjectural but measureable effects have been found [2].

Typical bruising can be reproduced by the intradermal injection of the patient's own erythrocytes and in some cases red-cell phosphotidyl-L-serine [15]. Gomi and Miura [16] described a case with associated thrombocytosis where busulfan therapy produced a reduction in attacks. Increased fibrinolytic activity has also been noted at the onset of fresh lesions in some patients [5,17]. One case seemed to have been made worse by a copper-containing intrauterine contraceptive [18]. Psychiatric treatment using psychotherapy [1,11] or psychotropics [15] has been reported.

Psychogenic purpura without autoerythrocyte sensitization but with other abnormalities [4,5]

A very similar clinical syndrome has been reported but with a negative reaction to intradermal red cells. Rowell [5] described two women with painful bleeding and bruises in association with increased fibrinolytic activity and mental stress. A further condition in this group consists of autosensitivity to DNA [4] described as painful itchy eccymoses, which recurred over a number of years.

Psychogenic purpura with no measurable abnormality [6,7]

Sorensen *et al*. [7] considered that patients with psychogenic purpura with no abnormal tests shared the same emotional background and other clinical features and should be regarded as part of the same syndrome. The lesions may be less tender and dramatic [6].

Purpura factitia [8–10]

Bleeding, bruising and purpura have all been reported as artefactual disease. Agle [8] described malingerers who misuse anticoagulants, while aspirin has also been taken to similar effect. Mechanical purpuras are ingenious and well reported [9,10].

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Factitious skin disease

The dermatologist, in common with most clinicians, is trained to believe what the patient says. Most physicians will maintain an endearing and undiscerning naivety even in the face of strong evidence of simulated or frau-

dulent illness. Clinical deception refers to a spectrum of illness that lies in a continuum which stretches from the unconscious processes (e.g. conversion and somatization) through the conscious and sporadic (e.g. dermatitis artefacta) to the falsification for deliberate gain (e.g. so-called malingering). The dilemma for the clinician is to determine the degree of voluntariness present in the patient for the consciousness of the action may not equate with the consciousness of the motive.

At a simple and elementary level, patients commonly exaggerate or minimize symptoms, may misattribute causation or have mistaken beliefs. This pattern is common and does not really constitute a fabrication although as a persistent behaviour it can alienate the clinician's objectivity. These distortions are singularly different from the factitious falsification of information (lying), the manufacture of skin lesions, the occult use of others (proxy disease) and disease produced for material profit or retribution.

The definition of factitious behaviour is not completely clear because the level of intention may vary, but for the dermatologist the definition by DSM-IV-TR criteria maintains the difference from malingering [1]. The DSM-IV-TR criteria for factitious disorder include:

1 Intentional feigning of physical or psychological signs or symptoms

2 The motivation is to assume the sick role

3 External incentives for the behaviour (such as economic gain, avoiding legal responsibility or improving physical well-being, as in malingering) are absent.

Dermatologists will encounter the subtype 300.19 presenting with predominantly physical signs and symptoms.

There are a series of recognized skin diseases characterized by the essential features that first are caused by the fully aware patient and, secondly, involve the desire to hide the cause from their doctors. This definition includes dermatitis artefacta, dermatological pathomimicry, dermatitis simulata and dermatitis passivata. These syndromes are additionally distinguishable from others where there is a secondary gain, such as Munchausen's syndrome, Munchausen's by proxy and malingering.

Dermatitis artefacta

Definition. Dermatitis artefacta is an artefactual skin disease caused entirely by the actions of the fully aware (not consciously impaired) patient on the skin, hair, nails or mucosae. These patients hide the responsibility for their actions from their doctors [2].

Epidemiology and aetiology. All studies have shown the preponderance of females, the ratio of female to male varying from 20 : 1 to 4 : 1 [2–6]. Lesions have been found in children from the age of 8 years [6], prepubertal children having an equal sex ratio rising to 3 : 1 female predominance by the early teens. In half of subjects the lesions are on the face, particularly in children [3,6]. While these series confirm that the majority of cases commence in adolescence and in adults under 30 years of age, there is an important subgroup whose age of onset is significantly older. This subgroup is distinguished by being more likely to be male (male to female ratio 1 : 2) to produce more subtle skin lesions [3,4] and to have a past history of somatizing illness [7–9]. These complaints may take the form of pseudoseizures, abdominal pain, syncope, chronic fatigue and backache. Previous work has suggested that dermatitis artefacta is more common in health care workers and their families [5,10,11] because this environment provides not only a ready 'model to copy' but also a social structure where illness is always understood and allowed for. However, this bias may now be less obvious [3] in a well-informed society whose medical symptoms, pathology and disease are more available via the media and the Internet.

Much has been written about the motivation to assume the sick role and the psychopathology underlying the production of artefact [7,12–14]. The idea that the patient *wants* the sickness role is the essential pathology because the primary gain of *being* a patient is usually to be expected of all illness. The main additional gains can be summarized as:

1 Strong masochistic needs (e.g. self-hate and guilt)

2 A sickness that allows inappropriate regression and avoidance of adult (especially sexual) responsibilities (e.g. marital trauma)

3 An illness that symbolizes anger at or conflict with authority figures (e.g. school phobia)

4 Psychiatric or medical care that fulfills massive dependency needs (e.g. inadequate coping strategies)

5 An illness that symbolizes attempts at mastery of past trauma (repetitive compulsion) (e.g. childhood abuse).

In many cases, the psychosocial stress of a major life event may be apparent. Children and adolescents commonly show anxiety and immaturity of coping styles in response to a dysfunctional parent–child relationship, bullying, physical body changes, or sexual and substance abuse. Adults may be neurotic and react to adverse situations in an immature impulsive manner [2,13]. However, there may also be significant depression [2,3]. The more chronic patients tend to have a demonstrable personality disorder, more particularly borderline or hysterical in females and paranoid in males [3,7,11,13]. There is a significant literature on the relationship between factitious disorder and illness falsification in both children and adults and previous factitious disorder by proxy victimization (Munchausen's by proxy; see below).

Clinical features. The nature of the clinical symptomatology in dermatitis artefacta is the 'hollow history' [15]. The patient describes the sudden appearance of complete lesions with little or no prodrome. There is no complete

description of the genesis of individual skin lesions. The signs invariably appear overnight, in a lunch break, on the way home from school or work. Lesions appear at the same identical stage in development in crops or groups, either symmetrically or scattered apparently at random. There is a significant lack of a history of a progression of lesions from an initial lesion to its fully developed state. By contrast, there is a prolonged and elaborate description of complications and failure to heal. Characteristically, established lesions may undergo sudden deterioration at the same time as new areas appear. It has been suggested that the patients show a 'belle indifference' to their predicament as part of a dissociative state and, in the presence of visible disease, manifest a nonchalance and innocence transmitted through an enigmatic 'Mona Lisa' smile. It is probably true to say that the patients are more often passive than aggressive, even though they have a widespread disfigurement. However, this is not always the case and considerable anger may be shown by the patient, but more particularly by parents, carers, husbands or partners, who rail at the incompetence of a succession of doctors. This may extend further to recruiting other doctors, university academics, nurses and social workers to support their case [3]. More than one person may be involved, as in the 'folie à deux' of two patients with factitious ulcers [16].

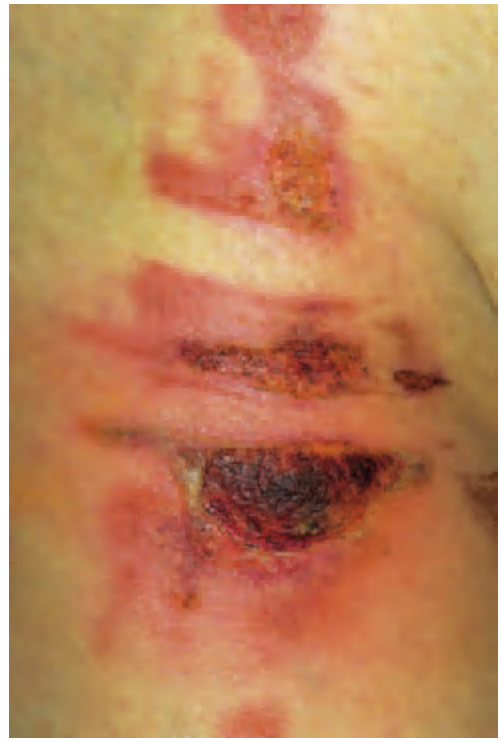

Fig. 61.3 Dermatitis artefacta: note the straight edges and sharp angulation of some of the lesions.

Clinical signs [5,11,15]. The most common site of involvement is the face, particularly cheeks. The dorsa of the hands rather than the palms are the next most common site then the forearms, most frequently the non-dominant limb. There is a particular covert pattern on covered skin where clothes hide significant mutilation of the breasts, abdominal areas and sometimes the genitalia. Involvement of the back, axillae and external ear is uncommon.

Cutaneous lesions are produced by every known means of damaging the skin. Crude destructive processes are the result of thermal, chemical or instrumental injury. Less commonly, dermal lesions from blunt trauma or injections are found. Oedema of limbs from constricting bands and hysterical dependent posture has been described (Secretan's syndrome) [17]. It is characteristic that one digit, usually a toe, will be constricted at a time while all others are healthy. A series of single ischaemic toes while all others are healthy should raise suspicion of artefact.

Excoriations may be made with nail files, sanding boards, wood or wire brushes to produce raw, crusty, linear or arciform lesions with characteristic angulated edges (Fig. 61.3). Punched out necrotic areas, sometimes with blisters developing into indurated necrotic scars are typical of thermal burns from cigarettes, soldering irons or ovens. These are usually uniform in size and scattered haphazardly. Urticarial lesions are initially produced by chemical damage and progress subsequently to crusting and scarring.

Characteristically, these areas may show the 'drip-sign', where corrosive liquids have been allowed to run over the skin (Fig. 61.4). Bleaches, soaps and household cleaners are most commonly employed by women; industrial acids and automotive fluids by men. These chemicals may produce a persistent detectable smell on the skin. Purpura and bruising are seen after suction, friction or blunt trauma. Children produce purpura on the chin by sucking on cups and on limbs by direct mouth suction or with the use of a toy or tool. Shearing stress also produces purpura, tending to present as linear lesions on the limbs.

Subtle artefact [3] is seen as fixed urticaria, vasculitis (Fig. 61.5), dermal nodules, panniculitis-type lesions and boggy fluctuant swellings. Considerable atrophy and pigment change occur with resolution. Careful examination may reveal the presence of a needle track where milk, air, faeces, urine, cooking oil, silicone, grease or engine oil has been injected [18,19].

In other specialties such as ophthalmology, oral medicine and otolaryngology artefact presents as non-healing infected wounds and excoriations [20–22].

The last common group is that presenting as non-healing surgical wounds. Commonly, this may follow a small operation after minor skin trauma, instrumentation such as an arthroscopy or breast biopsy. Unfortunately, further 'wound repairs' exacerbate and ligitimize the continuing wound. It is not unusual to see patients who

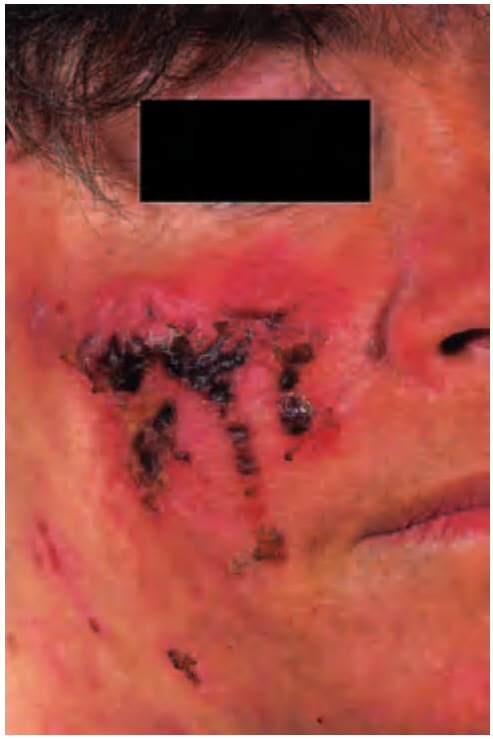

Fig. 61.4 Dermatitis artefacta showing the drip sign.

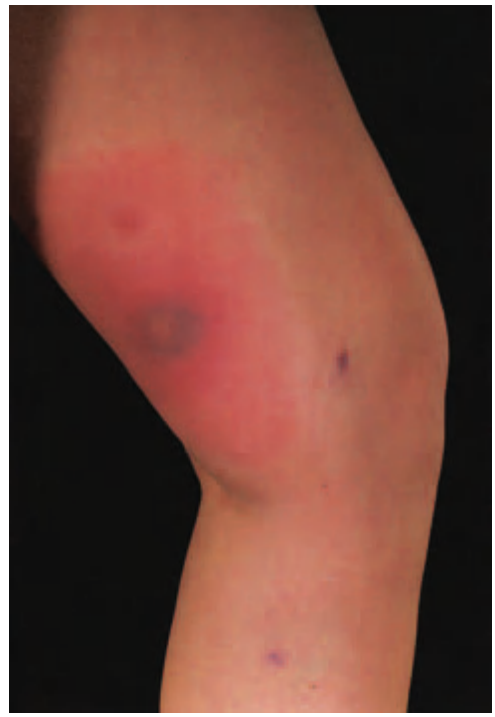

Fig. 61.5 Vasculitic lesions showing acute inflammatory lesions and old monomorphic atrophic scars.

have had up to eight operative revisions before a further referral is made to a dermatologist.

There may be unexpected complications to the artefactual damage leading to severe infection such as cerebral abscess [23] which may be life threatening [24].

Differential diagnosis. The distribution and physical characteristics of the crude dermatitis artefacta are diagnostic. However, blistering crusty lesions may simulate ecthyma, herpes simplex and bullous disorders. More subtle facial blisters may simulate porphyria cutanea tarda. The collagen–vascular diseases including vasculitis and pyoderma gangrenosum must be excluded in non-healing wounds as must atypical mycobacterial infections and imported tropical infections. The curious linear dermatoses such as Nékam's syndrome, cutaneous lymphomas and linear drug eruptions [25] must be excluded. The diverse hereditary sensory neuropathies can show chronic non-healing ulcers and be mistaken for artefact as can the cutaneous changes of reflex sympathetic dystrophy [26]. The purpuras and tissue purpuric reactions such as cutaneous amyloid can be perplexing and should be excluded [27].

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Factitious cheilitis (Fig. 61.6)

SYN. LE TIC DES LEVRES

Artefactual lesions of the lips are uncommon. Studies are small but it appears equally in males and females [1,2]. Such lesions manifest particularly as persistent inflammation with crusting and variable haemorrhage. This is caused by picking, biting, rubbing and licking [3]. Occasionally, young adolescents will develop a disuse crusting of the lips because they become dysmorphic about cleaning and washing their mouths [4].

Differential diagnosis includes contact dermatitis, actinic damage, chronic lip-licking habit and causes of granulomatous cheilitis.

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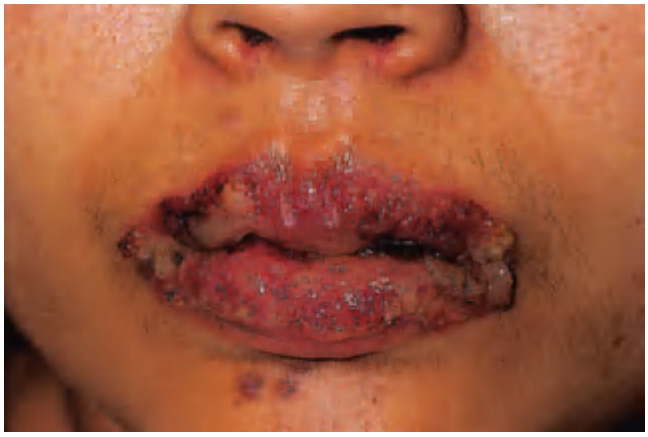

Fig. 61.6 Factitial cheilitis—a type of dermatitis artefacta of the lips.

Nail artefact

Chronic paronychia caused by the insertion of nails, pins or splinters has been recorded in soldiers avoiding duty and also in children [1]. The characteristic lesions show purpura and haemorrhage around the nail fold but also subungual haemorrhage and pustules. Similarly, Lyell [2] described a patient who induced haemorrhagic nail loss using a nail file. A significant sign is repeated traumatic nail loss occurring singly or multiply on one hand only. The differential diagnosis is described in Chapter 62.

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Hair artefact

A bizarre pattern of hair loss may occur after cutting or shaving. It differs from the plucked appearance of trichotillomania and usually appears acutely, either as rough cropped areas of hair loss or unnatural patterned alopecia of scalp or eyebrows (Fig. 61.7).

Differential diagnosis. See Chapter 63.

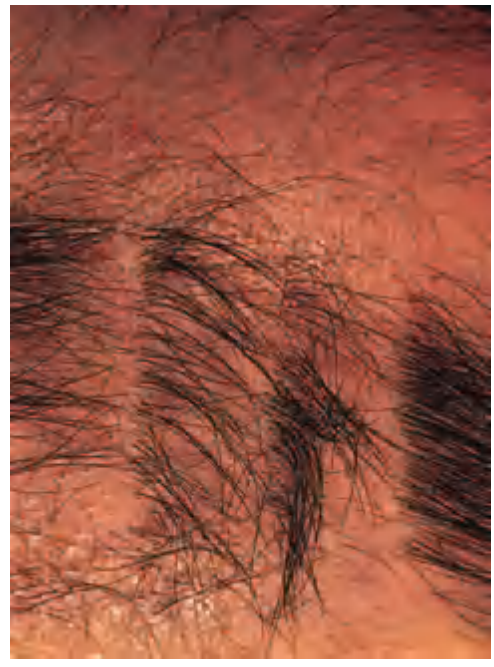

Fig. 61.7 Bizarre pattern of alopecia on the scalp with regimented rows of surviving hairs.

Artefact by proxy [1,2]

SYN. WITCHCRAFT SYNDROME

Artefact dermatitis can be provoked on an unknowing and unsuspecting victim by proxy. As an act of revenge, the daughter of a hairdresser applied benzyl ether of nicotinic acid to the customer's skin. This induced hyperaemia with some oedema within 10 min but not on the perpetrator because absorption of the agent is very low on the palm of the hand, so she could easily apply it to the customer's skin without harm to herself.

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Dermatitis artefacta with artefact of patch tests [1]

Bullous dermatitis artefacta in a female veterinary assistant healed with occlusive dressings. New bullae on the other arm prompted the parents to demand 'allergy' tests. Ten patch tests to yellow petrolatum were applied to the back, which provoked a non-inflammatory bulla on one of the sites 2 days later. Two other cases are cited.

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Investigations

The diagnosis of dermatitis artefacta is based upon major suspicions. In the absence of admission of deceit by the patient, suspicions are aroused by the presence of physiologically impossible symptoms, incompatable lesions, contradictory objective evidence and non-response to reasonable treatment. Other clinical diagnostic clues may be seen such as the sparing of decorative marks and areas of skin on the back [1]. While the diagnosis is based clinically upon a high index of suspicion, litmus paper has been reported as a valuable aid to diagnosis, because it detects strong alkali or acid, particularly in new lesions [2]. Ordinary histopathology will confirm the nature of skin damage in crude artefact, while deeper lesions of vasculitis and panniculitis may show injection tracks and foreign material [3–5]. It has also been shown that serial biopsy may be diagnostically helpful in sophisticated artefact [6].

There are psychometric tests that can be used for the assessment of factitial disorders, but these are essentially research tools [7].

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Co-morbidity

There are common overlap syndromes and related disorders that should be investigated. Twenty per cent of patients have a somatization disorder [1] and hypochondriasis. These are co-morbid with anxiety, depression and substance abuse [2]. Borderline personality disorder is a factor for chronicity in both sexes [3].

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Treatment. There are three therapeutic aims. The first is to treat the cutaneous damage. There is always significant skin damage, which will be both inflamed and infected. Topical and systemic antibiotics and anti-inflammatories establish the doctor–patient relationship and underlines to the patient that the physician is helpful, non-aggressive and sympathetic.

Secondly, there is a need to identify the nature and extent of the psychological problem. The dilemma has always been whether or not patients should be confronted [1]. In most cases, the urge to confrontation is stimulated by the aggression the physician feels because the doctor–patient relationship has apparently been betrayed. The doctor must avoid personalizing the episode and needs to consider the approach that is likely to change the patient's behaviour. Confrontation is a highly charged strategy and should only be done if the deliberate act is certain (e.g. if the self-damage has been witnessed) and there is sufficient support and advice available at the consultation. This will need the assistance of psychiatric advice and finally to effect a transference to psychiatric care if necessary. This catharsis can be achieved in a manner that allows the patient to express a positive decision to

change without dwelling on the deception and precipitating an aggressive defensive response [2,3].

Not surprisingly, other workers disagree with this approach, citing the high failure rate and the risk that the patient will strive even harder to legitimize the illness and himself by seeing other doctors [4].

For many years, a non-confrontational and non-punitive approach has been favoured. This passive acceptance of 'a cry for help' has the merit of a non-aggressive interview in the short term but may paradoxically give the patient consent to continue in the abnormal sickness role, albeit as a psychiatric patient [5]. This approach has been unsuccessful; although for a dermatologist it is the most comfortable because there are no rows. Unfortunately, many patients usually default the clinic or are referred elsewhere.

Efficient occlusive bandaging will allow most lesions to heal, except for those of the most devious and determined. The psychological problems should be approached in a non-confrontational manner [6–11], allowing the patient to express their difficulties in a passive confidential environment. Children usually respond well to this approach, particularly if a cause of psychosocial pressure is identifiable. However, chronic persistent self-damage is predictive of long-term emotional illness and referral to a child psychiatrist is imperative [6].

For adults, a non-confrontational approach that also displays surprising robustness is the 'narrow escape', 'quasi-confession', 'recovery' or 'face-saving' strategy. This is the suggestion that the patient finds a solution to their illness by offering a rationale for recovery. This may take the form of a self-explanation, however fantastic, as a mechanism to escape without public retribution. The patient may claim that alternative medicine such as hypnosis, homoeopathy or fringe methods such as kinaesthetic manipulation has 'cured' them [12]. One additional technique is the double bind strategy where the physician explains that the treatment carries an expectation for recovery. If this does not occur then they will be forced to conclude that the problem is psychological or factitious [12].

The management and prognosis in adults is that of the primary psychological disorder [6]. Acute stress reaction can be addressed in a series of short consultations at the time when the dressings are changed. Patients with depression responded well in two series to tricyclics or SSRI antidepressants [7,8], even when no precipitating event was identifiable. Tacit acceptance that the cause of the rash has been identified, without further challenge, helps to make the transfer to formal psychiatric care easier if needed [10]. Between one-third and half of patients continue to develop chronic lesions [6,11]. Such cases usually have a personality disorder, commonly hysterical, paranoid or borderline [10,11] and need psychiatric assessment [13]. Unfortunately, this is frequently unacceptable to the patient.

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Dermatological pathomimicry [1]

Some patients intentionally aggravate an existing dermatosis as an expression of their distress at the unresolved discomfort they feel towards their skin disease, or equally as a mechanism to recruit an existing sick role into another psychosocial situation. To this extent it is distinguishable from dermatitis artefacta because the disease appears as an exacerbation of established skin disease with none of the bizarre physical signs typical of mechanical, chemical or thermal interference. This is also to be differentiated from self-inflicted delayed healing of surgical and traumatic wounds that is achieved by external damage. However, a group of 13 patients who had deliberately caused recurrence of their existing skin disease by reintroducing the precipitating factor and invoking the original pathogenic mechanism have also been described [1,2]. The most common provocative agents were atopic allergens, contact allergens, drug sensitivities and irritants applied to chronic leg disorders. Other reports have described irritant contact dermatitis [3] and artificial oedema of an arm or leg [4]. Most patients were young women who had lost support from within their family group. More direct confrontational discussion without recrimination proved helpful and follow-up showed only minor recurrence in two patients 5 years later [2]. Since the original description there have been numerous reports of contrived exacerbations of common dermatoses. These include atopic eczema by deliberate exposure to individual known

personal aeroallergens such as pet danders or food allergens such as milk. In one case this was done by proxy by a mother. A patient with psoriasis covertly retook atenolol, which previously had caused problems (Dr L. Stankler, personal communication).

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Dermatitis simulata

Apparent skin disease can be represented by patients who are ingenious enough to use external disguise to simulate disease. Make-up has been used to paint on a rash [1], sugar to simulate chronic cheilitis, drugs to induce skin discoloration [2] and topical printing dyes to produce discolored sweat [3]. Red make-up has been used to simulate a port-wine stain on the face. These deceptions were clever enough to confuse doctors for months. Most of these patients were young and immature, but a somatizing illness was recorded in one older patient and previous treated depression in another.

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Dermatitis passivata

The cessation of normal skin cleansing will produce an accumulation of keratinous crusts. This is commonly seen in geriatric or demented patients who suffer from self-neglect and has been called the Diogenes syndrome [1]. Lesions are usually found on the upper central chest, over the back both upper and sacral and accumulated as coagulated debris in the groin creases. However, a group of patients were described [2] who showed lesions on the scalp, face or arms. Notably, they were young adults who were invariably accompanied by parents or family. Significant psychopathology such as schizoid thought disorder or hysterical limb palsy was present. Specialist psychological therapy was usually necessary either as day care or community psychiatric support [3].

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Munchausen's syndrome [1,2]

Asher [1] used this term to describe the notorious hospital hopper who presents with a dramatic and untruthful story of illness. This is a severe and chronic subtype of factitious disease [2]. The essential elements are the chronicity of the illness, and the frequency and similarity of the repetitive pattern of the complaint in different hospitals (peregrination). The simulated illnesses may be esoteric and rare. While dermatological complaints are uncommon in Munchausen's syndrome, patients with simulated porphyria and connective tissue disease, for example, may present to the dermatologist. The last element in the syndrome is pseudologica fantastica. This describes the telling of lies about past social history and connections, exploits, wealth and invention of an alias [3]. The patients are usually male, and travel widely from hospital to hospital complaining of abdominal pain, haemorrhage or some neurological incapacity. Skin lesions such as non-healing wounds, widespread blistering and multiple excoriations may be part of the syndrome of simulated disease [4]. The secondary gain is prolonged medical attention, although serious consequences such as septicaemia and paraplegia have occurred [5] from induced cutaneous ulceration. The Internet provides access to those interested in health and medicine and is a rich resource for the expansive personality of the Munchausen patient. Because the Internet offers 'virtual support groups', these individuals may offer 'virtual' factitious disorders. Four cases have been reported, showing the facility with which they can attract attention, mobilize sympathy and control others [6].

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Munchausen's syndrome by proxy [1,2]

In 1977, Meadow [1] had the clinical acuity and personal courage to described the syndrome of Munchausen's by

proxy where the illness is fabricated by the parent, usually the mother, or someone *in loco parentis*. Since then it is clear that not only do some parents harm their children but other carers may be involved and these may include health professionals. Doctors and others may not only fail to understand the origins of a child's symptoms but also institute further harm by inappropriate investigations, treatment and surgery [3]. The guidelines to identifying cases [2] mirror many of those discussed for dermatitis artefacta. The victims have a persistent or recurrent illness that cannot be readily explained. The diagnosis remains descriptive and not stringent. Symptoms do not respond and laboratory tests are incongruous. The reported symptoms are inconsistent with presenting health and the symptoms fail to appear in the absence of a certain parent (usually the mother). The perpetrator is reluctant to leave the child even for a few minutes, but remains oddly impassive even in an emergency. Characteristically, like patients with dermatitis artefacta, these carers attempt to make close relationships with medical staff with a blurring of the doctor–parent barrier. There may be fabrication of family details and a disturbed marital and social structure. Rarely, the parent exhibits the syndrome herself and produces proxy lesions on the child (Polle's syndrome) [4].

The victims are usually infants or toddlers with a mean age at diagnosis of 40 months [6]. The mean delay between presentation and diagnosis is 15 months. The signs and symptoms of illness were mostly produced in hospital. The most common presentation in one series was bleeding (44%), CNS depression (19%), apnoea (15%), diarrhoea (11%), vomiting (10%), fever (10%) and rash (9%) [6]. Skin lesions are usually crude forms of dermatitis artefacta [6,7] produced by scratching or caustic painting on skin. On one occasion the rash was the result of drug poisoning. A large review of countries outside English-speaking industrialized populations produced similar results in rather older children [8]. The long-term consequences of childhood victimization might contribute to the development of factitious disease in adult life. Elements of the child victim's experience, including feelings of powerlessness, lack of control and disappointment in the physican, are the suggested dynamics for the development of independent illness falsification [9].

Munchausen's by proxy may also rarely be seen in the elderly, mentally handicapped or other dependent persons [10], perpetrated by relatives, nurses and care home personnel.

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Malingering [1]

Asher [1] defined malingering as the imitation, production or encouragement of illness for a deliberate end. The American Psychiatric Association DSM-IV definition is 'the intentional production of false or grossly exaggerated physical or psychological symptoms, motivated by external incentives'. However, the taxonomy of the malingering is difficult because of the moralistic overtones of criminality and false compensation litigation [2,3].

Malingering may be co-morbid with conversion disorders, personality disorders and other factitial behaviour. However, usually it differs from most factitial disease in being short term and opportunistic, whereas other illness falsification is chronic and persistent. Fear, desire and escape are the three main motives to produce false or grossly exaggerated physical or psychological symptoms. Soldiers feigning disease and disability hope to avoid duty, suspend transfer or be discharged from the service. Workers can prolong sick leave, delay corporate change of job or seek to obtain early retirement with an apparently extended illness. Some patients may seek compensation for some contrived illness (e.g. alleged burns) or aggravate and continue an existing disease (e.g. industrial dermatitis) out of a sense of grievance or retribution. Prolonged legal cases of supposed medical negligence are common in those with manufactured illness whose dissatisfaction with their doctors or the care they have received may lead to a financial settlement as a reward [4].

Cutaneous lesions are usually crude forms of artefact dermatitis [5]. Chronic non-healing postoperative scars are manipulated with instruments, or even faecal injection to maintain sepsis [6]. Hand dermatitis, both irritant and allergic contact dermatitis, may be perpetuated to seek higher compensation awards [7].

Treatment depends on the underlying psychiatric illness if significant psychopathology can be found, but the opportunist response in patients with an underlying personality disorder is poor [8].

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Self-mutilation

There is a transition between some forms of self-decorative behaviour such as piercings and the development of pathological self-mutilation (SM). This will depend upon the psychological state of the individual, the acceptable fashion norms and the peer group pressures to conform [1]. In a study of adolescents, of 14% engaged in SM two-thirds were girls. Self-cutting was most common followed by self-hitting, pinching, scratching and biting. These students with SM showed significantly more anxiety and depressive symptoms than non-mutilators.

Dermatologists are seldom asked to manage patients who admit to SM but it may be seen as an incidental clinical finding. A group of female patients perform delicate self-cutting, which leaves fine linear non-sutured scars on the wrist and forearm [2]. The cutting is a form of emotional release, both immediately physical often accompanied by euphoria and in the longer term as a control of anxiety [3]. The most common mutilators are young women who are wrist slashers [3]. They are described further as usually attractive, unmarried, easily addicted and unable to relate to others. The patient slashes her wrist at the slightest provocation but does not commit suicide. They tend to be depressed and obsessional, attached and dominated by their mothers, often in the absence of a father. Other impulse control disorders may be evident such as anorexia and bulimia [4]. It is suggested that this form of self-harm is a substitute for masturbation, a form of self-purifying catharsis which modulates stress and anger in patients who remain infantile in outlook [5]. Child abuse and family psychiatric history were frequent in some studies where genital mutilation predominated [6,7]. The more severe forms of SM leading to autocastration or enucleation of an eye are usually reported in association with schizophrenia [8,9].

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Cutaneous disease and alcohol misuse [1,2]

Alcoholism and alcohol abuse rank among the three most common psychiatric disorders in the community. There are significant medical and economic consequences because of differing effects of alcohol on metabolism, health, treatment, behaviour and motivation [3]. Alcohol abuse can be missed as a diagnosis by experienced physicians even though the problem is common. Mechanisms for screening and brief interventions are well established and show robust stringency. The two-question screen consisting first of enquiry about past alcohol problems and, secondly, the period since the last drink shows 90% accuracy [4].

The psychosocial effects of chronic and disfiguring skin disease commonly produce feelings of stigma and rejection. Recreational substances, such as alcohol, are commonly used by affected patients [5]. A study of a large urban population suggested that male as well as female psoriatics showed an excess rate of alcoholism [6]. However, further studies suggested that while alcohol abuse was not a factor in the onset of psoriasis, it became significant in women after the disease was present and was significantly associated with the area of skin surface involvement [7] and severity, particularly in men [8]. Furthermore, a prospective study [9] showed that a daily intake of alcohol of more than 80 g was more frequently associated with less treatment-induced in-patient improvement in the percentage of the total body surface area affected by psoriasis. In two wide reviews [2,10], it appears that the changed character and distribution of psoriasis make it more difficult to treat. In studies of patients with psoriasis, alcohol abuse was not marked by elevated liver function tests. Alcohol abstinence helped to induce remission, and relapse was induced by reconsumption.

Discoid eczema appears to be more frequent in alcohol abusers and is a more reliable indicator of alcohol dependence, with significantly abnomal biochemistry and immunology related to alcohol excess. Atopic eczema appears to be unaffected by alcohol to the same degree. Seborrhoeic dermatitis is twice as common with alcohol abuse [11] and this may be related to immunosuppression and the effect on cutaneous microflora. The effects of alcohol on immune function and skin vasculature are thought to precipitate exacerbations of rosacea and post-adolescent acne.

Infestations of the skin and superficial skin infections were found more often in alcoholic vagrants than in non-alcoholics and those with other psychiatric disorders. This also suggests that more specific alcohol-related immune factors were active [12].

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AIDS, HIV infection and psychological illness (see Chapter 26)

Human immunodeficiency virus (HIV) and AIDS cause cognitive, motor, behavioural and psychiatric symptoms in children and adults [1]. The impact is variable and the progression of disease unpredictable. Poor compliance with retroviral therapy is related to psychiatric morbidity [2] and suicidal ideation, which may be found in 60% of some groups of HIV patients. Most CNS involvement complicating HIV infection occurs in the late phase of the disease. Such patients have been usefully classified first into those with headache or meningitic symptoms; secondly, those with focal CNS symptoms or signs; and, lastly, those with non-focal cerebral and/or motor dysfunction [3]. This latter group present with mental illness where alertness is characteristically impaired because of metabolic or toxic encephalopathy. It refers to a distinct subcortical dementia characterized by retarded and imprecise cognition and motor control. New-onset delusions and hallucinations may be either a result of the metabolic encephalopathy of AIDS or an opportunist cerebral infection, rather than a psychological reaction to having HIV and/or AIDS *per se* [4]. Psychosis develops in patients with late HIV infection and immunosuppression, and has been shown to have a higher incidence in those with CD4 counts of less than 100/μL [5]. A controlled study [6] showed that the neuropsychological deficit as measured by a broad range of cognitive functions was 44% in seropositive patients and up to 87% in those with AIDS.

Progression to AIDS is affected by many factors but significantly so by the effects of stress, lack of social support and depressive symptoms. The presence of all three made the progression to AIDS at least twice as likely [7]. Highly active antiretroviral therapy (HAART) has had a significant impact on patient survival but brings with it the psychosocial aspects of living with a chronic disease. While HAART therapy has a beneficial effect on the psychiatric manifestations of AIDS and HIV, depression responds to SSRI antidepressants used in tandem [1].

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Suicide in dermatological patients

Suicide refers to a range of self-destructive behaviours ranging from non-lethal acts which have been called suicidal gestures, attempted suicide, parasuicide and, more recently, self-injury. A lethal action in which a patient dies is defined as a completed suicide. The rates of completed suicide in the UK are 8–10 in 100 000 people. It is therefore one of the 10 most common causes of death in the UK [1]. Psychiatric disorders are the main risk factors but numerous studies have also identified physical illness as an important contributory factor [1,2]. Chronic illness is a risk factor in suicidal ideation and completed suicide and, not surprisingly, disfiguring chronic dermatoses have been shown to put patients at risk.

In a study of 217 patients with psoriasis, 10% of patients reported a death wish and 6% reported active suicidal ideation at the time of the study [3]. In another group, 2.5% of outpatients and 7.2% of in-patients with psoriasis expressed suicidal ideas. The severity of the psoriasis was reflected in the frequency of suicidal ideation and also measurable clinical depression [4]. Facial acne was also associated with significant risk (5.6%) of suicidal ideation, which is also higher than the levels reported in general medical patients [1]. Suicide ideation was found in seven of 11 patients with Darier's disease related to the dis-

figurement, the intractability, social exclusion and smell of the dermatosis [5].

Some dermatological patients become so disturbed that they do commit suicide successfully [6–8]. A group of 16 patients has been described [6]—seven males and nine females—who successfully committed suicide after presenting with dermatological problems to two dermatologists working in the same skin department. The majority of these patients had either body-image disorders (dysmorphophobia; BDD) or acne. It is important to recognize that patients with dermatological non-disease, and particularly females with facial complaints, may be extremely depressed and at risk of suicide [9]. Even more strikingly, BDD in children and adolescents carries a much larger risk; 67% experienced suicidal ideation and 21% had attempted suicide [10]. Acne scarring can have just as profound an effect, or even a more profound effect, on body image, self-esteem and confidence as inflammatory acne. The positive therapeutic role of isotretinoin was emphasized [1,11].

There is a definite risk of suicide in patients with active HIV disease [12], and rates of suicide for people with AIDS were 66 times higher than in the general population in New York City. Men with AIDS aged 20–59 years were 36 times more likely to commit suicide than their counterparts without such a diagnosis. Half of the people in this particular sample had expressed suicidal intents and one-quarter killed themselves by jumping from the windows of medical units in general hospitals. Assisted suicide has occurred in up to 23% of patients with AIDS [13].

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Treatment of psychocutaneous disorders [1]

General management

'Disease' is a perception of ill health rather than a physical entity. The same degree of physical damage will be translated into different 'diseases' by different patients. In many patients, psoriasis does not itch; in a few it is very itchy. The condition is the same; the perception and interpretation differ so that it is necessary first to understand the language in which the disease is expressed. Once translated, the key is provided for an understanding of a patient's particular concern, and for a valid channel of therapeutic communication.

When a rapid cure is possible, there is no great problem in management. However, where a disease is of unknown origin and unpredictable duration, it is likely to assume undue proportions in the patient's thoughts. In diseases of the skin, as in other spheres of life, the unknown is feared. The spots of acne are magnified in any mirror. The patient and the dermatologist see two different images. It is the patient rather than the spots that must be treated.

Psychiatry is not an exact science. Some anxiety or depression will be felt by many of the patients seen by a dermatologist. This may be unrelated to their skin disease but often plays some part in it or occasionally is the reason for its presentation. When the anxiety is reasonable and openly expressed—fear of cancer, ignorance of prognosis, anxiety about scarring and so on—it is sufficient to reassure the patient with a clear explanation, in easily understood terms. When anxiety is obviously present but at first denied, its nature must be elicited by careful questioning. Those whose conflicts are fully repressed, but whose skin lesions, often factitious in type, leave no doubt about the cause, present the most difficult problems.

All patients with skin disease respond to a receptive and sympathetic approach. Visible illness has a particularly disturbing emotional effect; itching intensifies this. The physician must have patience, sympathy and insight into human behaviour, and must inspire the patient to talk freely. Advice should be given sparingly and without expecting it always to be taken. The dermatologist must know when a psychological situation is out of control and must recognize organic mental disease and endogenous depression as such, and seek psychiatric help.

The therapeutic effect of the physician's personality is often underrated. The stronger this is, the less necessary are drugs. Even the act of touching a patient with skin disease relieves the anxiety of those who have marked feelings of guilt and ostracism. When it is necessary to draw out the patient's emotional difficulties, the 'listening ear' is as important as the 'seeing eye'. Tones of voice, hesitancy, a temporary stammer or an unguarded or ambiguous remark may provide the key to an important

emotional difficulty. Initial explanations given by a patient are often 'cover stories' and are not intended to be believed.

The first aim in management must be to determine whether any significant emotional situation is present, the second is whether the reaction is one of anxiety, depression or hysteria, and, thirdly, how environmental stresses can be reduced or the patient's frustration, guilt or aggression can be eased or rechannelled. Hidden fears can often be remedied once they are expressed; anxiety about a child, spouse or parent may lie behind apparent rudeness. Fatigue alone may provide a 'stressful situation' and the adjustment of household burdens, insistence on holidays or proper periods of rest, and the provision of 'emotional bunkers' when the situation cannot be avoided, are matters of common sense and experience of what is feasible. Feelings of guilt, 'dirtiness' and inadequacy, frequently components of a depressive state, are more difficult to dispel and may require expert help. Obsessional behaviour and phobias are also usually beyond the reach of superficial psychotherapy.

The English language is perhaps deficient in words that are not themselves emotive but can be used to describe emotional disturbances. To ask if a patient has 'any worries' is to invite a denial, which is often misleading. It may be more fruitful to ask about tiredness or depression. The manner of the reply matters more than the phrasing.

When a fuller assessment of the social and domestic situation is required, the services of a trained medical social worker are called for to extract information about family relationships and stresses and to indicate where these can be helped or eased.

The help of relatives must also often be enlisted, although their concern is not always disinterested if they are themselves part of the emotional situation. The parents of children with hair pulling or adolescents with artefacts must be approached tactfully. It is not they who have raised the cry for help, but they are often the cause of it. They may feel their honour impugned and their pride at stake. Employers, schoolteachers and rehabilitation officers can give further information or material help in particular situations. To some patients, a priest's aid is invaluable.

Three further general points have to be made. The patient may present with a dermatosis that represents only one facet of a complex psychocutaneous situation. It serves its function in expressing an emotional disturbance. If 'cured' too quickly, without attention being paid to the underlying emotional problem, the patient may develop other less accessible ills. Secondly, psychiatrists themselves are of different persuasions. Their views on aetiology and their approach to treatment differ considerably. It is well for the dermatologist to be aware of this lest the patient loses confidence by being given different explanations and advice. Finally, there is a small but important group of patients who do not want to get better [2]. They are skilled at deceiving their doctors, their spouses and their friends. They suffer from 'too good' husbands and 'too kind' doctors. Many have an histrionic personality. Once recognized, certain principles of management should be followed, even then the prognosis is not good. The patient has too much to lose by recovering.

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Psychotropic drugs

The use of psychotropic drugs in dermatology has become much more refined as the diagnostic criteria for the psychodermatoses has clarified. In addition, the awareness and detection of psychological accompaniments to organic skin disease, particularly depression, has presented a greater need for the dermatologist to become familiar with the use of psychotropic drugs.

The most useful are the antidepressants, both SSRIs and tricyclics. These vary in their specific activity, which can be an advantage as a sedative action may be beneficial in some circumstances, or an anticompulsion effect may be helpful. The indications for antidepressants and suggested regimens are provided in Table 61.2.

There are excellent descriptions of the use of antidepressants in dermatology [1–4]. In general, the patient should be started on a low dosage, which has the benefit of helping compliance, and then to increase the dosage over the next month to the therapeutic range. SSRIs are usually well tolerated. The effects should be evident in 4–6 weeks. If the response is slow or side effects are too intolerable, then another SSRI or tricyclic should be substituted. This should be achieved by gradually tailing the dosage of the original and building the dosage of the new drug [5–7]. SSRIs should be continued for at least 6–12 months. They should be gradually withdrawn over 2–3 months to prevent the serotonin withdrawal syndrome [6]. Sudden withdrawal can precipitate dizziness, anxiety, agitation, insomnia, flu-like symptoms, abdominal cramps and mood swings.

There has been a healthy reaction in recent years against the overuse of benzodiazepine drugs in the management of patients with psychoneurotic disorders. However, short-term therapy with anxiolytics or sedatives may be as helpful to anxious, itching patients as analgesics are to those in pain. Sedative SSRIs and tricyclics are very effective for anxiety and if additional sedation is needed hydroxyzine can be added. Sleep deprivation is common, and the restoration of a normal pattern is an adequate reason for giving hypnotics.

Table 61.2 Antidepressant drugs: usage and dosage.

Drug class	Activity	Dose (min–max)	Particular side effect
Sertraline SSRI	Depression, obsession, compulsion, BDD, panic, anxiety	50–200 mg mane	Caution hepatic/renal disease
Fluvoxamine SSRI	Depression, BDD	100–300 mg mane	Weight loss, rash, drowsiness
Citalopram SSRI	Depression	10–40 mg mane	Dry mouth
Venlafaxine SSRI, norepinephrine (noradrenaline) RI	Depression, pain syndromes	12.5–100 mg mane	Hypertension
Amitriptyline tricyclic	Depression, anxiety, pruritus, dynias	10–100 mg hs	Dry mouth, visual blurring, sedation
Clomipramine tricyclic	Depression, phobias, compulsive behaviour	25–150 mg/day	As above
Doxepin tricyclic	Depression, pruritus, anxiety	25–100 mg hs	Sedative

hs, at bedtime; mane, in the morning.
BDD, body dysmorphic disorder; RI, reuptake inhibitors; SSRIs, serotonin reuptake inhibitors.

Most dermatologists will not need to prescribe antipsychotic drugs. The primary indications for antipsychotic drugs are schizophrenia, acute mania and other psychotic states including paranoid disorders. In dermatological use, the indications for use are cutaneous delusions, dysaesthesias, pain syndromes and the compulsive self-picking disorders [2]. Drugs include pimozide, sulpiride, olanzapine and risperidone. The major disadvantages are extrapyramidal symptoms, although at low dosage there are minimal side effects.

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Hypnosis [1]

Hypnosis has always had its adherents and detractors but until recently there has been little attempt at scientific evaluation. Thus, there have been claims that hypnosis could induce inflammatory change and blisters in skin [2], and more than 30 years ago it was shown that immediate type 1 reactions, and even a Mantoux reaction, could be modified by hypnotic suggestion. The diminution in the Mantoux response was shown to be caused by a reduction in oedema rather than in the cellular response [3]. Hypnotic suggestion has been used to treat various types of ichthyosis [4–7]. It was claimed that the depth of the trance-like state could be important in determining the response to therapy, at least as far as patients with ichthyosis are concerned, and that the best results were obtained in deep-trance rather than light-trance subjects [5].

There are also many case reports detailing the response of warts to hypnosis [8–11], the most striking case being that where only half of each subject's body was treated. Disappearance of the warts on the treated side was observed while other warts on the control side remained unchanged [12].

Adults with extensive atopic dermatitis, resistant to conventional treatment, were treated with hypnotherapy with statistically significant benefit, measured both subjectively and objectively [13]. More encouragingly, the benefit was maintained at follow-up for up to 2 years. Moreover, 20 children with severe resistant atopic dermatitis were also treated by hypnosis and all but one showed immediate improvement, which was maintained subsequently. In 12 of the 20 children whose families replied to a questionnaire up to 18 months after treatment, 10 of them maintained improvement in mood. Long-term studies showed that a smaller proportion of patients with atopic dermatitis could be maintained without second-line therapy with regular hypnosis [14].

It may be that improvement with hypnosis can be achieved more by anxiety reduction and stress management than direct suggestion. Psychodermatoses such as acne excoriée, neurodermatitis and trichotillomania may all respond to hypnosis [15]. Relaxation techniques, which approximate to light hypnotic states, led to some improvement in patients with chronic urticaria, although the number of their weals did not lessen [16].

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Miscellaneous therapies

Biofeedback techniques

In recent years interest has grown in biofeedback techniques, during which patients are given visual or auditory information about the level of a particular autonomic function and then learn, through mechanisms that are not yet clear, to exercise some voluntary control over it. Biofeedback has been used for dyshidrotic eczema [1] and for hyperhidrosis [2].

Behaviour therapy

Behaviour therapy has sometimes been useful for patients who scratch repeatedly. In one study [3], parents were trained to withdraw their attentions when their child scratched; in another [4] a patient was required to monitor his own scratching and, to gain his therapist's attention, intervals without scratching were required. These therapeutic methods require regular reinforcement until autonomy has been obtained. These interactions assume that there will eventually be recognition of the patient's problem and the acceptance that there is a somatic component to the illness. The therapy can be used to reinforce positive adaptive illness responses, to extinguish maladaptive habits like excoriations, or to foster self-control over intrusive ruminative thinking (e.g. BDD) [5]. Habit reversal therapy helped a group of patients with atopic eczema [6,7].

Group therapy

Group therapy has been tried in psoriasis [8] and eczema [9]. Small groups of psoriatics met to discuss their problems with a trained fellow patient and a physician; illness behaviour, anxiety and feelings of depression all decreased. Help along similar lines can come from self-help groups [10]. A 6-week cognitive–behavioural therapy programme as an adjunct to pharmaceutical treatments produced significant improvement in severity of psoriasis as compared to pharmaceutical treatment alone [11].

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Psychiatric problems caused by dermatological treatment

It is well known that systemic glucocorticoid therapy can induce either depression or hypomania in 5% of cases. Steroid-induced psychosis is more likely with larger dosage, in females and those with systemic lupus erythematosus (SLE) or a history of affective disorder [1,2]. It is less well known that antimalarials such as chloroquine and mefloquine [3] can induce psychosis, as can dapsone [4]. Aciclovir-induced psychosis has also been described in patients with impaired renal function [5]. There is also a report of a man who applied 70% diethyltoluamide, the most common insect repellant, immediately before a sauna, and developed an acute manic psychosis after 2 weeks [6].

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Skin disease in patients with learning disability

Mental deficiency is not a disease in its own right but a condition resulting from a variety of causes, some inborn and others acquired. As a rough guide, some 3% of the population have learning difficulties, with an IQ of below 70, but the terms 'idiot', 'imbecile' and 'moron' are now obsolete in the professional sense. The class of subjects with higher grade learning disabilities shades into that of the less intelligent members of the ordinary population [1].

The number of syndromes in which cutaneous lesions and mental deficiency may be associated is large, and many of them have been delineated only during the last few years. Although many of these genetic or developmental conditions are rare, when put together they constitute a formidable part of present day paediatrics [2]. In addition, there are a number of other skin abnormalities that seem to affect those with learning disabilities in particular.

However, the available statistics must be interpreted with caution as they relate to patients in special institutions to which admission is largely determined by social factors. The proportion of patients with disabilities of the lowest grade, and of those of any grade with associated severe physical difficulties, is likely to be higher in such institutions than in the population of those with learning difficulties as a whole. In addition, institutional life itself may influence the prevalence of skin disease by allowing the rapid spread of infections, and other conditions may be favoured by unsuspected nutritional deficiencies.

The skin abnormalities of people with learning disabilities fall into three broad groups as outlined below.

Cutaneous lesions specifically associated with syndromes of genetic or developmental origin

Many of the numerous associations of this type are dealt with in detail elsewhere. Sometimes, the nature of the defect is understood at a biochemical level (Table 61.3) and sometimes chromosomal abnormalities have been demonstrated (Table 61.4) but, in most cases, the mechanism of both the cutaneous changes and mental impairment remains obscure (Table 61.5). The severity of the mental defect and of the cutaneous involvement may run more or less in parallel as in epiloia, but in most of these conditions there is no such relationship and the prevalence and severity of the mental impairment are highly variable.

Table 61.3 Some metabolic disorders that may be associated with mental defect and skin changes.

Anginosuccinic amino aciduria	Trichorrhexis nodosa
Cretinism	Coarse, dry skin and hair
Gangliosidosis (type 1) [3]	Extensive mongolian spots
Hartnup's disease	Photosensitivity
Homocystinuria	Fine hair, livedo reticularis
Hunter's syndrome [4]	Ivory white papules
Lesch–Nyhan syndrome	Self-mutilation
Lipoid proteinosis	Skin nodules and plaques
Phenylketonuria	Eczema, long eyelashes
Menkes' syndrome	Hair defects

Non-specific cutaneous lesions showing an increased prevalence in patients with learning disability

Moniliform hamartoma (see Chapter 15). Beaded strands of papules, mainly on the forehead and temples, develop at puberty in some patients, more often in black people than in white people.

Atypical keratosis pilaris. A symmetrical eruption of erythematous follicular papules extending from the base of the neck to the lumbar region is seen in young adults in institutions for those with learning difficulties [13]. This might represent *Pityrosporum* folliculitis.

Abnormal hair patterns [14]. The frequency of abnormal patterns of hair growth has been emphasized and is confirmed by our experience. Fusion of the eyebrows and a low frontal hairline are often seen; the latter is characteristic of those with true microcephaly but occurs in those with other learning difficulties. Hypertrichosis of the trunk or limbs is not unusual. The significance of the abnormal patterns is unknown and further surveys are required.

Atopic dermatitis. Only one patient with atopic dermatitis was found among over 200 children with learning

Table 61.4 Some conditions in which chromosomal abnormalities may be associated with mental defect and skin changes.

Down's syndrome	Ichthyosis
Familial X/Y translocation [5]	Facial hypertrichosis
Partial trisomy 2P	Scalp defect, haemangiomas
Patau's syndrome (trisomy 13)	Depigmented spots, café-au-lait patches
Ring chromosome 14 [6]	Nail hypoplasia, lymphoedema
Trisomy 18	Pre-auricular skin tags, scalp defects, flame naevi
Wolf–Hirschhorn syndrome (4P deletion)	Acne
XYY syndrome (see Chapter 12)	

Albinism	Monilethrix
Alopecia/retardation syndromes [7]	Moynahan's syndrome
Anhidrotic ectodermal dysplasia	Naevus sebaceous syndrome
Apert's syndrome	Netherton's disease
Ataxia–telangiectasia	Neurofibromatosis
Basal cell naevus syndrome	Onchotrichodysplasia with neutropenia [8]
Cockayne's syndrome	Papillon–Léage syndrome
Coffin–Siris syndrome [9]	Poikiloderma congenitale
De Sanctis–Cacchione syndrome	Richner–Hanhart syndrome [10]
Dystrophia myotonica	Rubinstein–Taybi syndrome [11]
Fanconi's anaemia	Russell–Silver dwarfism
Focal dermal hypoplasia	Sjögren–Larsson syndrome [12]
Hallermann–Streiff syndrome	Spina bifida
IBIDS syndrome [1]	Sturge–Weber syndrome
Incontinentia pigmenti	Treacher Collins' syndrome
Leprechaunism	Werner's syndrome
Marfan's syndrome	Wyburn–Mason syndrome

Table 61.5 Some other conditions in which mental defect may be associated with skin abnormalities.

IBIDS syndrome, ichthyosis, brittle hair, impaired intelligence, decreased fertility and short stature.

difficulties examined (A.J. Rook, unpublished data, 1953). Others have noticed a low prevalence of eczema [14], but atopic dermatitis is frequent in patients with Down's syndrome and phenylketonuria.

Traumatic keratoses and hypertrichosis [15]. Those with severe disabilities develop the habit of biting or chewing the forearm, hand, fingers or lips when excited or angry. Repeated biting at the same site induces thickening, hyperpigmentation and hypertrichosis. More rarely, there may be atrophic scarring, particularly on the hands. Keratoses in unusual sites may result from the repeated adoption of the same posture.

Prader–Willi syndrome is a genetic disorder that affects multiple systems and results in a cluster of behaviours including hyperphagia, emotional lability and compulsive destructive skin picking [16].

Traumatic alopecia. This is the result of a hair pulling tic. The patch selected for plucking is usually in the frontoparietal region, but may be anywhere on the scalp and even in the pubic region (A.J. Rook, unpublished data, 1953). Multiple self-mutilations including traumatic alopecia are seen in children with familial sensory neuropathy.

Crusted scabies. The crusted form of scabies [17] (see Chapter 33) is particularly frequent in those with severe learning disabilities.

Bacterial infections. Pyogenic infections accounted for 34% of patients referred from an institution for a dermatologist's opinion. The high incidence suggests low resistance to pyogenic organisms but the part played by the unhygienic habits of the patients is difficult to evaluate. Folliculitis of the thighs occurred in children and adolescents of both sexes, predominantly in males. Chronic suppurative hidradenitis was seen exclusively in adolescent boys. Erythrasma has a high prevalence [18].

Mycoses. Trichophyton infections are often common and refractory in those with learning difficulties. It is possible that enzyme induction by other drugs administered reduces the efficacy of griseofulvin.

Intertrigo and perleche. Genitocrural intertrigo is common in incontinent patients, especially those who are bedridden. Perleche, frequently complicated by fissuring and secondary infection, is seen in a large proportion of patients who dribble constantly.

Primary irritant dermatitis. The failure to take reasonable care in the use of disinfectants and cleansing agents is responsible for a relatively high incidence of primary irritant dermatitis in those patients who are encouraged to carry out simple domestic duties. Allergic contact dermatitis is said to be uncommon [14], perhaps because exposure to potential sensitizing agents is limited.

Drug reactions. The higher incidence of epilepsy in those with learning difficulties accounts for the relative frequency of reactions to drugs.

Non-specific cutaneous lesions, the prevalence and cause of which are not proved to differ significantly from those of the general population

There is no reliable evidence that the other common dermatoses are either more or less frequent in those with learning difficulties than in normal individuals [17]. Doubt has been cast upon the widely accepted association between epilepsy and acne [19].

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Chapter 62

Disorders of Nails

D.A.R. de Berker, R. Baran & R.P.R. Dawber

Introduction

The epithelial part of the nail apparatus develops *in utero* from the primitive epidermis. In generalized integumentary diseases, such as psoriasis, the nail apparatus, hair follicle and epidermis may all be structurally and functionally affected, presumably because of their common tissue of origin.

The main function of the nail apparatus is to produce a strong, relatively inflexible, keratinous nail plate over the dorsal surface of the end of each digit. The nail plate acts as a protective covering for the fingertip. By exerting counter-pressure over the volar skin and pulp, the flat nail plate allows precision and delicacy when picking up small objects and in many other subtle finger functions [1–3]. Fingernails typically cover approximately one-fifth of the dorsal surface, whereas on the great toe the nail may cover up to 50% of the dorsum of the digit.

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Anatomy and biology of the nail unit

Structure

Gross anatomy [1–5]

The component parts of the nail apparatus are shown diagrammatically in Fig. 62.1. The rectangular nail plate is the largest structure, resting on and firmly attached to the nail bed; it is less adherent proximally, apart from the posterolateral corners. Approximately one-quarter of the nail is covered by the proximal nail fold, and a narrow margin of the sides of the nail plate is often occluded by the lateral nail folds. Underlying the proximal part of the nail is the white lunula (half-moon lunule); this area represents the most distal region of the matrix [6]. It is most prominent on the thumb and great toe and may be partly or completely concealed by the proximal nail fold in other digits. The reason for the white colour is not known [7–9]. The natural shape of the free margin of the nail is the same as the contour of the distal border of the lunula. The nail plate distal to the lunula usually appears pink, due to its translucency, which allows the redness of the vascular nail bed to be seen through it. The proximal nail fold has two epithelial surfaces, dorsal and ventral; at the junction of the two, the cuticle projects distally onto the nail surface. The lateral nail folds are in continuity with the skin on the sides of the digit laterally, and medially they are joined by the nail bed. Some authorities term the lateral

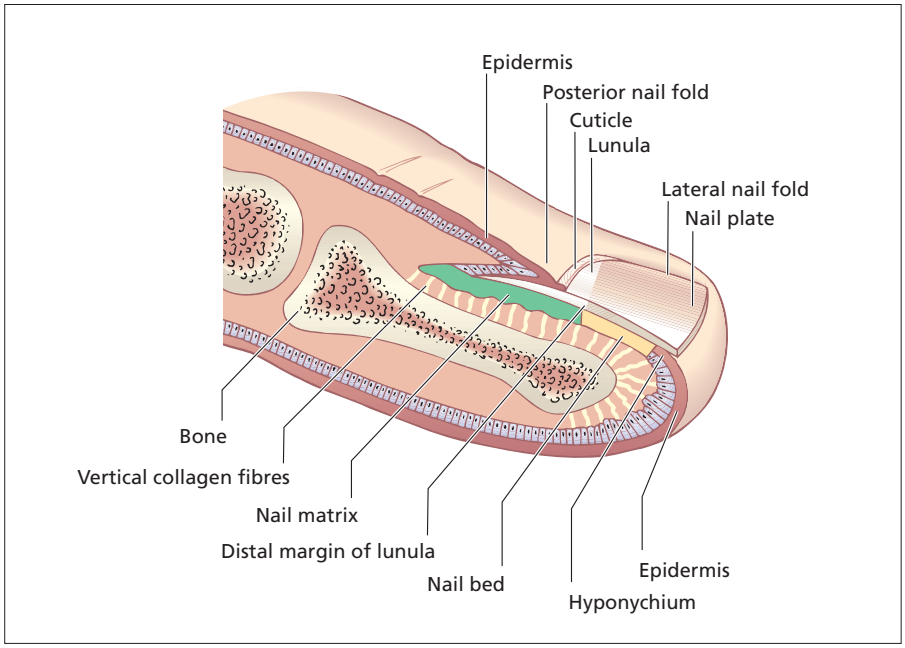

Fig. 62.1 Longitudinal section of a digit showing the dorsal nail apparatus.

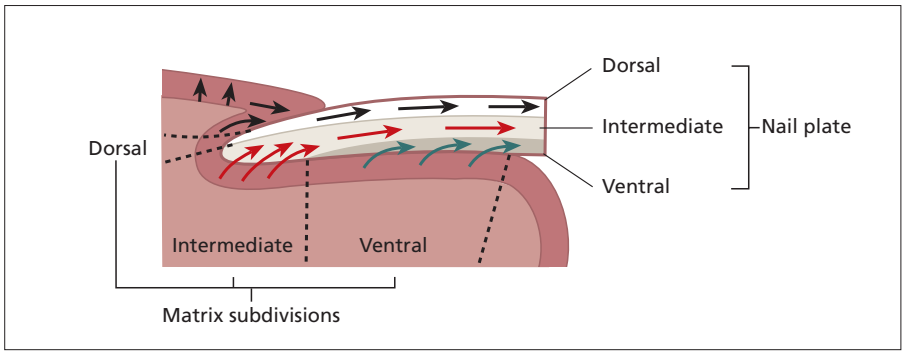

Fig. 62.2 Direction of differentiation and cell movement within the nail apparatus.

nail fold and adjacent tissue lateral to the nail fold the nail wall.

The definition of nail matrix is controversial [10]. There is common acceptance that there is a localized region beneath proximal nail which produces the major part of the normal nail plate. For those who consider this the sole source of nail it is termed simply the matrix, or germinal matrix. However, there is some evidence that other epithelial parts of the nail unit also contribute to the nail plate, and these are then also attributed matrix status. According to the histological criteria of Lewis and Montgomery [4] (Fig. 62.2), matrix can be subdivided into dorsal (ventral aspect of the proximal nail fold), intermediate (germinal matrix or matrix) and ventral (nail bed) sections. The nail bed is also termed the sterile matrix and its role in the production of nail is unclear. Although it appears that the nail plate may thicken by up to 30% as it passes from the distal margin of the lunula to the end of the nail bed [2], this is not associated with an increase in cell numbers and may represent compaction of the nail from distal tip trauma rather than nail bed or nail plate production [11]. The situation may change in disease, where the nail bed changes its histological appearance to gain a granular layer [12] and may contribute a false nail of cornified epithelium to the undersurface of the nail [5].

At the point of separation of the nail plate from the nail bed, the proximal part of the hyponychium may be modified as the *solehorn* [13]. This is a central thickened structure with a dermal core. It is usually found on the toes of elderly people, where there are often associated vascular abnormalities. Beyond the solehorn region, the hyponychium terminates at the distal nail groove; the tip of the digit beyond this ridge assumes the structure of the epidermis elsewhere.

When the attached nail plate is viewed from above, two distinct areas may be visible: the proximal lunula and the larger pink zone. On close examination, two further distal zones can often be identified: the distal yellowish-white margin and immediately proximal to this the onychodermal band [14]. Terry describes this as a barely perceptible,

narrow, transverse band 0.5–1.5 mm wide and more prominent in acrocyanosis. The exact anatomical basis for the onychodermal band is not known, but it appears to have a blood supply different from the main body of the nail bed; if the tip of the finger is pressed firmly, the band and an area just proximal to it blanch, and if the pressure is repeated several times the band reddens. Many changes in colour have been described in the onychodermal band in health and disease [13]. Histologically, it is defined as the most distal attachment of cornified epithelium to the undersurface of the nail. As such, it is structurally significant for the adherence of nail plate to the nail bed. Once breached, as in conditions such as psoriasis, separation of the nail bed from the nail plate can be progressive.

Microscopic anatomy [15]

Nail folds

The proximal nail folds are similar in structure to the adjacent skin but are normally devoid of dermatoglyphic markings and pilosebaceous glands. There is a normal granular layer. From the distal area of the proximal nail folds the cuticle adheres to the upper surface of the nail plate; it is composed of modified stratum corneum and serves to protect the structures at the base of the nail, particularly the germinal matrix, from environmental insults such as irritants, allergens and bacterial and fungal pathogens.

Nail matrix (intermediate matrix)

Nail matrix produces the nail plate in the absence of disease (Fig. 62.2). The basal compartment of the matrix is broader than the same region in normal epithelium or in other parts of the nail unit, such as the nail bed [10]. There is no granular layer, and cells differentiate with the expression of trichocyte 'hard' keratin as they become incorporated into the nail plate, alongside normal epithelial keratins [16,17]. During this process, they may retain their nuclei until more distal in the nail plate. These retained nuclei are called *pertinax bodies*. Apart from this, the detailed cytological changes seen in the matrix epithelium under the electron microscope are essentially the same as in the epidermis [18,19].

The nail matrix contains melanocytes in the lowest three cell layers and these donate pigment to the keratinocytes. The presence of 6.5 melanocytes per millimetre of matrix basement membrane can be used as a guide to a normal matrix melanocyte population [20]. The appearance of melanocytes separate from the basement membrane distinguishes them from those found in the nail folds, which are primarily basal [21]. Matrix melanocytes are further distinguished from those elsewhere by their failure to produce melanin in normal circumstances in white people. This can change, with melanotic streaks presenting in local inflammatory, naevoid or neoplastic disease. In non-white people, brown streaks are common and are almost universal in Afro-Caribbeans by the age of 60 years.

Langerhans' cells are detectable in the matrix by CD1a staining, and the matrix appears to contain basement membrane components indistinguishable from normal skin [22].

Nail bed

Nail bed consists of epidermis with underlying connective tissue closely apposed to the periosteum of the distal phalanx. There is no subcutaneous fat in the nail bed, although scattered dermal fat cells may be visible microscopically.

The nail bed epidermis is usually no more than two or three cells thick, although there may be tongues of epithelium that extend obliquely down. The transitional zone from living keratinocyte to dead ventral nail plate cell is abrupt, occurring in the space of one horizontal cell layer; in this regard it closely resembles the Henle layer of the internal root sheath of the epidermis [23]. Nail bed cells do not have any independent movement, and it is yet to be clearly demonstrated whether they are incorporated into an overlying nail plate as it grows distally [24]. The process of nail bed keratinization has been likened to that seen in rat-tail epidermis, possibly being affected by pressure changes. The loss of the overlying nail results in the development of a granular layer, which is otherwise present only in disease states [12,25,26].

The nail bed dermal collagen is mainly orientated vertically, being directly attached to the phalangeal periosteum and the epidermal basal lamina. Within the connective tissue network lie blood vessels, lymphatics, a fine network of elastic fibres and scattered fat cells; at the distal margin, eccrine sweat glands have been seen [1].

Nail plate

The nail plate comprises three horizontal layers: a thin dorsal lamina, the thicker intermediate lamina and a ventral layer from the nail bed [4]. This is not always apparent with normal light microscopy using routine stains, where the nail demonstrates a transition between flattened cells dorsally and thicker cells on the ventral aspect. Electron microscopy shows squamous cells with tortuous interlocking plasma membranes [18,19]. At high magnification, the contents of each cell show a uniform fine granularity similar to the hair cuticle [23].

The nail plate contains significant amounts of phospholipid, mainly in the dorsal and intermediate layers, which contribute to its flexibility. The detectable free fats and long-chain fatty acids may be of extrinsic origin. For further details of these and other histochemical changes in

the components of the nail apparatus, the reader is referred to more detailed texts [8,27].

The nail plate is rich in calcium, found as the phosphate in hydroxyapatite crystals; it is bound to phospholipids intracellularly [28]. The relevance of other metals (copper, manganese, zinc, iron and others), which are present in smaller amounts, is not known [25]. Calcium is present in a concentration of 0.1% by weight, 10 times greater than its concentration in hair. It is possible that calcium is not an intrinsic part of the nail but is incorporated from extrinsic sources. Calcium does not significantly contribute to the hardness of the nail [6].

Nail keratin

Nail keratin analysis shows essentially the same fractions as in hair:

1 fibrillar, low-sulphur protein;
2 globular, high-sulphur matrix protein;
3 high glycine–tyrosine-rich matrix protein.

Amino acid analysis shows higher cysteine, glutamic acid and serine and less tyrosine in nail compared with hair and wool [17,29].

An alternative classification of keratins defines them as 'soft' epithelial keratins or 'hard' trichocyte keratins. The latter are characteristic of hair and nail differentiation, where their high sulphur content is probably responsible for their rugged physical qualities. This is matched by the resistance of trichocyte keratins to dissolution in strong solvent.

Trichocyte and epithelial keratins are intermediate filaments representing the major cytoskeletal protein of epithelial cells. They share the normal classification into type I or type II based on gene hybridization, which reflects segregation on two-dimensional electrophoresis into acidic and basic proteins. Each acidic keratin is expressed in a tissue with a corresponding basic keratin to form specific heterodimers, which are assembled into higher-order protofibrils and protofilaments.

Keratin distribution in the nail and associated epithelium has been studied in adult [16,30], infant [17] and embryonic [31,32] digits. Immunohistochemistry of the epithelial structures of normal nail demonstrates that the suprabasal keratin pair K1/K10 is found on both aspects of the proximal nail fold and to a lesser degree in the matrix. However, it is absent from the nail bed. This is reversed when there is nail bed disease, such as onychomycosis or psoriasis, where a granular layer develops and K1/K10 becomes expressed at corresponding sites [23]. The nail bed contains keratin synthesized in normal basal layer epithelium, K5/K14, which is also found in nail matrix. An antibody marking the epitope characteristically associated with keratin expressed in the basal layer is found throughout the thickness of the nail bed, but only basally in the matrix [26].

Recent examination of the nail bed using monospecific monoclonal antibodies to the keratin pair K6/K16 demonstrates these proteins in the nail bed but not the germinal matrix [16]. This is paradoxical given our understanding that K6/K16 is characteristic of psoriasis and wound healing, where proliferation is a prominent feature. It has been shown that the nail bed has very low rates of proliferation [10,33], and it may be that K6/K16 more precisely illustrates a loss of differentiation, often associated with proliferation in skin but representing the resting state of nail bed epithelium.

The location of K6/K16 is reflected in the localization of the features of pachyonychia congenita. In this group of autosomal dominant disorders, there is thickening of the nail plate attributed to disease of the nail bed. In some forms of pachyonychia congenita, there is a missense mutation of the initiation peptide of K16 [34].

Trichocyte keratins can also be detected immunohistochemically within the epithelial structures of the nail unit. A monospecific antibody to Ha-1 has been created and characterized on nail, hair and skin. In the nail, it demonstrates a well-demarcated suprabasal region corresponding to the matrix [16]. Proximally, it does not extend onto the ventral aspect of the proximal nail fold, sometimes described as the dorsal matrix. Distally, the keratin expression is limited to a margin taken as corresponding to the lunula. Ha-1 is only one of at least 10 trichocyte keratins, but quantitatively it probably represents a large fraction of nail keratin. According to its distribution it appears to define a matrix consistent with the classic description of the germinal matrix.

Improved understanding of the distribution of keratins in the nail bed and matrix has accompanied further understanding of the molecular basis of pachyonychia congenita, where the various nail manifestations correlate with mutations within the keratin genes and corresponding phenotypes [35].

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Development and comparative anatomy [1–3]

The nail apparatus develops and matures from the primitive epidermis between the ninth and 20th weeks of intrauterine growth. At 20 weeks, the matrix cells show postnatal-type cell division, differentiation and keratinization, and the nail plate begins to form and move distally [4,5]; the nail bed loses its granular layer at this stage [6]. By 36 weeks, the complete nail plate reaches the tip of the digit and is surrounded by prominent lateral nail folds and a well-formed cuticle.

The structure of claws and hooves and their evolutionary relationship to humans has been well reviewed [2,3,7]. In higher primates, nails have evolved with the acquisition of manual dexterity; other mammals do not possess such flattened claws from which nails have evolved. Claws and talons are harder than human nails, probably because of their high content of calcium phosphate as crystalline hydroxyapatite within keratinized cells compared with human nails [8]. The hard 'soft plate' under hooves is produced from an area equivalent to the subungual part of the claw. In some animals, cloven hooves have only developed on the 'digits' that touch the ground; in horses, the single large hoof is produced from the third digit. The keratin biochemistry of the human nail has many similarities to that of the anteater or pangolin [6,9].

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Blood supply [1]

There is a rich arterial blood supply to the nail bed and matrix derived from paired digital arteries, a large palmar and small dorsal digital artery on either side. The palmar arteries are supplied from the large superficial and deep palmar arcades [2]. The main supply passes into the pulp space of the distal phalanx before reaching the dorsum of the digit (Fig. 62.3). Distally, the arteries are extremely tortuous and coiled, which allows them to be distorted without kinking to occlude supply. An accessory supply arises further back on the digit and does not enter the pulp space [3]. There are two main arterial arches (proximal and distal) supplying the nail bed and matrix, formed from anastomoses of the branches of the digital arteries. In the event of damage to the main supply in the pulp space, such as may occur with infection or scleroderma, there may be sufficient blood from the accessory vessels to permit normal growth of the nail.

There is a capillary loop system to the whole of the nail fold but the loops to the roof and matrix are flatter than those below the exposed nail [4]. The loops run longitudinally in the axis of splinter haemorrhages. Those in the nail bed are longest [5]. There are many arteriovenous

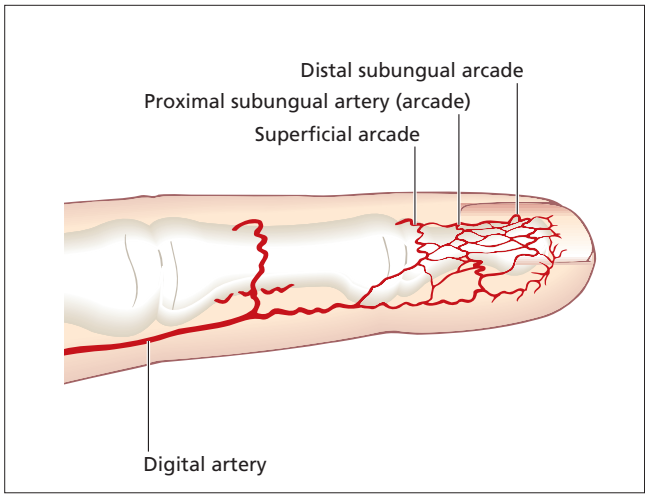

Fig. 62.3 Arterial supply of the distal finger.

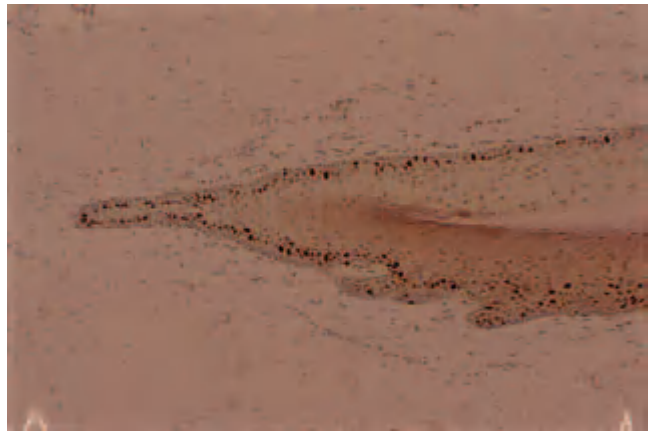

Fig. 62.4 Proliferating epithelial cells of the matrix and ventral aspect of the proximal nail fold, staining with the antibody MIB-1.

anastomoses beneath the nail—glomus bodies—which are concerned with heat regulation. Glomus bodies are important in maintaining acral circulation under cold conditions: arterioles constrict with cold but glomus bodies dilate [6]. These occupy the subdermal tissues and increase in number in a gradient towards the distal nail bed [7].

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Nail growth and morphology

Clinicians used to observing the slow rate of growth of diseased or damaged nails are apt to view the nail apparatus as inert, although it is biochemically and kinetically active throughout life. In this respect, it differs from the hair follicle, which undergoes periods of quiescence as part of the follicular cycle.

Cell kinetics

The kinetic activity of the matrix has been examined using many techniques. These include immunohistochemistry, autoradiography and direct measurement of matrix product (i.e. nail plate) by ultrasound [1], micrometer or histology.

There is a broad basal compartment of proliferating cells in the matrix, which can be detected immunohistochemically with antibodies to proliferating cell nuclear antigen and Ki-67 (Fig. 62.4); both antigens are associated with proliferating cells [2]. The matrix is also the site of maximal inclusion of tritiated thymidine if injected into the peritoneum of squirrel monkeys and followed subsequently by autoradiography [3]. Although there was some inclusion of thymidine into the nail bed, Zaias and Alvarez interpreted the findings as indicating that the nail bed had no role in creation of the nail plate. Norton [4] drew a similar conclusion from work with live human subjects where labelled thymidine and glycine were injected locally to act as markers of proliferating and metabolically active keratinocytes, and both primarily labelled the matrix.

However, the earlier work of Lewis [5] suggested on histological grounds that the nail plate is a trilaminar structure originating from three separate matrix zones: the dorsal matrix (ventral aspect of proximal nail fold), intermediate matrix (germinal matrix) and ventral matrix (nail bed). In support of this, Johnson *et al*. [6,7] demonstrated that 21% of the nail thickness is gained as it passes over the nail bed, implying that the nail bed is generating this fraction of the nail plate. De Berker *et al*. [2] noted that the increase in nail thickness did not coincide with corresponding increases of nail plate cells. This challenges the interpretation that nail thickens over the nail bed through the contribution from underlying structures. An alternative explanation may be appropriate, such as compaction arising through repetitive distal trauma. Others have also debated this issue [8], and although the nail bed may have a significant contribution to make in disease [9], the evidence for its contribution at other times is conflicting.

Table 62.1 Physiological and environmental factors affecting the rate of nail growth.

Faster	Slower
Daytime	Night
Pregnancy [25]	First day of life [14]
Right-hand nails	Left-hand nails [28,29]
Youth, increasing age	Old age [18,23,30]
Fingers	Toes [31]
Summer [18]	Winter or cold environment [32,33]
Middle, ring and index fingers	Thumb and little finger [28,31,34,35]
Male gender	Female gender [27,35]
Minor trauma/nail biting [26,27]	

Table 62.2 Pathological factors affecting the rate of nail growth.

Faster	Slower
Psoriasis [36]	Finger immobilization [41]
Normal nails [23]	
Pitting	
Onycholysis [37]	
Pityriasis rubra pilaris [21,38]	Fever [42]
	Beau's lines [43]
Etretinate, rarely [39]	Methotrexate [24], azathioprine [24], etretinate [39]
Idiopathic onycholysis of women [37]	Denervation [44]
Bullous ichthyosiform erythroderma [13]	Poor nutrition
	Kwashiorkor [45]
Hyperthyroidism [28]	Hypothyroidism [28]
Levodopa [40]	Yellow nail syndrome [13]
Arteriovenous shunts [28]	Relapsing polychondritis [46]

Nail morphology

Why the nail grows flat, rather than as a heaped-up keratinous mass, has generated much thought and discussion [10–14]. Several factors probably combine to produce a relatively flat nail plate: the orientation of the matrix rete pegs and papillae; the direction of cell differentiation [15]; and moulding of the direction of nail growth between the proximal nail fold and distal phalanx [16]. Containment laterally within the lateral nail folds assists this orientation, and the adherent nature of the nail bed is likely to be important. In diseases such as psoriasis, the nail bed can lose its adherent properties, exhibiting onycholysis. In addition, there may be subungual hyperkeratosis. These combined factors make psoriasis the most common pathology in which up-growing nails are seen. Onychogryphosis is characterized by upward growth of thickened nail. In this condition, the nail matrix may become bucket-shaped and the effect of the overlying proximal nail fold is lost.

Linear nail growth [17–19]

Over the last century, many studies have been carried out on the linear growth of the nail plate in health and disease; these have been reviewed [20,21] and are listed in Tables 62.1 and 62.2 [22]. Most of these studies have been performed by observing the distal movement of a reference mark etched on the nail plate over a fixed period of time; this may well correlate with matrix germinative cell kinetics but there is no direct proof that it does. However, studies on nail growth in psoriasis, and its inhibition by cytostatic drugs [23,24], suggest that cell kinetics and linear growth rate do have a direct correlation.

Fingernails grow approximately 1 cm every 3 months and toenails at one-third of this rate.

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Nails in childhood and old age

Childhood [1]

In early childhood, the nail plate is relatively thin and may show temporary koilonychia. This is particularly prominent on the great toes. Under the age of 5 years, nails are also prone to terminal onychoschizia (lamellar splitting). This can be most prominent on the sucked thumb, but is also seen on the toes. Sucking may also lead to paronychia, which can be a troublesome condition in childhood, with pain and nail dystrophy. Ingrowing can also cause pain and may present in different forms. At birth, there is often a degree of distal ingrowing, particularly in the great toe, as the nail has not surmounted the tip of the digit in its development [2]. In a more gross form, this may present as congenital hypertrophic lip of the hallux, where soft-tissue overgrowth may resemble fibrous tumours of the digit before spontaneously disappearing [3]. Painful distal embedding can lead to infection, but as long as the toenail is properly orientated with respect to the underlying phalanx, the condition usually subsides. In one series of seven children, two needed surgery due to painful persistence of the problem [4]. The changes associated with congenital malalignment of the great toe may also subside within 5–10 years in about 50% of children. In this condition, there is deviation of the tip of the great toe nail laterally, rotating on the distal phalanx. The nail is yellow, triangular, thickened and has transverse ridges [5].

Fungal infection is relatively uncommon in children, with a prevalence of 0.44% in one study [6].

Beau's lines can be seen in up to 92% of normal infants between 8 and 9 weeks of age [7]. One child demonstrated a transverse depression through the whole nail thickness on all 20 digits [8]. Normal surface markings of the nail can differ in children from those seen in adults. A herringbone pattern is common and gradually diminishes with time [9], which may reflect a gradual change in the pattern of matrix maturation.

Old age

Many of the changes seen in old age may occur in younger age groups in association with impaired arterial blood supply. Elastic tissue changes diffusely affecting the nail bed epidermis are often seen histologically [10]; these changes may be due to the effects of UV radiation, although it has been stated that the nail plate is an efficient filter of UVB radiation [11]. The whole subungual area in old age may show thickening of blood vessel walls with vascular elastic tissue fragmentation. Pertinax bodies are often seen in the nail plate. Nail growth is inversely proportional to age [12]; related to this slower growth, corneocytes are larger in old age [13].

The nail plate becomes paler, dull and opaque with advancing years, and white nails similar to those seen in cirrhosis, uraemia and hypoalbuminaemia may be seen in normal subjects. Longitudinal ridging is present to some degree in most people after 50 years of age and this may give a 'sausage links' or beaded appearance.

For details of the common traumatic abnormalities and

changes due to inadequate pedicure or neglect, detailed texts should be consulted [1,12].

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Nail signs and systemic disease

It is important for clinicians to understand and accurately describe nail findings if they are to communicate accurately with their colleagues and avoid the vagueness that often surrounds nail pathology. Signs fall into categories of shape, surface and colour.

Abnormalities of shape

Clubbing

In clubbing there is increased transverse and longitudinal nail curvature with hypertrophy of the soft-tissue components of the digit pulp. Hyperplasia of the fibrovascular tissue at the base of the nail allows the nail to be 'rocked' and in causes associated with cardiopulmonary disease there may be local cyanosis.

There are three forms of geometric assessment that can be performed. *Lovibond's angle* is found at the junction between the nail plate and the proximal nail fold, and is normally less than 160°. This is altered to over 180° in clubbing (Fig. 62.5). *Curth's angle* at the distal interphalangeal joint is normally about 180°. This is diminished to less than 160° in clubbing (Fig. 62.6). *Schamroth's window* is seen when the dorsal aspects of two fingers from opposite hands are apposed, revealing a window of light, bordered laterally by the Lovibond angles. As this angle is obliterated in clubbing, the window closes [1]. Assessment of clubbing at the bedside shows poor agreement between examiners [2] in milder cases and there are problems in firm morphometric analysis that do not lend themselves to routine clinical solutions [3].

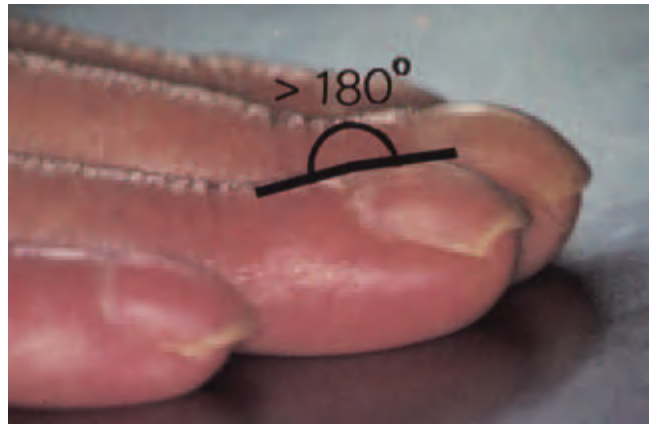

Fig. 62.5 Clubbing: Lovibond's profile sign. The angle is normally less than 160° but exceeds 180° in clubbing.

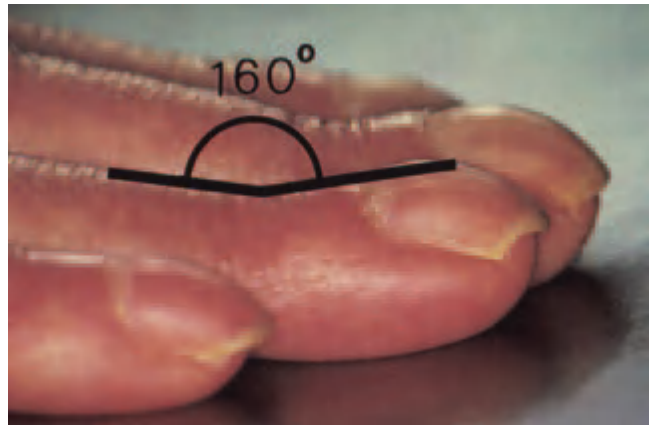

Fig. 62.6 Clubbing: Curth's modified profile sign.

Clubbing appears to be related more to increased blood flow through the vasodilated plexus of nail unit vasculature than to vessel hyperplasia. Altered vagal tone and microvascular infarcts have been implicated [4,5].

Pathological associations of clubbing include inflammatory bowel disease, carcinoma of the bronchus and cirrhosis. In forms associated with bronchiectasis or neoplasm, prominent inflammatory joint signs may also be seen, resulting in hypertrophic pulmonary osteoarthropathy. It has also been reported as a common finding in hemiplegic limbs [6] and can be a presenting feature of a subungual tumour when in a single digit [7]. In some cases of bronchiectasis, a variant of clubbing, *shell nail syndrome*, can be seen. This is distinguished from clubbing by the presence of atrophy of underlying bone and nail bed [8] and may have more in common with yellow nail syndrome than with clubbing.

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Koilonychia

In koilonychia (Greek: *koilos*, hollow; *onyx*, nail), there is reverse curvature in the transverse and longitudinal axes giving a concave dorsal aspect to the nail [1]. Fingers and toes may be affected, with signs most prominent in the thumb or great toe. The nail may be thickened, thinned, softened or unchanged in quality. Koilonychia is common in infancy as a benign feature of the great toenail, although in some infants its persistence may be associated with a deficiency of cysteine-rich keratin [2] in trichothiodystrophy. The most common systemic association is with iron deficiency [3] and haemochromatosis, although the majority of adults with koilonychia demonstrate a familial pattern which may be autosomal dominant [4]. In dermatoses such as psoriasis and dermatophyte infection, nail bed hyperkeratosis may push the nail up distally to produce a spoon-shaped nail. In mechanics, softening of the nail with oil may be a factor [5], and in hairdressers, permanent wave solutions may be causal [6].

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Pincer nail

SYN. INVOLUTED OR TRUMPET NAIL

Pincer nail describes a dystrophy where nail growth is pitched towards the midline, combined with increased transverse curvature. Although the changes in matrix geometry may only be slight, their effect is amplified by longitudinal growth of the nail such that the free edge may take on the shape of the apex of a cone in extreme cases. Pain may arise due to embedding of the pincer nail in the lateral nail folds and nail bed, which becomes most pronounced distally. Thumbs and great toes are the most commonly affected digits, with a gradient of involvement to more lateral digits. It occurs in several patterns [1–3]. It is seen as an isolated familial abnormality that usually becomes manifest in adulthood. It is also seen in association with psoriasis. Isolated digits may be affected as a result of trauma, degenerative joint changes or a subungual tumour that is displacing the nail upwards in the midline. Rarely, single associations with unusual presentations are reported [4–6].

Assessment should include imaging. Treatment is usually by surgery to relieve the pain. In toes it is usually best to perform a lateral ablation of the most embedded margin. This will sometimes lead to a shift of the nail such that the other side no longer embeds. If both sides require ablation, the dimensions of the toenail may mean that it is better to ablate the entire matrix rather than to leave a central zone of nail. The alternative of corrective surgery in toes has only a modest chance of success and ablation may ultimately be required as a definitive procedure. When treating the thumbs or fingers, the chance of success with corrective surgery is higher and the cosmetic and functional handicap of ablation may not be acceptable. Again, a lateral ablation may be adequate, but more complex procedures entail altering the alignment of the matrix [2,7,8] and addressing any midline hypertrophy of the distal phalanx. Some surgeons advocate a combination of reconstruction and ablation [9]. Nail braces rarely produce long-term benefit.

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Macronychia and micronychia

Macronychia and micronychia are conditions where a nail is considered too large or too small in comparison with

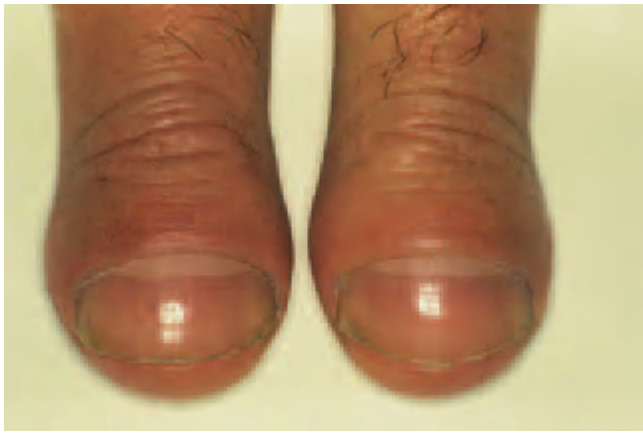

Fig. 62.7 Racket nail associated with clubbing.

other nails on nearby digits. The nail disorder is usually associated with an abnormal digit, arising from underlying bony abnormalities such as local gigantism causing macronychia or megadactyly [1]. This is also the basis of racket thumb (Fig. 62.7), the most common form of benign, dominantly inherited macronychia. Plexiform neurofibromas may cause nail changes, and duplication of the terminal phalanges may cause bifid or small nails [2].

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Anonychia

Anonychia is absence of all or part of one or several nails [1]. The term implies a permanent state, which can be congenital and associated with underlying bony changes [2]. If there is residual nail matrix, there may be some vestigial nail or hyperkeratosis. Temporary anonychia may arise from onychomadesis (nail loss) associated with transient local or systemic upset. If local, the appearance of the nail unit may reflect the precipitating cause.

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Abnormalities of nail attachment

Nail shedding

Nails can be lost through different mechanisms.
1 Complete loss of the nail plate due to proximal nail separation extending distally [1] is called onychomadesis and is a progression of profound Beau's lines. This may reflect local or systemic disease and in the latter may result in temporary loss of all nails.
2 Local dermatoses such as the bullous disorders and paronychia may cause nail loss. Generalized dermatoses may be manifest, for example toxic epidermal necrolysis (TEN) and severe/rapid onset of pustular psoriasis. Scarring of the nail unit is seen in lichen planus and following TEN, which may both provoke nail loss.
3 Trauma is a common cause of recurrent loss and may reflect the nature of the activity, such as football, or some underlying abnormality of footwear [2] or pedal mechanics. It is often associated with subungual haemorrhage [3]. In the long term, athletes often develop thickened dystrophic nails matching a history of recurrent shedding.
4 Temporary loss has also been described due to retinoids [4], and large doses of cloxacillin and cephaloridine during the treatment of two anephric patients [5].
5 Onychoptosis defluvium or alopecia unguium describes atraumatic, familial, non-inflammatory nail loss [6]. It may be periodic and associated with dental amelogenesis imperfecta.
6 Nail shedding can be part of an inherited structural defect, most obviously in epidermolysis bullosa [7], although at times the diagnosis may be occult [8].

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Onycholysis

Onycholysis is the distal and/or lateral separation of the nail from the nail bed [1,2]. Psoriatic onycholysis can be considered the reference point for other forms of onycholysis where it is typically distal, with variable lateral involvement. Areas of separation appear white or yellow due to air beneath the nail and sequestered debris, shed squames and glycoprotein exudate. Isolated islands of onycholysis present as 'oily spots' or 'salmon patches' in the nail bed. At the border of onycholysis, the nail bed is usually reddish-brown, reflecting the underlying psoriatic inflammatory changes. All the common causes are associated with diminished adherence of nail to nail bed

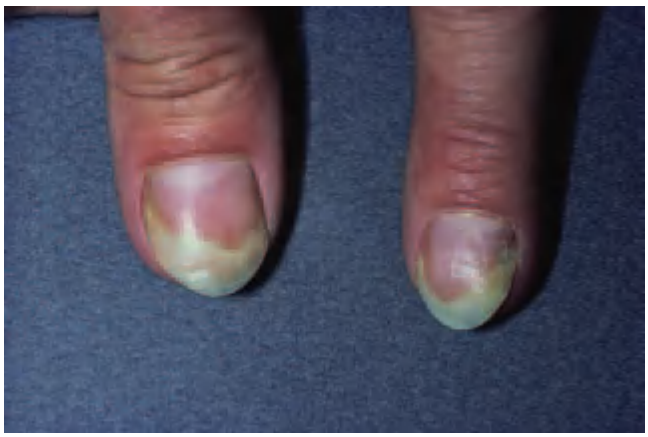

Fig. 62.8 Onycholysis: idiopathic type.

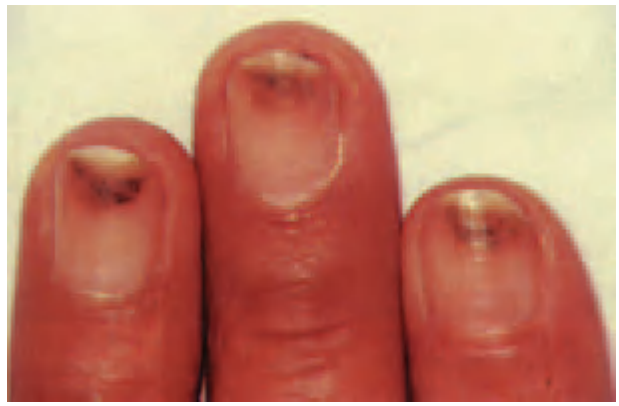

Fig. 62.9 Photo-onycholysis with a uniform pattern of discoloured onycholysis in the midline.

as a primary (idiopathic) or secondary event and include trauma, fungal infection, eczema and photo-onycholysis [3].

Idiopathic onycholysis

This is a painless separation of the nail from its bed, which occurs without apparent cause. Overzealous manicure, frequent wetting and cosmetic 'solvents' may be the cause but may not be admitted by the patient. There may, however, be a minor traumatic element, as the condition occurs rather more often in persons who keep their nails abnormally long. Maceration with water may also be a factor [3]. It must be distinguished from other causes of onycholysis (see below). The affected nails grow very quickly [4].

The condition usually starts at the tip of one or more nails and extends to involve the distal third of the nail bed (Fig. 62.8). Persistent manicure is attempted to remove the debris which accumulates within the onycholytic space, and this can result in a crescentic margin of onycholysis matching the onychocorneal band and appearing similar in all involved digits. Pain occurs only if there is further extension as a result of trauma or if active infection supervenes. More often there is microbial colonization of a mixed nature, including *Candida albicans* and several bacteria, of which *Pseudomonas pyocyanea* is the most common. If the condition persists for several months, the nail bed becomes dark and irregularly thickened.

The condition is mostly seen in women and many cases return to normal after a few months. The longer it lasts, the less likely is the nail to become reattached, due to keratinization of the exposed nail bed.

Treatment [5]. The patient should be advised to cut away as much as possible of the loosened nail and to apply a topical steroid preparation containing antibiotics and nystatin (e.g. Tri-Adcortyl cream) to the nail bed two or three times a day, or to use miconazole/hydrocortisone cream twice a day [1]. Reattachment is slow, and the loosened nail should be recut several times if necessary. The object of treatment is to prevent infection becoming established beneath the loosened nail, because this leads to thickening of the nail bed and prevents reattachment. Some authorities still recommend 4% thymol in chloroform (not available in the USA) as a means of preventing infection and further maceration of the nail bed [6]; however, 2% thymol is often as strong as the patient can tolerate and is usually effective. Where antimicrobial therapy is needed for *Pseudomonas*, gentamicin eye drops can be useful. Drying under the onycholytic nails with a hair dryer has been advocated in order to desiccate the environment in which *Pseudomonas* would otherwise grow.

Secondary onycholysis

There are many other causes of onycholysis, which is one of the commonest nail signs [5,7–9]. Psoriasis, fungal infections and dermatitis are common causes; congenital ectodermal defect is a rare one. Onycholysis occurs in general medical conditions, including impaired peripheral circulation, hypothyroidism [10], hyperthyroidism [11], hyperhidrosis, yellow nail syndrome and shell nail syndrome. Minor trauma is a common cause, and many occupational cases are due to trauma [6,12]. Immersion of the hands in soap and water may be considered traumatic, as also may the use of certain nail cosmetics. It has also been described after the application of 5% 5-fluorouracil to the fingertips [13]. There is a condition of hereditary partial onycholysis associated with hard nails [14]. Photo-onycholysis (Fig. 62.9) may occur during treatment with psoralens, demethylchlortetracycline and doxycycline [15,16], and rarely other antibiotics. This is sometimes associated with cutaneous photosensitivity (see Chapter 24). Drugs such as retinoids [17] and cancer chemotherapy [18] can also be implicated.

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Pterygium [1]

The term 'pterygium' describes the winged appearance achieved when a central fibrotic band divides a nail proximally in two. However, the fibrotic tissue may not always grossly alter the nail and can extend from the lateral nail fold as well as the more typical proximal nail fold. A large pterygium may destroy the whole nail.

An inflammatory destructive process precedes pterygium formation. There is fusion between the nail fold and underlying nail bed. The fibrotic band then obstructs normal nail growth. Superficial abnormal vessels may be seen and there are no skin markings. It most typically develops in trauma or lichen planus and its variants, including idiopathic atrophy of the nail [2] and graft-versus-host disease [3]. It can also occur in leprosy, where it may represent scarring secondary to neuropathic damage and secondary purulent infection [4].

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Ventral pterygium [1]

Ventral pterygium or pterygium inversum unguis [2] occurs on the distal undersurface of the nail, with forward extension of the nail bed epithelium dislocating the hyponychium and obscuring the distal groove. Causes include trauma, systemic sclerosis [2,3], Raynaud's phenomenon, lupus erythematosus, familial [4] and infective [5]. The overlying nail may be normal, but adjacent soft tissues can be painful.

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Subungual hyperkeratosis

Subungual hyperkeratosis entails hyperkeratosis of the nail bed and hyponychium and may occur in a range of conditions, including those where the primary diagnosis is not clear. Nail plate changes are variable, but thickening is common. Dry, white or yellow hyperkeratosis may crumble away from the overhanging nail. Hyperkeratosis may extend onto the digit pulp. Features of onychomycosis and wart virus infection (mainly toes) or psoriasis, pityriasis rubra pilaris and eczema (mainly fingers) may be found elsewhere to determine the aetiology.

The nail bed is an epithelium of low proliferative turnover. Any disease process that affects it is likely to result in an excess of squamous debris. The overlying nail prevents simple loss. The initial outcome is compaction of debris into layers of subungual hyperkeratosis. The only route of loss is by emerging distally with the growing nail.

Focal subungual keratoses are seen with Darier's disease, and keratotic debris beneath the nail in Norwegian (crusted) scabies may contain mites and eggs.

Nail thickening

Isolated thickening of the nail is associated with yellow discoloration as the nail bed vasculature is obscured. Common causes include psoriasis, eczema, trauma and onychomycosis, some of which may be associated with subungual hyperkeratosis. The shape of the nail may alter depending on the underlying cause, such as in yellow nail syndrome, where there is increased curvature in the longitudinal and transverse axes.

In the elderly and yellow nail syndrome, retarded longitudinal growth of the toenail is compensated for by

increased thickness [1]. Yellow nail may also develop where the nail bed produces abnormal nail [2]. Onychogryphosis describes thickened nails, usually the great toenail, which commonly grow upwards in a spiral. It is attributed to chronic distorting trauma and can be treated surgically or by conservative methods. These include trimming with an electric drill, chemical destruction with 40% urea paste, phenolization of the matrix to achieve total ablation (phenol time reduced to 2 min) or carbon dioxide laser.

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Changes in nail surface

Longitudinal grooves

Longitudinal grooves may run all or part of the length of the nail in the longitudinal axis, and need to be distinguished from ridges which are proud of the nail surface [1]. Grooves may be full or partial thickness.

The median canaliform dystrophy of Heller [2] is the most distinctive form [3]. The nail is split, usually in the midline, with a fir-tree-like appearance of ridges angled backwards. The thumbs are most commonly affected and the involvement may be symmetrical. The cuticle may be normal, as distinct from the cuticle in habit tic deformity (washboard nails). After a period of months or years the nails often return to normal, but relapse may occur [4] and a ridge may replace the original defect. Some patients give a definite history of trauma [1], or the disorder can be attributed to oral retinoids [5]. Familial cases have been recorded. Sutton [6] described involvement of a toenail in which a flabby filament of fleshy tissue was present in the canal. Treatment is unnecessary, although the patient should be advised to apply an emollient cream to the nail fold.

Physiological furrows and ridges are accentuated in lichen planus, rheumatoid arthritis, peripheral vascular disease, old age and Darier's disease. *Onychorrhexis* may occur where there are superficial grooves in the nail that lead to a distal split.

Tumours (warts, myxoid cysts) pressing on the matrix, or a proximal nail fold pterygium, may produce a longitudinal groove.

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Transverse grooves and Beau's lines [1]

Transverse grooves may be full or partial thickness through the nail. When they are endogenous they have an arcuate margin matching the lunula. If exogenous, such as those due to manicure, the margin may match the proximal nail fold and the grooves may be multiple as in washboard nails associated with a habit tic [2,3]. When multiple, it may be difficult to distinguish a habit tic from psoriasis. Transverse grooves may occur on isolated diseased digits (trauma, inflammation or neurological events) or may be generalized, reflecting a systemic event such as coronary thrombosis, measles, mumps or pneumonia. If endogenous, they are usually referred to as *Beau's lines* [4,5]. They arise through temporary interference with nail formation and become visible on the nail surface (Fig. 62.10) some weeks after the precipitant. The distance of the groove from the nail fold is related to the time since the onset of growth disturbance. The depth and width of the groove may be related to the severity and duration of disturbance, respectively. In many cases, grooves are seen on all 20 nails but are most prominent on the thumb and great toenail, and are deeper in the midline of the nail. Full-thickness grooves can be associated with distal extension

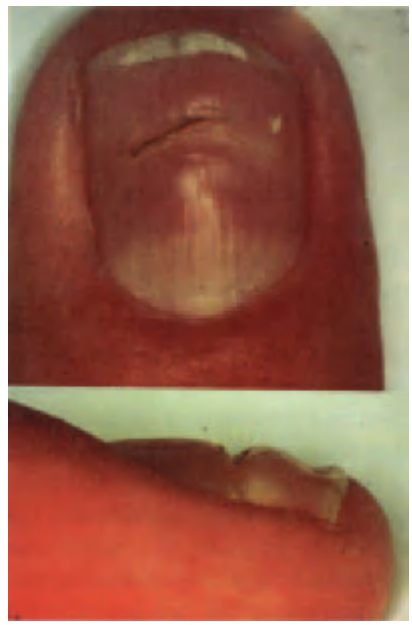

Fig. 62.10 Beau's lines present as transverse grooves in the nail matching the proximal margin of the nail matrix and lunula.

of the plane of separation of the nail plate. This can lead to nail loss, termed *onychomadesis*.

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Pitting

Pitting presents as punctate erosions in the nail surface. Individual pits may be shallow or deep, with a regular or irregular outline. The individual pits of psoriasis are said to be less regular in form and in overall pattern than those of alopecia areata, but this is not always the case. When numerous, they appear randomly distributed upon the nail surface or have a geometric pattern. The latter may cause rippling or create a grid of pits. Extensive pitting combined with other surface irregularities results in the appearance of *trachyonychia*. An isolated large pit may produce a localized full-thickness defect in the nail plate termed *elkonyxis*, which is found in Reiter's disease, psoriasis and following trauma.

Histologically, pits represent foci of parakeratosis, reflecting isolated nail malformation [1].

REFERENCE

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Trachyonychia

Trachyonychia presents as a rough surface affecting all of the nail plate and up to 20 nails (20-nail dystrophy) [1]. The original French term was 'sand-blasted nails', which evokes the main clinical feature of a grey roughened surface (Fig. 62.11). It is mainly associated with alopecia areata [2], psoriasis and lichen planus, although the most common presentation is as an isolated nail abnormality. In the isolated form, histology shows spongiosis and a lymphocytic infiltrate [3] of the nail matrix. It may present as a self-limiting condition in childhood or as a more chronic problem in adulthood. There is some response to potent topical, locally injected and systemic steroids, but this may be temporary. Topical 5-fluorouracil has also been used to good effect [4], although it is important to be wary of associated onycholysis where the diagnosis is psoriasis, as onycholysis can be exacerbated by 5-fluorouracil. Childhood forms normally resolve spontaneously.

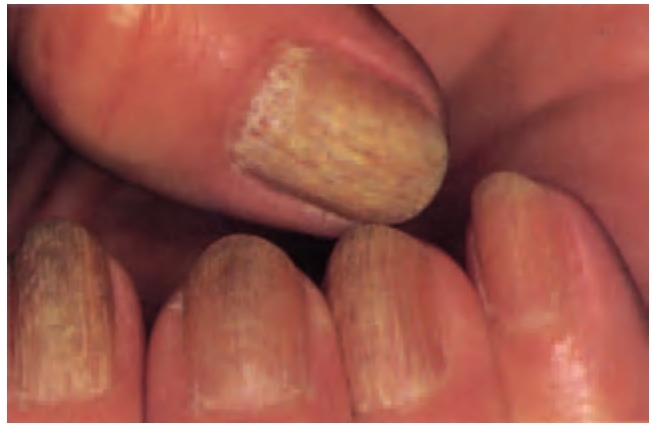

Fig. 62.11 Trachyonychia: roughened surface of up to 20 nails.

REFERENCES

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Onychoschizia

Onychoschizia is also known as lamellar dystrophy and is characterized by transverse splitting into layers at or near the free edge (Fig. 62.12) in fingers and toes, especially in infants [1]. This can result in discoloration because of sequestration of debris between the layers.

Fig. 62.12 Onychoschizia (lamellar splitting).

Variants include splitting at the lateral margins alone and multiple crenellated splits at the free edge. It is seldom associated with any systemic disorder, although it has been reported with polycythaemia [2], human immunodeficiency virus (HIV) infection [3] and glucagonoma [4].

Scanning electron microscopy illustrates the tendency of the lamellar structure of nail to separate after repeated immersion in water [5], although case–control studies show that occupation is not a major determinant of the condition [6]. However, efforts at retaining hydration (gloves, emollient and base coat with nail varnish) may help reverse clinical changes. Biotin has been used as systemic therapy, but the evidence for its efficacy is weak [7].

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Brittle nails

Brittle nails [1–3] are often associated with onychoschizia and frequent immersion of the hands in water, especially if alkaline. Treatment is the same as for onychoschizia. Other common causes are iron deficiency anaemia and impaired peripheral circulation. A rare cause is disturbance of arginine metabolism, when it is also associated with diffuse alopecia [4].

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Beading and ridging

Beading and ridging have been described as occurring more often than normal in patients with rheumatoid arthritis [1]. More recently, increased beading has been examined using optical profilometry in patients taking itraconazole for onychomycosis [2]. Itraconazole is known to increase the rate of nail growth, and it was proposed that beading may be a feature of this increase. As beading is more commonly a feature of old age, when nail growth rate slows down, one would not expect beading to correspond directly to faster linear nail growth. Both beading and ridging are common signs in normal ageing patients and at present their significance remains unclear.

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Changes in colour [1–7]

Alteration in nail colour may occur because of changes affecting the dorsal nail surface, the substance of the nail plate, the undersurface of the nail or the nail bed.

Exogenous pigment

Exogenous pigment on the upper surface is easy to demonstrate by scraping the nail. If the proximal margin of the pigment is an arc matching the proximal nail fold, this is a further clue confirming an exogenous source. Often, the cuticle is less absorbent than nail and there will be a narrow proximal margin of unstained nail. This margin will broaden as the period since exposure lengthens. Hence the 'quitters' nail, which demonstrates the cessation of smoking and nicotine-free fingers for 2 months.

Exogenous pigment on the undersurface of the nail is less easy to demonstrate and may mean that part or all of the nail needs to be avulsed in order to scrape the undersurface and examine it separate from the nail bed. The green pigment of *Pseudomonas* infection [6] in association with onycholysis is a typical situation where partial avulsion is the best way to demonstrate the site of pigmentation, although it may not always be the best treatment.

Nail plate changes

The substance of the nail plate can be changed by the addition of pigment or the alteration of the normal cellular and intercellular organization such that there is loss of normal lucency. Pigment is typically added in the form of melanin produced by matrix melanocytes during nail formation. This produces a brown longitudinal streak the entire length of the nail. In white people this is abnormal and requires thorough assessment and, in some instances, biopsy. In darker-skinned people it is a common variant. The incorporation of heavy metals and some drugs into the nail via the matrix can also produce altered nail plate colour, such as the grey colour associated with silver. The disruption of normal nail plate formation by disease, chemotherapy, poisons or trauma can result in waves of

parakeratotic nail cells or small splits between cells within the nail. Both make the nail less lucent and produce the white marks of true *leukonychia*. Transmission electron microscopy suggests that there is a change in collagen fibre organization, which might provide an intracellular basis for altered diffractive properties. This disruption can be achieved at nail formation or subsequently in the case of fungal nail infection, where discoloration may start distolaterally rather than via the matrix.

Nail bed changes

In addition to generalized vascular changes in the nail bed, there can be localized changes, as seen with nail bed tumours. In the instance of a glomus tumour, this may be the sole method of localization and arises because of the differential blood supply in the tumour and surrounding nail bed. Subungual hyperkeratosis or the incorporation of drugs (antimalarials, phenothiazines) may also change the apparent colour of the nail. Splinter haemorrhages, representing ruptured nail bed vessels, deposit haemoglobin on the undersurface of the nail, which grows out. Cyanosis makes the nail bed blue and carbon monoxide poisoning makes it bright red.

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True leukonychia

White discoloration of the nail attributable to matrix dysfunction occurs in a variety of patterns [1,2]. There is the rare, inherited form called total leukonychia, in which all nails are milky porcelain white [3]. In subtotal leukonychia, the proximal two-thirds are white, becoming pink distally. This is attributed to a delay in keratin maturation, and the nail may still appear white at the distal overhang (Fig. 62.13).

Transverse leukonychia (Mees' line) reflects a systemic disorder, such as chemotherapy or poisoning [4], or systemic infection [5] affecting matrix function. The 1–2-mm-wide transverse band is in the arcuate form of the lunula and is analogous to a Beau's line, with which it is occasionally found. Punctate leukonychia comprises white spots of 1–3 mm diameter attributed to minor matrix trauma (e.g. manicure) and is also seen in alopecia areata.

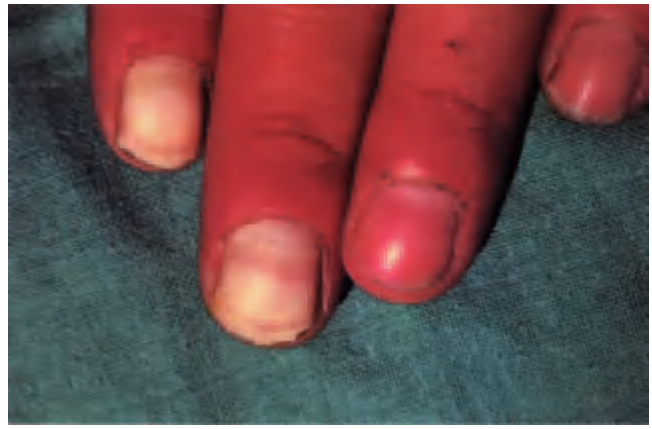

Fig. 62.13 True leukonychia with white nail in the distal free edge.

The pattern and number of spots may change as the nail grows. With longitudinal leukonychia, there is a parakeratotic focus in the matrix, sometimes attributable to Darier's disease or a small tumour.

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Apparent leukonychia

In apparent leukonychia, changes in the nail bed are responsible for the white appearance [1,2]. Nail bed pallor may be a non-specific sign of anaemia, oedema or vascular impairment. It may occur in particular patterns which have become associated with certain conditions.

Terry's nail

This is white proximally and normal distally and is attributed to cirrhosis, congestive cardiac failure and adult-onset diabetes mellitus [3]. Nail bed biopsy reveals only mild changes of increased vascularity. This is similar to *half-and-half nails*, where there is a proximal white zone and distal (20–60%) brownish sharp demarcation, the histology of which suggests an increase of vessel wall thickness and melanin deposition. It is seen in 9–50% of patients with chronic renal failure and after chemotherapy. It is unclear whether the variant *Neapolitan nails*, where there are bands of white, brown and red, is a version of half-and-half or Terry's nails, or a feature of old age.

Muehrcke's paired white bands

These bands are parallel to the lunula in the nail bed, with pink between two white lines. They are commonly associated with hypoalbuminaemia, the correction of which by albumin infusion can reverse the sign. They have also recently been reported following placement of a left ventricular assist device in a patient with congestive heart failure [4].

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Colour changes due to drugs [1]

There are a number of colour changes due to drugs. Yellowing of the nail is a rare occurrence in prolonged tetracycline therapy, which can also produce a pattern of dark distal photo-onycholysis associated with photosensitivity [2]. The whole nail is affected and returns to normal when the drug is discontinued. A similar effect, but of a bluish colour, is seen with mepacrine [3], the nails fluorescing yellow–green or white when viewed under Wood's light. Normal nails show slight fluorescence of violet–blue colour.

Chloroquine may produce blue-black pigmentation of the nail bed [4]. Other antimalarials may produce longitudinal or vertical bands of pigmentation on the nail bed or in the nail [5,6]. A fixed drug eruption of the nail bed can be dark blue [7]. Argyria may discolour the nails slate blue [8], and inorganic arsenic may produce longitudinal bands of pigment or transverse white stripes (*Mees' stripes*) across the nail.

Hyperpigmentation due to increased melanin in the nail and nail bed has been noted in children after 6 weeks of treatment with doxorubicin (adriamycin) [9,10]. Other similar cytotoxic drugs may cause a variety of patterns of increased pigmentation [1]. However, in acquired immune deficiency syndrome (AIDS), longitudinal melanonychia may be seen in untreated cases [11,12] as well as in those receiving zidovudine [9,13].

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Yellow nail syndrome

The nails in yellow nail syndrome are yellow due to thickening, sometimes with a tinge of green possibly due to secondary infection. The lunula is obscured and there is increased transverse and longitudinal curvature and loss of cuticle (Fig. 62.14). Occasionally, there is chronic paronychia with onycholysis and transverse ridging [1]. The condition usually presents in adults, but may occur as early as the age of 8 years [2]. Some of the clinical features may overlap with lichen planus [3,4], although the latter does not have the other systemic features normally seen in this syndrome. The features are usually accompanied by lymphoedema [5] at one or more sites and respiratory or nasal sinus disease. The nails grow at a greatly reduced rate: 0.1–0.25 mm/week for fingernails compared with the lowest normal rate of 0.5 mm/week. All 20 nails may be involved, although often a few are spared. Histologically, in the nail bed and matrix, dense fibrous tissue is found replacing subungual stroma, with numerous ectatic endothelium-lined vessels [6]. A foreign-body reaction has been noted [7]. It has been suggested that obstruction of lymphatics by this dense stroma leads to the abnormal lymphatic function found in the affected digits in some [8] but not all [9] cases.

Fig. 62.14 Yellow nail syndrome.

The oedema most frequently affects the legs, and may not be seen for some months after the nail change has been noted. Less often it affects the face or hands and occasionally it is universal. Recurrent pleural effusions have been noted in a few cases [10,11]. Chronic bronchitis and bronchiectasis may also occur [12]. The oedema has been shown to be due to abnormalities of the lymphatics, either atresia or, in some cases, varicosity [11]. As other cases seem to have normal lymphatics, it is possible that a functional rather than an anatomical defect may be present [13], or perhaps only the smallest lymph vessels are defective. Although the nail changes may draw attention to the underlying lymphatic abnormality, they are found only in a minority of patients with congenital abnormality of the lymphatics. The condition may be associated with an increased incidence of malignant neoplasms [11,14,15]. Other associations include D-penicillamine therapy [5] and nephrotic syndrome [16]. In hypothyroidism and AIDS [17] there may be yellow nails, but it is debatable whether these represent yellow nail syndrome or simply the discoloration of nail associated with retarded growth [18].

Although the nail changes, once established, are usually permanent, complete reversion to normal may occur at times. Attempted treatments include oral [19] and topical [20] vitamin E, oral zinc [21] and treatment of chronic infection at other sites [22]. There is debate as to whether itraconazole is of value as treatment. The drug has been demonstrated to increase the rate of longitudinal growth, but an open trial in eight patients demonstrated that half gained no benefit with respect to nail changes [23]. It is reported that results are better when itraconazole or fluconazole are combined with oral vitamin E [24].

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Red lunulae

Erythema of all or part of the lunula may affect all digits, but most prominently the thumb. Erythema is less intense in the distal lunula, where it can merge with the nail bed or be demarcated by a pale line, and can be obliterated by pressure on the nail plate. The appearance can fade over a few days. A single report of histological features failed to reveal vascular or epidermal changes [1]. Dotted red lunulae have been reported in psoriasis and alopecia areata, but otherwise the list of associations is so broad that it is unconvincing [2].

The exception to this is a red lunula seen in a single digit. In this setting, it often indicates a local disturbance of vascular flow, which is most likely to be a benign tumour. Glomus tumours and subungual myxoid cysts are the most common [3] and the colour may vary between blue and red.

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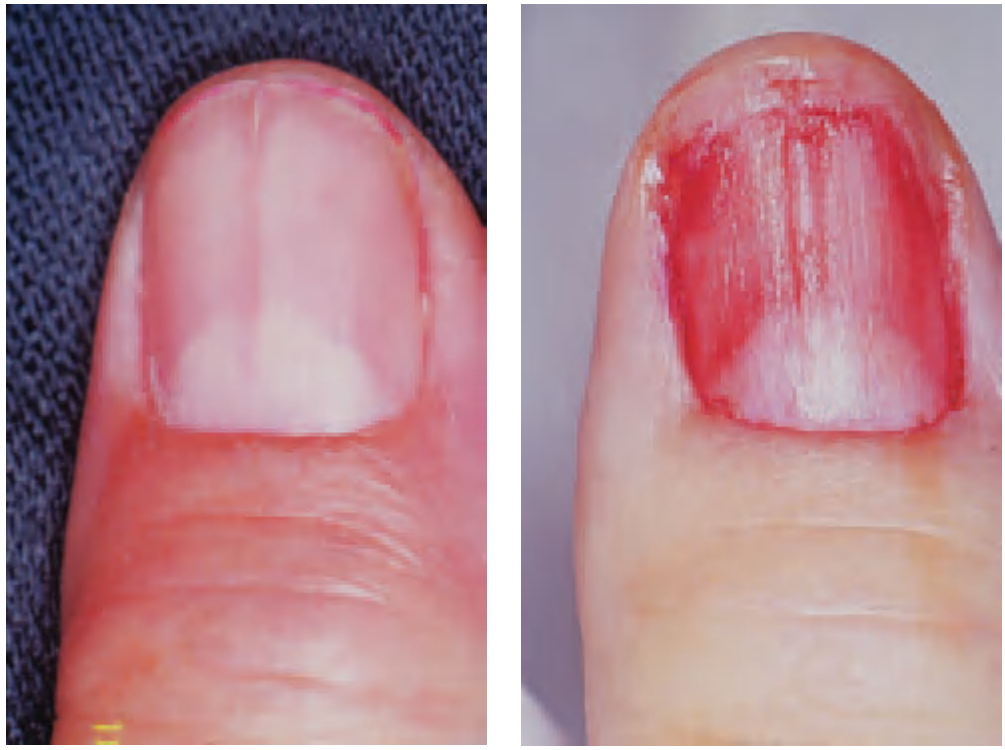
Longitudinal erythronychia (Fig. 62.15)

A longitudinal red streak in the nail can have several causes. All will have a corresponding band of thinned nail plate as part of the defect. The effect of this is a strip where the nail bed is less compressed by the overlying nail so that blood pools and is more apparent. Equally, the colour is more easily seen because the nail is thinner in this line. Splinter haemorrhages may lie longitudinally within the erythronychia.



(a) (b)

Fig. 62.15 (a) Longitudinal erythronychia. (b) The longitudinal ridge in the nail bed corresponds to the groove on the undersurface of the nail plate.

A strip of thinned nail arises because of focal reduction of matrix function. This can be due to direct matrix disease, such as an epidermal pathology, or as a result of pressure on the matrix with secondary loss of function. This second category contains the full range of dermal tumours as well as tumours of bone and cartilage that arise from the distal phalanx.

Matrix epidermal disease covers a spectrum of pathologies. One group of pathologies has histological features of acantholytic dyskeratosis and/or multinucleate giant cells [1]. The original model for this clinical presentation and histology is Darier's disease, where the thin longitudinal red streak may terminate at the free edge with a split and small subungual keratosis [2]. Acantholytic dyskeratotic naevus and warty subungual dyskeratoma [3] may both represent localized forms of Darier's disease. Acrokeratosis verruciformis of Hopf has a greater focus on nail fold disease, but also demonstrates longitudinal erythronychia and both clinical and pathological overlap with Darier's disease.

Baran has coined the term 'onychopapilloma' to describe the isolated benign warty distal nail bed lesions found in association with longitudinal erythronychia where the diagnosis lies outside those described above [4]. The papilloma is a secondary element, given that it is found distally in the nail bed while the cause lies proximally within the matrix. However, there is a category of this disease where the matrix disease remains unclear and the distal papilloma represents the identifiable entity. At other times, despite a similar clinical presentation with erythronychia and splinter haemorrhages, the matrix pathology may reveal a specific alternative diagnosis such as Bowen's disease [4] or basal cell carcinoma [5]. This means that an isolated longitudinal erythronychia needs careful assessment, and biopsy may be warranted if there is evolution.

Not all causes of longitudinal erythronychia conform to these rules. This is particularly the case where there are multiple red streaks associated with a dermatosis and additional nail changes. It can be a feature of lichenoid diseases of the nail unit, discoid lupus erythematosus, psoriasis, Langerhans' cell histiocytosis and a number of other diseases where there is patchy nail atrophy.

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Splinter haemorrhages

Splinter haemorrhages represent longitudinal haemorrhages in the nail bed conforming to the pattern of subungual vessels [1–4]. They are most frequently seen in the distal nail bed and on the fingers of the dominant hand, reflecting trauma as the cause. In dermatological practice, they are often found in association with psoriasis, dermatitis and fungal infection of the nails. As they occur under so many conditions, their importance as a sign of disease is often exaggerated. Focal pathology may also represent a cause, as in longitudinal erythronychia and onychomatricoma (see pp. 62.19 and 62.35).

Large numbers of proximal haemorrhages with no obvious traumatic origin may indicate a systemic cause [5], such as bacterial endocarditis or antiphospholipid syndrome [6]. Unilateral splinter haemorrhages may arise after arterial catheterization on the involved side. Examination under oil with a dermatoscope may reveal greater detail.

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Developmental abnormalities of the nails [1,2]

Anonychia

Absence of the nails from birth is a rare congenital anomaly. It may occur as an isolated sign or be accompanied by other defects of the digits and other structures. Littman and Levin [3] described a girl with seven nails missing, and reported that her brother was similarly affected; it was suggested that this was a recessive trait. The mode of inheritance of most of these disorders has not yet been established with certainty. The condition described as anonychia with ectrodactylia [4] has been investigated more fully, however, and has been shown to be inherited as a dominant trait without sex linkage. In this condition, there is usually complete absence of the nails on the index and middle fingers, and when there is any nail on the thumb it is often present on the proximal lateral corners of the nail fold. On the ring fingers, the radial half of the nail is often absent, and the nail bed is also missing. In a minority of affected individuals there are striking and bizarre defects of the digits, sometimes restricted to one hand or foot. The defects usually take the form of absence of one or more digits. Two sisters in a sibship of five, whose parents were first cousins, are recorded as having rudimentary nails associated with congenital deafness. The parents showed neither abnormality [5]. Bart *et al*. [6] described a family with congenital absence of areas of skin, blistering of skin and mucous membranes, and absence or deformity of the nails, inherited as an autosomal dominant trait. It is now classified as a subtype of dominantly inherited dystrophic epidermolysis bullosa, with the responsible gene mapped to chromosome 3p [7]. Verbov [8] described a case with bizarre flexural pigmentation and anonychia, thought to be an autosomal dominant condition.

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Nail–patella syndrome

This uncommon condition is of special interest because it involves abnormalities of ectodermal and mesodermal structure. It is inherited as an autosomal dominant trait. The disorder is caused by mutations in the LIM-homeodomain transcription factor β1 protein (LMX1B). This protein plays an important role in dorsoventral limb patterning during embryogenesis [1]. Gradients of expression of the protein determine the dominance of dorsal or ventral axon growth with concomitant trophic effects on mesoderm and ectoderm [2]. The gene maps to chromosome 9q34.1, with affected families showing a wide range of deletions and mutations [3]. In a typical case, the nails are grossly defective, being only one-third or half the normal size and never reaching the free edge of the finger [4]. In other cases, the thumbnails alone may be defective or only the ulnar half of each may be missing [5]. In every case, the thumbnails are most affected [6] and the remaining nails, if involved, are progressively less damaged from index to little finger. The lunulae may be triangular, with a distal peak (Fig. 62.16) in the midline [7]. Even when the

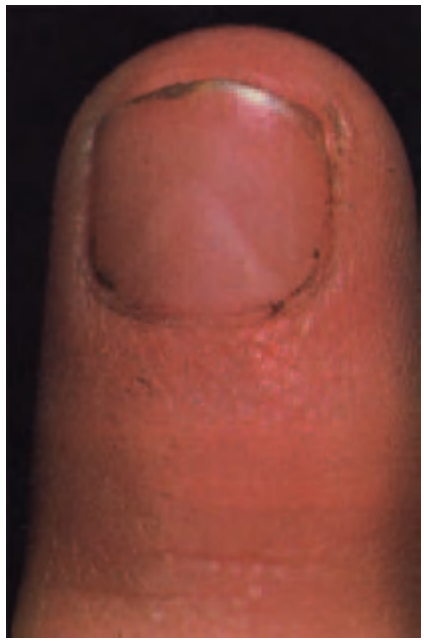

Fig. 62.16 Nail–patella syndrome with triangular lunula.

nail is completely missing, the nail bed is present. In addition to the nail changes, the patellae are smaller than normal and may be rudimentary, so that the knees are unstable. There are also bony spines arising from the posterior aspect of the iliac bones, visible on X-ray examination.

Other recorded features include hyperextension of the joints, skin laxity, hyperhidrosis [8] and renal abnormalities [9,10], and open angle glaucoma. LMX1B is known to influence transcription of genes affecting collagen IV in the glomerular basement membrane [11].

In 1965 there were 255 patients with this syndrome known to be living in the UK, and the prevalence is estimated at 1 per 22 million. The mutation rate is estimated at 1 per 1.9 million alleles per generation [12].

The condition must be distinguished from congenital ectodermal defects and pachyonychia congenita.

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Congenital onychodysplasia of the index fingers [1,2]

SYN. ISO KIKUCHI SYNDROME

In this condition, the nail of the index finger is absent, small or represented by two nails of unequal size. There may be a family history suggestive of autosomal dominant inheritance, although there is frequently no clear genetic pattern, and involvement of other digits has been reported [1,3,4]. Underlying changes in the distal phalanx can usually be demonstrated by lateral radiography, where bifurcation of the distal phalanx is the norm [4]. Syndactyly is an associated hand anomaly in some cases [2].

Variants include a similar form of onychodysplasia affecting other digits, including toes [5].

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Pachyonychia congenita (Fig. 62.17)

Pachyonychia congenita (PC) is a rare genodermatosis in which hypertrophy of the nails occurs, in some cases associated with nail bed and hyponychial hyperkeratosis [1,2]. Although Feinstein provides an excellent overview of the features, the disease divides best into two variants when the phenotype is interpreted in the light of the genotype. Autosomal dominant inheritance is the rule, although Haber and Rose [3] described cases transmitted in an autosomal recessive form.

The two variants of PC arise through mutations affecting the genes encoding keratins 6a and 16 in PC-1 [4,5] and 6b and 17 in PC-2 [6,7].

PC-1 (Jadassohn–Lewandosky type). The nails are normal at birth but within months they become discoloured and progressively thicken, more so on the hands than feet.

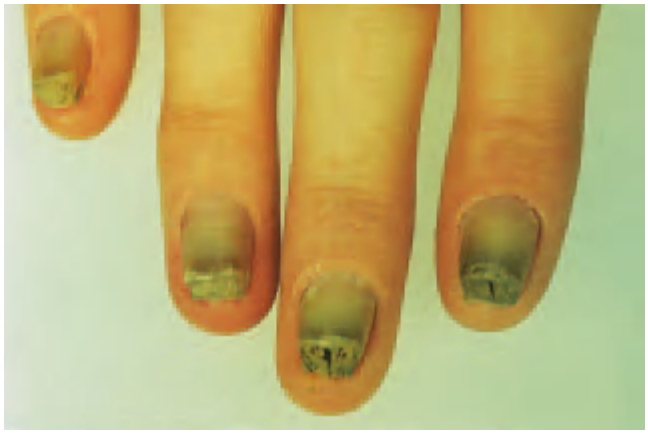

Fig. 62.17 Pachyonychia congenita.

Typical associated findings include palmar and plantar hyperkeratosis and warty skin lesions at various sites: knees, elbows, buttocks, legs, ankles and popliteal region. Acral bullae may be crippling and hyperhidrosis may be severe. Mouth and corneal dyskeratosis are less common findings.

PC-2 (Jackson–Lawler type). In this type, with less severe nail thickening and keratoses than type 1, many associations have been described: teeth may be present at birth; multiple epidermal cysts; sebocystomatosis; dry, lustreless and kinky scalp hair; eyebrows that stand straight out; and hamartomas.

The thickened nails can be treated surgically in some instances [8,9]. This is most likely to be warranted in PC-1. The localization of the four implicated keratins to the nail bed underlines that this is the main site of pathology [10]. Affected nails viewed end-on can appear almost normal, but with a dense wedge of subungual keratin, representing the focus of nail bed disease.

A range of associated features have been reported, including amyloidosis in one pedigree [11] and a case where PC coincided with tuberous sclerosis [12].

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Infections of the nail and nail folds

Fungal nail infections

See Chapter 31.

Paronychia

Bacterial paronychia

Acute paronychia is a common complaint and is usually due to staphylococcal infection. It may result from local injuries, splits, splinters or nail biting, or there may be no preceding injury. It also occurs frequently as a complication of chronic paronychia, when other organisms may be involved, including streptococci, *Pseudomonas pyocyanea*, coliform organisms and *Proteus vulgaris*.

The condition presents as a painful swelling of the nail fold. If superficial it may point close to the nail and can easily be drained by incision with a size 11 scalpel, without anaesthesia [1]. Deeper lesions are best treated by antibiotics initially, but if they do not improve within 2 days, incision under local anaesthesia is required, particularly in childhood. A broad-spectrum antibiotic is preferred because it is unlikely that the organisms can be identified in advance. Some authorities recommend removing the proximal one-third of the nail plate without initial incisional drainage. This gives more rapid relief and more sustained drainage. There may be a place for treatment with topical steroid at the same time as antibiotic therapy [2].

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Chronic paronychia

This is one of the most common specific nail complaints met within dermatological practice. It ranks in importance

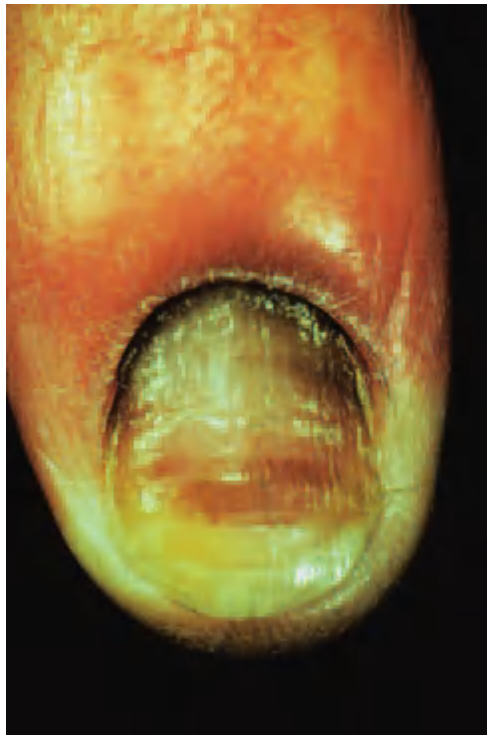

Fig. 62.18 Chronic paronychia with nail plate discoloration due to *Pseudomonas pyocyanea*.

with fungal infection and psoriasis as a cause of nail disease, but presents more commonly and is often misdiagnosed and mistreated. It is an inflammatory dermatosis of the nail folds, with secondary effects on the nail matrix, nail growth and soft-tissue attachments. It may be associated with infection on the background of the dermatosis. The dermatosis may be directly due to an irritant associated with wet work or caustic materials. Alternatively, it may be on the background of atopy or psoriasis, where minor provocation can result in active disease.

Wet cold hands are predisposed to chronic paronychia [1,2]. Wet foods are a combined source of factors, where the food may be an irritant [3]. It is predominantly a disease of domestic workers, bar staff, canteen workers and fishmongers [4]. The majority of cases are in patients between 30 and 60 years of age [1], although chronic paronychia is also seen in children, especially as a result of finger- or thumb-sucking [5].

Any finger may be involved, most often the index and middle fingers of the right hand and the middle finger of the left [4]. These fingers may be more subject to minor trauma than the remainder. The condition begins as a slight swelling at the base of one or more nails (Fig. 62.18), which is tender but much less so than in acute paronychia. The cuticle is soon lost and pus may form below the nail fold. Inflammation adjacent to the matrix disturbs nail growth, resulting in irregular transverse ridges and other surface irregularities, which may be combined with discoloration (Fig. 62.18). There is some evidence that the darkening is due to the pigment from *Pseudomonas* infection of the nail [6]. In long-standing cases, the size of the nail may be reduced, and this reduction is exaggerated by bolstering of the fold all around the nail. Most of the nail deformity is due to the inflammation interfering with the formation of the nail, but a true *Candida* infection of the nail plate is occasionally seen.

There is a complex relationship with *Candida*, usually *Candida albicans* [7], which may be identified by swabs or scraping. Stone and Mullins [8] showed that chronic paronychia can be produced by non-viable *C. albicans* introduced into a relatively sterile nail fold. Much of the chronic inflammation seen in this disorder probably arises from an irritant reaction to material sequestered beneath the proximal nail fold. The loss of the cuticle means that detergent and other solvents may gain access to this tight space and act like a prolonged irritant patch test. This chronic non-infective inflammatory component is why topical steroids are useful in addition to antimicrobials as part of the treatment [9]. Acute exacerbations occur from time to time and are due to secondary bacterial infection. Various organisms may be found, including *Staphylococcus aureus* or *albus*, *Proteus vulgaris*, *Escherichia coli* and *Pseudomonas pyocyanea*. Barlow *et al*. [9] consider that *S. aureus* plays a more active part in initiating the process by penetrating the keratin at the base of the nail and opening up the nail fold. The role of *S. aureus* as a superantigen may also be relevant. Ingested allergens may also play a part [10].

Pemphigus [11] and squamous cell carcinoma [12] can present as chronic paronychia. The latter usually involves a single digit, and underlines the need for biopsy in isolated periungual conditions where the diagnosis is unclear. Cancer chemotherapy, antiretroviral medication and retinoids can provoke acute paronychia with features of pyogenic granuloma which may become chronic.

Treatment. Treatment is a combination of avoidance of precipitants, hand care and medication. Perhaps the most important part of the treatment, but the one most difficult to achieve, is to keep the hands dry. For all wet work the patients should be advised to wear cotton gloves under rubber gloves and avoid manicure of the proximal nail folds. Covering the affected fingers with porous surgical tape may afford some protection, but normal occlusion aggravates the problem. General hand care with emollient and protection during rough work is useful. If this stage of the therapy is not adequately pursued, the condition is likely to fail to settle whatever medical treatment is provided.

Topical therapy requires a combination of steroid [13] and antimicrobial. A potent steroid may be used for short periods when there is adequate antimicrobial cover. Injected triamcinolone (2.5 mg/mL) is useful in some

instances. Topical imidazoles are usually sufficient to treat *Candida* and may provide a modest therapy against some bacteria. More potent topical antibacterials may be needed. Barlow *et al*. [9] suggest using gentamicin ointment during the day and nystatin ointment at night. When features are marked, oral antibiotics appropriate for *S. aureus* should be used. Because of the 'mixed' aetiology of the inflammation, many clinicians use antiseptic or antibiotic/anticandida/steroid creams in the chronic phase.

Incision is not indicated unless the condition enters an acute tender purulent phase, where removal of the proximal third of the nail may help. Attempting to clean out the nail fold with a sharpened orange stick is not recommended. If there is obvious candidal infection elsewhere, or *Candida* onychomycosis, this must also be treated. Surgical removal of the proximal nail fold and adjacent part of the lateral nail folds may cure recalcitrant cases [14].

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Pseudomonas infection

This is almost always a complication of onycholysis or chronic paronychia and is usually restricted to one or two nails (see Fig. 62.18). The nail plate has a characteristic bluish-black or green colour [1–3] and smells infected. This colour is due to accumulation of debris beneath the nail and the pigment pyocyanin adhering to the undersurface of the nail plate. Pigment may remain after the organism has been removed. In some cases, the nail plate appears to be invaded by the bacillus [2]. Subjects with nail extensions and nail wraps are susceptible to *Pseudomonas* colonization beneath the extensions. This has been documented as a risk factor for passing infection to patients in the medical setting [4]. Treatment [5] is as described for onycholysis or paronychia, whichever appears to be the prominent predisposing state. In addition, it is possible to treat with gentamicin or sulfacetamide (sulphacetamide) eye drops to eradicate the colonization where onycholysis is resistant to therapy.

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Herpetic paronychia [1,2]

SYN. HERPETIC WHITLOW

This uncommon condition is due to primary inoculation of the herpes simplex virus and presents as single or grouped blisters close to the nail; it may give a honeycomb appearance. Clear at first, the blisters soon become purulent and may break and be replaced by crusts. It is usually very painful and takes about 3 weeks to resolve, with pain settling in half that time. Lymphangitis sometimes occurs and may precede vesiculation. Diagnosis may be established by recovering the virus from a recent blister and by cytological examination of the blister floor. Contact cases may occur.

Treatment probably does little to shorten the course of the disorder, but cleaning with 1/6000 potassium permanganate followed by application of a bland cream is recommended. Relapse may occur as with other primary herpetic infections. The value of thymidine analogues, such as 5% topical idoxuridine and oral or topical aciclovir, remains unproven at this site; if the lesion is seen within 2 days of onset, topical aciclovir may inhibit progression.

Numbness of the finger has been reported following infection [1] and persistent lymphoedema may occur. Persistent cases may have an atypical presentation in patients with HIV infection [3].

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HIV infection

The most common nail changes in individuals with HIV infection are clubbing, transverse lines, onychoschizia, leukonychia and longitudinal melanonychia [1]. In addition, there is a lower threshold for infection with dermatophytes, yeasts and herpesvirus [1]. The patterns of infection may alter, such that proximal subungual white fungal infection is said to be a pointer to immunodeficiency and particularly HIV [2]. The nail folds may be red in the absence of infection [3] or be provoked into an appearance of pyogenic granuloma by retroviral therapy [4]. The nail can also manifest various patterns of melanonychia, which is usually ascribed to zidovudine therapy [5] but has also been attributed to hydroxycarbamide (hydroxyurea) [6].

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Dermatoses affecting the nails

Psoriasis

Psoriasis is probably the most common disorder affecting fingernails, with consequent dystrophy. Between 1.5 and 3% of the population have psoriasis, and up to 50% of psoriatics have nail involvement [1]. Over a lifetime, this may cumulatively increase to 80–90% [2]. In children, nail involvement ranges from 7% [3] to 39% [4], and pitting has been observed in the first week of life in the offspring of a mother severely affected with psoriasis [5]. Psoriatic nail changes are prominent in the childhood nail disease of parakeratosis pustulosa. Approximately one-third of these children will develop the manifest diagnosis of psoriasis in time, a smaller fraction will have variants of eczema and half of the total will get better [6]. De Jong *et al*. [7] reported that 93% of those with nail psoriasis considered it a significant cosmetic handicap, 58% found that it interfered with their job and 52% described pain as a symptom.

Clinical features. In order of reducing frequency, nail signs of psoriasis include pits, onycholysis, subungual hyperkeratosis, nail plate discoloration, uneven nail surface, splinter haemorrhages, acute and chronic paronychia, and transverse midline depressions in the thumbnails.

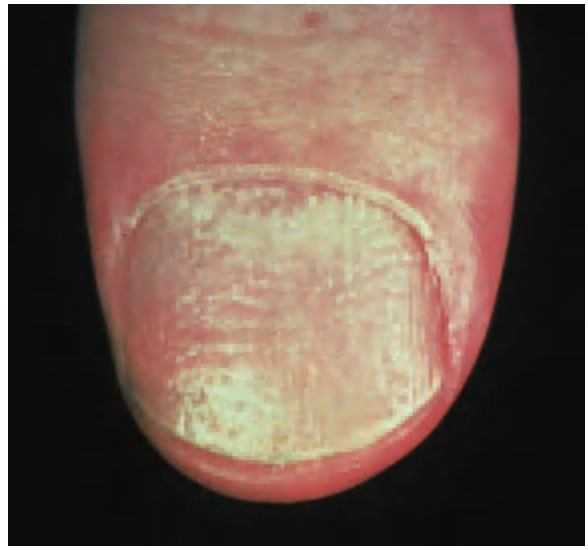

Fig. 62.19 Psoriasis: diffuse pitting.

Pits. Pits more commonly affect fingers than toes (Fig. 62.19). They represent punctate surface depressions arising from proximal matrix disease (Table 62.3). Zaias [1,8] has demonstrated small columns of pathological parakeratotic nail falling off the upper surface of the nail plate to produce a pit. Some authorities advocate nail plate histology as a means of diagnosing nail psoriasis [9]. This can be useful for exclusion of fungal infection, although the specificity of nail plate changes in psoriasis is yet to be established. The origin of pits means that they can be influenced by disease in the proximal nail fold and it is thought that injection of triamcinolone into the nail fold alone can suppress this clinical feature. The pattern of pitting may be disorganized or occur in transverse/longitudinal rows as seen in alopecia areata [2]. Pits may be shallow or large [8], to the point of leaving a punched-out hole in the nail plate (elkonyxis).

Onycholysis. Focal nail bed parakeratosis produces an 'oily spot' or 'salmon patch'. Extension of this area to the free edge gives onycholysis, which typically has a reddish-brown margin. Alternatively, onycholysis may commence at the distal edge (Fig. 62.20), representing disruption of the onychocorneal band [10]. Once this band of firm attachment has been breached, the condition is often progressive. Minor manicure, wet work and leverage from long nails exacerbates the condition.

Discoloration. Discoloration in psoriasis is multifactorial. The major factors are nail thickening and subungual hyperkeratosis. Both of these contribute to a yellow

Table 62.3 Relationship between clinical features and site of disease activity in psoriasis of the nail. (From Zaias [1].)

Clinical feature	Area of disease	Duration of disease
Changes in nail plate	*Matrix*	
Pits	Proximal matrix	Episodic: short
Transverse furrows	Proximal matrix; distal extension depends on depth of furrow	1–2 weeks
Crumbling nail plate	Entire matrix	Prolonged
Leukonychia with rough surface	Proximal matrix; leukonychia may involve distal matrix	Variable
Changes in nail bed and hyponychium	*Nail bed*	
Splinter haemorrhages	Nail bed dermal ridge haemorrhage	Short
Oily spot/onycholysis	Nail bed psoriasis	Prolonged
False nail following onychomadesis	Nail bed psoriasis	Prolonged
Subungual hyperkeratosis	Nail bed psoriasis	Prolonged
Yellow/green discoloration of nail bed	Secondary infection by yeasts or *Pseudomonas*	Prolonged

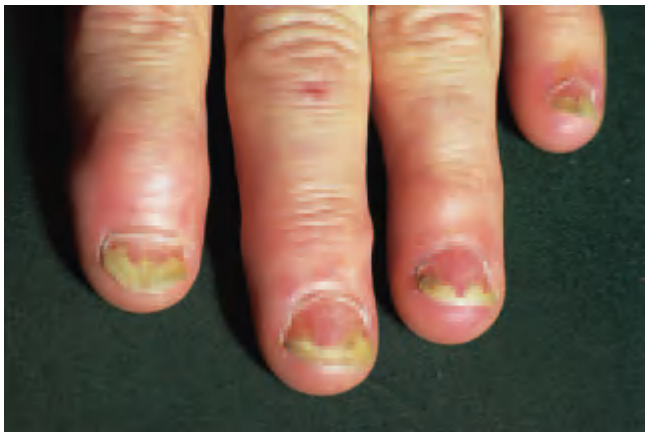

Fig. 62.20 Psoriasis: onycholysis.

appearance particularly common in the toes. It is possible that at this site repeated trauma elicits the isomorphic reaction, with local exacerbation of psoriasis. The coincidence of onychomycosis and psoriasis is also seen in the toenails [11] and can add to the pathological appearance. *Candida* spp. and *Pseudomonas* infection can result in green discoloration. While non-dermatophytes and bacteria are common, dermatophytes are rare [1].

Subungual hyperkeratosis. Subungual hyperkeratosis represents nail bed disease (Fig. 62.21). Substantial nail plate thickening may result from subungual hyperkeratosis, which is most marked distally and extends proximally. The fingertip may become very tender where there is gross subungual hyperkeratosis, as the nail plate attachment is greatly reduced and the nail can easily be caught and tug on the matrix attachment. Subungual hyperkeratosis is a prominent feature when pityriasis rubra pilaris affects the nail and is often seen with splinter haemorrhages [12,13].

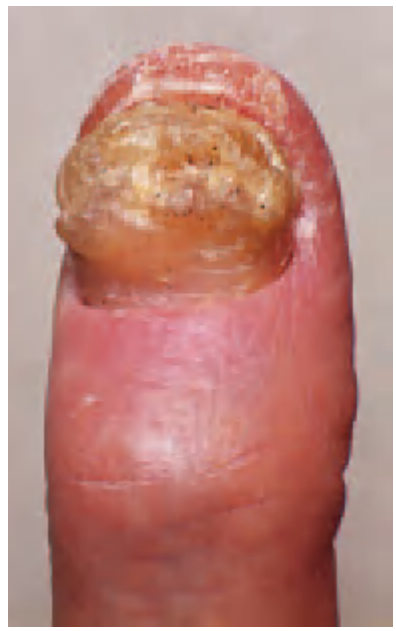

Fig. 62.21 Psoriasis: subungual hyperkeratosis.

Nail plate abnormalities. Splits, atrophy and fragility may be seen. The nail may also thicken, independent of subungual hyperkeratosis. Transverse midline depressions resembling the nail changes seen in 'washboard nails' [14] are also seen. Normally, they are attributed to the habit tic of disrupting the cuticle (Fig. 62.22) and although this may play a part in psoriasis, it appears that there is a lower threshold for the development of this midline feature in the presence of psoriasis.

Splinter haemorrhages. Splinter haemorrhages are seen in the nail bed of 42% of fingernails and 6% of toenails [15]. This may be due to the increased capillary prominence and fragility in nail bed dermis in psoriasis and the

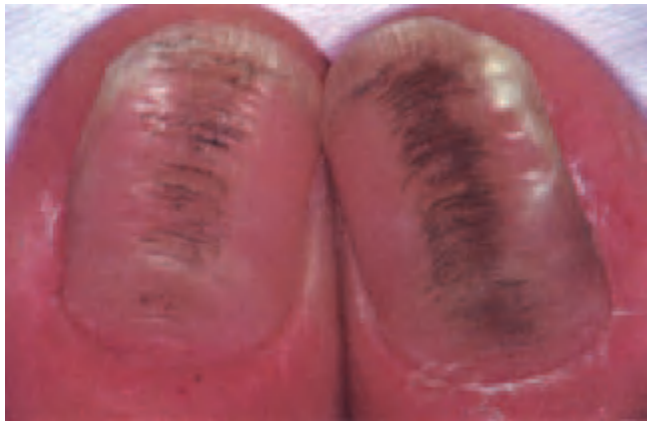

Fig. 62.22 Multiple transverse grooves of the thumbnails.

presence of dystrophy. Where transverse overcurvature occurs for reasons other than psoriasis, splinter haemorrhages are also common, suggesting that mechanical factors may contribute to splinter haemorrhage formation.

Subacute and chronic paronychia. Periungual involvement may be dramatic and inflammatory, giving rise to gross disruption of nail matrix. Loss of the nail may follow, with scaling of the nail bed or a deep transverse furrow.

Chronic psoriatic paronychia causes loss of the cuticle. The nail plate can become thin [16], although this may be offset by matrix disease, which can result in thickened nail. The nail fold may be scaly, in the form of psoriasis seen elsewhere.

Acropustulosis. This form of psoriasis involves destructive pustulation of the nail unit. It may present as part of pustular psoriasis, palmoplantar pustulosis [17], acrodermatitis continua of Hallopeau [18] or parakeratosis pustulosa (typically in young girls) on isolated digits. The nail plate may be lifted off by sterile pustules in the nail bed and matrix. There is associated erythema and discomfort of the end of the digit. There may be long-term nail loss, except in parakeratosis pustulosa, which usually resolves spontaneously. Parakeratosis pustulosa may affect only part of one digit. There is pitting and ridging combined with fine scaling erythema of the periunguium and only very rarely pustules. It is usually interpreted as a form of psoriasis [6], although it shares histological features with eczema [19], and some consider it a variant of eczema [20].

Acrodermatitis continua of Hallopeau can be very aggressive and result in resorptive osteolysis [21] or loss of toes and distal parts of fingers [22]. In a study of 20 patients with the condition, seven were male and 13 female, with a mean age of 46 years, and all had involvement of only one digit, with no features of psoriasis elsewhere [23].

Differential diagnosis. When the diagnosis of psoriatic nail dystrophy is in doubt, the main differential diagnoses are onychomycosis and lichen planus. In onychomycosis, the features usually present in the toes, whereas the fingernails are more commonly affected in psoriasis. Equally, there are often changes on the nail surface alone in psoriasis, whereas in onychomycosis features are usually within or beneath the nail plate. If there is fingernail involvement in onychomycosis, it is usually of only one or a minority of digits, in contrast with psoriasis where there are usually several digits affected.

Some forms of fingernail lichen planus and psoriasis are very difficult to distinguish. Both may result in roughened nails (trachyonychia) with subungual hyperkeratosis. If pits are prominent the diagnosis of psoriasis can be made, but if they are subtle and difficult to distinguish from other surface changes, they may be part of lichen planus. The nails in Reiter's disease and pityriasis rubra pilaris can also be difficult to distinguish from psoriasis [24,25], where distal subungual hyperkeratosis and splinter haemorrhages are common [8]. Aggressive forms of atypical nail psoriasis presenting in later life may represent acrokeratosis paraneoplastica. The patient is usually male, with subungual hyperkeratosis and scaling of the periunguium, ears and nose associated with malignancies of the upper gastrointestinal or respiratory tract [26–28].

Arthritis of the distal interphalangeal joint suggests a psoriatic cause of any associated dystrophy [29], with the exception of changes due to a myxoid pseudocyst associated with adjacent osteoarthritis. Baker *et al*. [30] found that there was no strict relationship between which joints are arthritic and which nails are dystrophic, although Jones *et al*. [31] noted that in a group of 100 psoriatics with arthritis, where there was nail involvement there was a significantly greater chance of joint disease in the adjacent distal interphalangeal joint. There was also a significant correlation between PASI (Psoriasis Area and Severity Index) score and scoring of nail disease, and nail disease increased with the duration of psoriasis. A variant of nail psoriasis presents with pain and soft-tissue swelling of the distal digit associated with psoriatic nail changes, and underlying bone erosion and periosteal reaction. This can be in the absence of joint involvement and has been termed 'psoriatic onycho-pachydermo-periostitis' [32].

Histopathology. Histopathology varies according to the clinical focus of the disease [1,33]. The matrix and nail bed develop a granular layer. Conversely, the hyponychium, where a granular layer is normally present, no longer has one [1]. Where there is subungual hyperkeratosis, there are mounds of parakeratotic keratinocytes beneath the nail plate. Neutrophils may be found throughout these mounds and Munro microabscesses may form. Similar features are seen in acrodermatitis continua of Hallopeau [23]. Amorphous material interpreted as glycoprotein

may accumulate within the keratotic mass [1]. Acanthosis and elongation of the rete ridges is present, with increased dilatation and tortuosity of the capillaries of the dermal papillae. Where the nail is lost, the nail bed may form a false nail of compacted hyperkeratosis [34]. The matrix can become quiescent, which can be demonstrated immunohistochemically by the absence of synthesis of the hard keratin Ha-1, which is normally a major constituent of nail [35].

The nail plate may show faults, clinically manifest as transverse splits and pits, which are lined with parakeratotic cells. These probably originate from the most proximal part of the matrix, or the ventral aspect of the proximal nail fold [1].

Treatment [36]. General hand care is important to avoid provocation of the isomorphic (Koebner) response, whereby minor trauma may elicit psoriasis. These measures include avoiding manicure, keeping the nails short, wearing gloves for wet work and heavy or greasy manual work, avoiding direct exposure to solvents and encouraging emollient usage. Concealment with nail lacquer is a reasonable approach to milder forms of psoriasis, and surface irregularities can be smoothed by the use of nail gel. This is a polymer, applied by a beautician and hardened by exposure to a table-top UVA source. The gel can then be shaped and buffed. Gel or other forms of sculptured or adherent artificial nails have the potential for aggravating onycholysis and are not usually recommended if this is a prominent feature.

Active treatments are mainly directed at the more dystrophic forms of nail involvement and may sometimes help with onycholysis. Often the focus of therapy is the proximal nail fold, where active psoriasis is disturbing the underlying matrix and lack of cuticle is promoting chronic paronychia. Medical treatments include the following.

Local steroids. Clobetasol propionate ointment may be used without occlusion, rubbed into the nail fold. Duration of treatment is limited by local atrophy. It is useful for psoriatic paronychia where there are secondary nail plate changes. Onycholysis may benefit if the nail is clipped back to the point of nail plate attachment and the nail bed treated topically. *Candida* is a frequent colonizer of this space and warrants treatment at the same time. Triamcinolone acetonide may be used by injection into the nail fold or nail bed with regional or digital ring block. Using 0.1-mL injections of 10 mg/mL triamcinolone acetonide at matrix and nail bed sites, on no more than two or three occasions, de Berker and Lawrence [37] report a good response in subungual hyperkeratosis, nail plate thickening and ridging. However, onycholysis and pitting improved in only 50% of nails. Alternative regimens employ more dilute triamcinolone (2.5–5 mg/mL) and are routinely used more than two or three times per digit, infiltrating the proximal nail fold alone and making a ring block optional. Triamcinolone has also been used with the Port-O-Jet or Dermojet, with improvement of pitting as well as other features [38]. There is a single anecdotal report that use of these devices has been associated with implantation epidermoid cysts, and many reports that local infection is more likely with this form of steroid delivery than with injection [39].

Topical vitamin D analogues. Calcipotriol can be useful where there is subungual hyperkeratosis and nail thickening [40]. It has also been used in combination with topical steroid on an alternating basis (a.m./p.m.) [41] and it is now possible to use it as a combined steroid and calcipotriol ointment. Calcipotriol has the advantage of avoiding the risk of atrophy with long-term use, but it is not as beneficial in treating the nail fold inflammation and consequent changes in proximal matrix function, which manifest as ridging and pitting.

Maintenance treatment with calcipotriol may also be one of the most effective topical therapies for pustular nail psoriasis [42].

Photochemotherapy. Subjects may improve as part of their general psoralen and UVA (PUVA) therapy or may have local PUVA to the nail unit. This can be done with topical or systemic psoralen. Specific high-dose handsets of UVA lamps have been advocated. As part of whole-body PUVA, 18 of 26 patients showed a greater than 50% improvement in nail changes, although pitting was unresponsive [43]. With local therapy, four of five patients improved: onycholysis was more responsive than pitting, but one patient with severe pitting showed improvement [44].

Retinoids. The nail plate is made thin by acitretin and etretinate. This reduces subungual hyperkeratosis. Pitting or onycholysis may be exacerbated [45,46]. Pustulation may be improved. Topical tazarotene 0.1% can be helpful for the treatment of onycholysis and pitting when applied under occlusion [47].

Others. Systemic methotrexate and ciclosporin (cyclosporin) may both help the nail unit but would not usually be advocated as therapy for this area of disease alone. Acrodermatitis continua of Hallopeau and psoriatic onychopachydermo-periostitis [48] are exceptions, and may respond to methotrexate.

Topical ciclosporin has been reported as useful in a single case report [49]. 5-Fluorouracil 1% has been used topically in 20% urea [50] and also in propylene glycol [51]. Pitting and subungual hyperkeratosis were thought to respond well to the former. Both are contraindicated in onycholysis.

Superficial radiotherapy [52] and electron-beam therapy [53] have been shown to be only of temporary benefit and are not usually recommended.

Treatment of coincident fungal infection may provide clinical benefit, although it is seldom a dermatophyte and positive cultures may only represent colonization.

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Darier's disease [1–5]

Nail involvement is common in Darier's disease; 96% of patients are reported to have acral changes, of which nail changes are the most common [2]. These include red and/or white longitudinal streaks in the nail, often terminating in a V-shaped nick (Fig. 62.23). The streak may represent a zone of fragile or thinned nail, which makes it prone to fragmentation at the tip with the consequent nick. In severe cases, the nails are almost lost by extension of the fragmentation process to involve the entire matrix. Subungual hyperkeratotic papules can be found in the hyponychium. Histologically, matrix and nail bed changes resemble the acantholysis seen in involved skin, with the addition of multinucleate giant cells and epithelial hyperplasia in the nail bed [5]. These histological features make it possible to diagnose Darier's disease when it is confined to the nail [1]. Excess ridging and a rough nail surface may also be found, as may total leukonychia. Occasionally, marked thickening of the nail plate occurs. It is probable

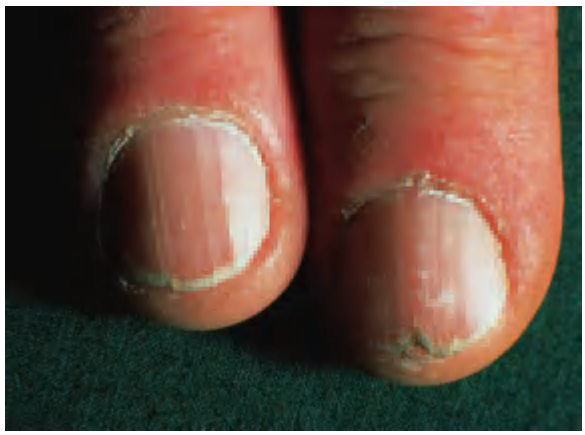

Fig. 62.23 Darier's disease: white and red longitudinal lines and distal notching.

that the nail is sometimes affected in the absence of disease elsewhere [1].

Hailey–Hailey disease has some histological similarities and may also present with longitudinal white streaks [2]. However, the disease does not have the same destructive effect and is not associated with hyperkeratoses or symptoms of the nail apparatus.

A case of squamous cell carcinoma developing in a nail bed with chronic changes of Darier's disease has been reported [6]. Pain or conspicuous uncharacteristic features in a nail apparatus affected by Darier's disease may therefore be indications for biopsy.

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Eczema

Nail changes in eczema may be seen in the context of eczema elsewhere or as an isolated finding. Endogenous and exogenous factors may contribute. The nail changes may reflect this division, in that they may be in response to a systemic atopic disposition, with pitting in the absence of inflammation, or may demonstrate the effects of local eczema in the nail unit influencing nail formation.

The common allergens such as nickel, fragrance and medicaments rarely have particular bearing on nail abnormalities. However, rubber, chrome and irritant dermatitis are significant factors in hand dermatitis. These materials, and hand dermatitis in general, are associated with particular occupations. Selective exposure to such allergens or strong irritants is as important as chronic low-grade irritation from milder agents, such as water, seen in catering workers.

Cyanoacrylates used in prosthetic nails can provoke local and distant allergic reactions. Formaldehyde, occasionally used as a nail hardener, can provoke painful onycholysis if the patient becomes sensitized, or sometimes when acting solely as an irritant. Some allergens may cause nail dystrophy without associated inflammation.

A combination of atopy and an exogenous irritant or allergic contact reaction is common.

Clinical features. Nail matrix disturbance is reflected in thickening, pits, nail loss, transverse ridges and furrows in a pattern similar to psoriatic nail disease (Table 62.4).

Nail bed disease can produce subungual hyperkeratosis, splinter haemorrhages, onycholysis and pain. Allergens and irritants can be sequestered beneath the free edge of the nail to achieve high concentrations and prolonged exposure.

Nail changes may betray eczema elsewhere and the nails may be buffed smooth and shiny, indicating their use as a tool for rubbing.

Associated hand dermatitis may show vesicles, scaling, erythema, cracks and swollen fingers, although the

Table 62.4 Differential diagnosis between four common nail disorders: fungal infections, psoriasis, chronic paronychia and dermatitis.

	Fungal infections	Psoriasis	Chronic paronychia	Dermatitis
Colour	Often yellow or brown; part or whole of nail	May be normal or yellow or brown	Edge of nail often discoloured brown or black	May be normal
Onycholysis	Frequent	Frequent	Usually absent	Confined to tip or absent
Pitting	Infrequent	Often present and fine	Uncommon	Coarse pits frequent
Filaments or spores in potash preparations	Filaments, usually abundant	Absent	May be spores in edge of nail; filaments and spores in scrapings from nail fold	Absent
Cross-ridging	Absent	Uncommon	Frequent	Frequent
Other	Associated fungal infections elsewhere	Associated psoriasis elsewhere or family history of psoriasis	Predominantly women; wet work and cold hands cause predisposition	Recent history of dermatitis on hands

presence of vesicles will not always distinguish the condition from psoriasis, which should be sought at other sites. The distribution on the hand or foot may give some clues as to possible local causes, such as gloves, shoes, prosthetic nails or nail varnish. Hands and feet should always be examined together, as the presence of disease in both diminishes the likelihood of a contact dermatitis.

Defining the presence of atopy or patch testing can be useful even in the absence of active eczema as subungual hyperkeratosis and discomfort may be disproportionate to the cutaneous features [1].

Treatment. General hand care is important, with the avoidance of soap, irritants, wet work and any identified cause. Protective gloves should be used, with copious emollient application. Barrier creams are not usually adequate protection once features have developed. Potent topical steroids may be needed, sometimes with additional topical or systemic antimicrobial therapy. These should be rubbed in around the nail folds. In the young, steroids may precipitate premature closure of the phalangeal epiphyses if too potent or used for too long [2]. Osteomyelitis has also been reported in children using potent topical steroids in this area.

Hand or foot PUVA can help.

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Lichen planus

Nails are involved in about 10% of cases of disseminated lichen planus [1]. In a study of 24 adults with nail lichen planus, nail changes were the sole manifestation of the disease in 75% [2,3], and the figure may be higher in children [4,5], in whom lichen planus of all types is rare. This suggests only a modest degree of overlap between the disease process in the nail unit and at other sites. Although the skin lesions may itch intensely, nail disease may be relatively asymptomatic except when nails are shed.

Clinical features. The disease can involve the proximal nail folds with bluish-red discoloration. Nail plate changes include thinning, onychorrhexis, brittleness, crumbling or fragmentation, and accentuation of surface longitudinal ridging. All these features are secondary to disease affecting the matrix, which can also produce transient or permanent longitudinal melanonychia [6] or leukonychia as a post-inflammatory phenomenon (Fig. 62.24). When inflammation is intense and widespread within the nail apparatus, nails may be shed. Single longitudinal depressions in the nail, with a distal notch or entire split, may arise from a pterygium. This is a fibrotic band of tissue fusing the proximal nail fold with the nail bed and matrix, following destructive local inflammation. Surviving proximal matrix is unable to push growing nail through the scar tissue, with a consequent split. Thickening, with features resembling yellow nail syndrome, is a less common pattern of presentation [7]. Where this occurs there is usually little difficulty in making the distinction in the fingernails as the prominent surface changes and/or atrophy of lichen planus are seen. However, these changes are less obvious in the toes, where yellow discoloration due to thickening can be marked [8].

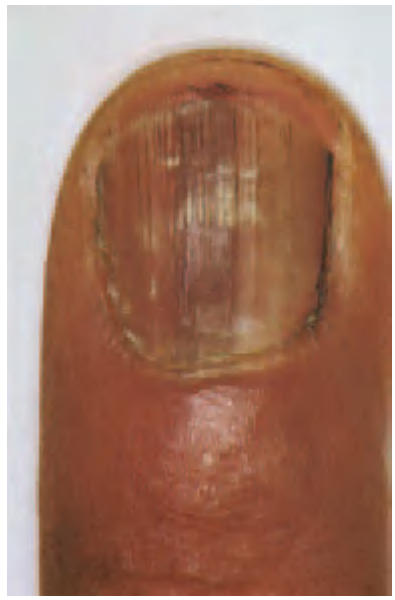

Fig. 62.24 Lichen planus with longitudinal melanonychia.

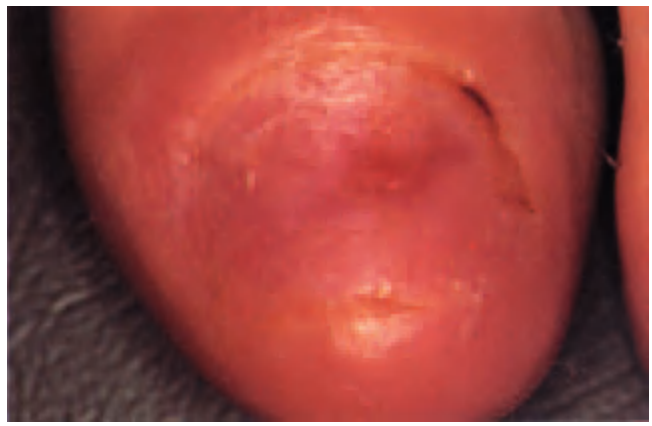

Fig. 62.25 Anonychia following lichen planus.

Nail bed disease can produce subungual hyperkeratosis and onycholysis. Bullous lichen planus may affect the soles of the feet and in particular the toenails. Permanent anonychia may follow [9] (Fig. 62.25).

Twenty-nail dystrophy, with stippling of the nail plate (see Fig. 62.11) in up to 20 nails, is seen in a range of autoimmune diseases [10], alopecia areata [3], primary biliary cirrhosis and possibly in pemphigus [11]. In itself, it does not indicate the diagnosis of lichen planus, but is one of the recognized forms of the disease. It is one of the more common childhood patterns of presentation in which the nails feel rough and lose their lustre [12]. It has a reasonably good prognosis, in contrast with idiopathic atrophy of the nails, which may also occur in children. In this form, the surface change is less marked and the change in overall nail morphology greater, with thinning and shrivelling of the nail plate. Although nail biopsy is seldom undertaken in children, it may be warranted where the diagnosis of lichen planus needs to be explored. If destructive lichen planus is not treated in childhood, there will be lifelong loss of nails.

In the related disorder, lichen nitidus, numerous pits giving a fine rippling effect have been reported [13]. Longitudinal ridging, beads and thickening may occur and nails become brittle.

In keratosis lichenoides chronica, although the skin condition may resemble hyperkeratotic lichen planus, the nail changes may mimic psoriasis; 30% have nail involvement, with hyperkeratotic hypertrophy of periungual tissues.

Lichen planus nail changes are seen in graft-versus-host disease [14] and in the disseminated lichenoid papular dermatosis of AIDS. There can be an overlap between lichen planus and discoid lupus erythematosus, both in the skin and nails. Coexistence of skin and nail lichen sclerosus has been reported [15]. Lichen striatus may extend down a limb to the nails [16].

The differential diagnosis for the range of appearances of lichen planus in the nail unit includes Stevens–Johnson syndrome, infection, peripheral vascular disease, trauma and radiodermatitis.

Histology. In 20-nail dystrophy, there is a granular layer in the nail bed and matrix, with marked spongiosis [3]. The hypergranulosis is believed to reflect the disordered keratinization that causes both subungual hyperkeratosis and the poor nail plate formation. In other forms of nail lichen planus, in addition to hypergranulosis, there is occasionally saw-toothing of the rete pattern, and colloid bodies are rarely seen [2,17,18].

In 20-nail dystrophy it may be useful to perform a screen for organ-specific antibodies because of the association with alopecia areata and the related autoimmune diathesis [3].

Treatment. Potent topical steroids may help when rubbed into the nail folds in the active stage. Triamcinolone acetonide may be instilled into the proximal nail fold under local anaesthetic. In children, potent steroid therapy puts them at risk of premature closure of the phalangeal epiphyses. Oral steroids at up to 60 mg/day have been used to arrest severe scarring nail lichen planus [2]. Triamcinolone acetonide can be given intramuscularly at a dose of 0.5–1 mg/kg per month for 3–6 months [12]. Failure to deliver effective treatment in progressive disease may result in permanent nail loss or dystrophy. Ciclosporin can also be of benefit and azathioprine has been used to good effect in erosive disease [19]. Ulcerative lichen planus of the nail unit may benefit from grafting the nail bed.

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Tumours under or adjacent to the nail

Tumours of the nail apparatus and adjacent structures are relatively common. Neoplasms of the nail area can be divided into benign, benign but aggressive lesions (e.g. keratoacanthoma, recurring digital fibrous tumours of childhood and some warts) and malignant tumours.

Clinical diagnosis is often difficult because of traumatic factors, infection, pigmentation, and because the translucent nail plate masks physical signs in the nail bed. Also, common tumours, easily recognized at other sites, may behave differently in the nail apparatus. An X-ray

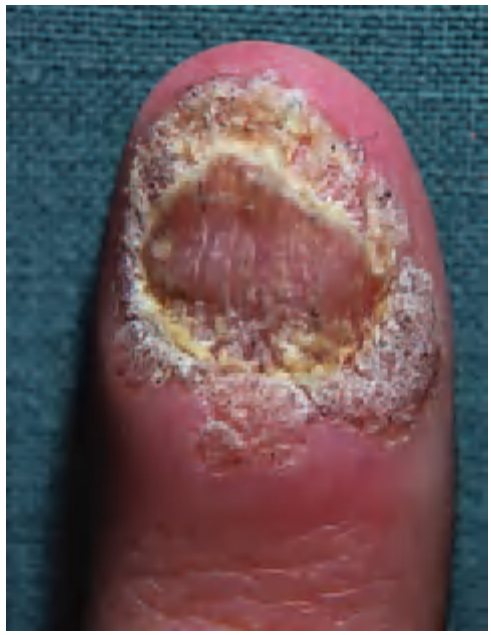

Fig. 62.26 The entire periunguium is affected by wart, with secondary nail changes.

investigation should be carried out on all swellings in or around the nail apparatus, particularly those affecting a single digit, to exclude osteoma. Where changes are primarily in soft tissues, magnetic resonance imaging (MRI) may be preferable [1].

Benign tumours

Viral warts

This is the most common tumour involving the nail, usually found in one of the nail folds but also seen in the digit pulp and less commonly on the nail bed. In the lateral nail folds, there may be no nail plate changes, although proximal nail fold warts can result in longitudinal ridging and nail plate distortion (Fig. 62.26) and nail bed warts may cause onycholysis (Fig. 62.27). Erosion of underlying bone has also been reported.

The causal human papillomavirus is usually type 1, 2 or 4. Nail biting and certain occupations, such as butcher, may predispose to warts and complicate therapy. Warts are more common and difficult to eradicate in the immunosuppressed, particularly in organ-transplant recipients.

The most significant lesion from which warts need to be distinguished is squamous cell (epidermoid) carcinoma. However, this malignancy often destroys part of the matrix and nail bed and is usually painful; both features are uncommon in benign viral warts, unless aggressive cryosurgery has been used or there has been bacterial infection. Other disorders, such as syringometaplasia,

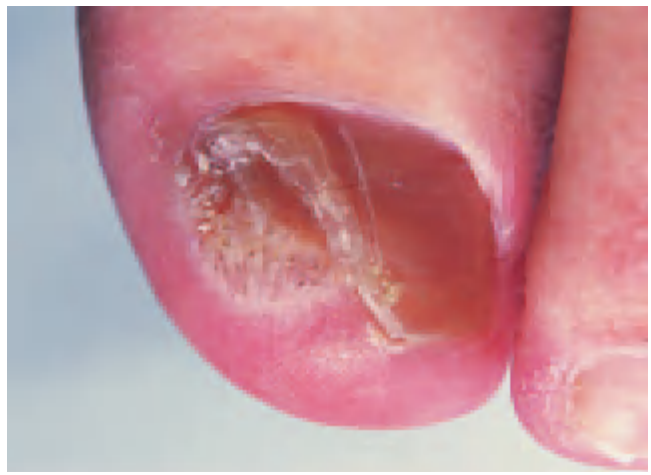

Fig. 62.27 Nail bed warts can cause onycholysis and nail plate disruption.

amyloid, subungual corn and verrucous epidermal naevus [2], may mimic viral warts.

Although most warts remit spontaneously, a wide range of therapies are available [3], including topical salicylic acid (paste, on plaster or in collodion), salicylic acid combined with abrasion [4], cryosurgery [4–7], bleomycin [8,9], cantharidin [10], imiquimod [11], curettage and carbon dioxide laser therapy [12,13], pulsed dye laser [14] and interferon [15]. Immunotherapy can be successful using sensitization to diphencyprone [16], or relying on naturally acquired immune sensitivity to pathogens such as mumps or *Candida* [17].

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Fibrous tumours

There are several types of fibrous tumours of the nail apparatus, which can be differentiated on clinical and histological grounds [1,2]. Koenen tumours are associated with tuberous sclerosis and present at puberty as periungual fibromas. They are often multiple, large or small, elongated or nodular, and may produce a longitudinal groove in the nail plate due to matrix compression. Histologically, they show loose collagen with numerous small vessels distally, but with dense collagen and few vessels proximally.

Acquired periungual fibrokeratoma [3] is probably the same as acquired digital fibrokeratoma and garlic clove fibroma (Fig. 62.28). They are all benign asymptomatic fibromas with a hyperkeratotic tip and narrow base arising in the periunguium, especially at the proximal aspect of the matrix. They grow out along the nail resulting in a longitudinal groove. There are three histological variants:
1 thick, dense, closely packed collagen bundles;
2 similar to type 1, but with increased fibroblasts in the cutis;
3 oedematous and loose dermis.

Fibrous dermatofibroma is a true fibroma presenting as a smooth-edged tumour, commonly in the periungual tissues rather than within the nail unit. There is no collar of elevated skin as is often seen in acquired fibrokeratomas and it lacks the hyperkeratotic tip. It is hypocellular but with prominent collagen bundles, and rarely has a histiocytic dermal component. Occasionally, fibromas can be confused with other lesions, such as Bowen's disease, exostosis, keloid, dermatofibrosarcoma, eccrine poroma, neurofibroma and verruca. Multiple soft fibromas presenting on the dorsal aspect of digits in childhood may be infantile digital fibromatosis. These are benign and resolve with age [4,5]. Periungual fibromas may act as a diagnostic clue for tuberous sclerosis, although they normally occur in association with at least one other feature such as hypomelanotic macules that allows corroboration [6]. They are rarely seen before the age of 5 years, but are present in 23% of subjects with tuberous sclerosis at 14 years, rising to 88% over 30 [6]. Presentation with a single periungual fibroma should lead to a full history and examination to establish whether it is a feature of undiagnosed tuberous sclerosis. However, if nothing else is found, it is unlikely that the tumour has broader significance [7].

Treatment is by excision. In acquired periungual fibrokeratoma arising in the proximal matrix, great care is needed to remove the origin of the tumour without damaging the matrix: there is a fine balance between allowing recurrence and producing long-term nail dystrophy. Koenen tumours are particularly prone to relapse, probably because of their dermal origin.

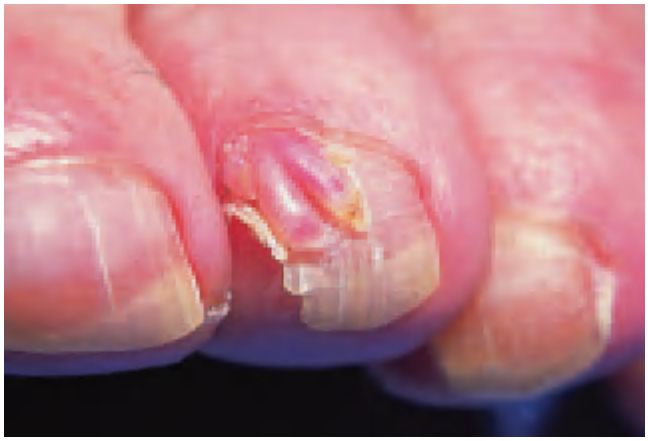

Fig. 62.28 Garlic clove fibroma.

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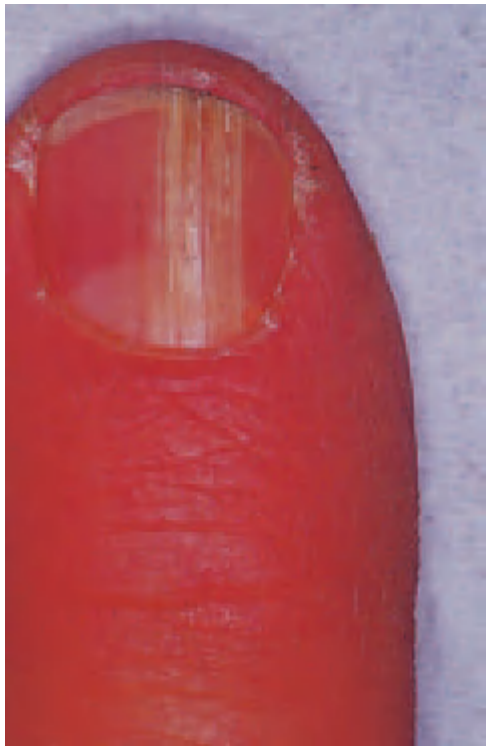
Onychomatricoma

Onychomatricoma may be considered a form of fibroma of the proximal nail fold [1,2], closely associated with the matrix. Its location means that the main features are those of altered nail, which becomes thickened with increased longitudinal ridging (Fig. 62.29). There may be increased transverse and longitudinal curvature in larger tumours. Splinter haemorrhages within the zone of altered nail are common. When the onychomatricoma is small it may occupy only a narrow band of altered nail which is thickened and grey or yellow. As it enlarges, the band broadens

(a)



(b)

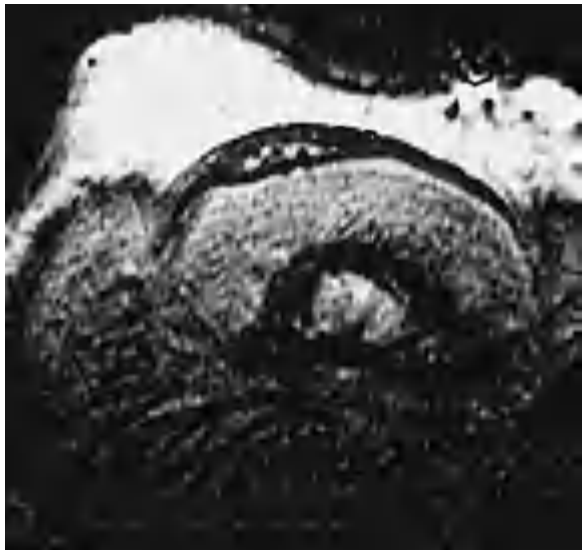


Fig. 62.29 (a) Subtle longitudinal thickening and opacity of the nail plate due to an onychomatricoma. (b) Onychomatricoma on MRI.

and thickens. When avulsed, the proximal aspect of the nail reveals multiple honeycomb channels corresponding to the digitations of the matrix, which has changed shape in response to the dermal matrix tumour. The tumour has normal immunohistochemical markers for a benign fibroma [2,3]. The matrix epithelium is normal in cytology and differentiation with respect to keratins [3]. Electron microscopy demonstrates decreased amounts of tonofilaments and desmosomes in basal epithelial cells [4]. It is the

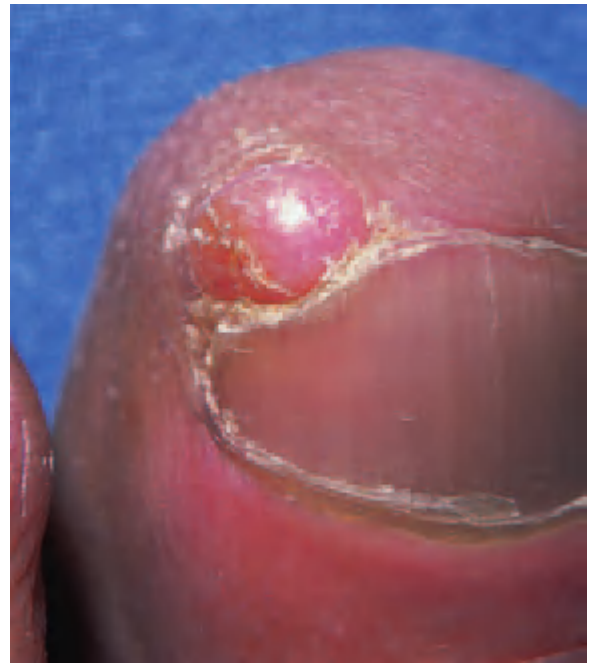


Fig. 62.30 Subungual exostosis.

marked change in shape that leads to the altered nail and characteristic clinical presentation.

Less classic presentations of the tumour may have nail features of melanonychia and onychomycosis [5].

Treatment is by excision. The margins need to include a proximal element of the proximal nail fold and extend down to bone and into proximal nail bed to obtain the whole tumour. This typically sacrifices a significant fraction of the matrix and may mean that total matrix excision is the best option.

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Subungual exostosis

A subungual exostosis is a benign bony outgrowth of the terminal phalanx. It is usually found on the great toe [1] or rarely a finger [2] in subjects between the ages of 10 and 35 years (Fig. 62.30). It is not clear whether trauma is causal or contributory. Where there are hereditary multiple exostoses, the problem is inherited in a dominant pattern and

attributable to mutations of the *EXT1* and *EXT2* genes on chromosomes 8q and 11p, respectively. These genes encode the proteins exostosin 1 and 2, which are part of a family of glycosyltransferases required for the synthesis of heparan sulphate chains. Heparan sulphate is integral to the expression of proteoglycans on the cell surface and in the extracellular matrix [3]. Mutations of *EXT1* and *EXT2* are also found in specimens of solitary exostoses [3]. This corresponds to the absence of heparan sulphate in the chondrocyte zones of exostosis growth plates [4], consistent with the proposal that such changes in chondrocyte biology are associated with abnormal cell signalling.

Pain as a presenting feature is common. It is usually associated with trauma, but is also caused by ingrowing of the nail plate as it is displaced by the tumour [5]. The nail plate is elevated laterally but rarely damaged by the tumour. Radiography reveals an outgrowth of trabeculated bone [6], which may seem modest in comparison with the clinical complaint because of the large radiolucent cartilaginous cap. The X-ray examination should include a lateral view, as typically a view from above will miss the pathology.

Distinction from a subungual osteochondroma may be possible histologically because fibrous cartilage caps the bony outgrowth in exostosis and hyaline cartilage in osteochondroma [7]. Whereas this rule is often stated, it is not clear whether an absolute distinction can be made between the two lesions.

Where multiple exostoses exist, autosomal dominant multiple exostosis syndrome must be considered. The tumours in this condition are 'near the knee and far from the elbow' and can be destructive to nail [8]. The importance of making the diagnosis lies in the remote possibility of transformation of individual tumours to chondrosarcoma —an estimated figure for malignant change is 0.5% [9]. Older patients may have a different variety of exostosis, which represents hyperostosis of the distal tuft. This can cause elevation of the nail and pincer deformity, whereby the distal and lateral borders of the nail curve downward and inward to act as a pincer upon the nail bed.

Treatment. Treatment of subungual exostosis is by partial nail avulsion or fish-mouth elevation of nail bed and plate and removal of the tumour using bone nibblers or a chisel [7]. A margin of normal bone should be removed at the base to prevent recurrence. There is a 10% relapse rate following surgery, and children are more prone to relapse than adults [5]. Permanent matrix damage may follow surgery if tumours undermine the matrix.

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Other bone tumours

Enchondroma

An enchondroma is a cartilage tumour, which may present as a painful solitary tumour of the distal phalanx with clubbing, paronychia, nail thickening, discoloration, ridging and elevation of the nail, and pathological fractures [1]. In Ollier's disease, multiple digits are usually affected. In Maffuci's syndrome there are multiple subcutaneous angiomas and hard cartilaginous nodules of the epiphyseal line, which may distort the entire hand or foot [2].

X-ray shows lucent expansion of distal phalanges alone, with spotty calcification in simple enchondromas. In Maffuci's syndrome there is widespread lucency in many phalanges of all the digits. Treatment is by enucleation of the tumour and autologous cancellous bone grafting. All these tumours can be associated with chondrosarcoma, angiosarcoma being an additional risk in Maffuci's syndrome [3].

Osteoid osteoma [4–6]

Osteoid osteomas of the distal phalanx present with enlargement of the entire digit tip in a young adult, with thickening of nail, clubbing, increased local sweating and violaceous skin changes. A tender tumour may be palpated within the diffuse swelling, and the tumour may cause a nagging pain, characteristically relieved by non-steroidal anti-inflammatory drugs.

X-ray reveals a small area of rarefaction surrounded by sclerosis, although symptoms may precede this appearance and an isotope bone scan or MRI may show the focus earlier. Arteriography and thermography demonstrate the hypervascularity. Surgical treatment of this benign condition is by en bloc resection through a fish-mouth incision.

Implantation epidermoid cyst

Implantation epidermoid cyst may produce gradual enlargement of the tip of the digit, with the appearance of clubbing, or pincer nail. Pain may arise due to disturbance

of the underlying bone where there is erosion, with distortion of cortical bone seen on X-ray, or a cyst may be demarcated on MRI. There is sometimes a history of previous trauma or surgery. Surgery is generally curative [7,8].

Metastases

Metastatic tumours present as inflamed swellings at the tip of a digit, with relatively few symptoms. X-ray reveals an osteolytic lesion, and systemic examination and investigation may reveal the primary focus; 50% will be from carcinoma of the lung [9,10].

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Vascular tumours

Glomus tumour

Glomus tumours are the most characteristic of vascular nail bed tumours. There is pain, which may be spontaneous or evoked by mild trauma or temperature change. Nail plate changes depend on the location of the tumour. Matrix tumours cause splitting and distortion of the nail plate. Nail bed lesions are most likely to appear as bluish or red foci, 1–5 mm in diameter, beneath the nail [1]. On X-ray, 36% show a depression in the underlying phalanx [1]; MRI can reveal the exact site of the tumour [2]. It is of particular value when there is pain after excision in order to help determine whether the pain is a complication of surgery or due to recurrent tumour [3]. High-resolution ultrasound has also been used with some success [4].

Histology is the definitive investigation and reveals vascular channels lined with endothelium and cuboidal glomus cells. These have dark nuclei and pale cytoplasm. Myelinated and non-myelinated nerves are found, which may account for the associated symptoms; neuromas must be considered in the differential diagnosis [5].

Treatment. Excision is the treatment of choice. Some surgeons advocate approaching the pathology by a fish-mouth incision, expecially when the tumour is in the nail bed [6]. However, this assumes a clear knowledge as to the location and nature of the tumour before surgery. Often it is necessary to remove the nail for preliminary assessment and this also facilitates matrix repair [5,7]. Where there is persistent pain after treatment, it may be due to the earlier surgery or further tumour. MRI can help in assessing this [2]. Residual scarring of the nail may remain, depending on the nature of the surgery and the extent of preoperative damage.

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Pyogenic granuloma and periungual vascular lesions

Pyogenic granulomas are benign eruptive haemangiomas. They may involve the nail fold, with a prominent collar of epithelium, or be subungual and penetrate the nail plate (Fig. 62.31). In this location, they almost invariably arise from the matrix and produce a localized deformity of the nail plate, visible as the nail grows distally. Mild penetrating injury, friction [1] and immobilization of the limb in a cast [2] are physical causes. Medication can also be relevant. Retinoids [3], ciclosporin [4], cancer chemotherapy and antiretroviral treatment for HIV infection are all potential initiating factors. With these medications, the presentation is often of excessive granulation tissue on more than one digit as part of an ingrowing nail, rather than the classic isolated lesion puncturing the matrix and emerging from beneath the proximal nail fold. There may be features that blur the distinction between focal lesions and areas of hyperaemia with inflammation [5] and onycholysis [5–7]. Pain can be a significant feature [7] and docetaxel, used in breast and prostate cancer, has been implicated in such cases. Where antiretroviral medication is implicated, it is usually in association with nucleoside reverse transcriptase inhibitors [8,9].

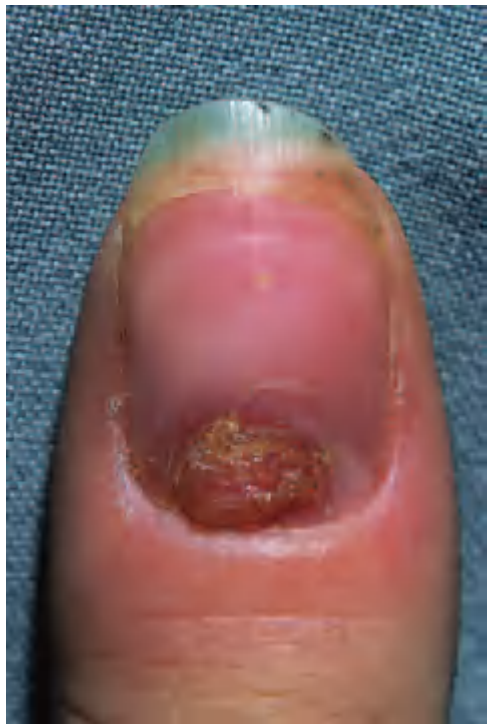

Fig. 62.31 Pyogenic granuloma penetrating the nail plate.

A pyogenic granuloma bleeds easily and must be distinguished from an amelanotic malignant melanoma, histiocytoid haemangioma [10], granulation tissue reaction to ingrowing nail and cavernous angioma. Where the clinical evolution is slow, the differential diagnosis includes squamous cell carcinoma and a range of benign tumours [11]. The possibility of malignancy and other progressive tumours makes histological examination important. Bacteriology is also required and may help with the diagnosis of coccal nail fold angiomatosis, which may resemble a pyogenic granuloma arising from the matrix. This can relapse locally and on other digits [12].

Treatment. Once histology is available, if the lesion persists, destructive therapy such as carbon dioxide laser or suppressive therapy such as a potent topical steroid can be used. The latter is preferable and adequate for matrix lesions where infection has been adequately treated. Potassium permanganate soaks, or local or systemic antibiotics, may be needed if there is secondary infection with excessive oozing.

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Arteriovenous abnormalities

Periungual and subungual arteriovenous tumours (cirsoid aneurysms) are firm, bluish, non-pulsatile nodules in a nail fold or penetrating the nail [1]. Treatment by excision reveals histology of thick-walled vascular channels with fibrous tissue boundaries and no internal elastic lamina. In the presence of a digital arteriovenous malformation, the digit and nail bed are purple, with gradual shrinkage and overcurvature of the nail plate [2]. Growth may be rapid in young people, in whom the digit may become bulbous and painful. X-ray may reveal aneurysmal destruction of the terminal phalanx, and more precise detail may be gained by MRI.

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Myxoid cyst

SYN. MYXOID OR MUCOID PSEUDOCYST

This benign cystic swelling has many names and is often termed a pseudocyst because a cellular cyst wall can seldom be demonstrated. It is usually located between the crease of the distal interphalangeal joint on the dorsal surface and the proximal nail fold. Less commonly it is found between the proximal nail fold and the nail plate, beneath the nail matrix or in the digit pulp. Pressure on the matrix results in a longitudinal groove or gutter in the nail plate (Fig. 62.32), which may have transverse ridges within it, reflecting episodes of decreased matrix pressure when the cyst is decompressed through discharge of its contents. When the tumour occupies the space between the nail and proximal nail fold, it may protrude from beneath the nail fold with what appears to be a keratotic tip, mimicking a fibrokeratoma. When located beneath the matrix, the nail becomes misshapen, with increased transverse curvature, and the lunula appears red [1].

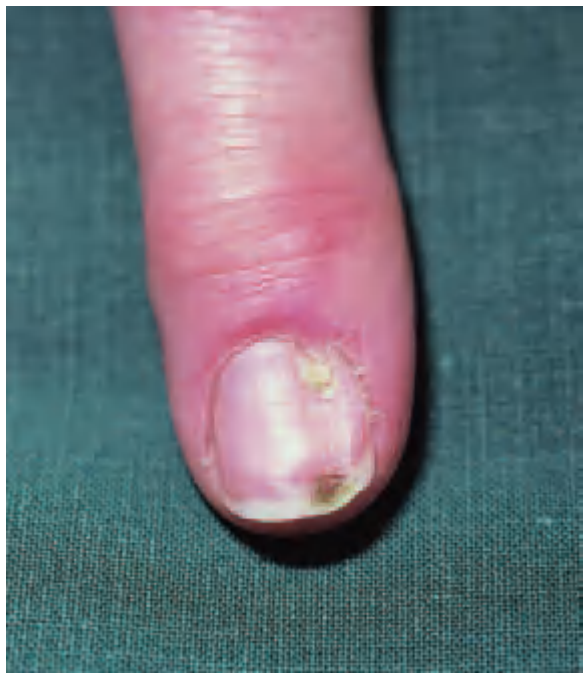

Fig. 62.32 Nail plate groove due to proximal myxoid cyst.

Myxoid cysts are more common in the fingers than the toes. They contain a clear gelatinous fluid that may discharge spontaneously or on minor trauma. This fluid may be the product of mucoid degeneration of connective tissue or be derived directly from the adjacent distal interphalangeal joint with which a communication is usually demonstrable by injection of methylene blue into the joint [2,3]. The condition of the joint is a major factor in the origin of the tumour, with osteoarthritic osteophytes damaging the joint capsule and provoking the flaw through which synovial fluid escapes. Infection of the ruptured pseudocyst may cause septic arthritis or local paronychia, although this is uncommon.

High-resolution ultrasound or MRI provides non-invasive visualization to confirm the diagnosis or to localize the pedicle in recurrent cases. However, it may be more practical to attempt transillumination with a pen torch. This will distinguish it from a giant cell tendon sheath tumour, which is usually found overlying the dorsal distal interphalangeal crease in women with osteoarthritis [4,5]. Giant cell tendon sheath tumours are often rubbery and fail to transilluminate. Alternatively, a myxoid cyst will easily puncture using a size 11 scalpel, with sterile technique, revealing the diagnostic gelatinous contents.

Histology usually reveals a pseudocyst cavity within a fibrous capsule containing a myxomatous stroma with scattered fibroblasts. Areas of myxomatous change may merge to form a multilobular pseudocyst. Some workers report a mesothelial lining to the pseudocyst, consistent with continuity with the synovial joint space. This is not always confirmed and may mean that there are different histological forms of myxoid pseudocysts.

Treatment. There are many conservative approaches to cure [6,7], none of which is definitive. These include incision and drainage (pricking with a sterile blade or needle) and which may be repeated by the patient [8], injected sclerosant [9] or steroid [10,11], cryosurgery [12,13], laser [14] and infrared photocoagulation [15].

Surgical therapy may entail removal of osteophytes involving the distal interphalangeal joint [16–19], excising the distal margin of the proximal nail fold if the tumour is located there [20], or tracing the communication between the joint and cyst with methylene blue and tying it off [3,21].

There is a high relapse rate after single treatments with less invasive therapies. More detailed surgical therapies are more effective [19,21].

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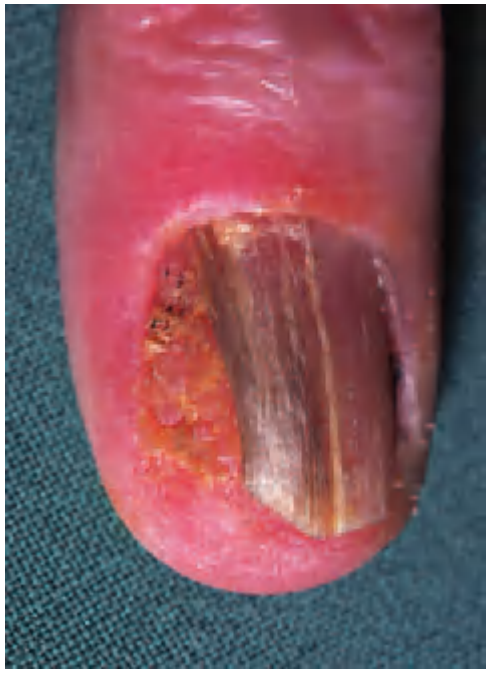

Fig. 62.33 Bowen's disease with melanonychia.

Squamous cell carcinoma

SYN. EPIDERMOID CARCINOMA

Squamous cell carcinoma of the nail unit includes *in situ* (Bowen's disease) and invasive forms (Fig. 62.33). A single biopsy may fail to make a distinction between them. A tumour that appears *in situ* at one site may be invasive elsewhere [1]. Periungual features include hyperkeratotic warty changes, erosions and fissuring, macerated cuticle, periungual swelling, erythema and occasional secondary infection. Subungual changes include onycholysis with a friable or warty nail bed, longitudinal melanonychia, nail dystrophy, ingrowing or loss. Some cases may be as subtle as a single red longitudinal streak [2] (see p. 62.19). Nodular change with ulceration and bleeding is a late development. The condition may affect many digits [3]. Common misdiagnoses include onychomycosis, periungual warts, recurrent paronychia, pyogenic granuloma and subungual exostosis. As some of these conditions do not warrant biopsy and clinicians seldom think of squamous cell carcinoma at this site, the diagnosis is frequently delayed. Mean periods of 52 months [4], 9 years [5] and 5 years [6] have been reported. This slow progression may mean that the diagnosis is never made on older people, with the consequent impression that the disease is less common than is the case [7].

Predisposing factors include radiation exposure [3,8], human papillomaviruses 16, 18 and 34 [4,5,8–10], and possibly ectodermal dysplasias and chronic trauma. Features of chronic radiation damage to the periunguium may precede the onset of malignancy [11]. History and examination should include a note of genital wart infection or cervical dysplasia in the patient or partner [8]. Appropriate investigation includes X-ray and biopsy of a large and representative area. Failed diagnosis can be attributed to poor diagnostic biopsy technique. Prognosis is good and there are only five cases of metastatic disease in the literature [9], two of which were in patients with ectodermal dysplasia [12,13].

Treatment. Mohs' micrographic surgery is the treatment of choice for ill-defined lesions, as long as there is no evidence of bone involvement [1,6,14]. The technique allows the digit to be preserved in most instances. Horizontal sections in the context of the complex three-dimensional anatomy and histology of the nail unit require careful and experienced interpretation [15]. Alternative treatments include local excision, digit amputation and radiotherapy [16].

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Epithelioma cuniculatum [1,2]

Epithelioma cuniculatum is a slow-growing, locally destructive, low-grade tumour, histologically related to squamous cell carcinoma [1,2]. It is typically found on

the sole of the foot, but may involve the periunguium, mucosal surfaces and other locations [3]. It is warty, with discharge of foul-smelling yellow material from nail bed sinuses. The overlying nail is disrupted by onycholysis or destruction at the matrix, and there may be paronychia. The underlying bone is usually affected and X-ray reveals destruction of the terminal phalanx in most cases. Biopsy confirms the diagnosis. A system of epithelium-lined channels within the tumour form fistulae extruding keratinous debris. Mitoses and dyskeratotic cells are rare and the benign appearance may lead to the misdiagnosis of pseudoepitheliomatous hyperplasia. Mohs' micrographic surgery is a useful treatment.

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Keratoacanthoma

Subungual or periungual keratoacanthomas are typically painful, rapidly enlarging lesions that are usually solitary [1,2]. They are often referred to by the acronym SUKA. Keratoacanthoma is a misleading term as there is no indication that the tumour follows the same pattern of involution seen in keratoacanthomas elsewhere; also, there is no apparent relationship with sun exposure. Although trauma and wire wool have been implicated [3], in most cases there is no obvious precipitating factor. Erosion of bone is seen on X-ray, which is an essential preliminary investigation [4–7]. This feature is likely to represent a pressure effect of rapid subungual expansion, rather than bone invasion. The diagnosis is made partly on the history but largely from the histology, which closely resembles that of a keratoacanthoma seen elsewhere but showing little or no squamous dysplasia [4]. Subungual wart, squamous cell carcinoma and subungual exostosis are among the differential diagnoses. Clinically, subungual keratotic incontinentia pigmenti tumours fall between the appearance of fibroma and keratoacanthoma [8,9]. They resemble the latter in often being painful and causing underlying bone changes. They are commonly multiple and seen with the other features of incontinentia pigmenti, which is usually lethal in males. These tumours can be treated with oral retinoids [10], but may eventually require surgery.

Treatment. Treatment of subungual keratoacanthoma can be by Mohs' micrographic surgery or curettage. More aggressive treatments, including amputation of the digit, have been employed in the past, but are not warranted. Given the concern that the tumour may represent a form of squamous cell carcinoma, micrographic surgery may be the treatment of choice.

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Melanocytic lesions

Benign melanocytic lesions usually present as longitudinal melanonychia (LM). This is also a common appearance of early malignant melanoma of the nail matrix [1]. An understanding of the causes of benign nail pigmentation is important in order to judge when biopsy is indicated to exclude melanoma.

Benign causes of LM

Laugier–Hunziker syndrome

Laugier–Hunziker syndrome gradually evolves with pale-brown LM on one or more digits [2,3]. There may be periungual involvement resembling Hutchinson's sign and the oral and genital mucosae may be affected with pigmented macules. The macules are amenable to laser treatment [4].

Subungual naevi

Subungual naevi may present in adulthood or early in life with LM or with naevoid melanosis of the nail plate [5] (Fig. 62.34). This has been described in European [6,7] and Japanese [8] adults and children.

Drug therapy

Drug therapy with minocycline, zidovudine [9] and antimalarials may produce brown streaks in the nail (see

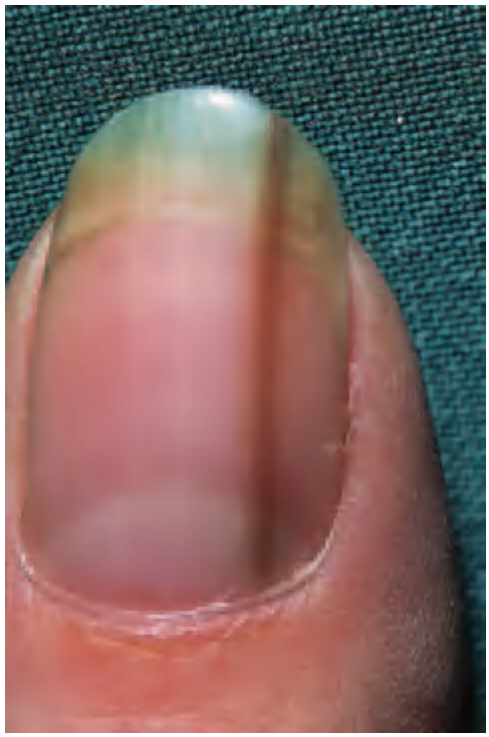

Fig. 62.34 Benign longitudinal melanonychia due to a subungual naevus.

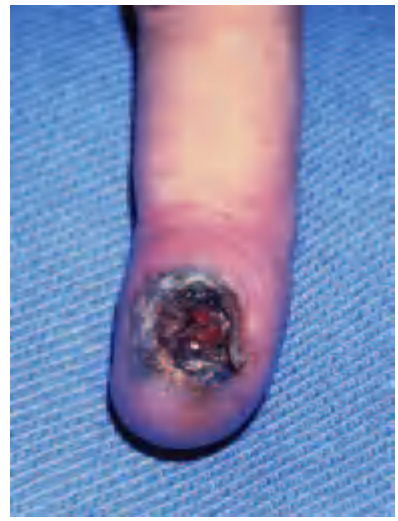

Fig. 62.35 Malignant melanoma arising in the nail matrix and invading the nail bed.

p. 62.18), as may dermatoses such as lichen planus [10] and onychomycosis [11], trauma [12] and non-melanocytic tumours such as squamous cell carcinoma *in situ* [13] (see Fig. 62.33). Subungual blood pigment may resemble melanin, but associated features in the history and appearance usually make it possible to distinguish the two.

Benign racial pigmentation

The most common cause of LM is racial variation; 77% of Afro-Caribbeans over 20 years of age have LM and this prevalence rises to almost 100% by the age of 50 years [14]. It is present in 10–20% of Japanese [15] and is more common in Mediterranean races than in northern Europeans. However, in this context, the percentage of malignant melanomas presenting in the nail unit is higher in Afro-Caribbeans (15–20%) [14] than in any other group (3% in white populations [16]). This contrasts with the low incidence of malignant melanoma at other skin sites in Afro-Caribbeans.

Malignant melanoma [17–20]

There are many features of LM that should suggest the possibility of malignant melanoma. These include the presence of brown-black periungual pigmentation (Hutchinson's sign) [21], especially when the pigmentation develops in a single digit in adult life and is evolving to become darker and broader and has blurred edges. Hutchinson's sign needs careful assessment and does not necessarily carry a bad prognosis [2,22]. Dermatoscopic examination through the nail may help with diagnosis [23,24]. The suspicion of melanoma is raised further if the individual has any other risk factors for melanoma, if the involved digit is a thumb, great toe or index finger, and if the nail has become dystrophic.

Despite the importance of LM as a warning sign, 25% of subungual melanomas present as amelanotic tumours. This exceeds the percentage of melanomas presenting as an amelanotic tumour elsewhere. It is difficult to determine whether these tumours were always amelanotic [25] or whether loss of pigment is due to development of the disease process (Fig. 62.35). This form of melanoma usually has associated nail plate damage and easily bleeds. With this appearance, the differential diagnosis includes pyogenic granuloma, chronic paronychia and vascular tumour.

The assessment of pigmented streaks in children is complex. The earlier dictum that they were all benign and could be left has some ramifications. Indeed they are almost all benign [7], although very rare cases of melanoma are reported [26]. This alone may make diagnostic biopsy warranted in some or all. In addition, it is documented that pigmented streaks arising in childhood can evolve into melanoma, even after an initial biopsy with benign histology (S. Goettmann-Bonvallot, personal communication). The implication of this is that repeated biopsies may be needed as a pigmented streak evolves, and lifelong monitoring is required for children with such signs. Faced with this, complete excision of the matrix origin can sometimes be the best option, even when there is permanent loss of all or part of the nail.

The significance of preceding trauma is unclear [25]. Such a history is present in a large number of cases. It is thought that primary malignant melanoma of the nail unit arises only from within the matrix and not from the nail bed. This is consistent with the absence of antigenically identifiable melanocytes in the nail bed [27,28] and can provide some reassurance when assessing pigmented lesions not arising from the matrix. However, such lesions may arise from the nail folds, or be secondary malignant melanomas.

Biopsy of LM

Given the gravity of the potential cause of melanonychia, there should be a low threshold for biopsy. The type of biopsy can be determined by a range of factors [12].

1 Periungual pigmentation present. This indicates high risk of malignancy. If there are no other factors to account for this pigmentation, the whole area of affected nail unit should be removed en bloc down to bone with a 1-mm margin of normal tissue. Cosmetic considerations are secondary.

2 Lateral third of nail plate involved. This indicates lateral longitudinal biopsy. The cosmetic outcome is reasonable and the assurance provided by complete removal of the affected area is usually worthwhile.

3 Mid portion of the nail plate involved. The cosmetic outcome of complete excision at this site is potentially bad. This is particularly so if the origin of melanocytes is proximal in the matrix. This may be determined by sampling the free edge of the nail plate and performing a Masson–Fontana stain. Pigment in the lower part of the nail reflects a distal matrix origin, compared with ventral nail pigment reflecting an origin in the proximal matrix. The latter carries a high risk of scarring following excision.

For lesions less than 3 mm wide. The potential for postoperative dystrophy in midline lesions warrants preliminary investigation of thin (< 3 mm) pigmented streaks with a matrix punch biopsy unless the clinical evidence of malignancy is overwhelming. This technique involves:

1 reflection of proximal nail fold to visualize the origin of the pigment;

2 a 3-mm punch biopsy through the nail down to bone at the pigment origin, but leaving the biopsy *in situ*;

3 proximal hemi-avulsion, which will leave the 3-mm biopsy of nail remaining;

4 examination of fully exposed matrix;

5 careful removal of 3-mm biopsy of matrix and nail with iris scissors;

6 after gentle undermining, partial approximation and suture of the wound with 7/0 monofilament may be attempted for proximal matrix wounds.

Removal of the nail plate before biopsy can mean one loses the site of pigment origin once the clue of melanonychia has gone. Removal of the 3-mm biopsy without hemi-avulsion of the surrounding nail is difficult and may result in damage to the specimen, which compromises histological interpretation. For these reasons, the method outlined above is preferred.

For lesions 3–6 mm wide. If the pigment arises from distal matrix, a transverse matrix biopsy can be performed. Proximal matrix pigment requires an en bloc removal and repair using a Schernberg and Amiel flap.

For lesions greater than 6 mm wide. Matrix punch or transverse biopsy is usually adequate as the preliminary investigation.

Treatment and prognosis

Nail unit melanoma has a record of delayed treatment and poor prognosis [29]. It affects light and dark skinned people, those of African origin representing 12% of patients in one North American series [30]. The most common pattern is of acral lentiginous melanoma [17], although one series reported the superficial spreading type as being marginally more common [31]. In the acral lentiginous form, there is lentiginous spread of pleomorphic, often dendritic, atypical melanocytes in the basal and suprabasal layers of the epidermis. Epidermal melanoma cells may be incorporated into the nail plate and seen on stained clippings of nail taken from the free edge. Dermal melanoma cells are pleomorphic, with spindle, epithelioid, polygonal, dendritic and bizarre shapes.

Hutchinson's sign is represented histologically by atypical melanocytes mainly in the basal layer, with a few higher in the epidermis. *In situ* subungual melanoma has junctional nests of melanoma cells. Nodular patterns of melanoma are rare.

Amputation of the digit is the routine treatment, although local excision is occasionally practised for small shallow lesions. Mohs' micrographic surgery is used in some centres, but is still at a relatively early stage of evaluation [32]. In one series of 14 patients, three had recurrence at the margins of treatment. Adjuvant isolated limb perfusion has failed to show benefit in stage 1 subungual melanoma [33], although use of a more aggressive regimen has possibly been associated with improved survival [34].

Recent British surveys suggest that the poor prognosis of subungual melanoma is related to the depth of invasion at diagnosis (4.7 mm). This reflects late diagnosis (3 months to 12 years) [31,35,36]. The mean 5-year survival was 41% compared with 61% for a control group of primary cutaneous malignant melanomas in the same study [35]. Other series have produced similar results, although recent Japanese evidence supports the idea that diagnosing subungual melanoma early, with a lower Breslow

thickness, improves prognosis, with an 87% 5-year survival rate [34].

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Nail surgery [1,2]

Nail surgery is delicate and requires attention to detail. It is important that anyone performing a nail biopsy appreciates the principles outlined in the preliminary section of this chapter on anatomy and physiology and that they obtain tuition in detailed technique. Once in this position, the outcome of nail unit surgery is usually excellent and provides useful and definitive diagnostic material [3].

For many procedures, the routine skin surgery pack needs to be supplemented by specialized instruments. These include a Freer septum elevator for finger work and a larger elevator for the great toenail. English nail splitters are essential for performing partial avulsion. They have a flat undersurface, which can be introduced beneath the nail to act as an anvil and a sharp upper part that cuts down upon the nail to meet the other half of the instrument. For bone surgery, such as removal of exostoses, bone rongeurs and McKindoes are needed.

Indications

A nail biopsy may perform several functions. It can provide useful positive diagnostic information or help exclude a malignant condition, such as squamous cell carcinoma of the nail bed. Painful conditions may be relieved by the drainage of pus with proximal hemi-avulsion, or ablation of an ingrowing toenail. Focal pathology, such as a glomus tumour or the origin of melanonychia, can be completely excised and provide the diagnosis. If a positive diagnostic and therapeutic attitude is taken to the nail disorder, a good outcome can be expected.

Diagnostic nail biopsy may be undertaken as part of the investigation of nail dystrophy of unknown cause in the presence of more than one negative mycology sample.

Biopsy of the nail plate alone, or with associated nail bed and occasionally matrix biopsy, may be needed to confirm fungal infection in atypical cases, although biopsies are more commonly directed at distinguishing between

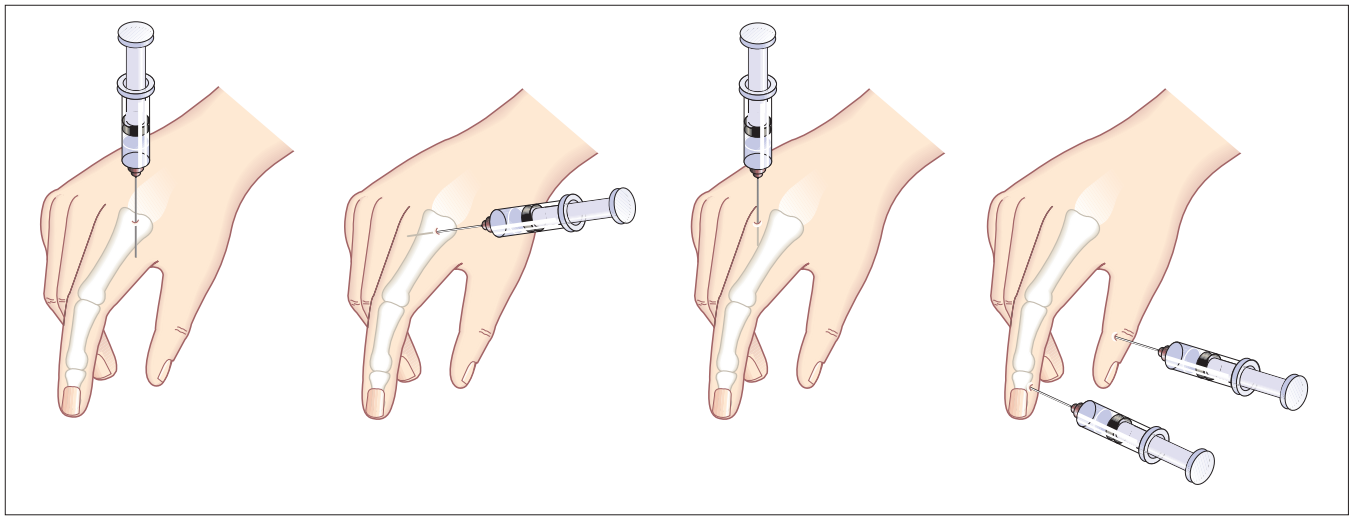


Fig. 62.36 Digital sites of injection for a ring block.

dermatoses affecting the nail, such as lichen planus, psoriasis or infiltrative disease. In instances of nail dystrophy of a single digit, it is appropriate to biopsy to exclude a neoplasm once necessary imaging has been performed.

Caution is needed in patients with relevant medical and circulatory problems. The latter are subject to poor reperfusion following the tourniquet and it may be necessary to abbreviate the procedure to ensure no inadvertent damage is done. The wound must be seen to bleed and the digit colour return before the dressing is applied in these cases, and this can take several minutes. This contrasts with the usual pace at which dressings are applied to prevent bleeding in a healthy digit. Diabetics may have ischaemia combined with immune impairment and frequently need attention to toenail problems. Paradoxically, they are cited as a group in whom cold steel surgery for nail problems is preferable to other techniques such as phenolic ablation or cryosurgery. This is because the course of healing in these wounds is predictable and often shorter than wounds produced by other therapies.

Preoperatively

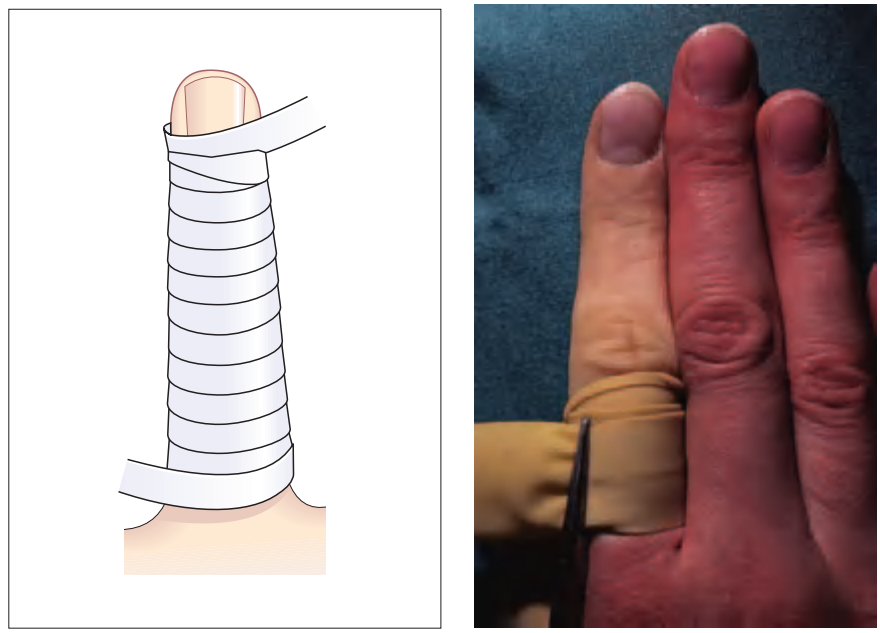
It is essential to prepare the patient for the procedure by a discussion on a day separate from surgery. In this discussion, the patient must appreciate the potential benefits and problems of the biopsy. It is useful to make it clear that it will be painful and that they will have a degree of disability postoperatively for which they must make provision at home and at work. The best surgical technique can be utterly confounded by a patient who goes back to a dirty workplace the next day. Much of the information concerning scarring, the need for elevation, dressings and analgesia needs to be repeated on the day of the procedure. The patient should have a means of transport home that does not involve them driving or standing for prolonged periods.

The affected digit should be soaked in warm antiseptic and scrubbed in a manner similar to that used by the surgeon prior to gloving. This will diminish the bacterial load beneath the free edge of the nail, which is a source of potential pathogens. Soaking for 10 min softens the nail and facilitates removal of parts of the nail plate, so avoiding complete avulsion. During this period, the local anaesthetic can take effect.

Anaesthetic (Fig. 62.36)

Lidocaine (lignocaine) 2% or equivalent can be used [4]. Bupivacaine can be used to provide prolonged analgesia. The use of epinephrine (adrenaline) in anaesthetic remains controversial. There are several publications illustrating how anaesthetic containing 1 in 200 000 epinephrine has been used safely [5]. The ischaemia and prolongation of anaesthesia is a potential advantage. If subjects with peripheral ischaemic or vasospastic disease are avoided, anaesthetic with 1 in 200 000 epinephrine appears safe. An alternative is to use ropivacaine. This local anaesthetic has physiological and pharmacological properties somewhere between bupivacaine and lidocaine. It has a moderately quick onset of action and can produce anaesthesia for over 12 h, combined with a modest short-term vasoconstrictive effect [6]. We use ropivacaine 7.5 mg/mL in the same way as lidocaine, with very good results. A 30-gauge needle causes less discomfort during injection than larger needles, and minimizes the risk of damage to digital nerves when inserting a ring block. Risk of nerve trauma may be reduced further by the use of nerve-block needles, which have less traumatic tips.

The most common form of anaesthesia is a ring block (digital nerve block), which is delivered by injection of



(a) (b)

Fig. 62.37 (a) A Penrose drain is applied from the tip and wound down the digit achieving exsanguination. (b) The drain is then unwound from the top, with the base maintained secure with artery forceps.

anaesthetic into the dorsolateral aspect of the digit at the base, with about 1–2 mL on each side of the phalanx. Greater than 5 mL may impair circulation, but this can be assessed visually during the procedure and is very variable according to the bulk of individual digits. Anaesthesia may take 10–20 min to become total. In the great toe, additional anaesthetic should be placed ventrally. After 10 min, efficacy of the block can be assessed at the digit tip with the same needle; if the anaesthesia is incomplete, it can be supplemented by a small local injection at the site of surgery. However, this can increase tissue turgor and render fine manipulation difficult.

Other ring block techniques can be employed, including a method that aims to infiltrate the anaesthetic via the flexor tendon as a transthecal block [7,8]. An alternative is the distal 'wing' block given 2–3 mm proximal to the junction of the proximal and lateral nail folds. The injection is first directed distally into the lateral nail fold. After partial withdrawal, it is redirected over the proximal nail fold. Sufficient is used to produce blanching in both nail folds. The procedure is repeated on the other side to achieve complete block. The digit is more sensitive distally than proximally and it is often more comfortable to provide the traditional proximal digital nerve block.

For invasive procedures on many digits concurrently, more proximal or regional blocks can be employed [9]. In children it can be worthwhile to use a topical anaesthetic as a preliminary measure before ring block. Evidence of its efficacy in adults is mixed [10,11].

Tourniquet

It is important that the area of applied pressure beneath the tourniquet is as broad as possible to avoid pressure damage to underlying structures. In particular, neuritis may be a long-term complication of a narrow, tight, prolonged tourniquet. This effect can be exacerbated by topping up anaesthetic near the tourniquet after it is in place. Ischaemia can be tolerated in a normal digit for 20 min and possibly longer, with no complications as long as there is no local trauma from the tourniquet.

The standard tourniquet for local anaesthetic is the Penrose drain (Fig. 62.37), which may be wound around the digit from the tip proximally. This exsanguinates the digit and provides a tourniquet effect that can be maintained with a pair of artery forceps. A sterile glove is an alternative. It is worn by the patient and the tip of the glove digit at the site of surgery is snipped off. It is then rolled back to the base of the digit, exsanguinating it, providing a tourniquet, and avoiding contamination from adjacent digits peroperatively. With general anaesthetic, an exsanguinating cuff can be used on the forearm or calf.

Specimen

The specimen must be delivered to the pathologist undistorted and with the maximum of clinical and operative information. It is useful to allow the specimen to adhere lightly to a piece of paper before immersion in fixative, or to enclose it in a small plastic mesh cassette. This should be matched with a detailed drawing on the histopathology request form. It is helpful to work regularly with the same pathologist for nail specimens, as processing requires specialized understanding of specimen preparation and histological interpretation.

Postoperatively

Dressings should be ready before removal of the tourniquet. They must be firm and moderately bulky. An acceptable dressing includes an antimicrobial ointment under a greasy tulle, padding and a small bandage. Calcium alginate dressings can also be useful if there is an area that needs to heal by secondary intention. Dressings should be held in place with oblique or longitudinal sticky tape to avoid a tourniquet effect if the digit swells. A sling or plastic overshoe should be provided.

The frequency of change of dressings is determined by the nature of the procedure and the patient. An antiseptic soak is normally needed to remove the dressing and clean the wound. Infection should be treated vigorously with systemic antibiotics combined with daily antiseptic soaks.

It is good practice to provide a moderately strong analgesic and to recommend taking it regularly in the first 48 h. It may prove unnecessary, but the distress of unrelieved pain in the few who suffer warrants caution. Some patients need night-time sedation.

In most cases, it is wise to arrange review within 2 days of surgery to change the dressing, assess the wound and answer any questions which have arisen.

Complications

Pain can sometimes be disproportionate to the wound [12]. When it is severe, the patient is at risk of reflex sympathetic dystrophy [13]. They should receive regular potent analgesics, including non-steroidal anti-inflammatory agents, amitriptyline and sometimes an anxiolytic such as diazepam.

Bleeding is very common and should be accommodated by firm, bulky dressings. Once blood has clotted in these dressings they can be rock-like and represent an infection risk—good reasons for an early dressing change.

Infection is a potential problem and can be devastating to the matrix. Prophylactic antibiotics are a reasonable precaution when the surgical site is likely to be heavily colonized due to skin changes or a dystrophic nail. Children or patients with poor hygiene may also warrant antibiotics.

Longer term, complications are mainly related to scarring dystrophy and loss of function. The former is always a potential risk of any surgery involving the matrix and should be discussed preoperatively as part of the risk assessment with the patient. Loss of function can be modest, with a tendency for the nail to catch, or more significant if associated with pain or marked paraesthesia. Mild paraesthesia is quite common in the short term and is sometimes seen with cold sensitivity. Complications involving the tendons of the distal interphalangeal joint are very rare and usually related to more proximal surgery.

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Patterns of nail biopsy

Nail avulsion [1,2]

Nail avulsion can be performed in order to examine underlying tissues or to provide temporary relief in cases of soft-tissue trauma. In isolation, it is not a treatment for ingrowing toenails. The procedure requires a distal or ring block, and an elevator in addition to the routine instrument pack. For a partial avulsion, nail splitters are also needed.

To minimize the trauma of the procedure, soft-tissue nail attachments should be loosened at all sites prior to removal. This minimizes tearing damage to the nail folds. The cuticle may need disrupting with fine scissors or a blade, but all other detachments can be performed with a septum elevator. Once this is done, the nail is gripped with a pair of rugged artery forceps and removed by a mixed twisting and lifting action (Fig. 62.38).

With a lateral partial avulsion, the nail splitter is used to define the medial margin and only the attachments of the piece of nail to be removed need to be interrupted.

Proximal hemi-avulsion of the nail plate entails the following technique.

1 The origin of the nail and its proximal lateral aspects are undermined with a septum elevator.

2 In nails with a shallow lateral nail fold, a nail splitter may be inserted and the nail transversely bisected.

3 In nails with a deep lateral nail fold, a deep transverse score is placed with a scalpel across the nail halfway down.

4 The septum elevator is then fully inserted through the transverse score to loosen and elevate the proximal nail.

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Nail bed biopsy [1–4]

Biopsy of the nail bed is usually performed to investigate a focal abnormality of nail bed or changes in the nail plate arising distally. Occasionally, it may be appropriate to biopsy through the nail plate where the histological relationship between nail bed and plate is under investigation. More commonly, the nail bed is visualized first, following complete or partial avulsion. A thin ellipse is taken down to bone in the long axis of the digit (Fig. 62.39). An alternative is to employ a double punch technique, where a 6-mm hole can be made in the nail plate with a biopsy punch over the area of nail bed to be examined. The nail bed may then be sampled using a smaller punch.

If there has been nail avulsion, it is possible to close the wound, which may require gentle undermining. In small biopsies this may be unnecessary, and the wound will heal well by secondary intention. When the nail is left *in situ* or if the double punch technique is used, closure is not possible. After a double punch, as long as there is complete haemostasis, the original disc of nail plate can be returned after soaking in antiseptic; it may reattach or at least provide a natural dressing during the early healing phase.

No scarring is anticipated from this biopsy if it is small and does not extend into the nail matrix.

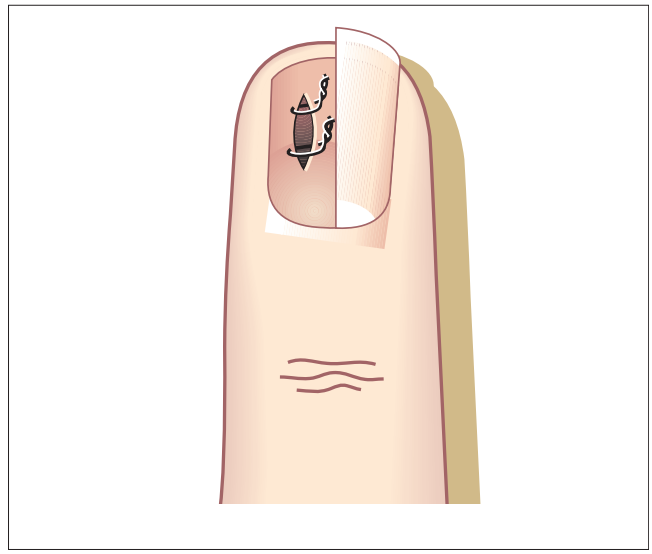

Fig. 62.39 After partial nail avulsion, the nail bed can be seen and biopsied along the longitudinal access.

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Matrix biopsy

Lateral longitudinal nail biopsy [1,2]

Lateral longitudinal nail biopsy is the definitive method for sampling all the tissues of the nail unit. It is most commonly required when there is dystrophy affecting the whole nail or for the excision of a melanonychia. If focal

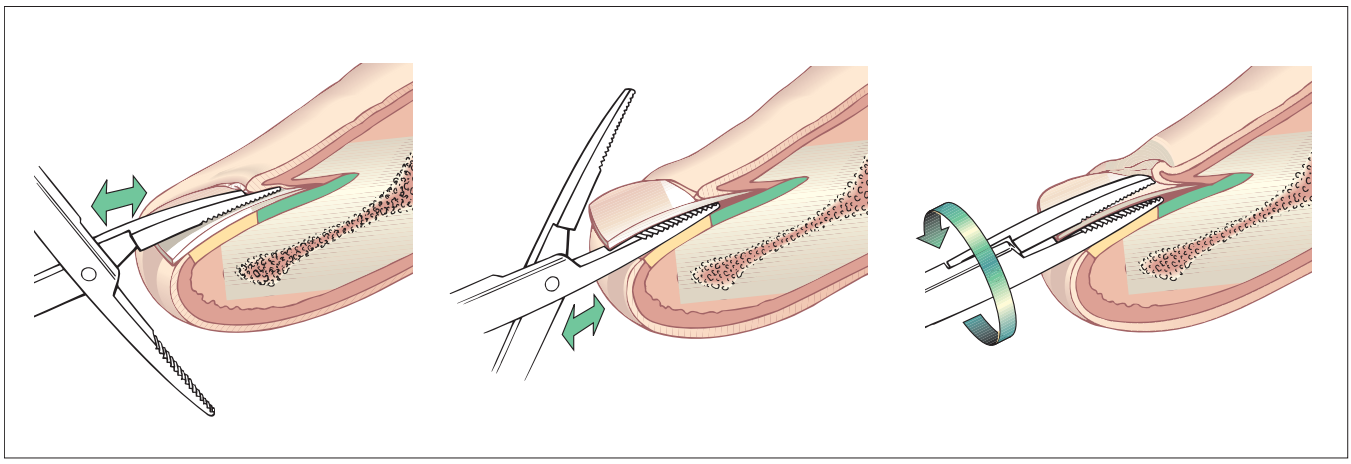

Fig. 62.38 The three stages of standard nail avulsion.

matrix pathology occurs laterally, longitudinal biopsy may be warranted to preserve the shape of the nail, which can otherwise be altered by local matrix surgery. Early literature suggested that longitudinal biopsies of less than 3 mm in width could be taken from the midline of the nail without scarring [3] but it is now accepted that this may produce long-term nail dystrophy.

The first incision starts in the lateral nail sulcus, between the nail and nail fold. The distal limit is just beneath the distal groove, in the tip of the digit. Proximally, the incision extends almost to the first of the transverse skin markings of the distal interphalangeal joint. The medial margin of the ellipse is formed by an incision through the nail plate, which has been softened by an antiseptic soak. Both incisions are down to bone and separated by 3 mm at the widest point. The specimen is released from its deep attachment from the distal point proximally. The nail can be lifted at the free edge with forceps, allowing the bottom of the specimen to be released with curved iris scissors. Particular care is needed at the proximal end to ensure that the matrix is fully sampled without damage.

A 3/0 or 4/0 monofilament suture is used for closure. One suture closes the wound through the proximal nail fold. One or two further sutures are needed through the nail plate and lateral nail fold. The suture is designed to elevate the lateral nail fold and enhance the embedding of the new nail edge in the nail fold (Fig. 62.40).

The nail will be permanently narrowed following this procedure and the contour of the lateral and proximal nail fold intersection is altered to provide a more acute angle. In spite of the specialized suture to elevate the lateral nail fold, the nail is seldom fully embedded in a new lateral sulcus. Where biopsies of greater than 3 mm width are taken, the nail may develop malalignment, with distal deviation towards the side of the biopsy [4].

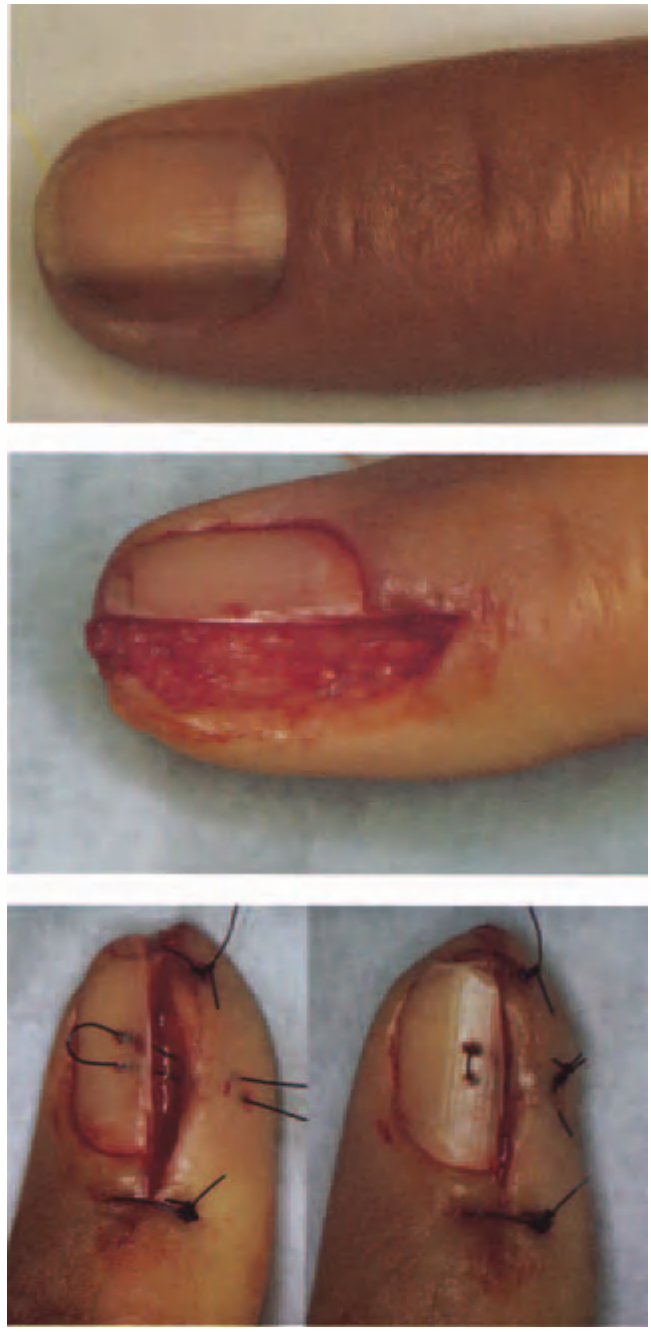

Fig. 62.40 A large, lateral, longitudinal nail biopsy is closed with sutures designed to reconstruct the lateral nail fold.

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Transverse matrix biopsy (Fig. 62.41)

A transverse matrix biopsy may be performed to investigate focal abnormality of a nail dystrophy arising from the matrix.

The proximal nail fold is reflected following an oblique incision at the junction with the lateral nail folds and gentle separation of the proximal nail fold from the dorsal aspect of the nail plate. The matrix is then visualized by performing a proximal hemi-avulsion. A thin ellipse is taken from the distal matrix with the distal margin of the excision matching the shape of the lunula.

The wound may be gently undermined, taking care with the extremely fragile matrix epithelium and undermining most on the distal nail bed margin. Loose sutures with resorbable 6/0 monofilament can be used.

Once healed, a blemish may remain in the margin of the lunula. The nail plate will show changes in thickness proportional to the extent of the biopsy.

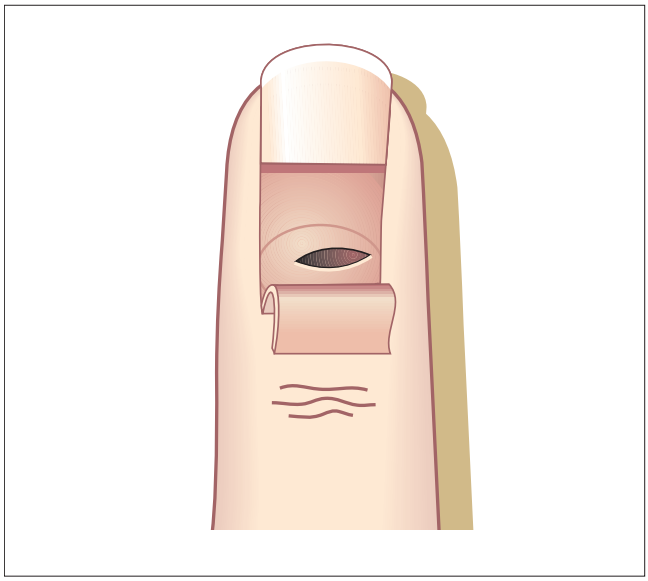

Fig. 62.41 Crescentic or narrow elliptical transverse matrix biopsy, which can be performed after removal of the proximal half of the nail plate alone.

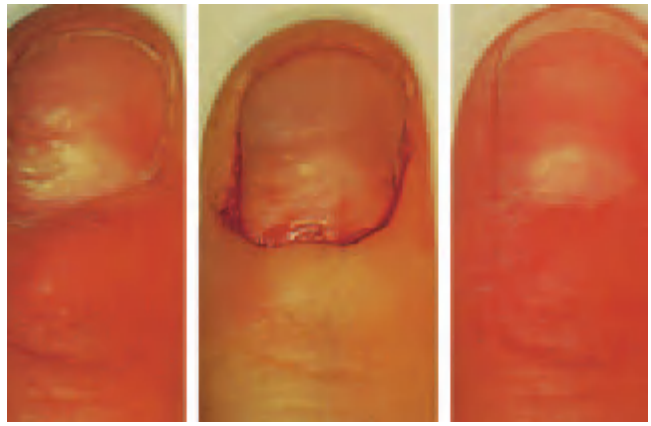

Fig. 62.42 Crescentic shave of the distal proximal nail fold and cuticle as treatment for chronic paronychia. Also provides histological specimen where biopsy relevant.

Nail fold biopsy [1–4]

Proximal nail fold biopsy

It may be necessary to biopsy the proximal nail fold to investigate a local dermatosis, connective tissue disease or focal tumour. The biopsy can be taken in different axes, but preservation of the symmetry and curvature of the proximal nail fold is a priority. If sutures are to be used, a distal wing block should be avoided, as the tissues will become turgid and difficult to manipulate.

Transverse nail fold biopsy

A transverse ellipse (for connective tissue disease), a 2-mm punch (far from the free edge) or a shave biopsy are simple nail fold procedures. The transverse ellipse and punch biopsies are down to the dorsal aspect of the nail plate. The matrix may require protection from cutting trauma and this can be achieved by inserting a septum elevator between the nail fold and the nail.

The transverse biopsy requires 4/0 monofilament suture. Wounds from other biopsy methods can be left to heal by secondary intention. Postoperatively, a thin line may remain in the nail fold after the transverse biopsy; otherwise, these techniques leave little or no scarring. There is no nail plate change.

Crescentic nail fold biopsy (Fig. 62.42)

A larger nail fold biopsy can be taken as a distal crescentic wedge. A crescentic incision is performed just proximal to the cuticle with the blade bevelled to direct trauma away from the proximal matrix if the nail is penetrated. Additional matrix protection may be provided by inserting a septum elevator beneath the proximal nail fold. The distal fraction of the proximal nail fold (including the cuticle) can be removed, although the width of the specimen should not exceed 4–5 mm in the midline. The contour is aimed at recreating a new edge to the entire nail fold. The wound heals by secondary intention and a new cuticle usually reforms, depending upon the original problem. The amount of exposed nail is permanently enlarged, but the nail surface is unchanged unless ridging or grooves produced by the original pathology are reversed.

This technique can be used for the excision of chronic paronychia resistant to routine therapy. It has also been recommended for the excision of digital mucous cysts occupying the most distal margin of the nail fold. At this site, it is argued that the lesions are solely degenerative and do not communicate with the joint space [3,4].

Focal nail fold biopsy

Focal pathology in the nail fold can be excised by a V-shaped incision into the nail fold. The excision is through the entire thickness of the nail fold, but should not penetrate underlying nail. Relaxing incisions are made at one or both of the lateral margins of the proximal nail fold (Fig. 62.43). The primary defect is closed with 4/0 monofilament and the relaxing incisions heal by secondary intention. Wounds in the midline of the nail fold can leave some scarring, but the nail plate is usually unaffected.

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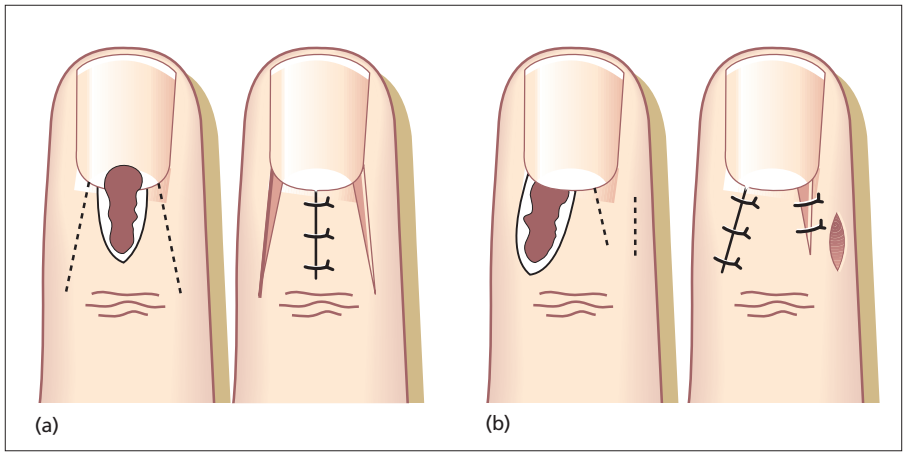

Fig. 62.43 Method for removing a small lesion from the proximal nail fold.

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Nail plate biopsy [1,2]

It is sometimes useful to biopsy the nail plate, with or without a small piece of the hyponychium. This may help differentiate between onychomycosis and psoriasis. If hyponychium is included, a small bleb of anaesthetic will be needed or a distal wing block can be performed. A chunk of distal nail plate of at least 3 mm width is then removed with large nail clippers. Subungual debris should also be obtained and a scalpel may be needed if hyponychium is attached. Hyponychial wounds heal by secondary intention after cautery haemostasis and leave no scarring.

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Lateral matrix phenolization [1,2]

Ingrowing nails, particularly toenails, are treated in many different ways [1–5]. However, phenolization is quick, relatively painless and has a high success rate [6]. Any area of matrix may be phenolized, including total ablation. The procedure yields no specimen other than the nail plate.

After anaesthetic, antiseptic soak and tourniquet, the margin of lateral ingrowing nail is avulsed using nail splitters to separate it from the rest of the nail plate. The nail folds are then protected with a layer of yellow soft paraffin and 85% aqueous phenol is applied on the end of an orange stick to the exposed matrix. This is done for 3 min (one stick per min), before douching with 70% alcohol to neutralize the chemical cautery. Although 3 min is common practice [1], in a series of 537 ingrowing nails, phenol was applied for 5–6 min and a 99% 1-year cure rate was achieved, with a mean healing period of 20 days [2].

As a result of this chemical burn, there is some ooze from the wound, which can occasionally last several weeks, but it is seldom infected and often pain-free. If the ooze is prominent, the toe should receive daily potassium permanganate or povidone–iodine soaks, after culture for specific microbes. The nail is permanently narrowed.

There is occasionally a small element of lateral nail regrowth, although further surgery is only indicated if there is repeated symptomatic ingrowing. Complete nail ablation can be achieved using the same technique applied to the entire matrix.

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Other surgical modalities

Mohs' micrographic surgery

This technique applied to the nail unit exploits the principle of maximum conservation of healthy tissue while ensuring tissue clearance of tumour. It is particularly use-

ful in squamous cell carcinoma of the nail unit (see p. 62.41), where it should be offered as an alternative to digit amputation when there is no evidence of invasion of bone by tumour [1,2]. At this site, the conservation of normal tissue is of considerable functional significance. The place of Mohs' surgery in treatment of pigmented lesions of the nail apparatus remains to be fully explored. There is limited evidence of its use in nail melanoma [3].

Cryosurgery

Cryosurgery is widely used for the treatment of periungual warts. There is a small risk of damage to the tendons in the finger with aggressive freezing techniques. It is also used for myxoid cysts [4,5]. The cysts should be evacuated of their mucoid contents before a double 20-s freeze–thaw cycle. EMLA (eutectic mixture of local anaesthetics) or injected local anaesthetic may sometimes be needed. This regimen produces cure in approximately 25% of cases [5], although more aggressive freezing can produce better results [4].

Infrared photocoagulation

This has been used as a treatment for myxoid cysts of the proximal nail fold [6]. The contents are evacuated through a puncture wound before treatment.

Carbon dioxide laser

There is a range of indications for carbon dioxide laser [7–9], and its virtue may be in provision of a bloodless wound which allows a good view of the surgical procedure. This can only normally be provided in cold-steel surgery by an effective tourniquet.

The bulk of laser work on the nail unit is for subungual and periungual warts. This uses the defocused mode with a 1–2 mm spot at 5–10 W output and can be intermittent, in 0.05-s bursts, or continuous. Haemostasis may not be complete, and both anaesthetic and tourniquet are usually used with the laser.

It is also useful as a focused destructive instrument in the treatment of myxoid cysts [10] and ablation of abnormal nail in irreversible nail disorders. This includes partial destruction of the matrix of nails in ingrowing nails [11] and in pachyonychia congenita to reduce nail thickness.

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Traumatic nail disorders

Nails may show signs of acute trauma, scars following acute trauma or chronic repetitive trauma.

Acute trauma

Acute trauma is classified with respect to severity, ranging from a small haematoma to digit amputation (Table 62.5).

Table 62.5 Classification of acute trauma. (From Van Beek *et al*. [1].)

Type	Effect	Therapy
I	Small haematoma associated with a small break in the nail bed	Fenestration of nail over the haematoma
II	Large haematoma with significant nail bed injury	Remove nail in order to identify site and nature of subungual damage
III	Large haematoma, nail plate displaced	X-ray may reveal fracture of terminal phalanx, usually in association with nail bed laceration which requires resorbable 6/0 suture
IV	Severe crush injury	Avulsion needed to reveal matrix, with multiple lacerations requiring careful reconstruction
V	Amputation of tip of digit, may include parts of matrix	If tip can be retrieved, it should be used as a graft. Otherwise nail bed from other sites may provide autologous grafts

Nail bed laceration

The nail bed may be lacerated by different forms of trauma, including incisions, crush and avulsion injuries. In simple injuries there is displacement of the nail plate, which may be found proximally avulsed but retaining distal attachment to the nail bed. In this form of trauma, and in many others, the nail plate can be used as a useful splint [1]. Initially, the nail bed damage should be assessed by avulsion, and then the nail can be replaced after any necessary nail bed repair has been performed; a small window for drainage of blood and exudate is made in the nail [2]. More complicated injuries may require flap or graft reconstructions and, in some instances, vascularized composite nail grafts are used with microvascular anastomoses. When the wounds arise from crush injury, fracture is relatively common. If the distal tuft has been fractured to leave fragments of bone dispersed in the soft tissues, it may prevent long-term morbidity if these are removed [3].

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Delayed trauma

The most common kind of chronic deformity following an acute injury is a split nail or reduction in the length of the nail bed with consequent overcurvature of the tip of the nail.

Cure of a split-nail deformity is difficult, with only a modest chance of success [1]. Sometimes, there is an associated pterygium. Treatment entails excision of the nail bed and matrix scar and, in the case of a pterygium, a split-skin graft may be placed on the ventral aspect of the proximal nail fold to help prevent recurrence of the pterygium. It is important to keep the wounded aspects of nail bed or matrix separate from the overlying nail fold after surgery, and this is often best done by returning the nail plate after soaking it in antiseptic during the procedure.

If treatment is required for a shortened distal phalanx with nail bed changes, there are two choices [2]: the entire nail can be phenolized, or a V–Y advancement flap can be performed based on two neurovascular pedicles.

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Haematoma [1,2]

Subungual bleeding is a common sign. It may present as a feature of acute trauma, with pain due to the recent event in combination with pain arising from the pressure exerted by the subungual accumulation of blood. A haematoma arising within the matrix will be incorporated into the nail plate [3]. The only treatment that can be offered is to relieve the pressure, and if seen soon after the injury this can be done by puncturing the nail, for instance with a hot pointed implement, cautery or a small drill. This procedure will relieve pain and may save the nail. The possibility of an underlying fracture must be considered for larger haematomas [1]. As a general rule, if more than 25% of the visible nail is affected, the nail plate should be removed. However, there is evidence to challenge this rule. A comparison between two groups of children having exploration and repair or trephination alone showed fewer complications in the latter group and considerably less investment in medical time [4]. With less extreme trauma, a haematoma may not develop immediately and may be painless. This is most common in the toes and may give rise to clinical uncertainty as to whether it represents early subungual melanoma. A history of traumatic sporting hobbies is useful, and signs of symmetrical nail trauma and inappropriate footwear all point towards trauma as the cause of the appearance. In this situation, making a small punch in the surface of the nail may reveal old blood as the source of pigment. Malignancies can bleed and so confirmation of blood does not refute the possibility of a tumour; however, as an isolated finding in the absence of other clues, this test should be sufficient to obviate the need for surgical exploration. An alternative is to score a transverse groove in the nail at the proximal margin of the pigment and observe over a few weeks as the discoloration grows out. If pigment continues to spread proximal to the groove, surgical exploration is needed.

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Chronic repetitive trauma

Chronic repetitive trauma may take several forms. Some have been considered in other sections detailing transverse ridges produced by a habit tic (see Fig. 62.22, p. 62.28), the canaliform dystrophy of Heller (Fig. 62.44; see p. 62.55) and chronic paronychia (see Fig. 62.18, p. 62.24).

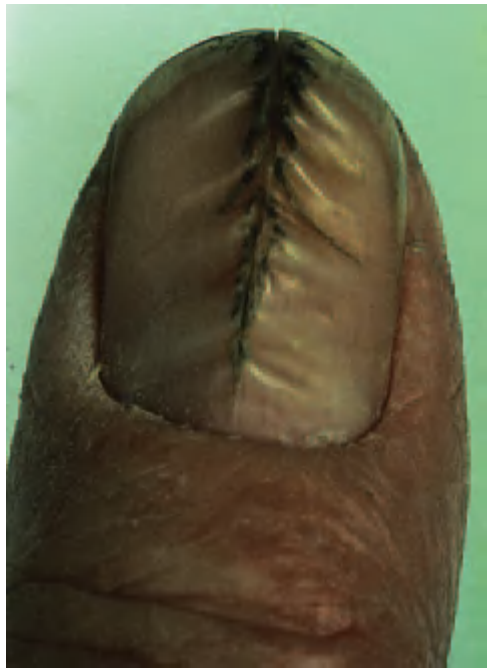

Fig. 62.44 Median canaliform dystrophy of Heller.

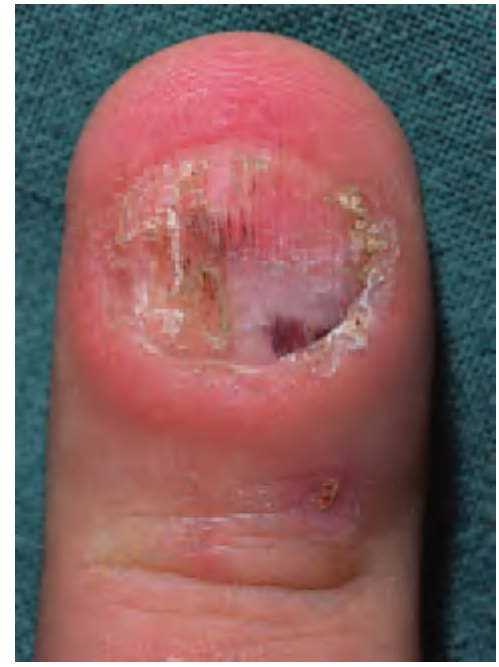

Fig. 62.45 Nail biting can be extensive, with damage to the nail folds and nail plate causing subungual haemorrhage.

Nail biting

The nail plate, periunguium and nail bed are all subject to nail biting and picking. Although fingers are most commonly involved, rarely toenails are also bitten [1]. This produces distinctive features, which are found in 60% of children, 45% of adolescents and 10% of adults [2]. The majority of moderate nail biters have no associated psychiatric disorder [3,4]. Focal abnormalities, such as viral warts, are often a complication, whether as a cause or as a result of the Koebner effect after biting. Severe damage may be associated with self-mutilating disorders such as Lesch–Nyhan syndrome.

The nails are typically short, with up to 50% of the nail bed exposed. The free edge may be even or ragged. Surface change may include splitting of the nail into layers or a sand-papered effect, and the nail may acquire a brown longitudinal streak [5]. The most aggressive nail biting (onychotillomania/onychophagia) can produce subungual haemorrhage, strips of nail loss, with residual spurs or loss of the entire nail (Fig. 62.45). Onychotillomania may be allied to parasitophobia when the patient picks off pieces claiming that they contain parasites [6]. A rough and irregular nail and nail fold may result. Many fingernails are involved. Oral pimozide may be beneficial [7].

Direct damage and secondary infection may make nail loss permanent or result in pterygium formation. The nail folds are sometimes bitten in addition to, or as a substitute for, the nail. This can lead to bleeding and chronic paronychia with acute infective exacerbations. This in turn may lead to nail plate damage or ridging and nail fold scarring. In cases associated with infection, osteomyelitis of the terminal phalanx can develop [8,9]. Subjects will sometimes deny nail biting and attribute the appearance to a disease that stops nail growth. Transverse grooves scored proximally in the nail plate will confirm that the nail is growing by moving distally with time. In aggressive nail biting, the groove may be eroded from the surface.

Trauma is sometimes inflicted by other nails, with pushing back of the proximal nail fold as part of a habit tic (see p. 62.28). This results in serial transverse ridges and depressions running up the midline of the nail, associated with loss of the cuticle. In more conscious forms of self-damage, sharp instruments are used to produce dermatitis artefacta of the nail unit, and the nail fold is commonly preserved [10].

Treatment. Treatment is often unsuccessful and cure relies largely on the motivation of the patient. Local antiseptics and antimicrobial ointments may help settle the infection secondary to nail unit damage. Those with the most bitter taste are often prescribed in the belief that this will discourage biting. This is seldom the case. Antidepressants [11] and behavioural therapy [12] have been used with some success in limited studies.

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Hang nails

These are due to hard pieces of epidermis breaking away from the lateral nail folds. Although often due to nail biting, they may result from many other minor injuries. The splits may be painful when they penetrate to the underlying dermis. They should be removed with sharp pointed scissors.

Nutcracker nails

Under this heading, Cohen [1] described splitting and onycholysis caused by the habit of separating the two halves of cracked walnuts over a period of 10 years.

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Damage from nail manicure instruments

Metal instruments, such as a nail file or scissors, wooden or plastic orange sticks, or nail whitener pencils may create acute or chronic injuries in the nail area. Onycholysis may result from using the sharp point for cleaning under the nail plate. Nails, however, are best cleaned with a nail brush and soap, because overzealous manicure, pushing back the cuticles, may result in white streaks across several nails. Cleaning around the nail with contaminated instruments may lead to acute or chronic paronychia. According to Brauer and Baran [1], it is not advisable to cut or clip the nail plate, as this produces a shearing action that weakens the natural layered structure and promotes fracturing and splitting. An emery board is preferred for shaping the fingernail by filing from the sides of the nail towards the centre.

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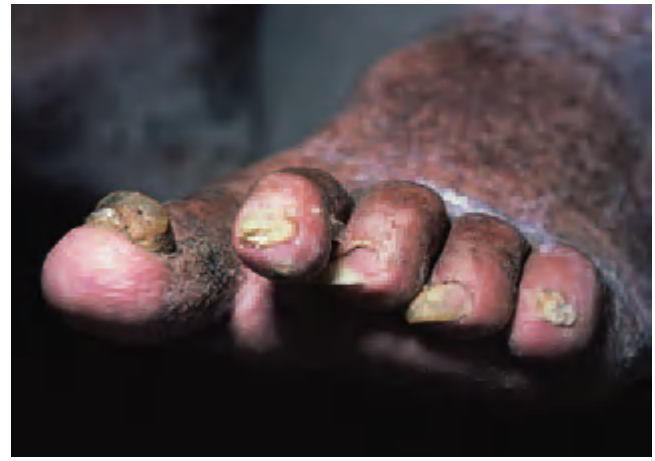

Fig. 62.46 Early onychogryphosis of the left great toenail.

Trauma from footwear

Onychogryphosis and nail hypertrophy [1–5]

Onychogryphosis is an acquired dystrophy usually affecting the great toenail, which is thickened, yellow and twisted. It is most commonly seen in the elderly [1,2,4], although trauma and biomechanical foot problems may precipitate similar changes in middle age or earlier.

At one time, onychogryphosis was known as ostlers' nail, owing to the fact that some cases could be traced to injury caused by a horse trampling on the foot of the ostler. Competitive sport is a more contemporary cause. The injury once sustained is aggravated by footwear and, as the nail becomes longer and thicker, the damage from the footwear becomes progressively more important. Nail hypertrophy implies thickening and increase in length, whereas onychogryphosis implies curvature also.

Some cases of nail hypertrophy are intrinsic, and this applies especially to toenails other than the nail of the great toe. The nail becomes thick and circular in cross-section instead of flat, and thus comes to resemble a claw. There are two possible explanations for this formation.

1 There is insufficient matrix under cover of the posterior fold to exert a flattening effect. The altered relationship between matrix and proximal nail fold in post-mortem specimens supports this.

2 The nail bed is contributing a greater quantity of keratin to the nail than usual. It is usually possible to exclude this on clinical grounds as there is often an element of onycholysis that separates the dystrophic nail from the nail bed.

Hypertrophy of fingernails is usually traumatic in origin and is often the result of a single injury.

In onychogryphosis, one or more nails become greatly thickened (Fig. 62.46) and, with neglect, increase in length, becoming curved like a ram's horn. The nails of the great toes are most often involved, but no toenail is exempt. It is possible that the nail plate distortion produced by chronic untreated onychomycosis may be partly responsible for

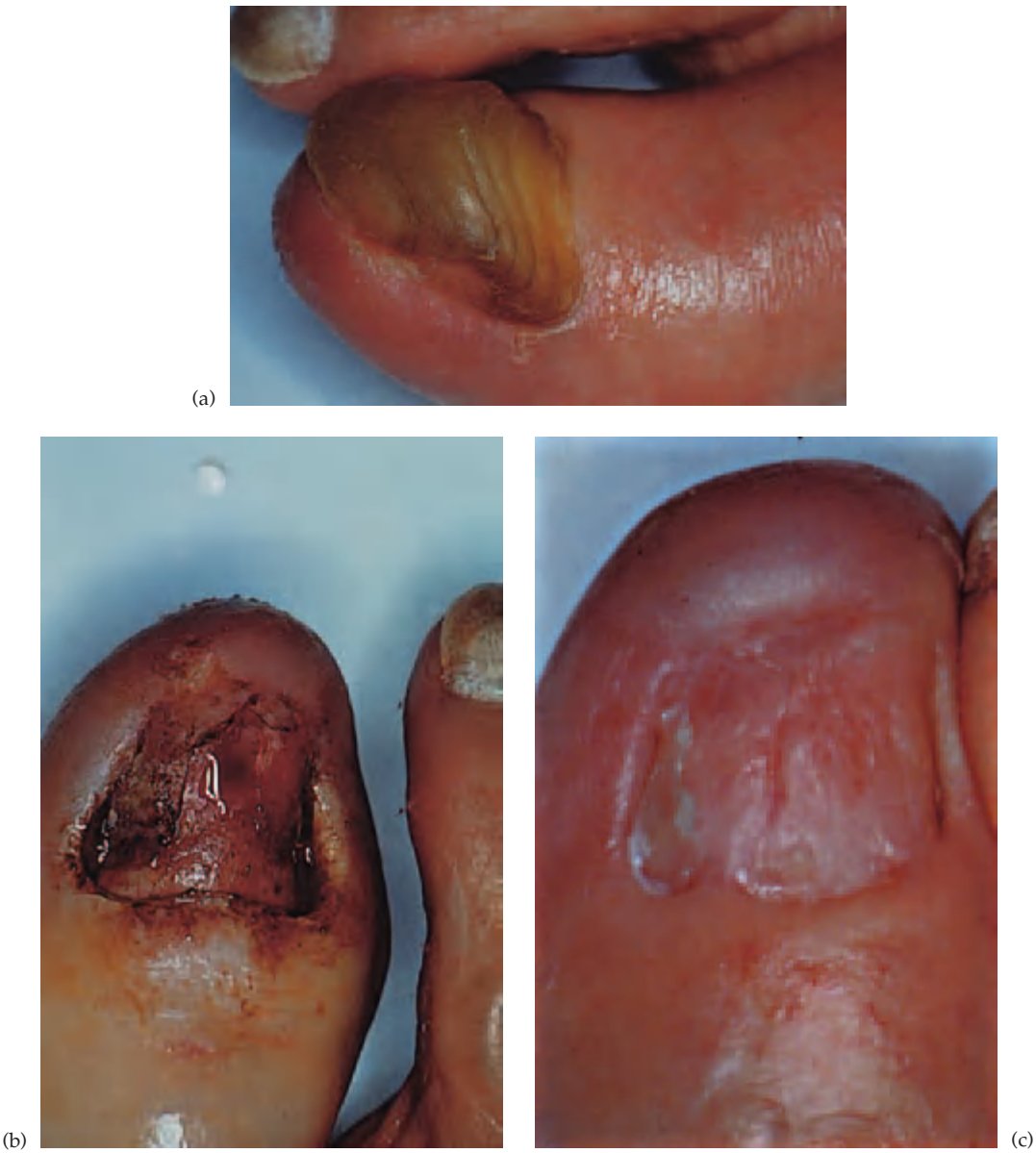

Fig. 62.47 (a–c) Onychogryphosis is often best treated with ablation of the nail matrix.

onychogryphosis at a later stage. In extreme cases, the free edge may press on or even re-enter the soft tissues of the foot.

Treatment of onychogryphosis and nail hypertrophy is either radical or palliative. Radical treatment consists of surgical removal of the nail and matrix and is recommended in those with good circulation (Fig. 62.47). Palliative treatment requires regular paring and trimming of the affected nails, usually by a chiropodist using nail clippers and a file or mechanical burr. The thickened nails are extremely hard and trimming is difficult. Not infrequently, the nail is invaded by granulation tissue from the nail bed, and incision of this during trimming will result in pain and haemorrhage.

Other causes of thickened nails are psoriasis, pityriasis rubra pilaris, Darier's disease, fungal infections, pachyonychia congenita, congenital ectodermal defects and congenital malalignment of the great toenails [6].

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Ingrowing toenail [1–3]

SYN. ONYCHOCRYPTOSIS

The soft tissue at the side of the nail (lateral nail fold) is penetrated by the edge of the nail plate, resulting in pain, sepsis and, later, the formation of granulation tissue [4]. Penetration is often caused by spicules of nail at the edge of the nail plate, which have been separated from the main portion of the nail. The great toes are those most often affected. The main cause for the deformity is compression of the toe from the side due to ill-fitting footwear, and the main contributory cause is cutting the toenails in a half-circle instead of straight across. Anatomical features, such as an abnormally long great toe and prominent lateral nail folds, are important in some cases. In recent years, the condition may have been caused in a minority of cases by the successful therapy of fungal infections of the nails with griseofulvin: a nail that has been infected for a long time is reduced in size, and the nail bed shrinks around it; when the infection is even partly overcome the nail plate is increased in size, the nail bed is no longer large enough to accommodate the whole of the new nail, and the lateral nail fold may be penetrated on each side.

In infancy, ingrowing toenail most commonly occurs before shoes are worn, associated with crawling, 'pedalling' or wearing undersized 'jumpsuits' [5]; acute paronychia may be associated [6]. Rarely, it is congenital [7] and even familial [2]. In children, ingrowing is commonly distal rather than lateral. Management is conservative in most instances, with topical steroid and antiseptic preparations. Surgery is occasionally required [8].

The first symptoms are pain and redness, shortly followed by swelling and pus formation. Granulation tissue then forms and adds to the swelling and discharge. More severe infection may follow. There is seldom any difficulty with diagnosis. Excess nail fold granulation tissue can also be a feature of amelanotic melanoma and reactions to medications such as retinoids, ciclosporin, antiretroviral drugs and chemotherapy [9–15].

Treatment. Treatment may be difficult and prolonged. The first essential is to insist on the patient wearing shoes sufficiently wide and pliable to remove lateral pressure [16]. Any abnormality of foot/toe function should be corrected. The patient must also be instructed to cut the nail straight across instead of in a semicircle. The nail must be allowed to grow until its edges are clear of the end of the toe before it is cut; this prevents the further formation of marginal spicules. In the early stages, the infection may be overcome by the application of antiseptics and by inserting a pledget of cotton-wool under the edge of the nail. Taping the toe or applying plastic gutters between nail edge and nail fold are alternatives [17]. Twice-daily warm-water baths followed by careful drying and powdering are helpful. If the infection is more severe and there is local cellulitis, an appropriate systemic antibiotic should be administered. When granulation tissue forms this should be destroyed by cauterization with a silver nitrate stick. It is important that an amelanotic melanoma is not missed [18], and if there are atypical features a biopsy should be performed.

If conservative measures fail, operative intervention will be necessary. Removing the nail alone is likely to result in recurrence of ingrowing when the nail returns [19] and so should be combined with a curative procedure such as phenolization of the relevant part of the matrix [4,20]. Although surgical excision of matrix can provide an excellent result, it is more dependent than phenolization on the skill of the practitioner. In large studies, phenol treatment results in a greater cure rate and less morbidity [19]. Where there is diabetes or impaired peripheral circulation, surgery may require avoidance of prolonged or tight tourniquet application, and close follow-up. Phenolization can be undertaken safely in diabetics [21]. Carbon dioxide laser has been used, although it lacks the analgesic properties intrinsic to phenol [22].

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The nail and cosmetics

Dermatologists need to know the therapeutic options open to a patient when drugs or surgery may not provide the ideal aesthetic or functional solution to a medical problem. Professional cosmetic advice may be the most appropriate step in some cases, such as individuals with permanent unsightly dystrophy. However, the dermatologist may gain most experience of nail cosmetic products through their adverse effects, as they occasionally cause injury to the nail and surrounding tissues and may cause reactions at distant sites. In this section, the basic ingredients of nail preparations are considered together with the pathological changes sometimes induced by them [1,2]. In assessing eczematous and other periungual reactions, it is important also to realize that nail tissues, particularly the subungual and paronychial areas, may be 'reservoirs' for small amounts of cosmetic preparations applied by hand to other parts of the skin, leading to 'ectopic dermatitis'; these may also, rarely, be responsible for dystrophy of the nail apparatus.

Nail coatings represent an attractive nail enhancement. They may harden upon evaporation (nail polish) or polymerize (sculptured nails, gels, preformed artificial nails).

Coatings that harden upon evaporation

Nail polish

The term 'nail lacquer' is sometimes used to include enamels, top coats and base coats, either as separate entities or combined in one product. Although chemically similar, they contain different ratios of the same constituents to lend different characteristics. The base coat is used to improve the adhesion or bonding of enamel to the nail. A top coat improves the depth and lustre of the enamel and increases its resistance to chipping and abrasion. Nail polishes consist of solids and solvent ingredients, the former representing about 30%, the latter 70% of the product. The ingredients can be divided into six principal groups.

1 Cellulose film formers (e.g. nitrocellulose): provide gloss, body and gel structure.

2 Resins (e.g. toluene sulphonamide formaldehyde resin): improve the gloss and adhesion of the film.

3 Plasticizers (e.g. dibutylphthalate): give the film pliability, minimize shrinkage, and soften and plasticize the cellulose.

4 Thixotropic suspending agents (e.g. bentonite) for non-settling and flow: keep pigments in suspension on shaking.

5 Solvents and diluents (e.g. toluene): keep nitrocellulose, resin and plasticizer in the liquid state and control the application and drying time.

6 Colour substances: these are either inorganic (iron oxides) or a variety of certified organic colours (D and C yellow A1 lakes).

Recently, there has been a move away from toluene and formaldehyde resin, and most recently avoidance of dibutylphthalate due to potential health risk.

'Pearls' or 'frosts' are produced by bismuth oxychloride and titanium dioxide coated with mica and guanine (obtained from fish scales). 'Clears' contain a small tint.

The base coat is formulated in a manner similar to standard lacquer, but it has a lower non-volatile content (less nitrocellulose) and lower viscosity, because a thinner film is desirable; it may also contain hydrolysed gelatine. In the top coat the nitrocellulose content is increased and the resin is reduced. A slight increase in plasticizer content improves elasticity of the film. There is no pigment. The top coat often has an added sunscreen.

Reactions such as an allergic contact dermatitis to nail polish frequently appear on any part of the body accessible to the nails, with paradoxically no signs in or around the nail apparatus [3]. The commonest areas involved are the eyelids, the lower half of the face, the sides of the neck and the upper chest. Generalized dermatitis may rarely occur. Sometimes the use of nail polish on stockings to stop 'runs' or on nickel-plated costume jewellery to prevent nickel dermatitis may induce nail-polish dermatitis on the legs or at the site of metal contact. Nail-polish dermatitis may occur in the user's partner or other close contacts. Although any ingredient may account for distant allergic contact dermatitis, toluene sulphonamide formaldehyde resin is the most common culprit. After the nail polish is removed, the dermatitis usually clears rapidly unless secondary infection or lichenification has occurred. Metal pellets present in some bottles to maintain a liquid state may cause nickel reactions and onycholysis.

Nail plate staining from the use of polish is most commonly yellow/orange in colour. It typically starts near the cuticle, extends to the nail tip and becomes progressively darker from base to tip. With time, the dyes penetrate the nail too deeply to be removed. Injury to the nail plate from nail lacquers is rare. However, 'granulation' of nail keratin, a superficial friability, can be observed in some instances where individuals leave nail lacquer on for many weeks or where there is poor formulation of the product. For patch testing, several nail lacquers should be used and tested 'as is'; they should be allowed to dry for 15 min because the solvents and diluents may cause false-positive reactions. The following substances should be included in the test battery.

Toluene sulphonamide formaldehyde resin (10% in petrolatum)

Nickel (5% in petrolatum); dimethylglyoxime spot test for nickel

Glyceryl phthalate resin (polymer resin) (10% in petrolatum)

Pearly material: guanine powder (pure)

Formaldehyde (1% aqueous)

Colophony (20% in petrolatum); drometrizole (Tinuvin P) (1–5% in petrolatum).

The resin contains no free formaldehyde. Formaldehyde is merely the chemical moiety on which the resin is formed. Usually, formaldehyde-sensitive individuals do not cross-react with this resin. However, it has been suggested that there is always a small amount of free formaldehyde present in many preparations. Various cosmetic companies now make varnishes that are formulated without the sensitizing resin and are toluene-free.

Nail polish removers. These are composed of various solvents such as acetone. Occasionally, nail polish removers cause trouble by excessive drying of the nail plate and may be responsible for some inflammation of nail folds.

Coatings that polymerize [4,5]

Sculptured nails

The basic kit of sculptured nails is sold as a set containing a template, a liquid monomer and a powdered polymer. Self-curing acrylic resins are created by polymerization of methyl methacrylate monomer and polymethyl methacrylate powder with an organic peroxide and an accelerator. They harden at room temperature. The compound has to be moulded on the natural nail. The acrylic compound is applied to the nail, which has been roughened on the surface. When hardened, the compound produces a prosthetic nail that is enlarged and elongated by repeated applications. The prosthesis can be filed and manicured to shape; as the plate grows out, further applications of acrylic can be made to maintain a regular contour.

Technicians who sculpt nails should be instructed to wash their hands before touching the face or eye area. Usually, the area involved is the chin, which technicians tend to rest in their hands. Additionally, they should be warned to avoid contact with the dust of freshly applied product and to avoid using the wet product.

Allergic reactions. Allergic reactions due to sculptured nails may occur 2–4 months, and even as long as 16 months, after the first application. The first indication is an itch in the nail bed. Paronychia, which is usually present in allergic reactions, is associated with excruciating pain in the nail area, and sometimes with paraesthesia. The nail bed is dry and thickened, and there is usually onycholysis. The natural nail plate becomes thinner, split and sometimes discoloured. It takes several months for the nails to return to normal. Permanent nail loss is exceptional, as is intractable prolonged paraesthesia [6].

Patch tests most commonly show reactions to the acrylic liquid monomer and not to the polymer; this is similar to denture allergy (see Chapter 20).

Improper application and maintenance. With continued wear, the edges of the sculptured nails become loose. These must be clipped and then rebuilt to prevent the development of an environment prone to bacterial and, beneath the nail plate, candidal infection. In fact, this is a result of improper application and maintenance. Failure to file the prosthetic nail every 2 weeks will result in the creation of a lever arm that predisposes to traumatic onycholysis or damage to the natural nail. Onycholysis is very common with nail extensions that are too long.

Irritant reactions. Irritant reactions to monomers are possible. These manifest as a thickening of the nail bed's keratin layer, which can sometimes cause the entire nail bed to thicken with or without onycholysis. Nonetheless, the overwhelming majority of cases result from physical trauma or abuse.

Damage to the natural nail is not unusual after 2–4 months of wear of a sculptured nail. If it becomes yellow or crumbly, this means that the product was applied and maintained incorrectly. The patient should find a better-qualified nail technician. The problem may well not be the acrylic nail materials but rather the thinning of the nail due to excessive filing with heavy abrasives.

Primer (methacrylic acid) is a strong irritant, which may produce third-degree burns. It is hazardous if the cuticles are flooded or spills are not washed out immediately. Primer can permeate the plate and soak into the nail bed if the nails are too thin. Soap or baking soda, used with water, are excellent neutralizers. If primer gets into the eye, it should be flushed with water for at least 15 min, and a Poisons Information Centre should be contacted.

Premixed acrylic gels

Gel system products are premixed and either acrylic-based (14% of the market) or cyanoacrylate-based (1% or less of the market). Their virtual lack of odour makes gels popular in full-service beauty salons. UV light-cured gels are the best known of the different gel technologies. These gels contain urethanes and (meth)acrylate compounds, a photoinitiator and cellulose, which necessitates antiyellowing agents and a UV light unit. The gel remains in a semi-liquid form until cured in a photobonding box. The proportion of resins to monomers determines the gel consistency. When the gel is exposed to light of an appropriate wavelength, polymerization occurs, resulting in hardening of the gel. UV gels never involve catalysts and often do not employ primers.

Gel enhancement products shrink by up to 20%, which may result in lifting and tip cracking. As an effect of excessive shrinkage, clients may comment that the enhancement feels tight on the nail bed. Other symptoms include throbbing or warmth below the nail plate. This may lead to tender, sore fingertips. Photobonded acrylate has been observed to cause nail reactions, sometimes with nail loss and paraesthesia. Hemmer *et al*. [7] have patch tested

'hypoallergenic' commercial products in patients wearing photobonded acrylic nails who had perionychial and subungual eczema. Triethyleneglycol dimethacrylate, hydroxyfunctional methacrylates, and (meth)-acrylated urethanes proved to be relevant allergens in photobonded nail preparations. Meth-acrylated epoxy resin sensitization was not observed. The omission of irritant methacrylic acid in UV-curable gels does not reduce the high sensitizing potential of new acrylates. Contrary to the manufacturers' declarations, all 'hypoallergenic' products continue to include acrylate functional monomers and therefore continue to cause allergic sensitization. Gels and acrylics, being chemically distinct entities, will not necessarily cross-react.

Unreacted UV gel in the dusts and filings may produce distant allergic reactions. Although sensitization to butylhydroxytoluene is possible, gels usually contain acrylated oligomers and monomers. Acrylates are far more likely to cause sensitization than methacrylates or stabilizers.

Finally, thick ornately painted gel false nails that may be difficult to remove present a real challenge to pulse oximetry. It appears to be the polish more than the sculpted nail that interferes with the readings [8,9].

Preformed plastic nails

Preformed plastic nails are packaged in several shapes and sizes to conform to the normal nail plate configuration. Such nails are trimmed to fit the fingertip and are fixed with cyanoacrylate adhesive supplied with the kit. The usefulness of these prosthetic nails is limited by the need for some normal nail to be present for attachment. Normal physical and chemical insults to the nails cause the preformed plastic nails to loosen. If the preformed nails remain in place for more than 3 or 4 days, they may cause onycholysis and nail-surface damage. Eczematous, painful paronychia due to cyanoacrylate nail preparations may be observed after about 3 months. Dystrophy and discoloration of the nails may become apparent and last for several months. In some cases, distant contact dermatitis of the face and eyelids occurs. On patch testing, the patients react far more often to the adhesive than to the prosthetic nails. Suggested test substances are *p*-tertiarybutylphenol resin (1% in petrolatum), tricresyl ethyl phthalate (5% in petrolatum), cyanoacrylates and other glues (5% in methylethylketone).

Nail-mending kits

These include paper strips of a basic film-forming product to create a 'splint' for the partially fractured nail plate. The split is first bonded with cyanoacrylate glue, then the nail is painted with fibred clear nail polish. A piece of wrap fabric is cut and shaped to fit over the nail surface. This is then embedded in polish of high solid content, and several coats are applied.

Nail wrapping

In nail wrapping, the free edge of the nail should be long enough to be splinted with paper, silk, linen, plastic film or fibreglass and fixed with cyanoacrylate glue. After drying, the edge is shaped, and the nail is coated with enamel.

Removal of nail coatings that polymerize. The most commonly used solvent for removal of nail products is acetone. Warming the solvent with great care can cut product removal time in half. However, most gels are difficult to remove because they are highly cross-linked and resistant to many solvents. Therefore, if gel enhancements have to be removed, slowly file (not drill) the enhancement with a medium-grit file, leaving a very thin layer of product. Soak in warm product remover and, once softened, scrape the remaining product away with a wooden pusher stick.

Cuticle removers

These are lotions or gels containing approximately 0.4% sodium or potassium hydroxide. The lotion is left in place for 1–3 min and then washed off. Creams containing 1–5% lactic acid (pH 3–3.7) are also used.

Nail hardeners

Nail keratin can be hardened by tissue fixatives such as formaldehyde. These are not commercially available in the USA because of their toxic effects. Nail changes caused by such nail hardeners may include pain, subungual haemorrhage and bluish discoloration of the nail. The nail returns to normal when the offending agent is discontinued. Formaldehyde nail hardeners have been reported as causing onycholysis and allergic contact dermatitis; they may also act as irritants. Patch testing should be with formaldehyde (1% aqueous). Because of its irritant qualities, reactions should be interpreted with caution.

Silicone rubber nail prosthesis [10]

In a wide variety of cases, ranging from deformed nail to complete loss of the terminal phalanx, a silicone rubber, thimble-shaped finger-cover may be indicated. This prosthesis is easily fitted on the finger stump, encasing the entire distal phalanx; it must be fine and flexible to maintain pulp sensitivity and must have the same marking and colouring as the finger. The fixation is excellent and the nail form takes nail varnish well.

Nail cream

This is an ordinary water-in-oil moisturizing cream, with low water (30%) and high lipid content. It is applied, after cleaning the hands, to prevent or diminish brittleness.

Nail buffing

Weekly buffing may be indicated for removing small particles of nail debris, thus enhancing the lustre and smoothness of the nail plate. Buffing creams, which contain waxes and finely ground pumice, and buffing powders are abrasive and should not be overused on thin nails.

Nail whitener

This is a pencil-like device with a white clay (kaolin) core used to deposit colour on the undersurface of the free edge of the nail.

Infection risks

Secondary infection with *Candida* or bacteria is a hazard for anyone with an irritant or allergic contact dermatitis of the periunguium. Where this is associated with artificial nails, the prosthetic nails may be longer than usual and so reduce the ability to keep the area clean. Prosthetic nails are sometimes worn because there are underlying problems with the natural nails, such as cracks or onycholysis. These features may also lower the threshold to certain types of infection.

Medical staff with artificial nails may put patients at risk through carriage of pathogens [11] and it is a common operating theatre rule that artificial nails should not be worn [12]. Nail varnish is also thought to be associated with bacterial carriage when it becomes chipped, although the evidence for this is less strong [13]. Infection through nail salons and the manicuring process is a further factor that adds to the risks for those with artificial nails [14].

Conclusion

Nail beauty therapy may certainly produce an attractive enhancement and disguise unsightly nail conditions but it may also represent a potential hazard due to instrument damage, and is not recommended for psoriatic nails as it may provoke the Koebner phenomenon.

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Chapter 63

Disorders of Hair

D.A.R. de Berker, A.G. Messenger & R.D. Sinclair

Anatomy and physiology

[A.G. Messenger, pp. 63.1–63.18]

Introduction

Hair has no vital function in humans, yet its psychological functions are extremely important, as any clinical dermatologist or cosmetician can readily attest from routine daily practice. If the inevitability of scalp baldness makes it reluctantly tolerable to genetically disposed men, in women, loss of hair from the scalp is distressing as is the growth of body or facial hair in excess of the culturally accepted norm.

The evolutionary history of hair is no less enigmatic. Mammals probably evolved from Therapsid reptiles during the Late Triassic period over 200 million years ago (MyA). The earliest direct evidence of hair in mammals comes from fossilized casts and impressions in coprolites and pellets from the Late Paleocene beds of Inner Mongolia [1]. Hairs from at least four extinct mammalian taxa were identified, notably the multituberculate *Lambdopsalis bulla*, all showing striking preservation of the cuticular scale pattern. The three extant mammalian groups—monotremes, marsupials and placental mammals—all possess hair, indicating its presence prior to their divergence which probably took place 115–130 MyA [2]. The multituberculate lineage extends back into the Triassic, suggesting that hair is a very ancient and possibly defining feature of mammals. Whatever its origin, it is clear that the warm-blooded mammals owe much of their evolutionary success to the properties of the hairy pelage as a heat insulator. Paradoxically, Man's movement from the ancestral forest home to populate the globe is linked with a reversion to relative nudity and an ability to keep cool. Moreover, hair serves other purposes: in particular, it is concerned with sexual and social communication by constructing adornments such as the mane of the lion or the beard of the human male, or assisting in the dispersal of scents secreted by complexes of sebaceous or apocrine glands.

For these evolutionary reasons, hair follicles are not all under identical control mechanisms. To match the animal coat to seasonal changes in ambient temperature or environmental background requires moulting and replacement of the hairs. The process appears to involve an inherent follicular rhythm, modified by circulating hormones such as melatonin, prolactin, androgens or thyroxine, whose secretion is geared to environmental cues through the pineal gland, hypothalamus and pituitary.

The control of sexual hair growth must be clearly differentiated from that of the moult cycle. The development of pubic, axillary and other body hair is delayed until puberty because it is dependent upon androgens in both sexes; that 'male' hormones are, in contrast, also a prerequisite

for the manifestation of androgenetic alopecia still defies adequate explanation.

In all mammals, including humans but with the possible exception of the merino sheep and the poodle dog, hair follicles show intermittent activity. Thus, each hair grows to a maximum length, is retained for a time without further growth, and is eventually shed and replaced.

Types of hair

Different types of hair may be produced by different kinds of follicle, and the type of hair produced in any particular follicle can change with age or under the influence of hormones. Animals characteristically have both an overcoat of stiff guard hairs and an undercoat of fine hairs [3], but many kinds of follicle and fibre have been described. Many species also have large vibrissae or sinus hairs, which are sensory and are produced from special follicles containing erectile tissue, but there are no strictly comparable follicles in humans. In humans, a prenatal coat of fine soft unmedullated and usually unpigmented hair, known as *lanugo*, is normally shed *in utero* in the eighth to ninth month of gestation. Postnatal hair may be divided at the extreme into two kinds: vellus, which is soft, unmedullated, occasionally pigmented and seldom more than 2 cm long; and terminal hair, which is longer, coarser and often medullated and pigmented. However, there is a range of intermediate kinds. Before puberty, terminal hair is normally limited to the scalp, eyebrows and eyelashes. After puberty, secondary sexual 'terminal' hair is developed from vellus hair in response to androgens.

Development and distribution of hair follicles

Human hair follicles appear first in the regions of the eyebrows, upper lip and chin at about 9 weeks of embryonic development, and in other regions in the fourth month [4]. Hair over most of the scalp passes through a complete cycle and is shed *in utero*, and follicles in these regions have re-entered anagen by the time of birth. In the occipital scalp, telogen is delayed until after birth and this may give rise to a patch of hair loss in this region in the neonatal period. A fuller account of embryonic development is given in Chapter 3.

In humans, the full complement of hair follicles is probably established by the time of birth. Follicle density is highest in the fetus, when it may be similar across the skin surface. With growth there is a progressive reduction in follicle density, which continues until adult life, as skin surface area increases (Table 63.1). This occurs to a greater degree over the trunk and limbs than over the head so that the reduction in follicle density is less marked on the head than elsewhere [5]. The highest hair follicle densities, in the region of 800/cm^2, are found on the forehead and cheeks, with rather lower values for visible vellus hairs on the forehead in young adults of both sexes, and on the cheeks in women (400–450/cm^2) [6]. Lower hair densities of 50–100/cm^2 are found on the chest and back in both sexes [6,7], and follicle densities of approximately 50/cm^2 on the thigh and leg [5]. Published values for the average scalp hair density in white people vary between 250 and 320 hairs/cm^2 [8–11]. Scalp hair density shows a normal distribution in the population, with a wide range [11]. There is also racial variation in scalp hair density: average hair density in Africans (187/cm^2) [12] and African Americans (171/cm^2) [13] is lower than in white people, and it is lower still in Koreans (128/cm^2) [14].

Table 63.1 Hair follicle density in human fetal and adult skin. In adults, hair follicle density is highest on the head and much lower on the trunk and limbs. At 24 weeks' gestational age hair follicle density is similar in forehead and thigh skin. There is a pronounced reduction in thigh hair follicle density by adult life but only a small fall on the forehead. (Adapted from Szabo [5].)

	Fetal skin					
	24 weeks		Full term		Adult	
	Mean	±	Mean	±	Mean	±
Cheek					830	40
Forehead	1060		1060	110	765	20
Scalp					350	50
Forearm					95	15
Thigh	1010	250	480	40	55	5
Lower leg					45	10
Abdomen					70	15
Chest					75	25

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Anatomy of the hair follicle (Fig. 63.1)

Hair is the keratinized product of the hair follicle, a tube-like structure continuous with the epidermis at its upper end. The follicles are sloped in the dermis, and longer follicles extend into the subcutaneous layer. An oblique muscle, the arrector pili, runs from the mid-region of the follicle wall to a point in the papillary dermis close to the dermal–epidermal junction. Above the muscle, one or more sebaceous glands, and in some regions of the body an apocrine gland also, open into the follicle. The hair fibre is made up of three cell layers: an outer cuticle, the cortex (which forms the bulk of the fibre in most hair types) and a variable central medulla, all of which derive from highly proliferative cells in the hair bulb at the base of the follicle. Cells in the hair bulb also give rise to the inner root sheath which surrounds the hair fibre and which disintegrates before the hair emerges from the skin. The inner root sheath is itself enclosed by the outer root sheath, which forms a continuous structure extending from the hair bulb to the epidermis, although the functions and microscopic structure of the outer root sheath vary along the length of the follicle. The hair follicle also has a specialized dermal component, which includes the dermal or connective tissue sheath surrounding the follicle, and the dermal papilla which invaginates the hair bulb.

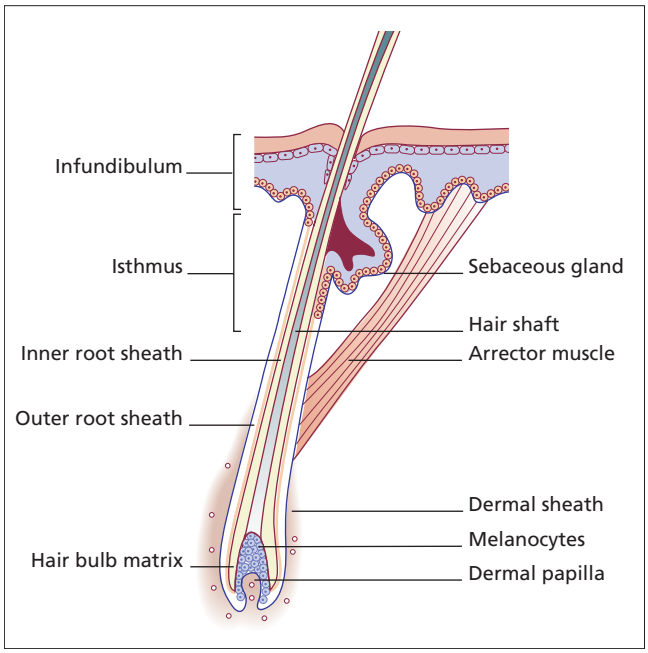

Fig. 63.1 Diagram of an anagen hair follicle.

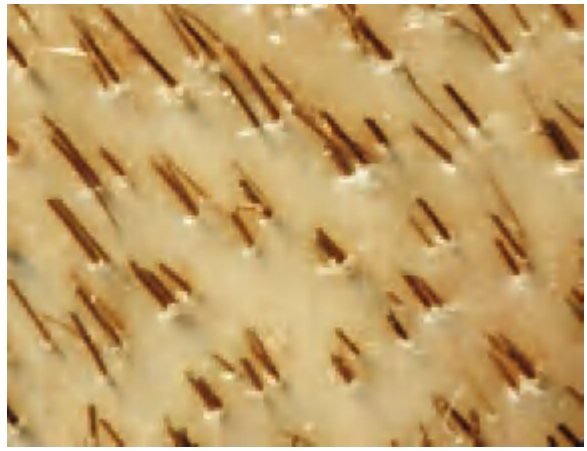

Fig. 63.2 Grouping of hairs in follicular units on human scalp. In some groups, multiple hairs emerge from a single follicular opening.

The hair follicle is conventionally divided into two regions: the upper part consisting of the infundibulum and isthmus and the lower part comprising the hair bulb and suprabulbar region. The upper follicle is a relatively constant structure, whereas the lower follicle undergoes repeated episodes of regression and regeneration during the hair cycle. On the scalp, and some other regions of the skin, hair follicles are arranged in groups of three or more follicles known as follicular units (Fig. 63.2). Several follicles within a follicular unit may coalesce so that hairs emerge through a common infundibulum.

The infundibulum

The infundibulum extends from the skin surface, where it merges with the epidermis, to the opening of the sebaceous duct at the junction with the isthmus. Infundibular epithelium differentiates in a similar manner to epidermis, producing a granular layer and stratum corneum which desquamates into the follicular lumen.

The isthmus

The isthmus extends from the opening of the sebaceous gland duct to the insertion of the arrector pili muscle. It consists of a multilayered outer root sheath that is continuous with the infundibulum but differs in its structure. The innermost cells lack a granular layer and undergo a pattern of differentiation known as trichilemmal keratinization. The keratinized inner root sheath, which lies within the outer root sheath, disintegrates at or about the level of the sebaceous duct. The arrector muscle loops around the follicle in the manner of a sling [1]. Each follicular unit is supplied by a single arrector muscle, which splits to encircle each follicle within the follicular unit [2].

Hair follicle stem cells are thought to reside in the lower part of the isthmus close to the insertion of the arrector

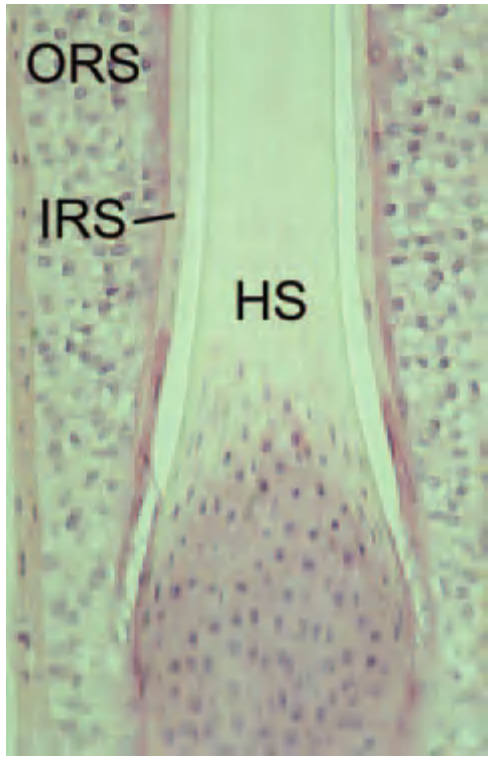

Fig. 63.3 Longitudinal section through suprabulbar region of an anagen follicle showing the keratogenous region of the hair shaft (HS). The inner root sheath (IRS) is keratinized at this level. ORS, outer root sheath.

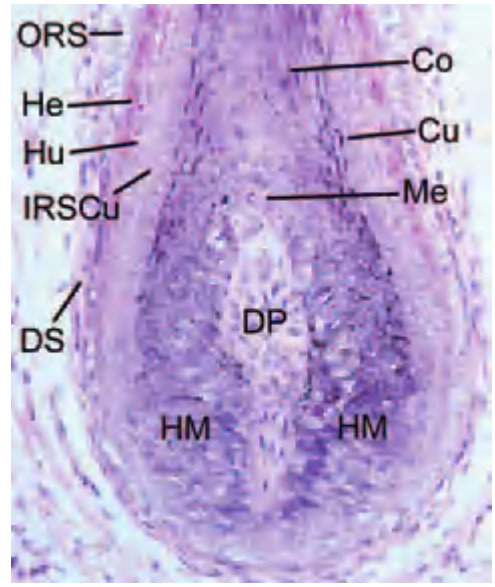

Fig. 63.4 Anagen hair bulb. Co, hair cortex; Cu, hair cuticle; DP, dermal papilla; DS, dermal sheath; He, Henle's layer; HM, hair matrix; Hu, Huxley's layer; IRSCu, inner root sheath cuticle; ORS, outer root sheath.

muscle [3]. During embryogenesis, and in adult follicles in other species, this region shows a distinctive bulge, although a clearly defined bulge is often not seen in human adult hair follicles. Hair follicle stem cells show distinctive biochemical properties, they are slow cycling and proliferate only during the onset of anagen. Daughter cells, known as transient amplifying cells, input into the outer root sheath of the lower part of the hair follicle whence they migrate in a downward direction. On entering the hair bulb matrix, they proliferate and undergo terminal differentiation to form the hair shaft and inner root sheath [4]. The progeny of hair follicle stem cells may also migrate distally to form the sebaceous gland and, under certain circumstances such as wound healing, the epidermis.

The suprabulbar region (Fig. 63.3)

The suprabulbar region of the follicle, below the isthmus and above the hair bulb, is comprised of three layers from outermost to innermost: outer root sheath, inner root sheath and hair shaft. The outer root sheath is a multilayered epithelium enclosing the inner root sheath which, at this level, is a fully keratinized structure. Cells of the hair shaft, at the centre of the follicle, undergo terminal differentiation within the keratogenous zone in the middle part of the suprabulbar region. Keratinization of the inner root sheath precedes that of the hair shaft, suggesting that the inner root sheath has a role in 'moulding' the shape of the hair fibre.

The hair bulb (Fig. 63.4)

In large terminal follicles, the deepest part of the follicle, the hair bulb, is situated in the subcutaneous fat. The hair bulb is invaginated at its base by the dermal papilla, which is connected to the perifollicular dermal sheath by a narrow stalk. The hair shaft and the inner root sheath are derived from epithelial cells surrounding the dermal papilla, a region known as the hair bulb matrix or germinative epithelium. These cells have a high mitotic rate, with a rate of cell turnover similar to that in the bone marrow. Daughter cells migrate in an upward direction and differentiate in a highly ordered fashion to form the concentric layers of the inner root sheath and the hair shaft. The inner root sheath derives from cells in the lower, more lateral part of the matrix, whereas the hair shaft is formed from the upper, centrally situated cells. In pigmented hair follicles, highly melanized melanocytes are situated amongst cells destined to form the hair cortex. Occasional Langerhans' cells may also be found in the matrix region. The outer root sheath surrounds the inner root sheath. At the level of the hair bulb it consists of a single layer of cells, which can be followed almost to the lower tip of the hair follicle.

The dermal papilla

In anagen follicles, the dermal papilla is a flask-shaped structure that invaginates the base of the hair follicle. It is made up of specialized fibroblast-like cells embedded in an extracellular matrix rich in basement-membrane proteins and proteoglycans, and in large follicles the dermal papilla often contains a loop of capillary blood vessels. It is connected to the dermal sheath surrounding the follicle by a narrow stalk. Both the dermal papilla and the dermal sheath are derived from a condensation of mesenchymal cells, which appear at an early stage in follicular embryogenesis. Tissue recombinant studies have shown that the dermal papilla plays an essential part in the induction and maintenance of follicular epithelial differentiation [5–8]. It is responsible for determining the follicle type, so that cultured dermal papilla cells derived from the rat vibrissae follicle induce the formation of a vibrissa-like follicle when implanted into ear skin [9]. The volume of the dermal papilla may also be responsible for controlling the size of the hair follicle, and that of the hair fibre [10,11]. This is of particular relevance to androgen-dependent changes in human hair growth, as the dermal papilla is probably the primary target of androgen action in the hair follicle.

The dermal sheath

The lower part of the hair follicle is enveloped by a collagenous layer known as the dermal or connective tissue sheath. Like dermal papilla cells, fibroblasts of the dermal sheath are highly specialized. In experimental circumstances, these cells can reconstitute the dermal papilla and induce the formation of new hair follicles in adult human skin [12]. As we move distally along the hair follicle, above the level of the arrector insertion, the dermal sheath becomes less distinct, both structurally and functionally, as it merges with the interfollicular dermis.

The inner root sheath

The inner root sheath consists of three layers (from outermost to innermost): Henle's layer, Huxley's layer and the inner root sheath cuticle. Inner root sheath cells accumulate filaments approximately 7 nm thick and, in contrast with the hair cortex, amorphous trichohyalin granules appear in the cytoplasm. As the cells move up the follicle towards the surface, the filaments become more abundant and the number and size of the granules increase. Each of the three layers of the inner root sheath undergoes abrupt keratinization. This occurs at different levels in each layer, although the patterns of change are identical. In the hardened cytoplasm, however, only filaments can be seen. The changes occur first in the outermost Henle's layer, then in the innermost cuticle and lastly in Huxley's layer, which is situated between them. Cells of the inner root sheath cuticle become flattened and overlap, with their free edges pointing downwards to interdigitate with the upwards-pointing cells of hair shaft cuticle, thus anchoring the hair shaft within the hair follicle. The inner root sheath hardens before the presumptive hair within it, and it is consequently thought to control the definitive shape of the hair shaft.

The outer root sheath

The outer root sheath forms the most peripheral layer of hair follicle epithelium, enclosing the inner root sheath. At the lower tip of the hair bulb it consists of a single layer of cuboidal cells, becoming multilayered in the region of the upper hair bulb. The cytoplasm of outer root sheath cells is rich in glycogen, giving a clear appearance with routine histological stains. In some follicles, particularly large beard follicles, there is a distinct single cell layer interposed between the outer and inner root sheaths, known as the companion layer [13]. Companion layer cells are flattened along the axis of the follicle and are relatively devoid of glycogen. They show numerous intercellular connections to the inner root sheath and are thought to migrate distally along with the inner root sheath to be lost in the isthmus region. The direction of movement of outer root sheath cells is unclear but they may migrate downwards towards the hair bulb, the companion layer forming the plane of slippage between the inner and outer root sheaths. The outer root sheath of the suprabulbar region merges imperceptibly with the isthmus where the innermost cells undergo tricholemmal keratinization.

The cuticle

The hair cuticle is formed initially as a single cell layer, but the cells become progressively imbricated (tile-like) as they move peripherally. The cells become flattened, first in a direction at right angles to the plane of the follicle, and then becoming progressively angulated so that the outer edges of the cells point in an upward direction. The flattened cells overlap, their free edges directed towards the tip (Fig. 63.5) and interlocking with the cuticle of the surrounding inner root sheath. In the fully formed hair shaft, the cuticle consists of 5–10 overlapping cell layers, each 350–450 nm thick (Fig. 63.6). The mature cells are thin scales consisting of compact cuticular keratin, associated with ultra-high sulphur proteins, which show three distinct layers by transmission electron microscopy: the outer A-layer, which is particularly rich in cystine; the exocuticle (also cystine-rich); and the inner endocuticle, which is virtually devoid of sulphur. The endocuticle has an irregular substructure of membrane-like elements which are probably the remnants of cytoplasmic structures [14].

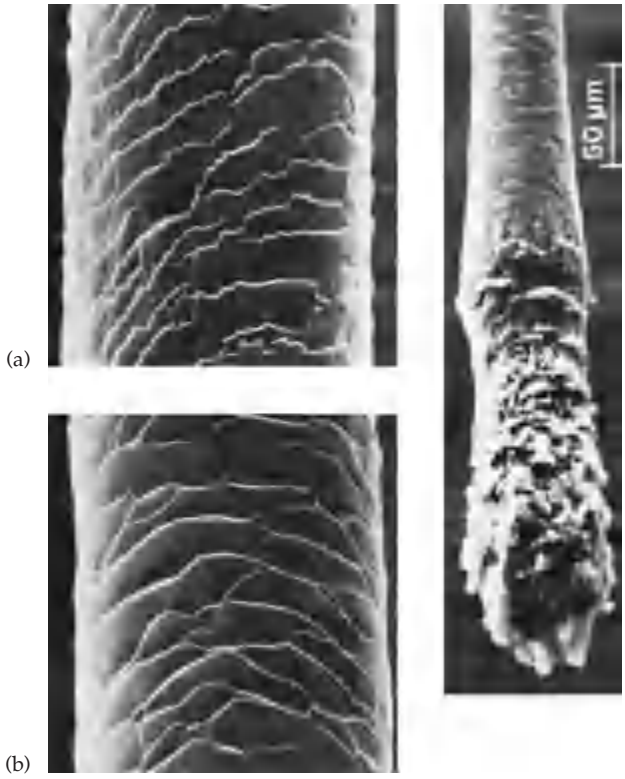

Fig. 63.5 (a) Surface view of weathered cuticular scales in the distal portion of the hair shaft. (b) Surface view of undamaged cuticular scales in proximal part of hair shaft. (Courtesy of Dr D. Jackson, University of Sheffield, Sheffield, UK.)

The outer surface of the cuticle is thought to be coated with long-chain (straight and branched) fatty acids linked to an underlying lipid–protein matrix [15]. This layer is 2–7 nm thick and is known as the fibre cuticle surface membrane or epicuticle. The cuticle has important protective properties. It acts as a barrier to physical and chemical insults, and also maintains the integrity of the hair shaft. Wear and tear (e.g. from cosmetic procedures) leads to gradual degradation of the cuticle ('weathering'), with breaking and lifting of the free margins of cuticular cells. Eventually this process may lead to exposure of the cortex and fracture of the hair shaft.

The cortex

Cells destined to form the cortex gradually become more fusiform in shape as they migrate upwards from the hair bulb. They develop a dense filamentous cytoskeleton in the upper hair bulb to become fully hyalinized in the suprabulbar region (the keratogenous zone) (Fig. 63.7). The hard α-keratin intermediate filaments (α-KIF) are the major structural component of the mammalian hair cortex. The molecule in α-KIF is an obligate heteropolymer containing a type I and a type II polypeptide chain [16,17], in which right-handed α-helices coil round one another in a left-handed manner to form a rod-like dimeric structure (a 'coiled coil') (Fig. 63.8). The 8-nm keratin filaments (microfibrils) are formed from multiple α-KIF molecules, on average 16 molecules or 32 chains in cross-section [18]. Keratin filaments are cross-linked to keratin-associated proteins, which form a matrix between the filaments. More than 60 hair keratin-associated proteins have been found in various species. They are classified into three major families: high sulphur, ultra-high sulphur and high glycine–tyrosine proteins [19]. In some species, notably the sheep, the cortex can be divided into two regions: the orthocortex and paracortex, which differ in the arrangement of KIFs and the proportion of keratin-associated

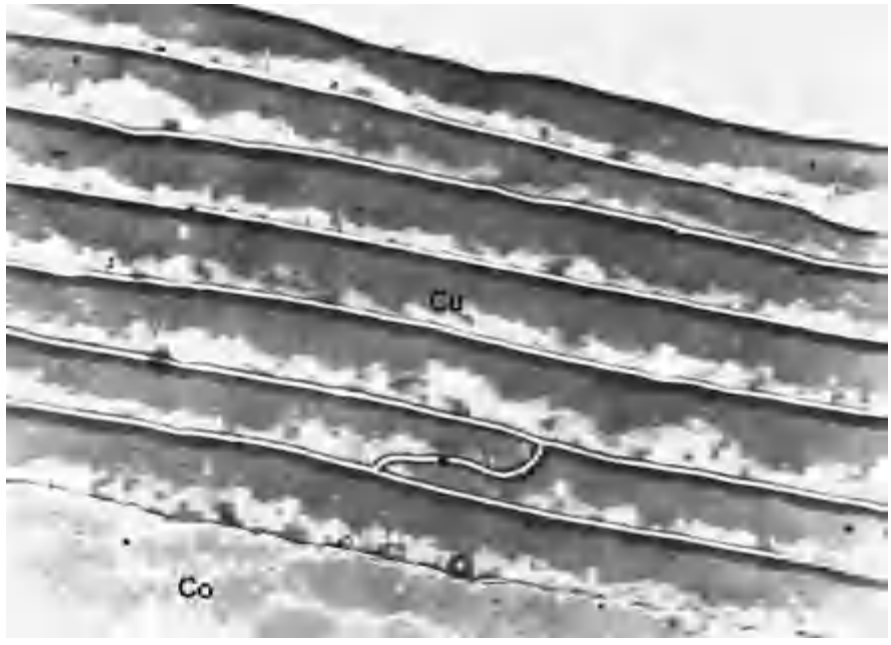

Fig. 63.6 Cross-section through hair shaft showing cuticle layers (Cu) surrounding the central cortex (Co). (Transmission electron micrograph, silver methenamine stain.)

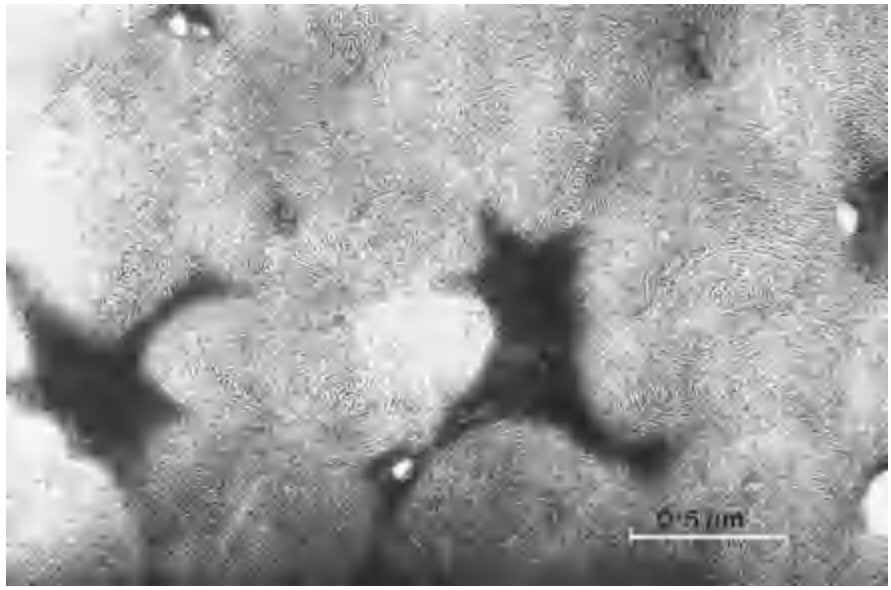

Fig. 63.7 Cross-section of transformed cortical cells of human hair. The relatively translucent filaments, set in a more dense sulphur-rich matrix, appear as concentric lamellae (macrofibrils), giving a characteristic fingerprint pattern.

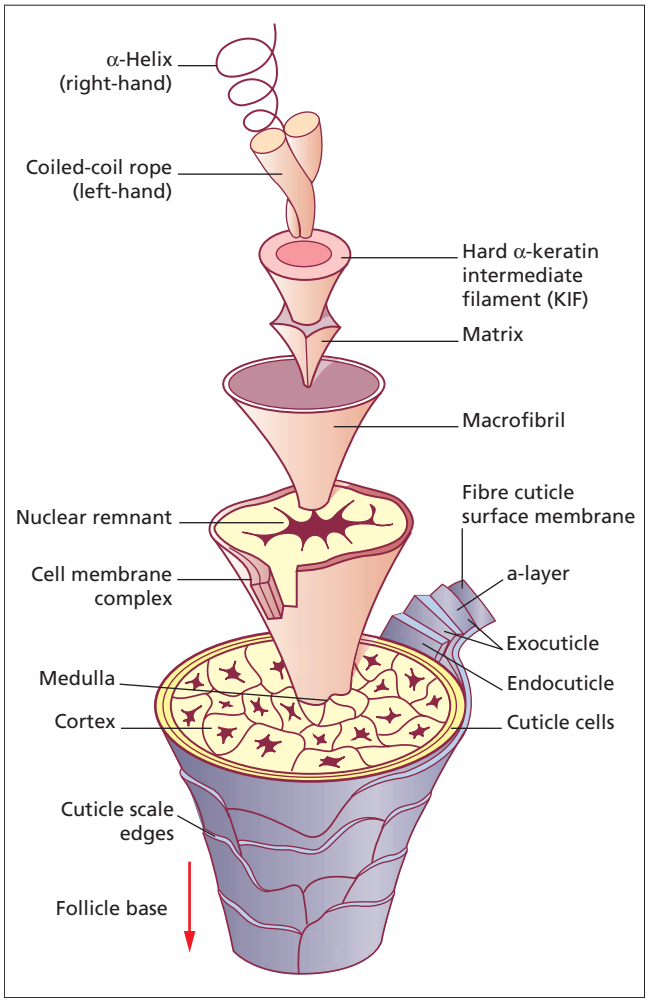

Fig. 63.8 Diagram showing an exploded view of the major structural components comprising a human hair fibre. Pigment granules that are normally dispersed throughout the cortex are not included. (Courtesy of Dr L. Jones [14].)

proteins. In humans, the hair cortex appears to contain mixtures of KIF arrangements within each cell.

The medulla

The medulla is a variable structure in human hairs, where it may be continuous, discontinuous or absent. Large diameter hairs are more likely to contain a medulla, although the relationship between hair diameter and medullation is not clear-cut. The medulla develops quite abruptly around the upper pole of the dermal papilla, without any obvious precursor cell population. Medullary cells contain distinctive eosinophilic granules that eventually form internal coatings within the membranes of mature cells. As these cells develop, arginine residues are converted to citrulline, and isopeptide bonds are formed to yield a highly insoluble protein complex [20]. Mature medulla cells have a spongy structure, with amorphous material bounding air spaces of varying sizes.

Hair follicle innervation

A plexus of longitudinally aligned sensory nerve fibres surrounds the isthmus region. Small nerve fibres may also be arranged in a circular fashion outside the longitudinal fibres. Several different types of nerve endings are found around human hair follicles, including free nerve endings, pilo-Ruffini nerve endings and Merkel nerve endings [21,22]. In other species, lamellated nerve endings are found in richly innervated sinus hair follicles (e.g. vibrissae follicles), which have specialized sensory function [22]. Merkel cells, with or without associated nerve endings, may be found within the bulge region epithelium and the surrounding connective tissue sheath, and it has been postulated that their secretions are involved in regulating the hair cycle [23].

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The hair cycle (Fig. 63.9)

Hair follicles undergo a repetitive sequence of growth and rest known as the hair cycle. The timing of the phases of the hair cycle and its overall duration varies between

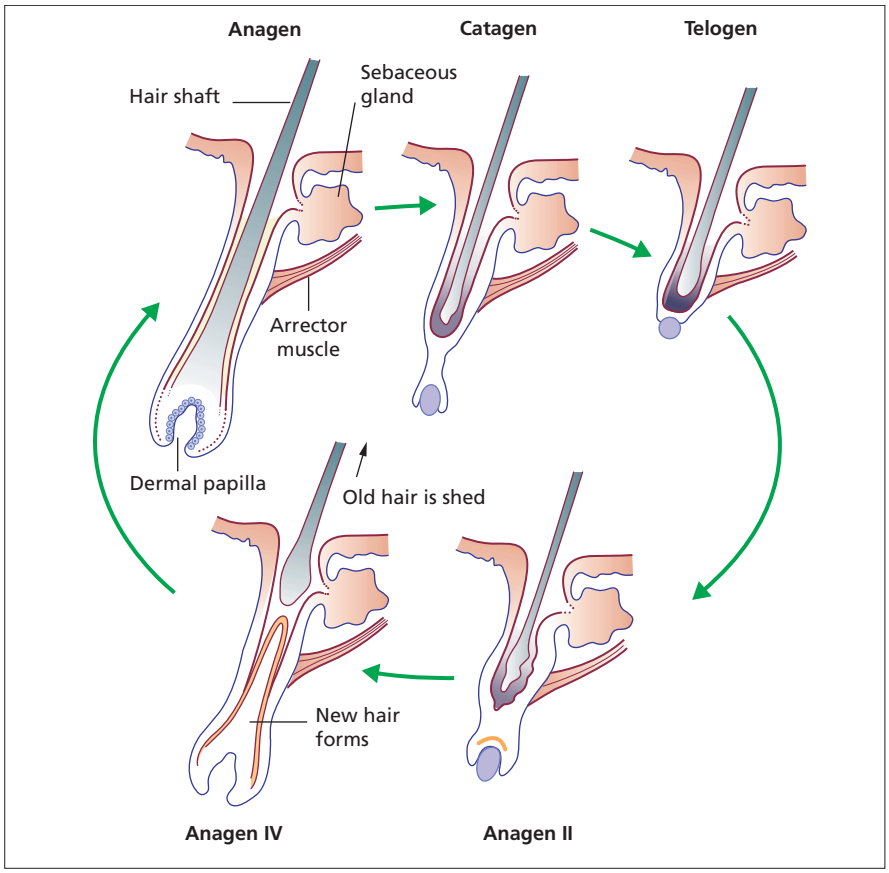

Fig. 63.9 The hair cycle. (From *Disorders of Hair Growth*, McGraw-Hill.)

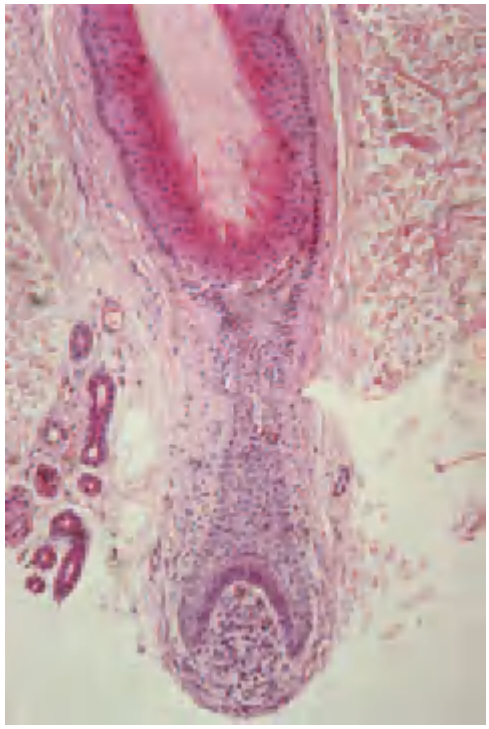

Fig. 63.10 Scalp hair follicle in Anagen 2 stage of development. The club hair from the previous cycle is still present within the follicle. (Courtesy of Dr A.J.G. McDonagh, Royal Hallamshire Hospital, Sheffield, UK.)

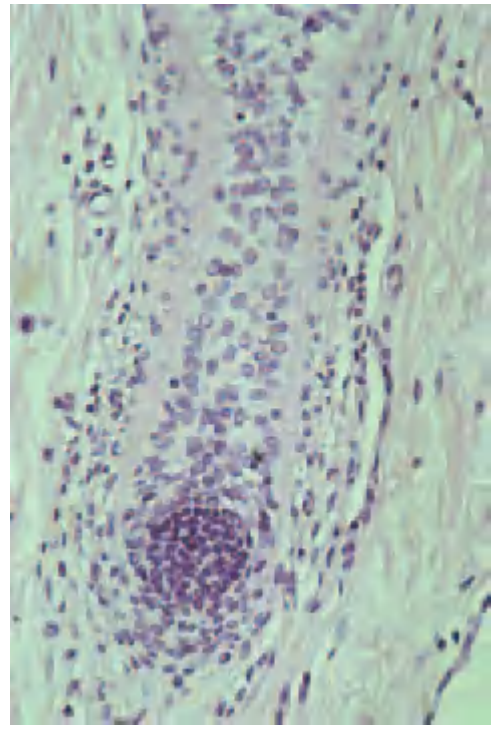

Fig. 63.11 Human hair follicle in mid-catagen. There is a prominent glassy membrane surrounding the regressing epithelial column. The dermal papilla has rounded and condensed. (Courtesy of McGraw-Hill.)

species, between follicles in different regions of the skin in the same species and, in some animals, between different follicle types, such as guard hairs and underhairs, in the same region of the skin.

The period of active hair growth is known as *anagen* and the duration of this phase is responsible for determining the final length of the hair. In most hair follicles in most animals, anagen is relatively brief, lasting a few weeks at most. In some hair follicles, such as those on human scalp, the horse's tail and wool follicles in the merino sheep, anagen may continue for several years, so that very long hairs are produced. Under normal circumstances, 80–90% of hair follicles on the human scalp are in anagen at any one time.

The entry of a resting hair follicle into anagen is heralded by the onset of mitotic activity in epithelial cells overlying the dermal papilla at the base of the follicle (the secondary epithelial germ). In most follicle types (vibrissa follicles are an exception), the lower part of the follicle elongates downwards along a preformed dermal tract (the stele). The developing hair bulb partly envelops the dermal papilla, and epithelial cells start to differentiate to form the inner root sheath and the hair shaft (Fig. 63.10). The dermal papilla expands from a tightly packed ball of cells into a flask-shaped structure where the cells become separated by an extracellular matrix rich in proteoglycans and basement-membrane proteins. A network of capillary blood vessels develops around the lengthening follicle, extending into the dermal papilla in larger follicles. In the fully developed anagen follicle, epithelial cells in the hair bulb undergo vigorous proliferative activity. Their progeny move distally and differentiate in an ordered fashion to form the layers of the inner root sheath and the hair shaft. At the end of anagen, epithelial cell division declines and ceases, and the follicle enters an involutionary phase known as *catagen*. During catagen, the proximal end of the hair shaft keratinizes to form a club-shaped structure and the lower part of the follicle involutes by apoptosis (Fig. 63.11). The basement membrane surrounding the follicle becomes thickened and corrugated to form the 'glassy membrane'. The base of the follicle, together with its dermal papilla, moves upwards, eventually to lie just below the level of the arrector insertion. The period between the completion of follicular regression and the onset of the next anagen phase is termed *telogen*. The club hair lies within an epithelial sac to which it is attached by tricholemmal keratin. The club hair is eventually shed through an active process termed *exogen*. In many species, follicles re-enter anagen prior to shedding of the club hair so that the old hair is not shed until the follicle is well into its next growth phase. This may also be

Fig. 63.12 Bactrian camel in spring moult.

seen in human follicles although it is unusual for a club hair to be retained much beyond the mid-stage of anagen development. In human scalp, hair follicles may remain in a state of latency for a prolonged period after the club hair is shed [1].

Control of the hair cycle

It is thought that hair cycling is controlled primarily within individual hair follicles but that this intrinsic rhythmic behaviour may be modulated by both local and systemic factors. In most newborn mammals, including humans, hair cycles are coordinated in a wave-like fashion (moult waves) across regions of the skin in the neonatal period. Moult waves are regulated within the skin and are accompanied by changes in other skin structures, such as epidermal and dermal thickness. Hence, skin flaps raised on the flanks of rats, rotated through 90–180° and then replaced, continue to moult in their original direction for a prolonged period [2,3]. Homografts between isogenic animals of different ages also retain the moult pattern of the donor, whereas autografts retain that of the recipient [4]. Hair cycles in homografts eventually come into phase with the surrounding skin as do those in rats of different ages joined parabiotically, suggesting that the factors regulating synchrony are able to diffuse into the grafted skin. In many mammals, living in their natural environment in temperate and higher latitudes, moult waves continue into adult life and occur on a seasonal basis. This allows adaptation of the thickness of the coat, and sometimes its colour, to different climatic conditions in summer and winter (Fig. 63.12). In humans, and some other mammals such as the guinea pig, synchronous hair cycling is lost rapidly with increasing age so that, beyond the neonatal period, hair follicles cycle independently of their neighbours. In these circumstances, hair cycling must be regulated by mechanisms intrinsic to the hair follicle.

Seasonal hair growth

Seasonal moulting is regulated by the endocrine system under the influence of environmental signals. The most important of these is change in day length (the photoperiod) [5,6]. Temperature may act as a modifying factor in some species. Changing levels of melatonin production by the pineal gland have a key role in orchestrating endocrine control of seasonal hair growth [7–9]; pinealectomy prevents seasonal moulting, whereas administration of melatonin advances onset of the growth of the winter coat and prevents growth of the summer coat. Prolactin production by the pituitary correlates inversely with melatonin levels, being raised during the summer and falling during the winter. Pinealectomy abolishes the fall in prolactin level in animals kept in short day length conditions and prevents the development of the winter coat [10]. The same response is seen in animals treated with prolactin. Prolactin receptors have been identified in the hair follicle, suggesting that prolactin can affect hair growth directly [11]. Pineal and pituitary hormones may also act indirectly by modulating the activity of peripheral endocrine glands. In rats, estradiol, testosterone and adrenal steroids delay the onset of anagen, whereas gonadectomy and adrenalectomy have the opposite effect [12]. Conversely, thyroid hormones accelerate the onset of follicular activity, whereas thyroidectomy or treatment with propylthiouracil delays it. Seasonal moults are also delayed by testosterone and accelerated by thyroxine in other species [13]. Hormones also act on the anagen phase of hair growth [12]. Estradiol and thyroxine both reduce the duration of anagen in rats, but estradiol decreases the rate of hair growth, whereas thyroxine has the opposite effect, suggesting these hormones have different points of action. In the mouse, oestrogen receptors are expressed in the dermal papilla and the inhibitory effect of exogenous oestrogen on hair growth is prevented by topical treatment with an oestrogen receptor antagonist [14].

Vestiges of seasonal variation in hair growth are present in humans [15], although the magnitude is seldom sufficient to be noticeable. The best example of a systemic influence on the human hair growth cycle is pregnancy (Fig. 63.13) [16]. During pregnancy, there is an increase in the proportion of follicles in anagen, although it is not clear whether this is caused by prolongation of anagen or more rapid shedding of telogen hairs, as there is also a reduction in hair density during the second and third trimesters [17]. Following childbirth, large numbers of follicles enter telogen, leading to increased shedding from about 3 months postpartum (postpartum telogen effluvium). Telogen shedding may also be caused by a number of drugs and by febrile and other catabolic illnesses [18].

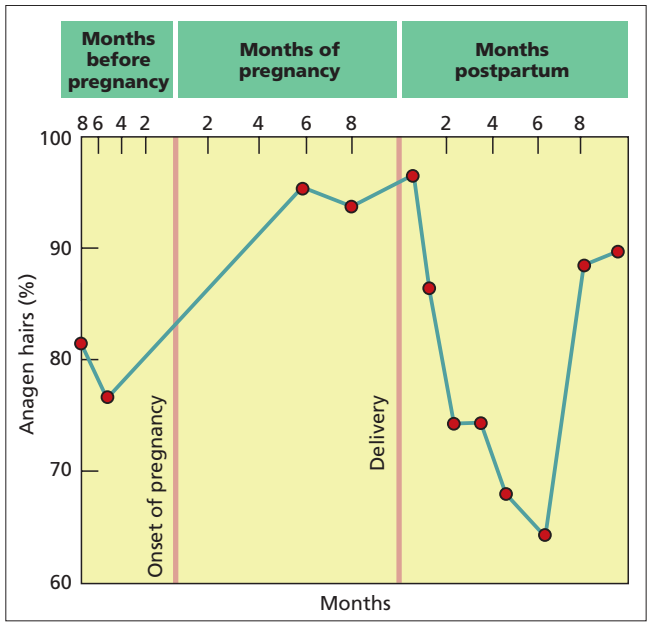

Fig. 63.13 Percentage of anagen hairs in a 25-year-old woman before, during and after pregnancy. (From Lynfield [16].)

Intrinsic control of the hair growth cycle

Although local and systemic factors modulate the hair cycle in some species, in humans and some other mammals hair cycling is asynchronous. Hair follicles in different regions of the skin may also cycle differently. In humans, for example, the duration of anagen on the scalp may last several years, whereas on the eyebrows anagen is very brief. Even in animals showing seasonal hair growth, hair cycles in different follicle types in the same skin region are not necessarily in phase. When scalp hair follicles are transplanted into other regions of the skin they retain the cyclical behaviour of the donor site, indicating that cycle control is determined within the follicle or its immediate tissue environment. Interactions between two key cell populations in the hair follicle, epithelial stem cells in the outer root sheath and mesenchymal cells in the dermal papilla and dermal sheath, are thought to underlie intrinsic control of hair cycling, and a large number of molecules have been implicated in this process. However, the location and the nature of the 'switch' that initiates and terminates anagen growth are unknown.

It has been known for many years that plucking of resting hairs from telogen follicles advances the onset of anagen. This led to the idea that the hair cycle is controlled by a locally active inhibitor which accumulates during anagen causing entry into catagen when present in sufficient concentration (the chalone hypothesis) [19]. The putative inhibitor would disperse during telogen, and plucking resting hairs could accelerate this process. The chalone hypothesis has been disputed because the plucking of resting hairs from follicles that have already entered anagen does not prolong the anagen in progress, although it does advance the onset of the next anagen cycle [12]. There is one report that murine skin contains a factor that inhibits hair growth *in vivo* and *in vitro* [20]. This inhibitory factor, which has not been characterized, appeared to be derived from the epidermis and was present in telogen skin but not in anagen skin.

Cotsarelis *et al.* [21] have suggested that anagen is initiated by signals from the dermal papilla which stimulate mitosis in stem cells in the bulge region of the outer root sheath (the bulge activation hypothesis). As transient amplifying cells, daughter cells have a limited mitotic potential. When this is exhausted, hair growth ceases and the follicle enters catagen, thus determining the duration of anagen and the onset of catagen.

Several other ideas to explain hair cycle periodicity have been proposed [22] but, for the present, these remain at a theoretical level.

Molecular control of hair cycling

A wide variety of molecules and genes have been implicated in controlling the hair cycle (Table 63.2). These include developmental genes, several families of growth factors and their receptors, nuclear receptors, neurotrophins, cytokines and intracellular signalling pathways. These molecules have generally been studied in isolation, although they undoubtedly operate in a complex milieu of interactions and cross-talk about which little is currently known. The expression level of many of these molecules fluctuates during the hair cycle, and it is difficult to know whether this is of functional significance or is secondary to the metabolic and structural cycle-related changes in the hair follicle. However, there are some examples where there is convincing evidence of a physiological role.

The origin of the signals that initiate anagen has not been identified, and it is not known whether these signals are negative, as proposed in the chalone hypothesis, or positive, or both. Locally synthesized parathyroid hormone-related peptide (PTHrp) is a possible inhibitor of anagen, as injection of a PTHrp antagonist into murine skin accelerates the onset of anagen and delays catagen. Several growth factors appear to be involved in promoting anagen, including insulin-like growth factor 1 (IGF-1), hepatocyte growth factor, keratinocyte growth factor and vascular endothelial growth factor. The *sonic hedgehog* gene and its receptor *patched* also promote anagen in adult follicles as well as being essential for follicular development. Anagen development is a time of extensive remodelling of the follicle and its tissue environment. Follicles grown *in vitro* synthesize a variety of metalloproteinases, suggesting that this process involves degradation of the surrounding extracellular matrix. Hair follicles also express tissue inhibitor of matrix metalloproteinase 3 (TIMP-3) in the outer root sheath during anagen, implying

Table 63.2 Molecular mediators of hair cycle control.

Growth factor	Location	Function
FGF5	ORS	Terminates anagen [23]
FGF7 (KGF)	DP	Induces hair growth in athymic nude mice [24] Hair shaft defect in KGF deficient mice [25]
EGF/TGF-α		Inhibits hair development and growth [26,27] Stimulates ORS proliferation *in vitro* [28]
EGF-R	Hair bulb and ORS	Wavy hair in EGF-R deficient mice [29]
TGF-α		Wavy hair in TGF-α deficient mice [30]
TGF-β1, 2, 3		Inhibits hair growth *in vitro* [31] TGF-β mRNA expressed in skin during anagen/catagen transition [32]
TGF-β receptors		TGF-β receptors expressed in hair follicle—maximal during anagen/catagen transition [33] Delayed catagen in TGF-β1 null mice [34]
IGF-1	DP, hair bulb	Maintains hair follicle growth *in vitro* [35]
IGF-1 receptors	DP, pre-cortex, ORS	Down-regulated in catagen [36]
IGF BP-3, -4, -5	DP and DS [37]	
HGF		Stimulates hair growth when injected into mouse skin [38] Expression in skin varies during hair cycle: high in anagen, low in telogen [39]
VEGF	DP, ORS	Probably regulates perifollicular angiogenesis. Increased follicle size in transgenic mice which overexpress VEGF in ORS. Systemic VEGF antibody retards hair growth in mice [40]
IL-1α, IL-1β		Inhibit hair growth *in vitro* [41]
TNF-α		Inhibits hair growth *in vitro* [41]. TNF-α receptor mRNA expression increased in late anagen [36]
Sonic hedgehog (SHH)		Overexpression in skin accelerates entry into anagen [42] SHH antibody inhibits pelage (but not vibrissae) follicle development in mice. Inhibits anagen in postnatal cycles [43]
Hairless		Required for normal catagen [44]
PTHrp	Follicle epithelium	Inhibits initiation and maintenance of anagen. PTHrp antagonist induces and prolongs anagen [45]
RXR		Required for normal catagen? [46]
Vitamin D receptor	DP, ORS	Variable expression during hair cycle [47] Alopecia in vitamin D receptor knockout mice [48] and in human vitamin D-resistant rickets [49]
Oestrogen receptor	DP	Oestrogen inhibits hair growth in mice [50]
Neurotrophins	Follicle epithelium	NGF, brain-derived neurotrophic factor, neurotrophin-3, neurotrophin-4, and p75 neurotrophin receptor, TrkB receptors promote progression of catagen [51,52]
Mast cells		Increased degranulation at end of anagen and fall in number during telogen. May be involved in control of catagen [53]

DP, dermal papilla; DS, dermal sheath; EGF, epidermal growth factor; FGF, fibroblast growth factor; HGF, hepatocyte growth factor; IGF, insulin-like growth factor; IGF BP, IGF binding proteins; IL-1, interleukin-1; KGF, keratinocyte growth factor; ORS, outer root sheath; PTHrp, parathyroid hormone-related peptide; RXR, retinoid X receptor; TGF, transforming growth factor; TNF, tumour necrosis factor; VEGF, vascular endothelial growth factor.

that remodelling involves a carefully controlled sequence of positive and negative influences.

The end of anagen and transition into catagen is a key period in the hair cycle, as its timing determines the final length of the hair. Catagen may be initiated as a passive process through exhaustion of the mitotic potential of transient amplifying cells in the hair bulb or the loss of action of growth promoting agents. Also, several growth factors and cytokines, including transforming growth factor-β (TGF-β), interleukin-1α (IL-1α) and tumour necrosis factor-α (TNF-α) have an inhibitory effect on hair growth and may be actively involved in triggering catagen. Transgenic mice with a null mutation in the gene for fibroblast growth factor 5 (*FGF5*) show a delay in the onset of catagen and grow abnormally long hair. The phenotype is identical to the naturally occurring *angora* mouse which has a mutation in the *FGF5* gene, suggesting that this growth factor has an active role in terminating anagen

[23]. *FGF5* is expressed in the outer root sheath towards the end of anagen, in keeping with this idea. However, although anagen is delayed in *FGF5*-deficient mice, it is not delayed indefinitely, indicating that other factors must also be involved.

Catagen proceeds in an orderly fashion as cells are deleted from the regressing epithelial column by apoptosis. The expression levels of several proto-oncogenes associated with apoptosis, including c-*myc*, c-*jun* and c-*myb*, change immediately prior to or coincident with the onset of catagen [32]. The apoptosis-inhibitory proto-oncogene *bcl*-2 is expressed in cycling follicular epithelium during anagen, disappears during catagen and is absent in telogen. *Bcl*-2 is expressed in the dermal papilla throughout the hair cycle, suggesting a possible protective role in this site [54].

For the follicle to maintain the ability to cycle, it must maintain its integrity during catagen regression. In the *hairless* mouse, the first coat develops normally but the pelage is then lost. Towards the end of the first anagen phase, cells in the hair bulb undergo extensive premature apoptosis, and formation of the epithelial column is disrupted during catagen. The dermal papilla loses contact with the base of the hair follicle epithelium and the follicle is unable to re-enter anagen. Follicular remnants subsequently undergo cystic degeneration [44]. A similar pattern of hair loss is seen in the human disorder, atrichia with papular lesions, in which there is a mutation in the human homologue of the mouse *hairless* gene [55]. The function of *hairless* in the hair follicle is not fully established but there is some evidence that it acts as a co-repressor of the thyroid receptor (TR). Atrichia with papules also occurs in some families with vitamin D-resistant rickets [48], which is caused by a mutation in the vitamin D receptor (VDR) gene. Like the TR, the VDR is a transcription factor and a member of the nuclear hormone receptor superfamily. Both TR and VDR bind to response elements in target genes as heterodimers with the retinoid X receptor (RXR), another nuclear hormone receptor. Transgenic mice with a null mutation in the RXR gene also show a *hairless* phenotype [46], suggesting there is a common pathway involving nuclear hormone receptors that regulates entry into catagen.

Although generally regarded as a state of quiescence, it is possible that active mechanisms are also needed to maintain a follicle in telogen. For example, expression of the oestrogen receptor in dermal papillae of murine hair follicles is increased during telogen, and oestrogens inhibit entry into anagen [56], although the physiological relevance of this observation is unknown. Release of the club hair from the follicle, a process that has been termed *exogen* [57], does not necessarily coincide with re-entry of the follicle into anagen, and this has led to the idea that shedding is controlled separately from the hair cycle. The club root lies embedded in tricholemmal keratin and its release presumably requires local proteolysis. The cells surrounding the club root are also rich in desmosomes. Transgenic mice with a null mutation in the gene for the desmosomal protein desmoglein 3 show defective anchorage of the club hair [58].

Role of the immune system in hair cycling

Cells in the lower part of the hair follicle, below the arrector insertion, show reduced or absent expression of class I major histocompatibility complex (MHC) molecules [59]. In rat skin the expression of class I MHC in follicular epithelium increases during catagen, and this is associated with a perifollicular accumulation of activated macrophages and loss of the proteoglycan-rich extracellular matrix [60]. These observations led to the suggestion that an immune process mediated by macrophages contributes to control of the hair cycle but other studies have failed to confirm these findings [61]. However, there is experimental support for the idea that the lower part of the hair follicle is an immunologically 'privileged' site not subject to classic immune surveillance [62,63]. This is relevant to disease states, such as alopecia areata, which may be explained by a breakdown of putative immune privilege.

Rate of hair growth

The rate of hair growth varies from species to species, and within one species from region to region, as well as with sex and age. For example, in the rat it can be more than 1 mm/24 h [64] and in the guinea pig up to 0.6 mm/24 h, whereas in humans it is much less. The rate has been determined by direct measurement of marked hairs *in situ* [65], by shaving and clipping at selected intervals [66,67] or by pulse labelling with ^{35}S-cysteine [68–70]. Most investigators now use macrophotographic methods (phototrichography), which may be analysed using computerized systems. Comparable measurements are obtained by all methods. The average rate of growth of human hair has been stated to be approximately 0.03 mm/24 h for the vellus on the male forehead [71], 0.21 mm/24 h on the female thigh and 0.38 mm/24 h on the chin of a young male. On the crown of the scalp it averaged approximately 0.5 mm/24 h, being slightly less on the margins. In another study in which graduated capillary tubes were fitted around the growing hairs, the average growth in males was as follows: vertex 0.44 mm/24 h; temple 0.39 mm/24 h; chest 0.44 mm/24 h; beard 0.27 mm/24 h [72]. The average rate on the vertex of women was 0.45 mm/24 h and there were no variations diurnally or during the menstrual cycle. Although scalp hair grows faster in women than in men [72,73], the rate before puberty is greater in boys than in girls [74]. The average rate over the whole body is greater in men than in women [67]. Irrespective of

sex, growth appears to be highest in the two decades between 50 and 69 years of age [67]. From studies on the guinea pig, it seems clear that the growth rate depends upon the time for which the activity of the follicle has been in progress [75].

There is agreement that shaving has no effect on the rate of growth [72,76]. Various endocrine factors have been shown to influence the rate of hair growth in animals; for example, oestrogens reduce it [64,77] and thyroxine increases it [78].

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Hair pigment and melanogenesis in the follicle

See p. 63.108.

Androgens and hair growth

Androgens influence hair growth in several ways. First, they participate in the endocrine control of moulting in animals that show seasonal hair growth [1]. Secondly, in some mammals, androgens stimulate the growth of hair follicles in certain regions of the skin following sexual maturity. Thirdly, in humans and some other primates, androgens are necessary for the development of balding on the scalp.

Androgen-stimulated hair growth

The growth of obvious facial, trunk and extremity hair in the male, and of pubic and axillary hair in both sexes, is clearly dependent on androgens. The development of such hair at puberty is, in broad terms and at least initially, in parallel with the rise in levels of androgen from testicular, adrenocortical and ovarian sources, which occurs in both sexes and is somewhat steeper in males. That testosterone from the interstitial cells of the testis is responsible for growth of beard and body hair in male adolescence and that testicular activity is itself initiated by gonadotrophic hormones of the pituitary is unquestioned. However, the findings that growth-hormone-deficient boys and girls are less than normally responsive to androgens, and that growth hormone is necessary as a synergistic factor to allow testosterone to be fully effective with respect to hair growth [2], as well as protein anabolism and growth promotion, suggest that hypophysial hormones also have a more direct role. Direct evidence of the role of testicular androgen is that castration reduces growth of the human beard [3], whereas testosterone stimulates it in eunuchs and elderly men. The role of androgen is further demonstrated in the treatment of hirsute women with the antiandrogen cyproterone acetate [4], which reduces the definitive length, rate of growth, diameter and extent of medullation of the thigh hairs [5].

At puberty, terminal hair gradually replaces vellus, starting in the pubic regions. In both sexes the first pubic hair is sparse, long, downy, slightly pigmented and almost straight. It later becomes darker, coarser, more curled and extends in area to form an inverse triangle. A British study showed that boys had the first recognizable pubic hair at an average age of 13.4 years, and the full adult 'male' pattern at 15.2 years, approximately 3.5 years after the start of development of the genitalia [6]. The corresponding mean ages for girls were considerably earlier, namely 11.7 years and 13.5 years [7]. In approximately 80% of men and 10% of women the pubic hair continues spreading until the mid-twenties or later; there is no absolute distinction between male and female patterns, only one of degree.

Axillary hair first appears approximately 2 years after the start of pubic hair growth. The amount, as measured by the weight of the fully grown mass, continues to

increase until the late twenties in males as well as in females, in whom, however, it is less at any age [3]. The mean amounts grown per day increase from late puberty until the mid-twenties and thereafter decrease steadily.

Facial hair in boys first appears at about the same time as the axillary hair, starting at the corners of the upper lip, and spreading medially to complete the moustache and then the cheeks and beard.

Terminal hair development is continued in regular sequence on the legs, thighs, forearms, abdomen, buttocks, back, arms and shoulders [8]. The extent of terminal hair tends to increase throughout the years of sexual maturity, but most patterns occur over a wide age range. The adult pattern is not achieved until the fourth decade, when the androgen levels are already somewhat lower than in early adult life. Moreover, aural hairs do not appear until late middle age, and a study of coarse sternal hair in men showed that the hairs continue to increase in length and number from puberty to the fifth or sixth decade.

There is considerable racial variability in androgen-dependent hair growth. The growth of facial and body hair is greater in European men than in Chinese men [3] and there is also variation within these broad racial categories—southern European men tend to be hairier than men from northern Europe [9].

Androgenetic alopecia

It has been known since ancient times that eunuchs do not go bald. Hippocrates noted that 'eunuchs are not subject to gout nor do they become bald' (Aphorisms VI, 28). The role of testosterone in male balding was first recognized by James Hamilton, a US anatomist [10]. He observed that men castrated before puberty retain a prepubertal hairline and do not go bald. Of 12 such men who were treated with testosterone, four developed typical male hair loss. Castration later in life halted the progression of hair loss but did not result in regrowth of hair.

The prevalence and severity of male balding increase with age. All races are affected but the prevalence is higher in white males, reaching at least 80% in men aged over 70 years, than in African American [11] and in Japanese men [12]. Chinese and Korean men are also less likely to show frontal recession [13,14]. Genetic factors undoubtedly predispose to the development of male balding, but little is known of the genes involved and the mode of inheritance is also uncertain.

The loss of hair in male balding is the result of a gradual reduction in the duration of anagen and a prolongation of the latent period of the hair cycle [15], and miniaturization of terminal hair follicles [16].

Androgen synthesis and metabolism

The initial stages in the synthesis of steroid hormones from cholesterol occur exclusively in the gonads and the adrenal glands. Circulating androgens are also derived from the peripheral conversion of weak precursor hormones into potent androgens, a process that takes place in many tissues including the skin and hair follicles. The majority of androgens in the circulation are bound to plasma proteins, principally sex hormone-binding globulin (SHBG), with approximately 20% bound to albumin. The remaining 1–2% circulates in a free unbound form and this comprises the biologically active pool. Androgen bound to albumin dissociates readily and can replenish the free pool. SHBG binds androgen with high affinity and its plasma concentration therefore has an important effect on the free and albumin-bound pools. High levels of SHBG reduce the biologically active androgen level and low levels of SHBG have the reverse effect. Free androgen is thought to enter cells by passive diffusion where it binds to a specific intracellular androgen receptor.

Testosterone is the major circulating androgen, but in most body sites the effect of testosterone on hair growth is mediated by its more potent metabolite 5α-dihydrotestosterone (DHT). The conversion of testosterone to DHT is catalysed by the enzyme 5α-reductase. There are two isoforms of 5α-reductase, which are encoded by different genes [17]. Although both enzymes catalyse the conversion of testosterone to DHT they differ in their pH optima, substrate affinities and tissue distributions. Type 1 5α-reductase is widely distributed in the skin, but expression of the type 2 isoform is restricted to androgen target tissues such as the prostate and the epididymis. Much of our knowledge of the biological role of DHT in hair growth comes from studies of men with 5α-reductase deficiency (type II pseudohermaphroditism, pseudovaginal perineoscrotal hypospadias) [18,19], which is caused by mutations in the 5α-reductase 2 gene [20]. In this autosomal recessive disorder, genetic males (46XY) are born with normally differentiated but usually undescended testes. The external genitalia are ambiguous with a small hypospadic phallus, a bifid scrotum and a blind vagina. Partial virilization of the genitalia occurs at puberty, the voice deepens and the musculature assumes a typical male distribution. Circulating testosterone levels are within or above the normal male range but DHT levels remain low, with testosterone : DHT ratios 3.5–5 times higher than normal. Subjects show a female pattern of androgen-dependent hair growth, with terminal hair largely restricted to the axillae and the lower pubic triangle, suggesting that hair growth in these sites responds to less potent androgens. In the large group of subjects studied in the Dominican Republic, beard growth was absent or sparse. More facial hair has been observed in affected men from other parts of the world, perhaps reflecting underlying racial differences in normal androgen-dependent hair growth, although this was reduced compared with normal males in the same communities [21,22]. None of the cases studied has shown

temporal recession of the hairline or balding. A role for DHT in balding is supported by studies in macaques in which treatment with 5α-reductase inhibitors prevented the development of balding [23] or increased scalp hair growth in balding animals [24], and a large clinical trial of the 5α-reductase type 2 inhibitor finasteride in balding men. This latter study showed that the progression of balding was prevented in almost all men taking finasteride orally, and about two-thirds showed an increase in hair growth [25].

Hair follicles possess 5α-reductase activity, suggesting that DHT acts as a paracrine or intracrine hormone (it is synthesized within or close to the target cell). It is possible that circulating DHT also contributes to androgen effects on hair growth. Other steroid metabolizing enzymes, including 3β- and 17β-hydroxysteroid dehydrogenase which interconvert weak and potent androgens, and aromatase which converts androgens to oestrogens, are also expressed in the hair follicle [26,27], but their role in hair growth is not currently known.

The androgen receptor

The tissue effects of androgens are mediated through binding to the intracellular androgen receptor. The androgen receptor is a nuclear hormone receptor [28], and like other members of the nuclear hormone receptor superfamily it acts as a gene transcription factor following ligand binding. Mutations in the androgen receptor gene are responsible for the androgen insensitivity syndrome [29]. Individuals with the complete form of the syndrome, in which there is failure of functional androgen receptor expression, have intra-abdominal testes but female external genitalia, breast development and psychosocial development. After puberty, circulating testosterone is in the normal or elevated male range but pubic and axillary hair fail to develop, there is no beard growth and no balding.

Mechanism of androgen action on the hair follicle

Hamilton [10] reported that balding did not progress following castration in older men but neither did it promote regrowth of hair. Similarly, although beard growth was prevented by castration before puberty and stimulated by subsequent treatment with testosterone, there was only partial regression of the beard in postpubertal men castrated before the age of 20 years and no effect in older men [3]. Hamilton's observations were relatively crude by modern standards and it is now clear from clinical trials of 5α-reductase inhibitors that some reversal of male balding is possible. However, the response is far from complete, indicating that androgens induce changes in gene expression in hair follicles that are only partially reversible in the absence of androgen and probably not at all once these changes are fully expressed.

The specificity of the response of hair follicles to androgens is determined within the skin. Hair follicles in occipital skin, a site that shows little or no response to androgens, retain their site-specific behaviour when transplanted into balding areas on the frontal scalp [30]. Conversely, hair follicles from balding scalp continue to regress when transplanted into skin of the forearm [31]. The success of micrografting techniques, in which individual follicles are transplanted, shows that androgen responsiveness is determined at the level of the follicle or its immediate tissue environment. Three lines of evidence suggest that the dermal papilla is the primary target of androgen action in the hair follicle.

1 Androgen receptor expression in the lower part of the follicle is restricted to dermal papilla cells [32,33]

2 The size of the hair follicle is probably determined by the volume of the dermal papilla [34–36]

3 Dermal papillae express 5α-reductase type 2 whereas hair follicle epithelium expresses only 5α-reductase type 1 [37].

However, it is not yet known how androgen action on dermal papilla cells causes changes in hair follicle size and hair cycling. Hence androgens may act on hair growth by altering the number of cells in the dermal papilla and its extracellular matrix [36]. Cells cultured from dermal papillae of human beard hair follicles also release growth factors in response to androgens that stimulate proliferation of keratinocytes [33,38], and the pattern of androgen metabolism by cultured and intact dermal papilla cells is consistent with that expected from their site of origin [39,40]. However, the molecular mechanisms whereby androgens inhibit hair growth on the scalp but stimulate growth in most other body sites are not yet understood.

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Alopecia

Common baldness and androgenetic alopecia

SYN. MALE PATTERN HAIR LOSS; FEMALE PATTERN HAIR LOSS; PATTERNED OR PREMATURE BALDNESS

[R.D. Sinclair, pp. 63.18–63.36]

Nomenclature. Common baldness is the result of a progressive patterned hair loss that only occurs in genetically predisposed individuals. The lack of balding in eunuchs, pseudohermaphrodites and individuals with androgen insensitivity syndrome confirms that androgens are a prerequisite for common baldness. As the pattern of hair loss differs between men and women, the terms male pattern hair loss and female pattern hair loss are also commonly used [1]. Whether someone is considered bald, and in particular prematurely bald, is in part a subjective assessment. The process by which common baldness occurs is androgen-mediated conversion of susceptible terminal hairs into vellus hairs, and has been termed androgenetic alopecia (AGA).

Aetiology. Most vertebrates show regional specificity in the induction and arrangement of skin appendages. The determinants of this are only beginning to be understood [2–4].

Four separate but interrelated factors determine whether an individual will become bald: susceptibility to AGA, age of onset, rate of progression and pattern of hair loss.

Hamilton [5] defined the progressive pattern of male baldness and produced the first useful grading scale. This classification was modified by Norwood [6], who added grades IIIa, III vertex, IVa and Va (Fig. 63.14). Although the grades are imprecise measures of the continuum of hair patterns that are seen in adult males, they are useful as diagnostic aides and in the classification of extent of hair loss in clinical investigations.

It is important to keep in mind that there is no gold standard for the diagnosis of early baldness. While it is safe to assume agreement that men with Hamilton–Norwood stage I are not balding and men with Hamilton–Norwood stage III are going bald, the fate of men who develop stage II pattern of scalp hair has not been followed prospectively.

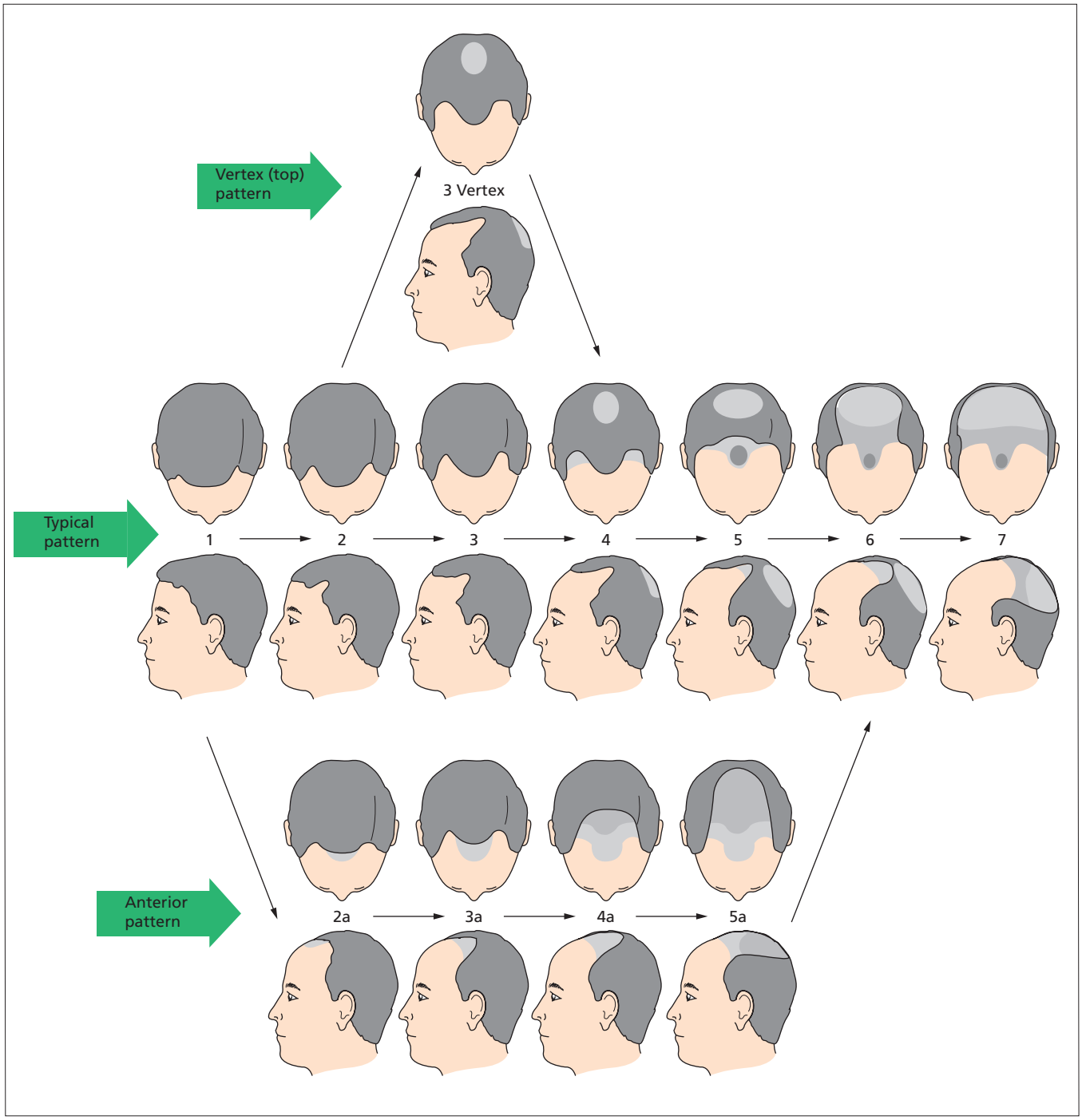

Fig. 63.14 Hamilton–Norwood scale for grading male patterned hair loss [2].

The lifetime risk of male pattern baldness (MPB) can be defined by studying hair patterns in men aged 80 years and above. In Norwood's cohort [6], 16% had a type I hair pattern and by definition are not bald. Fourteen per cent had a type 2 hair pattern, and although demonstrating at least some degree of AGA, would not be considered bald. The remaining 70% had a type III (16%), IV (12%), V (12%), VI (13%) or VII (17%) pattern of hair loss and would be considered to demonstrate MPB.

At least 94% of adult men develop some degree of frontoparietal recession of the hairline after puberty [5]. As the histology of this hair loss shows increased vellus hairs, and as Hamilton observed that three males castrated at the age of 15 and 16 years failed to develop even minimal recession along the frontal hairline, it is likely that this hair

loss occurs by androgen-mediated miniaturization of terminal follicles, and by definition is AGA [7]. However, 16% of 80-year-old men still have stage I hair density. Therefore, limited frontoparietal AGA does not always progress, and may be a benign manifestation of sexual maturity rather than a precursor of MPB.

The age of onset of MPB can also be determined by extrapolation of Norwood's data [6]. Sixty per cent of men aged 18–29 years, 36% aged 30–39 years, 33% aged 40–49 years, 28% aged 50–59 years, 19% aged 60–69 years, 17% aged 70–79 years and 16% of men aged 80 years or above were assessed as having no evidence of AGA. If early MPB is defined as stage II hair pattern, then 40% begin to develop MPB between the ages of 18 and 29, a further 24% first develop MPB in their thirties, 3% in their forties, 5% in their fifties, 9% in their sixties, 2% in their seventies and 1% at or beyond the age of 80 years. If this extrapolation of Norwood's data is valid, then a man with stage I hair at the age of 40 years has almost a 50% likelihood of still having stage I hair at the age of 80 years.

There is wide individual variation in the rate of progression of hair loss in MPB. A small number of men achieve type V or VI hair loss in their twenties, indicating a very rapid rate of progression. In contrast, approximately 25% of men with MPB show no visible hair loss on standardized clinical photographs over a 5-year period [8]. Norwood's data [6] also support the common observation that early-onset MPB progresses more rapidly. Men who develop MPB in their twenties tend to advance 1–2 stages per decade, whereas men with late-onset MPB may take two decades to progress a single stage. As stated above, not every man with AGA goes bald. Although 40% of men start losing their hair in their twenties, only 30% ever reach stage VI or VII. Hence, even for those with early-onset AGA complete baldness is not automatic.

Twin concordance studies in males indicate that susceptibility, age of onset, pattern and rate of progression of MPB are all under genetic influence [9,10]. The lower age-related prevalence of MPB and higher proportion of men with a Ludwig pattern hair loss among Koreans also confirms the profound influence of genes on susceptibility, age of onset and pattern of hair loss [11].

Patterned balding occurs in women, but the susceptibility, age of onset, rate of progression and pattern are different from men. Thirty-two per cent of women aged 80 years and above show no evidence of female pattern hair loss (FPHL). The age of onset of FPHL is later than that seen in men. Only 3% first develop clinically detectable FPHL by age 29 years, a further 13% first develop it by age 49 years, a further 8% by age 69 years and a further 6% after the age of 70 years. In addition, because many women wear their hair long, they are more aware of fluctuations in daily hair shedding. Women with AGA-related increased hair shedding often present prior to the development of reduction in hair volume over the crown (FPHL).

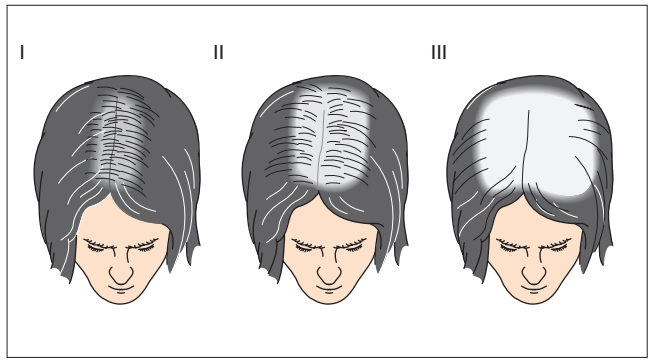

Fig. 63.15 Ludwig scale for grading female patterned hair loss [12].

Fewer than 1% of women progress to Hamilton–Norwood stage IV or above (equivalent to Ludwig stage III). Severe bitemporal recession (Hamilton–Norwood III) is uncommon and, as Ludwig pointed out, the most common pattern of hair loss seen in women is diffuse reduction of hair density over the crown with complete or near complete preservation of the frontal hairline [12]. Olsen observed the so-called Christmas-tree pattern, with widening of the central parting line most noticeably in the mid-frontal scalp. She also pointed out that the hair loss in women is often not confined to the crown but may extend ear to ear (Figs 63.15 & 63.16) [13].

The histology of the hair loss seen in women is indistinguishable from that seen in men. The process of FPHL involves androgen-mediated miniaturization of terminal hair follicles and therefore is AGA. The only caveat to this is that hair loss in an identical pattern has been observed in a female without androgens, indicating that other non-androgen-dependent mechanisms can produce hair loss that mimics AGA [14].

Minor bitemporal recession also occurs in more than 25% of women in their twenties and, as in men, is not necessarily a precursor of baldness, even though biopsy from these areas reveals AGA [15].

Inheritance. A familial tendency to MPB is well recognized, as is racial variation in the age-related prevalence of balding. A polygenic model of inheritance has been evoked in an attempt to explain the high prevalence of MPB in the population, the finding that baldness risk increases with the number of affected family members and, in particular, the high frequency of baldness in the fathers of balding men [16]. Of the 54 father–son relationships in the Victorian Family Heart Study, 81.5% of balding sons had fathers who had cosmetically significant balding.

Definition of MPB, particularly in its early stages, has confounded attempts to identify causative genes. By comparing DNA from young bald men with that of old non-bald men, Ellis *et al.* [17] identified an association of MPB

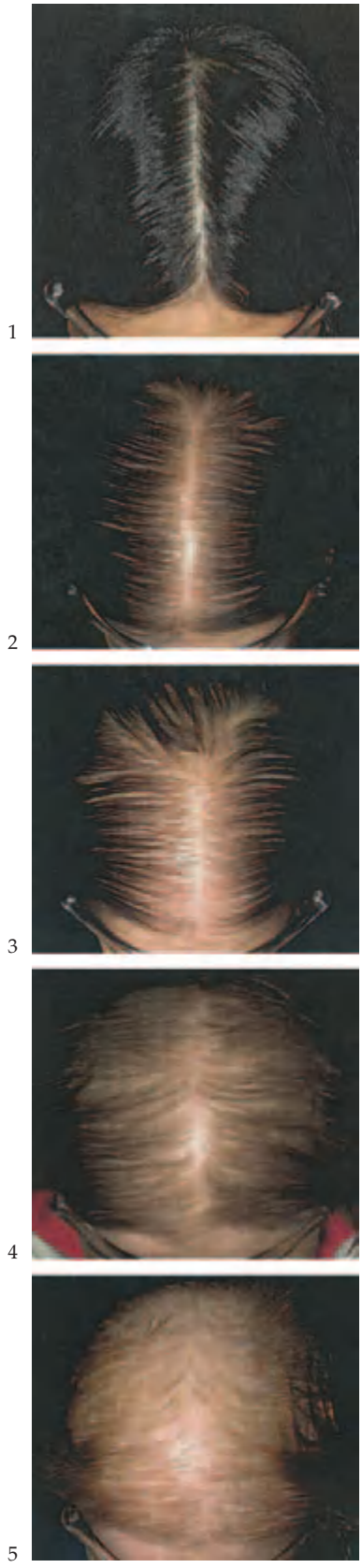

Fig. 63.16 Pattern of frontal hair loss in women with androgenetic alopecia. Stage 1 is normal.

with a polymorphism of the androgen receptor gene on the X chromosome. The androgen receptor gene *Stu1* restriction fragment length polymorphism (RFLP) was found in almost all (98.1%) young bald men, and most older bald men (92.3%), but only in 77% of non-bald men. This polymorphism appears to be necessary for the development of AGA, but its presence in non-bald men indicates that it is not sufficient for the development of AGA [17]. In addition, several shorter triplet repeat haplotypes were found in higher frequency in bald men than in normal controls. These RFLPs appear to be associated with a functional variant of the androgen receptor gene that is part of the polygenic inheritance of male common baldness. Of note is that the androgen receptor gene is located on the X chromosome, which is passed from the mother to a male child.

Current modelling suggests the involvement of at least four genes that combine to modify the age of onset, pattern of loss and rate of progression of MPB [16]. Other candidate gene and chromosomal regions have been examined. They include *SRDA1* and *SRDA5*, coding for the two variants of the 5α-reductase enzymes [18], the insulin gene [19], the aromatase gene, the gene for the Erα oestrogen receptor, the non-recombinant area of the Y chromosome and the type II IGF genes [16]. Thus far, no association has been found between any of the above-mentioned genetic areas and MPB.

Although a positive association between vertex balding and prostate cancer [20] has been identified, there is no clear association between MPB and dense hair patterns on the trunk [21], number of children [22] or coronary artery disease [23].

Regarding FPHL, Harrison examined DNA from 136 women with histologically proven AGA and compared them with 100 elderly female controls without hair loss, and suggested a possible role for both androgen receptor gene polymorphisms and polymorphisms in the aromatase gene in the development of FPHL [24].

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Hormonal influences

Systemic hormonal effects (see p. 63.15)

A number of studies have tried to identify increased circulating androgens in balding males, but no differences between patients and controls have been consistently found. Pitts [1] found elevated serum dihydroepiandrosterone sulphate (DHEA) but normal testosterone levels in 18 balding males compared with non-balding controls. A case–control study of 159 cases and 156 controls found a positive association between free testosterone and frontal and vertex baldness, compared with men who had only minimal hair loss [2]. The association with testosterone was also found in a cross-sectional study [3]. A positive association between IGF-1 and vertex balding has also been reported [4]. Sreekumar *et al.* [5] investigated a subset of patients with early-onset and advanced AGA and found no difference between patients and controls in the absolute levels of any androgens; however, the ratio of DHT : testosterone was elevated. All these studies suffer from a lack of reproducibility, and although differences in mean levels have been variously detected, the substantial overlap in the absolute levels of all androgens between cases and controls demonstrates that normal male levels of androgen are sufficient to make manifest the degree of baldness determined genetically for the individual.

The situation in women is more complex, as androgen-secreting tumours can trigger a sudden onset and rapidly progressive baldness [6]. Although hyperandrogenism was identified in 42 out of 109 women referred to an endocrinologist for hormonal evaluation of diffuse vertex alopecia, most of the abnormalities detected were inconsequential. For this survey, hyperandrogenism was defined as an increase in any plasma androgen. Of those 42 women, only 18 had polycystic ovary syndrome [7]. In contrast, no clinically significant hormone abnormality was found in 166 consecutive women with biopsy-proven AGA seen in a dermatology clinic [8].

Although the vast majority of women with FPHL have no discernible endocrine abnormality, in some women the hair loss may be accelerated by elevated circulating androgen levels [9–11]. Stated differently, androgens in the normal female range are sufficient to induce early baldness in women with a strong genetic predisposition. In women with a less strong genetic predisposition, balding will not occur until later in life unless androgen production is increased or drugs with androgen-like activity are taken. Some women with even grossly abnormal levels of androgen do not develop clinically significant baldness, although such patients are generally hirsute.

As there is no clear association between levels of circulating androgens and MPB, it is likely that the normal level of systemic androgen is adequate for the maximal production of dihydrotestosterone, and local factors determine individual susceptibility and severity of baldness. In females, local factors determine susceptibility, but severity is influenced by both local and systemic hormone factors.

Local hormonal effects

Beard dermal papilla cells are known to secrete growth-inducing autocrine growth factors in response to testosterone, leading to an increase in dermal papilla size and enlargement of the hair follicle and hair cortex. This response is not seen with occipital scalp hair follicles when subjected to the same testosterone challenge [12,13]. IGF-1 has been identified as a major component of secreted cytokines [14]. Similar investigations performed on dermal papilla cells from the balding scalp of the stump-tailed macaque showed that testosterone inhibited the growth and proliferation of keratinocytes [15]. TGF-β1 has been identified as a major component of the secreted cytokines in the vertex scalp and neutralizing anti-TGF-β1 antibody will reverse the androgen-induced inhibition of keratinocyte proliferation. It has been postulated that the androgen-induced anti-TGF-β1 derived from the dermal papilla cells mediates hair growth suppression in androgenetic alopecia [16]. Studies examining distribution and expression of androgen receptors have shown varying results. Two studies showed that androgen receptors are only found in the nuclei of dermal papilla cells [12,17].

However, another study found more extensive follicular distribution of receptors, including the hair bulb [18]. Comparing different anatomical sites, there appear to be higher numbers of androgen receptors in the pubic hair follicles and beard dermal papilla cells, with occipital scalp follicles expressing lower levels [19].

Hair loss on the scalp progresses in an orderly and reproducible pattern, and is a function of factors intrinsic to each hair follicle. *In vitro* experiments have shown that the hair follicles are able to self-regulate their response to androgens by regulating the expression of 5α-reductase and androgen receptors [20,21]. This self-regulation is postulated to produce the quantifiable difference in androgen receptor numbers [19,22] and 5α-reductase activity [20,23] that is observed between balding and non-balding areas of the scalp. This intrinsic regulation is best demonstrated in hair transplantation experiments; occipital hairs maintain their resistance to AGA when transplanted to the vertex, and scalp hairs from the vertex transplanted to the forearm miniaturize at the same pace as hairs neighbouring the donor site [24].

Hair cycle dynamics

In AGA, the duration of anagen decreases with each cycle, whereas the length of telogen remains constant or is prolonged. This results in a reduction of the anagen : telogen ratio. Balding patients often describe periods of excessive hair shedding, most noticeable while combing or washing. This is a result of the relative increase in numbers of follicles in telogen.

As the hair growth rate remains relatively constant, the duration of anagen growth determines hair length. Thus, with each successively foreshortened hair cycle, the length of each hair shaft is reduced. Ultimately, anagen duration becomes so short that the growing hair fails to achieve sufficient length to reach the surface of the skin, leaving an empty follicular pore. In addition, the latent phase is prolonged, reducing hair numbers, and further contributing to the balding process [25].

Hair follicle miniaturization

In addition to the changes in hair cycle dynamics, there is a stepwise miniaturization of entire follicles. It is not clear whether the same factors control the miniaturization and hair cycle changes. A significant proportion of men and women bald without ever being aware of increased hair shedding, but increased hair shedding can occur in the context of chronic telogen effluvium without associated follicular miniaturization.

As the dermal papilla is central to the maintenance and control of hair growth, it is likely to be the target of androgen-mediated events leading to follicle miniaturization and hair cycle changes [26–28]. The constant geometric relationship between the dermal papilla size and the size of the hair matrix [29] suggests that the size of the dermal papilla determines the size of the hair bulb and ultimately the hair shaft produced.

A greater than 10-fold reduction in overall cell numbers is likely to account for the decrease in hair follicle size [30]. The mechanism by which this decrease occurs is unexplained, and may be the result of either apoptotic cell death, cell displacement with loss of cellular adhesion leading to dermal papilla fibroblasts dropping off into the dermis, or migration of dermal papilla cells into the dermal sheath associated with the outer root sheath of the hair follicle [30].

In overall volumetric terms, change in the follicular extracellular matrix is unlikely to greatly affect follicle size. However, being a potential source of biologically active molecules, small changes in its volume may have significant effects on hair follicle function [31].

Smaller follicles result in finer hairs. The calibre of hair shafts reduces from 0.08 mm to less than 0.06 mm [32]. This is also followed by a reduction in pigment production. On the balding scalp, transitional indeterminate hairs represent the bridge between full-sized and miniaturized terminal hairs [33].

Follicular miniaturization has been traditionally thought to occur in a stepwise fashion. The cross-sectional area of individual hair shafts remains constant throughout fully developed anagen [31], indicating that the hair follicle, and its dermal papilla, remain the same size through each individual anagen stage of the cycle. Thus, miniaturization occurs between rather than within cycles.

In catagen, the entire bulb undergoes apoptosis and the base of the hair follicle retracts upwards to the level of the hair bulge. Entry into anagen occurs when the slow cycling stem cells in the bulge are activated, probably in response to signals from the dermal papilla. Daughter transient amplifying cells migrate downwards along the follicular stella, renew contact with the dermal papilla, and reform a new hair bulb and ultimately its differentiated cell product—the hair. This early part of the anagen cycle is the most likely point in time for miniaturization, and results in the stepwise reduction in follicle size between successive cycles [34].

Birch *et al.* [35] studied hair diameter in women in relation to hair density. The distribution of hair diameters showed wide variation between individual subjects, but narrow hair diameter was not associated with low hair density. They were not able to demonstrate a progressive reduction in the diameter of individual hairs with falling hair density, and concluded that miniaturization in FPHL occurs rapidly, possibly in the space of a single cycle.

Follicular miniaturization leaves behind stellae as dermal remnants of the full-sized follicle. These stellae, also known as fibrous tracts or streamers, extend from the subcutaneous tissue up the old follicular tract to the

miniaturized hair and mark the formal position of the original terminal follicle. Arao–Perkins bodies may be seen with elastic stains within the follicular stellae. An Arao–Perkins body begins as a small cluster of elastic fibres in the neck of the dermal papilla. These clump in catagen and remain situated at the lowest point of origin of the follicular stellae. With the progressive shortening of anagen hair seen in AGA, multiple elastic clumps may be found in stellae, like the rungs of a ladder [36].

Follicular miniaturization is also a prominent feature of the histology of alopecia areata. It has been postulated that inflammation and fibrosis within the follicular stellae of AGA account for the difficulty of reversing the miniaturization in AGA.

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Clinical features. The essential clinical feature of balding in both sexes is patterned hair loss over the crown. Pigmented terminal hairs are progressively replaced by finer hairs, which are short and virtually non-pigmented. This process may begin at any age after the onset of adrenarche and may precede pubarche.

Males. The clinical appearance of male androgenetic alopecia is instantly recognizable in most cases. The progression of the hair loss occurs in an orderly manner and has been well documented by Hamilton [1] and Norwood [2] (Fig. 63.14). The posterior and lateral scalp margins are spared, even in the most advanced cases, and even in old age. Twin concordance studies indicate that variations in the pattern are governed, at least in part, by genetic factors, as is the rate of progression [3].

The main significance of hair relates to socialization,

and hair is an essential part of an individual's self-image. Thus, the consequences of AGA are predominantly psychological. Bald men are likely to have fewer lifetime sexual partners than non-bald men, which may be a reflection of their physical attractiveness to the other sex [4]. Several studies have shown that the negative self-perception of balding patients appears to be consistent between Western [5,6] and Asian cultures [7]. The negative impact of AGA is often trivialized or ignored by the non-bald [8]. However, there is evidence that perception by others may compound the psychological problems suffered by balding men. A Korean study [7] of the perception of balding men by women and non-balding men found that their negative perception of men with AGA was similar to the psychosocial effects reported by the patients themselves. Of note was that a perception of bald men looking less attractive was found in more than 90% of subjects surveyed. Importantly, this view was more common in women than non-balding men. Such negative perceptions may further impair the social functioning of balding men.

However, it is important to note that most affected men cope well with AGA, and it does not have significant impact on their psychosocial function. Thus, those who do seek help are likely to be in greater emotional distress and to have been dissatisfied with any treatment they have received.

The most distressed balding men are those with more extensive hair loss, those who have very early onset, and those who regard their balding as progressive (often arising from observation of their father) and socially noticeable [5].

Females. The pattern of hair loss and the clinical presentation of AGA in women differ from men. Women may present with either an episodic or continuous increase in hair shedding without any noticeable reduction in hair volume, increased hair shedding with loss of hair volume over the crown or diffuse thinning over the crown with no history of hair shedding [9]. Women with FPHL commonly underestimate the severity of their loss [10]. Asking women with a loss of hair volume over the crown about the thickness of their ponytail often enables them to estimate and communicate the degree of hair loss. Diffuse thinning over the crown can be best detected when the hair is parted centrally. Widening of the central parting (part) often follows a Christmas tree pattern and can be used to grade the hair loss [11].

Ludwig [12] described the most common pattern of loss in women and his illustrations have been used as a grading scale. The earliest change (Ludwig grade I) is a rarefaction of the hair on the crown. This produces an oval area of alopecia encircled by a band of variable breadth with normal hair density. Frontally the fringe is narrow (1–3 cm) and at the sides the margin is 4–5 cm wide. Progression to Ludwig grade II results in further rarefaction of the crown, with preservation of the fringe. Grade III is near-complete baldness of the crown. As Ludwig only produced three illustrations (Fig. 63.15), other validated scales with more images should prove more useful for patient grading (Fig. 63.16) [13].

The relative incidence of Ludwig versus Hamilton pattern alopecia among balding women has been determined. Ludwig pattern I–III occurred in 87% of premenopausal women and Hamilton stage II–IV occurred in 13%. Among postmenopausal women, Ludwig I–III occurred in 63% and Hamilton II–V occurred in 37% [14].

In most women the hair loss is confined to the vertex scalp, but in a significant proportion hair loss also occurs diffusely over the parietal scalp. Generalized hair loss may preclude women from hair transplantation procedures because of a diminished donor population.

Most women who present with hair loss have no other evidence of virilization. However, if the hair loss is of sudden onset, rapidly progressive and advanced, a full medical history and examination, and endocrinological investigation are desirable to exclude virilization, which can rarely be caused by a virilizing tumour. Investigation is also indicated in women with AGA of gradual onset accompanied by menstrual disturbance, hirsutism or recrudescence of acne [15].

The principal differential diagnosis of early AGA is chronic telogen effluvium (CTE) [16]. Women with CTE present with chronic diffuse hair shedding without noticeable widening of the central parting. They may describe a loss in volume of the ponytail of up to one-third, and there is commonly mild bitemporal recession. Scalp biopsy of women who present in this fashion reveals AGA in approximately 60% of cases and CTE in 40% [13]. Scalp biopsy is not required in women who present with loss of hair volume either alone or associated with increased hair shedding.

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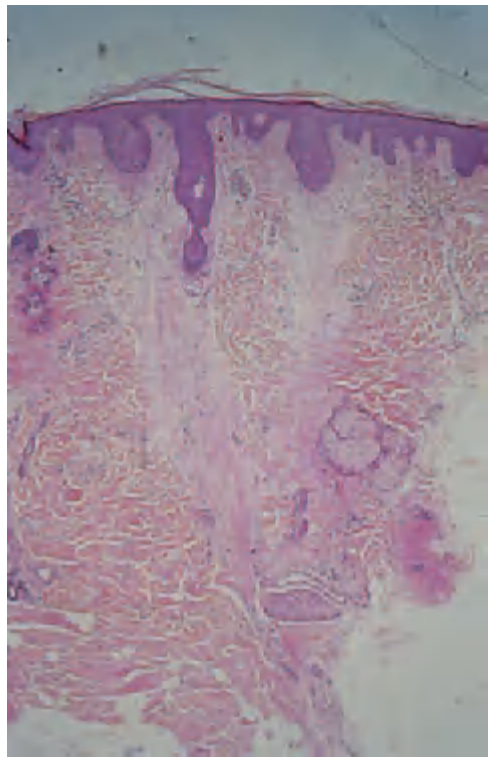
Pathology. The key elements of the histology of AGA are a marked reduction in terminal hairs, an increase in secondary vellus hair with associated angiofibrotic streamers, an increase in telogen and catagen hairs, and a mild or moderate perifollicular lymphohistiocytic infiltrate, with or without concentric layers of perifollicular collagen deposition (Fig. 63.17) [1].

A mild lymphohistiocytic inflammation is found in approximately one-third of cases of AGA and a similar number of controls, and is non-specific. In contrast, a moderate lymphohistiocytic inflammation is found in another one-third of cases of AGA, but in only 10% of controls [2]. Occasional eosinophils and mast cells can be seen. The cellular inflammatory changes also occur around lower follicles in some cases and occasionally involve follicular stellae. The diagnostic and prognostic significance of the degree of the inflammation is not known.

Many of these changes are best seen on horizontally sectioned scalp biopsies. Horizontal sections reveal numerous pseudovellus hair follicles in the papillary dermis, reflecting a miniaturization process. In the vast majority of cases there is no genuine reduction in the number of follicles, and follicular fibrosis is seen in less than 10% of cases. The presence of arrector pili muscles and angiofibrotic streamers distinguishes them from true vellus hairs. There is a change in the ratio of terminal : vellus hairs from greater than 8 : 1 to less than 4 : 1. Also, the anagen : telogen hair ratio reduces from 12 : 1 to 5 : 1 [3]. The increased proportion of catagen and telogen hairs reflects the shortened duration of anagen and the relative increase in telogen hairs.

As the balding scalp loses its protective covering of hair, solar degenerative changes may be seen. A reduction of blood supply has been observed [4], but whether it follows or precedes the hair loss is unknown.

The reduction in the size of the affected follicles, which is the essential histological feature of AGA, necessarily results in a reduction in the diameter of the hairs they produce. This reduction is said to be greater in women than in men [5,6]. Balding patients showed a wide spread of hair-shaft diameters, with peaks at 0.04 mm and 0.06 mm, whereas non-bald subjects showed a symmetrical distribution with a single peak at 0.08 mm. Increased hair


(a)

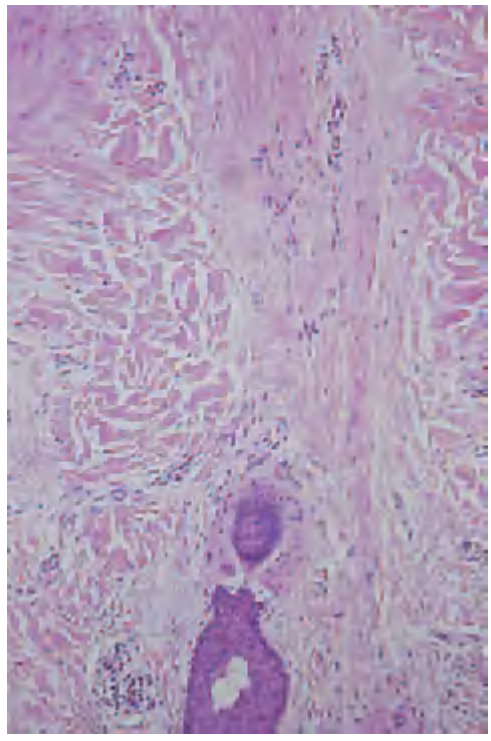

(b)

Fig. 63.17 Histology of androgenetic alopecia on vertically sectioned scalp biopsy. (a) The low-power photomicrograph shows a reduction in follicle number and size. (b) The high-power photomicrograph shows the follicular streamer and a light perifollicular inflammatory infiltrate.

diameter diversity has been used a diagnostic criterion for AGA [7].

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Pathogenesis. Any unifying hypothesis for AGA has to explain the following: the occurrence in humans and simian species; strong familial tendency; the involvement of both sexes; geographical patterning of hair loss on the scalp; the paradoxical effect of circulating and local androgens on scalp and body hairs; the phenomenon of donor dominance in hair transplantation; the alteration of hair cycle dynamics; follicular miniaturization; perifollicular inflammation; and the coexistence of greasy skin, acne and hirsutism in some women.

Treatment

Twenty-five years ago patterned baldness was thought to be irreversible, and although oral antiandrogens were advocated to arrest further hair loss for women, there were no medical treatments available for men. There are now a number of effective treatments to arrest the progression of the hair loss and stimulate regrowth in a significant proportion of individuals. Although the degree of regrowth achieved is often minor, a small proportion of men have a dramatic response to therapy.

As baldness is not life-threatening and the morbidity is variable, most people do not seek treatment. Some patients simply attend for a diagnosis, and when the currently available therapies are discussed, decline treatment. Without therapy baldness is progressive, although the rate of progression is extremely variable. Twenty-five per cent of men will have no visible progression after 5 years. Some will achieve Hamilton stage VII within 5 years, whereas others may take 50 years.

Before any patient embarks on therapy he or she should be counselled carefully and made aware of the need for maintenance therapy. It is preferable that advice is given by qualified medical practitioners who are fully aware of all the treatment options so that vulnerable individuals may be kept away from commercial centres where profit is the only motivation.

Surgery

All surgical procedures are attempts to spread parietal and occipital hairs thinly over the rest of the scalp. Hair can be redistributed using autografts or flaps. Either procedure can be performed alone or in combination with reduction of the bald area by excision and closure. Grafts may be as large as 4 mm in diameter, but better results are achieved with much smaller 'micrografts', which can be manipulated to produce a natural-looking frontal hairline. Reduction of the bald area by removal of an ellipse from the vault or repeated such operations may cover the top of the head by stretching the remaining parietal scalp. Expansion techniques have been used successfully to restore post-traumatic alopecia [1]. Hair transplantation techniques are constantly undergoing revision and improvement. They have been recently reviewed [2]. Artificial fibre implantation has been used for AGA but foreign body reactions and infections are potentially serious complications [3,4]. Use of artificial fibres has been banned in a number of countries.

Surgery is often performed long before the ultimate pattern of hair loss is clear. Without adjunctive medical therapy to prevent progression of the balding process, an unnatural appearance can evolve over time that may require further surgery to correct.

Camouflage and wigs

Camouflage is the simplest, easiest and cheapest way of dealing with mild AGA. Balding becomes most noticeable when the scalp can be seen through the hair. Camouflage treatments involve either adding small fibres held in place electrostatically or dyeing the scalp the same colour as the hair to create the illusion of thicker hair. Numerous brands are available, each in a range of colours. Although many of the newer agents are water-resistant, if the hair becomes wet in the rain the dye may still run.

Wigs are an alternative to scalp surgery. For many women, an alternative to a full wig is a smaller hair piece that can either be interwoven with existing hair or worn over the top of existing hair. Interwoven wigs tend to lift as the hair beneath grows, and they require periodic adjustment.

Wig hair is composed of either a synthetic acrylic fibre that withstands wear and tear very well, or natural fibre (usually Asian or European human hair). Natural fibre wigs look better, are easier to style and last longer, but are considerably more expensive. Wigs can be styled and washed, and modern wigs provide excellent coverage that looks natural. A drawback of wigs is that the head may be hot in the summer, and some patients find them difficult to wear for this reason.

Excellent advice on wigs is available from the alopecia patient support groups that exist in the UK, USA and Australia. In the UK, the National Health Service subsidizes wigs for 'medical hair loss'.

Medical management

Currently available medical management for women consists of oral antiandrogens and topical minoxidil. Antiandrogens may feminize males and therefore are not appropriate for use in balding men. They are potential teratogens, and women should be advised to take appropriate precautions to avoid pregnancy while taking these medications. Pharmacological therapy for men includes topical minoxidil and the 5α-reductase inhibitors finasteride and dutasteride. Finasteride and dutasteride are both teratogens with very long biological half-lives, and so should be avoided in women with child-bearing potential, as even if these agents were stopped as soon as a woman discovered she had become pregnant, activity may persist into the critical second trimester.

Medical treatment should be continued indefinitely, as the benefit is not maintained when therapy is stopped. Up to 1 year of treatment may be required before any clinical response is noticeable. The monitoring of this response can be problematic. Patients inspect their hair on a daily basis and subtle changes over time may not be readily observable. Doctors are essentially reliant upon the patient's subjective assessment of their hair density over time. Baseline photographs are helpful, but unlikely to detect changes of less than 20% in hair density. Periodic photography is useful for monitoring and maximizing patient compliance [5].

Management of male pattern baldness. Many therapies given systemically for other reasons may produce general hypertrichosis and concurrent improvement in AGA (e.g. ciclosporin and psoralen with UVA therapy [PUVA]), but these cannot be used as treatment. Only minoxidil has been shown to enhance regrowth significantly when used topically. Minoxidil is a piperidinopyrimidine derivative and a potent vasodilator that is effective orally for severe hypertension. When applied topically as a 2% solution in an alcohol and water base containing 10% propylene glycol, minoxidil has shown conversion of vellus to terminal hair in up to 30% of individuals [6,7]. Terminal hair appeared to regrow at the margins, but complete covering of the bald areas was seen in less than 10% of responders. De Villez [8] suggested that bald men who responded best to minoxidil were those in whom the balding process was at an early stage, with a maximum diameter of the bald area of less than 10 cm and in whom the pretreatment hair density was in excess of 20 hairs/cm^2. There is a slight increase in benefit if the concentration is increased to 5%. The benefit is most pronounced in the first 6 months of therapy and thereafter is marginal.

Topical minoxidil appears to be a safe therapy with side effects only of local irritation and hypertrichosis of the temples, and there is a low incidence of contact dermatitis [9]. If treatment is stopped clinical regression occurs, after 3 months, to the state of baldness that would have existed if treatment had not been applied [10]. Patients should be warned that in order to maintain any beneficial effect, applications must continue twice daily for the rest of their lives [7]. Whether the benefits are maintained in the longer term is uncertain [11].

Finasteride is a synthetic aza-steroid that is a potent and highly selective antagonist of 5α-reductase type 2. Being a non-competitive antagonist, it binds irreversibly to the enzyme and inhibits the conversion of testosterone to DHT. Thus, although the pharmacokinetic half-life is about 8 h, the biological effect persists for much longer. The underlying principle for its use is the reduction of DHT production and thus limitation of the miniaturization of scalp hair follicles. A scalp biopsy study of patients with AGA found that after 12 months of finasteride treatment, terminal hair counts increase and vellus hair counts decrease, demonstrating the ability of finasteride to reverse the miniaturization process and to encourage the growth of terminal hairs [12].

An oral dosage of 1 mg/day reduces scalp DHT by 64% and serum DHT by 68% [13]. Finasteride is also approved for the treatment of benign prostatic hypertrophy in a dosage of 5 mg/day. Dose-ranging studies have found no significant difference in clinical benefit between 5 and 1 mg/day regimens [14], nor is there any significant further reduction of scalp or serum DHT levels.

At the end of 1 year, patients on finasteride have a 10% increase in the mean number of terminal hairs compared with baseline counts. After 5 years of continuous therapy, hair counts remained close to the 1-year level, whereas the counts in the placebo patients had dropped by 30%. Using global photography to assess scalp coverage, 48% of patients taking finasteride had increased hair density, compared with 7% of the placebo group at the end of 1 year. At 2 years [15], coverage continued to improve in the finasteride group, with 66% having increased density, whereas only 7% of the placebo subjects had increased coverage. By 5 years [16], 10% of treated patients had a lowered hair density, 42% had no change, and 22%, 21% and 5% were assessed as moderately, markedly and greatly improved, respectively. In contrast, 19%, 31% and 25% of patients in the placebo group were greatly, markedly or moderately worse. Nevertheless, 25% of the patients in the placebo group showed no deterioration over the 5-year period, reflecting the variable rate of progression of balding among males.

These data suggest that the maximal number of finasteride-responsive follicles are recruited by the end of 1 year, and further improvement in scalp coverage results from increase in hair length, diameter and pigmentation [16]. At the end of the first year, some finasteride patients

were changed to placebo, resulting in a decrease in their hair counts after 12 months. Some in the placebo group were also crossed over, receiving finasteride for the second year; these subjects had an increase in their hair counts, although the average increase was less than that seen in the original group, indicating the potential for regrowth diminishes as the AGA progresses.

Studies using hair weight as the objective measure of outcome indicate that men on placebo had a reduction in hair weight of 9.2% of their hair at 48 weeks and 15.4% at 96 weeks, compared with the men on active treatment who had an increase of 25.6% at 48 weeks and 35.8% at 96 weeks. Factors that affect hair weight include the number of hairs, hair growth rate and hair thickness [17].

Work examining the effect of finasteride on frontal hair loss also confirmed efficacy here, albeit the magnitude of regrowth appears less [18].

Few adverse effects were reported in the phase III studies [15,16]. In the finasteride group, loss of libido was reported in 1.8% and erectile dysfunction in 1.3%. The placebo groups reported these same events, with frequencies of 1.3% and 0.7%, respectively. These events appeared to resolve on cessation of the drug and, in some cases, with continued treatment. It has been suggested that even these figures overstate the true incidence of sexual dysfunction [19].

Of note is that older men on finasteride experienced a 50% reduction in serum prostate-specific antigen (PSA) levels, which could result in an underestimation of prostatic cancer risk. It has been shown in the urology literature that PSA levels remain valid while patients are taking finasteride, but the value should be doubled to correct for the finasteride effect [20,21]. Men between 18 and 41 years of age have a negligible decrease in measured PSA [22].

Topical finasteride has been investigated as an alternative means of drug delivery. Although a 0.05% finasteride solution applied to the scalp was well absorbed and produced a 40% reduction in serum DHT, it had no effect on hair regrowth. One explanation is that inhibition of prostatic DHT production is an important factor in preventing hair loss with finasteride; a significant reduction in circulating DHT is required in addition to the local blockade of 5α-reductase at the hair follicle [23].

Finasteride is a teratogen. Male rats exposed to finasteride *in utero* develop hypospadias with cleft prepuce, decreased anogenital distance, reduced prostate weight and altered nipple formation [24]. As the drug is secreted in the semen and can be absorbed through the vagina during intercourse, it was originally advocated that men taking finasteride should avoid unprotected intercourse with pregnant women. In practice, the concentration of finasteride in the semen is well below the minimum effect dosage, and no recommendations regarding the use of condoms are made in the product information leaflet [25]. There are no reports of adverse pregnancy outcomes among women exposed to finasteride taken by their partners [26]. Finasteride has no effect on spermatogenesis or semen production [27].

With regard to long-term safety, finasteride has now been in widespread use for over 10 years. Many recipients are elderly men taking 5 mg/day. Very few side effects have been observed [28]. There is no effect of long-term use on bone mineral density [16,29]. Reversible painful gynaecomastia has been reported [30] and the incidence is thought to be approximately 0.001% [31]. The prostate cancer prevention trial has demonstrated that 5 mg daily of finasteride will reduce the incidence of prostate cancer by 25% among men aged 55 and over. More of the reduction occurred in low-grade prostate cancers (Gleason stage 2–6), whilst the incidence of high-grade cancers (Gleason stage 7–10) was increased [32].

Dutasteride is a combined type 1 and 2 5α-reductase inhibitor. There is a dose-dependent reduction in scalp DHT levels. At 0.5 mg/day a 53% reduction is scalp DHT is seen, and at 2.5 mg/day the reduction is 83%. The percentage reduction in scalp DHT seems to be the best indicator of clinical response. The drug is currently marketed at a 1 mg dosage for benign prostatic hypertrophy. Sexual side effects are more common with dutasteride than with finasteride, and are also dose related, but appear to be reversible on cessation.

Management of female pattern hair loss. Topical minoxidil has been demonstrated to either arrest hair loss or to induce mild to moderate hair regrowth in approximately 60% of women [33]. It may be used alone or in combination with oral antiandrogen therapy [34].

Oral antiandrogen therapy with cyproterone acetate, spironolactone and flutamide are of benefit in arresting AGA in women [35]. Most studies with these drugs have been performed in hirsutism and only a small number in AGA [36].

Spironolactone is a synthetic steroid, structurally related to aldosterone, which acts by competitively blocking cytoplasmic receptors for DHT. It also weakly inhibits androgen biosynthesis. Its primary use is as a diuretic and antihypertensive and many of its side effects and numerous drug interactions relate to this. Several studies have demonstrated the efficacy of spironolactone in the treatment of hirsutism [36], and some have found that it is also of benefit in AGA [37]. Dosage ranges from 100 to 300 mg/day, but most women require a minimum of 200 mg/day [38]. Side effects are dose related and include menstrual irregularities, postmenopausal bleeding, breast tenderness or enlargement, and fatigue [39]. Spironolactone has the potential to feminize a male fetus and women should not become pregnant while taking spironolactone. Concomitant use of oral contraceptives will reduce the hormonal side effects. The antialdosterone effect can result in an elevation of serum potassium and a slight reduction in blood pressure, although this is rarely significant in the absence of renal impairment. Rare cases

of hepatocellular carcinoma and hepatitis have been reported, but with substantially higher doses [40,41].

Cyproterone acetate is an androgen receptor blocker and potent progestin [42]. It also has an antigonadotrophic effect. It has been in common usage for over 40 years. It has been shown to be of benefit in AGA [43] and is widely used to treat it in women. However, it appears more effective at arresting progression than stimulating hair regrowth [44]. Although low-dose therapy with 2 mg/day cyproterone acetate may be useful in hirsutism [45], higher doses, in the order of 100 mg/day for 10 days of each menstrual cycle, seem to be required in AGA [46]. For postmenopausal women, cyproterone acetate may be used continuously, with or without oestrogens. The average dosage required is 50 mg/day.

The side effects of cyproterone acetate are dose dependent and include lassitude, weight gain, breast tenderness, loss of libido, depression and nausea [47]. Shortness of breath is an uncommon side effect [48]. Feminization of a male fetus may occur and so patients should be advised to cease the medication before conception. The combination of cyproterone acetate and oral oestrogen therapy provides effective contraception and stabilizes menstrual irregularities.

Flutamide is a non-steroidal antiandrogen that acts by inhibiting androgen uptake and by inhibiting nuclear binding of androgen within the target tissue. One study suggested that flutamide is superior to cyproterone acetate and finasteride in the treatment of androgenetic alopecia [49]. However, rare but potentially fatal hepatotoxicity limits the use of flutamide for this condition [36].

In a double-blind placebo-controlled study involving almost 100 postmenopausal women, 1 mg finasteride was found to be no better than placebo [50]. Subsequently, a case report and a case series have shown idiosyncratic benefit [51,52].

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Disturbances of hair cycle

Telogen effluvium

SYN. TELOGEN DEFLUVIUM

Definition. The term telogen effluvium, first coined by Kligman in 1961 [1], refers to the loss of club (telogen) hair in disease states of the follicle. Kligman's hypothesis was that whatever the cause of the hair loss, the follicle tends to behave in a similar way; the premature termination of anagen. 'The follicle is precipitated into catagen and transforms into a resting stage that mimics telogen.' The observation of increased telogen hair shedding does not infer a cause. To establish a cause, one requires a history to identify known triggers, biochemical investigation to exclude endocrine, nutritional or autoimmune aetiologies and, in persistent cases, histology to identify the earliest stages of AGA. The duration of the hair shedding at presentation helps predict those patients in whom further investigation will have the greatest yield.

Follicular cycling within anatomical regions is synchronous in infancy, in that all neighbouring hairs grow together, involute together and are shed together, producing a moult wave. Whereas the moult wave persists indefinitely in many animals, in humans synchronous hair growth disappears in childhood. Rather than periodically shedding all 100 000 scalp hairs over the course of a few months, adult humans tend to lose a few hairs each day, and therefore are never normally bald [2].

Scalp trichography reveals 86% of plucked hairs are in anagen, 1% in catagen and 13% are in telogen, whereas data from analysis of horizontal scalp biopsies puts these figures at 93% of follicles in anagen and 7% in telogen [3]. Based on biopsy data, if the average number of scalp hairs is 100 000, then 7000 hairs should be in telogen at any one time. As the approximate duration of telogen is 100 days, 77 hairs should be shed each day, but most people are not aware of shedding anywhere near this amount. Although this number is likely to correspond to the absolute number of hairs that are shed each day, it still remains to be defined what amount is normally noticed and how introspection heightens one's powers of detection [4].

Pathogenesis. Headington [5] described five functional types of telogen effluvium based on different phases of the follicular cycle: immediate anagen release, delayed anagen release, short anagen syndrome, immediate telogen release and delayed telogen release.

Immediate anagen release is a short-onset effluvium where follicles are stimulated to leave anagen and enter telogen prematurely, resulting in increased hair shedding at the end of telogen approximately 2–3 months later. It is common after a physiological stress such as severe illness, and with drug-induced hair loss. Reversal is associated with resumption of the normal cycle. Delayed anagen release is the cause of postpartum hair loss. During pregnancy, hairs remain in prolonged anagen rather than cycling into telogen. If a large number of follicles are involved, postpartum telogen conversion will be accompanied by increased shedding some months later. Short anagen syndrome is caused by an idiopathic shortening of the duration of anagen and can cause a persistent telogen hair shedding in some individuals [5].

It is not known precisely how long a telogen hair remains in the follicle, but it is believed that club hairs are released 4–6 weeks after the onset of anagen. This may explain the different anagen : telogen rates seen on trichogram versus biopsy. Immediate telogen release results from a shortening of normal telogen, with release of club hairs as the follicles are stimulated to re-enter anagen. Drugs such as minoxidil can precipitate immediate telogen release. Delayed telogen release occurs after a prolonged telogen followed by transition to anagen. It occurs in animals with synchronous hair cycles during shedding

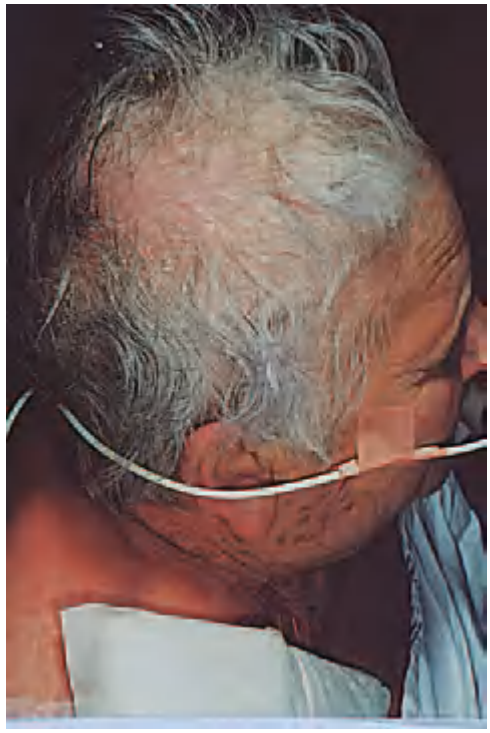

Fig. 63.18 Acute telogen effluvium.

of their winter coats. It may occur seasonally in some humans.

Acute telogen effluvium. Acute telogen effluvium is an acute-onset scalp hair loss that occurs 2–3 months after a triggering event such as a high fever, surgical trauma, sudden starvation or haemorrhage [2,4–6]. In approximately 33% of cases of acute telogen effluvium, no trigger can be identified. Acute telogen effluvium is commonly attributed to emotional stress, but the evidence for this is weak and there is no evidence that suggests the stresses of everyday life are sufficient to induce diffuse hair loss. The functional mechanism of shedding is immediate anagen release.

The patient may be particularly aware of increased loss on the brush or comb, or during shampooing. The daily loss ranges from under 100 to over 1000. If the lower rates of shedding are continued for only a short period there may be no obvious baldness, but if shedding occurs at higher rates, diffuse reduction in hair density is produced (Fig. 63.18). It may be severe but is never total. Unless the trigger is repeated, spontaneous complete regrowth occurs within 3–6 months. The proportion of follicles affected, and hence the severity of the subsequent alopecia, depends partly on the duration and severity of the precipitating cause and partly on unexplained individual variations in susceptibility.

Telogen gravidarum refers to the telogen hair loss seen 2–3 months after childbirth [7,8]. It is an example of delayed anagen release. It is universal to some degree, but is often subclinical. Most cases of telogen gravidarum resolve; however, a small proportion of women may experience persistent episodic shedding that may be diffuse or localized. It has been suggested that after pregnancy some hairs may not revert to an asynchronous growth pattern seen in normal adult hair follicles [5]. A similar state of affairs prevails when the contraceptive pill is discontinued after it has been taken continuously for some time [8,9].

Diagnosis. The diagnosis is usually simple. Abrupt-onset telogen effluvium is likely to be related to a specific event or trigger 6–16 weeks earlier. The hair pull test is positive, with normal club hairs. The hair loss is always diffuse and never total. Gradual onset or prolonged hair loss is more difficult to assess. Increased shedding of club hairs is a variable but often very obvious symptom of early AGA. Other differential diagnoses are discussed below under the heading of chronic diffuse telogen hair loss.

The hair pull test is notoriously difficult to interpret. In acute telogen effluvium, it is usually strongly positive for telogen hairs at the vertex and the scalp margins. However, a negative hair pull test does not exclude the diagnosis of telogen effluvium [10]. The trichogram from a hair pluck sample usually shows more than 25% of telogen hairs in acute telogen effluvium [2]. When an obvious explanation exists for a recent-onset telogen effluvium, expectant management and observation is appropriate. Shedding can be expected to cease within 3–6 months and thereafter recovery should be complete [2]. Histological examination shows no abnormality other than an increase in the proportion of follicles in telogen.

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Chronic diffuse telogen hair loss. A short-lived insult usually produces a sudden-onset diffuse shedding. If the insult is prolonged or repeated, shedding can develop insidiously. Chronic diffuse telogen hair loss refers to

telogen hair shedding persisting for longer than 6 months. It can be a result of a primary chronic telogen effluvium or be secondary to a variety of causes. To be a true cause of chronic diffuse telogen hair loss, the relationship between the trigger and the hair loss must be reversible and reproducible. The requirements of proof include exclusion of other known causes of shedding, in particular AGA, reversal of the hair loss following correction of the causative factor, and relapse on rechallenge.

Accepted causes of chronic diffuse telogen hair loss are thyroid disorders (Fig. 63.19), profound iron deficiency anaemia, acrodermatitis enteropathica and malnutrition [1]. Both hyperthyroidism and hypothyroidism (including drug-induced hypothyroidism) cause a diffuse telogen hair loss in approximately 50% and 33% of patients, respectively [2,3]. The mechanism of telogen hair shedding in thyroid disorders still remains unclear [4]. Hair loss is reversible when the euthyroid state is restored, except in long-standing hypothyroidism where the hair follicles are said to have atrophied [3]. If replacement therapy fails to correct the hair loss, alternate causes should be sought [5].

Profound iron-deficiency anaemia can cause a diffuse telogen hair loss that is corrected by iron replacement. It is thought that hair follicles that have shed their hair at the end of telogen may temporarily fail to re-enter anagen —leading to a slow-onset diffuse hair loss [6]. The relationship between iron deficiency with no anaemia or only mild anaemia and chronic diffuse hair loss is, however, more complex and controversial [7–9]. Depending on how it is defined, low iron stores are a common finding in women of child-bearing age. AGA is also common in this age group and the shedding in the early stages of female AGA can be diffuse and episodic, and mimic a telogen effluvium. It is important not to focus on the treatment of a subclinical iron deficiency while neglecting the underlying AGA, especially when therapy for female AGA is more reliable in arresting hair loss than stimulating regrowth. It is not uncommon for women presenting with increased telogen hair shedding caused by AGA to coincidentally have low iron stores. As the telogen hair loss in AGA can be episodic, it may even appear to abate with iron replacement. However, in patients with AGA the shedding tends to be chronic and relapsing, and recovery is generally incomplete. A punch biopsy can usually clarify the diagnosis.

Acrodermatitis enteropathica and acquired zinc deficiency (Fig. 63.20) brought about by long-standing parenteral nutrition can lead to a severe telogen effluvium [1,10]. However, low zinc levels found on routine blood biochemistry screening in patients being investigated for diffuse telogen hair loss are probably an incidental finding. Diffuse hair loss alone, with no other symptoms or signs, is never a result of dietary zinc deficiency [9]. Correction of a subclinical zinc deficiency often does not stop the increased hair shedding, and other forms of alopecia such as AGA or chronic telogen effluvium should be considered.

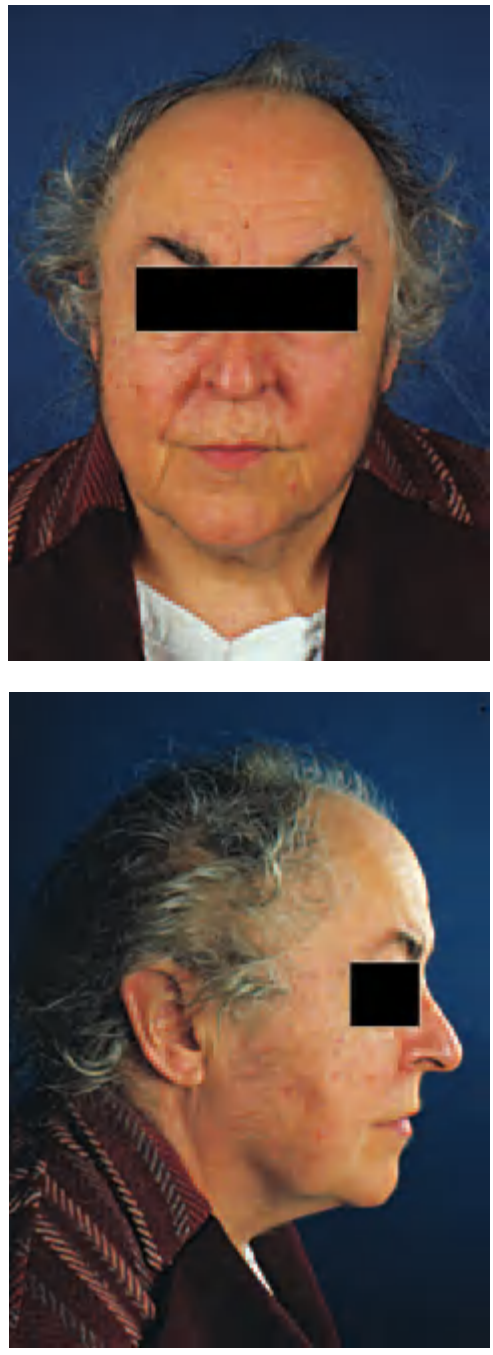
(a) (b)

Fig. 63.19 Diffuse alopecia in association with hypothyroidism.

Crash dieting with severe protein-calorie restriction can precipitate hair loss [11,12]. Chronic starvation, especially marasmus, causes a diffuse telogen hair loss often accompanied by hair shaft abnormalities [13]. Hypoproteinaemia of metabolic as well as dietary origin can cause hair loss [1]. Pancreatic disease and other forms of

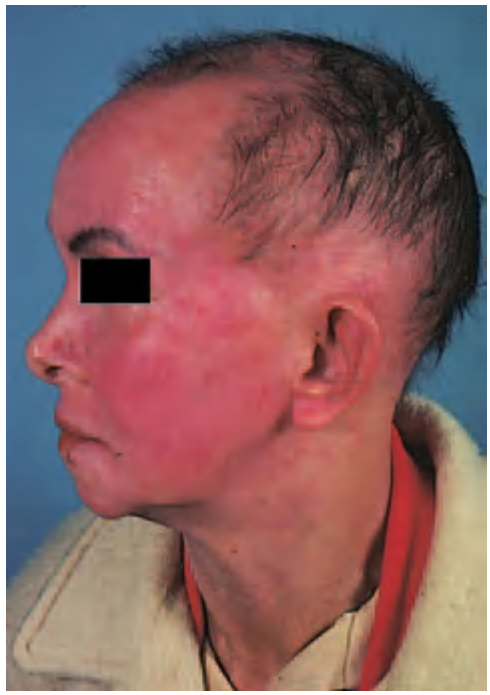

Fig. 63.20 Acquired zinc deficiency resulting from prolonged parenteral feeding and inadequate zinc supplementation.

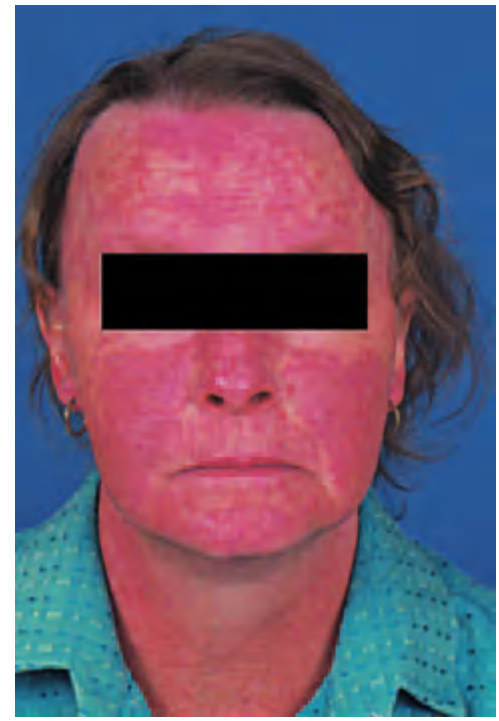

Fig. 63.21 Hair loss and photosensitivity caused by systemic lupus erythematosus.

malabsorption also cause a diffuse telogen hair loss [14], as do the essential fatty acid deficiencies seen in prolonged parenteral nutrition and hypervitaminosis A [15,16]. Metabolic disturbances such as liver disorders [1,17] and chronic renal failure can produce sparse scalp hair [18]. Hair loss in advanced malignant disease may be a result of hypoproteinaemia rather than the malignancy itself, but alopecia has occurred as an early sign of Hodgkin's disease [19]. Systemic lupus erythematosus (Fig. 63.21) and dermatomyositis can also cause telogen hair loss [20]. Diffuse hair loss may occur in secondary syphilis, but the characteristic moth-eaten appearance is not always present [21].

Drug-induced diffuse telogen hair loss usually starts 6–12 weeks after instigation of treatment and is progressive while the drug is continued [22,23]. It is most commonly a result of immediate anagen release [6]. The diagnosis of drug-induced telogen hair loss is made by demonstrating compatible chronology of drug exposure and the onset of the hair loss, and exclusion of the other causes of alopecia. Shedding can recur with drugs that are chemically unrelated, suggesting that true cross-reactivity is rare, and individual susceptibility exists to drug-induced telogen effluvium. CTE and AGA are important differential diagnoses. If a particular drug is suspected, testing involves stopping it for at least 3 months. Regrowth following discontinuation and recurrence on re-exposure to the drug supports the conclusion that the drug caused the alopecia. Many drugs have been said to cause a diffuse telogen hair loss but few have fulfilled the above criteria. A dose-related diffuse telogen hair loss is common with etretinate [24] and acitretin, but less common with isotretinoin. The retinoids appear to cause a telogen anchorage defect and reduce the duration of anagen. Occasionally, continued shedding is noted after retinoid-induced telogen effluvium, but such cases may be caused by coincidental AGA. Minoxidil has been reported to cause a short-lived telogen shedding by immediate telogen release [6,25].

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Chronic telogen effluvium. CTE has become a term used to describe a pattern of presentation in middle-aged women that is distinct from androgenetic hair loss and is distinguished from chronic diffuse telogen effluvium and its organic causes [1,2]. It is described as an idiopathic self-limiting condition with increased telogen shedding of at least 6 months' duration, but with no widening of the central parting, and no miniaturization of hair follicles on scalp biopsy [1]. CTE contrasts with acute telogen effluvium by its prolonged fluctuating course and much less frequent occurrence. It is common in females between 30 and 50 years of age [2]. Hair shedding is much less obvious in males with short hair, and for unknown reasons few males with long hair present with increased hair shedding [3]. Although some cases of CTE follow an acute telogen effluvium with a known trigger, such as pregnancy or systemic illness, in most cases a trigger cannot be identified. Any of the functional types of telogen effluvium could account for CTE, but it is believed to be related to shortening of the anagen phase of the hair cycle [4].

The diagnosis of CTE is made by exclusion of other causes of diffuse telogen hair loss. A thorough history is required, including a detailed drug and dietary history. A full clinical examination should be performed, including scalp examination and hair pull testing. The routine work-up includes full blood count and thyroid function tests. Syphilis serology, antinuclear antibody titre, serum zinc levels and other investigations of nutritional status should be performed if clinically warranted.

Affected women commonly present with persistent severe shedding that runs a fluctuating course over several years [4] (Fig. 63.22). They often give a history of the ability to grow their hair very long in childhood, suggestive of a long anagen phase, and report a high hair density prior to the onset of hair loss [5,6]. They usually have a negative family history of AGA. Clinical examination reveals marked bitemporal recession, but no widening of the central hair parting, which if present would support the diagnosis of AGA. However, these criteria are not absolute, and AGA can mimic this presentation. A positive hair pull test is common over the vertex and occipital scalp, and patients may describe a reduction in the thickness of their ponytail volume, stating it has decreased by up to 50% [4]. A negative hair pull test does not exclude the diagnosis of CTE.

Fig. 63.22 Idiopathic chronic telogen effluvium.

CTE has to be distinguished clinically from AGA as women with early AGA may present with periods of increased hair shedding without a discernible pattern to the loss. The mechanism of increased hair shedding in AGA is probably related to shortening of the anagen duration [7]. In an evaluation of 600 women presenting with chronic diffuse telogen hair shedding with little or no reduction of visible hair density, 60% were found on scalp biopsy to have hair miniaturization consistent with a diagnosis of AGA and 40% had CTE [8].

The natural history, prognosis and treatment of CTE and AGA differ [9]. The diagnosis of CTE can usually be suspected from the history and examination, but scalp biopsy is required to differentiate reliably between the two conditions [1]. The optimal scalp biopsy is a 4-mm punch biopsy taken from the vertex of the scalp for horizontal embedding. The vertex is the chosen site because AGA is a patterned disease that preferentially affects the vertex of the scalp, so diagnostic yields are greatest in this area. Histology of a scalp biopsy in CTE resembles normal scalp, but shows an anagen : telogen ratio of 8 : 1

compared with the ratio of 14 : 1 on normal scalp biopsies [1]. The total number of hairs in CTE is the same as that found in normal scalps and the terminal : vellus-like hair (miniaturized) ratio is similar in both, averaging eight terminal hairs per vellus-like hair [1]. These findings differ considerably from AGA. The mean terminal : vellus-like hair ratio in AGA is 1.9 : 1 [1].

Despite the assertion that CTE is a self-limiting process that does not evolve into AGA, its natural history remains poorly characterized, with only one published longitudinal study [9].

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Alopecia in central nervous system disorders

Alopecia has been described in association with a number of diseases of the central nervous system, but in many instances the association was probably fortuitous. There are four forms of hair loss in which the association appears to be valid, although the mechanism is unknown.

1 Total and permanent alopecia has accompanied lesions of the mid-brain and brainstem [1]—a glioma in the region of the hypothalamus or post-encephalitic damage to the mid-brain.

2 Temporary diffuse alopecia may follow head injuries, particularly in children [2], and may be associated with reversible hirsutism.

3 Total loss of hair occurred at approximately annual intervals for 20 years in a patient with syringomyelia and syringobulbia [3].

4 Androgenetic baldness occurs early in myotonic dystrophy [4]. A genetic linkage rather than a direct effect of the neurological changes is probably concerned.

Piloerection [5]

Episodes of piloerection may occur in patients with lesions close to the hypothalamus or involving some portion of the limbic system, but the symptom has no precise localizing value.

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Alopecia areata

[A.G. Messenger, pp. 63.36–63.46]

Alopecia areata is a chronic inflammatory disease that involves the hair follicle and sometimes the nails. Current evidence indicates that hair follicle inflammation in alopecia areata is caused by a T-cell-mediated autoimmune mechanism occurring in genetically predisposed individuals. Environmental factors may be responsible for triggering the disease.

In the only formal population study of alopecia areata, from Olmsted County, Minnesota, USA, the incidence rate was 0.1–0.2% with a projected lifetime risk of 1.7% [1]. Several large case series of alopecia areata have been reported from Europe [2], North America [3,4] and Asia [5,6], but these have generally been drawn from hospital clinic attenders and no accurate indication of variation in disease rates between populations is available.

Aetiology

Genetic factors

The importance of genetic factors in alopecia areata is underlined by the high frequency of a positive family history in affected individuals [7]. In most reports, this ranges from 10 to 20% of cases, but mild cases are often overlooked or concealed and the true figure may be greater. The lifetime risk of alopecia areata in the children of a proband is approximately 6% [8]. Price and Colombe [9] found a family history of alopecia areata was more common in those with disease onset before the age of 30 years (37% compared with 7.1% in patients with onset after 30 years). There have been several case reports of alopecia areata in twins [10–12], but only a single study looking at concordance rates in monozygotic and dizygotic pairs [13]. In this investigation, there was a concordance rate of 55% for alopecia amongst monozygotic twins with no concordance among the dizygotic pairs. However, the numbers studied were insufficient to allow a precise estimate of the genetic contribution in alopecia areata. Except in occasional families, alopecia areata is not inherited in a simple Mendelian fashion and the genetic basis appears to be multifactorial.

Major histocompatibility complex genes. No consistent associations with MHC class I antigens have been reported, but several studies have shown an association between alopecia areata and the MHC class II antigens HLA-DR4, DR11 (DR5) and DQ3. Earlier studies using serological typing techniques suggested that DR4 and DR5 were associated with severe forms of alopecia areata [7]. This severity association was subsequently confirmed by molecular typing. Colombe *et al.* [14] found an increase in the broad antigen DQ3 in all patients in their study, suggesting this may act as a susceptibility factor. The DQB1*0301 allele (a subtype of DQ3 that is in linkage disequilibrium with DR5) was associated with severe alopecia but not with newly diagnosed patchy disease. There was also a strong association between alopecia totalis and universalis and the DR11 allele DRB1*1104 (relative risk 30.2), which was absent in milder disease. The association with DQB1*0301 had previously been reported by Morling *et al.* [15] and Welsh *et al.* [16]. The latter group also showed an increase in the frequency of DQ3, which was greater in alopecia totalis and universalis than in patchy alopecia. De Andrade *et al.* [17] confirmed the importance of DQB1*03 alleles, which were present in 85% of alopecia areata patients compared with 46% of controls. In the only family-based study of HLA association and linkage in alopecia areata, these authors reported an association between alleles of HLA-DQB1*0302, *0601, *0603 and HLA-DR4, DR6 using the transmission disequilibrium test [17]. Linkage analysis in 75 families supported linkage between alopecia areata and HLA class II loci, with maximal LOD scores of 2.42 for HLA-DQB at 5% recombination and 2.34 for HLA-DR at 0% recombination.

Cytokine genes. IL-1 is a primary cytokine involved in mediating inflammatory responses. The IL-1 gene cluster on chromosome 2 includes genes for the pro-inflammatory IL-1 proteins, their cell membrane receptors, the anti-inflammatory IL-1 receptor antagonist (*IL1RN*) and its homologue, *IL1F5* (*IL1L1*). Associations between the severity of alopecia areata and polymorphisms in *IL1RN* and *IL1F5* have been reported [18,19]. *IL1RN* variants are also associated with the severity of several other inflammatory autoimmune diseases, including ulcerative colitis, lichen sclerosus, psoriasis, myasthenia gravis, multiple sclerosis and rheumatoid disease. However, a later family-based study by Barahamani *et al.* [20] using 131 trios, failed to confirm the association of *IL1RN* genotypes with alopecia universalis.

Like IL-1, TNF-α has a potent inhibitory effect on hair growth *in vitro* [21]. TNF-α is encoded by a gene in the HLA class III region and a polymorphism of this gene has been shown to be strongly associated with certain autoimmune/inflammatory diseases including systemic lupus erythematosus (SLE), rheumatoid arthritis, dermatitis herpetiformis and coeliac disease. TNF-α polymorphisms were investigated in alopecia areata in a small study of 50 cases by Galbraith and Pandey [22], who demonstrated a significant difference in TNF-α genotypes between patients with patchy disease and those with alopecia totalis and universalis. However, there was no difference between disease and control groups overall.

Chromosome 21. The frequency of alopecia areata is increased in Down's syndrome, with up to 8.8% of patients affected [23,24], suggesting possible involvement of genes on chromosome 21. There is an even stronger association with the autosomal recessive disorder autoimmune polyglandular syndrome type 1 (APS-1, autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy), in which approximately 30% of patients have alopecia areata [25]. The defective gene in APS-1 maps to the Down's critical region on chromosome 21 [26,27]. A potentially functional exonic polymorphism in the APS-1 gene has been associated with alopecia universalis [28].

Atopy. Several studies have reported an association between alopecia areata and atopic disease [4,5,29,30], and have suggested that alopecia areata in atopic subjects tends to have an earlier age of onset and be more severe than in non-atopic subjects. However, none of these studies has used a control group to which the same criteria for defining atopy have been applied, and the association has been disputed in a study from India [31].

Autoimmunity

The idea that alopecia areata is an autoimmune disease was first suggested by Rothman following a paper presented by Van Scott [32]. Alopecia areata is associated with other autoimmune diseases, such as myxoedema and pernicious anaemia [4,33]. Intriguingly, the frequency of type 1 diabetes mellitus is increased in the relatives of patients with alopecia areata but not in the patients themselves [34], suggesting that the predisposition to alopecia areata protects against the development of diabetes. In most published series, patients with alopecia areata have had an increased frequency of circulating organ-specific and non-organ-specific autoantibodies compared with normal subjects, and a variety of non-specific abnormalities in peripheral T-cell numbers and function have also been reported (reviewed in [7]). Circulating autoantibodies to hair follicle tissue have been found in patients with alopecia areata [35]. These antibodies also occur in normal subjects but less frequently and at lower titre. They recognize various epithelial compartments within the hair follicle and appear to be targeted against intracellular antigens [36]. Antibody binding has not been demonstrated *in vivo* in humans, and their role in the pathogenesis is unclear. Passive immunization with alopecia areata serum failed to induce hair loss in human skin grafted on to nude mice

[37]. However, one study reported that serum from a horse with alopecia areata-like hair loss caused local inhibition of hair growth when injected into murine skin, whereas serum from a normal horse did not [38].

The most convincing evidence implicating circulating immune factors in the pathogenesis of alopecia areata comes from the transplantation experiments carried out by Gilhar *et al*. They first showed that hair growth recovered in alopecic skin transplanted on to athymic nude mice [39]. In their later experiments (in which SCID rather than athymic nude mice were used as graft recipients), alopecia was induced in grafted skin by the injection of autologous T lymphocytes incubated with hair follicle extracts and antigen-presenting cells [40]. T cells not incubated with hair follicle extracts failed to cause hair loss. Taken together with the immunopathological features of the disease, and with the T-cell depletion studies on the Dundee experimental bald rat (DEBR) model (see below) [41,42], the results of these experiments suggest that alopecia areata is a T-cell-mediated disease.

Environmental factors

The idea that alopecia areata is caused by infection, either directly or as a consequence of a remote 'focus of infection', has a long history and still cannot be ruled out. It was the predominant aetiological theory until well into the twentieth century, and sporadic reports connecting alopecia areata with infective agents continue to appear. Skinner *et al*. [43] reported finding mRNA for cytomegalovirus in alopecic lesions, but this was not confirmed in a subsequent study from Italy [44]. There are also reports of alopecia areata in husband and wife, although this may be coincidence [45,46]. The 'external' factor most frequently implicated in triggering alopecia areata is psychological stress [47–50]. The significance of such an association is difficult to establish because of the problems in performing a controlled investigation. The published evidence is also conflicting, with some studies failing to show any relationship between stressful events and onset of hair loss [51,52], to the extent that no firm conclusion can be reached.

Despite the anecdotal nature of much of the evidence it is possible that environmental factors are responsible for triggering alopecia areata in some patients. If so, it seems likely that a diversity of factors can operate in this way.

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Pathogenesis

Pathology

Anagen follicles at the margins of expanding patches of alopecia areata characteristically show a perifollicular and intrafollicular inflammatory cell infiltrate, concentrated in and around the hair bulb (Fig. 63.23). The inflammatory infiltrate is composed mainly of activated T lymphocytes, with a preponderance of CD4 cells, and an admixture of macrophages and Langerhans' cells [1,2]. In contrast with the inflammatory scarring alopecias, little or none of the inflammatory infiltrate is seen around the isthmus of the hair follicle, the site for hair follicle stem cells [3]. This may explain why follicles are not destroyed in alopecia areata. Lymphocytic infiltration of the dermal papilla and bulbar epithelium may be accompanied by increased expression of HLA class I and II antigens and of intercellular adhesion molecule-1 (ICAM-1) [4–6], which are thought to be secondary to the local release of T-cell cytokines. Normal

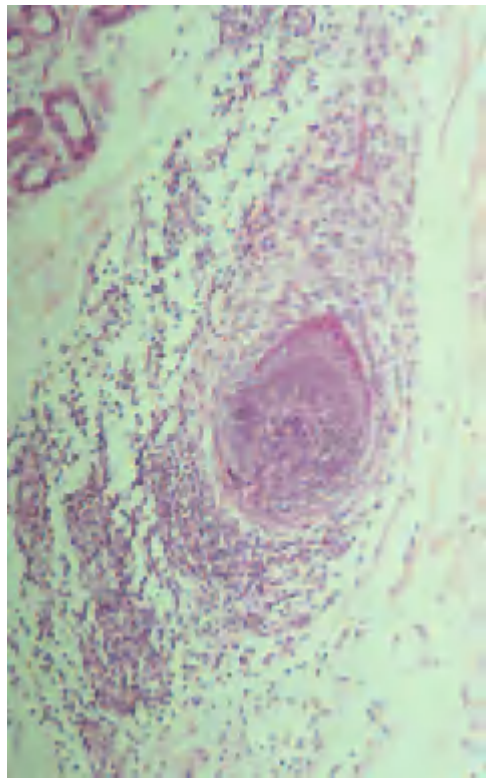

Fig. 63.23 Lymphocytic inflammatory infiltrate surrounding an anagen hair bulb in alopecia areata.

numbers of follicles are found in established bald patches and in alopecia universalis. Both anagen and telogen follicles are found in these sites, with a higher proportion in telogen than in normal scalp. Follicles are smaller than normal and anagen follicles do not develop beyond the Anagen 3–4 stage, when the hair shaft starts to be formed [7]. The inflammatory infiltrate tends to be less pronounced than in early lesions and is associated mainly with anagen follicles.

Pathodynamics

Eckert *et al*. [8] studied anagen : telogen ratios in hairs plucked from demarcated concentric zones around the periphery of expanding bald patches. They concluded that the initial event in alopecia areata is precipitation of anagen follicles into telogen. Less severely affected follicles may remain in anagen for a time but they produce a dystrophic hair and eventually also undergo telogen conversion. In keeping with these observations, biopsies from the margins of expanding lesions of alopecia areata show most follicles in catagen or telogen [9]. It is not clear whether follicles attain telogen via normal catagen. Exclamation mark hairs may have a well-formed club root identical to that of a normal telogen hair. However, the root is frequently narrowed and club hairs fall out more

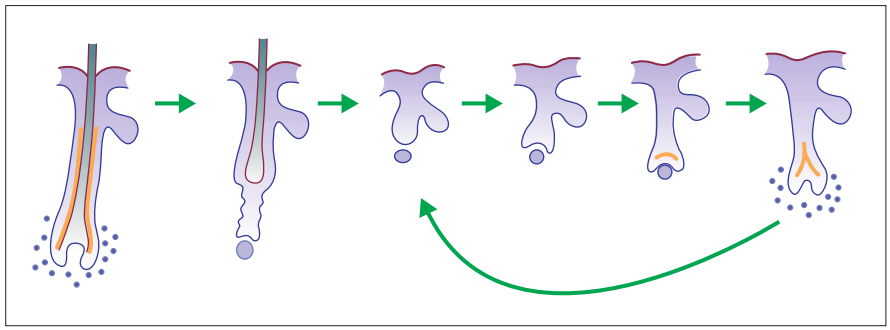

Fig. 63.24 Proposed pathodynamic changes in alopecia areata. An inflammatory attack on anagen follicles precipitates follicles into telogen. Follicles re-enter anagen but development is halted in Anagen 3–4 and follicles return to telogen prematurely.

readily than normal, suggesting that anchoring of the hair within the follicle is defective.

Van Scott [7] studied biopsies from patches of alopecia areata and found an average of 58% of follicles in anagen, suggesting that re-entry into anagen takes place. In early lesions there was a reduction in the size of the lower follicle, with preservation of the upper part of the follicle and the sebaceous gland. In long-standing disease, the entire follicle became smaller. The matrix of these miniaturized anagen follicles was mitotically active and produced a normal inner root sheath. However, the cortex was incompletely keratinized. Van Scott interpreted these changes as indicating arrest of follicle development in Anagen 4. A later study supported these findings and proposed that, while the disease is active, follicles are unable to develop beyond Anagen 3–4 and then return prematurely to telogen (Fig. 63.24) [9]. Follicles may pass through repeated truncated cycles until the disease activity subsides, and are then able to progress further into anagen.

Except in very long-standing alopecia, hair follicles are retained, even in clinically hairless scalp. When alopecia areata has persisted for many years, particularly in the universal form, there may be a decline in follicle density, possibly associated with fibrosis of the perifollicular connective tissues.

The hair follicle target

The inflammatory infiltrate in alopecia areata is concentrated in and around the bulbar region of anagen hair follicles. Cells of several different types and differentiation pathways are found in the hair bulb, but which of these is the primary focus of the pathology is unknown. Trichocytes in the hair bulb matrix undergoing early cortical differentiation may show vacuolar degeneration (Fig. 63.25) [10,11] and are also the predominant cell type showing aberrant class I and II MHC expression [4]. However, increased MHC expression is also seen in the dermal papilla, and pathological changes have been described in dermal papillae in clinically non-lesional sites [12]. Hence, it is possible that changes in the epithelial compartment of the hair follicle are secondary to dysfunction of the dermal papilla. The sparing of white hair sometimes seen in alopecia areata has raised the possibility that alopecia areata is primarily a disease of hair bulb melanocytes. Alopecia areata may show other pigmentary features including reduced pigmentation in regrowing hairs and an association with vitiligo [13,14]. However, the melanocyte hypothesis does not explain why sparing of white hair is often a relative phenomenon and is sometimes absent.

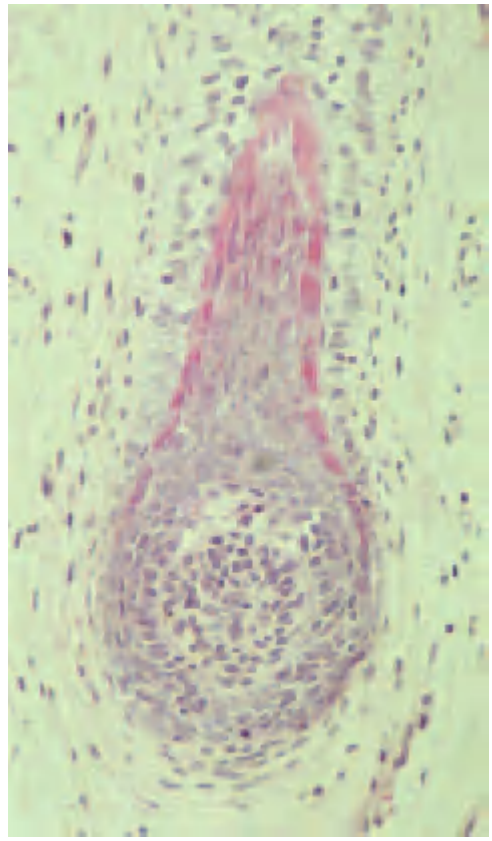

Fig. 63.25 An early anagen follicle in alopecia totalis showing vacuolation in the hair matrix epithelium around the upper pole of the dermal papilla.

Animal models

Alopecia areata occurs in mammals other than humans, including chimps, dogs, horses, rats and mice. Two rodent

strains, in which alopecia areata is common, the Dundee experimental bald rat (DEBR) and the CH3/HeJ mouse, have been used as experimental models of the disease.

Dundee experimental bald rat

In this strain of the brown hooded rat, animals grow a normal first coat of hair but then become progressively hairless [15]. Skin histological examination confirms the persistence of hair follicles, mostly in a dystrophic anagen state. Perifollicular and intrafollicular lymphocytic infiltration is a prominent feature and vacuolar degeneration occurs in the cortex of some lesional anagen follicles. Increased expression of HLA class I and II molecules in the dermal papilla and precortical matrix is seen in a pattern similar to human alopecia areata [16]. Hair regrowth in DEBR alopecia can be stimulated by photochemotherapy (PUVA), topical minoxidil, systemic ciclosporin [17] and topical tacrolimus [18]. Partial regrowth can also be induced by depletion of circulating CD4 or CD8 cells using monoclonal antibodies, suggesting that T cells have an active role in the pathogenesis [19,20].

C3H/HeJ mouse

A diffuse non-scarring alopecia with clinical and pathological features similar to alopecia areata was reported by Sundberg *et al*. [21] in a large production colony of C3H/HeJ mice. On the dorsal skin, the alopecia developed in circular areas, with disease involvement restricted to anagen follicles. Pedigree analysis suggested the disease was inherited. Alopecia was more common in ageing animals, and the frequency was highest in mice selectively bred for inflammatory bowel disease. Subsequent studies have revealed considerable similarity in histopathology, immunological features and response to therapeutic agents between C3H/HeJ alopecia and human alopecia areata.

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Clinical features

The onset of alopecia areata may be at any age, peaking between the second and fourth decades. The sex incidence is probably equal. The characteristic initial lesion is a circumscribed, totally bald, smooth patch (Fig. 63.26). It is often noticed by chance by a parent, hairdresser or friend. The skin within the bald patch appears normal or slightly reddened. Short, easily extractable broken hairs, known as exclamation mark hairs, are often seen at the margins of the bald patches during active phases of the disease (Fig. 63.27). Subsequent progress is very varied; the initial patch may regrow within a few months, or further patches

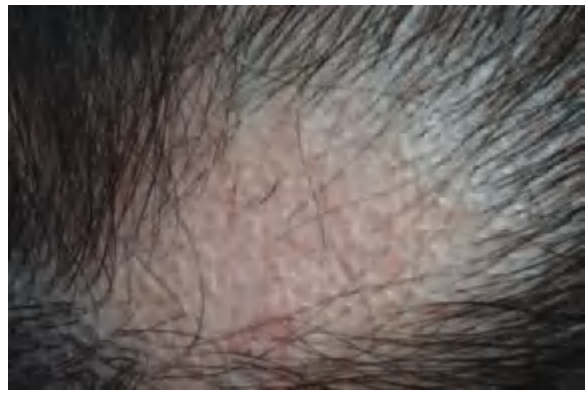

Fig. 63.26 Patch of alopecia areata. Broken 'exclamation mark hairs' are seen towards the margins of the patch.

Fig. 63.27 Exclamation mark hairs.

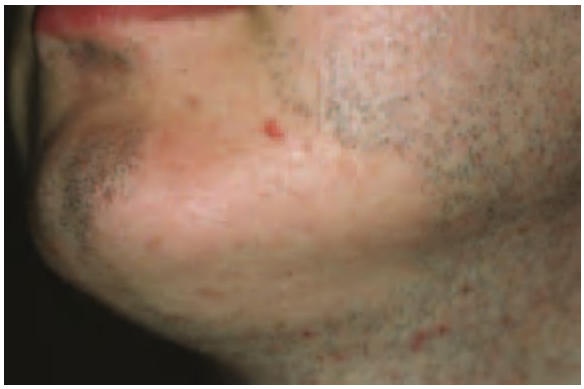

Fig. 63.28 Alopecia areata affecting the beard.

may appear after an interval of 3–6 weeks and then in a cyclical fashion. These intervals are of varying duration. A succession of discrete patches may rapidly become confluent by the diffuse loss of remaining hair. In some cases the initial hair loss is diffuse, and total denudation of the scalp has been reported within 48 h. However, diffuse hair loss may occur over part or the whole of the scalp without the development of bald areas. Regrowth is often at first fine and unpigmented, but usually the hairs gradually resume their normal calibre and colour. Regrowth in one region of the scalp may occur while the alopecia is extending in others.

The scalp is the first affected site in most cases, but any hair-bearing skin can be affected. In dark-haired men, patches in the beard are conspicuous and in such individuals are often the first to be noticed (Fig. 63.28). The eyebrows and eyelashes are lost in many cases of alopecia areata and may be the only sites affected. The term alopecia totalis is applied to total or almost total loss of scalp hair, and alopecia universalis is the loss of all body hair. The extension of alopecia along the scalp margin is known as ophiasis (Fig. 63.29).

An intriguing feature of alopecia areata is the sparing of white hairs. In patients with grey hair, which is an admixture of pigmented and non-pigmented hair, the disease process appears preferentially to affect pigmented hair, so

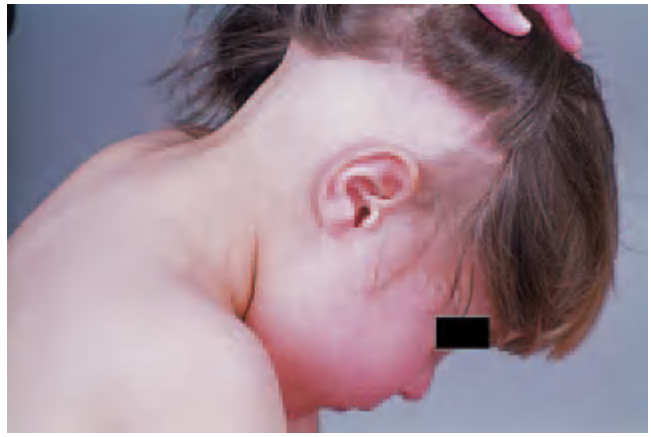

Fig. 63.29 The ophiasis pattern of alopecia areata.

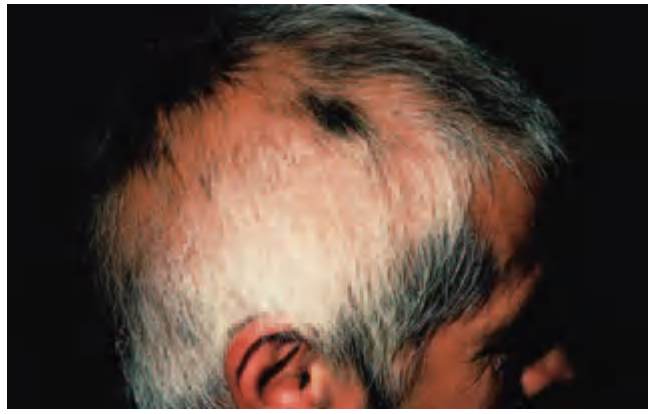

Fig. 63.30 Regrowth of hypopigmented hair in alopecia areata.

that non-pigmented or white hair is spared. This may result in a dramatic change in hair colour if the alopecia progresses rapidly, and is probably the explanation for historical accounts of people 'going white overnight'. Sparing of white hair is a relative phenomenon and it is clear that the white hairs, although less susceptible to the disease, are not immune. During the regrowth phase hairs may be non- or hypopigmented (Fig. 63.30) but hair pigmentation usually recovers completely. In exceptional cases where regrowing hairs remain non-pigmented the possibility of concurrent vitiligo should be considered.

In 10–15% of cases referred for specialist opinion alopecia areata also involves the nails, usually in the context of severe hair loss. Classically, alopecia areata causes fine stippled pitting of the nails (Fig. 63.31), but some cases show less well-defined roughening of the nail plate (trachyonychia) or a non-specific atrophic dystrophy. For some patients, the latter problem is the most troublesome aspect of the disease.

Differential diagnosis

In children the main sources of difficulty are tinea capitis

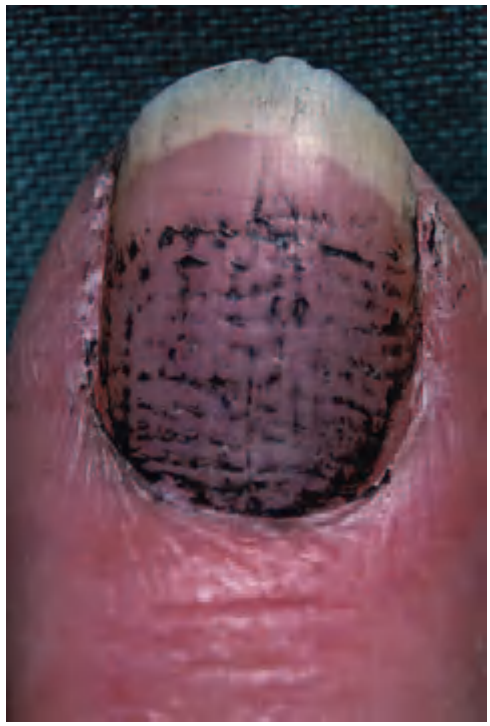

Fig. 63.31 An organized pattern of pitting present on all fingernails 8 months prior to onset of alopecia areata. Pits are highlighted with mascara.

and trichotillomania. Tinea capitis should always be considered in children presenting with patchy hair loss. There is usually evidence of scalp inflammation but this may be limited to mild scaling. The hair loss in trichotillomania may be asymmetrical or occur in artificial shapes. Broken hairs are usually present across the areas of hair loss, giving a bristly texture and, unlike exclamation mark hairs, are firmly anchored in the scalp. In most cases the true diagnosis will become evident with time; a biopsy is useful when doubt remains. Occasionally, the early stages of scarring alopecia can resemble alopecia areata. The diffuse form of alopecia areata is perhaps the most difficult to identify. A history of previous episodes of hair loss, nail dystrophy and the usually rapid progression may provide clues, but other causes of diffuse hair loss, such as SLE, may need to be excluded by appropriate serological tests and a scalp biopsy. Secondary syphilis sometimes presents with diffuse or patchy hair loss.

Prognosis

Alopecia areata does not destroy hair follicles, and the potential for regrowth of hair is retained for many years and is possibly lifelong. In some patients, patches of hair loss occur at infrequent intervals interspersed with long periods of normal hair growth. In others, alopecia areata is more persistent, so that new patches of hair loss continue to develop at the same time as regrowth occurs elsewhere. In a relatively small number of patients, hair loss progresses to involve all of the scalp (alopecia totalis) or the entire skin surface (alopecia universalis); in these cases, spontaneous recovery is the exception rather than the rule.

Data from secondary and tertiary referral centres indicate that 34–50% of patients will recover within 1 year, although almost all will experience more than one episode of the disease, and 14–25% progress to alopecia totalis or alopecia universalis, from which full recovery is unusual (less than 10%) [1,2]. One study from Japan reported that spontaneous remission within 1 year occurred in 80% of patients with a small number of circumscribed patches of hair loss [3]. The prognosis is less favourable when onset occurs during childhood [1,4–6] and in ophiasis [6]. The concurrence of atopic disease has been reported to be associated with a poor prognosis [3,6], but this was not found in a study from India [7].

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Management

A number of treatments can induce hair growth in alopecia areata, but none has been shown to alter the course of the disease. The high rate of spontaneous remission makes it difficult to assess efficacy, particularly in mild forms of the disease. Some trials have been limited to patients with severe alopecia areata where spontaneous remission is unlikely. However, these patients tend to be resistant to all forms of treatment and the failure of a treatment in this setting does not exclude efficacy in mild alopecia areata. Few treatments have been subjected to randomized controlled trials and, except for contact immunotherapy, there are few published data on long-term outcomes. These difficulties mean that counselling of the patient and, where relevant, of their family, are of paramount importance. This should include discussion of the nature of the disease and its natural history, the treatments available and their chances of success. Some patients have great difficulty coping with alopecia areata and require considerable support. Sources of support may include the physician, other patients, formal patients' sup-

port groups and, in some circumstances, professional counselling services.

Treatment. Leaving alopecia areata untreated is a legitimate option for many patients. Spontaneous remission occurs in up to 80% of patients with limited patchy hair loss of short duration (less than 1 year) [1]. Such patients may be managed by reassurance alone, with advice that regrowth cannot be expected within 3 months of the development of any individual patch. The prognosis in long-standing extensive alopecia is less favourable. However, all treatments have a high failure rate in this group and some patients prefer not to be treated, other than wearing a wig if appropriate.

Corticosteroids. Intralesional depot corticosteroids have a small but useful role in the management of alopecia areata [2,3]. They can be used to accelerate regrowth in a circumscribed patch of alopecia areata that is cosmetically disfiguring or difficult to conceal, and can be useful for maintaining regrowth of the eyebrows in alopecia totalis; but great care must be exercised to avoid steroid side effects in the eye. Hydrocortisone acetate (25 mg/mL) and triamcinolone acetonide (5–10 mg/mL) are commonly used, either by needle injection or jet injection. Localized atrophy is a common complication, particularly if triamcinolone is used, but this is temporary and recovers within a few months.

Potent topical corticosteroids are widely used to treat alopecia areata but there is little evidence that they produce significant regrowth of hair. In some cases, a troublesome folliculitis may result.

Long-term daily treatment with oral corticosteroids will produce regrowth of hair in some patients. One small, partly controlled study reported that 30–47% of patients treated with a 6-week tapering course of oral prednisolone (starting at 40 mg/day) showed more than 25% hair regrowth [4]. Unfortunately, in most patients, continued treatment is needed to maintain hair growth and the response is usually insufficient to justify the risks [5]. There are several case series reporting response to high-dose pulsed corticosteroid treatment employing different oral and intravenous regimens [6–8]. However, these studies were uncontrolled and, although none reported significant side effects, the potential toxicity of systemic corticosteroids remains a serious concern.

Contact immunotherapy. Contact immunotherapy was introduced by Rosenberg in 1976 [9] and is the most effective and best-documented treatment for alopecia areata, but problems associated with its use mean that it is available in only a few centres. The patient is sensitized to a potent allergen and the same allergen is then applied to the scalp, usually at weekly intervals, in a concentration sufficient to induce a mild contact dermatitis. The contact allergens that have been used in the treatment of alopecia areata include dinitrochlorobenzene (DNCB), squaric acid dibutylester (SADBE) and diphenylcyclopropenone (DPCP). Most centres now use DPCP [10]. A review of all the published studies of contact immunotherapy concluded that 50–60% of patients achieve a worthwhile response, but the range of response rates was very wide (9–87%) [11]. Patients with extensive hair loss are less likely to respond [12,13]. Other reported adverse prognostic features include the presence of nail changes, early onset and a positive family history [11]. In most studies treatment was discontinued after 6 months if no response was obtained. In one case series from Canada, clinically significant regrowth occurred in approximately 30% of patients after 6 months' treatment, but this increased to 78% after 32 months of treatment, suggesting that more prolonged treatment is worthwhile [14]. The response in patients with alopecia totalis and universalis was less favourable at 17% and this was not improved by treatment beyond 9 months. Relapses may occur following or during treatment. In the Canadian series, relapse following successful treatment occurred in 62% of patients. Two case report series of contact immunotherapy in children with alopecia areata reported response rates of 33% [15] and 32% [16]. A third study found a similar short-term response in children with severe alopecia areata, but less than 10% experienced sustained benefit [17].

Most patients will develop occipital and/or cervical lymphadenopathy during contact immunotherapy. This is usually temporary but may persist throughout the treatment period. Severe dermatitis is the most common adverse event, but the risk can be minimized by careful titration of the concentration. Uncommon adverse effects include urticaria [18], which may be severe [19], and vitiligo [20,21]. Cosmetically disabling pigmentary complications, both hyper- and hypopigmentation (including vitiligo), may occur if contact immunotherapy is used in patients with racially pigmented skin. Contact immunotherapy has been in use for 20 years and no long-term side effects have been reported.

The mode of action of contact immunotherapy is unknown. Happle [22] suggested that the contact allergen competes for CD4 cells, attracting them away from the perifollicular region ('antigenic competition'). Other suggested mechanisms include the non-specific stimulation of a local T-suppressor-cell response [23] and increased expression of TGF-β in the skin, which acts to suppress the immune response [24].

Photochemotherapy. There are several uncontrolled studies of photochemotherapy (PUVA) for alopecia areata, using all types of PUVA (oral or topical psoralen, local or whole body UVA irradiation) [25–28], claiming success rates of up to 60–65%. Two retrospective reviews have reported low response rates [29] or suggested that the response

was no better than the natural course of the disease [30], although these observations were also uncontrolled. The relapse rate following treatment is high and continued treatment is usually needed to maintain hair growth, which may lead to an unacceptably high cumulative UVA dose.

Minoxidil. An early double-blind study reported a significantly greater frequency of hair regrowth in patchy alopecia areata in patients treated with topical 1% minoxidil compared with placebo [31]. Subsequent controlled trials in patients with extensive alopecia areata using 1% or 3% minoxidil failed to confirm these results [32–34]. Two of these studies reported a treatment response during an extended but uncontrolled part of the trial [33,34]. In one study comparing 5% and 1% minoxidil in extensive alopecia areata, regrowth of hair occurred more frequently in those receiving 5% minoxidil, but few subjects obtained a cosmetically worthwhile result [35]. Topical minoxidil is ineffective in alopecia totalis and universalis.

Dithranol. There are a small number of case report series of the use of dithranol (anthralin) or other irritants in the treatment of alopecia areata [36–38]. The lack of controls makes the response rates difficult to evaluate but only a small proportion of patients seem to achieve cosmetically worthwhile results. In one open study, 18% of patients with extensive alopecia areata achieved cosmetically worthwhile hair regrowth [36]. The published data indicate that dithranol needs to be applied sufficiently frequently and in a high enough concentration to produce a brisk irritant reaction in order to be effective.

Summary

Alopecia areata is difficult to treat and few treatments have been tested in randomized controlled trials. The tendency to spontaneous remission and the lack of adverse effects on general health are important considerations in management, and counselling, with no treatment, is the best option in many cases. Intralesional corticosteroids can be helpful in disease of limited extent, especially in cosmetically obvious sites. Topical corticosteroids, minoxidil lotion and dithranol are widely used but there is little convincing evidence of efficacy. Contact immunotherapy is the most effective treatment for extensive alopecia areata, although it is not widely available, and the response rate in alopecia totalis and universalis is low. The place of systemic corticosteroids is controversial. In view of the lack of evidence of sustained efficacy and the potential hazards, their routine use in alopecia areata cannot be recommended.

Alopecia areata may cause considerable psychological and social disability and, in some cases, particularly those seen in secondary care, it may be a chronic and persistent disease causing extensive or universal hair loss. If the prognosis is poor (e.g. in a prepubertal atopic child with total alopecia), a full explanation and help in adjusting to the problems of hair loss will be of far greater value than the raising of unwarranted hopes.

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Acquired cicatricial alopecia

[R.D. Sinclair, pp. 63.46–63.61]

Hair follicles are self-regenerating organs. A new and distinct hair bulb is produced for every anagen phase of the hair cycle. Stem cells located within the outer root sheath (ORS) at the level of insertion of the arrector pili muscle have the potential to induce not only hair bulb regeneration, but also sebaceous gland formation and re-epithelialization of the epidermis [1]. Selective damage to the ORS in the isthmus that destroys hair follicle stem cells will ultimately lead to loss of the entire pilosebaceous unit and replacement by a fibrous tract or stella. Other non-selective forms of hair follicle damage can produce a similar outcome.

Cicatricial alopecia is the generic term applied to permanent areas of hair loss that are associated with destruction of hair follicles. Following recovery from the initial injury or inflammatory insult, there is little if any potential for hair regrowth. Histologically, the follicles are replaced by fibrous stellae, but as there is no scar *per se* the alternative generic term *scarring alopecia* is not favoured [2]. Replacement of follicular structures by fibrous tissue is the common final pathway for a number of diverse conditions and it is commonly not possible to infer the cause of the hair loss.

Cicatricial alopecia is by no means rare. In Whiting's series of 5860 patients presenting with hair loss between 1989 and 1999, 427 (7.3%) had cicatricial alopecia [3]. One of the earliest descriptions of cicatricial alopecia was by Brocq in 1885 [4]. He described what later became known eponymously as pseudopelade of Brocq [5], which is now regarded as a syndrome in which destruction of follicles leading to permanent patchy baldness is not accompanied by any clinically evident inflammatory pathology. Quainquad [6] described folliculitis decalvans, a form of scarring alopecia in which pustular folliculitis of the advancing margin was a conspicuous feature.

Cicatricial alopecia may result from a disease that affects the follicles primarily or a disease process external to the follicle that damages them secondarily. Secondary causes include trauma, as in burns or radiodermatitis, infections such as favus, tuberculosis or syphilis, or benign or malignant tumours. Chemicals used to straighten or curl hair may also cause a secondary cicatricial alopecia in susceptible persons.

Once the preliminary diagnosis of cicatricial alopecia has been made, the scalp should be examined for other clues as to the cause of the hair loss such as folliculitis, follicular plugging or broken hairs. These signs may help to establish the cause of a cicatricial alopecia, but no single sign is pathognomonic for a particular disease, and clinicopathological correlation is usually needed to make a specific diagnosis. An occasional sterile pustule can even be seen in some cases of lichen planopilaris and chronic cutaneous lupus. Hairs, even if grossly normal in appearance, should be extracted from the edge of the bald area for microscopy and culture. Any pustule should be swabbed and the fluid cultured. If no firm diagnosis is achieved, general examination of the skin, nails and oral mucosa should be carried out. Up to 40% of patients with scalp lichen planus and 30% of patients with discoid lupus of the scalp will have cutaneous disease elsewhere either at presentation or during follow-up.

In most cases, a diagnostic biopsy is indicated. The site for biopsy must be carefully selected and an early lesion is preferable. Several punch biopsies are preferable to a single elliptical biopsy; in this way, the biopsies can be orientated along follicles, and different stages of the disease process can be investigated. Ideally, at least one 4-mm biopsy should be taken from a clinically active area, prepared for horizontal section and stained with haematoxylin and eosin. If vertical sections or immunofluorescence are desired, a second 4-mm biopsy specimen from an area of similar clinical activity should be obtained. Additional biopsies from the centre of a patch of alopecia to establish whether follicular loss has occurred or to assess potential regrowth are optional, as are further biopsies for special stains (e.g. elastin, mucin, periodic acid–Schiff [PAS]) [2].

Classification of the primary causes of cicatricial alopecia is difficult because of changing clinical and histological features as these conditions evolve. The most common identifiable causes among white people are lichen planopilaris (LPP), folliculitis decalvans and discoid lupus erythematosus. Among black people, especially in North America and Europe where hair-straightening procedures are common, the most common cause is central centrifugal alopecia (see p. 63.54). Tumours, in particular metastatic nodules from renal, breast and lung carcinomas, should not be forgotten as a rare but important cause of cicatricial alopecia.

Despite multiple investigations a specific diagnosis is not always possible and a generic diagnosis of cicatricial alopecia is the best that can be done. In such cases, a trial of oral steroids or antimalarials may be considered to assess the potential for regrowth. Surgical correction of small areas can be considered once the underlying disorder has burned out. This can be done either by follicle transplantation or excision of the area. Larger areas may require the prior use of tissue expanders [7].

Classification [2]. The causes of cicatricial alopecia are classified here into broad groups, and the individual causes then considered in greater detail. Many of the causes are discussed in other chapters where appropriate.

1 *Primary cicatricial alopecia*

Inflammatory	Lymphocytic	Chronic cutaneous lupus erythematosus
		Lichen planopilaris (LPP)
		Classic LPP
		Graham-Little syndrome
		Frontal fibrosing alopecia
		Pseudopelade of Brocq
		Central centrifugal cicatricial alopecia
		Alopecia mucinosa
		Keratosis pilaris spinulosa decalvans
		Morphoea/scleroderma
	Neutrophilic	Folliculitis decalvans (including tufted folliculitis)
		Dissecting cellulitis/folliculitis
	Mixed	Acne keloidalis
		Acne necrotica
		Erosive pustular dermatosis
	Non-specific or end-stage cicatricial alopecia	

2 *Secondary cicatricial alopecia*

Traumatic	Radiodermatitis
	Mechanical trauma
	Postoperative (flap necrosis)
	Burns
	Accidental alopecia
	Dermatitis artefacta
	Traction alopecia
	Hot comb alopecia
Sclerosing disorders	Morphoea
	Scleroderma
	Lichen sclerosus
	Sclerodermoid porphyria cutanea tarda
	Chronic graft-versus-host disease
Granulomatous	Sarcoidosis
	Necrobiosis lipoidica
	Infectious granulomas
Infectious	Bacterial: Folliculitis
	Bacterial: Carbuncle/furuncle
	Fungal: Kerion
	Fungal: Favus
	Fungal: Tinea capitis (rarely scarring)
	Viral: Shingles
	Viral: Varicella
	Viral: HIV
	Protozoal: Leishmaniasis
	Protozoal: Syphilis
	Mycobacterial: Tuberculosis
Neoplastic	Benign: Cylindroma
	Benign: Other adnexal tumours
	Malignant: Primary: Basal cell carcinoma
	Malignant: Primary: Squamous cell carcinoma
	Malignant: Primary: Cutaneous T-cell lymphoma
	Malignant: Secondary: Renal, breast, lung, gastrointestinal
	Malignant: Secondary: Lymphoma, leukaemia

Developmental defects and hereditary disorders

Aplasia cutis
Facial hemiatrophy (Romberg's syndrome)
Epidermal naevi
Hair follicle hamartomas
Incontinentia pigmenti
Focal dermal hypoplasia of Goltz
Porokeratosis of Mibelli
Ichthyosis
Epidermolysis bullosa
Polyostotic fibrous dysplasia
Conradi–Hünermann syndrome (chondrodysplasia punctata)

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Non-specific cicatricial alopecia

Aetiology. This is by far the most common diagnosis made among patients presenting with cicatricial alopecia. In Whiting's series of 358 patients who were biopsied because of cicatricial alopecia this was the diagnosis made in 32% of cases [1]. Although often called pseudopelade, this term is best avoided because of confusion with pseudopelade of Brocq, a specific and distinct clinical disease. This entity of non-specific cicatricial alopecia encompasses a range of idiopathic non-inflammatory irregular permanent alopecias that are often slowly progressive. Many primary cicatricial alopecias ultimately burn out and the final common pathway is an irregular area of cicatricial hair loss of the scalp with no distinguishing clinical or histological features. Various authorities have estimated that between 15% and 90% of cases of non-specific cicatricial alopecia result from LPP, but there is no way of confirming this. That a small minority of patients initially diagnosed as having non-specific cicatricial alopecia later develop associated cutaneous lichen planus confirms significant overlap between this condition and LPP.

Pathology. The histology is variable and non-specific. Scalp biopsies taken from hairy skin at the edge of a scarred patch may be either completely normal or show a non-specific lymphocytic infiltrate around follicular infundibulum and mid-follicle, with or without a light superficial perivascular infiltrate. Follicles may be depleted and replaced by fibrous tracts, and sebaceous glands and follicular units may be disrupted. In the centre of areas of alopecia, follicles are absent or dramatically diminished in number and the epidermis is atrophic. Concentric lamellar fibrosis and follicular atrophy is seen around residual follicles. The adjacent dermis is sclerotic. Follicle rupture can produce hair granulomas or pustules.

Clinical features. The initial patch often occurs over the crown, but may occur anywhere on the scalp. The lesions tend to be oval, and several foci may coalesce to form irregular bald areas. There is usually no erythema and the patches are smooth, shiny and slightly depressed. Within any patch, a small number of terminal hairs may persist. These are often irregularly twisted and sometimes easily extracted. Folliculitis is rarely seen. The hairs at the edge of the patch of alopecia are also often irregularly twisted and easily extracted, even when in anagen, which indicates active extension of the alopecia.

Prognosis. The prognosis is extremely variable and unpredictable. Some patches extend almost imperceptibly over many years, whereas others enlarge rapidly. Whether this condition ever truly burns out, or merely extends too slowly to be noticed is uncertain.

Treatment. Much has been tried empirically, but nothing has been shown to be effective.

Lichen planus (see Chapter 42)

SYN. LICHEN PLANOPILARIS; FRONTAL FIBROSING ALOPECIA

Aetiology. Lichen planus is an idiopathic inflammatory disease that may affect the skin, hair and nails. There are numerous cutaneous variants of lichen planus. On the scalp it tends to produce a cicatricial alopecia. Three variants of cicatricial alopecia resulting from lichen planus are recognized: LPP, Graham-Little syndrome and frontal fibrosing alopecia. In each of these conditions the scalp may be affected alone or in conjunction with lichen planus elsewhere.

Lichen planus occurs throughout the world, but there are marked regional variations in its incidence and in its clinical manifestations. In the USA, lichen planus accounts for at least 10% of cases of cicatricial alopecia and the mean age of onset is 44 years [1]. In Europe and Australia, where follicular degeneration syndrome is less common, the incidence is higher. Although drug-induced lichen planus is well recognized, drug-induced LPP is not recognized.

Pathology [2]. The initial abnormality is in the epidermis; fibrillar changes in the basal cells lead to the formation of colloid bodies and at an early stage these, and macrophages containing pigment, may be seen in the dermis. By immunofluorescence, fibrin and immunoglobulin M (IgM) may be detected in the upper dermis, and various components of complement in the basement-membrane zone. The damaged basal cells are continually replaced by the migration of cells from neighbouring normal epidermis. In the established lesion, the horny layer and granular layer are thickened and there is irregular acanthosis. Flattening of the rete pegs gives rise to a saw-tooth configuration. There is liquefaction degeneration of the basal cells. Close up against the epidermis is a dense infiltrate of lymphocytes and some histiocytes. In many sections, colloid bodies can be seen. If the process involves hair follicles, the infiltrate extends around them and the hairs are replaced by keratin plugs. The follicles may ultimately be totally destroyed (Figs 63.32 & 63.33).

AGA with associated fibrosis may be confused with patterned LPP, especially as mild to moderate lymphohistiocytic inflammation is commonly seen in AGA [3].

Clinical features [4]. Lichen planus occurs at any age, but in over 80% of cases the onset is between 30 and 70 years [5]. Significant involvement of the scalp is relatively infrequent—only 10 of 807 patients in one series [5]—but the incidence is probably rather higher than such figures suggest, because they tend to exclude those patients in whom alopecia, classified as pseudopelade, was the only

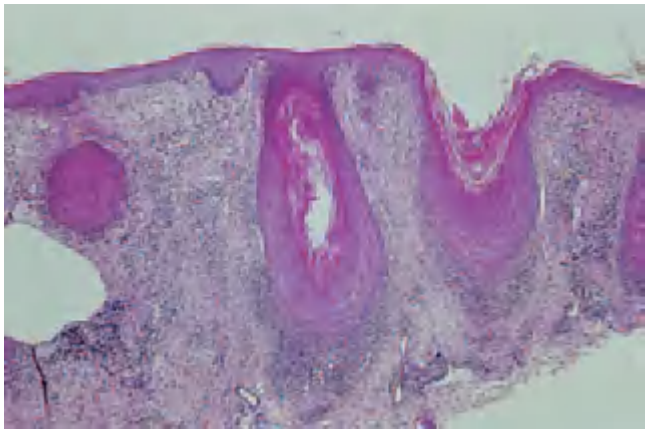

Fig. 63.32 Low-power photomicrograph showing lichen planopilaris. There is follicular plugging and a peri-appendageal inflammatory infiltrate.

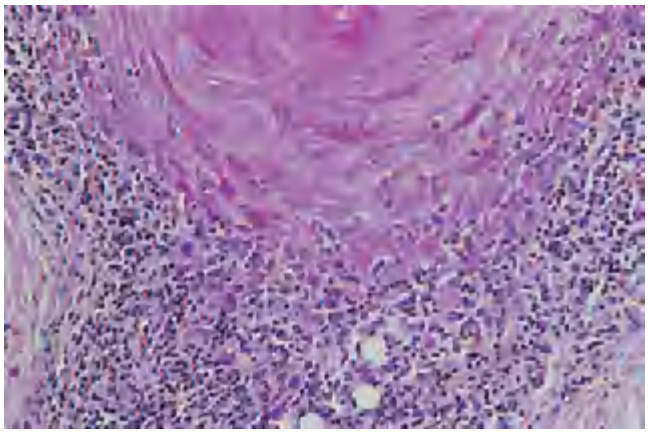

Fig. 63.33 Base of the hair follicle shows hydropic degeneration of the basal layer and a lichenoid mononuclear cell infiltrate.

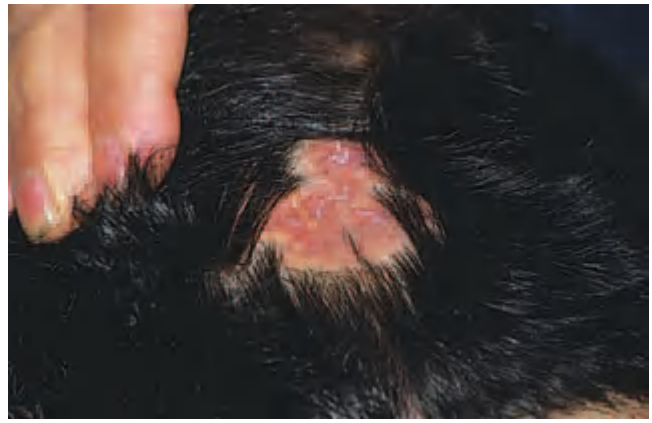

Fig. 63.34 Scarring alopecia caused by lichen planus showing active lesions.

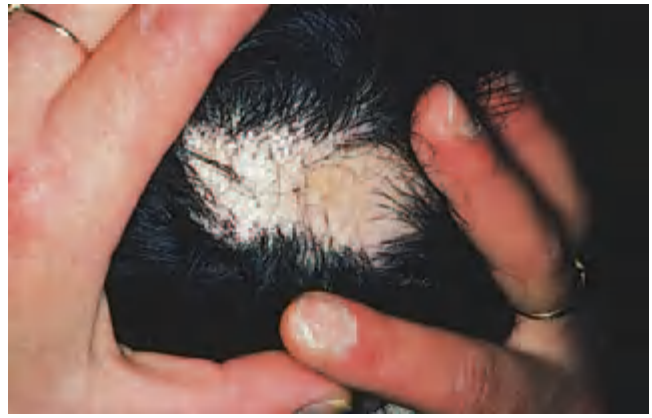

Fig. 63.35 More advanced lichen planus showing follicular plugs and scarring.

manifestation of the disease. Scalp involvement occurs in over 40% of patients with either of two unusual variants of lichen planus: the bullous or erosive form and LPP. Most patients seen with scalp lesions are middle-aged women, but a girl aged 13 years with scarring has been reported [6].

Recent scalp lesions may show violaceous papules, erythema and scaling (Fig. 63.34) [7]. These papules are replaced quickly by follicular plugs and scarring (Fig. 63.35). Eventually, the plugs are shed from the scarred area, which remains white, smooth and atrophic. Follicular orifices are absent within the area of alopecia. If the patch is extending, horny plugs may still be present in follicles around its margins, and the hair pull will be positive at the margins, with twisted anagen hairs being easily extracted by gentle traction.

Patients commonly present with pseudopelade-like patches of scarring that are non-specific. The diagnosis of lichen planus can be made only in the presence of unquestionable lesions elsewhere and lichen planus histology. These may take the form of bullous lichen planus with shedding of nails [8], of bullous lesions associated with typical lichen planus of the skin and mucous membranes [9], or of lichen planus of very limited extent involving, for example, the nails only [10].

One clinical variant of LPP is frontal fibrosing alopecia (Fig. 63.36) [11]. This condition superficially resembles AGA with frontal recession, but on close inspection there is loss of follicular orifices, and perifollicular erythema and hyperkeratosis at the marginal hairline. It typically occurs in postmenopausal women, although it can occur earlier. In contrast with AGA, the frontal hairline recedes in a straight line rather than bitemporally.

The natural history of frontal fibrosing alopecia is slow progression over many years. There is no effective treatment [11].

Prognosis. In some patients, the course of lichen planus of the scalp is slow and only a few inconspicuous patches are present after many years. However, particularly if the skin lesions are of bullous or planopilaris type, they may rapidly result in extensive and permanent baldness.

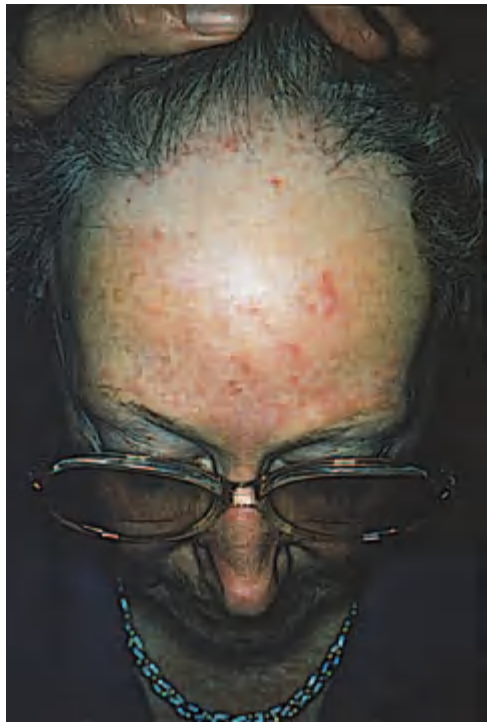

Fig. 63.36 Frontal fibrosing alopecia of Kossard.

Treatment. In some cases, a short course of systemic treatment with a corticosteroid may be desirable. In other cases, intralesional corticosteroids are helpful, but only at a stage when active inflammatory changes are still present. Potent topical steroids such as clobetasol propionate ointment twice daily usually relieve associated symptoms such as itch or pain, and may slightly inhibit the process [12]. Hydroxychloroquine and acitretin have been tried with variable success. Ciclosporin is very effective for cutaneous lichen planus, and has been reported as useful in Graham-Little syndrome [13], as has thalidomide [14,15].

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Graham-Little syndrome [1,2]

In 1915, Graham-Little reported the case of a woman aged 55 years who had suffered for 10 years from slowly progressive cicatricial alopecia and for 5 months from groups of horny papules [3]. Since then many further cases have been reported. Whether this syndrome is or is not a form of lichen planus is still unresolved, although the immunofluorescence in typical cases strongly suggests lichen planus [4]. However, whatever its cause or causes, the syndrome is distinctive. It is known eponymously and variously as the Graham-Little, Lassueur–Graham-Little or Piccardi–Lassueur–Little syndrome.

Pathology. In the scalp, the mouths of affected follicles are filled by horny plugs. The underlying follicle is progressively destroyed and eventually an atrophic epidermis covers sclerotic dermis. In the axillae and pubic region, the follicles are likewise destroyed, although the skin does not appear clinically to be atrophic.

Clinical features. Most patients are women between the ages of 30 and 70 years. The essential features of the syndrome are progressive cicatricial alopecia of the scalp, loss of pubic and axillary hair without clinically evident scarring, and the rapid development of keratosis pilaris [5].

In most patients, the earliest change has been patchy cicatricial alopecia of the scalp. In general, the scalp alopecia precedes the widespread keratosis pilaris by months or years [6]. In some patients, the alopecia and the keratosis pilaris appear to have developed more or less simultaneously, or the keratosis pilaris has preceded the discovery of the alopecia [7].

The scalp changes are commonly described simply as patches of cicatricial alopecia. Some authors specifically mention associated follicular plugging of the scalp [7]; others refer to ‘scaly red patches’.

The keratosis pilaris is referred to in early case reports as lichen spinulosus, which emphasizes that the horny papules are prolonged into conspicuous spines. In most cases they have developed aggressively over a period of weeks or months and have been grouped into plaques,

often on the trunk, or the trunk and limbs, but occasionally involving the eyebrows and the sides of the face. Pruritus is an inconstant symptom; it was noted in several reported cases [8]. Thinning and ultimately total loss of pubic and axillary hair has been noted in many cases.

Treatment. None is universally effective. Ciclosporin was reported as useful in a single case [9].

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Discoid lupus erythematosus [1]

Lupus erythematosus (LE) is an autoimmune connective tissue disease characterized by the presence of circulating non-organ-specific autoantibodies to cell nuclear antigens. Three different forms of LE are described: systemic (SLE), subacute and discoid (DLE) lupus. However, only DLE regularly produces cicatricial alopecia. Inflammation of the infundibular region of the hair follicle that contains the stem cells is thought to be the basis of the scarring alopecia that occurs in DLE, but this does not explain why the identical pattern of inflammation seen in SLE does not scar. The diffuse hair shedding that accompanies SLE is believed to be an acute telogen effluvium.

Pathology [2]. The histology of DLE, in common with SLE, shows hyperkeratosis with follicular plugging, a perivascular and periadnexal lymphoid infiltrate, which may be sparse, moderate or heavy, and the essential feature of focal basal layer vacuolar degeneration (Figs 63.37–63.39). This may be associated with colloid body formation, pigmentary incontinence, papillary dermal oedema, thickening of the basement-membrane zone and exocytosis of lymphocytes into the epidermis and follicular epithelium. Mucin can be seen in the dermis as a faint blue tinge between widely separated collagen bundles. Scarring only occurs in DLE and manifests as homogenized collagen fibres running parallel to the surface, a loss of appendages and lone arrector pili muscles. Staining for elastin shows that elastic fibres are absent from the scar.

Hypergranulosis, saw-toothed rete ridges, perifollicular fibrosis and clefts are not seen in lupus, and this helps to distinguish it from lichen planus. However, frequently it is not possible to separate these two conditions on routine histological examination and in such cases

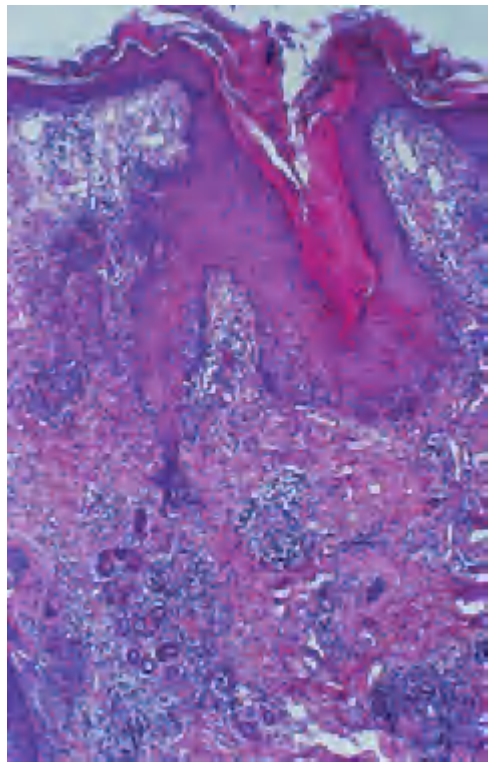

Fig. 63.37 Discoid lupus erythematosus. Low-power photomicrograph showing follicular plugging, superficial and deep perivascular and peri-appendageal lymphocytic infiltrate. (Courtesy of Dr G. Mason, Melbourne, Australia.)

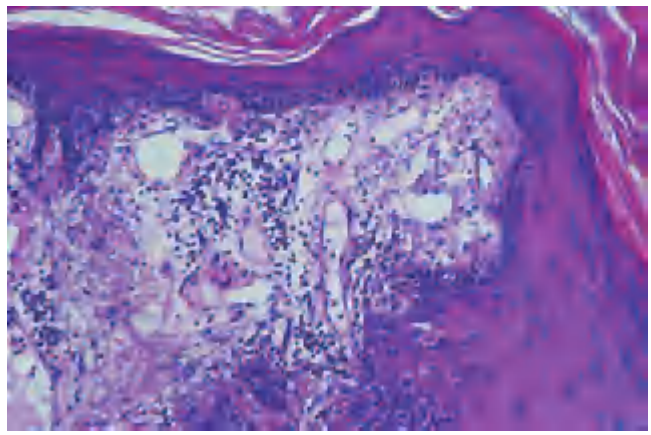

Fig. 63.38 Discoid lupus erythematosus. High-power photomicrograph showing the hydropic degeneration of the basal layer and the mononuclear cell infiltrate. (Courtesy of Dr G. Mason, Melbourne, Australia.)

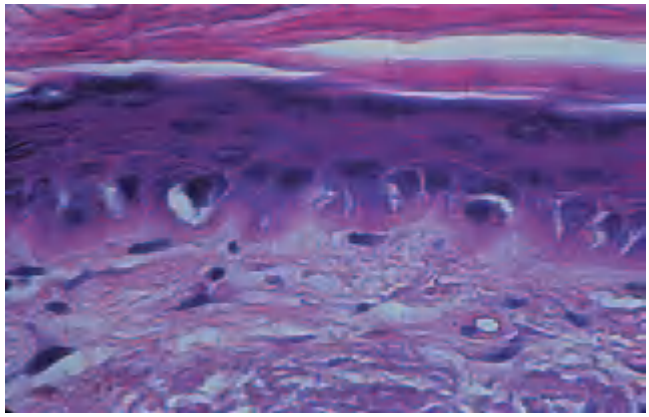

Fig. 63.39 Discoid lupus erythematosus. High-power photomicrograph showing the hydropic degeneration of the basal layer. (Courtesy of Dr G. Mason, Melbourne, Australia.)

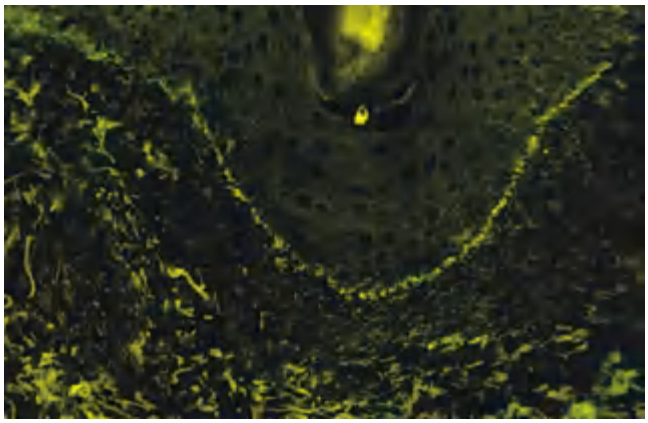

Fig. 63.40 Positive linear immunofluorescence to IgG: the lupus band test. (Courtesy of Dr G. Mason, Melbourne, Australia.)

immunofluorescence may be decisive. There is linear staining of deposits of complement (C3), IgM and IgG on the basement membrane in more than 80% of cases of LE, but not in lichen planus. Direct immunofluorescence is also positive in non-lesional skin in approximately 50–75% of cases of SLE, depending on whether sun-exposed or non-exposed skin is chosen. Only approximately 20% of cases of DLE will have positive immunofluorescence of uninvolved skin. A weak false-positive immunofluorescence to IgM can occur on the head and neck and is a source of confusion. Only positivity to IgG or very strong positivity to IgM (Fig. 63.40) should be used as supportive evidence of lupus on the scalp, as this only rarely occurs in the absence of lupus.

In old burnt-out lesions, the histology and immunofluorescence may be inconclusive and in such cases a non-specific diagnosis such as scarring alopecia is all that can be made.

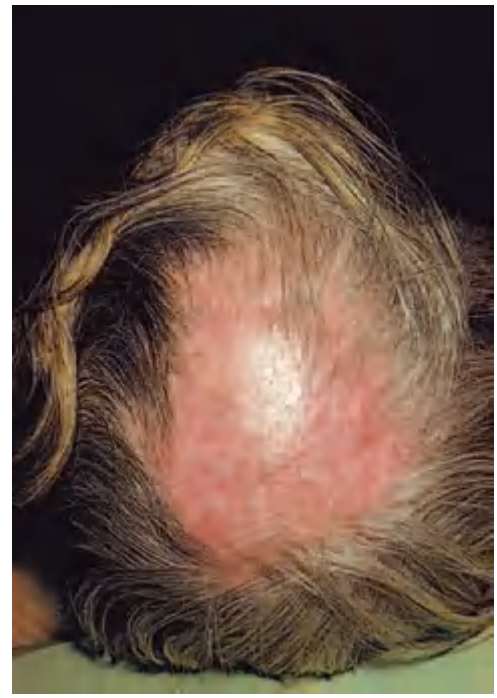

Fig. 63.41 Discoid lupus erythematosus producing cicatricial alopecia.

Clinical features [2]. DLE occurs most commonly in women (8 : 1 for SLE and 2 : 1 for DLE) and is about three times more common in African Americans than in white people. The incidence is approximately 1 in 2000. Familial cases occur in approximately 10%. The peak age of onset is around 40 years.

Scarring alopecia occurs in 20% of men and 50% of women affected with DLE, and the scalp is the only area affected in a significant number of patients. Patches on the scalp are often itchy. Areas of erythema and scaling with follicular plugging extend irregularly across the scalp and produce scarring (Fig. 63.41). Sometimes patches of scarring alopecia develop with little in the way of preceding inflammation and then resemble pseudopelade of Brocq. Ultimately, large areas of alopecia may form. Some cases burn out after 1–2 years, but others continue to progress for many years.

Pigmentary disturbance, particularly in dark-skinned people is common. Rarely, calcification occurs in the patches. Squamous cell carcinoma has been reported in chronic cicatricial LE of the scalp [3].

Antinuclear antibody (ANA) is positive in approximately 35% of patients with DLE. Anti-Ro antibodies are found in 10%. DLE may occur on its own or associated with SLE. If the initial DLE is confined to the head and neck, the risk is 1–2%, whereas if the lesions are generalized the risk is 22%. SLE first presents with DLE in 10% of cases and DLE can be found at some stage during the course of SLE in 33%.

Treatment [4]. Potent topical corticosteroids, intralesional triamcinolone and systemic prednisolone (1 mg/kg) may halt progression of active DLE. Antimalarials form the mainstay of treatment in chronic cases refractory to topical steroids. Hydroxychloroquine in a regimen of 200–400 mg/day produces a remission within 3 months in the majority and the dosage can then be tapered gradually. Scarring is permanent, but early treatment may produce a surprising amount of regrowth. Chloroquine, acitretin, dapsone, thalidomide or a combination of these medications may be useful in refractory cases. Cyclophosphamide, methotrexate and ciclosporin have also been used in severe, rapidly progressive cases where all other treatments have failed.

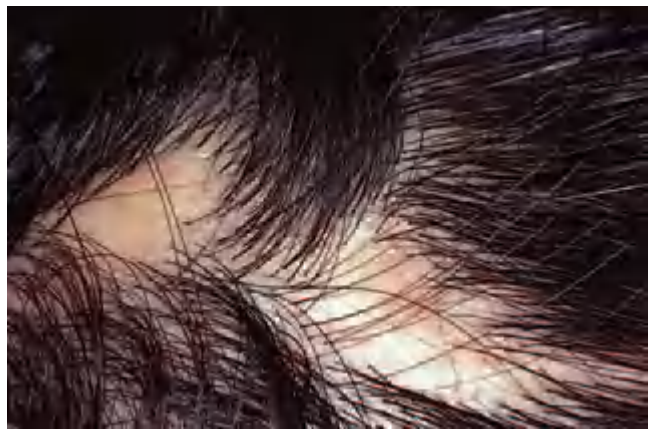

Fig. 63.42 Pseudopelade of Brocq.

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Pseudopelade of Brocq [1]

Pseudopelade of Brocq is an idiopathic, chronic, slowly progressive, patchy cicatricial alopecia that occurs without any evidence of inflammation. It is primarily an atrophy rather than an inflammatory folliculitis. The term pseudopelade was first used by Brocq to distinguish this condition from the 'pelade' of alopecia areata. The French term pelade had been in use at that time for more than 200 years and is derived from *pelage*—the fur, hair, wool, etc. of a mammal. In recent times, the term pseudopelade has been used to describe a generic scarring alopecia, the end result of any number of different pathological processes, and the interchangeable use by some of 'pseudopelade' and 'pseudopelade of Brocq' has led to confusion in the literature.

Pathology [2]. Early lesions may have a light lymphocytic infiltrate around the upper two-thirds of the hair follicle (including the hair bulge) that spares the epidermis and eccrine glands [3]. This infiltrate invades the walls of the follicles and sebaceous glands and eventually destroys the entire pilosebaceous unit. Single hairs may survive within a patch for many years.

Later patches are smooth, soft and slightly depressed and histological examination reveals only a thin atrophic epidermis overlying a sclerotic dermis containing fibrotic streams extending into the subcutis. There are no inflammatory changes at this stage. These fibrotic streams are follicular 'ghosts'. Arrector pili muscles may be seen inserting into these fibrous remnants of hair follicles. Elastic stains are important in differentiating pseudopelade of Brocq from lichen planus, DLE and other scarring alopecias. With an acid–alcohol orcein stain, elastic fibres are seen around the lower part of the follicle, whereas in all the other scarring alopecias the scar tissue consists of collagen devoid of elastin.

Clinical features [1]. Pseudopelade of Brocq may occur in both sexes at any age. Most commonly, women over 40 years are affected. Childhood cases are rare [4]. The aetiology and pathogenesis are unknown. The condition is almost always sporadic, but the occurrence in two brothers suggests a genetic factor may be important. There is no doubt that lichen planus can produce a very similar clinical picture and there are some authorities who maintain, on the basis of associated skin lesions and histopathological findings, that 90% of cases of 'pseudopelade' are caused by lichen planus [5].

The alopecia is asymptomatic and is often discovered by chance. It always remains confined to the scalp. The initial patch is often on the vertex but may occur anywhere (Fig. 63.42). On examination, the affected patches are smooth, soft and slightly depressed. At an early stage in the development of any individual patch there may be some erythema. The patches tend to be small and round or oval, but irregular bald patches may be formed by the confluence of many lesions. The hair in uninvolved scalp is normal, but if the process is active the hairs at the edges of each patch are very easily extracted.

The course is extremely variable. Most often there is slow development over many years of small round patches of alopecia that ultimately converge to produce larger irregular areas of hair loss. The hair in the uninvolved scalp is normal and the progression is sufficiently slow that even after 15–20 years patients may still be able to arrange their hair in such a way as to conceal the bald areas. The entire process can burn out spontaneously at

Table 63.3 Diagnostic criteria for pseudopelade of Brocq. (After Braun-Falco *et al*. [1].)

Clinical criteria
Irregularly defined and confluent patches of alopecia
Moderate atrophy (late stage)
Mild perifollicular erythema (early stage)
Female : male ratio = 3 : 1
Long course (more than 2 years)
Slow progression with spontaneous termination possible
Direct immunofluorescence
Negative (or only weak IgM on sun-exposed skin)
Histological criteria
Absence of marked inflammation
Absence of widespread scarring (best seen with elastin stain)
Absence of significant follicular plugging
Absence, or at least a decrease of sebaceous glands
Presence of normal epidermis (only occasional atrophy)
Fibrotic streams into the dermis

any stage, leaving behind only relatively small areas of alopecia.

The diagnostic criteria of Braun-Falco *et al*. [1] shown in Table 63.3, and based on the histological criteria of Pinkus [6], should be fulfilled before this specific diagnosis is made. Cases that do not fulfil these criteria should be diagnosed generically as scarring alopecia.

Treatment. The alopecia is irreversible and does not respond to topical or intralesional corticosteroids. No treatment is known to arrest progression. If the disfigurement is considerable and no active inflammatory changes are present, autografting from unaffected to scarred scalp may be considered [7], or surgical 'expansion' techniques in severe cases.

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Follicular degeneration syndrome [1]

This condition begins as a single focus of cicatricial alopecia over the vertex scalp in black women that gradually spreads outwards in a centrifugal pattern, but remains unifocal. It was originally called hot comb alopecia, but many patients have no preceding history of hot comb usage. A possible relationship to other hair-straightening procedures is postulated, but not conclusively proven. The name 'central centrifugal alopecia' has also been proposed, and this focuses attention on the clinical appearance of the hair loss rather than the histological identification of premature degeneration of the inner root sheath, which is variable and not entirely specific [2].

Pathology. A superficial perivascular and perifollicular lymphocytic infiltrate is seen in active areas. There is no associated interface change. Sebaceous glands are lost early, but eccrine glands are spared. Premature disintegration of the inner root sheath epithelium has been emphasized, but is not always found. Hair follicle destruction is severe and widespread and leaves prominent concentric lamellar fibrosis. Release of hair fragments into the dermis results in granulomatous inflammation.

Clinical features. Most patients are middle-aged black females who chemically straighten their hair. The alopecia is slowly progressive and the symmetrical forward progression follows a pattern similar to female pattern hair loss.

Treatment. Minimal hair grooming is recommended, but many patients find this difficult. No treatment has been found to help. Many patients resort to wearing a suitable hair piece.

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Folliculitis decalvans and tufted folliculitis [1]

Under the general term folliculitis decalvans we group the various syndromes in which clinically evident chronic folliculitis leads to progressive scarring. This is probably a heterogeneous group.

Aetiology. The cause of folliculitis decalvans is still uncertain. *Staphylococcus aureus* may be grown from the pustules. In the vast majority of people who develop a bacterial pustular folliculitis of the scalp it is transient, resolves with antibiotics and heals without scarring. In some, the folliculitis is more persistent, tends to recur in the same site after apparently successful treatment with antibiotics and produces a scarring alopecia. An abnormal host response to *Staph. aureus* is postulated, which may be the result of a defect in cell-mediated immunity.

Shitara *et al*. [2] reported severe folliculitis decalvans in two siblings who also had chronic candidiasis; defective cell-mediated immunity was demonstrated. Douwes *et al*. [3] reported simultaneous occurence in identical twins, with no identifiable immune abnormality.

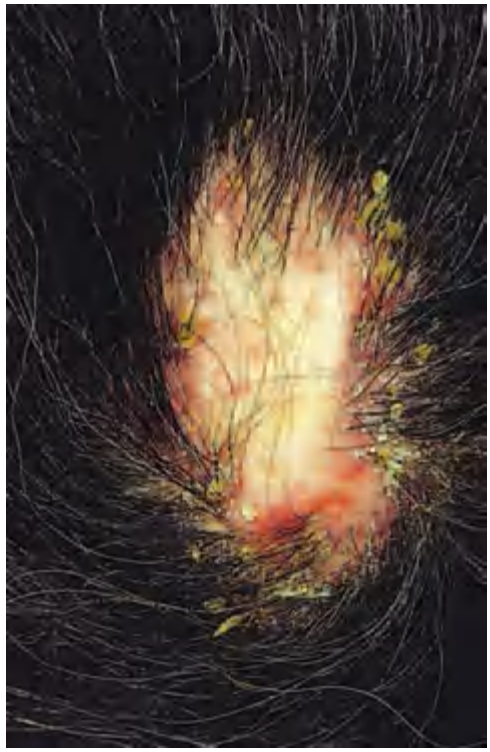

Fig. 63.43 Folliculitis decalvans showing active pustulation and scarring.

Pathology [1,4,5]. Histology reveals follicular abscesses, with a dense perifollicular polymorphonuclear infiltrate and scattered eosinophils and plasma cells. Foreign-body granulomas occur in response to follicular disruption, which is succeeded by scarring. Eventually all that remains of the follicle is extensive fibrosis.

Clinical features [1]. Men may be affected from adolescence onwards, whereas women tend not to develop this condition until their thirties. Following a pustular folliculitis of the scalp, usually one, but occasionally more, rounded patches of alopecia develop, each surrounded by crusting and a few follicular pustules. Successive crops of pustules appear and are followed by progressive destruction of the affected follicles (Fig. 63.43). In some cases the folliculitis spreads along the scalp margin in a coronal pattern, or along the edge of an AGA. The severity of the inflammatory changes fluctuates, but the course is prolonged.

Tufted folliculitis is a variant of folliculitis decalvans where circumscribed areas of scalp inflammation heal with scarring characterized by tufts of up to 15 hairs emerging from a single orifice (Fig. 63.44) [6–8]. The tufts consist of a central anagen hair surrounded by telogen hairs, each arising from independent follicles, converging towards a common dilated follicular infundibulum. Cases in which the tufts were comprised of only anagen hairs have also been described. Based on an animal model, it is suggested that erythema and scaling are the initial events and the tufting is a consequence of the emergence of hairs from beneath the free edge of the scales.

Fig. 63.44 Tufted folliculitis.

A scalp biopsy is required to confirm the diagnosis and swabs should be taken of any pustules. Investigation for an underlying defect in cell-mediated immunity is generally unrewarding, and only indicated when there is additional evidence of impaired immunity. As fungal kerion may mimic folliculitis decalvans, hairs should be plucked for fungal culture and a PAS stain should be performed on the scalp biopsy.

Treatment [1]. Essentially, treatment consists of attempts to eradicate *Staph. aureus* from the scalp. Prolonged courses of flucloxacillin induce remission, but relapse occurs when the antibiotics are stopped. For localized areas, topical clindamycin is useful. Tetracyclines are also commonly effective. Isotretinoin has been used to alter the follicular environment to make it less suitable for *Staph. aureus* colonization, but it may increase cutaneous carriage of this organism and make the condition worse. The only treatment shown to induce prolonged remission is rifampicin in a dosage of 300 mg twice daily. This should be given in combination with other antibiotics to prevent the emergence of resistant organisms. Drugs commonly used in combination include clindamycin 300 mg twice daily, fucidic acid 150 mg three times daily, ciprofloxacin, doxycycline and clarithromycin.

Tufting may be reduced by measures directed at reducing the scale, such as the use of tar shampoos and topical keratolytics.

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Dissecting cellulitis of the scalp [1]

SYN. DISSECTING FOLLICULITIS; PERIFOLLICULITIS CAPITIS ABSCEDENS ET SUFFODIENS

This rare condition manifests with a perifolliculitis of the scalp, deep and superficial abscesses in the dermis, sinus tract formation and extensive scarring. It occurs predominantly in black males aged between 18 and 40 years. Familial cases are exceptional, as is childhood onset.

Aetiology. The aetiology of this inflammatory condition is unknown. Although staphylococci, streptococci and *Pseudomonas* may be cultured from various lesions, no specific causative organism has been isolated. Dissecting cellulitis associates with hidradenitis suppurativa and acne conglobata in the follicular occlusion triad [2]. Other reported associations include pilonidal sinus and spondyloarthropathy. The activity of the arthritis parallels the activity of the skin.

Clinical features. Painful, firm, skin-coloured nodules develop near the vertex of the scalp and later become softer and fluctuant (Fig. 63.45). Confluent nodules form tubular ridges with an irregular cerebriform pattern, on a red and oedematous background. Thin blood-stained pus exudes from crusted sinuses, and pressure on one region of the scalp may cause discharge of pus from a neighbouring intercommunicating ridge. Cervical adenitis is present in some cases, but is more remarkable for its absence in many others. Progressive scarring and permanent alopecia occur. Characteristically, hair is lost from the summits of these inflammatory lesions and retained in the valleys. The condition is chronic, with frequent acute exacerbations. Fatal squamous cell carcinoma has developed within the areas of scarring after many years [3].

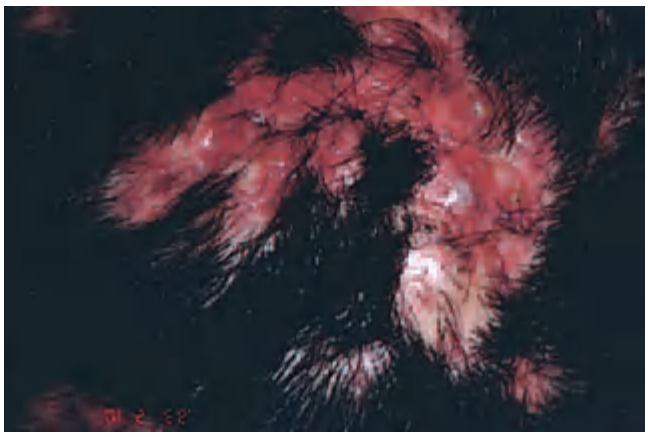

Fig. 63.45 Dissecting cellulitis of the scalp. (Courtesy of Dr D. Dyall-Smith and the *Australasian Journal of Dermatology* [5].)

Pathology [4]. Histology shows a perifolliculitis with a heavy infiltrate of lymphocytes, histiocytes and polymorphonuclear cells. Abscess formation results, and leads to destruction of the pilosebaceous follicles initially, and eventually the other cutaneous appendages. Keratin fragments induce a granulomatous reaction, with foreign-body giant cells, lymphoid and plasma cells. Special stains for bacteria, fungi and mycobacteria are negative.

Investigations. Culture from affected areas often grows bacterial organisms. Fungal cultures and a scalp biopsy for routine histology and direct immunofluorescence will exclude other causes of scarring alopecia.

Treatment. Although systemic antibiotics and topical or intralesional corticosteroids are sometimes helpful, relapses are frequent and the course is usually protracted. Isotretinoin in full dosage (1 mg/kg), in combination with prednisolone (1 mg/kg) and erythromycin 500 mg four times daily, may induce a rapid remission and significant hair regrowth in areas not yet irreversibly damaged [5]. Because the inflammation is predominantly perifollicular, a surprising amount of regrowth may occur. The antibiotics can be stopped after 4 weeks and the prednisolone gradually tailed off and replaced by topical steroids. The isotretinoin should be continued for at least 6 months, and reintroduced if the condition relapses. In recalcitrant cases, widespread excision and grafting may be considered, or alternatively in an older patient, X-ray epilation has been used with success [6]. Improvement has also been noted following laser-assisted hair removal [7].

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Fig. 63.46 Linear morphoea (en coup de sabre). After having this lesion since adolescence this lady recently developed biopsy-proven lichen sclerosus of the vulva.

Circumscribed scleroderma and linear morphoea

Circumscribed scleroderma is rare in the scalp, but may occur there as single or multiple lesions. The hair is shed at an early stage to leave a cicatricial alopecia. The diagnosis must be confirmed histologically. Linear circumscribed morphoea in the frontal region—'en coup de sabre' morphoea (Fig. 63.46)—is slightly more common (see Chapter 56). It has been suggested that lesions may follow the lines of Blaschko [1]. Histological examination of both conditions shows chronic inflammation of the upper and mid-follicle, and prominent fibrosis [2]. Linear morphoea has been associated with hereditary deficiency of complement C2 [3].

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Cicatricial pemphigoid

SYN. BENIGN MUCOSAL PEMPHIGOID

Cicatricial pemphigoid affects predominantly the elderly, and women more than men [1,2]. It is associated with autoantibodies to the basement-membrane-zone adhesion complex (see Chapter 41).

Bullae are formed at the dermal–epidermal junction. Direct immunocytochemical studies show that linear deposits of IgG, IgA, C3 and C4 may be found in the basement-membrane zone, but circulating basement-membrane-zone antibodies (IgG or IgA) are not always demonstrable [3,4].

Although the disease affects predominantly the ocular and/or genital mucous membrane, the skin is involved in 40–50% of cases, and skin lesions may precede the mucosal lesions by months or years [5]. The skin lesions repeatedly recur and leave scars. The favoured sites are the face and upper trunk, the scalp being involved in approximately 10% of cases [6]. Skin lesions, predominantly on the head and neck, are the major feature of the Brunsting–Perry variant.

Management is often dictated by the need to control mucosal lesions. If recurrent bullae in a localized area of skin are troublesome, excision and grafting may be successful [6]. Whether to prescribe oral corticosteroids or immunosuppressive drugs for skin lesions alone is controversial, but topical clobetasol propionate cream may inhibit the process to some degree.

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Erosive pustular dermatosis of the scalp

This clinical entity particularly affects the elderly [1,2]. Its cause is unknown but Grattan *et al.* [3], in their study of 12 cases, suggested that local trauma and sun damage are important. Surgery, cryosurgery, skin grafting and radiation therapy may all precipitate this condition [4].

Pathology. Histological examination shows areas of epidermal erosion, a chronic inflammatory cell infiltration in the dermis consisting predominantly of lymphocytes and plasma cells, and sometimes small foci of foreign body giant cells where hair follicles have been destroyed.

Clinical features. This condition almost always occurs in association with AGA. Initially, a small area of scalp becomes red, crusted and irritable; crusting and superficial pustulation overlie a moist eroded surface (Fig. 63.47). As the condition extends, areas of activity coexist with areas of scarring. Squamous carcinoma has developed in the scars [5].

Differential diagnosis. Pyogenic and yeast infection is excluded by bacteriological examination and the lack of response to antibacterial or antifungal agents. Biopsy may be necessary to exclude pustular psoriasis, cicatricial

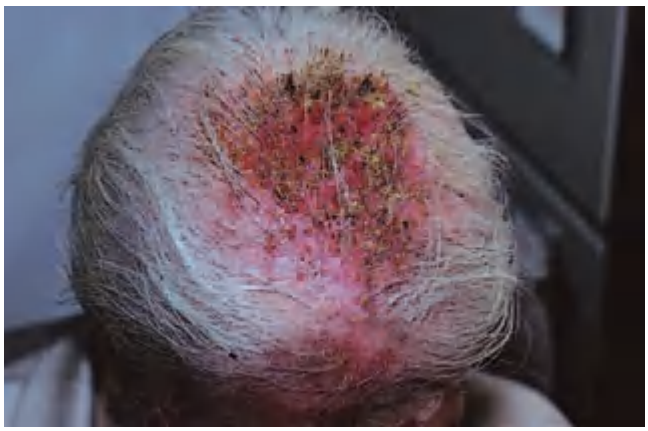

Fig. 63.47 Erosive pustular dermatosis of the scalp occurring on a sun-exposed bald scalp.

pemphigoid, 'irritated' solar keratosis or squamous cell carcinoma.

Treatment. The stronger topical corticosteroids (e.g. 0.05% clobetasol propionate) will suppress the inflammatory changes. Gradual reduction in the potency of topical steroid over a 6-month period may result in cure. Maintenance therapy with sun protection and intermittent moderate potency steroid can provide long-term relief. Ikeda *et al.* [6] suggested oral zinc sulphate and Boffa [7] suggested topical calcipotriol can be curative in some cases.

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Necrobiosis lipoidica, granuloma annulare and sarcoidosis

Necrobiosis lipoidica occurs in 0.2–0.3% of cases of diabetes mellitus, and approximately 70% of patients with necrobiosis have diabetes. The diabetic cases begin in childhood or early adult life, and the non-diabetic cases rather later and usually in women.

The oval atrophic plaques classically occur on the shins but may be seen on other parts of the body including the scalp. The patches are glazed and yellowish, often with conspicuous telangiectases. Scarring may be dense. The clinical features in the scalp vary from large plaques of cicatricial alopecia to multiple small areas of scarring [1].

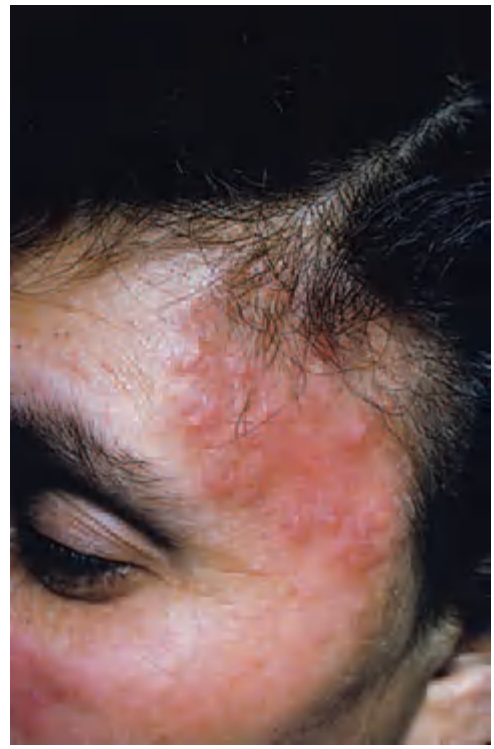

Fig. 63.48 Sarcoidosis of the scalp.

An atrophic form affecting predominantly the forehead and the scalp has been described [2,3]. In general, the differential diagnosis is from sarcoidosis and granuloma annulare [4–6].

Cutaneous sarcoidosis may produce plaques or nodules on the scalp as well as both cicatricial and non-cicatricial alopecia (Fig. 63.48) [7]. Affected areas may itch. There is a marked preponderance of females amongst reported cases. The histology is distinctive, with non-caseating granulomatous inflammation [5].

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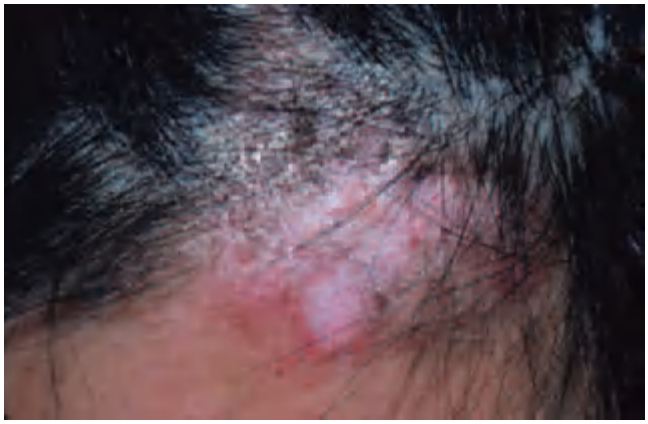

Fig. 63.49 Lichen sclerosus.

Lichen sclerosus et atrophicus

This disease affects females 10 times more often than males [1]. Lichen sclerosus of the scalp appears to be rare (Fig. 63.49). It may cause an extensive cicatricial alopecia that is relatively nondescript clinically, but which has all the characteristic features histologically. Associated lesions are usually found on the trunk and vulva [2,3].

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Developmental defects and hereditary disorders

Scarring follicular keratosis

Numerous syndromes have been described and elaborately named, all of them characterized by keratosis pilaris associated with some degree of inflammatory change leading to destruction of the affected follicles [1].

Only detailed clinical and genetic studies can provide the essential facts to allow reliable differentiation of syndromes that some authorities regard as forms or degrees of a single state and others accept as distinct entities. For the time being, the reported cases can be conveniently classified in three groups; in addition, certain apparently well-defined entities can be recognized.

1 *Atrophoderma vermiculata* (acne vermiculata, folliculitis ulerythematosa reticulata). There is honeycomb atrophy of the cheeks. Scarring alopecia may occur, but rarely.

2 *Keratosis pilaris atrophicans faciei* (ulerythema oophryogenes). The process is more or less confined to the eyebrow region.

3 *Keratosis pilaris decalvans* (keratosis follicularis spinulosa decalvans, follicular ichthyosis). Keratosis pilaris of variable extent is associated with cicatricial alopecia [2].

All these conditions are assumed to be genetically determined, although many cases occur sporadically. Such genetic data as are available are considered under the individual forms.

The follicles are initially distended by horny plugs, the dermis is oedematous and there is some lymphocytic infiltration around follicles and vessels. Later, the follicles are destroyed. Small epithelial cysts may be numerous, particularly in keratosis pilaris atrophicans faciei.

Clinical features. Atrophoderma vermiculata usually begins in childhood. Follicular plugs, often in the preauricular regions, are gradually shed to leave reticulate atrophy. On the face, the extent of the process is variable. Exceptionally, cicatricial alopecia of the scalp may be associated [3].

Keratosis pilaris atrophicans faciei (ulerythema oophryogenes) is present from early infancy. Erythema and horny plugs begin in the outer halves of the eyebrows, which they eventually destroy, and then advance medially and to a variable extent on the cheeks. Involvement of the scalp has apparently not been reported in cases in which the eyebrows are predominantly involved. However, there are reports of cases to which this diagnosis has been applied, but which appear to be more rationally classified in one of the other categories, in which alopecia has occurred. Such cases emphasize the need for improved diagnostic criteria.

Keratosis pilaris decalvans is also such a variable syndrome that several genotypes must be considered. Keratosis pilaris begins in infancy or childhood, often on the face. Ultimately, it may be confined to the face or to face and limbs, or may be more or less universal. It is often succeeded by atrophy on the face, but rarely on the limbs or trunk. Cicatricial alopecia is noted from early childhood or later, and may be localized or extensive [4]. Familial cases without significant eyebrow involvement are reported [5].

Three members of one family developed keratosis pilaris of the face in early childhood [6] and then extensively on the back and limbs, and on the scalp, where horny papules replaced hairs. A similar syndrome was reported in a young man who had keratosis pilaris and severe cicatricial alopecia [7]. The occurrence of cases similar to those reported by MacLeod [6] in other siblings, born of normal parents, suggested recessive inheritance but the evidence was incomplete. The pattern of hair loss in the family reported by Ullmo [8] was in the distribution of the Marie–Unna type of congenital alopecia, apart from the presence of keratosis pilaris on the face.

What may be another distinct syndrome associates extremely severe keratosis pilaris—'closely woven bristles'

—with almost complete alopecia, reduced sweating and deafness [9].

Treatment. Only symptomatic measures are available. Retinoic acid deserves a trial. The status of oral retinoids remains controversial, although anecdotal response has been noted.

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Porokeratosis of Mibelli

Porokeratosis of Mibelli commonly begins in childhood but may first appear at any age. It is most frequent on the limbs, particularly the hands and feet, the neck, the shoulders and the face, but may occur anywhere, including the scalp [1]. The initial lesion is a crateriform horny papule that gradually extends to form a circinate or irregular atrophic plaque with a raised horny margin, which may be surmounted by a furrow from which the lamina of horn projects. In the scalp there is loss of hair in the atrophic phase.

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Incontinentia pigmenti

Cicatricial alopecia has been present in at least 25% of reported cases of incontinentia pigmenti; it appears in early infancy and ceases to extend after a variable period of up to 2 years, but the loss of hair is permanent. Other hair defects present in some cases have been hypoplasia of the eyebrows and eyelashes, and woolly hair naevus of the scalp [1].

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Generalized follicular hamartoma

Cicatricial alopecia beginning in childhood was a feature of a syndrome described by Mehregan and Hardin [1]. Their patient was a woman aged 23 years. From infancy, she had widespread horny plugs over the trunk and limbs and small pits on the palms and soles. She later developed cicatricial alopecia, in which, from the age of 8 years, appeared follicular tumours. The tumours of the scalp were proliferating tricholemmal cysts. The lesions of palms and soles showed funnel-shaped dilatation of sweat ducts, which were plugged with parakeratotic material containing acid mucopolysaccharide. Ridley and Smith [2] described this entity with alopecia and myasthenia gravis.

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Epidermolysis bullosa

The term epidermolysis bullosa is applied to a group of distinct, genetically determined disorders characterized by the formation of bullae of skin, and often also of mucous membranes, in response to trauma, or spontaneously (see Chapter 40). Only one of these diseases is accompanied by abnormalities of scalp or hair—recessive dystrophic epidermolysis bullosa. However, Gamborg Nielsen and Sjolund [1] described a new syndrome of localized epidermolysis bullosa simplex associated with hair, nail and teeth abnormalities. Alopecia may also occur in junctional epidermolysis bullosa.

Bullae form at the dermal–epidermal junction and fragments of dermis may adhere to the roof.

The inexorable blistering of skin and mucous membranes dominates the picture. The blisters are followed by atrophic scarring. This may give rise to more or less extensive cicatricial alopecia of the scalp [2,3]. Of 30 cases studied by Videl [4], three had cicatricial alopecia.

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Cleft lip-palate, ectodermal dysplasia and syndactyly

This rare or rarely recognized syndrome is probably

hereditary, and determined by an autosomal recessive gene.

The constant features of the syndrome are mental retardation, cleft palate, genital hypoplasia, cicatricial alopecia, defective teeth and syndactyly [1].

REFERENCE

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Polyostotic fibrous dysplasia

The progressive enlargement over a period of 10 years of a bald patch present since childhood was shown histologically to be caused by the replacement of the follicles by coils of fibrous tissue. The patient had polyostotic fibrous dysplasia [1].

REFERENCE

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Infections

[A.G. Messenger]

Tinea capitis

See Chapter 31.

Infestations

See Chapter 33.

Syphilis

Hair loss occurs in approximately 10% of cases of secondary syphilis and may be the presenting feature [1,2]. The hair loss typically has a 'moth-eaten' appearance but may be diffuse in nature [3]. Other features of secondary syphilis are present in most cases, particularly lymph node enlargement and hepatomegaly, but hair loss has been reported as the only sign of the disease [4]. Histological features include an increase in catagen and telogen forms, and a peribulbar lymphocytic infiltrate, similar to the changes seen in alopecia areata [3]. Additional features in syphilis include lymphocytic infiltration of the isthmus region, parabulbar lymphoid aggregates and the presence of plasma cells within the infiltrate.

The serpiginous nodulo-squamous syphilide of tertiary syphilis may affect the scalp and the syphilitic gumma is a cause of scarring alopecia.

Human immunodeficiency virus (see Chapter 26)

A variety of alterations in hair growth have been described in patients with HIV infection. Telogen effluvium is a common cause of hair loss [5]. Causes include chronic HIV-1 infection itself, secondary infections, nutritional deficiencies and drugs. Hair loss has been reported with several antiretroviral drugs, particularly indinavir [6], which may cause loss of hair on the body as well as the scalp. There are also reports of alopecia areata occurring in patients with HIV infection [7–9].

There are several reports of hypertrichosis of the eyelashes (eyelash trichomegaly) in HIV infection [9–11]. The cause of this striking and unusual feature is not known. It is usually associated with advanced disease and has been noted to regress with antiretroviral treatment [11].

Straightening of the hair is a common feature of HIV infection in black patients [12].

Various forms of folliculitis are seen in HIV infection, including acneiform eruptions, staphylococcal folliculitis and eosinophilic pustular folliculitis.

Leprosy

Loss of eyebrow and body hair may occur in lepromatous leprosy but the scalp is rarely involved.

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Artefactual alopecia

[D.A.R. de Berker, pp. 63.61–63.65]

Cosmetic alopecia

The dictates of religion, custom and fashion have imposed an immense variety of physical stresses on human hair. Two types of hair loss occur as a result of cosmetic

Fig. 63.50 Traction alopecia from braiding.

practices: those characterized by structural damage to the hair shaft leading to excessive weathering and breakage, and those where hair follicles are injured by prolonged traction from hair styling. A third type, centrifugal cicatricial alopecia or follicular degeneration syndrome, which occurs in women of African extraction, has been ascribed to cosmetic procedures, but this is controversial.

Traction alopecia

Traction alopecia is brought about by hair styles that impose sustained pulling on the hair roots. The clinical features in the many variants of this syndrome include folliculitis, reduction in hair density with vellus hairs and sometimes broken hairs in the affected areas, and eventually scarring alopecia. Keratin cylinders ('hair casts') may surround many hairs just above the scalp surface [1]. The pattern of the hair loss is often distinctive and reflects the distribution of the traction.

Traction alopecia is seen most commonly in Afro-Caribbean hair styles where the hair is tightly braided. The hair loss commonly begins in the temporal regions and in front of and above the ears, but may involve other parts of the scalp margin, or even linear areas in other parts of the scalp (Fig. 63.50). If continued long term, permanent scarring alopecia may occur [2]. The use of rollers may cause alopecia in the frontal and temporal regions, as may 'ponytail' styles. Frontal and parietal traction alopecia has been reported in young Sikh boys as a result of twisting their uncut hair tightly on top of the head [3], and tight braiding and wooden combs produce traction alopecia in the Sudan; frontal loss is reported in Libyan women as a result of traction from a tight scarf [4].

Treatment. The diagnosis of traction alopecia is usually not difficult, provided the possibility is considered. The cause is not always recognized by the patient and may be received with suspicion. The patient, or parents of affected children, need to be educated to adopt hair styles that do not pull the hair tight [2].

Follicular degeneration syndrome

See p. 63.54.

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Physical trauma

The diagnosis and treatment of the consequences of physical injuries of the scalp will seldom confront dermatologists, but they may be consulted as to the cause of an apparent physical injury (e.g. aplasia cutis may be falsely attributed to forceps injury at childbirth). The attachment of an electrode to the scalp for monitoring the fetal heartbeat during labour may occasionally cause some superficial damage, and this may be followed by a small scar. Aplasia cutis has sometimes been mistaken for such a lesion [1].

An unusual case of cicatricial alopecia in a boy aged 13 years was caused by injury to the scalp by an intravenous infusion given in infancy for gastroenteritis [2]. Exceptionally, self-inflicted injuries may involve the scalp and leave scars.

Halo scalp ring [3]

A type of alopecia, which may be temporary or permanent, is an area of scalp hair loss resulting from prolonged pressure on the vertex by the uterine cervix during or prior to delivery, resulting in a haemorrhagic form of caput succedaneum.

Scalp necrosis after surgical embolization

Adler *et al.* [4] described a case in which ischaemic necrosis of the occipital scalp occurred following embolization and surgery for a large convexity meningioma.

Women who had undergone prolonged pelvic operations in the Trendelenburg position developed, 12–26 days later, a vertical patch of alopecia, which was preceded by oedema, exudation and crusting. Pressure ischaemia during the operation was considered to be the cause of the alopecia [5]. In one large clinic, over a period of 3 years, 60 cases of occipital pressure alopecia were observed after open-heart surgery [6]. In 29 of these cases,

the hair loss was permanent. Temporary alopecia followed prolonged pressure on the scalp by a foam rubber ring used to prevent such an occurrence [7].

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Chronic radiodermatitis [1,2]

Roentgen discovered X-rays in 1895. X-ray epilation of the face for hirsutism was frequently employed during the first two decades of the 20th century and, although Schultz [3] condemned this treatment, it continued to be so widely used that Cipollaro and Einhorn [4] entitled their paper: 'The use of X-rays for the treatment of hypertrichosis is dangerous'.

X-ray epilation for the treatment of scalp ringworm was introduced in Paris in 1904. The discovery of griseofulvin in 1958 gradually made X-ray epilation unnecessary, but it has been estimated that between 1904 and 1959 some 300 000 children throughout the world were treated with X-rays for ringworm of the scalp. Correct dosage did not cause toxicity; however, technical errors were frequent, from inadequate and poorly calibrated apparatus. The treatment produced complete epilation in approximately 3 weeks and regrowth after 2 months. The follow-up of 2043 patients treated in childhood showed a higher incidence of cancer in the patients than in a control group [1]. Radiodermatitis of the scalp may occur also as an unavoidable consequence of skin damage during the treatment of both internal malignant disease and malignant disease of the skin.

The use of X-rays for epilation depends on the high susceptibility of anagen hairs to radiation. Epilating and subepilating doses produced dystrophic changes in human hairs as early as the fourth day after exposure [5]. Chronic radiodermatitis may follow acute radiodermatitis, but may develop only slowly as degenerative changes induced by sun exposure and ageing become superimposed. In chronic radiodermatitis, the epidermis is generally atrophic, with loss of hair follicles and sebaceous glands, but there are also irregular areas of acanthosis. Degenerative changes and nuclear abnormalities are frequent in the epidermis. Dermal collagen stains irregularly. Superficial small vessels are telangiectatic, but deeper vessels are partially or completely occluded by fibrosis.

Clinical features. The development of a basal cell carcinoma in middle age or later in an area of the scalp should lead the dermatologist to enquire about X-ray epilation for ringworm in childhood [6]. In other cases, the patient complains of hair loss, which is apparently accentuated in certain areas, and these areas are found to show both AGA and reduction of follicle population as a result of the earlier radiation.

Chronic radiodermatitis produced by radiation therapy of a malignant tumour of the scalp presents a circumscribed area of cicatricial alopecia. Radiation necrosis may simulate a recurrence of carcinoma, but the edges of the necrotic ulcer are not raised. The diagnosis should be confirmed by a biopsy. Superficial X-ray of Grenz ray type does not penetrate deeply enough to damage scalp follicles. Malignant tumours arising in radiodermatitis should be excised [7].

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Trichotillomania (see also Chapter 61)

First described by Hallopeau in 1889 [1], trichotillomania is a psychiatric disorder with dermatological expression, in which there is a compulsive habit of pulling out the hair. It is probably a symptom of several different psychopathologies [2].

Pathology. The histological changes vary according to the severity and duration of the hair plucking. Numerous empty canals are the most consistent feature. Some follicles are severely damaged; there are clefts in the hair matrix, the follicular epithelium is separated from the connective tissue sheath, and there are intraepithelial and perifollicular haemorrhages and intrafollicular pigment casts (Fig. 63.51) [3]. Injured follicles may form only soft twisted hairs—a process that has been described as a separate entity under the name of trichomalacia [4]. Many follicles are in catagen, with very few or no follicles in

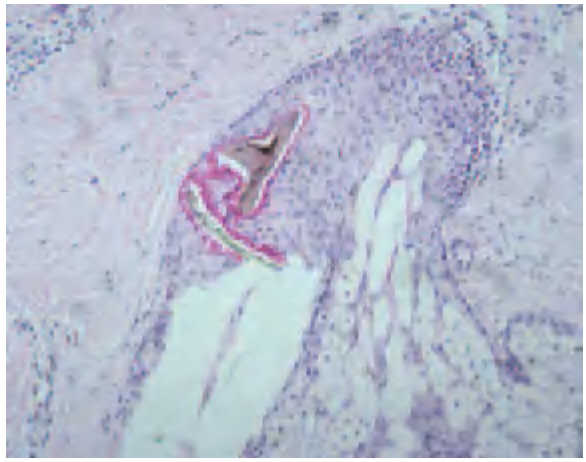

Fig. 63.51 Histology of trichotillomania showing fragmentation of the hair shaft.

Table 63.4 DSM-IV criteria for trichotillomania.

Recurrent pulling out of one's hair resulting in noticeable hair loss
An increasing sense of tension immediately before pulling out the hair or when attempting to resist the behaviour
Pleasure, gratification or relief when pulling out the hair
The disturbance is not better accounted for by another mental disorder and is not due to a general medical condition (e.g. a dermatological condition)
The disturbance causes clinically significant distress or impairment in social, occupational or other important areas of functioning

telogen. Some dilated follicular infundibula contain horny plugs [5].

Aetiology and psychopathology. Trichotillomania occurs in two main forms. In infants and young children it is usually a habit akin to thumb-sucking and nail biting. It seems slightly more common in boys and usually resolves spontaneously or with minimal treatment. Parents who have not noticed hair-pulling behaviour in their offspring may deny the diagnosis. In older children and adults trichotillomania is usually a chronic psychiatric problem, although periods of remission occur in some patients. This form occurs predominantly in females, with women outnumbering men by up to 7 : 1, although this figure may be skewed by a greater likelihood of women presenting for medical advice [2]. The American Psychiatric Association classifies trichotillomania as an impulse control disorder. Their diagnostic criteria are given in the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), and are listed in Table 63.4, although not all patients with trichotillomania fit these criteria.

Trichotillomania shares some features of obsessive–compulsive disorder (OCD), but some authorities consider it may be the result of a number of psychopathologies including OCD, personality disorders, body dysmorphobic disorders, mental retardation and psychosis. There is an extensive psychiatric literature on trichotillomania, but this may be biased because psychiatric help is likely to be sought only in those patients who accept that it is a self-inflicted problem. This is not true of all patients presenting to dermatologists.

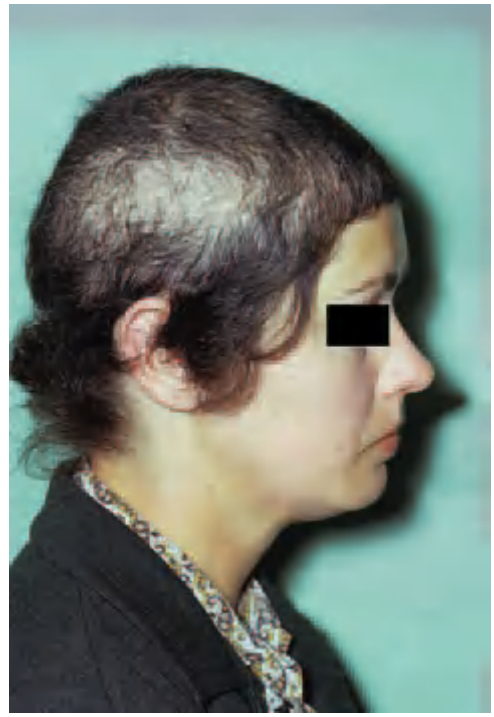

Fig. 63.52 Trichotillomania. Characteristic 'tonsure' pattern with scalp margin hair spared.

Clinical features. In young children, the hair-pulling tic develops gradually and unconsciously. Hair is plucked most frequently from one frontoparietal region. This results in a patch of hair loss, often in a bizarre or angular pattern, in which the hairs are twisted and broken at various distances from the clinically normal scalp. Older patients present with an area of scalp on which the hair has been reduced to coarse stubble uniformly 2.5–3 mm long. The plucked area may be asymmetrical or cover the entire scalp apart from the margin (Fig. 63.52). It is unusual for hair to be lost completely within the affected area (in contrast with alopecia areata). The scalp skin appears normal. Over time the extent of hair loss can vary, and hair growth may recover temporarily.

Hair in sites other than the scalp can also be affected, such as eyelashes, eyebrows and beard. Exceptionally, the patient may pluck hair also, or only, from other regions of the body, such as the mons pubis and perianal region.

A hairball (trichobezoar) is a rare accompaniment of trichotillomania in those who also eat the plucked hair (trichophagia) [6,7].

Differential diagnosis. The minor form in young children can be confused with ringworm or with alopecia areata. In ringworm, the texture of the infected hairs is abnormal and the scalp surface may be scaly. Alopecia areata may be difficult to exclude with certainty at the first examination, but the course of the condition usually establishes the correct diagnosis. Unlike alopecia areata, it is unusual for hair to be lost completely in trichotillomania and, in contrast with exclamation mark hairs, the broken hairs of trichotillomania are firmly anchored in the scalp. Where doubt remains a skin biopsy will usually establish the correct diagnosis. However, there are reports of the co-existence of alopecia areata and trichotillomania [8]. In rare cases, genetic disorders characterized by increased hair fragility, such as monilethrix, may resemble trichotillomania and should be excluded by hair microscopy.

Treatment. The establishment of a relationship between the physician and the patient, or with the parents of an affected child, is an important step in management of trichotillomania. A confident diagnosis is essential, but this is not always easy and may require observation over time and sometimes a scalp biopsy. The habit tic in young children is often self-limiting, but input from a paediatric psychologist can be very helpful. Trichotillomania in adolescents and adults is a different proposition, and can be an intractable problem [9]. Patients with insight should be referred to a psychiatrist or clinical psychologist. A number of psychotherapeutic approaches have been used, particularly behaviour therapy aimed at habit reversal, but none is uniformly successful. Various drugs have been reported to be helpful, including clomipramine [10] and neuroleptic agents [11], but relapse rates are high. Promising results have also been claimed for the selective serotonin reuptake inhibitor fluoxetine [12], but this was not confirmed in controlled trials [13,14]. Behavioural therapy appears more effective than either clomipramine [15] or fluoxetine [16]. Some patients are helped by contact with fellow patients, and there are several patient support groups and Internet websites devoted to trichotillomania. Patients who fail to admit the self-inflicted nature of the hair loss present particular difficulties, as they are unlikely to accept psychiatric referral and, like dermatitis artefacta, a confrontational approach will probably be unsuccessful. Management should be aimed at helping the patient recognize the cause for themselves. This can be a long and slow process requiring skill and empathy on the part of the physician.

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Scaling disorders of the scalp

[A.G. Messenger, pp. 63.65–63.67]

Scaling of the scalp is a feature of a number of clinical disorders including dandruff (pityriasis capitis), seborrhoeic dermatitis, psoriasis and pityriasis amiantacea. These disorders show overlapping clinical and histological features and, when confined to the scalp, it can be difficult to distinguish between them. Scalp scaling is also seen in other inflammatory dermatoses such as atopic dermatitis, tinea capitis, discoid lupus erythematosus and cutaneous T-cell lymphoma.

Pityriasis capitis

Pityriasis capitis, or dandruff, and seborrhoeic dermatitis confined to the scalp are generally regarded as the same entity, with dandruff representing the mild non-inflammatory end of a spectrum of scalp scaling. Its peak incidence and severity are reached at the age of approximately 20 years, and it becomes less frequent after 50 years of age. At age 20 years, some 50% of white people are affected to some degree. Although previously thought to be uncommon in children, an epidemiological study from Australia found that approximately 40% of children under the age of 6 years showed at least mild pityriasis capitis, and 10% of neonates had seborrhoeic dermatitis of the scalp [1].

Aetiology [2]. It is reasonably well established that pityriasis capitis and seborrhoeic dermatitis are related, in some way, to the presence on the skin of lipophilic yeasts of the genus *Malassezia*, previously known as *Pityrosporum*. This idea, which evolved in the 19th century when these organisms were first identified [3–5], is based largely on the clinical observations of improvement with antifungal treatment. For a time during the 1960s and 1970s the microbial hypothesis was disputed [6], but it became re-established with the advent of azole antifungal agents [7–9]. Treatment of patients with seborrhoeic dermatitis with azole antifungal agents such as ketoconazole is associated with improvement of the rash, a reduction in colonization of the skin by *Malassezia*, and relapse as the skin is recolonized following treatment [10]. Scalp skin affected by dandruff or seborrhoeic dermatitis tends to be more heavily colonized by *Malassezia* species than normal scalp [11] although, in seborrhoeic dermatitis, the colonization rates are highly variable and there is no clear relationship between the number of organisms present on the skin and disease activity [12]. As *Malassezia* is present on normal skin there must be other factors involved that lead to scalp scaling. Possible explanations have included a direct inflammatory effect of toxins released by the organisms and an altered immune response to *Malassezia* [2].

Clinical features. Small, white or grey scales accumulate on the surface of the scalp in localized, more or less segmental patches or more diffusely. After removal with an effective shampoo, the scales form again within 4–7 days. The condition first becomes a cosmetic problem during the second and third decades, but there are long- and short-term variations in its severity, without obvious cause. There are also variations in the ease with which the scales become detached and drift unaesthetically among the hair shafts or fall on the collar and shoulders. Although pityriasis usually clears spontaneously during the fifth or sixth decade, it may persist in old age. Pityriasis merges, almost imperceptibly, into seborrhoeic dermatitis where signs of inflammation and itching are also present, and other skin sites may be involved. Pruritus is not a feature of simple pityriasis.

Diagnosis. Asymptomatic scalp scaling in children also occurs in pediculosis and in tinea capitis. The latter is typically associated with broken hair shafts and patchy hair loss, but these features may be absent in carriers of anthropophilic dermatophyte infections. Pediculosis should also be considered in adults with scalp scaling. Other than in the neonatal period, seborrhoeic dermatitis is uncommon in children, and psoriasis should be considered in the presence of significant scalp inflammation. Differentiation between seborrhoeic dermatitis and scalp psoriasis can be difficult at any age. Psoriasis is suggested by more demarcated plaques, extension of lesions beyond the hairline and the silvery character of the scaling. Occasionally, atopic dermatitis is confined to the scalp, when pruritus is usually a major feature. Profuse adherent silvery scale should suggest pityriasis amiantacea.

Treatment. Pityriasis in its milder forms is a physiological process. The object of treatment is to control it at the lowest possible cost and inconvenience to the patient, appreciating that any procedure found to be effective will need to be repeated at regular intervals.

Shampoos containing the anti-yeast agents ketoconazole or zinc pyrithione are effective in most cases of pityriasis capitis. One controlled trial reported an excellent response in 88% of subjects using ketoconazole [13]. Another study showed a 71% reduction in the dandruff score after 4 weeks of treatment with ketoconazole shampoo and a 67% reduction in subjects using a shampoo containing zinc pyrithione [14]. The scaling will return if treatment is discontinued, but the frequency of relapse can be reduced by prophylactic treatment (e.g. once weekly treatment with ketoconazole shampoo [13]). Shampoos containing selenium sulphide or tar have also been widely used to treat pityriasis capitis. Topical steroids may be used in patients with seborrhoeic dermatitis who do not respond to a shampoo. Salicylic acid-containing preparations (e.g. sulphur and salicylic acid cream) can be helpful for heavy scaling.

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Pityriasis amiantacea

Pityriasis amiantacea is an inflammatory scaling reaction of the scalp, often without evident cause. One Scandinavian follow-up study reported that psoriasis occurred in 15% of patients with pityriasis amiantacea [1]. Another study failed to show an association with psoriasis but suggested that seborrhoeic dermatitis was more common [2]. In Knight's study of 71 patients, two had associated psoriasis and nine had eczema [3]; he pointed out that pityriasis amiantacea may occur at any age, but the average age was 25 years (range 5–40 years).

Pathology. Biopsies from 18 patients were examined by Knight [3]. The most consistent findings were spongiosis, parakeratosis, migration of lymphocytes into the epidermis and a variable degree of acanthosis. The essential features responsible for the asbestos-like scaling are diffuse hyperkeratosis and parakeratosis together with follicular keratosis, which surrounds each hair with a sheath of horn.

Clinical features. Masses of adherent silvery scales, overlapping like the tiles on a roof, adhere to the scalp and are attached in layers to the shafts of the hairs, which they surround (Fig. 63.53). The underlying scalp is usually reddened. The disease may be confined to discrete areas of the scalp, or may be very extensive, either involving a large area diffusely or affecting a number of small patches. The majority of patients notice some hair loss in areas of severe scaling. The hair regrows when the scaling is effectively treated, although scarring alopecia has been reported following pityriasis amiantacea [4].

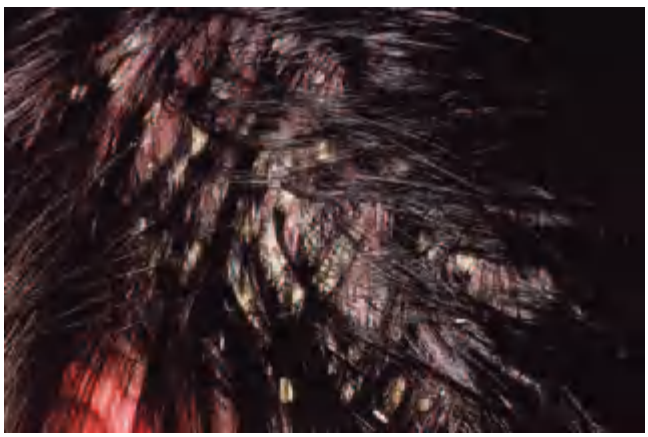

Fig. 63.53 Pityriasis amiantacea.

Diagnosis. The distinctive clinical appearance usually makes the diagnosis easy, but the identification of the underlying disease may not be straightforward; indeed, none may be established.

Treatment. Generous applications of an oil-based product are needed to remove the scales. Tar or salicylic acid ointments are commonly used. The preparation is left on the scalp for several hours and then washed out. The scales may be gently removed using a metal-toothed comb. Once the scaling is controlled an antidandruff or tar-based shampoo may help to maintain remission, but most patients will need to re-treat with an ointment from time to time. Potent topical corticosteroid lotions are beneficial in some cases, but are not effective in removing thick scales.

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Folliculitis

See Chapter 27.

Keloidalis nuchae

See Chapter 27.

Pseudofolliculitis

See Chapter 27.

Thickened scalp disorders

[D.A.R. de Berker, pp. 63.67–63.69]

Cutis verticis gyrata

The term cutis verticis gyrata (CVG) describes a morphological syndrome in which there is hypertrophy and folding of the skin of the scalp to present a gyrate or cerebriform appearance. Polan and Butterworth [1] established the classification of CVG, dividing it into primary and secondary forms. The classification was later modified by Garden and Robinson [2] who subdivided the primary form into primary essential CVG, in which there are no associated features, and primary non-essential CVG, which is associated with a wide range of mental, cerebral and ophthalmological abnormalities.

Primary CVG. The aetiology of primary CVG is not known. Most cases appear to be sporadic although familial forms

have been reported in the context of complex syndromes [3,4]. The skin changes typically develop after puberty and usually before 30 years of age. It is more common in men, with a male : female ratio of 5 : 1 or 6 : 1. There is a strong association with mental retardation. Akesson [5] found 47 cases (3.4%) of CVG in institutionalized mentally retarded subjects in Sweden, and CVG was observed in 22 out of 494 (4.5%) patients in an Italian psychiatric institution [6]. Cytogenetic analyses in the latter study showed chromosome fragile sites in nine subjects (chromosomes 9, 12 and X).

Secondary CVG. This has been described with a wide range of underlying causes. Congenital melanocytic naevi appear to be the most common but other naevoid abnormalities, such as naevus lipomatosus and connective tissue naevi, and acquired lesions such as neurofibroma, may also cause CVG [7–9]. CVG has been described in association with a variety of endocrine and genetic disorders, including acromegaly [10,11], myxoedema [12], insulin resistance [13] and Turner's syndrome [14,15]. The age of onset is more variable than in primary CVG and, in the naevoid forms, it may be present at birth.

Pachydermoperiostosis. This genetically determined syndrome also occurs mainly in men and has often been confused with CVG. It differs from it in several particulars. The scalp is folded but the skin of the face is affected, as is that of the hands and feet. The cutaneous changes, which are accompanied by thickening of the phalanges and of the long bones of the limbs, progress for 10–15 years, then become static.

Pathology. The essential abnormality appears to be overgrowth of the scalp in relation to the underlying skull. In primary CVG, the histology appears normal in most cases. The histopathology in the secondary form depends on the nature of the underlying pathology.

Clinical features. CVG typically affects the vertex and occipital scalp but it may involve the entire scalp. The folds are usually arranged in an antero-posterior direction but may be transverse over the occiput. Hair density may be reduced over the convexities of the folds.

Treatment. Investigations are aimed at identifying underlying causes. These may include neurological, endocrine, ophthalmological and cytogenetic studies. In early-onset CVG, a biopsy is advisable to identify those cases caused by a structural lesion, such as a melanocytic naevus. In the majority of cases treatment is symptomatic. Patients should be educated in scalp hygiene to avoid accumulation of skin debris and secretions in the furrows. Surgical correction can be helpful in selected cases, and may be indicated in cerebriform naevi.

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Lumpy scalp syndrome [1]

The inheritance of this syndrome is determined by an autosomal dominant gene of variable expressivity. Raw areas are present in the scalp at birth. They heal to leave irregular nodules of connective tissue that, on histological examination, are not keloidal in structure. The pinnae are deformed; the tragus, antitragus and lobule are small or rudimentary. The nipples are rudimentary or absent, and only areolae are present.

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Lipoedematous alopecia [1,2]

Lipoedematous alopecia is a rare condition of unknown aetiology. It is characterized by a thick boggy scalp with varying degrees of hair loss. This syndrome has been recognized mainly in black women. There is slowly progressive diffuse alopecia and obvious thickening of the scalp, with associated pruritus [3]. There are no associated medical or physiological conditions. The fundamental pathological finding consists of an approximate doubling

in scalp thickness resulting from expansion of the subcutaneous fat layer in the absence of adipose tissue hypertrophy or hyperplasia. There is associated atrophy and fibrous replacement of many hair follicles. Light and electron microscopy suggests that the increase in scalp thickness is caused by localized oedema, with disruption and degeneration of adipose tissue. Mucin is not seen [4].

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Congenital alopecia and hypotrichosis

[R.D. Sinclair, pp. 63.69–63.72]

Total or partial absence of hair of developmental origin occurs in a bewildering variety of clinical forms, either as an apparently isolated defect or in association with a wide range of other anomalies. A logical classification must be based on detailed histological and genetic investigations and these, unfortunately, are seldom carried out. Provisionally, a purely clinical classification is useful to enable the clinician at least to understand the clearly defined types [1].

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Total alopecia

SYN. ATRICHIA CONGENITA

As an isolated abnormality [1,2]

Aetiology. Total alopecia as an apparently isolated defect is usually determined by an autosomal recessive gene. Some pedigrees have been traced back to the early 19th century [1]. Dominant or irregular dominant inheritance has occurred in some families [3,4]. The two genotypes seem to be phenotypically indistinguishable, but detailed investigation would probably reveal differences. The term 'total' is relative, but if any hairs are present they are extremely few. Many isolated cases and families reported under the diagnosis of congenital alopecia are found on review of the original reports to be unquestionably examples of other syndromes; many were hidrotic ectodermal dysplasia.

Pathology. The hair follicles are absent in adult life, even when the fetal hair coat has been normal. Sebaceous glands are smaller than normal. When a few stray hairs have survived, the structure of the shaft appears to be normal.

Clinical features [4,5]. The scalp hair is often normal at birth but is shed between the first and sixth months, after which no further growth occurs. In some cases the scalp has been totally hairless at birth and has remained so [5]. Eyebrows, eyelashes and body hair may also be absent [6], but more often there are a few straggling pubic and axillary hairs and scanty eyebrows and eyelashes. Teeth and nails are normal, and general health, intelligence and life expectancy are unimpaired.

With associated defects

Total or almost total alopecia is unusual in hereditary syndromes.

Papular atrichia [7]. This rare autosomal recessive syndrome is associated with mutations in the zinc finger domain of the hairless gene [8]. Patients are born with hair that falls out and is not replaced. They are completely devoid of eyebrows, eyelashes, and axillary and pubic hair. Histological studies show the presence of the infundibular portion of the hair follicles, but the middle and lower portions of the follicle are replaced by small keratinizing epithelial cysts. No hair shafts are formed. At any age between 1 and 10 years, numerous small horny papules appear, first on the face, neck and scalp, and then gradually over the greater part of the limbs and trunk. Histologically, the papules are thick-walled keratin cysts [7]. Whitish hypopigmented streaks can be found on the scalp. Nails, teeth, sweating, growth and development are normal.

The underlying disorder in papular atrichia appears to be that towards the end of the first anagen phase the hair bulb, proximal inner root sheath and outer root sheath all undergo premature and massive apoptosis and disintegrate into separate cell clusters that lose contact with the dermal papilla. As a result the dermal papilla fibroblasts fail to migrate upward, and break up into clusters of shrunken cells stranded in the reticular dermis as dermal cyst precursors, and the follicle loses the ability to cycle [9].

The genetics are complex. Apart from cases of pseudodominant inheritance [10], there is phenotypic and genetic heterogeneity in inherited atrichias caused by mutations in the *hr* gene, suggesting different roles for the regions mutated in atrichia with papular lesions and in other forms of congenital atrichia during hair development [11]. Furthermore, mutations in a number of genes such as the vitamin D receptor [12], ornithine decarboxylase [13] and RXR-α genes result in a similar phenotype.

Progeria [14]. Scalp and body hair is totally deficient in this exceedingly rare syndrome, which is caused by mutation in the lamin A gene.

Hidrotic ectodermal dysplasia [15]. Total or almost total alopecia is associated with palmoplantar keratoderma and thickened discolored nails. Any hairs that are present are structurally normal but are often finer than the average. Mutations in the *GJB6* gene encoding the gap junction protein connexin 30 have been shown to cause this disorder.

Moynahan's syndrome [16]. This autosomal recessive syndrome, reported in male siblings, is associated with mental retardation, epilepsy and total baldness of the scalp; the hair may regrow in childhood between 2 and 4 years of age.

Baraitser's syndrome [17]. This autosomal recessive syndrome presents as almost total alopecia following the loss of some downy scalp hair present at birth.

Three cases are reported in an inbred family [9]; all had almost total alopecia of all sites, including eyebrows and lashes. There were occasional isolated hairs. Mental and physical retardation were associated.

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Hypotrichosis [1,2]

Aetiology and pathology. Congenital hypotrichosis of sufficient degree to cause social embarrassment is not uncommon, and is probably determined by an autosomal dominant gene. There are a number of distinct syndromes, but the two most common are hypotrichosis simplex [3] and hereditary hypotrichosis simplex of the scalp [4]. Both conditions are autosomal dominant.

Hypotrichosis simplex maps to 18p11.32-p11.23 [5] and is characterized by reduced hair growth on the scalp and body, although eyelashes, eyebrows and male beards are normal. In contrast, hypotrichosis simplex of the scalp only [6] is associated with mutations in the *CDSN* gene located on 6p21.3. *CDSN* encodes a protein called corneodesmosin that is exclusively expressed in cornified squamous epithelia.

Hypotrichosis is also a relatively common feature of many hereditary syndromes, usually in association with other ectodermal defects. In the majority, the hair is not only sparse but is structurally abnormal. Where hypotrichosis is the most prominent manifestation and the structural defect is distinctive and well characterized, it has given its name to the syndrome, as in monilethrix and pili torti. In other syndromes, the scanty scalp hair is a minor and sometimes inconstant manifestation, and the shaft defect is usually less specific, although often gross. The follicles are sparse and are reduced in size, and the hair shafts are brittle and deficient in pigment. The nature of the disturbance in keratinization is not known.

Clinical features [7]. When hypotrichosis occurs as an isolated abnormality, the scalp hair at birth is normal in quantity and quality, but is shed during the first 6 months and never adequately replaced. It is sparse, fine, dry and brittle, and seldom exceeds 10 cm in length. The eyebrows, eyelashes and vellus may be absent, sparse or normal. In exceptional cases, improvement or recovery has taken place at puberty, but the condition is usually permanent.

In some families, the hair is normal until the age of 5 years or later, when growth becomes retarded and the scalp is progressively denuded so that baldness is almost total by the age of 25 years [4].

There are many hereditary syndromes of which hypotrichosis is a constant or frequent feature. In the majority, the hair is not only sparse but fine and brittle, and is often hypopigmented. The hair shafts are often defective, but may show no consistent well-characterized structural abnormality. As the hypotrichosis is not the most prominent feature of these syndromes, they are described more fully in other chapters.

There are also other syndromes, as yet incompletely investigated, in which hypotrichosis is associated with other defects.

Hypohidrotic ectodermal dysplasia [8]. Affected males show hypotrichosis, abnormal teeth and absent sweat glands. The hair is fine and silky but thin and short. Both X-linked and autosomal dominant forms exist, with the X-linked condition being caused by mutations in the ectodysplasin gene and the autosomal dominant form because of mutations in the downless gene that encodes a member of the TNF receptor superfamily, which is an ectodysplasin receptor. Mutations in either the ectodysplasin gene or its receptor disrupt ectodysplasin-mediated cell–cell signalling, which regulates the morphogenesis of ectodermal appendages.

Hypotrichosis resulting from short anagen [9]. This autosomal dominant condition is characterized by hair that is fine and short from birth. While the growth rate is normal, shortening of the duration of the anagen phase limits hair length to a few centimetres.

Hypotrichosis with keratosis pilaris [10]. The hair is apparently normal at birth, but after the birth coat has been shed, between the second and sixth months, it fails to grow satisfactorily and remains sparse, short, brittle and poorly pigmented. Eyebrows and eyelashes may be normal or sparse. Keratosis pilaris is present on the occipital region and neck, and sometimes on the trunk and limbs. Nails, teeth and general physical development are normal. The hairs show no beading or other distinctive abnormality.

Hypotrichosis with keratosis pilaris and lentiginosis [10]. Seven females in three generations in a family of three males and 13 females developed hypotrichosis at or just after puberty, which progressed until the menopause. Axillary and pubic hair was completely lost. There was keratosis pilaris of the scalp and axillae, brittleness and longitudinal striation of the nails, and centrofacial lentiginosis.

Eyelid cysts, hypodontia and hypotrichosis. See [11].

Hypomelia, hypotrichosis, facial haemangioma syndrome [12]. This 'pseudothalidomide' syndrome, which is probably determined by an autosomal recessive gene, associates gross reduction defects of the limbs, a mid-facial capillary naevus and sparse silver–blonde hair.

Hypotrichosis, Marie–Unna type [13–15]. In this rare but very distinctive syndrome the hair in affected individuals may be normal, sparse or absent at birth. If present, it remains fine and sparse until during the second or third year when it becomes coarse and twisted. The coarse wiry unruly hair may resemble a poor quality wig.

Unna described two patterns of alopecia. In the more severe form, the child's hair is always sparse and is progressively lost, so that alopecia is advanced by puberty. In the other, milder form, the hair is initially thick and the hair loss only commences in the second or third decade. At puberty, progressive loss begins over the parietal scalp bilaterally and progresses from anterior to posterior. Ultimately, the hair loss joins up centrally over the vertex to resemble Hamilton stage VIII androgenetic alopecia. There is usually also a subtle simultaneous loss from around the scalp margins.

The eyelashes, eyebrows and body hair are typically absent from birth, and after puberty any axillary or pubic hair that develops is also sparse. General physical and mental development is normal. Scanning electron microscopy shows that the hair shafts are coarse, irregularly twisted and fluted [13].

Although a distinct gene close to the hairless locus on chromosome 8p underlies hereditary Marie–Unna hypotrichosis, it has not yet been identified [16]. Other disorders clinically very similar to Marie–Unna hypotrichosis, but genetically distinct, are now recognized and indicate that more than one form of progressive patterned alopecia with wiry hair exists [17].

Hypotrichosis in disorders of amino acid metabolism. In many disorders with amino aciduria, the hair is hypopigmented and is often also fine, friable and sometimes sparse. Fine sparse hair has been reported in phenylketonuria, arginosuccinic aciduria and hyperlysinaemia.

A number of case reports associate hypotrichosis with a variety of ectodermal defects. Some such cases may represent partial forms of recognized syndromes but it is probable that many additional distinct syndromes remain to be identified and characterized.

Differential diagnosis. Microscopy of plucked hairs will exclude the more distinctive structural defects (pili torti, monilethrix and pili annulati). Other ectodermal defects should be carefully sought and relatives should be examined.

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Circumscribed alopecia of congenital origin [1,2]

The differential diagnosis of circumscribed alopecia of congenital origin presents little difficulty if a reliable history is available. Without it, alopecia areata and the acquired cicatricial alopecias must be considered.

The most common forms are naevoid. Epidermal naevi are usually devoid of hair and present as warty or smooth but slightly indurated plaques. A zone of non-cicatricial alopecia sometimes develops around melanocytic naevi.

Aplasia of all layers of the skin gives rise to a congenital defect, usually a circular or rectilinear area of scarring, somewhat depressed below the scalp surface and commonly on the vertex.

Irregular areas of cicatricial alopecia not preceded by clinically apparent inflammatory changes produce the syndrome known as pseudopelade. Pseudopelade may develop during early infancy in association with certain hereditary syndromes (e.g. incontinentia pigmenti and Conradi's syndrome).

Circumscribed non-cicatricial alopecia is uncommon. It is the result of hypoplasia or aplasia of a group of follicles. The scalp is clinically normal and histologically shows no change other than a reduced number of follicles. Any follicles present are usually small and of vellus rather than terminal type. The first hair coat is normal and the patches develop between the third and sixth months, although if they are small and not completely bald they may not be noticed by the parents until considerably later.

Several clinical forms occur [1,2]. In *vertical alopecia*, a small and often irregular patch of alopecia is present on the vertex at birth. It has been confused with aplasia cutis, but the skin is normal apart from the absence of appendages. In *sutural alopecia*, which is one component of the Hallermann–Streiff syndrome, multiple patches overlie the cranial sutures. *Triangular alopecia* [3–6] was first recognized by Sabouraud. In the usual form, a triangular area overlying the frontotemporal suture just inside the anterior hairline, and with its base directed forwards, is completely bald or covered by sparse vellus hairs. Rarely, similar triangular patches have occurred on the nape of the neck.

Single or multiple small patches of total alopecia or hypotrichosis may occasionally occur in other sites, but are often inconspicuous.

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Abnormalities of hair shaft

[D.A.R. de Berker, pp. 63.72–63.120]

Structural defects of the hair shaft may be sufficient in degree to cause significant cosmetic disability, or they may render the hair abnormally susceptible to injury by minor degrees of trauma (excessive weathering). Hair microscopy can be a useful part of clinical assessment in some situations [1], including a range of hereditary or acquired metabolic disorders, where the hair shaft can sometimes provide clues to the diagnosis [2].

Price [3] classified anomalies of the shaft into those that are associated with increased fragility, and those that are not. This distinction is useful because only the former present clinically as patchy or diffuse alopecia. Price's classification will be followed throughout the present section. Whiting [4] and Rogers [5] have reviewed the structural abnormalities.

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Fig. 63.54 Monilethrix with the swollen (node) and narrow (internode) fluctuations in hair bore.

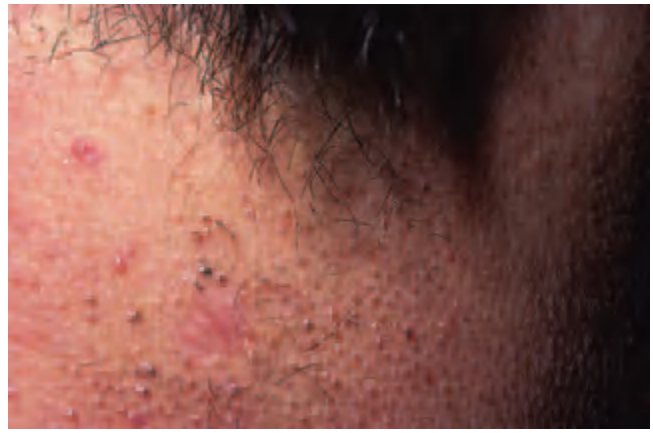

Fig. 63.55 Monilethrix. Nape of the neck showing follicular keratoses and short broken hairs.

Structural defects with increased fragility

Monilethrix (beading of hair)

Smith [1] initially called this condition 'a rare nodose condition of the hair'. Radcliffe Crocker subsequently suggested the term monilethrix. Nevertheless, some early reports, and even some more recent ones, confuse monilethrix with other shaft defects (e.g. trichorrhexis nodosa) when 'weathering' is severe.

Aetiology. Autosomal dominant transmission has been demonstrated in numerous large pedigrees [2–4]. The alleged occurrence of normal carriers of the dominant gene has not been proven, as a parent with only 5% of abnormal follicles is easily passed as normal [5]. Several pedigrees have suggested an autosomal recessive trait [6], but this is probably a result of the difficulty in making the diagnosis in a parent where the manifestations are subtle. Monilethrix can be a heterogeneous condition [7]. The abnormality is attributable to mutations in the genes coding for the human hair keratins hHb1 and hHb6. There is no clear correlation between the severity of the phenotype and the mutation responsible [8].

Pathology. The hair shaft is beaded and breaks easily (Fig. 63.54). Elliptical nodes 0.7–1 mm apart, are separated by narrower internodes with a form resembling the body and neck of a skittle. The widths of the nodes and the distances between them vary between the hairs of an individual and between members of the same family. The nodes and some of the internodes show a normal imbricated scale pattern, but most internodes show longitudinal ridging [9,10].

Histologically, the follicle shows wide and narrow zones corresponding to the nodes and internodes [11], but the general structure of the follicle is otherwise normal. Salamon and Schneyder [3] and Gummer *et al.* [12] noted that changes were visible in the zone of keratinization; the cell membranes of the deeper hair shaft cuticular cells are thrown into folds, particularly at the narrower internodes where breakage occurs.

Attempts have been made to investigate the mechanism of node formation and to relate it to the diurnal rate of hair growth. Klingmuller [13] claimed to have found a 48-h cycle in two patients. Baker [14] studied four cases in which he found that a complete nodal complex was formed in 24 h. Comaish [9] found no daily rhythm and no simple time cycle. Lubach and Traintos [15] showed no regular rhythm of node formation.

Intermittent administration of an antimitotic agent can give rise to zones of constriction alternating with zones of normal diameter [16].

Studies with the electron microscope [17] have shown that increased susceptibility of the hair shaft to the effects of trauma—premature weathering—is an important factor in the failure of the hair to attain a normal length.

Clinical features. Monilethrix shows considerable variation in age of onset, severity and course [18].

The hair may be obviously abnormal at birth but is most commonly normal, and is progressively replaced by abnormal hair during the first months of life; in other cases, normal hair is succeeded by horny follicular papules from the summit of which emerge fragile beaded hairs. The follicular keratoses and the abnormal hairs are most frequent on the nape and occiput but may involve the entire scalp. In a typical case, the short stubble of brittle hairs and rough horny plugs give a distinctive appearance (Fig. 63.55). In some cases, the eyebrows and eyelashes, pubic and axillary hair and general body hair may be affected.

In many patients, the condition persists with little change throughout life [4]. Spontaneous improvement or complete recovery has occurred [1] and has been reported during pregnancy [19]. Griseofulvin also has temporarily restored normal hair growth [20].

Associated defects. Some investigators thought the association with oligophrenia and with nail and tooth defects was significant [3]. It has been proposed that such associations may be a feature of the recessive phenotype, as oligophrenia and poor physical development were noted also in two siblings with monilethrix [21]. Association with juvenile cataract has been reported [22].

Reports of abnormalities of amino acid metabolism are conflicting. Argininosuccinic aciduria has been reported [23], but a technical error was subsequently detected [24]. No abnormality in the urinary amino acid pattern was found in the autosomal dominant type [19] or in an isolated case [25]. An apparent excess of aspartic acid and arginine in the urine of an affected mother and daughter was described by Marques Llagaria *et al.* [26].

Treatment. None is available, but Tamayo [27] has suggested that oral retinoids can induce some hair regrowth. This may result from a therapeutic effect on the keratosis pilaris, which lessens in combination with a reduction of shaft beading and modest increase in overall hair length [28]. Although improvement has been attributed to the hormone changes of menarche in one report [29], male and female cases may both improve at puberty. Iron supplementation has been reported to be of value in the presence of iron deficiency [30]. Reduction of hairdressing trauma may be followed by some improvement, by lessening the 'weathering' from chemical and physical insults.

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Pseudomonilethrix

It is not uncommon to see patients who complain that their hair is of poor quality or brittle. Microscopy of the hair to exclude the classical shaft defects is a routine procedure. Bentley-Phillips and Bayles [1] described a condition which they termed 'pseudomonilethrix' in South Africans of European or Indian descent. The status of the diagnosis is uncertain; some of the shaft deformities may be artefactual.

The patients present with alopecia starting in childhood. The family history suggests inheritance is determined by an autosomal dominant gene. The defect renders the hair so fragile that it readily breaks with the trauma of brushing, combing or other hairdressing procedures.

On microscopy, one, or occasionally two, of three abnormalities can be seen:

1 Pseudomonilethrix—irregular nodes, which on electron microscopy prove to be the protruding edges of depressions in the shaft

2 Irregular twists of 25–200° without flattening of the shaft

3 Breaks with brush-like ends in an apparently normal shaft.

There is no keratosis pilaris. Most authorities now believe that pseudomonilethrix microscopic changes are

Fig. 63.56 Hair lacquer can cause fusiform bulges along the hair shaft.

artefactual. They can be produced in normal hairs by trauma from tweezers or forceps, or compressing overlapping hairs between two glass slides; the indentation in one shaft caused by another overlying hair exactly mimics the appearance of pseudomonilethrix [2]. Hair lacquer and gel can also cause beading visible under the light microscope (Fig. 63.56) [3].

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Pili torti (twisting of hair)

The first definite description of pili torti was given by Schutz [1], although earlier authors had referred to the condition. Ormsby and Mitchell [2] twice presented the same patient to the Chicago Dermatological Society; on the first occasion the diagnosis was 'atrophia pilorum'; monilethrix. In discussion, attention was drawn to the fact that the hairs were twisted and not beaded. Galewsky [3] suggested the term 'pili torti', which was also adopted by Ronchese [4] in the USA.

In pili torti, the hairs are flattened and at irregular intervals completely rotated through 180° around their long axis (Fig. 63.57). True pili torti of Menkes' syndrome and the isolated expression of the abnormality in an otherwise unaffected person, demonstrate the same distinct twisting (Figs 63.58 & 63.59). Scanning electron microscopy has made it clear that twisted hairs occur in many distinct forms, and that the twisting may be associated with a number of other shaft defects. Occasional twists of varying angle should not be taken to be this distinctive genetically 'fixed' abnormality of pili torti—many dystrophies and distortions of the follicular zone of keratinization will vary the hair shaft 'bore', sometimes showing less than 180° irregular twists.

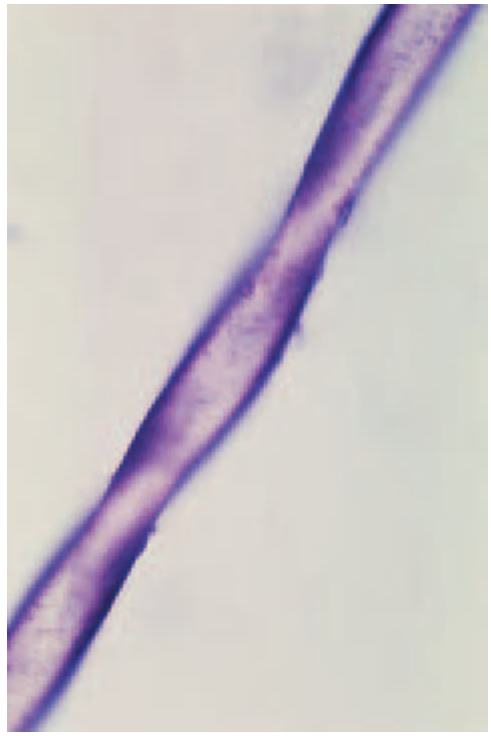

Fig. 63.57 Pili torti. Light micrograph showing 180° twists.

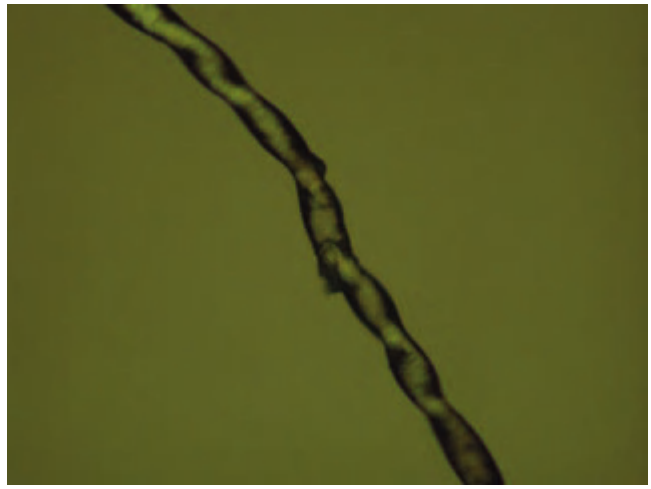

Fig. 63.58 Pili torti in a 6-month-old boy with Menkes' disease.

Syndromes in which twisted hair is a feature

Menkes' syndrome. Light-coloured twisted hair is a manifestation of a hereditary defect of intestinal copper transport; the inheritance is of sex-linked recessive type. Accumulation of copper in the neonatal period leads to brain damage, mental retardation and fitting. The latter

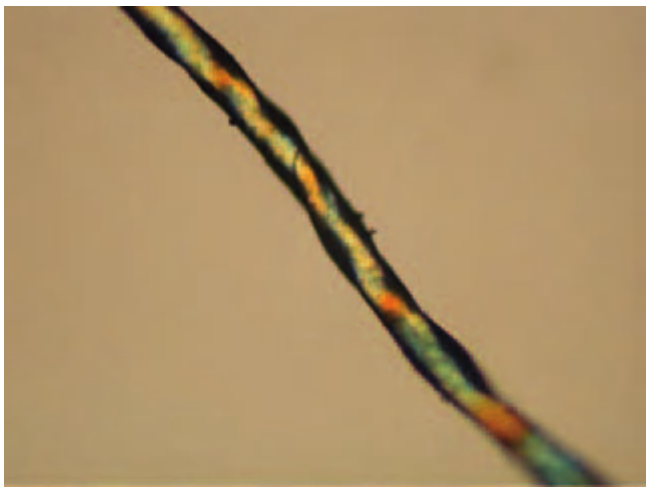

Fig. 63.59 Pili torti in a 27-year-old woman with no personal or family history of associated disorders.

may be the presenting complaint, with the diagnosis made later on hair microscopy. The twisting of the hair microscopically is generally exactly the same as in pili torti [5,6]. The disorder is caused by a mutation in the gene encoding Cu^{2+} transporting ATPase, α-polypeptide. The occipital horn syndrome is caused by mutation in the same gene.

Björnstad's syndrome (see below). Twisted hair with sensorineural deafness; probable autosomal dominant inheritance.

Crandall's syndrome. Twisted hair and deafness are associated with hypogonadism; probable sex-linked recessive inheritance. This may be a variant of Björnstad's syndrome.

Bazex syndrome. Twisted hair, with basal carcinomas of the face and follicular atrophoderma. Although this condition has come to be associated with the term pili torti, it illustrates how features of hair microscopy can be termed with low precision. The hair changes are probably more a form of irregular twisting than the tight distinctive changes seen with pili torti [7]. Vabres *et al.* [8] found evidence for X-linkage and regional assignment to Xq24–q27.

Hypohidrotic ectodermal dysplasia. Twisted hairs associated with characteristic facies and dental defects. The hairs are twisted irregularly and are not true pili torti.

Pseudomonilethrix. Twisted hair is associated, in the individual or the family, with apparently beaded hairs of autosomal dominant inheritance. However, the twists are irregular and the beads may be part of trauma sustained by the hair when plucked.

When patients with these syndromes are excluded, only pili torti remains, but there is evidence that it does not constitute a homogeneous entity: the hairs show considerable variation from patient to patient in their ability to withstand breaking and pulling; the hairs in some patients weather badly, but in others they do not [9].

Pollitt *et al.* [10] reported siblings with mental retardation, pili torti and trichorrhexis nodosa; their hair keratin was deficient in cysteine. However, dystrophic pili torti may occur with a normal cysteine content [11]. Reduction in cysteine implies the diagnosis of trichothiodystrophy, where the hairs are flattened and single twists are common—again illustrating the care needed to make a precise morphological diagnosis of pili torti rather than referring to isolated or heterogeneous twists by this term.

Aetiology. In those cases in which classic pili torti of early onset appears to have occurred as an isolated defect, inheritance has usually been determined by an autosomal dominant gene [12]. There are many reports of apparently sporadic cases [13]. However, there are also cases in which the siblings of consanguineous parents have been affected and in which recessive inheritance must be suspected [14].

Local inflammatory processes that distort the follicles can result in distorted and twisted hairs, such as may be found around the edges of patches of cicatricial alopecia [15]. Acquired pili torti-type changes may be produced by retinoids [16], but the hair is more 'kinked' than twisted. Non-scarring acquired pili torti has also been recorded in anorexia nervosa [17].

Pathology. The earlier reports emphasized that the affected hairs were flattened and twisted through 180° around their long axis at irregular intervals along the shaft. The load-extension curve (breaking stress analysis) resembles that of the wool of merino sheep; the hairs breaking more easily than normal. Histologically, the only abnormality is some curvature of the hair follicles. With the scanning electron microscope, the cuticle of the hair shaft appears normal [18], although severe weathering changes are not uncommon.

Clinical features. The hair is usually normal at birth, but is gradually replaced by abnormal hair, which becomes clinically evident as early as the third month, or not until the second or third year. There is a wide variation from case to case in the fragility of the hair, and hence in the clinical picture. Affected hairs are brittle and may break off at a length of 5 cm or less, or grow longer in areas of the scalp less subject to trauma. There may therefore be only a short coarse stubble over the whole scalp or there may be circumscribed baldness, irregularly patchy or occipital. Affected hairs have a spangled appearance in reflected light. The cosmetic appearance of isolated pili torti can improve greatly with transition from childhood to early adulthood [19].

The diagnosis should be suspected if the hair is brittle and dry. The typical spangled appearance in reflected light is present only if the hair is at least moderately severely affected, yet is not so brittle that it breaks to leave only a sparse stubble. Microscopic examination of several hairs must be made to confirm the diagnosis.

Other ectodermal defects may be associated with pili torti. Keratosis pilaris is the most recently reported, but nail dystrophies, dental abnormalities, corneal opacities and mental retardation have all been described [20]. The syndrome described as corkscrew hair [21] is microscopically separate, with an intrinsic spiral both in the axis of the hair and around the axis.

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Björnstad's syndrome [1,2]

SYN. CRANDALL'S SYNDROME

In this syndrome, pili torti is associated with sensorineural hearing loss. The loss of hair usually begins in infancy but in one case it was not noticed until the age of 8 years [3]. There is a correlation between the severity of the hair defect and the degree of hearing loss. On microscopy, the hair shafts show longitudinal ridging and irregular twisting. Pedigrees have suggested both dominant and recessive inheritance [4,5]. The disease gene maps to chromosome 2q34–q36 [5].

Two brothers were investigated after they had reached puberty and were found to have secondary hypogonadism [6] with deficiency of luteinizing and of growth hormones.

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Netherton's syndrome (bamboo hair) [1–4]

Netherton [5] observed bamboo-like nodes in the fragile hairs of a girl with 'erythematous scaly dermatitis'. It has gradually become apparent that ichthyosis linearis circumflexa (ILC) and 'bamboo hairs' (trichorrhexis invaginata) (Fig. 63.60) are two features of a single syndrome [6]. Most cases of Netherton's syndrome have had ILC but some have ichthyosis vulgaris [7] or both conditions, or ichthyosiform erythroderma. Features of ILC may be seen in variants of psoriasis. It is controversial as to whether it occurs as an isolated disease in the absence of Netherton's

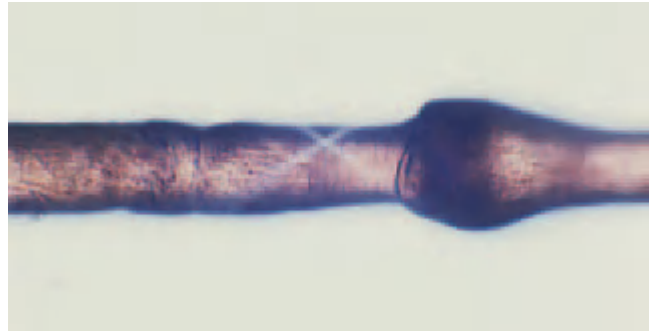

Fig. 63.60 Light microscopy revealing a trichorrhexis invaginata node likened to bamboo.

syndrome, or whether it is the fluctuating prevalence of the hair shaft changes that leads to difficulty in detecting both characteristics at the same time in some patients.

ILC is thus an almost constant feature of the syndrome, with hair shaft defects of various types and degrees of severity. Some authorities [8] question the variability of the syndrome.

The inheritance of Netherton's syndrome appears to be determined by an autosomal recessive gene of variable expressivity. Girls are affected more than boys. The underlying defect has been localized to a gene on chromosome 5q32, known as SPINK5, an acronym for serum protease inhibitor. The gene product is termed LEKTI (lympho-epithelial kazal-type-related inhibitor), as the gene is expressed in several lympho-epithelial tissues [9,10]. The protein has antitrypsin activities, but the mechanistic significance of this is not clear [11]. Examination of the SPINK5 gene in 13 families revealed 11 mutations, nine of which were associated with RNA instability. This is consistent with the low levels of SPINK5 gene product in those with the disease, where relevant RNA has decayed [12]. Immunohistochemical techniques are under development to allow tissue diagnosis of Netherton's syndrome on the basis of absence of LEKTI immunostaining. Identification of the gene has allowed prenatal diagnosis [13].

Pathology. As Netherton's syndrome results in fragile hair, samples should be cut at the scalp surface thus reducing the chances that the hair will break at the point of diagnostic interest, making diagnosis more difficult. Light microscopy is the best tool for detecting features of Netherton's syndrome in hair. However, an individual may have multiple hairs with characteristic changes in one sample and then no features in another sample taken some months later. Because of this it is important that samples of at least 100 hairs are carefully examined on several occasions before a definite negative is asserted. Alternatively, finding a single trichorrhexis invaginata node in a single hair is a conclusive positive (Figs 63.61 & 63.62).

To assess such large numbers of hairs it is necessary to use the light microscope, as electron microscopy will only allow assessment of small lengths of a small number of hairs. Detail of the surface features is enhanced using partially crossed polarizing filters, and the cortical anatomy of the hair is revealed if the hair is prepared on a slide in histological mounting medium. Scanning electron microscopy of the hair shafts shows focal defects that produce the development of torsion nodules, invaginated nodules (trichorrhexis invaginata) and trichorrhexis nodosa [14,15].

Where diagnosis is difficult, sampling the eyebrows may provide confirmation [16]. The proximal remnant of an invaginate node may resemble a golf tee and can allow diagnosis where classic nodes are absent [4].

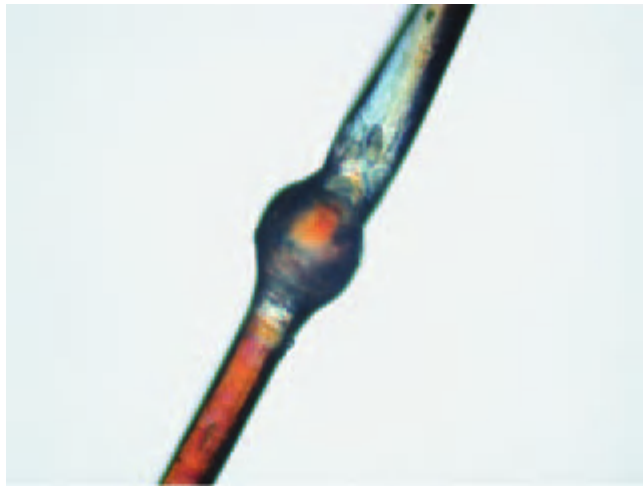

Fig. 63.61 Netherton's syndrome with an invaginate node showing partial twisting of the hair at the upper pole.

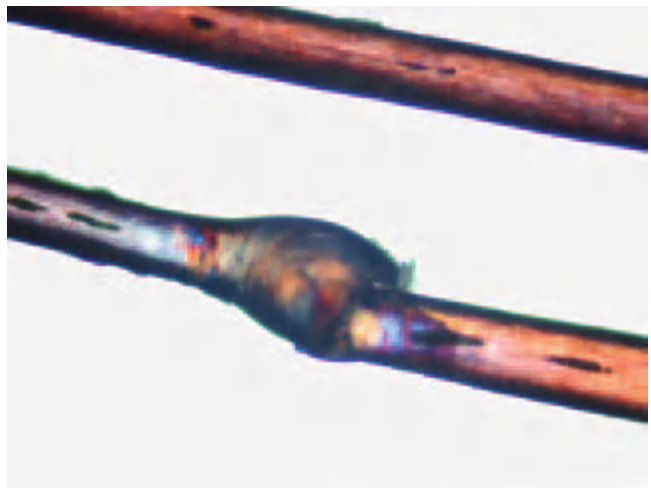

Fig. 63.62 Netherton's syndrome with the invaginate node acting as a point of weakness in the hair shaft.

Clinical features [17]. The patient may present primarily either with cutaneous changes or complaining of sparse and fragile hairs. Generalized scaling and erythema are present from birth or early infancy, but the degree, extent and persistence of the erythema are very variable. In some cases, the erythema may be slight and transient. In many it has the characteristics of atopic eczema accompanied by an elevated IgE. On the trunk and limbs, the fine dry scales are associated with a polycyclic and serpiginous eruption whose horny margin slowly changes its pattern.

The hair defects may be detected only if deliberately sought, but in most cases are readily apparent clinically [17]. The hair is short, dry, lustreless and brittle, and the eyebrows and lashes are sparse or absent. Jones *et al.* [18] described two cases in which neonatal hypernatraemia occurred. The severity of the phenotype does not show strict correlation with the mutation, and members of the

same kindred may share a mutation but have different degrees of disease [19].

Treatment. There is no specific effective skin treatment. Copious emollient use is standard. In spite of features shared with atopic eczema, there is a disappointing response of the skin to topical steroid, and persistence with this therapy can lead to systemic side effects. Topical tacrolimus 0.1% ointment has been used. Although the therapeutic response was reasonable, monitoring of blood levels revealed them to be at or above levels considered safe in organ transplant patients [20]. This raises the question as to whether it would represent a useful systemic therapy. Nagata [21] described some response to photochemotherapy. Oral retinoids, even at low dosage [17], do not produce significant benefit and can result in deterioration. Hair management entails avoiding chemical and physical trauma.

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Trichorrhexis nodosa

Trichorrhexis is best regarded as a distinctive response of the hair shaft to injury [1]. If the degree or frequency of the injury is sufficient, it can be induced in normal hair [2], and this is probably the most common scenario. The cuticular cells become disrupted, allowing the cortical cells to splay out to form nodes [3]. If, however, the hair is abnormally fragile, trichorrhexis may follow relatively trivial injury. The trauma of hairdressing procedures has often been incriminated [4]. Scratching may produce identical changes in pubic hairs [4]; and the severity of experimentally induced trichorrhexis nodosa is related to the degree of trauma in patients with or without pre-existing trichorrhexis. The cumulative effect of shampooing, brushing, sea bathing and sunlight has led to seasonal summer recurrences [5].

Congenital and hereditary defects of the hair shaft resulting in fragility can predispose to trichorrhexis nodosa.

Trichorrhexis nodosa is a feature of the rare metabolic defect argininosuccinic aciduria, in which it is associated with mental retardation [6]; there is a deficiency of the enzyme argininosuccinase. Some 20 patients have been reported [7,8]. The hair tends to be dry, brittle and lustreless and may show trichorrhexis nodosa, but it does not occur in all patients with this metabolic disorder.

Trichorrhexis nodosa may occur in certain families as an apparently isolated defect of the hair; node formation and fracture are induced by minimal trauma and develop during the early months of life. Wolff *et al.* [9] described as 'trichorrhexis congenita' the presence from birth of trichorrhexis nodosa confined to the scalp, with normal teeth and nails.

In a case of generalized trichorrhexis nodosa in a male adult [10], electron histochemical study showed evidence of a disorder in the formation of α-keratin chains within the globular matrix of the hair cortex with respect to cysteine.

Pathology. In simple trichorrhexis nodosa, the shaft may appear normal with the light or electron microscope, except at the nodes; or the shaft, apart from the proximal 1 cm, may show signs of abnormal wear and tear [3]. At the nodes, the cuticle bulges and is split by longitudinal fissures (Fig. 63.63). If fracture occurs transversely through a node (trichoclasis), the end of the hair resembles a small paintbrush.

Clinical features. In trichorrhexis nodosa complicating a congenital defect of the hair shaft, the hair breaks so easily

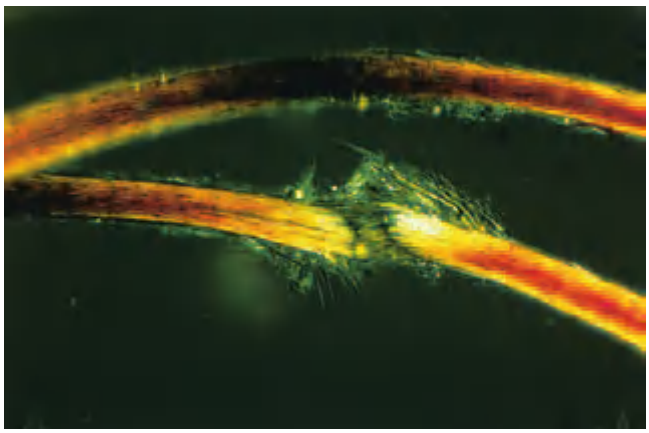

Fig. 63.63 Trichorrhexis nodosa. Polarized light examination demonstrates the splayed cortical fibres radiating from the transverse fracture in a trichorrhexis node.

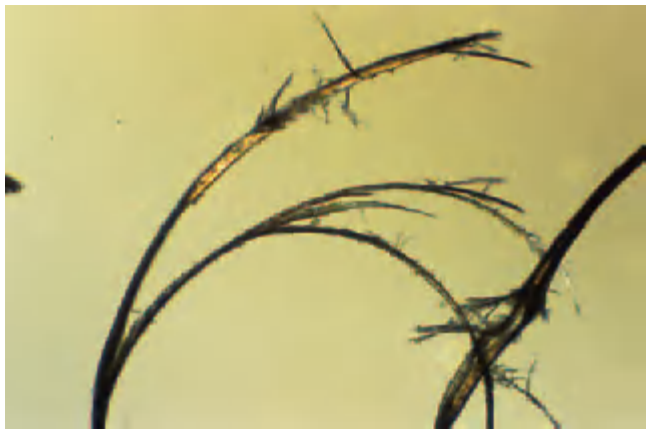

Fig. 63.64 Proximal trichorrhexis nodes and dramatic split ends (trichoptilosis) are visible in hair from an Afro-Caribbean woman.

that large or small portions of the scalp show only broken stumps and alopecia may be gross. However, the common situation is where trauma plays a major part and predisposition has a relatively minor role. In this setting there are three principal clinical presentations [11].

1 Distal trichorrhexis nodosa occurs in all races. Often it is discovered incidentally, and only a few whitish nodules are seen near the ends of scattered hairs. If many hairs are affected, the patient may complain that the hair is dry, dull or brittle. The longer the hair, the more likely it is to occur.

2 There is a generalized variant seen in Afro-Caribbean women called proximal trichorrhexis nodosa. The scalp hair is universally short and brittle and demonstrates severe weathering on light microscopic examination (Fig. 63.64). There may be an association with the follicular degeneration syndrome where there is a central scarring alopecia in the absence of an overt inflammatory process [12].

3 The third clinical form was well described by Sabouraud [13] but it appears now to be rare. In a localized area of scalp, moustache or beard, some hairs are broken and others show from one to five or six nodules [14].

Diagnosis. The congenital forms must be differentiated from other shaft defects. The distal acquired form may simulate dandruff or even pediculosis. In all cases, diagnosis depends on careful microscopy. Excessive physical and chemical (cosmetic) trauma must be avoided, apart from shampooing.

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Trichothiodystrophy

The term trichothiodystrophy (TTD) was coined [1,2] to describe brittle hair with an abnormally low sulphur content [3]. The term covers a range of phenotypes, with low sulphur fragile hair representing the central defining criterion [4–10]. TTD can be classified according to the constellation of features that accompany the hair changes [4].

Using current criteria, approximately 50% of those with TTD are photosensitive. In this group, there is phenotypic and genetic crossover with xeroderma pigmentosum (XP). Of the different complementation groups within XP, most of the photosensitive TTDs share features with XP complementation group D, some with XP complementation group B and a small group represent an isolated photosensitive category, termed TTD-A. The common genetic defect in XPD and photosensitive TTD is within the ERCC2 (excision repair cross-complementation 2) gene on chromosome 19q as defined by *in vitro* complementation studies. Mutations of the ERCC3 gene on chromosome 2q

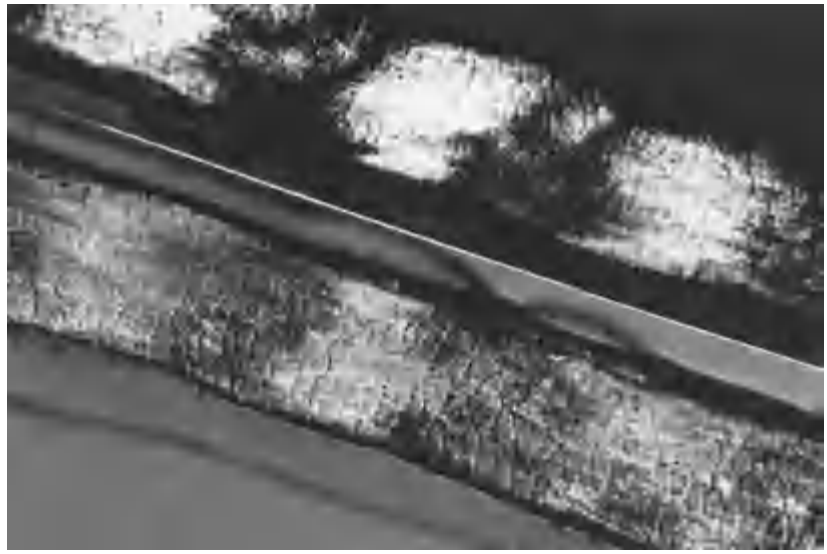

Fig. 63.65 Trichothiodystrophy. Alternating bright and dark zones in the polarizing microscope. (Courtesy of D. Van Neste, Brussels.)

have a corresponding role in XPB. These genes code for a transcription factor TFIIH, which has a dual function. First it acts as a helicase, which unravels the double helix of segments of photodamaged DNA as part of nucleotide excision and repair (NER). Secondly, it acts to enable transcription of segments of DNA to produce RNA and gene expression. A range of mutations in this gene can lead to changes in function of TFIIH. Where defects in NER occur, there is cumulative photodamage to the DNA, which is clinically expressed as photoageing and dysplasia. In XP, this ultimately predisposes to skin cancer, but not in TTD. Equally, the genetic basis for TTD can result in neuroectodermal changes that are not part of XP. A further mystery is that the genetic defect in Cockayne's syndrome arises within the same gene and affects the same transcription factor, but results in a different phenotype [5].

Currently, the genetic basis of the non-photosensitive forms of TTD has not been established.

Pathology. The hair is brittle and weathers badly [6]. With trauma it may fracture with a clean transverse break (trichoschisis) or may form nodes somewhat resembling trichorrhexis nodosa but without conspicuous release of individual spindle cells [1,2]. The hairs are flattened and can be twisted into various appearances—rather like a ribbon or shoe lace. Details of these changes are clarified by scanning electron microscopy. The shaft is irregular, with ridging and fluting, and the cuticular scales are patchily absent. Using crossed polarizing filters with a light microscope the hairs show alternating bright and dark zones (Fig. 63.65). This feature alone is not diagnostic of TTD and may occur in a range of genetic and acquired disorders where the longitudinal organization of cortical fibres within the hair is thrown into a sine wave pattern through loss of rigidity. As a sign, it may arise at different stages in infancy. In one instance it has been used prognostically when identified in a fetal eyebrow biopsy obtained *in utero* [7]. Other cases illustrate that the sign may fail to develop until a few months of age [8].

Using transmission electron microscopy, Gummer and Dawber [9] showed a decrease in high-sulphur protein staining in the hair shaft and a reduction of this protein in the exocuticular part of the cuticle cells. Gillespie and Marshall [10] demonstrated a quantitative reduction in high sulphur proteins in the hair shaft. A large proportion of these are termed keratin-associated proteins (KAPs), of which there are at least 11 classes. KAPs 1–5 are highest in cysteine and are the likely targets of a condition where this amino acid is deficient.

Clinical features. There is a wide range of phenotypic characteristics, depending on the variant of TTD (Table 63.5). The hair is sparse, short and brittle, but the degree of alopecia varies considerably. There may be lamellar ichthyosis. The nails may be dystrophic. Mental and physical development may be normal but one or both may be slightly, moderately or severely retarded. The central feature of altered hair remains the basis of diagnosis, but the mechanism linking the associated features requires further elucidation.

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Table 63.5 Classification of trichothiodystrophy.

Type	Findings	Eponym/acronym
A	Hair +/– nails	
B	Hair +/– nails + mental retardation	Sabinas
C	Hair +/– nails + mental retardation, folliculitis, retarded bone age +/– caries	Pollitt
D	Brittle hair +/– nails, infertility, developmental delay, short stature	BIDS
E	Ichthyosis, BIDS. Hair +/– nails, mental retardation, short stature +/– decreased gonadal function +/– lenticular opacities/cataracts + failure to thrive/'progeria' + microcephaly +/– ataxia +/– calcifications of the basal ganglia + erythroderma and scale	Tay and IBIDS
F	Photosensitivity and IBIDS	PIBIDS
G	TTD with immune defects. Hair +/– mental retardation + chronic neutropenia or immunoglobulin deficiency	Itin
H	Trichothiodystrophy with severe intrauterine growth retardation and failure to thrive, developmental delay, recurrent infections, cataracts, hepatic angioendotheliomas	

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Marinesco–Sjögren syndrome

This rare syndrome, of autosomal recessive inheritance, has as its principal features cerebellar ataxia, dysarthria, retarded physical and mental development, and congenital cataracts [1]. The teeth are abnormally formed and the lateral incisors may be absent. The nails are flat, thin and fragile.

The hair is sparse, fine, light in colour, short and brittle. On microscopy, transverse fractures (trichoschisis) can be seen at the sites of impending breaks. In polarized light the hair is irregularly birefringent. Scalp biopsy shows normal anagen follicles, but with incomplete keratinization of the internal root sheath [2]. The combination of neurological and physical retardation with fragile hair is reminiscent of non-photosensitive trichothiodystrophy, although there are no skin changes in Marinesco–Sjögren syndrome.

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Structural defects without increased fragility

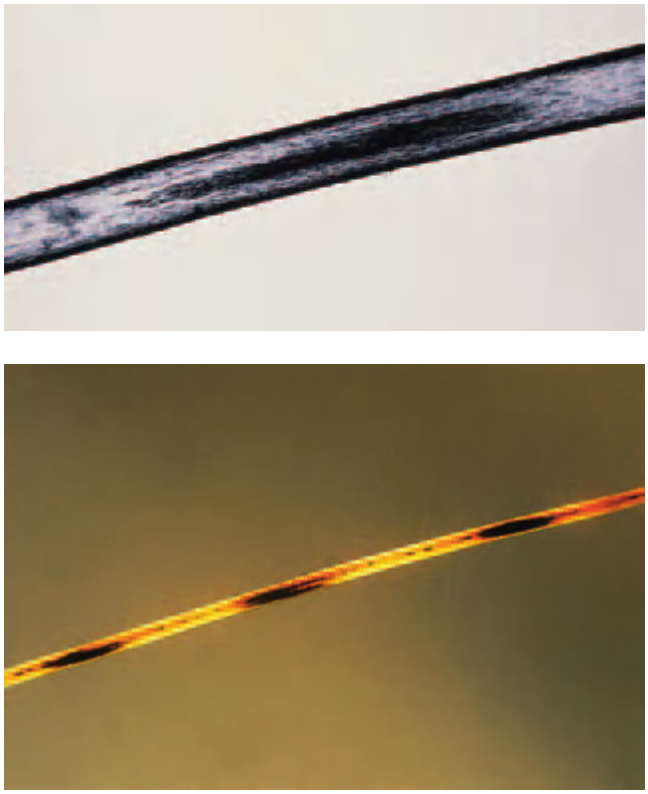
Pili annulati (ringed hair) [1,2]

Aetiology. This abnormality is characterized by hair showing alternate light and dark bands along its length, but which is otherwise normal. The inheritance of ringed hair has been shown in many extensive pedigrees to be determined by an autosomal dominant gene [3,4]. One pedigree was compatible with autosomal recessive inheritance [5]; sporadic cases have been described [6]. Blue naevus and ringed hair were associated in some members of a family, but the two conditions segregated [3].

Pathology and pathogenesis [7]. With the light microscope the abnormal dark bands alternating with normal light bands are reversed. The bright appearance of the abnormal bands in reflected light is caused by air spaces in the cortex (Fig. 63.66) [8]. Detection of the cortical defect is made easier if the hair is mounted in histological mounting medium because this enhances transmission of light through the hair.

The rate of growth has been measured in one case [3] and found to be 0.16 mm/day, which is less than half the average normal rate, but in our experience this is not a consistent finding. Breaking stress analysis showed no significant abnormality in ringed hair, but fractures were always in the normal bands. More recent studies have revealed protrusion of cortical fibres through the cuticle where there are cortical defects. Although this illustrates that the pathology can result in structural weakness, it only rarely leads to a clinical complaint of fragility [9].

Electron microscopic studies [10] showed that the clusters of air-filled cavities, randomly distributed throughout the cortex in the abnormal bands, lie partly within cortical cells and between macrofibrils, or in the case of larger cavities appear to replace cortical cells. Hairs from the family described by Dawber [3] showed an abnormal surface cuticle, which appeared 'cobble-stoned' on scanning electron microscopy. Electron histochemical methods confirmed this finding: cuticle cells are thrown into folds [11]. The pathogenesis of ringed hair remains uncertain. The abnormal alternating bands appear to be produced at random and not cyclically in relation to specific periods of growth [3].



(a)

(b)

Fig. 63.66 (a) Pili annulati. Hair shaft by transmitted light showing an abnormal dark band (central part) caused by multiple cortical air spaces. This corresponds to a bright region as seen by reflected light. (b) The abnormality is intermittent, causing the beaded or ringed appearance.

Clinical features. Pili annulati is normally diagnosed as a coincidental finding or as part of pursuance of the unusual, but quite attractive, spangled appearance. The condition has been reported in association with alopecia areata on several occasions. It is uncertain whether this represents a genuine association or if medical scrutiny reveals the otherwise subtle diagnosis [12]. If many hairs are affected and fragility is great, then short hair may attract attention in early life and the 'banded' and sandy appearance of the shafts in reflected light can be readily detected. The axillary hair is occasionally affected [13].

The diagnosis is readily established on microscopy of affected hair. A defect in which partially twisted shafts have an elliptical cross-section has been named pseudo-pili annulati because such hair may give an impression of alternating light and dark bands [14].

Prognosis and treatment. The prognosis is good in the sense that severity of the defect does not increase with age.

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Woolly hair

History and nomenclature. Woolly hair is more or less tightly coiled hair occurring over the entire scalp or part of it. In those of African origin, woolly hair is the norm and is dominantly inherited. Tight coiling, knots and fractures are common [1]. The investigation by Hutchinson *et al*. [2] was important in delineating the clinical types.

The types may be classified as follows:

1 *Dominant woolly hair*. Some families have woolly hair inherited as an autosomal dominant trait.

2 *Recessive woolly hair*. Early genetic evidence is inconclusive but the condition has occurred in siblings whose parents were normal. Autosomal recessive inheritance is probable. Kindreds manifesting woolly hair as part of two different syndromes with heart disease have demonstrated an autosomal recessive inheritance [3].

3 *Acquired woolly hair*. This is usually circumscribed, occurs from adolescence onwards, and is also termed acquired progressive kinking of hair.

4 *Woolly hair naevus*. This is a circumscribed developmental defect, present at or near birth.

In a further uncommon variant, there are woolly hairs interspersed with otherwise normal hair [4].

Hair microscopy in all the woolly hair disorders reveals non-specific features that are consistent with a woolly, stiff hair phenotype. This usually arises in association with grooves, partial twists, irregularity of bore and sometimes features of trauma. When a hair shaft has an irregular shape and is stiffer, it is more prone to damage. The changes are often subtle, and are better appreciated on assessment of at least 20 and preferably 50 hairs or more. Isolated reports describing hair morphology often fall

into the trap of describing individual hairs rather than the population of hairs as a whole. This mistake can be compounded by using scanning electron microscopy for the main assessment rather than as a supplementary tool. Although electron microscopy is excellent for revealing great detail in a small number of hairs, it is very poor at showing the characteristics of a population of hairs, which is the usual determinant of a phenotype.

Dominant woolly hair

In some pedigrees, the shaft diameter in affected individuals is reduced; the hair is fragile and may show trichorrhexis nodosa. Excessively curly hair is evident at birth or in early infancy; it has sometimes been described as negroid in appearance. Anderson [5] considered that the hair, although tightly coiled, was not negroid. The degree of variation in severity within a family is inconstant [1]. The hair shaft may be twisted [6]. In some cases the hair is brittle and breaks readily.

On the island of Naxos in Greece, a dominantly inherited condition has been identified, which now bears the name of the island. Naxos disease is characterized by woolly hair, palmoplantar keratoderma and a right ventricular cardiomyopathy that causes arrhythmia, heart failure and sudden death. The gene responsible for the disorder has been mapped to 17q21, which is the plakoglobin gene. Plakoglobin is an important constituent of desmosomes and adherens junction. Its loss in heart muscle leads to tissue replacement with fibrofatty material. The role in hair morphology is less clear [7]. A recent Dutch kindred were reported as having woolly hair as part of an ectodermal dysplasia, with dominant inheritance [8]. However, it should be noted that there are problems with terminology in hair science and genetics, and there is a type of hair change sometimes seen in ectodermal dysplasia that can be described as 'wiry' rather than 'woolly'.

In some cases of loose anagen syndrome, there may be associated woolly hair [9].

Recessive woolly hair

The hair is reported as brittle and on scanning electron microscopy shows signs of cuticular wear and tear [2]. In three cases [2], fine, tightly curled, poorly pigmented hair was present from birth; in two of them the hair never achieved a length of more than 2 or 3 cm. Eyebrows and body hair were sparse.

Two different variants of recessively inherited woolly hair have been defined in association with palmoplantar keratoderma and mutations causing defects in desmoplakin. One variant was associated with cardiomyopathy [10] and the other not [11].

Acquired woolly hair

There are a range of acquired patterns of woolly hair which have different and confusing names. They divide into those that develop as part of ageing and those that are attributable to trauma or drugs. The appearances may be indistinguishable when the drug is simply eliciting or catalysing an underlying process. Whisker hair describes the appearance seen in some cases, mainly males, from adolescence onwards. An irregular band of coarse, whisker-like hair extends around the edge of the scalp from above the ears towards the occipital region [12]. The hair shaft features are indistinguishable from acquired progressive kinking of hair [13], although the pattern and history may be different when drugs are implicated. Retinoids are most commonly cited [14,15]. In all these conditions the patient gradually becomes aware that the hair is changing in texture in one or more areas. On examination, the hair of the scalp is wiry, kinky, unruly, dry and lustreless. There are no sharply defined boundaries between normal and abnormal hair, although the appearance may be most marked in the frontal margins. In some of the cases described, the acquired kinking preceded hair loss, whether drug-induced or as part of the development of AGA [1].

Woolly hair naevus [16,17]

The hair in a circumscribed area of the scalp is woolly or curly and contrasts in colour and coarseness with the surrounding hair. The affected hair is usually finer at the outset, which also makes it more vulnerable to trauma. In time the contrasts may reverse, with hair in the naevoid patch becoming darker and coarser than the surrounding hair. The size of the affected area usually increases only proportionately with general growth. The abnormal hair is usually paler than that of the rest of the scalp [18]. In over half of the reported cases, a pigmented or epidermal naevus has been present, but not always at the same site. A woolly hair naevus has been reported in association with ocular defects [19], and with precocious puberty [20]. In the latter case the naevus was not limited to the scalp.

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Uncombable hair syndrome

SYN. SPUN-GLASS HAIR; CHEVEUX INCOIFFABLES; PILI TRIANGULI ET CANALICULI

Aetiology [1]. This is a combination of a striking clinical presentation and distinctive hair shaft defect first described by Dupré *et al*. [2]. Since then, many more cases have been reported, some of them under the name of 'spun-glass hair'. Others have preferred the term pili trianguli et canaliculi, with emphasis on the triangular cross-section and longitudinal groove that is commonly found on microscopy. The mode of inheritance is probably autosomal dominant [3].

Pathology. Light microscopy reveals the features in a hair shaft that makes it rigid: the triangular cross-section (Fig. 63.67) and longitudinal grooving (Fig. 63.68). Twisting can also be present and contributes to stiffness to a minor degree. The first two features are best sought using partially crossed polarizing filters with air-mounted hair. If a histological mountant is used, the surface contours of the hair are not seen. On histological (horizontal sections) examination of the scalp hair, cross-sectional characteristics are more easily seen but preparation is time consuming. Scanning electron microscopy can be helpful on selected hairs (Fig. 63.69) [4–6]. The term 'pili trianguli et canaliculi' has been proposed for these defects. The pili canaliculi are present in all cases, pili trianguli in the majority and pili torti in a few [6]. Van Neste *et al*. [7] have suggested that the misshapen dermal papilla alters the shape of the internal root sheath, which hardens (before the hair within) in a triangular cross-sectional shape; the hair then hardens into a shape complementing the root sheath. The defect resembles the 'straight hair naevus' of which it may be a diffuse form.

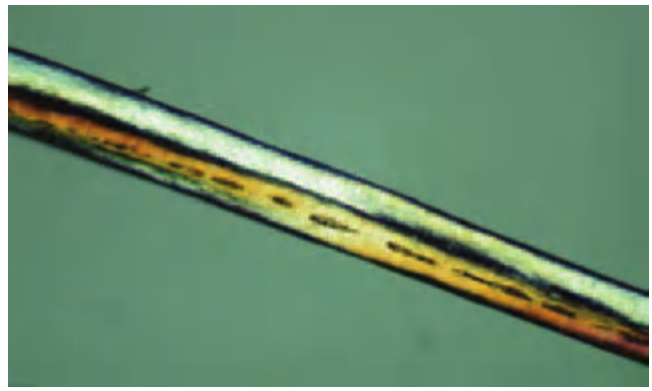

Fig. 63.67 Triangular cross-section of the hair contributes to stiffness.

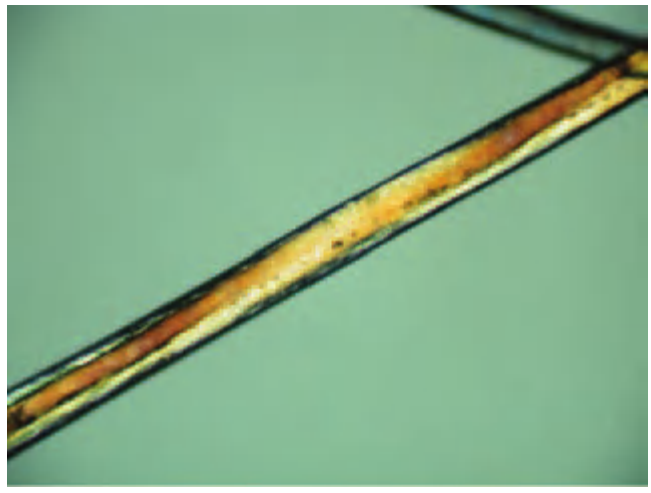

Fig. 63.68 Light microscopy reveals grooving when using partially crossed polarizing filters.

Clinical features [4,5]. The abnormality may first become obvious from 3 months to 12 years of age. The hair is normal in quantity and sometimes also in length, but its wild disorderly appearance totally resists all efforts to control it with brush or comb. In some cases, these efforts lead to the hair breaking, but increased fragility is not a constant feature [8]. The hair is often a rather distinctive silvery blonde colour. The eyebrows and eyelashes are normal. The appearance becomes less marked with time [9].

Fig. 63.69 Uncombable hair syndrome. Scanning electron micrograph showing essentially triangular cross-section and canalicular depression or gutter along one side.

The clinical appearance is usually distinctive. With light microscopy the diagnosis is dependent upon the experience of the microscopist as the three-dimensional aspect of the shaft changes can be difficult to establish. No treatment is known, although oral biotin therapy has been suggested [10].

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Straight-hair naevus

In the straight-hair naevus, the hairs in a circumscribed area of a negroid scalp are straight, and are round in cross-section. The abnormal hair may be associated with an epidermal naevus [1,2]. With the scanning electron microscope, the cuticular scales may appear small and their pattern disorganized.

It has been suggested that this is a localized form of cheveux incoiffables.

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Loose anagen hair syndrome [1]

This condition features anagen hairs that are loosely anchored and easily pulled from the scalp [2–4]. The majority of cases are fair-haired children, aged 2–9 years, mostly girls. There is usually a pattern of autosomal dominant inheritance. They typically have slightly unruly hair, which is of uneven length and patchy in quality. Variants of this include those with stiff, uncombable hair and those in whom shedding is the primary complaint. All three phenotypes may coexist within the same family [5]. The children may present with patchy alopecia, leading to a misdiagnosis of alopecia areata, but which, in fact, represents modest hair pulling. The child is well, and there are no other ectodermal abnormalities.

Hair is usually easily and painlessly plucked with the hair-pull test, although this is not a constant or specific finding [6]. Microscopy of plucked hair may show ruffling of the cuticle adjacent to the anagen bulb, giving the appearance of a 'floppy sock'. The hair shaft may have twists and grooves, and be angular in cross-section. The root sheath is absent or there may be a small everted remnant.

The hair becomes more normal with age, although the pull test may still yield abnormally large numbers of hairs into adulthood [7].

There have been isolated reports of loose anagen syndrome associated with hypohidrotic ectodermal dysplasia [8] and ocular coloboma [9].

Histological examination shows premature keratinization of the inner root sheath layers of Huxley and Henle. Trichograms show 98–100% anagen hairs. Keratin 6irs is an inner root sheath keratin proposed as a protein that might control manifestations of the disorder [10]. In one report, mutations in the gene coding for such a keratin supported this possibility [11].

Some authorities have had good results with 5% topical minoxidil [11], although it is not commonly employed and is not of clear value.

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Other abnormalities of the shaft

Trichoclasis

Trichoclasis is the common 'greenstick' fracture of the hair shaft. Transverse fractures of the shaft occur, partly splinted by intact cuticle. Cuticle, cortex and sulphur content are normal. This sign may be seen in a variety of congenital and acquired 'fragile' hair states.

In the condition termed trichorrhexis blastysis [1], with unusual facies, failure to thrive, unexplained diarrhoea and abnormal hairs, the scanning electron micrographs showed features resembling trichoclasis.

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Trichoptilosis

History and nomenclature. The term trichoptilosis describes longitudinal splitting of the hair shaft from the tip. The patient often refers to the condition as 'split ends'.

Aetiology. Trichoptilosis is the most common macroscopic response of the hair shaft to the cumulative effects of chemical and physical trauma. It can readily be produced experimentally by vigorous brushing of normal hair, and it occurs in the nodes of pili torti. It is one component of the 'weathering' process particularly seen in long hair in normal individuals and in any congenital 'brittle hair' syndrome.

Pathology. The distal end of the hair shaft is split longitudinally into two or several divisions. Other microscopic evidence of hair damage may be present. The split surface often lacks cuticle, and the split commences from the distal tip, thus distinguishing the problem from pili bifurcati or multigemini. The latter are abnormalities of hair genesis, rather than the results of hair damage.

Clinical features. Trichoptilosis is often an incidental finding in a person who complains that their hair is dry and brittle. Trichorrhexis nodosa and trichoclasis are often also present. Central trichoptilosis, a longitudinal split in the hair shaft without involvement of the tip, sometimes occurs [1]. Such a finding would be in the context of general hair damage and other more classic forms of trichoptilosis, which would distinguish it from pili bifurcati.

Treatment. Careful explanation is necessary to encourage the patient to avoid further hair trauma, because otherwise the condition will inevitably recur. Short hair and frequent trimming usually solve the problem.

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Circle hairs [1,2]

Circle and spiral hairs occur in middle-aged men on the back, abdomen and thighs as small dark circles next to hair follicles. They are an unusual form of ingrown hair lying in a coiled track just below the stratum corneum, and can be easily extracted. Keratin follicular plugging is not associated (cf. scurvy, which may demonstrate keratosis pilaris with rolled and 'corkscrew' hairs).

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Trichomalacia

Miescher [1] described as trichomalacia a patchy alopecia in which some follicles are plugged and contain soft deformed swollen hairs. The changes have been attributed to the repeated trauma resulting from a hair-pulling tic [2,3], and subsequent histological studies in trichotillomania confirm this opinion.

Pathology. Above the bulb, the cells of the hair shaft appear to be disconnected and the hair is shapeless or partially disintegrated. High in the follicle, the shaft is thin and may be coiled. Whiting [4] described biopsy specimens as showing partially avulsed hair roots that are deformed and twisted. Clefting occurs between matrix

cells and between hair bulb and outer connective tissue sheath. There is no inflammatory reaction; these changes are said to be pathognomonic of trichotillomania. One study of 26 patients with trichotillomania recorded trichomalacia in horizontal sections of 57% [5].

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Trichoschisis [1]

Trichoschisis is a clean transverse fracture across the hair shaft through cuticle and cortex; the fracture is associated with localized absence (loss) of cuticular cells. It is said to be a characteristic microscopic finding of trichothiodystrophy. It probably represents a clean fracture through hair with decreased high-sulphur matrix protein content and, in particular, a similar decrease in the exocuticle and A layer of cuticular cells. It may be prominent in the sulphur deficiency syndromes but it should not be considered as specific or pathognomonic.

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Pohl–Pinkus constriction [1]

In some individuals, a zone of decreased shaft diameter coincides in time with a surgical operation, an illness or the administration of folic acid antagonists or other drugs that inhibit mitosis; it was first described by Pohl in 1894—he later changed his name to Pinkus. The proportion of affected hairs is variable and it seems probable that hairs in early anagen are most susceptible to a period of hypoproteinaemia or disturbed protein synthesis. This phenomenon was present in 21 of 100 hospitalized patients [2]; whether the illness or operation had been associated with pyrexia was not a relevant factor.

These constrictions in the hair shaft have been considered to be analogous to the transverse furrows in the nails (Beau's lines), which also coincide with episodes of ill health. Longer narrowings, resembling monilethrix, may occur with 'bolus' doses of cytotoxic drugs that do not lead to anagen effluvium.

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Tapered hairs

Tapered hairs are those with a distal end that resembles the tip of a javelin. Most commonly, tapered hair is seen in any condition where there are many hairs regrowing after an effluvium, or where anagen is short. Regrowth after telogen effluvium, alopecia areata and trichotillomania may result in hairs with tapered ends. At body sites where the hairs are always short, such as the eyelashes, they are tapered. When scalp hair has a short anagen, such as in hypotrichosis simplex [1], the ends are also tapered. This is also the case in the newborn, as the duration of anagen has only been a few months from commencement *in utero*. As a feature on microscopy, tapered hairs are a useful sign that short hair is caused by the length of anagen rather than intrinsic hair shaft fragility.

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Bayonet hairs

Bayonet hairs are characterized by a 2–3 mm spindle-shaped hyperpigmented expansion of the hair cortex just proximal to a tapered tip, and may be associated with hyperkeratinization of the upper third of the follicle.

Trichonodosis

Michelson [1] first proposed the term noduli laqueati, and noted that naturally curly hair was most frequently affected. The term trichonodosis was popularized later by Kren [2], who found the condition in 35 out of 64 consecutively examined patients with skin disease.

Aetiology. The knotting of the hair shafts is induced by trauma. Short curly hair of relatively flat diameter is most readily affected [3]. Knots were seen most frequently in hair from people of African origin [4] and in short curly hair in white people; none was seen in long straight hair.

Some knotting is caused by braids and cosmetic manipulation. These knots are of a different form and scale to the inadvertent knotting brought about by hair type and random trauma. However, it is capable of inducing marked changes in the cuticle, which in turn results in a lower threshold for hair fracture.

Pathology. The only abnormalities are secondary to the knotting and are localized to that part of the shaft that forms the knot [3]. With the scanning electron microscope, the cuticle shows longitudinal fissuring and fractures, and cuticle scales are lost.

Clinical features [3]. Trichonodosis is usually an incidental finding, because it is inconspicuous and must be deliberately sought. One or few hairs are affected. The trauma of brushing or combing may cause the shaft to break at the site of the knot.

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Trichostasis spinulosa

This is probably a normal age-related phenomenon—easily overlooked—in which successive telogen hairs are retained in predominantly sebaceous follicles [1]. When it was specifically sought, 51 cases were seen in 1 month in Madras [2].

Aetiology. Ladany [3] thought trichostasis was no more than a variant of the comedo, and pointed out that 85% of comedones contain from one to 10 or more vellus hairs. Trichostasis is found most commonly in the middle-aged or elderly and is said by most authors to occur particularly on the nose and face [3]. Other sites were perhaps not always examined, for others have found it to be not uncommon on the trunk, limbs [4] and interscapular area [5].

Pathology. The affected follicles contain up to 50 vellus hairs embedded in a keratinous plug. A mild perifolliculitis is often present. The condition must be differentiated from the 'multiple hairs' of Flemming—Giovannini in which up to seven hairs grow from a composite papilla with a common outer root sheath [6]. Follicles may contain *Malassezia* yeasts and *Propionibacterium acnes* [5].

Clinical features [7]. Those reported to be affected have ranged in age from 17 to over 60 years. The lesions, which closely resemble comedones, may occur predominantly on the nose, forehead and cheeks, or the face may be spared and the nape, back, shoulders, upper arms and chest may be affected. The lesions vary greatly in number. On inspection with a hand lens, the 'comedones' seem to be unusually prominent and in some cases a tuft of hairs may be seen projecting through the horny plug.

Treatment. Keratolytic preparations have often been recommended but we have found them of little value. The most effective treatment is topical retinoic acid [8], which should be used as in the treatment of acne. Depilatory wax has also been successfully employed [7], and specialized cleaning pads have been advocated [9].

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Pili multigemini

SYN. PILI BIFURCATI

The term pili multigemini [1] describes an uncommon developmental defect of hair follicles as a result of which multiple matrices and papillae form hairs that emerge through a single pilosebaceous canal. The incidence of multigeminate hairs in the general population is unknown. Numerous follicles showing this defect have been seen in a patient with cleidocranial dysostosis [2].

Pathology. From two to eight matrices and papillae, each with its internal root sheath, form hairs that are often flattened, ovoid or triangular in configuration and may be grooved. In the follicular canal, contiguous hairs may adhere, bifurcate and then re-adhere.

Clinical features. Multigeminate follicles occur mainly on the face, especially along the lines of the jaw. Tufts of hair may be seen emerging from a few or many follicles. Their discovery is often a matter of chance, but the patient may complain of recurrent inflammatory nodules, leaving scars.

Treatment. If the hairs are plucked, they regrow [2]. A single report of ablation after three treatments with a ruby laser may indicate that this is a therapeutic option [3].

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Fig. 63.70 Circumferential keratin cast resembling a cuff around the hair shaft.

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Hair casts

Hair casts (peripilar keratin casts) are firm yellowish white accretions ensheathing, but not attached to, scalp hairs. They freely move up and down the affected shafts [1]. Such casts are often found in scaly and seborrhoeic disorders of the scalp, and in children with hairstyles requiring traction [2].

Pathology. In cross-section, casts are composed of a central layer of retained internal root sheath and an outer thick keratinous layer. Scalp histology shows the follicular openings packed with parakeratotic squames, which break off at intervals to form hair casts.

Casts are found quite commonly in scaly, mainly parakeratotic conditions of the scalp such as psoriasis and pityriasis amiantacea [3]. Cases have been described in association with traction hairstyles [2,4,5] and hair sprays [6].

Clinical features. Hair casts (Fig. 63.70) may occur as an isolated abnormality unrelated to any overt scalp disease and may mimic pediculosis capitis [7]—hence the designation 'pseudonits' [8,9]. Girls and young women are most commonly affected; hundreds of casts may develop within a few days. No cause is known, but sex-linked inheritance has been suggested [1]. It is possible that this type may represent an unusual manifestation of psoriasis.

If patients with scaly parakeratotic diseases of the scalp complain of persistent dandruff that resists apparently adequate treatment, this is likely to be caused by multiple hair casts.

Diagnosis. In the absence of associated scalp disease, casts may be mistaken for pediculosis capitis, trichorrhexis nodosa or hair knots [10]. Of these nodal shaft abnormalities, only hair casts are freely movable along the hair.

Treatment. Any causative scalp disease must be treated. Keratolytic preparations and shampoos that readily improve scalp scaling frequently fail to remove casts; prolonged brushing and combing is necessary to slide casts off the affected hairs [3,11].

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Weathering of the hair shaft [1,2]

All hair fibres undergo some degree of cuticular and secondary cortical breakdown from root to tip before being shed during the telogen or early anagen phase of the hair cycle. The term 'weathering' of hair has been limited by some authorities to structural changes in the hair shaft resulting from cosmetic procedures; indeed, both *in vivo* and *in vitro* studies carried out by cosmetic scientists have shown the type of damage that factors such as combing, brushing, bleaching and permanent waving can cause [3,4]. However, in considering the degeneration of hair fibres, cosmetic and other influences such as natural friction, wetting and UV radiation are so interwoven that it is more useful in practice to define weathering as the degeneration of hair from root to tip because of a variety of environmental and cosmetic factors. Scalp hair, having a long anagen phase and being subject to more frictional damage and cosmetic treatment, shows more deep cuticular and cortical degeneration than fibres from other sites.

Weathering of scalp hair has been studied in greater detail than hair from other sites. At the root end, surface cuticle cells are closely apposed to deeper layers. Within a few centimetres of the scalp, the free margin of these cells lifts up and breaks irregularly [5]. Increasing scale loss leads to surface areas denuded of cuticle. Many fibres show complete loss of overlapping scales well proximal to the tip (Fig. 63.71). This is particularly common on long hair shafts, which frequently have a frayed tip. Proximal to terminal fraying, longitudinal fissures may be present between exposed cortical cells. Hairs subjected to considerable friction damage may show transverse fissures and some nodes of the type seen in trichorrhexis nodosa [6,7]. Hair that has been bleached or permanently waved may show shaft distortion. The most severe changes are mostly

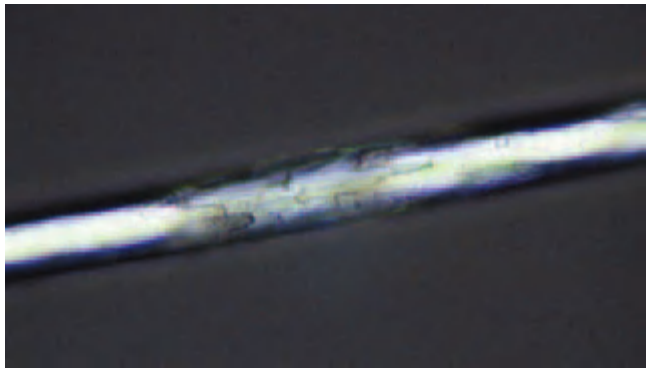

Fig. 63.71 Focal loss of cuticle in a weathered hair.

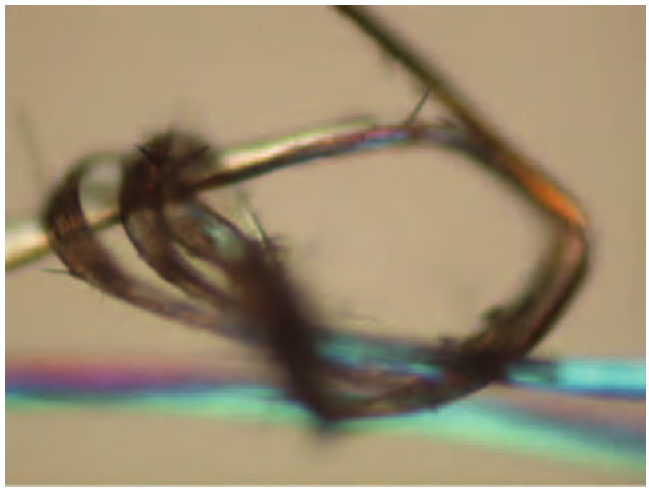

Fig. 63.72 Knotting of single and multiple hairs contributes to hair shaft trauma.

seen near the distal part of the hair shaft in normal scalp hair.

Hair knotting (Fig. 63.72) and braids (Fig. 63.73) are a significant source of hair shaft trauma, with loss of cuticle and damage to cortical fibres.

Trichorrhexis nodosa is the most severe form of weathering. Many of the changes seen in normal hair towards the tip are visible more proximally in congenitally weakened hair [8,9] and in trichorrhexis nodosa caused by overuse of cosmetic treatments [10].

In some hair structural abnormalities such as monilethrix and pili torti, specific weathering patterns may be seen.

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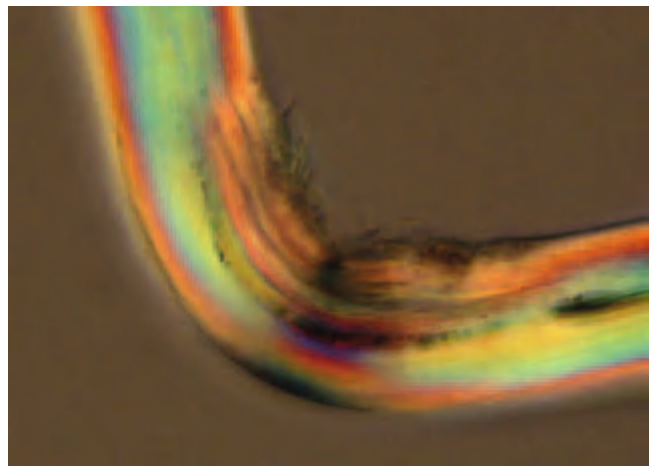

Fig. 63.73 Braiding damages hair shaft cuticle.

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Bubble hair

Brown [1] reported an unusual case of an acquired, localized, reversible hair shaft defect with intrinsic 'bubbles' within hairs, thought to be caused by repeated cosmetic trauma. Subsequent reports [2,3] have demonstrated that the bubbles are a sign of thermal injury, particularly of damp hair [3]. This may be because of poor thermostat control of a hair dryer, but most of us suffer bubble hairs by singeing over the cooker (Fig. 63.74).

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Excessive growth of hair [1–3]

Growth of hair that in any given site is coarser, longer or more profuse than is normal for the age, sex and race of the individual is regarded as excessive. The terms hirsutism and hypertrichosis are often confused and applied

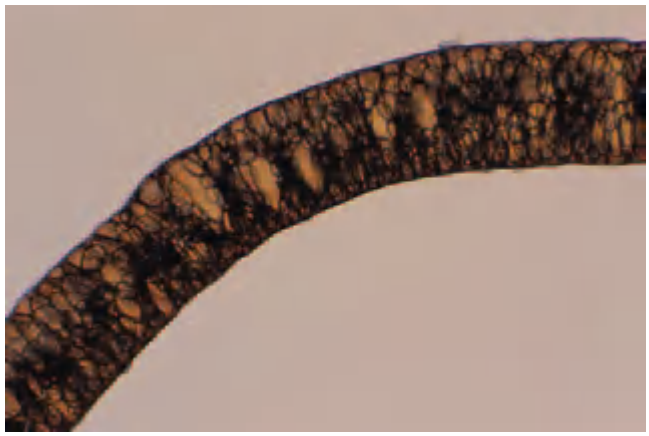

Fig. 63.74 Appearance of normal scalp hair after exposure to naked flame. Bubbles form within the cortex.

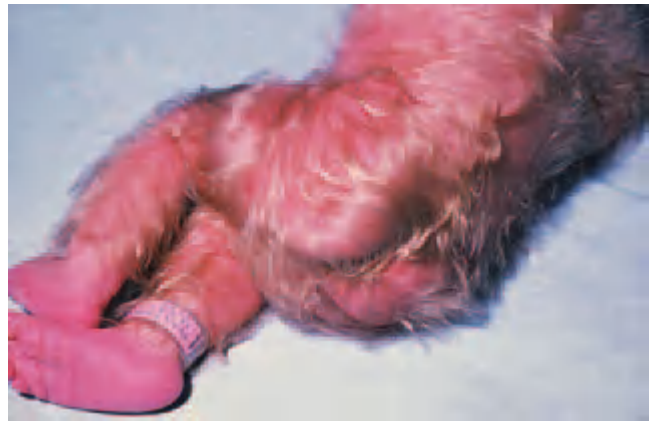

Fig. 63.75 Congenital hypertrichosis lanuginosa. (Courtesy of Dr Partridge, Leamington, UK.)

interchangeably and indiscriminately to excessive hair growth of any type in any distribution. On phylogenetic grounds, and on the basis of its specific androgenic induction, the growth in the female of coarse terminal hair in the adult male pattern should be differentiated clearly from the numerous other forms of excessive hair growth of widely varying aetiology. The term hirsutism will be restricted to androgen-dependent hair patterns of typically terminal hair and the term hypertrichosis will be applied to other patterns of excessive hair growth, typically vellus. In some areas it is difficult to make the distinction, such as in the excess facial hair in porphyria cutanea tarda. This is typically referred to as hypertrichosis, but the point can be argued.

There is much confusion in the literature concerning generalized congenital hypertrichosis because of a plethora of names such as apeman, bearman, dogman, manlion and wildman [4].

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Hypertrichosis

The terminology used in describing different patterns of hypertrichosis is inconsistent as reports have given synonymous terms to clinically different forms of the problem. Baumeister *et al.* [1] sought to unravel the matter. Hypertrichosis usually conforms to the classification of localized or generalized of congenital or acquired pattern, where congenital is loosely interpreted as that seen in early infancy.

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Congenital generalized hypertrichosis

Hypertrichosis lanuginosa

In congenital hypertrichosis, the fetal pelage is not replaced by vellus and terminal hair but persists, grows excessively and is constantly renewed throughout life. In the acquired form, the previously normal follicles of all types revert at any age to the production of hair with lanugo characteristics [1].

Aetiology. Traditionally, cases of congenital hypertrichosis have been classified into two groups—'dog faced' and 'simian'—but a survey [2] suggests that there may be only a single genotype, with considerable interfamily variation in the phenotype. With one exception [3], all published pedigrees suggest autosomal dominant inheritance.

Clinical features [2,4–7]. The child is usually noticed to be excessively hairy at birth (Fig. 63.75). The hair gradually lengthens until by early childhood the entire skin, apart from the palms and soles, is covered by silky hair, which may be 10 cm or more long. Long eyelashes and thick eyebrows are conspicuous features. Some affected individuals are normal at birth and sometimes for the first few years of life, before the universal replacement of other hair types by lanugo. Once established, the hypertrichosis is permanent, but some diminution of hairiness of trunk and limbs may be noted in later childhood. At puberty, axillary, pubic and beard hairs retain their downy character. Hypodontia or anodontia and deformities of the external ear are apparently associated in some families, but the physical and mental development of most patients has

been normal. In a Mexican family, hypertrichosis was associated with an osteochondral dysplasia [8].

The status of the apparently recessive form is still more uncertain. Three children of a normal mother were densely hairy at birth and died within a week. Neonatal shaving was of cosmetic benefit in one rare case [6].

Treatment of children with long-pulsed ruby laser can result in a useful reduction of hair, although the benefits tend to wane over 6–12 months. Morley reported a 63% reduction in hair counts at 6 months [9].

Universal hypertrichosis

Not all people with congenital universal hypertrichosis will represent the same entity. If it is possible to make the distinction between lanugo and vellus hair, those with vellus hair may be classified as a form of universal hypertrichosis known as the Ambras syndrome, in which there are dysmorphic features. There is a debate concerning the distinction between Ambras syndrome and other forms of generalized hypertrichosis. Baumeister [10] argues that the uniformity of facial growth and the hypertrichosis of the external ear help set Ambras syndrome apart from other extreme forms of universal hypertrichosis where facial hair is not uniformly distributed and the ear hair growth is less marked. Although those outside the diagnosis of Ambras syndrome may have other associated features, such as gingival hyperplasia [11], there are some areas of overlap with respect to rearrangements on chromosome 8 [12,13].

There are also individuals who might be classified as demonstrating universal hypertrichosis, but with less extreme manifestations and without associated or dysmorphic features. The hair pattern is normal but in any site the hairs are larger and coarser than usual. The eyebrows may be double. Inheritance is determined by an autosomal dominant gene. The features begin to merge into what is considered the normal spectrum.

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Congenital generalized hypertrichosis associated with other syndromes

Hurler's syndrome and other mucopolysaccharidoses (see Chapter 12). Hypertrichosis is usually present from early infancy or early childhood on the face, trunk and limbs and may be a conspicuous feature. The eyebrows are often bushy and confluent. In abortive forms, the hair growth may first appear after puberty and be more limited in extent.

Congenital macrogingivae (see Chapter 66) [1]. Exuberant overgrowth of the gingivae as an isolated congenital defect is not uncommon. The association with profuse hypertrichosis of trunk, limbs and lower face has been reported on several occasions. Some patients have markedly acromegaloid features [2] or thyroid disease [3].

Cornelia de Lange syndrome (see Chapter 12). These mildly microcephalic, mentally defective children have a low hairline and profuse overgrowth of the eyebrows. The forehead is covered with long fine hair. Hypertrichosis is usually also conspicuous on the lower back, and may be generalized.

Winchester syndrome. This rare hereditary disorder is characterized by dwarfism, joint destruction and corneal opacities. The skin in many parts of the body becomes thickened, hyperpigmented and hypertrichotic [4,5].

Berardinelli's syndrome [6]. From early life, growth and maturation are accelerated and there is lipodystrophy with muscular hypertrophy. Enlargement of the liver and hyperlipidaemia are other constant features. The skin is coarse and often hypertrichotic.

Trisomy 18 (see Chapter 12). Generalized hypertrichosis of variable degree is present in these patients.

Hypertrichosis has been reported in the rare hereditary globoid leukodystrophy, Krabbe's disease. Most patients die in infancy [4].

Teratogenic syndromes

Fetal alcohol syndrome [7]. Mental and physical retardation affects the infants of many mothers with chronic

alcoholism. The cutaneous changes include hypertrichosis and capillary haemangiomatosis.

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Congenital localized hypertrichosis

Naevoid hypertrichosis

The growth of hair abnormal for the site and the age of the patient in its length, shaft diameter and colour may occur as a circumscribed developmental defect, either isolated or associated with other naevoid abnormalities [1], such as duplication of the thumb [2].

Melanocytic naevi (see Chapter 38) may be accompanied by a vigorous growth of coarse hair. The hair may be present from infancy or may develop at puberty. Less often, circumscribed hypertrichosis may occur as the only clinical abnormality. Histologically, the epidermis is acanthotic and the follicles are large, but there is no excess of melanocytes.

Hypertrichosis is a characteristic feature of Becker's naevus (see Chapter 15). The coarse hairs develop in the same body regions as the pigmentation, usually the thoracic or pelvic girdle, but pigmentation and hypertrichosis are not coextensive. It has been suggested that this naevus is a functional one, being androgen dependent; acne may also occur in the same site [3]. It has also rarely been reported in association with limb asymmetry and other ipsilateral anatomical abnormalities [4].

True linear hypertrichotic naevi are rare and hair growth may not be sustained [5].

A tuft of hair in the lumbosacral region, the so-called faun-tail naevus, is often associated with diastematomyelia (Fig. 63.76).

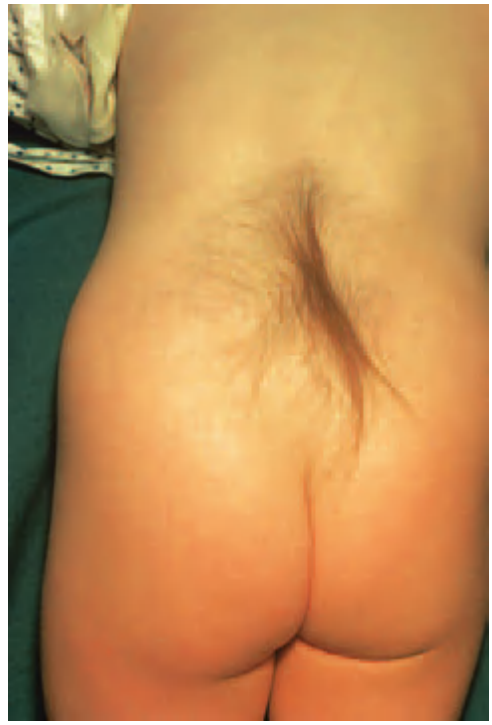

Fig. 63.76 Lumbosacral hypertrichosis ('faun tail'), here associated with diastematomyelia.

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Acquired generalized hypertrichosis

Acquired hypertrichosis lanuginosa associated with malignancy

Aetiology. In its most dramatic severe form, this syndrome is rare. It usually accompanies a serious and often fatal illness. Fine downy hair grows over a large area of the body, replacing normal hair and primary and secondary vellus. Approximately 60 cases have been reported and all except two (in which there was no follow-up) were suffering from malignant disease of the gastrointestinal tract, bronchus, breast, gall bladder, uterus, bladder or other organs [1–5]. One patient with lymphatic leukaemia had acquired ichthyosis as well as hypertrichosis, and one had a lymphoma. The hypertrichosis may precede the diagnosis of a neoplasm by several years [6].

Pathology. In one case [7] the lanugo follicles lay almost parallel to the surface, and were apparently derived from mantle follicles.

Clinical features [8–10]. In the milder forms ('malignant down' [7]), hair is confined to the face, where it attracts attention by its appearance on the nose and eyelids and other sites that normally are clinically hairless. As the growth of hair continues, it may ultimately involve the entire body, apart from the palms and soles. Existing terminal hair of scalp, beard and pubes may not be replaced, and may contrast in colour and texture with the very fine white or blonde lanugo. Such hair may grow abundantly, even on the previously bald scalp. The hair may grow exceedingly rapidly, up to 2.5 cm/week, and may be more than 10 cm long.

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Non-malignant acquired generalized hypertrichosis

There is a range of non-malignant systemic diseases in which hypertrichosis may develop. Generally, the hair is coarser and less profuse than the lanugo hair associated with systemic malignancy. However, at any single point early in the process, the distinction may not always be obvious.

Endocrine disturbances

Hypothyroidism [1]. A profuse growth of hair on the back and the extensor aspects of the limbs develops in some children with hypothyroidism.

Hyperthyroidism. Coarse hair often grows over the plaques of pretibial myxoedema as it may over other forms of inflammation on the anterior shin.

Possible diencephalic or pituitary mechanisms. Severe generalized hypertrichosis has been reported in young children after encephalitis [2] and after mumps followed by the sudden onset of obesity [3]. A diencephalic disturbance is postulated. Generalized hypertrichosis occurred in a girl after traumatic shock [4] and remitted in 6 months. There are many reports of hypertrichosis after head injuries, especially in children. The hair growth is first noticed 4–12 weeks after the injury (which seems to be of no consistent type) and appears as fine silky hair on the forehead, cheeks, back, arms and legs, and may be asymmetrical. It is sometimes shed after a few months, but may persist.

Other conditions

Malnutrition [5]. Gross malnutrition, which may be primary or occur in coeliac disease or other malabsorption states or in severe infections, may cause profuse generalized hypertrichosis in children.

Anorexia nervosa [6]. An increased growth of fine downy hair on the face, trunk and arms, sometimes of severe degree, has been reported in 20–77% of adult cases [7,8], and is also seen in children [9]. The prevalence of hypertrichosis in bulimia is reported to be half of that in anorexia, and both are associated with approximately 60% prevalence of scalp alopecia [7].

Acrodynia [5]. Some increased growth of hair on the limbs is common. In severe cases, the hypertrichosis is very conspicuous on the face, trunk and limbs. One child was described as monkey-like.

Dermatomyositis [10]. Excessive hair growth has been noted mainly in children and principally on the forearms, legs and temples, but it may be more extensive.

Epidermolysis bullosa. Gross hypertrichosis of the face and limbs has occurred in association with epidermolysis bullosa of the dystrophic type, although this is rare (see Chapter 40).

Hypertrichosis is seen affecting the extensor surface of the arm (Fig. 63.77) in a sporadic or familial form in children, resolving in adolescence. Although associations with

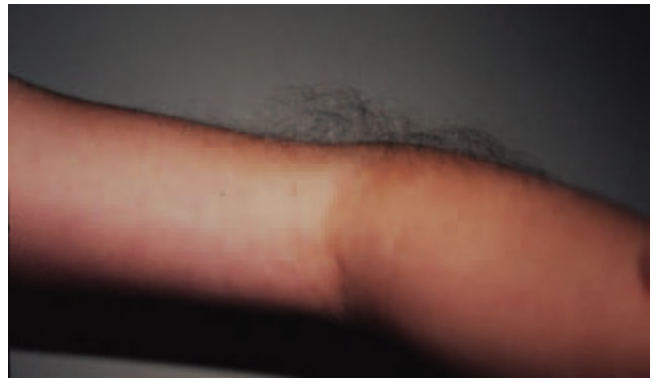

Fig. 63.77 Hypertrichosis of the elbows in a child.

other disorders have been sought, it appears as a largely isolated finding [11].

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Iatrogenic hypertrichosis

In iatrogenic hypertrichosis, there is a uniform increased growth of fine hair over extensive areas of the trunk, hands and face, unrelated to androgen-dependent hair growth.

The mode of action of the offending drugs on hair follicles is not known; the same mechanism is not involved in all cases. Cortisone, diphenylhydantoin and penicillamine are all known to affect connective tissue, but in different ways. Psoralens presumably induce hypertrichosis in predisposed subjects by accentuating the tendency of sunlight to induce this temporary change. The stimulation of hair growth on sun-exposed sites by benoxaprofen may have a similar mechanism. Existing vellus hairs increase in length and less so in diameter. The hairs are seldom more than 3 cm in length and are considerably finer than terminal hair.

Diphenylhydantoin induces hypertrichosis after 2–3 months. It affects the extensor aspects of the limbs, then the face and trunk, and clears within a year of cessation of therapy [1].

Diazoxide produces hypertrichosis in all of those treated but it seems to be a cosmetic problem in only half [2,3]; in adults, the anagen phase may last longer [4]. There are no associated changes in the sebaceous glands [2].

Minoxidil commonly induces hypertrichosis [5]. It is apparent after a few weeks' therapy [6].

Hypertrichosis of some degree develops in 60% of patients treated with ciclosporin [7–9]. Keratosis pilaris may precede the appearance of thick pigmented hair on the face, trunk and limbs. Changes in other parts of the pilosebaceous unit occur: keratosis pilaris (21%), sebaceous hyperplasia (10%) and acne (15%) [8].

Benoxaprofen induced a fine downy growth of hair on the face and exposed extremities after only a few weeks [10].

Streptomycin caused hypertrichosis in 22 of 27 children who had received 1 g/day for miliary tuberculous meningitis [11,12].

Prolonged administration of cortisone may induce hypertrichosis, most marked on the forehead, the temples and the sides of the cheeks, but also on the back and the extensor aspects of the limbs.

Penicillamine appears to cause lengthening and coarsening of hair on the trunk and limbs.

Psoralens, used in the treatment of vitiligo and psoriasis, may induce temporary hypertrichosis of light-exposed skin [13].

Latanoprost eye drops used for glaucoma may cause hypertrichosis of eyelashes and increased vellus hair on the eyelid skin [14]. This prostaglandin receptor agonist is the subject of current research in the sphere of hair regrowth products [15].

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Acquired localized hypertrichosis

Cutting or shaving the hair influences neither its rate of growth nor the calibre of the hair shaft. However, repeated or long-continued inflammatory changes involving the dermis, whether or not clinically evident scarring is produced, may result in the growth of long and coarse hair at

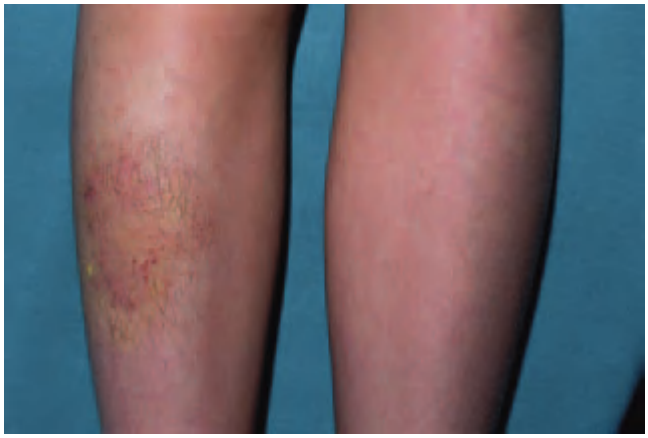

Fig. 63.78 Circumscribed hypertrichosis in an area of steroid-treated lichen simplex.

the site. The cause of the hair growth is usually obvious but may be overlooked when the trauma is occupational; for example, circumscribed patches of hypertrichosis on the left shoulder in people frequently carrying heavy sacks [1] or religious items during holy week in Spain [2]. A patch of hypertrichosis on one forearm has been reported in those with mental retardation who have acquired the habit of chewing the site [3]. Sometimes, hypertrichosis develops at the site of an accidental wound or a vaccination scar [4]. It has developed on the back of the hand and fingers 3 months after the excision of warts [5]. It has been reported also in an irregular pattern on the legs in chronic venous insufficiency [6], around the edges of a burn [7] and at the site of multiple clusters of excoriated insect bites [8]. Hypertrichosis of this type may occur near inflamed joints and has been reported particularly in association with gonococcal arthritis [9] and in the skin overlying chronic osteomyelitis of the tibia [10]. Very exceptionally, inflammatory dermatoses, especially in children, may induce a temporary overgrowth of hair; for example after eczema (Fig. 63.78) [11] and varicella [12]. A linear pattern of hypertrichosis on the leg has been described after recurrent thrombophlebitis that persisted for a year [13]. Hypertrichosis may occur in the indurated skin in melorheostotic scleroderma [14]. The damaged skin in epidermolysis bullosa may also become hypertrichotic [15]. Children have developed itching eczema and local hypertrichosis at the site of injection of diphtheria–tetanus vaccine adsorbed on aluminium chloride [16].

Hypertrichosis of one leg or forearm after a prolonged period of occlusion by plaster of Paris is a phenomenon well known to orthopaedic surgeons. It is seen in association with 55% of cases of reflex sympathetic dystrophy and may be accompanied by Beau's lines [17]. It occurs mainly in children. The hypertrichosis is likely to result from prolongation of anagen. It is not clear whether this is caused by local vascular changes, as occurs with hypertrichosis associated with areas of skin inflammation.

Porphyria (see Chapter 57). Hypertrichosis of exposed skin is a common feature of the very rare erythropoietic porphyria; appearing first on the forehead, it later extends to the cheeks and chin and, to a lesser degree, to other exposed areas. It is also present in many cases of the much more common erythropoietic protoporphyria [18].

In porphyria cutanea tarda, hypertrichosis is an inconstant finding, but may accompany the pigmentation, plethora, blistering and scleroderma-like changes on exposed skin, and is marked in some children with the disease [19]. Darkening of scalp hair in a subject with white hair at the onset of porphyria cutanea tarda has been reported [20], and hypertrichosis has been reported as the presenting complaint in one subject in whom porphyria cutanea tarda was the underlying cause [21]. In black people, hypertrichosis and pigmentation may be present without blistering [22].

The most extreme degree of hypertrichosis is seen in children with hepatic porphyria induced by hexachlorobenzene or other chemicals. Hypertrichosis is frequent in porphyria variegata. The temples, forehead and cheeks are covered with downy hair. There is also increased pigmentation.

Some forms of localized hypertrichosis are caused by the local application or effect of drugs and are discussed in the section on iatrogenic causes of hypertrichosis (see p. 63.96).

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Hirsutism

Perception of hirsutism is by definition subjective, and women present with a wide variation in severity [1]. Both the severity of the hirsutism and the degree of its acceptance are dependent on racial, cultural and social factors. Even the criteria for the definition of hirsutism used by physicians vary widely [2–6]. In order to resolve this issue, different groups have evolved different grading schemes for body hair growth. The scheme employed in the study by Ferriman and Gallwey [3], which has become the standard grading system, defined hirsutism purely on quantitative grounds. Hirsutism is graded as numerical scores beyond an upper limit of twice the standard deviation from the mean. Scoring can be on a global basis assessing 8–11 body sites, or it can be based on a single site. Others have examined women complaining of hirsutism and compared them with controls; they have demonstrated that there is a considerable overlap in the grades of hirsutism between the two groups [4,6]. Hair on the face, chest or upper back is a good discriminating factor between hirsute women and controls with similar hair growth scores. In clinical practice, it has often been suggested that 'real' hirsutism is simply that which the woman in question thinks is excessive.

Facial and body hair is less commonly seen on oriental people [7], black people and native Americans than on white people [8]. Even among white people there are differences; hair growth is heavier on those of Mediterranean than those of Nordic ancestry [9]. The pattern of hair growth in hirsutism within different racial groups is identical [3–6]. However, different criteria have made the determination of the comparative incidence and severity within these groups difficult to assess. Only one study of a random population stated how many women considered themselves to be hirsute. McKnight [5] examined 400 unselected students, 60% of whom were Welsh: 9% were considered by both the women and investigator to be hirsute and 4% were considered to be disfigured by their facial hair growth. This investigation also included studies of hair growth in women who were not complaining of hirsutism. It is important to the definition of hirsutism that a sizeable proportion of normal women have some terminal hairs on their face, breasts or lower abdomen.

Lorenzo [10] studied 90 hirsute women and found an increased incidence of hirsutism in their female relatives compared with control populations. McKnight [5] reported that 14% of hirsute Welsh women gave a positive family history. This tendency to familial clustering in hirsutism might be anticipated, as some of the underlying disorders that result in hyperandrogenism have a familial basis. For example, congenital adrenal hyperplasia is autosomal recessive and linked to MHC [11], and a very strong family relationship has been reported in the polycystic ovary syndrome (PCOS) [12].

In hirsutism, one role of society is to determine the threshold level for normality and this is now determined by the media. Women receive a barrage of advertisements for cosmetics that are based on the premise that only a woman with a hairless body can be normal, healthy and attractive. To some extent, men are falling victim to the same media aesthetic, with the advent of laser techniques capable of removing hair from large areas.

There have been few studies on the psychological status of hirsute women. Meyer and Zerssen [13] concluded on the basis of a small sample of patients studied within a psychoanalytic framework that many suffered reactive psychological problems. A small controlled study [14] revealed increased levels of anxiety. In contrast, Callan *et al*. [15] were unable to detect significant differences in comparison with normal.

Another approach to the psychological aspect of hirsutism has been to implicate 'stress' as an aetiological factor. Segre [16] states, in his monograph on the hirsute female, that: 'Lack of peace of mind appears at the core of the problem. We believe it to be both a cause and result of hirsutism.' This view has been endorsed [17]. The onset of hirsutism in four of 10 hirsute women was noted to coincide with a period of emotional stress [18]. Bush and Mahesh [19] reported stress-induced hirsutism in a young woman whose unstressed twin was not hirsute. Objective before and after data on this observation are difficult to identify.

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Endocrine factors and hirsutism [1]

Hirsutism attracts a wide range of endocrine investigations, which differ according to the presentation and the specialty background of the clinician. However, the assumption that hirsutism is wholly related to androgens can be challenged on an individual and general level. The increasing awareness of insulin metabolism and hirsutism has highlighted this and, on an individual level, it is very clear that many women with unwanted hair have no endocrinological disturbance.

There have been several attempts to correlate hair growth in women with plasma androgen levels but these reports have yielded conflicting results. Reingold and Rosenfield [2] noted a considerable variability between hair growth scores and free testosterone, but no significant relationship. Ruutiainen *et al.* [3] have calculated a complex formula for multiple plasma androgen levels:

Testosterone/SHBG + androstenedione/100 + dehydroepiandrosterone sulphate/100.

This correlates with hair growth only in women with idiopathic hirsutism. In a further study, the same group [4] found a relationship between hair growth and salivary testosterone levels, but in this study no selection of patients was required. A different ratio has been determined for female baldness [5]:

3α-androstanediol glucuronide/SHBG.

Both equations demonstrate the significance of SHBG as a factor modifying the effects of circulating androgen.

The first sign of androgen production in women occurs 2–3 years before the menarche and is caused by adrenal secretion [6]. The major androgens secreted by the adrenal are androstenedione, dehydroepiandrosterone (DHA) and DHA sulphate (DHAS). Their control during postpubertal life is unknown, but it is thought that androstenedione and DHA may be controlled by adrenocorticotrophic hormone (ACTH), as their serum levels mirror those of cortisol [7,8].

Ovarian androgen production begins under the influence of the pubertal secretion of luteinizing hormone (LH) and takes place in the theca cells. The predominant androgen secreted by the ovaries is androstenedione during the reproductive years, and testosterone after the menopause. Androgen secretion continues throughout the menstrual cycle but peaks at the middle of an ovulatory cycle [9]. Androstenedione secretion is greater from the ovary containing the dominant follicle [10].

In normal women, the majority of testosterone production (50–70%) is derived from peripheral conversion of androstenedione in skin and other extrasplanchnic sites [11–13]. The remaining proportion is secreted directly by the adrenals and ovaries. The relative proportion estimated from each gland varies between reported studies: 5–20% from the ovary and 0–30% from the adrenal [13,14]. DHA is the source of less than 10% of circulating androstenedione and 1% of circulating testosterone [15,16].

Androgen transport proteins

In non-pregnant women, the majority of circulating androgens are bound to a high-affinity β-globulin, SHBG. A further 20–25% is transported loosely bound to albumin, and approximately 1% circulates freely. The free steroid is believed to be active, and the binding protein is therefore of paramount importance. The affinity of the androgens for SHBG is proportional to their biological activity.

The function of SHBG is unknown. It is probable that its main role is to buffer acute changes in unbound androgen levels and to protect androgens from degradation. Burke and Anderson [17] suggested that it also acts as a biological amplifier. High oestrogen levels increase SHBG and therefore reduce available androgen; high androgen levels reduce SHBG and increase available free androgen.

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Androgen pathophysiology in hirsutism [1,2]

The growth of normal secondary sexual hair is a response of the hair follicles to androgens. Abnormal degrees of hair growth are therefore often seen in endocrine disorders characterized by hyperandrogenism. However, not all women with greater amounts of secondary sexual hair will have abnormal androgens. Many will lie within the range of normal for their age and ethnic origin—albeit possibly at an extreme of the spectrum. For those objectively classified as hirsute, many will have underlying PCOS. Most of the others will have no detectable hormonal abnormality and are usually classified as having 'idiopathic' hirsutism. This subgroup is gradually becoming smaller as diagnostic techniques for PCOS become more refined.

Polycystic ovary syndrome [3–5]. The perception of PCOS has changed dramatically since it was first described by Stein and Leventhal in 1935 [6]. They defined a syndrome consisting of obesity, amenorrhoea, hirsutism and infertility associated with enlarged polycystic ovaries. This diagnosis is complicated by the fact that it is defined by the appearance of organs that are difficult to visualize. This has led to the use of multiple diagnostic formulations based on clinical and biochemical abnormalities. A more fundamental issue has been raised by modern imaging techniques, which have revealed the presence of polycystic ovaries in normal women [7] or mildly polycystic ovaries in hirsute women with normal menses [8]. The latter finding has led to the inclusion of women who were previously labelled as having idiopathic hirsutism under the diagnosis of PCOS. An estimated one-third of women in the UK have polycystic ovaries—defined as 10 or more follicles/ovary detected on ultrasound [9]. One-third of these women will suffer from PCOS, which is now formally defined in the UK as the presence of polycystic ovaries in the presence of one or more of hirsutism, male pattern baldness, acne, oligomenorrhoea or amenorrhoea, obesity, or raised serum concentrations of testosterone and/or luteinizing hormone [10]. The pattern of these features will depend upon the presenting complaint, be it dermatological, endocrinological or gynaecological. Using ultrasound visualization of polycystic ovaries as the diagnostic criterion in those presenting to a gynaecologist, Conway *et al.* [11] found the following clinical features in a series of 556 patients: hirsutism (61%), acne (24%), alopecia (8%), acanthosis nigricans (2%), obesity (35%), menorrhagia (1%), oligomenorrhoea (45%), amenorrhoea (26%) and infertility (over 29%). However, those patients who present to a dermatologist will almost invariably have acne and/or hirsutism.

Laboratory investigations in PCOS usually reveal an elevated level of LH, often with an increased LH : follicle-stimulating hormone (FSH) ratio, and testosterone, androstenedione and oestradiol levels are also often raised [12], although these tests are neither wholly sensitive nor specific. The demonstration by ultrasound examination of multiple peripheral ovarian cysts around a dense central core will depend on the expertise of the operator [13].

Ideas concerning the pathogenesis of PCOS have been as controversial as the diagnosis, and different authorities embrace beliefs that it is primarily caused by an ovarian abnormality, inappropriate gonodotrophin secretion, a disorder of the adrenal glands or increased peripheral aromatase activity resulting in hyperoestrogenaemia [14]. Whether the increased androgen is of adrenal or ovarian origin remains unclear [15]. However, in addition to the presence of elevated testosterone, commonly in the range of 2.6–4.8 nmol/L [4], 50% or more of patients will have hyperinsulinaemia of varying degrees [16]. This appears to be the case for both the classically obese and the non-obese PCOS patient [17]. Insulin acts to inhibit production of SHBG and stimulates ovarian testosterone production. Both effects amplify androgenic features in PCOS. Excess insulin production is related to the feedback loop of peripheral insulin resistance which increases in PCOS. This is characteristic of type 2 diabetes mellitus, which is a disease more common in PCOS. Consistent with this association, PCOS patients are also at higher risk of dyslipidaemias and coronary artery disease [18]. Altered glucose tolerance, hyperinsulinaemia and hirsutism are all exacerbated by obesity, and the relationship between diabetes and hyperandrogenism in women, or 'diabetes of bearded women', has been recognized for many years [19].

Such features are not invariably part of PCOS. Hyperinsulinaemia may be an autonomous process causing acanthosis nigricans (AN), which acts as a cutaneous marker for the insulin resistance (IR). The combination of AN and IR occurs in 5% of women with hyperandrogenism (HA) [20] and in 7% of women presenting with

hirsutism [21]. Women with HAIR-AN have marked features of virilism: muscular physique, acne, alopecia and hidradenitis suppurativa [21]. The cause of hyperinsulinaemia is not always apparent, but its effects can be partly reversed by troglitazone [22], and its significance is illustrated by the evolution of HAIR-AN syndrome with an insulin-secreting tumour, cured by partial pancreatectomy [23].

Leptin is a protein secreted by adipocytes that increases energy expenditure and decreases appetite [24]. In genetically obese *ob*/*ob* mice, leptin is functionally deficient and the mice develop obesity, insulin resistance, diabetes and infertility. In recent years, there has been much interest in determining the role of this protein in PCOS. High serum levels appear primarily related to obesity rather than the diagnosis of PCOS alone [25] and there is evidence that its fluctuations are synchronized with those of luteinizing hormone [26]. However, although there is some correlation between polymorphisms of the leptin gene and insulin regulation, no mutation specific to PCOS has yet been identified [27]. Although family studies of PCOS suggest an autosomal dominant inheritance, no single gene has been defined. Linkage has been found to the follistatin gene on 5q (follistatin is a peptide with the ability to inhibit release of FSH). PCOS is also strongly associated with polymorphisms of the gene for cytochrome P-450, CYP, on chromosome 15q [28], and a susceptibility gene for PCOS located on chromosome 19p13.3, in the insulin receptor gene region, has been demonstrated [29].

SAHA syndrome. The term SAHA syndrome is used by some to describe the constellation of features that arise with cutaneous virilization [30]. The acronym stands for *s*eborrhoea, *a*cne, *h*irsutism and *a*ndrogenetic alopecia. The term does not suggest any specific aetiology; all the causes of hirsutism need to be considered and investigated where clinically indicated. As with all women with hirsutism, androgen receptor sensitivity can be implicated where there are no apparent endocrine abnormalities. The four features exist together in only 20% of women embraced by this diagnosis, but the concept is favoured by some as a clinical label encompassing the range of problems associated with the diagnosis of hirsutism.

Ovarian tumours. Hirsutism is an almost universal feature in virilizing ovarian tumours; however, functioning tumours that cause virilization represent approximately 1% of ovarian tumours [31]. Amenorrhoea or oligomenorrhoea develop in all premenopausal patients, and alopecia, clitoromegaly, deepening of the voice and a male habitus develop in approximately half of the patients [32,33]. The majority of patients with virilizing ovarian tumours have raised plasma testosterone levels [31,33]. As a rule, these levels exceed double the upper limit of normal and combine with the more extreme and evolving clinical picture to distinguish these women from those with PCOS.

Hirsutism in pregnancy. Hirsutism has only rarely been reported to develop during pregnancy; it may be caused by the development of PCOS or a virilizing tumour. PCOS has been reported to present with virilization during the first or third trimester and may regress postpartum [34]. Androgens freely cross the placenta and virilization of a female fetus may occur [35]. The range of tumours occurring during pregnancy has been reviewed by Novak *et al.* [36].

Congenital adrenal hyperplasia. Cholesterol is metabolized in the adrenal cortex, via a complex pathway, into aldosterone, cortisol, androgens and oestrogens. A defect in cortisol synthesis results in redistribution of the precursors to other pathways, which results in overproduction of the other hormones. In approximately 95% of cases, 21-hydroxylation is impaired [37] so that 17-hydroxyprogesterone (17-OHP) is not converted to 11-deoxycortisol. Because of defective cortisol synthesis, ACTH levels increase, resulting in overproduction and accumulation of cortisol precursors, particularly 17-OHP. This causes excessive production of androgens, resulting in virilization.

Congenital adrenal hyperplasia (CAH) is divided into four categories:

1 Salt-losing, which presents in infancy with dehydration
2 Simple virilizing, in which children present with precocious puberty and short stature
3 Non-classic, attenuated or acquired, and it is this variant that is likely to present to the dermatologist with degrees of hirsutism in otherwise well women
4 Cryptic.

The diagnosis of non-classic late-onset CAH (LO-CAH) cannot be made clinically, and dynamic endocrine investigations are required to differentiate between it, PCOS and idiopathic hirsutism. These women may have only mild degrees of hirsutism, normal physique, normal menses and no metabolic sequelae to the changes in cortisol pathways; however, approximately 80% will have polycystic ovaries [38].

21-Hydroxylase deficiency is the most common defect found with (more than 90%) LO-CAH. As many as 3–6% of women presenting with hirsutism may be affected with this form. It is an allelic variant of the classic childhood salt-wasting type. It is associated with a mutation of the gene controlling cytochrome P-450, CYP 21 on chromosome 6 [39]. Among a group of 56 women with LO-CAH, a range of mutations was found. Some put the woman at risk of progeny with classic salt-losing CAH if the father is heterozygous for the same mutation. This raises the significance of detailed analysis of this pathway in such women and the genotypic basis in the woman and male partner [40]. 3β- and 11β-hydroxylase deficiencies are less

common forms of CAH and are consequently less frequently found in hirsute women [41]. This is not a diagnosis made in men, although we must presume that they are equally affected and that it is not of any metabolic significance. Where men are heterozygous for mutations relevant to the salt-losing variant, the genotype of the mother will be relevant.

Acquired adrenocortical disease. Adrenal carcinomas usually present with abdominal swelling or pain; however, 10% of both adenomas and carcinomas may present with isolated virilization [42]. The combination of virilization and Cushing's syndrome strongly suggests the presence of a carcinoma. The testosterone level is usually markedly raised in the latter.

Patients with Cushing's syndrome are said to have both hypertrichosis, a generalized diffuse growth of fine hair resulting from hypercortisolaemia, and androgen-induced coarse hair in the usual male pattern [43].

Gonadal dysgenesis. Moltz *et al*. [44] described six patients with 46XY gonadal dysgenesis. All had unambiguously female genitalia but male skeletal characteristics: wide-span broad shoulders and chest; two were hirsute, two had temporal recession and three had deep voices. Rosen *et al*. [45] reported a further 30 patients with gonadal dysgenesis, of whom three (with Y chromosome material) presented with slowly progressive hirsutism and secondary amenorrhoea.

Hyperprolactinaemia. The exact relationship between prolactin and hirsutism is not clear. The incidence of hirsutism in the amenorrhoea–galactorrhoea syndrome has been reported as 22–60% [46]. This may be caused by a direct effect of prolactin on adrenal androgen production or to PCOS, with which it is frequently associated; prolactin has also been reported to attenuate cutaneous 5α-reductase activity both *in vivo* and *in vitro* [47].

Idiopathic hirsutism (Fig. 63.79). Idiopathic hirsutism is the diagnostic label given to those hirsute women in whom no overt underlying endocrine disorder can be detected. There are a number of subtle dynamic alterations in the androgen metabolism of some hirsute women compared with non-hirsute women: daily testosterone production can be increased 3.5–5-fold; the majority of androgen is secreted as testosterone (hirsute 75%, versus normal less than 40%) rather than as androstenedione [48]; increased androgens in hirsute women are associated with lower levels of SHBG, which binds less testosterone and increases its free level [49]. More free testosterone is therefore available for peripheral metabolism and clearance; these two factors disguise the increased rates of testosterone production.

Normal values for total testosterone are found in 25–60% of hirsute women and in 80% of those with regular menstrual cycles [50]. This may be a result of the effect of SHBG or to the wide fluctuations in plasma testosterone seen in hirsute women, or it may reflect the role of androgen receptor sensitivity. The finding of a small elevation of testosterone is not a holy grail, and the tendency to repeat the test many times in the setting of hirsutism is only warranted in progressive or extreme cases where a neoplasm is suspected. Although many women classified as having idiopathic hirsutism may have subtle PCOS, others may be completely normal.

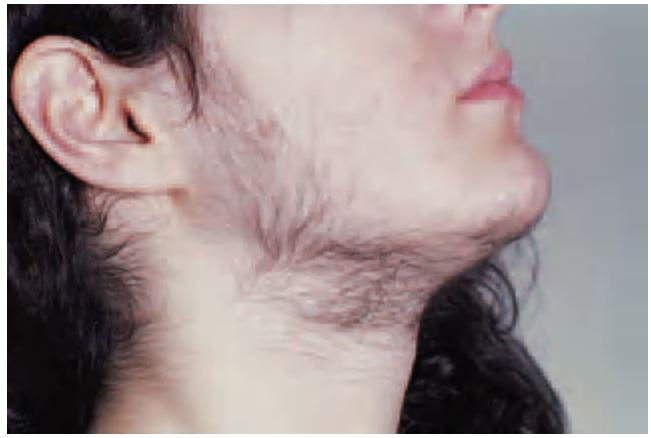

Fig. 63.79 Facial hirsutism: in this case not associated with any systemic disease or detectable biochemical endocrine abnormality.

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Diagnostic approach to the hirsute woman

Most hirsute women have noted excess hair since puberty; some will give a shorter history but it will be in the order of years. It is important to obtain information from the history regarding patterns of hirsutism, alopecia, other features of cutaneous virilism and evidence for PCOS, in particular irregular menses or infertility. A family history of childhood dehydration or precocious puberty in a brother might be a feature of CAH. A drug history may point to an ingested source of androgens (e.g. glucocorticoid or anabolic steroids) and those used to enhance athletic performance. The progestogenic components of many contraceptive preparations are relatively androgenic and this is often cited as a cause of hirsutism, but it has not been a major factor in our experience.

The cutaneous examination should include the pattern and severity of hair growth and the associated presence of acne, androgenetic alopecia and acanthosis nigricans. Systemic virilization is very rare, and likely to indicate significant pathology such as a testosterone-secreting tumour. Features include a deepening voice, increased muscle bulk and loss of the smooth skin contours, hypertension, striae distensae and clitoromegaly. Clitoromegaly is probably the most important physical sign of systemic virilization. These changes are set apart from cutaneous virilism, and if evolving over a short period (e.g. 12–18 months) they warrant detailed investigation.

The extent to which it is necessary for hirsute women without suspicious signs or history to be investigated is debatable. The main reason cited for investigation of most hirsute women is the inability to differentiate between idiopathic hirsutism, PCOS and LO-CAH on clinical grounds. Not all dermatologists consider it necessary to pursue a diagnosis of PCOS and its ramifications in a woman with normal menses who is not attempting to conceive. Equally, the value of pursuing a diagnosis of LO-CAH is doubtful when there is no clinical metabolic problem, and the therapeutic tools available at present are

too clumsy to warrant such diagnostic sensitivity [1,2]. However, it remains an overriding priority to exclude a virilizing tumour if this is suggested by the history and examination.

If it is necessary to undertake investigations, these should be directed by the presenting complaint and diagnostic objectives. In addition to clinical assessment, abnormal menses represent a trigger for investigation. The best screening test for an androgen-secreting tumour is plasma total testosterone. Mild elevations will usually occur in individuals with PCOS, and those in whom the level is more than twice the upper limit of normal require further investigation to exclude a neoplasm. However, if confirmation of a diagnosis of PCOS is required, estimation of plasma LH and FSH and pelvic ultrasound are indicated. In addition, the metabolic aspects of PCOS warrant a fasting glucose and lipid profile. Some authorities would suggest a full glucose tolerance test in those with established PCOS.

Prolactin levels, and assessment of adrenal and thyroid status would normally be undertaken if there were clinical clues suggesting abnormality of these systems. Pursuance of the diagnosis of LO-CAH is controversial. There is no record of women with this disorder being at risk of any significant salt-losing process. However, there may be reduced fertility [3] and if the woman is heterozygous for a mutation that predisposes to the salt-losing variant, her progeny may be at risk if their father is heterozygous for the same mutation [4]. This last point raises the question of whether the diagnosis should be sought more rigorously. Although it may not alter clinical management of the hirsutism, it may be of significance to the reproductive plans of the woman. At present, defining whether the woman is heterozygous for a mutation of the CYP 21 gene that can lead to the salt-losing variant of CAH in offspring is limited to gene analysis. The phenotype and endocrine investigations are not sufficiently sensitive to distinguish between heterozygosity for a range of CAH mutations of differing significance. The standard screening test for such mutations is estimation of the basal plasma 17-hydroxyprogesterone level.

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Treatment [1–4]

For most women, medical consultation concerning excess hair is on two levels. First it is necessary to determine whether the pattern is pathological and related to a definable aetiology. For some, weight loss will contribute to a reduction of insulin resistance, hyperinsulinaemia and hyperandrogenism. Often, medical intervention is not needed. However, the next level concerns whether there is a medical avenue for providing help, even with the acknowledgement that treatment is not for a disease, but in order to achieve a cosmetic norm.

Cosmetic measures

Where a woman has failed to make full use of physical methods of hair removal it is helpful if the dermatologist is familiar with what is available [4] or can direct her to a reliable beautician or other expert in cosmetic care for advice. The easiest measure is to bleach the hair with hydrogen peroxide. This produces a yellow hue because of the native colour of keratin. Hair plucking is widely performed, but the act of plucking not only removes the hair shaft but also stimulates the root into the anagen phase and there is only a brief delay while the shaft grows through the epidermis. Shaving avoids this problem by removing all the hairs but is followed by growth only of the hairs that were previously in anagen.

Depilatory creams contain thioglycolates that dissolve sulphur bonds within keratin molecules, making the hair gelatinous. They are irritant and require care in terms of strength of preparation and duration of exposure. It is often the case that the patient has used a depilatory cream once and given up because she became sore or it did not work. Results can be improved by employing the cream much in the same way that one might use dithranol when treating psoriasis, using small test areas to gain experience.

Waxing is performed by the application of a sheet of soft wax to the skin and, as soon as it has hardened with the hair shafts embedded, it is abruptly peeled off, removing all the shafts. This is a painful method and is often complicated by folliculitis. Certain natural sugars, long used in parts of the Middle East, are becoming popular in place of waxes as they appear to depilate as effectively, but with less trauma. Both methods require the hair to be long enough for the wax, resin or sugar to gain sufficient purchase on the hair shaft.

Electrolysis is a more permanent method of hair removal [4]. A fine electrical wire is introduced down the hair shaft to the papilla, which is destroyed by an electrical current. Laser thermolytic hair removal is now widely used. Although its long-term efficacy is not yet known [5], laser-assisted hair removal has been in use for sufficient time to allow a reasonable estimate of its efficacy and safety. Most practitioners will select patients for dark hair and light skin. This maximizes the absorption of laser energy by the hair and minimizes absorption by the skin. Nevertheless, it is still possible for soreness and crusting to occur following treatment. In darker skin this can be

associated with post-inflammatory pigmentary changes. Treatments are usually administered as part of a course of at least three visits separated by several weeks. This reflects the biology of the follicle, which is most responsive to abalation when in anagen. The gap between treatments allows those hairs initially in telogen to move into anagen. Sommer *et al.* [6] compared the hair counts 36 weeks after four treatments to the face with a normal pulse ruby laser with the effects of a single pulse. Hair counts were reduced by 61% and 41%, respectively. As well as laser techniques, there are alternatives to the use of lasers. Broad-band intense pulsed light represents a cheaper technology with less restriction on the licensing of those who use it. There are no good comparative studies of laser and pulsed light, but results from open trials of the latter suggest it is useful [7]. In a study of pulsed light therapy of hirsutism, 76% hair clearance was reported following a mean of 3.7 treatments [8].

Drug therapy [9]

Because hirsutism is a condition mediated by androgens, attempts have been made to reduce the growth of hair with antiandrogens. The complete spectrum of therapeutic agents evaluated in the treatment of hirsutism is described in the following text. However, it is our practice to use cyproterone acetate in combination with ethinylestradiol as first-line therapy for women whose hirsutism is so severe as to warrant systemic therapy. Spironolactone is the next alternative [1]. The oral contraceptive can be useful to avoid conception during therapy with antiandrogens. At the same time, it will increase the amount of SHBG and reduce free androgen. A progestogen in the oral contraceptive, such as norethisterone, is best avoided in favour of one of the synthetic progestogens to avoid any potential intrinsic androgenic effect.

It is important that hirsute women are carefully assessed prior to initiating therapy for the following reasons. First, the effect on hair growth takes several months to become apparent and only partial improvement may be expected. Secondly, antiandrogens feminize a male fetus and it is essential that the women do not become pregnant during therapy. Thirdly, these drugs only have a suppressive, and not curative, effect that wears off a few months after cessation of therapy [10]. Consequently, it may be necessary to take therapy indefinitely if improvement occurs. Finally, the long-term safety of these drugs is unknown and tumours in laboratory animals have been reported with several of the following agents.

Cyproterone acetate [11,12]. Cyproterone acetate (CPA) is a synthetic progestogen that acts as both an antiandrogen and an inhibitor of gonadotrophin secretion. It reduces androgen production, increases the metabolic clearance of testosterone and binds to the androgen receptor; in addition, long-term therapy is associated with a reduction in the activity of cutaneous 5α-reductase. Although CPA is a potent progestogen it does not reliably inhibit ovulation. It is usually administered with cyclical oestrogens in order to maintain regular menstruation and to prevent conception in view of the risk of feminizing a male fetus.

Several regimens have been advocated. Low-dose therapy (Dianette; Schering AG) is an oral contraceptive containing 35 μg ethinylestradiol and 2 mg CPA, taken daily for 21 in every 28 days. However, many of the dose-ranging and efficacy studies have been performed using the preparation that contained 50 μg ethinylestradiol; this may be relevant, as only the higher dose of oestrogen increases SHBG. Current dosage recommendations for CPA usually advise that 50 mg or 100 mg CPA should be administered for 10 days/cycle (e.g. day 1–10 or 5–15). However, there have now been many dose-ranging studies that suggest that there is no dose effect. Objective studies comparing Dianette with and without extra CPA found no difference in the reduction of overall hirsutism grades, although the rate of onset of benefit was faster with the additional cyproterone [13].

Side effects of CPA include weight gain, fatigue, loss of libido, breast tenderness, nausea, headaches and depression. All these side effects are more frequent with higher dosage. As with all medication for a cosmetic problem, safety can be a concern for those needing long-term treatment. Contraindications to its use are the same as for the contraceptive pill and include cigarette smoking, age, obesity and hypertension. Venous thromboembolism is the adverse effect of greatest medical significance. A case–controlled study indicated that risk of this was four times greater in women taking an oral contraceptive containing CPA as the progestogen in comparison with those containing levonorgestrel [14].

One retrospective study of 188 women taking CPA 50–100 mg/day, described side effects in 23%. Nine per cent of the total group stopped therapy on account of these effects, but it is difficult to discern whether the problems were a result of the CPA or ethinylestradiol that many also took. Most of the problems were related to mood, weight or menstrual disturbance. Within the group, 24 had been treated for 5 years or more, nine for 10 years or more and two for 15 years [15].

Spironolactone [16,17]. Spironolactone is a popular and relatively safe treatment for hirsutism. Formal proof of its efficacy is not to the highest standards, although a Cochrane review concluded that it was of some value [18]. The discovery of its benefit in hirsutism was serendipitous—a 19-year-old hirsute woman with PCOS was treated with spironolactone (200 mg/day) for concurrent hypertension and she noted after 3 months the need to shave less frequently.

Spironolactone has several antiandrogenic pharmacological properties. It reduces the bioavailability of testosterone by interfering with its production and increases its

metabolic clearance. It binds to the androgen receptor and, like CPA, long-term therapy is associated with a reduction in cutaneous 5α-reductase activity [19]. Different regimens of spironolactone have been studied, varying between 50 and 200 mg taken either daily or cyclically (daily for 3 weeks in every 4). Within this dosage range, the one chosen will depend on the severity of the hirsutism. A 3 out of 4 week cycle will result in a withdrawal bleed in the fourth week which is similar to that seen with the oral contraceptive. However, spironolactone cannot be relied on as a contraceptive and care must be taken to avoid conception while on the drug.

Spritzer *et al.* [20] compared the relative benefits of a combination of CPA 50 mg/day and ethinylestradiol 35 µg/day with spironolactone 200 mg/day over 12 months. Both groups were stratified for those with PCOS and idiopathic hirsutism. In both groups, those with idiopathic hirsutism did equally well. However, those with PCOS did significantly better with the CPA/ethinylestradiol combination. Where spironolactone is used in combination with ethinylestradiol 35 µg and CPA 2 mg, there may be some modest advantage [21].

When compared with finasteride 5 mg, spironolactone 100 mg produced a significantly greater improvement during a 9-month trial [22]. Spironolactone may feminize a male fetus. Long-term high-dose spironolactone has been shown to produce tumours in rodents. Some clinicians feel that this finding makes long-term use inappropriate in healthy young patients with hirsutism.

5α-Reductase inhibitors. 5α-Reductase inhibitors are a potential systemic therapy for hirsutism. Finasteride inhibits the type 2 isoenzyme of 5α-reductase and has been assessed in small placebo-controlled trials, with some benefit after 6 months' therapy. In open trials, maximal benefit was seen in idiopathic hirsutism after 12 months [23]. Controlled comparative trials suggest that flutamide [24] and spironolactone [22] are more effective. Topical finasteride has been trialled with mixed results [25]. Other similar systemic and topical 5α-reductase inhibitors are likely to be available in the near future. This group of drugs feminizes a male fetus, which is a drawback in the therapy of women of child-bearing potential and has precluded a drug licence for the treatment of hirsutism.

Corticosteroids. Corticosteroids have a logical place in the treatment of LO-CAH. However, any benefits that they may have in this setting need to be balanced against their well-described side effects. Although their use is justified on the basis of physiological replacement, it is likely that pharmacological regimens will far exceed this, with consequent problems. Spritzer *et al.* [26] demonstrated the superiority of ethinylestradiol 35 µg with CPA 2 mg over hydrocortisone in treatment of hirsutism associated with LO-CAH [26].

Metformin. Metformin is a biguanide originally used in the treatment of type 2 diabetes mellitus. It has found a place in the treatment of hirsutism associated with hyperinsulinaemia and insulin resistance. In this setting, it can reduce levels of insulin, increase insulin sensitivity and, particularly when associated with a low-calorie diet, result in weight loss [27]. In many, this constellation of problems will be part of PCOS, and metformin has also been shown to assist in normalization of menstruation and improvement in lipid profiles [28]. These broader metabolic effects can make it a useful therapy where hirsutism is not the only problem, although its use in PCOS requires further assessment [29,30].

Eflornithine. Eflornithine was originally used orally in the treatment of hyperactivity in childhood. It is an inhibitor of ornithine decarboxylase and is able to delay the initiation of anagen [31]. Consequently, it can help to keep hair in telogen. Limited studies show some reduction in hirsutism when used as a cream on women's faces [32].

Medroxyprogesterone acetate. Medroxyprogesterone acetate (MPA) is a synthetic progestogen that was introduced as an anovulatory agent because of its ability to block gonadotrophin secretion. It lowers androgen levels by reducing the production of testosterone and increasing its metabolic clearance.

A comparison of topical (0.2% ointment) with systemic therapy, either by intramuscular injection of MPA (150 mg every 6 weeks) or subcutaneous injection (100 mg every 6 weeks), was said to give a beneficial response in most patients [33]. MPA given alone may result in menorrhagia.

Desogestrel. This is the progestogen used in the Marvelon® contraceptive pill (Organon Ltd), which contains 30 µg ethinylestradiol and 150 mg desogestrel. All the studies undertaken have reported subjective and/or objective reductions in hair growth of 20–25% after 6–9 months' therapy, with a high degree of patient satisfaction [34].

Ketoconazole. This is a potent inhibitor of adrenal and ovarian steroid synthesis. There have been only isolated reports of its use in hirsutism but these have demonstrated a marked reduction in hair growth after 6 months [35]. However, this treatment cannot be recommended in view of the risks of hepatic toxicity during long-term therapy.

Flutamide [36]. This acts as a pure antiandrogen and works by binding to androgen receptors. However, it has no antigonadotrophic effect, and the result of binding to central androgen receptors is that it prevents the negative feedback effect of testosterone, and consequently androgen levels rise. There has been a single study in hirsutism in which flutamide (250 mg twice daily) was administered

with an oral contraceptive for 7 months; 12 out of 13 patients demonstrated a subjective reduction in hair growth and improvement in acne [37]. Flutamide is potentially hepatotoxic and requires close monitoring to avoid liver complications. This has limited its use.

Gonadotrophin-releasing hormone agonists. Gonadotrophin-releasing hormone (GnRH) agonists inhibit LH production and this results in profound suppression of ovarian androgen production. These agents are presently under investigation, but preliminary studies suggest that they effectively reduce hair growth and acne in women with PCOS [38] and may be superior to finasteride [39]. Drawbacks are cost and the need for monthly injections.

Cimetidine. Cimetidine is an H_2 receptor blocker, and weak antiandrogen as indicated by androgen receptor-binding studies. A study of patients with idiopathic hirsutism demonstrated a marked reduction in hair growth using hair weight, whereas no such effect was seen in controls given only a placebo [40].

Bromocriptine. This is a dopamine agonist, and long-term therapy with bromocriptine regulates menstrual cycle length, but 12 months' therapy produced no measurable effect on linear hair growth in women with polycystic ovaries [41].

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Hair pigmentation [1–3]

In humans, hair pigmentation depends entirely on the presence of melanin from melanocytes. The perceived colour will depend also on physical phenomena. The range of colours produced by melanins is limited to shades of grey, yellow, brown, red and black, depending on the amount and ratio of eumelanin (black) and phaeomelanin (red).

It is important to remember that much of the research on melanogenesis and its cellular control is in relation to epidermis outside the follicle. Many aspects of hair bulb melanogenesis are likely to be the same. Hair melanin is formed by melanocytes situated in the hair bulb epithelium around the upper half of the dermal papilla amongst cells destined to form the hair cortex. Ultrastructurally, hair bulb melanocytes appear more melanogenic than epidermal melanocytes and their population density is much greater than in the epidermis (approximately one melanocyte to four basal keratinocytes in the upper hair bulb compared with a ratio of 1 : 25 in the basal layer of the epidermis [4]). Melanocytes are also present in the basal layer of the infundibulum and, in small numbers, in the outer root sheath of the lower part of the follicle. These latter cells are DOPA-negative and non-melanized and are thought to form a melanocyte reservoir in the skin. Under certain circumstances (e.g. during repigmentation of vitiligo), outer root sheath melanocytes proliferate and migrate to the epidermis [5]. In humans, hair bulb melanocytes donate pigment almost exclusively to cells undergoing early differentiation to form the hair cortex (Fig. 63.80). Therefore there is a close spatial and functional relationship between hair bulb melanocytes and the cells that act as pigment receptors (cortical keratinocytes).

Melanogenic activity in the hair follicle is closely linked to the hair cycle. In the telogen follicle, non-melanogenic melanocytes are found in the basal layer of the outer root sheath and in the secondary germ region [6]. These cells are assumed to be the precursors of active melanocytes during the next anagen phase and either migrate or are carried into the hair bulb in early anagen development. They congregate in the upper part of the anagen hair bulb amongst cells destined to form the hair cortex. Melanogenesis begins well after epithelial proliferation has started and coincides with the onset of morphological evidence of cortical differentiation. Tyrosinase activity becomes apparent in Anagen 3 and pigment transfer to cortical epithelium begins in the Anagen 4 stage of development [7–9]. In pigmented hair follicles, intense melanogenesis continues throughout the remainder of anagen (Anagen 5 and 6) and then ceases with the onset of catagen. The close anatomical and functional association of hair bulb melanocytes with cells to which pigment is donated, cells destined to form the hair cortex, suggests that interaction between these two cell types has a key role in regulating pigmentary activity. The fate of hair bulb melanocytes during catagen is uncertain. Non-melanizing melanocytes have been observed in the regressing epithelial column in human catagen follicles [10] but apoptotic deletion of follicular melanocytes has also been described during this stage of the hair cycle [11].

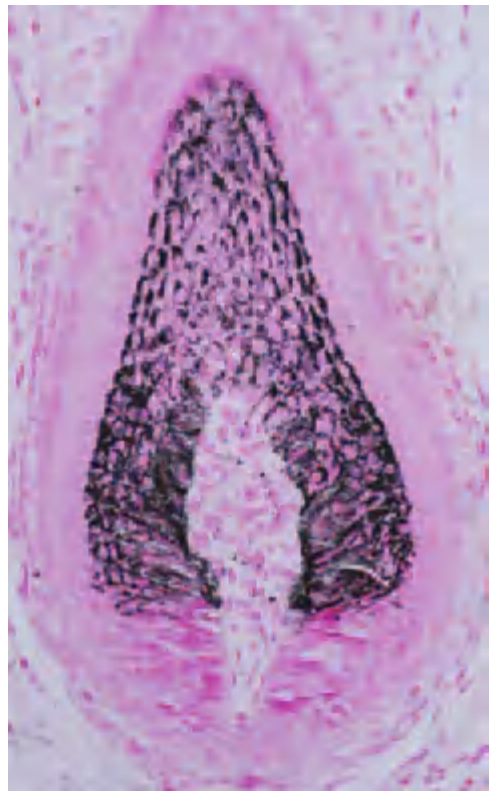

Fig. 63.80 Human anagen follicle showing pigment donation to the hair cortex. There is pigment incontinence in the dermal papilla (Masson–Fontana stain).

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Melanogenesis [1–3]

Functional melanocytes respond to the peptide hormones α-melanocyte stimulating hormone (α-MSH) or ACTH through the MC1R receptor to stimulate melanin production. This receptor is a transmembrane G-protein. When bound to melanocortin peptides, intracellular cyclic adenosine monophosphate (AMP) rises, resulting in tyrosinase gene expression, melanocyte proliferation and increased dendricity. There may also be switching of melanin type. Loss of function mutations in the *MC1R* gene are associated with a switch from eumelanin (dark) to phaeomelanin (red) production [4,5]. The phaeomelanosome, containing the key enzyme of the tyrosinase pathway, produces light red-yellowish melanin, whereas the eumelanosome produces darker melanins via induction of additional TYRP1, TYRP2, SILV enzymes, and the P-protein. Intramelanosomal pH, governed by the P-protein, may act as a critical determinant of tyrosinase enzyme activity. There is significant genetic variation in the genes from which these proteins arise. Over 30 variant alleles have been identified in the *MC1R* gene alone. Functional correlation of *MC1R* alleles with skin and hair colour provides evidence that this receptor molecule is a principal component underlying normal human pigment variation.

In black hair follicles, deposition of melanin within melanosomes continues until the whole unit is uniformly dense. Lighter coloured hair shows less melanin deposition, and blonde hair follicles show melanosomes with a moth-eaten appearance. Red and blonde hair follicles have spherical melanosomes; those in brown and black hair are ellipsoidal.

Pigment is incorporated into hair cortex. No pigment is donated to presumptive cuticular and internal root sheath cells, although pigment granules have been detected in the cuticle of human nostril hair and in the coats of many animals [6]. Melanocytes are functional only during the anagen phase of the hair cycle. They were formerly thought to disappear during telogen but it is now known that they remain at the surface of the papilla in a shrunken adendritic form. Jimbow *et al*. [7] found melanocytes with mature melanosomes in resting (telogen) feather follicles. It is possible that the full complement of melanocytes present during successive anagen phases is the result not only of reactivation of 'dormant' cells, but also of new cells resulting from melanocyte replication [8].

Hair colour resulting from physical phenomena

The whiteness of hair seen when melanin is absent is an optical effect resulting from reflection and refraction of incident light from various interfaces at which zones of different refractive index meet. Thus, in general, non-pigmented hair with a broad medulla appears paler than non-medullated hair. Normal 'weathering' of hair along its length may lead to the terminal part appearing lighter than the rest as a result of a similar mechanism—the cortex and cuticle become disrupted and form numerous interfaces from internal reflection and refraction of light. This also applies in trichorrhexis nodosa (excessive 'weathering'), in which patients often note a lightening in colour of the brittle hair, and in the white bands of pili annulati. Because these optical lightening effects are caused by reflection and refraction of incident light, when such hairs are viewed by transmitted light microscopy they appear dark. Newly formed unpigmented hair with no medulla appears yellowish rather than white. This is probably the intrinsic colour of dense keratin as orientated in hair fibres. Findlay [9] showed that the perceived colour is affected by the physical characteristics of the hair shaft and may bear little relationship to the true chromaticity of the shaft.

Hair fibre tryptophan content increases with age and within age groups, and is higher in dark hair than fair hair. The exception is with white hair and the significance of these findings is uncertain [10].

Lanugo hair present *in utero* is unpigmented. Vellus hair is also typically unpigmented but, in men in particular, some vellus fibres may pigment slightly after puberty. Hair colour varies according to body site in most people. Eyelashes are usually the darkest. Scalp hair is generally lighter than genital hair, which often has a reddish tint even in subjects having essentially brown hair. Grobbelaar [11] showed that hair on the lower and lateral scrotal surfaces is lighter than on the pubes. Apart from individuals with red scalp hair, a red tint to axillary hair is most common in brown-haired individuals.

Hairs on exposed parts may be bleached by sunlight. Very dark hair first lightens to a brownish red colour but rarely becomes blonde even after strong sunlight exposure; brown hair, however, may be bleached white.

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Variation in hair colour

Genetic and racial aspects [1–3]

Ethnic differences in hair colour are very conspicuous, as are the differences in hair morphology, although colour and hair form are inherited separately [4]. Dark hair predominates in the world. Among white people there is wide variation in colour within geographical regions. Blonde hair is most frequent in northern Europe and black hair in southern and eastern Europe; foci of blondeness are to be found even in North Africa, the Middle East and in some Australoids. Congoid, Capoid, Mongoloid and Australoid hair is mainly black.

Red hair (rutilism)

This has attracted more attention than other colours because it is less common and because it is so distinctive. The pigment is phaeomelanin, not eumelanin. In Italy, and in the UK excluding East Anglia, the distribution of red hair is similar to that of blood group O [5]. The incidence of red hair varies from 0.3% in northern Germany to as high as 11% in parts of Scotland. Like hair of many other colours, red hair often darkens with age from red through brown to sandy or auburn in the adult. The skin of redheads is generally pale, burns easily in sunlight and pigments very little even after prolonged and frequent sun exposure. The loss of eumelanin production is caused by a range of mutations in the *MCR1* gene that alter the function of the receptor and consequently melanin synthesis.

Heterochromia

This implies the growth of hair of two distinct colours in the same individual. A colour difference between scalp and moustache is not uncommon. In fair-haired individuals, pubic and axillary hair, eyebrows and eyelashes are much darker than scalp hair. In humans, eyelashes are generally the most darkly pigmented hairs.

In general, scalp hair darkens with age. Rarely, a circumscribed patch of hair occurs of different colour. This generally has a genetic basis, although the type of inheritance is not known in humans. Patchy differences of hair colour are of six types.

1 Tufts of very dark hair growing from a melanocytic naevus
2 Hereditary, usually autosomal dominant heterochromia (e.g. tufts of red hair at the temples in a black-haired subject or a single black patch in a blonde)
3 Perhaps as a result of somatic mosaicism; partial asymmetry of hair and eye colour may occur sporadically
4 The white forelock of piebaldism
5 The 'flag' sign in kwashiorkor
6 Fair fine woolly hair growing from a scalp woolly hair naevus.

Greying of hair (canities)

Greying of hair is usually a manifestation of the ageing process and results from a progressive reduction in melanocyte function [6]. The larger medullary spaces of older people may contribute to the process.

There is a gradual dilution of pigment in greying hairs: the full range of colour from normal to white can be seen both along individual hairs and from hair to hair. Loss of hair-shaft colour is associated with decrease and eventual cessation of tyrosinase activity in the lower bulb [7]. In white hairs, melanocytes are infrequent or absent [8] or possibly dormant. It has been suggested that autoimmunity plays a part in the pathogenesis of greying; grey hair certainly has an association with the autoimmune disease pernicious anaemia (see below) [9,10].

The age of onset of canities is primarily dependent on the genotype of the individual although acquired factors may play a part. The visual impression of greyness is more obvious (seen earlier) in the fair-haired. In white races, white hair first appears at the age of 34.2 ± 9.6 years, and by the age of 50 years 50% of the population have at least 50% grey hairs [14]. The onset in black people is 43.9 ± 10.3 years, and in Japanese between 30 and 34 years in men and between 35 and 39 years in women. The beard and moustache areas commonly become grey before scalp or body hair. On the scalp, the temples usually show greying first, followed by a wave of greyness spreading to the crown and later to the occipital area.

Rapid onset, allegedly 'overnight', greying of the hair has excited the literary, medical and anthropological worlds for centuries [11,12]. Many reports have been overdramatized but it certainly occurs. Historical examples often quoted include Sir Thomas More and Marie Antoinette whose hair became grey over the night preceding their executions. The probable mechanism for rapid greying is the selective shedding of pigmented hairs in diffuse alopecia areata, the non-pigmented hairs being retained (Figs 63.81 & 63.82).

Despite occasional reports to the contrary, in general, greying of hair is progressive and permanent, although melanogenesis during anagen may be intermittent for a time before finally stopping. Most of the reports of the

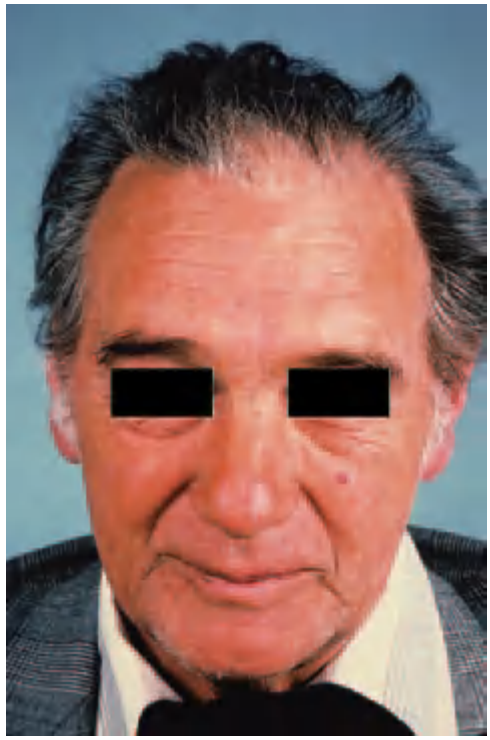

Fig. 63.81 Slight greying of hair. (Courtesy of Dr D. Fenton, St Thomas' Hospital, London, UK.)

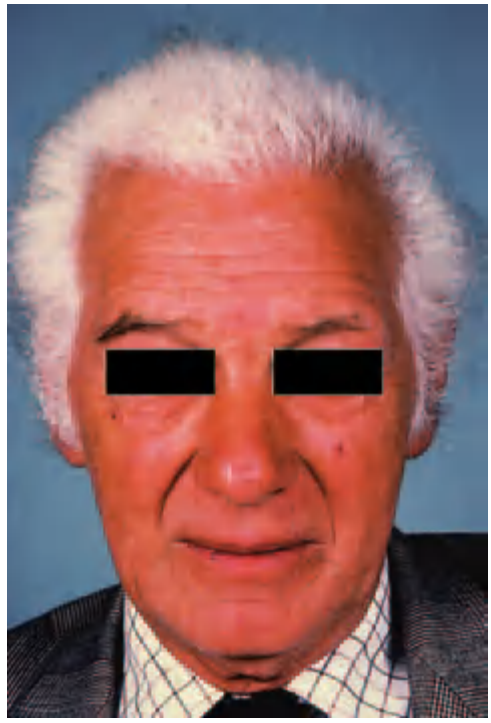

Fig. 63.82 Rapid greying of the hair. Same patient as Fig. 63.81 taken 1 week later. Caused by alopecia areata. (Courtesy of Dr D. Fenton, St Thomas' Hospital, London, UK.)

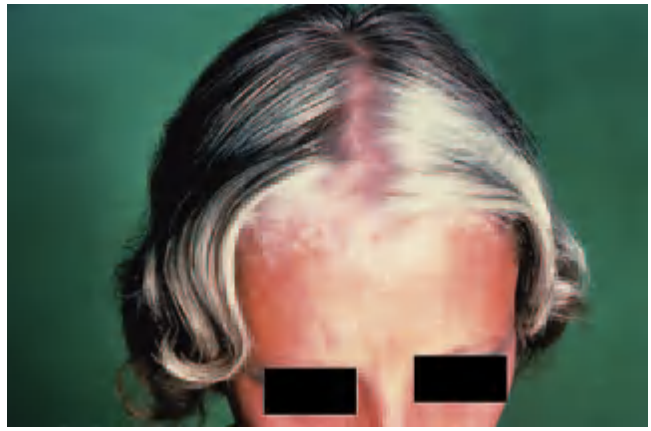

Fig. 63.83 Premature greying of hair, which commenced at 19 years of age in this individual.

return of normal hair colour from grey are examples of a pigmented regrowth following alopecia areata, which eventually repigments in many cases. The reported repigmentation of grey hair in association with Addisonian hypoadrenalism may result from a mechanism similar to that in alopecia areata or vitiligo, in view of the known association between these diseases [13–16]. Darkening of grey hair may occur following large doses of *p*-aminobenzoic acid [17].

Premature greying (Fig. 63.83)

Premature greying of hair has been defined as onset of greying before 20 years of age in white people and 30 years of age in black people. It probably has a genetic basis and occasionally occurs as an isolated autosomal dominant condition. The association between premature greying and certain organ-specific autoimmune diseases is well documented. The relationship is probably not one of common pathogenesis but on the basis of genetic linkage. It is often stated that premature greying may be an early sign of pernicious anaemia, hyperthyroidism and, less commonly, hypothyroidism, and all autoimmune diseases that have a genetic predisposition. In a controlled study of the integumentary associations of pernicious anaemia, 11% had premature greying [9]. In Book's syndrome, an autosomal dominant trait, premature greying is associated with premolar hypodontia and palmoplantar hyperhidrosis [18]. In the early stages, it may be partially reversible [19].

The premature ageing syndromes, progeria and Werner's syndrome (pangeria), may have very early greying as a prominent feature. It does not occur in metageria or total lipodystrophy [17]. In progeria it is associated with marked loss of scalp hair as early as 2 years of age.

In dystrophia myotonica the onset of grey hair may precede the myotonia and muscle wasting.

Premature canities is an inconstant feature of the Rothmund–Thomson syndrome; when present, it typically commences in adolescence.

One-third of patients with chromosome 5p syndrome (cri du chat syndrome) have prematurely grey hair [20].

Poliosis

Poliosis is defined as the presence of a localized patch of white hair resulting from the absence or deficiency of melanin in a group of neighbouring follicles. Essentially, the changes in melanogenesis are the same in the hair follicle as in the affected epidermis. Pigment absence can be congenital or acquired. In many cases of the former it is brought about by physically or functionally abnormal melanocytes from birth, or abnormal migration during embryogenesis. Such migratory defects may be restricted to the skin, but there can be associated abnormalities in other organs such as the ear or eye, where melanocytes or related neural crest cells have an important role.

Acquired forms of poliosis have more varied causes, although some of the most significant relate to autoimmunity where the melanocyte has attracted autoimmune attack.

Hereditary defects [21]

Piebaldism (white spotting or partial albinism) is an autosomal dominant abnormality with patches of skin totally devoid of pigment, which remain unchanged throughout life. The borders of unpigmented areas are hyperpigmented. Heterochromia iridis occurs in some. Most commonly, a frontal white patch occurs—the white forelock—which may be the only sign. Melanocytes are decreased in number, but are morphologically abnormal and contain normal non-melanized premelanosomes, and also premelanosomes and melanosomes of abnormal appearance [22]. Piebaldism can be caused by mutation in the *KIT* proto-oncogene [23] mapping to chromosome 4q12. In one kindred with a severe and progressive phenotype, the *KIT* mutation affected function of tyrosine kinase [24].

Similar pathological changes are seen in Tietz's syndrome of generalized 'white spot' loss of skin and hair pigment, complete deaf mutism and eyebrow hypoplasia [25]. This disease can be caused by a mutation in the microphthalmia-associated transcription factor gene, and mutations in other regions of this gene have been found to produce Waardenburg's syndrome (WS) type 2 [26].

WS [27] is a heterogeneous condition, usually divided into four types, with absence of melanocytes from cochlear, skin, eye, hair and other structures. Features are present at birth. Type 1 WS is characterized by dystopia canthorum with lateral displacement of the medial canthi, hypertrophy of the nasal root and hyperplasia of the inner third of the eyebrows with confluent brows [28,29]. Total or partial iridial heterochromia may occur, as may perceptive deafness. The white forelock is present in 20% of cases. Premature greying may develop with or without the white forelock [30]; a minority have piebaldism and congenital nerve deafness but no other overt signs of WS, suggesting that this association may be genetically distinct. Type 1 WS is caused by loss of function mutations in the *PAX3* gene which plays a part in control of neural crest cells during embryogenesis. Type 3 WS (Klein–Waardenburg syndrome, with abnormalities of the arms) is an extreme presentation of type 1, and affected individuals are usually homozygotes. Type 4 WS (Shah–Waardenburg syndrome with Hirschsprung's disease) can be caused by mutations in the genes for endothelin-3 or one of its receptors, EDNRB. Type 2 WS is a heterogeneous group, approximately 15% of whom are heterozygous for mutations in the *MITF* (microphthalmia-associated transcription factor) gene. All these forms show marked variability even within families, and at present it is not possible to predict the severity, even when a mutation is detected.

In vitiligo, the white patches of skin frequently have white hairs within them. The histological changes are consistent with an 'autoimmune injury' to the melanocytes.

Alezzandrini's syndrome combines unilateral facial vitiligo, retinitis and poliosis of eyebrows and eyelashes [31]; perceptive deafness is rarely associated.

In alopecia areata, regrowing hair is frequently white. It may remain so, particularly in cases of late onset. Although absent hair pigment is only evident at the stage of resolution, melanocytes are lost from the hair bulb quite early and migrate to the dermal papilla.

Poliosis occurs in 60% of people with tuberous sclerosis. Depigmented hair may be the earliest sign of the disease [32].

The pathognomonic signs of Von Recklinghausen's neurofibromatosis relate to hyperpigmented areas—café-au-lait macules and axillary and perineal freckling. Scalp hypopigmented patches must not be mistaken for vitiliginous changes.

Acquired defects [33]

Permanent pigmentary loss may be induced by inflammatory processes that damage melanocytes (e.g. herpes zoster). X-irradiation often causes permanent hair loss but less intense treatment leads to hypopigmented and, rarely, hyperpigmented hair. Patchy white hair may develop on the beard area after dental treatment.

The Vogt–Koyanagi–Harada syndrome [34,35] consists of a post-febrile condition comprising bilateral uveitis, labrynthine deafness, tinnitus and vitiligo, poliosis and alopecia areata. It is likely to be an autoimmune disease, with the melanocyte, tyrosinase or tyrosinase-related protein as targets.

Albinism [36]

In autosomal recessive oculocutaneous albinism (complete, perfect or generalized albinism) changes in the hair bulb melanocytes are similar to those in the epidermis [25]. This applies to tyrosine-positive and -negative types. Melanocytes are structurally normal and active in producing melanosomes of grades I and II. However, they are enzymically inactive. The melanocyte system is never completely devoid of melanin. In white people, the hair is typically yellowish white, although it might be cream, yellow, yellowish red or vibrant red. This range of colour parallels that seen in normal blonde white people. In Negroid albinos, the hair colour is white or yellowish brown.

Chediak–Higashi syndrome

This syndrome is basically an autosomal recessive defect of the membrane-bound organelles of several cell types [37]. It combines oculocutaneous hypopigmentation with a defect of leukocytes, which is lethal in some forms, but other affected individuals live to adulthood. The defect lies in the lysosome trafficking regulator gene found on 1q [36]. The hair is silvery grey or light blonde and may be sparse.

Colour changes induced by drugs and other chemicals

Some topical agents temporarily change hair colour. Dithranol and chrysarobin stain light-coloured or grey hair mahogany brown. Resorcin, formerly used a great deal in a variety of skin diseases, colours black or white hair yellow or yellowish brown.

Some systemic drugs alter hair colour by interfering with the eumelanin or phaeomelanin pathway; in others, the mechanism is not known. Chloroquine interferes with phaeomelanin synthesis [38] and affects only blonde and red-haired individuals; the changes are completely reversible. Mephenesin, a glycerol ether used for diseases with muscle spasms, causes pigmentary loss in dark-haired people [39]. Triparanol, an anticholesterolaemic drug, and fluorobutyrophenone, an antipsychotic drug, both interfere with keratinization and cause hypopigmentation and sparse hair. Minoxidil and diazoxide [40,27], two potent antihypertensive agents, both cause hypertrichosis and darkening of hair. The colour produced by diazoxide is reddish, whereas minoxidil darkens hair mainly by converting vellus hair to terminal hair. Hydroquinone and phenylthiourea interfere with tyrosine activity, causing hypopigmentation of skin and hair [41].

Darkening of white hair occurred in a patient with Parkinson's disease following the addition of carbidopa and bromocriptine therapy [42].

Colour changes induced by nutritional deficiencies

Because specific dietary deficiencies are rare in humans, most clinical knowledge of their effects is derived from laboratory and animal studies. Copper deficiency in cattle causes achromotrichia because it is the prosthetic group of tyrosinase; loss of hair colour from this mechanism occurs in humans as Menkes' kinky hair syndrome. In protein malnutrition, exemplified by kwashiorkor, hair colour changes are a prominent feature; normal black hair becomes brown or reddish, and brown hair becomes blonde [43,44]. Intermittent protein malnutrition leads to the 'flag' sign of kwashiorkor (signe de la bandera). Alternating white (abnormal) and dark bands occur along individual hairs. Changes similar to those in kwashiorkor have been described in severe ulcerative colitis and after extensive bowel resection.

The lightening of hair colour from black to brown described in severe iron-deficiency anaemia may be an effect on keratinization rather than on melanocytic function [45].

Noppakun and Swasdikul [46] described a case of reversible white hair in vitamin B_{12} deficiency and commented on a variety of reversible and other hair colour changes in adult coeliac disease.

Hair colour in metabolic disorders

Phenylketonuria is an autosomal recessive disorder in which the tissues are unable to metabolize phenylalanine to tyrosine because of phenylalanine hydroxylase deficiency. Mental retardation, fits and decreased pigmentation of the skin, eyes and hair occur with eczema and dermographism. Black hair may become brown, and older institutionalized patients with phenylketonuria may have pale blonde or grey hair. Tyrosine treatment causes darkening towards normal colour within 1–2 months.

The paling of hair seen in homocystinuria is probably caused by keratinization changes resulting from the error in methionine metabolism.

Light, almost white hair and recurrent oedema are manifestations of the hair condition, 'oast house' disease. Methionine concentration in the blood is raised.

Darkening of grey hair has been reported in porphyria cutanea tarda [47].

Accidental hair discoloration

Hair avidly binds many inorganic elements and thus hair colour changes are occasionally seen after exposure to certain substances.

Exposure to high concentrates of copper in industry or from inadvertently high concentrations in tap water [48] or in swimming pools may cause green hair, particularly visible in blonde-haired subjects [49,50]. Cobalt workers

may develop bright blue hair and a deep blue tint may be seen in indigo handlers [51]. A yellowish hair colour is not uncommon in white- or grey-haired heavy smokers resulting from the tar in cigarette smoke; yellow staining may also occur from picric acid and dithranol. Trinitrotoluene (TNT) workers sometimes develop yellow skin and reddish brown hair.

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Hair cosmetics [1,2]

Women and men have always been concerned about their hair, and have sought to modify it by grooming, colouring, cutting and wigs. There are references in Egyptian papyruses to the importance of arranging the hair prior to seduction [3,4]. Now, hair care and hair cosmetics are big business and many of the advances have come from cosmetic science laboratories [5,6]. Some aspects of cosmetic management can lead to secondary hair problems, such as traction alopecia (see p. 63.62) or follicular degeneration syndrome (see p. 63.54).

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Shampoos [1–5]

In modern terms, a shampoo may be defined as a suitable detergent for washing hair that leaves the hair in good condition. Originally, shampoos were used solely for cleansing hair, but their range of function has extended in recent years to include conditioning, and the treatment of some hair and scalp diseases.

In principle, to wash hair a shampoo must remove grease, as it is the latter that attracts dirt and other particulate matter. The polar group of a detergent achieves this by displacing oil from the hair surface. The evaluation of shampoo detergency is difficult and complicated. The consumer tends to equate detergency with foaming; in Western society, few shampoos sell unless they possess good foaming power. In the evaluation of detergents as shampoos no single criterion can be used, although instrumental methods have been devised. Efficacy can be based only on the subjective impression of the consumer.

Shampoo formulations

These vary enormously but the basic ingredients can be resolved into a few groups: water, detergent and some fatty material. Soap shampoos are made from vegetable or animal fats and remove dirt and grease as efficiently as detergents; however, a scum forms with hard water and most shampoos contain detergents as the principal washing ingredient. Detergents are synthetic petroleum products and form no hard-water scum.

Shampoos contain:

1 Principal surfactants for detergency and foaming power
2 Secondary surfactants to improve and 'condition' hair
3 Functional additives to control pH and viscosity, or ingredients such as tar or antifungal agents
4 Preservatives
5 Aesthetic additives such as colourants and fragrance.

Whatever the claims of some manufacturers, most special additives end up down the sink [6]!

In general, cosmetic shampoos can be dry (powder types), liquid, solid cream, aerosol or oily. Antidandruff, 'medicated' and scalp treatment shampoos contain antiseptics and active agents such as coal- and wood-tar fractions or selenium sulphide. Clear liquid shampoos are the most popular, including 'cleansing' types, sold for treating greasy hair, and 'cosmetic' types having good conditioning action and popular among women with dry or 'normal' hair. For details of other specific formulas, the reader is recommended to read more specialized texts [3,4,7].

Shampoo safety

Shampoos obviously must be non-toxic, and at concentrations used by the consumer not irritate either skin or eyes. New shampoo formulations are tested exhaustively prior to marketing, particularly to assess their propensity to cause eye irritation, scarring and corneal opacities. Skin irritation is not usually encountered from shampoos that have low eye irritancy potential. Eye safety is assessed by the technique known as the Draize test; standard solutions of shampoo are instilled into the conjunctival sac of an albino rabbit. In general, the eye irritancy of detergents is greatest with cationics, followed by anionics, and least with non-anionics. There are exceptions to this, suggesting that shampoo irritancy may be caused by properties other than detergency including surface activity, pH, wetting power, foaming power (Ross–Miles test), and wetting and foaming power together. Most shampoos are, in fact, irritant but not dangerously so. Allergic contact dermatitis resulting from biocides does occur (see Chapters 20 and 21).

Conditioners

Dry hair lacks gloss and lustre and is difficult to style. This results from natural weathering and is worsened by chemical and physical processes applied to the hair. Conditioners have a range of characteristics that may contribute to shine, reduction of static electricity, protection from ultraviolet radiation and possibly increased hair strength [8]. Conditioners comprise fatty acids and alcohols: natural triglycerides (e.g. almond, avocado, corn and olive oil); waxes (e.g. beeswax, jojoba oil, mink oil, lanolin); phospholipids (e.g. egg yolk and soya bean); vitamins A, B and E, protein hydrolysates of silk, collagen, keratin (horn and hoof), gelatin and other proteins; and cationic polymers. Conditioners are available in a variety of forms and are widely used. They provide lubrication and gloss and render the hair easier to comb and style. The most commonly used are those combined with a shampoo as a 2-in-1 preparation. These cationic chemicals bind with the hair at the negatively charged surface and areas of weathering. In so doing they reduce static by electrically neutralizing the hair and provide a physical coating to the areas of damaged hair shaft with materials such as dimethicone. Other forms of conditioner may be applied as a separate procedure and can take the form of creams and emulsions

applied for a few minutes after washing and then rinsed off. Deep conditioners are left on for up to 30 min, often with damp heat. Fluids, gels and aerosol foams aid styling. Hair oils are traditional conditioners. Men may use brilliantines, greases or oils to leave the hair glossy and sleek [3].

Where the hair is significantly dry or damaged, or the scalp is inflamed or eczematous, conditioner may be used as a shampoo substitute in the same manner that one might advocate an emollient as soap substitute on the skin of someone with eczema. The conditioner will mix with water to remove surface dirt and odour, but will not subject the hair and scalp to the powerful solvent effects of the shampoo.

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Cosmetic hair colouring [1–4]

Since the days of the pharaohs, women in particular have used hair dyes to hide grey hair. Use has increased enormously during the past 50 years and now men are using hair dyes. Or perhaps they always did!

The penetration of dyes into hair depends on molecular size and the aqueous swelling of the hair at the time of application of the dye; basicity of the dye is also important. The most successful dyes are relatively small molecules.

Excluding bleaches, hair-colouring materials can be divided into three groups: vegetable, metallic and synthetic organic dyes. Synthetic organic materials are thought to give more 'natural' colours than those obtained with vegetable and metallic hair colourants.

Vegetable dyes

Henna may be used to give reddish auburn shades. It is obtained from shrubs found in North Africa and the Middle East: *Lawsonia alba*, *L. spinosa* and *L. inermis*. The dye is produced from dried leaves, which are removed before the plant flowers. The active principle is an acidic naphthoquinone (lawsone). Traditionally, it is applied as a thick paste 'pack', which is left *in situ* for 5–60 min. The effects last for up to 10 weeks. This process is non-toxic but messy, and fingernails may become stained. Henna rinses are mixtures of henna and powdered indigo leaves that produce blue-black shades. A wide range of products containing compound henna exist [5]. Ground flower heads of a Roman or German chamomile yield a yellow dye: 1,3,4,-trihydroxyflavone (apigenin). It stains only the cuticle and can be used to lighten or brighten hair. Other vegetable dyes include extracts from logwood and walnut shell and these can be used by patients who are *para*-phenylenediamine sensitive. These products are obtainable at herbalists and beauty shops.

Metallic dyes

Traditionally, hair dyes for men have been of this type, as the colour changes occur less rapidly and are not as immediately obvious as with the oxidative dyes. Inorganic salts are used, which are altered by the hair and coat the surface as either oxides from reduction of the metal salts by keratin, or sulphides from the action of the sulphur in keratin on the metal. They all give a rather dull (metallic) appearance and may cause brittle or damaged hair if used too often.

Lead acetate, with precipitated sulphur or sodium thiosulphate, gives brown to black shades; grey hair may be changed through yellow to brown or black. Silver nitrate used alone produces a greenish black colour; pyrogallol is used as developer. Colours from ash blonde to black are possible by mixing silver nitrate variously with copper, cobalt or nickel; brownish black skin staining is the great disadvantage. Bismuth salts give shades of brown. Newer metallic dyes, containing a metal plus an organic ligand, are used on textile fibres and in some hair-dye patents. Metallic dyes cannot be removed without hair damage and should be left to grow out.

Synthetic organic dyes

This group has now been in use for more than 60 years. They are the most important type because of the comprehensive range of 'natural' colours that can be obtained. Most penetrate the hair cuticle so are potentially permanent, but in recent years less permanent types have been introduced.

Synthetic organic colourants are of three types:

1 *Temporary*. These wash out with one shampoo and last no longer than 1 week. Many temporary rinses belong to this group, including fashionable unnatural colours used by avant-garde sects and groups. They are available in aerosol sprays by incorporation into transparent polymeric plastics such as PVP; the disadvantage of such vehicles is their tendency to flake off on to clothing.

2 *Semipermanent*. In the UK, these have the widest appeal. They are used frequently at home and also in salons to brighten or subdue a natural colour, modify a permanent

or bleached colour, or modify white or grey. They are of sufficiently small molecular size to penetrate the cortex. They are intrinsically coloured; no developing is required (see the oxidative permanent group). They are relatively easy to wash out with shampoos containing ammonia; other shampoos must be used 6–10 times to remove them. Some semipermanent dyes have an affinity for thioglycolate-waved hair. Many are now used in colour shampoos.

3 *Permanent* (developed or oxidation dyes). These do not rely on the natural colour of a single chemical dye-stuff, (see semipermanents), but require an oxidative developer —hydrogen peroxide—to produce the final colour:

Paraphenylenediamine (PPD) and/or
paratoluenediamine (PTD)
+
Hydrogen peroxide
↓
Applied to hair
↓
Quinone diamine (small molecule)
↓
Penetrate hair—to cortex
↓
Large molecules produced
(by diamine 'self' condensation and modifiers,
e.g. pyrogallol)

Other substances may be included in specific formulations to give greater intensity to the dye (e.g. resorcinol and polyhidric phenols).

Oxidative dyes are potentially hazardous. The need for hydrogen peroxide enables lighter shades to be obtained and is chiefly responsible for the structural damage to hair that may occur if care is not exercised. Additives such as pyrogallol and resorcinol are potential irritants. The greatest problem is the potential of PPD (less so with PTD) to cause allergic dermatitis. Up to 10% of users may develop type IV allergy [6,7]. All dyes in this group are therefore sold with instructions to carry out preliminary patch testing 24–48 h before the proposed dye is used. Thus, the dye system is applied to skin either behind one ear or on the forearm—any redness, swelling or blistering implies allergy and the dyeing should not therefore proceed. A negative patch test does not mean that subsequent allergy cannot develop; it simply shows the subject is not allergic at the time the test is carried out. If allergy is shown, it is not sufficient merely to stop all future use of oxidative dyes; unfortunately, cross-sensitization also occurs with other aromatic benzenes (e.g. sulphonamides and some local anaesthetics), which must also be avoided for life. Modern formulations seem to cause less problems with allergy [8]. Hair dyes of this group have been incriminated as possible carcinogens [9]. Chromosome breaks have occurred under experimental conditions [10] and an increased incidence of tumours has been found in regular users [11]. It has also been intimated that aplastic anaemia could be produced by hair dyes [12]. None of these reports is sufficiently conclusive to warrant the withdrawal of such dyes.

Permanent dyes last for several months; they must not be applied more frequently than every 2–3 weeks because hair damage will occur. Permanently dyed hair must therefore be allowed to grow out. However, if a light shade has been produced and the subject wishes a darker shade, then temporary rinses may safely be used as these only coat the hair surface and have no propensity to cause structural damage.

For less commonly used permanent dye formulations, such as 'highlights', the reader is referred to specialized texts [4].

Bleaches [13–15]

Women have bleached their hair since Roman times. Bleaching is used both to lighten hair and to prepare it to take up hair dyes. Bleaching is an oxidative alkaline treatment that oxidizes and bleaches melanin. The hair lightens to reddish or yellow tones, depending on the underlying hair colour, and ultimately to platinum. Bleaching is very damaging to the hair, rendering it dry, porous and more prone to tangle. Overuse may cause disruption and fracture of the hair. Thus, it is advisable to perform permanent waving before bleaching. Home bleaching is usually performed with 6% hydrogen peroxide (20 volumes) with ammonia to speed the reaction, which otherwise takes 12 h. Salons use more powerful bleaching creams, powders and pastes, which are much faster. They are often applied to individual strands of hair, others being left untreated to give highlights, which lessens the problem of the darkened roots. Bleaching is terminated by shampooing or an acid rinse. The human eye perceives a more aesthetically acceptable blonde ('platinum' blonde) when the bleached hair is treated with a blue or lilac colourant.

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Permanent waving [1–3]

Permanent waving is often referred to as 'a perm'. It has been defined as the process of changing the shape of the hair so that the new shape persists through several shampoos. During the last 70 years, increasing knowledge of keratin chemistry has enabled semipermanent chemical methods to be developed. Whatever the process used, three stages are involved in hair waving:

1 Physical or chemical softening of the hair
2 Reshaping
3 Hardening of fibres to retain the reshaped position.

Softening

Water can extend the hydrogen bonds between adjacent polypeptides in the keratin molecule, allowing temporary reshaping to be carried out—exposure to high humidity or rewetting immediately reverses the process. To obtain a more durable effect from water, steam may be used which, in a limited way, disrupts disulphide bonds. Heat and steam alone are rarely acceptable to modern women because their effects are temporary and the treatment is uncomfortable. Heat can be more effectively employed in conjunction with ammonium hydroxide and potassium bisulphite or triethanolamine as agents to reduce disulphide bonds; great skill is involved in this process as failure to judge the time of application of chemicals and heat may cause severe damage.

Since 1945, cold wave processes using substituted thiosulphates (thioglycolates) have largely superseded hot waving. Thioglycolates are potent reducers of disulphide bonds in the keratin molecule:

—S=S— → 2—SH.

A typical cold waving lotion contains thioglycolic acid plus ammonia or monoethanolamine.

Acid permanent waves have recently become popular for salon use. They contain glyceryl monothioglycolate and produce a softer curl, and can be used on damaged and bleached hair. Their disadvantage is the high frequency of sensitization in the hairdressers using the product and, occasionally, sensitization of the client [4].

Reshaping

The type of rollers or curlers used to reshape the softened hair depends on the training of the hairdresser and the fashion desired. The degree of curl or tightness of the permanent wave depends both on the diameter of the roller and the size of the strand wound round the roller. Increasing the time of the exposure to the perming solution up to 20 min increases the curl, but longer times do not give a further increase. The strength of the solution used depends on the hair type, texture and previous bleaching. Home permanent waves are weaker and cannot achieve the same degree of curl. 'Tepid' waving involves using a weaker thioglycolate solution plus warm air. Neutralization is carried out initially with the curlers in place and again after they have been carefully removed. The reshaping stage is thus a great test of hairdressing skill and experience.

Hardening (neutralizing or setting)

In general, this process involves a reversal of the softening (reduction) stages:

$$2\text{—SH} \xrightarrow{\text{oxidation}} \text{—S=S—}.$$

It is important to note that complete reversal to presoftened 'strength' cannot occur because many free SH groups may not be in a position for oxidation to be effective, for example:

2—SH → —S—C—S— (C = carbon)
2—SH → —S—Ba—S— (Ba = barium)

Atmospheric oxidation may efficiently neutralize the waving process. This method is slow and rollers must be left in position for several hours overnight. Chemical oxidation is now the rule. Hairdressers generally use hydrogen peroxide whereas most solutions for home use contain sodium perborate or percarbonate (UK) or sodium or potassium bromate (USA). This is why hair is lighter after permanent waving. Some neutralizers contain shellac, which may react with alcohol groups to cause hair discoloration.

Practical procedures

Hot waving

This is almost never used. The procedure is:

1 Shampooing
2 Hair divided and rollers or curlers applied under slight tension
3 Waving solution applied
4 Heating.

Heating varies according to the solution used or the type of wave required. Electric rollers or exothermic reactive chemicals may be used. The latter allow free head movement during the waving. The skill of this procedure

lies in good hair sectioning, judging the right amount of solution, correct winding tension and appropriate steaming time.

Cold waving

This also involves initial shampooing, hair division into locks, moistening with waving lotion and application of croquignole curlers. Further solution may then be applied. The softening time is 10–20 min. Occasionally, mild heat is included, using exothermic chemicals or the natural heat from the head by enclosing the scalp in a plastic bag. These may add to the comfort of the process. Rinsing then takes place, followed by neutralization with the oxidizing solution for up to 10 min. After removing the curlers, further 'hardening' solution is usually applied. 'Loose' curl waves last for no more than a few weeks but 'tight' curl styles may persist for 4–12 months.

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Hair straightening (relaxing) [1,2]

In principle, the methods used to straighten hair are similar to those used in permanent waving. The practice is almost exclusively used to straighten negroid hair and is also called relaxing. One survey found that relaxing formulations were used in 45% of black American women [3]. These practices are associated with a range of problems and ultimately may contribute to scarring alopecia [4].

Pomades

These are mostly used by men with relatively short hair. They are greasy and act by 'plastering' hair into position.

Hot-comb methods

Shampooing is carried out and the hair is towelled dry; oil is then applied (e.g. petroleum jelly or liquid paraffin), which acts as a heat-transferring agent. Heat pressing with hot combing is then used (148–260°F), causing breakage and reforming of disulphide bonds, allowing the hair to be moulded straight. Structural damage (and breakage) of hair is common with this process and scarring alopecia may occur as a result of hot waxes entering the follicles. Sweating and rain reverse this procedure.

Cold methods

The chemical methods employed use alkaline reducing agents (caustics), thioglycolates, ammonium carbonate or sodium bisulphite. Caustic soda preparations are usually creams and require the application of protective scalp oil or wax. They are combed through the hair and left for 15–20 min; the hair is combed and straightened again, then rinsed and neutralized. These preparations are limited to salon use because of their potential to cause irritant dermatitis and damage to the hair. Thioglycolate creams are the most common agents used; the cream is applied liberally to the hair, which is then combed until it is straight. The cream is then washed off and a neutralizer (oxidizing agent) applied. Other straighteners ('relaxers') do not contain thioglycolates (e.g. sodium bisulphite and ammonium carbonate, acidic ethylene glycol or 1,3-propylene glycol). Bisulphite straighteners are suitable for home use in combination with alkaline stabilizers.

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Hair setting [1]

Setting lotions have changed considerably in recent years. The traditional semiliquid gels based on water-soluble gums (e.g. tragacanth, karaya and acasia) have been replaced by various synthetic polymers in a bewildering array of forms—aerosol foams and sprays, liquids and gels. Most are based on PVP in a gelled aqueous solution and give an attractive glossy non-greasy appearance [2]. Some preparations incorporate other ingredients to condition or to add antistatic action, lustre or sheen.

Setting lotion and spray formulations are considered safe, after early reports of foreign body granulomatous inflammation [3,4] had been questioned and not supported by further cases. Hair sprays were incriminated as a possible cause of peripilar casts [5] but this was not confirmed by later work [6].

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Methylolated compounds

Many cosmetic preparations, by their action on the keratin molecule, irreversibly weaken the hair. The cosmetic scientist has produced chemicals that attempt to combat this problem. The formulations contain methylolated compounds of varying strength depending on the type of hair under treatment and the solubility of the compound. Most preparations containing alkylated methylol compounds have greater stability and release very little formaldehyde [1].

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Complications

Hair loss is often attributed to cosmetics, with relatively little evidence in support [1]. Matting of scalp hair is most commonly a sudden, usually irreversible, tangling of scalp hair resulting from shampooing [2]. Excessive bleaching, permanent waving and straightening procedures may induce excessive weathering and fragility of hair.

Complications from the use of synthetic hair fibre implantation for male pattern balding can be severe [3].

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Chapter 64

The Skin and the Eyes

J.N. Leonard & J.K.G. Dart

Introduction

This chapter is not intended to be a comprehensive account of all diseases that affect the skin and eyes, for which there are several reviews [1–6]. The main focus is on those conditions that commonly occur in clinical practice and present a problem with management. It is also intended to alert the dermatologist to conditions that might threaten visual acuity and require urgent referral to an ophthalmologist. Also, many systemic diseases affect both the skin and eyes, and ophthalmic assessment will be of help in making the correct diagnosis and in long-term management of the patient.

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Anatomy and physiology of the eye [1,2]

The eye and skin share a common embryological origin. The structure of the lid, conjunctiva, the lacrimal gland and associated drainage apparatus are of surface ectodermal origin while the remainder of the eye arises from epithelium of the ectodermal neural plate. The only mesodermal contribution to the eye is the myoblasts of the extra-ocular muscles. The anatomy of the eye is shown in Fig. 64.1. The eye appendages are as follows.

The eyebrows

This hair-bearing area rests on a very mobile fat and muscle pad overlying the superior orbital ridge. Its mobility is important as a means of facial expression. The eyebrows help protect the eye from bright light and sweat.

The eyelids

The eyelids have distinct anatomical layers, comprising the skin with subcutaneous tissue, the tarsal plate and conjunctiva, and striated muscles that effect lid movement (Fig. 64.2).

The skin is thin and modified in several ways to protect the eyeball. It contains sebaceous glands associated with

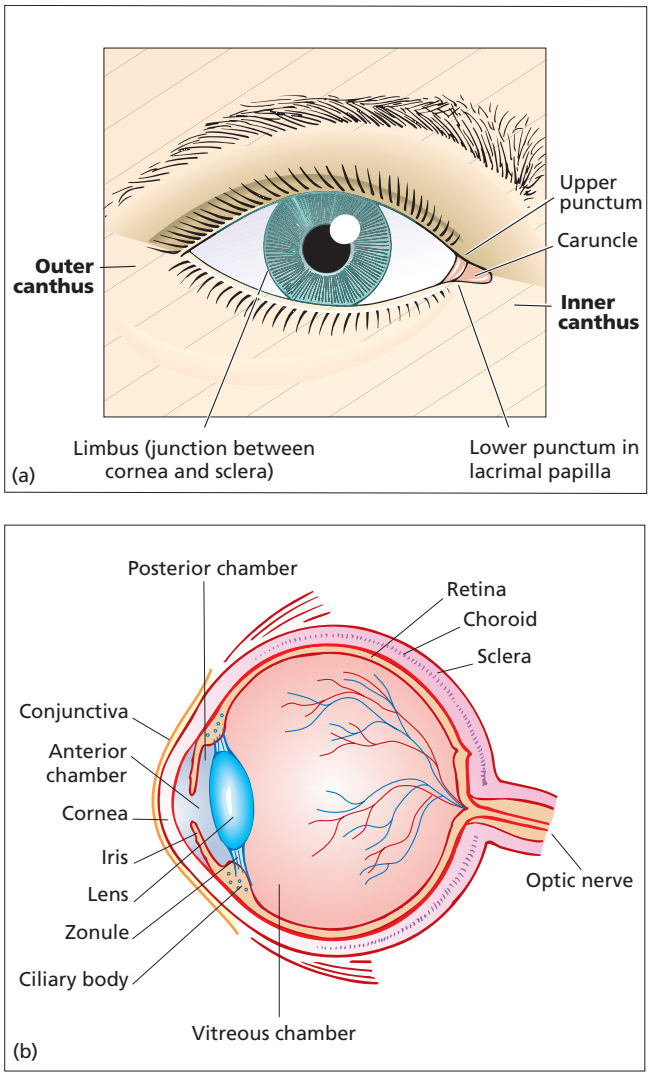

Fig. 64.1 Anatomy of normal eye. (a) The external appearance of the right eye. (b) Cross-section of the human eye.

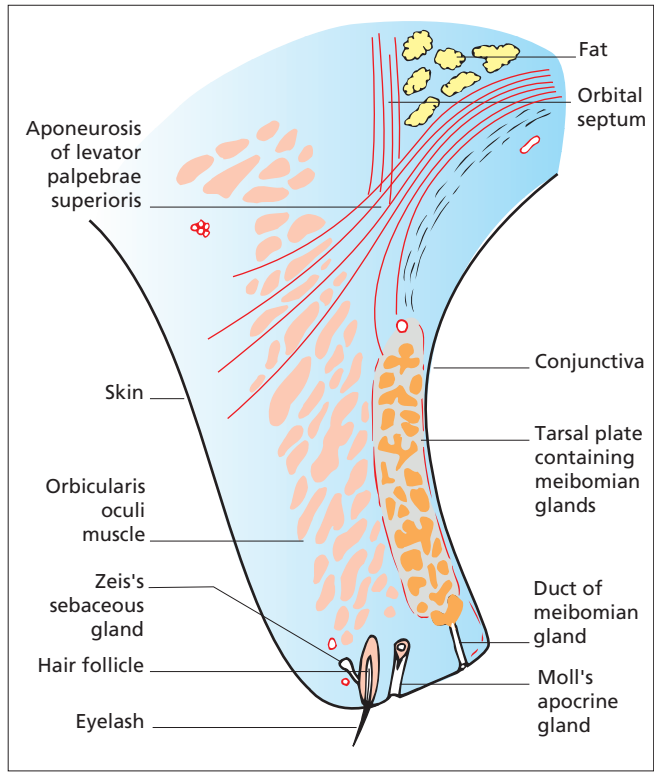

Fig. 64.2 Cross-section of upper eyelid.

the fine hairs of the eyelashes (cilia) and both apocrine and eccrine sweat glands. There are about 300 eyelashes arising in two rows along the eyelid margin, two thirds of which are in the upper lid. They have no associated erector muscles, but rudimentary sebaceous glands (of Zeis) are present. Some lashes, particularly those of the lower lid, are associated with ancillary apocrine sweat glands (of Moll). The ducts of these glands open both into the lash follicles and directly onto the anterior lid margin between the lashes. The eyelashes help to protect foreign bodies from impinging on the eyeball. Each lash follicle has a rich nerve plexus, which is easily excited and light touch initiates reflex closure.

The tarsal plate of each eyelid gives the palpebral aperture shape and stability. They comprise dense, fibrous tissue surrounding modified sebaceous glands (meibomian glands). These secrete the outer lipid layer of the precorneal tear film through openings along the mucocutaneous junction of the eyelid margin. This lipid helps stabilize the tear film and reduce evaporation. There are about 30 glands in the upper tarsal plate and 20 in the lower. Meibomian glands have up to 20 acini surrounding a central vertical duct and are visible through the conjunctiva.

The eyelids are lined by a mucous membrane called the palpebral conjunctiva. It is reflected over the anterior portion of the eyeball up to the edge of the cornea as the bulbar conjunctiva. The folds formed by the reflection of the conjunctiva from the lids onto the eyeball are called the superior and inferior palpebral fornices. The conjunctiva contains numerous goblet cells secreting mucin into the tear film. It also contains about 50 accessory lacrimal glands and its substantia propria contains neural tissue, mast cells, lymphocytes and lymphoid follicles, which are important in mediating local immunological reactions.

The striated muscle of the levator palpebrae superioris opens the eye, and the striated orbicularis oculi muscle closes it. Both are innervated by the facial nerve. Two divisions of the trigeminal nerve supply sensation to the eyelids; the upper lid and medial canthus are supplied by the ophthalmic division, and the remainder of the lower lid by the maxillary division.

The eyelid has a rich blood supply mainly through the medial and lateral palpebral arteries, which are branches of the ophthalmic artery. There is also a rich anastomosis

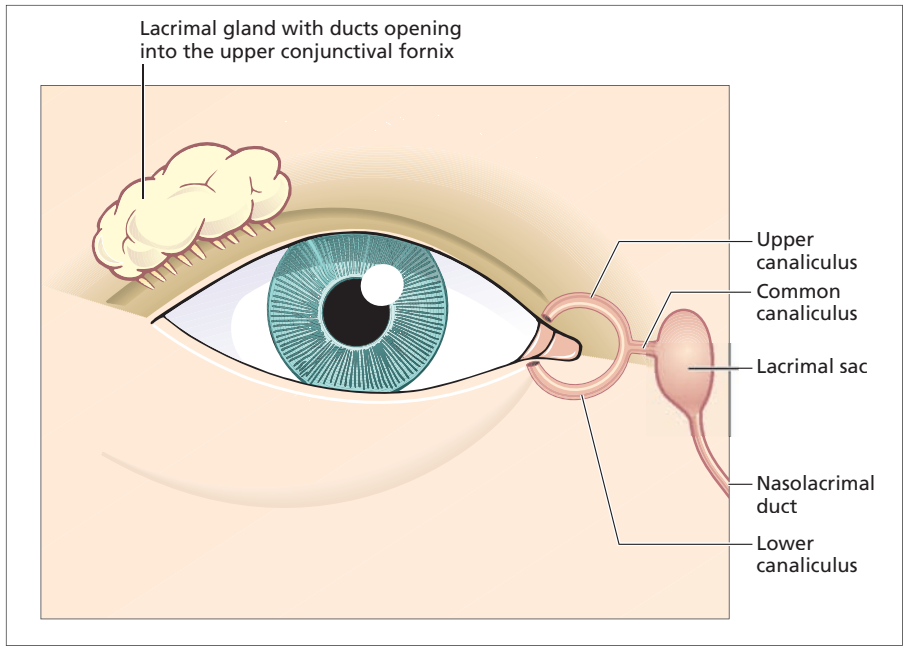

Fig. 64.3 The lacrimal apparatus of the right eye.

between adjacent arteries arising from the internal and external carotid. The blood drains through a network of veins to the facial and orbital veins and the cavernous sinus. Lymphatics drain the conjunctiva and tarsal plate to the post-tarsal plexus and the skin and orbicularis to the pre-tarsal plexus. The medial canthus and lower lid subsequently drain to the submandibular nodes whilst the lateral canthus and upper lid drain to the parotid and preauricular nodes.

The lacrimal glands

The main lacrimal gland is a modified sweat gland located in the lacrimal fossa, a bony depression just under the upper and outer margin of the orbit. It produces an aqueous secretion, which discharges through a network of ductules onto the conjunctiva of the palpebral conjunctiva. In addition, there are a variable number of accessory lacrimal glands in the upper and lower conjunctival fornices. The lacrimal gland is innervated whereas the accessory glands are not.

The pre-corneal tear film

The eyelids make a vital contribution to the composition and stability of the precorneal tear film, which is about 40 µm thick. It is a three-layered structure consisting of a lower hydrophilic mucin layer secreted by goblet cells of the conjunctiva, a central aqueous layer secreted by the lacrimal gland, and a surface hydrophobic lipid layer secreted by the meibomian glands (as discussed above). Blinking consists of a lateral to medial movement of the eyelids, which enables resurfacing of the tear film of the cornea and propels the tears to the punctum of the tear duct; from here, they are actively removed by the lacrimal pump mechanism through the lacrimal canaliculi into the common canaliculius and lacrimal sac, and then via the nasolacrimal duct into the nose (Fig. 64.3).

The tear film has a number of functions:

1 To supply oxygen and other nutrients to the cornea
2 To remove particulate matter from the surface of the eye
3 To prevent drying of the eye
4 To act as a lubricant and prevent adhesion of the palpebral to the bulbar conjunctiva
5 To protect the eye surface through its antibacterial role. It contains white blood cells, various proteins, lysozyme and immunoglobulins.

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Glossary of ophthalmological terms

A glossary is provided in Table 64.1.

Disorders affecting the eyebrows and eyelashes

There is a wide variation in the colour distribution and density of the eyebrow hairs. The inheritance of the appearance of the eyebrows is polygenic. Some hereditary variations are of no known significance, but others are

Table 64.1 Glossary of ophthalmological terms.

Astichiasis	Absence of lashes
Anophthalmia	Absence of eye
Blepharitis	Inflammation of the eyelid margin
Blepharochalasis	Elastic tissue atrophy causing loose eyelid skin
Bruch's membrane	The retinal layer sandwiched between the retinal pigment epithelium and the vascular choroid
Coloboma	Congenital cleft created by failure of development of a portion of the eye or adnexal structures
Dermatochalasis	Laxness of the skin of the eyelids
Distichiasis	Accessory row of eyelashes
Ectropion	Eversion of the eyelid
Entropion	Inversion of the eyelid
Epicanthal fold	Accessory fold of skin at the inner canthal region of the eye
Epicanthus inversus	Lower lid fold larger than upper lid fold
Epiphora	Excess tearing
Episcleritis	Inflammation of the superficial scleral tissues
Hypertelorism	Increased distance between the two eyes measured radiologically
Hypopyon	The presence of pus in the anterior chamber
Keratopathy	Corneal abnormalities including: *exposure keratopathy*—from corneal exposure and drying of the cornea
Keratitis	Inflammation of the cornea—various types are recognized, including *filamentary keratitis*—the development of epithelialized mucous filaments on the corneal surface; *interstitial keratitis*—inflammation of the corneal stromal layer
Keratoconjunctivitis sicca	Corneal and conjunctival inflammation associated with impaired tear secretion and ocular dryness
Keratoconus	Conical distortion of the central cornea as a result of a degenerative process in the stroma
Lagophthalmos	Persistent exposure of the eyeball despite closure of the eyelid
Limbus	Boundary between the cornea and sclera
Madarosis	Loss of the eyelashes
Pannus	Vascularized corneal scar
Phlyctenule	Wedge-shaped, peripheral corneal or conjunctival, nodule
Preseptal cellulitis	Cellulitis of the eyelids that has not penetrated through the orbital septum to involve the orbit
Symblepharon	Adhesions between the bulbar and palpebral conjunctiva resulting in complete or partial obliteration of the eyelid fornices
Telecanthus	Increased distance between the inner canthi
Trichiasis	Lashes that turn inward toward the cornea usually as a result of entropion
Uveitis	Inflammation of the uveal tract. It is subdivided into anterior uveitis, which is the most common, intermediate uveitis, posterior uveitis and pan uveitis. *Anterior uveitis* is subdivided into iritis, in which the inflammation predominantly affects the iris, and iridocyclitis, in which both the iris and the anterior part of the ciliary body (pars plicata) are equally involved. *Intermediate uveitis* involves the posterior part of the ciliary body (pars plana) and the extreme periphery of the choroid and retina. *Posterior uveitis* is inflammation located behind the vitreous base. *Pan uveitis* is involvement of the entire uveal tract

associated with other development defects or are part of a recognized syndrome.

Disorders of the eyebrows [1]

Synophrys

This term is applied when the eyebrows are profuse with a tendency to meet in the centre of the face. Synophrys is a feature of some genodermatoses (Chapter 12). The eyebrows also tend to become more bushy in the ageing male for reasons that are unknown. Bushy eyebrows may also occur in other acquired forms of hypertrichosis, for example due to drugs such as diazoxide, and fusion of the eyebrows has been reported in kwashiorkor.

Hypoplasia of eyebrows

Some inherited diseases are characterized by hypoplasia of the eyebrows (Chapter 12). Acquired conditions can cause sparsity of the eyebrows. They may be the only site affected in alopecia areata. Thinning of the eyebrows also occurs in hypothyroidism, erythroderma, follicular mucinosis and secondary syphilis. Lepromatous leprosy causes thinning of the outer third of the eyebrows in the early stages, often with depigmentation, and this progresses to total loss of the brows and lashes. Tuberculoid leprosy, by contrast, does not cause loss of the eyebrows. Plucking the eyebrows for cosmetic reasons is common, but true trichotillomania of the eyebrows is unusual.

Inflammatory disorders affecting the eyebrows

The eyebrows are often involved in seborrhoeic dermatitis and psoriasis. Post-inflammatory cicatricial alopecia from discoid lupus erythematosus, folliculitis decalvans, lupus vulgaris or tertiary syphilis may cause eyebrow loss. Scarring with loss of eyebrows may also follow chemical

and thermal burns or radiation. Loss of eyebrows can be camouflaged by the use of eyebrow pencils, permanent tattooing or by a hair prosthesis glued in place daily.

Disorders of the eyelashes

Trichomegaly [2–4]

This may be due to a genetic trait. Increased growth of the eyelashes has also been described in human immunodeficiency virus (HIV) infection and related to various drugs including ciclosporin, zidovudine or interferon. Long lashes also occur in some patients with phenylketonuria.

Madarosis [1]

Madarosis is a decrease in the number or complete loss of lashes. A number of causes have been recognized and include alopecia areata, chronic anterior lid margin blepharitis, infiltrating tumours of the lid, burns, cryotherapy and radiotherapy, trichotillomania and discoid lupus erythematosus. Systemic diseases such as hypothyroidism and syphilis may also be responsible.

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Abnormality of the eyelids

These include dermatochalasis, blepharochalasis and lid laxity. Numerous developmental defects can affect the palpabral fissure or size and shape of the eyelids. A number of hereditary dermatoses affect the eyelids (Chapter 12).

Ptosis

Drooping of the eyelids on one or both sides is a common genetic defect. Mild ptosis commonly develops in the elderly due to the laxity of the connective tissue. There are many important acquired causes, such as third nerve palsy, Horner's syndrome and myasthenia gravis, which require neurological referral. Ptosis may be associated with other ocular abnormalities.

Skin diseases affecting the eyelids

A large number of dermatological conditions can affect the eyelids as part of a generalized process. Usually there is little diagnostic difficulty as the diagnosis is made by examination of the rest of the skin. Psoriasis and lichen planus can both involve the lids and cause considerable irritation. These are chronic diseases and management can become a problem with use of potent topical corticosteroids on the eyelids over a prolonged period of time. Use of the new topical immunosuppressants such as tacrolimus and pimecrolimus may offer some promise for the future in reducing topical corticosteroid exposure. Unilateral involvement of an eyelid raises the possibility of infective conditions, including tinea and mycobacterial infections.

Psoriasis [1]

Eyelid involvement can occur in about 10% of patients with psoriasis. Men are more susceptible to ocular disease. Involvement of the eyelid gives rise to blepharitis, madarosis and development of psoriatic plaques. Chronic non-specific conjunctivitis may occur over time and lead eventually to keratoconjunctivitis sicca with symblepharon formation and trichiasis. Conjunctivitis usually complicates eyelid margin involvement; white or yellow psoriatic plaques can spread from the lid on to the conjunctiva itself. Corneal changes are rare and are most commonly related to exposure and trichiasis. Anterior uveitis is rare but has been reported in patients with psoriatic arthritis and is similar to that seen in Reiter's syndrome. Ocular psoriasis is treated with use of lubricants and topical corticosteroids. Patients with chronic eyelid involvement should be referred for ophthalmological assessment.

Contact dermatitis [2–8]

Contact dermatitis is the responsible cause in approximately half of patients with an eyelid dermatitis. The remainder have manifestations of atopic or seborrhoeic dermatitis. The eyelid skin is very sensitive to primary irritants. These can cause a dermatitis in their own right or can aggravate an underlying constitutional tendency in patients with either atopic or seborrhoeic dermatitis.

Allergic contact dermatitis can present after many years of exposure to the culpable allergen. Clinically it is characterized by severe itching, erythema and swelling of the eyelid, progressing to formation of vesicles. A large variety of allergens have been reported as causing an allergic contact dermatitis of the lid and include preservatives (used in cosmetics, topical medications and contact lens cleaning solutions), fragrances and the resin used in nail polish. Patients with suspected contact dermatitis of the eyelids should be patch tested. Careful history taking is of paramount importance to make sure the relevant allergens are included in the test battery. The possibility of transferring antigen from the hands to the eyelids needs to be considered. Maibach described the upper eyelid dermatosis syndrome in which patients have discomfort

of the eyelids with or without dermatitis; it is thought to be unrelated to use of cosmetics.

Periorbital oedema [9]

The subcutaneous tissue of the eyelids is lax and prone to oedema. There are many systemic and dermatological causes of eyelid oedema that need to be considered. Systemic causes include angio-oedema, glomerulonephritis, hypoalbuminaemia (especially nephrotic syndrome), cardiac failure, superior venocaval obstruction and thyroid disease. Some systemic infections such as infectious mononucleosis and scarlatina cause periorbital oedema. It may be the presenting feature of dermatomyositis and has been reported in systemic lupus erythematosus.

The most common dermatological causes of periorbital oedema are angio-oedema, lymphoedema, allergic contact dermatitis and blepharochalasis; they are usually distinguished by the history. Angio-oedema is transient and often part of a more generalized urticarial eruption. Lymphoedema is permanent and tends to be worse first thing in the morning and improves during the day; it may be associated with underlying sinus disease or a chronic inflammatory condition such as granulomatous rosacea. Allergic contact dermatitis presents acutely with swelling, redness and itching. Blepharochalasis is an uncommon condition which may be inherited (autosomal dominant) or sporadic; it presents in the second decade with recurrent episodes of painless lid oedema, resulting in the development of excess skin and thickened subcutaneous tissue which may require treatment by blepharoplasty. Senile orbital fat prolapse through a deficient orbital septum may mimic periorbital oedema but is differentiated by the fact that there is minimal fluctuation in the associated swelling.

Changes in pigmentation [10–14]

There are considerable racial and familial variations of the degree of pigmentation of the eyelids (Chapter 39). Marked periorbital melanosis is seen as a genetic trait. Pigmentation of the periorbital skin can also be post-traumatic, post-inflammatory or can accompany melanocyte-stimulating hormone-induced melanosis of any cause. Chemical pigmentation can occur from prolonged use of a mercurial or silver preparation producing a slate-blue or grey-brown discoloration. Mauve discoloration of the eyelids and periorbital area is an early part of chrysiasis from parenteral gold therapy. A grey discoloration can complicate long-term treatment with minocycline. Local increase in pigmentation may also be due to cosmetics containing phototoxic agents, usually psoralens. Increased pigmentation can also follow inflammatory dermatoses such as eczema and lichen planus. The eyelids may be involved in vitiligo. Hypopigmentation can complicate the use of topical medications including thiotepa eye drops and mercurial ointments.

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Chronic blepharitis, rosacea and seborrhoeic dermatitis [1–4]

Description. Chronic blepharitis is a term that is used to describe a group of disorders in which the lid margin is always involved. These disorders often occur simultaneously. Not all of them result in inflammation of the lid margin. They are frequently associated with a conjunctivitis or keratoconjunctivitis. Chronic blepharitis may occur in the absence of any significant dermatological association and its classification is further complicated, both by the variable association of chronic blepharitis with rosacea and seborrhoeic dermatitis, and also by the term ocular rosacea, a condition which may occur in the absence of dermatological rosacea.

It is hardly surprising that this classification causes confusion amongst practitioners. This situation has arisen partly because there is no consensus about the terminology (although most modern authors use similar classifications based on McCulley's modification of Thygeson's classification) and, more probably, because the pathogenesis is very poorly understood with few unifying concepts.

Table 64.2 summarizes a current classification, associations and features. It includes ocular rosacea amongst the meibomian gland disorders with which it is always

Table 64.2 Classification of types of chronic blepharitis (lid margin disorders).

Anterior lid margin*		Posterior lid margin*		
Staphylococcal blepharitis	Seborrhoeic blepharitis	Meibomitis/ocular rosacea	Meibomian gland dysfunction	Meibomian seborrhoea
Associations with other types of blepharitis				
Secondary meibomitis	Any posterior lid margin condition	Staphylococcal & seborrhoeic blepharitis	Seborrhoeic blepharitis	Seborrhoeic blepharitis
Associated skin disease				
Atopic eczema Impetigo Rosacea (rare)	Seborrhoea Rosacea (rare)	Acne rosacea in up to 50% of cases	Acne rosacea in up to 50% of cases	
Associated eye disease				
Dry eye Atopic kerato-conjunctivitis		Scleritis and episcleritis in ocular rosacea		
Main features				
Symptoms				
Burning Itching Photophobia	Minimal	Foreign body sensation Burning Discomfort Photophobia with ocular rosacea	Variable: Foreign body sensation Burning Discomfort	Variable: Foreign body sensation Burning Discomfort
Lid signs				
Unilateral/patchy lid margin involvement (Fig. 64.4d) Brittle fibrinous scales bleed when detached, form collarettes at lash base (Fig. 64.4a) Dilated vessels, styes Poliosis and madarosis (Fig. 64.4b)	Bilateral greasy scales (not fibrinous)	Chalazia (Fig. 64.5b) Irregular lid margins Distorted meibomian orifices Inspissated secretions Expression difficult Surrounding inflammation For lid signs in ocular rosacea see Table 64.3		Plugged and elevated orifices without inflammation
Conjunctival & corneal signs				
Follicles, papillae and hyperaemia of lower tarsal conjunctiva and fornix (Fig. 64.4c) Coarse punctate keratitis in lower third of cornea. Marginal keratitis (Fig. 64.4e) and vascularization. Conjunctival scarring (Fig. 64.5a)		Early tear break up time Foam/debris in tears Punctate keratitis (dry eye) For conjunctival and corneal signs in ocular rosacea see Table 64.3		Minimal injection ± Foamy tear film

* The anterior lid margin is the portion anterior to the meibomian gland orifices and the posterior lid margin is behind this, including the meibomian glands. Anterior and posterior lid margin disorders are commonly mixed; frequent associations are shown in the table.

associated. Table 64.2 classifies the five types of blepharitis (including ocular rosacea) into those principally affecting the anterior lid margin structures (cutaneous margin with lash-bearing skin and associated glands) or the posterior lid margin (mucocutaneous junction, meibomian orifices). This classification simplifies the treatment because this differs between the anterior- and posterior-lid margin disorders but not between the individual conditions within the anterior- and posterior-lid margin groups. The commoner clinical signs of staphylococcal blepharitis are shown in Fig. 64.4. Ocular rosacea (Table 64.3, Fig. 64.5) is an important condition because of its severity and wide spectrum of clinical features.

In addition to these very common types of blepharitis, there are other chronic causes in which the pathogenesis is clear. These are all uncommon and are often misdiagnosed as one of the types of chronic blepharitis described in Table 64.2. They include fungal infection (e.g. *Candida*), parasitic infection (e.g. phthiriasis), protozoal infection (e.g. leishmaniasis), some neoplasms, and autoimmune conditions such as lupus erythematosus; some of these are illustrated in Fig. 64.6. They should be considered when therapy for conventional blepharitis fails.

Acute blepharitis is a clearly defined group of conditions, which may overlap with the chronic blepharitis causes summarized in Table 64.4.

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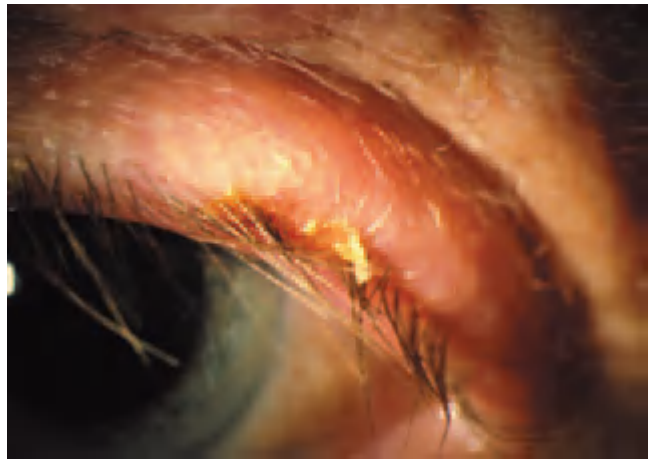

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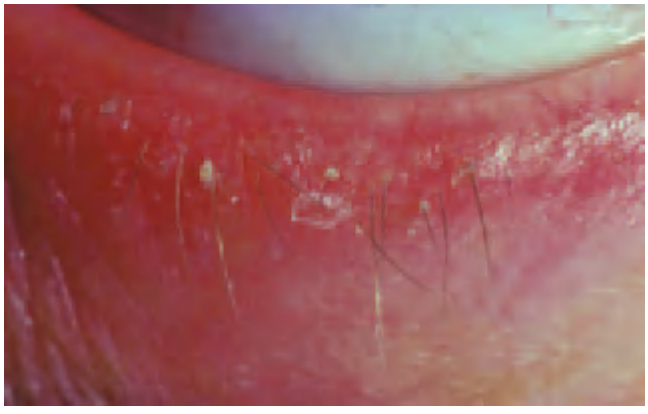

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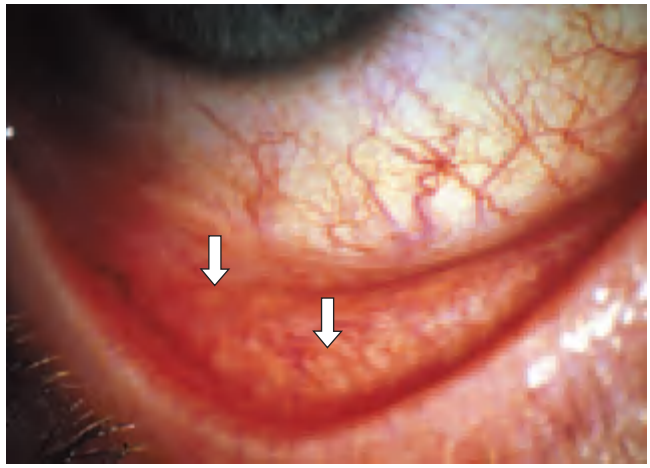


(c)

Fig. 64.4 Staphylococcal blepharitis. (a) Fibrinous 'collarettes' lifting away from the skin as the lashes grow. (b) Fibrinous scales on the anterior lid margin with the madarosis (loss of lashes) and poliosis (white lashes) that accompanies chronic blepharitis. (c) Follicular conjunctivitis with arrows showing the white/yellow follicles. (d) Localized ulcerative blepharitis. Sectoral disease like this is quite common in staphylococcal blepharitis which can also be largely unilateral. (e) Marginal ulceration, a common corneal complication of staphylococcal blepharitis.

Epidemiology

The epidemiology has been dogged by difficulties of disease definition and the different perspectives of dermatologists and ophthalmologists. Chronic blepharitis is one of the commonest disorders in both ophthalmic and general medical practice. In general medical practice it makes up about 70% of ophthalmic referrals, which themselves account for between 2% and 7% of all outpatient consultations. Meibomian gland dysfunction is probably the commonest type of blepharitis and affects 20–40% of all patients consulting ophthalmologists for routine eye examinations. Between 3% and 58% of patients with rosacea have ocular involvement, this wide variation being the result of differences in disease definition. Approximately half the patients with rosacea have signs of ocular rosacea whereas one quarter of patients with ocular rosacea have no dermatological disease.

Table 64.3 Clinical signs of ocular rosacea.

Signs	Common	Uncommon	Rare
Lid	Meibomitis (Fig. 64.5a) Seborrhoeic blepharitis Lid margin telangiectasia Lid notching Retroplacement of the mucocutaneous junction Chalazia (Fig. 64.5b) Hordeoleum	Entropion	
Conjunctiva	Conjunctival hyperaemia Papillary conjunctivitis	Reticular and linear tarsal scarring and fornix shortening	
Cornea	Phlyctenular keratoconjunctivitis Marginal corneal infiltration and ulceration (Fig. 64.5d,e)	Pseudopterygium	Corneal perforation
Sclera and episclera		Episcleritis	Scleritis

Immunopathogenesis [5]

There is some evidence to support hypotheses of pathogenesis in staphylococcal blepharitis and in meibomian dysfunction, but the pathogenesis is even more poorly understood in the other types of chronic blepharitis.

Staphylococcal blepharitis

In staphylococcal blepharitis [6–13] there is an association with *Staphylococcus aureus* and *S. epidermidis* colonization of the lid margins, although colonization by *S. aureus* is often transient and the numbers of either organism are often no greater than in normal controls. Although folliculitis, styes and lid margin ulcers may be due to infection by *S. aureus*, the persistence of lid inflammation after treatment and the sterile marginal ulcers are not explained by infection alone. The importance of cell-mediated immunity in the pathogenesis of the disease was shown by experimental studies in rabbits; when these were immunized with either whole *S. aureus* or with cell wall ribitol–teichoic acid, both ulcerative keratitis, phlyctenules and marginal corneal ulcers developed after secondary challenge, providing evidence for the hypothesis that these changes were due to the development of hypersensitivity to both viable and killed organisms. These finding could not be reproduced for *S. epidermidis*. However the evidence for a similar pathogenesis in humans is lacking; the relationship between the clinical signs of staphylococcal blepharitis and hypersensitivity to subcutaneous injections of either whole *S. aureus* or of *S. aureus* cell wall protein A is poor. *Staphylococcus epidermidis* is more often isolated than *S. aureus* from the lids of patients with staphylococcal blepharitis, but the evidence of the role of a hypersensitivity response is assumed and not supported by any data. The pathogenesis of the, often severe, follicular and papillary conjunctivitis that accompanies this condition is assumed to be due to a combination of transient infection and hypersensitivity.

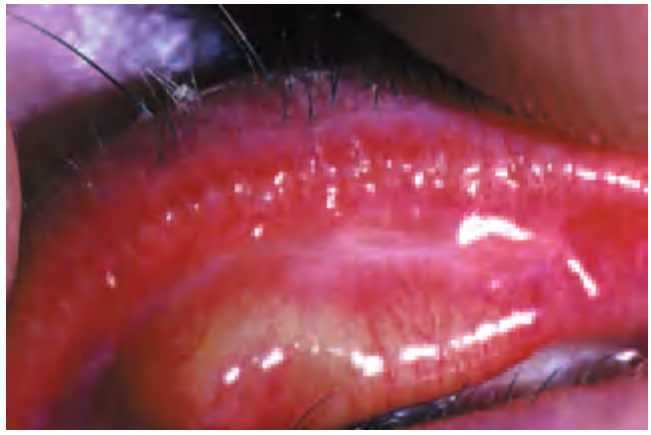
Meibomian gland disease (MGD) [14–16]

The meibomian lipids (meibum) are a complex mixture of cholesterol esters and esterified unsaturated fatty acids. These lipids are responsible for maintaining a stable tear film, reducing tear film evaporation and, therefore, drying of the ocular surface, preventing tear spill over the lid margins by lowering surface tension and reducing ocular surface contamination, by sebum, from the cutaneous surface of the lids which otherwise forms dry spots.

Three factors have been invoked as contributing to MGD: (i) keratinization of the meibomian ductules; (ii) the effect of bacterial lipases on the meibum at the lid margin; and (iii) primary abnormalities in the production of meibum by individuals with MGD.

Normal meibomian gland ducts open just anterior to the mucocutaneous junction. As the duct lining is partially keratinized, abnormalities of keratinization, analagous to those present in the sebaceous glands of patients with rosacea, may be important in the pathogenesis of MGD by altering gland function. Bacterial lipases are produced by all the bacteria that colonize the lid margin and have the potential to break down meibum into free fatty acids that will destabilize the tear film. These bacteria colonize the gland orifices and expression of lipid from deeper within the glands can stabilize the tear film. Meibomian lipids differ between individuals and, as analytical methods increase in sensitivity, the relative roles of primary abnormalities of meibum, and those secondary to the effects of bacterial lipases in the pathogenesis of MGD, are likely to become clearer.

Neither the pathogenesis of the conjunctival inflammation that is common in meibomitis (and which is a feature of ocular rosacea), nor that of the keratitis in ocular rosacea, has been explained.



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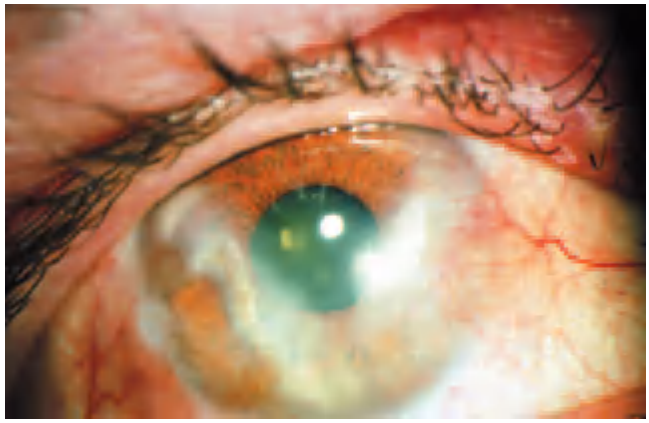

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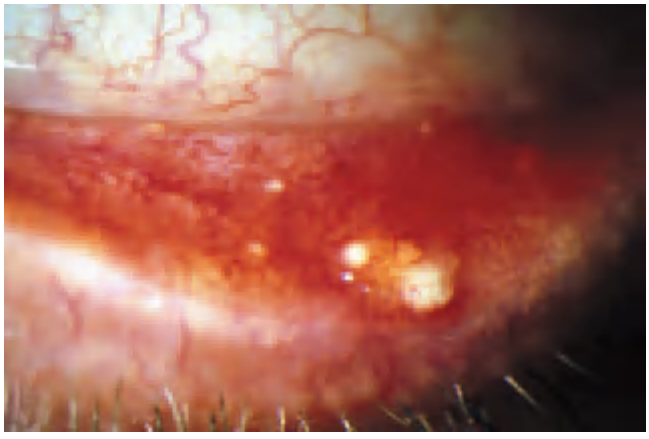

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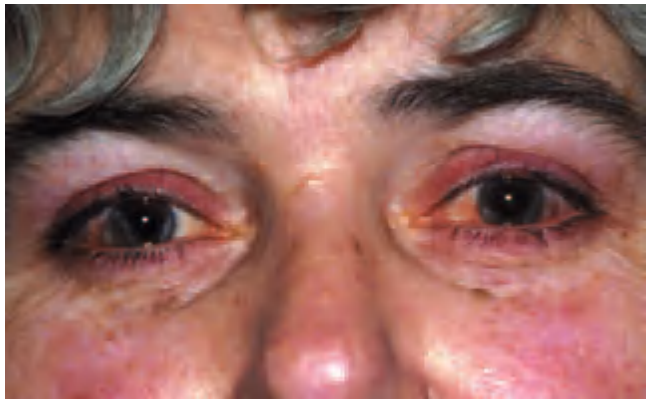

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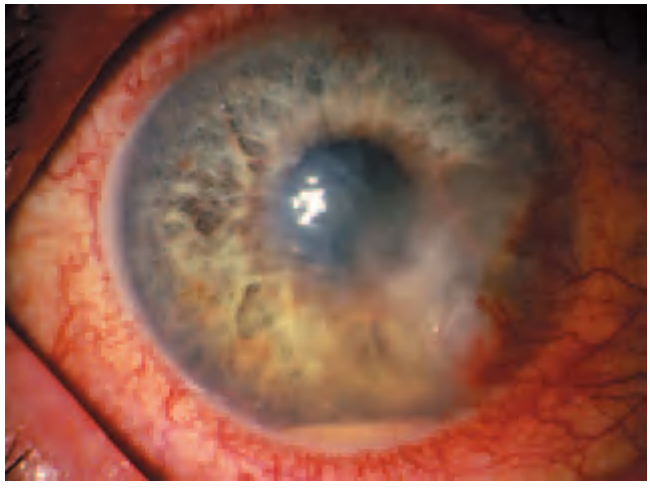

(c)

Fig. 64.5 Ocular rosacea. (a) Scales on the anterior lid margin, meibomitis with posterior migration of the orifices associated with loss of the normal posterior lid margin architecture and scarring in the superior tarsal marginal sulcus. Entropion and trichiasis may result from this degree of scarring. (b) Meibomian dysfunction with blocked glands and small chalazia. (c) Marginal ulceration complicated by frank bacterial superinfection with an hypopyon ulcer. (d,e) Rosacea keratitis showing the right cornea (d) of the patient whose eyes are shown in (e).

Treatment [17–23]

The treatment of blepharitis is that of the underlying cause, if a specific cause can be identified. Treatment for the principal causes of chronic blepharitis is outlined in Table 64.5. The blepharitis should initially be classified into either anterior or posterior lid disease or both (Table 64.2). It is important to decide whether blepharitis is the cause of the symptoms; seborrhoea rarely causes symptoms and should not be used as a scapegoat to explain away symptoms possibly due to other, or undiagnosable, conditions. Other conditions that give rise to similar symptoms and signs (Table 64.2) should be excluded or treated. Symptoms of dry eye and associated skin disorders should also be treated.

Diffuse folliculitis is generally caused by *S. aureus* and requires a course of an appropriate systemic antibiotic. Laboratory investigations are of limited value—bacteriology

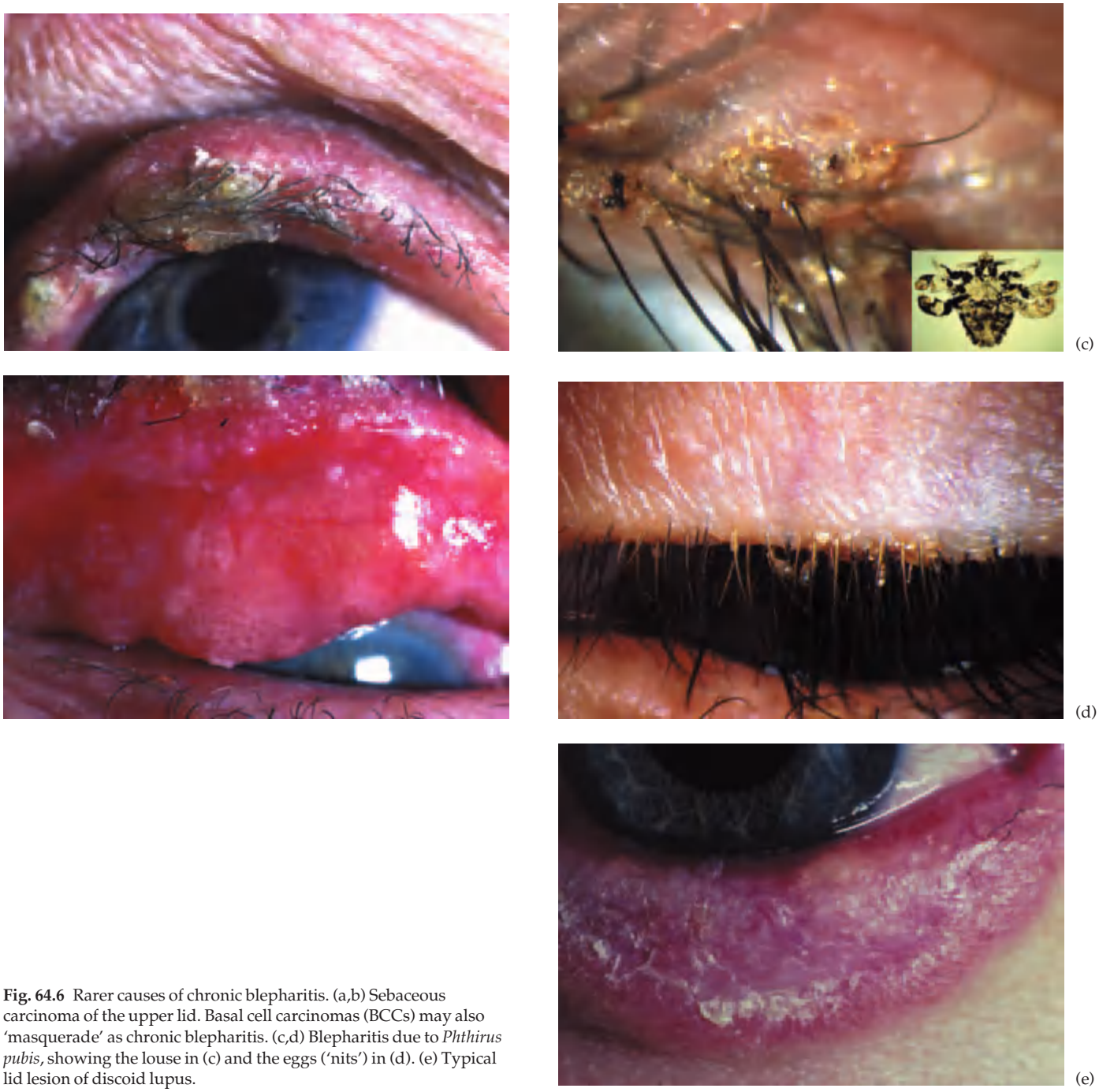

Fig. 64.6 Rarer causes of chronic blepharitis. (a,b) Sebaceous carcinoma of the upper lid. Basal cell carcinomas (BCCs) may also 'masquerade' as chronic blepharitis. (c,d) Blepharitis due to *Phthirus pubis*, showing the louse in (c) and the eggs ('nits') in (d). (e) Typical lid lesion of discoid lupus.

Table 64.4 Causes of acute blepharitis.

Acute anterior lid margin	Folliculitis (infected lash follicles) External hordeoleum (stye) Angular (at lateral canthus) Impetigo Pustular (herpes infections)
Acute posterior lid margin	Chalazion Internal hordeoleum
Generalized anterior and posterior	Necrotizing fasciitis

samples can be taken from lid margins using swabs dipped in trypsin digest broth, but are usually only performed for recurrent disease that has not responded to initial therapy.

Chalazion will resolve in time, approximately 60% of lesions will resolve in 6 months and the remainder will resolve spontaneously given longer. Resolution of chalazia can be hastened by incision and curettage; the lid is incised, usually from the conjunctival surface under local anaesthesia, and the necrotic granulomatous tissue in the

Table 64.5 Treatment of chronic blepharitis.

Aims of treatment	Therapeutic guidelines
For anterior lid margin disease (ALMD)	
Treat infection	Staphylococcal and mixed staphylococcal/seborrhoeic groups Topical antibiotics—chloramphenicol or fucidic acid—four times daily to lid margins Oral oxytetracycline or erythromycin 500 mg b.d. for 10 days
Clean lid margins	'Lid scrubs': 1–2 times daily with cotton wool bud dampened in boiled water or with proprietary lid cleaning pads, to remove debris
Lid hyperaemia and exudate	Topical chloramphenicol and hydrocortisone 0.5–1.0% to lid margins 2–4 times daily for 1 month
For posterior lid margin disease (PLMD)	
Mechanically unblock meibomian glands	Apply hot compresses for 3–5 min to liquefy meibomian secretions, followed by massage* of tarsal plate with cotton wool bud (or finger), to express lipid from glands, 1–2 times daily
Alter meibomian secretions	Oral oxytetracycline (doxycycline 100 mg o.d.) or erythromycin 250–500 mg b.d. for 12 weeks minimum
For the tear film	
Restore tear film	Artificial tears—drops 2–4 hrly, or Viscotears 3–4 times daily
For associated conjunctivitis (papillary or mixed follicular and papillary)	
Reduce inflammation	Fluoromethalone 0.1% four times daily for 1 week, progressively reducing to one time daily over a further 4 weeks
Treat associated skin disease	Seborrhoea—medicated soap and shampoo (ideally containing glycolic acid 10–15%) Rosacea—oral oxytetracycline (or doxycycline 100 mg) or erythromycin 250–500 mg b.d. for 12 weeks
For keratitis	
Coarse punctate keratitis and/or marginal keratoconjunctivitis	Fluoromethalone 0.1% four times daily for 1 week, progressively reducing to once daily over a further four weeks†
Corneal thinning and perforation	Exclude and treat any concomitant microbial keratitis and establish disease control by methods summarized above, apply tissue glue to perforations. Carry out tectonic keratoplasty, if necessary, once the inflammation is controlled.

* Lid scrubs, lid massage and low dose systemic antibiotics take about 4–6 weeks to start to work. DO NOT assume treatment has failed until at least 8 weeks on treatment has elapsed, and continue the regime for a minimum of 2–3 months if benefit is shown. Then advise a maintenance regime of lid scrubs (for ALMD), hot compresses and tarsal massage (for PLMD), ± artificial tears. In the case of relapse, repeat a 3-month course of oral antibiotic treatment.
† More prolonged courses of corticosteroid or more potent corticosteroids may be needed under specialist ophthalmological supervision.

centre of the lesion removed with a curette. This leaves a linear conjunctival and tarsal scar. It is only recommended for cosmetic reasons or to improve vision in large lesions affecting the upper lid which can cause temporary astigmatism.

Practice points for dermatologists are that the association between blepharitis and skin disease is variable, that treatment with tetracyclines may be beneficial for both the ocular and dermatological manifestations of these disorders, and that ocular rosacea and staphylococcal blepharitis may produce sight-threatening complications.

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Atopy and atopic eye disease

Description and epidemiology [1–5]

This group of disorders, usually known as the allergic eye diseases, is better termed the atopic eye diseases to distinguish them from disorders which result from other hypersensitivity mechanisms. The atopic eye diseases comprise a group of disorders which have in common a papillary conjunctivitis and evidence of a type 1 allergic mechanism; the immunopathogenesis has recently been shown to be more complex than this. Table 64.6 summarizes these disorders and Fig. 64.7 shows the commoner clinical signs.

Of these disorders only atopic keratoconjunctivitis (AKC) (Figs 64.7b,g), atopic blepharoconjunctivitis (ABC) and vernal keratoconjunctivitis (VKC) (Figs 64.7c,d) are of interest to the dermatologist because of their association with atopic dermatitis and will be described here. Of these AKC and VKC are sight-threatening disorders that are often difficult to treat; VKC occurs in children and 90% of cases resolve in adult life. All of these diseases are uncommon. Only a small proportion of patients with atopic dermatitis have ocular disease. The severity of symptoms is closely related to disease activity, and patients with minimal symptoms will respond to simple treatment with antihistamines and/or mast cell stabilizers that have an excellent safety profile. However, acute exacerbations of AKC and VKC must be recognized and treated promptly as these may develop within hours and can lead to blinding corneal complications within 1–2 days.

Symptoms are similar for all of these atopic eye diseases. Typically there is itching, watering and the production of a sticky white and stringy mucous discharge. During exacerbations the symptoms increase in severity very rapidly—the itching may be superseded by extreme discomfort with soreness and a foreign body sensation, and the vision deteriorates. The lids may be difficult to open in the morning because of a combination of discomfort and discharge.

Signs that can be seen without a slit-lamp examination are thickened lids; in AKC and ABC the lid margins are usually inflamed, crusted and excoriated with madarosis (Fig. 64.7g). Lid margin signs are uncommon in VKC. The bulbar conjunctiva is inflamed during exacerbations but otherwise grossly normal except for the limbal region which may be thickened and nodular (Fig. 64.7d) with the presence of pinpoint Trantas' dots at the apices of the nodules; these may be present in AKC and in the limbal type of VKC. The distinction between limbal and palpebral VKC is principally of interest to the ophthalmologist; in the UK the limbal form of the disease is generally easier to manage although this may not be the case in Africa. The lower tarsal conjunctiva is usually less abnormal than that of the upper lid, which can be seen to be thickened and velvety when the lid is everted. In VKC, and in some cases of AKC, 'giant' compound papillae are easily seen (Fig. 64.7c). In adults with long-standing disease there is sheet-like scarring of the upper tarsal conjunctiva and shortening of the lower conjunctival fornix. During exacerbations the tarsal conjunctiva becomes very inflamed and covered in adherent mucous. The corneal signs, with the exception of plaque (Fig. 64.7e) or ulceration due to superadded infection (Fig. 64.7f), are difficult to see without a slit lamp but fluorescein staining is diffuse during flare-ups of disease.

Diagnosis

The clinical features, together with a personal or family history of atopy, are usually sufficient for diagnosis. Laboratory investigations are only needed in patients who do not respond to therapy or who require topical (or systemic) immunosuppressive therapy for relief of symptoms, or when the diagnosis is uncertain. Serum IgE and skin prick tests have no value in the diagnosis of atopic conjunctivitis as the results do not indicate the antigens precipitating the eye disease. Ophthalmic investigations are the province of the ophthalmologist and are summarized in Table 64.6.

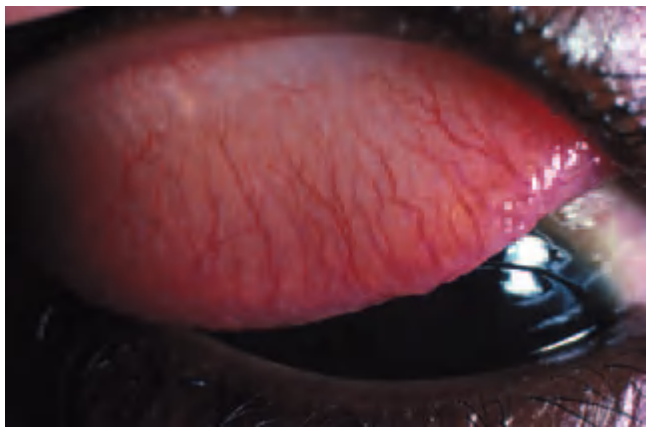
Immunopathogenesis [6–9]

Recent advances in the understanding of these diseases have come from investigations of the humoral mediators of inflammation in the tears, and analysis of the cellular components by immunostaining and *in situ* hybridization. These techniques have shown that seasonal allergic conjunctivitis (SAC) and perennial allergic conjunctivitis (PAC) are primarily typical type 1 hypersensitivity diseases, whereas the others show varying degrees of a coexisting type 4 hypersensitivity response. SAC and PAC show mast cells and eosinophils in the conjunctival mucosa and submucosa, with high levels of locally produced IgE to specific allergens being present in the tears.

Table 64.6 Clinical characteristics and distinguishing features and diagnosis of the atopic eye diseases.

Disease	Disease course	Conjunctival signs	Corneal signs	Disease associations	Diagnostic tests
Seasonal allergic conjunctivitis (SAC)	Onset 5–20 years Spontaneous remissions common Rare in old age Strikingly seasonal	Hyperaemia. Stringy white discharge. Oedema Micropapillae if severe	None	Personal or family history of atopy including atopic dermatitis	*Cytology*: usually normal. Serum & tear IgE often elevated but not diagnostic
Perennial allergic conjunctivitis (PAC)	As for SAC but symptoms all year round with seasonal exacerbations	Hyperaemia, stringy white discharge, micropapillae common	None	Personal or family history of atopy including atopic dermatitis	
Atopic keratoconjunctivitis (AKC)	Onset between 20–50 years. Chronic course over many years (Fig. 64.7g). Spontaneous resolution in old age Non-seasonal	Micropapillae with intense infiltrate (Fig. 64.7b). Reticular and sheet scarring. Shortened fornices in some cases Trantas' dots*	Punctate epithelial keratopathy, pannus, macroerosion† and plaque‡ Pseudogerontoxon§. Herpes keratitis and bacterial keratitis (Fig. 64.7f) common	*Systemic*: atopy and atopic dermatitis in all cases *Ocular*: staphylococcal lid disease, cataract, keratoconus, herpes simplex keratitis (often bilateral)	*Cytology*: shows eosinophils and mast cells. Serum IgE elevated. Skin prick tests positive to many allergens but not diagnostic *Upper tarsal conjunctival punch biopsy*: the gold standard for disease confirmation after a 2 week abstention from use of topical corticosteroids *Tear IgE*: useful unless the serum IgE is very high; an office test is now available (*Lacrytest* from Adiatec SA, France)
Atopic blepharoconjunctivitis (ABC)	As for AKC	Micropapillae with intense infiltrate, reticular scarring	None	Personal or family history of atopy	
Vernal keratoconjunctivitis (VKC)—*palpebral, limbal and mixed forms*	Onset between 5–15 years. Spontaneous resolution in 95% after 10 years Seasonal exacerbations usual	*Palpebral form*: giant upper tarsal papillae (Fig. 64.7c) often bilaterally asymetrical *Limbal form*: micropapillae on upper tarsus but gelatinous macropapillae at limbus (Fig. 64.7d). Trantas' dots in both *Mixed form*: combines features of both diseases	*Palpebral form*: punctate epithelial keratopathy affecting upper half of cornea. Adherent mucous appearing as superficial syncytial opacity progressing to macroerosion and vernal plaque (Fig. 64.7e) *Limbal form*: keratopathy extending in from limbus with associated epithelial dysplasia	*Ocular*: keratoconus and cataract *Systemic*: atopy in variable proportions from 0–100% depending on geographical location (atopy common in Northern Europe but rare in Middle East)	

* Trantas' dots: white pinhead sized dots consisting of eosinophils and necrotic epithelial cells.
† Macroerosion: large epithelial erosions usually in upper half of cornea.
‡ Plaque (vernal plaque): laminated structure of protein and polysaccharide adherent to the anterior stroma with destruction of Bowman's layer.
§ Pseudogerontoxon: arcus-like appearance in relation to limbal pannus; may disappear in remissions.



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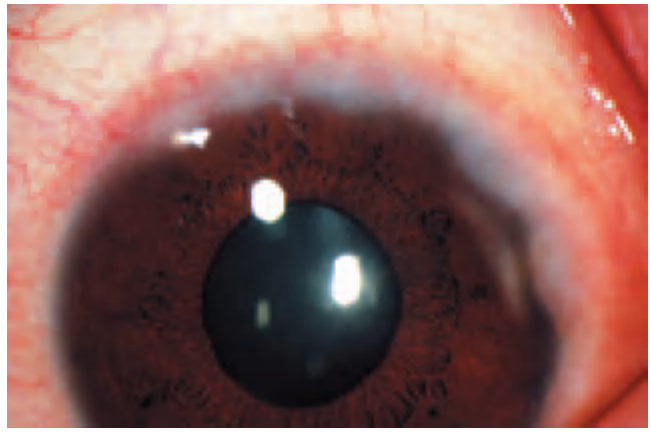

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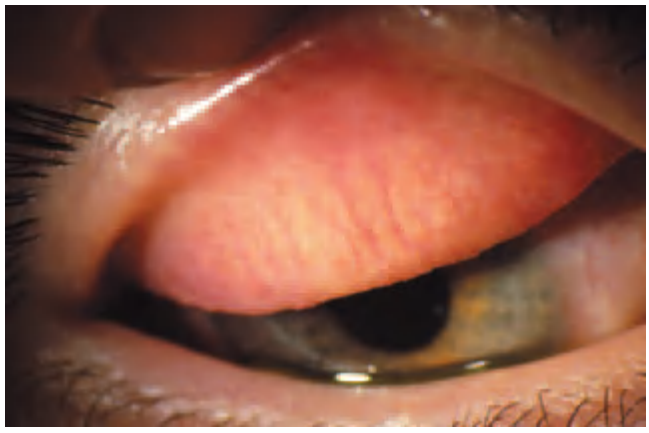

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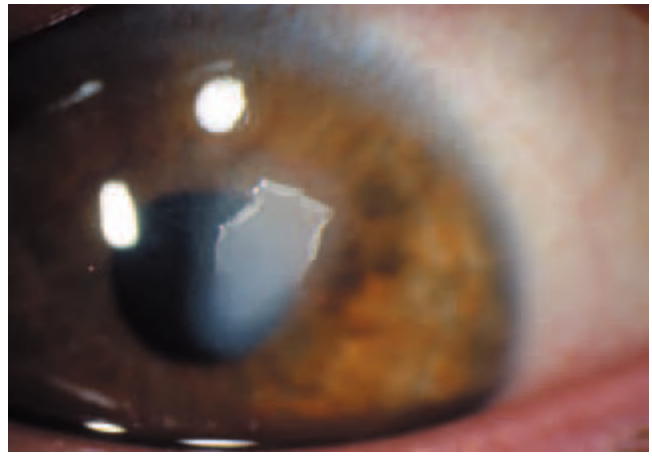

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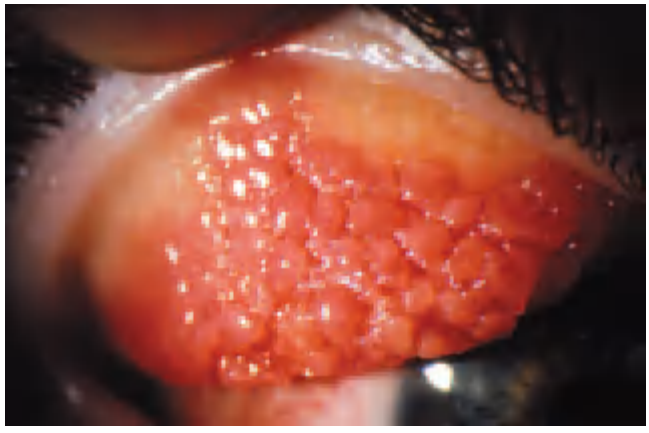

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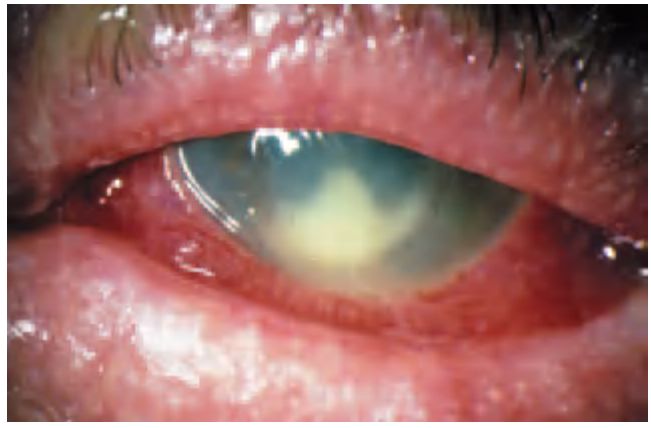

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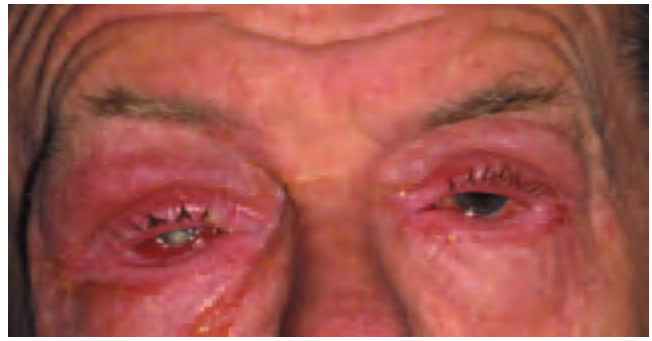

(g)

Fig. 64.7 Atopic eye disease. (a) Normal upper tarsal conjunctiva; the tarsal vessels are clearly visible through the healthy conjunctival epithelium and substantia propria. (b) Atopic keratoconjunctivitis with an infiltrated, papillary, upper tarsal conjunctiva. Compare with the normal tarsal conjunctiva in (a). (c) Showing 'giant' or compound upper tarsal papillae and the mucous exudate that develops during an exacerbation. (d) Vernal keratoconjunctivitis (VKC) (limbal form) showing the typical pale limbal papillae. (e) Fully developed vernal plaque. (f) Bacterial keratitis complicating atopic keratoconjunctivitis (AKC) showing a corneal infiltrate. The eyes of this patient are shown in (g), with atopic eczema localized to the eyelids; the eczema is often generalized. The right eye shows the infection in (f).

The diseases can be mimicked by topical instillation of antigen; this reaction is blocked by drugs that are active against mast cells. AKC and VKC show both the cellular components present in SAC and VKC but also connective tissue hyperplasia, CD4 T lymphocytes and plasma cells, together with different subsets of mast cells. The T cells are probably important inducers of the cellular inflammatory response in these diseases. Differences in AKC and VKC phenotypes may be explained by differences in the predominance of T-helper subsets; the Th1 subset, predominant in delayed type hypersensitivity responses and inactivated by ciclosporin, is more predominant in AKC than in VKC, in which the Th2 subset, with a B-cell-helper role, may be more important. Mast cells and eosinophils are found in larger numbers in VKC than in AKC and functional heterogeneity in their populations may also be determinants of disease phenotype.

These effector cell types are known to cause atopic eye diseases by the following mechanisms. Mast cells release preformed mediators by exocytosis when they degranulate in response to binding of IgE with allergen. The important mediators released are histamine, resulting in hyperaemia, oedema and mucous production, and prostaglandins. Histamine has been detected in the tears in these diseases. Eosinophils release cationic proteins including major basic protein, which is epitheliotoxic and has been identified in the tears in VKC. It is probably a major factor responsible for the development of corneal epithelial erosions and macroerosion. The presence of the latter, with the mucous and debris present in an acute exacerbation of keratopathy, accounts for the formation of plaque. B cells produce IgE locally in atopic conjunctivitis; locally produced IgE is an important factor in the pathogenesis of SAC, PAC and some cases of VKC, but less so in AKC and ABC.

Management [10,11]

The management of VKC and AKC requires specialized ophthalmological care, as these diseases are uncommon, and some of the management strategies are outside the remit of the general ophthalmologist. Topical cromones (sodium cromoglycate 2–4% or the more recently introduced nedocromil or lodoxamide) are the first-line treatment given 1–4 times daily depending on symptoms. The newer cromones have been more effective in trials of SAC. Addition of a potent topical antihistamine (levocabastine or emedastine) or a systemic antihistamine may help relieve itch. These treatments are very safe and do not require ophthalmological supervision but are only effective for very mild disease. Cromones are often not tolerated until the inflammation is brought under control with high dose topical corticosteroids such as dexamethasone 0.1% or prednisolone acetate 1%. These will precipitate glaucoma in 10% of patients as well as contributing to cataract; as soon as the disease is brought under control, a 'safe' corticosteroid with a lower risk of precipitating glaucoma (about 1% risk) should be substituted (fluoromethalone, rimexolone or clobetasone). Cromones are used topically, whenever possible, as corticosteroid-sparing drugs.

Topical ciclosporin is not yet available commercially, although a preparation designed for use in dry eye is expected to be available soon (Restasis, Allergan, USA). It has shown promise in trials for AKC. Trials of ciclosporin 2% (available from some hospital pharmacies) have been very encouraging and a 0.02% veterinary ointment (Optimmune, Schering) has been successfully used by the authors. Adverse effects, apart from stinging, are infrequent and introduction of the drug as a corticosteroid sparing agent, for patients requiring high doses of topical corticosteroids, has allowed reduction or complete withdrawal of corticosteroids in many cases. Topical ciclosporin is most successfully tolerated if introduced during remissions.

Systemic immunosuppression is needed in severe exacerbations of disease; a 3–4 week course of systemic corticosteroids starting at a prednisolone dose of 60 mg daily, may be necessary to bring the disease under control while topical therapy is introduced. These also carry a risk of glaucoma. Patients with a previous history of labial or ocular herpes simplex (HSV), or serological evidence of previous exposure to HSV, should be aware that they may develop herpetic keratitis while on systemic or topical corticosteroids. Patients who have had previous episodes of ocular HSV should receive prophylaxis with oral aciclovir 400 mg b.d. (or valaciclovir 500 mg o.d.); topical prophylaxis is unnecessary and may complicate the clinical signs in patients with a complex keratoconjunctivitis. Patients with AKC are predisposed to bilateral herpes keratitis and prophylactic antivirals are advisable when they are using corticosteroids.

For a small number of patients, systemic ciclosporin (usually starting at 5 mg/kg) can be very helpful. Patients who need systemic ciclosporin for management of their atopic eczema will usually obtain substantial collateral ocular benefits.

Severe staphylococcal blepharitis often accompanies AKC and ABC and can be treated with a course of azithromycin followed by local therapy with an antibiotic ointment to which the skin flora is sensitive, usually chloramphenicol, together with a topical ophthalmic corticosteroid ointment such as hydrocortisone 0.5% or 1.0%. Combined preparations often contain aminoglycosides which frequently cause toxicity or allergy and should be avoided.

The management of the corneal complications that often accompany these conditions (vernal plaque, bacterial keratitis and herpes keratitis) are beyond the scope of this summary but present challenging management problems in the context of these conditions.

Practice points for dermatologists are that the dermato-

logist should be aware that any sudden deterioration in vision may herald one of the blinding complications of these diseases and should be treated as an emergency. Good control of the underlying condition aims to reduce the frequency with which the blinding corneal complications develop, whilst minimizing the potentially serious side effects of corticosteroid treatment.

The interaction of drugs used for the management of atopic eye disease and atopic dermatitis

Most cases of atopic eye disease are managed with topical ocular therapy which has no effect on the dermatological aspects of the disorder. However treatment with courses of systemic corticosteroid and/or ciclosporin, when needed either for the dermatological or ophthalmological aspects of atopy, are beneficial to the management of both. The risk of glaucoma from systemic corticosteroids, while occurring, is very low whereas topical application of corticosteroid around the eyelids probably constitutes a higher risk; patients who chronically use corticosteroid cream around the eyes should have glaucoma screening.

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Cicatrizing conjunctivitis and the immunobullous disorders

Description and epidemiology [1–4]

Cicatrizing conjunctivitis, although uncommon, is one of the most difficult management problems in ophthalmology because of the widespread effects on the ocular surface leading to corneal blindness in many victims. The classification of the conjunctival disorders follows the dermatological classification although not all the dermatological disorders are associated with conjunctivitis (Table 64.7).

Table 64.7 Immunobullous diseases (those associated with conjunctivitis are shown in italics).

Intraepithelial	Subepithelial
• Pemphigus *vulgaris* vegetans sebhorreic	• Pemphigoid *Bullous* *Cicatricial* (Fig. 64.8a–f)
• Pemphigus foliaceous	• Pemphigoid gestationis
• Pemphigus erythematosis	• *Epidermolysis bullosa aquisita*
• Brazilian pemphigus	• Bullous systemic lupus erythematosis
• *Paraneoplastic pemphigus*	• *Linear IgA disease*
	• *Dermatitis herpetiformis*
	• *Lichen planus*
Graft-versus-host disease	
Erythema multiforme • Minor • *Major (Stevens–Johnson syndrome)*	
Toxic epidermal necrolysis (Lyell syndrome)	

The severity of the conjunctival involvement varies but is mild, without scarring, in pemphigus vulgaris, and with variable degrees of scarring and severity in the remainder.

Cicatricial pemphigoid (CP) [5–9]

CP is the commonest of these rare disorders. It is a systemic disease with involvement of the skin (25% of cases), oro-pharyngeal mucosa (85% of cases) and conjunctiva (65% of cases) and may be localized to one of these sites alone. About 70% of patients presenting to a dermatologist will have conjunctival involvement, in addition to skin disease, whereas disease confined to the conjunctiva alone is found in 50% of patients in ophthalmology clinics and is known as ocular cicatricial pemphigoid (OCP). Some authorities feel that the term mucous membrane pemphigoid should be adopted but this belies the scarring nature of the disease when it affects the eye and will not be used in this discussion.

Epidemiology of CP

Unambiguous data on the epidemiology of the disease is difficult to obtain because studies have been based on the site of involvement. However the incidence of dermatological disease is about 1/million/year. This is likely to be an underestimate of the disease as a whole because mucosal presentations are more common. In ophthalmology centres CP affects between 1 : 8000 and 1 : 46 000 patients. The male : female ratio is 1 : 3 and age range

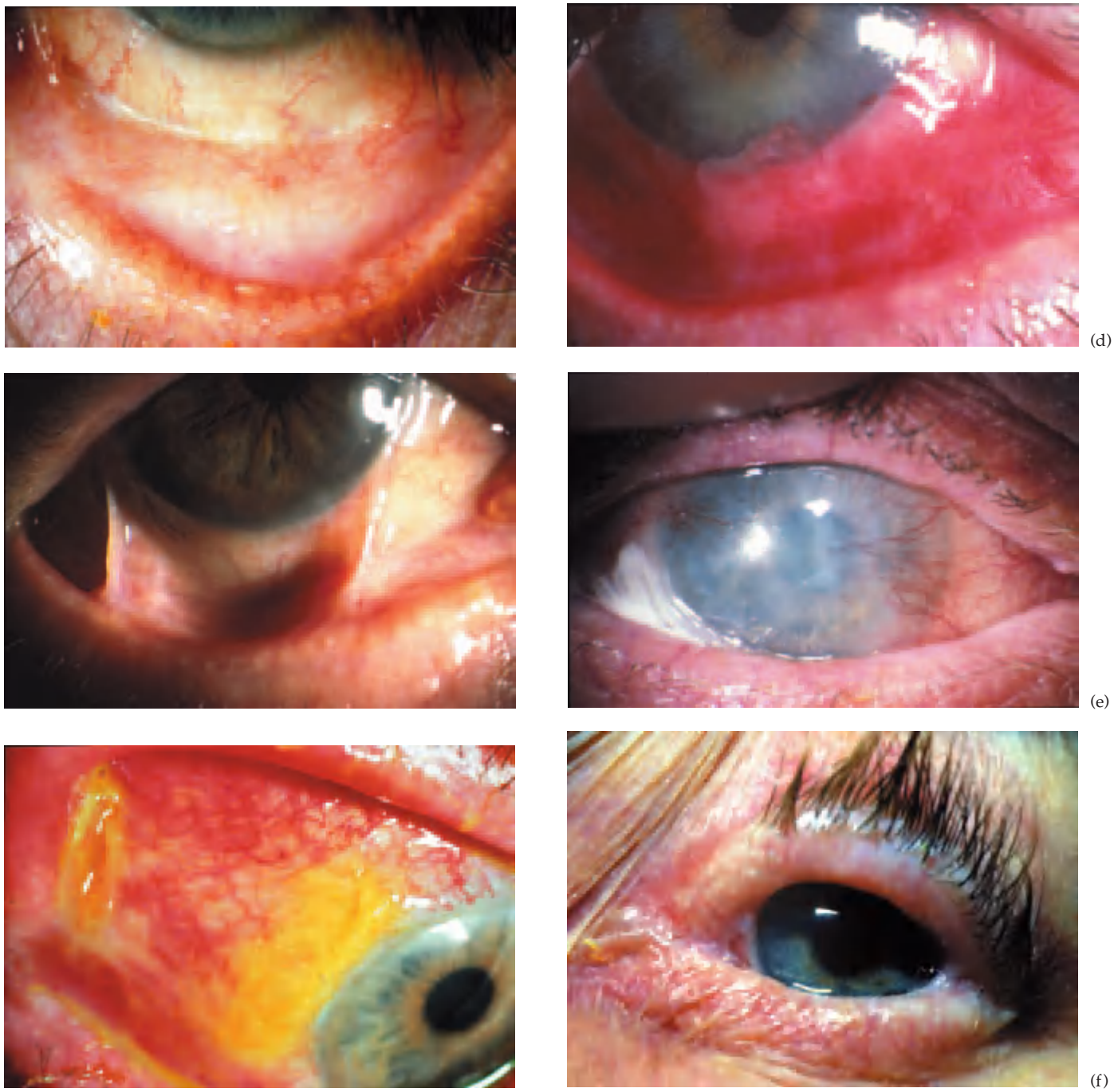


Fig. 64.8 Ocular signs of cicatricial pemphigoid (CP). (a) Inferior fornix shortening and subconjunctival scarring. (b) Conjunctival symblepharon tethering the globe to the lower lid. (c) Acute exacerbation of conjunctival CP showing conjunctival ulceration. This occurs in only 10% of patients presenting with CP affecting the eye. (d) Severe conjunctival inflammation and limbitis. This leads rapidly to the ocular surface failure and corneal blindness shown in (e) unless it is promptly controlled with adequate immunosuppressive therapy. (e) Ocular surface failure and keratinization (the white area) in advanced pemphigoid. This eye is blind. (f) Advanced ocular pemphigoid showing loss of the medial canthal structures (plica and caruncle) with a reduced interpalpebral aperture secondary to shortening of the fornices (as in (a)) and fusion of the tarsal and bulbar conjunctiva.

30–90 years with peak onset in the seventh decade, although patients may rarely present in childhood and in extreme old age. At presentation between 25 and 38% of patients with ocular disease have significant visual loss and about 30% become legally blind. Treatment has been shown to slow disease progression. A genetic predisposition has been found in an association with the *DQw7* gene and expression of the HLA-DR4 antigen.

Clinical features [10]

Most patients with OCP have progressive disease. However, early presenting disease is usually milder and progresses more slowly than late-presenting disease. Current aggressive treatment regimens, with systemic immunosuppression, have been shown to reduce the rate of progression by about 50%. Because patients can occasionally progress to blindness within months from the onset, both early diagnosis and effective treatment are critical in improving the prognosis.

In most patients the onset is insidious, with non-specific conjunctival symptoms including irritation, hyperaemia and discharge. Dry eye and mucous deficiency are late signs. Acute disease occurs in about 20% of new patients with severe inflammation and conjunctival ulceration; this presentation may follow lid surgery for entropion on undiagnosed cases.

Signs, in order of progression, often start at the medial canthus with loss of the plica and later of the caruncle (Fig. 64.8f), subepithelial reticular fibrosis of tarsal conjunctiva (Fig. 64.8a), conjunctival infiltrate due to increased cellularity and collagen formation (Figs 64.8c.d), hyperaemia, shortening of the fornices (Fig. 64.8a), symblepharon (Fig. 64.8b), blepharitis, trichiasis and entropion, punctate keratopathy, limbitis, conjunctival and corneal keratinization, and corneal surface failure (Fig. 64.8e). Late disease results in fusion of the lids and globe (Fig. 64.8f), and may obscure the cornea completely. Persistent epithelial defect, microbial keratitis and corneal perforation are common and, with the corneal surface failure, account for the management challenges posed by the disease. Cicatricial pemphigoid is associated with the autoimmune diseases rheumatoid arthritis, systemic lupus erythematosus and polyarteritis nodosa.

Diagnosis

Laboratory investigations [11–13] require specialized services and are only positive in 40–60% of cases so that for practical purposes a clinical diagnosis, based on a history of progression and the presence of the typical clinical signs, is adequate in most cases outside a clinical research setting. However, laboratory investigations for OCP may be useful. Indirect immunofluorescence for circulating antibodies to conjunctival basement membrane are present in 50% of cases of CP but the ability to perform this test requires a constant source of conjunctival substrate. The sensitivity of indirect immunofluorescence can be significantly increased using 1.0 mol/L sodium chloride split skin as the substrate.

Bulbar conjunctival biopsy is easy and safe providing the inferior fornix is avoided. Routine histopathology is of little value in the diagnosis because the conjunctiva is fragile and detection of basement membrane zone cleavage unreliable. Squamous metaplasia of the conjunctival epithelium and a reduction in goblet cells are non-specific findings as is an increased inflammatory cell infiltrate. In acute disease there is a neutrophil-rich infiltrate. Direct immunofluorescence for IgA, IgG, IgM, and complement is positive with linear staining at the conjunctival basement membrane in 50% of cases and is characteristic of OCP. However biopsies are often negative in acute disease and may revert to normal in time or after treatment.

Table 64.8 Causes of non-autoimmune cicatrizing conjunctivitis.

Infective conjunctivitis
Trachoma
Corynebacterium diphtheriae conjunctivitis
Streptococcal conjunctivitis
Adenoviral keratoconjunctivitis
Systemic diseases
Sarcoidosis
Progressive systemic sclerosis
Sjögren's syndrome
Atopic keratoconjunctivitis
Trauma
Iatrogenic conjunctivitis (pseudo-pemphigoid)
Chemical, thermal or mechanical trauma
Factitious (self-induced) conjunctival trauma
Others
Ocular rosacea
Staphylococcal blepharoconjunctivitis

Differential diagnosis

The conjunctival signs in CP and OCP may be identical to those produced by the other immunobullous disorders that are summarized in Table 64.7. However, in these conditions the skin disease precedes the ocular disease so that there is rarely any confusion. In erythema multiforme major, exacerbations of conjunctival inflammation can occur many years after the acute disease leading to a condition indistinguishable from OCP both in terms of the clinical signs and immunopathology. The principal problems in differential diagnosis relate to diseases other than the immunobullous disorders, that may also cause cicatrizing conjunctivitis (Table 64.8). Patients with conjunctival cicatrization secondary to infective causes are sometimes referred for investigation of what has been longstanding conjunctival scarring, following a long forgotten episode of infection, in whom the absence of a recent history of inflammation, or of progressive symptoms, usually indicates static disease. Patients with sarcoidosis or systemic sclerosis normally have a well-established diagnosis by the time conjunctival scarring develops. However, Sjögren's syndrome may mimic early OCP but can usually be differentiated by the presence of Sjögren's

specific antibodies and/or a positive labial biopsy. AKC can occasionally be difficult to differentiate from slowly progressive OCP but the history and clinical signs of severe eczema, and a tarsal conjunctival biopsy (performed after withdrawal of topical corticosteroids for 2 weeks) that shows excessive numbers of mast cells and eosinophils, can confirm the diagnosis. Iatrogenic conjunctivitis is non-progressive, except in the case of drug-induced OCP, which is indistinguishable from classical OCP. Awareness that conjunctival scarring can occur in ocular rosacea and in staphylococcal bleph-aroconjunctivitis (see Fig. 64.5a) is usually enough to distinguish these conditions from OCP. Factitious conjunctival trauma is rare and usually more focal than classical OCP but can mimic OCP while the self-trauma is active.

Pathogenesis [14,15]

OCP is probably primarily an autoimmune disease directed at the conjunctival basement membrane; progression occurs as a result of inflammatory disease and cicatrization, secondary ocular surface disease, infection and treatment toxicity. Drug-induced pemphigoid (pseudopemphigoid), and Stevens–Johnson syndrome lead to an identical situation, suggesting that conjunctival damage may precipitate OCP. OCP may be the final common pathway for one type of conjunctival insult.

Inflammatory mechanisms in OCP are reasonably well understood and provide a rationale for immunosuppressive therapy. In chronic disease macrophages and T cells are present, of which the Th1 subset is active, as demonstrated by the presence of the cytokines, interleukin-2 and interferon-γ, as opposed to the Th2 subset that is involved in B-cell activation. This, coupled with the low numbers of B cells but increased number of plasma cells, suggests that B-cell activation must be occurring in the extraocular tissues with homing of mature plasma cells to the conjunctiva. Major histocompatibility complex (MHC) class II expression is increased, suggesting the potential for local antigen presentation to T-helper cells. There is a slight increase in activated T cells, which are involved in the recruitment of fibroblasts and macrophages. In acute disease, neutrophils and antigen-presenting (dendritic) cells are also present together with an increase in CD4 (helper) T cells, which probably reflects their role in recruiting other inflammatory cells.

Growth factors including fibroblast growth factor (FGF), platelet-derived growth factor (PDGF) and transforming growth factor-β (TGF-β) are all present in OCP. PGDF up-regulates the extracellular matrix component (ECM) thrombospondin, which is itself important in activating latent TGF-β. PDGF is a powerful chemoattractant for macrophages and fibroblasts and is probably pivotal to the scarring response. However only TGF-β is capable of stimulating fibroblasts to produce collagen and ECM components. It also blocks matrix degradation by decreasing protease synthesis and increasing protease inhibition. In acute disease, TGF-β is significantly increased and is produced by macrophages and fibroblasts in OCP conjunctiva. Once macrophages and fibroblasts are present in large numbers and activated they may become self regulating; T-cell deficient models have shown that T cells are not necessary for wound healing to occur, and fibroblasts from OCP conjunctiva display abnormal activity in cell culture after several passages.

This inflammatory cell infiltrate is also associated with the presence of increased amounts of an abnormal type II 'curly' collagen.

Implications of immunopathological findings for therapy

Inflammation is important in acute disease; severe inflammation is associated clinically with rapid scarring and therefore demands effective immunosuppression to reduce scarring. Inflammation may also play a role in chronic disease although scarring often continues even in the presence of minimal inflammation, suggesting that growth factor production by macrophages and fibroblasts is relatively independent of the other inflammatory cells. Therefore modulation of growth factor activity, collagen metabolism or fibroblast activity may be necessary to halt the disease process. Of these, growth factor activity can potentially be specifically blocked or inhibited, thus holding promise for new treatments.

Other subepithelial immunobullous disorders and conjunctivitis [16]

Other immunobullous disorders are much less frequently associated with conjunctival cicatrization. As a result little is known about the pathogenesis of the conjunctival disease as opposed to the events in the skin. Bullous pemphigoid generally results in mild conjunctivitis although severe cicatrization has been reported. Epidermolysis bullosa aquisita, linear IgA disease, dermatitis herpetiformis and lichen planus may all be associated with progressive conjunctival scarring indistiguishable from that of CP.

Erythema multiforme major and toxic epidermal necrolysis [17–21]

The ocular complications of these two conditions are identical (Table 64.9); about 70–80% of patients admitted for treatment of these diseases will develop eye disease. It is the eye disease which leads to the most profound long-term morbidity in many such patients. In addition the eye disease, unlike the lesions affecting the remaining

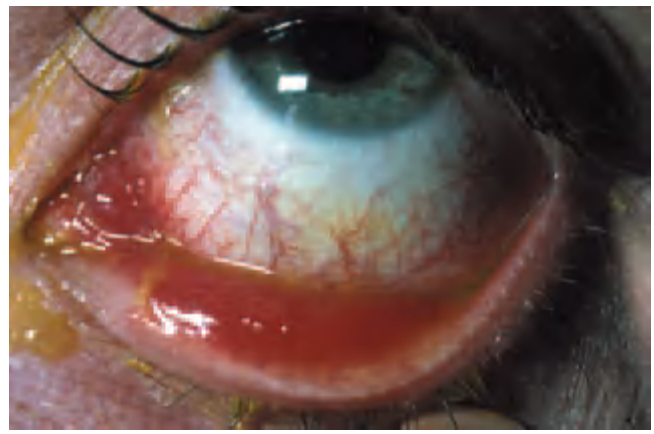
Table 64.9 Ocular effects of Stevens–Johnson syndrome and toxic epidermal necrolysis.

Ocular effects	Resulting symptoms and signs
Loss of goblet cells	Disrupted tear film leading to poor vision and punctate keratopathy (Fig. 64.9b)
Loss of accessory lacrimal glands	
Scarring of meibomian gland orifices	
Metaplasia of meibomian gland epithelium with development of metaplastic lashes	Trichiasis secondary to metaplastic lashes (Fig. 64.9b)
Conjunctival scarring and obliteration of lacrimal gland ductules	Very dry eye with secondary conjunctival and corneal squamous metaplasia (Fig. 64.9b)
Keratinization due to squamous metaplasia	Exacerbates drying and discomfort
Conjunctival scarring with fornix shortening and symblepharon formation	May cause lagophthalmos
Retroplacement of meibomian gland orifices	Disrupts tear film
Entropion of upper and lower lids with trichiasis of both metaplastic and normal lashes	
Lid shortening	
Corneal epithelial failure secondary to limbal inflammation	Blindness

mucosal surfaces, may progress years after the acute episode has resolved.

Acute ocular complications usually occur concurrently with the skin disease but may sometimes precede it by several days. The conjunctivitis varies from a papillary reaction with watery discharge (Fig. 64.9a) to a membranous conjunctivitis with sloughing of the conjunctival epithelium. Corneal epithelial defects are common and may progress to corneal ulceration with or without bacterial superinfection. The morbidity of the disease may be due to the acute corneal complications but is more usually due to conjunctival scarring.

Chronic ocular complications are numerous. The severe conjunctival inflammation leads to loss of goblet cells and the accessory conjunctival lacrimal glands as well as disruption of the meibomian gland orifices leading to MGD. This results in a disrupted tear film and a secondary punctate keratinopathy. In mildly affected patients this causes chronic mild discomfort, photophobia and slightly reduced vision. In more severely affected patients the conjunctival inflammation leads to cicatrization of the lacrimal ductules resulting in a severely dry eye accompanied by squamous metaplasia and keratinization of both the conjunctival and corneal components of the ocular surface, resulting in more severe discomfort and loss of vision (Fig. 64.9b). In addition the meibomian gland ductal epithelium undergoes metaplasia resulting in the development of fine metaplastic lashes. The conjunctival shortening leads both to entropion, resulting in ocular surface abrasion by normal as well as by any metaplastic lashes, and may also cause lid shortening leading to reduced eye closure (lagophthalmos) which is easily overlooked. Lash abrasion and trichiasis lead to the development of corneal epithelial defects which, as



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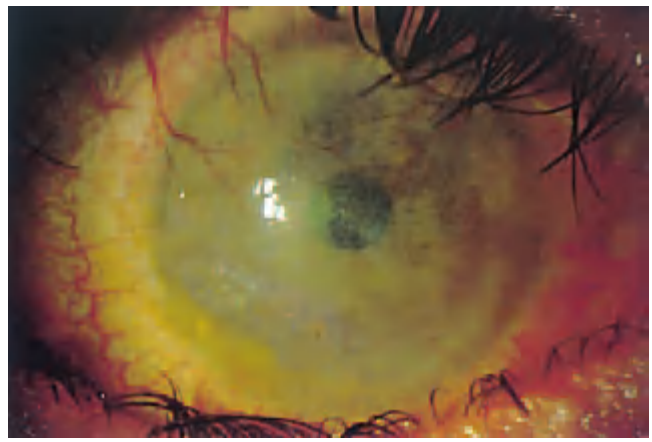

(b)

Fig. 64.9 Ocular disease in Stevens–Johnson syndrome. (a) Acute conjunctivitis in a patient with mild Stevens–Johnson syndrome. The conjunctiva is hyperaemic with a papillary reaction and mucopurulent discharge. (b) The late ocular complications of Stevens–Johnson syndrome showing entropion, a dry eye with ocular surface failure (in this case an opaque keratinized epithelium).

a result of the poor tear film, may persist. Persistent epithelial defect predisposes to corneal stromal melts and perforation, which are often precipitated by infection. The severe inflammation may also lead to ocular surface failure, not only as a result of squamous metaplasia, but also by loss of corneal epithelial progenitor cells (stem cells). This evolution of changes is not the direct consequence of the acute disease but is secondary to the effects on the tear film and lids, compounded in some cases by chronic or acute episodes of inflammation for which the pathogenesis is obscure. Late onset scleritis may also occur.

Graft-versus-host disease [22–28]

Ocular complications are common in patients with graft-versus-host disease (GVHD) and result from involvement of both the conjunctiva and the lacrimal gland. In acute GVHD, conjunctivitis ranges from hyperaemia through chemosis to a pseudomembranous conjunctivitis, with or without corneal epithelial sloughing. Severe conjunctival involvement is a marker for the severity of acute GVHD and was found to occur in 12% of patients in one study; this subset had 90% mortality [26]. In chronic GVHD the same study found conjunctival involvement in 11% of patients for whom it was also associated with disease severity. Some of these patients develop a severe scarring response like that of CP. Lacrimal gland involvement occurs in about 50% of patients with chronic GVHD who develop a Sjögren type picture of dry eyes.

The pathogenesis of the conjunctival disease has been examined in a few cases and appears to be similar to that in the skin.

Treatment of cicatrizing conjunctivitis and the ocular complications of the immunobullous disorders [29–35]

The same strategies can be used to treat the ocular aspects of all these disorders. The three principal treatment aims are: (i) management of the ocular surface disease; (ii) eliminating or minimizing treatment toxicity; and (iii) suppressing inflammation.

These three components of the treatment strategy are not required for all of these diseases. For example, in Stevens–Johnson syndrome most patients have relatively little inflammation once the surface disease has been treated, and any treatment toxicity eliminated, so that it is the minority of these patients, with recurrent inflammation or progressive cicatrization, who require suppression of inflammation. On the other hand most, but not all, OCP patients require use of all three components with 80% of patients requiring systemic immunosuppressive therapy to control inflammation that persists once the surface disease and toxicity has been controlled.

Successful management demands identification and treatment of all of the components of the disorder, including surface disease, treatment toxicity and inflammation related to activity of the underlying disease, as well as the early detection and treatment of secondary corneal infection.

Management of the ocular surface disease

The ocular surface disease is secondary to previous or current lid and conjunctival scarring and inflammation. The surface disease causes much of the damage to the cornea and is responsible for additional inflammation. Trichiasis and entropion, blepharitis, dry eye and filamentary keratitis, keratinization, persistent epithelial defect, microbial keratitis and corneal perforation may all result from a combination of a poor tear film, poor lid closure, and corneal damage secondary to trichiasis. These are treated as follows:

Trichiasis: epilate in the short term, use electrolysis or laser for odd lashes, cryotherapy for misdirected lashes and surgery for entropion (inferior retractor plication for lower lid and anterior lamellar reposition for upper lid).

Blepharitis: use oral tetracyclines and institute a lid hygiene regimen.

Dry eye and filaments: use non-preserved lubricants, topical acetylcysteine 5–10% as a mucolytic, and punctal occlusion to conserve tears (once any blepharitis has been controlled).

Keratinization: topical retinoic acid is effective in 30% but only available in specialized centres.

Persistent corneal epithelial defect: exclude infection, treat ingrowing lashes, use non-preserved lubricants, therapeutic lenses (silicone rubber or silicone hydrogel in dry eyes) and, if these measures are unsuccessful, close the eye with a botulinum toxin protective ptosis or with temporary tarsorraphy. Other more specialized treatments may be needed.

Corneal perforation: temporize with therapeutic contact lenses and/or corneal glue followed by keratoplasty only if absolutely necessary.

Eliminating or minimizing treatment toxicity

Treatment toxicity results principally from the preservative benzalkonium chloride, a component of most reusable bottles of eye drop preparations as well as of topical glaucoma medications and aminoglycoside eye drops.

Unnecessary topical treatment should therefore be avoided and unpreserved drops or saline used as far as possible. The effects of topical treatment toxicity are hard to distinguish from those of the ocular surface disease. After withdrawal of toxic topical therapy the mean recovery period is 2 weeks but may extend to 3 months.

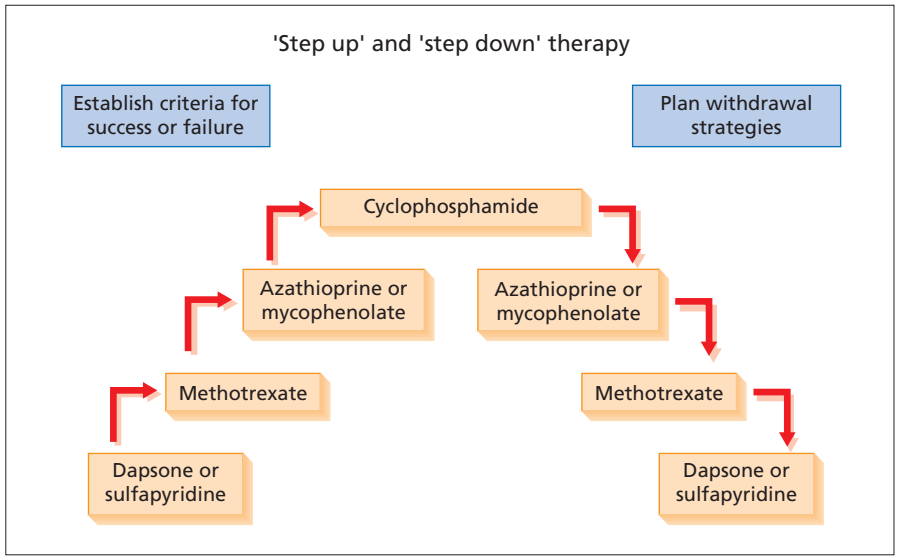

Fig. 64.10 Immunosuppressive therapy for progressive conjunctival cicatrization. 'Step up' and 'step down' therapy. For acute severe disease start at the top of the stepladder and 'step down' to the right (the withdrawal strategy). For less severe disease step up from the bottom left of the figure. The criterion for success is a reduction in inflammation when the surface disease, that may be contributing to it, has been controlled.

Suppressing inflammation—immunosuppressive therapy

Monitoring and side effects of the main immunosuppressive agents are discussed in Chapter 72 and are not repeated here.

In *mild disease* (*hyperaemia and oedema*), low-dose topical corticosteroid may be helpful for a few cases.

For *moderate disease* (*hyperaemia, intense infitration*), sulphapyridine 500 mg daily for 2 weeks then 1 g daily (sulfasalazine 1–2 g daily is an alternative). Fifty-five per cent of patients respond in 1–2 months, but 15% develop an allergic reaction. If response is poor, dapsone 75 mg daily, increased each month by 25 mg daily to 125 mg, can be used; there is a 70% response in 1–2 months reducing to 50% after 1 year. Other agents that may be considered are azathioprine (1–2 mg/kg/day), methotrexate (7.5–25.0 mg once weekly) or mycophenolate mofetil (1–2 g daily) depending on the severity of the disease.

For *severe disease* (*hyperaemia, limbitis, conjunctival ulceration*), start prednisolone 1 mg/kg/day, reduce the dose after 2 weeks and tail off after 2–4 months. This is ineffective at low doses in the long term and a steroid-sparing immunosuppressive agent is generally added for long-term disease control. The most effective currently is cyclophosphamide 1 mg/kg/day. The dose is adjusted until the lymphocyte count is between 0.5 and 1.0×10^9; other haematological parameters should remain normal. Cyclophosphamide therapy is usually discontinued after 1 year and substituted by sulphonamides or immunosuppressive agents as described above.

Most of this therapy is empirical and a sulphonamide (dapsone or sulphapyridine) is often used together with an alkylating agent (cyclophosphamide) or an antimetabolite (azathioprine, methotrexate or mycophenolate) to control inflammation. This immunosuppressive strategy is summarized in Fig. 64.10, and can be modified as necessary for all these disorders; generally any systemic therapy will benefit the underlying disease.

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Systemic diseases with skin and eye involvement

Some multisystem diseases affect both the skin and the eye [1–23]. It is not possible to catalogue every complication of all these diseases but the most frequent are summarized in Table 64.10.

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Infections

A number of infections involve the eyelids, but the following are important to recognize because they are common or require urgent therapy or referral to an ophthalmologist [1].

Viral infections

Warts

These are common and are found on the eyelid margins often as a long thin projection. Lesions in this site are best treated with careful cryotherapy and accurate application of liquid nitrogen to the tip of the lesion using a cotton wool bud rather than cryospray.

Molluscum contagiosum [2]

This condition mainly affects children and young adults. It is also prevalent in patients with acquired immune deficiency syndrome (AIDS), who may develop multiple lesions around the eyelids. Lesions may grow in the lash line as well as on the lid skin and, occasionally, on the mucocutaneous junction. Lesions can be easily overlooked or mistaken for a sebaceous cyst; this condition must always be considered in the differential diagnosis of

Table 64.10 Systemic diseases with skin and eye involvement.

Systemic disease	Eye disease
Sarcoidosis *Epidemiology*: ocular involvement the presenting feature in 10%. 20–30% of patients have eye disease at some stage [1–7]	*Lids & orbital findings*: clusters of granulomatous eyelid swellings. Proptosis from orbital granulomas. Dry eye from lacrimal gland involvement *Heerfordt's syndrome*: (uveo-parotid fever) consists of uveitis and parotid gland enlargement, fever and facial nerve palsy. *Lofgren's syndrome*: acute iritis, bilateral hilar lymphadenopathy, erythema nodosum and arthralgia. *Mikulicz's syndrome*: bilateral swelling of lacrimal and salivary glands *Anterior segment findings*: *conjunctivitis*: occasionally a granulomatous conjunctivitis mimicking a follicular conjunctivitis. *Uveitis*: usually, but not always, bilateral granulomatous anterior uveitis in 80% of patients with eye manifestations with redness, pain, photophobia and blurred vision with floaters *Posterior segment findings*: rare
Systemic lupus erythematosus [8–10]	*Anterior segment findings*: dry eye, peripheral corneal ulcers. Scleritis is rare. Episcleritis occurs in 10% causing a red eye *Posterior segment findings*: retinal vasculitis common during exacerbations of systemic disease with flame shaped haemorrhages and cotton wool spots. May be associated with severe central nervous system vasculitis or lupus nephritis
Sjögren's syndrome [11]	*Lids & orbital findings*: lacrimal gland inflammation causing dry eye *Anterior segment findings*: *symptoms*: often severe with chronic discomfort, foreign body sensation, dryness and blurred vision. *Conjunctiva*: conjunctivitis and scarring in some cases. *Cornea*: punctate keratopathy, persistent corneal epithelial defects leading to corneal ulceration and perforation or corneal infection
Reiter's syndrome *Epidemiology*: ocular involvement in about 30% of patients [1]	*Anterior segment findings*: *symptoms*: red irritable eyes resolving spontaneously within 7–10 days *Conjunctiva*: bilateral mucopurulent conjunctivitis is the most frequent manifestation affecting approximately 30% of patients; this usually follows a urethritis by about 2 weeks and precedes the onset of arthritis. *Cornea*: keratitis may occur in isolation and is rare. *Uveitis*: anterior uveitis (iritis) occurs in about 20% of patients either with the first attack of Reiter's syndrome or during a recurrence
Behçet's syndrome *Epidemiology*: ocular involvement in 60% to 70% of patients [12, 13]	*Anterior segment findings*: *external eye diseases*: conjunctivitis, keratitis and episcleritis may occur but are not specific for the condition. *Uveitis*: is the commonest manifestation of the disease *Posterior segment findings*: visual impairment or blindness is a frequent complication of Behçet's syndrome as a result of the retinal ischaemia
Inflammatory bowel disease *Epidemiology*: ocular manifestations in about 5% of patients [14,15]	*Anterior segment findings*: *external eye diseases*: conjunctivitis, limbitis, peripheral corneal infiltrates and episcleritis may occur. *Uveitis*: acute iritis in about 5% of patients which may occur at the same time as exacerbation of colitis
Acquired immune deficiency syndrome (AIDS) *Epidemiology*: ocular complications occur in about 75% of patients [16,19]	*Common features*: (i) opportunistic infections with viruses mycobacteria and fungi; (ii) malignancies e.g. Kaposi's sarcoma; (iii) retinal microangiopathy; and (iv) neuro-ophthalmic lesions with intracranial infections and tumours. *Anterior segment findings*: *external eye diseases*: *Molluscum contagiosum* is a common ocular finding in patients with AIDS, they tend to be large and when located on the lid margin can give rise to follicular conjunctivitis. The lesions can be complicated by epithelial keratitis with associated pannus formation. Kaposi's sarcoma may involve the lids and conjunctiva. *Herpes simplex* keratitis tends to be severe with more frequent relapses. The peripheral cornea is more often involved in contrast to central disease in immunocompetent patients. *Herpes zoster ophthalmicus* is common and may be a presenting feature of HIV infection, especially if severe disease presents in young patients *Posterior segment findings*: retinal microangiopathy is common and characterized by retinal haemorrhages, microaneurysms and cotton wool spots. *Cytomegalovirus* retinitis and *Pneumocystis carinii* choroiditis are serious ophthalmic complications signifying severe systemic involvement
Porphyria [20, 21]	*Common feature*: ocular involvement results from either photosensitization and/or neurological dysfunction. Photosensitization can affect the eyelids, conjunctiva, cornea, sclera and possibly the retina. *Lids & orbital findings*: inflammation can lead to vesicle and bulla formation, secondary infection scarring with ectropion and hyperpigmentation *Neuro-ophthalmic complications*: include optic neuritis, optic atrophy, ptosis and cranial nerve palsies
Wegener's granulomatosis [22]	Episcleritis is very common in active stages. Also retinal vasculitis, optic neuritis, orbital pseudotumour
Polyarteritis nodosa	Episcleritis scleritis and keratitis

HIV, human immunodeficiency virus.

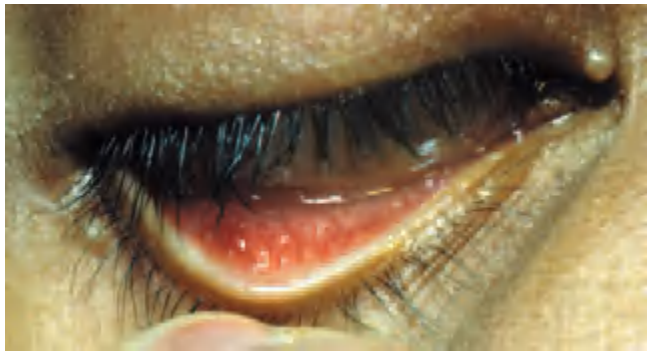

Fig. 64.11 Molluscum contagiosum. Molluscum contagiosum at medial aspect of the upper lid margin with an associated follicular conjunctivitis.

patients with unilateral or bilateral follicular conjunctivitis. There is associated conjunctival discharge and a variable, often severe, follicular conjunctival response (Fig. 64.11). A superficial epithelial keratitis may develop in long-standing cases, which can progress to pannus formation across the cornea. Treatment involves removal of the lesions by curettage; cryotherapy is also effective, but either of these will cause depigmentation in pigmented skins and are unnecessary for the management of a few localized lesions. In a co-operative adult this can be done under local anaesthetic, but for children a general anaesthetic is required.

Herpes simplex virus [3,4]

Primary HSV infection is asymptomatic in many patients; in others it causes blepharoconjunctivitis. However most of the ocular manifestations of HSV infection are due to reactivation of latent infection in the trigeminal ganglion. Both the primary infection, and reactivation of latent disease, may be particularly severe in patients with atopic dermatitis or with immunodeficiency. The blepharoconjunctivitis of HSV usually results in crops of small vesicles, which may be associated with mild oedema of the lids with or without a conjunctivitis. As with HSV elsewhere, the vesicles dry to a crust and heal within a few days. The conjunctivitis can be treated with aciclovir ointment five times daily for 5 days or with oral aciclovir 400 mg three times daily. Neither the blepharitis nor conjunctivitis present a serious problem for most patients. The serious and sight-threatening ocular complications of HSV infection of the eye are due to recurrent keratitis or keratouveitis. Herpetic keratitis may affect the epithelium alone (dendritic keratitis), the stroma (in stromal herpetic keratitis, geographical corneal ulceration and metaherpetic keratitis), or the endothelium (disciform keratitis or herpetic endotheliitis). Dendritic keratitis is in itself a benign disease unless treated with topical corticosteroids when the disease will rapidly spread, resulting in geographical keratitis, which may cause destructive corneal disease. Most cases of corneal disease represent reactivation of latent HSV and patients may develop any of the corneal manifestations. Stromal and endothelial disease can progress to blinding corneal vascularization, scarring and ulceration. Fortunately the disease is normally unilateral except in atopic individuals when it may often be bilateral. The management of the stromal and endothelial keratitis is beyond the scope of this review except to state that this involves the judicious use of topical corticosteroids with systemic or topical antivirals. Keratouveitis involves the endothelium and stroma and may also be associated with secondary glaucoma. Dendritic keratitis may occur during treatment with topical corticosteroids. Because of the difficulties of managing the ocular manifestations of this disease, patients with suspect HSV involvement of the eye should be referred for urgent ophthalmological assessment. Topical corticosteroids must not be used alone as these will mask the symptoms and signs, leading to spread of the ulcer and corneal perforation with catastrophic consequences for the patient's vision.

Herpes zoster [5]

Herpes zoster of the ophthalmic division (HZO) of the trigeminal nerve is an important condition to recognize. As with other sites, it often presents with a non-specific flu-like illness with fever and malaise and symptoms of unilateral neuralgia. This develops over the distribution of the affected nerve and varies in severity from a mild tingling in the skin to a deep severe pain. The characteristic lesions of herpes zoster may appear up to a week after the initial symptoms. Erythematous macules develop into clusters of papules and vesicles becoming pustular and haemorrhagic after 3–4 days. The lesions then scab and are dry by 7–14 days, separating to leave pitted scars. Involvement of the nasociliary nerve, which supplies the skin on the side of the nose (Hutchinson's sign), occurs in about 35% of patients and carries a high risk of ophthalmic complications. Ocular involvement may occur in the absence of nasociliary involvement but it is usually milder. Patients whose eyes cannot be examined due to persistent lid oedema, or those with ocular signs and symptoms, should be referred for urgent ophthalmological assessment. The disease can affect any part of the eye, including the orbit, extraocular muscles, optic nerve and cornea, and may give rise to long-term complications including severe relapsing keratitis, glaucoma and cataract.

Oral aciclovir is indicated when given within 3 days of the onset of the rash; using it later in the course of the disease is probably valueless. Topical aciclovir is also unhelpful. Topical corticosteroid therapy is needed to control the numerous corneal manifestations of the disease and may need to be continued for several years. Some

of these complications may be delayed and occur months after the initial skin eruption.

Prolonged or severe post-herpetic neuralgia is a painful and unpleasant sequel to herpes zoster infection. It occurs in about half of elderly patients but is rare in children. There is some evidence that the use of amitriptyline in the early stages of infection is helpful in reducing the incidence and severity.

Bacterial infection

Staphylococcal infection

Impetigo

Impetigo is a common skin infection that mainly affects children. It can involve the eyelids, but usually as part of a general infection over the face. It presents as rapidly spreading erythematous macules, developing into flaccid vesicles that subsequently rupture to give rise to surface crusting. The lesions need to be swabbed for bacteriology and appropriate oral and topical antibiotics given.

Hordeolum

External hordeolum (stye) is caused by staphylococcal infection of an eyelash follicle and its associated glands. It presents with a tender, red, inflamed swelling on the lid margin, which subsequently points anteriorly and discharges close to the lash roots. No treatment is usually required beyond the application of local soothing compresses and removal of the affected lash. If there is a local cellulitis then systemic antibiotics should be given. An internal hordeolum is a staphylococcal abscess of the meibomian glands and needs incision and drainage.

Streptococcal infection

Erysipelas [6]

This represents subcutaneous spreading cellulitis, usually caused by β-haemolytic *Streptococcus*. It usually presents with a rigor followed by a red, raised, erythematous plaque with a well-demarcated edge that spreads rapidly over the skin. Erysipelas is a serious skin infection that needs to be treated urgently with appropriate systemic antibiotics.

Necrotizing fasciitis [7]

This is a very rare condition, most commonly caused by *Streptococcus*, which mainly affects elderly or debilitated patients. A spreading purple discoloration of the eyelid rapidly progresses to gangrene. Unlike erysipelas the periorbital tissue is not usually affected. Early recognition, immediate institution of intravenous antibiotics and referral to an ophthalmic plastic surgeon for debridement of the necrotic tissue are mandatory as the condition carries a high mortality.

Mycobacterial infection

Tuberculosis [8,9]

There are no specific ocular findings in tuberculosis, and diagnosis is often based on indirect evidence such as intractable uveitis that is unresponsive to corticosteroid therapy, with negative findings for other causes of uveitis, and in the presence of tuberculosis at a distant body site. Chronic iridocyclitis, which is usually granulomatous, is the commonest feature. Choroiditis and retinal vasculitis may occur.

Leprosy [8,9]

Ocular complications of leprosy are common, most frequently madarosis, conjunctivitis, episcleritis or scleritis. Keratitis results from a combination of corneal anaesthesia, lagophthalmus, trichiasis and secondary infection. Iritis and its complications are the most common causes of blindness and leprosy. Lepromatous disease is more commonly associated with uveitis than is tuberculoid leprosy.

Treponemal infection

Syphilis [10]

Ocular syphilis is very rare and there are no pathognomonic signs. Eye involvement mainly occurs during the secondary and tertiary stages, though primary chancre of the conjunctiva may occur. External features include madarosis, scleritis and interstitial keratitis. Uveitis and chorioretinitis are rare but serious complications of syphilis and lead to blindness. Neuro-ophthalmic features include Argyll Robertson pupils, optic nerve lesions, and palsies of the third and sixth cranial nerves. Gummatous involvement of the brain can cause visual field defects.

Lyme disease [11,12]

Ocular manifestations of Lyme disease involve all parts of the eye. As with syphilis, the ocular manifestations vary according to the stage of the disease. In stage 1, a localized conjunctivitis with photophobia occurs in 10% of patients. This is mild and brief and ophthalmologists are rarely consulted. In stage 2, various ophthalmic complications have been described including cranial nerve palsies; these may occur within 1 month of the rash appearing. It is in the late stage 3 that most of the severe ocular complications are seen, including episcleritis, symblepharon, interstitial keratitis, uveitis, chorioretinitis and retinal vasculitis.

Parasitic infection

Phthiriasis (lice) [13]

An infestation of the eyelashes by the pubic louse, *Phthirus pubis*. It mainly affects children and causes chronic itching, irritation and rubbing of the lids. As with louse infection elsewhere, the adult lice can be difficult to see, though nits and their shells are visible adhering to the eyelashes (see Fig. 64.6c,d). The skin nearest to the base of the lashes may show small bluish spots due to the louse bites (maculae caeruleae). A number of measures have been used to treat louse infestation of the eyelids, including mechanical removal with forceps, epilation of infested lashes, and application of fluorescein, yellow mercuric oxide ointment, physostigmine or aqueous malathion.

Filiriasis (onchocerciasis) [14]

Onchocerciasis or river blindness is caused by the filarial organism, *Onchocerca volvulus*. It is the second most common cause of preventable blindness in sub-Saharan Africa with an estimated prevalence of 500 000 cases with visual impairment and 270 000 with blindness. It appears that *Wolbachia endobacteria*, a bacterial symbiont, produces an endotoxin-like product which constitutes a major pro-inflammatory stimulus in the eye, causing corneal inflammation and sclerosing keratitis.

Protozoal infection

Ocular disease may complicate leishmaniasis. In *Leishmania donovani* infection, bilateral retinal haemorrhages may be a feature. In *L. tropica* and *L. braziliasis* infection, eyelid and corneal lesions occur, and subsequent destruction may lead to loss of the eye. In trypanosomiasis, unilateral oedema of the lids may occur.

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Inherited disorders

A large number of inherited disorders affect the skin and eyes. Major reference texts are cited [1–3]. The main ocular features are summarized in Table 64.11 [4–51].

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Table 64.11 Inherited disorders affecting the skin and eyes.

Group	Condition	Inheritance	Ocular features
Bullous disorders	Acrodermatitis enteropathica [4]	AR (MIM #201100)	Loss of eyebrows and eyelashes, conjunctivitis, blepharitis, photophobia
Connective tissue disorder	Ehlers–Danlos syndrome [5]	Mainly AD (see MIM 130000)	Lax eyelid skin with redundant folds, epicanthal folds, hypertelorism, strabismus, blue sclera, corneal abnormalities including keratoconus, angioid streaks, ectopic lens. Retinal detachments occasionally occur
	Marfan's syndrome [6]	AD (MIM #154700)	Subluxation of lens—60–80% of patients in early childhood. Amblyopia, myopia, cataract, corneal abnormalities, glaucoma. Retinal detachment is most serious complication
	Pseudoxanthoma elasticum [7]	Types I & II AR (MIM #264800, 264810) Types III & IV AD (MIM #177850, 177860)	Angioid streaks (breaks in Bruch's membrane) in majority. Haemorrhagic maculopathy after trauma may cause visual loss
Dysplasias, hyperplasia, atrophies and aplasias	Ablepharon macrostomia [8] syndrome	Unknown (MIM 200110)	Absent eyelids and ectropion
	Aplasia cutis congenita [9]	AD (MIM #107600) AR (MIM 207700)	Congenital absence of skin leading to eyelid colobomas, corneal opacities, scleral dermoids and lamellar cataracts
	Blepharophimosis ptosis epicanthus inversus syndrome [10]	AD (MIM #110100)	Blepharophimosis, ptosis, epicanthus inversus, telecanthus. Amblyopia in 50% of patients
	Cockayne's syndrome [11]	AR (MIM *216400)	Corneal opacities, cataracts in 30%, retinitis pigmentosa, optic atrophy, strabismus, photophobia
	Dyskeratosis congenita [12]	XR (MIM #305000)	Obliteration of the lacrimal puncta in 80% of cases, conjunctivitis, blepharitis, ectropion, loss of eyelashes and eyebrows
	Ectodermal dysplasias—a complex group of disorders with various inheritance patterns and a variety of ocular findings [13] Examples are given:		
	(i) Christ–Siemans–Touraine syndrome	XR	Photophobia dry eye
	(ii) Fischer–Jacobson–Clouston syndrome	AD	Usually normal
	(iii) Ellis–van Cleveld syndrome	AR (MIM #225500)	Coloboma of iris, microphthalmia occasional cataract
	Focal dermal hypoplasia (Golz's syndrome) [14]	XD (MIM *305600)	40% have ocular abnormalities, the commonest being colobomas of iris choroid retina or optic nerve
	Fraser's syndrome [15]	AR (MIM *219000)	Bilateral or unilateral absence of palpebral fissure with loss of eyebrows, anophthalmia, microphthalmia
	Frydman's syndrome [16]	AR	Synophrys, blepharophimosis, weakness of extra-ocular and frontal muscles
	Hallerman–Streiff syndrome [17]	Unknown (MIM *264090)	Loss of hair of eyebrows and eyelashes, microphthalmos, cataracts, amblyopia and nystagmus
	MIDAS syndrome [18]	XD	Microphthalmia, sclerocorneal
	Pachyonychia congenita [19]	AD (PC1 MIM #167200 PC2 MIM #167210)	Cataract and corneal dyskeratosis
Hair disorders	Brachmann–Lang syndrome [20]	AR	Synophrys thick, long eyelashes, narrow palpebral fissure, myopia, nystagmus and strabismus
	Monilethrix [21]	AD (MIM #158000)	Loss of eyebrows and lashes

(*continued overleaf*)

Table 64.11 (*cont'd*)

Group	Condition	Inheritance	Ocular features
	Pili torti [22]	AR (MIM 261900)	Loss of eyebrows and lashes
	Chondrodysplasia punctata [23]	AD (MIM 215105) XR (MIM #302950)	Cataracts Ocular albinism, cataracts, microphthalmia
Keratinization disorders	The ichthyoses [24]		
	(i) Ichthyosis congenita gravis	AR (MIM *242500)	Severe ectropion
	(ii) Ichthyosiform erythroderma	AD (MIM 242100)	Early development of ectropion is characteristic
	(iii) Lamellar ichthyosis	AR (various types)	Cicatricial ectropion with exposure keratitis Direct conjunctival involvement may occur
	(iv) X-linked ichthyosis	XL (MIM *308100)	Deep corneal opacities
	KID syndrome [25]	XD (MIM #148210)	Keratitis
	Refsum's syndrome [26]	AR (MIM #266500)	Night blindness, posterior subcapsular cataracts develop in most cases
	Sjögren–Larson syndrome [27]	AR (MIM *270200)	Blepharitis, conjunctivitis, punctate corneal erosions and pigmentary degeneration of the retina
	Ulerythema ophryogenes [28]	AD	Erythema and perifollicular papules on eye to eyebrows spreading medially causing thinning of eyebrows
Metabolic disorders	Alkaptonuria [29]	AR (MIM #203500)	Scleral pigmentation is early sign, eyelid pigmentation
	Angiokeratoma corporis diffusum [30]	XL (MIM *301500)	Angiokeratomas of conjunctiva, corneal opacities, posterior capsular cataracts
	Homocystinuria [31]	AR (MIM *236200)	Myopia, cataracts, subluxation of lens, secondary glaucoma, retinal detachment
	Hurler's syndrome [32]	AR (MIM *252800)	Early clouding of cornea
Neurocutaneous syndromes	Richner–Hanhart syndrome [33]	AR (MIM 276600)	Corneal lesions vary from erosions to deep ulcers Nystagmus and lens opacities
	Neurofibromatosis type I [34]	AD (MIM *162200)	Neurofibromas of eyelid, corneal clouding, Lisch nodules of iris, optic nerve glioma, palsies from cranial nerve involvement
	Neurofibromatosis type II	AD (MIM #101000)	Cataract fundus lesions. Extraocular motility abnormalities
Photosensitive disorders	Tuberous sclerosis [35]	AD (MIM #191100)	Tumours of the lids or nodules on conjunctiva and retina
	Basal cell naevus syndrome [36]	AD (MIM #109400)	Basal cell carcinoma of eyelid and periorbital area, hypertelorism, strabismus, colobomas of the choroid, cataracts, glaucomas in 5–10%
	Bloom's syndrome [37]	AD (MIM #210900)	Telangiectasis on lower lids, blistering and scarring lower eyelids
	Rothmund–Thomson syndrome [38]	AR (MIM #268400)	Sparse eyebrows and eyelashes, degenerative changes in cornea, 50% of patients have bilateral cataracts which develop in childhood, strabismus
	Xeroderma pigmentosum [39]	AR (various types)	Angiomas, keratoses, papillomas, carcinomas develop on eyelids, sometimes extending on to conjunctiva and cornea, scarring and atrophy of lids with exposure keratitis leading to corneal ulceration symblepharon formation. Ocular melanoma
	Chediak–Higashi syndrome [40]	AR (MIM #214500)	Oculocutaneous albinism, corneal opacities

(*continued*)

Table 64.11 (*cont'd*)

Group	Condition	Inheritance	Ocular features
Pigmentation disorders	Cross syndrome [41]	AR (MIM *257800)	Microphthalmia, small opaque cornea, coarse nystagmus
	Epidermal naevus syndrome [42]	Sporadic	Ocular melanocytic naevi, coloboma of the lids, iris and choroid. Lipodermoid of conjunctiva or choroid
	Incontinentia pigmenti [43]	XD (MIM #308300)	35% of patients have eye abnormalities including strabismus, cataract and microphthalmia. Retinal detachment may occur
	Hypomelanosis of Ito [44]	Sporadic (MIM *300337)	Hypertelorism, strabismus, myopia
	Oculocutaneous albinism [45]	AR (various types; Chapter 39)	Total loss of pigment in eyes, nystagmus, absence of binocular vision
	Piebaldism [46]	AD (MIM #172800)	Absent pigmentation medially of eyebrows, eyelids and eyelashes, heterochromia of iris
	Waardenberg's syndrome [47]	AD (MIM #193150)	Telecanthus, synophrys, partial albinism, heterochromia of iris
Vascular and haematological syndromes	Congenital telangiectatic cutis marmorata [48]	Unknown (MIM 219250)	Clouding of cornea, glaucoma
	Fanconi pancytopenia syndrome [49]	AR (MIM #227650)	Microphthalmia strabismus, nystagmus and colobomas
	Lymphoedema–distichiasis syndrome [50]	AD (MIM #153400)	Double row of eyelashes on upper and lower eyelids
	Sturge–Weber syndrome [51]	Sporadic (MIM 185300)	50% of patients have angiotomatous changes of the ipsilateral choroid causing glaucoma

AD, autosomal dominant; AR, autosomal recessive; XD, X-linked dominant; XL, X-linked; XR, X-linked recessive.

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Ocular complications of dermatological therapy

A number of drugs used by dermatologists have significant side effects on the eye and require careful monitoring.

Corticosteroids [1–15]

The use of corticosteroids can cause significant side effects on the eye. Both systemic and topical corticosteroids are responsible, though the greatest risk is to those receiving prednisolone at a dose of 10–15 mg a day for over a year.

Continuous therapy is more likely to cause side effects than intermittent therapy.

Posterior subcapsular cataracts are induced by long-term systemic corticosteroids in as many as 30% of patients. They rarely occur at doses less than 10 mg/day and for less than 1 year. Children are particularly vulnerable. Reversibility of cataracts is not common and progression of cataracts may occur in spite of reduction or discontinuation of corticosteroid therapy.

Patients also risk developing open angle glaucoma, particularly if genetically predisposed. The precise mechanism is unknown, though it is thought to be due to decreased aqueous outflow. Particular risk factors include type 1 diabetes, high myopia, connective tissue disorders and a family history of glaucoma. Topical corticosteroids induce a rise in intraocular pressure more quickly than systemic corticosteroids. Medium or high potency dermatological corticosteroids applied for long periods to, or near, the eyelids may spread over the lid margin and are absorbed through the cornea, reaching sufficient concentrations to elevate ocular pressures. Patients on long-term topical or systemic corticosteroids need to have their eye pressures monitored regularly at 1–6 monthly intervals depending on their degree of risk.

Topical corticosteroids predispose patients to cataract, glaucoma and secondary surface infection. Injudicious use in HSV infection masks the clinical signs of dendritic ulcer and risks perforation. Wearing a soft contact lens is a contraindication to topical ocular corticosteroid usage. Other ocular complications from corticosteroids include angioneurotic oedema, papilloedema from raised intracranial pressure and toxic amblyopia. Systemic treatment with corticosteroids may cause serous chorioretinopathy or diffuse retinal pigment epitheliopathy.

Oral retinoids [16–22]

Both isotretinoin and acitretin can cause ocular side effects. The most common is dry eye with associated conjunctivitis and blepharoconjunctivitis giving rise to blurred vision. The blepharoconjunctivitis is frequently associated with staphylococcal infection. Exposure keratopathy and corneal ulceration rarely occur; asymptomatic corneal opacities may develop but resolve after 6–8 weeks. Patients should be warned that they may be unable to tolerate contact lenses whilst on retinoid therapy. Use of tear substitutes, humidification of the environment and lid hygiene measures help. Retinal abnormalities may also occur, with poor night vision and increased sensitivity to glare, and can be a significant problem in those who drive at night. The cause is unknown but may be due to competitive inhibition of ocular retinol dehydrogenase causing local vitamin A deficiency and reduction in rhodopsin formation. More serious side effects include papilloedema from raised intracranial pressure, optic atrophy and cataract. Although these are rare, a history of visual disturbance should be asked for when patients come for follow-up. Severe headache early in the course of treatment is significant. The ocular manifestations are dose-dependent and usually reversible, provided they are recognized and the treatment regimen adjusted. However, there have been reports of the dry eye syndrome and night blindness persisting after retinoids have been discontinued.

Antimalarials [23–27]

The most serious potential side effect of antimalarial drugs is retinopathy. The mechanism is uncertain but seems to depend on the ability of the drug to bind the retinal pigment epithelium. Ocular side effects from antimalarials are much less common now that hydroxychloroquine rather than chloroquine is the drug of choice. However, both drugs should be used with caution in patients with hepatic or renal impairment. The Royal College of Ophthalmologists and American Academy of Ophthalmologists have issued clear guidelines on screening protocols for use of chloroquine and hydroxychloroquine. Baseline ophthalmic assessment of patients, for whom these drugs are proposed, is carried out by the dermatologist and requires questioning the patient about any known visual impairment (uncorrected by spectacles) and the recording of near visual acuity using a test type. If visual impairment is reported or detected then referral to an optometrist is advised; the optometrist will refer any patient with abnormal findings to an ophthalmologist. Patients should not be treated with more than the maximum daily dosage (hydroxychloroquine at a maximum dosage of 6.5 mg/kg or chloroquine phosphate not exceeding 4 mg/kg daily) and should have this visual screening repeated annually and recorded in their notes. Referral to an ophthalmologist is appropriate if visual impairment is detected at baseline, if changes are detected on the annual screening or if the patient develops visual symptoms. The ophthalmologist will then carry out a range of tests including visual acuity, colour vision, visual fields, Amsler fields, corneal and retinal examinations. If long-term treatment is required, for more than 5 years, the risks of ocular complications are increased; in this instance, individual arrangements for screening should be agreed with a local ophthalmologist. No screening is recommended for mepacrine as it is not associated with ophthalmological side effects.

Antibiotics for acne [28–32]

Oxytetracycline, minocycline and doxycycline can all cause raised intracranial pressure. The mechanism is unknown but is thought to be related to interference with energy-dependent absorption mechanism of cereb-

rospinal fluid, which is mediated by cyclic adenosine monophosphate (AMP) at the arachnoid granulations. Patients who complain of headache should be examined carefully with fundoscopy through dilated pupils to look for papilloedema, and should have formal testing of visual acuity and of visual fields. The condition is far from benign; permanent visual field loss can occur if the condition is not recognized early and the drug stopped. Sometimes treatment with acetazolamide is required to reduce the pressure. Erythromycin or trimethoprim may cause erythema multiforme and associated ocular changes. Pigmentation due to minocycline can occur in the skin (Chapter 39) and has also been reported in the sclera.

Psoralens [33–44]

Psoralens have been shown to bind to the lens proteins, and some animal studies have shown induction of anterior cortical opacities though others have not. 8-Methoxypsoralen can be detected in the human lens 12 h after oral ingestion. There has been a longstanding concern about the risk of cataract in patients having psoralen and long-wave UV radiation (PUVA) therapy. Although PUVA has been used in treatment of skin diseases for 30 years, and clinical studies have not yet shown any convincing evidence of an increase in cataract as compared with the general population, it is still recommended that ultraviolet light A (UVA)-filtered spectacles are used for 12 h after ingestion of psoralens in case significant long-term sequelae eventually develop. Care must be taken to ensure that the spectacles are suitable for ultraviolet protection.

Botulinum toxin [45]

With the increased use of botulinum toxin for the treatment of facial wrinkling and eyebrow position dermatologists need to be aware of the potential side effects. These include haematoma, ptosis, ectropion, diplopia and eyelid drooping, and are often related to poor injection technique.

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Tumours

Benign tumours of the eyelid

As would be expected of such complex tissue, the eyelid gives rise to a large number of skin tumours. Tumours can arise from the epidermis and dermis in addition to the adnexal structures, which include the meibomian and Zeis sebaceous glands, eccrine and Moll's apocrine sweat glands, and the specialized hair follicles of the eyelashes. They may also originate from lymphoid neural and vascular tissue found in the preseptal tissues of the eyelid. Although optimal treatment of the tumours begins with accurate diagnosis, many are rather non-specific in their appearance and are only diagnosed with certainty by histology.

Keratoses

Both seborrhoeic and actinic keratoses occur on the eyelid. They have similar clinical features to those elsewhere on the skin and are treated in the same way with local destructive measures, using carefully applied cryotherapy, curettage and cautery or laser ablation under local anaesthetic. Recurrent actinic keratosis should be biopsied and sent for histological examination to make sure it is not a deceptive manifestation of an early skin cancer.

Xanthelasma [1,2]

These present as yellowish cutaneous plaques, most commonly located on the medial part of the eyelids. They are usually bilateral and are much more common in elderly patients. About 60% of patients have an associated hypercholesterolaemia and lipid levels should be measured. Patients often request treatment for cosmetic reasons. Although 90% trichloroacetic acid applied with a cotton wool bud is used there is a significant risk of spillage into the eye. More effective treatment is by surgical excision or ablation with carbon dioxide laser. Necrobiotic xanthogranuloma may look similar to xanthelasma but they are thicker and more nodular. These lesions may involve the conjunctiva and sclera. On the rare occasions that they infiltrate the orbit they may cause proptosis.

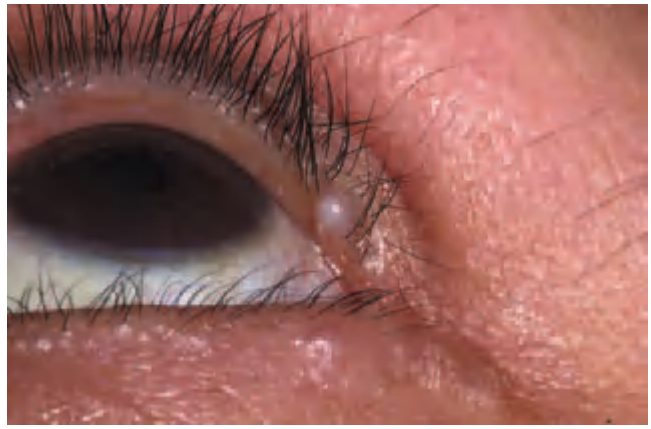

Fig. 64.12 Cyst of Moll. Small translucent cyst on anterior lid margin. (Courtesy of Mr N. Joshi, Chelsea & Westminster Hospital/Medical Illustration UK, London, UK.)

Juvenile xanthogranuloma [3]

These lesions occasionally involve the eyelid, conjunctiva or uveal tract. They may be associated with glaucoma and threaten sight. Patients need screening by an ophthalmologist.

Adnexal tumours [4]

Syringomas, milia, trichoepitheliomas and tricholemmomas present as small papules around the eyelids. They can be very difficult to distinguish from each other. Syringomas are the most common, but histology from a biopsy is the only way to make a definite diagnosis. Treatment is by local destruction of the lesions. Eccrine hidrocystomas can present in an eruptive fashion on the face and eyelids; they may respond to topical atropine.

Benign cysts of the eyelid

Retention cysts may arise from either the glands of Moll or of Zeis. A cyst of Moll usually presents as a small translucent lesion on the anterior lid margin close to the lacrimal punctum (Fig. 64.12). Glands of Zeis are sebaceous glands and their retention cysts contain oily secretions and are more opaque than a cyst of Moll. An eccrine gland hidrocystoma is similar in appearance to a cyst of Moll but is not confined to the lid margin. These cysts are treated by excision.

Chalazion [5]

This lesion represents a chronic granulomatous inflammatory reaction around a blocked sebaceous gland.

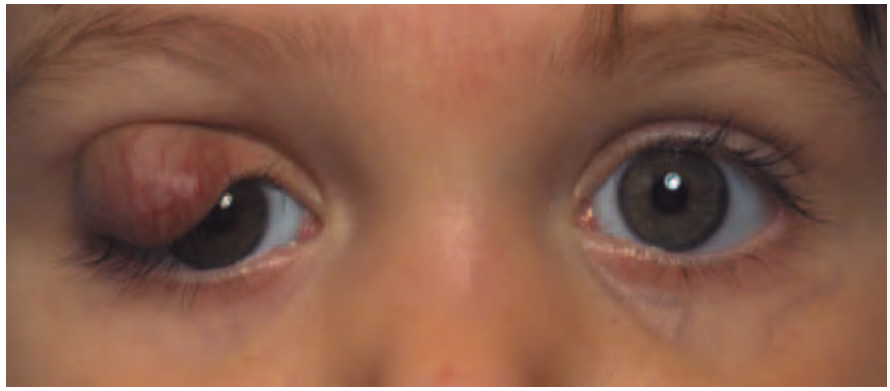

Fig. 64.13 Capillary haemangioma. Enlarging lesion on right upper lid starting to occlude vision. (Courtesy of Mr N. Joshi, Chelsea & Westminster Hospital/Medical Illustration UK, London, UK.)

Patients with seborrhoeic dermatitis and rosacea are at increased risk of chalazion formation. A chalazion presents as a firm lump in the eyelid, which is clearly visible when the lid is everted; an association with chronic posterior blepharitis is common. Large and troublesome lesions can be treated by everting the lid with a special clamp, incising the cyst and curetting the contents through the tarsal plate. Patients who develop recurrent chalazion associated with seborrhoeic dermatitis and rosacea benefit from long-term antibiotic treatment using tetracyclines. Hot saline compresses reduce the inflammation.

Pigmented naevi

The skin on the eyelid can develop pigmented naevi. Their appearance, classification and potential malignant change applies as elsewhere on the skin.

Naevus of Ota

This lesion affects the eyelids, conjunctiva and sclera. Occasionally the pigmentation is confined to the eye with no cutaneous involvement. Naevus of Ota carries an increased risk of ocular melanoma and glaucoma and patients need to be referred for ophthalmic examination and long-term review.

Melanoacanthoma [6]

These are small, shining, black papules situated along the line of the lashes and are a form of dermatosis papulosa nigricans.

Vascular naevi [7–10]

Strawberry naevus (capillary haemangioma) can affect the eyelids. It is more common on the upper lid and presents as a unilateral red raised lesion, which grows quickly during the first year of life (Fig. 64.13). Spontaneous involution occurs usually by age 9 years. Amblyopia is the main complication of larger periorbital lesions and results either from physical closure of the eye and occlusion of the pupil, giving rise to stimulus deprivation, or from refractive errors caused by changes in local pressure. Both systemic and intralesional corticosteroids can reduce the bulk of the haemangioma. Surgical resection or laser therapy is helpful in certain cases.

Port-wine stain

This is a rare congenital vascular lesion, which may affect the eyelids. It presents as a sharply demarcated red patch. Extensive lesions involving the periocular region have a high risk of central nervous involvement and of ipsilateral glaucoma (especially if the upper lid is involved), which may not develop until adult life.

Keratoacanthoma

Keratoacanthomas may develop on the eyelid. They present as a small papule, which grows rapidly developing a characteristic keratin-filled crater and may reach up to 3 cm in diameter (Fig. 64.14). The lesions then stop growing and remain static for 2 or 3 months before spontaneously involuting, which can lead to significant scarring of the eyelid. Because of this, the lesion should be excised at an early stage.

Malignant tumours of the eyelid [11,12]

Basal cell carcinomas (BCCs), squamous cell carcinomas (SCCs) and malignant melanomas all occur on the eyelid as on other areas of the skin. The same rules for management apply on the eyelid as at any site, but the eyelid poses specific problems in preserving good cosmesis and residual function. Clinical examination is an unreliable way of determining the extent of many of these lesions, particularly sclerosing BCC. Early referral to an oculoplastic surgeon is advisable with a view to Mohs micrographic surgery if appropriate.

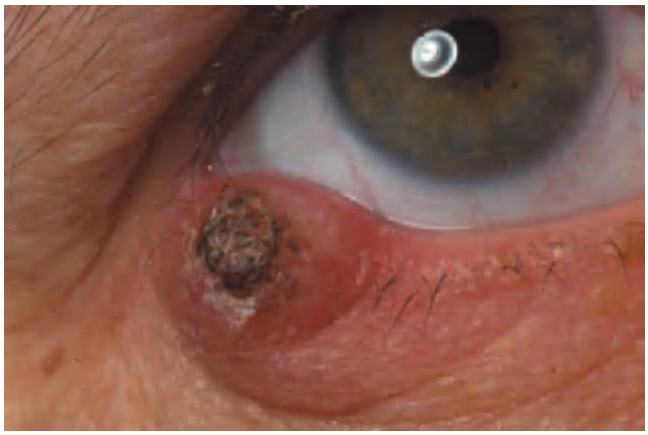

Fig. 64.14 Keratoacanthoma. Keratin-filled crater on lid margin. (Courtesy of Mr N. Joshi, Chelsea & Westminster Hospital/Medical Illustration UK, London, UK.)

Basal cell carcinomas [13–16]

These are the most common skin malignancy and in most series account for 90% of malignant tumours. They rarely metastasize but cause problems by local tissue destruction and invasion of periorbital tissue. Over 70% arise on the lower eyelid followed in order of frequency by the medial canthus, upper eyelid and lateral canthus. Tumours located near to the medial canthus can invade the orbit and sinuses. They are more difficult to excise than those elsewhere, because of the high risk of damaging the tear duct. The majority of BCCs are solid or cystic and fairly straightforward to recognize (Fig. 64.15). Sclerosing or morphoeic BCCs are less common and can be difficult to diagnose as they infiltrate beneath the epidermis forming a flat indurated plaque with indistinct margins, which may simulate a localized area of chronic dermatitis. The paucity of reticular dermis and subcutaneous fat to resist deep invasion presents a particular problem with the eye. Once the orbital septum is penetrated the BCC can rapidly invade, threatening the orbit. At the medial canthus the lacrimal sac and the rich anastomosis of blood vessels offers little barrier. Curettage and cautery is generally not advised for the treatment of eyelid lesions. The skin is thin and tears easily and the sensitivity of the curette is lost in the soft tissue. Successful initial treatment with surgery and accurate margin assessment to ensure complete excision is mandatory in management of these tumours. Mohs' micrographic surgery is usually the treatment of choice where margins are in doubt. Radiotherapy damages and scars the eyelid tissues and lacrimal system and should be reserved for situations when surgery is otherwise inappropriate. Cryotherapy is best avoided due to the risk of leaving residual tumour.

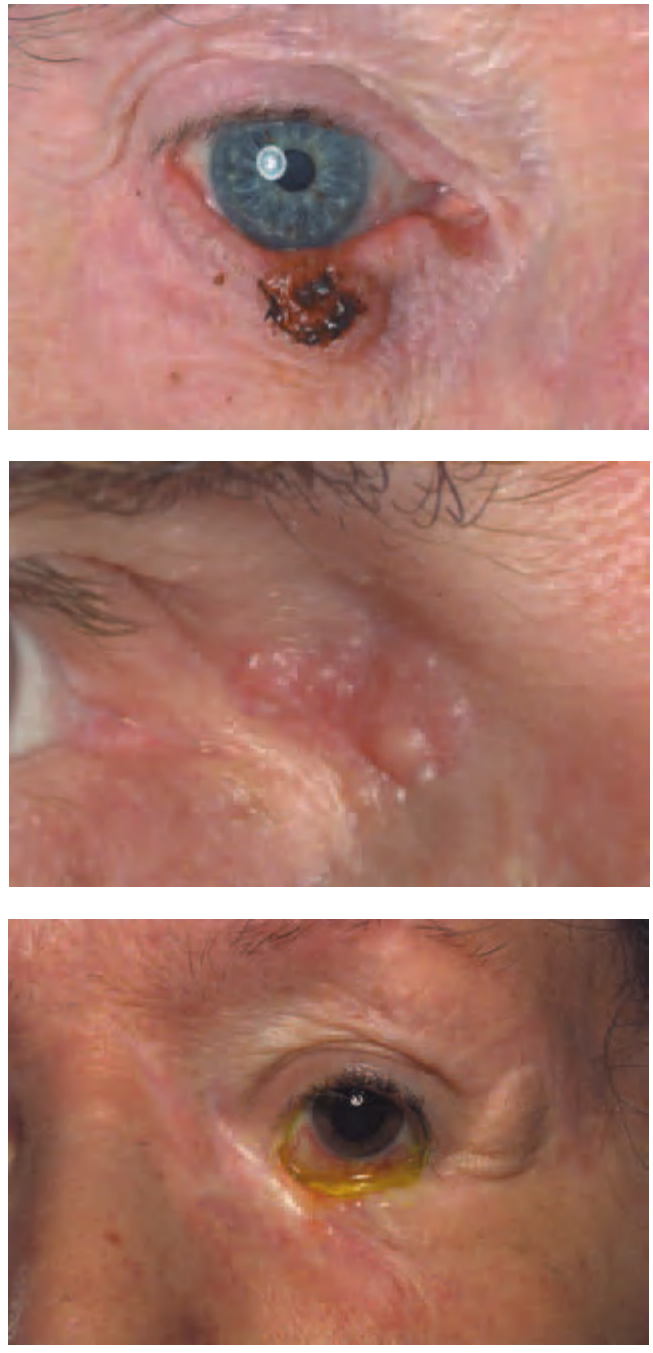

Fig. 64.15 Basal cell carcinoma (BCC). (a) Ulcerated BCC on lower lid. (b) Poorly defined BCC at medial canthus. (c) Morphoeic BCC along lower lid. (Courtesy of Mr N. Joshi, Chelsea & Westminster Hospital/Medical Illustration UK, London, UK.)

Squamous cell carcinomas [17]

This is much less common than BCCs, accounting for between 5 and 10% of eyelid malignancies. SCCs occur on a background of marked actinic damage. They mainly affect the lower eyelid and lid margin, and may arise *de*

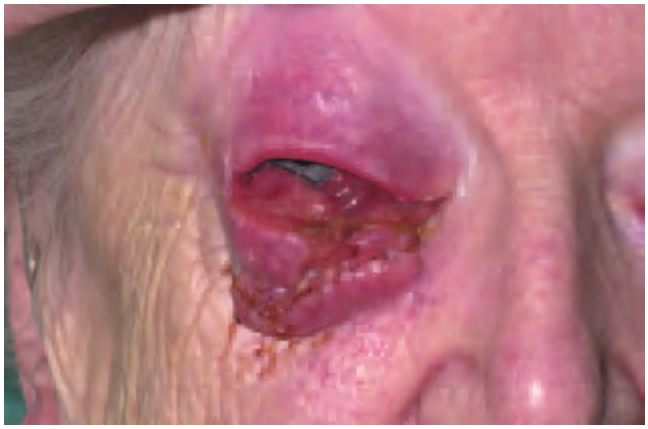

Fig. 64.16 Squamous cell carcinoma (SCC). Infiltrating ulcerated SCC on lower lid. (Courtesy of Mr N. Joshi, Chelsea & Westminster Hospital/Medical Illustration UK, London, UK.)

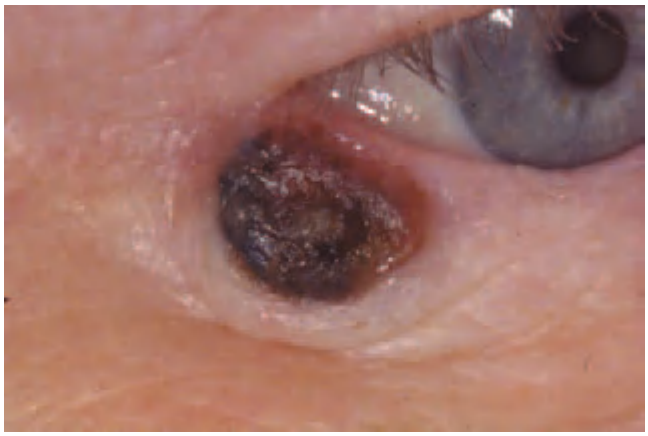

Fig. 64.17 Malignant melanoma. Irregularly pigmented lesion on lower lid. (Courtesy of Mr N. Joshi, Chelsea & Westminster Hospital/Medical Illustration UK, London, UK.)

novo or from pre-existing actinic keratoses. SCC of the eyelids may be nodular, plaque like or ulcerated (Fig. 64.16). Excision with adequate margins is the treatment of choice. Tumours greater than 2 cm in diameter and those with deep penetration have a higher risk of metastasis. Histological evidence of poor differentiation or of perineural invasion are also poor prognostic factors requiring more aggressive treatment. Mohs' surgery is indicated where the initial margins are not free of tumour and offers a good long-term prognosis. As with BCC, cryotherapy and radiotherapy are reserved for situations where surgery is inappropriate.

Malignant melanoma

This may occur on the eyelids or conjunctiva. As elsewhere, melanomas are characterized by a change in size, shape or colour of a pigmented lesion (Fig. 64.17). However, a significant proportion of lid melanomas are amelanotic and this may give rise to difficulties with clinical diagnosis.

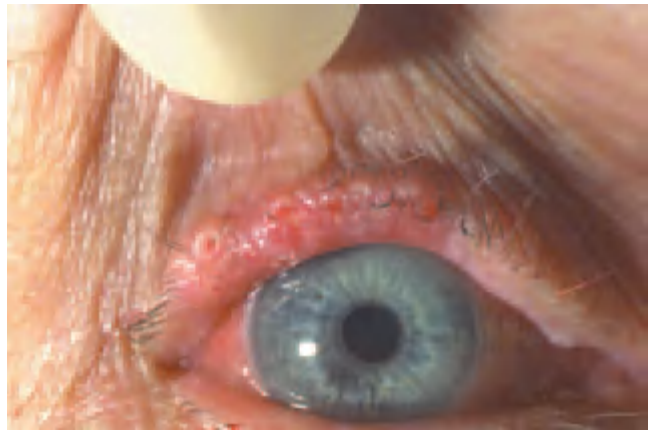

Fig. 64.18 Sebaceous gland carcinoma. Infiltrating lesion on upper lid. (Courtesy of Mr N. Joshi, Chelsea & Westminster Hospital/Medical Illustration UK, London, UK.)

Sebaceous gland carcinoma and epithelioma [18,19]

These are very rare tumours, accounting for less than 1–5% of malignant tumours of the eyelid. Sebaceous gland carcinoma usually arises from the meibomian glands, occasionally from the glands of Zeis. In contrast to BCC or SCC, the majority of lesions affect the upper lid. Most lesions are nodular and look very much like a chalazion (see Figs 64.6a, 64.6b & 64.18), causing delay in diagnosis; a sebaceous tumour should always be suspected if a 'chalazion' lasts for more than 6 months, and a 'chalazion' that recurs should be viewed with great suspicion, excised and sent for histology. Because of late diagnosis, sebaceous gland carcinoma carries a significantly mortality. Wide local excision is the treatment of choice. The multicentric nature of the tumour may limit the use of Mohs' surgery.

Eccrine carcinoma [20]

These are rare cancers of the eye and may present as an indurated thicking of the lid or with a signet-ring appearance. They are commonest in middle-aged or elderly men and recur after excision.

Merkel cell carcinoma

A very rare tumour. It can also mimic a chalazion in its early stages, with delay in diagnosis. It is highly malignant and has often metastasized by the time of excision.

Kaposi's sarcoma

A vascular malignancy. It presents as a purple lesion on

the eyelid or conjunctiva and can be mistaken for a benign haemangioma. However, it grows rapidly and may ulcerate and bleed. When it presents on the eyelid it is associated with AIDS, of which it may be the sole manifestation at the time of presentation. These lesions are very radiosensitive, and this is the preferred mode of treatment once a biopsy has been taken to confirm the diagnosis.

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Chapter 65

The External Ear

C.T.C. Kennedy

Anatomy and physiology [1–3]

The external ear consists of the auricle, the external auditory canal and the outer layer of the tympanic membrane.

The auricle, or pinna (Fig. 65.1), is a convoluted, elastic and cartilaginous plate covered by skin which is continuous medially with the lining of the external auditory canal. Except on the non-cartilaginous lobe and at the back of the ear, the skin is bound firmly to the cartilage. The auricle is attached to the head by fibrous ligaments and three vestigial auricularis muscles. The size and general detail of the auricle can vary greatly between individuals, and may be characteristically affected in a number of congenital syndromes. In humans, the auricle is largely functionless and motionless.

The epidermis of the ear has a complex dermal–epidermal junction, a conspicuous stratum granulosum and a thick, compact stratum corneum [4]. The dermis contains abundant elastic tissue. Sebaceous glands are numerous, particularly on the tragus and lobe, and fine vellus or terminal hairs occur over the entire surface, but are especially prominent on the helix and tragus. Coarser terminal hair is seen in some men as a Y-linked and androgen-dependent inherited trait (Fig. 65.2). Eccrine sweat glands are sparsely and irregularly distributed except in the external auditory canal, which has, instead, a large number of modified apocrine or ceruminous glands. The pinna has a variably thick fatty layer that extends between the perichondrium and the reticular dermis and that also forms the main fibrofatty core of the lobe of the ear.

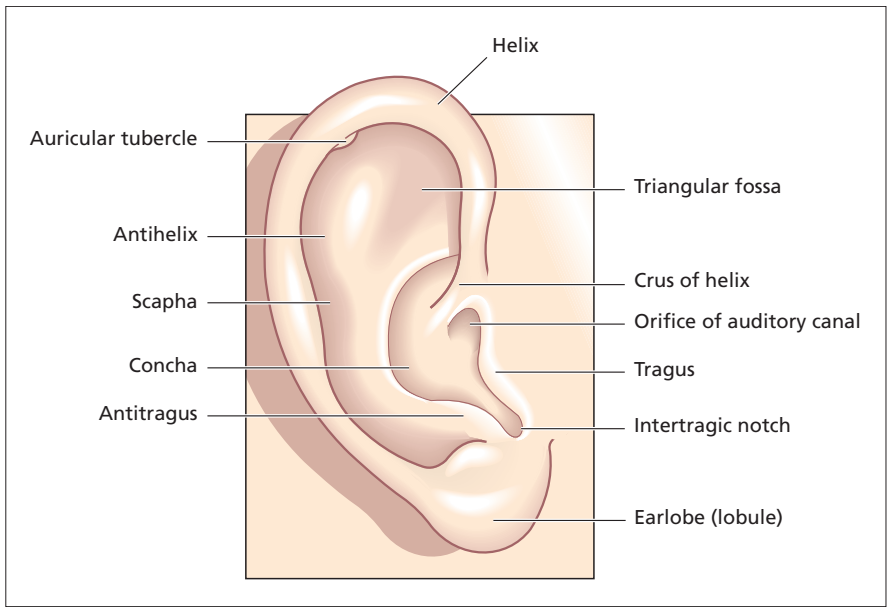

Fig. 65.1 Anatomical landmarks of the auricle.

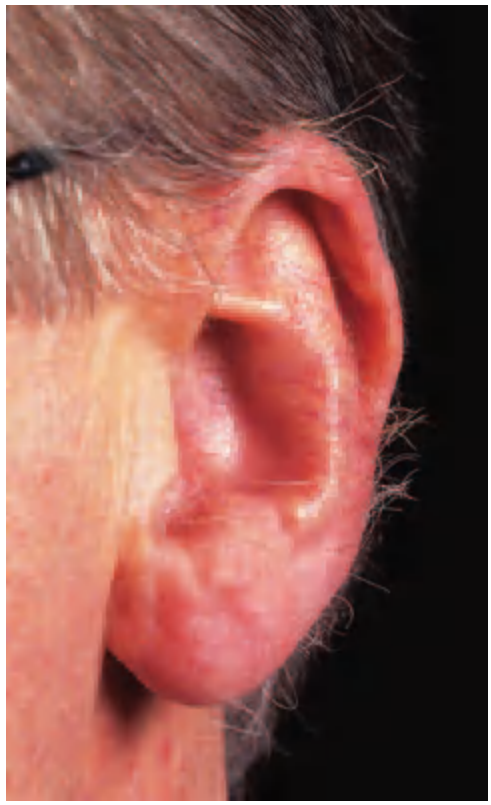

Fig. 65.2 Coarse terminal hair on the auricle: a trait associated with the Y chromosome.

The blood supply to the auricle is provided by anastomosing branches of the superficial temporal and posterior auricular arteries, which drain via posterior auricular and superficial temporal veins into the external jugular vein and via the superficial temporal, maxillary and facial veins into the internal jugular vein. Lymphatic drainage is to the superficial parotid, retro-auricular and superficial cervical lymph nodes. Embryonic fusion planes and minute deficiencies in the cartilaginous portion of the external auditory canal provide potential pathways for the spread of infection and tumours.

There is a complex nerve supply to the ear involving elements of the Vth, VIIth, IXth and Xth cranial nerves as well as cervical branches of the greater and lesser auricular nerves. The back of the ear is supplied by the greater auricular nerve (C2,3), the concha by the auricular branch of the vagus (Xth) and the anterior part of the pinna and the external auditory canal by the auriculotemporal branch of the Vth cranial nerve. Intercommunicating branches of the VIIth, IXth and Xth supply the deeper parts of the ear. With this complicated nerve supply, otalgia is more commonly due to referred pain than to disease in the ear itself [5]. Within the dermis, the nerve supply is abundant, especially around hair follicles where there are complicated basket-like networks of acetylcholinesterase and butyrylcholinesterase nerve fibres [4]. Free nerve endings are also present, but there are no organized nerve endings as occur on glabrous skin elsewhere [6].

The external auditory canal extends upwards and backwards in an S-shaped curve from the concha to the tympanic membrane. The angle of curvature varies between races and individuals, being more marked in white people than in black people or Polynesians. This has a bearing on trauma, infection and the retention of moisture. The length of the canal is 2.5 cm as measured from the concha to drum. The outer third of the canal is cartilaginous and is lined by a thicker layer of skin than the inner portion within the temporal bone. Anteroinferiorly there are two horizontal fissures in the cartilaginous canal, the fissures of Santorini. These can allow infection or tumour to pass beyond the external auditory canal, for example to the parotid gland. Subcutaneous tissue is scanty, and the epithelium is firmly bound to the perichondrium. Sebaceous glands are plentiful, and open into the follicles of extremely fine vellus hairs. Occasionally, larger terminal hairs (tragi) arise in the canal or around the meatus and these, if they become matted with wax or debris, may interfere with normal epidermal 'migration' and ventilation of the ear and hence may play a part in the development of 'hot-weather ear' (see p. 65.22).

Eccrine sweat glands are not present in the auditory canal but modified apocrine (ceruminous) glands are numerous. They increase in size and activity at puberty. There is great individual and racial variability, and although concentrated in the cartilaginous part of the canal, they may also occur, albeit sparsely, in the osseous portion.

The inner osseous part of the acoustic canal constitutes two-thirds of its total length. The skin is firmly bound to the periosteum, subcutaneous tissue being nearly absent and only 30–50 μm thick. The epidermis here is thin and easily traumatized, and rete ridges are absent [1]. The skin of the external auditory canal and tympanic membrane is unique in that there is no frictional loss of stratum corneum; cerumen (wax) and epithelial debris have therefore to be removed by a special 'migratory' property of the external ear canal epithelium [7]. A slight narrowing of the canal, the isthmus, occurs at or just medial to the junction of the two parts. When marked, it may impede the flow of cerumen to the exterior. Just medial to the isthmus, inferiorly and anteriorly, is the tympanic sulcus. Debris often collects here, especially in patients with chronic external otitis.

The surface pH of the auditory canal varies from 5.6–5.8 at the concha to 7.3–7.5 at 5–10 mm within the canal. With inflammation, the pH becomes slightly more acid [8].

Microbiology

The skin of the external auditory canal in most healthy

individuals supports the growth of multiple bacterial species, especially *Staphylococcus epidermidis*, *Corynebacterium* spp., *Bacillus* spp. and less often *Staphylococcus aureus*. *Pseudomonas aeruginosa*, often relevant to external otitis, and fungi are not normally found [3]. The normal flora can include organisms such as *Turicella otidis*, which can cause otitis media [9].

Cerumen (wax) [10]

Cerumen is the combined product of sebaceous and apocrine glands. It contains both squalene and insoluble fatty acids. Analysis by flash pyrolysis–gas chromatography/mass spectrometry has shown numerous diterpenoids [11]. Its main function is to waterproof the external auditory canal. Extrusion is aided by mastication and by the peripheral movement and desquamation of the epithelial cells of the canal. It is impeded if the ear canal is too narrow or tortuous, or when inflammation interferes with the normal process of 'migration'.

There are genetically determined differences in cerumen composition and character: so-called 'dry' ear wax is light grey, dry and flaky; 'wet' ear wax is golden brown and sticky. The former is very common in Asians. Wax phenotype is determined by a single gene pair, the wet wax allele being dominant [10]. Cerumen darkens with exposure to air.

Although not bactericidal, cerumen does not encourage bacterial or fungal growth. Possible reasons include the presence of lysozyme, immunoglobulins and polyunsaturated fatty acids.

Two populations have been shown to have excessive production and/or impaction of cerumen: individuals with mental retardation and the elderly [10]. An increased secretion of cerumen occurs in patients treated with aromatic retinoids [12,13].

If wax becomes impacted or adherent, it can cause various symptoms such as hearing loss, tinnitus, vertigo, pain and itching, and can be a contributory factor to external otitis. It may be removed by irrigation techniques or suction under direct vision [14]. Although it is generally thought that cerumenolytics such as 10% aqueous sodium bicarbonate or 2.5% aqueous acetic acid are of little value, they may have a use in children [15]. Docusate sodium is more effective than some traditional agents [16]. Although not yet studied in controlled trials, the bile acids may be very effective for removing ear wax [11].

Contact dermatitis from medicaments or irritant cerumenolytics [17] is well recognized. Inflammation interferes with normal epidermal migration and tends therefore both to induce and to encourage the retention of scale. The pruritus associated with excess cerumen, and the low-grade inflammation that often accompanies this, frequently leads to a persistent form of low-grade neurodermatitis.

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Examination [1]

As well as examining the pinna, the dermatologist may need to examine the ear canal. Equipment available should include a headlight or equivalent, otoscope, several sizes of ear speculae, ear curettes, metal applicators, bayonet forceps, ear irrigation apparatus and cotton.

General inspection of the auricles should take account of their symmetry, size, shape and position, and completeness of development.

The ear canal is best inspected when the auricle is pulled gently upwards, outwards and backwards, and the largest possible speculum is used. It is essential to avoid traumatizing the thin skin of the canal, particularly beyond the isthmus. If inspection reveals accumulation of cerumenous debris, this can sometimes be removed carefully using a curette or wire loop along the posterior wall. If the material is against the drum, gentle suction may be feasible. Irrigation should only be used if the drum is known to be intact.

Samples may need to be taken for bacteriology, mycology and histology. If a biopsy is required from the canal, this should be devolved to a surgeon with the necessary expertise.

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Developmental defects

The auricle begins to develop at the end of the fifth week of embryonic life in the first branchial groove, contributed to by the first (mandibular) and second (hyoid) arches [1]. Six hillocks appear on these arches and later fuse to form the complex shape of the fully developed auricle.

Developmental defects are considered in detail in Chapter 15. Only those defects of the ear sufficiently common to constitute a part of general dermatological practice are therefore considered here, together with some general principles relating to congenital ear abnormalities and their more important medical and otological associations [2–6]. Pinna abnormalities are associated sufficiently often with conductive hearing loss that screening tests should be carried out [7].

About 30% of infants with external ear anomalies have a renal anomaly identifiable by ultrasound examination, and this combination is a strong pointer towards a multiple congenital anomaly syndrome, in particular Townes–Brocks, CHARGE, branchio-oto-renal, Nager and diabetic embryopathy syndromes [8].

Many developmental defects are of unknown aetiology. Some, however, are associated with chromosomal abnormalities, for example those occurring in Down's syndrome, or are associated with syndromes that have well-recognized Mendelian inheritance patterns, for example the *e*ctrodactyly, *e*ctodermal dysplasia and *c*left lip–palate (EEC) syndrome. Environmental factors may be implicated as in fetal alcohol syndrome and fetal hydantoin syndrome, and maternal exposure to isotretinoin and thalidomide.

Congenital ear abnormalities exhibit great variability, even within syndromes or families, and any one aetiological factor may be associated with a variety of ear malformations. External ear malformations as part of a genetic syndrome account for less than 10% of all external ear abnormalities; isolated cases of ear malformation may either be non-genetic in origin or have a genetic basis but with poor gene penetrance [9].

Microtia (small ears)

Microtia designates a spectrum of underdevelopment of the pinna, from small ears to absence of an ear or ears. Small ears are often associated with hearing deficit and may be a feature of many syndromes. In addition to being small, the pinna may be rudimentary, resembling the hillocks from which it is embryologically derived. The more primitive the appearance, the greater the likelihood of hearing abnormalities, usually due to defects or atresia of the ossicles. There may also be a narrowing or atresia of the auditory canal [9–11] and various abnormalities of the middle ear [12] and inner ear [5]. A wide variety of non-aural abnormalities are associated with small ears, multiple malformations occurring in 56% in one large series [13]. Small ears are a feature of many syndromes, including Down's syndrome, Treacher Collins syndrome, Goldenhar's syndrome, Apert's syndrome, various first and second branchial arch and first branchial cleft syndromes, Mohr's orofaciodigital syndrome, Duane's retraction syndrome and thalidomide embryopathy [5,6,14].

Familial microtia inherited as an autosomal dominant trait has been described [15]. Microtia is one of the birth defects that occurs more on the right than the left side [16].

Macrotia (large ears)

Macrotia is a developmental variation in which the amount of tissue between the helix and antihelix is increased, causing the ears to wing out. The ear may also be diffusely enlarged, or elongated. Such changes are common in Turner's syndrome, and there may be associated sensorineural deafness. Larger ears are well described in fragile X syndrome [17] and Kabuki's syndrome, although in the latter they may also be smaller than normal [18]. Generally enlarged ears are sometimes seen in patients with the XXXXY chromosome defect. The cartilaginous parts of the ears are enlarged and soft in Laband's syndrome [19,20]. In this rare disorder the ears are large and floppy, in association with a bulbous soft nose, gingival fibromatosis and a variety of other findings including absence or dysplasia of nails and/or of terminal phalanges, hyperextensibility of joints, hepatosplenomegaly, and rarely hypertrichosis and mental retardation.

Low-set ears

Normally, the top of the helix is at the same level as the eyebrow, the earlobe is above the angle of the mandible and the external auditory meatus is at the level of the ala nasi. Low-set ears may in addition be posteriorly rotated, and are often small. The condition is usually bilateral. Although it may be isolated, it is often associated with major middle-ear or systemic malformations, appearing for example in Turner's, Noonan's, Patau's and Crouzon's syndromes.

Peri-auricular anomalies

Pre-auricular pits, sinuses (Fig. 65.3) and tags are relatively common, with an incidence of approximately 1% [9,21]. Lesions on or near the tragus are probably best

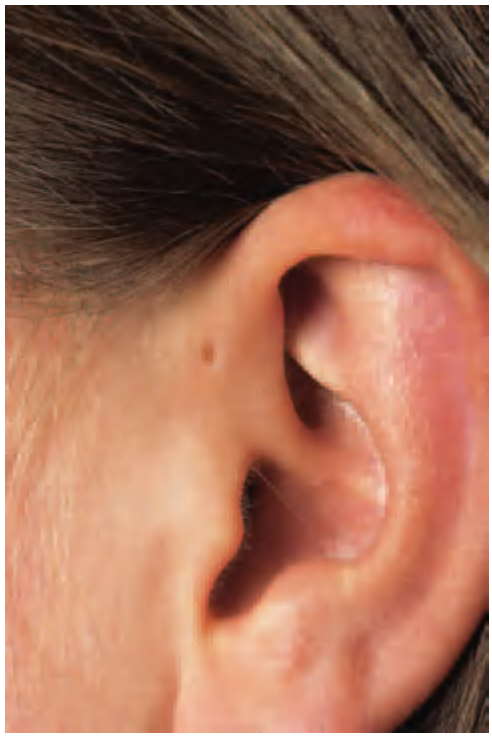

Fig. 65.3 Pre-auricular sinus.

termed 'accessory tragus' [22]. The term 'accessory auricle' is sometimes used for this, and for similar firm elevations of skin and cartilage just near the ascending crus of the helix. They may be single or multiple and may occur anywhere in a line from the tragus to the angle of the mouth. Accessory auricles, congenital fistulae and other external ear manifestations may occur alone or may be associated with more widespread first and second branchial arch abnormalities, for example Treacher Collins and Goldenhar's syndromes [3,4,8,21], or with developmental abnormalities of the genito-urinary tract [8,21], as well as with isolated hearing defects.

Variations in the shape of the pinna

Minor variations in size and shape are common and not usually associated with any other abnormality. These include *bat ear* or protruding ear, in which the antihelix lacks the usual bulge; *lop ear*, in which there is an unrolled helix, a poorly developed antihelix and scapha, and a large concha resulting in a somewhat floppy ear; and *prominent auricular* (*Darwin's*) *tubercle*. Variations in the contour of the helix and antihelix to produce a bulge of the anterosuperior part of the pinna account for so-called *Mozart's ear*, and in *Wildemuth's ear* the antihelix is prominent and the formation of the helix is poor. These minor ear anomalies can be a syndromic feature or can be associated with conductive and occasionally sensorineural hearing loss, but in most instances they are isolated. They may, however, be inherited, as in the Mozart family. A distinctive *railroad track abnormality* with marked prominence of the crus of the helix is said to occur in up to 30% of children with fetal alcohol syndrome [10,14] and a protruding auricle may, rarely, be a sign of neuromuscular disease [23]. Various abnormalities of the configuration of the pinna have been described in the distinctive *lumpy scalp syndrome* [24], in which other features include absent or rudimentary nipples and dermal nodules on the scalp [25]. The lobule can show isolated abnormalities, for example pits and clefts. Absence of the lobule is, however, usually associated with a syndrome of a more serious nature [6]. Diagonal linear creases in the lobule are seen in Beckwith–Wiedemann syndrome, and in adult life in association with some degenerative diseases (see p. 65.6), although they are a common finding in normal individuals.

Developmental anomalies of ear hair

Hypertrichosis of the pinnae was originally described as a Y chromosome-linked trait [26]. An autosomal dominant genetic basis for hairy ears has also been noted in South Indians [27] and Maltese [28]. Acquired hairy ears have been described in infants born of diabetic mothers [29,30] and in association with human immunodeficiency virus (HIV) infection [31].

Management [32]

The infant with obvious malformation of the pinna that might have auditory system or other associations should be assessed by a paediatrician. The history may reveal exposure to a teratogen (e.g. isotretinoin) or family history of a syndrome and examination may show evidence of other anomalies. Investigations may include radiological evaluation [33], an auditory brainstem evoked response hearing test and a renal ultrasound. It may be appropriate for an ear, nose and throat (ENT) specialist and plastic surgeon [34,35] to become involved with correction of complications and the physical deformity, respectively.

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Ageing changes

Many changes seen on the skin of the pinna attributed to ageing are a result of its exposure to environmental factors, especially UV radiation, cold (perniosis) and infrared radiation. The elderly exposed pinna often shows varying degrees of dermal and epidermal atrophy, solar keratoses and lentigines, solar elastosis, telangiectasia and venous lakes. If the pinna is at least partially light protected, as in many women, the skin may still appear somewhat thinned due to intrinsic ageing changes.

Ear length

It is recognized in Chinese culture that length of the ear in men is a predictor for longevity [1]. Two studies would appear to confirm this: one from Kent, UK [2], and one from Japan [3]. The increase in length of the male ear from the age of 30 years onwards may have a 7-year periodicity [4].

Earlobe creases

First described in 1973 [5], and now known as Frank's sign, a diagonal crease in the earlobes of adults has been associated in many studies with an increased risk for atherosclerotic coronary artery disease. A meta-analysis in 1983 gave a relative risk of 2.06 for heart disease if there are bilateral creases [6] and there is approximately double the risk for death from heart disease [7,8]. The crease can be graded in terms of length and depth, and deeper longer creases have the strongest association. The ear crease appears to be separate from other risk factors for coronary artery disease, and is not simply a function of age [9]. A more recent case–control series suggests a relative risk of 1.37 for myocardial infarction [10] and a lower specificity for the sign than previously estimated [11].

Diagonal earlobe creases are seen in other contexts, for example Beckwith–Wiedemann syndrome [12] (Fig. 65.4),

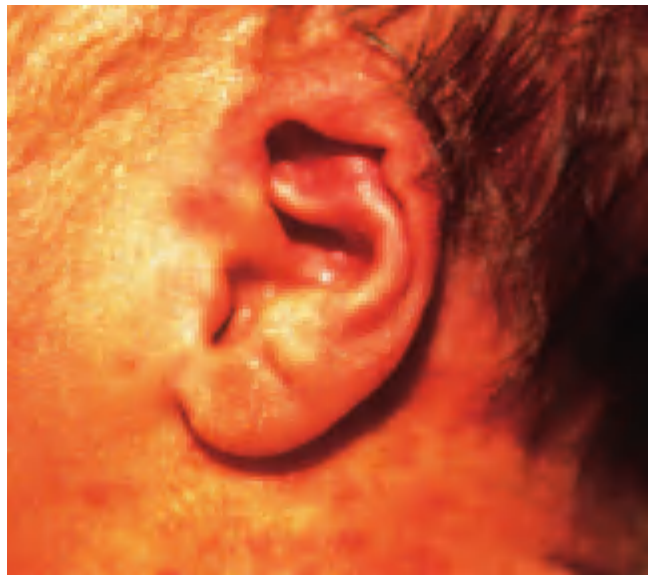

Fig. 65.4 Diagonal earlobe crease in an infant with Beckwith–Wiedemann syndrome.

and do not seem to be associated with coronary artery disease in Hawaiians [13], native Americans [14] or Chinese [15].

Earlobe creases have also been associated with primary open-angle glaucoma [16].

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Traumatic conditions

Contusion and haematoma

Bruises of the ear are usually due to blunt trauma and are common in contact sports, such as boxing, wrestling and rugby. In children, physical abuse may need to be excluded [1,2]. A distinctive condition known as *tin ear syndrome* has been considered pathognomonic of child abuse: a triad of isolated ear bruising, haemorrhagic retinopathy and a small ipsilateral subdural haematoma [3].

Following trauma, blood and serum collects in the plane between perichondrium and cartilage, and will undergo fibrosis if not removed early. The patient should be carefully examined for concurrent auditory canal, middle ear, parotid and central nervous system trauma.

Repeated trauma may result in the distorted nodular deformity known as *cauliflower ear*, which is due to varying degrees of cartilage necrosis, fibrosis and dystrophic calcification.

Treatment. Subperichondrial haematomas must be treated promptly, with full aseptic technique to avoid secondary perichondritis. Small collections of fluid can sometimes be aspirated by syringe, but usually need to be drained through a small incision and a laterally placed pressure dressing applied to prevent reaccumulation [4,5]. Another useful technique is to use a through-and-through suture technique to maintain bolsters over the area where the haematoma has been evacuated [6]. Other approaches include a posterior incision and suction drainage [7], or fenestrations in the cartilage to promote adhesion of the opposing perichondrial layers [8]. Prophylactic antibiotics are sometimes given. Improvement of cauliflower ear usually requires multiple corrective procedures.

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Laceration and avulsion

Lacerations of the pinna vary from the trivial to amputation [1]. Because of the risk of cartilage infection, potentially dirty wounds should always be carefully cleaned and a course of prophylactic antibiotic given. It is probably best to avoid suturing the cartilage itself unless pieces overlap or are severely displaced [2]. Injuries that expose cartilage will need to be covered with a skin graft, for example taken from behind the ear or the upper eyelid. If the anterior perichondrium is destroyed, cartilage may need to be excised so that the graft can be placed on the posterior perichondrium. If the post-auricular area is not injured, a pedicled island flap of post-auricular skin may be pulled through the area of excised cartilage and sutured into place. If the helix or antihelix is exposed, it may be possible to cover it with an advancement or rotation flap from the posterior surface of the auricle. Large areas may need to be covered with a pedicled flap of temporoparietal fascia, which in turn is covered with a split-skin graft. The lobule of the ear can be repaired by direct closure, although a cosmetically superior result may be obtained by a broken line repair or Z-plasty [3]. Many techniques have been described for repair of major

trauma, including even complete avulsion of the pinna [1,4,5], but these are likely to be beyond the scope of the dermatologist. Following total ear replantation there is lack of cutaneous sensation and this may explain the cold intolerance that can occur [6].

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Dermatitis artefacta

The ear is occasionally the sole site for self-mutilation and there may be underlying psychodynamic reasons for this [1].

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Ear piercing

Earrings have been worn by men and women since antiquity, and tend to follow the dictates of fashion. Current trends include using rings or studs in almost all parts of the body, the use of up to 10 or more in a single ear, and the piercing of cartilage.

Complications are very common, with rates of about 30% whether the procedure is carried out by medical personnel, friend or relative, or in a store; they are also independent of technique, there being little difference in frequency of complications from piercing by needle, staple gun or sharpened stud [1]. Minor infection is the most common adverse effect, with contact dermatitis, keloid and traumatic tear occurring less often [2]; other consequences occur occasionally. Although case series indicate that so-called 'high' ear piercing, i.e. through cartilage, has a significant risk for perichondritis [3,4] and chondritis [5], such events were not found in a population study of 1000 nurses [2]. Embedding of the earring seems to be a common problem in children [6].

The ear is also pierced in acupuncture as used in traditional medicine, and complications have been reported [7,8].

Complications. Various infections and reactions may occur after ear piercing.

Localized bacterial infection, usually with Gram-positive cocci, is common; predisposing factors include skin disease, such as atopic or contact dermatitis. Life-threatening septicaemia has been described [9]. Infants with unsuspected immunodeficiency and individuals with valvular heart disease may be at particular risk. When cartilage is pierced the usual bacterial infection is with *Ps. aeruginosa*, which causes perichondritis [3] or chondritis [5], and for which the best treatment is ciprofloxacin [4]. Any purulent material should be cultured, since other pathogens have been described (e.g. *Lactobacillus* [10]). Primary tuberculosis has been described [11].

Viral hepatitis may also be a hazard [12,13].

Oedema and haematoma [1,14] usually respond to cold compresses, pressure and removal of the earring. Haematoma may require incision and drainage [15].

Trauma can occur from pressure on the lobe and postauricular skin, or from inaccurate insertion of the post of the earring. Heavy earrings can tear the earlobe, sometimes making it bifid. Repair of the latter is probably best by excision of the cleft and simple closure with eversion of the edges [16], although a staggered repair such as a Z-plasty may be appropriate in some cases.

Sensitization to nickel from earrings remains a major problem, and ear piercing is one explanation for the higher incidence of nickel allergy in females [17]. Even stainless steel studs and clasps, which can produce irritant as well as allergic effects, may release sufficient nickel to elicit contact dermatitis [18]. Gold sensitization, although less common [19], can be a protracted cause of dermatitis even after the earrings are removed [20]. Contact dermatitis from other materials used in earrings, such as olive wood [21], copper [22], cobalt [23,24] and chromium [25], has been described, and may also occur from the use of topical antiseptics, antibiotics and dressings used to treat infection.

Granulomatous and lymphoid reactions. Reddish brown and purple papules and nodules at sites of ear piercing may denote a granulomatous response to gold [26,27] and a lymphocytoma cutis-like reaction has been described [28–30]. Sarcoidosis has presented after ear piercing [31].

Embedded earrings. The spring-loaded gun method of ear piercing can result in the earring backing becoming embedded in the back of the ear [32]. The 'vanishing earring' [33] can resemble a keloid [34]. The embedded metal can usually be pulled out, or if necessary an incision can be made to locate it.

Epidermoid cyst formation. Implantation epidermoid cysts due to ear piercing often present as tender, chronic,

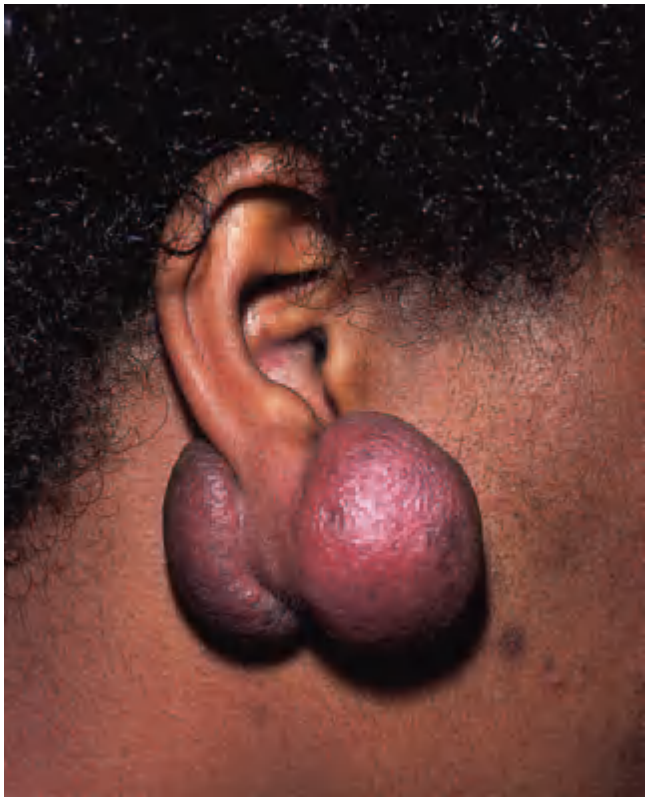

Fig. 65.5 Keloids following ear piercing.

inflammatory swellings, sometimes with drainage. There is usually an epithelial lined track as well as cysts, and all epithelial tissue must be removed, for example with a skin punch [35].

Keloids quite commonly follow ear piercing, especially in those ethnic groups with a predisposition (Fig. 65.5). The keloids seem to occur more on the back surface than the front of the earlobe [36]. As well as being unsightly, they can itch and be painful.

Treatment options include intralesional steroid, pressure [37], and excision with or without concurrent use of intralesional steroid [38] or radiotherapy (see Chapter 76) [39]. Prospective controlled trials are needed to assess these approaches.

A recent study has shown efficacy and acceptability of intralesional steroid followed by Zimmer splints which can be decorated to look like earrings [40].

Localized argyria. Bluish macules have been described on the posterior surface of the earlobe [41,42].

Frostbite has followed the use of ethyl chloride topical anaesthesia [43].

Measures to prevent complications [44]. Many of the complications of ear piercing are avoidable. The procedure is best not carried out on children under the age of 5 years or those with immunodeficiency, valvular heart disease or sarcoidosis, and there is clearly a risk if the individual has a tendency to keloid formation. For a dermatologist who wishes to pierce ears or instruct others, a simple method with a low likelihood of complications has been described [45]. The use of a surgical-grade, stainless steel, one-piece earring with an interlocking groove has been recommended. Gold-plated or gold-alloy earrings should be avoided for at least 6 weeks after the ear has been pierced. Sterile technique is important. Piercing of cartilage should be avoided. Only nickel-free earrings should be used. Large or heavy earrings should be removed prior to activities that may result in tearing the earlobes. A technique using a piece of intravenous catheter to avoid reactions in metal-sensitive individuals has been described [46].

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Acanthoma fissuratum

This chronic response to friction and pressure from the spectacle frame can present with papules or nodules, sometimes with ulceration, in the supra-auricular or retro-auricular folds (Fig. 65.6); even when bilateral, basal cell carcinoma is a differential diagnosis. Acanthoma fissuratum is discussed in Chapter 22.

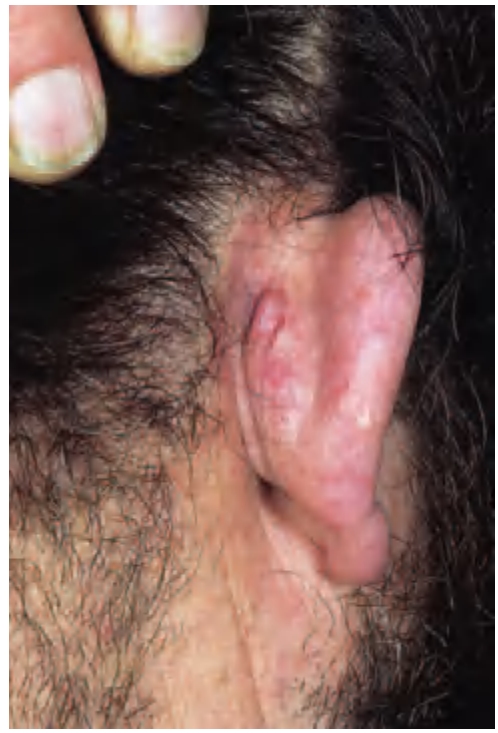

Fig. 65.6 Acanthoma fissuratum. Nodular thickening behind the pinna superficially resembling basal cell carcinoma.

Cold injury

The ears are extremely susceptible to cold, and the pinna may be affected by chilblains in winter (Fig. 65.7). Extreme cold will cause frostbite (see Chapter 23). Similar changes have also been reported as a consequence of using excessive amounts of ethylchloride spray for ear piercing [1]. Frostbite may result in vesiculation, blisters and ischaemic necrosis of both skin and cartilage. Ears that have previously been damaged by cold may subsequently become calcified and even ossified [2,3].

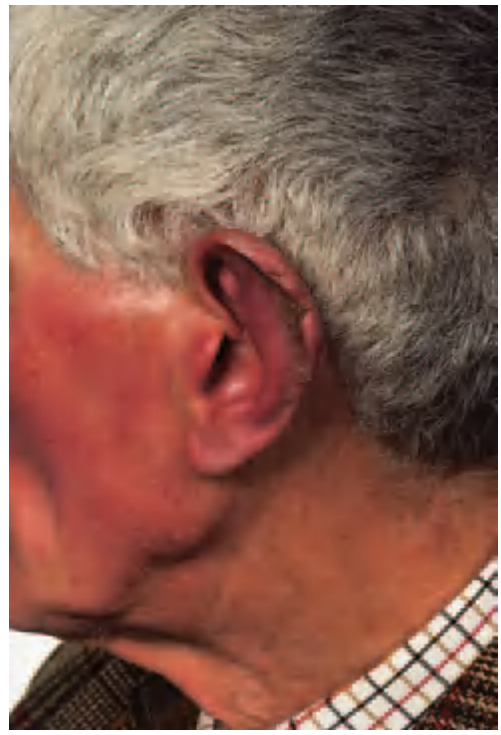

Fig. 65.7 Perniosis. Purple discoloration, soft-tissue loss and crusting due to acute-on-chronic cold injury.

Cold is also a provoking factor in many conditions that can affect the ear, for example chondrodermatitis nodularis helicis, chilblain lupus erythematosus and cryoglobulinaemia.

The ear subjected to frostbite should be thawed rapidly by the application of wet, sterile cotton pledgets warmed to 38–42°C for about 20 min [4] with adequate analgesic cover.

Emollients have traditionally been thought to protect against frostbite [5], at least in Finland. However, those who use them experience more frostbite, probably through conferring a false sense of safety, and only thermal protection from clothing can be expected to have protective value [6].

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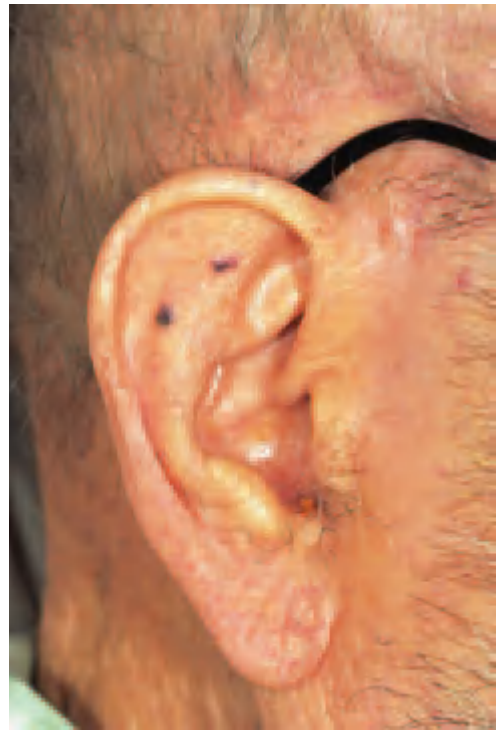

Fig. 65.8 Venous lakes on a sun-damaged pinna.

Solar damage

The external ear is often exposed to solar radiation and is therefore liable to acute and chronic sequelae. A significant hazard from severe sunburn is the development of perichondritis (see below). Many photosensitivity disorders will present on the ear, for example polymorphic light eruption, juvenile spring eruption, lupus erythematosus and porphyria (see Chapter 24).

The full gamut of chronic solar damage is frequently seen on the ears, including erythema, telangiectasia, atrophy, blotchy pigmentation, solar keratoses and cutaneous malignancies. As on the lower lip, venous lakes may be seen (Fig. 65.8). Solar elastosis is often evident, and distinctive elastotic nodules may be seen particularly on the anterior crus of the antihelix [1–3]. These lesions are usually bilateral and asymptomatic, and present as pale papules or nodules. Occasionally, they can occur on the helix and be painful, simulating chondrodermatitis nodularis. They differ from 'weathering' nodules (Fig. 65.9), which, like chondrodermatitis nodularis, occur on the helix of the ear [4].

For treatment of mild acute sunburn, cold compresses may be sufficient. More severe cases may benefit from a course of systemic corticosteroid, given for 5 days and then tapered. Preventive measures are discussed in Chapter 24.

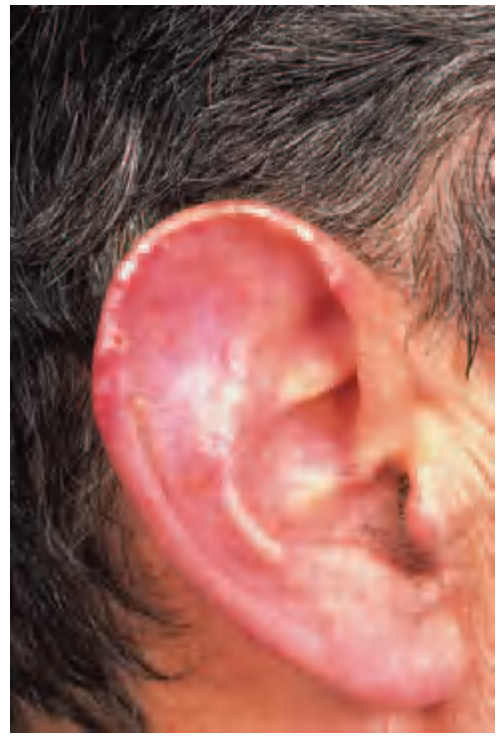

Fig. 65.9 Several firm, white, 'weathering' nodules on the helical rim.

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Altitude injury

A distinctive presentation of petechiae and haemorrhagic bullae in the skin of the external auditory canal and tympanic membrane has been described in air pilots descending from high altitudes or in pressure chambers while wearing well-sealed earplugs as noise protectors [1].

For treatment, a steroid–antibiotic ear drop has been advised, and if sizeable clots are present they can be gently dislodged by suction after the application of hydrogen peroxide. Preventive methods include the use of perforated earplugs on high-altitude descent.

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Radiation injury

Therapeutic use of radiation may result in characteristic acute and chronic changes (see Chapter 76). The cartilage can be susceptible to destruction if inappropriate techniques are used. Post-radiation changes on the external auditory canal include thickening of the canal epithelium, subepithelial fibrosis and resorption of underlying bone, as well as ulceration of the epithelium and the development of cholesteatoma [1].

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Foreign bodies

A variety of vegetable, animal and mineral substances may be encountered lodged in the external ear and external auditory canal, and are frequently unsuspected. Presenting symptoms include pain, hearing loss, inflammation and discharge.

Vegetable matter, such as beans, peas and cotton, tends to absorb water and swell, impacting in the ear canal. Arthropods are the commonest animal material. While alive, their motion within the ear can produce distinctive symptoms, even vertigo. Flies can deposit eggs in the external auditory canal and the resulting myiasis has produced severe complications [1]; larvae in the triangular fossa of the pinna can also cause marked inflammation [2]. Mineral materials include beads, sand and pebbles, fragments of plaster and metallic substances. Even batteries have been found lodged in the ear and can produce serious consequences [3–5]. Impacted cerumen can behave like a foreign body in the ear canal. Loose hairs in the ear canal have been reported as a cause of noise [6].

Retrieval of foreign bodies should only be undertaken if appropriate instrumentation and expertise is available. For children, with whom the problem is more common, general anaesthesia is required. Small foreign bodies can usually be extracted with a curette or alligator forceps. Live insects should first be killed by drowning, for example in 2% lidocaine (lignocaine) [7], ether, chloroform or spirit. If some vegetable materials have absorbed water and become impacted, it may be necessary to divide the foreign body *in situ* and remove the fragments. It may be necessary to control bleeding from the skin of the canal, for example with epinephrine (adrenaline)-soaked gauze, and the canal should then be packed with an antibiotic-impregnated dressing. In cases of a battery lodged in the ear canal, it is essential that an ENT surgeon is involved in the management, because of the likelihood of serious destructive change to the middle ear and beyond.

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Chondrodermatitis nodularis

This painful condition usually involves the superior portion of the helix, but may appear on the antihelix, concha, tragus and antitragus. It has formerly been known as painful nodule of the ear [1].

Aetiology. The principal factors in its pathogenesis are pressure and a compromised local blood supply. It is much more common in patients who habitually sleep on one side at night but can be triggered off by other factors, including cold, and by other types of pressure (e.g. from headgear, earphones). Alteration of connective tissue by chronic sun exposure may also be a factor [2]. The age of onset is over 40 years in most cases and the condition is commoner in males than females. We have encountered chondrodermatitis nodularis in juveniles, but only when

there is an abnormality such as marked prominence of the antihelix or a history of injury (e.g. from contact sports). Chondrodermatitis nodularis has been reported in a series of patients with systemic sclerosis [3] and in childhood dermatomyositis [4].

Pathology [5,6]. A typical lesion of chondrodermatitis nodularis consists of a nodule of degenerate homogeneous collagen surrounded by vascular granulation tissue with an overlying acanthotic epidermis, and there may be a central ulcer through which the damaged collagen is extruded. In nearly all cases there is inflammation and fibrosis of the underlying perichondrium, and degenerative changes may be seen in the cartilage. Although many authors view the condition as an example of transepidermal elimination of altered connective tissue, it has been suggested that the infundibular portion of the hair follicle is primarily involved, with perforation of the follicular contents into the dermis [7,8].

Clinical features. The patient, usually a middle-aged to elderly man, seeks advice on account of pain. The more stoical may postpone consultation until the lesion interferes with sleep. The pain, which is sometimes severe, is initiated by pressure and occasionally by cold. It may be brief but can persist and throb for an hour or more. Occasionally, and particularly in women, there is little discomfort. The lesion is a globular or oval nodule, about 0.5–2 cm in diameter, raised above the often hyperaemic surrounding skin (Fig. 65.10). The surface is frequently scaly or crusted, concealing a small ulcer.

In men, nearly 90% of nodules are situated on the helix, usually at the upper pole and more frequently on the right, but may occur on the antihelix [9], tragus, concha and antitragus, in order of decreasing frequency [10]. Occasionally, there are multiple nodules or lesions, and they may occur bilaterally [11]. In women, the left and right ears are affected equally and the proportion of lesions on the antihelix and tragus is greater [12]. The nodules attain a maximum size in a few months and then remain unchanged indefinitely.

Diagnosis. Although the associated pain and tenderness are characteristic, the lesion is often misdiagnosed. Differential diagnosis includes basal and squamous cell carcinomas, solar keratosis, calcification of the pinna, elastotic nodules and 'weathering nodules' [13].

Treatment. For chondrodermatitis nodularis of the helix, excision with a narrow margin of normal skin has been recommended as standard treatment [14,15] and the approach can usefully be modified by the additional use of a curette, to define the extent of necrotic cartilage [16]. Cosmetic results are often poor and long-term recurrence rates rarely reported. Removal of cartilage only can provide excellent results and this technique can be applied to other sites such as the antihelix and tragus. The results are often cosmetically superior [17]; long-term cure rates in excess of 80% have been reported [18]. Other treatments include intralesional steroid therapy [19], liquid nitrogen cryotherapy and carbon dioxide laser [20,21]. In all patients, efforts must be made to reduce pressure or trauma to the helix. Where facilities exist for construction of individualized pressure-relieving devices, these can be useful [22].

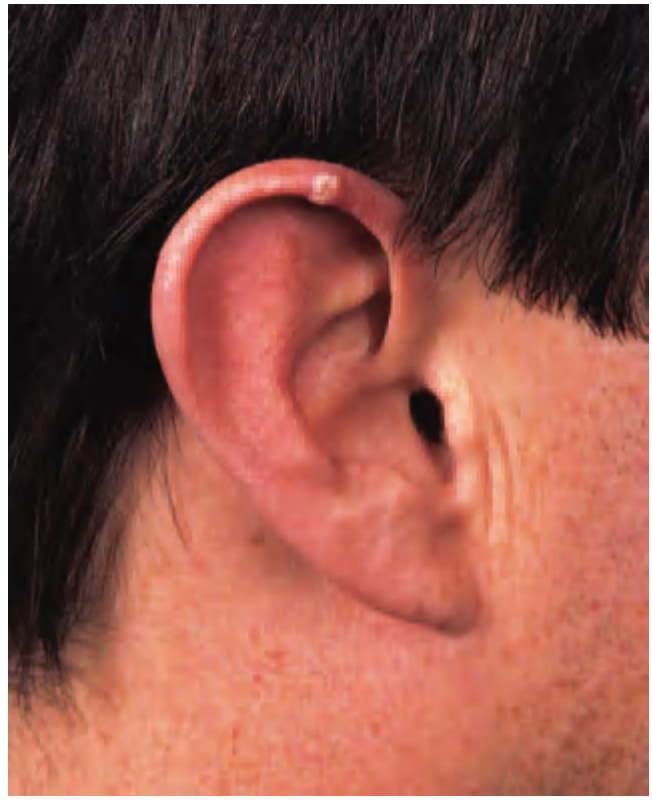

Fig. 65.10 Chondrodermatitis nodularis of the helix. A superficially ulcerated, exquisitely tender nodule.

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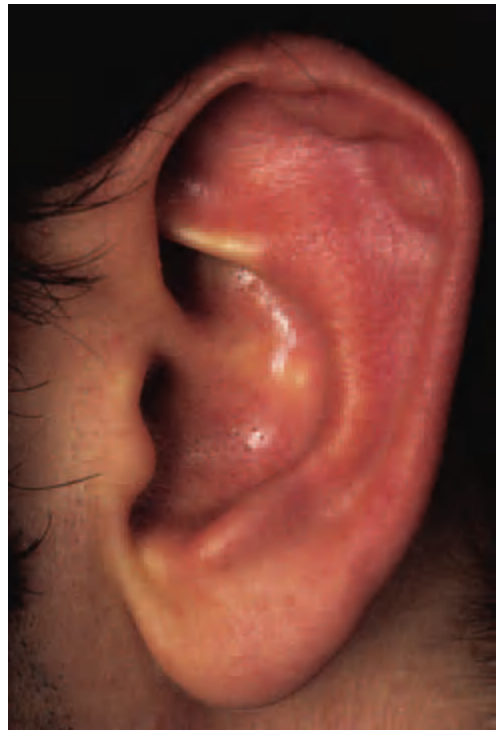

Fig. 65.11 Pseudocyst. Asymptomatic fluctuant swellings on the upper pinna.

Pseudocyst of the ear

SYN. ENDOCHONDRIAL PSEUDOCYST; IDIOPATHIC CYSTIC CHONDROMALACIA

A non-inflammatory, fluid-filled cavity within the cartilage of the ear.

Aetiology. Although the cause is unknown in most cases, trauma is likely to be important at least in some, as in fracture in the ear cartilage [1], habit-twisting of the ears [2] and rubbing due to atopic eczema [3]. Most speculations about the pathogenesis include an underlying malformation of the cartilage [4] and degeneration due to release of lysosomal enzymes from chondrocytes. A role for cytokines has also been suggested [5].

Pathology. There is a cavity within the cartilage, the walls of which show the presence of eosinophilic amorphous material [6,7]. There may be focal fibrosis, especially in older lesions.

Clinical features. Most cases are young men, although the condition is seen over a wide age range [8] including infants [9]. Occasional cases have been recorded in females [4]. All races are affected [10]. There may be a predilection for Chinese, although this could be reporting bias [11,12]. The condition is usually unilateral and presents as an asymptomatic swelling, which is non-tender and fluctuant. Occasionally, there are signs of inflammation and some tenderness. The commonest location is on the upper half of the ear (Fig. 65.11), on the scapha, less commonly over the helix and antihelix. Sometimes, coalescent swellings are seen. Aspiration usually yields serous fluid, which soon reaccumulates.

Diagnosis. The differential diagnosis includes traumatic perichondritis, relapsing polychondritis (see Chapter 46), haematoma, dermoid cyst and epidermoid cyst, and various benign and malignant tumours; any of these can if necessary be excluded by histological examination.

Treatment. Needle aspiration followed by the introduction of a few drops of 1% tincture of iodine [10] or corticosteroid [13] and then application of a contour pressure bandage is often successful. Thermoplastic material as used for mobilizing extremities can be used to provide the pressure [14].

For recurrences, excision of the anterior wall of the cyst, suturing the skin flap back and use of a pressure dressing can produce a cosmetically satisfactory result in most cases [12].

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Dermatoses and the external ear

Atopic dermatitis

A crusted eczematous fissure at the junction of the earlobe and the face is a common finding in atopics, and can be regarded as a reliable feature of atopy [1–3]. In the series of Tada *et al*. [3], 45 of their 46 patients with severe atopic dermatitis had infra-auricular fissures. In addition to involvement of the infra-auricular crease, the tragal notch and sometimes the whole of the pinna may be commonly involved. Treatment of eczema and the secondary infection that often accompanies it is discussed in Chapter 18.

Seborrhoeic dermatitis

In its mildest form, seborrhoeic dermatitis simply causes a little scaling and inflammation at the entrance to the external auditory meatus, in the concha or in the auricular folds. When severe, the whole pinna may be affected and there may be infective eczematoid dermatitis both in and around the ear or post-auricularly. The relationship between seborrhoeic dermatitis and otitis externa is discussed in Chapter 17.

Asteatotic eczema

The exposed position of the ear renders it vunerable to the climatic changes that can induce asteatotic eczema (see Chapter 17). This common cause of a dry itchy ear is mainly seen in the elderly. Aggravating factors include overzealous cleansing, cold, windy weather, low humidity indoors and air-conditioned air during the summer. There may be little to see other than slight scaling. Similar changes can occur in the ear canal, where additional factors include drying vehicles used in ear drops, for example alcohol and acetone. Management will include avoidance of provocative factors, and use of emollients.

Contact dermatitis

The external ear is commonly affected by both irritant and allergic contact dermatitis [4]. Causes of contact allergy may be grouped as follows.

1 Products used for the hair and scalp: hairspray, shampoos, hair dyes, hair nets, bathing caps.
2 Items worn or placed in or on the ear: jewellery, especially nickel alloys (see p. 65.8).
3 Plastic, rubber or metal ear appliances, for example hearing aids, spectacles, headphones, telephone receivers, earplugs, hair nets.
4 Objects used to clean or scratch the ear, for example hairpins, matches.
5 Cosmetics and toiletries: make-up, perfumes, soaps and creams.
6 Topical medicaments.
7 Others (transferred to the ear by fingers): nail varnish, plant resins (e.g. poison ivy, oak or sumac).

The role of occult allergic contact dermatitis in patients with otitis externa is discussed on p. 65.24.

Psoriasis

Both guttate and plaque psoriasis involve the external ear. Sometimes this is by extension from the scalp, face or neck. Like seborrhoeic dermatitis, psoriasis often involves the concha and distal part of the external auditory canal, but usually its colour, the nature of the scaling and the presence of psoriasis elsewhere allow it to be differentiated. Sometimes both conditions appear to coexist.

Acne

Comedones frequently involve the concha, and are occasionally found on the helix, tragus or earlobe. Inflammatory cysts may be found on the lobe, at the entrance to the external auditory canal, or in both the pre- and post-auricular areas. Pressure from spectacle frames, telephone receivers or headsets can aggravate acne lesions.

Darier's disease

Occasionally, Darier's disease can present with involvement of the external ear as the principal affected site, with erythema, oedema and crusting mimicking an eczematous reaction [5].

Transepithelial elimination disorders

The ear may occasionally be the site for lesions of Kyrle's

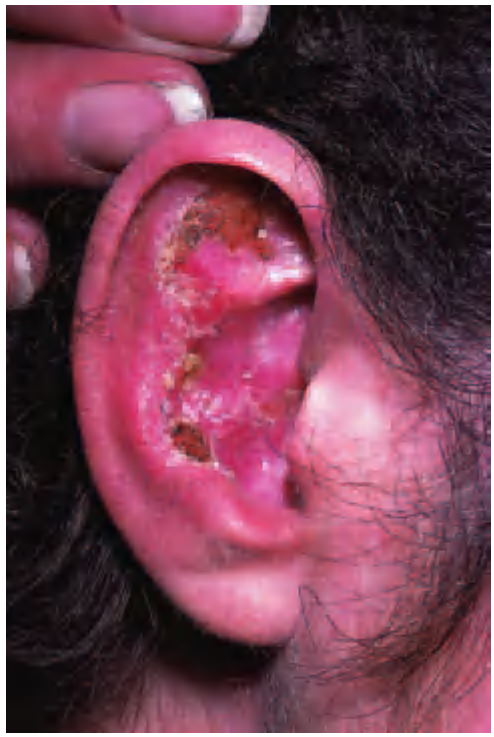

Fig. 65.12 Cutaneous lupus erythematosus. Acute erythema and erosions following sun exposure.

disease, elastosis perforans serpiginosa, perforating folliculitis and perforating papules of diabetic dialysis patients. These conditions are discussed in Chapter 46.

Lupus erythematosus (Fig. 65.12)

Although most parts of the pinna may be involved in lupus erythematosus, pits and scarring in the concha are distinctive features [6,7]. Atrophy often occurs, and even perforation of the pinna [8].

Mudi-chood

This distinctive dermatosis, which typically affects the nape of the neck and upper shoulders of girls and young women in the state of Kerala in South India, can occur on the ears. It is thought to be the result of the frictional and occlusive effects of moist oily hair in a hot and humid environment. Individual lesions are hyperpigmented papules with a thin surrounding rim of scale, occurring on the posterolateral aspects of the pinnae [9].

Lymphocytoma cutis

When the ear is involved, the lobe is characteristically affected, often with a large single nodule. Possible causative factors include *Borrelia burgdorferi* infection [10] and gold earrings [11,12].

Jessner's benign lymphocytic infiltration

This condition occasionally involves the ear and postauricular region, and sunlight may precipitate or worsen the eruption.

Granuloma annulare

Typical papular and annular dermal lesions of granuloma annulare may involve the pinna, sometimes in the absence of lesions elsewhere [13].

Primary cutaneous amyloidosis

Asymptomatic papules on the helix and concha of the ear have been described as the sole manifestation of cutaneous amyloidosis [14]; such lesions can also occur with more generalized papular amyloid [15] and with macular amyloid of the back [16].

Angiolymphoid hyperplasia with eosinophilia
SYN. PSEUDOPYOGENIC GRANULOMA; NODULAR ANGIOBLASTIC HYPERPLASIA WITH EOSINOPHILIA

This is a reactive proliferative disorder of blood vessels with a variable component of inflammatory cells [17]. Opinions vary as to whether it is identical with Kimura's disease, a condition mainly found in Eastern orientals (see Chapter 53). Angiolymphoid hyperplasia with eosinophilia occurs in both a dermal [18] and a subcutaneous [19] form, and is most commonly found on the head and neck. The two forms are regarded as variants of the same condition [20–22].

Aetiological factors include trauma, pregnancy and immunization procedures [23].

Histology. There are circumscribed collections of vessels whose endothelial cells are epithelioid, i.e. have abundant eosinophilic cytoplasm and large nuclei. These cells sometimes proliferate into the lumen, and may occur in solid clumps. The associated inflammatory infiltrate consists of lymphocytes, sometimes lymphoid follicles, and there are varying numbers of eosinophils. At least in some cases there may be an underlying associated arteriovenous malformation [24]. In typical Kimura's disease there is more prominent lymphoid hyperplasia.

Clinical features. The dermal form commonly affects the pinna, external auditory meatus (Fig. 65.13) and postauricular area. The lesions are red-brown papules or nodules. Occasionally, they itch and can be painful or pulsatile [23]. The condition mainly affects young to middle-aged adults, and in some series there is a female preponderance [25].

Kimura's disease has been reported as involving the

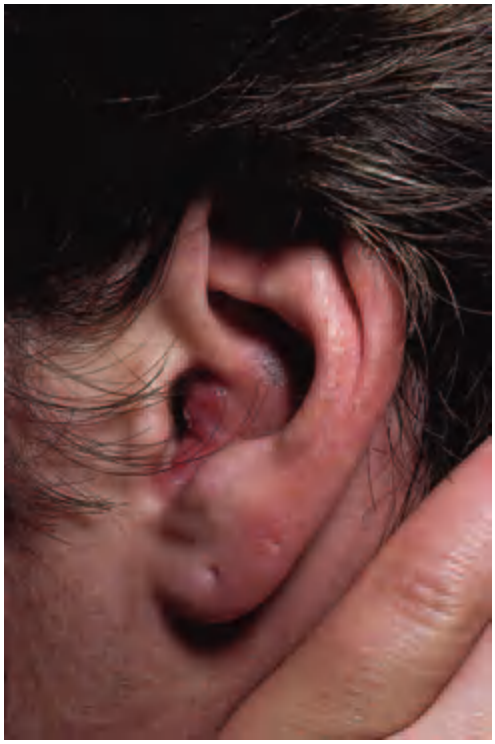

Fig. 65.13 Angiolymphoid hyperplasia with eosinophilia. Firm red-brown nodules at the entrance to the external auditory canal.

ears [26,27] but more commonly produces subcutaneous, lymph node and salivary gland-related masses in the head and neck.

Differential diagnosis includes pyogenic granuloma (rare at this site), bacillary angiomatosis and angiosarcoma.

Treatment. The treatment of choice is surgical excision, although there is often recurrence. Intralesional corticosteroids, pulsed dye laser [28], radiotherapy or oral immunosuppressive agents have been used in some cases with benefit.

Skin reactions to osseo-integrated implants

Restoration of the pinna following traumatic loss or congenital absence may be achieved using an osseo-integrated skin-penetrating titanium fixture. About 10% of such patients have skin reactions [29,30]. The reaction consists of erythema and crusting, sometimes with significant infection, which should be adequately treated.

Elephantiasis of the external ears

Chronically red swollen ears may occur for a number of reasons, including long-standing eczema, psoriasis [31] and chronic streptococcal infection. Long-standing head louse infection has also been reported as a cause [32].

Psychocutaneous disorders

Dermatitis artefacta and delusions of parasitosis (see Chapter 65) may occasionally result in self-induced lesions on the ears and even in the ear canals.

Granuloma faciale

The ear is an occasional site for this distinctive disorder [33].

Bullous diseases

Pemphigus, pemphigoid, dermatitis herpetiformis and epidermolysis bullosa aquisita may all involve the ear, and occasionally the auditory canal. Blistering of the pinna and stenosis of the canal can occur in dystrophic epidermolysis bullosa [34].

Verruciform xanthoma

This uncommon condition is typically found in the mouth but has been reported on the ear, where it can mimic squamous cell carcinoma [35].

Adult-onset xanthogranuloma

Symmetrical yellow-red nodular lesions with the same histology as juvenile xanthogranuloma have been described on the earlobes [36].

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Systemic disease and the external ear

Many conditions described more fully elsewhere will occasionally present on the external ear with lesions of diagnostic value.

Granulomatous disorders

These include sarcoidosis [1,2], especially the lupus pernio variety. Metastatic Crohn's disease may rarely involve the ear [3]. Atypical facial necrobiosis may involve the ear, as well as the more typical location on the face and scalp. Wegener's granulomatosis can present with serous or suppurative otitis and conductive or sensorineural deafness [4,5]. A similar allergic granulomatosis affected both ears in a young black South African who died from glomerulonephritis [6]. Infective granulomatous diseases involve the ear, notably leprosy, in which the earlobe is a valuable site for taking smears [7]. Lupus vulgaris, other manifestations of tuberculosis, atypical mycobacterial infection (e.g. *Mycobacterium marinum* from swimming-pool injuries), deep fungal infections and even syphilis [8] can involve the ear.

Collagen vascular diseases

As well as discoid lupus, subacute cutaneous lupus erythematosus and systemic lupus erythematosus may also involve the ears. Scleroderma can produce pallor and telangiectasia of the auditory canal. Rheumatoid disease is characterized by nodules, which can occur on the ear, where they may ulcerate due to pressure from the pillow or spectacles. Redness, tenderness and swelling of the ear, but sparing the lobe, is characteristic of relapsing polychondritis (see Chapter 46).

Pyoderma gangrenosum

The ear is an occasional presenting site [9] for this primary ulcerative disorder, discussed in Chapter 49. Vasculitis and factitial disease may be mimicked.

Metabolic disorders

Xanthomas occasionally occur on the ears, presenting as yellow nodules. Gouty tophi frequently involve the pinna (Fig. 65.14), and may antedate the onset of joint disease or

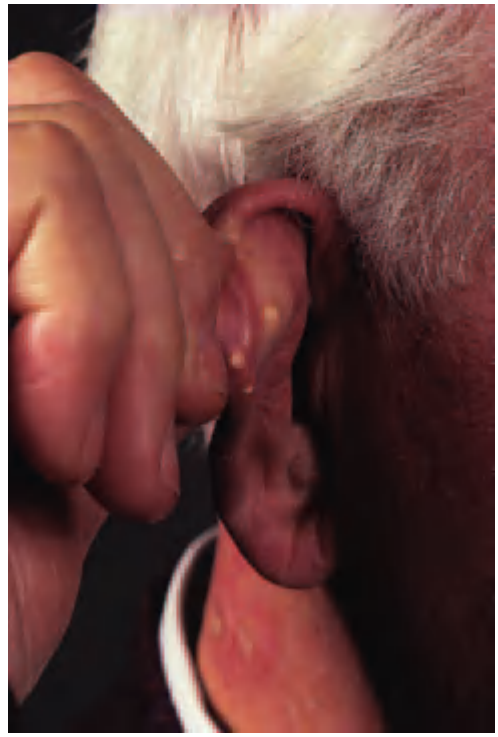

Fig. 65.14 Gouty tophi. Yellowish dermal nodules.

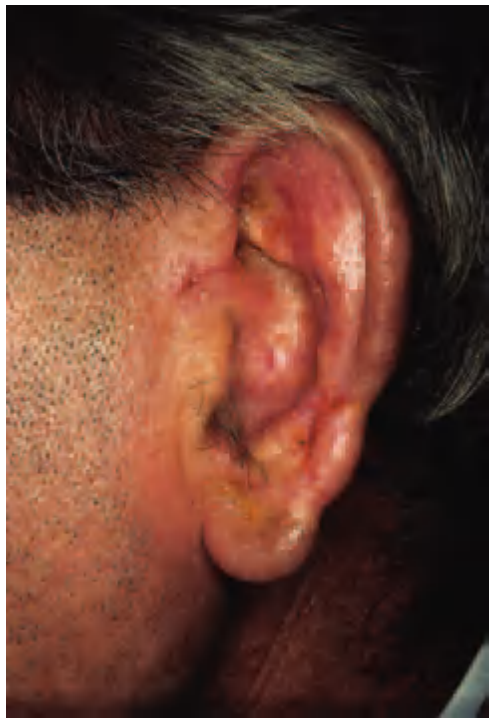

Fig. 65.15 Porphyria cutanea tarda. Firm, whitish, sclerodermoid changes at the site of repeated blistering.

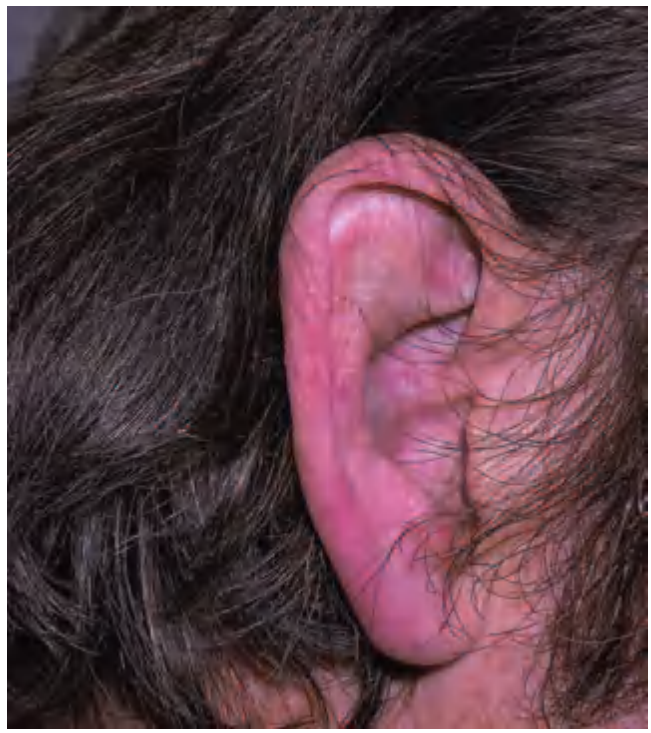

Fig. 65.16 Alkaptonuria. The auricular cartilage has a distinctive blue colour. (Courtesy of Dr P. Hollingworth, Southmead Hospital, Bristol, UK.)

appear decades after the initial attack. The helix and antihelix are typical sites. Histology is distinctive. Porphyria cutanea tarda (Fig. 65.15) may present with vesicles and bullae, often on a background of scarring, hyperpigmentation, milia, sclerodermoid plaques and hypertrichosis. Pseudocysts of the auricle and perichondritis may be simulated [10].

Diseases of connective tissue

Cutis laxa may result in distinctive pendulous earlobes [11].

Alkaptonuria

SYN. OCHRONOSIS

This is typically associated with a bluish discoloration of the auricular cartilage due to oxidation of bound homogentisic acid (Fig. 65.16). The cerumen in such patients may be very dark, a finding that can precede other clinical manifestations.

Calcium deposition

Calcium deposition may occur in many circumstances (see Chapter 57) and occasionally the ear is involved. The so-called petrified ear has been described in association with diabetes mellitus [12]. Usually, calcium deposits in the ear occur for local reasons, for example degenerative changes in the cartilage. In infants, congenital nodular calcification of Winer should be considered [13].

Endocrine disorders

In Addison's disease, the pigmentary changes may involve the ear, and ossification of the auricular cartilage may occur [14]. In acromegaly, there is usually enlargement of the auricular cartilage and coarsening of the overlying skin.

Paraneoplastic syndromes

Bazex's syndrome (acrokeratosis paraneoplastica) (see Chapter 59) commonly affects the ears and is an important marker for internal malignancy [15].

Drug-related effects

Purpura of the ears has been described in a series of children receiving levamisole for nephritic syndrome [16]. Both vasculitis and thrombotic changes occurred, and there was an association with circulating autoantibodies.

Hypertrophy of the retro-auricular folds may be seen as a consequence of phenytoin therapy [17]. Hypertrichosis of the ear canal due to minoxidil therapy can be a predisposing factor for external otitis [18].

Lymphoma

Systemic lymphoma can occasionally present as an isolated lesion on the ear [19].

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Infection

The anatomy of the ear, with its many folds and the semi-occluded nature of the external auditory canal, make it particularly susceptible to intertriginous infection, especially with Gram-negative organisms. The close anatomical relationship between the middle and external ear means that infections can pass relatively easily from one to the other, and the eardrum should always be examined. The cartilaginous and bony structures close to the skin are particularly vulnerable to infection. Although chondritis and perichondritis may have other causes, they are included in this section.

Infections of the pinna

Staphylococcus aureus, alone or in association with group A β-haemolytic *Streptococcus*, may cause impetigo contagiosum of the ear. This is a relatively common site for infection in infants and young children. *Staphylococcus aureus* is also the most common causative organism of furuncles (boils) and carbuncles, which are more common in the external auditory canal than on the pinna. Cracks and fissures around the auricle are often the portal of entry for β-haemolytic streptococcal infection manifesting as erysipelas. This is more common in the elderly, the newborn and those suffering from malnutrition, disability, alcoholism, diabetes or immune deficiency states.

Erysipelas typically begins with high fever and constitutional upset, including malaise, vomiting and headache, and there is rapidly spreading erythema and oedema from the pinna on to the face. There is often lymphadenopathy. Recurrent attacks of cellulitis of the face may have the same predisposing factors as at other body sites. Recurrent attacks of cellulitis lead to fibrosis and lymphoedema. Treatment of erysipelas and cellulitis is discussed in Chapter 27.

Necrotizing fasciitis has rarely been described arising from an initial infection of the pinna [1].

The term *infective eczematoid dermatitis* is still used for an oozing, crusted, eczematous condition occurring on and often below the pinna in association with chronic discharge from the ear. Coagulase-positive staphylococci are the most frequently isolated bacteria. The ear canal is oedematous and erythematous, and purulent discharge may be seen coming from a perforated tympanic membrane. The condition should be differentiated from impetigo, secondarily infected contact dermatitis, seborrhoeic dermatitis and atopic dermatitis.

Treatment. Primary infection of the ear must be treated appropriately, usually with a systemic antibiotic; any associated chronic otitis media or mastoiditis is likely to be managed by an otologist. Involved skin can be cleansed with saline, 1 in 10 000 potassium permanganate or dilute aluminium acetate soaks and then treated with a topical steroid. Surgical intervention will be required for necrotizing fasciitis.

Perichondritis and chondritis

Inflammation of the cartilage itself (chondritis), or more commonly the vascularized lining (perichondritis), can be indistinguishable from infection of these structures, and infection is a common complication whatever the cause [2,3].

Aetiology. There are many causes, including physical trauma (Fig. 65.17), thermal and chemical burns, frostbite, pressure (e.g. from tight headphones and head-dresses [4]) and ear piercing (see p. 65.8) including acupuncture [5,6]. Perichondritis may occasionally follow superficial

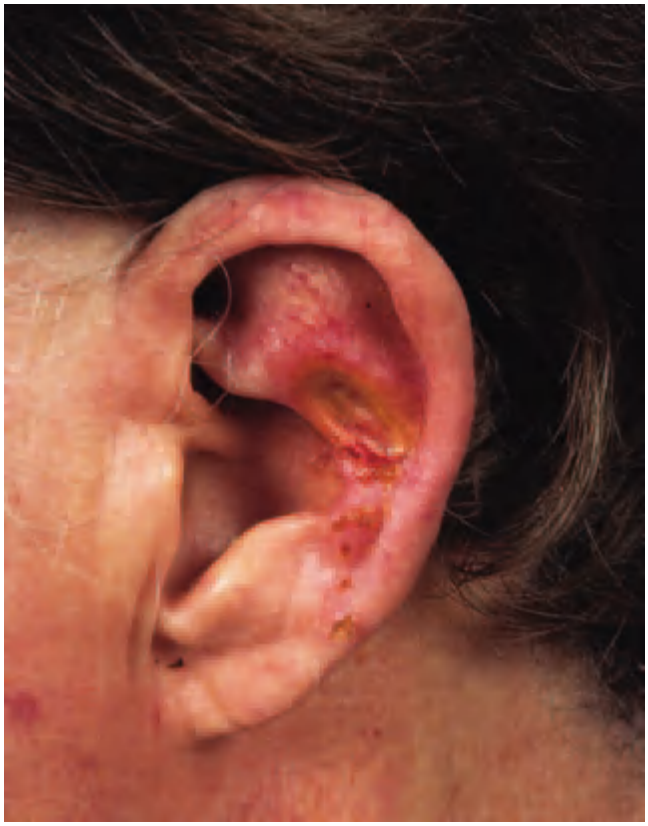

Fig. 65.17 Pressure ulcer exposing cartilage, a potential cause of chondritis.

infections of the ear such as furunculosis or otitis externa. The most common infecting organism is *Ps. aeruginosa*, although other Gram-negative organisms or staphylococci may at times be responsible.

Clinical features. Chondritis and perichondritis are typically painful. The pinna becomes hot, painful and swollen, with loss of normal contour due to oedema, and there may be accumulation of pus in the subperichondrial layer. Constitutional symptoms are common. The inflammation can spread back to the adjoining face. The destruction of cartilage results in deformity of the ear, which may be severe. Necrotizing fasciitis can follow perichondritis of the pinna [1], and if suspected must be treated by urgent débridement.

Diagnosis. Perichondritis may be difficult to distinguish from cellulitis, although perichondritis is usually more painful and does not involve the lobule of the ear, which lacks cartilage. Relapsing polychondritis (see Chapter 46) usually also involves cartilage at other body sites, and is often recurrent.

Treatment. Treatment should be instituted promptly. If an abscess has developed, early drainage is necessary. Ciprofloxacin or other quinolones are probably the treatment of choice [7,8]. Necrotic cartilage may subsequently need to be excised, and fluid collections aspirated.

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Other bacterial infections of the pinna

Mycobacterial infection can rarely involve the external ear. Lupus vulgaris can produce extensive destruction [1] and mimic other conditions [2]. Secondary involvement from underlying lymph-node disease (scrofuloderma) can present with hearing loss, tinnitus and peri-auricular lymphadenopathy, with only minimal secretion in the ear canal [3].

Atypical mycobacteria that may involve the ear include *M. marinum* acquired from swimming-pool injuries.

In leprosy, the ear is almost always involved in the lepromatous type, and there may be evident infiltration of the skin. The earlobe is often used for taking smears [4].

Syphilis may occasionally involve the ear, usually in the secondary stage [5].

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Viral infections

Herpes simplex occasionally involves the ear. It is often transmitted during contact sports such as rugby and wrestling. Herpes zoster may present as an isolated herpetiform eruption of the external ear or may be associated with ipsilateral facial palsy and auditory symptoms (Ramsay–Hunt syndrome; geniculate herpes). The condition usually begins with pain and may initially be

mistaken for erysipelas. Vesicles usually appear on about the fifth day and involve the pinna, the external auditory meatus and, rarely, the tympanic membrane. There is usually malaise, pyrexia and lymphadenopathy. Facial palsy, when it occurs, is usually transient, but more severe and persistent cases do occur. Taste and lacrimation may also be affected. Compression damage to the VIIIth cranial nerve may lead to tinnitus, vertigo, nystagmus, nausea and deafness. Management of herpes zoster is discussed in Chapter 25. Orf affecting the ear has been described, presenting as an inflammatory nodule on the tragus [1].

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Superficial and deep mycoses

Dermatophyte fungi may rarely involve the ear, and when present can simulate granulomatous disease [1] and chondritis [2].

Pityriasis versicolor may involve the ears, but is usually easy to diagnose.

In cases of ulcerative granulomatous disease of the ear, deep fungal infections, for example sporotrichosis [3], should be considered. Biopsy, examination of smears, cultures and serological studies should enable accurate diagnosis. Deep fungal infection may prompt an enquiry for underlying immune deficiency.

Otomycosis is discussed under otitis externa.

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Infections of the external auditory canal and meatus

External otitis

SYN. OTITIS EXTERNA

Otitis externa [1] is a loose term that embraces more than one disease process. Aetiologically, it is rarely unifactorial [2]; constitutional, traumatic, environmental and microbial factors usually coexist. The condition is characterized by inflammation of the canal epithelium and by varying degrees of pain, itch, deafness and discharge. The term 'external otitis' sometimes includes furunculosis of the ear canal, and is then subclassified as acute localized external otitis; furunculosis is described separately below.

Pathogenesis. Otitis externa can be divided, for convenience, into two main groups [3]: (i) a *reactive* group consisting of patients suffering from eczema, psoriasis or seborrhoeic dermatitis; and (ii) a predominantly *infective* group in which either bacteria or fungi are involved. However, the two components often coexist. The cause in many cases is not apparent [4] but the following predisposing factors appear to be important.

Genetic and constitutional. There are significant racial and individual differences in susceptibility to otitis externa. This may be due to anatomical differences in the curvature of the external auditory canal or narrowing of the isthmus—natives of New Guinea with wide straight canals only rarely suffer from external otitis [5]—or, possibly, to differences in the type, amount or composition of cerumen, whose waxy consistency and low pH are protective against bacteria. *Pseudomonas aeruginosa*, the commonest bacterial pathogen in external otitis, binds to cells by a lectin-mediated process, and binding occurs more in individuals expressing blood group A on their epithelial cells [6].

Abundant tragal hair or plugs of wax and debris increase the relative humidity and reduce ventilation of the external auditory canal so that the canal epithelium becomes macerated and more susceptible to infection. Hypertrichosis of the canal due to minoxidil has been associated with external otitis [7]. Dental abnormalities and poor mastication [8] may also retard expulsion of wax and epithelial squames.

The atopic and seborrhoeic states predispose to external otitis not only by interfering with the integrity of the auricular epithelium but also by encouraging scratching and secondary infection. Both too much and too little cerumen and alterations in skin pH have at times been held responsible [9].

Environmental. Heat, humidity and moisture are undoubtedly important in 'hot-weather ear' or 'swimmer's ear' [10]. This condition is common, especially among white people in tropical and subtropical regions. High temperature, high relative humidity and swimming [11] all encourage maceration and secondary bacterial or fungal infections of the canal epithelium. Freshwater swimming appears to be a particular risk factor [12]. Failure to dry the ears completely after swimming, shampooing or showering may also be a factor in some cases [4].

Traumatic. Trauma, in the opinion of many investigators [2,11,13,14], is one of the prime factors in both the initiation and the persistence of many cases. In one series of 113 patients, 58 admitted using wool-tipped matches, two admitted using bare matches and seven used hairgrips to relieve itching [2]. Patients suffering from eczema or those with neurodermatitis tend to scratch, rub or

'fiddle' with their ears; other patients appear obsessed about cleaning their ears and by doing so excessively they interfere with the normal homeostatic and self-cleaning properties [15]. Impacted cerumen may cause irritation, which is often increased by inexpert attempts to remove it; pressure from hearing aids and transistor ear pieces may also cause irritation and, especially with the 'internal' hearing aid, a combination of pressure and occlusion often leads to the development of external otitis.

Bacterial and mycotic infection. The epidermis of the external auditory canal is normally fairly resistant to infection. The bacterial flora, although varying with race, geography and season, tends to resemble that of the skin but with a higher likelihood of finding *Ps. aeruginosa* [16]. In hot humid environments, however, and particularly among swimmers, whose ears are habitually wet, the incidence of *Ps. aeruginosa* and other Gram-negative infections rises substantially [17,18] as does the frequency with which *Aspergillus* or *Candida* species are isolated [13]. An outbreak of *Pseudomonas* otitis has been reported in association with contaminated pool water [19] but a source has rarely been found in other series, and it is assumed that *Pseudomonas* infections are of endogenous origin.

In more temperate climates, *S. aureus* is often isolated. This may be associated with evidence of skin disease elsewhere or with staphylococcal carriage. Certainly, patients with recurrent staphylococcal otitis externa should have nasal and perianal swabs sent for bacterial culture; occasionally it may be necessary to swab and 'destaph' the whole family. In other cases, there may be an underlying tympanic perforation or coexistent otitis media. The eardrums should therefore always be examined, especially in patients with unilateral or recurrent disease. Occasionally, infection spreads out from the ear canal and causes impetigo or infective eczema of the auricle and surrounding skin.

In the tropics, mycotic infections of the external ear canal are relatively common [20,21]. *Aspergillus*, *Candida*, *Penicillium* and *Mucor* spp. are the organisms most often incriminated, most cases being due to either *Aspergillus niger* or *Candida albicans*. There is some debate, however, as to whether these fungi are pathogenic, opportunistic, saprophytic or simply commensal [21–24].

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Histopathology [1–4]. In most cases of external otitis, there is acanthosis, elongation of the rete ridges and an increase in orthokeratosis and parakeratosis. Spongiosis occurs in eczematous and seborrhoeic forms. The nature of the dermal infiltrate varies with both cause and chronicity. The histopathology is seldom diagnostic except when fungal mycelia are seen.

Clinical features. The condition can be acute, subacute or chronic. In patients seen at hospital, it tends to be severe, chronic or chronic relapsing, but in the community it is less severe and recalcitrant [5,6].

Mild attacks may present with pain or itching without discharge and with a minimally congested or swollen meatus. The degree of irritation or discomfort is often out of all proportion to the appearance. This stage probably represents early damage to the meatal skin [7]. Most cases of this type will resolve with simple therapeutic measures, but a minority, perhaps due to trauma, secondary infection or failure to keep the ear dry and clean, progress to more severe disease.

Fully developed acute external otitis (diffuse otitis externa) is characterized by a sudden onset of ear pain, itching, a sense of fullness or stuffiness if there is significant oedema, and a variable degree of hearing loss. The

otalgia is often exacerbated by jaw movements. With progression, there is usually drainage of malodorous pus, which tends to be bluish-green in colour if *Ps. aeruginosa* is the dominant infecting organism. Examination shows erythema and swelling, which may spread from the external auditory meatus to involve the concha or beyond. The external auditory canal shows erythema and oedema, and there is macerated debris and perhaps greenish pus present. In severe cases, inflammation can extend to involve the tympanic membrane. Hearing loss is due to oedema of the canal, and this may be sufficient to obscure vision of its full length. Traction on the pinna to examine the canal and pressure over the tragus characteristically elicit pain. There may be associated fever, malaise and regional lymphadenopathy.

It is important to gently remove debris in the process of a full examination, and to try to determine whether the disease is secondary to otitis media and whether or not the tympanic membrane is intact.

Bullous external otitis [8] is an uncommon variant in which there is a sudden onset of severe pain followed by discharge of blood from the ear canal. Bluish-red haemorrhagic bullae are visible on the osseous canal walls.

In granular external otitis the lining of the meatus and canal is replaced in part or whole by granulation tissue, which can project inwards as pedunculated masses. These are usually found near the tympanic membrane, arising from the osseous end of the canal. Granular external otitis is associated with a severe or neglected course [9,10].

The term 'chronic external otitis' is sometimes used for cases that have had persistent symptoms for more than 2 months [11]. Microbiological assessment has shown a significant organism in 82% in one series: *S. aureus* in one-third, *Pseudomonas* in one-third and various other Gram-negative and Gram-positive organisms in the remainder. In addition, 17 of the 99 patients had fungal disease alone [12]. There is often a dry canal due to lack of cerumen. It is likely that in most cases of chronic otitis externa, particularly when treatment has been used for the acute attack and symptoms have continued, concurrent dermatological disorders are present (Fig. 65.18). Patients in whom the disorder behaves in a recalcitrant manner may have an underlying systemic disease such as acquired immune deficiency syndrome (AIDS), malnutrition or uncontrolled diabetes mellitus; poor therapeutic response is also seen in patients treated with high-dose steroids or chemotherapeutic agents [13].

Seborrhoeic dermatitis, atopic dermatitis and psoriasis usually occur only at the meatus but may sometimes extend further into the canal. Seborrhoeic otitis externa is extremely common and has been regarded by some dermatologists as the basis for most cases of otitis externa. The symptoms and signs, however, are normally mild unless complicated by secondary factors and usually consist of no more than superficial scaling and a little discomfort or itching. Signs of pityriasis capitis or seborrhoeic dermatitis elsewhere are usually present. The condition may deteriorate at times of stress or fatigue. Secondary bacterial infection is common. In this 'reactive' group the appearance is often that of a dermatitis spreading into the ear, in contrast with those cases with a primarily 'infective' aetiology where infection and/or inflammation often appears to be spreading out from the ear and where the entire length of the canal is often affected. The clinical appearance, however, is often non-diagnostic.

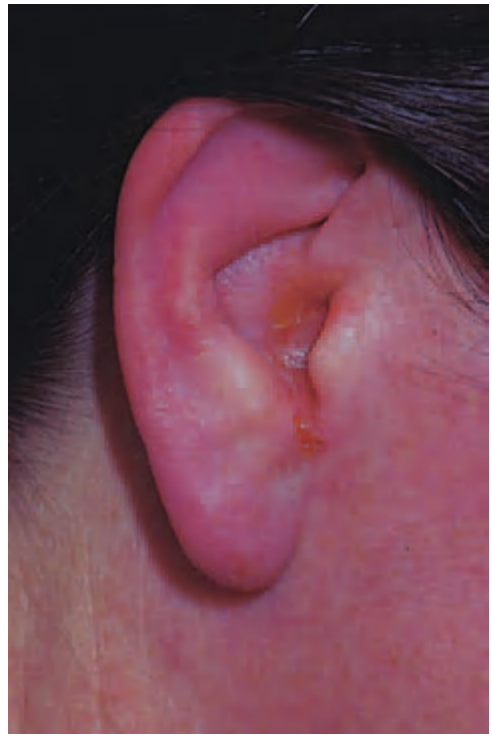

Fig. 65.18 Chronic otitis externa in an atopic patient with a history of recurrent streptococcal infection and resultant lymphoedema contributing to narrowing of the canal.

In infective eczema there is usually intense pruritus associated with exudate. The condition may complicate both otitis media and otitis externa and is usually associated with some degree of otorrhoea. In others it appears to develop from seborrhoeic dermatitis that has become secondarily infected. The condition may affect the meatus, concha, lobe and peri-auricular skin and often spreads widely. The post-auricular fold is commonly affected. The symptoms and signs are those of eczema with an accompanying or preceding aural discharge. In seborrhoeic individuals, other areas may be involved at the same time. Fissures and cellulitis are common complications.

Contact dermatitis is often occult [14] and easily overlooked. Sensitivity to topically applied medicaments is common in chronic otitis externa. Occlusion, the recurrent nature of the disease and frequent use of antibiotics on an already damaged skin probably account for the high

incidence of contact dermatitis at this site. Other sensitivities include nickel from hair pins, metal implements, chromate and phosphorus sesquisulphide in matches, and nail varnish. It is characteristic that the degree of itching and burning is often markedly out of proportion to the amount of erythema and oedema present. Contact dermatitis may also rarely occur with ear moulds [15]. Clinically, it is often difficult to differentiate neurodermatitis from contact dermatitis.

Lichen simplex (neurodermatitis) may be localized to one area of the meatus or may occur more diffusely over the tragus, triangular fossa and adjoining skin. The condition is usually diagnosed by the history rather than the signs. Itching is intense, but often intermittent. The need to scratch or rub is compulsive, although often denied. Signs of inflammation are often minimal, but some degree of oedema and scaling is common. Complications from trauma, infection and sensitization are frequent. Intermittent itching of the external auditory canal (non-specific external otitis [2]) can also occur, irregularly and over a long period, without any obvious cause and with minimal signs of disease.

Whatever the primary aetiology, with the passage of time chronic external otitis becomes an increasingly complex diagnostic and therapeutic problem.

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Differential diagnosis. The part played by trauma, environment, infection, sensitization and altered physiology and anatomy must be assessed and evaluated as accurately as possible. Difficulties often arise in the interpretation of bacteriological and mycological findings. 'Hearing-aid dermatitis' is more often due to traumatic and physical factors than to allergic sensitivity. Sensitivity to topical antibiotics may be occult, especially when they are prescribed in combination with corticosteroids, and are one cause of chronicity. Contact hypersensitivity to aural treatments (see below) may produce eczema that extends onto facial skin anterior to, or below, the ear. The importance of perineal and nasal transfer of infection should not be underestimated, and mechanical interference with the external auditory canal in patients with otitis externa tends to be the rule rather than the exception.

External otitis is unlikely to be confused with any other condition except perhaps psoriasis and eczema, and these, of course, may coexist. Middle-ear disease, past and present, should always be excluded.

Swabs should be taken for bacteriological culture and epithelial debris examined and sent for mycological culture. Potassium hydroxide preparations showing evidence of epithelial invasion with hyphae are probably more important in this respect than a positive culture, which may simply indicate commensal or saprophytic infection.

In any long-standing or resistant case, patch testing with a special 'ear battery' [1] should be undertaken to rule out unsuspected contact dermatitis. If there is excess granulation, middle-ear disease should be ruled out, and if the patient is diabetic, debilitated, very young, elderly or immunosuppressed, malignant otitis externa must also be excluded.

Another condition that may need to be considered is *bullous myringitis*, an uncommon condition probably due to upper respiratory tract viral infection (e.g. influenza), which presents with single or multiple bullae on the tympanic membrane and adjacent canal wall. It can resemble bullous external otitis, which is usually due to *Pseudomonas*. Sudden severe pain is a feature, but this resolves rapidly after rupture of the bullae. Furuncles of the external auditory canal are described below. Other bacteria may be a rare cause, for example gonococcal otitis externa [2].

Complications. Recurrent otitis externa may also develop into hypertrophic otitis externa or localized elephantiasis nostra [3] of the ears as a result of the effects of chronic lymphatic obstruction. The resultant narrowing of the external acoustic canal coupled with the underlying lymphoedema makes recurrent and repeated infections even more likely.

Secondary trauma. Once an irritable focus occurs in the canal, energetic attempts to remove wax or debris or to satisfy the urge to rub or scratch the infected area often intensify the inflammation. Cotton buds, although frequently regarded as safe, are a common cause of tympanic perforation [4].

Secondary sensitization. This is usually a consequence of treatment or a reaction to objects placed in the ear to

alleviate itching. Therapeutic agents may therefore enhance and perpetuate the condition for which they were prescribed. Penicillin, neomycin, framycetin (Soframycin) and chloramphenicol are all well-known topical sensitizers, but even gentamicin, Vioform (chinoform), polymyxin and bacitracin may sensitize at times [1]; allergy to topical corticosteroids used in the ear may also occur [5]. Allergy to topical medicaments is found in as many as 40% of patients with chronic or treatment-resistant otitis externa [1,6]. In only about 20% of cases is there improvement after discontinuing topical agents to which patients have been shown to be allergic [5].

Sensitivity to nail varnish may be misconstrued as lichen simplex and, in women who are nickel sensitive, otitis externa may be aggravated by using metal objects to alleviate itching or to clear the ear. Otoscopes themselves may release nickel. Another source of contact dermatitis is chromate [7] or phosphorus sesquisulphide in match heads, which some people use to scratch their ears.

Benign non-necrotizing otitis externa. This usually presents as chronic, non-painful otorrhoea with an ulcer present in the floor of the external canal. Surgery may be a better alternative than long-term medical management [8].

Allergic and 'ide' reactions [9,10]. A few well-documented cases have been reported in which recurrent pruritus, oedema and scaling of the ear canal have occurred in response to fungal infection at a distant body site, or associated with food or drug allergies. Some such cases also have an 'ide' reaction affecting the hands or other areas.

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Treatment [1]. The general principles of treatment of otitis externa are to relieve pain, reduce itching, prevent trauma and avoid known or potential sensitizers. Significant infective organisms should be identified and treated appropriately.

Many mild cases of otitis externa will respond to simple aural toilet, optimally with careful suction and under direct vision, followed by the use of an acidifying and drying agent. Moderately severe cases are likely to require antibiotic or antiseptic drops.

When there is coexistent eczema, combined steroid–antiseptic or steroid–antibiotic drops or wicks can be used. It should be noted, however, that many of the common infecting organisms are frequently antibiotic resistant; swabs for culture and sensitivity should therefore be taken before prescribing topical or systemic antibiotics. When *S. aureus* is the infecting organism, this is increasingly likely to be methicillin-resistant *S. aureus* (MRSA), especially when there has been recent hospital exposure [2]. In chronic cases, a great variety of treatments will already have been given and medicament contact dermatitis will therefore be more likely. Because this is often occult, patch testing should be done in all patients with chronic disease.

Pain is often severe, especially with acute staphylococcal infections, and strong analgesics may be required. Local heat also often helps. Bed rest and daily wicks or dressing may be needed in the more severe case.

If there is significant pyrexia (> 38.3°C), lymphadenopathy or failure to improve with topical therapy, an oral antibiotic should be used, for example a cephalosporin or fluoroquinolone. If pain is very severe, granulations are present in the canal or the patient is diabetic or immunocompromised, there should be suspicion for invasive (necrotizing) otitis (see p. 65.27).

Topical treatment. This is the essential part of therapy and the most difficult to carry out satisfactorily. Ear drops are of less value than regular cleaning of the ear, and this initially needs to be done daily by a doctor or an experienced nurse. Less severe cases may be treated once a week. Having cleaned the ear of debris and wax, preferably by suction under direct vision, a wick may be inserted or the patient instructed to apply ear drops regularly. When the cartilaginous portion of the canal alone is involved, the patient can be shown how to apply the prescribed medicament by holding a loose wool-tipped orange stick 2.5 cm from its end and inserting this until the fingers touch the tragus.

If wax is impacted, this can be softened with oil, glycerine or sodium bicarbonate eardrops and then removed either manually or by syringing, as long as the drum can be visualized and there is no perforation. Obstinate cases should be referred to an otologist. Some proprietary cerumenolytics are irritant and should be left in the ear for only 15–30 min before syringing.

In most chronic or complicated cases, treatment must be continued regularly for some weeks after apparent cure. Care must be taken to prevent cross-infection from other body sites, especially from the anterior vestibule of the

nose or the perineum, and the ear should be kept as dry and as clean as possible.

A very large number of medicaments have been used in the treatment of otitis externa. Alcohol 70–85% (isopropyl alcohol), 1–2% acetic acid, aluminium subacetate solution and 2% salicylic acid in 60% spirit are all safe and effective, aluminium acetate solution being especially useful against the expected pathogens [3]. If acidic ear drops cause a burning sensation, ophthalmic hydrogen peroxide drops are a practical substitute. Wicks with 8–13% aluminium acetate, 0.25–0.5% silver nitrate, or glycerine and ichthyol are used to treat hypertrophic otitis externa. Although the use of corticosteroids with or without antimicrobials is a common practice, the evidence to support their use is controversial [4]. Neomycin, framycetin (Soframycin), gentamicin and polymyxin are probably acceptable as short-term treatments for acute otitis externa but the risk of sensitization and cross-sensitization increases with more protracted usage. The combination of neomycin and polymyxin will cover both *S. aureus* and *Ps. aeruginosa*. Topical ofloxacin is as effective and only has to be used twice daily [5]. For patients with chronic or chronic relapsing otitis externa, iodochlorhydroxyquinoline (Vioform, chinoform) can be used alone or in combination with corticosteroids.

The imidazoles have largely replaced nystatin and amphotericin as antifungal agents, as they are active against *Aspergillus* as well as *Candida*, although acetic acid, boric acid and 25% *m*-cresyl acetate may still at times be useful; 2% salicylic acid in spirit is useful for prophylaxis. Several ear-drops, for example the aminoglycosides, chlorhexidine, polymyxin and chloramphenicol, are potentially ototoxic [6,7] and should be avoided in the presence of tympanic perforation.

In all cases of external otitis, treatment should be prolonged beyond the time of apparent recovery and patients should be advised how best to avoid recurrence and about the dangers of indiscriminate or prolonged self-medication.

Surgical treatments. Occasionally, chronic otitis externa is due to narrowing of the external auditory meatus. Surgical enlargement of the meatus can then bring about resolution [8,9].

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Invasive external otitis [1,2]

SYN. MALIGNANT EXTERNAL OTITIS; NECROTIZING EXTERNAL OTITIS

This is an infection of the skin of the external ear canal that spreads to deeper structures and causes necrosis.

Aetiology. In most cases, the infecting organism is *Ps. aeruginosa*, although occasionally other organisms have been involved: *S. aureus* [3], *S. epidermidis* [4], *Klebsiella oxytoca* [5], *Aspergillus* [6–10], *Malassezia sympodialis* [11], *Scedosporium apiospermum* [12] and *Actinomycetes*. The condition characteristically occurs in elderly diabetics [13–16] but is also seen with some frequency in the immunocompromised, including patients with HIV infection [1,16,17]; it has also been reported in association with diabetes insipidus [18]. Cases have been reported in children [19–21] in whom chronic illness or immunosuppression are usually present. In diabetics, microangiopathy may be important in the pathogenesis [1]. It is possible that abnormalities of cellular immunity and polymorphonuclear function are important in some cases [22,23], but in many instances the pathogenesis is poorly understood.

Pathology. In most cases, there is evidence of osteomyelitis [5]. An early event is acellular necrosis of cartilage [24].

Clinical features. Quite often there is a preceding history of irrigation of the ear. The commonest presenting symptom is pain, which is usually very severe and persistent. It may spread from the region of the ear to the vertex, temporal or occipital areas, and there may be temporomandibular joint pain. Pain progresses more quickly in children than adults. The second most common symptom is discharge from the ear. In up to 50% there is some degree of hearing loss. Systemic symptoms, including fever, are uncommon [1]. There may be symptoms due to involvement of cranial nerves, particularly dysphagia.

On examination the external auditory canal is always abnormal, with varying degrees of oedema and erythema, and extensive granulation tissue formation is evident. This is particularly seen on the posterior and inferior aspect of the wall and at the junction between the bony and cartilaginous segments of the canal. There may be swelling of the soft tissues around the ear. The tympanic membrane is frequently necrotic in children but characteristically spared in adults [21]. Cranial neuropathies may be found in up to 40% of patients [1,17]. Facial palsy is the most common finding but involvement of cranial nerves

IV, VI, VIII, IX, X and XII may be variably present. When such nerve involvement is found, the disease is more extensive.

Investigations usually show elevation of the erythrocyte sedimentation rate, but the white-cell count is often normal.

Diagnosis. Invasive external otitis is usually diagnosed on clinical suspicion. It is essential to obtain material for culture to determine the infective cause, and samples should be taken from the ear canal, granulations, soft tissue and bone, depending on the case. Blood cultures may also be valuable.

Imaging techniques can be helpful, particularly in diagnosing bony involvement and following progress of the disease, and should enable granular external otitis to be distinguished from the much more serious invasive external otitis. Plain films, computed tomography (CT), bone scans and magnetic resonance imaging (MRI) have all been used. MRI with or without gadolinium enhancement is probably the best technique for imaging soft-tissue involvement, and for evaluation of the meninges and changes within the osseous medullary cavity, although CT is preferred for the initial diagnosis and recognition of cortical bone erosion [25,26].

Complications. Spread of the disease can produce parotitis, mastoiditis or osteomyelitis of the base of the skull and thence spread to the contralateral side. Meningitis can occur, and is an important cause of death. Cranial nerve paralysis may result in aspiration pneumonia. A rare complication is destructive osteomyelitis of the temporomandibular joint [27]. Overall, there is a mortality of 10–20%; in the presence of cranial neuropathies the mortality is 70% [1,17].

Treatment. Because of the range of possible infections, it is essential to base treatment on the result of culture. For *Pseudomonas*, the traditional approach has been to use an extended-spectrum antipseudomonal penicillin for 4–8 weeks and an aminoglycoside for 4–6 weeks [1]. Ciprofloxacin [28,29] can be successful if used early in the course of disease. When there is evidence of extensive bone destruction, removal of necrotic material is necessary. Some cases fail to respond to antibiotic therapy and, if the facility is available, hyperbaric oxygen can improve the outlook [30]. Ascorbic acid has also been recorded as an adjuvant therapy [22].

When the infective cause is bacteria other than *Pseudomonas* or is a fungus, advice on the choice of antimicrobial agent should be taken from a microbiologist.

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Furunculosis

SYN. ACUTE LOCALIZED EXTERNAL OTITIS

A furuncle is a staphylococcal infection of a hair follicle [1]. A common site is between the junction of the tragus

and the anterior crus of the helix. Furuncles also may occur in the skin of the external auditory canal at the junction with the concha. Coalescence of adjacent infected follicles results in a carbuncle.

The patient presents with pain, which can be aggravated by chewing if there is involvement of the anterior wall of the canal. There may be sufficient swelling to obstruct the entrance to the canal. There is often regional lymphadenopathy and sometimes fever.

Furunculosis can usually be distinguished from external otitis by the normal appearance of the canal epithelium and an absence of discharge; the two conditions can, however, coexist. If possible the tympanic membrane should be examined, in order to exclude otitis media and mastoiditis.

Localized lesions associated with mild swelling usually respond to an oral antistaphylococcal antibiotic [1]. If an abscess or carbuncle is present, incision and drainage is usually necessary. The latter can be achieved with a wick. Any draining material should be sent for culture and antibacterial sensitivities.

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Otomycosis

Otomycosis is an inflammatory process due to a variety of yeast and fungal organisms as the primary aetiological agent. The same range of fungi may be found in patients with multifactorial or bacterial external otitis (see above).

Aetiology. The species of fungus and yeast involved vary somewhat depending on ambient climate. In most tropical regions of the world *Aspergillus* species account for the majority of isolates, whereas in temperate areas *Candida albicans* is the most frequent [1]. Others include phycomycetes, *Rhizopus*, *Actinomyces* and *Penicillium*. The fact that these organisms can be pathogenic as well as saprophytic has been confirmed in a number of studies [2–5].

The factors that convert organisms that are normally saprophytic into pathogens are similar to those that apply to bacterial external otitis. Heat and humidity are foremost, and account for the frequency of otomycosis in the tropics and in those using hearing aids or occlusive ear moulds. Diabetes mellitus, immunosuppression, systemic and topical antibiotics, and steroids are also important.

Clinical features. The principal symptom is usually itching, which can have a quality of being deep inside the ear. This is often accompanied by a sensation of fullness. Pain is uncommon, in contrast to bacterial external otitis. Discharge, if any, is usually slight. There may be hearing loss of a conductive type. Because of the irritation, patients are liable to traumatize the canal and may then initiate the symptoms and signs of bacterial external otitis. The most important complication is perforation of the eardrum [6].

On examination the dominant feature is the presence of wispy filamentous masses, which may be isolated or diffusely present in the canal. These masses are white, grey or stippled black if *Aspergillus* is present. Inflammation of the canal epithelium is usually mild. There may be some epithelial debris, which may be either moist or dry.

Diagnosis. The clinical appearance is usually distinctive. As always with external canal disorders it is important to check for other pathology. Material can be taken for mycological examination and culture.

Treatment [7]. Careful cleaning followed by drying is a prerequisite to successful management. The canal can then be wiped out, for example with *m*-cresyl acetate or 1% thymol in 70% alcohol, and the specific treatment applied on a wick. Treatment should be changed daily until a satisfactory result has been achieved. Many agents have been advocated for otomycosis, but there is little evidence to promote one above the others. They include aluminium acetate, acetic acid, *m*-cresyl acetate, thiomersal, gentian violet, clioquinol, nystatin, amphotericin and the imidazoles.

In rare situations, usually in immunosuppressed patients, there may be cellulitis of the surrounding soft tissues directly due to fungal infection. In such cases, itraconazole is likely to be the treatment of choice. Oral terbinafine has also been used when other treatments have failed [8].

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AIDS and the external ear

The consequences of HIV infection will at times be seen on the pinna and in the external auditory canal [1]. The ear is a relatively common site for manifestation of Kaposi's sarcoma. Florid seborrhoeic dermatitis is often a presenting feature of AIDS. The occurrence of molluscum contagiosum lesions in an adult should prompt a suspicion of immunodeficiency; on the ear the lesions can resemble

basal cell carcinoma. Bacillary angiomatosis may produce vascular papules and nodules on the ear. Herpes simplex and zoster can be more florid in patients with AIDS. Polyps in the external auditory canal due to *Pneumocystis carinii* have been described [2] and can invade the middle ear and middle cranial fossa [3]. Invasive external otitis (see p. 65.27) is a well-recognized consequence of HIV-related immunosuppression [4]. Excessive growth of ear hair has been noted [5].

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Tumours of the pinna and external auditory canal [1]

Benign tumours

On the pinna, these will present as papules or nodules, sometimes with distinctive morphology. In the external auditory canal, benign tumours tend to present with hearing loss and may predispose to infection [2].

Benign tumours found on the pinna include melanocytic naevus, seborrhoeic keratosis (Fig. 65.19), squamous cell papilloma, pilomatrixoma [3,4], trichoepithelioma [5], trichofolliculoma [6,7], Winer's dilated pore [8], myoma, chondroma, osteoma, fibroma [9], neurofibroma [10], neurilemmoma [11], granular cell tumour, haemangioma (Fig. 65.20) and lymphangioma [12]. Benign glandular tumours may occur on the pinna, but are more common in the canal, especially sebaceous adenoma. Occasional unique lesions have been described [13].

Benign mass lesions in the canal include exostosis and osteoma, fibrous dysplasia both monostotic and polyostotic (Albright's syndrome), eosinophilic granuloma, cholesteatoma and keratosis obturans (see p. 65.36), benign ceruminous gland tumours (see p. 65.31) and temporomandibular joint herniation [14].

Papillomatosis of the external auditory canal presents with multiple rounded papules; it has been associated with human papillomavirus (HPV) 6 [15].

Extra-adrenal paraganglioma (glomus jugulare tumour) of the temporal bone can manifest in the external ear canal as a friable haemorrhagic neoplasm and can cause conductive hearing loss [1]. This tumour can be locally aggressive, and there are rare instances of metastasis.

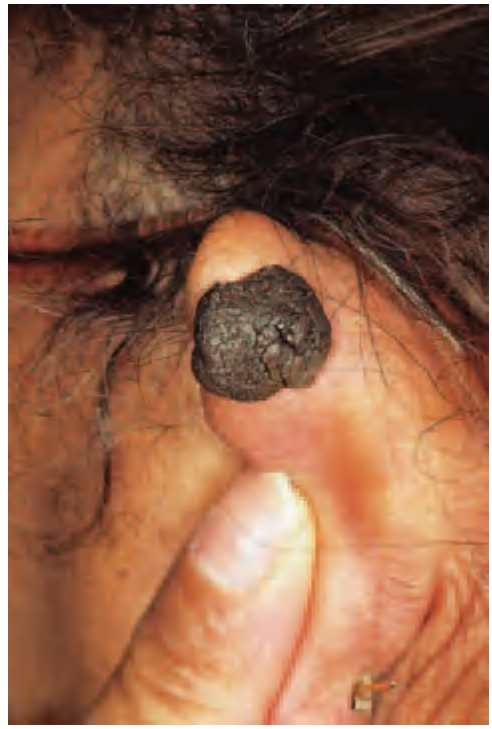

Fig. 65.19 Seborrhoeic keratosis (basal cell papilloma) of the pinna.

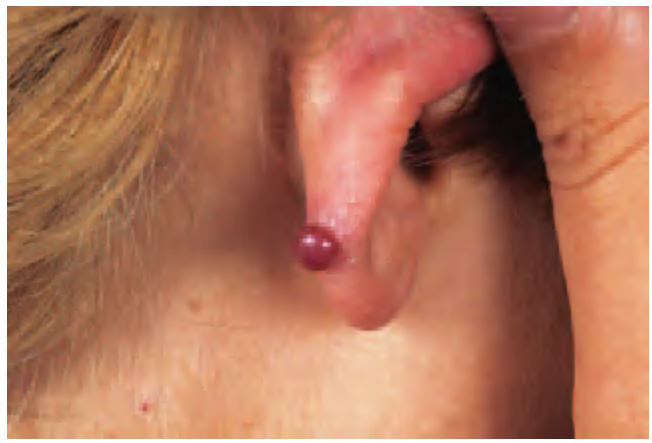

Fig. 65.20 Lobulated capillary haemangioma (pyogenic granuloma). A bright-red nodule with a surrounding collarette of keratin.

Various conditions can mimic benign tumours. On the pinna, these include cysts of various types, viral warts and molluscum contagiosum, chondrodermatitis, elastotic and weathering nodules, keloids, congenital malformations such as accessory tragi, nodular calcinosis [16], gouty tophi, deposits of amyloid, angiolymphoid hyperplasia with eosinophilia and 'pseudolymphoma', inflammatory polyps, hamartomas [17], choristomas [18] and congenital cysts of branchial arch origin in the external auditory

canal. Cholesteatoma (see p. 65.36) may also occur in the external canal.

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Exostosis and osteoma

Exostoses of the external auditory canal are usually bilateral, symmetrical, multiple, diffuse, broadly based growths of bone arising from the tympanic bone in the external auditory canal [1,2]. Frequent exposure to cold water is an aetiological factor in nearly all cases [3]. Exostoses are very common in surfers, especially those who have surfed for more than 10 years [4,5].

Osteomas can usually be differentiated by their solitary and unilateral distribution, although they may be similar to exostoses histologically [6]. They are often attached by a narrow pedicle to the tympanosquamous or tympanomastoid suture line [1].

Occasionally other fibro-osseous lesions are found which are neither exostosis nor osteoma [7,8].

Osteomas and exostoses are normally asymptomatic unless they enlarge sufficiently to block the external auditory canal [9]. Surgical removal may be indicated [10].

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Glandular tumours

Tumours of the ceruminous glands are rare. It is often difficult to distinguish between adenoma and carcinoma on histological grounds [1–3] and the term 'ceruminoma' [4] is probably best avoided. The tumours comprise benign and pleomorphic adenomas, adenocarcinomas, adenoid cystic carcinomas and perhaps others including mucoepidermoid carcinomas. Tumours of the cerumen glands have been reported in association with other sweat gland tumours elsewhere [5].

Isolated cases of syringocystadenoma papilliferum, apocrine cystadenoma, benign eccrine cylindroma, hidradenoma papilliferum and carcinomas of eccrine and sebaceous origin have also been reported [6,7].

Extramammary Paget's disease of the external ear and/or canal resembles Bowen's disease or a dermatosis [8].

Benign tumours produce symptoms of obstruction and hearing loss. Pain is the usual presenting feature of the more malignant tumours. They are usually seen as polypoid masses in the canal. Other symptoms include bleeding, otorrhoea and, with spread of the neoplasm, nerve palsies.

Treatment is the province of the otorhinolaryngologist. Because of the potential for malignant behaviour, all ceruminous gland tumours should be fully excised with an adequate margin of normal tissue [9].

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Premalignant epithelial neoplasms of the auricle

Because of its high level of exposure to UV radiation [1], especially in men, the auricle is a common site for premalignant and malignant lesions of epidermal origin. Other predisposing factors include prior ionizing radiation, a chronic dermatosis such as lupus vulgaris, and genetic factors such as xeroderma pigmentosum and Gorlin's syndrome.

The commonest premalignant lesion is the solar keratosis, which can occur on all sun-exposed aspects of the auricle, but is especially common on the upper surface of the helix [2,3]. The clinical presentations include an erythematous telangiectatic patch, a focal area of scaling or hyperkeratosis, or a cutaneous horn. Solar keratoses on the auricle are often multiple. Solar elastosis may be evident in the surrounding skin. On the auricle, progression to squamous carcinoma from solar keratosis may occur more readily than at other sites [4].

Other premalignant lesions include Bowen's disease, radiation and tar keratoses and, rarely, keratoacanthoma [5,6].

Treatment. Several forms of treatment can eradicate premalignant lesions from the auricle, but there are no adequate data to compare them. They include excision, curettage, electrosurgery, cryotherapy, 5-fluorouracil and photodynamic therapy. The choice will depend on a number of factors, including the need for a tissue diagnosis, size and location of the lesion, likely cosmetic outcome and the available facilities. Follow-up is important for detection of recurrences and the appearance of new lesions. Lesions closely resembling squamous carcinoma, such as keratoacanthoma, should probably be totally excised to ensure accurate diagnosis [6].

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Squamous cell carcinoma of the auricle

Although the ratio of basal cell carcinoma (BCC) to squamous cell carcinoma (SCC) is about 4 : 1 on the head and neck generally, on the ear SCC is relatively more common (BCC : SCC, 1.3 : 1) [1].

In most instances, SCC evolves from a premalignant lesion, usually a solar keratosis, and occurs predominantly in elderly white men, although at a younger age in the immunosuppressed. The most common site is the helix [2]. Early SCC may be suspected when there is induration of the base of a scaly papule, nodule or cutaneous horn. With progression, SCC usually ulcerates and with invasion of cartilage can become grossly destructive (Fig. 65.21). Local spread along perichondrial, periosteal and neurovascular planes can make SCC of the auricle very difficult to control. With the exception of the lip, auricular SCC is more likely to metastasize than is SCC at any other sun-exposed site (11% compared with 2%) [3]. There is a small but significant mortality [2,4,5]. Adverse prognostic factors for both local recurrence and metastasis of SCC include size (> 2 cm), depth of invasion (> 4 mm, Clark levels 4 and 5), perineural involvement and poor differentiation of the tumour [6]. The pre-auricular site

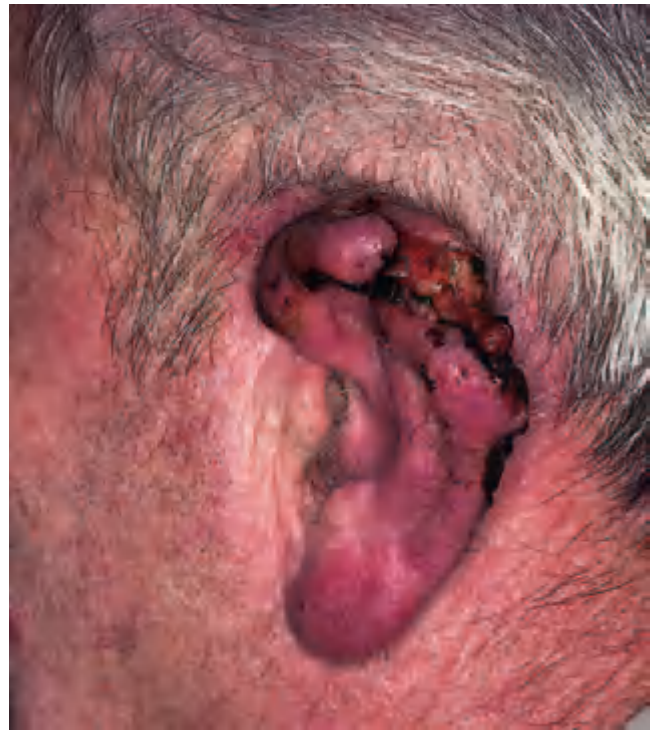

Fig. 65.21 Squamous carcinoma of the auricle. An advanced tumour with extensive destruction of the ear cartilage. (Courtesy of Mr D. Baldwin, Southmead Hospital, Bristol, UK.)

may also confer a poor prognosis [7]. It is not clear, however, to what extent these are independent variables; shallow lesions with large surface area (i.e. > 2 cm diameter) do not seem to have a poor prognosis. If SCC recurs after primary treatment, there is a much greater risk for further recurrence and metastasis [6].

Treatment. It is important to achieve control of the disease with the initial treatment for SCC. For small, minimally invasive lesions, simple excision, cryotherapy or curettage with cautery/electrodesiccation may be adequate. Excellent results have been reported from the combination of curettage and cryotherapy for carefully selected cases [8]. For larger lesions, and especially for those with adverse prognostic factors, the choice is likely to be between wide margin excision, Mohs micrographic surgery and radiation therapy.

The surgical procedure used will depend on the location and extent of the tumour. Smaller lesions can often be removed by wedge excision with primary repair by advancement flaps. Larger and ill-defined lesions are best closed by temporary grafts pending a histopathological assessment of the margins before definitive repair is carried out. Partial or total amputation may be needed for large tumours. If there is spread beyond the pinna, resection of the parotid, temporal bone, temporomandibular joint or mandibular ramus may be be required, with appropriate repair.

Several authors have recommended minimal resection margins, for example 1 cm [9], 6 mm with frozen section control [10], 8 mm for 1-cm-diameter tumours and 1.5 cm for 3-cm-diameter tumours [11], all with removal of the underlying cartilage. Overall, there is an incidence of 18.7% recurrence during follow-up for 5 years or more with non-Mohs modalities compared with 5.3% for Mohs micrographic surgery, suggesting that the latter is the treatment of choice [6,12].

SCCs in the tragal and pretragal location appear to have a greater tendency to spread along embryonic fusion planes and may only be curable by radical surgery, for example parotidectomy in association with removal of the tumour [7,13].

Various techniques are needed to reconstruct the ear after curative surgery [14–19].

Radiotherapy can be successful as a primary treatment for SCC of the auricle [20], with megavoltage electron-beam therapy having therapeutic and cosmetic advantages over conventional orthovoltage X-ray treatment [21]. There may, however, be a higher recurrence rate [22,23] compared with surgery, particularly for large tumours [2,24,25]. Radiation therapy can be complicated by damage to the cartilage and associated chronic infection; deformity of the pinna is another long-term consequence. Radiotherapy may improve the outlook for cases with extensive local spread requiring radical surgery.

The management of SCC with metastasis to regional lymph nodes and beyond is outside the scope of the dermatologist.

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Basal cell carcinoma of the auricle

BCC of the auricle is somewhat less common than SCC (Fig. 65.22). It is also mainly due to the effects of solar

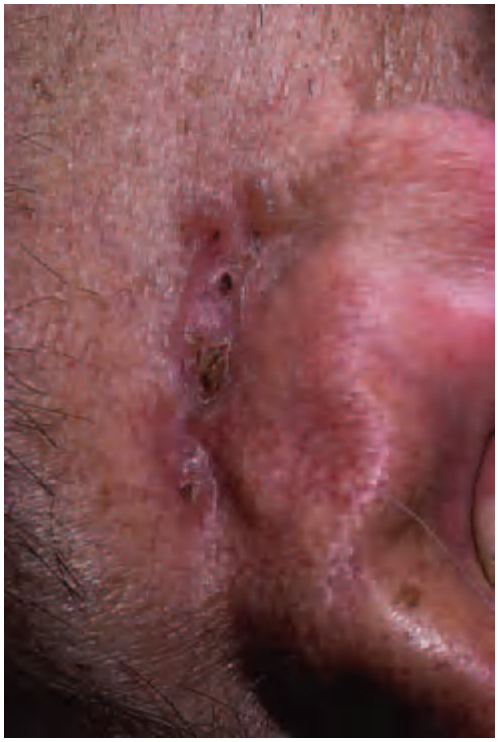

Fig. 65.22 Basal cell carcinoma. Translucent ulcerated nodules in the retro-auricular fold.

radiation, but is much less liable to metastasize [1,2]. Presentation is generally as for BCC elsewhere, although could be missed when resembling a cleft earlobe [3].

The approach to treatment is essentially similar to that outlined for SCC. Mohs micrographic surgery is the most likely modality to achieve cure with lesions that are extensive, deeply invasive or recurrent, or which have a morphoeic growth pattern.

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Squamous and basal cell carcinoma of the external auditory canal

Non-glandular carcinomas of the external auditory canal are uncommon. Most are squamous in type (Fig. 65.23). They affect a younger age group (50–65 years) and, in contrast to SCC of the auricle, there is much less of a male preponderance. A preceding history of chronic otitis is common [1,2]. Pseudo-epitheliomatous hyperplasia secondary to chronic infection or inflammation can sometimes be difficult to distinguish from SCC [3].

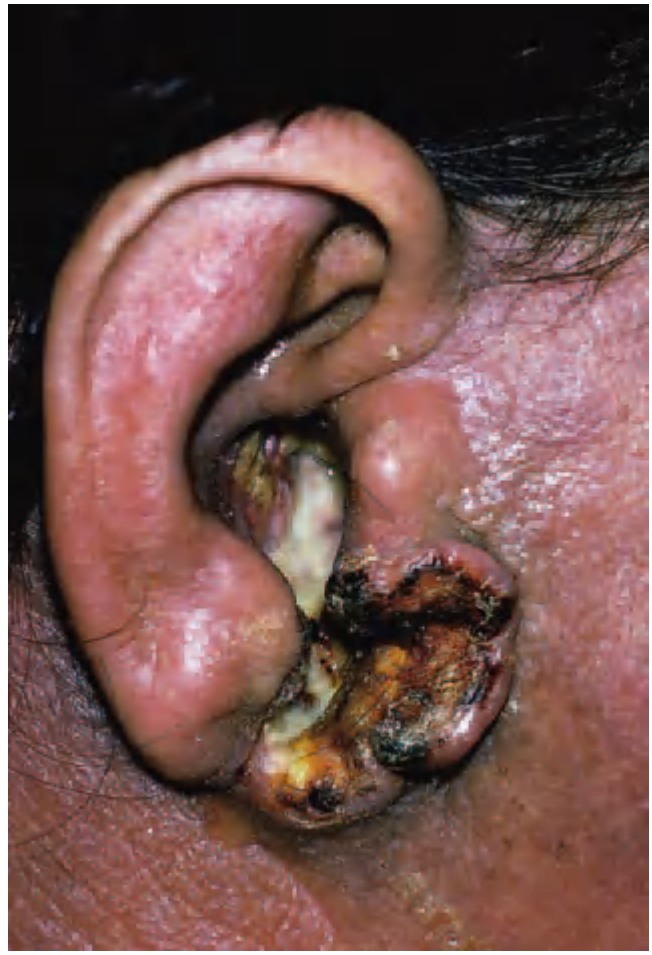

Fig. 65.23 Squamous carcinoma of the external auditory canal. Purulent discharge, inflammation and destruction of the meatus. (Courtesy of Mr D. Baldwin, Southmead Hospital, Bristol, UK.)

Most squamous carcinoma of the canal has an infiltrative growth pattern. It tends to grow along the canal, escaping anteriorly through Santorini's fissures in the cartilaginous segment and Huschke's foramen in the bony portion, into the temporomandibular joint and parotid. Spread also occurs posteriorly into the mastoid, and through the tympanic membrane into the middle ear and thence to the carotid canal, apex of the petrous temple bone, the internal auditory canal, base of the skull and the dura. Metastasis to lymph nodes and distantly is common.

Overall, there is a much poorer prognosis than for SCC of the pinna, with 5-year survival rates of about 40% [4]. Adverse factors are a large lesion, invasion of cartilage or bone, facial nerve palsy, spread to the middle ear and beyond, and lymph node metastasis. The extent of the disease can be determined accurately by CT [5]. Staging using clinical and imaging data is important for assessing prognosis and the likelihood of benefit from adjuvant radiotherapy [6,7].

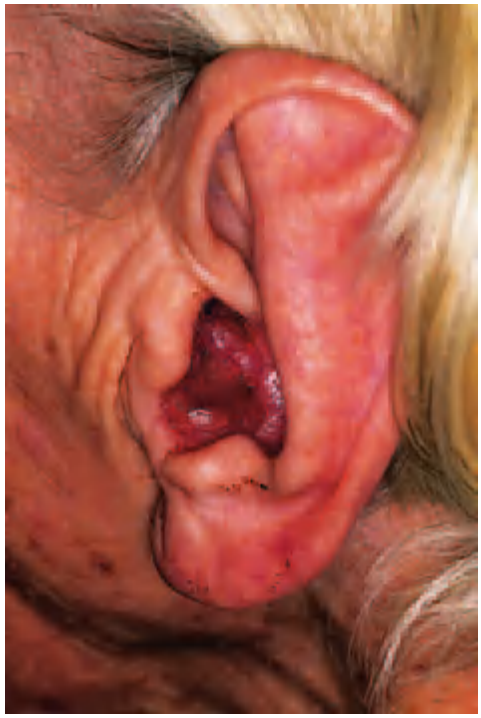

Fig. 65.24 Basal cell carcinoma of the external auditory canal. An erythematous tumour presenting as obstruction at the entrance of the canal. (Courtesy of Mr M. Birchill, Southmead Hospital, Bristol, UK.)

Verrucous carcinoma of the external auditory canal is an uncommon variant that can appear cytologically banal but nevertheless invade bone, by a pushing rather than an infiltrative growth pattern [8,9].

BCC of the external auditory canal can be locally destructive (Fig. 65.24), but does not metastasize and has a much better prognosis than SCC [10].

The most common symptoms of invasive SCC of the canal are purulent and bloody discharge from the ear, followed by pain, hearing loss and facial paralysis. Examination reveals a friable tumour, partially or completely obstructing the external auditory canal.

Treatment. Surgery has been regarded as the treatment of choice, the extent determined by an assessment of the limits of tumour growth. However, radiotherapy alone may be as effective if the disease is limited to the site of origin, i.e. there is no evidence of nerve or bone involvement [11]. Post-operative radiotherapy improves the outlook [6,7,12–15], but for lesions that have spread deeply or have metastasized cure is most unlikely.

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Malignant melanoma

Malignant melanoma of the external ear is relatively uncommon, constituting about 1% of all cutaneous melanomas [1]. It accounted for 4.8% of all auricular malignancies in one series [2] and represented 7% of all melanomas in another series [3]. Melanomas at this site are about three times more common in males than females [3,4]. Melanoma is found in a similar frequency distribution on the ear as SCC and its precursors, i.e. about half occur on the helix and one-quarter on the antihelix [3], but they are rarely found in the external auditory canal [5,6]. Most melanomas on the ear are of superficial spreading or nodular type, the latter being relatively more common than at other head and neck sites [7,8]. The major determinant for prognosis is Breslow thickness [4].

Treatment is in principle no different from malignant melanoma elsewhere (see Chapter 38), and relatively conservative excision followed by reconstruction can be safe [9]. Sentinel lymph node mapping may be valuable for accurate staging, particularly for melanoma of the ear, since its lymphatic drainage is notoriously unpredictable [10].

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Other malignant tumours

Other malignant tumours involving the external ear or the external auditory canal are all rare. The pathology is reviewed in Friedman and Arnold's monograph [1]. The dermatologist may encounter sebaceous carcinoma [2], atypical fibroxanthoma, trichilemmal carcinoma [3], Merkel cell tumour [4], Kaposi's sarcoma [5,6] or rhabdomyosarcoma (mainly in children) [7–9]. Angiosarcoma of the pinna has the same gloomy outlook as it does on the scalp [10]. Other sarcomas have been recorded but are exceptionally rare. Lymphomas may occur on the external ear [11], particularly mycosis fungoides [12]. Perichondritis can be mimicked by non-Hodgkin's lymphoma [13,14], and both lymphoma [15,16] and myeloma [17] can present with an external auditory canal tumour. The ear may be involved by direct extension from tumours nearby, for example the parotid, and also by metastases from distant sites [18].

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Miscellaneous conditions

Cholesteatoma of the external auditory canal

Cholesteatoma of the middle ear space is accumulation of keratinous debris within a sac-like squamous epithelial lining. It can grow at the expense of normal structures and if it ruptures, the associated foreign body-type inflammatory reaction can produce serious damage.

A similar condition occurs rarely in the external auditory canal, although its status as a true cholesteatoma is disputed [1,2]. The accumulation of stratum corneum occurs within a cyst-like penetration of the bony portion of the canal wall by the epithelial lining. There is localized ulceration of the skin of the floor of the canal, with underlying osteitis and sometimes necrosis of bone. A necrotic sequestrum may become incorporated into the cholesteatoma. The cause is unknown, although trauma, for example from hard wax and manipulation of the canal, seems important in some cases [3].

Cholesteatoma usually occurs in patients over the age of 40 years. Symptoms are a dull pain in one ear and otorrhoea. Examination shows a white cystic mass protruding into the canal. The main differential diagnosis is from neoplasms and keratosis obturans [4,5]. External auditory canal cholesteatoma can occasionally behave aggressively, and may erode into the mastoid cavity, middle ear, temporomandibular joint and adjacent soft tissue. CT can be useful to assess the extent of the disease. Treatment is within the province of the otorhinolaryngologist.

Keratosis obturans

In this uncommon condition there is a localized accumulation of desquamated keratin in the ear canal. It may be due to a defect in the normal epithelial migration [6]. It is usually bilateral and typically occurs in younger patients than those presenting with external auditory canal cholesteatoma, which it can resemble. There is conductive hearing loss, sometimes with otalgia. Keratosis obturans can be associated with paranasal sinus disease and bronchitis; it has also been described in association with the yellow nail syndrome [7]. Treatment consists of careful removal of the accumulated keratin. Irrigation with water should be avoided [4,5].

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Referred pain

Due to the complicated nerve supply to the ear, referred pain is commoner than pain due to lesions in the ear itself [1]. Non-otological causes of such pain include the otomandibular syndrome [2] due to dysfunction of the temporomandibular joint, cervical arthritis with involvement of the cervical nerves, tonsillitis and carcinoma of the pharynx. Hair in the ear canal is an occasional cause [3]. Psychogenic otalgia has also been reported [4].

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Chapter 66

The Oral Cavity and Lips

Crispian Scully CBE

Introduction

Oral lesions are usually the result of local disease but may be the early signs of systemic disease, including dermatological disorders, and in some instances may cause the main symptoms. This chapter mainly discusses disorders of the dental, periodontal and mucosal tissues that may be related to skin disease and that may present at a dermatology clinic. It should be borne in mind that the professionals most competent in diagnosing and treating oral diseases are dentally qualified; few without this formal training and education are in a position to understand the full complexities of the region.

The chapter is an overview only and is divided into a brief discussion of the biology of the mouth, an overview of the more common signs and symptoms affecting specific oral tissues, discussion of the disorders of the oral mucosa of most relevance to dermatology and a tabulated review of oral manifestations of systemic diseases. Diseases affecting the jaws or temporomandibular joint are not discussed in any depth.

Only the more classic oral lesions are illustrated. About 20 of the colour illustrations are from the *Colour Atlas of Oral and Maxillofacial Disease*, 1996 (reproduced by kind permission of C. Scully, S. Flint, S.R. Porter and K. Moos, and publishers Martin Dunitz, London). More detail of histology is available elsewhere [1].

Biology of the mouth

Oral epithelium

The oral epithelium consists of a *functional compartment* —the progenitor cells (basal and parabasal cells)—which is the site of cell division; a *maturation compartment* (spinous and granular cells) where the cells become more terminally differentiated; and a superficial *cornified compartment* of squames and areas of keratinization, either orthokeratotic or parakeratotic. In the non-keratinized regions such as the buccal (cheek) and floor-of-mouth mucosae, overt keratinization and granular cells are absent and the surface cells are flattened, with elongated nuclei [2].

Lips

The lips extend from the lower end of the nose to the upper end of the chin. They mainly consist of bundles of striated muscle, particularly the *orbicularis oris* muscle, with skin on the external surface and mucous membrane on the inner surface, which has a profusion of minor salivary glands.

The vermilion zone, the transitional zone between the glabrous skin and the mucous membrane, is found only in humans. The vermilion zone contains no hair or sweat glands but does contain sebaceous glands (Fordyce spots, see below). The epithelium of the vermilion is distinctive, with a prominent stratum lucidum and a very thin stratum corneum. The dermal papillae are numerous at this site, with a rich capillary supply, which produces the reddish-pink colour of the lips in white people. Melanocytes are abundant in the basal layer of the vermilion of pigmented skin, but are infrequent in white skin.

The *oral commissures* are the angles where the upper and lower lip meet. The upper lip includes the *philtrum*, a midline depression, extending from the columella of the nose to the superior edge of the vermilion zone [3].

Oral mucosa

The mucosa is divided into masticatory, lining and specialized types. *Masticatory mucosa* (hard palate, gingiva) is adapted to the forces of pressure and friction and is keratinized, with numerous tall rete ridges and connective tissue papillae and little submucosa. *Lining mucosa* (buccal, labial and alveolar mucosa, floor of mouth, ventral surface of tongue, soft palate, lips) is non-keratinized, with broad rete ridges and connective tissue papillae and abundant elastic fibres in the lamina propria [4,5].

Specialized mucosa on the dorsum of the tongue, adapted for taste and mastication, is keratinized, with numerous rete ridges and connective tissue papillae, abundant elastic and collagen fibres in the lamina propria and no submucosa. The tongue is divided by a V-shaped groove, the *sulcus terminalis*, into an anterior two-thirds and a posterior third. Various papillae on the dorsum include the *filiform papillae*, which cover the entire anterior surface and form an abrasive surface to control the food bolus as it is pressed against the palate, and the *fungiform papillae*. The latter are mushroom-shaped, red structures covered by non-keratinized epithelium. They are scattered between the filiform papillae and have taste buds on their surface. Adjacent and anterior to the sulcus terminalis are eight to 12 large *circumvallate papillae*, each surrounded by a deep groove into which open the ducts of serous minor salivary glands. The lateral walls of these papillae contain taste buds.

The *foliate papillae* consist of four to 11 parallel ridges, alternating with deep grooves in the mucosa, on the lateral margins on the posterior part of the tongue. There are taste buds on their lateral walls. The *lingual tonsils* are round or oval prominences with intervening lingual crypts lined by non-keratinized epithelium. They are part of *Waldeyer's oropharyngeal ring* of lymphoid tissue. The lingual tonsil is a mass of lymphoid tissue in the posterior third of the tongue, between the epiglottis posteriorly and the circumvallate papillae anteriorly. It is usually divided in the midline by a ligament.

Teeth

The teeth develop from neuroectoderm [6]. Tooth development begins in the fetus, at about 28 days *in utero*. Indeed, all the deciduous and some of the permanent dentitions commence development in the fetus. At around the sixth week of intrauterine life the oral epithelium proliferates over the maxillary and mandibular ridge areas to form primary epithelial bands that project into the mesoderm, and produce a dental lamina in which discrete swellings appear—the enamel organs of developing teeth. Each enamel organ eventually produces tooth enamel, and the mesenchyme, which condenses beneath the enamel organ (actually neuroectoderm), forms a dental papilla that produces the dentine and pulp of the tooth. The enamel organ together with the dental papilla constitute the tooth germ, and this becomes surrounded by a mesenchymal dental follicle, from which the periodontium forms, ultimately to anchor the tooth in its bony socket. Mineralization of the primary dentition commences at about 14 weeks *in utero* and all primary teeth are mineralizing by birth. Permanent incisor and first molar teeth begin to mineralize at, or close to, the time of birth, mineralization of other permanent teeth starting later. Tooth eruption occurs after crown formation and mineralization is largely complete but before the roots are fully formed.

Teeth comprise a crown of insensitive enamel, surrounding sensitive dentine, and a root which has no enamel covering (Fig. 66.1). Teeth contain a vital pulp (nerve) and are supported by the periodontal ligament via which roots are attached into sockets in the alveolar process of the jaws (maxilla and mandible). The fibres of the periodontal ligament attach through cementum to the dentine surface. The alveolus is covered by the gingivae, or gum, which in health are pink, stippled and tightly bound down, and form a close-fitting cuff, with a small sulcus (gingival crevice), round the neck of each tooth.

The first or primary (deciduous or milk) dentition comprises two incisors, a canine and two molars in each of the four mouth quadrants (total 20 teeth). There are 10 deciduous (primary or milk) teeth in each jaw: all are fully

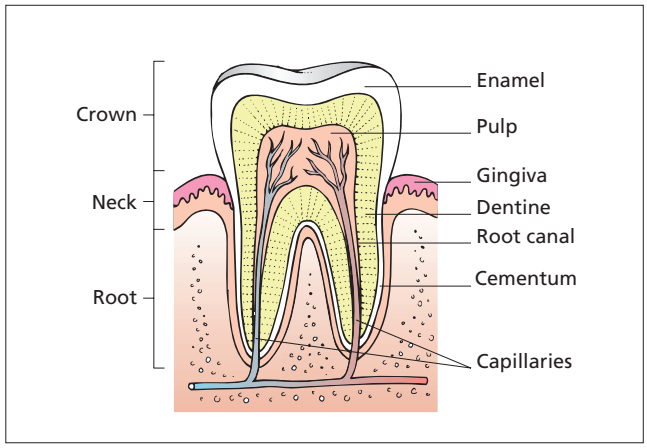

Fig. 66.1 Tooth structure.

Table 66.1 Tooth eruption timings (average timings; there is a wide range).

	Upper	Lower
Deciduous (primary) teeth		
A Central incisors	8–13 months	6–10 months
B Lateral incisors	8–13 months	10–16 months
C Canines (cuspids)	16–23 months	16–23 months
D First molars	13–19 months	13–19 months
E Second molars	25–33 months	23–31 months
Permanent teeth		
1 Central incisors	7–8 years	6–7 years
2 Lateral incisors	8–9 years	7–8 years
3 Canines (cuspids)	11–12 years	9–10 years
4 First premolars (bicuspids)	10–11 years	10–12 years
5 Second premolars (bicuspids)	10–12 years	11–12 years
6 First molars	6–7 years	6–7 years
7 Second molars	12–13 years	11–13 years
8 Third molars	17–21 years	17–21 years

erupted by the age of about 3 years (Fig. 66.2; Table 66.1). The secondary or permanent teeth begin to erupt at about the age of 6–7 years and the deciduous teeth begin to be slowly lost by normal root resorption.

The normal permanent (adult) dentition comprises two incisors, a canine, two premolars and three molars in each quadrant (total 32 teeth). The full permanent dentition consists of 16 teeth in each jaw: normally most have erupted by about 12–14 years of age. However, some milk teeth may still be present at the age of 12–13 years. The last molars (third molars or wisdom teeth), if present, often erupt later or may impact and never appear in the mouth.

Junction of the mucosa with the teeth

The dentogingival junction represents a unique anatomical feature concerned with the attachment of the gingival

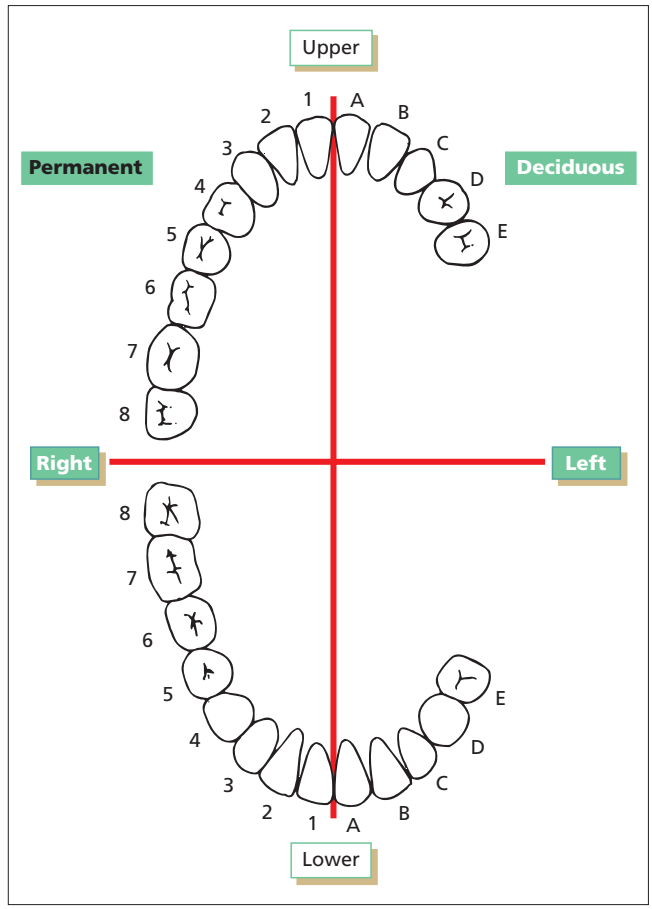

Fig. 66.2 Tooth notations.

(gum) mucosa to the tooth. Non-keratinized gingival epithelium forms a cuff surrounding the tooth, and at its lowest point on the tooth is adherent to the enamel or cement. This 'junctional' epithelium is unique in being bounded both on its tooth and lamina propria aspects by basement membranes. Above this is a shallow sulcus or crevice (up to 2 mm deep), the gingival sulcus or crevice. Neutrophils continually migrate into the gingival crevice, and there is also a slow exudate of plasma (crevicular fluid).

Immunity in the oral cavity

Movement of the soft tissues during speech and swallowing, and salivation, ensures that much foreign material is swallowed. The need for this cleaning mechanism is clearly apparent in patients with facial paralysis, or in those with xerostomia, in whom there is accumulation of oral debris and subsequent infection.

Saliva also aggregates bacteria and deters their attachment to surfaces. Salivary lysozyme, thiocyanate, peroxides and various mucins and other components may be

antimicrobial and saliva is inhibitory to various microbial agents including, for example, human immunodeficiency virus (HIV).

Salivary tissue derives its B cells from the gut-associated lymphoid tissue (GALT) system [7]. Salivary acinar cells produce secretory component (transport piece) needed for transport of IgA into the saliva and its stability in the presence of salivary or gastric proteolytic enzymes. Although the exact contribution to oral defence made by salivary IgA antibodies is difficult to assess, some patients who have IgA deficiency suffer from oral infections, and in animals it is possible to induce protective salivary IgA antibodies to caries-producing organisms such as *Streptococcus mutans*.

Neutrophils and other leukocytes are particularly essential for oral health as shown by the fact that patients with HIV infection, neutropenia, agranulocytopenia, leukaemia or chronic granulomatous disease are predisposed to severe gingivitis and rapid periodontal breakdown, as well as mouth ulceration and infections.

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Examination of the mouth and perioral region

Examination includes inspection and palpation of the lymph nodes, temporomandibular joints, jaws, salivary glands and oral cavity.

Lymph nodes (Table 66.2)

Lymph from the superficial tissue of the head and neck generally drains first to groups of superficially placed lymph nodes, then to the deep cervical lymph nodes.

- Systematically, each region needs to be examined lightly with the pulps of the fingers, trying to roll the lymph nodes against harder underlying structures.
- Parotid, mastoid and occipital lymph nodes can be palpated simultaneously using both hands.
- Superficial cervical lymph nodes are examined with lighter palpation as they can only be compressed against the softer sternomastoid muscle.
- Submental lymph nodes are examined by tipping the patient's head forward and rolling the lymph nodes against the inner aspect of the mandible.

Table 66.2 Drainage areas of cervical lymph nodes.

Area	Draining lymph nodes
Scalp, temporal region	Superficial parotid
Scalp, posterior	Occipital
Scalp, parietal region	Mastoid
Ear, external	Superficial cervical over upper part of sternomastoid muscle
Ear, middle	Parotid
Over angle of mandible	Superficial cervical over upper part of sternomastoid muscle
Medial part of frontal region, medial eyelids, skin of nose	Submandibular
Lateral part of frontal region and lateral part of eyelids	Parotid
Cheek	Submandibular
Upper lip	Submandibular
Lower lip	Submental
Lower lip, lateral part	Submandibular
Mandibular gingivae	Submandibular
Maxillary teeth	Deep cervical
Maxillary gingivae	Deep cervical
Tongue tip	Submental; remainder drains to submandibular nodes
Tongue, anterior two-thirds	Submandibular; some midline cross-over of lymphatic drainage
Tongue, posterior third	Deep cervical
Tongue, ventrum	Deep cervical
Floor of mouth	Submandibular
Palate, hard	Deep cervical
Palate, soft	Retropharyngeal and deep cervical
Tonsil	Jugulodigastric

• Submandibular lymph nodes are examined in the same way with the patient's head tipped to the side being examined. Differentiation needs to be made between the submandibular salivary gland and submandibular lymph glands. Bimanual examination with one finger in the floor of the mouth may help.
• The deep cervical lymph nodes which project anterior or posterior to the sternomastoid muscle can be palpated. The jugulodigastric lymph node should be specifically examined, as this is the most common lymph node involved in tonsillar infections.
• The supraclavicular region should be examined at the same time as the rest of the neck; lymph nodes here may extend up into the posterior triangle of the neck on the scalene muscles, behind the sternomastoid.
• Parapharyngeal and tracheal lymph nodes can be compressed lightly against the trachea.
• Some information can be gained by the texture and nature of the lymphadenopathy.
• Tenderness and swelling should be documented. Lymph nodes that are tender may be inflammatory (lymphadenitis). Consistency should be noted. Nodes that are increasing in size and are hard or fixed to adjacent tissues may be malignant.
• Both anterior and posterior cervical nodes should be examined as well as other nodes, liver and spleen if systemic disease is a possibility.

Temporomandibular joints and muscles of mastication

Although disorders that affect the temporomandibular joint often appear to be unilateral, the joint should not be viewed in isolation but always considered together with its opposite joint, as part of the stomatognathic system. The area should be examined as follows.

Inspection

• Facial symmetry.
• Evidence of enlarged masseter muscles (masseteric hypertrophy) suggestive of clenching or bruxism.
• Mandibular opening and closing paths.
• Mandibular opening extent: (i) measure the interincisal distance at maximum mouth opening; (ii) measure the amount of lateral excursions achievable; (iii) listen for joint noises (a stethoscope placed over the joint can help).

Palpation

• Both condyles: via the external auditory meatus to detect tenderness posteriorly, and by using a single finger placed over the joints in front of the ears to detect pain, abnormal movements or clicking within the joint.
• Masticatory muscles on both sides.

Masseters: by intraoral/extraoral compression between finger and thumb. Palpate the masseter bimanually by placing a finger of one hand intraorally and the index and middle fingers of the other hand on the cheek over the masseter over the lower mandibular ramus.
Temporalis: by direct palpation of the temporal region. Palpate the temporal origin of the temporalis muscle by asking the patient to clench the teeth. Palpate the insertion of the temporalis tendon intraorally along the anterior border of the ascending mandibular ramus.
Lateral pterygoid (lower head): by placing a little finger up behind the maxillary tuberosity (the 'pterygoid sign'). Examine the lateral pterygoid muscle, which cannot readily be palpated, indirectly by asking the patient to open the jaw against resistance and to move the jaw to one side while a gentle resistance force is applied.
Medial pterygoid muscle intraorally lingually to the mandibular ramus.

Some palpate using a pressure algometer to standardize the force used, and undertake range-of-movement measurements.
• Examination of the dentition and occlusion: this may require monitoring of study models on a semi-adjustable or fully adjustable articulator. Note particularly missing premolars or molars, and attrition.
• Examination of the mucosa: note particularly occlusal lines and scalloping of the tongue margins, which may indicate bruxism and tongue pressure.

Jaws

There is wide normal individual variation in morphology of the face. Most individuals have facial asymmetry but of a degree that cannot be regarded as abnormal.
• Maxillary, mandibular or zygomatic deformities or lumps may be more reliably confirmed by inspection from above (maxillae/zygomas) or behind (mandible). The jaws should be palpated to detect swelling or tenderness.
• Maxillary air sinuses can be examined by palpation for tenderness over the maxillary antrum, which may indicate sinus infection. Transillumination or endoscopy can be helpful.

Salivary glands

Inspect and palpate the major salivary glands (parotid and submandibular) for:
• symmetry;
• evidence of enlarged glands;
• evidence of salivary flow from salivary ducts;
• appearance of saliva.

Parotid glands. Palpate by placing fingers over the preauricular glands, to detect pain or swelling. Early enlargement of the parotid gland is characterized by outward

deflection of the lower part of the earlobe, which is best observed by looking at the patient from behind. This simple sign may allow distinction from simple obesity. Swelling of the parotid sometimes causes trismus. Swellings may affect the whole or part of a gland or tenderness may be elicited. The parotid duct (Stensen's duct) is most readily palpated with the jaws clenched firmly since it runs horizontally across the upper masseter where it can be gently rolled; the duct opens at a papilla on the buccal mucosa opposite the upper molars.

Submandibular glands. Bimanually palpate using fingers inside the mouth and extraorally. The submandibular gland is best palpated with a finger of one hand in the floor of the mouth lingual to the lower molar teeth, and a finger of the other hand placed over the submandibular triangle. The submandibular duct (Wharton's duct) runs anteromedially across the floor of the mouth to open at the side of the lingual fraenum.

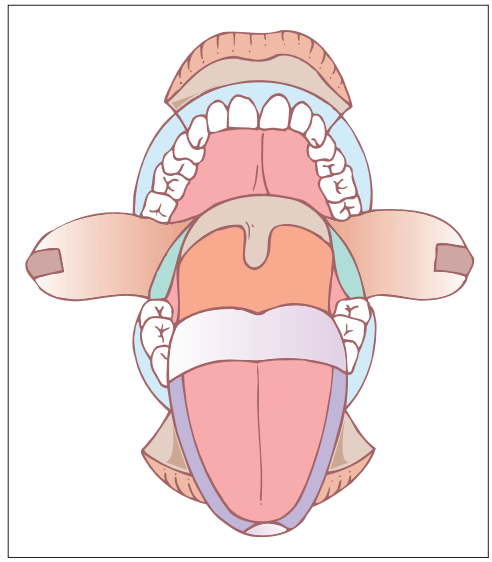

Fig. 66.3 Diagram of oral cavity.

Intraoral examination

The examination should be conducted in a systematic fashion to ensure that all areas are included. If the patient wears any removable prostheses or appliances, these should be removed in the first instance, although it may be necessary later to replace the appliance to assess fit, function and relationship to any lesion.

Complete visualization with a good source of light is essential. All mucosal surfaces should be examined, starting away from the location of any known lesions or the focus of complaint. The lips should be inspected first. The labial mucosa, buccal (cheek) mucosae, floor of mouth and ventrum of tongue, dorsal surface of the tongue, hard and soft palates, gingivae and teeth should then be examined in sequence and lesions noted on a diagram of the oral cavity (Fig. 66.3).

Lips. Features such as cyanosis are seen mainly in the lips in cardiac or respiratory disease; angular cheilitis (stomatitis) is seen mainly in oral candidiasis or in iron, vitamin or immune deficiencies. Examination is facilitated if the mouth is gently closed at this stage, so that the lips can then be everted to examine the mucosa.

Labial mucosa. Normally appears moist with a fairly prominent vascular arcade. In the lower lip, the many minor salivary glands which are often exuding mucus are easily visible. The lips therefore feel slightly nodular and the labial arteries are readily felt. Many adults have a few yellowish pinhead-sized papules in the vermilion border (particularly of the upper lip) and at the commissures; these are usually ectopic sebaceous glands (Fordyce spots), and may be numerous especially as age advances.

Cheek (buccal) mucosa. This is readily inspected if the mouth is held half open. The vascular pattern and minor salivary glands so prominent in the labial mucosa are not obvious in the buccal mucosa but Fordyce spots may be conspicuous, particularly near the commissures and retromolar regions in adults. Place the surface of a dental mirror against the buccal mucosa. The mirror should lift off easily; if it adheres to the mucosa, then xerostomia is present.

Floor of mouth and ventrum of tongue. These are best examined by asking the patient to push the tongue first into the palate then into each cheek in turn. This raises for inspection the floor of the mouth, an area where tumours may start (the 'coffin' or 'graveyard' area of the mouth). Its posterior part is the most difficult area to examine well and one where lesions are most easily missed. Lingual veins are prominent and, in the elderly, may be conspicuous (lingual varices). Bony lumps on the alveolar ridge lingual to the premolars are most often tori (torus mandibularis). During this part of the examination the quantity and consistency of saliva should be assessed. Examine for the normal pooling of saliva in the floor of the mouth; normally there is a pool of saliva in the floor of the mouth.

Dorsum of tongue. This is best inspected by protrusion, when it can be held with gauze. The anterior two-thirds is embryologically and anatomically distinct from the posterior third, and separated by a dozen or so large circumvallate papillae. The anterior two-thirds is coated with many filiform but relatively few fungiform papillae. Behind the

circumvallate papillae, the tongue contains several large lymphoid masses (lingual tonsil) and the foliate papillae lie on the lateral borders posteriorly. These are often mistaken for tumours. The tongue may be fissured (scrotal) but this is usually regarded as a developmental anomaly. A healthy child's tongue is rarely coated but a mild coating is not uncommon in healthy adults. The voluntary tongue movements and sense of taste should be formally tested. Abnormalities of tongue movement (neurological or muscular disease) may be obvious from dysarthria or involuntary movements and any fibrillation or wasting noted. Hypoglossal palsy may lead to deviation of the tongue towards the affected side on protrusion. Taste sensation can be tested by placing the tongue across the terminals of a pocket torch battery when a metallic taste may be obvious. Formal testing with salt, sweet, sour and bitter should be carried out by applying solutions of salt, sugar, dilute acetic acid and 5% citric acid to the tongue on a cotton swab or cotton bud.

Palate and fauces. These consist of an anterior hard and posterior soft palate, and the tonsillar area and oropharynx. The mucosa of the hard palate is firmly bound down as a mucoperiosteum (similar to the gingivae) and with no obvious vascular arcades. Rugae are present anteriorly on either side of the incisive papilla that overlies the incisive foramen. Bony lumps in the posterior centre of the vault of the hard palate are usually tori (torus palatinus). Patients may complain of lumps distal to the upper molars that they think are unerupted teeth but the pterygoid hamulus or tuberosity is usually responsible for this complaint. The soft palate and fauces may show a faint vascular arcade. Just posterior to the junction with the hard palate is a conglomeration of minor salivary glands. This region is often also yellowish. The palate should be inspected and movements examined when the patient says 'Aah'. Using a mirror, this also permits inspection of the posterior tongue, tonsils, oropharynx, and can even offer a glimpse of the larynx. Glossopharyngeal palsy may lead to uvula deviation to the contralateral side.

Gingivae. In health they are firm, pale pink, with a stippled surface, and have sharp gingival papillae reaching up between the adjacent teeth to the tooth contact point. Look for gingival redness, swelling or bleeding on gently probing the gingival margin. The 'keratinized' attached gingivae (pale pink) are normally clearly demarcated from the non-keratinized alveolar mucosa (vascular) that runs into the vestibule or sulcus. Bands of tissue which may contain muscle attachments run centrally from the labial mucosa onto the alveolar mucosa and from the buccal mucosa in the premolar region onto the alveolar mucosa (fraena).

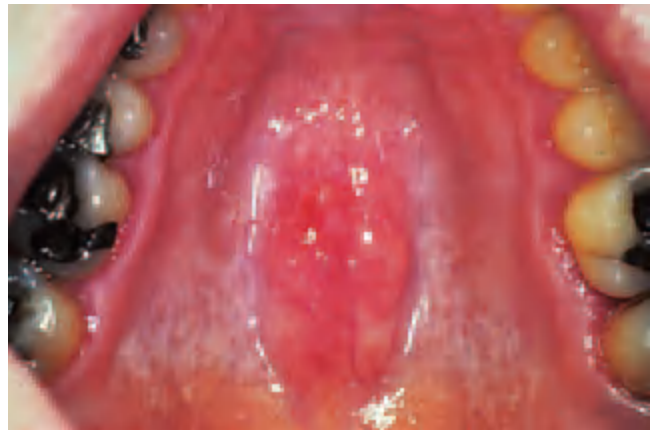

Fig. 66.4 Torus palatinus.

Teeth. The dentition should be checked to make sure that the expected complement of teeth is present for the patient's age. Extra teeth (supernumerary teeth) or deficiency of teeth (partial loss or hypodontia; oligodontia; complete loss or anodontia) can be features of many syndromes but teeth are far more frequently missing because they are unerupted, or lost as a result of caries or periodontal disease. The teeth should be fully examined for signs of disease, either malformations such as hypoplasia or abnormal colour, or acquired disorders such as dental caries, erosion or abrasion. The occlusion of the teeth should also be checked; it may show attrition or may be disturbed, as in some jaw fractures or dislocation of the mandibular condyles.

Anatomical variants

Patients sometimes become concerned after noticing various anatomical variants in the mouth. These include tori and exostoses [1,2], which are developmental bony lumps seen especially in Mongoloid and Negroid races. Most common is torus palatinus, a slow-growing, asymptomatic, benign bony lump in the midline of the palate (Fig. 66.4). Torus mandibularis are bilateral, asymptomatic, benign bony lumps lingual to the premolars.

The diagnosis is confirmed by radiography. Surgery is rarely indicated. These are excised or reduced only if causing severe difficulties with dentures.

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Disorders affecting the teeth

Disorders of tooth eruption

Teething

'Teething' in infancy is a poorly understood condition and the soreness and fever is often due to infection such as herpes simplex stomatitis. Nevertheless, there may be a very minor degree of pyrexia around the time of tooth eruption [1].

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Premature eruption of teeth [1–4]

Erupted teeth, particularly in the mandibular central incisor region, may be present at birth (natal teeth) or appear within the first few days or weeks of life (neonatal teeth). This rare event (about 0.1% of live births) occasionally has a familial basis or is associated with some other developmental anomaly. Such teeth occasionally cause ulceration of the infant's tongue or mother's nipple but usually they can be safely left *in situ*.

Retarded eruption of teeth

Congenital hypopituitarism, congenital hypothyroidism (cretinism), Down's syndrome, cleidocranial dysplasia, cytotoxic drugs and radiotherapy may cause retarded eruption of teeth, but most cases are of local aetiology (e.g. impactions).

Extra teeth

Extra (supernumerary) teeth are uncommon and usually of an unknown cause. They are generally found in the premaxilla. Supernumerary teeth are common in cleidocranial dysplasia.

Missing teeth

It is important to remember that teeth may be apparently missing simply because they are unerupted.

Dental aplasia

SYN. HYPODONTIA; ANODONTIA

Wisdom teeth (third molars), second premolars and upper lateral incisors are sometimes absent in otherwise normal individuals, probably because of some unidentified genetic trait. Up to 25% of white people lack a third molar. Absence of several teeth may indicate systemic disease such as cleidocranial dysplasia, incontinentia pigmenti or ectodermal dysplasia.

Hypodontia is often associated with microdontia and is often bilaterally symmetrical.

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Loosening and early loss of teeth (Table 66.3)

Early loss of teeth is usually caused by trauma, dental caries or destructive periodontal disease, as discussed below [1,2]. Congenital disorders that may predispose to periodontal breakdown include Down's syndrome, Papillon–Lefèvre syndrome, neutropenia and other immune defects. Acquired disorders such as diabetes mellitus or immune defects also predispose to periodontal breakdown. Teeth are also lost early in other rare systemic disorders, for example eosinophilic granuloma or hypophosphatasia.

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Table 66.3 Pathological causes of loosening and early loss of the teeth.

Local causes
Trauma
Periodontitis
Neoplasms
Systemic causes
Disorders with some immune deficit
Down's syndrome
Diabetes mellitus
Leukopenia or leukocyte defects
Human immunodeficiency virus disease
Juvenile periodontitis
Rapidly progressive periodontitis
Papillon–Lefèvre syndrome
Hypophosphatasia
Ehlers–Danlos syndrome (type VIII)
Others
Acrodynia
Neoplasms
Eosinophilic granuloma

Table 66.4 Causes of discoloration of teeth.

Extrinsic
Poor oral hygiene
Smoking
Beverages/food
Drugs, e.g. iron, chlorhexidine, sweetened medication
Stains, e.g. from betel chewing
Intrinsic
Trauma
Caries
Restorative materials, e.g. amalgam
Pink spot (internal resorption)
Drugs: mainly tetracyclines
Fluorosis
Dentinogenesis imperfecta
Amelogenesis imperfecta
Porphyria
Kernicterus (severe neonatal jaundice)

Malformed and discoloured teeth (Table 66.4)

There is a wide range of normal variation in tooth morphology and colour, especially between races.

Most dental discoloration is caused by smoking, foods and beverages (such as tea), medicines such as iron or chlorhexidine, or poor oral hygiene. The regular use of sweetened medication at night (e.g. trimeprazine syrup in a child with eczema) can cause discoloration due to dental caries. Erosion of teeth may occur because of the repeated use of acidic drinks or sucking citrus fruits, or as a feature of gastric regurgitation in bulimia, anorexia nervosa or alcoholism.

Teeth may be malformed for genetic reasons. Peg-shaped teeth may be normal variants (Fig. 66.5) or may be found in some ectodermal dysplasias (see p. 66.11). Taurodontism (see below) can be found in a range of dermatological disorders [1]. Genetic defects that may cause tooth discoloration include dentinogenesis imperfecta (Fig. 66.6), which may be seen in some patients with osteogenesis imperfecta, and amelogenesis imperfecta (Fig. 66.7) [2,3].

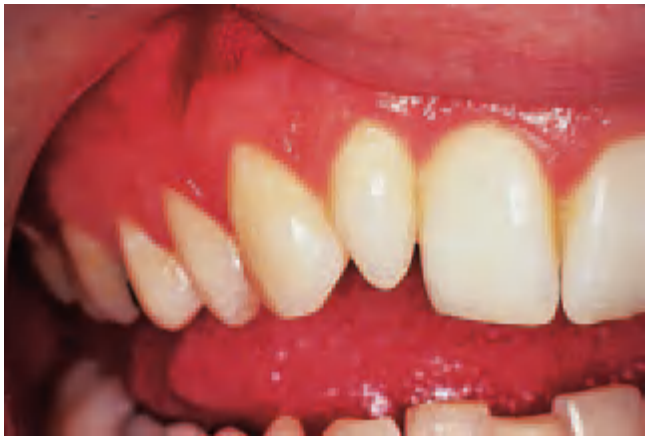

Fig. 66.5 A peg-shaped maxillary lateral incisor, a fairly common variant.

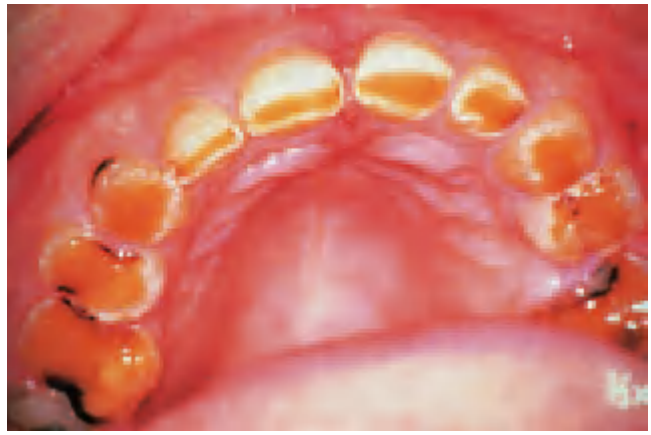

Fig. 66.6 Dentinogenesis imperfecta: staining and severe attrition.

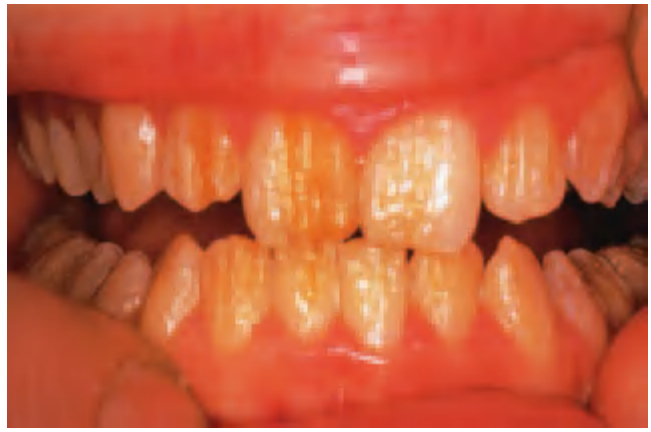

Fig. 66.7 Amelogenesis imperfecta: one variant showing longitudinal ridging of teeth.

Teeth may be damaged during their development. Local infection or trauma, or unknown factors, may cause malformation of a single tooth (or a few). The lower premolars are usually affected because there is caries and periapical infection related to their deciduous predecessors; such hypoplastic teeth are termed *Turner's teeth*. The upper permanent incisors may be malformed if there is trauma to the deciduous incisors. Radiotherapy or cytotoxic therapy may cause hypoplasia, as may congenital rubella or cytomegalovirus infection. However, classical *Hutchinsonian* (*screwdriver-shaped*) *incisors* and *Moon's* (*or mulberry*) *molars* of congenital syphilis are extremely rare.

Hypoplasia is relatively common in apparently healthy persons [4–7] and is also seen in early-onset malabsorption syndromes, many severe childhood illnesses (Fig. 66.8) and organ transplantation [8–10] and in some forms of epidermolysis bullosa (see below). Neonatal jaundice can produce greenish teeth.

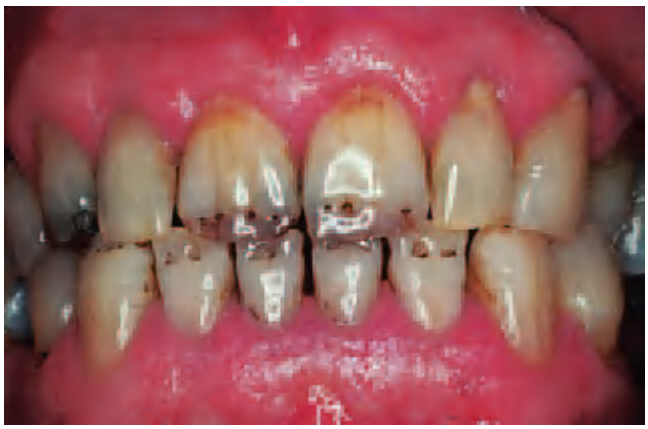

Fig. 66.8 Hypoplasia of teeth related to severe childhood respiratory infection.

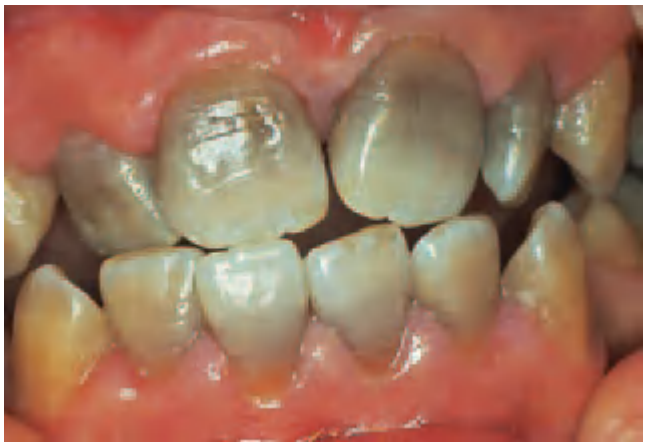

Fig. 66.9 Pronounced intrinsic tooth discoloration from use of tetracyclines in childhood.

Fluoride, at the concentrations present in water supplies in Western countries or given prophylactically, may occasionally produce inconsequential minute white flecks; however, concentrations over 2 ppm may produce significant fluorosis. Tetracyclines given to a pregnant or lactating mother may discolour the child's teeth and, if given to a child, particularly one under the age of 12 years, may cause significant brown intrinsic tooth staining (Fig. 66.9).

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Taurodontism

Taurodont teeth have an enlarged pulp chamber and a more inferiorly placed root furcation in premolars and molars. They are not readily detectable on clinical examination and are therefore most easily diagnosed on radiographs (Fig. 66.10). However, on clinical examination, lack of constriction of the tooth at the neck may be suggestive of taurodontism. Taurodontism is generally most obvious in molars of both deciduous and permanent dentitions, and may be found in single or several teeth, with or without evidence of other disorders.

Most studies have shown an overall prevalence of the order of 2% with no sex predilection, but oriental people and some other racial groups are especially affected [1–3]. XXY and other syndromes with additional X chromosomes may be affected [4–6] as may other chromosomal anomalies [7–9]. Dermatological conditions with which taurodontism may be associated are shown in Table 66.5 [10].

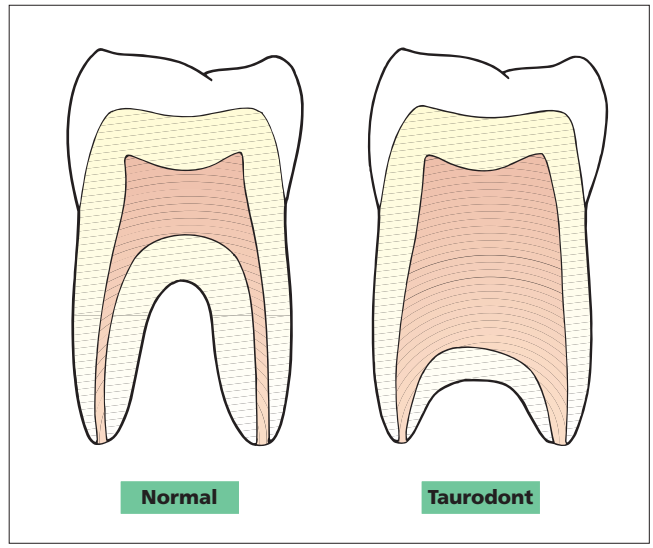

Fig. 66.10 Taurodontism.

Table 66.5 Dermatological disorders in which taurodontism may occasionally be found.

Some ectodermal dysplasias
Trichodento-osseous syndrome
Tricho-onychodental syndrome
Epidermolysis bullosa
Dental oculocutaneous syndrome
Otodental dysplasia
Orofacial digital syndrome type II
Dyskeratosis congenita

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Ectodermal dysplasia

Ectodermal dysplasia is typically characterized by developmental abnormalities in at least two different ectodermally derived systems. Oral abnormalities are common, especially missing teeth and abnormally shaped teeth (Fig. 66.11). There are many variations, as discussed in the following sections and in Chapter 12.

X-linked hypohidrotic ectodermal dysplasia [1–3]

Hypodontia is common in X-linked hypohidrotic ectodermal dysplasia. Some anterior teeth are usually present but their crowns are typically conical or peg-shaped. The posterior teeth, when present, are smaller but otherwise normal. Overclosure of the jaws, together with maxillary hypoplasia and frontal bossing, give a characteristic facial appearance. There may be a degree of impaired salivary gland function.

Female carriers of this syndrome may have hypodontia and/or microdontia.

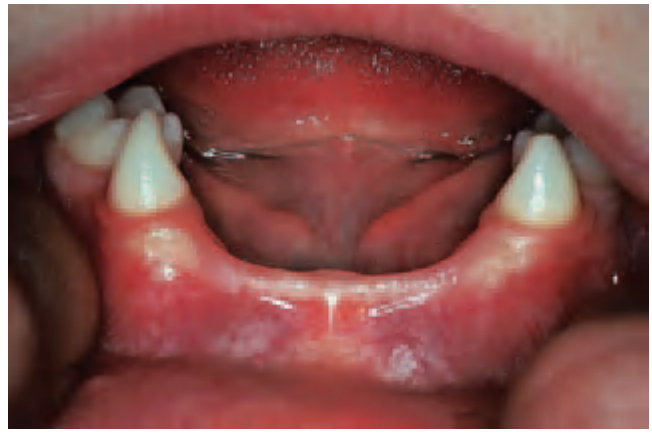

Fig. 66.11 Hypodontia and malformed teeth are common in ectodermal dysplasia.

Autosomal recessive ectodermal dysplasia [1,4]

Dental and oral anomalies in this condition are identical to those in the X-linked form of ectodermal dysplasia, although relatives may have a normal dentition.

Hypodontia, taurodontism and sparse hair [5]

There are a few reports of a variant of ectodermal dysplasia where there is taurodontism, and somewhat lesser hypodontia than in the more classic forms of ectodermal dysplasia.

Autosomal dominant hypodontia with nail dysgenesis [6]

Hypodontia, conical deciduous and permanent teeth, and dysplastic nails characterize this variant of ectodermal dysplasia.

Incontinentia pigmenti [7]

SYN. BLOCH–SULZBERGER SYNDROME

Hypodontia and retarded eruption affect both dentitions and the anterior teeth are small. The teeth tend also to be conical, often with accessory cusps.

Chondroectodermal dysplasia [8–10]

SYN. ELLIS–VAN CREVELD SYNDROME

Ellis–van Creveld syndrome, also called chondroectodermal dysplasia, is a rare autosomal recessive condition that manifests with chondrodysplasia of tubular bones resulting in disproportionate dwarfism, polydactyly and syndactyly of hands and feet, severe dystrophic nails, anomalous teeth, bilateral partial clefts of the alveolar bone and malocclusion. Half of the cases have cardiac malformations.

The most obvious oral anomalies are the multiple fraena extending from the lips and buccal mucosae to the alveolar ridges of both jaws. Natal teeth, mild hypodontia or hyperdontia, malformed or small teeth and accessory cusps are common.

Cranioectodermal dysplasia [11]

Deciduous teeth are small and may have dysplastic enamel, although the condition is so rare that the permanent teeth have not been clearly described. There may be hypodontia or taurodontism. Dolicocephaly, hair anomalies and shortened arms, fingers and toes are associated.

Nance–Horan syndrome [12]

X-linked congenital cataracts with supernumerary teeth constitute the Nance–Horan syndrome. The incisor teeth may also be morphologically abnormal and can resemble Hutchinson's incisors of congenital syphilis.

Trichodental syndrome [13,14]

The trichodental syndrome is a rare dominantly inherited condition in which there is fine short hair, thinning of the lateral ends of the eyebrows, hypodontia and/or conical teeth.

Trichodento-osseous syndrome [15–18]

Tight curly hair, sclerotic cortical bone and oral anomalies (especially thin enamel) are found in this autosomal dominant condition. The hypoplasia–hypomaturation type of amelogenesis imperfecta, enamel hypoplasia, unerupted teeth and taurodontism may be associated.

Trichonychodental syndrome [19]

This autosomal dominant trait of fine curly hair and thin dysplastic nails may be associated with taurodontism and enamel or dentinal developmental defects.

Curry–Hall syndrome [20]

Deciduous teeth are small and conical, and the incisors are often retained since their permanent successors may be congenitally absent. The remaining permanent teeth do erupt but are small. Other features include short limbs, polydactyly and nail dysplasia.

Otodental dysplasia [21–23]

Globe-shaped posterior teeth (globodontia) in both dentitions are the most common oral feature of this autosomal dominant condition, which is associated with sensorineural hearing loss. The incisors are not affected and the patients are otherwise well.

Other oral anomalies may include taurodontism, microdontia and hypodontia.

Clouston syndrome [24] (see Chapter 12)

Palmoplantar hyperkeratosis, hair defects, nail dysplasia and oral white lesions characterize this autosomal dominant form of hidrotic ectodermal dysplasia. There may be diffuse white lesions in the buccal mucosa, palate, tongue and elsewhere but reports of malignancy are rare.

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Table 66.6 Oral features in rare ectodermal dysplasia variants [1–3].

Syndrome	Oral manifestations	Facial manifestations	Other features
GAPO (*g*rowth retardation, *a*lopecia, *p*seudoanodontia, *o*ptic atrophy)	Failure of both dentitions to erupt	Frontal bossing Midface hypoplasia	*See left-hand column*
Johanson–Blizzard	Hypodontia in both dentitions Roots of deciduous teeth are short and deformed, crowns are conical	Microcephaly Hypoplastic alae nasi	Hearing loss Pancreatic dysfunction Learning disability
Waardenburg	—	Cleft lip/palate	Deafness Hair depigmentation
LEOPARD (*l*entigines, *e*lectrocardiographic anomalies, *o*cular hypertelorism, *p*ulmonary stenosis, *a*bnormal genitalia, *r*etarded growth, *d*eafness)	No mucosal lentigines	Triangular face with hypertelorism and ptosis, may be granular cell tumour	*See left-hand column*
Congenital erythrokeratoderma with sensorineural hearing loss	Hyperkeratosis Occasional carcinoma	—	*See left-hand column*

23 Sedano HO, Moreira LC, de Souza RA, Moleri AB. Otodental syndrome: a case report and genetic considerations. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2001; **92**: 312–7.
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Other rare ectodermal dysplasias [1]

Other rare ectodermal dysplasias and pachonychia congenita are discussed in Chapter 12. Others are summarized in Table 66.6.

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Alstrom syndrome

Alstrom syndrome is a rare disorder characterized by early obesity, diabetes mellitus, loss of central vision, hearing loss and short stature. Light yellow-brown discolored enamel bands have been observed on the anterior teeth in some patients [1].

REFERENCE

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Disorders affecting the periodontium

Gingival disorders affecting the periodontium

Bleeding

Bleeding from the gingival margins is common, usually a consequence of inadequate oral hygiene leading to the accumulation of dental bacterial plaque and thus gingivitis (Table 66.7). The tendency to gingivitis is slightly increased in patients taking oral contraceptives and in some pregnant women (especially during the second trimester).

Table 66.7 Causes of gingival bleeding.

Local
Chronic gingivitis
Chronic periodontitis
Acute necrotizing gingivitis
Systemic
Any condition causing exacerbation of gingivitis (e.g. pregnancy)
Leukaemia
Human immunodeficiency virus infection
Other causes of purpura
Clotting defects
Drugs, e.g. anticoagulants
Scurvy

Gingival haemorrhage may, however, also be an early feature in some vascular or platelet disorders and is commonly a problem, for example, in leukaemic patients.

Swelling

Localized gingival swellings (epulides) may be of local aetiology or can be manifestations of pregnancy, a neoplasm or systemic disease (Table 66.8).

Gingival swelling affecting many areas is most commonly seen in chronic gingivitis, may be produced by drugs such as phenytoin, ciclosporin (cyclosporin) and calcium channel blockers (Fig. 66.12), and is occasionally hereditary. Gingival swelling is seen with hypertrichosis in both drug-induced hyperplasias and hereditary gingival fibromatosis.

A degree of gingival swelling may also be seen in herpetic stomatitis, pregnancy, leukaemia, Crohn's disease,

Table 66.8 Causes of gingival swelling.

	Generalized swelling	Localized swelling
Local	Chronic gingivitis Hyperplastic gingivitis due to mouth breathing	Abscesses Cysts Pyogenic granuloma Neoplasms and warts (various)
Systemic	Hereditary gingival fibromatosis and associated syndromes Drugs (phenytoin, ciclosporin, nifedipine, diltiazem) Pregnancy Sarcoidosis Crohn's disease Leukaemia Wegener's granulomatosis Scurvy Amyloidosis Mucopolysaccharidoses Mucolipidosis Lipoid proteinosis Juvenile hyaline fibromatosis Hypoplasminogenaemia	Pregnancy Sarcoidosis Orofacial granulomatosis Crohn's disease Wegener's granulomatosis Amyloidosis Neoplasms (various)

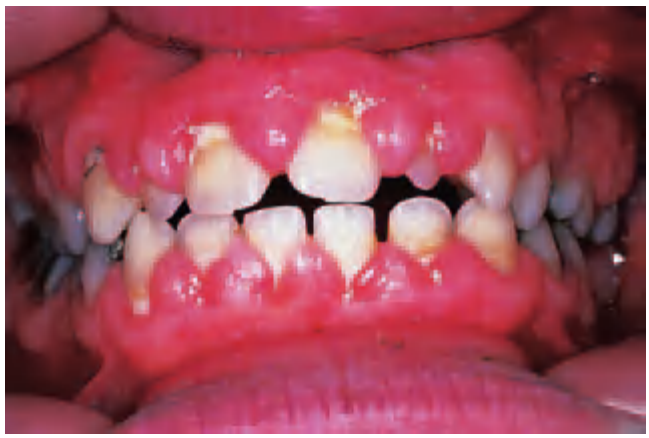

Fig. 66.12 Gingival hyperplasia in phenytoin therapy. Concomitant folate deficiency in this patient also caused mouth ulcers, seen in the maxillary buccal vestibule.

scurvy, Wegener's granulomatosis, sarcoidosis, amyloidosis, lipoid proteinosis, hypoplasminogenaemia, mucopolysaccharidoses and other disorders.

Redness

Chronic marginal gingivitis is the usual cause of gingival redness, and then is usually restricted to the gingival margins and interdental papillae.

More widespread erythema, particularly if associated with soreness, is usually caused by primary herpes simplex stomatitis, desquamative gingivitis (usually due to lichen planus or mucous membrane pemphigoid), rarely by pemphigus or other dermatoses, or occasionally by allergic responses.

Telangiectasia may be a manifestation of hereditary haemorrhagic telangiectasia, primary biliary cirrhosis or systemic sclerosis, or may follow radiotherapy. Haemangiomas are usually isolated but may occasionally extend deeply and rarely involve the ipsilateral meninges, producing a facial angioma and epilepsy, sometimes with learning disability (Sturge–Weber syndrome). Intraoral haemangiomas may be seen in Maffucci's syndrome.

Localized red areas may represent erythroplasia, carcinoma, candidiasis, lichen planus or lupus erythematosus. Kaposi's sarcoma may present as a red, purple, brown or bluish macule or nodule as may epithelioid angiomatosis. Hereditary mucoepithelial dysplasia is a rare cause of oral erythema. Irradiation-induced mucositis is a further cause of a red sore mouth.

White patches (Table 66.9)

Thrush (acute candidiasis) is a 'disease of the diseased' and produces oral white patches.

Leukoplakia is often associated with friction or smoking, occasionally with syphilis, candidiasis or chronic renal failure, but most cases are idiopathic. Lichen planus and lupus erythematosus may present as white lesions. Rarely, lichenoid lesions are associated with various drugs, liver disease or graft-versus-host disease (GVHD). Carcinoma may present as a white lesion.

Inherited causes of white patches, such as white sponge naevus and dyskeratosis congenita, are rare [1,2].

Pigmentation

Gingival pigmentation is usually seen in dark-skinned races (but may be seen even in white people) (Fig. 66.13).

Table 66.9 Main causes of oral white lesions.

Local
Frictional keratosis
Smoker's keratosis
Idiopathic keratosis
Carcinoma
Burns
Skin grafts
Systemic
Candidiasis
Lichen planus
Lupus erythematosus
Papillomas (some)
Hairy leukoplakia (mainly human immunodeficiency virus disease)
Syphilitic keratosis
Chronic renal failure
Inherited lesions (e.g. white-sponge naevus)

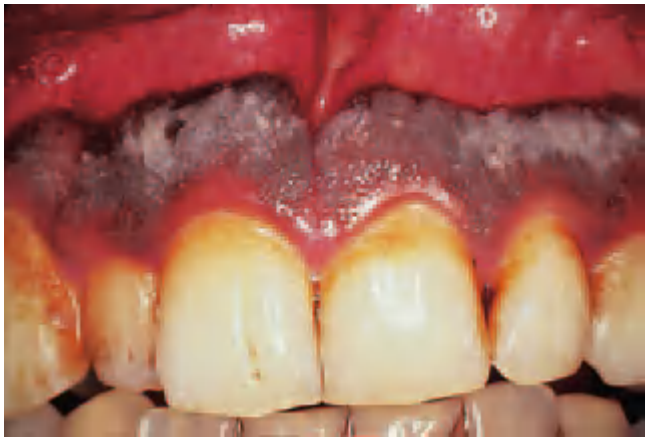

Fig. 66.13 Gingival hyperpigmentation of racial origin. The white lesion is due to accumulated oral debris—oral hygiene is very poor.

Other common causes include amalgam tattoo and melanotic macules.

Addison's disease, Kaposi's sarcoma and melanoma are the most important acquired causes of pigmented lesions but drugs such as hydroxychloroquine and minocycline may also cause hyperpigmentation.

Ulcers

Gingival ulcers are sometimes self-induced (artefactual) [1,2]. Herpesviruses can cause gingival ulceration, often with ulcers elsewhere in the mouth. Acute ulcerative (necrotizing) gingivitis causes ulceration of the interdental papillae and though usually a consequence of poor oral hygiene, it or a similar disorder is a rare complication of HIV infection, neutropenia or leukaemia, and in the malnourished or some immunosuppressed patients may spread to the cheek (*noma*, or *cancrum oris*). Other bacterial infections (e.g. syphilis, tuberculosis) and mycoses (deep mycoses) are uncommon causes of ulceration. Aphthae (sometimes) and other causes of mouth ulcers (rarely) involve the gingiva (Table 66.10).

Table 66.10 Main causes of mouth ulcers associated with systemic disease.

Microbial disease
Herpetic stomatitis
Chickenpox
Herpes zoster
Hand, foot and mouth disease
Herpangina
Infectious mononucleosis
Human immunodeficiency virus disease
Tuberculosis
Syphilis
Rarely fungal infections
Malignant neoplasms
Cutaneous disease
Erosive lichen planus and chronic ulcerative stomatitis
Pemphigus
Pemphigoid
Erythema multiforme
Dermatitis herpetiformis and linear IgA disease
Epidermolysis bullosa
Other dermatoses
Blood disorders
Anaemia
Leukaemia
Neutropenia
Other white cell dyscrasias
Gastrointestinal diseases
Coeliac disease
Crohn's disease
Ulcerative colitis
Rheumatic diseases
Lupus erythematosus
Behçet's syndrome
Sweet's syndrome
Reiter's disease
Drugs
Cytotoxic, NSAIDs, nicorandil, alendronate and other agents
Acrodynia
Radiotherapy
Disorders of uncertain pathogenesis
Angina bullosa haemorrhagica
Hypereosinophilic syndrome
Eosinophilic ulcer
Necrotizing sialometaplasia

Blisters

Blisters may be seen as a result of burns or mucoceles, but the most important vesiculobullous disorders affecting the gingivae are pemphigoid (including cicatricial pemphigoid) and pemphigus and the typical presentation is of desquamative gingivitis. Vesicles may be seen in viral infections, especially in herpes simplex stomatitis,

chickenpox, herpangina and hand, foot and mouth disease [3–6].

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Genetic disorders affecting the periodontium

Hereditary gingival fibromatosis

Aetiology. An autosomal dominant condition due to chromosome 2 or 5 anomalies, resulting in transforming growth factor (TGF)-β1 autocrine stimulation of fibroblast proliferation with alteration in expression of matrix metalloproteinases (MMP)-1 and MMP-2 [1–14].

Pathology. The gingival connective tissue is mainly composed of thick interlacing collagen fibres forming a dense, almost avascular, mass in which many fibrocytes have dark shrunken nuclei. Mucoid material and some giant cells may be found.

Clinical features. There is generalized gingival enlargement, especially obvious over the anterior maxilla and during the transition from deciduous to permanent dentitions [1]. If the enlargement is gross, it may move or cover the teeth and even protrude from the mouth. The changes initially involve the gingival papillae and later the attached gingiva. The affected gingiva is usually of normal colour but firm in consistency, and the surface becomes coarsely stippled. Patients may also be hirsute, as may patients with drug-induced gingival hyperplasia. The prognosis is good, but gingival surgery is often indicated.

Although most patients have only gingival fibromatosis, there are occasional associations with supernumerary teeth [15] or with Zimmermann–Laband, Rutherford's, Cowden's and Cross's syndromes [16–18].

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Juvenile hyaline fibromatosis (see Chapter 46)

SYN. MURRAY–PURETIC–DRESCHER SYNDROME

Gingival enlargement may be seen in juvenile hyaline fibromatosis. It may precede tooth eruption or may present only in the first decade. It increases with age. Histology shows dilated capillaries in a hyaline PAS (periodic acid–Schiff)-positive matrix with pseudocartilaginous cells [1–5].

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Hypoplasminogenaemia

Gingival swelling and ulceration may be seen in this disorder in which there can also be ligneous conjunctivitis [1].

REFERENCE

1 Scully C, Gokbuget AY, Allen C *et al*. Oral manifestations indicative of plasminogen deficiency (hypoplasminogenemia). *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2001; **91**: 344–7.

Neutrophil defects (see p. 66.56)

A number of genetic disorders affecting neutrophil counts or function can lead to early-onset periodontitis, often with oral ulceration [1] (see p. 66.56).

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Leukocyte adhesion deficiency

Defects in cell-surface receptors on neutrophils and other leukocytes result in a range of disorders, especially recurrent cutaneous, respiratory and middle-ear infection, as well as periodontal destruction in both dentitions.

Local efforts to preserve the dentition, using débridement together with antimicrobials have been of little value [1–4].

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Papillon–Lefèvre syndrome (see Chapter 34)

This is a rare, autosomal recessive condition of palmoplantar hyperkeratosis with periodontal breakdown (periodontosis or periodontoclasia) that manifests from childhood [1–3] and is related to a defect in cathepsin C [4] with defective polymorphonuclear leukocyte function [5].

The major oral feature of Papillon–Lefèvre syndrome is premature periodontal breakdown. The teeth develop and erupt normally in both the deciduous and permanent dentitions but the gingiva become red, swollen and bleed easily with the formation of periodontal pockets, loss of alveolar bone, loosening and loss of the teeth. The teeth are involved roughly in the order they erupt. The deciduous teeth are often lost by the age of 5 years and the permanent teeth are almost invariably lost by the age of 16 years. There are no obvious abnormalities in either the tooth cementum or dentine.

Hyperkeratosis of the palms and particularly the soles appears at about the age of 3–5 years, concurrent with periodontal breakdown of the deciduous dentition. Similar plaques may also be seen on the lips, cheeks and eyelids. The affected skin shows diffuse hyperkeratosis, hypergranulosis and acanthosis. There may also be calcification of the dura and some patients have recurrent pyogenic infections [6].

Similar syndromes include Haim–Munk syndrome [7], late-onset Papillon–Lefèvre syndrome [8], a condition including arachnodactyly and acro-osteolysis [9], and Unna–Thost syndrome (see below).

Diagnosis is on clinical and radiographic grounds. Intensive dental care is needed. Retinoids may be useful in suppressing oral and cutaneous lesions and minimizing the pyogenic infections [6,10,11] and it is possible to retain the dentition for some years [12].

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Unna–Thost syndrome (hereditary palmoplantar keratoderma)

The Unna–Thost variety of hereditary palmoplantar keratoderma may be associated with oral keratosis and/or periodontitis [1–3].

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Ehlers–Danlos syndrome [1–5]

Early-onset periodontitis is seen in Ehlers–Danlos syndrome, particularly type VIII (see Chapter 46).

REFERENCES

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Down's syndrome [1,2]

Early-onset periodontitis is common in Down's syndrome.

REFERENCES

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Prader–Willi syndrome [1–3]

Early-onset periodontitis has been recorded in Prader–Willi syndrome, presumably as a consequence of the diabetes.

REFERENCES

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Congenital epulis

SYN. GRANULAR CELL TUMOUR OR MYOBLASTOMA

Epulis is the term applied to a swelling on the gingiva. Congenital epulis is a rare, benign, pedunculated, firm pink swelling on the maxillary alveolus, seen in an infant [1,2]. It can be a prenatal ultrasonographic diagnosis [3,4]. There is an 8 : 1 female predominance.

It is probably a reactive mesenchymal lesion and is usually treated by excision. Histology shows large polygonal cells with a fine granular eosinophilic cytoplasm.

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Epstein's pearls

SYN. GINGIVAL CYSTS OF THE NEWBORN

Epstein's pearls are superficial, white, keratin-containing cysts seen on the palatal or alveolar mucosa of about 80% of neonates. They are symptomless and inconsequential, usually being shed within a few weeks, sometimes found with cleft lip and palate [1–3].

REFERENCES

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Acquired disorders affecting the periodontium

Chronic gingivitis

This is an extremely common condition. Over 90% of dentate adults exhibit some degree of gingivitis. The accumulation of dental bacterial plaque because of inadequate oral hygiene produces non-specific chronic inflammation. It is painless but may manifest with bleeding from the gingival crevice. The gingival margins are red and slightly swollen [1].

Dental advice on improved oral hygiene is needed. If untreated it may progress to periodontitis and tooth loss.

REFERENCE

1 Page RC. Gingivitis. *J Clin Periodontol* 1986; **13**: 345–59.

Chronic periodontitis

Chronic periodontitis (inflammation of the gingiva and periodontal membrane) may be a sequel of chronic gingivitis usually because of plaque accumulation and calculus (tartar) [1]. Smoking is a risk factor. The gingiva

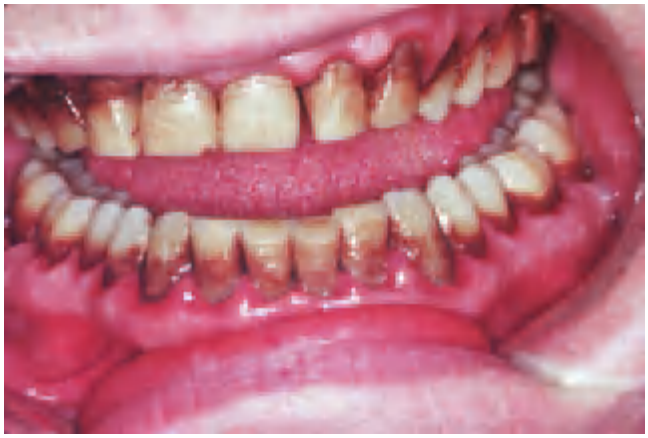

Fig. 66.14 Periodontitis.

detaches from the tooth neck, the periodontal membrane and alveolar bone are damaged, and an abnormal gap (pocket) develops between the tooth and gum. The tooth may slowly loosen and eventually be lost (Fig. 66.14).

Diagnosis. Chronic periodontitis is typically seen in adults. It is painless but may be associated with bleeding, halitosis and a foul taste. Debris and pus may be expressed from the pockets (pyorrhoea), and there may be increasing tooth mobility.

Management. Although periodontal disease has a bacterial component, systemic antibiotics have no place in routine treatment. Management comprises improvement in oral hygiene, although in this case plaque accumulates below the gumline, within periodontal pockets. Toothbrushing and mouthwashes have effect only above, or very slightly below, the gum level and are therefore ineffective in the treatment of periodontitis. Surgical removal of the pocket wall and removal of diseased tissue may be needed to facilitate future cleansing, or attempts to regenerate lost periodontal tissue (such as guided tissue regeneration) may be indicated. Periodontal attention is therefore required.

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Early-onset periodontitis

Periodontal breakdown (periodontitis) is usually a consequence of inflammatory destruction as a result of poor oral hygiene and the subsequent accumulation of dental bacterial plaque [1] and is seen mainly in adults. The host response and periodontal microbiota can both be implicated in a heterogeneous group of causes of early-onset periodontitis [2–10]. If present in children or adolescents, it can be a manifestation of severely neglected oral hygiene, such as seen in some patients with learning disability, or may be a feature of an immunocompromised host.

That host defences are extremely important in maintaining periodontal health is demonstrated well in the periodontal breakdown that may accompany leukaemias, leukocyte defects, diabetes and HIV infection. Periodontal breakdown is also a feature of Down's syndrome, Ehlers–Danlos syndrome type VIII and Papillon–Lefèvre syndrome.

Periodontal breakdown in a child or adolescent who is capable of maintaining good oral hygiene almost invariably suggests an immune or other systemic defect.

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Diabetes

Uncontrolled diabetes can lead to accelerated periodontitis [1].

REFERENCE

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HIV infection

HIV disease can be complicated by necrotizing ulcerative gingivitis (see p. 66.74), periodontitis, candidiasis, herpetic ulceration, Kaposi's sarcoma, lymphomas and other gingival lesions [1].

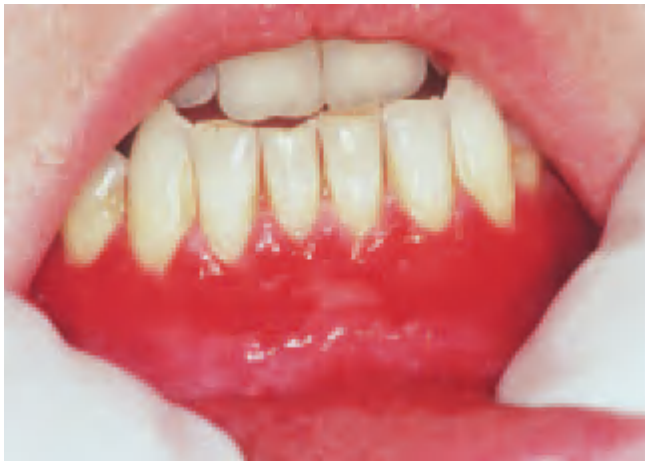

Fig. 66.15 Desquamative gingivitis.

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Desquamative gingivitis

In this fairly common condition, the labial gingiva are persistently glazed, red and sometimes sore but the gingival margins may be spared, differentiating desquamative gingivitis from chronic marginal gingivitis (Fig. 66.15).

Desquamative gingivitis typically affects middle-aged or elderly women and is usually a manifestation of mucous membrane pemphigoid or lichen planus [1–5]. Rarely, it may be seen in pemphigus, dermatitis herpetiformis, linear IgA disease, chronic ulcerative stomatitis with epithelial antinuclear antibodies or other dermatoses [4,5].

Desquamative gingivitis tends to be chronic and recalcitrant. The underlying condition should be treated where possible. Improved oral hygiene and topical corticosteroids in a nocturnally worn polythene splint may help. Dapsone or topical ciclosporin or tacrolimus may be beneficial in severe cases.

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Allergic gingivostomatitis

SYN. ATYPICAL OR PLASMA-CELL GINGIVOSTOMATITIS

Diffusely red, swollen gingivae with or without oral ulceration may occasionally follow exposure to various allergens and other substances. Such reactions have followed the use of certain chewing gums, confectionery such as mints, and dentifrices [1–7] and dental materials [8], particularly 'tartar control' dentifrices containing cinnamon or cinnamaldehyde [2].

Biopsy is usually not indicated and is fairly non-specific with epithelial atrophy, oedema and a variable cellular infiltrate in the lamina propria which, in the earlier reported cases due to chewing gum, was often predominantly plasmacytic [1,3,5–7]. The lesions resolve on withdrawal of the causal agent and reappear on rechallenge. Patch testing may be of value in diagnosis.

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Idiopathic plasmacytosis (see also Plasma-cell balanitis, Chapter 68)

This term refers to red, velvety gingival lesions associated with a plasmacytic infiltrate. Most cases are restricted to the gingiva (atypical gingivostomatitis, plasmacyte gingivitis, allergic gingivostomatitis) [1], while a few have supraglottic laryngeal lesions [2]. Corticosteroids are the main treatment but irradiation may be required [3].

REFERENCES

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Fibroepithelial polyp

SYN. FIBROUS LUMP

Fibrous lumps are common in the mouth and are seen

mainly in adults. They appear to be purely reparative in nature. They may attain their full size (which rarely exceeds 2.5 cm diameter) quite rapidly, and then stop growing. Fibrous lumps should not be confused with the true fibroma, a benign neoplasm derived from fibroblasts, which is rare in the mouth (see below).

The variable inflammatory changes account for the different clinical presentations of fibrous lumps from red, shiny, soft lumps to those which are pale, stippled and firm [1]. Commonly, they are round pedunculated swellings arising from the marginal or papillary gingiva (epulides), sometimes adjacent to sites of irritation (e.g. a carious cavity). They are usually painless. They may reach quite a large size, but the prognosis is good.

Fibrous epulides should be removed down to the periosteum, which should be curetted thoroughly.

Fibroma [1]

The true fibroma, a benign neoplasm of fibroblastic origin, is rare in the oral cavity and many lesions in the past called fibromas were probably fibroepithelial polyps.

Histology shows marked proliferation of fibroblasts, with nuclei of uniform shape, size and staining characteristics.

The true fibroma is a continuously enlarging new growth, not necessarily arising at a site of potential trauma. It is a pedunculated growth with a smooth, non-ulcerated, pink surface.

Removal should be total, deep and wide.

REFERENCE

1 Lee KW. The fibrous epulis and related lesions. *Periodontics* 1986; **6**: 277–99.

Pyogenic granuloma (see Chapter 53)

Pyogenic granuloma commonly affects the gingiva, the lip or the tongue [1]. In these sites, the lesion should be excised completely. It will readily recur if excision is not adequate.

REFERENCE

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Giant cell epulis

SYN. PERIPHERAL GIANT CELL GRANULOMA

The giant cell epulis probably arises because chronic irritation triggers a reactionary hyperplasia of muco-periosteum and excessive production of granulation tissue. Giant cell granulomas are occasionally a feature of hyperparathyroidism.

The giant cell epulis characteristically arises interdentally, adjacent to permanent teeth that have had deciduous predecessors [1], i.e. not the permanent molars. Classically, the most notable feature is the deep-red colour, although older lesions tend to be paler.

This is a benign lesion which is cured by excision.

REFERENCE

1 Giansanti JS, Waldron CA. Peripheral giant cell granuloma: review of 720 cases. *J Oral Surg* 1969; **27**: 787–91.

Pregnancy gingivitis and epulis

There can be an exaggerated inflammatory reaction to dental bacterial plaque in pregnancy, and chronic gingivitis may therefore be aggravated giving rise to 'pregnancy gingivitis' [1,2] and, occasionally, a pyogenic granuloma (pregnancy epulis).

Pregnancy gingivitis is characterized by soft reddish enlargements, usually of the gingival papillae, varying from small smooth enlargements to more extensive, ragged, granular lumps resembling the surface of a strawberry. Changes of pregnancy gingivitis usually appear about the second month of pregnancy, and reach a peak at the eighth month. Poor oral hygiene predisposes to these changes. A similar appearance may occur with oral contraceptives.

Sometimes there is a localized epulis (pregnancy epulis) that, although unsightly, is usually painless. Occasionally it ulcerates or interferes with eating. Despite the vascularity, the immaturity of the vessels may lead to superficial ischaemia and ulceration. Larger lesions are prone to trauma, which may contribute to the ulceration.

Oral hygiene should be improved. Most lesions tend to resolve on parturition. There is one report of a beneficial effect of folic acid on pregnancy gingivitis [3]. An epulis requires excision only if it is being traumatized or is grossly unaesthetic [2].

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Drug-induced gingival swelling

Gingival swelling is a recognized adverse effect of medication, especially following use of phenytoin, calcium-channel blockers and ciclosporin.

Phenytoin

Phenytoin induces gingival swelling presumably by an effect on fibroblast activity. There is no correlation between the extent of overgrowth and the dose of phenytoin, its serum level, or the age and sex of the patient. Rather, the hyperplasia is aggravated by poor oral hygiene.

Phenytoin can produce a variable degree of gingival enlargement, which characteristically affects the interdental papillae first but which may later involve the marginal and even attached gingiva. The palatal and lingual gingivae are usually involved less than the buccal and labial gingivae [1–4].

The enlargement is characteristically firm, pale and tough, with coarse stippling, although these features may take several years to develop, and earlier lesions may be softer and redder (see Fig. 66.12).

The patient's level of plaque control should be improved [5] and a 0.2% aqueous chlorhexidine mouthwash may be helpful. Excision of the enlarged tissue may be indicated but the swelling unfortunately readily recurs, although this is less likely with meticulous oral hygiene, particularly if the phenytoin can be stopped. Folic acid may improve the condition and systemic isotretinoin may be of some value [2].

Calcium-channel blockers

Nifedipine can cause gingival swelling, typically affecting the papillae in a similar fashion to phenytoin [3,6]. Several other calcium-channel blockers have a similar effect [7].

Improved oral hygiene may reduce the hyperplasia [8]. Excision of the enlarged tissue may be followed by recurrence, and patients should be warned accordingly. If possible the medication should be changed.

Ciclosporin

Ciclosporin also causes gingival hyperplasia, initially of papillae [3,9]. Only about one-third of patients are affected, more commonly children, and this change may be lessened by meticulous removal of plaque before the drug is introduced.

REFERENCES

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Scurvy (see Chapter 57)

Scurvy (vitamin C deficiency) causes gingival swelling, bleeding and oral purpura, but is now rare in the West.

Disorders affecting the oral mucosa or lips

Swellings

Mucosal swelling may be seen after trauma and in angio-oedema, Crohn's disease, orofacial granulomatosis, sarcoidosis, Wegener's granulomatosis, amyloidosis and other disorders. Localized swellings may be of local aetiology or can be manifestations of neoplasia or systemic disease.

Pigmentation

Mucosal pigmentation is usually seen in dark-skinned races (but may be seen even in white people) (see Fig. 66.13). Other common causes include amalgam tattoo and melanotic macules.

Addison's disease, Kaposi's sarcoma, melanoma, Laugier–Hunziker syndrome, pigmentary incontinence and other causes must be excluded. Peutz–Jeghers disease is the association of circumoral and sometimes intraoral melanosis with small-intestinal polyposis (see Chapter 59). Oral petechiae are usually caused by trauma or suction. More widespread purpura is most frequently a manifestation of a bleeding tendency caused by thrombocytopenia and may also be seen in infectious mononucleosis, rubella, HIV infection, leukaemia or scurvy. Petechiae may also occur in amyloidosis.

Redness

Red lesions may be inflammatory, or represent erythroplasia, haemangiomas or neoplasms such as carcinoma, Wegener's granulomatosis or Kaposi's sarcoma [1,2].

Candidiasis is a common cause of red lesions, which may be sore. Widespread erythema, particularly if associated with soreness, is usually caused by primary herpes simplex stomatitis or a mucocutaneous disorder such as lichen planus or mucous membrane pemphigoid, rarely by pemphigus or other dermatoses and occasionally by allergic responses.

Localized red areas may represent erythroplasia, carci-

noma, candidiasis, lichen planus or lupus erythematosus. Kaposi's sarcoma may present as a red, purple, brown or bluish macule or nodule as may epithelioid angiomatosis. Hereditary mucoepithelial dysplasia is a rare cause of oral erythema.

Telangiectasia may be a manifestation of hereditary haemorrhagic telangiectasia, primary biliary cirrhosis or systemic sclerosis, or may follow radiotherapy. Haemangiomas are usually isolated but may occasionally extend deeply and rarely involve the ipsilateral meninges, producing a facial angioma and epilepsy, sometimes with learning disability (Sturge–Weber syndrome). Intraoral haemangiomas may be seen in Maffucci's syndrome.

Lingual depapillation in deficiencies of iron, folate or vitamin B_{12} may produce the red tongue termed 'glossitis'. Geographical tongue may also produce red patches.

Mucositis can readily be induced by irradiation or chemotherapy.

Ulcers

Oral ulcers are often caused by trauma or recurrent aphthae (see p. 66.43). Malignant neoplasms may present as ulcers. Various infections or systemic disorders, particularly those of blood, gastrointestinal tract or skin, also produce mouth ulcers, as may drugs and irradiation (see Table 66.10).

Blisters

Blisters may be seen as a result of burns but the most important vesiculobullous disorders affecting the oral mucosa are pemphigoid (including cicatricial pemphigoid) and pemphigus (see Table 66.10). The bullae of mucous membrane pemphigoid may or may not be blood-filled and, in the former case, a bleeding tendency must be excluded. Blood-filled blisters may also be caused by localized oral purpura (angina bullosa haemorrhagica) or amyloidosis. The bullae of pemphigus are rarely seen as they break down rapidly to produce ulcers. Epidermolysis bullosa and erythema multiforme may present with oral bullae or vesicles, although ulcers are more common. Vesicles may be seen in viral infections, especially in herpes simplex stomatitis, chickenpox, herpangina and hand, foot and mouth disease.

Mucoceles, caused by extravasation of mucus from minor salivary glands, produce isolated blisters, typically in the lower labial mucosa.

White patches (see Table 66.9)

Thrush (acute candidiasis) is a 'disease of the diseased' and produces oral white patches.

HIV infection causes hairy leukoplakia, a white lesion on the tongue (see p. 66.89).

Leukoplakia is often associated with friction or smoking, occasionally with syphilis, candidiasis or chronic renal failure, but most cases are idiopathic. Lichen planus and lupus erythematosus may present as white lesions. Rarely, lichenoid lesions are associated with various drugs, liver disease or GVHD. Carcinoma may present as a white lesion.

Inherited causes of white patches, such as white sponge naevus and dyskeratosis congenita, are rare [1–5].

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Genetic disorders affecting the oral mucosa or lips

This section discusses the main congenital causes of white or whitish lesions, pigmented lesions, red lesions, vesiculoerosive lesions, lumps and swellings, and some orocutaneous disorders.

White or whitish lesions

Sebaceous glands

Fordyce spots

SYN. FORDYCE'S GRANULES

Fordyce spots are yellowish small grains seen beneath the buccal or labial mucosa. Fordyce spots are sebaceous glands containing neutral lipids similar to those found in skin sebaceous glands [1] but are not associated with hair follicles.

Fordyce spots are extremely common: probably 80% of the population have them. They are usually seen in the buccal mucosa, particularly inside the commissures (Fig. 66.16), and sometimes in the retromolar regions and upper lip [1–5]. Fordyce spots are often not noticeable in children until after puberty (although they are present histologically), and they seem to be more obvious in males, patients with greasy skin and the elderly, and they may be increased in some rheumatic disorders [6].

Fordyce spots are totally benign, although the occasional patient or physician becomes concerned about them or misdiagnoses them as thrush or lichen planus. Occasionally they may be mistaken for leukoplakia [7].

No treatment is indicated, other than reassurance. The spots may become less prominent if isotretinoin is given [8].

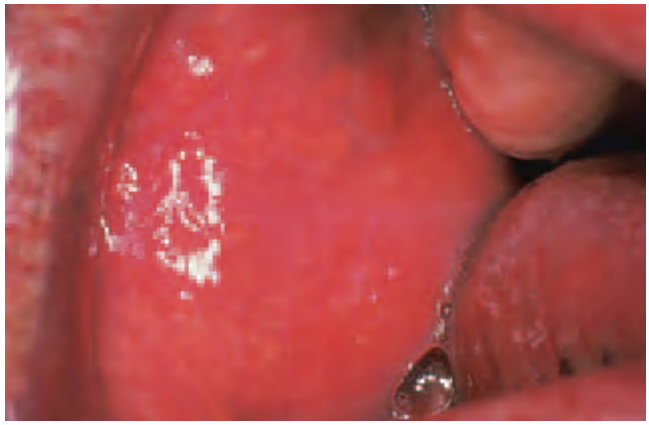

Fig. 66.16 Fordyce spots: sebaceous glands in the buccal mucosa.

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Sebaceous adenoma

Sebaceous adenomas are exceedingly rare in the mouth, except in association with salivary glands but have been described in the buccal mucosa [1–5].

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Nevus sebaceus of Jadassohn

SYN. LINEAR NAEVUS SYNDROME

Oral manifestations may rarely occur as fibroepitheliomatous nodules in patients with a sebaceous naevus of the skin but are extremely rarely seen in isolation [1–3].

REFERENCES

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Epithelium

Leukoedema

Leukoedema is not a mucosal disease but simply the name given to the faint whitish lines seen in some normal buccal mucosae, often prominent in black people. The whitish lines disappear if the mucosa is stretched—a diagnostic test [1–3]. Confusion with lichen planus should thereby be avoided.

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Clouston syndrome (see above)

See also Chapter 12.

White-sponge naevus

SYN. CANNON'S DISEASE; PACHYDERMIA ORALIS; WHITE FOLDED GINGIVOSTOMATOSIS

Aetiology. A rare familial disorder usually first seen in childhood and inherited as an autosomal dominant trait [1,2]; there appear to be defects in keratins 4 and 13 with abnormal tonofilament aggregation [3–6].

Pathology. There is hyperplastic acanthotic epithelium in which gross oedema causes a basket-weave appearance. The superficial epithelium has a 'washed-out' appearance as it stains only very lightly.

Clinical features. The oral mucosa is almost invariably involved in white-sponge naevus. Painless shaggy or folded white lesions typically affect the buccal mucosa bilaterally but may also involve other areas, although rarely the gingival margins.

Similar lesions may also affect the upper respiratory tract, genitalia and anus [1,2].

Diagnosis. The family history and clinical examination are usually adequate to differentiate this from other more

common causes of white lesions such as cheek biting, burns, lichen planus and candidiasis.

Treatment. This is a benign condition with an excellent prognosis. Reassurance is all that is required, although some have suggested that tetracyclines clear the lesions [7,8].

REFERENCES

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Dyskeratosis congenita (see Chapter 12)

SYN. ZINSSER–ENGMAN–COLE SYNDROME

Dyskeratosis congenita usually presents with oral lesions between the ages of 5 and 10 years, when the tongue and sometimes the buccal mucosa and palate develop diffuse white lesions with a malignant potential [1,2]. The lesions resemble leukoplakia or lichen planus and show non-specific hyperkeratosis, a prominent granular cell layer and mild acanthosis [1–5].

Other manifestations include lesions of other mucosae, skin and appendages, and bone marrow dysfunction. Other rare oral features include taurodont or hypocalcified teeth and mucosal hyperpigmentation.

REFERENCES

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Pachyonychia congenita (see Chapter 62)

SYN. JADASSOHN–LEWANDOWSKY SYNDROME

Pachyonychia congenita is a benign disorder associated with mutations in keratin 16 [1,2]. About 60% of patients have oral keratosis, 16% have natal or neonatal teeth, and 10% have angular stomatitis. Some patients also develop chronic intraoral candidiasis [3–5].

The keratosis requires no treatment. Dental advice should be sought regarding natal or neonatal teeth.

REFERENCES

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Tylosis [1–4] (see Chapter 34)

Tylosis is an autosomal dominant syndrome of palmoplantar hyperkeratosis that may predispose to oesophageal carcinoma but although oral white lesions have also been described, there is little evidence that these are premalignant.

REFERENCES

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Focal palmoplantar and oral hyperkeratosis syndrome (keratosis palmaris et plantaris)

Focal hyperkeratosis at weight-bearing areas of the palms and soles, with hyperkeratosis of the attached gingiva and occasionally other sites, is an autosomal dominant trait [1–3].

REFERENCES

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Olmsted's syndrome [1–3] (see Chapter 34)

SYN. CONGENITAL PALMOPLANTAR AND PERIORIFICIAL KERATODERMA WITH CORNEAL EPITHELIAL DYSPLASIA

Perioral keratoderma may be seen associated with palmoplantar keratoderma and corneal epithelial dysplasia.

REFERENCES

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Hereditary benign intraepithelial dyskeratosis [1–3]

SYN. WITKOP–VON SALLMANN SYNDROME

Aetiology. Hereditary benign intraepithelial dyskeratosis is a rare, benign, autosomal dominant condition associated with chromosome 4 anomalies, seen mainly in some groups of mixed ethnic origin, predominantly in North Carolina, USA.

Pathology. There is pronounced epithelial acanthosis, vacuolization in the stratum spinosum and eosinophilic cells apparently engulfed by normal squamous cells ('tobacco cells').

Clinical features. Oral milky white, smooth, somewhat translucent plaques appear in childhood and become more obvious by adolescence. These lesions affect predominantly the buccal mucosae, lips and ventrum of the tongue.

Ocular lesions include conjunctivitis with gelatinous conjunctival plaques, which become evident in infancy. There may be photophobia and eventual corneal involvement.

Oral biopsy is usually indicated for diagnosis.

Treatment. No treatment is required.

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Darier's disease (see Chapter 40)

Oral lesions are seen in up to 50% of patients with skin lesions of Darier's disease. The oral changes are most marked in patients with the most severe skin changes and are typically flattish, coalescing, red plaques that eventually turn white and affect the keratinized mucosa of the dorsum of the tongue, palate and gingiva (Fig. 66.17) and then may resemble nicotinic stomatitis clinically [1–3].

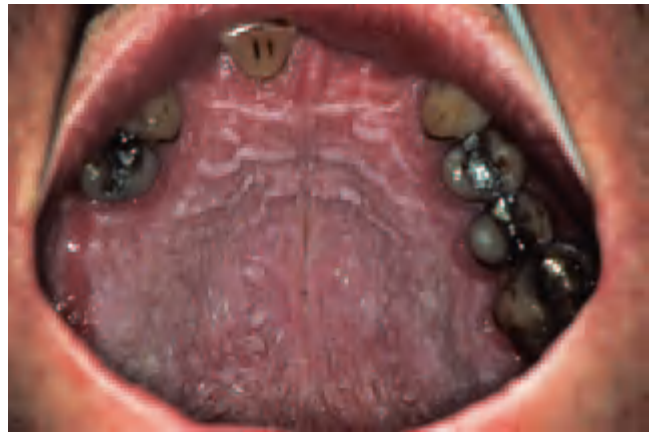

Fig. 66.17 Darier's disease: oral white lesions resemble those of nicotinic stomatitis.

Salivary duct anomalies, including dilatations with periodic strictures and indentations, may affect the main ducts [4,5].

REFERENCES

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Warty dyskeratoma [1–4] (see Chapter 34)

SYN. FOCAL ACANTHOLYTIC DYSKERATOSIS

Warty dyskeratoma, oral warty dyskeratoma or focal acantholytic dyskeratosis is rare in the oral cavity but typically presents as a nodule or papule on the gingiva, palate or alveolar ridge. The histology is similar to that of Darier's disease and transient acantholytic dermatosis, with suprabasal epithelial splits and corps ronds.

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Keratitis, ichthyosis and deafness syndrome (see Chapter 34)

SYN. KID SYNDROME

Dental dysplasia, persistent oral ulceration, chronic mucocutaneous candidiasis and occasional carcinoma may be seen in the KID syndrome of keratitis, ichthyosiform dermatosis and deafness [1,2].

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Chronic mucocutaneous candidiasis (see Chapter 31)

Chronic mucocutaneous candidiasis includes a range of congenital disorders characterized by chronic candidiasis involving mouth, nails and other sites. Persistent adherent white lesions are seen in the mouth, often with angular stomatitis [1–4]; in candidiasis–endocrinopathy syndrome, there may also be enamel hypoplasia [5,6] and, rarely, oral carcinoma [7].

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Pigmented lesions

Most oral hyperpigmentation is racial in origin (see Fig. 66.13). Seen mainly in blacks and Asians it can also be noted in patients of Mediterranean descent, sometimes even in some fairly light-skinned people. It is most obvious in the anterior labial gingivae and palatal mucosa and pigmentation is usually symmetrically distributed. Patches may be seen elsewhere. Pigmentation may be first noted by the patient in adult life and then incorrectly assumed to be acquired rather than congenital in origin.

Melanotic macule

The melanotic macule is an acquired, small, flat, brown to brown-black, asymptomatic, benign lesion, unchanging in character [1,2]. Oral melanotic macule is similar to the ephelis and lentigo.

Melanotic macules may be seen in up to 3% of normal persons, at any age. Melanotic macules are usually solitary, discrete, pigmented brown collections of melanin-containing cells. The macules are less than 2 cm in diameter, seen especially on the vermilion of the lips, gingiva, buccal mucosa or palate. Most on the lips are seen near the midline, on the lower lip vermilion. Most are solitary and seen in white adults and their colour ranges from brown to black [1,3,4]. Occasional cases are seen in HIV infection [5].

Clinically, the melanotic macule may resemble other lesions such as early melanoma and ephelides, although the latter tend to fade in winter and darken in summer. Histopathologically, the mucosal epithelium is normal apart from increased pigmentation of the basal layer, accentuated at the tips of rete ridges. There are no naevus cells or elongated rete ridges [3]. There is melanin in the epithelial basal layer and/or upper lamina propria. Occasionally they are seen along with melanonychia striata (Laugier–Hunziker syndrome, see below).

Melanotic macules can be excised to exclude melanoma or for cosmetic reasons, or hidden by lipstick.

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Peutz–Jeghers syndrome (see Chapter 39)

Peutz–Jeghers syndrome is as an autosomal dominant trait characterized by hamartomatous intestinal polyposis and mucocutaneous melanotic pigmentation, especially circumorally. Those affected have discrete, brown to bluish black macules mainly around the oral, nasal and ocular orifices. The lips, especially the lower, have pigmented macules in about 98% of patients (Fig. 66.18). Oral brown or black macules, unlike the circumoral lesions, do not

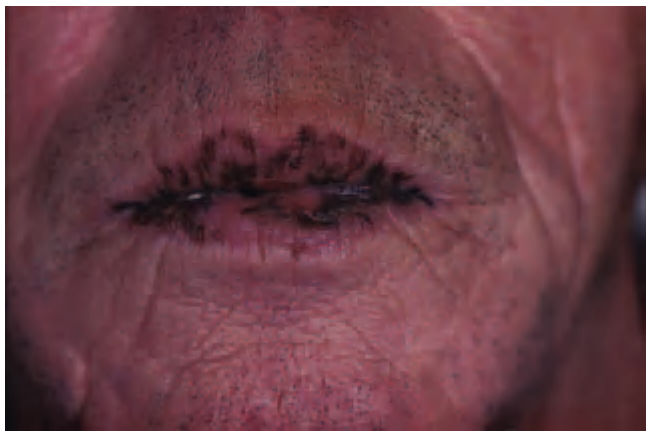

Fig. 66.18 Peutz–Jeghers syndrome.

fade after puberty. Mucosal and facial hyperpigmentation may also be seen in relatives [1–3].

Intestinal polyps are found mainly in the small intestine in Peutz–Jeghers syndrome. They rarely undergo malignant change but if they produce intussusception, surgical intervention is required. There is a slightly increased risk of gastrointestinal carcinoma and carcinomas of the pancreas, breast and reproductive organs [4–7].

Ruby and argon lasers have been used to treat the pigmentation of the lips and oral mucosa [8] (see Chapter 77).

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Laugier–Hunziker syndrome

SYN. LAUGIER–HUNZIKER–BARAN SYNDROME
[1–4]

Laugier–Hunziker syndrome presents with labial, oral mucosal and nail hyperpigmentation. A possible variant of this or Peutz–Jeghers syndrome has been termed *idiopathic lenticular pigmentation* [5], in which there are oral, labial, perianal and digital hyperpigmented lenticular macules. Similar patients have been reported previously [6–8].

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Pseudoxanthoma elasticum

See Chapter 46.

Lentiginoses

The lentiginoses (or lentigenoses) include Peutz–Jeghers syndrome (Chapter 39) and the LEOPARD syndrome, which comprises:

- *l*entigines (multiple);
- *e*lectrocardiographic conduction abnormalities;
- *o*cular hypertelorism;
- *p*ulmonary stenosis;
- *a*bnormalities of genitalia;
- *r*etardation of growth; and
- *d*eafness.

The lentiginoses also include the syndrome of arterial dissections with lentiginosis, Laugier–Hunziker syndrome, Cowden disease, Ruvalcaba–Myhre–Smith (Bannayan–Zonana) syndrome, and the centrofacial, benign patterned and segmental lentiginoses, all of which can be associated with a variety of developmental defects.

Centrofacial lentiginosis syndrome

SYN. TOURAINE'S CENTROFACIAL LENTIGINOSIS

Centrofacial lentiginosis [1] is associated with bone abnormalities, malformations due to dysraphia, endocrine dysfunctions and neurological diseases.

REFERENCE

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Complex of myxomas, spotty pigmentation and endocrine overactivity

SYN. CARNEY'S SYNDROME; CARNEY COMPLEX

This autosomal dominant trait causes cardiac and cutaneous myxomas, with mammary myxoid fibroadenomas, spotty cutaneous hyperpigmentation, primary pigmented nodular adrenocortical disease, testicular Sertoli cell tumours and growth hormone-secreting pituitary adenoma. It may present with oral hyperpigmentation and myxomas [1–4]. The hyperpigmentation in Carney complex is facial and occurs on the vermilion of the lips in about 35%, although about 8% have pigmented lesions on the oral mucosa and about 2% have oral myxomas, usually on the palate or tongue [2]. Carney complex differs clinically from Peutz–Jeghers syndrome in that hyperpigmentation is less common intraorally but more common on the conjunctiva, and other manifestations are also present.

Cases previously described as NAME syndrome (*n*aevi, *a*trial myxoma, *m*yxoid neurofibromas, *e*phelides) and LAMB syndrome (*l*entigines, *a*trial myxoma, *m*ucocutaneous myxoma, *b*lue naevi) may represent this complex, which also has close similarities to LEOPARD syndrome and the syndrome of arterial dissections with lentiginosis (see Chapter 39).

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Inherited patterned lentiginosis in black people

This autosomal dominant condition is characterized by small, discrete, hyperpigmented macules on the face, lips, extremities, buttocks and palmoplantar areas [1]. No patients have been reported with oral mucosal lesions or internal organ system abnormalities.

This condition can resemble other lentiginosis syndromes, especially Peutz–Jeghers syndrome, centrofacial lentiginosis syndrome and Carney complex.

REFERENCE

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Naevi

Pigmented naevi are much less common in the oral mucosa than in skin. Approximately half of naevi are histologically of the intradermal (intramucosal) type; one-third are blue naevi, many others are compound naevi and some are junctional naevi.

Pathology. They are formed from increased melanin-containing cells, are flat or raised, do not change rapidly in size or colour, are painless and are seen particularly on the palate. The intramucosal type of naevus is most common (about 60%), while another 25% are blue naevi. Compound and junctional naevi and combined naevi are rare in the mouth. The intramucosal naevus consists of a collection of melanocytic cells in the lamina propria without involvement of the epithelium. The blue naevus consists of spindle cells at any level in the lamina propria. The junctional naevus consists of clusters of benign naevus cells at the epithelio-mesenchymal junction and the lamina propria is otherwise not involved.

Clinical features. Pigmented naevi are seen particularly on the vermilion border of the lip and on the palate or buccal mucosa [1]. These lesions are usually brown, macular, do not change rapidly in size or colour and are painless. The prognosis is good.

Treatment. There is no evidence that most naevi, except junctional naevi, progress to melanoma. However, they may resemble melanomas. If early detection of oral melanomas is to be achieved, all pigmented oral cavity lesions should be viewed with suspicion. Therefore, excision biopsy is recommended to exclude malignancy, because of the premalignant potential of some, particularly the junctional naevus, and for cosmetic reasons (Table 66.11). This is particularly important if the lesions are raised or nodular [2].

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Red lesions

Vascular anomalies

Hereditary haemorrhagic telangiectasia (see Chapter 51)

SYN. OSLER–RENDU–WEBER SYNDROME

This syndrome is characterized by multiple telangiectasia on the lips, perioral skin, oral and nasal mucosae [1,2] as

Table 66.11 Causes of mucosal pigmentation.

Localized
Amalgam tattoo
Ephelis (freckle)
Naevus
Malignant melanoma
Kaposi's sarcoma
Peutz–Jegher syndrome
Laugier–Hunziker syndrome
Melanotic macules
Complex of myxomas, spotty pigmentation and endocrine overactivity
Generalized
Racial
Localized irritation, e.g. smoking
Drugs, e.g. phenothiazines, antimalarials, minocycline, contraceptives, mephenytoin
Addison's disease
Nelson's syndrome
Ectopic adrenocorticotrophic hormone (e.g. bronchogenic carcinoma)
Heavy metals
Albright's syndrome
Other rare causes, e.g. haemochromatosis, generalized neurofibromatosis, incontinentia pigmenti
Malignant acanthosis nigricans

well as the gastrointestinal tract. Occasionally there are colonic or hepatic complications [3,4]. Oral haemorrhage can be controlled by cryotherapy, cautery, infrared coagulation or Nd-Yag laser [5,6].

REFERENCES

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Haemangioma

Haemangiomas are usually deep red or blue–purple, blanch on pressure, are fluctuant to palpation, and are level with the mucosa or have a lobulated or raised surface [2]. Most are small and of no consequence [1,2].

Most haemangiomas are seen in isolation but a few may be multiple and/or part of a wider syndrome such as Maffucci syndrome [3]. Large facial haemangiomas, which can involve the lips, may be associated with Sturge–Weber syndrome (Fig. 66.19) [3] or Dandy–Walker syndrome, or other posterior cranial fossa malformations [4].

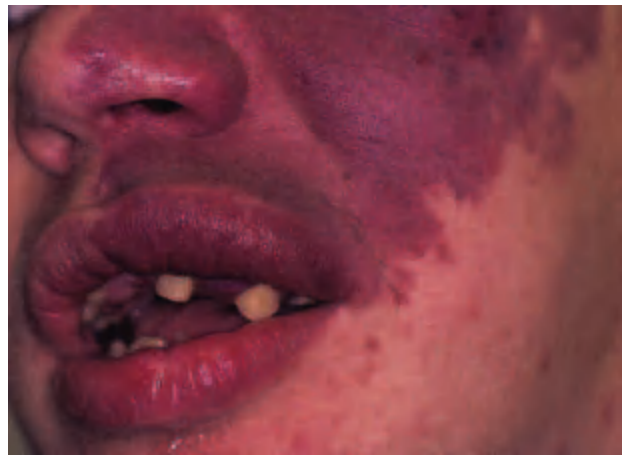

Fig. 66.19 Haemangioma affecting the lip in Sturge–Weber syndrome.

Haemangiomas are at risk from trauma and prone to excessive bleeding if damaged (e.g. during tooth extraction). Occasionally, oral haemangiomas develop phlebolithiasis.

Oral lesions suspected of being haemangiomatous should not be routinely biopsied; aspiration is far safer. Kaposi's sarcoma and epithelioid angiomatosis should be excluded. After intravenous administration of contrast medium, enhancement is observed in haemangiomas in areas corresponding to those with high signal on T_2-weighted magnetic resonance imaging (MRI).

Oral haemangiomas are left alone unless causing symptoms, when they are best treated with cryosurgery or laser if small, or by ligation or embolization of feeding vessels if large.

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Sturge–Weber–Krabbe syndrome [1–5] (see Chapter 15)

The haemangioma in the trigeminal area in Sturge–Weber syndrome is usually unilateral, may involve the mouth but fortunately rarely involves bone. It may be associated with hypertrophy of affected tissues and, if the patient is treated with phenytoin, with gingival hyperplasia [3].

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Klippel–Trenaunay–Weber syndrome (see Chapter 15)

Haemangiomas of the buccal mucosa and tongue, macroglossia, maxillary hyperplasia and an anterior open bite have been recorded in this syndrome [1–5]. Postextraction bleeding can be a problem [6].

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Blue rubber–bleb naevus syndrome (see Chapter 15)

SYN. BEAN'S SYNDROME

Oral haemangiomas may be seen [1–3].

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Maffucci's syndrome (see Chapter 15)

Oral haemangiomas may be seen [1–4].

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Hereditary mucoepithelial dysplasia

Hereditary mucoepithelial dysplasia is an autosomal dominant dyskeratotic epithelial syndrome affecting oral, nasal, vaginal, urethral, anal, bladder and conjunctival mucosae, causing cataracts, follicular keratosis, nonscarring alopecia and terminal lung disease [1–4].

Pathology. The condition is probably a pan-epithelial cell defect of desmosomal and gap junction structure. Histochemically there is a lack of cornification and keratinization. Electron microscopy shows an abnormality in desmosomes and gap junctions, with a lack of keratohyalin granules, a paucity of desmosomes, intercellular accumulations, cytoplasmic vacuolization, and formation of bands and aggregates of filamentous fibres and structures in the cytoplasm resembling desmosomes and gap junctions. There is some acantholysis as well as benign dyskeratosis of individual cells [1,2]. Histologically the mucosal epithelium shows dyshesion, thinning of the epithelial layer and dyskeratosis. Mucosal Papanicolaou smears show lack of epithelial maturation, cytoplasmic vacuoles and inclusions, and individual cell dyskeratosis.

Clinical features. Red, periorificial mucosal lesions are typically noted during infancy and may persist throughout life. The oral lesions are painless red macules or maculopapules and are seen predominantly on the palate and gingiva.

Severe photophobia, tearing and nystagmus in infancy herald the development of keratitis, corneal vascularization and lens cataracts.

In addition there may be various cardiorespiratory complications, especially potentially lethal bullous lung disease—spontaneous pneumothorax and bullous emphysema, terminating in cor pulmonale. Chronic rhinorrhoea and repeated upper respiratory infections frequently progress to bilateral pneumonia. Loss of hair, diarrhoea, melaena, enuresis, pyuria and haematuria may also be seen.

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Wiskott–Aldrich syndrome (see Chapter 14)

Oral petechiae and infections such as candidiasis may occur in the Wiskott–Aldrich syndrome of thrombocytopenia, immune deficiency and eczema [1–3].

REFERENCES

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Vesiculoerosive disorders

Acrodermatitis enteropathica

Acrodermatitis enteropathica is an inborn error of metabolism resulting in zinc malabsorption and severe zinc deficiency [1–4].

Clinical features. Diarrhoea, mood changes, anorexia and neurological disturbance are reported most frequently in infancy. Growth retardation, alopecia, weight loss and recurrent infections are prevalent in affected toddlers and schoolchildren. A vesiculobullous dermatitis with perioral involvement may be seen, often sparing the vermilion [2]. Zinc deficiency during growth periods results in growth failure and lack of gonadal development in males. Other effects of zinc deficiency include skin changes, poor appetite, mental lethargy, delayed wound healing, neurosensory disorders and cell-mediated immune disorders. Skin lesions and poor wound healing are observed in severe forms and the disorder can be lethal.

Diagnosis. Assays of zinc in granulocytes and lymphocytes provide better diagnostic criteria for marginal zinc deficiency than plasma zinc assays. In cases of doubt, zinc absorption tests using radioisotopes (^{65}Zn or ^{69m}Zn) may be performed. Levels of alkaline phosphatase are reduced.

Management. Management includes zinc sulphate 2 mg/kg daily, at least until adult life.

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Epidermolysis bullosa (see Chapter 40)

Epidermolysis bullosa is characterized by blisters, sometimes preceded by white patches, which develop rapidly, particularly where there is trauma. Blisters rupture to produce ulcers, often with eventual scarring, particularly in the recessive dystrophic types [1–5]. Oral lesions are fairly common in dystrophic and lethal forms of epidermolysis bullosa but are rare in most simplex types except the superficial type, where they are found in 70% of patients [2,6–8]. Overall, oral mucosal lesions are found in about 30% of patients with epidermolysis bullosa [1–5]. There is a predisposition to oral squamous cell carcinoma, mainly in the Hallopeau–Siemens type.

Dental hypoplasia and other defects and delayed tooth eruption may also be a feature, especially in junctional epidermolysis bullosa (Table 66.12) and, with the difficulty in maintaining adequate oral hygiene, there is a predisposition to caries [4].

Patients with recessive dystrophic epidermolysis bullosa suffer from severe growth inhibition due to reduced food intake as a result of severe oropharyngeal and oesophageal blistering or scarring, with smaller maxillae and smaller mandibles than normal [9–11]. Treatment is improved with modalities such as implants [12–14].

The oral manifestations in the various inherited forms of this condition are summarized in Table 66.12 and epidermolysis bullosa acquisita is discussed in Chapter 41.

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Table 66.12 Oral manifestations in epidermolysis bullosa (EB).

Type	EB subtype	Mucosal lesions	Dental hypoplasia
I Epidermolytic (simplex); autosomal dominant	Generalized (Koebner)	±	–
	Localized (Weber–Cockayne)	–	–
	Localized (Kallin)	–	Anodontia
	With mottled pigmentation and punctate keratoderma	+	–
	With bruising (Ogna)	–	±
	Herpetiform (Dowling–Meara)	+	–
	Superficial	+	–
II Junctional; autosomal recessive	Generalized, severe (Herlitz)	+	++
	Generalized, mild	+	+
	Localized	±	+
	Inverse	±	+
	Progressive	+	–
III Dermolytic (dystrophic) Autosomal dominant	Hyperplastic (Cockayne–Touraine)	±	–
	Albopapuloid (Pasini)	+	–
	Pretibial (Kuske–Portugal)	–	–
Autosomal recessive (Hallopeau-Siemens)	Localized	+	±
	Generalized	++	++
	Mutilating	+++	+++
	Inverse	+	–
VI Acquired type	Adult form	±	–
	Child form	+	–

–, absent; +, mild; ++, moderate; +++, severe.

Felty's syndrome

Oral ulceration may be seen in Felty's syndrome [1–3].

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Immune defects

Mouth ulcers (and early-onset periodontitis) feature in congenital immune defects [1–7], including Chédiak–Higashi syndrome, Papillon–Lefèvre syndrome, familial neutropenia, cyclic neutropenia, Job's syndrome, chronic granulomatous disease and glycogen storage disease type 1b.

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Lumps and swellings

Hereditary angio-oedema (C1 esterase inhibitor deficiency)

Hereditary angio-oedema mimics allergic angio-oedema (see Chapter 47), although it produces a more severe reaction, with oedema affecting the lips, mouth, face and neck region, the extremities and gastrointestinal tract after minor trauma [1,2].

Blunt injury is the most consistent precipitating event. The trauma of dental treatment is a potent trigger, and some attacks even follow emotional stress. Oedema may persist for many hours and even up to 4 days. Involvement of the airway is a constant threat. The mortality may be as high as 30% in some families but the disease is compatible with prolonged survival if emergencies are avoided or effectively treated.

Diagnosis. In 85% of cases plasma C1 esterase levels are reduced (type 1 hereditary angio-oedema) but in 15% the

enzyme is present but dysfunctional (type 2 hereditary angio-oedema). In both types, plasma C4 levels fall but C3 levels are normal.

Management. C1 esterase concentrates are available for treatment [3]. Plasminogen inhibitors such as tranexamic acid can be used to mitigate attacks [4], although more effective agents are the androgenic steroids danazol and stanozolol, which raise plasma C1 esterase inhibitor levels to normal [1,2].

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Focal dermal hypoplasia (see Chapter 12)

SYN. GOLTZ–GORLIN SYNDROME

Focal dermal hypoplasia is a rare, presumably X-linked, genodermatosis [1] involving developmental anomalies of tissues and organs of mesoectodermal origin. Thus there are abnormalities of the eyes, skin, musculoskeletal system, central nervous system (CNS) and oral structures.

Papillomas, usually of the oral mucosae and lips, dental anomalies and occasional cleft lip and palate are the main oral features [2,3]. The dental anomalies, seen in about half of affected individuals, include hypodontia, enamel defects and taurodontism [4–6].

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Acanthosis nigricans (see Chapter 34)

Oral papilliferous lesions may be a feature of both familial [1,2] and malignant [1,3–6] acanthosis nigricans. Between 30 and 50% of patients with acanthosis nigricans secondary to neoplasia (malignant acanthosis nigricans) have oral lesions, which involve the tongue and lips predominantly.

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Lymphangioma (see Chapter 51)

Lymphangioma is uncommon in the mouth. At least some are hamartomas and many are of similar structure to haemangiomas and can clinically resemble them, with a 'frog-spawn' appearance, but they contain lymph rather than blood (Fig. 66.20).

Lymphangiomas are usually solitary and affect the tongue predominantly. They are occasionally associated with cystic hygroma [1–5].

Small lymphangiomas need no treatment. Larger lesions may require excision, although cryotherapy can be useful. Contrast-enhanced T_1-weighted MRI can be used to differentiate between lymphangiomas and deep haemangiomas [6]. One study has found blue, domed lymphangiomas on the alveolar ridges of about 4% of newborn black children [3]. These lesions, which were usually bilateral, often regressed spontaneously.

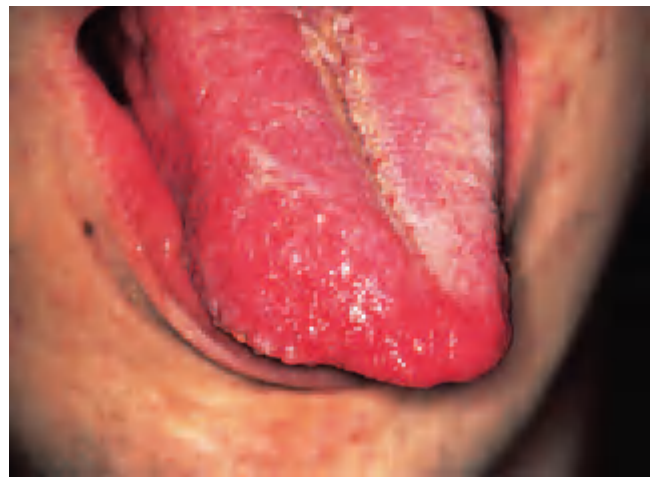

Fig. 66.20 Lymphangioma of the tongue: a common site.

REFERENCES

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Dermoid cyst (see Chapter 15)

Dermoid cyst is a hamartoma, a developmental lesion commonly arising in the midline of the neck, above the mylohyoid muscle, occasionally elsewhere, even in the tongue or antrum [1–4]. It usually becomes clinically obvious in the second decade of life and causes elevation of the tongue.

Occasionally dermoid cysts become infected and then painful. Treatment is by surgical excision.

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Lingual tonsil

The lingual tonsil is a mass of lymphoid tissue in the posterior third of the tongue, between the epiglottis posteriorly and the circumvallate papillae anteriorly [1,2]. It is usually divided in the midline by a ligament (Fig. 66.21). Although usually small and asymptomatic, it may become enlarged, especially in atopic individuals, in patients taking phenytoin or in some infections. It may be so prominent that it fills the vallecula and impinges against the epiglottis. If the lingual tonsil is large, it may cause a globus sensation, alteration of the voice, obstructive sleep apnoea or airways obstruction [3–6]. It tends to involute with increasing age.

Occasionally, there may be lingual tonsillitis with a red, swollen, painful tongue, fever and neutrophilia [7].

The condition must be distinguished from benign and malignant tumours of the tongue, including lingual thyroid, but the symmetry of the lingual tonsil and its midline division are helpful diagnostic pointers.

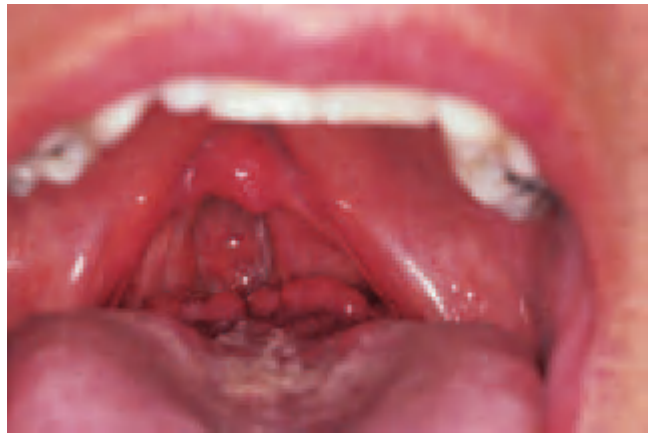

Fig. 66.21 Lingual tonsil showing a well-demarcated midline groove. (Courtesy of Dr C.T.C. Kennedy, Bristol Royal Infirmary, Bristol, UK.)

Treatment may be required if the enlarged tonsil causes symptoms. Surgery may be hazardous because of the copious blood supply to the tongue base. Electrocautery and cryotherapy are generally regarded as the safer procedures [1].

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Lingual thyroid

Ectopic thyroid tissue may rarely present in the mouth. Some 10% of cadaver tongues contain thyroid tissue, although clinical presentation is much less common. Typically, there is an asymptomatic smooth-surfaced lump in the midline of the base of the tongue, between the sulcus terminalis and epiglottis at the site of the foramen caecum [1–4]. Occasionally, a lingual thyroid may produce dysphagia, cough, pain or, rarely, airways obstruction [1–10].

Not all lingual thyroid tissue is functional, and function tends to decline with age. Where thyroid-stimulating hormone levels are high, thyroid hormone supplements are indicated [1]. Malignant change is rare in lingual thyroid,

although follicular carcinomas have been recorded. MRI and ^{99m}Tc pertechnetate scintiscanning is important to ensure the presence of normal thyroid tissue in the neck [11,12] before considering treatment of a lingual thyroid by surgery or radioiodine [1,2,13].

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Multiple mucosal neuroma syndrome

The syndrome of multiple endocrine neoplasia (MEN) type 2b (also called type 3) is inherited as an autosomal dominant, although new cases often arise sporadically. The gene locus is on chromosome 10.

MEN2b is characterized by medullary carcinoma of the thyroid and phaeochromocytoma, in association with multiple mucosal neuromas and an abnormal phenotype—a striking facial appearance, with thick, slightly everted lips that usually have a slightly bumpy surface due to multiple neuromas [1,2]. These are actually mucosal and submucosal hamartomatous proliferations of nerve axons, Schwann cells and ganglion cells.

Lesions may also involve the tongue and commissures but are less frequent on the buccal mucosa, gingivae, palate, pharynx or larynx (Fig. 66.22). Ganglioneuromatosis may also occur throughout the gastrointestinal tract, and this may result in constipation or megacolon [3]. Ocular changes include yellowish masses on the conjunctivae, thickened corneal nerves and keratitis due to decreased tear production [4].

Most patients have an asthenic marfanoid habitus, with high arched palate, pectus excavatum, arachnodactyly and kyphoscoliosis, but the lens subluxation and cardiovascular abnormalities of Marfan's syndrome are not present [5–8].

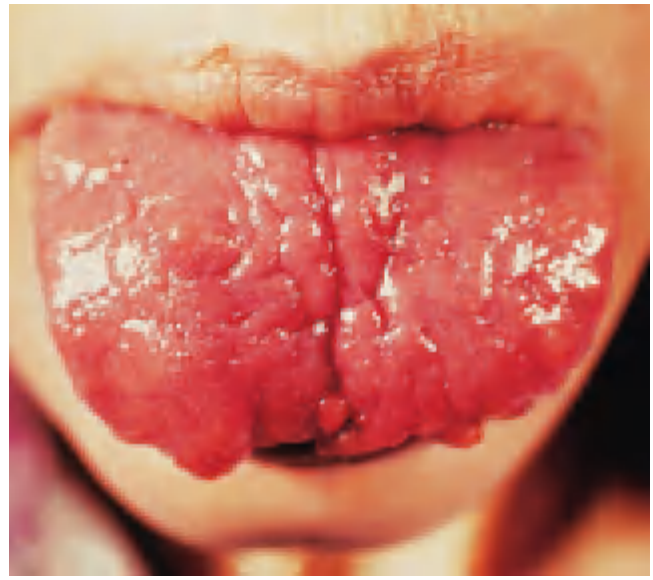

Fig. 66.22 Multiple neuromas of the lips and tongue in a patient with multiple endocrine neoplasia syndrome (type 2). (Courtesy of Dr M. Hartog, Bristol Royal Infirmary, Bristol, UK.)

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Other congenital anomalies

Ankyloglossia

Ankyloglossia, or tongue-tie, is an uncommon and typically isolated anomaly in which the lingual fraenum is tight and the tongue cannot be fully protruded [1].

There may be a family history and sometimes deviation of the epiglottis or larynx [2]. The association of cleft palate with ankyloglossia is inherited as a semi-dominant

X-linked disorder previously described in several large families of different ethnic origins and related to chromosome Xq21: the T-box transcription factor gene *TBX22* is mutated [3,4].

Speech is not usually affected in patients with ankyloglossia but the ability to suckle [5] and to cleanse the buccal sulcus with the tongue may be, and there can be effects on jaw development [6]. If necessary, surgery to the fraenum will relieve ankyloglossia [7,8].

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Fissured tongue

Fissured tongue (plicated or scrotal tongue) is a common condition affecting more than 5% of the population [1]. The cause is unclear, but it is often accompanied by geographical tongue (Fig. 66.23).

Patients with Down's syndrome often have a fissured tongue and it is a feature of the rare Melkersson–Rosenthal syndrome.

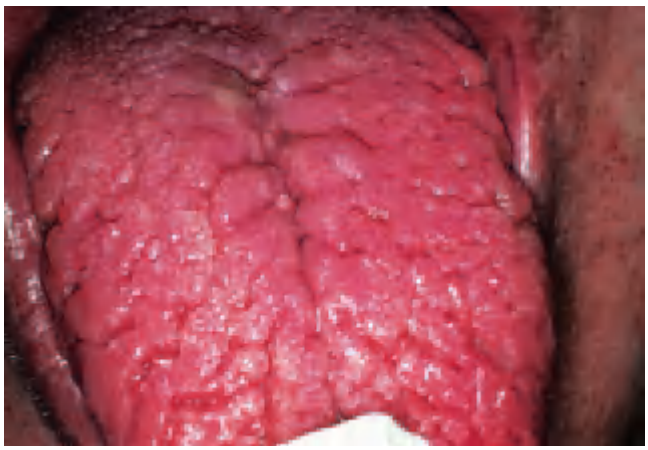

Fig. 66.23 Fissured or scrotal tongue.

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Oral hair

Oral hair is a rare innocuous anomaly [1], not to be confused with hairy tongue (see p. 66.90).

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Various orocutaneous syndromes

Cleft lip

Cleft lip and/or palate are the most common congenital craniofacial abnormalities. Cleft lip occurs in about 1 per 1000 white-skinned neonates. The prevalence is higher in oriental neonates (about 1.7 per 1000 births) and lower in black neonates (approximately 1 per 2500 births) and appears reduced if women take multivitamins containing folic acid early in pregnancy [1]. Clefts are often accompanied by impaired facial growth, dental anomalies, speech disorders, poor hearing and psychosocial problems [2]. Clefts can be seen in over 300 different syndromes [3].

Cleft lip is not always complete (i.e. extending into the nostril). A cleft may involve only the upper lip or may extend to involve the nostril and the hard and soft palates. In about 9% of the cases, the cleft is associated with skin bridges or Simonart's bands.

Isolated cleft lip may be unilateral or bilateral (approximately 20%). When unilateral, the cleft is more common on the left side (about 70%).

Lips are more frequently cleft bilaterally (approximately 25%) when combined with cleft palate. Cleft lip and palate is more common in men. Cleft lip and palate comprises about 50% of the cases, with cleft lip and isolated cleft palate each comprising about 25%. About 85% of bilateral cleft lips and 70% of unilateral cleft lips are associated with cleft palate. One subgroup have cleft lip and palate with median facial dysplasia and cerebrofacial malformations [4], others with laryngotracheal oesophageal clefts (Opitz–Firas or G syndrome) or cranial asymmetry (Opitz or B syndrome) [5].

Clefts in the middle of the upper lip may be true or false. True median clefts have been described in association with bifid nose and ocular hypertelorism. Other cases of true median labial cleft are associated with polydactyly or other digital anomalies, constituting an autosomal recessive trait called *orofaciodigital syndrome II*.

Pseudocleft of the middle of the upper lip may occur in *orofaciodigital syndrome I*. A somewhat similar central defect, but of mild degree, is seen in chondroectodermal dysplasia (Ellis–van Creveld syndrome). Clefts in the lower lip are rare and usually median but may involve the mandible and sometimes the tongue. Management of cleft lip is discussed elsewhere [6,7].

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Cowden's syndrome (see Chapter 12)

SYN. MULTIPLE HAMARTOMA SYNDROME

Cowden's syndrome may be associated with the *PTEN* gene [1] and multiple hamartomas [2]. Oral mucosal lesions may be found in the presence or absence of cutaneous stigma [3–7]. The oral lesions are typically smooth, pink or whitish benign fibromas found especially on the palatal, gingival and labial mucosae. Oral squamous carcinoma is a rare complication [8]. There may be overlap with Bannayan–Riley–Ruvalcaba syndrome [9,10].

Treatment with acitretin may lead to regression of the hypertrophic lesions of the lip and mouth [11].

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De Lange syndrome

SYN. AMSTERDAM DWARF

Classical Brachmann or Cornelia de Lange syndrome presents with a striking face, pronounced growth and learning disability, and variable limb deficiencies. Most cases are sporadic [1]. A long philtrum and crescent-shaped mouth with down-turned corners is typical [2,3].

The characteristic face of classical de Lange syndrome is present at birth and changes little throughout life, although there is some lengthening of the face with age and the jaw becomes squared.

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Double lip

Double lip is a developmental anomaly usually involving the upper lip. A fold of redundant tissue is found on the inner aspect of the involved lip [1]. It is reported to be common among some groups of Africans [2].

Double lip may occur alone or in association with other anomalies. The association with blepharochalasis (laxity of the upper eyelid skin) and sometimes non-toxic thyroid enlargement is known as *Ascher's syndrome* [3] (see Chapter 46).

Double lip requires no treatment except for cosmetic purposes.

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Down's syndrome

The incidence of angular cheilitis is increased in people with Down's syndrome, caused by an increased level of *Staphylococcus aureus* and *Candida albicans*, possibly because of the immune defects [1–3]. Lip fissures may appear intermittently over a period of years or be intractable and long-standing (see p. 66.120).

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Erythropoietic protoporphyria

Erythropoietic protoporphyria is an autosomal dominant disorder of ferrochelatase, resulting in inhibition of the conversion of protoporphyrin to haem.

Shallow elliptical or linear scars around the lips and linear perioral furrowing (pseudorhagades) are subtle changes that are pathognomonic when observed in children [1,2].

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Focal mucinosis

Oral focal mucinosis is an uncommon clinicopathological entity considered to be the oral counterpart of cutaneous focal mucinosis and/or cutaneous myxoid cyst. The nature of the lesion is unclear but may be the result of fibroblastic overproduction of hyaluronic acid. It comprises a clinically elevated mass with a histological picture of localized areas of myxomatous connective tissue. Most of the lesions affect the gingiva and alveolar mucosa [1–3].

All these diseases share distinct histological features. There is an increased number of fibroblast-like cells in early lesions, whereas these are diminished or predominantly at the margin in advanced ones. The myxomatous areas show slight to absent reticulum and elastic fibres, and collagen fibres are fragmented and replaced by variable amounts of mucin. Vimentin is consistently present and correlates with the number of fibroblast-like cells, these being negative for S-100 protein, Leu7, desmin and α-SMA [4].

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Gardner's syndrome (see Chapter 12)

Multiple jaw osteomas are a feature of Gardner's syndrome of familial adenomatous polyposis coli [1,2]. Some 80% of patients with familial adenomatosis coli have osteomas and 30% have dental anomalies such as supernumerary or impacted teeth, or odontomes [3–9].

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Gorlin's syndrome (naevoid basal cell carcinoma syndrome) (see Chapter 36)

Odontogenic keratocysts (primordial cysts) of the jaws are a prominent feature of Gorlin's syndrome [1–3]. The syndrome is caused by mutations in the Sonic Hedgehog *patched* gene, a tumour-suppressor gene [4]. A single point mutation in one *patched* allele may be responsible for the various malformations found in the syndrome [5–10]. Inactivation of both *patched* alleles results in the formation of tumours and cysts (basal cell carcinomas, odontogenic keratocysts and medulloblastomas) [4].

The keratocysts should be surgically removed but have a tendency to recur. There are also occasional reports of oral neoplasms, notably fibrosarcoma, ameloblastoma and squamous carcinoma [5–10].

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Jacob's disease

Jacob's disease is a rare condition consisting of new joint formation between the coronoid process of the mandible and the inner aspect of the zygomatic arch [1].

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Kindler syndrome

Kindler syndrome is characterized by bulla formation, which starts at birth on areas of the skin that receive pressure and may lead to bilateral incomplete syndactylies involving all web spaces [1].

Oral lesions may include atrophy of the buccal mucosa, trismus (an inability to fully open the mouth) and a form of desquamative gingivitis [2].

Histology shows classical features of poikiloderma, namely epidermal atrophy with flattening of the rete ridges, vacuolization of basal keratinocytes, pigmentary incontinence and mild dermal perivascularization. Ultrastructural studies demonstrate reduplication of the basal lamina with branching structures within the upper dermis and cleavage between the lamina densa and the cell membrane of the keratinocytes. Antibody against type VII collagen shows extensive broad bands with intermittently discontinuous and reticular staining at the dermal–epidermal junction.

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Lip pits and sinuses

Dimples are common at the commissures. They should be distinguished from *commissural pits*, which are distinct definite pits ranging from 1 to 4 mm in diameter and depth [1,2] present from infancy, often showing a familial tendency and probably determined by a dominant gene

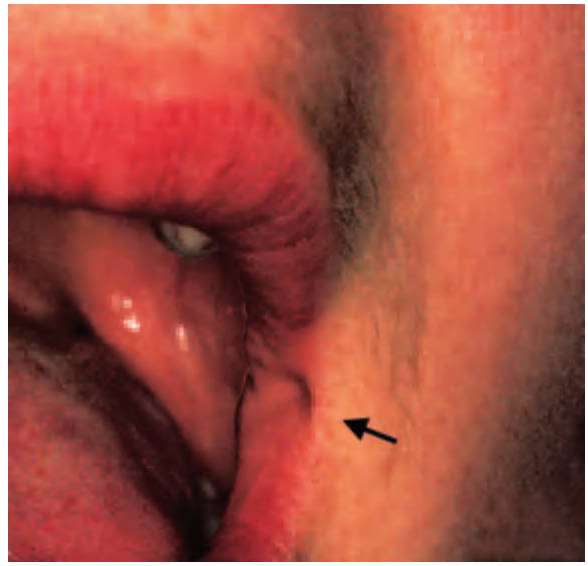

Fig. 66.24 Angular sinus (lip-pit), a congenital anomaly.

(Fig. 66.24). Their incidence is 1–20% in various population groups [2,3]; for example, in one series they were found in 12% of white people and 20% of black people [4]. Commissural pits are sometimes associated with aural sinuses or pits. Rarely, they may be infected and present as recurrent or refractory angular cheilitis.

Congenital lip pits or sinuses are small blind fistulae on the vermilion border [5]. They are usually bilateral and symmetrical, often just to one side of the philtrum. The pits may be up to 3–4 mm in diameter and up to 2 cm deep. They may communicate with underlying minor salivary glands. They may appear as isolated findings, but are often (67%) associated with cleft lip and/or palate (Van der Woude syndrome) [6–9]. This autosomal dominant syndrome [10,11] has a frequency of 1 in 75 000 to 1 in 100 000 in white populations (see Chapter 12).

Surgical removal may be indicated for cosmetic purposes.

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Noonan's syndrome

SYN. ULLRICH–TURNER SYNDROME

Ullrich–Turner syndrome is caused by monosomy X or a structural abnormality of the second X chromosome. It is seen in females with a syndrome of short stature, sexual infantilism and a pattern of characteristic minor anomalies including pterygium colli. This syndrome was later called Noonan's syndrome, and it was shown that central giant cell lesions or cherubism of the jaws may be present [1–7]. Oral keratosis is sometimes seen [8].

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Tuberous sclerosis (see Chapter 12)

SYN. EPILOIA; BOURNEVILLE DISEASE

Oral manifestations in tuberous sclerosis include pit-shaped enamel defects in both dentitions, and gingival fibromatosis [1–6] and rare instances of myxoma or desmoplastic fibroma [7,8].

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Van der Woude syndrome

Van der Woude syndrome is a rare autosomal dominant syndrome [1] in which lower lip pits are associated with cleft lip and/or palate [2–5], sometimes seen with syndactyly or talipes equinovarus.

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Von Recklinghausen's neurofibromatosis

Neurofibromatosis (NF) consists of distinct variants due to *NF* gene mutations [1]: type I (NF-I), often referred to as von Recklinghausen's disease or generalized neurofibromatosis; and type II (NF-II), a much less common disorder of bilateral acoustic schwannomas. The incidence of head and neck manifestations in patients with NF varies between 14 and 37%. Cosmetic lesions include pigmentary changes (café-au-lait spots) and prominent neurofibromas [2–6].

Neurofibromas may be seen mainly in NF-I. Neurofibromas may also be seen in NF-II, but bilateral acoustic neuromas are the hallmark of this disease and neurilemmomas and acoustic neuromas are this predominant neural tumours. Neurofibromas may also be part of the MEN syndrome (see Chapter 59).

Oral lesions are not uncommon in von Recklinghausen's generalized NF [7–14]. About two-thirds of patients have intraoral neurofibromas affecting predominantly the tongue, lips, buccal mucosa or palate. Neurofibroma represents a benign overgrowth of all elements of a peripheral nerve (axon cylinder, Schwann cells and fibrous connective tissue), arranged in a variety of patterns. Enlarged fungiform papillae are found in about 50% of patients. About 60% of patients have radiographic evidence of disease, especially enlargement of the inferior alveolar canal or foramen, or branching of the canal.

Neurofibromas may occur multiply as a feature of NF but only rarely undergo sarcomatous change [15]. Other rare malignant tumours include nerve sheath tumour [16], triton tumour [17] and Merkel cell carcinoma [18].

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Xeroderma pigmentosum

Squamous cell carcinoma of the lip may arise in patients with xeroderma pigmentosum [1,2] and therefore it is crucial to institute sun protection. Oral retinoids such as etretinate or isotretinoin may be of prophylactic value [3,4]. Topical 5-fluorouracil or surgery may be used to treat potentially malignant lesions (see Actinic cheilitis, p. 66.115).

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Acquired disorders of the oral mucosa or lips

This section discusses the main acquired causes of mouth ulcers, other causes of oral soreness, white, pigmented or red lesions, and lumps and swellings. Further detail is available elsewhere [1–5].

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Mouth ulcers

The causes of mouth ulcers are diverse (Tables 66.10 & 66.13), partly because lesions such as vesicles rapidly break down in the mouth as a result of trauma, moisture and infection. Ulcers are usually caused by the following.

1 Local factors
2 Recurrent aphthous stomatitis
3 Neoplasms
4 Systemic conditions
  (a) Hematological
  (b) Gastroenterological
  (c) Dermatological
  (d) Infective
  (e) Vasculitis
  (f) Iatrogenic
  (g) Uncertain causes
5 Drugs.

Mouth ulcers of local aetiology

It is surprising that oral ulceration due to local factors is not more frequent. Accidental cheek biting or facial trauma may cause ulceration in any individual; the his-

Table 66.13 Causes of mouth ulcers (see also Table 66.10).

Local causes (e.g. trauma)
Recurrent aphthae (and Behçet's syndrome)
Malignant neoplasms
Ulcers associated with systemic disease
Drugs
Irradiation of the oral mucosa
Disorders of uncertain pathogenesis

tory is usually quite clear and a single ulcer of short duration (5–10 days) is present. Ulceration due to biting an anaesthetized lower lip or tongue following a dental local analgesic injection is a fairly common problem in young children.

Orthodontic appliances or, more commonly, dentures (especially if new) are responsible for many traumatic oral ulcers. These ulcers are usually clearly related to the appliance and have been a problem in the care of cleft-palate patients [1]. Chronic trauma may cause a well-defined ulcer with a whitish keratotic halo [2].

The possibility of some other aetiology for ulcers of apparently local cause should always be borne in mind. Child abuse may cause ulcers, especially over the upper labial fraena. Self-mutilation may be seen in some psychologically disturbed patients [3,4], patients with learning disability, individuals with sensory impairment, and in Lesch–Nyhan syndrome [5–9]. Oral purpura or ulceration may be seen on the lingual fraenum or palate due to cunnilingus or fellatio respectively [10]. Other local causes of ulceration include thermal burns, especially of the tongue and palate (e.g. 'pizza burn—now more common with microwave oven use'), chemical burns from the holding of medicaments or drugs (e.g. aspirin or cocaine) against the mucosa [11], and irradiation mucositis.

Prognosis. Most ulcers of local cause heal spontaneously within 7–14 days if the cause is removed.

Treatment. Maintenance of good oral hygiene and the use of hot saline mouthbaths and 0.2% aqueous chlorhexidine gluconate mouthwash aid healing. A 0.1% benzydamine mouthwash may help give relief. Occasionally, mechanical protection with a plastic guard may help [7].

Patients should be reviewed within 3 weeks to ensure healing has occurred. Any patient with a single ulcer lasting more than 2–3 weeks should be regarded with suspicion and investigated further, usually by biopsy—it may be a neoplasm or other serious disorder.

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Eosinophilic ulcer [1–4]

SYN. TRAUMATIC EOSINOPHILIC GRANULOMA

Eosinophilic ulcer is a rare self-limiting disease that often appears on the tongue in older adults or children. Its aetiology remains obscure and may be associated with traumatic factors. Eosinophilic ulcers are unifocal, with a benign course. Pathological features show an extensive inflammatory cell infiltration, with predominantly eosinophilic cells throughout the submucosa. The peripheral blood eosinophil count is normal. Diagnosis and treatment is with either conservative excision or incisional biopsy.

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Recurrent aphthous stomatitis

SYN. APHTHAE; CANKER SORES

Recurrent aphthous stomatitis (RAS) is characterized by recurring episodes of ulcers, typically from childhood or adolescence, each lasting from 1 to about 4 weeks before healing. Aphthae typically are multiple round or ovoid ulcers with a circumscribed margin, erythematous halo and a yellow or grey floor (Fig. 66.25). The term 'recurrent oral ulcer' is rather imprecise and should be avoided [1–4].

Aetiology. The aetiology of RAS is not clear. A positive family history is found with about one-third of patients and there is an increased frequency of human leukocyte antigens (HLA)-A2, HLA-A11, HLA-B12 and HLA-DR2, supporting a genetic basis for susceptibility in some patients [1–4].

There are identifiable predisposing factors in some patients (Table 66.14). A minority (about 10–20%) of patients attending outpatient clinics with RAS have an

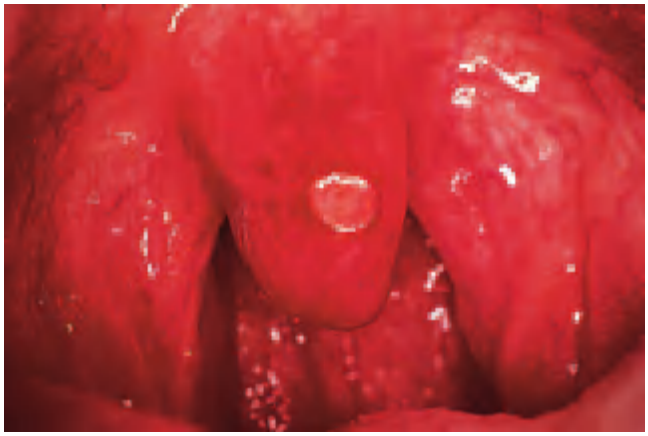

Fig. 66.25 Recurrent aphthae.

underlying haematological abnormality, usually a low serum iron or ferritin, or deficiency of folate or vitamin B_{12}. A few have multiple deficiencies [5,6]. Up to 3% of RAS patients have coeliac disease but in others a gluten-free diet is of no value [7]. Patients with deficiency states often, but not always, have gastrointestinal symptoms, and their RAS is often of recent onset. Other aetiological factors in RAS can include stress, trauma and cessation of tobacco smoking. Ulcers similar to aphthae are also seen in Behçet's syndrome; Sweet's syndrome; HIV infection, cyclic neutropenia and other immunodeficiencies; and, rarely, in children in association with fever and pharyngitis (periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis; PFAPA) [8,9]. Orogenital ulceration with aphthae is probably a forme fruste of Behçet's syndrome.

There is no evidence that RAS is an autoimmune disease [1–4]. There is no known association with systemic autoimmune disorders, none of the common autoantibodies are found, and RAS tends to resolve or decrease spontaneously with increasing age. The serum immunoglobulin levels are usually normal, although IgA and IgG may be increased, and immune complexes may be found.

It now seems likely that there is a minor degree of immunological dysregulation underlying aphthae. Attempts to implicate a variety of viruses or bacteria in the aetiology of RAS have largely been unsuccessful, but there may be cross-reacting antigens between the oral mucosa and microorganisms such as *Streptococcus sanguis* or its L form, or heat-shock protein [10].

Cell-mediated immune mechanisms appear to be involved in the pathogenesis of RAS. In the lesions, helper T cells predominate early on, with some natural killer cells. Cytotoxic cells then appear and there is evidence for an antibody-dependent cellular cytotoxicity reaction [1–4].

Clinical features. RAS is a common disease that probably afflicts at least 20% of the population. There is a high prevalence in higher socio-economic classes.

There are three main clinical types of RAS. Most common are minor aphthous ulcers, which account for 80% of all RAS. Some 10% of patients with RAS have major aphthous ulcers, and a further 10% suffer from a herpetiform type of ulceration (Table 66.15).

Table 66.14 Systemic and other factors that may occasionally underlie or be associated with recurrent aphthous stomatitis (RAS).

	Comments
Behçet's syndrome	Association of RAS with ocular lesions, genital ulcers and multisystem disease
Sweet's syndrome	See Chapter 49
Haematinic deficiency	In some studies, 10–20% of patients with RAS have deficiencies of iron, folic acid or vitamin B_{12}
Gastrointestinal disease	Malabsorption states (pernicious anaemia, coeliac disease and Crohn's disease) may precipitate RAS in a small minority
Endocrine factors	In some women, RAS is clearly related to a fall in progestogens in the luteal phase of the menstrual cycle; hormone therapy may be beneficial
Immunodeficiency	A few patients with RAS have an immune defect such as human immunodeficiency virus disease
Other factors	Trauma, certain foods, stress and cessation of smoking may play a part

Table 66.15 Main features of recurrent aphthous stomatitis.

	Minor aphthae	Major aphthae	Herpetiform ulcers
Age of onset	Childhood or adolescence	Childhood or adolescence	Young adult
Ulcer size	2–4 mm	May be 10 mm or larger	Initially tiny but ulcers coalesce
Number of ulcers	Up to about 6	Up to about 6	10–100
Sites affected	Mainly vestibule, labial, buccal mucosa and floor of mouth; rarely dorsum of tongue, gingiva or palate	Any site	Any site but often on ventrum of tongue
Duration of each ulcer	Up to 10 days	Up to 1 month	Up to 1 month
Other comments	Most common type of aphthae	May heal with scarring	Affects females predominantly

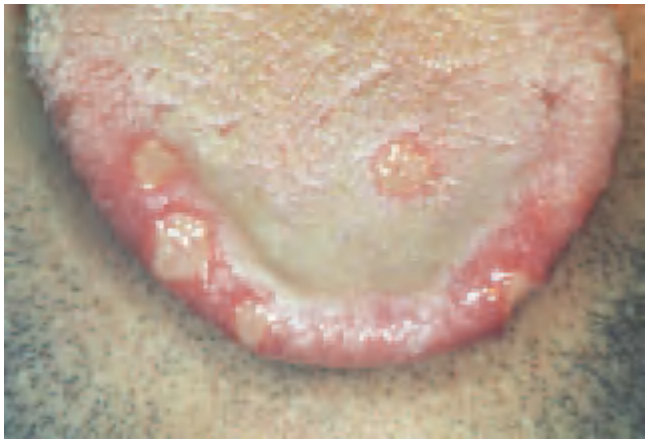

Fig. 66.26 Major aphthous ulcers.

Minor aphthous ulcers (syn. Mikulicz ulcers). Minor RAS (MiRAS) occur mainly in the 10–40-year age group, and often cause minimal symptoms. MiRAS are usually 2–4 mm in diameter and found mainly on the non-keratinized mobile mucosa of the lips, cheeks and floor of the mouth, sulci or ventrum of the tongue. They are uncommon on the gingiva, palate or dorsum of the tongue. Only a few ulcers (one to six) appear at a time; they heal in 7–10 days and recur at variable intervals. MiRAS are usually round or ovoid, but are often more linear when in the buccal sulcus, a common site. The ulcer floor is initially yellowish but becomes greyish as epithelialization proceeds. There is an erythematous halo and some oedema but MiRAS heal with little or no evidence of scarring.

Major aphthous ulcers (syn. Sutton's ulcers). Previously known as periadenitis mucosa necrotica recurrens (PMNR), major RAS (MaRAS) are larger, recur more frequently, last longer and are more painful than MiRAS. They may reach a large size, even more than 1 cm in diameter. MaRAS are found on any area of the oral mucosa, including the dorsum of the tongue or palate. Usually only a few ulcers (one to six) occur at one time; they heal slowly over 10–40 days, and recur frequently. MaRAS are round or ovoid with an inflammatory halo, and may heal with scarring (Fig. 66.26). Occasionally, a raised erythrocyte sedimentation rate or plasma viscosity is found.

Herpetiform ulceration. Herpetiform ulceration (HU) is found in a slightly older age group and there is a female predominance. Herpetiform ulcers are often extremely painful and recur so frequently that ulceration may be virtually continuous. HU begins with vesiculation, which passes rapidly into multiple, minute (2 mm), discrete ulcers at any oral site. The ulcers increase in size and coalesce to leave large ragged ulcers that heal in 10 days or longer. Their similarity to herpetic stomatitis gives herpetiform ulcers their name, but there is no evidence that herpes simplex virus is involved.

Prognosis. RAS in most patients resolves or abates spontaneously with age. An underlying identifiable predisposing cause is particularly likely where RAS commences or worsens in adult life.

Diagnosis. Diagnosis is based on history and clinical features, since specific tests are unavailable. Biopsy is indicated only where some other cause of ulceration is suspected. To exclude relevant systemic predisposing factors it is often useful to perform:

- full blood count;
- haemoglobin assay;
- white cell count and differential;
- red cell indices;
- iron studies;
- red cell folate level;
- serum vitamin B_{12} measurements;
- serum antiendomysial antibodies.

The relevance of HLA studies for differentiating RAS from Behcet's syndrome is discussed on p. 66.46.

Management. Few patients have spontaneous remission until after several years and thus treatment is often indicated [11]. Fortunately, the natural history of RAS is one of eventual remission in most cases.

Predisposing factors should be corrected. If there is an obvious relationship to certain foods, the causal food should be excluded from the diet [12]. Good oral hygiene should be maintained: chlorhexidine or triclosan mouthwashes help achieve this and may help reduce ulcer duration [1–4].

Ulcer pain can usually be reduced, and the time to healing reduced, with hydrocortisone hemisuccinate pellets (Corlan) 2.5 mg or triamcinolone acetonide in carboxymethylcellulose paste (Adcortyl in Orabase) used four times daily; failing the success of these, a stronger topical corticosteroid (e.g. betamethasone, beclomethasone, fluticasone, mometasone) [13] or systemic corticosteroid (e.g. prednisolone) may be required (see Chapter 49).

Other therapies for RAS, such as sucralfate [14], colchicine and pentoxifylline (oxpentifylline), may have a role in individual cases but are not generally very effective or have adverse effects [3,15,16].

Thalidomide, in doses from 50 mg up to 300 mg daily, can frequently induce remission, especially in major aphthae, but its important teratogenic effects and the risk of neuropathy must be considered [17]. Topical tacrolimus may be effective but randomized trials are awaited.

There are multiple other therapies available for RAS, including carbenoxolone, benzydamine, dapsone, cromoglicate, levamisole and many others, but generally their

Table 66.16 Behçet's syndrome.

	Features	Incidence (%)
Major criteria		
Oral	Aphthae	90–100
Genital	Ulcers	64–88
Neuro-ocular	Iridocyclitis	10–90
	Retinal vasculitis	
	Optic atrophy	
	Syndromes resembling disseminated sclerosis, pseudobulbar palsy or neurosyphilis	
	Meningoencephalitis	
	Others	
Dermatological	Pustules	48–88
	Erythema nodosum	
	Pathergy	
Minor criteria	Proteinuria and haematuria	
	Thrombophlebitis	
	Aneurysms	
	Arthralgias	

efficacy has not been well proven or they have unacceptable adverse effects [3].

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Behçet's syndrome

SYN. ADAMANTIADES SYNDROME

Definition. Behçet's syndrome (BS) is the association of RAS with genital ulceration and eye disease (especially iridocyclitis and retinal vasculitis) [1–5]. There may be a number of other systemic or cutaneous manifestations (Table 66.16).

Aetiology. The aetiology of BS is uncertain but it appears to be becoming more common. There is a genetic background and, as in RAS, there are occasional familial cases and associations with HLA types, in BS particularly with HLA-B5 (Bw51 split). HLA-B51 or its B101 allele is significantly associated with BS in Japan, Korea, Turkey and France, as well as with the ocular manifestations in Britain. The MICA6 allele, a member of the polymorphic MHC class I-related gene A (MICA) family, is thought to be in linkage disequilibrium with HLA-B51 and has been shown to be significantly associated with BS in Japan and France [6]. HLA-DR/DQ haplotypes are more important than individual HLA-DR and HLA-DQ phenotypes for the development of mucocutaneous type of BS and for disease shift from RAS to mucocutaneous type of BS [7].

The aetiopathogenesis of BS is still unclear [8,9]. It does not appear to be infectious, contagious or sexually transmitted. The disease is found worldwide but is most common in the eastern Mediterranean countries and eastern Asia, along the Silk Road taken by Marco Polo. In these countries, it is a leading cause of blindness though this is not the case in the Western world.

There are many immunological findings in BS:

- circulating autoantibodies against a number of components, including intermediate filaments found in mucous membranes, cardiolipin and neutrophil cytoplasm;

Table 66.17 Oculomucocutaneous syndromes.*

	Main lesions		
Disease	Oral and genital	Ocular	Skin
Behçet's syndrome	Aphthae	Uveitis	Erythema nodosum
Sweet's syndrome	Aphthae	Conjunctivitis, episcleritis	Inflamed papule or nodule
Erythema multiforme	Erosions	Erosions	Target lesions
Cicatricial pemphigoid	Bullae Erosions	Erosions Scarring	Occasional dome-shaped bullae
Pemphigus	Erosions	Erosions	Multiple, flaccid bullae
Reiter's syndrome	Ulcers	Conjunctivitis	Keratoderma blenorrhagica

* Ulcerative colitis, herpes simplex, syphilis, lupus erythematosus, mixed connective tissue disease and other disorders may also cause oral, cutaneous and ocular lesions.

• circulating immune complexes and changed levels of complement;
• immunoglobulins and complement deposition within and around blood vessel walls;
• decreased ratio of T-helper (CD4) cells to T-suppressor (CD8) cells.

These immunological changes mimic those seen in patients with RAS—various T-lymphocyte abnormalities (especially T-suppressor cell dysfunction), changes in serum complement and increased polymorphonuclear leukocyte motility. There is also evidence that mononuclear cells may initiate antibody-dependent cellular cytotoxicity to oral epithelial cells, and evidence of disturbance of natural killer cell activity.

The common denominator in all systems is vasculitis, usually leukocytoclastic vasculitis. Many of the features of BS (erythema nodosum, arthralgia, uveitis) are common to established immune complex disease and, indeed, immune complexes (usually antigen–antibody complexes) are found in the sera. The antigen responsible has not been reliably identified but may include herpes simplex virus or streptococcal antigens [10–12]. As in RAS, heat-shock proteins have been implicated.

Clinical features. BS is a chronic multisystem disorder, most patients being male, usually in their third or fourth decade.

Because BS is rare and symptoms of the disease overlap symptoms of other diseases, it can be very difficult to diagnose. Spontaneous remission is common for patients with BS; this can add to the difficulty in diagnosis.

BS is characterized mainly by a triad of RAS [13,14], genital ulcers [15,16] and ocular lesions. The CNS, heart and intestinal tract may be involved.

One variant of BS (MAGIC syndrome) is associated with *m*outh *a*nd *g*enital ulcers and *i*nflamed *c*artilage [17]. Other oculomucocutaneous syndromes (Table 66.17) may cause similar manifestations [18,19].

Diagnosis. BS is usually diagnosed on clinical grounds, although findings of HLA-B5101 and pathergy are supportive, as are antibodies to cardiolipin and neutrophil cytoplasm. Disease activity may be assessed by serum levels of acute phase proteins or antibodies to intermediate filaments, or by erythrocyte sedimentation rate; all are raised in active BS.

Differential diagnosis is mainly from the following.
• Sweet's syndrome: aphthae, conjunctivitis, episcleritis, inflamed tender papule or nodule.
• Erythema multiforme: erosions, target (iris) lesions.
• Pemphigoid: bullae, erosions.
• Pemphigus: erosions, multiple flaccid bullae.
• Reiter's syndrome: ulcers, conjunctivitis, keratoderma blenorrhagica.
• Ulcerative colitis.
• Herpes simplex.
• Syphilis.
• Lupus erythematosus.
• Mixed connective tissue disease.

The diagnosis is often made on the basis of RAS plus two or more of recurrent genital ulceration, eye lesions, skin lesions and pathergy [20,21].

Major criteria include:
1 RAS: in 90–100% of cases.
2 Recurrent painful genital ulcers that tend to heal with scars in 64–88% of cases. Genital ulcers are especially common in females with BS, and resemble RAS.
3 Ocular lesions: uveitis with conjunctivitis (early) and hypopyon (late), retinal vasculitis (posterior uveitis), iridocyclitis and optic atrophy. The most common ocular manifestation is relapsing iridocyclitis but uveitis, retinal vascular changes and optic atrophy may occur. Both eyes are eventually involved and blindness may result.
4 CNS lesions: meningoencephalitis, cerebral infarction, psychosis, cranial nerve palsies, cerebellar and spinal cord lesions, hemiparesis and quadriparesis.
5 Skin lesions: erythema nodosum, papulopustular lesions and acneform nodules. Venepuncture is, in some patients, followed by pustulation (pathergy).

Minor criteria are:

1 Arthralgia: large joint arthropathies that are subacute, non-migratory, self-limiting and non-deforming.
2 Superficial or deep migratory thrombophlebitis, especially of lower limbs.
3 Intestinal lesions: inflammatory bowel disease with discrete ulcerations.
4 Lung involvement: pneumonitis.
5 Haematuria and proteinuria.

However, very non-specific signs and symptoms, which may be recurrent, may precede the onset of the mucosal membrane ulceration by 6 months to 5 years. These include malaise, anorexia, weight loss, generalized weakness, headache, perspiration, decreased or elevated temperature, lymphadenopathy and pain in the substernal and temporal regions.

A history of repeated sore throats, tonsillitis, myalgias and migratory erythralgias without overt arthritis is also common.

Management. Unlike RAS, BS is not self-limiting. It causes morbidity (especially in terms of ocular and neurological disease) and mortality. Most patients present with oral and ocular disease but there follows a relapsing and remitting but variable course. CNS involvement, thromboses of major vessels and gastrointestinal perforation result in a poor prognosis. Few patients with BS have spontaneous remission and thus treatment is indicated [22,23].

Chronic morbidity is usual; the leading cause is ophthalmic involvement, which can result in blindness. The effects of the disease may be cumulative, especially with neurological, vascular and ocular involvement. Mortality is low but can occur from neurological involvement, vascular disease, bowel perforation, cardiopulmonary disease or as a complication of immunosuppressive therapy. In the face of the serious potential complications, patients with suspected BS should be referred early for specialist advice.

Topical treatment for RAS (see p. 66.45). Oral ulcers may respond to topical corticosteroids or 5-aminosalicylic acid [24]. Even nicotine patches may have some success [25].

Systemic treatment includes mainly colchicine 0.5–1.5 mg daily.

Other systemic treatments include corticosteroids, azathioprine, ciclosporin, chlorambucil, cyclophosphamide, dapsone, interferon-alpha, levamisole or thalidomide. Ocular lesions usually respond to ciclosporin, but tend to relapse when treatment is stopped. Thalidomide at a dose of up to 400 mg daily may be of value in recalcitrant orogenital ulceration, although it must be used with caution as it is teratogenic and carries a risk of neuropathy [26,27].

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Sweet's syndrome (see Chapter 49)

Pustular lesions leading to aphthous-like ulcers may be

found in Sweet's syndrome and there are occasional associations with BS and Sjögren's syndrome, each of which has oral manifestations. About 5% of patients in the UK with Sweet's syndrome have oral aphthae, although up to 30% of Japanese patients suffer aphthae [1–3].

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Malignant neoplasms

More than 90% of malignant neoplasms in the mouth are squamous cell carcinomas. Nearly 30% of all squamous cell carcinomas affect the lip; some 25% affect the tongue, the most common intraoral site [1–5]. Most intraoral cancers involve the posterolateral border of the tongue and/or the floor of the mouth (the 'graveyard' area).

Oral cancer is a significant world health problem, being overall the sixth most common malignant neoplasm. In parts of South-East Asia for example, particularly India, some 40% of all malignancy is oral cancer. High levels are also seen in other parts of the developing world such as Brazil, but also in parts of Europe such as areas of northern France and eastern Europe.

Oral squamous cell carcinoma

Cancer of the oral cavity is classified according to site:
- lip (International Classification of Diseases [ICD] 140);
- tongue (ICD 141);
- gum (ICD 143);
- floor of the mouth (ICD 144); and
- unspecified parts of the mouth (ICD 145).

Carcinoma of the lip

Squamous carcinoma is the commonest malignancy to affect the vermilion zone and, as with squamous carcinoma of the glabrous skin, it is usually due to actinic damage [1]. Like actinic cheilitis it is most common on the lower lip of fair-skinned, outdoor workers in sunny climates, and is relatively rare in pigmented skin [2–4]. Lip cancer is common in certain population groups in the UK, Romania, Hungary, Poland, Spain, Finland, Israel, Canada, the USA and Australia, but in most areas reported the incidence is falling [4–7].

Lip cancer generally occurs in men who are employed in outdoor activities such as farming and fishing [8]. Squamous cell carcinomas occur on the lower lip in 89%, with 3% on the upper lip and 8% at the commissures [9]. Although sunlight is accepted as the major aetiological factor, some studies have shown a poor correlation between the incidence of lip cancer and the rate of annual solar radiation [10]. *Actinic radiation* may predispose to lip cancer. Facts that support such a relationship include the following.
- Lip cancer involves the more exposed lower lip, rather than the upper lip.
- There is a higher incidence of lip cancer in outdoor workers and rural populations than in office workers or urban populations.
- Fair-skinned more than dark-skinned people tend to develop lip cancer (as well as skin cancer and melanoma) in sunny climates.

Other risk factors may include low social class, tobacco smoking, syphilis, poor dentition, infection with herpes simplex virus [3,5,8] and immune suppression [11]; for example lip cancer is increased in immunosuppressed renal transplant recipients.

The initial features are a keratinous growth or swelling of the lip (Fig. 66.27), soreness and ulceration. Most lesions are amenable to surgical excision, with more than 70% surviving for 5 years.

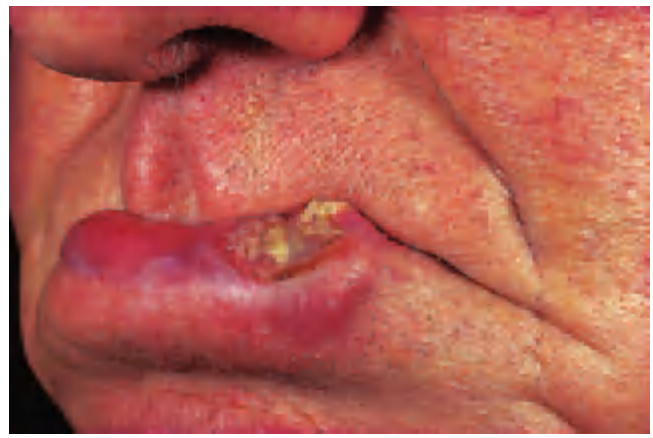

Fig. 66.27 Squamous cell carcinoma of lip.

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Intraoral carcinoma

Most intraoral carcinoma is squamous cell carcinoma [1–3]. In many countries there is evidence for an increase in oral squamous cell carcinoma (OSCC) over recent years [4–7], especially in young persons. There is marked inter-country variation in both the incidence of, and mortality from, OSCC [8]. In addition, there is also growing evidence of intra-country ethnic differences in incidence and mortality, especially in the UK and USA.

In the developing world, particularly South-East Asia and Brazil, the incidence of OSCC varies widely in different areas and there are ethnic differences in incidence, often attributed to lifestyle habits.

In the developed world OSCC is uncommon. The incidence varies between countries and between different regions of the same country. For example, parts of France and Newfoundland have the highest incidence in the West, with about 10 times the incidence of oral carcinoma in the UK. Oral cancer is more than twice as common in Scotland than in England and Wales and, for example, even within Scotland there are regional differences.

Potentially malignant states. Some potentially malignant (precancerous) lesions that can progress to OSCC include especially [9] *erythroplasia* (erythroplakia), the most likely lesion to progress to severe dysplasia or carcinoma (see p. 66.96); and *leukoplakia* (see p. 66.85), particularly proliferative verrucous leukoplakia, sublingual leukoplakia, candidal leukoplakia and syphilitic leukoplakia.

Some other potentially malignant (precancerous) conditions include:

- lichen planus—there are also cases of dysplasia with a lichenoid appearance (lichenoid dysplasia);
- discoid lupus erythematosus;
- submucous fibrosis;
- atypia in immunocompromised patients;
- dyskeratosis congenita;
- Paterson–Kelly syndrome (sideropenic dysphagia, Plummer–Vinson syndrome).

One of the main features that appears to precede the onset of malignancy is epithelial dysplasia, although dysplasia can also be seen in regenerating tissue and some non-precancerous lesions such as ulcers, viral infections, candidal infections and granular cell tumours.

Dysplasia varies in severity, and it is the more severe grades that are associated with higher malignant potential.

Predisposing factors (risk factors) [1–3,10–13]. In the developed world, OSCC is seen especially in tobacco users, alcohol users, lower socio-economic groups and ethnic minority groups.

In the developing world, OSCC is seen especially in tobacco users, alcohol users, 'betel quid' users (some 20% of the world's population use betel) and lower socio-economic groups. In peoples from parts of Asia, tobacco-chewing, along with a variety of ingredients in 'betel quid' (betel vine leaf, betel [areca] nut, catechu, slaked lime, together with tobacco), appears to predispose to OSCC, particularly when it is started early in life and is used frequently and for prolonged periods. Various other risky chewing habits, usually containing tobacco, are used in different cultures (e.g. khat, shammah, toombak).

Microorganisms such as *Candida* and human papillomavirus (HPV) have been detected in some potentially malignant lesions and some OSCC, where they may play a role. HPV is especially implicated in tonsillar carcinoma; HPV-16 is particularly implicated.

In contrast, diets rich in fresh fruits and vegetables and vitamin A may have a protective effect.

Clinical features. OSCC may present as the following [1–3] (Fig. 66.28).

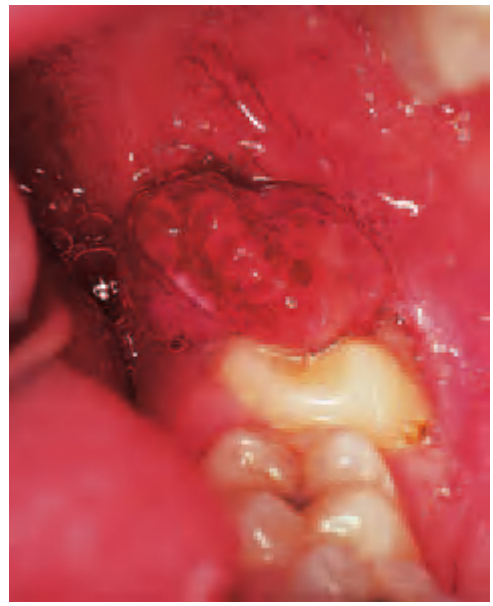

Fig. 66.28 Oral squamous cell carcinoma.

Table 66.18 TNM classification of malignant neoplasms.*

Primary tumour size (T)	
Tx	No available information
T_0	No evidence of primary tumour
T_{is}	Only carcinoma *in situ*
T_1, T_2, T_3, T_4	Increasing size of tumour†
Regional lymph node involvement (N)	
Nx	Nodes could not or were not assessed
N_0	No clinically positive nodes
N_1	Single clinically positive homolateral node less than 3 cm in diameter
N_2	Single clinically positive homolateral node 3–6 cm in diameter, or multiple clinically positive homolateral nodes, none more than 6 cm in diameter
N_{2a}	Single clinically positive homolateral node 3–6 cm in diameter
N_{2b}	Multiple clinically positive homolateral nodes, none more than 6 cm in diameter
N_3	Massive homolateral node(s), bilateral nodes, or contralateral node(s)
N_{3a}	Clinically positive homolateral node(s), one more than 6 cm in diameter
N_{3b}	Bilateral clinically positive nodes
N_{3c}	Contralateral clinically positive node(s)
Involvement by distant metastases (M)	
Mx	Distant metastasis was not assessed
M_0	No evidence of distant metastasis
M_1, M_2, M_3	Distant metastasis is present. Increasing degrees of metastatic involvement, including distant nodes

* Several other classifications are available, e.g. STNM (S, site).
† T_1, maximum diameter 2 cm; T_2, maximum diameter 4 cm; T_3, maximum diameter > 4 cm; T_4, massive tumour > 4 cm diameter, with involvement of antrum, pterygoid muscles, base of tongue or skin.

- A red lesion (erythroplasia).
- A granular ulcer with fissuring or raised exophytic margins.
- A white or mixed white and red lesion.
- A lump sometimes with abnormal supplying blood vessels.
- An indurated lump/ulcer, i.e. a firm infiltration beneath the mucosa.
- A non-healing extraction socket.
- A lesion fixed to deeper tissues or to overlying skin or mucosa.
- Cervical lymph node enlargement, especially if there is hardness in a lymph node or fixation.

Enlarged nodes in a patient with oral carcinoma may be caused by infection, reactive hyperplasia secondary to the tumour, or metastatic disease. Occasionally, a swollen lymph node is detected in the absence of any obvious primary tumour.

In patients with OSCC for over 3 years, second primary neoplasms in the aerodigestive tract may be seen in up to 25% and in up to 40% of those who continue to smoke.

Diagnosis. Early diagnosis is important since it improves prognosis and minimizes the extent of interventions [14–16]. There should be a high index of suspicion, especially of a solitary lesion present for over 3 weeks: biopsy is invariably indicated. Clinicians should be aware that single ulcers, lumps, red patches or white patches, particularly if any of these persist for more than 3 weeks, may be manifestations of frank malignancy. Scalpel biopsy is required and toluidine blue staining may help highlight the most appropriate area for biopsy [17–19].

The whole oral mucosa should be examined as there may be widespread dysplastic mucosa ('field change') or even a second neoplasm and the cervical lymph nodes must be examined. Frank tumours should be inspected and palpated to determine extent of spread; for tumours in the posterior tongue, examination under general anaesthesia may facilitate this.

OSCC should be staged according to the TNM classification of the International Union against Cancer, where T represents tumour size, N nodal metastases and M distant metastases (Table 66.18), since this classification relates well to overall survival rate, i.e. the earlier the tumour, the better the prognosis and the less complicated the treatment.

Investigations. The principles include the following.

1 Confirm the diagnosis histopathologically and determine the presence of malignant disease elsewhere.

(a) Are bone, muscles or cervical lymph nodes involved?

(b) Are there other primary tumours (typically in the upper aerodigestive tract—mouth, nares, pharynx, larynx, oesophagus)? There is controversy as to the need for endoscopy in all cases to detect such tumours.

(c) Are there metastases, initially to regional lymph nodes and later to liver, bone and brain? Imaging may detect abnormalities that escape clinical examination.

2 Ensure that the patient is as prepared as possible for the major surgery required, particularly in terms of general anaesthesia, potential blood loss and ability to metabolize drugs.
3 Address any potential dental or oral problems preoperatively, to avoid later complications such as osteoradionecrosis.

The following investigations are therefore almost invariably indicated.

- Lesional biopsy. Incisional biopsy, which is invariably required, should be sufficiently large to include enough suspect and apparently normal tissue. Red, rather than white, areas are most likely to show dysplasia, and hence should be biopsied. Attempts to highlight probable dysplastic areas before biopsy, for example by using toluidine blue dye, are unfortunately not reliable, but may be of some help in deciding which area is best to biopsy where there is widespread 'field change'. An excisional biopsy should be avoided unless the lesion is extremely small, since this is unlikely to have excised an adequately wide margin of tissue if the lesion is malignant, but will have destroyed for the surgeon or radiotherapist clinical evidence of the site and character of the lesion.
- Biopsy of equivocal neck lymph nodes.
- Jaw radiography (often rotating pantomography), although this is inadequate to exclude bone invasion.
- Chest radiography: important as a pre-anaesthetic check, especially in patients with known pulmonary or airways disease, and to demonstrate metastasis to lungs or hilar lymph nodes, ribs or vertebrae.
- MRI or computed tomography (CT) of the primary site, head and neck, and suspected sites of distant metastases, and MRI of the neck to delineate the extent of cervical node metastases. Some units routinely examine chest and abdomen. MRI is particularly useful for determining tumour spread, bone involvement and nodal metastases.
- Electrocardiography.
- Blood tests.
- Full blood picture and haemoglobin.
- Blood for grouping and cross-matching.
- Urea and electrolytes.
- Liver function tests.

In selected cases, the following may also be useful.

- Bronchoscopy: if chest radiography reveals any lesions.
- Endoscopy of the upper aerodigestive tract: especially if there is a history of tobacco use.
- Gastroscopy: if a per-endoscopic gastrostomy is to be used for feeding.
- Liver ultrasound: if there is hepatomegaly or abnormal liver function.
- Doppler duplex flow studies: in planning radial free forearm flaps.
- Angiography: in planning lower limb free flaps.

Treatment. The prognosis of OSCC is around 30% survival at 5 years [20]. The major impact that treatment has had on the prognosis of oral cancer has been in relation to improved anaesthetic and medical care. Surgical reconstruction has also been markedly improved [21] and there are fewer side effects from modern radiotherapy.

The treatment of oral cancer involves one or a combination of radiotherapy, surgery and, very occasionally, chemotherapy. Serious consideration must be given to the complications of the various modalities [22,23] and the quality of life achieved [24,25].

There is now evidence that vitamin A derivatives may be of benefit in patients with premalignant lesions, and in preventing second primary neoplasms [26–27].

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Verrucous carcinoma

Verrucous carcinoma is an uncommon, warty, white neoplasm that is rarely ulcerated [1–4]. It may develop from proliferative verrucous leukoplakia (see p. 66.86). Risk factors include a possible association with HPV and some verrucous carcinoma develops as a result of the local use of snuff or tobacco. Confirmation of diagnosis by biopsy is particularly important because verrucous carcinoma responds well to excision but, if irradiated, may undergo anaplastic change, with subsequent acceleration of growth and invasiveness [5]. Methisoprinol may be of value [6].

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Florid oral papillomatosis

Florid oral papillomatosis is a rare but well-defined clinical entity of unknown pathogenesis. Risk factors include possible association with HPV, tobacco, and chronic inflammation or irritation.

Florid oral papillomatosis is essentially a verrucous carcinoma, a clinicopathological variant of squamous cell carcinoma also known by a confusing array of names such as Ackerman's tumour, Buschke–Loewenstein tumour, epithelioma cuniculatum, carcinoma cuniculatum and cutis papillomatosis carcinoides of Gottron.

Clinical features. The lesions are exuberant, warty or verrucous, and characterized by their benign appearance on histology, although this is usually associated with a marked capacity for recurrence and and a tendency for carcinomatous change. Its apparent clinical benignity may lead to lengthy periods of misdiagnosis, during which it slowly but relentlessly destroys and extends into underlying tissue but rarely metastasizes to lymph nodes [1–3].

Diagnosis. Biopsy is required, although to those unfamiliar with the diagnosis the relatively bland histological features are often more suggestive of verruca vulgaris or pseudoepitheliomatous hyperplasia than of squamous cell carcinoma. Alternatively, when it extends into underlying tissues, it may be mistaken for a benign adnexal tumour or even a cyst.

Management. Treatment in the early stage of the disease is usually successful. Etretinate therapy (200 mg/day) or chemotherapy with bleomycin may reduce the lesion bulk [4–6]. Surgical or laser excision is favoured. The use of radiotherapy is controversial since in numerous reported cases this has produced an anaplastic squamous cell carcinoma.

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Basal cell carcinoma

Actinic radiation is a major aetiological factor in the development of basal cell carcinoma (BCC), greater than 85% occurring on the sun-exposed areas of the head and neck [1]. Fair-skinned individuals who burn and those whose occupations require excessive exposure to sunshine are at greatest risk; the tumour is rare in dark-skinned persons, and 95% occur after the age of 40 years [2].

Other significant risk factors for the development of BCC include prior burns, vaccinations, irradiation, exposure to inorganic arsenic, genetic syndromes (e.g. xeroderma pigmentosum, naevoid BCC syndrome, albinism and Bazex's syndrome) and immunosuppression [3–8].

Clinical features. On the lip these manifest as a pearly, sometimes ulcerated, nodule or papule. Unlike squamous cell carcinomas, BCCs only rarely originate on the vermilion but commonly occur periorally [9–11]. In contrast to squamous cell carcinomas, BCCs more commonly arise on

the upper than the lower lip. The lesions can also arise *de novo* on the vermilion [12] or occasionally the mucosa of the lip, although spread of a tumour from an adjacent site may rarely occur.

BCC has multiple forms that can be simplistically divided as follows.

- Nodular: the most frequent type around the lips presents as a waxy translucent nodule with fine telangiectasias, often ulcerated.
- Morphoeic: an atrophic plaque resembling a scar, with an aggressive infiltrative growth pattern and high rate of recurrence after excision.
- Superficial: appears as an erythematous plaque with elevated borders and central atrophy or ulceration. It is rare around the lips.

Although the tumour rarely metastasizes, it is responsible for considerable functional and cosmetic morbidity.

Multiple lesions are commonly encountered and the various forms have overlapping clinical features. BCC can be frequently pigmented, resembling melanomas and other melanocytic lesions. BCC may of course be a feature of naevoid BCC syndrome (Gorlin–Goltz syndrome, see p. 66.39). Furthermore, in addition to having a significantly increased risk for new skin cancers, patients with BCC have been shown to have an increased risk of developing non-cutaneous cancers, including respiratory cancers, testicular cancer, breast cancer and non-Hodgkin's lymphoma [13,14].

Diagnosis. BCC of the lips must be differentiated from other nodules, including squamous cell carcinoma, keratoacanthoma, trichoepithelioma and sebaceous adenoma. Since lesions that arise periorally are often aggressive, and early detection and confirmation by biopsy will prevent infiltration and destruction of the underlying structures.

Management. Various treatment modalities for BCC include scalpel, electrosurgery, cryosurgery and laser surgery, radiation, curettage and intralesional chemotherapy. Selection of the treatment modality depends on size, site and histological pattern of the tumour as well as the age of the patient. Since lip lesions are often of the nodular or morphoeic types, Mohs' micrographic surgery, utilizing microscopically controlled excision, potentially offers the highest cure rate with the greatest preservation of tissue. The cure rate for BCC is over 90% [15].

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Keratoacanthoma

Keratoacanthoma is a benign, often rapidly growing lesion that probably arises from the supraseboglandular part of a sebaceous gland. Keratoacanthomas are common, self-limiting, proliferative tumours that arise most frequently in men after the sixth decade of life [1,2].

The lesions mimic squamous cell carcinoma both clinically and microscopically. Although some believe keratoacanthomas represent well-differentiated squamous cell carcinomas, significant differences between the two entities have been demonstrated [3]. A number of well-documented variants, many with generally distributed eruptive keratoacanthomas, have been described. One variant, Ferguson–Smith syndrome, is a familial trait.

Aetiology. The role of actinic damage is strongly supported by the fact that the majority of lesions occur on sun-exposed skin (90%), with up to 10% occurring periorally or on the vermilion border of the lips. HPV has also been suggested as an aetiological agent [4], and increased numbers of keratoacanthomas have been reported in immunocompromised patients.

Clinical features. Keratoacanthomas often manifest at the vermilion border, as indurated dome-shaped nodules displaying a characteristic central, keratin-filled, crusted and frequently darkened crater. Cutaneous lesions are asymptomatic but oral and lip lesions are frequently painful [5–7]. Intraoral keratoacanthomas are rare [8,9]. They usually appear as an ulcer with a rolled margin, clinically indistinguishable from squamous cell carcinoma, usually on the anterior or maxillary gingiva. It is unclear whether intraoral keratoacanthomas regress

spontaneously, as all have been excised for diagnosis. Keratoacanthomas grow rapidly, attaining a size typically greater than 1 cm, may be locally invasive and result in significant tissue damage but, if left untreated, many undergo spontaneous involution after 1–2 months.

Diagnosis. Keratoacanthomas require differentiation from squamous cell carcinoma. When lesions develop intraorally or on the lips, they should immediately be subjected to biopsy for confirmation, since squamous cell carcinomas at these sites frequently metastasize.

Management. Management is often by surgical excision. Intralesional therapy with methotrexate or 5-fluorouracil can also be employed with excellent results. Other suggested medical therapies include intralesional interferon alpha-2a and systemic isotretinoin [10–12].

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Other oral malignant primary neoplasms

The following comprise up to 10% of all oral malignant tumours.

1 Salivary gland tumours.
2 Malignant melanoma.
3 Lymphomas: non-Hodgkin's lymphomas are increasingly seen in the fauces in HIV disease and immunocompromised persons.
4 Sarcomas.
5 Kaposi's sarcoma: oral Kaposi's sarcoma is typically seen in HIV disease or other immunocompromised persons and especially in the posterior palate as a brown or purple macule that becomes nodular and ulcerates.
6 Some odontogenic tumours.
7 Maxillary antral carcinoma (or other neoplasms).
8 Langerhans' cell histiocytosis.
9 Neoplasms of bone and connective tissue.
10 Other neoplasms.

Abrikossoff's tumour

Abrikossoff's tumour is a disease that develops between the second and sixth decades of life, more frequently among women and blacks. The head and neck area is affected in 45–65% of cases and, of these, 70% are located intraorally (tongue, oral mucosa, hard palate) [1].

The benign form shows polygonal cells with granular eosinophilic cytoplasm and small nuclei. The malignant form, however, is associated with a high mitotic index and pleomorphic cellular tissue.

The clinical feature of either is a swelling covered by mucosa of normal clinical appearance. Histological examination is required. The treatment is surgery.

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Metastatic oral neoplasms

Metastases to the oral tissues are rare, accounting for only 1% of all oral tumours and most appear in bone, especially the mandibular premolar or molar area or condyle. Most oral metastases originate from carcinomas of breast, lung, kidney, thyroid, stomach, liver, colon or prostate [1–10].

Metastases may present with pain, paraesthesia, sensory loss, loosening of teeth, delayed healing of an extraction wound or pathological fracture. Metastases may occasionally appear as an alveolar or gingival swelling or ulcer.

Tumour deposits arise from lymphatic or haematogenous spread.

Clinical features. Metastases usually present as a lesion arising in the jaw, sometimes only revealed coincidentally by imaging, at other times causing symptoms. In up to one-third of patients the jaw lesions are the first manifestation of the tumour. Non-Hodgkin's lymphomas are frequently gingival or faucial in location.

Many metastases are asymptomatic but others manifest with:

- pain;
- paraesthesia or hypoaesthesia;
- swelling;

- tooth mobility;
- non-healing extraction sockets;
- pathological fracture;
- radiolucency or radio-opacity.

Diagnosis. Diagnosis is from history and clinical features supplemented by radiography and histopathology.

Treatment. Radiotherapy, surgery or chemotherapy.

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Ulcers in association with systemic disease

Aphthae (see p. 66.43) are occasionally associated with systemic disease. However, a wide range of systemic diseases, especially haematological, gastrointestinal and dermatological disorders, may cause other oral lesions which, because of the moisture, trauma and infection in the mouth, tend to break down to leave ulcers or erosions. Oral ulceration is also frequently caused by infections and can be caused by iatrogenic problems such as drugs or irradiation (see Table 66.13).

Haematological diseases

Deficiency states

Low iron, folate or vitamin B_{12} levels may predispose to aphthae. A few of these patients also have anaemia, sometimes with other oral features such as glossitis or angular stomatitis, but many have a deficiency state with no established anaemia [1,2]. Occasionally, patients with deficiency of B vitamins may develop other types of oral ulcer, and sometimes epithelial dysplasia [3].

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Leukopenias and agranulocytosis

White cell dyscrasias and HIV infection are also often complicated by oral ulceration (Fig. 66.29). Oral ulceration may be a major symptom in patients with leukopenias, and may be the first manifestation of drug-induced agranulocytosis. Painful, deep, irregular ulcers, often with only a minimal inflammatory halo, involve the mouth and/or pharynx and tend to extend and penetrate slowly. In cyclic neutropenia, ulcers appear episodically at 21-day intervals in association with the neutropenic episodes. Severe periodontitis is often also a feature of leukocyte and other immune defects and the patients may suffer from recurrent infections elsewhere [1–3]. Methotrexate can cause oral ulceration in the absence of leukopenia.

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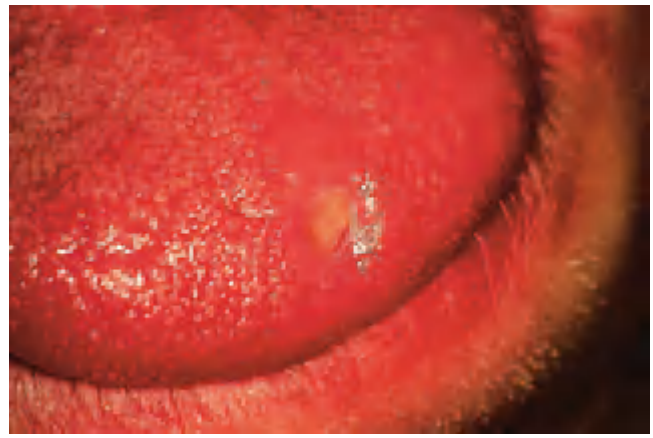

Fig. 66.29 Aphthous-like ulceration in HIV disease.

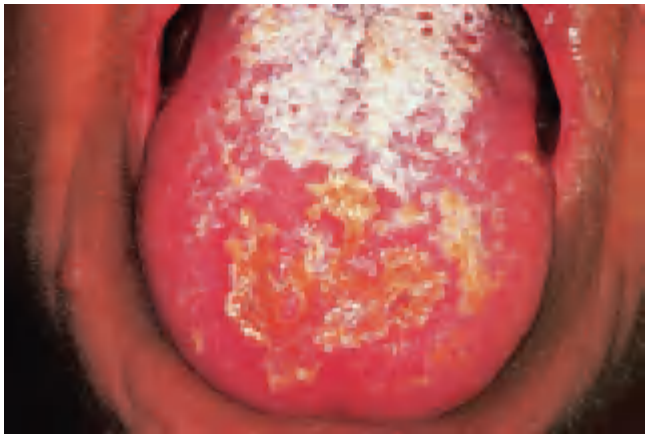

Fig. 66.30 Herpes simplex lingual recurrence, and candidiasis in leukaemia: similar lesions may be seen in HIV infection.

Leukaemias

Oral ulceration may be a prominent feature, especially in the acute leukaemias. Other oral manifestations of leukaemia include mucosal pallor, gingival haemorrhage, gingival swelling, petechiae and ecchymoses [1–4]. Oral infections with *Candida albicans* and Gram-negative bacteria including *Pseudomonas* species, *Escherichia coli*, *Proteus*, *Klebsiella* and *Serratia* species are common, especially in acute leukaemias, and may act as a portal for septicaemia [5]. Herpes simplex or zoster–varicella virus ulcers are also common (Fig. 66.30). Chemotherapy complicates the situation because it too can produce oral ulceration [1,6].

Other findings include paraesthesia (particularly of the lower lip), extrusion of teeth or bone, painful swellings over the mandible and parotid swelling (Mikulicz's syndrome) [7].

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Granulocytic sarcoma

SYN. CHLOROMA

Granulocytic sarcomas are rare in the oral cavity. Most present with swelling or symptoms related to skeletal involvement [1–3]. The maxilla is particularly involved [1,4].

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Myelodysplastic syndrome

Oral manifestations in myelodysplastic syndrome include particularly ulceration but also paraesthesiae, petechiae, burning mouth, gingival swelling, xerostomia and herpes labialis [1–4].

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Lymphomas

Some 2–10% of lymphomas present first in the oral cavity. Of these oral lymphomas, 80% are composed of follicular centre cells or post-follicular cells [1–5]. Lymphomas usually occur on the pharynx or palate, but occasionally on the tongue, gingivae or lips; they may appear as oral swellings, which sometimes ulcerate and may cause pain or sensory disturbance. Oral herpes zoster and herpes simplex infections are common in patients with lymphomas.

There is an increased incidence of oral lymphomas in HIV disease [6] including oral plasmablastic lymphomas [7,8].

Lethal midline granuloma. Lethal midline granuloma is the term sometimes used to include a spectrum of conditions including Wegener's granulomatosis, polymorphic reticulosis (lymphomatoid granulomatosis) and idiopathic midline destructive disease.

Wegener's granulomatosis. Although not a lymphoma, Wegener's granulomatosis is discussed here. Oral manifestations are common and may be the first sign of Wegener's granulomatosis [9–20]. A painless progressive

swelling of the gingiva in a previously healthy mouth, particularly associated with swollen inflamed papillae, should arouse suspicion of Wegener's granulomatosis. The gingival enlargement may have a fairly characteristic 'strawberry-like' appearance. Wegener's granulomatosis may also present with oral ulceration, failure of an extraction socket to heal or occasionally swelling of the lip or salivary gland.

Polymorphic reticulosis (syn. lymphomatoid granulomatosis). The most common oral presentation of polymorphic reticulosis is palatal ulceration but ulceration may occur elsewhere [17].

Idiopathic midline destructive disease [21–23]. Downward spread from nasal disease can lead to palatal necrosis and ulceration in idiopathic midline destructive disease. Occasionally the disease presents with delayed healing of an extraction socket.

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Mycosis fungoides

Oral lesions in mycosis fungoides typically are red or white areas on the tongue but are usually late manifestations of this disease [1–6].

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Pseudolymphoma

Rare tumour-like lymphoproliferative infiltrates that lack the malignant potential of lymphomas may be seen intraorally, notably in the palate [1].

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Histiocytoses

The histiocytoses typically produce lytic bone lesions but gingival swelling, periodontal destruction with loosening of teeth, non-healing extraction sockets and mouth ulceration may be seen. ^{111}In-pentetreotide imaging may be useful in diagnosis of Langerhans' cell histiocytosis [1–7].

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Multicentric reticulohistiocytosis

Oral lesions are seen in up to 50% of patients with multicentric reticulohistiocytosis [1]. Lesions are collections of histiocytes that form nodular or granular lesions, particularly in the labial or buccal mucosa. The temporomandibular joint may also be involved as part of the polyarthropathy.

REFERENCE

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Hypereosinophilic syndrome

Oral erosions affecting buccal, gingival or labial mucosae may be a feature of the hypereosinophilic syndrome [1–4] and may herald cardiac involvement [2]. Etoposide therapy may be effective [4].

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Hypoplasminogenaemia

Gingival swelling and ulceration are features of hypoplasminogenaemia [1].

REFERENCE

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Gastrointestinal diseases

Aphthae in gastrointestinal diseases are discussed on p. 66.45. Other types of mouth ulcer are also sometimes found in ulcerative colitis and Crohn's disease.

Pyostomatitis vegetans

The oral lesions termed pyostomatitis vegetans are deep fissures, pustules and papillary projections. Less than 50 cases have been recorded and most patients have had inflammatory bowel disease, i.e. ulcerative colitis or Crohn's disease [1–12]. The course of these lesions tends to follow that of the associated bowel disease [1–5].

Although the oral lesions may respond at least partially to topical therapy (e.g. corticosteroids), systemic treatment is often needed [1–5,12].

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Orofacial granulomatosis (OFG)

Aetiology. Crohn's disease can affect the mouth but some patients appear to develop similar oral lesions because

of an adverse reaction to various food additives, such as cinnamaldehyde or benzoates, butylated hydroxyanisole or dodecyl gallate (in margarine), or to menthol (in peppermint oil) or cobalt, although these reactions are by no means always relevant [1–15]. For example, the lesions in only one of nine patients in one study had any relationship to food intake [15]. The genetic background [16], any role of allergy [17] and diverse possible other aetiological factors such as *Mycobacterium paratuberculosis* [18] is unclear.

The term 'orofacial granulomatosis' is preferred in some centres since it is unclear where in the spectrum of Crohn's disease/sarcoidosis/allergy/infection these lesions (and related conditions such as Melkersson–Rosenthal syndrome and granulomatous cheilitis) lie [8,19–21].

Pathology. Non-caseating granulomas and lymphoedema may be seen but the granulomas tend to be sparse and deep, close to the muscle.

Clinical features. Ulcers classically involve the buccal sulcus where they appear as linear ulcers, often with granulomatous masses flanking them.

Mucosal lesions also include thickening and folding of the mucosa to produce a 'cobblestone' type of appearance and mucosal tags. Purple granulomatous enlargements may appear on the gingiva. The lips or face may swell and there may be splitting of the lips and angular stomatitis [22,23].

Diagnosis. The oral history is not specific, and investigation of the gastrointestinal tract is mandatory. Investigations such as chest radiography, serum angiotensin-converting enzyme and a gallium scan may be required to exclude sarcoidosis. Patch tests may be indicated to exclude reactions to various foodstuffs or additives.

Treatment. Elimination diets may be warranted in patients with OFG if allergy is suspected [11]. Topical or intralesional corticosteroids may effectively control the oral lesions [6]. Intralesional corticosteroid injections may also reduce the swelling. The injection of up to 10 mL triamcinolone (10 mg/L) into the lips after local analgesia may be effective [15,24–26]. The injections may have to be repeated every 4–6 months once a response plateau has been reached. Systemic corticosteroids are rarely indicated and in any event not all patients respond [26]. Metronidazole may be of value in some cases [3].

Clofazimine in a dose of 100 mg twice daily for 10 days, then twice weekly for 4 months appears to help the majority of patients [27,28]. Clofazimine appears to be most effective during the early stages and works by clearing granulomas.

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Crohn's disease

Crohn's disease lesions are indistinguishable from OFG.

Dermatological diseases

Several dermatoses can be associated with oral ulcers or erosions; lichen planus (LP) is the most common, pemphigus the most serious and pemphgoid is intermediate.

Lichen planus (see Chapter 42)

Oral LP may affect up to 1–2% of the population and is probably about eight times more common than cutaneous LP. The oral mucosa may be involved alone or in association with lesions on skin or other mucosa, and oral lesions may precede, accompany or follow lesions elsewhere [1–4]. The association of oral LP with gingival involvement, together with vulvovaginal lesions, has been termed the *vulvovaginal–gingival syndrome*.

Aetiology. Most oral LP is idiopathic but significantly greater anxiety and depression are observed among patients with oral LP compared with controls [5].

Some lichenoid lesions may be related to dental materials: the prevalence of positive reactions to potential allergens in the North American Contact Dermatitis Group (NACDG) is higher in oral LP for chromate, gold and thimerosal [6]. Other lichenoid reactions may be caused by GVHD, drug use (e.g. non-steroidal anti-inflammatory agents), diabetes [7] or liver disease. Chronic liver disease, especially chronic active hepatitis and hepatitis C virus (HCV) infection, may be associated with erosive LP in persons of southern European, Japanese or some other extractions [8] and there may be anticardiolipin antibodies [9]. In persons of northern European extraction, oral LP is only rarely associated with liver disease or with hepatitis C, hepatitis G or transfusion-transmitted virus [10–12].

Pathology. The pathology is similar to that of cutaneous LP, although sawtooth rete ridges are rarely seen in oral biopsies, and other epithelial changes may be less distinct.

Clinical features. The common oral lesions of LP are bilateral white lesions in the buccal and/or lingual mucosa. They may be reticular, papular or plaque-like (Figs 66.31–66.35). They are often symptomless but may cause soreness [1–4].

Erosive LP, which frequently affects the dorsum and lateral borders of the tongue or the buccal mucosae on both sides, is uncommon. The erosions are often large, slightly depressed or raised with a yellow slough, and have an irregular outline (Fig. 66.34), but they are not always as painful as might be imagined. The surrounding mucosa is often erythematous and glazed in appearance, with loss of filiform papillae of the tongue, and there are often pathognomonic whitish striae. LP may also produce

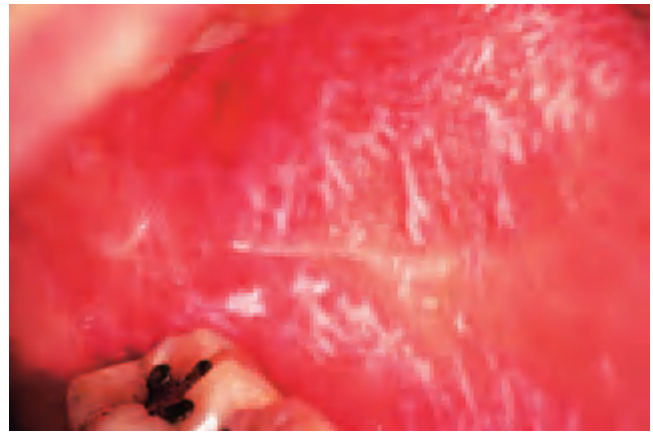

Fig. 66.31 Lichen planus: reticulopapular lesions in the common oral site, the buccal mucosa.

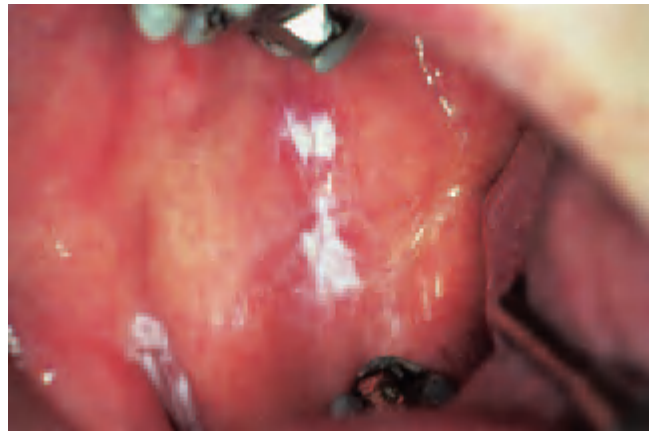

Fig. 66.32 Lichen planus: plaque-like lesions resemble leukoplakia.

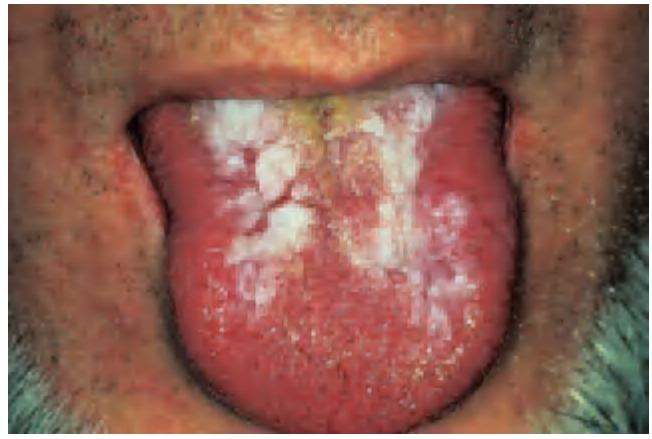

Fig. 66.33 Lichen planus on the tongue.

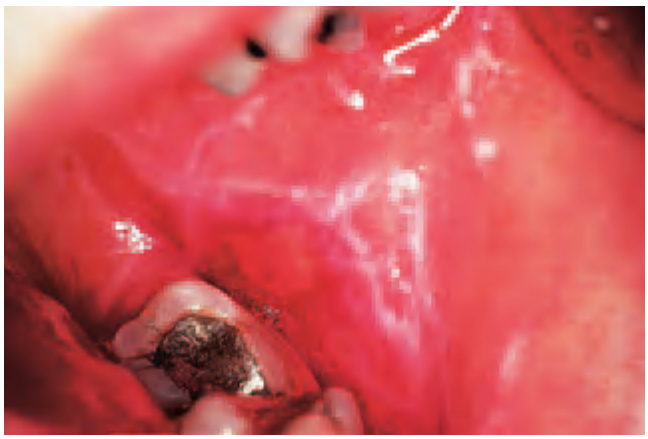

Fig. 66.34 Erosive lichen planus.

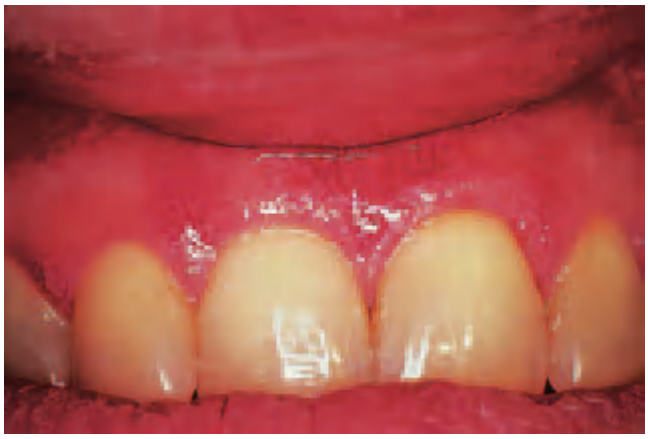

Fig. 66.35 Lichen planus on the gingivae: white and desquamative lesions.

a desquamative gingivitis (see p. 66.100). Candidiasis may complicate oral LP.

Reticular LP is the most frequent clinical presentation in both HCV-positive and HCV-negative patients. HCV-positive patients particularly have lip, tongue and gingival lesions [13].

Prognosis. There appears to be a predisposition for some oral LP, particularly the non-reticular forms, to develop carcinoma—possibly a risk of up to 5% over 10 years [1–4].

Diagnosis. Biopsy with immunofluorescence is often indicated to exclude keratosis, chronic ulcerative stomatitis with stratified epithelium-specific antinuclear antibodies, lichen sclerosus, lupus erythematosus, malignancy and other disorders.

Management. Treatment is not always necessary, unless there are symptoms. Unfortunately, although the natural history of cutaneous LP is one of remission in most cases, in few patients with oral LP does the disorder remit, and thus treatment is indicated for symptomatic oral LP [1–4,14].

- Predisposing factors should be corrected. It may be wise to consider removal of dental amalgams if the lesions are closely related to these, or are unilateral, but there are no tests (e.g. patch tests) that will reliably indicate which patients will benefit from this.

If drugs are implicated, the physician should be consulted as to possible changes in therapy. If there is diabetes or HCV infection, this should be treated by a physician.

- Improvement in oral hygiene may result in some subjective benefit. Thus good oral hygiene should be maintained. Chlorhexidine or triclosan mouthwashes may help.
- Symptoms can often be controlled with topical medication: topical corticosteroids, such as betamethasone valerate aerosol or pastes containing fluocinonide, fluocinolone, triamcinolone, betamethasone valerate or clobetasol [15,16]; or topical tacrolimus [17,18]. Antifungals may help, especially where there is candidal superinfection.

1 *Mild LP*. Topical corticosteroids are the mainstay of therapy (e.g. triamcinolone acetate, betamethasone or fluocinolone). Erosive and gingival lesions are often recalcitrant. Next, high-potency corticosteroids such as clobetasol, fluocinonide or fluticasone may be employed initially and then changed to a lower potency drug.

2 *Moderate LP*. If there is severe or extensive oral involvement, topical ciclosporin or tacrolimus may be of significant benefit, often being used with a high-potency or super-potent topical steroid such as clobetasol, fluticasone or mometasone. Topical creams or pastes can be applied in a suitable customized tray or veneer to be worn at night. This regimen is useful in the management of LP-related desquamative gingivitis recalcitrant to other therapies.

3 *Severe LP*. In severe LP in multiple sites, patients may require systemic corticosteroids, azathioprine, cyclophosphamide, hydroxychloroquine, acitretin, thalidomide or ciclosporin. Dapsone is occasionally effective.

- Other therapies for LP include retinoids, dapsone, low-molecular-weight heparin [19] and many others, but either their efficacy has not been well proven or they have unacceptable adverse effects.
- Patients with non-reticular LP should be monitored to exclude development of carcinoma. Tobacco and alcohol use should be minimized.

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Overlap syndromes

Lichen planus pemphigoides. Oral lesions in LP pemphigoides may be similar to those of LP or pemphigoid, clinically and histologically [1,2].

Lichen planus/lichen sclerosus overlap syndrome. This may involve the oral and/or vulval mucosae [3].

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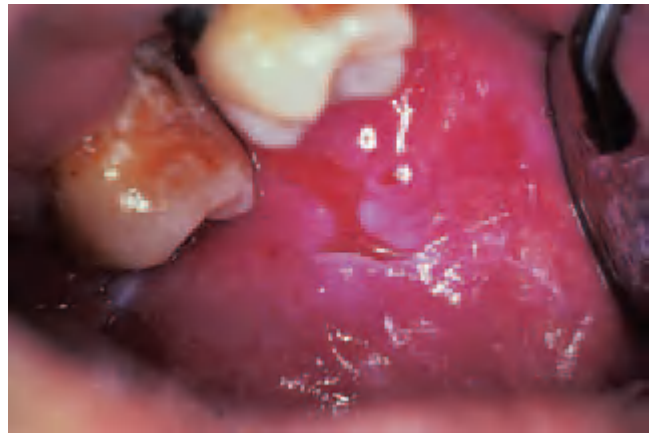

Fig. 66.36 Pemphigus vulgaris: irregular persistent oral erosions.

Pemphigus (see Chapter 41)

Oral lesions are the rule in pemphigus vulgaris (PV), but rare in the superficial forms of pemphigus [1].

Pemphigus vulgaris. The main antigen in PV is desmoglein (Dsg) 3. However, 50% of patients with PV also have autoantibodies to Dsg1 (the main antigen in pemphigus foliaceus) and the proportion of Dsg1 and Dsg3 antibodies appears to be related to clinical severity. Those cases of PV which are predominantly oral have only Dsg3 antibodies. Dsg1 autoantibodies are found in over 50% of cases of PV, and the frequency may differ with race since they are found in a significantly greater proportion of patients of Indian origin than white northern Europeans [1–4]; such variations may be HLA-related [5].

Typically, an individual patient develops a single variant of pemphigus, although cases have been described of transition to another variant, presumably through epitope spread, and the clinical manifestations of a single variant can change over time, possibly related to changes in the proportions of Dsg1 and Dsg3 autoantibodies.

The oral mucosa is almost invariably involved in PV and oral lesions are commonly the presenting feature (Fig. 66.36). Bullae appear on any part of the oral mucosa including the palate, but break so rapidly that they are rarely seen [1,6–12]. Usually, the patient presents with large, painful, irregular and persistent red lesions which, by the time they become secondarily infected, can be difficult to differentiate clinically from those of other erosive conditions, such as pemphigoid and other immune blistering disorders, although intact bullae are more commonly seen in these, whereas the Nikolsky sign is more often positive in pemphigus. Oral lesions of PV are typically seen in adults, rarely in childhood.

The prevalence of oral involvement varies: one multicentre study involving patients from several countries showed that Bulgarian patients with PV had oral mucous

Table 66.19 Immunostaining in oral mucosal vesiculobullous disorders.

Disease	DIF	Oral mucosal deposits mainly:	Pattern of IF	IIF	Autoantibodies against:
Pemphigus	+	IgG C3	Epithelial intercellular	+	Epithelial intercellular cement
Mucous membrane pemphigoid	+	C3 IgG	Linear epithelial basement membrane	±	Epithelial basement membrane
Bullous pemphigoid	+	IgG C3	Linear epithelial basement membrane	+	Epithelial basement membrane
Dermatitis herpetiformis	+	IgA C3	Granular epithelial basement membrane	–	Reticulin
Linear IgA disease	+	IgA C3	Linear epithelial basement membrane	–	–
Erythema multiforme	±	C3 IgM	Vessel walls in lamina propria	–	–
Lichen planus*	±	Fibrin† IgM, IgG, IgA, C3	Globular epithelial or lamina propria and in Civatte bodies	–	–
Discoid lupus erythematosus*	+	IgG, IgA IgM, C3	Granular epithelial basement membrane	±	None, or antinuclear
Angina bullosa haemorrhagica	–	–	–	–	–
Superficial mucoceles	–	–	–	–	–

DIF, direct immunofluorescence (biopsy); IF, immunofluorescence; IIF, indirect immunofluorescence (serology); +, present; –, absent; ±, sometimes.
* Rarely vesiculobullous.
† Non-specific deposits.

membrane lesions less frequently (66%) than Italian (83%) or Israeli (92%) patients [8]. Rarely in PV there can be an acquired macroglossia [11] or desquamative gingivitis [12].

Diagnosis should be confirmed by biopsy and immune studies. A biopsy of perilesional mucosa should be taken for H+E sections and immunostaining (Table 66.19) and serum collected for autoantibody titres, which can help diagnosis and monitoring of disease activity. Differential binding of anti-Dsg antibodies suggests that both human skin and monkey oesophagus should be used in the diagnosis of PV, since patients with predominantly oral disease may only have Dsg3 antibodies, which are not always detectable using human skin [13]. Oral smears for cytology are of little practical value.

Treatment is largely based on systemic immunosuppression using corticosteroids, with azathioprine, dapsone, methotrexate, cyclophosphamide, gold or ciclosporin as adjuvants or alternatives; this has significantly reduced the mortality [1,14]. Adverse effects of these drugs are common, though deflazacort may have slightly fewer effects [15]. Mycophenolate mofetil offers the hope of relatively safer immunosuppression with no nephrotoxicity or hepatotoxicity [16,17].

Mucosal lesions are recalcitrant, often only healing after skin lesions have resolved when immunosuppressive therapy is given, and they may persist even though skin lesions are controlled. Topical corticosteroids may then help, or possibly prostaglandin E_2 [18]. Tacrolimus may well prove to have a place in the control of oral lesions [19].

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Paraneoplastic pemphigus. Apart from PV, the other important pemphigus variant affecting the mouth is paraneoplastic pemphigus, usually associated with lymphoproliferative disease or thymoma [1], although one case associated with OSCC has been reported [2]. Oral lesions may be the sole manifestation [3] and have also been seen in all reported cases of paraneoplastic pemphigus [4–8]. Oral lesions may be seen in isolation [1].

Painful extensive stomatitis, painful paronychia and lichenoid papules may be seen, and histology may show lichenoid changes, acantholytic blister formation and apoptotic keratinocytes. Direct immunofluorescence is positive for IgG both in the epidermal intercellular spaces and along the basement membrane zone. Indirect immunofluorescence is similarly positive in a PV pattern.

There is often only a partial response to intravenous corticosteroids. Recent therapeutic advances include the use of anti-CD20 monoclonal antibody (rituximab) [9] and mycophenolate [10].

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Pemphigus vegetans. Oral lesions in pemphigus vegetans are hyperplastic masses which, on the tongue, can give a cerebriform appearance [1,2].

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Other pemphigus variants. Oral lesions may be seen in less common pemphigus variants, especially in most cases with IgA pemphigus (intraepithelial IgA pustulosis or intraepidermal neutrophilic IgA dermatosis) [1–3], and in some cases of pemphigus associated with inflammatory bowel disease [4–9].

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Subepithelial immune bullous diseases

A spectrum of immune-mediated subepithelial bullous diseases can present with oral blisters and/or erosions, and with immune deposits at the epithelial basement membrane zone. Several distinct groups, and probably several overlap syndromes, are now recognized to exist.

Mucous membrane pemphigoid (see Chapter 41). Mucous membrane pemphigoid is a mucocutaneous, immune-mediated,

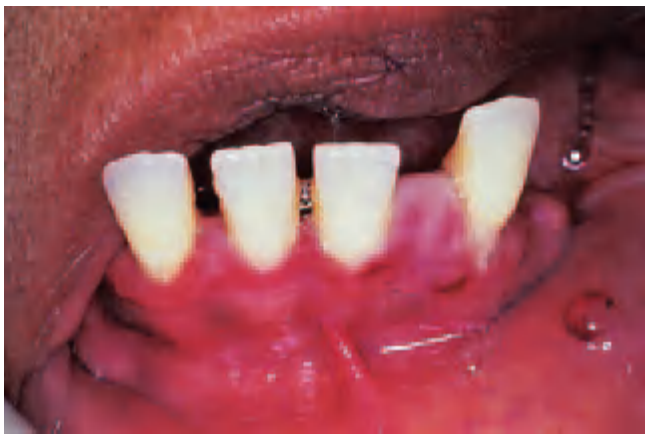

Fig. 66.37 Pemphigoid: vesicles and desquamative gingivitis.

subepithelial blistering disease characterized by autoantibodies to different molecules in the basement membrane zone [1,2]. The mouth may be involved as part of a wider disease, though in many patients only oral lesions are seen. Sera of oral pemphigoid patients selectively and specifically bind to human α6 integrin, a 120-kDa protein that appears to be a target antigen in this particular variant [3].

Mucous membrane pemphigoid involves the oral mucosa in more than one-third of cases, commonly causing gingival lesions [1,2,4,5]. The usual lesion, desquamative gingivitis, is characterized by erythematous, glazed, sore gingivae (Fig. 66.37). Bullae are less common, and are seen particularly on the soft palate. They rupture to form erosions [1–5].

The bullae in mucous membrane pemphigoid are subepithelial and tend to persist for longer than those of pemphigus. Oral lesions may scar but this is uncommon. The bullae are typically filled with serous fluid and should be distinguished from superficial mucoceles (see p. 66.81), epidermolysis bullosa acquisita, dermatitis herpetiformis and linear IgA disease. Occasionally blisters are blood-filled, and then must be differentiated from angina bullosa haemorrhagica (see p. 66.80).

A biopsy is required for diagnosis [5]. Serum autoantibodies to epithelial basement membrane may be detected in a few patients (see Table 66.19) but many have immune deposits at the epithelial and mucous gland basement membrane zone. A very small minority of patients have an associated internal malignancy which should be excluded.

Topical corticosteroids usually help if the lesions are restricted to the oral mucosa; azathioprine may be an alternative [6]. Systemic corticosteroids may occasionally be required but tetracyclines with or without nicotinamide may help [7,8]. Dapsone may be useful, especially in the treatment of desquamative gingivitis [9,10]. The evidence for efficacy of tacrolimus or mycophenolate mofetil is weak [11,12].

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Vegetating cicatricial pemphigoid (syn. pemphigoid vegetans). A subset of bullous pemphigoid, although clinically indistinguishable from pemphigus vegetans and sometimes producing oral blisters and erosions, vegetating cicatricial pemphigoid shows linear deposits of IgG and C3 at the epithelial basement membrane zone on oral biopsy but no circulating basement membrane antibodies [1].

Palate and gingiva have been especially involved in the rare cases described [2,3].

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Epidermolysis bullosa acquisita (see Chapter 41). Blisters or ulcers may be seen in the oral mucosa in epidermolysis bullosa acquisita, with antibodies directed against collagen VII. Lesional biopsy shows IgG and C3 in the sublamina densa zone of the epithelial basement membrane using immunoelectron microscopy [1–3].

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Dermatitis herpetiformis and adult linear IgA disease. Oral lesions may occur in dermatitis herpetiformis and in most patients with linear IgA disease. Macules, papules, petechiae, vesicles, bullae and erosions are the usual manifestations [1–10]. These disorders must be differentiated, especially from pemphigoid, angina bullosa haemorrhagica, superficial mucoceles and LP.

Salivary IgA antigliadin antibodies may be found but this is not useful diagnostically. Dapsone and sulfapyridine are the most effective therapeutic agents along with a gluten-free diet in dermatitis herpetiformis.

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Chronic bullous dermatosis of childhood (see Chapter 41). Oral ulceration has been reported [1,2].

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Erythema multiforme (see Chapter 74). The aetiology of erythema multiforme (EM) is unclear in most patients, but appears to be an immunological hypersensitivity reaction with the appearance of cytotoxic effector cells ($CD8^+$ T lymphocytes) in the epithelium, inducing apoptosis of scattered keratinocytes and leading to satellite cell necrosis.

Predisposing factors. There may be a genetic predisposition, with associations of recurrent EM with HLA-B15(B62), HLA-B35, HLA-A33, HLA-DR53 and HLA-DQB1*0301. HLA-DQ3 has been proven to be especially related to recurrent EM and may be a helpful marker for distinguishing this herpes-associated EM from other diseases with EM-like lesions. Patients with extensive mucosal involvement may have the rare HLA allele DQB1*0402 [1].

The reaction is triggered by the following.

- *Infective agents*, particularly herpes simplex virus (herpes-associated EM), which is implicated in 70% of recurrent EM. Bacteria (*Mycoplasma pneumoniae*, and many others), other viruses, fungi or parasites are less commonly implicated [2,3].
- *Drugs* such as sulphonamides (e.g. co-trimoxazole), cephalosporins, aminopenicillins, quinolones, barbiturates, oxicam non-steroidal anti-inflammatory drugs, anticonvulsants, protease inhibitors, allopurinol and many others may trigger severe EM or toxic epidermal necrolysis in particular [4,5].
- *Food additives or chemicals* such as benzoates, nitrobenzene, perfumes, terpenes.
- *Immune conditions* such as BCG or hepatitis B immunization, sarcoidosis, GVHD, inflammatory bowel disease, polyarteritis nodosa or systemic lupus erythematosus (SLE).

Clinical features. Most patients with EM (70%), of either minor or major forms, have oral lesions. The oral mucosa may be involved alone or in association with skin lesions. Mucosal lesions begin as erythematous areas that blister and break down to irregular, extensive, painful erosions with extensive surrounding erythema. The labial mucosa is often involved, and a serosanguinous exudate leads to crusting of the swollen lips [6–11].

Mucosal erosions plus typical or raised atypical targets and epidermal detachment involving less than 10% of the body surface and usually located on the extremities and/or the face characterize herpes simplex-induced EM major.

Mucosal erosions plus widespread distribution of flat atypical targets or purpuric macules and epithelial detachment involving less than 10% of body surface on the trunk, face and extremities are characteristic of drug-induced Stevens–Johnson syndrome [12].

Diagnosis. A diagnosis of EM can be difficult to readily establish, and there may be a need to differentiate from

viral stomatitides, pemphigus, toxic epidermal necrolysis and the subepithelial immune blistering disorders (pemphigoid and others). There are no specific diagnostic tests.

The diagnosis is mainly clinical; the Nikolsky sign is negative. It may be helpful to undertake serology for *Mycoplasma pneumoniae* or herpes simplex virus, or other microorganisms. Biopsy of perilesional tissue with immunostaining and histological examination may help, although pathology can be variable and immunostaining is not specific.

Management. Spontaneous healing can be slow, up to 2–3 weeks in EM minor and up to 6 weeks in EM major. Treatment is thus indicated but controversial. No specific treatment is available but supportive care is important; a liquid diet and intravenous fluid therapy may be necessary. Electrolytes and nutritional support should be started as soon as possible. Oral hygiene should be improved with 0.2% aqueous chlorhexidine mouthbaths.

The use of corticosteroids is controversial [13–14].

- EM minor may respond to topical corticosteroids, although systemic corticosteroids may still be required.
- EM major should be treated with systemic corticosteroids (prednisolone 0.5–1 mg/kg/day tapered over 7–10 days) and/or azathioprine or other immunomodulatory drugs. Levamisole [15] and thalidomide have occasionally been used to some effect. Plasmapheresis possibly has a place in the management of severe disease.

Antimicrobials may be indicated [16,17].

- Aciclovir in EM related to herpes simplex virus (HSV). Give a 5-day course at the first sign of lesions, or give 400 mg four times daily for 6 months for prophylaxis in EM related to HSV. Continuous therapy with valaciclovir 500 mg twice a day has also been reported to be effective [17].
- Tetracycline is indicated in EM related to *Mycoplasma pneumoniae*.

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Toxic epidermal necrolysis

SYN. LYELL'S DISEASE

Toxic epidermal necrolysis is a rare clinicopathological entity, with a high mortality, characterized by extensive detachment of full-thickness epithelium. Toxic epidermal necrolysis and Stevens–Johnson syndrome appear to be severity variants of the same disease, which differs from EM. The distinction from EM is unclear, however, but most cases of toxic epidermal necrolysis are drug-induced and the lesions are extremely widespread [1,2].

Recently, an increased number of cases in patients with HIV/acquired immune deficiency syndrome (AIDS) has been recorded [3].

Clinical features. Toxic epidermal necrolysis presents with cough, sore throat, burning eyes, malaise and low fever, followed after about 1–2 days by skin and mucous membrane lesions. Oral lesions can be seen in over 95% of patients with toxic epidermal necrolysis. The entire skin surface and oral mucosa may be involved, with up to 100% sloughing off. Gingival lesions are common and clinically are inflamed, with blister formation leading to painful widespread erosions. The blisters and erosions may precede the skin lesions by a day or so and may persist [3–6].

Diagnosis. Sheet-like loss of the epithelium and a positive Nikolsky sign are characteristic. Biopsy of perilesional tissue with immunostaining and histological examination are essential to the diagnosis. Histopathological examination is characteristic, showing necrosis of the whole epithelium detached from the lamina propria.

Management. Patients must be admitted to an intensive care unit as soon as possible for management [7]. There is no specific therapy for oral lesions but 2% lidocaine (lignocaine) and 0.2% aqueous chlorhexidine mouthbaths may provide symptomatic relief.

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Lichen sclerosus (see Chapter 56). Oral lichen sclerosus et atrophicus is uncommon but since it presents with whitish plaques, papules or a reticular pattern, or erosions, all features of LP [1–8], it may be underdiagnosed. Histologically, however, lichen sclerosus has epithelial atrophy with hyperkeratosis, oedema in the papillary corium and the lymphocytic infiltrate is less close to the epithelium than in LP. It has been suggested that mucosal lichen sclerosus is more common than formerly thought and may even cause dysplasia [5].

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Chronic ulcerative stomatitis with epithelial antinuclear antibodies. Chronic erosive or ulcerative stomatitis often presents as desquamative gingivitis with or without lesions on buccal or lingual mucosa and sometimes resembles LP, and may be associated with lichenoid histology, but is associated with antinuclear antibodies directed against stratified squamous epithelia [1–3]. These autoantibodies are directed against a 70-kDa epithelial nuclear protein homologous to the p53 tumour suppressor and the p73 putative tumour suppressor, and shown to be a splicing variant of the *KET* gene [4,5].

The lesions may respond to hydroxychloroquine [1–3].

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Lupus erythematosus (see Chapter 56)

Almost half of the patients with SLE suffer from oral lesions, which begin as red patches that break down to irregular slit-like ulcers which often heal with scarring [1]. Lesions particularly affect the palate. Sjögren's syndrome may occur in SLE. Oral petechiae and herpetic infections are also common. Rarely, dental surgery has been followed by facial swelling [2].

Similar erosions, with a white border, occur in discoid lupus erythematosus (Fig. 66.38). Discoid lupus erythematosus may predispose to oral carcinoma [3]. Oral ulceration has also been described in drug-induced lupus.

Systemic corticosteroids, often with an immunosuppressant, may be required in severe cases.

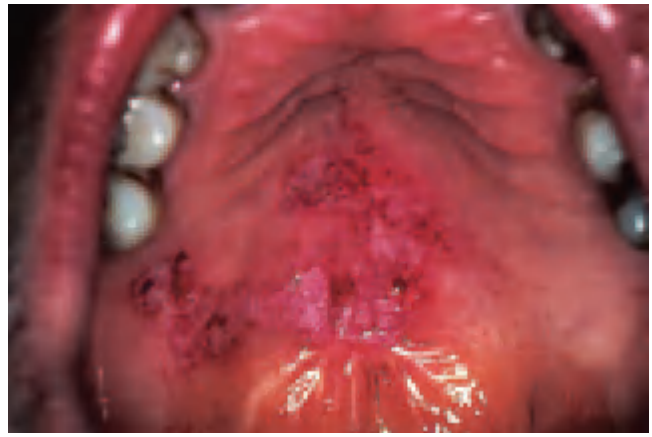

Fig. 66.38 Chronic oral lesions in discoid lupus erythematosus.

Other collagen–vascular diseases

Dermatomyositis and mixed connective tissue disease may be associated with non-specific mucosal erosions [4].

Oral involvement in Reiter's syndrome may include red patches or superficial painless mucosal erosions which may resemble erythema migrans (geographical tongue) both clinically and histologically.

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Infective diseases

Oral ulceration is common worldwide in some viral infections, typically in the herpesvirus or enterovirus infections seen in childhood. It can also be seen in several bacterial diseases, notably acute necrotizing gingivitis (but also in tuberculosis and syphilis), but is rare in fungal infections in the developed world, although the deep mycoses may be responsible for infection in the developing world, in travellers or in the immunocompromised.

Herpesviruses

Oral infection is common with the herpesviruses, which thereafter remain latent, are often excreted in saliva (especially in immunocompromised persons), and are sometimes implicated in clinical recurrences and malignant complications.

Herpes simplex stomatitis

Aetiology. HSV infection is a very common oral infection. In general, HSV-1 causes primary herpetic stomatitis (and the secondary infection of recurrent herpes labialis). There are no precise distinctions nowadays, presumably with more frequent orogenital and oroanal sexual practices, and oral infection with HSV-2 is also frequently seen [1,2].

With improving socio-economic circumstances and standards of hygiene, a larger number of children are not exposed to HSV and enter adult life without immunity. Cases of primary herpetic stomatitis are therefore now seen occasionally in adults, and the manifestations can be severe. HSV is usually transmitted in saliva and can be shed in asymptomatic individuals [3,4].

Clinical features. The incubation period is 3–7 days. Many infections with HSV occur in childhood and are subclinical and, where there is disease, it varies greatly in severity. In many it is trivial and misdiagnosed or passed off as 'teething' [5,6].

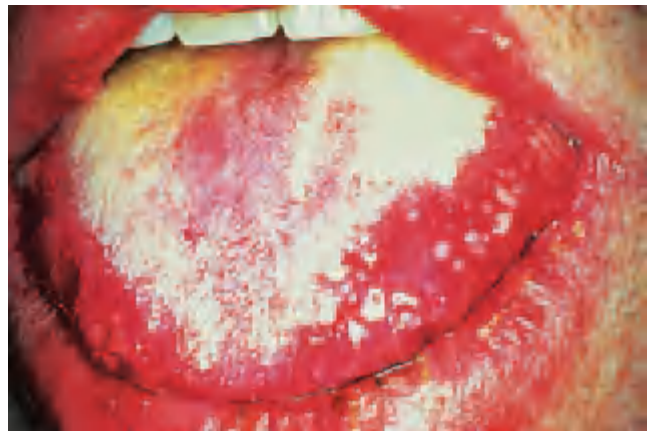

Fig. 66.39 Scattered ulcers and a furred tongue in primary herpetic stomatitis.

Primary herpetic stomatitis typically presents with malaise, anorexia, irritability, fever, enlarged and tender anterior cervical lymph nodes, and a diffuse, purple, boggy gingivitis (hence the alternative term *herpetic gingivostomatitis*), especially anteriorly, with multiple vesicles followed by round or ovoid ulcers 1–3 mm in diameter scattered across the oral mucosa and gingiva (Fig. 66.39) in an acute illness lasting only up to about 14 days [1,2]. In immunocompromised persons, diagnosis can be difficult since herpes may manifest with chronic ulcers [7–11].

Prognosis. Herpetic stomatitis resolves spontaneously in 7–14 days but HSV remains latent in the trigeminal ganglion. The most obvious sequel is that about one-third of patients are thereafter predisposed to recurrences. HSV is shed intermittently into the saliva [3,4]. HSV is implicated in many instances of EM (see p. 66.67) and may cause chronic ulcers in the immunocompromised (see below).

Diagnosis. The main differential diagnoses of herpetic stomatitis in otherwise healthy persons are chickenpox and other viral causes of mouth ulcers, and acute leukaemia. In immunocopromised persons, the differential is wider. A full blood picture, white-cell count and differential, and viral studies may therefore be required [1,2,12,13]. The latter include the following:

- Culture: this takes days to give a result.
- Electron microscopy: this is not always available.
- Polymerase chain reaction (PCR) detection of HSV DNA: this is sensitive but expensive.
- Immunodetection: detection of HSV antigens is of some value. Conventional enzyme-linked immunosorbent assays (ELISA) for serum antibodies have poor sensitivity and specificity; newer assays based on HSV glycoproteins

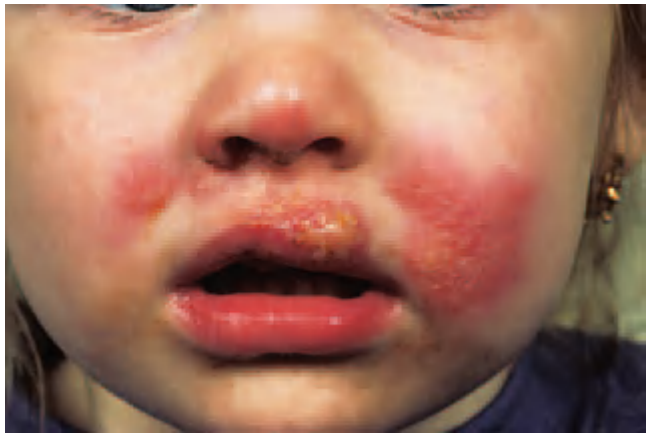

Fig. 66.40 Primary herpetic stomatitis with extraoral lesions.

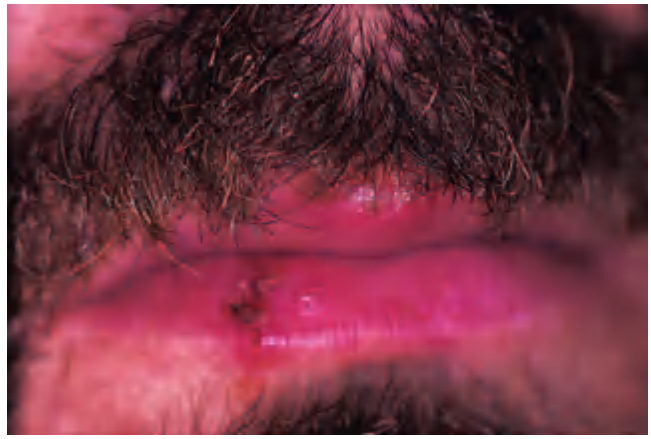

Fig. 66.41 Herpes labialis.

are comparable with Western blot assays. A rising titre of serum antibodies is confirmatory but only gives the diagnosis retrospectively.

- Smears for viral-damaged cells: now rarely used.

Treatment. Specific antiviral agents are most useful in the very early stages of disease (though most patients present later) and for immunocompromised patients who may otherwise suffer severe infection. Both oral and intravenous aciclovir appear to be effective, as are the newer antivirals [14,15].

For most, however, management is supportive with antipyretic analgesics (e.g. acetaminophen/paracetamol), sponging with tepid water and a high fluid intake. Analgesics (as elixirs or syrups for children) and, in adults, lidocaine mouthbaths help ease discomfort and 0.2% aqueous chlorhexidine mouthbaths aid resolution.

An antihistamine such as promethazine may help sedate an irritable child.

Recurrent labial HSV infection. Primary oral infection by HSV may produce perioral lesions (Fig. 66.40). However, recurrent herpes labialis involving the lip is the more common cause of blisters at the mucocutaneous junction (Fig. 66.41) [1,2]. The lesions arise at the mucocutaneous junction as itching papules which progress to vesicles, pustules and then scab. They are unsightly and occasionally become infected with *Staphylococcus* or *Streptococcus*, resulting in impetigo (Fig. 66.42). In immunocompromised persons, extensive and persistent lesions may result. In atopic persons, the lesions may spread to produce eczema herpeticum (Fig. 66.43). Aciclovir has been the standard treatment used as a 5% cream, although penciclovir 1% is more effective [16].

Recurrent intraoral HSV infection. Chronic oral herpetic ulcers, often with a raised white border and sometimes with a dendritic appearance, may occasionally affect

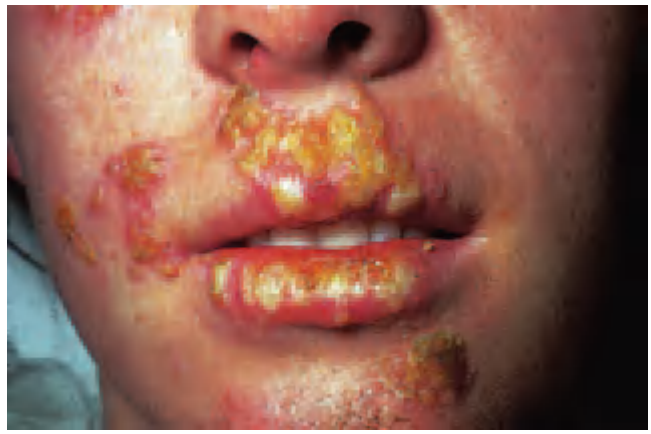

Fig. 66.42 Impetigo.

apparently healthy individuals, especially at sites of trauma, for example following palatal infiltration of a local anaesthetic. Chronic indolent lesions, usually ulcerative or nodular, may be seen in patients with neutropenia or chronic leukaemia; in patients with more severe immunosuppression, such as acute leukaemia or HIV infection, more aggressive chronic ulcers may be seen [7–11]. Aciclovir may be indicated systemically [8].

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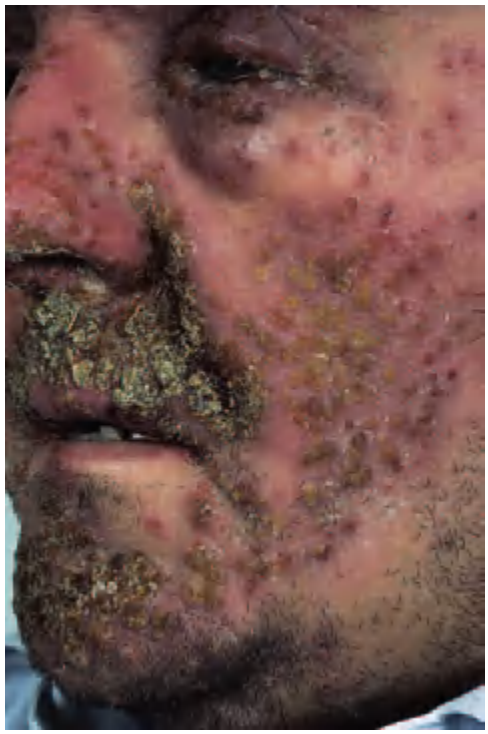

Fig. 66.43 Eczema herpeticum.

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Chickenpox

SYN. VARICELLA (see Chapter 25)

Chickenpox affects children predominantly and may present with mouth ulcers that resemble those of herpetic stomatitis, but there is no gingivitis [1]. There may be a contact history. Many primary infections with varicella-zoster virus are subclinical or produce so few lesions as to pass almost unnoticed. Varicella-zoster virus remains latent in sensory ganglia and may be reactivated to produce shingles.

Herpes zoster

SYN. SHINGLES

If shingles affects the maxillary or mandibular divisions of the trigeminal nerve, mouth ulcers are usually seen [2,3].

Clinical features. The pain of trigeminal zoster may simulate toothache. Severe pain often precedes, accompanies and follows the rash, and post-herpetic neuralgia may persist for months or years.

The rash is restricted to a dermatome and is unilateral, but sometimes a few chickenpox-type lesions can be found elsewhere. Oral ulcers appear in the distribution of the involved nerve division [3]. There is ulceration of one side of the tongue, floor of mouth and lower labial and buccal mucosa if the mandibular division of the trigeminal nerve is involved. One side of the palate, the upper gingiva and buccal sulcus are involved in maxillary zoster. Rarely, mandibular or maxillary zoster may disturb the formation of developing teeth [4] or cause jaw necrosis [5].

If the geniculate ganglion of the facial nerve is affected, there may be unilateral facial palsy, with vesicles in the ipsilateral ear and ulcers in the soft palate ipsilaterally (Ramsay–Hunt syndrome) [6].

Occasionally there is misdiagnosis of toothache, leading to extraction, the true diagnosis becoming apparent only when the rash appears. Zoster resolves spontaneously but post-herpetic neuralgia can be distressing.

Management. An underlying immune defect, such as AIDS or malignancy, should be excluded in patients with zoster, although most zoster is related simply to lesser problems in advanced age.

Treatment is mainly supportive but antivirals such as aciclovir can be useful. Analgesics are indicated in zoster, although the pain may prove refractory to even potent analgesics [7], when antidepressants such as amitriptyline and fluphenazine may have a place [8].

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Epstein–Barr virus infections (see Chapter 25)

Epstein–Barr virus (EBV) is responsible for infectious mononucleosis and is found in pharyngeal epithelium and appears in the saliva of patients and for several months after clinical recovery. Infection appears to be spread by close oral contact, especially kissing. It is typically a disease of the student population.

Infection is often subclinical. Infectious mononucleosis is also protean in its clinical manifestations, which include particularly lymphadenopathy, sore throat, fever, malaise and rashes. In the anginose type (sore-throat type), the throat is sore with soft-palate petechiae and a whitish exudate on oedematous tonsils. There may be non-specific oral ulceration or pericoronitis [1]. The glandular type of infectious mononucleosis is characterized by generalized lymph node enlargement and splenomegaly; the febrile type is characterized by fever.

Similar syndromes may be caused by cytomegalovirus (CMV), human herpesvirus (HHV)-6, toxoplasmosis and HIV. Characteristic of infectious mononucleosis are large numbers of atypical mononuclear cells in the blood and a wide variety of serological changes, particularly heterophil antibodies, which are detectable by the Paul–Bunnell or Monospot tests, usually during the first or second week of illness. Several other antibodies against EBV appear during the course of infectious mononucleosis, but the most frequent is the antibody to viral capsid antigen, the titre of which reaches a peak at about 4 weeks.

No specific treatment is available for infectious mononucleosis, but supportive care is important, not only because of the potential for airways obstruction but also because of the associated lassitude. Systemic corticosteroids are required if there is pharyngeal oedema severe enough to hazard the airway.

EBV is also commonly found in the mouths of immunocompromised patients [2–5], and is implicated in oral hairy leukoplakia (see p. 66.89), oral ulceration [6] and some oral lymphomas, although any relationship with other malignancies such as OSCC is controversial [7,8].

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Cytomegalovirus infection

CMV may cause a glandular fever type of syndrome, and rarely causes oral ulceration. Indolent CMV-induced oral ulcers may be seen in immunosuppressed patients and in AIDS [1–4].

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Herpesviruses 6, 7 and 8

Oral lesions have yet to be demonstrated in infections with HHV-6 or HHV-7. However, HHV-8 is implicated in oral Kaposi's sarcoma [1–4]. Treatment with highly active antiretroviral therapy (HAART) may reduce HHV-8 infection [5].

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Enteroviruses

Herpangina

Aetiology. Herpangina is caused by Coxsackieviruses mainly. The incubation period is 3–7 days and young children are predominantly affected.

Clinical features. Many infections are subclinical but features of the clinical syndrome include malaise, anorexia, irritability, low fever, slightly enlarged and tender anterior cervical lymph nodes and mouth ulcers, predominantly on the soft palate [1].

Diagnosis. There may be a contact history. It is possible to culture Coxsackieviruses in suckling mice if absolutely necessary.

The main differential diagnosis is primary herpetic stomatitis, but in herpangina there is less fever, no acute gingivitis and ulceration is mainly restricted to the soft palate.

Treatment. The condition is self-limiting and treatment is supportive only.

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Hand, foot and mouth disease (see Chapter 25)

Aetiology. Hand, foot and mouth disease is caused particularly by Coxsackie A viruses but sometimes by Coxsackie B viruses or enteroviruses.

Clinical features. The incubation period is 3–10 days and, although young children are predominantly infected, there are occasional outbreaks in adults. Many infections are subclinical but features of the clinical syndrome include the following.

- General features: malaise, anorexia, irritability and fever may be present but usually only in severe cases.
- Anterior cervical lymph nodes may occasionally be slightly enlarged and tender.
- Mouth ulcers are round or ovoid, usually sparse and may affect any site [1–3].
- Rash: painful, sometimes deep-seated vesicles may appear, usually on the hand and/or feet, particularly on digits or at the base of the phalanges.

Hand, foot and mouth disease is self-limiting and only rarely complicated by systemic illness such as encephalitis. The condition tends to be more severe when it occurs in adults.

Diagnosis and management are as for herpangina.

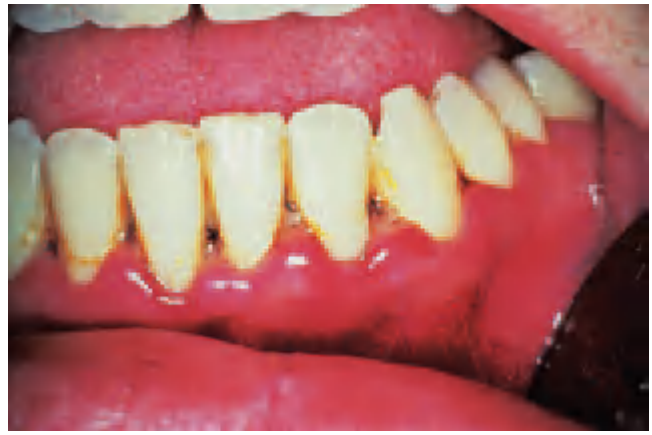

Fig. 66.44 Acute necrotizing gingivitis showing typical ulceration of interdental gingival papillae. This was in HIV infection.

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Bacterial infections

Acute necrotizing (ulcerative) gingivitis and noma

Aetiology. There is no firm evidence of communicability of acute necrotizing gingivitis, although it may occur in epidemic form, especially in institutions or in the military (trench mouth). Viral respiratory infections, overwork and fatigue, smoking or immune defects may precede the onset of disease, suggesting depression of immunity as a predisposing cause. A similar lesion may be a feature of HIV infection and related diseases.

A mixed, mostly anaerobic, flora (the fusospirochaetal complex), consisting mainly of *Fusobacterium nucleatum* (*F. fusiformis* or *Bacillus fusiformis*) and *Borrelia vincentii*, is associated with this infection [1,2].

Clinical features. The mouth ulceration is usually restricted to the gingiva, specifically the interdental papillae, which appear blunted (Figs 66.44 & 66.45). The history is characteristic, with an acute onset of gingival soreness, bleeding and halitosis. Acute necrotizing gingivitis occurs especially in the anterior part of the mouth where the affected gingiva are extremely tender to touch and readily bleed on minimal pressure. Occasionally the ulceration extends elsewhere on the gingiva, or onto the adjacent mucosa. There is often enlargement of the cervical lymph nodes and there may be pyrexia and malaise.

Prognosis. Failure to adequately treat acute necrotizing gingivitis may predispose to recurrence and, in malnour-

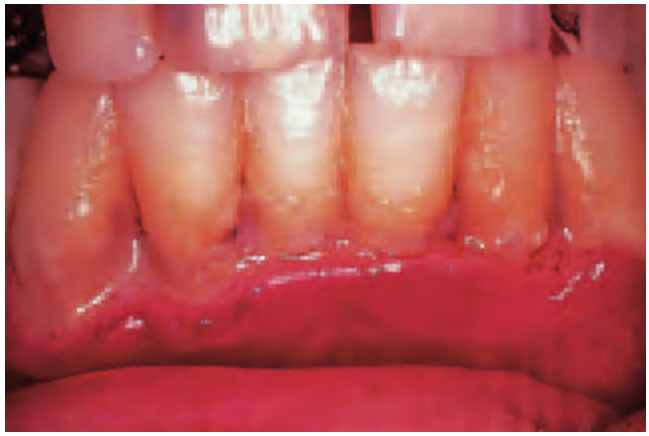

Fig. 66.45 Untreated acute necrotizing gingivitis can lead to extensive gingival ulceration and irreparable damage.

ished or immunocompromised individuals, may lead to noma (cancrum oris) [3–7]. Similar lesions of gangrenous stomatitis are increasingly reported in HIV disease.

Diagnosis. Diagnosis is mainly from gingival lesions in primary herpetic stomatitis, leukaemias and HIV disease. A bacteriological smear may be helpful.

Treatment. Gentle cleansing with a hydrogen peroxide mouthwash and a soft toothbrush is remarkably effective. Oral metronidazole 200 mg should be given three times daily for 3–7 days to limit the tissue destruction. Penicillin is equally effective. The patient should also be referred for dental advice [1].

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Syphilis

Oral ulcers may be seen at any stage but particularly in secondary syphilis [1–3]. In primary syphilis, a primary chancre (hard or Hunterian chancre) may involve the lips, tongue or palate. A small, firm, pink macule changes to a papule which ulcerates to form a painless round ulcer with a raised margin and indurated base [4]. Chancres heal spontaneously in 3–8 weeks but are highly infectious

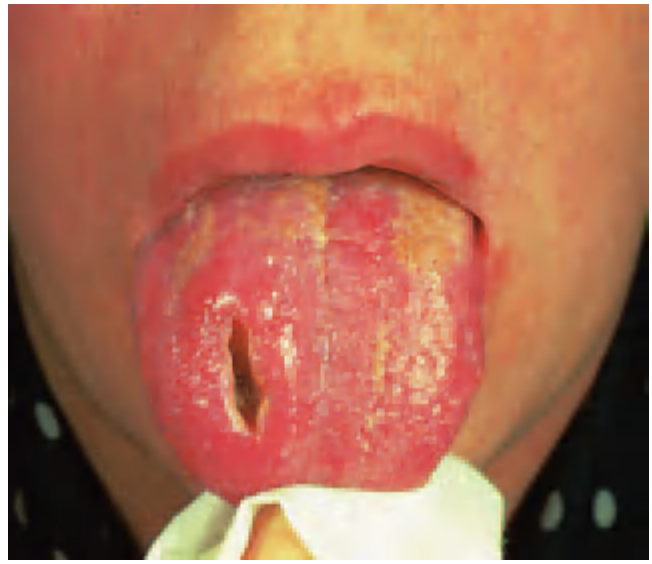

Fig. 66.46 Gumma.

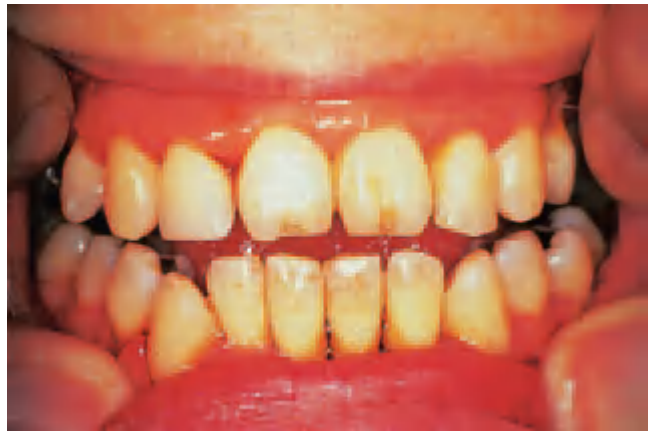

Fig. 66.47 Hutchinson's maxillary central incisors.

and are associated with enlarged, painless regional lymph nodes.

Secondary syphilis follows after 6–8 weeks, with oral lesions in about one-third of patients [1,3]. These are highly infectious and are usually fairly painless ulcers (mucous patches and snail-track ulcers).

The most characteristic oral lesion of tertiary syphilis is a localized granuloma (gumma) that varies in size from a pinhead to several centimetres, affecting particularly the palate, or the tongue. Gummas break down to form deep chronic punched-out ulcers that are not infectious (Fig. 66.46). However, the most common oral manifestation of tertiary syphilis is leukoplakia, which particularly affects the dorsum of the tongue and has a high potential for malignant change.

Congenital syphilis may, when the permanent teeth erupt, present with dental anomalies such as Hutchinson's teeth (Fig. 66.47). Oral ulcers are rare.

Exudate from a suspected oral lesion of syphilis should be examined for treponemes by dark-ground microscopy; however, since the diagnosis can be confused by oral commensal treponemes, lesions should first be thoroughly swabbed with a sterile gauze or cotton-wool and then gently scraped with a sterile spatula, the scraping being examined immediately by dark-ground microscopy. Serology is indicated. Biopsy is not usually indicated, but lesions are characterized by a dense plasma cell infiltrate.

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Gonorrhoea

Oral mucosal erythema, sometimes with oedema and ulceration, is occasionally seen in oropharyngeal gonorrhoea. Oropharyngeal asymptomatic carriage of gonococci is more common, found in around 4% of those attending clinics for sexually transmitted diseases [1,2].

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Tuberculosis

Oral lesions can develop in pulmonary tuberculosis but are not common. A chronic ulcer, usually of the dorsum of the tongue, is the most common oral presentation but jaw lesions or cervical lymph node involvement may be seen [1–4]. Atypical mycobacteria are not uncommonly involved.

Mycobacterial oral ulcers, particularly caused by *Mycobacterium avium–intracellulare*, have been reported as a complication of AIDS and occasionally in apparently healthy individuals [5]. Cervicofacial infection is occasionally caused by *M. chelonei*, usually in the form of lymph node abscesses, or occasionally as intraoral swellings [6–9].

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Epithelioid (bacillary) angiomatosis (see Chapter 27)

Oral lesions clinically and, to some extent, histologically reminiscent of Kaposi's sarcoma have been seen in HIV disease [1–3], sometimes as the first manifestation of HIV infection [3].

REFERENCES

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Fungal infections

Oral fungal infections, apart from candidiasis, which rarely causes mouth ulcers in Western societies, are usually seen in the West only in immunocompromised or debilitated patients, including those with AIDS. However, they may be seen occasionally in otherwise healthy persons from the tropics (Table 66.20).

Aspergillosis. Rhinocerebral aspergillosis may ulcerate through to the mouth. This is a rare event, except in the severely immunocompromised [1]. Occasionally, solitary aspergillosis arises as a consequence of endodontic treatment where root canal filling material enters the antrum [2] but this does not cause oral ulceration. Surgical débridement is usually indicated.

REFERENCES

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Table 66.20 Rare orofacial fungal infections.

Infection	Oral manifestations
Aspergillosis	Aspergilloma Rhinocerebral type causes palatal necrosis Disseminated in immunocompromised patients
Blastomycosis	
North American	Oral ulcers or suppurating granulomas
South American (paracoccidioidomycosis)	Oral ulcers and lymphadenopathy
Coccidioidomycosis	Rarely oral ulcers
Cryptococcosis	Oral ulcers
Histoplasmosis	Lumps or ulcers in mouth
Phycomycosis (mucormycosis, zygomycosis)	Antral involvement with palatal ulceration in immunocompromised patients, especially diabetics
Sporotrichosis	Oral lesions rare

Blastomycoses. Blastomycoses may produce oral lesions which are typically mulberry-like, ulcerated swellings especially seen on the gingiva and alveolus [1,2].

REFERENCES

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2 Sposto MR, Scully C, Almeida OPD *et al.* Oral paracoccidioidomycosis: a study of 36 South American patients. *Oral Surg* 1993; **75**: 461–5.

Cryptococcosis. *Cryptococcus neoformans* may occasionally produce indolent oral ulcers in immunocomprised patients [1,2].

REFERENCES

1 Glick M, Cohen SG, Cheney RT *et al.* Oral manifestations of disseminated *Cryptococcus neoformans* in a patient with acquired immunodeficiency syndrome. *Oral Surg* 1987; **64**: 454–9.
2 Lynch DP, Naftolin LZ. Oral *Cryptococcus neoformans* infection in AIDS. *Oral Surg* 1987; **64**: 449–53.

Geotrichosis. Geotrichosis is a rare, livid, sharply defined enanthema of the oral mucosa with ulcerations seen in immunocompromised persons, such as those with leukaemia or HIV infection. *Geotrichum capitatum* is responsible and there may also be pneumonic lung infiltrates [1].

Treatment includes amphotericin, 5-fluorocytosine and itraconazole.

REFERENCE

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Histoplasmosis. Oral lesions of histoplasmosis are uncommon. They are typically seen in chronic disseminated histoplasmosis, usually as a non-specific lump or ulcer on the tongue, palate, buccal mucosa or gingiva [1–5], sometimes in AIDS [6–8].

REFERENCES

1 Adekeye EO, Edwards MB, Williams HK. Mandibular African histoplasmosis: imitation of neoplasia or giant cell granuloma. *Oral Surg* 1988; **65**: 81–4.
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8 Casariego Z, Rey Kelly G, Perez H *et al.* Disseminated histoplasmosis with orofacial involvement in HIV-1-infected patients with AIDS: manifestations and treatment. *Oral Dis* 1997; **3**: 184–7.

Mucormycosis. Rhinocerebral mucormycosis typically commences in the nasal cavity or paranasal sinuses and invades the palate to produce a black necrotic ulcer, although it might occasionally commence in the palate [1–3]. Most cases are seen in diabetics or in immunocompromised patients such as those with AIDS [4]. Biopsy and radiography are required for diagnosis. Treatment is surgical débridement together with amphotericin intravenously and/or azoles.

REFERENCES

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4 Moraru RA, Grossman ME. Palatal necrosis in an AIDS patient: a case of mucormycosis. *Cutis* 2000; **66**: 15–8.

Protozoal infestations

Leishmaniasis is rare in northern Europe and the USA; it is not uncommon, however, in hotter climes and may cause ulcers in the mouth or more commonly on the lips [1–4], and is seen increasingly in HIV disease [5–9] or in other immunocompromised persons.

REFERENCES

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Immune defects

Human immunodeficiency virus infection [1–5]
(see Chapter 26)

Oral ulceration in patients infected with HIV may be due to any of the causes of mouth ulceration (see p. 66.42), and aphthous-like ulcers are also seen. However, it is important to exclude infections, mainly herpesviruses. There are also occasional examples of mouth ulcers due to mycobacteria, *Rochalimaea*, syphilis, *Histoplasma*, *Cryptococcus*, leishmaniasis and others. Malignant disease (mainly Kaposi's sarcoma or non-Hodgkin's lymphoma) may result in lumps that can ulcerate.

Aphthous-like ulcers in HIV may respond to local treatment or, failing that, 100 mg thalidomide at night for 2 weeks and then 100 mg every fifth day may prove effective [5].

Other mouth ulcers should be treated as appropriate.

REFERENCES

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Vasculitides

Periarteritis nodosa

Transient submucosal oral nodules may occur singly or in crops along the path of vessels and especially in the tongue. Other mucosal lesions include erythema, papules, haemorrhages, ulceration or necrosis [1–4].

REFERENCES

1 Cowpe JG, Hislop WS. Oral presentation of polyarteritis nodosa. *Oral Surg* 1983; **56**: 597–601.
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Giant cell arteritis
SYN. HORTON'S DISEASE

Patients may suffer ischaemic pain during mastication, intermittent claudication of the tongue [1] or, rarely, facial palsy [2] or lumps [3,4]. Ulceration and necrosis of the tongue [5–11] or occasionally the lip [12] have also been observed [2,3].

REFERENCES

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Iatrogenic conditions

Mucositis

Mucositis, sometimes called *mucosal barrier injury*, is the term given to the widespread oral erythema, ulceration and soreness that is a common complication of a number of therapeutic procedures involving chemotherapy, radiotherapy or chemoradiotherapy, used largely in the treatment of cancer but also in the conditioning prior to bone marrow transplantation (i.e. haematopoietic stem cell transplantation). Mucositis appears 3–15 days after cancer treatment, earlier after chemotherapy than after radiotherapy.

Mucositis invariably follows external beam radiotherapy involving the orofacial tissues, and is also common in upper mantle head and neck radiation, and particularly in total body irradiation.

Some 40–90% of patients on chemotherapy develop mucositis. Patients on fluorouracil and cisplatin in particular develop mucositis, while etoposide and melphalan cause particularly severe mucositis. Oral mucositis is particularly severe after haemopoietic stem cell transplantation, because of radiation damage and myeloablation, and the course follows the polymorphonuclear leukocyte count.

The impaired mucosal barrier in mucositis predisposes to life-threatening septic complications; the prevalence of an oral focus in febrile neutropenia has been reported in up to 30% of cases [1–4].

Mucositis typically presents with pain (which can be so intense as to interfere with eating and significantly affect the quality of life), erythema, ulceration and sometimes bleeding.

Diagnosis is clinical and it is helpful to score the degree of mucositis in order to monitor progression and therapy.

Management. The basic strategies in management of mucositis aim at pain relief, efforts to hasten healing and prevention of infectious complications. However, prophylaxis is the goal.

Pain relief is usually achieved with opioids given by patient-controlled analgesia and benzydamine can aid relief. Oral cooling with ice chips ameliorates chemotherapy-induced mucositis [5,6].

Other treatments currently used but for which hard data for reliable efficacy are unavailable include the following.

- Medications to reduce salivation and thus exposure of the mucosa to chemotherapeutic drugs that are secreted in saliva.
- Anti-inflammatory medications.
- Cytokines such as interleukin (IL)-1, IL-11, TGF-beta3 and keratinocyte growth factor.
- Granulocyte–macrophage colony-stimulating factor (GM-CSF) and granulocyte colony-stimulating factor (G-CSF).
- Thalidomide: an angiogenesis-inhibiting drug.
- Amifostine: a cytoprotector.
- Melatonin: the pineal hormone.
- Protegrin antimicrobial peptides, which possess activity against Gram-positive and Gram-negative bacteria and yeasts.
- Low-energy lasers.
- Other agents such as sucralfate, tretinoin, glutamine and misoprostol [1–4,6].

Monitoring microbial colonization and the institution of antiviral prophylaxis and antifungal prophylaxis, to avoid colonization and superinfection, is particularly important in patients with low neutrophil counts.

Invasive fungal infections of the oral cavity can be associated with systemic fungal infection and are indications for the use of liposomal amphotericin.

REFERENCES

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Bone marrow transplantation (haematopoietic stem cell transplantation)

Oral complications are common and can be a major cause of morbidity following bone marrow transplantation. Mucositis, infections, bleeding, xerostomia and loss of taste result from the effects of the underlying disease, chemotherapy or radiotherapy, and GVHD. The ventrum of the tongue, buccal and labial mucosa and gingiva may be affected by ulceration or mucositis [1–6].

REFERENCES

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5 Seto BG. Oral mucositis in patients undergoing bone-marrow transplantation. *Oral Surg* 1985; **60**: 493–7.
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Graft-versus-host disease

The oral manifestations of acute GVHD consist of painful mucosal desquamation and ulceration, and/or cheilitis, and the presence of lichenoid plaques or striae. Small white lesions affect the buccal and lingual mucosa early on, but clear by day 14. Erythema and ulceration are most pronounced at 7–11 days, and may be associated with obvious infection. Candidiasis is common, as is herpes simplex stomatitis (occasionally zoster) and there may be oral purpura, especially in adults [1,2].

The oral lesions in chronic GVHD are coincident with skin lesions, and include generalized mucosal erythema, lichenoid lesions, mainly in the buccal mucosa, and xerostomia. There may be depressed salivary IgA levels in minor gland saliva [3]. Xerostomia is most significant in the first 14 days after transplant and is a consequence of drug treatment, irradiation and/or GVHD.

Lip biopsy is useful in the diagnosis of chronic GVHD and should include both mucosa and underlying minor salivary glands [4]. Histology shows changes similar to those seen in Sjögren's syndrome.

REFERENCES

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Drugs

A wide range of drugs can occasionally induce mouth ulcers, by a variety of effects [1]. Oral use of caustics or agents such as cocaine can cause erosions or ulcers [2]. Oral ulcers are regularly produced by cytotoxic agents [3] (see Mucositis above). Aphthous-like ulcers may follow the use of the potassium channel blocking cardioactive agent nicorandil [4].

Drugs may also cause mucocutaneous lesions. Oral ulcers of a lichenoid type may follow exposure to non-steroidal anti-inflammatory drugs and other agents (see p. 66.61). Erythema multiforme may follow the use of a range of drugs (see p. 66.67). Drug-induced mouth ulcers may also resemble toxic epidermal necrolysis (see p. 66.68) or may have features reminiscent of other dermatological disorders.

The ulcers usually resolve in 10–14 days if the offending drug can be identified and withdrawn.

REFERENCES

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Acrodynia

SYN. PINK DISEASE

Oral and perioral ulceration, hypersalivation, gingivitis and early tooth loss are features of acrodynia caused by mercury poisoning, now rarely seen [1].

REFERENCE

1 Dinehart SM, Dillard R, Rainer SS *et al*. Cutaneous manifestations of acrodynia (Pink disease). *Arch Dermatol* 1988; **124**: 107–9.

Disorders of uncertain pathogenesis

Angina bullosa haemorrhagica

SYN. LOCALIZED ORAL PURPURA

This is the term given to a benign, fairly common condition of unknown aetiology that usually presents in the elderly with oral blood blisters. These subepithelial blisters are seen mainly in the soft palate and after a few hours rupture to leave ulcers (Fig. 66.48). The patients appear well otherwise, with no detectable immunological or bleeding disorder [1–3]. Occasional cases are related to the use of corticosteroid inhalers. Only symptomatic care is available.

REFERENCES

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2 Stephenson P, Lamey P-J, Scully C *et al*. Angina bullosa haemorrhagica: clinical and laboratory features in 30 patients. *Oral Surg* 1987; **63**: 560–5.
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Monoclonal plasmacytic ulcerative stomatitis

Ulcerative stomatitis may occasionally appear with a lichenoid rash, related to a plasmacytic infiltrate [1,2].

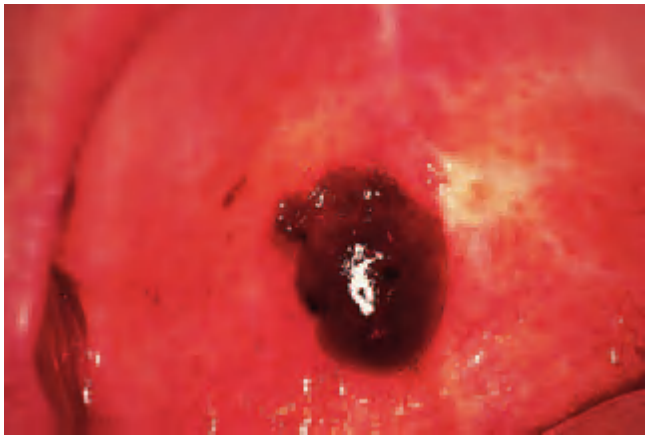

Fig. 66.48 Angina bullosa haemorrhagica: a large blood blister in a typical site on the soft palate. The adjacent whitish lesions are from scarring after a previous biopsy.

REFERENCES

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Mucocutaneous lymph node syndrome

SYN. KAWASAKI DISEASE (see Chapter 27)

Mucocutaneous lymph node syndrome is a disorder of uncertain, but possibly infectious, aetiology. Male children are predominantly affected.

At least one oral feature should be present for the diagnosis to be made. The oral and pharyngeal mucosa become generally red and sore and the lips dry and fissured. There may be oral ulceration and a 'strawberry tongue' appearance [1,2].

Cervical lymphadenopathy, conjunctivitis and fever also occur, followed later by the characteristic desquamation of the skin of the hands and feet.

Early therapy with immunoglobulin is essential to avoid cardiac complications.

REFERENCES

1 Ogden GR, Kerr M. Mucocutaneous lymph node syndrome (Kawasaki disease). *Oral Surg* 1989; **67**: 569–72.
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Superficial mucoceles

Superficial extravasation mucoceles of the intraoral minor salivary glands in the palate, buccal mucosa or labial mucosa are not uncommon, especially associated with oral LP in middle-aged or elderly women. This is a benign self-limiting condition that may cause confusion with vesiculobullous disorders [1].

REFERENCE

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Necrotizing sialometaplasia

Necrotizing sialometaplasia is an uncommon, benign, self-limiting condition seen predominantly in the posterior hard palate of young adult males, most of whom smoke tobacco [1]. A painless deep ulcer persists for several weeks before spontaneously healing. Biopsy reveals necrosis and pseudoepitheliomatous changes probably resulting from squamous metaplasia following infarction of minor salivary glands. This benign lesion must be differentiated from malignancy.

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Mucha–Haberman disease

Erythematous and ulcerative oral lesions have been reported in pityriasis lichenoides et varioliformis acuta (Mucha–Haberman disease) [1,2].

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Metabolic disorders

Glucagonoma

Oral ulceration can be a severe manifestation in glucagonoma [1].

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Oral soreness

Most oral pain is of local aetiology, usually resulting from odontogenic infections. Neurological, vascular and referred causes are less common, but must also be excluded. Psychogenic pain is all too frequent and this is discussed below.

Chronic oral soreness may be particularly caused by ulceration, or by mucosal lesions in geographical tongue,

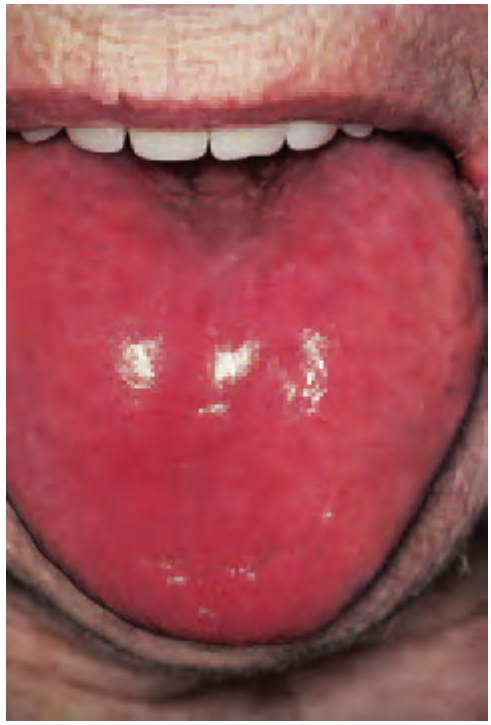

Fig. 66.49 Atrophic glossitis in vitamin B_{12} deficiency.

LP or deficiency states. Geographical tongue and burning mouth syndrome are the common causes of a sore tongue. LP is the most common cause of chronic soreness in the buccal mucosae. Desquamative gingivitis is the common cause of persistently sore gingivae.

Geographical tongue (see p. 66.94)

Lichen planus (see p. 66.61)

Deficiency glossitis

Aetiology. Deficiency glossitis may be related particularly to deficiency of iron, folate or vitamin B_{12}, and may then be associated with angular stomatitis and/or mouth ulcers. Deficiencies of other B-group vitamins occasionally cause glossitis, usually in chronic alcoholics or in those with malabsorption [1–3].

Pathology. Epithelial atrophy, rarely with some dysplasia, is seen.

Clinical features. In anaemic glossitis the tongue is red, sore and smooth (Fig. 66.49). Occasionally pernicious anaemia can also produce red areas or patterns of red lines.

In many other patients the tongue can become sore but appear clinically completely normal and such patients' complaints are liable to be mislabelled as psychogenic.

Diagnosis. A full blood picture and assays of iron, folate and vitamin B_{12} are essential in management, as sore tongue can be the initial symptom of a deficiency and can precede any fall in the haemoglobin level.

Treatment. The cause of the deficiency should be sought before replacement treatment is given.

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Burning mouth syndrome

SYN. ORAL DYSAESTHESIA; GLOSSOPYROSIS; GLOSSODYNIA

Burning mouth syndrome (BMS) most frequently affects middle-aged and elderly females [1–4].

Aetiology. Several organic lesions, for example haematinic deficiency states, erythema migrans, ulcers, mucositis, LP and candidiasis, can cause oral soreness or burning sensation.

BMS with a tongue of normal clinical appearance may be seen in deficiency states, and with psychogenic causes, drugs (e.g. angiotensin-converting enzyme inhibitors such as captopril, enalapril, lisinopril; protease inhibitors; cytotoxic agents; clonazepam) and diabetes mellitus. A monosymptomatic hypochondriasis or an underlying anxiety about cancer or venereal disease with perhaps excessive tongue activity appear to be the basis for the complaint of BMS in many patients (Table 66.21) [1–8].

Uncommon causes that may need to be considered include hypothyroidism, lupus erythematosus, hypersensitivity (to sodium metabisulphite, nuts, dental materials and other substances) and galvanic reactions to metals in the mouth [9–12]. However, BMS is often a medically unexplained symptom.

Clinical features. Although the tongue is most frequently involved, the patient may also occasionally complain of burning lips, gums or palate. The burning sensation is usually bilateral and often relieved by eating and drinking [1]. In contrast, oral discomfort associated with inflammatory lesions is typically aggravated by eating.

Diagnosis. Oral examination very occasionally reveals an organic cause. Xerostomia should be excluded as this may predispose to candidiasis. Laboratory screening for anaemia, diabetes, a deficiency state or candidiasis should be undertaken.

Table 66.21 Causes of burning mouth.

Local
Candidiasis
Other infections
Geographical tongue
Lichen planus
Oral submucous fibrosis
Dentures
Systemic
Psychogenic
Cancerophobia
Depression
Anxiety states
Hypochondriasis
Deficiency states
Pernicious anaemia and other vitamin B deficiencies
Folate deficiency
Iron deficiency
Diabetes
Drugs (captopril)

Management. Few patients with BMS have spontaneous remission in the short term, and thus an attempt at treatment is indicated. Reassurance, treatment of any defined underlying organic abnormality and, occasionally, psychological treatment, antidepressants or psychiatric care are indicated, but active dental or oral surgical treatment, or attempts at 'hormone replacement', in the absence of any specific indication, should be avoided. However, treatment is rarely completely successful, although the condition only infrequently becomes severe. Fortunately, about 50% remit spontaneously over 6 or 7 years.

- Patients should avoid anything that aggravates symptoms, such as sparkling wines, citrus drinks and spices.
- Reassurance and attention to any factors such as dentures or haematinic deficiencies may be indicated. There are few treatments of proven benefit [13]. Cognitive–behavioural therapy or a specialist referral may be indicated [14].
- Some patients respond to medication:
  (a) effects of vitamin B are controversial [15,16];
  (b) topical benzydamine 0.01% rinse or spray [17];
  (c) although antidepressants must be given for at least 2–3 weeks to achieve any antidepressive effect, most patients with medically unexplained symptoms show benefit within 1 week [18–20];
  (d) topical capsaicin cream 0.025% (Zacin) or 0.075% (Axsain);
  (e) clonazepam tablet sucked locally;
  (f) α-lipoic acid systemically [21].

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White lesions

Acquired white lesions in the mouth are usually innocuous keratoses or caused by cheek biting or chemical burns, but infections, dermatoses (usually LP), neoplastic disorders and other conditions must be excluded (see Table 66.9). Congenital lesions are discussed on p. 66.24.

Cheek biting

SYN. MORSICATIO BUCCARUM

Cheek biting causes a whitish shredded appearance usually of the buccal or lower labial mucosa at the occlusal line (adjacent to where the teeth meet) (Fig. 66.50) [1–3]. The habit is most common in tense or anxious individuals who may also show bruxism, mandibular pain dysfunction or other oral features of psychogenic disorders. The

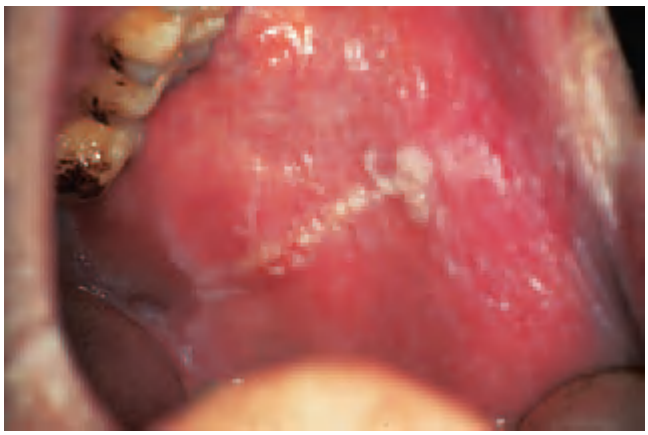

Fig. 66.50 Frictional keratosis and cheek biting (morsicatio buccarum) at the occlusal line.

lesion is benign but may simulate white-sponge naevus (see p. 66.24).

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Burns

Chemical burns (due, for example, to holding mouthwashes in the mouth or drugs against the buccal mucosa) or burns caused by heat, cold or irradiation can cause white sloughing lesions of the mucosa [1–8]. Such lesions typically heal spontaneously within 1–3 weeks.

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Lichen planus

See Chapter 42.

Candidiasis

Up to 50% of the healthy population harbour *Candida albicans* as an oral commensal. Carriage is more common in cigarette smokers. *Candida* resides particularly on the posterior dorsum of the tongue [1–5].

Infection is likely to result from xerostomia, local disturbances in salivary flora such as occurs during broad-spectrum antimicrobial treatment, or depressed immune responses [1–4]. Of the several clinical presentations of oral candidiasis, only thrush, candidal leukoplakia and chronic mucocutaneous candidiasis present as white lesions; the other types, acute and chronic atrophic candidiasis, are red (Table 66.22).

Table 66.22 Intraoral candidiasis.

Type of candidiasis	Usual age at onset	Predisposing factors*
Acute pseudomembranous candidiasis (thrush)†	Any	Local: dry mouth, antimicrobials General: corticosteroids, leukaemia, HIV
Acute atrophic candidiasis ('antibiotic mouth'; antibiotic sore mouth)	Any	Broad-spectrum antibiotics or corticosteroids
Erythematous candidiasis	Any	HIV especially
Chronic atrophic candidiasis (denture-induced stomatitis)	Adults	Denture wearing, especially at night
Chronic hyperplastic candidiasis (candidal leukoplakia)†	Usually middle-aged or elderly	Tobacco smoking, denture wearing, immune defect
Median rhomboid glossitis	Third or later decades	Tobacco smoking, denture wearing, HIV
Chronic mucocutaneous candidiasis†	Usually first decade	Often immune defect; rarely endocrinopathy

HIV, human immunodeficiency virus.
* Immune defects can predispose to any form.
† White lesions.

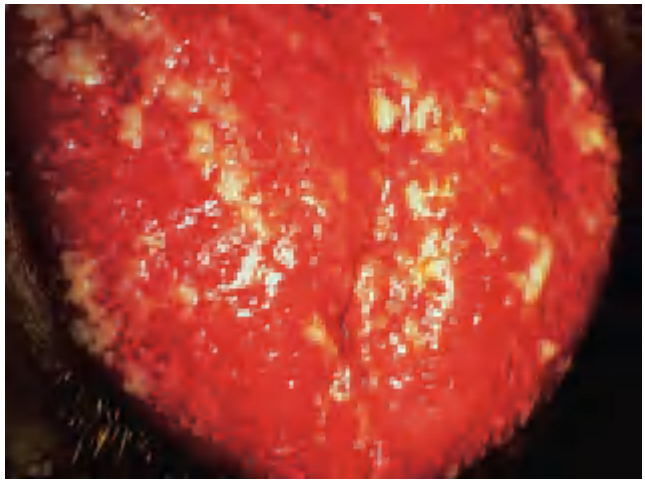

Fig. 66.51 Thrush: scattered white lesions on an erythematous background.

Thrush

SYN. ACUTE PSEUDOMEMBRANOUS CANDIDIASIS

Healthy neonates, who have yet to develop immunity to *Candida* species, may develop thrush. In other patients, predisposing factors include antibiotic or corticosteroid use, xerostomia and severe T-cell immune defects associated with immunosuppression (e.g. given to prevent graft rejection in organ transplantation) or immunodeficiencies such as leukaemia or HIV disease. Oral candidiasis is a common and early feature of HIV infection and may be a portent of developing AIDS [1–4].

The soft creamy patches of thrush, which resemble milk curds, can be wiped off the oral mucosa with gauze, leaving an area of erythema (Fig. 66.51).

Chronic candidiasis

Long-standing oral candidiasis may produce tough, adherent white patches (chronic hyperplastic candidiasis or candidal leukoplakias) which can have a premalignant potential, and may be indistinguishable from other leukoplakias except by biopsy. Candidal leukoplakias may, however, be speckled. In only a few patients with this type of chronic oral candidiasis can either a local cause or underlying immune defect be identified [1–3]. Chronic mucocutaneous candidiasis syndromes are rare (see Chapter 31).

Diagnosis. The diagnosis of oral thrush is usually clinical but it tends to be overdiagnosed by physicians. In contrast, erythematous candidiasis is probably underdiagnosed. In immunosuppressed patients, a Gram-stained smear should be taken to distinguish thrush from the plaques produced by opportunistic bacteria. Hyphae seem to indicate that the *Candida* organisms are acting as pathogens and not simple commensals.

Suspected candidal leukoplakia should be biopsied, both to distinguish it from other non-candidal plaques and also because of possible dysplasia. Although candidal hyphae and a neutrophil infiltrate may be seen on haematoxylin and eosin staining, PAS will demonstrate the purple staining of the hyphae.

Treatment

Acute candidiasis. Except in healthy neonates, possible predisposing causes should be looked for and treated. Topical polyenes such as nystatin or amphotericin, or imidazoles such as miconazole are often indicated but, in HIV infection, fluconazole may be required.

Chronic hyperplastic candidiasis. The oral lesions of chronic hyperplastic candidiasis may respond poorly to the polyenes. These cases, and some cases of chronic mucocutaneous candidiasis, may respond only to flucytosine, ketoconazole, fluconazole or itraconazole [1,6–8].

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Leukoplakia

The World Health Organization defines leukoplakia as a white patch or plaque on the mucosa that cannot be rubbed off and that is not recognized as a specific disease entity [1], which implies a diagnosis of exclusion (e.g. of LP, candidiasis). The term is also used irrespective of the presence or absence of epithelial dysplasia, although there is a small premalignant potential to some keratoses [1–3].

Leukoplakia is common in adults: around 1% are affected, although some populations show higher prevalences. Most cases are seen in the 50–70 age group [4–9].

Leukoplakia can be totally benign or sometimes can be precancerous or a marker for cancer elsewhere in the upper aerodigestive tract.

Oral keratoses

Aetiology. The cause of most keratoses is unknown (idiopathic keratoses or leukoplakia) but some are caused by chronic irritation, particular lifestyle habits or infective agents [10–17].

Tobacco-induced keratoses. Consumption of tobacco products has long been causally connected with oral cancer and is a common cause of keratosis. Tobacco use also predisposes to cancers elsewhere in the upper aerodigestive tract, bladder and other sites. Tobacco use should thus be discouraged; the drug amfebutamone (Zyban) may help users break the habit.

Tobacco chewing. Tobacco is chewed in many parts of the world and may induce keratosis. In many communities from the developing world, tobacco is a component of betel quid, along with areca nut and betel leaf, and sometimes slaked lime and spices. Sometimes betel is used without tobacco (pan or paan), though others use paan with tobacco. Oral carcinoma can result.

Reverse smoking (bidi). In some communities, especially in Asia, cigarettes are smoked with the lit end within the mouth. Palatal or other oral carcinoma can result.

Cigarette-induced keratoses. Mild keratosis may be seen especially on the palate, lip (occasionally nicotine-stained) and at the commissures, along with nicotine-stained teeth. Malignant change is uncommon.

Pipe smoking. Diffuse whiteness over the palate is termed 'smoker's keratosis' or 'stomatitis nicotina'. The palatal minor salivary gland orifices appear red against this white background. Malignant change is uncommon.

Cigar smoking. Cigar smokers may develop stomatitis nicotina and nicotine-stained teeth. Malignant change is uncommon.

Snuff dipper's keratosis and other smokeless tobacco lesions. Snuff may produce keratosis—white hyperkeratotic lesions caused by snuff-dipping (holding flavoured tobacco powder in the oral sulcus or vestibule), together with gingival recession at the site of use, often the buccal sulcus. Malignant change is rare.

Other aetiological factors

- Proliferative verrucous leukoplakia is often associated with HPV. Malignant change is uncommon.
- Candidal leukoplakias may be associated with an increased risk of malignant change, although it is uncommon.

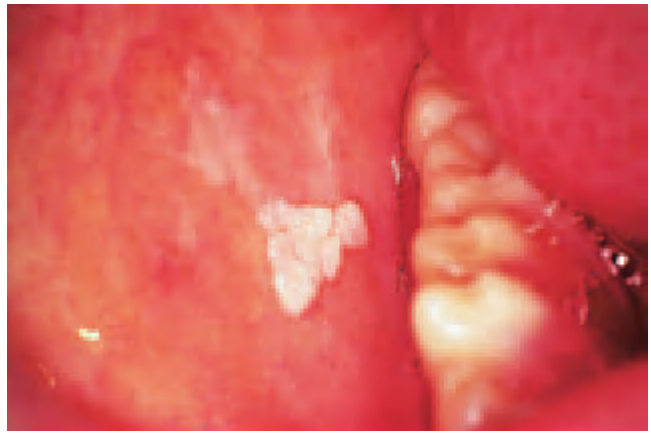

Fig. 66.52 Homogeneous leukoplakia in the buccal mucosa.

- Syphilitic leukoplakia is rarely seen now. Malignant change is uncommon.
- Hairy leukoplakia is caused by EBV and seen especially in HIV disease. Malignant change is not recorded.

Clinical features. Leukoplakias vary in size: some are small and focal, others more widespread, occasionally involving very large areas of the oral mucosa; in other patients several discrete separate areas of leukoplakia can be seen. Leukoplakia has a wide range of clinical presentations, from homogeneous white plaques that can be faintly white or very thick and opaque, to nodular white lesions or lesions admixed with red lesions [1–4]. The malignant potential depends on the following.

Appearance. Homogeneous leukoplakia, the most common, presents with uniformly white plaques, common in the buccal (cheek) mucosa and usually of low premalignant potential (Fig. 66.52).

Non-homogeneous or heterogeneous leukoplakias are nodular, verrucous and speckled leukoplakias that consist of white patches or nodules in a red, often eroded, area of mucosa (Fig. 66.53). They have a high risk of malignant transformation and are therefore far more serious.

Site. High-risk sites for malignant transformation include the soft palate complex and ventrolateral tongue and floor of the mouth (where sublingual keratosis has a particularly high risk of malignant change; Fig. 66.54). Sublingual keratosis is more common in women than men, has a typical 'ebbing-tide' appearance clinically and has a high malignant potential.

Aetiological factors

- Proliferative verrucous leukoplakia is a diffuse white and/or papillary lesion seen in elderly patients, often associated with HPV, and shows an inexorable slow progression over one or two decades to verrucous or squamous cell carcinoma.

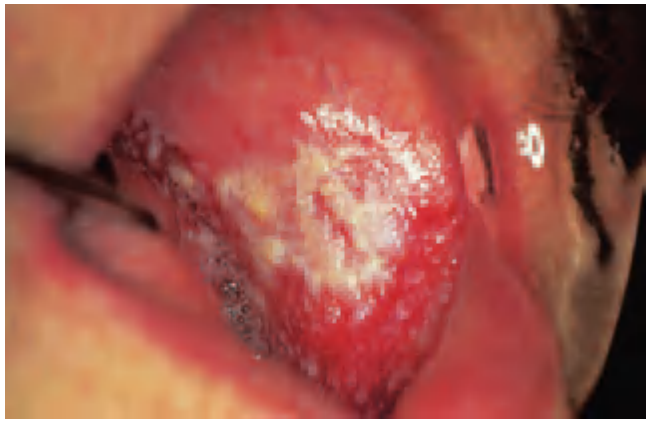

Fig. 66.53 Speckled leukoplakia.

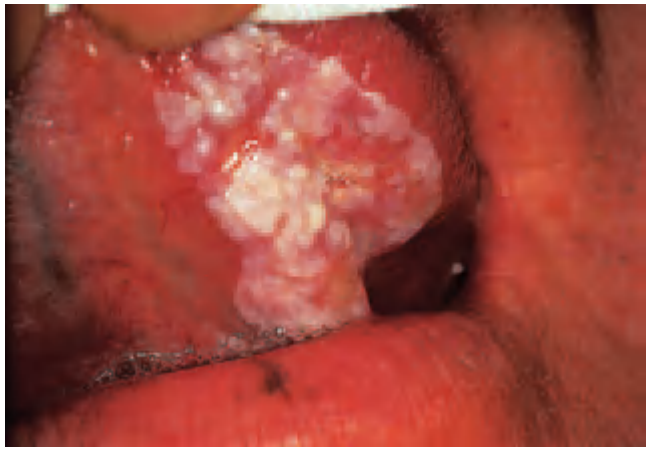

Fig. 66.54 Sublingual keratosis.

• Candidal leukoplakias may be associated with an increased risk of malignant change. Chronic candidal infection is common in speckled leukoplakias and *C. albicans* can cause or colonize other keratoses, particularly in smokers, and is especially likely to form speckled leukokplakias at commissures. It may be dysplastic and have higher malignant potential than some other keratoses. Candidal leukoplakias may respond to antifungals and cessation of smoking.
• Syphilitic leukoplakia, especially of the dorsum of tongue, is a feature of tertiary syphilis rarely seen now, although the malignant potential is high.
• Hairy leukoplakia is caused by EBV. It usually has a corrugated surface and mainly affects margins of the tongue almost exclusively. It is seen in the immunocompromised and is a complication of HIV infection. It is seen in all groups at risk of HIV infection. The condition appears to be benign and self-limiting. Leukoplakia in chronic renal failure causes similar symmetrical soft keratoses, and may be caused by EBV.

Diagnosis. There are no signs or symptoms which reliably predict whether a leukoplakia will undergo malignant change, and thus histology must be used to detect dysplasia. Scalpel or punch biopsy is therefore generally indicated. Biopsy is mandatory for those leukoplakias that exhibit the following characteristics:
• found in patients with previous or concurrent head and neck cancer;
• are non-homogeneous, i.e. have red areas and/or are verrucous and/or are indurated;
• in a high-risk site such as floor of mouth or tongue;
• focal;
• with symptoms;
• without obvious aetiological factors.

Pathology. Keratoses show, to a varying degree, increased keratin production, change in epithelial thickness and disordered epithelial maturation. Mild dysplasia is not usually regarded as of serious significance. The presence of severe epithelial dysplasia is thought to indicate a considerable risk of malignant development [18]. Pagetoid dyskeratosis is considered a selective keratinocytic response in which a small part of the normal population of keratinocytes is induced to proliferate in response to friction [19]. Pagetoid dyskeratosis has been found in 42.2% of lip biopsies, more frequent in younger patients and in women. Pagetoid cells are more common in suprabasal location and in the labial mucosa. These cells show positivity for high-molecular-weight cytokeratin and negative reaction for low-molecular-weight cytokeratin, epithelial membrane antigen, carcinoembryonic antigen and HPV. The immunohistochemical profile is different from the surrounding keratinocytes, indicating premature keratinization. The morphological features of dyskeratotic pagetoid cells are distinctive and easily recognized as an incidental finding, thus preventing confusion with other important entities including an intraepidermal tumour.

The main differential diagnoses include white-sponge naevus, leukoedema, oral koilocytoses, hairy leukoplakia, pagetoid squamous cell carcinoma *in situ* and extramammary Paget's disease of the oral mucosa.

Prognosis. Overall, around 2–5% of leukoplakias become malignant in 10 years and 5–20% of leukoplakias are dysplastic. Of leukoplakias with dysplasia, 10–35% proceed to carcinoma. There is thus clear evidence of the malignant potential of some oral leukoplakias, although some leukoplakias (15–30%) regress clinically, not only when supposed aetiological factors have been removed but also sometimes spontaneously. Malignant change to carcinoma is most frequent in women older than 50 years and in large lesions. Interestingly, leukoplakias developing in non-smokers have a higher rather than lower risk of malignant change.

At present, it is not possible to reliably predict which dysplastic lesions will progress to carcinoma and which will regress, and there is concern over observer and inter-observer variation in diagnosis of dysplasia [20,21]. Over the recent past, much effort has gone into identifying tissue markers of malignant potential [22], in particular the genetic changes that underlie oral carcinoma, resulting in the identification of biomarkers such as DNA ploidy, p53, and chromosome 3 and 9 changes that might predict neoplastic change in potentially malignant lesions [23–30].

Management. Management can be difficult, not least because of the wide extent of some lesions, their frequent admixture with areas of erythroplasia (speckled leukoplakias), and controversy as to the prognosis and long-term benefit and effects of various therapies. Indeed, no controlled studies are available [31]. Treatment therefore is empirical [32,33].

Removal of known risk factors (tobacco, alcohol and trauma) is a mandatory first step. The patient should be re-examined 3 months after instituting this. If the lesion persists, it should be removed [33–36].

Surgery (scalpel or laser excision) is an obvious option for the management of leukoplakias with a high predisposition to malignant transformation, such as leukoplakias that are:

- speckled;
- verrucous;
- from high-risk sites (e.g. floor of mouth/ventrum of tongue, or soft palate/fauces);
- in a patient with previous cancer of the upper aerodigestive tract;
- dysplastic;
- polysomic (aneuploidy or tetraploidy);
- positive for genetic markers such as mutated tumour-suppressor factor p53, or for loss of heterozygosity on chromosomes 3p or 9p—such advances in molecular biology mean that it should soon be possible to ascertain the malignant potential of leukoplakia from genetic and DNA studies.

Chemotherapy and chemoprevention are attractive possibilities [37]. Topical 0.5% bleomycin in dimethyl sulfoxide (dimethyl sulphoxide) is being evaluated [13]. Although they may induce regression of some leukoplakias and may inhibit their development, topical or systemic vitamin A derivatives, methisoprinol and calcipotriol have not been widely used because of adverse effects or their uncertain long-term consequences [38–42].

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Actinic cheilitis (see p. 66.115)

Hairy leukoplakia

Aetiology. Hairy leukoplakia (HL) is seen in severe immune defects, especially HIV infection, and occasionally in the apparently immunocompetent [1,2]. HIV is not found within the genome of epithelial cells in HL and it is more likely that the features are a consequence of an opportunistic infection with EBV. It is now clear that normal human oral mucosa from HIV-negative and HIV-positive individuals may contain latent EBV [3,4].

EBV has been shown to be present in HL, especially in the upper layers of the epithelium. The oral site of predilection for HL appears to relate to the presence of EBV receptors only on the parakeratinized mucosae such as the lateral margin of the tongue. HL regresses on treatment with antivirals but fails to resolve with antifungals, despite the frequent presence of *Candida* species.

Pathology. Histological features of HL include hyperparakeratosis, hyperplasia and ballooning of prickle cells, few or absent Langerhans' cells, and only a sparse inflammatory cell infiltrate in the lamina propria.

Clinical features. HL is a white patch, usually seen on the parakeratinized mucosa of the tongue, frequently bilaterally (Fig. 66.55). The lesions are corrugated or have a shaggy or hairy appearance, are mostly symptomless and, unlike some oral keratoses, have no known premalignant potential [1,5]. The majority of the affected patients who are HIV positive appear eventually to develop AIDS. HL also occurs in HIV-negative persons [6–12].

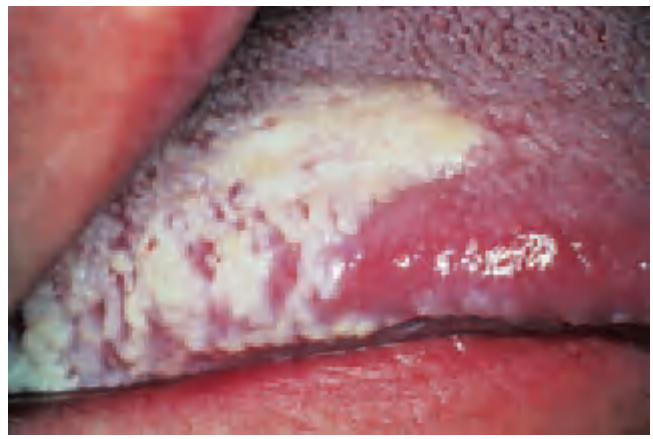

Fig. 66.55 Hairy leukoplakia. Found mainly in HIV infection, vertical white ridges on the lateral margin of the tongue.

Diagnosis. Some of the histological features typical of HL, especially the hyperparakeratosis, can be seen in oral white lesions other than HL in HIV-infected persons [13]. Not only are there oral lesions that mimic HL in HIV infection, but lesions similar to HL can be seen in other immunocompromised persons and even in some apparently healthy individuals.

However, most cases can be distinguished from the HL of HIV infection by the absence of EBV DNA on histology and, of course, by examination for HIV serum antibody.

Treatment. HL really needs no treatment but in HIV-infected individuals may occasionally improve spontaneously or with the antiretroviral agents aciclovir or ganciclovir.

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Psoriasis (see Chapter 35)

The oral mucosa appears to be rarely involved in psoriasis, with less than 100 cases reported, although there are occasionally lip lesions or white oral lesions, especially in the buccal mucosa, or lesions clinically indistinguishable from geographical tongue (sometimes termed 'annulus migrans' or 'erythema circinatum'), particularly in generalized pustular psoriasis [1–12].

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Koplik's spots (see Chapter 25)

White specks may be seen in the buccal mucosa in early measles.

Pigmented lesions

Congenital lesions are described on p. 66.27. The tongue is often discoloured due to superficial staining from foods, drinks or habits such as tobacco or betel use. Localized hyperpigmented lesions are usually due to pigmentary incontinence, amalgam tattoos, melanotic macule or naevi, although melanomas, Kaposi's sarcoma and epithelioid angiomatosis must be excluded. Generalized oral mucosal hyperpigmentation is usually racial in origin and only occasionally has a systemic cause such as Addison's disease.

Furred, brown and black hairy tongue

Aetiology and pathology. Children rarely have a furred tongue in health but it may be coated with off-white debris in febrile and other illnesses.

Adults, however, not infrequently have a coating on the tongue in health, particularly if they are edentulous, are on a soft non-abrasive diet, have poor oral hygiene or are fasting. The coating appears more obvious in xerostomic and in ill patients, especially those who cannot maintain oral hygiene.

The coating in most cases appears to be of epithelial, food and microbial debris; indeed, the tongue is the main oral reservoir of some microorganisms, such as *Candida albicans* and viridans streptococci. The filiform papillae are excessively long and stained by the accumulation of squames and chromogenic microorganisms.

Habits such as tobacco and betel use, and various medicaments such as chlorhexidine or iron, can cause a black or brown superficial staining of the tongue (and teeth).

Occasionally, a brown hairy tongue may be caused by drugs that induce xerostomia, lansoprazole or antimicrobial therapy, when it may be related to overgrowth of microorganisms such as *Candida* species and may respond to withdrawal of the drug [1,2].

Clinical features. Black hairy tongue affects mainly the posterior part of the dorsum of the tongue, especially centrally (Fig. 66.56) [3,4].

Treatment. Patients with black hairy tongue may find the condition improves if they avoid habits or drugs that stain the tongue, increase their standard of oral hygiene, brush the tongue with a hard toothbrush, use sodium bicarbonate mouthwashes, chew gum or suck a peach stone. Topical tretinoin may be effective [5].

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Pigmentary incontinence

Melanin pigment ingested by macrophages in the upper

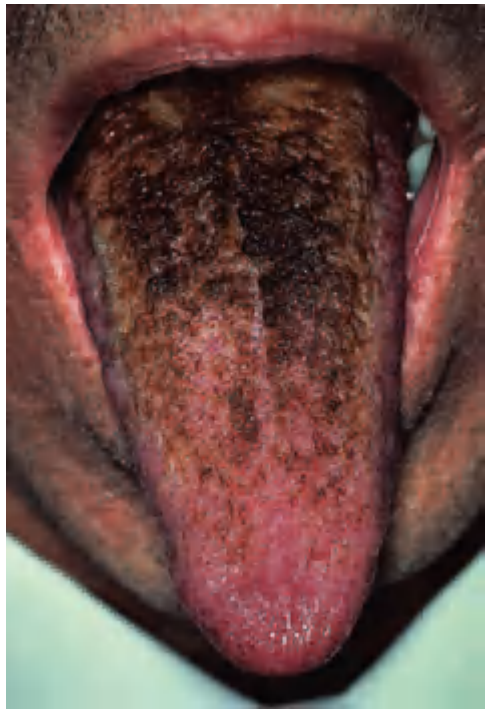

Fig. 66.56 Black hairy tongue.

lamina propria (pigmentary incontinence) may give rise to hyperpigmentation in LP, especially in dark-skinned people [1].

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Tattoos

Amalgam tattoos are common causes of blue-black pigmentation, usually seen in the mandibular gingiva or at least close to the teeth (Fig. 66.57), or in the scar of an apicectomy where there has been a retrograde root-filling [1–3]. The amalgam associates with elastin fibres [4]. Radio-opacities may or may not be seen on radiography. Similar lesions can result if for some reason pencil lead or other similar foreign bodies become embedded in the oral tissues [5].

Radiography may help to confirm the diagnosis. Biopsy may be indicated to exclude a melanoma but otherwise these innocuous lesions can be left alone.

Deliberate tattooing is a rare cause of oral pigmentation [6,7].

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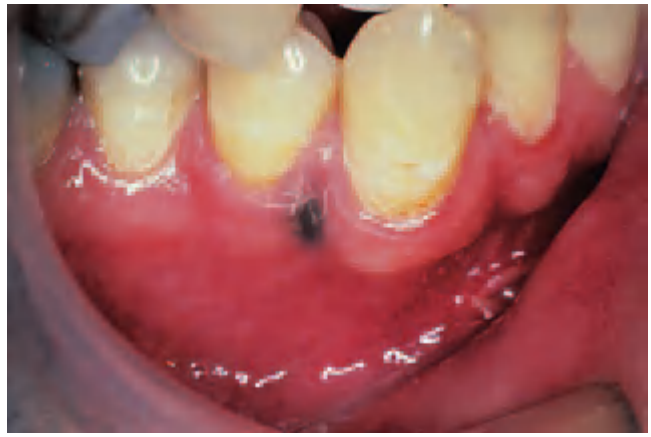

Fig. 66.57 Amalgam tattoo in a common site. This was presumably related to filling of the deciduous predecessor.

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Body art

Tattooing of the lower lip may occasionally be seen. A tattooed lower lip in a Sudanese woman, for example, signifies that she is married [1]. The Wodaabe people of Nigeria and Cameroon may tattoo on the skin surface at the angle of the mouth, a practice which has its basis in ritual warding-off of the 'evil eye'. Similar tattoos may be seen on Bedouin women of North Africa. Tattooing of the chin is seen increasingly in Maoris ('Moki') and tattooing inside the lip may now be seen in developed countries. Mathur and Sahoo [2] reported an instance of fatal septicaemia following the placement of tribal tattoo marks at the angle of the mouth in a Nigerian infant.

The practice of piercing oral and facial soft tissues and then placing foreign objects in the defects on a more or less permanent basis is one which has also been largely confined until recently to certain tribal groups in continental Africa and isolated Amazon regions of South America, for example the Suia and Txukahameis tribes of Brazil, but it is now not uncommon in developed countries.

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Food, habits, heavy metal and drug-induced hyperpigmentation

Causes (see Table 66.11) [1–4] include:

- Foods and beverages (such as beetroot, red wine, coffee and tea) cause superficial staining.
- Confectionery (such as liquorice) causes superficial staining.
- Smoking tobacco is now a fairly common cause (smoker's melanosis) and may produce extrinsic discoloration but also intrinsic pigmentary incontinence, with pigment cells increasing and appearing in the lamina propria. This is especially likely in persons who smoke with the lighted end of the cigarette within the mouth (reverse smoking), as practised mainly in some Asian communities [5,6].
- Chewing betel may cause superficial brownish-red discoloration mainly in the buccal mucosa (and on the teeth), with an irregular epithelial surface that has a tendency to desquamate, seen mainly in women from South and South-East Asia. The epithelium in betel chewer's mucosa is often hyperplastic, and brownish amorphous material from the betel quid may be seen on the epithelial surface and intracellularly and intercellularly, with ballooning of epithelial cells [7]. Betel chewer's mucosa is not known to be precancerous but betel use predisposes to submucous fibrosis and cancer.
- Drugs such as chlorhexidine, iron salts, griseofulvin, crack cocaine, minocycline, bismuth subsalicylate, lansoprazole and hormone replacement therapy. Chlorhexidine and iron salts cause superficial staining. Drugs that cause intrinsic staining include the following [8–16].
  - Antimalarials produce a variety of colours in the mucosa, ranging from yellow with mepacrine to blue–black with amodiaquine.
  - Minocycline may cause blackish discoloration of teeth, gingivae and bone, skin, sclera and even breast milk. Minocycline can, in a minority of patients, produce blue–grey gingival pigmentation caused by staining of the underlying bone, and some intrinsic faint bluish-grey staining, mainly at the anterior teeth.
  - Busulphan, some other cytotoxic drugs, oral contraceptives, phenothiazines and anticonvulsants may also occasionally produce, or increase, brown pigmentation. Adrenocorticotrophic hormone (ACTH) therapy may also produce brown pigmentation, as may zidovudine and clofazimine.
  - Gold may produce purplish gingival discoloration. Many of the heavy metals formerly implicated in producing oral hyperpigmentation (such as mercury, lead and bismuth) are not used therapeutically now, although industrial or accidental exposure is still occasionally seen [17]. Metallic sulphides deposited in the tissues were seen especially where oral hygiene was poor, with bacteria producing sulphides that resulted in pigmentation at the gingival margin (e.g. lead line).

Management. Some drug-induced hyperpigmentation resolves on cessation of exposure to the drug and improved oral hygiene, although resolution can take months or years.

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ACTH-induced hyperpigmentation

Oral hyperpigmentation may be seen in ACTH therapy, Addison's disease, Nelson's syndrome or ectopic ACTH production (e.g. by bronchogenic carcinoma). The brown or black pigmentation is variable in distribution but is seen typically on the soft palate, buccal mucosa and at sites of trauma [1–7].

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HIV infection

Oral hyperpigmentation may be seen in HIV infection, sometimes related to adrenal hypofunction or drug use [1,2].

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Oral mucosal melanotic macule, reactive type

SYN. MELANOACANTHOMA; MELANOACANTHOSIS

Melanotic macules occasionally appear suddenly as reactive lesions following trauma [1–9]. Melanoacanthoma is a misnomer: most reported cases have been in black people as reactive lesions [4]. A hyperpigmented symptomless macule appears over a course of days or weeks. The course is benign, and some cases resolve spontaneously within 6 months.

Pigment-filled dendritic cells that appear to be melanocytes are found in the stratum malpighii but, in contrast to melanoma, basal layer melanocytes are not increased.

Excision biopsy may be indicated to exclude melanoma.

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Malignant melanoma (see Chapter 38)

Oral malignant melanoma is rare. Most patients are over 50 years of age and there is a male preponderance.

Malignant melanoma may arise in apparently normal oral mucosa or in a pre-existent pigmented naevus, most commonly in the palate or maxillary alveolus [1–5]. Metastatic melanoma is rare [4]. Features suggestive of malignancy include a rapid increase in size, change in colour, ulceration, pain, bleeding, the occurrence of satellite pigmented spots, or regional lymph node enlargement. The prognosis is poor unless detected very early [2,3]. The histology may show anaplastic spindle-shaped or squamoid cells. However, the histology is quite varied and staining with dopa or antibodies may be required to help the diagnosis. Most cases are positive for S-100, tyrosinase, and Mart-1/melana-A. Lesions suspected to be malignant melanoma should not be biopsied until the time of definitive surgical excision [6–10].

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Kaposi's sarcoma (see Chapter 53)

Kaposi's sarcoma (KS) is seen predominantly as a consequence of HIV infection, mainly in men who have sex with men. It appears to be associated with HHV-8 [1,2]. Up to 50% of male homosexual AIDS patients have developed oral KS, although it appears to be declining in frequency and is rare in other HIV-infected patients.

Oral KS is the first presentation of HIV in 20–60% of affected patients, often associated with oral candidiasis. KS affects the hard-palate mucosa in particular (Fig. 66.58). Up to 95% of lesions are seen in the palate, 23% in the gingiva and others on the tongue or buccal mucosa. A red-purple macule is the early lesion, progressing to a purple nodular swelling that may be extensive and ulcerated.

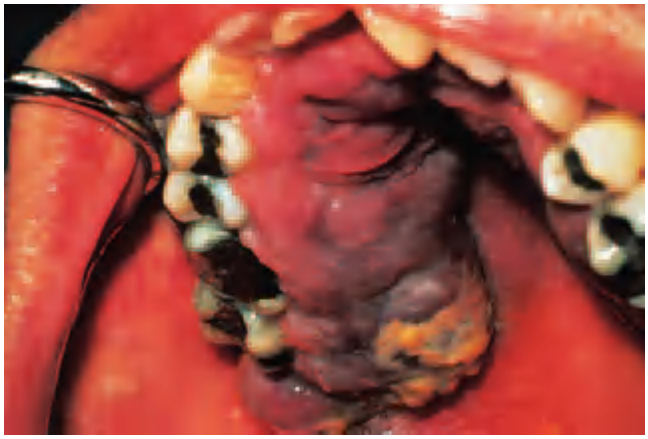

Fig. 66.58 Kaposi's sarcoma in a typical site with a characteristic purplish appearance. (Courtesy of Dr J.B. Epstein, Cancer Control Agency, Vancouver, Canada.)

Multiple lesions are common [3–6]. Lesions are often asymptomatic but more than 25% are painful and about 8% bleed. Oral KS is also occasionally seen in other non-HIV-infected immunocompromised patients.

Oral KS may regress occasionally spontaneously, or with HAART, zidovudine or systemic vinca alkaloids, etoposide or interferon, but the more usual treatment is local radiotherapy, laser removal or intralesional vinblastine. The latter produces fewer adverse effects than radiotherapy [4,7–9].

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Purpura

Petechiae are usually caused by trauma, often from suction, but a bleeding tendency (as in infectious mononucleosis or HIV infection) or leukaemias must be excluded

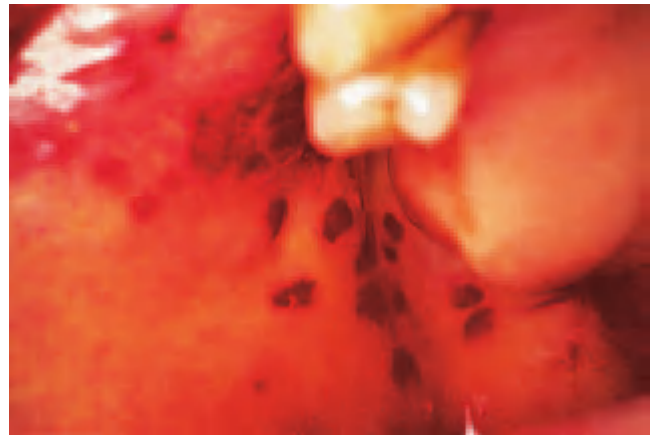

Fig. 66.59 Oral purpura in thrombocytopenia.

(Fig. 66.59). Blood-filled blisters may be seen in localized oral purpura (angina bullosa haemorrhagica) and pemphigoid, and occasionally in amyloidosis. Rarely a purpuric lesion may be seen in pigmented purpuric stomatitis [1].

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Red lesions

Many oral red lesions are inflammatory in nature, although epithelial thinning (in geographical tongue) and desquamation (in desquamative gingivitis) are fairly common, and epithelial atrophy is an important cause, especially in deficiency glossitis and erythroplasia. Telangiectases are usually red and haemangiomas purplish in colour.

Benign migratory glossitis

SYN. LINGUAL ERYTHEMA MIGRANS; GEOGRAPHICAL TONGUE

Definition. A benign inflammatory condition of the tongue with map-like areas of erythema which are not constant in size, shape or location. Lingual erythema migrans is unrelated to cutaneous erythema migrans.

Aetiology. Unknown, but many patients with a fissured tongue (scrotal tongue) also have lingual erythema migrans. It is a common condition, affecting about 1–2% of the population [1,2]. A positive family history may be obtainable. HLA findings have been equivocal, with reports of associations with B15 and DR7 [3].

Some patients with lingual erythema migrans have atopic allergies such as hay fever and a few relate the oral

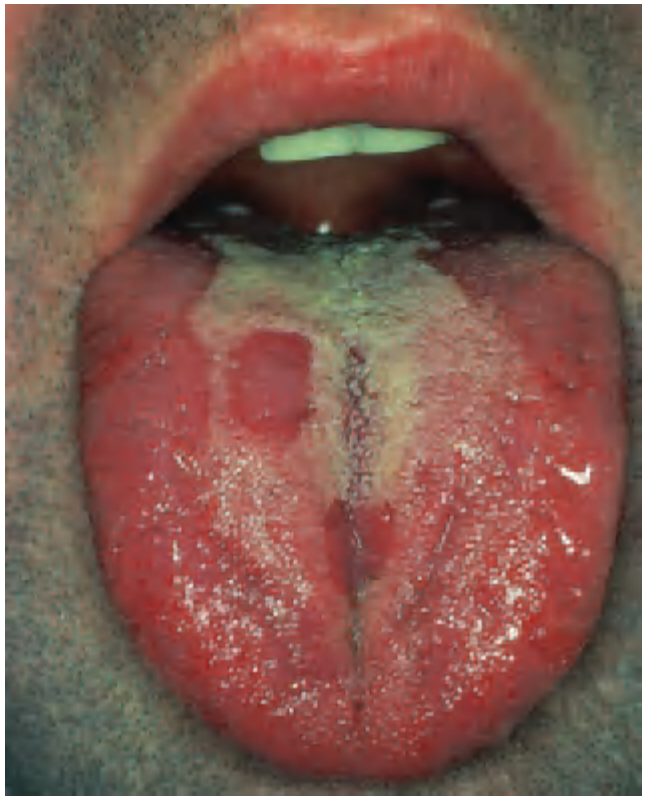

Fig. 66.60 Classical geographical tongue (lingual erythema migrans).

lesions to a particular food, for example cheese, or to stress. Similar oral lesions may be seen in Reiter's syndrome, generalized pustular psoriasis and acrodermatitis continua of Hallopeau [4]. Purported associations with diabetes [5] may be coincidental.

Pathology. There is epithelial thinning at the centre of the lesion with an inflammatory infiltrate mainly of polymorphonuclear leukocytes [1,2].

Clinical features. Geographical tongue may be asymptomatic or cause a sore tongue. Patients of any age may be affected but why the condition sometimes gives rise to symptoms after it has been present asymptomatically for decades is unclear [6–8].

Geographical tongue is characterized by map-like red areas with increased thickness of intervening filiform papillae. Alternatively, there are rounded, sometimes scalloped, reddish areas with a white margin (Figs 66.60 & 66.61). These patterns change from day to day and even within a few hours.

Rarely, other sites, such as the labial or palatal mucosa, are affected. The tongue is usually, but not invariably, affected simultaneously with the other sites [9].

There are no complications.

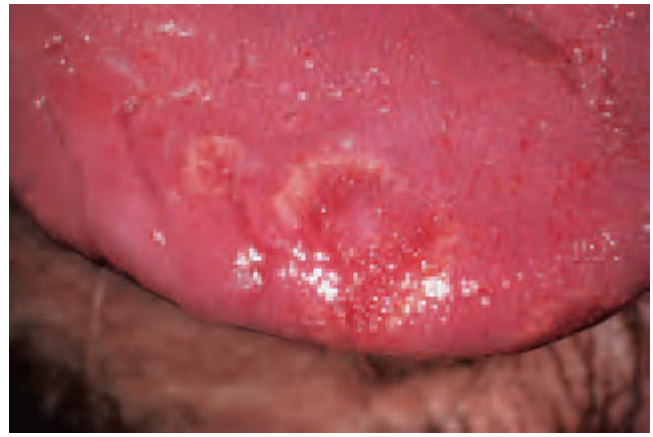

Fig. 66.61 Somewhat less obvious signs of lingual erythema migrans.

Diagnosis. Clinical examination usually suffices to differentiate the condition from LP, candidiasis, psoriasis, larva migrans or deficiency glossitis.

Treatment. Blood and urine examination may be necessary to exclude anaemia and diabetes. In those with no systemic disorder, no effective treatment is available except reassurance.

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Larva migrans (see Chapter 32)

Cutaneous larva migrans is rarely seen in the mouth, where it presents as irregular linear lesions with an inflammatory border resembling erythema migrans [1].

REFERENCE

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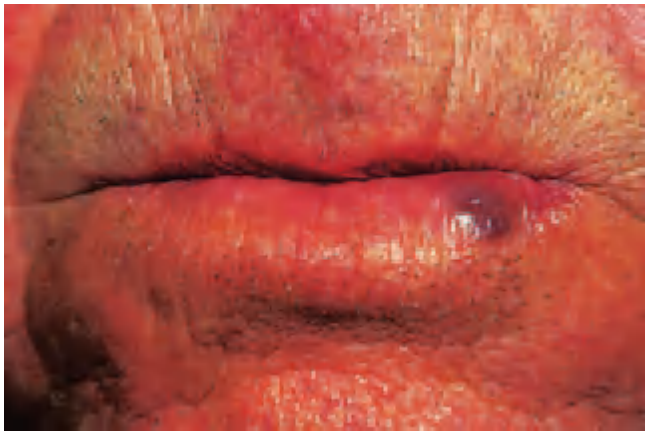

Fig. 66.62 Venous lake of the lip. (Courtesy of Addenbrooke's Hospital, Cambridge, UK.)

Glossitis (see p. 66.82)

Strawberry tongue

Prominence of the lingual papillae may be seen in scarlet fever, Kawasaki disease and Riley–Day syndrome (familial dysautonomia), giving rise to an appearance similar to a strawberry.

Telangiectasia (see Chapter 51)

Oral telangiectases occur mainly in hereditary haemorrhagic telangiectasia, CREST (*c*alcinosis, *R*aynaud's, *e*sophageal, *s*clerodactyly, *t*elangiectasia) syndrome [1] (see Chapter 56), chronic liver disease, pregnancy and after irradiation.

REFERENCE

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Venous lake

SYN. VENOUS VARIX; SENILE HAEMANGIOMA OF LIP

This is a bluish-purple soft swelling, 2–10 mm in diameter, usually seen on the lower lip of an elderly person, due to a venous dilatation (Fig. 66.62). The lesion is lined by a single layer of flattened endothelial cells with a thick wall of fibrous tissue. The lesion empties on prolonged pressure [1,2].

A venous lake may be only a trivial cosmetic problem or it can bleed severely after trauma. It can be excised, but careful cryotherapy, electrocautery or treatment with an argon laser [2] can also give good results.

REFERENCES

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Proliferative vascular lesions

Benign atypical vascular lesions may exhibit cytological or architectural features that simulate angiosarcoma such that considerable caution is required in diagnosis [1]. The head and neck region is a common location particularly for lobular capillary haemangioma (pyogenic granuloma), while the lip is an especially common site for lobular capillary haemangioma [2] and intravascular papillary endothelial hyperplasia (Masson's haemangioma or pseudoangiosarcoma) [3,4]. Intravascular papillary endothelial hyperplasia is a benign, non-neoplastic, vascular lesion characterized histologically by papillary fronds lined by proliferating endothelium and probably represents an organizing thrombus. Seen mainly in the lip or tongue in females, it may simulate angiosarcoma histologically [5]. Excision suffices.

Vascular lesions such as epithelioid haemangioma, epithelioid haemangioendothelioma, spindle-cell haemangioendothelioma, acquired progressive lymphangioma, or angiosarcoma and KS may also occasionally be seen.

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Varicosities

Bluish oral varicosities may often be seen in elderly patients, particularly in the ventrum and lateral margin of the tongue. They are benign and inconsequential.

Erythroplasia

Erythroplasia (erythroplakia) is a red velvety lesion level with, or depressed below, the surrounding mucosa. It is uncommon and affects patients of either sex in their sixth and seventh decades [1–3]. Erythroplasia usually involves the floor of the mouth, the ventrum of the tongue, or the

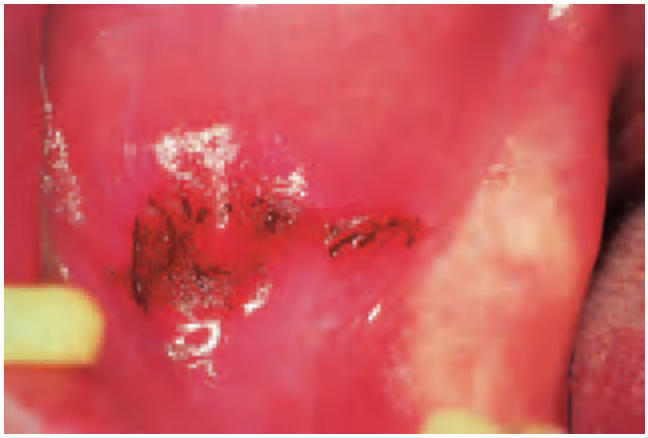

Fig. 66.63 Erythroplasia. (Courtesy of Professor R.A. Cawson, Eastman Dental Institute, London, UK.)

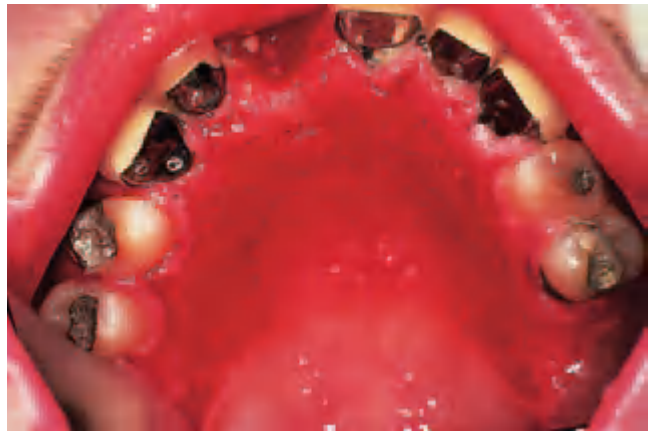

Fig. 66.64 Denture-induced stomatitis showing diffuse erythema in the denture-bearing area.

soft palate (Fig. 66.63) [1–4]. With regard to the risk of erythroplasia, a more than additive interaction has been found between tobacco chewing and low vegetable intake, whereas a more than multiplicative interaction has been found between alcohol drinking and low vegetable intake, and between drinking and low fruit intake [5].

Some 75–90% of cases of erythroplasia prove to be carcinoma or carcinoma *in situ* or show severe dysplasia. The incidence of malignant change in erythroplasia is 17 times higher than in leukoplakia.

Areas of erythroplasia should be excised and sent for histological examination.

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Erythematous candidiasis

Oral candidiasis can cause erythema and soreness of the oral mucosa, with or without the more usual thrush.

Denture-related stomatitis

SYN. DENTURE SORE MOUTH

This common form of mild, chronic, atrophic oral candidiasis occurs only beneath a denture, usually a complete upper denture, and is not often sore despite its name [1,2]. Dentures worn throughout the night, or with a dry mouth, favour development of this infection with *Candida* species. It is not caused by allergy to the denture material and it is not clear why only some denture wearers develop the condition. It is a disease mainly of the middle-aged or elderly and is more prevalent in women than men. Patients appear otherwise healthy. In some studies of institutionalized elderly patients, as many as 70% have been found to have denture-related stomatitis but overall it is considerably less common, particularly in normal healthy subjects.

Denture-related stomatitis consists of mild inflammation and erythema of the mucosa beneath a denture (Fig. 66.64).

Aetiopathogenesis [5–8]. Dentures can produce a number of ecological changes, including the following:

- Changes in the oral flora.
- Plaque accumulation between the mucosal surface of the denture and the palate.
- Saliva present between the maxillary denture and the mucosa may have a lower pH than usual.
- Accumulation of microbial plaque (bacteria and/or yeasts) on and in the fitting surface of the denture and the underlying mucosa.

In some persons, the cause appears to be related to a non-specific plaque [1–4]. This plaque undergoes sequential development, and is colonized by *Candida* organisms. Although there is no increased aspartyl proteinase production from the *Candida* involved, the decreased salivary flow and a low pH under the denture probably results in a high *Candida* enzymatic activity, which can cause inflammation.

Yeasts such as *Candida* are isolated in up to 90% of persons with denture-related stomatitis but even 66% of denture wearers have them. The most frequently isolated species is *Candida albicans*. Of the *C. albicans* isolates, 75% are serotype A and 25% serotype B, a significant increase in serotype B compared with a control group of non-denture-wearing HIV-seronegative individuals with oral candidiasis. Resistogram strain-C is the most

predominant (24% of total isolates), while strain A-CDE is the least (1.5% of total isolates). Adherence of *C. albicans* to denture-base materials *in vitro* is related to the hydrophobicity of the organism. When *Candida* is involved in denture-related stomatitis, the more common terms '*Candida*-associated denture stomatitis', 'denture-induced candidiasis' or 'chronic atrophic candidiasis' are used. However, denture-induced stomatitis is not exclusively associated with *Candida* and, occasionally, other factors such as bacterial infection or mechanical irritation are at play.

Histological examination of the soft tissue beneath dentures has shown proliferative or degenerative responses with reduced keratinization and thinner epithelium.

However, it not clear why only some denture wearers develop denture-related stomatitis, since most patients appear otherwise healthy. There have been few studies. Patients with denture-related stomatitis have no serious cell-mediated immune defects but they may sometimes be deficient in migration inhibition factor and may have overactive suppressor T cells or other T-lymphocyte/phagocyte defects. Mean concentrations of serum IL-6 and tumour necrosis factor (TNF)-α are statistically significantly higher and soluble TNF receptors lower in denture wearers compared with controls but there are no differences when stomatitis is present [9].

Predisposing factors. Dental appliances (mainly maxillary dentures), especially when worn throughout the night, or with a dry mouth, are the major predisposing factor. Diabetes or a high-carbohydrate diet occasionally predispose [10–12] and HIV is a rare underlying factor.

Factors that are usually *not* significant include allergy to the dental material (if it were, denture-related stomatitis would affect mucosae other than just that beneath the appliance), trauma (the condition is more common beneath maxillary dentures than mandibular dentures, yet trauma is more common with the latter), pharmacological agents and smoking.

Clinical features. The characteristic presenting features of denture-related stomatitis are:

- chronic erythema and oedema of the mucosa that contacts the fitting surface of the denture (usually a complete upper denture);
- the mucosa below lower dentures is rarely involved;
- erythema is restricted to the denture-bearing area;
- usually there are no symptoms;
- uncommon complications include angular stomatitis, and papillary hyperplasia in the vault of the palate.

Diagnosis. Denture-related stomatitis is a clinical diagnosis; the lesions have been classified into three clinical types (Newton's types), increasing in severity.

- Type 1: a localized simple inflammation or a pinpoint hyperaemia.
- Type 2: an erythematous or generalized simple type presenting as more diffuse erythema involving a part of, or the entire, denture-covered mucosa.
- Type 3: a granular type (inflammatory papillary hyperplasia) commonly involving the central part of the hard palate and the alveolar ridge.

Management. Any underlying systemic disease should be treated where possible.

The denture plaque and fitting surface is infested, usually with *C. albicans*. This must be removed regularly. Therefore, to treat and prevent recurrence of denture-related stomatitis, dentures should be removed from the mouth at night, cleaned and disinfected, and stored in an antiseptic. Cleansing is crucial to therapeutic success [13]. Denture cleansers can be divided into groups according to their main components: alkaline peroxides, alkaline hypochlorites, acids, yeast lytic enzymes, proteolytic enzymes and disinfectants such as hypochlorite. Denture soak solution containing benzoic acid completely eradicates *C. albicans* from the denture surface as it is taken up into the acrylic resin. An oral rinse containing chlorhexidine gluconate also results in complete elimination of *C. albicans* on the acrylic resin surface of the denture, and in reduction of palatal inflammation. A protease-containing denture soak (Alcalase) is also an effective way of removing denture plaque, especially when combined with brushing. Hypochlorite is an effective anticandidal but can turn chrome cobalt dentures black.

The mucosal infection is eradicated by brushing the palate and using antifungals for at least 4 weeks. Effective agents include nystatin pastilles or suspension, amphotericin lozenges, miconazole gel or fluconazole suspension or tablets, administered concurrently with an oral antiseptic such as chlorhexidine, which itself has antifungal activity. Isolates are usually sensitive to amphotericin and nystatin but less sensitive to miconazole. Fluconazole is as effective as newer agents such as itraconazole. The cyclodextrin solution and the capsule preparations of itraconazole are equally effective adjuncts in the treatment but, because of side effects, the capsules are preferred. Miconazole lacquer or fluconazole in tissue conditioners applied to the denture fitting surface are also effective [14–16].

Surgery may be needed to excise papillary hyperplasia [17].

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Acute candidiasis

Acute oral candidiasis may complicate corticosteroid or antibiotic therapy, particularly with long-term broad-spectrum antimicrobials such as used in transplant or terminally ill patients [1–3]. There is widespread erythema and soreness of the oral mucosa, sometimes with thrush, particularly noticeable on the tongue.

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HIV-associated candidiasis

Candida infections in and around the mouth have increased greatly, particularly as the HIV epidemic has spread, and now other species (especially *C. krusei*) and antifungal resistance are serious clinical realities [1–4]. There may be transmission of *Candida* species from HIV-infected persons [5] and new species and clades are being recognized [6]. The most dominant oral species, in decreasing order of frequency, are:

- *C. albicans*;
- *C. tropicalis*;
- *C. glabrata*;
- *C. parapsilosis*;
- *C. krusei*;
- other *Candida* species such as *C. dubliniensis*, *C. africanus* and *C. inconspicua*;
- other genera (*Rhodotorula*, *Saccharomyces*, etc.), which are rare and transient.

Erythematous or atrophic candidiasis may arise as a consequence of persistent acute pseudomembranous candidiasis when the pseudomembranes are shed, may develop *de novo*, or in HIV infection may precede pseudomembranous candidosis. The clinical presentation is of erythematous areas generally on the dorsum of the tongue, palate or buccal mucosa. Lesions on the dorsum of the tongue present as depapillated areas. Red areas are often seen in the palate in HIV disease. There can be an associated angular stomatitis and/or thrush.

Thrush is a well-recognized feature of T-cell immunodeficiencies, particularly after the severe T-cell immunosuppression necessary for organ transplantation and in other secondary immunodeficiencies, such as leukaemia, diabetes or HIV/AIDS. It is a common and early feature of AIDS.

Furthermore, with increasing use of antimycotic therapy, especially in HIV disease, there is a shift towards not only resistant *C. albicans*, as well as the appearance of novel species, but also other species such as *C. glabrata* and *C. krusei*. Thrush is characterized by white patches on the surface of the oral mucosa, tongue and elsewhere. The lesions develop to form confluent plaques that resemble milk curds, and can be wiped off to reveal a raw, erythematous and sometimes bleeding base. Complications of oropharyngeal thrush may sometimes present as lesions of the adjacent mucosa, particularly in the upper respiratory tract and the oesophagus. The combination of oral and oesophageal candidiasis is particularly prevalent in HIV-infected patients. Antifungal therapy is indicated.

REFERENCES

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Median rhomboid glossitis

SYN. CENTRAL PAPILLARY ATROPHY OF THE TONGUE

Aetiology. This red, depapillated, rhomboidal area in the centre line of the dorsum of the tongue, just anterior to the sulcus terminalis, was formerly thought to be caused by persistence of the tuberculum impar. However, it is now thought to be associated with candidiasis [1–3]. Multiple oral lesions may occasionally be present, especially a 'kissing' lesion in the palatal vault [4,5]. Smoking, denture wearing and, occasionally, immune defects (including HIV) and diabetes predispose to this lesion [6,7].

Pathology. Histology shows irregular pseudoepitheliomatous epithelial hyperplasia that may resemble a carcinoma but it is not a malignant condition.

Clinical features. There is typically a red central lesion of somewhat rhomboidal shape anterior to the sulcus terminalis on the dorsum of the tongue (Fig. 66.65). Occasionally, there is a nodular component.

There may also sometimes be a coexistent erythematous candidiasis in the palate [4,5], which some have termed 'chronic oral multifocal candidiasis'.

Diagnosis and management. Median rhomboid glossitis is usually diagnosed on clinical grounds, although biopsy may be indicated, since some lesions are nodular and may simulate a neoplasm. It may respond to the use of antifungals and to cessation of smoking.

REFERENCES

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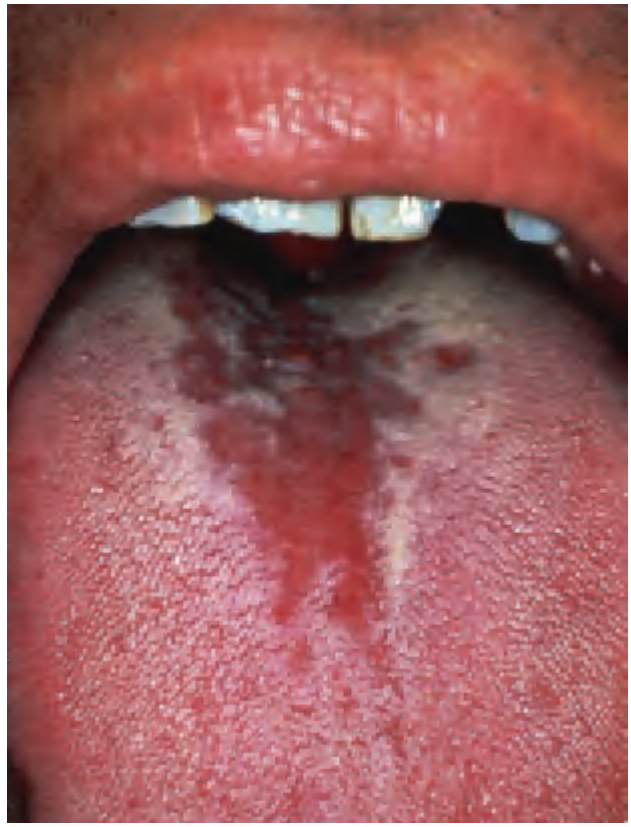

Fig. 66.65 Median rhomboid glossitis.

Desquamative gingivitis

This is usually caused by pemphigoid or lichen planus.

Loss of elasticity of oral tissues

Fibrosis of oral tissues can follow burns or irradiation. It may also be associated with habits such as the chewing of betel nut (areca), which predisposes to oral submucous fibrosis (see below) and may be caused by a connective tissue disorder such as scleroderma. Rarely it is occupational (polyvinylchloride workers). Epidermolysis bullosa and mucous membrane pemphigoid may cause scarring and the orofacial region is occasionally involved in multiple idiopathic fibrosis [1].

REFERENCE

1 Lewin IG, Carter JLB, Evans N *et al*. Multiple idiopathic fibrosis presenting as facial pain and trismus. *Br J Oral Surg* 1985; **23**: 135–9.

Oral submucous fibrosis

Aetiology. Oral submucous fibrosis is a chronic disease of the oral mucosa that appears to be caused by exposure to constituents of the areca nut. It is found virtually exclusively in persons from the Indian subcontinent; most of

those affected chew areca nut with tobacco, betel leaf and lime [1,2].

Pathology. There is a subepithelial chronic inflammatory reaction with fibrosis extending to the submucosa and muscle. Epithelial changes range from atrophy to keratosis and there may be dysplasia.

Clinical features. Oral submucous fibrosis develops insidiously, often initially presenting with oral dysaesthesia and a non-specific vesicular stomatitis [3]. Later there may be symmetrical fibrosis of the cheeks, lips or palate, which may be symptomless and noted only as bands running through the mucosa. This can, however, become so severe that the affected site becomes white and firm, with severely restricted opening of the mouth.

Oral submucous fibrosis appears to be restricted to the mouth, although many patients are also anaemic. Oral submucous fibrosis may predispose to the development of oral carcinoma, which occurs in 2–10% of patients over a period of 10 years [4,5].

The diagnosis can be confirmed by biopsy.

Treatment. Management is difficult. Intralesional corticosteroids and jaw exercises may be useful in the early stages, but surgery may be needed to relieve the fibrosis [1,6].

REFERENCES

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Systemic sclerosis (see Chapter 56)

Oral features are common in systemic sclerosis and are generally more obvious in those with diffuse than localized scleroderma. About 70% of patients have xerostomia, and there is an increase in both caries and periodontal disease. A characteristic finding is of increased width of the periodontal ligament space of all teeth on radiography [1]. There are mandibular erosions in the angle particularly, but also in the condyle, coronoid or digastric regions. Telangiectasia may be seen and most patients have restricted oral opening with linear wrinkles of the lips [2,3].

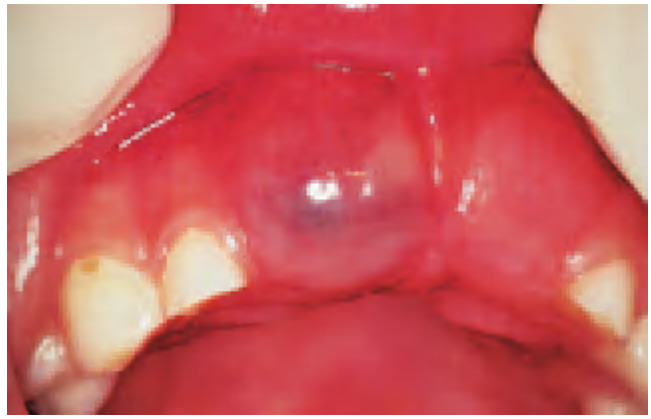

Fig. 66.66 Bluish, fluctuant swelling of an oral cyst, in this case an eruption cyst over an erupting maxillary permanent incisor. (The lesion on the maxillary canine is early dental caries.)

REFERENCES

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2 Masmary Y, Glais R, Pisanty S. Scleroderma: oral manifestations. *Oral Surg* 1981; **52**: 32–7.
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Lumps and swellings

Lumps in the mouth range from simple anatomical variants, which can cause the patient considerable concern, to lumps caused by inflammatory, cystic (Fig. 66.66), neoplastic and other disorders (Table 66.23).

Foliate papillitis

The foliate lingual papillae may become inflamed and swell. Because of their location on the posterolateral tongue this may give undue concern about malignancy. The condition resolves spontaneously.

Angio-oedema

Oral swelling may be a feature of acquired angio-oedema. The swelling is of acute onset, may affect the lips, tongue or other areas, and is often only mild and transient, although there is always the potential for obstruction of the airway. Local anaesthetics [1] or more commonly angiotensin-converting enzyme inhibitors [2–6] may cause angio-oedema, which can occasionally be lethal [4].

It may respond to a sympathomimetic agent such as epinephrine (adrenaline) or to antihistamines.

REFERENCES

1 Yaman Z, Kisnisci RS. Idiopathic swelling of the lower lip associated with topical anaesthesia. Report of three cases. *Aust Dent J* 1998; **43**: 324–7.

Table 66.23 Lesions that may cause the complaint of lumps or swellings in the mouth.

Normal anatomical features
Pterygoid hamulus
Parotid papillae
Foliate or other lingual papillae
Unerupted teeth
Developmental
Haemangioma
Lymphangioma
Maxillary and mandibular tori
Hereditary gingival fibromatosis
Von Recklinghausen's neurofibromatosis
Cysts of developmental origin
Odontomes
Inflammatory
Abscess
Pyogenic granuloma
Oral Crohn's disease
Orofacial granulomatosis
Pulse granuloma
Sarcoidosis
Wegener's granuloma
Others
Traumatic
Epulis
Fibroepithelial polyp
Denture-induced granuloma
Mucocele
Herniation of buccal fat pad
Infective
Various papillomatous lesions
Cystic
Cysts of odontogenic origin (e.g. dental cysts)
Drug therapy (gingival swelling only)
Oral contraceptive (pill gingivitis)
Phenytoin
Calcium-channel blockers
Ciclosporin
Hormonal
Pubertal gingivitis
Pregnancy epulis/gingivitis
Blood dyscrasias
Leukaemia, lymphoma and myeloma
Benign neoplasms
Various
Malignant neoplasms
Primary and secondary
Others
Angio-oedema
Amyloidosis
Fibro-osseous diseases
Acanthosis nigricans

2 Ebo DG, Steven WJ. Angioedema of ACE inhibitors. *Allergy* 1997; **52**: 354–5.
3 Lapostolle F, Borron SW, Bekka R, Baud FJ. Lingual angioedema after perindopril use. *Am J Cardiol* 1998; **81**: 523.
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Oral allergy syndrome

Oral allergy syndrome is the combination of oral pruritus, irritation and swelling of the lips, tongue, palate and throat, sometimes associated with other allergic features such as rhinoconjunctivitis, asthma, urticaria–angio-oedema, and anaphylactic shock, precipitated mainly by fresh foods such as fruits and vegetables, sometimes by pollens because of cross-reacting allergens [1,2]. Cooking often destroys the allergens.

It may respond to antihistamines or to a sympathomimetic agent such as ephedrine which can be taken by mouth.

REFERENCES

1 Escribano MM, Serrano P, Munoz-Bellido FJ, De la Calle A, Coude J. Oral allergy syndrome to bird meat associated with egg intolerance. *Allergy* 1998; **53**: 903–4.
2 Liccardi G, D'Amato M, D'Amato G. Oral allergy syndrome after ingestion of salami in a subject with monosensitisation to mite allergens. *J Allergy Clin Immunol* 1996; **98**: 850–2.

Osteoma mucosae

SYN. OSSEOUS CHORISTOMA

There are rare cases of osteoma of the oral mucosa, usually in the tongue. Most have been in females in the third and fourth decades and have arisen as pedunculated, hard, painless lumps on the dorsum of the tongue immediately posterior to the foramen caecum [1–3]. They may arise from thyroid anlages. Simple excision suffices.

REFERENCES

1 Busuttil A. An osteoma of the tongue. *J Laryngol* 1977; **91**: 259–61.
2 Markaki S, Gearty J, Markakis P. Osteoma of the tongue. *Br J Oral Surg* 1987; **25**: 79–82.
3 Sheridan SM. Osseous choristoma: a report of two cases. *Br J Oral Surg* 1984; **22**: 99–102.

Abscesses

Most intraoral abscesses are odontogenic in origin, as a final consequence of dental caries. Most abscesses discharge in the mouth on the buccal gingiva but occasionally discharge palatally, lingually, on the chin or submental region (Fig. 66.67), or elsewhere. Very occasionally abscesses follow trauma or a foreign body, or rarely are related to unusual oral infections such as actinomycosis [1], nocardiosis or botryomycosis [2]. Drainage and appropriate antimicrobials are indicated [3]. Dental

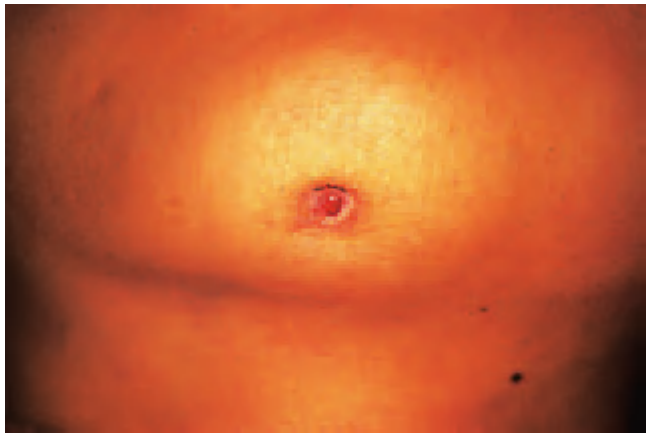

Fig. 66.67 Sinus on chin related to a dental abscess on a mandibular incisor tooth.

attention is required; dental abscesses are drained by tooth extraction, incision and drainage, or through the root canal (endodontics).

REFERENCES

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Sarcoidosis

Isolated nodules [1,2], gingival lesions [3], facial or labial swelling [4] and salivary gland involvement are the main oral or perioral lesions of sarcoidosis, but are uncommon. However, even where the mucosa is clinically normal, patients with sarcoidosis may have characteristic changes in palatal or labial salivary gland biopsies [5].

REFERENCES

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5 Van Maarsseveen ACMTH, Van der Waal I, Stam J *et al*. Oral involvement in sarcoidosis. *Int J Oral Surg* 1982; **11**: 21–9.

Pulse granuloma

SYN. LEWAR'S DISEASE

Chronic mandibular periostitis caused by embedded vegetable matter of dietary origin is uncommon but typically presents as a submucosal lump over the lower alveolus. Histology shows amorphous hyaline material and a granulomatous inflammatory reaction [1]. Excision suffices.

REFERENCE

1 Keirby FAR, Soames JV. Periostitis and osteitis associated with hyaline bodies. *Br J Oral Surg* 1985; **23**: 346–50.

Denture-induced hyperplasia

SYN. DENTURE GRANULOMA; EPULIS FISSURATUM

Where a denture flange is overextended and irritates the vestibular mucosa, a linear reparative process may result, eventually producing an elongated fibroepithelial enlargement known as denture-induced hyperplasia [1]. The pathology is that of a fibrous lump (see p. 66.20).

Firm, leaf-like, painless swellings are seen, usually in the buccal or labial vestibule.

A denture-induced granuloma should be excised and examined histologically, if modification of the denture does not induce regression. Rarely, a denture granuloma arises because some other lesion develops beneath a denture and causes the mucosa to be irritated.

REFERENCE

1 Budzt-Jorgensen E. Oral mucosal lesions associated with the wearing of removable dentures. *J Oral Pathol* 1981; **10**: 65–80.

Mucocele (mucous cyst)

SYN. MUCOUS RETENTION CYST; RANULA; MUCOCELE; MYXOID CYST OF LIP

Superficial mucoceles are seen mainly in lichen planus. Deeper mucoceles are more common and are usually seen in the lower labial mucosa (Fig. 66.68), usually resulting from the escape of mucus into the lamina propria from a damaged minor salivary gland duct.

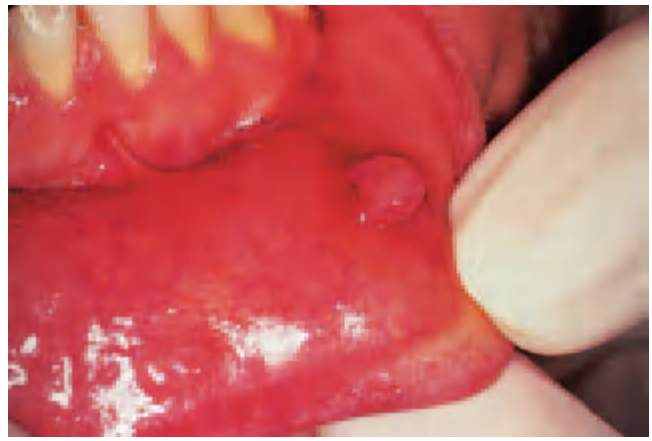

Fig. 66.68 Mucocele in a typical site.

They appear as painless dome-shaped, translucent, whitish blue papules or nodules [1].

Care should be taken to ensure that the lesion is not a salivary gland tumour with cystic change, especially when dealing with an apparent mucous cyst in the upper lip. The cysts can be excised but they also respond well to cryosurgery, using a single freeze–thaw cycle [2].

REFERENCES

1 Lattanand A, Johnson WC. Mucous cyst (mucocele): a clinico-pathologic and histochemical study. *Arch Dermatol* 1970; **101**: 673–8.
2 Bohler-Sommeregger K. Cryosurgical management of myxoid cysts. *J Dermatol Surg Oncol* 1988; **14**: 1405–8.

Buccal fat-pad herniation

Trauma may rarely cause the buccal pad of fat to herniate through the buccinator muscle, producing an intraoral swelling [1]. This usually occurs in males under the age of 4 years. Surgery is indicated.

REFERENCE

1 Fleming P. Traumatic herniation of buccal fat pad: a report of two cases. *J Oral Surg* 1986; **24**: 265–8.

Oral papilloma

Aetiology. These are caused by HPV [1].

Pathology. Histology includes acanthotic and sometimes hyperkeratotic epithelium with occasional koilocytosis.

Clinical features. Papillomas can appear anywhere in the mouth, but are most common at the junction of the hard and soft palate. The papilloma is a white or pink, cauliflower-like lesion that may resemble a wart. Papillomas of normal colour may be confused with the commoner fibroepithelial polyps, although the latter are commonest at sites of potential trauma.

Prognosis. Unlike some papillomas of the larynx or bowel, oral papillomas remain benign.

Diagnosis. Oral papillomas should be examined histologically to establish a correct diagnosis.

Treatment. Excision must be total, deep and wide enough to include any abnormal cells beyond the zone of the pedicle.

REFERENCE

1 Scully C, Cox MF, Prime SS *et al*. Papillomaviruses: the current status in relation to oral disease. *Oral Surg* 1988; **65**: 526–32.

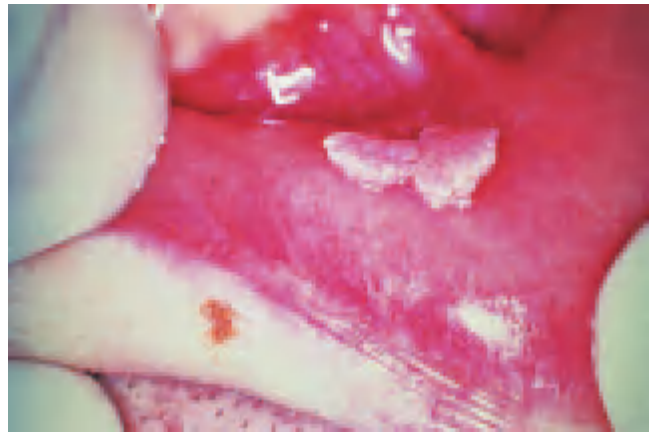

Fig. 66.69 Genital warts on the lower lip in HIV infection. (There is also a healing herpes simplex lesion on the lip.)

Warts (see Chapter 25)

Common warts (verrucae vulgaris) and venereal warts (condyloma acuminatum) are both caused by papillomaviruses [1–3]. They are rare in the mouth (Fig. 66.69) but are more common in HIV disease. None is known to be premalignant. Most can be removed by excision, cryosurgery or laser, or podophyllum or imiquimod.

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Focal epithelial hyperplasia

SYN. HECK'S DISEASE

Focal epithelial hyperplasia is a rare, benign, familial disorder with no sex predisposition, characterized by multiple, soft, circumscribed, sessile, nodular elevations of the oral mucosa [1,2].

Heck's disease occurs particularly in native Americans and in Inuits in Greenland but has been reported rarely from many other countries. The prevalence in Greenland and Venezuela approaches 35% [1,3,4].

Aetiology. The papillomaviruses HPV-13 and HPV-32 appear to be causal in patients with the genetic predisposition to focal epithelial hyperplasia [5–8].

Pathology. The characteristics of focal epithelial hyperplasia are local epithelial hyperplasia, acanthosis and elongated 'Bronze Age axe' rete ridges, together with a ballooning type of nuclear degeneration. Epithelial cells have a pseudomitotic appearance.

Clinical features. Among native Americans, focal epithelial hyperplasia mainly affects children and usually involves the lower lip, whereas in the Inuit and in white people the lesions are found mainly in the fourth decade and later and often affect the tongue. This is a benign asymptomatic condition, requiring only reassurance.

REFERENCES

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8 Hernandes-Juaregui P, Eriksonn A, Tamayo-Perez R *et al.* Human papillomavirus type 13 DNA in focal epithelial hyperplasia among Mexicans. *Arch Virol* 1987; **93**: 131–7.

Papillary hyperplasia

Papillary hyperplasia may be seen in the vault of the palate, typically in persons with chronic denture-related stomatitis and occasionally in its absence [1,2]. It may require excision or laser removal.

REFERENCES

1 O'Driscoll PM. Papillary hyperplasia of the palate. *Br Dent J* 1965; **118**: 77–80.
2 Schmitz JF. A clinical study of inflammatory papillary hyperplasia. *J Prosthet Dent* 1964; **14**: 1034–9.

Rhabdomyoma

Rhabdomyomas are rare but most extracardiac rhabdomyomas present in the mouth, typically as lumps in the floor of mouth, tongue or soft palate [1,2]. Most are seen in the sixth decade, predominantly in males. Surgery is effective provided total excision is achieved.

REFERENCES

1 Corio RL, Lewis DM. Intraoral rhabdomyomas. *Oral Surg* 1979; **48**: 525–31.
2 Reid CO, Smith CJ. Rhabdomyoma of the floor of the mouth: a new case and review of recently reported intraoral rhabdomyomas. *Br J Oral Surg* 1985; **23**: 284–91.

Rhabdomyosarcoma

Some 45% of soft-tissue sarcomas in the head and neck region are rhabdomyosarcomas. The most common oral presentation is a progressively enlarging mass; some 20% have enlarged regional lymph nodes [1]. In advanced disease there may be pain, paraesthesia, trismus or loosening of teeth.

The prognosis is poor. Treatment includes cytotoxic chemotherapy, surgery and radiotherapy.

REFERENCE

1 Bras J, Batsakis JG, Luna MA. Rhabdomyosarcoma of the oral soft tissues. *Oral Surg* 1987; **64**: 585–96.

Nodular fasciitis (see Chapter 53)

Nodular (pseudosarcomatous) fasciitis affects the head and neck in 20% of cases but rarely involves the mouth [1,2].

REFERENCES

1 Davies HT, Bradley N, Bowerman JE. Oral nodular fasciitis. *Br J Oral Surg* 1989; **27**: 147–51.
2 Kawana T, Yamamoto H, Deguchi A *et al.* Nodular fasciitis of the upper labial fascia. Cytometric and ultrastructural studies. *Int J Oral Surg* 1986; **15**: 464–8.

Verruciform xanthoma

Although verruciform xanthoma was originally described as a distinct oral entity, it is now also known occasionally to affect the skin and non-oral mucosae [1]. The aetiology is unknown but may be a reaction to some irritant.

The lesions consist of parakeratotic verruciform epithelium, with large foamy xanthoma cells containing slightly PAS-positive granules and abundant lipid in the lamina propria between the epithelial pegs [2].

Verruciform xanthoma is usually a solitary symptomless lesion, typically on the gingiva, with a normal, pale, reddish or keratotic surface [1,2]. Excision is only rarely followed by recurrence.

REFERENCES

1 Neville BW, Weathers DR. Verruciform xanthoma. *Oral Surg* 1980; **49**: 429–34.
2 Nowparast B, Howell FV, Rick GM. Verruciform xanthoma: a clinicopathologic review and report of fifty-four cases. *Oral Surg* 1981; **51**: 619–25.

Lipoma (see Chapter 55)

Lipomas are uncommon in the mouth, comprising less than 5% of oral benign tumours [1]. They present as slow-growing, spherical, smooth and soft semi-fluctuant lumps with a characteristic yellowish colour. Most involve the buccal mucosa or floor of mouth. Occasionally, although benign, they infiltrate. Histology shows adult fat cells

gathered into lobules by vascular septa of fibrous connective tissue. Surgery is rarely indicated except for infiltrating lipomas.

REFERENCE

1 Batsakis JG, Regezi JA, Rice DH. The pathology of head and neck tumors: part 8. *Head Neck Surg* 1980; **3**: 145–68.

Myxoma

Myxomas are rare in the oral cavity. They can arise in bone or soft tissue and, although benign, are aggressive and difficult to eradicate because of the tendency to infiltrate normal tissue.

Leiomyoma

This benign tumour of smooth muscle is rare in the oral cavity but usually affects the tongue or palate.

Macroglossia

The tongue may be congenitally enlarged (macroglossia) in Down's syndrome or Beckwith–Wiedemann syndrome or where there is an angioma. It may also enlarge in angio-oedema, gigantism, acromegaly or amyloidosis.

Myeloma and paraproteinaemias

Multiple myeloma very occasionally presents with an intraoral mass or oral bleeding. Bone lesions are more common. Solitary plasmacytomas may also be seen; indeed, some 80% of these rare tumours are found in the head and neck region but typically in the nasal cavity or pharynx rather than in the mouth [1,2].

Waldenström's macroglobulinaemia

Oral manifestations in Waldenström's macroglobulinaemia include purpura, ulceration and occasional mental nerve anaesthesia [3–5].

REFERENCES

1 Epstein JB, Boss NJS, Stevenson-Moore P. Maxillofacial manifestations of multiple myeloma. *Oral Surg* 1984; **57**: 267–71.
2 Woodruff RK, Whittle JM, Malpas JS. Solitary plasmacytoma. 1. Extramedullary soft tissue plasmacytoma. *Cancer* 1979; **43**: 2340–3.
3 Gamble JW, Driscoll EJ. Oral manifestations of macroglobulinaemia of Waldenstrom. *Oral Surg* 1960; **13**: 104–10.
4 Klokkevold PR, Miller DA, Friedlander AH. Mental nerve neuropathy: a symptom of Waldenstrom's macroglobulinaemia. *Oral Surg* 1989; **67**: 689–93.
5 Zulian M, Bellome J, DeBoom GW. Multiple linear ulcers on the dorsum of the tongue in a patient with Waldenstrom's macroglobulinaemia. *J Am Dent Assoc* 1987; **114**: 79–80.

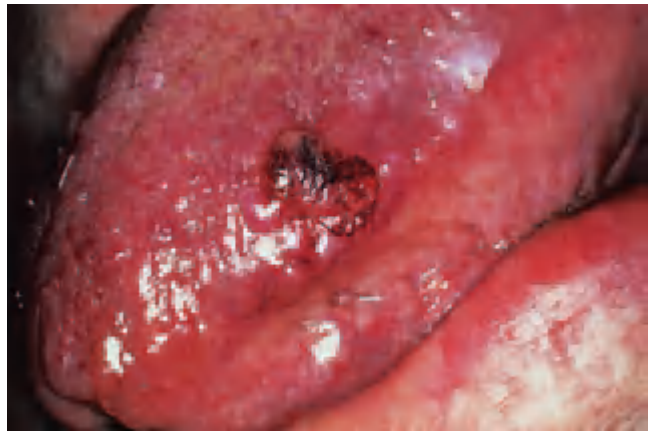

Fig. 66.70 Macroglossia and oral petechiae in amyloidosis.

Franklin's disease

SYN. HEAVY-CHAIN DISEASE

Palatal oedema and oral ulceration have been described in a few patients with heavy-chain disease, but the former feature is not as invariable as initially described [1,2].

REFERENCES

1 Kanoch T, Takigawa M, Niwa Y. Cutaneous lesions in heavy chain disease. *Arch Dermatol* 1988; **124**: 1538–40.
2 Seligmann M. Heavy chain diseases. In: Delamore IW, ed. *Multiple Myeloma and Other Paraproteinaemias*. Edinburgh: Churchill Livingstone, 1986: 263–85.

Thrombotic thrombocytopenic purpura

This may present with oral purpura and/or spontaneous gingival haemorrhage [1,2]. Gingival biopsy is a recommended investigation [3,4].

REFERENCES

1 Fox P, Gordon RE, Williams AC. Thrombotic thrombocytopenic purpura: report of a case. *J Oral Surg* 1977; **35**: 921–3.
2 Ridolfi R, Bell W. Thrombotic thrombocytopenic purpura: report of 25 cases and review of the literature. *Medicine* 1981; **60**: 413–28.
3 Goodman A, Ramos P, Petrelli M *et al*. Gingival biopsy in thrombotic thrombocytopenic purpura. *Ann Intern Med* 1978; **89**: 501–4.
4 Nishioka GJ, Chilcoat CC, Aufdenorte TB *et al*. The gingival biopsy in the diagnosis of thrombotic thrombocytopenic purpura. *Oral Surg* 1988; **65**: 580–5.

Amyloidosis (see Chapter 57)

In primary amyloidosis the tongue is enlarged and hard. There may also be yellowish submucosal nodules, lumps or petechiae (Fig. 66.70). Rarely, there are similar deposits elsewhere (e.g. in the soft palate), jaw claudication, salivary gland swelling or xerostomia [1–5].

Secondary amyloidoses rarely involve the mouth except in the case of multiple myeloma or haemodialysis-

associated amyloid, which may occasionally produce oral nodules [6,7].

Some 10% of patients with oral amyloidosis have amyloid in their submandibular glands. Solitary intraoral amyloid is rare [8].

Congo red or thioflavine T staining of a biopsy usually confirms the diagnosis, although in extreme cases the deposits are seen on haematoxylin and eosin staining. Treatment is unsatisfactory but the underlying disease, where present, should be treated.

REFERENCES

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6 Reinish EI, Raviv M, Srolovitz H, Gornitsky M. Tongue, primary amyloidosis, and multiple myeloma. *Oral Surg* 1994; **77**: 121–5.
7 Guccion JG, Redman RS, Winne CE. Hemodialysis-associated amyloidosis presenting as lingual nodules. *Oral Surg* 1989; **68**: 618–23.
8 Raymond AK, Sneige N, Batsakis JG. Amyloidosis in the upper aerodigestive tracts. *Ann Otol Rhinol Laryngol* 1992; **101**: 794–6.

Oral manifestations of systemic diseases

Oral manifestations can occasionally occur in many systemic diseases (Tables 66.24–66.38). Space precludes all but a brief tabular synopsis here. Further details can be found elsewhere [1–10].

REFERENCES

1 Jones JH, Mason DK, eds. *Oral Manifestations of Systemic Disease*, 2nd edn. London: Baillière-Tindall, 1990.

Table 66.25 Liver diseases.

Disease	Oral manifestations
Most liver diseases with jaundice	Bleeding tendency Jaundice
Alcoholic cirrhosis	Bleeding tendency Sialosis
Chronic active hepatitis	Lichen planus
Primary biliary cirrhosis	Sjögren's syndrome Lichen planus
Hepatitis C	Lichen planus Sjögren's syndrome

Table 66.26 Psychiatric disease.

Disease	Oral manifestations
Depression, hypochondriasis and various psychoses	Various complaints such as dry mouth, discharges, pain, disturbed taste and sensation Drug reactions Often multiple complaints Artefactual ulcers
Anxiety states	Cheek biting Bruxism (teeth grinding)
Bulimia	Tooth erosion

Table 66.24 Endocrine disorders.

Disease	Oral manifestations
Pituitary dwarfism	Microdontia Retarded tooth eruption
Congenital hypothyroidism	Macroglossia Retarded tooth eruption
Congenital hypoparathyroidism	Dental hypoplasia May be chronic candidiasis if associated immune defect
Gigantism/acromegaly	Spaced teeth Mandibular prognathism Macroglossia Megadontia (in gigantism)
Hyperparathyroidism	Bone rarefaction Brown tumours
Addison's disease	Mucosal hyperpigmentation
Diabetes mellitus	Periodontal disease Xerostomia Candidiasis Sialosis Lichen planus
Pregnancy	Gingivitis Epulis
Precocious puberty	Accelerated tooth eruption (fibrous dysplasia in Albright's syndrome)

Table 66.27 Drug effects.

Tissue	Drug effect	Drugs commonly implicated
Teeth	Discoloration	Tetracyclines
		Chlorhexidine
	Root anomalies	Phenytoin
		Cytotoxic drugs
Gingiva	Swelling	Phenytoin
		Ciclosporin
		Nifedipine
		Diltiazem
Salivary glands	Dry mouth	Tricyclic antidepressants
		Phenothiazines
		Antihypertensives
		Lithium
Taste	Disturbed	Metronidazole
		Penicillamine
Facial movements	Dyskinesias	Phenothiazines
		Metoclopramide
Mucosa	Thrush	Broad-spectrum antimicrobials
		Corticosteroids
		Cytotoxic drugs
	Ulcers	Cytotoxic drugs
		Non-steroidal anti-inflammatory agents
	Lichenoid lesions	Non-steroidal anti-inflammatory agents
	Erythema multiforme	Barbiturates
		Sulphonamides

Table 66.28 Gastrointestinal diseases.

Disease	Oral manifestations
Pernicious anaemia	Ulcers
	Glossitis
	Angular stomatitis
	Red lesions
Any cause of malabsorption	Ulcers
	Glossitis
	Angular stomatitis
Any cause of regurgitation	Tooth erosion
	Halitosis
Tylosis	Leukoplakia
Crohn's disease (and orofacial granulomatosis)	Facial swelling
	Mucosal tags
	Gingival hyperplasia
	Cobblestoning of mucosa
	Ulcers
	Glossitis
	Angular stomatitis
Coeliac disease	Ulcers
	Glossitis
	Angular stomatitis
	Dental hypoplasia
Peutz–Jegher syndrome (small intestinal polyps)	Melanosis
Chronic pancreatitis	Sialosis (rarely)
Cystic fibrosis	Salivary gland swelling
Gardner's syndrome (familial colonic polyposis)	Osteomas

Table 66.29 Renal diseases.

Disease	Oral manifestations
Chronic renal failure of any cause	Xerostomia
	Halitosis/taste disturbance
	Leukoplakia
	Dental hypoplasia in children
	Renal osteodystrophy
	Bleeding tendency (especially if anticoagulated)
Post renal transplant (immunosuppressed)	Infections, particularly herpetic and candidal
	Bleeding tendency if anticoagulated
	Gingival hyperplasia if on ciclosporin
	Kaposi's sarcoma (rarely)
	Hairy leukoplakia (rarely)
Nephrotic syndrome	Dental hypoplasia
Renal rickets (vitamin D resistant)	Delayed tooth eruption
	Dental hypoplasia (rarely)
	Enlarged pulp

2 Scully C, Flint S, Porter SR. *Colour Atlas of Oral Diseases*. London: Martin Dunitz, 1996.
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4 Scully C, Cawson RA. Oral medicine. *Med Int* 1986; **28**: 1129–51.
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7 Scully C, Porter SR. Oral medicine. *Med Int* 1990; **76**: 3145–74.
8 Porter SR, Scully C. HIV: the surgeon's perspective. *Br J Oral Maxillofac Surg* 1994; **32**: 222–47 (3 parts).

Table 66.30 Haematological diseases.

Disease	Oral manifestations
Deficiency of the haematinics (iron, folic acid or vitamin B_{12})	Burning mouth sensation Ulcers Glossitis Angular stomatitis
Sickle-cell anaemia	Jaw deformities Osteomyelitis or pain
Thalassaemia major	Jaw deformities
Aplastic anaemia	Ulcers Bleeding tendency
Haemolytic disease of newborn	Tooth pigmentation Enamel defects
Any leukocyte defect	Infections, especially herpetic and candidal Ulcers
Any cause of purpura	Bleeding tendency Purpura
Leukaemia/lymphoma	Infections Ulcers Bleeding tendency and purpura (in leukaemias only) Gingival swelling in myelomonocytic leukaemia
Multiple myeloma	Bone pain Tooth mobility Amyloidosis
Amyloid disease	Enlarged tongue Purpura

Table 66.31 Cardiovascular diseases.

Disease	Oral manifestations
Any disorder causing right-to-left shunt, e.g. Fallot's tetralogy	Cyanosis Delayed tooth eruption
Angina pectoris	Pain referred to jaw
Hereditary haemorrhagic telangiectasia	Telangiectasis
Giant cell arteritis (cranial or temporal arteritis)	Tongue pain or necrosis
Polyarteritis nodosa	Ulcers
Any disorder in which anticoagulants are used	Bleeding tendency
Hypertension	Dry mouth and other problems caused by some antihypertensives, e.g. gingival hyperplasia (nifedipine or diltiazem), lichenoid lesions (methyldopa and others)

9 Scully C, Welbury RA, Flaitz C, Almeida ODP. *A Colour Atlas of Orofacial Diseases in Children and Adolescents*. London: Martin Dunitz, 2001.
10 Scully C, Samaranayake LP. *Clinical Virology in Oral Medicine and Dentistry*. Cambridge: Cambridge University Press, 1992.

Acquired lip lesions

Cheilitis

SYN. INFLAMMATION OF THE LIPS

Cheilitis may arise as a primary disorder of the vermilion zone or the inflammation may extend from nearby skin or, less often, from the oral mucosa (Table 66.39) [1].

REFERENCE

1 Scully C, Bagan JV, Eisen D, Porter S, Rogers RS. *Dermatology of the Lips*. Oxford: Isis Medical Media, 2000.

'Chapping' of the lips

Chapping is a reaction to adverse environmental conditions usually caused by exposure to freezing cold or to hot dry winds. The keratin of the vermilion loses its plasticity, so that the lips become sore, cracked and scaly. The affected person tends to lick the lips, or to pick at the scales, which may aggravate the condition.

Table 66.32 Primary and secondary immunodeficiencies.

Disease	Oral manifestations
Severe combined immunodeficiency	Candidiasis
	Viral infections
	Ulcers
	Absent tonsils
	Recurrent sinusitis
Sex-linked agammaglobulinaemia	Ulcers
	Recurrent sinusitis
	Absent tonsils
Common variable immunodeficiency	Recurrent sinusitis
	Candidiasis
Selective IgA deficiency	Tonsillar hyperplasia
	Ulcers
	Viral infections
	Parotitis
DiGeorge's syndrome	Abnormal facies
	Candidiasis
	Viral infections
	Bifid uvula
Ataxia-telangiectasia	Recurrent sinusitis
	Ulcers
	Telangiectasia
Wiskott–Aldrich syndrome	Candidiasis
	Viral infections
	Purpura
Hereditary angio-oedema	Swellings
Chronic benign neutropenia	Ulcers
	Severe periodontitis
Cyclic neutropenia	Ulcers
	Severe periodontitis
	Eczematous lesions of the face
Chronic granulomatous disease	Candidiasis
	Enamel hypoplasia
	Acute gingivitis
	Ulcers
Myeloperoxidase deficiency	Candidiasis
Chédiak–Higashi syndrome	Ulcers
	Periodontitis
Job's syndrome	Abnormal facies
Secondary immune defects	Ulcers
	Periodontitis
	Candidiasis
	Viral infections
	Malignant neoplasms
	Hairy leukoplakia

Table 66.33 Metabolic disorders.

Disease	Oral manifestations
Congenital hyperuricaemia (Lesch–Nyhan syndrome)	Self-mutilation
Mucopolysaccharidoses	Spaced teeth
	Retarded tooth eruption
	Cystic radiolucencies
	Temporomandibular joint anomalies
	Enamel defects
	Gingival hyperplasia
Niemann–Pick disease	Retarded tooth eruption
	Loosening of teeth
	Mucosal pigmentation
Mucolipidoses	Gingival hyperplasia
Hypophosphatasia	Loosening and loss of teeth
Erythropoietic porphyria	Reddish teeth
	Bullae/erosions
	Dental hypoplasia
Amyloidosis	Macroglossia
	Purpura
Vitamin B_{12} or folic acid deficiency	Ulcers
	Glossitis
	Angular stomatitis
Scurvy	Gingival swelling
	Purpura
	Ulcers
Rickets (vitamin D dependent)	Dental hypoplasia
	Large pulp chambers
	Large tooth eruption

Table 66.34 Collagen–vascular diseases.

Disease	Oral manifestations
Any collagen–vascular disease	Sjögren's syndrome
Rheumatoid arthritis	Temporomandibular arthritis
	Drug reaction (e.g. lichenoid)
	Ulcers in Felty's syndrome
	Temporomandibular ankylosis in juvenile arthritides
Lupus erythematosus	White lesions
	Ulcers
Systemic sclerosis	Stiffness of lips, tongue, etc.
	Trismus
	Telangiectasia
	Mandibular condylar resorption
	Periodontal ligament widened on X-ray

Treatment is by application of petroleum jelly and avoidance of the adverse environmental conditions.

Eczematous cheilitis

The lips are often involved secondarily to atopic eczema (see Chapter 18). The treatment is with emollients and topical corticosteroids. A potent steroid such as fludrocortisone may be required to bring the condition under control.

Contact cheilitis

Contact cheilitis is an inflammatory reaction provoked by the irritant or sensitizing action of chemicals. Many cases are caused by lipsticks or lipsalves but a large number of substances have been incriminated.

Lipsticks and lipsalves (Table 66.40). Lipsticks are composed of mineral oils and wax (which form the stick), castor oil as a solvent for the dyes, lanolin as an emollient, preservatives, perfumes and colours [1]. The dyes may include azo dyes and eosin, a bromofluorescein derivative. An eosin

Table 66.35 Miscellaneous disorders.

Disease	Oral manifestations
Sarcoidosis	Xerostomia Salivary gland swelling Heerfordt's syndrome (parotid swelling, lacrimal swelling, facial palsy) Gingival swelling
Behçet's syndrome	Ulcers like aphthae
Sweet's syndrome	Ulcers like aphthae
Reiter's syndrome	Ulcers
Langerhans' cell histiocytosis	Loosening of teeth Jaw radiolucencies
Wegener's granulomatosis	Gingival swellings Ulcers
Kawasaki disease (mucocutaneous lymph node syndrome)	Sore tongue Cheilitis
Ellis–van Creveld syndrome (chondroectodermal dysplasia)	Multiple fraena Short roots Hypodontia
Tuberous sclerosis	Enamel defects Gingival fibromatosis

Table 66.36 Other infections.

Disease	Oral manifestations
Syphilis	Chancre Mucous patches Ulcers Gumma Pain from neurosyphilis Leukoplakia Lymph node enlargement Hutchinson's teeth in congenital syphilis
Gonorrhoea	Pharyngitis (occasionally) Gingivitis (occasionally) Temporomandibular arthritis (rarely)
Tuberculosis (including atypical mycobacteria)	Ulcers (rarely)
Leprosy	Cranial nerve palsies (rarely)
Lyme disease	Facial palsy
Candidiasis	White lesions Red lesions Angular stomatitis
Cryptococcosis	Ulcers
Coccidioidomycosis	Ulcers
Histoplasmosis	Ulcers (especially in immune defects)
Blastomycosis	Ulcers
Paracoccidioidomycosis	Ulcers
Mucormycosis, aspergillosis	Antral infections or ulcers (especially in immune defects)

Table 66.37 Viral infections.

Disease	Oral manifestations
Herpes simplex	Ulcers in primary infection Gingivitis in primary infection Vesicles on lips in recurrence (rarely oral ulcers)
Herpes zoster–varicella	Ulcers in chickenpox, or in zoster of maxillary or mandibular divisions of the trigeminal nerve Pain in maxillary or mandibular zoster
Coxsackieviruses and echoviruses	Ulcers in herpangina and hand, foot and mouth disease
Epstein–Barr virus (in infectious mononucleosis)	Sore throat Tonsillar exudate Palatal petechiae Recurrent parotitis (possibly) Hairy leukoplakia
Measles	Koplik's spots
Mumps	Salivary gland swelling
Papillomaviruses	Warts Papillomas Focal epithelial hyperplasia
Human immunodeficiency virus	
Common	Candidiasis Hairy leukoplakia Gingival and periodontal disease Herpes simplex infection Herpes zoster infection Papillomavirus infection Kaposi's sarcoma Aphthous-like ulcers Xerostomia
Uncommon	Infections *Cryptococcus* Mycobacteria *Histoplasma* Cytomegalovirus Others Salivary gland swelling Sjögren's syndrome-like disease Cranial neuropathies Fetal AIDS syndrome

impurity used to be an important sensitizer [2] but is now rarely if ever used. Other ingredients occasionally incriminated include azo dyes, carmine, oleyl alcohol [3], lanolin, perfumes, azulene, propyl gallate, sesame oil [4], stearates [5], shellac and colophony [6]. Sunscreens in lipstick or lipsalve (e.g. cinnamic aldehyde) can also cause contact cheilitis [7]. Phenyl salicylate and antibiotics have also been incriminated [8,9]. Petrolatum chapsticks may cause an unusual form of acne with a single row of large open comedones along the cutaneous margin of the upper lip [10].

Mouthwashes and dentrifices [11]. Sensitizers used in some toothpastes include essential oils, such as peppermint, cinnamon, clove and spearmint; carvone along with imonene, pinene, phellandrene, dipentene, cineole, linalool, and esters of dihydrocuminyl alcohol and dehydrocarveol; bactericidal agents; propolis, derived from resin collected by bees [12,13]; and tartar-control dentifrices, which contain pyrophosphate compounds [14].

Table 66.38 Neurological disorders.

Disease	Oral manifestations
Facial palsy of any cause	Palsy and poor natural cleansing of mouth on same side
Trigeminal neuralgia	Pain
Bulbar palsy	Fasciculation of tongue
Parkinsonism	Drooling
	Tremor of tongue
	Dysarthria
Neurosyphilis	Pain (rarely)
	Dysarthria
	Tremor of tongue
Cerebral palsy	Spastic tongue
	Dysarthria
	Attrition
	Periodontal disease
Choreoathetosis	Green staining of teeth in kernicterus
	Hypoplasia of deciduous dentition in congenital rubella
Epilepsy	Trauma to teeth/jaws/mucosa
	Gingival hyperplasia if taking phenytoin
Down's syndrome	Delayed tooth eruption
	Macroglossia
	Scrotal tongue
	Maxillary hypoplasia
	Anterior open bite
	Hypodontia
	Periodontal disease
	Cleft lip or palate in some

Table 66.39 Causes of cheilitis.

Chapping due to cold and wind
Eczematous cheilitis
Contact cheilitis
Drug-induced cheilitis
Infective cheilitis
Angular cheilitis
Ultraviolet irradiation
Actinic cheilitis
Actinic prurigo of the lip
Glandular cheilitis
Granulomatous cheilitis
Exfoliative (factitious) cheilitis
Plasma cell cheilitis
Nutritional cheilitis
Dermatoses
Trauma

Table 66.40 Possible allergens in lipsticks and lipsalves.

Azo dyes
Azulene
Benzoic acid
Carmine
Castor oil
Cinnamon
Colophony
Eosin
Ester gum
Eusolex
Lanolin
Oleyl alcohol
Oxybenzone *p*-tertiary-butylphenol
Phenyl salicylate
Propolis
Propyl gallate
Ricinoleic acid
Salol
Sesame oil
Shellac
Vanilla
Wax

Table 66.41 Possible fruit and vegetable allergens.

Apple
Artichoke
Asparagus
Banana
Carrot
Celery
Cherry
Fennel
Garlic
Kiwi fruit
Lemon
Lime
Mango
Onion
Orange
Parsley
Parsnip
Peach
Pear
Pineapple
Plum
Potato
Tomato

Dental preparations. Mercury, eugenol, and plastics including epimine-containing materials can cause cheilitis [15–17].

Foods (Table 66.41). Peppermint, carvone, spearmint [18], citrus fruits [19], artichokes [20], nuts [21], pineapple [22], mangoes [23–25], asparagus [26] and cinnamon oil [27,28] occasionally cause allergic cheilitis and perioral dermatitis. The oil on the peel of citrus fruits is irritant to the skin; in addition, some sweet oranges contain a weakly phototoxic agent that can cause a reaction in pale-skinned people [29].

Miscellaneous objects. Metal hair clips, metal pencils, the cobalt paint on blue pencils [30], nail varnish [31], and the metal, wooden, nickel and reed mouthpieces of musical instruments [32–34] may cause cheilitis.

Clinical features. Lipstick cheilitis is sometimes confined to the vermilion but more often extends beyond. There

may be persistent irritation and scaling or a more acute reaction with oedema and vesiculation.

The other forms of cheilitis vary greatly in their clinical appearance. Those caused by foods commonly also involve the skin around the mouth. If a small, sucked object is responsible, the reaction may be confined to one part of the lips.

Diagnosis. If acute eczematous changes are obviously present, the diagnosis of contact cheilitis presents no difficulty. If the changes are confined to irritation and scaling, the various forms of exfoliative cheilitis must be excluded.

If an allergic reaction is suspected, patch tests should be carried out.

Treatment. Topical corticosteroids will give symptomatic relief but the offending substance must be identified and avoided.

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Drug-induced cheilitis

Haemorrhagic crusting of the lips (Fig. 66.71) is a feature of erythema multiforme (particularly in Stevens–Johnson syndrome) (see p. 66.67), but cheilitis can also occur as an isolated feature of a drug reaction.

Aromatic retinoids such as etretinate and isotretinoin cause cheilitis, dryness and cracking of the lips in many patients.

Infective cheilitis

Viral. Rare viral infections such as orf [1,2] and vaccinia [3] can affect the lips.

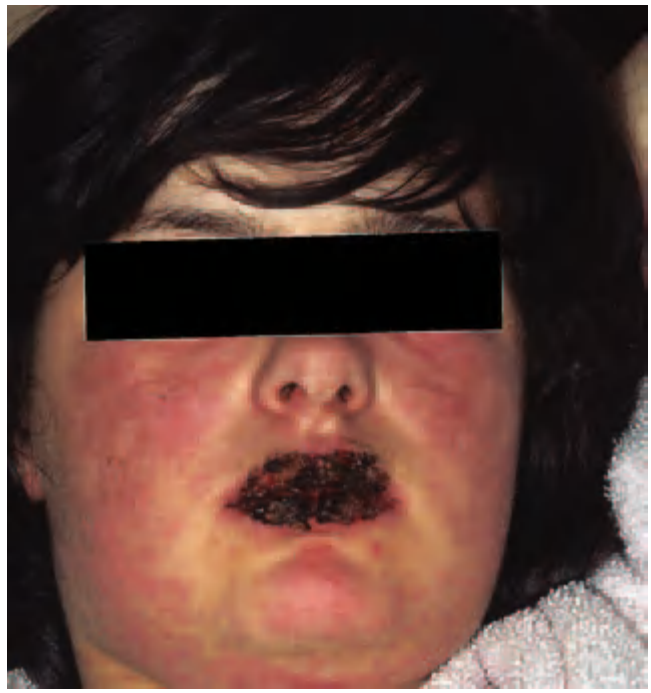

Fig. 66.71 Haemorrhagic crusting of the lips in Stevens–Johnson syndrome.

Bacterial. Dental infection or occasionally a furuncle or carbuncle may cause swelling of the lip. Impetigo may mimic herpes labialis (see Chapter 27). Cancrum oris (fusospirochaetal infection) may cause labial and buccal necrosis [4,5].

The lip is the most common extragenital site for a primary syphilitic lesion. Most lip chancres in males tend to occur on the upper lip, in females on the lower lip. In secondary syphilis, moist, flat, papulonodular lesions (condylomata lata) often appear at the mucocutaneous junctions and on mucosal surfaces especially at the commissures [6]. The tropical treponematoses may present similarly to syphilis.

Rhinoscleroma initially affects the nasal mucosa but may spread slowly to the upper lip, producing plaques or nodules with sunken centres. The extreme hardness of the infiltrations is characteristic. The lip can appear to fuse to the alveolar process but the overlying skin and mucosa remain normal.

Protozoal. Cutaneous or mucocutaneous leishmaniasis typically causes swellings on the upper lip with later enlargement and destruction of the lip [7–10], reflecting the three stages of oedema, granulomatous proliferation and then necrosis.

Fungal. Blastomycosis and paracoccidioidomycosis are uncommon causes of chronic ulceration affecting the lip, producing very similar clinical lesions to leishmaniasis [11].

Others. Red swollen lips with fissuring and exfoliation are prominent in mucocutaneous lymph node syndrome (Kawasaki disease).

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Angular cheilitis

SYN. ANGULAR STOMATITIS

Angular cheilitis is an acute or chronic inflammation of the skin and contiguous labial mucous membrane at the angles of the mouth [1].

Aetiology. Most cases in adults are due to mechanical and/or infective causes, but in children nutritional or immune defects are more prominent causes.

Infective agents. These are the major cause. *Candida* or staphylococci are isolated from most patients [2–4]. Permanent cure can be achieved only by eliminating the *Candida* beneath the upper denture [5]. Candidiasis was probably responsible for some of the cases of cheilitis attributed to allergy to denture materials, since contamination of denture material by *Candida* may cause false-positive patch-test reactions [6].

Immune deficiency, such as diabetes and HIV infection, may present with angular stomatitis. Outbreaks of acute pustular and fissured cheilitis may occur in children, particularly if they are malnourished, and in some cases streptococci or staphylococci have appeared to be causative [7].

Mechanical factors in edentulous patients who do not wear a denture or who have inadequate dentures, and also as a normal consequence of the ageing process, produce an oblique curved fold and keep the small area of skin constantly macerated. The recurrent trauma of dental flossing is a very rare cause of angular cheilitis [8].

Nutritional deficiencies, particularly deficiencies of riboflavin, folate, iron and general protein malnutrition, may produce smooth, shiny, red lips associated with angular stomatitis, a combination called *cheilosis* [1,9–11]. Crohn's disease or orofacial granulomatosis may be found in some [12].

Clinical features. Angular cheilitis presents as a roughly triangular area of erythema and oedema at one, or more commonly both, angles of the mouth (Fig. 66.72). Linear furrows or fissures radiating from the angle of the mouth (rhagades) are seen in the more severe forms, especially in denture wearers.

Diagnosis. This is usually obvious. *Candida* should be sought not only in the lesions but also beneath the denture.

Treatment. Dentures should be removed from the mouth at night and stored in a candidacidal solution such as hypochlorite. Denture-related stomatitis should be treated with an antifungal. Miconazole may be preferable

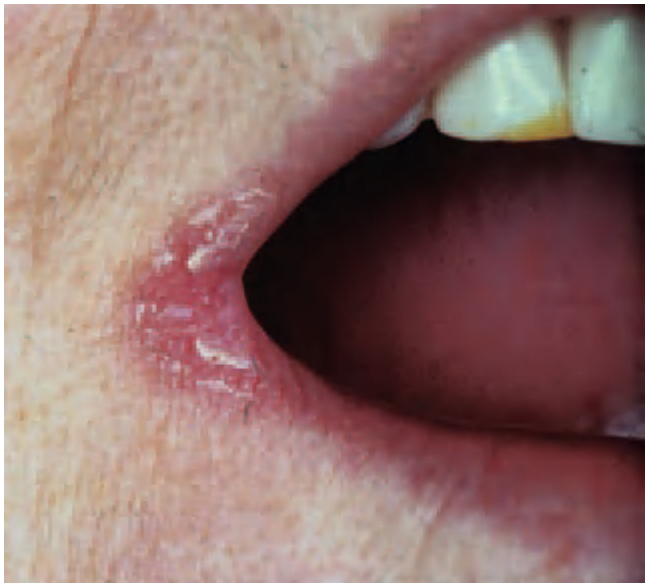

Fig. 66.72 Angular cheilitis.

treatment for candidiasis (cream applied locally, together with the oral gel) as it has some Gram-positive bacteriostatic action. New dentures that restore facial contour may help. The skin lesions should be swabbed and staphylococcal infection treated with fusidic acid ointment or cream at least four times daily.

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Actinic cheilitis

SYN. ACTINIC KERATOSIS OF LIP; SOLAR CHEILOSIS

This is a premalignant keratosis of the lip caused by exposure to solar irradiation.

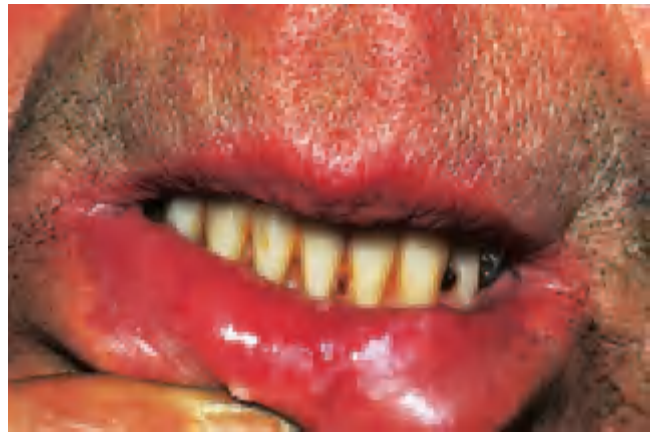

Fig. 66.73 Chronic actinic cheilitis with leukoplakia. (Courtesy of Addenbrooke's Hospital, Cambridge, UK.)

Aetiology. Actinic cheilitis is most common in hot dry regions, in outdoor workers and in fair-skinned people (skin types I and II). The vermilion of the lower lip receives a high dose of UV irradiation because it is almost at right angles to the rays of the midday sun and is poorly protected by keratin and melanocytes. Most actinic cheilitis is seen on the lower lip of fair-skinned men in their fourth to eighth decade of life.

Pathology. Histology shows a flattened or atrophic epithelium, beneath which is a band of inflammatory infiltrate in which plasma cells may predominate [1]. Nuclear atypia and abnormal mitoses may be seen in the more severe cases, and some develop into invasive squamous carcinoma [2]. The collagen generally shows basophilic (elastotic) degeneration [3].

Clinical features (Fig. 66.73). Actinic cheilitis tends to affect the lower lip of adults who have had prolonged exposure to sunlight [4]. In the early stages there may be redness and oedema, but later the lips become dry and scaly. Later still, the epithelium becomes palpably thickened with small greyish-white plaques and, eventually, warty nodules may form. Eventually these may undergo malignant change, the possibility of which must always be considered when ulceration develops or when there are other suspect features such as:

- a red and white, blotchy appearance with an indistinct vermilion border;
- generalized atrophy with focal areas of whitish thickening;
- persistent flaking and crusting [5,6].

Diagnosis. This is clinical.

Treatment. Treatment of actinic cheilitis is required to relieve symptoms and to prevent development of squamous carcinoma.

• Topical agents: 5% fluorouracil three times daily for 10 days is suitable [7]. Topical tretinoin [8] or trichloracetic acid [9] may also be effective.
• Vermilionectomy (lip shave) [10–12].
• Laser ablation [13–16].

Following treatment, prevention of recurrence by the regular use of a sunscreen lipsalve containing *p*-aminobenzoic acid probably gives the best protection [17,18].

Particular care should be taken to protect the vermilion of the lips with adequate sunscreens in patients with photosensitivity disorders, such as xeroderma pigmentosum, and in those whose exposure to UVB is high, such as mountaineers, windsurfers and skiers.

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Actinic prurigo (see Chapter 24)

Actinic prurigo is a type of familial photodermatitis, seen mainly in native Americans living at high altitudes [1,2] especially in Latin America, and in China [3]. It usually presents in young women as a photosensitive facial rash with pruritic lower lip cheilitis, and it may be associated with conjunctivitis, eyebrow alopecia and pterygia.

Actinic prurigo is due to enhanced sensitivity to sunlight and is distinguished from actinic cheilitis, which is due to prolonged and excessive exposure to UV irradiation, by the relative absence of epidermal dysplasia and solar elastosis [4]. Polymorphous light eruption is almost invariably present in the actinic prurigo of native Americans [5,6].

Treatment is with sunscreens, β-carotene, psoralen and UVA (PUVA), and antihistamines. Oral thalidomide may be tried [7].

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Glandular cheilitis

Definition. Glandular cheilitis is characterized by inflammatory changes and swelling of salivary glands in the lips [1–3].

Aetiology. This is an uncommon idiopathic condition which in a few cases has apparently been familial [4]. Although it was originally thought that the condition was due to inflammation of enlarged heterotopic salivary glands, the glands are often normal in size, depth and histology [5]. It is possible that the excessive salivary secretion from minor salivary glands in this condition might be an unusual clinical response to irritation of the lip from some other cause such as actinic damage or repeated licking.

Pathology. In the milder forms there is some fibrosis surrounding the salivary glands, while in the more severe forms there may be a dense chronic inflammatory infiltrate. Only rarely do patients show genuine hyperplasia of the salivary glands or duct ectasia.

Clinical features. The onset is at any age from childhood onwards. In simple glandular cheilitis, the lower lip is slightly thickened and bears numerous pinhead-sized orifices, from which mucous saliva can readily be squeezed. The upper lip is rarely involved [6].

In the more severe suppurative form (*Volkmann's cheilitis*) the lip is considerably and permanently enlarged, and subject to episodes of pain, tenderness and increased

enlargement. The surface is covered by crusts and scales, beneath which the salivary duct orifices may be discovered. In the most severe forms there may be deep-seated infection with abscess formation and fistulous tracts.

The condition can evidently be premalignant; in some series 20–30% of cases progress to squamous cancer. This does, of course, support the suggestion that in many cases glandular cheilitis is a consequence of actinic cheilitis [5].

Treatment. Actinic cheilitis, if identified, should be treated appropriately. If the lips are grossly enlarged, excision of an elongated ellipse of tissue may be required; in other cases shave vermilionectomy may be all that is necessary. Other conditions such as atopic disease or factitial cheilitis would require different treatment.

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Granulomatous cheilitis

SYN. MIESCHER'S CHEILITIS

Definition. A chronic swelling of the lip due to granulomatous inflammation of unknown cause.

Nomenclature. Melkersson in 1928 [1] described labial oedema in association with recurrent facial palsy. Rosenthal in 1930 emphasized the role of genetic factors and added scrotal tongue to the syndrome. The full syndrome has since been called Melkersson–Rosenthal syndrome [2].

In Miescher's cheilitis the granulomatous changes are confined to the lip, and this is generally regarded as a monosymptomatic form of Melkersson–Rosenthal syndrome, although the possibility remains that these may be two separate diseases.

Aetiology. The cause is unknown, but there may be a genetic predisposition to Melkersson–Rosenthal syndrome [3]; siblings have been affected and a scrotal tongue may be present in otherwise normal relatives.

There is no convincing evidence that granulomatous cheilitis is due to an infective agent. Some cases may represent a localized form of sarcoidosis [4] or ectopic Crohn's disease [5,6] or orofacial granulomatosis. There is increasing evidence that some patients with granulomatous cheilitis are predisposed to Crohn's disease [6]. In some cases, granulomatous cheilitis is followed some years later by regional ileitis [7–10]. A few patients react to cobalt [11] or to food additives such as cinnamic aldehyde [12–14] and have no extra oral lesions, although these reactions are by no means always relevant; for example, in one study only one of nine patients had a relationship between cheilitis and food intake [15].

Pathology. Biopsy of the swollen lip or facial tissues during the early stages of the disease shows only oedema and perivascular lymphocytic infiltration. In some cases of long duration no other changes are seen, but in others the infiltrate becomes more dense and pleomorphic and small focal granulomas are formed, indistinguishable from sarcoidosis or Crohn's disease. Similar changes may be present in cervical lymph nodes [16–19]. In some cases, small granulomas occur in the lymphatic walls [20].

Clinical features. The condition affects the sexes equally. The earliest manifestations usually develop in childhood or adolescence but may be delayed until middle or old age. The earliest cutaneous manifestation is sudden diffuse or nodular swellings [21] involving the upper lip, the lower lip and one or both cheeks in decreasing order of frequency [5,19]. Labial swelling occurs in about 75% and facial swelling in 50% of patients [22]. Less commonly, the forehead, eyelids or one side of the scalp may be involved. The attacks are sometimes accompanied by fever and mild constitutional symptoms, including headache and even visual disturbance. At the first episode the oedema typically subsides completely in hours or days, but after recurrent attacks the swelling may persist, and slowly increases in degree (Fig. 66.74). It gradually becomes firmer and eventually acquires the consistency of firm rubber. After some years, the swelling may very slowly regress.

A fissured or scrotal tongue is seen in 20–40% of cases. It is present from birth in some, which may indicate genetic susceptibility. There may be loss of sense of taste and decreased salivary gland secretion [19].

The regional lymph nodes are enlarged in 50% of cases [3] but not usually very greatly.

Facial palsy of the lower motor neurone type occurs in some 30% of cases. It may precede the attacks of oedema by months or years, but more commonly develops later. Although intermittent at first, the palsy may become permanent. It may be unilateral or bilateral, and partial or complete [19]. Other cranial nerves (olfactory, auditory, glossopharyngeal and hypoglossal) may occasionally be involved. Involvement of the CNS has also been reported, but the significance of the resulting symptoms is easily overlooked as they are very variable, sometimes simulating disseminated sclerosis but often with a poorly defined association of psychotic and neurological features. Autonomic disturbances may occur.

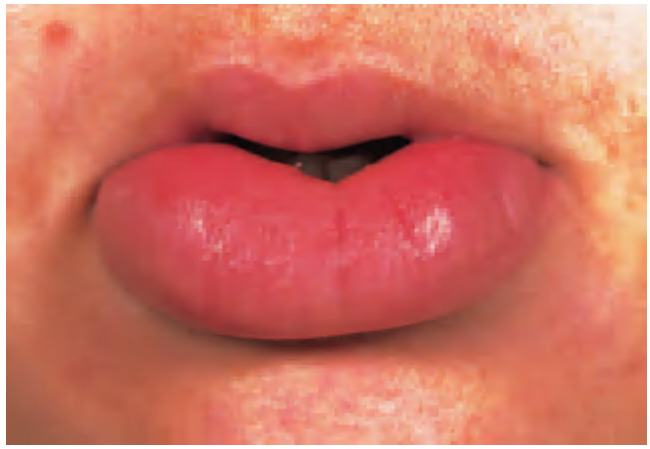
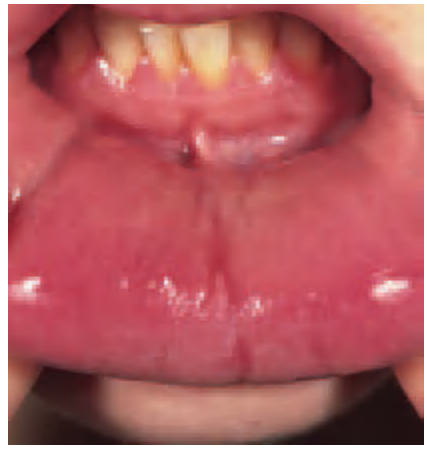
(a)   (b)

Fig. 66.74 Granulomatous cheilitis of the lower lip. (Courtesy of Addenbrooke's Hospital, Cambridge, UK.)

Diagnosis. The essential feature of the syndrome is the granulomatous swelling of lip or face. In the early attacks clinical differentiation from angio-oedema may be impossible in the absence of either scrotal tongue or facial palsy. Persistence of the swelling between attacks should suggest the diagnosis, which can sometimes be confirmed by biopsy. However, the histological changes are not always conspicuous or specific.

In established cases, other causes of macrocheilia (Table 66.42) must be excluded. Ascher's syndrome associated with blepharochalasia is likely to cause confusion, although the swelling of the lip is caused by redundant salivary tissue and is present from childhood. Lymphoma is a rare differential diagnosis [23].

Treatment. Reactions to dietary components should be sought and possible antigens avoided. The injection of up to 10 mL triamcinolone (10 mg/L) into the lips after local analgesia may be effective [15,24,25]. The injections may have to be repeated every 4–6 months once a response plateau has been reached. This treatment has also been successfully combined with surgical reduction (cheiloplasty) [26,27]. The injections must be continued periodically after the surgery or there may be an exaggerated recurrence of the condition. Surgery alone is relatively unsuccessful [28].

Systemic corticosteroids are rarely indicated [29]. Not all respond [27,30] and adverse effects may be a problem. Clofazimine appears to help the majority of patients [31,32], in a dose of 100 mg twice daily for 10 days, then twice weekly for 4 months. Metronidazole may also produce resolution in granulomatous cheilitis [33,34].

Other treatments which have occasionally been helpful include long-term penicillin, erythromycin, sulfasalazine (sulphasalazine) or ketotifen.

Table 66.42 Macrocheilia: acute or chronic enlargement of one or both lips.

Acute	Chronic
Traumatic	Developmental
Infective	Familial idiopathic
Pyococcal	Double lip
Anthrax	Ascher's syndrome
Diphtheria	Lymphangioma
Primary syphilis	Haemangioma
Trichophytosis	Neurofibroma
Leishmaniasis	Mucopolysaccharidoses
Herpes simplex	Fucosidosis
Trichiniasis	Coffin–Siris syndrome
Angio-oedema	Acquired
Erythema multiforme	Post-traumatic
Actinic cheilitis	Post-infective on basis of developmental
Other forms of cheilitis	lymphatic defect
	Infective
	Tuberculosis
	Leprosy
	Rhinoscleroma
	Leishmaniasis
	Neoplastic
	Melkersson–Rosenthal syndrome
	Cheilitis glandularis
	Sarcoidosis
	Crohn's disease
	Orofacial granulomatosis

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Exfoliative cheilitis

SYN. FACTITIOUS CHEILITIS; LE TIC DE LÈVRES

Exfoliative cheilitis is a chronic superficial inflammatory disorder of the vermilion borders of the lips characterized by persistent scaling (Fig. 66.75). The diagnosis is now restricted to those few patients whose lesions cannot be attributed to other causes, such as contact sensitization or light (see actinic cheilitis, p. 66.115). Many of these cases are now thought to be factitious, owing to repeated lip sucking, chewing or other manipulation of the lips [1,2]. There is no association with dermatological or systemic disease, although rare cases are seen in HIV infection. Some are infected with *Candida* species [3].

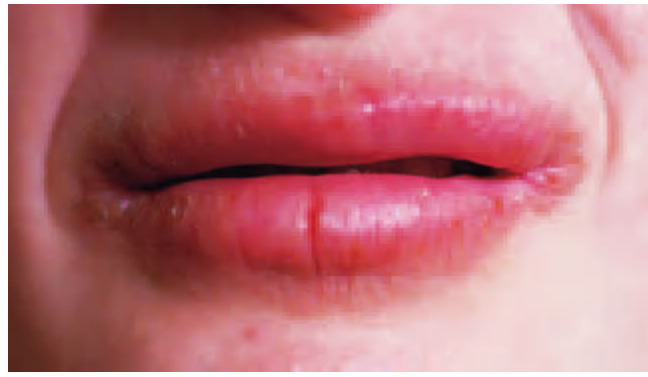

Fig. 66.75 Factitious cheilitis due to repeated lip sucking.

Most cases occur in girls or young women, and the majority have a personality disorder [4,5]. The process, which often starts in the middle of the lower lip and spreads to involve the whole of the lower or both lips, consists of scaling and crusting, more or less confined to the vermilion border, and persisting in varying severity for months or years. The patient often complains of irritation or burning, and can be observed frequently biting or sucking the lips. In some cases the condition appears to start with chapping or with atopic eczema, and develops into a habit tic.

In a large Russian series, almost half the cases had associated thyroid disease [6], but this observation has not been confirmed.

Diagnosis. Contact and active cheilitis must be carefully excluded. Chronic exfoliative cheilitis is readily contaminated by *Candida*. In such cases the clinical features are variable and may simulate carcinoma, LP or lupus erythematosus.

Treatment. Some cases resolve spontaneously [2,7] or with improved oral hygiene [8]. Reassurance and topical corticosteroids may be helpful in some cases [1], but others require psychotherapy or tranquillizers [7,9].

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Plasma cell cheilitis

SYN. PLASMA CELL ORIFICIAL MUCOSITIS

Plasma cell cheilitis is an idiopathic benign inflammatory condition, characterized by dense plasma cell infiltrates in the lips and other mucosae close to body orifices [1–3]. The condition has been reported (under a wide variety of names) to affect the penis, vulva, lips, buccal mucosa, palate, gingiva, tongue, epiglottis and larynx.

Plasma cell cheilitis is the counterpart of Zoon's plasma cell balanitis (see Chapter 68). It presents as circumscribed flat or elevated patches of erythema, usually on the lower lip in an elderly person. The cause is unknown, but it responds to the application of powerful topical corticosteroids such as clobetasol, or to the intradermal injection of triamcinolone [4], or to systemic griseofulvin [5].

A similar lesion, which tends to form a tumorous mass with a hyperkeratotic surface and needs to be differentiated from extramedullary plasmacytoma [6], has been called *plasma-acanthoma* [7,8].

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Lupus erythematosus

Involvement of the vermilion zone is quite common in both discoid erythematosus and SLE [1]. Discoid lupus can be premalignant, and should be treated vigorously with topical steroid ointments and sunscreens [2,3]. The cheilitis of SLE tends to be more severe, with erosions and haemorrhagic crusts.

Lupus erythematosus can be very difficult to distinguish from LP of the lips, both clinically and by histology (Fig. 66.76).

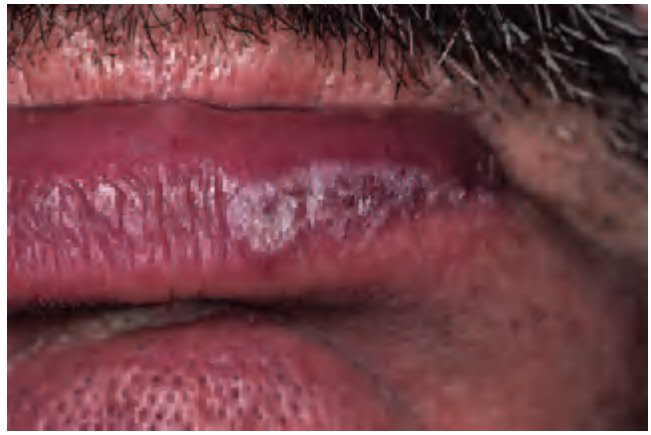

Fig. 66.76 Discoid lupus erythematosus of the lower lip.

REFERENCES

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Sarcoidosis (see Chapter 58)

Sarcoidosis may cause chronic violaceous lesions on, or swelling of, the lips [1].

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Lip fissure

A lip fissure may develop when a patient, typically a child, is mouth-breathing (Fig. 66.77). Otherwise the aetiology may be obscure, though sun, wind, cold weather and smoking are thought to predispose. A hereditary predisposition for weakness in the first branchial arch fusion seems to exist.

Lip fissures are common in Down's syndrome and the lips may also crack in this way if swollen, for example in cheilitis granulomatosa [1–4].

Clinical features. Most lip fissures are seen in males, typically median in the lower lip and chronic, causing discomfort and possibly bleeding from time to time. Contrary to the clinical impression that fissures are seen only in the lower lip, there is also a high prevalence in the upper lip.

Diagnosis. The diagnosis is clinical.

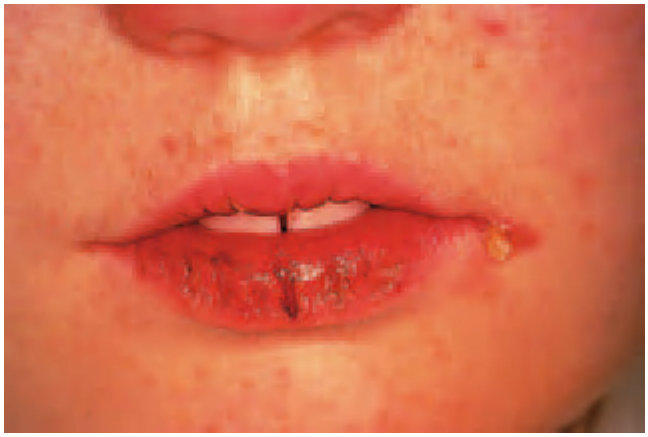

Fig. 66.77 Lip fissure.

Management. Predisposing factors should be managed. Bland creams may help the lesion heal spontaneously. Otherwise, local applications of 1–2% silver nitrate, 0.5% balsam of Peru, salicylic acid and topical antimicrobials seem less effective than excision, preferably with a Z-plasty [5–7] or cryosurgery [8].

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Lip ulcer due to calibre-persistent artery

A calibre-persistent artery is defined as an artery with a diameter larger than normal near a mucosal or external surface. When such arteries occur in the gut wall (Dieulafoy malformation) they may bleed, but in the lip they tend to cause chronic ulceration that can be mistaken for a squamous cancer. The ulcer is attributed to continual pulsation from the large artery running parallel to the surface, although the exact mechanism is obscure [1,2].

Ligation of the artery appears successful [3].

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Reactive perforating collagenosis (see Chapter 46)

Crateriform papules of the lower lip have been reported in reactive perforating collagenosis [1].

REFERENCE

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Chapter 67

The Breast

D.A. Burns

The terms 'breasts' and 'mammary glands' are often accepted as equivalent, but they are not strictly synonymous, because the breasts contain tissues (fat, vessels, nerves, etc.) other than the glandular elements.

In the evolutionary sense, the mammary glands are believed to be related to the apocrine sweat glands. They develop from ectodermal mammary ridges ('milk lines'). The classical view, derived from comparative anatomy, that the mammary ridges extend from the base of the upper limb bud to the base of the lower limb bud, is now questioned. It is considered that the mammary ridge extends only over the axillopectoral area [1].

The skin of the breast does not differ structurally from that of the neighbouring chest wall, but the skin of the nipple and areola is very highly specialized. There are individual and racial variations in the size, shape and colour of the nipple and areola. The periphery of the areola contains hair follicles, and the development of coarse terminal hairs in this site may be a cosmetic problem for some women.

The nipple is glabrous. Lactiferous ducts and sebaceous glands open only at its tip. Sensory nerve end organs are also confined to the tip of the nipple. The areola has clusters of large sebaceous glands [2] and the so-called tubercles of Montgomery. These elevations on the areola are produced by the glands of Montgomery [3]. Each of these is a combined sebaceous unit and lactiferous gland, with the lactiferous duct opening into the sebaceous duct close to the areola or occasionally directly onto the areola [1]. The glands of Montgomery are an integral part of the lactiferous apparatus, secreting milk during lactation.

The development of the breasts at puberty requires oestrogens and progesterone, and, in a more minor role, insulin, growth hormone, corticosteroids and prolactin. The adult breast consists of several lobes, each of which is drained by a ductal system ending in a lactiferous duct which opens at the nipple. Each lobe contains up to 40 lobules, and each lobule 10–100 alveoli, the basic secretory units [1].

The breasts enlarge during pregnancy, and the veins become prominent. The areolae also enlarge and become darker. This pigmentation decreases after parturition but does not fade completely.

Although most of the more serious diseases of the breast come within the province of the surgeon, the gynaecologist or the endocrinologist, there are some diseases which affect only the breast skin and are wholly the concern of the dermatologist, and others which may involve the skin and present difficult problems in differential diagnosis.

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Supernumerary breasts or nipples [1,2]

Supernumerary (accessory) breasts (polymastia) and the far more common supernumerary nipples (polythelia) usually develop along the course of the milk lines. Accessory glandular tissue most frequently occurs in the axillae [3], but rarely breast components occur in other sites [4–6].

Accessory breast tissue may consist of nipple, areola or glandular tissue singly, or in any combination (Fig. 67.1). The condition is very common in women, with an incidence of around 2–4%, although in the majority of cases the accessory nipple is insignificant, appearing as a small brown papule, usually on the chest wall, just below the breast. Much more rarely, the condition occurs in men, and in one case a fully developed breast was located on the posterior aspect of the thigh of a male [7]. A familial incidence is sometimes noted [8,9].

Polythelia has been found in association with various rare genodermatoses [10–17]. A suggested association between the presence of supernumerary nipples and urinary tract anomalies in children [18–20] prompted debate about whether to investigate the renal tract in children with supernumerary nipples and no other obvious anomaly [21,22]. However, more recent publications have not demonstrated an association between supernumerary nipples and urinary tract malformations [23,24].

The Simpson–Golabi–Behmel syndrome is an X-linked overgrowth syndrome caused by deletions in glypican 3. It is characterized by a specific facial appearance, supernumerary nipples, polydactyly, midline defects and mild mental retardation [25].

An accessory nipple is usually recognized if the diagnosis is considered, but is often otherwise confused with a pigmented naevus. If functional breast tissue is present, enlargement at puberty or in pregnancy may be embarrassing or painful. Simple excision is advisable, as carcinoma may occur.

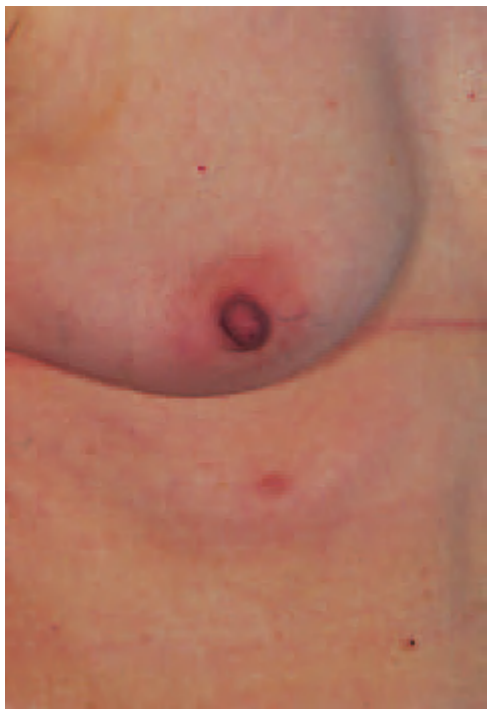

Fig. 67.1 Supernumerary nipple and breast tissue.

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Breast hypertrophy

Unusually large breasts may be problematic for a number of reasons, and postural abnormalities, backache and psychological disturbance may prompt referral to a plastic surgeon for a reduction mammaplasty. A dermatologist may be consulted about associated problems such as submammary intertrigo.

Breast enlargement in the setting of human immunodeficiency virus (HIV) infection is a relatively recently described phenomenon. It may be a component of the lipodystrophy syndrome (lipomastia), or there may be true gynaecomastia (see below). Breast ultrasonography allows these two states to be differentiated [1].

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Gigantomastia (macromastia)

Gigantomastia is a condition in which the female breasts enlarge rapidly until they reach a tremendous size. The overlying skin may become inflamed, oedematous and tender, and there may be striae or even severe ulceration [1]. The condition may occur at puberty [2–4] or during pregnancy [1,5]. The aetiology is obscure, but a suggested cause is increased sensitivity of the breast tissue to normal levels of circulating hormones.

The condition is occasionally familial [6].

Penicillamine therapy can also cause gigantomastia [7,8].

Bromocriptine may be of benefit in patients in whom the condition occurs during pregnancy, but in many patients, and certainly in pubertal cases, reduction mammaplasty is usually required.

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Gynaecomastia [1–4]

Gynaecomastia, which may be defined as benign enlargement of the male breast caused by proliferation of the glandular components, can occur as an isolated defect or as a manifestation of a wide range of different pathological states in which it may be a valuable diagnostic sign. The multiplicity of syndromes associated with gynaecomastia reflects the complexity of the hormonal mechanisms concerned in breast enlargement. The patient complains of enlargement of the breast, which may be unilateral or bilateral, and is often tender.

Gynaecomastia can be distinguished from fatty enlargement of the breast in obesity (pseudogynaecomastia) by grasping the breast between thumb and forefinger and moving the digits up towards the nipple with the patient supine. In gynaecomastia a rubbery, mobile, disc-like mound will be felt beneath the areola.

Oestrogens stimulate and androgens inhibit development of breast tissue, and gynaecomastia occurs as a result of a disturbance of the ratio of free androgen to free oestrogen, with a relative increase in oestrogen levels. Peripheral conversion of androgens to oestrogen by aromatization contributes to oestrogen production. Local susceptibility of hormone receptors or local hormone conversion presumably play a role in unilateral gynaecomastia.

The histopathological changes [5] are related to the duration of gynaecomastia and not to its cause. At early stages, there are active proliferating ducts in a vascular fibroblastic stroma. Later, there is progressive fibrosis and hyalinization, and the number of ducts is reduced.

Gynaecomastia may be either physiological or pathological. Some of the causes are listed in Table 67.1.

Physiological gynaecomastia

There are three peaks in the age distribution of physiological gynaecomastia. It occurs in most male neonates due to transplacental passage of oestrogen from the mother. It is usually bilateral, but may be unilateral, and it regresses spontaneously. Some enlargement of the breast occurs at puberty in about 38% of normal boys [6]. The peak incidence is around the age of 14 years. It is unilateral in about 25% of cases. The degree of enlargement is usually slight, but may be sufficient to cause embarrassment and

Table 67.1 Causes of gynaecomastia.

Physiological
Neonatal
Adolescent
Old age
Endocrine disorders
Hypogonadism, e.g. Klinefelter's syndrome
Excess oestrogen or chorionic gonadotrophin, e.g. from testicular tumour
Hyperthyroidism
Other diseases
Starvation, cachexia or refeeding
Renal disease and haemodialysis
Liver disease
Paraplegia
Erythroderma
Idiopathic
Drugs (see Table 67.2)

Table 67.2 Drugs which may produce gynaecomastia.

Amiloride
Anabolic steroids
Antiandrogens, e.g. cyproterone acetate
Amiodarone
Amphetamines
Androgens
Busulphan
Cannabis
Captopril
Chorionic gonadotrophin
Cimetidine
Cytotoxic agents
Diazepam
Diethylpropion
Digitalis
Domperidone
Finasteride
Highly active antiretroviral therapy (HAART)
Isoniazid
Ketoconazole
Melatonin
Methyldopa
Metoclopramide
Methotrexate
Nifedipine
Nitrosoureas
Oestrogens
Omeprazole
Penicillamine
Phenothiazines
Phenytoin
Reserpine
Spironolactone
Tricyclic antidepressants
Vincristine

anxiety. Spontaneous regression usually takes place within a few months, but the enlargement occasionally persists for 2–3 years.

Gynaecomastia also appears to be frequent over the age of 65 years, increasing with age.

Gynaecomastia in endocrine disorders

Gynaecomastia occurs in a very wide range of endocrine disorders. Primary or secondary reduction of testicular androgen production is of special importance. Some tumours of the testis are associated with gynaecomastia, notably seminoma, Leydig cell tumour, Sertoli cell tumour and certain teratomas.

Gynaecomastia occurs in most men with Klinefelter's syndrome, and there is an increased risk of breast cancer in this syndrome [7,8], although other causes of gynaecomastia are not associated with an increased risk of cancer [1].

In other endocrine disorders, gynaecomastia is less common, but may occur in association with tumours or hyperplasia of the adrenal gland, pituitary tumours and hyperthyroidism [9].

Gynaecomastia in nutritional, metabolic, renal and hepatic disease

Gynaecomastia may occur during starvation or on resumption of a more adequate diet after prolonged starvation [10].

Chronic renal failure and haemodialysis may also be associated with gynaecomastia [11–13], although the incidence of gynaecomastia in dialysis patients has decreased in recent years.

Hepatic cirrhosis is usually listed as a cause of gynaecomastia, but one study found that palpable gynaecomastia was not a uniform feature in advanced cirrhosis, and that its prevalence was similar to that in a non-obese, non-cirrhotic, age-matched control population [14].

Gynaecomastia occasionally occurs in association with erythroderma [15].

Drug-induced gynaecomastia [16–33]

Drugs which may produce gynaecomastia are listed in Table 67.2.

They produce their effect by different mechanisms, for example spironolactone and cimetidine are antiandrogens, and neuroleptic drugs produce hyperprolactinaemia (Fig. 67.2). Testosterone might act by peripheral aromatization to oestrogens.

True gynaecomastia, as opposed to breast hypertrophy secondary to lipodystrophy syndrome, can occur with all currently available classes of antiretroviral agents. The mechanism responsible is unclear, but it has been proposed that it may be related to improvement in the T-helper cytokine response after starting highly active antiretroviral therapy (HAART) [28]. Cytokines produced

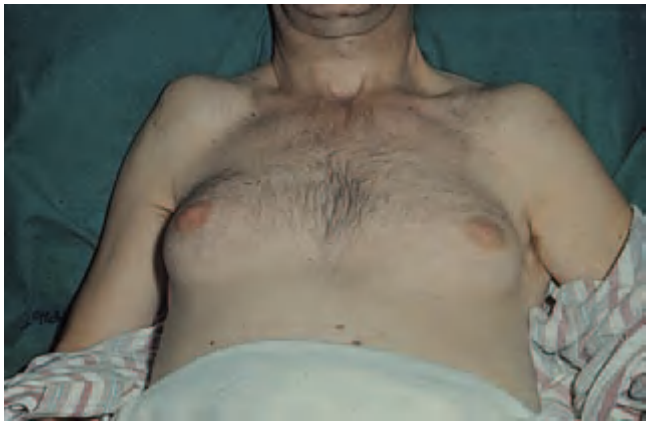

Fig. 67.2 Gynaecomastia in a man taking stilboestrol for carcinoma of the prostate.

during the immune restoration process have an effect on breast tissue, resulting in gynaecomastia. Once immune restoration has occurred, the cytokine levels fall, and the gynaecomastia resolves spontaneously.

Finasteride treatment of male androgenetic alopecia may be associated with gynaecomastia [29,30], and it has also been recorded in individuals who have used oestrogen-containing hair preparations [31,32] and in a men's hairdresser who had massaged the scalps of his balding customers with an oestrogen-containing lotion [33].

Management of gynaecomastia [3]

In the majority of patients, history and examination will suggest the likely cause of the gynaecomastia. Careful examination for underlying disease and a full drug history are required, particularly if the gynaecomastia is symptomatic, progressive or of recent onset in an adult, but it should be remembered that a large proportion of otherwise normal men have some slight gynaecomastia.

In unilateral disease, particularly in older men, breast cancer should be excluded.

Spontaneous resolution occurs in many 'physiological' cases, or following cessation of the causative drug when it is drug related.

For patients with considerable breast discomfort, or if the condition is severe enough to cause embarrassment, treatment with tamoxifen, clomiphene or danazol has been employed.

In extreme cases, subcutaneous mastectomy or liposuction may be performed by a plastic surgeon.

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Black galactorrhoea

Galactorrhoea is sometimes caused by drugs such as phenothiazines. In one patient taking perphenazine, the

droplets of milk were stained black, due to the concomitant administration of minocycline for acne [1]. The pigment which produces the black discoloration of breast milk in women taking minocycline is thought to be due to an iron chelate of minocycline within macrophages [2].

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Hypomastia or amastia [1]

Very small breasts are fairly common in otherwise normal women, in whom they may cause considerable psychological distress. There is some evidence of an association between hypoplastic breasts (defined as a breast size of 200 mL or less) and mitral valve prolapse [1].

Becker's naevus is occasionally associated with unilateral breast hypoplasia [2,3], possibly as a result of high androgen-receptor activity on the affected side, and with areolar hypoplasia in males [4,5].

Unilateral symbrachydactyly and ipsilateral aplasia of the sternal head of the pectoralis major muscle, aplasia of the breast and absence of axillary hair, are features of the *Poland syndrome* [6].

Breast hypoplasia or aplasia is a feature of the *AREDYLD* (acrorenal field defect, ectodermal dysplasia, and lipoatrophic diabetes) *syndrome* [7].

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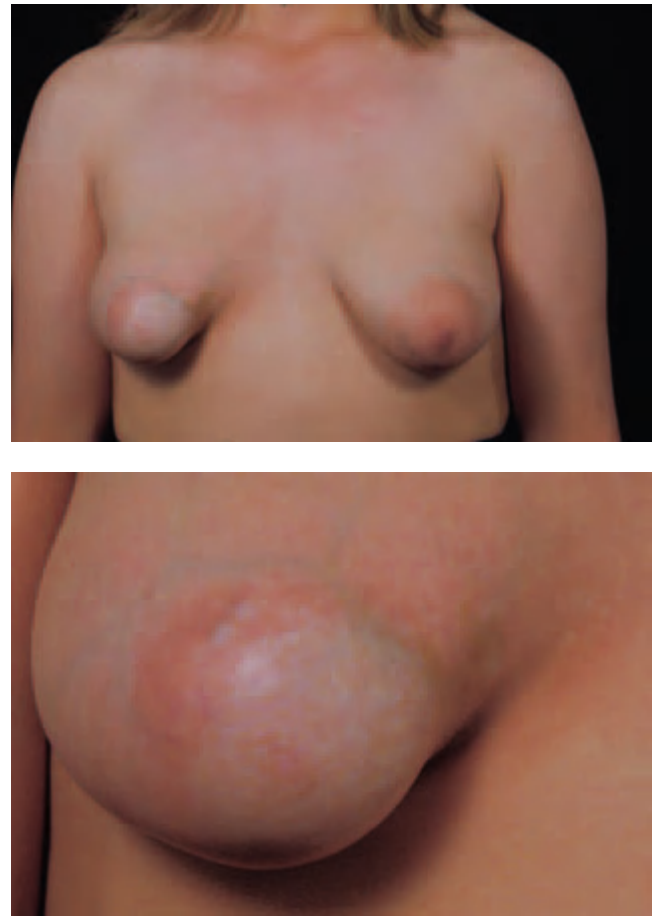
Morphoea [1]

If morphoea occurs on the chest wall prior to or during breast development, severe hypoplasia of the breast may result [2,3] (Fig. 67.3).

A feature of generalized morphoea is sparing of the nipples and areolae. Christianson *et al*. [4] noted that the skin was pinched or squeezed like 'rising biscuits on a platter' (Fig. 67.4).



(a) (b)

Fig. 67.3 (a, b) Breast hypoplasia associated with a plaque of morphoea which occurred during breast development.

There is a well-described occurrence of localized morphoea at the site of radiotherapy for breast cancer [5–9].

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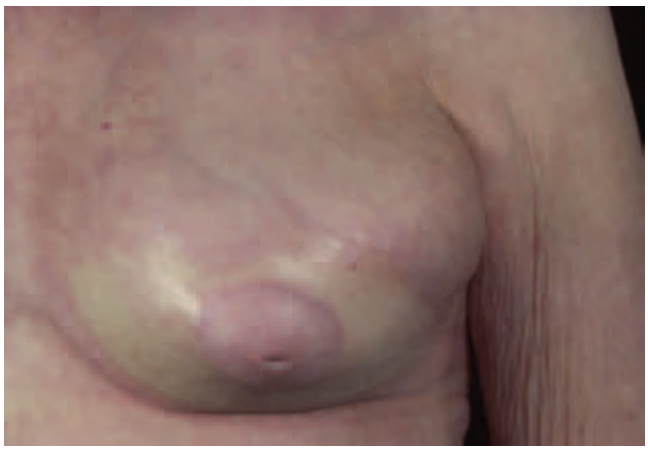
(a)



(b)

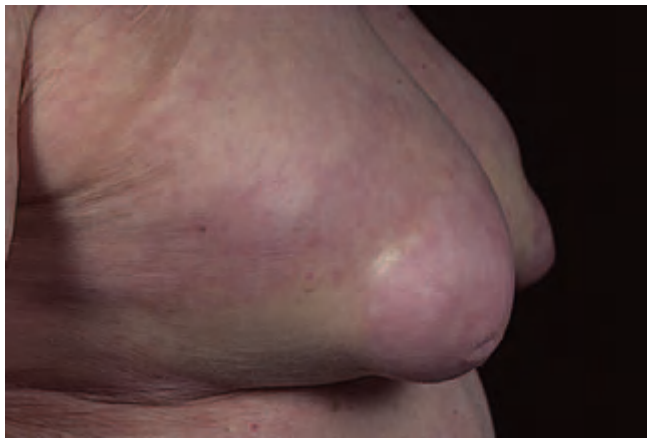


Fig. 67.4 (a, b) A patient with generalized morphoea, showing sparing of the nipple and areola.

Silicone breast implants and autoimmune disease

In the early 1990s, a major controversy arose about a possible relationship between silicone gel breast implants and subsequent development of connective tissue disease. Although the most common specific disease was scleroderma, many cases had a non-specific syndrome. Because of safety concerns, the US Food and Drug Administration imposed a moratorium on the use of such implants in 1992. The UK Medical Devices Directorate reviewed the scientific evidence relating to connective tissue disease and silicone gel breast implants, and in April 1992 presented a report to an independent Expert Advisory Group. The Group concluded that, on the basis of all available data, there was no evidence of an increased incidence of connective tissue disease associated with silicone gel breast implants [1]. An Independent Advisory Committee in Canada concluded that there was an absence of evidence establishing that women with silicone gel implants were more likely than those without such implants to have autoimmune disorders [2]. The issue provoked intense medicolegal activity.

Although a retrospective cohort study of 395 542 female health professionals, involving self-reported data, suggested a small increased risk of connective tissue diseases among women with breast implants [3], numerous controlled epidemiological studies did not demonstrate any statistically significant association between a recognized connective tissue disease and silicone breast implants [4], and three meta-analyses of the data failed to show an association [5–7]. However, the controversy continued [8,9]. Further studies showed no evidence of an association [10,11], and the UK Independent Review Group on Silicone Gel Breast Implants concluded that these implants were not associated with any greater health risk than other surgical implants, and that if there was any risk of connective tissue disease it was too small to be quantified [12]. At about the same time as this report was issued, a settlement of the medicolegal issues was proposed [13].

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Rudimentary nipples

The association of absent or rudimentary nipples with abnormalities of the scalp and ears has been reported as an autosomal-dominant trait [1–3].

Rudimentary nipples are also a feature of the ablepharon–macrostomia and Barber–Say syndromes, whose other features include absence of the eyelids or ectropion, macrostomia, ear anomalies, redundant skin, abnormal genitalia and hypertrichosis in the Barber–Say syndrome [4,5].

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Adnexal polyp of neonatal skin [1,2]

This is a small, usually solitary, tumour which occurs mainly on the areola of the neonate. It is firm and pink, but becomes dry and brown and falls off within a few days of birth. Histologically, it contains hair follicles, eccrine glands and vestigial sebaceous glands. A survey in Tokyo showed that the condition occurred in 4% of 3257 newborn infants.

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Inverted nipple

Inverted nipple is common, affecting up to 10% of adult females [1], and potentially leading to functional problems with breastfeeding, and psychological distress. There are three main causes: congenital, periductal inflammation and tumour infiltration. It is also important to remember that in postmenopausal women it may result from the involutional process of periductal fibrosis. In most cases, the abnormality is congenital, and the fault lies in failure of the normal eversion process [2]. The lactiferous ducts are shortened and there is a reduction in the amount of dense connective tissue which is present beneath a normal nipple [3]. The abnormality is usually bilateral, but may affect only one nipple.

Many women with inverted nipples are able to breastfeed without difficulty, probably because the nipple itself plays a relatively small part in the anatomical aspects of suckling, as the infant makes a 'teat' from the surrounding breast tissue as well as the nipple [2].

If inverted nipples pose a cosmetic problem, surgical correction may be considered. Numerous techniques have been described, suggesting that none is ideal. Procedures which involve division of the lactiferous ducts are probably more effective, but breast function is destroyed. One of the more recent suggestions, which preserves breast function, involves piercing the base of the nipple and inserting a stainless steel barbell of a type employed in decorative body piercing [4].

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The duct ectasia/periductal mastitis complex [1]

A number of pathological processes contribute to the clinical features of this complex. These features include nipple discharge, subareolar abscess, mammary duct fistula and nipple retraction. It is a rare occurrence in males, but has been described in association with HIV infection [2].

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Hyperkeratosis of the nipple and areola

On the basis of reported cases, hyperkeratosis of the nipple and areola is considered to be a rare condition. The classical Levy-Franckel classification includes three categories [1,2]: as an extension of an epidermal naevus, in which involvement tends to be unilateral and both sexes may be affected; in association with ichthyosis, in which involvement is bilateral and both sexes are affected; a naevoid type, usually bilateral, and occurring predominantly in women in the second or third decade of life. Pérez-Izquierdo *et al*. [3] suggested an alternative classification of two types: (i) idiopathic or naevoid (unilateral or bilateral); and (ii) secondary, local (unilateral or bilateral)—acanthosis nigricans, verrucous naevus or seborrhoeic keratosis; systemic (bilateral)—dermatosis, ichthyosis, malignant lymphomas, Darier's disease, chronic eczemas; or drug-related—diethylstilboestrol, spironolactone. Another classification, proposed by Mehanna *et al*. [4], includes a suggestion that the term 'naevoid' should be replaced by 'idiopathic'.

Whether described as naevoid or idiopathic, there is a distinct entity of verrucous thickening and brownish discoloration of the nipples and areolae which occurs predominantly in women in the second or third decade of life [5], in the absence of associated skin disease. It is usually bilateral, although unilateral involvement has been described [6,7], and it occasionally occurs in men [8]. Histology shows hyperkeratosis, filiform acanthosis and papillomatosis and keratin plugging.

Hyperkeratosis of the nipples may also occur in association with ichthyosis, ichthyosiform erythroderma, acanthosis nigricans, Darier's disease (in association with other skin lesions, but also described as an isolated presenting phenomenon [9]), and T-cell lymphoma [10,11]. It has also been described in men with carcinoma of the prostate treated with oestrogens [12,13].

An appearance resembling verrucous naevi around both areolae has been described as a manifestation of inadequate hygiene [14].

Suggested treatments for naevoid hyperkeratosis include topical retinoic acid [3], topical calcipotriol [15], cryotherapy [6] and the carbon dioxide laser [16].

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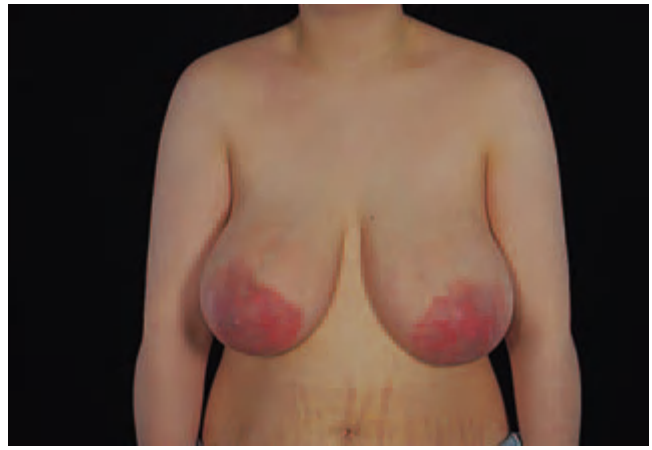
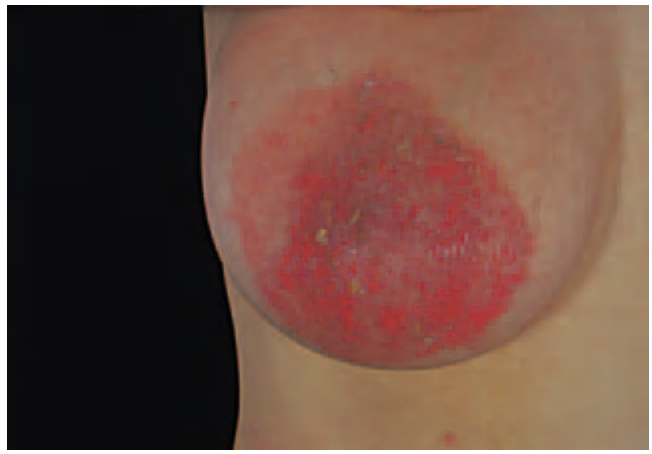
Eczema of the nipple and areola

Although eczema of the nipple and areola occurs mainly in women (Fig. 67.5), it is an occasional occurrence in men (Fig. 67.6); it may be unilateral or bilateral [1,2]. Often no cause can be established, although there is an association with atopy [3].

Contact dermatitis is a possibility, and allergic contact dermatitis of the nipples has been reported in a breast-feeding woman using a beeswax nipple protector [4], and two others applying Roman chamomile ointment [5].



(a)



(b)

Fig. 67.5 (a, b) Severe bilateral nipple eczema in a young woman.

Irritation from friction must also be considered (see the section on jogger's and cyclist's nipple, below), and unilateral nipple dermatitis in three women with large asymmetrical breasts was attributed to friction between the larger breast and the seam of the brassiere cup [6].

Treatment of nipple eczema is with mild to moderate potency topical steroids.

The intermittent course, more severe itching, indefinite margin and lack of distortion of the nipple help to distinguish eczema from Paget's disease (Chapter 36, Fig. 67.7). Erosive adenomatosis of the nipple (see p. 67.11) may have an eczematous appearance, and a case of clear cell acanthoma presenting as nipple eczema has been described [7]. If the diagnosis is at all doubtful, biopsy should be performed, particularly if there has been no response to topical steroids.

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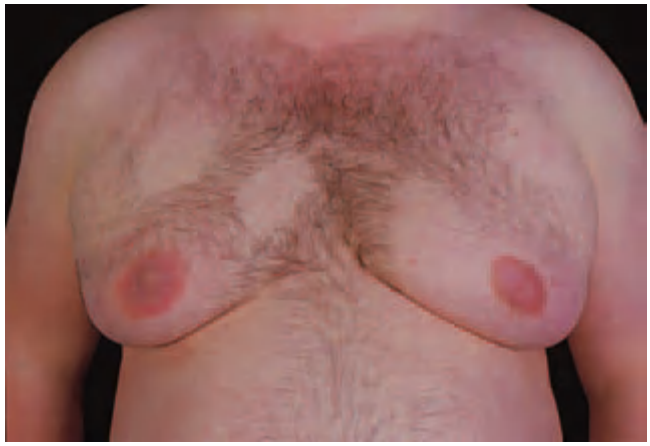
(a)



(b)

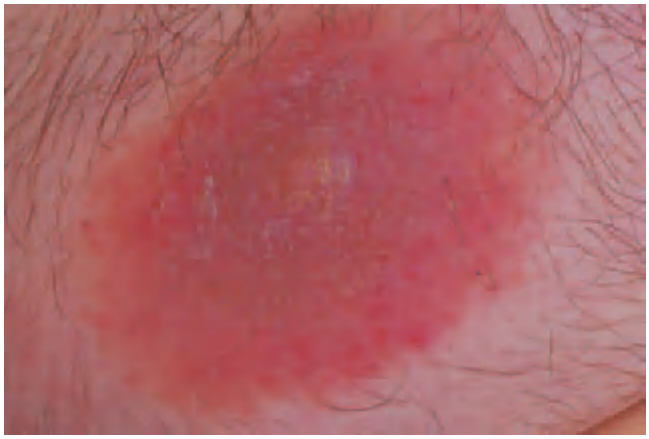


Fig. 67.6 (a, b) Bilateral nipple eczema in a man.

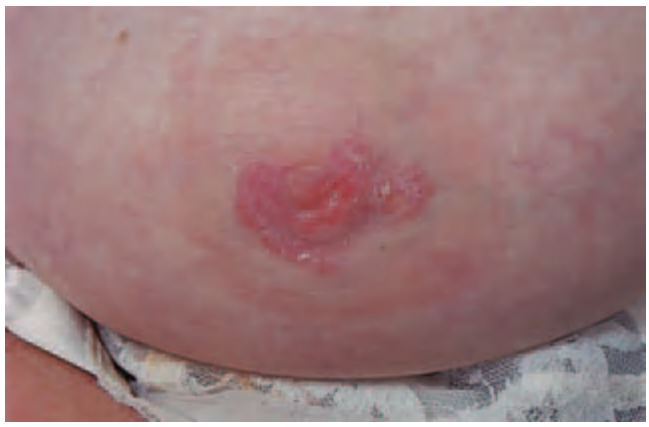


Fig. 67.7 Paget's disease of the nipple.

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'Cracked' nipples in lactation

Many women experience discomfort, irritation and fissuring of the nipples early in the puerperium when they are trying to establish breastfeeding. Anatomical features, such as relatively flat nipples, contribute to the development of this problem. Mastitis and deep abscesses may occur due to penetration of the broken skin by pyogenic bacteria. The problem is, in essence, one of friction and irritancy resulting from vigorous suckling, and can be eased considerably by the judicious use of gentle cleansing and emollients such as white soft paraffin.

Jogger's and cyclist's nipples [1,2]

Long-distance runners of either sex may suffer from irritation of the nipples caused by prolonged friction against a shirt. The problem is more pronounced in women who do not wear a brassiere. The condition is self-healing; prevention includes the application of petrolatum or powder to the nipples to reduce friction, and the use of a sports brassiere.

Cyclists may suffer from cold injury to the nipple as evaporation of perspiration and wind chill combine to lower the temperature of the nipple on a cold day [3]. Pain, which may last for several days, soreness and tenderness are the result. Cycling jackets made of wind-resistant fabric offer a solution.

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Nipple piercings

Body piercing has been practised in some societies since antiquity, but it has usually been confined to the ears and nose. In recent years it has become 'fashionable' in Western countries, and devotees indulge not only in piercings on the face and ears, but also the genitalia and nipples. In a recent study of American undergraduates, 3% of males and 6% of females had pierced nipples [1]. Of these, 21% had experienced trauma or bleeding and the piercing had been removed in a third (mainly male).

Nipple piercings may cause problems either due to trauma or infection [2,3] or the development of allergy to the metal. Lactiferous ducts may be damaged when the nipple is pierced, but this does not appear to lead to problems with breastfeeding [4].

Tassel ornaments suspended from the breasts have

been popular in some cultures, particularly in the Middle East, for many generations. Some dancers have their nipples pierced to accommodate a ring from which ornaments are suspended and this can cause breast duct ectasia [5].

REFERENCES

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Artefactual breast disease

There are relatively few reports of artefactual breast disease, but the features of reported cases are as varied and bizarre as factitial lesions elsewhere on the body [1–6].

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Vasculitis of the breast

Vasculitis affecting breast tissue is rare. It may occur as part of a systemic vasculitis, or as localized disease.

There are several reported cases of polyarteritis nodosa presenting as tender breast nodules [1,2], and breast lesions may also be a feature of Wegener's granulomatosis, sometimes as an initial manifestation [3,4].

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Lupus panniculitis

SYN. LUPUS ERYTHEMATOSUS PROFUNDUS; LUPUS MASTITIS [1–4]

Lupus panniculitis can result in breast nodules, which may be mistaken for carcinoma. Lesions are usually chronic and disfiguring. The treatment of choice is antimalarial therapy.

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Sarcoidosis of the breast [1–5]

Although involvement of the breast with sarcoidosis is rare, it is important to be aware of its occurrence, as it mimics breast carcinoma. It can present as solitary or multiple, unilateral or bilateral subcutaneous masses, which may be associated with other manifestations of the disease or occur as an isolated phenomenon. Lesions may be fixed or mobile, tender or non-tender, and with or without palpable axillary lymphadenopathy.

REFERENCES

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Erosive adenomatosis of the nipple [1–5]

SYN. BENIGN PAPILLOMATOSIS OF THE NIPPLE; FLORID PAPILLOMATOSIS OF THE NIPPLE DUCTS; PAPILLARY ADENOMA OF THE NIPPLE; SUBAREOLAR DUCT PAPILLOMATOSIS; SUPERFICIAL PAPILLARY ADENOMATOSIS

Definition. A complex benign tumour arising from the lactiferous ducts of the nipple.

Incidence. This is an uncommon tumour, which occurs mainly in middle-aged women, but it can occur at any age [6], and occasionally in males [7–9]. In one case, the lesion developed 10 years after treatment for carcinoma of the prostate by bilateral orchidectomy and diethylstilbestrol [10].

Pathology [1,4,11–14]. The lesion consists of tubules, with an inner layer of columnar cells and an outer layer of cuboidal myoepithelial cells. A major feature is the presence of superficial keratocysts lined by both squamous and columnar epithelium, and filled with keratin flakes and an eosinophilic material, apparently secreted by the columnar cells. The cysts seem to reproduce the terminal portion of the nipple duct system. Within some of the superficial cysts or ducts, foreign-body giant cells may be seen. Some degree of intraluminal growth (intraductal papillomatosis) is present in many cases. This ranges from small papillary epithelial tufts to almost complete occlusion of the lumina by solid epithelial plugs, and there may be evidence of apocrine decapitation secretion. The overlying epidermis may show acanthosis and hyperkeratosis.

The major histopathological diagnostic pitfall is confusing erosive adenomatosis with sweat gland tumours, and as it may also be difficult to differentiate from papillary breast carcinoma, immunohistological techniques are of value in demonstrating the layer of myoepithelial cells [12,13].

Clinical features. These are variable. The condition may start with a blood-stained or serous discharge, and the nipple may be enlarged, eroded, crusted or eczematous. There may be a small nodule on the nipple, and the symptoms may be worse in the premenstrual phase. The condition is commonly misdiagnosed as Paget's disease or eczema. It is usually unilateral, but bilateral involvement has been reported [15,16], and it has been described in an accessory nipple [17].

Treatment. Excision is curative—either simple local excision, or partial or complete resection of the nipple, depending on the size of the tumour [18]. There are reports of successful treatment by cryosurgery [19] and Mohs surgery [20].

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Sebaceous hyperplasia of the areolae

This is a rare abnormality characterized clinically by yellowish thickening of the areolae, and histologically by large numbers of hyperplastic sebaceous lobules [1–3].

REFERENCES

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Breast telangiectasia

White [1] described a 77-year-old man with bilateral patches of perfectly circular, symmetrical telangiectasia of the areolae. The condition had been present for as long as he could remember, with no associated abnormalities.

Blue areolae were one feature of a familial disorder named 'hereditary acrolabial telangiectasia' [2], and Schlappner and Shelley reported a 35-year-old woman with symmetrical essential telangiectasis of the breasts, recurrent aphthous stomatitis and hypersplenism [3].

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Mammary duct fistula [1]

SYN. RECURRENT SUBAREOLAR ABSCESS

This condition typically occurs in a young adult woman who has a history of recurrent abscesses in a breast which

have been treated by surgical drainage or have discharged spontaneously. There is typically partial inversion of the nipple and a scar or scars at the edge of the areola.

The condition is treated by passing a probe into the opening of the discharging sinus, along the track of the fistula, and out of the nipple. The fistula is then laid open (fistulotomy) and left to heal by granulation, or the whole tract is excised (fistulectomy) and the wound allowed to granulate.

REFERENCE

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Breast abscess [1]

Breast abscesses may be classified as lactational (occurring in the puerperium) and non-lactational. The majority of lactational abscesses are caused by *Staphylococcus aureus*, and present as a painful, red, swollen breast, associated with fever.

Non-lactational abscesses include subareolar abscess, which is seen mainly in women in their reproductive years in association with the duct ectasia/periductal mastitis complex, and peripheral abscess, which occurs as a typical inflammatory breast abscess in postmenopausal women. The former is associated with a mixed bacterial spectrum, and the latter with *S. aureus*. Lactational abscesses are now uncommon in comparison with the frequency of non-lactational lesions [2].

REFERENCES

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Breast cancer (Fig. 67.8)

This common and important condition lies in the province of the surgeon rather than the dermatologist, but all physicians have a duty to detect and diagnose early breast cancer, which can sometimes be discovered on routine examination. Inspection and palpation of the breasts should be included in any full examination. The breasts should be inspected with the arms by the side, above the head and pressing on the hips, because in some cases these manoeuvres will demonstrate a visible mass, or a change in contour of the breast, or early retraction or dimpling of the skin caused by a breast cancer. The dermatologist should also remember that redness or oedema of the breast skin can be due to underlying cancer. Breast cancer can also cause flattening, broadening or inversion of the nipple. It is important that all four quadrants of the breast, including the axillary tail and axillary lymph nodes, should be palpated.

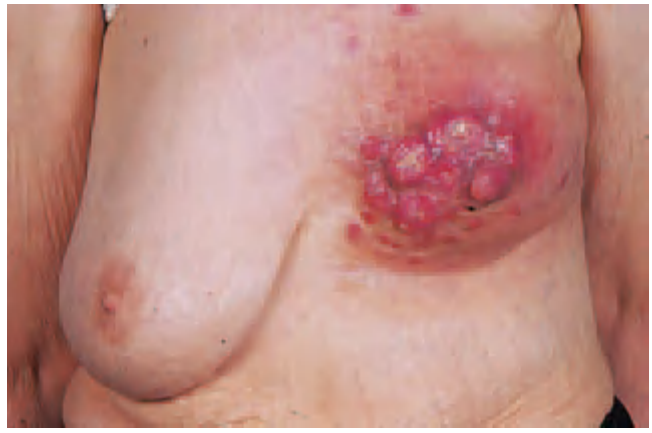

Fig. 67.8 Advanced carcinoma of the breast.

The dermatologist should examine the breasts carefully in all patients presenting with skin disease which may be associated with systemic malignancy, for example acanthosis nigricans or dermatomyositis.

The term *peau d'orange* is applied to dimpled oedematous or indurated skin resembling the surface of an orange. The finding of peau d'orange should lead to an intensive search for underlying carcinoma. Rarely, it occurs in the absence of any clinically palpable tumour. It has also been reported as a complication of anasarca, nephrotic syndrome and cardiac failure [1].

Breast cancer frequently involves the skin, and there are several different clinicopathological types of cutaneous involvement [2]. These include Paget's disease of the nipple, inflammatory metastatic carcinoma (carcinoma erysipeloides), carcinoma en cuirasse, telangiectatic metastatic carcinoma, nodular metastatic carcinoma, alopecia neoplastica, carcinoma of the inframammary crease and metastatic mammary carcinoma of the eyelid. Carcinoma metastatic to the eyelids is a rare phenomenon, and breast carcinoma is responsible for a sizeable proportion of these cases. Involvement may be unilateral, with the right eyelids affected more frequently than the left [3], or bilateral [4,5]. In many of the reported cases, the histology has shown prominent histiocytoid features [2].

Pigmented primary carcinoma of the breast is rare, and may mimic malignant melanoma clinically and histologically [6,7]. Metastatic melanoma may be responsible for inflammatory changes in breast skin [8].

Other conditions which may mimic breast carcinoma include postsurgical lymphoedema [9] and sarcoidosis [10].

Virgili *et al*. [11] described four patients with what were thought to represent cutaneous tumour-related granulomatous lesions following mastectomy for carcinoma of the breast. The lesions developed on the arm on the same side as the previous mastectomy.

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Breast cancer in men

Breast cancer in men is relatively rare, accounting for around 0.2% of all cancers in men in the USA and less than 1% of all cases of breast cancer [1].

Risk factors include conditions associated with reduced testicular function, excess oestrogen exposure, Klinefelter's syndrome [2], and a family history of breast carcinoma. Case–control studies indicate that the disease is commoner in black men and in those who have never married [3].

The mean age of presentation is 60–65 years, and is approximately 5 years older than that for breast carcinoma in women.

As in women, the clinical features include a breast mass, which is typically subareolar, nipple inversion and nipple discharge (Fig. 67.9). Infiltrating ductal carcinoma is the predominant histological type. Paget's disease may be the presenting feature [4,5].

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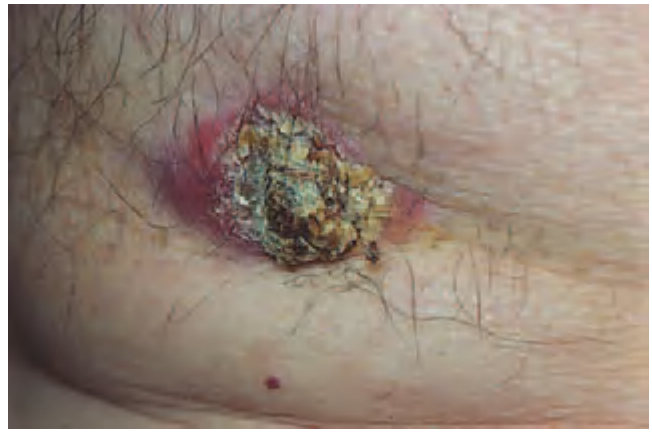

Fig. 67.9 Breast carcinoma in a man, showing destruction of the nipple and areola.

Basal cell carcinoma of the nipple [1–4]

This is a very rare lesion. It can occur in either men or women, usually in old age. It usually presents as a red, eczema-like patch of the nipple or areola and runs a long, indolent course. Biopsy is essential to differentiate it from Paget's disease.

Paget's disease, which is a marker of an underlying breast carcinoma, is discussed in Chapter 36.

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4 Yamamoto H, Ito Y, Hayashi T *et al*. A case of basal cell carcinoma of the nipple and areola with intraductal spread. *Breast Cancer* 2001; **8**: 229–33.

Hair sinus of the breast

Hair sinus of the periareolar area of the breast has been observed in women engaged in sheep shearing (roustabout's breast) and hairdressing [1] (Fig. 67.10), and in canine beauticians whose work leaves them covered in dog hairs [2]. The lesions are similar to the interdigital pilonidal sinuses which may occur in barbers and dog groomers [3]. The histology shows a granulomatous reaction. Repeated breast abscesses in female sheep shearers may provoke concern about the ability to breastfeed or even lead to women contemplating mastectomy. This problem prompted the manufacture, in New Zealand, of a protective brassiere, the Baa Bra [4].

REFERENCES

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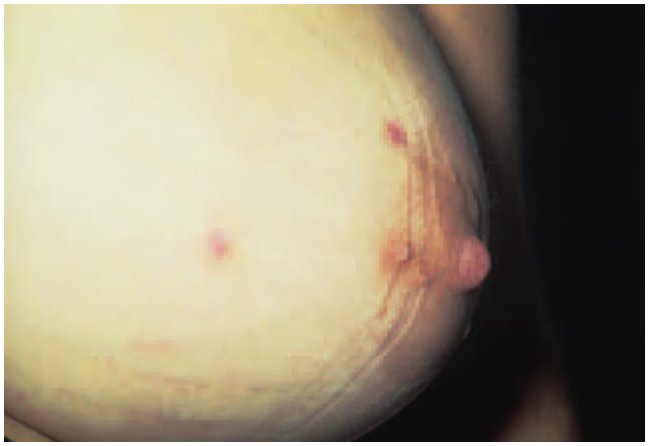

Fig. 67.10 Hair sinuses in a sheep-shearer. (Courtesy of Dr W. Bowers, Treliske Hospital, Truro, UK.)

2 Banerjee A. Pilonidal sinus of the nipple in a canine beautician. *BMJ* 1985; **291**: 1787.
3 Price SM, Popkin GL. Barbers' interdigital hair sinus. *Arch Dermatol* 1976; **112**: 523–4.
4 Gardiner G. Breast infections due to wool. *N Z Med J* 1994; **107**: 494.

Seborrhoeic warts

SYN. BASAL CELL PAPILLOMAS (Chapter 36)

These are particularly common in the submammary creases in middle-aged or elderly women, often in association with intertrigo (Fig. 67.11). Seborrhoeic warts may also occur as sharply demarcated papules or plaques on the nipple and areola [1].

REFERENCE

1 Baykal C, Büyükbabani N, Kavak A, Alper M. Nevoid hyperkeratosis of the nipple and areola: a distinct entity. *J Am Acad Dermatol* 2002; **46**: 414–8.

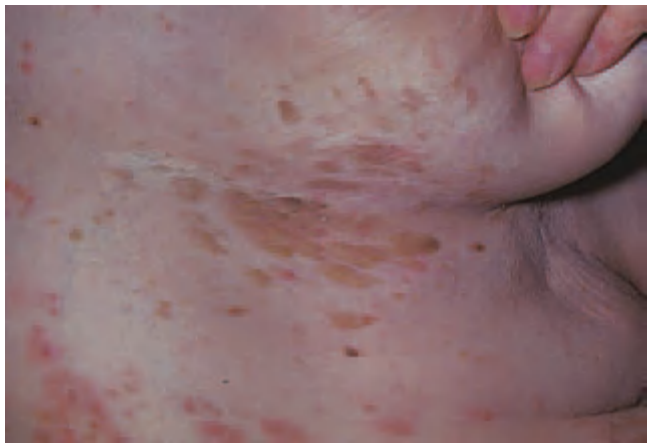

Fig. 67.11 Submammary seborrhoeic warts.

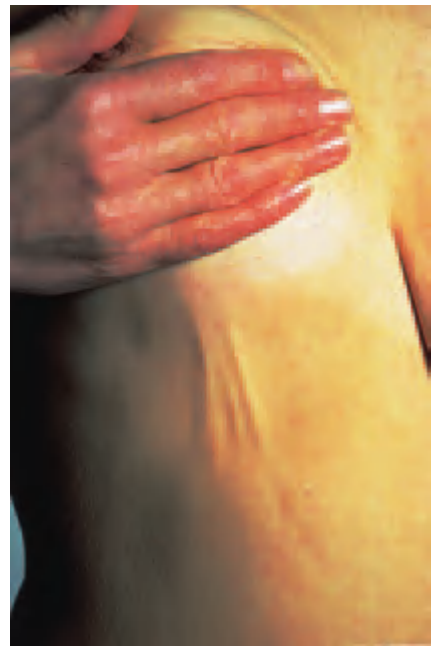

Fig. 67.12 Mondor's disease of the chest wall. (Courtesy of Professor A.Y. Finlay, University of Wales College of Medicine, Cardiff, UK.)

Mondor's disease (Fig. 67.12)

SYN. SCLEROSING PERIPHLEBITIS OF THE CHEST WALL

Mondor's disease is usually regarded as an obliterative phlebitis affecting the thoracoepigastric, lateral thoracic or superior epigastric vein. It occurs mainly between the ages of 30 and 60 years and affects women much more frequently than men [1,2]. Risk factors cited for the development of the condition include large, pendulous breasts, strenuous physical activity, direct trauma, breast surgery and infection near the affected vessels. Breast cancer is an occasional cause [3], and mammography is recommended even when no mass is palpable [4–6]. Mondor's disease has characteristic mammographic and sonographic features [5,6]. It has also been described in association with metastatic axillary adenopathy 2 years after radical mastectomy for breast carcinoma [7], and in a patient with metastatic lung cancer in the breast [8].

In a case of recurrent Mondor's disease of the thoracoepigastric vein, resolution occurred after excision of a lipoma which was in close proximity to the vein [9]. It is a rare occurrence in pregnancy [10,11].

Other rare causes include intravenous drug abuse, following use of the breasts as injection sites [12], jellyfish stings [13] and a lupus erythematosus-like syndrome probably induced by procainamide [14]. However, often no cause is apparent.

Rarely, the condition is bilateral [14], and in one such case potential aetiological factors included breast surgery,

the use of oral contraceptives, hereditary protein C deficiency and anticardiolipin antibodies [15].

There may be some tenderness or discomfort, but there are often no symptoms until the patient discovers a red linear cord running from the lateral margin of the breast, crossing the costal margin and extending to the abdominal wall. The cord is 2–3 mm in diameter and is attached to the skin but not to the deep fascia. It is usually only a few centimetres long, but may extend to 30–40 cm. The symptoms subside in a few weeks and there are no known complications.

REFERENCES

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14 Skipworth GB, Morris JB, Goldstein N. Bilateral Mondor's disease. *Arch Dermatol* 1967; **95**: 95–7.
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Other conditions which may involve the breast

Vitiligo sometimes shows a striking symmetrical involvement of the breasts.

Psoriasis may be provoked by the trauma of suckling.

Pityriasis rosea commonly presents with a herald patch on the breast, and has been reported as a localized eruption on one breast [1].

REFERENCE

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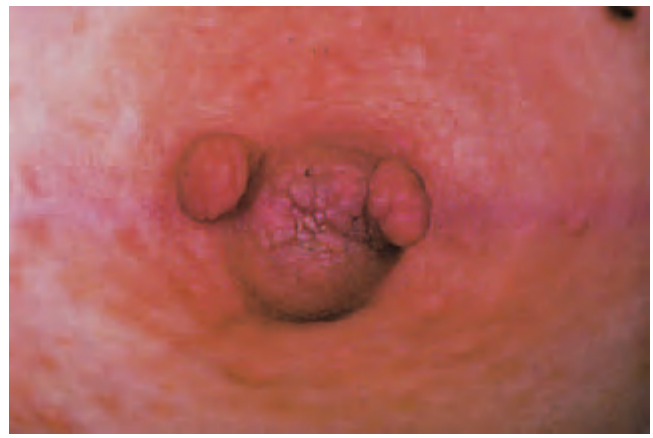

Fig. 67.13 Neurofibromatosis, showing the predilection of this condition for the nipple.

Cutaneous larva migrans may occur on the breast when women have lain 'topless' on a tropical beach in the prone position.

Neurofibromas have a predilection for the areola (Fig. 67.13) [1].

REFERENCE

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Scabies often produces papules around the nipple, which may persist after treatment.

Granular parakeratosis of the submammary regions has been described [1].

REFERENCE

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Lichen sclerosus et atrophicus confined to the areola has been reported [1].

REFERENCE

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Fox–Fordyce disease (Chapter 45) may produce intensely irritable papules on the areolae.

Carney complex (myxomas, spotty pigmentation and endocrine overactivity) is associated with breast myxoid fibroadenomas and ductal adenomas [1,2].

REFERENCES

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Cowden's syndrome (multiple hamartoma syndrome) [1] is an autosomal-dominant disorder associated with hamartomas of various tissues and an increased risk of breast cancer, usually ductal carcinoma.

REFERENCE

1 Schrager CA, Schneider D, Gruener AC *et al*. Clinical and pathological features of breast disease in Cowden's syndrome: an underrecognized syndrome with an increased risk of breast cancer. *Hum Pathol* 1998; **29**: 47–53.

Hidradenitis suppurativa of the breasts tends to affect the inter- and inframammary folds [1].

REFERENCE

1 Hughes LE, Mansel RE, Webster DJT. *Benign Disorders and Diseases of the Breast*, 2nd edn. London: Saunders, 2000: 242–4.

Diffuse dermal angiomatosis of the breast, responding to isotretinoin, has been reported by McLaughlin *et al*. [1].

REFERENCE

1 McLaughlin ER, Morris R, Weiss SW, Arbiser JL. Diffuse dermal angiomatosis of the breast: response to isotretinoin. *J Am Acad Dermatol* 2001; **45**: 462–5.

Mucinosis of the areolae has been described as a presenting feature of mycosis fungoides [1].

REFERENCE

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Chapter 68

The Genital, Perianal and Umbilical Regions

C.B. Bunker & S.M. Neill

Introduction

A number of common skin diseases affect the umbilical, perianal, genital and genitocrural skin only incidentally, and may present in these areas with unusual features. These will be dealt with briefly or by cross-reference to their full description elsewhere. However, those conditions that are entirely or predominantly confined to these regions are discussed in detail.

General approach to the patient and the problem

Clinical assessment begins with the history and examination. Patients with anogenital symptoms may be embarrassed and present late, or present to specialties (urology, gynaecology, general or colorectal surgery, genitourinary medicine) where training and experience are not focused on dermatological diagnosis and management.

Itching, rashes and tumours are the major components of general dermatology and the anogenital area is not spared. The pruritic diseases that may affect the anogenital region are listed in Tables 68.1–68.3. Itch occurring in the absence of specific diagnostic skin lesions is not usually confined to the anogenital area, but if so it should not be labelled as psychogenic until all possible causes have been excluded. The intensity with which itch can be perceived in the anogenital area may be a result of the vagaries of cortical representation afforded the region in the sensorium as well as anxiety about exposure to sexually transmitted disease and anogenital cleanliness.

Table 68.1 Common causes of anogenital pruritus. (After Bunker [1]. © 2004, with permission from Elsevier.)

Pruritus ani
Eczema/dermatitis
Exogenous
Contact
irritant
allergic
Endogenous
Atopic
Seborrhoeic
Lichen simplex
Psoriasis
Lichen sclerosus
Lichen planus
Perianal streptococcal dermatitis
Erythrasma
Herpes simplex
Candidosis
Tinea
Onchocerciasis (in developing countries)
Phthiriasis
Scabies

Table 68.2 Rare causes of anogenital pruritus. (After Bunker [1]. © 2004, with permission from Elsevier.)

Insect bites/papular urticaria
Radiodermatitis
Hirsutism
Hyperhidrosis
Fox–Fordyce disease
Urticaria and dermographism [2]
Dermatitis herpetiformis
Chlamydia
Gonorrhoea
Syphilis
Other sexually transmitted diseases
Trichosporosis
Larva currens
Cutaneous larva migrans
Onchocerciasis (in Western practice)
Bowen's disease
Extramammary Paget's disease
Langerhans' cell histiocytosis
Drugs
Foods
Senile pruritus
Dysaesthesia syndromes

Table 68.3 Causes of genital itching in the absence of fixed clinical findings. (After Bunker [1]. © 2004, with permission from Elsevier.)

Symptomatic dermatographism
Contact urticaria
Non-immunological (e.g. mechanical friction of pubic hair, topical substances)
Immunological (latex, body fluids)
Contact dermatitis
Incognito disease
Psoriasis
Candidosis
Scabies
Drugs and foods
Senile pruritus
Delusions of parasitosis
Dermatological non-disease
Dysaesthesia syndromes
Psychosexual

Table 68.4 Common causes of anogenital intertrigo.

Eczema
Exogenous
irritant contact
Endogenous
seborrhoeic
Psoriasis (inverse pattern/flexural)
Erythrasma
Candidosis
Tinea
Trichosporosis (in India)
Pseudoacanthosis nigricans

Table 68.5 Rare causes of anogenital intertrigo. (After Bunker [1]. © 2004, with permission from Elsevier.)

Eczema
Exogenous
allergic contact
Endogenous
atopic
Reiter's syndrome
Lichen sclerosus
Hailey–Hailey disease
Darier's disease
Streptococcal dermatitis
Gonorrhoea
Secondary syphilis
Part of a syphilide
Mucous patch
Congenital syphilis (in the infant)
Trichosporosis (in industrialized countries)
Extramammary Paget's disease
Kaposi's sarcoma
Langerhans' cell histiocytosis
Carcinoma erysipeloides

The symptomatology of anogenital dermatology is more extensive than the standard symptomatic presentation of skin disease. This obliges the clinician to elicit symptoms resulting from sexual dysfunction (e.g. preputial dysfunction—soreness, pain, bleeding or tearing on intercourse) and the components of sexual function (erection, lubrication, libido, ejaculation, orgasm, fertility), urinary dysfunction (frequency, discharge, dysuria) or colorectal symptomatology (pain, bleeding, discharge).

History taking must involve attention to the sexual history (orientation, marital status, last sexual activity (when; how—vaginal, oral, anal; contraception), regular partner(s), partner symptomatology) and drug history (topical and systemic, prescribed and over-the-counter). The personal and family history of atopy, psoriasis and seborrhoeic dermatitis is often relevant. Smoking habits should be documented; smoking is a risk factor for anogenital cancer.

Complete examination is mandatory because common diagnoses will be reached with the assistance of important signs at extragenital sites. Often the patient will not have had his/her genitalia or perineum examined. The practice of anogenital dermatology demands careful inspection and often requires internal examination and urinalysis. Drawings are made and photographs obtained. Signs are described in conventional and specific terms (e.g. posthitis, phimosis).

Intertrigo describes any dermatosis occurring in skinfolds; frictional abrasion and a degree of epithelial loss may result in erosion that renders the site especially susceptible to secondary infection (e.g. with *Candida*). Causes are listed in Tables 68.4 and 68.5.

Pigmentary change is common. Causes of anogenital hypopigmentation and leukoderma include striae, vitiligo, lichen sclerosus, viral warts, leukoplakia and post-inflammatory changes (Table 68.6). Rarer causes include

Table 68.6 Causes of anogenital post-inflammatory hypopigmentation. (After Bunker [1]. © 2004, with permission from Elsevier.)

Following cryotherapy
Electrotherapy
Chemocautery
Laser surgery
Contact dermatitis
Lichen sclerosus
Systemic sclerosis
Lichen planus
Cicatricial pemphigoid
Gonococcal dermatitis
Syphilis
Leukoderma—post-secondary syphilide
Gumma
Post-gummatous atrophic scar
Herpes simplex
Pityriasis versicolor
Onchocerciasis 'leopard skin'
Peyronie's disease
Pseudoepitheliomatous micaceous and keratotic balanitis (PEMKB)

Table 68.7 Causes of anogenital post-inflammatory hyperpigmentation. (After Bunker [1]. © 2004, with permission from Elsevier.)

Post-traumatic
Lichen planus
Herpes simplex
Fixed drug eruption

Candida, extramammary Paget's disease, mycosis fungoides and melanoma. Common causes of anogenital hyperpigmentation include tattoos, purpura, lentigines, naevi, pseudoacanthosis nigricans and post-inflammatory changes (Table 68.7). Rarer or potential causes include Addison's disease, Nelson's syndrome, genital melanosis, Laugier–Hunziker syndrome [3], Peutz–Jeghers syndrome [4,5], LAMB syndrome (lentigines, atrial myxoma, mucocutaneous myxoma, blue naevi) [6,7], LEOPARD syndrome, Ruvalcaba–Myhre–Smith syndrome [8,9], acanthosis nigricans, acral lentiginous melanoma, drugs and metals. Both post-inflammatory hypo- and hyperpigmentation are possible after acute and chronic inflammation from diverse causes; both may be more pronounced in ethnically darker skin. Lichen planus, fixed drug eruptions and recurrent herpes simplex are the common causes of post-inflammatory hyperpigmentation. Genital trauma from a zipper injury can lead to macular pseudolentiginous lesions on the glans and shaft of the penis.

A mucosal white patch or plaque is sometimes called leukoplakia (Table 68.8). This is not a diagnostic term, and it is unhelpful as it evokes connotations from oral medicine of premalignancy or even frank neoplasia.

Anogenital ulceration requires meticulous elucidation. The principal causes are benign aphthae, sexually transmitted and non-sexually transmitted infection, cancer and artefact. Tables 68.9 and 68.10 list all the causes. Several causes can co-present, especially in HIV/AIDS.

Table 68.8 Causes of white patches and plaques. (After Bunker [1]. © 2004, with permission from Elsevier.)

Post-traumatic or surgical scar
Lichen simplex
Lichen sclerosus
Vitiligo
Mucous membrane (cicatricial) pemphigoid
Peyronie's disease
Syphilis
Leukoderma—post-secondary syphilide
Gumma
Post-gummatous atrophic scar
Viral warts
Pityriasis versicolor
Pseudoepitheliomatous micaceous and keratotic balanitis (PEMKB)
Intraepithelial neoplasia
Squamous cell carcinoma

Table 68.9 Common causes of anogenital ulcers. (After Bunker [1]. © 2004, with permission from Elsevier.)

Trauma
Pressure sores
Aphthae
Pilonidal sinus
Anal fistula
Anal fissure
Erythema multiforme/Stevens–Johnson syndrome
Hidradenitis suppurativa
Crohn's disease
Chancroid
Donovanosis/granuloma inguinale
Lymphogranuloma venereum
Syphilis—primary chancre
Squamous carcinoma

Commonly required investigations include microbiology or virology of a swab or smear, scrapings for fungal microscopy and culture, scrapings for mite identification, skin biopsy, Wood's light to demonstrate vitiligo and erythrasma, and blood tests (e.g. ASOT, HLA B27, HIV). Investigations pertinent to the evaluation of sexually transmitted diseases are not discussed further, but it bears re-emphasis that if a diagnosis of a potentially sexually transmitted disease is reached (warts, molluscum contagiosum, herpes simplex, scabies, pediculosis) then the patient should be referred for a genitourinary opinion and advised to inform their partner(s) so that they may be screened also.

The opinion of another specialist may be necessary and should be sought as dictated by the urological, gynaecological, colorectal or genitourinary situation. Combined clinics are the ideal.

Table 68.10 Rare causes of anogenital ulcers. (After Bunker [1]. © 2004, with permission from Elsevier.)

Extrusion of testicular prosthesis
Embolization
Dermatitis artefacta
Penile necrosis
Spontaneous scrotal ulceration
Sarcoid
Autoimmune bullous diseases
Bullous pemphigoid
Mucous membrane (cicatricial) pemphigoid
Linear IgA disease
Necrobiosis lipoidica
Pyoderma gangrenosum
Necrotizing vasculitis
Degos' malignant atrophic papulosis
Calciphylaxis
Hypereosinophilic syndrome
Pseudomonas
Ecthyma gangrenosum
Necrotizing anorectal ulcer in leukaemia
Gonorrhoea
Chancroid
Donovanosis (granuloma inguinale)
Lymphogranuloma venereum
Fournier's gangrene
Tuberculosis and tuberculides
Syphilis—snail track ulcers
Yaws
Non-syphilitic spirochaetal ulcerative balanoposthitis
Herpes simplex
HIV
Deep fungal infections
Histoplasmosis
Blastomycosis
Cryptococcosis
Actinomycosis
Paracoccidioidomycosis
Leishmaniasis
Amoebiasis
Filariasis
Langerhans' cell histiocytosis
Extramammary Paget's disease
Basal cell carcinoma
Squamous carcinoma
Verrucous carcinoma
Sweat gland carcinoma
Melanoma
Kaposi's sarcoma
Leukaemia
Lymphoma
Drug reaction

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Genitocrural dermatology

Introduction

The genitocrural folds represent a region of the body that is particularly prone to intertrigo and flexural forms of common dermatoses, probably because of koebnerization. Moisture and friction also lead to maceration and fissuring, and secondary infections readily supervene. Vegetating reactions can prove resistant to treatment. Itch may be prominent in psoriasis, infections and infestations of the area. Crab louse and *Oxyuris* infestation must be excluded as primary causes of rash. Lichenification occurs readily.

Inflammatory dermatoses

Intertrigo

Intertrigo is a generic name for an inflammatory dermatosis involving the body folds, notably those of the submammary and genitocrural regions. There may be no clear distinction between constitutional and infective causes (listed in Tables 68.4 & 68.5). Physical factors such as obesity, sweating, friction, incontinence and faecal soiling may cause erythema or fissuring, and render the skin vulnerable to the effects of other agents. Initially, it is marked by soreness or slight itching, and a superficial mild erythema of the apposed surfaces. Secondary infection occurs rapidly, and the condition is then perpetuated as an infective dermatitis. In eczematous subjects this will take on the physical characteristics of eczema; in others, the infection may progress to crusting, pustular or vegetating lesions. The organisms concerned are *Staphylococcus aureus*, rarely the haemolytic streptococcus, *Escherichia coli*, *Proteus* spp. and, occasionally, *Pseudomonas aeruginosa*. In infants, diabetics and the obese, yeasts are often present. Latent diabetes should be borne in mind when the disease is refractory to treatment. Overtreatment may compound the irritation or lead to a sensitization dermatitis.

Candidosis and contact dermatitis are differentiated by the history, the appearance and microscopic examination. The diffuse macerated erythema, often with fissures at the apex of the fold and without a sharply defined edge, distinguishes intertrigo from psoriasis and dermatophytosis, although scrapings and culture should always be

undertaken. Mistakes in diagnosis arise from failure to recognize that two or more aetiological factors may co-exist [1]. In India, *Trichosporon* species, which normally cause white piedra trichomycosis, have been implicated in causing cutaneous lesions resembling genitocrural intertrigo [2]. Langerhans' cell histiocytosis (see Chapter 52) has a predilection for the perineum or inguinal regions [3] and is a rare cause of genitocrural intertrigo; likewise extramammary Paget's disease. Congenital syphilis may present as intertrigo in an infant.

In the early stages, the condition can be controlled by avoidance of friction and tight clothing. Driving or sitting for long periods should be avoided. In severe cases, the patient must rest in bed, preferably with groins unclothed and bedclothes lifted by a cradle, the apposed skin surfaces being kept apart with appropriate dressings. Obesity, diabetes and incontinence should receive attention. Wet dressings are often useful initially in acute cases, and may be followed by bland or mild antibacterial creams or lotions. The aniline dyes and magenta paints still have a place in therapy. In general, lotions, paints and powders are more acceptable than creams. Nystatin, hydroxyquinoline and imidazoles can be applied alone or with topical steroids for a few days.

Genitocrural dermatitis

Lichen simplex is a result and/or cause of severe and spasmodic itch; the psychological mechanisms involved are similar to those discussed in relation to pruritus vulvae and pruritus ani. The 'giant' form of lichenification described by Pautrier [4] may be extremely resistant to treatment. Local treatment with corticosteroid applications is supplemented by reassurance, rest and sedation. All factors provoking local itching must, as far as possible, be removed.

Contact dermatitis (see Chapters 19–21) may present suddenly with pruritus, oedema and erythema, or insidiously as a gradual intensification of a pre-existing dermatitis. Sensitization to applied medicaments, contraceptives or, in men, industrial or other contact agents transferred by hand may be responsible for allergic contact dermatitis, especially if the scrotum and thighs are also affected. Irritant contact dermatitis is common and caused by excessive or exuberant use of soap and toiletries. A good example is nappy (diaper) rash where urine, occlusion, friction and *Candida* contribute to the clinical presentation. Classically, the convex surfaces are affected and the flexures are spared, distinguishing it from psoriasis [5]. Nappy rash has become much less common with the availability of absorbent disposable paper napkins. A severe erosive form (Jacquet's dermatitis) is still occasionally seen in children with urinary or faecal incontinence.

Constitutional eczema should be considered in the differential diagnosis of napkin erythema in an infant (see Chapter 14). In adults, the genitocrural and lower abdominal folds are likely to be involved in seborrhoeic or intertriginous dermatitis.

Miscellaneous

Psoriasis and lichen planus are recognized by their special characteristics, although the diagnosis may be difficult when they arise in an exclusively flexural distribution. In the flexures and at anogenital sites, seborrhoeic dermatitis and psoriasis may be indistinguishable.

Impetigo herpetiformis frequently starts in the groin with small inflammatory yellowish green pustules, which rupture to produce scabs and crusts. Acrodermatitis enteropathica and the acquired zinc deficiency syndrome may well be overlooked as causes of genitocrural dermatitis. The distinction of Jacquet's eruption from congenital syphilis and from the exuberant plaques and nodules of infantile gluteal granuloma [5,6] is important. Hidradenitis suppurativa usually involves the area widely, although localized lesions are sometimes seen.

All forms of pemphigus and pemphigoid (especially pemphigus vegetans [7] and pyodermite végétante [8]) affect this region, and juvenile pemphigoid and pemphigoid gestationis affect it selectively and sometimes exclusively. Pemphigus vegetans must be distinguished from vegetating forms of pyoderma, which are not uncommon in the groins, and from blastomycosis and other mycoses, verrucoid forms of tuberculosis and granuloma inguinale. Mucous membrane (cicatricial) pemphigoid [9] may affect the groin. Benign familial pemphigoid (Hailey–Hailey disease) affected the groins or genitalia in 14 out of 21 patients in one series [10]. It can involve the groins in isolation. Secondary infection with herpes simplex has been reported after treatment with retinoids [11]. Very rarely, papular plaques similar in appearance to genital warts have been reported. Darier's disease (see Chapter 34) involving the flexures is mild in most patients but does occur in the vast majority. It can be very sore and malodorous. The intertriginous features are similar to those of Hailey–Hailey disease. There have been several reports of a genital, inguinal and perineal eruption, with clinical and histological similarity to Darier's disease and Hailey–Hailey disease, called genitocrural papular acantholytic dermatosis. The patients had no rash elsewhere, no family history and negative immunofluorescence [12]. Subcorneal pustular dermatosis extends outwards from the inguinal folds as flaccid pustules, rapidly rupturing to form gyrate and circinate crusted lesions. Dystrophic forms of epidermolysis bullosa may cause separation of the skin during delivery or, if less severe, bullae and erosions at these sites of friction.

Epidermal necrolysis may present as desquamation, sometimes involving the whole region. Severe erythema multiforme involves the genital or anal mucosa in half of the cases. Necrolytic migratory erythema also extends in waves from this area [13].

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Infections

Erythrasma

Erythrasma (see Chapter 27) is a common genitocrural infection, especially of the male. It is caused by *Corynebacterium minutissimum*, an organism that is normally a commensal but which in warmer climates may become pathogenic. Tawny, slightly scaly plaques are seen on the upper inner thighs. In the inguinal folds, erythrasma may present as an intertrigo and can be macerated and eroded. It is not usually very itchy, but can be slightly sore. Lesions are usually also found in the axillae or toe webs. It may coexist with *Trichophyton rubrum* [1] and candidosis. Pruritus ani has also been reported [2]. Erythrasma is a clinical diagnosis confirmed by demonstration of coral pink fluorescence under Wood's light (resulting from a porphyrin elaborated by the bacterium). Treatment is with topical clindamycin, erythromycin or an imidazole, or with oral erythromycin. It is prone to recur.

Candidosis

Candidosis (thrush) presents as an intertrigo. Symptoms of burning and soreness are more common than itch. Coalescent red patches or plaques involve the folds, often with superficial erosions. Pustulosis extends out onto the skin of the abdomen, buttocks or thighs from the irregularly marginated intertriginous lesions. It can be a primary infection, particularly in infants, and in pregnancy and diabetes, but *Candida* may be more often a secondary pathogen in anogenital dermatoses. Observing the signs of candidosis or demonstrating the presence of the organism does not prove that it is the cause of all the symptoms and signs. *Candida albicans* is such a ready opportunist because it is a part of the resident flora of the gastrointestinal tract and may be retrieved from intertriginous areas, including the preputial folds, in the absence of symptoms and signs. A search for an underlying dermatological or medical cause should be undertaken. The symptoms and signs of *Candida* may be more florid than the underlying predisposing cause. Obesity predisposes to candidal intertrigo but medical causes include diabetes mellitus, iatrogenic immunosuppression and systemic antibiotic treatment. Although oropharyngeal candidosis is almost invariably found in HIV infection, anogenital candidosis is not generally associated, perhaps because it is overlooked or because many patients take long-term imidazole antifungals orally.

Underlying disease should be identified and treated, and predisposing factors rectified. Treatment includes topical nystatin, clioquinol or an imidazole, often very usefully combined with hydrocortisone or a moderately potent corticosteroid. If the infection is severe, an oral imidazole may be indicated.

Tinea cruris

Tinea (see Chapter 31) is a common disease of the groins and is usually caused by *Trichophyton rubrum*. It is generally rare in women, but occurs more frequently in hot climates. Spread occurs onto the thighs, buttocks and pubis. Many patients have been previously misdiagnosed and/or partially treated with topical corticosteroids and/or topical antifungal agents. Tinea and *Candida* may complicate other dermatoses such as psoriasis. Tinea incognito/occulta is therefore common. There is a fine peripheral scaling (eczema marginé of Hebra). Cases have been described in infants [3].

Microscopy will confirm the clinical diagnosis, and in tinea incognito/occulta there are numerous fungal elements.

Dermatophyte infection of the anogenital skin usually requires oral treatment with griseofulvin, terbinafine or itraconazole. Topical treatments often fail because the anatomical complexity of the area makes topical treatment difficult, and there may be reinfection from concomitant involvement of feet or hands, toe or finger nails.

Miscellaneous

Bacterial or candidal infections complicate intertrigo, eczema, napkin erythema, scabies and many tropical diseases. Vincent's organism, *Pseudomonas aeruginosa* and a wide variety of Gram-negative organisms are commonly found. Gangrenous ecthyma of infants may, very rarely, affect the inguinocrural area. Bullous impetigo occurs in

childhood, often secondary to scabies. Giant condylomata acuminata may infiltrate the groin [4]. Gangrene has followed operations for inguinal hernia [5]. Sacral herpes zoster may present with groin lesions and retention of urine or constipation.

Phthiriasis pubis is sometimes overlooked as a cause of pruritus in the female. In the hirsute male, the infestation may be widespread. Oxyuriasis can cause localized urticaria as well as pruritus. Scabies in children is diffuse, and the inguinal glands are often enlarged from secondary infection. Seabather's eruption and 'seaweed dermatitis' affect the bathing trunk area.

Schistosomiasis and amoebiasis cause phagedenic necrosis, fistulae and pseudoelephantiasis, and may also give rise to granulomas and condylomatous masses [6]. Onchocerciasis causes depigmentation, nodules, atrophy, lymphadenopathy and a 'hanging groin' [7]. Trichosporosis is a common cause of genitocrural intertrigo in India, with symptoms of itching or burning. Scaly papules may accompany the intertrigo. Coexisting dermatophyte, *Candida*, trichomycosis and erythrasma infection may be found. Dequalinium chloride is applied topically for treatment [8]. Trichomycosis presents with malodour and discolored broken hairs [9], which should be distinguished from those of trichorrhexis nodosa, caused by repeated scratching [10]. Blastomycosis, actinomycosis and other deep fungal infections (see Chapter 31) simulate tuberculosis, but are more prone to form fissures, sinuses and vegetating or exuberant granulomatous lesions. They are distinguished by histological and bacteriological examination.

Among chronic infections, tuberculosis, tertiary syphilis and leishmaniasis are diagnosed by their characteristic features, which are described elsewhere. Congenital syphilis can be overlooked as a cause of genitocrural intertrigo in an infant. In tropical countries, tuberculous inguinal lymphadenopathy may be a cause of genitocrural lymphoedema. Amoebiasis involves the groins and perineum by extension from the anus.

Sexually transmitted diseases are fully discussed in Chapters 27 and 30. Granuloma inguinale affects the genitalia in less than half of cases, causing coalescing nodules, serpiginous ulcers and fungating masses. The buboes and fistulae of lymphogranuloma venereum are characteristic. Vulval (rarely scrotal) lymphoedema and elephantiasis may occur in both diseases.

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Miscellaneous

In the 'short bowel syndrome', kwashiorkor-like changes include an 'enamel paint skin' [1]. Dowling–Degos disease (reticulate pigmented anomaly of the flexures) involved the flexures in eight out of 10 patients [2], but may be restricted entirely to the vulval skin [3].

Acanthosis nigricans almost invariably affects the groins. Pseudoacanthosis nigricans can present as a macerated intertrigo and with secondary infection. These can be distinguished from each other and from lichenification in pigmented skins by a rubber silicone impression technique [4]. Calcinosis involving the upper inner thighs may resemble pseudoxanthoma elasticum [5].

The following entities are encountered in the genitocrural area. Angiomas and angiokeratomas—diffuse angiomas or lymphangiomas may cause irregular subcutaneous swellings; angiokeratoma corporis diffusum may be a feature of several very rare congenital diseases affecting lysosomes, with the pinhead-sized lesions of Anderson–Fabry disease (α-galactosidase deficiency) occurring around the lower limb girdle and upper thighs from the navel to the knees. Epidermal naevi are not uncommon. Seborrhoeic warts may be mistaken for viral warts [6] or Bowenoid papulosis, as may melanocytic naevi or acrochordons. Papilliferous naevi and skin tags often become large and pedunculated on the inner aspect of the thighs. Inguinogenital epidermoid cysts may become infected; lesions containing molluscum contagiosum have been described [7]. Pilar cyst, including giant forms, is much rarer [8].

Pubic hair problems are relatively rare in men, whereas women may be troubled by hirsutism or pili incarnati. Alopecia areata rarely affects this region alone. Vitiligo is common in the groins.

Extramammary Paget's disease can involve the genitocrural folds and present as an intertrigo.

Carcinoma erysipeloides (from anogenital disease) [9] is probably more common in the genitocrural area than reports would suggest. Carcinoma of the cervix, bladder and prostate may be the cause [10].

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Male genital dermatology

Introduction

Male patients with non-venereological and non-urological skin problems commonly present to genitourinary or urology clinics where the training and expertise are not orientated to adequate dermatological diagnosis and treatment [1].

Careful dermatological evaluation, including a full history and complete examination, usually allows confident clinical differential diagnosis. A biopsy and other investigations are sometimes indicated. It is important to consider the possibility of sexually transmitted disease or a urological disorder and refer accordingly; combined clinics are useful.

History taking and the primary symptomatology of anogenital dermatology are discussed on pp. 68.1–68.4. It may be necessary actively to elicit symptoms caused by sexual dysfunction, and it should be remembered that male sexual function amounts to more than erectile potency; libido, ejaculation and orgasm are the other components [2].

Complete examination is mandatory to elicit important signs at extragenital sites. The physical examination of the male at any age is incomplete without examination of the genitals and scrotum (but this is frequently not carried out in general clinical settings) and urologists teach that there are three primary reasons for careful examination of the scrotum: pain, swelling and absence of contents. The presence or absence of the prepuce, phimosis or paraphimosis should be sought and the foreskin retracted gently (if present). The gluteal and crural folds should be parted to allow adequate inspection. Sometimes it is useful to elicit dermatographism of the inner thighs. Urinalysis completes the physical examination.

Findings specific to the male genitalia include phimosis, paraphimosis, balanitis and posthitis. Phimosis ('muzzling') refers to a non-retractable foreskin. The literature can be confusing; Rickwood [3] has defined it as scarring of the tip of the foreskin. There are several possible causes of phimosis (Table 68.11). In adults, phimosis is usually the consequence of disease processes. It has also been attributed to titanium formulated in proprietary topical preparations [4]. Diabetes was diagnosed in 36% of men between 17 and 59 years of age presenting with phimosis of less than 2 years' duration, with no specific preputial pathology identified histologically [5]. In boys, the histological findings may be normal in nearly half of those circumcised [6].

Table 68.11 Causes of phimosis. (After Bunker [7]. © 2004, with permission from Elsevier.)

Non-specific balanoposthitis (e.g. in diabetes)
Lichen sclerosus
Lichen planus
Hidradenitis suppurativa
Crohn's disease
Cicatricial pemphigoid
Chronic penile lymphoedema
Kaposi's sarcoma

Table 68.12 Causes of paraphimosis. (After Bunker [7]. © 2004, with permission from Elsevier.)

Acute contact urticaria
Acute allergic contact dermatitis
Lichen sclerosus

Paraphimosis refers to a foreskin fixed in retraction. Although some authors have used the term to describe a foreskin that is tight in retraction around the flaccid penile shaft, 'waisting' may be a better term [7]. Rickwood [8] has said that paraphimosis results from abuse not disease of the foreskin, but some medical causes can be identified (Table 68.12).

Balanitis is inflammation of the glans penis; posthitis is inflammation of the prepuce [9]. Balanoposthitis means inflammation of the glans and prepuce and can be regarded as a special form of intertrigo (Tables 68.13 & 68.14). By definition therefore, balanoposthitis cannot occur in the circumcised male. Generally, dermatologists feel that balanitis, posthitis and balanoposthitis are probably more commonly caused by inflammatory and precancerous dermatoses than do genitourinary physicians, who teach that most cases are caused by infection, usually with *Candida* [10,11]. However, the evidence for *Candida* as a cause for balanoposthitis is not strong [12].

General aspects of anogenital ulceration are discussed on pp. 68.3–68.4 and in Tables 68.9 and 68.10. The principal causes of male genital ulceration are sexually transmitted and non-sexually transmitted infection, cancer and artefact [13]. Several causes can co-present, especially in HIV/AIDS. Dorsal perforation of the prepuce is a recently highlighted complication of several ulcerative penile diseases, sexually and non-sexually acquired, as listed in

Table 68.13 Common causes of balanoposthitis. (After Bunker [7]. © 2004, with permission from Elsevier.)

Eczema
Exogenous
allergic contact
irritant contact
Endogenous
seborrhoeic
Psoriasis
Reiter's disease
Zoon's plasma cell balanitis
Lichen sclerosus
Gonorrhoea
Human papillomavirus
Herpes simplex
Candidosis

Table 68.14 Rare causes of balanoposthitis. (After Bunker [7]. © 2004, with permission from Elsevier.)

Crohn's disease
Streptococcal dermatitis
Staphylococcal cellulitis
Gonorrhoea
Syphilis
Chancre with balanitis of Follman
Mucous patch
Mycoplasma
Trichomonas vaginalis
Lymphogranuloma venereum
Non-syphilitic spirochaetal ulcerative balanoposthitis
Tinea
Amoebiasis
Myiasis
Scabies
Eccrine syringofibroadenomatosis
Erythroplasia of Queyrat
Kaposi's sarcoma
Chronic lymphatic leukaemia
Fixed drug eruption

Table 68.15 Causes of dorsal perforation of the prepuce.

Hidradenitis suppurativa
Pyoderma gangrenosum
Florid condylomata
Podophyllin
Chancroid
Herpes simplex

Table 68.15 [14,15]. Penile necrosis is a rare but devastating presentation with an important differential diagnosis.

Special investigations appropriate to anogenital cases are discussed on p. 68.3. In genitourinary clinics, application of 3–5% acetic acid to the penis is used as an aid to the clinical diagnosis of viral warts and is held to reveal subclinical infection [16], but is not in routine use in dermatological practice. Human papillomavirus (HPV) polymerase chain reaction (PCR) screening suggests that the acetowhite test is not very specific [17–19]. A penis biopsy can be highly informative in selected cases [20]. It is safe to use small amounts of adrenaline in the local anaesthetic. Beware of the distal ventral midline area where the urethra is very close to the skin surface. It is often not necessary to suture a punch biopsy site.

Structure and function of the male genitalia

The penis is the male organ of urinary elimination and sexual function for the insemination of the female. The prepuce and its secretions provide physical and immunological protective functions, and it has erogenous properties (e.g. the penile dartos muscle and the corpuscular receptor-rich ridged band), but none of these is indispensible for erogenous function in copulation [21]. The scrotum maintains the testes at the ideal temperature for spermatogenesis. The male genital structures are illustrated in Fig. 68.1. The anatomical position is that of full penile erection.

The anatomy is explained by the embryology [22]. At about the third week of fetal development, mesenchymal tissue from the primitive streak forms cloacal folds

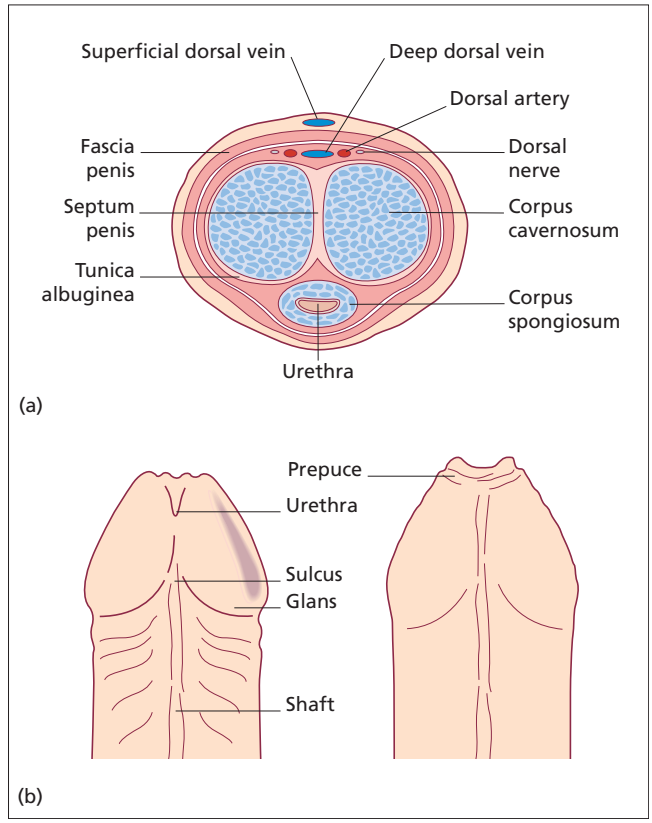

Fig. 68.1 (a) Cross section of the body of the penis. (b) Circumcised and uncircumcised glans penis. (Adapted from *Last's Anatomy*, 9th edn. Reproduced from Bunker CB. *Male Genital Skin Disease*, © 2004, with permission from Elsevier.)

around the cloacal membrane, joined anteriorly and cranially to form the genital tubercle, posteriorly and caudally to form an annulus. The cloacal membrane is thus divided into urogenital and anal membranes craniocaudally, and lateral genital swellings appear as precursors of either the scrotum or labia majora.

Fetal and testicular androgens then induce lengthening of the genital tubercle to form first an urethral groove and then the urethral canal. The urethral epithelium of the penis is therefore derived from endoderm. Initially, it is incomplete cranially where the glans has developed from the genital tubercle. The glandular urethra and the meatus form from an invading canalizing cord of ectoderm. The scrotal swellings fuse posteriorly at about 14 weeks but are empty until birth.

The prepuce [21] is formed by a midline fusion of ectoderm, neuroectoderm and mesenchyme, resulting in a pentalaminar structure consisting of (from the inner layer outwards) squamous mucosal epithelium, lamina propria, dartos muscle, dermis and glabrous skin. The preputial fold progressively extends, but there is also an ingrowth of a cellular lamella. It then fuses with the mucosa of the glans. The female analogue is the clitoral hood.

The anogenital area is densely endowed with eccrine and apocrine sweat glands. Also in plentiful number are holocrine sebaceous glands, usually in association with hair follicles but also occurring as free glands at some sites such as the anal rim or around the coronal sulcus (Tyson's glands). These secretions exist to lubricate hair, lubricate the mucocutaneous junctions to assist in the voiding of excreta and protect the epithelia from irritation and to lubricate the penis for sexual activity (probably mainly the retraction of the foreskin rather than the penetration of the vagina).

Pubic hair appears in puberty as vellus hair that is focally replaced by terminal hair. The pattern of pubic hair in men is different from that in woman, and its distribution varies widely between men. McGregor [23] defined three patterns (Fig. 68.2). Generally, the abdominal wall, pubic mound, groins, scrotum and perineum are hairy but the natal cleft, perianal skin, distal penile shaft, prepuce and glans are hairless.

The pattern of keratinization of the epithelium is different throughout the anogenital area, particularly at the mucosal junctions, the prepuce and distal penile shaft and the glans in the circumcised male. The spectrum of differentiation of the male urogenital tract is manifest in the expression of differing epithelial cytokeratins [24].

Normal variants

Normal male genital variants include pigmentary variation, hair variation as above, skin tags, pearly penile papules, sebaceous prominence (Fig. 68.3), melanocytic naevi, prominent veins, angiomas and angiokeratomas, common congenital abnormalities and circumcision.

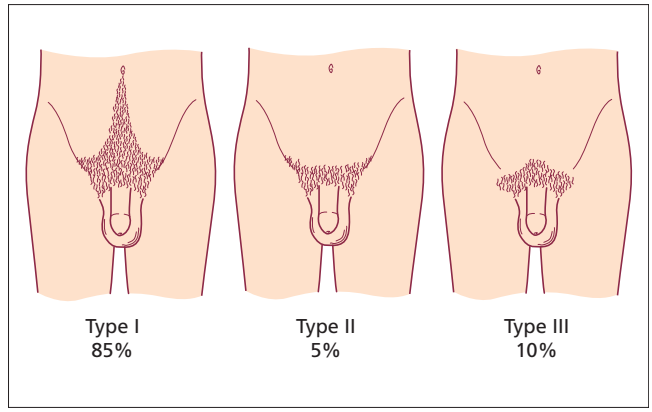

Fig. 68.2 Normal distribution of pubic hair in men. (After McGregor [23]. Reproduced from Bunker CB. *Male Genital Skin Disease*, © 2004, with permission from Elsevier.)

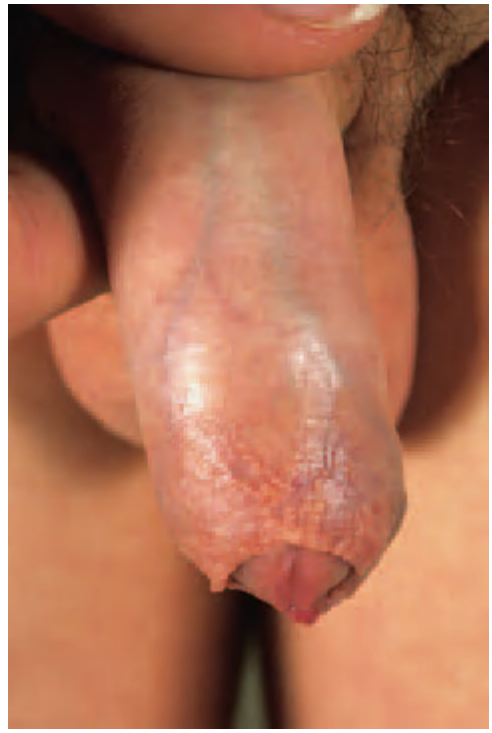

Fig. 68.3 Prominent sebaceous glands on the penis. (Courtesy of Dr F.A. Ive, Durham, UK.)

Skin tags are common in the groins, especially of obese men. They may catch on clothing, bleed and become infected. Treatment is by electrocautery or scissor amputation and cautery. Fibrosed haemorrhoids result in perianal skin tags. Larger, fleshier, more oedematous skin tags should arouse the suspicion of Crohn's disease. They can predate gastrointestinal disease by several years. Sigmoidoscopy and biopsy should be considered [25].

Pearly pink penile papules [26] are common; they may be found in up to 50% of men [27]. They present as flesh-coloured smooth rounded 1–3 mm papules, occurring predominantly around the coronal margin of the glans,

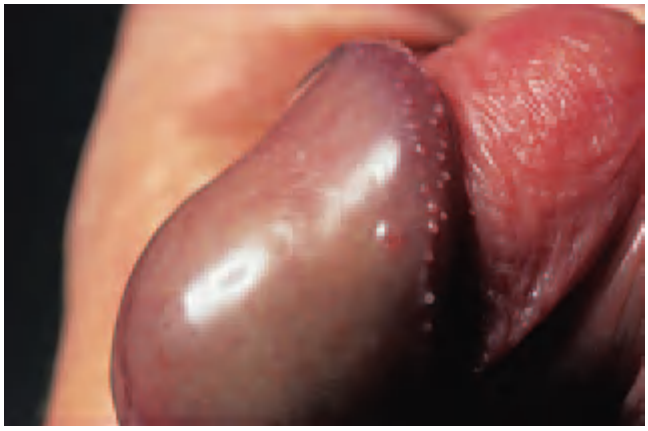

Fig. 68.4 Pearly penile papules. (Courtesy of Dr D.A. Burns, Leicester, UK.)

rarely on the glans, in rows or rings (Fig. 68.4). Ectopic lesions on the penile shaft have been reported [28]. They are frequently mistaken for warts and misdiagnosed as Tyson's or ectopic sebaceous glands of Fordyce. The patient is often an anxious adolescent. The histology is that of angiofibroma. The lesion is analogous to other acral angiofibromas such as adenoma sebaceum, subungual and periungual fibromas, fibrous papule of the nose, acquired acral angiofibroma and oral fibroma [29]. Reassurance is usually sufficient but cryotherapy and laser treatment can be effective [30, 31].

Sebaceous gland prominence, Tyson's glands, sebaceous hyperplasia and ectopic sebaceous glands of Fordyce are all virtually synonymous, common, normal variants of the skin of the scrotal sac and penile shaft, but they may cause concern to the patient. Fordyce's condition also commonly affects the vermilion border of the lips. Naevoid linear lesions on the penile shaft have been seen [32]. The glans can be affected [33]. Reassurance is usually all that is required, but dysmorphophobia can occur.

Congenital and acquired melanocytic naevi are common. It is possible that naevi on the penis occur more frequently in patients with the atypical naevus syndrome, but this has not been formally documented. Genital epithelioid blue naevus is very rare [34]. Divided or 'kissing' naevus (analogous to the entity recognized on the eyelids) has been reported, with one component located on the glans and the other on the distal penile shaft or prepuce, separated by uninvolved skin across the coronal sulcus [35]. Large 'bathing trunk' naevi frequently involve the anogenital area and pose significant management problems (see Chapter 38).

Prominent veins are common, if not universal, and occasionally give rise to concern. Vascular white spots are sometimes seen on the glans, and are possibly analogous to Bier's spots seen on the palms and forearms.

Cherry Campbell de Morgan angiomas may, unusually, be confined to the genitalia. Angiokeratomas on the

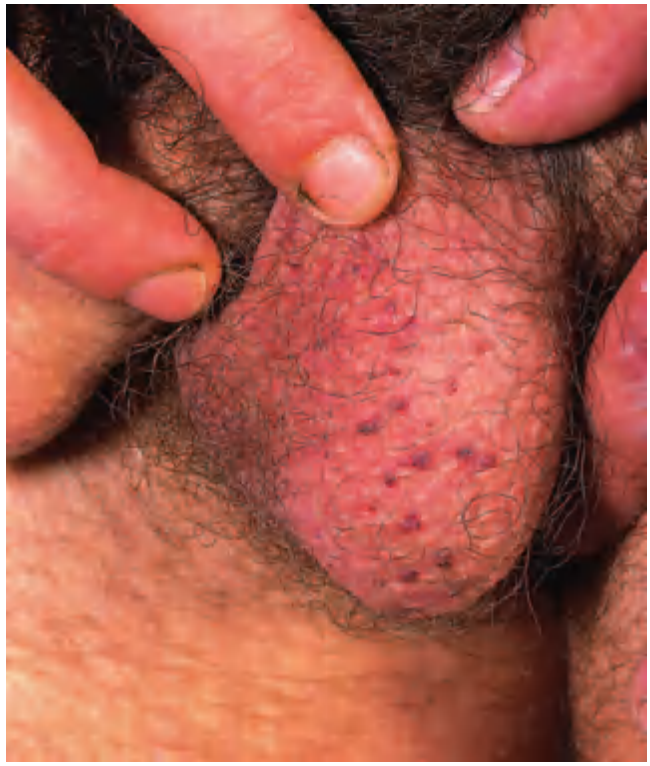

Fig. 68.5 Scrotal angiokeratoma of Fordyce (Courtesy of Dr D.A. Burns, Leicester, UK.)

genitalia have also confusingly been given the Fordyce eponym (Fig. 68.5). They are multiple, rarely solitary, blue to purple, smooth, 2–5 mm papules on the scrotum or penile shaft, rarely the glans. Angiomas and angiokeratomas may bleed following trauma. The differential diagnosis includes angiokeratoma corporis diffusum, acquired capillary and cavernous haemangiomas, Masson's tumour, glomus tumour, epithelioid haemangioma, bacillary angiomatosis, Kaposi's sarcoma and epithelioid haemangioendothelioma. Hyfrecation, electrocautery or laser ablation [36] can be offered, but lesions recur. Many patients are content with reassurance and a biopsy is not usually necessary.

The foreskin

The prepuce has been present in primates for 65–100 million years. It is usual for it to be adherent to the glans at birth. Four per cent of boys have a retractable foreskin at birth, 15% at 6 months, 50% at 1 year and 80–90% at 3 years; the process should be complete by 17 years [21]. The foreskin varies in length and retractability: 'short' and 'long' variants are seen.

Circumcision

Circumcision has been performed for religious, cultural or medical reasons throughout history [37]. Worldwide, it

has been estimated that approximately 25% of men have been circumcised [38]. Routine neonatal circumcision is controversial [39]. The UK General Medical Council (GMC) undertook a review of infantile circumcision in 1997, which 'demonstrated widely conflicting views in society that neither doctors nor the GMC can resolve' [40].

During infancy, circumcised boys have a higher incidence of penile problems than the uncircumcised, but after infancy the situation is significantly reversed [41,42]. Many have concluded that circumcision protects men from cancer of the penis and urinary tract, and sexually transmitted infections including HIV [43]. However, the incidence of penis cancer is low in countries where circumcision is uncommon [44], so other factors are important in penile carcinogenesis (see pp. 68.36–68.38). Also, the effects of circumcision on the other outcomes may be small [45] (e.g. urethritis may be more common in the circumcised, whereas ulcerative disease is more common in the uncircumcised). Circumcision protects men from inflammatory genital dermatoses including psoriasis, seborrhoeic dermatitis, lichen planus and lichen sclerosus [46].

Circumcision is important in the management of disorders of the penis and the foreskin, including dermatological disease. However, variability exists between clinicians in the indications for circumcision, especially in children. They include true phimosis, recurrent balanoposthitis, lichen sclerosus, penile lymphoedema, intraepithelial neoplasia and carcinoma.

The consensus is that circumcision has insignificant adverse effects on health, but it is not risk or complication free: bleeding, infection, adhesions, fistula, keloid, concealed or buried penis, amputation, excision of excessive penile skin, meatal stenosis, meatitis and meatal ulcer, cysts, chordee, hypospadias and epispadias, amputation neuromas, abnormal sexual behaviour, psychological distress and dysmorphophobia [47–53]. 'Uncircumcision' describes preputial restoration performed throughout history for various reasons [54,55].

Congenital and developmental abnormalities

Congenital and developmental anomalies are common because of the complicated embryogenesis and subsequent sexual differentiation of the anogenital region. The dermatologist may not be called upon to make a primary diagnosis, but needs to be aware of anatomical and functional abnormalities because these additionally predispose the area to dermatoses and infections.

Naevi are discussed above. Other common abnormalities include meatal pit, sacral pit, hypospadias [56], median raphe cysts, canals and sinuses, and ambiguous genitalia.

Other rare anomalies include hypospadias variants, epispadias, penile hypoplasia, mucoid or urethral cysts, dermoid cyst, juvenile xanthogranuloma, buried penis, urethral atresia, penoscrotal transposition, congenital lymphoedema, giant prepucial sac, megaprepuce, accessory scrotum, haemangiomas, strawberry naevus, os penis, true aposthia and faun tail [7].

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Trauma and artefact

Penile haematoma and rupture

The genitals may be readily traumatized by sexual activity. The penis is very vascular but haematoma formation and 'fracture' (penile rupture) are quite rare [1]. Pain, swelling and deformity associated with the history of a cracking noise during strenuous or contorted intercourse characterize the diagnosis. Splitting of the tunica albuginea of the corpus cavernosum can result in urethral damage, haematoma and retention. The prognosis is generally good but Peyronie's disease can occur [2]. Injection of drugs for erectile dysfunction can be complicated by haematoma.

Sclerosing lymphangitis

Non-venereal sclerosing lymphangitis/penile venereal oedema/Mondor's phlebitis/localized penile (venereal) lymphoedema/penile lymphocoele presents with a serpiginous mass in the coronal sulcus. The lesion usually arises after prolonged or frequent sexual intercourse with a passive or unenthusiastic partner; subsequent sexual activity may result in tenderness and enlargement. The circumferential scar left by circumcision may be a predisposing factor. There may be spontaneous resolution, or surgical excision may be needed [3]. It is not known whether lymphangitis or phlebitis is the cause [4]. True phlebitis of penile and scrotal veins has been reported in three patients, one of whom had been injured by a golf ball but the others were idiopathic [5]. Thrombophlebitis of superficial penile and scrotal veins is analagous to Mondor's phlebitis of the chest wall (see Chapter 67), but it may be associated with polyarteritis nodosa and thromboangiitis obliterans [6]. Penile thrombophlebitis has been misdiagnosed as Peyronie's disease, and has also been the initial manifestation of a paraneoplastic migratory thrombophlebitis resulting from pancreatic cancer [7].

Strangulation of the penis

The penis may be strangulated by ring devices [8] , including vacuum erection equipment [9], condom rings [10], rubber bands, string, rings (washers), nuts, bushes and sprockets, which are placed deliberately on the penis by the patient for masturbation or by his partner to prolong erection [11,12]. In boys, strangulation can occur following experimental use of rubber bands or string or thread to control enuresis, or resulting from encoiled hair after circumcision [13]. Penile strangulation—the tourniquet syndrome—causes pain, swelling, urethral fistula, pseudoainhum, gangrene and amputation.

Foreign body

Self-instrumentation of the external genitalia may have an autoerotic, psychiatric, therapeutic (relief of itch [14], aiding voiding, cleaning) or accidental aetiology [15]. Complications include frequency, haematuria, abscess, retention, fistulae and calculi. The diagnosis is made by palpation and radiography. Endoscopic removal is usually possible for foreign bodies below the urogenital diaphragm.

Glass beads, spheres of plastic or small round smooth stones (even pearls) may be introduced under the skin of the penis for erotic reasons, causing clinical and radiographical confusion. If oil, petroleum jelly or silicone is

used then a paraffinoma, silicone granuloma or (sclerosing) lipogranuloma can result. In the Philippines, this practice is called 'bulleetus', in Sumatra 'persimbraon', in Korea 'chagan ball' and in Thailand it is called 'mukhsa' or 'tancho' [16].

Extrusion of a testicular prosthesis has been reported to cause scrotal ulceration because of a sinus tract [17].

Lipogranuloma

Mineral oil, petroleum jelly and silicone introduced into the genital skin can elicit lipogranuloma. Most cases are self-induced, either to create testicular prostheses or to increase penile size, enhance sexual pleasure, mutilate or malinger, although some may be accidental [18,19]. One patient injected his penis with an industrial high-pressure pneumatic grease-gun [20]. Endogenous fat liberation is a possible mechanism and idiopathic cases have been reported, predominantly from Japan [21].

Dermatitis artefacta

Dermatitis artefacta on the genitalia does occur. Lesions are typically geometrical, angulated and rectilinear. Sometimes they are induced by needles, knives or cigarette burns, and extraneous foreign material may be introduced into the skin (lipogranuloma and silicone granuloma are discussed above).

Psychotic patients may mutilate their genitalia, as can transvestites [22], but non-psychotic genital self-mutilation can also occur. Australian aborigines slit the penis—open the urethra ventrally, creating hypospadias—and this is called subincision [23]. Ritual female circumcision in Islam, and male circumcision in the Jewish culture, Islam and Western society may be perceived as similar practices.

Biopsy and other investigations may be necessary to exclude penile cancer. It is important also to consider pyoderma gangrenosum, which is rare but frequently omitted from the differential diagnosis of penile ulceration by non-dermatologists.

Child abuse

Physical and sexual child abuse should be suspected in the differential diagnosis of cutaneous disease of the anogenital area in children (Table 68.16), but signs should be interpreted with caution and re-examination should be avoided [25–29]. Child abuse may be erroneously suspected (Table 68.17) when the anogenital area is involved by a dermatosis or a diarrhoeal illness [30].

The significance of anogenital warts in suggesting possible child sexual abuse is controversial. However, early recognition as a marker for child sexual abuse is in the child's long-term best interest [31].

Table 68.16 Anogenital signs of child abuse. (After Bunker [24].)

Overall context
Emotional disturbance
Passivity on anogenital examination
Anal relaxation/dilatation
Purpura, bruising, tearing
Signs of sexually transmitted disease

Table 68.17 Anogenital mimics of child abuse. (After Bunker [24].)

Nappy rash
Innocent skin tags and fissures
Threadworms
Eczema
Phytophotodermatitis
Lichen sclerosus
Henoch–Schönlein purpura
Acute haemorrhagic oedema of childhood
Anogenital streptococcal dermatitis
Causes of diarrhoea
Haemolytic–uraemic syndrome
Crohn's disease
Causes of constipation
Hirschsprung's disease

Miscellaneous

Sometimes the penis is bitten by another individual or an animal [32]. Purpura and ecchymoses may develop after oral sex ('love bites') or the use of vacuum erection devices [33]. Degloving injuries can occur in accidents with industrial or agricultural equipment [34]. Electric burns are rare [35]. Sex aids can result in abrasions, eczema and ulceration. Anogenital tattoos are commonplace [36].

Localized gangrene of the scrotum and penis resulting from arterial embolization with particulate matter complicating accidental femoral self-injection of heroin in an addict has been reported [37].

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Inflammatory dermatoses

Urticaria and dermographism

These are usually generalized eruptions (see Chapter 47) but it has been proposed that they may account for some of the symptomatology in some patients with unexplained genital itching (and pruritus ani—see below). Stroking the inside of the thigh might induce a weal; indeed, stroking can cause itching without any discernible redness or wealing [1,2]. Contact urticaria is discussed below. Lisinopril has been reported to cause genital angio-oedema [3].

Fig. 68.6 Scrotal lichen simplex. (Courtesy of Dr F.A. Ive, Durham, UK.)

Eczematous dermatoses

Itching and lichenification, particularly around the scrotum, are common presenting problems. Contributory factors include pre-existing dermatoses such as xerosis, atopy and psoriasis, sedentary occupations, motor car and aeroplane travel, and tight underclothing and trousers.

Irritation is a key adverse exogenous influence to which anogenital sites are vulnerable, and sweat, sebum, desquamated corneocytes, dirt, excreta, sexual secretions, clothing, detergents, toiletries, cosmetics, contraceptives and some therapeutic topical treatments are all potential irritants.

Frequently underrated are the effects of overwashing and the excessive use of soap and toiletries, especially in the presence of skin symptoms or urinary or bowel problems, and particularly if patients feel that they might have been exposed to a sexually transmitted disease.

Lichen simplex

Lichen simplex is common around the male genitalia. It is not usually a flexural condition but can be seen on the penile shaft and scrotum (Fig. 68.6). Giant forms (of Pautrier) occur, giving a pineapple appearance [4]. The skin may be broken by excoriations and become secondarily impetiginized or colonized by *Candida*.

Treatment follows the lines of management above and below relating to irritants. There is emphasis on the relief of scratching, soap substitution and moisturization are recommended and the area occluded if possible with a bland dressing—wet if the skin is fiercely eczematized. A potent topical corticosteroid ointment can be used for a few days and then tailed off. Preparations containing tar or combinations of antibacterial and anticandidal and antifungal agents are also useful. Two cases of extensive

Table 68.18 Anogenital irritants. (After Bunker [5]. © 2004, with permission from Elsevier.)

Sweat
Sebum
Desquamated corneocytes
Dirt
Excreta
Sexual secretions
Clothing
Soap and detergents
Toiletries
Toilet paper
Cosmetics
Contraceptives
Therapeutic
Friction
Maceration

Table 68.19 Allergens of particular relevance to anogenital contact dermatitis. (After Bunker [5]. © 2004, with permission from Elsevier.)

Euxyl K 400 (methyldibromoglutaronitrile)
Kathon CG (isothiazolinones)
Lidocaine (lignocaine) and other topical anaesthetics
Neomycin
Nystatin
Steroid moieties
Thiuramdisulphide—rubber
Latex condoms
Spermicides
Mitomycin C

giant lichen simplex of the scrotum have been successfully treated by hemiscrotectomy [4].

Irritant contact dermatitis

Anogenital irritants are discussed above and listed in Table 68.18. Friction [6], maceration, overwashing, concomitant anorectal or urological disease are the chief influences. There may be an association with atopy; Birley [7] diagnosed irritant dermatitis in 72% of patients presenting to a genitourinary clinic with 'balanitis' (probably meaning balanoposthitis) of whom a possible 67% had a history of atopy, but none of these patients was patch tested. An irritant scrotal dermatitis in cellists has been described [8]. Topical 5-fluorouracil used to treat keratoses at extragenital sites has caused genital irritant dermatitis [9]. Acute or chronic, sterile or superinfected (with staphylococci or *Candida*, or both), eroded or hyperkeratotic presentations are seen, depending on the scenario. A good example is nappy (diaper) rash (see Chapter 14).

Management follows lines similar to those for pruritus ani (see p. 68.87). Irritants should be identified and eliminated or reduced. Advice is given about soap substitutes, moisturizers, towels and toilet paper. Topical corticosteroid ointments, with or without antibiotic and anticandidal agents, are employed to control the dermatitis. Oral antihistamines are useful. Topical local anaesthetics should be avoided because of the risk of sensitization. Occasionally, secondary infection may be severe; a swab should be taken and oral antibiotics and oral antifungals prescribed.

A more acute picture (itch, burning or pain, swelling, erythema, vesiculation) may occur if highly irritant chemicals in high concentration are accidentally or deliberately used on the genitalia. Patients with a genital rash who are frightened that it may have been sexually acquired will sometimes self-treat with unsuitable preparations and in the process increase their morbidity and conceal an underlying sexually transmitted disease or dermatosis. Treatment is with potassium permanganate soaks, very potent topical corticosteroid creams (sometimes systemic corticosteroids) and systemic antibiotics.

Allergic contact dermatitis

The risks of allergic contact dermatitis of the genital skin come about from: (i) direct contact with the allergen (e.g. medicaments—even coal tar allergy has been reported [10]), contraceptive usage and prosthetic limbs in amputees [11]; or, very rarely, (ii) transfer of allergen (e.g. urushiol as in poison oak, poison ivy and poison sumac dermatitis) to the genitalia [12] and possibly subsequent exposure to sunlight (e.g. psoralens from fig or citrus plants, as in phytodermatitis); and (iii) involvement in a more generalized eczematous response (e.g. to a medicament or dressing used on venous eczema or ulceration, as in the autosensitization/secondary spread/secondary generalization syndrome).

Acute or chronic eczematous symptomatology appears approximately 1 week after first contact with the allergen if previously unsensitized, or within a few hours if already allergic. The patient may present with pruritus ani [13] or paraphimosis [14]. More immediate symptomatology and acute erythema and angio-oedema suggest a contact urticaria, which can occur with some of the rubber constituents of condoms and gloves [15].

The principles of management are the identification of the potential allergen (Table 68.19) and its likely source, and then its elimination. There may be clues to these factors at presentation but subsequent patch testing is often required. Following patch testing, Bauer *et al.* [16] made a final diagnosis of allergic contact dermatitis in 35% of patients with anogenital skin problems. Allergic contact dermatitis can persist even with the withdrawal of the trigger allergen. Management is otherwise as for irritant contact dermatitis, lichen simplex and pruritus ani (see above and p. 68.87).

The most common relevant sensitivities are to rubber, contraceptives, preservatives and fragrances in toiletries

and medicaments, and the active agents (antibiotics, steroids, anaesthetics) in medicaments.

Genital rubber dermatitis is not confined to young sexually active male condom users and their partners [17–20]. Incontinent men who use external urinary collection devices (Paul's tubing) are also at risk. Latex allergy may be a problem in patients with spinal cord injury using rubber products for the management of urinary difficulties; life-threatening anaphylactic reactions have occurred [19]. Condoms made from lamb caecum are available for rubberallergic patients but they may provide less protection against sexually transmitted disease than latex. Creating hypoallergenic condoms by washing in an ammonium solution to remove the residues of the accelerator chemicals that actually cause the hypersensitivity has proved unsuccessful [21]. Patients may become sensitized to the spermicide [17].

Celandine juice [14] and clothing dye dermatitis of the scrotum [22] have been reported.

Atopic dermatitis

Genital skin disease caused by atopic dermatis (AD) is not uncommon but rarely occurs in isolation, unlike other common chronic dermatoses such as seborrhoeic dermatitis and psoriasis. It is not known how genital AD is related to circumcision, sexual activity and sexually transmitted disease. Evidence of atopy was found in a possible 67% of a total of 72% of patients diagnosed as having irritant dermatitis from a consecutive series of men presenting to a genitourinary clinic with 'balanitis'—probably balanoposthitis [6]. AD in HIV/AIDS is discussed in Chapter 26.

Radiodermatitis

Radiodermatitis (see Chapter 76) is not usually a diagnostic challenge or a therapeutic problem in the acute stage after radiotherapy to the anogenital skin for skin disease or internal cancer. In the chronic state, there may be pruritus together with the typical poikiloderma. Radiotherapy confers a long-term increased risk of skin cancer, especially basal cell carcinoma. There is concern that radiotherapy for Bowen's disease or erythroplasia of Queyrat may increase the subsequent risk of invasive carcinoma.

Seborrhoeic dermatitis

Genital involvement is frequent with this common dermatosis. The groins and penis may be the only sites involved. A good history (including family history) and careful examination of other sites typically affected aid the diagnosis. On the scalp, the face, in the flexures and at anogenital sites seborrhoeic dermatitis and psoriasis may be indistinguishable. Seborrhoeic dermatitis in HIV/AIDS is discussed in Chapter 26.

Diagnosis is established on clinical grounds, including response to therapy, and it is not usually necessary to perform a biopsy.

No treatment may be required other than reassurance that it is not sexually transmitted or related to poor hygiene. However, treatments that diminish the *Malassezia* load and reduce irritation and eczematization can be successfully and safely used long term. These include topical antifungals (such as clioquinol, nystatin and imidazoles) as ointments, creams, lotions or shampoos, and mixtures of the same agents with mild and moderately potent topical corticosteroids used alongside emollients and soap substitutes. In severe cases, patients with concomitant seborrhoeic folliculitis, or in patients with HIV/AIDS, treatment with an oral imidazole and/or an oral tetracycline may be suitable.

Psoriasis

Approximately 2% of the population are said to have psoriasis but it is possible that many more than 2% of men may have or have had anogenital psoriasis at some time; it is certainly a common anogenital diagnosis in isolation.

Psoriasis and its clinical manifestations are discussed in Chapter 35; the relationship of psoriasis with HIV/AIDS is discussed in Chapter 26. Anogenital presentations of psoriasis may be vague in symptomatology and nonspecific on examination. It is not usually itchy; significant itch should arouse suspicions of another dermatosis such as an eczematous dermatitis or tinea. Soreness occurs with superinfection, especially with *Candida*. Other typically affected sites should be examined for signs of the disease. Genital appearances may be challenging to interpret, especially in the uncircumcised patient, because a mucosal site is affected rather than keratinized skin. The diagnosis is usually easier in the circumcised male where the morphology is similar to extragenital lesions.

Inverse pattern psoriasis refers to the manifestation of the disease on intertriginous skin in the axillae, natal cleft, gluteal folds, groins and in the preputial sac and on the glans of the uncircumcised male, where its occurrence is probably brought about by the Koebner phenomenon.

Usually, the diagnosis of psoriasis is clinical, but a biopsy may be necessary (e.g. of a solitary mucosal lesion in an uncircumcised individual) to distinguish psoriasis from Zoon's balanitis, lichen planus, erythroplasia of Queyrat or Kaposi's sarcoma. Bowen's disease and extramammary Paget's disease may be misdiagnosed as psoriasis when there are single or several foci on the penile shaft and/or in the groins.

Topical treatment includes emollients, soap substitutes, corticosteroids combined with antibiotic and antifungal agents or weak tar solutions. Strong crude tar preparations should be avoided at this site given that anogenital skin has a propensity to increased absorption of topical agents and because of the risk of genital cancer; one of the first

occupational diseases described was scrotal carcinoma in chimney sweeps. Dithranol is usually avoided in this region. The vitamin D analogue calcipotriol can be helpful. Topical ciclosporin (100 mg/mL in wet dressings three times daily) has been advocated [23]. Phototherapy is contraindicated because of the risk of anogenital cancer. Severe anogenital psoriasis can be an indication for systemic treatment.

Reiter's disease or syndrome (part of the same continuum as psoriasis in genetically predisposed individuals) is discussed in Chapter 35. Characteristic, sometimes severe, involvement of the penis (circinate balanitis) occurs. The penile lesions have the same histopathology as psoriasis [24].

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Zoon's balanitis

Aetiology. Zoon's plasma cell balanitis (ZB) is a disorder of the middle-aged and older uncircumcised male [1,2], although an analogous condition has been reported to afflict the vulva (see p. 68.59), mouth, lips [3] and epiglottis [3,4]. Since Zoon's original reports there have been many accounts in the literature but the aetiology remains uncertain.

The evidence suggests that ZB is a chronic, reactive, principally irritant mucositis brought about by a dysfunctional prepuce. Retention of urine and squames between two tightly apposed and infrequently and inadequately separated and/or inappropriately bathed, commensally hypercolonized, desquamative, secretory epithelial surfaces leads to a disturbed 'preputial ecology' and excessive frictional trauma (ZB is often located on the dorsal aspect of the glans and/or the adjacent prepuce, sites of maximal friction on foreskin retraction) and irritation by urine [5–7]. There is no evidence of an infectious cause, and immunohistochemical findings suggest that ZB represents a non-specific polyclonal tissue reaction [8,9], consistent with an irritant mucositis.

Clinical features. The presentation is classically indolent and asymptomatic, although staining of the underclothes with blood has been reported [10]. Well-demarcated, glistening, moist, bright red or autumn brown patches involve the glans and mucosal prepuce [7], with sparing of the keratinized penile shaft and foreskin (Fig. 68.7). The urethra (fossa navicularis) may be involved. Other signs include dark red stippling—'cayenne pepper spots'—and purpura with haemosiderin, solitary or multiple lesions of differing sizes (guttate or nummular), characteristically symmetrical about the axis of the coronal sulcus and 'kissing'. Although vegetative and nodular presentations have been recorded, atypical or unusual morphology should be viewed with great suspicion and biopsied.

Histopathology. The classic histology is of epidermal attenuation with absent granular and horny layers, and diamond- or lozenge-shaped basal cell keratinocytes with sparse dyskeratosis and spongiosis. There is a band of dermal infiltration with plasma cells of variable density. Extravasated erythrocytes, haemosiderin and vascular proliferation are also seen. Although Zoon stressed the presence of the plasma cell infiltrate in this condition, the plasma cell numbers can be very variable [7,11].

Differential diagnosis. The differential diagnosis includes erosive lichen planus, psoriasis, seborrhoeic dermatitis, contact dermatitis, fixed drug eruption, secondary syphilis, histoplasmosis [12], erythroplasia of Queyrat [13] and Kaposi's sarcoma. A confident clinical diagnosis is not always possible or safe [6], so a biopsy is advisable and the

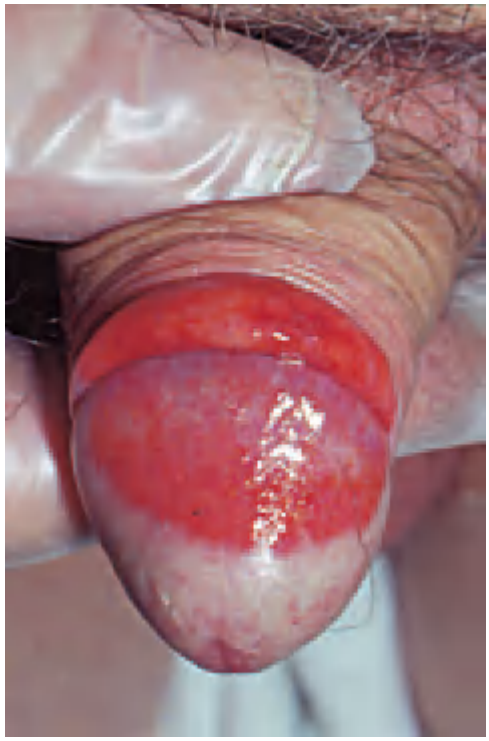

Fig. 68.7 Zoon's balanitis. Symmetrical moist erythema of glans and prepuce. (Courtesy of Dr C.B. Bunker, with permission from Medical Illustration UK, Chelsea & Westminster Hospital, London, UK.)

pathologist should be asked to look for concomitant disease. Frank cases of lichen sclerosus, lichen planus, Bowenoid papulosis and penile cancer often appear to have ZB-like changes on clinical examination and on histology. In other words, the signs of ZB may be secondary to underlying preputial disease. It is likely that some of the clinical and histological variants that have been reported [14–16], and a recent claim that ZB *per se* is a premalignant condition in a single case report [17], are a consequence of this phenomenon. ZB indicates a dysfunctional foreskin and a more sinister dermatosis may be concealed.

Treatment. Although ZB can improve with altered washing habits and the intermittent application of a mild or potent topical corticosteroid (with or without an antibiotic and anticandidal agent), it usually persists or relapses. Definitive curative treatment is circumcision [7]. Again, the pathologist should be asked to examine the whole specimen for signs of another underlying dermatosis. It has been claimed that the carbon dioxide laser is effective [18].

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Lichen sclerosus

Aetiology. Lichen sclerosus is discussed in Chapter 56. The aetiopathogenesis is not known. Poorly understood are the predilection for the genitalia generally (in males, particularly the uncircumcised [1]), the association with organ-specific autoimmune disease and the propensity to progress to squamous carcinoma [2–5]. HPV (types 6, 16 and 18) is present in 70% of cases of childhood penile lichen sclerosus [6,7], but the epidemiology and clinical tenor of lichen sclerosus is not that of an infectious or sexually transmitted disease [5,8]. Anatomical abnormality and trauma seem to be contributing factors [5,9]. Specifically, lichen sclerosus has been related to hypospadias and its repair [10]. The presence of the histopathological features of lichen sclerosus in a percentage of acrochordons (skin tags) has led to the suggestion that occlusion of flaccid skin is a pathogenic factor [11].

Clinical features. Lichen sclerosus of the penis may be asymptomatic, but diverse, often vague, symptomatology is usually encountered [12]. Patients may describe itching, burning, bleeding, tearing, splitting, haemorrhagic blisters, any manner of symptoms signifying sexual dysfunction or dyspareunia, discomfort with urination and narrowing of the urinary stream, and/or be concerned about the changing anatomy of their genitalia [5]. Other presentations are non-retractile foreskin (phimosis)

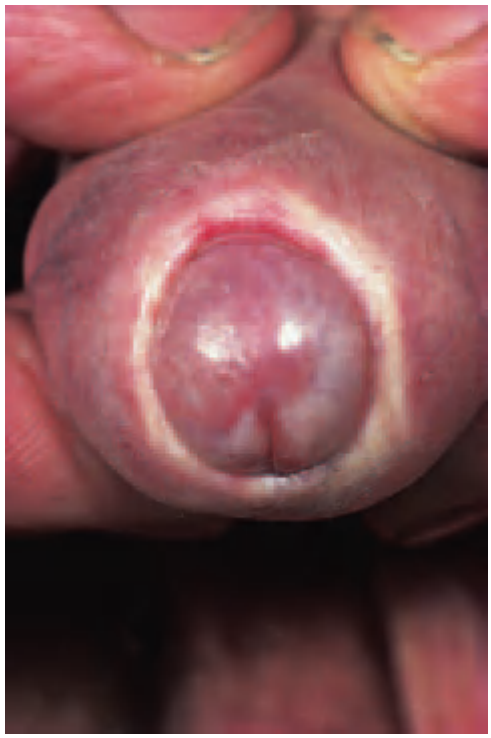

Fig. 68.8 Lichen sclerosus causing phimosis. (Courtesy of Dr D.A. Burns, Leicester, UK.)

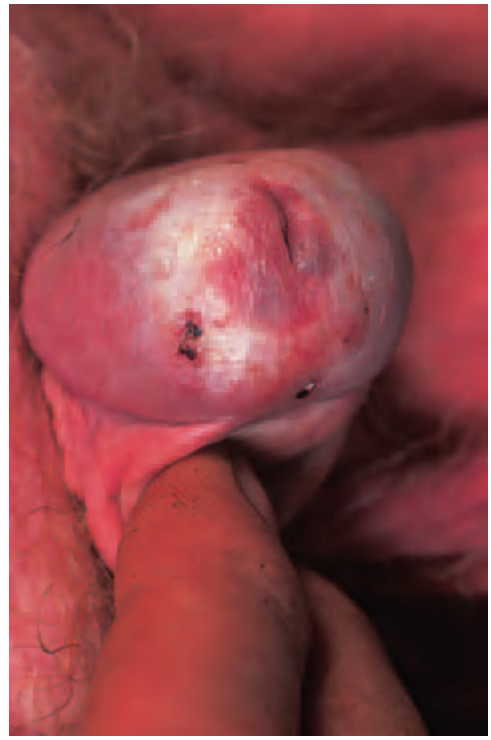

Fig. 68.9 Lichen sclerosus. White plaques and haemorrhagic areas on the glans. (Courtesy of Dr D.A. Burns, Leicester, UK.)

(Fig. 68.8), foreskin fixed in retraction (paraphimosis) and urinary retention, even renal failure.

Genital, like extragenital, lichen sclerosus can manifest as atrophic leukodermic patches or plaques, or lilac, slightly scaly patches with telangiectasia and sparse purpura (Fig. 68.9). Predominant purpura, bullae, erosions and ulceration may be encountered [5,13,14]. The signs may be subtle, with meatal 'pin hole' narrowing, slight tightening of the retracted prepuce because of sclerotic plaques and bands, with or without difficulty in retraction—incomplete paraphimosis or 'waisting' (Fig. 68.10) or they may be florid, with severe changes caused both by the lichen sclerosus and by associated Zoon's balanoposthitis-like changes: adhesions, loss of anatomical definition and dissolution or effacement of the normally sharply defined architectural features, especially of the frenulum and the coronal sulcus. Changes resulting from ZB may be more florid than the underlying lichen sclerosus. Post-inflammatory hyper- and hypopigmentation are occasionally seen.

Whereas posthitis xerotica obliterans refers to chronic damage to the prepuce by lichen sclerosus, balanitis xerotica obliterans (BXO) properly describes involvement of the glans penis (although the term has been used imprecisely). BXO can be a consequence of other scarring dermatoses such as lichen planus and cicatricial pemphigoid [15].

Genital lichen sclerosus is more common than extragen-

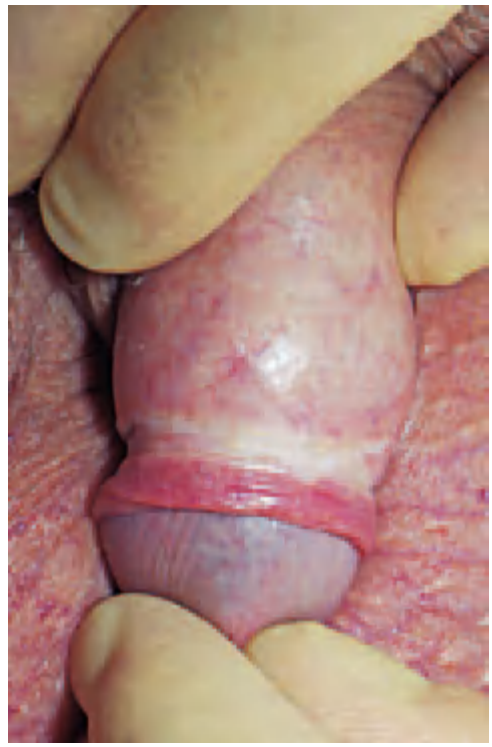

Fig. 68.10 Lichen sclerosus. Sclerotic band of the prepuce causing 'waisting'. (Courtesy of Dr C.B. Bunker, with permission from Medical Illustration UK, Chelsea & Westminster Hospital, London, UK.)

ital or oral disease, but there may (rarely) be concomitant involvement of these sites. In adults, anogenital lichen sclerosus is said to be about 10 times more common in women than men. Perianal disease seems rare in the male. The involvement of the anterior urethra can be serious: 29% of patients undergoing urethroplasty for urethral stricture had pathological evidence of lichen sclerosus [16].

The first report of genital lichen sclerosus in boys appeared only in 1977 [17], and lichen sclerosus may be much more frequent than is generally supposed in young boys. The development of secondary phimosis in school-age boys is highly suggestive of lichen sclerosus [18]. In the older male, persistent primary phimosis or the secondary development of phimosis in a previously retractable foreskin may be related to lichen sclerosus [5].

Most cases of genital lichen sclerosus can be diagnosed clinically. Lichen planus and the much rarer mucous membrane pemphigoid are in the differential diagnosis. A biopsy should be performed if there is clinical doubt or if the lesion is eroded or verrucous.

Histopathology. The histology is classic (see Chapter 56). The occasional association of endarteritis led originally to the usage of the term 'obliterans' [19]. In two cases in boys, a dermal lymphohistiocytic and granulomatous phlebitis has been found, and one also had evidence of HPV [20]. A garland-like basal lamina has been found ultrastructurally [21]. Sometimes, lichen sclerosus may be difficult to differentiate from lichen planus, and criteria to assist, in the vulva, have been proposed by Fung and LeBoit [22].

Treatment. Guidelines for the management of lichen sclerosus have been published by the British Association of Dermatologists [23]. A very potent topical corticosteroid (used under supervision) is effective [24]. The plasticity of the epithelium at this site seems to allow significant remodelling, with the relief of phimosis, improvement of incomplete phimosis or waisting, improvement in the histological changes and avoidance of circumcision [5,12]. Secondary candidal and bacterial infection should be treated. There are reports of the efficacy of long-term systemic antibiotic therapy (penicillin and azithromycin) in cases of lichen sclerosus thought to be associated with *Borrelia* infection [25,26]. Testosterone propionate ointment, oral stanozolol, freezing with ethyl chloride, liquid nitrogen cryotherapy, carbon dioxide laser and adrenocorticotrophic hormone (ACTH) have been used with variable success [5].

If medical treatment is not possible or fails, then surgery may be indicated. Circumcision, frenuloplasty, meatotomy and sophisticated plastic repair, depending upon the clinical presentation, can be offered. In boys, complete circumcision is the treatment of choice because all affected tissue is removed and any secondary involvement of the glans probably regresses or resolves [18]; it is the unproven impression that this phenomenon also occurs in most adult patients. Lichen sclerosus can recur in donor grafts from unrelated sites [13,27]. Carbon dioxide laser circumcision has been advocated [28].

Squamous carcinoma of the penis is the most serious potential complication of lichen sclerosus; *in situ* change can occur often after long periods [5,29]. A risk of 4–9.5% has been claimed, depending on length of follow-up; the latent period may be one to three decades [30–32]. Verrucous carcinoma (Buschke–Löwenstein tumour) has been associated with previous lichen sclerosus [33,34]. Carcinoma complicating lichen sclerosus constituted one-third of all cases of penile cancer seen by Campus *et al.* [35] and, of 20 patients with penile squamous cell carcinoma (SCC) studied by Powell *et al.* [36], 11 had a clinical history and/or histological evidence of lichen sclerosus. Involvement of the glans penis confers a greater risk [32].

The effect of medical and surgical treatment on the subsequent incidence of penile cancer is not known [37,38]. Liatsikos *et al.* [39] report SCC of the glans developing in one of eight patients followed-up after circumcision for lichen sclerosus. Patients should be followed-up long term, especially if circumcision has not been performed or if symptoms persist or recur after any form of treatment.

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Lichen planus

Aetiology. Lichen planus is discussed in Chapter 42. It is a common inflammatory dermatosis with a particular predilection for the mucosae [1]. The aetiopathogenesis of lichen planus is not known. Drugs can cause a generalized lichenoid eruption; a case of a lichenoid drug eruption confined to the penis resulting from propranolol has been reported [2].

Clinical features. Lichen planus can present in, and remain localized to the anogenital area, including the groins and perianal skin. Like the classical disease at other sites, it presents as itchy red–purple papules, also as patches or plaques and annular lesions (Fig. 68.11) or as phimosis [3]. The Koebner phenomenon may partly explain the orogenital predilection [4].

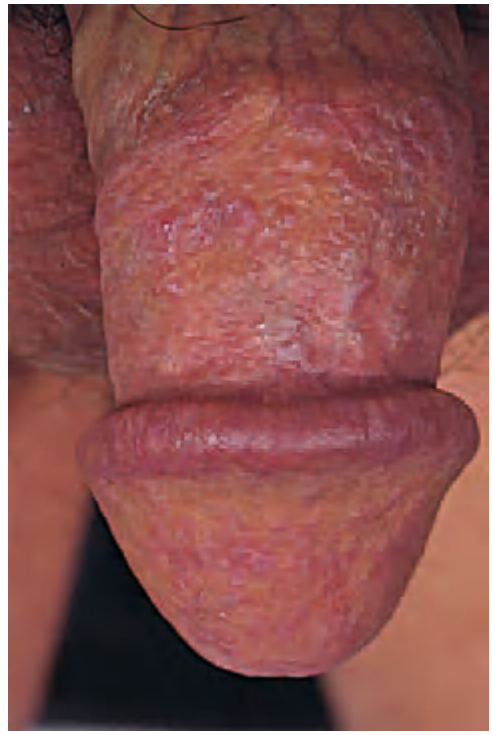

Fig. 68.11 Lichen planus. Papules and annular lesions with Wickham's striae on the glans and shaft. (Courtesy of Dr C.B. Bunker, with permission from Medical Illustration UK, Chelsea & Westminster Hospital, London, UK.)

Occasionally, an erosive form is encountered. There is a male equivalent of the vulvovaginal syndrome of Hewitt—the genito-gingival syndrome—with chronic erosive gingival and genital lesions [5]. In most cases, anogenital lichen planus is self-limiting, although some patients relapse and remit. Adhesions can form. Post-inflammatory hyperpigmentation can persist for months or years. A case of paraneoplastic lichen planus with orogenital and cicatrizing conjunctival involvement in a patient with thymoma has been reported [6].

Chronic mucosal erosive lichen planus is associated with a risk of progression to SCC but most reports concern oral lichen planus. SCC may complicate hypertrophic lichen planus of the glans penis [7,8].

Lichen nitidus has an affinity for the penis. It can be difficult to diagnose because the signs may be subtle, even when the lesions are widespread.

The differential diagnosis of anogenital lichen planus includes psoriasis, ZB, lichen sclerosus, viral warts, Bowenoid papulosis and porokeratosis. A biopsy is frequently necessary for diagnostic purposes and in the

follow-up of cases of chronic anogenital disease if erosive, ulcerative or verrucous features arouse concern about the development of SCC.

Treatment. Potent and ultrapotent topical corticosteroids usually suffice for treatment. Patients are told to continue with the treatment until the lesions are non-itchy and flat; they are warned about post-inflammatory hyperpigmentation. Topical and oral ciclosporin have been used [9,10]. Circumcision may be necessary for phimosis [11] and should be considered in refractory erosive disease [12]. The rationale being that the abolition of koebnerization influences and facilitates resolution of the lichen planus. Photodynamic therapy was used inadvertently in one patient with lichen planus of the glans penis, to good effect [13].

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Ulcerative disease and penile necrosis

Aphthous ulceration of the penis and scrotum can occur, including in HIV/AIDS (see Chapter 26), but specific exclusion of sexually transmitted diseases and consideration of other causes of genital ulceration, especially Behçet's syndrome, is necessary. The causes are obscure and the histology is non-specific.

Five cases of spontaneous scrotal ulceration in young, previously fit men have been described [1]. Histology showed non-specific vasculitis, and spontaneous resolution occurred. This entity may be related to idiopathic scrotal panniculitis and fat necrosis. This condition is distinct from other causes of the acute scrotum in prepubertal boys. It presents as acute tender, sometimes painful, swelling (classically, but not always, after swimming in cold water). Masses may be palpable in the scrotal wall. Otherwise, the boy is well, with no fever or leukocytosis. Idiopathic scrotal necrosis in a 2-month-old boy has been documented by Sarihan [2], where trauma, extreme cold and Fournier's gangrene were excluded. Management is expectant and conservative [3,4]. In adults, one case of idiopathic scrotal panniculitis has been reported [5] and another associated with pancreatitis [6].

Subtle or severe orogenital ulceration can occur in erythema multiforme or the Stevens–Johnson syndrome (see Chapter 74).

Behçet's disease is discussed in Chapter 66. Recurrent genital ulceration is not mandatory for the diagnosis; if patients do not have genital ulceration then they must have ophthalmic and dermatological involvement or a positive pathergy test [7]. In practice, there are many patients who have an incomplete syndrome. Other anogenital manifestations include epididymitis and urethritis [8], spontaneous haematocoele from venous rupture resulting from lymphocytic venulitis [9] and erectile dysfunction [10]. The genital ulcers in men can be very painful and occur anywhere on the anogenital area, including the perianal skin. Generally, they are larger, deeper, fewer and less recurrent than those in the mouth. Patients with relapsing polychondritis and Behçet's disease have been reported, and the acronym MAGIC (mouth and genital ulcers with inflamed cartilage) syndrome has been proposed [11,12]. The histology of Behçet's disease is usually non-specific and does not enable it to be distinguished from idiopathic aphthae, although sometimes necrotizing vasculitis can be present.

Degos' malignant atrophic papulosis (see Chapter 48) has caused penile ulceration, which preceded the development of the rash and eventual fatal involvement of other organs, despite aggressive treatment [13].

The hypereosinophilic syndrome involves the skin in up to 50% of cases, with orogenital ulceration, erythroderma and urticaria [14]. It may occur in HIV infection.

Penile necrosis has a wide differential diagnosis (Table 68.20). Many of the causes are discussed in this or other sections.

Two cases of necrobiosis have been reported presenting as erythematous ulcerated lesions of the glans penis. One patient was diabetic and had lesions on the legs [22]; the other had penile lesions only and was treated with oral pentoxifylline [23].

There are a number of case reports of pyoderma gangrenosum (see Chapter 49), including the variant superficial granulomatous pyoderma, involving the penis and scrotum in adults and children (where the anogenital area is a site of predilection as well as the head and neck)

Table 68.20 Causes of penile necrosis. (After Bunker [15]. © 2004, with permission from Elsevier.)

Decubitus ulcer
Spider bite
Priapism
Embolism
Strangulation and tourniquet syndromes
Vacuum erection device
Vasculitis [16]
Diabetes mellitus [17,18]
Chronic renal failure [19]
Thrombocytopenia
Polycythaemia
Cryoglobulinaemia
Coagulopathy [20]
Pyoderma gangrenosum
Calciphylaxis
Ecthyma gangrenosum
Fournier's gangrene
Herpes simplex
Leukaemia
Mucormycosis (in acute myeloblastic leukaemia) [21]
Warfarin
Fixed drug eruption

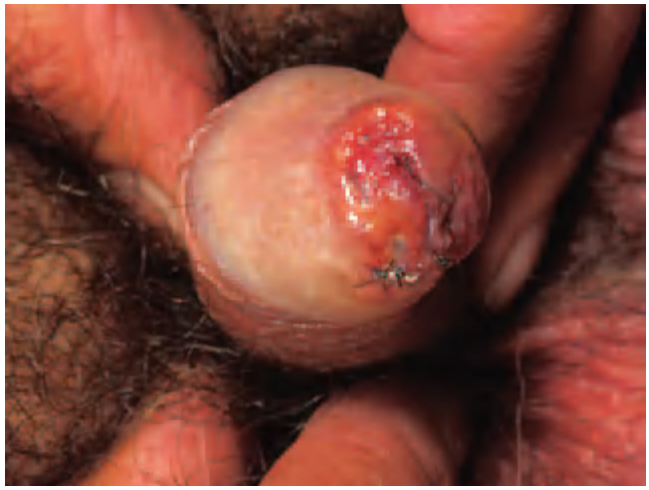

Fig. 68.12 Pyoderma gangrenosum in a patient with severe seronegative arthropathy. (Courtesy of Dr F.A. Ive, Durham, UK.)

(Fig. 68.12) [24,25]. Genital pyoderma gangrenosum may occur following local trauma such as urological surgery [26], or complicate ulcerative colitis [27] or chronic lymphocytic leukaemia, or it may be idiopathic [28–31]. Pyoderma gangrenosum is a diagnosis made when other causes of purulent ulceration, such as infection (sexually acquired and exotic), malignancy and artefact have been excluded.

Calciphylaxis (see Chapter 59) is a rare and serious complication of chronic renal failure in which extending ischaemic gangrenous necrosis affects acral tissues and sometimes the thighs, buttocks and genitals [32–34].

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Pilonidal sinus

Pilonidal sinus very rarely affects the penis, but when it does it is usually in the coronal sulcus. Some of the reported cases have been complicated by actinomycosis [1,2] and another has been associated with a dermoid cyst [3].

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Penile acne

There is no literature on this condition but it is occasionally encountered. Patients have comedones, papules, pustules and inflammatory nodules of the proximal shaft of the penis. The differential diagnosis should include chloracne (see Chapter 43). Patients respond to conventional treatment for acne.

Peyronie's disease

Peyronie's disease [1,2], which affects middle-aged and older men, is a localized fibrotic disorder involving tissue immediately adjacent to the erectile tissues. It presents with pain and curvature on erection, a sensation of a cord within the penis, palpation of a lump or knot, decreased erection distal to the plaque, interference with intercourse and progressive impotence. It may be subclinical in many men, given that 23% of autopsies have shown histological evidence of the condition [1]. Psychological complications and marital difficulties occur. The penis curves towards the lesion, with dorsal curvature being most common. Peyronie (a physician to Louis XIV) described nodules as 'rosary beads' but plaques vary in size. It has been associated with systemic sclerosis [3], and such patients may have penile Raynaud's phenomenon [4]. It has occurred as a complication of the use of a vacuum erection device [5], but in most men the cause is unknown. Some evidence has been advanced for an autoimmune pathogenesis [6].

The differential diagnosis includes congenital curvature, fibrosis secondary to trauma or urethritis and abscess, syphilitic gumma, lymphogranuloma venereum, and infiltrative tumours (e.g. lipogranuloma). Penile thrombophlebitis as the initial presentation of a paraneoplastic migratory thrombophlebitis resulting from pancreatic cancer has been misdiagnosed as Peyronie's disease [7].

In some men there may be spontaneous regression. Treatments include intralesional corticosteroid injection [8], including delivery by Dermojet [9]. Surgery is avoided, but some specialized techniques are available [10]. Symptomatic relief has been claimed following iontophoresis of drugs such as dexamethasone, lidocaine (lignocaine) and verapamil [11].

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Drug reactions

The penis is a site of predilection for fixed drug eruption, like the face and extremities (see Chapter 73). The symptoms are itch or burning. The eruption is acute with a swollen plaque, sometimes with central blister formation, erosion and ulceration. Gruber *et al.* [1] describe the case of a man with known sensitivity to co-trimoxazole who developed a penile fixed drug eruption after intercourse with his wife while she was taking the drug for a sore throat. The differential diagnosis includes herpes simplex and erythema multiforme.

Ulceration has been reported following the inadvertent subcutaneous injection of papaverine for the treatment of erectile impotence [2]. Dequalinium is a topical antibacterial that was used for the treatment of impetigo and moniliasis in the 1950s and 1960s, but it caused a necrotizing balanitis with ulceration when used for the treatment of balanitis in uncircumcised men [3]. Warfarin necrosis can affect the genitalia [4]. All-*trans*-retinoic acid has been reported to induce scrotal ulceration in a patient with acute promyelocytic leukaemia [5]. Foscarnet is a recognized cause of genital ulceration in HIV-infected patients [6–8]. Erosion following the use of topical steroids has been seen.

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Miscellaneous

It is not unusual for the herald patch of pityriasis rosea to appear on suprapubic skin or in the groin. Incomplete or limited presentations (e.g. affecting the pelvic girdle) are not rare, although careful examination may elicit another patch on the neck or in the axilla.

Bottomley and Cotterill [1] have described an acutely tender erythematous scrotum associated with zinc deficiency in a patient with Crohn's disease. Necrolytic migratory erythema can be localized to the genitalia [2].

Autoimmune bullous diseases such as pemphigus can involve the penis (the glans is the usual site) (Fig. 68.13), but very rarely in isolation [3]. Pemphigus vegetans presenting with a 4-year history of indolent tender balanitis, where the glans penis was involved with a moist vegetative plaque with beefy red erosions separating irregular hyperkeratotic mounds, has been reported [4]. Linear immunoglobulin A (IgA) disease commonly involves the mucosae. Mucosal lesions of bullous pemphigoid are uncommon; their presence suggests another diagnosis or an underlying neoplasm. Pelvic girdle lesions are often seen, but rarely in isolation.

Cicatricial pemphigoid or (benign) mucous membrane pemphigoid is a rare variant of bullous pemphigoid in which blisters affect the skin and the mucous membranes. Skin lesions are usually less widespread than in bullous pemphigoid and they may heal with scarring. Oral lesions predominantly involve the palate and gingivae, but there may be oesophageal involvement with dysphagia, and conjunctival disease can lead to blindness. Involvement of the penis may be with blisters, erosions, ulcers, transcoronal adhesions, scarring and phimosis [5,6]. Although direct immunofluorescence is usually positive, circulating antibodies to the basement membrane zone are rarely found. The disease often responds poorly to oral steroids,

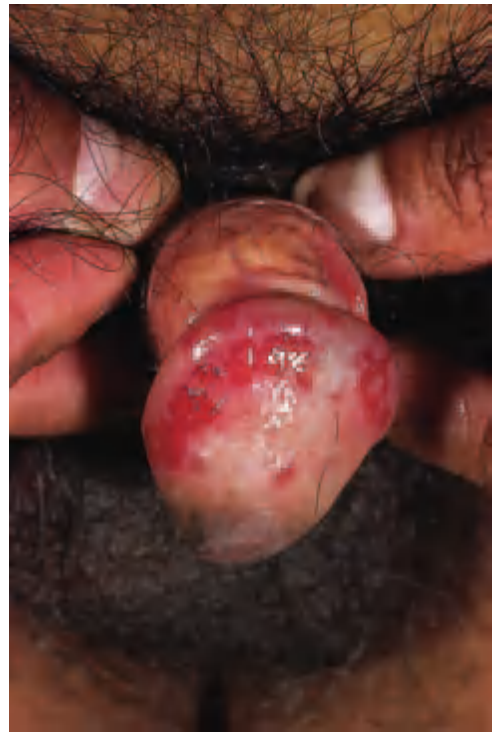

Fig. 68.13 Pemphigus of the penis. (Courtesy of Dr F.A. Ive, Durham, UK.)

but dapsone or other sulpha drugs such as sulphamethoxypyridazine can be effective. Regular haematology screening is mandatory with dapsone because of the risk of agranulocytosis.

One patient with Darier's disease developed an HPV 16-associated squamous carcinoma of the scrotum during oral isotretinoin treatment; he had not previously had radiotherapy to the genitocrural area [7]. Genitocrural papular acantholytic dermatosis can involve the penis, as can granuloma annulare. Erythematous smooth, round and linear nodules are described in the latter. Most patients are uncircumcised. Extragenital granuloma annulare is uncommon in these patients.

Occasionally, patients with generalized cutaneous sarcoid present with genital lesions [8]. Tender erythematous induration of the distal shaft of the penis and several yellowish subcutaneous nodules on the glans have been described [9]. A case presenting with penile ulceration has been reported [10]. Importantly, sarcoid can masquerade as testicular malignancy [11–13].

A granulomatous lymphangitis may be found histologically in the investigation of penile lymphoedema [14]. It can be a rare feature of the Melkersson–Rosenthal syndrome. Crohn's disease can involve the penis and scrotum [15–20].

A soft-tissue mass in the penis associated with systemic amyloid has been reported [21]. Primary amyloid of the

urethra is very rare indeed, but accurate diagnosis is essential, as its presentation simulates carcinoma, with dysuria, bloody discharge and tender induration of the penis [22], or as an obstructive voiding syndrome, with tender periurethral masses and irregular urethral strictures [23].

One case each of eccrine syringofibroadenomatosis with penile involvement manifesting as a balanoposthitis [24], benign mucinous metaplasia with a prepucial 0.6 cm papule replacing the superficial epidermis [25], and mucinous syringometaplasia with an ulcerated papule on the shaft of the penis [26] have been reported.

Acute scrotum is a clinical syndrome defined as acute painful swelling of the scrotum or its contents, usually in boys, accompanied by local signs and general symptoms [27]. The critical differential diagnosis is torsion of the testis or spermatic cord. Other causes include idiopathic scrotal oedema, epididymitis, orchitis, hernia and haematocoele. Thromboangiitis obliterans has been found in two cases [28]. Acute scrotal swelling may be a physical sign of primary peritonitis in children and infants [29] or secondary peritonitis resulting from appendicitis, healed meconium peritonitis in the neonate, haemoperitonitis (ruptured spleen) and pseudotorsion resulting from ventriculoperitoneal shunts inserted for hydrocephalus that have migrated into the scrotum from the peritoneum. Acute idiopathic scrotal oedema usually affects children aged 4–12 years old. Allergy, infection (umbilical sepsis), trauma, insect bites, urinary extravasation and Henoch–Schönlein purpura have all been considered as causes. It is rare in adults, but cases in association with septic diabetic foot have been reported [30].

Henoch–Schönlein purpura/anaphylactoid purpura may affect the genitalia. Ureteritis, renal pelvic haemorrhage and pain and swelling of the spermatic cord have been reported. The incidence of scrotal involvement ranges from 2 to 38%. In some cases, the presentation has masqueraded as testicular torsion, resulting in unnecessary surgical exploration. Ultrasonography can help to distinguish between them [31]. However, testicular torsion can also be a serious complication of Henoch–Schönlein purpura [31].

Acute haemorrhagic oedema of childhood may present as tenderness, redness and swelling of the penis and scrotum with the development of more widespread haemorrhagic lesions [32]. The differential diagnosis includes acute febrile neutrophilic dermatosis, erythema multiforme, Henoch–Schönlein purpura and child abuse. The prognosis for complete recovery is excellent. Acute inflammation of the scrotum in patients with familial Mediterranean fever can occur [33]. It is manifested by pain, erythema and swelling, fever, leukocytosis and elevated erythrocyte sedimentation rate (ESR). It may occur in isolation or accompanying peritonitis. The differential diagnosis includes torsion, orchitis and epididymitis in boys.

Polyarteritis nodosa may be associated with testicular and epididymal involvement, with scrotal pain and swelling. In one case these were the sole presenting features and testicular biopsy provided the diagnosis [34–36].

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Non-sexually transmitted infections

Staphylococcal cellulitis

Cellulitis may affect the penis. Piercing and genital jewellery predispose to infection. Cellulitis and abscess formation can complicate cysts, sinuses and fistulae and sexually transmitted infections. The exact relationship between episodes of acute infection and chronic penile oedema (CPL; see below), which often is complicated by cellulitis, is uncertain.

Anogenital infection in patients with malignant disease is serious, and potentially life-threatening necrotizing fasciitis and Fournier's gangrene may occur.

Streptococcal dermatitis/perianal cellulitis

This syndrome in children [1] probably also has a corollary in adults [2], but it is much more common in boys in whom, if the penis is involved, there may be dysuria, erythema and swelling of the penis and balanoposthitis.

Chronic idiopathic penile oedema

Chronic penile lymphoedema (CPL) is a relatively rare, reactive, disfiguring condition that causes sexual dysfunction and phimosis [3]. It has previously been called tumorous lymphoedema or elephantiasis verrucosa nostra [4]. Evidence of streptococcal infection may be present, and this could lead to irreversible lymphatic damage, whereas other cases seem idiopathic, and are perhaps brought about by primary hypoplastic lymphatics. Some patients have another penile dermatosis. Few cases of CPL have been reported before [3,5,6], and the aetiopathogenesis may have been misunderstood. Penoscrotal oedema has also been attributed to continuous ambulatory peritoneal dialysis [7], amputation of septic limbs in diabetes [8], acute necrotizing pancreatitis [9] and streptococcal infections [10]. Penile venereal oedema has been associated with gonococcal and herpes infection, and scabies infestation, and resolves after treatment of the underlying disease [11]. Similarly childhood penile oedema is self-limiting [12].

Filariasis and pelvic mass lesions should be excluded. Imaging of lymphatic channels is not particularly helpful [13]. It is possible that cases of CPL are related to any of the above factors and/or temporally unrelated but repetitive sexually transmitted disease. Persistent lymphatic insult from whatever cause could result in an inflammatory process affecting genital and pelvic vessels and nodes. Therefore all cases of penoscrotal oedema should be treated aggressively at first presentation, because the more chronic the genital lymphoedema the more difficult it is to treat, both medically and surgically [14]. The aim of treatment of CPL must be prophylaxis against further infective episodes and aggressive treatment of relapses.

Patients with CPL present with chronic swelling of the penis, foreskin, scrotum, pubic mound, buttocks and thighs, which may be warm and red. There may be intercurrent attacks of cellulitis and/or erysipelas with systemic upset.

Acute attacks require admission to hospital and treatment with systemic broad-spectrum antibiotics; a short course of prednisolone may also be helpful. Long-term treatment with erythromycin, clarithromycin or ciprofloxacin appears to improve and stabilize the process, and improves the appearance and function of the penis. The success of this approach argues the importance of infection as a factor in the perpetuation if not initiation of the process. Medical control with antibiotics then allows surgical intervention in the form of circumcision. Plastic repair may be necessary after excision of affected tissue [15,16].

Ecthyma gangrenosum

Ecthyma gangrenosum has a predilection for the acral and anogenital regions, and may affect the penis in isolation, leading to gangrene [17]. The prognosis is poor. A case has been reported that was probably caused by direct arterial septic embolization of the penis from femoral heroin injection [18].

Fournier's gangrene

Fournier's gangrene is analogous to necrotizing fasciitis and Meleney's gangrene. In 1883, the Parisian dermatologist Alfred Fournier described five cases of spontaneous genital gangrene and ulceration, but Baurienne (1764) probably first reported this condition [19]. The disease begins with urethral or appendageal polybacterial infection. Most of the organisms isolated are resident urethral or lower gastrointestinal flora, and most patients have mixed infections. In children, staphylococci and strepto-

Table 68.21 Risk factors for Fournier's gangrene.

Diabetes mellitus
Alcoholism
Anogenital infection
Chemotherapy
HIV
Post-instrumentation in the immunocompromised
Postoperative (urological and colorectal)
Heroin addiction
Trauma
Unconventional sexual practices

Table 68.22 Differential diagnosis of Fournier's gangrene. (After Bunker [25]. © 2004, with permission from Elsevier.)

Trauma
Herpes simplex
Cellulitis (streptococcal, staphylococcal)
Streptococcal necrotizing fasciitis
Gonococcal balanitis and oedema
Ecthyma gangrenosum
Allergic vasculitis
Polyarteritis nodosa
Necrolytic migratory erythema
Vascular occlusion syndromes
Warfarin necrosis

cocci are most commonly isolated [20]. A necrotizing vasculitis, possibly exotoxin-mediated, ensues with devastating consequences for involved skin, subcutis, fascia and muscle. It is held to be the human counterpart of the local Shwartzman phenomenon [21,22]. Painful erythematous swelling of the genitals (a black spot may appear on the scrotum [23]), perianal or lower abdominal skin with no suppuration but marked systemic toxicity (may be absent in children [20]), and urinary retention, is a typical presentation. Necrosis of skin and deeper tissues can occur rapidly, and there is a very high mortality unless the diagnosis is made promptly and radical mangement undertaken. Plain X-rays may show soft-tissue gas [24]. Predisposing factors are listed in Table 68.21. Preceding surgery, including vasectomy and instrumentation, especially in patients with the listed risk factors, is particularly important. The differential diagnosis is given in Table 68.22.

If a diagnosis of Fournier's gangrene is made, radical surgical débridement of all affected tissue is undertaken and broad-spectrum systemic antibiotic therapy initiated. Plastic repair can be undertaken if the patient survives. Hyperbaric oxgen and high-dose systemic steroid treatment have been used [22,26,27]. Children can be treated with more conservative surgery, and the mortality rate is lower [20,28]. In adults, the mortality is approximately 25%.

Trichomycosis pubis

Trichomycosis pubis causes asymptomatic yellow, red or black micronodules around hair shafts [29]. Pubic and axillary hair may be involved. The skin is normal but the sweat may be discolored. Trichomycosis pubis is rare in Western dermatological practice but is common in the Middle East [30], and may occur concomitantly with trichosporosis in India [31]. It is caused by *Corynebacterium* spp. The differential diagnosis includes true mycoses such as white or black piedra. Treatment is with topical benzoic acid, salicylic acid, clindamycin or naftifine [29].

Tuberculosis

Tuberculosis of the penis is rare [32] but important given the resurgence of the disease. Primary penile ulceration (solitary and multiple), with or without inguinal lymphadenopathy, caused by sexual infection or contact with infected clothing may occur [33], or the ulceration may be secondary to tuberculosis elsewhere (e.g. the lung) [34]. A cold abscess (presenting as erectile impotence) has been reported [35]. Tuberculides have involved the penis, including in isolation [36].

Non-syphilitic spirochaetal ulcerative balanoposthitis

This condition is recognized in the Tropics and South Africa, presenting as large serpiginous foul-smelling ulcers in uncircumcised men, associated in some with non-tender inguinal lymphadenopathy. Treatment is with penicillin or metronidazole [37].

Yaws

An ulcerated, crusted and papillomatous lesion has been reported on the prepuce as part of disseminated early yaws (with other skin lesions elsewhere) in a patient in an endemic region. Several family members were also infected. The genital lesion probably arose from autoinnoculation [38].

Candidosis

Genitourinary physicians maintain that *Candida* can be the cause of urethritis and balanoposthitis [39]. The glans penis and prepuce may be eroded. *Candida* of the penis (with a prevalence of approximately 10% of that of vaginal candidosis) has attracted very little research interest [40].

Candida may be more often a secondary pathogen than a sexually acquired infection. Observing the signs of candidosis, or demonstrating the presence of the organism, does not prove that it is the cause of all the symptoms and signs. An underlying dermatological or medical cause should be excluded. The symptoms and signs of *Candida*

may be more florid than the underlying predisposing cause. Medical causes include diabetes mellitus, iatrogenic immunosuppression and systemic antibiotic treatment. Although oropharyngeal candidosis is almost invariably found in HIV infection, candidal balanoposthitis is not generally associated, perhaps because it is overlooked or because many patients take long-term imidazole antifungals orally.

Candida albicans is such a ready opportunist organism because it is a part of the resident flora of the gastrointestinal tract and may be retrieved from intertriginous areas, including the preputial folds, in the absence of symptoms and signs. Candidal balanoposthitis could be a sexually transmitted disease that may have an affinity for the anatomically or physiologically abnormal penis, or in individuals predisposed by other factors or disease, and where there is chronic vaginal or anal carriage in a partner. Screening should be performed for other sexually transmitted diseases.

Diagnosis is discussed in Chapter 31. Underlying disease should be identified and treated, and predisposing factors rectified. Treatment includes topical nystatin, clioquinol or an imidazole, often very usefully combined with hydrocortisone or a moderately potent corticosteroid. In severe disease, an oral imidazole may be indicated.

Tinea

Tinea of the penis or scrotum is uncommon and when it occurs it is usually associated with crural disease. Rarely encountered is the occurrence of tinea on the glans penis as a seat of itch or pain, and producing an erythematous patch or a crop of scaly papules [41–46]. Penile tinea in India has been associated with occlusion resulting from the wearing of a langota—a T-shaped piece of cloth tied over the genitalia [43].

Deep fungal infections

Although histoplasmosis is a common cause of disseminated fungal infection in the USA, urological and anogenital disease, usually ulceration and adenopathy in an ill patient, is rare [47,48]. An otherwise well man with a small warty nodule on the glans penis has been reported [49]. One patient with a penile ulcer transmitted the disease venereally to his wife [50].

In blastomycosis, although the genitourinary (prostate and epididymis) tract is involved in 20–30% of cases [51], involvement of the genital skin is rare. However, lesions of the prepuce and perianal skin have been recorded [52,53].

Paracoccidioidomycosis can be the cause of scrotal swelling and genital nodules and erosions [54].

Miscellaneous

Bacillary angiomatosis (see Chapter 26) is important in the differential diagnosis of AIDS-related Kaposi's sarcoma. A case in which the presenting tender red nodules affected the scrotum and groins has been published [55].

The penis is rarely affected by pityriasis versicolor and probably almost never in isolation [56,57]. Occasionally, the anterior pelvic girdle is the site involved.

One case only of superficial phaeohyphomycosis manifesting as multiple, 1–3 mm, pigmented papules, resembling seborrhoeic keratoses, on the scrotum of an HIV-positive patient has been described. Microscopy showed a mass of mycelia, and two dematiaceous fungi were cultured [58].

Occasionally, genital herpes simplex may be acquired non-sexually (e.g. during contact sports such as rugby football [59]). A phenomemenon of chronic erosive and verrucous herpes as part of immunoreconstitution disease has been described in HIV infection [60].

Sacral herpes zoster is discussed in Chapter 25. Lesions may be found on the scrotum and penis, and urinary retention and constipation can occur.

Amoebiasis can rarely present as a painful ulcerative balanitis, with swelling, frequency, dysuria and retention in tropical countries [61]. Self-inoculation from concomitant intestinal infection, by heterosexual intercourse where the female partner has amoebic vaginitis, or by sodomy, are the putative mechanisms. Amoebiasis as the cause of genital ulceration should lead to the suspicion of underlying HIV infection [62].

Cutaneous leishmaniasis can affect the genitalia [63,64]. An erythematous scaly plaque on the glans has been reported [65] and post-kala-azar dermal leishmaniasis of the penis and scrotum is encountered. Rarely, genital skin lesions may lead to the diagnosis of schistosomiasis. They occur because ova shed by worms enter the perineal vessels [66]. The papules and nodules may be skin-coloured, pink or brown, scattered or grouped, affecting the penis and scrotum. They can spread onto the perineum and around the anus, and may develop into soft warty vegetating lesions. Ulceration is rare and, even more rarely, concomitant carcinoma has been reported [67].

The anogenital consequences of onchocerciasis are 'leopard skin' hypopigmentation (the scrotum is commonly involved), ileal crest and scrotal nodules, 'hanging groin', and scrotal enlargement [68,69]. The differential diagnosis of the scrotal enlargement includes bancroftian filariasis [68]. Other filarial infections can lead to mild hydrocoele or gross elephantiasis. Filariasis can cause secondary lymphangiectasis. Excision, grafting and genital reconstruction can be undertaken [70].

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Dermatological aspects of sexually transmitted disease

Syphilis

Syphilis (see Chapter 30) is endemic throughout the world. It is enjoying a resurgence in homosexual men. All manifestations of syphilis can affect the genital region [1]. Balanoposthitis can complicate and obscure penile chancre. The granulomatous gumma may affect the genital area as an ulcer, a white plaque or as an atrophic scar. Pseudochancre redux describes gummatous (tertiary stage) recurrence at the site of the primary chancre [2]; it is very rare.

Viral warts

Circumcised men are more likely to have genital warts than the uncircumcised [3]. The risk of acquiring genital warts is significantly reduced by using condoms [4]. Clinically inapparent disease may present as balanoposthitis [5]. Subclinical or latent genital HPV infection may be 100 times more common than classical condylomas [6]. The 5% acetic acid test is not a very specific aid to the identification of warts or dysplastic lesions [7]. Congenital and acquired immunosuppression increases the susceptibility of the anogenital region to HPV infection and progression to dysplasia and frank malignancy [8].

The clinical diagnosis of HPV infection is usually certain but condylomata lata (secondary syphilis), lichen planus, molluscum contagiosum, Bowenoid papulosis and pearly penile papules enter the differential diagnosis. Solitary lesions have a wider differential diagnosis, including giant condyloma, squamous carcinoma and transitional cell carcinoma of the distal urethra, which can present as a warty lesion at the urethral meatus [9]. Biopsy should be performed if there is diagnostic doubt or dysplasia. Patients with anogenital warts and their partners may require full sexually transmitted disease and sometimes colorectal assessment.

Molluscum contagiosum

Molluscum contagiosum is discussed in Chapter 25. Young men are commonly seen with penile and pubic lesions and it is assumed that this is a sexually transmitted infection, but this may not always be the case.

Table 68.23 Causes of penile and scrotal ulcers in HIV infection.

Pseudomonas
Syphilis
Chancroid
Herpes simplex
Penicilliosis
Amoebiasis
Fournier's gangrene
Squamous cell carcinoma
Kaposi's sarcoma
Drugs (e.g. foscarnet)

Human immunodeficiency virus infection

Ulcerative genital disease is a risk factor for HIV [10], but anogenital ulceration may be a consequence of HIV infection (see Chapter 26) [11]. Table 68.23 lists the main causes. Biopsy, with special stains and culture, is mandatory. Other genital problems in HIV, such as psoriasis, warts, intraepithelial neoplasia, squamous carcinoma and Kaposi's sarcoma, are discussed elsewhere.

Phthiriasis

Phthiriasis (see Chapter 33) can present with marked genital and pubic itching with few overt physical signs, or as an infected genitocrural and pubic eczema that conceals the underlying primary signs. In hirsute men, the abdomen, chest, axillae and thighs may also be involved. Screening for other sexually transmitted diseases should be offered to the patient and partner(s).

Scabies

Scabies may present with anogenital itch, 'folliculitis' (including of the buttocks) and penile, scrotal and pubic nodules (Fig. 68.14). The patient must be told to advise close physical contacts and family to be treated simultaneously.

Benign tumours

The following entities are all encountered in the male genital area: angiomas and angiokeratomas, and angiokeratoma corporis diffusum; basal cell papillomas may be mistaken for viral warts [12] or Bowenoid papulosis, as may melanocytic naevi; inguinogenital epidermoid cysts may become infected: lesions containing molluscum contagiosum have been described [13]; pilar cyst, including giant forms, is much rarer [14].

Median raphe cysts

Congenital cystic median raphe anomalies may remain unobtrusive until adulthood. Cystic or nodular and linear

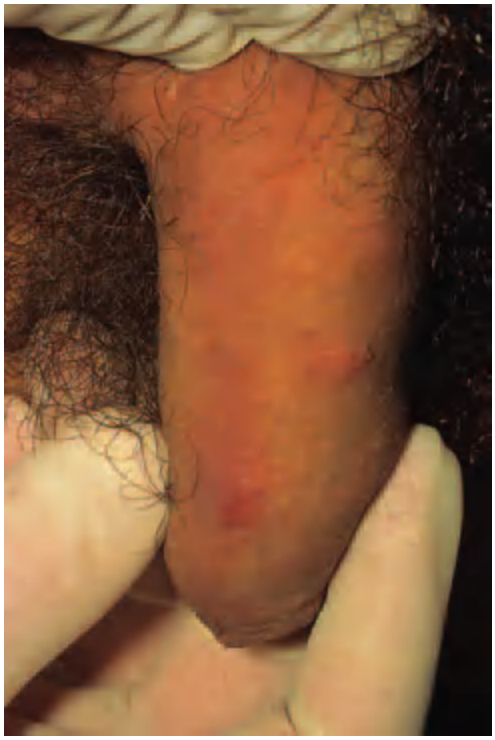

Fig. 68.14 Papules on the penis in scabies. (Courtesy of Dr C. White, University Hospital of North Durham, Durham, UK.)

swellings of the ventral penis occur near the glans. In adolescence or adulthood they may become traumatized or infected with staphylococci, gonococci or *Trichomonas* and present as tender erythematous purulent nodules [1]. Histologically, they are either dermoid or mucoid, depending on their embryology or epithelial lining [15]. Very rarely, the basal epithelial lining of the cysts may contain melanocytes, imparting a brown-black pigment to the lesion [16].

Mucoid cysts

These are rare lesions that present from birth or childhood as small flesh-coloured mobile cystic papules or nodules with no punctum, commonly on the ventral glans or foreskin, rarely in the perineum. They can be asymptomatic, become infected or interfere with intercourse. The histological features suggest that they arise from ectopic urethral tissue during embryological development [17].

Scrotal calcinosis

Scrotal calcinosis is a relatively common benign idiopathic disorder presenting as solitary or multiple, hard, smooth, white papules or nodules on the scrotum, rarely the penis (Fig. 68.15). Interestingly, these lesions are much rarer on the vulva [18]. Occasionally, they may become secondarily inflamed or infected following trauma.

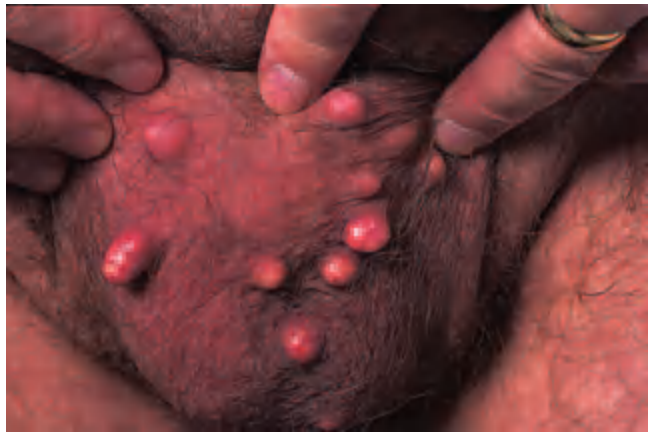

Fig. 68.15 Scrotal calcinosis. (Courtesy of Dr D.A. Burns, Leicester, UK.)

Their occurrence was first described by Hutchinson [19]. Their origin has been debated: they have been said to arise from epidermoid cysts, eccrine duct milia, eccrine epithelial cysts, dystrophy of the dartos muscle, trauma and the presence of foreign bodies [1,20–30]. Scrotal calcinosis may occur after meconium peritonitis, with leakage of meconium through the processus vaginalis, and in testicular tumours such as teratomas, gonadoblastomas and Leydig cell tumours [27]. In endemic areas of onchocerciasis, calcified scrotal cysts may be caused by the living or dead nematodes, and patients have evidence of the disease elsewhere [31,32]. Onchocercal nodules are more common on the iliac crests and the rib cage (see Chapter 32).

The unsightly and embarrassing lesions can be treated by incision and eventration under local anaesthesia.

Verruciform xanthoma

Verruciform xanthoma mainly affects the mouth (see Chapter 66). The genitalia are the next most frequently involved, where it presents as a painless, yellow-brown or red, verrucous, sessile or papillary plaque. Fewer than 20 cases have been reported [33]. The histological findings are hyperkeratosis, focal parakeratosis, acanthosis and fat-filled foam cells in the papillary dermis. Verrucous xanthoma is thought to represent epidermal degeneration, with keratinocyte lipid then taken up by dermal macrophages [34] or fibroblasts to form the foam cells. HPV 6 has been implicated in one case [35]. Treatment is by surgical excision.

Miscellaneous

Naevus comedonicus of the glans penis, generally devoid of pilosebaceous structures, has been reported [36].

Keloid is rare, but can complicate circumcision [37,38], and other surgery and trauma [39,40]. Keloid has been

simulated on the dorsum of the penis by chronic oedema caused by a condom catheter [41].

Dermoid cyst affecting the penis, presenting with pain, swelling and suppuration from abscess formation, has been reported [42].

Acanthosis nigricans almost always affects the groins. In pseudoacanthosis nigricans, the associated obesity is almost always responsible for associated intertrigo and skin tags.

Some cases of multiple syringoma localized to the penis have been described, mimicking genital warts or lichen planus [43–46].

Other benign tumours that have been reported rarely to affect the anogenital area include apocrine cystadenoma [47,48], mixed syringocystadenoma papilliferum and papillary eccrine adenoma occurring in a scrotal condyloma [49], dermatofibroma [50], giant cell fibroblastoma (scrotum) [51], connective tissue naevi (scrotum) [52], fibrous hamartoma of infancy (scrotum) [53], leiomyoma [50,54], genital smooth muscle hamartoma (scrotum) [55], neurofibroma, neurilemoma, granular cell myoblastoma [50,56–58], varicosities (venous lakes), acquired capillary and cavernous haemangioma of the penis have been described [50] (other angiomatous lesions are very much rarer, and controversy exists as to whether they represent a true neoplasm, herniation of the corpus spongiosum or vascularization of a haematoma or thrombus [59]), Masson's vegetant intravascular haemangioendothelioma [60], angiokeratoma circumscriptum of Mibelli [61], glomus tumour [50,62], port-wine stain, strawberry naevus [63–65], epithelioid haemangioma [66], epithelioid haemangioendothelioma [50,67], angiolymphoid hyperplasia with eosinophilia/Kimura's disease (penis and spermatic cord) [68,69] and lymphangioma circumscriptum [70,71].

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Precancerous dermatoses

Squamous hyperplasia

Such lesions consist of white patches or plaques. Although it is the most common epithelial abnormality found in association with invasive squamous carcinoma of the penis, histologically there is *no* cytological atypia; acanthosis and orthokeratotic hyperkeratosis are found [1].

Penile horn

It is rare for cutaneous horn to affect the penis [2]. The underlying causes include pseudoepitheliomatous micaceous and keratotic balanitis [3], verrucous carcinoma [4–6] and squamous carcinoma [7]. Chronic inflammation and recent circumcision for long-standing phimosis are said to be important predisposing factors. The lesion is premalignant or, in one-third of cases, malignant at presentation, with squamous carcinoma the underlying pathology. Treatment should be dictated by precise diagnosis achieved by adequate excision and histology of the whole lesion. Follow-up is mandatory because recurrence may occur.

Porokeratosis

Genital porokeratosis of Mibelli is rare, but classical lesions have been found on the penis and scrotum. Ulceration may occur [8]. Porokeratosis may be confused with psoriasis, Bowen's disease, granuloma annulare or lichen planus; biopsy differentiates these conditions [9]. Topical 5-fluorouracil can be used [10].

Pseudoepitheliomatous micaceous and keratotic balanitis

Pseudoepitheliomatous micaceous and keratotic balanitis (PEMKB) is a rare penile condition. It presents as thick scaly micaceous patches (possibly a cutaneous horn) on the glans penis in older uncircumcised men [3,11]. Histological examination shows hyperkeratosis, parakeratosis, acanthosis, prolongation of the rete ridges and mild lower epidermal dysplasia, with a non-specific dermal inflammatory infiltrate of eosinophils and lymphocytes. Some consider that PEMKB is a form of locally invasive verrucous carcinoma [12], others that it is a variant of lichen sclerosus [13]. Metastastic spread has not occurred except where there was a penile horn [14], and in one patient who developed an aggressive soft-tissue sarcoma of the penis [15]. Recurrence is common. Topical 5-fluorouracil, radiotherapy and surgery are the principal treatment choices [3].

Erythroplasia of Queyrat, Bowen's disease of the penis and bowenoid papulosis

Erythroplasia of Queyrat (EQ), Bowen's disease of the penis (BDP) and bowenoid papulosis (BP) are three clinical variants of carcinoma *in situ* of the penis [16–18]. Penile intraepithelial neoplasia (PIN—corresponding to cervical, vulval and anal intraepithelial neoplasia; CIN, VIN and AIN) is the term favoured by some, and may be a convenient umbrella term, but there is no formal consensus on clinicopathological classification (particularly

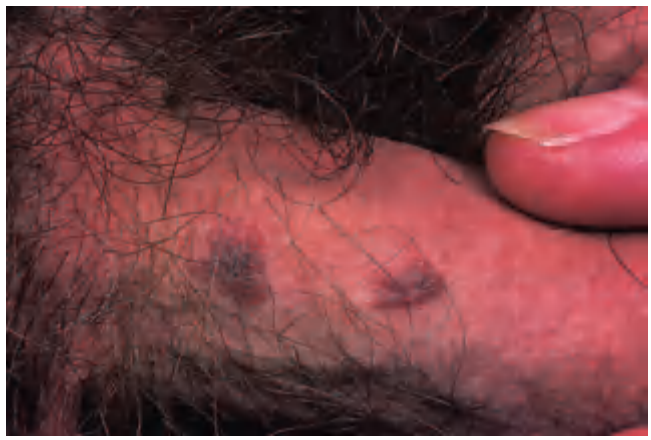

Fig. 68.16 Bowenoid papulosis. (Courtesy of Dr D.A. Burns, Leicester, UK.)

'grade') and clinical utility. An alternative expression 'squamous intraepithelial lesion' (SIL) has been proposed, and qualified by the descriptor 'high-' or 'low-grade' [19]. EQ, BDP and BP all describe disorders of the penis predominantly in uncircumcised white men, although EQ has been recorded in a circumcised man [20]. CIN, VIN and AIN are terms analogous to PIN.

Although EQ and BDP are synonymous in describing carcinoma *in situ* of the penis, BD is used to refer to squamous carcinoma *in situ* at other cutaneous sites. EQ should be used to describe red shiny patches or plaques of the mucosal penis (glans and prepuce of the uncircumcised). BDP should be used to describe red, sometimes slightly pigmented, scaly patches and plaques of the keratinized penis. This distinction has not always been made in the literature. BP is analogous to, but clinically different from, EQ and BDP. The term should be used to describe multiple warty lesions, which are often pigmented in keratinized sites, and more numerous and more inflamed at mucosal sites (Fig. 68.16). BP lesions are less papillomatous, smoother topped, more polymorphic and more coalescent than common genital viral condylomata acuminata, and occur in younger, sexually active men, as opposed to the patches or scaly plaques of EQ and BDP, respectively, seen in older men. BP may be associated with a lesser risk of squamous carcinoma than EQ and BDP. It is associated with HPV infection (especially HPV 16) and HIV infection. Voltz *et al.* [21] found anogenital warts in 16% of all HIV-positive males, nearly half of whom showed histological signs of intraepithelial neoplasia.

The aetiology of EQ, BDP and BP is unknown. Local carcinogenic influences in uncircumcised men such as poor hygiene, smegma, trauma, friction, heat, maceration, inflammation, phimosis, dermatoses such as lichen sclerosus and smoking (tar metabolites in urine) have been proposed [22], as have HPV, particularly in BP [23]. BP is probably virus-induced epithelial dysplasia associated mainly with HPV 16, but other types have been found [24,25]. Recently, EQ has been shown to be associated with co-infection with the rare epidermodysplasia verruciformis-asssociated HPV 8 and the genital high-risk HPV 16 [26]. There is a high prevalence of PIN in male sexual partners of women with CIN [27,28], but many patients with PIN have consorts with no evidence of warts or CIN. Immunosuppression is important: 50% of HIV patients with anogenital warts had squamous carcinoma *in situ* on histology [21]. Nothing is known about the influence of immunogenotype. The evidence confirming that EQ/BDP may result in squamous carcinoma has been reviewed comprehensively [22,29]. The risk of progression of BP to invasive squamous carcinoma is not known, but is probably low in the absence of other risk factors, especially immunocompromise. The grade of the intraepithelial neoplasia and the development of invasive carcinoma are related to age [30]. *p53* mutations do not appear to be important in male genital carcinogenesis [31].

Some patients with these lesions may be quite young [32]. There may be several foci of BDP or EQ and they may occur concomitantly. The non-specificity of the clinical appearances makes for an important differential diagnosis, which includes psoriasis, lichen sclerosus, erosive lichen planus, ZB and extramammary Paget's disease. The differential diagnosis of BP includes lichen planus, common warts, seborrhoeic warts, naevi and condylomata lata. A biopsy is indicated in instances where the clinical diagnosis is uncertain. Aynaud *et al.* [33] have suggested that shrewd clinical interpretation predicts which lesions will show squamous carcinoma histologically and which will contain oncogenic HPV. Occasionally, it may be necessary to perform a second biopsy if the initial histology is inconclusive. It has been suggested that, where glans and shaft are both involved, the glans may be the preferential biopsy site. On histological examination, there are the features of an intraepithelial carcinoma.

Treatment. Treatment depends on many factors. Circumcision removes a major risk factor for cancer and provides extensive tissue for histology. Topical 5-fluorouracil as a 5% cream is a well-established conventional option for the treatment of BD, EQ and BP [17] but there have been no clinical trials.

Other treatments include cryosurgery, curettage and electrocautery, excisional surgery, radiotherapy (controversial), Mohs' micrographic surgery, laser and photodynamic therapy. Topical imiquimod is under evaluation [34,35]. Patients presenting with these conditions should be counselled and screened for HPV and other sexually transmitted diseases, including HIV infection. This advice should be extended to sexual partners. Follow-up should be long term [17,30].

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Squamous carcinoma

Genital squamous carcinoma is sometimes called epidermoid carcinoma. The aetiology is not clearly understood but HPV is implicated [1,2]. Diagnosis and management can present difficulties. Squamous carcinoma should be suspected in all nodulo-ulcerative genital disease, especially in the context of lichen sclerosus, lichen planus, hidradenitis suppurativa, intraepithelial neoplasia and immunocompromise. Genitourinary and urological assessment should be sought. Proctoscopy and sigmoidoscopy are necessary to exclude anorectal cancer. Suspect lesions should be biopsied.

Carcinoma of the penis

Incidence and aetiology. Carcinoma of the penis accounts for less than 1% of deaths from cancer in the USA (100 per year in the UK, and unchanged over several decades) but constitutes 10–20% of tumours seen in males in either underdeveloped countries or in areas where early circumcision is not routinely practised [3–6].

The earliest stages of penis cancer and precancer form a spectrum of disease [7]. Although some penile cancers arise *de novo*, others develop from premalignant states, which may be misdiagnosed or may be difficult to diagnose [8], and there are the issues of multifocality and field change [9] to acknowledge.

The precise aetiology of the types of PIN, verrucous carcinoma and frank invasive squamous carcinoma of the penis is unknown, as is their precise relationship to the various types of precursor lesion. However, Cubilla *et al*. [10] have defined several types of preceding epithelial abnormality: squamous hyperplasia and SIL (squamous, basaloid or warty, high or low grade).

The presence of a foreskin confers cancer risk (Table 68.24). Circumcision appears to protect against penile carcinoma [11–13], unless the circumcision was performed for penile disease [14,15]. However, there have been very rare cases in Jews and others circumcised at birth [16–18].

Carcinoma of the penis is more common in males in either underdeveloped countries or in areas where early circumcision is not routinely practised [4,19], but the incidence of penis cancer is low in Japan and Denmark,

Table 68.24 Risk factors for squamous carcinoma of the penis.

Uncircumcised
Phimosis
Poor hygiene
Chronic irritation, inflammation, scarring
Smoking
Lichen sclerosus
Lichen planus
Human papillomavirus
HIV
Squamous hyperplasia
Bowen's disease
Erythroplasia of Queyrat
Bowenoid papulosis
Giant condyloma/verrucous carcinoma
Photochemotherapy
Iatrogenic immunosuppression
Renal transplantation
Systemic lupus erythematosus

where circumcision is rare [20,21], so other factors are important in carcinogenesis.

Phimosis and balanitis are known risk factors for penile cancer [3,11,22–24]. Poor personal and sexual hygiene [12] and phimosis may lead to the retention of smegma and development of balanitis. However, the carcinogenicity of human smegma has not been ascertained [25] and it is not widely appreciated that phimosis is a physical sign and not a diagnosis. Hence, there may be more in the carcinogenic propensity of phimosis than simply physical retention of smegma.

Lichen sclerosus is a common cause of phimosis in males and it predisposes to penile carcinoma [26–30]. Powell *et al.* [31] found that half of patients with penis cancer had a clinical history and/or histological evidence of lichen sclerosus. Chronic erosive and hypertrophic lichen planus are premalignant conditions, and lichen planus is a cause of phimosis [32,33]. An underlying skin disorder was found in 22 out of 23 patients with vulval squamous carcinoma [34].

Chronic irritation and inflammation or scarring are all risk factors for squamous carcinoma of the skin generally and the penis is no exception; penis cancer complicating a burn scar has been reported [35]. Quantifying the malignant potential of the precancerous dermatoses, BDP, EQ and PIN, is not possible, but they are acknowledged risks for penile cancer [36–38].

Smoking is a risk factor, independent of phimosis, for penile carcinoma [23], and is also a recognized risk factor for anal [39] and cervical cancer [3]. Smoking may cause squamoepithelial cancer, not only in parts of the body in contact with smoke but also at distant sites by dissemination of carcinogens in the circulation or in secretions [40,41]. The presence of tobacco-specific nitrosamines in the preputial secretions of rats has been demonstrated [42].

Penile carcinoma is a complication of psoralens and UVA therapy (PUVA) [43,44], and posssibly other treatments for psoriasis [45,46]. The photodye treatment of genital herpes simplex ceased in the 1970s because of the occurrence of BDP in young men who did not have other risk factors for erythroplasia [47]. However, increased UV exposure of the genitals from sunlamps and sunbeds had not led to an increase in genital skin cancer in the USA by 1986 [48].

Although penile cancer is associated with multiple sexual partners and previous sexually transmitted disease, including HIV, the epidemiological features are not those characteristic of a sexually transmitted disease [25]—unlike carcinoma of the cervix and, to a lesser extent, anal carcinoma [49]. In cervical cancer, the evidence is that it is a sexually transmitted disease and that HPV is the aetiological agent [50–52]. Yet penile cancer puts wives and consorts at risk of cervical cancer [53], there is a high prevalence of PIN in sexual partners of women with CIN [54,55] and PIN can be found in men being screened for HPV infection [56].

HPV is implicated [1,2], but its role is still uncertain, as many patients with penis cancer have no evidence of infection. Oncogenic HPV types 16 and 18 have been incriminated [24,57–65]. In Brazil, Villa and Lopes [59] found HPV 18 in seven out of 18 penile squamous carcinomas and, in Argentina, Picconi *et al.* [65] found HPV DNA in 71% of 65 penis cancers, 81% of which were 'high-risk' HPV with predominance of HPV 18. Gregoire *et al.* [66] associated HPV with higher grade, more aggressive squamous carcinomas of predominantly the glans penis showing basaloid changes. The overall frequency of HPV in penile squamous carcinoma suggests [10,66] that a proportion of these cancers can arise from HPV-associated SIL. As in vulval cancer [67,68], a bimodal hypothesis of HPV-related and non-HPV-related causation has evolved [10,69].

Penis cancer has been reported to complicate immunosuppression in renal transplantation [70] and HIV infection [71].

Clinical features. Itch, irritation, pain, bleeding, discharge, ulceration or the discovery of a mass are the presenting symptoms of squamous carcinoma. There is often a long history of preceding problems with the penis and foreskin manifest as dyspareunia, balanoposthitis or phimosis and dysuria. Irregular nodular and ulcerative morphology is found on examination (Figs 68.17 & 68.18) and there may be background BDP, EQ and BP, lichen sclerosus or lichen planus. Phimosis should be regarded as a sinister situation, not least because it does not allow complete inspection and palpation of the glans and coronal sulcus. The inguinal lymph glands must be palpated, although in penile cancer only 50% of enlarged glands will be found to contain tumour [4]. The concomitant presence of sexually

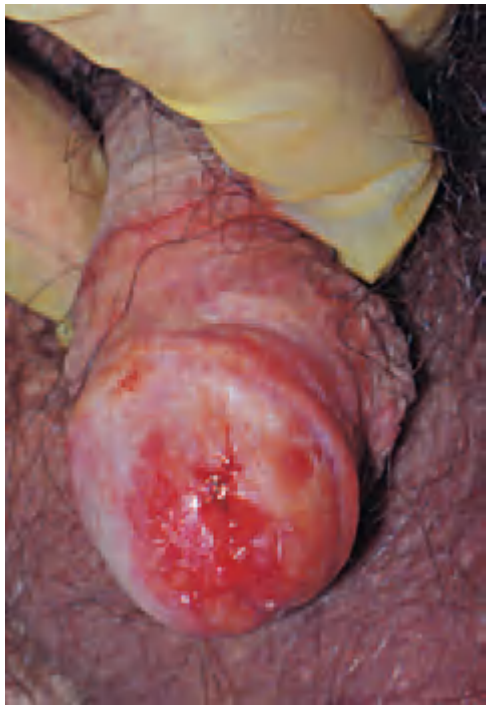

Fig. 68.17 High-grade dysplasia and invasive squamous carcinoma. (Courtesy of Dr C.B. Bunker, with permission from Medical Illustration UK, Chelsea & Westminster Hospital, London, UK.)

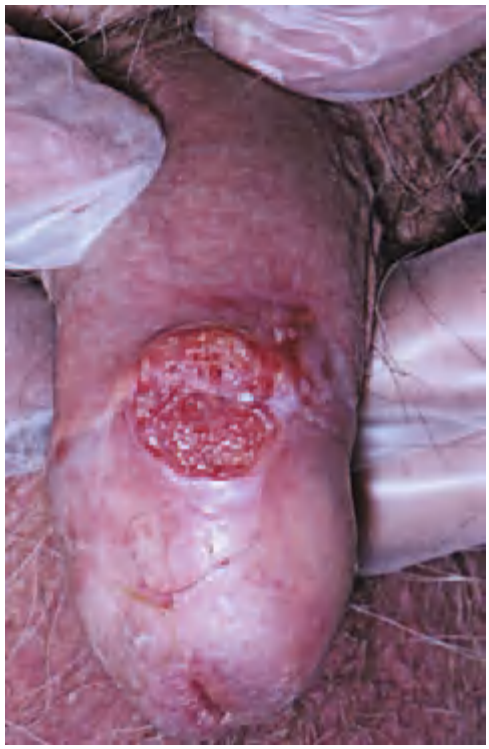

Fig. 68.18 Squamous carcinoma. Severe background lichen sclerosus. (Reproduced from Bunker CB. Skin conditions of the male genitalia. *Medicine* 2001; **29**: 9–13, by kind permission of The Medicine Publishing Company.)

transmitted diseases and immunocompromise should be excluded [72]. The differential diagnosis includes the manifestations of intraepithelial neoplasia (and the differential diagnosis of these), erosive or ulcerative sexually transmitted disease, basal cell carcinoma, Kaposi's sarcoma, pyoderma gangrenosum and artefact. Genitourinary and urological assessment should be sought.

Histopathology. Diagnosis is confirmed histologically. A biopsy should be of adequate size and depth, and it may be necessary to sample several sites. The biopsy(ies) may need to be performed by a urologist under general anaesthesia. Patients who have negative or equivocal biopsies, but who have risk factors or in whom there is a high index of suspicion, should be followed-up closely and rebiopsied if indicated.

Histologically, squamous carcinoma manifests tongues of invasive atypical keratinocytes penetrating the dermis, and contains foci of aberrant and ectopic keratinization called squamous pearls [23]. Background histological signs of lichen sclerosus are commonly found in penile cancer in men, as in vulvar cancer [73]. Verrucous carcinoma is discussed below. Spindle cell carcinoma of the penis is a very rare variant [74]. Telomerase activity is high in penis cancer [75].

Cubilla *et al.* [9] have identified four histological types of squamous carcinoma of the penis:

1 *Superficial spreading* (42%): a biphasic infiltrative and radially extensive carcinoma *in situ* contiguously involving several anatomical sites or compartments (glans, coronal sulcus, foreskin, even urethra)

2 *Vertical growth* (32%): unifocal high-grade deeply invasive, unassociated with carcinoma *in situ*

3 *Verrucous* (18%): low-grade, papillary or endophytic (see below)

4 *Multicentric* (8%): two or more independent primary tumours without contiguous field change.

These observations have implications for the pathogenesis of the different types, and in determining management in individual cases.

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Carcinoma of the scrotum

Squamous carcinoma of the scrotum has been recognized in chimney sweeps (exposed to carcinogens in soot) [1], mule spinners (exposed to carcinogens in lubricating oils for the spinning jenny in the cloth industry), Persian nomads (who travelled with pots of burning charcoal between their legs) and Indian jute oil processors [2–6]. Oil-mist exposure in industry continues to be widespread and, apart from scrotal cancer, has been associated with other cutaneous problems (such as contact dermatitis and oil acne) and respiratory diseases, including cancer [7].

Other individuals at risk of scrotal squamous carcinoma include those with a history of psoriasis treated with arsenic, coal tar, UVB and PUVA [8–13], previous radiotherapy treatment [8], scrotal HPV infection, hidradenitis suppurativa and multiple cutaneous keratoses and epitheliomas [14–17]. Rarely, black men may be affected [18].

The presentation of scrotal carcinoma is similar to that of penis cancer, with itch, irritation, pain, bleeding, discharge, ulceration or the discovery of a lump, and irregular nodular and ulcerative clinical features. A pigmented squamous carcinoma of the scrotum has been reported [19]. The differential diagnosis includes the manifestations of intraepithelial neoplasia (and the differential diagnosis of these), erosive or ulcerative sexually transmitted disease, basal cell carcinoma, Kaposi's sarcoma, pyoderma gangrenosum and artefact. The diagnosis is confirmed by biopsy.

Treatment of squamous carcinoma

The treatment of anogenital squamous carcinoma is not generally the province of the dermatologist. The overriding general principle is to offer adequate surgical excision, including circumcision, for disease of the penis. The penile surgery may need to be radical, total or partial, depending on location and extent [20–22]. To minimize residual sexual dysfunction, conservative plastic techniques are increasingly used [23], as are laser treatment [24] and Mohs' micrographic surgery [25–28] for squamous carcinoma of the penis, but the concepts of field change and the implications of infection by HPV and multifocality must be considered. Combination chemotherapy has been used for palliation and proposed for adjuvant treatment of carcinoma of the penis, but remains under evaluation [29].

Lymphatic or haematogenous dissemination of genital cancer dictates individualized multidisciplinary treatment. The management of ilioinguinal lymphadenopathy is controversial [20,22,30].

The prognosis of penis cancer relates to the extent of inguinal lymphadenopathy [31,32] and involvement of the corpus [33]. It does not correlate with HPV status [34]. The prognosis for scrotal carcinoma is not good, despite apparently adequate primary surgical treatment: the 5-year mortality is 50–60% [3,4].

Penile cancer puts wives and consorts at risk of cervical cancer [35]. In black men who develop penile cancer there is a substantial risk (18%) of the later development of a second primary malignancy [36].

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Verrucous carcinoma/giant condyloma/Buschke–Löwenstein tumour

Buschke–Löwenstein tumour and verrucous carcinoma can probably be regarded as synonymous. They represent verrucous low-grade well-differentiated squamous carcinoma. It is perhaps more accurate and more clinically useful to consider giant condyloma as a separate HPV-related entity with a better prognosis, but controversy exists [1–7].

Verrucous carcinoma is rare. It produces dramatic polypoid or cauliflower-like clinical lesions (Fig. 68.19). Presentation as a penile cutaneous horn has been described [8,9]. Although locally deeply invasive, the tumour is well demarcated from surrounding tissue and is unlikely to metastasize. Both sexes can be affected.

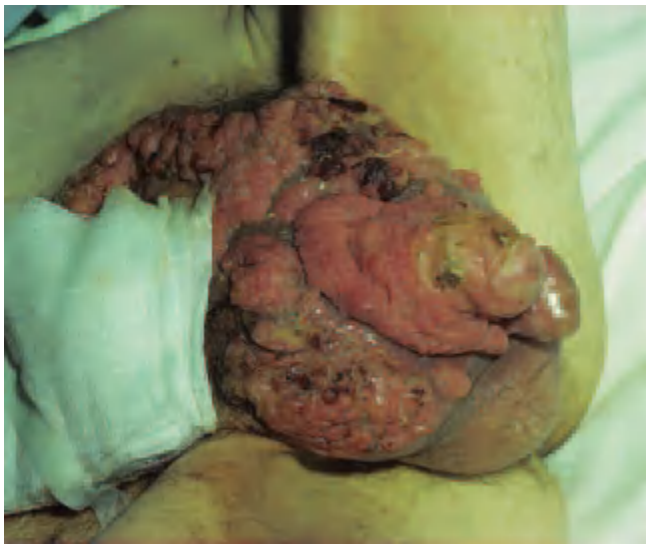

Fig. 68.19 Gross condylomas of Buschke–Löwenstein of the penis. (Courtesy of Professor R.M. MacKie, Glasgow University, Glasgow, UK.)

A specific aetiology for verrucous carcinoma of Buschke–Löwenstein has not been unequivocally identified, but an origin from genital warts is likely. HPV types 6 and 11 are the most commonly associated [1,3,4,10–16]. A patient taking ciclosporin for psoriasis developed a verrucous carcinoma containing HPV 6 and 16 [17]. Multiple HPV types were found in a transplant patient [18]. Tumours containing several HPV types may be mixed, containing verrucous carcinoma adjacent to squamous carcinoma [19]. Cases emanating from background lichen sclerosus have occurred [20,21]. Chronic hidradenitis suppurativa may rarely be a predisposing factor [22].

If verrucous carcinoma is suspected, then a deep surgical biopsy must be planned. The tumour has a different histology from squamous carcinoma, showing deep lobular invaginations of well-defined proliferative epithelium consisting of typical clear pale keratinocytes [23]. Frank squamous carcinoma [24] and foci of invasive squamous carcinoma [25] have been reported in some cases of anogenital verrucous carcinoma. Ultrastructurally, verrucous carcinoma is distinct from condyloma acuminatum but similar to SCC [26].

Clinical, histological and virological differences may distinguish verrucous carcinoma (potential for aggressive lethal behaviour) from Buschke–Löwenstein tumour and giant condyloma (no malignant potential) and this distinction should direct treatment [3,4,11,13,16].

Surgical excision is the treatment usually recommended (e.g. glansectomy [27] or penectomy). Mohs' micrographic surgery [28–30], cryotherapy [31], laser treatment [32], interferon-α [33–36], radiotherapy [37] or bleomycin [38] are alternatives.

The prognosis is poor because the tumour can continue to grow and invade locally, causing death by exsanguination from femoral arterial invasion or cachexia [39]. Even with treatment, recurrence and progressive malignant transformation do occur [40,41], so follow-up is necessary.

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Other malignant neoplasms

Extramammary Paget's disease

Extramammary Paget's disease (EMPD) presents as irritating, itchy, burning, red scaly patches or plaques that may be solitary or multifocal. EMPD can occur anywhere in the anogenital area, including the glans penis, and may be multicentric [1–3]. An 'underpants' pattern of erythema has been reported in a number of patients [4]. EMPD is frequently misdiagnosed as psoriasis or eczema [5], or Bowen's disease. Subclinical EMPD has been documented, where the skin looks normal macroscopically but is involved microscopically. EMPD behaves indolently, spreading by local extension and metastasis [6,7].

The concurrence of genital and extragenital EMPD is extremely rare, but overt and latent axillary EMPD can coexist and change daily in association with penile and pubic EMPD [8]. Also very rare is depigmented EMPD of the genitalia, evoking the differential diagnosis of vitiligo, hypopigmented mycosis fungoides and lichen sclerosus [9]. A focus of cutaneous squamous carcinoma has been reported complicating genital EMPD [10].

Diagnosis is by biopsy. Histological examination shows nests of large vacuolated cells with circular nuclei and foamy pale cytoplasm in the epidermis (Paget's cells). Dermal involvement signifies a poor prognosis. Pagetoid dyskeratosis can be found in a number of benign lesions such as naevi, skin tags and lentigines [11]. Pale cells resembling Paget's cells can be seen incidentally in benign papular intertriginous conditions, and in nearly 40% of prepuces sent for histological examination following circumcision for phimosis [11–13]. Anogenital Paget's disease can be accompanied by epidermal hyperplasia similar to fibroepithelioma of Pinkus [14]. Immunohistochemical and enzyme histochemical evidence points to sweat gland epithelium as the source of Paget's cells in EMPD [15]. The distribution along the 'milk line' has led to the suggestion that the 'clear cells of Toker' are the histogenic precursors of both clear cell papulosis and mammary and extramammary Paget's disease, respectively [9]. HPV is not present [16], but the c-erbB-2 oncoprotein may have a role in the pathogenesis of EMPD [17].

Mammary Paget's disease is an epidermal manifestation of an underlying breast adenocarcinoma [18]. EMPD is found in areas rich in apocrine sweat glands, such as the axillae and anogenital region. EMPD can also be associated with an underlying malignancy [6]. In a large series, 24% of patients had a proximate cutaneous adnexal adenocarcinoma, 12% were found to have a concurrent, and another 17% to have a non-concurrent internal malignancy [19].

Although properly regarded as a type of carcinoma *in situ*, EMPD may itself become invasive and metastatic [20–22]. There may be subjacent carcinoma (e.g. in periurethral glands) [23] or distant carcinoma (e.g. prostate [24] or bladder [25]), or both (e.g. periurethral glands and bladder [26]). Pagetoid epidermal invasion of inguinal cutaneous metastatic mesothelioma of the tunica vaginalis of the testis has been reported [27].

Treatments used for EMPD include cryotherapy and topical 5-fluorouracil [28], wide excisional surgery [20], micrographic surgery [29,30], radiotherapy [7,31] and photodynamic therapy [32].

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Malignant melanoma

This is a very rare condition of the penis (fewer than 100 cases reported). It is estimated to account for 1–1.5% of all malignancies of the penis [1,2] and less than 0.15% of all melanomas [3]. Melanoma is even rarer on the scrotum, with only four cases appearing in the literature [4,5].

Genital melanoma presents as a pigmented macule or as a pigmented or amelanotic papule or nodule (possibly developing from a lentiginous area or pre-existing dysplastic naevus), which may ulcerate or bleed [1,2,6–14]. Patients are usually middle-aged or older, although it has been reported in a boy [15]. It is exceedingly rare in Asians and has not been reported in black people (although a case of melanoma of the urethra has been seen) [16].

Sixty to 70% of lesions occur on the glans. There may be a family history of melanoma and other atypical or 'dysplastic' naevi on examination. The inguinal and other nodes, as well as the abdomen, should be palpated. Forty to 50% of patients have lymphatic or other metastatic dissemination at the time of presentation. Clinically atypical lesions should be biopsied and the histology critically reviewed [7,11]. Malignant melanoma of any histological subtype may be encountered [17].

Treatment is by primary excision. Subsequent management depends on the Breslow thickness of the lesion and complete clinical staging. Radical surgery and chemotherapy may be needed, but the prognosis is poor for all melanomas that have already metastasized [1,15,18].

Kaposi's sarcoma

Solitary Kaposi's sarcoma (KS) of the penis was very rarely seen before the HIV epidemic and cases are still occasionally seen in HIV-negative patients [19,20], but genital KS is essentially an HIV-associated problem. It presents as a dull red patch or plaque of the glans or prepuce, or anywhere else on the penis or scrotum, perineum or perianal skin in one of its classic forms: purple, slightly scaly patches or plaques, nodules or ulcerative lesions [21]. More atypical presentations that have been seen include engorgement with hypervascularity [22], penile lymphoedema [23] and phimosis. The differential diagnosis includes cellular naevus, histiocytoma, angioma, angiokeratoma, pseudo-Kaposi's sarcoma [24], bacillary angiomatosis and melanoma.

Miscellaneous

Although basal cell carcinoma is the most common type of skin cancer, it is rare in the anogenital area, although over 100 cases have been reported [25], including one case report of fibroepithelioma of Pinkus affecting the base of the penis [26]. A case of multiple erosive scrotal basal cell carcinomas with metastasis has been described [27].

Fibrosarcoma, haemangiopericytoma, leiomyosarcoma, malignant fibrous histiocytoma, epithelioid sarcoma, dermatofibrosarcoma protuberans and spindle cell sarcoma may occur, presenting as painful or painless nodules, masses or swelling with dysuria and erectile difficulties (e.g. masquerading as Peyronie's disease) [19,28]. Other rarities include Merkel cell carcinoma [29], malignant eccrine poroma [30], malignant schwannoma [19,31] and solitary reticulohistiocytic granuloma of the scrotum [32].

Involvement of the penis with Langerhans' cell histiocytosis is very rare; a fleshy papule on the dorsal penis and primary penile ulceration have been reported [33].

Mycosis fungoides can be confined to or concentrated in the genital region. Localized perianal involvement has been described [34].

Although lymphoma is the most frequent secondary tumour of the testis, it is rare in other parts of the male urogenital tract [19]. Penile lymphoma can present as painless subcutaneous nodules, erythematous swelling and ulceration [35–37]. There may be no evidence of systemic lymphoma. A fungating nodular scrotal lymphoma has been reported [38], as have scrotal and penile ulceration resulting from leukaemic infiltration [39,40].

Metastases to the penis are rare, but several hundred cases have been reported [41]. They are usually secondary to cancer of the urogenital tract [42] or gastrointestinal system, or other common cancers such as of the lung [43], and present with pain, swelling, priapism, urinary symptoms or haematuria. A very rare cause is secondary melanoma [41].

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Miscellaneous

Pigmentary change is dealt with in the general introduction on pp. 68.2–68.3, and causes of anogenital hypo- and hyperpigmentation are listed in Tables 68.6 and 68.7.

Penile melanosis

Pigmented macules are not uncommon on the glans and shaft of the penis [1]. They are benign but, because they may be large or enlarging, with irregular edges and multifocal and variegated pigmentary patterns, they arouse concern about atypical melanocytic proliferation and acral lentiginous melanoma. Such clinical concerns should lead to biopsy [2]. Post-inflammmatory hyperpigmentation (e.g. lichen sclerosus, lichen planus) may be the cause in many patients. Some cases have been associated with previous treatment with anthralin, or PUVA therapy for psoriasis, or diabetes [3,4]. On histological examination there may be increased basal epidermal pigmentation, with or without benign lentiginous melanocytic hyperplasia, or an increase in basal melanocyte number. Breathnach *et al.* [5] have proposed that depigmentation is an essential element of penile melanosis and demonstrated melanocytic hyperplasia in areas of hyperpigmentation.

Penile melanosis is the term for lesions without lentiginous hyperplasia [4,6]. Revuz and Clerici [6] proposed the grouping of penile melanosis, vulvovaginal melanosis and the predominantly oral mucosal hyperpigmentation of the Laugier–Hunziker syndrome under the umbrella of essential melanotic hyperpigmentation of the mucosa. Lenane *et al.* [7] used the term genital melanotic macules.

Patients ask for treatment of penile melanosis as it is unsightly and embarrassing. Laser treatment may help [8].

Hypopigmentation

Striae as a consequence of growth or weight surges are common around the pelvic girdle or represent a complication of topical corticosteroid application [9]. Initially, they are often purple-red in colour. Vitiligo is a commonly observed affliction of the male genitalia, although patients may be unaware of it and clinicians might not always observe it [10].

Acral lentiginous melanoma is very rare but important [11,12].

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Pain and swelling

Some presentations of many entities can be painful but generally pain is an unusual presentation for a dermatosis. Swelling is more common and may be painful or not. A common factor in many but not all causes of swelling may be oedema or lymphoedema. Causes of anogenital lymphoedema and penoscrotal swelling are listed in Tables 68.25–68.27.

Iatrogenic swellings and lymphoedema

Congenital defects of the inguinal canal and other non-inguinal peritoneal leaks can lead to scrotal and penile swelling as a manifestation of dialysate oedema in patients with end-stage renal failure treated by continuous ambulatory peritoneal dialysis [7]. Genital oedema is

Table 68.25 Causes of anogenital lymphoedema. (After Bunker [6].)

Idiopathic congenital lymphoedema (Milroy's disease)
Lipogranuloma and silicone granuloma
Strangulation of the penis
Iatrogenic
Radical abdominopelvic surgery
Radiotherapy
Granulomatous lymphangitis
Post-infectious
Cellulitis and erysipelas
Chancroid
Lymphogranuloma venereum
Tuberculosis
Leprosy
Syphilis
Filariasis/onchocerciasis
Carcinomatosis
Lymphatic involvement
Lymphatic blockage
Lymphoma

Table 68.26 Commoner causes of penoscrotal swelling. (After Bunker [6]. © 2004, with permission from Elsevier.)

Paraphimosis
Foreign body
Strangulation of the penis
Iatrogenic
Continuous ambulatory peritoneal dialysis
Genital oedema resulting from raised right heart filling pressure in ITU
Postoperative
Post-radiotherapy
Varicocoele
Hydrocoele
Priapism
Peyronie's disease
Epididymitis and orchitis
Cellulitis
Idiopathic penile oedema
Testicular tumours

Table 68.27 Rarer causes of penoscrotal swelling. (After Bunker [6]. © 2004, with permission from Elsevier.)

Idiopathic congenital lymphoedema [1]
Giant haemangioma
Urethral diverticulum
Segmental urethral hypospadias
Accessory scrotum [2,3]
Herniation of scrotal contents into penile shaft
Foreign body
Lipogranuloma and silicone granuloma
Aortic aneurysm [4]
Scrotal fat necrosis
Henoch–Schönlein purpura
Familial Mediterranean fever
Acute haemorrhagic oedema of childhood
Granulomatous lymphangitis
Sarcoid
Infected cyst
Abscess of corpus cavernosum [5]
Tuberculosis
Paracoccidioidomycosis
Giant scrotal tumours (e.g. neurilemoma)
Epithelioid haemangioma
Kaposi's sarcoma
Epithelioid haemangioendiothelioma
Lymphoma
Sarcoma
Drugs (e.g. angio-oedema caused by lisinopril)

Table 68.28 Complications of plastic surgery to the penis. (After Bunker [6] (© 2004, with permission from Elsevier) and Alter [11].)

Hypertrophic scars
Wide scars
Proximal penile hump (thick hair-bearing Y flap)
Low-hanging penis
Loss of fat
Nodules
Deformed shaft

commonplace in intensive care units, because of the practice of maintaining a raised right heart filling pressure. Radical cancer surgery and/or radiotherapy to the anogenital area and the lymphatics can cause swelling because of lymphoedema, early or delayed [8]. Chronic oedema, resembling keloid, of the penis has been caused by a condom catheter for neurogenic bladder [9].

Increasingly, patients seek plastic surgery to the penis [10] for psychosexual reasons (e.g. dysmorphophobia) but surgery can result in significant complications (Table 68.28).

Idiopathic lipogranuloma

Cases of characteristic, spontaneously resolving, painless, Y-shaped swelling of the scrotum embracing the penile root, with sclerosing eosinophilic lipogranuloma on histology and electron microscopy (but no exogenous lipids) and associated with blood eosinophilia (one patient had arthralgia), have been reported from Japan [12].

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Priapism

Priapism is defined as the prolonged painful erection of the penis, unassociated with sexual desire and not relieved by ejaculation. Although not predominantly a dermatological concern, it has an important differential diagnosis. The principal causes are listed in Table 68.29. It results in impotence in more than 50% of those affected [3,4] and can lead to gangrenous penile necrosis [5].

Levine *et al*. [1] distinguish veno-occlusive priapism from arterial priapism. Veno-occlusive priapism results from persistent obstruction to venous outflow from the lacunar spaces. It is a potential vascular emergency because, as the corporeal bodies expand to maximal volume, an obstructed outflow causes decreased arterial inflow, with the potential for ischaemia, pain, fibrosis and hence impotence. Arterial priapism is usually secondary to trauma, such that a damaged cavernosal artery causes unregulated blood flow to the lacunar spaces; it is thus non-ischaemic [1].

Table 68.29 Causes of priapism. (After Levine *et al*. [1] and Bunker [2]. © 2004, with permission from Elsevier.)

Idiopathic
Os penis
Congenital
Acquired—ageing, trauma, metabolic disorder
Perineal trauma
Strangulation
Hypertension
Nephrotic syndrome
Neurological causes
Quadriplegia
Spinal canal stenosis
Cauda equina compression
Sickle cell disease
Coagulopathy
Protein C deficiency
Factor V Leiden
Warfarin necrosis
Peyronie's disease
Rheumatoid arthritis
Vasculitis
Tuberculosis
Pelvic tumours
Leukaemia
Lymphoma
Penile metastases
Drugs
Papaverine
Antipsychotics—chlorpromazine, trazodone
Antihypertensives—hydralazine, guanethidine, prazosin
Marijuana
Adrenal corticosteroids
Warfarin necrosis

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Dermatological non-disease, dysaesthesia and chronic pain syndromes

'Dermatological non-disease' may be the diagnosis where there is a paucity or even absence of primary dermatological signs to account for florid symptomatology. Genital symptoms include itching, excessive redness, burning and discomfort—in some cases so severe that it prevents the patient from sitting down. Dysmorphophobia, depression and psychosis may be present, and attempted suicide is a real risk in such patients [1,2].

Itching of the urethra may lead to insertion of a foreign body into the urethra in an attempt to relieve the sensation [3], or this might be done for sexual gratification.

Patients with symptoms of itching, burning and pain localized to the penis or scrotum are not uncommonly encountered. The skin is usually completely normal. The situation is analogous to vulvodynia in women, and terms such as penodynia and scrotodynia have been coined to describe the syndrome in men. Doxepin, amitriptyline and paroxetine can afford some relief.

Fisher [4] has defined the red, burning scrotum syndrome as 'persistent redness of the anterior half of the scrotum that may involve the base of the penis . . . usually accompanied by a persistent itching or burning sensation and hyperalgesia'. It is a chronic condition that is resistant to treatment and its cause is unknown [4,5]. Accompanying the erythema there may be telangiectasia. It is related to idiopathic penile and scrotal pain syndromes [6]. Prednisolone and antidepressants have given some relief to some patients.

Localized dermatographism should be sought by stroking the inside of the thigh, because such patients may be helped by oral antihistamine treatment.

The possibilities of zinc deficiency and necrolytic migratory erythema should be entertained.

Chronic urogenital and rectal pain syndromes include penile pain (penodynia), scrotodynia, orchialgia, prostatodynia, coccygodynia, proctalgia fugax, perineal pain, the descending perineum syndrome and vulvodynia

[7–9]. The neuroanatomy of the pelvis is complicated and the neurophysiological basis of the pathogenesis of these syndromes is poorly understood, but their clinical presentations are well recognized. The differential diagnosis is addressed above.

A diagnosis of a chronic pain syndrome implies the prospect of considerable psychological morbidity. Treatment is challenging and only empirical at best. Most agree that invasive and irreversible procedures should be avoided if at all possible. Multidisciplinary management is recommended [6].

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Hair disorders

Alopecia areata can affect the pubic hair, but usually as part of more widespread involvement as in alopecia universalis. Loss of pubic hair occurs in secondary syphilis and has been reported in primary systemic amyloid [1]. Trichotillomania of the pubic hair has been described [2,3].

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Female genital dermatology

Introduction

Disorders of the vulval epithelium have proved confusing to the many and varied specialists who have been involved in their diagnosis and treatment. The difficulty has arisen because the majority of the problems are dermatological and the specialists—gynaecologists, urologists, paediatricians and genitourinary physicians—have had little or no training in dermatology. The problem is compounded by the fact that the normal characteristics of common diseases at this flexural site are lost or modified, making the diagnosis difficult even for an experienced dermatologist. Over the years, classifications of vulval disorders have been devised to help, but unfortunately these have only resulted in further confusion. There is no need for a separate classification for vulval disorders, as the current classifications that exist for dermatology and pathology can be used [1,2].

Dystrophy, leukoplakia and kraurosis vulvae have all now been abandoned as diagnostic terms [3]. Over the years, the term leukoplakia has unfortunately had the sinister implication that it always represented a premalignant condition [4], but now leukoplakia is used as a descriptive term only and may represent anything from a patch of lichen simplex to an SCC. Similarly, squamous cell hyperplasia is not a diagnosis but a histological description, and can be seen in many disorders including psoriasis, candidosis and hypertrophic lichen planus.

Vulval clinics have been an important step forward in the diagnosis and management of women with vulval problems [5,6]. These clinics ideally should be multidisciplinary with input from dermatology, gynaecology, genitourinary medicine and pathology. It is important that there are links with other specialists including paediatricians and plastic surgeons, as well as psychologists and psychosexual therapists.

The development of these clinics has been extremely important, not only for improved patient care but also for the valuable interdisciplinary education of the doctors involved.

An accurate diagnosis depends on a thorough history, examination of the affected skin and skin at extragenital sites, and pertinent investigations. The history must include the chief complaint, how long it has been present, how the problem changes in certain circumstances (e.g. variation with the menstrual cycle), what treatment has been prescribed and what were the effects of the treatment. A drug history is important, and should include direct questioning about over-the-counter oral and topical medications, oral contraceptives and hormone replacement therapy (HRT). The latter two are included in this direct questioning as patients do not always consider these as medications, particularly if the HRT is in a topical formulation. A personal and family history of autoimmune disease, atopy or psoriasis should be established, and any known skin sensitivities. The patient should also be asked about vaginal discharge, urinary symptoms and bowel function. Finally, as the vulva is important for normal sexual function, it is important to include relevant questions on problems with intercourse where appropriate.

The complaint of irritation has many meanings and it is sometimes helpful to ask the patient exactly what they mean by the term. It may be the sensation of itch, dryness, pain, burning or rawness. This point is important as a

patient with itch will scratch or rub the skin, and the response will be lichen simplex or lichenification, whereas with discomfort or pain there will be no such change as the patient avoids touching the area.

Lichen simplex and lichenification. Lichen simplex and lichenification are terms used to describe the exaggerated normal rhomboidal patterning of the skin surface. Lichen simplex is used to describe the changes seen on apparently normal skin secondary to itching and rubbing, although the provoking symptom of itch may be initiated by a low-grade dermatosis such as psoriasis or seborrhoeic eczema. The term lichenification is used for similar changes arising on a background of a visible dermatosis.

The lesions of lichen simplex tend to be in one isolated area, usually on the labia majora or mons pubis. They are well defined, with a pale grey or white surface.

The histological changes of lichen simplex and lichenification are similar, except that there are the changes of the background dermatosis in the latter. There is hyperkeratosis, acanthosis, a prominent granular layer, lengthened rete ridges and a chronic inflammatory dermal infiltrate. In addition, lamellar thickening of the papillary dermis and perineural fibrosis can be seen. Twelve cases of what was termed multinucleated atypia of the vulva have been reported [7], but this is thought to be a non-specific change found in lichenified skin [8,9].

Treatment of the underlying dermatosis will usually resolve the lichenification. In cases of lichen simplex with no underlying dermatosis, the treatment is the application of a potent topical steroid to encourage a disruption of the itch–scratch cycle. A soap substitute should be introduced and possible irritants avoided. If these measures are unsuccessful, patch testing should be performed to exclude the possibility of an unsuspected allergen.

The examination is often very embarrassing for the patient, so it must be carried out sympathetically to ease any tension. It is important that there is good lighting, and a means of magnification. The skin and the mucosae are examined in the anogenital area for changes in colour, epithelial integrity and texture. If there is scarring this will be seen in loss of characteristic features (e.g. introital narrowing, loss of the labia minora or sealing of the clitoral hood). The examination must also include examination of other flexural sites and mucosae, the scalp and nails. It is also useful to determine if the patient exhibits dermographism [10]. The vagina and cervix should be examined in patients who have dermatoses that affect mucosal surfaces and in patients with symptoms of dyspareunia, vaginal discharge or postcoital bleeding. Investigations are determined by the specific problem and include microbiological assessment. The investigation of the common bacterial or fungal problems can be easily performed by a dermatologist but if an exotic bacterial or sexually transmitted infection is high on the differential diagnosis, it is important to involve a genitourinary physician in the investigation and work-up of these patients and their partners. A biopsy is important, particularly in cases where there is no response to treatment. If a biopsy is performed, it is important to let the pathologist know what area has been biopsied, as the vulva is a mucocutaneous junction and the normal histological changes of a mucosal epithelium differ significantly from those of cornified epithelium and may be misinterpreted as pathological changes. Other investigations include those performed routinely for skin problems elsewhere (e.g. patch testing, examination with Wood's light, Tzanck smears). Some investigations are not the usual remit of the dermatologist but are necessary in patients with anogenital dermatoses, and will include a cervical smear and proctoscopy.

On occasions, the vulval changes are not caused by a primary problem of the vulval skin but are the secondary consequences of pathology at another site (e.g. an irritant vulval dermatitis resulting from a vaginal discharge because of cervical, uterine or vaginal pathology).

Table 68.30 Causes of vaginal discharge.

Physiological
Ovulation
Iatrogenic
Medications (e.g. tamoxifen, oral contraceptive pill)
Infective
Candidosis
Bacterial vaginosis
Cervicitis
Inflammatory
Lichen planus
Mucous membrane pemphigoid
Pemphigus
Erythema multiforme
Stevens–Johnson syndrome
Vaginal adenosis
Cervical erosion
Neoplastic
Langerhans' cell histiocytosis
Vaginal, uterine or fallopian tube tumours

Diagnosis and management of vaginal discharge

The diagnosis usually falls into one of the following categories: physiological, iatrogenic, infective, inflammatory or neoplastic (Table 68.30).

Physiological

Between 5 and 10% of women complaining of vaginal discharge do not have an infection. The discharge may be caused by an excess physiological secretion of mucus, usually resulting from a cervical erosion or an increase in the amount of vaginal transudate. The discharge is thick,

with a grey-white appearance, and is odourless and non-irritant. Vaginal pH is normal.

Iatrogenic

This is usually secondary to medications that have an effect on the vaginal epithelium (e.g. tamoxifen, which has an oestrogenic effect on the vagina); oral contraceptive pills can cause a cervical erosion and an increase in vaginal discharge.

Infective

This is the most common cause of a vaginal discharge, and a pH greater than 6 is highly predictive of an infectious cause [11]. Bacterial vaginosis is the usual diagnosis [12]. The patient complains of excessive grey watery discharge, associated with a 'fishy' malodour, which is worsened with intercourse. Vulval irritation is slight or absent in this group, and the smell is the most distressing symptom. The condition is invariably associated with infection by a small aerobic Gram-negative rod known as *Gardnerella vaginalis*, after its discoverer Gardner [13]. It would appear that this organism alone is incapable of causing infection, and non-specific vaginitis is now regarded as a complex interrelationship between *Gardnerella* and anaerobic species of bacteria [14], two of which belong to the genus *Mobiluncus*. The fishy odour of the discharge can be accentuated by the addition of an alkali such as 10% potassium hydroxide (the Whiff test). A wet mount of a vaginal smear in saline will identify 'clue cells'. These are vaginal epithelial cells with a granular cytoplasmic appearance and indistinct cellular outlines. This indistinct border is caused by the attachment of the small Gram-negative rods to the cell [15]. Bacterial vaginosis is not always sexually acquired—its incidence is equal in virginal and sexually active groups [16,17]. This type of abnormal bacterial colonization may be associated with preterm delivery and late miscarriage in pregnant patients [18]. Treatment is with metronidazole 400 mg twice daily for 5 days or 2 g as a single dose.

Patients with infective cervicitis will also present with an increased vaginal discharge. The four most common pathogens involved are *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Trichomonas vaginalis* and herpes virus hominis. *Chlamydia trachomatis* has been grown from the cervices of 50% of women with mucopurulent cervicitis [19]. The main symptoms are discharge, deep pelvic pain and dyspareunia.

Infestation with thread worms, *Enterobius vermicularis*, has also been recorded as a cause of a vulvovaginitis [20].

Inflammatory

Vaginal or cervical ulceration and erosion resulting from inflammatory conditions can give rise to an increased vaginal discharge. The most common inflammatory conditions are lichen planus and pemphigus [21]. The diagnosis is often missed, particularly if these sites are affected in isolation. There is a chronic odourless discharge, which may be blood-tinged. The patient will also complain of postcoital bleeding if she is sexually active. An accurate diagnosis requires a biopsy, and immunofluorescence studies should be performed both on tissue and serum. Examination of eyes and mouth may help if the patient also has disease at these sites. Treatment requires topical steroids in the form of foams or pessaries that are currently used for inflammatory bowel disease.

Neoplastic

Tumours of the fallopian tubes, uterus, cervix and vagina may all cause an increased vaginal discharge. Rarer causes of a chronic vaginal discharge include Langerhans' cell histiocytosis.

Management of vulval disorders depends upon the diagnosis, but general measures include the use of a soap substitute and avoidance of irritants (e.g. bubble baths, shampooing hair in the bath). If there is an incontinence problem, a barrier ointment helps to protect the skin. Weak potassium permanganate solution or Burow's solution can be used when there is erosive disease. Topical steroids are best used in an ointment formulation to avoid the irritant effect of preservatives and alcohol. Many of the patients are elderly and may have difficulty treating themselves. It is often helpful to take time in the clinic, using a mirror, to explain exactly where the treatment should be applied.

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Structure and function of the female genitalia

The vulva is the collective term for the structures that comprise the female external genitalia. Anatomically, it is the region known as the urogenital triangle, bounded anteriorly by the symphysis pubis, the pubic rami laterally and the transverse perineal body posteriorly. The vulval structures included within this area are the mons pubis, paired labia majora and labia minora, clitoris and vulval vestibule. The epithelia that cover the vulva change from skin on the outer aspects to mucosa on the innermost region.

The mons pubis lies in front of and above the upper part of the symphysis pubis. It is softly rounded because of a thick cushion of subcutaneous fat. The epithelium is densely covered in hairs and possesses all the adnexal structures usually found in skin.

The labia majora are paired rounded folds of skin and are the homologue of the scrotum. They extend downwards and backwards from the mons pubis and meet posteriorly in the midline to form the posterior commissure, which lies approximately 2 cm anterior to the anus. The epithelium is similar in structure to that on the mons pubis in that there is a thick layer of adipose tissue and a dense distribution of hair on the outer surfaces of the labia. Hair is absent from the inner surfaces but numerous sebaceous glands remain. The inner aspects of the labia majora fuse into the outer aspects of the labia minora laterally, forming the interlabial sulci. The labia majora enclose an elliptical fissure which is known as the pudendal cleft—this contains the vestibule with the openings of the vagina and urethra.

The labia minora are the equivalent of the prepuce, and part of the ventral portion of the penis and the floor of the spongy part of the male urethra. They are paired pendulous folds, which lie between the labia majora and the vulval vestibule. Anteriorly they split into two folds on each side, which fuse in the midline. The superior folds cover the clitoris like a hood, forming the prepuce of the clitoris, and the lower folds fuse on the inferior aspect of the clitoris, forming the clitoral frenulum. Posteriorly, the labia minora fuse to form the fourchette, and sometimes form a depression in the midline, the fossa navicularis. The labia minora possess little subcutaneous fat. Their epithelium lacks hair but there are numerous sebaceous glands and sweat glands. The epithelium is cornified but its barrier function is not as effective as skin elsewhere.

The clitoris is the homologue of the penis and contains all the vascular and muscular structures found in its male counterpart. The end of the clitoris is surmounted by a small rounded tubercle, the glans clitoris.

The vestibule is usually considered as part of the vulva, although many anatomy books refer to it as the vestibule of the vagina. It is the area that lies between the labia minora and contains the openings of the urethra and vagina. The vaginal opening is partially closed by the hymen. When the hymen is ruptured, its remnants form rounded crenulations, the hymenal caruncle. The fold between the hymenal caruncle and the vestibular floor is the nymphohymenal sulcus. Sometimes a clear line of demarcation between the labia minora and the epithelium of the vestibule can be seen, Hart's line. The vestibule is a mucosal epithelium and lacks hairs and sebaceous glands. On each side, the duct of the major vestibular gland, Bartholin's gland, can be seen sited between the hymenal ring and posterior part of the labium minus. The ducts of the minor vestibular glands, Skene's glands, open on either side of the urethral orifice. The epithelial surface is usually smooth, but occasionally tiny frond-like papillae may be seen distributed symmetrically laterally and posteriorly on the vestibule (Fig. 68.20). These vestibular papillae are a variant of normal and not related to HPV infection.

Normal flora

The skin of the perineal area has a higher pH, temperature and degree of humidity than skin elsewhere and, because of its proximity to the vagina and rectum, harbours many of the flora from these sites [1,2]. The main resident organisms are micrococci, diphtheroids and lactobacilli. Lactobacilli are probably the most common organisms, particularly on the labial mucosa, as the glycogenated epithelium of the vagina, under the influence of oestrogen, encourages colonization by them. The lactobacilli in turn metabolize the glycogen to lactic acid, which keeps the vaginal pH at approximately 4.5, restricting the growth of many organisms.

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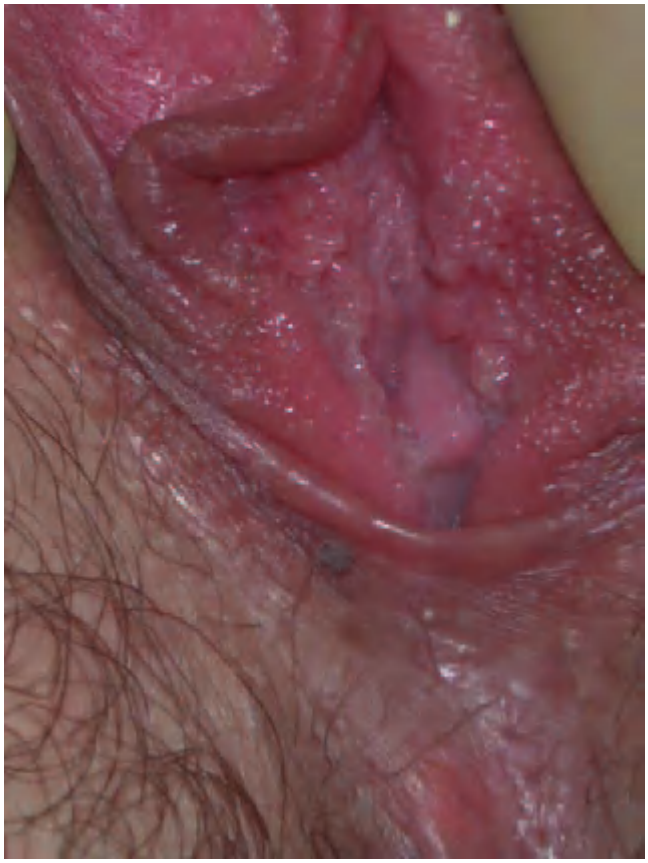

Fig. 68.20 Vestibular papillae.

Normal variants

Angiokeratomas are small vascular 1–4 mm papules found on the labia majora [1]. They vary in colour from red to blue-black and are normally asymptomatic, but can become quite large and bleed if traumatized, particularly in pregnancy.

Sebaceous gland hyperplasia is seen on the inner aspects of the labia majora and labia minora where the glands do not usually have an associated hair unit. The glands open directly onto the surface, and may be very prominent and numerous. The yellow uniform papules are often best seen when the skin is stretched. Prominent and numerous glands may be associated with pruritus. Occasionally, they can become very large and be mistaken for a sebaceous gland adenoma [2].

Vestibular papillomatosis is the term used to describe the occasional normal finding of myriad tiny filiform or soft frond-like projections on the vestibular epithelium and inner aspects of the labia minora. These lesions have had various names in the past, including papillomatosis labialis, hirsuties papillaris [3], hirsutoid papillomas of the vulva [4], vestibular papillae [5], pseudocondylomas, vestibular microwarts and vulval squamous papillomatosis [6]. The last two suggest that HPV is implicated but the evidence now suggests that the known HPV types are not associated with these papillae [7–9]. Clinically, vestibular papillae are unlike the lesions induced by HPV as they are symmetrically arranged and each papilla has a solitary base. Histologically, problems arise if the pathologist is unaware that the tissue is the vestibule, which has heavily glycogenated epithelial cells that become vacuolated on processing and may resemble koilocytes. The problem is also compounded by the fact that koilocyte-like lesions can be found on vulval biopsies but these are not necessarily associated with HPV infection [10]. Currently, it is believed that this entity is a normal variant and the female equivalent of pearly penile papules.

Varicosities of the labial veins may occur unilaterally in association with limb varicosities, or appear in pregnancy. The other changes in pregnancy include a fall in the pH and increased pigmentation. At the menopause, vascularity decreases and the sebaceous glands become less active.

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Congenital and developmental abnormalities [1]

Ambiguous external genitalia

In some individuals, the external genitalia are not phenotypically characteristic of either male or female. An attempt at classification of these abnormalities is based on aetiology and clinical syndromes; there are three main groups [2,3]:

1 Female hermaphroditism
2 Male pseudohermaphroditism
3 Abnormal external genitalia in females may also be associated with abnormalities of the upper reproductive tract or urinary system [4].

Labial problems

There may be persistence of most caudal elements of the milk line in the labia majora, and there is great variation in the size and symmetry of normal labia minora. There may be very marked hypertrophy of the labia minora, some cases of which are examples of neurofibromatosis [5].

Labial adhesions may occur as an inherited familial trait [6] or in association with abnormal sexual differentiation. In general, most occur in the neonatal period and early infancy, and usually divide spontaneously by the time the child is 6 years old. No intervention is necessary unless there is a problem with urination. Some cases of labial adhesions result from lichen sclerosus.

Accessory labioscrotal folds are rare in women and are divided into two types, depending on whether or not there is an associated perineal lipoma [7].

The clitoris may be absent because of a failure of the genital tubercle to fuse, remain hypoplastic [8] or be enlarged because of congenital adrenal hyperplasia. The Lawrence–Seip syndrome, which is a congenital generalized lipodystrophy with the onset of insulin-resistant diabetes around the time of puberty, may also result in clitoral hypertrophy. There are clitoral tumours that may mimic genital sexual ambiguity (e.g. haemangioma, neurofibroma, lipoma [5,9–11]).

Virilization of the external genitalia may also occur with maternal ingestion of testosterone or synthetic progestogens in the first trimester, and if taken later in pregnancy there may be clitoral hypertrophy alone.

An imperforate hymen is usually discovered at puberty and is caused either by failure of the epithelial cells of the hymen to degenerate or by scarring after an inflammatory reaction in the hymen at birth.

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Trauma and artefact

Factitial dermatitis

There are various causes of vulval trauma, including accidental injury, obstetrical tears, damage at the time of surgery in a nearby site and coital and sexual mutilation, both cultural and self-induced [1–3].

Nymphohymenal tears induced by sexual intercourse are not uncommon and may mimic the symptoms of vulval vestibulodynia (see p. 68.82).

Sclerosing lipogranuloma [4] is a granulomatous response induced artefactually.

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Female genital mutilation [1]

Ritual and cultural female genital mutilation (FGM), although banned in most European countries, is still forced on millions of women worldwide [2,3], particularly in Africa and in some countries where there is a large Muslim population. However, it is not practised in certain Muslim countries, including Saudi Arabia [4]. Although it is unusual in Western society, many cases are now being seen in the UK because of the rise in immigration of women who have had previous FGM.

There are four types of operation performed, which vary according to the country and culture:

1 *Circumcision*: removal of the clitoris or the clitoral hood (Sunna circumcision).

2 *Excision*: removal of the clitoris and part or all of the labia minora.

3 *Infibulation*: removal of the clitoris, labia minora and partial removal of the labia majora. The introitus is then sutured leaving a tiny opening for urination and menstruation.

4 Another type includes a variety of different practices. It might involve cauterization, applying corrosive material, piercing or cutting of the clitoris, surrounding skin or vagina.

FGM may be carried out at any age from the neonate to the adolescent. It is often performed without an anaesthetic in unhygienic circumstances. There may be damage to the urethra and vagina at the time of the operation, and later there may be severe damage to the urethra, bladder or anal sphincter during delivery in those that have had infibulation. Many of the women who have had FGM

experience difficulties with sexual intercourse, urination and pregnancy and seek help in the clinics of their new country of residence, where unfortunately many of the health care professionals have not encountered their specific problem [5]. There are now a number of clinics being set up to deal specifically with these patients. The initial findings of a specialized clinic set up by a central London maternity unit found that many of the patients referred to them for problems in pregnancy were reluctant to volunteer the fact that they had been circumcised, and less than 10% refused to continue the tradition of FGM [6].

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Dermatological manifestations of sexual abuse of children

Childhood sexual abuse is not the usual domain of the dermatologist, but occasionally it can be encountered when a dermatological opinion is sought on a genital skin problem. Lichen sclerosus and other dermatoses can be mistaken for sexual abuse [1–4], but sometimes the sexual abuse may be the initiating or exacerbating factor of the dermatological condition [5]. The possibility of sexual abuse sometimes has to be considered in a child whose lichen sclerosus, despite appropriate treatment and compliance, has not responded as expected. Sexual abuse always has to be excluded in the child who presents with a sexually transmitted disease [6,7], but conditions such as molluscum contagiosum, bacterial vaginosis [8] and genital warts are not necessarily indicative of sexual activity, and can be acquired by non-sexual means [9,10]. Genital warts in children may carry both genital and skin-type viruses [11]. If gonorrhoea or semen is found the situation is clear-cut, with the exception of neonatal infection and gonococcal eye disease [12]. Herpes simplex of the prepubertal genitalia is relatively uncommon [13] and sexual transmission may be implicated in both HSV-1 and -2 infections [14]. In a review of six cases, sexual abuse was proved in four. In the two innocently acquired cases, HSV-1 infection of the oral cavity immediately preceded the genital signs [15].

There are strict protocols for the examination and assessment of a child who is suspected to be a victim of sexual abuse [16]. It is important that this evaluation is carried out by a skilled specialist, usually a paediatrician [17].

HIV has rarely been reported as being transmitted by sexual abuse of children [18,19], but direct transmission is possible, and sexual abuse may be a risk factor for HIV in later life [20–22].

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Inflammatory dermatoses

Eczema

Atopic eczema can involve the vulva but the eczematous dermatoses affecting the vulva in isolation are seborrhoeic

eczema, irritant contact dermatitis and allergic contact dermatitis.

Seborrhoeic eczema

This condition has both eczematous and psoriasiform features, sometimes making differentiation between it and psoriasis difficult. The inguinal and genitocrural folds, labia majora, mons pubis, perineal body and perianal skin are the usual sites involved. Vulval involvement may be associated with skin changes on the scalp and changes at other flexural sites. Histological examination is not always helpful, as there may be features of both eczema and psoriasis. There is moderate acanthosis with slight spongiosis and a mild dermal inflammatory infiltrate.

Irritant contact dermatitis

The barrier function of the vulval skin is impaired, as measured by transepidermal water loss [1], and there is an increased susceptibility to irritant contact eczema [2,3]. The problem may occur because of the dampness and maceration secondary to a heavy vaginal discharge, or increased contact with urine in the incontinent patient. Contact with irritant chemicals in topical agents, particularly cleansing agents, bubble baths, disinfectants, lubricants, perfumed products, deodorants and medicaments (e.g. 5-fluorouracil, podophyllotoxin and dequalinium), may all be responsible for an irritant dermatitis.

Allergic contact dermatitis

In spite of the frequent use of topical agents in the vulval area, allergic contact dermatitis is extremely rare in clinical practice. However, high incidences of contact dermatitis in vulval dermatoses have been reported [4,5]. An explanation for these unexpected high incidences may be that the patients in the studies had perianal skin involvement as well as vulval involvement, and allergic contact dermatitis to topical medicaments is more frequently encountered in perianal skin. One study has shown a higher incidence of positive patch tests in patients with anogenital dermatoses if both the genital and perianal areas are involved, compared with dermatoses affecting the genital skin alone [6].

There are reports of allergy to vaginal preparations and an intrauterine device [7–9], sanitary wear [10] and condoms [11]. Oestradiol may rarely cause a localized allergic contact dermatitis at a transdermal patch site, or generalized contact dermatitis with oral therapy [12].

Allergic contact urticaria

The two most common causes of contact urticaria in the vulvovaginal area are latex and semen [13], and there is usually a history of atopy [14]. Seminal fluid usually induces an urticarial immediate type I reaction and rarely produces a type IV contact allergy. There are reports of mixed sensitivities: one patient was allergic to semen and latex and another to her husband's semen and sweat [15,16]. However, semen itself may not be the responsible allergen, the problem being caused by a medication or other allergen carried in the seminal fluid [17–19]. Specific immunotherapy against semen has been successfully employed on occasion [20]. A fixed eruption to seminal fluid has been reported [21], and familial allergy to semen [22].

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Psoriasis

The pattern of psoriasis affecting the anogenital skin is

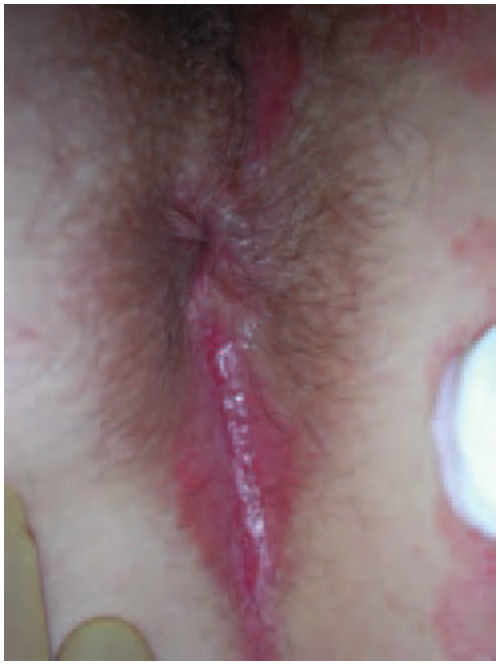

Fig. 68.21 Fissured psoriasis in the natal cleft.

most frequently flexural. The areas involved include the genitocrural folds, mons pubis, outer aspects of the labia majora, the perianal skin and the natal cleft (Fig. 68.21). The characteristic silvery scaling is absent in these occluded sites and the main clinical picture is intense erythema with a well-defined margin. Rarely, there may be some scarring associated with vulval psoriasis with loss of the labia minora and fusion of the clitoral hood.

The histology is not always typical, and there may be marked spongiosis and papillary oedema.

Reiter's disease (circinate ulcerative vulvitis)

Circinate balanitis is well recognized but the corresponding vulvitis is much rarer [1–4]. The lesions may be eroded, ulcerative or scaly. Histologically, the changes are of those seen in pustular psoriasis [5], with hyperkeratosis, parakeratosis, psoriasiform hyperplasia, an absent granular layer and collections of polymorphs in the epidermis.

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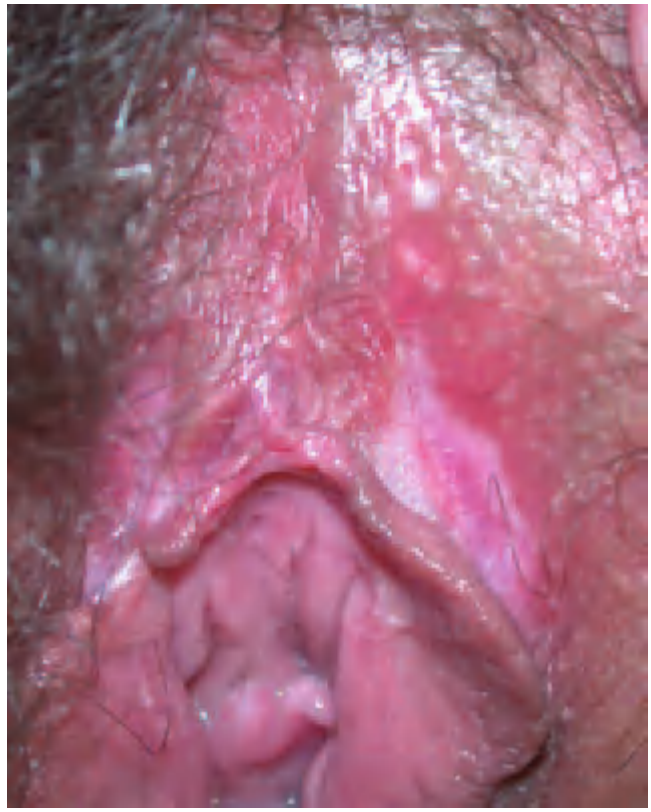

Fig. 68.22 White patches of lichen planus in the interlabial sulci.

Lichen planus [1–3]

Lichen planus (LP) can affect the vulva in isolation or at the same time as a generalized outbreak, when approximately 20% of patients will have genital lesions. The vulval lesions are similar to those seen at other sites and may be violaceous or erythematous papules, white (Fig. 68.22) or annular plaques, and erosions with or without a lacy white border. These lesions may all ulcerate. Wickham's striae occur infrequently (Fig. 68.23). If the vulva is affected in isolation, the disease is more often erosive, with most of the lesions around the labia minora, clitoris and clitoral hood. Confluent white and red patches will also be seen in this variant. A careful examination of the oral mucosae is helpful, as LP be may found on the tongue, palate, gingivae and lateral buccal mucosae.

The other clinical forms of vulval LP include the following.

1 *Pigmented flexural lichen planus* (Fig. 68.24). This variant of LP can affect the vulval area, particularly the mons pubis, the inguinal and genitocrural folds. The characteristic and striking finding is brown pigmented patches, some so deeply pigmented that they resemble melanocytic naevi. If the disease is seen in the early stages, a violaceous erythema is also observed. This form of LP is also found in the inframammary areas and axillae.

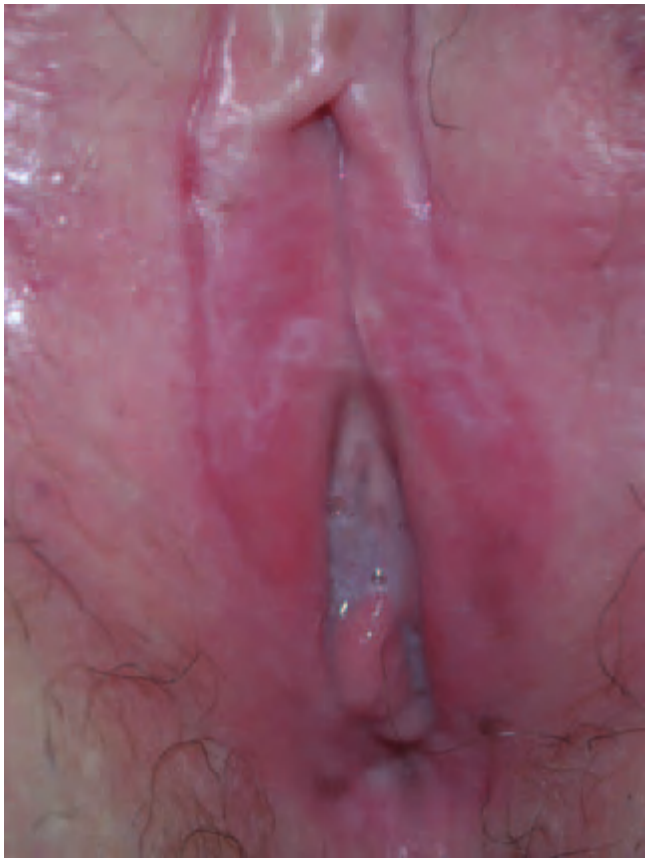

Fig. 68.23 Delicate white striae of lichen planus, with the labia minora flattening and fusing into the surrounding skin.

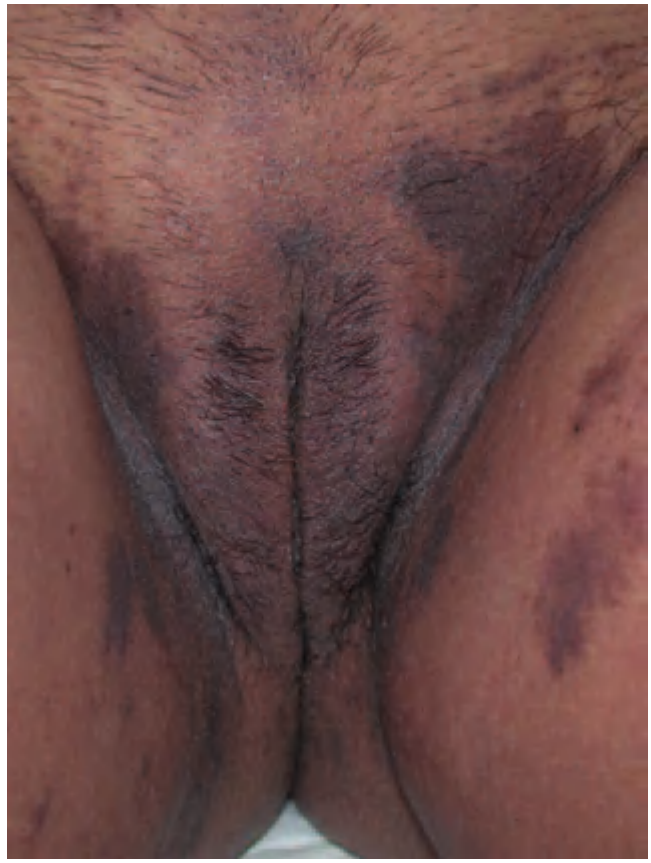

Fig. 68.24 Patches of pigmented flexural lichen planus.

2 *Vulvovaginal–gingival lichen planus* (VVG-LP) (syndrome of Hewitt and Pelisse; desquamative vaginitis). This distinctive erosive form of LP is clinically very similar to mucous membrane pemphigoid [4,5]. In the past, many cases labelled desquamative vaginitis were probably this entity [6,7]. VVG-LP principally affects the inner aspects of the labia minora, vestibule and vagina. The condition is chronic and painful, and there is an increase in vaginal discharge, dysuria, dyspareunia and postcoital bleeding. Clinically, the epithelia are eroded and often there is a distinctive fine white lacy border. There may be marked loss of architecture (Fig. 68.25). The anal margin may also be involved. The vaginal lesions are velvety red erosions or bright red, glazed erythema, which is friable and bleeds when touched. Vaginal synechiae and adhesions develop, leading in some cases to vaginal stenosis. The cervix may also be involved [5,8,9]. Oral LP lesions can occur at any site, but the characteristic finding is an intense erythema of the gingivae, which may be asymptomatic (Fig. 68.26). Unusual extragenital lesions have been described on the conjunctiva [10], lachrymal gland canal [11], oesophagus [12–15] and the auditory canal [16]. The manifestations of this syndrome do not necessarily all occur synchronously.
3 *Lichen planopilaris* has been described on the vulva [17].

Histopathology. On cornified epithelium there is hyperkeratosis, irregular acanthosis with a typical saw-tooth appearance of the rete pegs, an increased granular layer, and disruption of the basal layer with a closely apposed dermal band-like lymphocytic infiltrate. The acanthosis and hyperkeratosis are marked in the hypertrophic form and, because of the chronicity of this form, the characteristic band-like infiltrate is not obvious but will be found focally. Eosinophilic colloid bodies may be seen. Immunofluorescence studies reveal uneven staining of the basement membrane zone for fibrinogen and IgM, cytoid bodies and, on occasion, IgG or IgA.

Differential diagnosis. The main differential diagnosis is usually lichen sclerosus, but mucous membrane pemphigoid and morphoea could also be included. In some cases, the differentiation between lichen sclerosus (LS) and LP can be extremely difficult, even impossible, as the two diseases share so many features in common [18,19]. If a definite diagnosis cannot be made on a combination of clinical, histological and immunofluorescence findings and response to treatment, it is perhaps best to allocate the case as an overlap of the two disorders. Frequently, there are cases of LP misdiagnosed as Zoon's vulvitis.

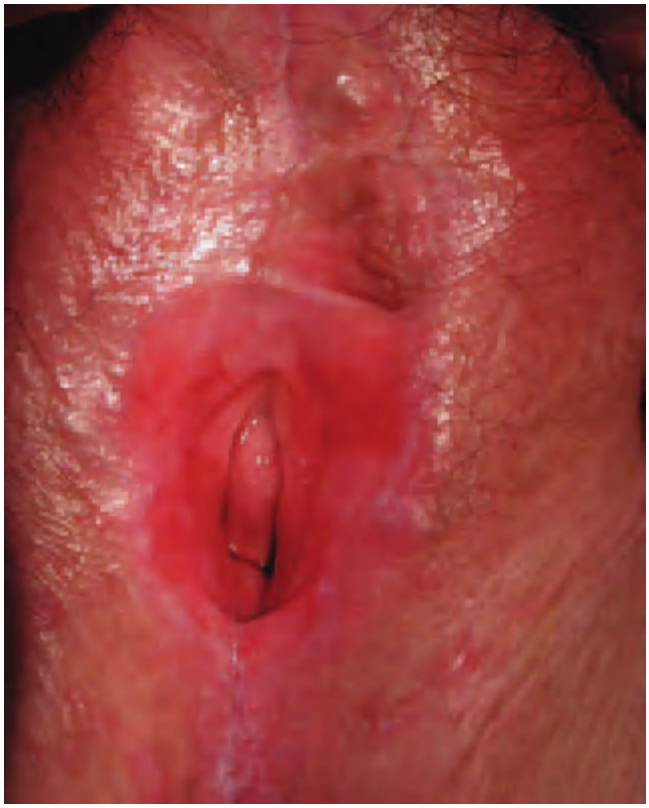

Fig. 68.25 Lichen planus: vulval aspect showing glazed erythema and distortion of the architecture, with a remnant of the left labium minus and buried clitoris above it.

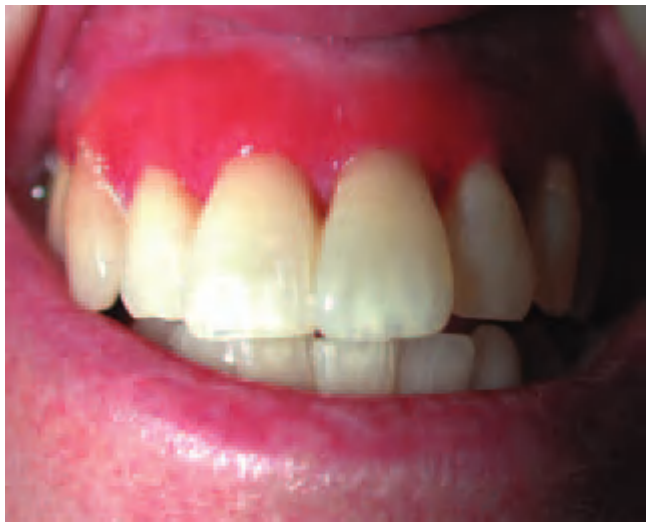

Fig. 68.26 Lichen planus. Intense glazed erythema of gingiva.

Treatment. First-line treatment is with potent topical steroids. If the vagina is involved, a topical steroid can be introduced with a vaginal applicator, or steroid foams or suppositories that are available for inflammatory bowel conditions can be used [20,21]. Topical retinoids are useful for hyperkeratotic and hypertrophic LP, and recently topical tacrolimus has been used [22]. Other treatments tried with variable success include oral steroids, oral and topical retinoids, methotrexate [23], ciclosporin [24] and azathioprine.

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Zoon's vulvitis

It is likely that plasma cell vulvitis (PCV; vulvitis

circumscripta plasmacellularis) is not a single disease entity but represents a reaction pattern to another inflammatory condition. A plasma cell-rich infiltrate in a vestibular biopsy may be a misleading finding, because plasma cells are commonly found in inflammatory conditions of the vestibule as it is a mucosal epithelium.

Many of the cases are examples of unrecognized dermatoses such as LP, and in others the persistent change may represent a chronic post-inflammatory phenomenon.

The first descriptions of the female equivalent of ZB were by Garnier and Zoon [1–3]. The lesions described in these reports were erythematous patches with a glazed appearance, with the histological findings of a plasma cell-rich dermal infiltrate and no cytological atypia. The disorder followed a chronic but benign course. The disorder appears to be less common in women, and in one series of 20 cases there was only one female [4].

Most of the reports of this condition in women describe the lesions in the vestibule and labia minora, whereas the typical site in men is the glans and prepuce. The glans clitoris is rarely, if ever, affected.

Histology. The criteria needed to make the diagnosis have varied in the literature, and there is some doubt whether PCV is a distinct clinicopathological entity, as many of the reports of vestibular Zoon's are probably LP [5].

The essential features are epidermal thinning, absent horny and granular layers and distinctive lozenge-shaped keratinocytes with widened intercellular spaces; in the dermis there is a dense inflammatory infiltrate composed largely of plasma cells, with dilated blood vessels and usually much haemosiderin. Russell bodies and dermal–epidermal splitting have also been described [6].

Treatment. Treatment depends on the underlying inflammatory dermatosis responsible for this histological change. In the majority of cases this is LP, and a potent topical steroid should be tried. If the inflammatory phase of disease has resolved and the patient is complaining of a sensation of rawness or burning, then topical 5% lidocaine can be effective. Finally, a barrier ointment such as Vaseline petroleum jelly may offer some relief if there is an irritant component to the problem.

Chronic vulval purpura

It is not uncommon to find patients with purpuric patches, often at the vestibule, in which haemosiderin and plasma cells are found without any specific epidermal change, and the term chronic vulval purpura may be a more accurate description [7]. An association with lichen aureus has been suggested, as pressure factors are thought to be relevant in the extravasation of blood [8].

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Lichen sclerosus [1–6]

Lichen sclerosus (LS) was first described as a variant of LP with a tendency to affect the genital area. The old terms leukoplakia, leukoplakic vulvitis and kraurosis vulvae were clearly applied to examples of LS or LP, and the use of these terms led to confusion. The term vulval dystrophy was introduced in the 1960s in an attempt to overcome the problems in distinguishing and classifying vulval dermatoses characterized by pallor and scarring [7]. This terminology unfortunately proved unsuccessful in its objectives, as its use discouraged attempts to differentiate between disorders such as LS, LP and mucous membrane pemphigoid. In 1983, the Terminology Committee of the International Society for the Study of Vulvovaginal Dermatoses recommended a new classification with discontinuation of the term dystrophy [8]. The term vulval squamous cell hyperplasia was introduced with this classification (see p. 68.49).

Aetiology and pathogenesis. The aetiology is still unknown but there is mounting evidence that LS is a genetically determined autoimmune disorder. A positive family history is recognized [9] and the disorder has been described in twins, both identical [10] and non-identical [11]. An association of LS in females with other autoimmune disease has been noted [12–14]. Attempts to establish a specific HLA linkage in patients with LS were initially inconclusive [15] but a later study has shown an increased incidence of DQ7 [16]. Similar findings have been reported in LS in girls [17].

The role of *Borrelia burgdorferi* as an aetiological trigger is controversial. A study in the UK showed no evidence histologically of spirochaetes but did show 'cocci' with a Fite stain, which later proved to be mast cells when stained with toluidine blue [18].

Clinical features. LS can affect females of any age, but the majority of patients are either prepubertal or menopausal. There is still uncertainty whether LS in prepubertal girls

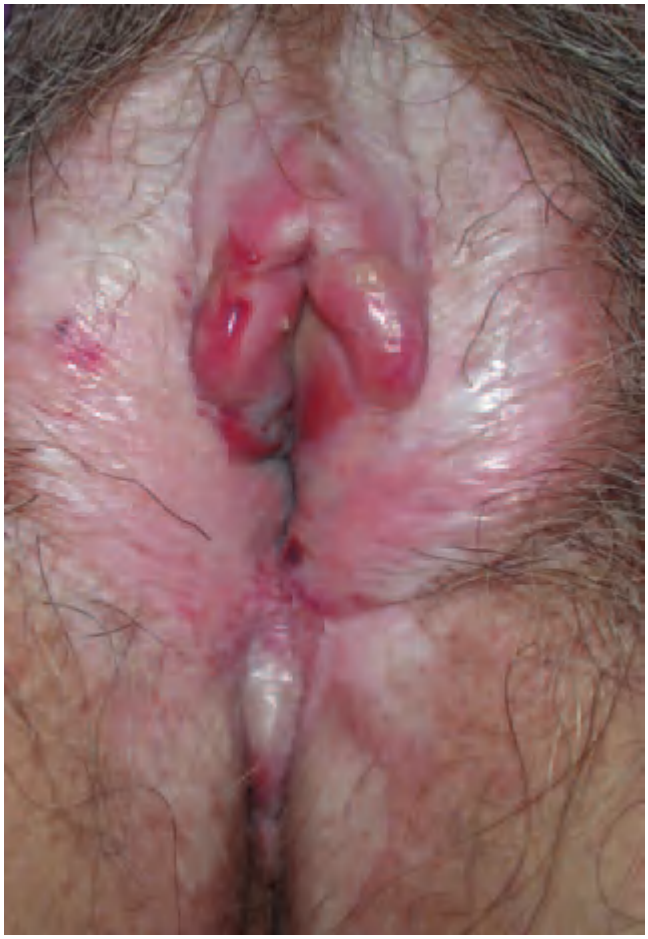

Fig. 68.27 Oedema and ecchymosis of lichen sclerosus.

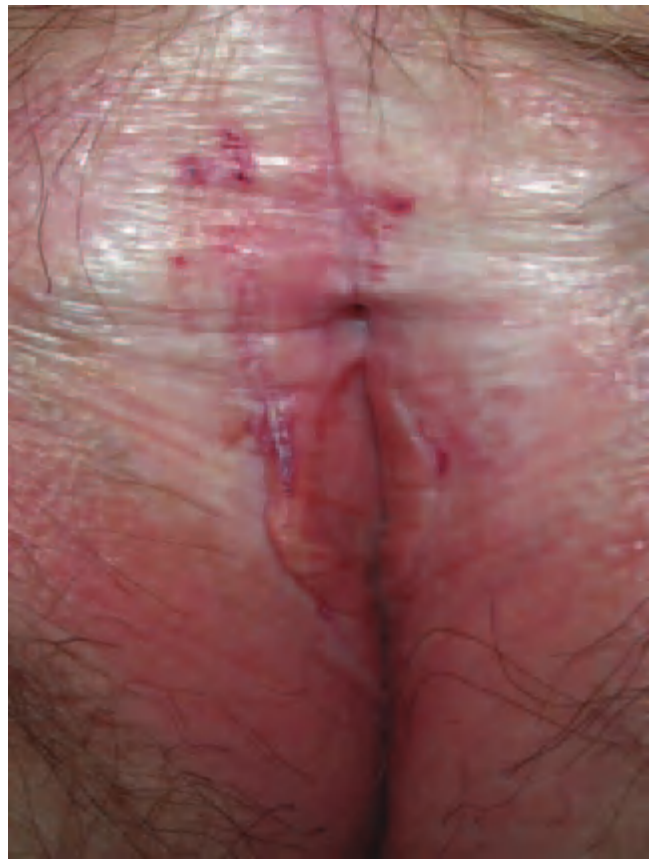

Fig. 68.28 Lichen sclerosus. Pallor and atrophy of the vulval skin with loss of the labia minora and burying of the clitoris.

remits spontaneously at puberty. The presenting symptom is usually itching, which is often severe and distressing.

The classical lesions seen on the extragenital skin are ivory white papules and plaques with follicular delling. Anogenital disease tends to be characterized by flatter lesions of atrophic whitened epithelium, which may become confluent, extending around the vulval and perianal skin in a figure-of-eight configuration. There may also be oedema, ecchymosis, bullae, erosions and ulceration (Fig. 68.27). The sites most commonly affected are the genito-crural folds, the inner aspects of the labia majora, labia minora, clitoris and clitoral hood. Vestibular involvement is rare and vaginal lesions do not occur, as LS seems to spare non-cornified stratified squamous epithelia (mucosal epithelium). Perianal lesions occur in approximately 30% of female patients, in contrast with men who do not seem to develop perianal involvement. Extragenital lesions occur in 10% of women with vulval disease. The extragenital areas may be truncal, at sites of pressure, upper back, wrists, buttocks and thighs. The Koebner phenomenon has also been reported at sites of radiotherapy [19], scar tissue [20], vaccination [21] and congenital haemangioma [22]. Facial [23], scalp [24] and nail involvement [25,26] have been recorded.

Lesions of LS in the oral cavity are extremely rare. Many of the reports of oral involvement in the literature have often not been confirmed histologically [27] and may have been examples of LP. It is not uncommon for patients with vulval LS to have coexistent oral LP [28].

The author (SMN) has seen two cases of oral LS, confirmed histologically, and both were on the tongue. This is one of the few sites in the mouth that has cornified stratified squamous epithelium.

LS is a scarring dermatosis and the changes that can occur on the vulva include loss of the labia minora, and sealing over of the clitoral hood, burying the clitoris (Fig. 68.28). Introital narrowing resulting from anterior and posterior labial fusion sometimes results in a tiny opening into the vestibule. Milia may occur [29].

Histology. The classic histology is a thinned epidermis with flattening of the rete pegs. The underlying dermis is hyalinized and there are often extravasated red cells. Below the hyalinized area is a band-like zone of chronic

inflammatory cells. There is an absence of elastic fibres in the upper dermis. There have been attempts to grade the histological appearances [30] but there is probably little correlation between the timing of a lesion and its histological appearance [31].

In some cases the epidermis is thickened, and this is LS with squamous cell hyperplasia. It is found in approximately 30% of cases of LS in association with vulval SCC [32].

There are abnormalities of the basement membrane, but it is uncertain whether these are a primary or secondary event [33]. Immunofluorescence studies are usually negative or demonstrate non-specific fibrin deposition at the dermal–epidermal junction. There is also an alteration of the elastin and fibrillin in the affected dermis [34].

Differential diagnosis. Vitiligo, mucous membrane pemphigoid, LP and morphoea may present with a similar clinical appearance. There can be clinical and histological overlap between morphoea, LP and LS, and they may represent a spectrum of disease rather than three distinct conditions [35,36].

Lichen sclerosus and vulval malignancy

There is undoubtedly an association between vulval SCC and LS that was probably underestimated in the past (Fig. 68.29) [37]. The incidence of SCC developing on LS in clinical practice is of the order of 4% or less [1]. However, in retrospective reviews of pathological specimens of vulval carcinoma, histological evidence of LS is found in approximately half of the cases [37–40]. These series included patients presenting with SCC as well as those on long-term follow-up. A longitudinal cohort study of 211 patients showed that the number of invasive SCCs significantly exceeded that in an age-matched group [41]. It is not known whether good control of LS reduces this risk.

There appears to be a bimodal pattern for vulval SCC. In younger women the tumour is associated as a rule with oncogenic types of HPV and intraepithelial neoplasia, and in the older woman with a chronic dermatosis without evidence of HPV infection [42–44].

The histological patterns associated with SCC arising on LS include epithelial hyperplasia and differentiated intraepithelial neoplasia (dysplastic changes that are confined to the basal layers) [45].

LS has been reported in association with verrucous carcinoma [46,47], basal cell carcinoma [48] and melanoma [49]. However, malignant melanoma is known to be difficult to diagnose in the presence of LS [50], and the validity of the case report of an association between malignant melanoma and LS was questioned [51]. However, the original authors upheld their view.

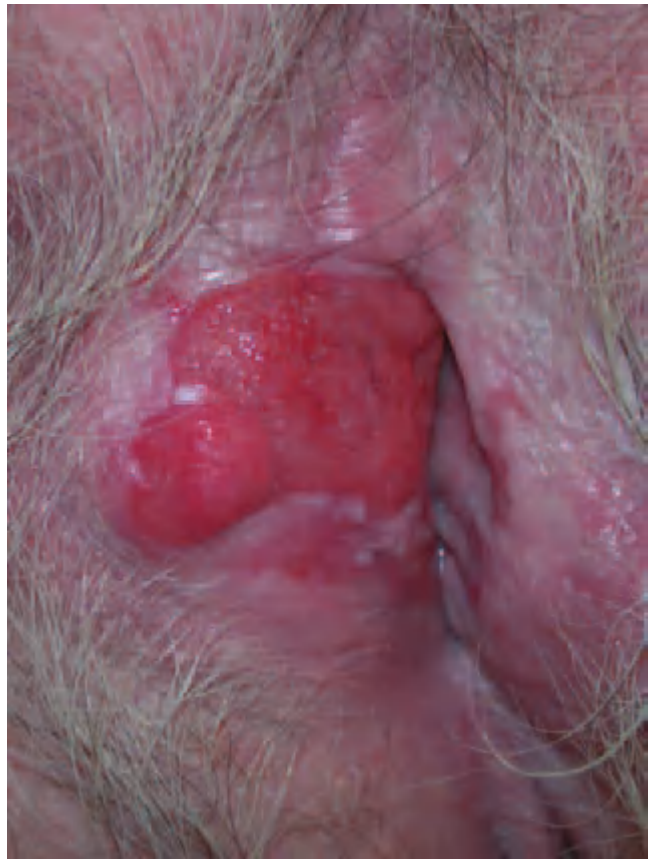

Fig. 68.29 Squamous cell carcinoma arising on a background of lichen sclerosus.

Treatment [52,53]. The current and recommended treatment for uncomplicated LS is the potent topical corticosteroid, clobetasol propionate. There are no randomized controlled trials providing evidence for any particular corticosteroid or treatment regimen being more effective than any other. The regimen recommended by the author (SMN) for a newly diagnosed case is initially clobetasol propionate once nightly for 4 weeks, then alternate nights for 4 weeks, and twice a week for a further month. A 30-g tube of clobetasol propionate should last 12 weeks, and the patient is then reviewed. The clobetasol propionate is then used as and when required to control itching. Most patients seem to require 30–60 g annually. A proportion of patients go into complete remission and do not require further treatment. Others will continue to have flares and remissions and they are advised to use clobetasol propionate as required. A soap substitute is also recommended and an information sheet on LS, including instructions for the use of the topical steroid, is provided.

Topical testosterone currently has no role in the management of LS. It is expensive and is not as effective as clobetasol propionate [54].

Surgical excision is not necessary in the management of most cases of LS and it should be used exclusively for the management of functional problems caused by post-

inflammatory scarring [55,56], premalignant lesions and malignancy.

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Crohn's disease

Anogenital lesions occur in approximately 30% of patients with intestinal Crohn's disease, either as a direct extension of active intestinal disease or as metastatic disease. Vulval disease may present many years before intestinal involvement, and in some cases there is vulval oedema only, with no evidence of granulomatous inflammation [1,2]. The more usual presentation is ulceration, abscess, sinus and fistula formation, with a granulomatous histology. There may be deep linear fissures (knife cut sign) along the skin creases.

A separate form of vulval granuloma akin to the orofacial lesions seen in Melkersson–Rosenthal syndrome has been described [3,4].

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Ulcerative and bullous disorders

Any of the blistering disorders of the skin can occur on the vulva and vagina, either as part of the generalized disease or in isolation. Diagnosis can be more difficult in the latter case.

There are many causes of vulval ulceration and some features are important in narrowing down the differential diagnosis. It is helpful to divide them into acute and chronic types.

Acute genital ulceration

Benign aphthae

Many eponymous names have been assigned to acute vulval ulcers and several of these disorders are probably examples of benign aphthae. Reiter's syndrome may be associated with an ulcerative vulvitis [1].

Benign aphthae of the vulva may or may not occur with concomitant oral lesions. The age of onset is in childhood, about the age of 6 years, and there may be a family history. The lesions are usually multiple and small, and less commonly solitary or few and larger—referred to as giant aphthae. Herpetic infection should be excluded. There are often premenstrual exacerbations once the menarche is reached. The aetiology remains unknown.

The lesions are superficial and painful, with a yellow base surrounded by a red areola. They are distributed most frequently on the labia minora, and heal quickly (Fig. 68.30).

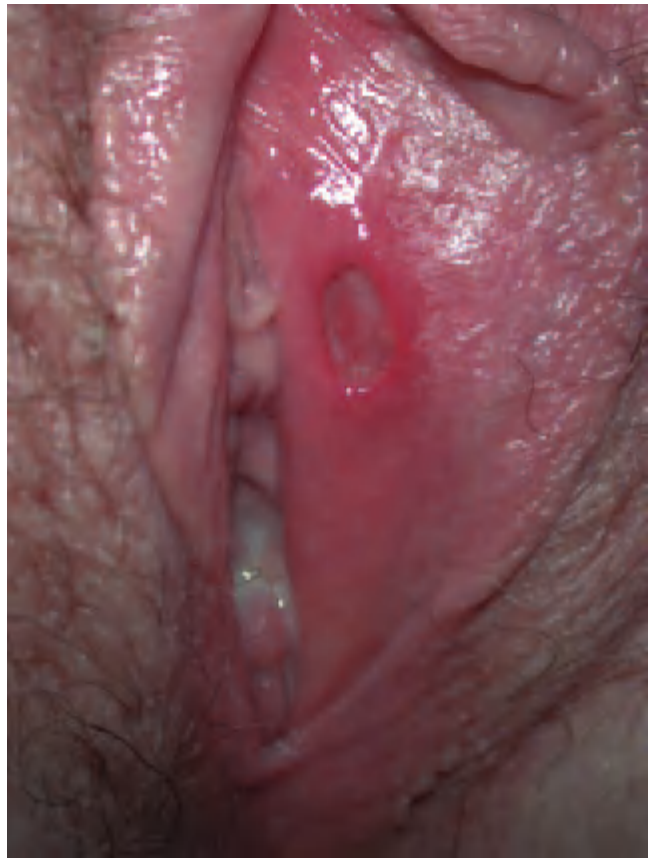

Fig. 68.30 Solitary benign aphthous ulcer of the left labium minus.

Sutton's ulcer (periadenitis mucosa necrotica recurrens) was originally reported in the mouth [2] but vulval lesions have also been given this label. The ulcer is characterized as being solitary, painful and recurring [2]. This type of ulceration, in the light of today's knowledge, would now be regarded as an example of benign aphthosis or a manifestation of Behçet's syndrome. Lipschutz's ulcer, described 2 years after Sutton's report, encompassed three types of ulcer (ulcus vulvae acutum), two of which today would be assigned to either aphthous ulceration or Behçet's syndrome. Only one is still regarded as being a separate entity [3]. This remaining form of ulceration is sometimes associated with a systemic infection such as infectious mononucleosis [4,5], typhoid or paratyphoid fever. Epstein–Barr virus (EBV) has been isolated from the ulcers [6], and there is one case of a mistaken diagnosis of lymphoma [7]. The Lipschutz-type ulcer usually affects adolescent girls and has a rapid onset. The ulcer may be very deep and large, and has a surrounding red areola and a thick adherent slough. It is most often solitary on one side of the vulva, usually the inner aspect of the labium minus, but lesions may occur bilaterally. Healing is spontaneous, but may take several weeks and leaves some scarring.

Treatment includes analgesics, potassium permanganate soaks and the application of a topical steroid with or without a topical tetracycline. In very severe ulceration, a short course of oral steroids may be required.

Erythema multiforme

The pattern of recurrent acral erythema multiforme is rarely associated with genital lesions, whereas oral lesions are nearly always present. The vulva is affected in Stevens–Johnson syndrome, often with erosions.

Bullous fixed drug eruptions

These are less common (or less commonly recognized) on the vulva than on the penis, where the commonly implicated medications include paracetemol and tetracycline. It is now rare to see cases involving phenolphthalein, sulphonamides and barbiturates.

Chronic genital ulceration

Any chronic ulcer of the genital mucosa must be considered malignant until proved otherwise. The differential diagnosis of chronic ulceration includes the diseases listed below, which are discussed fully in the relevant sections of this and other chapters.

1 *Genetic.* Epidermolysis bullosa, Hailey–Hailey disease and Darier's disease may all be responsible for chronic recurring ulceration. Exacerbations may follow friction, infection, irritants and herpes simplex infections.

2 *External trauma.* Nymphohymenal tears, dermatitis artefacta and radiation damage. Nymphohymenal tears may occur with sexual intercourse but most heal spontaneously. They tend to occur around the nymphohymenal sulcus, usually in the inferior segment at the 5 and 7 o'clock positions (Fig. 68.31). Those that do not heal can be excised radially.

3 *Malignancy.* The two most common malignant ulcers of the vulva are squamous cell carcinoma and basal cell carcinoma. Melanoma may also present as an amelanotic ulcerating nodule. Langerhans' cell histiocytosis may present with vulval and vaginal ulceration.

4 *Infection.* Chronic infective ulcers occur in tuberculosis, actinomycosis and other deep mycoses. The late stages of lymphogranuloma venereum cause ulceration and scarring.

5 *Inflammatory.* LS, LP and lupus erythematosus can all cause chronic ulceration. Pyoderma gangrenosum may be mistaken for malignancy on the vulva [8]. Hidradenitis suppurativa and Crohn's disease can sometimes be difficult to distinguish, particularly if they occur together. Pilonidal sinuses have been recorded on the vulva and clitoris [9].

Several of the autoimmune bullous diseases affect the vulva. Juvenile pemphigoid, mucous membrane pemphigoid (Fig. 68.32), pemphigus vulgaris and vegetans may all present with vulval and vaginal ulceration.

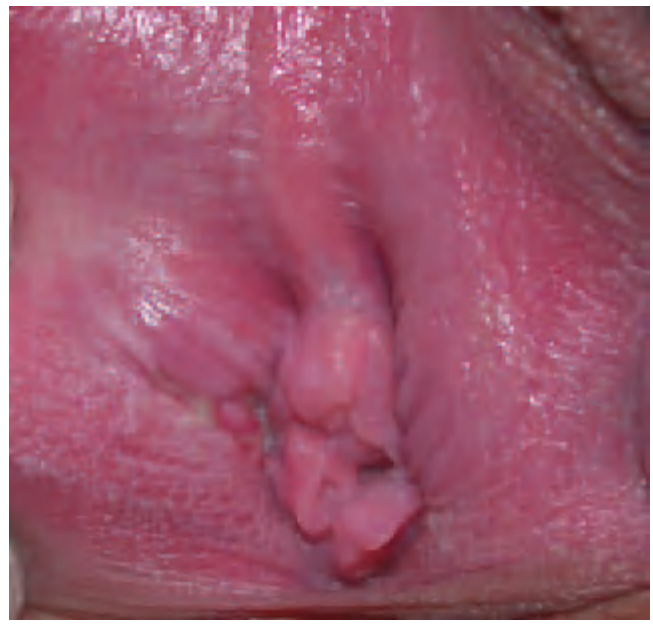

Fig. 68.31 Tear of the right inferior aspect of the nymphohymenal sulcus.

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Non-sexually transmitted infections

Bacterial infections

Staphylococci

Staphylococcus aureus is usually the causative agent in infective folliculitis, boils and abscesses of the vulva. It is often associated with an underlying problem (e.g.

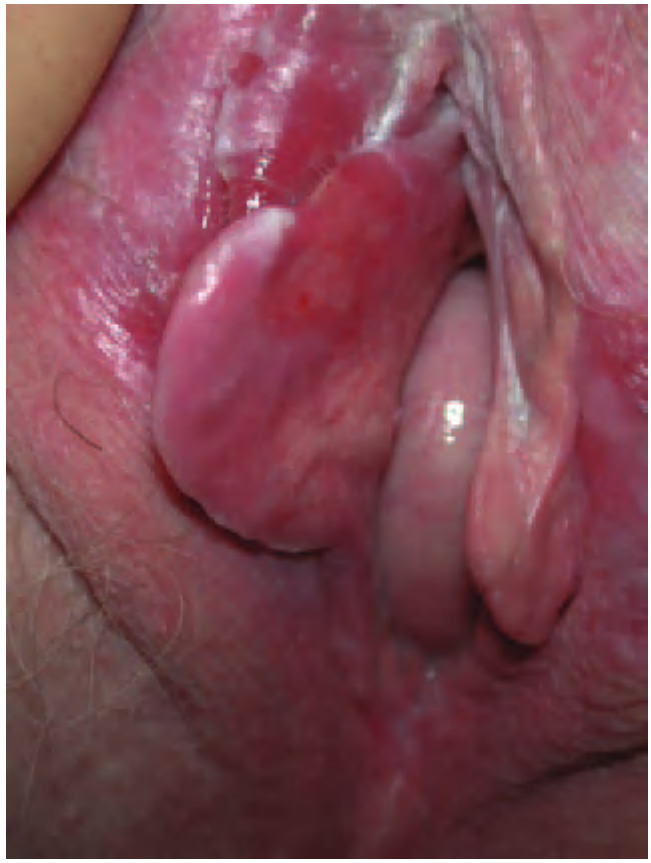

Fig. 68.32 Erosions in vulval mucous membrane pemphigoid.

diabetes, immunosuppression). Pseudofolliculitis is a sterile folliculitis that may follow shaving and is caused by the newly regrowing hairs inducing an inflammatory reaction. It is a foreign body reaction and results in changes from mild inflammation to the formation of abscesses and sinuses. A staphylococcal folliculitis on the buttocks may occur secondary to the pruritus induced by intestinal infestation with pin worm.

An exotoxin associated with phage group 1 staphylococci has been implicated in production of the collapse, fever and morbilliform rash seen in the toxic shock syndrome. Although the syndrome occurs most commonly in menstruating women who use tampons, the association is not exclusive.

Histology. The impetiginous lesion shows subcorneal pustules filled with neutrophils and some spongiosis, with a moderate inflammatory response in the papillary dermis.

The acute folliculitis may be superficial with a subcorneal pustule present at the follicular opening, or deep and associated with a perifollicular abscess, and destruction of the follicle wall and sebaceous gland. Chronic deep intrafollicular abscesses may have the additional features of fibrosis and foreign body giant cells.

Streptococcal infections

Beta-haemolytic Lancefield group A bacteria may be the cause of vulval cellulitis. The erythema and oedema may be extreme, and vesicles and bullae develop. There are usually associated systemic signs. The infection arises at sites of trauma where there is a wound and it is commonly seen following a vulvectomy with lymphadenectomy. If there is residual lymphoedema then further attacks of cellulitis are more common. Streptococcal dermatitis usually affects the anogenital area of children [1].

Synergistic bacterial gangrene

This severe and rapidly extending disease is caused by the synergistic effect of a microaerophilic streptococcus and *Staphylococcus aureus* (see Chapter 27).

Hidradenitis suppurativa

This is dealt with fully in Chapter 27, but mention is made here as staphylococcal and streptococcal infection have a secondary role. The primary problem is an abnormality of the follicular epithelium of the apocrine gland ducts, which starts with a spongiform infundibular folliculitis [2]. *Streptococcus milleri* is often found as a secondary pathogen [3].

Histology. This is characterized by distension and inflammation of apocrine ducts, with polymorphs in and around the ducts. The apocrine glands may become necrotic, with an infiltrate of lymphocytes, plasma cells and macrophages. Sinuses are lined by keratinized epithelium. Fibrosis and a foreign body reaction with granulomatous changes are common. Pseudoepitheliomatous hyperplasia may be seen, and at least nine cases of SCC have been reported—two of these were in females with buttock lesions [4].

Treatment is with long-term antibiotics, and in some cases oral isotretinoin may be helpful. The important differential diagnosis is Crohn's disease, but hidradenitis suppurativa and Crohn's disease may coexist [5,6].

Gram-negative bacilli

Pseudomonas aeruginosa is a common problem in patients with bladder problems but it is not a cause of vulvovaginitis. There has been a report of blue staining of napkins in infants with this infection [7].

Despite its name, *Trichomycosis* is caused by species of corynebacteria, which lead to red, yellow or black nodules on the shafts of the axillary and pubic hairs (see Chapter 27). Histological examination shows that these nodules consist of concretions of bacteria. The hair shafts may be damaged [8].

Diphtheria, caused by *Corynebacterium diphtheriae*, is rare in developed countries. Vulval infection takes the form of ulcers, often with a greyish membrane. It has been described in children [9,10] and in adults [11,12].

Mycobacterial infections

Vulval tuberculosis, caused by *Mycobacterium tuberculosis*, is uncommon in the UK. It may occur by means of haematogenous spread from foci outside the genital tract, by distal spread from the upper genital tract, or as a primary exogenous infection contracted from sputum or sexual intercourse. Vulval tuberculosis has been reported in a renal transplant patient [13], and three cases were described in a series of 26 patients with genital tuberculosis [14]. Genitourinary tuberculous infection is more common in HIV-positive subjects. In a primary infection the initial lesion may be inconspicuous, the main feature being a caseating lymphadenopathy. In other cases the lesions are masses or nodules that may ulcerate and lead to lymphoedema [15]. Bartholin's gland may be involved [16].

Leprosy (see Chapter 29)

The female genital tract may be involved in infection by *Mycobacterium leprae* [17], but vulval lesions are rare [18]. Pubic hair may be lost [19].

Higher bacterial infection

Higher bacteria is the name assigned to those bacteria that, like filamentous fungi, are capable of forming true branches. They include the genera *Streptomyces*, *Actinomyces* and *Nocardia*.

Actinomycosis

The Gram-positive acid-fast organisms responsible for actinomycosis are predominantly *Actinomyces israelii* and *Actinomyces gerencseriae*. They may colonize intrauterine devices and are usually asymptomatic, but invasion of the genital tract can occur [20,21]. Genital infection usually arises from bowel disease [22]. Lesions of the vulva alone have been reported [23].

Mycoplasmas

Mycoplasma hominis and *Ureaplasma urealyticum* are found in the vagina and rarely cause disease. There are rare reports of *M. hominis* being isolated from cases of Bartholin's abscess [24,25].

Abscesses of Bartholin's gland may be caused by pyococcal organisms, gonococcus and *Chlamydia trachomatis* [26]. In one study, only 21 of 109 cases were caused by staphylococci, whereas 50 were caused by *Escherichia coli* and 46 by *Streptococcus faecalis* [27]. The abscess results from distal blockage of the duct. The patient presents with fever, malaise and a tender swelling arising posterior to the origin of the labium minus. Episodes of bartholinitis may be mild and recurrent until fibrosis supervenes.

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Fungal infections

Candidal vulvovaginitis

Candida and *Torulopsis* are both yeasts that can infect the vulva and vagina. *Torulopsis* accounts for very few

infections, whereas *Candida albicans* is the most frequently isolated.

Candida albicans is dimorphic, with both yeast and mycelial forms. It is a non-pathogenic commensal in the intestinal tract in 30% of the normal population. Infection in women is usually a vulvovaginitis. Changes in host factors are probably responsible for transition to pathogenicity, and are generally not directly associated with sexual contact. Factors related to cell-mediated immunity are doubtless important, but as yet are ill-understood. Pregnancy, diabetes, possibly oral antibiotics, high-dose oestrogen oral contraceptive pills and immunosuppression may all be predisposing factors. The primary infection arises in the vagina, causing inflammation and a heavy white curdy discharge, which then leads to a secondary vulvitis with well-demarcated sheets of erythema on the outer aspects of the vulva, sometimes extending on occasions into the genitocrural folds and perianally. There may be a scaly or vesiculopustular edge. Beyond this edge lie grouped or isolated superficial small pustules, which rupture rapidly, leaving a slightly scaly periphery. In all cases of candidal vulvovaginitis, but particularly in the middle-aged patient, late-onset diabetes should be considered, and appropriate tests carried out.

Diagnosis is confirmed by direct microscopy and culture.

Treatment of vulvovaginal candidiasis requires vaginal pessaries or creams and/or oral imidazoles.

In some cases of vulval eczema and psoriasis, *Candida* is cultured from skin swabs, but the candidal overgrowth is a secondary problem arising on a background of an inflamed epithelium. Treating the dermatosis alone with a topical steroid will usually resolve the problem, without the addition of anticandidal agents.

Dermatophyte fungi

Dermatophyte infections of the vulval skin are uncommon in cooler climates. The sites affected are usually the inguinal folds and perianal area. The causative agents are *Trichophyton rubrum* or *Epidermophyton floccosum*. The vulval epithelium in the adult seems to be relatively immune to dermatophyte infections. The lesions are erythematous and scaly, with a spreading raised circinate edge. Folliculitis is also seen, particularly in the perianal area. Tinea incognito may also occur perianally following the injudicious use of a topical steroid in the presence of an unrecognized dermatophyte infection. The diagnosis is usually made by direct microscopy and culture of skin scrapings, and treatment is usually oral terbinafine or griseofulvin because the skin is hair-bearing.

Miscellaneous

Pityriasis versicolor classically occurs on the trunk, but in severe widespread infection there may be vulval involvement [1,2].

The black and white forms of piedra (trichosporosis) are caused by *Piedraia hortai* and *Trichosporon beigelii*, respectively, the latter acting synergistically with a corynebacterium. The hair-bearing parts of the vulva can be affected with black and white nodules along the hair shafts [3]. The diagnosis is made by microscopy and culture.

Vulval phycomycosis has been described [4]. Subcutaneous infections occur in children and young adults. Histologically, the epidermis is unremarkable but subcutaneously there are deep granulomatous masses containing hyphae.

There is one case report of chromomycosis (chromoblastomycosis) affecting the vulva [5].

Cryptococcus neoformans can induce painless ulceration of the vulva in the immunosuppressed patient [6].

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Infections with protozoa

Infection with *Trichomonas vaginalis* causes a frothy malodorous greyish green watery discharge, and a bright red vaginal mucosa studded with petechiae. The vaginal discharge may cause a secondary vulvitis, with erythema and swelling of the vestibule and labia minora. Colonization of the urethra and paraurethral glands often occurs. The diagnosis is made by microscopic examination of wet preparations and culture.

Treatment is with metronidazole 400 mg twice daily for 5 days or 2 g in a single dose.

The flagellate protozoan *Leishmania tropica* causes cutaneous, mucocutaneous and visceral forms of leishmaniasis. The vulva is mainly affected by the cutaneous form, which is endemic in areas of the eastern Mediterranean, Asia Minor and India; and to a lesser extent by the mucocutaneous form, found in Central and South America. An example of sexual transmission from post-kala-azar dermal leishmaniasis has been reported [1]. Transmission of infection is usually by sandflies. The lesions are nodular or ulcerative.

Entamoeba histolytica is found worldwide and intestinal amoebiasis may be transmitted from the bowel to other areas including the genital tract, although such involve-

ment is rare [2]. It appears as warty or ulcerative masses of the vulva, perineum and cervix. Live amoebae may be recovered from scrapings, or the organism seen as a small eosinophilic body in an inflammatory histological reaction.

Vulval schistosomiasis is usually caused by *Schistosoma haematobium*. The lesions are chronic, scarring and granulomatous, and may ulcerate and calcify [3–5].

Histologically, there is inflammation surrounding the organisms and their remains, with granuloma formation and many eosinophils. Ova may be found in the vagina, urine and faeces.

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Viruses

Three groups of viruses are important causes of infection in the genital area: the poxviruses, papillomaviruses and herpesviruses. Other viruses seldom give rise to distinctive clinical pictures, although vulval lesions may occur as part of a generalized viral infection.

Genital HPV infection and herpes simplex are discussed later in the section on sexually transmitted infections (see p. 68.70).

The most common poxvirus is mollusum contagiosum virus, two types of which have been identified. There is no relationship between virus type and anatomical distribution of lesions [1]. Vulval lesions in childhood are common and usually acquired innocently, but they are more likely to be acquired sexually in adults. Lesions are often found on the mons pubis and labia majora, and if inflamed they may mimic folliculitis. The clinical diagnosis is straightforward when there are multiple pearly lesions with an umbilicated centre, but solitary large lesions can cause diagnostic problems. It is the solitary giant lesion that may miss immediate diagnosis until it is biopsied. Lesions of molluscum contagiosum can be profuse and large in immunosuppressed women, especially in those with AIDS. The condition is more fully described in Chapter 26.

Other poxvirus infections of the vulva are rare, but there are isolated reports of orf [2] and cowpox [3].

Herpes simplex (see below).

Varicella-zoster virus. This may also affect the vulva if the third sacral dermatome is involved. It may be accompanied by bowel and bladder dysfunction [4].

Epstein–Barr virus. This has been found rarely in genital ulcers at the time of infectious mononucleosis [5–7]. EBV may also be shed from the cervix [8] but there is no link with vulval malignancy [9].

Cytomegalovirus (CMV). CMV inclusions were seen in a biopsy and a positive culture for CMV was obtained in an infant with congenital HIV disease who presented with pustular and ulcerative lesions on the perineum [10].

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Malakoplakia of the vulva [1–4]

Malakoplakia (meaning 'soft plaque') is a granulomatous response to infection. It is not usually caused by one specific agent but the organisms involved include *Escherichia coli*, *Pseudomonas* and *Staphylococcus aureus*. Malakoplakia most often affects the urinary or gastrointestinal tract but cutaneous lesions may occur on the vagina, vulva and perineum. Involvement of Bartholin's gland has been described [5]. The lesions include persistent plaques, ulcers, nodules and sinuses. There is often underlying immunosuppression, the aetiology of which may include malignancy, dermatomyositis [6], lupus erythematosus, rheumatoid arthritis and organ transplantation [7].

Histopathology. There are confluent sheets of histiocytes with eosinophilic granular cytoplasm and small eccentric nuclei. Round, sometimes laminated structures are found with these cells and are known as Michaelis–Gutmann bodies. The histiocytic infiltrate may be mixed with neutrophils, lymphocytes and plasma cells, with associated granulation tissue. Electron microscopy of malakoplakia shows that the histiocytes contain numerous

phagolysosomes within which there may be occasional intact and partly digested bacteria.

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Sexually transmitted disease

A brief outline of the main sexually transmitted diseases that can affect the vulval skin is given below. Fuller descriptions of the individual diseases are given elsewhere (see Chapters 25–27 and 30).

Herpes simplex virus

Once this sexually transmitted DNA virus is acquired it lies dormant in dorsal root ganglia and can give rise to recurrent symptomatic lesions. It exists in two types: I and II. Type I usually affects non-genital sites and type II is responsible for 50–80% of genital infections. Ninety-five per cent of infections are acquired sexually and the rest are cases of autoinoculation or non-sexual contact. The lesions are typically painful vesicles or ulcers, which are often multiple in primary infection but are fewer and usually localized to one side with recurrences. There may be prodromal symptoms of tingling or tender enlarged inguinal nodes. Paraesthesiae may occur, affecting S2–4, which may lead to urinary retention. Pain and oedema may also lead to retention, particularly in primary infections. It is important to obtain a definite diagnosis with a positive culture of HSV and it is necessary to perform the test as soon as the blisters arise, as the virus is harder to culture from older lesions. However, a negative test does not exclude an infection with HSV.

The treatment is either oral aciclovir 200 mg five times daily for 5 days, valaciclovir 500 mg twice daily for 5 days or famciclovir 250 mg three times daily for 5 days.

Suppressant therapy is sometimes required for patients with frequent recurrences (six or more in a year).

Human papillomavirus infection

HPV is a small DNA virus, and is discussed in more detail in Chapter 25. Those that most commonly infect the vulval skin are HPV 6, 11, 16 and 18. The warty lesions are known as condylomata acuminata. Extensive vegetating masses can cover the vulva and perianal area, particularly in diabetes, pregnancy and immunocompromised patients. Patients with genital warts should be screened for other sexually transmitted diseases. Secondary syphilis may also present with extensive papulosquamous lesions and has to be considered in the differential diagnosis.

Types 16 and 18 are linked with cervical and anogenital intraepithelial neoplasia and SCC.

The histology of genital warts is characterized by the koilocyte, a vacuolated squamous cell with a basophilic and pyknotic nucleus in the upper part of the epidermis; it is important not to confuse it with the heavily glycogenated clear cells of vestibular epithelium. Other histological features are elongated dermal papillae, acanthosis, a prominent granular layer often containing koilocytes, and a stratum corneum of variable thickness.

Treatment. Podophyllotoxin is the recommended initial treatment. It is applied twice daily for 3 consecutive days each week for 4 weeks. This treatment is contraindicated in pregnancy because of the theoretical risk of teratogenicity. Diathermy, hyfrecation, topical trichloroacetic acid, cryotherapy and carbon dioxide laser have been used with variable success. These treatments are successful in patients where the lesions are few or filiform in morphology.

The new immune response modulating cream, imiquimod, is now used for resistant cases or patients with extensive lesions. This has to be used with care as it also induces an inflammatory response in patients who have a background dermatitis. It should not be used in patients who have benign vulval aphthous ulcers.

In pregnancy, only cryotherapy or destructive techniques with cautery or hyfrecation can be used safely.

Gonorrhoea

The urethra, cervix and rectum may be infected by *Neisseria gonorrhoea* and spread occurs to the endometrium and fallopian tubes. Vulval involvement is rare in adults, and infection is sited in the paraurethral and Bartholin's glands, resulting in painful abscess formation. In children, the infection is usually a result of sexual abuse, and an acute vulvitis may develop [1].

Syphilis

The causative organism is *Treponema pallidum* and vulval lesions may occur in both early and late syphilis. The primary chancre is an ulcerative lesion and is usually accompanied by unilateral or bilateral lymphadenopathy. In secondary syphilis, condylomata lata, flat-topped warty papules, affect the vulva, as may also mucous patches,

which are greyish white moist-looking lesions. Gummas, which are a manifestation of tertiary syphilis, are extremely rare on the vulva, and clinically they occur as either single or multiple swellings or nodules.

Bullous, papular, papulosquamous lesions and mucous patches occur on the vulva in early congenital syphilis and condylomata lata may develop later.

The diagnosis of syphilis is made by dark ground microscopy, immunofluorescence of scrapings or serology.

Histologically, the findings are very variable but, typically, early lesions show inflammation with perivascular plasma cells and lymphocytes together with an endarteritis. There is marked epithelial hyperplasia in lesions of condylomata lata, with a prominent perivascular lymphocytic and plasma cell infiltrate.

Chancroid [2]

This sexually transmitted disease, caused by *Haemophilus ducreyi*, is rare in the UK [2] as it is normally found in tropical and semitropical countries, although the incidence is falling in Africa [3]. Single or multiple small tender ulcers appear on the labia majora, perineum and perianal area, and may also affect the vagina and cervix. The inguinal lymph glands are involved in half of cases and the adenitis is unilateral in most. Buboes develop, which are fluctuant, and rupture leaving extensive ulceration. Co-infections with *Treponema pallidum* or HSV are frequent [4].

Diagnosis may be confirmed by culture of scrapings from the ulcer base or aspirated pus. Microscopy of scrapings or pus will show Gram-negative coccobacilli. PCR may also be used. The histological features include epithelial hyperplasia adjacent to the ulceration, with three relatively distinct zones at the base of the ulcer. The superficial zone consists of a thin band of neutrophils, fibrin and necrotic debris; the middle zone of oedema with thin-walled, dilated and vertically orientated blood vessels; and the deep zone of a dense perivascular infiltrate of lymphocytes and plasma cells. A Giemsa or Brown–Brenn stain may reveal organisms in the superficial zone staining blue or red, respectively.

Treatment. Azithromycin, ceftriaxone, ciprofloxacin or erythromycin can be used. The recent guidelines issued by the Communicable Disease Centre (CDC) should be consulted (http://www.cdc.gov/std). Special considerations should be given to patients with HIV infection.

Donovanosis [5]

SYN. GRANULOMA VENEREUM; GRANULOMA INGUINALE

The causative organism is *Calymmatobacterium granulomatis*, formerly known as *Donovania granulomatis*. The disease is sexually transmitted and found in New Guinea, India, South Africa and Brazil. Papules or nodules break down to form ulcers with a rolled edge. Large areas are involved, and granulomatous masses may involve any part of the genitocrural area, although the lymph nodes themselves are not affected. The vagina and cervix may be involved. Scarring and lymphoedema may ensue.

Histopathology shows epithelial hyperplasia adjacent to the ulcer, sometimes with spongiosis and intraepithelial neutrophilic abscesses, and a dense dermal or submucosal infiltrate with neutrophilic abscesses surrounded by plasma cells, histiocytes and lymphocytes. The organisms occasionally are visible with silver stains, which show intracytoplasmic inclusions (Donovan bodies), seen as black oval or rod-shaped structures in the cytoplasm of histiocytes. The organisms are more reliably demonstrated on smear preparations than tissue sections.

Chlamydia **(lymphogranuloma venereum)**

Chlamydia trachomatis is a Gram-negative intracellular bacterium that is an obligatory parasite. The serovars L1–3 cause lymphogranuloma venereum, which occurs in tropical and subtropical countries. The incubation period varies from a few days to a few weeks. A small papule develops on the vulva, usually at the fourchette, heals quickly and is followed weeks later by striking lymphadenopathy. The nodes may form a suppurative mass that heals with scarring, leading to lymphoedema, which may be gross. Generalized chronic infection leads to abscess and fistula formation, and finally genital and anal strictures and elephantiasis.

Rectal lesions present as a proctocolitis with subsequent stricture formation.

The histology of the vulval ulcers is non-specific, but the affected nodes show epithelioid cells and giant cells, and later stellate abscesses develop that are surrounded by epithelioid cells, granulomatous tissue and plasma cells. Fibrosis and necrosis are seen in chronic lesions.

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Benign tumours and tumour-like lesions of the vulva [1,2]

Most of the tumours that arise on the anogenital skin are similar to those that occur on the skin elsewhere. Fibromas arise from deeper connective tissue structures, particularly

those surrounding the introitus and perineal body. They usually occur on the labia majora, are often pedunculated or pendulous, and can attain a very large size. Fibroepitheliomatous polyps (skin tags) are usually solitary and appear as soft wrinkled polypoidal nodules. There is a fibrovascular connective tissue core covered by squamous epithelium, which may be atrophic or, more commonly, mildly acanthotic and hyperkeratotic. Cellular atypia is occasionally seen in the stromal cells. Lipomas develop from the fatty tissue of the labia majora, but there have been reports of localization to the clitoris [3], as has also been reported with haemangiomas [3,4,].

Two types of lymphangioma may occur on the vulva: lymphangioma circumscriptum, which are localized thin-walled vesicles [5], and cavernous lymphangioma, which arise in childhood and present as a soft compressible mass, which, although usually located in the labia minora, can involve the whole of the vulva [6]. Acquired lymphangiectasia is discussed on p. 68.81.

Melanocytic naevi include junctional, intradermal and compound types, which generally share the same clinical and histological features as naevi at other sites of the body, with the exception that in premenopausal women vulval naevi sometimes have atypical histological features [7]. The atypia may extend into the adnexal structures, but the overall symmetry of the lesion, with cellular maturation in the deeper dermis, should help to distinguish it from a truly malignant lesion. Sometimes, differentiation from melanoma can be difficult and evaluation by an experienced dermatopathologist may be necessary.

Epidermal cysts of the vulva may develop from epithelial implants following surgical trauma, from epidermal inclusions occurring at fusion sites during embryogenesis, or from obstructed sebaceous gland ducts that have undergone squamous metaplasia. They may be single or multiple, and occur most commonly in the labia majora. Steatocystoma may present as a solitary cyst in the vulval region [8]. Calcified nodules have been recorded [9].

Syringomas

These are considered to be adenomas of the intraepidermal eccrine sweat gland ducts. They do not require treatment as they are usually asymptomatic, although there may be pruritus [10]. Vulval syringomas are multiple, bilateral and symmetrical, although a solitary lesion may occur. One case was reported that had the typical histological features of a syringoma mixed with pilosebaceous elements [11].

Papillary hidradenoma

This sweat gland adenoma with apocrine differentiation occurs almost exclusively in the anogenital region of middle-aged white women. It has been associated with anogenital glands [12]. It is a firm asymptomatic papule or nodule, which can occasionally be painful, and occurs most commonly on the labia majora, interlabial sulcus, lateral surfaces of the labia minora or perineal region [13]. Although usually single, there are occasionally multiple lesions. Curiously, when they are multiple all the lesions tend to develop on one side of the vulva. In most patients, the covering epidermis remains intact, but in a proportion the elevated epithelium may become ulcerated [14].

Malignant change within a papillary hidradenoma has been reported: apocrine carcinoma [15] and adenosquamous carcinoma [16].

Fox–Fordyce disease

In this condition, described in detail in Chapter 45, the apocrine ducts become blocked, with retention of sweat. Itchy skin-coloured papules appear on the mons pubis, labia majora, axillae and on the breast. They develop around the time of puberty and there are menstrual exacerbations. There is some improvement in pregnancy and after the menopause.

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Mucinous cysts

Mucinous cysts of the vulva are not uncommon. They are usually found in the vestibule where they develop secondary to obstruction of the duct of one of the many minor vestibular mucus-secreting glands. The cysts are of urogenital sinus origin and not, as was once thought, of Müllerian origin [1,2].

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Bartholin's duct tumours

These are very rare and there is debate as to whether they are true neoplasms or better regarded as examples of hyperplasia or hamartoma [1,2].

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Neurofibroma and neurofibromatosis

Vulval neurofibromas may occur either as solitary lesions with no other features of neurofibromatosis, or as part of generalized neurofibromatosis. In one series, 18% had vulval lesions [1]. Vulval neurofibromas have also been described as one component of a localized neurofibromatosis of the female genitourinary tract [2,3]. Some cases have led to confusion by mimicking an intersex problem [4–7].

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Glomus tumour

There are rare reports of this tumour on the labia minora giving rise to dyspareunia [1,2].

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Leiomyoma

Vulval leiomyomas are uncommon [1,2], and there is no association with uterine leiomyomas. It is unclear whether these tumours originate from the smooth muscle of the vulval erectile tissue, from the muscular elements of the round ligament, or from the myoepithelial cells of Bartholin's gland.

Vulval leiomyomas occur during the reproductive years and usually present as well-circumscribed painless non-tender nodules or swellings in the labia. Lesions may enlarge in pregnancy. A clitoral leiomyoma can cause a mistaken diagnosis of an intersex disorder. A clitoral leiomyoma associated with a leiomyoma of the oesophagus has been reported [3].

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Rarer tumours include granular cell myoblastoma [1,2], which present as flesh-coloured, occasionally pedunculated or ulcerated lesions. Verruciform xanthomas have a predilection for the oral mucosa and the genital skin. They are rare on the vulva [3,4]. Clinically, they present as solitary plaques or warty lesions and vary in colour from yellow to grey or pink. There is acanthosis, papillomatosis and parakeratosis, and the presence of foamy macrophages in the papillary dermis and tips of the elongated rete ridges distinguishes this entity from a viral wart. Nodular fasciitis presents as a painless mass and has rarely been reported on the vulva [5].

Urethral caruncle and urethral prolapse, which are common, can sometimes be mistaken for neoplasms. A urethral caruncle occurs in postmenopausal women as a red fleshy lesion around the urethral meatus and is a chronically inflamed eversion of the urethral mucosa. It may measure from a few millimetres to a few centimetres in diameter and is usually asymptomatic; it may cause dysuria or bleeding if ulcerated. Histologically, it is essentially the same as a pyogenic granuloma, showing a highly vascular connective tissue with a heavy inflammatory infiltrate of lymphocytes and plasma cells. Enmeshed in

this inflamed stroma are varying quantities of glandular structures or solid islands of urethral epithelium.

Prolapse of the urethra may occur at any age. Histologically, there is marked oedema of the underlying connective tissue, and the overlying urethral mucosa may be focally ulcerated. The underlying stroma shows marked vascular distension and engorgement, often with thrombosis. The epithelial inclusions typically seen in a urethral caruncle are not present.

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Precancerous dermatoses

Vulval intraepithelial neoplasia

This term was introduced by the International Society for the Study of Vulvovaginal Diseases (ISSVD) to replace the previous terms dystrophy with atypia, Bowen's disease, bowenoid papulosis, erythroplasia of Queyrat and squamous carcinoma *in situ* [1–3]. It is defined as loss of the normal orientation and architecture of the epithelium with cellular atypia. It was also graded into VIN1–3, according to the percentage of the epithelium involved. This classification also included EMPD and melanoma *in situ*. There are now proposals to change this classification, reserving the term VIN exclusively for squamous cell dysplasia that has a risk of malignant transformation. This would not include Paget's disease or melanoma *in situ*. The newer terminology for VIN also recommends abolishing the current grading system. The three tier grading of VIN is often misleading [4,5], as many cases of VIN1 with basal atypia are not truly premalignant but reparative (e.g. LP). The important VIN with malignant potential is that with atypia involving two-thirds to full thickness of the epithelium (undifferentiated VIN [VIN2 and VIN3]), or severe atypia confined to the basal layers with fairly normal differentiation of the upper layers (differentiated VIN). The rete ridges may be long and forked, with keratin pearls. This change on a background of LS/LP represents either very early invasive disease or heralds its imminent onset.

Undifferentiated vulval intraepithelial neoplasia

SYN. BOWEN'S DISEASE; BOWENOID PAPULOSIS; CARCINOMA IN SITU; CARCINOMA SIMPLEX

There is a complete loss of cellular stratification throughout the epidermis, with large hyperchromatic cells, dyskeratosis, multinucleated cells and numerous typical and atypical mitoses. Originally, two distinct histological types of VIN were described: bowenoid, characterized by individual cell keratinization and abnormal cellular differentiation; and basaloid, with atypical parabasal cells extending throughout the full thickness of the epithelium. However, both types can sometimes be found in the same histological section so it is no longer considered helpful to distinguish the two.

Multifocal anogenital disease is strongly associated with the oncogenic papillomaviruses, particularly HPV 16 and 18, and almost exclusively occurs in smokers [6,7]. The condition is caused by a failure of the host to mount an immune response to the HPV. Patients who are immunocompromised have a higher incidence of this problem, but the majority of young women with this problem do not have an identifiable immunodeficiency. In addition to being multifocal, VIN may be associated with multicentric disease, with lesions of intraepithelial neoplasia involving the cervix, vagina and perianal skin. Up to two-thirds of patients with VIN have a current or past history of CIN [8].

Clinically, the lesions of intraepithelial neoplasia can be solitary or multiple. The morphology of the lesions is also very diverse, with lesions that resemble viral warts, plaques that may be shiny and smooth, skin-coloured, red or white, or others that are warty and pigmented and resemble seborrhoeic keratoses [9,10]. Less commonly, the lesions may be large and papillomatous, particularly perianally, where they may be polypoid. The main symptom is pruritus, which can be severe and troublesome (Figs 68.33–68.35).

Vaginal involvement is uncommon. Initially, it was felt that BP could be distinguished histologically from Bowen's disease but time has proved this not to be the case.

The risk of progression to invasive disease is estimated as 10% or less in multifocal disease, but this risk is higher in immunocompromised patients, particularly with perianal disease [11] and in the older woman with a solitary plaque [12].

There also have been reports of vulval cancer in patients with Fanconi's anaemia [13,14].

Treatment. This is tailored to the individual patient's needs. In the case of a solitary lesion that is amenable to simple excision, this is the treatment of choice. In the woman with extensive disease, surgery would be mutilating physically and distressing psychologically, and does not guarantee a cure as the risk of recurrence is significant

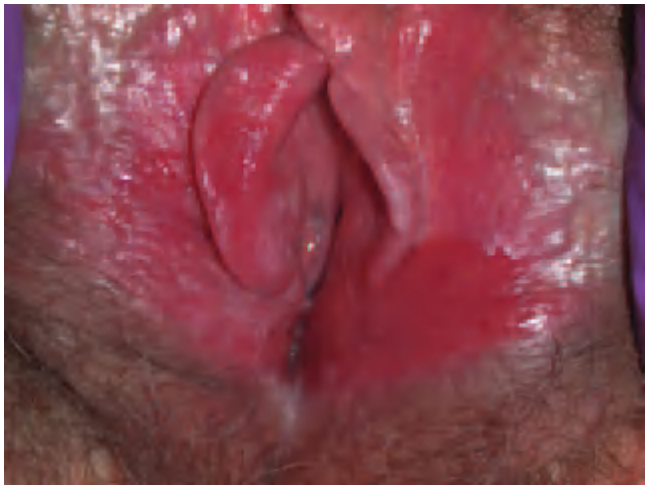

Fig. 68.33 Vulval intraepithelial neoplasia. Erythematous patches with one warty plaque inferiorly on the inner aspect of the right labium minus.

[15,16]. Such patients require regular and long-term follow-up, with biopsies of suspicious areas. Thick or polypoid lesions should be excised, as early invasive changes are difficult to detect in these areas [17]. Cryotherapy is not effective, but 5-fluorouracil can be used successfully for lesions of the labia minora, vestibule and clitoral area [16]. It is not effective on the hair-bearing parts of the vulva, probably because of the deep adnexal structures, which can all be involved. Laser vaporization has a high recurrence rate, particularly if the hair-bearing parts of the vulva are involved, and there is the additional danger that early invasive disease may be missed and therefore inappropriately treated. It is also extremely painful postoperatively.

As VIN is a multicentric problem, the other sites that need to be monitored are the cervix, vagina and perianal area. If there is perianal disease, anoscopy should be performed to exclude involvement of the anal canal.

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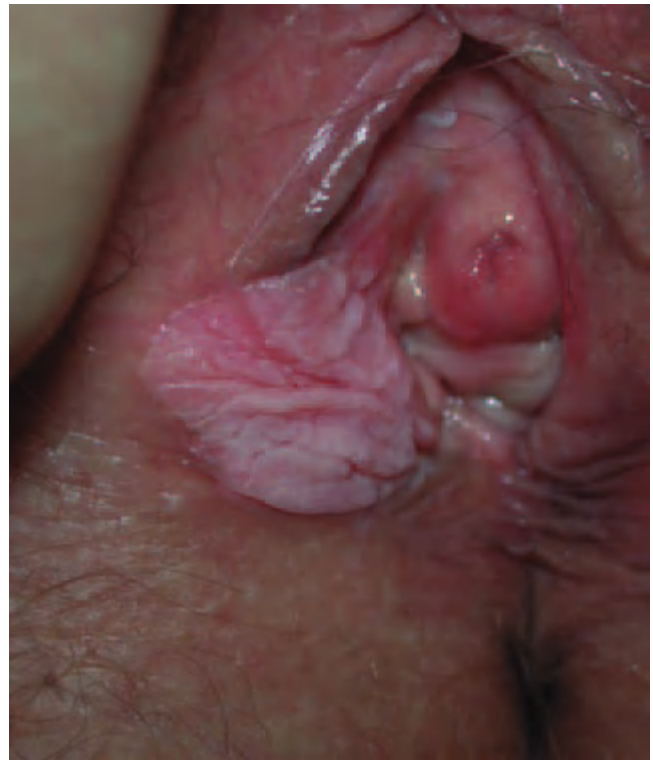

Fig. 68.34 Vulval intraepithelial neoplasia. Solitary warty plaque.

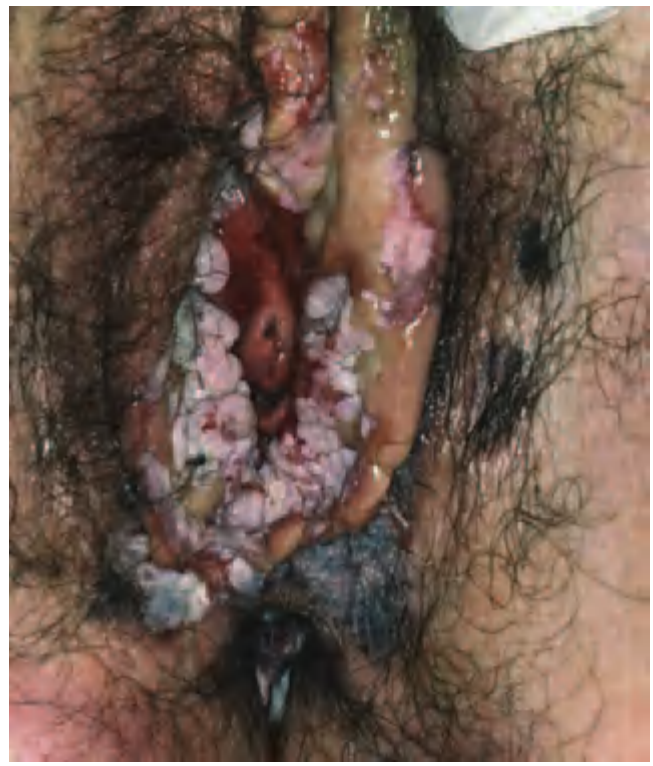

Fig. 68.35 Vulval intraepithelial neoplasia. Pigmented seborrhoeic keratosis-like lesions.

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Vulval malignancy [1]

The most common malignancy by far is SCC, followed by basal cell carcinoma, adenocarcinoma, melanoma and verrucous carcinoma.

Squamous cell carcinoma

Aetiologically, there appear to be two types of vulval squamous cell carcinoma [2–5]. The first and largest group occurs in elderly women on a background of a chronic dermatosis such as LS or LP. The second type, which accounts for approximately 40% of cases, occurs in younger women and is associated with intraepithelial neoplasia associated with oncogenic-type HPV infection. A link with HPV has not yet been established with the first group [6].

In the 1990s, the staging of vulval cancer was replaced by a combined clinical and surgical staging [7]. One of the reasons for this change was to remove the term microinvasive carcinoma of the vulva, as at that time its definition was misleading. In this new classification, stage I tumours are less than 2 cm diameter and are further subdivided into Ia and Ib. Ia are lesions with less than 1 mm depth of invasion. There are some difficulties as to how this measurement should be made. The most recent recommendation is to measure from the dermal–epidermal junction of the nearest dermal papilla to the deepest point of invasion [8]. Lymph node dissection is mandatory for all lesions greater than 1 mm but can be avoided in those with stage Ia. There are three histological types of SCC: keratinizing, basaloid and warty carcinomas.

Keratinizing tumours are those seen in the older women, which are not HPV-related, and the basaloid and warty tumours are those found in younger women with HPV-related VIN.

There is also an adenoid variant of SCC with acantholysis in the centres of some of the infiltrating nests, producing cystic spaces lined by cubocolumnar nests. These pseudocysts do not contain mucin, which differentiates them from adenosquamous cell carcinoma.

Treatment. Surgical excision is tailored to the individual, and is determined by the size and site of the tumour.

The overall 5-year survival is approximately 75%, which rises to 90% or greater in those with no nodal metastases. The main reason for failure of treatment is the inability to control lymphatic and distant metastases, lymphatic spread being the most important factor. The vulval lymphatics drain to the inguinal and femoral nodes and from there to the pelvic nodes. Central lesions (those placed near the clitoris, urethra, vagina, fourchette and perianal area) have a bilateral lymphatic drainage, and it is important in these cases that the inguinofemoral nodes on both sides are excised. Radiotherapy is used as an adjuvant in patients with positive nodes and in those with inoperable tumours. It is also sometimes used as a primary treatment in tumours of the anus and urethra, to reduce their size before surgery and to try to preserve sphincter function.

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Verrucous carcinoma

SYN. GIANT CONDYLOMA OF BUSCHKE–LÖWENSTEIN

This tumour occurs in older women, and many arise on a background of LS [1]. There is also a strong relationship to vulval condylomas. Clinically, the lesions appear as a warty plaque or cauliflower-like tumour, which can ulcerate and become extremely large (Fig. 68.36).

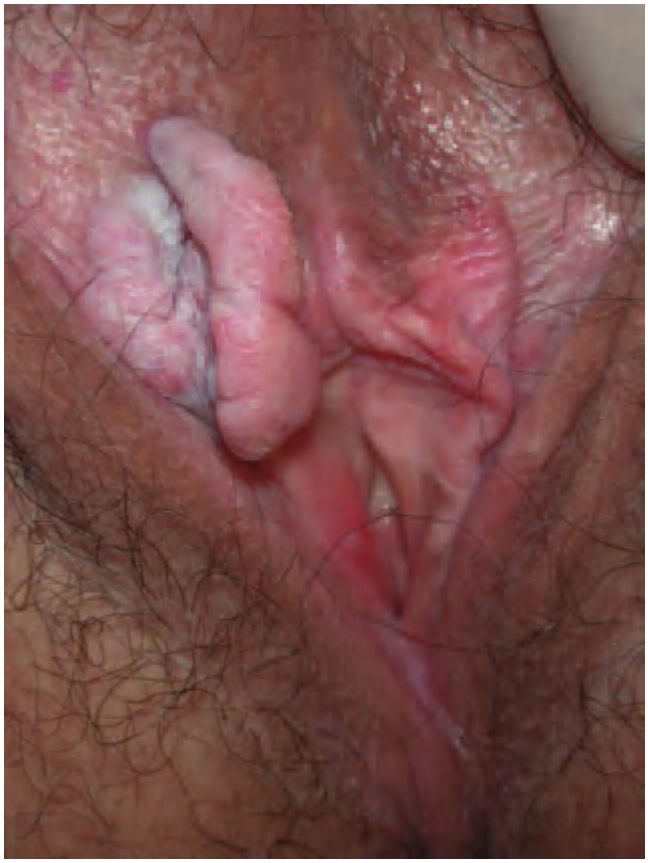

Fig. 68.36 Verrucous carcinoma on a background of lichen sclerosus.

The histological changes include epidermal acanthosis, with large bulbous rete ridges which compress and push down the underlying stroma. There is very little cellular atypia and the few, if any, mitoses are confined to the basal layers. Koilocytes are usually present. Lymph node and distant metastases occur rarely.

Treatment is wide local excision. Radiotherapy is not used as it is associated with a worse prognosis, probably because it can induce anaplastic transformation [2]. Oral retinoids may also be helpful [3].

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Basal cell carcinoma

Vulval basal cell carcomas are not uncommon and present as an eroded plaque, which may be pigmented. Less commonly, the tumour may form a nodule or ulcer. They occur most frequently on the labia majora (Fig. 68.37) [1].

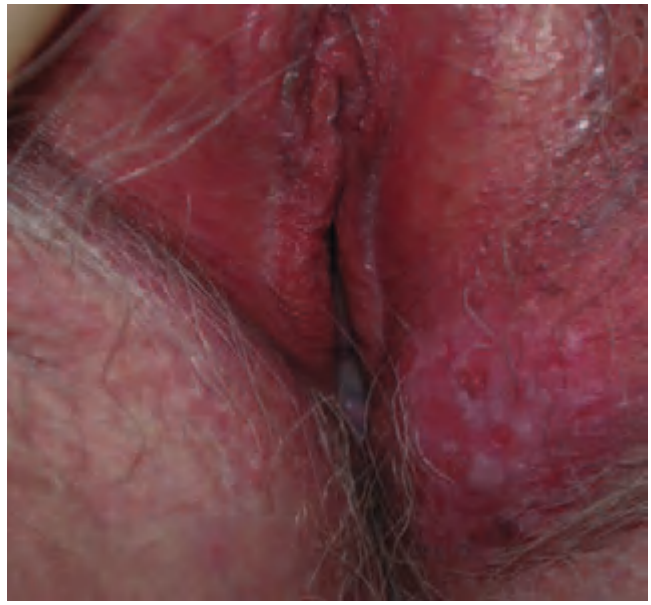

Fig. 68.37 Basal cell carcinoma: lower left labium majus.

Histologically, the appearances are identical to BCCs seen elsewhere. Inadequate excision accounts for a high recurrence rate and metastases to regional lymph nodes [2]. Mohs' surgery is often recommended to ensure adequate local excision [3,4].

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Adenocarcinoma

Primary adenocarcinoma unrelated to underlying glandular adnexae is exceedingly rare. The lesion usually presents as a painless subcutaneous nodule which, as it expands, becomes fixed and painful. The tumour can invade deeply into fat, muscle or bone and may be associated with a Bartholin's gland abscess. Adenocarcinoma may be associated with EMPD.

Many of the mucinous carcinomas that arise are possibly of cloacal origin [1].

There is one report of a mucinous carcinoma with neuroendocrine differentiation [2].

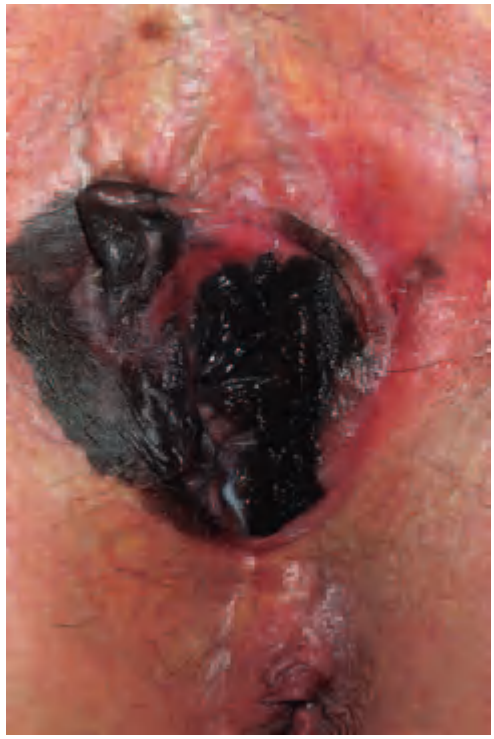

Fig. 68.38 Melanoma of the vulva. (Courtesy of Dr F.A. Ive, Durham, UK.)

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Melanoma

Vulval melanomas account for approximately 5% of vulval malignancy. Any of the variants of melanoma may occur on the vulva, and the clinical and histological features are the same as for melanomas elsewhere (Fig. 68.38). However, in one cohort of 219 patients, 27% of lesions were amelanotic [1,2]. Melanomas at this site carry the same prognosis according to the Clarke level of invasion, the Breslow thickness and the presence or absence of a vertical growth phase. They may be mistakenly diagnosed as EMPD.

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Vulval extramammary Paget's disease

EMPD is fully discussed in Chapter 36. EMPD is a rare dermatosis, and is distinct from Paget's disease of the nipple, which is always associated with underlying breast neoplasia. The vulva is the most common site for EMPD, which is subdivided into primary and secondary disease. Primary, or cutaneous EMPD, is an intraepithelial adenocarcinoma arising in the epidermis or the epithelia of the local skin appendages. Secondary EMPD is epidermal involvement from a non-cutaneous internal neoplasm, either by direct extension or metastasis. The two most common tumours associated with secondary vulval EMPD are anorectal adenocarcinoma and urothelial carcinoma of the bladder or urethra. Other associated tumours reported include cervix, endometrium and ovary [1,2].

The differentiation between primary and secondary disease is not always straightforward clinically and sometimes relies on immunohistological investigations [3,4].

Additional changes to the vulval EMPD classification have been proposed, based on aetiology [5]. The primary and secondary categories are retained, but each is divided into three types. The primary intraepithelial disease, primary with invasion, and EMPD as a manifestation of an underlying primary adenocarcinoma of a vulval skin appendage or subcutaneous vulval gland. The secondary category has three groups according to the tumour from which it arises: EMPD secondary to anorectal adenocarcinoma, EMPD secondary to urothelial carcinoma and EMPD secondary to an adenocarcinoma or related tumour at other sites.

It is important to distinguish primary from secondary EMPD as management depends on the correct diagnosis.

Clinical features. Clinically, the lesion is typically a moist red oozing plaque, which looks like impetiginized eczema or psoriasis. The associated symptoms include pruritus and burning (Fig. 68.39).

Histopathology. There is frequently epidermal hyperplasia. The epidermis is infiltrated with pale-staining Paget's cells. The Paget's cells are PAS-positive and diastase-resistant, and stain with Alcian blue and markers for the simple keratins. In the lower epidermis, the tumour cells may compress the basal cells.

Treatment. In primary EMPD, excision of visible disease is often recommended for treatment and to exclude underlying appendageal adenocarcinoma. Sometimes in the very elderly, with extensive disease or recurrence after vulvectomy, this is not always an option that the patient wishes to accept. Patients should be regularly monitored, and topical steroids can be used if there is troublesome pruritus. Topical 5-fluorouracil, bleomycin and imiquimod have been used, as well as oral retinoids, with some

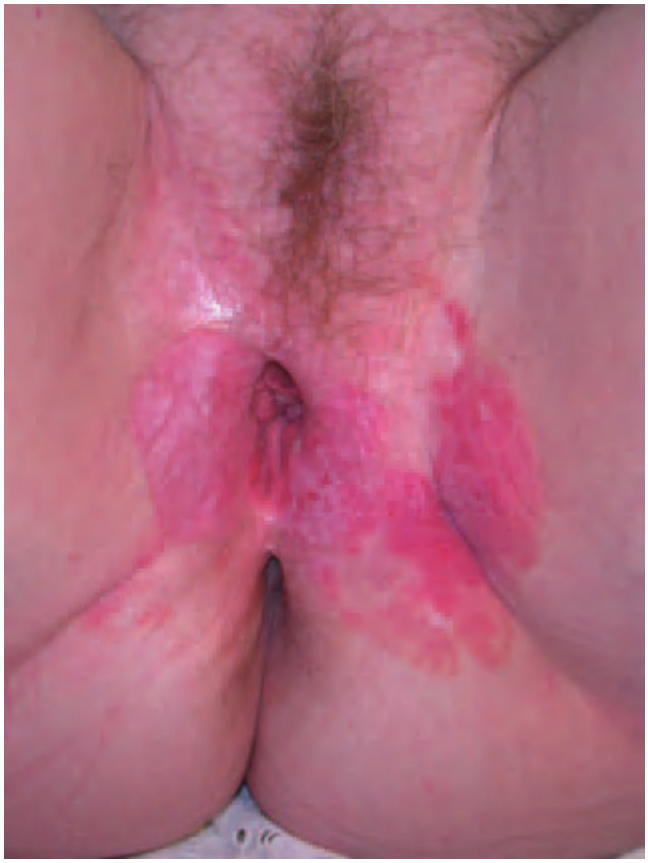

Fig. 68.39 Extramammary Paget's disease.

success. The recurrence rates are high after carbon dioxide laser and radiotherapy.

In secondary disease, the treatment is directed predominantly at the associated carcinoma.

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Other malignancies

Langerhans' cell histiocytosis

The anogenital skin may be one of the sites involved in disseminated Langerhans' cell histiocytosis (LCH), but lesions may occur at this site only. Perianal ulceration is the most common presentation in adults and children [1,2], and genital involvement is more common in women [3,4]. The lesions may be plaques, nodules, erosions, ulcers or pustules. The Letterer–Siwe form consists of a seborrhoeic dermatitis-like eruption on the intertriginous zones and scalp. Some of the lesions may be purpuric.

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Lymphomas

Non-Hodgkin's lymphoma of the vulva is more frequently reported [1,2] than Hodgkin's lymphoma [3]. Non-Hodgkin's lymphoma has also been reported post-transplantation [4] and in association with HIV infection [5].

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Miscellaneous tumours

There are a few reports of vulval dermatofibrosarcoma protuberans on the labia majora [1], slow-growing liposarcoma [2], epithelioid sarcoma [3], Merkel cell carcinoma [4] and Bartholin's gland carcinoma [5].

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Metastatic tumours

These are uncommon and may be from malignancies of the cervix, endometrium, vagina, ovary, urethra, kidney, breast and lung, in descending order of frequency [1].

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Miscellaneous

Pigmentary disorders

Hypopigmentation

As at other sites, this can be naevoid, a post-inflammatory problem or vitiligo.

Hyperpigmentation

The increased pigmentation may be caused by haemosiderin, which results in a reddish brown discoloration. It is the result of extravasation of red blood cells and is seen in capillaritis, urethral caruncle, lichen sclerosus, Zoon's vulvitis and chronic vulval purpura. However, increased pigmentation is more commonly related to melanin. There is considerable variation in the distribution and amount of melanocytes and melanin in the normal vulva, depending on site, age, ethnicity and hormonal status.

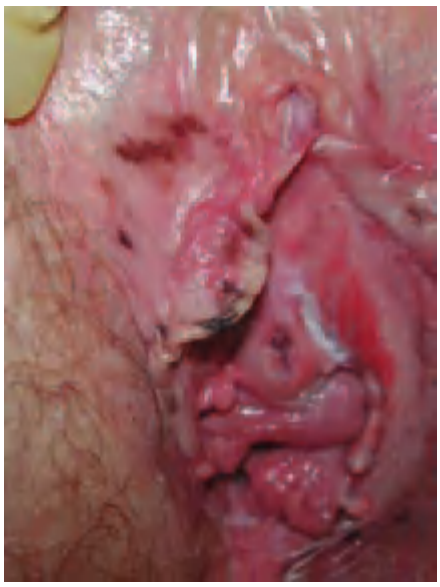
Post-inflammatory pigmentation may follow any inflammatory dermatosis, particularly if there has been a disruption of the dermal–epidermal junction and in darker skins. It is a common sequela of LP and sometimes LS.

Vulval melanosis. Intense macular hyperpigmentation of vulval skin can be difficult to categorize, and a biopsy is essential for an accurate diagnosis and to exclude malignant melanoma (Fig. 68.40a) [1]. If the lesions are widespread and accompanied by oral pigmentation, they may be considered as examples of Laugier–Hunziker syndrome [2,3]. The term vulval melanosis is used for those cases where there is extensive macular pigmentation affecting the vulval skin, with the histological changes of basal hypermelanosis and a slight increase in the number of melanocytes. There may also be some pigmentary incontinence, but there is no abnormal junctional melanocytic proliferation (Fig. 68.40b) [4–8]. There have been other suggested terms: idiopathic lenticular mucocutaneous pigmentation [9] and genital lentiginosis, particularly if there is melanocytic hyperplasia [10].

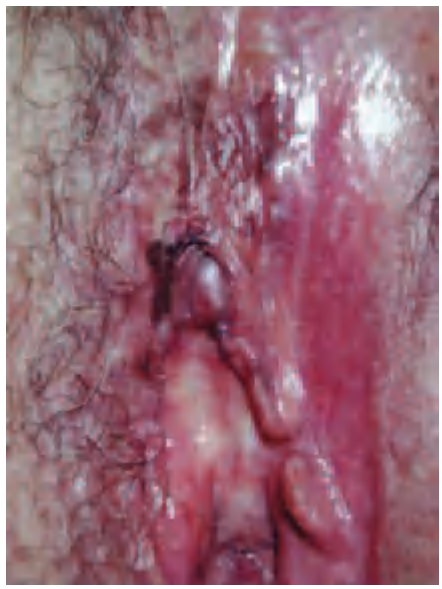
The accepted view is that vulval melanosis is a benign condition, but there are no long-term follow-up studies reported. Therefore, most clinicians advise continuing observation, using photographs or diagrams as an aid.

Lentigines. Vulval lentigines may be sporadic or part of a syndrome (e.g. LAMB syndrome) [11,12]. There is an increase in the number of basal melanocytes, with increased melanin in the epidermis and stratum corneum. Pigment-laden macrophages are found in the papillary dermis, and the rete ridges are elongated.

Acanthosis nigricans. This condition is usually associated with insulin resistance and rarely with malignancy. Initially, the appearance is of a dark and velvety thickening of



(a)



(b)

Fig. 68.40 (a) *In situ* melanoma. (b) Vulval melanosis.

the skin in the genitocrual folds and upper inner thighs, which later becomes warty. Skin tags may also occur.

A fixed drug eruption leaves behind residual hyperpigmentation. Some laxatives are reduced in the bowel to dithranol and this may stain the skin in contact with faeces and lead to a reddish brown discoloration of the urine and vaginal secretions [13,14]. Trichomycosis and chromidrosis may cause some discoloration.

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Necrolytic migratory erythema

This rare dermatosis occurs on the genital skin and lower abdomen and is almost always associated with an underlying pancreatic glucagonoma, although there are exceptional cases where it is not [1].

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Vulval oedema, lymphoedema and lymphangiectasia

Oedema, hereditary angio-oedema [1] and dermographism [2] may all involve the vulva. Vulval oedema may be the only manifestation of Crohn's disease [3].

Lymphoedema occurs when there is impairment of the lymph drainage and it is a frequent complication following surgery and lymphadenectomy for vulval carcinoma. Lymphangiectasia is acquired dilatation of the skin lymphatics secondary to obstruction of the lymphatic vessels. It is most frequently reported following treatment of cervical carcinoma with surgery and/or radiotherapy [4–6]. Lymphangiectasia may be very profuse in Crohn's disease and carbon dioxide laser treatment can be used in patients with troublesome lymphorrhoea [7]. Repeated episodes of cellulitis may also result in lymphangiectasia, but there may be an underlying abnormality of the lymphatics that predisposed the patient to the cellulitis initially. Lymphangiectasia may be mistaken clinically for viral warts [8].

Endometriosis

Endometriosis occasionally occurs on the vulva or in the vagina as a direct implantation. The condition may follow a previous surgical procedure [9,10], and in episiotomy scars after delivery [11,12]. It presents as firm bluish nodules, which become tender or bleed during menstruation. Clear cell adenocarcinoma has arisen in vulval endometriosis [13].

Genital papular acantholytic dyskeratosis

This was first described in 1984 [14], and is characterized by the presence of multiple papules or, less frequently, a single papule or plaque-like lesions on genital skin [15–18]. Cases with disseminated lesions have been described [19]. The histological changes are similar to those seen in Darier's disease or Hailey–Hailey disease, but there is no positive family history or evidence of these diseases at other sites. It is considered a distinct entity, although it may represent a forme fruste of Hailey–Hailey or Darier's disease.

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Vulval pain syndromes

Vulvodynia

The term vulvodynia was first introduced in 1983 by the ISSVD to categorize those patients who complained of a chronic sensation of burning or rawness of the vulval skin [1]. Initially, vulvodynia included several subcategories [2], but these proved unsatisfactory in the light of further experience [3].

A diagnosis of vulvodynia should be strictly reserved for those patients who have the symptoms of pain or discomfort for 3 months or more in the absence of any visible abnormality or explanation that would account for their symptoms. If any active dermatosis or dermographism is found that could account for the symptoms then that condition is the diagnosis rather than vulvodynia.

Advances in the last decade have improved our knowledge and understanding of pain in general, and the existence of complex regional pain syndromes is now well recognized. Chronic pain syndromes are rarely caused by primary psychiatric disorders as originally thought, but are the result of peripheral and/or central neuronal sensitization.

In the 1990s it was felt that vulvodynia fulfilled many of the criteria of a complex regional pain syndrome. In clinical practice there appeared to be two major types of vulvodynia: vestibulitis and dysaesthetic vulvodynia. The main differentiation between the two was that vestibulitis was characterized by pain localized to the vulval vestibule that was precipitated by touch alone, whereas dysaesthetic vulvodynia was diffuse vulval pain that occurred spontaneously and which might or might not be aggravated by touch. The term vestibulitis was unfortunate and misleading as it suggested an inflammatory condition.

The 1999 meeting of the ISSVD recognized that there was a need for further changes in the nomenclature to fit in with the classification used for chronic pain syndromes elsewhere. It was suggested that the term dysaesthetic vulvodynia be retained for vulval pain that was diffuse, constant and spontaneous. Localized pain triggered by touch alone, previously termed vestibulitis, would be referred to by the newer and more accurate term vestibulodynia. It was also proposed that in those cases where the pain is localized at another site that this should be specified (e.g. clitorodynia if the pain is localized to the clitoris). There will probably be further terminology as our knowledge about these chronic pain syndromes increases.

Vestibulodynia

SYN. VESTIBULITIS

The term vulval vestibulitis was first defined as a triad of clinical signs and symptoms that included dyspareunia, vestibular tenderness to light touch and erythema of the vestibular epithelium [4]. This syndrome was certainly recognized earlier and terms such as focal vulvitis, hyperaesthesia of the vulva and vestibular adenitis had been used to describe the condition. It is usually a disorder of younger women, who present with the complaint of secondary dyspareunia. Most patients give a history of a precipitating event and some recall that it started during a particularly stressful time. Vestibulitis it is not an inflammatory condition [5], and for this reason alone vestibulodynia is a better term. There is no evidence to support an association with chronic infection with either *Candida* or HPV. The aetiology remains unknown and it is currently best categorized as a chronic pain syndrome [6]. The majority of patients affected by vestibulodynia are psychologically normal but they do have higher anxiety and somatization scores [7,8]. Patients also seem more susceptible to irritants, not only on the vulval skin but also at other sites (e.g. hand dermatitis, poor tolerance to earrings if made of base metals). However, patch testing is usually negative [9]. It is important to assess if the patient is dermographic, as dermographism may mimic or exacerbate vulvodynia. Sometimes it is helpful to perform an examination after recent intercourse as nymphohymenal tears, fourchette fissuring and herpes simplex infection can all be overlooked as the cause of recurrent vulval pain precipitated or exacerbated by intercourse.

Dysaesthetic vulvodynia

Dysaesthetic vulvodynia is most frequently seen in older, postmenopausal women who are often not sexually active and there is usually no precipitating event. The pain is spontaneous and often occurs independently of touch. Many of these patients are depressed, but it is difficult to establish whether this is a primary phenomenon or secondary to chronic pain. Much of the literature on the psychological profiles of patients with vulvodynia is difficult to interpret, as very often the distinction between vestibulitis and dysaesthetic vulvodynia is unclear. Dysaesthetic vulvodynia is a frequent problem following inflammatory conditions of the vulva, particularly the vestibule. It is seen most frequently following LP, when the patient still has symptoms despite the fact that the

dermatitis has responded to treatment. The use of 5% lidocaine ointment usually resolves this problem.

Some of the younger patients who develop dysaesthetic vulvodynia initially had vestibulodynia.

Treatment. Management requires an unrushed and sympathetic consultation, with time spent explaining the problem of pain syndromes and the rationale for the planned treatment. Initially, topical agents are used, which include a soap substitute, avoidance of irritants and regular application of the local anaesthetic 5% lidocaine ointment. The other topical 'caine' anaesthetics should be avoided because of the risk of contact sensitivity, which is rare with lidocaine. If the patient is dermographic, an oral antihistamine should be added. If the topical measures are of no benefit or only partially effective, a tricyclic antidepressant may be used for its central action on pain. Alternative medications include gabapentin and carbamazepine. If there are secondary psychological or sexual issues, the input from a specialist in this field will be important. Biofeedback may improve some patients, particularly if there is associated vaginismus [10]. The patients may also wish to join a self-support group; in the UK this is the Vulval Pain Society.

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Perineal and perianal dermatology

Introduction

Dermatologists should be able to assess the area competently and know when to involve colleagues in other disciplines. The perineum involves the perianal skin, groins and scrotum or vulva.

Pruritus ani is a symptom, not a diagnosis, unless qualified as constitutional or idiopathic, and, in roughly half of patients with pruritus ani, a cause will be established after dermatological evaluation [1–6]. The topic is discussed at length below (see p. 68.85).

Inflammatory and infectious disorders of the area may be difficult to differentiate. The presence of an infective condition in this area may overlie and disguise a more important lesion of the colon or rectum [7].

The differential diagnosis of anogenital ulceration is addressed on p. 68.3 and in Tables 68.9 and 68.10. Many banal conditions take on a vegetating appearance in this area, especially in hot humid climates and in the presence of infection. For these, the term dermatitis vegetans can be used.

Elephantiasis forms of progressive tuberculosis [8] and syphilis are now seldom seen, but deep fungal infections must not be overlooked.

Anal and perianal symptoms and signs in homosexual males [9] have become of greater significance because of the increasing prevalence of AIDS [10–12]. Whatever the presentation of the patient, it is important to look for infective conditions and suspect the possibility of two or more concomitant diseases. Painful lesions of the anus in homosexual men are common [13], and may include traumatic lesions and herpes genitalis. Anorectal sepsis, including chronic intersphincteric abscesses, anal fistulae, fissures and ulcerated haemorrhoids were seen more frequently in a group of male homosexuals than in heterosexuals [14]. Anal intraepithelial neoplasia may be clinically subtle and invasive carcinoma is not rare. The dermatology of HIV infection is discussed generally in Chapter 26, and of the perianal and anal area below.

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Structure and function

The anus is principally for the evacuation of faeces from the gastrointestinal tract [1], but may also be an organ of sexual utility.

The deep natal cleft, the inguinal (crural) folds and the infragluteal folds are special sites because they are areas where two layers of skin come into close apposition. Together these sites function as part of the hinge between the lower limbs and the trunk, as well as abutting the mucocutaneous junctions of anus and genitalia. The natal cleft is deep and firmly fixed to underlying fibrous and fascial tissues, and its sides are steep and closely apposed. Mucous discharges, excreta and moisture are retained easily within it. Proximity to the genital organs and anus give it a special physical and psychological importance.

The perineum is endowed with numerous eccrine sweat glands whose function is retained after lumbar and thoracolumbar sympathectomies. Sweating may be caused by an alternative parasympathetic sudomotor pathway from the fourth sacral anterior root. Apocrine glands are present but many are functionless. A variable number of sebaceous glands are present both in pilosebaceous units and as individual 'free' sebaceous glands at the transitional part of the anal canal.

The cloacal membrane is where ectodermal and endodermal tissues are in direct apposition caudally in the embryo. The separation into urogenital membrane and anal membrane with the formation of the perineum at about 7 weeks of gestation is brought about by the separation of the cloacal portion of the hindgut by the urorectal septum growing caudally between the allantois anteriorly and the hindgut posteriorly, thus partitioning the cloaca into the urogenital sinus anteriorly and the anorectal canal posteriorly. The anal membrane disintegrates at about 9 weeks to open into an ectodermal anal pit formed in the posterior cloacal folds.

Congenital and developmental abnormalities

Gross anomalies will be seen only incidentally by the dermatologist because of skin complications. Minor abnormalities such as haemangiomas, skin tags and papilliferous acanthomas are common on the inner sides of the thighs and infragluteal region. Pigmented, hairy naevi may involve one or both buttocks. Involvement of the buttocks with atypical naevi is a feature of the dysplastic naevus syndrome.

Developmental cysts, fistulae, sinuses and tumours

These are not uncommon, and frequently become infected. They may be mistaken for hidradenitis suppurativa or furuncles. Dermoid cysts occur on or adjacent to the perineal raphe and scrotum. Cloacal sinuses form fistulae from the anus to the adjoining skin; others involve the urethra and perineum.

Chordoma cutis

Chordomas [2] arise from the embryonic precursor of the axial skeleton, the notochord. They can involve the skin of the perineum, sacral area and buttocks by direct extension, recurrence or metastasis. They present as single or multiple, smooth, skin-coloured, non-tender nodules. Sacrococcygeal pain of a persistent nature may precede the diagnosis for years, in a manner that may mimic the presentation of sacral cysts [3], and require scanning procedures to differentiate between them.

Miscellaneous

Congenital hypertrichosis over the midline in the lumbosacral area—faun tail—is a sign of underlying spinal dysraphism (e.g. spina bifida occulta). Pilonidal sinus is discussed on p. 68.88.

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Trauma and artefact

Anal trauma is not uncommon. The two most common causes of acute painful anal ulceration in homosexual men are trauma and herpes simplex. Primary syphilis, chancroid, lymphogranuloma venereum, granuloma inguinale and amoebiasis, in decreasing order of frequency, are much less common [1]. Foreign bodies are occasionally inserted into the rectum. Anogenital tattoos have become commonplace [2].

Pressure sore

Pressure sores (decubitus ulcers) in the sacral area are common. In elderly, debilitated or bedridden patients, a persistent patch of erythema on the sacral or ischial region is a sign of impending ulceration. Squamous carcinoma is a potential complication, as with all chronic ulceration.

Umbilical artery catheterization

Unilateral skin necrosis of the buttock has been reported following indwelling umbilical artery catheterization [3–5], probably resulting from thrombosis leading to

occlusion of the inferior gluteal artery. A similar case was caused by misdirection of the tip of the arterial catheter [6].

Child sexual abuse

The significance of anogenital warts in suggesting possible child sexual abuse is controversial. However, early recognition as a marker for child sexual abuse is in the child's long-term best interest [7].

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Inflammatory dermatoses

The causes of perianal inflammation in infants are dealt with in Chapter 14. In adults, inflammation may result from the coexistence of several factors: haemorrhoids, anal discharge, proctitis, the presence of fissures or the effect of scratching. Five common conditions cause diagnostic difficulties: seborrhoeic dermatitis, psoriasis, contact dermatitis, lichen simplex and mycotic infections. *Oxyuris* infestation is sometimes postulated but seldom confirmed in adults. Phthiriasis pubis must be excluded.

The lesions of seborrhoeic dermatitis are brownish red, with branny or large, greasy scales towards the edge, extending beyond and outside the fold, and involving other areas of the body.

Psoriasis has a smooth glazed surface and a dull red hue, and is often fissured; other signs of the disease are nearly always present.

Contact dermatitis is markedly inflamed, and has an ill-defined spreading border. Irritant dermatitis results mainly from detergents; allergic dermatitis can have many causes (Table 68.19). In 43 suspected cases, neomycin (27%) and 'caine mix' (24%) were the most frequent offenders; quinolines (7%), lanolin (7%) and ethylenediamine (5%) were less common [1]. When resulting from a medicament, the hands may be involved. Other reports concern biocide preservatives and fragrances in moistened toilet tissue [2–5], lidocaine [6,7] and tetracaine (amethocaine) hydrochloride [8] used in topical antipruritics for piles, and Mitomycin C [9]. The role of food allergy in causing perianal symptoms is debatable [10]. Anoreceptive homosexual men may be susceptible to condom hypersensitivity.

Gross lichenification (lichen simplex) simulates psoriasis but is usually unilateral, except when it involves the perianal area. It may occur as a small, intensely irritable area, localized to the edge of the anus in one site, which is indicated exactly by the patient.

Tinea corporis presents classical signs unless there has been prior use of topical corticosteroids, which modify the features and thus create diagnostic confusion.

In all cases of perianal and perineal inflammation, the urine should be tested for sugar, and swabs and scrapings examined for organisms. A vaginal or rectal examination is mandatory. Any irregularity of the bowels that causes straining or soiling should be corrected.

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Pruritus ani

The symptom complex of pruritus ani has many causes: it is not a diagnosis unless qualified as constitutional or idiopathic. Fifty per cent of patients with pruritus ani will have a cause after dermatological evaluation [1–6]. Pruritus ani is seen especially in middle-class middle-aged white males [7]. It occurs less frequently in females, either alone or with pruritus vulvae. It can be associated with most forms of anal disease and with skin conditions involving the perianal area. The contributory factors are complex and may complement or perpetuate each other. Anal itching occurs to a variable degree with any inflammatory or eczematous condition of the skin of that area, with anal fissures, whatever their aetiology, and with malignant tumours. Mycotic infection often causes intense pruritus, and diabetes must be excluded in all severe or persistent candidal infections. Threadworm

infestation is a well-recognized cause in childhood and occasionally in adults. Idiopathic anal itching, in which there is no obvious primary dermatological cause, is discussed further here. Lichenification, excoriation and secondary bacterial and candidal infection (induced by scratching) can supervene, and a contact dermatitis can be caused by overwashing and treatment, both self-directed and physician-prescribed.

The common factor linking most cases of pruritus ani is faecal contamination [2,8]. Faeces are themselves irritant and may generate perianal itch [8,9]. The itch may be triggered by a bowel movement or wiping with toilet paper, but often occurs at night, waking the patient from sleep. Faeces also contain potential allergens and endopeptidases of bacterial origin [10,11]. In the presence of pre-existing skin disease (e.g. seborrhoeic dermatitis or flexural psoriasis), or even in the absence of visible disease, these enzymes are capable of inducing both itching and inflammation [12].

Pruritus ani may be associated with anal leakage resulting from coexisting anal disease or an exaggerated recto-anal inhibitory reflex [13] and anal sphincter dysfunction [14], or be precipitated by broad-spectrum antibiotics and diarrhoea. Hypertrophy of anal papillae is probably not relevant [15]. Many patients have a dermatosis and some will have irritant or allergic contact dermatitis [16–18].

Psychological factors often contribute to pruritus ani, particularly when the itching appears to be out of proportion to the changes observed. However, as Whitlock [19] points out in a careful review, the evidence is unsatisfactory, except perhaps in primary lichen simplex. Psychosexual connotations of suppressed homosexuality do not withstand critical assessment. It is quite understandable, however, that prolonged pruritus ani can lead to tension, irritability or depression, and the treatment of this is an important part of the management of the condition. Idiopathic pruritus ani has been attributed to stress and anxiety and sedentary occupations.

The causes of faecal contamination are as follows (more than one factor may be operative).

Difficulty in cleansing the area. This may be caused by the following factors:

1 *Simple obesity*: poor ventilation and maceration have an additional role.

2 *Frequency of defaecation*: patients with a colostomy never suffer from perianal itching. Patients with pruritus ani are rarely constipated, although they may sit long at stool owing to faulty training techniques, with resultant prolapse or haemorrhoids and soiling [2,14,20]. Patients frequently admit to two or more motions a day. They are often tense individuals in whom everyday problems induce a profound colonic reflex, resulting in defaecation and soiling.

3 *Anatomical factors*: it is often noted that the anus is deeply placed. The association of this 'funnel anus' with marked hirsutism causes mechanical problems in the maintenance of hygiene.

Anal leakage. This may result from the following factors:

1 *Local causes*: such as haemorrhoids, perianal tags or fissures, which interfere with the efficient functions of the anus.

2 *Primary anal sphincter dysfunction*: anal canal manometry studies have shown that leakage of infused saline occurs early [13], and in one common group of patients the sphincter relaxes in response to rectal distension in a more rapid and profound manner than in a control group [14]. The arrival of faeces or flatus in the rectum may then regularly result in reflex faecal soiling.

Bacterial contamination. This is frequently a secondary cause, but rarely a primary cause alone. However, cross-infection of staphylococci may occur (e.g. between the ears and the anus).

Food and drink. The role of ingested metabolites or food chemicals in inducing pruritus ani is still uncertain and virtually unexplored, but anecdotal evidence in individual cases is sometimes compelling [21].

Clinical features. Clinical features vary somewhat, with possible contributions from the effects of rubbing, secondary infection, contact dermatitis or an underlying psoriatic diathesis.

1 Lichen simplex may be present in a 'pure' form, often localized to a small area at the edge of the anus or slightly away from it. The perception of itch from 'easily alerted' nerve endings is more acute in those of anxious temperament or at times of psychic trauma or fatigue.

2 A more general area of maceration, lichenification and fissuring—the 'mossy bank' anus—may be present. The architecture of the anal margin may be distorted by haemorrhoids, tags, oedema and infection. There is usually a gross degree of discharge [14].

3 Features of acute eczema may be caused by secondary infection of possibly minimal seborrhoeic dermatitis or psoriasis, or by contact dermatitis. The last mentioned should always be suspected when there has been any sudden change of pattern or intensity of a rash. The fingers may also be involved. One of the most common offenders is the 'caine' group of drugs [22], often self-prescribed.

4 Intense erythema with no obvious features of eczema may occur. This tends to vary in intensity over short periods, and probably represents the pruritic stage of the next group.

5 There may be no visible abnormality at the time of examination. These patients may have noticed erythema at times, or intense itching, and commonly give a story of

an intermittent sensation of wet anal margins and slight faecal soiling. It is in this group that dyskinesia of the sphincter appears to be a primary factor.

Diagnosis. A full history is essential and a search for underlying disease must be carried out. It is important to exclude staphylococcal infection, folliculitis, erythrasma, *Candida*, tinea, warts and thread/pinworms, and to establish whether there are other underlying skin diseases such as psoriasis [23], atopic dermatitis, LP, LS or EMPD [15]. Anal fistulae are particularly prevalent in chronic pruritus ani [24]. However, the majority of patients with piles, skin tags, fissures, warts, diarrhoea or faecal soiling do not itch [3]. Systemic diseases that have been associated with pruritus ani include lymphoma, pellagra, hypovitaminosis A and D and diabetes mellitus [4].

A rectal examination and referral for proctoscopy and sigmoidoscopy may be indicated [25]. In the young, threadworms should be sought with the Sellotape test or by stool examination for parasites. Patch testing is helpful to explore sensitivity to lanolin, medicaments, rubber, perfumed paper, etc.

Treatment. Management [2] begins with attention to the patient's washing habits. Soap is replaced with a suitable substitute and a moisturizer prescribed. A moisturizer (others recommend talcum powder) should be applied after each wash. A barrier preparation can be pre-applied to the perianal skin before the bowels are opened. Washing after defaecation in a bidet is preferable to wiping with toilet paper, if possible. Rubbing with toilet paper should be discouraged and dabbing recommended. Premoistened toilet papers should be avoided because of the potential irritancy of the moisturizing agent, which may be alcohol, and the risk of developing allergic sensitivity to fragrance or preservative components. Underwear should be loose and preferably made of cotton. Patients are best advised not to use topical anaesthetics in order to avoid sensitization to their constituents [26].

Coffee consumption might be curtailed [21]. Any other foods, such as nuts, that provoke the pruritus should be excluded from the diet, and a high-fibre diet should be encouraged if there is any history of constipation or haemorrhoids [27].

Local applications should be mild and soothing. A topical corticosteroid/antibiotic/antifungal preparation is useful for acute episodes. A wick of bandage impregnated with hydrocortisone 1% and silicone 10% inserted in the natal cleft is anti-inflammatory and lubricating. Other treatments that have been advocated include zinc paste with 1–2% phenol, St Mark's lotion, half-strength Castellani's paint, weak (0.05–0.25%) silver nitrate solution (if wet), cryotherapy, oral antihistamines, corticosteroid suppositories, intralesional triamcinolone, a 10-day tapering course of prednisolone, and intralesional methylene blue, with or without marcaine/epinephrine/xylocaine [3,4,28,29]. Caution should be exercised with topical steroid treatment because the anal skin is 'quasi-occluded' and is easily damaged by fluorinated corticosteroids.

Concomitant proctological disease (haemorrhoids, fissures, anal spasm and occult mucosal prolapse) should be treated, if found [30]. When active pathology such as fissures, haemorrhoids or anal spasm are present, surgery will be needed. Lord's stretch procedure [31] has proved helpful. The long-term results are particularly satisfactory in those patients with strong ultra-low-pressure waves [27]. However, it may not always relieve the pruritus [32]. Simple excision of anal tags is unhelpful in relieving symptoms [15].

Some authorities see a psychosexual significance in pruritus ani in men [19], and this may rarely require attention. Patients should be reassured that they do not have cancer [1].

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Danthron erythema

This form of irritant contact dermatitis per rectum is caused by the use of a laxative containing danthron [1,2]. It is seen in those with Hirschsprung's disease or encopresis, and sometimes in elderly incontinent patients [2–4]. Danthron (1,8-dihydroxyanthroquinone) is reduced in the large bowel to 1,8-dihydroxyanthron, which is the active agent [2]. This is chemically identical to dithranol, and the lesions produced by faecal incontinence are equivalent to dithranol 'burns'. A bizarre livid erythema in the perianal area, groins, thighs and buttocks, with sharp outlines, corresponds to the area of contact with the faeces. Danthron erythema is easily differentiated from other causes of perianal or inguino-crural lesions.

Lichen sclerosus et atrophicus

The perianal skin is rarely affected alone, but is involved in up to two-thirds of the cases in which the vulva is affected [5], forming a characteristic figure-of-eight distribution. One case of carcinoma has been reported [6]. Perianal LS is rare in males.

Anal fissure

Small erosions and fissures may occur in the sulcus beneath oedematous haemorrhoids or in any area of dermatitis. The presence of even a small fissure in an area of dermatitis maintains the pruritus and prolongs the course.

A true anal fissure is a midline linear perianal ulcer; 90% posteriorly, 10% anteriorly. Many are idiopathic; the cause is probably related to defaecation of hard stool causing pressure trauma and necrosis, or it may be a postoperative complication. Sexually transmitted diseases and Crohn's disease should be excluded. Intense pruritus, pain, bleeding, mucous discharge and constipation constitute the symptomatology. On examination there may be a 'sentinel pile' at the anal pole of the ulcer. Management is surgical: proctoscopy is mandatory if the aetiology is in doubt, and especially if the fissure extends to the anal margin or within. Benign fissures are superficial and not indurated, but when persistent they may be painful and cause bleeding, especially in the elderly. Unless they heal quickly under treatment, a biopsy should always be performed to exclude malignancy.

Small erosions and excoriations frequently heal with treatment for anogenital pruritus. If they are hidden between haemorrhoids or anal tags, protective pastes are helpful. Fissures in psoriasis and seborrhoeic dermatitis are difficult to heal, particularly in the natal cleft. If the underlying disease is satisfactorily controlled, the lesion will heal without special attention. Intralesional corticosteroids may be effective in non-infective inflammatory conditions.

Anal fistula

A perianal fistula is a communication between the anal canal and the perianal skin. Most are on the midline posteriorly, but there may be multiple openings. The origin is from infection and abscesses within the anal glands, but Crohn's disease, foreign body and tuberculosis are classic causes and hidradenitis suppurativa is an important differential diagnosis. Squamous carcinoma is a rare complication. The presentation is usually of pruritus ani related to seropurulent discharge but there may be pain resulting from abscess formation. Surrounding skin may be indurated. Management is surgical.

Pilonidal cyst/sinus

Pilonidal sinus probably derives from the perineal pilosebaceous unit and precursor pits (not the common congenital sacral pits) associated with trapped hairs [7,8]. Clinically, pilonidal sinus constitutes part of the 'follicular–occlusion tetrad' alongside hidradenitis suppurativa, acne conglobata and dissecting cellulitis of the scalp. Symptoms include itch, pain, recurrent abscess, purulent discharge and persistent nodule. Pilonidal sinus occurs in the midline. The sacrococcygeal location is the most common site but it can occur on the pubis, anterior perineum and, very rarely, the penis. It may present as a nodule or cyst, often with a pigmented or hairy surface, which ruptures and quickly becomes infected (Fig. 68.41). The sinus usually extends to the sacrum and causes sacrococcygeal fistulae with deep ramifications. This heals if the track is thoroughly cleaned. Treatment is surgical [8,9]. Squamous carcinoma can supervene [10].

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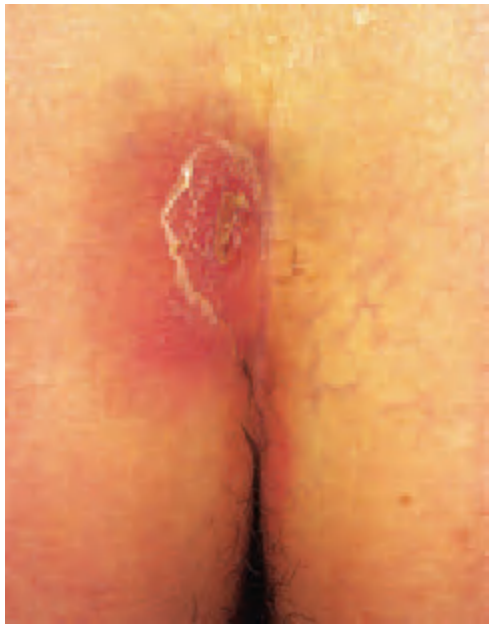

Fig. 68.41 Pilonidal sinus. (Courtesy of Dr D.A. Burns, Leicester, UK.)

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Hidradenitis suppurativa

Hidradenitis suppurativa ('chronic perianal pyoderma' in Japan) (see Chapter 27) can give rise to all degrees of inflammation and scarring. Friction and pressure accentuate the inflammatory changes that invade the fat and cause further granulomatous change extending widely over the buttocks and thighs. Persistent perineal sinuses are frequent, and deep lesions cause anal fistulae. In mild cases, only a few isolated lesions are present. Secondary bacterial invasion, often from the gut [1], is an important complicating factor. Seven cases have been associated with an oestrogen–progesterone contraceptive pill [2].

There is a clinical spectrum overlapping with chronic folliculitis (e.g. of the buttocks and 'penile acne'). In established hidradenitis, bridged comedones, folliculitis and furunculosis, deep burrowing discharging sinuses, nodules, cysts, fluctuant abscesses, scarring and fibrosis in the groins and axillae, the natal cleft and buttocks [3] may all be present. Some patients may also have conglobate acne, dissecting cellulitis and pilonidal sinus. Hidradenitis is more common in black and Mediterranean individuals. It affects the axillae preferentially in women and the perineum in men. A urethral–cutaneous fistula and phimosis have been reported [4]. Scarring from the disease and its treatment can be extensive. The morbidity of hidradenitis may be severe, interfering with sitting, sleeping, walking, defaecation and sexual activity, and responsible for depression. Disease that has persisted for more than 20 years carries a significant risk of progression to SCC [5–7] and rarely verrucous carcinoma [8].

Differential diagnosis. Hidradenitis is usually a clinical diagnosis. Swabs should be taken for bacteriological evaluation and to guide therapy, but the patient should be fully evaluated for sexually transmitted diseases should the presentation be in any way suspicious. An important differential diagnosis of acneiform disease presenting at any site is chloracne (see Chapter 43). A biopsy may be necessary to exclude carcinoma or Crohn's disease. Perineal Crohn's disease mimics hidradenitis, with its granulomatous inflammation, ulceration and fistula formation, but it is less painful. Also, the disease is absent from the axillae and it is rare for patients to be free of overt gastrointestinal symptoms. Very florid perianal disease can be seen in myeloma and leukaemia [9], and in homosexual men and in AIDS [10].

Mild or localized forms are frequently misdiagnosed as furunculosis or 'infected cysts', and confusion occurs with severe acne, developmental fistulae and lymphogranuloma venereum. The relatively painless recurrences in the same or other sites, and oblique sinuses that end in soft swollen inflamed nodules, are characteristic.

Treatment. This is challenging [11]. Small localized sinuses may be phenolized successfully, and early lesions may respond to intralesional corticosteroids. However, this treatment may have to be repeated, and recurrent or extensive lesions may require a more radical approach. Marsupialization (as with pilonidal sinuses) [12] and diathermy destruction of the affected tissue have been very successful in some cases, even those involving the scrotum. Treatment with carbon dioxide laser, with secondary intention healing, is very effective [13,14]. The use of Silastic foam dressing may facilitate healing [15]. Otherwise, plastic surgery with complete excision of all the involved skin may be required [16]. Long-term antibiotic therapy (erythromycin, flucloxacillin, ciprofloxacin, metronidazole) is often given 'blind', but is seldom of lasting value, although elimination of specific secondary invaders such as *Streptococcus milleri* [1] has given good

results. Oral prednisolone can be used alongside antibiotics to control intercurrent exacerbations. More recently, isotretinoin (1 mg/kg) for 6–8 months has been used with mixed results, but is occasionally helpful in difficult cases [17,18]. Antiandrogen therapy has yet to be evaluated.

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Crohn's disease

SYN. REGIONAL ILEITIS

It is a well-known aphorism that Crohn's disease can affect any part of the gut and its cutaneous borders from the mouth to the anus. The cutaneous manifestations of Crohn's disease are listed in Table 68.31. Perianal disease may occur in up to 75–90% of patients [7,8]. Table 68.32 lists the perianal features of Crohn's disease [9]; it includes those common to most chronic diarrhoeal illnesses such as pruritus ani, skin maceration, and erosions with secondary infection. Perianal manifestations of Crohn's disease in childhood are a major cause of morbidity, but only rarely progress in a destructive manner (Fig. 68.42) [9].

Table 68.31 The cutaneous manifestations of Crohn's disease [1–6].

Erythema nodosum
Anal and perianal lesions
Spreading ulceration of perineum and buttocks after colectomy
Skin changes around ileostomies and colostomies
Genital lesions
Balanitis, posthitis and granulomatous lymphangitis
Vulval lesions
'Sarcoid' type lesions in remote sites
Pyoderma gangrenosum
Granulomatous cheilitis
Epidermolysis bullosa acquisita
Non-specific changes resulting from malabsorption

Table 68.32 Perianal features of Crohn's disease.

Pruritus ani
Maceration
Erosion
Secondary infection
Skin tags
Fissures
Anal stenosis
Fistula-*in-ano*
Abscess
'Metastatic' granulomatous plaques

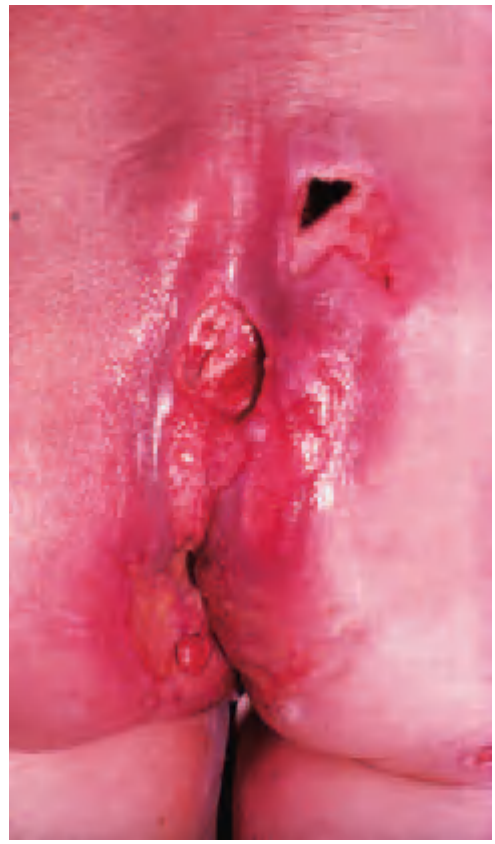

Fig. 68.42 Crohn's disease: perianal lesions. (Courtesy of Dr D.I. McCallum, Inverness, UK.)

Clinical features. The skin tags of Crohn's disease are larger, thicker and harder than ordinary tags. Deep undermined angulated fissures with cyanotic edges may fuse to form 'flying buttress' skin bridges, characterized by relative lack of pain. Fistulae are less common than fissures; they may be asymptomatic even when multiple. Pain usually means that an abscess has formed because of blockage of a fistula. Multiple external openings can be encountered all over the buttock, on the scrotum and on the thigh; a distinctive sign is the cyanotic hue of the indurated skin. Anal stenosis, faecal incontinence and carcinoma are complications [10].

Clinical diagnosis may be achieved based on symptoms, signs and investigation results (e.g. radiography and gut biopsy) consistent with Crohn's disease. Any anal lesion in a patient who is known to be suffering from Crohn's disease is likely to be perianal Crohn's [11]. Difficulty arises when the anogenital disease represents the first manifestation. Histologically positive perianal disease of all clinical types may predate frank gastrointestinal Crohn's disease by several years [12], including in children [9]. The relative lack of pain, multiplicity of lesions, oedema of skin tags and eccentricity of fissures are important pointers [11]. Biopsy of skin lesions is helpful, and sigmoidoscopy and biopsy of intestinal mucosal lesions is mandatory. Swabs should be taken and the patient fully evaluated for sexually transmitted diseases should the presentation be in any way atypical.

Differential diagnosis. The differential diagnosis includes the causes of pruritus ani and non-specific anal fissures and fistulae. Similar, although less extensive, lesions occur, but much less commonly, in ulcerative colitis, and only very rarely in diverticulitis [2]. Hidradenitis suppurativa presents with nodules, sinuses and purulence but is more painful; other sites may be involved and severe acne is often present. Similarily florid perianal disease can be seen in myeloma and leukaemia [11]. Proctitis, perianal ulceration, abscess, fissure and fistula are prevalent in homosexual men and those with HIV/AIDS [13,14]. Perineal pyoderma gangrenosum has been misdiagnosed as Crohn's disease. A solitary granulomatous nodule, with or without ulceration, carries a differential diagnosis that includes sarcoid, schistosomiasis, leishmaniasis, tuberculosis, atypical mycobacterial infection, deep fungal infection, granuloma inguinale, lymphogranuloma venereum, chancroid, amoebiasis and syphilis. Florid condylomata acuminata [15], anorectal carcinoma presenting with an ischiorectal abscess [16] and other mucocutaneous malignancies (basal cell carcinoma, Kaposi's sarcoma and amelanotic malignant melanoma) may rarely be encountered.

Treatment. The treatment of the anogenital manifestations of Crohn's disease depends to some extent on the treatment of active intestinal disease. Local measures include soaks with potassium permanganate and aluminium acetate, potent or very potent topical corticosteroid/antibiotic combinations and oral antibiotics (as for hidradenitis). A role has been advocated for long-term oral metronidazole (20 mg/kg/day in divided doses) [17,18]. Perianal abscess may respond to sulfasalazine and anal fissure to prednisolone and azathioprine [5]. The surgical philosophy is conservative [3,9]. Resection of the affected segment of bowel does not always cure the lesions or prevent their recurrence, especially at ileostomy or colostomy sites.

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Miscellaneous

Radiodermatitis is occasionally encountered following previous treatment for *in situ* or frank carcinoma or, decades ago, pruritus ani. LP involving the buttocks and perianal region is extremely irritable and may become excoriated or hypertrophic; LP must be considered in the differential diagnosis of pruritus ani and perianal fissures. Solitary involvement of the perianal skin may occur (Fig. 68.43).

Behçet's disease occasionally presents with multiple shallow ulcers and fissures of the anal margin.

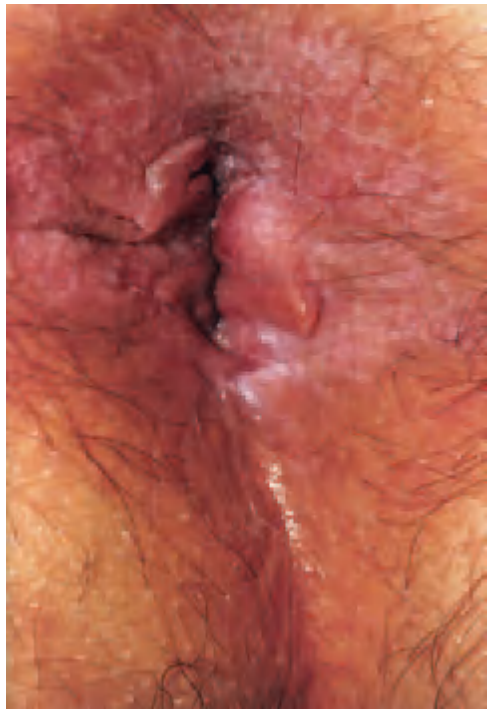

Fig. 68.43 Perianal lichen planus. (Courtesy of Dr F.A. Ive, Durham, UK.)

Calciphylaxis sometimes affects the thighs and buttocks [1–3].

Acrodermatitis enteropathica should be considered in the differential diagnosis of perianal eczema, psoriasis or candidosis in the paediatric setting, or in the presence of gastrointestinal disease causing malabsorption syndromes (e.g. Crohn's disease), extensive gastrointestinal surgery such as small intestinal bypass, malnutrition in alcoholism and recent prolonged parenteral nutrition where zinc supplementation may not have been optimal. A reticulate eczematous eruption may be found on the extensor aspects of the limbs in alcoholics but has also been reported to affect the perianal and scrotal skin [4,5]. Other deficiency diseases with some similarity to acrodermatitis enteropathica are pellagra, maple syrup urine disease and neonatal citrullinaemia.

Benign mucosal pemphigoid (cicatricial pemphigoid) [6] may affect the groin, perineum and perianal skin, and may cause anal stenosis. The drug clonidine may have been responsible in one case [7]. Pyodermite végétante can be distinguished by the histology and by immunofluorescence studies. Ulcerative colitis may be present [8].

The anus is involved in about 5% of cases of Stevens–Johnson syndrome. A connection has been recognized between epidermolysis bullosa acquisita [9] and inflammatory bowel disease, particularly Crohn's disease [10–12].

Fixed drug eruption may produce striking pigmentation. Prolonged use of potent topical corticosteroids causes a dusky erythema, atrophy or induration.

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Primary systemic cutaneous anosacral amyloid

This has a predilection for the anogenital region, particularly the sacrum, in elderly Japanese people [1–3]. Moderately pruritic pigmented macules and glossy hyperkeratotic lesions fan out in lines from the anus. There are no systemic changes. Amyloid deposits are seen in the upper reticular dermis and around hair follicles. It is thought to represent an ageing process.

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Infections

Folliculitis and furunculosis

The anogenital area, particularly the buttocks and thighs of men, can be susceptible to infection with *Staphylococcus aureus*. Severe involvement with furunculosis and abscesses suggests an overlap with hidradenitis suppurativa. Although the high temperature and humidity of this area, combined with pressure [1] and friction, encourage colonization by staphylococci, primary pyococcal infections are now uncommon in countries with cultural or acquired habits of cleanliness. The perineal carriage of staphylococci [2] may not cause local lesions in the host, but is especially important in acting as a reservoir from which

Table 68.33 Differential diagnosis of anogenital cellulitis. (After Bunker [5]. © 2004, with permission from Elsevier.)

Hidradenitis suppurativa
Crohn's disease
Staphylococcal cellulitis
Streptococcal cellulitis
Gonococcal cellulitis
Fournier's gangrene and necrotizing fasciitis
Extramammary Paget's disease
Carcinoma erysipeloides (bladder and prostate)

S. aureus may be disseminated to other sites or to eczematous lesions elsewhere. In adults, the carriage rate is of the order of 13–22%; in neonates it may be higher. Some persons are better 'dispersers' of staphylococci than others, and the organisms may remain (and even increase) after washing. The risk of dispersion of staphylococci from this site is of obvious importance in hospital operating theatres, where attempts have been made to minimize it by the provision of special clothing [3]. Nasal carriage, diabetes and immunodeficiency should be considered. Bacterial perianal infection is commonly seen in leukaemic patients [4].

Staphylococcal cellulitis

Cellulitis and abscess formation can complicate cysts, sinuses and fistulae. The differential diagnosis is given in Table 68.33.

Anorectal infection in patients with malignant disease is serious and potentially life-threatening [6]. Although some cases of anorectal cellulitis will respond to antibiotics alone, necrotizing fasciitis and Fournier's gangrene are risks. Swelling and fluctuance signifying abscess formation may develop late. It is difficult to decide on the timing of surgery. Perianal infiltration, ulceration or abscess occurs in 5% of haematological malignancies and may rarely be the presenting feature [7].

Streptococcal dermatitis/perianal cellulitis

This syndrome in children [8] probably has a corollary in adults [9]. A child may present with pruritus, painful defaecation, anal soreness and redness (without nappy/diaper rash) and satellite pustulosis of the buttocks. Examination of the anus shows a pronounced, sharply demarcated, boggy erythema and causes discomfort to the child. Rarely, there may be a systemic presentation with fever and rash [10]. It is much more common in boys, and the penis may be involved. An association with acute guttate psoriasis has been reported [11,12]. Group A β-haemolytic streptococci is the usual cause, although *S. aureus* has been retrieved from one child who also had satellite pustules on the buttocks [13]. Proctocolitis has occurred [14]. Perianal disease may be misinterpreted as sexual abuse [15]. Streptococcal infection of the upper respiratory tract in other members of the family may be found. Communal bathing has been blamed for outbreaks. Treatment is generally with systemic penicillin or topical mupirocin, or erythromycin if clinically less acute [16].

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Perianal abscess

Perianal/anorectal/ischiorectal abscess presents with painful swelling and suppuration and is commonly complicated by anal fistula. The likeliest cause of perianal abscess is infection of the anal glands but trauma (e.g. impacted fish bone), diabetes and anal cancer predispose to its development. Crohn's disease, hidradenitis, tuberculosis and *Enterobius vermicularis* [1] should be considered.

Ecthyma gangrenosum

Gram-negative organisms are seldom pathogenic unless the balance of the skin flora is grossly disturbed. *Pseudomonas aeruginosa* may be found in deep ulcers and fissures. Ecthyma gangrenosum has a predilection for the anogenital (and acral) extremities. The prognosis is poor. Ill patients with leukaemia may develop a necrotizing anorectal ulcer caused by *Pseudomonas*, presenting with severe anal

pain, anorectal ulceration and septicaemia. Anorectal ulceration may be the portal of entry of the infection or a consequence of it [2]. The mortality is high.

Thread/pinworms

Thread/pinworms can cause pruritus ani. Excoriations, eczematization and impetiginization may be present, sometimes away from the site of infestation on the buttocks and upper thighs, particularly in the younger child. However, often there are few physical signs. Perianal abscess may occur very rarely [1].

Common mycoses

Candidosis causes a bright red, glazed area, often with outlying small pustules, and may spread to the groins or natal cleft. Microscopy and culture distinguish it from other fungal infections, and from psoriasis and pyococcal infections.

The well-defined scaly circinate edge, the spread and the chronicity of *Trichophyton rubrum* infection offer clues to diagnosis, which can be confirmed by microscopy and culture. However, prior treatment with corticosteroids may disguise the appearance. The possibility of fungal infection should therefore be considered in all unusual forms of perianal dermatitis.

Necrotizing infections

A number of overlapping severe gangrenous and necrotizing diseases may affect the anorectal and perineal (and genital) skin and subcutaneous tissues. Although they may often be a complication of surgery or trauma, they are mentioned here because of the crucial importance of their early recognition and treatment (see also Chapter 27). These conditions are described under several names [3]:

1 Clostridial and non-clostridial gangrene [3–5]
2 Streptococcal cellulitis and myositis
3 Synergistic necrotizing cellulitis
4 Necrotizing fasciitis [6–8]
5 Meleney's progressive bacterial synergistic gangrene [9]
6 Synergistic gangrene [10]
7 Fournier's gangrene, etc.

Clinical features. Although middle-aged and elderly subjects are most often affected, the conditions can follow trauma in young adults, and the prognosis in the latter, given vigorous early treatment, is good [3]. They have also been described in children [11], particularly following circumcision or scalds, but sometimes after a bout of severe diarrhoea [12], or even spontaneously [13]. The problem may present as a primary perirectal abscess in the perineum (or on the scrotum or labia). Pain is generally the first symptom, and may be severe. A distinct dusky red to black spot may appear in affected tissue and is of ominous significance. Tenderness and a dusky erythema extend with extreme rapidity to involve wide areas, and all the perirectal and perineal spaces (hence the terms fasciitis and myositis). Crepitus is an important feature, as is the presence of a dark brown, turbid fluid without pus. Many patients are diabetic [3,7] or leukaemic; in these, the mortality is much higher than the overall rate of 12–25% [7]. A perianal distribution, old age and delay in treatment also greatly reduce the survival rate.

Bacteriology. Swabs should be taken from the margin of the lesion [10]. An immediate Gram stain will distinguish clostridial infections by the finding of large Gram-positive rods. *Clostridium perfringens* was the most common organism in one series [3], but other clostridia, aerobic and anaerobic streptococci, and *Pseudomonas* species [11] have all been isolated. Anaerobes may easily be missed. A wide variety of secondary organisms are commonly cultured.

Treatment. Early recognition and immediate and aggressive treatment are essential in this devastating condition. Electrolyte and fluid balance must be established, and high-dosage antibiotic therapy started without waiting for the result of culture. This will normally consist of intravenous penicillin (24–30 million units/day [3]) together with a broad-spectrum antibiotic, usually an aminoglycoside or a cephalosporin; this regimen can be modified later.

The most important single therapeutic manoeuvre is rapid and extensive débridement of all affected tissue. Other surgical procedures, such as colostomy, may also be necessary. The value of hyperbaric oxygen [14] is disputed.

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Dermatological aspects of sexually transmitted disease

Gonorrhoea can result in anal inflammation and discharge, or an oedematous perianal dermatitis with multiple fissures and erosions.

Chancroid can cause extremely painful anal lesions instead of the classic multiple soft chancres. The initial rapidly ulcerating papule of granuloma inguinale (see Chapter 27) may occur in the perianal region in homosexual males. It is soft, painless and bleeds easily on trauma. It may be hypertrophic, sclerotic or phagedenic. There is normally no regional adenopathy, but a 'pseudobubo' may be present. In the anal canal, the lesion never extends beyond the stratified epithelium and strictures do not occur, but anal stenosis or, rarely, epitheliomatous change can supervene. If undiagnosed, lymphogranuloma venereum causes widespread vegetating and scarring lesions of the genitoperineal area. The Frei and complement fixation tests distinguish it from hidradenitis suppurativa.

Syphilis (see Chapter 30) [1] is becoming more common in homosexual men. It should never be forgotten as a possible cause of anal ulceration. Anal chancres are often mistaken for fissures; at the anal margin their significance may not be appreciated. Pain on defaecation or at night may be severe if there is secondary infection of the chancre, but is often absent. The posterior midline is the site of election. Bilateral lymphadenopathy is extremely rare with other perianal ulcers. Dark-ground examination may not be diagnostic if lubricants or ointments have been used. Discharge and bleeding, fissures (especially laterally) and fistulae should also arouse suspicion of anorectal primary syphilis. Painful syphilitic proctitis in the absence of anal lesions can occur [2,3]. Moist flat condylomata lata (Fig. 68.44) can affect all anogenital intertriginous sites and the differential diagnosis includes intertrigo as well as warts, lichen planus and bowenoid papulosis. The granulomatous gumma may affect the anal area as an ulcer, a white plaque or as an atrophic scar.

Perianal viral warts (condylomata acuminata) (Fig. 68.45) occasionally occur in infants and young children, but they are normally seen in young adults, and are not always sexually transmitted. They may be extraordinarily profuse, extending into the anal canal, especially in homosexuals or in immunodeficient (congenital or acquired) subjects in whom there is also a higher risk of progression to dysplasia and frank malignancy [4]. For example, anogenital warts are common in HIV-positive males, nearly half of whom show histological signs of intraepithelial neoplasia. The clinical diagnosis of HPV is usually certain but condylomata lata (secondary syphilis), LP, molluscum contagiosum and BP enter the differential diagnosis. Solitary lesions have a wider differential diagnosis, including giant condyloma and squamous carcinoma. Biopsy should be performed if there is diagnostic doubt or if dysplasia or worse is suspected. Morphology and histology cannot distinguish virus-associated from non-virus-associated lesions; molecular techniques may be preferable but are not yet routinely available [5].

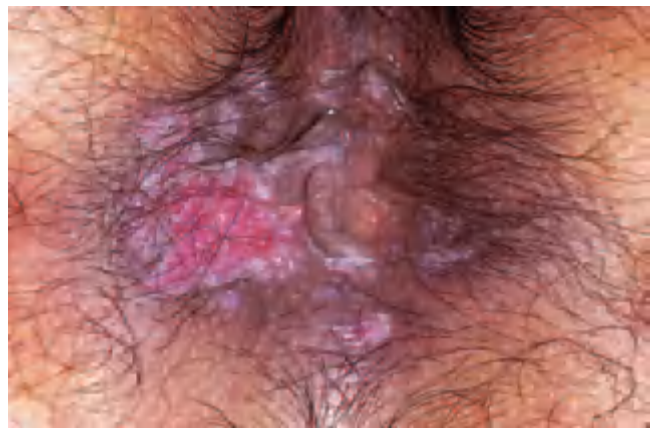

Fig. 68.44 Condylomata lata. (Courtesy of Dr S.C. Gold, London, UK.)

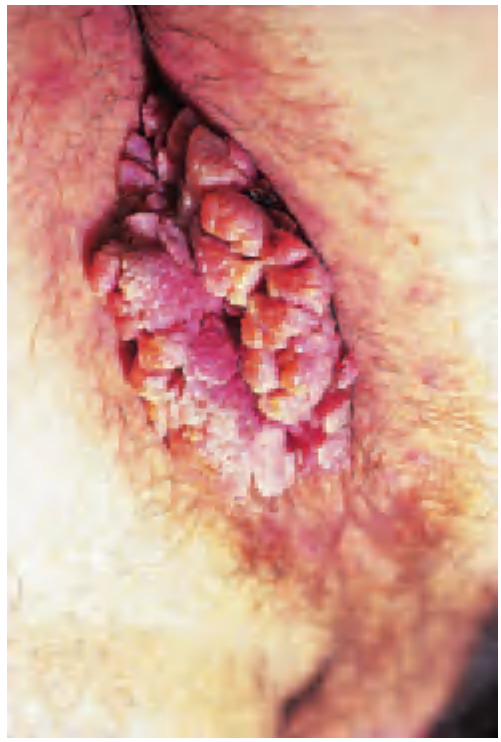

Fig. 68.45 Perianal condylomata acuminata. (Courtesy of Dr F.A. Ive, Durham, UK.)

Table 68.34 Causes of anal ulceration in HIV infection.

Idiopathic
Haemorrhoids
Fissures
Sepsis
Syphilis (chancre)
Herpes simplex
Cytomegalovirus
Kaposi's sarcoma
Non-Hodgkin's lymphoma
Squamous carcinoma

Patients with anogenital warts, and their partners, may require full STD and sometimes colorecral assessment. Anogenital HPV can be very difficult to treat.

A phenomenon of chronic erosive and verrucous herpes simplex as part of immunoreconstitution disease has been described in HIV infection [6].

Human immunodeficiency virus infection

Anal ulceration may be a feature of HIV infection; Table 68.34 lists the main causes. Biopsy with special stains and culture is mandatory.

Other problems in HIV infection, including psoriasis, warts, intraepithelial neoplasia, squamous carcinoma and KS are discussed elsewhere.

CMV has been recorded in persistent perineal ulcers in immunosuppressed patients [7]. EBV DNA has been found in epithelial cells from the anal canals of asymptomatic HIV-positive male homosexuals, indicating possible sexual transmissibility [8]. Herpes simplex, gonorrhoea and anal condylomas were commonly associated in a US study on early HIV positivity [9]. Similar findings relate to a central African group with more advanced disease [10]. The importance of primary rectal syphilis has been emphasized [2]. Amoebiasis [11] may be overlooked. Dark-ground examination, and culture and microscopy for ova, should be obligatory [12]. In the absence of organisms, if pus cells are found, a rectal biopsy is indicated. KS of the rectum has been recorded in HIV-positive males [13]. The relationship of KS to anoreceptive anal intercourse and HHV 8 is discussed in Chapter 26 [14,15].

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Miscellaneous

Pruritus ani has been attributed to erythrasma [1]. Erythrasma, present also at other sites, was found in 15 of 81 patients examined using Wood's light [1]; all were males. In infants, coxsackie A infections can cause a transient papular or papulovesicular eruption of the perianal area and buttocks. An erythematous desquamating perineal eruption occurring in the first week of the disease may be the first cutaneous feature in up to two-thirds of children with Kawasaki disease [2].

Fournier's gangrene and its differential diagnosis (Table 68.22) is discussed on pp. 68.28–68.29. Anorectal presentation is more serious than urogenital disease because the presentation may be more cryptic and there may be a longer delay in diagnosis [3].

Perianal tuberculosis (see Chapter 28) [4] is still seen where tuberculosis is common, but must always be considered, even in western Europe [5]. A primary lesion is exceptional; the accompanying unilateral lymphadenopathy is an important feature. Indolent, irregular, painful ulcers, fistulae and abscesses may be difficult to distinguish from those accompanying Crohn's disease [6]. Lupus vulgaris and verrucous tuberculosis may spread widely over the buttocks and postanal region, or assume a fungating and vegetating appearance. Tuberculosis cutis orificialis is thought to arise from autoinoculation of organisms contained in swallowed sputum from pulmonary lesions. It may occur in the immunocompromised and has been reported in association with Evans' syndrome (autoimmune haemolytic anaemia and immune

thrombocytopenia) [7]. Perineal scrofuloderma (secondary skin involvement from underlying lymph node disease) may cause diagnostic confusion [8]. Pyoderma gangrenosum, Crohn's disease, hidradenitis, neoplasia, artefact, sexually transmitted diseases, amoebiasis and deep mycoses appear in the differential diagnosis [9].

Daughter yaws (see Chapter 30), initially papules but rapidly becoming ulcerated crusted plaques, have a predilection for periorificial sites on the face and around the perineum.

The giant condyloma of Buschke–Löwenstein (see p. 68.42) is rare. It is probably HPV-related [10].

Non-genital herpes simplex (see Chapter 25) occurs frequently around the pelvic girdle. Vaccinia, usually acquired by indirect transmission [11], is now never seen, but orf still occurs occasionally [12].

Sacral herpes zoster [11] is rare but can be cryptic in presentation; when involving S2–S4 or, less commonly, the ileoinguinal segment of L1–L2, it may cause significant morbidity from acute cystitis or urinary or faecal retention [13–15]. Hospitalization and urological and colorectal assessment are required, and treatment should be with intravenous aciclovir. AIDS has presented as anogenital herpes zoster [16].

Trichosporosis is a common cause of genito-crural and perianal intertrigo in India. Symptoms are itching or burning. Accompanying the intertrigo may be scaly papules. Coexisting dermatophyte, *Candida*, trichomycosis and erythrasma infection may be found. Topical dequalinium chloride is used for treatment in India [17].

Amoebiasis (see Chapter 32) of the perianal skin [18] is usually associated with bowel infections but, where the disease is endemic, direct inoculation of abraded skin or operation wounds can occur. Abscesses and fistulae may at first be indolent and symptomless. Ulcers typically extend slowly, with serpiginous outlines, firm cord-like edges and a whitish slough [19]. Sometimes, however, progression is rapid and remorseless, until a phagedenic ulcer completely destroys the perianal and sacral tissues [20]. A black foul-smelling eschar is surrounded by a violaceous edge, resembling pyoderma gangrenosum. The patient is extremely ill. Vegetating or condyloma-like lesions of intermediate severity occur less frequently. Amoebiasis should be suspected when such a lesion occurs unexpectedly in the course of 'ulcerative colitis' or in a prolonged mild undiagnosed colitis. Cases have been described in infants [21]. Destructive [21] perianal and buttock ulceration may masquerade as squamous carcinoma; however, very rarely, concomitant carcinoma has been reported [22]. The diagnosis is made by finding the *Entamoeba* species in a biopsy specimen from the edge of a lesion (which is always secondarily infected) or by examination, while warm, of a fresh high sigmoidoscopy swab. Treatment with metronidazole may be dramatically effective, but in severe cases surgery may also be required.

Perineal granulomatous lesions are a rare manifestation of schistosomiasis (bilharziasis), which may present as pruritic papules in the genital, umbilical and perineal regions in countries where it is endemic [23,24]. It is usually preceded by rectal or intestinal symptoms. The papules and nodules may be skin-coloured, pink or brown, scattered or grouped, affecting the penis, scrotum and vulva. They can spread onto the perineum and around the anus, and may develop into soft warty vegetating lesions, but remain relatively asymptomatic. Genital lesions simulating warts have been seen in travellers returning from endemic areas [25]. Ulceration is rare and, even more rarely, concomitant carcinoma has been reported [22]. The unusual occurrence of anogenital lesions results from ova shed by worms that have entered the perineal vessels [23]. Viable or calcified ova are found in the dermis.

Larva currens caused by *Strongyloides stercoralis* commonly occurs around the anus and on the buttocks. Likewise, cutaneous larva migrans resulting from the dog hookworm *Ancylostoma brasiliense* may occur around the pelvic girdle.

Perianal histoplasmosis and blastomycosis have also been recorded. Actinomycosis has resulted in multifocal perineal and buttock ulceration in G6PD deficiency [26]. Ulcerating and vegetating lesions, often unrecognized and of long duration, have followed trauma in patients with actinomycosis [27]. Correct diagnosis depends on histological confirmation, but the yellow or red granular pus should arouse suspicion [26].

Classic lesions of scabies commonly involve the buttocks, and nodules are sometimes seen in the perineum.

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Benign tumours

The following entities are encountered in the perineal/perianal area: angiomas and angiokeratomas; basal cell papillomas may be mistaken for viral warts or BP, as may melanocytic naevi; inguinogenital epidermoid cysts may become infected; lesions containing molluscum contagiosum have been described; pilar cyst, including giant forms, is much rarer.

Haemorrhoids

Haemorrhoids/piles (Latin *pila*, a ball) are dilatations in the venous system draining the anus, mucosal prolapse or loose tethering of mucosa to the anal wall [1]. Symptoms are rectal bleeding, mucous discharge, pruritus ani and prolapse. The complications of piles are thrombosis, strangulation, ulceration, fibrosis, infection and abscess, which give rise to pain. Patients presenting with these symptoms should be assessed by a proctologist, and by proctoscopy and sigmoidoscopy. Signs depend on the presentation. Perianal skin tags from fibrosed piles are extremely common. The differential diagnosis includes distal bowel cancer, as well as naevi, Crohn's disease, KS and perianal metastases. Treatment is the domain of the colorectal surgeon and gastroenterologist.

Premalignant dermatoses and frank malignancies

The anogenital area is not exposed to solar radiation, the principal cutaneous carcinogen. Treatment of pruritus in the past with radiotherapy or tar preparations, and the use of radiotherapy for gynaecological malignancy, carry theoretical hazards and can occasionally be incriminated in carcinogenesis. However, they do not appear to have influenced greatly the frequency of perineal tumours. Post-granulomatous scarring is an important background to perianal malignancy in some parts of the world, and other chronic inflammatory processes, such as LS, are a potential hazard. There are cases where condylomata acuminata have preceded SCC of the anal or perianal skin [2,3] and HPV has become a major suspect in the precancerous process.

Porokeratosis

Genital porokeratosis of Mibelli is rare but classic lesions have been found on the penis, scrotum and in the natal cleft. Ulceration may occur [4]. Porokeratosis may be confused with psoriasis, Bowen's disease, granuloma annulare or LP. Histopathology of a biopsy confirms the diagnosis [5]. Topical 5-fluorouracil can be used [6].

Anal intraepithelial neoplasia

Anal intraepithelial neoplasia (AIN) describes full-thickness dysplasia of the anus and perianal skin [7]. It can present relatively asymptomatically as red, shiny or scaly patches like Bowen's disease, or as warty lesions like BP. AIN is frequently associated with homosexuality, anal warts, HPV and HIV, although it is not a prominent feature of other conditions involving immunosuppression. Women with anogenital Bowen's disease have an increased risk of intraepithelial neoplasia or invasive malignancy elsewhere in the genital tract [8,9], and a full gynaecological examination is thus obligatory in such cases. In AIDS, the overall risk of progression of AIN associated with HPV to invasive squamous carcinoma is low [10]. Immunoreconstitution with highly active antiretroviral treatment (HAART) may not achieve regression of AIN [11]. Routine screening of the HIV-positive patient with anal cytology is advocated [11]. Treatment options are similar to those for PIN. Relapse is common. Expert proctological advice should be sought.

Carcinoma of the anus

Anogenital squamous carcinoma is sometimes called epidermoid carcinoma. Fifty-six per cent of all anal carcinomas are of the squamous variety [12]. They are slightly more common in women, but seem to be more aggressive in men [13]. In Denmark, the incidence of anal carcinoma has tripled since 1960 to 0.74 cases per 100 000 population [14].

Although associations with smoking, cervical intraepithelial dysplasia and changing sexual habits, including homosexual anal intercourse, have been postulated

[14,15] and coexistent Crohn's disease has been said to be associated with a 10-fold increase in anal carcinoma [16], the aetiology is not clearly understood. HPV is implicated [17,18], especially in verrucous carcinoma (see below) [19]. Anal carcinoma is often associated with a history of anogenital warts. More than 90% of anogenital condylomata contain HPV 6 or 11, although these subtypes are not associated with cancer, and it is rare for condylomata to contain HPV 16, which has a well-documented association with anal carcinoma. Homosexual men have a higher incidence of both perianal warts and anal carcinoma (both *in situ* and invasive), and this may be related to receptive anal intercourse [15], and HPV as well as other sexually transmitted diseases such as gonorrhoea, herpes simplex and *Chlamydia trachomatis* infection [20]. These infections are also risk factors for anal carcinoma in heterosexual men and women, as is cigarette smoking [21]. A role for seminal fluid prostaglandins in homosexual anal cancer has been proposed [22]. Immunosuppression, including by HIV infection, is a risk factor for AIN and anal cancer [23]. A case of Peutz–Jeghers syndrome associated with anal squamous carcinoma has been reported [24].

Diagnosis can present difficulties. Symptoms may include bleeding, pain, presence of a mass and change in bowel habit. Examination will reveal a hard mass that may be flat, raised or polypoid [25]. Squamous carcinoma should be suspected in all nodulo-ulcerative anal and perianal disease, especially in the context of LS, LP, hidradenitis suppurativa, intraepithelial neoplasia and immunocompromise.

Regarding the differential diagnosis [26], it must be appreciated that anal carcinoma often presents with similar symptoms to benign anal lesions such as piles and fissures (pruritus, discomfort or pain, and bleeding). The most common tumours of the anal margin are viral warts, which are distinguished by their multiplicity, their lack of induration and ulceration, and their rapid evolution. Rarely, these may give rise to anal carcinoma [27]. Syphilitic condylomas are also multiple and not indurated. A syphilitic chancre of the anal margin or canal may be more easily mistaken for carcinoma. Amoebiasis and tuberculosis must also be considered. The differential diagnosis includes the manifestations of intraepithelial neoplasia (and the differential diagnosis of these), erosive or ulcerative sexually transmitted disease, basal cell carcinoma, KS, hidradenitis suppurativa, Crohn's disease, pyoderma gangrenosum and artefact. The differential diagnosis also includes ischiorectal or perianal abscess [28–30]. Colorectal assessment should be sought. Proctoscopy and sigmoidoscopy are necessary to exclude anorectal cancer [28–30].

An important consideration in the management of anal carcinoma is the preservation of sphincter function, and this frequently involves combined radiotherapy and chemotherapy [31,32]. Surgical excision of the tumour, and of the inguinal lymph nodes when these are involved, is the treatment of choice. For small well-differentiated tumours, particularly adenocarcinomas, a local excision and repair is ideal. Small squamous carcinomas may respond well to radiotherapy.

Lymphatic or haematogenous dissemination of anogenital cancer dictates individualized multidisciplinary management. The management of ilioinguinal lymphadenopathy is controversial [33–35].

The prognosis for anal carcinoma is variable [32].

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Extramammary Paget's disease (see Chapter 36)

Seventy-three per cent of cases of extramammary Paget's disease (EMPD) present as pruritus ani [1]. The association with an underlying malignancy is variable. Two reviews of the literature revealed only a 25% association [2,3]. Despite this, a search for a primary adenocarcinoma of underlying secretory glands should be carried out in perianal EMPD [4]. In some cases, the primary tumour is an anorectal, or even more distant, carcinoma [5,6]. The primary tumour and the Paget's cells in the epidermis are usually mucus secreting. Electron microscopy has shown the Paget's cells to be squamous in character in some patients, but more recent immunohistochemical and enzyme histochemical methods have demonstrated a close relationship between Paget's cells and sweat gland epithelial cells [7]. Anorectal carcinomas may arise from rectal mucosa or from the intramuscular glands. In the latter case, the malignant cells may track to the buttock through the ischiorectal fossa, and the Paget's plaque may begin at a distance from the anal margin, rather like an ischiorectal abscess. Topographical studies have shown that the plaque of Paget's disease is much larger than the visible lesion [8]. Any attempt at removal must be radical and histologically controlled [9].

Extensive surgery in conjunction with photodynamic therapy involving infusion of dihaematoporphyrin and an argon pumped dye laser has been effective in curing a patient with previous postoperative recurrences [10].

The pattern of the intramuscular glands and of the wide range of tumours that arise from them ('cloacogenic' carcinoma) resembles genitourinary rather than intestinal endothelium [11]. The carcinoma may spread, either to involve the anorectal mucosa, or through the perianal tissue to produce a chronic fistula-*in-ano* [12]. It may on occasion mimic a basal cell carcinoma both in clinical and histological appearance [13].

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Miscellaneous

Extramucosal anorectal carcinoma presents as an inflammatory rather than a malignant condition and so is not biopsied (or not biopsied deeply) and the diagnosis is missed or delayed; there are many cases in the literature of cancers arising from anal glands adjacent to the anorectal wall and not emergent from the mucosa [1]. Cloacogenic carcinoma constitutes only 2–3% of anorectal cancer, but may behave aggressively [2]. It derives from remnants of the cloacal membrane proximal to the pectinate line where there is an area of transitional mucosa (between keratinized and non-keratinized squamous epithelium) penetrated by the anal glands. Most rectal cancer is adenocarcinoma (columnar epithelium).

Although basal cell carcinoma is the most common type of skin cancer, it is rare in the anogenital area, but over 100 cases have been reported [3,4]. Small basal cell carcinomas may respond well to irradiation.

Anorectal melanoma accounts for only 1% of all tumours of this area [5]; it may occur concomitantly with melanosis of the gastrointestinal tract [6].

Anogenital KS is essentially an HIV-related problem.

Fibrosarcoma, haemangiopericytoma, leiomyosarcoma, malignant fibrous histiocytoma, epithelioid sarcoma, dermatofibrosarcoma protuberans and spindle cell sarcoma may occur, presenting as painful or painless nodules, masses or swellings [7]. Other rarities include Merkel cell carcinoma [8], malignant eccrine poroma [9] and malignant schwannoma [7,10].

Non-Hodgkin's lymphoma of the perianal area has been described in HIV/AIDS [11].

Perianal infiltration, ulceration or abscess occurs in 5% of haematological malignancies [12]. Chronic lymphocytic leukaemia has presented as a painless firm white mass at the anal orifice, associated with weight loss and inguinal lymphadenopathy [13]. Perianal ulceration and suppuration have been reported as the presenting manifestations of primary lymphoma of the anus [14].

Perineal/perianal metastases from transitional cell carcinoma of the distal urethra [15], from rectal carcinoma [16] and from epidermoid anal canal carcinoma [17] have occurred. Carcinoma erysipeloides has been observed in the perineum and on the thigh in carcinoma of the bladder and prostate [18].

A periorificial form of Langerhans' cell histiocytosis/eosinophilic granuloma may cause ulcerating and vegetating lesions within the anal canal and in the perianal skin [19].

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Anal manifestations of intestinal disease

These have been well documented [1]. Although they are usually non-specific, the particular skin manifestations of tuberculosis, amoebiasis, schistosomiasis and Crohn's disease may lead to diagnosis of the underlying disease by their typical histology.

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Miscellaneous

Effects of topical corticosteroids

The prolonged use of potent topical corticosteroids for inflammatory conditions of the groins or perianal area can produce misleading appearances. Tinea incognito [1] is well recognized, but a persistent, deep, livid erythema of the perianal skin may not be regarded as primarily infective. Striae occur readily on the thighs. Multiple perianal comedones followed the application of a topical corticosteroid for 3 years [2]. 'Infantile gluteal granuloma' [3] (see Chapter 14), usually affecting infants of 4–6 months, may also occur in incontinent elderly patients [4].

Chronic perianal pain and the 'perineal syndrome'

A number of names have been given to sensations of pain localized to the anogenital region in the absence of evident organic cause [5,6]. Proctalgia fugax affects young adult males, and occurs chiefly at night in the form of a sudden cramp-like pain, which resolves in a few minutes. 'Coccygodynia', 'descending perineum syndrome' and 'chronic idiopathic anal pain' chiefly affect females. The pain is described as dull and throbbing. In 35 such patients, it was noted that the pain was precipitated by sitting, and that these three conditions differed from proctalgia fugax [5]. Electrophysiological studies gave variable results. There was a high incidence of previous sciatica and damage to the pelvic floor musculature. Treatment was disappointing. Rarely, sacral cysts and even chordoma can present with this symptomatology.

Such patients will present to surgeons or gynaecologists; however, dermatologists may be confronted by a similar problem in which a patient complains of short-lived episodes of intense burning, which may be accompanied by sweating, limited to the perineum or occasionally the scrotum. Attacks occur without warning, but may be brought about by a full rectum. In one patient, the attacks were severe enough to cause him to stop walking for some minutes. The patients tend to be stressed individuals, as are those with proctalgia fugax [6]. The skin is entirely normal.

The mechanism is unknown. Two patients appeared to have been helped by propantheline, suggesting a cholinergic mechanism [7]. However, the condition may also fall into the group of 'dermatological non-disease' [8],

in which the perineum was affected in eight out of 24 patients. The condition has also been reported in children suffering from intrafamilial stresses [9] (see also pp. 68.48 and 68.82).

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Umbilical dermatology

Introduction

The umbilicus is considered here for convenience. Although the umbilicus is not strictly part of the genital apparatus, its evolution and connections link it to the pelvic region.

Structure and function

At birth, the umbilical cord contains two arteries and a vein, the rudimentary arachus (allantois) and the vitelline (omphalomesenteric) duct, enveloped in Wharton's jelly. After separation and retraction of the stump, an umbilicus of variable depth is formed. Persistence of the urachal or vitelline ducts at this 'carrefour embryologique' may cause trouble in early or later life. A deeply retracted umbilicus may be the site of infection or foreign bodies.

Congenital and developmental abnormalities [1]

These are all rare, more common in males, and usually brought about by failure of obliteration of the omphalomesenteric duct or urachus. They present as fistulae, cysts or polypoid tumours.

Patent urachal duct

The umbilical opening is lined by skin or a pouting mucous membrane. Urine may be seen to escape from it, particularly in the elderly, when an obstruction to micturition exists. The condition is rare.

Persistent vitelline duct and polyp

If a connection with the intestine persists, it may become inflamed or cause a faecal umbilical discharge. More commonly, the remains of the duct give rise to a polyp in later life [2]. This may be accompanied by intermittent bleeding or a more persistent mucoid discharge, sometimes profuse. A symptomless sterile umbilical discharge should always arouse suspicion. The histopathological features are those of intestinal mucosa. It may be mistaken for a pyogenic granuloma [3].

Periumbilical 'choristia'

Under this title (meaning dysgenetic translocation of tissue), Bellone *et al*. [4] described extending crusted erythematous periumbilical plaques, in which islands of intestinal mucosal cells were found in the epidermis.

Omphalocele

This form of abdominal hernia appears to be more common in African people. In 5 years in Ibadan, 33 cases were seen [5]. The minor form is caused by herniation of the umbilical cord; a major form is probably because of a fault of embryonic folding of the fetus.

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Trauma and artefact

The umbilicus in the newborn

Haemorrhages may occur from slipped ligatures. The cord normally separates within a week of birth, and the raw surface is epithelialized by day 15. During this time, the umbilicus is prone to infection, especially in maternity hospitals and nurseries. Impetigo (pemphigus neonatorum) or, rarely, more severe bacterial infections may occur (see below). The 'absent navel' syndrome has been described as a sign of dystrophic epidermolysis bullosa [1].

Talc granuloma

This lesion, which is probably more frequent than is recognized, occurs in infants and very young children. It is

distinguished histologically from a pyogenic granuloma (on which it may supervene) by the doubly refractile talc crystals [2].

Pyogenic granuloma

This is a dull-red fleshy polypoid lesion, often pedunculated. Bleeding readily takes place from trauma. If it occurs early in life, it may be confused with a capillary haemangioma.

Ileo-umbilical fistula

This may follow laparotomy for Crohn's disease, or may rarely occur spontaneously [3].

Omphalith

In deeply set umbilici, an accumulation of sebum and keratin may lead to the gradual formation of a hard stone-like mass, which may remain unnoticed for many years until discovered accidentally or revealed by secondary infection or ulceration.

'Spontaneous gangrene'

This can occur without catheterization, possibly owing to minor trauma to the umbilicus [4]. Very rarely, the bladder and kidney may also be involved.

Unilateral skin necrosis of the buttock has been reported following indwelling umbilical artery catheterization [4–6], probably caused by thrombosis leading to occlusion of the inferior gluteal artery. A similar case was caused by misdirection of the tip of the arterial catheter [7].

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Inflammatory dermatoses

Eczematous conditions and psoriasis

Allergic contact dermatitis is usually brought about by medicaments. Irritant dermatitis from soap and quaternary ammonium compounds also occurs. Psoriasis commonly involves the umbilicus.

Miscellaneous

A pilonidal sinus may occur [1]. Granulomas [2] may present as such, or with an associated discharge, infection, bleeding or profuse sterile purulent exudate. The umbilicus is not infrequently involved in bullous and cicatricial pemphigoid; it may be the site of presentation of the latter (see Chapter 41).

Perforating pseudoxanthoma elasticum occurs in the umbilicus, and was the only site involved in six obese multiparous American black females [3]. It is only rarely associated with systemic problems [4,5].

Pregnancy, Addison's disease and other pigmentary disorders increase the pre-existing pigmentation. Acanthosis nigricans causes acanthotic and papillomatous lesions in the perineum. Periumbilical staining (Cullen's sign) occurs in acute pancreatitis, and occasionally in ruptured ectopic pregnancy or with duodenal ulcer perforation [6].

Umbilical haemorrhage has been described as a complication of cirrhosis following gross ulceration of the umbilical vein [7].

Infections

Infection of the umbilicus in the newborn used to carry a high mortality. It still occurs in some countries. A number of bacterial organisms may be responsible, but staphylococcal, *Pseudomonas* and clostridial species [8] are the most important. Minor forms consist of oozing, crusting and cellulitis, but a spreading oedematous erythema, progressing to necrotizing fasciitis, is of very serious import. Septicaemia and its complications may supervene [9]. At any time in later life, but usually after middle age, the umbilicus may be the seat of intertrigo or candidosis. This is more common in the obese or in those with poor personal hygiene. Genital and perianal warts can occasionally be associated with similar lesions within the umbilicus [10]. Foreign bodies, inserted by children or psychotics, may be overlooked as a cause of purulent infection in a deeply set umbilicus. The periumbilical skin is a common site of schistosomiasis when it affects the skin [11]. Disseminated strongyloidiasis has presented as periumbilical purpura [12].

Tumours and implantations

The umbilicus is a site of implantation of endometriomas [13], which may clinically resemble melanomas. A unique case of postoperative endosalpingosis has also been reported [14]. Colonic mucosa was implanted in an infant, after colostomy for Hirschsprung's disease [15]. A single case of carcinoid of the umbilicus has been noted [16]. Paget's disease has also been recorded [17,18]. Skin metastases from neoplasms of the digestive tract occurred in

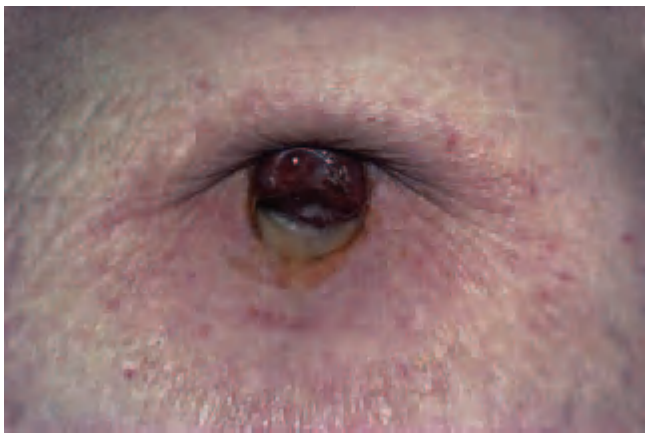

Fig. 68.46 'Sister Joseph's nodule'. (Courtesy of Dr J. Marks, Newcastle-upon-Tyne, UK.)

only 3% of 2187 cases [19], but the umbilicus is a characteristic site, especially for cancer of the stomach (Sister Joseph's nodule) (Fig. 68.46) [20], which was the primary source in 33 out of 40 cases [20]. The ovary, uterus and colon are responsible for most of the others [21–23], although the pancreas has also been a rare primary site [24]. A leiomyosarcoma of the small intestinal wall has presented in this way, as has a malignant peritoneal mesothelioma [25,26]. The lesions usually present as firm irregular nodules, but can occasionally infiltrate diffusely, or ulcerate and produce a fetid discharge. Such metastases were the presenting sign in 18 out of 40 cases, and were a major diagnostic feature in 28 cases [27]. The prognosis is always poor, but not entirely hopeless [28]. Histological identification of the site of the primary tumour may be difficult, and proved possible in only 21 of 85 cases [29,30]. Fine-needle aspiration of the nodule is not particularly helpful in reaching a diagnosis [30]. CT and surgical intervention are obligatory, because it may represent the earliest and only metastasis [23].

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Chapter 69

Racial Influences on Skin Disease

D.J. Gawkrodger

Definition and classification of race

The concept of race was first developed in the 18th century as an arbitrary classification to help understand evolution and human variation [1]. The division of our species *Homo sapiens* into 'races' is to some extent artificial, given that the species shows a continuous variability of characteristics and all humans are apparently derived from common ancestors (see Chapter 2). However, there are obviously differences between groups of humans that, in the present context, have an influence on the appearance and susceptibility to disease. The classification into racial groups therefore allows an examination of the genetic and environmental influences on human morphology and on disease.

Definitions

Many definitions are unsatisfactory. A race has been defined as 'a group united by heredity', or 'a major segment of a species' or 'a breeding population' [2]. It can also be regarded as 'one of the divisions of humankind as differentiated by physical characteristics' [1].

Scientifically, race is a matter of genetic variation. A definition that takes this into account is that of Boyd, who defined race as 'a population which differs significantly from other populations in regard to the frequency of one or more of the genes it possesses' [3]. Even this gives considerable latitude to defining quite a small subgroup as a 'race'.

Ethnicity

Another concept to consider is that of ethnicity. This is different from race, but equally difficult to define. Ethnicity can be regarded as a 'people or tribe' and implies shared origins or social background, shared cultural traditions that are maintained between generations and, often, a common language or religion [1,4,5]. One or more of these things leads to a sense of identity as a group.

Racial origins

Little is known about how the races originally differentiated and why they assumed their own characteristics. Conventional theory outlines that a change in gene frequency can occur due to mixture (with other races), mutation, natural selection and genetic drift (i.e. the accidental loss of a gene from the communal pool) [6]. It is assumed that some differences, such as skin pigmentation, are an adaptation to environmental conditions, although often it is still unclear as to exactly what advantage is conferred. Migrations of populations over the last few thousand years have meant that in certain places there has long been

an admixture of genes. For example, many invaders who have swept over Europe in the last 2000 years, including Romans, Celts, Slavs and Moors, have left a genetic legacy behind them. In view of this, it is difficult to accept the concept of a 'pure' race. Isolated groups such as the Australian aborigines, who are thought to have migrated from the South Pacific Islands, may not have had much intermixture of genes from other races until recent times.

No racial group is characterized by a completely distinctive genetic make-up [7]. There is considerable genetic variation within racial groups and sharing of genetic characteristics between them.

Classification of races

In the past, classifications have relied on various physical characteristics such as stature, cephalic index, nasal index, prognathism, capacity of the skull, hair texture, hairiness, skin colour, hair and eye colour, and other special traits such as the epicanthic fold of the eyelid (a Mongoloid feature) or steatopygia (a heavy deposit of fat in the buttocks, seen in Bushmen and Hottentot women) [8]. A satisfactory classification must take most of these factors into account. There are three main divisions—namely, Mongoloid, black African and Caucasoid—which account for over 90% of the world's population [8]. The remaining groups, grouped together by Coon [9] as the Australoid and Capoid races, occupy a doubtful position, as they frequently show some features of the other races. These main races broadly show a geographical grouping. Within each 'geographical' race, it is possible to define 'local' races and so on. A convenient division of the geographical races, albeit with some reservations, is as follows [8–10]:

1 Australoid: Australian aborigines, Melanesians, Papuans and Negritos.
2 Capoid: Bushmen and Hottentots.
3 Caucasoids: Europeans, peoples of the Mediterranean, Middle East and most of the Indian subcontinent, and the Ainu of Japan.
4 Mongoloids: peoples of East Asia, Indonesia and Polynesia, native Americans and Eskimos.
5 Negroids: black people and pygmies of Africa.

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Characteristics and variations between racial groups

There is a considerable overlap of features between the racial groups; for example, not all black Africans have tightly curled hair and not all Caucasoids have a lightly pigmented skin. Some characteristics may show considerable variation within a race—for example, head shape for Caucasoids is very variable, but other features are much more constant; for example, straight, black hair is almost universal in Mongoloids.

Australoids. Australian aborigines show some black African features such as black skin, a broad nose and prognathism, but their hirsutism, full beards and wavy hair are more Caucasoid. In addition, they have heavy eyebrow ridges [1–3].

Capoids. Bushmen and Hottentots show mainly black African characteristics, but some of their features are possibly Caucasoid (e.g. thin lips) or Mongoloid (e.g. a type of epicanthic fold) [1,4,5].

Caucasoids. There are at least four Caucasoid subraces extending from Europe, the Mediterranean and North Africa across to the Indian subcontinent. All show wavy hair and abundant facial and body hair. The skin colour is fair to brown and the nose is usually narrow. The Ainu of Japan are classified as Caucasoids, mainly because of their heavy body hair, curly scalp and beard hair and European-like facial features [1,4,5].

Mongoloids. This group extends through the extremes of climatic conditions, from the extreme north (Eskimos) to the equator (Malaysian types) and includes the Chinese and the native Americans in North and South America. Body hair is scanty and scalp hair is straight and black [2,3].

Negroids. Originally confined to Africa. The main characteristics are dark pigmentation, tightly curled hair and a broad nose [4,5].

Jews. Jews, on the whole, are not a race but a cultural community. They usually approximate genetically to the community in which they live [2,5]. However, certain genes are more frequent in certain Jewish communities than in the surrounding population.

The black people of North America are regarded by some as a local race [6]. A study of blood groups in American

blacks has revealed the following admixture of Caucasoid genes: in Oakland (California) 22%, in Detroit 26%, in New York 19%, in Charleston 4% [3]. Some also may have native American genes [4]. Many of the studies on dermatology in 'Negroids' have been done on black Americans and hence may not be strictly applicable for all black Africans.

There is now a tendency in the USA and elsewhere for individuals with any degree of black African descent to adopt the term 'black'. This has come about because of a new consciousness by this group of a shared identity. In some places, the term 'black' has been more widely used and may be implied to include some darkly skinned Caucasoids, such as Mediterranean or Indian people [7]. Quite often, the description 'Afro-Caribbean' is used and, in North America, recently there has been a tendency to use 'African American'. The term 'black African' will therefore often be used to avoid any confusion about which group is being referred to. The terms Australoid, Mongoloid and Caucasoid will also be used to describe racial groups.

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Ethnic groups

Some groups of humans do not fit easily into a race, for example pygmies, but ethnicity creates a new category for each group [1,2]. Ethnicity is a social phenomenon with imprecise and fluid boundaries. It is often used, incorrectly, as interchangeable with 'race' [3]. Broad ethnic divisions, for instance into Asian or Afro-Caribbean, may have limited value due to the great diversity of cultural and other variations within the groups. Nonetheless, because of the association with social and cultural factors, ethnicity often has a bearing on disease.

A current recommendation is that, in describing disease or characteristics in a racial or ethnic group, the most precise description possible is given for that group [4]. This will be followed when appropriate, but where it seems desirable to look at racial characteristics more generally, the broad racial groupings will be applied.

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Racial variations in the structure and function of the skin

The degree of pigmentation is one of the most obvious and immediate factors in distinguishing the main geographical races. Other differences in the structure and function of the skin are less obvious and not so well studied, but are of some importance [1].

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Pigmentation

Variation

Skin colour depends largely on the content and distribution of melanin in the epidermis. In Caucasoids, the constitutive skin colour (i.e. the amount of melanin pigmentation in the absence of sun exposure) is darkest on the upper thigh and lightest on the lumbar area, whereas in black Africans the abdomen is darkest, although the lumbar area is also the lightest [1]. Males are normally darker than females. In general, the geographical distribution of the intensity of racial pigmentation correlates with the areas of greatest sun exposure, although there are anomalies such as the Tasmanian Australoids, who were dark although they lived in a temperate latitude, and native Americans (Mongoloids), who have a similar pigmentation across the whole continent of North America.

Melanosomes

The density of melanocytes differs between various parts of the body [2] and is similar in most races, although melanocytes may be more numerous in the Australian aborigine [3]. There are differences in the size, distribution and shape of melanosomes. In Caucasoids, the melanosomes are small and aggregated in groups of three or more within a membrane in the keratinocyte [4] and are broken up by lysosomal enzymes before reaching the stratum corneum [5]. In black Africans and Australoids, the melanosomes are larger, distributed singly within keratinocytes, and persist up to the stratum corneum.

Inheritance

Skin colour is continuously variable and its inheritance is

complex. Over the last few years, mutations have been found in redheaded people, in the melanocortin 1 receptor (MCR1), for which the ligand is α-melanocyte-stimulating hormone, that lead to a shift from eumelanin to phaeomelanin production [6]. Between races, there is allelic diversity at the MCR1 and this is greater in pale non-African populations [7]. The exact interpretation of this is still to be resolved.

Physiological effects of skin pigmentation

The minimal erythema dose in black African skin is about 33 times that for Caucasoid [4]. Obviously, a pigmented skin protects against sunlight and particularly against sunburn and skin cancer. However, it seems doubtful that protection against skin cancer conveys an evolutionary advantage, as under 'natural' conditions survival is unlikely to be affected. According to Wasserman [8,9], racial pigmentation is a secondary phenomenon, related to resistance to infection. The disadvantages of a pigmented skin are increased heat absorption and reduced vitamin D synthesis. Black Africans absorb 30% more heat than Caucasoids, although this is partially offset by more efficient sweating [10,11]. Ultraviolet B radiation at low dose enhances natural killer cell activity in black individuals but not in white subjects, suggesting increased immunological resistance to disorders such as photoinduced skin cancer [12].

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Hair

Variations in hair depend on a wide range of genetically controlled factors, both between and within races [1]. Hair form is inherited separately from skin colour, and of the two is the more dominant.

Hair forms

Hair form depends on the three-dimensional structure of the hair shaft. There are broadly four hair types—straight, wavy, helical and spiral [2,3]. The helical forms coil with a constant diameter. Spiral forms coil with a decreasing diameter outwards; the extreme of this is 'peppercorn' hair, which is tightly curled and shows multiple kinks [4]. Hair that is elliptical in cross-section is curly, whereas round hair is straight.

Mongoloid hair is usually straight, circular in diameter, and with the largest diameter of all the races. The hair in black Africans and Capoids tends to be short, helical or spiral, flattened or elliptical in cross-section, and midway between the Mongoloid and Caucasoid in thickness. Spiral hair is produced by hair follicles that are curved and upwardly convex towards the epidermis. Black African hair tends to be drier and more brittle than the hair of other races, probably due in part to its intrinsic properties [5]. Hair density in black Africans is less than in Caucasoids (mean ± SD 190 ± 40; 227 ± 55 hairs/cm^2) and hair growth is slower (256 ± 44; 396 ± 55 μm/day) [6]. Telogen counts are higher in black Africans than in Caucasoids, although this contrasts with the lesser degree and later onset of androgenetic hair loss observed [6].

In Caucasoids, the hair is variable and may be straight, wavy, or helical and round or oval in cross-section. It tends to be the thinnest in diameter of all the races. Despite these variations for scalp hair, beard, pubic and eyelash hair is elliptical in all races. The morphology and chemical composition of hair is similar in all races [7].

Hair colour

Mongoloids, black Africans, Capoids and Australoids have hair that is predominantly black, although it may be red in colour. Caucasoid hair is widely variable: in northern Europe it tends to be blond, in southern and eastern Europe it is commonly black [8]. However, blond hair may be found in North Africa and the Middle East, and is even seen in some Australoids. Greying of the hair starts on average in the third decade in Caucasoids, and in the fourth decade in black Africans. Caucasoids show more balding over the vertex than do black Africans [9].

Body hair

Caucasoids have earlier and greater axillary and beard growth than Mongoloids [10] and more extensive male secondary sexual hair. In general, Mongoloids have less body hair than Caucasoids, with black Africans and Capoids occupying an intermediate position.

Selective advantage of hair forms

Any evolutionary advantage conferred by the different hair forms is unclear. Short, curly hair facilitates evaporation of sweat, but thick wavy hair provides a greater degree of physical protection. Hair, especially on the scalp, protects against ultraviolet radiation.

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Sweat glands

Eccrine glands

There is little or no difference in the sweating ability of black Africans in comparison with Caucasoids [1]. A study in the Bantu did show a greater number of sweat glands per unit area than in European Caucasoids [2], but such changes are now thought to be due to adaptation to climatic factors [3]. Increased sweating is known to be accompanied by hypertrophy of the sweat glands [4]. Indeed, in Australoids, sweat glands were noted to be larger but not more numerous than in Caucasoids [1].

Keratosis punctata, a hyperkeratosis of the acrosyringeal orifice seen on the palmar creases, is found in 1–2% of black Africans and in less than 0.1% of Latin Americans, but it is not seen in European or Middle Eastern Caucasoids [5].

Apocrine glands

An early paper mentions that apocrine glands are more numerous in black African skin than in Caucasoid skin [6], but the variation in the distribution of apocrine glands between individuals is so great [7] that it is difficult to place much emphasis on this report.

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Sebaceous glands

Black African skin showed no consistent difference in sebaceous gland activity as compared with Caucasoid skin [1]. There have been no substantial studies on the comparative number of sebaceous glands in the different races.

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The epidermis

Comparative studies have been performed on black African and Caucasoid epidermis. The stratum corneum in both has an equal thickness, although in black skin there are more cell layers and it requires more tape strips to remove it than Caucasoid stratum corneum [1]. The stratum corneum in black subjects seems to show greater intracellular cohesion than in Caucasoids. It has a higher lipid content [2] and an increased electrical resistance [3]. There is no difference in corneocyte surface area between Caucasoids, Mongoloids and black Africans, but desquamation was up to 2.5 times greater from black skin, compared with the other two races [4]. Recently, it has been found that quantities of cerumides in the stratum corneum are lower in black Africans than in Caucasoids [5]. The composition of ear wax (cerumen) varies between different races: in black Africans and Caucasoids, it is honey-coloured, wet and sticky; in Mongoloids, it is grey, dry and brittle [6].

Not surprisingly, black African epidermis is more effective at blocking the transmission of ultraviolet radiation, transmitting only 7.4% of UVB as compared to 29.4% for Caucasoid epidermis [7]. Black African skin shows a higher transepidermal water loss than Caucasoid [8]; this is thought to be due to differences in thermoregulation and in the stratum corneum lipids. Some substances do not penetrate black skin as well as Caucasoid, but this is not universally the case [9].

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The dermis

Black African skin may be slightly more extensible than Caucasoid [1], although the difference is small. The vasodilatory response after exposure to nicotinate is reduced in black Africans compared with Caucasoids, and hyperaemia after vasoconstrictive stimuli may be different [1,2].

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Peripheral vascular responses to cold

Eskimos (Mongoloids) are able to maintain a higher hand blood flow than Caucasoids under identically cold conditions [1]. At –12°C, the finger temperature in black Africans fell more rapidly (and the metabolic rate rose less rapidly) than in Caucasoids under similar conditions [2]. The extent to which these observations represent physiological adaptations, rather than significant interracial differences, is not known.

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Common diseases that show racially dependent variations

Many dermatoses manifest themselves similarly in the different races, but not infrequently—due to differences in pigmentation, hair or other factors—the appearance of a disorder varies depending on the racial constitution of the individual. It is not intended here to provide a comprehensive list of every possible racially influenced dermatosis, but rather to select the most important differences, especially for the commonest conditions.

Dermatoses that in white Caucasoid skin appear red or brown appear black, grey or purple in pigmented skin. Furthermore, any pigmentation may mask an erythematous reaction. Inflammation in pigmented skin may provoke reactions of a hyperpigmentary or hypopigmentary nature that persist after the initiating eruption has faded [1]. These pigmentary reactions may be of greater concern to the patient than the eruption itself and are often the reason why medical help is sought. Pigmented skin may have an inherent tendency to show reaction patterns that are different from those seen in white Caucasoid skin. For example, follicular, papular and annular patterns are seen more frequently in Afro-Caribbean skin than in Caucasoid [1].

There are few data on the frequency with which people of different races attend a dermatologist. In an office-based study in the USA, patients classified as 'white' or 'Asian or Pacific Islander' attended a dermatologist proportionally more than 'black' people or 'native Americans or Eskimos', but this may well have been because of economic or social reasons [2].

Some general texts give a useful overview of this topic [3,4].

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Acne

The prevalence of acne seems to be similar in both North American black Africans and Caucasoids [1], although it may be more severe in the latter [2]. However, acne is less common in the Mongoloid Japanese [3]. In pigmented skin, acne lesions may become hyperpigmented (Fig. 69.1).

'Pomade' acne is seen in certain Afro-Caribbean groups, due to the custom of anointing the scalp hair with pomades, oils and creams. Up to 70% of long-term users of pomades suffer from this complication [4]. It may be seen in children as well as adults. There is some evidence that black Africans react to comedogenic substances in a different way from Caucasoids. Kaidbey and Kligman studied the comedogenic effects of coal tar in Caucasoids and

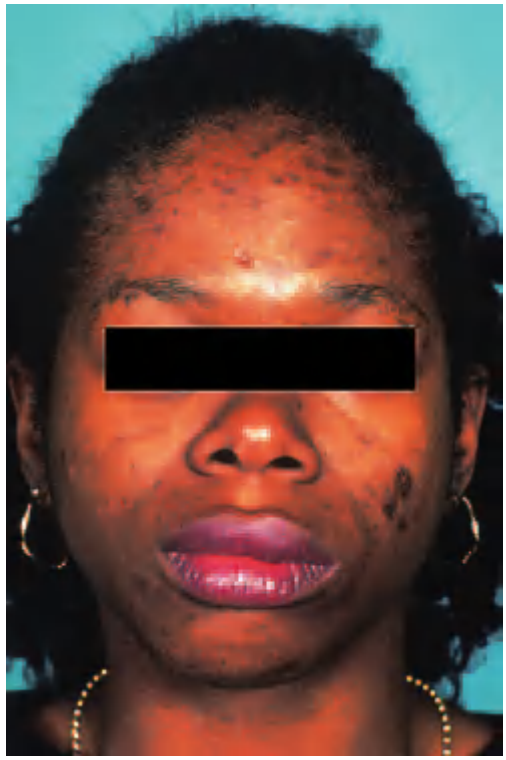

Fig. 69.1 Pigmentation associated with acne. (Courtesy of Dr A.G. Messenger, Royal Hallamshire Hospital, Sheffield, UK.)

black Africans and found that whereas Caucasoids produced an inflammatory response with papules and pustules, black Africans did not usually show this but rather developed small comedones [5].

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Atopic eczema

The inheritance of atopic eczema is 'polygenic'. It is a disease that is seen worldwide and in all races. Comparative figures are not generally available. There was an impression in the UK that atopic eczema may be more common in Caucasoids from the Indian subcontinent [1], but a subsequent cohort study has not confirmed this [2]. It may be that over-representation of Asian children with atopic eczema in dermatology clinics results from a lower level of familiarity with the disease in this community. In another study, from London, UK, it was suggested that

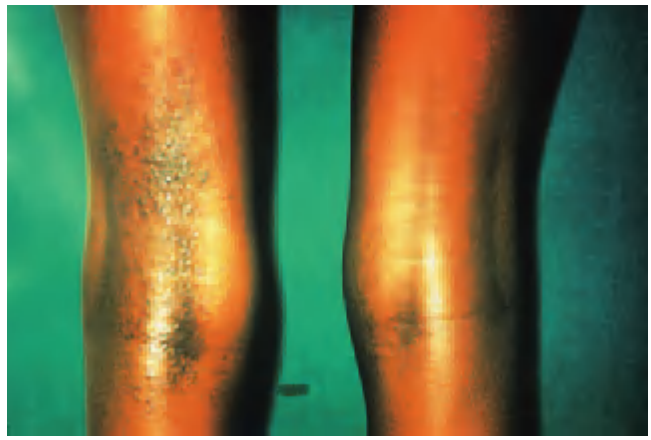

Fig. 69.2 Hyperpigmentation associated with atopic eczema.

atopic eczema is more prevalent in 'black Caribbean' children than in other ethnic groups, including Asians [3]. In India, it is suggested that atopic eczema is not as severe as in Western countries [4].

In black Africans, there is a tendency towards the development of follicular lesions in atopic eczema, and a micropapular follicular form of lichenification resembling lichen nitidus is common [1,5,6]. The follicular eruption may predate the onset of other features of the disease [5,6]. Flexural involvement may be less common than in other races, but the severity of the eczema seems to be no different [3].

Lichenification is seen in all races, but is particularly pronounced in Mongoloids. Postinflammatory hyperpigmentation is a problem in black skin (Fig. 69.2).

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Contact dermatitis

Studies using irritants suggest that black African skin is less susceptible to irritants than Caucasoid skin [1], although the difference is not detectable when the stratum corneum has been removed. A comparison of the susceptibility of the skin of Japanese and Caucasoid women revealed that for acute and—to a lesser extent—cumulative irritant exposures, Japanese skin was more easily irritated than was Caucasoid [2].

There is little evidence that there is any racial predisposition for the development of allergic contact dermatitis. A comparative study of Caucasoids and African Americans found similar rates of sensitization to common allergens, the only differences being higher frequency of contact allergy to *para*-phenylenediamine (PPD, e.g. in hair dye) and imidazolidinyl urea (a preservative) in African Americans [3]. The differences are probably due to increased use of hair dyes and hair-care products in African Americans, although racial differences in N-acetylation in the skin may also explain the PPD finding [3]. Others have confirmed few differences between races in contact sensitization [4]. A study from Singapore of contact allergy to topical medicaments showed no differences between Chinese, Malays and Indians [5]. Overall rates for a 'sensitive skin', as judged by telephone interview, did not differ between Afro-American, Asian, Euro-American or Hispanic women, but Afro-Americans had less reactivity to environmental factors, Asians complained more of itch and reacted more to temperature and wind, Euro-Americans had less reactivity to cosmetics but reacted more to wind, whilst Hispanics had lower skin reactivity to alcohol [6].

However, certain patterns of contact dermatitis are recognized in specific groups due to the use of traditional or ethnic preparations. Indian women may develop an allergic contact dermatitis to materials in 'Bindi', a pigment applied as a paste or powder to the central forehead for religious and social reasons [7].

Some reported differences in the prevalence of contact allergy to certain allergens are likely to represent a difference in exposure. The equal sex incidence of nickel allergy in Nigeria [8], distinct from the female preponderance in most Western countries [9], is probably due to the equal popularity of the wearing of jewellery by both men and women in Nigeria. Clinically, contact dermatitis appears different in black skin as compared with Caucasoid. In the latter, acute contact dermatitis produces vesiculation and exudation, whereas in black skin, lichenification and disordered pigmentation are more common. Hyperpigmentation occurs after contact with mild irritants [10], and certain chemicals—for example, phenolic detergents [11]—cause hypopigmentation.

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Kaposi's sarcoma

The appearance of the lesions of acquired immune deficiency syndrome (AIDS)-related Kaposi's sarcoma can show variation between the different races. In black Africans, lesions may vary from being slightly hyperpigmented to being a deep purple in colour [1]. The classical form of Kaposi's sarcoma is commonest in mid-European Caucasoids of Jewish lineage, and occurs 10 times more frequently in males than in females [2]. Another, more rapidly progressive form, affects black Africans in central Africa [3].

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Keloid formation

Keloids occur in all races, but are more common in black Africans and Mongoloids than in Caucasoids. The exact incidence ratio for black Africans over Caucasoids varies from twice to 19 times, according to the study consulted [1]. In Malaysia, Chinese are more prone to keloids than Indians or Malays [2]. In Hawaii, keloids are five times more common in the Japanese, and three times more frequent in the Chinese, than in Caucasoids [3]. Keloids can occur anywhere on the body, but have a predilection for the shoulders, ears, upper back and anterior chest (Fig. 69.3). They usually follow trauma to the skin, but can arise spontaneously. In black Africans, they may develop in areas of scarification. Treatment options have been reviewed in detail recently [4].

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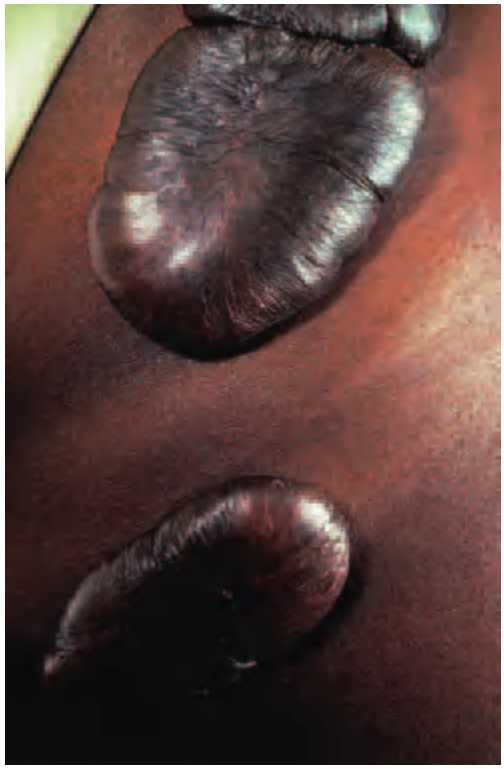

Fig. 69.3 Huge spontaneous keloids in an African. (Courtesy of Professor J.L. Burton, Bristol Royal Infirmary, Bristol, UK.)

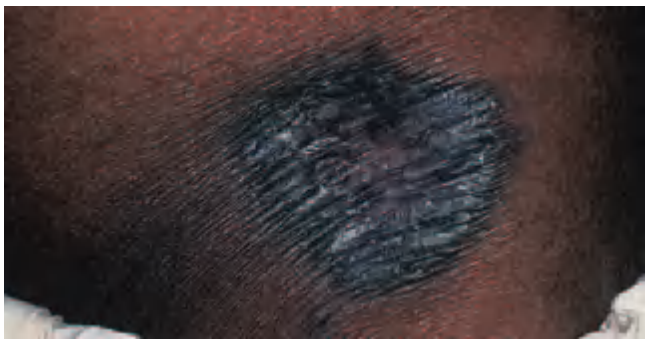

Fig. 69.4 Hyperpigmented lichen planus.

Lichen planus

Lichen planus is a worldwide problem and occurs in all races. In Singapore, lichen planus was proportionally more common in Indians and less common in Chinese and Malays than would be expected, given the composition of the local population [1]. There are no other studies to suggest a racial predisposition, although the appearances may differ between races. In darkly pigmented patients, papules of lichen planus typically are purple in colour (Fig. 69.4). Oral lesions are said to be uncommon in black Africans but frequent in Caucasoids, while the hypertrophic variant, and possibly the erosive type, are more often seen in black Africans [2]. In black Africans,

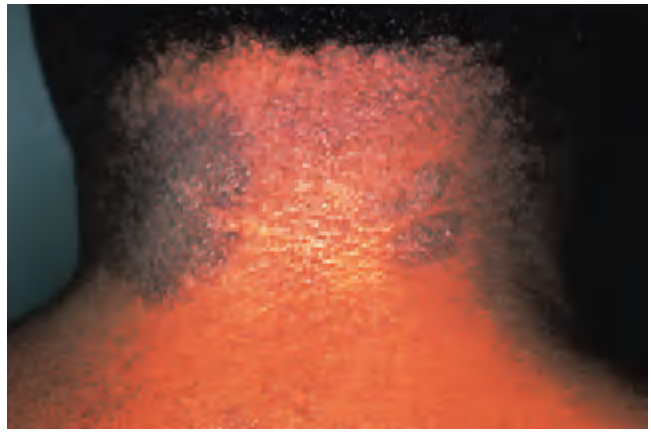

Fig. 69.5 Hyperpigmented lichen simplex chronicus.

postinflammatory hyperpigmentation may be prolonged [3]. In Asian Caucasoids, itching is often not prominent and hyperpigmentation is a more common presentation [4]. Histologically, Asian Caucasoids show less inflammation and basal cell degeneration than black Africans or European Caucasoids [4].

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Lichen simplex chronicus

Lichenification is particularly readily induced in Mongoloid and black African skin (Fig. 69.5). Lichen simplex chronicus may affect the neck, forearms and lower legs, and be associated with hyperpigmentation [1]. A common variant is lichen simplex chronicus of the scrotum in elderly black African males.

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Lupus erythematosus

It used to be said that lupus erythematosus was uncommon in black Africans, but this is no longer believed to be the case. Indeed, the black populations of North America and North Africa seem to develop severe forms of the disease [1]. In New Zealand, systemic lupus erythematosus was found to be three times as common in Mongoloids as in Caucasoids [2].

Lupus erythematosus is closely associated with certain genetic and human leukocyte antigen (HLA) markers. North American and European Caucasoids with systemic lupus erythematosus show an increased frequency of a C4A, CYP21A gene deletion, often in association with the HLA-B8, -DR3, C4A*Q0 extended haplotype [3]. In African Americans, a large C4A, CYP21A gene deletion, particularly associated with HLA-B44, -DR2 and -DR3 alleles, is a strong genetic risk factor for the development of systemic lupus erythematosus [3]. Complete or partial deficiency of C4A allele has also been identified as a genetic determinant of systemic lupus erythematosus in Chinese and Japanese Mongoloids [4]. West Indian, and to a lesser extent North African, black people have a more severe form of systemic lupus erythematosus than European Caucasoids, mainly due to a higher prevalence of renal disease [1]. The mortality from systemic lupus erythematosus in African Americans is higher than in Caucasoids [5]. Discoid lupus erythematosus also seems to have a nearly similar incidence in all races. In those with a dark skin, the face, scalp and—commonly—the lower lip tend to be affected. Hypopigmentation and gross scarring may result.

Although the difference in prevalence of lupus erythematosus and other autoimmune diseases in Africans in West Africa compared with American Africans may be due to genetic admixture, exposure to malaria has also been proposed as being important [6–9]. Whilst on the one hand scanty congenital *Plasmodium* parasites have been proposed as a cause of autoimmune disease [8], several studies have suggested that malaria may induce a form of tolerance against autoimmune disease; altered macrophage function, tumour necrosis factor levels and nitric oxide production have been suggested to be protective. Antinuclear antibodies and antiphospholipid antibodies occurring in patients with malaria have different specificities compared with those in autoimmune disease [7]. Experimentally, serum from mice infected with *Plasmodium chabaudi* slows development of autoimmune disease when injected into a strain of lupus-prone mice [9].

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Melanocytic naevi

Caucasoids have more melanocytic naevi than other races. Black Africans have the fewest naevi, with Mongoloids occupying an intermediate position [1]. Caucasoid children had a median total number of 17 naevi, compared with 2.5 in non-Caucasoids [1]. Young Caucasoid adults had a median of 61 naevi, compared with 16 for non-Caucasoids [1]. A study of schoolchildren in Queensland, Australia, confirmed these findings, but found an even higher prevalence of naevi [2]. Children less than 12 years old had a mean of 28 naevi, with boys having significantly more than girls, and those with a pale skin and light-coloured hair having the highest prevalence [2]. Non-Caucasoid heritage has a protective effect for naevus development, independent of pigmentary characteristics [2].

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Palmoplantar keratodermas (Chapter 34)

Some palmoplantar keratodermas are said to be seen more often in black Africans than in other races [1]. One example is keratosis punctata of the palmar creases [2], in which small crateriform pits are visible on the palmar creases (Fig. 69.6). *Focal acral hyperkeratosis* is a type of papular keratoderma, dominantly inherited in familial cases, that occurs almost exclusively in black Africans [3]. It is characterized by oval or polygonal papules, which may show central pigmented pits, situated on the borders of the palms and soles.

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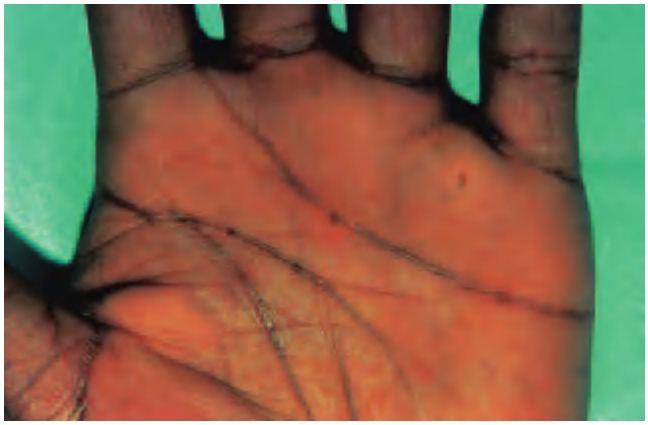

Fig. 69.6 Keratosis punctata of the palmar creases with hyperpigmentation. (Courtesy of Dr D.J. Barker, Bradford Royal Infirmary, Bradford, UK.)

Photodermatoses

Racial pigmentation protects from some of the immediate and long-term adverse effects of sunlight. However, even a pigmented skin may be sunburnt, although it may be difficult to see the erythema because of the pigmentation [1]. Conditions such as polymorphic light eruption occur in all races, but some have a particular presentation depending on the race of the individual. In black Africans or Australoids, for example, an actinic cheilitis (or discoid lupus erythematosus) may affect the lower lip, which may not be protected by the same amount of pigment as on other sites of the body.

One photodermatosis that seems to have a racial predilection is actinic prurigo of native Americans [2], although it may be a form of polymorphic light eruption [3] (Chapter 24). It may present as a lower lip cheilitis, but also produces a conjunctivitis, pterygium and eyebrow alopecia [2]. Actinic prurigo has a female : male ratio of 3 : 1 and usually has an onset in the first two decades of life [4]. Those with an early onset tend to have cheilitis and may improve; those with a later onset have a milder disease, which may be more persistent [4].

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Pityriasis rosea

In black Africans, this eruption shows several unusual features. It shows an 'inverse' pattern, with lesions on the face, neck, extremities and lower abdomen, rather than on the trunk as is usual [1]. In addition, it may be papular, may affect the palms and soles, and shows a brown-grey or even purple pigmentation [2,3]. The recurrence rate seems to be higher in black Africans than in other races [4] and the hyperpigmentation that may follow can persist for some months.

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Postinflammatory pigmentary changes

Pigmented skin shows more of a pigmentary reaction following trauma or inflammation than non-pigmented or lightly pigmented skin. In black Africans, it is also not uncommon to see secondary hypopigmentation after eczema, pityriasis alba, sarcoidosis, leprosy, herpes zoster, pityriasis versicolor or other common eruptions [1,2]. It may also follow cryotherapy and the topical use or intralesional injection of corticosteroids. Table 69.1 lists causes of hypopigmentation in a pigmented skin [1–3]. Sometimes unusual patterns of pigmentation are found; for example, black Africans with systemic sclerosis may develop a

Table 69.1 Causes of hypopigmentation in a pigmented skin.

Division	Disorders
Congenital or genetic	Albinism, piebaldness
Infections	Leprosy, onchocerciasis, pinta, pityriasis versicolor, herpes zoster
Papulosquamous disorders	Pityriasis alba, pityriasis rosea, pityriasis lichenoides chronica, psoriasis, seborrhoeic dermatitis
Physical or chemical agents	Burns, cryotherapy, ammoniated mercury, hydroquinone products, fluorinated corticosteroids
Postinflammatory	Discoid lupus erythematosus, systemic sclerosis, sarcoidosis, some eczematous eruptions
Miscellaneous	Vitiligo, idiopathic guttate hypomelanosis

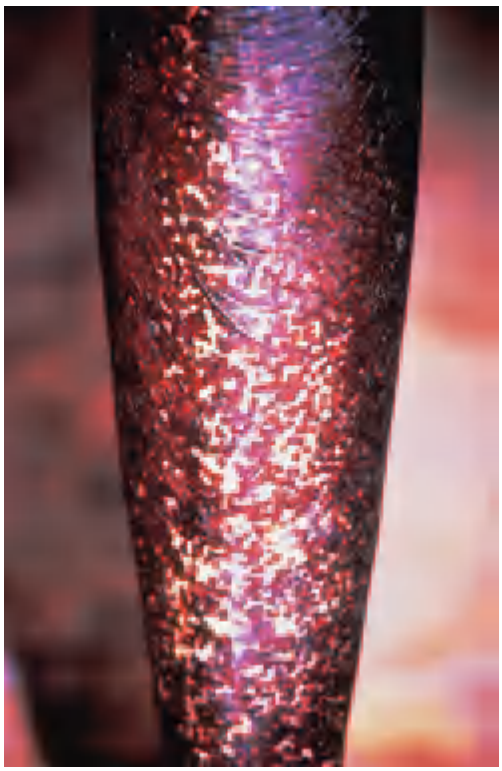

Fig. 69.7 Onchocerciasis showing 'leopard skin' depigmentation. (Courtesy of Dr M.E. Murdoch, Watford District General Hospital, Watford, UK.)

mottled and vitiligo-like hypopigmentation [3] (Chapter 56). Complete or patchy 'leopard skin' depigmentation may be seen with onchocerciasis (Fig. 69.7). On the other hand, some dermatoses result in hyperpigmentation, and it is not unusual to find both hyper- and hypopigmentation coexisting in the same individual.

Hyperpigmentation may occur in black African skin with acne, eczema, sarcoidosis, psoriasis, mycosis fungoides, lichen planus, fixed drug eruption and lupus erythematosus, and frequently is seen when the skin is lichenified, as in chronic eczema [2]. Hyperpigmentation, particularly of the face, may also be acquired due to exposure to a variety of agents. These include exogenous ochronosis from hydroquinone-containing skin-bleaching creams, and mercury deposition from skin-lightening creams containing mercury, and also from exposure to photosensitizing drugs and herbal potions [4].

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Psoriasis

The genetic basis for psoriasis is well established, although not well understood. It is relatively common in European Caucasoids (prevalence about 2%), although within the Caucasoid group it is said to vary, being more common in Parsees than in Hindus or Moslems [1]. A high prevalence is reported in East Africans [2] and a low prevalence in West Africans [3–5], which may explain the low prevalence in African Americans. Psoriasis is almost unknown in the Mongoloid native Americans [3] and Eskimos [6], and in Australian aborigines [7]. It is rare in the Japanese (Mongoloid), although the prevalence in the latter is increasing [8]. The prevalence in Mongoloids in Hong Kong, mainland China and Japan was estimated to be 0.3% [9].

In black skin, psoriatic plaques may appear violaceous or bluish black due to pigmentary incontinence. Grey, silvery scales may be seen. Postinflammatory hyperpigmentation may be left after clearing of the lesions [10]. This may be a persistent cosmetic disability.

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Sarcoidosis

In the USA, sarcoidosis is 10 times more common in African Americans than in Caucasoids [1]. Skin signs are seen in between one-tenth and one-third of patients with sarcoidosis [2]. Erythema nodosum is the commonest non-specific lesion of sarcoidosis, but is much more frequent in Caucasoids than in black Africans [3,4]. In Africans, the commonest sarcoidal skin lesions are flesh-coloured or slightly hypopigmented papules which tend to occur around the nose, mouth and occiput [2]. Hypopigmented macules, violaceous plaques (often on the face or arms) and subcutaneous nodules are also seen.

Ulceration may occur. Lupus pernio is apparently infrequent in black Africans [2].

In contrast to the American experience, sarcoidosis was said to be uncommon in West Africans, but this may not be the case [5]. It has a very low reported prevalence in the Far East.

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Skin cancer

Most forms of skin malignancy and sun-induced degenerative change are more common in North European Caucasoids than in other racial groups. Black Africans have the lowest incidence (1/70 that of Caucasoids) of non-melanoma skin cancer [1], with Mongoloids occupying an intermediate position. Genetic variations that have a racial aspect, e.g. the allelic diversity seen in pale non-Africans for the MC1R locus, will have a bearing on racial susceptibility to skin cancer [2]. In black people, squamous cell carcinoma is the commonest skin tumour [3], as opposed to basal cell carcinoma in Caucasoids. Scarring—for example, from burns or discoid lupus erythematosus—is a predisposing factor in squamous cell carcinoma in Africans [4]. The prognosis in black Africans in the USA is generally worse than in Caucasoids, because of later presentation or more aggressive disease [5]. Basal cell carcinoma is often pigmented in non-Caucasoids.

Malignant melanoma is 10 times more common in North American 'European' Caucasoids than in African Americans, with an incidence in New Mexican Hispanic Caucasoids and Puerto Rico Hispanic Caucasoids of 3.7 and 1.6 times that of African Americans [6]. Puerto Rico Hispanics have more admixture of African genes than Hispanics from New Mexico. In black Africans, malignant melanoma mostly affects the soles or palms [3]. Presentation may be delayed. Malignant melanoma of the sole of the foot, in North America, has a similar incidence in black people as in Caucasoids [7]. Extradermal acrolentiginous tumours with a poor prognosis—e.g. those involving the vulva, cervix, vagina or the anorectal area—made up 44% of new primary malignant melanomas in a study of black American women [8]. In the Mongoloid Japanese, the acral lentiginous type of malignant melanomas makes up a large proportion of cases and the incidence at this site is similar to that for Caucasoids in other sites [9].

Japanese residents in Hawaii had a rate for non-melanoma skin cancer that was 88 times higher than that reported in Japan [10]. This higher rate was attributed to increased sun exposure, and possibly to arsenic exposure. The incidence of basal cell carcinoma in Hong Kong Chinese trebled between 1990 and 1999 (0.32–9.2/100 000/year) and that of squamous cell carcinoma doubled (0.16–0.34) [11].

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3 Halder RM, Bang KM. Skin cancer in blacks in the United States. *Dermatol Clin* 1988; **6**: 397–405.
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10 Leong GK, Stone JL, Farmer ER *et al*. Nonmelanoma skin cancer in Japanese residents of Kauai, Hawaii. *J Am Acad Dermatol* 1987; **17**: 233–8.
11 Cheng SY, Luk NM, Chong LY. Special features of non-melanoma skin cancer in Hong Kong Chinese patients: 10-year retrospective study. *Hong Kong Med J* 2001; **7**: 22–8.

Syphilis

The primary chancre is similar in Caucasoids and black Africans, but the manifestations of secondary syphilis can be different. In Caucasoids, macular lesions are common, but in black Africans, follicular and papular forms are more frequent and may be hyperpigmented [1]. Annular secondary syphilis is almost unique to Negroids [2]; corymbose forms (a central lesion with surrounding small satellites) are also seen [1]. Palmoplantar lesions in black Africans may be keratotic. The non-venereal treponematoses yaws, pinta and bejel are endemic in certain parts of the world. No racial predilection exists, although the appearances may be modified in different races.

REFERENCES

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Systemic sclerosis

There are racial differences in the patterns of disease for

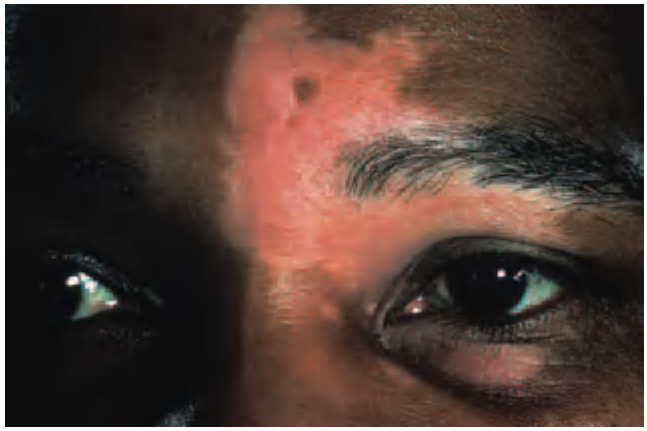

Fig. 69.8 Vitiligo. (Courtesy of Dr A.G. Messenger, Royal Hallamshire Hospital, Sheffield, UK.)

people affected by systemic sclerosis (scleroderma). African Americans and Hispanics (who often have inherited some black African genes) are more likely to have diffuse skin involvement, pigmentary change, digital ulceration and pulmonary hypertension than Caucasoids, who exhibit more facial telangiectasia and associated hypothyroidism [1]. The Choctaw Native American Indians (Mongoloids) have a high prevalence of systemic sclerosis that has been identified as being due to a defect in a gene for fibrillin 1 on chromosome 15q, dating from 10 generations ago ('founder effect') [2].

REFERENCES

1 Reveille JD, Fischbach M, McNearney T *et al*. Systemic sclerosis in 3 US ethnic groups: a comparison of clinical, socioeconomic, serological and immunogenetic determinants. *Semin Arthritis Rheum* 2001; **30**: 332–46.
2 Tan FK, Stivers DN, Foster MW *et al*. Association of microsatellite markers near the fibrillin 1 gene on human chromosome 15q with scleroderma in a Native American Indian population. *Arthritis Rheum* 1998; **41**: 1729–37.

Vitiligo

Vitiligo has the same incidence in all races [1] but its manifestations are much more significant in those with a dark skin than in lightly pigmented individuals (Fig. 69.8). In Afro-Caribbeans, vitiligo may show a 'trichrome' pattern, with hypopigmented as well as depigmented areas.

REFERENCE

1 Kenney JA. Vitiligo. *Dermatol Clin* 1988; **6**: 425–34.

Diseases with a distinct racial or ethnic predisposition

Several disorders have a significant racial predisposition as discussed below and in general reference texts [1,2].

REFERENCES

1 Johnson BL, Moy RL, White GM. *Ethnic Skin. Medical and Surgical*. St Louis: Mosby, 1998.
2 Archer CB, Robertson SJ. *Black and White Skin. An Atlas and Text*. Oxford: Blackwell Scientific Publications, 1995.

Hair disorders

Dissecting folliculitis (Chapter 63)
SYN. DISSECTING CELLULITIS; PERIFOLLICULITIS CAPITIS ABSCEDENS ET SUFFODIENS

This is an uncommon, chronic, progressive and suppurative scalp disorder that almost exclusively affects Afro-Caribbean males. Painful, boggy, sterile abscesses form on the scalp (Fig. 69.9) and are connected by sinus tracts [1]. As the disease progresses, scarring and alopecia are seen, and keloids may form [2]. The cause is unknown. Treatment has been difficult in the past as intralesional steroids and systemic antibiotics provide only partial relief, but it is now known that isotretinoin is effective in this condition, although it needs to be continued for 4 months after clinical control is achieved to prevent relapse [3]. Resistant cases may require surgical excision and grafting [4]. Dissecting folliculitis may be associated with acne conglobata and hidradenitis suppurativa, to form the so-called 'follicular occlusion' triad, in which abnormal follicular keratinization and occlusion occur [5].

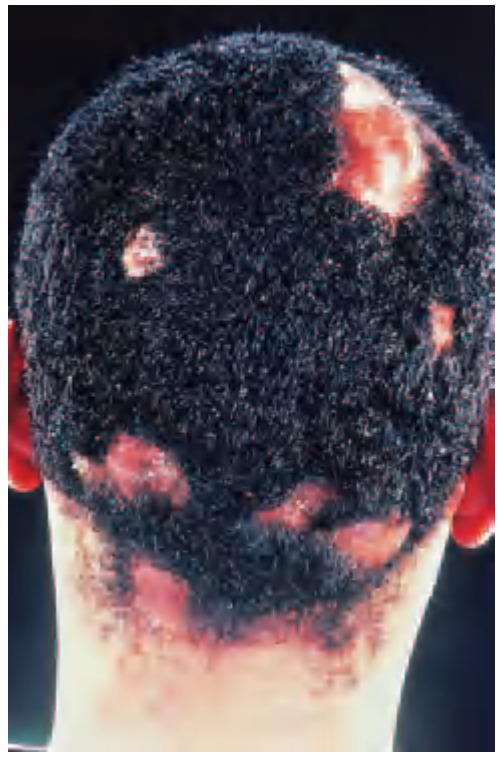

Fig. 69.9 Dissecting cellulitis of the scalp. (Courtesy of Professor H.C. Williams, Queen's Medical Centre, Nottingham, UK.)

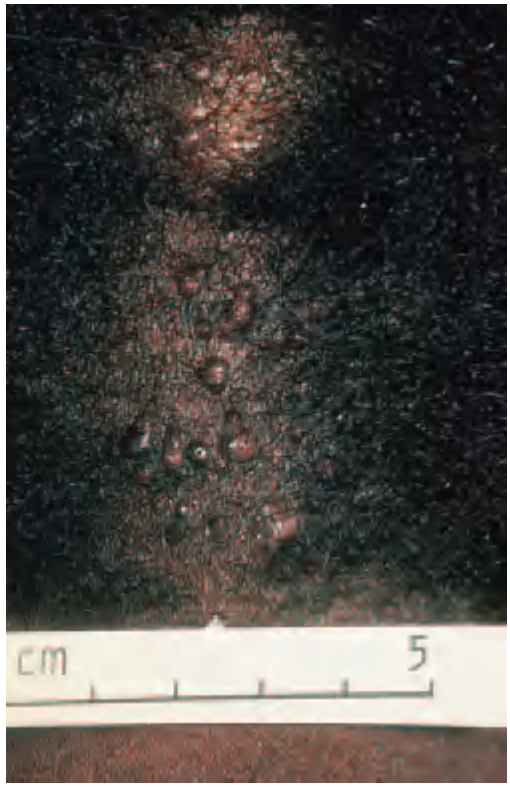

Fig. 69.10 Folliculitis keloidalis. (Courtesy of Dr A.G. Messenger, Royal Hallamshire Hospital, Sheffield, UK.)

REFERENCES

1 Halder RM. Hair and scalp disorders in blacks. *Cutis* 1983; **32**: 378–80.
2 Scott DA. Disorders of the hair and scalp in blacks. *Dermatol Clin* 1988; **6**: 387–95.
3 Scerri L, Williams HC, Speight EL, Allen BR. Dissecting cellulitis of the scalp: response to isotretinoin. *Br J Dermatol* 1995; **133** (Suppl. 45): 41.
4 Dellon AL, Orlando JC. Perifolliculitis capitis. surgical treatment for the resistant case. *Ann Plast Surg* 1982; **9**: 254–9.
5 Baden HP. *Diseases of the Hair and Nails*. Chicago: Year Book Medical Publishing, 1987.

Folliculitis keloidalis (Chapter 27)

SYN. ACNE KELOIDALIS NUCHAE

This condition is seen almost exclusively in black Africans, with males being mostly affected [1]. Firm, discrete, follicular and perifollicular papules develop, usually on the nape of the neck, but often extending into the occipital scalp or beyond (Fig. 69.10). Complications include pustule formation, hypertrophic scars, keloids and alopecia [2]. The aetiology is unknown, but probably related to the curved shape of the hair follicle. Treatment includes intralesional steroid injection and topical and systemic antibiotics [1].

REFERENCES

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Hot-comb alopecia (Chapter 63)

Hot combing is a method of straightening curly black hair, although it has to a large extent been replaced by chemical methods [1]. Oil is applied to the hair and acts as a lubricant and heat conductor. A metal comb, heated to 150–260°C, is applied to the hair, re-arranging the hydrogen and disulphide bonds and straightening the hair [2]. The hot comb and oil may break the hair and a traction alopecia may also result. Repeated contact of the hot oil with the scalp can produce a scarring alopecia [3]. Recent evidence suggests that hot combing may not be the reason for the hair loss, which is usually seen in young adult women, and that the histological end-result, follicular degeneration, may have some other cause [4].

Hair-shaft breakage may also be seen with the inappropriate use of chemical relaxers and straighteners [1]. A scarring alopecia may also be seen, again in young women, following the use of hair-straightening chemicals [5].

REFERENCES

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2 Halder RM. Hair and scalp disorders in blacks. *Cutis* 1983; **32**: 378–80.
3 LoPresti P, Papa CM, Kligman AM. Hot comb alopecia. *Arch Dermatol* 1968; **98**: 234–8.
4 Sperling LC, Sau P. The follicular degeneration syndrome in black patients: 'hot comb alopecia' revisited and revised. *Arch Dermatol* 1992; **128**: 68–74.
5 Nicholson AG, Harland CC, Ball RH *et al*. Chemically induced cosmetic alopecia. *Br J Dermatol* 1993; **128**: 537–41.

Pseudofolliculitis barbae (Chapter 22)

This is a disorder common in black African males who shave and is related to the curved hair follicles found in such individuals [1]. Once shaved, the cut hair retracts beneath the skin surface into the curved follicle and grows in a circular direction. The sharpened hair end either penetrates the wall of the follicle, causing a foreign-body reaction, or grows out of the follicle but re-enters the skin and penetrates the dermis, again setting up an inflammatory reaction [1]. Perifollicular papules and pustules develop and scarring may result (Fig. 69.11). The beard area is usually affected, but pseudofolliculitis may involve any site that is shaved, including the pubic area and the scalp [2]. Recommended treatment is to grow a beard, use electric clippers, depilatory creams or a manual razor, sometimes with topical or systemic antibiotics [3].

REFERENCES

1 Scott DA. Disorders of the hair and scalp in blacks. *Dermatol Clin* 1988; **6**: 387–95.
2 Smith JD, Odom RB. Pseudofolliculitis capitis. *Arch Dermatol* 1977; **113**: 328–9.
3 Brown LA. Pathogenesis and treatment of pseudofolliculitis barbae. *Cutis* 1983; **32**: 373–5.

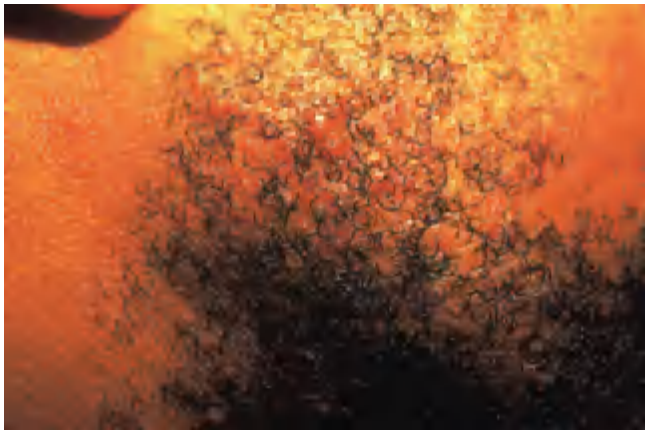

Fig. 69.11 Pseudofolliculitis barbae. (Courtesy of Dr C. St J. O'Doherty, Queen Elizabeth II Hospital, Welwyn Garden City, London, UK.)

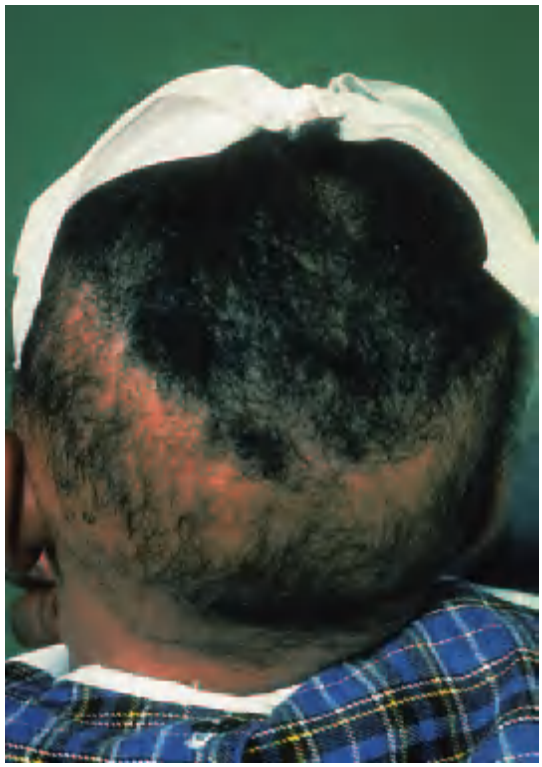

Fig. 69.12 Traction alopecia. (Courtesy of Dr A.G. Messenger, Royal Hallamshire Hospital, Sheffield, UK.)

Traction alopecia (Chapter 63)

Traction alopecia (Fig. 69.12) is mainly seen in black Africans, because of the practices of plaiting or tightly braiding the hair into multiple braids (corn rowing), although it is not entirely confined to this group [1]. It may also follow the use of tight rollers or 'picking out' the hair with a hard comb to create the 'Afro' hairstyle [2]. Hairs are loosened from their follicles and inflammation and

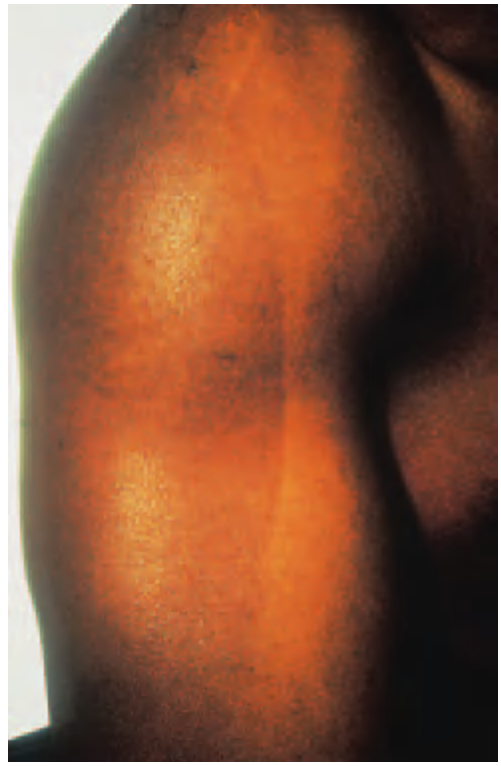

Fig. 69.13 Futcher's lines. (Courtesy of the late Dr R.R.M. Harman, Bristol Royal Infirmary, Bristol, UK.)

atrophy may result. The distribution depends on the pattern of braiding, but often involves the temporal regions. Treatment consists of persuading the patient to discontinue the offending practice. In long-standing cases, alopecia may be permanent.

REFERENCES

1 Scott DA. Disorders of the hair and scalp in blacks. *Dermatol Clin* 1988; **6**: 387–95.
2 Halder RM. Hair and scalp disorders in blacks. *Cutis* 1983; **32**: 378–80.

Variations of normal pigmentation

Futcher's or Voigt's lines

These are sharply demarcated bilateral lines of pigmentation (Fig. 69.13) that are seen at the anterolateral junction usually of the upper arms, where there is a transition from extensor to flexor surface and from darker to lighter pigmentation [1]. The lines correspond to a dermatome [2]. A second hyperpigmented line may occur on the posteromedial part of the lower aspect of the limbs [3]. The presence of Futcher's lines is proportional to the degree of pigmentation of the individual; they are present in 25% of black Africans [3]. Overall, about 75% of black people have at least one hypo- or hyperpigmented line [3]. These lines may be seen to a lesser extent in other races.

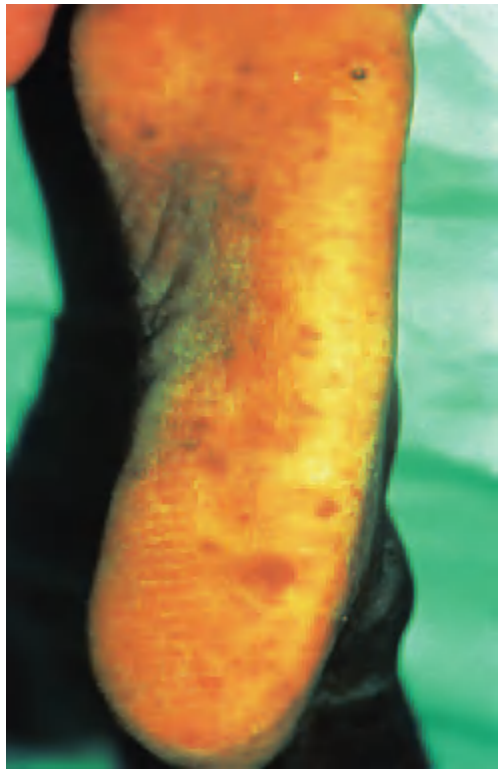

Fig. 69.14 Mottled macular pigmentation on the soles. (Courtesy of Dr D.J. Barker, Bradford Royal Infirmary, Bradford, UK.)

REFERENCES

1 Henderson AL. Skin variations in blacks. *Cutis* 1983; **32**: 376–7.
2 Futcher PH. A peculiarity of pigmentation of the upper arms of negroes. *Science* 1938; **88**: 570–1.
3 McLaurin CI. Cutaneous reaction patterns in blacks. *Dermatol Clin* 1988; **6**: 353–62.

Hyperpigmentation of the palms and soles

Discrete, ill-defined or mottled macular pigmentation is frequently seen on the palms and soles (Fig. 69.14) of African patients, especially those with a darker skin colour [1].

REFERENCE

1 Chapel TA, Taylor RM, Pinkus H. Volar melanotic macules. *Int J Dermatol* 1979; **18**: 222–5.

Midline hypopigmentation

This appears as a line or band of hypopigmentation, or as discrete oval macules, on the anterior chest and midsternal area. Lesions sometimes extend down to the abdomen or up to the neck, where lines of hypopigmentation may radiate out to the clavicles [1,2]. It is commonly seen in black African males, but may occur in other races.

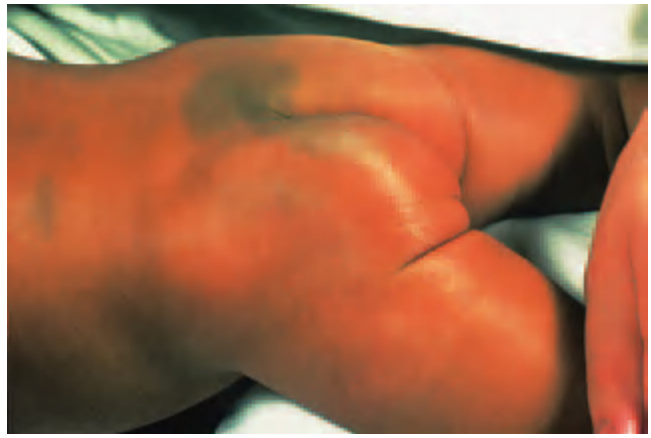

Fig. 69.15 Mongolian spot. (Courtesy of Professor S.S. Bleehen, Royal Hallamshire Hospital, Sheffield, UK.)

REFERENCES

1 Selmanowitz V, Krivo JM. Hypopigmented markings in negroes. *Int J Dermatol* 1973; **12**: 229–35.
2 Weary PE, Behlen CH. Unusual familial hypopigmentary anomaly. *Arch Dermatol* 1965; **92**: 54–5.

Mongolian spot (Chapter 39)

SYN. CONGENITAL DERMAL MELANOCYTOSIS

Mongolian spot refers to a slatey brown or blue-grey macular pigmentation observed at birth or in the neonatal period (Fig. 69.15). It is present in 100% of Mongoloid babies [1], between 70 and 96% of black Africans, and in up to 10% of Caucasoids [2,3]. The pigmentation is usually faint, round or oval in shape, and ranges in size from a few millimetres to greater than 10 cm in diameter. Mongolian spots are normally located over the sacral area, but the buttocks, flank or shoulders may be involved. Occasionally, multiple or extensive lesions are seen. The pigmentation generally reaches its peak at 2 years and fades by the age of 6 or 7 years.

REFERENCES

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2 Cordova A. The Mongolian spot: a study of ethnic differences and a literature review. *Clin Pediatr* 1981; **20**: 714–9.
3 Osburn K, Schosser RH, Everett MA. Congenital pigmented and vascular lesions in newborn infants. *J Am Acad Dermatol* 1987; **16**: 788–92.

Nail pigmentation

Longitudinal bands of brown or black pigmentation may be seen (Fig. 69.16); they occur with a higher frequency on the thumb and index fingernails [1,2]. They are present in more than 50% of black Africans, are more common in those with heavy pigmentation, and increase with advancing age.

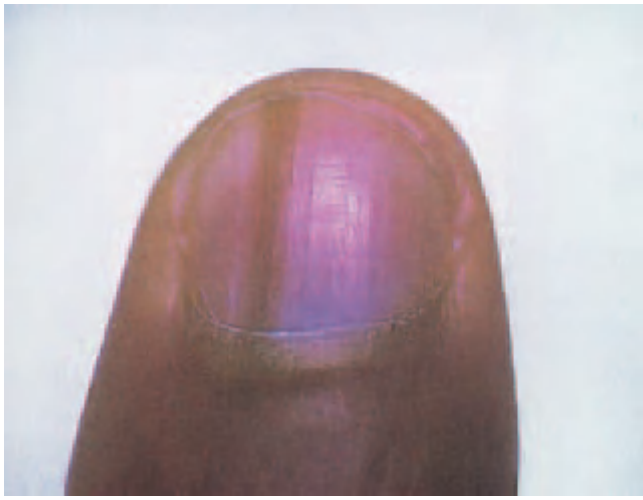

Fig. 69.16 Nail pigmentation.

REFERENCES

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2 Monash S. Normal pigmentation in the nails of the negro. *Arch Dermatol* 1932; **25**: 876–81.

Oral pigmentation

Oral macular pigmentation is seen in black Africans. It most often affects the gingivae, but may also involve the hard palate, buccal mucosa and tongue [1].

REFERENCE

1 Dummett CO, Sakumura JS, Barens G. The relationship of facial skin complexion to oral mucosal pigmentation and tooth color. *J Prosthet Dent* 1980; **4**: 392–6.

Pigmentary disorders

Acanthosis nigricans (Chapter 34)

In some Mongoloid native American tribes, acanthosis nigricans is very common [1]. It may indicate a high risk of diabetes mellitus.

REFERENCE

1 Stuart CA, Smith MM, Gilkison CR *et al.* Acanthosis nigricans among Native Americans: an indicator of high diabetes risk. *Am J Public Health* 1994; **84**: 1839–42.

Dermatosis papulosa nigra (Chapter 36)

This condition is characterized by hyperpigmented, smooth-surfaced, round or filiform papules usually on the face (Fig. 69.17), but sometimes on the neck or upper trunk

Fig. 69.17 Dermatosis papulosa nigra.

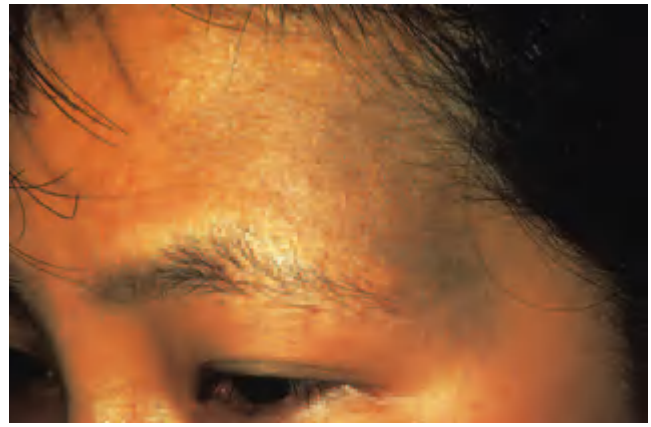

Fig. 69.18 Naevus of Ota.

[1,2]. The papules measure 1–5 mm in diameter. It is most common in black Africans, affecting up to three-quarters of adults (the majority being women), but is occasionally found in Caucasoids and Mongoloids [1]. The cause is unknown.

REFERENCES

1 Grimes PE, Arora S, Minus HR *et al.* Dermatosis papulosa nigra. *Cutis* 1983; **32**: 385–92.
2 Hairston N, Reed R, Derbes V. Dermatosis papulosa nigra. *Arch Dermatol* 1964; **89**: 655–8.

Naevus of Ota (Chapter 38)

Macular pigmentation, due to dermal melanocytes, is seen adjacent to the eye and also involves the sclera (Fig. 69.18). The pigmentation in naevus of Ota is variable and may be blue, slatey blue or brown. The naevus is usually unilateral and affects the eyelid, maxillary and zygomatic areas—regions that are innervated by the first and second branches of the trigeminal nerve [1]. It is most common in Mongoloids, but may occur in other racial groups. The

prevalence in the Japanese is 0.4–0.8% [2]. Over 80% of cases appear in women. About two-thirds of patients have ocular involvement, commonly of the sclera, but also of the cornea, conjunctiva and retina [1]. Malignant melanoma may develop in the naevus of Ota, more frequently in Caucasoid than Mongoloid patients [3].

REFERENCES

1 Kopf AW, Weidman AI. Nevus of Ota. *Arch Dermatol* 1962; **85**: 195–208.
2 Jimbow M, Jimbow K. Pigmentary disorders in oriental skin. *Clin Dermatol* 1989; **7**: 11–27.
3 Jay B. Malignant melanoma of the orbit in a case of oculodermal melanocytosis (naevus of Ota). *Br J Ophthalmol* 1965; **49**: 359–63.

Naevus of Ito (Chapter 38)

This is a variant of the naevus of Ota, and is characterized by macular pigmentation involving the shoulder, supraclavicular area, sides of the neck and upper arm—the areas supplied by the posterior supraclavicular and lateral brachial nerves [1,2]. It is more common in the Japanese and may occur alone or associated with a naevus of Ota.

REFERENCES

1 Ito M. Studies on melanin: nevus fusco-caeruleus acromiodeltoideus. *Tohoku J Exp Med* 1954; **60**: 10.
2 Mishima Y, Mevorah B. Nevus Ota and nevus Ito in American negroes. *J Invest Dermatol* 1961; **36**: 133–54.

Other conditions

Ainhum (Chapter 46)

Ainhum is characterized by the development of a constricting band around a digit (often the fifth toe) which may progress to spontaneous amputation of the digit [1]. It is generally found in black inhabitants of tropical countries, but has been described in African Americans [2]. The trauma and infection associated with walking barefoot may stimulate fibrosis. Pseudo-ainhum occurs in all races as a feature of mutilating keratoderma.

REFERENCES

1 Browne S. Ainhum: a clinical and etiological study of 83 cases. *Ann Trop Med Parasitol* 1961; **55**: 314–20.
2 Hucherson DC. Ainhum (dactylolysis spontanea): review of 10 cases. *Ann Surg* 1950; **132**: 312–4.

Cutaneous amyloidosis (Chapter 57)

Both the lichenoid type and the macular type are more common in Mongoloid subjects, but may be seen in any racial group [1–3]. Lichen amyloidosis consists of discrete, firm papules which often involve the lower leg, extensor aspect of the arms and lower back. The pigmented macular variant commonly affects the scapular region and shows a rippled pattern of pigmentation.

REFERENCES

1 Black MM, Wilson-Jones E. Macular amyloidosis: a study of 21 cases with special reference to the role of the epidermis and its histogenesis. *Br J Dermatol* 1971; **84**: 199–209.
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3 Looi LM. Primary localised cutaneous amyloidosis in Malaysians. *Aust J Dermatol* 1991; **32**: 39–44.

Disseminate and recurrent infundibulofolliculitis (Chapter 27)

This is a type of follicular eczema mainly seen in black Africans [1,2]. Pruritic, follicle-based papules are present on the neck, trunk or limbs. Juxtaclavicular beaded lines are a somewhat similar condition. They consist of asymptomatic parallel rows of skin-coloured papules on the neck and overlying the clavicles [1]. They are also seen in Caucasoids.

REFERENCES

1 McLaurin CI. Cutaneous reaction patterns in blacks. *Dermatol Clin* 1988; **6**: 353–62.
2 Rosen T, Martin S. *Atlas of Black Dermatology*. Boston: Little, Brown, 1981.

Facial Afro-Caribbean childhood eruption

In facial Afro-Caribbean childhood eruption (FACE), monomorphic flesh-coloured or hypopigmented papules are seen on the face, particularly around the mouth (Fig. 69.19), eyelids and ears, in Afro-Caribbean children [1,2]. The eruption persists for several months, but resolves spontaneously without scarring. The cause is unknown.

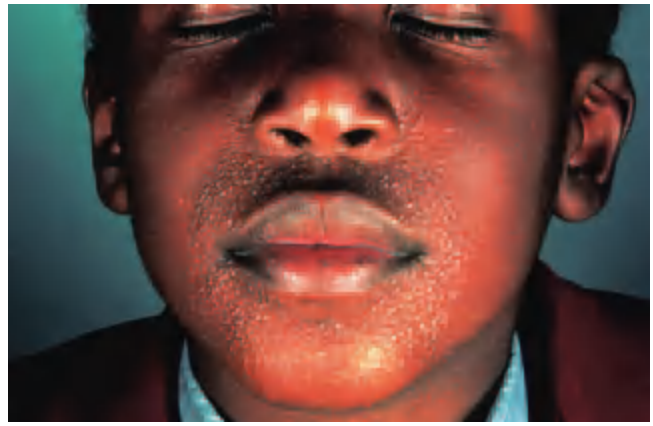

Fig. 69.19 Facial Afro-Caribbean childhood eruption. (Courtesy of Professor H.C. Williams, Queen's Medical Centre, Nottingham, UK.)

REFERENCES

1 Marten RH, Presbury DGC, Adamson JE *et al*. An unusual papular and acneiform facial eruption in the negro child. *Br J Dermatol* 1976; **91**: 435–8.
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Fogo selvagem (endemic pemphigus foliaceus) (Chapter 41)

One report suggests this type of pemphigus, seen in clusters in jungle areas of South America, is more common in Native Indians (Mongoloids), who may be genetically predisposed to develop the disorder [1].

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Hamartoma moniliformis (Chapter 15)

An asymptomatic disorder of small, discrete, flesh-coloured papules seen over the face and neck [1]. Histology reveals an increase in collagen and elastic fibres, capillary endothelial hyperplasia and proliferation of dermal nerves. The condition was first recognized in mentally retarded black children [1], but may occur in Caucasoid children and in mentally normal children.

REFERENCE

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Infantile acropustulosis (Chapter 14)

Crops of small, intensely itchy papules appear between 2 and 10 months of age. The papules evolve into pustules and are mostly found on the palms, soles, wrists and ankles [1,2]. Lesions clear within 3 weeks, but recur until the disease resolves spontaneously at the age of about 2 or 3 years. It occurs predominantly in black African infants and the cause is unknown.

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Mudi-chood

A papular eruption with a firm adherent scale, known as mudi-chood, is seen on the nape of the neck and upper back in young Dravidian women in Kerala State, south India. It seems to be due to the effects of oils applied to the hair [1,2]. The early lesions are follicular pustules, although later, flat-topped brownish black papules, with a keratinous rim, are seen (Fig. 69.20). Histologically, there is parakeratosis and acanthosis [1]. The Dravidians were the original inhabitants of India. Their racial origin is not quite clear, but they differ from the Caucasoid peoples of central and northern India, e.g. the Punjabis and Rajasthanis (who are descended from invaders from Persia and Central Asia). Dravidians have a darker skin colour and are shorter than their compatriots from north India: they have a prominent premaxilla, black hair and dark irises (P. Sugathan, personal communication). Mudi-chood can be improved by the application of 5% salicylic acid ointment, which removes the scales to leave hyperpigmented macules. Reducing the use of oils or cutting the hair shorter results in cure.

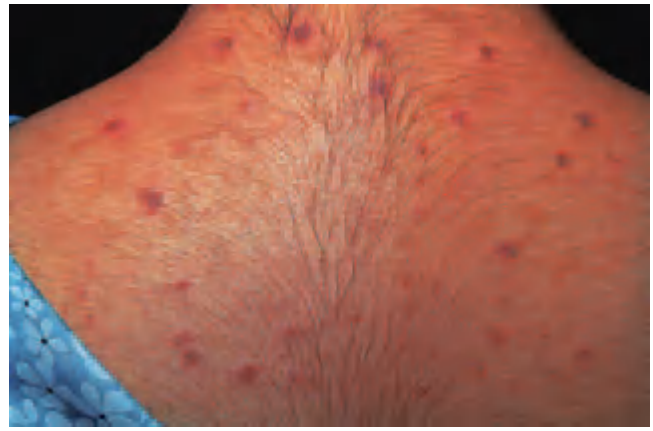

Fig. 69.20 Mudi-chood. (Courtesy of Dr P. Sugathan, Baby Memorial Hospital, Calicut, India.)

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2 Gharpuray MB, Kulkarni V, Tolat S. Mudi-chood: an unusual tropical dermatosis. *Int J Dermatol* 1992; **31**: 396–7.

Papular eruption in black males

Described in young African American males, this monomorphic eruption consists of pruritic dermal papules with a predilection for the trunk, upper arms and postauricular area [1]. The condition may be persistent and resistant to treatment. The cause is not known.

REFERENCE

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Papuloerythroderma of Ofuji (Chapter 17)

The unusual eruption, characterized by solid papules coalescing into erythroderma with sparing of the body folds, was first described in elderly Mongoloid Japanese men, but has since also been reported in Caucasoids [1]. The cause is unknown.

REFERENCE

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Pityriasis rotunda (Chapter 34)

An eruption of asymptomatic discrete, large, scaly, oval or circular plaques on the trunk, mostly reported in Mongoloid or black African individuals [1,2]. It is a type of acquired ichthyosis and in some cases is associated with serious disease such as tuberculosis, leprosy, cirrhosis or underlying malignancy.

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Sickle cell disease (Chapter 50)

Sickle cell disease occurs in black African races. The main cutaneous findings are the hand–foot syndrome and leg ulceration. The hand–foot syndrome is the most common and often the initial manifestation of the disease in children and consists of painful, non-pitting oedema of the hands and feet, caused by infarction of the small bones [1]. Ischaemic leg ulcers are, overall, the most frequent skin complication of sickle cell disease, but are rare under the age of 15 years [2].

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Transient neonatal pustular melanosis (Chapter 14)

A transient eruption of sterile vesicles and pustules, with surrounding erythema, which is present at birth. The vesicles rupture easily and leave pigmented macules that fade within the first few weeks of life [1,2]. It affects 4.4% of black Africans and 0.2% of Caucasoid neonates and tends to involve the face, neck, lower back and shins.

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Vascular naevi (Chapter 15)

Vascular birthmarks, such as the naevus flammeus usually seen on the neck (the 'stork mark') or sometimes on the forehead or eyelids, or the port-wine stain naevus, are more common in Caucasoids than in black Africans or, to a lesser extent, in Mongoloids [1]. Naevus flammeus is seen in 30% of Caucasoid newborns and in 22% of black newborns [1]. Port-wine stain naevi are found in 1% of Caucasoid infants, but are rarer in other races [1].

REFERENCE

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Chapter 70

The Ages of Man and their Dermatoses

R.A.C. Graham-Brown

Introduction

Human life is a continuum, but within the continuum there are several identifiable phases, which we (the present and previous authors and editors) have called, after Shakespeare, the 'Ages of Man' [1]. We all begin by passing through a period of development to the point of 'maturity', which is then followed by a process of intrinsic ageing leading inexorably to senescence. During these ages, alterations take place in the structure and function of the skin, and there are important differences in the range, presentation, prognosis and treatment of skin disorders at various points in life. Indeed, some of the physiological events that accompany puberty, pregnancy, the menopause and old age can, of themselves, be sufficient reason for the patient to seek specialist dermatological advice.

This chapter aims to provide an overview of these stages in the life of the skin. The dermatological problems of the neonatal period and infancy have been dealt with elsewhere (see Chapter 14). This chapter deals principally with the skin and skin disorders of puberty, the menstrual cycle, pregnancy, childbirth and the puerperium, the menopause and old age.

REFERENCE

1 Shakespeare W. *As You Like It* II. vii. 139.

Birth to puberty

Somatic growth

Growth, defined as an increase in size, occurs in most tissues, including the reproductive system. In particular, the changes in the skeleton, which can be monitored radiologically, and in the visible teeth, have been used as indices of maturity [1].

Between birth and maturity the skeleton and body keep in step with increases in weight of 20–25-fold, whereas the somatic muscles increase by 30–40-fold, and the nervous system by less than fivefold. The surface area of the skin increases sevenfold. In the first year after birth the body length increases by approximately 50% to around 75 cm, and another 12–13 cm are added in the second year. Subsequently, growth remains steady at 6 cm/year until the spurt associated with puberty. Weight follows a similar pattern.

Postnatal growth is dependent on growth hormone, or somatotrophin, secreted by the anterior pituitary, although other hormonal interactions may also be involved [2,3]. Human growth hormone is a protein with 191 amino acids. It exerts an effect on a number of tissues including the viscera and bone. In particular, it affects stature by stimulating proliferation of cartilage cells at the epiphyseal plates until the point when the epiphyses of the long bones have fused. Growth hormone also antagonizes the

actions of insulin, possibly by reducing the binding of insulin at its target sites, or by interacting with a second-messenger system.

Some of the effects of growth hormone are indirect, in the sense that they are mediated through the production of polypeptide growth factors in the target tissue. The most important of these, which affects the uptake of sulphate into cartilage, is somatomedin C, initially called 'sulphation factor' but now known to be identical with insulin-like growth factor 1 (IGF-1) and closely similar to IGF-2. Somatomedins have also been shown to stimulate incorporation of [^{14}C] leucine into glycosaminoglycans in cartilage and of [^{14}C] proline into collagen.

The secretion of growth hormone from the pituitary is mediated primarily by the interaction between hypothalamic growth hormone-releasing hormone and somatostatin, a 14-amino acid polypeptide that has numerous regulatory and neuromodulatory effects [4]. Negative feedback by both somatomedin C and growth hormone itself may also be involved. The basal concentration of growth hormone in the plasma is below 1 mIU/L, but it can reach peaks of up to 60 times this amount in adolescence. Bursts of secretion occur every 1–2 h during sleep, but can also be produced by physiological and psychological stresses.

Excessive secretion before puberty gives rise to gigantism, but once the epiphyses of the long bones have fused it results in thickening of the bones and enlargement of the hands and feet, known as acromegaly. Acromegalics also have, on average, abnormally high sebum secretion.

Deficiency of growth hormone, either in isolation or as a component of general hypopituitarism, is one cause of short stature.

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Sexual development

The period between infancy and puberty that we call childhood is, in relation to sexual development, a hiatus in hormonally controlled events that have already been initiated in the fetus. While the dermatological problems of the neonatal period are so distinctive and of such practical importance as to merit a separate chapter, an understanding of the hormonal status of the fetus and the neonate, and of the cutaneous implications, is an essential starting point for a journey through the 'Ages of Man'.

Males become differentiated from females by their possession of a Y chromosome, which causes the indifferent gonads to become testes [1,2]. The fetal testis secretes a factor known as anti-Müllerian hormone, which induces regression of the Müllerian ducts between the seventh and eighth weeks of gestation, and testosterone, which causes virilization of the Wolffian duct to form most of the male system. Conversion of testosterone to 5α-dihydrotestosterone (see Chapter 4) is necessary for the development of the prostate from the urinogenital sinus, and of the external genitalia. In the latter trimesters of intrauterine life, the testicles descend to their position in the scrotum in response to gonadotrophin from the fetal pituitary, in addition to testosterone.

In females, where testicular secretions are lacking, the Müllerian ducts persist and give rise to the female reproductive tract.

The fetal testis continues to secrete testosterone even after birth [3]. At 50 days of age the level of plasma testosterone (250 ng/100 mL) is more than seven times that in umbilical cord blood (35 ng/100 mL), and is unlikely to be of maternal origin. It falls to the low level of the rest of childhood by about the age of 6 months.

In males, this production of testosterone appears at first sight to be related to the activity of the sebaceous glands, which become functional by 17 weeks of gestation. The glands are large at birth and the skin surface lipid is high, approximately 400 g/cm^2, remaining so for approximately 3 months [4,5]. The level throughout the rest of childhood is maintained at approximately 100 g/cm^2.

Neonatal skin-surface lipid is, however, as high in females as in males, although the hormonal pattern is quite different; the maximum plasma testosterone occurs immediately after birth and falls very rapidly [3]. The pattern of dehydroepiandrosterone, however, very closely follows that of the casual sebum levels in both sexes [6]. For these reasons, it seems possible that the production of sebum in the neonatal period and the occurrence of acne in prepubertal children may be related to adrenal activity.

Sebaceous activity starts to increase again towards the end of childhood, in advance of other signs of approaching puberty [7,8]. Dramatic changes take place between the ages of 8 and 9 years, in both males and females [9], and it seems possible that these are related to an increase in output of adrenal androgens. Comedones start to increase around this period [10].

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The skin in childhood

The skin, along with other organ systems, undergoes some degree of maturation during the hiatus of childhood, before the resumption of sexual development at puberty and the transition to adulthood. The skin disorders seen in children in part reflect these physiological changes, but many of the most troublesome cutaneous problems encountered result from intrinsic genetic abnormalities conditioned by environmental influences. Perhaps the best example is atopic dermatitis (see Chapter 18), which has now reached very high levels of prevalence in some societies [1]. The ways in which the environment affects the child changes as he or she becomes more mobile and travels further and further afield.

School years bring exposure to a wide variety of infections and contagions, such as measles, chickenpox, impetigo, warts, molluscum contagiosum, scabies and head lice. There is also a gradual increase in contact with potential irritants: at school during lessons, in sporting activities such as swimming and team games, and in hobbies. The wearing of jewellery and cosmetics, and exposure to sensitizers such as rubber chemicals in footwear and preservatives in medicaments, bring a further range of dermatological problems in the form of allergic contact dermatitis, which is not as rare before puberty as is often suggested [2]. One disorder that seems to have a definite predilection for the prepubertal period in girls is lichen sclerosus et atrophicus [3], which may improve and disappear as puberty approaches, although this is not always the case [4]. In boys, the same pathological changes are frequently found in prepuces removed to relieve phimosis.

There has also been an increasing awareness in recent years that both girls and boys may present to the dermatologist with symptoms and signs that indicate sexual abuse [5]. Vulval or perianal soreness and inflammation for which no other cause can be found should be considered suspicious, as should the presence of anogenital warts [6], although some are undoubtedly acquired innocently. Proof of sexual abuse is always difficult unless there has been disclosure or confession from within the family unit. Furthermore, the social and legal implications of formal investigations for the child and his or her family are enormous. Inquiries must therefore be undertaken with care, although there is a well-established framework in many countries to deal with the problem, generally involving paediatricians, social workers and the police [5]. It is important to note that the changes associated with lichen sclerosus and Crohn's disease in childhood can be mistaken, by non-dermatologists, for evidence of sexual abuse [2], although their presence does not exclude it.

Syndromes of short stature

There is no uniformly agreed definition of short stature, although a reasonable cut-off would seem to be below the third centile for the child's community [7]. There are several disorders in which abnormal or delayed growth and development are accompanied by cutaneous changes. Some lead to short stature (a term preferred to 'dwarfism'), which is a common feature of chromosomal abnormalities. In others, delayed sexual development (infantilism) is also present, and this will be discussed briefly in relation to premature and delayed puberty. It is important to note that due allowance must be made for parental height in assessing possible delayed growth in a child [8].

Some of the more important of the disorders in which skin changes accompany short stature are listed in Table 70.1.

Furthermore, it is well known that severe skin disease of any kind in childhood can have a considerable impact on general physical development. Atopic dermatitis is a good example, short stature being very common in severely affected individuals, at least until puberty [9], although the assessment of this may be complicated by systemic or topical steroid therapy.

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Table 70.1 Disorders in which short stature may occur with cutaneous changes.

Often severe	Moderate
Rothmund–Thomson syndrome	Turner's syndrome
Bloom's syndrome	Hypohidrotic ectodermal dysplasia
Cockayne's syndrome	Marinesco–Sjögren syndrome
Bird-headed dwarfism	Xeroderma pigmentosum
Progeria	Trichorhinophalangeal syndrome
Cornelia de Lange syndrome	Focal dermal hypoplasia
Cartilage–hair hypoplasia	Werner's syndrome
Conradi's disease	Darier's disease
Polydysplastic epidermolysis bullosa	Atopic dermatitis
Ataxia–telangiectasia	
Leprechaunism	
GAPO	
Short stature, alopecia and macular degeneration	

GAPO, growth retardation, alopecia, pseudo-anodontia, optic atrophy.

Puberty and adolescence

Hormonal events and cutaneous changes

Puberty is the period over which the secondary sexual characteristics gradually become manifest as the reproductive system develops to full capacity, and there is rapid somatic growth [1–3]. The term adolescence embraces these events, but is also used in a wider sense to include the phase of psychological and social adjustment to the physical changes. Thus, depending on the society, adolescence may be prolonged well beyond the completion of puberty.

The onset of puberty in the male is heralded by an increase in testicular volume resulting from the appearance of a lumen in each seminiferous tubule and an increase in the size and number of the testosterone-producing Leydig cells. Testosterone is responsible for most of the secondary changes such as enlargement of the penis and larynx, growth of pubic, axillary and beard hair, and also for a rise in sebum excretion and increased axillary sweating. Slight growth of pubic hair, probably provoked by adrenal androgens, may precede the rest and be one of the earliest visible signs of impending puberty. Facial hair usually only starts to appear about 2 years later. A full account of the patterns of hair development is given in Chapter 63.

The age at which these changes occurs is highly variable but Tanner's data on white British boys give some guidance [4–6]. In 95%, the genitalia started to enlarge at between 9.5 and 13.5 years (mean 11.6 ± 0.9 years of age), and functional maturity, indicated by ability to ejaculate, was achieved between the ages of 13 and 17 (mean 14.9 ± 1.1) years. The adolescent growth spurt, when the average gain in height reached a peak of 10 cm/year, a velocity of growth similar to that at the age of 2 years, usually occurred between 12.5 and 15 (mean 14.1 ± 0.9) years, approximately 3 years after the first signs of genital enlargement.

In girls, one of the first signs of puberty is the onset of breast development (thelarche), indicated by the elevation of the breast and papilla to form a small mound known as the breast bud [5,7]. The average age in white North American girls is 9.96 ± 1.82 years and 8.87 ± 1.93 years in their African American compatriots [8], but the breasts continue to enlarge for approximately 2 more years. Breast growth is provoked by the secretion of ovarian oestrogens; the further development of the secretory alveoli during pregnancy requires the action of progesterone as well. Pubic hair also starts to develop early (see Chapter 63). The most obvious feature of puberty, namely first menstruation or menarche, occurs at an average age of 13 years, but within an age range of 10–16.5 years. The early menstrual cycles do not usually involve ovulation, so full reproductive function is generally delayed for a further year or two. The growth spurt, with a peak height gain of 8 cm/year occurs between 10.5 and 13 years of age in white British girls [7]. This is approximately 2 years earlier than in boys. It is also noteworthy that rapid somatic growth precedes the major events of sexual maturation in girls but accompanies or succeeds them in boys.

The pubertal growth spurt appears, in both sexes, to be dependent on androgenic steroids as well as on growth hormone. Boys with growth hormone deficiency respond less well to testosterone than do normal subjects, not only in relation to acceleration of growth but also for development of the secondary sexual characteristics [9].

Gonadal function in both sexes is initiated by two gonadotrophic hormones of the pituitary, namely follicle-stimulating hormone (FSH) and luteinizing hormone (LH). In the male, initiation of spermatogenesis requires both hormones, but secretion of testosterone by the Leydig cells needs only LH. It may be noted that when the earliest sign of puberty in the female is the appearance of pubic hair, this probably results from stimulation by androgens from the adrenal cortex, so-called adrenarche, and is thus

dependent on an output of hypophyseal adrenocorticotrophic hormone (ACTH).

Levels of serum FSH and LH rise in both sexes between the ages of 6 and 17 years [10]. As puberty develops, LH is released in pulses, at first only at night but later also during the day [11,12]. The secretion of both gonadotrophins from the pituitary is controlled by a single releasing hormone, gonadotrophin-releasing hormone (GnRH), a decapeptide produced in the hypothalamus. This is influenced by negative feedback of the gonadotrophins, steroid hormones and a peptide called inhibin, which is produced by the gonads [13].

The important question therefore is what initiates the pulsatile release of GnRH to invoke the onset of puberty [14,15]? Animal studies show that the central component of the neuroendocrine mechanism that governs gonadal function is fully mature by birth [14]. Pulsatile GnRH release occurs during infancy, but there is then a hiatus in GnRH release between infancy and puberty [16]. The mechanisms that control this juvenile quiescence and eventual pubertal reawakening remain uncertain.

It has long been assumed that the initiation of puberty depends on the achievement of a particular body size or composition, suggesting the existence of a central growth tracking device or 'somatometer', rather than chronological age [14,17]. It is not understood how the central nervous system detects such changes in somatic development. The metabolites or hormones that are used by the brain as signals of metabolic maturity have yet to be identified. One suggestion is that developing bone produces a peptide that enters the circulation and imposes the prepubertal hiatus. This would explain the congruence of puberty with bone age rather than with chronological age. For example, it is known that in children with constitutional delay of growth and puberty or with isolated growth hormone deficiency, sexual maturity is chronologically delayed but occurs at normal skeletal age [14].

It is also unclear whether season influences the timing of puberty, as it does for the majority of species that live in changing habitats (see [18] for a review). An annual rhythm in human reproductive success exists in most societies, but it has long been controversial whether this is related to biological or sociological factors [19]. Marked seasonal effects on the timing of puberty have been noted in the female rhesus monkey [20], and, in common with most mammals in temperate latitudes, it is the changing photoperiod that is used to time puberty [18]. Studies in sheep and various species of hamster establish unequivocally that the daily pattern of melatonin secretion from the pineal gland provides an endocrine measure of day length, and mediates its effect on reproductive function. Melatonin is secreted during the hours of darkness, and provides an accurate measure of the length of night. Melatonin is not directly pro- or antigonadotrophic; it solely provides a seasonal cue. Humans show a clear daily rhythm of melatonin secretion [21], so the question arises whether it has a role in triggering puberty. Tumours of the pineal gland have been associated with both precocious and delayed puberty [22,23], although there is no experimental evidence that abnormal melatonin secretion causes reproductive malfunction in such cases. The amplitude of the nocturnal rise in melatonin secretion declines over the period of childhood, and has led to a hypothesis that puberty results from a decrease in melatonin secretion [24]. This view is not supported by animal studies. In both the rhesus monkey and sheep, puberty occurs in the autumn, when the periods of melatonin secretion are actually increasing [18,20]. It may be noted that the initial increase in LH secretion in the pubertal human first occurs at night, when melatonin secretion is high, rather than during the day when melatonin secretion is basal [25]. It seems likely that, although the human has retained a melatonin secretory system, the seasonal information that it conveys, at least, has become disregarded in the course of evolution.

Social cues may also play a part in the induction of gonadal activity, as demonstrated in many mammalian species. For example, introduction of a ram can induce an increase in LH pulse frequency and ovulation in both the seasonally anoestrus and prepubertal sheep, and this appears to be effected through a pheromonal mechanism [16,26]. The demonstration that extracts of male axillary secretions can affect the menstrual cycle when applied to the female upper lip [27] suggests that similar cues may have a role in humans.

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Dermatoses of puberty and adolescence

Adolescence is a difficult period for most people. It is a time when the whole emphasis of relationships is supposed to change from the herd bond of the 'gang' to the pair bond of courtship and sexual involvement, but this does not happen all at once or completely. Most of us retain a need for the approbation of our peers throughout life, as well as a desire to develop a close one-to-one relationship. The tensions involved in this are at their most acute during adolescence and, for this reason, many skin diseases, which first presented during childhood, only begin to exert their most damaging influences after the onset of puberty. Adolescence is a bad time to have skin disease, especially on the face or on the extremities.

The physiological changes that occur in the skin during puberty and adolescence also have several effects, and may result in sufficient distress to cause the individual to seek medical advice. There are several examples of this: the increase in sebum production often results in unacceptably greasy hair, on which many hours and much money is expended; teenagers often present with secondary sexual hair that they perceive to be abnormal, largely as a result of the pressure exerted by the media; young men become anguished when male-pattern balding begins in the teenage years; members of both sexes become disturbed by the onset of 'body odour'.

Table 70.2 Disorders that present in or cause particular problems during adolescence.

Acne vulgaris
Acne excoriée and neurotic excoriation
Self-mutilation and dermatitis artefacta
Seborrhoeic dermatitis
Pityriasis versicolor
Hyperhidrosis
Axillary bromhidrosis (body odour)
Hidradenitis suppurativa
Fox–Fordyce disease
Polymorphic light eruption
Epidermolysis bullosa simplex (Weber–Cockayne syndrome)
Psoriasis
Atopic dermatitis

It has been pointed out that the pressures of coping with a maturing skin are particularly acute for a girl who is persuaded by advertisers that she should have plenty of hair on her head, but none on her face, under her arms or on her legs. Her skin should be free from grease, spots and wrinkles and, moreover, should be odourless [1]. Puberty makes this ideal image virtually impossible to achieve. Several disorders cause special problems or make their first appearance in adolescence. The classic example is acne vulgaris but there are several others (Table 70.2).

Teenagers may present with a variety of skin disorders in which self-inflicted injury is an important component (Fig. 70.1), varying from mild excoriated acne to severe habitual mutilation. The mental state of these individuals ranges from simple mild anxiety to gross personality disorder, psychotic disturbance and instability. Extreme forms of deliberate self-harm almost invariably begin in adolescence, but most continue for many years [2].

Seborrhoeic dermatitis is generally seen only from adolescence onwards, as is pityriasis versicolor in temperate climates. An explanation for this may lie in the alterations in sebum that appear to occur at puberty [3], especially if it is accepted that yeast organisms have a role in seborrhoeic dermatitis (see Chapter 17). This alteration in sebum is also said to be responsible for the virtual disappearance of scalp ringworm after puberty.

Teenagers may seek help for a number of different axillary problems. Severe eccrine hyperhidrosis can be a very distressing complaint, but usually responds well to treatment (see Chapter 45), as does axillary odour (bromhidrosis). More difficult to deal with are abnormalities of the apocrine glands (hidradenitis and Fox–Fordyce disease).

Polymorphic light eruption often presents for the first time in adolescence, and can ruin summer holidays. So does psoriasis [4]; 25% of 5600 patients with psoriasis

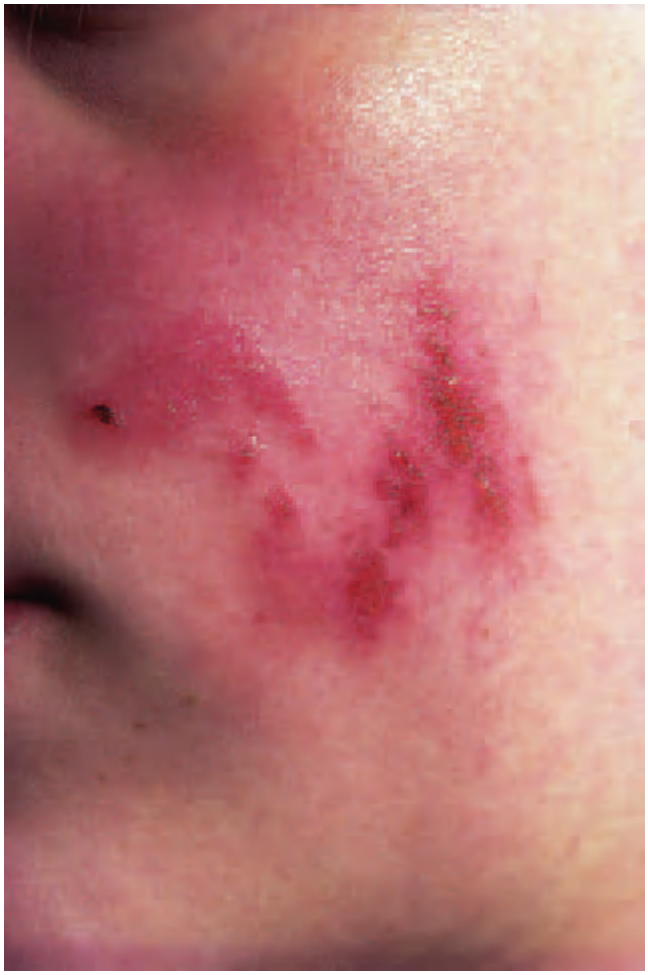

Fig. 70.1 Self-inflicted lesions on the cheek of a teenager.

dated the onset of their disease to between the ages of 10 and 20 years [5]. The impact of the appearance of psoriasis on a teenager should not be underestimated. The patient will be told that psoriasis is probably genetic, that it is likely to continue to be a lifelong problem and that there is no satisfactory cure. All this has to be assimilated during a period of increasing awareness of the importance of being attractive.

Atopic dermatitis can also be a major problem for the teenager and his or her family. It may present for the first time in adolescence, but this is rare. More commonly, children do not grow out of it as they have been led to believe, or atopic dermatitis may disappear during childhood only to reappear in adolescence. In this situation, the skin changes and pruritus are often severe, and usually have already affected the enjoyment of childhood. The adolescent is then quite abruptly faced with the prospect of the skin problem continuing for an apparently indefinite period into adult life. Many, if not all, affected teenagers become increasingly depressed and frustrated, and a sense of hopelessness can descend on the whole family. Many patients completely lose faith in orthodox medicine and seek advice from homeopaths, herbalists, naturopaths and others. A truly sympathetic and holistic approach is therefore required if the dermatologist is to retain the confidence of his or her young patient and their relatives through this difficult period. Good communication needs to be cultivated and maintained. Professional counselling facilities can be very helpful, but are often neglected or not available.

Another troublesome aspect of atopic dermatitis in adolescence is that there is a greater tendency to develop involvement of the hands (and feet) as the years go by. This can lead to difficulties in choosing a suitable occupation (see below). Furthermore, treatment parameters usually differ in adolescents and adults from those in childhood atopic dermatitis [6]. In particular, the information and support needs differ and, in practical therapeutic terms, steroid-sparing strategies may become more important.

Some congenital and genetic diseases, such as tuberous sclerosis and neurofibromatosis, may progress during the teenage years, causing increasing physical and cosmetic disability. Others (e.g. ichthyotic disorders, pigmentary anomalies and port-wine stains), even though largely static, may exert a greater effect because of the social and psychological tensions of adolescence.

However, some disorders improve at puberty. For example, atopic dermatitis clears in many individuals, and autosomal dominant ichthyosis tends to improve.

Skin disease and career

Young people with skin disease are often not aware that they may be at a major disadvantage in pursuing some occupations.

The armed forces medically examine all recruits, and are unlikely to accept anyone with psoriasis, significant atopic dermatitis or bad acne. It is therefore preferable for acne to be eradicated before rather than after application.

Psoriasis and eczema of the hands can be troublesome for those hoping to work in catering. Although they may be accepted by colleges to study, such individuals often find it difficult to obtain subsequent employment.

Hand dermatitis among hairdressers is a far greater problem in those with active atopic dermatitis and in those who have been troubled in the past than in those who are unaffected [7]. A teenager with atopic dermatitis may work in a hair salon for months or even years suffering with hand dermatitis before eventually giving up. The same applies to nursing, where many committed individuals are rejected at the occupational health screen because of eczema. The reasons given include the exposure to irritants that the skin will inevitably have during a nurse's normal duties, and the increased risk of contracting hepatitis and acquired immune deficiency syndrome (AIDS) through broken skin.

Any teenager with a chronic skin disease, especially of the hands, should therefore be made aware of the potential difficulties that he or she may face in the choice of a future occupation. It is better that a change be made early on than after working hard to achieve a set of educational and vocational goals that are unobtainable.

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Premature and delayed puberty and hypogonadism

Although it must be acknowledged that the measurement of the onset and progress of puberty remains somewhat controversial [1], the dermatologist will occasionally see patients with what is a clearly abnormally early or delayed puberty, or with various hypogonadal syndromes. The appearance or non-appearance of sexual hair, or the onset of acne lesions in late childhood are the usual reasons for such referrals. Premature and delayed puberty are matters for endocrinological investigations, but the dermatologist should at least be aware of the range of diagnostic possibilities.

Premature puberty

Signs of puberty before the age of 10 years are generally held to be abnormal. This may result from an early onset of complete (or true) puberty, in which the changes are triggered by early activation of the normal hypothalamo–pituitary–gonadal axis. In some instances, early signs of puberty are caused by false (or pseudo-) puberty, in which sex hormone secretion is independent of the normal control mechanisms. Partial or incomplete puberty is also recognized, and there are two forms: thelarche (isolated breast development) and pubarche (isolated development of pubic and axillary hair). The former may be unilateral and be confused with tumours. It is not clear what causes isolated breast enlargement, although tissue hypersensitivity to oestrogen has been suggested (see Chapter 67). Pubarche is often associated with adrenal androgen secretion, and this may be a priming phenomenon in the early phases of normal pubertal development [2]. Indeed, the very early, isolated appearance of sexual hair may presage a true early puberty, and the distinction can be a very fine one. Table 70.3 gives a clinical classification of early puberty.

Table 70.3 Classification of premature puberty. (From Rayner [3].)

Complete (true)	*False (pseudopuberty)*
Constitutional	Adrenal lesions
Sporadic	Congenital adrenal hyperplasia
Familial	Tumours
Cerebral/neurogenic	Cushing's syndrome/hyperplasia
Tumours	Ovarian tumours
Development defects	Testicular tumours
CNS infections	Iatrogenic (sex hormones)
CNS trauma	*Extrapituitary gonadotrophin-secreting tumours*
McCune–Albright syndrome	Teratoma
Neurofibromatosis	Chorionepithelioma
Tuberous sclerosis	Hepatoblastoma
Silver's syndrome	
Hypothyroidism	
Pineal lesions	
Incomplete	
Premature thelarche, pubarche	

CNS, central nervous system.

Most instances of premature, complete puberty are constitutional. Although this may be sporadic, there is often a strong family history. Indeed, it seems likely that many families never present at all, accepting that it is quite normal for them. This is particularly true for girls, in whom approximately 80% of premature puberty is thought to be constitutional [3]. There is no difference in the order of events, but mental and emotional development may lag behind the physical changes. In boys, where the event is rarer, there is more often an underlying pathological condition [4].

The investigation of complete premature puberty is obviously a complex process, especially if a neurogenic origin is suspected, but the dermatologist should always look for other features of the specific syndromes listed in Table 70.3: McCune–Albright syndrome, neurofibromatosis, tuberous sclerosis and Silver's syndrome (short stature, craniofacial disproportion and clinodactyly [4]), as well as hypothyroidism.

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Delayed puberty and hypogonadism

Puberty can be considered delayed if there is no sign of sexual development by the age of 15 years in boys and 14 years in girls [1]. There are a number of important causes, listed in Table 70.4. Constitutional delay accounts for at least 50% of male cases, and is much more common than in girls [1].

As with premature puberty, pubertal delay requires endocrinological investigation. However, a dermatologist can make a useful contribution if the patient presents first in the skin clinic. Examination can reveal the obesity, short stature and mental retardation of the Prader–Willi syndrome, the polydactyly of the Laurence–Moon–Biedl syndrome, or the increased height and gynaecomastia of Klinefelter's syndrome.

Table 70.4 Causes of delayed puberty. (From Chaussain [1], Kulin [2] and Santen & Kulin [3].)

Constitutional delay
Hypogonadotrophism
Isolated gonadotrophin deficiency
Hypogonadotrophic eunuchoidism (Kallmann's syndrome)
Multiple hormonal deficiency states
Idiopathic
Tumours
Langerhans' cell histiocytosis
Tuberculosis
Sarcoidosis
Vascular disease
Haemochromatosis
Hyperprolactinaemia
Specific syndromes with hypogonadotrophism
Prader–Willi
Laurence–Moon–Biedl
Multiple lentigines
Rud's
Cerebellar ataxia
Systemic disease
Chronic renal failure
Congenital heart disease
Cystic fibrosis
Thalassaemia major
Diabetes mellitus
Hypothyroidism
Gluten intolerance
Anorexia nervosa
Excessive exercise
Hypergonadotrophic hypogonadism
Klinefelter's syndrome
Ullrich–Turner syndrome
Dystrophia myotonica
Trisomy 21 (Down's syndrome)
17β-Hydroxylase deficiency
Androgen insensitivity (testicular feminization syndrome)
Surgical accidents (e.g. during herniorraphy)
Testicular torsion
Anorchia and bilateral cryptorchidism
Irradiation and cytotoxic drugs
Orchitis (e.g. mumps)
Polycystic ovarian disease

Many extraneous factors can also affect the onset of puberty. Malnutrition and extreme forms of exercise, such as long-distance running and ballet training, may markedly delay onset of puberty, probably by interfering with hypothalamic triggering mechanisms [4,5].

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The menstrual cycle

Hormonal influences [1,2]

The menstrual cycle involves changes in the genital tract, which are brought about by two hormones from the ovary. At the start of each cycle, after menstruation is completed, the repair and proliferation of the endometrium, and the synthesis of receptors for progesterone and oestradiol within its cells, are effected by the rising secretion of oestradiol. Following ovulation and the formation of the corpus luteum, the rise in progesterone causes the endometrium to double in thickness and the tubular glands to become tortuous and sacculated. The maintenance of this secretory phase is dependent on both oestradiol and progesterone, and the breakdown of the endometrium that causes menstrual bleeding is a consequence of the withdrawal of these hormones. The cyclic hormonal changes also affect the vaginal epithelium, which can be monitored through desquamated cells in vaginal smears, the consistency and pH of the cervical mucus, and several features of the skin.

Synthesis of oestrogens in the ovary first involves the production of the androgens androstenedione and testosterone, in the theca interna cells of the follicle, and then their conversion to oestrone and oestradiol in the granulosa cells. These processes are stimulated by LH from the pituitary. However, the increased production of oestradiol between the eighth and tenth days of the cycle is also dependent on FSH in the sense that this is responsible for the development of numbers of primary follicles in the early follicular phase, which increases the number of granulosa cells.

Ovulation in the middle of the cycle is associated with surges in both LH and, to a lesser extent, FSH. The surge in LH lasts for approximately 36 h, and is affected by

pulsatile output of GnRH from the hypothalamus. It appears that feedback by oestradiol is responsible: in the early follicular phase, oestradiol acts to inhibit secretion of gonadotrophin but, as the follicle ripens, a threshold is exceeded which switches the feedback from negative to positive.

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Cutaneous changes

Many women notice changes in their skin and hair during the course of the monthly cycle. For example, 70% of Scottish women reported a few acne papules during the premenstrual phase of their cycle, and a significant number of others experienced textural variations. Some found the skin and hair greasier (35%), others drier (16%) [1], despite the fact that sebum production has not reliably been shown to alter significantly. Pre-existing skin disorders, other than acne, may also undergo premenstrual exacerbation; examples are psoriasis, rosacea, atopic dermatitis, lupus erythematosus, anogenital pruritus, recurrent aphthae and herpes simplex [2,3].

Some women experience premenstrual flushing identical in quality to that associated with the menopause. In one study of 120 women with classical features of the so-called premenstrual syndrome, 72% were observed to have such flushing episodes [4]. This phenomenon may be related in part to the general increase in cutaneous vascularity during the second half of the menstrual cycle [5], but detailed investigation of one of these women revealed that each flush (recorded using skin resistance and finger temperature) coincided with a measurable pulse of LH. Identical findings are reported in menopausal flushes (see p. 70.20), suggesting a common pathogenesis.

Other cutaneous disturbances described in the 'premenstrual syndrome', include minor non-specific abnormalities and recurrent boils. Premenstrual oedema has also been described, most commonly of the feet and ankles, but occasionally involving the hands and even the face. In rare individuals this may be very marked.

It is not at all clear what causes most of the symptoms associated with the 'premenstrual syndrome', but there have been many suggestions, including hormonal influences, abnormalities of fluid balance, nutritional changes (including essential fatty acid depletion), neurotransmitters and psychological factors. It seems most probable that the syndrome is a complex of interrelated problems, each with a different basic cause or causes [6].

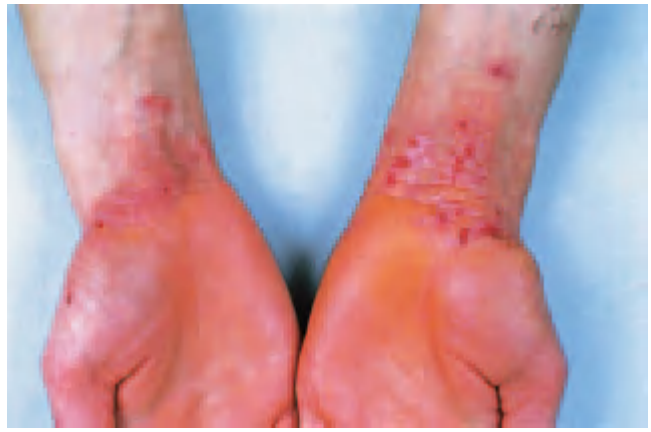

Fig. 70.2 Autoimmune progesterone dermatitis. (Courtesy of Dr J.D. Wilkinson, Amersham Hospital, Amersham, UK.)

Autoimmune progesterone dermatitis (Fig. 70.2)

There are also patients in whom the regular appearance of skin changes in the premenstrual period is associated with evidence of hypersensitivity to progesterone. This has generally been established by skin testing, deliberate challenge with progesterone or the presence of antibodies [7], and the term autoimmune progesterone dermatitis has been coined for this syndrome. The cutaneous lesions that have been described are very variable, resembling eczema, particularly the pompholyx type; urticaria; erythema multiforme [8]; or dermatitis herpetiformis [9]. Many patients develop the eruption after receiving exogenous synthetic progesterone preparations.

Treatment of autoimmune progesterone dermatitis can be difficult. Most patients are unresponsive to topical steroids and antihistamines, but some respond to oestrogen or tamoxifen therapy [7]. One resistant patient required bilateral oophorectomy [9].

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Pregnancy, childbirth and the puerperium

Pregnancy, childbirth and the puerperium are associated with profound physiological endocrine upheavals. Many of the consequent cutaneous changes should be considered normal, although not every woman is happy to accept them in this light. The physiological events of pregnancy and its resolution can also modify a number of concomitant dermatoses and tumours, and there are also some pathological skin conditions that are virtually pregnancy-specific.

Endocrine background [1–3]

Pregnancy is characterized by the advent of a new and unique endocrine organ (the placenta). The endocrine changes of pregnancy start soon after the fertilized ovum becomes implanted in the endometrium, when the developing trophoblast begins to secrete chorionic gonadotrophin. This, in turn, stimulates production of oestrogen and progesterone by the corpus luteum. The increase in the concentration of these steroids suppresses the production of FSH by the pituitary and thus prevents further ovulation. At about the ninth week of pregnancy the fetoplacental unit begins to synthesize pregnenolone and progesterone. Pregnenolone crosses to the fetus and is converted to dehydroepiandrosterone by the developing fetal adrenal. This, in turn, returns to the placenta to be aromatized to oestriol. From about the 12th week there are increasing amounts of oestriol and progesterone, and the corpus luteum of pregnancy regresses.

The placenta also produces lactogen (hPL) in quantities as great as 1 g/day by late pregnancy. This hormone has some somatotrophic as well as lactogenic properties. A human chorionic thyrotrophin (hCT), structurally different from pituitary thyroid-stimulating hormone (TSH), has also been isolated.

Placental hormones are partly responsible for the physiological adaptations that occur in pregnancy including, for example, a considerable increase in blood volume. The thyroid enlarges and takes up more iodine. The pituitary also enlarges and increases its output of ACTH, prolactin and gonadotrophins. Circulating cortisol rises, caused mainly by a decrease in its rate of clearance combined with an increase in cortisol-binding globulin.

The breasts enlarge during pregnancy, most noticeably towards term. In the early phases of a first pregnancy there is a rapid growth and branching of the terminal portions of glandular tissue, together with an increase in the vascularity of the breast as a whole. Later, true acini appear for the first time, and alveolar secretion begins during the second trimester. In the last weeks there is considerable parenchymal cell enlargement and the alveoli become distended with colostrum [3].

The state of pregnancy is ended, at least in part, by an alteration in the balance of the antagonistic actions of oestrogen and progesterone. This is probably 'fine-tuned' by the fetal pituitary–adrenal axis and its effect on oestrogen production [1]. Thus, abnormalities of the fetal brain, such as anencephaly, may lead to abnormally early or late onset of parturition. The tendency of labour to be delayed in mothers bearing children with X-linked ichthyosis is caused by a reduction in the processing of hormones by the placental enzyme steroid sulphatase (see Chapter 34).

After birth, the mother's hormonal status changes yet again. Levels of prolactin rise steadily towards the end of pregnancy, and at childbirth the apparently inhibitory effect of the fetoplacental steroid hormones is suddenly lost, leaving prolactin acting unopposed. This initiates lactation [3].

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Physiological skin changes related to pregnancy

Pigmentation (see Chapter 39)

Most women notice a generalized increase in skin pigmentation during pregnancy, and the change is more marked in dark-haired than in fair-haired women. Areas that are already pigmented become darker, in particular the nipples, areolae, genital areas and the midline of the abdominal wall. In consequence, the 'linea alba' ('white line') may become brown. The pigmentation usually fades after delivery, but seldom to its previous level. Many women also notice an increase in the size, activity and number of melanocytic naevi.

In approximately 70% of women, especially those of dark complexion, chloasmal pigmentation also develops during the second half of pregnancy. Its intensity is not necessarily proportional to that of the general melanosis. Irregular, sharply marginated areas of pigmentation develop in a roughly symmetrical pattern either on the forehead and temples, or on the central part of the face, or both. It usually fades completely after parturition, but may persist.

Similar changes occur in other species. The pigmentary changes of pregnancy have been induced experimentally in non-pregnant guinea pigs by the injection of small doses of oestrogen and progesterone [1]. The extent to which human pigmentary changes are brought about by

these steroids or by melanocyte-stimulating hormones derived from pro-opiomelanocortin (see Chapter 39) is uncertain [2–4].

Hair and nail changes

Many women maintain that hair growth on the scalp is more vigorous during pregnancy. In the latter part, the proportion of follicles in anagen rises, but a compensatory decrease after parturition associated with shedding of hairs may result in noticeable postpartum alopecia [5,6]. Spontaneous recovery is usual. Mild frontoparietal recession may also occur [7].

Minor degrees of hypertrichosis are not uncommon. Hirsutism, accompanied by acne and, in severe cases, by other evidence of virilization, occurs rarely, usually during the second half of pregnancy. It may result from an androgen-secreting tumour, luteoma, lutein cysts or polycystic ovary disease [8,9]. All cases should be thoroughly investigated. A female fetus may be masculinized. In the absence of a tumour that can be eradicated, the problem tends to recur in subsequent pregnancies. Hirsutism may regress between pregnancies, but this is not always complete.

Pregnant women often report brittleness of the nail plate, and some develop distal onycholysis, similar to that seen occasionally in thyrotoxicosis [7].

Eccrine, apocrine and sebaceous gland activity

Eccrine activity may be noticeably increased during pregnancy [7], although palmar sweating diminishes [10]. This may be responsible for the recognized increased frequency of miliaria. It is often said that apocrine gland activity is reduced during pregnancy, but the evidence is conflicting. Hurley and Shelley [11] were unable to find any increase in apocrine sweating immediately postpartum, but they pointed out that Fox–Fordyce disease usually improves in pregnancy, which suggests that apocrine activity has been reduced.

Although there is considerable individual variation, the rate of sebum excretion tends to increase during pregnancy and return to normal after delivery [12].

The rise in sebum excretion during the last trimester of pregnancy, at a time when oestrogens, which suppress sebum secretion, are being produced in large quantities, suggests that a powerful sebotrophic stimulus is released. The sebum excretion rate in women with twins or triplets is no greater than the rate in women with a single fetus, suggesting that the sebotrophic factor comes from the pituitary rather than the placenta [13]. Sebum excretion does not fall in women who are lactating [14], and suckling presumably promotes secretion of pituitary factors, such as prolactin, which either stimulate sebaceous glands directly or enhance their response to androgens.

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Vascular changes

The vascular changes of pregnancy do not differ qualitatively from those in hyperthyroidism or cirrhosis. All are thought to be brought about by the sustained high levels of circulating oestrogen. Vascular 'spiders' are very common in white women but said to be less so in black women [1]. They usually disappear postpartum. Palmar erythema is also common, affecting at least 70% of white women and 30% of black women [2]. In some, it takes the form of a diffuse pink mottling of the whole palm, whereas in others the changes are confined to the thenar and hypothenar eminences [3]. Palmar erythema and vascular spiders commonly occur together.

Less commonly, pregnant women develop small haemangiomas [4,5]. These usually affect the head and neck (Fig. 70.3), and occur in approximately 5% of pregnancies [4].

Varicose veins of the legs and haemorrhoids are frequent complications of pregnancy. A rarer but more serious event is the development of deep-vein thrombosis, which can lead to permanent damage to the leg veins and, occasionally, death from pulmonary embolism. Many pregnant women (possibly 50%) also develop non-pitting oedema of the face, eyelids, feet and hands [6]. The swelling is usually most pronounced in the early morning and disappears during the course of the day. There is no known treatment, but it is important to recognize and differentiate the condition from cardiac, renal or pre-eclamptic oedema.

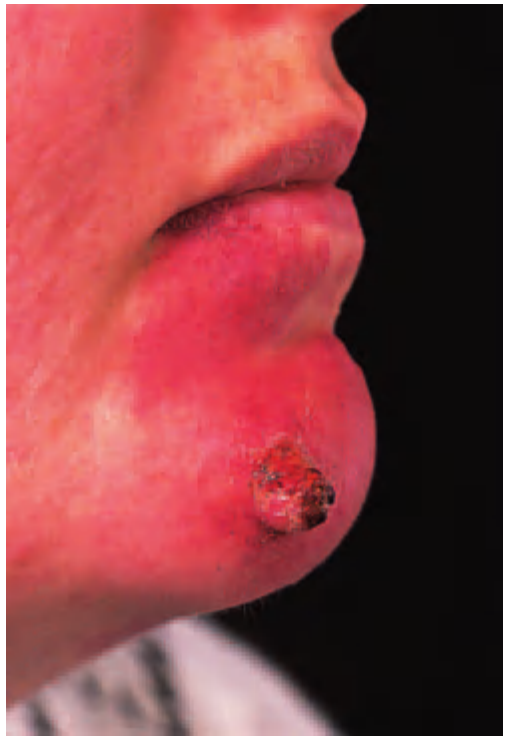

Fig. 70.3 Pyogenic granuloma in a port-wine stain during pregnancy. This woman had similar lesions in three successive pregnancies.

Gingivitis and pregnancy 'epulis'

Eighty per cent or more of pregnant women develop some gingival oedema and redness [6,7]. This can become painful and ulcerative, especially if oral hygiene is poor. In approximately 2%, the gingival changes are associated with the appearance of a small vascular lesion similar to a pyogenic granuloma, known as a pregnancy epulis or granuloma gravidarum. This may bleed profusely on contact. These phenomena, like palmar erythema and vascular spiders, are probably brought about by the general increase in vascularity associated with high oestrogen levels.

In most women, gum changes resolve after parturition. Vitamin C has been used to try to improve the symptomatology.

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Dermatoses modified by pregnancy

Some dermatoses worsen during pregnancy, some improve, and many are unpredictable. Table 70.5 lists those dermatoses and tumours that are commonly modified by pregnancy and the puerperium. The details of most of these are discussed elsewhere in this book; however, some specific points should be noted here.

Infections and immunity in pregnancy

Cell-mediated immunity is depressed during normal pregnancy [1], which probably accounts for the increased frequency and severity of certain infections such as candidiasis. Condylomata acuminata too can be exacerbated, growing very rapidly and occasionally obstructing the birth canal. *Candida*, genital warts and herpes simplex can be transmitted to the baby during childbirth. In babies

Table 70.5 Dermatoses and tumours modified by pregnancy.

Infections
Candidiasis
Trichomoniasis
Condylomata acuminata
Pityrosporum folliculitis
Herpes simplex
Herpes varicella/zoster
Leprosy
Autoimmune disorders
Lupus erythematosus
Dermatomyositis/polymyositis
Pemphigus
Systemic sclerosis
Metabolic disorders
Porphyria cutanea tarda
Acrodermatitis enteropathica
Disorders of connective tissue
Ehlers–Danlos syndrome
Pseudoxanthoma elasticum
Tumours
Bowenoid papulosis
Langerhans' cell histiocytosis
Mycosis fungoides
Malignant melanoma
Neurofibromatosis
Miscellaneous
Atopic dermatitis
Erythema multiforme
Erythrokeratoderma variabilis
Psoriasis (and 'impetigo herpetiformis')
Acne
Hidradenitis suppurativa
Fox–Fordyce disease

of very low birth weight, candidiasis and herpes simplex can be life-threatening [2]. In view of the known oncogenic potential of some strains, there is a debate about whether mothers infected with human papillomavirus should routinely be offered caesarean section, as generally practised for active herpes simplex infection. However, there is doubt whether this practice prevents neonatal infection [3] either by herpesvirus or by genital warts [4]. Bowenoid papulosis (see Chapter 68), a condition closely linked with wart virus infection, may appear for the first time or deteriorate during pregnancy [5].

Podophyllin should never be used in the treatment of warts during pregnancy because of potential maternal and fetal toxicity; physical treatments are preferable [6].

The immune alterations of pregnancy, childbirth and the puerperium have an adverse effect on leprosy in more than one-third of patients [7]. Leprosy reactional states are more common, and the decline in immune reactivity may also lead to an increase in drug resistance [7]. Furthermore, there are specific problems with some antileprosy drugs: thalidomide cannot be used because of its teratogenicity, and clofazimine has been associated with unexplained fetal deaths [8].

Autoimmune disorders

The outcome of most pregnancies in women with systemic lupus erythematosus is undoubtedly better than was once thought, although a few develop renal damage, and disease exacerbation may be severe enough to cause death [6]. Lupus in the mother may affect the baby (neonatal lupus; see Chapter 14). Cutaneous lupus does not appear to be affected by pregnancy [9].

Most women with systemic sclerosis do not experience major problems, and some appear to improve [10]. Occasionally, however, there is severe progressive deterioration of renal function, with hypertension and pre-eclampsia. This may lead to fetal loss or even maternal death [11].

Dermatomyositis and polymyositis are generally unaffected by pregnancy, but some patients may deteriorate.

Metabolic disease

There is no consensus about the effects of pregnancy on porphyria cutanea tarda. Some women experience few problems, and Marks [12] suggested that endogenous oestrogen might be less harmful than exogenous compounds because of the complete absence of deterioration of the porphyria during one normal pregnancy. However, some cases do show clinical and biochemical deterioration, and on one occasion this was shown to be parallel to the physiological rise in oestrogen [13]. Acrodermatitis enteropathica is said always to deteriorate in pregnancy [14].

Disorders of connective tissue

Women with Ehlers–Danlos syndrome types I and IV often have major problems, including bleeding, wound dehiscence and uterine lacerations (see Chapter 46) [6]. They should probably be counselled to avoid pregnancy altogether. Some patients with pseudoxanthoma elasticum have suffered major gastrointestinal bleeds necessitating blood transfusion [15].

Tumours

The relationship between malignant melanoma and pregnancy (and, indeed, exogenous oestrogens) has been discussed for many years [6]. One large series suggests that melanoma developing during pregnancy carries a slightly worse prognosis, but that pregnancy following excision of a tumour does not affect prognosis [16]. Epidemiological studies from the USA have failed to show significant associations between melanoma and reproductive and other hormonal factors in women [17]. Neurofibromas may grow during pregnancy, or appear for the first time. Rupture of major blood vessels in neurofibromatosis has also been reported [18,19], and hypertension is a common complication. Pregnancy may exacerbate mycosis fungoides [20] and the eosinophilic granuloma form of Langerhans' cell histiocytosis [21].

Miscellaneous dermatoses

Atopic dermatitis often improves in pregnancy, but this is unpredictable; in some patients it is exacerbated. Breastfeeding is often a problem for those suffering from atopic dermatitis because of nipple eczema, and the puerperium may herald a deterioration in hand eczema because of exposure to irritants.

Pregnancy may trigger erythema multiforme, and vaginal stenosis has been described in severe Stevens–Johnson syndrome occurring in pregnancy [22].

Marked deterioration in erythrokeratoderma variabilis occurred during pregnancy in two related women [23].

The effects of pregnancy on psoriasis are variable, although often consistent in the same individual. A rare occurrence is the sudden eruption of acute pustular psoriasis. This used to be considered as a distinct entity called *impetigo herpetiformis*, but this term is probably best discarded.

Acne may improve, but is occasionally exacerbated during pregnancy. This can cause management problems, because a number of antiacne drugs are contraindicated in pregnancy.

Hidradenitis suppurativa and Fox–Fordyce disease often improve considerably, and it is generally presumed that this is a result of a reduction in apocrine gland activity.

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AIDS and pregnancy

AIDS is a worldwide problem, and there have now been many pregnancies in women infected by human immunodeficiency virus (HIV). The infection has often only become apparent after birth when the children developed AIDS. Although it appears that pregnancy may subsequently accelerate the development of AIDS symptoms [1,2], there does not seem to be a tendency for HIV disease to progress during pregnancy itself [3]. If opportunistic infections, such as *Pneumocystis* pneumonia or listeriosis, develop in a pregnant woman with AIDS, the outcome is generally fatal [4,5]. This contrasts with the more usual 70% recovery rate in non-pregnant AIDS patients and suggests that the immune suppression of pregnancy may be additive to that of HIV infection. Kaposi's sarcoma has also been reported in AIDS in pregnancy [6]. The effects of maternal HIV infection on the child can be devastating [7].

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The dermatoses of pregnancy

Irritation, rashes and other skin changes are common in pregnancy [1]. The possibility that the patient has an unrelated skin condition such as scabies must not be overlooked. However, there are several skin changes that appear to be specifically related to pregnancy and the puerperium, distinct from physiological events, and not caused by exacerbation of a pre-existing condition.

Pruritus gravidarum

Itching in pregnancy is dealt with here because it is uncertain whether it is an extension of the physiological changes or a specific dermatosis [2,3].

As many as one-fifth of pregnant women experience some itching [4]. In most, this can be attributed to some identifiable skin disorder such as scabies, eczema, urticaria, a drug eruption or one of the specific pregnancy-related inflammatory dermatoses discussed below. However, there is also a small group of women who experience intense pruritus without evident primary cutaneous changes, and it is to these patients that the term pruritus gravidarum is applied.

It is generally considered that pruritus gravidarum is a mild variant of recurrent cholestasis of pregnancy, and occurs in 0.02–2.4% of pregnancies [5]. The itching begins in the second or third trimester and is often localized to the abdomen, or the palms and soles, although it may also be very widespread. The patient may be mildly icteric.

Liver function tests are occasionally abnormal, with a raised alkaline phosphatase [2].

The cause is thought to be multifactorial [6], although it is probable that the irritation itself results from abnormal hepatic excretion of bile acids induced by metabolites of both oestrogen and progesterone, both of which have been shown to affect the handling of bile acids [6,7]. The condition also occurs more commonly in mothers of patients with rare inborn cholestatic syndromes [6].

The itching usually subsides rapidly after childbirth, but may persist for some weeks into the puerperium. It may also recur with subsequent pregnancies and the use of oral contraceptive pills. Recurrent attacks increase the liability to cholelithiasis [4]. Treatment with ursodeoxycholic acid is effective in reducing itch and abnormal liver function tests [6].

Striae

Striae distensae (striae gravidarum) are a common and striking feature of most pregnancies. They are dealt with fully in Chapter 46.

Skin tags

SYN. MOLLUSCUM FIBROSUM GRAVIDARUM

Multiple tags often appear in the second half of pregnancy. These are most common on the face, the side of the neck, in the axillae and under the breasts. The histological features are those of ordinary skin tags [8]. They are usually small, but may reach 5 mm in size. They generally regress in the puerperium, and it has been suggested that they are probably a result of hormonal factors [2].

'Cracked' and sore nipples

Many women experience discomfort, irritation and fissuring of the nipples, especially early in the puerperium as they are trying to establish breastfeeding. Anatomical features, such as relatively flat nipples, contribute to the development of this problem. Mastitis and deep abscesses may occur because of penetration of the broken skin by pyogenic bacteria. The problem is, in essence, one of friction and irritation, and can be eased considerably by the judicious use of gentle cleansing and emollients.

Inflammatory dermatoses specific to pregnancy

Classification. The older literature is confusing. Dermatoses considered distinct by some authors are lumped together by others. Holmes and Black [9] have suggested a rationalization of the terminology, and have proposed a classification that seems the most logical for practical use (Table 70.6), even though alternatives are still employed. Ackerman *et al*. [10] argue that there really are only two dermatoses in this category: pruritic urticarial papules and plaques of pregnancy (PUPPP) and pemphigoid gestationis. However, some of the other dermatoses that have been reported as being pregnancy-associated are discussed here, drawing attention to those descriptions that appear to be at least clinically distinct from PUPPP or pemphigoid gestationis, and reviewing whether others are really distinct entities or not.

Table 70.6 Specific dermatoses of pregnancy. (From Shornick [12].)

Pemphigoid (herpes) gestationis
Polymorphic eruption of pregnancy
Prurigo of pregnancy
Pruritic folliculitis of pregnancy

Pemphigoid (herpes) gestationis [11,12]

This rare and highly characteristic disorder affects approximately 1 in 150 000 pregnancies and is considered in detail in Chapter 41. The disease usually appears in the second or third trimester, and presents with an intensely itchy urticarial or vesiculobullous eruption. Immunofluorescence reveals a linear band of immunoglobulin G (IgG) at the basement-membrane zone, identical to that seen in bullous pemphigoid. Recent studies involving tissue typing have supported earlier suggestions of a genetic predisposition [13].

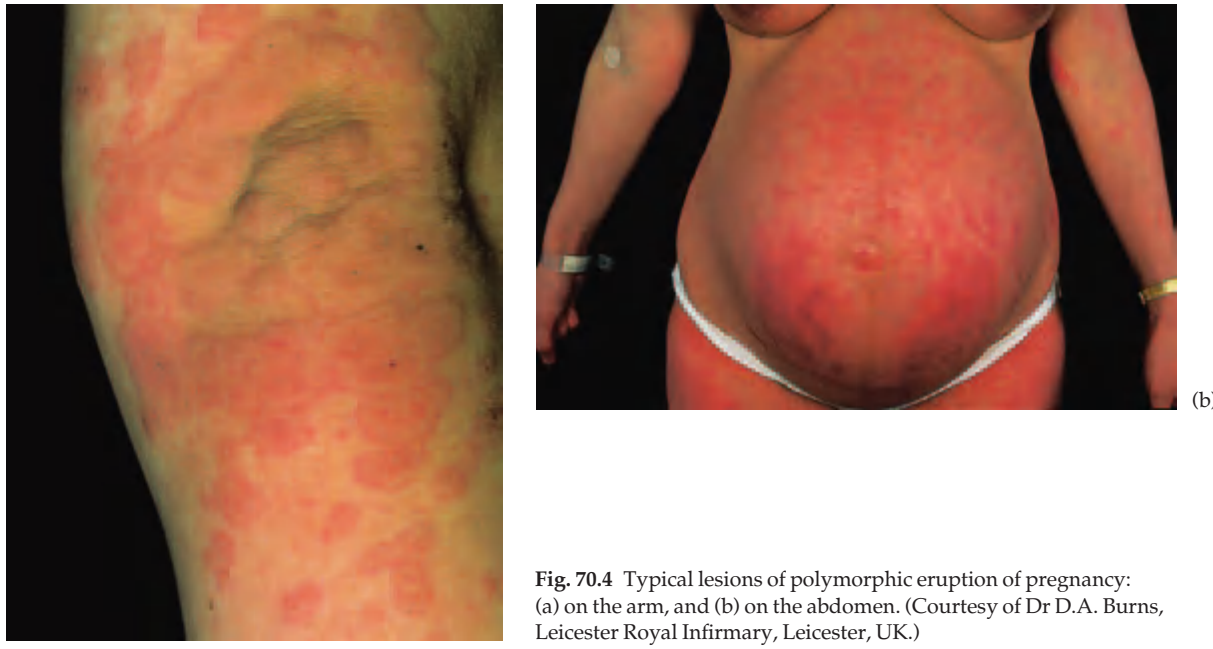
Polymorphic eruption of pregnancy

SYN. PRURITIC URTICARIAL PAPULES AND PLAQUES OF PREGNANCY

In addition to the above designations, these skin changes have been known as toxaemic rash of pregnancy [14], toxic erythema of pregnancy [15] and 'late onset' prurigo of pregnancy [16]. It is probable also that some patients with this condition have been recorded in the literature as prurigo gestationis (see below), erythema multiforme and pemphigoid (herpes) gestationis.

If there is agreement that all these disorders are one and the same, there is still no consensus on which name to use. In the UK, as proposed by Holmes and Black [9,11], the term polymorphic eruption of pregnancy is favoured. Elsewhere, the lengthy descriptive phrase 'pruritic urticarial papules and plaques of pregnancy' or 'PUPPP', as suggested by Lawley *et al*. [17], still finds favour, especially in the USA [18].

Incidence. Polymorphic eruption of pregnancy occurs in approximately 1 in 240 pregnancies [2]. The eruption begins in the third trimester, usually of a first pregnancy, but is occasionally delayed until a few days postpartum. It rarely recurs in subsequent pregnancies [11,17,18], but when it does it is often less severe [2].



(a) (b)

Fig. 70.4 Typical lesions of polymorphic eruption of pregnancy: (a) on the arm, and (b) on the abdomen. (Courtesy of Dr D.A. Burns, Leicester Royal Infirmary, Leicester, UK.)

Aetiology. The cause remains obscure, although the condition has been related to abnormal weight gains in the mother and the newborn, and to twin pregnancy [19]. As the disorder occurs predominantly in primigravidae in the third trimester, it has been postulated that excessive abdominal distension may act as a trigger for the skin changes. The typical distribution (see below) may lend some credence to this view. It has also been shown that serum cortisol levels are low in patients with polymorphic eruption of pregnancy, while human chorionic gonadotrophin (hCG) and oestradiol are normal [20].

Pathology [11,16,17]. The histology of this condition is non-specific, and there are many similarities with the early prebullous phase of pemphigoid gestationis. Most biopsies show epidermal and upper dermal oedema, with a perivascular infiltrate of lymphocytes and histiocytes. There may be a striking number of eosinophils (as there may be in pemphigoid gestationis). Spongiotic vesicles are also seen, and there may be patchy parakeratosis.

Immunofluorescence is uniformly negative, even by immunoelectron microscopy, and this provides the best means of distinguishing this disorder from pemphigoid gestationis, should there be any diagnostic doubt [21].

Clinical features [11,16,17]. The patient usually complains of intense itching. The skin lesions closely resemble the very early stage of pemphigoid gestationis. The eruption consists predominantly of urticated papules and plaques. Less commonly, vesicles, target lesions and polycyclic erythematous areas are seen.

The most striking feature, however, is the distribution of the lesions. They usually begin and predominate on the abdomen, often closely following the lines of the striae, where present (Fig. 70.4). The umbilicus is frequently spared. Lesions often also appear on the upper arms and thighs.

Despite the outdated term toxaemic rash of pregnancy, there is no suggestion that polymorphic eruption has any adverse effect on the outcome of the pregnancy. Indeed, the babies tend to be larger than normal [19].

Treatment. Some patients improve with topical calamine or steroids and systemic sedative antihistamines. Most women are relieved to learn that the condition is not serious, that all should be well with them and their baby, and that the rash will disappear at or soon after childbirth.

Prurigo of pregnancy [16]

SYN. EARLY ONSET PRURIGO OF PREGNANCY; PRURIGO GESTATIONIS OF BESNIER

The main differences between this disorder and polymorphic eruption of pregnancy are that it begins earlier—usually between 25 and 30 weeks' gestation—and that there are no urticated lesions. It occurs in 1 in 300 pregnancies. Clinically, there are multiple excoriated papules over the abdomen and on the extensor surfaces of the limbs. Histology reveals acanthosis and parakeratosis, with perivascular lymphocytic infiltration around upper dermal vessels. Immunofluorescence is negative. The lesions tend to persist throughout pregnancy, and may continue well into the puerperium, although the pruritic element often settles shortly after delivery [2]. As with polymorphic eruption of pregnancy, the mother and fetus are unaffected, but prurigo of pregnancy may recur in successive

pregnancies, which can cause significant distress to the pregnant woman. It has been suggested that cases labelled 'prurigo of pregnancy' may, in fact, have been eczema [20].

Only symptomatic treatment is available, and this is often rather unsatisfactory.

Pruritic folliculitis of pregnancy [22]

This disorder begins in the second or third trimester, and usually resolves within 2 weeks of delivery. The eruption consists of masses of itchy red follicular papules. It strongly resembles steroid-induced acne. Histology reveals a non-specific folliculitis. Immunofluorescence is negative. There is no adverse effect on mother or baby.

Less well-defined dermatoses

Papular dermatitis of pregnancy

Considerable controversy surrounds this entity. It was first described by Spangler *et al*. [23] in 1962, who reported a widespread papular eruption, which they estimated to occur only once in every 2400 pregnancies. In the original description, the rash consisted of widespread, 3–5 mm, intensely itchy papules with a smaller central crust. There were several laboratory abnormalities, including markedly raised urinary chorionic gonadotrophin levels and low urinary oestriol. Of most significance was the observation that there appeared to be a 30% fetal mortality with this eruption. However, there have been no other convincing reports, and a recent review of 85 patients found no evidence of increased fetal loss [24]. The confusion may have arisen because Spangler *et al*. [23] included fetal deaths in pregnancies unaffected by a rash, and spontaneous abortions, without qualifying these by gestational age [2].

It is now generally accepted that the changes reported as papular dermatitis of pregnancy are probably those of pregnancy prurigo, and that the fetal loss in Spangler *et al*.'s series was overestimated.

Autoimmune progesterone dermatitis of pregnancy

There is a single case report of a patient who developed an odd acneiform rash on the extremities and buttocks in two successive pregnancies [25]. There was an associated arthritis and a positive skin test reaction to progesterone. The author used the term autoimmune progesterone dermatitis to describe this phenomenon, thereby leading to confusion with the condition of the same name that is not pregnancy-associated (see above). However, the clinical features of the two disorders are quite distinct.

Prurigo annularis

Two reported cases [7] had annular scaly lesions that persisted for years postpartum. Whether it really had anything to do with the pregnancy must be in doubt.

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The menopause

Hormonal and physiological changes

Strictly speaking, the term *menopause* is used to define the fixed single point in a woman's life characterized by her last menstrual period [1–4]. This is established formally after 12 months of amenorrhoea in the middle years of life [5]. The surrounding years, or climacteric, are a time of change and readjustment to the new phase heralded by the menopause and its loss of fertility: literally, *climacteric*

means a step up the ladder. It is a crucial phase for a woman, preparing her for the years to come which, in modern societies at least, may now represent as much as 30 years, or one-third of her life [6,7]. It has been estimated that by 2030, there will be 1.2 billion postmenopausal women worldwide [8].

The age of onset of menopause has been the subject of much study, and some of the data have been criticized because of flaws in their collection and interpretation [5,9]. However, menopause occurs between the ages of 45 and 55 years in 65–70% of women, and the median age in most Western populations is around 50 years. Factors that may influence menopausal age include heredity (age of mother's menopause is highly predictive), smoking, parity, socio-economic factors, exposure to toxins and nutrition [5]. The onset appears to occur a little earlier in developing countries than in Western societies [9].

True premature menopause before the age of 40 years occurs in less than 1% of women [10], but can follow surgery, irradiation, viral infections (especially mumps), accompany various enzymatic and hormonal defects, or be associated with a number of systemic disorders such as Addison's disease, rheumatoid arthritis, diabetes or myasthenia gravis [1].

During the reproductive years, oestrogen is produced mainly by ovarian follicles, but at the menopause there are major changes. There are very few follicles left, the ovaries become atrophic, and the levels of ovary-derived oestrogen fall. The endocrinology of this period of a woman's life results from the interrelationship of reduced ovarian function and resultant changes in gonadotrophins. Although there may be intermittent bursts of oestrogen in the immediate postmenopausal period because of residual follicular activity, the level of plasma oestradiol ultimately falls to less than 20 pg/L and remains there for the rest of the woman's life [9]. The ratio of oestradiol : oestrone changes, with oestrone becoming the more abundant hormone [11], and most oestrogens being derived from the direct peripheral conversion to oestrone of androstenedione, which has been produced by the adrenals. Some oestrone may arise through the alternative pathway via testosterone and oestradiol [6]. The pituitary–gonadal feedback loop is virtually absent, and levels of gonadotrophins are elevated in consequence. In addition, a number of granulosa cell-derived peptide hormones influence FSH levels [12].

These hormonal changes are reflected in a number of physiological alterations [1]. In the breast, glandular tissue decreases and fibrous tissue increases. The body of the uterus becomes smaller and its muscle is partly replaced by fibrous tissue, and the endometrium regresses and becomes atrophic. However, it still retains the capacity to respond to exogenous hormones. The vagina becomes shorter and narrower, and the vaginal epithelium atrophies. The pH of the vagina rises, and infections become more frequent. The external genitalia atrophy, with a loss of vulval subcutaneous fat and thinning of the vulval epithelium. Pubic hair diminishes.

The epithelium of the lower urinary tract also atrophies and this, together with the increased tendency to prolapse, increases the frequency of urinary tract infections. There is a loss of elasticity in the pelvic supporting ligaments, contributing to prolapse and urinary incontinence [13].

There are no structural cutaneous changes that are specifically associated with the menopause, but there are oestrogen receptors in the skin, suggesting that the skin is a target organ for oestrogen and that its withdrawal may be important [14]. It is interesting that there is a far greater concentration of oestrogen receptors in facial skin than in skin on the breasts or thigh. Some of the changes seen after the menopause, such as dryness, epidermal thinning and loss of dermal elasticity, may result, in part, from lower circulating oestrogen levels. Certainly, administration of oestrogen to castrated animals leads to thickening of the dermis and decreased breakdown of collagen. Oestrogen given to postmenopausal women also increases dermal thickness [15], and in preliminary studies has been shown to improve skin elasticity and deformability [16]. The application of topical oestrogens to the face in menopausal women has also been reported to improve various parameters, including reduction in the depth of wrinkles [17]. However, the picture is not as clear-cut with regard to the epidermis. Hormone replacement therapy (HRT) may increase the skin's water-holding capacity [18].

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Skin disorders of the menopause

Atrophic vulvovaginitis

It has been known for many years that the atrophic changes in the female external genitalia described above respond, at least partially, to topical oestrogens [1].

Menopausal flushing

The most consistent and distressing complaint associated with the menopause is flushing [2]. This is usually described as a sudden feeling of intense heat in the face, neck and chest, often accompanied by discomfort and sweating. Although the intensity and duration vary, it typically lasts 3–5 min. Visible changes occur in approximately 50% of women, and generally consist of a blotchy erythema on the face, neck, upper chest and breasts. Some women also develop palpitations, throbbing in the head and neck, headaches, waves of nausea and anxiety attacks. Sleep disturbance is not uncommon [3]. It is possible to measure several physiological changes during hot flushes, including increased temperature, pulse rate and respiratory rate [4,5].

Flushes are associated with pulsatile release of LH [6], presumably because of failure of the normal feedback mechanisms. However, flushing can occur after hypophysectomy [7], and so LH itself cannot be responsible for the observed vasomotor instability. One suggested mechanism involves alteration of hypothalamic catecholamine levels, and a failure of normal central thermoregulatory centres through LH-releasing hormone neurones [2]. Flushes similar to those seen in the menopause can be induced by an enkephalin analogue and blocked by naloxone infusions [8], indicating that menopausal hot flushes may also be mediated by an opiate-dependent central mechanism [9].

The consensus is that oestrogen therapy is the most effective treatment for symptomatic hot flushes [2], although not all authorities have always agreed [5]. Alternatives that can be considered when oestrogens are contraindicated include various progestins [10], clonidine [11] and methyldopa [12]. A mixture of ergotamine, belladonna alkaloids and phenobarbital failed to stand up to double-blind trial analysis [13], but may still be worth trying if all else fails.

Keratoderma climactericum

This term has been used to describe the appearance of hard skin on the palms and soles, especially around the heels. Although originally reported as a specific association with the menopause [14], the same changes are seen in men and women at other ages, many of whom are obese. It may therefore be a non-specific effect. There has been a report of a therapeutic response to systemic retinoids [15].

Lichen sclerosus et atrophicus

This disorder is considered in detail in Chapters 56 and 68 but is mentioned here because of its frequent presentation at or around the menopause, and because of the significant symptomatology it may cause.

Complications of HRT

The increasing use of HRT, largely to prevent osteoporosis and cardiovascular disease, has revealed a number of problems associated with this treatment. There is an ongoing debate regarding the relationship between HRT and cancers of the breast and genital tract, but this is beyond the scope of this chapter. However, HRT may be responsible for a number of cutaneous problems, which should at least receive a mention here.

Oestrogen therapy may trigger or exacerbate, amongst others, chloasma (melasma); spider angiomas; darkening of naevi; the skin changes of porphyria cutanea tarda; and acanthosis nigricans [16,17]. Many clinicians also report encountering urticarial or eczematous dermatoses that appear in patients on HRT and subside on cessation of treatment. Allergic reactions have been reported to the transdermal patches frequently used as delivery systems for HRT. These may be to the adhesives or to the oestrogens themselves [18].

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Old age

Introduction

Senescence in the skin is a gradual process that ultimately results in the appearances and functional differences that we associate with old age. However, by no means all of these changes are purely intrinsic. The skin is particularly vulnerable to the 'ageing' effects of a number of environmental insults, especially UV radiation, and in women there are additional hormonal changes at the menopause (see p. 70.18). These factors are superimposed on the background changes of intrinsic senescence, and care needs to be exercised in interpreting which are most important in determining any particular aspect of the appearance and function of the skin in an elderly person. However, there have been increasing efforts to disengage the roles of these intertwined and contemporaneous processes.

Biology of ageing

Ageing is the decline in the power of self-maintenance, the increase in susceptibility to disease and the growing probability of death as age advances. Ultimate senescence is as much a biological necessity as initial survival; evolutionary progress has occurred because animals are programmed for both. In the words of Macfarlane Burnet [1], 'The two basic evolutionary needs of all species of higher animal are survival to reproductive age, and death when survival offers no reproductive advantages to the species.'

Modern theories of ageing fall into two categories that, philosophically speaking, start from opposite poles. The first views ageing as an ordered process delicately programmed by the genes [2]; the second suggests that ageing is caused by the progressive retention and amplification of errors in the replication of genetic information in the somatic cells [1]. From the practical viewpoint, both types of theory emphasize the intrinsic inevitability of the process.

If the ageing of most of the bodily organs has, however reluctantly, to be accepted, the ageing of the facial skin appears to be a matter of widespread concern. The reason is that the skin plays a major part in our social and sexual interactions; the concern is not so much to do with physiological functions, which may remain adequate in old age, but about continuing effectiveness, particularly of the facial skin, in communication. To display sexuality or assert social status it is necessary to have skin and hair that look, feel and smell attractive.

The ageing of skin has so far been studied for social and commercial reasons in affluent white populations. Some of these subjects are ill adapted for the environments they now occupy or the lifestyles they endure or enjoy. It must not therefore be assumed that the data obtained will necessarily apply to skin with greater pigmentation, especially that of Mongoloid and Negroid populations.

The most obvious signs of an ageing skin are atrophy, laxity, wrinkling, sagging, dryness, yellowness, a multiplicity of pigmented and other blemishes, and sparse grey hair. Some of these stigmata clearly have genetic components, and some are mimicked by heritable disorders. The abnormal texture of the dermis in cutis laxa makes young children look old; in progeria, on the other hand, the connective tissue remains evenly dense, although the epidermis shows mottled pigmentation [3].

Intrinsic changes of ageing fall into two categories: those that appear to be engendered within the tissues themselves, and those that are the result of alterations, including hormonal, caused by senile changes in other organs. An example of the former is the greying of hair, and of the latter, the lowering of sebaceous gland activity consequent upon reduction of androgen secretion.

Into a third category must be put changes that are mainly the result of environmental factors. These may be overriding; for example, it has been stated that on exposed skin more than 90% of age-associated cosmetic problems are caused by UV radiation [4].

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The ageing skin

Dermis

It cannot be doubted that wrinkling of senescent skin is almost entirely the result of changes in the dermis. The debatable questions concern the nature of these changes

and the extent to which they are intrinsic or environmentally caused [1,2].

The dermis diminishes in bulk, and in absolute terms the collagen per unit area of unexposed skin decreases with age [3]. There also appears to be a steady decrease in the number and size of mast cells and fibroblasts [2]. Although it is often assumed that the lax skin of the aged results from lack of water, there is evidence that, on the contrary, water content increases between the fourth and ninth decades [4].

Gross morphological changes, especially in the collagen and elastin fibres, have been revealed by electron and light microscopy. Their relationship to molecular changes as determined by physical and chemical methods requires interpretation. Moreover, it has long been clear that such changes are largely the result of exposure to solar radiation (photoageing) [5].

Accumulating evidence indicates that intrinsically aged skin shares a number of features with photoaged (environmentally aged) skin. Commercial interests have dictated a more detailed interrogation of the mechanisms underlying photoageing. However, the same research techniques are now being applied to intrinsically aged skin. There is an age-related loss of fibroblast frequency and size, coupled with a decrease in their synthetic ability [6]. Over the age of 70 years, there is loss of collagens I and III in the papillary dermis with an associated increase in matrix metalloproteinases [7]. Reactive oxygen species and free radicals are key drivers of degeneration so characteristic of aged skin. This oxidative damage is produced in part by the action of mitogen-activated protein (MAP) kinases. In aged skin, stress-activated MAP kinase activity is elevated [8].

In the dermis of young adults, the collagen bundles are well organized. They form a rhomboid network with the individual bundles lying at angles to one another. Intertwined among the collagen bundles lie single branching elastic fibres, apparently aligned haphazardly, in planes parallel with the surface at all levels beneath the dermal–epidermal junction. The network of collagen bundles, although composed of inextensible fibres, is itself extensible as the bundles rotate relative to one another to form parallel alignments. It seems likely that the return of the network to its unstretched state is brought about by the interwoven elastic fibres [9]. Thus, in cutis laxa, an uncommon disorder in which the skin hangs in folds, the elastic fibres appear to be reduced in number and degenerate (see Chapter 46).

The various descriptions of changes in ageing based on histological staining techniques are often confusing. In general, it appears that the collagen bundles become fragmented and disorientated, and elastin fibres become progressively reduced [10]. However, in senile skin from exposed areas there may, paradoxically, be a striking increase in fibres that take up elastin stains in actinic elastosis (see Chapter 46).

Elastic fibres gradually disintegrate with age, even in protected skin, and after the age of 70 years most fibres appear abnormal [11–13]. These changes are most likely a combination of reduced synthesis and elastolysis. Similar changes can be produced in protected buttock skin within hours by incubating it with pancreatic elastase and bovine chymotrypsin [11].

Epidermis

Many differences between a senile and young epidermis have been described, but a consistent interpretation of the ageing process has proved difficult. In part, this is because the epidermis varies from site to site. Young skin from the back [14], like that from the scalp and axilla [15], has deep and complex rete ridges, whereas that of the face [15] has a fairly flat dermal–epidermal junction. It is widely agreed that in areas where the junction is corrugated in youth, it becomes flattened in the aged [15–20].

Similarly, there are differences in epidermal thickness, even in young skin. On the face or on the dorsum of the hand, for example, it is considerably greater than on the arms, legs or trunk [15]. In many areas, the whole epidermis becomes thinner with age, and the cells become less evenly aligned on the basement membrane and less regular in size, shape and staining properties [15,19–22].

The question of whether these changes result from alterations in the rate of cell replication has also engendered controversy, largely because of differing methods of study [23]. However, there is now some consensus that the cell turnover rate is halved between the third and seventh decades of life [21,24,25], notwithstanding an earlier finding that the frequency of mitoses in abdominal skin increases from childhood until the fifth decade and then levels out [26]. The evidence that the rate of epidermal repair and wound healing declines with age [27] is consonant with the view that epidermopoiesis is decreased.

The permeability of the skin also changes with age, although some of the data are contradictory [28]. According to Christophers and Kligman [16], the capacity of the isolated horny layer *in vitro* to restrict water loss does not differ between young adults and persons over 70 years of age, but the aged skin is decidedly more permeable to chemical substances. However, *in vivo*, they found that the percutaneous absorption of testosterone appeared to be reduced in old age. A possible explanation is that, although substances enter aged skin more easily than young skin, they are removed more slowly into the circulation because of changes in the dermal matrix and reduction in the vasculature [4]. The response to blistering agents, such as 50% ammonium hydroxide, is initially quicker in elderly than in young subjects, but the formation of the full blister takes longer [29].

These physiological differences must be largely related to changes in the stratum corneum, yet neither its thickness nor the number of cell layers seem to vary with age, at

least on the back [16]. However, Marks [30] showed that the surface area of individual corneocytes from unexposed areas of the arms, thighs and lower abdomen increases with age, and suggested that this might reflect an increased transit time [31].

A change in the nature of the corneocytes is also indicated by the tendency of the senescent epidermal surface, especially that of the lower legs, to become dry, flaky and sometimes itchy. Apart from reduced function of the skin glands, the water-binding capacity of the stratum corneum appears to be reduced [32], coupled with an increase in renewal time if damaged [33].

Pigmentation

The most obvious senile change in white skin is irregularity of pigmentation. Yellow or brown macules, known as 'liver spots' or 'age spots', develop on the backs of the hands and exposed parts of the face in more than 50% of persons over 45 years of age. Very rarely, such *senile lentigines* develop into *lentigo maligna*, which is a precancerous condition, although it progresses very slowly [33].

The senile lentigo consists of a localized proliferation of melanocytes at the dermal–epidermal junction [34]. In general, however, the number of dopa-positive melanocytes in both exposed and unexposed skin decreases in old age, although their size increases. The reduction is in the order of 8–20% per decade compared with young adult skin [35]. Their reaction to dopa becomes variable, and some no longer donate pigment [33,36,37].

Even heavily pigmented skin darkens. A study of 578 adult natives of New Guinea revealed that pigmentation increased with age in skin exposed to the sun, but not in axillary skin, and that males darkened more than females [38].

Greying of hair

Greying usually becomes evident around the age of 50 years, by which time about half the population has approximately 50% grey or white body hairs and an even greater proportion has some depigmented scalp hair [39].

The bulbs of grey or white hairs show various abnormalities, but it is uncertain which are critical. In general, the bulbs appear to lack or be deficient in tyrosinase, the enzyme necessary for the first stages of melanin synthesis [40]. Structurally, the follicles of grey hairs still have melanocytes placed normally over the dermal papilla, but the cytoplasm may contain large vacuoles and the melanosomes may be only lightly melanized [33]. The follicles of fully white hairs may completely lack melanocytes. However, among grey or white hairs, there may be a few normal bulbs producing dark hairs.

An unexplained fact is that at all ages from their appearance on the chest in males, and probably elsewhere, grey hairs tend to be thicker and longer than pigmented ones [38].

Premature greying of hair, even before the age of 20 years, is a feature of several hereditary syndromes, and is also associated with a number of disorders induced by organ-specific antibodies. A survey of the age prevalence of normal greying of hair in men [41] showed that it fitted a simple mathematical model of ageing consonant with the view that the condition is 'autoaggressive' or 'autoimmune' in character and arises from somatic gene mutations.

Hair follicles [42]

Changes in the hair follicles vary greatly between sites. For example, it can be widely observed that hair becomes sparse on the vertex while it is still luxuriant on the occiput, and that greying usually starts at the temples.

In the scalp, the density of hair follicles steadily decreases with age, more rapidly in bald than in non-bald persons [43]. The overall capacity of the follicles to produce long hairs is progressively reduced, at least on the vertex, and especially in males. This cannot be accounted for by any diminution in the rate of growth, which remains substantially unchanged [44]. It must therefore result from a shortening of the duration of anagen. This is reflected by the gradual rise in the proportion of follicles in telogen, both in non-bald subjects [45] and in persons with pattern alopecia, where it becomes evident in advance of visible baldness [46].

Scalp hair also becomes finer, especially in persons with visible alopecia. In a group of 58 white women with diffuse alopecia, 13 of whom were clinically hypothyroid, there was a gradual reduction in mean diameter which appeared to be an exaggeration of a trend also found in normal subjects [47]. The diameters showed a wide range, with a single peak around 0.08 mm in normal persons, but two peaks at 0.04 and 0.06 mm, respectively, in patients with alopecia, suggesting that not all the follicles behave identically.

The weight of beard grown per day reaches a peak in the fourth decade, and starts to decrease slightly in the seventh decade [48]. As the density of the hairs remains constant, the decrease in weight must be accounted for by a reduction in the rate of growth, in diameter, or in both. Evidence that the linear growth of beard hair is correlated solely with levels of 5α-dihydrotestosterone (DHT) in the plasma, not with testosterone, whereas hair density is significantly correlated solely with testosterone, not with DHT [49], suggests that the age changes may result not so much from reduced production of testosterone as by lessened peripheral metabolism.

Chest hairs, which are also androgen-dependent, reach a maximum in number, breadth and length around the fifth decade, and then start to diminish markedly [39].

Axillary hair reaches a peak in mass and in rate of production towards the end of the third decade in males and females alike, and this is followed by a rapid decline,

somewhat more severe in females [48,50]. Pubic hair appears to follow a similar pattern.

If most of the changes with ageing involve reductions in the amount of hair, this is not true of all sites. In the male, the eyebrows may become more bushy, and visible hairs develop around the external auditory meati. In the female, hirsutism may occur as a result of endocrine changes associated with the menopause (see p. 70.18).

Sebaceous and apocrine glands

Sebum production is at its greatest in early adulthood, and lessens in old age. A view that it remains unchanged until past the age of 70 years in men, but falls after the menopause in women, has not been entirely sustained [51,52].

Measurements of the sustainable rate of wax ester secretion after depletion of the sebum reservoir by absorption with bentonite clay suggest that sebum secretion declines steadily through each decade by approximately 23% in men and 32% in women [53]. The fatty acid composition also changes [54].

The predominant belief is that, in spite of their decreased output, the sebaceous glands increase in size because turnover of cells is slower in senility [55,56]. However, in one study in 14 women the glands appeared to become smaller and the sebocytes flatter with age [57].

The axillary apocrine glands also regress with age and produce less odour [15].

Eccrine glands

Spontaneous sweating on the fingertips declines in old age, as a result of a combination of a reduction in the number of glands [58] and of the output per gland [59]. On the forearm, the response to epinephrine has been shown to be reduced by ageing equally in men and women, suggesting an intrinsic deterioration of the glands, an interpretation supported by histological evidence. In contrast, the effect of age on the response to acetylcholine is much greater in the male than in the female, suggesting that ageing affects cholinergic sweating indirectly through the hormonal balance in the blood [59]. Such a hypothesis is borne out by the evidence that the maximum rate of cholinergic sweating is much greater in adult males than in females or in juveniles, and is thus probably androgen-dependent [60].

Nail growth

The rate of linear nail growth increases until well into the third decade. From about the age of 25 years it starts to decrease. Until the age of 70 years, nail growth is greater in men than in women, but thereafter the situation appears to be reversed [61]. Nails are more brittle in the elderly and are characterized by beaded ridging—sometimes called 'sausage links'. Brittleness may be caused by a reduction in the nail content of lipophilic sterols and free fatty acids [62].

Nerves and sensation

Age often decreases sensory perception and increases the threshold for pain [29,63]. There is evidence for progressive disorganization or loss of some sense organs; for example, the density of Meissner corpuscles in the little finger falls from over 30/mm^2 in young adults to approximately 12/mm^2 by the age of 70 years [64].

Langerhans' cells and immune functions

Langerhans' cells become considerably reduced in number in elderly people, even in light-protected areas [65,66]. Recent work has confirmed the reduction in number of epidermal Langerhans' cells with age, coupled with a reduced ability to migrate from the epidermis in response to tumour necrosis factor-α [67]. T cells, similarly, are reduced in percentage and absolute number, and lose their responsiveness to specific antigens [4,68]. The number of B cells does not seem to be affected by age, but their dysfunction is reflected by increased autoantibody formation and serum levels of IgA and IgG [68–71]. Elderly skin appears to have a much reduced capacity to produce cytokines such as interleukin-2 (IL-2) [72]. However, the production of some cytokines (e.g. IL-4) increases with age [72]. The decreased intensity of delayed hypersensitivity reactions [73], the increased risk of photocarcinogenesis and the greater susceptibility to chronic skin infections are some consequences of the ageing of the immune system [24].

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Skin disease in old age

The demography of most nations is changing. Higher standards of housing, hygiene and nutrition, together with improvements in health care services have meant that the average lifespan has increased considerably over the last century. Added to this, many couples are now limiting their families to two or three children at most. Virtually every Western society is therefore experiencing an increase in the average age of its population. The provision of health care for elderly people is consequently becoming more and more important, and disease of the skin is no exception to this [1]. Elderly patients present in dermatology clinics and consulting rooms with a wide variety of skin problems; a few are more or less specific to old age, but most are familiar skin disorders whose clinical expression, physical and emotional consequences, and management may be altered by the age of the patient and the problems that increasing age bring with it.

The reasons an individual seeks advice for skin changes in old age may be as much influenced by personality and social conditioning as by the absolute severity of the problem. Although some societies are still said to view the outward signs of age, such as wrinkles and grey hair, as marks of distinction, it is clear that in much of the world, 'Westernization' is resulting in an increasing degree of social stigmatization associated with looking old. Furthermore, it has long been recognized that, contrary to the popular belief of the young, elderly people are often anxious to look attractive [2].

Thus, particularly in rich and highly developed societies, there is an increasing reluctance to accept the physiological consequences of old age and the effects of environmental exposure. A myth has begun to develop that these ageing changes are abnormal, and many older people with plentiful spare time and financial resources have become obsessed with the pursuit of an eternally youthful appearance (Fig. 70.5). One reason for this is that the pharmaceutical and cosmetic industries have invested heavily in the promotion of the concept that 'young is beautiful'. A great deal of money is being and will continue to be devoted to the study of compounds that may arrest or reverse the visible effects of ageing. Some are claiming success, most notably with retinoic acid for wrinkles. Such research is also increasingly gaining credence in mainstream medical circles, and dermatologists are becoming more and more involved in this area of practice.

However, most people accept (albeit increasingly reluctantly) that ageing is a natural process, and only seek medical advice when skin changes are particularly troublesome or severe, or develop earlier than might otherwise have been expected.

Skin changes of sufficient severity to warrant medical attention in elderly patients may result from the interplay of several factors:

1 Alterations in structure and function of the ageing skin
2 Cumulative effects of exposure to a variety of environmental insults, especially UV radiation
3 Cutaneous consequences of ageing or age-related disease in other organ systems
4 Changes in the environment—decreasing occupational exposure, increasing leisure exposure to potential irritants and sensitizers
5 Social circumstances, with poor nutrition, home care and mobility often contributing to the expression, perpetuation and failure to resolve of skin problems
6 Physiological problems, such as dementia, increasing rigidity of attitude and refusal to accept advice
7 Increasing physical frailty, resulting in a relative incapacity to carry out tasks correctly.

Of particular practical importance are the latter three problems, which are frequently ignored. An elderly patient may be too proud to point out that physical incapacity prevents the twice daily application of a cream, or may deliberately refuse or forget to relate relevant facts about the home situation. The onus is very much on the dermatologist to consider these factors when dealing with skin disease in the elderly patient.

Incidence of skin problems in old age

It is hard to estimate the true frequency of skin disease in the population as a whole, let alone specifically in older age groups. One problem is that the line between that which is physiological and the 'truly' pathological becomes increasingly difficult to draw with advancing years. Another is that studies of skin problems in the elderly have used different types of population and diagnostic groupings which are not directly comparable (Table 70.7). It is probably better therefore to think of skin problems rather than just skin disease in this age group.

However, it is clear that skin problems are common in elderly people. The general scale of this can be gauged from the findings of a large US study, in which dermatological examination of 20 000 non-institutionalized US citizens revealed that 40% of those aged between 65 and 74 years had some significant dermatological problem [3]. 'Significant', in this context, was defined as requiring, in the view of the examining doctor, a dermatological

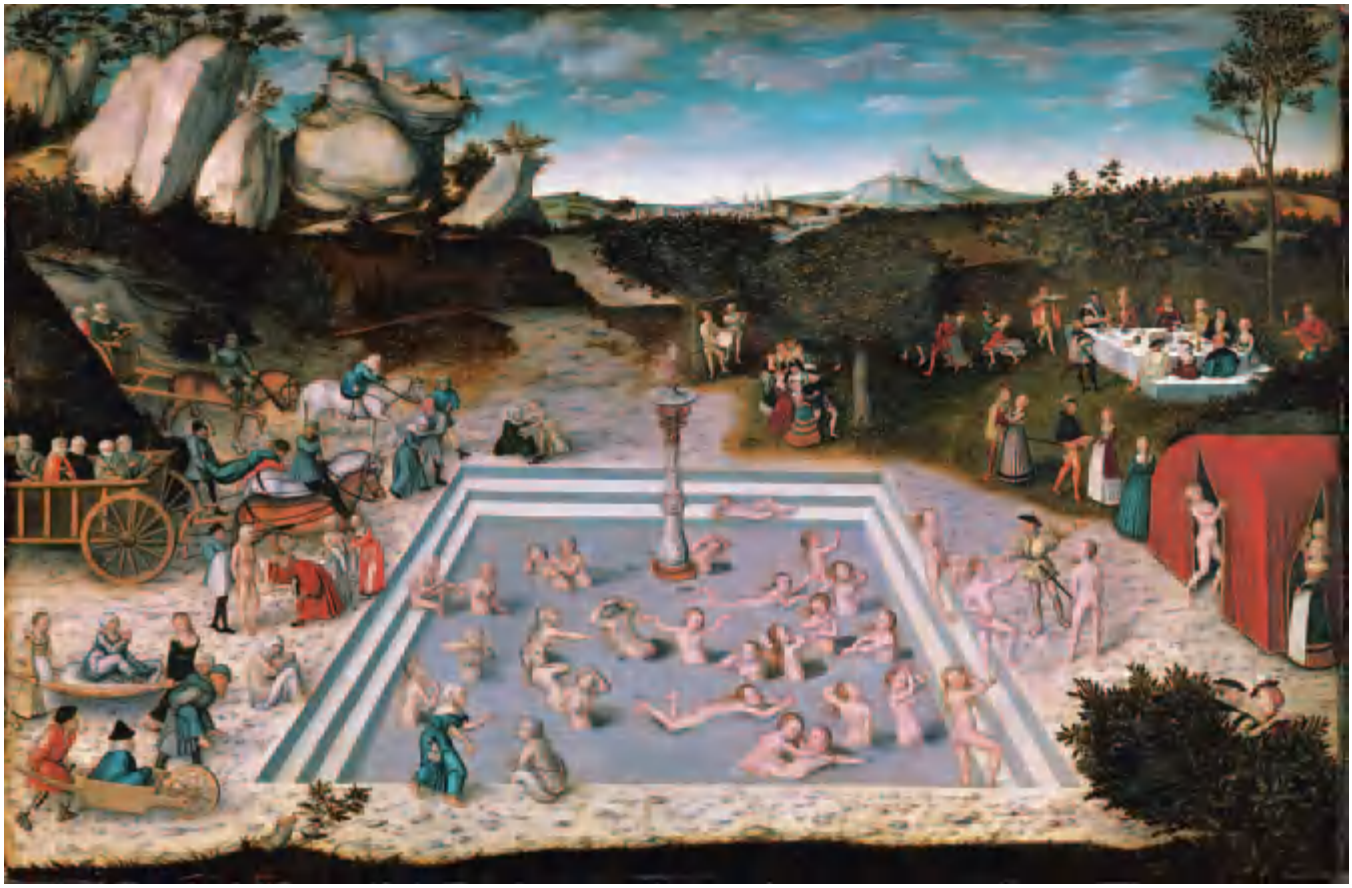

Fig. 70.5 *Der Jungbrunnen*. Lucas Cranach the Elder painted this picture of the Fountain of Youth in 1546, when he was 72 years of age. On the left, a succession of aged and decrepit women are brought to the fountain by an interesting variety of primitive transport. As they move through the basin they are transformed into lovely young maidens. The eternal desire for and, indeed, the possible advantages of rejuvenation are wonderfully expressed. (Courtesy of Staatliche Museen zu Berlin, Gemäldegalerie, Berlin, Germany.)

opinion. Smaller studies on elderly individuals selected randomly and not from skin clinics give much the same impression [4–7]. For example, of 68 volunteers aged between 50 and 91 years, living in Boston, USA, two-thirds of the entire group and 83% of those aged over 80 years complained of skin problems of some kind [4]. In a European study, 77.4% of a population of 584 elderly residents of a municipal old peoples' home in Denmark were found to have a skin problem [7].

Many of the skin problems that are found most commonly on random examination of elderly people are not those for which elderly patients necessarily seek attention from specialist or non-specialist doctors. Although eczemas, pruritus, easy bruising and dryness (under various headings) are certainly seen in skin clinics, tumours, both benign and malignant, tend to figure more prominently than inflammatory problems [8–12].

Table 70.7 Studies on the incidence of skin disease in elderly people.

Reference	No. of patients	Population studied
Droller [5]	476	Random; at home
Young [8]	330	Ambulatory outpatients from skin clinic; chosen 'at random'
Epstein [9]	687	US private practice
Tindall & Smith [6]	163	Volunteers; at home; black and white people
Verbov [12]	170	Mainly outpatients; some in-patients
Weisman *et al*. [7]	584	Residents of old peoples' homes
Beauregard & Gilchrest [4]	68	Volunteers: housing projects, geriatric home visits, medical centre employees
McFadden & Hande [10]	257	Dermatology outpatients

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Specific skin problems in old age

Most of the skin disorders that are particularly troublesome in the elderly patient are described elsewhere in this book. However, one or two points should be emphasized about certain specific disorders.

Wrinkles and elastosis

These changes, together with greying of the hair, are most readily associated with an aged appearance. The different clinical forms of wrinkles, and the clinical syndromes associated with elastosis, are described in Chapter 46, and the histological changes of the ageing dermis are discussed above. Plastic surgeons and dermatologists are becoming increasingly involved in their management. Chemical peels, collagen implants and facelift operations are in widespread use, and topical retinoids are employed in the treatment and prevention of wrinkling [1–3].

Pruritus

Itching in old age can be so severe that it ruins quality of life completely [4]. The itch may be localized or generalized, and may or may not be accompanied by skin changes. It is crucial to examine an itchy elderly person carefully for primary cutaneous disease. In one study, 142 of 162 elderly patients had an identifiable cause for their itching (including xerosis), leaving only 20 to whom the term senile pruritus was applicable [5]. Diagnoses that are particularly easy to miss are scabies (often caused by the inadequate examination facilities in residential homes for the elderly) and bullous pemphigoid, which often begins with a non-specific or even no rash [6]. Non-specific skin changes in anogenital itch may also conceal important diagnoses: candidiasis in undiagnosed diabetes; lichen sclerosus et atrophicus, the classical signs of which may easily be obscured by secondary excoriation and inflammation.

If a primary skin disorder has been ruled out, it is important to investigate any elderly patient with generalized itching for systemic causes: renal disease, cholestasis (especially chronic liver disease), thyroid disease, anaemia or cancer. The relationship between carcinomas and pruritus in the elderly patient is controversial, but there is no doubt that lymphomas, leukaemias and other myelodysplastic disorders may present in this way [7]. The frequency with which a systemic cause is found varies, but is high enough to justify a routine search [4], and a useful algorithm for this has been provided by Champion [8].

When all these causes have been excluded, there remains a small core of elderly patients with intractable pruritus. In some, the itching is accompanied by xeroderma, but in others the skin feels relatively normal to the touch. The management of such patients is extremely difficult, and is often totally unsatisfactory for all concerned. The topical use of emollients, soothing preparations such as menthol in calamine, and potent topical steroids may be helpful. However, many of those with the worst pruritus are quite unable to manage topical therapy by themselves, and it is necessary to resort to relatively sedative systemic drugs, such as phenothiazine-type antihistamines. These, too, have their drawbacks, not the least of which is the development of confusion and disorientation.

Senile xerosis and asteatotic eczema

SYN. ECZÉMA CRAQUELÉ

The ageing skin often feels 'dry' to the touch, although the reason for this is not clear. Water loss is not increased in aged skin [9], but the water content of the epidermis appears to be somewhat reduced [10]. It has been suggested that xerosis reflects minor abnormalities in epidermal maturation [7].

The dryness is often worse in the winter, a fact that has given rise to many of the alternative names used for these changes: winter eczema, prurigo or pruritus hiemalis. The changes are often most pronounced on the legs. In some patients, the surface texture of the skin assumes a cracked appearance resembling crazy paving. This is known as asteatotic eczema or eczéma craquelé (Fig. 70.6). Frequent washing is certainly a causative factor in susceptible individuals [11], and central heating may also play a part by reducing atmospheric humidity. Perhaps it is not surprising that this problem is commonly seen in geriatric in-patients.

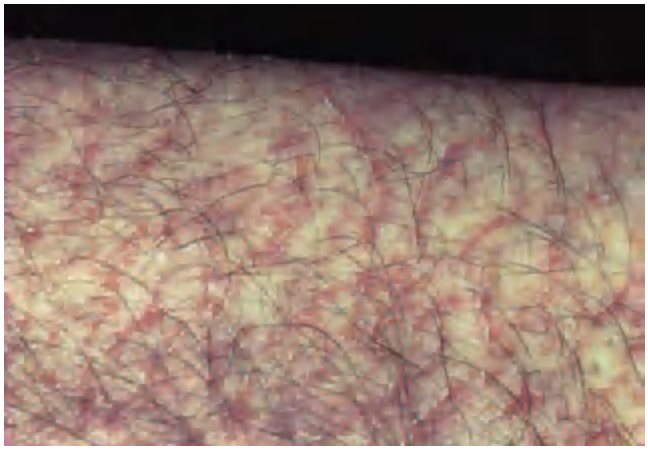

Fig. 70.6 Eczéma craquelé.

The use of emollients to reduce requirements for soaps and detergents will improve xerosis in most patients and, because high water temperature appears to increase the tendency to irritant reactions [12], so will reducing the bath temperature. Moisturizing preparations in the bath are generally held to be effective [4], but bath oils can make the bath very slippery, which has its risks in the elderly and frail patient.

Eczema

The aged may suffer from any of the clinical types of eczema. Atopic dermatitis, for example, occasionally continues into old age or even appears for the first time. However, certain patterns such as asteatotic eczema are more common and more troublesome in elderly subjects.

Seborrhoeic dermatitis may be more common in the elderly infirm and in those confined to bed [13]. In the aged patient, especially the obese, a flexural pattern is often encountered, which may mimic intertrigo and flexural psoriasis.

Some elderly patients present for the first time with a discoid or nummular eczema, and most patients with Sulzberger–Garbe disease (generally considered to be a variant of discoid eczema) are elderly.

Gravitational eczema is much more common in the elderly patient (see Chapter 17), and may be complicated by contact sensitivity.

Contact dermatitis of irritant or allergic origin is generally considered to be less common in elderly people, partly because of decreased occupational exposure [14]. This may also reflect the decline in immune reactivity that occurs with age [15] and the fact that irritant responses to some substances are reduced in intensity [16]. However, patch-test positivity remains quite common, presumably from exposure earlier in life. Allergic contact dermatitis remains a significant problem in elderly people, especially resulting from local medicaments, such as aminoglycosides, lanolin, parabens, antihistamines and anaesthetics. Other sensitizers that continue to cause trouble in old age include rubber in gloves and shoes, plastics in hearing aids and spectacle frames, plants and hair dyes [14].

Marked secondary lichenification and chronic lichen simplex are also often seen in older patients.

Bullous disorders

Pemphigoid (see Chapter 41) is much more frequent in the elderly than in other age groups. Old age modifies the management of all blistering diseases because of unwanted effects of drugs, or because of physical and social circumstances. Steroids precipitate glucose intolerance more often in the elderly, and sulfapyridine or sulfamethoxypyridazine may be better first-line drugs than dapsone for dermatitis herpetiformis because of the tendency for dapsone to cause haemolysis [17]. Drug regimens should be kept simple, and written down where necessary.

Psoriasis

There is a distinct peak of onset of psoriasis in later life that is not as clearly associated with a family history as in patients whose disease begins earlier. This is reflected in different human leukocyte antigen (HLA) associations [18].

Psoriasis causes increased problems in the elderly patient. Disease of lesser extent and severity may be relatively more disabling in old age than in youth, and the systemic effects of widespread or acute pustular psoriasis are less well tolerated than in younger individuals. Flexural psoriasis is a particular problem in the elderly patient [19], but other patterns are also seen. Eruptive guttate disease, however, is rare in old age.

Treatment can be difficult. The patient may be unable to apply topical therapies, and there may be problems in travelling to and from the hospital for outpatient dithranol, or in standing for psoralen and UVA (PUVA) therapy. One solution is the use of systemic therapy, especially methotrexate. There is less reason for concern over long-term toxicity in the elderly patient, relatively small doses may keep the patient comfortable (perhaps because of diminished renal clearance) and the drug is generally well tolerated.

Leg ulcers (see Chapter 50)

Leg ulcers are a major problem. Most are caused by venous hypertension, but arterial disease becomes increasingly important with advancing years. Poor wound healing in elderly people [20], perhaps associated with other illnesses and poor nutrition, may also have a role in the perpetuation of some ulcers.

In managing chronic leg ulcers in the elderly patient it is important to take an overview of the whole situation. Strenuous efforts to heal a stable ulcer in someone who is coping independently at home may be inappropriate in some cases if long-stay in-patient treatment will be required.

Decubitus ulcers [21]

See Chapter 22.

Herpes zoster and post-herpetic neuralgia [22]

Shingles is much more common in old age, the relative incidence rising from 4 in 1000/year at age 55 years to 10 in 1000/year at age 90 years. It has been estimated that 25% of people over the age of 65 years develop shingles at some time, and that all who have had chickenpox would do so were they to live to 100 years old. Post-herpetic neuralgia is also much more common in elderly people. Approximately 50% of patients over the age of 60 years experience pain, and the incidence rises to as many as 75% of the over-70s.

Skin tumours

Most skin tumours are more common in elderly people: benign, such as seborrhoeic keratoses, senile lentigines and skin tags; dysplastic, such as actinic keratoses; and cancers, especially basal and squamous cell carcinomas. Lentigo maligna is seen predominantly in the elderly, and the highest age-specific incidence rates for invasive malignant melanoma are also in those over 60 years [23]. There is also an association between increasing age and decreasing 5-year survival in malignant melanoma [24]. It is not clear why this should be, but elderly patients seem to present with thicker lesions [24,25], and recent evidence suggests that the proportion of nodular melanomas may rise with increasing age [25]. The tendency to wait longer before presenting for treatment also extends to other tumours, and lesions such as that shown in Fig. 70.7 are essentially restricted to elderly people.

Infections with ectoparasites

Outbreaks of scabies in residential homes for the elderly are not uncommon, and are usually attributable to one individual with a heavy infection, verging on Norwegian or crusted scabies. Clothing lice (see Chapter 33) are, in the UK, almost exclusively seen in elderly vagrants.

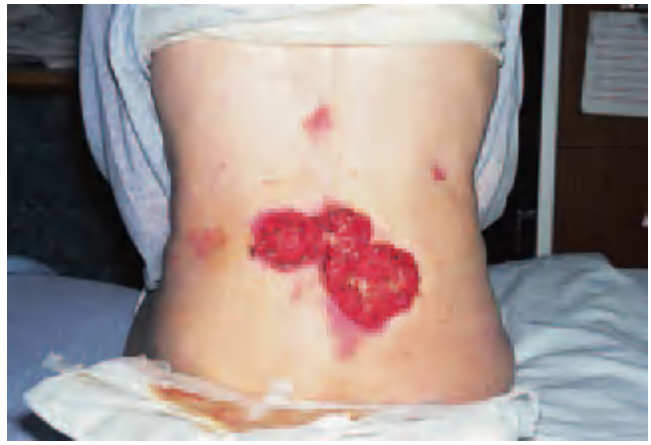

Fig. 70.7 A large neglected basal cell carcinoma on the back of an elderly lady.

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Chapter 71

General Aspects of Treatment

J.A. Cotterill & A.Y. Finlay

General principles

The general principles for the treatment of skin diseases are essentially the same as for other branches of medicine. There are, however, important aspects and details peculiar to dermatology that readily escape the non-specialist, attention to which may make so much difference to the success or otherwise of therapy. In particular, topical therapy in many situations may be in danger of being relegated to an unimportant role. Patients may decry local applications. During history taking, many patients say they have had no treatment, 'only a few ointments'. They may also be unaware of the potential harm that can be done by topical therapy, whether self-administered or iatrogenic. Careful nursing and instruction of the patient on how to use any remedy can be much more important than in other branches of medicine.

Although dermatologists have available to them many more agents of proven beneficial pharmacological activity than were available to their predecessors, they still have to persuade, console and counsel and must convince many patients that no specific treatment is available for their particular problem.

Thus, the central aspect of dermatological management is the consultation, which often demands great skill in communication techniques. Improving doctor–patient communication is not an option but a necessity [1].

The dermatological consultation

The various manoeuvres employed by patients and doctors in the consultation 'gamesmanship' have been described [2].

The individual dermatologist will, however, develop his or her own preferred technique of consultation as he or she matures in the specialty over the years. Thus, there are those dermatologists who like to see their patients completely naked so that they can be sure they are missing no other dermatological pathology. However, seeing a patient initially entirely naked may lead to a considerable loss of valuable data. The patient's dress provides psychosocial information, and the gait of the patient as he or she walks into the consulting room can give some useful information. In particular, the depressed patient often has a characteristic 'droop', whilst the anxious patient is moving in all directions at the same time, typically sitting on the edge of the chair. The depressed patient may be slow in all his or her responses to questions. An anxious person may continuously twirl a ring on a finger, and the quivering lips or the moistening of an eye in response to a question may indicate important stress-provoking factors. The language employed by the patient in describing the symptoms is also important. Whilst photosensitivity eruptions such as porphyria may produce a burning sensation in the skin, very few other skin conditions do this, and symptoms described emotively in this way may indicate that functional factors are important in pathogenesis. The patient who brings in an enormous bag of medicaments, all of which have done 'nothing at all' to help, may also indicate a psychological or psychiatric aspect to the case. A 'hollow' history and the '*belle indifference*' of the classical patient with dermatitis artefacta can be appreciated only by taking a good history. Little matchboxes and plastic bags containing detritus are very characteristic of patients with delusions of parasitosis.

What do patients want? [3–8]

Patients consult dermatologists because they want help with their skin problems. Patients require not only information and medical treatment, but also explanation, understanding and emotional support [3,4]. Whilst patients may hold elaborate, and sometimes sophisticated, theories about their own skin problems, most patients need to know the answers to three basic questions: 'Why me?', 'Why now?' and 'Why this particular illness?' [3]. Sadly patients may receive no diagnosis, few explanations, inadequate advice and leave the consultation feeling the doctor is uninterested and believes all symptoms are unimportant [5]. Above all, the patient values a doctor who listens, although not all doctors may yet have learned to hear what their patients are saying [6]. The doctor must recognize that the patient is now a key medical decision maker in reaching an optimal management choice tailored to the particular needs and views of an individual patient [7]. A paternalistic consultation style is of historical interest only, and care should be patient rather than disease centred.

Eye contact is vital if meaningful data are to be gathered from the patient [8]. Doctors with a mechanistic interrogative style who offer no eye contact usually turn off any meaningful verbal communication from the patient.

Body image, self-esteem and the leper complex

An individual's body image is largely cutaneous, so skin disease affecting any part of the body surface may produce considerable depression in body image, self-esteem, confidence and secondary depression [9]. This is particularly true where skin disease affects areas such as the scalp, hair, face, hands and genital area. The stigma of skin disease can readily produce a 'leper complex' in the individual patient, which compels the patient to withdraw from society and physical contact with other human beings [10,11]. It is vital therefore that the dermatologist provides reassurance by touching the patient at some stage during the consultation.

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Timing

A dermatosis is rarely a static event. The effect of the patient's actions and attitudes, the frequent development of anxiety or depression and the daily variations in the internal and external milieu require frequent reappraisal and adjustment of treatment. Topical corticosteroids should be reduced in strength as the disease recedes.

The timing of a return to work often involves a difficult decision; even the return of a patient from hospital to his or her environment may be misjudged. In either case, a relapse may cause the patient to lose confidence. In all dermatological therapy, Napoleon's dictum may be remembered with advantage: 'la puissance ne consiste pas à frapper fort ou à frapper souvent, mais à frapper juste'.

Failure to appreciate the natural history of disease has been responsible for much unnecessary therapy, and for a wrong assessment of therapeutic needs. For instance, in alopecia areata, specific therapy is lacking, and the average duration is unaffected by empirical measures. Infantile eczema tends to improve with time and nummular eczema 'burns itself out' in months or years. In these diseases, the patient is ill-served by measures that can only alter the immediate situation without an additional planned campaign to sustain him or her over this prolonged period. A diminishing concentration of topical corticosteroids, measures designed to distract attention from the disease and manoeuvres designed to help morale are necessary parts of the whole treatment. In diseases with a short-lived but hectic course, such as erythema multiforme exudativum, oral steroids, if given at all, should be 'tailed off' once the expected peak of the disease is past. In chronic diseases, such as psoriasis, systemic sclerosis, lichen sclerosus of the vulva, ichthyosiform erythroderma or dermatitis herpetiformis, therapy should be on the lines of a siege operation or, sometimes, as a deliberately planned retreat in which the disease is contained and held in check. Whenever possible, it is a wise precaution to hold a therapeutic reserve for periods of exceptional activity of the disease process.

Compliance

Hippocrates warned that '(the physician) should be aware . . . that patients often lie when they state they have taken their medicine'. Dermatology patients may not deliberately lie, but there may be many reasons why patients are not able to carry out a therapy regimen. It is essential that the clinician understands these potential difficulties and

takes steps within the consultation to plan therapy which is practical and with which the patient agrees. The term 'concordance' or 'adherence' is now preferred over 'compliance', as the concept of compliance with treatment implies a patient passive in the treatment decision process —a situation likely to ensure inadequate or inappropriate use of therapy. Although concordance issues are of relevance to every dermatology consultation [1], there is relatively little published on the subject; there have however, been two workshops at international meetings [2,3].

Influences on adherence include the degree of motivation of patients, the extent to which their quality of life is impaired by their disease and the attitude of the patient towards their disease and their relationship with their doctor [4]. A longitudinal study [5] has shown that dissatisfaction with care and psychiatric morbidity are significantly and independently associated with poor medication adherence: the physician's interpersonal skills play a major influence in medication adherence. The strongest predictor of adherence to skin-care treatment in childhood atopic dermatitis is a good doctor–patient (mother) relationship [6]. Other factors that are likely to improve adherence with therapy include patient education about how to apply topical preparations, the use of as few different preparations as possible and the use of preparations that are cosmetically acceptable. Realistic and simple regimens with preferably once daily applications are much better than regimens with frequent applications, but a simple manoeuvre such as using a cream in the morning and an ointment at night may improve adherence [7].

The use of therapy that gives early improvement is preferable but where this is not possible the patient must understand the reality of the likelihood of speed of improvement. The patient must have the opportunity to express concerns about treatment so that unfounded fears can be allayed. For patients with psoriasis, even more important than the speed of action of a topical treatment is the opportunity to be involved in the decision taking [8]. Joint discussion and decisions between doctor and patient should be taken. Patients need information about possible side effects and how to handle them: for example if a patient is warned that there may be transient stinging, the patient may continue to use a drug instead of being alarmed and stopping it. The cost and affordability of therapy is an obvious factor in many health care settings.

When systemic drugs are used in an outpatient setting in cardiology and internal medicine clinics, there are widespread discrepancies in drug usage with 76% of patients not taking the planned medication correctly [9]. There are similar problems with patients using topical preparations [10]. The likelihood of a patient taking oral medication as planned is inversely proportional to the number of times per day that the drug should be taken [11]. Even in a controlled research setting, when a patient is asked to record the therapy used for skin disease there is poor correlation between reported treatment use and weighed ointment usage [12]: the use of electronic monitoring may be helpful in the future to monitor medication adherence [13].

There are particular cultural and age-related issues in trying to maximize the likelihood of adolescents taking medication effectively. This is of particular relevance to acne therapy [14]: the use of topical therapy that has a more rapid onset of action is likely to be an advantage in increasing usage.

When topical corticosteroids were introduced into clinical practice in the 1950s their great benefit to patients with inflammatory disease was immediately apparent. It is unlikely that the phobia surrounding their use, especially in children, would have been predicted. The phobia comes from a lack of understanding about the different potencies of corticosteroids available and a concern over side effects, the risk of which is minimal if they are used correctly. The phobia may lead to inappropriate under use and consequent poor control, especially of atopic dermatitis [15]. Surprisingly, however, the mother's anxiety about using topical steroids did not influence reported use of topical steroids in a Japanese study [6]. It is important that clinicians are aware of this issue and address it in discussions about advising their use. An approach to improving treatment compliance in occupational dermatitis has been the concept of a specialist nurse-led 'eczema school' to contribute to the education of patients and carers [16].

Only 33% of patients with psoriasis who were asked to apply an ointment twice daily actually did so [10]. Patients with psoriasis who report that they have not complied with treatment are more likely to believe that both psoriasis and their treatment interfered with their quality of life [17]. Self-reported non-adherer patients with psoriasis demonstrate more negative views towards all aspects of health care [18]. In both psoriasis [19] and in acne [20] adherence with therapy is poorer the greater the severity of the disease. It is possible that having severe skin disease leads to poor life quality, which in turn leads to a degree of depression and a sense of 'giving up'. This may result in poor concordance with therapy and in turn further deterioration in the disease. Strategies are needed to break this negative feedback loop. It is likely that treatment failure is much more often due to non-adherence than has been previously recognized.

There is a major challenge for dermatologists to identify those factors that contribute to non-adherence and to develop strategies that make it more likely that a patient will use medication appropriately and in their best interests.

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Side effects

Worldwide more and more people, especially the elderly, are taking not only prescription but also over-the-counter drugs, including herbal remedies. Moreover the pharmaceutical industry is constantly introducing new drugs. The individual doctor is faced with a massive task in keeping up to date with all these drugs, including side effects and cross-reactions. Whilst information technology may help this is no substitute but can complement the practice of a well-informed and competent medical practitioner. The consultation is all-important in warning the patient about possible side effects [1], but skill and care are necessary. The doctor may be guilty of negligence if major side effects are not explained, but, on the other hand, if too much emphasis is placed on side effects the doctor may invite non-compliance. Particular care must be taken during pregnancy [2–4] and lactation [3,4]. Children pose special problems and neonates are at special risk of side effects because of immature renal and liver function [5]. Poor renal function leads to the accumulation of drug and metabolite(s) in the body increasing the risk of side effects [6,7]. In liver disease the reduction in first-pass metabolism may lead to toxic drug levels whilst reduced protein binding may lead to increased bioavailability and side effects [8].

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Therapy

General management

Explanation

Like all doctors, but perhaps more than most, dermatologists must achieve rapid rapport with their patients and be seen either to assuage the symptoms and signs of visible disease or to bring the patient—and the relatives or parents—to accept chronicity or irreversible changes. Dermatology has been called an 'applied intuitive art': if so, an easy understanding must be achieved between the artist and sitter. Allowance must be made for symptoms of anxiety—aggression, lack of faith, mistrust. If necessary, the dermatologist must gradually overcome these to become therapeutic in the clinical situation.

Patients nowadays demand and deserve a far fuller explanation of their disease than was formerly either possible or even considered desirable. No longer is it appropriate to give a learned diagnosis, a prescription and little else.

Patients may be well-informed or misinformed, but they are informed. Recourse to the Book of Proverbs or Job is not received with the understanding it used to command. It is never easy to explain autoimmune diseases or the aetiology of atopic dermatitis in easily comprehensible terms. The intelligence of the patient must be gauged; a suitable metaphor or simile is often apt. In any case, the

patient's questions must be answered. In seeking clues to the causation of conditions such as contact dermatitis or chronic urticaria, one should always listen attentively to the patient's explanation. He or she may well be wrong, but occasionally the patient is right, however, unexpected the answer.

Nevertheless, his or her account of the onset and course of the disease may have become distorted by time or for medicolegal reasons, and can never be believed in cases of dermatitis artefacta. The patient's memory (or suppression of memory) of drug or topical medicaments given is usually defective, especially if self-administered.

Avoidance of aggravating factors

General advice that might be considered common sense to the dermatologist may be quite unfamiliar to some patients. Such advice includes care with environmental temperature and, at times, humidity. Advice should be given on appropriate clothing, which should not be too constricting, too hot or too harsh. Irritants and sensitizers should be avoided where possible. Many patients retain the belief that skin disease is a manifestation of dirt or germs to be expunged with vigour and exorcized with soap and water or worse. Care should indeed be taken with soap, but it is seldom necessary to proscribe bathing. It is surprising how often patients will be applying inappropriate household germicides, and in totally inappropriate concentrations. Advice to stop scratching usually causes more frustration and alienation unless something is done to help the sensation of itching.

Regimen

Rest and relaxation can play a major part in treating many dermatoses. With others there are positive benefits in remaining at work or at school. Decisions, including economic ones, are often neatly balanced, but the patient will often require positive guidance on how much activity is to be encouraged.

The arguments for and against admission to hospital clearly depend on so many variables other than the purely medical ones. The last 30 years have seen a great reduction in beds for dermatology patients in many countries. The reasons include better treatments, which remove the need for admission, improved facilities for home nursing, and better transport to outpatient facilities. The dramatic rises in cost of maintaining patients in hospital, whether at the expense of themselves or of their health services, also militate against admission.

No firm guidelines can be laid down about which particular diseases need to be treated on an inpatient basis. These will vary from culture to culture and even from town to town. No doubt many diseases might benefit from time in hospital but this may not be feasible. Sometimes, a short stay before complete remission has been achieved will allow the acute crisis to be averted, allow patients to be taught how to manage themselves, and also build up a better relationship between patient, doctors and nurses.

Recent years have seen the emergence of dermatological intensive care units for the management of such acute, life-threatening emergencies as toxic epidermal necrolysis, pemphigus and erythroderma. These have been pioneered at Creteil, France [1,2] and have pointed the way forward to improving what can be a poor prognosis.

Quite often, the need for hospitalization is avoided if the patient is given precise instructions on how to do at home almost everything that might have been done in hospital.

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Systemic drug therapy

Drug therapy may be specific, empirical or placebo in its effect. Dermatology has suffered more than most specialties from an abundance of empirics and placebos. It has not been shown that dermatological patients respond more to placebos than others, but the presence of an obvious and visible disease and the anxiety that this engenders endow all forms of treatment with an aura of suggestibility that often confuses the judgement of the patient and physician alike. The past records of dermatological therapy give abundant evidence of the 'wish to believe'. The results of 'double-blind' trials have destroyed the edifice of this belief. Drugs should not be despised if they help the patient, but they should never be regarded as pharmacologically active without unequivocal evidence of their effectiveness. There must be no confusion in the dermatologist's mind. At his or her command there are a few specific remedies, a number of empirical ones and many placebos. The first are accepted because their action is known. The second are effective in 'double-blind' trials, although their mode of action remains unknown. The third are effective in a manner that bears no relation to the pharmacology of the drug or the pathogenesis of the disease; often, the physician endows them with his or her personality. It is important to be acquainted with the concept of the doctor as a drug and that problems may arise, as with any drug, with overdose, underdose or idiosyncratic reactions [1,2].

The placebo [2–5]

Potentially any treatment may have a dual effect related to the intrinsic property of the active drug and also to the perception that treatment is being received [3]. This latter

is known as the placebo effect [4]. Distinction must be made between placebo and placebo effect [2] as any sort of therapy can act as a placebo but the response of the individual patient determines whether there is a placebo effect. Despite claims to the contrary, no consistent placebo-reactor profile has been demonstrated [2,3] but the effects of placebos can be very specific depending on patient information, i.e. patient expectations. Thus, placebos can induce opposite effects on blood pressure or heart rate depending on whether they are administered as perceived tranquillizers or stimulants and this makes a precise definition of the placebo effect difficult [3]. Moreover, variations in the placebo response to tablets of different colours—green is best for anxiety—has been demonstrated [5].

Recent evidence suggests that the placebo effect is mediated by dopaminergic reward mechanisms in the human brain and related also to the expectation of clinical benefit [3].

The placebo response in dermatology

The less effective any existing treatment, the more likely are any favourable effects to be of placebo type. Lichen planus, alopecia areata and chronic urticaria have been 'cured' in the past with many different preparations, which have not been shown to be pharmacologically effective in these diseases. But the patient has been sustained through the natural course by receiving a potion or a lotion that at least sustains the faith and the hope and, at most, is free from potential toxicity. The placebo effect is also apparent in the control of insomnia and pruritus, and extends to physical methods of treatment, notably acupuncture.

Preparations. Placebos must be harmless. Many drugs that are *not* harmless are really only being given as placebos. Lactose tablets are commonly given but even this substance is not totally harmless. Aspirin should be avoided. Carefully worded instructions may reinforce a placebo effect [3], as may an unusual size or shape of tablet.

No official placebo is included in the British National Formulary, but many manufacturers will supply inert preparations matched to their own products.

In general, physicians should be aware that the effect of a drug they are prescribing may be a placebo effect. On the other hand, it has been cogently argued that a placebo works better if the physician also believes in it!

Ethics. Most but not all physicians would agree that the administration of a placebo as a therapeutic measure is justifiable if no known effective treatment exists. In any case, it is less likely to harm the patient than a poorly tested or a powerful 'new' drug of uncertain value. In some cases, the deliberate use of a placebo initially may be valuable in ensuring rapport with a patient who claims to be prone to all the side effects known for all drugs taken; and to assess the placebo response reactions. It also gains time for the anxious patient to accept a prolonged or incurable condition while a situation of rapport is being built up. This presupposes, of course, that no widely accepted active agent is available that is likely to be more beneficial.

In all cases, particularly in drug trials, the overriding consideration must always be the benefit to the patient. The doctor is always in a particularly authoritative position and must not abuse this authority. The patient's fully informed consent (with a witness) must always be obtained if a 'controlled' trial is embarked on. It is doubtful whether the use of 'dummy' preparations is ever justified in children, even with the parents' consent.

It is very important that none of us loses sight of the fact that we should not do harm to the patient, especially in an experimental situation. The so-called experiment where a mother aged 80 years was injected with malignant melanoma cells from her 50-year-old daughter, which led to the mother's most unpleasant death from metastatic malignant melanoma, must never be repeated [6]. It is essential that any proposed research is vetted by a well-qualified ethical committee before any projects are undertaken.

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Antihistamines

These are discussed in Chapter 72. In the hands of many non-dermatologists, the sight of a rash evokes a reflex desire to prescribe antihistamines. These drugs are, of course, no panacea. If they are to be prescribed, there should be some thought whether they are being used for their ability to antagonize other mediators such as acetylcholine (usually considered as a side effect), or for a central effect. Otherwise, their use must be considered as placebo, albeit usually a harmless placebo. The advent of new 'non-sedating' antihistamines, said not to cross the blood–brain barrier, makes it important not to thoughtlessly prescribe the newest antihistamine for the management of all types of pruritus (Chapters 16 & 72). Every general practitioner should have a working knowledge of short-acting, long-acting, sedative and non-sedative types of antihistamine.

Psychopharmacological agents

In recent years, there has been a marked trend, in the UK at least, away from reliance on psychopharmacological agents or willingness to take them on the part of the patient. Even the conservative dermatologist, who may feel on occasions that the short-term administration of sedatives or hypnotics would be of help in reducing itching or restoring normal sleep patterns, may encounter unexpected resistance by the patient. Unfortunately, reasonable alternatives—discussion, the encouragement of the development of relaxation or autosuggestive techniques—are time-consuming and seldom carried out by busy practitioners. Thus, anxiety may intensify until the acute 'emergency' situation, so well known to dermatologists, develops. In such cases, rest, adequate sleep and some form of sedation become imperative and may be obtained only by removal of the patient from his or her environment to hospital.

Two situations in which the rational use of psychopharmacological agents may be necessary are anxiety and depression. Many agents are available for the treatment of these conditions, and national and individual differences in prescribing are widespread. One drug often replaces another for reasons of improved efficacy. The dermatologist is best advised to choose two or three, preferably having short- or medium-term and more prolonged effects, and to use them appropriately.

Anxiety

Environmental sources of anxiety and tension have increased in modern industrialized life. Anxiety, not always recognized or acknowledged by the patient, may be an essential driving force in some individuals ('trait' anxiety) [1]; only when this increases, as a result of extra stresses or the presence of disease, may it become marked ('state' anxiety). Then, the symptoms themselves, for example the intensity of pruritus, may become part of a general stress response characterized by emotional overarousal [2]. It is recognized that pathological anxiety is more common in patients with a chronic medical problem than in those without [3]. So detecting and treating anxiety is an integral part of dermatological management. Successful treatment has several benefits including better quality of life, less disability and less use of resources. Rather than prescribe an anxiolytic initial management should include effective communication, information giving and reassurance. Whilst behavioural therapy is one of the most effective treatments for anxiety [4] most dermatologists are not skilled in this technique. Developing an effective liaison with an interested clinical psychologist or psychiatrist, or even in a dermatological liaison clinic, is the optimal way of delivering this type of care to anxious dermatological patients.

Whilst the benzodiazepines [2–4] are the safest and most effective anxiolytics, there is concern about habituation and addiction to these drugs [5,6] so these drugs should only be used in the short term and for emergencies [3]. Their use in adequate dosage in the short term to prevent nocturnal pruritus and to give the very itchy patient a good night's sleep can be justified. However, conventional doses of sedative antihistamines such as hydroxyzine may be equally effective and not accompanied by the risk of addiction or habituation. A large number are available: the main difference lies in their different plasma half-lives [2]. They are equally effective for treating both anxiety and insomnia, although the causes of the latter should be examined before recourse to drug therapy [7]. They are widely used, especially by older females in the lower socio-economic groups [8]. Diazepam and chlordiazepoxide are the best known. Nitrazepam, used as a hypnotic, has a half-life of about 30 h and may thus accumulate on repeated use. A single dose of diazepam is frequently given to allay apprehension in young children before minor operative procedures [9,10]. When appropriate, a suitable analgesic should be given before the diazepam [11]. The intravenous use of benzodiazepines carries a risk of thrombosis or ischaemia [12,13]. This drug should be diluted with blood and given slowly [12] and resuscitation facilities should be to hand. The benzodiazepines have no antidepressive effect and may, in fact, enhance depression. The side effects are those of any drug affecting the central nervous system, including oversedation [14]. Effects of alcohol are potentiated [15].

Depressive states

Depression is common in dermatological patients and may present in many different guises. It is unusual for the patient to say 'I am depressed'. However, the condition is so common in dermatological patients that the attending dermatologist should always ask him- or herself 'is this particular patient depressed or not?' Dermatologists therefore should become adept at recognizing depression in their patients. Whilst criteria for major depression [16] (Table 71.1) are recognized, it has been claimed that simply asking two questions may be as effective in detecting depression as longer screening instruments [17] (Table 71.2).

Depression with suicidal ideation is common, both in patients with psoriasis [18] and Darier's disease [19], and any extensive skin disease, particularly if it affects important body image areas such as the face, may produce a very severe reactive depression. It is known that patients with chronic urticaria and generalized pruritus are more likely to be depressed than controls [20], and acne scarring, particularly in males, may produce severe reactive depression and even suicide [21]. Dermatological patients may become significantly depressed when they are treated

Table 71.1 Symptoms of depression.*

Depressed mood
Substantial weight loss or gain
Insomnia or hypersomnia
Feelings of guilt or worthlessness
Suicide ideation or suicide attempt
Decreased interest or pleasure*
Psychomotor agitation or retardation
Fatigue or loss of energy
Diminished ability to think or concentrate

* One of these symptoms must be present. Two or more of the above should be present within the same 21-week period.

Table 71.2 Two simple questions to detect depression [17].

1 Over the past 2 weeks have you ever felt down, depressed or hopeless?
2 Have you ever felt little interest or pleasure in doing things?

Table 71.3 Main classes of antidepressants.

Tricyclics
Selective serotonin inhibitors
Monoamine oxidase inhibitors
Norepinephrine (noradrenaline) reuptake inhibitors
Others

with corticosteroids orally or parenterally, and depressed dermatological patients are twice as likely to be admitted to hospital, and to remain as inpatients twice as long as non-depressed dermatological patients [22]. The commonest psychiatric disease present in patients with dermatological delusional disease and with body dysmorphic disorder (dermatological non-disease), in particular, is depression [23]. Depression is a well-recognized risk factor for non-compliance with medical treatment so depressed patients are three times more likely to be non-compliant than non-depressed patients [24].

Finally, dermatological patients who go to litigation are more likely to be depressed than their non-litiginous peers [25]. The treatment of depression therefore is of vital importance in dermatological practice.

The main classes of antidepressants available are shown in Table 71.3.

Rather than continuously experimenting with a wide range of available antidepressants the clinician is best advised to become familiar with one drug from each class [16]. The response to treatment may be slow and there may be little clinical benefit during the first month of therapy. Moreover, side effects are usually worse at this time, especially during the first 2 weeks of treatment [16]. Many patients with significant depression are treated with inadequate doses of antidepressants for an inadequate time. 4–6 months of treatment are necessary to avoid relapse and continuous maintenance therapy is necessary if the patient has had two or more episodes of depression within the previous 5 years [16].

The generally lower side effect profile of selective serotonin reuptake inhibitors compared to, for example, the tricyclic group of antidepressants, and, in particular, lower cardiotoxicity, make these drugs the first-line treatment of depression [26]. It may be difficult to make a clear clinical distinction between anxiety and depression and the depression may become more apparent when a patient fails to respond to anxiolytics. Whilst tricyclic antidepressants such as amitriptyline in adequate dosage are effective in anxious, depressed patients, they also have some sedative properties and are not particularly helpful in patients with pure primary anxiety [2].

Doxepin is both a potent antidepressant and has very marked antihistamine activity. This antidepressant is useful in the itchy, depressed, elderly patient and in some patients with neurodermatitis [26].

Other drugs in use

Butyrophenone derivations such as haloperidol are also used for anxiety, depression and alcohol withdrawal symptoms. Chloral hydrate (0.3–2.0 g) should not be despised as a hypnotic, particularly in children. The unpleasant taste of paraldehyde has limited its oral use, but it is an effective and quick-acting hypnotic, especially for hypomanic states, given by intramuscular injection (5–10 mL). Beta-adrenoceptor antagonists ('β-blockers') have not found much place in dermatology, although symptoms mediated by the β-division of the sympathetic nervous system have been helped by propranolol [27]. A number of side effects have been reported [28]. Pimozide has a special place in the management of patients with delusions of parasitosis [29,30].

Topical therapy

The dictum 'primum non nocere' has a special significance in relation to the vulnerability of damaged skin, often with an impaired barrier function, to develop either sensitivity or irritant reactions to local applications that the same patient might find harmless at other times. There is a particular temptation to be overzealous in treatment when faced with a disease that fails to react to initial therapy. Visual evidence of failure is particularly hard to accept with equanimity. Full details of topical therapy are given in Chapter 75.

EMLA cream (a eutectic mixture of 5% lidocaine (lignocaine) and prilocaine) is particularly useful as a local anaesthetic cream in children to try and ensure pain-free venepuncture, and may also be used to try and minimize distress during curettage of lesions of molluscum contagiosum or in removing genital warts. Its use may ensure that the injection of keloids in children causes minimal

distress, and it has a place in anaesthetizing the skin in children with port-wine stains during laser therapy. The cream is best applied under occlusion 1–4 h before the planned procedure [31]. An amethocaine-containing gel has been claimed to be more effective than the EMLA local anaesthetic in patients with port-wine stains [32].

Cosmetic camouflage

Cosmetic camouflage is very useful in the management of a wide range of dermatological problems ranging from scarring to vitiligo, and vascular anomalies such as port-wine stains. In the UK, the Red Cross offers a voluntary service and in some hospitals the occupational therapists are trained to do this work. Cosmetic camouflage has been shown to improve quality of life [33].

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Physical measures

Physiotherapy

The role of physiotherapists has assumed increased importance in recent years. Their duties have extended far from massage and simple forms of heat and light therapy of the past. They have become valuable members of a team devoted to a wide range of physiotherapeutic manoeuvres and to rehabilitation in the widest context.

In dermatology, the physiotherapist is probably not sufficiently invited to participate in the overall management of the patient with chronic or disabling diseases. Rehabilitation is discussed below, but techniques of relaxation are of benefit to many tense patients with irritable or vasolabile skin disease. Muscular relaxation is a key that opens the door to emotional relaxation, but it requires some experience and training to use the key effectively. Relaxation techniques [1] are a valuable adjunct to drug therapy and may even supplant it. Massage and re-education in limb movement are of great practical value in patients with constricting scars and deforming linear scleroderma, for which we have so little to offer. The influence of communal participation of physiotherapeutic activities, in which warmth, touch and encouragement combine to create an ambience conducive to relaxation and to a feeling of positive activity, should not be underestimated.

Massage [2] is valuable in the treatment of lymphoedema (Chapter 51) and rosacea.

Some physiotherapists have expertise in the management of venous leg ulceration and can participate in treatment from an early stage through the period of healing and rehabilitation.

Tap water iontophoresis is performed by many physiotherapy departments and is particularly useful in patients

with hyperhidrosis of the hands, feet and axillae [3]. The need for this therapeutic approach has probably lessened following the introduction of botulinum toxin for the management of not only hyperhidrosis of the axillae and, to a lesser extent, the palms [4,5] but also dyshidrotic hand eczema [6].

Other modes of physical medicine, such as short-wave diathermy, play a small part in dermatological management.

Ultrasound has found a secure place in the treatment of soft-tissue disease and injury [7,8] and may occasionally be of adjuvant value in conditions such as scleroderma [9], panniculitis and other dermatological conditions affecting deeper tissues.

Phototherapy, often performed by physiotherapists, is discussed in Chapter 35.

Acupuncture

The empirical basis on which this technique rested for so long has been dramatically changed by the discovery of the endorphins, and that the response to acupuncture can be mediated centrally by endorphins and enkephalins [10]. It has been shown that acupuncture can reduce the effect of histamine-induced itch and flare in healthy subjects [11]. The acupuncture points described in ancient Chinese medical literature correspond to some of the so-called trigger points described in Western medicine, and are said to represent areas of low electrical resistance.

Low-dose helium neon laser light and other types of lasers directed at acupuncture points have been claimed to be effective in a wide variety of conditions, but no valid double-blind clinical trials have been carried out. Anecdotally, post-herpetic neuralgia and atopic dermatitis seem to be helped in some patients by acupuncture, but it is difficult to assess the results of treatment. However, there are few risks as long as the needles are properly sterilized [12].

Biofeedback techniques

These involve the induction of a learned response aimed at controlling or modifying vascular responses [13] or inappropriate bodily responses to various centrally mediated stimuli. They may reduce emotional intensification of erythema and have been used to control flushing, for patients with dyshidrosis whose disease flared with stress [14] and in patients with atopic dermatitis [15]. Thirty-three patients with eczema were trained to decrease or increase electrical conductivity of the skin. Those who were trained to decrease skin conductance showed clinical improvement, while the controls who were trained in the opposite direction did not. The positive response was accompanied by a significant decrease in measured conductance and anxiety [16]. Eleven of 14 patients with chronic hyperhidrosis improved following biofeedback training. The most important aspect of the treatment was thought to be relaxation [17]. However, there is considerable individual variability in responses [1], and the main value may lie in anxiety reduction [18] and in the active involvement of the patient in self-help. It has been suggested that the techniques may be the 'ultimate placebo' [19] and their place in dermatology may remain limited by the time and patience required. Nevertheless, further developments in these methods may prove rewarding in specific dermatological situations, given a highly motivated and suitable subject.

Behaviour therapy

The use of behaviour therapy in dermatology was well summarized by Bar and Kuypers, who described four main therapeutic approaches [20].

Systemic desensitization is employed mainly in neurotic disorders where anxiety is the main clinical feature. An attempt is made to induce inhibition of anxiety following repeated exposures to weak anxiety-raising stimuli, after which progressively stronger stimuli are introduced. This type of behaviour therapy has limited application in dermatological practice.

In aversion therapy, patients with persistent behaviour disorders such as compulsive scratching or pathological hair pulling can be treated. The patient is given an unpleasant stimulus, for example a mild electric shock, whenever the unadaptive habit is demonstrated or displayed.

Operant techniques can be used to modify compulsive habits, and awards are given to reinforce good behaviour and bad behaviour is either punished or ignored. In children, a token may be given after a period of good (non-scratching) behaviour as part of a so-called token economy system.

Assertiveness training is employed in patients who are afraid of expressing their emotions and also experience extreme social fear. This technique is said to be most useful in patients with facial erythema or erythrophobia and also has a place in the treatment of patients with hyperhidrosis.

An operant technique was used successfully to modify the scratching behaviour in a patient with long-standing severe dermatitis, which had defied all traditional therapy [21]. As soon as the patient was observed scratching he was asked to fold his arms and think of something pleasant. Normal social attention was then withheld as a mild punishment. This man improved. The technique of habit reversal has an important place in the management of both adults and children with atopic eczema [22,23]. The patients were taught situation awareness so that they could recognize situations that made them itch. The patients were also instructed either to grasp an object or to keep the hands firmly on the itching area and pinch it if

necessary but not scratch it. A strong correlation was demonstrated between a reduction in scratching and an improvement in skin status [22,23].

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Hypothermia and hyperthermia

Cooling of the scalp to 25°C with ice turban packs or chemical coolants has been used to prevent or reduce hair loss during the critical period after administration of chemotherapeutic drugs [1]. Cooling of port-wine stains prior to treatment with the argon laser has also been tried to improve the efficacy of laser therapy and also to minimize scarring [2]. Some controversy still surrounds the use of skin cooling in laser dermatological surgery [3].

Resulting from the demonstration of the potential of hyperthermia as an antitumour agent [4,5], there have been occasional reports of its value in treating deep mycoses [6], leishmaniasis and myobacterial infections. Some similarity between the kinetics of tumour cells and psoriasis cells has prompted its use in the form of ultrasound in this disease [7]. Chemically generated heat in exothermic bags was used in 22 psoriatics in comparison with Goeckerman's regime [8], with apparent success and without side effects. This convenient and simple form of treatment may have a place in difficult therapeutic situations and merits further study [9].

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Homeopathy [1–3]

Homeopathy is a system of therapy originated by Samuel Hahnemann in the latter part of the 18th century. Central to the theory of homeopathy is the thesis that those agents that produce symptoms of any given disease will, in a much smaller dosage, cure that disease. Others have described homeopathy as a harnessing of an energy unknown to orthodox science.

Proponents of homeopathy state that there are three essential processes in the preparation of remedies, namely dilution, succussion and trituration. By diluting the drug, the toxicity of the original product disappears and during succussion and trituration some supposed mechanical energy is imparted to the remedy, imprinting the pharmacological message of the original drug upon the molecules in the diluent. From the practical point of view there seems no doubt that many patients are happy to consult with homeopathic practitioners, and most of these consultations do no harm unless a patient is advised to stop their oral or topical steroids suddenly. There is no doubt that homeopathic practitioners spend a great deal of time with the patient and some patients undoubtedly benefit from this enhanced level of communication which they are unlikely to find in a busy National Health Service clinic.

Despite two centuries of work, there are very few controlled clinical trials that allow homeopathy to be assessed [1].

In a study of alternative medicine, utilized by patients with atopic dermatitis and psoriasis, it was found that over 50% of patients with atopic eczema and over 40% of patients with psoriasis reported previous or current use of one or more forms of alternative medicine, and homeopathy, health-food preparations and herbal remedies were used the most. The use was related to disease duration and disease severity and inefficiency of therapy prescribed by physicians as judged by the patients. The author concluded that the use of alternative medicine is commonplace and should be of concern to dermatologists [4]. This work was confirmed by a later study [5].

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Occupational therapy and rehabilitation

A person conditioned to an active life does not take kindly to bed rest. Patients with skin diseases should be encouraged to become mobile as soon as their state allows it. Those with venous leg ulcers should not be kept in bed for long periods (although periodic elevation of the leg is important), but should have active and passive leg exercises to reduce the risk of thrombosis, foot drop and atrophy of the leg muscles. They should be encouraged to walk for increasing periods, rather than sitting, in order to re-educate their leg movements. The elderly patient with exfoliative dermatitis or pemphigus should be stimulated to pass his or her time without boredom, which passes imperceptibly in the aged into depression and despondency. In the alien milieu of a hospital ward, the elderly patient quickly deteriorates mentally and physically. Subsequent discharge or rehabilitation may then be extremely difficult. Occupational therapy should not only engage manual skill but also satisfy the emotional and intellectual needs of the patient of any age.

Patient self-help groups [1]

Increasingly, patients want to know more about their skin disease and its treatment. It is not always possible to meet all the patient's needs in an outpatient appointment, and, moreover, there is a limit to how much a patient can take in at one outpatient visit. This is where the self-help groups are increasingly important. The concept of self-help is that patients 'own' their disease find out more about their disease for themselves and are not just passively reliant on doctors and nurses for information and help. Such groups generate information, emotional support and advice. Patients can meet others with similar skin diseases and so realize that they are not alone. Patient self-help groups usually raise funds to support their activities, which will include research grants. They also lobby Members of Parliament to ensure that the needs of skin patients are heard and met. Pressure is often put on the purchasing health authority and the provider units to improve their service and to increase the amount of money spent on dermatology. Lastly, such groups attempt to diminish the stigma of skin disease that still exists in the community. The role of the patients' self-help group in dermatology is increasingly important to patients with skin disease and their general practitioners, dermatologists and nurses alike.

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Quality of life impairment by skin disease

What does quality of life mean?

Being able to assess the impact of skin disease on patients is essential in order to understand and meet what dermatology patients really need [1]. There is however, considerable controversy about the definition of quality of life and whether it can be meaningfully assessed [2,3]. There have been several attempts to define quality of life and the closely associated concept of health-related quality of life (HRQoL) [4]. The need for all outcome measures used in dermatology, including quality of life measures, to be properly validated has been emphasized [5]. There is however, very little information in the literature about the absolute meaning of different overall quality of life measurement scores or the interpretation of degrees of change in scores [6]. Concepts relating to life quality in dermatology are well reviewed in a book by Rajagopalan *et al*. [7].

Why measure quality of life?

All clinical dermatologists are aware of the impact that skin disease may have on their patients. However it is only over the last two decades [8] that there have been attempts to develop methodology to measure the adverse

impact of skin disease on quality of life. There are several reasons why measurement may be helpful.

Clinical therapeutic research. When new drugs are assessed, the outcome measures used are usually clinical measures such as the degree of scaling or the area of skin affected. Pharmaceutical companies and regulatory authorities are realizing that although these measures of disease activity are of course important, it is necessary to have in addition a patient-orientated outcome. There may be a 50% improvement in a psoriasis area severity index (PASI), but if the handicap experienced by the patient is only slightly improved because visible skin remains abnormal, the intervention may not have been very successful from the patient's point of view. It has been argued that a quality of life standard is better than a body-surface-area measurement for identifying patients with severe psoriasis [9]. The addition of (not the replacement by) a HRQoL measure may be essential to make a proper assessment. The introduction of several new therapies in dermatology over the last 10 years has been supported by such information [10,11].

Health service research and audit. Within many health care systems it is becoming mandatory to produce evidence of the effectiveness of care given, and to have systems in place to monitor effectiveness and assess improvement against agreed criteria. An essential part of this process has to involve having patient-orientated measures and simple but well-validated HRQoL questionnaires are well suited for this need [12–15]. The use of these measures can give additional insight into the acceptability of new methods of providing dermatology advice, such as teledermatology [16]. Sound epidemiological data are essential for the planning of health services: HRQoL data can measure the extent of problems caused by skin disorders in a community [17] and be used to compare the HRQoL of people with specific skin diseases, such as psoriasis, to the general population [18].

Research into psychological aspects of dermatology and patient behaviour. Quality of life measures can be used to gain insight into patient attitudes: stress resulting from the anticipation of other people's reactions to their psoriasis contributed more to the variance in patients' disability than any other variable [19]. It is important that the problems relating to compliance with treatment, often not recognized by dermatologists, are better understood. Quality of life indices have been used to provide patient-orientated measures in studies of compliance in psoriasis and acne.

Political/resource allocation. Patients with skin diseases are rarely given any priority for resource allocation in any health care systems. Conditions that result in death are much more likely to find political support for service development. It is the responsibility of dermatologists to argue for appropriate resource allocation and appropriate funding of dermatology services and of the education of doctors about skin problems. One way in which the arguments for this can be strengthened is by using HRQoL data that demonstrate the devastating effects of skin disease on patients' lives. If general HRQoL measures are used it is possible to quantify the effects of skin disease compared to other system disease [20,21]. It may be necessary to demonstrate to managers or politicians and defend the value of dermatology clinical services that is self-evident to clinicians, e.g. in-patient dermatology beds [22–24], patch testing [25], cosmetic camouflage advice [26] and outpatient clinical services [12]. Dermatology-specific measures can also be used to demonstrate the value from the patients' point of view of expensive or unusual therapy such as climate therapy [27].

Informing clinical decisions. Most dermatologists probably consider that they have a reasonably accurate insight into the impact of skin disease on individual patients. The assumptions made about this influence clinical decisions; for example, whether or not to start a patient on a systemic therapy which has risks of side effects. Unfortunately, dermatologists may not have as much insight as they think they have into the degree of their patients' problems [28–30]. The use of a standard HRQoL measure may therefore potentially inform a clinician more accurately about their patient and allow better judgement concerning risk/benefit of therapy change. This will only become relevant on a routine basis if the absolute meaning of HRQoL scores can be more clearly defined than at present [6].

How do quality of life measures relate to other clinical indices?

It is self evident there is likely to be a relationship between the clinical severity of skin disease and the impact that the disease has on life quality. This has been demonstrated in atopic dermatitis in children where the Children's Dermatology Life Quality Index (CDLQI) was shown to be significantly correlated with the Severity Scoring of Atopic Dermatitis (SCORAD) [31]. However there are many influences on the disability experienced and individual patients show a wide variation in their responses to similar degrees of disease [8]. Particular body site affected is an important factor with visible sites such as the face having much greater significance to a patient. The psychological attitudes of patients to their disease vary widely and these attitudes have a major influence on the degree of disability experienced. Clinical scoring systems may reflect sign changes which are not of relevance to a patient's life. For example, in psoriasis, the successful reduction of scaling and thickness may result in a large percentage reduction in PASI, but if the redness persists the quality of

life improvement may be much less [32]. Quality of life measures therefore should not be used instead of clinical measures, as they are designed to assess a completely different, though interrelated, aspect of skin disease.

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Methods of measuring quality of life in dermatology

There are several different approaches to the measurement of HRQoL. One depends on the use of fixed repeatable questionnaires that are scored. A second approach uses questionnaires that allow a variable response from the patient, taking into account the particular values of the patient. Another method is to assess the value that a patient or society places on the presence or absence of particular disease states—the utility approach. Decisions concerning which measures are appropriate to use can be confusing: general guidance is given in a review article [1]. Comparisons of assessment of quality of life in cutaneous disease [2] and in psoriasis [3] have been reviewed, and advice has been given [4] concerning understanding research about quality of life.

Some techniques are designed to be used across all disease states, some for use across a range of diseases of the same organ system and some for use in patients with specific diseases. Most published questionnaires are for use in adults, but there have been techniques described for measuring HRQoL in children with skin disease, infants with atopic dermatitis and the secondary impact of having a child with dermatitis on the family.

HRQoL measures are usually designed to assess the impact of skin disease at a particular time (e.g. 'today') or over a fixed period of time (e.g. 'over the last week'). Measures are usually designed in this way so that they can be used for example to compare data before and after intervention. However it should be noted that the long-term 'importance' or impact on a patient's life may therefore not be captured by these indices. Patients with basal cell carcinomas at the time of presentation to dermatologists generally have little or no reduction in their current quality of life [5], but of course if the disease was not treated there could be major problems in the future. It is therefore important that if HRQoL measures are used to inform priorities for resources in a health care organization, these measures should not be used in isolation.

Examples of quality of life measures

General health measures

General health measures are designed to be used across a wide range of disease states. Their use is essential if comparisons are to be drawn between the impact of skin diseases, the impact of diseases of other systems and the general population. Examples of tools available include the 36-Item Short-Form Health Survey (SF-36) [6], the Sickness Impact Profile (SIP) [7], the Nottingham Health Profile (NHP) [8] and the EuroQol and EuroQol Five Dimensions (EQ-5D) [9]. The General Health Questionnaire (GHQ) [10] is designed to detect psychiatric disorder.

Many of these general health measures have been used in dermatology. The UK SIP has been used in psoriasis [11] and atopic dermatitis [12]. The SF-36 has been used in psoriasis [13–15] and acne [16]. The twelve-question version of the GHQ (GHQ-12) has been shown to be of value in assessing psychological distress in patients with skin disease [17], and specifically in vitiligo [18]. In many investigations both a generic measure and a dermatology-specific measure have been used together [14] and the advantages of this have been emphasized in a study using the EuroQol and EG-5D in acne [16].

Dermatology-specific measures

Dermatology-specific measures are useful when comparisons need to be made between the impact of different skin diseases and where there is a need to measure change before or after intervention in any skin disease. Having a single simple measure that can be used across all skin disease is of great practical advantage, especially in a busy clinical setting.

The two dermatology-specific measures that have been most widely used are the Dermatology Life Quality Index (DLQI) [19] and Skindex [20]. Other measures that have been described include the Dermatology Quality of Life Scales [21], the Dermatology-specific Quality of Life instrument [22] and a German instrument, the Deutsches Instrument zur Erfassung der Lebensqualität bei Hauterkrankungen (DIELH) [23].

The DLQI consists of 10 questions covering a wide range of ways in which patients' lives are affected by skin disease (Fig. 71.1). They are answered by a simple tickbox method and each scored 0–3. The DLQI takes on average only 2 min to complete [24]. There are over 170 references describing the use of the DLQI in a wide range of skin conditions and in many languages worldwide [25]. Validation studies have been carried out in the UK in secondary care [19] and primary care [26], and in Spain [27,28], Germany [29], Denmark [30], the USA [31] and Norway [32]. Its use has also been described from France, The Netherlands, Belgium, Sweden, Switzerland, Russia, Yugoslavia, Canada, India, Australia, Malaysia, Hong Kong, South Africa, Tanzania, the Canary Islands and Guyana. When illustrations are added next to the text of the DLQI, the questionnaire tends to be completed more rapidly but there is an influence on the way the questionnaire is answered [24].

Skindex has been developed and thoroughly validated in three versions with 61 [20], 29 [33] or 16 [34] questions. Further validation studies have been carried out in Spain [35], Italy [36] and Japan [37]. The appropriateness of using Skindex-29 in psoriasis along with the generic SF-36 has been emphasized [3].

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick one box for each question.

1 Over the last week, how **itchy, sore, painful** or **stinging** has your skin been?
2 Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?
3 Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?
4 Over the last week, how much has your skin influenced the **clothes** you wear?
5 Over the last week, how much has your skin affected any **social** or **leisure** activities?
6 Over the last week, how much has your skin made it difficult for you to do any **sport**?
7 Over the last week, has your skin prevented you from **working** or **studying**?
If 'no', over the last week how much has your skin been a problem at **work** or **studying**?
8 Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?
9 Over the last week, how much has your skin caused any **sexual difficulties**?
10 Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?

Please check you have answered every question. Thank you.

Each question is answered either 'Very much' (score 3), 'A lot' (score 2), 'A little' (score 1) or 'Not at all' (score 0). Questions 3–10 also have the option 'Not relevant' (score 0). The first part of question 7 has the choices 'Yes' (score 3), 'No' or 'Not relevant'. The second part of question 7 has the choices 'A lot', 'A little' or 'Not at all'. The maximum score (indicating highest possible impairment of quality of life) is 30 and the minimum 0. Further information: www.ukdermatology.co.uk.

Fig. 71.1 The Dermatology Life Quality Index (DLQI) [19].

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Disease-specific measures

Because the questions in disease-specific measures reflect as closely as possible the problems encountered by patients with that disease, disease-specific measures have the potential of being the most sensitive to change. They are therefore particularly suitable for comparative purposes within a cohort of same-disease patients. In many skin diseases however, for example in the widespread inflammatory skin diseases, patients lives are broadly affected in similar ways, and so dermatology-specific measures can also be used. There is therefore no need for every skin disease to have its own disease-specific measure.

Psoriasis. A landmark study of quality of life issues in over 17 000 patients with psoriasis [1], using a study-specific questionnaire, demonstrated the major impact that psoriasis can have on patients' lives and revealed that many patients with psoriasis do not feel that their physicians are aggressive enough with their therapy.

The Psoriasis Disability Index (PDI), originally described in 1987 [2] and revised in 1995 [3] has been extensively used in international studies [4], and is available in several languages.

The stigmatizing effects of psoriasis can be recorded using a 33-item questionnaire [5]. Another technique for measuring this effect has been described [6] and used to demonstrate the high stigmatization experienced by patients with psoriasis compared to patients with other skin diseases [7]. The stress that can be caused by the

impact of psoriasis on quality of life can be measured by the Psoriasis Life Stress Inventory, in its 41- [8] or 15-item versions [9].

A new construct for psoriasis which allows separate recording of signs (disease activity), psychosocial disability and history of interventions has been proposed [10]. The Salford Psoriasis Index (SPI) consists of three independent scores describing each of these aspects. This approach may be of great value in the recording and monitoring of this chronic disease.

Atopic dermatitis. The CDLQI and the DLQI have been used extensively in the monitoring of patients with atopic dermatitis. In a large managed care organization in the USA, patient-assessed severity of atopic dermatitis demonstrated a stronger correlation with the DLQI and CDLQI than did provider-assessed severity, emphasizing the importance of directly assessing the patients' attitudes [11]. The disease-specific measures for use in infants (Infant's Dermatitis Quality of Life Index, IDQOLI) and in families (Dermatitis Family Impact questionnaire, DFI) are described below. Assessment of quality of life in atopic dermatitis has been reviewed [12].

Acne. An initial attempt to produce an Acne Disability Index (ADI) [13] has been largely superseded by the more compact five-question Cardiff Acne Disability Index (CADI) [14], which was derived from it. This simple instrument has demonstrated good reliability and validity [15]. The 'Assessments of the Psychological and Social Effects of Acne' (APSEA) questionnaire [16] has 15 questions some of which relate to the overall impact and some to the recent past. A nine-item Acne Quality of Life Scale [17] has been proposed for use in acne: the questions relate specifically to the social impact of acne. The Acne-specific Quality of Life questionnaire (Acne-QoL) [18] is a 19-question tool which has been validated but not yet widely used.

Other disease-specific measures. Other disease-specific measures have been described for ulcers [19], urticaria [20], excessive axillary sweating [21], scalp dermatitis [22] and for women with androgenetic alopecia [23].

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Patient-specific and utility measures

HRQoL measures are, or should be, derived from information gathered from patients' experiences and not from health care professionals' concepts of what they suppose to be the impact of disease. Despite this all fixed questionnaires suffer from the disadvantage that for an individual patient, the weighting given to different aspects of life quality impairment may be different from that assigned in the questionnaire, or the specific issues may be missed. The Patient Generated Index [1] overcomes these problems by being structured in a different way: patients are asked to identify the five ways in which their life is most affected and then assign them comparative values. This technique is effective for identifying individual's specific problems as in atopic dermatitis [2] but it is difficult to incorporate in large scale before and after studies.

Utility measures are methods to assess the hypothetical value placed by people on their health. There are a variety

of different approaches described. Standard gamble, time trade-off and vertical rating scales have been proposed [3] as a method to inform decisions relating to methotrexate therapy for psoriasis. A simple 'financial value' method is to ask patients how much they would be prepared to pay for a cure of their disease if such a cure existed. This has been used in acne [4], psoriasis [5] and atopic dermatitis [6].

Another approach is to ask patients to consider how much time they would be prepared to give up for the sake of a cure. These 'trade off' questions can be related to years of shortening of life, as in the Quality Adjusted Life Year (QALY), or be related to hours trade off. The hours trade off method has been described in psoriasis [5] and in atopic dermatitis [6], whereas the QALY method has been described in acne [7]. In contrast to the concept of hypothetical time that a patient would be prepared to give up, there is no correlation between the measurement of actual time spent on treatment and quality of life scores [8].

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Children, infants and family impact

Children. The assessment of quality of life impairment in children is more difficult than in adults because of issues relating to communication, rapid change in lifestyle at different ages and differing rates of maturing. The different general measures and disease-specific measures have been reviewed [1].

The Children's Dermatology Life Quality Index (CDLQI) [2] is designed to be used by children aged 4–15 years old. It can be completed unaided by older children but parents can help younger children as necessary. An illustrated cartoon version, using the same text, has been validated [3]. Overall, children preferred the cartoon version and completed it more rapidly than the text only version. The CDLQI has been used in the assessment on children's lives of the effects of atopic dermatitis, the impact of admission for treatment, the impact of a nurse consultant, and the effect of new topical and systemic anti-inflammatory agents. There are several different validated language translations of the CDLQI. Another measure that has been used in paediatric dermatology is the Pediatric Symptom Checklist [4], which consists of 35 questions answered by the parent. It has been used for psychosocial screening in paediatric dermatology clinics.

The lives of infants with atopic dermatitis may be severely disrupted, even though the affected children may not be able to explain their distress, or have the insight to know that what they are experiencing is abnormal. The Infant's Dermatitis Quality of Life Index (IDQOL) [5] has been proposed to encapsulate and attempt to measure the impact of atopic dermatitis on infants.

Family impact. When a patient is affected by a skin disease, those closest to the person are usually also affected. Having a child with atopic dermatitis can have a major impact on the functioning of a family. Two methods [6,7] have been proposed to measure this secondary impact. The Dermatitis Family Impact (DFI) questionnaire [6] has been used to demonstrate the relationship of dermatitis severity to family life quality [8].

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Declaration of interest. The author (AYF) is joint copyright holder of the following questionnaires described above: DLQI, CDLQI, PDI, IDQOL, CADI, ADI and DFI.

Some specific groups for whom problems of readjustment and rehabilitation may be important are outlined below.

Infants with atopic eczema. The main need is for dialogue with the parents and sustained contact to help relieve the inevitable tensions and emotional stresses that the condition imposes on them. Special problems arise in children where hospital admission is required. This is best dealt with in children's units. Joint management with nursing staff trained for the special requirements of sick children

and expertise in basic dermatological therapy is invaluable. The parents should be encouraged to participate in the ward activity and will gain confidence in helping in the management of the problem.

The young adult atopic eczema patient. The problems here are often those of personality and environmental stresses rather than of working conditions. Apparent resolution in the protected environment of a hospital ward does not always survive exposure to the harsher emotional stresses of outside life. However, a temporary withdrawal from an adverse environment is usually helpful. It is important that the dermatologist discusses with both the patient and his or her family possible future employment. For instance, the youngster with severe hand eczema is unlikely to be able to nurse or become a hairdresser, or be able to follow a successful career in catering or engineering involving the continued exposure to coolant oils. Early counselling about future work prospects can prevent a lot of misery later on.

The older child. Children with disabling or disfiguring diseases demand special attention towards adjustment to the various epochs of their life relationships with other children, the first school, and passage through puberty. Play and companionship in the early years mark the transition from maternal social relationships. Disfigurement or disease is always a source of childish cruelty and integration into the social group requires much skilled help from nursing staff and mother figures. The transition to school and pressure of examinations call for guidance and careful management. The difficulties of a spastic, deaf or mute child are evident enough to arouse sympathy. The emotionally volatile, scratching atopic or the obviously disfigured child receives less sympathy and attention, although his or her needs are as great.

The young manual worker. There will be much anxiety about the manual worker's future working capacity. After all relevant investigations have been carried out, the work possibilities should be assessed. With the patient's consent, contact with his or her firm's medical officer and general practitioner should be routine, and the results of patch tests, etc. should be conveyed with an interpretation that is relevant to the occupation. To a worker, persistent hand eczema may mean the difference between a livelihood or disablement. Anxieties may not be readily revealed and may require patience to uncover. Re-education in working procedure, an explanation of irritant (or allergic) dermatitis and attention to the causes of persistence and relapse should be part of the normal procedure of treatment. After suffering a severe attack of dermatitis, a patient is likely to be suspicious of any agent to be handled on return to work, but he or she should be encouraged to persist at work during the first critical weeks in which non-specific factors may temporarily exacerbate the condition. The patient should be seen at intervals for at least 3 months after return to work. The employers should be willing to grant time to attend hospital for this purpose.

Medicolegal aspects of dermatology [1]

A survey among members of the British Association of Dermatologists indicated that a significant proportion of dermatologists in the UK were concerned about the possibility of being sued, and an even greater percentage had altered their practice because of this concern [2].

The problem is not confined to the UK, with major concerns about potential litigation amongst dermatologists in the USA, Irish Republic and, more recently, in several other European countries.

There are several measures that minimize the possibility of litigation, and good and effective communication between the dermatologist and the patient is the most important. Moreover, continuing effective communication is necessary after the patient has been seen, especially if there has been dermatological surgery, so that if there are any problems these can be dealt with rapidly and effectively. There is nothing more frustrating for the patient than to find the dermatologist elusive, and resulting patient anger can initiate speedy legal retribution. It is important that not only the dermatologist but also all associated staff adopt an open and easy policy as far as communication with patients is concerned.

A second necessary line of defence against possible litigation involves making adequate and comprehensive case notes. This is particularly important as far as pigmented lesions are concerned, where it is prudent to record the variability or otherwise of the shape, the size and degree of pigmentation of the lesion. There has been a recent increase in litigation involving patients with malignant melanoma, not only over allegations about failure to make an accurate diagnosis, but also in regard to possible delay in seeing the patient after referral by the general practitioner. It is good practice for the dermatologist to see all the referral letters from the primary care physician so an informed assessment of urgency can be made. Even so, the vast numbers of anxious patients referred on account of recent change in pigmented lesions, the majority of which turn out to be absolutely benign, makes running an effective dermatological service very difficult. Particular difficulties arise when the general practitioner does not label the referral letter 'Urgent' and the patient subsequently turns out to have a malignant melanoma. In this instance, the information given by the general practitioner in the referral letter may or may not be sufficient to allocate an urgent appointment.

Dissatisfaction with scars after lesion removal is another potential area of litigation. It is good practice to explain that spread scars are the almost universal accompaniment

of excision of lesions on the back and legs and the development of not only hypertrophic scarring but also keloid scarring should be emphasized, particularly in keloid-prone areas such as presternal skin and over the deltoid area. Comprehensive notes recording that a full discussion has taken place about the future cosmetic appearance of the scar, including possible diagrams of how a lesion will be excised, are both very helpful in rebutting potential litigation.

Consultant dermatologists have a responsibility to train others, and faulty technique using liquid nitrogen is a relatively common cause of litigation against general practitioners. Skin necrosis, and even peripheral neuropathy, are the commonest causes for litigation following inappropriate liquid nitrogen treatment.

Skin and subcutaneous atrophy following injections of triamcinolone in inappropriate sites, such as the arm, or too superficially, or at the same site in the buttock are also relatively common causes of cosmetic litigation as far as the general practitioner dermatologist is concerned.

It is very important that colleagues refrain from making disparaging remarks about other colleagues in front of patients. It is also important not to use emotive words, such as 'dermatitis' to, for example, an engineering worker, who may equate this diagnosis immediately with a diagnosis of industrial dermatitis, and therefore financial compensation.

One other potential pitfall for the dermatologist is the side effects from the use, not only of oral, but also of topical, steroids. Skin atrophy, striae, depression of the pituitary–adrenal axis and avascular necrosis of the femoral neck are particular examples. Avascular necrosis of the femoral neck is more common in alcoholic individuals and special care should be exercised, not only using oral steroids, but also topical steroids, in such patients [3]. It should be remembered, however, that avascular necrosis of the femoral neck has also been described in patients receiving physiological corticosteroid replacement therapy [4]. Patients on long-term oral steroid therapy should be advised about prophylaxis for osteoporosis [5].

The possibility of inducing not only cataracts but also glaucoma, especially if there is a family history of glaucoma, following the long-term use of tropical corticosteroids on the face and around the eyes in particular, should be remembered in patients, for instance, with long-standing eczema of the face [6].

Particular care needs to be exercised to avoid prescribing drugs that have previously caused an allergic reaction in a particular patient [1]. Although the resulting medical problem may not be severe, there is always a chance of a much more severe allergic reaction leading to the development of potentially fatal toxic epidermal necrolysis.

Avoidance of drug interactions is also important, particularly where potent drugs, such as methotrexate, ciclosporin, warfarin and corticosteroids are concerned. A recent study of 790 claims against general practitioners has shown that the largest proportion (25%) were related to errors in prescribing, monitoring or administering medicine [7].

Careful systems of work are vital to prevent burning of normal skin during the use of various forms of ultraviolet (UV) light, including psoralen and long-wave UV radiation (PUVA) therapy and topical dithranol (anthralin) treatment. Management changes in the British National Health Service, attempting to achieve a skill mix, have led to relatively inexperienced nurses being given the task of administering dithranol or UV therapy. Hospital managers should be told about the possible disastrous consequences of such a policy in dermatological patients, where nursing treatment expertise, built up over many years, is vital to ensure best results. Care also needs to be exercised in the topical treatment of ulcers, where the prescription of topical agents containing neomycin have led to the development of deafness [8].

Why do patients go to litigation? [9]

There are four main reasons why people sue their doctors, and the decision to take legal action is not only determined by the original 'injury' but also by insensitive handling and poor communication after the original incident. The patient seeks explanations when things go wrong and these explanations are often considered inadequate by patients who sue their doctors. The four main reasons that emerged from a recent analysis of 227 patients and relatives were, firstly, a concern with standards of care. Both patients and relatives wanted to prevent similar incidents in future. Secondly, there is a need for an explanation to know how the injury happened and why. Thirdly, there was a belief that the doctor or hospital involved should have to account and apologize for their actions. Lastly, financial compensation for pain and suffering was a significant factor. Moreover, the patients and their relatives all expressed a desire for greater honesty and assurances that lessons had been learned from their experiences [9].

Litigation and patients with psychiatric problems

Whilst patients may quite correctly seek financial compensation for errors made by their dermatologist, it is possible that some patients are more likely to go to litigation than others.

In a recent study involving nearly 100 patients, suing either their doctors or their employers and seen for medicolegal purposes, a very significant past or present history of psychiatric disturbance was found in almost 70% of the litigants. The commonest psychiatric disease present was depression, but anxiety, alcoholism and personality disorder were all represented. The medicolegal patient may also be trying to deceive both the dermatologist and the

court. In this series there were two patients with artefact dermatitis and one with dermatitis simulata.

It is easy to miss a diagnosis of depression in dermatological patients, and it is thought that perhaps 50% of depressed patients in medical practice go unrecognized [10]. The depressed patient with dysmorphophobia is particularly likely to be angry, and this anger can be directed at the dermatologist or general practitioner, but, more commonly, internally, resulting ultimately in suicide [11].

Dysmorphophobic patients tend to haunt dermatologists, particularly those who are undertaking cosmetic procedures, such as laser treatment and skin resurfacing. Even though the results of treatment are good, the patient may remain dissatisfied and litigious. Before any cosmetic procedures are undertaken in a depressed patient, it is very important to make sure that communication between the patient and the doctor is optimum. Photography before and after any procedure is also important, so that there is some objective measure of the outcome. Preoperative assessment by a psychiatrist may be indicated in patients with long-standing or gross psychopathology.

Preparing a medicolegal report [1]

The data necessary to prepare a medical report on a patient seen with possible occupational dermatosis are described in Chapter 21.

Dermatologists may be asked by solicitors to prepare medicolegal reports. The commonest request is to prepare a report about alleged industrial dermatitis. Less often, a report on the dermatological consequences of an accident, either on the road, in the factory or, for instance, following a badly performed perm, may be sought. Thirdly, there may be a request to prepare a report about alleged medical negligence.

Until recently in the UK it was normal practice to appoint one expert witness to prepare a report for a claimant and a second expert witness to carry out a similar role for the defence. The present position is that normally one joint expert only is appointed by the court under Civil Proceedings Rules Part 35:3. Such a joint expert owes a duty to the court and will be expected to make a detailed declaration at the end of the expert report (Table 71.4).

It should be noted that the report has to be based on a complete and detailed enquiry of the relevant events, and a conventional medical history is not sufficient [1].

It should be remembered that the medical report may eventually go before a judge in court and it is humiliating for an expert witness to be questioned by a barrister about numerous spelling and grammatical errors. It is important that the dermatologist does not become biased on one side or the other. The expert witness has a duty to the court, and the medical report should be formulated to help the court. Solicitors may try and manipulate individual reports, asking the dermatologist to omit certain sentences and add others. As a generalization, this type of pressure should be resisted. Although the solicitor may wish you to amend the report for a tactical reason, the best guideline to follow is that the report should not be changed to such an extent that the writer can no longer agree with the content [12].

In a civil case involving, for instance, a claim for compensation for industrial dermatitis, the test of whether there is a causal relationship between exposure to coolant oil and the development of subsequent dermatitis depends on balance of probabilities. If, on balance of probabilities, there is more than a 50% chance that an individual's skin problem was caused, for instance, by coolant oil, that is sufficient for the claimant to establish the case. In contrast, in a criminal matter, the burden of proof has to be beyond all reasonable doubt, i.e. 99% or above certainty. In a medical negligence case, the solicitor may seek a report dealing mainly with diagnosis, causation and prognosis and seek a separate report dealing with liability and negligence.

The essence of negligence is that there has been a breach of a duty of care resulting in damage, and in medical cases this occurs in a context of diagnosis and/or treatment. There are four essential components, and all four must be present and proven before the patient can succeed in the action against the doctor [13].

Table 71.4 Expert's declaration.

1 I understand that my overriding duty is to the court, both in preparing reports and in giving oral evidence
2 I have set out in my report what I understand from those instructing me to be the questions in respect of which my opinion as an expert is required
3 I have done my best, in preparing this report, to be accurate and complete. I have mentioned all matters which I regard as relevant to the opinions I have expressed. All of the matters on which I have expressed an opinion lie within my field of expertise
4 I have drawn to the attention of the court all matters, of which I am aware, which might adversely effect my opinion
5 Where I have no personal knowledge, I have indicated the source of factual information
6 I have not included anything in this report which has been suggested to me by anyone, including the lawyers instructing me, without forming my own independent view of the matter
7 Where, in my view, there is a range of reasonable opinion, I have indicated the extent of that range in the report
8 At the time of signing the report I consider it to be complete and accurate. I will notify those instructing me if, for any reason, I subsequently consider that the report requires any correction or qualification
9 I understand that this report will be the evidence that I will give under oath, subject to any correction or qualification I may make before swearing to its veracity
10 I have attached to this report a summary of my instructions
11 I confirm that in so far as the facts stated in my report are within my own knowledge I have made clear which they are and I believe them to be true and that the opinions I have expressed represent my true and complete professional opinion

1 The doctor must have had a duty of care to the plaintiff.
2 There must have been a breach of that duty.
3 The plaintiff must have suffered damage.
4 The damage must be a consequence of a breach of duty of care.

The Bolam test is often used to determine whether there has been a breach of duty of care. In this particular case the judge stated that 'a doctor is not guilty of negligence if he has acted in accordance with the practice accepted as proper by a responsible body of medical men skilled in that particular art'. This Bolam principle remains vital and central to how a doctor's professional behaviour is to be judged by other doctors, and not by lawyers, politicians or administrators. The Bolam test has been modified in the last decade so that a court in the UK can now reject medical opinion if it is not reasonable or responsible [14].

It should be noted that in exercising reasonable care, there may be an act of either commission or omission and each of these categories could lay the dermatologist open to litigation if harm has occurred. Moreover, a distinction must be made between an error of clinical judgement and negligence.

It is reassuring that the medical defence organizations in the UK still regard dermatology as a low-risk specialty, with few and relatively low-cost claims. On the other hand, plastic and reconstructive surgery involves a higher risk, as does cosmetic practice, especially when not carried out by consultant dermatologists or plastic surgeons.

It is important to remember that if something has gone wrong with patient care, a full and frank explanation with as little delay as possible will do much to diffuse the anger, upset and resentment that the patient feels and ultimately may reduce the risk that the patient will go to litigation [9]. There is a need for an explanation of how the injury has happened and why [9]. The doctor adopting this open type of approach could find him- or herself in direct conflict with the 'never admit anything' insurance type of mentality and it is important that Trust managers in the UK National Health Service, for instance, do not put pressure on their medical practitioners to adopt this approach. A prompt explanation is vital, as any delay would be seen as an attempt at cover up.

Consent [15]

Any treatment that entails the physical touching of a competent adult patient without consent constitutes the tort of battery. Consent provides a defence that makes the touching lawful. From the legal profession's point of view it is important to establish whether a competent adult patient consented to treatment or not and a requirement to obtain consent is imposed by law. In English law, once a patient has been informed in broad terms of the nature of the intended procedure and gives consent, the consent is valid, although there may be difficulties in deciding what constitutes the nature of the treatment or procedure and information in broad terms. It is very important to continue to review the information given to patients before obtaining consent. The use of information leaflets and documentation for the patient to read about treatment or surgical procedures is very helpful in this regard [16] but some doctors are still not providing enough information [14]. Medicolegally, times are changing so courts of law in the UK are putting more emphasis on the needs of patients and this can be seen as part of a wider social movement to give greater respect for individual rights.

The court appearance

Fortunately, less than 1% of cases where a medical report has been requested ever threatens to reach court, and in the majority of these cases a settlement is often reached out of court before the scheduled hearing. Should your appearance be necessary as an expert witness in court, it is important to follow several rules, but usually the expert witness drifts into this type of work without any training. Good preparation before the scheduled hearing is important and the original clinical notes, taken when preparing the medical report, can also be very useful. It is important to take the attitude that you are there to help the court, rather than to take one side or the other. Speak clearly and slowly enough to allow the judge to make notes. Do not fidget and do keep your evidence simple [17]. Take your time, when you need to, before answering the barrister's questions. When you are unclear as to what the barrister is asking, you may politely ask if the question might be rephrased. Emotionally, it may be difficult to switch from the role of a caring medical practitioner to an adversarial court system. Do not try and cross swords with an aggressive barrister, and address your comments at the judge, or jury if present. Remember, you are perfectly at liberty to ask for a short break if you have been in the witness box for some time and are getting tired.

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Chapter 72

Systemic Therapy

S.M. Breathnach, C.E.M. Griffiths, R.J.G. Chalmers & R.J. Hay

Introduction

Topical therapy is generally preferable for skin diseases, because it minimizes the risk of systemic toxicity. However, there are quite a number of drugs that are only effective when administered systemically. This chapter gives a brief survey of some of the more important systemic agents used by dermatologists. The reader is also directed to additional information on drug therapy for specific conditions dispersed amongst other chapters in these volumes.

The important subject of drug reactions and interactions is referred to in Chapter 73. The particular problems of prescribing for special groups, such as children, pregnant and lactating women and elderly people are dealt with in some detail in the *British National Formulary* [1] (and other national formularies), as are the difficulties in prescribing for patients with liver failure, renal failure and diseases affecting other organs. Where there is any doubt, the advice of a clinical pharmacologist, a pharmacist or the drug manufacturer should be sought, or information obtained from such reference works as *Martindale* [2] and Goodman and Gilman [3]. The *ABPI Data Sheet Compendium* [4] is also valuable. The dosage for children is often calculated roughly on the basis of age, but should more accurately be based on body weight or, even better, body surface area [1].

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Systemic corticosteroid therapy

Corticosteroids were first introduced into dermatology by Marion Sulzberger [1]. Most of their effects are mediated by the intracellular glucocorticoid receptor via activation or repression of gene expression [2,3]. Activation requires DNA binding of the receptor, while repression is mediated by protein–protein interactions with other transcription factors. The immunosuppressive and anti-inflammatory effects are exerted mainly by an interaction of the glucocorticoid receptor with the activating protein 1 (AP-1) and nuclear factor κB (NF-κB) families of transcription factors without DNA binding. Cytokines such as tumour necrosis factor-α (TNF-α) and interleukin 1 (IL-1) activate the hypothalamus–pituitary–adrenal (HPA) axis; glucocorticoids inhibit IL-1 and TNF-α forming a cytokine–HPA axis feedback circuit. In addition, glucocorticoids induce apoptosis of inflammatory cells

of the haematopoietic system, such as monocytes, macrophages and T lymphocytes, while protecting resident tissue cells [4]. Corticosteroids, by evoking formation of a cell-membrane protein termed lipocortin, also inhibit phospholipase A_2 (PLA_2), a membrane enzyme that generates a variety of pro-inflammatory lipids from membrane phospholipids, including the prostaglandins, the leukotrienes and platelet-activating factor [5]. Other proposed mechanisms of corticosteroids include a cytostatic action, a 'stabilizing' action on lysosomal membranes, and suppression of cytokine expression. Glucocorticoid effects on bone result from inhibition of bone formation because of a decrease in the number and function of osteoblasts, and increased bone resorption resulting from osteoclastogenesis (with increased expression of RANK ligand and decreased expression of its decoy receptor, osteoprotegerin), as well as stimulated expression of collagenase 3 [6].

Indications

Systemic corticosteroid treatment, rather than topical corticosteroid therapy, is indicated in special circumstances only. These include the following.

1 Acute self-limited steroid-sensitive disorders (e.g. acute contact allergic dermatitis), where the offending allergen is evident. In these circumstances a 1-week course of oral prednisone in reducing dosage may be sufficient.

2 Acute anaphylactic reactions (e.g. following a bee or wasp sting or a drug to which the patient is sensitized). Hydrocortisone should be given intravenously in a dose of 100 mg, after prior administration of epinephrine (adrenaline) 0.5 mg intramuscularly, and chlorphenamine (chlorpheniramine) 4 mg intramuscularly (adult doses).

3 Acute autoimmune connective tissue diseases and generalized immunological vascular disorders (e.g. systemic lupus erythematosus, dermatomyositis, polyarteritis nodosa, giant cell arteritis, Wegener's granulomatosis).

4 Chronic disabling immunological bullous diseases (e.g. pemphigus vulgaris, pemphigoid).

5 Acute generalized exfoliative dermatitis (e.g. resulting from a severe drug reaction).

6 A number of miscellaneous disorders including severe lichen planus, pyoderma gangrenosum and sarcoidosis, in which there is evidence of cardiac, renal, ocular or extensive pulmonary or cutaneous involvement.

7 Although systemic steroids are often used, the value of such treatment is unproven in erythema multiforme, Stevens–Johnson syndrome, toxic epidermal necrolysis, chronic urticaria and cutaneous T-cell lymphoma.

Pharmacological considerations

Corticosteroids are anti-inflammatory, immunosuppressive, antiproliferative and vasoconstrictive.

Prednisone and prednisolone

Like cortisone and hydrocortisone, prednisone and prednisolone differ chemically only in the presence of a hydroxy group instead of a keto group at C11. The biological properties are similar, but prednisone has to be metabolically transformed in the liver to the 11β-hydroxy derivative to acquire biological potency, and hence prednisone should not be given to patients with liver disease. Both drugs possess four times the glucocorticoid potency and relatively less mineralocorticoid (salt-retaining) activity than hydrocortisone and cortisone.

Route of administration

Intramuscular

The intramuscular route, especially for triamcinolone, is popular in the USA for systemic steroid administration for short-term (less than 4 weeks) treatment. Triamcinolone does not differ significantly from prednisolone in its actions on a short-term basis, although in the long term it possesses greater mineralocorticoid activity. In the longer term, intramuscular steroids, especially in depot formulation, can cause marked HPA suppression and severe local atrophic changes, although the latter partially remit after a year or more. In the event of untoward steroid-induced complications, the drugs cannot be withdrawn promptly.

Intravenous

The intravenous route is useful in emergency treatment of acute anaphylaxis and in the pre- and postoperative cover of patients who have previously been receiving systemic steroid treatment for 4 weeks or more. A suitable regimen is 25 mg hydrocortisone preoperatively at the time of induction of anaesthesia, 100 mg during the operation and 100 mg on the first postoperative day—all doses being intravenous.

Thereafter the patient can be maintained on oral therapy as required. In fact, hypotensive crises attributable to adrenal insufficiency are extremely rare in patients withdrawn from glucocorticoid therapy and subsequently undergoing surgery without supplemental corticosteroid cover.

Pulsed steroid therapy

This is usually administered as doses of 1 g of methylprednisolone given intravenously over several hours using an intravenous line. The dose can be repeated daily for up to 5 days. It may be indicated in patients with severe bullous dermatoses, especially pemphigus vulgaris. It is a potentially hazardous procedure, and thromboembolism,

cardiac arrest and steroid psychosis are occasional complications [7].

Oral steroids

Route of administration and dosage. Oral steroids may be taken in a single daily dose or using an alternate-day regimen.

Single daily dose. Short-term systemic steroid therapy is best given as a single daily dose. Prednisone and prednisolone have minimal mineralocorticoid activity and have a sufficiently prolonged action to ensure the sustained effectiveness of a single daily dose. The single dose should be given first thing in the morning. This is because the maximum rate of adrenocortical cortisol secretion occurs early in the morning and therefore less pituitary–adrenal suppression occurs at this time, while therapeutic efficacy is maintained [8].

Alternate-day dosage. Prolonged therapy may be instituted using an alternate-day regimen (twice the daily dose on alternate days with no steroid treatment on the other days) [9]. Conversion from a daily to an alternate-day regimen should be carried out gradually rather than abruptly (e.g. by progressive diminution of the dose on even-numbered days while building up the dose on odd-numbered days). In order to prevent alternate-day relapses, it may be necessary to maintain a small dose on the even-numbered day. Institution of an alternate-day systemic steroid regimen reduces but does not prevent steroid toxicity. Posterior subcapsular cataracts and osteoporosis may remain problems [10,11]. Alternate-day systemic steroid therapy is not always as effective as daily treatment when given in equivalent dosage.

Systemic steroid toxicity

A comprehensive account of the range of unwanted side effects consequent upon systemic steroid therapy is beyond the scope of this text, and is addressed in Chapter 73 [12–15]. Betamethasone and deflazacort may be used in emergencies in patients with adverse immunoglobulin E (IgE)-mediated allergic reactions to hydrocortisone and methylprednisolone [16].

The approximate physiological daily cortisol secretion by the adrenal cortex is 20 mg/day for an average adult (prednisone equivalent 5 mg/day). Short courses of prednisolone (e.g. up to 30 mg/day for less than 2 weeks), although suppressing pituitary–adrenal function, do not require tapering because recovery is rapid. However, for patients with a longer history of oral steroid treatment, gradual reduction of dosage prior to discontinuation is important, because abrupt reduction may lead to the 'steroid-withdrawal' syndrome, which resembles the clinical features of adrenocortical insufficiency. Random plasma-cortisol determination may be within normal limits and stimulation tests of pituitary and adrenal function may also be normal [17].

One of the major problems with prolonged systemic corticosteroid therapy is osteoporosis. Patients receiving the equivalent of prednisolone 7.5 mg/day or more for over 3 months should receive prophylactic therapy to prevent bone resorption, such as calcium, bisphosphonates (alendronate, etidronate or risedronate), calcitriol or gonadal steroids (hormone replacement therapy in women, testosterone in men) [18,19].

Tests of pituitary–adrenal function

Baseline plasma-cortisol levels and study of diurnal variation of plasma cortisol are crude estimates of HPA integrity. The adrenocorticotrophic hormone (ACTH) stimulation test measures adrenal but not hypothalamo-pituitary integrity. The metyrapone test is based upon inhibition of an enzyme involved in synthesis of a cortisol precursor (2-deoxycortisol) resulting in reduction in cortisol levels and a consequent increase in ACTH. The cortisol precursors are measured in the urine and the resultant values give an indication of HPA integrity. Stress tests including insulin-induced hypoglycaemia measure the integrity of the whole HPA system, and are best carried out with the assistance of a specialized unit.

Systemic corticosteroids and pregnancy

There is little concrete evidence that systemic corticosteroids are harmful in pregnancy. Although the literature contains sporadic reports of stillbirth, spontaneous abortion and cleft palate associated with systemic corticosteroids [20], a recent review concluded that they are not teratogenic. Very little corticosteroid ingested by a mother enters her breast milk [21].

Systemic corticosteroids and cataracts

Posterior subcapsular cataracts are a recognized complication of systemic corticosteroid therapy. Screening by slit-lamp examination for patients in whom prolonged treatment with systemic corticosteroids is contemplated may help to obviate medicolegal consequences [10].

ACTH and tetracosactide

Although these agents are not corticosteroids, they provoke increased secretion of endogenous adrenal corticoids. There is little or no evidence to support the use of ACTH or tetracosactide (tetracosactrin) in place of systemic steroids. Their anti-inflammatory actions depend entirely upon increased hydrocortisone production by the adrenal

cortex. They also suffer from the disadvantage that they stimulate adrenal androgen as well as hydrocortisone production, and therefore cause more salt and water retention than prednisolone [22]. Maximum response of adult adrenals is no more than 100 mg/day cortisol. ACTH and tetracosactide have to be given by injection and can cause severe anaphylactic reactions. There is no sound evidence for the often asserted view that these drugs are associated with less growth retardation in children than with oral corticosteroids. The only arguable advantage of ACTH or tetracosactide therapy is a reduced likelihood of pituitary–adrenal suppression, and this view has been challenged [22]. Certainly, overall, and dose for dose, manifestations of steroid toxicity are at least as frequent as in oral corticosteroid treatment.

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Sex hormones and related compounds

Androgens

Testosterone is the most potent androgen and is currently only used for replacement therapy. Although many derivatives of testosterone have been developed with a pronounced anabolic action (the 'anabolic steroids'), they nevertheless retain significant and often troublesome virilizing activity.

Anabolic steroids

Danazol (100–600 mg/day). Danazol is a synthetic steroid derived from ethisterone. It has a high affinity for androgen receptors, and although itself a weak androgen, it has marked antiandrogenic activity. It also inhibits gonadal steroid production and reduces secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) by the pituitary. It increases the hepatic synthesis of a number of proteins including complement C1-esterase inhibitor and antitrypsin [1,2], and is of great value in hereditary angio-oedema because of C1-esterase inhibitor deficiency [3]. It causes enhanced production by the liver of functional C1-esterase inhibitor, but its beneficial effect is probably a result of more complex actions [4]. It can also be used to treat more severely affected patients with cholinergic urticaria who are unresponsive to antihistamines [5], probably because of its ability to enhance hepatic synthesis of antitrypsin, and can be used to inhibit ovulation in autoimmune progesterone dermatitis. Apart from its troublesome virilizing actions, it may cause hepatotoxicity; liver function tests should be carried out before and at monthly intervals during treatment.

Stanozolol (2.5–10 mg/day). Stanozolol is also a potent anabolic steroid with mild virilizing activity. It is just as effective as danazol in hereditary angio-oedema and with similar side effects, but considerably cheaper. Additionally, it has marked fibrinolytic properties, and has been advocated in the management of lipodermatosclerosis [6]. Its side effects are similar to those of danazol.

Anti-androgens [7–9]

Pregnancy must be avoided during therapy with anti-androgens because of the possible risk of abnormal development of a male fetus.

Cyproterone acetate. Cyproterone is a potent anti-androgen that competes with androgens at receptor sites and inhibits gonadotrophin secretion. In low doses (2 mg/day), usually in combination with ethinylestradiol in a reverse sequential regimen, it can be used for treatment of acne in females. It can also be used to treat hirsutism and other

signs of virilization in females (at 12.5–50 mg/day in a reverse sequential regimen). Liver toxicity is an occasional problem and the drug is contraindicated in pregnancy.

Spironolactone [10]. Spironolactone blocks androgen receptors, but at low dosage it is less effective than other anti-androgens; high dosage (200 mg/day) is very effective at the cost of several adverse effects (particularly dysfunctional uterine bleeding). The concomitant use of a combined oral contraceptive may prevent these.

Flutamide. This also blocks androgen receptors, and at 250–500 mg/day for 6 months may be effective at treating hirsutism. Dry skin is very frequent, and hepatotoxicity is possible with high dosage.

Finasteride. Finasteride, a 5α-reductase type 2 inhibitor that blocks conversion of testosterone to dihydrotestosterone in the skin, is the least effective anti-androgen, but a dosage of 5 mg/day may decrease hirsutism without adverse effects. At a dosage of 1 mg/day, the drug produced clinical improvement in up to 66% of men with androgenetic alopecia treated for 2 years [11,12].

Oestrogens

Oestrogens prevent skin ageing [13], and may be useful in the management of autoimmune progesterone dermatitis [14].

Ethinylestradiol (10–35 μg/day). Ethinylestradiol (ethinyl oestradiol) is valuable replacement therapy in the treatment of postmenopausal symptoms including hot flushes, vaginitis and vaginal atrophy [15]. Plasma levels of FSH and LH, which are elevated in postmenopausal females, are useful guides to dosage. Ethinylestradiol should be avoided in patients with a history of breast cancer, liver or thromboembolic disease.

Anti-oestrogens

Tamoxifen (20 mg/day). Tamoxifen is an anti-oestrogenic drug that acts at receptor sites to block oestrogen binding. It therefore inhibits ovulation in fertile women. It may be useful in the treatment of progesterone-induced dermatitis or erythema multiforme [16]. Side effects are those associated with the menopause, together with abnormal vaginal bleeding. Bone density may be affected in the course of long-term treatment.

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Antihistamines

Historical note

The first effective and safe antihistamine, neoantergan, was based upon a molecule '2786 RP' discovered by Parisian investigators, Bovet and Walthert, in 1944 [1]. This antihistamine, known as anthisan or mepyramine maleate, was one of a series of diamethylamino-*N*-propyl phenothiazine compounds. Soon afterwards in the USA, diphenhydramine (Benadryl®) was launched and found to be effective by O'Leary and Faber [2] in chronic urticaria. In the UK, definition of the actions and potential role of the first-generation antihistamines was pioneered by Bain *et al.* [3,4] in urticaria.

It had long been recognized that not all of the actions of histamine, notably that of stimulation of gastric acid secretion, could be blocked by antihistamines. This puzzle was unravelled by Black *et al.* [5] who described a subset of histamine receptors designated H_2, which led to the development of the first clinically useful H_2 antihistamine, cimetidine, subsequently to be found effective in the management of chronic urticaria [6]. The later discovery of a third subset of histamine autoreceptors, H_3 [7], has as yet not generated any clinically useful applications in dermatology. However, the new class of H_1 antihistamines, in which troublesome sedative side effects of the classical

Table 72.1 Histamine receptors.

Receptors	Main action relevant to skin	Expression in skin	Antagonist
H_1	Vasodilatation Vasopermeability Itch	Yes	Chlorphenamine Terfenadine
H_2	Vasodilatation Vasopermeability	Yes	Cimetidine Ranitidine
H_3	Regulation of histamine Neurotransmitter release	?	Thioperamide*
H_{ic}	Intracellular messenger for promotion of cell growth	?	DPPE*

DPPE, *N*,*N*-diethyl-2-[4-(phenyl methyl) phenoxy] ethanamine HCl.
* Experimental antagonists.

antihistamines are minimalized by substitutions on the basic imidazole ring, thus preventing the drug from crossing the blood–brain barrier, has been the biggest recent milestone in the long history of antihistamines [8–12]. In 2002, 17 different oral H_1 antihistamines were available in the UK for treating allergic disorders [13].

Histamine receptors

Four classes of histamine receptor are presently recognized (Table 72.1). The discovery of H_2 receptors [5], alluded to above, was followed by demonstration of expression of H_1 and H_2 receptors in human skin. Histamine-induced vasodilatation and wealing are mediated by both classes of receptor, whereas itching is only served by H_1 receptors [14–16]. H_3 receptors are responsible for the ability of histamine in some tissues to regulate, by inhibitory feedback, its own biosynthesis and release. H_3 receptors, which also regulate transmitter release at autonomic nerve terminals, have not been convincingly shown to be represented in skin. On the other hand, the recently described intracellular (H_{ic}) histamine receptors that are responsible for the ability of histamine to promote cell and tissue growth (e.g. in embryonic tissue and wound healing) [17] are probably expressed in skin, although this has not yet been specifically demonstrated.

Other actions of antihistamines

Most H_1 antihistamines also express anticholinergic activity, resulting in the well-known side effects of the earlier 'classic' antihistamines, which include dryness of the mouth, blurring of vision and constipation. Drowsiness is also a feature of many early antihistamines. Available evidence suggests that histamine plays a part in the maintenance of the waking state, which may go some way towards explaining the sedative actions of some H_1 antihistamines. Many H_1 antagonists also prevent release of mediators from activated mast cells, although in most cases only in a higher concentration than that achieved clinically. This response does not involve H_1 receptors [18]. Two H_1 antagonists, ketotifen and cetirizine, deserve mention as they have been claimed to be potent inhibitors of release of mast cell products [19–21]. However, no evidence of reduced urinary excretion of histamine or its metabolites was detected in patients with mastocytosis treated by the H_1 antihistamine, ketotifen [20]. Cetirizine has also been claimed to possess selective inhibitory activity against eosinophil-rich dermatoses [21,22] but the clinical relevance of this action is unclear.

Table 72.2 Pharmacokinetic and pharmacodynamic activity of representative first- and second-generation antihistamines [8,23].

H_1 antagonist	T_{max} (h)	Half-life (h)	Weal suppression duration (h)
Chlorphenamine	2.8	27.9	24
Hydroxyzine	2.1	20.0	24
Diphenhydramine	1.7	9.2	12–24
Terfenadine	1.0	17	12–24
Astemizole	3.0	9.5 days	Variable
Loratadine	1.0	7.8–11.0	12–24
Cetirizine	0.9	7.4	24

T_{max}, time of maximum plasma concentration.

H_1 antihistamines (Table 72.2 [8,23])

These are conveniently classified as first- and second-generation H_1 antihistamines. The first-generation drugs, although potent, are accompanied by troublesome atropine-like side effects, and also cause drowsiness [24], which may be useful or disadvantageous depending upon the clinical context.

First-generation H_1 antihistamines

These are exemplified by chlorphenamine (an alkylamine), diphenhydramine (an aminoalkyl ether) and hydroxyzine (a piperazine). Plasma half-lives of these drugs are variable (chlorphenamine approximately 24 h; hydroxyzine

20 h; diphenhydramine 9 h), although peak plasma concentrations are reached in approximately 2 h. Protein binding is almost total, and metabolism occurs via the hepatic microsomal cytochrome P-450 system. Thus, the half-life of certain H_1 antihistamines may be prolonged in patients receiving microsomal oxygenase inhibitors such as ketoconazole, erythromycin, doxepin or cimetidine.

The principal actions of H_1 antihistamines are on vasodilatation and increased vascular permeability, thus reducing the redness, weal and axon reflex flare reactions in acute urticaria, and suppressing the associated itching. The clinical effects of these H_1 antihistamines usually persist longer than measurable plasma levels would suggest, because of persistence of tissue levels or because of active metabolites. Once-daily administration is therefore adequate. In urticaria, first-generation H_1 antagonists reduce the size, duration and frequency of weals and greatly alleviate the itching. Although more often a nuisance, the sedative effects of first-generation H_1 antihistamines have been claimed to be highly beneficial in suppressing itching in some patients with atopic eczema [25]. Their effect is enhanced by other sedative drugs, especially alcohol. Other side effects of these antihistamines include tachycardia, with prolongation of the Q–T interval on the electrocardiogram and other arrythmias, as well as psychological disturbances.

Second-generation H_1 antihistamines [8]

These are exemplified by terfenadine, astemizole, loratadine and cetirizine, none of which produces sedation significantly greater than that caused by an otherwise identical placebo, provided recommended dosage is used. The absorption and metabolism of second-generation H_1 antihistamines resembles that of the first generation described above. The plasma half-lives of terfenadine, astemizole and cetirizine are listed in Table 72.2. These drugs in recommended regimens do not significantly cross the blood–brain barrier, thus accounting for their minimally sedating characteristics. Terfenadine is almost completely devoid of histamine H_2 or cholinergic receptor blockade and is effective in the treatment of chronic urticaria [26]. Agents including grapefruit juice and certain drugs (ketoconazole, itraconazole, erythromycin, other macrolide antibiotics, cimetidine and doxepin), which inhibit hepatic metabolism via the cytochrome P-450 system, should not be given concurrently with terfenadine, because they may promote adverse effects including cardiac arrhythmias, Q–T interval prolongation and torsades de pointes (ventricular tachycardia) [27–29]. Terfenadine is also contraindicated in patients with liver or heart disease. Terfenadine may cause rashes, which occasionally (and paradoxically) include urticaria [30,31]. The UK Committee on Safety of Medicines withdrew terfenadine from over-the-counter sale, as did the US Food and Drug Administration, because of the cardiac complications. Recently, fexofenadine, the major active metabolite of terfenadine, has been introduced as an alternative to terfenadine [32].

Astemizole also undergoes first-pass metabolism via the liver cytochrome P-450 system but its half-life together with its active metabolite dimethylastemizole is prolonged at 9.5 days [8]. It binds with greater avidity to H_1-receptor sites than any other H_1 antihistamine, evidence of histamine weal suppression being evident 4 weeks or more after discontinuation [33], but it has not been shown to be teratogenic. Like terfenadine, it must not be co-administered with macrolide antibiotics, imidazole antifungals or doxepin, because of the risk of cardiac arrhythmia [34]. Patients with a pre-existing Q–T interval prolongation are especially at risk. Other side effects of astemizole include increase in appetite and excessive weight gain [8].

Loratadine is a potent minimal-sedation antihistamine that is also substantially free of anticholinergic side effects. Loratadine is not metabolized through the liver cytochrome P-450 enzyme system to any great extent and is therefore believed free of cardiac arrhythmic complications. It inhibits evoked release of leukotrienes from human lung *in vitro* but is less active in suppressing histamine release [35]. How relevant these 'antiallergic' properties are to its therapeutic action is unclear. Desloratadine has now replaced loratadine in the UK.

Like loratadine, cetirizine, which is an active metabolite of hydroxyzine, is only minimally metabolized via the liver and therefore can be administered safely with macrolide antibiotics, imidazole antifungals and doxepin. In recommended dosage it has minimal sedative and anticholinergic actions. Cetirizine is claimed to be effective in diseases involving heavy eosinophil infiltration [21,22]. It has been proposed, on this basis, that cetirizine is especially valuable in patients with the common physical urticaria, delayed pressure urticaria [36], although adequate confirmation of this claim is lacking. Levocetirizine is also available.

H_1-antihistamine therapy in childhood

The second-generation low-sedation antihistamines are probably safer in children than the older 'classic' antihistamines; liquid formulations of astemizole, cetirizine and loratadine are available in the UK. Overdose of the first-generation antihistamines may cause severe toxicity including hyperpyrexia and convulsions in children.

H_1-antihistamine therapy in pregnancy

No antihistamines administered systemically should be deemed safe in the first trimester of pregnancy. However, of the available H_1 antihistamines, chlorphenamine [37]

and tripelennamine [38] have shown little or no evidence of teratogenicity experimentally and are probably the least risky to use.

Development of tolerance during H_1-antihistamine therapy

Although tolerance of the first-generation H_1 antihistamines was reported soon after their introduction into medical practice [39], little or no information is available on the molecular basis of this phenomenon [40]. Suppression of wealing because of mast cell activation and histamine progressively dwindled in response to single doses of 75 mg hydroxyzine given daily for 3 weeks; no tolerance was demonstrated in response to chlorphenamine 16 mg/day in the same study [41]. Interestingly, this study showed that hydroxyzine, but not chlorphenamine, caused tolerance not only to itself but to several other first-generation antihistamines.

H_2 antihistamines

Cimetidine and ranitidine

The presence of H_2 receptors expressed on human skin blood vessels [14,15] prompted exploration of the value of H_2 antihistamines, co-administered with H_1 antihistamines, in the treatment of chronic urticaria. The object was to achieve an H_1-antihistamine-sparing effect, thus mitigating unwanted first-generation H_1 antihistamine side effects including drowsiness and atropine-like side effects. This strategy proved modestly successful [6,12,42–44]. However, the subsequent availability of the second-generation low-sedation antihistamines has undermined the need for an H_1-antihistamine-sparing regimen. Because ranitidine, unlike cimetidine, is not metabolized via the liver cytochrome P-450 system, it should probably be used in preference to cimetidine if H_2 antihistamine therapy is instituted.

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Other antiallergic drugs

Sodium cromoglycate. Although ineffective in suppressing mast cell activation in the skin [1], it inhibits release of histamine and other mast cell-derived mediators from mast cells of lung, conjunctiva, nose and gastrointestinal tracts. It therefore has no proven role in the skin; however, it does ameliorate the diarrhoea associated with mastocytosis [2].

Leukotriene receptor antagonists. Montelukast and zafirlukast may be useful in chronic urticaria [3].

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Systemic non-steroidal anti-inflammatory therapy

Non-steroidal anti-inflammatory drugs (NSAIDs) are defined as substituted phenolic or benzene-ring compounds that owe their pharmacological actions mainly to inhibition of the enzyme cyclo-oxygenase (COX) (prostaglandin synthetase). This enzyme complex was shown by Vane [1] in 1971 to transform arachidonic acid into prostaglandins. However, NSAIDs undoubtedly influence other pro-inflammatory molecular pathways. NSAIDs have been advocated in a large number of common and uncommon dermatoses, including acne, psoriasis, sunburn, erythema nodosum, cryoglobulinaemia, Sweet's syndrome and systemic mastocytosis, as well as in urticarial, livedoid and nodular vasculitis [2].

Transformation of arachidonic acid and the mode of action of NSAIDs

There are two forms of COX: a constitutive enzyme (COX-1) and an induced enzyme (COX-2) (Fig. 72.1). NSAIDs act mainly by inhibition of COX-2 [3]. In contrast, inhibition of COX-1 by NSAIDs probably accounts for some of their unwanted side effects including gastric ulceration.

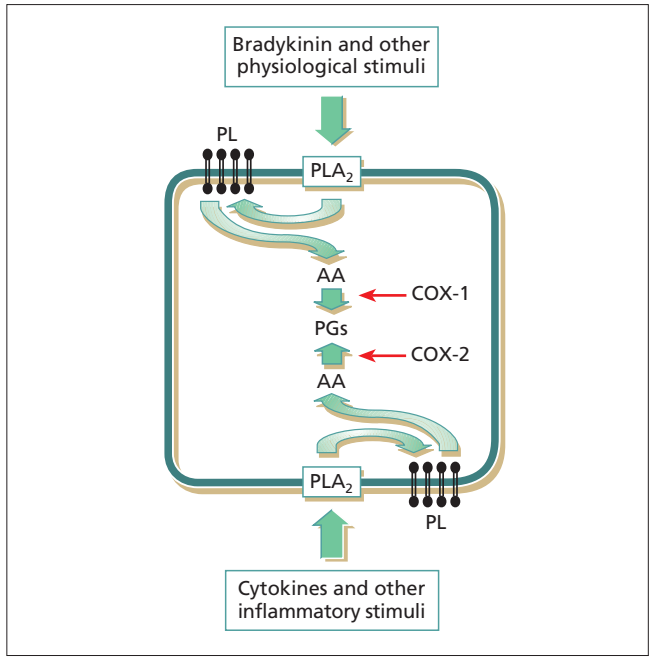

Fig. 72.1 Transformation of arachidonic acid (AA) to prostaglandins (PGs) by cyclo-oxygenases (COX) 1 and 2. PLA_2, phospholipase (PL) A_2.

Arachidonic acid is also transformed via the lipoxygenase pathways (5-lipoxygenase; 12-lipoxygenase) to form a group of strongly pro-inflammatory hydroxy fatty acids of which the best known is leukotriene B_4 (LTB_4) (Fig. 72.2) [4]. Because of the proposed role of the leukotrienes and other hydroxy fatty acid products of arachidonic acid in the pathogenesis of psoriasis [5] and other inflammatory dermatoses [6], several generally unsuccessful attempts have been made to develop selective lipoxygenase-inhibiting NSAIDs for clinical dermatological use [7]. These compounds have generally proved ineffective, toxic or both.

Acetylsalicylic acid (aspirin) is the archetypal NSAID and has been shown to owe its anti-inflammatory action to inhibition of COX-2 [1]. Its role in the management of skin diseases is limited. Administration of aspirin has been shown to suppress ultraviolet erythema in humans [8]. Furthermore, Roberts *et al.* [9] have proposed that aspirin be co-administered with H_1 and H_2 antihistamines in the management of the diarrhoea of systemic mastocytosis, which is believed to be mainly caused by overproduction of prostaglandin D_2 by the increased population of mast cells in the involved tissues. Although originally proposed to be antipruritic, aspirin administration probably does not allay the itching of atopic eczema [10].

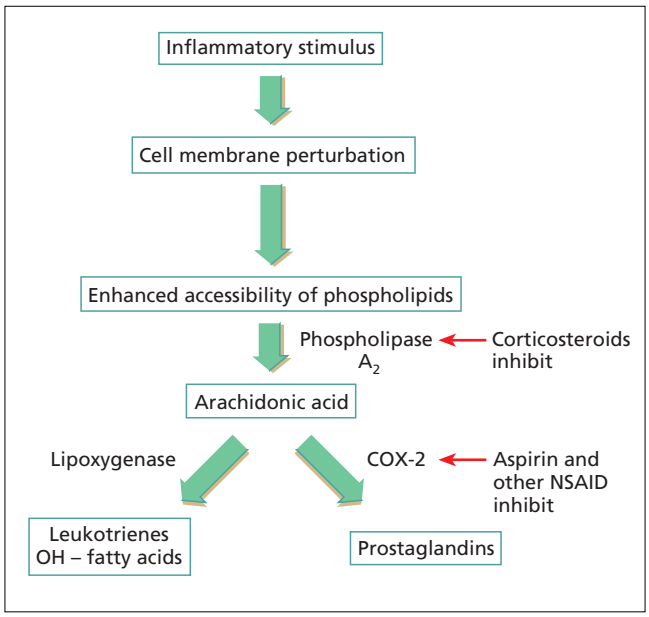

Fig. 72.2 Generation of eicosanoids from cell membrane lipids in the inflammatory response. Arachidonic acid, released from cell membrane phospholipid by the action of phospholipase A_2, is further transformed by cyclo-oxygenase 2 (COX-2) to prostaglandin, and by lipoxygenase to leukotrienes and related fatty acids. NSAID, non-steroidal anti-inflammatory drugs.

The early phase of UVB-induced erythema is caused, at least in part, by release of vasoactive prostaglandins [11]. Oral administration of indometacin (indomethacin) has been demonstrated to reduce the erythema and concurrently to suppress the increased tissue levels of COX products in UVB-irradiated skin [12]. Proposed clinical indications for oral indometacin include cutaneous vasculitis [13] and erythema nodosum [14], although these indications have not yet been confirmed by placebo-controlled double-blind trials. The value of oral indometacin in the management of psoriatic arthritis is well established; reports that oral indometacin may exacerbate the skin lesions of psoriasis have not been substantiated (see Chapter 73).

Adverse reactions to systemic NSAIDs, including urticaria and angio-oedema, are unfortunately commonplace (see Chapter 73) [15]. Reactions occur most frequently in response to piroxicam, sulindac, meclofenamate, tolmetin and phenylbutazone [16]. The best known and probably the most severe include Stevens–Johnson syndrome and toxic epidermal necrolysis. Photosensitivity is very common, especially with piroxicam, but the underlying mechanisms, which involve phototoxicity in many instances, are unknown [17].

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Cytokines

Cytokines are small polypeptides, molecular mass less than 60 kDa, which act as intercellular messengers; they have a pivotal role in cutaneous inflammation. They can be either pro-inflammatory or anti-inflammatory; however, a single cytokine may have several different functions and may act on many cellular targets. DNA technology has facilitated the large-scale manufacture of recombinant human cytokines, several of which have been used to treat skin disease.

Interferons

Interferons are naturally occurring endogenous glycoproteins, which are now available for therapeutic use through recombinant DNA technology. This group of compounds exhibits antiviral, cytostatic and immunomodulatory properties and has therefore found application in both malignant and inflammatory dermatoses. Three types of interferon are available: interferon-α (IFN-α), IFN-β and IFN-γ. Unfortunately, side effects are common, including influenza-like symptoms with fever, hepatotoxicity and leukopenia; this has limited clinical usage.

Kaposi's sarcoma

Because of its antiviral, antiangiogenic and tumoristatic properties, interferon ought to be an ideal treatment for acquired immune deficiency syndrome (AIDS)-related Kaposi's sarcoma, which is probably caused by human herpesvirus 8. There have been numerous reports of remissions induced by IFN-α, invariably at the cost of troublesome side effects. In earlier studies [1], high doses did induce remissions, especially in patients without associated opportunistic infections [2]. Subsequent studies suggested that better results were obtained in the presence of sustained CD4 T-lymphocyte counts [3]. There is some evidence of synergism between IFN-α and zidovudine [4,5]. Patients who respond to treatment with IFN-α appear to have fewer opportunistic infections [6]. Co-administration of granulocyte–macrophage colony-stimulating factor (GM-CSF) with IFN-α has been shown to limit the bone marrow-suppressant side effects of the latter [7]. Both IFN-α and IFN-β inhibit neoangiogenesis—a further explanation for their effectiveness in Kaposi's sarcoma [8]. IFN-γ is ineffective in Kaposi's sarcoma.

Melanoma

There has been considerable interest in the use of IFN-α to treat metastatic melanoma. Approximately 5% of treated patients may achieve total remission. The optimal drug regimens of IFN-α are not known but up to 20% of patients may respond [9]. This response rate can be significantly increased by combination therapy with cisplatin and other antimetabolites [10]. Despite the mixed results, IFN-α is approved in the USA and Europe for high-risk melanoma patients [11]. IFN-α has been administered subsequent to melanoma lysate vaccine, leading to a response rate higher than that produced by either IFN-α or vaccine alone [12].

Cutaneous T-cell lymphoma

Cutaneous T-cell lymphoma (CTCL) is a Th2 cytokine disease in that peripheral blood mononuclear cells secrete increased amounts of IL-4 and IL-5. IFN-α, which suppresses IL-4 and IL-5 production, is effective in up to 50% of patients—particularly those with Sézary syndrome [13]. Remission rates as high as 70% have been reported when subcutaneously administered IFN-α-2a is used in combination with psoralen with UVA treatment (PUVA) or extracorporeal photopheresis [14].

Atopic dermatitis

Recombinant IFN-γ has been administered on a double-blind placebo-controlled basis to patients with atopic dermatitis with demonstrably superior effect compared with placebo control [15]. The rationale for IFN-γ treatment is based upon the findings of high-serum IgE levels and predominant Th2 cells producing IL-4 and IL-5, coupled with low production of IFN-γ by Th1 cells in atopic subjects. Administration of IFN-γ, according to this scheme, results in isotype switching away from IgE production, because of inhibition of growth of IL-4- and IL-5-producing Th2 cells [16]. Approximately one-half of the IFN-γ treated patients, but only one-quarter of the placebo-treated patients, experienced significant clinical improvement [15]. There was no reduction in serum IgE in the IFN-γ-treated group but the blood eosinophil count fell in these patients. Side effects including leukopenia were frequent in the actively treated patients. Long-term studies have demonstrated efficacy and safety for up to 2 years if IFN-γ is delivered subcutaneously at 50 μg/m^2 three times weekly. The most commonly reported side effects are influenza-like symptoms [17,18].

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Interleukins

Interleukins are an expanding group of endogenous soluble mediators in use for therapy of inflammatory dermatoses, malignancy and infection.

Melanoma

IL-2 is the most widely used of the interleukins for therapy of melanoma in a variety of regimens ranging from IL-2 monotherapy to combinations with lymphokine-activated killer cells or polychemotherapy. Following a trial that demonstrated that high-dose IL-2 could induce complete remission in 6% of patients with metastatic melanoma, this approach has been approved for the indication in the USA [1]. Combining IL-2 with chemotherapy or IFN-α does not appear to improve efficacy [2].

GM-CSF as adjuvant therapy appears to prolong overall and disease-free survival in patients with stage III or IV melanoma [3].

Psoriasis

Psoriasis is a Th1-mediated disease—with a predominance of Th1 cytokines in plaques. Systemic administration of Th2 cytokines, such as IL-4, IL-10 or IL-11, is a logical cytokine-modulating approach to restore the cytokine balance in psoriasis. Recombinant human IL-4 administered five times weekly over 6 weeks in an open study produced a highly significant reduction in psoriasis severity [4]. IL-10 inhibits antigen presentation and production of pro-inflammatory cytokines such as TNF-α. Several studies [5–7] have confirmed the effectiveness of subcutaneously administered IL-10 (8 μg/kg/day or 20 μg/kg three times weekly). An open study of recombinant IL-11 (approved for treatment of chemotherapy-induced thrombocytopenia) indicated significant reduction in psoriasis severity [8].

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Cytokine blocking agents

DNA technology has allowed large-scale production of neutralizing or inhibitory antibodies to pro-inflammatory cytokines. This approach to the therapy of inflammatory disease has been pioneered in the fields of rheumatoid arthritis and Crohn's disease. In dermatology, the anticytokine agents have been most extensively trialled in psoriasis with very little controlled trial evidence from other dermatoses.

TNF-α, as a key pro-inflammatory cytokine, is perhaps the most attractive target for anticytokine approaches for the treatment of inflammatory skin disease. The two agents used currently to neutralize activity of TNF-α are infliximab and etanercept.

Infliximab is a chimeric (human–mouse) monoclonal antibody against TNF-α composed of a human constant and a murine variable region of the IgG antibody [1]. Infliximab was developed initially for treatment of rheumatoid arthritis and Crohn's disease. It is now licensed, with different regimens, for treatment of both conditions. In rheumatoid arthritis the preferred regimen is combination with methotrexate, infliximab being given as 3–5 mg/kg infusions at baseline and at weeks 2 and 6 followed by regular infusions every 8 weeks, irrespective of disease activity. For Crohn's disease, a single 5 mg/kg infusion is given and repeated at 2 and 6 weeks if fistulae are present.

Following anecdotal reports [2] of effectiveness of infliximab for concurrent psoriasis in patients receiving it for Crohn's disease, a double-blind placebo-controlled trial [3] was performed in severe plaque psoriasis. Infliximab infusions of 5 or 10 mg/kg were compared with placebo delivered as monotherapy at baseline and at weeks 2 and 6. Eighty-two per cent and 91% of patients treated with 5 and 10 mg/kg infusions, respectively, achieved a highly significant reduction in clinical severity of psoriasis. Subsequent studies have borne out this remarkable and rapid response [4]. Combination with methotrexate [5] is also effective. It is probable that if licensed for psoriasis, the preferred regimen for use will be 5 mg/kg infusions according to the above loading

dose, with infusions repeated at 8-week intervals. Side effects include risk of infections, reactivation of pulmonary tuberculosis [6], infusion reactions and development of antibodies against double-stranded DNA [3].

Case reports attest to the efficacy of infliximab in Behçet's disease [7], pyoderma gangrenosum [8], graft-versus-host disease [9], subcorneal pustular dermatosis [10], toxic epidermal necrolysis [11] and hidradenitis suppurativa [12].

Etanercept is a recombinant fusion protein comprising two extracellular ligand-binding proteins of the p75 TNF receptor linked to the Fc portion of human IgG [13]. The drug is administered subcutaneously twice weekly. In the USA, etanercept is approved for the treatment of rheumatoid arthritis and psoriatic arthritis; in the UK for rheumatoid arthritis only. Most trials of etanercept have been for the treatment of psoriasis—some as a secondary end point in studies on psoriatic arthritis [14]. Etanercept significantly reduces clinical severity of psoriasis in approximately 26% of patients over the course of 12 weeks [14]. Side effects include respiratory tract infections, headaches, rhinitis and, rarely, demyelination [15]. Etanercept is also reported anecdotally to show some efficacy in the treatment of scleroderma [16] and cicatricial pemphigoid [17].

There is little doubt that cytokine blockers will become commonplace in the treatment of psoriasis and perhaps other inflammatory skin diseases. Their utility will be improved by the development of oral agents that block TNF-α indirectly by approaches that include inhibition of mitogen-activated protein (MAP) kinases.

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Receptor targeted therapies

Monoclonal antibodies can either be humanized, consisting of a human Fc fragment and a mixed human–mouse Fab (antigen binding) portion; or chimeric, in which the Fc fragment is human and the Fab portion is murine. Fusion proteins link a human or murine Fab domain to a human molecule, usually an immunoglobulin. These biotechnological approaches have been intensively trialled for the treatment of psoriasis but to date only one compound has been approved for use in treatment of skin disease. These agents are delivered parentally by intravenous, intramuscular or subcutaneous injection; overall they are well tolerated with low immunogenicity.

Monoclonal antibodies directed at the CD4 molecule on T cells have been used for the therapy of psoriasis. The first in 1991—a murine IgG1 antibody—produced significant improvement in three patients with severe psoriasis [1]. The only formal placebo-controlled trial [2] was for the use of a humanized anti-CD4 IgG4 monoclonal antibody in severe psoriasis. Patients only responded after a second course of treatment, with a reduction of 66% in clinical severity at 3 months.

Most new biological therapies under development for treatment of psoriasis are targeted at the co-stimulatory or accessory molecule ligand pairs binding T cells to antigen-presenting cells. Alefacept, a recombinant human LFA-3–IgG1 fusion protein, blocks the binding between CD2 on T cells and LFA-3 on antigen-presenting cells thereby inhibiting T-cell activation. Furthermore, this approach selectively targets the disease-causing $CD45RO^+$ memory-effector T cells and produces apoptosis of circulating T cells. Once weekly intravenous or intramuscular administration over a 12-week cycle produces significant clinical improvement in approximately one-third of patients, some of whom achieve prolonged remission [3]. Alefacept appears safe in the short to medium term, although there are significant decreases in circulating peripheral blood T

cells [4]. In 2003, alefacept became the first biological agent to be licensed for the treatment of severe psoriasis. At the time of writing this approval is limited to the USA.

Other agents targeting co-stimulatory molecules and under development for psoriasis include efalizumab, a monoclonal antibody against CD11a (LFA-1), which blocks CD11a–ICAM-1 binding and may inhibit lymphocyte binding to endothelium via the same mechanism. Efalizumab is delivered subcutaneously once weekly and produces significant clinical improvement in approximately one-quarter of patients treated over a 12-week cycle [5]. A primatized antibody to CD80 (IDEC-114) blocks binding of CD80 to CD28; intravenous administration results in modest improvement in psoriasis [6].

Cytotoxic T-lymphocyte-associated antigen 4 (CTLA4) is expressed on T cells and binds CD80 and CD86 on antigen-presenting cells. CTLA4-Ig is a chimeric protein that binds CD80 and CD86 thereby inhibiting co-stimulation. An open study of intravenous administration demonstrated efficacy in psoriasis [7].

CD25 is the high-affinity IL-2 receptor expressed on T cells. Two monoclonal antibodies against CD25—basiliximab and daclizumab—are licensed for treatment of allograft rejection. Both agents are effective in psoriasis—daclizumab as monotherapy [8] and basiliximab in combination with ciclosporin [9,10]. It appears that the anti-CD25 approach is only effective if used in patients with rapidly progressive and/or generalized pustular psoriasis rather than in stable but extensive disease. Basiliximab has also been reported effective, in a case report, in atopic dermatitis [11] but ineffective for graft-versus-host disease [12].

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Essential fatty acids

Essential fatty acids are simply defined as those that cannot be synthesized by humans. The major essential fatty acids found in humans are the ω-6 fatty acids linoleic acid and its products, γ-linolenic acid and arachidonic acid, precursors of important mediators of inflammation, the eicosanoids. Arachidonic acid is synthesized from linoleic acid in the liver. Although vertebrates cannot synthesize linoleic acid *de novo*, plants can synthesize both linoleic and γ-linolenic acids, important constituents of evening primrose oil. Skin, unlike liver, is devoid of δ-5 desaturase and cannot convert γ-linolenic acid to arachidonic acid directly. Thus, arachidonic acid found in skin is not directly dietary in origin.

Linoleic acid and γ-linoleic acid in atopic dermatitis

Current interest in essential fatty acids in atopic dermatitis originates in an observation by Hansen [1] that patients with this disorder had elevated serum levels of linoleic acid but reduced levels of its δ-6-desaturase products, γ-linoleic acid and dihomo-γ-linolenic acid. A number of reports suggested that oral replacement therapy using oil from the seed of evening primrose caused clinical improvement in the skin of patients with atopic dermatitis [2]. The evidence base from controlled trials of evening primrose oil indicated that there is no good evidence to support a useful therapeutic effect in atopic dermatitis [3].

Eicosapentaenoic acid and related fatty acids

These polyunsaturated fatty acids possess a longer chain length than linoleic acid and more double bonds, and are found in large quantities in fish oils, in which eicosapentaenoic acid (EPA) and docosahexaenoic acid predominate. Attempts have been made to modify the severity of psoriasis by long-term administration of diet supplemented by fish oil [4]. Subsequent experience [5] suggests that EPA dietary supplementation, which by itself causes only marginal improvement of psoriasis, may enhance the efficacy of co-administered conventional psoriatic therapy such as phototherapy [6]. The most frequently prescribed dietary source of fish oil is Maxepa®, a concentrated fish oil product. The daily intake is 60–75 g flavoured with fruit juice and containing 180 mg EPA and 120 mg docosahexaenoic acid per gram of oil.

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Retinoids

This class of compounds covers both the synthetic and the natural forms of vitamin A (the term vitamin A includes the preformed vitamin A alcohol, retinol; its aldehyde, retinal; and its acid, *trans*-retinoic acid, as well as the provitamin, β-carotene). Chemical manipulation of retinol has led to numerous new compounds that are less toxic than the parent molecule.

The mode of action of the retinoids has not been completely elucidated but they have profound effects on differentiation, cell growth and immune response. They are used especially in dermatology but also have a role or a potential role in cancer prevention and perhaps cancer therapy.

Effect on differentiation

It has been known for many years that vitamin A deficiency results in epithelial squamous metaplasia and that vitamin supplements reverse this effect. Retinoids have now been shown to induce differentiation in a number of cell types (e.g. mouse teratocarcinoma and human myeloid leukaemia cells), and to cause regression of bronchial metaplasia in heavy smokers [1]. Epidermis undergoes profound changes and shows hypergranulosis and hyperplasia with decreased numbers of tonofilaments and desmosomes and widening of intercellular spaces [2]. The effect on desmosomes appears to contribute to the keratolytic effect of retinoids in hyperkeratotic disorders.

Effect on carcinogenesis [2,3]

In models of carcinogenesis, induction of the enzyme ornithine decarboxylase occurs during transformation [4]. The enzyme induction is inhibited by retinoids and this inhibition has been used to test the anticarcinogenic effect of new retinoids.

Tumour growth [3]

The growth of a number of human tumour cell lines (e.g. melanoma) seems to be inhibited by retinoids but the response may be variable. Retinoids have not yet established themselves as of major importance in cancer treatment. High concentrations of retinoids cause cytotoxicity through membrane labilization, although at lower doses membrane stabilization may occur.

Receptors

There are specific retinol and retinoic acid receptors. The activity of retinoids is mediated through these in a similar manner to steroid hormones. There are at least six retinoic acid and retinoid X receptors, all of which belong to the family of steroid–thyroid–vitamin D receptors. The receptors have a more significant effect on differentiation [5] than on the inhibition of tumour growth.

Cell surface effects

Retinoids affect transformed cell surfaces and lead to loss of anchorage-independent growth, cell adhesiveness and density-dependent growth [6]. It is not clear whether these effects are exerted directly by the retinoid involvement in glycosyl transfer reactions or through changes in gene expression.

Immunostimulation

In animal models, retinoids may act as an adjuvant and stimulate antibody formation to antigens that were previously not immunogenic [7,8]. In addition, retinoids may stimulate cell-mediated cytotoxicity.

Neutrophil migration

The migration of neutrophils is reduced by retinoids, both in experimental models of inflammation [9] and in patients with acne [10]. The mode of action is unknown.

Skin flora

Retinoids do not seem to have an appreciable direct action on the skin flora.

Ageing

The effects of retinoids on the ageing process, particularly ageing skin, are complex. The emphasis is currently on topical therapy.

Isotretinoin (13-*cis*-retinoic acid)

Oral isotretinoin has been shown to be very effective in the treatment of severe recalcitrant cystic acne unresponsive to antibacterial agents and to be superior to etretinate.

Dose ranges have varied considerably from 0.1 to 2.0 mg/kg/day, but the most widely used regimen at present is 1.0 mg/kg/day as a 16-week course. This produces prolonged remission in the majority of patients (see Chapter 43). Topical isotretinoin also appears to suppress acne [11].

In a long-term study of up to 10 years (mean 9 years), post-isotretinoin, 85% clinical improvement has resulted from a 4-month course and 69% of patients were still free of acne. Twenty-three per cent required a second course, the relapse occurring within 3 years in 96% of patients [12]. The need for a second course of isotretinoin is more likely if low-dose regimens are used (0.1 and 0.5 mg/kg). The most effective dose commensurate with side effects is 1 mg/kg/day for 4 months [13]. In addition to acne, isotretinoin has been used in the treatment of Gram-negative folliculitis, rosacea and, rather less successfully, in hidradenitis suppurativa and steatocystoma multiplex.

In acne, the major therapeutic effect seems to be a profound reduction in sebaceous gland size and activity. There are reductions in bacterial flora, but it is likely that these changes are secondary to the reduction in sebum secretion. The anti-inflammatory and desquamating effects of retinoids may also have a beneficial role.

A wide range of disorders of keratinization have been found to be responsive to isotretinoin. In Europe, this group of disorders is now usually treated with acitretin.

Etretinate

This retinoid has now been superceded by acitretin, which is the hydrolysis product and active metabolite of etretinate [14]. The major disadvantage of etretinate is its binding to body fat for up to 2 years after a course has been completed, during which it is advised that female patients should not become pregnant. Etretinate is 50 times more lipophilic than acitretin [15]. The elimination half-life of etretinate is over 100 days, whereas for acitretin it is 2 days [16,17].

Acitretin

In most respects, this drug resembles the parent compound. It is less bound to fat than etretinate, and it had been hoped that the advisable time interval in which female patients should avoid pregnancy after stopping the drug might be shortened. However, it has been shown in some patients that there is reverse metabolism to etretinate (particularly in the presence of alcohol) and therefore the same restriction of 2 years is advised between the end of a course and pregnancy [18]. The efficacy of acitretin is very similar to etretinate and in general is used in slightly lower doses. Acitretin is effective in various forms of psoriasis, although in plaque psoriasis the results are often disappointing [19,20]. The efficacy can be improved by adding UVA, photochemotherapy (PUVA) or UVB phototherapy (see Chapter 35) [19].

Acitretin is effective in pustular psoriasis, both palmoplantar or generalized (von Zumbusch) [21,22], also in erythrodermic psoriasis.

In many skin conditions, reports have been confined to etretinate prior to the development of acitretin. Most clinicians would agree that the effects are similar with slightly lower doses of acitretin being required. The following disorders of keratinization are often responsive to retinoids: epidermolytic hyperkeratosis, keratoderma, X-linked ichthyosis, ichthyosis vulgaris, erythrokeratoderma variabilis, pityriasis rubra pilaris, discoid lupus erythematosus and lichen planus, Darier's disease, lamellar ichthyosis and non-bullous ichthyosiform erythroderma. Long-term treatment is required as worthwhile remissions following cessation of treatment have not been reported. Toxicity therefore may prove to be a problem in these patients.

A range of skin tumours may sometimes clear with retinoids. These include solar keratoses, keratoacanthoma, epidermodysplasia verruciformis, basal cell epithelioma and leukoplakia. However, these preparations may be of particular value in the prevention of tumours in those patients with high-risk disorders such as xeroderma pigmentosum, porokeratosis of Mibelli, familial self-healing squamous epithelioma of the skin and in those transplantation patients with extensive sunlight-damaged skin.

A number of side effects are common to all the retinoids. These appear to be dose-related and are largely cutaneous. They include cheilitis, conjunctivitis, dryness of mucous membranes and epistaxis, desquamation of hands and feet, pruritus, myalgia, arthralgia, lethargy and alopecia [23–25]. Intracranial hypertension may occur and is a reason not to combine isotretinoin with tetracyclines. Likewise, it is better to avoid supplementary therapy with vitamin A in patients on synthetic retinoids. Retinoids also appear to increase the hepatotoxicity of methotrexate. There are reports [26] of depression and suicidal intention in patients taking isotretinoin, but a causal relationship has not been demonstrated [27,28].

Patients may develop abnormal liver enzyme levels during therapy with retinoids; not all values have returned to normal on cessation of the drug [29].

Increase in very-low-density lipoprotein (VLDL) cholesterol and reduction in high-density lipoprotein (HDL) cholesterol have been reported with retinoid therapy. Many patients receiving isotretinoin have been reported with elevated serum VLDL triglyceride in the absence of a preceding hyperlipoproteinaemia. These levels have returned to normal on cessation of treatment, but all patients should be screened for hyperlipoproteinaemia prior to treatment with any retinoid.

An ossification disorder resembling idiopathic skeletal hyperostosis has been reported in patients receiving long-

term retinoids. These drugs should only be given to younger children when there are good indications [30–32].

Teratogenicity

Retinoids are known to be teratogenic. Maternal ingestion of retinoids early in pregnancy can lead to fetal abnormalities [33] and the infants seem to have a characteristic appearance [34,35].

It is important that women are not pregnant prior to starting treatment. Effective contraception is mandatory during and after a course of treatment. Isotretinoin has a short half-life and therefore contraceptive measures need to be taken for only 1 month after cessation of treatment, but etretinate has a long half-life. The manufacturers recommend that conception should not occur for 2 years after cessation of acitretin therapy. It is preferable to check blood levels at that time to confirm that no drug is detectable, even though it is recognized that only a minority of patients back-metabolize acitretin to etretinate. Males can safely father children even when they are taking the drug.

Bexarotene

Synthetic third-generation oral retinoids are under development. Bexarotene is a retinoid X receptor (RXR)-selective retinoid 'rexinoid' approved for the treatment of cutaneous T-cell lymphoma [36]. A 45% response rate for monotherapy is reported in regimens of 300 mg/m^2/day; the main side effects are hypertriglyceridaemia (79%) and central hypothyroidism. Combination therapy with either PUVA, interferon-α or extracorporeal photopheresis is reported to enhance the response [37].

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Immunosuppressive and cytotoxic drugs

These drugs, which have been primarily developed for use in oncology, must be approached with great caution when they become part of a dermatologist's armamentarium; it is essential that the treatment is not more disabling than the disease. An understanding of the clinical

pharmacology of these drugs and their possible side effects is required for the proper management of patients [1]. Brief details are given below of those drugs that may be of value in dermatological practice. A more complete review can be found in Friedmann [2].

Alkylating agents

The effect of these drugs is dependent on proliferation and is expressed only when cells enter the S phase. Alkylation of DNA by these drugs leads to impaired replication.

Cyclophosphamide [3]

Dose: 1–3 mg/kg body weight daily in two or three divided doses. Cyclophosphamide is inactive *in vitro* but is metabolized to an active antimitotic agent that also has profound immunosuppressive activity. It has been successfully used together with corticosteroids in the treatment of pemphigus and pemphigoid, Wegener's granulomatosis, systemic lupus erythematosus, polymyositis, mycosis fungoides and histiocytosis X.

Chlorambucil

Dose: 0.1–0.2 mg/kg/day in one or two doses. Chlorambucil is slow acting and rather less toxic than cyclophosphamide. It has been successfully used in the treatment of mycosis fungoides, Behçet's disease, lupus erythematosus, Wegener's granulomatosis, steroid-resistant sarcoidosis and in combination with prednisone for Sézary syndrome. Benefit has been reported in lichen myxoedematosus [4], granuloma annulare [5] and as a steroid-sparing agent for patients with recalcitrant dermatomyositis [6].

Dacarbazine

Dose: 2–4.5 mg/kg/day intravenously for 10 days. This is an imidazole derivative whose mode of action is unknown. It is used particularly for the treatment of metastatic malignant melanoma (see Chapter 38).

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Antimetabolites

Methotrexate

Methotrexate has been used for the treatment of severe psoriasis and psoriatic arthritis since the 1950s [1–6]. It is a structural analogue of folic acid and is a potent competitive inhibitor of dihydrofolate reductase, which converts dietary folic acid via dihydrofolate to tetrahydrofolate. These steps are essential in the generation of 1-carbon fragments needed for the synthesis of nucleic acids. Methotrexate is converted to methotrexate polyglutamates, which have prolonged intracellular storage. They block not only dihydrofolate reductase but also other essential enzymes involved in nucleotide synthesis including thymidylate synthase and AICAR (5-aminoimidazole-4-carboxamide ribonucleotide) transformylase [7,8]. The latter is involved in purine biosynthesis and indirectly inhibits the metabolism of intracellular adenosine, which is known to be toxic to T lymphocytes and is potently anti-inflammatory. Indirect evidence of adenosine accumulation has been shown in psoriasis patients, whose adenosine excretion was found to be double that of controls following each methotrexate dose; greater increases were seen in those showing clinical improvement than in those without [9]. Although originally hypothesized that the effects of methotrexate in psoriasis were brought about by a direct interference in epidermal cell division [10,11], it is now recognized that it significantly inhibits proliferating lymphoid cells but has little effect on epidermal cells at therapeutic doses [12]. Inhibition of epidermal proliferation, on the other hand, is probably relevant in the context of acute methotrexate toxicity.

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Therapeutic indications and efficacy

Psoriasis and psoriatic arthritis. Methotrexate is of particular value in the management of acute generalized pustular psoriasis and psoriatic erythroderma [1–3], but has been most widely employed for inducing and then maintaining control of psoriasis in patients with extensive chronic plaque disease, especially in those who also have psoriatic arthritis [4]. Published studies suggest that methotrexate can produce a reduction in disease severity of at least 50% in more than three-quarters of patients treated [5–10]. Its efficacy in a controlled trial was slightly less than that of ciclosporin [11].

Cutaneous sarcoidosis. Small open studies have demonstrated improvement in skin lesions of various morphologies [12,13]. However, methotrexate was less effective in pulmonary sarcoidosis where improvement in lung function was seen in only one-third of patients [13], and it is important to be aware that improvement in skin lesions is often slow. The side effect profile appears to be similar to that seen in psoriasis patients, although the significance of liver biopsy abnormalities may be more difficult to assess because many patients with sarcoidosis will show granulomatous infiltration in the liver [13].

Dermatomyositis. Methotrexate is increasingly advocated for cutaneous lesions. Eight of 13 patients given weekly low-dose oral methotrexate (2.5–30 mg) for skin disease inadequately controlled either by topical and systemic corticosteroids or by antimalarials, were considered to have had a good or excellent response and in all 13 it was possible to reduce or discontinue corticosteroid therapy [14]. Early introduction of methotrexate in children with juvenile dermatomyositis has been claimed to hasten recovery and allow a more rapid reduction in corticosteroid dosage [15,16].

Cutaneous lupus erythematosus (LE). Small studies suggest benefit from methotrexate for cutaneous lesions of LE [17–20]. In a larger prospective randomized controlled trial of patients with mild systemic LE only three of 18 patients receiving low-dose methotrexate (15–20 mg/week) had residual cutaneous disease after 6 months of therapy compared to 16 of 19 patients given placebo [21]. Although there is less evidence in chronic discoid LE [22], there is thus reasonable evidence to suggest that methotrexate may enable corticosteroid dosage to be reduced in patients with systemic lupus and that it is worth considering for patients with cutaneous LE unresponsive to more standard therapies.

Systemic sclerosis and morphoea. In one randomized double-blind study of 29 patients with active systemic sclerosis allocated to weekly injections of either methotrexate 15 mg or placebo for 24 weeks, a predefined favourable response was seen in a significantly greater proportion of patients in the methotrexate group (8 of 17; 47%) than in the placebo group (1 of 12; 8%) [23]. However, a larger double-blind controlled trial of 71 patients with early diffuse systemic sclerosis randomized to the same interventions failed to demonstrate significant benefit after 12 months' treatment [24], although even this study was insufficiently powered. However, both studies showed improvement in skin scores. In a small open study, nine of 10 children with active localized morphoea responded to a combination of pulsed intravenous methylprednisolone and weekly low-dose methotrexate within a median of 3 months [25]. Methotrexate has been advocated for arresting progression of linear morphoea en coup de sabre and facial hemiatrophy in children [26]. A small uncontrolled study of methotrexate 15 mg/week for 24 weeks claimed some benefit in nine patients with widespread morphoea but these claims must be treated with caution in a disease where spontaneous improvement is not uncommon [27].

Atopic dermatitis. There are no good case series let alone randomized controlled trials of the use of methotrexate for atopic dermatitis. Recently, however, it has been claimed that, whereas the weekly regimen used in psoriasis appears not be effective, methotrexate taken as 2.5 mg on four consecutive days each week can help to control selected patients with widespread moderately severe atopic dermatitis [28]. However, there must be concerns that long-term use of such a regimen may increase the risks of liver toxicity and further data are required before this approach can be generally recommended.

Other dermatoses. Benefit from weekly low-dose methotrexate has been claimed in individual case reports or small series for polyarteritis nodosa [29], Behçet's disease [30], cutaneous small vessel vasculitis [31], antiphospholipid syndrome [32], pyoderma gangrenosum [33], pityriasis lichenoides [34–36], bullous pemphigoid [37], pemphigus [38], multicentric reticulohistiocytosis [39], scleromyxoedema [40] and Langerhans' cell histiocytosis [41].

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Safety precautions and side effects

Haematological or renal abnormality. Myelosuppression is the most important cause of methotrexate-associated death. Methotrexate should be avoided in patients with significant haematological abnormalities or renal impairment. Because methotrexate is eliminated largely via the kidneys, toxic levels may build up rapidly in patients with renal impairment, and even low doses of the drug may then produce acute myelosuppression [1]. This is particularly liable to occur in the elderly when concomitant drug administration or illness such as fever or diarrhoea may result in sudden deterioration of renal function; elderly patients especially should be warned to omit methotrexate doses whenever they are at risk of acute dehydration.

Drug interactions. Certain drugs may increase toxicity of methotrexate by increased antifolate effect (e.g. sulphonamides, trimethoprim, phenytoin) or by decreasing renal elimination (e.g. aspirin and NSAIDs, probenecid, ciclosporin) [2]. As life-threatening myelosuppression may result from interactions between methotrexate and such drugs, patients and all their medical attendants should be made aware of these risks.

Liver disease, alcohol and diabetes. Methotrexate should not be administered to patients with significant current or previous liver disease, especially if caused by viral hepatitis or to alcohol. Any patient suspected of alcohol abuse is unsuitable for methotrexate, although many dermatologists allow patients receiving methotrexate to continue taking small amounts of alcohol (e.g. 4–6 units of alcohol weekly). Obese diabetic patients are also at increased risk of liver damage from methotrexate [3].

Fertility. Because methotrexate is both arbortifacient and teratogenic [4–7], it is strictly contraindicated in pregnancy. Adequate contraceptive measures must be taken by women of child-bearing potential during methotrexate therapy and for at least one menstrual cycle after stopping the drug [8]. It should also be avoided during lactation. Although low-dose methotrexate has not been found to be mutagenic in sperm [9] and normal children have been born where the father was taking methotrexate at the time of conception [10], the drug may depress spermatogenesis [11]. It is customary to advise men to avoid fathering children during therapy and for at least 3 months thereafter [8].

Miscellaneous precautions. Other important contraindications to the use of low-dose methotrexate include active peptic ulceration, hepatitis virus infection, active infectious disease such as tuberculosis, immunodeficiency states and unreliability of the patient.

Management of the patient

The risks and benefits of therapy should be clearly explained to the patient both verbally and in writing. Adequate contraceptive measures must be commenced where appropriate and baseline blood tests obtained.

Methotrexate is usually given orally and is given as a single weekly dose as it is well-established that the toxicity for a given total dose is considerably increased when it is administered daily [12]. Unambiguous instructions including which day of the week the tablets are to be taken should be given to the patient and specified on the prescription. Deaths have occurred where prescribers, dispensers or patients have confused 10 mg for 2.5-mg tablets. It is thus good practice always to specify 2.5-mg tablets for inflammatory diseases. The rationale proposed for giving methotrexate in three divided doses once weekly [13] is now thought unlikely to be valid [14] and may have higher risk of hepatic fibrosis [15].

Most serious problems and the rare deaths associated with low-dose methotrexate arise because of an absolute or relative overdosage. A small test dose, usually 5 mg, should be given in order to detect those patients who may be unduly sensitive to the drug [16]. If the full blood count is stable at 7 days then subsequent doses may be gradually increased (usually in 2.5–5 mg steps) according to clinical response and any accompanying toxicity. The aim of therapy should not be to induce complete clearance of psoriasis but to achieve sufficient control that it may readily be managed with topical therapy. Most patients are adequately controlled on doses of 7.5–15 mg weekly and few patients require more than 20 mg. Even lower doses may suffice, particularly in the elderly.

Folic acid supplementation. There is little evidence that folate supplementation diminishes methotrexate efficacy [17,18], although methotrexate toxicity is enhanced by folate depletion. Recent studies in both rheumatoid arthritis and psoriasis patients have shown that low-dose methotrexate increases circulating concentrations of homocysteine and that this rise can be reversed by folic acid administration [19,20]; elevated homocysteine levels are associated with increased risk of cardiovascular disease. Given the fact that folic acid also has protective effects on the bone marrow, it seems appropriate to recommend that all patients treated with methotrexate should receive supplemental folic acid. There is as yet insufficient information to determine the most appropriate dosage but 1–5 mg/day appears to be adequate to correct these problems without affecting clinical response to therapy [17,18].

Monitoring schedule. Initially, patients should be assessed weekly by clinical examination and laboratory measurement of full blood count, plasma urea, electrolytes and creatinine, and liver enzyme tests. Once therapy has been stabilized, assessments should be performed every 2–3 months. Results should be carefully monitored; recording of results such as haemoglobin or platelets in a table or graph makes it easier to detect abnormal trends. In any individual, the dosage of methotrexate required to maintain adequate control of psoriasis will vary from time to time and should be adjusted accordingly.

As alcohol abuse greatly increases the risks of liver damage in patients receiving methotrexate, they should be reminded regularly of the need to restrict alcohol intake. Liver damage cannot be reliably detected by standard liver enzyme tests or imaging techniques and regular liver biopsy for all patients receiving low-dose methotrexate for psoriasis is still advocated by several authorities [8,21]. However, several studies suggest that the risk of serious liver damage in carefully monitored patients receiving once weekly low-dose methotrexate is small [22–24] and that the cost and morbidity of repeated biopsy may be difficult to justify when compared with the low yield of significant liver pathology. If there are concerns about pre-existing liver damage then it may be appropriate to obtain a liver biopsy as a baseline soon after successful methotrexate therapy has been established.

It can reasonably be argued that liver biopsy need no longer be performed routinely in all patients receiving long-term methotrexate but, to provide greater reassurance that significant damage is not overlooked, several investigators have recommended the use of a serological marker of fibrosis, the aminoterminal peptide of type III procollagen (PIIINP). They have concluded that patients whose PIIINP levels are consistently normal are very unlikely to have significant liver damage [25–27]. If PIIINP assay is available it should be performed 3 monthly and liver biopsy may be restricted to the small minority in whom PIIINP levels are repeatedly elevated.

Management of problems

Inadequate response. A small minority of patients are unable to absorb methotrexate adequately but may respond satisfactorily if it is given intramuscularly or intravenously. Patients with psoriasis who relapse while receiving methotrexate may frequently be brought satisfactorily under control by a course of intensive topical therapy and/or UVB phototherapy [28]; in contrast to the combination of methotrexate and PUVA, which should be avoided, a major increased risk of skin cancer from combining UVB with methotrexate has not been demonstrated [29]. Combination of methotrexate with other systemic agents is discussed further in Chapter 35.

Nausea. This occurs in 25%, usually appears within 12 h of methotrexate ingestion, and may last up to 3 days. It is usually mild but may limit therapy [30]. Folic acid 5 mg/day has been found to be more helpful than antiemetics, taking methotrexate with the evening meal or dividing the dose, although any of these manoeuvres may help some patients. Ondansetron 8 mg orally 2 h before and, if necessary, 12 and 24 h after the weekly methotrexate dose, can be dramatically effective [31].

Liver inflammation and fibrosis. An acute rise in liver enzymes to greater than three times the upper limit of normal is usually an indication to discontinue methotrexate. If PIIINP levels are repeatedly abnormal over a 12-month period then liver biopsy should be considered. The decision to discontinue methotrexate depends not only on the results of liver biopsy but also on the ease with which an individual patient's psoriasis may be managed by other means. In general, severe fibrosis and cirrhosis are considered contraindications to further methotrexate therapy. Nevertheless, some dermatologists have continued treatment in patients with documented cirrhosis without encountering significant deterioration of liver disease [32]. In patients with hepatic inflammation or mild to moderate fibrosis without cirrhosis, continuation of methotrexate therapy is probably still safe so long as alcohol is strictly avoided and patients are closely monitored. If PIIINP remains elevated then a further liver biopsy should be considered after 12 months to 2 years of continued therapy.

Respiratory disease. Methotrexate-induced pneumonitis is rare in psoriasis. It is characterized by acute onset with fever, cough and dyspnoea. Chest X-ray shows pulmonary infiltration. It resolves rapidly with withdrawal of methotrexate and systemic corticosteroids [29]. Pulmonary fibrosis is a rare complication.

Haematological abnormalities. A rise in mean corpuscular volume (MCV) is common in patients receiving long-term methotrexate and usually indicates relative folate deficiency although it is important to exclude other causes of macrocytosis. If MCV rises above 106 fl despite folate replacement then further methotrexate therapy is probably contraindicated [33]. Falls in haemoglobin, white cell or platelet counts should prompt a reduction in dose or, if severe, withdrawal of methotrexate.

Acute toxicity and overdosage. Absolute or relative overdosage of methotrexate can result in acute toxicity, manifested clinically by myelosuppression, mucosal ulceration and, rarely, cutaneous necrolysis. Early treatment may be life-saving. The metabolic effects of methotrexate can be bypassed by administration of folinic acid. As soon as overdose is suspected, serum should be collected for measurement of methotrexate levels and folinic acid should be administered intravenously. The dose of folinic acid should be at least as high as the total dose of methotrexate thought to be responsible for the overdose and should in any event not be less than 20 mg. Subsequent doses (which may be taken orally if no more than 20 mg) should be given at 6-hourly intervals until the serum methotrexate is less than 0.01 μmol/L. The dose of folinic acid required will vary according to the serum methotrexate concentration. A dose of 20 mg suffices where the methotrexate concentration is 0.5 μmol/L or less, but at higher concentrations the dose can be calculated at 100 mg for every 1 μmol/L of measured serum methotrexate concentration [34].

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Azathioprine

Azathioprine is one of many immunosuppressive drugs used in dermatology following original use in transplant surgery. It is converted in the body to 6-mercaptopurine (6-MP), an inhibitor of purine synthesis and an immunosuppressive agent; this in turn is metabolized to purine thioanalogues by hypoxanthine guanine phosphoribosyl transferase (HGPRT). Additionally, an imidazole metabolite appears to have powerful anti-inflammatory properties. It is now known that thiopurine methyltransferase (TPMT) is a major enzyme involved in the metabolism of azathioprine. TPMT activity is determined by an allelic polymorphism for either high or low enzymic activity. Homozygotes for the low activity allele (0.5% of the population) are known to be at high risk for myelosuppression [1,2]. It is recommended that patients starting azathioprine should have blood TPMT levels measured beforehand and the dose titrated accordingly [3].

Indications

The licensed indications for azathioprine are dermatomyositis [4], systemic lupus erythematosus (also useful in severe cutaneous disease [5]) and pemphigus vulgaris [6,7]. Other dermatological conditions in which it may be useful include bullous pemphigoid [8,9], intractable atopic dermatitis [3,10], chronic actinic dermatitis [11], Behçet's disease [12], Wegener's granulomatosis [13] and other vasculitides [5], pyoderma gangrenosum [14], psoriasis [15] and perhaps pityriasis rubra pilaris in adults [16]. It appears to be inferior to methotrexate in the treatment of psoriasis but may be useful for psoriatic arthritis.

Management of the patient

The usual azathioprine regimen is 1–3 mg/kg/day. Baseline TMPT assay is recommended, with dose adjustment if necessary. Doses at the lower end of this range are generally recommended in the elderly. Azathioprine is usually used as a steroid-sparing agent, but has been used as monotherapy (e.g. in atopic dermatitis or psoriasis). It takes a few weeks to reach a steady state; dose titration may be required. Weekly blood monitoring is required initially (probably for 4 weeks), gradually extending to every 3 months.

Contraindications include low TPMT activity, pregnancy, hypersensitivity, concurrent malignancy and concurrent allopurinol therapy (because of risk of marrow toxicity). Other drugs that may interact with azathioprine include sulfsalazine, warfarin, angiotensin-converting enzyme inhibitors and any drug that suppresses bone marrow function.

Complications of treatment

Myelosuppression is a relatively common side effect of azathioprine and can develop very quickly, certainly between regular blood monitoring, and can be severe. It is more common at the start of treatment, especially in those with TPMT deficiency, but may also occur in those with normal TPMT activity.

Hypersensitivity may be manifest by rash or hepatitis, often with eosinophilia. Pancreatitis may occur [17]. Azathioprine-induced shock in dermatology patients has only been reported rarely but can be life-threatening [18].

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Bleomycin

This is a polypeptide antibiotic given parenterally. It has no immunosuppressive action and its toxicity is confined to the skin (pigmentation, inflammatory lesions especially on the palms and fingers) and the lungs. It is effective against squamous cell carcinoma of the skin and elsewhere, and in inducing remission in mycosis fungoides and other lymphomas. It has been used intralesionally for the treatment of intractable virus warts [1,2] but vasospasm, sometimes severe, is a potential side effect.

Hydroxyurea

Dose: 500 mg two or three times daily. Hydroxyurea blocks pyrimidine synthesis. It causes much more short-term marrow suppression than methotrexate, necessitating frequent blood counts. However, it is less effective than methotrexate and has little effect on psoriatic arthropathy. A combination of hydroxyurea with retinoids has been reported to be particularly effective [3]. Hydroxyurea is easy to administer, relatively inexpensive and has few contraindications or side effects. Leukopenia can develop and regular blood monitoring is needed. Hydroxyurea does have a place for those patients who cannot take other drugs because of systemic disorders such as hyperlipidaemia, mild renal impairment, cardiopulmonary disease and mild liver disease [4]. It may occasionally cause a dermatomyositis-like rash or leg ulceration.

Mycophenolate mofetil

Dose: 0.5–1 g twice daily. Mycophenolate mofetil (MMF) is the ester of mycophenolic acid (MPA), but provides advantages over MPA in that it has increased bioavailability. After ingestion, MMF is hydrolysed to MPA—the active acid form. MPA inhibits the enzyme inosine monophosphate dehydrogenase (IMPDH), a key enzyme in *de novo* purine synthesis. Thus, MPA blocks the production of guanosine nucleotides needed for RNA and DNA synthesis. MPA is particularly effective in blocking the type II isoform of IMPDH expressed mainly in T and B cells, thereby inhibiting T- and B-cell activation and proliferation. Monotherapy with MMF for psoriasis is not as effective as ciclosporin [5]; indeed MMF is probably best used in psoriasis as combination therapy as a ciclosporin-sparing agent [6]. Efficacy in atopic dermatitis is uncertain, with efficacy at 1 g twice daily reported with long-term remission for up to 20 weeks [7] but other studies not being able to discern benefit [8]. MMF is understandably beneficial for therapy of autoimmune bullous diseases, particularly bullous pemphigoid and pemphigus, and may be used as a steroid-sparing agent [9,10]. Beneficial use of MMF has been reported in a variety of skin diseases including pyoderma gangrenosum [11], bowel-associated dermatitis–arthritis syndrome [12], systemic lupus erythematosus [13], chronic actinic dermatitis [14] and extensive lichen planus [15].

Adverse effects include mild to moderate leukopenia and anaemia [16], immunosuppression and gastrointestinal symptoms. There is no significant toxic effect on renal or hepatic function.

Melphalan

This is used mainly in the treatment of myelomatosis and polycythaemia. Other indications include scleromyxoedema (see Chapter 57) [17].

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Ciclosporin [1]

This drug was isolated and purified in 1972 from a soil fungus found in Norway. Its main use until recently has been as an immunosuppressant in patients following kidney, liver, heart, bone marrow or other transplants. It has increasing uses in dermatology, but its use demands careful monitoring. Ciclosporin is a cyclic polypeptide made up of 11 amino acids. The main mode of action is on helper T cells whose cell cycle is blocked in G0 or early G1 and whose production of various lymphokines, notably IL-2, is inhibited. It may also have some direct effect on DNA synthesis and on proliferation of keratinocytes [2]. Apart from its use in transplant patients, ciclosporin has been used to treat a wide range of general medical diseases in which T cells contribute—rheumatoid arthritis, systemic lupus erythematosus, polymyositis and dermatomyositis, uveitis, thyrotoxicosis, diabetes, biliary cirrhosis, various nephropathies, colitis, Crohn's disease and others. Dermatological uses [3–5] include notably psoriasis [6], pustular psoriasis [7] and psoriatic arthritis. Ciclosporin is particularly effective in widespread plaque psoriasis. Treatment at low dosage (3–5 mg/kg/day) for 1–3 months will produce substantial improvement in over 60% of patients [8]. The preferred treatment regimen for psoriasis is short-course intermittent therapy—using ciclosporin for no more than 3 months at a time but reinstituting therapy on relapse [9]. Using this regimen, most patients require four or fewer courses of ciclosporin (average dosage 3.4 mg/kg/day) over 2 years [10]. Most patients relapse once ciclosporin is discontinued.

The other main use of ciclosporin in skin diseases is atopic dermatitis. It is a very effective treatment [11], but relapse occurs within a few weeks of discontinuing the drug, although at 1 year later and still off the drug, the disease was only approximately 50% of the severity before ciclosporin treatment was started [12]. Ciclosporin has also been reported to benefit patients with chronic hand dermatitis [13].

Ciclosporin is also used for pemphigus and pemphigoid. There are reports of benefit of ciclosporin in dermatomyositis [14], pyoderma gangrenosum [15] and chronic idiopathic urticaria [16].

Absorption of the drug from the gut is variable, often approximately 30%, although a microemulsion formulation of ciclosporin that has better absorption has replaced the original product. Excretion is mainly via the liver but again the rate is variable. For practical purposes, assessment of blood levels of ciclosporin is unnecessary when using 'dermatological doses' in otherwise well patients, and monitoring renal function (by serum creatinine estimations) and blood pressure suffice.

Ciclosporin has little toxicity on the bone marrow or liver but does have a considerable and largely reversible toxicity on the kidney [17]. Short-term (mean 2.4 months) ciclosporin at a dosage of 5 mg/kg/day was associated with a significant but small and reversible increase in blood pressure, but only a transient mild reduction in glomerular filtration rate (GFR), which did not reach significance [18]. Renal function and biopsy findings have been studied in patients who have taken ciclosporin continuously for 5 years (average 3.3 mg/kg/day). Six of eight patients who had renal biopsies showed tubular atrophy and arteriolar hyalinosis, four had increase in interstitium and two showed increased instance of glomerular obsolescence. Renal function was assessed by GFR and serum creatinine. Both a fall in the GFR and a rise in serum creatinine correlated with the severity of the ciclosporin nephrotoxicity seen on biopsy [19]. Other side effects include nausea and vomiting, hypertension, hypertrichosis, tremor and hyperkalaemia.

Long-term toxicity may include an increased tendency for lymphomas. Although a recent epidemiological study of 1252 patients over 5 years did not demonstrate an increased incidence of lymphoma, it did reveal a sixfold increase in skin cancer, particularly in those patients who had received prior PUVA [20]. There are notable interactions with ketoconazole, erythromycin and other drugs that increase blood levels; with rifampicin and hydantoinates, which decrease blood levels; and with

NSAIDs, which seem to increase the nephrotoxicity without changing the blood levels.

New oral calcineurin inhibitors, structurally dissimilar to ciclosporin but with similar mechanisms of action, have been developed, such as pimecrolimus (a derivative of ascomycin). Oral pimecrolimus appears effective in the treatment of moderate to severe psoriasis but apparently without risk of nephrotoxicity or hypertension [21].

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Fumaric acid esters (fumarates)

For more than 20 years fumarates have been used extensively in northern Europe, particularly German-speaking countries, for the treatment of moderate to severe psoriasis [1,2]. The commercially available preparation of fumarates, Fumaderm®, comprises a mixture of dimethylfumarate and the calcium, magnesium and zinc salts of monoethylfumaric acid. After ingestion, dimethylfumarate is hydrolysed to momomethylfumarate—the main active metabolite. Clinical trials [3–5] attest to the efficacy of fumarates. The drug is introduced gradually, starting at 30 mg/day, building up over several weeks to a maximum dose of 240 mg three times daily. It is estimated that, if they tolerate the drug, approximately 57% of patients will achieve a 70% reduction in severity of psoriasis. Two-thirds of treated patients develop gastrointestinal symptoms such as dyspepsia and diarrhoea; one-third of patients develop flushing. In most patients these side effects settle down over time. Lymphocyte counts fall in nearly all treated patients, sometimes by 50% [3–5]. Renal function and liver function should be monitored but impairment is unusual. The mechanism of action of fumarates appears to be an ability to promote the secretion of Th2 cytokines [6], such as IL-10, which are beneficial in psoriasis.

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PUVA [1]

Photochemotherapy with 8-methoxypsoralen followed by UVA radiation for psoriasis is considered in detail in Chapter 35. If necessary, 5-methoxypsoralen can be substituted, or 8-methoxypsoralen bath PUVA used, especially if a patient is nauseated by 8-methoxypsoralen.

PUVA is also of value in mycosis fungoides (MF) (see Chapter 54) [2]. Seventy-three patients with MF were treated with PUVA, which produced clinical and histological clearance in a very high proportion of patients with pretumour-stage MF. The response of patients with tumours was less satisfactory, such patients requiring, in addition, radiotherapy.

PUVA may be used in selected children with severe atopic dermatitis [3]. Fifty-three children (mean age 11.2 years) had twice-weekly PUVA; 39 (74%) of them achieved

a clear or nearly clear skin. The mean duration of treatment to remission was 37 weeks, with mean cumulative UVA dose of 1118 J/cm. This relatively high UVA exposure is of concern. However, 22 children remained in remission 1 year after discontinuing PUVA.

PUVA has been described to be of benefit in a whole range of dermatological conditions. Some of the reports involve large numbers of patients and others only single-case reports. For an excellent review of the uses of PUVA in conditions other than psoriasis, including hand eczema, nodular prurigo, vitiligo, the various photodermatoses, granuloma annulare, lichen planus, lyphomatoid papulosis, urticaria, aquagenic pruritus, urticaria pigmentosa, idiopathic pruritus and many other conditions, refer to [4].

It is undisputed that solar UV radiation is a major aetiological factor in squamous and basal cell carcinoma and malignant melanoma in humans. Tumours have been induced in the skin of hairless albino mice by PUVA exposure using both 8-MOP and 5-MOP [5]. An early report suggested that PUVA therapy accelerated the development of skin tumours in patients with xeroderma pigmentosum [6], and it appeared to have an obvious promoter effect in a patient previously exposed to X-irradiation, arsenic and several cytotoxic drugs, who developed 25 basal or squamous cell carcinomas, the first within 21 months of onset of PUVA therapy [7].

There is now substantial literature dealing with the incidence of skin tumours in groups of PUVA-treated patients. Although certain studies have failed to show a clear relationship between PUVA and tumour development [8–10], long-term follow-up of a large US cohort has provided conclusive evidence for the carcinogenicity of PUVA [11]. In this study, an initial cohort of 1380 PUVA patients was followed up for a mean of 13.2 years. Squamous cell carcinoma (SCC) developed in one-quarter of patients exposed to high doses of PUVA, giving a relative risk of SCC of 5.9-fold by comparison with patients receiving low-dose PUVA. High-dose PUVA was regarded as a total of over 299 treatments; low-dose less than 160 [11]. Precise UVA doses were not given, but taking an average dose of 11 J/cm^2 after clearing, the high-dose group can be estimated to have had more than approximately 3200 J and the low-dose group less than 1760 J. The latter figure may therefore be taken as a cumulative dose, which should ideally not be exceeded. However, a study in Northern Ireland, where there is a high population of sun-sensitive Celtic subjects, indicated increased risk for non-melanoma skin cancer (including particularly basal cell carcinoma) with cumulative UVA doses above only 250 J/cm^2 [12]. Therefore, far more conservative UVA limits may be needed with certain populations, and safety limits may be better expressed as numbers of treatments rather than cumulative UVA doses. In the Northern Ireland study, a cumulative UVA dosage of 250 J/cm^2 equated with approximately 100 treatments. The US study showed that fair-skinned persons had an approximately twofold higher risk of SCC than those with skin types III or IV. Overall, there was no substantial increase in the risk of basal cell carcinoma with high-dose PUVA in the US study [11]. Metastatic SCC was seen in seven patients, but two of these were elderly and had had little PUVA. Four were younger (41–57 years) and had had moderate- to high-dose PUVA, although methotrexate or ionizing radiation may have played an additional part [11].

The substantially increased risk of SCC with high-dose PUVA therapy has been supported by a large Swedish study [13]. The male genitalia appear to be particularly at risk [14–16]. In a prospective cohort study [11,16] of 892 men first exposed to PUVA in 1975–76, 24 (2.7%) had developed a total of 51 genital neoplasms. It appears that increased risk is associated with high-dose PUVA in association with UVB and coal tar. Shielding of the genitalia during PUVA therapy reduces the risk.

PUVA lentigines may exhibit cytologically atypical melanocytes [17]. There is an increased risk (incidence rate ratio 8.4) in patients who have received PUVA—the 1380 patient cohort study of patients who first received PUVA in 1975–76 calculated that high-dose PUVA (more than 250 treatments) and passage of time were contributing factors. PUVA is best avoided in those predisposed to malignant melanoma (e.g. those with numerous melanocytic naevi or atypical moles, and a family history of melanoma) [18,19].

There is no evidence of any internal carcinoma hazard, but acute leukaemia [20,21] and a preleukaemic state [22] have been reported. In addition, a patient transformed from myelodysplasia to acute fatal myeloid leukaemia after 4 months of PUVA [23].

These findings have led to a recommendation that PUVA patients should not receive more than 1000 J/cm or more than 150 treatments in a lifetime unless there are strong indications otherwise [24]. The male genitalia should be protected while receiving PUVA treatment.

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Photopheresis

The use of extracorporeal photoimmunochemotherapy (ECP; photopheresis) was pioneered in the early 1980s. Primarily developed for the treatment of cutaneous T-cell lymphoma (CTCL), ECP has been used to treat a variety of dermatological diseases. Derived from PUVA treatment, ECP involves the extracorporeal exposure of peripheral blood mononuclear cells (PBMC) to 8-methoxypsoralen and UVA irradiation before being returned to the patient. The machine used for this process provides the leukopheresis step prior to UVA exposure. 8-Methoxypsoralen is delivered directly to the collected buffy coat containing the PBMCs (for a detailed review of the procedure refer to Knobler and Jantschitsch [1]). Various protocols are under development for ECP but the one used most widely is photopheresis on two successive days, repeated at 2–4-week intervals. It is estimated that during one treatment session 5–10% of the circulating T-cell pool is treated. The exact mechanism of action is not fully understood but it is believed that the patient's immune system is stimulated to destroy the altered and/or damaged malignant T cells.

CTCL was the first disease for which ECP was evaluated and as a consequence most evidence of efficacy comes from treatment of this disease. Indeed, ECP is approved in the USA for palliative treatment of Sézary syndrome. The original study by Edelson *et al*. [2] demonstrated partial or complete remission in 27 out of 37 CTCL patients. Subsequent studies [3,4] confirmed this observation and it is accepted that complete remission may occur in 25% of patients with no response in a further 25%. A good therapeutic response is dictated by short disease duration, normal numbers of CD8 cells and a normal CD4 : CD8 ratio [5]. An advantage of ECP is the low side effect profile [3]. Some patients with Sézary syndrome are less responsive to ECP, and combination therapy with IFN-α, methotrexate, PUVA, bexarotene or superficial electron beam therapy may be required [6–8]. It should be noted that although the Sézary syndrome form of CTCL is responsive to ECP, some workers have questioned this high rate of response, mainly disputing the definition of Sézary syndrome—if a strict definition of clonal disease is instituted, only 16% of patients have a complete response [9]. Long-term survival is good with survival rates of 100 months from time of diagnosis [7]. Unsurprisingly, ECP has been used to treat a variety of inflammatory disease where autoreactive T cells are believed to be an important contributor to the disease process. ECP may be an important therapy for graft-versus-host disease after allogeneic bone marrow transplantation [10], and perhaps in the treatment of acute or chronic rejection of organ transplants [11]. Systemic sclerosis [12], systemic lupus erythematosus [13], atopic dermatitis [14], pemphigus vulgaris [15] and psoriatic arthritis [16] have all been reported to respond to ECP.

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Plasmapheresis

Plasmapheresis (plasma exchange) has been used for many years in patients with severe systemic lupus erythematosus in whom high-dose corticosteroids and immunosuppressants were not controlling their disease [1,2]. However, the evidence that it is effective when added to immunosuppressive treatment with prednisolone and ciclosporin in severe lupus nephritis is lacking [3]. It can also be life-saving in Goodpasture's syndrome [4]. It is used in myaesthenia gravis, Waldenström's macroglobulinaemia, cryoglobulinaemia, thrombotic thrombocytopenic purpura and Guillain–Barré syndrome. Plasmapheresis is occasionally used in acute polymyositis or dermatomyositis, but in a controlled trial involving 39 patients, it was shown to be no more effective than sham apheresis [5].

Plasmapheresis is an effective treatment for pemphigus vulgaris and bullous pemphigoid unresponsive to conventional therapy—it is particularly useful for rapid control of severe active disease and as a means of reducing the dosage of corticosteroid and other immunosuppressive therapy. Between seven and 14 therapeutic plasma exchanges are required [6]. Side effects of plasmapheresis may include hypertension.

Plasmapheresis was effective in a series of eight patients with pemphigus vulgaris, in whom the treatment was added to their glucocorticoid and immunosuppressive therapy, which had not been controlling their disease [7]. Bullous pemphigoid seems to be less successfully treated by plasmapheresis. In a study involving 100 patients, it was found that neither azathioprine nor plasmapheresis was effective as an adjuvant to corticosteroid [8]. Solar urticaria has been reported to respond to plasmapheresis when added to photochemotherapy (PUVA) that had not been effective on its own [9].

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Intravenous immunoglobulin [1]

High-dose intravenous immunoglobulin (IVIg) is produced from pooled human plasma. There are at least seven licensed IVIg preparations available, but differences between these preparations may affect outcome. IVIg has been used to treat a variety of autoimmune bullous and inflammatory dermatoses. Most reports are anecdotal with few randomized controlled trials. Treatment with IVIg is best performed in an inpatient setting but if patients are low risk, then infusions can be performed in an ambulatory setting. High doses (1–2 g/kg) are recommended, usually delivered as a 5 consecutive day cycle of 0.4 mg/kg/day, although a 3-day cycle may be used. Each infusion is given over 4–4$^1/_2$ h. Initially, cycles are repeated every 3–4 weeks until there is effective control of disease—once this has been achieved the time intervals between cycles can be gradually increased. A proposed end point is two infusions 16 weeks apart. Adverse effects are usually mild and self-limiting—common side effects include headache, chills, flushing and vomiting. More serious adverse events have included aseptic meningitis, thrombosis and anaphylaxis, particularly in IgA-deficient patients who have anti-IgA antibodies. There is a potential risk of transference of infectious agents but batches are screened for human immunodeficiency virus (HIV), syphilis and hepatitis [1].

IVIg is believed to work as an immunomodulatory agent—reducing levels of IL-1 in serum [2], it may also down-regulate expression of Fas and Fas ligand on keratinocytes, thereby preventing apoptosis [3].

Most use of IVIg in dermatology is for therapy of autoimmune mucocutaneous blistering diseases [1]. Small case series of pemphigus vulgaris [4–6] indicate that 2 g/kg IVIg produces prolonged clinical remission sustained after cessation of therapy. IVIg also has a corticosteroid-sparing

effect in pemphigus vulgaris [5]. Pemphigus foliaceus is responsive to IVIg and prolonged remission has been achieved [7]. In 27 of 32 cases of bullous pemphigoid non-responsive to conventional therapy reported in the literature as having received IVIg therapy, there was significant and long-lasting clinical improvement [1]. Mucous membrane pemphigoid appears, on the basis of case reports and small uncontrolled series, to respond to IVIg to the extent that disease progression (particularly eye disease) is halted [8]. Cases of epidermolysis bullosa acquisita [9], pyoderma gangrenosum [10], dermatomyositis [11], atopic dermatitis [12] and psoriasis [13], amongst a large list of dermatoses [14], have all been treated successfully with IVIg. The use of IVIg for the treatment of toxic epidermal necrolysis is perhaps the most contentious—a rationale for its use is the ability to prevent keratinocyte apoptosis. No randomized controlled trial has been performed, but some groups [3,15] advocate it as the treatment of choice while others believe it has no benefit [16].

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Gold (sodium aurothiomalate)

Dose: 10 mg intramuscularly as a test dose, followed by 50 mg at weekly intervals. Although this regimen was devised for treatment of rheumatoid arthritis it has been successfully used in the treatment of pemphigus [1]. If there has been no improvement by the time the total dose reaches 1 g, treatment should be stopped. If improvement does occur, the frequency of the injections is reduced to every 2–3 weeks. Renal, hepatic and marrow damage must be looked for and rashes are common.

Auranofin is an oral preparation of gold, rather less effective than the parenteral preparation. Its main advantage is that its tissue half-life is much less than with injectible gold. Dose: 3–6 mg/day, increasing to 9 mg/day after 3–6 months. It has also been used in discoid lupus erythematosus.

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Chelating agents

Chelating agents are available that form complexes with a number of heavy metals. They are only occasionally of use in dermatology.

d-Penicillamine [1]

This is a degradation product of penicillin and chelates copper, mercury, zinc and lead. It is used for Wilson's disease, lead poisoning, cystinuria and rheumatoid arthritis [1,2]. Its dermatological interest lies in its ability to cause a variety of diseases, including systemic lupus erythematosus-like syndrome, pemphigus-like bullous eruptions, lichenoid and other eruptions and elastosis perforans serpiginosa (see Chapter 73). Earlier reports of possible benefit in scleroderma have not been substantiated [3–5].

Desferrioxamine

This is used in the treatment of various iron-storage diseases. In general, acute iron overload seems to respond much more satisfactorily. However, it is logical to use it in porphyria cutanea tarda as long as iron overload is present, although its value has yet to be proved (see Chapter 57).

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Antibiotics and antibacterial agents

Antibiotics were originally substances synthesized by microorganisms that were toxic to other microorganisms at high dilution. The term is now more widely applied to any drug with therapeutic activity against living organisms, particularly bacteria. Antifungals and antivirals are drugs with activity against fungi and viruses, respectively.

Most modern antibiotics are synthetic or semi-synthetic. They are usually divided into bacteriostatic and bactericidal groups, although the distinction is not complete; erythromycin, for example, may be either bactericidal or bacteriostatic depending on the nature of the infecting organism and the drug concentration achieved.

In clinical use, antibiotics are divided into those with a narrow spectrum of activity and those broad-spectrum drugs that act against Gram-positive and Gram-negative organisms. In the laboratory, antibiotics can be further divided into five main groups:

1 Antibiotics that interfere with bacterial cell wall synthesis (e.g. the penicillins, cephalosporins and glycopeptide antimicrobials such as vancomycin and teicoplanin)
2 Antibiotics affecting bacterial cell-membrane permeability (e.g. the polymyxins)
3 Antibiotics that inhibit bacterial protein biosynthesis (e.g. the tetracyclines, aminoglycosides, macrolides, lincosamides and chloramphenicol)
4 Antibiotics that affect bacterial nucleic acid metabolism (e.g. the rifamycins and quinolones)
5 *Para*-aminobenzoic acid (PABA) antagonists (e.g. the sulphonamides).

Drug resistance

Bacterial resistance can emerge in three ways. When all sensitive bacteria have been eradicated, any remaining inherently resistant bacteria are free to multiply; this is the most common form of resistance. Less frequently, bacteria may acquire resistance, by mutation, to a drug to which they were initially sensitive. The third form, which is cause for concern, is transferable drug resistance. Here, extrachromosomal genetic information affecting the expression of resistance contained in a plasmid or a transposable section of chromosomal DNA can be transferred from one bacterium, which may be non-pathogenic, to another previously susceptible bacterium. This often takes place in the bowel or skin and may involve a variety of different organisms. Information on multiple drug resistance can be transferred with a single plasmid.

The mechanisms of drug resistance are variable and include changes in permeability of the cell membrane or antibiotic efflux, alterations in ribosomes, altered cell-wall precursors or target enzymes and the emergence of auxotrophs that have different growth substrates.

Sulphonamides

These antibacterial drugs were introduced into clinical practice in the 1930s, but the frequency of resistance combined with adverse events have limited their use. The combination of a sulphonamide (sulfamethoxazole) with trimethoprim, known as co-trimoxazole, however, is still used in dermatology although less frequently than previously. Resistance is widespread.

Sulphonamides are derivatives of *para*-amino-benzenesulphonamide. They act by inhibiting the bacterial enzyme dihydrofolic acid synthetase, which converts PABA to dihydrofolic acid. Mammalian cells and resistant bacteria do not synthesize folic acid and are unaffected.

Sulphonamides are bacteriostatic and most are well absorbed orally. They are distributed through all body tissues, metabolized in the liver and excreted mainly by the kidneys.

Adverse effects. Although the frequency of serious adverse events is low, sulphonamides can cause a number of serious problems. Besides crystalluria, a risk if there is inadequate fluid intake, they may rarely cause blood dyscrasias such as acute haemolytic anaemia (particularly in patients with glucose-6-phosphate dehydrogenase deficiency), fever, serum sickness and a large variety of skin reactions including erythema nodosum and erythema multiforme. Potentially fatal cases of the severe form of erythema multiforme have followed the use of long-acting sulphonamides [1]. Because of the relatively high incidence of this reaction, the long-acting sulphonamides are little used.

Uses. There are now very few situations where they are drugs of first choice. They are of value in lymphogranuloma venereum, chancroid, nocardiosis and toxoplasmosis (combined with pyrimethamine). Sulfapyridine is now used only as an alternative to dapsone in dermatitis herpetiformis and allied conditions.

Sulfapyridine

Dose: 0.5–1.5 g/day as an alternative to dapsone in dermatitis herpetiformis.

Silver sulfadiazine

This has a role as a topical non-absorbable antimicrobial with a broad spectrum.

REFERENCE

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Trimethoprim [1]

Trimethoprim is a synthetic antimicrobial agent in its own right. It is a potent inhibitor of bacterial dihydrofolic acid reductase, which converts dihydrofolic acid to tetrahydrofolic acid, but has many thousand times less effect on the comparable mammalian enzyme. Trimethoprim is very well absorbed orally, distributed widely through most body tissues and is excreted almost completely by the kidney. Although available as a separate drug, it has been used mainly in combination with sulfamethoxazole in the proportions 1 to 5 as co-trimoxazole. This is a logical mix as these drugs inhibit successive stages in bacterial folate metabolism and it is not surprising that their combined effect is synergistic. Both drugs used singly are bacteriostatic but co-trimoxazole appears to be bactericidal.

Co-trimoxazole tablets BP

There are two strengths containing sulfamethoxazole 400 or 800 mg and trimethoprim 80 or 160 mg, respectively. The dose is two tablets twice daily. The combination is effective against a wide range of Gram-positive and Gram-negative bacteria as well as *Nocardia* and actinomycetoma agents and is in general well tolerated. However, it is best avoided in pregnancy and in infants under 6 weeks and therefore in lactating mothers feeding young babies. Adverse reactions are similar to those seen with sulphonamides. Typical skin reactions may occur in up to 8% of patients and this has limited its use for relatively benign conditions such as acne. Impairment of red cell folate utilization may occur, particularly in the elderly, and supplements of folinic acid may be necessary [1]. Rarer side effects include renal impairment and hepatic reactions.

Co-trimoxazole may be used for urinary tract and respiratory infections but, in infections affecting the skin, is of value in chancroid, atypical mycobacterial infections [2] and mycetoma. Co-trimoxazole has potential value in the treatment of *Pneumocystis* infections, particularly in AIDS patients in whom, unfortunately, there is a high frequency of adverse reactions.

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Penicillins

The basic structure of a penicillin consists of a thiazolidine ring, a β-lactam ring and a variable side-chain. The starting point for the semi-synthetic penicillins, of which there are now many, is 6-aminopenicillamic acid. It is convenient to divide the penicillins into five main groups according to their antibacterial properties and consequent clinical usage [1]:

1 Penicillinase-sensitive penicillins (natural penicillins) (e.g. benzyl penicillin (penicillin G), and phenoxymethyl penicillin (penicillin V))

2 Penicillinase-resistant penicillins (e.g. methicillin, flucloxacillin)

3 Amino penicillins, which are broad-spectrum penicillins (vulnerable to penicillinase) (e.g. ampicillin, amoxicillin). By combining clavulanic acid, a potent β-lactamase inhibitor, with amoxicillin (Augmentin®), the spectrum of activity has been broadened to cover penicillin-resistant staphylococci

4 Carboxy penicillins (e.g. carbenicillin)

5 Other penicillins, which include extended-spectrum penicillins (e.g. piperacillin), aminopenicillins and penicillins that are stable against Gram-negative lactamases (e.g. temocillin).

Toxicity. The main problems with their use are hypersensitivity reactions, which are not uncommon. An incidence between 1 and 10% is usually accepted [2], and it appears that administration of these drugs by the oral route is associated with a lower frequency of adverse reactions than the intravenous route [3]. These reactions range from urticaria and vasculitis to anaphylaxis. Cross-reactivity in this allergy is usual. Rare side effects include interstitial nephritis, haemolytic anaemia and pancytopenia.

Penicillinase-sensitive penicillins (penicillin)

Penicillin is the drug of choice against *Streptococcus pyogenes* group A, *Treponema pallidum* and meningococcal septicaemia as well as in yaws, actinomycosis and diphtheria. Because of the emergence of resistant strains of the organism, its use in the treatment of gonorrhoea has largely been superceded. In most serious infections, penicillin is given by injection as benzyl penicillin but treatment may be continued with oral penicillin V and this drug also has a role in prophylaxis against streptococcal cellulitis in patients with lymphoedema.

Benzyl penicillin injection BP (penicillin G). Dose: 300 mg (0.5 mega-units) four times daily up to 1.8 g (3 mega-units) daily. Long-acting injectable preparations are available.

Phenoxymethyl penicillin (penicillin V). Dose: 250–500 mg orally every 6 h.

Penicillinase-resistant penicillins

For practical purposes this means cloxacillin or flucloxacillin, which are resistant to staphylococcal β-lactamase and are drugs of choice against penicillin-resistant staphylococci [4]. Flucloxacillin is somewhat less effective against other Gram-positive infections. Adequate levels are achieved by the oral route but parenteral administration is preferred in serious infections.

Flucloxacillin. Dose: 250–500 mg every 6 h and at least 30 min before food.

Amino penicillins

Ampicillin is commonly used, having a spectrum of activity against Gram-positive and Gram-negative bacteria. It is acid stable and therefore absorbed orally, but is not resistant to penicillinase. It is little used in dermatology but is important as a cause of drug rashes. These occur in about 5–10% of all patients treated but in a majority of those with infectious mononucleosis, cytomegalovirus infections or lymphatic leukaemia [2]. The typical morbilliform rash is thought to be toxic in nature and unrelated to true penicillin hypersensitivity. Amoxicillin is almost identical, is twice as well absorbed as ampicillin but is more expensive. It should probably only replace ampicillin in the patient known to be susceptible to antibiotic-induced diarrhoea [5]. Where an even broader spectrum is needed, perhaps in the treatment of heavily infected leg ulcers with surrounding cellulitis, amoxicillin with clavulanic acid (Augmentin) is worth consideration [6,7]. However, its role in dermatology is a limited one.

Ampicillin. Dose: 250 mg to 1 g every 6 h and at least 30 min before a meal.

Amoxicillin capsules. Dose: 250–500 mg every 8 h.

Amoxicillin 250 mg and clavulanic acid (Augmentin) tablets. Dose: 1–2 tablets every 8 h.

Other penicillins

Carbenicillin, piperacillin, ticarcillin and azlocillin must all be given by injection or infusion and have little place in dermatology.

Imipenem

Imipenem is a carbapenem, a bi-cyclic β-lactam compound with a broad spectrum [8]. It shows considerable activity against many Gram-positive bacteria as well as *Neisseria* spp. It is also used in *Nocardia* infections. It is seldom used in dermatology and is given intravenously.

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Cephalosporins [1,2]

The cephalosporins are derivatives of 7-amino-cephalosporamic acid and are similar in structure and properties to the penicillins. They are bactericidal, acting on peptidoglycans in bacterial cell walls, and have wide spectra of activity encompassing Gram-negative organisms and staphylococci—penicillin-resistant staphylococci are generally susceptible but the degree of effectiveness varies between cephalosporins. Many are given parenterally but some orally effective ones are available (e.g. cefalexin, cefaclor). They are excreted by the kidney but unlike penicillin may cause tubular damage. Their main role is perhaps as alternative therapy in penicillin hypersensitivity, but this is not without risk as some 8–10% of all penicillin-allergic patients react to cephalosporins. Apart from this they have little dermatological use.

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Quinolones [1]

The chief quinolone antibiotics are more correctly classified as fluoroquinolones or 4-quinolones. Their mode of action is via inhibition of DNA synthesis. Their spectrum of activity is broad and generally includes both Gram-positive and Gram-negative bacteria. The principal quinolone in wide use is ciprofloxacin; others include norfloxacin and ofloxacin. This can be given orally in doses of 750 mg twice daily for soft-tissue infections [2]. Ciprofloxacin is active *in vitro* against a wide range of bacteria from *Escherichia coli* to *Bacillus anthracis* and *Yersinia enterocolitica*. It is also active against staphylococci and streptococci as well as *Mycobacterium tuberculosis*, although atypical mycobacteria are generally less sensitive. In dermatology, ciprofloxacin is best reserved for

severe infections such as those occurring in the immunocompromised patient, but other indications include Gram-negative folliculitis, rhinoscleroma and cutaneous anthrax. It is an alternative treatment for chancroid and genital chlamydial infections.

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Tetracyclines

These are orally effective broad-spectrum antibiotics with relatively low toxicity. The original three tetracyclines were chlortetracycline, oxytetracycline and tetracycline. Later derivatives include demethylchlortetracycline, methacycline, doxycycline and minocycline (the last three being synthetic). They act by inhibition of protein synthesis through ribosomal binding. With the exception of minocycline they all have similar spectra of activity; differing, however, in their absorption, distribution and excretion.

Both streptococci and staphylococci may be resistant to tetracyclines, although the incidence of staphylococcal resistance is less than previously and such strains are sensitive to minocycline [1]. However, as much more effective agents are available for these organisms, the tetracyclines are generally not used in these infections.

The tetracyclines are bacteriostatic against many Gram-positive and Gram-negative bacteria and are also active against rickettsiae, *Mycoplasma*, *Chlamydia*, which cause lymphogranuloma venerum, psittacosis and trachoma, as well as amoebae.

Absorption of some tetracyclines is impaired by simultaneously taking milk, aluminium, calcium or magnesium salts or iron preparations, because of chelation. However, food does not interfere with the absorption of doxycycline or minocycline. All tetracyclines are concentrated in the liver and excreted into the bile, whence they enter an enterohepatic circulation. Urinary excretion is significant and renal failure may be exacerbated by all except doxycycline [2].

Side effects [3–5]. A variety of rashes has been described (see Chapter 77), including phototoxicity, especially shown by demethylchlortetracycline [6]. Glossitis, cheilitis and persistent pruritus ani may occur. Gastrointestinal disturbances are dose dependent [7] and are much more common with doses of 2 g/day or more, which are rarely used in dermatology. Nausea and vomiting are direct irritant effects; diarrhoea may be the result of superinfection, resistant staphylococci being especially dangerous. Minocycline can cause vertigo and hyperpigmentation. The latter is usually slate grey and can affect the skin, nails and sclerae [8]. Tetracyclines are deposited in growing teeth and bones [9] and their use should be avoided in pregnancy, during lactation and in childhood. Rarely, there may be diffuse fatty degeneration of the liver. An uncommon dermatological problem is the development of Gram-negative folliculitis after tetracycline therapy of acne [10,11].

Dermatological uses. Apart from the infections mentioned above, tetracyclines are rarely drugs of first choice. The exception, of course, is the treatment of acne vulgaris (see Chapter 42) [12,13] and rosacea (see Chapter 46).

Tetracycline, chlortetracycline, oxytetracycline

Dose: daily doses range from 500 mg (for acne) up to 3 g.

Doxycycline, minocycline

Dose: 100–200 mg/day. Doxycycline is the ordinary tetracycline of choice in patients with renal impairment. Minocycline is usually effective against staphylococci resistant to other tetracyclines and is used increasingly as a first-line treatment of acne (50 mg twice daily).

Preparations are also available as syrups, and injections for intramuscular, intravenous or intralesional use. Tetracycline resistance has been reported in *Propionibacterium acnes* and caution should be exercised over the use of repeated courses of these antibiotics. Resistance may also be passed to other bacteria [13].

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Macrolides

The main macrolide antibiotics are erythromycin and its derivatives azithromycin and clarithromycin. They work by binding to ribosomes and inhibiting protein synthesis.

Erythromycin [1]

Dose: 1–2 g/day in divided doses. This is the most widely used member of the macrolide group of antibiotics. It is active mainly against Gram-positive organisms such as staphylococci and streptococci. Staphylococci may rapidly develop resistance, especially in hospital, where in some studies as many as 50% of strains may be resistant; streptococci are also occasionally resistant.

Side effects include an allergic cholestatic hepatitis that occurs only with erythromycin estolate. Otherwise gastrointestinal problems such as dyspepsia and diarrhoea are not uncommon. Erythromycin is an extremely useful drug for the outpatient treatment of staphylococcal or streptococcal pyodermas, especially in the penicillin-allergic patient. It may also be used for atypical mycobacterial infections. Particular dermatological uses are for erythrasma and acne; it may safely be given in renal failure as less than 5% is excreted in the urine.

Azithromycin and clarithromycin [2]

These are newer macrolide agents with a somewhat different spectrum of activity than erythromycin and longer half-life. At present they are little used in dermatology, although they show promise as treatment for atypical mycobacterial infections, particularly those caused by the *Mycobacterium avium* complex, but *M. marinum* is also responsive [3].

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Aminoglycosides

This group includes streptomycin (see below), neomycin, gentamicin, amikacin and tobramycin. They are little used in dermatological practice, their chief use being against Gram-negative infections. They inhibit protein synthesis; bacteria may rapidly become resistant, and cross-resistance occurs within the group. Normally there is almost no absorption by mouth. They are ototoxic and, to a lesser degree, nephrotoxic.

Dermatological uses. These are few. Streptomycin is still used in some countries for tuberculosis, is effective in tularaemia and some forms of actinomycetoma and can be used as an alternative to tetracyclines in granuloma venereum. The topical use of neomycin is discussed in Chapter 78.

Gentamicin [1] *and amikacin* [2]

Amikacin is now more widely used than gentamicin [2]. Its use is mainly restricted to the treatment of serious Gram-negative infections, especially those caused by *Pseudomonas aeruginosa* [3,4] and to *Nocardia* infections [5]. Gentamicin has a synergistic effect with carbenicillin against *Pseudomonas* and other Gram-negative organisms and is used in combination with penicillin for some forms of endocarditis. Aminoglycosides should not be used in pregnancy and should be controlled by measurements of plasma concentration.

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Spectinomycin

This is an aminocyclitol antibiotic derived from a streptomycete species and is related to the aminoglycosides. Its use in dermatology is limited but it is very effective in the management of gonorrhoea as a single intramuscular injection [1].

REFERENCE

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Lincosamides

Lincomycin and its derivative clindamycin (which ought to be used in preference to lincomycin) act against Gram-positive cocci including some penicillin-resistant staphylococci. They are highly active against *Bacteroides* infections and penetrate well into bone.

Side effects. Diarrhoea may occur in up to 20% of cases; pseudomembranous colitis may supervene and may last

for weeks after the drug has been withdrawn [1,2]. There have been a number of deaths from this complication; one severe case has been reported in a patient treated for acne.

Clindamycin

This is an effective alternative drug for the treatment of acne [3]; however, in view of its known toxicity, it is now rarely used systemically for this condition. It is useful in a 1% formulation for the topical treatment of mild to moderate acne.

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Chloramphenicol

This would be a useful drug for a number of infections were it not for bone marrow aplasia, which occurs in 1 in 40 000 courses of treatment [1]. This has been known for 25 years, and yet a survey of 576 cases of blood dyscrasia caused by chloramphenicol concluded that in most cases there had been no indication to justify its use. Nevertheless, it remains an alternative treatment for typhoid fever and *Haemophilus influenzae* meningitis.

REFERENCE

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Rifamycins

See p. 72.37.

Polymyxins

Polymyxin B and polymyxin E (colistin) are relatively toxic drugs that are not absorbed from the gastrointestinal tract. Their use for Gram-negative infections has been largely superceded by gentamicin and ciprofloxacin. Polymyxin B is used topically.

Glycopeptide antibiotics

The two main examples of this group are vancomycin and teicoplanin. They act by inhibition of peptidoglycan polymer formation in bacterial cell walls. Vancomycin is chiefly used for the treatment of serious staphylococcal infections such as septicaemia as well as other life-threatening conditions such as pseudomembranous colitis. It has no obvious use in skin disease [1].

REFERENCE

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Fusidic acid [1]

This is produced by a strain of *Fusidium coccineum* and has the basic structure of a steroid, although it shows little in the way of metabolic effects. It is a very safe drug, primarily used for staphylococcal infections, although it is also active against other Gram-positive bacteria and the Gram-negative cocci. Nearly all strains of staphylococci are outstandingly sensitive to fusidic acid [2] but there have been increasing reports of resistant mutants, which can multiply rapidly. However, concomitant administration of penicillin can be used to kill any resistant mutants as they emerge. It is available for oral use, as an injection and for topical application. It is a useful drug for staphylococcal osteomyelitis in particular, and its indiscriminate prescription for minor infections should be discouraged for fear of encouraging resistant strains that are now emerging.

REFERENCE

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Metronidazole [1,2]

Metronidazole is a synthetic agent active against protozoa and anaerobic bacteria. It is particularly useful in trichomoniasis, bacterial vaginosis [2], amoebiasis and giardiasis, and has proved extremely valuable against *Bacteroides* and *Helicobacter* species [3]. For the dermatologist it has a limited role in the treatment of tetracycline-failed rosacea [4]. Metronidazole is well absorbed by the oral or rectal route and it may be applied topically. It may also be given intravenously. It is available as 200 and 400 mg tablets, the usual adult oral dosage being 200 mg twice daily for rosacea, 200 mg every 8 h for *Trichomonas* infections, 400 mg every 8 h for anaerobic bacterial infections and 800 mg every 8 h for amoebiasis. The suppositories contain 500 mg, and in anaerobic infections are prescribed in the adult dosage of 1 g every 8 h at first, dropping to 1 g every 12 h. Topical formulations are available for the treatment of rosacea.

The fate and mode of excretion of metronidazole are not fully understood [5]; it is generally regarded as safe in hepatic and renal disease. There is no evidence that it is a human teratogen, and it may be given to lactating mothers, although it causes darkening of milk and may give it a bitter taste. In normal doses and for short periods it is generally a remarkably safe drug but minor gastrointestinal side effects such as nausea and an unpleasant taste in the mouth are not uncommon. Vomiting, abdominal pain and diarrhoea may follow. Darkening of urine, headache and drowsiness also occur, and leukopenia may be noted. Much less common adverse reactions are peripheral neuropathy, particularly associated with prolonged treatment, and central nervous system effects (dizziness, ataxia and fits) from high dosage. The only important interaction is with alcohol, which produces a disulfiram-like reaction in some patients.

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Antituberculous drugs (see Chapter 28)

The important first-line drugs for the treatment of *Mycobacterium tuberculosis* infections are isoniazid, rifampicin, ethambutol and, in some cases, streptomycin [1,2]. In the initial period of treatment, usually 60 days or until sensitivities are available, three of these drugs are used concurrently. For the continuation phase of therapy, two drugs to which the organism is sensitive are sufficient for cure without the occurrence of resistant strains (for details see Chapter 28).

Second-line drugs such as pyrazinamide, ethionamide, cycloserine, PABA or thiacetazone may be required where drug resistance or adverse reactions preclude the use of more than one of the four first-line agents.

The emergence of multidrug-resistant strains of *Mycobacterium tuberculosis* (MDR-TB) is a major potential threat [3], particularly as they may affect AIDS patients who expectorate large numbers of bacilli.

Isoniazid

This is a synthetic, orally absorbed bactericidal agent usually given in a dosage of 300 mg/day to adults (5–10 mg/kg every 24 h). It is excreted mainly by the kidney after acetylation and further metabolism. It can be used in pregnancy [4] but during lactation should be supplemented with pyridoxine because of the theoretical risk of toxic side effects (see below). In severe renal failure, the adult dosage should be reduced to 200 mg/day. Adverse reactions may be divided into toxic and allergic. Toxic reactions are more common in slow acetylators and include most commonly peripheral neuropathy but also convulsions, mental disturbances and a pellagra-like rash [5]. They are usually reversible on cessation of therapy. Pyridoxine 10 mg/day given prophylactically will reduce the incidence of these problems where high doses are used. The main allergic reactions are rashes, agranulocytosis and hepatitis, this last being apparently more common in patients with pre-existing liver disease [6].

Rifampicin

This is a synthetically modified antibiotic of the rifamycin group. It is bactericidal and very effective against *M. tuberculosis*, many atypical myobacteria and Gram-positive cocci. It is also useful in leprosy. To counter the emergence of resistant strains, it is always used in combination with other antimicrobials.

Rifampicin is well absorbed orally and is available as 150 mg capsules and a 100 mg/5 mL mixture. In adults it is usual to prescribe 450–600 mg/day as a single dose before breakfast (10 mg/kg/day). Excretion is predominantly in the bile and so hepatic impairment is an indication for avoidance or at least lower dosage. In pregnancy, rifampicin is best avoided but where it has been used the incidence of abnormalities noted at birth has not been excessively high—4.3% compared with 1.8% in tuberculous controls [7]. If used in late pregnancy it may cause haemorrhagic problems in neonates. Rifampicin is generally regarded as a relatively non-toxic antituberculous drug but many different adverse reactions have been described: mild gastrointestinal disturbances and rashes —particularly flushing [8,9]. Transient impairment of liver function as revealed by elevation of transaminase levels is common but need not usually interrupt therapy. Orange-red discoloration of urine, saliva and sweat may be noticed. Thrombocytopenia, however, is an uncommon side effect that must not be ignored. Three other serious adverse reactions are a flu-like illness, a syndrome of dyspnoea, wheezing and hypotension, and the occurrence of renal failure, all of which are characteristically associated with intermittent or irregular medication [10]. Drug interactions occur with warfarin (diminished anticoagulant effect), oral contraceptives (possibly) and corticosteroids (diminished steroid effect).

Other rifamycins. Rifabutin has particular activity against *M. avium–intracellulare* in addition to *M. tuberculosis*. It is used, for instance, as prophylaxis in patients with low CD4 counts. It may also be useful where there is a high risk of rifampicin resistance.

Streptomycin

This is an aminoglycoside antibiotic used mainly in the treatment of tuberculosis. It must be administered parenterally and is commonly given in a dosage of 500–1000 mg/day by intramuscular injection. Lower dosage is preferred in patients over 40 years [11]. Excretion is by the kidney so that dosage should be reduced in renal impairment. Dosage reduction is also important in the premature infant. Of the important side effects, the most common is vertigo, which is especially troublesome in elderly people. Deafness may also develop and both these eighth-nerve effects are dose related [12]. These two adverse reactions provide a strong contraindication to the use of streptomycin in pregnancy and lactation as the infant may be affected, and in patients with pre-existing vestibular or auditory impairment. Allergic reactions include skin eruptions from the trivial to exfoliative dermatitis, eosinophilia and drug fever. Contact sensitization to streptomycin is a well-recognized hazard among nurses, justifying precautions to avoid skin contamination (e.g. by wearing gloves). Because streptomycin is a neuromuscular-blocking agent, it may increase the effects of suxamethonium and other similar drugs, and should be used only with extreme caution in myasthenia gravis.

Ethambutol

This is a synthetic agent effective only against *M. tuberculosis* and some atypical mycobacteria. It is orally absorbed and is available on its own as 100 and 400 mg tablets and in combination with isoniazid in a variety of strengths. The usual initial dosage is 15 mg/kg/day in adults and 25 mg/kg/day in children, reducing later in that age group to 15 mg/kg/day. It may also be used as intermittent treatment in a dosage of 45–50 mg/kg twice weekly. Excretion is mainly via the kidney, necessitating reduction of dosage in renal impairment. Optic (retrobulbar) neuritis with diminished visual acuity and red-green colour blindness, slowly reversible on cessation of therapy, was a relatively common side effect of higher dosage regimens but should be rare with currently recommended levels [13,14]. It seems to be more effective to train patients to check their own vision regularly when on this drug than to rely on periodic ophthalmic examinations. Ethambutol may also, although rarely, cause peripheral neuropathy and renal damage, and may precipitate attacks of gout. It appears not to be a teratogen in humans and is not contraindicated during lactation.

Para-aminosalicylic acid

This drug is much less active than the above drugs, but has a role in preventing the emergence of resistant strains of *M. tuberculosis*. It is given in the high dosage of 10–20 g/day and unfortunately is associated with a high incidence of minor but unpleasant side effects [15]—gastrointestinal symptoms occur in nearly all patients. Allergic reactions with rashes and fever are common and there seems to be either cross-hypersensitivity with streptomycin or potentiation of streptomycin allergy. Although once a valued drug in triple therapy, its use is now largely restricted to poorer countries where its low cost is a major consideration.

Other antituberculous drugs [2]

A number of other antituberculous drugs are available and may be required if resistance or hypersensitivity reactions preclude the use of standard treatment. They include pyrazinamide, capreomycin, ethionamide and cycloserine. Pyrazinamide is bactericidal and low-priced [16].

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Antileprosy agents

Sulphones

The sulphones were the first effective compounds used for the treatment of leprosy. The principal agent is 4,4-diaminodiphenyl sulphone (dapsone). The sulphones are related to the sulphonamides, and probably act in the same way. *Mycobacterium leprae* is usually extremely sensitive [1] but may become resistant. The sulphones are bacteriostatic, not bactericidal.

Dapsone. This drug is orally absorbed and is available in the form of 50 and 100 mg tablets. The usual adult dosage in leprosy is 50–100 mg/day. It is excreted mainly in the urine [2]. Some degree of haemolysis is an extremely common adverse reaction [3,4]. In pregnancy and lactation there is clearly a risk of haemolysis and methaemoglobinaemia in the baby, but the presence of dapsone in breast milk may have prophylactic value against leprosy [5]. Resistance to dapsone is known to occur in approximately 20% of patients who receive the drug for the treatment of leprosy as a single agent. With the use of multiple-drug regimens, this complication is thought to be much rarer. Leprosy apart, dapsone is a well-established means of suppressing the cutaneous lesions of dermatitis herpetiformis [6] and several other diseases. Most dermatologists are more familiar with the use of the drug in this way and further details are described in Chapter 41.

Clofazimine (Lamprene®) [7,8]

This oral synthetic drug is a phenazine dye. The usual dosage is 100 mg three times a week or 100 mg/day in combination with rifampicin if sulphone resistance has occurred [9]. It has an anti-inflammatory effect that may prevent erythema nodosum from developing. For lepra reactions, 300 mg/day is recommended. Clofazimine has a very long half-life: 70 days or more. It accumulates in the tissues and is slowly excreted in urine, sweat, sebum and milk.

The main side effect is the emergence of red-brown to black discoloration of skin and conjunctivae, but urine and sputum become red too and breast milk may be discolored. Mild gastrointestinal reactions may occur and ichthyosiform rashes [10]. In general, clofazimine is a well-tolerated drug that may be prescribed in pregnancy and during lactation. In renal and hepatic impairment, biochemical tests of function are recommended from time to time but the drug may be used. Clofazimine may be valuable in treating pyoderma gangrenosum [11] and perhaps also in discoid lupus erythematosus.

Rifampicin

This drug has been discussed previously (under Antituberculosis drugs). It seems to be bactericidal for *M. leprae* in very low dosage and acts much more rapidly than dapsone, rendering the patient non-contagious in a few days or weeks [12]. It does not shorten the total duration of treatment, which should be continued with dapsone.

Thiambutosine

This is a diphenylthiourea, useful as a second-line drug when dapsone cannot be used. Resistance may develop, especially after 1 year of treatment.

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Antifungal drugs [1–3]

The drugs available for systemic use against fungal diseases are few in number. There are three main families of antifungals: the polyenes (amphotericin B); the azoles, which include the imidazoles (e.g. ketoconazole, miconazole) and the triazoles (fluconazole and itraconazole); and the allylamines. There is also a miscellaneous group of drugs such as griseofulvin, tolnaftate and flucytosine. Most antifungals work through damage to or inhibition of the fungal cell membrane. The main exceptions are the pyrimidine analogue, flucytosine, which affects RNA and DNA synthesis, and potassium iodide which probably affects phagocytic function.

Polyenes [4]

Nystatin [4]

Nystatin was the first polyene antibiotic discovered and is still valuable today as a topical anti-*Candida* agent. It is not absorbed from the gut in significant amounts.

Amphotericin B [1,4]

This is a polyene antibiotic derived from *Streptomyces nodosus*. It has a very wide range of activity against *Candida* spp. and almost all deep fungal pathogens. Resistance is rare. Absorption from the gut is negligible and so, as with nystatin, tablets and lozenges are for practical purposes topical therapy for the mouth or prophylaxis. For systemic use, amphotericin B must be given by slow intravenous infusion in 5% dextrose. This solution is unstable; it should

be used promptly and other drugs should not be added, except heparin or hydrocortisone. The definitive adult dosage range is normally in the range of 0.4–1 mg/kg/day but toxicity is minimized if there is a build-up from a very low dose (1 mg) on the first day, to full dosage by days 3–5. In the seriously ill patient, a more rapid build-up to full dosage over 24–48 h is necessary.

The fate of amphotericin in the body is not fully understood [5]. Only small amounts appear in urine; much is probably bound to sterol-containing membranes. Adverse reactions are common: initially, fever, rigors, hypotension, nausea, vomiting, tinnitus and bronchospasm. Phlebitis at the site of infusion is also frequent. Hypokalaemia and hypochromic anaemia may occur and, rarely, liver function abnormalities. Nephrotoxicity is of great importance; renal clearance may be decreased and tubular damage may develop. These are particularly problems of extended treatment but are potentially reversible. If renal impairment is severe, therapy must be interrupted and should be restarted at a lower dosage.

Amphotericin B is used principally for systemic mycoses such as candidosis, aspergillosis, mucormycosis and cryptococcosis as well as the endemic respiratory infections such as histoplasmosis.

Lipid-associated amphotericins

Three formulations of lipid-associated amphotericin B have been developed: a liposomal formulation (AmBisome), a colloidal dispersion (Amphocil®) and a lipid complex (Abelcet®). They can be used at much higher dosage (usually 3 mg/day) without nephrotoxicity [6].

Flucytosine [7]

This is a synthetic cytosine analogue that is converted to 5-fluorouracil in the body. It is effective against yeasts, including *Candida* spp., *Cryptococcus neoformans* and many of the fungi involved in chromoblastomycosis. It is orally absorbed but may be given intravenously too. The tablets contain 500 mg, the usual adult dosage being 150 mg/kg/day. Lower doses are necessary in renal failure. It is important to monitor serum levels, aiming to achieve 40–60 mg/L and to avoid toxic levels—above 120 mg/L. Because resistance, both primary and secondary, is well recognized, sensitivity testing initially and at intervals is strongly recommended. It is rarely used on its own. In cryptococcal meningitis in the non-AIDS patient, flucytosine and amphotericin B are given in combination. They appear to be more effective as a combination than amphotericin B on its own and the daily dosage of the latter can be reduced to 0.4–0.6 mg/kg.

The main side effects are nausea, vomiting, diarrhoea and rashes, but thrombocytopenia and neutropenia may also occur.

Azoles

Miconazole

This is a commonly used topical imidazole, poorly absorbed by the oral route. It may be administered intravenously by slow infusion three times in 24 h, the usual adult dosage being 1.8–3 g/day. Side effects are not particularly common. They include pruritus, rashes, fever, faintness and venous thrombosis at the infusion site. Anorexia, nausea, vomiting and diarrhoea occur and anaphylaxis is a rare but genuine problem. It is seldom used now except in infections caused by *Scedosporium apiospermum* [8].

Ketoconazole [9,10]

Ketoconazole is a broad-spectrum imidazole, which is available in different topical formulations from cream to shampoo or as an oral agent. The drug is well absorbed after oral administration, although lower levels are seen in patients who are neutropenic. It is effective in chronic mucocutaneous candidosis and widespread dermatophytosis. It can also be used topically for pityriasis versicolor. It also appears to be effective in mycetoma infections caused by *Madurella mycetomatis* but not in sporotrichosis. Certain systemic mycoses such as paracoccidioidomycosis and those with soft-tissue lesions are the most sensitive [10].

Adverse events are not common but include headache, vomiting and giddiness as well as nausea. It also leads to blockade of androgen biosynthesis by interference with cytochrome P-450 at high dosage [11]. This results in symptoms such as gynaecomastia in men and menstrual irregularities in women. In addition, it causes asymptomatic changes in liver function and overt hepatitis on occasions [12]. The true frequency of the latter is estimated to be about 1 in 10 000 but it may be more common in patients receiving treatment for nail disease. It is more common also in those with a prior history of liver disease. While this is a comparatively uncommon complaint, it is sufficient to limit the use of the drug in superficial fungal disease. Also, much of its function has been assumed by the development of itraconazole and fluconazole (see below). Drug resistance is also seen rarely [13].

Itraconazole [14]

Itraconazole is a triazole antifungal drug that is avidly bound in tissue, including skin. Its serum levels are generally low after a 100–200-mg dose. It is given orally and has a broad spectrum of action against the main fungal pathogens. It is effective in dermatophytosis, candidosis and *Malassezia* infections. Originally used in a dosage of 100 mg/day, it is now often given at 200 or 400 mg. At

higher doses it is possible to use shorter courses such as 400 mg/day for 1 week in tinea corporis. Because it is retained for very long periods in the nail, it is used in pulses of 400 mg/day for 1 week per month for 3–4 months [15].

In vaginal candidosis it is given as a single treatment of 600 mg/day and it produces responses in oropharyngeal candidiasis in doses of 100–200 mg/day. For recalcitrant pityriasis versicolor, a total dose of 1000 mg is necessary. Other infections responding to itraconazole include sporotrichosis, chromomycosis, paracoccidioidomycosis and histoplasmosis [14]. It has also been reported to be effective in cryptococcal meningitis, particularly as a long-term suppressive therapy of HIV-positive patients. Itraconazole is unusual amongst azoles in producing responses against aspergillosis.

Although itraconazole may occasionally cause nausea and headache, more serious adverse reactions, such as hepatic reactions and anaphylaxis, are extremely rare.

A new formulation of itraconazole in cyclodextrin, as well as an intravenous form, are also available. This oral solution is much better absorbed in AIDS patients than the conventional formulation.

Fluconazole [16]

Fluconazole is a triazole antifungal that is well absorbed after oral administration. It may also be given intravenously. Unusually for an azole, it is mainly excreted via the kidney. It is active against a range of fungal pathogens.

The principal uses of fluconazole in dermatology are in the treatment of oropharyngeal and vaginal candidosis [17]. In the latter disease, it is effective in a single dose of 150 mg; with oropharyngeal infections, treatment responses are rapid, often within 3 days of starting therapy with 50–100 mg/day [18]. For dermatophytosis, it has been found that weekly doses of 150 mg may be effective after 2–3 weeks and a similar weekly pulse has been used for onychomycosis. In systemic mycoses it is used in the management of cryptococcosis, either as primary therapy or long-term suppression, and in systemic candidosis [19].

Few adverse effects apart from nausea and dyspepsia have been attributed to fluconazole. The dosage of the drug has to be reduced in patients with renal impairment.

Certain fungi such as *Candida krusei*, *C. glabrata* and some strains of *C. albicans* may be primarily resistant to fluconazole and secondary resistance may develop in immunocompromised patients [16].

Other azoles

Two new orally active triazoles in development, voriconazole and posaconazole, have not been evaluated in superficial fungal disease. They show promise in the management of a range of systemic infections.

Allylamines

Terbinafine [20]

Terbinafine is a fungicidal allylamine antifungal, similar to naftifine. It works by the inhibition of squalene epoxidation in the synthesis of the ergosterol in the fungal cell membrane [21]. The accumulation of squalene in the cell is thought to contribute to its *in vitro* fungicidal activity. It may be given orally or topically in a dosage of 125 mg twice daily. Its chief use is in dermatophytosis, where it is highly effective even in patients with chronic infections of the hands and feet. In onychomycosis it is given in a regimen of 250 mg/day for 6 weeks for fingernails and 12 weeks for toenails [22]. It is less active when given orally in superficial candidosis and pityriasis versicolor. In dermatophytosis there is a particularly low relapse rate with this drug. Recently, it has been shown to be active in a range of other deep fungal infections, from sporotrichosis to chromoblastomycosis.

There are few side effects apart from the occasional episode of gastrointestinal discomfort. Loss of taste may occur but is reversible. Skin rashes have also been reported. Hepatic reactions are extremely rare.

Griseofulvin [23]

Griseofulvin is derived from a number of *Penicillium* species. It is a fungistatic drug whose principal activity is directed against dermatophytes. Its mode of action is via the inhibition of the formation of intracellular microtubules.

The usual human dosage is 10 mg/kg/day in tablet or, in children, solution form. Treatment duration varies between 2 and 4 weeks for tinea corporis to over 1 year for onychomycosis. The success rate even after 1 year of treatment for toenail infections is less than 30–40%.

Drug interaction with phenobarbital and coumarin anticoagulants occur. Side effects include headaches and nausea, but serious reactions are extremely rare. There are a few reports of apparent precipitation or exacerbation of systemic lupus erythematosus and porphyrias by griseofulvin.

Potassium iodide [2]

In the form of a saturated aqueous solution (100 g in 100 mL water), this is the preferred treatment for lymphocutaneous sporotrichosis and subcutaneous zygomycosis (basidiobolomycosis). It is administered orally, starting with 0.6 mL three times daily and gradually increasing until a level of four or five times the dose is attained in an adult. The mode of action is obscure. Progress must be expected to be slow and treatment should be continued until 4 weeks after apparent cure. Iodides are best avoided in pregnancy because of the risk of goitre and

hypothyroidism in the infant. Adverse reactions include iododerma, salivary and lacrimal gland swelling and hypersecretion, and gastrointestinal disturbances, as well as anxiety, depression and hypothyroidism.

Cell wall antagonists

A number of new antifungals are in development that have a different site of action, the inhibition of the cell wall. Caspofungin is an echinocandin that blocks glucan synthase [24]. It is available as an intravenous drug for use in the treatment of aspergillosis or candidosis, particularly caused by resistant *Candida* species.

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Antiviral drugs

With the spread of HIV infection, considerable efforts have now been expended in searching for new antiviral drugs. Despite this there are still few effective antiviral agents [1]. Because there are fewer steps involved in the assembly of viruses, and these are inextricably associated with human metabolic and other cellular functions, the ratio between antiviral activity and host toxicity is often a narrow one. Many agents employed in the treatment of viral infections of the skin have one of three viral targets: inhibition of viral polymerase (e.g. aciclovir), inhibition of reverse transcriptase (e.g. zidovudine) or protease inhibition (e.g. indinavir). The two latter groups are mainly used for the treatment of retroviral infections.

Other approaches to treatment have involved the use of interferons, which have proved to be of limited value in most viral infections apart from some genital papillomavirus infections, and many of the available preparations are associated with dose-limiting side effects when given intravenously.

Drug resistance will occur with antivirals but often it involves a modification of the viral genome that may, in turn, affect viral pathogenetic mechanisms. This alteration in viruses may affect their capacity to cause disease except in severely immunocompromised patients such as those with AIDS.

Vidarabine (adenosine arabinoside, ARA-A)

This purine nucleoside acts by inhibiting viral DNA synthesis. It has effects mainly against the herpes group of viruses and appears to be effective in early cases of herpes simplex encephalitis and in varicella-zoster infections of immunocompromised subjects. However, its use has largely been superceded by aciclovir. At a dosage of 10 mg/kg/day intravenously it causes mainly mild gastrointestinal side effects, and rashes in 5% of subjects. CNS and haematological side effects have also been reported [2]. A 3% ointment has an established place in the topical treatment of herpes simplex keratoconjunctivitis.

Idoxuridine

This synthetic nucleoside is effective against DNA viruses, particularly the herpes group. Its use is now restricted to topical application because of severe bone marrow and hepatic toxicity when given intravenously. It has been used in 5–40% concentration in dimethyl sulfoxide (DMSO) to shorten the duration of clinical symptoms in herpes zoster infections. It can also be used in herpes keratitis but is less effective in genital herpes simplex infections [3].

Aciclovir [4–7]

This antiviral agent works by inhibition of DNA synthesis. Its mode of action involves activation by thymidine

kinase and subsequent inhibition of viral polymerase. Resistance to aciclovir has been recorded sometimes, following alterations to or deficiency of thymidine kinase. This has been associated with lack of response to therapy [8,9].

Aciclovir is very active against herpesviruses. In serious infections it has been used intravenously but it is also available as 200-mg tablets, as an ophthalmic ointment and as a cream [5]. Unfortunately, it has no effect on the latent phase of either herpes simplex or zoster and is apparently ineffective in clinical practice against other viruses. The intravenous dosage for serious systemic herpes simplex infections is 5 mg/kg every 8 h by slow infusion (over 1 h). In herpes zoster, 10 mg/kg every 8 h is advised. Orally, 200 mg every 4 h (five times daily) is effective and a remarkably safe treatment for severe vulvovaginal herpes simplex [10], for example.

Studies with aciclovir have shown that it is possible to suppress recurrences of herpes simplex by intermittent administration over a long period. This has given rise to concerns over the risk of drug resistance and this approach is really only indicated in a few patients with incapacitating recurrent attacks of infection [11].

Aciclovir is less effective against herpes zoster unless given in higher dosage (e.g. 10 mg/kg intravenously 8 hourly [12]. It is therefore mainly used for treatment of varicella-zoster infection in immunocompromised patients.

The main route of excretion is renal [13]. Side effects include elevation of blood urea and creatinine, which may rarely progress to acute renal failure. In patients with established renal impairment, lower doses are indicated. Although animal and human evidence shows no teratogenic activity, aciclovir is best avoided in pregnancy. Levels are reported to be higher in human milk than in serum when given during lactation.

Newer drugs related to aciclovir

These include famciclovir, penciclovir, ganciclovir and valaciclovir [14].

Famciclovir. This is well absorbed after oral administration. It is used at a dosage of 250–500 mg up to three times daily. At these dosages it appears to be as effective as the higher dose regimen of intravenous aciclovir and is well tolerated. There is also a lower frequency of post-herpetic neuralgia after its use.

Penciclovir. This is a promising treatment for severe herpes simplex infections and, because of its pharmacokinetic properties, is given less frequently than aciclovir.

Ganciclovir [15]. This is another deoxyguanosine analogue, which can be used in the treatment or prophylaxis of cytomegalovirus (CMV) infections. It is also active against other herpesviruses. Its use is generally reserved for CMV infections in severely immunocompromised patients when it is given in a starting dosage of 5 mg/kg/12 h intravenously. It can also be used as long-term suppressive therapy to prevent relapse. However, there is a high frequency of nephrotoxicity as well as metabolic disturbances such as hypokalaemia or hypocalcaemia.

Valaciclovir. This has a similar antiviral spectrum to aciclovir. It is mainly used for the treatment of herpes zoster infections (1000 mg for 7–14 days). It is also used for shorter periods (5 days) for herpes simplex infections [16].

Zidovudine (AZT, Retrovir®) [17]

AZT has been developed for the treatment of human retrovirus infections. Its principal site of action is the inhibition of virus-RNA-dependent DNA polymerase (reverse transcriptase) [18]. AZT is given by the oral route and the normal dosage is 250–500 mg/day; variations to this regimen and drug combinations are under assessment. The use of AZT in patients with AIDS or symptomatic HIV infections has been found to result in higher levels of circulating CD4 lymphocytes and, in some studies, a decrease in mortality over the short term. Treated patients are still infectious and the therapy does not cure the infection. It is currently used to treat HIV patients with CD4 counts lower than 500/mm^3 [19]. It has been suggested that AZT may benefit some skin complications of AIDS such as psoriasis. Administration of AZT to infected women in the second and third trimesters of pregnancy significantly reduces the risk of neonatal infection [20].

The main toxic side effects of zidovudine are neutropenia and anaemia, which occur in the majority of patients, particularly at higher doses. This is a particular problem in advanced disease. Other side effects include headache, myalgia and nausea. Progressive nail pigmentation has been described in black patients [21]. Resistance to AZT occurs regularly with long-term use.

Other antiretroviral agents

These include zalcitabine (DDC), a dideoxynucleotide analogue, and stavudine, which is a thymidine analogue. Both have been used for the treatment of patients with very low CD4 counts or where there is AZT resistance. Zalcitabine causes a painful neuropathy. Pancreatitis, rashes, ulceration and hepatitis have been described. Stavudine also causes a painful neuropathy.

Protease inhibitors

In order to circumvent the rising problem of drug resistance with antiretrovirals, a new family of drugs whose main focus of action is on the inhibition of aspartic proteases

encoded by retroviruses has been developed. These cleave the Gag and Gag-Pol proteins into smaller moieties needed for maturation. The main compounds are saquinavir, indinavir, ritonavir and nelfinavir but there are others in development. Most work by mimicking the transitional state that occurs during peptide bond cleavage by aspartic proteases. Generally, they are used in combination, usually with AZT or other reverse transcriptase inhibitors and/or further protease inhibitors to prevent viral replication and increase CD4 counts. These compounds differ in structure and in the specific sites inhibited [22–24]. At present, treatment using combinations of these drugs is known as highly active antiretroviral therapy (HAART), and successful maintenance therapy can be given for HIV-infected individuals. However, it is likely that resistance will ultimately develop.

Foscarnet phosphonoformate [25]

Foscarnet is a pyrophosphate analogue that inhibits herpesvirus polymerase. It is active against most herpesviruses including CMV. It also inhibits reverse transcriptase and has activity *in vitro* against HIV, particularly in combination with AZT. It is given intravenously in severe herpes simplex and CMV infections, or topically. It is an alternative drug for severe aciclovir-resistant herpes simplex infections and for this indication the usual initial treatment is 40 mg/kg every 8 h. Adverse effects include renal tubular damage, malaise, nausea and headache. Tremor and hallucination may occur at high dosage.

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Antiparasitic agents

Drugs that are used to treat parasitic infections which affect the skin include antibacterial agents such as metronidazole and co-trimoxazole as well as those with specific activity against parasites. This section is largely concerned with the latter group.

Drugs used to treat roundworms

The benzimidazoles. Mebendazole and albendazole are the best known of these compounds. Mebendazole (methyl 5-benzoylbenzimidazole-2 carbamate) is a synthetic drug that is active against diverse species such as *Ascaris*, *Enterobius* and *Trichuris* [1]. It is also active against the adult forms of *Trichinella spiralis* and some filariae such as *Loa loa*. It works through blocking the assembly of microtubules. It is poorly absorbed from the gastrointestinal tract. Adverse events are not common and are mainly seen at high dosage. The more common but trivial side effects are abdominal pain and diarrhoea.

Albendazole (methyl 5-*N*-propoxythio-2-benzimidazole carbamate) has broad-spectrum activity for parasites from *Ascaris* to *Trichuris* [2,3]. Albendazole is absorbed after oral administration but this is enhanced in the presence of a fatty meal. Once again it is well tolerated and abdominal pain and diarrhoea are the main side effects. Liver and bone marrow toxicity occur only at high dosage.

Tiabendazole is less used than previously. It is well absorbed and is active against a range of nematodes as well as some fungi. However, side effects such as nausea and vomiting are common.

Diethylcarbamazine

Diethylcarbamazine (DEC) is discussed in Chapter 32. It is a piperazine derivative used in the treatment of microfilariae [4]. It rapidly kills these microorganisms, an event that leads to considerable inflammation, which can cause damage in the eye and skin. It acts by affecting microfilarial muscle activity and affects their membranes, leading to increased host killing capacity. In onchocerciasis it can cause severe itching, oedema, erythema and hypotension—the DEC reaction. The dosage is usually built up from an initial 50-mg dose, depending on the infection.

Ivermectin

This is a macrocyclic lactone derived from avermectin B1, which is used for intestinal parasites in animals and for the management of onchocerciasis and other nematode infections [5–7]. It blocks the transmission of signals from interneurones to excitatory motor neurones. It is also effective against *Sarcoptes scabiei*. Its advantage in onchocerciasis is that it is microfilaricidal but does not lead to severe inflammatory responses. Ivermectin is well absorbed after oral administration. Side effects are not common but include fever, itching and headache. A mild DEC-like reaction may occur in some patients. Its usual dose is 150 µg/kg orally, repeated when necessary every 6–12 months.

Pentavalent antimony

The main variants used for the treatment of leishmaniasis are sodium stibogluconate and meglumine antimoniate. Neither is orally active and both have to be given parenterally (intramuscularly or intravenously) [8]. There is a slow elimination phase, which may give rise to toxicity at high dosage. Common adverse events include abdominal pain, nausea and headache [9]. Other effects are renal impairment, pancreatitis and alterations in electrocardiogram (ECG) and cardiac arrhythmias. In particular the Q–T interval may be prolonged.

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Drugs to improve the peripheral circulation

Raynaud's phenomenon and perniosis are the principal dermatological indications for systemic vasodilator therapy. Raynaud's phenomenon occurs in a primary, usually mild, form unassociated with systemic disease, or secondary to various underlying causes. The most common of these is connective tissue diseases; others include hyperviscosity disorders, cervical rib, drugs with a vasoconstrictor action and, rarely, occupational causes (see Chapter 23). The management of Raynaud's phenomenon has been extensively reviewed [1–4], and includes the use of calcium-channel blockers, angiotensin II receptor antagonists, prostacyclin analogues, serotonin antagonists, calcitonin gene-related peptides and newer agents such as endothelin-1 receptor antagonists and nitric oxide donors.

Calcium-channel blocking agents are of moderate benefit, and of these nifedipine is the treatment of choice [5,6]. It acts by inhibiting contraction of smooth muscle cells by reducing the cellular uptake of calcium, a process fundamental to vasospasm; it also reduces platelet aggregability. Modified release nifedipine 20–60 mg/day is usually effective. Diltiazem is also useful, but verapamil less so. Side effects include flushing, headaches and peripheral oedema. The response of primary Raynaud's phenomenon is usually more impressive than that secondary to connective tissue disease. Use of calcium-channel antagonists can occasionally precipitate erythromelalgia [7]. The angiotensin II receptor type 1 losartan has been recorded as useful in Raynaud's phenomenon [8].

Severe Raynaud's phenomenon (see Chapter 23), especially that secondary to systemic sclerosis and other connective tissue diseases, is more difficult to treat and may be poorly responsive to nifedipine. For these patients, intravenous prostacyclin or one of its stable analogues such as iloprost may be necessary [9–14]. Prostacyclin inhibits platelet adhesion and aggregation, and vascular smooth muscle proliferation, increases red cell deformability, and decreases blood viscosity. For reasons that are poorly understood, it causes sustained clinical benefit, a single low-dose infusion (0.5 ng/kg/min) often causing clinical remission for several weeks. Side effects include flushing, headaches and hypotension.

The serotonin antagonist ketanserin is not clinically beneficial [15], but fluoxetine, a selective serotonin-reuptake inhibitor, has been reported to be effective [16], as have dazoxiben, a thromboxane synthetase inhibitor

[17], and prazosin [18]. α-Adrenergic-blocking agents (e.g. thymoxamine, a non-selective α-adrenoceptor blocker) 40 mg three times daily, or prazosin, a selective α-adrenergic-blocking agent, 0.5–1.0 mg three times daily, may suffice in mild cases. The use of intravenous calcitonin gene-related peptide (CGRP) has been recommended for severe Raynaud's phenomenon [19]. CGRP, which was given in a dosage of 0.6 μg/min for 3 h/day on 5 consecutive days, causes flushing, diarrhoea, headache and hypotension.

Perniosis also responds well to calcium-channel antagonists. A double-blind cross-over placebo-controlled study of nifedipine in 10 patients [20] showed a convincing response in the nifedipine phase of the trial. Other drugs reported anecdotally to improve the peripheral circulation include oxpentifylline (pentoxifylline), fibrinolytic agents including stanozolol, and low-molecular-weight dextran infusion.

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Miscellaneous drugs used in special ways in dermatology

Antimalarials

A variety of drugs have been used in the treatment of malaria. However, for over 35 years it has been well known that several of these drugs may have other useful properties in the management of skin diseases [1,2]. There are several diseases where there is an undoubted beneficial effect: discoid and systemic lupus erythematosus, polymorphic light eruption and solar urticaria (see Chapters 56 and 24). They are of some value in rheumatology, where there is a resurgence of their use, as well as their more obvious application in diseases caused by some protozoa. Their use in porphyria cutanea tarda and sarcoidosis is discussed elsewhere (see Chapters 57 and 58).

The mode of action of antimalarials is complex and their usage is largely on empirical grounds. They can interfere with many biological processes. They bind to DNA, stabilize membranes, inhibit hydrolytic enzymes, interfere with prostaglandin synthesis and block chemotaxis [1,2].

The major problem with chloroquine is retinopathy and potential blindness [3,4]. There are considerable problems in defining the criteria for the diagnosis of retinopathy and the estimate that 3–5% of patients who receive the drug may develop this complication is almost certainly too high. A number of questions remain unanswered. It is generally agreed that the risk to the retina of giving chloroquine sulphate 250 mg/day for 3 months is virtually negligible, although the drug is cumulative to some extent from one year to another. It has long been thought that it is the total cumulative dose that determines the retinal toxicity. It has been suggested that it is the daily dose that counts and that 4 mg/kg/day chloroquine is likely to be safe [5].

Because of the potential retinopathy with chloroquine, hydroxychloroquine or mepacrine are the two antimalarial drugs now used. Hydroxychloroquine is more effective than mepacrine but is said to have some ocular toxicity, albeit less than with chloroquine. It is likely that in the dosage used by dermatologists (up to 400 mg/day) the risk of ocular toxicity is negligible. In many hospitals, the ophthalmologists will not agree to screen or monitor patients as they think the risk is so small, but if hydroxy-

chloroquine is continued for more than a few months it would seem prudent to obtain ophthalmological screening, which should also be sought before starting treatment. Mepacrine lacks ocular toxicity, and is often an effective drug, especially in discoid lupus erythematosus and Hutchinson's chilblain lupus. In effective dosage (200 mg/day), it usually causes the skin to turn yellow and occasionally produces lichenoid reactions. Ocular toxicity of antimalarials as used in dermatology is well reviewed by Cox and Paterson [6].

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Dapsone and sulfapyridine [1–5]

Dapsone (DDS) has been the mainstay in the treatment of leprosy for many years (see Chapter 29). It also has some action against malaria and other parasites, and has also proved a very valuable drug in the management of a wide range of mainly uncommon dermatoses. Its mode of action is not fully understood. Although many of the diseases found empirically to respond to this drug have in common the involvement of either polymorphs or immune complexes, the metabolic action of dapsone cannot be explained simply in these terms. The diseases for which dapsone is particularly effective are dermatitis herpetiformis and erythema elevatum diutinum. Other diseases also favourably but not invariably influenced include other bullous diseases (pemphigoid, mucous membrane pemphigoid, linear IgA disease, chronic bullous disease of childhood, bullous eruption of systemic lupus erythematosus, subcorneal pustular dermatosis), pyoderma gangrenosum, rheumatoid arthritis and collagen diseases, relapsing polychondritis, acne conglobata, leukocytoclastic vasculitis and granuloma faciale.

Toxicity is a considerable problem with dapsone but overall the drug has probably fewer long-term side effects than do corticosteroids or sulfapyridine. The main toxic side effect is haemolysis, which is not usually dependent on glucose-6-phosphate dehydrogenase deficiency, although that enzyme defect may compound the problem. Some haemolysis is almost invariably found on therapeutic dosage. Methaemoglobinaemia is also common and is responsible for the bluish lips commonly seen in patients on this drug. A level of 3% methaemoglobinaemia is often unnoticed, 12% may be acceptable, but 20% is usually not. Regular blood checks of haemoglobin and reticulocytes but also including white cells and platelets should therefore be undertaken in all patients for the first few months after starting dapsone. Dapsone has several other but less common side effects, including agranulocytosis, peripheral neuropathy, drug rashes, renal damage, hypoalbuminaemia, cholestasis, psychoses and reversible male infertility. A dosage of 100 mg/day is often used as a starting dose. Many patients with dermatitis herpetiformis can be controlled on very much less. Some diseases can only be controlled by larger doses, but the incidence of side effects then rises very sharply and most dermatologists prefer not to exceed a dosage of 100–150 mg/day. It is possible to reduce dapsone-dependent methaemoglobinaemia by the concomitant administration of cimetidine (400 mg three times daily) [6].

Other drugs that share some of the useful assets of dapsone include sulfapyridine and, to a lesser extent, sulfamethoxypyridazine. Sulfapyridine is in general less effective than dapsone and, in doses that are effective, tends to cause more side effects, especially marrow suppression, although not haemolysis. The usual dose is 0.5 g twice or three times daily.

Clofazimine

This antileprotic drug has also been used especially in pyoderma gangrenosum and in lupus erythematosus and Sweet's disease.

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Sulfasalazine

This drug is best known for its activity in inflammatory bowel disease and rheumatoid arthritis with their associated skin problems. The mode of action is uncertain [1,2]. It is not very well absorbed from the gut and does have side effects. Among other activities it may be a 5-lipoxygenase inhibitor. It has been found to be of some value in pustular psoriasis, arthropathic psoriasis and psoriasis vulgaris [1–5]. Its use in other conditions such as dermatitis herpetiformis, scleroderma and acne [6] has been recommended but is less well established. Sulfasalazine

has been reported to be useful in metastatic cutaneous Crohn's disease [7,8]. A recent report suggested benefit in a minority of patients with alopecia areata [9].

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Thalidomide

Thalidomide is an interesting drug but it is linked with the causation of severe birth defects, so that its use is very restricted, and it must never be given to pregnant women. It also has other toxic side effects, notably peripheral neuropathy [1–3]. It can be helpful in severe leprosy reactions (see Chapter 29). It may also be beneficial in some but by no means all patients with nodular prurigo [4], lupus erythematosus [5–7], actinic prurigo and other light-sensitive dermatoses, aphthosis [8], Behçet's disease, Weber–Christian disease, pyoderma gangrenosum, sarcoidosis, graft-versus-host disease, adult Langerhans' cell histiocytosis [9] and certain dermatological conditions associated with HIV infection [10]. It is a drug the use of which must always be kept under the strictest control and it must be used only by patients who are able to understand the problems. It is important to check regularly for peripheral neuropathy. Guidelines for the clinical use and dispensing of thalidomide have been drawn up [11–13].

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Colchicine [1–3]

Colchicine has been used in the treatment of gout for many centuries and is still a valuable remedy. It is also of use in familial Mediterranean fever. It has an antimitotic action (for which it is sometimes used topically) but its useful anti-inflammatory effects in skin diseases probably depend more on its suppression of various aspects of polymorph activity, notably chemotaxis. It may also inhibit histamine release from mast cells. Its use is somewhat restricted by its side effects, especially those on the gastrointestinal tract, but the bone marrow and kidney may also be affected. It should be avoided in pregnancy. It is not therefore a first-line drug but can prove of value in Behçet's disease [4], chronic bullous dermatosis of childhood (linear IgA disease) [5], pustular psoriasis [6], relapsing polychondritis [7], leukocytoclastic vasculitis, urticarial vasculitis [8], epidermolysis bullosa acquisita [9] and Sweet's syndrome—all diseases in which polymorphs are presumed to have a role. A common regimen is 0.5–1 mg/day orally, although larger doses are used by rheumatologists.

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Traditional Chinese herbal medicine

The treatment involves taking a 'tea' prepared from a decoction of plant materials. Usually 10 or so plant materials are included. Trials have also been performed using a tablet form of treatment (Zemaphyte®) and showed a beneficial response in children [1] and adults [2] with atopic eczema. Even when treatment is effective and continued, the benefit often wears off after 6–12 months. Relapses occur once treatment is stopped. Of concern are the reports of hepatotoxicity [3–6] and renal toxicity [7] potentially associated with Chinese herbal remedies. While Chinese herbs cannot yet be recommended for the routine treatment of children with atopic eczema, they did help approximately half of the children who took part in the Great Ormond Street Hospital Trial [8]. Further adequate randomized controlled trials are necessary [9]. Chinese herbs have also been advocated for psoriasis [10].

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Transdermal delivery systems

The blood is the target for penetration in transdermal delivery systems. There are two major routes for drug penetration through skin: the stratum corneum, and shunts via hair follicles and eccrine sweat gland ducts [1].

With drugs metabolized in the liver, achievement of therapeutic blood levels is enhanced by transdermal delivery because the 'first pass' effect inherent in oral administration is avoided. Thus, transdermally delivered drugs show reduced differences in 'peak' and 'trough' blood levels, and a different profile of metabolites [2]. Efficiency of transdermal delivery is greater with lipid-soluble drugs. Additional advantages include ability to use short half-life drugs, better patient compliance, reduced dosage frequency, avoidance of unpredictable intestinal absorption and gastric irritation, and fewer complications.

Recent examples of drugs marketed in a transdermal form include scopolamine, clonidine, nitroglycerine, estradiol, nicotine and prostaglandin E1 ethyl ester for the treatment of trophic acral skin lesions in systemic scleroderma [3]. Within the transdermal 'patch', the drug, which may be formulated in a liquid, solid, ointment or cream form, behaves as a reservoir. The blood levels are proportional to the active surface area of the 'patch', and drug delivery occurs over a period of 1–7 days. Skin irritation and sensitization are significant difficulties with transdermal delivery systems, which contain several sources of problems besides the drug itself, including the adhesive, vehicle penetration enhancers and polymers. More advanced transdermal delivery systems are now available that should enable continuous or pulsed delivery of new drugs including genetically engineered products [3].

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Chapter 73

Drug Reactions

S.M. Breathnach

Introduction [1–4]

A drug may be defined as a chemical substance, or combination of substances, administered for the investigation, prevention or treatment of diseases or symptoms, real or imagined. The distinction between drugs and 'other chemicals' is not always easily made, as chemicals of very diverse structure are increasingly added to foods and beverages as dyes, flavours or preservatives. Such chemicals may cause harmful side effects. Moreover, chemicals used in agriculture or in veterinary medicine may contaminate human food. In addition, with the advent of therapeutic agents that may be useful for improving the appearance, as with minoxidil for androgenetic alopecia and tretinoin for photo-aged skin, the distinction between drugs and cosmetics has become blurred [5].

An adverse drug reaction (ADR) may be defined as an undesirable clinical manifestation resulting from administration of a particular drug; this includes reactions due to overdose, predictable side effects and unanticipated adverse manifestations. Another definition is that of 'an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product' [6]. It has been proposed that therapeutic ineffectiveness should also be regarded as an ADR [7]. ADRs may be said to be

the inevitable price we pay for the benefits of modern drug therapy [8]. They are costly both in terms of the human illness caused and in economic terms, and can undermine the doctor–patient relationship.

Sometimes, ADRs result from human error [9]. In one study, 0.9% of 530 medication errors resulted in ADRs [10]; these usually involved errors at the ordering stage, but also occurred at the administration stage [11]. In hospitals, medication errors occur at a rate of about one per patient per day; dispensing errors made by pharmacy staff range from 0.87 to 2.9% [12]. ADRs are under-reported and are an underestimated cause of morbidity and mortality; it has been estimated that ADRs represent the fourth to the sixth leading cause of death [13]. The actual frequency of fatal adverse drug events is unknown; estimates in the USA are as high as 140 000/year, although this number is heavily disputed [14]. In one study, 68% of fatal ADRs were judged to have been preventable; of these, a pharmacist could have prevented 57% [15]. Approximately 1 in 2000 of all deaths for which there were records of coroner's inquests in one district were related to drugs; of these, 20% were due to errors [16]. During 1995, 206 deaths were attributed to ADRs on death certificates in the USA, but the spontaneous post-marketing surveillance system (MedWatch) of the Food and Drug Administration (FDA) tabulated 6894 fatalities. The numbers of deaths in these datasets varied 34-fold and were up to several 100-fold less than values based on extrapolations of surveillance programmes [17]. Confusion may occur between drugs with similar spelling of their brand names [18,19]. It has been proposed that licensing authorities should exercise more control over the naming of new proprietary formulations, that non-proprietary and new proprietary names should be internationalized, and that doctors should issue printed prescriptions if possible [20].

The average extra length of stay for patients with an adverse drug event in one study in the USA was 1.9 days, and the average extra cost of hospitalization was $1939 [21]. In another study, at a university-affiliated hospital, the mean cost of an ADR or medication error varied from $95 for additional laboratory tests to $2640 for intensive care; the estimated total cost for the medication-related problems reported in 1994 was almost $1.5 million [22]. In a European study, ADRs occurred at 10.1 per 1000 patient-days, and the cost of ADRs leading to hospitalization was estimated at €11 357 per hospital bed per year [23]. Another estimate of the cost of an ADR during hospitalization or leading to hospitalization was approximately €2800 [24]. Litigation was reported for 14% of fatal ADR cases at one centre; judgements and settlements averaged $1.1 million [15]. Drug reactions, principally to corticosteroids and methotrexate, accounted for 32% of claims and 26% of dollar losses in dermatology malpractice suits in the USA from 1963 to 1973 inclusive [25]. Medication side effects, most frequently to corticosteroids, antibiotics and chemotherapeutic agents, represented 26% of lawsuits in a study of dermatology residency programmes in the USA between 1964 and 1988 [26]. If legal consequences are to be avoided, consistent care is needed at every stage from drug manufacture to administration [27].

It is in everyone's interests to minimize the chances of their occurrence, and to this end government regulatory bodies and the pharmaceutical industry collaborate to ensure adequate screening of new products. In addition to extensive *in vitro* and animal testing, prolonged and strictly controlled clinical trials are essential. Even so, hazards cannot be completely eliminated, for a serious reaction of low incidence may not be suspected until a very large number of patients have been treated with a new drug. Premarketing clinical trials conducted before a new drug is licensed will not identify adverse reactions occurring in less than 0.1–1% of patients, or those occurring only after prolonged administration, or with a long latency period, or only in susceptible patients, or when the drug is combined with some other factor, such as another drug [28,29].

Another problem is that only a very small fraction of all adverse reactions are ever reported to monitoring agencies, and first warning is still often given by anecdotal reports published in medical journals [30,31]. Many of these reports are subsequently validated but a substantial proportion of poorly documented reports are not [31,32]. In an analysis of 5737 articles from 80 countries between 1972 and 1979, only half the reports contained enough information for the calculation of the frequency of a particular reaction [32]. The usefulness of anecdotal case reports has again been called into question [33]. As incorrect reports may have serious legal and other consequences, a heavy responsibility rests with medical editors; a chance association or coincidental reaction should not be allowed to enter the literature. Criteria for assessment of potential drug reactions have been promulgated and include recurrence on challenge; existence of a pharmacological basis for the reactions; the occurrence of immediate acute or local reactions at the time of administration, of previously known reactions with a new route of administration, or of repeated rare reactions; and the presence of immunological abnormalities [31,34]. In the assessment of an unrecorded new reaction, the existence of similar but unpublished reports to the manufacturer or to the Committee on Safety of Medicines is of particular importance.

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Incidence of drug reactions [1,2]

Data collection

It is difficult to obtain reliable information on the incidence of drug reactions, despite attempts at monitoring by government and the pharmaceutical industry. One problem is the lack of standardized coding for drug reactions [3]. Moreover, the information that is available must be interpreted with considerable care, because data will be biased, depending on the method of collection [1,2]. Thus, data on medical in-patients, especially from acute care facilities, may indicate a relatively high incidence, because these patients are generally sicker and receive more intensive drug treatment. In contrast, spontaneous reporting may underestimate the true incidence [4]. National schemes for collating reported ADRs exist in many countries, and the World Health Organization's Adverse Reaction Collaborating Centre, in Uppsala, provides a very large database [2], as does the Adverse Event Reporting System of the US FDA [5,6]. The UK's 'yellow card' reporting scheme solicits ADR reports from doctors, dentists, coroners, and drug manufacturers; the wide availability of reporting forms is important in encouraging reporting [2]. The scheme has recently encouraged reporting by nursing staff, midwives and health visitors [7]. Yellow reporting cards may be obtained electronically on http://www.mca.gov.uk/yellowcard. Pharmacists also play an important role in reporting ADRs [8]. The advisability of direct reporting of ADRs by patients is becoming an increasingly important topic for discussion in the world of pharmacovigilance [9]. 'Pharmacovigilence' in France, which involves reporting to regional centres, along with most other national schemes, also relies entirely on spontaneous reporting [10,11]. Institution of an ADR reporting project in Rhode Island in the USA increased the rate of reporting of such reactions more than 17-fold over a 2-year period [12]. The quality of ADR reporting to the FDA improved following introduction of the MedWatch scheme [13]. Specialty-based systems for spontaneous reporting of ADRs (e.g. the Adverse Drug Reaction Reporting System of the American Academy of Dermatology [14] and the Gruppo Italiano Studi Epidemiologici in Dermatologia [15]) have been introduced. In the UK, in contrast, the speciality-based Cutaneous Reactions Database established at the Institute of Dermatology in 1988 was unfortunately closed in 1990 because of a meagre response [16].

Reporting of ADRs in clinical trials is neglected, compared with efficacy outcomes; of 192 randomized trials analysed, only 46% specified reasons for withdrawals due to toxicity, and only 39% of clinical adverse effects and 29% of laboratory-determined toxicity were adequately documented [17]. Inherent difficulties with spontaneous reporting are that reactions associated with newly marketed drugs, those of unusual morphology, and reactions starting soon after initiation of therapy are more likely to be notified; at best only a crude estimate of true incidence is provided [18–20]. Thus, drugs with a high potential for eliciting clinically significant ADRs are usually detected and either withdrawn from the market or placed on

restricted use within the first year or two of marketing [21]. In contrast, spontaneous reports do not reliably detect ADRs widely separated in time from the original use of the drug, or that occur more commonly in populations not usually exposed to the drug [22]. They are an unreliable measure of risk, and may simply provide evidence of the relative awareness among physicians of specific toxic effects [23].

All national spontaneous reporting systems are compromised by under-reporting [2,4]; in the UK, surveys suggest that only around 10% of serious reactions are notified to the Committee on Safety of Medicines [24,25]. A survey of 44 000 patients receiving one or other of seven new drugs suggested that under-reporting by the spontaneous system may be as high as 98% when compared with information collected by the more objective 'event monitoring' system [10]. Heavy prescribing by a minority of doctors immediately following licensing may place patients at unnecessary risk, and affects safety monitoring of new drugs; the 10% of doctors who prescribed most heavily accounted for 42% of total prescribing in a survey of 28 402 general practitioners asked to supply post-marketing data on 27 new drugs dispensed in England between September 1984 and June 1991, but returned proportionately far fewer questionnaires [26]. Reasons for under-reporting include lack of time, lack of report forms and the misconception that absolute confidence in the diagnosis of an adverse reaction was important [27]; workload may affect reporting [28]. Another factor is the perceived deterrent to reporting ADRs caused by fear of involvement in litigation [29]; reporting of errors should be free of recrimination [30]. The offer of a small fee increased the rate of reporting in one hospital study almost 50-fold [31].

Pharmacoepidemiology, the epidemiological assessment of adverse drug effects, and pharmacovigilance, the process of identifying and responding to safety issues about marketed drugs, necessitate making use of information from clinical trials, spontaneous reporting systems, specialty-based reporting systems, case reports, prescription monitoring, case series, cohort studies, case–control studies, population-based registries using computerized material, and special surveillance programmes (e.g. Boston Collaborative Drug Surveillance Program in the USA) [32–34]. Crude inspection of lists of spontaneously reported drug-event combinations can be supplemented by quantitative and automated numerator-based methods such as Bayesian data mining; pharmacovigilance specialists should not be intimidated by the mathematics [35]. Computerized detection of adverse events may soon be practical on a widespread basis [36]. This is just as well, as it has been estimated that the top 20 drug companies will each need to launch four to six times the number of drugs they currently produce merely to maintain shareholder returns, with more trials, and more safety reports for evaluation [37].

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General incidence of adverse drug reactions

The incidence of ADRs varies from 6% [1] to 30% [2], with at least 90 million courses of drug treatment given yearly in the USA [3]. The reported percentage of patients who develop an ADR during hospitalization varies markedly in different studies from 1.4 to 44%, although in most studies the incidence is about 10–20% [4–6], of which about one-third are allergic or pseudoallergic [6]. In one study, 0.23% of a total of 90 910 admissions had drug allergy; antimicrobials and antiepileptic drugs comprised 75% of the drug allergies reported [7]. The incidence of drug allergy in hospitalized patients was 4.2 per 1000; drug allergy developed during in-patient treatment in 2.07 per 1000 hospitalizations [7]. About 3–8% of hospital admissions are a consequence of ADRs [8–10]. A survey of 30 195 randomly selected hospital records in 51 hospitals in the state of New York found that 19% of adverse events caused by medical treatment were the result of drug complications; the most frequently implicated classes of drugs were antibiotics, antitumour agents and anticoagulants [11]. Negligence accounted for 18% of ADRs, while allergic/cutaneous complications constituted 14% of all drug-related complications.

Less information is available about the incidence among outpatients. It has been estimated that about 1 in 40 consultations in general practice is the result of ADRs [12], and eventually 41% of patients develop a reaction [13]. In one multicentre general practice study in the UK, the percentage of consultations involving an ADR increased from 0.6% for patients aged 0–20 years to 2.7% for patients aged over 50 years [14]; in another study, 2.5% of consultations were the result of iatrogenic illness [15].

Fatal reactions to drugs are more common than is generally realized. It was previously estimated that penicillin caused 300 deaths each year in the USA alone [16]. Anaphylactic reactions to penicillin were reported in 1968 to occur in about 0.015%, and fatal reactions in up to 0.002% (i.e. 1 per 50 000), of treatment courses [17]. These figures may be somewhat less today, with use of newer β-lactam antibiotics. The risk of fatal aplastic anaemia with chloramphenicol therapy was reported as at least 1 in 60 000 [18], and the risk of a fatal outcome from treatment with monoamine oxidase inhibitors may be of the same order. It has been estimated that the incidence of fatality as a result of a drug reaction among in-patients is between 0.1 and 0.3% [5,19,20]; fatality due to allergy occurs at a rate of 0.09 per 1000 cases [7].

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Risk of adverse drug reactions among different patient groups

Certain patient groups are at increased risk of developing an ADR. Women are more likely than men to develop ADRs [1]. The incidence of such reactions increases with the number of drugs taken in both hospital in-patients [2–4] and outpatients [5,6]. Although data are somewhat conflicting [7], the burden of evidence suggests that the incidence of adverse reactions increases with patient age [1,8,9]. Although those over 65 years of age comprise only 12% of the population in the USA, 33% of all drugs are prescribed for this age group, and the elderly have a significantly higher incidence of ADRs, related to decreased organ reserve capacity, altered pharmacokinetics and pharmacodynamics, and polypharmacy [10]. Similarly, in

the UK the elderly are dispensed twice as many prescriptions as the national average [11]. Potential adverse drug interactions are more common in elderly patients because of the higher number of concurrent medications, rather than age-based factors [12].

ADRs contribute to the need for hospitalization in 10–17% of elderly inpatients [13–15]. Inappropriate medication is a major cause of ADRs in elderly patients; 27% of elderly patients on medication admitted to a teaching hospital experienced ADRs, of which almost 50% were due to drugs with absolute contraindications and/or that were unnecessary [16]. ADRs occur in 6–17% of children admitted to specialist paediatric hospitals [17].

Patients with Sjögren's syndrome (SS) have also been reported to have a high frequency of drug allergy. In different series, drug allergy has been reported in 43% of SS patients compared with 9% of patients with systemic lupus erythematosus (SLE) without SS [18], in 62% of SS patients [19], and in 41% of rheumatoid arthritis patients with SS compared with 17% of those without SS [20]. Antibiotic allergy is increased in SLE [21].

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Acquired immune deficiency syndrome

Patients with acquired immune deficiency syndrome (AIDS) appear to be at increased risk for ADRs [1–7], up to 100-fold by some estimates [7]. The reasons are likely to be multifactorial, and include changes in drug metabolism, oxidative stress, cytokine profiles and immune hyperactivation. Human immunodeficiency virus (HIV)-positive individuals have been postulated to have a systemic glutathione deficiency, resulting in a decreased capacity to scavenge reactive hydroxylamine derivatives of sulphonamides, although this has been disputed (see pharmacogenetic mechanisms of drug reactions, p. 73.13). In the past, drugs especially implicated included sulphonamides such as co-trimoxazole (trimethoprim–sulfamethoxazole) [8–14], other sulphur congeners, for example dapsone [15], pentamidine, antituberculosis regimens containing thioacetazone (thiacetazone) [16,17] or isoniazid and rifampicin, amoxicillin–clavulanate [18,19], clindamycin, pyrimethamine [20] and thalidomide. Patients with AIDS are more likely to have particularly severe reactions, ranging from erythema multiforme to toxic epidermal necrolysis (TEN) (especially with sulphonamides, clindamycin, phenobarbital (phenobarbitone) and chlormezanone) [21,22], and to demonstrate multiple cutaneous drug reactions [3] (see Chapter 74). Drugs that are implicated in hypersensitivity have changed since the advent of highly active antiretroviral therapy, including abacavir, non-nucleoside reverse transcriptase inhibitors such as nevirapine, and protease inhibitors such as amprenavir [7]. There has been a decrease in the use of antimicrobials such as co-trimoxazole, and in Europe nevirapine has replaced sulphonamides as the leading cause of Stevens–Johnson syndrome and TEN related to AIDS [23] (see also Chapter 74).

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Drug reaction frequency in relation to types of medication

The incidence of reactions to a particular drug must obviously be related to the quantity prescribed [1]. Nearly one in every 10 prescriptions in the USA in 1981 contained either hydrochlorothiazide or codeine [2]. One in every five prescriptions was for a diuretic or other cardiovascular drug; analgesics and antiarthritics constituted 13%, anti-infectives 13%, and sedatives and other psychotropics 11% of prescriptions. Of the 10 drugs most frequently reported by the yellow-card system to the UK Committee on Safety of Medicines in the first 6 months of 1986, seven were non-steroidal anti-inflammatory drugs (NSAIDs) (accounting for 74% of serious adverse reactions); the remaining drugs were the angiotensin-converting enzyme (ACE) inhibitors enalapril and captopril (accounting for 19% of serious reactions) and co-trimoxazole (accounting for 7% of serious adverse reactions) [3]. In another study, anti-inflammatory agents were the drugs responsible for almost 50% of the reactions necessitating admission to a general medical ward; most of the drug-related admissions to the hospital as a whole were caused by digoxin, phenytoin, tranquillizers, antihypertensives, cardiac depressants and antineoplastic agents [4]. ADRs accounted for 8% of 1999 consecutive admissions to medical wards in yet another study [5]; the drugs most frequently involved were antirheumatics and analgesics (27%), cardiovascular drugs (23%), psychotropic drugs (14%), antidiabetics (12%), antibiotics (7%) and corticosteroids (5%). Nitrofurantoin and insulin were associated with admission rates of 617 and 182 per million daily doses, compared with 10 for diuretics and seven for benzodiazepines. ADRs were responsible for the admission of 2% of 5227 consecutive patients to the University Hospital Centre in Zagreb [6]; drugs incriminated included acetylsalicylic acid (aspirin) (38%), other NSAIDs (23%), cardiovascular agents (20%) and antimicrobials (3%).

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Incidence of drug eruptions (adverse cutaneous drug reactions)

Drug eruptions are probably the most frequent of all manifestations of drug sensitivity, at 24% of all ADRs in one study [1], although their incidence is difficult to determine. Even where the eruption is apparently the only manifestation, death can result from exfoliative dermatitis, erythema multiforme or TEN. For information on the incidence of drug-induced erythema multiforme, Stevens–Johnson syndrome and TEN, the reader is referred to Chapter 74. Epidemiological data suggest that a relatively small number of drugs are responsible most often for the most serious reactions [2]. Cutaneous reactions to common drugs such as digoxin, antacids, paracetamol (acetaminophen in the USA), glyceryl trinitrate, spironolactone, meperidine, aminophylline, propranolol, prednisone, salbutamol and diazepam are very rare.

The baseline rate of rash development, reflecting a variety of different causes, was similar for 36 marketed drugs

in the UK, at around 1 per 1000 patients per month from the second to the sixth month of one study; however, the rate for rash in the first month after prescription varied substantially from 0.9 to 6.4 per 1000 patients per month, and was highest for diltiazem [3]. Most estimates of the incidence of drug eruptions are inaccurate, because many mild and transitory eruptions are not recorded and because skin disorders are sometimes falsely attributed to drugs. There have been several studies of the incidence of drug eruptions [3–13]. The reaction rate has been reported as about 2% [6,9], or 5.5 adverse skin reactions per 100 000 of the population in four Italian regions [10].

A survey [8] of adverse cutaneous drug reactions (ACDRs) among in-patients found that one-third were fixed drug reactions, one-third were exanthematous and 20% were urticaria or angio-oedema; the high frequency of fixed drug reactions in this series reflects the fact that patients under study had been admitted to hospital. Antimicrobial agents were most frequently incriminated (42%), then antipyretic/anti-inflammatory analgesics (27%), with drugs acting on the central nervous system accounting for 10% of reactions. A few drugs gave specific reactions (e.g. phenazone salicylate caused a fixed eruption, and penicillin and salicylates caused urticaria); however, most were capable of causing several types of eruption. Morbilliform exanthematous eruptions, urticaria and generalized pruritus were the commonest reactions in other large series [9,13]. The average patient had received eight different medications, which contributed considerably to the difficulties in identifying the causative drugs [9]. Antibiotics, blood products and inhaled mucolytics together caused 75% of the eruptions; amoxicillin (51 cases/1000 exposed), trimethoprim–sulfamethoxazole (33 cases/1000 exposed) and ampicillin (33 cases/1000 exposed) caused the most reactions. Reaction rates varied in the range of 1–8% for several classes of antibiotic [13]. In a study of ACDRs among children and adolescents in northern India, antibiotics were responsible for most eruptions, followed by antiepileptics; co-trimoxazole was the commonest antibacterial culprit, followed by penicillin and its semi-synthetic derivatives, and then sulphonamides, with antiepileptics being the most frequently incriminated drugs in erythema multiforme, Stevens–Johnson syndrome and TEN [11]. A more recent study from India found that the drugs most often incriminated included antimicrobials (especially sulphonamides), anticonvulsants and NSAIDs [12]. Antimicrobials, NSAIDs, analgesics and radiological contrast media were the most frequent culprits in a study from Italy [10], and the most common drug classes involved in yet another study were cardiovascular agents (36%), contrast media (20%), drugs affecting blood clotting (13%) and anti-infectives (14%) [1].

Desensitizing vaccines, muscle relaxants, intravenous anaesthetics and radiological contrast media were the most frequent causes of anaphylaxis or anaphylactoid reactions reported to the UK Committee on Safety of Medicines in 1986/1987 [14]. The chairman of the Committee accordingly advised in 1986 that desensitizing vaccines only be given where full cardiorespiratory resuscitation facilities are available. Quinidine, cimetidine, phenylbutazone, hydrochlorothiazide (especially in combination with amiloride) and furosemide (frusemide) have also been frequently implicated in drug eruptions [15,16]. In the USA and the UK, antibiotics, hypnotics and tranquillizers are the most frequent offenders; on a reaction per dose basis, penicillin, warfarin and imipramine are the three drugs most frequently incriminated [17]. The prevalence of a history of penicillin allergy in the US population has been estimated to be between 5 and 10% [18]. An international study of 1790 patients from 11 countries documented the frequency of allergic reactions to long-term benzathine benzylpenicillin (benzathine penicillin) prophylaxis for rheumatic fever at 3.2%; anaphylaxis occurred in 0.2% (1.2/10 000 injections) and the fatality rate was 0.05% (0.31/10 000 injections) [19]. Reactions to sulphonamides may affect up to 5% of those treated [20]. Rashes occurred in 7.3% of children given commonly used oral antibiotics [21]. Based on the number of patients treated, the frequency of rash with cefaclor was 12.3%, with penicillins 7.4%, with sulphonamides 8.5%, and with other cephalosporins 2.6%.

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Classification and mechanisms of drug reactions [1–11]

Drug reactions may arise as a result of immunological allergy directed against the drug itself, a reactive metabolite or some contaminant of the drug or, more commonly, by non-immunological mechanisms, such as pseudoallergic reactions caused by non-immune-mediated degranulation of mast cells and basophils. Autoimmune reactions, in which the drug elicits an immune reaction to autologous structures, may also occur. Drug reactions may be predictable (type A) or unpredictable (type B) (Table 73.1). About 80% of drug reactions are predictable, usually dose related, are a function of the known pharmacological actions of the drug and occur in otherwise normal individuals. Side effects are unavoidable at the regular prescribed dose. Unpredictable reactions are dose independent, are not related to the pharmacological action of the drug, and may have a basis in pharmacogenetic variation in drug bioactivation and drug or metabolite detoxification or clearance. Intolerance refers to an expected drug reaction occurring at a lower dose, and idiosyncratic and hypersensitivity reactions are qualitatively abnormal unexpected responses. Type C reactions include those associated with prolonged therapy (e.g. analgesic nephropathy), and type D reactions consist of delayed reactions (e.g. carcinogenesis and teratogenicity). The skin has a limited repertoire of morphological reaction patterns in response to a wide variety of stimuli, and it is therefore often impossible to identify an offending drug, or the pathological mechanism involved, on the basis of clinical appearances alone. We therefore remain relatively ignorant about the mechanisms underlying many clinical drug eruptions.

Table 73.1 Classification of adverse drug reactions.

Non-immunological
Predictable
Overdosage
Side effects
Cumulation
Delayed toxicity
Facultative effects
Drug interactions
Metabolic alterations
Teratogenicity
Non-immunological activation of effector pathways
Exacerbation of disease
Drug-induced chromosomal damage
Unpredictable
Intolerance
Idiosyncrasy
Immunological (unpredictable)
IgE-dependent drug reactions
Immune complex-dependent drug reactions
Cytotoxic drug-induced reactions
Cell-mediated reactions
Miscellaneous
Jarisch–Herxheimer reactions
Infectious mononucleosis–ampicillin reaction

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Non-immunological drug reactions

Overdosage

The manifestations are a predictable exaggeration of the desired pharmacological actions of the drug, and are directly related to the total amount of drug in the body. Overdosage may be absolute, as a result of a prescribing or dispensing error or due to deliberate excess intake by the patient. It may also occur despite standard dosage due to varying individual rates of absorption, metabolism or excretion (see below). An inappropriately large dose may be given to an infant or very old person or to one with renal impairment. Drug interaction (see below) may also cause drug overdosage.

Side effects

These include unwanted or toxic effects, which are not separable from the desired pharmacological action of the drug. Examples are the drowsiness induced by antihistamines; the atropine-like anticholinergic properties of some phenothiazines, many antihistamines, and tricyclic antidepressants; and the anagen alopecia caused by cytotoxic drugs.

Cumulative toxicity

Prolonged exposure may lead to cumulative toxicity. Accumulation of drugs in the skin may lead to colour disturbance, as a result of either deposition within phagocytic cells or mucous membranes (e.g. prolonged administration of gold, silver, bismuth or mercury) or binding of the drug or a metabolite to a skin component (e.g. high-dose chlorpromazine therapy).

Delayed toxicity

Examples are the keratoses and skin tumours that appear many years after inorganic arsenic, and the delayed hepatotoxicity associated with methotrexate therapy.

Facultative effects

These include the consequences of drug-induced alterations in skin or mucous membrane flora. Antibiotics that destroy Gram-positive bacteria may allow the multiplication of resistant Gram-negative species. Broad-spectrum antibiotics, corticosteroids and immunosuppressive drugs may promote multiplication of *Candida albicans* and favour its transition from saprophytism to pathogenicity. Corticosteroids promote the spread of tinea and erythrasma. Antibiotics such as clindamycin and tetracycline may be associated with pseudomembranous enterocolitis following bowel superinfection with *Clostridium difficile*.

Drug interactions

Interactions between two or more drugs administered simultaneously may occur before entry into the body (in an intravenous drip), in the intestine, in the blood and/or at tissue receptor sites; interaction may also occur indirectly as a result of acceleration or slowing in the rate of drug metabolism or excretion. It should be remembered that the adverse consequences of drug interactions may occur not only on introduction of a drug but also on removal of a drug that causes acceleration of drug metabolism, as this may result in effective overdosage of the remaining drug. The subject of drug interactions has been extensively reviewed [1,2]. Combinations of drugs with potential adverse interactions continue to be prescribed [3].

Intestinal drug interactions. Examples include inhibition of griseofulvin absorption by phenobarbital [1], inhibition of tetracycline absorption by antacids [4] and decreased absorption of the oral contraceptive by tetracycline [5]. Whether the latter is of real significance is a matter of debate [6].

Displacement from carrier or receptor sites. Most drugs are reversibly bound to carrier proteins in plasma or extracellular fluid; bound drug acts as a reservoir, preventing excessive fluctuation in the level of the active unbound fraction. Displacement from a carrier protein augments drug activity, whereas displacement from a receptor site diminishes it. Many acidic drugs such as salicylates, coumarins, sulphonamides and phenylbutazone are bound to plasma albumin, and compete for binding sites. Thus, a sulphonamide may displace tolbutamide from albumin leading to hypoglycaemia; or aspirin, sulphonamides, clofibrate or phenylbutazone may displace warfarin from albumin, causing bleeding and ecchymoses. Similarly, sulphonamides and aspirin may increase methotrexate toxicity. Ciprofloxacin increases plasma levels of theophylline.

Enzyme stimulation or inhibition [2]. A drug may either stimulate or inhibit metabolic enzymes important to its own degradation or that of another agent, with significant clinical consequences. Thus, some drugs induce synthesis of drug-metabolizing enzymes in liver microsomes. The liver microsomal hydroxylating system (which mediates metabolism of phenytoin and debrisoquine) is based on cytochrome P-450, and appears to be a family of enzymes capable of acting on different substrates including barbiturates, fatty acids and endogenous steroids. The cytochrome P-450-dependent system also catalyses deamination (e.g. amfetamine (amphetamine)), dealkylation (e.g. morphine, azathioprine), sulphoxidation (e.g. chlorpromazine, phenylbutazone), desulphuration (thiopental (thiopentone)) and dehalogenation (e.g. halogenated anaesthetics). This lack of specificity accounts for the ability of an inducing agent to stimulate metabolism of many other drugs, and of one drug to inhibit metabolism of a structurally unrelated drug. Antibiotics, if administered over a period of time (e.g. rifampicin for tuberculosis), can be enzyme inducers. Barbiturates stimulate metabolism of griseofulvin, phenytoin and coumarin anticoagulants, and griseofulvin induces increased metabolism of coumarins. Similarly, rifampicin, phenytoin and carbamazepine increase the metabolism of ciclosporin [7]. Drugs causing enzyme inhibition include chloramphenicol, cimetidine, monoamine oxidase inhibitors, *p*-aminosalicylic acid, pethidine and morphine. Dicoumarol, chloramphenicol and phenylbutazone inhibit metabolic inactivation of tolbutamide. Allopurinol inhibits metabolism of azathioprine and mercaptopurine by xanthine oxidase. Cimetidine inhibits liver enzymes and decreases

hepatic blood flow, thereby potentiating the action of some β-blockers (propranolol) and benzodiazepines, carbamazepine, warfarin, morphine, phenytoin and theophylline. Ketoconazole may potentiate oral anticoagulants [8] and erythromycin may potentiate carbamazepine [9]; both may potentiate ciclosporin. Nifedipine and ciclosporin are both metabolized by the same cytochrome P-450 enzyme, P-450cpn; ciclosporin potentiates the action of nifedipine, phenytoin and to a lesser extent valproate by decreasing P-450cpn availability by competitive inhibition [10].

Altered drug excretion. Examples include the well-known probenecid-induced reduction in the renal excretion of penicillin, and aspirin-induced reduction in renal clearance of methotrexate.

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Metabolic changes

Drugs may induce cutaneous changes by their effects on nutritional or metabolic status. Thus, drugs such as phenytoin that interfere with folate absorption or metabolism increase the risk of aphthous stomatitis, and isotretinoin may cause xanthomas by elevation of very low-density lipoproteins [1].

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Teratogenicity and other effects on the fetus [1–6]

The advent of isotretinoin has focused the attention of dermatologists considerably on the problem of teratogenicity in general [5]. The fetus is particularly at risk from drug-induced developmental malformations during the period of organogenesis, which lasts from about the third to the tenth week of gestation. Thalidomide, retinoids and cytotoxic drugs are proven teratogens. Heavy alcohol intake (which produces fetal alcohol syndrome), smoking, anticonvulsants (especially phenytoin and trimethadione (troxidone)), warfarin and antiplatelet drugs, inhalational anaesthetics, lithium, quinine, ACE inhibitors, misoprostol, certain antimicrobials (e.g. trimethoprim, aminoglycosides, 4-quinolones and itraconazole) and cocaine are probably teratogenic. High-dose corticosteroids have been linked to cleft palate. A major correlation has been found between the incidence of glucocorticoid-induced cleft palate and the chromosome 8 segment identified by *N*-acetyltransferase in mice [7]. 6-Aminonicotinamide-induced cleft palate and phenytoin-induced cleft lip with or without cleft palate are also influenced by this genetic region but not as strongly. Sex hormones, psychotropic drugs, benzodiazepines, tetracycline, rifampicin, penicillamine and the folate antagonist pyrimethamine are possibly teratogenic and should be avoided in the first trimester of pregnancy. Chlorpheniramine appears safe to use. The potential adverse effects on the fetus and on the breastfed infant of a number of drugs not infrequently used by the dermatologist have been reviewed [4].

Drugs may also cause fetal damage later in pregnancy. Warfarin may cause haemorrhage, and phenytoin near to term produces a coagulation defect in the neonate, which is correctable by vitamin K. Antithyroid drugs and iodides may cause neonatal goitre and hypothyroidism. Fetal adrenal atrophy may follow high-dose maternal corticosteroid therapy. NSAIDs have various ill effects, although aspirin has been advocated in pregnancy for the prevention of fetal growth retardation. Tetracyclines are deposited in developing bones and cause discoloration and enamel hypoplasia of teeth [8]. Aminoglycoside antibiotics are ototoxic, and chloroquine has caused a neonatal chorioretinitis. Androgens and progestogens may virilize the fetus. Diethylstilbestrol (stilboestrol) administered from early pregnancy for several months has been associated with female and male genital tract abnormalities, and carcinoma of the vagina 20 years later in the offspring.

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Effects on spermatogenesis

Most chemotherapeutic agents potentially damage sperm; conception should also be avoided after griseofulvin for 3 months. A number of drugs cause oligospermia [1], which may come to light only as a result of infertility investigations; oestrogens, androgens, cyproterone acetate, cytotoxic drugs, including methotrexate given for psoriasis [2], colchicine, most monoamine oxidase inhibitors, ketoconazole and sulfasalazine (sulphasalazine) have all been incriminated. The synthetic retinoids isotretinoin and etretinate do not seem to affect the numbers of sperm [3,4].

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Non-immunological activation of effector pathways (anaphylactoid reactions)

Certain drugs, such as opiates, codeine, amfetamine, polymyxin B, D-tubocurarine, atropine, hydralazine, pentamidine, quinine and radiocontrast media, may release mast cell mediators directly to produce urticaria or angio-oedema [1–7]. Some drugs, such as radiocontrast media, may activate complement by an antibody-independent method [8]. Anaphylaxis-like responses to cyclo-oxygenase inhibitors such as aspirin and other NSAIDs may lead to amplified mast cell degranulation and enhanced biosynthesis of lipoxygenase products of arachidonic acid, which cause vasodilatation and oedema [9,10]. ACE inhibitors, which cause or exacerbate angio-oedema, may potentiate bradykinin activity; they have been reported to enhance bradykinin-induced cutaneous weals in normal individuals [11,12].

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Exacerbation of disease

Examples of adverse drug effects on pre-existing skin conditions include lithium exacerbation of acne and psoriasis, β-blocker induction of a psoriasiform dermatitis [1] and corticosteroid withdrawal resulting in exacerbation of psoriasis; cimetidine, penicillin or sulphonamide exacerbation of lupus erythematosus (LE); and vasodilator exacerbation of rosacea. Sometimes, a drug may unmask a latent condition, as when barbiturates precipitate symptoms of porphyria.

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Intolerance

The characteristic effects of the drug are produced to an exaggerated extent by an abnormally small dose. This may simply represent an extreme within normal biological variation. Alternatively, the intolerance may be contributed to by delayed metabolism or excretion due to impaired hepatic or renal function, or by genetic variation in the rate of drug metabolism (see below).

Idiosyncrasy

This describes an uncharacteristic response, not predictable from animal experiments, and not mediated by an immunological mechanism. The cause is often unknown, but genetic variation in metabolic pathways may be involved. Such genetic abnormalities include glucose-6-phosphate dehydrogenase deficiency, hereditary methaemoglobinaemia, porphyria, glucocorticoid glaucoma and malignant hyperthermia of anaesthesia, all of which

are characterized by unusual pharmacological responses to various drugs.

Pharmacogenetic mechanisms and genetic influences underlying intolerance and idiosyncratic reactions [1–4]

The pharmacokinetics of drugs, including their absorption, plasma protein binding, distribution, metabolism and elimination, may be influenced by genetic factors. Oxidation, hydrolysis and acetylation are the three metabolic pathways most subject to genetic influence. Genetic factors also influence pharmacodynamics, i.e. tissue or organ responsiveness. Thus, genetic variations in all these areas may underlie both intolerance and idiosyncrasy. Variation in the regulation and expression of the human cytochrome P-450 enzyme system may play a key role in both interindividual variation in sensitivity to drug toxicity and tissue-specific damage [5]. Pharmacogenetic variability probably underlies reactions such as TEN. It has been proposed that most patients who have a severe ACDR have an abnormal metabolism of the offending drug [6].

Examples of genetically mediated intolerance include pupil size responses to phenylephrine and parasympatholytics, and the very rare dominantly inherited familial resistance to coumarin anticoagulants, the result of mutation in the receptor for vitamin K and anticoagulants. Low levels of red cell glucose-6-phosphate dehydrogenase, inherited as a sex-linked dominant trait, are common in black people, certain Levantine peoples and Filipinos, and result in a chronic deficit of reduced glutathione sulphydryl (SH) groups. Affected individuals are at risk of acute haemolysis on exposure to antimalarials, sulphonamides, dapsone, nitrofurantoin, phenacetin, aspirin and chloramphenicol, all of which may oxidize the few reduced SH groups in older red cells. Genetic variation in thiopurine methyltransferase activity may be linked to the side effects of azathioprine therapy, as homozygotes for the low-activity allele are at risk of myelosuppression, whereas homozygotes for high activity are inadequately immunosuppressed with conventional doses of azathioprine [7]. Increased susceptibility to aminoglycoside-induced deafness in two Japanese pedigrees was associated with a particular mitochondrial DNA polymorphism [8].

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Oxidation. Anticonvulsants, many hypnotics, tricyclic antidepressants, anticoagulants and various anti-inflammatory and anxiolytic agents are eliminated by oxidation. For many drugs, oxidation rates vary as a continuous spectrum within the population. Genetic differences in metabolism of sulphonamides may underlie idiosyncratic toxicity [1–6]. Oxidative metabolism of sulphonamides by cytochrome P-450 enzymes and *N*-acetylation yields a reactive hydroxylamine intermediate [7], which is inactivated by glutathione conjugation. The hydroxylamine metabolite is toxic to lymphocytes, and the lymphocyte toxicity is markedly increased in patients with a history of hypersensitivity or with glutathione synthetase deficiency. HIV-positive individuals have been reported in some studies to have a systemic glutathione deficiency, resulting in a decreased capacity to scavenge hydroxylamine derivatives of sulphonamides, which may partially explain the increased frequency of sulphonamide reactions [8–10]. However, other studies have not been able to confirm intracellular glutathione deficiency in peripheral blood cells of HIV-infected patients [11,12].

Phenytoin, phenobarbital and carbamazepine are oxidized by the cytochrome P-450 enzyme system into potentially reactive arene-oxide intermediates; liver microsomal epoxide hydrolase converts such reactive intermediates to non-toxic dihydrodiols [13–17]. Phenytoin hypersensitivity syndrome appears to be associated with an inherited deficiency of epoxide hydrolase, which is primarily responsible for detoxifying the toxic arene-oxide intermediate [13–16]. Activated phenytoin has been shown to be toxic to lymphocytes from patients with phenytoin reactions and, to a lesser degree, to lymphocytes from their parents [15]. However, in another study a genetic defect altering the structure and function of the microsomal epoxide hydrolase protein was thought unlikely to be responsible for predisposing patients to anticonvulsant adverse reactions [17].

Culprit drug-reactive metabolites, generated by a microsomal oxidation system, had increased toxic effects on lymphoid cells from patients with TEN (13 each with sulphonamide and anticonvulsant reactions) and on those from first-degree relatives, whereas oxygen free radical and/or aldehyde detoxification pathways were normal [18].

Impaired metabolism of phenacetin and phenformin, inherited as a result of genetic polymorphism in liver

microsomal oxidation, may result in adverse reactions [19,20]. The induction of liver enzymes responsible for drug oxidation may itself be under genetic control [21]. There is a fourfold increase in toxicity to penicillamine in patients with rheumatoid arthritis with a genetically determined poor capacity to sulphoxidate the structurally related mucolytic agent, carbocysteine [22].

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Hydrolysis. Genetic influence on drug hydrolysis is well illustrated in the case of suxamethonium, which normally results in only very brief neuromuscular blockade due to rapid hydrolysis by plasma pseudocholinesterase. Genetically determined atypical cholinesterases cannot hydrolyse the drug, leading to prolonged apnoea in affected individuals; conversely, dominantly inherited resistance to suxamethonium, mediated by a highly active cholinesterase, has been reported.

Acetylation. Isoniazid, many sulphonamides, hydralazine, dapsone, procainamide, etc. are inactivated by conversion to acetyl conjugates. Acetylation rates vary greatly, with a bimodal frequency distribution, and there is marked ethnic variation. Rapid inactivation is dominantly inherited, and is commonest among Eskimos and Japanese and least common among certain Mediterranean Jews. The LE-like syndrome due to procainamide may occur more in fast acetylators, implying that a conjugate and not the parent compound is responsible [1]. Slow acetylators, in whom higher and more persistent drug levels occur, are more liable to develop adverse reactions to isoniazid (pellagra-like syndrome and peripheral neuritis), dapsone (haemolysis) [2] and hydralazine (LE-like syndrome) [3,4]. A slow acetylation phenotype is a risk factor for hypersensitivity to trimethoprim–sulfamethoxazole in HIV-infected subjects [5,6], and for sulphonamide-induced TEN and Stevens–Johnson syndrome independent of HIV infection [7,8].

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Influence of human leukocyte antigen (HLA) types. An association between HLA types and susceptibility to drug eruptions has been reported on several occasions, particularly in relation to gold (HLA-DRw3, HLA-DR5 and HLA-B8) and penicillamine toxicity [1–6]. Penicillamine toxicity is associated with HLA phenotypes as follows [1]: HLA-DR3 and HLA-B8 with renal toxicity; HLA-DR3, HLA-B7 and HLA-DR2 with haematological toxicity; HLA-A1 and HLA-DR4 with thrombocytopenia; and HLA-DRw6 with

cutaneous adverse reactions. DR1/DR4 heterozygosity, or the DR5 subtypes DRB1*1102 or DRB1*1201, have been found in 61% of patients with intolerance to tiopronin given for rheumatoid arthritis [7].

A positive association with HLA-Aw33 and HLA-B17/Bw58 haplotypes, and a negative association with the HLA-A2 haplotype, has been reported in southern Chinese patients with drug eruptions after exposure to allopurinol [8]. Aspirin-sensitive asthma is associated with HLA-DQw2 [9]. HLA-linkage associations with certain bullous disorders have been reported [10,11]. Hydralazine-induced LE is commonest in female patients with the HLA-DRw4 haplotype [12,13]. Fixed drug eruptions to feprazone and trimethoprim–sulfamethoxazole are linked, respectively, to HLA-B22 and HLA-A30 B13 Cw6 [14,15]. The above findings indicate that there may be genetic predisposition to develop certain drug eruptions.

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Drug-induced chromosomal damage [1–3]

This may be studied by examining the chromosomes of patients or animals exposed to drugs, or *in vitro* by the addition of drugs to cell cultures; substances capable of inducing chromosomal damage are termed clastogens. Effects may be dose related, but *in vitro* results may not be representative of the *in vivo* situation. Antimitotic and antibiotic agents have been the most studied, although psychotropics, anticonvulsants, hallucinogens, immunosuppressants and oral contraceptives have also been investigated and shown to cause, in varying degree, chromosomal damage. Damage ranges from staining variations through 'gaps' in staining, chromosome breaks, gross aberrations (such as deletions, fragments, translocations and inversions) to polyploidy. Such damage may be stable and retained over a succession of cell divisions, or transient.

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Miscellaneous

Jarisch–Herxheimer reaction

This is the focal exacerbation of lesions of infective origin when potent antimicrobial therapy is initiated, and is classically observed in the treatment of early syphilis with penicillin; it may also occur 3 days after starting griseofulvin therapy, during therapy with diethylcarbamazine for onchocerciasis and tiabendazole (thiabendazole) for strongyloidiasis, and with penicillin or minocycline for erythema chronicum migrans due to *Borrelia burgdorferi* infection [1]. The reaction has been attributed to sudden release of pharmacologically and/or immunologically active substances from killed microorganisms or damaged tissues. However, there is little evidence that it is an allergic reaction [2]. Clinically there may be fever, rigors, lymphadenopathy, arthralgia, and transient macular urticarial eruptions; a vesicular eruption has also been described [3].

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Infectious mononucleosis–ampicillin reaction

Ampicillin almost always causes a severe morbilliform eruption when given to a patient with infectious

mononucleosis or lymphatic leukaemia (see later). The reaction occurs much less frequently with amoxicillin. The exact mechanism is not known, although a recent report suggests that real sensitization to ampicillin and amoxicillin occurs, and is detectable *in vivo* and *in vitro* by skin tests and the lymphocyte transformation test [1].

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Immunological drug reactions

Allergic hypersensitivity reactions are caused by immunological sensitization to a drug, as a result of previous exposure to that drug or to a chemically related cross-reacting substance [1–7]. It has been estimated that only about 6–10% of ADRs are immunologically mediated [8]. Although drugs frequently elicit an immune response, clinically evident hypersensitivity reactions are manifest only in a small proportion of exposed individuals. Thus, using highly sensitive passive haemagglutination assays, IgM class antibodies to the penicilloyl group (the major hapten determinant derived from penicillin) are detectable in almost 100% of normal individuals, even in the absence of a history of penicillin therapy; 40% of patients receiving more than 2 g of penicillin for more than 10 days develop IgG class antibodies [9]. Macromolecular drugs such as protein or peptide hormones, insulin or dextran are antigenic in their own right. In contrast, most drugs are small organic molecules with a molecular mass of less than 1 kDa; conjugation of free drug as a hapten with a macromolecular carrier is then required to initiate an immune response [10]. Fortunately, many drugs have only a limited capacity to form covalent bonds with tissue proteins. Clinical sensitization may also result from allergy to reactive drug metabolites as haptens, or to minor contaminants.

Clinical features distinguishing allergic from non-allergic drug reactions. Prior exposure before sensitization should have been without adverse effect. If there has been no previous exposure, there should be a latent period of several days of uneventful therapy before the reaction supervenes, during which primary sensitization occurs. Thereafter, reactions may develop within minutes (or even seconds) and certainly within 24 h. Allergic reactions do not resemble the pharmacological action of the drug, may follow exposure to doses far below the therapeutic level, and are reproducible on readministration (if judged safe).

Factors concerned in the development of hypersensitivity. The route of administration of a drug may affect its immunogenicity and the nature of any allergy. Topical drug exposure is more likely to result in sensitization than oral administration, and favours development of contact dermatitis; thus, poison ivy is a potent contact sensitizer but oral ingestion may promote tolerance. Anaphylaxis is more likely to be associated with intravenous drug administration. However, anaphylaxis may sometimes occur as quickly after oral penicillin administration [11]. Whether allergy develops may also depend on the antigenic load in terms of degree of drug exposure, and individual genetic variation in drug absorption and metabolism. Thus, as stated above, an LE-like syndrome with antinuclear antibody formation following hydralazine therapy occurs more frequently in slow acetylators of the drug [12]. Hydralazine-related SLE is 10 times more frequent in HLA-DR4-positive patients than in the population at large, and is commoner in females. Allergic drug reactions are less common in childhood and possibly in the aged; in the latter, this may be related to impaired immunological responsiveness. Immunosuppression may increase the risk by inhibiting the regulatory function of suppressor T cells [13]. Environmental factors may also affect susceptibility to drug hypersensitivity, as for example the well-recognized increase in ampicillin-induced morbilliform eruptions associated with infectious mononucleosis, and photoallergic reactions to drugs such as thiazide diuretics or phenothiazines.

Duration of hypersensitivity. The duration of allergic sensitivity is unpredictable. Although there is a general tendency for immunological responses to a drug to fall off with time, provided the patient is not re-exposed to the drug or a related substance, this can never be relied on; where necessary, safe confirmatory procedures (if available) should be carried out.

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Drug eruptions may occur as a result of a variety of different immunological mechanisms as described below.

IgE-dependent (type I) drug reactions: urticaria and anaphylaxis [1]

In vivo cross-linkage by polyvalent drug–protein conjugates of two or more specific IgE molecules, fixed to sensitized tissue mast cells or circulating basophil leukocytes, triggers the cell to release a variety of chemical mediators, including histamine, peptides such as eosinophil chemotactic factor of anaphylaxis, lipids such as leukotriene C_4 or prostaglandin D_2, and a variety of pro-inflammatory cytokines [2]. Interleukin-5 (IL-5) and eotaxin play a role in activating and recruiting eosinophils in drug-induced cutaneous eruptions [3]. Such cytokines in turn have effects on a variety of target tissues including skin, respiratory, gastrointestinal and/or cardiovascular systems. Eosinophil degranulation may also result in release of pro-inflammatory mediators [4]. Dilatation and increased permeability of small blood vessels with resultant oedema and hypotension, contraction of bronchiolar smooth muscle and excessive mucus secretion, and chemotaxis of inflammatory cells, including polymorphs and eosinophils, occurs. Clinically, this may produce pruritus, urticaria, bronchospasm and laryngeal oedema, and in severe cases anaphylactic shock with hypotension and possible death. Immediate reactions occur within minutes of drug administration; accelerated reactions may occur within hours or days, and are generally urticarial but may involve laryngeal oedema. Penicillins are the commonest cause of IgE-dependent drug eruptions.

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Antibody-mediated (type II) drug reactions

Binding of antibody to cells may lead to cell damage following complement-mediated cytolysis. The classical example of immune complex formation between a drug (as hapten) bound to the surface of a cell (in this case, platelets) and IgG-class antibody, with subsequent complement fixation, was the purpura caused by apronalide (Sedormid). A further example is the thrombocytopenic purpura that may result from antibodies to quinidine–platelet conjugates [1,2]. A number of drugs, including penicillin, quinine and sulphonamides, may rarely produce a haemolytic anaemia via this mechanism. Methyldopa very occasionally induces a haemolytic anaemia mediated by autoantibodies directed against red cell antigens.

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Immune complex-dependent (type III) drug reactions

Urticaria and anaphylaxis. Immune complexes may activate the complement cascade, with resultant formation of anaphylatoxins such as the complement protein fragments C3a and C5a, which trigger release of mediators from mast cells and basophils directly, resulting in urticaria or anaphylaxis.

Serum sickness. Serum sickness-like reactions and other immune complex-mediated conditions necessitate a drug antigen to persist in the circulation for long enough for antibody, largely of IgG or IgM class, to be synthesized and to combine with it to form circulating antibody–antigen immune complexes. They therefore develop about 6 days or more after drug administration. Serum sickness occurs when antibody combines with antigen in antigen excess, leading to slow removal of persistent complexes by the mononuclear phagocyte system. It was usually seen in the context of serum therapy with large doses of heterologous antibody, as with horse antiserum for the treatment of diphtheria. It has been reported more recently with antilymphocyte globulin therapy [1]. Clinical manifestations of serum sickness include fever, arthritis, nephritis, neuritis, oedema, and an urticarial or papular rash.

Vasculitis [2–4]. Drug-induced immune complexes play a part in the pathogenesis of cutaneous necrotizing vasculitis. Deposition of immune complexes on vascular endothelium results in activation of the complement cascade, with generation of the anaphylatoxins C3a and C5a, which have chemotactic properties. Vasoactive amines and pro-inflammatory cytokines are released from basophils and mast cells, with resultant increased vascular permeability and attraction of neutrophil polymorphonuclear cells. Immune complex interaction with platelets via their Fc receptors causes platelet aggregation

and microthrombus formation. Release by neutrophils of lysosomal enzymes contributes further to local inflammation. These events lead to the histological appearance of leukocytoclastic vasculitis. Deposition of immunoglobulins and complement in and around blood vessel walls is detectable by direct immunofluorescence staining of skin biopsies. Hydralazine and the hydroxylamine metabolite of procainamide bind to complement component C4 and inhibit its function; this may impair clearance of immune complexes, and predispose to development of an LE syndrome [4].

Arthus reaction. The Arthus reaction is a localized form of immune complex vasculitis. Intradermal or subcutaneous injection of antigen such as a vaccine into a sensitized individual with circulating precipitating antibodies, usually of IgG1 class, leads to local immune complex formation and the cascade of events described above. Clinically, there is erythema and oedema, haemorrhage and occasionally necrosis at the injection site, which reaches a peak at 4–10 h, and then gradually wanes.

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Cell-mediated (type IV) reactions

The role of delayed-type cell-mediated immune reactions in contact drug hypersensitivity, as with penicillin [1], is well established, but the importance of such mechanisms involving specific effector lymphocytes in other varieties of cutaneous drug allergy is uncertain. Nevertheless, it is thought that a number of ACDRs, including some morbilliform and bullous ACDRs, fixed drug reactions, lichenoid reactions, LE-like reactions and erythema multiforme, Stevens–Johnson syndrome and TEN, involve T-lymphocyte responses to altered self. An intercurrent infectious disease (especially respiratory tract and urinary tract infections in the case of maculopapular eruptions) was documented in 58.5% of patients with ACDRs, compared with 7.5% of a control group [2]. It has been proposed that viruses may non-specifically stimulate cytotoxicity in general, which spills over to affect target cells altered by drug antigen [3]. Viruses incriminated, especially in the drug hypersensitivity syndrome, include human herpesvirus 6, Epstein–Barr virus, cytomegalovirus and hepatitis C virus [4–10].

The involvement of the skin immune system in cell-mediated drug eruptions, and graft-versus-host disease as a model for cutaneous drug eruptions, have been reviewed [11,12]. There is increasing evidence of a role for T cells and cell-mediated immunity in some drug eruptions. Sulfamethoxazole-reactive lymphocytes can be detected in peripheral blood of patients with drug-induced eruptions, at a frequency of 1/172 000, within the frequency range of urushiol-reactive T cells in patients with urushiol (poison ivy) dermatitis [13]. Patients with acute drug allergy to carbamazepine, phenytoin, sulfamethoxazole, allopurinol or paracetamol had activated drug-specific $CD4^+$ or $CD8^+$ T cells in the circulation [14]. In one study, predominant $CD8^+$ T-cell activation was associated with more severe (bullous) skin lesions or liver involvement, whereas predominant activation of $CD4^+$ cells elicited mainly maculopapular reactions [15]. Drug-specific T-cell clones from drug-induced exanthems contained heterogeneous T-cell subsets with distinct phenotypes ($CD4^+ > CD8^+$, perforin and granzyme B positive) and cell functions (strong IL-5 production, moderate interferon-γ (IFN-γ) production, and cytotoxic potential) [16,17]. Perivascular predominantly $CD4^+$ T cells, with 30% $CD8^+$ cells, basal keratinocyte HLA-DR and intercellular adhesion molecule (ICAM)-1 expression, and E selectin expression by endothelial cells, were seen in maculopapular or exfoliative antibiotic-induced ACDRs [18,19]. However, in other studies $CD8^+$ T cells predominated in the epidermis in drug-induced maculopapular and bullous eruptions and patch-test reactions to β-lactam antibiotics [20,21]. β-lactam-specific peripheral and epidermal T lymphocytes from bullous exanthems were predominantly $CD8^+CD4^-$, displayed a Th1-like cytokine pattern, proliferated in an antigen- and major histocompatibility complex (MHC)-specific manner and were cytotoxic against epidermal keratinocytes in lectin-induced cytotoxicity assays. In contrast, T-cell lines from patients with penicillin-induced urticarial exanthems were predominantly $CD4^+CD8^-$, with a Th2-like cytokine pattern. Drug-specific T-cell clones and cell lines from a phenobarbital-induced eruption were heterogeneous with regard to CD4/CD8 phenotype, T-cell receptor Vβ repertoire, antigen recognition pattern and cytokine production [22]. Epicutaneous test reactions to antibiotics contained a heterogeneous population of drug-specific T cells [23]; it has been proposed that T cells producing IL-5 might contribute to eosinophilia, whereas cytotoxic $CD4^+$ T cells might account for tissue damage [23–25]. Drug-specific T cells also contribute to the neutrophil infiltration in drug-induced acute generalized exanthematous pustulosis, by secreting the chemokine IL-8 [26–28].

Proliferation of $CD8^+$ dermal T cells, from a sulfamethoxazole-induced bullous exanthem, to sulfamethoxazole was significantly increased in the presence of liver microsomes, suggesting that microsomal enzymes, such as the cytochrome P-450 system, generate highly reactive metabolites, which are the nominal antigens for T-cell activation

[29,30]. The expression of ICAM-1 by target keratinocytes plays an important role in the cytotoxicity of epidermal T cells in bullous drug eruptions [31]. Penicilloyl-modified MHC-associated peptides may act as T-cell epitopes; T cells may have specificity for both the backbone and the side-chain of penicillin [32]. Penicillin G may also stimulate T cells directly by binding to MHC molecules on the cell surface. Alternatively, it may bind to soluble proteins like human serum albumin, which require processing for presentation in an immunogenic form. These different modes of presentation, which elicit a variety of immunological reactivities, may explain the heterogeneity of clinical pictures seen in penicillin allergy [33]. Morbilliform drug hypersensitivity reactions in HIV-infected subjects showed spongiosis, hydropic generation of the basal layer, Civatte bodies, an epidermal lymphocytic infiltrate, and perivascular lymphocytes and macrophages [34]. Immunohistochemistry demonstrated $CD8^+$ HLA-DR-positive T lymphocytes, marked depletion of epidermal Langerhans' cells and strong keratinocyte IL-6, tumour necrosis factor-α (TNF-α) and, to a lesser degree, IFN-γ expression.

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Erythema multiforme, Stevens–Johnson syndrome and TEN. The reader is referred to Chapter 74.

Lichenoid drug eruptions. The mechanisms underlying lichenoid drug eruptions are essentially unknown, but they may develop as a result of autoreactive cytotoxic T-cell clones directed against a drug–class II MHC antigen complex, such that keratinocytes and Langerhans' cells are viewed by the immune system as 'non-self'. Cloned murine autoreactive T cells produce a lichenoid reaction in recipient animals following injection [1]. The presence of epidermotropic T cells correlates with that of class II MHC (HLA-DR)-expressing keratinocytes and Langerhans' cells in lichenoid eruptions [2].

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LE-like syndrome induced by drugs. Drug-induced LE, with production of antihistone antibodies, may result from interaction between the drug and nuclear material to produce a drug–nucleoprotein complex that is immunogenic. Alternatively, drugs may alter immunoregulation in such a way that autoantibody production is favoured; procainamide and hydralazine modulate lymphocyte function directly and induce autoreactivity. Thus, drugs may cause an SLE-like condition by a mechanism analagous to that in immunostimulatory graft-versus-host disease [1]. Hydralazine, isoniazid and the hydroxylamine metabolites of procainamide and practolol may also predispose to the development of an LE-like syndrome by inhibiting binding of C4 and in turn of C3 to immune complexes, thus preventing complement-mediated clearance of immune complexes by solubilization and opsonization [2].

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Drug-induced pemphigus. Immunoprecipitation studies have shown that patients with drug-induced pemphigus foliaceus and pemphigus vulgaris often have circulating autoantibodies with the same antigenic specificity at a molecular level as autoantibodies from patients with idiopathic pemphigus [1]. Binding of an active thiol group in a drug to the pemphigus antigen complex might result in autoantibody production, or culprit drugs may result in immune dysregulation. In addition, drugs with thiol groups in their molecule, such as penicillamine, captopril and thiopronine, and piroxicam can cause acantholysis directly *in vitro* in the absence of autoantibody [2].

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Fixed drug eruptions. Graft autotransplantation investigations carried out in the 1930s demonstrated cutaneous memory in involved skin in fixed drug eruption [1]. Serum factors from patients with fixed drug eruption have been reported to cause inflammation on injection into a previously involved site, but not when injected into normal skin [2], and to induce lymphocyte blast transformation [3,4]. However, cell-mediated rather than humoral immunity is thought to play the major role in the development of lesions in this condition.

Lesional skin contains increased numbers of both helper and suppressor T lymphocytes [5–8], and T suppressor/cytotoxic T cells may be seen adjacent to necrotic keratinocytes in the epidermis [6]. T cells may persist within lesional skin and contribute to immunological memory [7,9]; $CD8^+$ suppressor/cytotoxic T cells were present in suprabasal epidermis in involved skin 3 weeks after challenge [5]. Intraepidermal $CD8^+$ T cells phenotypically resembling effector memory T cells are greatly enriched in the resting lesions of fixed drug eruption; upon activation, they can rapidly produce large amounts of IFN-γ followed by localized epidermal injury [10].

T cells from lesional epidermis in two patients with fixed drug eruption utilized a very limited range of Vα and Vβ genes compared with peripheral blood T cells, indicating some expansion or preferential migration of T cells recognizing a restricted set of antigens [11]. Keratinocytes in lesional skin express ICAM-1 [12], which is involved in interaction between keratinocytes and lymphocytes, HLA-DR [6] and the chemotactic protein IP-10 [8], findings that suggest a role for cytokines in the evolution of the histological changes [8,13]. ICAM-1 was noted to be induced on endothelium and keratinocytes 1.5 h after drug challenge, and there was increased reactivity in lesional skin *in vitro* to TNF-α and IFN-γ, as well as to the causative drug [13]; drug-induced, TNF-α-dependent keratinocyte ICAM-1 expression in lesional skin may provide a localized initiating stimulus for epidermal T-cell activation. Early release of histamine from mast cells or basophils has been reported in fixed drug eruption, based on suction blister fluid levels [14]. Significantly higher frequencies of HLA-B22 and HLA-Cw1 antigens were found in 36 patients with fixed drug eruption, and familial cases occur, suggesting a genetic predisposition [15].

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Histopathology of drug reactions [1]

In most patterns of reaction to drugs, the histological changes are no more distinctive than are the clinical features. For example, urticaria, erythema multiforme, TEN and exfoliative dermatitis provoked by drugs cannot be differentiated from the same reactions resulting from other causes. Graft-versus-host disease-type drug eruptions in the acute phase show a predominance of epidermal $CD8^+$ T cells, reduced epidermal OKT6-positive Langerhans' cells, and increased keratinocyte expression of HLA-DR and ICAM-1 [2]. In contrast, Langerhans' cells from lesional maculopapular drug eruptions reportedly increased in number by 66% and displayed more intense staining and more prominent dendrites in one study [3].

The histological changes in the vegetating iododermas and bromodermas, certain lichenoid eruptions and fixed drug eruptions are not pathognomonic, but are sufficiently characteristic to be of importance in differential diagnosis. The histology of a number of other drug eruptions has been reviewed [4]. Amiodarone-induced hyperpigmentation shows a lymphocytic dermatitis and yellowish-brown granules within several cell types; the drug or a metabolite composes at least a portion of the deposits. Clofazimine-induced hyperpigmentation involves accumulation of a ceroid lipofuscin within lipid-laden macrophages. The cutaneous eruption of lymphocyte recovery after chemotherapeutic agents is a maculopapular eruption with a non-specific superficial perivascular dermatitis. Chemotherapy-induced acral erythema reveals a non-specific interface dermatitis. Specific reactions occur with etoposide (starburst cells) and busulfan (busulphan) (large atypical keratinocytes), and other chemotherapeutic agents may involve sweat glands: neutrophilic eccrine hidradenitis is characterized by neutrophil infiltration and by necrosis; syringosquamous metaplasia involves squamous metaplasia of the sweat duct. Drug-induced generalized pustular toxic erythema is characterized by subcorneal pustules and occasional eosinophils. Cephalosporins may produce a syndrome clinically and histologically like pemphigus, and naproxen produces one like porphyria cutanea tarda. The photosensitive dermatitis associated with quinine and piroxicam is histologically a non-specific spongiotic dermatitis. A lichenoid giant cell dermatitis may be caused by methyldopa or chlorothiazide, and phenytoin and carbamazepine dermatitis histologically imitates mycosis fungoides.

Bromodermas and iododermas

In bromoderma, verrucous pseudoepitheliomatous hyperplasia is associated with abscesses containing neutrophils and eosinophils in the epidermis, and a dense dermal infiltrate initially consisting mainly of neutrophils and eosinophils and later containing many lymphocytes, plasma cells and histiocytes. The abundant dilated blood vessels may show endothelial proliferation. In iododermas, ulceration is more marked, but there is usually less epithelial hyperplasia. Both conditions must be differentiated from blastomycosis and coccidioidomycosis, and from pemphigus vegetans.

Fixed eruptions

In the acute stage, the epidermal changes may be indistinguishable from erythema multiforme, with loss of cell outlines and necrosis of the lower epidermis. In less acute lesions, the epidermis may show little abnormality but the dermis is oedematous and there is a conspicuous perivascular lymphocytic infiltrate. Later, there is increased melanin in the epidermis and within melanophages in the dermis.

Lichenoid eruptions

The changes may be non-specific or may resemble idiopathic lichen planus, although the cellular infiltrate tends to be more pleomorphic and less dense, and the presence of focal parakeratosis, focal interruption of the granular layer, and cytoid bodies in the cornified and granular layers suggest a drug cause [5]. Later, there may be scarring, with destruction of the sweat glands.

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Types of clinical reaction [1–13]

The mucocutaneous reactions that may result from ADRs have been the subject of extensive reviews, to which the reader is referred for further information. The following section details a number of different drug-induced reaction patterns; see also the discussion of adverse effects of individual drugs later. It is unfortunate that although certain drugs are commonly associated with a specific reaction, most drugs are capable of causing several different types of eruption.

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Exanthematic (maculopapular) reactions

These are the most frequent of all cutaneous reactions to drugs, and can occur after almost any drug at any time up to 3 (but usually 2) weeks after administration; they may be accompanied by fever, pruritus and eosinophilia. It is not possible to identify the offending drug by the nature of the eruption. The clinical features are variable; the lesions may be scarlatiniform, rubelliform or morbilliform, or may consist of a profuse eruption of small papules showing no close resemblance to any infective exanthem (Fig. 73.1). Less common are eruptions with large macules, polycylic and gyrate erythema, reticular eruptions and sheet-like erythema. The distribution is also variable but is generally symmetrical. The trunk and extremities are usually involved, and not uncommonly intertriginous areas may be favoured, but the face may be spared. Palmar and plantar lesions may occur, and sometimes the eruption is generalized. Purpuric lesions, especially on the legs, and erosive stomatitis may develop. There may be relative sparing of pressure areas. If the administration of the drug is continued, an exfoliative dermatitis may develop, although occasionally the eruption subsides despite continuation of the medication.

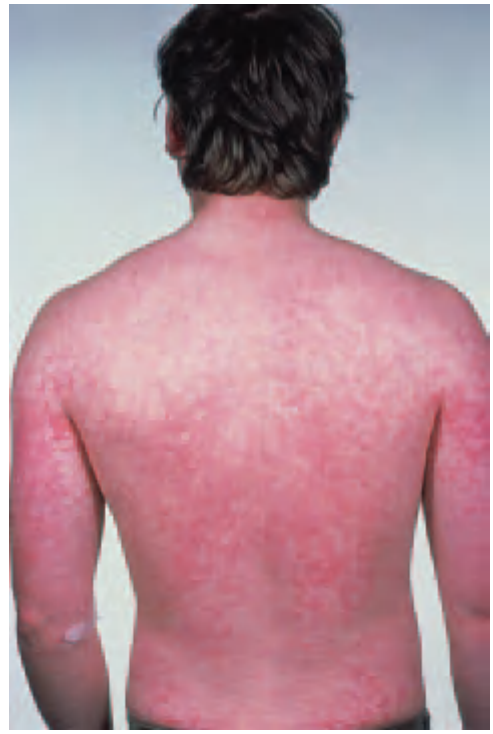

Fig. 73.1 Maculopapular erythema caused by ampicillin.

Morbilliform drug eruptions usually, but not always, recur on rechallenge. The main differential diagnosis is from viral rashes. In a recent series of atypical exanthems, morphology and laboratory investigations led to an aetiological diagnosis in about 70% of cases [1]. It is useful, in differentiating exanthematic drug eruptions from viral exanthems, to remember that viral rashes may start on the face and progress to involve the trunk, and are more often accompanied by conjunctivitis, lymphadenopathy and fever. Maculopapular drug eruptions usually fade with desquamation, sometimes with post-inflammatory hyperpigmentation. Commoner causes are listed in Table 73.2.

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Table 73.2 Drugs causing exanthematic reactions.

Most common	Less common
Ampicillin and penicillin	Cephalosporins
Phenylbutazone and other pyrazolones	Barbiturates
Sulphonamides	Thiazides
Phenytoin	Naproxen
Carbamazepine	Isoniazid
Gold	Phenothiazines
Gentamicin	Quinidine
	Meprobamate
	Atropine

Purpura

A purpuric element to a drug eruption is not uncommon, but primarily purpuric drug-induced rashes also occur. Many drugs may interfere with platelet aggregation [1] but, with the exception of aspirin, this does not usually result in bleeding. A number of drugs have been implicated in the development of drug-induced purpura [2–4]. Several mechanisms may be involved. These include altered coagulation after anticoagulants or some cephalosporins, allergic and non-allergic thrombocytopenia, altered platelet function (as after valproic acid) or vascular causes, including steroid-induced fragility and loss of support. Cytotoxic drug therapy may result in non-allergic purpura due to bone marrow depression, with a platelet count of less than 30 000/mm^3. Bleomycin may induce thrombocytopenia by causing endothelial damage and consequent platelet aggregation [5]. A large number of drugs have been reported to cause allergic thrombocytopenia [2–4]. Heparin may cause purpura with overdosage or due to an allergic thrombocytopenia [6]. The classical example of complement-mediated destruction of platelets, following immune complex formation between a drug (as hapten) bound to the platelet surface and IgG class antibody, was the purpura caused by apronalide (Sedormid). Quinine, quinidine [7,8] and chlorothiazide may also cause allergic purpura. Tissue plasminogen activator (alteplase) has been associated with painful purpura [9]. A purpuric vasculitis-like rash followed secondary spread of a contact dermatitis to balsam of Peru [10].

Capillaritis (pigmented purpuric eruption) may be due to aspirin, carbromal or more rarely to thiamine or meprobamate [11–14], carbamazepine, phenacetin, as well as glipizide, pefloxacin, lorazepam, aspirin, paracetamol, polyvinyl pyrrolidone plasma expander, ciclosporin and griseofulvin [15,16]; it may be due to formation of antibody to a drug–capillary endothelial cell complex [12]. Chronic pigmented purpura is recorded with thiamine propyldisulphide and chlordiazepoxide [13] and aminoglutethimide [17]. NSAIDs, diuretics, meprobamate and ampicillin were the commonest drug cause of pigmented purpuric eruptions in one study [18].

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Annular erythema

Erythema annulare centrifugum has been reported in association with chloroquine and hydroxychloroquine [1], oestrogens, cimetidine [2], penicillin, salicylates and piroxicam, as well as with hydrochlorothiazide [3], spironolactone [4], thioacetazone [5], the phenothiazine levomepromazine [6] and etizolam [7]. Annular erythema has occurred with vitamin K [8].

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Table 73.3 Drugs causing pityriasis rosea-like drug reactions.

Arsenicals	Captopril
Bismuth	Griseofulvin
Gold	Isotretinoin
Barbiturates	Metronidazole
β-Blockers	Pyribenzamine
Clonidine	Methoxypromazine
	Omeprazole

Table 73.4 Drugs reported to exacerbate psoriasis.

Antimalarials
β-Blockers
Lithium salts
Non-steroidal anti-inflammatory drugs
Ibuprofen
Indometacin (indomethacin) (disputed)
Meclofenamate sodium
Pyrazolone derivatives (phenylbutazone, oxyphenbutazone)
Miscellaneous
Captopril
Chlortalidone (chlorthalidone)
Cimetidine
Clonidine
Gemfibrozil
Interferon
Methlydopa
Penicillamine
Penicillin
Terfenadine
Trazodone

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Pityriasis rosea-like reactions

The best-known drug cause of a pityriasiform rash is gold therapy [1], but several other drugs have been implicated, including metronidazole [2], captopril [3], isotretinoin [4] and omeprazole [5] (Table 73.3).

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Psoriasiform eruptions

See Chapter 35 and Table 73.4.

Table 73.5 Drugs causing erythroderma and exfoliative dermatitis.

Allopurinol	Hydantoins
p-Aminosalicylic acid	Isoniazid
Ampicillin	Lithium
Barbiturates	Nitrofurantoin
Captopril	Penicillamine
Carbamazepine	Penicillin
Cefoxitin	Phenylbutazone
Chloroquine	Quinidine
Chlorpromazine	Streptomycin
Cimetidine	Sulphonamides
Diltiazem	Sulphonylureas
Gold	Thioacetazone (thiacetazone)
Griseofulvin	

Exfoliative dermatitis

Exfoliative dermatitis is one of the most dangerous patterns of cutaneous reaction to drugs [1–5]. It may follow exanthematic eruptions or may develop, as in some reactions to arsenicals and the heavy metals, as erythema and exudation in the flexures, rapidly generalizing. The eruption may start several weeks after initiation of the therapy. A dermatitis in patients previously sensitized by contact may also become universal.

The main drugs implicated are listed in Table 73.5. In one large series, sulphonamides, antimalarials and penicillin were most frequently implicated [1]. In another series from India [3], the commonest associated drugs were isoniazid (20%), thioacetazone (15%), topical tar (15%) and a variety of homeopathic medicines (20%), with phenylbutazone, streptomycin and sulfadiazine (sulphadiazine) each accounting for 5% of cases. Phenytoin is a well-recognized cause [6]. Recently incriminated drugs have included captopril, cefoxitin, cimetidine and ampicillin.

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Anaphylaxis and anaphylactoid reactions

This systemic reaction, which usually develops within minutes to hours (the vast majority within the first hour), is often severe and may be fatal [1–3]. Fatal drug-induced anaphylactic shock was estimated at 0.3 cases per million

Table 73.6 Drugs causing urticaria or anaphylaxis.

Animal sera	Dextrans
Vaccines containing egg protein	Mannitol
Desensitizing agents including pollen vaccines	Sorbitol complexes
Antibiotics	Enzymes
Penicillins	Trypsin
Cephalosporins	Streptokinase
Aminoglycosides	Chymopapain
Tetracyclines	Steroids
Sulphonamides	Progesterone
Antifungal agents	Hydrocortisone
Fluconazole	Polypeptide hormones
Ketoconazole	Insulin
Blood products	Corticotrophin
Angiotensin-converting enzyme inhibitors	Vasopressin
Radiographic contrast media	Food and drug additives
Non-steroidal anti-inflammatory drugs (NSAIDs)	Benzoates
Salicylates	Sulphites
Other NSAIDs (e.g. phenylbutazone, aminopyrine, propyphenazone, metamizole, tolmetin)	Tartrazine dyes
	Hydantoins
Narcotic analgesics	Hydralazine
Anaesthetic agents: local and general	Quinidine
Muscle relaxants	Anticancer drugs
Suxamethonium	Vitamins
Curare	Protamine

inhabitants per year, based on notifications to the Danish Committee on Adverse Drug Reactions and to the Central Death Register during the period 1968–90 [3]. The most frequent causes were contrast media for X-ray examinations, antibiotics and extracts of allergens. In less severe cases, there may be premonitory dizziness or faintness, skin tingling and reddening of the bulbar conjunctiva, followed by urticaria, angio-oedema, bronchospasm, abdominal pain and vasomotor collapse. It usually develops on second exposure to a drug, but may develop during the first treatment if this lasts sufficiently long for sensitization to occur. Anaphylaxis is unlikely to occur with a drug taken continuously for several months; in contrast, intermittent administration may predispose to anaphylaxis [1]. It is commoner after parenteral than oral drug administration. The β-blockers enhance anaphylactic reactions caused by other allergens, and may make resuscitation more difficult [4].

The principal drug causes are shown in Table 73.6. Antibiotics (especially penicillin) and radiocontrast media are the most common known causes of anaphylactic events [2]; the incidence of such reactions for each is about 1 in 5000 exposures [5,6], of which less than 10% are fatal [2]. The risk for recurrent anaphylactic reactions is 10–20% for penicillins [5] and 20–40% for radiocontrast media [7]. Anaphylaxis to paracetamol-containing tablets has occurred, although it was the additive polyvinyl pyrrolidone that was reponsible [8].

Anaphylactoid reactions are those that clinically resemble an immediate immune response but in which the mechanism is undetermined. Some drugs and agents, such as mannitol and radiographic contrast media, can stimulate mediator release by an as yet unknown direct mechanism independent of IgE or complement. Anaphylactoid reactions may be produced by non-steroidal analgesics and anti-inflammatory agents (NSAIDs) [9,10], including aspirin and other salicylates, indometacin (indomethacin), phenylbutazone, propyphenazone, metamizole and tolmetin [11], as well as by radiographic contrast media, *d*-tubocurarine, benzoic acid preservatives [12], tartrazine dyes, sulphite preservatives [13] and ciprofloxacin [14]. The HLA-DRB1*11 allele showed a positive association with NSAID-induced anaphylactoid systemic reactions but not with purely cutaneous reactions [15].

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Urticaria

Urticaria (see Chapter 47) is, after an exanthematous eruption, the second most common type of ACDR [1] (Fig. 73.2). Drug-induced urticaria is seen in 0.16% of medical in-patients and accounts for 9% of chronic urticaria or angio-oedema seen in dermatology outpatient departments [1]. Occurring within 24–36 h of drug ingestion, it is most commonly caused by penicillins, sulphonamides and NSAIDs. Drug-induced urticaria is seen in association with anaphylaxis, angio-oedema and serum sickness. On rechallenge, lesions may develop within minutes. Angio-oedema, involving oedema of the deep dermis or subcutaneous and submucosal areas, is more rarely seen than urticaria as an ACDR, and occurs in less than 1% of patients receiving the particular drug.

The commoner drug causes of urticaria/angio-oedema are listed in Table 73.6. The frequency of urticaria/angio-oedema or anaphylactic responses to aspirin and other NSAIDs is about 1% in an outpatient population and is familial [2]. Aspirin (salicylates) may also aggravate chronic urticaria [3,4]. In addition, an unsuspected agent, for example the yellow dye tartrazine, may really be responsible for an urticaria attributed to aspirin or another drug. The analgesic codeine is also a cause of urticaria [5]. Penicillin is a very well-documented cause of acute urticaria, but the role of this drug in chronic urticaria is controversial [6]. Urticaria develops in about 1% of patients receiving blood transfusions [7]. There have been numerous papers on the potential role of food and drug additives [8–16], including preservatives such as benzoic acid, butylated hydroxyanisole, butylated hydroxytoluene, sulphites and rarely aspartame, as well as tartrazine dyes, in the development of chronic urticaria. However, one study suggested that common food additives are seldom if ever of significance in urticaria [9]. Urticaria may follow alcohol consumption [17], intra-articular methylprednisolone [18] and even cetirizine [19].

Certain drugs, such as opiates, codeine, amfetamine, polymyxin B, *d*-tubocurarine, atropine, hydralazine, pentamidine, quinine and radiocontrast media, may release mast cell mediators directly. Cyclo-oxygenase inhibitors, such as aspirin and indometacin, and ACE inhibitors, such as captopril and enalapril, may cause urticaria or angio-oedema by pharmacological mechanisms. ACE inhibitors may cause increased frequency, intensity and duration of bouts of idiopathic angio-oedema during long-term use [20,21].

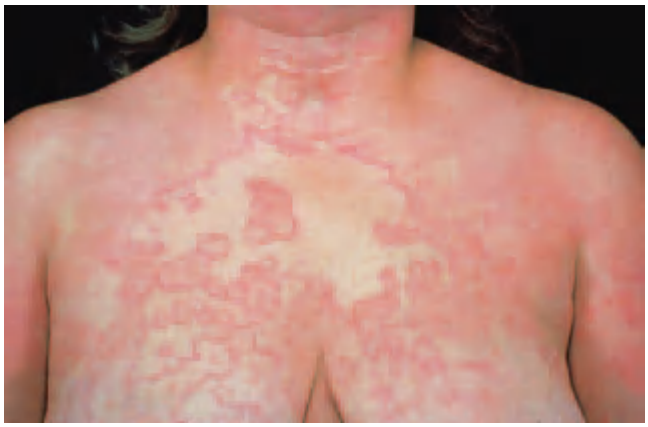

Fig. 73.2 Urticaria induced by acetylsalicylic acid. (Courtesy of St John's Institute of Dermatology, London, UK.)

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Serum sickness

Serum sickness, a type III immune complex-mediated reaction, may occur between 5 days and 3 weeks after initial exposure [1–5], and in its complete form combines fever, urticaria, angio-oedema, joint pain and swelling, lymphadenopathy, and occasionally nephritis or endocarditis, with eosinophilia. In minor forms of serum sickness, fever, urticaria and transitory joint tenderness may be the only manifestations.

Drugs implicated include heterologous serum [1,2], immune globulin (as treatment for Kawasaki disease) [6], aspirin, antibiotics [7,8] such as penicillin [3,7,9], amoxicillin [7], flucloxacillin [7], cefaclor [10–14], cefprozil [15], piperacillin [16], ciprofloxacin [17], cefatrizine [18], cotrimoxazole [7], troleandomycin (triacetyloleandomycin) [7], streptomycin, sulphonamides and sulfasalazine [19], thiouracils, intravenous streptokinase [20,21], *N*-acetylcysteine [22], staphylococcal protein A immunomodulation [23] and amfebutamone (bupropion) [24]. Of 32 women in an *in vitro* fertilization programme, 15% developed serum sickness 8–12 days after oocyte retrieval by echographic puncture, when a medium containing bovine serum was employed for rinsing follicles [25]. Patients had specific IgG antibodies against, and positive intradermal skin testing to, bovine serum albumin. A characteristic serpiginous, erythematous and purpuric eruption developed on the hands and feet at the borders of palmar and plantar skin in a series of patients treated with intravenous infusions of horse antithymocyte globulin for bone marrow failure [1,2]. Circulating immune complexes, low serum C4 and C3 levels, and elevated plasma C3a anaphylatoxin levels were found. Direct immunofluorescence revealed the presence of immunoreactants including IgM, C3, IgE and IgA in the walls of dermal blood vessels.

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Erythema multiforme, Stevens–Johnson syndrome and toxic epidermal necrolysis

See Chapter 74.

Drug hypersensitivity syndrome

The drug hypersensitivity syndrome [1–3], also known as *d*rug *r*ash with *e*osinophilia and *s*ystemic *s*ymptoms (DRESS) syndrome [4] or as *d*rug-*i*nduced *d*elayed *m*ulti-*o*rgan *h*ypersensitivity *s*yndrome (DIDMOHS) [2], has been reported with the anticonvulsants phenytoin, carbamazepine, phenobarbital and lamotrigine (see also anticonvulsant hypersensitivity syndrome, p. 73.45), and with trimethoprim–sulfamethoxazole, minocycline, procarbazine, allopurinol, terbinafine and dapsone. Superimposed viral infection may have a role in the aetiology [5] (see also mechanisms of drug reactions, cell-mediated immune reactions, p. 73.18). The syndrome comprises fever, facial oedema with infiltrated papules, generalized papulopustular or exanthematous rash which may extend to exfoliative dermatitis, lymphadenopathy, haematological abnormalities (hypereosinophilia in 90% of cases, atypical lymphocytes/mononucleosis in 40% of

cases), and organ involvement such as hepatitis, possible nephritis, pneumonitis, myocarditis and hypothyroidism, occurring after 3–6 weeks of drug therapy. The cutaneous histological pattern shows a lymphocytic infiltrate, sometimes mimicking a cutaneous lymphoma. The mortality is of the order of 10%; the syndrome may proceed to Stevens–Johnson syndrome or TEN (see Chapter 74). Management is usually with oral corticosteroids. This syndrome should be distinguished from drug-induced pseudolymphoma syndrome, which has a more insidious beginning with nodules and infiltrated plaques appearing several weeks after starting the drug, without constitutional symptoms (see below).

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Fixed eruptions [1–9]

A fixed drug eruption characteristically recurs in the same site or sites each time the drug is administered; with each exposure, however, the number of involved sites may increase. Usually, just one drug is involved, although independent lesions from more than one drug have been described [10]. Cross-sensitivity to related drugs may occur, such as between phenylbutazone and oxyphenbutazone, between tetracycline-type drugs, and between anticonvulsants [11]. There may be a refractory period after the occurrence of a fixed eruption.

Acute lesions usually develop 30 min to 8 h after drug administration as sharply marginated, round or oval itchy plaques of erythema and oedema becoming dusky violaceous or brown, and sometimes vesicular or bullous (Fig. 73.3). The eruption may initially be morbilliform, scarlatiniform or erythema multiforme-like; urticarial, nodular or eczematous lesions are less common. Lesions are sometimes solitary at first, but with repeated attacks new lesions usually appear and existing lesions may increase in size. A multifocal bullous fixed drug eruption due to mefenamic acid resembled erythema multiforme [12]. Occasionally, involvement is so extensive as to mimic TEN [13,14].

Lesions are commoner on the limbs than on the trunk; the hands and feet, genitalia and perianal areas are

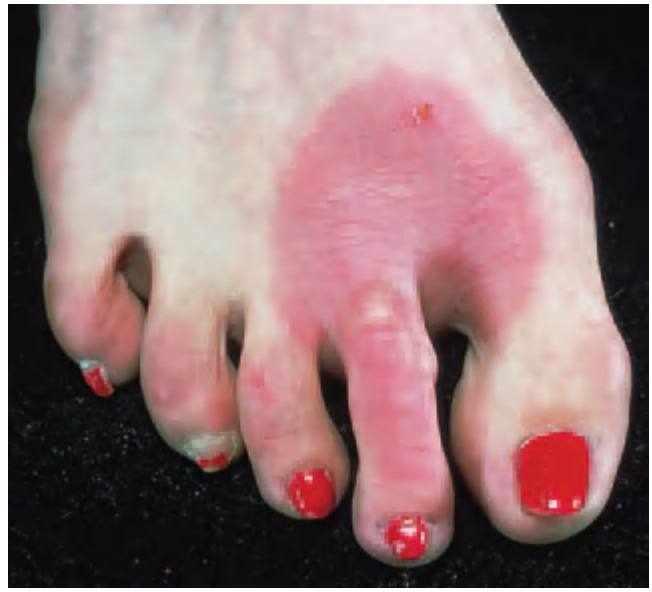

Fig. 73.3 Bullous fixed drug eruption with hyperpigmentation. (Courtesy of St John's Institute of Dermatology, London, UK.)

favoured sites. Perioral and periorbital lesions may occur. Genital [15] and oral mucous membranes [16] may be involved in association with skin lesions, or alone. In the case of isolated male genital fixed drug eruption (often affecting only the glans penis), the drugs most commonly implicated in one series were co-trimoxazole (trimethoprim–sulfamethoxazole), tetracycline and ampicillin [15]. With oral fixed drug eruption, co-trimoxazole, oxyphenbutazone and tetracycline were the most common causative drugs [16]. Pigmentation of the tongue may occur as a form of fixed drug eruption in heroin addicts [17]. As healing occurs, crusting and scaling are followed by pigmentation, which may be very persistent and occasionally extensive, especially in pigmented individuals; pigmentation may be all that is visible between attacks. Non-pigmenting fixed reactions have been reported in association with the sympathomimetic agents pseudoephedrine [18,19] and tetryzoline (tetrahydrozoline) hydrochloride, diflunisal, thiopental (thiopentone), piroxicam, the radiopaque contrast medium iothalamate, arsphenamine [20], paracetamol [21], intra-articular triamcinolone acetonide [22] and eperisone hydrochloride [23].

The number of drugs capable of producing fixed drug eruption is very large. However, most fixed drug eruptions are due to one or other of the substances listed in Table 73.7. Earlier series incriminated particularly analgesics, sulphonamides and tetracyclines. In a report from Finland, phenazones caused most eruptions, with barbiturates, sulphonamides, tetracyclines and carbamazepine causing fewer reactions [24]. A series from India reported that acetylsalicylic acid was the drug most commonly

Table 73.7 Drugs causing fixed eruptions.

Antibacterial substances
Sulphonamides (co-trimoxazole)
Tetracyclines
Penicillin
Ampicillin
Amoxicillin
Erythromycin
Trimethoprim
Nystatin
Griseofulvin
Dapsone
Arsenicals
Mercury salts
p-Aminosalicylic acid
Thioacetazone (thiacetazone)
Quinine
Metronidazole
Clioquinol

Barbiturates and other tranquillizers
Barbiturate derivatives
Opium alkaloids
Chloral hydrate
Benzodiazepines: chlordiazepoxide
Anticonvulsants
Dextromethorphan

Non-steroidal anti-inflammatory drugs
Aspirin (acetylsalicylic acid)
Oxyphenbutazone
Phenazone (antipyrine)
Metamizole
Paracetamol (acetaminophen)
Ibuprofen
Various non-proprietary analgesic combinations

Phenolphthalein and related compounds

Miscellaneous
Codeine
Hydralazine
Oleoresins
Sympathomimetics
Sympatholytics
Parasympatholytics: hyoscine butylbromide
Magnesium hydroxide
Magnesium trisilicate
Anthralin
Chlorthiazone
Chlorphenesin carbamate
Food substitutes and flavours

implicated in children [25]; a more recent study found that co-trimoxazole was the usual culprit in children [26]. Co-trimoxazole has been implicated as the most frequent cause in many studies [6,8,27]. A fixed drug eruption apparently caused by co-trimoxazole was reported in a man following intercourse with his wife, who was taking the drug [28]. Trimethoprim has caused a linear fixed drug eruption [29]. A report in 1991 showed that co-trimoxazole caused the maximum incidence (36.3%), followed by tetracycline (15.9%), pyrazolones (14.2%), sulfadiazine (12.4%), dipyrine (9.3%), paracetamol (7.9%), aspirin (1.7%), thioacetazone (0.88%) and levamisole (0.88%) [27]. Co-trimoxazole was also the most common cause of fixed drug eruption (75%), followed by naproxen sodium (12.5%), dipyrone (9.5%), dimenhydrinate (1.5%) and paracetamol (1.5%) in a study in 2000 [8]. However, a survey of current causes of fixed drug eruption in the UK listed NSAIDs including aspirin, paracetamol, antibacterial agents, systemic antifungal agents, psychotropic drugs, proton pump inhibitors, calcium channel blockers, ACE inhibitors and hormonal preparations [9], reflecting the decreased use of co-trimoxazole.

A drug-specific clinical pattern in fixed drug eruptions based on a study of 113 patients has been reported [8,27]. Sulphonamides, including co-trimoxazole, induced lesions on the lips, trunk and limbs, with only minimal involvement of mucosae. Naproxen predominantly affected the lips and face. Tetracycline and co-trimoxazole caused lesions mainly on the glans penis. Pyrazolones affected mainly the lips and mucosae, with a few lesions of the trunk and limbs. Dipyrine, aspirin and paracetamol caused lesions of the trunk and limbs, sparing the lips, genitalia and mucosae. Levamisole caused associated constitutional disturbances with extensive skin lesions, as did thioacetazone [27]. Paracetamol is a rare cause of fixed drug eruption [30–33]; other drugs implicated have included codeine [34], naproxen [35], rofecoxib [36], ciprofloxacin [37], clarithromycin [38], rifampicin [39], metronidazole [40], terbinafine [41], fluconazole [42], lamotrigine [43], dimenhydrinate [44], cetirizine [45], loratadine [46], ticlopidine [47], phenylpropanolamine hydrochloride [48], and lactulose in an injected botulinum toxin preparation [49]. Familial fixed drug eruption has occurred occasionally [50,51].

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Lichenoid eruptions

Lichenoid drug eruptions and lichen planus are discussed in Chapter 42. Some of the drugs that induce this pattern of reaction are listed in Table 73.8 [2]. Photodistributed lichenoid lesions may occur with a number of drugs, including thiazide diuretics (Fig. 73.4).

Photosensitivity

Drug–light reactions, which cause eruptions on exposed areas, with sparing of upper eyelids, submental and retroauricular areas, may be phototoxic or photoallergic; these cannot always be distinguished clinically, and some drugs may produce cutaneous involvement by both mechanisms [1–5]. The main drugs implicated in photosensitivity reactions are listed in Table 73.9.

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Phototoxic reactions

Phototoxic reactions are commoner than photoallergic reactions, and can be produced in almost all individuals given a high enough dose of drug and sufficient light irradiation. They occur within 5–20 h of the first exposure, and resemble exaggerated sunburn. Erythema, oedema, blistering, weeping, desquamation and residual hyperpig-

Table 73.8 Drugs causing lichenoid eruptions.

Gold salts	Antitubercular drugs
Antimalarials	Ethambutol
Mepacrine (quinacrine, atabrine)	Isoniazid
Chloroquine	*p*-Aminosalicylic acid
Quinine	Streptomycin
Quinidine	Cycloserine
Pyrimethamine	Antifungal drugs: ketoconazole
Penicillamine	Chemotherapeutic agents
Diuretics	Hydroxyurea
Thiazides	5-Fluorouracil
Furosemide (frusemide)	Heavy metals
Spironolactone	Mercurials
Diazoxide	Arsenicals
Antihypertensive agents	Bismuth
β-Blockers	Miscellaneous
Angiotensin-converting enzyme inhibitors: captopril, enalapril	Tetracyclines
	Carbamazepine
Methyldopa	Phenytoin
Calcium channel blockers	Procainamide
Nifedipine	Allopurinol
Phenothiazine derivatives	Iodides and radiocontrast media
Metopromazine	Tiopronin
Levomepromazine	Pyritinol
Chlorpromazine	Cyanamide
Sulphonylurea hypoglycaemic agents	Dapsone
Chlorpropamide	Amiphenazole
Tolazamide	Levamisole
Non-steroidal anti-inflammatory drugs: phenylbutazone	Nandrolone furylpropionate
Sulfasalazine (sulphasalazine) and mesalazine	Cinnarizine
	Flunarizine

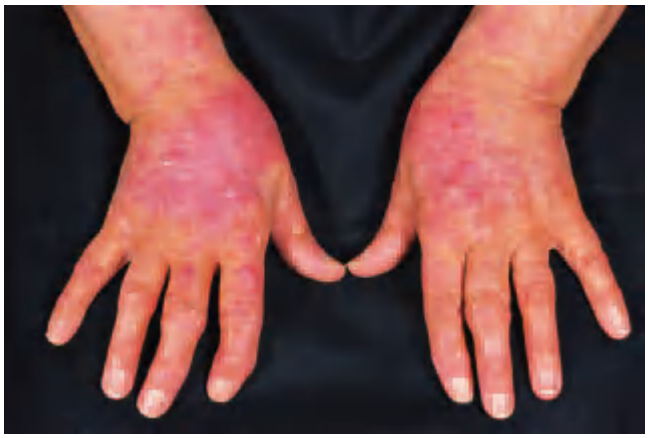

Fig. 73.4 Lichenoid photosensitivity eruption caused by thiazide diuretic. (Courtesy of A. Ive, Durham, UK.)

mentation occur on exposed areas; there may be photo-onycholysis. The following are well-recognized causes of phototoxicity:

- tetracyclines [1–4], especially demeclocycline, less frequently doxycycline, oxytetracycline and tetracycline, and rarely minocycline and methacycline;
- other antibacterials including sulphonamides and fluoroquinolones [4];
- phenothiazines, especially chlorpromazine, promethazine and less commonly thioridazine;
- furosemide [5] and nalidixic acid [4,6], both of which produce a pseudoporphyria syndrome, with blistering of the exposed areas;
- NSAIDs, including ibuprofen [7], piroxicam [8–11], carprofen and tiaprofenic acid [12];
- psoralens;
- amiodarone (which causes photosensitivity in over 50% of cases) [13];
- certain anticancer drugs [14], including dacarbazine [14,15], 5-fluorouracil, mitomycin and vinblastine;
- coal tar and its derivatives;
- fibric acid derivatives, including bezafibrate and fenofibrate [16,17];
- the non-steroid antiandrogen flutamide given for prostatic carcinoma [18,19].

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Table 73.9 Drugs causing photosensitivity.

Frequent
Amiodarone
Phenothiazines
  Chlorpromazine
  Promethazine
Psoralens
Sulphonamides: co-trimoxazole
Tetracyclines: demeclocycline
Thiazides
Non-steroidal anti-inflammatory drugs
  Azapropazone
  Piroxicam
  Carprofen
  Tiaprofenic acid
  Benoxaprofen (withdrawn)
Nalidixic acid
Coal tar

Less frequent: topical
Antihistamines
Local anaesthetics
Benzydamine
Hydrocortisone
Sunscreens
  p-Aminobenzoic acid
  Benzophenone
Halogenated salicylanilides

Less frequent: systemic
Ampicillin
Antidepressants (tricyclic)
  Imipramine
  Protriptyline
Antidepressants (monoamine oxidase inhibitors): phenelzine
Antifungal agents
  Griseofulvin
  Ketoconazole
β-Blockers
Carbamazepine
Cimetidine
Cytotoxic agents
  Dacarbazine
  Fluorouracil
  Mitomycin
  Vinblastine
Diazepam
Furosemide (frusemide)
Methyldopa
Oral contraceptives
Quinine
Quinidine
Sulphonylureas
  Chlorpropamide
  Tolbutamide
Retinoids
  Isotretinoin
  Etretinate
Triamterene

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Photoallergic reactions

Photoallergic reactions require a latent period during which sensitization occurs, and usually appear within 24 h of re-exposure to drug and light in a sensitized individual; unlike phototoxic reactions, they may spread beyond irradiated areas. Most systemic drugs causing photoallergy also cause phototoxicity. There may be cross-reactivity with chemically related substances.

Photoallergic reactions may occur as a result of local photocontact dermatitis to a topical photoallergen. Photocontact dermatitis is a relatively common cause of photosensitivity, accounting for 9% of cases in a multicentre study [1]. Topical photoallergens include antihistamines, chlorpromazine, local anaesthetics, benzydamine, hydrocortisone, desoximetasone (desoxymethasone) and sunscreens containing *p*-aminobenzoic acid (PABA) and its derivatives. Contact allergy and photoallergy to benzophenones in PABA-free sunscreens may be commoner than is realized [2]. Halogenated salicylanilides, previously used as a disinfectant in soaps, and related compounds also cause photocontact dermatitis.

Photoallergic reactions may also occur as a result of systemically administered drugs [3], such as phenothiazines (chlorpromazine, promethazine), sulphonamides, aromatic sulphonamides such as thiazide diuretics

[4,5] and oral hypoglycaemic agents (chlorpropamide and tolbutamide), griseofulvin [6] and quinidine [7,8]. Quinidine-induced photo-eruptions may be either eczematous or lichenoid; a persistent livedo reticularis-like eruption may be seen in severe cases of quinidine photosensitivity. Enalapril has caused a photosensitive lichenoid eruption [9]. Tricyclic antidepressants may cause allergy as well as photosensitivity [10]. NSAIDs, disinfectants, sunscreens, phenothiazines and fragrances caused photoallergic reactions most often in a 5-year survey by the German, Austrian and Swiss photopatch test group [11].

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Porphyria and pseudoporphyria

A number of drugs may precipitate porphyria cutanea tarda with resultant photosensitivity, or cause a pseudoporphyria syndrome with bulla formation. The reader is referred to Chapter 57.

Photorecall reactions

A curious photorecall-like eruption, restricted to an area of sunburn sustained 1 month previously, occurred in a patient treated with cefazolin (cephazolin) and gentamicin [1]. An ultraviolet recall-like eruption has been reported with piperacillin, tobramycin and ciprofloxacin [2]. A recurrent cutaneous reaction localized to the site of pelvic radiotherapy for adenocarcinoma of the prostate followed sun exposure in one patient [3]. Methotrexate is associated with severe reactivation of sunburn [4,5].

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Photo-onycholysis

Photo-onycholysis may be caused by tetracycline, psoralens and UVA (PUVA) therapy, and the fluoroquinolone antibiotics pefloxacin and ofloxacin.

Pigmentation reactions

Hyperpigmentation (Table 73.10)

Drug-induced alteration in skin colour [1–3] may result from increased (or more rarely decreased) melanin synthesis, increased lipofuscin synthesis, cutaneous deposition of drug-related material, or most commonly as a result of post-inflammatory hyperpigmentation (e.g. fixed drug eruption). Oral contraceptives may induce chloasma [4]. Other drugs implicated in cutaneous hyperpigmentation include minocycline [5,6], antimalarials [7,8], chlorpromazine [9,10], imipramine (photodistributed) [11–13] and desimipramine [14], amiodarone [15], carotene and heavy metals. Long-term (more than 4 months) antimalarial therapy may result in brownish or blue-black pigmentation, especially on the shin, face and hard palate or subungually. Yellowish discoloration may occur with mepacrine (quinacrine) or amodiaquine. Long-term high-dose phenothiazine (especially chlorpromazine) therapy results in a blue-grey or brownish pigmentation of sun-exposed areas, the result of a phototoxic reaction, with

Table 73.10 Drugs causing pigmentation.

Oral contraceptives	Chemotherapeutic agents
Minocycline	Miscellaneous
Antimalarials	Amiodarone
Chloroquine	Carotene
Hydroxychloroquine	Clofazimine
Mepacrine	Pefloxacin
Antidepressants	Sulfasalazine (sulphasalazine)
Chlorpromazine	
Imipramine	
Heavy metals	
Gold	
Lead	
Silver	

pigment deposits in the lens and cornea [10]. The cancer chemotherapeutic agents may be associated with pigmentation as follows [16]. Skin pigmentation may be caused by bleomycin, busulfan, topical carmustine, cyclophosphamide, daunorubicin, fluorouracil, hydroxyurea, topical mechlorethamine, methotrexate, mithramycin, mitomycin and thiotepa. Busulfan and doxorubicin cause mucous membrane pigmentation. Nail pigmentation may result from bleomycin, cyclophosphamide, daunorubicin, doxorubicin and fluorouracil. Methotrexate may induce pigmentation of the hair, and cyclophosphamide of teeth. Sulfasalazine has caused reversible hyperpigmentation [17], and pefloxacin blue-black pigmentation of the legs [18].

Gold may cause blue-grey pigmentation in light-exposed areas (*chrysiasis*) [19,20] and silver may cause a similar discoloration (*argyria*) [21]. Lead poisoning can cause a blue-black line at the gingival margin and grey discoloration of the skin. Clofazimine produces red-brown discoloration of exposed skin and the conjunctivae, together with red sweat, urine and faeces [22]. Slate-grey to blue-black pigmentation may occur after long-term topical application of hydroquinone, causing ochronosis [23].

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Hypopigmentation

Topical thiotepa has produced periorbital leukoderma [1]. Hypopigmentation has occurred as a result of occupational exposure to monobenzyl ether of hydroquinone, *p*-tertiary-butylcatechol, *p*-tertiary-butylphenol, *p*-tertiary-amylphenol, monomethyl ether of hydroquinone and hydroquinone [2]. In addition, hypopigmentation may result from phenolic detergent germicides [3], and following use of diphencyprone for alopecia areata [4,5]. Depigmentation of the skin and hair occurred after a phenobarbital-induced eruption [6]. Photoleukomelanodermatitis occurred due to afloqualone for cervical spondylosis; photopatch and oral challenge tests were positive [7]. Generalized cutaneous depigmentation followed a sulphamide-induced ADR [8].

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Acneiform and pustular eruptions

The term 'acneiform' is applied to eruptions that resemble acne vulgaris [1,2] (see Chapter 43). Lesions are papulopustular but comedones are usually absent. Adrenocorticotrophic hormone (ACTH), corticosteroids

[3], dexamethasone in neurosurgical patients, anabolic steroids for body-building [4], androgens (in females), oral contraceptives, iodides and bromides may produce acneiform eruptions. Isoniazid may induce acne, especially in slow inactivators of the drug [5]. Other drugs implicated in the production of acneiform rashes include dantrolene [6], danazol [7], quinidine [8], lithium [9,10] and azathioprine [11]. Acne rosacea was temporally associated with daily high-dose vitamin B supplement therapy in one patient [12], and eosinophilic pustular folliculitis (Ofuji's disease) developed in association with use of the cerebral activator indeloxazine hydrochloride [13].

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Acute generalized exanthematous pustulosis (toxic pustuloderma)

Pustular reactions (toxic pustuloderma, acute generalized exanthematous pustulosis) have been reported in association with a number of drugs [1]. The main differential diagnosis of a generalized pustular drug eruption is pustular psoriasis [2]. Two histological patterns may be seen: (i) a toxic pustuloderma with spongiform intraepidermal pustules, papillary oedema and a mixed upper dermal perivascular inflammatory infiltrate; or (ii) a leukocytoclastic vasculitis with neutrophil collections both below and within the epidermis, suggesting passive neutrophil elimination via the overlying epidermis [3,4]. The presence of eosinophils in the inflammatory infiltrate is a helpful pointer to a drug cause [2]. A responsible drug was found in 87% of a series of 63 patients with acute generalized exanthematous pustulosis; antibiotics were implicated as the causative agent in 80% of individuals [4]. The latter included particularly ampicillin, amoxicillin, spiramycin, erythromycin and cyclins. Hypersensitivity to mercury was also recorded as a precipitating cause. Pustulosis developed within 24 h of drug administration. It often started on the face or in flexural areas, rapidly became disseminated, with fever, and settled spontaneously with desquamation. Facial oedema, purpura, vesicles, blisters and erythema multiforme-like lesions were also seen; transient renal failure was noted in 32% of cases. Occasionally, TEN may be mimicked [5].

Acute generalized exanthematic pustulosis is usually due to penicillins or macrolides [6,7]. There have been individual reports of pustular drug reactions with ampicillin (which may be localized [8]), amoxicillin (with or without clavulanic acid) [9], propicillin [10], imipenem [11], the cephalosporins cefalexin (cephalexin) and cefradine (cephradine) [12,13], co-trimoxazole [14], doxycycline [15], chloramphenicol [16], norfloxacin [17], ofloxacin [18], teicoplanin [19], streptomycin [20], isoniazid, metronidazole [21], terbinafine [22–24], fluconazole [25], itraconazole [26], nystatin [27], salazosulfapyridine/salazopyrine [28], mesalazine [29], diltiazem [30], captopril [31] and enalapril [32], furosemide [33], hydrochlorothiazide [34], cytarabine [35], high-dose chemotherapy [36], sertraline [37], chlorpromazine [38], nitrazepam, acetylsalicylic acid [39], naproxen [40], allopurinol [41], hydroxychloroquine [42], pyrimethamine, piperazine ethionamate, the mucolytic agent eprazinone [43], dextropropoxyphene [44], icodextrin [45] and mexiletine [46]. Cases of generalized pustulation in association with the anticonvulsant hypersensitivity syndrome caused by phenytoin [47] and carbamazepine [48] have been recorded. Patch testing with the culprit drug may be positive in patients with acute generalized exanthematous pustulosis [49].

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Eczematous eruptions

Allergic contact dermatitis is discussed in Chapter 20. This section concerns the entity termed 'systemic contact-type dermatitis medicamentosa' [1–5] (Table 73.11). A patient initially sensitized to a drug by way of allergic contact dermatitis may develop an eczematous reaction when the same, or a chemically related, substance is subsequently administered systemically. The eruption tends to be symmetrical, and may involve first, or most severely, the site(s) of the original dermatitis, before becoming generalized. Patients with a contact allergy to ethylenediamine may develop urticaria or systemic eczema following injection of aminophylline preparations containing ethylenediamine as a solubilizer for theophylline [6,7]. Patients with contact allergy to parabens may develop systemic eczema on medication with a drug containing parabens as a preservative [8]. Similarly, sensitized patients may develop eczema following oral ingestion of neomycin or hydroxyquinolines [9]. Diabetic patients sensitized by topical preparations containing *p*-amino compounds, such as *p*-phenylenediamine hair dyes, PABA sunscreens and certain local anaesthetic agents (e.g. benzocaine), may develop a systemic contact dermatitis with the hypoglycaemic agents tolbutamide or chlorpropamide. Sulphonylureas may also induce eczematous eruptions in sulphanilamide-sensitive patients as a result of cross-reactivity. Phenothiazines can produce allergic contact dermatitis, photoallergic reactions and eczematous contact-type dermatitis, and may cross-react with certain antihistamines. Tetraethylthiuram disulphide (disulfiram, Antabuse) for the management of alcoholism can cause eczematous reactions in patients sensitized to thiurams via rubber gloves. 'Systemic contact-type dermatitis' reactions have also been described with [4] acetylsalicylic acid, codeine [10], phenobarbital, pseudoephedrine hydrochloride and norephedrine hydrochloride [11], ephedrine [12], erythromycin [13], isoniazid [14], dimethylsulfoxide, hydroxyquinone, nystatin, subcutaneous hydromorphone

Table 73.11 Systemic drugs that can reactivate allergic contact eczema to chemically related topical medicaments. (From Fisher [1].)

Systemic drug	Topical medicament
Ethylenediamine antihistamines Aminophylline Piperazine	Aminophylline suppositories and ethylenediamine hydrochloride
Organic and inorganic mercury compounds	Ammoniated mercury
Tincture of benzoin inhalation	Balsam of Peru
Procaine Acetohexamide *p*-Aminosalicylic acid Azo dyes in foods and drugs Chlorothiazide Chlorpropamide Tolbutamide	Benzocaine (*p*-amino compound) and glyceryl *p*-aminobenzoic acid sunscreens
Chloral hydrate	Chlorobutanol
Iodochlorhydroxyquinoline	Halogenated hydroxyquinoline creams (Vioform)
Iodides, iodinated organic compounds, radiographic contrast media	Iodine
Streptomycin, kanamycin, paromycin, gentamicin	Neomycin sulphate
Glyceryl trinitrate tablets	Glyceryl trinitrate ointment
Disulfiram (Antabuse)	Thiuram (rubber chemical)

given for cancer pain [15], amlexanox [16], enoxolone [17], vitamin B_1, vitamin C, parabens, butylated hydroxyanisole, hydroxytoluene and tea-tree oil [18]. Allergic eczematous reactions to endogenous or exogenous systemic corticosteroids, including hydrocortisone and methylprednisolone, have been documented in patients who are patch-test positive to topical corticosteroids [19,20].

The term 'baboon syndrome' denotes a characteristic pattern of systemic allergic contact dermatitis [21–23], in which there is diffuse erythema of the buttocks, upper inner thighs and axillae, provoked by penicillin [24], ampicillin, amoxicillin [25], nickel, heparin, mercury (including that found in a homeopathic medicine [26]), terbinafine [27] and hydroxyurea [28]. Patch tests are commonly positive and usually vesicular, although histology of the eruption itself may show leukocytoclastic vasculitis; oral challenge with the suspected antigen may be required to substantiate the diagnosis. Disulfiram therapy of a nickel-sensitive alcoholic patient may induce this syndrome, as the drug leads to an initial acute increase in blood nickel concentration [21]. Cases have been described from Japan under the name 'mercury exanthem' following inhalation of mercury vapour from crushed thermometers in patients with a history of mercury allergy.

The term 'endogenic contact eczema' [29] refers to the occurrence of an eczematous contact drug reaction following primary sensitization by oral therapy, as in the case of a patient with a drug-related exanthem who later develops localized dermatitis due to topical therapy. Thus, eczematous eruptions may develop following therapy with penicillin [30], methyldopa, allopurinol, indometacin, sulphonamides, gold, quinine, chloramphenicol, clonidine or bleomycin [31]. The alkylating agent mitomycin C administered intravesically for carcinoma of the bladder has been associated with an eczematous eruption, particularly on the face, palms and soles in some patients; these may have positive patch tests to the drug [32,33].

Some of the more important causes of eczematous drug reactions are listed in Table 73.11. Sensitivity to the suspected drug may be confirmed by subsequent patch testing, when the skin reaction has settled.

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Bullous eruptions

Bullous drug eruptions encompass many different clinical reactions and pathomechanisms [1,2]. Isolated blisters, often located preferentially on the extremities, may be caused by a wide variety of chemically distinct drugs. Fixed drug eruptions and drug-induced vasculitis may have a bullous component; these are reviewed elsewhere in this chapter. Erythema multiforme, Stevens–Johnson syndrome and drug-induced TEN are discussed in Chapter 74. The specific drug-induced entities of porphyria and pseudoporphyria, bullous pemphigoid, pemphigus and linear IgA disease are discussed here.

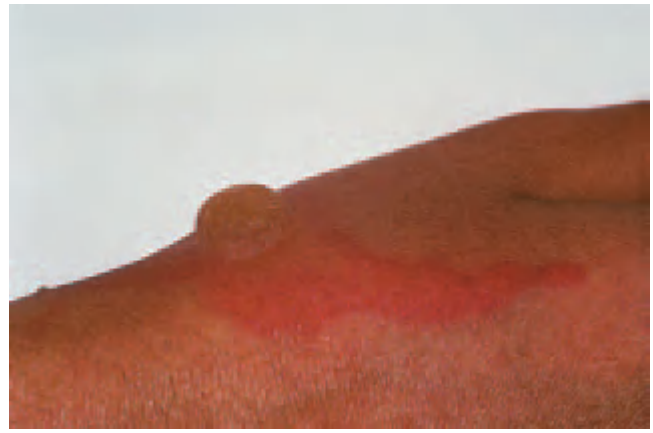

Fig. 73.5 Bullous eruption in barbiturate overdose. (Courtesy of Charing Cross Hospital, London, UK.)

Bullous eruption in drug overdosage

Bullae, often at pressure areas, may be seen in patients comatose after overdosage with barbiturates (Fig. 73.5), methadone, meprobamate, imipramine, nitrazepam or glutethimide [1–5].

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Drug-induced porphyria

Porphyria is discussed in Chapter 57. Drugs reported to exacerbate the acute hepatic porphyrias are listed in Table 73.12; these either cause excess destruction of haem or inhibit haem synthesis [1–3].

Pseudoporphyria

Pseudoporphyria, in which porphyria-like blistering of exposed areas on the extremities occurs in the absence of abnormal porphyrin metabolism, may be caused by high-dose furosemide [4], naproxen [5,6] and other NSAIDs [7–9], combined carisoprodol and aspirin [10], nalidixic acid [11], tetracyclines [12] and sulphonylureas. Phototoxic mechanisms have been implicated in some cases. A similar syndrome has been reported in a patient taking very large doses of pyridoxine (vitamin B_6) [13].

Table 73.12 Drugs that are unsafe to use in patients with acute intermittent porphyria, porphyria cutanea tarda or variegate porphyria.

Aminoglutethimide	Meprobamate
Barbiturates	Novobiocin
Carbamazepine	Oestrogens
Carbromal	Primidone
Chlorpropamide	Progestogens
Danazol	Pyrazolone derivatives
Diclofenac	Rifampicin
Diphenylhydantoin (phenytoin)	Sulphonamides
Ergot preparations	Tolbutamide
Glutethimide	Trimethadione
Griseofulvin	Valproic acid

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Drug-induced bullous pemphigoid

Idiopathic bullous pemphigoid is discussed in Chapter 41. In drug-induced bullous pemphigoid, patients tend to be younger; tissue-bound and circulating anti-basement-membrane zone IgG antibodies may be absent, or additional antibodies such as intercellular or antiepidermal cytoplasmic antibodies may be detected. Some cases of drug-induced bullous pemphigoid are short-lived, whereas others become chronic. Drug-induced bullous or cicatricial pemphigoid have been reported with a number of medications [1–5], especially furosemide [6,7] but also bumetanide [8], spironolactone [9,10], penicillamine [11,12], the penicillamine analogue tiobutarit [13], penicillin [14] and its derivatives [15], ciprofloxacin [16], sulfasalazine, salicylazosulfapyridine, phenacetin [17], enalapril [18], fluoxetine [19], novoscabin, topical fluorouracil, and PUVA therapy [20]. In the case of enalapril-induced bullous pemphigoid, the IgG antibody was directed against the 230-kDa bullous pemphigoid antigen [18]. Cicatricial pemphigoid has been described in association with penicillamine [12] and clonidine [21]. An association with vaccination for influenza and with tetanus toxoid and induction of bullous pemphigoid has been noted rarely [22–25].

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Table 73.13 Drugs implicated in the development of pemphigus.

Thiol drugs
Penicillamine
Captopril, ramipril
Gold sodium thiomalate
Pyritinol
Thiamazole (methimazole)
Tiopronin (mercaptopropionylglycine)

Non-thiol drugs
Antibiotics
Penicillin and derivatives
Rifampicin
Cefalexin (cephalexin)
Cefadroxil
Ceftazidine

Pyrazolone derivatives
Aminophenazone
Aminopyrine
Azapropazone
Oxyphenbutazone
Phenylbutazone

Miscellaneous
Glibenclamide
Hydantoin
Levodopa
Lysine acetylsalicylate
Nifedipine
Phenobarbital (phenobarbitone)
Piroxicam
Progesterone
Propranolol
Interferon-β and interleukin-2
Heroin

Drug-induced pemphigus

The variants of idiopathic pemphigus are discussed in Chapter 41. A number of drugs have been implicated in drug-induced pemphigus (Table 73.13) [1,2], usually of foliaceus type, although the erythematosus, herpetiformis and urticaria-like forms also occur; drug-induced pemphigus vulgaris is rare. Most patients with drug-induced pemphigus have tissue-bound and/or low-titre circulating autoantibodies with the same antigenic specificity at a molecular level as autoantibodies from patients with the corresponding subtype of idiopathic pemphigus [3,4]; however, in the case of penicillamine-induced pemphigus, 10% do not have tissue-bound, and more than 30% do not have circulating, autoantibodies. About 80% of cases are caused by drugs associated with a thiol group in the molecule, especially penicillamine [5–11], but also the structurally related ACE inhibitors captopril [3,12–14] and ramipril [15], gold sodium thiomalate, drugs with disulphide bonds such as pyritinol [16], *S*-thiopyridoxine, tiopronin (mercaptopropionylglycine; which is chemically related to penicillamine and used as an alternative therapy in penicillamine intolerance) [4,17,18], and bucillamine [19], as well as those with a sulphur-containing ring that may undergo metabolic change to the thiol form, such as piroxicam [20]. Penicillin [21,22], and its derivatives ampicillin [22], procaine penicillin and amoxicillin, may also cause pemphigus. Other drugs that cause pemphigus may contain an active amide group [23].

Rifampicin [24], cefalexin [25], cefadroxil, ceftazidime [26], pyrazolone derivatives [27] including dipyrone [28], propranolol, propranolol–meprobamate [29], optalidon, pentachlorophenol, phenobarbital [30], nifedipine [31], phosphamide, hydantoin, combinations of indometacin and aspirin [32], glibenclamide [33], as well as heroin [34], have all been established as rare causes of a pemphigus-like reaction. Fatal pemphigus vulgaris has been recorded after IFN-β and IL-2 therapy for lymphoma [35]. Fludarabine has been implicated in the development of paraneoplastic pemphigus [36,37].

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Linear IgA disease

Idiopathic linear IgA disease is discussed in Chapter 41. The drugs implicated as a cause of this condition have been reviewed [1–3], and include vancomycin especially [1–9], but also amiodarone, ampicillin, atorvastatin [10], captopril [11], carbamazepine [12], cefamandole (cephamandole), diclofenac, furosemide [13], glibenclamide, IFN-γ, iodine, lithium, penicillin [14,15], phenytoin [16] and somatostatin, as well as tea-tree oil [17]. Most patients lack circulating antibodies to the basement membrane; resolution of the rash follows discontinuation of medication.

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Drug-induced epidermolysis bullosa acquisita

This entity has been linked to antibiotics, including vancomycin [1].

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Vasculitis

Drug-induced cutaneous necrotizing vasculitis [1–3] may also involve internal organs, including the heart, liver and kidneys, with fatal results. The patterns of polyarteritis nodosa, Henoch–Schönlein vasculitis and hypocomplementaemic vasculitis are not seen commonly with drugs. Drugs that have been implicated are listed in Table 73.14. These include ampicillin, sulphonamides, furosemide [4], thiazide diuretics, phenylbutazone and other NSAIDs, quinidine, amiodarone [5], hydralazine [6], enalapril [7], propylthiouracil [8,9], mefloquine [10], cimetidine [11], coumadin [12,13], anticonvulsants including phenytoin and in isolated cases carbamazepine and trimethadione [14,15], zidovudine (azidothymidine) [16], indinavir [17], fluoxetine [18], didanosine [19], piperazine [20], centrally acting appetite suppressants [21], hyposensitization therapy [22,23], bacille Calmette–Guérin (BCG) vaccination (which may cause a papulonecrotic type of vasculitis) [24], radiographic contrast media [25], food and drug additives including dye excipients such as tartrazine (FD&C yellow no. 5), ponceau, sodium benzoate, 4-hydroxybenzoic acid [26,27], vitamin B_6 [28] and the use of a nicotine patch [29].

Table 73.14 Drugs recorded as inducing vasculitis.

Additives	Levamisole
Allopurinol	Maprotiline
Aminosalicylic acid	Mefloquine
Amiodarone	Methotrexate
Amfetamine (amphetamine)	Penicillin
Ampicillin	Phenacetin
Aspirin	Phenothiazines
Arsenic	Phenylbutazone
Captopril	Phenytoin
Carbamazepine	Piperazine
Cimetidine	Procainamide
Coumadin	Propylthiouracil
Didanosine	Quinidine
Enalapril	Radiocontrast media
Erythromycin	Streptomycin
Etacrynic acid (ethacrynic acid)	Sulphonamides
Fluoroquinolone antibiotics	Trazodone
Fluoxetine	Tetracycline
Furosemide (frusemide)	Thiazides
Griseofulvin	Trimethadione
Guanethidine	Vaccines
Hydralazine	Zidovudine
Iodides	

Leukocytoclastic vasculitis and necrotizing angiitis have also been documented in drug abusers [30–32].

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Lupus erythematosus-like syndrome

A reaction resembling idiopathic LE has been reported in association with a large variety of drugs [1–9], although only about 5% of cases of SLE are drug induced. Cutaneous manifestations are in general rare: 18% and 26%, respectively, of patients with procainamide- and hydralazine-induced LE had skin changes in one series [6]. Photosensitivity may be prominent; some patients develop discoid LE lesions; urticarial or erythema multiforme-like lesions may also be seen. Constitutional symptoms may be present, and there may be evidence of Raynaud's disease, arthritis or polyserositis. Renal involvement is rare, as is central nervous system involvement. The condition usually, but not always, resolves after discontinuation of the drug. Abnormal laboratory findings include the presence of LE cells, and of antinuclear antibodies directed against ribonucleoprotein, single-stranded DNA and especially histones [10,11]. Antibodies against native double-stranded DNA are rarely found in drug-induced LE, and complement levels are normal; deposition of immunoreactants in uninvolved skin is rare. Patients with drug-induced LE may have the lupus anticoagulant [12,13].

A partial list of drugs reported to induce an SLE-like syndrome or exacerbate idiopathic LE is given in Table 73.15. Drugs most commonly implicated in inducing LE include especially hydralazine [14,15] and procainamide [16,17], and less commonly β-blockers, methyldopa [18,19], isoniazid, most anticonvulsants in clinical use

Table 73.15 Drugs inducing lupus erythematosus-like syndromes.

Angiotensin-converting enzyme inhibitors (captopril)	Lithium
Anticonvulsants	Methyldopa
Carbamazepine	Methysergide
Hydantoins	Nitrofurantoin
Primidone	Oral contraceptives
Trimethadione	Penicillin
Valproate	Penicillamine
Allopurinol	Phenothiazines (chlorpromazine)
Aminoglutethimide	Phenylbutazone
p-Aminosalicylic acid	Procainamide
β-Blockers	Quinidine
Calcium channel blockers	Streptomycin
Clonidine	Sulfasalazine (sulphasalazine)
Co-trimoxazole	Sulphonamides
Ethosuximide	Terbinafine
Gold salts	Tetracycline
Griseofulvin	Thiazide diuretics
Hydralazine	Thionamide
Ibuprofen	Thiouracils
Isoniazid	

including phenytoin, carbamazepine, ethosuximide, trimethadione, primidone and valproate (but not phenobarbital or benzodiazepines) [20], and quinidine [21,22]. LE following penicillamine therapy [23,24], 2-mercaptopropionylglycine [25], rifampicin [26], etanercept [27] and the tetracycline derivative COL-3 used in antiangiogenesis [28] has also been documented. Minocycline may induce an autoimmune syndrome of which LE may form part [29–31].

Subacute LE with positive Ro/SSA antibodies has been reported in association with a number of drugs [9], including phenytoin [32], thiazide diuretics such as hydrochlorothiazide [33–36], ACE inhibitors [37,38], calcium channel blockers [39], terbinafine [40–42], griseofulvin [43], piroxicam, oxprenolol, interferons and statins. The oral contraceptive induced LE lesions on the palms and feet of a patient [44]. In addition, a number of drugs may exacerbate pre-existing SLE, such as griseofulvin, β-blockers, sulphonamides [45], testosterone and oestrogens.

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Dermatomyositis reactions

Dermatomyositis has been reported to be precipitated by a variety of drugs, including penicillamine [1–3], NSAIDs (niflumic acid and diclofenac) [4], carbamazepine [5] and vaccination, as with BCG [6]. Acral skin lesions simulating chronic dermatomyositis have been reported during long-term hydroxyurea therapy [7]. Allergy to benzalkonium chloride has caused a dermatomyositis-like reaction [8].

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Scleroderma-like reactions

Penicillamine [1,2], bleomycin [3,4], bromocriptine [5], vitamin K (phytomenadione) [6,7], sodium valproate [8] and 5-hydroxytryptophan combined with carbidopa [9,10] (see also the eosinophilia–myalgia syndrome below) have all been implicated in either localized or generalized morphoea-like, or systemic sclerosis-like, reactions. Eosinophilic fasciitis has been associated with tryptophan ingestion in some cases [11], as well as with phenytoin [12].

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Chemical and industrial causes of scleroderma-like reactions [1]

Scleroderma-like changes formed part of the clinical spectrum of the Spanish toxic oil syndrome, which resulted from contamination of rapeseed cooking oil with acetanilide [2]. Scleroderma-like changes have been induced by industrial exposure to vinyl chloride [3], epoxy resins [1,4], organic solvents [5] including perchlorethylene [6], trichlorethylene and trichlorethane [7], and in coalminers due to silica exposure [8,9].

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Eosinophilia–myalgia syndrome

Ingestion of tryptophan, taken as a mild antidepressant, a 'natural hypnotic', or by athletes to increase pain

tolerance, was associated with eosinophilia–myalgia syndrome [1–4], characterized by eosinophilia, myalgia, arthralgia, limb swelling, fever, weakness and fatigue, respiratory complaints, pulmonary hypertension, arrhythmias, ascending polyneuropathy and a variety of cutaneous manifestations. The latter included diffuse morbilliform erythema, urticaria, angio-oedema, dermatographism, livedo reticularis, alopecia and papular mucinosis. Some patients developed chronic muscle weakness, with diffuse scleroderma-like or fasciitis-like skin changes. The eosinophilia–myalgia syndrome is now thought to have been caused by a contaminant of L-tryptophan following a change in the manufacturing process between October 1988 and June 1989 [5,6].

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Erythema nodosum [1]

Sulphonamides, other antibiotics [2], a variety of analgesics, antipyretics and anti-infectious agents, as well as the contraceptive pill [2–5], oestrogen replacement therapy [6], treatment of haematological disorders with granulocyte colony-stimulating factor [7], all-*trans*-retinoic acid [8] and *Echinacea* herbal therapy [9] have all been implicated in the aetiology of erythema nodosum. Erythema nodosum leprosum was induced by prolonged treatment with recombinant IFN-γ (in 60% of patients within 7 months) [10] and by co-trimoxazole [11].

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Pseudolymphomatous syndrome: anticonvulsant hypersensitivity syndrome

This syndrome should be differentiated from the drug hypersensitivity syndrome, which has a more acute onset (see above). A number of drugs may produce a reaction pattern that simulates a lymphoma [1–6]. Skin involvement may consist of erythematous plaques, multiple infiltrative papules or solitary nodules; there may be facial oedema. Pseudolymphomatous syndrome develops between 2 weeks and 5 years after starting drug therapy, but usually within 7 weeks. Histopathologically, there is epidermotropism of atypical lymphocytes, often with Pautrier's microabscess-like structures; pseudolymphomatous syndrome differs from mycosis fungoides in that there may be moderate to marked spongiosis, necrotic keratinocytes, epidermal eosinophils, papillary dermal oedema and extravasated erythrocytes, and a mixed dermal inflammatory infiltrate including neutrophils. Misdiagnosis of pseudolymphomatous syndrome as malignant lymphoma may lead to patients being treated unnecessarily with chemotherapy.

Phenytoin especially, but also phenobarbital and carbamazepine, mephenytoin, trimethadione and sodium valproate have been implicated [7–12]. Cutaneous lesions in patients with reactions to phenytoin or carbamazepine may show histological features of mycosis fungoides; cutaneous lesions resembling those of mycosis fungoides in the absence of fever have been reported with phenytoin and carbamazepine. Phenobarbital has produced a hypersensitivity syndrome resembling Langerhans' cell histiocytosis [13].

Other drugs have been associated with mycosis fungoides-like drug eruptions, including allopurinol, antidepressants (e.g. fluoxetine [14,15] and amitriptyline [15]), phenothiazines [16], thioridazine, benzodiazepines, antihistamines [4], β-blockers (e.g. atenolol [17]), ACE inhibitors [18], calcium channel blockers, salazosulfapyridine [19], lipid-lowering agents, mexiletine, ciclosporin [20], penicillamine, amiloride hydrochloride with hydrochlorothiazide, bromocriptine [21] and gemcitabine [22]. A generalized cutaneous B-cell pseudolymphoma was induced by neuroleptics [23]. Cutaneous T-cell lymphoma

and Sézary syndrome have been reported in association with silicone breast implants [24,25].

Pseudolymphomatous syndrome usually responds to drug withdrawal, although not for many months in some cases [5]. Occasionally, a true lymphoma may develop.

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Acanthosis nigricans-like and ichthyosiform eruptions

See Chapter 34.

Erythromelalgia [1]

Drugs implicated include iodide contrast media, vaccines (influenza and hepatitis), nifedipine, felodipine, nicardipine, bromocriptine, norephedrine, pergolide and ticlopidine.

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Hair changes (see also Chapter 63)

Drug-induced alopecia

A considerable number of drugs have been reported to cause hair loss [1–5]; the most important causes are listed in Table 73.16. Cytotoxic drugs may cause alopecia by either anagen or telogen effluvium. Chemotherapeutic agents implicated in the production of alopecia include amsacrine, bleomycin, cyclophosphamide, cytarabine, dactinomycin, daunorubicin, doxorubicin, etoposide, fluorouracil, methotrexate and the nitrosoureas [2]. Telogen alopecia has been caused by anticoagulants (heparins and coumarins), antithyroid drugs (carbimazole and thiouracils), levodopa, propranolol, albendazole and oral contraceptives. Retinoids cause alopecia by disrupting

Table 73.16 Drugs causing alopecia.

Anticoagulants	Retinoids
Coumarins	Acitretin
Dextran	Etretinate
Heparin	Isotretinoin
Heparinoids	Miscellaneous
Anticonvulsants	Albendazole
Carbamazepine	Allopurinol
Valproic acid	Amfetamine (amphetamine)
Cytotoxic agents	Antithyroid drugs
Drugs acting on the central nervous system	Bromocriptine
	Captopril
Amitriptyline	Cholestyramine
Doxepin	Cimetidine
Haloperidol	Dixyrazine
Lithium	Gentamicin
Hypocholesterolaemic agents	Gold
Clofibrate	Ibuprofen
Nicotinic acid	Levodopa
Triparanol	Metoprolol
Antithyroid drugs	Oral contraceptives
Carbimazole	Propranolol
Thiouracils	Trimethadione

Table 73.17 Drugs causing hypertrichosis.

Androgens	Penicillamine
Corticosteroids	Phenytoin
Ciclosporin	Psoralens
Diazoxide	Streptomycin
Minoxidil	

keratinization. Hydantoins may cause scalp alopecia and hypertrichosis elsewhere, and clofibrate may cause alopecia by interfering with keratinization. Temporary hair loss has been described after 5-aminosalicylic acid enemas [6] and bromocriptine [7], and danazol has induced generalized alopecia [8]. Certain β-blockers have caused increased hair loss [9–11] as have dixyrazine [12] and ibuprofen [13].

Drug-induced hirsutism and hypertrichosis

The hirsutism induced in women by corticosteroids, androgens and certain progestogens is well recognized. Other drugs that may cause hypertrichosis are listed in Table 73.17 [3,4]. Up to 50% of children treated with diazoxide, and up to 40% of patients on ciclosporin, develop hypertrichosis. Zidovudine has caused excessive growth of eyelashes [14].

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Drug-induced hair discoloration (see Chapter 63)

Drug-induced change in hair colour, usually occurring 3–12 months after the onset of treatment, is a rare but well-recognized phenomenon [1,2]. Darkening of hair has occurred during treatment with verapamil [3], tamoxifen [4], carbidopa [5] and PABA. Etretinate has caused darkening as well as lightening, curling and kinking of hair [6]. Greying of hair has been reported with chloroquine and mephenesin [7]. Chloroquine depigmentation is reversible and occurs only in red- or blonde-haired individuals; both IFN-α [8] and chloroquine are capable of arresting phaeomelanin synthesis.

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Nail changes

Drug-induced nail abnormalities have been the subject of several reviews [1–7] (see Chapter 62). Heavy metals may induce the following changes: arsenic causes transverse, broad, white lines (Mee's lines); silver causes blue discoloration of the lunulae; gold results in thin and brittle nails with longitudinal streaking, yellow-brown discoloration and onycholysis; and lead produces partial leukonychia. Penicillamine therapy is associated with the yellow nail syndrome and nail dystrophy. Cytotoxic agents may produce transverse or longitudinal pigmentation, splinter haemorrhages, Beau's lines, leukonychia, Mee's lines, onycholysis, shortening of lunulae, pallor, atrophy, nail shedding and slow growth; acute paronychia has occurred with methotrexate. The β-blockers may induce a psoriasiform nail dystrophy, with onycholysis and subungual hyperkeratosis. Thiazide diuretics may result in onycholysis. Discoloration or pigmentation occurs with antimalarials (blue-brown discoloration), lithium (golden discoloration), phenolphthalein (dark-blue discoloration), phenothiazines (blue-black or purple pigmentation), phenytoin (pigmentation), psoralens and tetracyclines (yellow pigmentation). Oral contraceptives may induce photo-onycholysis and onycholysis, and are associated with an increased growth rate and reduced splitting and fragility. In contrast, heparin reduces nail growth and causes transverse banding and subungual haematomas. Retinoids cause thinning and increased fragility, onychoschizia, onycholysis, temporary nail shedding, onychomadesis, ingrowing nails, periungual granulation tissue and paronychia.

Table 73.18 Drugs causing onycholysis.

Antibiotics	*Miscellaneous*
Cefaloridine (cephaloridine)	Acridine
Cloxacillin	Captopril
Chloramphenicol	Norethindrone and mestranol
Chlortetracycline	Practolol (discontinued)
Demethylchlortetracycline	Psoralens
Doxycycline	Phenothiazines
Fluoroquinolones	Retinoids
Minocycline	Sulpha-related drugs
Tetracycline hydrochloride	Thiazides
Chemotherapeutic agents	*Photo-onycholysis*
Adriamycin	Oral contraceptives
Bleomycin	Psoralens
5-Fluorouracil	Fluoroquinolones
Mitoxantrone	Tetracyclines

Onycholysis

Drugs causing onycholysis [6,7] and photo-onycholysis are listed in Table 73.18.

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Oral conditions (see also Chapter 66)

ADRs affecting the mouth have been extensively reviewed [1–4]. Disturbance of taste has been reported with a wide variety of drugs [5,6], including captopril, griseofulvin, metronidazole and protease inhibitor antiretrovirals. Orofacial effects of antiretroviral therapies have been reviewed [6]. These include mouth ulcers due to bone marrow suppression, erythema multiforme (e.g. with didanosine), lichenoid reactions with zidovudine, xerostomia (seen in up to one-third of patients taking didanosine), oral and perioral paraesthesiae (especially with ritonavir), and cheilitis with indinavir.

Xerostomia

Dryness of the mouth (xerostomia) may result from anticholinergic side effects of drugs. Xerostomia has been recorded in association with antidepressants, tranquillizers, antiparkinsonian drugs, antihypertensives and gastrointestinal antispasmodics (Table 73.19). Parotitis with salivary sialadenitis has been reported in up to 15% of patients taking phenylbutazone, and may be associated with fever and a rash [7]. A similar syndrome may occur with repeated administration of iodinated contrast media [8] and with nitrofurantoin [9].

Table 73.19 Drugs associated with xerostomia.

Antidepressants (tricyclic)	Minor tranquillizers
Amitriptyline	Diazepam
Doxepin	Chordiazepoxide
Imipramine	Hydroxyzine
Antidepressants (monoamine oxidase inhibitors)	Antiparkinsonian drugs
Isocarboxazid	Antihypertensives (ganglion blockers)
Phenelzine	Gastrointestinal antispasmodics
Psychotropic agents	Atropine
Chlorpromazine	Propantheline bromide
Thioridazine	Phenobarbital (phenobarbitone)
Haloperidol	
Prochlorperazine	

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Stomatitis

Type I immediate hypersensitivity and type IV delayed hypersensitivity reactions may be involved in allergic stomatitis [1]. The allergic stomatitides may present with clinical appearances that mimic classic oral vesiculobullous and ulcerative lesions. Stomatitis may form a part of drug-induced lichenoid reactions, fixed drug reactions or erythema multiforme, but may also arise separately from these conditions as a side effect of a number of drugs (Table 73.20). Chemotherapeutic agents causing stomatitis or buccal ulceration include [2] actinomycin D, adriamycin, amsacrine, bleomycin, busulfan, chlorambucil, cyclophosphamide, dactinomycin, daunorubicin, doxorubicin, fluorouracil, IL-2, mercaptopurine, methotrexate, mithramycin, mitomycin, nitrosoureas, procar-

Table 73.20 Drugs causing stomatitis or buccal ulceration.

Chemotherapeutic agents	Antihypertensive agents
Antirheumatic drugs	Captopril
Gold	Hydralazine
Naproxen	Methyldopa (rare)
Indometacin (indomethacin)	Miscellaneous
Penicillamine	Chlorpromazine
Zomepirac	Valproic acid
Antidepressants	
Amitriptyline	
Doxepin	
Imipramine	

bazine and vincristine. Penicillamine may induce stomatitis or ulceration as part of drug-induced pemphigus [3] or a lichenoid drug eruption. Gold therapy is another well-recognized cause of stomatitis [4–6]. Allergic reactions to dental materials and therapy may cause stomatitis. Positive patch tests to mercuric chloride were seen in 42%, and to copper sulphate in 16%, of patients with oral mucosal lesions associated with amalgam restorations, compared with 9% of controls, in one series [7]. It has been postulated that mercury released from dental amalgams can cause hypersensitivity/toxic reactions resulting in lichen planus lesions, and may play a major role in the pathogenesis of gingivitis, periodontitis and periodontal disease [8]. Mercuric chloride caused statistically significant increased IFN-γ release, but not proliferation, in lymphocyte cultures from patients with hypersensitivity to amalgam restorations [9]. β-Blockers have been implicated in aphthous ulcers [10].

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Hyperpigmentation

Hyperpigmentation of the buccal mucosa may occur with chemotherapeutic agents [1]. Oestrogen is associated with gingival hypermelanosis [2]. Amalgam tattoos with localized hyperpigmentation of the buccal mucosa result from implantation of amalgam in soft tissues, especially of the gingival or alveolar mucosa [3].

Reactions caused by antibacterial, antifungal and immunosuppressive therapy

Systemic antibiotics or immunosuppressive medication [4], and corticosteroids administered by aerosol [5], may lead to the development of candidiasis of the buccal mucosa. Black hairy tongue may be associated with broad-spectrum antibiotic therapy and with griseofulvin treatment.

Gingival hyperplasia

Gingival hyperplasia may be caused by phenytoin [6], nifedipine [7], diltiazem [8], felodipine, verapamil and ciclosporin [9].

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Important or widely prescribed drugs

Antibacterial agents

β-Lactam antibiotics

Inaccurate histories of allergy to antibiotics are frequently documented in medical records by hospital doctors [1]. Reactions to β-lactam antibiotics may be immediate, accelerated or delayed [2–5]. Non-immediate reactions to penicillins are a reproducible phenomenon, suggesting that a specific mechanism is responsible [6]. In one study, 39% of 74 subjects with a cutaneous reaction to a penicillin derivative had a non-immediate reaction, in 93% to an aminopenicillin (10.3% ampicillin, 82.7% amoxicillin).

There was a positive delayed direct challenge and a delayed skin-test response in 65% of cases, and a lymphomonocytic infiltrate on skin biopsy [6]. Cross-reactivity exists between several members of this group of antibiotics, but restricted sensitivity to a single penicillin derivative also occurs [7]. As a group, penicillins had a higher frequency of allergic reactions than cephalosporins in a study of patients with cystic fibrosis treated with parenteral β-lactam antibiotics [8]. Serum sickness reactions occur [9]. (See also acute generalized exanthematous pustulosis, p. 73.35.)

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Penicillin

Toxic reactions to penicillin are extremely rare and usually only follow massive doses, but can occur with normal doses in patients with renal impairment; encephalopathy with epilepsy may result from binding of the β-lactam ring to γ-aminobutyric acid receptors [1]. In contrast, immunological reactions are common [2–4]; allergy to penicillin has been reported in up to 10% of patients treated [5]. All forms of penicillin, including the semisynthetic penicillins, are potentially cross-allergenic; in general, allergic reactions to semi-synthetic compounds are commoner than to natural penicillins. All four types of immunological reaction may occur: urticaria and anaphylactic shock (type I), haemolytic anaemia or agranulocytosis (type II), allergic vasculitis or serum sickness-like reaction (type III) and allergic contact dermatitis [6] (type IV). Immediate reactions occur within 1 h, and take the form of urticaria, laryngeal oedema, bronchospasm and/or anaphylactic shock. So-called accelerated reactions with the same clinical features develop 1–72 h later. Reactions occurring more than 72 h after exposure are termed late reactions; these include maculopapular rashes with scarlatiniform and morbilliform exanthems, urticaria, serum sickness, erythema multiforme, haemolytic anaemia, thrombocytopenia and neutropenia. Fever is the commonest reaction.

The antigenic structures responsible for penicillin allergy include a 'major determinant', the penicilloyl group formed by spontaneous hydrolysis of penicillin (penicilloyl polylysine is used for skin testing), and additional antigenic compounds to which benzylpenicillin is metabolized, termed 'minor determinants' [3]. Most immediate-type anaphylactic hypersensitivity reactions are mediated by IgE antibodies to minor antigenic determinants, whereas accelerated reactions are usually the result of IgE antibodies directed against the major antigenic determinant [3,7]. For information on skin testing for penicillin, see the diagnosis section at the end of the chapter (p. 73.174).

Anaphylactic reactions to penicillin reportedly occur in about 0.015% of treatment courses; fatal reactions occur in 0.0015–0.002% (i.e. 1 in 50 000 to 1 in 100 000) of treatment courses [8]. Young and middle-aged adults aged 20–49 years are at most risk [9]. Atopy does not augment the risk of a reaction to β-lactam antibiotics, but may increase the risk of any reaction being severe [3]. Anaphylaxis is commoner after parenteral administration, and is very rare, but has been recorded, after oral ingestion [9]. Maculopapular reactions occur in about 2% of treatment courses [3]; where there is a history of a prior penicillin reaction, the risk of a subsequent reaction increases to about 10% [10]. A fair proportion (33% in one study) of children may lose their skin-test reactivity within a year [11]. In practice, when penicillin is given to children said to be allergic to penicillin, very few experience an adverse reaction [7]. In adults, the rate of disappearance of penicillin-specific IgE is highly variable, from 10 days to indefinite persistence [3]. For a group of penicillin-allergic patients, the time lapsed since a previous reaction is inversely related to the risk of a further IgE-mediated reaction [10]. In one study, 80–90% of patients were skin-test positive 2 months after an acute allergic reaction, but less than 20% were skin-test positive 10 years later [12]. Nevertheless, patients with a prior history of an IgE-dependent reaction remain at risk of recurrence, even though IgE antibodies become undetectable by skin testing [13]. Most serious and fatal allergic reactions to β-lactam antibiotics occur in individuals who have never had a prior allergic reaction; a negative history should therefore not induce a false sense of security [3]. Continuous prophylactic treatment is associated with a very low incidence of reactions [14].

Activation of allergy in a sensitized individual may require only minute amounts of the drug, as from contaminated syringes, dental root-canal fillings, viral vaccines, contaminated milk or meat products, and contamination of transfused blood [15]. Urticaria and wheezing occurred in the penicillin-sensitive spouse of a man receiving

parenteral mezlocillin, and was postulated to have arisen as a result of seminal fluid transmission of penicillin [16]. Hypersensitivity reactions have occurred after intrauterine placement, in penicillin-sensitive patients, of spermatozoa or embryos exposed to penicillin *in vitro* [17].

Penicillin has been reported to cause erythema multiforme [18], vesicular and bullous eruptions, exfoliative dermatitis [19], vascular purpura or fixed eruptions, post-inflammatory elastolysis (cutis laxa), which was generalized and eventually fatal in one case [20], and a very few cases of pemphigus vulgaris [21,22], pemphigoid [23] and pustular psoriasis [24]. It has been proposed that penicillin may have a role in chronic 'idiopathic' urticaria [25].

Cloxacillin and flucloxacillin

Cloxacillins cross-react with penicillins, but unlike ampicillin do not produce distinctive eruptions. Flucloxacillin rarely elicits primary penicillin hypersensitivity. In one case report, parenteral cloxacillin was tolerated but oral administration caused progressive generalized erythema with pruritus, facial angio-oedema and tachycardia [27]. Flucloxacillin has been implicated as a cause of cholestatic jaundice; this complication is rare, and the risk is greater in elderly patients and those receiving therapy for more than 2 weeks [27].

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Ampicillin

A morbilliform rash, with onset on the extremities and becoming generalized, occurs in 5–10% of patients treated with ampicillin, and usually develops 7–12 days after onset of therapy. This time interval suggests an allergic mechanism, although the rash disappears spontaneously even if ampicillin is continued, and may not develop on re-exposure [1]. Skin tests are generally negative. An urticarial reaction, present in about 1.5% of patients, indicates the presence of type I IgE-mediated general penicillin allergy [2,3]. Administration of ampicillin when a patient has infectious mononucleosis leads to florid morbilliform and sometimes purpuric eruptions in up to 100% of patients [4–6]. Cutaneous reactions to ampicillin are increased in cytomegalovirus infection [7], chronic lymphatic leukaemia [8], renal insufficiency or when allopurinol is administered concomitantly [9]. Ampicillin has been reported to cause a fixed drug eruption [10], erythema multiforme and Stevens–Johnson syndrome [11,12], TEN [13], Henoch–Schönlein purpura [14], serum sickness [15] and pemphigus vulgaris [16] in individual cases. Administration of ampicillin to a patient with a history of psoriasis resulted in erythroderma on two separate occasions [17]. A recurrent, localized, pustular skin eruption developed on the cheeks with ampicillin in one case [18].

Delayed intradermal skin tests and patch tests, indicating delayed hypersensitivity, were positive in about half of 60 subjects with maculopapular reactions to the aminopenicillins ampicillin and amoxicillin [19]; in another study, hypersensitivity to an antigenic determinant in the side-chain structure was suggested, as intradermal and patch tests were positive to ampicillin but there was good tolerance to benzylpenicillin [20]. Re-exposure of patients to ampicillins and other penicillins is contraindicated after urticarial reactions; anaphylactic reactions to ampicillin

have been recorded. The risk is far less after morbilliform rashes but is not negligible.

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Amoxicillin

Cutaneous eruptions including urticaria or morbilliform or maculopapular rashes occur in 1–2% of treatment courses with amoxicillin [1–3]. Immediate allergy (anaphylaxis or urticaria/angio-oedema) to amoxicillin has occurred in patients with good tolerance of benzylpenicillin, aztreonam and ceftazidime [4,5]. However, amoxicillin has been reported to cross-react with penicillin on first exposure [6]. Amoxicillin caused an unusual intertriginous eruption in two patients [7]. Serum sickness has been reported with amoxicillin in children [8]. Amoxicillin has caused a fixed eruption [9], and a curious, recurrent, localized, pustular eruption [10]. This drug has also been implicated in the development of an acute generalized exanthematous pustulosis [11]. There may be an increased frequency of rash with amoxicillin and clavulanate therapy in HIV-positive patients [12]. Amoxicillin, like clavulanic acid and flucloxacillin, may cause a cholestatic hepatitis [13]. This occurs at a frequency of 1 in 6000 adults when the drug is combined with clavulanic acid (co-amoxiclav) [14]. Amoxicillin has also been implicated in the baboon syndrome [15], palmar exfoliative exanthem [16] and localized peri-buccal pustulosis [17].

Methicillin

Methicillin caused reappearance of a recently faded ampicillin rash in a patient with glandular fever [18].

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Cephalosporins [1]

In general, cephalosporins are fairly well tolerated [1–3], adverse reactions ranging from 1 to 10% [1]; parenteral administration may cause minor adverse reactions, including thrombophlebitis and pain. The most common adverse effects are allergic reactions, occurring in 1–3% of patients [2]; haematological toxicity occurs in less than 1% of patients. Anaphylaxis is rare (less than 0.02%) [1]. Other reactions include localized gastrointestinal disturbances, hepatotoxicity, nephrotoxicity and mild central nervous

system effects. Cephalosporin reactions are minimally, if at all, increased in patients with histories of penicillin allergy [1]. Post-marketing studies of second- and third-generation cephalosporins showed no increase in allergic reactions in patients with a history of penicillin allergy. Cephalosporin antibiotics are safe in penicillin-allergic patients and penicillin skin tests do not identify potential reactors [1]. Isolated independent hypersensitivity to individual cephalosporins, such as cefazolin [4,5], cefonicid [6] and cefuroxime [7], with good tolerance to other β-lactam antibiotics, has been described.

Hypersensitivity reactions include various exanthems and contact urticaria [8]; cases of anaphylaxis to cefaclor [9] and of fatal anaphylactic shock related to cefalotin (cephalothin) [10] have been reported. Vulvovaginitis and pruritus ani are not uncommon. Delayed reactions have been reported with cefonicid [6] and cefuroxime [11]. Serum sickness reactions occur [12–15], especially with cefaclor; the latter drug may also cause urticaria and erythema multiforme [15]. Exfoliative dermatitis has been attributed to cefoxitin [16]. Disulfiram-like reactions to alcohol have been described with newer members of this group. Pustular reactions have been documented with cefradine, cefalexin and cefazolin [17–19]. Ceftazidime has been implicated in the development of erythema multiforme [20]. Cephalosporins [21] including cefalexin [22] have been reported to cause TEN, and cefalexin has precipitated pemphigus vulgaris [23]. Cefazolin has caused an unusual fixed drug eruption [24]. A curious photo-recall-like phenomenon followed the use of cefazolin and gentamicin sulphate, in that the eruption was restricted to an area of sunburn sustained 1 month previously [25]. Cefotaxime has caused a photodistributed phototoxic telangiectasia [26].

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Monobactams

Monobactams (e.g. aztreonam) show weak and rare cross-reactivity with IgE antibodies to penicillin [1–3], although immediate hypersensitivity on first exposure to aztreonam in penicillin-allergic patients has been recorded [4,5]. In general, aztreonam is well tolerated in high-risk patients allergic to other β-lactam antibiotics, but there is a 20% sensitization rate following exposure [6]. However, aztreonam and the monobactams can be safely given to penicillin-allergic patients [7]. Generalized urticaria to aztreonam but good tolerance of the other β-lactams has been recorded [8].

Carbapenems

Cross-reactivity and allergic reactions to imipenem occur in patients known to be allergic to penicillin [9]. Carbapenems should be avoided in patients with penicillin allergy [7]. Imipenem combined with cilastatin, a non-antibiotic enzyme inhibitor that prevents breakdown of imipenem to nephrotoxic metabolites, may cause phlebitis or pain at the site of infusion [10]. Imipenem has been associated with a pustular eruption [11], and imipenem–cilastatin with palmoplantar pruritus during infusion in a child with AIDS [12].

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Tetracyclines

Many of the side effects are common to all drugs within the group, and cross-sensitivity occurs [1]. Nausea, vomiting and diarrhoea are well-recognized dose-related effects. Oral or vaginal candidiasis may occur as a result of overgrowth of commensals. Resumption of therapy does not necessarily lead to recurrence of the vaginitis [2].

Photosensitivity

All tetracyclines, but especially demethylchlortetracycline, may cause phototosensitive eruptions [1,3–6], which clinically resemble exaggerated sunburn, sometimes with blistering. Phototoxicity is thought to be involved, in that high serum levels predispose to its occurrence. Reactions to both UVA and UVB have been reported. High concentrations of tetracycline are found in sun-damaged skin [3]. Symptoms may persist for months [1]. Photo-onycholysis may develop in fingernails and (if exposed) toenails; the thumb (normally less exposed) may be spared [7,8]. Tetracycline therapy is best avoided if there is a prospect of considerable sun exposure. Porphyria cutanea tarda-like changes may develop after chronic sun exposure [6,9]. A photosensitive lichenoid rash has been attributed to demethylchlortetracycline [10].

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Pigmentation

Methacycline is a rare cause [1]. Long-term minocycline therapy for acne may result in pigmentation. Although this is generally held to be a rare event, it may occur in about 1.4% of patients [2–5]. The average time for the development of pigmentary changes was 5 months, and onset of this complication did not seem to be related to cumulative dosage of the drug [3]. Facial hyperpigmentation was reported in two sisters on long-term minocycline therapy, who were also being treated with Dianette (cyproterone acetate and ethinylestradiol); it was suggested that pigmentation occurred either as a result of a genetic alteration in the metabolic handling of the drug or because of accentuation by the concomitant therapy [6]. Other drugs, including amitriptyline [2], phenothiazines and 13-*cis*-retinoic acid, have been implicated in the accentuation of minocycline-related hyperpigmentation.

Three types of pigmentation are described with minocycline and may occur in combination or isolation [3]. A focal type with well-demarcated blue-black macules is seen in areas of previous inflammation or scarring, especially in relation to acne scars. Minocycline has been associated with post-inflammatory hyperpigmentation in women who have undergone sclerotherapy [7]. Macular or more diffuse hyperpigmentation may appear distant from acne sites, especially on the extensor surface of the lower legs and forearms and on sun-exposed areas. These two types resolve on cessation of therapy, with a mean time to resolution of 12 months [3]. A more persistent diffuse brown-grey change may develop, especially in sun-exposed areas [5]. Minocycline pigmentation may respond well to laser therapy [8–11].

The oral cavity and lips may be involved [12,13]. Conjunctival pigmentation may occur with tetracyclines [14,15] and scleral pigmentation with minocycline [16,17]. Minocycline can cause nail pigmentation and longitudinal melanonychia [5,18,19], and tetracycline may produce yellow discoloration of the nail [20]. Cutaneous osteomas presenting as blue skin nodules that fluoresce yellow under UV light may rarely develop in patients being treated with tetracycline [21] or minocycline [22] for acne.

Black galactorrhoea occurred in a patient taking both minocycline and phenothiazines [23].

Pigmentation may also involve bones, teeth, thyroid, aorta and endocardium [19,24]. Histological and electron microscopic studies have demonstrated increased melanin, haemosiderin and either minocycline or a metabolite in the skin [25–27]; pigment may be seen in dermal histiocytes and eccrine myoepithelial cells [26]. Minocycline is metabolized to form a brown-black degradation product [28].

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Other cutaneous side effects

Allergic reactions are far less common than with penicillin. Morbilliform, urticarial, erythema multiforme-like and bullous eruptions [1,2], exfoliative dermatitis and erythema nodosum [3] have been reported, as well as a recurrent follicular acneiform eruption in one patient [4]. Minocycline has caused eosinophilic cellulitis and pustular folliculitis with eosinophilia [5]. Gram-negative folliculitis of the face is uncommon but well recognized; *Proteus* may be responsible, and the condition responds to ampicillin [6]. Tetracyclines are a well-known cause of fixed drug eruptions [7–9], and minocycline [10] and doxycycline [11] have caused Stevens–Johnson syndrome. TEN has been recorded [12]. It has been suggested that tetracyclines may exacerbate psoriasis [13,14]. An eruption resembling Sweet's syndrome has occurred with minocycline, tetracycline and doxycycline [15–17]. Pruritus at the site of active acne has been recorded within 2–6 weeks of starting oral tetracyclines (oxytetracycline, doxycycline or minocycline) [18].

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Gastrointestinal absorption and drug interactions

Absorption of tetracyclines is reduced when taken with meals, especially those containing calcium or iron such as milk, or with drugs such as iron or antacids [1]. The decrease in serum levels following a test meal has been reported as follows: oxytetracycline 50% [1], minocycline 13% [1] and doxycycline 20% [2]. Oxytetracycline may have a hypoglycaemic effect in insulin-dependent diabetics [3]. Tetracyclines can potentiate the action of warfarin by depressing prothrombin activity, and elevate serum levels of lithium given simultaneously [4].

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Systemic side effects of tetracyclines

Long-term use of tetracycline for acne may rarely result in benign intracranial hypertension [1,2]. As retinoids may potentiate this effect, it is safest not to use them in combination with tetracycline therapy for acne. Oesophageal ulceration has been described in a number of patients [3]. With the exception of doxycycline and minocycline, tetracyclines may exacerbate renal failure. Combination therapy with tetracyclines and nephrotoxic drugs such as gentamicin or diuretics should be avoided [4]. Deteriorated tetracyclines have caused nephropathy accompanied by an exanthematic eruption. Patients should be warned not to use outdated or poorly stored tetracycline, because degraded tetracycline can cause a Fanconi-type syndrome comprising renal tubular acidosis and proteinuria [5,6] and lactic acidosis [7]. Dose-related vestibular disturbance has been reported with minocycline [8]. Reversible pulmonary infiltration with eosinophilic or neutrophilic alveolitis has been rarely described in association with tetracycline [9] and especially minocycline [10–12] therapy. There have been isolated case reports linking tetracycline with SLE [13].

Minocycline has been reported to cause other serious, albeit rare, adverse events. Serum sickness-like reactions occur at about 15 days [14,15]. A hypersensitivity syndrome may develop at about 23–35 days, with a severe self-limiting eruption, sometimes exfoliative dermatitis, associated with eosinophilia and acute hepatic failure, occasionally fatal [16–20]. A drug-induced autoimmune syndrome with hepatitis or vasculitis and some features of SLE occurs rarely with minocycline, on average 1–2 years after the start of therapy, and is commoner in women [20–25]. Hepatitis, sometimes with the histological features of chronic active hepatitis, may be associated with polyarthralgia and positive antinuclear antibodies but negative or only weakly positive anti-DNA antibodies, and is only rarely fatal; patients usually recover within 3 months of drug cessation. Perinuclear antineutrophilic cytoplasmic antibody (p-ANCA) may be a marker for development of minocycline-induced autoimmunity [26–28]; in one study, all such patients were p-ANCA positive and had the haplotype HLA-DR4 or HLA-DR2, and all had the HLA-DQB1 allele, suggesting genetic susceptibility [28]. Systemic reactions to minocycline are certainly more frequent than those to oxytetracycline or doxycycline [29], and it has therefore been suggested that the use of minocycline in acne should be restricted to patients unresponsive to other tetracyclines [30].

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Effects on the fetus and on teeth

There is little evidence that tetracycline is teratogenic [1]. There is an isolated case report of congenital abnormalities in a child whose mother took clomocycline for acne [2]. Yellow discoloration of the teeth due to tetracycline exposure during mineralization of the deciduous or permanent teeth is well known [3–5]. A yellow-brown fluorescent discoloration is formed as a result of a complex with calcium orthophosphate. Tetracyclines should not be given to pregnant women or children under the age of 12 years. Tetracyclines are excreted in breast milk, but chelation with calcium decreases their absorption so that tooth discoloration is probably prevented [1].

Tetracycline may be deposited up to late adolescence in calcifying teeth such as the molars, but as these are not normally visible this is not a problem [5]. Minocycline may rarely stain the teeth of adults [6–8].

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Tetracyclines and the contraceptive pill

Tetracyclines have been reported to interfere with the action of the contraceptive pill [1,2], and it is standard practice to inform female patients of this and to suggest use of an additional or alternative method of contraception while on medication. However, there is controversy as to whether there is really a significant risk of interaction [3–6]. It has been argued that there is a baseline pill failure rate of at least 1% per year, and that antibiotics commonly used in dermatology do not increase the risk of pregnancy [6].

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Sulphonamides and trimethoprim

Reactions occur in 1–5% of those exposed [1–5]. They are commoner in patients with AIDS [6–8], and slow acetylators are at greater risk [9]. Type I reactions (urticaria and anaphylaxis) are rare but recorded. Phototoxic and photoallergic eruptions occur [10,11]. Morbilliform and rubelliform rashes are seen, and erythema multiforme, Stevens–Johnson syndrome and TEN [12–17], erythema nodosum [1], generalized exfoliative dermatitis [1,18,19] and fixed eruptions [20] are all well known. In addition, an LE-like syndrome and allergic vasculitis [21] are documented. Agranulocytosis or haemolytic anaemia is occasionally precipitated.

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Sulfasalazine

Rashes occur in 1–5% of patients, and may be widespread as part of a hypersensitivity syndrome with hepatitis and encephalopathy [1–5], but desensitization is possible [6]. Blood disorders attributable to sulfasalazine occur at a rate of 3 per 1000 users [7]. An autoimmune syndrome has been described [8]. Photosensitivity [9] and a fixed eruption [10] have been documented. TEN, erythroid hypoplasia and agranulocytosis have been reported [11]. Bronchiolitis obliterans and alveolitis are well-recognized complications, and acute hypersensitivity pneumonia is recorded. LE, including cerebral LE, may be induced [12]. Reversible oligospermia may occur [13], and reversible hair loss has been attributed to use of this drug in enemas [14]. Many of the above adverse effects are attributable to the carrier molecule, sulfapyridine, which delivers 5-aminosalicylic acid, the component of sulfasalazine active in ulcerative colitis, to its site of action in the colon; patients who are slow acetylators may be especially prone to side effects [15]. Urticaria, and possibly the renal toxicity, are due to the 5-aminosalicylic acid component [16].

Mesalazine (5-aminosalicylic acid)

Fever, erythematous skin eruption and lung involvement [17], and fever, diarrhoea, exfoliative dermatitis, marked atypical lymphocytosis and severe hepatotoxicity [18] have been described in patients with a previous history of sulfasalazine hypersensitivity. Additional cutaneous hypersensitivity reactions including vasculitis [19], a Kawasaki-like syndrome [20] and an LE-like syndrome [21] have been documented. This drug may cause renal damage, and is associated with blood dyscrasia [22] including fatal bone marrow suppression and thrombocytopenia [23]. A pustular reaction is recorded [24].

Olsalazine

This drug, which consists of a dimer of two molecules of 5-aminosalicylic acid linked by an azo bond, dispenses with the unwanted effects of sulfapyridine. Nonetheless, up to one in five patients experience diarrhoea, rash, nausea and abdominal pain severe enough to stop treatment with the drug [16].

Sulfamethoxypyridazine

Obliterative bronchiolitis and alveolitis have been documented in a patient with linear IgA disease of adults [25].

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Sulfadoxine

This sulphonamide is used in malaria prophylaxis in combination with pyrimethamine. The risk of reactions seems to be very low, but drug fever, TEN and photodermatitis have been recorded [1]. Stevens–Johnson syndrome may occur with Fansidar (pyrimethamine and sulfadoxine) for malaria prophylaxis [1–4] or with sulfadoxine alone [5]. TEN has occurred with Fansidar in an AIDS patient [6].

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Trimethoprim–sulfamethoxazole (co-trimoxazole)

The general incidence and patterns of reactions to this mixture of sulfamethoxazole and trimethoprim are about the same as for sulphonamides in general; cutaneous reactions are seen in 3.3% of patients [1–3]. Severe cutaneous reactions of all types occur in about 1 per 100 000 users of the drug [2,3]. In view of these severe reactions, the drug is now indicated primarily for *Pneumocystis carinii* pneumonia, and for acute exacerbations of chronic bronchitis and urinary tract infections, and otitis media in children, only where there is good reason to prefer this combination [4]. There is a greatly increased incidence of reactions in patients with AIDS [5–13]. In one study, 18 of 38 patients with AIDS and *P. carinii* pneumonia treated with trimethoprim–sulfamethoxazole developed cutaneous reactions within a median of 11 days. It is sometimes possible to continue treatment through a hypersensitivity reaction, as reported for 67% of cases in the above study [14]. Adjuvant corticosteroids reduce the incidence of adverse cutaneous reactions to co-trimoxazole in patients with AIDS who are treated for hypoxaemic *P. carinii* pneumonia, but the incidence of mucocutaneous herpes simplex virus infection is higher [15]. If it is deemed essential to continue the drug, desensitization can be attempted [16,17].

Fixed eruptions occur [18–22], and may be due to the sulphonamide or trimethoprim components; a widespread fixed eruption mimicking TEN has been documented in one case [23]. Pustular reactions [24] and Sweet's syndrome [25] have been documented. Severe reactions have included erythema multiforme or Stevens–Johnson syndrome [26,27] that has been fatal [27], TEN in AIDS patients [5,11,12], cutaneous vasculitis [28] and fatal agranulocytosis [29]. One patient developed a rapidly progressive subepidermal bullous eruption within hours of intravenous trimethoprim–sulfamethoxazole [30].

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Trimethoprim

Used alone, this substance causes less reactions than sulphonamides; fixed eruption has been proven [1–3] and was linear in one case [4]. Two patients experienced life-threatening immediate reactions and one patient developed generalized urticaria following oral trimethoprim–sulfamethoxazole; prick tests and oral challenge tests were positive with trimethoprim but not sulfamethoxazole [5].

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Aminoglycosides

Gentamicin, tobramycin, streptomycin and kanamycin cross-react and are all potentially ototoxic and nephrotoxic. Exanthematic eruptions are common with streptomycin, developing in 5% or more of patients. Continued treatment may lead to generalized exfoliative dermatitis with these drugs [1] in a minority, but in a proportion of patients the rash subsides and treatment can be continued. Fever and eosinophilia may be associated with the reactions. Urticaria [2], maculopapular rashes, fever and eosinophilia are well recognized with this group of drugs. Skin necrosis following subcutaneous injection of aminoglycoside antibiotics (gentamicin, sisomicin and netilmicin) has been reported in elderly females with a history of thrombosis being treated with heparin anticoagulant therapy [3–5]. The reaction has also occurred following intramuscular sisomicin in a patient with defective fibrinolysis and abnormal neutrophil function [6]. A toxic erythema with generalized follicular pustulosis has been documented with streptomycin [7]. Deafness has rarely followed topical therapy with neomycin, including administration of aerosol preparations in the treatment of extensive burns. An anaphylactic reaction due to streptomycin occurred during *in vitro* fertilization immediately after embryo transfer [8].

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Macrolide antibiotics

Macrolides account for 10–15% of the worldwide oral antibiotic market, with severe adverse reactions being rare [1]. Gastrointestinal reactions occur in 15–20% of patients on erythromycins and in 5% or fewer patients treated with some recently developed macrolide derivat-

ives that seldom or never induce endogenous release of motilin, such as roxithromycin, clarithromycin, dirithromycin, azithromycin and rikamycin. Except for troleandomycin and some erythromycins administered at high dose and for long periods of time, the hepatotoxic potential of macrolides is low. Transient deafness and allergic reactions to macrolide antibacterials are highly unusual and are more common with the erythromycins than with the recently developed 14-, 15- and 16-membered macrolides.

Azithromycin

This drug has caused toxic pustuloderma [2].

Clarithromycin

Fixed drug eruption is recorded [3].

Erythromycin

This is one of the most innocuous antibiotics in current use. Cholestasis caused by the estolate ester is the only potentially serious side effect. Hypersensitivity skin reactions are rare but when they occur skin tests may be positive [4,5]. Erythema multiforme, Stevens–Johnson syndrome, toxic pustuloderma [6], systemic contact dermatitis [7] and vasculitis have all been recorded.

Spiramycin

Rashes, usually transient erythema, may occur in up to 1% of cases. Spiramycin, given for toxoplasmosis in pregnancy, was associated in one case with an erythematous maculopapular pruritic eruption with eosinophilia and raised γ-glutamyl transpeptidase [8]. The drug has caused an allergic vasculitis [9].

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Clindamycin and lincomycin

These antibiotics have become particularly associated with a potentially lethal pseudomembranous colitis due to superinfection with *Clostridium difficile* [1–3]. Vancomycin or metronidazole is the treatment of choice for this complication. Hypersensitivity skin reactions are rare with lincomycin but common with clindamycin, occurring in up to 10% of patients [4]. Erythema multiforme and anaphylaxis are very rare [5].

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Miscellaneous antibiotics

Chloramphenicol

Although contact dermatitis from topical application is common, hypersensitivity skin reactions to oral therapy are rare. Macular, papular and urticarial eruptions are reported [1], as is acute generalized exanthematous pustulosis [2]. Pruritus may be prominent. Erythema multiforme and TEN [3] occur rarely. There is a risk of aplastic anaemia [4] and death has exceptionally followed the use of eye drops [5].

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Fusidic acid

Topical use can lead to contact dermatitis but hypersensitivity reactions to oral or parenteral use are very rare; jaundice has accompanied intravenous use. Acanthosis nigricans-like lesions have been reported after local application [1].

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Metronidazole and tinidazole

Metronidazole. Pruritus, fixed eruptions and generalized erythema [1–4] are rare. A pityriasis rosea-like eruption has been described [5]. A reversible peripheral neuropathy may complicate prolonged therapy.

Tinidazole. A fixed eruption with cross-reactivity with metronidazole has been reported [6,7].

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Nitrofurantoin

Pruritus, morbilliform rashes and urticaria may be seen occasionally. Erythema multiforme, erythema nodosum [1], exfoliative dermatitis and an LE-like syndrome [2] are documented. Acute or chronic pulmonary reactions may accompany these skin manifestations, and may lead to pulmonary fibrosis [3]. Polyneuritis is a dose-dependent toxic reaction. Hepatitis, cholestatic jaundice and marrow suppression may occur rarely. Abnormal immunoelectrophoretic patterns may be induced [4].

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Quinolones

These compounds are related to nalidixic acid; central nervous system toxicity, upper gastrointestinal tract reactions and phototoxicity have been recorded [1–7]. Cross-reactivity occurs [8]. Gastrointestinal side effects occur in up to 6% of patients. Hypersensitivity reactions involving the skin have been reported in 0.5–2% of patients, and in up to 2.4% of patients receiving cinoxacin; they most frequently manifest themselves as rash or pruritus. Fever, urticaria, angio-oedema and anaphylactoid reactions are rare. Anaphylactic or anaphylactoid reactions have been documented with cinoxacin [9], ciprofloxacin (1.2 per 100 000 prescriptions) [10,11] and pipemidic acid [12]. Fixed drug eruption due to pipemidic acid is recorded [13]. Norfloxacin [14] and ofloxacin [15] have caused a pustular eruption. Ciprofloxacin [16,17], pefloxacin, fleroxacin [18] and enoxacin [19] have been associated with photosensitivity. Pefloxacin and ofloxacin have caused photo-onycholysis [20], and sparfloxacin has been implicated in photosensitivity and a lichenoid tissue reaction [21]. Hypersensitivity leukocytoclastic vasculitis has been reported with both ofloxacin and ciprofloxacin [22,23] and serum sickness with ciprofloxacin [24]. Intravenous administration of ciprofloxacin through small veins on the dorsa of the hands may be associated with local reactions at the site of infusion [25]. Stevens–Johnson syndrome or TEN has been described with quinolones [26] including ciprofloxacin [27]. Ciprofloxacin has caused bullous pemphigoid [28].

Nalidixic acid. Cutaneous reactions are common, occurring in up to 5% of patients; various hypersensitivity reactions are seen, including exfoliative dermatitis. Phototoxicity is now well recognized [29–33]. A bullous photodermatitis may occur, usually on the hands or feet; chronic scarring and increased skin fragility may mimic porphyria cutanea tarda. Long-wave UV light is responsible [32]. An LE-like syndrome has been reported [34], as well as transient alopecia.

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Synergistins

An eczema-like drug eruption is recorded after oral antibiotic synergistins, pristinamycin and virginiamycin, following contact sensitization with topical virginiamycin [1].

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Vancomycin

Allergic skin reactions are not uncommon, occurring in up to 5% of patients. Rapid intravenous infusion of vancomycin can cause a histamine-induced anaphylactoid reaction characterized by flushing, a maculopapular eruption of the neck, face, trunk and extremities (so-called 'red man syndrome'), prolonged hypotension and, in rare cases, cardiac arrest [1–3]. Desensitization has been successfully achieved in patients with vancomycin hypersensitivity [4–6]. TEN has occurred [7]. Vancomycin has been reported to have induced linear IgA bullous dermatosis [8–12], which may mimic TEN [13].

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Topical antibiotics

The side effects of topical antibiotics have been reviewed [1]. Allergic contact dermatitis is rare with topical clindamycin, erythromycin and tetracycline, polymyxin B, gentamicin and mupirocin, but is more frequent with neomycin.

Bacitracin

Anaphylaxis due to bacitracin allergy has followed topical application of this antibiotic [2–5]. The patients had had multiple prior exposures and previous local reactions of pruritus, urticaria or possible allergic contact dermatitis. Two patients with anaphylactic reactions to Polyfax ointment, containing polymyxin B and bacitracin, have been

reported; one had previously documented positive patch tests to Polyfax, and the other had clinical intolerance to the preparation [5]. Another patient developed anaphylaxis to a similar proprietary mixture (Polysporin) [6]. Intracutaneous injection of bacitracin in sensitive individuals induces histamine release with large weal-and-flare reactions [7].

Chloramphenicol

Urticaria and angio-oedema have been described with topical use [8]. Fatal aplastic anaemia has followed the use of eye drops containing this antibiotic [9].

Sulphonamides

Erythema multiforme and Stevens–Johnson syndrome have been reported from topical preparations [10,11].

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Antituberculous drugs

Severe cutaneous reactions (such as Stevens–Johnson syndrome and TEN) and multiple drug reactions to antituberculous drugs (including thioacetazone, streptomycin and isoniazid) occur more often in HIV-positive patients [1–5]. The World Health Organization has advised against the use of thioacetazone in tuberculosis patients with known, or suspected, HIV infection in view of the severe cutaneous hypersensitivity [3–5]. The following drugs are reported to cause contact dermatitis: isoniazid, rifampicin, ethambutol, *p*-aminosalicylic acid, streptomycin and kanamycin [6]. The incidence of other reactions to individual drugs is difficult to assess because several drugs are usually used in combination.

Cycloserine

A lichenoid drug eruption with positive patch tests and resolution 4 months after withdrawal has been reported [7].

Ethambutol

Hypersensitivity reactions are very rare. Side effects are largely confined to visual disturbances, with loss of acuity, colour blindness and restricted visual fields; these are usually reversible if the drug is stopped promptly. Patients should have ophthalmic assessments prior to and during therapy. Lichenoid reactions occur and may be restricted to light-exposed sites [8,9].

Ethionamide

Eczema chiefly affecting the forehead, acneiform eruptions, butterfly eruptions on the face, stomatitis, alopecia and purpura have been reported.

Isoniazid

Allergic skin reactions occur in fewer than 1% of patients. An acneiform eruption, usually occurring in slow inactivators of the drug, is well recognized [10,11]. Urticaria, purpura and an LE-like syndrome [12,13] have been reported, as have photosensitive lichenoid eruptions [14]. Rarely, a pellagra-like syndrome has been induced in malnourished patients, due to metabolic antagonism of nicotinic acid with resultant pyridoxine deficiency [10,15]. Exfoliative dermatitis [16] and Stevens–Johnson syndrome [2] have been reported.

Pyrazinamide

Hepatitis, arthralgia, flushing, photosensitivity, lichenoid photodermatitis, maculopapular rashes, urticaria and pellagra are recorded [17].

Rifampicin

Cutaneous hypersensitivity reactions are very uncommon. There have been isolated reports of LE [18], erythema nodosum leprosum-like eruption in borderline lepromatous leprosy [19], exacerbation of bullous erythema multiforme, TEN [20] and pemphigus [21,22]; existing pemphigus may also be exacerbated [23]. Altered liver function, usually transient, and thrombocytopenic purpura may occur. Rifampicin has precipitated porphyria cutanea tarda [24]. It induces liver enzymes and may thus reduce the effectiveness of a number of drugs, including oral contraceptives.

Streptomycin

See aminoglycosides section on p. 73.60.

Thioacetazone

Severe cutaneous hypersensitivity reactions have been reported, including maculopapular rashes (which progress to mucosal involvement with constitutional symptoms), Stevens–Johnson syndrome and TEN, especially in HIV-seropositive patients [2,3,5,25,26]. Cutaneous hypersensitivity reactions have been reported in 20% of HIV-seropositive patients compared with 1% of HIV-seronegative patients who receive the drug as part of treatment for tuberculosis [26]. Figurate erythematous eruptions resembling erythema annulare centrifugum may occur [27].

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Antileprotic drugs

Clofazimine

This drug regularly causes a reversible, dose-dependent, brown-orange pigmentation of the skin [1–3]. Biopsy specimens from two lepromatous leprosy patients on long-term clofazimine therapy revealed ceroid-lipofuscin pigment as well as clofazimine inside macrophage phagolysosomes [3]. Reddish-blue pigmentation occurred in scarred areas of LE in one patient [4]. Xeroderma, pruritus, phototoxicity, acne and non-specific rashes are described [2]. Gastrointestinal symptoms may occur early due to direct irritation of the gut and are quickly reversible; ulcerative enteritis may occur after 9–14 months of treatment. After prolonged high-dose therapy, persistent diarrhoea, abdominal pain and weight loss, associated with deposition of crystalline clofazimine in the small intestinal submucosa and mesenteric lymph nodes, may occur [5,6]. Splenic infarction has been associated with this syndrome [7,8].

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Dapsone

Reactions have been reviewed [1]. Fixed eruptions occur in 3% of West Africans being treated for leprosy. Erythema multiforme [2] and exfoliative dermatitis [3] have been described during leprosy treatment. Another uncommon side effect is a hypersensitivity reaction (dapsone or sulphone syndrome) within the first month or so, with fever, a widespread erythematous eruption studded with pustules, exfoliative dermatitis, hepatitis, lymphadenopathy and anaemia [4–10]. In Vanuatu, 24% of 37 patients treated over 4 years with daily dapsone 100 mg, clofazimine, and monthly rifampicin and clofazimine for leprosy developed the dapsone syndrome, with a fatality rate of 11% [11]. The increase in reactions may have related to a high starting dose of dapsone, possibly enhanced by the combination with clofazimine and rifampicin and by a genetic susceptibility of the Melanesian population.

Red cell life is always shortened, but clinical haemolytic anaemia is uncommon; patients with low red cell glucose-6-phosphate dehydrogenase levels [12] and those who are slow acetylators [13] are at a special risk of developing this complication. Methaemoglobinaemia and Heinz body formation are seen [14]. Agranulocytosis is rare but well recognized and may occur in the first weeks of therapy [15–17]. For patients receiving the drug for dermatitis herpetiformis, this side effect occurred at a median dosage of 100 mg/day and a median duration of therapy of 7 weeks [16]. The total risk was one case per 3000 patient-years of exposure to the drug; however, agranulocytosis was estimated to occur in 1 in 240 to 1 in 425 new patients receiving dapsone for dermatitis herpetiformis [16]. Agranulocytosis occurred in approximately 1 in 10 000 to 1 in 20 000 US soldiers receiving dapsone for malarial prophylaxis [18]. Elderly patients do not tolerate dapsone well, and sulfapyridine or sulfamethoxypyridazine (the latter obtainable on a named-patient basis from Lederle Laboratories) is to be preferred for IgA-related diseases. A fatal haematological reaction developed in a Burmese boy during induction of treatment for lepromatous leprosy [19].

Severe but usually reversible hypoalbuminaemia due to failure of albumin production [20,21] or an atypical nephrotic syndrome may occur. Rarely, dapsone causes a peripheral neuropathy, usually purely motor or mixed sensorimotor and usually recovering within a year [22–25], and optic atrophy [25]. Permanent retinal damage has followed overdosage [26]. Headaches [27], and occasionally a psychosis [28], may be precipitated.

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Thalidomide

Teratogenicity (phocomelia), gastric intolerance, drowsiness, neuropsychiatric upset and a sensory peripheral neuropathy developing after several months have been reported [1]. Minor to moderate skin eruptions occur in up to 46% of patients taking thalidomide, including morbilliform, seborrhoeic, maculopapular and non-specific rashes; severe skin reactions such as exfoliative ery-

throderma, erythema multiforme and TEN are rare [2]. A dermatitis associated with eosinophilia develops in a few cases of erythema nodosum leprosum treated with thalidomide over several years [3]. Hypersensitivity reactions characterized by fever, tachycardia and an extensive erythematous macular eruption developed on rechallenge in a number of patients with HIV infection treated with thalidomide for severe aphthous oropharyngeal ulceration [4]. In addition, brittle fingernails, exfoliative erythroderma [5], toxic pustuloderma [6], face or limb oedema, pruritus, red palms and xerostomia have been described [7].

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Antifungal drugs

Dermatological aspects of antifungal drugs have been reviewed [1–3]. Rashes occur as follows.

- Itraconazole: in 1.1% of cases, with pruritus in 0.7%; the drug is teratogenic.
- Fluconazole: in 1.8% of cases; exfoliative dermatitis is recorded.
- Terbinafine: in 2.7% of cases, including erythema, urticaria, eczema, pruritus, and isolated Stevens–Johnson syndrome and TEN [3].

Relevant interactions between itraconazole, fluconazole and terbinafine have been discussed [4].

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Amphotericin

Skin reactions are rare. The 'grey syndrome', characterized by ashen colour, acral cyanosis and prostration, may occur as an immediate reaction to infusion. Allergic reactions occur to liposomal amphotericin [1,2].

Fluconazole

Angio-oedema has occurred [3], as has fixed drug eruption [4]. An anaphylactic reaction developed in a patient who had previously received ketoconazole and metronidazole, suggesting cross-sensitization [5], and Stevens–Johnson syndrome has been reported in a patient with AIDS [6]. Thrombocytopenia is described [7].

Itraconazole

Serum sickness [8] and acute generalized exanthematous pustulosis [9] are recorded.

Flucytosine

Transitory macular and urticarial rashes have been seen. A toxic erythema occurred in a patient [10]. Anaphylaxis has been reported in a patient with AIDS [11]. Bone marrow depression can occur.

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Griseofulvin

Reactions to griseofulvin are uncommon and usually mild; headaches and gastrointestinal disturbances are the most frequent. Morbilliform, erythematous or, rarely, haemorrhagic eruptions are occasionally seen [1,2]. Photodermatitis [3,4] with sensitivity to wavelengths above 320 nm is by no means rare; clinically, the features are mainly eczematous, although pellagra-like changes may be seen [4]. The reaction is thought to be photoallergic and

photopatch tests are positive in some cases; there may be photo cross-reactivity with penicillin [4]. Histology may be non-specific; direct immunofluorescence showed immunoglobulin and complement at the dermal–epidermal junction and around papillary blood vessels in one series [4]. Urticaria and a fixed drug eruption [5,6], cold urticaria [7], severe angio-oedema [8], erythema multiforme [9,10], serum sickness [11], exfoliative dermatitis [12] and TEN [13,14] are recorded. Exacerbation of LE has been reported [15–19], with fatality in one case [18]. Patients with anti-SSA/Ro and SSB/La antibodies may be at increased risk of developing a drug eruption [19,20]. Temporary granulocytopenia has been reported, and proteinuria may occur. Hepatitis and a morbilliform eruption are recorded [21]. Griseofulvin may interfere with the action of anticoagulants and the contraceptive pill [22], and should be avoided in pregnancy as potentially teratogenic; men should avoid conception for 6 months after taking the drug.

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Ketoconazole

Pruritus and gastrointestinal upset are the most frequent side effects [1]. Urticaria and angio-oedema are recorded [2]. Severe anaphylaxis has been observed in two patients, one of whom had previously reacted to topical miconazole [3]. Other adverse reactions include exfoliative erythroderma [4]. The drug may block testosterone synthesis, causing dose-dependent lowering of serum testosterone and resultant oligospermia, impotence, decreased libido and gynaecomastia in some men [5–7]. It also blocks the cortisol response to ACTH, and may lead to adrenal insufficiency [7–9]. Hypothyroidism has been documented [10]. The most serious side effect is idiosyncratic hepatitis, which occurs in about 1 in 10 000 patients, and which may lead to fulminant and potentially fatal hepatic necrosis [11–17]. Trichoptilosis has resulted from misuse of ketoconazole 2% shampoo [18].

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Nystatin

A fixed drug eruption has been reported [1], as has Stevens–Johnson syndrome in an isolated case [2].

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Terbinafine

This drug is well tolerated with relatively few side effects [1]. Idiosyncratic hepatitis has been reported [2], with serious hepatobiliary dysfunction occurring in 1 in 54 000 [3]. Neutropenia, pancytopenia and thrombocytopenia are recorded [4–8]. Cutaneous adverse effects occur in 3% of patients [3,9]; these include severe urticaria, pityriasiform rashes, erythroderma, erythema multiforme [10,11] and TEN [12], serum sickness-like reactions, acute generalized exanthematous pustulosis [13–17], LE-like rashes [18–20], induction or exacerbation of psoriasis which may be pustular [21–24], baboon syndrome [25], fixed drug eruption [26] and alopecia [27].

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Antiviral agents

Aciclovir (acyclovir)

In general, there are very few side effects [1]. Vesicular reactions, palm and sole dermatitis, peripheral oedema, erythema nodosum, exanthems, hyperhidrosis, acne, lichenoid eruption, pruritus, urticaria, vasculitis, alopecia and fixed drug eruption are recorded [2–4]. Intravenous use may cause inflammation and phlebitis. A nephropathy may develop with intravenous use, especially in patients with renal failure, due to renal precipitation of the drug; the dose should be reduced in patients with impaired renal function. An encephalopathy may occur. Peripheral oedema has been reported very rarely [5,6].

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Idoxuridine

This drug is used only topically for herpes simplex and herpes zoster, in view of its toxicity on systemic administration. Severe alopecia and loss of nails followed parenteral use [1].

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Foscarnet

This drug is used for cytomegalovirus retinitis in AIDS, and for mucocutaneous herpes simplex virus unresponsive to aciclovir in immunocompromised patients. A generalized cutaneous rash has been reported with use of this drug in AIDS [1]. Genital ulceration, both of the penis [2,3] and vulva [4], is documented. In one study [2], 15% of 60 patients treated with intravenous foscarnet developed penile ulceration [2]. Eosinophilic folliculitis has been reported [5].

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Ribavirin (tribavirin)

This synthetic guanosine analogue used in the treatment of relapsing chronic hepatitis C infection has been implicated in the development of Grover's disease [1].

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Antiretroviral drugs

Cutaneous side effects of antiretroviral agents have been reviewed [1–4]. There are three categories of agent: nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors and protease inhibitors. Nucleoside reverse transcriptase inhibitors have resulted in alterations of the nails, nail and mucocutaneous pigmentation, hair changes, vasculitis and morbilliform eruptions. Drug hypersensitivity is associated with the non-nucleoside reverse transcriptase inhibitors nevirapine, delavirdine and efavirenz, as well as the nucleoside reverse transcriptase inhibitor abacavir and the protease inhibitor amprenavir [2]. Protease inhibitors have been associated with lipodystrophy syndrome, hypersensitivity reactions, urticaria, morbilliform eruptions and a large number of drug interactions.

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Nucleoside reverse transcriptase inhibitors

Abacavir. This drug is associated with a hypersensitivity syndrome in 4% of cases [1]. Stevens–Johnson syndrome is recorded [2].

Zidovudine. This drug may cause gastrointestinal upset and marrow suppression (with serious anaemia in 32% and leukopenia in 37%), myalgia, headache and insomnia [3–6]. Such side effects have been reported in healthcare workers treated with zidovudine for attempted prophylaxis of HIV infection following accidental needlestick injury [7,8]. Zidovudine-related thrombocytopenia resulted in ecchymoses around Kaposi's sarcoma lesions in a patient with AIDS, simulating rapid intracutaneous spread of neoplasm [9]. Vaginal tumours have been documented in rodents. Diffuse pigmentation, as well as isolated hyperpigmented spots on the palms, soles and fingers, and pigmentation of the fingernails and toenails (usually starting at 4–8 weeks into therapy but up to 1 year) and buccal mucosa have been described [10–15]. Postural hypotension has been recorded [16]. Hypertrichosis of the eyelids has occurred [17]. A possible link with neutrophilic eccrine hidradenitis has been postulated in HIV-infected patients [18]. Hypersensitivity reactions from rash to anaphylaxis have been documented [19,20]. Other reported cutaneous reactions include acne, pruritus, urticaria and leukocytoclastic vasculitis [21].

Lamivudine. Paronychia is recorded [22].

Dideoxycytidine. A maculopapular reaction with oral ulceration developed in 70% of patients treated with this anti-AIDS agent, but resolved spontaneously in those who continued on therapy [23].

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Non-nucleoside reverse transcriptase inhibitors

Delavirdine. Various rashes occur in 18–50% of cases.

Efavirenz. Mild rashes are recorded within the first 2 weeks of therapy [1].

Nevirapine. Severe rashes have been observed in 3% of patients taking nevirapine in clinical trials, 85% of whom were men [2,3]. A hypersensitivity syndrome is well recorded [4,5]. The drug is the leading cause of Stevens–Johnson syndrome and TEN related to AIDS in Europe [6–9].

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Protease inhibitors

Saquinivir causes rashes, and indinavir causes taste disturbance and dry skin [1]. Indinavir has been associated with the development of cheilitis in 40% of cases, diffuse cutaneous dryness and pruritus in 12%, asteatotic dermatitis on the trunk, arms and thighs, and scalp hair loss in 12% [2]. Multiple pyogenic granulomas were observed in the toenails in 6% and softening of the nail plate in 5% of subjects. Multiple subcutaneous lipomas are associated with protease inhibitors [3]. Paronychia is a recognized complication [4,5]. Angiolipomas shortly after initiation of therapy [6] and leukocytoclastic vasculitis [7] have been documented with indinavir. A peripheral lipodystrophy syndrome has been linked to therapy with protease inhibitors [8–12] and was noted in 14% of patients on indinavir [2]. It comprises peripheral lipoatrophy, relative central adiposity, sometimes with a 'buffalo hump', insulin resistance and serum lipid abnormalities. The mix of features is variable in individual patients.

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Antimalarials [1–4]

Pruritus, lichenoid eruptions, exfoliative dermatitis, pigment changes, bleaching of hair, alopecia, photosensitivity with exacerbation of psoriasis and porphyria cutanea tarda, retinopathy and corneal opacities have all been reported.

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Chloroquine and hydroxychloroquine

Adverse cutaneous reactions to hydroxychloroquine are commoner in patients with dermatomyositis than in those with cutaneous LE [1]. Pruritus is common in Africans on acute or prolonged treatment, but rare in Europeans [2–5]. Pigmentary changes develop in about 25% of patients receiving any of the antimalarials for more than 4 months [6–9]; chloroquine binds to melanin [9]. Blackish-purple patches on the shins are often seen, and brown-grey pigmentation may appear in light-exposed skin [8]. The nail beds may be pigmented diffusely or in transverse bands, and the hard palate is diffusely pigmented. In contrast, red-blonde (but not dark) hair may be bleached [10]. Chloroquine has been associated with vitiligo-like depigmentation [11].

Photosensitivity may be seen [12]; in addition, certain types of porphyria may be provoked [13]. Effects on psoriasis are unpredictable, but precipitation of severe psoriasis has long been recognized [14–19], including erythroderma [19]. However, 88% of a series of 50 psoriatics who were treated with standard doses of chloroquine noted no change in their psoriasis [20]. Lichenoid eruptions are uncommon, and erythema annulare centrifugum is rare [21]. TEN with oral involvement has been documented. A pustular eruption with hydroxychloroquine has been reported [22]. Toxic psychosis has been described with hydroxychloroquine [23]. All antimalarials are potentially teratogenic.

Chloroquine and hydroxychloroquine may cause serious ophthalmic side effects [24,25]. Corneal deposits occur in 95% of patients on long-term therapy, but of these 95% are asymptomatic [26]. A potentially irreversible retinopathy leading to blindness may develop in 0.5–2% of cases [27,28]. The retinal changes may progress after the drug is stopped. Use of less than 250 mg (or 4 mg/kg) daily of chloroquine, with pretreatment and 6-monthly ophthalmological assessment using an Amsler grid, is recommended. Malaria prophylaxis with two tablets weekly is said not to carry an appreciable risk. Ocular toxicity with hydroxychloroquine is rare below 6.5 mg/kg; guidelines for screening include baseline renal and liver function tests, assessment of near visual acuity and yearly visual acuity [29].

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Mefloquine

Dizziness, nausea, erythema and neurological disturbance are documented. Pruritus occurs in 4–10% and maculopapular rash in up to 30% of cases; urticaria, facial lesions, cutaneous vasculitis, Stevens–Johnson syndrome and TEN [1,2], and exfoliative dermatitis [3] have been recorded.

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Mepacrine (atabrine, quinacrine)

This drug constantly causes yellow staining of the skin, which may involve the conjunctiva and may mimic jaundice [1]. Lichenoid eruptions are well known. Large numbers of military personnel given mepacrine for malaria prophylaxis in the Second World War developed a tropical lichenoid dermatitis, which was quickly followed by anhidrosis, cutaneous atrophy, alopecia, nail changes, altered pigmentation and keratoderma [2,3]. A few patients developed localized bluish-black hyperpigmentation confined to the palate, face, pretibial area and nail beds after prolonged administration of more than a year. Years later, lichenoid nodules, scaly red plaques, atrophic lesions on the soles, erosions and leukoplakia of the tongue, and fungating warty growths appeared [3,4]. Progression to squamous cell carcinoma, especially on the palm, has occurred. Ocular toxicity is much less than with chloroquine.

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Pyrimethamine

This folate antagonist can cause agranulocytosis even in very low dosage, especially when combined with dapsone [1]. A lichenoid eruption has been reported [2], as has photosensitivity. The reported rate for all serious reactions to pyrimethamine–sulfadoxine (Fansidar) in one study was 1 in 2100 prescriptions and for cutaneous reactions including Stevens–Johnson syndrome 1 in 4900, with a fatality rate of 1 in 11 100 [3]. In another study [4], severe cutaneous adverse reactions to Fansidar, including erythema multiforme, Stevens–Johnson syndrome and TEN, were estimated at 1.1 (0.9–1.3) per million. Similar rates for severe reactions to pyrimethamine–dapsone (Maloprim) were 1 in 9100 prescriptions and for blood dyscrasias 1 in 20 000, with a fatality rate of 1 in 75 000. For developing countries with mainly single-dose use, the risk was estimated at 0.1 per million, compared with mainly prophylactic use in Europe and North America at a risk of 10 and 36 per million respectively. Prophylactic use thus had a 40 times higher risk than single-dose therapeutic use [4]. Reactions to pyrimethamine are more common in patients with HIV infection [5]. Epidermal necrolysis, angioedema, bullous disorders and serious hepatic disorders also occurred. Because few serious reactions have been recorded with chloroquine and proguanil, it has been recommended that use of compound antimalarials should be restricted [3].

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Quinine

Purpura due to quinine may or may not be thrombocytopenic [1,2]. Erythematous, urticarial, photoallergic [3–5], bullous and fixed eruptions are recorded. Lichenoid eruptions are rare. If contact allergic sensitivity is already present, eczematous reactions may occur, as in 'systemic contact-type eczema' [6]. Splinter haemorrhages, and a maculopapular and a photosensitive papulonecrotic eruption, due to a lymphocytic vasculitis, have been recorded in one case [7].

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Anthelmintics

Amocarzine (CGP 6140)

This macrofilaricidal and microfilaricidal drug used for the therapy of onchocerciasis may be associated with dizziness and pruritus with or without a rash [1].

Benzimidazole compounds

These are used for the therapy of both intestinal helminthiasis and hydatid disease; fever, gastrointestinal upset, reversible neutropenia and transient abnormalities in liver function are reported. Telogen effluvium has been documented with both albendazole [2,3] and mebendazole.

Ivermectin

Fever, rash, pruritus, local swelling and tender regional lymphadenopathy are documented [4]. The incidence of moderate adverse reactions including pruritus, localized rash and fever was 4% in a study of patients with onchocerciasis from Ecuador [5], and increased itching and/or rash occurred in 8% of cases in another study [6]. Patients with reactive onchodermatitis (sowda) may have severe pruritus and limb swelling with ivermectin [7]. A 3-year, placebo-controlled, double-blind trial involving 7148 patients given ivermectin annually for onchocerciasis by mass distribution identified musculosketetal pains, oedema of the face or extremities, itching and papular rash as adverse reactions; bullous skin lesions that did not recur developed in five persons [8].

Levamisole

Prolonged use at high dosage as an immunostimulant is associated with type I reactions, with itching, pruritus and urticaria. Lichenoid [9] and non-specific [10] rashes, leukocytoclastic vasculitis with a reticular livedo pattern due to circulating immune complexes [11] and cutaneous necrotizing vasculitis [12] have been reported. A distinctive purpuric eruption of the ears is recorded [13].

Niridazole

Urticaria and a pellagra-like dermatitis have been described.

Piperazine

Occupational dermatitis has been caused [14]. Previous contact sensitization induced by ethylenediamine has led to severe cross-reactions on subsequent oral administration of piperazine, including generalized exfoliative dermatitis [15].

Tetrachlorethylene

This drug has caused TEN.

Tiabendazole

An unusual body odour is well known after the administration of this drug. Skin reactions, consisting of urticaria or maculopapular rashes, are infrequent and usually mild and transient. Erythema multiforme [16] and TEN [17] have been reported.

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Drugs for *Pneumocystis*

Pentamidine

This drug is increasingly being used in the treatment and

prophylaxis of *Pneumocystis carinii* pneumonia in patients with AIDS. Urticaria, including contact urticaria [1], or maculopapular eruption proceeding to erythroderma have been reported with nebulized therapy [2,3]. TEN may occur with systemic therapy [4,5].

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Non-steroidal anti-inflammatory drugs

Acetylsalicylic acid and related compounds

Aspirin

Reactions to aspirin [1–4] occur in 0.3% of normal subjects [2,4]. These are usually sporadic, but occasionally more than one family member may be affected, and an HLA linkage has been reported [5]. Urticaria or angio-oedema is the commonest reaction [1]. Two types of specific IgE antibody were found in sera from aspirin-sensitive patients with salicyloyl and *O*-methylsalicyloyl discs using radioallergosorbent tests, favouring an IgE-dependent mechanism [6]. Chronic idiopathic urticaria is often aggravated by aspirin [7,8]; this exacerbation probably has a non-allergic basis. It has been estimated that patients with chronic urticaria or angio-oedema have a risk of up to 30% of developing a flare in the condition following administration of aspirin or an NSAID [3]. The reaction is dose dependent and is greater when the urticaria is in an active phase. Aspirin may render the skin of such patients more reactive to histamine [5]. The syndrome of nasal polyposis, bronchial asthma and aspirin intolerance is well known [4,9]; up to 40% of patients with nasal polyps, and 4% of patients with asthma, may develop bronchoconstriction on exposure to aspirin, but only 2% develop urticaria [4]. Anaphylactoid responses may occur [3]; these may involve abnormalities of platelet function [10]. Cross-sensitivity between aspirin and tartrazine is now thought to be rare [3]. Oral desensitization is feasible if essential, and may be maintained by daily aspirin intake [3].

Other reported reactions include purpura, scarlatiniform erythema, erythema multiforme, fixed eruption and a lichenoid eruption (which recurred on challenge) [11], but all are rare [1]. Neonatal petechiae may result from aspirin therapy of the mother [12]. Aspirin has been reported to provoke generalized pustular psoriasis [13]. Oral ulceration may follow prolonged chewing of aspirin [14], and at the site of an insoluble aspirin tablet placed at the side of an aching tooth.

Nephropathy, marrow depression and gastric haemorrhage are well-recognized hazards. The elderly are at increased risk of developing such complications [15]. The drug may interfere with renal clearance, for example of methotrexate. Aspirin is safe to administer to patients with glucose-6-phosphate dehydrogenase deficiency [16].

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Diflunisal

Various cutaneous reactions have been reported in up to 5% of patients, including pruritus, urticaria, exanthems, Stevens–Johnson syndrome, erythroderma [1] and a lichenoid photoreactive rash [2]. A non-pigmenting fixed drug eruption has been documented [3].

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Paracetamol (acetaminophen)

This drug is a major metabolite of phenacetin, and has largely replaced it. Allergic reactions are very rare, considering that it has been estimated that more than 1.4 billion tablets are sold per annum in the UK [1,2]. Urticaria [3], anaphylaxis, a widespread maculopapular eruption, a fixed eruption [2,4–8] that may be non-pigmenting [8], exfoliative dermatitis [9], delayed hypersensitivity reactions [10], linear IgA bullous dermatosis [11] and figurate purpura [12] have been seen.

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Phenacetin

Capillaritis, vasculitis and a bullous pemphigoid-like eruption [1] have been documented.

Salicylamide

Use of teething jellies containing this substance has resulted in severe urticaria in infants [2].

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Other NSAIDs

Dermatological aspects of the NSAIDs have been extensively reviewed [1–13]. All these drugs inhibit the enzyme cyclo-oxygenase, and decrease the production of prostaglandins and thromboxanes [6]. NSAIDs represent about 5% of all prescriptions in the UK [5] and USA [2]; nearly one in seven Americans were treated with an NSAID in 1984, and in 1986 100 million prescriptions for these drugs were written in the USA [14]. NSAIDs accounted for 25% of all suspected ADRs reported to the UK Committee on Safety of Medicines in 1986 [5,15]. Reactions to NSAIDs occur in about 1 in 50 000 administrations; NSAIDs should be avoided in patients known to be intolerant of aspirin [6]. In a large series, allergic or pseudoallergic reactions were observed in 0.2% of patients exposed to minor analgesics (including aspirin and pyrazolones, mainly metamizole, propyphenazone) and in 0.8% of patients exposed to NSAIDs (including the pyrazolone oxyphenbutazone); most reactions were cutaneous, mainly maculopapular exanthems, urticaria and angio-oedema [10]. Piroxicam, meclofenamate sodium, sulindac and zomepirac sodium had the highest reaction rates relative to the number of new prescriptions in the USA [1,2]. In contrast, naproxen, fenoprofen, ibuprofen and indometacin all had low rates of reaction; ibuprofen is available as a non-prescription drug in the USA and the UK. In another study of 2747 patients with rheumatoid arthritis, toxicity index scores computed from symptoms, laboratory abnormalities and hospitalizations attributed to NSAID therapy indicated that indometacin, tolmetin sodium and meclofenamate sodium were the most toxic, and buffered aspirin, salsalate and ibuprofen the least toxic [16].

Cutaneous adverse reactions to NSAIDs were, in order of frequency in one study [11], urticaria/angio-oedema, fixed eruptions, exanthems, erythema multiforme and Stevens–Johnson syndrome. Drug exanthems and urticaria occur in 0.2–9% of patients treated with NSAIDs [2,6]. Drug exanthems develop in 1% of patients on phenylbutazone and 0.3% of patients on indometacin [6]; they are most frequently associated with diflunisal, sulindac, meclofenamate sodium, piroxicam and phenylbutazone. All the NSAIDs, but particularly aspirin and tolmetin, may cause urticaria and anaphylactoid reactions, especially in a patient with a history of aspirin-induced urticaria. Pyrazolone NSAIDs, feprazone, nimesulide, piroxicam and flurbiprofen cause fixed drug eruptions. Although all NSAIDs may precipitate exfoliative erythroderma, this is commonest with phenylbutazone [6]. All the NSAIDs, but particularly phenylbutazone, piroxicam, fenbufen and sulindac, may cause Stevens–Johnson syndrome or TEN [6]. Oral lichenoid lesions have also been recorded with NSAIDs [17]. Psoriasis has been reported anecdotally to be exacerbated by indometacin and meclofenamate sodium, but there is no definitive evidence that NSAIDs consistently exacerbate psoriasis [5]. Contact dermatitis induced by topical NSAIDs is rare but increasing; ketoprofen and bufexamac are major contact allergens [13].

Children on NSAIDs were 2.4 times as likely to have shallow facial scars, as described in drug-induced pseudoporphyria, in one study; this relative risk was increased to 6 with naproxen [18].

Most of the NSAIDs causing photosensitivity are phenylpropionic acid derivatives: carprofen, ketoprofen, tiaprofenic acid, naproxen and nabumetone [19–24]. NSAIDs that cause photosensitivity absorb UV radiation at wavelengths longer than 310 nm, resulting in the generation of singlet oxygen molecules, which damage cell membranes [12]. The cutaneous photosensitivity appears to be elicited by a phototoxic mechanism [19–21,24]. The phototoxic reactions with NSAIDs are immediate, consisting of itching, burning, erythema and at higher fluences wealing; this contrasts with the delayed reactions associated with psoralens and tetracyclines, which produce abnormal delayed erythema or exaggerated sunburn. Propionic acid derivatives may also precipitate photourticaria by mast cell degranulation [23]. Piroxicam, an enolic acid derivative structurally unrelated to phenylpropionic acid, is the most frequently cited non-phenylpropionic acid NSAID to cause photosensitivity [20,21,25]; phototoxicity to the parent drug has not been elicited in volunteers or experimental animals, although a phototoxic metabolite has been identified *in vitro*. Indometacin, sulindac [26], meclofenamate sodium and phenylbutazone have all been associated with photosensitivity [2]. NSAIDs may cause pseudoporphyria changes [27].

Apart from the cutaneous complications, NSAIDs may cause a variety of adverse effects [14,28–30], including gastrointestinal bleeding, intestinal perforations and acute deterioration in renal function with interstitial nephritis [28]; the elderly and patients with impaired renal function or receiving concomitant diuretic therapy are most at risk. NSAIDs may inhibit platelet aggregation and increase bleeding times [29]. Aplastic anaemia is a recognized complication, and has occurred in the same individual with two different NSAIDs (sulindac and fenbufen) [31]. Hepatic syndromes [30], pneumonitis (naproxen, ibuprofen, fenoprofen and sulindac can elicit pulmonary infiltrates with eosinophilia [32]) and neurological problems, such as headache, aseptic meningitis and dizziness, are recorded [14]. Niflumic acid and diclofenac both precipitated a dermatomyositis-like syndrome in a patient [33]. The potential for adverse interactions between NSAIDs and other drugs is considerable [14].

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Propionic acid derivatives

Carprofen. This drug causes photosensitivity [1].

Fenbufen. Morbilliform and erythematous rashes, erythema multiforme [2], Stevens–Johnson syndrome and allergic vasculitis have been recorded rarely. Fenbufen has caused exfoliative dermatitis, haemolytic anaemia and hepatitis [3], and was the drug implicated most commonly in adverse reactions reported to the UK Committee on Safety of Medicines in 1986 and 1987. A florid erythematous rash with pulmonary eosinophilia has been described in four cases [4].

Fenoprofen. This drug has caused pruritus, urticaria, vesicobullous eruption, thrombocytopenic purpura and TEN [5].

Ibuprofen. Pruritus is the only common cutaneous reaction. When used in rheumatoid arthritis, rashes are rare, although patients with SLE are liable to develop a generalized rash with fever and abdominal symptoms [6]. Angio-oedema/urticaria [7,8], anaphylaxis [9], fixed eruptions [8], a linear eruption [10], vesicobullous rashes, erythema multiforme, vasculitis [11] and alopecia [12] occur. Psoriasis has been reported to be exacerbated [13]. This drug is available over the counter in the UK.

Ketoprofen. Topical application has caused photoallergic contact dermatitis [14] and systemic ketoprofen has caused pseudoporphyria.

Naproxen. The incidence of side effects is low given the widespread and long-term use of naproxen. Rashes occur in about 5% of patients; pruritus is the commonest symptom. Naproxen is associated with a photosensitivity dermatitis [15] and pseudoporphyria [16–20]; most photo-urticarial reactions are evoked by the UVA band. Urticaria/angio-oedema, anaphylaxis [21], purpura and thrombocytopenia [22], hyperhidrosis, acneiform problems in women [23], vasculitis [24,25], vesicobullous and fixed drug eruptions [26], erythema multiforme, a pustular reaction [27] and lichen planus-like reaction [28] have all been reported, as has recurrent allergic sialadenitis [29].

Tiaprofenic acid. This drug may cause photosensitivity [30].

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Phenylacetic acids

Diclofenac. A variety of cutaneous adverse effects [1,2], including pruritus, urticaria, various exanthems, papulovesicular eruptions [3], delayed allergy [4], vasculitis [5], a bullous eruption associated with linear basement membrane deposition of IgA [6] and fatal erythema multiforme [1] have been recorded.

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Oxicams

Piroxicam. This drug may cause adverse cutaneous reactions in 2–3% of patients [1,2]. More than two-thirds of affected patients have photosensitivity; lesions may be vesicobullous or eczematous, and occur within 3 days of starting therapy in 50% of cases [3–10]. Photosensitivity may result from phototoxic metabolites [7]. Photocontact dermatitis developed in three patients after the application of a gel containing 0.5% piroxicam. Patch tests were positive to thiomersal and thiosalicylic acid and photopatch tests with piroxicam were positive. Patch tests in patients with systemic photosensitivity to piroxicam were also positive for thiomersal and thiosalicylic acid. Contact allergic sensitivity to the latter is a marker for patients with a high risk of developing photosensitivity reactions to piroxicam [10,11].

Other eruptions include urticaria, maculopapular [12] or lichenoid rashes, alopecia, erythema multiforme [13] and vasculitis [14]. Piroxicam was well tolerated in patients with an urticarial reaction to a single NSAID, but provoked urticaria in 27% of patients with allergy to at least two different NSAIDs, indicating that mechanisms other than interference with prostaglandin synthesis and release of inflammatory mediators participate in allergic reactions to NSAIDs [15]. Classical fixed drug eruption [16,17] and a non-pigmenting fixed drug reaction [18], with cross-sensitivity among piroxicam, tenoxicam and droxicam in one case [19], have also been reported. Contact sensitivity to piroxicam is recorded [20]. Piroxicam was thought to have triggered subacute LE in a patient with Sjögren's syndrome and seronegative arthritis [21]. Isolated case reports of linear IgA bullous dermatosis [22], fatal pemphigus vulgaris [23] and fatal TEN [24] have appeared. The drug has caused peripheral neuropathy and erythroderma [25]. Blood dyscrasias have been reported.

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Anthranilic acids

Meclofenamate sodium. Rashes occur in up to 9% of patients. More than two-thirds of reactions have been exanthematous, with prominent pruritus; vasculitic, purpuric or petechial reactions are also noted, as well as occasional urticaria, fixed drug eruption, erythema multiforme [1], exfoliative erythroderma and a vesicobullous reaction. It has been reported to exacerbate psoriasis [2]. Selective adverse reactions to glafenine and meclofenamate occurred in a patient tolerating aspirin and other cyclo-oxygenase inhibitors [3].

Mefenamic acid. Urticaria, a morbilliform eruption, fixed drug eruption [4,5], pseudoporphyria [6] and generalized

exfoliative dermatitis are documented. Acute renal failure, severe thrombocytopenia and jaundice developed after a small dose of mefenamic acid in one patient with drug-dependent antibodies reacting against platelets [7].

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Heterocyclic acetic acids

Indometacin (indomethacin). Allergic reactions are very uncommon, but pruritus, urticaria, purpura and morbilliform eruptions are documented. Stomatitis [1] and thrombocytopenia occur rarely, as well as a generalized exfoliative dermatitis and TEN [2]. Vasculitis has been documented [3]. There have been rare reports of exacerbation of psoriasis [4,5]; however, indometacin in a standard dose of 75 mg/day had no significant harmful effect on psoriasis in a series of patients treated with the Ingram regimen of coal-tar bath, suberythemal UVB phototherapy and dithranol in Lassar's paste [6]. Exacerbation of dermatitis herpetiformis has been recorded [7].

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Sulindac. Rashes occur in up to 9% of patients. The drug has caused anaphylaxis [1] and anaphylactoid reactions [2], photosensitivity [3], facial and oral erythema, a pernio-like reaction [4] and fixed drug eruption [5]. Stevens–Johnson syndrome [6–8], TEN [6,9], serum sickness and exfoliative erythroderma are documented. Blood dyscrasias, toxic hepatitis, pancreatitis, and aseptic meningitis in patients with SLE are recorded.

Tolmetin. Anaphylactoid reactions are well recognized [10]. TEN has been recorded.

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Pyrazolones

Amidopyrine (aminophenazone). This is the most dangerous of all analgesics and has caused hundreds of deaths due to blood dyscrasias. It has been withdrawn from western Europe and North America but is still available in certain parts of the world. TEN, exfoliative dermatitis and erythema multiforme are all well known.

Azapropazone. Photosensitivity is recognized [1]. A multifocal bullous fixed drug eruption resembling erythema multiforme has been reported [2]. A bullous eruption on the face and extremities, with histological features suggestive of pemphigoid but negative immunofluorescence, has been reported [3]. The drug is contraindicated in patients receiving warfarin, as the latter medication is potentiated [4].

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Phenylbutazone and oxyphenbutazone. Reactions have been frequent and often fatal [1,2]. Therefore, in the UK oxyphenbutazone has been withdrawn and phenylbutazone is restricted to hospital use for ankylosing spondylitis.

Pruritus, morbilliform eruptions, urticaria and buccal ulceration are most common; erythema multiforme, fixed eruptions (especially with oxyphenbutazone), generalized exfoliative dermatitis and TEN [3] are all well-documented hazards. Drug exanthems or erythroderma may occur in up to 4% of patients treated with phenylbutazone. Occasional reports of exacerbation of psoriasis have occurred [4]. Rarer reactions have included generalized lymphadenopathy, a Sjögren-like syndrome, non-thrombocytopenic purpura, allergic vasculitis [5] and polyarteritis nodosa. Provocation of temporal arteritis has been reported. A haemorrhagic bullous eruption of the hands was observed in three patients [6]. Cutaneous necrosis has been seen after intramuscular injection. Phenylbutazone causes fluid retention, gastrointestinal bleeding and bone marrow depression [2]; the hazards of the latter are greatly increased if the dose exceeds 200 mg/day.

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Cyclo-oxygenase-2 inhibitors

Celecoxib. Fixed drug eruption and Sweet's syndrome are documented [1,2].

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Miscellaneous anti-inflammatory agents

Benzydamine

Photoallergy has been described to both topical and systemic administration of this drug [1].

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Allopurinol

Dermatological complications occur in up to 10% of cases [1–7]. Acute sensitivity reactions are well known, including scarlatiniform erythema, morbilliform rashes, urticaria or generalized exfoliative dermatitis, which may be associated with fever, eosinophilia, hepatic abnormalities and a nephropathy. Vasculitis (perhaps triggered by oxypurinol, the principal metabolite of allopurinol, which has a long half-life and accumulates in renal failure [5]), erythema multiforme [7], Stevens–Johnson syndrome and TEN [5,8,9] have been reported. Cell-mediated immunity directed towards allopurinol and more importantly to its oxypurinol metabolite is thought to be involved in the pathogenesis of allopurinol-induced hypersensitivity [10]. Hypersensitivity reactions occur on average within 2–6 weeks of starting the drug, although the interval may be much longer. Eruptions are commoner in the setting of impaired renal function [11] and with concomitant thiazide therapy [12], and may first appear up to 3 weeks after the drug has been discontinued [13]. The mortality is about 20% [5]. Other allopurinol-induced cutaneous changes include alopecia and ichthyosis [14]. Allopurinol potentiates the risk of a reaction to ampicillin [15] and increases blood ciclosporin levels [16]. Desensitization may be successful in cases with minor rashes induced by allopurinol [17–19].

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Drugs acting on the central nervous system

The adverse effects of psychotropic medication have been reviewed [1–4]; the prevalence of skin reactions to psychotropic medications is about 5% [2].

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Antidepressants

Tricyclics and related compounds

Antidepressants are associated with a range of idiosyncratic reactions affecting the liver, skin, haematological and central nervous systems; reactions are mediated by chemically reactive metabolites formed by the cytochrome P-450 enzyme system either directly or indirectly via an immune mechanism. Individual susceptibility is determined by genetic and environmental factors, which result in inadequate detoxification of the chemically reactive metabolite [1]. Sedative, cardiovascular, anticholinergic and gastrointestinal side effects are well known [2,3]. Agranulocytosis may occur occasionally. Cutaneous reactions are rare [2] but include maculopapular rashes, photosensitivity (protriptyline and imipramine), urticaria, pruritus, hyperhidrosis, vasculitis or acne (maprotiline), and TEN (amoxapine).

Amineptine. Severe acne [4,5] and rosacea [6] have been reported.

Amitriptyline. A bullous reaction in a patient with overdosage of amitriptyline and clorazepate dipotassium has been reported [7]. Alopecia is documented.

Clomipramine. A photoallergic eruption has been documented [8].

Imipramine. This drug has caused urticarial or exanthematic eruptions occasionally [9] and agranulocytosis has occurred. Oedema of the feet is seen in older people. Glossitis and stomatitis are rare, as are transient erythema of the face, photosensitivity and exfoliative dermatitis. Slate-grey pigmentation of exposed skin may develop; golden-yellow granules, which ultrastructurally are electron-dense inclusion bodies in phagocytes, fibroblasts and dendrocytes, are seen in the papillary dermis [10–12]. Q-switched alexandrite and ruby lasers may be helpful in treating the pigmentation [13]. Cutaneous vasculitis is well documented. Atypical cutaneous lymphoid hyperplasia has been documented [14].

Maprotiline. Acne [15] and vasculitis [16] are recorded.

Mianserin. Erythema multiforme has recently been reported [17], as has a severe allergic reaction [18].

Trazodone. This drug has caused leukonychia [19], erythema multiforme [20] and vasculitis [21], and has been implicated in causing a psoriasiform eruption. Skin swelling is recorded [22].

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Monoamine oxidase inhibitors

Iproniazid. Vasculitis and peripheral neuritis are documented.

Phenelzine. Hypersensitivity skin reactions are rare.

Selective serotonin reuptake inhibitors

Fluoxetine

This drug has caused urticaria [1], urticarial vasculitis [2] and hypersensitivity [3], and serum sickness [4]; familial cases are documented [5]. Atypical cutaneous lymphoid hyperplasia [6], including pseudomycosis fungoides [6–8], is recorded.

Paroxetine

Cutaneous vasculitis has been reported [9].

Miscellaneous selective serotonin reuptake inhibitors

The 5-HT_3 receptor antagonists granisetron, ondansetron and tropisetron are antiemetic medications used during chemotherapy. Effects include headache and gastrointestinal symptoms, and rarely hypersensitivity reactions [10]. There were no cross-over reactions to citalopram or paroxetine among patients hypersensitive to zimeldine [11].

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Lithium

Skin reactions [1–5] are relatively uncommon. Pustular and psoriasiform lesions induced by this drug have received particular attention [6]. The pustular propensities of lithium have been attributed to lysosomal enzyme release and increased neutrophil chemotaxis [2]. Tetracycline should be avoided in treating these pustular eruptions as it may precipitate serious lithium toxicity. The acneiform 'erysipelas' eruption consists of monomorphic pustules on an erythematous base, tends to affect mainly the arms and legs, is not associated with comedones or cystic lesions, and may be very persistent. Various patterns of folliculitis may occur. Lithium can aggravate pre-existing psoriasis, making it more difficult to control [6–10], and may precipitate a palmoplantar pustular reaction [11] or even generalized pustular psoriasis [12]. Psychiatrists should avoid the use of lithium in psoriatics if possible. Darier's disease may also be exacerbated or initiated [13,14].

Additional reactions described include morbilliform rashes, erythema multiforme [15], a dermatitis herpetiformis-like rash [16], linear IgA bullous dermatosis [17] and a generalized exfoliative eruption [18]. An LE-like syndrome [19] with increased prevalence of antinuclear antibodies [20], toenail dystrophy [21] and hair loss [22,23] have been reported. Keratoderma has been documented [24], as has hidradenitis suppurativa [25]. None of these effects is related to excessive blood levels of lithium or other evidence of toxicity.

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Hypnotics, sedatives and anxiolytics

Barbiturates

A toxic bullous eruption may appear at pressure points in comatose patients after overdosage [1–4]. In one series, 8% of patients admitted with drug-induced coma had such bullae [3] (see Fig. 73.5). The bullae are few, large and may lead to ulceration [2]. Necrotic lesions are seen in 4% of patients recovering from, and in 40% of fatalities related to, barbiturate-induced coma [4]. Allergic reactions are very uncommon and may be scarlatiniform or morbilliform. Exfoliative dermatitis has proved fatal [5], as has erythema multiforme. Urticaria and serum sickness are very rare, as is purpuric capillaritis. Fixed eruptions are well known [6] and particularly occur on the glans penis. TEN, LE-like syndrome, purpura and photosensitivity are recorded [7]. Phenobarbital is one cause of the anticonvulsant hypersensitivity syndrome (see p. 73.45) [8,9]. In one case, a syndrome resembling Langerhans' cell histiocytosis was produced [10]. Hypopigmentation may follow a severe reaction [11]. Exfoliative dermatitis is recorded [12].

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Benzodiazepines

Allergic reactions are very rare [1].

Alprazolam. Photosensitivity has been recorded with this newer benzodiazepine [2].

Chlordiazepoxide. Morbilliform erythema, urticaria [3], fixed eruption [4], photoallergic eczema [5] and exacerbation of porphyria have been recorded. Erythema multiforme and chronic pigmented purpuric eruption occur rarely [6].

Clobazam. A generalized erythematous pruritic eruption [7] and TEN confined to light-exposed areas [8] have been reported. There has been a report of coma-induced bullae and sweat gland necrosis associated with the drug [9].

Diazepam and nitrazepam. Bullae similar to those seen after barbiturates may occur in comatose patients after overdosage [10,11]. Thrombophlebitis may follow intravenous injection of diazepam [12]. Hyperpigmentation in previously dermabraded scars has been attributed to diazepam [13]. Vasculitis is documented [14]. An eruption comprising oedema, moon face and generalized erythema, with erosions of cheeks, axillae and the genitocrural area was attributed to nitrazepam; a provocation test was positive [15].

Lormetazepam. A fixed drug eruption has been reported [16].

Temazepam. An extensive fixed drug eruption has been reported [17]. Extravasation following attempted femoral vein injection of a suspension of the contents of capsules in tap water, by an addict, resulted in extensive necrosis of genital and pubic skin [18].

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Miscellaneous hypnotics, sedatives and anxiolytics

Carbromal

This drug, now rarely used, commonly produced a characteristic capillaritis with punctate purpura and haemosiderin giving a golden-brown discoloration of the skin, especially on the legs [1].

Chloral hydrate

Hypersensitivity reactions are very rare. Chloral is now virtually given only in tablet form as dichloralphenazone, in which the phenazone may cause a fixed eruption [2].

Ethchlorvynol

Overdose has caused bullous lesions [3].

Glutethimide

Dermographism with subsequent erythema, and vesicles that lasted several days, were reported in one comatose patient [4] and bullae in another patient [5] following overdosage. Fixed eruptions are recorded [6].

Meprobamate

Anorexia, drowsiness, dizziness, flushing and gastrointestinal symptoms may occur, especially with high doses. Fixed eruptions may occur [7]. The most characteristic cutaneous reaction, preceded by itching, malaise and fever, is an erythema starting in the limb flexures that rapidly gives way to a fierce non-thrombocytopenic purpura [8]. A widespread toxic erythema was associated with an anaphylactoid reaction in a patient in whom patch testing proved useful in diagnosis [9].

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Antipsychotics

The most important clinical side effects include those on the central nervous and cardiovascular systems and the ocular effects [1,2]. Drugs with high potency, such as haloperidol and pimozide, tend to have fewer cardiovascular and anticholinergic effects and are less sedating, but have more neurological effects. Long-term use of antipsychotic agents results in tardive dyskinesia.

Phenothiazines

The side effects of this group of drugs have been reviewed [1–4].

Chlorpromazine. This drug is still widely used, although many related compounds are now available. Pigmentation of the skin in light-exposed areas after chronic use may be a problem, especially in women and black people [5–11]. Rarely, a purplish or slate-grey pigmentation develops [6]. There may be brown discoloration of cornea and lens [5], and bulbar conjunctiva [7]. Chlorpromazine has an affinity for melanin *in vitro* [8]. Electron microscopy shows many melanosome complexes within lysosomes of dermal macrophages, and electron-dense 'chlorpromazine bodies' in macrophages, endothelial cells and Schwann

cells [9,10]; energy-dispersive X-ray microanalysis has revealed the abundant presence of sulphur in these granules, which is a constituent of the chlorpromazine molecule [10]. Similar pigmentary deposits are found in internal organs [11] and in blood neutrophils and monocytes.

Chlorpromazine has caused lichenoid eruptions [12], exfoliative dermatitis, erythema multiforme, an LE-like illness [13] with positive antinuclear factor [14] and the lupus anticoagulant [15], and Henoch–Schönlein vasculitis [16]. Phototoxicity is well known [17–19] and phenothiazine-derived antihistamines may cause photosensitivity in atopics and subsequent development of actinic reticuloid [19]. Photocontact urticaria has been documented [20]. A pustular reaction is recorded [21]. Cholestatic jaundice is an important hazard.

Fluspirilene. Subcutaneous nodules may develop at injection sites after long-term high doses of this depot preparation [22].

Thioridazine. Vasculitis is documented [23].

Thiothixene. A sensitivity reaction has been recorded [24].

Trifluoperazine. A fixed eruption has been recorded [25].

Loxapine. Dermatitis, pruritus and seborrhoea have been recorded, and photosensitivity eruptions may occur occasionally [26].

Levomepromazin. An erythema annulare centrifugum-like pseudolymphomatous eruption has been reported [27].

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Miscellaneous antipsychotic agents

Clozapine. An acute severe adverse reaction resembling SLE is recorded [1].

Haloperidol. This drug causes reactions at injection sites [2,3].

Olanzapine. A pustular reaction is documented [4].

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Anticonvulsants

Allergic rashes to antiepileptic drugs are usually mild, taking the form of urticarial or morbilliform eruptions; the rare occurrence of a severe reaction indicates that the drug should be ceased, and this can be done abruptly with minimal risk of status epilepticus [1,2]. There may be cross-reactivity in terms of clinical reactions to the aromatic anticonvulsants (phenytoin, phenobarbital, carbamazepine, primidone and clonazepam), which may all cause the so-called drug hypersensitivity syndrome (see

p. 73.27), with fever, mucocutaneous eruptions, lymphadenopathy and hepatitis, 1 week to 3 months into therapy; there may be multiorgan involvement with renal and pulmonary lesions [3–10]. The reaction may develop into TEN. Arene oxide metabolites may be involved in the pathogenesis of these eruptions [3]. Sodium valproate may usually be substituted safely. The drug hypersensitivity syndrome reportedly occurs at a rate of 1 in 1000 to 1 in 10 000 exposures; siblings of patients may be at increased risk of developing this syndrome [9]. Generalized pustulation may be a manifestation of anticonvulsant hypersensitivity [11]. A severe form of hypersensitivity vasculitis, with extensive visceral involvement and poor prognosis, is seen very rarely with phenytoin and in isolated cases with carbamazepine and trimethadione [12]. Drug-induced SLE is much more frequent, and has been described with most anticonvulsants in clinical use (phenytoin, carbamazepine, ethosuximide, trimethadione, primidone and valproate) [12]. Of the newer anticonvulsant drugs, vigabatrin is usually well tolerated, but lamotrigine is associated with rashes [13,14]. Anticonvulsants may be associated with pseudolymphoma (see p. 73.45).

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Carbamazepine [1]

Eruptions occur in 3% [2–5] to 12% [6–8] of patients and include diffuse erythema, miliary exanthem, maculopapular or speckled morbilliform reddish rash, urticaria, purpuric petechiae or a mucocutaneous syndrome, any of which may occur from day 8 to 60. The drug hypersensitivity syndrome [9–11], erythroderma and exfoliative dermatitis, erythema multiforme and TEN [3,4,12] are well recognized. Eczema and photosensitivity [13], an LE-like syndrome and dermatomyositis [14], as well as a pustular [15–17] and a lichenoid [3,18] reaction, are very rare. Lesions with clinical and histological features suggestive of mycosis fungoides (pseudolymphoma) have been reported [18–21]. Patch testing has been advocated for the diagnosis of carbamazepine eruptions [9,10,22,23], but has resulted in reinduction of exfoliative dermatitis [24]. A psoriasiform eruption has been reported [25], as has thrombocytopenia and leukopenia complicated by Henoch–Schönlein purpura [26]. Cross-reactivity may occur with oxcarbazepine [27,28]. Other adverse effects include nausea, vomiting, ataxia, vertigo and drowsiness. Abnormal liver function [29] and bone marrow suppression with occasional deaths due to aplastic anaemia have been recorded [3]. Development of a rash may act as an early warning of marrow toxicity. Carbamazepine therapy during pregnancy carries a 1% risk of development of spina bifida in the offspring [30].

Oral steroid therapy enabled 16 of 20 patients successfully to continue on carbamazepine after development of a rash shortly after introduction of the drug [31]. Desensitization has been achieved by induction of tolerance in patients in whom there was no suitable alternative therapy [32,33].

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Diphenylhydantoin (phenytoin, Dilantin)

Cutaneous manifestations related to phenytoin have been reviewed [1–7]. The various diverse presentations share certain histopathological findings: adhesion of the infiltrated cells to the basal layer of the epidermis, cell infiltration into the epidermis, vacuolation of the basal cells, and dyskeratotic cells in the epidermis and epidermal necrosis, with $CD8^+$ T cells predominant in the epidermis [5].

About 5% of children develop a mild transient maculopapular rash within 3 weeks of starting treatment. This is more likely to occur if high loading doses are given initially [3,4]. In other series, between 8.5% [8] and 19% [9] of patients receiving phenytoin developed exanthematic rashes [10]. A phenytoin-induced hypersensitivity state, with generalized lymphadenopathy, hepatosplenomegaly, fever, arthralgia and eosinophilia, occurs in about 1% of patients, and may be accompanied by hepatitis, nephritis and haematological abnormalities [7,11–13]. Skin involvement may lead to a suspicion of lymphoma, the phenytoin-induced pseudolymphoma syndrome [14–19]. Cutaneous lesions may be restricted to a few erythematous plaques [18], or cutaneous nodules [15], or consist of a generalized erythematous maculopapular rash [14], generalized exfoliative dermatitis [16,20] or TEN [21,22]. Generalized pustulation has been recorded as a manifestation of the anticonvulsant drug hypersensitivity syndrome [23]. Universal depigmentation has resulted from TEN [24]. Cutaneous histopathology in the pseudolymphoma syndrome is often indistinguishable from that of mycosis fungoides, with infiltrating cells having cerebriform nuclei and forming Pautrier microabscesses [17,19]. The rash resolves after cessation of the drug; systemic corticosteroids may aid resolution [25]. However, there is a threefold risk of true lymphoma on long-term therapy [26–28], and T-cell lymphoma has been reported in an adult [29].

Long-term treatment causes fibroblast proliferation, and may result in dose-dependent gingival hyperplasia [30,31] or coarsening of the features [32]; hypertrophic retro-auricular folds were reported in an isolated case [33]. Hypertrichosis may be seen. Other reactions have included fixed eruptions [34], including a widespread fixed drug eruption mimicking TEN [35], erythema multiforme [1,3], TEN with cholestasis [36], cutaneous vasculitis [37], an LE-like syndrome [38,39] and eosinophilic fasciitis [40]. Linear IgA bullous dermatosis has been provoked [41]. Localized reactions to intravenous phenytoin have included delayed bluish discoloration, erythema and oedema, sometimes with bullae, distal to the site of injection; immediate burning pain and swelling, and a delayed erythematous eruption with superficial sloughing, partial epidermal necrosis and frequent multinucleate keratinocytes on histology have also been reported [42,43].

Treatment during pregnancy may lead to a characteristic 'fetal hydantoin syndrome', with general underdevelopment and hypoplasia of phalanges and nails [44]; neonatal acne may be associated [45]. However, recent controlled observations suggest that acne is neither caused nor worsened by hydantoins [46], despite reports to the contrary [47].

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Lamotrigine

Dosage-related allergic rashes occur in about 5–10% of patients, usually in the first 8 weeks, leading to a withdrawal rate of 2% of patient exposures [1–4]. In one study, six of eight patients with a prior lamotrigine-related rash had no recurrence on rechallenge, and two other patients had only mild rashes [5]. Rashes leading to hospitalization, including hypersensitivity syndrome [6], Stevens–Johnson syndrome and TEN [7], occurred in 1 in 100 to 1 in 300 individuals in clinical trials, and appeared to be increased with over-rapid titration when starting therapy and with concurrent valproate medication [3,8].

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Sodium valproate

Occasional transient rashes and stomatitis are documented. Temporary hair loss may be followed by increasing curliness of the regrowing hair [1]. Alteration in hair colour has been noted [2]. One case of generalized morphoea [3] and two cases of cutaneous leukocytoclastic vasculitis recurring on challenge [4] have been reported. An extrapyramidal syndrome may be induced [5], and the drug may be teratogenic [6].

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Trimethadione

Serious hypersensitivity reactions may occur, including erythema multiforme, urticaria and generalized exfoliative dermatitis.

Vigabatrin

An allergic vasculitis developed in one patient 6 months after commencement of this drug [1].

REFERENCE

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Opioid analgesics and amfetamine (amphetamine)

Cutaneous side effects common to drug abuse, most frequently cocaine, heroin and pentazocine, following parenteral injection include [1,2] infections, abscesses, septic phlebitis, subcutaneous and deep dermal cellulitis, necrosis, tetanus, widespread urticaria, cutaneous manifestations of primary and secondary syphilis, HIV infection and endocarditis. Starch and talc granulomas, lymphangitis and lymphadenitis in draining lymph nodes, pigmentary abnormalities including hyperpigmentation over the injected veins, accidental 'soot' tattoos (caused by needles sterilized over an open flame), scarring, ulceration, necrotizing angiitis and leukocytoclastic vasculitis may supervene. Skin popping refers to injection of drugs beneath the skin without concern for vascular access; this may result in ulcers being delayed for a number of years [3].

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Buprenorphine

An addict accidentally injected a suspension of crushed tablets into the superficial pudendal artery instead of the femoral vein, and developed pain, oedema and mottling of the penis [1].

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Codeine

This drug has been associated with pruritus, urticaria (usually due to non-immunological release of histamine) [1,2], angio-oedema, macular and maculopapular eruptions, scarlatiniform rashes [1,3,4], fixed eruption, bullous eruption, generalized eczema [5], erythema multiforme and erythema nodosum.

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Heroin

Use of the dorsal vein of the penis for administration of the drug has produced ulceration [1]. Systemic infections, such as candidiasis, may supervene [2]. Leukocytoclastic vasculitis and necrotizing angiitis have been reported in drug abusers [3–5]. Pigmentation of the tongue may occur as a form of fixed drug eruption in heroin addicts [6]. A possible association with development of pemphigus erythematosus has been suggested [7].

REFERENCES

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Morphine

Morphine is a potent histamine releaser and may cause pruritus and urticaria [1]. Profuse sweating is a common effect. Morphine provokes facial flushing blocked by naloxone [2]. Local skin irritation during subcutaneous morphine infusion is recorded [3].

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Pentazocine

Woody induration of the skin and subcutaneous tissues at injection sites, perhaps with central ulceration and peripheral pigmentation, and a granulomatous histology, is well recognized [1–8]. Pigmentation, ulceration and a chronic panniculitis have supervened after many years of use. Phlebitis, cellulitis, fibrous myopathy [9] and limb contractures can complicate these changes. Generalized eruptions are rare [10]. There is an isolated report of TEN [11].

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Methylamfetamine

A link with necrotizing angiitis has been recorded when this drug is used alone or with heroin or D-lysergic acid diethylamide [1].

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Antiparkinsonian drugs

Amantadine

Reversible livedo reticularis has occurred in a high percentage of patients receiving amantadine, a tricyclic amine used in the treatment of Parkinson's disease [1,2].

Apomorphine

Panniculitis, ranging from mild pruritic erythema to painful nodules, has been observed [3].

Bromocriptine

Transient livedo reticularis [4], erythromelalgia [5], acrocyanosis with Raynaud's phenomenon [6,7], morphoea [8] and swelling of the legs with a sclerodermatous histology [9] have been reported rarely, as have alopecia [10], pseudolymphoma [11] and psychosis.

Carbidopa

Scleroderma-like reactions have occurred when this drug has been given in conjunction with tryptophan [12,13].

Levodopa

There have been several isolated reports of the occurrence of malignant melanoma [14–16], in certain instances involving multiple primaries, but the association may be by chance alone.

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Antivertigo drugs and cerebrovascular dilators

Cinnarizine

This drug [1], and its derivative flunarizine [2], have been implicated in the precipitation of lichenoid eruptions. In the case of cinnarizine, clinical and immunofluorescence features of lichen planus were combined with the presence of a circulating anti-basement-membrane zone IgG antibody [2]. Other side effects include drowsiness, depression and parkinsonism.

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Miscellaneous nervous system drugs

Drugs for alcoholism

Cyanamide. This inhibitor of alcohol dehydrogenase, used in the treatment of alcoholism in some countries, has been implicated in the development of a lichen planus-like eruption with oesophageal involvement [1,2], as well as exfoliative dermatitis [2].

Disulfiram. This drug causes vasomotor flushing, morbilliform rash and urticaria, as well as eczema in patients sensitized to rubber; it cross-reacts with rubber [3–5]. A toxic pustular eruption is recorded [6].

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Drugs to aid smoking cessation

Amfebutamone. This antidepressant drug, structurally related to the phenylethylamines (amfetamines) and used in aiding smoking cessation, has been implicated in causing liver dysfunction, pruritus and urticaria [1], serum sickness [2,3], and generalized pustular and erythrodermic psoriasis [4].

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Appetite suppressants and stimulants

Centrally acting appetite suppressants may induce urticarial vasculitis [1]. Megestrol, a synthetic orally active progesterone derivative used to stimulate appetite and weight gain in cachectic patients, caused a generalized morbilliform rash in a man; skin testing with progesterone acetate was positive [2]. Sibutramine, a centrally acting drug used in weight management, caused an erythema multiforme-like reaction [3].

Pyritinol

This drug, given for cerebral concussion, caused an unusual erythema multiforme-like eruption and severe headache after 10 days' treatment [4].

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Drugs acting on the cardiovascular system

Adverse cutaneous reactions due to cardiovascular and antiarrhythmic drug therapy have been reviewed [1,2].

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Cardiac antiarrhythmic drugs

Amiodarone

This iodinated antiarrhythmic drug causes photosensitivity in around 40% of patients [1–13]. Symptoms develop within 2 h of sun exposure as a burning sensation followed by erythema; the action spectrum is UVA, extending to a degree into visible light wavebands above 400 nm [4]. Light sensitivity may persist for up to 4 months after the drug is stopped [1,2]. Blue or grey pigmentation of the face and other sun-exposed areas, resembling that in argyria, is a much less common late effect, occurring in 2–5% of cases; areas not exposed to the sun may also be involved [3,6–12]. It is induced by a phototoxic reaction involving both UVB and UVA [3,6], and is related to both duration and dosage of the drug [11]. However, although cutaneous side effects are more likely with increasing duration of treatment and cumulative dosage, neither the serum amiodarone level nor the serum metabolite level have any predictive power [13]. Amiodarone-pigmented skin contains the drug and its metabolities in higher concentrations than non-pigmented skin [3]. Iodine-rich amiodarone and its metabolites have been detected bound to lipofuscin within secondary lysosomes in perivascular dermal macrophages [7–10]. Electron-dense granules and myelin-like bodies are also found in peripheral blood leukocytes [12]. The cutaneous pigmentation slowly fades after discontinuation of therapy, but may persist for months to years [8].

Iododerma has occurred with long-term therapy. Vasculitis [14] and linear IgA disease [15] have been recorded. A fatal case of TEN has been reported [16]. The most severe adverse effect seen with amiodarone is pulmonary fibrosis, which occurs in 5–10% of exposed patients and which has a 10% mortality rate. Other problems have been cardiac dysrhythmias, thyroid dysfunction, peripheral neuropathy and reversible corneal deposits [17].

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Digoxin

Allergic reactions are very rare [1], but exanthematic erythema, urticaria, bullous eruptions and thrombocytopenic purpura are documented. In one patient, a psoriasiform rash occurred, confirmed by later re-exposure [2].

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Procainamide

This drug is well known for precipitating an LE-like syndrome [1–6], perhaps partly as a result of binding of the hydroxylamine metabolite of procainamide to complement component C4, with resultant impaired complement-mediated clearance of immune complexes [5,6]. A lichenoid eruption followed the occurrence of drug-induced LE in one case [7]. Urticarial vasculitis has been reported [8].

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Quinidine

An eczematous photosensitivity is well described [1–5]; fever is common. Thrombocytopenic purpura may be induced, resulting from antibodies to drug–platelet conjugates [6,7]. Urticarial, scarlatiniform and morbilliform eruptions occur; the latter may proceed to generalized exfoliative dermatitis if the drug is continued. Fixed and lichenoid eruptions [8–14], often induced by light, are recorded, as well as an acneiform rash [15]. Livedo reticularis has been documented; the mechanism is unknown, although recent exposure to sunlight was a feature common to all cases [16–18]. Drug-induced LE [19–21] and Henoch–Schönlein vasculitis [22,23] have been seen. Psoriasis may be exacerbated [24,25]. Localized blue-grey pigmentation of the shins, hard palate, nails, nose, ears and forearms has been recorded [26].

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β-Adrenoceptor-blocking agents

This group of drugs shares certain potential side effects in common [1,2]. Peripheral ischaemia may be aggravated, and cold extremities and Raynaud's phenomenon [3] may present as new symptoms. Peripheral gangrene and peripheral skin necrosis have been reported [4,5]. An LE-like syndrome [6,7], and eczematous or lichenoid eruptions [1,2] may be induced rarely. Psoriasis vulgaris is occasionally aggravated or precipitated by a number of β-blockers including atenolol, oxprenolol and propranolol [8–14]. Cross-sensitivity is not usual [15], but cross-reactivity between atenolol, oxprenolol and propranolol has been reported [16]. Peyronie's disease (induratio penis plastica) has been attributed to labetalol, metoprolol and propranolol [17,18]. Aphthous ulcers have been linked to β-blockers [19], and vasculitis occurred with sotalol [20]. β-Blockers may enhance anaphylactic reactions caused by other allergens, and may make resuscitation more difficult [21–23]. Vitiligo may be exacerbated [24]. Topical ophthalmic β-blockers, especially timolol, have been implicated in pruritus [25], alopecia [26], chronic erythroderma [27] and LE [28].

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Acebutolol

Rashes with mixed lichenoid and LE-like features have been reported [1]. The LE syndrome may have pleuropulmonary features [2].

Atenolol

Conjunctivitis and a periocular dermatitis [3], as well as a psoriasiform rash [4], pseudolymphomatous reaction [5] and vasculitis [6], are recorded.

Cetamolol

A psoriasiform eruption has been documented [7].

Labetalol

Mixed eruptions with psoriasiform and pityriasis rubra pilaris-like changes [8], a bullous lichenoid eruption [9] and an SLE-like syndrome [10] are documented.

Metoprolol

Various psoriasiform or eczematous rashes may follow long-term therapy [11,12]. Conjunctivitis and periocular dermatitis have occurred [3]. Peyronie's disease appears to be a rare but confirmed side effect and may be reversible. Telogen effluvium has been noted [13].

Oxprenolol

This drug, like practolol, has caused an oculocutaneous syndrome [14]. An eruption combining well-defined, eroded or scaly red rings with a lichenoid histology [15,16] is recognized. Acute psoriasis with arthropathy has been described [17]. Peripheral skin necrosis associated with Raynaud's phenomenon, an LE syndrome, various patterns of dermatitis [3] and generalized pigmentation [18] are all documented.

Practolol

This drug has been withdrawn, but is discussed in view of its important side-effect profile. It caused an oculocutaneous syndrome comprising dry eyes and scarring, fibrosis and metaplasia of the conjunctiva; a psoriasiform, lichenoid or mixed eruption with a characteristic histology; pleural and pericardial reactions; fibrinous peritonitis; and serous otitis media [19,20]. Subsequent treatment with another β-blocker did not elicit cross-sensitivity reactivation of the syndrome [21]. Ocular cicatricial pemphigoid was seen [22], and exacerbation of psoriasis was recorded [23].

Pindolol

Psoriasiform [24] and lichenoid rashes with pemphigus-like antibodies demonstrated by immunofluorescence have been seen, as well as an SLE syndrome [25].

Propranolol

This is probably the most widely used β-blocker, and many adverse cutaneous reactions have been reported [26–29]. Rashes may be lichenoid [30], psoriasiform [29] or generalized and exfoliative. Other miscellaneous reported reactions include alopecia [31], erythema multiforme [32] and a cheilostomatitis with ulceration of the lips. Peyronie's disease has developed. Generalized pustular psoriasis [33] and pemphigus [34] have occurred.

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Antihypertensive drugs and vasodilators

The dermatological side effects of antihypertensive agents have been reviewed [1].

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ACE inhibitors

In addition to dermatological problems, these drugs may be nephrotoxic, cause cough and electrolyte disturbances, and are teratogenic [1,2]. The overall incidence of adverse effects from ACE inhibitors is estimated at 28%, of which about 50% occur in the skin. Cutaneous reactions comprise life-threatening angio-oedema, pruritus, bullous eruptions, urticaria, other generalized rashes, photosensitivity and hair loss [3]. Angio-oedema has been reported with captopril, enalapril maleate and lisinopril [4–11]. The cumulative incidence of angio-oedema, almost always on the head and neck, has been estimated at 0.1–0.7% of cases treated; it usually occurs in the first week of treatment [5,9], although onset more than 6 weeks after starting treatment occurs in 20% of patients [6]. In addition, increased frequency, intensity and duration of bouts of angio-oedema have been recorded during long-term use of ACE inhibitors [7–9]. There may be cross-reactivity between drugs; angio-oedema has developed after substituting lisinopril for captopril [10]. Fatal angio-oedema occurred in a patient on captopril for 2 years [11]. Anaphylactoid reactions have been reported during haemodialysis with AN69 membranes in patients receiving ACE inhibitors; the role of bacterial contamination of dialysate is controversial [12–14]. Anaphylactoid reactions have also occurred with LDL apheresis with dextran sulphate [15].

ACE inhibitors have been implicated in both the exacerbation and induction of psoriasis [16–19]. ACE inhibitors most commonly produce a dose-related pruritic maculopapular eruption on the upper trunk and arms, especially with captopril (2.4–7%) and less with enalapril (1.5%), which is often transitory and rarely requires discontinuation of the drug. Urticaria, a pemphigoid-like reaction, a pityriasis rosea-like reaction, a lichenoid eruption, erythroderma, alopecia and Stevens–Johnson syndrome have been reported [20]. Captopril and enalapril may produce eruptions with histological similarities to mycosis fungoides [21]. An interstitial granulomatous drug reaction characterized by violaceous plaques with a predilection for skinfold areas and by histology resembling the diffuse interstitial phase of granuloma annulare without complete collagen necrobiosis has been documented with ACE inhibitors [22].

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Captopril. Dermatological complications occur in 4% [1] to 12% [2] of patients treated with captopril, and less commonly with other ACE inhibitors; side effects are more likely with renal impairment. Loss of sense of taste, or a metallic taste (augesia), ulceration of the tongue and aphthous stomatitis [3] are reported. Early changes within the first months [4–6] include pruritus, urticaria [7] and angio-oedema, which occurs in about 1 in 1000 patients and may occasionally be fatal [8], and pityriasis rosea-like [9] and morbilliform rashes. These are dose dependent and have a good prognosis. Late changes [4–6] consist of pemphigus-like [10–12] and lichenoid [13–17] eruptions. SLE-like eruptions have been recorded [18,19]. Antinuclear antibodies may develop [20,21]. Oral changes may be due to a leukocytoclastic vasculitis [22], and a serum sickness-like syndrome has been induced [23]. Psoriasis has been reported to be exacerbated or triggered [24,25].

Severe reactions [26,27] have included exfoliative dermatitis [28–30], and marrow depression with neutropenia or agranulocytosis [31]. Lymphadenopathy may be induced [32]. Alopecia [33] and an acquired IgA deficiency [34] have been reported. The merits of skin testing in the prediction of captopril reactions have been discussed [35]. It has been postulated that some toxic effects are related to the presence of a sulphydryl group, as enalapril (another ACE inhibitor lacking this group) has been safely substituted in certain cases of captopril hypersensitivity [36].

Cilazapril. Cilazapril had more neurological (mainly headache) but fewer skin reactions than the other ACE inhibitors, lisinopril, enalapril and captopril [37].

Enalapril. Enalapril produces rashes in approximately 1.4% of patients, requiring discontinuation in about 0.4% [38]. Toxic pustuloderma is recorded [38]. A single report of pemphigus foliaceus has appeared; part of the structure of this drug is identical to that of captopril, although it does not contain a sulphydryl group [39]. Bullous eruptions [40] and lichenoid eruptions [41] occur.

Lisinopril [42]. Vasculitis has been recorded [43], as has pallor, flushing and oedema [44].

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Angiotensin II receptor antagonists

Sartans, angiotensin II receptor antagonists, have been implicated in the induction of psoriasis [1] and of Henoch–Schönlein purpura [2].

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Calcium channel blockers

Cutaneous reactions are rare and have been reported in six per million prescriptions of nifedipine, 17 per million prescriptions of verapamil, and six per million prescriptions of diltiazem [1,2]. In one study, reactions to the dihydropyridine drugs (including nicardipine, nifedipine and nisoldipine), verapamil and diltiazem occurred after an average of 95 days (range 7 days to 10 years) [3]. Pruritus, maculopapular rashes, and urticaria/angio-oedema, alopecia and a hypersensitivity syndrome have been described with all these drugs, as have Stevens–Johnson syndrome and erythema multiforme; TEN has occurred with diltiazem. There is a suggestion that the more severe reactions are commoner with diltiazem. Peripheral oedema as a side effect is common to the dihydropyridine calcium antagonists, including nifedipine, nicardipine, isradipine and amlodipine; it occurs in 7–30% of patients depending on the specific drug, but is usually mild [4]. Psoriasiform eruptions are described [3], as are photosensitivity and erythromelalgia. Amlodipine has caused pruritus [5], a lichenoid eruption [6] and photosensitivity presenting as telangiectasia [7]. Felodipine has also been associated with photodistributed telangiectasia [8].

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Diltiazem. Cutaneous reactions to diltiazem have been reviewed [1–3]. They include pruritic macular exanthem, toxic erythema with fever and occasionally facial angio-oedema [4–6], generalized cutaneous reactions [7], erythema multiforme [8], subcorneal pustular dermatosis, a generalized pustular dermatitis [9,10], a lichenoid photodistributed eruption with pigmentary incontinence [11], a photosensitive erythroderma [12], psoriasiform eruptions [2], exfoliative dermatitis in a patient with psoriasis [13], a subacute cutaneous LE-like syndrome [14], vasculitis [15] and vasculitic leg ulcers [16], recurrent nail dystrophy, hyperplastic gingivitis [17], and proptosis and periorbital oedema [18]. Generalized lymphadenopathy has occurred [19]. Patch tests may be positive in diltiazem reactions

[5,6,10]. Dermatological cross-sensitivity between diltiazem and amlodipine is reported [20].

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Nicardipine. Erythromelalgia is recorded [1].

Nicorandil. Oral ulceration is documented [2,3].

Nifedipine. Headache, tachycardia and flushing are common side effects. Gingival hyperplasia is well recognized [4]. Burning sensations, erythema, painful oedema and erythromelalgia have been described [5–8]. There have been isolated reports of a truncal morbilliform rash [9], fixed drug eruption [10], a generalized bullous eruption, vasculitis [11], purpura, photosensitivity [12] in one case confirmed by rechallenge [13], gynaecomastia [14], erysipelas-like lesions on the shins with erythematous plaques on the trunk [15], exfoliative dermatitis [16,17] and pemphigoid nodularis [18].

Verapamil. Erythema multiforme has been reported [19], as have gingival hyperplasia, gynaecomastia [20], alopecia, maculopapular eruptions, ecchymosis, vasculitis, urticaria and hyperkeratosis.

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Centrally acting antihypertensive drugs

Clonidine. Hypersensitivity rashes occur in up to 5% of patients. A pityriasis rosea-like and LE-like syndrome, exacerbation of psoriasis [1] and an isolated instance of anogenital cicatricial pemphigoid [2] have been documented. Transdermally administered clonidine has caused allergic contact dermatitis, but also erythema, scaling, vesiculation, excoriation, induration and dyspigmentation [3].

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Methyldopa. An eczematous eruption of discoid or seborrhoeic pattern is characteristic, is more likely to occur in previously eczematous subjects and persists until the drug is stopped [1]. Eczema of the palms and soles has also been described and may become widespread. The reaction is probably allergic as it may be dose related. Purpuric, erythematous and lichenoid rashes occur, sometimes in association with fever and other allergic symptoms [2,3]. Lichenoid eruptions may be ulcerated [4,5] and persistent ulceration of the tongue has been described. Fixed eruptions are very rare. An LE-like syndrome is documented [6,7] and an autoimmune haemolytic anaemia is well known [5]. Psoriasis may be precipitated. An extensive erythematous skin eruption, fever, lymphadenopathy and eosinophilia due to methyldopa, recurrent on re-exposure, has been recorded [8].

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Adrenergic neurone-blocking agents

Guanethidine. Hypersensitivity eruptions are very rare but polyarteritis nodosa has been attributed to this drug [1].

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Vasodilator antihypertensive drugs

Diazoxide. Transient flushing is common. During long-term treatment, up to half the patients develop hypertrichosis without other signs of virilization [1]. A clinical picture resembling hypertrichosis lanuginosa may develop [2,3]. Oedema occurs in at least 10% of patients; photosensitivity is very uncommon but well recognized. Lichenoid [3,4] and other rashes occur rarely.

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Hydralazine. The LE-like syndrome due to this drug is well known [1–7]. Hydralazine binds to complement component C4 and inhibits its function; this may impair clearance of immune complexes, and predispose to development of an LE syndrome [6,7].

Orogenital ulceration may be part of the picture [8], and the syndrome has presented as a leg ulcer [9]. Cutaneous vasculitis may be severe and necrotizing [10,11]. An association between hydralazine-induced LE syndrome and the development of Sweet's syndrome has been noted rarely [12]. Fixed drug eruption has been reported [13]. Characteristic lung changes are attributed to the drug [14].

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Minoxidil. This arterial vasodilator causes hypertrichosis, especially of the arms and face, which may be unacceptable to women [1,2]; the hair disappears slowly after the drug is withdrawn. Fluid retention may require diuretic therapy to control it. Thrombocytopenia [3], bullous eruptions [4], erythema multiforme or Stevens–Johnson syndrome [5] and pseudoacromegaly [6] have been described.

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Nitrate vasodilators

Glyceryl and pentaerythritol tetranitrate. Reactions to nitrate vasodilators are rare, but erythroderma with cross-reactivity to glyceryl trinitrate has been caused by this drug [1].

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Diuretics

Carbonic anhydrase inhibitor

Acetazolamide. This drug has caused hirsutism in a child [1]. Hypersensitivity reactions are rare.

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Loop diuretics

Bumetanide. Occasional hypersensitivity rashes occur. Pseudoporphyria has been reported wih this sulphonamide-derived drug [1].

Etacrynic acid (ethacrynic acid). A Henoch–Schönlein type of vasculitis has been documented.

Furosemide (frusemide). Reactions are rare: only two patients of 3830 receiving this medication in one study developed cutaneous complications [2]. Phototoxic blistering has followed very high dosage (2.0 g/day) in chronic renal failure [3] but erythema multiforme [4,5], bullous pemphigoid [6,7], other bullous haemorrhagic eruptions [8] and an acquired blistering disorder with skin fragility [9] have apparently been precipitated by conventional dosage. The skin changes may mimic those of porphyria. Several cases of generalized exfoliative dermatitis have been documented. Anaphylaxis [10], a necrotizing vasculitis [11] and an eruption resembling Sweet's syndrome [12] have been reported. Cross-reactivity between furosemide, hydrochlorothiazide and sulphonamides is recorded, but the use of one of these drugs in a patient known to have allergy to another involves only low risk [13].

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Potassium-sparing diuretics

Spironolactone. This drug, which is also used for the treatment of acne vulgaris and hirsutism [1], may cause gynaecomastia [2–4], gastrointestinal upset, hyperkalaemia and rarely agranulocytosis [1]. Spironolactone has an anti-androgenic effect [4] and may result in loss of libido and impotence or menstrual irregularities. A maculopapular eruption [5], LE-like syndrome [6], annular LE [7], erythema annulare centrifugum [8] and a lichenoid eruption [9] have been seen.

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Thiazides and related diuretics

Photosensitivity is uncommon, occurring in 1 in 1000 to 1 in 100 000 prescriptions [1–7]. Hydrochlorothiazide causes considerably more reactions than bendroflumethiazide (bendrofluazide). The mechanism is unknown, and both phototoxic [1,4,7] and photoallergic [2,3] mechanisms have been proposed. The commonest reaction is lichenoid [8], but petechial and erythematous eruptions may occur in exposed skin. Xerostomia has been reported, as has a vasculitis [9]. An eruption resembling subacute cutaneous LE has been described in patients taking a combination of hydrochlorothiazide and triamterene [10,11] and with hydrochlorothiazide alone [12]. Other side effects include hypokalaemia, short-term elevation of LDL cholesterol, impotence, a diabetogenic effect and exacerbation of gout [13].

Chlortalidone (chlorthalidone). Pseudoporphyria has been documented with this thiazide-related diuretic [14]. Psoriasis has been triggered in a patient also receiving captopril [15].

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Miscellaneous cardiovascular drugs

Dobutamine

Two patients with local dermal hypersensitivity at the site of dobutamine hydrochloride injection, consisting of erythema, pruritus and phlebitis with or without bullae, have been described [1]. Dermal cellulitis has also been reported [2].

Dopamine

This positive inotropic agent has caused local skin necrosis, due to extravasation at the site of an intravenous cannula [3], and acral gangrene secondary to distal vasoconstriction [4,5]. Localized piloerection and vasoconstriction proximal to the site of infusion have been documented [6]. Allergic reactions may occur [7].

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Vasopressin

This drug, when used intravenously for control of bleeding oesophageal varices or as a local vasoconstrictor agent, has caused cutaneous necrosis at sites of extravasation, and occasionally at distant sites, with a bullous eruption [1]. Mottling, cyanosis, ecchymoses, bullae, ulcers and gangrene are often preceded by coolness and paraesthesiae [2].

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Rutosides (Paroven)

This mixture of oxerutins, used for relief of symptoms of oedema related to chronic venous insufficiency and for reduction of lymphoedema, has been associated with transient urticaria [1].

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Drugs acting on the respiratory system

β-Agonists

Albuterol

Patchy erythema of the hands developed in a pregnant patient following infusion [1].

Salbutamol

LE-like acral erythema developed after infusion in three pregnant patients with premature labour [2].

Salmeterol

An urticarial reaction that recurred on challenge was attributed to this drug administered from a metered dose inhaler [3].

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Aminophylline

This drug is a mixture of theophylline and ethylenediamine. Urticaria, generalized erythema and exfoliative dermatitis have followed systemic administration, probably as a result of reactions to the ethylenediamine component rather than to theophylline itself [1]. Cross-reactions may occur with ethylenediamine in antihistamines and topical preparations [1,2]. Patch tests may or may not be positive [3].

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Miscellaneous respiratory system drugs

Sodium cromoglicate (sodium cromoglycate)

Hypersensitivity reactions are rare, but urticaria, angio-oedema and anaphylactic shock are recorded [1].

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Pseudoephedrine

This drug is present in nasal decongestants and has caused a fixed drug eruption [1–3], recurrent pseudoscarlatina [4,5], allergic reactions [6], systemic contact dermatitis [7] and a reaction simulating recurrent toxic shock syndrome [8].

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Drugs acting on the renal system

Icodextrin

This new osmotic agent used in peritoneal dialysis has caused a variety of allergic reactions [1,2], a psoriasiform eruption limited to the palms and soles [3], and acute generalized exanthematous pustulosis [4].

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Drugs acting on the skeletal system

Alendronate

This drug for osteoporosis has caused urticaria [1] and a gyrate erythema [2].

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Drugs for erectile dysfunction

Sildenafil (Viagra)

A lichenoid reaction is reported [1].

REFERENCE

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Metals and metal antagonists

Metals

Arsenic

Features of acute [1] and chronic [2] arsenic poisoning have been reviewed. Bullous eruptions, photosensitivity, exfoliative dermatitis, erythroderma with pustulation, and alopecia may be acute manifestations of arsenic toxicity. Occupational exposure may occur, especially in agriculture. Inorganic arsenic is sometimes present in Chinese proprietary medicines [2]. Fowler's solution (containing 1% potassium arsenite) and sodium arsenate were used in the past for psoriasis; as little as 0.19 g has been carcinogenic and the interval between exposure and tumour induction may be as long as 47 years [3]. Subjects with an abnormally high retention of ingested arsenic may be at particular risk [4]. The cutaneous manifestations of arsenic exposure, including macular pigmentation, palmoplantar punctate keratoses and intraepidermal (Bowen's disease), basal cell or squamous carcinomas of the skin, are well known [2–11]. Keratoses and tumours may be present without pigmentation. In one series of patients, there was a dose-related development of palmar and plantar keratoses in 40%, and carcinomas of the skin in 8%, of patients who received arsenic in the form of Fowler's solution for 6–26 years; the minimum latent period before development of keratoses was 2.5 years, and the average was 6 years [5]. In another series, Bowen's disease occurred within 10 years and invasive carcinomas within 20 years [9]. The lag times for development of keratoses, Bowen's disease and squamous cell cancer were, respectively, 28, 39 and 41 years in another series [2]. Arsenic contamination of well water in Taiwan resulted in numerous affected individuals with arsenical keratoses and cutaneous carcinomas [7]. Carcinomas may arise in the arsenical keratoses [7]. Groundwater contamination leads to an endemic problem [12,13]. Cutaneous electron microscopic changes are said to be characteristic [10]. The diagnostic significance of the skin arsenic content is disputed. A 42-year-old man who took arsenic for 35 years for psoriasis developed melanoderma, keratoses, muscular dystrophies, hyperlipidaemia, testicular atrophy, gynaecomastia, skin tumours and an obliterating angiitis of leg vessels, which led to amputation [6]. The role of arsenic in causing internal malignancy is the subject of controversy [9,14,15].

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Gold

The use of gold in rheumatoid arthritis is associated with a 23–30% incidence of reactions [1–3]; most of these are minor, but about 15% may be severe or even fatal [4]. Possession of the HLA-DR3 and HLA-B8 phenotypes reportedly predisposes to thrombocytopenia, leukopenia and nephrotoxicity, HLA-DR4 is linked to leukopenia, and

HLA-B7 is associated with cutaneous adverse reactions [2]. In another study, HLA-DR5 was significantly associated with mucocutaneous lesions, whereas HLA-B8 and HLA-DR3 antigens were associated with proteinuria in rheumatoid arthritis patients after gold therapy; HLA-DR7 was negatively associated with reactions and may confer protection, and HLA-B27 was associated with chrysiasis due to gold therapy [5]. A further study showed that gold dermatitis in patients with rheumatoid arthritis was associated with HLA-B35 and disease duration [6]. Antibodies to the Ro 52-kDa antigen are associated with skin eruptions in rheumatoid arthritis patients treated with gold [7].

Rashes and mouth ulcers are common [1,2,8–13], representing about 50% of all complications with parenteral gold and 35% of those with oral gold. Localized or generalized pruritus is an important warning sign of potential toxicity. Gold reactions may simulate exanthematic eruptions [14], erythema annulare centrifugum [15], seborrhoeic dermatitis or lichen planus [16,17]; a mixture of these patterns, sometimes with discoid eczematoid lesions, is characteristic. Lichen planus is often of the hypertrophic variety especially on the scalp, and severe and irreversible alopecia may follow [18]. There may be striking and persistent post-inflammatory hyperpigmentation. Permanent nail dystrophy has followed onycholysis [19]. Yellow nails have been described [20].

In one study, eczematous or lichenoid rashes persisted up to 11 months after cessation of therapy [21]. Histology was characterized by a sparse dermal perivascular infiltrate, predominantly of $CD4^+$ HLA-DR-positive helper T lymphocytes, an increase in the number of dermal Langerhans' cells and epidermal macrophage-like cells, and Langerhans' cell apposition to mononuclear cells. A patient with a lichenoid and seborrhoeic dermatitis-like rash on gold sodium thiomalate therapy had a positive intradermal test to gold thiomalate; patch tests were positive to thiomalate (the thiol carrier of gold thiomalate) but negative to gold itself [22]. Interestingly, the same patient subsequently developed a seborrhoeic dermatitis-like eruption, but not a lichenoid eruption, while on auranofin; this time, patch tests were positive to both auranofin and gold. A previous contact dermatitis from gold jewellery may be reactivated [23].

Other reactions documented include erythema nodosum [24], severe hypersensitivity reactions [25], vasculitis [26], polyarteritis, an SLE-like syndrome, generalized exfoliative dermatitis and TEN. Psoriasis was reported to be exacerbated in a patient with arthritis treated with gold [27].

Prolonged administration of gold may cause a distinct grey, blue or purple pigmentation of exposed skin (chrysiasis), which is a dose-dependent reaction that occurs above a threshold of 20 mg/kg; gold granules are seen within dermal endothelial cells and macrophages [28–32]. Even in the absence of pigmentation, gold can be detected histochemically in the skin up to 20 years after therapy. Localized argyria with chrysiasis has been caused by implanted acupuncture needles [33]. An unusual late cutaneous reaction involved the appearance of widespread keloid-like angiofibromatoid lesions [34].

A benign vasodilatory 'nitritoid' reaction, consisting of flushing, light-headedness and transient hypotension, may occur immediately after the first injection of gold [2,35]. It occurs in roughly 5% of patients taking gold sodium thiomalate. Non-vasomotor effects, including arthralgia, myalgia and constitutional symptoms within the first 24 h, are recognized. Mucous membrane symptoms include loss of taste, metallic taste, stomatitis, glossitis and diarrhoea. Punctate stomatitis may occur with or without skin lesions. Gold is also deposited in the cornea and may cause a keratitis with ulceration. A polyneuropathy is recorded. In general, auranofin is less toxic than intramuscular gold [2]. Eosinophilia is common and may sometimes herald another complication; serum IgE may be raised [36]. Other immunological reactions are rare, although pulmonary fibrosis is recorded [37]. Blood dyscrasias, especially thrombocytopenic purpura, and occasionally fatal neutropenia or aplastic anaemia occur in a small proportion of cases and usually present within the first 6 months of therapy. Jaundice occurs in about 3% of cases, and may result from idiosyncratic intrahepatic cholestasis [38]. Proteinuria and renal damage are well known.

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Iron

Iron-induced brownish discoloration has been noted at the site of local injection (local siderosis) [1].

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Mercury

Skin manifestations of mercury exposure have been reviewed [1,2]. Mercury-containing teething powders have long been banned, but occasional occupational or environmental exposure can occur. Mercury amalgam in dental fillings has caused buccal pigmentation. Stomatitis may occur as a toxic reaction. Allergic reactions may be scarlatiniform or morbilliform, and can progress to generalized exfoliative dermatitis. Eczema is recorded [3]. Pink disease or acrodynia, a distinctive pattern of reaction to chronic exposure to mercury in young infants and children, is now very rare [4]. Painful extremities, pinkish acral discoloration, peeling of the palms and soles, gingivitis and various systemic complications may occur. Acrodynia developed in a child following inhalation of mercury-containing vapours from phenyl-mercuric acetate contained in latex paint [5]. A mercury-containing drug given for 3 weeks to a patient with long-standing pustular psoriasis of the palms was associated with development of generalized pustular psoriasis [6]. (See also exogenous ochronosis from topical mercury-containing preparations, p. 73.168.) Cutaneous granulomas are recorded [1], and a nodular reaction occurred after intake of a duck soup that contained metallic mercury for a neck abscess 18 years previously [7].

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Silver

Ingestion of silver or topical application of silver preparations to the oral mucosa or upper respiratory tract can produce slate-blue discoloration, especially of exposed skin, including oral and conjunctival mucosae [1–8]. Argyria localized to the left hand occurred in an antique restorer due to polishing silver [9]. Topical application may also cause systemic argyria, in which visceral organs are also discoloured [10]. Localized argyria can result when the backs of earrings become embedded [11]. In some patients, the nail beds of the fingers but not the toes may show bluish discoloration [12]. Silver granules are found free within the dermis; melanin may be increased in the epidermis or within melanophages [13–15].

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Metal antagonists

Deferoxamine (desferrioxamine)

Itching, erythema and urticaria are occasionally seen [1]. An indurated erythema with oedema lasting 2 weeks has been reported following infusion of this drug [2].

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Penicillamine

There is a fourfold increase in toxicity with this drug in patients with rheumatoid arthritis who have a genetically determined poor capacity to sulphoxidate the structurally related mucolytic agent carbocysteine [1,2]. In addition, penicillamine toxicity is independently associated with HLA phenotype [1–3]. HLA-DR3 and HLA-B8 are associated with renal toxicity, HLA-DR3, HLA-B7 and HLA-DR2 with haematological toxicity, and HLA-A1 and HLA-DR4 with thrombocytopenia. Cutaneous adverse reactions are linked to HLA-DRw6. Anti-Ro(SSA)-positive patients with rheumatoid arthritis more often developed rashes and acute febrile reactions [4].

The cutaneous side effects of this chelating agent comprise three distinct types: (i) acute hypersensitivity reactions occurring early during treatment, (ii) late reactions including disturbances of autoimmune mechanisms leading to pemphigus foliaceus or erythematosus and cicatricial pemphigoid, and (iii) lathyrogenic effects on connective tissue [2,5–9]. Hypersensitivity reactions are common and consist of urticarial or morbilliform rashes appearing within the first few weeks; the eruption clears on drug withdrawal and does not always recur on re-exposure. It is possible to desensitize patients to penicillamine [10].

Autoimmune syndromes caused by penicillamine are well documented. The development of pemphigus during the treatment of both Wilson's disease and rheumatoid arthritis with penicillamine was first noted in the French literature [11,12]. Since then, there have been numerous case reports [13–25]; about 7% of patients receiving penicillamine for more than 6 months develop drug-induced pemphigus [13]. The reader is referred to the section on drug-induced pemphigus (p. 73.40). Findings with direct immunofluorescence mimic the idiopathic disorder, with epidermal intercellular deposition of immunoreactants [16]. Most patients develop pemphigus foliaceus, although there have been isolated reports of pemphigus vulgaris [14] and of pemphigus erythematosus with both epidermal intercellular and subepidermal deposition of IgG [15,17]. In some patients, clinical appearances may resemble dermatitis herpetiformis [21,22]. Oral lesions may be indistinguishable from those seen in idiopathic pemphigus, with cheilosis, glossitis and stomatitis [23]. Painful erosive vulvovaginitis may lead to scarring. Penicillamine-induced pemphigus usually subsides rapidly after cessation of the drug; occasionally it may be more persistent [13] and fatalities have occurred [24,25]. A curious bullous dermatosis without the features of pemphigus has been described recently [26]. Other autoimmune manifestations include a bullous pemphigoid-like reaction [27], cicatricial pemphigoid [28,29], both discoid and systemic LE [30–33], dermatomyositis [34–37], and both morphoea and systemic sclerosis [38,39]. Pre-existing lichen planus [40] may be exacerbated, and lichenoid eruptions develop *de novo* [41,42]. Alopecia, facial dryness and scaling, nail changes and hypertrichosis are recorded. The yellow nail syndrome has been reported frequently in association with penicillamine [43].

Prolonged high-dose therapy for more than a year, as for Wilson's disease, has effects on collagen and elastin [44,45], resulting from inhibition of the condensation of soluble tropocollagen to insoluble collagen. There is anisodiametricity of connective tissue fibres, resulting in the 'lumpy-bumpy' elastic fibre [46–48]. The skin becomes wrinkled and thin, aged looking and abnormally fragile; asymptomatic, violaceous, friable, haemorrhagic macules, papules and plaques develop on pressure sites, and minor trauma causes ecchymoses [49]. There may be light-blue anetoderma-like lesions [50], and small white papules at

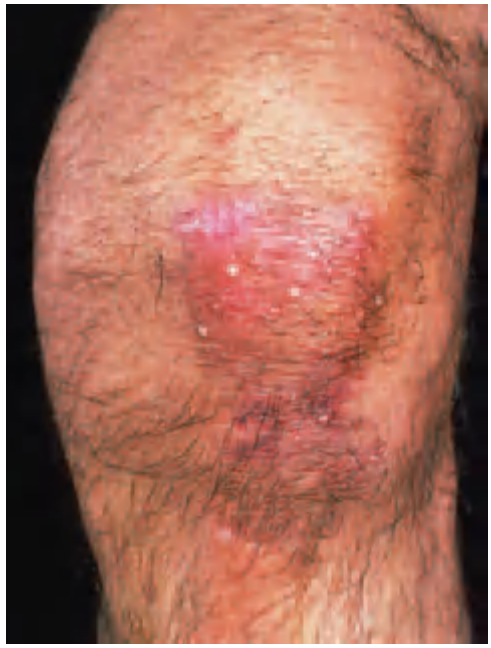

Fig. 73.6 Penicillamine dermopathy with milia. (Courtesy of St John's Institute of Dermatology, London, UK.)

venepuncture sites. Lymphangiectasis may develop [49]. Blisters may occur, with a picture resembling epidermolysis bullosa with scarring and milia formation (Fig. 73.6) [51]. Cutis laxa and elastosis perforans serpiginosa [52–58], which may be verruciform [52,53], are described. Lesions resembling pseudoxanthoma elasticum have been documented rarely [59–62].

Penicillamine may induce impaired taste sensation in up to 25% of patients, but other gastrointestinal effects are usually minor. Important non-dermatological complications [2,8] include marrow suppression; various renal problems, such as reversible proteinuria, in up to 30% of patients on therapy for more than 6 months; established nephrotic syndrome; and Goodpasture's syndrome. Thrombocytopenia occurs in up to 3% of patients, and may be either of gradual or precipitous onset. Immunological abnormalities include acquired IgA deficiency [63] and development of myasthenia gravis [64]. The bones may be involved in the connective tissue disorder. A chronic bronchoalveolitis is recognized [65]. Breast enlargement and breast gigantism [66] are documented.

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Tiopronin (N-(2-mercaptopropionyl) glycine)

This drug, used in Japan for the treatment of liver disease, mercury intoxication, cataracts and allergic dermatoses, dissociates disulphide bonds, like penicillamine. Morbilliform, urticarial and lichenoid eruptions, bullous in one case, have occurred [1].

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Anticoagulants, fibrinolytic agents and antiplatelet drugs

Oral anticoagulants

Adverse reactions to oral anticoagulant drugs have been reviewed [1–3].

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Coumarins

There may be cross-sensitivity across the group comprising acenocoumarol (nicoumalone), phenprocoumon and warfarin [1].

Phenprocoumon. A patient on long-term anticoagulation developed repeated episodes of skin and subcutaneous fat necrosis related to episodes of excessive anticoagulation with acquired functional deficiency of protein C, thought to be due to hepatic dysfunction resulting from congestive cardiac failure [2].

Warfarin. Haemorrhage is the commonest adverse reaction. Maculopapular rashes occur [1], and may be seen after a single dose of warfarin [3]. Rarely, an oral loading dose may lead to one or more areas of painful erythema and ecchymosis, which rapidly progress to central blistering and massive cutaneous and subcutaneous necrosis

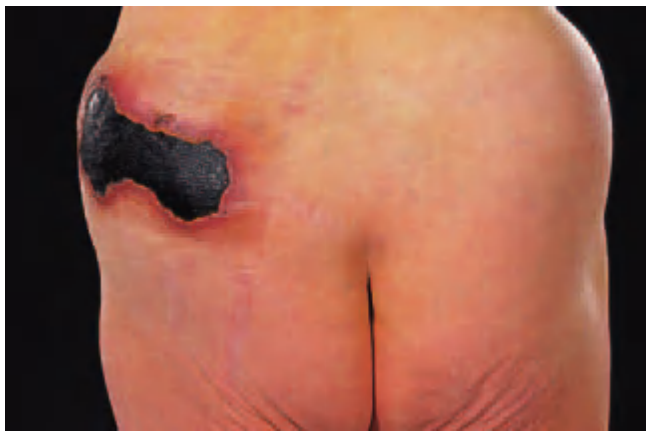

Fig. 73.7 Warfarin necrosis. (Courtesy of A. Ive, Durham, UK.)

(Fig. 73.7) [4–12]; if extensive, the condition may be fatal [3]. The lesions usually start after 2–14 days of treatment (usually 3–5 days), tend to be symmetrical, and occur over fatty areas, for example the breasts, buttocks, thighs, calves and abdomen. Most patients have been women, but lesions of the penis may occur [6]. Warfarin necrosis has been associated with the heterozygous state for deficiency of protein C, a vitamin K-dependent serine protease [8–10]. Activated protein C is a potent anticoagulant that selectively inactivates co-factors Va and VIIIa and inhibits platelet coagulant activity by inactivation of platelet factor Va. Continued coumarin therapy does not aggravate the condition, but resumption of therapy with loading doses may lead to new lesions [7]. The condition is preventable by vitamin K_1 injections. Other side effects are rare, and include urticaria [13], dermatitis, gastrointestinal upset, purple erythema of the dependent parts (purple toe syndrome) [14–16], acral purpura [17] and alopecia [18].

Oral anticoagulants and quinidine act synergistically to depress vitamin K-sensitive hepatic clotting synthesis [19]. Their combined use can precipitate serious hypoprothrombinaemic haemorrhage. Azapropazone displaces warfarin from protein-binding sites and also alters renal clearance of *R* and *S* isomers of warfarin; this may lead to effective warfarin overdosage [20]. Itraconazole may potentiate the action of warfarin [21].

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Indandiones

Hypersensitivity reactions occur in up to 0.3% of patients within 3 months of onset of treatment with phenindione. Scarlatiniform, eczematous, erythema multiforme-like or generalized exfoliative eruptions are seen [1,2]. Alopecia and stomatitis may accompany the rash. Brownish-yellow or orange discoloration of the palmar or finger skin on handling the tablets develops after contact with soap alkali [3]. Cutaneous necrosis occurs rarely.

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Heparin: parenteral anticoagulant

The most frequent side effect is haemorrhage [1,2]. Other common side effects include osteoporosis and (temporary) telogen effluvium 6–16 weeks after administration. Hypoaldosteronism may occur. Hypersensitivity reactions including urticaria and anaphylactic shock are well documented but very uncommon [3]. Rapid desensitization was achieved in a patient with heparin urticarial hypersensitivity who required cardiac surgery [4]. Hypereosinophilia is recorded [5]. Vasospastic reactions, including pain, cyanosis and severe itching or burning plantar sensations, are described.

Erythematous infiltrated plaques developing 3–21 days after commencement of heparin therapy [6–14] may

closely mimic contact dermatitis both clinically and histologically, and patch tests may be positive [8,9]. Delayed-type hypersensitivity reactions in patients receiving heparin may occur with both unfractionated and low-molecular-weight heparins. Delayed-type hypersensitivity to heparins is characterized by considerable cross-reactivity between low-molecular-weight heparins, unfractionated heparins and danaparoid [13]. Unfractionated heparins may be tolerated even if low-molecular-weight heparins are not. Subcutaneous provocation testing with a panel of heparins, danaparoid and desirudin (hirudin) is recommended for determining acceptable treatment options for patients allergic to specific heparins. Low-molecular-weight heparin analogues may be satisfactorily substituted in some patients with this reaction [6,15], but are not always tolerated [7,16,17]; a panel of different low-molecular-weight heparin preparations should be checked by subcutaneous provocation tests before reinstitution of heparin therapy. Chlorocresol may be responsible for some reactions attributed to heparin [7,18], including anaphylactoid reactions.

Skin necrosis occurring 6–8 days after onset of subcutaneous heparin is rare, but may occur at injection sites and occasionally at distal sites elsewhere [19–27]. Diabetic women on high-dose antibiotics are predisposed to this complication. A scleroderma-like evolution has been recorded [22]. Clinically, the skin necrosis resembles that of coumarin necrosis [25]. It may occur with use of low-molecular-weight heparin [23,26].

Heparin may cause an allergic thrombocytopenia [28–35]. Thrombocytopenia is usually asymptomatic, but may be associated with arterial or venous thrombosis in about 0.4% of cases [29,33,34]; thromboembolism may occasionally be lethal [30]. Thrombocytopenia usually begins 3–15 days after initiation of therapy, but may occur within hours in previously exposed patients, and is thought to be caused by an IgG–heparin immune complex involving both the Fab and Fc portions of the IgG molecule [29]. Heparin-induced antiendothelial cell antibodies, which recognize heparin-like glycans on the cell surface of platelets and endothelial cells, may lead to platelet aggregation and endothelial cell expression of procoagulant tissue factor, with resultant thrombocytopenia and thrombosis [21]. Thrombocytopenia may occur with both unfractionated and low-molecular-weight heparins [20]. Clinical cross-reactivity between heparin and the polysulphated chondroitin-like substance Arteparon, used in the treatment of degenerative joint disease, has been described [32].

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Protamine: heparin antagonist

This low-molecular-weight protein, derived from salmon sperm and/or testes, is used for neutralization of heparin anticoagulation after cardiac surgery. Adverse reactions have been reviewed [1]. Idiosyncratic responses or those related to complement generation of anaphylatoxins are recorded [2]. IgE-dependent anaphylaxis [3], as well as delayed reactions causing skin nodules [4–6], which may be granulomatous [6], may occur in diabetics treated with protamine-containing insulin.

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Fibrinolytic drugs

Haemorrhage is the most common untoward effect from use of thrombolysins [1]. Allergic complications are rare, particularly with alteplase or urokinase. These agents should be used electively in all patients previously exposed to streptokinase or anistreplase [2].

Alteplase (tissue-type plasminogen activator)

Painful purpura occurring within hours of administration has been recorded [3].

Aminocaproic acid

A maculopapular eruption occurring 12–72 h after administration of ε-aminocaproic acid, with positive patch tests to the drug, has been described [4]. A transient, non-inflammatory, subepidermal, bullous eruption on the legs, with fibrin thrombi in papillary dermal vessels, has also been recorded [5].

Anistreplase (anisoylated plasminogen streptokinase activator complex)

Anistreplase given for acute myocardial infarction was associated with leukocytoclastic vasculitis [6]. Maculopapular rashes and urticaria are described; patients with maculopapular rashes had significantly higher rises in serum IgM, IgG, IgA and IgE antistreptokinase level [7].

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Streptokinase

Allergic reactions have been reported in up to 6% of patients [1–3], ranging from minor rashes to angio-oedema or anaphylaxis (which may be fatal [4–6]), bleeding, strokes and a syndrome resembling adult respiratory distress syndrome [3]. Patients who develop reactions to streptokinase cannot be predicted on the basis of antistreptokinase IgG antibody titres at presentation; minor reactions to streptokinase would not appear to be antibody mediated [7]. However, streptokinase-related thrombolytic agents should be avoided in reinfarction thrombolysis therapy in patients with raised antistreptokinase antibody titres, as hypersensitivity reactions including serum sickness may occur [8–10]. This drug has been reported in association with a hypersensitivity vasculitis [11,12], serum sickness with leukocytoclastic vasculitis [13,14] and a lymphocytic angiitis [15]. Skin necrosis is recorded [16].

Urokinase

Haemorrhagic bullae occurred as a complication of urokinase therapy for haemodialysis catheter thrombosis [17].

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Antiplatelet drugs

Clopidogrel

This drug, a novel thienopyridine derivative chemically related to ticlopidine and used in patients at risk of thromboembolic disorders, has caused a photosensitive lichenoid eruption [1].

Ticlopidine

This antiplatelet drug, indicated for coronary artery disease, cerebrovascular disease, peripheral vascular disease and diabetic retinopathy, is also a thienopyridine derivative [2,3]. Gastrointestinal symptoms, thrombocytopenia with minor bleeding including bruising, neutropenia, rashes in 10–15% of patients, and hepatic dysfunction in 4% of cases have been reported. Thrombotic thrombocytopenic purpura has also been documented [4]. Cutaneous reactions, including urticaria, pruritus, maculopapular and fixed drug eruptions, erythromelalgia and erythema multiforme, are recorded in up to 11.8% of patients [5]. Acute generalized exanthematous pustulosis has been documented [6].

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Vitamins including retinoids

Vitamin A

Generalized peeling may be a delayed manifestation of acute intoxication [1]. Chronic intoxication produces the following epithelial problems: pruritus, erythema, hyperkeratosis, dryness of mouth, nose and eyes, epistaxis, fissuring, dryness and scaling of the lips, peeling of the palms and soles, and alopecia. A yellow-orange skin discoloration, photosensitivity and nail changes have also been observed [2–5]. Headache, pseudotumour cerebri, anaemia, hepatomegaly and skeletal pain may be present. Cortical hyperostoses and periosteal reaction of tubular bone [6], and more rarely premature epiphyseal closure and change in the contour of long bones [7], are seen.

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Retinoids

The cutaneous and systemic side effects of these synthetic vitamin A-related compounds resemble those of hypervitaminosis A, and have been extensively reviewed [1–12].

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Acitretin

The side effects of this principal metabolite of etretinate are similar to those of the parent compound [1–6], comprising cheilitis, alopecia, conjunctivitis, peeling of the palms and soles, xerosis, myalgia and pancreatitis; elevated levels of serum triglyceride, cholesterol and liver transaminase are seen. There has been no biopsy-proven hepatotoxicity [7]. Alopecia is particularly frequent [4], and scaling of the palms and soles appears more prominent than with etretinate [5]. There is a higher occurrence of vulvovaginal candidiasis during acitretin exposure [8]. Multiple milia have occurred [9]. Skeletal effects may be significant, but are not an absolute contraindication to therapy [10]. Acitretin does not seem to cause osteoporosis [11].

Persistent levels of etretinate have been detected in plasma following a change to acitretin therapy. Detectable plasma etretinate was present in 45% of current acitretin users and 18% of those who had stoppped acitretin, whereas detectable subcutaneous tissue etretinate was present in 83% of current acitretin users and 86% of those who had discontinued the drug [12]. Inability to detect plasma etretinate is therefore a poor predictor of the absence of etretinate in fat. Acitretin and/or etretinate were detectable in fat and in some cases plasma from women who had ceased acitretin therapy for up to 29 months [12]. It has been proposed that subcutaneous tissue levels of acitretin and etretinate should be monitored when plasma measurements are negative, and that the recommended contraception period of 2 years after cessation of acitretin therapy should be reconsidered to avoid the risk of teratogenicity [13]. It has been suggested that acitretin is only converted to etretinate following alcohol intake [14].

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Etretinate

This drug has been largely superseded by acitretin. The dermatological side effects are dose dependent, and resemble those associated with isotretinoin therapy [1–3]. With dosage over 0.5 mg/kg, cheilitis with dryness, scaling and fissuring of the lips is almost universal. There may be pruritus, a dry mouth, dry nose, epistaxis, meatitis, desquamation including the face, hands and feet, and reduced tolerance of sunlight [4] and therapeutic products such as tar or dithranol. Pseudoporphyria has been reported in a renal transplant recipient treated with etretinate to suppress cutaneous neoplasia [5]. A 'retinoid dermatitis' resembling asteatotic eczema may develop in up to 50% of patients [6]. Increased stickiness of the palms and soles, possibly due to increased quantities of carcinoembryonic antigen and other glycoproteins in eccrine sweat [7,8], has been reported. Mucosal erosions, conjunctivitis, paronychia, alopecia [9] and curling, kinking or darkening of hair [10] are all well documented. Intertriginous erosions have also been described [11]. Oedema [12], excess granulation tissue [13] and multiple pyogenic granulomas [14] develop rarely. Erythroderma has been reported [15].

Prolonged therapy may lead to skin fragility [16,17]; blistering, erosions and scarring have been reported in one patient [18]. Softening of the nails is seen [19], and chronic paronychia, onycholysis, onychomadesis, nail shedding, onychoschizia and fragility may occur [20,21]. Parakeratotic digitate keratoses appearing after treatment of disseminated superficial actinic porokeratosis may arise as a result of etretinate-resistant regions in the ring of the cornoid lamella [22]. There has been a single case of generalization of palmoplantar pustulosis following cessation of etretinate therapy [23].

Systemic side effects of etretinate include benign intracranial hypertension [24]. Minor disturbances in tests of liver function are not uncommon, and may not always be reversible; liver changes range from non-specific reactive hepatitis to acute hepatitis, chronic active hepatitis and severe fibrosis or cirrhosis [25–28]. Fatal liver necrosis occurred in a patient with ichthyosiform erythroderma [29], but other factors may have been relevant. However, several studies involving liver biopsies have indicated good tolerance of etretinate without significant hepatotoxic side effects [30–32]; in one study, patients were followed for 3 years [32]. Etretinate, like isotretinoin, can cause increase in triglycerides and cholesterol [33–36] but to a lesser extent [36]. There have been isolated reports of possible etretinate-related thrombocytopenia [37]. Retinal toxicity has been postulated [38], although a recent report has not confirmed this [39]. Erectile dysfunction has been documented occasionally [40].

Skeletal abnormalities, such as periosteal thickening, vertebral hyperostosis, disc degeneration, osteoporosis and calcification of spinal ligaments, occur in a significant number of adults receiving long-term therapy for disorders of keratinization, but the severity of the changes is minor [41,42]. Radiological evidence of thinning of long bones may be seen in children [43], and premature epiphyseal closure has been recorded [44].

Etretinate, like isotretinoin, is grossly teratogenic, and because of its deposition in body fat stores is excreted only very slowly, especially in the obese [45]. Detectable serum levels have been found in some patients more than 2 years after discontinuation of therapy. It is therefore recommended that female patients of child-bearing years should be advised to prevent pregnancy not only during the course of treatment but also for at least 2 years after stopping therapy; if pregnancy is contemplated after this period of time, an estimation of circulating levels of retinoid metabolites should be obtained.

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Isotretinoin (13-cis-retinoic acid)

Dermatological complications have been reviewed [1,2]; erythema and scaling of the face, generalized xerosis, skin fragility, pruritus, epistaxis, dry nose and dry mouth may be seen in up to 80% of cystic acne patients. A dose-related cheilitis occurs in over 90% and conjunctivitis in about 40% of patients. Transient exacerbation of acne may occur, especially in the early stages of therapy. Exuberant granulation tissue, or pyogenic granulomas at the site of healing acne lesions, has been reported frequently [3–7].

Rashes, including erythema, and thinning of the hair (in rare cases persistent) occur in fewer than 10% of patients. Both isotretinoin and etretinate may cause curliness or kinking of hair [8]. Nasolabial follicular sebaceous casts have been reported [9]. The following have occurred in approximately 5% of cases: peeling of the palms and soles, skin infections and possible increased susceptibility to sunburn. Phototesting confirmed photosensitivity in some patients in one study [10] but not another [11]. A photoaggravated allergic reaction has been documented in which the patient had positive patch tests to isotretinoin [12]. Reversible melasma is recorded [13], as is facial cellulitis [14]. Scarring, which may be keloidal, may occur after dermabrasion or laser therapy within a year of isotretinoin therapy; such procedures are best postponed during this period [15–17].

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Systemic side effects. These include headache, which is not uncommon; anorexia, nausea and vomiting are much more common than with etretinate, as are lethargy, irritability and fatigue [1]. Isotretinoin therapy has been associated with benign intracranial hypertension [2]; in some cases, there was concomitant use of tetracyclines, so this combination should be avoided. A variety of central nervous system reactions have been reported, but may bear no relationship to therapy. The issue of whether isotretinoin may be associated with initiation or exacerbation of depression is a particular matter of controversy [3,4]. Anecdotal reports suggested this possibility; resolution usually, but not always [5], occurs within a few weeks of cessation of therapy. Psychiatric symptoms occurred in seven of 700 patients in one study, with recurrence of depression following rechallenge in some cases [6]. Of 5 million individuals exposed to isotretinoin in the USA between 1982 and 2000, 37 patients committed suicide, 100 were hospitalized for treatment of depression and 284 were managed as outpatients [7]. This incidence of suicide is less than that predicted for a group of comparable age and sex distribution. A large study comparing 7195 patients treated with isotretinoin with 13 700 patients treated with antibiotics, drawn from Canadian and UK databases, concluded that there was no increase in depression or suicide in the isotretinoin-treated group [8]. However, the study has been criticized as flawed with regard to the UK data, because it was provided by general practitioners who were not responsible for prescribing the drug, and there may have been selection bias in the

ascertainment of mental disorders. A recent study of 2821 patients found no evidence to support an association between use of isotretinoin and onset of depression [9]. The field is complicated by the fact that there may be a confounding effect of acne on the development of psychological or psychiatric effects [10,11]. In addition, there is an increased frequency of pretreatment anxiety in patients and their families [7]. Conversely, isotretinoin therapy may lead to an improvement in mental state [10,11].

Patients treated for disorders of keratinization have developed corneal opacities, which improved when the drug was withdrawn [12]. Blepharoconjunctivitis, dry eyes with decreased tolerance of contact lenses and blurred vision due to myopia may occur [13]. Decreased night vision has been documented rarely, as have cataracts and other visual disturbances [13–17]; decreased night vision after isotretinoin therapy may be more permanent than generally suspected [17], and many asymptomatic patients have abnormal electroretinograms [14]. Loss of sense of taste is recorded [18].

Transient chest pain is uncommon. Non-specific urogenital findings and non-specific gastrointestinal symptoms have occurred in approximately 5% of cases. Isotretinoin therapy has been associated with onset of inflammatory bowel disease [19] and with impairment of pulmonary function in patients with systemic sclerosis [20,21].

Approximately 16% of patients develop musculoskeletal symptoms, including arthralgia, of mild to moderate degree; cases of acute knee aseptic arthritis have been documented [22]. High-dose prolonged therapy in a child for epidermolytic hyperkeratosis was associated with premature closure of epiphyses [23]. A high prevalence of skeletal hyperostosis has been noted in patients on prolonged (1 year or more), relatively high-dose (2 mg/kg daily) isotretinoin therapy for disorders of keratinization [24–28]. The syndrome of *d*iffuse *i*diopathic *s*keletal *h*yperostosis (DISH) includes ossification of ligaments and accretion of bone onto vertebral bodies, especially of the cervical spine. Mild osteoporosis has also been seen. X-ray changes have been minimal in prospective studies of patients with cystic acne treated with a single course of isotretinoin at recommended doses [29–31]. Nasal bone osteophytosis has been described with short-term therapy for acne [32].

Mild to moderate elevation of liver enzymes occurs in about 15% of cases; in some patients these return to normal despite continued administration of the drug. A single case of fatty liver developing in a patient (with low to normal levels of α_1-antitrypsin) on low-dose isotretinoin has been reported [33]. Elevated sedimentation rates occur in about 40% of patients. Between 10 and 20% of patients show decreased red blood cell parameters and white blood cell counts, elevated platelet counts and pyuria. Thrombocytopenia may occur [34].

Isotretinoin induces reversible changes in serum lipids in a significant number of treated subjects [35–40]. A dose-related increase in triglycerides occurs in about 25% of individuals according to the Roche data sheet; five of 135 cystic acne patients, and 32 of 298 patients treated for all diagnoses, showed triglyceride levels above 500 mg/dL. In another study, 17% of patients taking isotretinoin for 20 weeks exhibited hypertriglyceridaemia, but in 15% this was of only mild to moderate degree [38]. About 15% showed a mild to moderate decrease in serum high-density lipoprotein levels, and 7% experienced minimal elevations of serum cholesterol during therapy; some patients had increases in LDL cholesterol [38]. Lipid abnormalities peaked within 4 weeks in men, but not until 12 weeks in women. If sustained over a long period, these alterations in lipoproteins might be risk factors for coronary artery disease. Patients with an increased tendency to develop hypertriglyceridaemia include those with diabetes mellitus, obesity, increased alcohol intake or a familial history. Some patients have been able to reverse triglyceride elevation by reduction in weight, restriction of dietary fat and alcohol, and reduction in dose while continuing the drug. An obese male patient with Darier's disease developed elevated triglycerides and subsequent eruptive xanthomas [41].

Major human fetal abnormalities related to isotretinoin therapy during pregnancy have been documented [42–45]. The most frequently reported abnormalities involve the central nervous system (microcephaly or hydrocephalus and cerebellar malformation) and cardiovascular system (anomalies of the great vessels). Microtia or absence of external ears, microphthalmia, facial dysmorphia and thymus gland abnormalities have also been reported. There is an increased risk of spontaneous abortion. Women of child-bearing potential should sign a consent form and be instructed that they should not be pregnant when isotretinoin therapy is started (preferably on the second or third day of the next normal menstrual period) and should use effective contraception during, and for 1 month after stopping, therapy. Isotretinoin has a much shorter half-life than etretinate, so that pregnancy is permissible 1 month after stopping therapy. Analysis of data voluntarily reported to Hoffmann La Roche Inc. in the USA enabled prospective study of 88 patients who had completed or discontinued isotretinoin therapy prior to becoming pregnant; 90% of all pregnancies occurred within 2 months after cessation of therapy, and 64% within 1 month [46]. There were no significant increases in the rates of spontaneous abortion or of congenital malformations among the live births. There appears to be no adverse effect of isotretinoin on male reproductive function [47,48].

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Tazarotene

Pyogenic granuloma-like lesions have been associated with the use of this topical retinoid in the treatment of psoriasis [1,2].

Tretinoin

Oral tretinoin administered as differentiation therapy of acute promyelocytic leukaemia was associated with mild rashes, the nature of which was unspecified [3]. An acute neutrophilic dermatosis with a myeloblastic infiltrate occurred in a leukaemic patient receiving all-*trans*-retinoic acid therapy [4].

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Vitamin B

Vitamin B_1

Anaphylaxis following intravenous administration has occurred [1].

Vitamin B_6 (pyridoxine)

Vasculitis is recorded [2], as is a pseudoporphyria syndrome with megadosage [3]. A photosensitive eruption [4] and rosacea fulminans are documented [5].

Nicotinic acid

Flushing is common; other transient rashes, urticaria, pruritus, scaling, hyperpigmentation and an acanthosis nigricans-like eruption [6,7] are all documented. Persistent rashes and hair loss have rarely occurred.

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Vitamin C (ascorbic acid)

Patients with cutaneous and respiratory allergy have been described.

Vitamin E (α-tocopherol)

White hair developed at injection sites in infants given intramuscular vitamin E for epidermolysis bullosa, probably due to quinones formed during vitamin E degradation [1].

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Vitamin K

Skin reactions with vitamin K have been reviewed [1–11]. Three distinct types of cutaneous reaction are seen: (i) localized eczematous at the injection site (onset 4–16 days, dose range 10–410 mg); (ii) localized morphoea-form (average onset 8.5 months, range 5 weeks to 1.5 years, dose range 30–2080 mg); and (iii) very rarely, a diffuse maculopapular eruption [10,11]. The pruritic, erythematous, macular lesions or plaques may last for up to 6 months, whereas the prognosis for resolution of the morphoea-form changes is very poor. Patch and intradermal skin tests may be positive, suggesting an immunological basis. Most, but not all [3,6,8], cases have occurred in patients with liver disease. In addition, a proportion of these reactions progress to produce scleroderma-like changes [9,12–16]. An annular erythema has been documented [17].

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Hormones and related compounds

ACTH and systemic corticosteroids

The side effects of these agents have been reviewed [1–13].

Well-known side effects include acne, cutaneous thinning and atrophy, telangiectasia, striae distensae, purpura and ecchymoses, hypertrichosis, impaired wound healing, pigmentary changes, cushingoid (moon) facies, truncal adiposity [14] and buffalo hump of the upper back. Acne occurred in one of 51 patients treated with intravenous corticosteroids in one study [15]. Other systemic side effects include fluid and electrolyte abnormalities, weight gain, oedema, hypertension, cardiac failure, peptic ulcer disease, pancreatitis, diabetes, muscular weakness, myopathy, tendon rupture, glaucoma, posterior subcapsular cataracts, mental changes including psychosis, osteoporosis, vertebral collapse, necrosis of the femoral head, growth suppression in children, opportunistic infection, masking of infection or reactivation of a dormant infection (e.g. tuberculosis), polycythaemia and suppression of the hypothalamic–pituitary axis. Pulse steroid therapy with systemic methylprednisolone has resulted in sudden death due to anaphylaxis, arrhythmia or ischaemic heart disease, but not particularly in dermatological patients [16].

Adrenocorticotrophic hormone

Allergic reactions to ACTH are recorded but are uncommon. Urticaria and dizziness, nausea and weakness are the most frequent, but severe anaphylactic shock has occurred. Synthetic ACTH is usually tolerated by patients sensitive to animal ACTH [17]. Depot preparations containing tetracosactide (tetracosactrin) adsorbed on a zinc phosphate complex have produced reactions [18] and may induce melanoderma [19].

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Systemic corticosteroids

In addition to those listed above, the cutaneous side effects of systemic corticosteroids include allergic and immediate reactions [1,2]. In one study, seven of 25 patients with cutaneous delayed-type hypersensitivity to hydrocortisone had an immediate reaction following intradermal injection of hydrocortisone sodium succinate, and had significantly increased levels of IgG antibodies to hydrocortisone. These patients are at risk of developing type III and possibly type I reactions following systemic hydrocortisone [3].

Protein binding of hydrocortisone or a degradation product may be important in the development of corticosteroid allergy [4]. Urticarial reactions have followed the intra-arterial injection of prednisone, prednisolone, hydrocortisone [5] or methylprednisolone [6], but are rare. Anaphylaxis occurred after intradermal injection of triamcinolone for alopecia areata [7]. Anaphylactoid reactions have been reported to topical and parenteral hydrocortisone, but may represent pseudoallergic reactions rather than IgE-mediated immediate hypersensitivity [8,9].

Generalized skin reactions, including urticaria and maculopapular eruptions, developed in patients after therapy with oral triamcinolone acetonide [10], prednisone [11], or dexamethasone and betamethasone [12]; the patients were subsequently shown to be patch-test positive to these corticosteroids. In another study, five patients reacted with diffuse erythema principally on the trunk or on the face, appearing within a few hours to 24 h and fading in 1–3 days, on treatment with systemic or intralesional hydrocortisone, methylprednisolone, prednisolone or betamethasone [2]. On patch testing, one patient reacted to prednisolone and methylprednisolone and two patients were positive to pivalone. Patients sensitive to hydrocortisone or methylprednisolone reacted to these corticosteroids in intradermal tests. A combination of intradermal and patch tests is recommended when allergy to systemic or intralesional corticosteroids is suspected [2].

Other cases of generalized delayed systemic corticosteroid reactions, including eczematous or exanthematous eruptions and erythroderma, with or without bullae or

purpura, often with positive patch or intradermal testing, have been recorded [13–18]. Systemic administration of hydrocortisone, and provocation of endogenous cortisol secretion by injection of the ACTH analogue tetracosactide, provoked dose-dependent allergic skin reactions at sites of previous allergic reactions to topical steroids in two patients with proven topical corticosteroid sensitivity (i.e. systemic allergic contact-type dermatitis); in one case, this was at a positive patch-test site to hydrocortisone 17-butyrate [19]. Thus, it has been postulated that high stress levels, which cause increased secretion of endogenous adrenocortical hormones, could be implicated in exacerbations of eczema in corticosteroid-sensitive patients, and a persistent autoimmune skin reaction to cortisol might occur following topical sensitization to topical hydrocortisone [19]. The fact that, in steroid-sensitive patients, systemic provocation testing with hydrocortisone results in a reaction confined to the skin may be partly explained by the observation *in vitro* that only enriched Langerhans' cells, and not peripheral blood mononuclear antigen-presenting cells, are capable of presenting corticosteroid to T cells of corticosteroid-sensitive subjects [20].

Perioral dermatitis has been recorded in renal transplant recipients on corticosteroids and immunosuppressive therapy [21]. Panniculitis following short-term high-dose steroid therapy in children manifests as subcutaneous nodules on the cheeks, arms and trunk [22]. Reversible panniculitis occurred in a child treated with steroids for hepatic encephalopathy [23]. Juxta-articular adiposis dolorosa developed in a patient treated with high doses of prednisone for the L-tryptophan-induced eosinophilia myalgia syndrome [24]. Acanthosis nigricans may occur with corticosteroid therapy [25]. Immunosuppression with corticosteroids has been associated with the development of Kaposi's sarcoma during the treatment of temporal arteritis [26].

Inhaled corticosteroids have been associated with purpura and dermal thinning [27] as well as acne [28,29], perioral dermatitis and tongue hypertrophy [30], allergic reactions [31], an eczematous dermatitis [32] and adrenal suppression [29]. Nasal corticosteroids may cause nasal congestion, pruritus, burning and perforation of the septum, urticaria and eczema of the face [33]. Intralesional corticosteroid injection may also lead to allergic reactions [34], including a disseminated morbilliform and persistent urticarial dermatitis following intra-articular triamcinolone acetonide [35], erythroderma following intradermal budesonide [36] and erythema multiforme after intradural injection of prednisolone acetate [37]. Facial flushing and/or generalized erythema has followed epidural steroid injection [38]. Anaphylactic shock has been recorded after intra-articular injections of corticosteroids containing carboxymethylcellulose, benzylic acid, polysorbate 80 and merthiolate; skin tests to carboxymethylcellulose were positive [39].

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Topical corticosteroids

The dermatological complications of topical corticosteroids have been reviewed [1–4]. Concerns have been expressed about the illegal availability of potent topical steroids in the UK, and their consequent unregulated use [5]. Many of the adverse reactions are related to the potency of the preparation; thus, in general, fluorinated steroids are associated with more significant side effects. Topical steroids cause decreased epidermal kinetic activity [6], decreased synthesis of dermal collagen types I and III and ground substance, and thinning of the dermis and epidermis [7–11]. Initial vasoconstriction of the superficial small vessels is followed by rebound vasodilatation, which becomes permanent in later stages. There are resultant striae, easy bruising, purpura, hypertrichosis and telangiectasia; stellate pseudoscars or ulcerated areas may be seen. Reversible hypopigmentation may develop. Local injection of a potent steroid may result in atrophy with telangiectasia, and localized lipoatrophy may occur. Perilymphatic atrophy is recorded following intradermal steroid injection. Long-term daily use of a potent steroid, especially under plastic occlusion as for fingertip eczema, may result in acroatrophy of terminal phalanges of the fingers [12,13].

Topical steroids may exacerbate acne, or lead to acne rosacea, with papules, pustules and telangiectasia, or perioral dermatitis, characterized by erythema, papules and pustules at the perioral area [14–16]. They decrease the number and antigen-presenting capacity of epidermal Langerhans' cells [17], and mask or potentiate skin infections, including fungal (tinea incognito) and bacterial infections and verruca vulgaris. Their withdrawal may provoke conversion of plaque- to pustular-type psoriasis [18]. Topical steroid therapy around the eye has been associated with development of glaucoma.

Topical corticosteroids may induce allergic contact dermatitis [19–25]. The prevalence of positive patch tests to corticosteroids in contact dermatitis clinics ranges from 2 to 5% [19,20]. The allergen may be the steroid itself, or a preservative or stabilizer such as ethylenediamine. There may be cross-reactivity between different steroids [21–23]. Cross-reactivity is more likely between steroids with similar substitutions at C-6 and C-9 positions. Intradermal tests may be a more sensitive means of detecting corticosteroid hypersensitivity than patch testing [24].

Systemic side effects of topical corticosteroids occur particularly from the use of large amounts of high-potency topical corticosteroids, especially under plastic occlusion [26,27]. Oedema due to sodium retention occurs more frequently with halogenated corticosteroids [27]. Hypothalamic–pituitary axis suppression may occur [28,29]; a single application of 25 g of 0.05% clobetasol propionate ointment suppressed plasma cortisol for 96 h [30]. Cushing's syndrome [31,32] may result, and growth retardation in children is a hazard [33]. Glycosuria and hyperglycaemia may rarely occur [34].

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Sex hormones

Gonadotrophins

These drugs may cause allergic reactions [1]. Menotrophin (Pergonal) has been associated with localized keratosis follicularis (Darier's disease) [2]. Intracutaneous administration of two human menopausal gonadotrophin preparations (Organon and Pergonal) caused local induration and erythema [3].

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Gonadorelin analogues

Buserelin. A pigmented roseola-like eruption has been documented [1].

Leuprorelin. This drug, given for precocious puberty, has caused anaphylaxis [2], rashes [3] and local reactions [4].

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Oestrogens and related compounds

Oestrogens. Spider naevi and melanocytic naevi may develop under oestrogen therapy, as may chloasma. Severe premenstrual exacerbation of papulovesicular eruptions, urticaria, eczema or generalized pruritus occurred in seven women; several had a positive delayed tuberculin-type skin test to oestrogen [1]. Patients with generalized chronic urticaria had an urticarial reaction to intradermal oestrogens. Elimination of oral oestrogen therapy or anti-oestrogen therapy with tamoxifen proved effective. In another patient, a premenstrual urticarial reaction was exacerbated by oestrogen; oophorectomy cured the eruption [2]. A bullous autoimmune oestrogen dermatitis has been delineated [3].

Diethylstilbestrol therapy of pregnant women has been associated with female and male genital tract abnormalities in the offspring. Diethylstilbestrol is a transplacental carcinogen and has caused adenocarcinoma of the vagina 20 years later in young women whose mothers took the drug in the first 18 weeks of pregnancy [4–6]. Acanthosis nigricans has resulted from use of diethylstilbestrol [7]. Hyperkeratosis of the nipples developed in a man treated for adenocarcinoma of the prostate with diethylstilbestrol [8]. Porphyria cutanea tarda may also be precipitated [9,10].

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Oral contraceptives. Cutaneous complications of oral contraceptives have been reviewed [1–4]. These drugs combine an oestrogen with a progestogen. Candidiasis is common; the sexual partner may suffer penile irritation after coitus without physical signs or frank candidal balanoposthitis. Genital warts may increase. Facial hyperpigmentation (chloasma) is well recognized [5,6], as are hirsutism and acne. Gingival epithelial melanosis has been recorded [7]. Alopecia related to contraceptive therapy may be of either androgenic or postpartum telogen pattern following withdrawal of the drug. Erythema nodosum is a well-recognized but rare complication [8,9].

The relapse of herpes gestationis is well documented [10]. Rare lichenoid, eczematous and fixed eruptions have been described, as have a lymphocytic cutaneous vasculitis and an eruption resembling Sweet's syndrome [11]. Oral contraceptives have been implicated in both the provocation [12] and induction of remission of pityriasis lichenoides. An SLE-like reaction has also been reported [13]. An oral contraceptive-induced LE-like eruption, with erythematous lesions on the palms and feet in association with a weakly positive antinuclear factor and C1q deposition at the dermal–epidermal junction on direct immunofluorescence, developed in a patient. It resolved on cessation of medication [14].

The jaundice rarely induced by these drugs resembles cholestatic jaundice of pregnancy. The hepatotoxic effects may result in provocation of variegate porphyria, porphyria cutanea tarda [15,16] and hereditary coproporphyria [17]; onycholysis may occur [16]. Photosensitivity unrelated to porphyrin disturbances has also been reported [18,19]. Benign hepatomas may also be a hazard [20].

Other hormonal contraceptives. Keloid formation has followed levonorgestrel implantion [21]. Vaginal erythematous areas were associated with use of a levonorgestrel-releasing contraceptive ring in 48 of 139 subjects [22]. Rosacea has been associated with a progesterone-releasing intrauterine contraceptive device [23].

Hormone replacement therapy. Melasma of the arms is recorded [24–26].

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Anti-oestrogens

Clomifene (clomiphene). Hot flushes [1] and recurrent petechiae and palpable purpura of the legs with neutrophilic infiltration in a woman treated for infertility with multiple courses of clomifene [2] have been reported.

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Tamoxifen. This oestrogen receptor antagonist used in the therapy of breast cancer in women has caused hirsutism, hair loss, dry skin and a variety of rashes [1].

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Progesterone and progestogens

Autoimmune progesterone dermatitis. A number of eruptions, including urticaria, eczema, pompholyx, erythema annulare centrifugum and erythema multiforme, have been reported to recur cyclically in the second (luteal) phase of the menstrual cycle, with the period immediately before menstruation peaking in severity [1–8]. Oral and perineal lesions may occur. It has been proposed that they result from sensitization to endogenous progesterone. There is frequently, but not always, a history of prior exposure to synthetic progesterones [1,3]. Confirmation is with a positive intradermal test with progesterone, preferably in an aqueous or aqueous alcohol solution, and/or existence of circulating antibody to progesterone, and by suppression of symptoms with agents that inhibit ovulation and result in decreased serum progesterone [7]. Two patients with recurrent premenstrual erythema multiforme and autoreactivity to 17α-hydroxyprogesterone have been described [5,6]; in one case, the eruption spread in pregnancy, cleared after abortion and was associated with a high-affinity binding factor to 17α-hydroxyprogesterone in the serum [6]. In another case with recurrent erythema multiforme, cured by oophorectomy, progesterone sensitivity was confirmed by challenge with medroxyprogesterone acetate [9].

Medroxyprogesterone acetate. A pigmented purpura [10] and skin necrosis following intramuscular Depo-Provera [11] are recorded.

Megestrol. A generalized morbilliform rash developed in a cachectic man treated with this synthetic orally active progesterone derivative to stimulate appetite and weight gain; skin testing with progesterone acetate was positive [12].

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Androgens

Anabolic steroids. Exacerbation of acne vulgaris with development of acne conglobata has been reported [1]. Both the size of sebaceous glands and the rate of sebum secretion are increased [2,3]. A lichenoid eruption was reported in a patient with aplastic anaemia treated with nandrolone furylpropionate (Cemelon) [4].

Danazol. This 17-ethinyltestosterone derivative, which is an inhibitor of pituitary gonadotrophin, is a very weak androgen. Of 530 recipients of danazol, 29% reported at least one adverse event within 45 days after receiving the drug, but there were no known long-term sequelae [5]. Acne, hirsutism, seborrhoea, rash and generalized alopecia are documented [6–8]. Exacerbation of LE-like eruptions has been reported in patients receiving this drug for non-C1-esterase inhibitor-dependent angio-oedema [9] or for hereditary angio-oedema [10].

Gestrinone. This derivative of 19-nortestosterone, like danazol, may cause weight gain, hirsutism, acne, voice change or irregular menstrual bleeding [11].

Testosterone. Severe acne or acne fulminans has followed therapy with testosterone, with [2,12] or without [13] anabolic steroids.

Yohimbine. Yohimbine is an indole alkaloid obtained from the yohimbe tree in West Africa and is used in the treatment of male impotence. A case of generalized erythrodermic skin eruption, progressive renal failure and LE-like syndrome is recorded [14].

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Antiandrogens

Cyproterone acetate. Fixed drug eruption is recorded [1].

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Insulin

Adverse reactions to insulin [1–5] used to be relatively common, with bovine insulin having the most potential for production of allergic reactions, followed by porcine and human insulin. Insulin allergy and other local cutaneous reactions are rarely seen with highly purified and biosynthetic preparations [3,4], although local symptoms still occur in approximately 5% of patients [3]. Lipoatrophy, which was reported in 10–55% of patients treated with non-purified bovine/porcine insulin preparations, has almost disappeared since the advent of exclusive human insulin treatment. Allergic symptoms to human insulin are found in less than 1% of *de novo*-treated patients, but still occur when human insulin is used in the insulin-allergic patient [3]. Anaphylaxis may occur with recombinant human insulin [6]. Local allergic reactions are often of immediate hypersensitivity type; they are more common in the first few months, and usually subside with continued therapy. Generalized pruritus and urticaria occur rarely. Typically, more severe anaphylactoid reactions follow reintroduction of insulin in patients who have previously received long-term therapy. Delayed reactions may also occur, and take the form of pruritic erythema and induration, sometimes with papulation, within 24 h of injection [7]. Biphasic responses may be seen in the same individual, with initial immediate urticaria and a delayed reaction after 4–6 h. Allergy may develop to the insulin itself (i.e. bovine or porcine protein), to preservatives such as parabens and zinc [8,9] or to protamine (Surfen) present in depot preparations [10–13]. Sterile furunculoid lesions at injection sites, which heal with scars and which have a granulomatous histology, may result. Lipoatrophy at injection sites, or more rarely distally, occurred especially with longer-acting preparations; affected patients had lesional immunoglobulin deposits and circulating anti-insulin antibodies [14]. Exceptionally, hypertrophic lipodystrophy [15], or hyperkeratotic verrucous plaques at the site of repeated injections [16], may develop.

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Thyroxine

Chronic urticaria and angio-oedema was reported in a patient, associated with exogenous thyrotoxicosis, related to thyroid replacement therapy [1].

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Antithyroid drugs

Thiouracils

Hypersensitivity reactions include drug fever, pruritus,

urticaria, angio-oedema, exanthems, acneiform rashes, depigmentation of hair and LE-like syndromes. Propylthiouracil has caused allergic vasculitis [1–3], and methylthiouracil has resulted in erythema multiforme. Thiouracils may cause excessive hair loss. These drugs may cause marrow failure [4].

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Chemotherapeutic (cytotoxic) agents

General side effects

There have been a number of excellent reviews of the dermatological complications of these compounds [1–10], including histopathological reactions [11,12]. Bone marrow depression, with aplastic anaemia, agranulocytosis or thrombocytopenia, and gastrointestinal intolerance may occur with any of these drugs. Mucocutaneous surfaces are especially vulnerable to the toxic effects of this group of drugs on rapidly dividing cells. Common side effects therefore include alopecia (see p. 73.46) and stomatitis [13]. Cytotoxic drugs may cause alopecia by either anagen or telogen effluvium. Severe alopecia of anagen type within 2 weeks of administration of the drug is frequently seen with cyclophosphamide, doxorubicin and the nitrosoureas; it is usually reversible with cessation of therapy. Other chemotherapeutic agents implicated in the production of alopecia include amsacrine, bleomycin, cyclophosphamide, cytarabine, dactinomycin, daunorubicin, etoposide, fluorouracil and methotrexate. Stomatitis occurs most frequently with acridinyl anisidide, dactinomycin, daunorubicin, doxorubicin, fluorouracil and methotrexate; it may respond to reduced dosage. Similarly, a number of drugs may cause pigmentation of the buccal mucosa [14] or of the nails [15–17]. Onycholysis may be induced [18].

Hypersensitivity or allergic reactions such as urticaria and angio-oedema [19,20] occur with all cancer chemotherapeutic agents except altretamine, the nitrosoureas and dactinomycin. With L-asparaginase and mitomycin (administered intravesically) they occur in about 10% of patients, and are relatively frequent with cisplatin; they are very rare with methotrexate. Type I reactions are commonest, but all four types of reactions are represented.

Many of these agents have distinctive cutaneous side effects, ranging from localized or diffuse hyperpigmentation to less usual ones, including radiation enhancement and recall phenomena, photosensitivity and hypersensitivity reactions, and phlebitis or chemical cellulitis. Confluent erythematous and hyperpigmented patches, with focal basal layer vacuolar degeneration, occurred within flexural areas during the first month after autologous peripheral stem cell transplantation [21]. Photosensitivity reactions occur with dacarbazine, fluorouracil, mitomycin and vinblastine. Radiation recall effects involve reactivation of an inflammatory response in areas irradiated months or years previously. Clinically, these range from erythema to vesiculation, with erosions and subsequent hyperpigmentation. They have most often been reported in association with dactinomycin and doxorubicin therapy [22] but also with edatrexate [23] and gemcitabine [24]; melphalan, etoposide, vinblastine, bleomycin, fluorouracil, hydroxyurea and methotrexate may also cause radiation enhancement. UV recall is recorded with mitomycin and the combination of etoposide and cyclophosphamide [25]. Rare complications such as diffuse sclerosis of the hands and feet, Raynaud's phenomenon [26], sterile folliculitis and flushing reactions may also occur. Multiple drug regimens may pose special problems in trying to elucidate the cause of a specific reaction, such as white-banded nails [27] or multiple Beau's lines [28]. A pityriasis lichenoides-like eruption occurred during therapy for myelogenous leukaemia with vincristine and mercaptopurine, antibiotics and aciclovir [29]. Fingertip necrosis occurred during chemotherapy with bleomycin, vincristine and methotrexate for HIV-related Kaposi's sarcoma [30].

Most cytotoxic drugs are teratogenic and are contraindicated during pregnancy, especially during the first trimester. Alkylating drugs usually cause sterility in males, and may shorten reproductive life in women.

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Extravasation

Extravasation, leading to skin necrosis with ulceration, occurs with several agents [1–5]. Phlebitis and chemical cellulitis have been recorded with most antimitotic agents. Residual drug should be aspirated and the limb elevated; plastic surgical advice should be sought as soon as possible. High dermal concentrations of doxorubicin have been documented as late as 28 days after accidental extravasation [6]. Histological examination of doxorubicin-related extravasation lesions demonstrated exaggerated interface-type dermatitis with thrombosis of venous tributaries [7].

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Acral erythema

Several cytotoxic drugs (especially cytosine arabinoside, fluorouracil, docetaxel and doxorubicin, and rarely cyclophosphamide, hydroxyurea, mercaptopurine, methotrexate and mitotane) can cause dose-dependent acral erythema, often preceded by paraesthesiae, either alone or in combination [1–17]. Bulla formation, desquamation and subsequent re-epithelialization may occur. Reactions may occur sooner (from 24 h to 3 weeks) and more severely with bolus or short-term chemotherapy than with low-dose continuous infusion, and are usually reproducible on challenge. Intravenous ciclosporin, given in bone marrow transplant patients, reportedly worsens the pain of acral erythema [12]. The condition should be distinguished from graft-versus-host disease in patients who receive chemotherapy followed by bone marrow transplantation, and from chemotherapy-induced Raynaud's phenomenon. This may not be easy, as histological changes may suggest graft-versus-host disease [18].

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Neutrophilic eccrine hidradenitis

Neutrophilic eccrine hidradenitis may represent a reaction pattern to a variety of chemotherapeutic agents [1–8], but particularly cytarabine and bleomycin. It has been induced by granulocyte–macrophage colony stimulating factor [9]. Clinically, erythematous papules or plaques or nodules are most frequent, although hyperpigmented plaques, pustules, purpura and urticaria have been described. Lesions resolve spontaneously over several days. The histology is characterized by infiltration of eccrine coils with neutrophils and necrosis of the secretory epithelium. The condition has also been described in a patient receiving haemodialysis without chemotherapy [10] and in a patient without a malignancy who was taking paracetamol [11].

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Syringosquamous metaplasia

A related but distinct entity termed 'syringosquamous metaplasia', which may be confused with well-differentiated squamous cell carcinoma histologically, has been described in patients receiving chemotherapy for leukaemia and other cancers [1–3]. Clinically, this may appear as an erythematous, blanching, papular crusted eruption, or as erythematous oedematous plaques or confluent erythematous macular areas, in the axillae or groins, with painful erythema and oedema on the palms and soles [4].

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Side effects related to immunosuppression

The cutaneous manifestations of immunosuppression have been reviewed [1–4]. Immunosuppressive therapy, such as azathioprine and prednisone for renal transplant patients, may encourage skin infections of various types, for example warts, herpes simplex and herpes zoster [5], pityriasis versicolor and fungal infections [6]. Development of disseminated superficial actinic porokeratosis [7–9], porokeratosis of Mibelli [10–13] and increased numbers of benign [14,15] or eruptive dysplastic [16] melanocytic naevi may be promoted. Eruptive keratoacanthomas occurred in a patient with SLE on prednisolone and cyclophosphamide [17].

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Internal malignancy

The frequency of internal cancers common in the general population is not increased in transplant patients. However, that of a variety of otherwise uncommon malignancies is increased [1–3], including non-Hodgkin's lymphoma (mostly B-cell, with 14% of T-cell, and less than 1% of null-cell, origin), which accounts for 21% of cancers in transplant recipients; Kaposi's sarcoma; other sarcomas; carcinoma of the vulva and perineum; carcinoma of the kidney; and hepatobiliary tumours. Non-Hodgkin's lymphoma appears commoner and develops earlier where potent immunosuppressive agents such as ciclosporin and/or the monoclonal antibody OKT3 have been used; however, although cancer develops in 6% of all transplant recipients, only 1% of patients die from this complication [3]. Leukaemia may develop following chemotherapy [4], and bladder cancer has been associated with cyclophosphamide therapy [5].

Skin cancers

Actinic keratoses, squamous cell and basal cell cancer of the lip and skin [6–12], and malignant melanoma [13] have been reported to be more common, especially in immunosuppressed renal transplant patients. The majority of these patients have received azathioprine and corticosteroids. Interestingly, the immunosuppressed renal transplant recipients have been reported to be at high risk for skin cancer unless they express the HLA class I allele A11 [14]. Furthermore, patients with long-standing renal grafts mismatched for HLA-B have a significantly higher incidence of squamous cell cancers than other mismatches, and patients who are homozygous for HLA-DR are at increased risk for actinic keratoses and skin cancer [15]. These findings imply that MHC gene products participate in the pathogenesis of skin cancer in immunosuppressed patients, probably via influences on T-cell recognition of neoantigens [16]. There was no difference from control levels in the number of $CD1^+$ $HLA\text{-}DR^+$ antigen-presenting Langerhans' cells in the epidermis of immunosuppressed renal transplant recipients treated with either azathioprine/prednisone or ciclosporin/prednisone [17].

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Alkylating agents

These drugs interfere with cell replication by damaging DNA. Gametogenesis is often severely affected, and their use is associated with a marked increase in non-lymphocytic leukaemia, especially when used in conjunction with radiotherapy.

Alkyl sulphonates

Busulfan. Reactions are rare, but have included urticaria, bullous erythema multiforme [1], Addisonian-like pigmentation [2,3] due to increased epidermal and dermal melanin, and drug-induced porphyria cutanea tarda [4]. Vasculitis has been reported. Keratinocyte nuclear abnormalities with abundant pale cytoplasm have been described [5]. Progressive pulmonary fibrosis may occur.

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Nitrogen mustard derivatives

Chlorambucil. Morbilliform rashes occur; urticarial plaques and periorbital oedema have been described rarely [1–4]. A delayed allergic reaction on the third cycle of chemotherapy, with generalized erythroderma with exfoliation and oedema of the face and arms, as well as immune haemolytic anaemia and TEN, have been described [5]. Alopecia is uncommon. Sterility with azoospermia and amenorrhoea is documented.

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Cyclophosphamide and mesna. Alopecia is common and occurs in 5–30% of cases [1]. Pigmentation, which may be widespread or localized to the palms, soles or nails, is well documented and usually reversible [2,3]. Nail dystrophy may be seen. Allergic exanthems are rare, but anaphylactic and urticarial reactions less so [4–7]. Type I hypersensitivity with a markedly delayed onset (from 8 to 16 h up to 10 days), associated with immediate skin-test results to cyclophosphamide metabolites but not the parent drug, has been documented [7]. There may be cross-sensitivity to other alkylating agents, especially mechlorethamine and chlorambucil [8]. Sterility may supervene.

Haemorrhagic cystitis, the result of toxicity of the metabolite acrolein, is a complication in up to 40% of cases if cyclophosphamide is used alone. Introduction of the thiol compound mesna (2-mercaptoethane sulphonate) has virtually eliminated this complication. There have been recent reports of urticaria, angio-oedema, allergic maculopapular pruritic rashes, generalized fixed drug eruption, and occasional more severe reactions with flushing, widespread erythema and ulceration or blistering of mucous membranes related to mesna; patch tests may be positive [9–13].

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Lomustine. Flushing has been reported.

Mechlorethamine. Angio-oedema and pruritus have been recorded [1]; however, in view of the large number of patients receiving this drug as part of the MOPP (mechlorethamine, Oncovin (vincristine), procarbazine, prednisone) regimen for lymphoma, these side effects must be exceedingly rare. Topical mechlorethamine [2] used to treat psoriasis or mycosis fungoides may cause hyperpigmentation of involved and uninvolved skin [3], contact sensitization [4,5] and rarely immediate-type hypersensitivity with urticaria or anaphylactoid reactions [6].

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Melphalan. Trivial morbilliform rashes are relatively common [1]. Severe anaphylactic reactions may occur after intravenous use, especially in patients with IgA κ myeloma

[2]. Urticaria or angio-oedema after oral use is very rare [3]. Vasculitis has been documented, and melanonychia striata has been recorded [4]. Scleroderma has supervened after isolated limb perfusion [5]. Radiation recall is uncommon [6]. Sterility with azoospermia and amenorrhoea are recorded.

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Ethylenemine derivatives

Thiotepa (triethylenethiophosphoramide)

Intravesical installation caused pruritus, urticaria or angio-oedema in five of 164 patients with bladder carcinoma [1]. Intravenous administration resulted in patterned hyperpigmentation confined to skin occluded by adhesive bandages or electrocardiograph pads, probably due to secretion of the drug in sweat [2]. In contrast, topical thiotepa has produced periorbital leukoderma [3].

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Nitrosoureas

Carmustine

Topical carmustine (BCNU) used for the treatment of cutaneous T-cell lymphoma may result in erythema, skin tenderness and telangiectasia. Contact sensitization may develop [1]. Mild bone marrow suppression has been recorded.

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Dacarbazine (DTIC)

Photosensitivity [1,2] and a fixed eruption-like rash [3] have been reported. A patient with malignant melanoma treated with DTIC developed sudden hepatic vein thrombosis (Budd–Chiari syndrome) following intravenous administration [4]. Increasing blood eosinophilia appears to be a sign of the imminent development of this complication. Chemical cellulitis occurs following extravasation.

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Procarbazine

Type I reactions are rare; recurrent angio-oedema, urticaria and arthralgia with decreased serum complement have been reported [1,2]. Hypersensitivity to procarbazine in patients treated with mechlorethamine, vincristine and procarbazine (MOP) for high-grade glioma manifested as a maculopapular rash, fever, reversible abnormal liver function and interstitial pneumonitis [3].

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Cytotoxic antibiotics

Bleomycin

The principal problem of systemic therapy is progressive pulmonary fibrosis. Alopecia, glossitis and buccal ulceration occur, and drug fever is common, usually 1–4 h after injection. Distinctive, localized, erythematous, tender macules, nodules or infiltrated plaques on the hands, elbows, knees and buttocks have been documented [1–3]. Their causation is uncertain, and the rash may resolve despite continued therapy [4]. Raynaud's phenomenon with or without ischaemic ulcerations, and systemic sclerosis-like changes in men, have been described [5–7]. Capillary microscopy has been advocated for the invest-

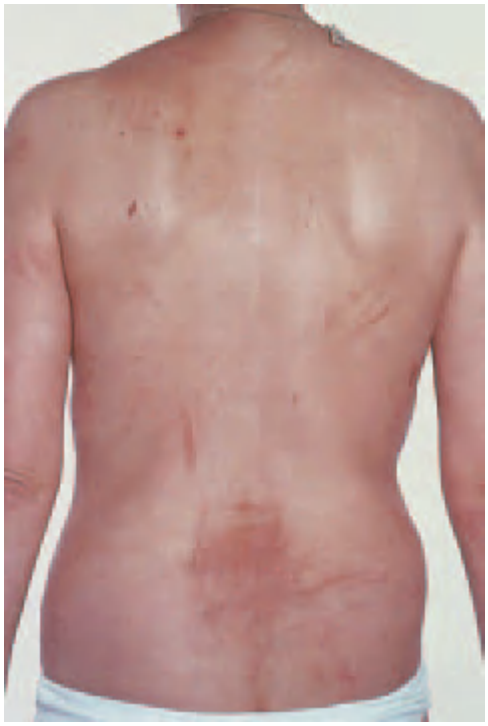

Fig. 73.8 Flagellate pigmentation caused by bleomycin. (Courtesy of Dr A. Ilchyshyn, Coventry and Warwickshire Hospital, Coventry, UK.)

igation of bleomycin acral vascular toxicity [8]. In normal human skin, intradermal bleomycin induced a localized time- and dose-dependent inflammatory reaction and persistent post-inflammatory hyperpigmentation; histology showed neutrophilic eccrine hidradenitis, with keratinocyte necrosis, HLA-DR and ICAM-1 expression, and endothelial cell ICAM-1 up-regulation and E-selectin induction [9]. Intralesional bleomycin therapy for warts induced keratinocyte apoptosis and complete epidermal necrosis with diffuse neutrophil accumulation and microabscess formation at the granular layer [10]. Clinically, intralesional therapy may cause persistent Raynaud's phenomenon [11,12] and loss of nails [13].

Cutaneous erythema or hyperpigmentation, which may be diffuse [14], patchy or linear, and prominent over pressure areas, especially the elbows or in striae distensae [15], is seen in approximately 30% of patients [16]. 'Flagellate' streaked erythema or pigmentation [17–24] on the trunk and proximal extremities is common (Fig. 73.8); it recurs in previously involved sites, and develops in new sites, within 24 h of rechallenge [21]. It has been proposed that trauma from scratching induces localized vasodilatation, with increased concentration of cutaneous bleomycin; hyperpigmentation has been documented in a patient treated with bleomycin where a heating pad had been applied [25]. There may be darkening of the nail cuticle and palmar creases.

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Dactinomycin (actinomycin D)

A papulopustular acneiform sterile folliculitis, spreading from the face to the trunk and buttocks, and which may mimic septic cutaneous emboli, is common [1]. Dactinomycin-related lesions with the histology of an

interface dermatitis with syringometaplasia developed in the axillae, groins and central line exit site of two children [2]. Radiation recall occurs [3]. Persistent serpentine supravenous hyperpigmentation was recorded in combination dactinomycin and vincristine therapy [4].

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Daunorubicin

Angio-oedema with generalized urticaria [1], and hyperpigmentation of the oral mucosa, skin and nails [2–4] have been described.

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Doxorubicin (Adriamycin)

Short-lived localized erythema or urticaria with pruritus along the vein proximal to the injection site may occur in up to 3% of patients [1]. Angio-oedema, generalized urticaria with or without anaphylaxis and chronic urticaria have been reported rarely [2]. Cutaneous and nail pigmentation are well recognized [3,4]. Erythema and desquamation of palmar and plantar skin, with or without onycholysis, occurs frequently in patients receiving doxorubicin [5–7]. Liposomal doxorubicin is associated with a dose-limiting hand–foot syndrome and stomatitis [8,9] and with psoriasiform pustular reactions [10]. Allergic cross-reaction occurs with daunorubicin. Toxic epidermal injury after intra-arterial injection [11], phlebitis and chemical cellulitis with extensive tissue necrosis and ulceration following extravasation [12] are well documented.

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Mitomycin

Urticaria and dermatitis [1–3], particularly on the face, palms and soles, or genitals and sometimes more generalized, have been reported after intravesical therapy. Sunlight-induced recall of ulceration following extravasation has been recorded [4].

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Antimetabolites

Aminoglutethimide

This inhibitor of adrenal steroid synthesis has been reported to induce SLE [1].

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Azathioprine

The dermatological aspects of this derivative of the antimetabolite mercaptopurine have been reviewed [1–3]. Bone marrow suppression is the main problem; blood counts should be performed weekly for the first month, then

monthly thereafter. Homozygotes for the low-activity allele for thiopurine methyltransferase are at risk of myelosuppression [4–7]. It is therefore recommended that thiopurine methyltransferase levels should be measured before commencing patients on azathioprine [6]. Gastrointestinal upset is common and may necessitate discontinuation of therapy. Hypersensitivity reactions [8–10], including fever [11], maculopapular rashes, urticaria, vasculitis, erythema multiforme or erythema nodosum, cholestatic jaundice, hepatitis, liver necrosis, interstitial pneumonitis, polyneuropathy, pancreatitis, shock [12] with hypotension, nephritis and oliguria are well recognized.

An acneiform exanthem has been described, confirmed on challenge [13]. An eruption comprising tiny superficial blisters and peeling in the flexures is described [14]. Multiple large resistant warts are common on the hands of renal transplant recipients maintained on long-term azathioprine and prednisolone therapy; herpes simplex and herpes zoster infection may occur [15], and Norwegian scabies may be promoted [16]. Disseminated superficial actinic porokeratosis [17] and porokeratosis of Mibelli [18] have been documented. Keratoacanthomas and squamous cell carcinomas may develop [19]. Long-term therapy may predispose to the development of malignancy, especially non-Hodgkin's lymphoma [20]. Azathioprine crosses the placenta, although there is little evidence that azathioprine is teratogenic in humans, and detailed analysis of successful pregnancies notified to the European Dialysis and Transplant Association did not suggest an excessive rate of congenital abnormality [21]. However, depressed fetal haemopoiesis and resultant neonatal thrombocytopenia and leukopenia have been documented [22]. Pregnancy may be best avoided in patients receiving this drug [23]. Allopurinol may potentiate the effect of azathioprine by inhibiting its metabolism; the dose of azathioprine should therefore be reduced to one-quarter of the regular dose.

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Cytarabine (cytosine arabinoside)

This drug interferes with pyrimidine synthesis. A self-limited palmoplantar erythema, occasionally with bullae, may occur [1–4]. Neutrophilic eccrine hidradenitis has been reported [5]. A syndrome with fever, malaise, arthralgia, conjunctivitis and diffuse erythematous maculopapular rash is documented [6]. The overall incidence of cutaneous reactions, including morbilliform eruptions, acral erythema, swelling and generalized urticaria, was almost 53% in one series [7].

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Fluorouracil

Anaphylaxis is rare; alopecia and recall phenomena [1] may be seen. Erythema followed by hyperpigmentation of sun-exposed areas occurs in up to 5% of patients [2]. Photosensitivity is recorded; pellagra may be caused by direct inhibition of the transformation of tryptophan into nicotinamide. Rarely, hyperpigmented streaks (serpentine supravenous hyperpigmentation) develop over arm veins used for injection [2–5]. Continuous infusion may be followed by the development of erythema, oedema and desquamation of the hands [6–10]. Pyridoxine may decrease the intensity and pain of fluorouracil-induced acral erythema [8]. Oral administration resulted in painful erythema multiforme-like erosions and blisters on the soles and arms in one case [9]. Systemic fluorouracil may result in marked inflammation of metastatic skin lesions [11] and of solar keratoses [12]. Topical application may lead to hyperpigmentation with or without a preceding irritant or allergic contact dermatitis [13].

Capecitabine

Capecitabine is a fluoropyrimidine carbamate that is metabolized to fluorouracil, and has been recorded as causing hand–foot syndrome in 50% of patients, and rarely leopard-like vitiligo, onycholysis and periungual pyogenic granulomas [14].

Gemcitabine

This drug has caused radiation recall [15].

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Methotrexate

Dermatological aspects. These have been reviewed [1–3]. Methotrexate is a folic acid analogue and antagonist that inactivates dihydrofolate reductase. There is marked individual variation in absorption from the gastrointestinal tract, and hence in expression of toxic effects. Alopecia occurs in 6% of patients receiving low-dose therapy for psoriasis and in 8% of patients on high-dose regimens for malignancy, and is usually the result of telogen effluvium. Intermittent high dosage has resulted in horizontal pigmented banding of hair (the 'flag sign' of chemotherapy) [4]. Urticaria develops in about 4% of patients on low-dose oral or parenteral therapy for psoriasis [5]. Exacerbation of urticarial vasculitis has been documented [6]. Photosensitivity occurs in up to 5% of cases. Methotrexate use has been associated with severe reactivation of sunburn [7,8]; in one case, there was sparing of chronically sun-exposed skin [8]. Chronic viral wart and molluscum infections may result from immunosuppression. Cutaneous toxicity with local epidermal necrosis may occasionally occur [9,10]. A macular erythema occurring in 15% of patients, and biopsy-proven capillaritis, have been reported with high-dose therapy [3]. An eruption of erythematous indurated papules on the proximal parts of the limbs has been documented in patients with collagen vascular disease [11]. Anaphylactic reactions [12] and pain, burning, erythema and desquamation of the palms and soles [13–15] are seen with high-dose intravenous methotrexate, but are extremely rare. Vasculitis has been very rarely documented with both intermediate dosage therapy for leukaemia [16] and high-dose therapy [17]. TEN is recorded [18,19], and occurred after a single injection of 25 mg for pustular psoriasis [19].

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Systemic complications. Because folic acid is an essential co-factor for DNA synthesis and cell division, bone marrow suppression may occur even on low-dose therapy [1–4]. Thrombocytopenia may develop after a single test dose [5]. Severe bone marrow suppression [6] with the dosage used in the therapy of psoriasis is fortunately not common. Stomatitis may be a warning sign of overdosage. The risk of myelosuppression is much greater in the presence of renal impairment. Gastrointestinal upset is common. Abnormalities of taste sensation occur rarely [7].

The main hazard is hepatotoxicity with long-term use [8]. The risk of developing severe hepatotoxicity is related to the daily dose, the dose frequency and the cumulative dose [9]. Alcohol consumption, underlying liver disease and obesity, especially in the presence of diabetes, are aggravating factors. Recommendations have included obtaining baseline haematological, renal and hepatic function tests and a liver biopsy before or within 4 months of starting therapy, and repeating after every 1.5 g [10]. Liver function tests may be unreliable indicators of fibrosis or cirrhosis. These guidelines appear prudent but have never been rigorously tested, and are variously applied in clinical practice [10,11]. There seems to be a discrepancy between the degree of hepatotoxicity in rheumatoid arthritis and that in psoriasis, and many rheumatologists do not routinely carry out liver biopsy [11]. The requirement for liver biopsies in psoriasis patients on long-term, low-dose, once-weekly oral methotrexate has been questioned [12]. Radionuclide liver scans are thought to be of little value in the detection of methotrexate-induced liver disease, but liver ultrasound may be of some assistance [13]. Abnormal liver biopsy may improve after cessation of therapy [14]. Assay of serum levels of the aminopropeptide of type III procollagen is being used in some centres to screen for patients in whom liver biopsy is mandatory [15–17].

Acute renal failure may follow high-dose methotrexate therapy, although renal damage is rare in patients treated for psoriasis. Pulmonary complications, such as pneumonitis or fibrosis, are rare [18,19]. There do not appear to be adverse effects on humoral or cellular immunity from low weekly doses as given for rheumatoid arthritis or psoriasis [20].

Methotrexate is a known teratogen, and may cause oligospermia [21,22]. It is recommended that patients avoid pregnancy or impregnation during, and for 12 weeks after cessation of, methotrexate therapy [23].

Care must be taken with regard to potential drug interactions with methotrexate [24,25]. Drugs that also interfere with folate metabolism, such as trimethoprim–sulfamethoxazole [26–28], may cause pancytopenia; both trimethoprim and sulfamethoxazole bind to dihydrofolate reductase. Drugs that displace methotrexate from plasma protein-binding sites, such as salicylates, sulphonamides and diphenylhydantoin, as well as drugs that impair the renal clearance of methotrexate, such as NSAIDs and sulphonamides, may also cause pancytopenia. A toxic reaction occurred in a patient treated with penicillin and furosemide [29].

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Vinca alkaloids and etoposide

These drugs cause metaphase arrest by interfering with microtubule assembly.

Etoposide (VP-16)

This semi-synthetic podophyllotoxin derivative causes bone marrow suppression, alopecia and gastrointestinal symptoms. It has caused Stevens–Johnson syndrome and radiation recall. Four cases of a diffuse, erythematous, maculopapular rash occurring 5–9 days after initiation of therapy, with spontaneous resolution within 3 weeks, have been reported [1]. On histology, scattered, markedly enlarged individual keratinocytes with a 'starburst' nuclear chromatin pattern were seen. Hypersensitivity reactions are generally held to be rare [2–4], but 51% of patients with newly diagnosed Hodgkin's disease had one or more acute hypersensitivity reactions to etoposide administration, including flushing, respiratory problems, changes in blood pressure and abdominal pain [5].

Vincristine

Peripheral neuropathy is well recognized with long-term therapy [6].

Vinblastine

Photosensitivity is common [7]. Acute alopecia and radiation recall are documented. Erythema multiforme-like reactions are described following intravenous injection [8].

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Enzymes

L-Asparaginase (crisantaspase)

Dose-dependent IgE-mediated hypersensitivity reactions, including urticaria and anaphylaxis, are frequent, especially when the drug is used alone [1]. Allergic reactions to intramuscular L-asparaginase include local painful erythema, and urticaria or a general exanthem; continuous infusion is better tolerated [2].

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Miscellaneous chemotherapeutic agents

Acridinyl anisidide (AMSA)

Skin reactions are rare but widespread erythema has been reported [1].

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Bromodeoxyuridine

A distinctive eruption comprising linear supravenous papules and erythroderma has been described with bromodeoxyuridine given in combination with radiotherapy for central nervous system tumours [1]. Ipsilateral facial dermatitis with epilation of eyebrows and eyelashes, ocular irritation, bilateral nail dystrophy, oral ulceration, exanthem or erythema multiforme have also been described [2].

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Carboplatin

Hypersensitivity reactions occur in 1–30% of patients [1–5]; acute allergic reactions include urticaria, bronchospasm, hypotension, facial erythema and facial swelling. Desensitization can be successful [5]. A pruritic maculopapular rash occurred in 10 of 40 patients treated with carboplatin, etoposide and ifosfamide plus mesna followed by autologous stem cell reinfusion; the rash was distributed at the extremities or was confluent on the trunk and face, with facial oedema and painful swelling of hands and feet, and resolved spontaneously with hyperpigmentation in all patients [6].

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Cisplatin

Periungual hyperpigmentation [1] and acral erythema [2] or digital necrosis [3] have been documented. Severe hypersensitivity reactions, including flushing, erythema, maculopapular eruptions, urticaria and anaphylaxis, occur in about 5% of cases when this drug is used as a single agent, and in up to 20% when given with other chemotherapeutic agents [4,5]. Cross-reactivity with carboplatin may occur [5]. Atopic subjects are especially at risk. Local reactions follow extravasation [6]. Severe allergic exfoliative dermatitis with ischaemia and necrosis of the hands developed in a patient who had received multiple doses of cisplatin [7].

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Colchicine

Alopecia is recorded [1].

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Flutamide

A photosensitive dermatitis [1,2] and pseudoporphyria [3] have been reported with this non-steroid antiandrogen used in the treatment of prostatic carcinoma.

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Hydroxycarbamide (hydroxyurea)

Dermatological aspects of this drug have been reviewed [1–6]. Impaired renal function has been reported in some, but not all, studies [3]. A modest fall in haemoglobin and development of macrocytosis is almost constant.

Stomatitis occurs especially with high-dose therapy and has been accompanied by soreness, violet erythema, and oedema of the palms and soles with subsequent intense universal hyperpigmentation [7], but alopecia is rare. Morbilliform erythema occurs, and hyperpigmentation, generalized or localized to pressure areas, was recorded in up to 5% of cases [2]. A more recent survey reported mucocutaneous adverse reactions after a mean duration of 6.4 weeks of treatment in up to 65% of patients, with pigmentation of nails, skin or mucosa seen in 58.6% [6]. Other less common findings were xerosis, diffuse alopecia, oedema of the legs, oral ulcers and actinic psoriasis; scleral pigmentation and acquired ichthyosis were also noted. Nail pigmentation changes [8], such as multiple pigmented nail bands [9], or onycholysis with nail dystrophy occurs. Fixed drug eruption has been reported [3], as has baboon syndrome [10]. Dermatomyositis-like acral erythema, scaling, and atrophy especially on the dorsum of the hands, with lesser involvement of the feet [1,4,11–14], and palmar and plantar keratoderma have been rarely described with long-term therapy for chronic myeloid leukaemia. Photosensitivity is documented, and LE [15] and vasculitis have been reported. An ulcerative lichen planus-like dermatitis has been recorded [16]. Lichenoid eruptions similar to graft-versus-host disease are documented [17,18]. Several reports have recorded an association with leg ulcers [12,13,19–23]. Accelerated development of skin malignancies occurs, and eruptive squamous and basal cell cancers on light-exposed areas may be seen [24]. Radiation recall occurs [25].

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Imatinib

This protein tyrosine kinase inhibitor, used in the therapy of chronic myeloid leukaemia, has caused oedema, pruritus, and exanthematous, psoriasiform and exfoliative dermatoses [1].

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Suramin

Suramin sodium, a polysulphonated naphthylurea used in the treatment of metastatic prostatic and other cancers, has caused generalized, erythematous, maculopapular eruptions within the first 24 h of therapy (which were self-limited despite continued drug infusion), keratoacanthoma and disseminated superficial actinic porokeratosis [1–3]. Distinctive findings include scaling erythematous papules (suramin keratoses) and a predilection for previously sun-exposed areas (UV recall). Severe cutaneous reactions occur in 10% of cases [3]. Histopathological findings have included hyperkeratosis, parakeratosis, spongiosis, acanthosis, exocytosis, apoptosis, a perivascular

lymphohistiocytic infiltrate, upper dermal oedema and increased dermal mucin [3]. Erythema multiforme [4] and TEN [5,6] are recorded.

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Taxanes

Docetaxel. Docetaxel, a semi-synthetic analogue of paclitaxel from the needles of the European yew *Taxus baccata* and used in the treatment of advanced and/or metastatic cancer, caused neutropenia, skin reactions (81%) and nail changes (41%), neurosensory toxicity (59%), fluid retention with oedema and hypersensitivity reactions (16–55%) [1–3]. The commonest skin reaction is characterized by discrete erythematous to violaceous patches or oedematous plaques similar to acral erythema [4]. Nail changes recorded [5,6] include horizontal banding [7], dyschromia [8] and subungual abscess [9]. Squamous syringometaplasia [10] and supravenous discoloration of the skin are documented [11].

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Paclitaxel. Paclitaxel, a diterpenoid taxane derivative found in the bark and needles of the western yew *Taxus brevifolia*, interrupts mitosis by promoting and stabilizing microtubule formation, and shows substantial activity against advanced refractory cancer. Neutropenia is the major dose-limiting toxic effect; other adverse effects include severe hypersensitivity reactions including anaphylaxis, cardiac toxicity, neurotoxicity, arthralgia or myalgia, mucositis, nausea and vomiting, and alopecia [1–6]. Local necrosis has followed accidental subcutaneous extravasation of paclitaxel [7], and administration via a central vein has produced a recall reaction at a site of prior extravasation [8]. Bullous fixed drug eruption is recorded [9], as is a scleroderma-like reaction [10,11]. Desensitization is possible [12].

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Triazinate

Acanthosis nigricans-like hyperpigmentation has been recorded [1].

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Topical nitrogen mustard

Urticaria, anaphylactoid reactions and a local bullous reaction have been recorded [1,2]. Contact dermatitis is well recognized.

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Drugs affecting the immune response

Ciclosporin

Ciclosporin is a ligand for the immunophilin, cyclophilin A, and is thought to block early events in T-cell gene activation by interfering with the intracellular translocation of a substance known as nuclear factor of activated T cells [1,2]. It selectively inhibits antigen-induced activation of, and IL-2 production by, $CD4^+$ helper T lymphocytes, thereby blocking T-cell proliferation [3,4]. It inhibits transcription of genes encoding for IL-2 and IFN-γ [5], and blocks expression of IL-2 receptors. Ciclosporin also inhibits Langerhans' cell antigen-presenting function [6–8] and suppresses ICAM-1 expression by papillary endothelium in inflamed skin, thus reducing T-cell recruitment [9]. Much of the information on side effects was derived from patients who underwent organ transplants, and in diseases such as rheumatoid arthritis [10]. The drug is now used by dermatologists [11–18] especially in the management of difficult psoriasis [13–16], refractory atopic eczema [17] and a number of other conditions [16].

Dermatological complications. Hypertrichosis develops in a high proportion of patients; it affects especially the face and eyebrows, the upper back along the spinal column and the lateral upper arms [18–23]. The hypertrichosis is reversible, and children and adolescents seem to be at greater risk of developing this complication [23]. Other cutaneous complications include gingival hyperplasia [21,24], angio-oedema [25] and hyperplastic pseudofolliculitis barbae [26]. Acne keloidalis is recorded [27]. Anaphylaxis may occur in response to intravenous ciclosporin [11], probably due to the solvent. A mild capillary leak syndrome has resulted in purpuric lesions in the flexures and at pressure points [28], and cutaneous vasculitis is recorded [29].

There have been isolated reports of the development of benign lymphocytic infiltrates in patients with psoriasis or alopecia areata [30,31], of pseudolymphoma after therapy of actinic reticuloid [32] and of an aggressive T-cell lymphoma after ciclosporin therapy for Sézary syndrome [33]. Squamous cell skin cancer may develop [34,35] and could potentially be predisposed to by previous PUVA [36]. A study showed no difference in the incidence of cutaneous malignancy in renal allograft recipients treated with either ciclosporin or azathioprine [34]. Kaposi's sarcoma may occur; a renal transplant patient treated with ciclosporin and methylprednisolone developed a Kaposi's sarcoma, which completely regressed on reducing the dosage of both drugs [37]. There have been isolated reports of development of malignant melanoma in ciclosporin-treated patients, but the incidence of this complication does not seem to be increased above the risk in the general population [38,39].

Systemic side effects. Headache and rarely seizures [40], gastrointestinal and musculoskeletal symptoms are well recognized. There is an increased risk of nephrotoxicity [41,42], which appears to be caused by arteriolar vasoconstriction due to local thromboxane A_2 release [43], and consequent hypertension [44]. Impaired renal function may develop after short- as well as long-term treatment for psoriasis [45]. Both renal dysfunction and hypertension are reversible, and lymphoma development unlikely, in patients on short-term low-dose (less than 5 mg/kg) therapy. Adverse effects on renal function and systolic blood pressure appear greater in psoriasis patients receiving higher doses [15]. Some degree of renal impairment is inevitable with longer term therapy [46]. Rarely, a serious capillary leak syndrome occurs, with marked fluid retention and periorbital oedema, and may be fatal; there may be associated gastrointestinal bleeding, pneumonitis, uraemia and urinary sodium loss followed by hypertension and convulsions [21].

Hepatotoxicity is a complication [47] and hypercholesterolaemia is recorded [48]. Ciclosporin may be associated with myopathy without rhabdomyolysis or with rhabdomyolysis; the latter occurs in the setting of concomitant lovastatin or colchicine therapy [49]. Lymphoma and other cancers have developed on high dosage as used for organ grafting [19,50]. Transplant patients treated with ciclosporin have not been shown to have a higher incidence of neoplasms than those receiving other immunosuppressive agents.

Successful pregnancies have occurred in patients receiving ciclosporin for psoriasis [51,52]. There is no evidence of a teratogenic effect in humans, based on the experience of 107 transplant recipients [53].

Interactions of ciclosporin and other drugs have been reviewed [54]. Ciclosporin blood levels may be increased by concomitant therapy with erythromycin or ketoconazole, as a result of inhibition of the hepatic microsomal cytochrome P-450 enzyme system [55], as well as with danazol, oral contraceptives and calcium channel antagonists. Decreased blood levels may be caused by drugs that induce hepatic enzymes, including phenytoin, phenobar-

bital and tuberculostatic therapy with rifampicin and isoniazid. Aminoglycoside antibiotics, melphalan, amphotericin and trimethoprim (alone or in combination with sulfamethoxazole) interact with ciclosporin by altering renal function. Patients should avoid grapefruit juice taken within 1 h of oral ciclosporin as it contains a psoralen that inhibits the CYP 3A subfamily of cytochrome P-450 and reduces metabolism of ciclosporin [56].

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Sirolimus

This macrolide immunosuppressant, which impairs lymphocyte activation by IL-2, IL-4 and IL-12, has caused a capillary leak syndrome [1].

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PUVA therapy

See Chapter 35.

Immunotherapy

Sera

Animal immune sera can produce any type of early or late hypersensitivity reactions, from urticaria, asthma or fatal anaphylaxis to serum sickness. Clinical manifestations of serum sickness include fever, arthritis, nephritis, neuritis, myocarditis, uveitis, oedema and an urticarial or papular rash. A characteristic serpiginous, erythematous and purpuric eruption developed on the hands and feet, at the borders of palmar and plantar skin, in patients treated with equine antithymocyte globulin [1,2]. Low serum C4 and C3 levels, elevated plasma C3a anaphylatoxin levels, and circulating immune complexes were found. Immunoreactants, including IgM, C3, IgE and IgA, were deposited in the walls of dermal blood vessels on direct immunofluorescence [1,2]. Patients with autoimmune disease may have a particular liability to react to antilymphocyte globulin.

Intravenous immunoglobulin

Angio-oedema-like hypersensitivity eruptions and eczematous, purpuric, petechial/purpuric, lichenoid and vasculitic reactions are recorded [3].

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Vaccines

Overall the incidence of significant side effects is very low. Egg, gelatin, antibiotics and preservatives in vaccines may cause reactions [1]. Needle gauge and length may affect the incidence of local reactions [2]. In Canada during 1990, from more than 12 million doses of vaccines there were 2832 reports of adverse events associated with immunizing agents received by the Childhood Immunization Division of the Laboratory Centre for Disease Control [3]. Only 39 of 43 618 Alaskan natives who received 101 360 doses of hepatitis B plasma-derived vaccine developed side effects, including myalgia/arthralgia lasting longer than 3 days, rashes (eight patients) and dizziness [4]. Influenza vaccination in the elderly is, however, reported to cause no more systemic side effects than placebo [5]. In contrast, another study found local reactions in 17.5% of patients, including swelling, itching and pain [6]. Leukocytoclastic vasculitis has been reported with influenza vaccination [7]. Measles and measles–mumps–rubella vaccine, hepatitis B vaccine, and diphtheria and tetanus toxoids have been statistically associated with anaphylaxis [8], and measles–mumps–rubella vaccine with thrombocytopenia and purpura [8,9] and Gianotti–Crosti syndrome [10]. A variety of reactions have been documented following hepatitis B vaccination [11], including urticaria/angio-oedema [12], erythema multiforme [13], erythema nodosum [14], polyarteritis nodosa and pityriasis rosea [15], and lichenoid eruptions [16,17].

Local reactions include erythema, swelling and tenderness, which may result from an Arthus reaction [18–20]. Keloid scarring may develop. Local inflammatory reactions, fever, lymphadenopathy, urticaria and lichenoid rashes have been observed following vaccination in patients sensitive to the preservative merthiolate; patch testing and intradermal testing may be positive [21,22]. Inflammatory nodular reactions may occur as a result of aluminium sensitization, as with hepatitis B, diphtheria and tetanus vaccination [23,24]; patch testing to aluminium may be positive [23]. Itching, eczema and circumscribed hypertrichosis developed over nodules following immunization with vaccines adsorbed on aluminium hydroxide in three children [24]. Transient subcutaneous nodule formation at the injection site, and increased regional adenopathy, have been rarely noted in patients with HIV infection treated with gpl60 vaccination [25].

Urticaria, angio-oedema or anaphylaxis may occur in patients allergic to egg protein who are vaccinated with live measles vaccine. However, in a series of children with egg allergy and a positive skin-prick test to egg white, 0.98% developed a mild reaction not requiring therapy

following immunization with a full dose of vaccine [26]. Of 98 patients with a history of previous inoculations with human diploid cell rabies vaccine, 3% developed generalized urticaria or wheezing within 1 day, and a further 3% developed urticaria 6–14 days, after booster vaccination [27]. Urticaria and systemic symptoms including malaise and fever, or Stevens–Johnson syndrome may follow tetanus toxoid vaccination [28,29]. Vaccination may result in development of an autoimmune state; dermatomyositis has been provoked. Fatalities have rarely occurred following vaccination as a result of anaphylaxis [30,31]. Vaccination against Japanese encephalitis caused serious adverse reactions, including urticaria, angio-oedema, hypotension and collapse [32]. An association with vaccination for influenza and with tetanus toxoid and induction of bullous pemphigoid has been noted rarely [33–35].

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Hyposensitization immunotherapy

Hyposensitization immunotherapy is a standard treatment for recalcitrant hay fever and bee or wasp stings in many countries in the world, including the USA, Scandinavia and the continent of Europe [1]. However, in the UK, allergen-injection immunotherapy for IgE-mediated diseases has been largely discontinued, following the recommendations of the Committee on Safety of Medicines in 1986 [2], because of concern about deaths related to bronchospasm and anaphylaxis. The Committee recommended that immunotherapy be given only where full facilities for cardiopulmonary resuscitation are available and that patients be kept under medical observation for at least 2 h. The necessity for the latter recommendation has been questioned, as serious reactions occur within minutes [1]. The British Society for Allergy and Clinical Immunology Working Party concluded that specific allergen immunotherapy for summer hay fever uncontrolled by conventional medication and for wasp and bee venom hypersensitivity has an acceptible risk/benefit ratio, provided that treatment is given by experienced practitioners in a clinic where full resuscitative facilities are immediately available; a symptom-free observation period of 60 min after injection is sufficient [3,4]. Patients with asthma should be excluded, however, in view of an increased frequency of reactions [4,5]. Fatalities from allergen immunotherapy are extremely rare [6]. In one series, β-blocker drugs did not increase the frequency of systemic reactions in patients receiving

allergen immunotherapy, but patients developed more severe systemic reactions that were more refractory to therapy [7].

In contrast, local urticarial reactions are common [1]. Desensitization injections for hay fever have resulted in occasional tender nodules lasting for several months or years [8,9]; these are thought to develop as a result of allergy to aluminium, as it is present in the lesions and patch tests may be positive [9,10]. Inflammatory nodules at injection sites, first developing several years later, have also been described [11]. Injections of mixtures of grass pollens, cereal pollens and dust-mite allergens have resulted in multiple cutaneous B-cell pseudolymphomas [12]. Polyarteritis nodosa [13], vasculitis [14,15] and serum sickness [16,17] have been described following hyposensitization therapy for allergy to pollen, house-dust mite and wasp venom. Cold urticaria developed during the course of hyposensitization to wasp venom [18].

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BCG vaccination

Vaccination with BCG causes a benign self-limiting lesion consisting of a small papule, pustule or ulcer, which heals to leave a small scar within weeks. Axillary lymphadenitis and abscesses occurred after vaccination of rural Haitian children [1], and disseminated BCG infection in children born to HIV-1-infected women [2]. Occasionally, local abscess formation may follow vaccination of strongly tuberculin-positive individuals, administration of too much vaccine, or injection of vaccine too deeply [3–5]. BCG abscesses may also rarely arise following needlestick injury in health-care professionals [6]. In Austria, where the Ministry of Health's recommendation is for all neonates to be vaccinated, the normal complication rate is 0.3–0.6%, with suppurative lymphadenitis, generalized lymphadenopathy and osteitis [7]. Following a change to a more virulent vaccine strain, this rate temporarily increased substantially, with 5% of 659 children vaccinated at the University Hospital, Innsbruck requiring surgical excision of suppurating lymph nodes [7]. Anaphylactoid reactions to BCG vaccine, probably as a result of immune complex reactions mediated by antibodies to dextran in the vaccine, have been reported [8]. A papulonecrotic type of vasculitis has been documented [9]. Dermatomyositis may occasionally be a complication [10].

BCG immunotherapy for malignant melanoma [11] has been associated with local ulceration [11,12], local recurrent erysipelas, keloid formation, influenza-like symptoms, lymphadenopathy, urticaria and angio-oedema, granulomatous hepatitis, arthritis [13] and reactivation of pulmonary tuberculosis. Widespread miliary granulomas were present in a patient with fatal disseminated infection following intralesional immunotherapy of cutaneous malignant melanoma [14].

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Cytokines

Cytokines are being increasingly used in the management of neoplastic and haematological disorders and AIDS, and in addition are starting to be used for the therapy of specific dermatological disorders; side effects have been reviewed [1]. Reactions range from minor injection-site reactions, pruritus and flushing to life-threatening autoimmune disorders, severe erythroderma or bullous skin reactions [2].

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Colony-stimulating factors

Recombinant haematopoietic colony-stimulating factors used in the treatment of haematological disorders are usually well tolerated, but may induce itching and erythema or lichenoid reactions [1] at the site of injection, thrombophlebitis with intravenous infusion, facial flushing and a transient maculopapular eruption, fever, chills, myalgias, arthralgia and bone pain, transient leukopenia, decreased appetite, nausea and mild elevation of transaminase levels [2]. Neutrophilic dermatoses have been recorded in children [3]. Two types of recombinant human granulocyte colony-stimulating factor are in use for neutropenia: one is a glycosylated natural product from mammalian cells, and the other a non-glycosylated form from *Escherichia coli*. A drug eruption may occur with either type without detectable antibodies; intradermal tests may be useful and there may not be cross-reactivity [4]. Both local reactions at the site of injection and diffuse maculopapular eruptions may be seen [4–7]. Local pustular reactions [8] or subcorneal pustular dermatosis [9] are documented. Intravenous recombinant granulocyte–macrophage colony-stimulating factor (GM-CSF) therapy for leukaemia resulted in a widespread confluent maculopapular eruption in three patients, associated with a dermal lymphocyte, macrophage and granulocyte infiltration, exocytosis, and keratinocyte ICAM-1 expression [10]. Of 23 patients with advanced malignancy treated with GM-CSF, nine had a cutaneous eruption characterized by local erythema and pruritus at the injection site, recall erythema at previous injection sites or a generalized maculopapular rash [11]. Other studies have reported widespread rashes [12,13], in one series manifested as annular erythematous papules and plaques on the extremities, becoming generalized and clearing with fine desquamation [13]. Recurrent exacerbation of acne [14], widespread folliculitis [15], toxic folliculitis [16] and a Sweet's syndrome-like rash [17–19] have been recorded. A capillary leak syndrome with pleural and pericardial effusions, ascites and large-vessel thrombosis has been noted only with high-dose GM-CSF therapy [20]. Necrotizing vasculitis developed at GM-CSF injection sites in one patient with white cell aplasia, but not in over 150 other neutropenic patients who received the drug [21]. However, vasculitis was reported in a large series [22]. Thrombotic and necrotizing panniculitis has been documented [23]. Psoriasis [24], and arthritis in Felty's syndrome with rheumatoid arthritis [25], have been reported to deteriorate.

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Interferon

Cutaneous reactions to recombinant IFN [1–12] given to patients with chronic hepatitis C, cancer or AIDS are frequent (5–10%) but usually of moderate degree. No adverse cutaneous side effects resulted from intralesional injection of IFN-γ in 10 patients treated for keloid scarring [13]. Most patients experience influenza-like symptoms following systemic therapy; reversible leukopenia and thrombocytopenia are recorded with higher dosage. Local reactions consist of erythema, eczema, epilation, or induration at injection sites or urticaria. More serious reactions include vesiculobullous reactions, vasculitis, necrosis, ulceration, alopecia and exacerbation of psoriasis. Skin ulceration or necrosis may be a serious problem with both IFN-α and IFN-β [7–12]. Raynaud's phenomenon and digital necrosis induced by IFN-α is recorded [14].

Of 63 patients treated with IFN-γ for prophylaxis of infection in chronic granulomatous disease, one had a severe cutaneous reaction (unspecified), and rashes or injection-site erythema or tenderness occurred in 17% and 14% of cases respectively [1]. Diffuse inflammatory lesions have occurred with IFN-α and ribavirin therapy for hepatitis C [15]. Transient, localized or disseminated oedematous, erythematous and/or papular changes, vesicles or petechiae were seen in six patients during intravenous IFN-α for chronic active hepatitis C, 5–14 days after starting therapy [2]. Eruptions disappeared in 10–14 days despite continuation of IFN-α; histology revealed upper dermal perivascular $CD4^+$ lymphoid infiltration and oedema, with endothelial cell but not keratinocyte ICAM-1 and E-selectin expression, suggesting a non-allergic mechanism.

Capillaritis is recorded with IFN-α [16], as is lichen planus [3,17]. Reactivation of oral herpes simplex and enhanced radiation toxicity have been recorded. IFN-α-2a for the treatment of cutaneous T-cell lymphoma has induced temporary alopecia [18]. In contrast, IFN-α therapy has caused increased eyelash and eyebrow growth [19], as well as straight hair [20]. Severe urticaria has been documented with IFN-α-1a [21] and mucinoses with IFN-α-1b [22]. Both IFN-α and IFN-α-1b have been associated with granulomatous or sarcoidal reactions [23–25]. IFN-α has caused hypertriglyceridaemia [26] and IFN-β has been related to squamous cell cancer following ulceration [27].

IFN-α used in the treatment of disseminated carcinoma [28,29] or intralesionally for viral warts [30], and IFN-β therapy for multiple sclerosis [11,31], have been reported to exacerbate or trigger onset of psoriasis; psoriatic arthritis has also been triggered by IFN-α [32] and IFN-γ [33], and Reiter's syndrome by IFN-α [34]. Psoriasis appeared at the site of subcutaneous injection of recombinant IFN-γ in patients with psoriatic arthritis [35], and at the site of intralesional injection in a patient receiving recombinant IFN-β for a basal cell carcinoma [36]. Exacerbation of underlying autoimmune disease is documented with IFN-α [37]. Neutralizing antibodies to recombinant IFN-α may be produced [38]. Systemic sclerosis has been associated with IFN-α [39]. Systemic LE has been recorded following IFN therapy of myelogenous leukaemia [40], and pemphigus vulgaris after IFN-β and IL-2 therapy for lymphoma [41].

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Interleukins

IL-1. Mucositis and an erythematous eruption with erosions in intertriginous areas and under occlusive tape have been documented [1].

IL-2. Immunotherapy with IL-2, either alone or in conjunction with lymphokine-activated killer cells, is used in the treatment of metastatic cancer; mild influenza-like symptoms are common. Cutaneous complications [2–8] include mucositis, macular erythema (principally restricted to the head, neck and upper chest), burning and pruritus (which resolves with mild desquamation), erythroderma and petechiae. Transient urticaria, necrotic lesions and blisters may be seen [8]. Type I hypersensitivity reactions, ranging from pruritus, erythema and oedema to hypotension, within hours of chemotherapy in patients previously treated with high-dose IL-2 have occurred [9]. A generalized capillary leak syndrome, with non-pitting oedema and diffuse pulmonary infiltrate on chest X-ray, is recorded [6] and is also documented with denileukin difitox, formed from the fusion of human IL-2 with diphtheria toxin [10]. Exacerbation of psoriasis (including erythroderma) has been described [2–6]. IL-2 treatment predisposes to acute hypersensitivity reactions to iodine-containing contrast media [6]. Glossitis, telogen effluvium, punctate superficial ulcers and erosions in scars may be seen. Erythema nodosum has been documented [11]. Local inflammatory painful nodules with a central multiloculated vesicle have occurred at the site of subcutaneous injections of IL-2 and IFN-α [12]. Linear IgA bullous dermatosis has been associated with IL-2 therapy [13]. TEN is a rare complication [14]. It is of interest that lymphocytes activated by IL-2 can non-specifically destroy keratinocytes *in vitro* [15].

Other side effects include hypothyroidism (antithyroid antibodies are present in 50% of patients), neurological and psychiatric disturbances, musculoskeletal disorders, impaired renal function, cardiovascular injuries, cholestasis, pancreatitis, anaemia, thrombocytopenia, lymphocytopenia and eosinophilia [6].

IL-3. Erythema and purpura at the site of injection, and urticaria [16] may be induced.

IL-4. Transient acantholytic dermatosis is recorded [17].

IL-6. Coalescent, erythematous, scaling macules and papules occurred [18].

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Stem cell factor

Human recombinant stem cell factor, a cytokine that acts on haematopoietic progenitor cells and which is used for human anaemic disorders and for speeding haematological recovery after chemotherapy, causes reversible hyperpigmentation at sites of injection; there are increases in melanocyte numbers, dendrite extension and melanin [1].

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Tumour necrosis factor

Subcutaneous or intramuscular administration of TNF for advanced malignancy is limited by local pain, erythema and swelling or frank ulceration, and intravenous infusion may cause hypotension [1].

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Inhibitors of tumour necrosis factor

Etanercept. This fusion protein, comprising the extracellular ligand-binding domain of the 75-kDa receptor for TNF-α and the constant domain of human IgG1, has been associated with injection-site reactions [1–3], follicular hyperkeratosis at distant sites and necrotic and purpuric reactions [3], urticaria [4], autoimmune rashes [5], leukocytoclastic vasculitis [6] and onset of cutaneous squamous cell cancer [7].

Infliximab. Various dermatological complications are recorded, including an atopic dermatitis-like rash [8], eczematid-like purpura [9], erythema multiforme and lichenoid reactions [10], and necrotizing fasciitis and sepsis [11].

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Monoclonal antibodies

Basiliximab. This IL-2 receptor monoclonal antibody has caused myalgia [1].

Cetuximab. Paronychia and aphthous ulcers [2,3], follicular papulopustules [4], and a facial acneiform follicular eruption [3] are recorded with this chimeric antiepidermal growth factor receptor antibody.

OKT3. Orthoclone OKT3, a murine monoclonal antibody directed against the CD3 subset of T lymphocytes, has been used as an immunosuppressive agent in renal transplant recipients, and has been anecdotally associated with anaphylaxis [5].

Rituximab. This murine–human chimeric antibody (IDEC-C2B8) has caused vasculitis and serum sickness [6,7].

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Miscellaneous drugs affecting the immune response

Diphencyprone

Diphencyprone [1] used for alopecia areata has resulted in urticaria [2,3] and erythema multiforme [4], and has been linked to the development of vitiligo [5–7]. Severe contact dermatitis reactions may be induced.

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Erythropoietin

This drug has caused a generalized eczematous reaction [1].

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Roquinimex

The incidence of graft-versus-host reactions is enhanced in patients treated with the cytokine inducer carboxamide–quinoline immunotherapeutic agent roquinimex (Linomide), used for post-transplantation immunotherapy in autologous bone marrow transplantation for acute and chronic myelogenous leukaemia [1,2]. Cutaneous graft-versus-host reactions were associated with eccrine sweat gland necrosis.

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Antihistamines

H_1 antihistamines

All traditional H_1 antagonists cause side effects [1–4], especially sedation, most marked with the aminoalkylether and phenothiazine groups. Dizziness, poor coordination, blurred vision and diplopia, as well as nervousness, insomnia and tremor may occur. In addition, atropine-like anticholinergic effects including dryness of mucous membranes, urinary retention, palpitations, agitation, increased intraocular pressure and gastrointestinal upset are seen. Phenothiazine-derived drugs may cause photosensitivity or cholestatic jaundice. The effects of nervous system depressants, such as alcohol, hypnotics, sedatives, analgesics and anxiolytics, may be potentiated. Decreased efficacy of drugs metabolized by the liver microsomal enzyme system, including oral anticoagulants, phenytoin and griseofulvin, may occur as a result of liver-enzyme induction by antihistamines. The newer antihistamines (e.g. terfenadine, astemizole, loratadine, cetirizine) are much less likely to cause sedation [1–4].

Terfenadine and astemizole rarely cause QT interval prolongation and torsade de pointes. Arrhythmias occur when metabolism of terfenadine is impaired, as with inhibition of the cytochrome P-450 isoform CYP 3A4 by ketoconazole, itraconazole and related imidazole antifungals, erythromycin, clarithromycin and related macrolide antibiotics, grapefruit juice, or liver disease [5–7]. Patients on terfenadine or astemizole should be instructed accordingly. The UK Committee on Safety of Medicines

withdrew terfenadine from over-the-counter sale, as did the US FDA. However, no increased risk of life-threatening ventricular arrhythmic events or cardiac arrest with terfenadine compared with over-the-counter antihistamines, ibuprofen or clemastine was found in one study [8].

True hypersensitivity reactions are rare. Fixed eruptions have been caused by thonzylamine and cyclizine [9], cetirizine [10], hydroxyzine [11] and loratadine [12]. Skin eruptions have been documented with terfenadine [13,14], including possible exacerbation of psoriasis [15]; alopecia has been reported rarely [16]. Cetirizine has been linked to maculopapular eruptions and precipitation of urticaria [17–20]. Lichenoid and subacute LE-like dermatoses are recorded with antihistamine therapy [21]. Hydroxyzine caused a systemic contact dermatitis in one case [22]. A pityriasis lichenoides et varioliformis acuta-like drug exanthem was reportedly caused by astemizole, with a positive challenge test [23]. Antihistamines are associated with atypical lymphoid hyperplasia, presenting as solitary or multiple nodules and plaques, or multiple papules, in some patients [24].

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H_2 antihistamines

Severe adverse reactions are rare with cimetidine, ranitidine, nizatidine and famotidine [1]. Gastrointestinal upset, headache, drowsiness, fatigue or muscular pain occur in fewer than 3% of patients. Confusion, dizziness, somnolence, gynaecomastia or galactorrhoea with increased prolactin levels (cimetidine and ranitidine only), impotence and loss of libido (with cimetidine), bone marrow depression, hepatitis, abnormal renal function or nephritis, arthralgia, myalgia, cardiac abnormalities, and minor or severe skin reactions occur in fewer than 1% of patients.

Cimetidine. Mucocutaneous reactions are rare in relation to the enormous worldwide use of this drug. Reported reactions include a seborrhoeic dermatitis-like rash [2] and asteatotic dermatitis [3], erythema annulare centrifugum [4], erythrosis [5], giant urticaria [6], transitory alopecia [7], erythema multiforme [8] and exfoliative dermatitis [9]. Other effects have included thrombocytopenia [10] and leukocytoclastic vasculitis [11]. Exacerbation of cutaneous LE [12] and SLE with granulocytopenia [13] are documented. Cimetidine binds to androgen receptors, thereby blocking the binding of dihydrotestosterone, and gynaecomastia and hypogonadism are now well-known side effects [14]. The drug augments cell-mediated immunity *in vitro* by blockade of H_2 receptors on T lymphocytes [15].

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Famotidine. This drug has been associated with the development of symptomatic dermographism [1], pruritic exanthem [2–4], contact eczema [4], leukocytoclastic vasculitis [5] and TEN.

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Ranitidine. Urticaria [1] and anaphylaxis [2] are recorded, as are allergic dermatitis and allergic contact dermatitis [3,4]. Immune complex-mediated rashes [5], lichenoid eruptions [6] and photosensitivity with UVA sensitivity on monochromator light testing [7] have been documented, as has cholestatic hepatitis [8]. This drug has a less marked effect on androgen receptors than cimetidine, but gynaecomastia has occurred [9].

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Leukotriene receptor antagonists

Montelukast. This drug for asthma, occasionally used in urticaria, has been associated with cutaneous lesions of Churg–Strauss syndrome [1].

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Injections, infusions and procedures

Radiographic contrast media and radiopharmaceuticals

Radiographic contrast media

Reactions to radiographic contrast media were previously reported to occur in about 4–8% of cases; severe reactions occurred in 1 in 1000 administrations, and occasionally fatal anaphylactoid reactions developed (1 in 3000 for intravenous cholangiograms and between 1 in 10 000 and 1 in 100 000 for intravenous urography) [1–3]. Although IgE-mediated mechanisms may be involved [4], the vast majority of contrast reactions are not due to iodine allergy but rather to non-immunological release of mast cell mediators or to direct complement activation [5,6]. The risk of severe reactions is increased in atopics, asthmatics, those taking β-blockers, and with higher doses of contrast media; up to 40% of patients with a previous reaction may develop a recurrence [7,8].

Newer low-osmolality radiocontrast media are associated with fewer reactions [8–14], for example administration of iohexol in 50 660 patients undergoing excretory urography resulted in a frequency of adverse reactions of any type of 2.1% [9]. In another series, there was a 7.0% incidence of mild adverse reactions to low-osmolar iodine contrast medium in 4550 radiological procedures including computed tomography (CT), intravenous urography, arteriography, venography and myelography [12]. There were only two cases of severe anaphylactoid reactions during 783 consecutive cases undergoing voiding cystourethrography or retrograde pyelography [14]. The incidence of contrast media complications in the catheterization laboratory is 0.23%, with one death per 55 000 [15].

Low-osmolality radiocontrast media (e.g. iohexol or iopamidol) should be the contrast media of choice for patients with a prior immediate generalized reaction to conventional contrast media; in addition, patients should receive H_1 antihistamines and corticosteroid prophylaxis therapy [8,13,15]. However, although in one study the relative risk for all adverse drug reactions was three to

six times higher for ionic vs. non-ionic contrast media [16], in another study mortality was not lower with the newer low-osmolar media than with the older high-osmolar media [17]. In this latter large study, the overall mortality was 13 per million intravenous injections of radiocontrast media, rising to 35 per million in those over 65 years of age [17]. A further study in the USA found that in a clinical trial comparing the safety of low- vs. high-osmolality radiologic contrast media in patients who underwent either cardiac angiography or contrast-enhanced body CT, 19% of 1004 patients had at least one adverse reaction [18]. The mean cost per patient of treating adverse reactions was $459 (range $0–39 057).

In addition to immediate reactions, widespread erythema and oedema at 6 h, reaching a maximum at 9–12 h, followed intravenous injection of a CT contrast medium (iotrolan) [19]. Fixed drug eruptions have been recorded with iopamidol and iomeprol [20,21]. Mild to moderate delayed allergy-like reactions to contrast media of the maculopapular exanthematous and urticarial/angio-oedematous types have been reported in 0.5–2% of recipients [22]. Isolated cases of reticulate purpura [23], bullous lichen planus [24], iododerma [25], vasculitis [26] and erythrodermic psoriasis [27] have been documented. There has been a single case report of fatal TEN following second exposure to diatrizoate solution for excretory pyelography [28].

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Radiopharmaceuticals

The reported incidence of reactions to agents used in nuclear medicine is low; these usually take the form of immediate urticaria or angio-oedema [1–3]. Urticarial or anaphylactic reactions to technetium (^{99m}Tc) sulphur colloid and ^{99m}Tc human albumin microspheres together accounted for 50% of reported reactions [2]. The bone-scanning agent ^{99m}Tc methylene diphosphonate produces a delayed-onset erythematous pruritic eruption within 4–24 h [4].

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Halides

Bromides

Bromides have a long half-life and are excreted slowly by the kidney; bromism may develop in patients with impaired renal function, and eruptions may not develop until as much as 2 months after the drug has been discontinued. Acneiform and vegetating lesions occur more often, and bullae less frequently, than with iodism [1,2]. Vegetating bromoderma presents as single or multiple papillomatous nodules or plaques, studded with small pustules, on the face or limbs. Bromoderma tuberosum has been caused by anticonvulsive treatment with potassium bromide [3]. Bromism is also characterized by weakness, restlessness, headache, ataxia and personality changes [2].

Iodides

Serious and even fatal reactions of anaphylactic type have been caused by radiograpic contrast media containing organic iodine [4]. Iodism, nasal congestion and conjunctivitis, often accompanied by an exanthematic eruption, may be associated with a wide variety of systemic symptoms [5,6]. Prolonged administration of small doses of iodide, as in many cough mixtures, may provoke eruptions with or without mucosal or systemic symptoms. Lesions may first develop some days after the drug is discontinued. The following may occur: urticaria, an acneiform rash, papulopustular lesions, nodules, anthracoid or carbuncular lesions, or clear or haemorrhagic bullae on the face, forearms, neck and flexures or on the buccal mucosa [6]. If the iodine is continued, the bullae may be replaced by vegetating masses, which simulate pemphigus vegetans or a granulomatous infection [7]. Iododerma has developed after administration of oral [8] and intravenous [9,10] radiographic contrast media, and during thyroid protection treatment [11]. Iododerma seems more frequent in patients with renal failure, and may be accompanied by leukocytoclastic vasculitis [2]. The eruption recurs within days of readministration in a sensitized individual [12]. Cell-mediated [5] and 'hyperinflammatory' [13] mechanisms have been postulated. Vegetating iododerma may be an idiosyncratic response that is commoner in patients with polyarteritis nodosa or paraproteinaemia [14]. Fixed eruptions occur rarely [15]. Generalized pustular psoriasis has been reportedly provoked by potassium iodide [16].

Histology of bromoderma and iododerma

In bromoderma, verrucous pseudoepitheliomatous hyperplasia is associated with abscesses containing neutrophils and eosinophils in the epidermis, and with a dense dermal infiltrate initially consisting mainly of neutrophils and eosinophils and later containing many lymphocytes, plasma cells and histiocytes. The abundant dilated blood vessels may show endothelial proliferation. In iododermas, ulceration is more marked, but there is usually less epithelial hyperplasia. Both conditions must be differentiated from blastomycosis and coccidioidomycosis, and from pemphigus vegetans [17].

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Agents used in general anaesthesia

Neuromuscular blocking agents, skeletal muscle relaxants and general anaesthetics

The incidence of life-threatening anaphylactic or anaphylactoid reactions during anaesthesia has been variously reported to occur in 1 in 1000 to 1 in 20 000, and minor reactions probably occur in more than 1% of cases; neuromuscular blocking agents are the triggering agents in 50–69% of these reactions, with latex being less frequently incriminated (about 12%) [1–10]. The mortality rate in anaphylactic reactions to drugs used in general anaesthesia is between 4 and 6% [8]. Reactions were most likely with suxamethonium and gallamine, then D-tubocurarine and alcuronium, and least likely with pancuronium and vecuronium [3,6,9]; in another study, succinylcholine and rocuronium were most frequently incriminated [10]. Mucocutaneous manifestations including erythema, urticaria

and angio-oedema are reported in up to 80% of reactions, but may only be recognized after the acute phase has passed. Reactions are more frequent in women and in atopic patients. Proposed mechanisms for anaphylactic reactions include type I (IgE antibody-mediated) hypersensitivity [9,11–13], with antibodies persisting for up to 29 years [12], and direct histamine release. Only one reaction in three is likely to be IgE-mediated (type I) anaphylaxis, but non-immune reactions are no less hazardous than type I reactions [9]. Cross-reactivity is widespread with most of the drugs but is least with pancuronium. It has been suggested that pancuronium should be used where muscle relaxation during anaesthesia is essential but sensitivity to another relaxant exists [3], although others have questioned the safety of this procedure [7]. IgE-dependent sensitivity to thiopental may result in anaphylactic reactions [5].

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Local anaesthetic agents

Local anaesthetics may cause both immediate anaphylactic reactions and contact dermatitis [1–10]. True allergic reactions caused by local anaesthetics are extremely rare [9,11]; more often, the allergic response is caused by a metabolite, preservative or unrelated substance. Acute anaphylactic reactions are uncommon, but are probably less likely to occur when amide linkage agents are used [4,5]. Necrosis of the fingertip has followed local injection for nail extraction [12]. Dizziness and confusion due to systemic absorption followed repeated application of topical lidocaine (lignocaine) [13]. Severe lidocaine intoxication with progressive neurological and psychiatric abnormalities and cardiorespiratory arrest occurred following topical application to painful ulcerated areas in a patient with cutaneous T-cell lymphoma [14].

Tetracaine (amethocaine). Tetracaine in the form of a self-adhesive patch caused slight or moderate erythema at the site of application in 26% of patients, and slight oedema in 5% [15].

EMLA cream (proprietary name). A eutectic mixture of prilocaine and lidocaine in a cream base (EMLA cream) has been associated with methaemoglobinaemia [16–18]; two metabolites of prilocaine, namely 4-hydroxy-2-methylaniline and 2-methylaniline (*o*-toluidine), have been incriminated. A 3-month-old infant became cyanosed after application of 5 g, but concomitant sulphonamide therapy may have made a contribution [16]. Small but significant increases in methaemoglobin levels have been reported in children aged 1–6 years following routine administration of 5 g before surgery, and these may persist for at least 24 h [17], so it is recommended that the minimum effective dose be used in children requiring daily application. Blanching following application of EMLA cream is common [19]. Hyperpigmentation is recorded [20]. Contact dermatitis can arise to both lidocaine and prilocaine [21–23].

Bupivacaine. A delayed hypersensitivity rash may occur after injection of arthroscopy portals with bupivacaine [24].

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Infusions and injections

Intravenous infusion

Pain, oedema, induration and thrombophlebitis are well-recognized complications [1–4]. Localized bullous eruptions following infusion of commonly used non-vesicant fluids, such as saline, have been described [5]. Extravasation was reported to occur in 11% of 16 380 administrations to children monitored over a 6-month period [6]. Skin necrosis following intravenous infusion of chemotherapeutic agents occurs in up to 6% of patients [1,3,5–9].

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Blood transfusion

Urticaria occurs in about 1% of transfusions [1], and may be the result of allergy to soluble proteins in donor plasma. Post-transfusion purpura may rarely occur as a result of profound thrombocytopenia about 1 week after transfusion, and is associated with antiplatelet alloantibodies. Other potential side effects include transmission of infectious diseases, including syphilis, hepatitis B and HIV-related syndromes (AIDS).

Graft-versus-host disease may develop following transfusion of unirradiated blood in immunosuppressed patients [2–8], including those with malignancies [2], and infants with severe congenital immunodeficiency [3]. Isolated reports of fatal transfusion-associated graft-versus-host disease in presumed immunocompetent hosts receiving fresh unirradiated blood have been reported [9–11]. This paradoxical situation may be partly explained by situations in which recipients heterozygous for a given MHC haplotype receive a transfusion from a donor homozygous for this haplotype, as the recipient would not react to the donor haplotype but the donor lymphocytes would react to the non-identical recipient haplotype [8]. Thus, some recipients of non-irradiated blood from their offspring may be at risk of developing graft-versus-host disease. An acute fatal illness, characterized by fever, diffuse erythematous rash and progressive leukopenia, has been described in Japanese patients 10 days after surgical operation and has been termed 'postoperative erythroderma' [12]. Histologically, scattered single cell epidermal cell eosinophilic necrosis, satellite cell necrosis, basal cell liquefaction degeneration and a scanty dermal infiltrate may be seen; the reaction is compatible with an acute graft-versus-host reaction following blood transfusion [12].

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Hydroxyethyl starch

Hydroxyethyl starch (hetastarch) is used as a plasma expander for hypovolaemia, to prime cardiopulmonary bypass machines, as a sedimenting agent to increase the yield of granulocytes during leukapheresis, and to improve microcirculation as in the treatment of sudden deafness. It has been implicated in the development of lichen planus [1], and severe generalized pruritus in up to 32% of recipients, beginning 2 weeks after exposure and taking up to 2 years to settle [2–6].

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Fluorescein

A psoriasiform eruption followed parenteral administration for fluorescein angiography [1].

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Renal dialysis

Dermatological complications of renal dialysis have been reviewed [1,2]. These include marked premature ageing, hyperpigmentation, xeroderma, decreased sebaceous and sweat gland secretion, Raynaud's syndrome, generalized pruritus and carpal tunnel syndrome due to amyloid β deposition [1]. Extravasation, phlebitis and bacterial infection of the cannula, with resulting septicaemia, may occur and are related to the site of insertion of the cannula into the arteriovenous fistula. A bullous dermatosis of haemodialysis has been described [2,3]. This resembles porphyria clinically and histologically, and porphyrins may be elevated [3], although cases with pseudoporphyria in which there are no abnormalities of porphyrin metabolism have also been documented [2]. Two-thirds of patients with dialysis-associated anaphylaxis have IgE antibodies to ethylene oxide/human serum albumin [4]. Allergic contact dermatitis due to rubber chemicals in the haemodialysis equipment may be seen around the arteriovenous shunt [5]. Porokeratosis localized to the access region for haemodialysis has also been reported [6].

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Necrosis from intramuscular injections

Severe painful local necrosis at the site of an injected medicament (embolia cutis medicamentosa, also known as Nicolau's syndrome) may follow intramuscular therapeutic injections and was originally described with bismuth. It occurs particularly with preparations containing corticosteroids, local anaesthetics, antirheumatic drugs and antihistamines; more rarely, chlorpromazine, penicillin, phenobarbital and sulphonamides have been implicated [1,2]. The condition has also followed sclerotherapy [3]. Clinically, stellate erythema and infiltration are followed by central deep necrosis that heals with scarring.

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Polidocanol

The sclerosing solution polidocanol is said to cause allergic reactions in up to 0.06% of cases; systemic allergic reactions may be more common than previously recognized [1].

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Drugs affecting metabolism or gastrointestinal function

Hypoglycaemic drugs

Dermatological aspects of the oral hypoglycaemic drugs have been reviewed [1–4].

Biguanides

Rashes are much less frequent with metformin and phenformin than with sulphonylureas. Transient erythemas, pruritus and urticaria have been noted.

Sulphonylureas

Chlorpropamide and tolbutamide are most often prescribed, and both can give rise to toxic or allergic reactions. Angio-oedema with glibornuride, urticaria with glibenclamide and a bullous dermatitis with carbutamide have been described [5]; there was no cross-reactivity between first- and second-generation sulphonylureas.

Chlorpropamide. Eruptions occur in 2–3% of patients on chlorpropamide [2]. These include maculopapular rashes, photosensitivity [6], erythema annulare, Stevens–Johnson syndrome [7], erythema nodosum [1], lichenoid eruptions [8,9], purpura and exfoliative dermatitis [10]. Porphyria has been provoked [11]. A disulfiram-like effect, with flushing of the face, headache and palpitations after taking alcohol, occurs in up to 30% of patients [12,13]. The fact that the flush is blocked by naloxone suggests that opioids may be involved in the response.

Glibenclamide. Bullae and cholestasis have occurred together [14].

Glipizide. Pigmented purpuric eruption is documented [15].

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Lipid-lowering drugs

Acipimox

This nicotinic acid analogue causes less prostaglandin-mediated flushing and itching than nicotinic acid [1].

Clofibrate

Erythema multiforme and a variety of other erythematous rashes have been described [2].

Gemfibrozil

This lipid-lowering drug, which mainly lowers triglycerides, has been associated with exacerbation of psoriasis [3,4].

Statins

The lipid-lowering drugs lovastatin, simvastatin and pravastatin can cause eczema [4,5]; these drugs block an early step in cholesterol biosynthesis by inhibiting the activity of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. Simvastatin has caused a lichenoid eruption with skin and mucosal involvement [6,7], and chronic actinic dermatitis [8]. Pravastatin has also been associated with a lichenoid rash [9]. Atorvastatin has caused linear IgA bullous dermatosis [10] and TEN [11].

Triparanol and diazacholesterol

These drugs inhibit a late step in cholesterol biosynthesis (Δ^{24} sterol reductase) and can induce ichthyosis or palmoplantar hyperkeratosis [4].

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Drugs for gastrointestinal ulceration

Omeprazole

This proton pump inhibitor, a substituted benzimidazole, has gained widespread use in the treatment of gastric and duodenal ulceration and reflux oesophagitis. Adverse events with the drug are rare and involve mainly the gastrointestinal and central nervous systems, with diarrhoea, headache and dizziness, and confusion in the elderly, moderate elevation of aminotransferases and possible leukopenia [1–3]. The prevalence of cutaneous reactions to omeprazole is approximately 0.5–1.5% [1–4]. A variety of eruptions are recorded, including angio-oedema and urticaria [4,5], anaphylaxis [6], maculopapular rashes, lichen planus [7,8], pityriasiform eruption [9], erythema multiforme and erythroderma [10], exfoliative dermatitis [11], bullous eruption [12] and photosensitivity. Gynaecomastia is recorded [13].

Tripotassium dicitratobismuthate (De-Nol)

The Netherlands Centre for Monitoring of Adverse Reactions to Drugs has received several reports of skin reactions, on average 2 days after starting treatment, including maculopapular exanthema, angio-oedema and erythema [14].

Bismuth subsalicylate (PeptoBismol)

Black granules at follicular orifices have been reported [15]. Blue linear pigmentation of the soft palate, oral mucosa and vagina, ulcerative stomatitis, generalized pigmentation, dermatitis and erythroderma are recorded.

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Laxatives

Side effects of laxatives have been reviewed [1].

Dantron (danthron)

A highly characteristic irritant erythema of the buttocks and thighs has been observed in patients who are partially incontinent. The erythema results from skin soiling by faecal matter containing an anthralin (dithranol)-like breakdown product [2].

Phenolphthalein

Fixed eruptions are well known [3–5]. Bullous erythema multiforme and an LE-like reaction are documented.

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Miscellaneous drugs

Food and drug additives

Dermatological complications of food and drug additives

have been reviewed [1–14]. These substances have been implicated in the causation of urticaria [4–7], anaphylaxis, purpura and vasculitis [8–12]. However, one study suggested that common food additives are seldom if ever of significance in urticaria [11]. In another study, only 0.63% of food additive provocation tests resulted in exacerbation in 1110 patients with urticaria; tests were again not positive on re-provocation [13]. The prevalence of adverse reactions to food additives is estimated to be 0.03–0.23% [15]. The necessity for double-blind, placebo-controlled testing to substantiate alleged food additive allergy has been emphasized [16]. Information about excipients ('inert ingredients') has been reported in a study that examined the sweeteners, flavourings, dyes and preservatives present in chewable and liquid preparations of 102 over-the-counter and prescription brands of antidiarrhoeal, cough and cold, antihistamine/decongestant, analgesic/antipyretic and liquid theophylline medications [17]. An average preparation contained two sweeteners, primarily saccharin and sucrose, followed by sorbitol, glucose, fructose and others. The type of flavouring was not specified in 36 of the 102 preparations; cherry was the most common flavouring, followed by vanilla and lemon. Twenty-one different dyes and colouring agents were used; red dye no. 40 was the most common, followed by yellow no. 6. Sodium benzoate and methylparabens were the commonest of eight preservatives used. Mandatory labelling of excipients in all pharmaceutical preparations is the only way that physicians and patients can be fully informed [17]. It is important to appreciate that peanut oil, to which patients may be strongly allergic, is found in certain medications [18]. Caffeine in coffee and cola beverages caused urticaria in a 10-year-old child, confirmed by prick test and oral challenge test with caffeine [19].

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Colouring agents

Colourings in food and medications (including some antihistamines), such as tartrazine, sunset yellow and other azo dyes, have been reported to cause adverse reactions [1,2], including urticaria [3,4] or vasculitis [5,6].

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Flavouring agents

Aspartame. Aspartame, a synthetic dipeptide composed of aspartic acid and the methyl ester of phenylalanine and used under the trade name of NutraSweet (G.D. Searle & Co., Skokie, Illinois, USA) as a low-calorie artificial sweetener, has been associated with relatively few adverse side effects despite its widespread use [1]. Cutaneous side effects reported include urticaria, angio-oedema and other nondescript 'rashes' [2], granulomatous septal panniculitis [3] and lobular panniculitis [4]. However, in a recent study of patients with a history of aspartame sensitivity, it was not possible to identify any subject with a clearly reproducible adverse reaction [5]. Similarly, a multicentre, placebo-controlled, challenge study showed that aspartame and its conversion products are no more likely than placebo to cause urticaria and/or angio-oedema reactions in subjects with a history consistent with hypersensitivity to aspartame [6].

Cyclamates. Cyclamates, used as sweeteners in soft drinks, have caused photosensitivity [7].

Quinine. Quinine in tonic water and other bitter drinks may cause fixed eruptions [8].

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Preservatives

The antioxidant food preservatives butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT) have been reported to exacerbate chronic urticaria [1]. Sodium benzoate has been associated with urticaria, angio-oedema, asthma and rarely anaphylaxis [2]. Parabens used as preservatives may also cause urticaria [3].

Sulphiting agents are commonly used in parenteral emergency drugs, including epinephrine (adrenaline), dexamethasone, dobutamine, dopamine, norepinephrine (noradrenaline), phenylephrine, procainamide and physostigmine [4]. Published anaphylactic or asthmatic reactions have been associated with sulphited local anaesthetics, gentamicin, metoclopramide, doxycycline and vitamin B complex. The reactions have a rapid onset and do not always coincide with a positive oral challenge, although patients with a history of positive oral challenge to 5–10 mg of sulphite may be at increased risk of developing a reaction to parenteral sulphites. Sulphites added as antioxidant preservatives may provoke urticaria, asthma, anaphylaxis and shock [4–10], as well as urticarial vasculitis [11]. Intolerance due to metabisulphite as an antioxidant in a dental anaesthetic has led to angio-oedema; patch tests were positive [12]. Basophil activation induced by sulphites may be IgE dependent [13]. It has been claimed that there is a high specificity of patch testing in the diagnosis of patients with sulphite sensitivity [14].

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Miscellaneous food additives

Agricultural or veterinary chemicals may leave residues in animals and plants used as human food, for example penicillin in milk or meat, with resultant urticaria [1,2]. The exposure of a rural Turkish population to flour contaminated with hexachlorobenzene induced an outbreak of cutaneous porphyria [3]. Contaminated rapeseed cooking oil containing acetanilide resulted in the Spanish 'toxic oil syndrome'; the central feature of the illness was a toxic pneumonitis, but fixed rashes and scleroderma-like changes in survivors were seen [4–6]. Outbreaks of atypical erythema multiforme and other exanthems in the Netherlands were attributed to an additive in margarine [7,8]. The high arsenic content of a rural water supply in Taiwan caused arsenicism [9]. Chemicals added to tobacco, for example menthol in cigarettes, have caused urticaria [10]. *N*-Nitroso compounds, which are known to be carcinogenic in animals, occur in food products and certain alcoholic drinks, but there is no direct proof as yet of a causal role in human disease [11].

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Herbal remedies, homeopathy and naturopathy (alternative therapy)

Adverse cutaneous effects of herbal drugs have been reviewed [1–4]. Virtually all herbal remedies may cause allergic reactions, and several cause photosensitization. Some herbal medicines, particularly Ayurvedic remedies, contain arsenic or mercury that may produce typical skin lesions. Other popular remedies that can cause dermatological side effects include St John's wort, kava, aloe vera, eucalyptus, camphor, henna and yohimbine. In addition, some herbal treatments used specifically for dermatological conditions, for example Chinese oral herbal remedies for atopic eczema, have been reported to cause systemic adverse effects. There is concern that some agents, notably Chinese herbal creams, have been shown repeatedly to be adulterated with corticosteroids [5,6].

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Chinese herbal medicine

Adverse effects of Chinese herbal medicines, including life-threatening 'dazao'-induced angio-oedema and liquorice-induced hypokalaemic periodic paralysis, accounted for 0.2% of medical admissions to a hospital in Hong Kong over an 8-month period [1]. Herbal poisoning in Hong Kong, Taipei and Kuala Lumpur has occurred as a result of addition of adulterants (*Podophyllum emodi*) or erroneous substitutes (*Datura metel*) [2]. A fatality due to total liver necrosis associated with ingestion of Chinese herbal medicines is believed to have occurred because the patient prepared a decoction from a herbal mixture containing *Eurysolen gracilis* Prain (Labiatae), a herb not used in Chinese medicine [3]. A multisystem illness developed in a patient after ingestion of Chinese herbal medicines containing the potentially toxic compounds benzaldehyde, cinnamoyl alcohol and ephedrine [4]. Some Chinese patent medicines contain mercurial ingredients, cinnabar (red mercuric sulphide) and calomel (mercurous chloride) [5]. Alopecia and sensory polyneuropathy from thallium in a Chinese herbal medication has been reported [6]. Cutaneous aspects of thallium poisoning include palmar and plantar scaling, acneiform lesions on the face and diffuse alopecia, accompanied by acute nervous system and gastrointestinal symptoms [7]. Chinese herbal medicine may contain camouflaged prescription anti-inflammatory drugs, corticosteroids and lead [8], and some practitioners of Chinese medicine supply 'herbal creams' that actually contain potent topical steroid ointments [9,10]. Fixed drug eruption has been documented with use of a Chinese traditional herbal medicine containing mainly pseudoephedrine and ephedrine [11].

There are major concerns about hepatotoxicity [12–16] and nephrotoxicity [17–23] with Chinese herbal medicine. In one case, hepatotoxicity was associated with ingestion of the Chinese herbal product jin bu huan anodyne tablets (*Lycopodium serratum*) [14]. A rapidly progressive fibrosing interstitial nephritis developed in young women who followed the same slimming regimen containing two Chinese herbs (*Stephania tetrandra* and *Magnolia officinalis*) [17–19]. The known carcinogen, aristolochic acid, has been suspected in some cases of nephropathy [19,20]. Urothelial malignancy has supervened [22]. Acquired Fanconi's syndrome was induced by a mixture of Chinese crude drugs [23].

The need for correct identification of herbs in herbal poisoning [24], and for monitoring of the safety of herbal medicines [25], has been emphasized. Greater awareness of their toxicity is required [26,27]. Special licensing of herbal remedies exists in Germany, France and Australia and has been advocated in the UK [28].

Analgesic and anti-inflammatory Chinese medicinal materials, especially those containing fragrance, may cause contact sensitization and can cause systemic contact dermatitis [29,30]. Erythema multiforme [30], exanthem [31] and erythroderma [32] are described. Fever with oedematous erythema was caused by a decoction of the crude drug Boi of Kampo (Sino-Japanese traditional) medicine for the alleviation of arthralgia; oral ingestion tests incriminated the constituent sinomenine [33].

A 'tea' prepared from a decoction of herbs has been reported to be of benefit in eczema [34,35]. The decoction contains paenol (2'-hydroxy-4'-methoxyacetophenone), which is known to have platelet antiaggregatory, analgesic and antipyretic properties [36]. Hepatotoxicity was described in a 9-year-old girl who consumed a Chinese herbal tea for 6 months [37] and was reported in a further patient [38]. Reversible abnormal liver function tests have been reported in two children receiving Chinese herbal therapy (Zemaphyte) [39]. Toxicology screening in a

group of adults on Zemaphyte for 1 year revealed no abnormalities in haematological or biochemical parameters; transient nausea and abdominal distension, with a mild laxative effect, was noted in about one-third of patients [40]. Dilated cardiomyopathy followed therapy of atopic eczema with Chinese herbal medicine [41].

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Kava dermopathy

The kava plant, a member of the black-pepper family, is used ceremonially by many traditional societies of the southern Pacific in the form of an intoxicant beverage prepared from roots to induce relaxation and sociability and promote sleep. Herbal drugs containing kava have been used for insomnia, nervousness and depression. A reversible ichthyosiform kava dermopathy resulted from excessive use of kava [1,2]. Systemic contact-type dermatitis occurred after oral administration of kava extract [2].

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Homeopathic drugs

Cases of erythroderma, confluent urticaria and anaphylaxis have been reported following homeopathic medication [1]. Treatment of a diaper dermatitis and mild respiratory and enteral infections with the homeopathic mercurial medicine Mercurius 6a (cinnabar dilute $1 \times 10(6)$) was followed by dissemination of the dermatitis, irritability and albuminuria [2]. Baboon syndrome was associated with use of a homeopathic medicine containing mercury [3].

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Naturopathy

Bizarre and unpredictable cutaneous reactions may follow topical application or ingestion of naturally occurring substances. A curious gyrate erythematous eruption was seen in a patient following local application of onion rings as a home remedy for arthralgia [1]. Substantial amounts of psoralen may be absorbed from vegetables; a patient who consumed a large quantity of celery root (*Apium graveolens*) 1 h before a visit to a suntan parlour developed a severe generalized phototoxic reaction [2]. A bullous phototoxic reaction developed after exposure to aerosolized bergamot aromatherapy oil in a sauna and subsequent UVA radiation in a tanning salon [3]. Phytophotodermatitis followed application of *Citrus hystrix* as a mosquito repellent [4]. Phototoxicity has been reported from herbal remedies for vitiligo incorporating powdered seeds of *Psoralea corylifolia*, which contains psoralen, isopsoralen and psoralidin [5].

Contact sensitization has been caused by alternative topical medicaments containing plant extracts [6–9], including tea-tree oil [7,8], which has also caused systemic contact dermatitis [7]; allergic airborne contact dermatitis has been caused by benzaldehyde, eucalyptus oil, laurel oil, pomerance flower oil, lavender oil, rosewood oil and jasmine oil used for aromatherapy [9]. Application of henna as a decoration may cause allergic contact eczema [10]. A diffuse morbilliform eruption occurred with a *Gingko biloba* supplement [11], recurrent erythema nodosum with *Echinacea* therapy [12], erythroderma with intake of St John's wort (*Hypericum perforatum*) [13], and tea-tree oil dermatitis has been associated with linear IgA disease [14].

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Miscellaneous

Canthaxanthin, a synthetic non-provitamin A carotenoid deposited in epidermis and subcutaneous fat, caused fatal aplastic anaemia when ingested to promote tanning [1].

REFERENCE

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Industrial and other exposure to chemicals

For a discussion of sclerodermatous reactions to environmental agents, see p. 73.44. A form of fluoride toxicity occurred due to industrial poisoning in the Italian town of Chizzolo, resulting in pinkish brown, round or oval macules seen in hundreds of the local population [1]. Similar small outbreaks have occurred in North America [2]. Exfoliative dermatitis has been recorded with trichloroethylene [3]. Occupational exposure to trichloroethylene has also caused Stevens–Johnson syndrome [4].

Patients exposed to dioxin after an industrial accident at Seveso, Italy developed early irritative lesions, comprising erythema and oedema of exposed areas, vesicobullous and necrotic lesions of the palms and fingertips, and papulonodular lesions; later lesions were those of chloracne [5]. Contamination of rice-bran cooking oil with polychlorinated biphenyls in Taiwan resulted in chloracne, and congenital abnormalities in offspring [6].

Pruritus, urticaria, and discoid and diffuse eczema may occur following the use of brominated disinfectant compounds such as 1-bromo-3-chlor-5,5-dimethylhydantoin (Di-halo, Aquabrome) in public swimming pools [7]. Accidental occupational exposure to high concentrations of methyl bromide during a fumigation procedure resulted in erythema with multiple vesicles and large bullae, with predilection for moist flexures and pressure areas [8]. Idiopathic thrombocytopenic purpura has been associated with industrial exposure to wood preservatives [9], turpentine [10], and to insecticides such as chlordane and

heptachlor [11]. Reversible alopecia occurred with occupational exposure to borax-containing solutions [12].

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Local and systemic effects of topical applications

Many topical therapeutic agents may cause serious or even dangerous systemic side effects if absorbed in sufficient quantity; such absorption may be facilitated through diseased skin, and with use of newer vehicles or occlusive polythene dressings. The risk of serious systemic effects is greatest in infancy and in the old and frail. The quantity absorbed in relation to body weight is greatest in infancy, when the surface area is relatively greater; moreover, neonatal skin is more permeable. Most dangerous or fatal reactions have occurred because either the physician was unaware of the potential hazard or the patient continued self-treatment without medical supervision.

Topical therapy

Anthralin (dithranol)

Topical anthralin, used in the therapy of stable plaque psoriasis, is well known for causing erythema, irritation and a sensation of burning in normal skin; it stains the skin and clothing [1]. Application of 10% triethanolamine following short-contact anthralin treatment has been reported to inhibit anthralin-induced inflammation without preventing the therapeutic effect [2]. Allergic contact dermatitis to anthralin is very rare. The natural and synthetic anthranols have toxic effects on liver, intestines and the central nervous system, but systemic toxicity in humans under therapeutic conditions has not been established [3].

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Boric acid

Poisoning has usually occurred in infants treated for napkin eruptions. Almost all cases have been caused by the use of boric ointments or lotions. However, use of borated talc proved fatal in one infant [1]. Wet boric dressings caused the death of an adult woman [2].

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Calcipotriol

This vitamin D_3 analogue has been reported to cause transient local irritation, and facial or perioral dermatitis [1]. Contact allergy is recorded [2]. Topical application of calcipotriol for 5 weeks to a mean of 16% of the body surface of psoriatic patients did not result in detectable systemic alteration of calcium metabolism [3]. The manufacturer's data sheet (Leo Laboratories) states that increased serum calcium may occur with application in daily doses of 50–100 g of the 50 μg/g ointment. Severe symptomatic hypercalcaemia developed after application of about 200 g of the ointment over 1 week to exfoliative psoriasis covering 40% of the body surface [4]. It is recommended that treatment be confined to stable mild to moderate psoriasis, and that the recommended dose of 100 g/week should not be exceeded. Hyperpigmentation occurred at the site of topical calcipotriol application in two patients receiving photochemotherapy [5].

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Coal tar

Coal tar vapour inhalation precipitated severe symptomatic bronchoconstriction in an atopic asthmatic subject following application of coal-tar bandages for treatment of eczema, confirmed by challenge [1].

REFERENCE

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Chlorhexidine gluconate (Hibitane)

Urticaria, dyspnoea and anaphylactic shock have occurred following topical application as a disinfectant [1,2], as have contact urticaria, photosensitive dermatitis [3] and deafness.

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Dequalinium chloride

Necrotic lesions have occurred following its use in the treatment of balanitis [1].

REFERENCE

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Dimethylsulfoxide

Topical application can cause erythema, pruritus and urticaria, but systemic reactions are very rare; a generalized contact dermatitis-like reaction followed intravesical instillation in a sensitized individual [1].

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Doxepin

Doxepin cream causes allergic contact dermatitis and systemic contact dermatitis [1,2].

REFERENCES

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Formaldehyde

Industrial exposure is recognized to be a health hazard, and a threshold limit of 2 ppm is allowed in the UK and the USA [1]. Irritant or allergic dermatitis is common in exposed workers [2]. Systemic symptoms including breathlessness, headache and drowsiness have been attributed to prolonged exposure to very low levels in the home [3].

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Lindane (g-benzene hexachloride)

Lindane therapy for scabies has potential toxicity, which includes neurotoxicity with convulsions, especially in children [1–7]. Most reports have occurred with overexposure or misuse, although side effects have followed single applications, particularly when the epidermal barrier has been compromised. Whether this constitutes a significant problem in normal individuals is doubtful [6]. Nevertheless, it has been suggested that permethrin may be a safer and less toxic alternative [8].

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Hexachlorophene (hexachlorophane)

This substance has potential neurotoxicity. Exposure of babies to a talc containing 6.3% hexachlorophene due to a manufacturing error resulted in deaths, with ulceration, skin lesions and a characteristic demyelinating encephalopathy [1]. A 3% emulsion has produced milder neurological changes but a 0.33% concentration in talc is apparently safe. Encephalopathy has occurred in burns patients [2].

REFERENCES

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Hydroquinone

Depigmenting creams containing 6–8% hydroquinone, used especially by black South African women, have caused rebound hyperpigmentation and coarsening of the skin, with ochronotic changes in the dermis, colloid degeneration and colloid milium [1–6]. Collagen degeneration may be seen histologically [2]. Similar changes have been seen in black women in the USA [3] and in a Mexican American woman [4]. Interestingly, ochronosis does not develop in areas of vitiligo [7]. The Q-switched ruby laser may be helpful in treating exogenous ochronosis [8]. The nails may be pigmented [9].

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Iodine

Povidone-iodine scrub for acne (Betadine) induced hyperthyroidism [1].

REFERENCE

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Latanoprost

Topical latanoprost for glaucoma may induce eyelash hypertrichosis [1].

REFERENCE

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Lead lotions

The continued use of wet dressings of lead subacetate in the treatment of exfoliative dermatitis caused lead poisoning, with punctate basophilia and an elevated urinary lead level [1].

REFERENCE

1 Kennedy CC, Lynas HA. Lead poisoning by cutaneous absorption from lead dressings. *Lancet* 1949; **i**: 650–2.

Mercury

Poisoning is now fortunately rare, but was seen from continued application of large amounts of a topical application, as for psoriasis [1,2]. Idiosyncratic poisoning after much smaller doses is also recognized [3]. Intoxication has followed the use of a mercury dusting powder [4] and poisoning of a suckling infant has followed the use of perchloride of mercury lotion for cracked nipples [5]. Fever, a generalized morbilliform rash and oedema of the extremities have been the usual clinical features. Exfoliative dermatitis and encephalopathy have developed; permanent damage to the renal tubules is manifest as persistent albuminuria or frank nephrotic syndrome [6]. Rarely, gross symptoms, such as loose teeth [7], swollen bleeding gums and weight loss, may be observed.

Application of a mercury-containing cream to the face over many years can produce slate-grey pigmentation, especially on the eyelids, nasolabial folds and neck folds (exogenous ochronosis) [8–10]; mercury granules lie free in the dermis or within macrophages [11]. Mercury is a moderate sensitizer and leads to contact sensitivity.

REFERENCES

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after topical application of a metallic mercury ointment. *Dermatologica* 1986; **172**: 48–51.
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Methyl salicylate (oil of wintergreen)

Topical application of methyl salicylate and menthol as a rubifacient, with use of a heating pad, resulted in local skin necrosis and interstitial nephritis [1].

REFERENCE

1 Heng MCY. Local necrosis and interstitial nephritis due to topical methyl salicylate and menthol. *Cutis* 1987; **39**: 442–4.

Mexiletine

Mexiletine hydrochloride induced contact uriticaria in a patient receiving iontophoresis [1]. A generalized drug eruption followed topical provocation on previously involved skin [2].

REFERENCES

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2 Kikuchi K, Tsunoda T, Tagami H. Generalized drug eruption due to mexiletine hydrochloride: topical provocation on previously involved skin. *Contact Dermatitis* 1991; **25**: 70–2.

Minoxidil

Topical minoxidil, as used for androgenetic alopecia, is associated with cutaneous problems in up to 10% of patients, with allergic contact dermatitis occurring in 4% of individuals [1]. The contact allergen is often propylene glycol [2]. Diffuse hypertrichosis occurred during treatment with 5% topical minoxidil in female patients [3]. Acute non-allergic eruptions of the scalp resulted from combined use of minoxidil and retinoic acid [4].

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Non-steroidal anti-inflammatory drugs

Allergic and photoallergic contact dermatitis and phototoxicity have resulted from topical NSAIDs [1–3]. An erythema multiforme-like reaction followed acute contact dermatitis from two different bufexamac-containing topical preparations [4].

REFERENCES

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Phenol

Severe systemic reactions, such as abdominal pain, dizziness, haemoglobinuria, cyanosis and sometimes fatal coma, have followed the application of phenol to extensive wounds. Accidental application of pure phenol to a small area of skin in an infant has proved fatal. The prolonged use of phenol as a dressing for a large ulcer may give rise to exogenous ochronosis, with darkening of the cornea and of the skin of face and hands.

Podophyllin

Excessive application may lead to severe local irritation or ulceration [1]. There have been occasional reports of confusional states, coma, peripheral neuropathy, vomiting and even death following the application of this resin to large areas of genital warts, especially in pregnancy [2,3]. However, careful review of the reports suggests that in the majority the effects could not be attributed with certainty to podophyllin [2]. Animal experiments suggest teratogenicity; although teratogenicity is controversial in humans, the drug is best avoided in pregnancy.

REFERENCES

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Resorcinol

Acute resorcinol poisoning is very rare but an ointment

containing 12.5% resorcinol applied to the napkin area produced dusky cyanosis, a maculopapular eruption, haemolytic anaemia and haemoglobinuria in an infant [1]. The continued application to large leg ulcers of ointments containing resorcinol has caused myxoedema and widespread blue-grey pigmentation mimicking ochronosis [2]. Application for warts caused generalized urticaria with angio-oedema, pompholyx of palms and soles, or papulovesicular eczema with pompholyx [3].

REFERENCES

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Salicylic acid and salicylates

The frequent application of salicylic acid ointments to extensive lesions will produce symptoms of salicylism even in adults [1–7]. Most cases of poisoning have occurred in children with psoriasis or ichthyosis [1,2]; fatal cases have been recorded [4]. Drowsiness and delusions are followed by acidosis, coma and death from respiratory failure.

REFERENCES

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Silver sulfadiazine

Topical application has caused hyperpigmentation [1], contact sensitivity [2] and dermatitis [3].

REFERENCES

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Tretinoin

Topical tretinoin, used for the management of photo-aged skin, may cause erythema, peeling, burning and itching of the skin within days [1,2]. Pink discoloration without other signs may also develop, as may inflammation in solar keratoses.

REFERENCES

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2 Weinstein GD, Nigra TP, Pochi PE *et al*. Topical tretinoin for treatment of photodamaged skin. *Arch Dermatol* 1991; **127**: 659–65.

Vitamin E

Vitamin E in deodorants has caused contact dermatitis [1].

REFERENCE

1 Minkin W, Cohen HJ, Frank SB. Contact dermatitis from deodorants. *Arch Dermatol* 1973; **107**: 774–5.

Warfarin

An epidemic of haemorrhagic disease with fatalities occurred due to warfarin-contaminated talcs [1]. Poisoning has also been attributed to preparation of rodent baits [2].

REFERENCES

1 Martin-Bouyer G, Linh PD, Tuan LC *et al*. Epidemic of haemorrhagic disease in Vietnamese infants caused by warfarin-contaminated talcs. *Lancet* 1983; **i**: 230–2.
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Transdermal drug-delivery systems

Transdermal delivery systems are available for clonidine, estradiol (oestradiol), glyceryl trinitrate, scopolamine and nicotine, and systems for other drugs are being developed. Erythema, irritancy, scaling, vesiculation, excoriation, induration, pigmentary changes and contact sensitization are not uncommon; the occlusive element may lead to miliaria rubra [1–13]. Systemic reactions may occur. Allergic skin reactions occur in up to 50% of patients with clonidine, but with glyceryl trinitrate, scopolamine, estradiol and testosterone they are much less frequent [2]. Reactivation of an area of contact dermatitis may develop via oral medication rarely [2]. Transdermal compared with oral metoprolol had comparable efficacy, and systemic side effects were comparable; 69% of patients had local side effects at the patch site (erythema, papular exanthem, pruritus, localized urticarial exanthem) [4]. Allergic contact dermatitis is recorded with nicotine

[8–11], glyceryl trinitrate and estradiol [12]. Use of transdermal oestrogen patches resulted in systemic sensitization to ethanol [14]. Transdermal fentanyl patches have been associated with a diffuse rash [15].

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Management of drug reactions

Diagnosis

Drug reactions, apart from fixed drug eruption, have non-specific clinical features, and it is often impossible to identify the offending chemical with certainty, especially when a patient with a suspected reaction is receiving many drugs simultaneously. Drug reactions may be mistaken for naturally occurring conditions and may therefore be overlooked. By the same token, it may on occasion be very difficult to state that a given eruption is drug induced. Experience with the type of reaction most commonly caused by particular drugs may enable the range of suspects to be narrowed, but familiar drugs may occasionally produce unfamiliar reactions and new drugs may mimic the reactions of the familiar. The assessment of a potential adverse drug reaction always necessitates taking a careful history, and may involve a trial of drug elimination, skin tests, *in vitro* tests and challenge by re-exposure [1].

A drug reaction may first become evident after the offending medication has been stopped, and depot injections may have delayed effects. Interpretation of elimination tests should be tempered by the knowledge that drug reactions may take weeks to settle. *In vivo* and *in vitro* tests are only applicable to truly allergic reactions. Skin tests, including prick and intradermal testing and patch testing, are for the most part unreliable, even when apparently appropriate antigens are used; they may be hazardous [2–4]. *In vitro* tests are not widely available and are essentially research tools.

All too frequently therefore the diagnosis is no more than an assessment of probability. The fact that major disagreements occurred between clinical pharmacologists asked to assess the likelihood of adverse drug reaction in two series confirms that identification of a responsible drug is often a subjective judgement [5,6]. An algorithm has been reported that provides detailed criteria for ranking the probability of whether a given drug is responsible for a reaction, based on (i) previous experience, (ii) the alternative aetiological candidates, (iii) timing of events, (iv) drug level and (v) the results of drug withdrawal and rechallenge [7,8]. A number of other algorithms have been developed to assist in the diagnosis of which, if any, drug is the cause of a given eruption [9–12]. The difficulties inherent in the diagnosis of drug reactions have been reviewed [1,13,14].

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Drug history

Patients should be specifically questioned about laxatives, oral contraceptives, vaccines, homeopathic medicines, etc. as these may not be volunteered as medications. They should be asked when they last took a tablet for any reason. The history should include information on when each drug was first taken relative to the onset of the reaction, whether the same or a related drug has been administered previously, and whether there is a prior history of drug sensitivity or contact dermatitis. Allergic drug reactions do not usually develop for at least 4 days, more commonly 7–10 days, after initial drug administration in a previously unsensitized individual. However, this time relationship cannot be relied on to differentiate between allergic and non-allergic reactions, as a previous sensitizing exposure may not have produced a clinically evident reaction.

Drug elimination

Resolution of a reaction on withdrawal of a drug is supportive incriminatory evidence but not diagnostic. Failure of a rash to subside on drug withdrawal does not necessarily exonerate it, as traces of the drug may persist for long periods and some reactions, once initiated, continue for many days without re-exposure to the drug. The unwitting substitution of a drug that is chemically closely related may perpetuate a reaction, as when an antihistamine of phenothiazine structure is prescribed to alleviate the symptoms of a reaction caused by another phenothiazine. Elimination diets have been advocated for diagnosis of food additive intolerance leading to urticaria [1,2].

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Skin testing

Skin testing has been reviewed [1–7]. Drug skin tests are of three types: patch tests for delayed cellular hypersensitivity, prick tests for immediate hypersensitivity, and intradermal tests for both immediate or delayed hypersensitivity [5]. The quick patch test (application under a Finn chamber for 30 min) can be used in patients with severe hypersensitivity [8]. Prick tests and intradermal tests performed with sequential dilutions may be useful in the identification of patients who present with immediate IgE-related hypersensitivity reactions, and are sensitive to one of a number of drugs, including penicillin and other β-lactam antibiotics, agents used in general anaesthesia, tetanus toxoid, streptokinase, chymopapain, heterologous sera or insulin, and may thus aid in the prevention of anaphylaxis [1]. Vasculitis related to circulating immune complexes cannot be reproduced by skin tests. Delayed cellular hypersensitivity is involved in inducing maculopapular rashes, baboon syndrome, localized or generalized eczema or acute generalized exanthematous pustulosis. In such reactions, drug patch tests or delayed positive reactions on intradermal tests occur in more than 50% of patients [5]. Significantly higher numbers of positive patch tests are seen in maculopapular than in urticarial reactions [4]. Diluted drug patch tests can be positive in the drug hypersensitivity syndrome (drug rash with eosinophilia and systemic symptoms). Drug skin tests are not of great value in investigating Stevens–Johnson syndrome or TEN; relevant positive patch tests were seen in only 9% of 22 patients with Stevens–Johnson syndrome/TEN compared with 50% of 14 patients with acute generalized exanthematous pustulosis [9].

The results of skin-test reactions, including intradermal testing and patch testing, were evaluated in 242 patients with delayed-type (non-immediate) drug eruptions [6]. Intradermal testing was positive in 89.7% of patients, and patch tests were positive in 31.5% of cases; overall, 62% of patients had either a positive intradermal or patch test. Intradermal testing was more frequently positive in maculopapular rashes, erythema multiforme and erythrodermic rashes than in eczematous reactions, whereas positive patch tests were comparatively frequent in erythroderma, eczematous reactions and anticonvulsant-induced reactions. It was concluded that a combination of patch testing and intradermal testing is useful in the demonstration of causative agents in delayed-type drug eruptions [6]. Unfortunately, the usefulness of this approach is limited, because the significant antigenic determinants are unknown for most drugs [1]. Moreover, intradermal testing is not always safe. False-negative skin testing may occur because of poor absorption through the skin, because a metabolite rather than the substance administered in the test is the sensitizing antigen, or because testing is performed either too soon after a reaction, in a refractory period, or too late, so that the patient no longer demonstrates skin-test reactivity.

Drug skin tests should be performed 6 weeks to 6 months after complete resolution of the reaction [3]. For patch tests, the commercial form of the drug should be tested diluted at 30% in petrolatum and/or water; the pure drug should be tested diluted at 10%. Lower concentrations are used in severe drug reactions. Sodium lauryl sulphate in the commercial form of some drugs can induce irritation when they are patch tested as such, and positive patch tests to drugs can be related to an excipient rather than the drug itself [4]. It is useful to carry out the test on the site most affected in the initial reaction [10].

Re-elicitation of an exfoliative dermatitis has followed patch testing [9].

Drug prick tests are performed on the volar forearm skin with the commercialized form of the drug, but with sequential dilutions in cases of urticaria. Intradermal tests are performed with sequential dilutions (10^{-4}, 10^{-3}, 10^{-2}, 10^{-1}) of 0.04 mL of a pure sterile or injectable form of the drug. Prick tests and intradermal tests should be read at 20 min and at day 1, and patch tests at day 2 and day 4; these tests also need to be read at 1 week.

The success of skin testing varies with the drug tested, with a high percentage of positive results on patch testing with β-lactam antibiotics, pristinamycin, carbamazepine and tetrazepam, or with β-lactam antibiotics and heparins on delayed readings of intradermal tests. The results of drug skin tests also depend on the clinical features of the adverse drug reaction. Appropriate controls are necessary to avoid false-positive results.

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Patch testing

Patch testing in drug eruptions may be helpful in identifying the drug responsible, especially in systemic contact-type dermatitis medicamentosa, photosensitivity (photopatch testing) or fixed drug reactions [1–7]. Positive patch tests have been found overall in about 15% of patients with drug eruptions [1,2] and 25% of patients with penicillin allergy [1–3]. Patch testing in a previously involved site, but not in normal skin, yielded a positive response in a proportion of cases of fixed drug eruption, especially with phenazone (pyrazolone) derivatives (e.g. phenylbutazone), but also with a sulphonamide, doxycycline, trimethoprim, chlormezanone, a barbiturate and carbamazepine [5]. In a series of 30 patients [6], positive reactions were always seen with phenazone salicylate (16 patients) and carbamazepine (three patients), and in one case with chlormezanone. Both positive and negative reactions were seen with trimethoprim (three and two, respectively), doxycycline (two and one) and sulfadiazine (one and one). The vehicle used as a diluent for the drug may be important in determining whether a reaction is seen; use of dimethylsulfoxide as the vehicle may increase the number of positive patch tests [5,8,9]. Topical provocation of fixed drug eruption has also been reported with sulfamethoxazole [10], dimenhydrinate [11] and metronidazole [12]. However, other reports in the literature do not suggest that patch testing is helpful in fixed drug eruption [13].

Patch testing has supported a diagnosis of allergy, in the absence of topical sensitization, to diazepam, meprobamate and practolol [14], anticonvulsants including hydantoin derivatives and carbamazepine [15–17] (but only in patients with exfoliative dermatitis and maculopapular exanthem and not with fixed drug eruption, erythema multiforme or urticaria [16]), tartrazine dyes [18], chloramphenicol [19], diclofenac-induced maculopapular eruption [20], and in TEN induced by ampicillin [21]. Antibiotics (especially penicillin, ampicillin and other β-lactam antibiotics [22,23] and aminoglycosides), NSAIDs (pyrazolone derivatives and occasionally aspirin), neuroleptics (phenothiazines, barbiturates, meprobamate, benzodiazepines), β-blockers, gold salts, carbimazole, amantadine, corticosteroids, mitomycin, heparin and amide anaesthetics have all been associated with positive patch tests in allergic subjects. Positive patch tests to the following drugs have been found in patients with acute generalized exanthematous pustulosis: diltiazem [24,25], metronidazole [26], nystatin [27] and terbinafine [28].

However, care must be exercised, because anaphylactoid responses may occur even in response to the small amounts of drug absorbed from a patch test. Moreover, patch testing has produced exfoliative dermatitis in a patient sensitized to carbamazepine [29] and relapse of a generalized drug eruption in the case of clobazam [30]. A patch test with a solution of the drug will sometimes induce a generalized petechial reaction in patients with purpura caused by drug sensitivity, for example in carbromal or apronalide (Sedormid) purpura.

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Penicillin

It is clearly important to exclude from treatment with penicillin those patients truly at risk of developing hypotensive episodes or fatal anaphylaxis. The role of skin testing in this situation has been reviewed [1–12]. Skin tests should be carried out using major-determinant antigens (benzylpenicilloyl polylysine, PPL) and minor-determinant mixture (benzylpenicillin, benzylpenicilloate and benzylpenilloate) antigens [13]. Procedures have been published, and the reader is referred to the original articles for details about methodology [13–15]. Epicutaneous testing should precede intradermal testing, and positive (histamine or opiate) and negative (diluent) controls should be included. False-negative results may be found after a systemic allergic reaction, as a result of a refractory period or temporary desensitization, so that skin testing should be postponed for at least 4–6 weeks [13].

There is a high incidence of wrongly diagnosed penicillin allergy on the basis of history, and a considerable proportion of patients who have had proven allergic reactions to penicillins eventually stop producing the IgE antibody responsible. In a large study, only 1% of 566 patients with a history of penicillin allergy, and negative skin tests to major determinant (PPL) and minor-determinant mixture and its components (potassium benzylpenicillin, benzylpenicilloate and benzylpenicilloyl-*N*-propylamine), had possibly IgE-mediated reactions [4]. In another study [7], 7.1% of 776 individuals with a previous history of penicillin allergy and 1.7% of 4287 subjects negative by history had positive skin tests to major determinant (PPL) and/or a minor-determinant mixture. Positive skin tests were seen in 17% and 12% of patients with a history of anaphylaxis or urticaria, respectively, but in only 4% with a history of an exanthem. Mild adverse reactions to skin tests occurred in 1% of patients positive by history and 9% of those with positive skin tests. In patients with negative skin tests who received benzylpenicillin or ampicillin, mild acute allergic reactions occurred in 0.5% of subjects negative by history and 2.9% of subjects positive by history. Thus, routine penicillin skin testing can facilitate the safe use of penicillin in 90% of individuals with a previous history of allergy [7]. Positive skin tests, an average of 5 years later, to major and minor determinants of benzylpenicillin and/or minor-determinant mixtures of ampicillin, amoxicillin or cloxacillin were found in 19% of 112 patients with a history of urticaria and angio-oedema or exanthem to penicillins and other semi-synthetic penicillins (most frequently ampicillin and amoxicillin) [8]. Skin-test reactivity was limited in about half to the semi-synthetic penicillin reagents derived from ampicillin, amoxicillin or cloxacillin. The existence of isolated skin-test positivity to reagents specific for ampicillin or amoxicillin, with good tolerance of major and minor penicillin determinants, has been confirmed in other reports [9,16,17], emphasizing the necessity for using reagents specific for the side-chains of these aminopenicillin drugs to exclude possible immediate hypersensitivity in patients who reacted to these antibiotics clinically [8–11,16,17]. Thus 7% of 288 patients with a history of penicillin allergy reacted only to skin testing with amoxicillin and not to

benzylpenicillin or phenoxymethylpenicillin diagnostic reagent determinants [16]; these would have been missed if the latter agents had been used alone.

Patients treated with penicillin after a negative skin test to PPL and to minor-determinant mixture develop IgE-mediated reactions only very rarely, and these are almost always mild and self-limited [1,4,7]. Thus, when adequately performed, negative skin tests indicate that the risk of a life-threatening reaction is almost negligible, and that any β-lactam antibiotic may be safely given. In contrast, the risk of an acute allergic reaction, including respiratory obstruction or hypotension, with a positive history and positive skin test is 50–70%; the risk in a patient with a negative history but a positive skin test is about 10% [1,13,18].

Intradermal skin testing is generally safe, with few reactions, and although skin testing may rarely cause sensitization [19], it does not usually do so [13]. However, there is a risk, albeit very small, of fatality from skin testing [20]. A more major problem with skin testing is that use of the major determinant (PPL) alone misses about 10–25% of all positive subjects, and that even addition of benzylpenicillin G as the sole minor-determinant antigen misses 5–10% of positive subjects [21,22]. This is significant because patients with reactivity to minor antigenic determinants are thought to be at a higher risk for anaphylaxis [13,23]. In addition, as detailed above, reagents for detecting sensitivity to aminopenicillins (ampicillin and amoxicillin) should be used [15]. Comprehensive skin testing is therefore only practicable in specialized centres. Skin tests can give both false-positive and false-negative reactions [18]. Thus, it has been argued that a positive or negative result in an individual patient cannot be used to entirely reliably predict outcome [24].

Further difficulties are that skin tests have no predictive value in non-IgE-mediated reactions such as serum sickness, haemolytic anaemia, drug fever, interstitial nephritis, contact dermatitis, maculopapular exanthems or exfoliative dermatitis. Accelerated or late IgE-mediated reactions may occur despite a negative pretreatment skin test [1,13]. Positive intradermal skin-test reactions occurred in only 87% of patients with a history of delayed-type rashes induced by penicillins and cephalosporins and who had positive oral provocation tests [25]. Oral challenge was positive in 18 of 33 patients with positive delayed skin testing and patch testing to ampicillin or amoxicillin, but also in 16 of 27 patients with negative allergy tests [26]. Skin testing is contraindicated where there is a history of exfoliative dermatitis, Stevens–Johnson syndrome or TEN.

There is clearly individual variation in the approach to the diagnosis and management of β-lactam allergy [12], based on a survey of 3500 physician members and fellows of the American Academy of Allergy and Immunology and of allergy training programme directors in the USA. PPL and fresh penicillin G were used for skin testing by more than 86% of both respondent groups, whereas minor-determinant mixtures were used by only 40%. Epicutaneous followed by intradermal injection was the skin-test technique used by 86% of these allergists.

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Agents used in general anaesthesia

Intradermal [1–4] or prick [5,6] testing may be helpful in identifying the causative drug [7], and is essential in confirming lack of sensitivity to pancuronium before use in cases of documented sensitivity to other relaxants [3]. In one series of patients with a history of anaphylaxis during induction of general anaesthesia, skin testing was performed by the prick and intracutaneous methods with dilutions of thiobarbiturates, muscle relaxants or β-lactam antibiotics [8]. No patient experienced a recurrence of anaphylaxis during subsequent general anaesthesia when agents producing positive skin tests were avoided, provided a premedication regimen of prednisone and diphenhydramine was given [8].

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Local anaesthetics

Avoidance of local anaesthetics on the basis of a vague or equivocal history of a prior adverse reaction may result in substantial increased pain and risk. True allergic reactions probably constitute no more than 1% of all adverse reactions to these drugs, some but not the majority of which are due to preservatives, especially parabens. Skin testing and/or incremental challenge beginning with diluted drug is a safe and effective method for identifying a drug that a patient with a history of an adverse reaction can tolerate [1–7]. Patients with positive patch tests to local anaesthetics and a negative history of anaphylactoid reactions rarely have positive intradermal skin tests. The risk of anaphylactic reactions with amide local anaesthetics (except butanilicaine) is therefore low in such patients [3]. Conversely, patients with anaphylactic reactions to local anaesthetics are usually patch-test negative [3]. Skin testing may produce systemic adverse reactions, especially with undiluted drug. False-positive reactions occur, but false-negative reactions have not been reported, and most skin-tested patients who tolerate a local anaesthetic are skin-test negative to the drug. The choice of a drug for use in skin testing and incremental challenge may be facilitated by current concepts of non-cross-reacting groups of local anaesthetics. Thus, benzoic acid esters, both those with and without *p*-aminobenzoyl groups, do not cross-react with amide local anaesthetic agents.

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Analgesics and NSAIDs

Prick tests were positive in only 13% of 117 patients with a history suggestive of anaphylactoid reactions to a variety of mild analgesics including NSAIDs [1].

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Heparin

Provocation testing may be a useful diagnostic measure [1–6]. Low-molecular-weight heparin analogues may be satisfactorily substituted in some patients with this reaction, but are not always tolerated [2]. Subcutaneous testing of a panel of heparins, danaparoid and desirudin (hirudin) is recommended for determining acceptable treatment options for patients allergic to specific heparins [3,6]. In type I reactions, or in the presence of skin necrosis with or without heparin-induced thrombocytopenia, a low-molecular-weight heparin should be replaced by danaparoid sodium or hirudin. In the presence of a negative subcutaneous provocation test, the compound can be used with little risk. If all types of low-molecular-weight heparin and danaparoid sodium show positive skin tests, oral anticoagulants should be used, and intravenous injections of any kind of heparin should be avoided because of the potential for anaphylactic shock.

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Skin testing in urticaria

Skin tests have been advocated as useful in the investigation of chronic urticaria [1,2]. Patch testing with a series of penicillins was positive in 6.9% of patients in one study [1], and there were positive intracutaneous tests to cilligen and/or penicillin G in 21.5% of patients. Avoidance of dietary dairy produce, which potentially might have contained penicillin, alleviated the urticaria in 50% of the penicillin-allergic patients. The reported prevalence of positive intracutaneous tests to penicillin was much higher in this study than in other reported series in the literature.

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In vitro tests

Tests for IgE antibody

The detection of drug-specific circulating antibodies does not prove an allergy. It is important to record when a blood test is taken in relation to the evolution of a drug reaction, as the antibody response to a drug has a finite duration. For example, antipenicillin IgE antibodies begin to disappear within 10–30 days. Radioallergosorbent tests (RASTs) for drug-specific IgE class antibody are available for penicillin, insulin and ACTH. RAST detects specific IgE antibody to the penicilloyl determinant, and is positive in 60–90% of patients with a positive skin test to PPL [1,2]; however, there is no *in vitro* test for minor-determinant antigens, and therefore in practice this test is of very limited use [2,3]. Investigation of cross-reactivity of antibodies to penicillin in 123 patients with a history of penicillin allergy, using enzyme-linked immunosorbent assay, detected IgE antibodies specific to amoxicillin, ampicillin or flucloxacillin, respectively, in three patients [4]. These antibodies did not cross-react with other penicillin antigens, and would have been missed had testing involved only use of benzylpenicillin. Thus, allergy to semi-synthetic penicillins can occur without allergy to benzylpenicillin, negative tests specific for benzylpenicillin or phenoxymethylpenicillin cannot be generalized to other penicillins, and exclusive reliance on benzylpenicilloyl RAST to detect allergy to semi-synthetic penicillins could lead to serious adverse consequences [5]. IgE antibodies specific for 1-phenyl-2,3-dimethyl-3-pyrazoline-5-one were found in 17 of 19 serum samples from individuals sensitive to pyrazoline drugs with 4-amino-antipyrine discs by RAST [6].

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Miscellaneous in vitro tests

The histamine-release test [1], basophil degranulation test [2–4] and passive haemagglutination test [5] are of strictly limited use. A positive basophil degranulation assay, which involves binding of drug to specific IgE on the basophil surface, has been reported with penicillin, erythromycin, sulphonamides and aspirin, but false-negative results are common [3,4]. The leukocyte and macrophage migration inhibition tests [6–9], platelet-activating factor release from white blood cells after antigenic challenge as tested by platelet aggregation [10], and the lymphocyte toxicity assay [11–14] are the subject of investigation but are essentially research tools.

A number of drugs have been reported to induce lymphocyte proliferation, as determined by incorporation of ^{3}H-thymidine, in patients with drug eruptions, including penicillin, carbamazepine, phenytoin, furosemide, sulfamethoxazole and hydrochlorothiazide [15–20]. However, in general only low levels of stimulation are observed, perhaps because the antigen responsible for the reaction is a drug metabolite rather than the parent compound, and the significance of the test is difficult to interpret. Addition

of human liver microsomes containing cytochrome P-450 enzymes to the reaction medium of the lymphocyte transformation test, in order to aid generation of potentially reactive drug metabolites, may increase the sensitivity of *in vitro* detection of T-cell reactivity [21,22].

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Challenge tests

A drug suspected of causing a drug eruption may be reliably incriminated by the reaction in response to a test dose administered after recovery. However, fatal reactions have occurred to test doses, for example penicillin and quinine, and provocation tests should only be performed in exceptional circumstances [1–6]. A history of Stevens–Johnson syndrome or TEN constitutes an absolute contraindication to drug challenge, and test dosing in reactions of anaphylactic type, blood dyscrasia or SLE-like reaction is seldom advisable. Challenge tests are open to misinterpretation [6], because a very small challenge dose may fail to elicit a reaction that a therapeutic dose would provoke, because of false positives, and because false negatives may occur as a result of a refractory period following a reaction [7].

Test dosing in patients with drug reactions such as fixed drug eruption, which are not potentially fatal, may be helpful [5]. Topical challenge in the form of patch testing in a previously involved site may yield a positive response in a high proportion of such cases [8]. Oral provocation tests using tartrazine, and other food additives such as sodium benzoate, have been advocated for the investigation of chronic urticaria or food intolerance [9–12]. Protocols for the analysis of adverse reactions to foods and food additives have been published [13].

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Treatment

Clearly, prevention is better than cure [1,2]. Drugs implicated in a previous reaction should be avoided; the patient should be asked about allergies, and hypersensitivity records in the notes and on prescription charts should be checked. In the case of suspected penicillin allergy, an alternative antibiotic, preferably with a non-β-lactam structure such as erythromycin, should be substituted;

use of griseofulvin should be avoided as it has a 5–10% cross-reactivity based on non-structural mechanisms [2]. However, lack of a positive history does not eliminate the possibility of an allergic reaction, as in the case of penicillin hypersensitivity [3]. Where it is essential to readminister one of a group of drugs to a patient with a previous history of an adverse reaction to a related medication, as with radiographic contrast media and agents used in general anaesthesia, then if possible preliminary skin testing should be carried out to enable identification of safe alternative therapy. In addition, the procedure should be covered by premedication with oral corticosteroids and antihistamines, with or without epinephrine, in order to obtund the onset of an anaphylactic reaction. In the situation where there is no acceptable alternative for an essential drug, then rapid desensitization therapy should be considered.

The approach to treatment of an established presumed drug eruption obviously depends on the severity of the reaction. For many minor conditions, withdrawal of the suspected drug, and symptomatic therapy with emollients, mild to moderately potent topical corticosteroids and systemic antihistamines where indicated, is all that is necessary. When a patient is receiving multiple drugs, it is wise to withdraw all but the essential medications, and to consider substituting alternative non-cross-reacting drugs for the remainder. Because of the wide variety of patterns of drug reaction, it is only possible to summarize the therapy of individual reactions here. The reader is referred to the discussion of the more serious conditions in this book and elsewhere [1–7].

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Anaphylaxis

The management of severe acute urticaria and anaphylaxis is detailed in Table 73.21.

Table 73.21 Management of anaphlyaxis.

Stop drug administration
Give 0.5–1 mL epinephrine (adrenaline) 1 in 1000 i.m. immediately
Check airway and give oxygen
Antihistamines
Chlorpheniramine maleate 10–20 mg i.v. *or*
Hydroxyzine 25–50 mg i.m. and four times daily orally *or*
H_1 and H_2 antagonists *or*
Cimetidine 300 mg i.v. 6 hourly
Corticosteroids
Hydrocortisone 250 mg i.v. and 100 mg 6 hourly
Prednisolone 40 mg/day for 3 days
Give i.v. 0.9% NaCl or 5% glucose
Monitor blood pressure and pulse
For bronchospasm
Aminophylline 250 mg i.v. over 5 min and 250 mg in 500 mL 0.9% NaCl over 6 h *or*
Nebulized terbutaline, salbutamol or metaproterenol

Exfoliative dermatitis/erythroderma

The complications of this potentially serious drug-induced condition include hypothermia, fluid and electrolyte loss, infection, high-output cardiac failure, stress ulceration and gastrointestinal haemorrhage, malabsorption and venous thrombosis. The management [1,2] includes maintenance of body temperature and fluid and electrolyte balance, treatment of cardiac failure by use of digitalization and diuretics (avoiding vasodilator drugs), and administration of intravenous albumin for hypoalbuminaemia. If the patient does not respond rapidly to potent topical corticosteroids, prednisolone 40–60 mg/day should be given. This approach also applies to the anticonvulsant hypersensitivity syndrome; oral corticosteroid therapy has been helpful [3,4].

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Toxic epidermal necrolysis

See Chapter 74.

Desensitization

It is possible to induce a state of antigen-specific mast cell unresponsiveness, in patients with type I IgE-mediated reactions, if a drug is essential for a patient's well-being and no alternative is available. Desensitization markedly diminishes the risk of anaphylactic reactions but not of non-IgE-mediated reactions; it should only be carried out in an intensive care setting. Mechanisms proposed to explain the development of tolerance following

desensitization procedures include mediator depletion, tachyphylaxis, production of blocking antibodies, or change in the level of specific IgE antibodies.

Desensitization is most frequently carried out for patients with penicillin allergy, with increasing doses of penicillin being administered over 3–5 h [1–3]. The drug is usually given orally; increasing doses are given, starting with a very weak concentration (e.g. one millionth of the therapeutic dose) and working up to a full dose. There have been no severe allergic reactions recorded in patients who completed oral desensitization to penicillin; about 35% experience minor cutaneous reactions including pruritus or urticaria. Although the protection is usually short-lived, tolerance can be maintained by long-term administration of low doses of oral penicillin. Patients with sensitivity to vancomycin [4], 5-aminosalicylic acid [5] and allopurinol [6] have been successfully desensitized.

Patients with HIV infection with previous cutaneous reactions to sulphonamides [7–11] or antituberculous medication [12] have also been desensitized. A 10-day oral desensitization regimen was described for trimethoprim–sulfamethoxazole in 28 HIV-infected patients [8]; 82% were successfully desensitized, and four of the 28 patients had relatively severe rashes (three maculopapular, one erythroderma) during the desensitization phase. Four patients subsequently had rashes 12–33 weeks after desensitization [8].

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Chapter 74

Erythema Multiforme, Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis

S.M. Breathnach

Definition and terminology

Clinically, erythema multiforme involves macular, papular or urticarial lesions, as well as the classical iris or 'target lesions', distributed preferentially on the distal extremities. Lesions may involve the palms or trunk, as well as the oral and genital mucous membranes with erosions. Stevens–Johnson syndrome (SJS), first described in 1922, comprises extensive erythema multiforme of the trunk and mucous membranes, accompanied by fever, malaise, myalgia and arthralgia [1,2]. Toxic epidermal necrolysis (TEN; Lyell's syndrome), first described in 1956 [3], is characterized by extensive sheet-like skin erosions with widespread purpuric macules or flat atypical target lesions, accompanied by severe involvement of conjunctival, corneal, irideal, buccal, labial and genital mucous membranes [4,5]. Historically, the three presentations were considered to form a spectrum from mild to fulminatingly severe cases. More recently, there has been a re-evaluation of this concept and a tendency to consider erythema multiforme minor and major as part of one spectrum, often related to (especially herpesvirus) infections and perhaps on occasion to drug reactions, but to separate off SJS and TEN, both of which are more closely linked to drug sensitivities, and which may be regarded as severe variants of a single disease [6–10].

Erythema multiforme major occurs in younger males, frequently recurs, has less fever and milder mucosal lesions, and lacks association with collagen vascular diseases, human immunodeficiency virus (HIV) infection or cancer; herpes simplex is associated with SJS in up to 10% of cases [10]. SJS, with occasional skin blisters and erosions covering less than 10% of the body's surface area, is differentiated from TEN, in which typically sheet-like erosions involve more than 30% of the body surface. However, there are a number of cases (10–20% in adults, and a higher percentage in children) that even experienced clinicians and histopathologists are unable to classify, as they seem to have features of both groups.

There may be significant differences between countries in the clinical classification of severe cutaneous reactions, indicating the need for precise definitions [11]. Thus, the term 'acute disseminated epidermal necrosis (ADEN)' has been proposed [12], with ADEN type 1 corresponding to SJS, type 2 to transitional SJS/TEN with epidermal detachment between 10 and 29% and type 3 to full-blown TEN, while it has even been advocated by Lyell that the term 'exanthematic necrolysis' should replace TEN [13].

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Erythema multiforme

Aetiology

Immunology

The clinical picture would seem to be a reaction pattern to many different triggering factors; it appears to have an immunological basis. Human leukocyte antigen (HLA) studies have shown an association with HLA-B62 (B15), HLA-B35 and HLA-DR53 in recurrent cases [1–3]. Immune complexes have been demonstrated, both in the skin and circulation [4,5], autoantibodies against epithelial cells have been demonstrated [6], and autoantibodies against desmosomal plaque proteins desmoplakin I and II, with suprabasal acantholysis, were found in seven of 10 patients with erythema multiforme major [7]. However, these findings are probably simply epiphenomena. The histology suggests delayed hypersensitivity; $CD4^+$ lymphocytes have been found in the dermis and $CD8^+$ cells in the epidermis. Herpesvirus-infected peripheral blood mononuclear cells induced up-regulation of CD54 and major histocompatibility complex class I molecules in adjacent non-infected human dermal microvascular endothelial cells *in vitro*, and consequent increased endothelial binding of peripheral blood mononuclear cells [8]. Herpes simplex virus (HSV) DNA can be identified in lesions of herpes-induced erythema multiforme [9,10]. It has been proposed that peripheral blood mononuclear cells (macrophages or Langerhans' cells) pick up HSV DNA and transport fragments to distant skin sites, leading to recruitment of HSV-specific $CD4^+$ Th1 cells that produce interferon-γ (IFN-γ) [11]. This initiates an inflammatory cascade that includes expression of IFN-γ induced genes, increased sequestration of circulating leukocytes, monocytes and natural killer (NK) cells, and recruitment of autoreactive T cells. By extrapolation, drug hapten-specific T cells could be involved in the pathogenesis of drug-induced erythema multiforme. Peripheral blood mononuclear cells obtained from a patient with carbamazepine-induced erythema multiforme at the time of disease showed increased binding to intercellular adhesion molecule-1^+ (ICAM-1^+) heterologous keratinocytes, and to autologous keratinocytes *in vitro*, which could be inhibited completely by antibodies to lymphocyte function-associated antigen-1 (LFA-1), the ligand for ICAM-1 [12]. Perforin-positive cells may mediate apoptotic cell death in erythema multiforme and SJS [13]. MCP-1, RANTES, macrophage IFN-γ inducible gene (Mig), and IFN-γ inducible protein 10 (IP 10) were expressed by basal keratinocytes above and mononuclear cells within inflammatory foci. These cytokines contribute to the cell-specific and spatially restricted recruitment of mononuclear cells in the acute inflammation of erythema multiforme [14].

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Triggering factors

Potential triggering factors are listed in Table 74.1 [1–21]. In up to 50% of cases, there is no known provoking factor. The most common association is with a preceding

Table 74.1 Some causes of erythema multiforme.

Virus infections [1]
Herpes simplex [2,3]
'Primary atypical pneumonia', *Mycoplasma* infections [4,5]
Acquired immune deficiency syndrome
Adenovirus [6]
Cytomegalovirus [7]
Hepatitis B
Infectious mononucleosis [8,9]
Lymphogranuloma inguinale
Milker's nodes
Mumps
Orf
Poliomyelitis
Psittacosis
Variola
Vaccinia
Varicella [10]
Bacterial infections
A wide range has been recorded
Rickettsiae [11]
Fungal infections [12]
Histoplasmosis [13,14]
Vaccination [15]
Drug reactions
Contact reactions
Carcinoma, lymphoma, leukaemia
Lupus erythematosus (Rowell's syndrome) [16,17]
Polyarteritis nodosa
Pregnancy, premenstrual, 'autoimmune progesterone dermatitis' [18]
Sarcoidosis [19]
Wegener's granulomatosis
X-ray therapy [20,21]
Unknown

herpes simplex infection (facial or genital) [2,3], or with a *Mycoplasma* infection [4,5]; other viral or bacterial infections have also been incriminated.

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Drug induced

Erythema multiforme has been regarded as a well-recognized pattern of adverse cutaneous drug reaction [1–7], although in a prospective study of cases of erythema multiforme only 10% were drug related [2]. In another study, antecedent medication use, especially cephalosporins, was recorded in 59% of erythema multiforme patients and 68% of SJS patients [4]. Often drugs are blamed on inadequate evidence; confirmation of drug sensitivity necessitates re-exposure to the drug, which may carry an unacceptable risk.

Drugs implicated (Table 74.2), often on anecdotal evidence, include sulphonamides and co-trimoxazole, barbiturates, pyrazolone derivatives (phenylbutazone), phenolphthalein, rifampicin, penicillins, hydantoin derivatives, carbamazepine, phenothiazines, chlorpropamide, thiazide diuretics and sulphones. Recent reports have incriminated phenazone, minoxidil, fenbufen, mianserin, sulindac, methaqualone, ceftazidime [8], trazodone [9], progesterone [10], lithium [11], ampicillin [12], amoxicillin [13], vancomycin [14], ofloxacin [15], danazol [16], intradural prednisolone acetate [17], indapamide and sertraline [18], allopurinol [13,19], suramin [20], terbinafine [21,22], fenoterol [23], antiretroviral agents including didanosine [24], griseofulvin [25], celecoxib and rofecoxib [26,27], sulfaguanidine [28], porfirin sodium as part of photodynamic therapy [29], the H_2-blocker roxatidine [30], granulocyte macrophage stimulating factor [31], thalidomide [32] and amfebutamone [33]. Erythema multiforme may follow vaccination [34,35].

Table 74.2 Drugs reported as causing erythema multiforme or Stevens–Johnson syndrome.

Antibiotics
Sulphonamides
  Co-trimoxazole
  Sulfadoxine–pyrimethamine
Sulphones
Penicillins and ampicillin
Cephalosporins
  Ceftazidime
Quinolones
Rifampicin
Tetracyclines
Erythromycin
Thiacetazone

Antifungal or antiyeast preparations
Terbinafine
Griseofulvin
Nystatin

Antiretroviral drugs
Abacavir
Nevirapine

Non-steroidal anti-inflammatory drugs
Salicylates
Fenbufen
Ibuprofen
Sulindac
Paracetamol (acetaminophen)
Pyrazolone derivatives
  Antipyrine
  Phenylbutazone
  Phenazone

Metals
Arsenic
Bromides
Mercury
Gold
Iodides

Anticonvulsants
Barbiturates
Carbamazepine
Hydantoin derivatives
Lamotrigine
Trimethadione

Antihypertensives
Frusemide (furosemide)
Hydralazine
Minoxidil
Thiazide diuretics

Drugs acting on the central nervous system
Danazol
Lithium
Mianserin
Phenothiazines
Trazodone

Miscellaneous
Allopurinol
Chlorpropamide
Codeine
Cyclophosphamide
Methaqualone
Nitrogen mustard
Pentazocine
Phenolphthalein
Progesterone
Topical agents (see text)
Vaccination

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Topical agents and erythema multiforme-like reactions

Topical sensitivities reportedly also provoke erythema multiforme. The substances involved are usually potent sensitizers such as *Primula obconica* [1], poison ivy, a variety of weeds [2], diphenyl cyclopropenone and bromofluorene [3–5]. A large number of topical medications can induce erythema multiforme-like eruptions, including balsam of Peru, chloramphenicol, econazole, ethylenediamine, furazolidone, mafenide acetate cream used to treat burns, the muscle relaxant mephenesin, neomycin, nifuroxime, promethazine, scopolamine, sulphonamides, ophthalmic anticholinergic preparations (scopolamine hydrobromide and tropicamide drops), vitamin E, the antimycotic agent pyrrolnitrin, as well as proflavine, budesonide [6], topical nitrogen mustard [7], sesquiterpene lactones in herbal medicine [8], bufexamac [9] and phenylbutazone [10], nitroglycerin patch [11], tea tree oil [12] and a paint-on henna tattoo [13].

Erythema multiforme has also been associated with use of rubber gloves [14] and with blister beetle dermatitis [15]. In addition, contact with a number of environmental substances may induce erythema multiforme-like reactions [16], including nickel, formaldehyde, trichloroethylene, phenyl sulphone derivative, the insecticide methyl parathion, nitrogen mustard, epoxy compounds, trinitrotoluene, cutting oil [17] and bisphenol A [18].

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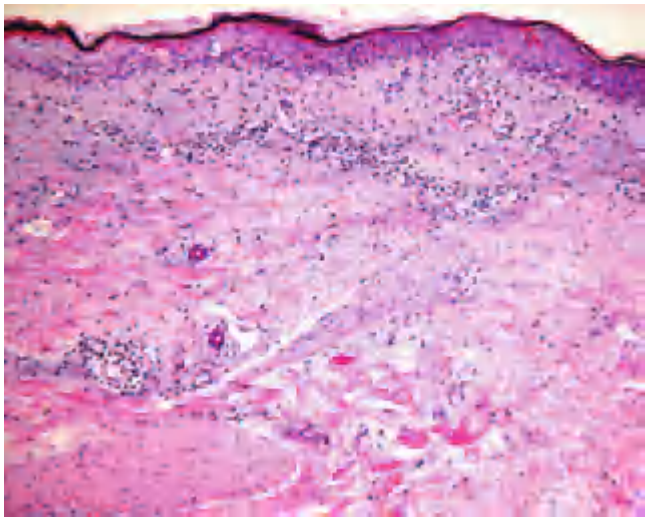
Pathology [1–4]

The most important changes are in the upper dermis and lower epidermis. Some cases have prominent dermal inflammatory changes, with a lymphohistiocytic infiltrate rich in T lymphocytes around blood vessels, oedema and vasodilatation, but little epidermal change. There may also be vacuolar degeneration of the lower epidermis or individually necrotic epidermal cells (Fig. 74.1). Such changes occur especially in classical erythema multiforme with target lesions. In more severe bullous cases, there is more dramatic necrosis of the whole epidermis. Electron microscopy demonstrates the damaged basement membrane in the floor of the bulla, with a few ragged islands of epidermal cells showing some evidence of regeneration. The histology of the oral lesions is similar to that in the

(a)



(b)

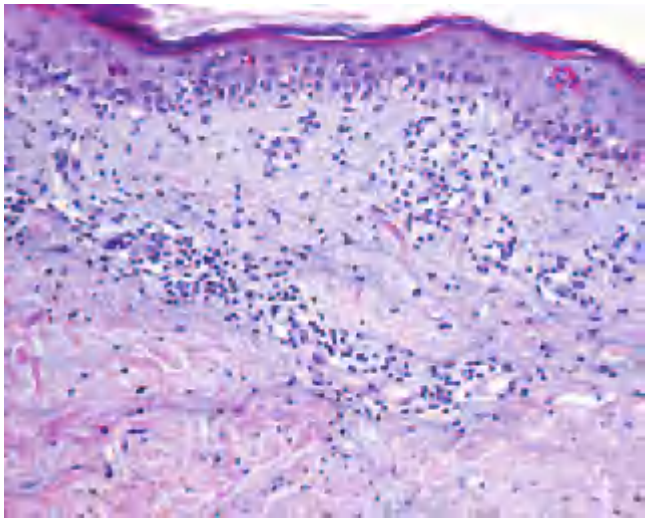


Fig. 74.1 (a,b) Histopathology of erythema multiforme. Note upper dermal perivascular lymphocytic infiltration, epidermal vaculoar degeneration and scattered individual necrotic keratinocytes (H&E). (Courtesy of Dr E. Calonje, St John's Institute of Dermatology, London, UK.)

skin, and there may be very marked degenerative changes in the epithelium [5].

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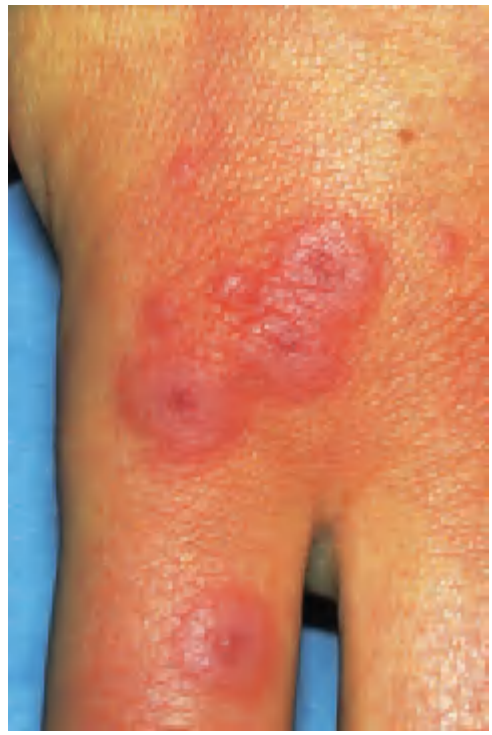

Fig. 74.2 Erythema multiforme. Typical target lesions over knuckles.

Clinical features [1–4]

Erythema multiforme can occur at any age, including neonates [5,6] or young children [7]. In general, the course is that of an eruption developing over a few days and resolving in 2–3 weeks. Repeated attacks associated with recurrent herpes simplex are frequent.

Erythema multiforme minor; papular or simplex form. This accounts for approximately 80% of cases. Clinically, macular, papular or urticarial lesions, as well as the classical iris or 'target lesions' (Fig. 74.2), are distributed preferentially on the distal extremities. Lesions may involve the palms or trunk, as well as the oral (Fig. 74.3) and genital mucous membranes. The lesions are dull red, flat or slightly raised maculopapules, which may remain small or may increase in size to reach a diameter of 1–3 cm in 48 h. Typical cases show at least some target (or iris) lesions. Target lesions are less than 3 cm in diameter, rounded and have three zones: a central area of dusky erythema or purpura, a middle paler zone of oedema and an outer ring of erythema with a well-defined edge. Atypical target lesions have only two of the zones. The lesions appear in successive crops for a few days and fade in 1–2 weeks, sometimes leaving dusky discoloration. There may be a few lesions, or they may be very profuse.

Classically, the backs of the hands, palms, wrists, feet and extensor aspects of the elbows and knees are affected;

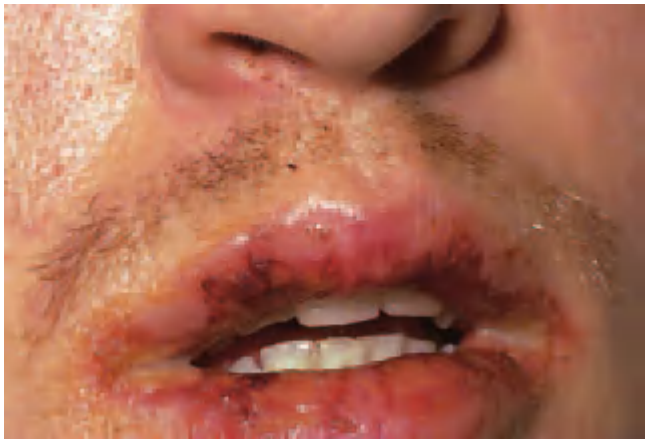

Fig. 74.3 Erythema multiforme. Mucosal lesions.

less commonly the face. Often the hands are selectively involved. Thus, the typical distribution is acral. The Koebner phenomenon is not uncommon, and accounts for some bizarre distributions. There may be occasional erythematous lesions, erosions or bullae on the mucous membranes. Photoaggravation of erythema multiforme is well recognized [8].

Localized vesiculobullous form. This form is intermediate in severity. The skin lesions present as erythematous macules or plaques, often with a central bulla and a marginal ring of vesicles (herpes iris of Bateman). Mucous membranes are quite often involved. In this type, the skin lesions tend to occur in the classical acral distribution, but may be few in number.

Erythema multiforme major. This is a severe illness associated with more extensive target lesions and mucous membrane involvement. The onset is usually sudden, although there may be a prodromal systemic illness of 1–13 days before the eruption appears.

Atypical cases. Because the diagnosis of erythema multiforme depends on the clinical and pathological appearance, criteria for the diagnosis of atypical cases are difficult to apply. However, there are cases where the clinical picture is atypical but the histology nevertheless shows the characteristic changes. Erythema multiforme-like lesions have been reported in the setting of acute generalized exanthematous pustulosis [9]. Lesions many centimetres across may remain stationary or slowly enlarge over several weeks or months (persistent erythema multiforme) [10,11]. On rare occasions, cases with otherwise typical morphology and histology may develop lesions almost continuously rather than episodically [10]. Erythema multiforme along Blaschko's lines has been reported [12], as has disseminated granuloma annulare following erythema multiforme minor [13].

Rowell's syndrome. This syndrome comprises lupus erythematosus associated with erythema multiforme-like lesions, and immunological findings of speckled antinuclear antibodies, anti-La antibodies and a positive test for rheumatoid factor [14–19]. However, the existence of the syndrome as a defined entity has been questioned [19].

Differential diagnosis

Drug eruptions and lupus erythematosus must be excluded, along with pemphigoid and toxic erythemas of unknown cause. The distinction between atypical erythema multiforme and urticarial vasculitis can be difficult. Kawasaki disease (see Chapter 27) may resemble erythema multiforme, but the characteristic red lips, strawberry tongue, red and swollen palms and soles, and the lymphadenopathy should permit a clinical diagnosis. Differential diagnosis of mouth lesions is considered in Chapter 66.

Treatment [7,20]

Symptomatic treatment only is necessary in the papular and localized bullous forms. Ocular involvement requires the early help of an ophthalmologist. In the more severe cases, good nursing is of paramount importance; such cases may require the sort of attention used for TEN (see below), in a dermatological intensive care unit or burns unit. The value of systemic corticosteroids is still debated [7,20–22], but relief of systemic symptoms such as fever is achieved. For more severe cases, prednisolone at an initial dosage of 30–60 mg/day, decreasing over a period of 1–4 weeks, may be given.

Antiviral therapy with agents such as aciclovir for erythema multiforme following overt herpes simplex infections tends to be disappointing once the eruption has appeared; this is so for recurrent cases, even when given at the very first sign of recurrent herpes. However, long-term prophylactic use may be quite helpful [23–25]. A dosage of 200 mg three times daily may be appropriate, but smaller or larger doses may be needed. Relapses tend to occur when the drug is omitted. It is of interest that some patients who suffer from recurrent erythema multiforme without overt herpes infection are helped by prophylactic aciclovir, implying that recurrent herpes infection may nevertheless be responsible. Aciclovir prevented recurrent polyarthritis associated with erythema multiforme [26].

Thalidomide has been used in a few cases to prevent relapses of recurrent erythema multiforme [27]. Other drugs used have included dapsone [11,28], azathioprine [11] and mycophenolate mofetil [29].

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Stevens–Johnson syndrome and toxic epidermal necrolysis

Incidence of reactions

The incidence of TEN has been estimated at 1.2 cases per million per year in France based on nationwide surveillance between 1981 and 1985 inclusive [1]. Another study, based on the data of the Group Health Cooperative of Puget Sound, Seattle, Washington (which covers about 260 000 individuals), investigated hospitalized patients from 1972 to 1986 inclusive. The incidence of erythema multiforme, SJS and TEN was estimated at 1.8 cases per million person-years for patients aged between 20 and 64 years; the incidence for patients aged less than 20 years, and 65 years or more, increased to 7 and 9 cases per million person-years, respectively [2]. The incidence of TEN was estimated at 0.5 per million per year. Reaction rates per 100 000 exposed individuals were as follows: phenobarbital 20, nitrofurantoin 7, co-trimoxazole and ampicillin 3 and amoxicillin 2. An Italian study estimated the incidence of TEN at about 1.2 cases per million per year [3]. A study based on computerized Medicaid billing data for 1980–84 from the states of Michigan, Minnesota and Florida reported an incidence of SJS of 7.1, 2.6 and 6.8 per million per year, respectively; penicillins, especially aminopenicillins, were most frequently implicated [4]. In West Germany, the overall annual risk of TEN and of SJS was estimated over the years 1981–85 as 0.93 and 1.1 per million, respectively; drugs most frequently implicated were antibiotics (sulphonamides and beta-lactam agents), and analgesics and non-steroidal anti-inflammatory agents (NSAIDs) [5]. In this study, it was possible to attribute the cause of the TEN to a drug in 88% of cases. Another study estimated the incidence for West Germany and Berlin for SJS and TEN as up to 1.89 per million inhabitants per year [6]. An ongoing international case–control study of TEN and SJS in relation to the use of drugs is being carried out, based on data collection in France, Italy, Germany and Portugal [7]. The incidence of SJS/TEN with long-acting sulphonamides, sulphones, antibiotics, anticonvulsants, NSAIDs or allopurinol is fortunately rare, occurring only once per 10 000–100 000 courses of drug given [8,9]. The incidence of TEN (cases/million/year) has been reported to be 2.7 times higher, and the fatality twice as high (51% compared with 25%), in the elderly compared with younger adults; the same drugs (NSAIDs, antibacterials and anticonvulsants) are incriminated in both groups [10].

Patients with AIDS have a dramatically increased incidence of TEN [11]; 14 of 80 consecutive cases of TEN patients were HIV infected, and 15 cases of AIDS-associated TEN occurred in the Paris area over a study period, compared with the expected 0.04 cases [12]. Sulphonamides (sulfadiazine, co-trimoxazole, sulfadoxine), clindamycin, phenobarbital and chlormezanone were implicated [12],

as were sulfadiazine and pyrimethamine/clindamycin [13]. Patients with AIDS are more likely to demonstrate multiple cutaneous drug reactions [14].

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Aetiology

Immunology

SJS and TEN, like erythema multiforme, would seem to have an immunological pathogenesis. In general, $CD4^+$ T cells predominate in the upper dermis, while epidermal $CD8^+$ T cells and macrophages are variable and Langerhans' cells virtually disappear. Keratinocytes express HLA-DR and ICAM-1, and there is endothelial cell ICAM-1, vascular cell adhesion molecule 1 (VCAM-1) and E-selectin expression [1–7]. $CD3^+$ activated T cells expressing the skin-homing receptor (cutaneous leukocyte antigen, CLA) in both skin and peripheral blood parallel the severity of the disease, and tumour necrosis factor-α (TNF-α), IFN-γ and interleukin-2 (IL-2) are overexpressed in peripheral blood mononuclear cells, suggesting an important role for T cells in TEN [7]. Soluble TNF-α (sTNF-α), sTNF-R1 and sTNF-R2 levels were significantly higher in TEN blisters than in burns [8]. sTNF-R1 and sTNF-R2 were significantly more abundant in TEN blisters than serum, indicating that TNF-α processing was mainly a local event in TEN skin [8]. Significantly higher levels of sIL-2R and lower levels of IL-1α were present in blister fluid, but not serum, of patients with TEN compared with patients with burns [9]. Cytokines released by activated mononuclear cells and keratinocytes may contribute to local cell death in TEN. Prominent involvement of the monocyte–macrophage lineage, including factor $XIIIa^+$ $HLA\text{-}DR^+$ dendrocytes and $CD68^+$ $Mac387^+$ macrophages before, during and especially after epidermal necrosis has been reported [6], with dense labelling of the epidermis for TNF-α. Factor-$XIIIa^+$ dendrocytes appear activated in the skin, and depleted from lymph nodes [10].

Keratinocytes from TEN patients have been reported to undergo extensive apoptosis [11]. Activated lymphocytes might induce apoptosis via an interaction between *Fas* antigen (CD95), expressed by keratinocytes after exposure to IFN-γ, and its ligand *Fas*-ligand (FasL), expressed on the surface of and secreted by lymphocytes [12]. Sera from TEN and SJS patients contained high concentrations of soluble FasL (sFasL), and induced abundant keratinocyte apoptosis *in vitro*, compared with sera from patients with an erythema multiforme-type drug eruption [13]. Moreover, peripheral blood mononuclear cells from TEN and SJS patients secreted high levels of sFasL on stimulation with the causal drug [13].

Alternatively, it has been proposed that keratinocyte necrosis may be mediated by cytotoxic lymphocytes via the perforin granzyme route. The key role of drug-specific T lymphocytes in the mechanisms of most drug reactions has been confirmed by *in vitro* studies of many clones of T lymphocytes [14]. $CD3^+$, $CD8^+$, $CD28^-$, KIR/KAR^+ (killer inhibitory receptor), CLA-positive cells demonstrating cytotoxic T lymphocyte (CTL)- and NK-like cytotoxicity predominated in blister fluid obtained early in one study [15]. In a case of co-trimoxazole-induced TEN, blister fluid lymphocytes were predominantly $CD8^+$, DR^+, CLA^+, $CD56^+$ perforin-positive T lymphocytes, cytotoxic only in the presence of the drug towards autologous Epstein–Barr virus (EBV) transformed lymphocytes and allogeneic cells sharing HLA-Cw4 [16]. Cytotoxicity occurred in the presence of either co-trimoxazole, sulfamethoxazole, or the nitroso metabolite of sulfamethoxazole, but not with the hydroxylamine metabolite of sulfamethoxazole. In a patient with carbamazepine-induced TEN, lymphocytes were more susceptible to cytotoxic killing by liver microsome-induced carbamazepine intermediates than by the parent drug [17].

Inducible nitric acid synthase is demonstrable in skin in TEN/SJS, which might indicate that nitric oxide mediates

apoptosis and necrosis [18]. The matrix metalloproteinase MMP2 has a significant role in epidermal detachment, inflammation and re-epithelialization. Increased levels of the activated forms of MMP2 were higher in TEN blister fluid compared with bullous pemphigoid, second-degree burns or suction blisters, indicating a potential role for MMP2 in the inflammatory reaction and repair process in TEN skin [19].

The reason why some individuals develop such marked immune reactions against medications is unknown. A widely accepted hypothesis is that patients suffering from severe drug reactions are exposed to increased amounts of reactive (oxidative) metabolites because of decreased production of normal soluble non-toxic metabolites, and/or a lowered ability to detoxify reactive metabolites [20]. Alteration in detoxification enzymes could be explained on a genetic basis (e.g. slow acetylation genotype) or on a functional basis (e.g. enzyme dysfunction in AIDS or other diseases). This 'reactive metabolites' hypothesis for drug eruptions still lacks definitive proof.

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Drugs implicated in Stevens–Johnson syndrome

Drugs potentially causing SJS are listed in Table 74.2 [1–8]. A retrospective study from Malaysia reported that the most common causes of SJS were sulphonamides, tetracycline and the penicillin derivatives [8]. In the USA, NSAIDs were reported to be an important cause [9]. Severe SJS-like reactions have been described resulting from sulphonamides with or without trimethoprim [10–12] and following malaria prophylaxis with Fansidar (pyrimethamine and sulfadoxine) [13,14]. Patients with AIDS are at an increased risk of developing severe SJS reactions to co-trimoxazole and thiacetazone [15–17]. The culprit drugs in a study from Thailand included the following: antibiotics (penicillin, sulphonamides, tetracycline, erythromycin); anticonvulsants (phenytoin, carbamazepine, barbiturates); antitubercular drugs (thiacetazone); analgesics (acetylsalicylic acid, fenbufen); sulphonylurea; and allopurinol. The total mortality rate was 14%: 5% for SJS and 40% for TEN [7]. Data from surveillance networks in France, Germany, Italy and Portugal on 245 people hospitalized because of SJS or TEN [18] indicated that for drugs usually used for short periods, relative risks were increased as follows: co-trimoxazole and other sulphonamide antibiotics 172, chlormezanone 62, aminopenicillins 6.7, quinolones 10 and cephalosporins 14, and for paracetamol (acetaminophen) 0.6 in France but 9.3 in the other countries. For drugs used for months or years, the increased risk was largely in the first 2 months, and was as follows: carbamazepine 90, phenobarbital 45, phenytoin 53, valproic acid 25, oxicam NSAIDs 72, allopurinol 52 and corticosteroids 54. For many drugs, including thiazide diuretics and oral hypoglycaemic agents, there was no significant increase in risk. The excess risk did not exceed five cases per million users per week for any of the drugs. Acetylsalicylic acid and other salicylates are not associated with a measurable increase in the risk of SJS or TEN [19].

Other drugs implicated in SJS include the antiretroviral drugs nevirapine [20–23] and abacavir [24], lamotrigine

[25], terbinafine [26], nystatin [27], ciprofloxacin [28], the antimalarials mefloquine [29] and hydroxychloroquine [30], cyclophosphamide [31], methotrexate [32], rituximab [33], the specific tyrosine kinase inhibitor STI571 used in leukaemia therapy [34], propylthiouracil [35], ranitidine [36], mebendazole and metronidazole [37], bezafibrate [38], diltiazem, nifedipine and verapamil [39], sertraline [40], fluoxetine and fluvoxamine [41] and tetrazepam [42]. SJS has followed vaccination [43], ingestion of a health drink (Eberu) containing ophiopogonis tuber [44] and use of cocaine [45].

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Drugs and other factors implicated in toxic epidermal necrolysis

There is a degree of overlap between SJS and TEN; SJS may evolve into TEN, and several drugs can produce both entities (Tables 74.2 & 74.3) [1–17]. A large number of

Table 74.3 Drugs causing toxic epidermal necrolysis.

Antibiotics	*Anticonvulsants*
Sulphonamides	Barbiturates
Co-trimoxazole*	Phenobarbital*
Sulfadoxine	Carbamazepine*
Sulfadiazine	Lamotrigine*
Sulfasalazine	Phenytoin*
Penicillins	Valproic acid†
Amoxicillin†	
Ampicillin†	*Antifungal agents*
Cephalosporins†	Terbinafine
Ethambutol	Griseofulvin
Fluoroquinalones†	
Isoniazid	*Antiretroviral drugs*
Streptomycin	Abacavir
Tetracycline	Nevirapine*
Thiacetazone*	
	Gastrointestinal drugs
Non-steroidal anti-inflammatory drugs	Famotidine
Phenylbutazone*	Omeprazole
Oxyphenabutazone	Ranitidine
Oxicam-derivatives	
Meloxicam*	*Miscellaneous*
Piroxicam*	Allopurinol*
Tenoxicam*	Chlorpromazine
Isoxicam	Dapsone
Diclofenac†	Gold
Fenbufen	Nitrofurantoin
Salicylates	Pentamidine
Naproxen	Tolbutamide
Pyrazolon derivatives	Vaccination

* Definite high risk.
† Probable low-risk association.

different drugs have been implicated anecdotally, but the most common triggers (Table 74.3) include antiepileptic drugs (phenytoin, barbiturates, carbamazepine and lamotrigine [18–20]), sulphonamides and trimethoprim [21], ampicillin and other β-lactam antibiotics [22], allopurinol [23], NSAIDs (especially pyrazolon derivatives, e.g. phenylbutazone, and oxicam derivatives) [23] and pentamidine. A high proportion of adult cases of SJS or TEN related to anticonvulsants occur in patients receiving radiotherapy for brain tumour. It is suspected that cancer and/or radiotherapy increases the risk.

In France, a survey showed two main classes of drug were most often responsible: antibacterial agents (especially sulphonamides); NSAIDs including oxyphenabutazone, and fenbufen; and phenytoin [24]. The incidence of erythema multiforme, SJS and TEN in a US series with the following drugs were reported as follows: phenobarbital 20, nitrofurantoin 7, co-trimoxazole and ampicillin each 3, and amoxicillin 2, per 100 000 exposed patients [7]. Review of the English language literature from 1966 to 1987 suggested that allopurinol, NSAIDs, phenytoin and the sulphonamide antibiotics were most frequently responsible [25]. A study from the USA reported that penicillins, especially aminopenicillins, were most frequently implicated [9]. In West Germany, drugs most frequently implicated were antibiotics (sulphonamides and β-lactam agents) and analgesics and NSAIDs [10]. In India, by contrast, one-third of cases were the result of drugs used for the treatment of tuberculosis, especially thiacetazone and isoniazid [26]. The absolute incidence of phenytoin-induced TEN is very low, with nine cases reported in the USA over a decade, compared with 2 million Americans who took phenytoin [11]. Similarly, 4 in 232 390 patients on co-trimoxazole developed erythema multiforme or SJS, while only 1 in 196 397 prescribed cephalexin developed TEN [21]. The risk of SJS/TEN is highest in the first 8 weeks of therapy with phenytoin, phenobarbital, carbamazepine and lamotrigine; the risk with valproic acid is less [27]. Terbinafine [26–28] and antiretrovirals including nevirapine [29] have also been associated with TEN. In Europe, nevirapine has replaced sulphonamides as the leading cause of SJS and TEN related to AIDS [30]. By contrast, the following medications are not associated with a moderate or high risk of causing TEN: contraceptive pills, benzodiazepines, thiazide diuretics, sulphonylurea antidiabetics, angiotensin-converting enzyme inhibitors, β-blockers, acetyl salicylic acid and fibrate cholesterol-lowering agents [17].

More than 100 different medications have been reported as having caused TEN, but case reports are of limited significance because publications are biased toward 'original' and new associations. Nonetheless, other antibiotics, antifungals and antiprotozoal drugs incriminated include ciprofloxacin [31,32], vancomycin [33,34], ofloxacin [35], thiacetazone [36], fluconazole [37], griseofulvin [38,39], Fansidar [40] and foscarnet [41], as well as the antimalarials mefloquine [42] and hydroxychloroquine [43]. Miscellaneous causes include fluoxetine and fluvoxamine [44,45], tetrazepam [46], diltiazem, nifedipine and verapamil [47], thalidomide [48], methotrexate [49,50], cytosine arabinoside [51], IL-2 [52], etretinate [53], omeprazole [54], ranitidine [55], famotidine [56] and cimetidine [57], atorvastatin [58], valdecoxib and celecoxib [59,60]. Even acetaminophen (paracetamol) has rarely been recorded as causing TEN [61].

Immunization with diphtheria–pertussis–tetanus (DPT), measles, poliomyelitis, smallpox and influenza vaccines has been recorded as a cause of TEN [11,62,63]. Single cases of TEN have followed use of the radiological contrast media diatrizoate solution for excretory pyelography [64] and iopamidol for cardiac catherization [65], use of a terconazole vaginal suppository [66] and contact with a toxic fumigant, acrylonitrile [67]. TEN has been described in association with graft-versus-host reactions [68,69] and with lupus erythematosus [70]. It is not yet clear whether SJS and TEN are always drug-induced or may have other causes. A few well-documented cases have been attributed to *Mycoplasma pneumoniae* or *Klebsiella pneumoniae* infections.

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Pathology

The histology of early lesions is characterized by moderate perivascular mononuclear cell infiltration in the papillary dermis, with epidermal spongiosis and exocytosis. Satellite cell necrosis, with close apposition of mononuclear cells to necrotic keratinocytes, may be seen. In established TEN (Fig. 74.4), there is full-thickness necrosis of the whole epidermis with blister formation. The necrotic process involves the epithelial lining of sweat ducts, while hair follicles are much less affected. There is little in the way of any dermal abnormality. Macrophages and dendrocytes with a strong immunoreactivity for TNF-α predominate in a cell-poor infiltrate [1]. TEN may be rapidly differentiated from the staphylococcal scalded skin syndrome (SSSS), in which blister formation results from intraepidermal subcorneal splitting caused by a toxin produced by *Staphylococcus aureus* group II, phage type 71, by examination of frozen sections of blister roof material [2,3]. The level of splitting is subcorneal in SSSS, while in TEN it is much lower, because the full thickness of the necrotic epidermis forms the roof of the blister. Differentiation from graft-versus-host disease may be difficult [4]. Direct immunofluorescence is negative, with the exception of a possible 'lupus band test' in cases associated with SLE.

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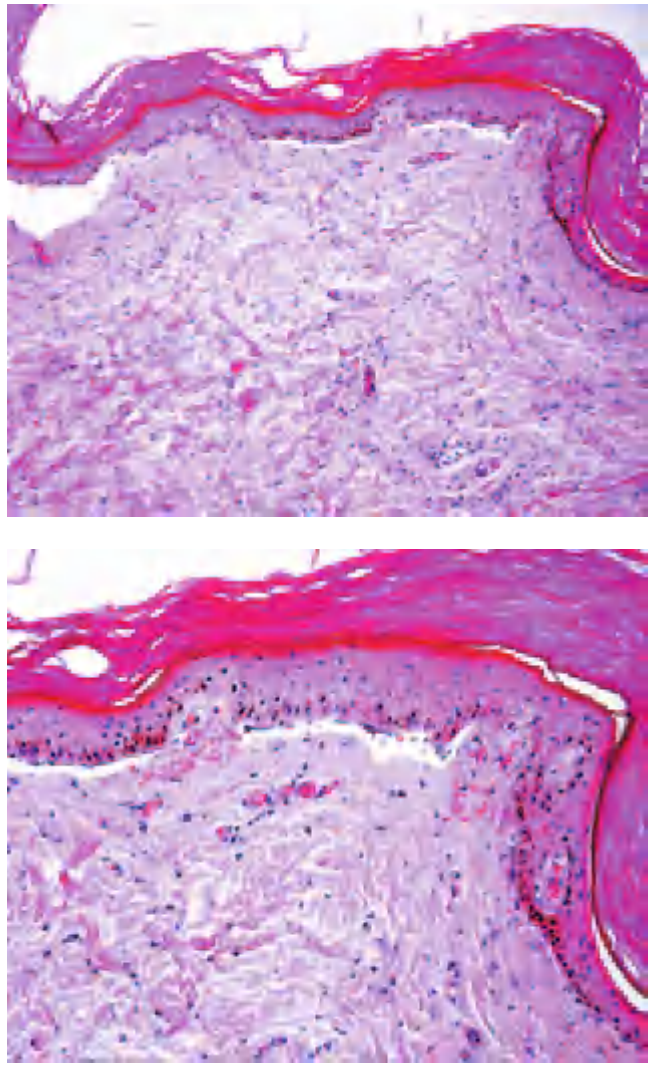

(a) (b)

Fig. 74.4 (a,b) Histopathology of toxic epidermal necrolysis. Note full-thickness necrosis of epidermis, dermal–epidermal separation, and paucity of upper dermal cellular infiltration (H&E). (Courtesy of Dr E. Calonje, St John's Institute of Dermatology, London, UK.)

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Clinical features

Stevens–Johnson syndrome [1–6]

SJS is a severe illness of usually sudden onset, associated with marked constitutional symptoms of high fever, malaise, myalgia, arthralgia and extensive erythema multiforme of the trunk, with occasional skin blisters and erosions covering less than 10% of the body's surface area.

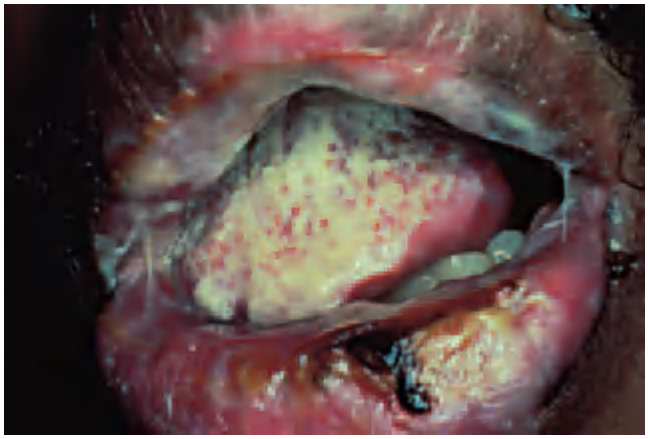

Fig. 74.5 Stevens–Johnson syndrome. Severe erosions at the lips.

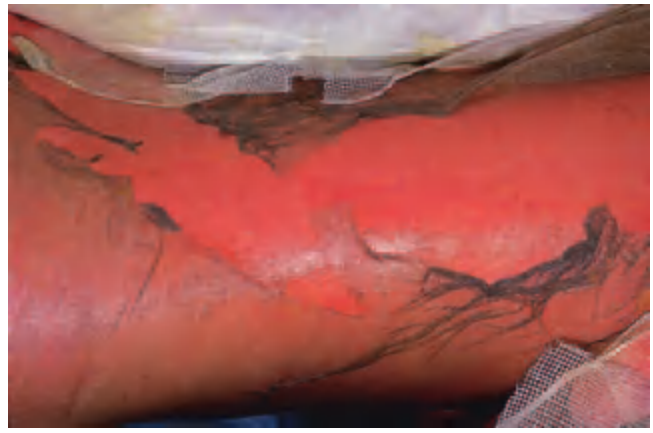

Fig. 74.6 Toxic epidermal necrolysis showing dusky erythema and stripping off of necrotic epidermis.

A prodromal systemic illness lasting 1–13 days before the eruption may occur. The skin lesions are variable in extent, and consist of typical maculopapular lesions of erythema multiforme, bullous or, rarely, pustular lesions. New crops of lesions develop over a period of 10 days, or sometimes 3–4 weeks. There is significant involvement of mucous membranes: the frequency in one review of 81 cases was oral mucosa 100%, eyes 91%, male genitalia 57% and anal mucous membrane 5%, while bronchitis and pneumonitis occurred in 6% and 23% of cases, respectively [6].

The oral mucous membrane shows extensive bulla formation followed by erosions and a greyish white membrane, so that the mouth and lips show characteristic haemorrhagic crusting (Fig. 74.5) [7]. The most common change in the eyes is a severe catarrhal or purulent conjunctivitis, but bulla formation may occur. Corneal ulceration is frequent, and anterior uveitis or panophthalmitis may occur. The eye changes often regress completely, but synechiae, corneal opacities and rarely blindness are possible sequelae. Genital lesions are frequent; retention of urine may occur, as may involvement of the bladder. Respiratory symptoms may occur, and often the radiological changes within the lungs are far greater than the symptoms. Abnormalities of liver function may be present. Renal involvement with haematuria or even renal tubular necrosis has been reported and may lead to progressive renal failure. Less common symptoms include diarrhoea, paronychia, shedding of nails, polyarthritis and otitis media. Untreated, this disease used to have a mortality of 5–15% from infection, toxaemia or renal damage, but the mortality rate is now lower. The eruption usually heals without sequelae, although the eyes may be permanently damaged.

Toxic epidermal necrolysis [8–17]

SJS should be differentiated from TEN, in which typically sheet-like erosions involve more than 30% of the body surface with widespread purpuric macules or flat atypical target lesions, and in which there is severe involvement of conjunctival, corneal, irideal, buccal, labial and genital mucous membranes [8–10]. SJS may, however, evolve into TEN.

Clinically, TEN presents with a prodromal period with flu-like symptoms (malaise, fever, rhinitis and conjunctivitis), sometimes accompanied by difficulty in urination, which usually lasts 2–3 days; however, it may last from 1 day to 3 weeks before signs of skin involvement develop. The acute phase of TEN is characterized by persistent fever, severe mucous membrane involvement and generalized epidermal sloughing to leave large raw painful areas, and lasts from 8 to 12 days. There may be an initial 'burning' maculopapular, urticarial or erythema multiforme-like eruption. This may start on the face and on the upper part of the body and rapidly extends. Most frequently, the initial individual skin lesions form poorly defined macules with darker purpuric or blistering centres, progressively merging on the chin, upper parts of chest and back. Less frequently, the initial manifestation may be a more confluent erythema. Sometimes the lesions are predominantly in photoexposed areas.

There is rapid progression to areas of confluent erythema, often starting in the axillae and groins, followed by blistering and sloughing of large areas of skin (Fig. 74.6). Nikolsky's sign, the ability to extend the area of superficial sloughing by gentle lateral pressure on the surface of the skin at an apparently unaffected site, may be positive. Detachment of the full thickness of the epidermis at sites of pressure or trauma, such as the back, shoulders or buttocks, leaves a dark red oozing dermis. In other areas, the pale necrotic epidermis remains *in situ*, with a wrinkled appearance. Blisters on the palms and soles may remain intact. However, the entire skin surface may be involved, with up to 100% of the epidermis sloughing off. Only the

Acute	Chronic
Similar to burns: depends on extent	*Ocular complications* (up to 35%)
Massive fluid and electrolyte loss (3–4 L/day)	Conjunctivitis, ectropion or entropion, corneal scarring
Prerenal renal failure	Symblepharon, Sjögren-like sicca syndrome
Bacterial infection and septicaemia	*Other mucous membrane involvement*
Hypercatabolism: insulin resistance	Oesophageal stricture
Diffuse interstitial pneumonitis	Phimosis
Mucous membrane involvement	Vaginal synechiae
	Oro-genital ulcers
	Miscellaneous
	Wound infection
	Pigmentary changes
	Nail dystrophy
	Hypohidrosis
	Scarring alopecia
	Contractures
	Development of melanocytic naevi

Table 74.4 Complications of toxic epidermal necrolysis.

hairy portion of the scalp is never affected. The process tends to occur in waves, over a 3–5-day period (sometimes a week), but involvement of the whole of the body surface occurs within 24 h in approximately 10% of cases.

Mucous membranes (particularly the buccal, and less commonly the conjunctival, genital, perianal, nasal, tracheal, bronchial, pharyngeal and oesophageal membranes) are involved in nearly all patients (85–95%). Widespread painful erosions cause crusted lips and increased salivation, and redness and soreness of the eyes is conspicuous, with photophobia. Mucous membrane lesions may precede the skin lesions by up to 3 days in one-third of cases [10]. Urethritis develops in up to two-thirds of patients, and may lead to urinary retention. Stomatitis and mucositis lead to impaired oral intake with consequent malnutrition and dehydration. Intestinal involvement has been documented [12]. Healing occurs by re-epithelialization; this may occur within a few days on the anterior thorax, but is slower on the back and at intertriginous areas. Most patients' skin lesions are completely healed in about 3–4 weeks, but mucosal lesions take longer and the glans penis may take up to 2 months to heal over.

Investigations. Approximately 50% of patients have a slight increase in aminotransferases, and approximately 10% have overt hepatitis. A rise in serum amylase is often present during the first few days, probably secondary to involvement of salivary glands. Anaemia is constant after a few days, and lymphopenia is usual, with a selective and transient depletion of $CD4^+$ T lymphocytes. Neutropenia is observed in approximately 30% of patients, and thrombocytopenia in 15%; eosinophilia is very unusual. Hypophosphataemia is nearly constant, and hyperglycaemia is frequent, as are increased urea and creatinine levels. Subclinical interstitial oedema is often noted on early chest X-rays.

Complications (Table 74.4). Acute complications are similar to those of extensive burns. The total daily fluid loss averages 3–4 L in adult patients with TEN affecting 50% of body surface area. It induces a reduction of intravascular volume and functional renal failure. If not corrected, hypovolaemia may lead to haemodynamic alterations and organic renal failure. Pneumonia or pneumonitis occurs in up to 30% of patients, contributed to by sloughing of the tracheobronchial tree [18]. Adult respiratory distress syndrome (ARDS) is one of the main complications. Anaemia or leukopenia, caused by selective depletion of $CD4^+$ helper T cells, is moderately common [16]. Oesophageal and intestinal erosions, with an endoscopic appearance reminiscent of ulcerative or pseudomembranous colitis, are recorded [19]; strictures may result. Disseminated intravascular coagulation is documented. Septicaemia, primarily the result of *Staphylococcus aureus* or *Pseudomonas* but on occasion caused by Gram-negative organisms or *Candida*, may result from infection of the skin, lungs, urinary tract catheters and intravenous (especially central) lines. Patients are usually febrile and shivering, even in the absence of infection. Hypothermia is infrequent and usually a marker of severe infection and irreversible septic shock. Protein loss, from skin lesions and increased catabolism, may reach 150–200 g/day. Inhibition of insulin secretion and/or insulin resistance in peripheral tissues is frequent, resulting in elevated plasma glucose levels and glycosuria.

Mucocutaneous complications of TEN [20,21] include wound infections, pigmentary changes (either hyper- or hypopigmentation) which may or may not resolve with time, nail shedding or dystrophy, hypohidrosis or hyperhidrosis, scarring alopecia and hypertrophic scarring which may lead to contractures. Development of melanocytic naevi has been reported [22]. Mucosal involvement may lead to chronic xerostomia, oesophageal strictures,

phimosis, and chronic oro-genital erosions or vulvovaginal stenosis [23]. Appearances may resemble scarring from cicatricial pemphigoid or lichen planus.

Ocular complications occur in 40–50% of survivors [16], and include conjunctivitis, watery eyes because of tear duct obstruction, pseudomembrane formation, photophobia, ectropion, entropion with trichiasis, symblepharon and corneal vascularization, corneal opacities, and corneal ulceration and scarring [19]. Blindness may result. Lacrimal duct destruction may result in xerophthalmia. A Sjögren-like sicca syndrome may be seen [24]. A 'post-SJS/TEN' ocular syndrome with punctuate keratitis and formation of a corneal pannus may result in photophobia, burning eyes and visual impairment. Ankylosymblepharon (fusion of eyelids to each other and to the globe) may follow secondary infection.

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Prognosis

There is an appreciable mortality as a result of TEN, increasing from 5% in SJS, to 10–15% in transitional SJS–TEN and 30–40% in TEN. ARDS and multiple organ failure are the usual causes of death [1]. They are often precipitated by sepsis with septicaemia, mainly resulting from *Staphylococcus aureus* and *Pseudomonas aeruginosa* [2]. Other causes of death are pulmonary embolism and gastrointestinal bleeding. Early withdrawal of the causative drug improves the prognosis, and drugs with a long half-life are associated with an increased risk of death [3,4]. Increased age in most [5] but not all [1] studies, extensive TEN, delay (more than 3–4 days) in referral to a regional centre [6], early thrombocytopenia and early empirical antibiotic treatment elsewhere are associated with a worse prognosis. It has been claimed that severe granulocytopenia is a poor prognostic indicator [7], although this has been disputed on the basis that lymphopenia is more usually found in severe TEN [8]. A specific severity-of-illness score to determine prognosis for cases of TEN (SCORTEN) based on seven independent risk factors for death as assessed on the first day of hospitalization, has been advocated (Table 74.5) [9].

Table 74.5 SCORTEN prognosis score.

*Parameter**
Age > 40 years
Presence of a malignancy
Epidermal detachment > 30%
Heart rate > 120/min
Bicarbonate < 20 mmol/L
Urea > 10 mmol/L
Glycaemia > 14 mmol/L

1 point awarded for each parameter; SCORTEN derived by totalling scores

SCORTEN	Probability of death (%)
0–1	3
2	12
3	35
4	58
≥ 5	90

* Worst recorded value in the 24 h after admission.

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Diagnosis

Toxic shock syndrome, which usually occurs in menstruating women, may cause widespread erythema and desquamation, but skin tenderness and bullae are absent. Similarly, SSSS can generally be differentiated on clinical appearances and on the basis of histology. Linear IgA bullous dermatosis, whether idiopathic or drug-induced (e.g. vancomycin), may mimic TEN clinically [1], as may a widespread bullous fixed drug eruption [2,3]. The subcorneal aseptic pustules of acute generalized exanthematous pustulosis (AGEP) or acute pustular psoriasis (von Zumbusch) are usually distinctive but may coalesce to produce extensive superficial detachment mimicking TEN. Paraneoplastic pemphigus may closely resemble SJS, but direct immunofluorescence is positive.

Identification of the responsible drug is often difficult, because patients frequently take more than one medication (an average of 4.4 in one series) [4,5]. A helpful guideline is that most drugs that cause TEN have been first given between 1 and 3 weeks previously [6–8]; another very suggestive guide is that of recurrence within 48 h on administration of a drug previously recorded as having caused a similar reaction. A given drug is unlikely to be responsible for TEN if it was first given 24 h previously, or if the duration of treatment exceeds 3 weeks [4,7]. In case–control analyses, the risk with drugs used on a long-term basis was restricted to the first few weeks [8]. However, phenytoin-induced TEN may occur any time between 2 and 8 weeks after initiation of therapy, and may progress despite discontinuation of phenytoin days or weeks earlier [9]. Skin testing is unfortunately unreliable. Relevant positive patch tests were found in only 9% of 22 patients with SJS/TEN, compared with 50% of 14 patients with AGEP [10]. The *in vitro* lymphocyte transformation test is of no value [11]. In summary, there is no reliable test to confirm the aetiological role of a given drug in an individual case [6]. Re-exposure to drugs suspected of causing a reaction has resulted in fatality, and should not be carried out for diagnostic purposes [12].

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Treatment [1–10]

The management of TEN is summarized in Table 74.6, and is perhaps best carried out on a dermatology intensive care or a burns unit. Clearly, presumptive causative drugs should be stopped as soon as possible. It should be remembered that HIV-1 infected patients with TEN are an occupational risk for health care workers [11]. The main principles of symptomatic therapy are the same as for major burns and include fluid replacement, anti-infectious therapy, aggressive nutritional support, warming of environmental temperature and skin care with appropriate dressings. The extent of the detachment of the epidermis should be evaluated daily as a major prognostic factor. It is expressed as a percentage of body surface area (BSA), using burn tables or the simple rule that one hand (palm and fingers) corresponds to 1% of the BSA. Hyperventilation and mild hypoxaemia on blood gas analysis indicate a high risk of progression to ARDS.

There is a significant incidence of disabling long-term complications in survivors, especially in relation to ocular and other mucous membranes. It is therefore particularly important to be aware of these and to take preventative

Table 74.6 Management of toxic epidermal necrolysis.

Intensive therapy or burns unit
Air-fluidized bed
Maintain fluid and electrolyte balance (replace up to 5 L/day)
Maintain body temperature
Maintain nutrition; oral hygiene
Frequent ophthalmological assessment
Antiseptic/antibiotic eye drops 2-hourly
Disrupt synechiae frequently
Limitation of infection
Neutropenia: reverse barrier nursing
Frequent cultures of erosions, and blood cultures
Culture tips of Foley catheters and intravenous lines
Prophylactic broad-spectrum systemic antibiotics (controversial)
Topical cleansing/antibacterial agents
0.5% silver nitrate solution on gauze *or* 10% chlorhexidine gluconate washes *or* saline washes *or* polymixin/bacitracin *or* 2% mupirocin
Avoid silver sulfadiazine
Wound care
Remove necrotic epidermis (controversial)
Paraffin gauze or hydrogel dressings
Biological dressings (xenografts, allografts, skin substitutes)

measures. Physical contact with patients during nursing procedures may produce loss of large sheets of skin, and the use of a turning frame or a ripple or air-fluidized bed will lessen discomfort and facilitate nursing care. Trauma, as with adhesive dressings or ECG electrode attachment pads, should be minimized. Eyelids and conjunctivae should be lubricated with soft paraffin, and gently separated to prevent the formation of adhesions. Opthalmological advice should be sought. Use of gas-permeable scleral contact lenses resulted in improved quality of life in 90% of patients by reducing photophobia and discomfort, and also improved visual acuity and healed corneal epithelial defects in 50% of patients [12]. Amniotic membrane has been used as a dressing for eye lesions in TEN [13]. Autologous germinal cells taken from the limbus and grafted on a support of amniotic membrane may be beneficial in the most severe cases [14]. Skin or other infection must be treated promptly. Good mouth care is important in preventing parotitis. Vaginal examination should be repeated in women and appropriate dressings used to avoid synechiae if erosions are seen. The issue of whether necrotic tissue should be removed is controversial; some authorities feel that this impairs healing. Eroded areas should be treated with biological [15] or synthetic dressings. Use of silver nitrate impregnated dressings [16] has been advocated.

There is no consensus on the merits of therapy with moderately high-dose corticosteroids for TEN. Some authorities maintain that high-dose steroid therapy promotes or masks the signs of infection, delays healing, precipitates gastrointestinal bleeding, prolongs hospitalization and increases mortality [1,2,17–19]. However, others favour steroid therapy on the basis that it may reduce inflammation and keratinocyte necrosis [20]. It is generally agreed that if steroids, or any other immunosuppressive agent, are to be given, then they should be administered as early as possible in the evolution of the disease. There have been anecdotal reports on the beneficial use of plasmapheresis [21–23], but this has been questioned [24]. Both cyclophosphamide [25] and ciclosporin A [26–28] have produced improvement in anecdotal cases. Thalidomide therapy for TEN was associated with increased mortality [29]. *N*-acetyl cysteine has been documented to be useful in a few patients [30], perhaps because it enhances drug metabolism. On the basis that potential *Fas* (CD95) -mediated keratinocyte death in TEN might be blocked by naturally occurring *Fas*-blocking antibodies included in human immunoglobulin preparations, there have been several reports, mostly favourable, on human intravenous immunoglobulin (IVIG) therapy for TEN [31–39]. Early infusion of high-dose (1 g/kg/day for 3 days in adults) IVIG appears safe and well tolerated, but there may be variations in the efficacy of different batches of IVIG [36]. However, a recent report found no benefit from IVIG therapy [38], and there is currently no consensus on the best management for TEN [40]. There has been a single case report on the efficacy of treatment with monoclonal chimeric IgG anti-TNFα antibodies [41]. Because of the rarity of the condition, controlled trials assessing these different treatment approaches are very difficult to carry out.

Prevention and future use of drugs

Patients should be advised to avoid re-exposure to the suspect drug(s). Published cases of recurrences have all been attributed to the same generic drug or to compounds chemically closely related (e.g. aromatic anticonvulsants). Therefore, there is no rationale for restricting the use of all classes of 'high-risk drugs'. Because some familial cases have been reported, first-degree relatives should be alerted to their elevated risk of reaction to the same drug(s). Cases should be notified to regulatory agencies.

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Chapter 75

Topical Therapy

J. Berth-Jones

Dermatologists have the good fortune to work on the most accessible organ of the body. This gives us numerous advantages and greatly facilitates not only the diagnosis but also the treatment of skin disease. While systemic administration of drugs is often necessary in dermatology, many inflammatory and neoplastic conditions can be effectively managed using the wide range of externally applied physical or pharmacological modalities that are available, the latter being the subject of this chapter. Some of these are time-honoured treatments which have been used for a century or more, while others belong to the ever-expanding range of newer and increasingly potent agents constantly being developed and formulated for topical use.

Topical treatment offers the potential to achieve high concentrations of a drug in the skin with minimal exposure of other organs. This can greatly increase efficacy and also safety relative to systemic administration. When side effects do occur, they are most likely to take the form of localized reactions.

Prescribing topical treatment

Prescribing topical medication requires careful consideration of several factors if optimal results are to be achieved. When the treatment contains an active pharmaceutical agent it is necessary to specify the concentration of the drug, the vehicle and the frequency of application. The patient requires advice on the quantity to be used, precisely where it should be applied and often further explanation about precise timing of application in relation to bathing and other treatments. The prescriber needs to be aware of the hazards associated with a topical treatment, particularly the likelihood of the medication inducing irritant or allergic reactions. It is also important to understand the factors that influence systemic absorption.

Drug concentration

The conventions for defining the concentration of a drug in topical formulations are summarized in Table 75.1. The efficacy of a topically applied drug is usually not proportionate to the concentration. Doubling or halving the concentration of a drug often has a surprisingly modest effect on the response. In the case of topical corticosteroids, for example, different concentrations of active drug often have a similar biological effect [1]. However, the effect of changing the concentration in an individual case may be much greater than the apparent effect when two concentrations are compared in a clinical trial. There may also be differences between adults and children. The difference in efficacy between two concentrations of tacrolimus for example, appears to be larger in adults than in children.

Table 75.1 Prescribing conventions for specifying concentration.

1 The concentration of a drug contained in a topical medication is usually written as a percentage representing the proportion of the formulation, by weight, which is the active constituent. A concentration of 1% indicates that 1 g of drug will be contained in 100 g of the formulation. A wide range of concentrations can be specified in this way. Thus, salicylic acid may be used in concentration as high as 60% for treatment of plantar warts or corns, whereas calcitriol is used at a concentration of 0.003% in treatment of psoriasis. A very low concentration such as this is more often written as 3 μg/g

2 A frequently used alternative, especially for liquid preparations, is to express the percentage of the drug as a proportion of the volume of the formulation. Thus, a 1% solution contains 1 g of drug in 100 mL of the formulation. The abbreviations w/w (weight in weight) and w/v (weight in volume) are often employed to indicate which convention is being used

3 Another convention often used to describe the concentration of a solution is in 'parts'. Thus, a 1 part in 1000 solution of potassium permanganate contains 1 g in 1 L of solution, which could be expressed as 0.1% (w/v)

Choice of vehicle

Topical medication must be applied to the skin in a suitable vehicle. This term encompasses all the constituents of the formulation apart from the active pharmaceutical agent. The properties of some types of vehicle are summarized below. The choice of vehicle depends on the anatomical site to be treated and the condition of the skin. As a rule, acutely inflamed skin is best treated with fairly bland preparations, which are least likely to irritate. Moist or exudative eruptions are conventionally treated with 'wet' medications such as lotions or creams, while dry skin responds well to the occlusive action of ointments. Hair-bearing skin, especially the scalp, can be treated with medicaments formulated into shampoos, lotions, gels or mousses. The cosmetic properties of the vehicle assume particular importance when treating the face. Oily skin affected by acne is often best treated with lotions, while the more sensitive skin affected by rosacea may benefit from the emollient effect of a cream.

The characteristic features of various types of formulation are as follows (British Pharmacopoeia; BP).

Ointments. These are semi-solid vehicles composed of lipid; for example, white soft paraffin BP (petrolatum). They have useful occlusive and emollient properties. Some ointments contain emulsifying agents such as polyhydric alcohols (macrogols, polyethylene glycol) or cetostearyl alcohol (e.g. Emulsifying Ointment BP). The latter have the advantage of being less greasy, with good solvent properties, and are easily washed off. Ointments require fewer preservatives than other vehicles because they contain no water and do not sustain growth of microorganisms.

Creams. These are semi-solid emulsions containing both lipid and water. Emulsions are suspensions, either of lipid droplets in water or of water droplets in lipid (see emulsifiers, p. 75.7). In the former category are aqueous or vanishing creams (e.g. Aqueous Cream BP). These are water-miscible, cooling and soothing, and are well absorbed into the skin. In the latter category are water-in-oil creams (e.g. Oily Cream BP). These are immiscible with water and more difficult to wash off. They are emollient, lubricant and mildly occlusive (but less so than ointments).

Pastes. These are semi-solid preparations containing a high proportion of finely powdered material such as zinc oxide or starch. Protective (fatty) pastes are greasy and therefore messy and water insoluble. They are difficult to apply and remove, but their stiffness permits accurate localization of the paste and any constituent medication. They are occlusive, protective and hydrating. The consistency of these pastes can be 'softened' by adding oils or 'hardened' with hard paraffin. Drying pastes, also called cooling pastes, are mixtures of powder with liquid. These are non-greasy, water-miscible and easy to apply and remove. They are drying and soothing, and can be used in conjunction with dressings as paste bandages or as vehicles for active medicaments.

Lotions. These are liquid formulations that are usually simple suspensions or solutions of medication in water, alcohol or other liquids. Those containing alcohol often sting, especially when applied to broken skin. When left on the skin the liquid will evaporate, leaving a film of medication on the surface. Aqueous suspensions of powders such as calamine, which require shaking prior to each application, are known as *shake lotions*.

Gels. These are thickened aqueous lotions. They are semi-solid preparations containing high-molecular-weight polymers, such as carboxypolymethylene (Carbomer BP) or methylcellulose, and can be regarded as thickened aqueous lotions. Lotions and gels are especially suitable for treating the scalp and other hairy areas of skin. Like lotions, gels tend to dry when left on the skin. Gels can provide cosmetically acceptable formulations for use on the face.

Powders. These are applied directly to the skin and are also known as *dusting powders*. They can reduce friction (talc) or excessive moisture (starch). They are occasionally used to deliver drugs such as antifungal agents applied to the feet.

Paints. These are liquid preparations, either aqueous, hydro-alcoholic or alcoholic (*tinctures*), which are usually applied with a brush to the skin or mucous membranes and then evaporate. Collodion preparations are also sometimes referred to as paints.

Collodions. These (e.g. Flexible Collodion BP) are liquid preparations consisting of cellulose nitrate in organic solvent. They evaporate rapidly to leave a flexible film that can hold medicaments in contact with the skin. They are most frequently used to apply salicylic and lactic acids to warts. They may also be used as protectives to seal minor cuts and abrasions. They are easy to apply and are water repellent, but are inflammable.

Microsponges [2]. These are a novel approach to formulation, involving the use of porous beads, typically 10–25 μm in diameter, forming a reservoir loaded with the drug. This approach has been used for cosmetics and sunscreens as well as for medications such as benzoyl peroxide and retinoids. The aim is to provide sustained release of the drug while reducing irritation.

Liposomes. These are structures comprising an aqueous phase surrounded by a lipid capsule, ranging widely in diameter from several nanometers to several micrometers. They may contain several lipid layers so that the structure can be likened to that of an onion. Under certain conditions liposomes can release their contents close to a target cell, fuse with the cell membrane or be endocytosed by the cell [3]. They can be formulated into creams and gels. This technology is used in cosmetics but has so far had little impact on dermatological treatment. However, it may prove useful for reducing irritation from topical use of agents such as tretinoin, benzoyl peroxide and dithranol, and in reducing the staining of skin and clothes from the latter [3–5]. Liposomes do not appear to penetrate intact into the intracellular compartment of the epidermis, although an *in vitro* study using reconstructed human skin has suggested that liposomal lipids can be incorporated into the intercellular lipids of the stratum corneum and cell membranes in the uppermost viable layers of the epidermis [6].

Frequency of application

The frequency of application must be specified in order to maximize the response while avoiding side effects such as irritation. Excessive frequency of application may also result in unnecessary systemic exposure to the drug. Emollients should be applied frequently enough to maintain their physical effect. This may require several applications daily. Active preparations are usually applied just once or twice a day. As a general rule, twice daily application of drugs such as corticosteroids or deltanoids is only marginally more effective than once daily application, while requiring double the amount of medication and increasing systemic exposure to the drug. The pharmacological actions of a drug may persist long after it has left the surface of the skin. Thus, the ability of a potent topical corticosteroid to inhibit flares of atopic dermatitis when applied just twice weekly [7] seems unlikely to be explained simply by persistence of a reservoir of the drug. Increasing the interval between applications can be a useful method of gradually reducing the intensity of a treatment, especially when it is difficult to do so by using a lower concentration or less potent agent.

Quantity to be applied

The total quantity to be dispensed should be specified, and it is helpful to inform the patient how long the prescribed quantity is expected to last. There is a tendency, especially in the case of topical steroids, for patients to be overcautious in their interpretation of the advice to 'apply sparingly' which will be found on the package insert. Minute quantities are rarely effective. Conversely, inappropriate use of active medicaments as emollients is not only wasteful but often hazardous. The potential for systemic absorption must be taken into account when prescribing, for example, topical corticosteroids, deltanoids or salicylic acid.

Estimates of the quantity of cream or ointment required for a single total body treatment of a male adult have varied considerably. In one study, a range of 12–27 g (average 18 g) was required for applications by 'trained operators' [8], while a range of 8–115 g (average 44 g) was required when the treatment was self-administered. In another study, in which treatment was applied by nurses, an average of 12 g of ointment was required [9]. In a more recent study, male patients treating themselves applied an average of 20 g of ointment, and females applied 17 g [10].

Based on these latter figures, the quantity required for 1 week of once daily application to the whole body would be approximately 140 g for males and 120 g for females, while for twice daily application, male and female patients require 280 and 240 g/week, respectively.

Table 75.2 provides approximate quantities required for single applications to specific anatomical regions in adults, while Table 75.3 provides a guide to total quantities required for a week of twice daily total body treatment for children of various ages. These guidelines can only be approximate and should be interpreted very flexibly. In addition to the obvious large differences between

Table 75.2 Approximate quantities (g) required for each application of medication to different anatomical regions. (Adapted from [10].)

Region	Males	Females
Trunk (including buttocks)	6.6	5.8
One leg	2.9	2.5
One foot	0.9	0.7
One arm and forearm	1.7	1.3
One hand	0.6	0.5
Face, neck and ears	1.3	0.9
Whole body	20	17

Table 75.3 Quantities (g) of medication required for twice daily application to the entire body at various ages. (Adapted from [13].)

Age	3 months	6 months	12 months	18 months	2 years	3 years	4 years	5 years	7 years	10 years	12 years
Daily requirement (g)	8	10	12	13	14	16	19	20	25	30	37
Weekly requirement (g)	56	67	84	93	95	112	135	140	172	210	256

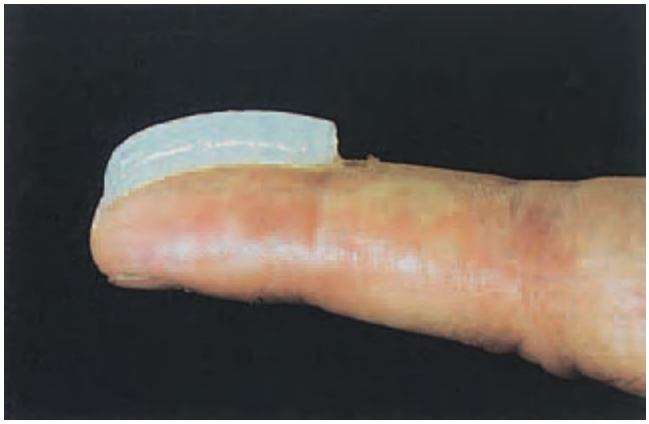

Fig. 75.1 The fingertip unit. From [13]. (Courtesy of Dr A.Y. Finlay and with permission from the Editor of *British Journal of Dermatology*.)

individuals of any age in body surface area, the condition of the skin may influence how far the medication will spread. Creams and ointments seem to cover a very similar area per unit of weight [8,9].

Simple practical guides to the quantity of a topical medication to apply are provided by the fingertip unit [10] and the rule of hand, as follows.

The *fingertip unit* is an approximate but practical measure of topical medication. It is the quantity of ointment extruded from a tube with a nozzle of 5 mm diameter (note that nozzles do vary somewhat) that extends from the distal crease of the forefinger to the ventral aspect of the fingertip (Fig. 75.1). This unit weighs approximately 0.49 g in males and 0.43 g in females [11] and covers, on average, an area of approxiamtely 300 cm^2. The number of units required for a single treatment of each anatomical region in adults and children of various ages is given in Table 75.4.

The '*rule of hand*' states that an area of the size that can be covered by four adult hands (including the digits) can be treated by 1 g of ointment or 2 fingertip units [12].

The figures discussed above are based on application of active medicaments. Emollients are applied for their physical properties rather than for delivery of a drug, and are generally used much more liberally. Emollient treatment of the whole body may require 100 g/day when the skin is very dry.

Advice to patients

Detailed instructions are often required as to the timing of applications. In many cases it is most convenient to apply the medication immediately after bathing. If other topical treatments are in use it is important to explain how the applications should be timed relative to each other. For example, application of an emollient immediately after application of an active agent will inevitably dilute the active medication and probably spread it over areas of skin where it is not required. When using a medication with a tendency to induce irritation it is helpful to warn patients about this in advance and to give advice on the best course of action when this occurs.

If it is planned to use any form of occlusion, bandaging or other dressing with topically applied medication, detailed instruction is required and this should ideally take the form of a demonstration by a specially trained nurse. Occlusion will invariably increase the level of penetration of a drug into the skin. The mechanism of this effect is not fully understood but seems to be partly the result of retaining a reservoir of the medication on the surface of the skin, and partly the effect of increased hydration of the stratum corneum. The simplest method of occlusion is the use of polythene gloves on the hands or 'clingfilm' on the feet or limbs. Self-adhesive hydrocolloid dressings can be very useful for limited areas on the limbs or trunk. 'Wet wrap' bandaging is described in the treatment of atopic dermatitis. Various additional types of bandaging (e.g. paste bandages) can be used to increase the penetration of topical medication and have the added benefit of preventing scratching.

Age	Face and neck	One upper limb	One lower limb	Trunk	Whole body
3–6 months	1	1	1.5	2.5	8.5
1–2 years	1.5	1.5	2	5	13.5
3–5 years	1.5	2	3	6.5	18
6–10 years	2	2.5	4.5	8.5	24.5
Adult	2.5	4.5	7.6	13.5	40

Table 75.4 Fingertip units required for a single treatment of various regions in children and adults. (Adapted from [10,13].) Note that the unit is measured using an adult finger.

When self-treatment fails, the efficacy of topical therapy can almost invariably be improved if the treatment can be applied by a specialist nurse in an outpatient department. Many dermatology departments are able to provide this service for patients with severe skin disease who are able to attend on a daily basis. The response to treatment is improved even further by admission to hospital for a period of rest and regular supervised treatment.

Hazards associated with topical treatment

The most frequent adverse effects associated with topical medication are localized irritant or allergic reactions. Irritant reactions can be minimized by applying treatment at the optimal concentration and treatment intervals and by selection of the correct vehicle. Sensitization is more difficult to anticipate and to prevent. Contact allergy can develop not only to the active medicament but also to constituents of the vehicle. Almost any component may sensitize: notable examples include ethylenediamine [14], propylene glycol [15], emulsifiers [16], sorbic acid [17,18], cetyl and stearyl alcohols [19] and fragrances [20]. Patients with chronic venous eczema or leg ulcers appear to be particularly susceptible [21,22]. Sensitivity to topical medication is often overlooked as the symptoms tend to be attributed to the disease being treated.

Systemic side effects from topically applied medication are relatively rare. Nonetheless, all topically applied drugs are absorbed to some degree and on occasions unexpected systemic toxicity occurs. Absorption varies very considerably depending on the region of skin being treated (Table 75.4) [23]. Occlusion greatly enhances absorption [24,25]. Systemic exposure can be greater than expected in children because of their relatively high ratio of skin surface to body mass. In the elderly, penetration of drugs may be increased as a result of changes in the structure of the skin. This effect is most pronounced on those drugs that are most hydrophilic [26]. Inflammation of the skin impairs barrier function and significantly increases drug absorption. This is especially significant in the erythrodermic patient [27–29].

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Formulation of topical treatment

The formulation of the vehicle in which a drug is delivered topically to the skin is critical in obtaining effective and consistent results. The vehicle has many roles. It must provide rapid delivery of the drug to the stratum corneum and into the viable layers of the skin. It must be soothing and comfortable to use and preferably also cosmetically acceptable. The vehicle must also provide a chemical environment in which the drug remains sufficiently stable prior to use to have a practical shelf life.

Most topical treatments are now commercially formulated in vehicles that have been carefully designed for optimal results. Some caution is therefore required when adding diluents or other medicaments to such a

formulation. The role of the dermatologist in formulating topical treatment has been reduced over recent years by stricter financial, legislative and safety controls, which have resulted in the increasing reluctance of pharmacists to prepare extemporaneous or personalized formulations. Nonetheless, an understanding of the parts played by the various constituents of vehicles remains important. Only the most frequently used components are reviewed here. Further information regarding many of the materials and formulations discussed in this chapter is available in the British and US pharmacopoeias (BP, USP) and British Pharmaceutical Codex (BPC).

The simplest role of a vehicle is dilution of an active drug to the desired concentration. Agents such as beeswax, liquid paraffin, polyethylene glycol and powders are often added for their physical properties to adjust the thickness or texture of the medication. In addition to this, various constituents act as emollients, emulsifiers, fragrances, humectants, penetration enhancers, preservatives or solvents. Some of the constituents most often employed are listed in Table 75.5 and some are discussed further below. A single constituent often serves more than one function.

Table 75.5 Frequently employed constituents of vehicles.

Lipids
Castor oil
Cetyl alcohol
Cocoa butter
Isopropyl myristate
Isopropyl palmitate
Lanolin
Liquid paraffin
Stearic acid
Stearyl alcohol
White soft paraffin (petrolatum)
Emulsifiers
Alkyl sulphates and sulphonates
Glyceryl monostearate
Lanolin and derivatives
Phosphoric acid esters
Polyethylene glycols
Polyvalent metallic soaps
Propylene glycol fatty acid esters
Quaternary ammonium cationic compounds
Sorbitan monolaurate, monopalmitate and mono-oleate
Triethanolamine oleate
Humectants
Glycerin
Propylene glycol
Urea
Pyrrolidone carboxylic acid
Gelatin
Sorbitol
Penetration enhancers
Azone
Dimethyl sulfoxide
Propylene glycol
Salicylic acid
Urea
Preservatives
Benzyl alcohol
Butylated hydroxyanisole
Butylated hydroxytoluene
Chlorocresol
Edetic acid/disodium edetate
Hydroxybenzoates (parabens)
Propylene glycol
Sodium metabisulphite
Sorbic acid/sorbates
Solvents
Acetone
Ethanol
Ether
Chloroform
Glycerin
Isopropyl alcohol
Methanol
Propylene glycol
Water

Lipids

Lipids incorporated into vehicles can act as diluents and solvents but are especially valuable as emollients: they have the ability to form a coating on the surface of the stratum corneum which inhibits evaporation of water, thus providing a softening and moisturizing effect. Generally speaking, the greater the proportion of lipid in the formulation, the greater will be the emollient action. Ointments are therefore more emollient than oily creams, which are more so than aqueous creams, while most lotions have no emollient effect. Lipids from a variety of sources are incorporated into topical treatments for skin disease.

Vegetable oils

Oils can be obtained from numerous vegetable sources by pressing or by solvent extraction. Vegetable oils are largely composed of triglycerides, which tend to contain large proportions of unsaturated fatty acids such as the 18-carbon fatty acids oleic acid (monoenoic) and linoleic acid (dienoic). The presence of these unsaturated fatty acids renders vegetable oils vulnerable to oxidation. This results in rancidity, which manifests as an unpleasant odour and is a major constraint on the use of vegetable oils in medicaments.

Arachis oil, derived from the groundnut or peanut, has been the subject of some concern recently over possible contamination with allergens that could cause hypersensitivity reactions in peanut-sensitive individuals. Cocoa butter, also known as theobroma oil, is a product of the cocoa bean and consists chiefly of the triglycerides of palmitic, stearic and oleic acids. It also contains antioxidants, which make it remarkably stable for a vegetable oil and which can even help to preserve other constituents with which it is compounded. It is brittle at room

temperature but melts at between 30 and 35°C. Castor oil is obtained from the castor bean *Ricinus communis* and is composed almost entirely of triglycerides of the 18-carbon long-chain fatty acid ricinoleic acid. Olive oil contains a large proportion of oleic acid.

Mineral oils and greases

Extracts of crude oil (crude petroleum) resembling those we use today have been used for treatment of skin disease since a US patent was obtained, in 1872, by Robert Chesebrough for a product he called vaseline.

Emollient products extracted from crude oil can be produced as fluids, semi-solids or solids and include Liquid Paraffin BP, Mineral Oil USP, Yellow and White Soft Paraffin BP, Petrolatum USP. The extraction process involves treatments to remove elements other than hydrogen and carbon. Aromatic and unsaturated compounds are also eliminated, leaving a diverse range of hydrocarbon molecules, some straight chained, some branched and some polycyclic [1]. As a result of their fully saturated nature, these hydrocarbons are far more stable than the constituents of vegetable oils. They are remarkably inert and are not vulnerable to oxidation or rancidity. For this reason, mineral oils have substantially replaced vegetable oils as the lipids used in emollients and topical treatments.

Lanolin

The use of wool extracts for cosmetic and medicinal purposes dates back at least as far as ancient Greece. Lanolin (wool fat) is extracted from wool and is essentially the product of the sheep sebaceous gland [2]. It is available in abundance and, because its natural purpose is to protect the skin and wool of the sheep, it is perhaps an obvious choice of lipid material for use as an emollient.

Lanolin comprises a complex mixture of higher fatty acids esterified with mono- and dihydric alcohols, including aliphatic alcohols, and cholesterol and related sterols. Its precise composition varies qualitatively and quantitatively with humidity, temperature and method of collection. It is prone to auto-oxidation and is therefore often formulated with the antioxidant butylated hydroxytoluene. Lanolin is miscible with water and is a useful emulsifying agent when mixed with other lipids.

Lanolin has gained a reputation as a frequent contact sensitizer, although this remains questionable [3]. Small quantities of anionic detergent may be present in lanolin and may increase the apparent incidence of hypersensitivity [4]. It has also been suggested that misleadingly high proportions of positive patch tests to lanolin and wool alcohols have arisen partly because of selection of groups of patients who are particularly vulnerable to irritant reactions which are misinterpreted as allergy [3]. Sensitization to lanolin in the general population remains rare, of the order of 1 in a million, even though this material has so many applications that it is ubiquitous [3].

Partly because of its reputation as a sensitizer, numerous lanolin extracts and derivatives are often used instead of the natural material. These are produced by a range of processes including hydrolysis (to yield the constituent acids and alcohols), acetylation, ethoxylation and solvent fractionation. Eucerin (Wool Alcohols BP) is the wool alcohol fraction of wool fat, and contains cholesterol and isocholesterol. It is mixed with liquid, soft and hard paraffin to form Ointment of Wool Alcohols BP, which, on the addition of water, produces Hydrous Ointment BP, a vehicle for many water-in-oil (W/O) creams.

Fatty acids and alcohols

Long-chain fatty acids (e.g. palmitic and stearic acids and their alcohols, cetyl and stearyl) are very frequently used as emollients and, in creams, also serve as emulsifiers. Cetostearyl alcohol is a frequently used mixture of cetyl and stearyl alcohols. They can be obtained by hydrolysis of triglycerides from many different animal and vegetable fats and oils.

Waxes

Beeswax is secreted by worker bees to make the cell walls of the honeycomb. It has a melting point of approximately 60°C and is composed mainly of free cerotic acid and myricyl palmitate. It is used as a thickening agent for creams, ointments and lip salves. Emulsifying wax comprises cetostearyl alcohol, sodium lauryl sulphate and water. This is a constituent of emulsifying ointment BP.

Polyethylene glycols

Polyethylene glycols, also known as PEGs or macrogols, are dihydric alcohols. They are polymers of ethylene glycol linked by ether bonds with the general formula $H(O\text{-}CH_2\text{-}CH_2)_n\text{-}OH$ in which n may range from 2 to 90 000. PEGs can be designated by a number indicating the average molecular weight. At low molecular weights, up to 2000, they are hygroscopic. They variously serve as emollients, emulsifiers or thickeners and can also be used to impart a pleasant feel or texture to a formulation.

Cetomacrogols are cetylethers of polyethylene glycol (e.g. cetomacrogol 1000 is the monocetyl ether of polyethylene glycols with average molecular weight 1000). It is useful as a non-ionic emulsifying agent.

Emulsifiers

An emulsion is a two-phase system consisting of two immiscible components: one (the dispersed or inner phase) being suspended in the other (the continuous or outer phase) as small droplets. One phase is aqueous, the

other oily. Stable emulsions remain in this form; unstable emulsions, with a large droplet size, tend to separate as cream does from milk. Production of a stable emulsion requires the presence of an emulsifier, which is a large molecule with both strongly polar (water-soluble) and non-polar (oil-soluble) groups allowing it to bridge the gap between polar and non-polar substances. A large and chemically diverse range of compounds can be used for this purpose; some examples are given in Table 75.5.

W/O systems result from the dispersion of an aqueous phase in an oily phase, as in Oily Cream BP. Oil-in-water (O/W) systems are formed when oil is the dispersed phase and water the continuous phase, as in Aqueous Cream BP. The former constitute, in general, oily creams or 'cold creams', the latter aqueous or 'vanishing creams'. It is sometimes possible to produce both types of emulsion in the same system [5]: these are called ambiphilic creams. Emulsions can be diluted with the outer (continuous) phase only. A simple method of determining the nature of an emulsion is to interpose on a filter paper a drop of the emulsion between one of oil and one of water. In 15 min the continuous phase will mix with, or be dispersed by, one or other of the neighbouring drops. Alternatively, it may be tested by adding a larger quantity of water. If the emulsion separates, it is of W/O type; if not, it is of O/W type, the continuous phase being (within limits) able to expand and still retain its contained disperse phase.

The relative affinity of an emulsifier for water and for oil is quantified by a value denoting its emulsification tendency known as the hydrophilic lipophilic balance (HLB) value [6]. Emulsifiers with an HLB value of 3–6 tend to give W/O systems and those with higher values O/W systems.

Humectants

These are compounds with a high affinity for water (hygroscopicity). They draw water into the stratum corneum and therefore have an emollient effect on dry skin. However, most of the water is drawn out from within the skin and in dry atmospheric conditions water loss from the skin surface may be increased by the presence of humectants.

Penetration enhancers

Agents that have been shown to enhance penetration of drugs through the skin include propylene glycol [7,8], azone [9], urea [10] and dimethyl sulfoxide (DMSO) and related compounds [11–14]. Mechanisms for this effect include hydration of the stratum corneum and keratolytic actions. The effect of salicylic acid as a penetration enhancing agent seems to be variable. *In vitro* studies have suggested that penetration of drugs is enhanced but this effect was not observed during *in vivo* studies of steroid penetration through normal skin [15,16]. However, in treatment of psoriasis, the addition of salicylic acid does seem to improve the response to topical corticosteroids [17,18].

DMSO is a highly polar, stable substance with exceptional solvent properties [19–23]. It releases histamine *in vivo* and may induce weals when applied topically. It reacts with water, liberating heat. The stratum corneum retains significant amounts of DMSO and, as most drugs are more soluble in DMSO than in water, this tends to promote percutaneous absorption [22]. This quality has been shown to be of particular value in increasing the effectiveness of idoxuridine in herpes simplex [24] and zoster [25]. Toxicological considerations have precluded its more widespread use.

Powders

Inorganic powders are an important component of many dermatological treatments and include zinc oxide, titanium dioxide, talc, bentonite and calamine. Organic powders include various starches and zinc stearate. *Zinc oxide* is widely used as a component of many dusting powders, shake lotions and pastes. It has covering and protective properties, gives consistency to creams and pastes, and is said to have cooling and slightly astringent properties. *Titanium dioxide* is chemically very inert and for this reason it can be used instead of zinc oxide in pastes containing salicylic acid. Like zinc oxide, it has useful UV-reflecting properties. *Talc* is inert magnesium polysilicate, with a very low specific gravity. It contributes 'slip' and has a cooling effect. *Calamine* may be either zinc carbonate or zinc oxide, coloured with a little ferric oxide, and has bland, soothing and antipruritic properties. *Starch* is more absorbent than inorganic powders, but tends to deteriorate and is prone to microbiological decomposition. Some powders, for example *bentonite* (colloidal hydrated aluminium silicate), *aluminium magnesium silicate*, *tragacanth*, *methylcellulose* and *carbomer* are used in gels or as stabilizers in shake lotions.

Preservatives

Ointments and some creams with oil as the continuous phase do not usually require preservatives. Lotions, O/W creams and gels, however, because they contain accessible water, are easily contaminated by moulds or bacteria. Animal and vegetable oils, unless protected from oxidation, tend to become rancid. The ideal preservative should be non-toxic, non-irritant, non-sensitizing, odourless, colourless and effective even at very low concentrations and under conditions of normal usage. In addition, it must be chemically compatible with both the vehicle and the active ingredients.

The parahydroxybenzoic acid esters (parabens) are effective and widely used preservatives. Because, indi-

vidually, they are only sparingly water soluble, and as their effects are additive, mixtures are usually preferred. This also increases their spectrum of activity and lowers the risk of sensitization. Considering their widespread use, their sensitizing potential appears to be low [26].

Chlorocresol is a preservative used especially in the UK. It is more effective in acid than in alkaline solution. It has a low sensitizing potential. It is used in several corticosteroid creams.

Sorbic acid (2,4-hexadienoic acid) is also a good preservative, which maintains its activity in the presence of non-ionic detergents. It also has a low sensitization index. It can only be used, however, in preparations with a pH of less than 6.5.

Propylene glycol can inhibit the growth of moulds and fungi, and can therefore be used as a preservative.

Organic mercurials such as thiomersal are used as preservatives in many ophthalmic preparations and in some vaccines and prick-test solutions and are occasionally incorporated in some topical preparations [27]. Ethylenediaminetetra-acetate is a widely used preservative in ear, nose and eye drops. Gallates and other antioxidants such as butylhydroxyanisole and butylhydroxytoluene are used to prevent rancidity in oily and fatty preparations.

Other preservatives, including those mainly used in cosmetic products, are discussed in Chapters 19 and 20.

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Topical treatments used in the management of skin disease

Antiperspirants

Most antiperspirants marketed for cosmetic purposes contain aluminium chloride hexahydrate. In contemporary products, refined formulations of aluminium chlorohydrates (or aluminium zirconium complexes) are often used to maximize precipitation of aluminium hydroxide within the sweat duct [1]. Cosmetic antiperspirants are often combined with antimicrobial agents that reduce axillary odour by inhibiting the action of bacterial metabolism on various components of apocrine sweat. Fragrances are often added to mask or adjust the odour in various ways [2].

In treatment of hyperhidrosis of the axillae, palms and soles, higher concentrations of aluminium chloride hexahydrate (e.g. 20–25% in ethanol) are generally used as first-line treatment. These are more effective, more irritant and more likely to damage clothing than cosmetic formulations. Blockage of the sweat duct is regarded as the principal mechanism of action [1,3], although secondary degeneration of the secretory cells may develop after long-term use as a result of the increased pressure in the duct [4]. For maximal efficacy, the treatment should be applied when the skin is dry and sweating is minimal. Application at night is often recommended; this also helps

to minimize damage to clothing. Polythene occlusion may enhance efficacy and irritancy. Irritation often limits the use of this treatment but may settle with reduced frequency of application and with use of a mild or moderately potent topical steroid.

Traditional remedies that have fallen out of favour include the aldehydes. These are believed to work by a similar mechanism to aluminium salts. Aqueous glutaraldehyde solution (up to 10%) can be applied on a swab to the soles of the feet [5,6]. The keratin stains orange-brown when higher concentrations are used. Formaldehyde solution BP (1–3%), used as a twice daily soak, also helps mild cases. Both compounds are frequent sensitizers, and are therefore not ideal for prolonged use. Methenamine, an agent that releases formaldehyde and ammonia, seems to cause less sensitization and has been used as a 10% solution or at 5% concentration in a firm gel-stick formulation [7].

Anticholinergic agents inhibit the anomalous sympathetic (cholinergic) innervation of the sweat glands and can be applied topically to minimize the side effects associated with systemic administration. Poldine methylsulphate [8] and glycopyrronium bromide [9] can be very effective when administered by iontophoresis. Dry mouth is common and visual accommodation may be disturbed for 24–48 h following treatment. Iontophoresis with tap water is also effective, by an unknown mechanism [10,11], and avoids these side effects. Glycopyrrolate cream 2% or lotion has been used with success in patients suffering from severe gustatory sweating following parotidectomy [12].

Surgical treatments and injection of botulinum toxin are considered in Chapter 45.

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Antibiotics

Topical antibiotics are most frequently used in the treatment of superficial infections such as impetigo, superficially infected surgical wounds or infected leg ulcers, and also in acne vulgaris and rosacea.

When treating infected skin lesions it is important to establish the identity and antibiotic sensitivity of the organism whenever possible. Although staphylococcal infections are common, it should not be assumed that a cutaneous infection is brought about by this organism. Before using an antibiotic, consideration should always be given to the alternative of using an antiseptic, in order to reduce the risk of promoting antibiotic resistance. Antiseptics usually have the added advantage of covering a wider spectrum of organisms.

The value of many antibiotics is limited by their tendency to sensitize when used topically (e.g. chloramphenicol and neomycin). Once sensitization has developed this generally precludes future systemic use of the antibiotic. It is therefore preferable, when possible, to select an antibiotic for topical application that is not related to agents used systemically.

The topical antibiotics most used in treatment of acne and rosacea are tetracyclines, erythromycin and clindamycin. Topical metronidazole has proved useful in rosacea. In general, topical antibiotics work about as well as benzoyl peroxide or tretinoin in acne vulgaris. As in other indications, consideration should be given to alternatives to topical antibiotics, especially for long-term treatment, in order to reduce the emergence of resistant organisms. The detailed use of antibiotics in acne and rosacea is described in Chapters 43 and 44, respectively.

Bacitracin

This is an antibiotic that is too toxic for systemic use. Its antibacterial action is principally against Gram-positive organisms, so it is generally used topically in combination with other antibiotics, such as neomycin or polymyxin B. Allergic reactions of an anaphylactoid nature have been recorded [1]. In leg ulcer patients it was reported to be the most potent sensitizer of all the topical antibiotics tested [2].

Clindamycin

This is an effective topical treatment for acne vulgaris [3]. It is as effective as oral minocycline 50 mg twice a day [4], and oral tetracyline [5]. It was somewhat less effective than topical nicotinamide gel in a trial involving 76

patients [6]. It was found to be as effective as 5% benzoyl peroxide gel in patients with papular or pustular acne [7]; fewer side effects were seen with topical clindamycin. A small trial in rosacea has indicated that the response was comparable to that from oral tetracycline [8].

Erythromycin

Only the lipid-soluble forms (e.g. the base, propionate or stearate) are effective in acne vulgaris. Several authors have considered the problem of erythromycin-resistant propionibacteria [9,10]. It is equivalent in effect to topical clindamycin, is safe and well tolerated [11,12]. A topical 2% erythromycin gel has been shown to be as effective as 1% clindamycin phosphate in patients with mild to moderate acne [13], and 1.5% erythromycin and 1% clindamycin phosphate solutions were found to be equally effective [12].

Fusidic acid

Derived from *Fusidium coccineum*, this antibiotic is active against staphylococcal infections and effective in erythrasma [14]. It is used as a first-line treatment for pitted keratolysis [15] although there is surprisingly little published about this indication. It is also used in combination with topical steroids in the treatment of infected eczema.

Sensitization occurs only very rarely [16,17], but bacterial resistance is not uncommon.

Gentamicin sulphate

The particular dermatological value of gentamicin sulphate lies in its broad spectrum of activity, including against *Pseudomonas aeruginosa*. Contact allergy is fairly frequent in patients with chronic otitis externa [18] and, compared with other agents, it remains a common sensitizer [19]. Cross-sensitivity can develop with other aminoglycosides [20].

Metronidazole [19]

Metronidazole 0.75–1% has been shown to be a safe and effective treatment for rosacea [21,22]. Topical metronidazole has also been used with some success in patients with decubitus and other ulcers, eliminating malodour in 36 h [23]. In a double-blind placebo-controlled trial, topical metronidazole was ineffective in reducing the inflammatory lesions of acne [24].

Mupirocin

This topical antibiotic is derived from *Pseudomonas fluorescens* [25]. It is chemically unrelated to other antibiotics, and its mode of action in arresting bacterial protein synthesis is novel [26]. It is active against a wide range of Gram-positive organisms and some Gram-negative organisms [27]. Naturally, it is not active against *Pseudomonas* and may allow overgrowth of this organism. It can be highly effective in cutaneous bacterial infections [28,29]. It has also proved useful in the elimination of nasal carriage of staphylococci [30], including multiply-resistant organisms, but strains resistant to mupirocin are now an increasing problem.

Neomycin and framycetin

SYN. SOFRAMYCIN

These are aminoglycoside antibiotics with a broad spectrum of action against Gram-positive and Gram-negative organisms. Both are considered too toxic for systemic use. Many preparations containing one or other of these are marketed in the UK, and are widely used, although sensitization reactions are common, especially around leg ulcers, under occlusion and in patients with chronic otitis externa, pruritus ani or vulvae, or with recurrent eye problems. Neomycin was among the most common sensitizers reported by Wilkinson *et al*. [31]. Simultaneous contact allergy to neomycin, bacitracin and polymyxin has been reported [32].

Polymyxin B

This antibiotic is used in several proprietary topical formulations for application to skin, eyes and ears. It has useful activity only against Gram-negative organisms and is therefore usually combined with other antibiotics. The relatively low toxicity of polymyxin to keratinocytes may explain the good cosmetic results observed when it is used following dermabrasion [33].

Silver sulfadiazine

First introduced over 20 years ago [34,35], this compound has become established as a safe and convenient dressing for burns [35]. Even when applied over wide areas, systemic absorption is minimal and the risk of renal damage is thought to be slight [36]. It is applied as a 1% cream. It appears to have a low potential for sensitization and is useful in the management of leg ulcers where it provides good prophylaxis against *Staphylococcus aureus* and some Gram-negative organisms. Some patients may become sensitive to the cetyl alcohol contained in the base of one proprietary formulation. When sulphonamide-resistant Gram-negative bacilli were present, a silver nitrate/chlorhexidine cream was found to be of value [37].

Tetracyclines

These are used alone in the topical treatment of acne [38],

but are also present in several proprietary topical corticosteroid preparations. Bacterial resistance is common, especially in staphylococci. Tetracyclines tend to stain skin and clothing yellow.

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Antifungal agents

Topical application of antifungal agents is used by dermatologists mainly for treatment of mild dermatophyte and yeast infections. As management of specific infections is described elsewhere, this chapter provides only a description of the antifungal agents available for topical application. Severe and extensive infections and infections of hair and nails are usually treated systemically (see Chapters 62 and 63). The most frequently prescribed topical antifungal agents are allylamines, imidazoles, morpholines and polyenes. Older compounds such as tolnaftate and undecylenate acid are mainly sold over-the-counter.

Allylamines

These inhibit fungal synthesis of ergosterol, an essential component of fungal cell membranes, by inhibiting squalene epoxidase. This also results in toxic accumulation of squalene within the organism, which is fungicidal. This class includes naftifine, butenafine (neither are marketed in the UK) and terbinafine. The fungicidal nature of these compounds results in rapid response of dermatophyte infection to topical application. Naftifine and butenafine also possess anti-inflammatory activity. Terbinafine is active topically against pityriasis versicolor as well as against dermatophytes.

It is of concern that a strain of *Trichophyton rubrum* apparently resistant to squalene epoxidase inhibitors has recently been reported [1].

Imidazoles

This is a large group of compounds which includes bifonazole, clotrimazole, econazole, fenticonazole, ketoconazole, isoconazole, miconazole, oxiconazole, sulconazole, terconazole, tioconazole and others. These have largely similar properties and act by inhibiting synthesis of ergosterol. They are fungistatic. They are active against a wide range of fungal organisms including *Candida* and *Pityrosporum* yeasts as well as dermatophytes. They also have potentially useful antibacterial properties and, at least *in vitro*, can suppress growth of *Staph. aureus* [2]. The range of formulations includes creams, powders, sprays, suspensions and nail lacquer.

There are also combined formulations available which contain imidazoles and corticosteroids. The precise role of these combined formulations is controversial. They can occasionally be useful to accelerate resolution of symptoms when infected skin is very inflamed and pruritic. However, it is also possible that they may impair the response to the antifungal agent [3] and the familiar hazards of topical corticosteroids include the potential to mask a persisting infection.

Morpholines

Amorolfine inhibits two separate stages in the synthesis of ergosterol and is fungicidal. It is marketed as a nail lacquer containing 5% amorolfine, for treatment of onychomycosis. An advantage of amorolfine in this application is that, in addition to efficacy against dermatophytes, it is also active against other filamentous fungi that cause onychomycosis, such as *Scytalidium* spp. and *Scopulariopsis* spp. The water-resistant properties of the lacquer allow the convenience of once or twice weekly application. Twice weekly application may be marginally more effective [4]. Cure rates are approximately 50% at 6 months. Amorolfine can act synergistically with other antifungal agents including azoles and allylamines, improving cure rates when topical amorolfine is combined with systemic itraconazole [5] or terbinafine for 3 months [6].

Polyenes

The important member of this group is nystatin—one of the earliest antifungal agents developed. It derives its name from the New York State health laboratory where it was discovered in the 1950s. Nystatin is a fungal metabolite with activity against *Candida albicans* and several other *Candida* species. It damages the fungal cell membrane by binding irreversibly to ergosterol, an action that is fungistatic at low concentrations and fungicidal at high concentrations. It is not effective against dermatophytes. It is a safe and well-tolerated compound which is not significantly absorbed when taken orally or when used topically on skin and mucous membranes. Nystatin is available in a range of formulations including cream, ointment, oral suspension, lozenges and pessaries. There are also a range of creams and ointments containing combinations of nystatin with antiseptics, antibiotics and various potencies of corticosteroids.

Ciclopirox olamine [7]

This hydroxypyridone compound has a different mode of action to most other antifungal agents and does not directly inhibit sterol synthesis. It binds with high affinity to trivalent cations such as Fe^{3+}, which are essential for the functioning of numerous enzymes including cytochromes. Several metabolic pathways are likely to be disrupted by this process, including mitochondrial electron transport. It demonstrates activity against a broad spectrum of dermatophytes, yeasts and moulds including *Scytalidium* spp. and *Scopulariopsis* spp. and is also effective against Gram-positive and Gram-negative bacteria including methicillin-resistant *Staph. aureus*. Ciclopirox is commercially formulated in a variety of creams, lotions, powder and as a nail lacquer but is not currently marketed in the UK.

Tolnaftate

This compound is available in a variety of formulations (creams, lotions, powder) that are generally sold over-the-counter for topical treatment of dermatophyte infections. It is a thiocarbamate derivative, chemically unrelated to other antifungal drugs, and is an inhibitor of squalene epoxidase. It is considered less effective than more recently developed agents but is superior to placebo [8].

Undecylenic acid

Undecylenic acid, a mono-unsaturated fatty acid, is largely used as an over-the-counter topical treatment for dermatophyte infection. In addition to its fungistatic activity, it has antiseptic and antiviral properties. Formulations include cream, ointment, paint, spray and powder. It is probably less effective than newer agents although it has proved superior to placebo and equivalent to tolnaftate in controlled trials [8,9]. Sensitization is occasionally reported.

Other topical antifungal agents

Whitfield's ointment, a combination of 6% benzoic acid and 3% salicylic acid, is effective in treatment of superficial

dermatophyte infections. Studies in the tropics suggest that cure rates are quite acceptable when very low cost is a priority [10]. However, this formulation is not very cosmetically acceptable.

The antiseptic properties of benzoyl peroxide have been put to use in treatment of dermatophyte infection and pityriasis versicolor, although this compound is irritant and bleaches clothing so some caution is required [11].

Zinc pyrithione 1% and selenium disulphide 2.5% are used in shampoos to treat dandruff and seborrhoeic dermatitis. Both compounds have also been shown in placebo-controlled trials to be effective in treatment of pityriasis versicolor in the same concentrations. Zinc pyrithione shampoo can be lathered over the affected skin for 5 min then rinsed off every day for 2 weeks [12]. Selenium sulphide has been shown to be effective used in the same way but applied for 10 min/day for 7 days [13]. Some irritation may develop.

Resorcinol (1,3 dihydroxybenzene) is an antiseptic agent and preservative which is also added to some shampoos to suppress dandruff by inhibition of *Pityrosporum* yeasts.

Azelaic acid demonstrates antifungal properties and is discussed under the heading of depigmenting agents.

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Antiparasitic agents

The principles of treatment of lice infestations and scabies are discussed in Chapter 33. Insecticide resistance has emerged as a significant problem in the treatment of head lice [1] and may necessitate treatment with a second agent or by using non-pharmacological approaches.

Pyrethroids

Pyrethroids are highly effective [2,3] and are now probably the most widely used agents. These are insecticides that are neurotoxic to parasites. Permethrin 5% cream is a first-line treatment for scabies. It should be applied from the neck down for 12 h. The 5% 'dermal cream' for treatment of scabies should not be confused with the 1% 'creme rinse' marketed for treatment of head lice. This has caused treatment failure in scabies [4]. The creme rinse is applied to the scalp for 10 min to treat head lice. For pubic lice, the 5% cream should be used as for scabies.

Phenothrin is another pyrethroid used for head and pubic lice. For head lice, the formulations available include in an aqueous 0.5% lotion (washed off after 12 h), an alcoholic 0.2% lotion (washed off after 2 h) and a 0.5% concentration in a mousse (washed off after 30 min). For pubic lice, the aqueous lotion should be applied to the whole body for 12 h.

Whether treating head lice, pubic lice or scabies, two treatments at an interval of 1 week are generally recommended for both these agents.

Malathion

Malathion is an organophosphorus cholinesterase inhibitor that paralyses parasites. In treatment of scabies, a 0.5% aqueous lotion is applied to the skin for 24 h and repeated after 1 week. For head lice, 0.5% aqueous or alcoholic lotions can be applied for 12 h on three occasions at 3-day intervals. For crab lice, the aqueous preparation should be applied all over the body for 12 h and repeated after 7 days.

Other antiparasitic agents

Benzyl benzoate is also believed to be neurotoxic to parasites. It can be used as a scabicide in a 25% emulsion applied daily for 3 days but is somewhat irritant. Carbaryl is another organophosphorus insecticide that can be used for head and pubic lice. It is available as 1% aqueous and 0.5% alcoholic lotions which are usually left on the skin for 12 h. A single application may be effective but is often repeated after 7 days. Gamma benzene hexachloride (lindane), used as a 1% lotion, is an effective scabicide although it has been withdrawn in the UK as a result of concern over systemic absorption and possible neuro-

toxicity [5]. It is applied for 12 h and this is sometimes repeated after 1 week. The risks seem small but are relatively greater in infants and young children, and when multiple applications are used. Both topical and oral ivermectin have been successfully used for both scabies and head lice [6–8]. A 1% solution in propylene glycol applied twice with a 1-week interval has proved highly effective in scabies [9]. Crotamiton has weak scabicidal activity and is an antipruritic. It is often used as a follow-up treatment to other therapies.

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Antiviral agents

There are few topical agents available with specific antiviral activity although many antiseptics, especially povidone iodine [1,2], are known to inactivate viruses. The use of imiquimod, 5-fluorouracil and podophyllin in treatment of viral warts is discussed elsewhere in this chapter. Aciclovir, penciclovir and idoxuridine are used topically in management of herpes simplex and the latter is also used for herpes zoster.

Aciclovir and penciclovir

Topical aciclovir is used in the treatment of primary and recurrent herpes simplex types I and II [3]. The drug is a nucleoside analogue and is phosphorylated by a viral thymidine kinase to an active form that inhibits effective replication of viral DNA. A recommended regimen is application of 5% aciclovir cream at 4-hourly intervals for 5 days. Both labial and genital lesions can respond. Severe episodes are best treated systemically. Some protective effect may be obtained by regular prophylactic application of aciclovir cream [4]. Penciclovir has a similar mechanism of action. This is applied as a 1% cream 2-hourly for 4 days. Both of these agents should be applied as early as possible in the course of the episode.

Idoxuridine

Idoxuridine was the first agent to become available for topical treatment of herpes infections. It is a thymidine analogue that inhibits viral DNA replication. It is effective in reducing symptoms in treatment of herpes simplex [5] and zoster infections [6] applied topically at concentrations of 5–15%. A 5% solution in DMSO can be applied to affected areas of skin with a brush 4 times daily for 4 days. At lower concentrations, idoxuridine appears effective in treatment of genital warts [7]. Topical use of idoxuridine can occasionally sensitize [8].

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Astringents

Astringents are compounds used to reduce exudation, acting by precipitation of protein. Those most frequently employed are aqueous solutions of potassium permanganate, aluminium acetate and silver nitrate.

Potassium permanganate

This is an oxidizing agent with antiseptic and fungicidal activity. It is used at concentrations of 1 : 4000–1 : 25 000. It can be applied as a rinse or soak or as a bath. A bath containing 1 : 25 000 $KMnO_4$ can be prepared by adding 2 g to each 50 L of water. The astringent and antiseptic properties of this solution are invaluable in treatment of very acute exudative eczematous dermatoses. However, it is messy and stains the skin and other materials.

Aluminium acetate

Also known as Burow's solution, this astringent is also mildly antiseptic and has the advantage of not causing the

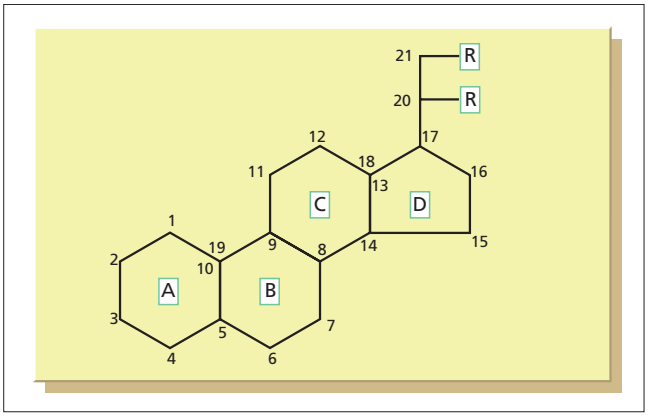

Fig. 75.2 The configuration of the basic corticosteroid structure.

staining associated with potassium permanganate. The solution is prepared using aluminium sulphate, acetic acid, tartaric acid and calcium carbonate. The solution contains 5% aluminium acetate and is diluted 1 : 10–1 : 40 with water for use in soaks, rinses or wet dressings.

Silver nitrate

In concentrations of 0.1–0.5% silver nitrate is an effective astringent and antiseptic, often used in management of leg ulcers and burns. Higher concentrations may cause pain. Silver nitrate causes staining of skin and most other materials.

Corticosteroids

Topical corticosteroids have now been in use for treating skin disease for over half a century, since the introduction of 'compound F' or hydrocortisone (cortisol) in 1952 [1]. Their impact has been immense. In addition to becoming the mainstay of treatment in eczematous dermatoses, they are used, either regularly or occasionally, in the management of most inflammatory skin diseases.

During the decades since hydrocortisone was introduced, numerous analogues have been developed from this molecule. The basic structure of the steroid moiety is shown in Fig. 75.2. Modifications to both the ring structure and the side-chains have increased specificity of action, increased penetration, dramatically increased potency and, to some degree, reduced side effects.

Hydrocortisone has considerable mineralocorticoid activity, which can be reduced by methylation or hydroxylation at position 16. Esterification at positions 16, 17 and 21 increases lipid solubility, promoting greater penetration of the stratum corneum barrier. This strategy lead to the development of highly lipophilic compounds such as betamethasone dipropionate and triamcinolone acetonide. Fluorination of the 9α position, the introduction of an unsaturated bond between the first two carbon atoms and changes in the nature of the side-chains, particularly in the 21 position, brought about enhanced glucocortioid activity [2]. Fluticasone propionate has a fluoride thioester carbothiate at C21, a propionate ester at C17 and a methyl group at C16; this molecule is inactivated rapidly on first passage through the liver, confering greater systemic safety. Similar properties are demonstrated by methylprednisolone aceponate and mometasone furoate, while systemic exposure to prednicarbate is minimized by metabolism within the skin.

In view of the great differences in potency between different corticosteroids, it is essential for the dermatologist to be able to rank or classify them by potency in order to predict the response and possible adverse effects. This classification ideally needs to take account not only of the relative potency of the molecules, but also factors such as the concentration and the nature of the vehicle, which can significantly alter penetration.

Perhaps the ideal approach would be a large series of clinical trials to compare clinical efficacy of all the available corticosteroids. However, even if this were possible, it is by no means certain that the same ranking would be obtained in two different diseases. Many different approaches have therefore been developed to compare potencies of topical corticosteroids. Some of these employ various animal models of inflammation such as the implantation of a pellet of cotton into a subcutaneous pocket in rats. The potency of the antimitotic action of steroids can be assayed by applying the compound to the skin of hairless mice and measuring the level of suppression of the mitotic index after tape stripping [3]. However, the most widely used approach has been the vasoconstrictor assay, which depends upon the vasoconstricting property of glucocorticosteroids. This has the advantage of using human subjects and evaluates not only the intrinsic potency of the molecule but also its ability to penetrate the stratum corneum from a specific vehicle and even takes into account certain aspects of the removal and metabolism of the drug [4,5]. The degree of pallor produced following application of a compound to the skin seems to correlate fairly well with clinical potency and with the potential for side effects such as atrophogenicity. Typically, pallor reaches a peak at around 9–12 h after application and then falls, initially fairly rapidly over the next 10 h, then more slowly [6]. The total duration of action varies considerably between different compounds.

The various classifications adopted to provide a guide to the relative potencies of different compounds are substantially based on the vasoconstrictor assay but also take into account other evidence such as comparative clinical trials. The *British National Formulary* employs a four-point scale: mild, moderate, potent and very potent. In the USA, topical corticosteroids are ranked using a scale ranging from class 1 (super potent) to class 7 (mild).

Mechanism of action

Corticosteroids diffuse through the stratum corneum barrier and through cell membranes to reach the cytoplasm of keratinocytes and other cells present in the epidermis and dermis. Diffusion through the stratum corneum is generally considered to be the rate-limiting step in delivery of the drug. In the cytoplasm they bind to a specific receptor, the glucocorticoid receptor (GR). Clinical potency of corticosteroids seems to be strongly related to receptor binding affinity, which is very sensitive to certain structural changes in the steroid. Thus, the introduction of a double bond in the A ring, esterification in the 17α position, and fluorination at position 9α increase binding affinity, whereas esterification in the 21 position reduces binding affinity (Fig. 75.2).

The glucocorticoid receptor (glucocorticoid receptor α; GRα) is a protein of molecular weight 330 kDa and is a member of the same receptor superfamily as receptors for other classes of steroid, thyroid hormone, calcitriol, etc. When not associated with a steroid ligand, this receptor is found in the cytoplasm as a component of a heterotetrameric structure containing two molecules of the 90 kDa heat shock protein hsp90, and a 59-kDa protein p59. Interestingly, p59 seems to belong to the family of immunophilins that interact with other immunosuppressant drugs. The binding of the receptor to its ligand results in activation of the receptor, which dissociates from the other components of the tetrameric complex [7]. The ligand-bound receptor then enters the nuclear compartment and interacts with specific response elements on the genome, glucocorticoid response elements (GREs). This modulates transcription of numerous genes. In addition, the ligand-bound receptor can inhibit, directly or indirectly, the activity of other transcription factors including NFκB, AP-1 and NFAT [8]. These interactions lead to changes in the expression of a wide range of genes, resulting in diverse cellular effects, which include suppression of the production of inflammatory cytokines, inhibition of T-cell activation, changes in the function of endothelial cells, granulocytes, mast cells and fibroblasts, and inhibition of proliferation. Part of the anti-inflammatory activity of corticosteroids may be explained by their ability to induce synthesis of lipocortin [9,10], a family of glycoproteins that regulate the activity of phospholipase A_2. This enzyme effects the production of arachidonic acid, the precursor for leukotrienes and prostaglandins.

The transcriptional activity of the steroid receptor seems likely to be regulated by an alternative isoform of the receptor known as glucocorticoid receptor β (GRβ), formed by alternative splicing. GRβ is an endogenous inhibitor of glucocorticoid action, which does not bind steroid ligands but competes with ligand-bound receptor for binding to GREs [11]. Staphylococcal superantigen can up-regulate expression of GRβ [12], providing a potential mechanism by which these bacteria might induce corticosteroid resistance.

Side effects of topical corticosteroids

The potential side effects of topical corticosteroids are significant but must be kept in proportion. When these compounds are prescribed appropriately, they can be of enormous benefit and clinically significant side effects are rare, especially in the short term (over a few days or weeks). Dermatologists have been very successful in making pharmacists, general practitioners and the public aware of the hazards. Patients are now frequently encountered whose dermatosis requires potent corticosteroids but who are denied effective treatment by the inappropriate prescription of hydrocortisone or simple emollients. Others apply the medication so 'sparingly' that it is completely ineffective. At times, the fear of using topical corticosteroids can be quite out of proportion to the likelihood of side effects developing. This situation is often termed 'steroid phobia'.

With the exception of structural changes introduced to minimize systemic exposure to topical corticosteroids, it has proved difficult to separate the various unwanted actions of these compounds from those that are so desirable. The side effects of topical steroids are directly related to their potencies. It is often appropriate to use more than one compound simultaneously so that mild or moderate steroids are used on areas where they are often effective, such as the face and flexures, while the more potent preparations are used only where they are required.

Local effects

The most common side effects are localized to application sites. The most worrying is cutaneous atrophy because this may become permanent. Other problems include the development of contact allergy and the risk of promoting infection. When treating the face, there are the additional risks of inducing acneiform eruptions. There are also potential risks from absorption and systemic exposure to the steroid.

Atrophic changes affect both the epidermis and the dermis. The epidermis becomes thinned. This results initially from a reduction in the size of epidermal cells, which reflects a reduction in metabolic activity [13]. After intense or prolonged steroid exposure, the number of cell layers is reduced, the stratum granulosum disappears and the stratum corneum is thinned [14–16]. There is suppression of many aspects of cell metabolism including the synthesis of stratum corneum lipids, synthesis of keratohyalin granules and the formation of corneodesmosomes required for structural integrity of the stratum corneum [17]. Inhibition of melanocyte function may develop, giving rise to localized hypopigmentation. This complication is

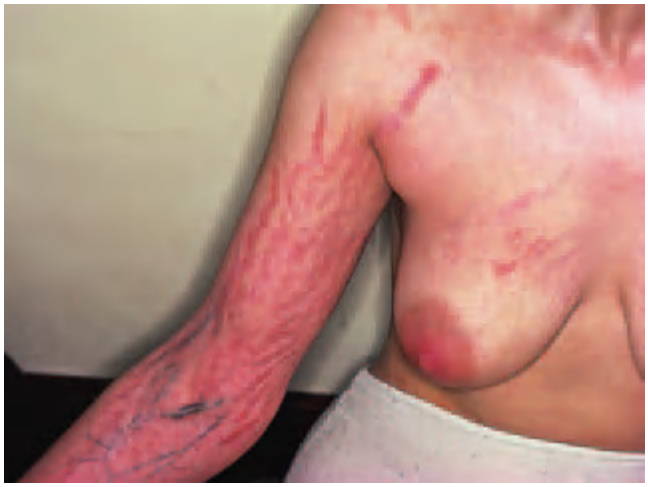

Fig. 75.3 Atrophy and striae induced by topical steroids. (Courtesy of St John's Institute of Dermatology, London, UK.)

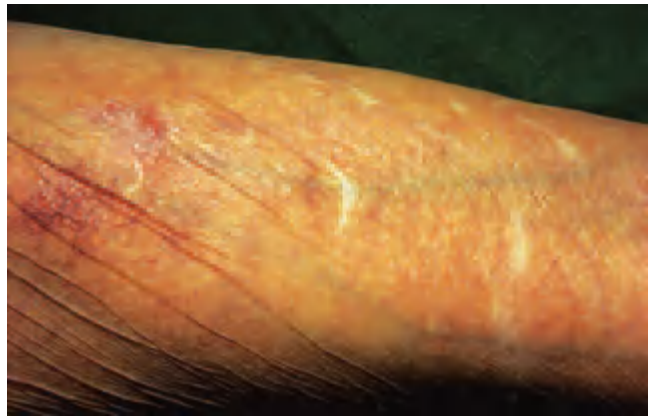

Fig. 75.4 Atrophy and scars induced by topical steroids. (Courtesy of St John's Institute of Dermatology, London, UK.)

Table 75.6 Relative levels of absorption of hydrocortisone applied at various sites. (Adapted from [23].)

Forearm	1
Sole	0.1
Ankle	0.4
Palm	0.8
Back	1.7
Scalp	3.5
Axilla	3.6
Forehead	6
Scrotum	42

most likely to occur with steroids applied under occlusion or with intracutaneous steroid injections [18,19].

In the dermis, topical corticosteroids induce resorption of mucopolysaccharide ground substance. This is likely to explain the rapid development of thinning, which reaches approximately 15% reduction in skin thickness after 3 weeks of treatment under occlusion with 0.1% betamethasone valerate [20]. Collagen synthesis is suppressed within 3 days of treatment with this compound [21]. Even mild corticosteroids such as hydrocortisone have been shown to inhibit collagen synthesis [22,23]. In a study in which betamethasone valerate was applied for 3 days there was still significant inhibition of collagen synthesis 2 weeks after treatment was discontinued [24]. When steroid exposure persists, thinning becomes clinically evident and fragility and striae may develop. The loss of connective tissue support for the dermal vasculature results in erythema, telangiectasia and purpura. With long-term use of potent preparations, these atrophic changes can become irreversible (Figs 75.3 & 75.4). The areas most vulnerable to developing atrophy are those where the skin is already relatively thin, including the flexures and especially the face (Table 75.6). In general, potent steroids should be used on the face only when treating severe dermatoses such as chronic discoid lupus erythematosus.

Contact allergy may develop to corticosteroids as well as to preservatives and other components of the vehicle. Contact sensitivity to hydrocortisone was first reported in 1959 but was initially considered a rare problem [25]. It is now clear that this is, in fact, a common event. In a large series of patients who were patch tested, 4.9% yielded positive results to one or more corticosteroids [26]. Tixocortol pivalate, considered the best patch test reagent for screening, was positive in just over 90% of those with a positive test to one or more corticosteroids. The most frequent sensitizers in this series were hydrocortisone, budesonide and hydrocortisone butyrate. Sensitivity to more than one topical corticosteroid is common and four groups have been identified within which cross-reactivity is most likely to occur (Table 75.7) [27]. Reactivation of contact dermatitis after inhalation of a corticosteroid may also be under-recognized [28].

Caution is required when applying topical corticosteroids in the presence of infection as there is a risk of exacerbation. Clinically unequivocal bacterial superinfection of eczema is usually treated prior to use of topical corticosteroids. However, there is evidence that colonization with *Staph. aureus* can be reduced by improving the condition of the skin with potent or very potent topical corticosteroid treatment [29,30]. It is advisable to avoid the use of topical corticosteroids, whenever possible, in the presence of active viral infection including lesions of herpes simplex, viral warts or molluscum contagiosum. When dermatophyte infections are inadvertently treated with corticosteroid, the symptoms and signs may transiently improve, giving rise to the situation known as tinea incognito. Scabies presents a similar trap, as the pruritus can be improved by topical corticosteroids while the infestation persists unless a scabicidal treatment is also applied. However, topical corticosteroids are invaluable for treating the eczema associated with scabies. Infantile gluteal

Table 75.7 Groups of topical corticosteroids within which cross-sensitization is most likely to occur [27].

Group A
Cloprednol
Cortisone
Cortisone acetate
Fludrocortisone
Hydrocortisone
Hydrocortisone acetate
Methylprednisolone acetate
Prednisolone
Prednisolone acetate
Prednisone
Tixocortol pivalate
Group B
Amcinonide
Budesonide
Desonide
Fluocinolone acetonide
Fluocinonide
Halcinonide
Triamcinolone acetonide
Triamcinolone alcohol
Group C
Betamethasone
Betamethasone sodium phosphate
Dexamethasone
Dexamethasone sodium phosphate
Fluocortolone
Group D
Alclometasone dipropionate
Betamethasone valerate
Betamethasone dipropionate
Clobetasol-17-propionate
Clobetasone-17-butyrate
Flucortolone caproate
Flucortolone pivalate
Fluprednidene acetate
Hydrocortisone-17-butyrate
Hydrocortisone-17-valerate

granuloma (see Chapter 14) is found only in infants who wear napkins (diapers) and is often associated with the use of topical corticosteroids. Impairment of the immune response to *Candida* by steroids has been suggested as the cause [31].

The use of topical corticosteroids on the face can result in eruptions resembling rosacea (Fig. 75.5) and perioral dermatitis (Fig. 75.6) (see Chapter 44). Eruptions of inflammatory papules may also develop around the eyes and have been termed periocular dermatitis [32]. On other occasions, an eruption more closely resembling acne vulgaris, comprising inflammatory papules and pustules as well as comedones, may develop in treated areas of skin, usually on the face or upper trunk. Comedones have also been induced in perianal skin by the application of potent steroids [33]. The mechanisms involved in these eruptions are not well understood.

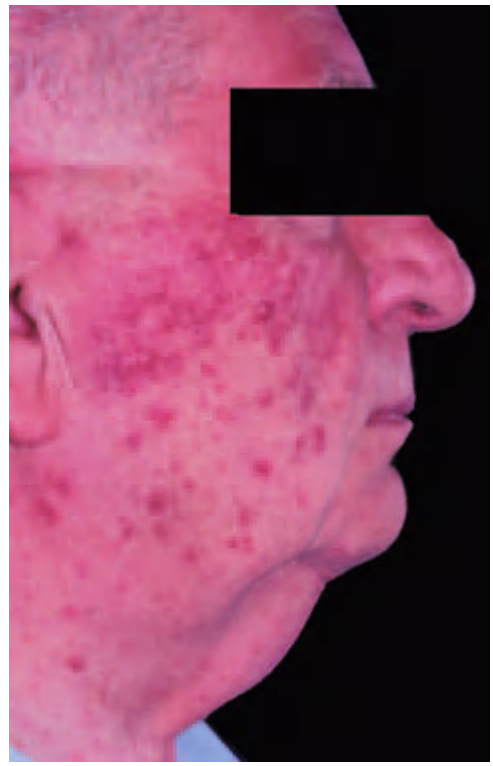

Fig. 75.5 Steroid rosacea.

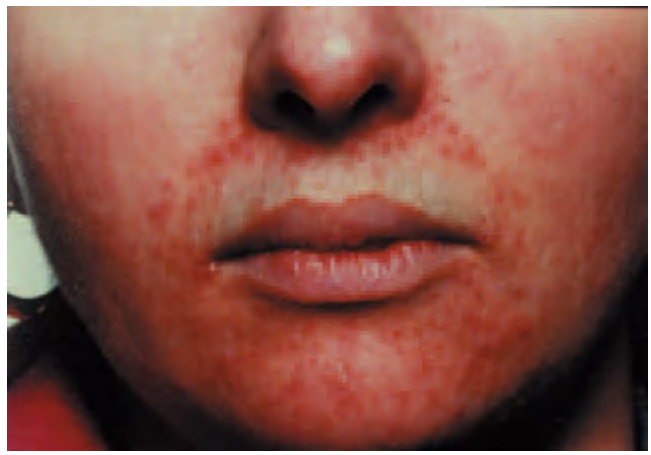

Fig. 75.6 Perioral dermatitis induced by a potent topical steroid. (Courtesy of St John's Institute of Dermatology, London, UK.)

It is possible that the use of topical corticosteroids on the eyelids and periorbital skin can result in some exposure of the eye to the steroid. The use of corticosteroid eye drops is known to raise intraocular pressure, increase risk of cataract formation and to aggravate infections, especially herpes simplex. There have been only occasional reports of such ocular complications arising from the use of topical steroids applied around the eyes to treat skin disease [34–36]. Glaucoma has also been reported in a patient

regularly treating hand eczema with betamethasone valerate at night, presumably resulting from inadvertent contamination of the eyes with the steroid [37]. These scant reports should be offset against the benefit of treating periocular skin disease, especially atopic dermatitis which is associated with keratoconus (probably as a result of frequent rubbing around the eyes) [38].

Locally applied corticosteroids have been demonstrated to impair wound healing and re-epithelialization in a variety of animal and humans models [39–41].

The question of whether tachyphylaxis develops during continued treatment with corticosteroids remains controversial. It is certainly common for patients to report that a topical corticosteroid which was highly effective during the first few days of application has subsequently lost efficacy. On occasions, withdrawal of corticosteroids is followed by a flare of disease. The hypothesis that these phenomena are caused by tachyphylaxis is supported by data from vasoconstrictor assays showing that successive applications of topical corticosteroids are associated with a decreasing response [42]. Furthermore, inhibitory effects on epidermal cell proliferation decreased during repeated administration of topical corticosteroids to hairless mice [43].

However, tachyphylaxis has not been shown to occur in clinical trials of corticosteroids in treatment of atopic dermatitis or psoriasis. It has therefore been proposed that patients report that the effect of the corticosteroid is diminishing when the underlying disease activity is increasing. Physicians observing patients intermittently may mistake stable disease activity for a failure to improve, even when there has been improvement from baseline, and may interpret this as tachyphylaxis. In a survey of dermatologists with 70 respondents, 57% believed that tachyphylaxis occurred within 8 weeks of initiating treatment of chronic plaque psoriasis with a potent corticosteroid. When this was put to the test in a clinical trial of 12 weeks' treatment duration, tachyphylaxis was not observed [44].

Rebound phenomena when topical corticosteroids are withdrawn have principally been of concern in the management of psoriasis. In several cases, withdrawal of treatment with potent or very potent corticosteroids has been followed by the eruption of severe generalized pustular psoriasis. This seems to have been especially likely to happen after potent or very potent corticosteroids have been used in large quantities or applied under occlusion [45]. In these cases it is likely that significant systemic exposure to the steroid was occurring and this was consequently withdrawn at the same time. The risk of this happening when unoccluded treatment with topical corticosteroids is used for chronic plaque psoriasis of moderate severity and disease extent are clearly very small, as this treatment has been so widely used, especially in the USA, yet generalized pustular psoriasis remains rare. Nonetheless, this phenomenon has resulted in a general reluctance of dermatologists in the UK to rely on topical steroids in the treatment of psoriasis vulgaris and this approach has the undoubted benefit of sparing patients other side effects such as cutaneous atrophy.

Vascular effects of corticosteroids include initial vasoconstriction of the superficial small vessels, followed by a phase of rebound vasodilatation. After prolonged treatment the vasodilation may become fixed and more conspicuous as a result of dermal and epidermal atrophy (Fig. 75.6) [46].

Systemic effects

Inhibition of the pituitary–adrenal axis by excessive application of moderately potent topical steroids or by relatively modest use of stronger steroids is well documented [47]. Temporary reversible suppression was seen after using 49 g/week of superpotent steroids for 2 weeks [48] in eight out of 40 patients, and similar results were seen in two further studies [49,50]. Significant suppression was reported in three patients using less than 50 g/week [51]. Recommended weekly dosage is less than 50 g of superpotent steroids and 100 g of potent steroids. In addition, prolonged usage at this level is best avoided. Children and babies have a high ratio of surface area to body volume and are more vulnerable to pituitary–adrenal suppression as a result of systemic absorption. Even hydrocortisone applied topically may suppress the adrenocortical response in some children [52]. Cushingoid features may be seen in infants inappropriately treated [53]. Severe medical problems are fortunately rare despite alarmingly abnormal biochemical parameters.

Vehicles and formulations

There is a large range of topical formulations of corticosteroids on the market. At first glance this may seem more than necessary but it is undoubtedly helpful to have a range of compounds available in a range of formulations. It is clearly important to be able to adjust the potency of the steroid being used so that the least potent compound that is effective can be employed at each site and at each stage in the progression of the dermatosis. It is necessary to be able to avoid corticosteroids to which patients are known or suspected to be sensitized. It is also helpful to have a range of formulations for each compound. Thus, ointments are helpful when eczema is dry, while creams are more effective if the eruption is moist or exudative. Lotions, gels or a mousse formulation are useful for the scalp. When the distribution is limited, as is often the case in lichen simplex chronicus or prurigo, the use of a steroid-impregnated tape will simultaneously prevent scratching and increase drug penetration by effective occlusion [54].

Several antimicrobial agents are commercially formulated in combination with topical steroids including clioquinol, clotrimazole, fusidic acid, miconazole, neomycin and nystatin. These compound formulations are the subject of some controversy. They can be helpful when there is a clear indication for each constituent but are probably used more often when the diagnosis is unclear in the hope of 'covering all the possibilities'. The latter approach is not recommended. Disadvantages include the risks of obscuring the diagnosis, promoting development of microbial resistance to antibiotics and sensitization of patients to antimicrobial agents that may then be impossible to use topically or systemically in future. The aminoglycosides, including neomycin, carry a particularly high risk of sensitization [55].

The case for use of these combinations is much stronger in the treatment of eczemas with evidence of secondary infection, although many dermatologists still prefer to give an antibiotic systemically. It seems very likely that some cases of atopic dermatitis are exacerbated by the presence of *Staph. aureus* on the skin. Superantigen production by these bacteria may have a role in this exacerbation of the disease [56] and may also have the effect of reducing sensitivity to corticosteroids [12].

There is also a special case for combining clioquinol with topical steroids in treatment of nickel dermatitis. This antiseptic is a potent chelating agent that can effectively inactivate nickel [57].

There are also commercially developed formulations combining corticosteroids with other active constituents. Mixtures containing tar, salicylic acid or calcipotriol can be useful in treatment of psoriasis. As in the case of antimicrobial agents, it is important that these compounds should only be used when there is a clear indication for each constituent and potent corticosteroids should only be used when they are really necessary.

Many dermatologists have found it useful to create their own formulations by dilution of proprietary products or addition of other medicaments such as tar and salicylic acid. There are some disadvantages to these practices. The stability of the steroid in a different formulation is unpredictable [58]. Changes in the vehicle may also alter levels of steroid penetration into the skin and systemic absorption [59].

Occlusion and topical steroids

The penetration of a topical corticosteroid can be greatly increased by occlusion using polythene film or gloves, or by using hydrocolloid dressings [60]. Polythene gloves are most easily used overnight, although they are uncomfortable, especially in warm weather. A similar occlusive effect is obtained when a steroid is covered by paste bandages and by the use of wet wrap bandaging in the treatment of atopic dermatitis. Using corticosteroids in this way will undoubtedly increase adverse as well as beneficial effects. However, judicious use of occlusion can be an invaluable strategy in the management of pompholyx, a refractory plaque of psoriasis on the leg, or a patch of lichen simplex. The incorporation of a corticosteroid such as fludroxycortide (flurandrenolone) into the adhesive of a plastic tape provides another effective method of using occlusion.

Whole-body occlusion of corticosteroids was formerly used, but adverse effects were common so this has fallen out of favour.

Intralesional steroids

Recalcitrant dermatoses (e.g. alopecia areata, keloid scars, lichen simplex, nodular prurigo) may respond to injection of steroid into the lesions. Triamcinolone is often used, but dermal atrophy and leukoderma may occur.

Indications for topical corticosteroids

The anti-inflammatory, immunosuppressant and antiproliferative properties of corticosteroids find numerous applications in dermatology, which are considered in more detail in the relevant sections of this text. Table 75.8 lists some of these applications together with the potencies of compounds that are most often used and the level of evidence available to support their efficacy [61].

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Table 75.8 Indications for topical corticosteroids, efficacy and potency of preparations generally employed.

Indication	Potency	Evidence grade	Occlusion and intralesional use
Actinic prurigo	P, VP	C	
Alopecia areata	P, VP	B	Ocl, I/L
Aphthous stomatitis	P	A	
Atopic eczema	M, Mod, P	A	
Bullous pemphigoid	P, VP	D	
Chronic actinic dermatitis	Mod, P	C	
Contact allergic dermatitis	Mod, P	B	
Contact irritant dermatitis	M, Mod, P, VP	C	
Cutaneous T-cell lymphoma	Mod, P	B	
Discoid eczema	P, VP	C	
Discoid lupus	P, VP	B	I/L
Geographic tongue	P	C	
Granuloma annulare	P, VP	E	Ocl, I/L
Granuloma faciale	Mod, P	E	Ocl, I/L
Grover's disease	P	D	
Hailey–Hailey disease	M, Mod, P	C	
Juvenile plantar dermatosis	Mod, P	C	
Langerhans' cell histiocytosis	Mod, P	C	
Lichen nitidus	P	E	
Lichen planopilaris	P, VP	D	I/L
Lichen planus	P, VP	C	Ocl, I/L
Lichen sclerosus	P, VP	A	
Lichen simplex	P, VP	A	Ocl, I/L
Lymphocytoma cutis	P	E	I/L
Lymphomatoid papulosis	P, VP	E	
Morphoea	P	E	I/L
Necrobiosis lipoidica	P	D	Ocl, I/L
Pemphigoid gestationis	P, VP	C	
Pityriasis rosea	Mod, P	E	
Pompholyx	P, VP	A	Ocl
Polymorphic eruption of pregnancy	P	B	
Pretibial myxoedema	P	C	Ocl
Prurigo nodularis	P, VP	E	Ocl, IL
Pruritus ani	M, Mod	A	I/L
Pruritus vulvae	Mod, P	B	
Psoriasis	M, Mod, P, VP	A	Ocl
Pyoderma gangrenosum	P, VP	D	
Sarcoidosis	P, VP	C	Ocl, I/L
Scleromyxoedema	P	E	Ocl, I/L
Seborrhoeic eczema	M, Mod	A	
Strawberry haemangioma	VP	D	
Subacute cutaneous lupus	Mod, P	E	
Subcorneal pustular dermatosis	Mod, P	D	
Sweet's syndrome	P	D	I/L
Urticaria pigmentosa	P, VP	C	Ocl
Vitiligo	P, VP	A	

Potency generally employed: M, mild; Mod, moderate; P, potent; VP, very potent.
Level of evidence available for efficacy [61]: A, double-blind trial; B, clinical trial; C, small trial or more than 20 cases reported; D, at least five cases reported to respond; E, less than five cases reported.
Modalities other than simple external application: Ocl (occlusion) and I/L (intralesional injection) indicate that these approaches have been reported to be useful in selected cases.

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Cytotoxic and antineoplastic agents

Bleomycin

Bleomycin is a cytotoxic agent with antitumour, antibacterial and antiviral activity. It binds to DNA, causing strand scission and elimination of pyrimidine and purine bases.

A number of reports document successful treatment of recalcitrant viral warts with intralesional injections of 0.1% bleomycin [1–3]. Two large double-blind placebo-controlled trials gave similar results [2,3]. Seventy-five to 95 per cent of warts on the hands and 60% of plantar warts cleared following 1–3 injections. Local pain is significant, but tolerated by patients who had previously received many unsuccessful treatments. The mechanism of action in warts is not yet known. The small volumes used do not cause systemic toxicity. Treatment of a periungual wart resulted in a permanent nail dystrophy [4]; Raynaud's phenomenon may occur after treatment on digits. The compound must be handled with care.

Bleomycin has also been used in treatment of oral leukoplakia. A 1% solution in DMSO administered for 5 min over 14 consecutive days reduced the size of lesions and histological dysplasia in a trial with 22 patients [5].

5-Fluorouracil

This pyrimidine analogue is an antimetabolite that inhibits pyrimidine metabolism and DNA synthesis.

In the form of a 5% cream, 5-fluorouracil (5-FU) is a very effective treatment for multiple solar keratoses. Lesions on the scalp and face respond more readily than lesions on the limbs. A commonly used regimen comprises twice daily application for 2 weeks but there are many variations on this which are used to improve tolerability. A single daily application is sometimes adequate. Some dermatologists suggest a 1 week on, 1 week off regimen, or use the treatment for 1 week each month, or use it continuously but omit treatment at the weekend. Some patients require longer periods of treatment, and others are cleared only by occlusion of the agent with polyethylene film. A brisk inflammatory response should occur within the keratoses, otherwise clearing is incomplete. Severe ulcerative reactions occur in a few patients. Combination with a fluorinated steroid has been shown to limit the intensity of the inflammatory response without reducing the efficacy of 5-FU [6]. Combination of topical 5-FU applied twice daily with oral isotretinoin 20 mg/day for a median treatment duration of 21 days proved highly effective in a series of cases with disseminated actinic keratoses [7]. Actinic cheilitis and keratosis of the lip can be improved, although the treatment may cause some transient discomfort and dysplastic changes can persist histologically after apparently satisfactory clinical response [8].

5-FU can be effective in Bowen's disease, with 24 out of 26 lesions being cured in a series with 10-year follow-up [9]. However, a recent comparison with photodynamic therapy indicated that the latter was more effective [10]. Bowenoid papulosis can be treated with 5-FU and erythroplasia of Queyrat can also respond [11].

In treatment of basal cell carcinoma (BCC), topical 5-FU is considered most useful for low-risk lesions on the trunk and lower limbs [12]. It has proved successful in reducing the number of lesions appearing in the basal cell naevus syndrome [13]. Intralesional 5-FU has also been used with success in this indication [14].

5-FU, applied daily under adhesive plasters, proved effective in a placebo-controlled trial for the treatment of common viral warts [15]. Applied once or twice a week it has also been shown to be effective and well tolerated in curing resistant vaginal condylomas [16]. A proprietary combination of 5-FU and salicylic acid, applied on a daily basis, resulted in complete healing of genital warts in an average of 12 days [17].

5-FU can also be effective in extramammary Paget's disease [18]. It has been used with variable results in naevoid keratotic conditions including Darier's disease [19], and in superficial actinic porokeratosis [20].

T4 endonuclease V

This is a bacterial DNA repair enzyme that excises damaged sections of DNA. This is the initial step in repair of a DNA strand that has sustained photodamage. Remarkably, in a placebo-controlled study of 1 year duration, a liposomal formulation containing this enzyme has been demonstrated to reduce the occurrence of new neoplasms in patients with xeroderma pigmentosum [21]. This has implications not only for patients with this rare group of diseases; if one enzyme can be delivered into cells simply by application to the skin within liposomes, then it is possible that many other enzyme treatments might be delivered in similar vehicles.

Mechlorethamine

Mechlorethamine (mustine, nitrogen mustard) is a cytotoxic drug that is highly active when applied topically. It is an alkylating agent and acts by binding covalently to DNA and thus inhibiting replication. Its use is often constrained by its marked tendency to induce contact allergic dermatitis. Immediate hypersensitivity reactions can also occur but are less common. It is also potentially carcinogenic, although the precise level of risk is difficult to establish as many groups of treated patients have received additional carcinogenic treatments. Mechlorethamine has a number of dermatological applications.

The most frequent use is probably in the treatment of cutaneous T-cell lymphoma. Concentrations used most frequently are 0.01–0.02% and the treatment is applied once daily [22]. Aqueous solutions and also ointment formulations are highly effective. The latter seem to carry a lower risk of sensitization, although irritant reactions still occur. In a large, recently published series, 137 patients with stage T1 or T2 disease were treated with topical mechlorethamine alone for a median period of 5 years. Complete remission was achieved in the majority and only four progressed to a more advanced stage [22].

Topical mechlorethamine 0.02% can be highly effective and seems to be well tolerated in children with Langerhans' cell histiocytosis [23]. In this series, treatment was initially applied daily to affected areas of skin and the children were bathed to remove excess medication 10 min after the application was completed. The frequency of application was later reduced to every second or third day as the skin improved. Only two out of 20 children treated developed an irritant dermatitis [24].

Topical mechlorethamine has been recognized as effective in the treatment of psoriasis since a placebo-controlled trial was published in 1970 [25]. A solution containing 0.05% was effective after weekly application for 4–20 weeks but most patients eventually became sensitized and this has proved a major disadvantage. Some patients

have successfully maintained long-term control of the disease using a concentration of 0.02% [26]. The risk of sensitization can be reduced by concurrent use of ultraviolet B (UVB) [27] or psoralen with UVA (PUVA) [28].

An encouraging report of alopecia areata and totalis responding to topical mechloethamine 0.02% has not yet been followed up by further reports of success [29]. In a subsequent report, no response was obtained in seven patients with alopecia totalis, although the treatment was well tolerated [30]. However, a recent study on a mouse model of alopecia areata did yield a positive response [31].

In single cases, pyoderma gangrenosum [32], and ulcerating lesions of chronic granulocytic leukaemia [33], have been reported to respond to topical mechlorethamine.

Imiquimod

This interesting compound belongs to a group known as imidazoquinolones. The actions of these compounds seem likely to be mediated by the Toll-like receptor 7 (TLR-7) [34]. This is a cell surface receptor found on cells of monocyte lineage. The naturally occurring ligands for TLRs are highly conserved microbial products, essential for microbial survival, which are responsible for stimulating the relatively primitive innate immune response. Interaction of TLR-7 with ligands activates a signalling pathway leading to release of large amounts of interferon-α, interleukin-12 (IL-12), tumour necrosis factor-α (TNF-α) and other potent cytokines. In addition to stimulating the innate response, these cytokines promote the development of antigen-specific cell-mediated immune responses. Imiquimod is therefore viewed as an immune response modulator.

The first clinical application in which imiquimod proved useful was for treatment of genital warts. In large placebo-controlled [35] and open-label [36] trials, imiquimod 5% cream applied three times weekly for 16 weeks produced complete clearance in 48–50% of patients. Relapse rates in those who had cleared (relapse being defined as recurrence of at least one visible wart) were 13% at 3 months [35] and 23% at 6 months post treatment [36]. Common warts may also respond. Thirty per cent of patients were cleared in a series of 50 treated with 5% imiquimod cream on 5 days each week for up to 16 weeks [37]. Sixteen of 18 children with warts of 2–7 years' duration were cleared of lesions after applying 5% imiquimod cream twice daily for 2–11 months [38]. Facial planar warts responded convincingly in a report of a single case [39]. In one case, stucco keratoses responded to imiquimod [40]; interestingly, human papillomavirus was detected in the lesions. Molluscum contagiosum has also been reported to respond in an uncontrolled study [37].

Imiquimod would seem to have potential in many additional applications including treatment of *in situ* malignancy. Actinic keratoses have been shown to respond in a placebo-controlled trial. Eighty-four per cent of patients were cleared after using imiquimod three times weekly for up to 12 weeks [41]. There was no response to the vehicle control. Fourteen of 15 patients with Bowen's disease had no residual lesion after daily application for up to 16 weeks [42]. Local skin reactions were common but these are thought to reflect the immune response to the tumour. In a series of similar size, actinic cheilitis responded well to imiquimod applied three times weekly for up to 6 weeks [43]. Partial and complete responses have been observed in treatment of cervical, vaginal and vulvar intraepithelial neoplasia and Bowenoid papulosis, although results have not been consistent [44–46]. Extramammary Paget's disease resolved in response to imiquimod in two cases treated daily or on alternate days, as tolerated, for 7.5 and 16 weeks [47]. Both of these patients experienced systemic symptoms (flu-like illness and nausea). Complete resolution was reported in a case of porokeratosis [48].

Trials on BCC have demonstrated unequivocal efficacy in dose ranging and placebo-controlled studies. In superficial BCC, resolution occurred in 81–88% of lesions treated daily, or on 5 days per week, for 6 or 12 weeks [49,50]. Treatment for 6 weeks appeared as effective as 12 weeks. Applying imiquimod on 3 days weekly for 6 weeks produced cure rates of 76%, or 87% when occluded [51]. In nodular BCC, daily treatment has yielded somewhat lower cure rates at 71% or 76% after 6 weeks or 12 weeks, respectively [52]. Treatment on 3 days weekly cured 50%, and 65% with the use of occlusion [51].

Imiquimod may find at least a palliative role in treatment of lentigo maligna and melanoma. In treatment of lentigo maligna, several cases and small series have reported apparently complete clinical resolution [53–55], in some cases confirmed histologically. However, one report describes lentigo maligna that apparently resolved following treatment with imiquimod but the course of the resolution was complicated by the development of a nodular melanoma and microsatellites; these were excised with the patient remaining disease-free after 17 months of follow-up [56]. Complete clinical and histological resolution has been reported in two cases of cutaneous metastatic melanoma [57], while marked improvement has been observed in additional cases [58,59]. In a further case, the cutaneous metastases resolved but lymph node metastasis developed [60].

Imiquimod may prove effective in suppressing the recurrence of keloids following excision. In an uncontrolled study with 12 subjects, the cream was applied nightly for 8 weeks, starting immediately after excision [61]. No recurrences were seen at 6 months.

Diclofenac

This compound is a non-steroidal anti-inflammatory drug that appears to be effective in topical treatment of actinic keratoses. A gel formulation containing 3% diclofenac and 2.5% hyaluronic acid has been developed specifically for this purpose. The mechanism of action remains uncertain. It has been proposed that excessive arachidonic acid metabolism resulting from overactivation of cyclo-oxygenase enzymes is carcinogenic [62]. If so, diclofenac may help suppress actinic keratoses by inhibition of cyclo-oxygenase.

In an open-label study, this formulation was applied twice daily until patients were clear, or for up to 180 days. Twenty-two (81%) of 27 patients who completed the study, and were assessed 30 days after treatment was discontinued, had a complete response and another four (15%) showed marked improvement [63]. These results have been supported by double-blind trials in which 3% diclofenac gel has been applied twice daily for 30–90 days and proved superior to vehicle in clearing solar keratoses [62,64,65]. Consistently, the largest and most statistically significant difference between diclofenac and vehicle has been observed at follow-up 30 days after treatment has been discontinued. This has occurred even when the difference has not been significant at the end of treatment [65]. As assessed at this follow-up visit, the proportions of patients completely cleared have been approximately 16% when treatment duration was 30 days [52], 31% when this was 60 days [52], 38% for 12 weeks [65] and 47% when the duration was 90 days [64]. It would therefore seem that the clearance rate continues to increase with increasing treatment duration.

The treatment seems to be well tolerated, although pruritus has not been uncommon and dermatitis, confined to the treated site, has developed occasionally.

Podophyllin and podophyllotoxin

Podophyllin (podophyllum) is a plant extract traditionally used to treat genital warts. Podophyllotoxin is the most active constituent. This is now available in standardized formulations free of the unwanted constituents of podophyllin. Podophyllotoxin is an antimitotic agent which arrests cells in metaphase by binding to tubulin. Podophyllin is known to be highly mutagenic and although podophyllotoxin may be less hazardous, both of these treatments should be avoided in pregnancy. Irritant reactions are common with these agents.

Podophyllin 0.5% in ethanol may be applied on 3 consecutive days each week to treat penile warts [66]. Podophyllin 10–25% in tincture of benzoin compound may be applied once or twice a week to genital or perianal warts (washed off after 6–12 h). Podophyllotoxin can be used at a 0.5% concentration in ethanol as a once daily application. It will clear 60–70% of genital warts within 3–5 days [67]. A cream formulation containing 0.15% podophyllotoxin is also available and can be applied twice daily for 3 days each week.

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Depigmenting agents

Depigmenting agents are most frequently used by dermatologists in the treatment of melasma. Hydroquinone, used alone in concentrations usually ranging from 2 to 5%, or in combination with retinoic acid in 0.025–0.1%, is currently the most widely used treatment for this indication.

Post-inflammatory hyperpigmentation is another commonly encountered problem and this is particularly difficult to treat as much of the pigment is often contained in dermal melanophages. Nonetheless, depigmenting compounds such as tretinoin, hydroquinone or azelaic acid are sometimes prescribed.

In severe cases of vitiligo when depigmentation is already extensive, depigmenting agents can improve the appearance of the skin by removing residual patches of normal pigmentation.

Solar lentiginosis is another indication for which depigmenting agents can prove useful. Retinoic acid has the best evidence base in this indication.

There is also a demand among populations with pigmented skin for agents to reduce the intensity of pigmentation for purely cosmetic purposes. In parts of Africa, treatments abused for this purpose include very potent topical corticosteroids, mercury compounds and high concentrations of hydroquinone [1–3].

Hydroquinone

Hydroquinone (1,4 dihydroxybenzene) is widely used as a depigmenting agent both in clinical and cosmetic contexts.

The efficacy of 4% hydroquinone cream in treatment of melasma was demonstrated in a placebo-controlled trial in which treatment was applied nightly for 3 months [4]. Higher concentrations are sometimes used in extemporaneous formulations for severe or resistant cases of chloasma or for post-inflammatory hyperpigmentation. The efficacy of hydroquinone in post-inflammatory hyperpigmentation is likely to be highly variable as this is a very heterogeneous entity. Hydroquinone is used at 5% concentration as a constituent of Kligman cream (see below) [5]. It can cause both irritant and allergic reactions. The addition of a weak topical steroid reduces the irritant effect. It is unstable and tends to darken as a result of autooxidation. Hydroquinone probably reduces pigmentation, at least partly, as a result of inhibition of melanin synthesis, because it is known to inhibit tyrosinase. However, the mechanism is not fully understood. It has also been proposed that its action may be partly mediated by release of free radicals. In animal models, the effect of the drug is potentiated by the use of buthionine sulfoxime or cystamine to inhibit synthesis of the protective free radical scavenger glutathione [6].

Epidemiological studies indicate that a very large proportion of the African population (perhaps the majority of women) have used hydroquinone cosmetically as a skin lightening agent [1–3]. This practice has been strongly associated with the development, in these black-skinned individuals, of exogenous ochronosis [1–3,7,8]. This disease, like endogenous ochronosis (alkaptonuria), derives its name from the colour of the cutaneous pigment deposits that characterize these conditions (Greek *ochro*, yellow). When these are examined histologically they appear yellow or brown, although clinically the pigment appears dark brown or black. Endogenous ochronosis is an inborn error of metabolism in which deficiency of homogentisic acid oxidase results in accumulation of homogentisic acid, a metabolite of tyrosine and phenylalanine. Oxidation products of homogentisic acid are thought to constitute the pigment deposited in the skin, cartilage and elsewhere.

The pigment in exogenous ochronosis strongly resembles that in the endogenous form and may result from inhibition of homogentisic acid oxidase by hydroquinone. Milder cases show only macular sooty pigmentation while more advanced cases develop irregular stippling, papulation and pigmented colloid milia [8,9]. These features tend to be most prominent over the areas of skin most intensely exposed to the sun. Histologically, deposits of pigment are observed in the papillary and reticular dermis and probably represent accumulations of the pigment in association with degenerated collagen [9,10]. In many countries, the concentration of hydroquinone in cosmetic products has been legally restricted to 2% with the aim of reducing the risk of causing ochronosis. However, it is not established that this risk is dependent on the concentration [11].

In striking contrast to Africa, exogenous ochronosis seems to be rare in the USA, even though hydroquinone-containing compounds are widely used there [12,13]. Possible explanations put forward for this paradox include under-reporting, combined use with other compounds in Africa, the need for intense solar irradiation as a synergistic factor, the use of different formulations (especially hydroalcoholic solutions) in Africa, or that the use of these compounds in the USA may be relatively cautious.

Exogenous ochronosis occurs almost entirely in black skin. It does not seem to be a hazard in white skin, although occasional cases have occurred in Hispanics. The relatively high levels of enzyme activity associated with melanin synthesis in black skin and additional stimulation of these pathways by intense sun exposure seem to be required for ochronosis to develop.

Monobenzyl ether of hydroquinone

Skin bleaching with 20% monobenzyl ether of hydroquinone (monobenzone) is generally reserved for treatment of carefully selected cases of vitiligo. The resulting depigmentation may be permanent so this treatment is only suitable for those with extensive disease in whom the appearance of the skin would be improved by removing the residual pigment. Patients should be warned that results are unpredictable. Treatment may need to be prolonged and is not always successful [14]. Depigmentation may be permanent and may occur at sites other than those being treated. Conversely, spontaneous repigmentation may occur unexpectedly after cessation of the treatment, slowly or rapidly, at both treated and untreated sites [15]. Contact dermatitis can develop [14,16]. It has also been reported that this treatment may cause corneal and conjunctival pigmentation [17].

The addition of monobenzone to cosmetic skin lightening preparations caused an epidemic of leukomelanoderma in South Africa during the early 1970s [9].

Additional phenol derivatives

Mequinol (4-hydroxyanisole, 4-methoxyphenol) is another phenol derivative with depigmenting properties. It is a constituent of a commercially formulated solution containing 2% mequinol and 0.01% retinoic acid marketed for treatment of solar lentiginosis. In trials with treatment duration of 24 weeks, this combination appeared more effective than either of the constituents used alone, or than placebo [18]. Mequinol 20% cream has been successfully used to remove residual pigmentation in severe vitiligo with efficacy considered comparable to monobenzone [19].

N-acetyl-4-*S*-cysteaminylphenol (*N*-Ac-4-*S*-CAP) produces reversible depigmentation in the Yucatan pig model [20,21]. In one report of its use in melasma, 8% of

patients showed complete depigmentation, 66% marked improvement and 25% moderate improvement [22].

Retinoic acid

Retinoic acid (tretinoin) has been successfully used to reduce pigmentation in a variety of disorders including melasma [23], solar lentiginosis [24,25] and post-inflammatory hyperpigmentation [26]. In most trials, tretinoin 0.1% cream has been used for 40 weeks. Retinoid dermatitis is a common side effect and may result in post-inflammatory hyperpigmentation. Some mild reduction of pigment may occur in normal skin surrounding the treated areas. The mechanism of action is not fully understood but may be at least partly explained by reduction in melanogenesis consequent upon reduction of tyrosinase activity [27].

Attempts have been made to use other retinoids for this purpose with variable results. All-*trans* retinol gel 10% proved effective, although irritant, in a Japanese study [28]. A study on the use of topical 0.05% isotretinoin in melasma showed no difference from placebo after 40 weeks [29].

Kligman cream

This formulation comprises 5% hydroquinone, 0.1% tretinoin and 0.1% dexamethasone in hydrophilic ointment [5]. It has been widely used as a depigmenting treatment, especially for melasma. The combined formulation is considered more effective than any of the individual constituents.

Azelaic acid

This dicarboxylic acid is a relatively safe, although mildly irritant agent, with several roles in dermatology.

As a depigmenting agent, azelaic acid is moderately effective in treatment of melasma. The proposed mechanism is direct or indirect inhibition of tyrosinase [30]. Azelaic acid 20% cream proved more effective than 2% hydroquinone cream after 24 weeks of treatment [31]. In two other studies with the same treatment duration, 20% azelaic acid proved equivalent in efficacy to 4% hydroquinone cream [32,33]. Another study on facial hyperpigmentation in darker skinned individuals compared a combination of azelaic acid 20% cream with glycolic acid 15% or 20% lotion, versus 4% hydroquinone cream; similar efficacy was observed from the two regimens [34]. The addition of tretinoin enhances the depigmenting effect [1,2]. Azelaic acid has also proved effective in treatment of Kitamura's reticulate acropigmentation [35].

Azelaic acid also has antineoplastic properties, inhibiting mitochondrial function and DNA synthesis [36], and has been used as a palliative treatment for lentigo maligna and malignant melanoma [37–39]. However, because some cases of lentigo maligna have progressed to invasive melanoma while using this treatment, it must be regarded as purely palliative in these indications [37].

Azelaic acid 20% cream is effective in treatment of acne vulgaris [40]. This is likely to be a result of a combination of antimicrobial and anti-inflammatory properties. It can inhibit growth of *Propionibacterium acnes* and *Staphylococcus epidermidis* and inhibits production of free radicals by polymorphs [41]. The latter property may also explain why it is effective in rosacea [42,43]. It may also prove to have a role as an antimycotic inhibiting growth of dermatophytes [44,45], and as a topical antimicrobial agent with activity against antibiotic-resistant *Staph. aureus* [46].

Kojic acid

This is a fungal metabolite known to inhibit tyrosinase [47]. It is a constituent of over-the-counter depigmenting creams sold mainly in Japan. In treatment of melasma, 1% kojic acid proved equally effective as 2% hydroquinone when each was used in combination with glycolic acid [48].

Liquiritin

This compound, which can be extracted from liquorice (*Glycyrrhiza glabra*) and other herbal sources, has been reported to effectively reduce the pigmentation of melasma in a double-blind trial [49].

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Depilatories

Depilation can be defined as temporary removal of hair, while epilation denotes permanent destruction of the follicle. Epilation therefore requires physical methods of destruction of the follicle such as electrolysis, lasers and intense pulsed light. Depilation can be achieved by shaving, waxing, plucking, threading and by use of topical depilatory creams. Systemic androgen antagonists have a part to play in some cases. All these techniques are described further in Chapter 63; only topical treatments are discussed here.

Traditional depilatory creams depend upon breaking the disulphide bonds in hair. Three main classes are currently used. The oldest are various sulphides, which have a powerful effect but may irritate, and which in the presence of water generate hydrogen sulphide which has an unpleasant odour. Strontium or barium sulphide 20% are widely used. They are effective on the terminal hair in the axillae. Thioglycollates are being used more frequently, but they are slower to work than sulphides. Concentrations of 2.5–4% produce an effect in 5–15 min. Substituted mercaptans (thioalcohols) are most widely used. They work slowly, but are suitable for use on the face.

Eflornithine hydrochloride is an irreversible inhibitor of ornithine decarboxylase, an enzyme required for hair growth. This is marketed as a 13.9% cream, which can slow the growth of facial hair. A response takes 4–8 weeks to develop and the effect wears off over a similar period when the treatment is discontinued. The benefit seems to

be rather modest in many cases, with only 32% of patients reporting marked improvement [1,2]. Some irritation may occur.

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Dithranol

Dithranol (anthralin) [1] is a time-honoured topical treatment for psoriasis, similar in its irritating and staining properties to chrysarobin, which it supplanted in the early 20th century, but more effective. It is used in ointments, pastes, creams and as a pomade for use on the scalp.

The mechanism of action of dithranol is still uncertain. It inhibits glycolytic enzymes *in vitro* [2]. Reactive oxygen species are generated during auto-oxidation of dithranol [3] and these may inhibit mitochondrial function [4]. It has been suggested that enzyme inactivation may result from lipid peroxidation, leading to cross-linkage of enzyme proteins [5]. *In vitro* studies with human skin showed decreased oxygen consumption and inhibition of the pentose phosphate shunt [6]. The level of cyclic guanosine monophosphate is known to be increased in psoriasis. Dithranol has been shown to restore cyclic nucleosides in skin to normal levels [7]. It induces a marked antiproliferative effect [8,9].

The use of dithranol has proved remarkably safe. Staining of the skin and of other materials is certainly inconvenient although, as a result, the appearance of the skin provides a reliable guide to compliance (Fig. 75.7). Local reactions are common and irritation of normal skin accidentally contaminated with dithranol can be severe (Fig. 75.8). However, there is no evidence of systemic toxicity and it is not considered to be carcinogenic.

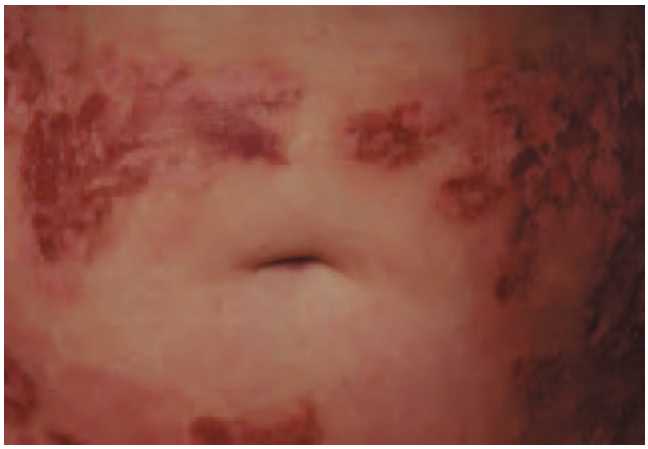

Fig. 75.7 Staining of the skin resulting from dithranol treatment.

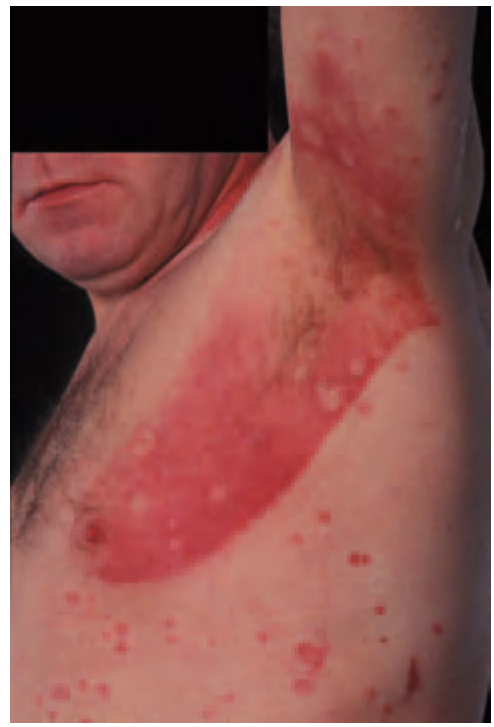

Fig. 75.8 An irritant reaction following accidental contamination of normal skin with dithranol.

Dithranol, especially when incorporated in zinc oxide, is slowly oxidized by alkaline impurities to an inactive pink anthrone [10]. The effect of salicylic acid in preventing this has been known for a long time [11–13]. Salicylic acid neutralizes hydroxyl ions in an alkaline medium, and perhaps reacts with free zinc ions to form an inactive zinc–dithranol complex. It has been found that zinc ions and salicylic acid, like dithranol itself, inhibit glucose-6-phosphate dehydrogenase, thus further justifying the time-honoured combination of these three agents [6]. The combination of tar with dithranol is said to reduce dithranol irritancy without inhibiting therapeutic effect [14].The use of a water-soluble antioxidant, ascorbic acid, has allowed the production of stable dithranol cream preparations [10]. These are not as therapeutically potent as equivalent strengths of pastes or ointments but show much greater patient acceptability for home usage [15]. The development of lipid-encapsulated cream formulations also seems likely to increase acceptability by further reducing staining and irritation [16,17].

Short-contact applications of strong dithranol pastes or creams are known to be almost as effective as prolonged contact and facilitate treatment on an outpatient basis and self-treatment at home [18–20].

Dithranol has also been used to stimulate an inflammatory response and regrowth of hair in patients with alopecia areata [21], and for the treatment of warts [22].

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Emollients

The word emollient is derived from the Latin verb *mollire*, to soften. The term is used by dermatologists to denote materials that soften and moisturize the surface of the skin. Most of the formulations used as emollients are creams, ointments, bath oils or soap substitutes. Emollient creams and ointments are formulated using the various materials described earlier in this chapter as constituents of vehicles and are essentially vehicles without a drug to deliver. They are applied to the skin purely to take advantage of their physical properties (protecting, lubricating and moisturizing effects). The efficacy of an emollient is not related to the cost, although this may have some impact on cosmetic acceptability. The most effective emollient is probably white soft paraffin (petrolatum).

The value of bath oils is not well established, although these are widely used in the UK. Most contain lipids such as liquid paraffin, which probably help reduce the drying effect of bathing by protecting the stratum corneum with a layer of lipid. Some also contain antiseptics and antipruritic compounds which can be of additional value. The use of bath oils is best avoided for elderly patients as they tend to make the bath slippery.

The use of soaps on inflamed skin, especially in atopic dermatitis, is generally considered harmful and likely to exacerbate damage to the stratum corneum [1,2]. Compounds used as soap substitutes are lipid materials containing emulsifiers such as Aqueous Cream BP or Emulsifying Ointment BP. Most emollient creams can be used in this way. These can effectively remove lipid-soluble dirt and contamination from the skin surface while avoiding the damage done to the stratum corneum by irritant surfactants. Patients with dry skin conditions report that soap substitutes improve the condition of the skin [3]. Paradoxically, the introduction of washing with common toilet soap was accompanied by improvement in atopic dermatitis in one study [4], possibly reflecting increased compliance with other aspects of treatment.

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Immunomodulators

SYN. CALCINEURIN INHIBITORS

Several topical medications alter immune responses, but are discussed elsewhere in this chapter—for example, corticosteroids or imiquimod, which is viewed as an immune response modulator. This section considers the calcineurin inhibitors.

These compounds have been developed for topical treatment of atopic dermatitis but seem likely to find numerous additional applications. There are currently two agents, tacrolimus and pimecrolimus, available in this class and others are likely to follow. The mechanism of action is similar to that of ciclosporin. Lymphocyte activation is suppressed by inhibition of calcineurin, a calcium- and calmodulin-dependent serine/threonine phosphatase. This cytoplasmic enzyme activates the

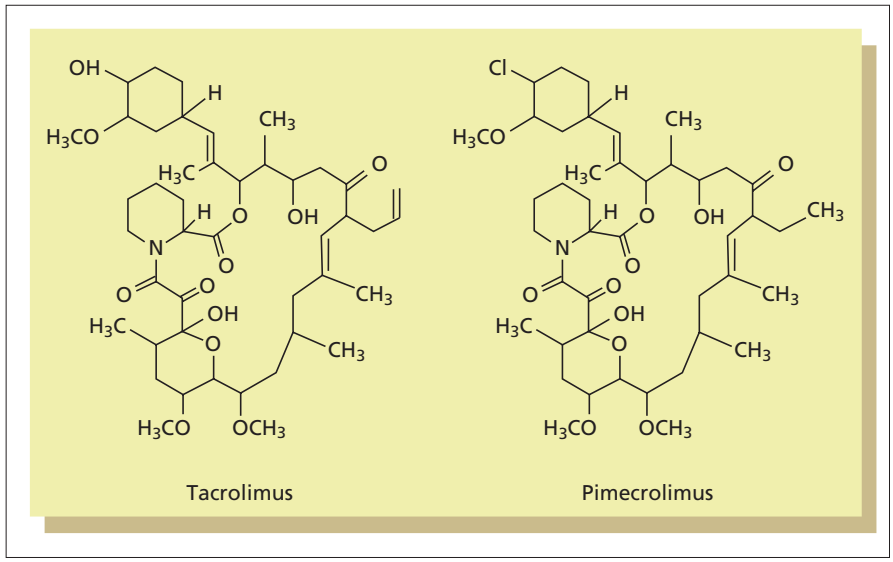

Fig. 75.9 The structures of tacrolimus and pimecrolimus.

nuclear factor of activated T cells (NFAT), a transcription factor regulating numerous lymphokines in both Th1 and Th2 lymphocyte subsets, and constitutes an important link in signal transduction from the T-cell receptor to the nucleus [1]. Similar mechanisms operating in other cell types, including mast cells [2,3], antigen-presenting cells [4] and keratinocytes [5], may provide additional targets for these drugs. In contrast to ciclosporin, these molecules have a sufficiently low molecular weight to penetrate the stratum corneum, at least when barrier function is impaired as is the case in atopic dermatitis. They are therefore active when applied topically. Both compounds have been under investigation in clinical trials for over 9 years now. A notable advantage of these agents is that they do not induce cutaneous atrophy [6,7], even with long-term regular application [8–10], and it is therefore possible to apply them to facial and flexural areas where prolonged use of topical corticosteroids causes concern. Theoretically, the local immunosuppression related to these compounds could increase the risks of infections and neoplasia. In the numerous trials on atopic dermatitis, infections have not been more frequent than expected. The risk of neoplasia also remains theoretical.

Tacrolimus

Tacrolimus (FK-506) is a macrolide lactam antibiotic (macrolactam) discovered in Japan where it was first isolated from a soil fungus, *Streptomyces tsukubaensis*. It has been used systemically in transplantation for over 15 years and is known to be effective, used systemically, in treatment of psoriasis [11]. It has a molecular weight of 822 Da and a complex structure (Fig. 75.9). The efficacy of tacrolimus in atopic dermatitis has been demonstrated in several placebo-controlled trials in both adults [12,13] and children [14,15]. In comparative trials, tacrolimus ointment 0.1% applied twice daily is comparable in efficacy to potent topical corticosteroids such as hydrocortisone butyrate 0.1% [16] and betamethasone valerate 0.12% ointment [17]. It is been more effective than hydrocortisone acetate 1% ointment in children [15] and was more effective than the moderately potent alclometasone dipropionate 0.1% ointment in treatment of eczema on the face and neck in adults [18]. In children, a lower concentration of 0.03% tacrolimus has proved nearly as effective as 0.1% [14,15], while in adults there is a more marked difference between these concentrations and 0.1% is clearly more effective [16,19]. The most frequently encountered side effect is a burning sensation lasting for a few minutes after application. This tends to resolve after a few days and is rarely of sufficient severity to require withdrawal of the treatment. Systemic exposure is low and drug levels in blood are usually too low to measure [14,20,21]. Using data obtained from application of 0.3% tacrolimus ointment, systemic bioavailability has been estimated at 0.5% of that obtained by intravenous administration [21]. It is therefore unlikely that topical application of tacrolimus will exhibit systemic activity. Furthermore, systemic exposure tends to fall as the eczema improves, indicating that penetration of the drug is reduced as barrier function is restored [22].

Additional applications for topical tacrolimus have currently been less formally investigated and it should be noted, in particular, that extensive safety data relating to systemic exposure are available only for atopic dermatitis. The use of topical tacrolimus in Netherton's syndrome (ichthyosis linearis circumflexa) can result in clinically significant systemic exposure to the drug [23], indicating that some care is required.

Reports indicate that topical tacrolimus is effective in

treatment of several other varieties of eczema including chronic actinic dermatitis [24], endogenous hand eczema [25] and eyelid dermatitis [26]. In a guinea pig model, irritant and allergic contact dermatitis have been suppressed [27]. Treatment of psoriasis has so far proved less successful [28], although the author has treated facial and flexural psoriasis with unequivocal improvement and similar reasonably successful results have been reported by others [29]. This relatively modest response in psoriasis is somewhat surprising given that systemic use of calcineurin inhibitors (ciclosporin and tacrolimus) is highly effective and a good response has also been observed when tacrolimus was applied under occlusion in a microplaque assay [30]. It would seem, however, that penetration of the drug through the plaques of psoriasis vulgaris is not adequate. Sadly, the efficacy of topical tacrolimus in the Dundee experimental bald rat model of alopecia areata [31] has not so far been reproduced in the treatment of human cases of this disease. Development of a more appropriate formulation might improve results in psoriasis and alopecia areata.

There are more encouraging reports of efficacy of topical tacrolimus in a variety of other dermatoses including oral and genital erosive lichen planus [32–36], pyoderma gangrenosum [37–39], cutaneous graft-versus-host disease [40], rheumatoid leg ulceration [41], cutaneous sarcoidosis [42], steroid-induced rosacea [43], uraemic pruritus [44], vitiligo [45,46], discoid lupus erythematosus [47], eosinophilic folliculitis [48] and epidermolysis bullosa [49]. Oral and perineal lesions of Crohn's disease have responded [50] and topical tacrolimus has been effective in suppression of skin allograft rejection [51]. Improvement has been observed in Netherton's syndrome [23,52], although, as discussed above, significant systemic absorption may occur in this disease. Three cases of erosive pustular dermatosis of the legs responded to topical tacrolimus [53].

Pimecrolimus

Pimecrolimus (SDZ ASM 981) is another macrolactam with a structure similar although not identical to tacrolimus and molecular weight 810 Da (Fig. 75.9). The relatively small differences in structure compared to tacrolimus confer greater lipophilicity but reduce potency. Most of the clinical research on this compound has so far been in atopic dermatitis. Placebo-controlled trials have demonstrated efficacy and safety of pimecrolimus 1% cream in adults [54–56] and children from 3 months of age upward [57,58]. In a comparative study, this treatment was less effective than betamethasone valerate 0.1% cream [55]. Used in long-term studies, pimecrolimus has effectively inhibited flares of the disease and reduced the requirement for topical corticosteroids [56,58]. Systemic absorption of pimecrolimus has been low and usually undetectable [59,60]. Topical pimecrolimus has been safe and well tolerated. Although a burning sensation is sometimes reported in the treated areas, this usually resolves after a few days. Infections have not been increased and there has been no evidence of increased neoplasia.

Experience with pimecrolimus in other skin diseases has been very limited so far. In animal models, pimecrolimus inhibits induction of contact allergic dermatitis [61]. An initial report suggests that it may suppress established nickel dermatitis [62]. Used systemically [63] and also applied topically under occlusion, it can be effective in psoriasis [64]. A response has also been reported in a case of seborrhoeic dermatitis [65].

Ciclosporin (cyclosporin)

Despite the best endeavours of many investigators over the years to develop topical uses for ciclosporin, this has failed to find any consistently useful role. Ciclosporin has a high molecular weight of 1202 Da and this is probably the reason why it does not penetrate through the skin in sufficient concentration to be effective. Early reports of efficacy in oral erosive lichen planus may have been the result of significant systemic absorption. A controlled study using triamcinolone as comparator found no difference between the treatments and the improvement observed was only modest [66].

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Retinoids

The retinoids can be defined either as compounds related structurally to retinol (vitamin A) or as compounds that are able to interact with retinoid receptors. The latter definition has become more useful as an increasing number of synthetic 'retinoids' are developed with diverse structures. Topical retinoic acid has been used in treatment of acne vulgaris for over three decades. During this period much has been learned about the fundamental part played by endogenous retinoids in the regulation of cell differentiation and proliferation and about the mechanisms involved. Retinoids are now used for many indications including psoriasis, photo-ageing and numerous disorders of keratinization as well as for suppression of dysplasia and malignancy.

The activity of endogenous retinoids within the cell is regulated by binding proteins known as cellular retinol binding proteins (CRBP I and II), and cellular retinoic acid binding proteins (CRABP I and II). These proteins are widely distributed throughout the body in many cell types. CRABP II predominates in skin, and is found in keratinocytes and fibroblasts [1]. This protein is up-regulated by retinoic acid [2] and by other compounds demonstrating retinoid activity, and is believed to have a role in regulating the availability of free retinoic acid within the cell.

Within the nucleus, retinoids bind to specific receptors, retinoic acid receptors (RAR α, β and γ) and retinoid X receptors (RXR α, β and γ). Alternative splicing of each of these receptors generates further diversity (the subtypes being known as RAR-α1, RAR-α2, etc.) [3]. All-*trans* retinoic acid is the endogenous ligand for the RARs while 9-*cis* retinoic acid is the endogenous ligand for the RXRs. The receptors most abundantly expressed in the epidermis are RAR-γ and RXR-α, while RAR-α and RXR-β are present at relatively low levels. These receptors bind to specific elements of DNA, known as response elements, within the regulatory regions of numerous genes and this interaction may increase or decrease transcription of the gene. There are usually several such response elements involved in regulating the transcription of any single gene. The retinoid receptors are mainly active as heterodimers of RXR and RAR. RXRs can also dimerize with several other similar receptors such as the vitamin D receptor, the thyroid receptor and orphan receptors (which have no established endogenous ligand). This range of different receptors and their dimers, the various possible states of binding with different ligands and the wide range of different response elements allows for the highly diverse and complex signalling required to regulate cellular metabolism. The end result of these processes acting on numerous different genes is that retinoids demonstrate a tendency to normalize keratinocyte differentiation in diverse circumstances where this is disturbed.

Metabolism of retinoids takes place within keratinocytes. The initial step is usually 4-hydroxylation by cytochrome P-450 enzyme systems, such as CYP 2S1 and CYP 26, which can be induced by their substrate and may show considerable interindividual variation [4]. This variation may explain some of the variability between individuals in responses to topical retinoids.

Systemic retinoids are known to be highly teratogenic when administered in doses sufficient to induce the mucocutaneous symptoms associated with hypervitaminosis A. This has led to some concern about the potential for the topical application of retinoids to exert teratogenic effects. Fortunately, this risk is entirely hypothetical. Systemic exposure to retinoids applied topically seems to be minimal [5,6], but it is generally recommended that even the topical use of retinoids should be avoided during pregnancy.

The naturally occurring 'endogenous' retinoids include retinol, which is metabolized within most cells, including keratinocytes, to retinoic acid. This process seems to be regulated by a variety of mechanisms so that the level of free retinoic acid is tightly controlled. Retinoic acid can isomerize to 13-*cis* and 9-*cis* retinoic acid, a process that occurs readily in the presence of visible light.

The synthetic retinoids currently used in the topical treatment of skin disease are adapalene, bexarotene and tazarotene. All these compounds are effectively absorbed into the epidermis when applied topically.

Retinol

SYN. VITAMIN A

Retinol is used widely in cosmetic products and tends to be regarded as a vitamin supplement rather than a medicament in this context. However, it is clear that retinol applied topically to the skin is absorbed into the epidermis and exhibits many of the pharmacological properties of retinoic acid. Topical application of retinol increases levels of retinyl esters within the epidermis [7]. These are esters of retinol with long-chain fatty acids which constitute an intracellular reservoir of inactive retinol. Esterification of retinol is induced by retinoic acid and this probably represents an autoregulatory mechanism that inhibits excess synthesis of retinoic acid [8]. In addition, topically applied retinol induces 4-hydroxylase activity, and thus increases metabolism and inactivation of retinoic acid [9]. Levels of CRABP II and CRBP are also induced by topical application of retinol [7].

Retinol increases epidermal thickness in a manner similar to retinoic acid but causes much less irritation [7,10]. Retinol 10% gel has been used as a component of a depigmenting regimen with results considered comparable to those obtained from retinoic acid. However, this high concentration was irritant [11].

Retinoic acid

SYN. TRETINOIN; ALL-*TRANS*-RETINOIC ACID; VITAMIN A ACID

Retinoic acid is well absorbed into the skin when applied topically and exerts potent local effects on cellular metabolism. This is the endogenous ligand for the RARs. Isomerization of retinoic acid results in formation of 13-*cis* and 9-*cis* retinoic acid [12], the latter being the naturally occurring ligand for the RXRs. These isomerizations are accelerated in visible light.

Retinoic acid is most frequently used in treatment of acne vulgaris. It is normally applied once or twice daily at a concentration of 0.01–0.025% in a lotion, cream or gel. Higher concentrations (e.g. 0.1%) have often been used in the past. It is particularly effective in reducing comedones [13,14] and is therefore often used in cases where these non-inflammatory lesions are prominent. It may cause some initial exacerbation of the symptoms for the first 6 weeks of treatment. During this period comedones are expelled and then prevented from reforming if its use is continued. Inflammatory lesions of acne are also reduced, possibly as a secondary event following the reduction in comedones. Irritant reactions are common and may even accelerate the response. However, neither erythema nor peeling is essential for response to be achieved [15]. The irritation can be managed by reducing the concentration or frequency of application. Topical retinoic acid is also effective for treatment of comedonal acne induced by systemic corticosteroids [16].

Topical retinoic acid improves several features of photo-ageing including fine and coarse wrinkling, and dyspigmentation [17]. The clinical improvement is accompanied by reversal of epidermal atrophy and dysplasia, and increasing collagen synthesis in the papillary dermis [18]. Similar effects can also be induced in intrinsically aged skin [19]. Treatment may need to be applied daily for 4 months or more to achieve these effects. A formulation containing 0.05% retinoic acid in an emollient cream base is marketed specifically for treatment of photo-ageing. Lower concentrations can also be effective [20].

Tretinoin has both a therapeutic and prophylactic effect on chemically induced skin tumours, and may be both a promoter and inhibitor of UVB carcinogenesis. Clinically, it exhibits an antineoplastic effect, and may be used to treat small solar keratoses either alone [21] or in combination with 5% 5-FU cream [22]. It also has a 'normalizing' effect on the histological appearance of dysplastic naevi [23].

Despite theoretical mechanisms and early claims that it could be effective, topical application of retinoic acid has not found a role in the treatment of psoriasis.

Retinoic acid can be effective in reducing various forms of hyperpigmentation (see depigmenting agents above).

Another interesting property of tretinoin is its ability to accelerate wound healing [24]. It needs to be applied before wounding, preferably for several weeks. Results of application after wounding have not been consistent, probably because of the irritant effect. The ability of retinoic acid to promote healing has been used to improve results from procedures such as chemical peeling [25] and dermabrasion [26].

A number of other conditions have been treated with topical retinoic acid with varying success. It is of value in the treatment of senile comedones [27]. Comedo and warty naevi may show some response, as may plane warts and reactive perforating collagenosis. Some cases of Darier's disease respond, especially if mild or localized [28]. Keratosis pilaris was reported to respond by eight of 49 respondents in a patient survey [29]. Of the ichthyoses, the lamellar variety appears to be helped most, although ichthyosis vulgaris was also responsive in a four-centre trial [30], as was erythrokeratoderma variabilis [31]. It can be useful in oral lichen planus [32], and in geographic tongue [33]. Fox–Fordyce disease (apocrine miliaria) has been effectively treated with a 0.1% solution [34]. Hydrocortisone cream (1%) has been recommended to control the associated axillary discomfort [35]. Hypertrophic scars and keloids have been reported to respond to a daily application of a 0.05% solution [36,37].

Although sensitization to retinoic acid has been reported this seems to be a rare event [38].

Isotretinoin

SYN. 13-*CIS* RETINOIC ACID

Isotretinoin is readily isomerized to tretinoin and vice versa. It therefore exhibits a similar receptor specificity to tretinoin, interacting with RARs. Isotretinoin is used both topically and systemically for treatment of acne vulgaris. When used topically it is considered somewhat less irritant than tretinoin but may be more so than adapalene [39]. The efficacy of isotretinoin 0.05% gel in acne vulgaris has been confirmed in comparison with placebo [40], and seems similar to that of retinoic acid [41]. In a trial comparing topical isotretinoin with benzoyl peroxide, the latter treatment improved inflammatory lesions more rapidly, although both comedones and inflammatory lesions eventually responded to a similar degree [42]. Topical isotretinoin is believed to work mainly by inhibiting comedogenesis, although it is also known to penetrate into sebaceous glands [43] and may reduce sebum secretion [44].

Isotretinoin cream does not appear effective in treatment of chronic plaque psoriasis [45]. However, it shares with tretinoin the ability to reduce features of photo-ageing [46,47]. It also demonstrates antineoplastic properties. A limited degree of response is seen in treatment of

actinic keratoses when applied twice at a concentration of 0.1% for up to 24 weeks [48], and a degree of efficacy was shown in a trial on topical treatment of BCC although complete regression was only observed in four out of 50 cases treated [49].

In isolated reports, topical isotretinoin has proved helpful in treatment of perifolliculitis capitis abscedens et suffodiens [50], oral [51] and vulval [52] leukoplakia, oral lichen planus [53], hyperkeratosis of the nipple [54] and actinic granuloma [55]. It has not proved effective in melasma [56]. In treatment of Darier's disease, isotretinoin can prove helpful in treatment of small areas of hyperkeratosis but is also irritant [57,58].

Adapalene

Adapalene is a synthetic retinoid that has been developed for treatment of acne vulgaris. In randomized comparative trials, adapalene gel 0.1% has proved equally effective and better tolerated than retinoic acid gel 0.025% [39]. In comparison with topical isotretinoin, adapalene was slightly more effective and less irritant [59,60]. Adapalene appears to retain comedolytic activity while showing less potential for irritancy than retinoic acid. It exhibits specificity for RAR-β and -γ receptors with low affinity for RAR-α relative to retinoic acid [61]. It is highly lipophilic, a property likely to enhance efficacy by increasing penetration of the hair follicle. In addition, adapalene has anti-inflammatory properties that may improve both efficacy and tolerability [61]. Formulations available are cream, aqueous gel, lotion and single use pledgets, all containing 0.1% adapalene.

Bexarotene

Bexarotene is a novel synthetic retinoid with specificity for RXRs. Compounds with this pattern of receptor specificity are sometimes called rexinoids. It has proved helpful in the treatment of cutaneous T-cell lymphoma and can be used orally as well as topically in this indication. In a study on early (plaque stage) cutaneous T-cell lymphoma, topical treatment with bexarotene gel in concentrations ranging up to 1% applied up to four times daily achieved complete clinical clearance in 21% of cases and partial response in a further 42% [62]. The median time to response was 20 weeks. Topical bexarotene is produced as a 1% gel formulation. Treatment is usually commenced cautiously with applications on alternate days and gradually stepped up to four times daily [63].

Tazarotene

Tazarotene is a synthetic retinoid. It is a pro-drug that is rapidly hydrolysed to its active form, tazarotenic acid. The molecule has a rigid structure, in contrast to that of retinoic acid which can undergo conformational changes. Tazarotene exhibits a degree of receptor specificity, interacting with RAR-α, -β and -γ. The latter receptor is likely to be most important in the epidermis. Tazarotene does not bind to RXRs and, unlike retinoic acid, it is not susceptible to isomerization into a conformation that might do so [64].

It has been developed mainly for treatment of psoriasis and acne vulgaris. It is also known to be effective in treatment of psoriasis when administered orally.

The efficacy of topical tazarotene in psoriasis has been established in placebo-controlled trials, around 65% of patients showing 50% or greater improvement after 12 weeks of treatment with 0.1% tazarotene gel once daily [65]. In more recent studies investigating a cream formulation, 39–51% of patients were reported to experience clinical success after application of 0.1% tazarotene cream once daily for 12 weeks [66]. In a comparative study, the global improvement on 0.1% tazarotene gel applied once daily was slightly less than that obtained from 0.05% fluocinonide cream applied twice daily. In all these trials, and in contrast to fluocinonide, the response to tazarotene was notably well maintained during the 12 weeks after treatment was stopped [67]. Psoriatic onycholysis and nail pitting were improved by tazarotene in a small controlled trial [68]. Irritant reactions at the application site are common so tazarotene is sometimes used in conjunction with a topical corticosteroid. It has also been used with phototherapy. There are isolated reports of severe genital ulceration [69] and of pyogenic granuloma developing during topical treatment of psoriasis with tazarotene. The latter is a well-recognized side effect associated with systemic retinoids [70].

Tazarotene 0.1% gel has been shown to be effective in acne vulgaris in a placebo-controlled trial even when applied once daily for short contact periods of 30 s to 5 min [71]. In comparison with tretinoin in a 0.1% microsponge gel, tazarotene 0.1% gel proved more effective. The tolerability of the two treatments was considered comparable [72]. In a comparative study using once daily applications, tazarotene 0.1% gel proved more effective than adapalene 0.1% gel although it was also slightly more irritant [73].

Tazarotene seems to share with retinoic acid the ability to improve photo-ageing. In a trial of 1 year treatment duration, 0.1% tazarotene cream applied once daily significantly improved several features of photo-aged skin [74].

In small trials, tazarotene 0.1% gel was effective in management of oral lichen planus [75], and an O/W emulsion containing 0.01% tazarotene applied each night for up to 8 weeks proved helpful in keratosis pilaris [76]. In single cases or small series, useful responses to topical application of tazarotene have been reported in lamellar ichthyosis [77–79], X-linked ichthyosis and ichthyosis vulgaris [78], confluent and reticulate papillomatosis [80],

elastosis perforans serpiginosa [81], Darier's disease [82,83] and warty dyskeratoma [84], pseudoacanthosis nigricans [85], spiny keratoderma [86], keratoderma blenorrhagica [87] and discoid lupus erythematosus [88].

Tazarotene is produced in gel and cream formulations at concentrations of 0.1 and 0.05%. The higher concentration appears more effective in psoriasis but also more irritant. In treatment of acne, the higher concentration is used most frequently.

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Sensitizing agents

These chemicals (dinitrochlorobenzene, squaric acid, diphencyprone, etc.) are known as universal sensitizers. Almost every individual will develop allergic dermatitis after repeated contact with these substances on the skin. Animals are also readily sensitized. For many years dermatologists have tried to use the induction of contact sensitization, using these and other allergens, to manipulate immune responses to advantage in a wide variety of benign and malignant skin diseases [1]. Numerous attempts have been made, with some reported success, to use sensitizers to stimulate an immune response to malignancies including melanoma [1,2]. Currently, topical sensitizers have found two main roles in dermatology: for the treatment of alopecia areata and viral warts [1]. The sensitizers that have been most intensively investigated are dinitrochlorobenzene (DNCB), squaric acid dibutylester and diphencyprone. The earliest of these to be used was dinitrochlorobenzene, which was found to be mutagenic. The use of squaric acid dibutylester or diphencyprone avoids this hazard and diphencyprone has the advantage of a practical shelf life. The latter has therefore become the most widely used sensitizer for treatment of alopecia areata and warts. Diphencyprone does not cross-sensitize patients to any other household or medicinal substances. An additional advantage of this compound is that it is photochemically unstable and degrades in the presence of visible light, so accidental spills will not indefinitely contaminate the environment; however, it also follows that diphencyprone must be stored in the dark.

The precise mechanisms by which induction of contact allergy can induce hair regrowth in alopecia areata have not been established. It seems likely that regulatory mechanisms activated to modulate the contact allergic reaction also down-regulate the autoimmune reaction responsible for the alopecia. Increased production of IL-10 may explain this effect [3]. There is no doubt that these agents can stimulate regrowth of hair. DNCB [4], squaric acid

dibutyl ester [5] and diphenylcyclopropenone [6] have all been shown to stimulate hair regrowth on treated areas of the scalp in studies using untreated areas as a control. The same effect has been achieved, in sensitized individuals, by use of *Primula* leaves [7] or by nickel patch-test reagent [8]. The demonstration of hair regrowth on one side of the scalp that has been treated with allergen, while there is none on the other side, constitutes a well-controlled experiment which has been repeated regularly by the author. Sensitization can usually be achieved by application of 2% or higher concentration of diphencyprone to a small area of the scalp once weekly until a reaction is seen. Subsequent treatment can begin with a 0.01% solution and usually continues on a weekly basis, adjusting the concentration as required to maintain mild dermatitis. Attempts have been made to achieve the same effect by use of a simple inflammatory response induced by contact irritants. Phenolics, cantharides, camphor and other irritants have been used for many years, mostly without controlled trials [9]. Trials using croton oil and retinoic acid have not confirmed a response to these irritants [8,10]. With the possible exception of dithranol [11], it has proved difficult to establish the efficacy of irritants.

The efficacy of topical sensitizers in treatment of warts is still not so clearly established. Published controlled trials have been small and inconclusive [1,12]. Uncontrolled data are fairly convincing but inconsistent, perhaps because treatment regimens have also been variable [1]. The best results with diphencyprone have been obtained by first sensitizing patients at a site remote from the warts and then applying diphencyprone 0.01–6% to the lesions at intervals of 1–4 weeks. Complete clearance was reported in 70% of patients with this method [13]. Again, the mechanism of action has not been fully clarified but it is likely that the induction of an inflammatory reaction within the wart induces an influx of immunocompetent cells which can then promote an appropriate immune response to the infecting human papillomavirus.

The induction of contact allergic dermatitis is occasionally complicated by the development of pigmentary disturbances including vitiligo. This treatment modality is therefore probably best reserved for patients with white skin.

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Sunscreens

It is likely that in the early evolution of *Homo sapiens*, pigmentation of the skin developed primarily as protection from the risk of sunburn. Subsequent migration away from our equatorial origins reduced the risk of sunburn and skin pigmentation was lost in order to facilitate adequate penetration of UVB into the skin for photochemical synthesis of vitamin D. The adverse consequences of this loss of endogenous sunscreen may not have impaired reproductive potential of the species because the deleterious effects of sunlight tend to occur mainly in later life. However, individuals with white skin are clearly at greater risk from malignant melanoma, non-melanoma skin cancer, preneoplastic disorders and the premature ageing effects of UV irradiation. The sadly fashionable trend over recent decades to purposely expose the skin to solar irradiation in order to obtain a suntan has undoubtedly increased the frequency of these diseases.

It seems a logical approach to attempt to replace the pigment with an exogenous sunscreen applied to the skin surface and a large number of formulations are marketed for this purpose. Used properly, these compounds can reduce UV exposure and probably also the risks associated with photodamage, notably neoplasia. Regrettably, sunscreens are often used in such a way as to make it possible for individuals with pale skin, who could not normally withstand any significant sun exposure without burning, to lie in the sun for hours on end. Such 'abuse' of sunscreens seems likely to be harmful because it can result in significantly greater cumulative UV irradiation than would otherwise be possible. This is especially likely to happen if sunscreens with low sun protection factor ratings (see below) are used.

The ideal sunscreen should completely block the transmission of both UVB (280–315 nm) and UVA (315–400 nm) while at the same time being cosmetically acceptable and pleasant to use. Additional important properties are durability on the surface of the skin and water resistance. The latter is especially important if the sunscreen is

Table 75.9 Compounds used as active constituents of sunscreens.

Physical agents	Chemical agents
Zinc oxide	*Para*-aminobenzoic acid (PABA) and derivatives UVB
Titanium dioxide	Anthranilates UVA
Ferrous oxide	Cinnamates UVB
	Salicylates UVB
	Octocrylene UVB
	Benzotriazoles (Tinosorb) UVB, UVA
	Dibenzoylmethanes (Parsol 1789) UVA
	Benzophenones UVA
	Camphor derivatives (Mexoryl) UVA

to be used when swimming. Sunscreens are generally more effective in blocking UVB than UVA but effective filtration of UVA is important because these wavelengths contribute to photo-ageing [1], cutaneous immunosuppression [2,3] and carcinogenesis [4], and can have a central role in photodermatoses such as polymorphic light eruption [5]. No single compound can achieve all the desired aims so most commercial formulations contain a mixture of active constituents. These fall into two broad categories: physical sunscreens which act by reflecting and scattering UV light, and chemical agents which absorb UV light [6–8]. Frequently used compounds are listed in Table 75.9.

Physical agents such as titanium dioxide and zinc oxide can block a broad spectrum of UVB, UVA and visible light (ability to block the latter can be useful in some photodermatoses). However, their efficacy against UVA and visible light depends on particle size. Larger particle size results in superior efficacy but reduced cosmetic acceptability because of the increased whitening of the skin (which is, of course, reflection of visible light). There has been some concern over the potential for the interaction of both zinc and titanium oxides with UV light to release free radicals [9] but fortunately the harmful effects of these seem likely to be very limited as the oxide particles do not seem to penetrate below the surface layers of the stratum corneum into viable skin [10].

Chemical agents are each effective against a different range of wavelengths of UV light. Some absorb UVB and others UVA. Relatively few absorb long-wave UVA approaching the visible range, exceptions being butyl methoxydibenzoylmethane which has an absorption spectrum of 320–400 nm, and terephthalylidene dicamphor sulphonic acid, with absorption spectrum 290–400 nm. Chemical sunscreens can occasionally cause dermatitis. Irritant, allergic, phototoxic or photoallergic reactions may occur and may be caused not only by the active constituents but also by the base or by additives such as fragrances and stabilizers. Benzophenones are probably the most common sensitizers, while dibenzoylmethanes, *para*-aminobenzoic acid (PABA) and cinnamates may cause photoallergic dermatitis [11,12].

The concept of sun protection factors (SPF) was introduced to help consumers evaluate the level of protection from UVB and the risk of sunburn. Unfortunately, different systems of assay are used in different countries, making direct comparisons very misleading. However, all depend on deriving a ratio of the time or the amount of energy to reach a given end-point (such as minimal erythema) when using the screen, compared with that required without using the screen. Thus:

$$\text{SPF} = \frac{\text{Dose of UVB radiation producing minimal erythema with sunscreen}}{\text{Dose of UVB radiation producing minimal erythema without sunscreen}}$$

It should be noted that the SPF is based on application of an adequate quantity of the sunscreen, usually 2 mg/cm^2 of skin. This is probably more than is routinely applied by most users. As a guide, SPFs of up to 10 can be regarded as mild, 10–15 as medium and over 15 as strong protectors. International agreement is needed to standardize end-points, light sources and conditions of testing. As a result, the classification of sunscreens into the broad categories listed above is helpful but comparisons between one product and another are not as accurate as they might appear. This is especially true of comparisons between products with high SPF values (above 15). There is currently even less standardization of the assessment of protection against UVA. Measurement of resistance to water has also not been standardized but can be assessed by several methods [13,14].

While it would seem likely that correct use of sunscreens will reduce the risk of malignancy, this has not been easy to confirm, especially in retrospective studies. Part of the difficulty is the likely association between use of a sunblock and sun exposure.

Suncreens have been shown to reduce UV-induced immunosuppression, which is considered to have a role in cutaneous carcinogenesis. Both the sensitization [15] and elicitation [2] phases of immune responses can be preserved by sunscreens.

In a placebo-controlled trial on a high-risk population, appropriate strength sunscreens have been shown to be effective in reducing the incidence of actinic keratoses [16]. In an Australian prospective controlled study, regular use of sunscreen reduced the total number of SCCs but not of BCCs [17]. A study of BCCs indicated that there were fewer p53 mutations in those BCCs that developed in patients who had used sunscreen. This might be indicative of effective protection against UV-induced DNA mutation by the sunscreen [18], while some BCCs develop as a result of other causes.

The prevention of melanoma by the use of sunscreens is a further controversial topic because two case–control studies have linked sunscreen usage to a higher incidence of melanoma [19,20]. This may be related in part to the likelihood that the subjects studied had previously used

sunscreens that provided protection against UVB radiation alone, and exposed themselves to higher doses of solar radiation than those who did not use sunscreen. Other studies have examined the development of naevi as a marker for risk of melanoma. A retrospective epidemiological study from Israel found that use of sunscreen was associated with a higher number of naevi [21]. Conversely, a prospective controlled trial from Vancouver demonstrated a reduced rate of development of naevi over a 3-year period in children provided with sunblock and instructed on its use. The effect was especially evident in those children who were freckled [22].

In addition to the protection of healthy skin, sunscreens have an important role in the management of patients with photodermatoses. The most common of these, polymorphic light eruption, often seems to show rather limited benefit from sunscreens but may be effectively prevented by formulations that block a broad spectrum of UVA including longer wavelengths [5]. Sunscreens effective in blocking the offending wavelengths of UV light can also be helpful in management of less common photodermatoses including actinic prurigo, chronic actinic dermatitis, hydroa vacciniforme, lupus erythematosus, porphyrias and solar urticaria (see Chapter 24).

Whether sunscreens are applied to prevent solar damage to healthy skin or to alleviate a photodermatosis, it is important that these should not be regarded as the only means of limiting sun exposure. Staying indoors during the hours of peak sunlight intensity and, when outdoors, covering the skin with suitable clothing and headwear, constitute more effective strategies than using sunscreens.

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Tars

Tars are distillation products of organic material. There are three main sources of therapeutic tars: wood, shale and coal.

Wood tars

Oils of cade (juniper), beech, birch and pine are widely used, particularly in Scandinavian countries. Wood tars lack certain basic chemical structures characteristic of coal tars, such as pyridine, quinoline and quinaline rings [1]. They may sensitize but do not photosensitize.

Wood tars are used for treating eczema and psoriasis in some countries. Oil of cade is particularly used in scalp preparations or when tar preparations are needed on the face. They are normally applied in 1–10% strength in ointments or pastes, or as a paint in 95% alcohol.

Shale tars

Oils were extracted from shale (sedimentary rock containing fossilized fish) for centuries before crude oil became available. Various extracts and distillates have long been used for medicinal purposes. Ichthammol (ichthyol) is a shale tar (bituminous tar). This contains a very high proportion of sulphur (about 10%), as compounds of thiopen. Shale tars have antiseptic and anti-inflammatory properties but are generally less effective than coal tars and may have a different mode of action. They are not photosensitizers. Ichthammol is often used in paste bandages for treating atopic eczema.

Coal tar

Coal tar [2–4] is a black, viscous fluid with a characteristic smell. Attempts to remove the colour, odour, photosensitizing property and carcinogenicity have not been entirely successful [5], and variations in this natural product have made the assessment of active ingredients particularly difficult [3,4]. Of some 10 000 different constituents believed to make up coal tar, only 400 have been identified. These constitute 55% of the whole.

All coal tars are products of different distillates of heated coal. The content of the tar depends on the type of coal used and the temperature of the distillation. 'Low-temperature' tar was found to contain a greater number of components but to be less effective in producing orthokeratosis in mouse-tail skin than 'high-temperature' tar [3,4]. It was also more irritating. However, a comparison of high- and low-temperature tars showed no eventual difference in effect in the treatment of psoriasis itself, although crude (high-temperature) coal tar gave quicker results [6]. This suggests that the reversal of parakeratosis is only one factor in the control of psoriasis. The authors of this study point out that dithranol was not very effective in the mouse-tail test [7].

The hydrocarbons, which constitute about half the composition of tar, include benzol, naphthalene and anthracene. The high-boiling-point tar acids (phenolics) include isomers of substituted polyhydroxyphenols, and it seems likely that it is such phenols which may be responsible for the therapeutic effect of tar [3,4,8]. However, the exact mechanism by which tar exerts its effect remains unknown. These high-temperature fractions may have a direct effect on the granular layer by release of lysosomes followed by mitotic stimulation. Low-temperature extracts appear to cause epidermal thickening without restitution of the granular layer [3,4], and may be the reason for the indifferent action of some synthetic and proprietary tar preparations [3,4,9]. Until a more suitable preparation is available, many dermatologists will continue to believe that crude tar remains therapeutically superior [9,10].

The combination of tar with UV light (the Goeckerman regimen) has long been known to be helpful in psoriasis. In recent years, attempts have been made to identify the critical wavelengths of radiation involved [11,12]. Generally, UVB radiation has been found to be more effective than UVA [13,14]. Refined tars are less phototoxic than the crude product, but phototoxicity is directly related to therapeutic efficacy. UVA [15] did not appear to be a useful adjunct to tar and UVB in the treatment of psoriasis in one study. Laboratory studies have shown that tar plus UV light reduces epidermal DNA synthesis [12,16]. This may be related to the formation of cross-links between opposite strands on the DNA double helix [17].

A cytostatic effect of crude coal tar has also been postulated [18] following the finding that prolonged application to normal skin produces epidermal thinning associated with retention hyperkeratosis. More studies are still required, particularly to identify the more active fractions of tar distillates.

The well-established carcinogenicity of pitch and heavy tar fractions has aroused renewed interest in the current climate of therapeutic conservatism. Concerns about the oncogenic potential of polycyclic hydrocarbons [19] and consumer protection [20,21] have been fuelled by reports that urine from patients with psoriasis using crude coal tar was mutagenic to certain bacterial strains [5]. Reports of malignant tumours in humans in relation to tar therapy are rare. Rook *et al*. [22] reported five cases and Greither *et al*. [23] reported 13. Most had genital or groin involvement, but these are nowadays unlikely sites for tar application. Reassuringly, several large long-term follow-up studies have shown no increased incidence of skin tumours [14,24–27].

Coal tar is now mainly used in treatment of psoriasis and is the basis of the Goeckerman regimen (see Chapter 35). Prior to the advent of topical corticosteroids, coal tar was widely used in treatment of eczematous dermatoses and it can still prove useful as a steroid-sparing agent and antipruritic. Coal tar can be added to paste bandages although ichthammol is often preferred.

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Vitamin D analogues (deltanoids, secosteroids)

The therapeutic potential of vitamin D in psoriasis has been recognized for many years. Systemic use of these compounds can be highly effective but requires monitoring to avoid causing disturbance of calcium homoeostasis. Used topically, considerable efficacy can be maintained with a wide safety margin. The advent of calcipotriol in the early 1990s has greatly increased the use of this modality. Tacalcitol and calcitriol, which were known to be effective even earlier, have only more recently become widely available for treatment of psoriasis. The novel analogue maxacalcitol is also known to be effective.

Vitamin D is not strictly a vitamin because an exogenous source is not essential. Photochemical cleavage of 7-dehydrocholesterol to form vitamin D (cholecalciferol) takes place in the skin and requires fairly minimal exposure to UVB to generate physiological quantities of the product. It is this break in the steroid nucleus that characterizes vitamin D and its analogues and gives rise to the term secosteroids. Cholecalciferol requires two hydroxylations for activation. The first is 25-hydroxylation, which takes place mainly in the liver and is not a tightly controlled step [1]. 25-Hydroxycholecalciferol is the main storage form of vitamin D within the body. This is finally 'activated', mainly in the kidney, by a very tightly regulated hydroxylation to 1α,25-dihydroxycholecalciferol [2,3]. As the latter has three hydroxyl groups, it is also known as calcitriol (Fig. 75.10). Calcitriol is a potent hormone first characterized by its ability to increase calcium absorption from the gut. It has subsequently become recognized that the receptor for this potent hormone is expressed in virtually all types of cell. Calcitriol is of

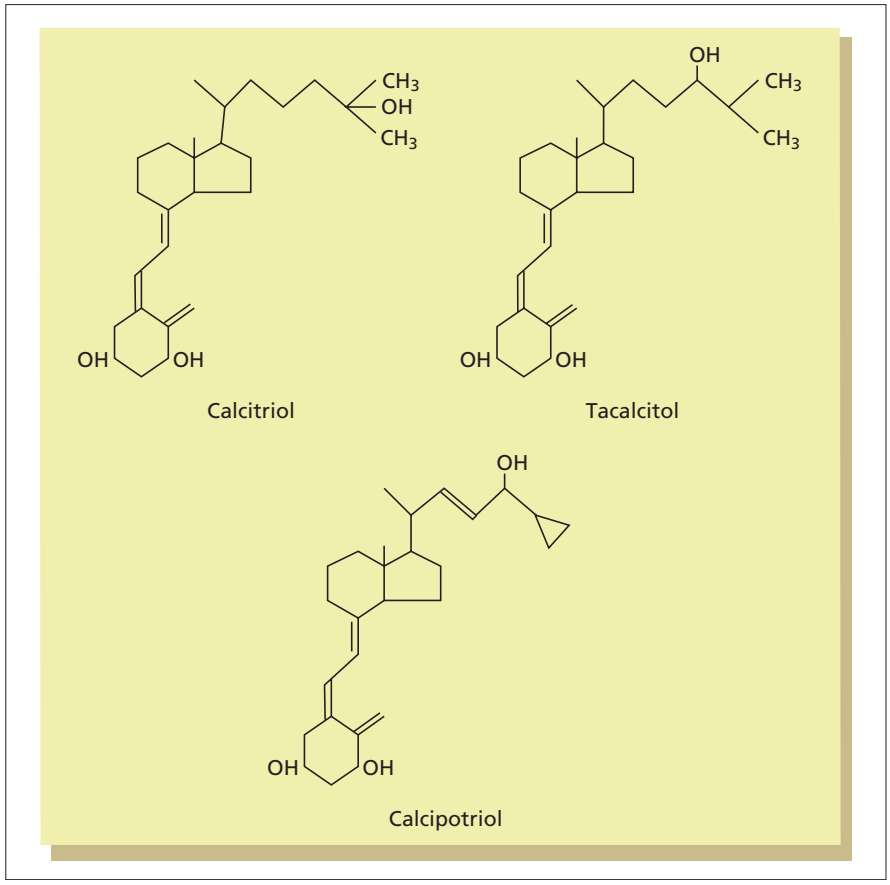

Fig. 75.10 Formulae of calcitriol, tacalcitol and calcipotriol.

fundamental importance in the regulation of differentiation and proliferation.

The vitamin D receptor is a phosphopeptide with molecular weight of approximately 60 kDa, able to move freely between the cytoplasm and the nucleus. It is a member of the steroid receptor superfamily, being similar in structure to the retinoid receptors, the thyroid hormone (T_3) receptor and receptors for other classes of steroid hormone. It is active mainly as a heterodimer in combination with the RXR [4]. The vitamin D receptor complex regulates transcription of numerous genes by binding to regulatory regions of DNA–vitamin D response elements. These are specific but heterogeneous regions of DNA generally situated upstream of regulated genes [4].

The therapeutic actions of vitamin D appear to result from a potent antiproliferative effect [5–8], the ability to promote differentiation [9–12] and perhaps also from immunosuppressive activity. *In vitro* secosteroids inhibit IL-2 release and lymphocyte activation [13,14], and release of IL-8 [15]. They also up-regulate expression of the receptor for the anti-inflammatory cytokine IL-10 [16]. They inhibit monocyte differentiation into dendritic cells, possibly by promoting expression of colony-stimulating factor 1 [17]. They inhibit keratinocyte synthesis of RANTES and IL-8 [18]. *In vivo*, they have been shown to inhibit expression of IL-8 [19], IL-6 [20] and other cytokines. During treatment of psoriasis they have been reported to reduce infiltration with lymphocytes and neutrophils [8,21,22] and to reduce expression of IL-8 and adhesion molecules (ICAM 1, ELAM 1, LFA 1, VLA 3, VLA 6) [23,24].

Vitamin D, especially in activated (1α-hydroxylated) forms, increases calcium absorption from the bowel. At a low level this can be compensated by increased calcium excretion in urine but at higher levels of exposure the serum calcium will rise. All the analogues currently used in treatment of psoriasis are 1α-hydroxylated compounds, which effectively bypass the regulatory step of 1α-hydroxylation. They can potentially cause hypercalcaemia in overdose. This 'calciotropic activity' of vitamin D analogues constitutes the main constraint on the safe use of these compounds. The goal of secosteroid research, to develop an analogue that would normalize proliferation and differentiation without influencing calcium metabolism, has yet to be effectively realized.

In comparison to traditional treatments for psoriasis, vitamin D analogues have the advantage that they are more pleasant to use than tar or dithranol. They also have the advantage over topical corticosteroids that they are not atrophogenic. However, they can all cause irritant reactions that are concentration dependent [25]. Sensitization can also occur but seems to be rare [26]. A characteristic pattern of circumlesional scaling appears around psoriatic lesions treated with vitamin D analogues (Fig. 75.11), which gives a guide to compliance almost as reliable as the staining produced by dithranol [27]. It is not clear whether this is a manifestation of irritancy or a pharmacological effect.

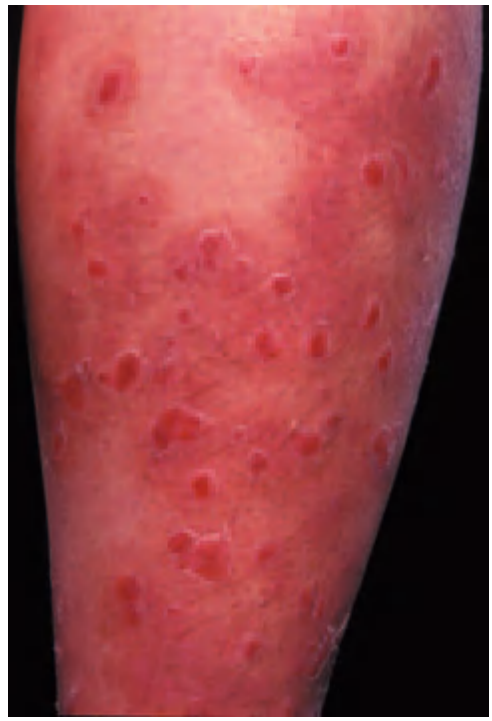

Fig. 75.11 Circumlesional scaling characteristic of psoriasis lesions treated with vitamin D analogues.

Tacalcitol (1,24 dihydroxycholecalciferol)

This analogue has been used for topical treatment of psoriasis for many years in Japan, where the concentrations employed have ranged from 1 to 20 μg/g [28,29]. In Europe, tacalcitol is often used once daily at a concentration of 4 μg/g. Efficacy of this regimen has been demonstrated in placebo-controlled and dose-ranging studies [30,31]. Tacalcitol 4 μg/g applied once daily is less effective than calcipotriol 50 μg/g applied twice daily [32]. However, the lower concentration of tacalcitol results in a low irritant potential and it can therefore be safely used for treating facial or flexural psoriasis [33]. A long-term trial has indicated that, in patients who have responded well, the benefit can be maintained for up to 18 months, although only 64 out of 299 subjects completed the full duration of this trial [34]. Tacalcitol has been used in conjunction with both UVB [35] and PUVA [36] and accelerates the response to these treatments, potentially reducing the UV exposure required.

Currently, the recommended maximum dose of tacalcitol 4 μg/g is 10 g/day. However, no significant increase in serum or urine calcium was observed with daily doses of 15–20 g for up to 26 days [37]. It also appears safe to

use tacalcitol at the higher concentration of 20 μg/g [29]. Hypercalcaemia has not yet been reported in association with topical application of this analogue. Sensitization may rarely occur [38].

Other indications in which topical tacalcitol has been employed with reported success include Nekam's disease [39], confluent and reticulate papillomatosis [40], Grover's disease [41], subcorneal pustular dermatosis [42], Hailey–Hailey disease [43], disseminated superficial actinic porokeratosis [44] and prurigo [45].

Calcitriol (1,25 dihydroxycholecalciferol)

Calcitriol is the naturally occurring form of activated vitamin D. This is known to be active both topically and systemically in treatment of psoriasis [46,47]. Like other analogues, it is rarely used systemically because of the need to monitor calcium homoeostasis although the hazards are probably not out of proportion to the potential benefit.

Calcitriol has been used topically at various concentrations ranging from 0.3 to 15 μg/g [48,49]. At the higher end of this range, changes are seen in urine and/or serum calcium levels, especially when large areas of skin are treated. At the lower end, efficacy is very limited. When applied twice daily at a concentration of 3 μg/g, controlled trials have demonstrated that a degree of efficacy can be maintained with minimal risk of effects on calcium homoeostasis [50]. The efficacy of this regimen was comparable to that of short-contact dithranol therapy in an 8-week trial with 114 subjects, although the overall improvement was not very impressive in either group, suggesting that the dithranol regimen may not have been optimal [50]. Calcitriol 3 μg/g is less effective than calcipotriol 50 μg/g [51]. In a long-term study, it was disappointing that only 75 out of 253 subjects continued to use the treatment for 1 year. Lack of efficacy was given as the main reason for withdrawal by 108 of the subjects. Twice daily treatment with calcitriol has shown a dose-sparing effect on UVB exposure when used in conjunction with broad-band phototherapy [52]. Calcitriol ointment 3 μg/g seems to have very little potential for irritancy or sensitization [53].

Calcipotriol (calcipotriene, MC 903)

Although developed relatively recently, calcipotriol has now been more intensively investigated than any other secosteroid for the treatment of psoriasis. The molecule has a cyclopropane group at the end of the side-chain, which facilitates rapid metabolism (Fig. 75.10). It is therefore ideal for topical administration and can be safely used in higher concentration than calcitriol or tacalcitol [54]. Placebo-controlled and dose-ranging trials demonstrated maximal response at the concentration of 50 μg/g [55,56]. Virtually all subsequent research has investigated the use of calcipotriol at this concentration.

Efficacy and safety of calcipotriol in childhood psoriasis has been confirmed in trials on children from 2 years upwards [57,58]. It has also proved useful in an infant [59].

Reports indicate that topical calcipotriol can be useful in generalized pustular psoriasis [60,61] and in erythrodermic psoriasis [62,63]. However, absorption of the drug can be significantly higher in these circumstances and careful monitoring is required. In one case, generalized pustular psoriasis was thought to have been precipitated by calcipotriol [64]. Acrodermatitis continua [65] and nail psoriasis [66,67] may respond, although results are not consistent.

In comparative studies, calcipotriol 50 μg/g generally compares well to other topical treatments for psoriasis [68]. It has shown efficacy similar to potent topical corticosteroids such as betamethasone-17-valerate [69] and superior to tacalcitol 4 μg/g [31], calcitriol 3 μg/g [50] and to self-treatment with dithranol [70]. The response has been relatively well sustained over time in long-term trials [71,72]. It is notable, however, that only 26% of the patients on this treatment are able to discontinue the vitamin D analogue altogether (the rest requiring continuous treatment).

The use of calcipotriol has also been investigated in a wide range of combinations with other antipsoriatic medication. Combinations with topical corticosteroids can be particularly useful to increase efficacy and reduce irritation. When each medication is applied once daily, the combination with moderately potent or potent steroid reduces irritation and a potent steroid increases efficacy relative to twice daily application of calcipotriol alone [73]. A combined formulation (Dovobet®) containing betamethasone dipropionate 0.05% and calcipotriol 50 μg/g has proved more effective applied once daily than twice daily application of calcipotriol alone. The combined formulation was also less irritant [74]. A regimen combining short contact dithranol with twice daily application of calcipotriol proved more effective than dithranol alone [75].

Topical calcipotriol can also be used concomitantly with second-line therapies and exerts a useful dose-sparing effect when combined with UVB [76,77], PUVA [78–80], ciclosporin [81], retinoids [82] and fumaric acid esters [83].

Occlusion with polythene or hydrocolloid dressings can be used to augment the efficacy of calcipotriol [84]. This technique can be particularly useful for refractory plaques of psoriasis on the shins. Systemic absorption is also likely to be increased.

Calcipotriol not uncommonly induces irritant reactions, especially when applied to the face. Sensitization can also occur to calcipotriol although this seems to be rare [85–87]. In one case, propylene glycol in the base was responsible for the reaction [88].

The maximum recommended rate of usage is 100 g/week of ointment. Exceeding this dose can induce hypercalcaemia although the safety margin seems reasonable and the use of higher doses can improve efficacy [89]. It is advisable to monitor urine and serum calcium in situations where there is a risk of inducing hypervitaminosis D (e.g. when the recommended dose is exceeded or when calcipotriol is used for indications other than psoriasis vulgaris, especially if large areas of skin are treated). Monitoring of serum calcium presents little difficulty but measurement of urine calcium excretion depends on obtaining accurate 24-h urine collections.

There are now a wide range of dermatoses in addition to psoriasis that have been reported to respond to calcipotriol, although the evidence is largely anecdotal in nature. These include confluent and reticulate papillomatosis [90], disseminated superficial actinic porokeratosis [91], erythema annulare centrifugum [92], extragenital lichen sclerosus [93], Flegel's disease [94], Grover's disease [95,96], inflammatory linear verrucous epidermal naevus [97], keratosis lichenoides chronica [98], lichen amyloidosus [99], lichen planus [100], nodular prurigo [101], naevoid hyperkeratosis of the nipple [102], morphoea [91], pityriasis rubra pilaris [91], Reiter's syndrome [91], ichthyoses [103,104], vitiligo [105] and Vorner's syndrome (epidermolytic palmoplantar keratoderma) [106].

Calcipotriol has not proved beneficial in trials on actinic keratosis [107], alopecia totalis [108], Darier's disease [103], hereditary palmoplantar keratoderma [103], keratosis pilaris [103] or seborrhoeic dermatitis [109].

Maxacalcitol (22-oxa-calcitriol)

This is an effective but currently unmarketed analogue with efficacy similar to calcipotriol [110].

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Traditional remedies

Camphor

Camphor is an extract from the camphor laurel *Cinnamonum camphora*, best known as a moth repellant. It is sometimes added to lotions for its antipruritic and cooling effects. It is widely used in proprietary chilblain preparations.

Dyes

Gentian (crystal) violet. This is a triphenylmethane dye, which has antiseptic properties against bacteria and yeasts. Employed for many years as a topical treatment for bacterial and fungal skin infections, its use was drastically curtailed after experimental studies demonstrated that it interacted with DNA of living cells [1] and was linked to malignancies in mice [2]. No reports of human malignancy attributed to the use of gentian violet on the skin have been found in the recent literature. It is now licensed for topical application, as a 0.5% aqueous solution, to unbroken skin, and is not recommended for application to mucous membranes or open wounds. It has the advantages of being cheap, chemically stable and easy to prepare.

Brilliant green. This is also a triphenylmethane dye and has properties similar to gentian violet. It was often used in combination with the latter but does not seem to increase the spectrum of activity [3]. It has suffered similar restrictions in usage, as have other members of the group, such as malachite green.

Magenta. Magenta, or basic fuchsin, is a major component of Castellani's paint. It is known to have activity against Gram-positive bacteria and fungi, but is no longer used because of potential carcinogenicity. Colourless Castellani's paint, the same formula without the magenta (boric acid, resorcinol, phenol), has been used to reduce secondary bacterial contamination in onycholysis and in chronic paronychia.

Eosin. This is the disodium salt of tetrabromofluorescein. It is used as an astringent for areas of weeping eczema or superficial ulcers, and in dermatoses such as seborrhoeic dermatitis. Efficacy equivalent to flumethasone pivalate 0.02% has been demonstrated in infantile seborrhoeic dermatitis [4], and greater than clobetasone butyrate 0.05% in napkin dermatitis [5]. It has the advantage of being used in aqueous solution (usually 2%), which avoids problems with stinging, but allergy can occur, especially in patients with leg ulceration [6].

Menthol

Menthol is still mainly extracted from the Japanese mint (*Mentha arvensis*) although synthetic sources are now available. It is added to calamine and other lotions and creams to induce a cooling sensation and relieve pruritus.

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Miscellaneous agents

Capsaicin

Capsaicin is a remarkably potent compound extracted from hot peppers and responsible for the gustatory discomfort they induce. It is a very stable alkaloid probably produced by these plants to prevent the seeds being eaten by animals. Capsaicin stimulates release of substance P, which is subsequently depleted in sensory neurones [1]. It is also a potent ligand of the vanilloid receptor (VR1), which is expressed on sensory neurones [2]. Stimulation of this receptor by capsaicin can result in a refractory state in the neurone, probably explaining the hypoalgesia that can be induced by capsaicin.

The first application to be established for this drug was in treatment of post-herpetic neuralgia [3]. However, an increasing range of conditions are being reported to benefit including diabetic neuropathy [4], glossodynia [5], nodular prurigo [6], notalgia paraesthetica [7], pruritus ani [8], and pruritus caused by pityriasis rubra pilaris [9], psoriasis [10,11], PUVA [12] or uraemia [13].

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Minoxidil

This vasodilating agent was initially introduced as a systemic treatment for hypertension and was found to cause hypertrichosis. Subsequently, lotions containing minoxidil have been employed in various situations where hair is wanting. Formulations containing 2% and 5% solutions of minoxidil are currently available commercially. The most established indication is androgenetic alopecia although results are usually modest. Minoxidil can also accelerate hair regrowth after chemotherapy and there is possibly some modest benefit in patients with alopecia areata.

Topical application of minoxidil has proved remarkably safe. One potential hazard arising from long-term use is sensitization to the minoxidil or to components of the vehicle. A more common problem is hypertrichosis, usually on the face but sometimes more generalized [1]. This seems most likely to result from contamination of facial skin with minoxidil but systemic absorption has also been proposed to explain the most generalized cases. It is more problematic in female patients and is more likely to occur when the higher concentration is used.

The mechanism by which minoxidil stimulates hair growth remains to be established. It may exert direct effects on keratinocyte differentiation and proliferation within the hair follicle [2], it may alter the pattern of androgen metabolism in the dermal papilla [3] and it may improve vascularization of the papilla [4].

Androgenetic alopecia shows a positive although modest response to topical minoxidil in males and females. In a double-blind multicentre trial of 2% minoxidil in the USA, 256 females with androgenetic alopecia were treated for 32 weeks. Terminal (non-vellus) hairs increased from 140 to 163/cm^2 compared with a rise from 139 to 149/cm^2 in the placebo group. At the end of the study no dense regrowth was observed. Investigators reported moderate regrowth in 13% of the patients on active treatment and minimal regrowth in 50%, whereas the patients' assessments were more optimistic at 20% and 40%, respectively. The patients receiving placebo reported moderate and minimal regrowth in 7% and 33%, respectively [5]. In a similar European trial involving 294 female subjects, there was an increase in non-vellus hair of 33/cm^2 in

the active group and 19/cm^2 in the placebo group [6]. In an Australian trial on males with early pattern alopecia, only 12% had moderate regrowth after 48 weeks [7]. Response to the 5% lotion is somewhat better. In a recent study of 48 weeks' treatment duration completed by 351 male subjects, 5% solution was superior to 2% lotion and placebo from 8 weeks onward. At 48 weeks the mean terminal hair count had risen from 151 to 170/cm^2 in the 5% group, from 144 to 156 in the 2% group and from 152 to 156 in the placebo group [8]. In male patients topical minoxidil is sometimes combined with oral finasteride [9].

Alopecia areata is sometimes treated with topical minoxidil, although cosmetically useful responses have not been frequent in most studies. The best results were reported by Fenton *et al*. [10] who conducted a double-blind crossover trial in which 30 subjects applied 1% minoxidil (lotion or ointment) or placebo twice daily, each for 3 months. By the end of the study 16 patients had grown cosmetically acceptable terminal hair, only one of them while on placebo. In a subsequent trial of very similar design on 23 patients, 13 demonstrated some degree of regrowth on the active medication while none did so on placebo—however, the result was cosmetically satisfactory in only one case [11]. In another study using 1% lotion on 48 subjects with severe disease, no difference was detected from placebo [12]. Similarly, no difference was observed between placebo and 3% minoxidil lotion after 3 months in a trial on 30 subjects with extensive disease [13]. In a study comparing 1% and 5% solutions, a total of 66 patients applied treatments twice daily [14]; patients with extensive (75% or greater) scalp hair loss showed a response, defined as terminal hair growth, in 38% of cases with 1% minoxidil versus 81% with 5% minoxidil. However, even in this high-dose group, only 6% showed a cosmetically acceptable response. A slightly higher rate of cosmetic response, 11%, was observed in an uncontrolled study in which 45 patients with severe disease applied 5% minoxidil twice daily and 0.5% dithranol (anthralin) cream once daily for 6 months [15]. Application of 2% minoxidil three times daily appeared to prolong the response to a 6-week tapering course of prednisolone in a double-blind study, although the numbers were too small to achieve statistical significance relative to placebo [16].

Other applications for topical minoxidil have included reduction in the duration of alopecia caused by chemotherapy. In a controlled trial on patients undergoing chemotherapy for breast carcinoma, the duration of baldness was 87 days in patients applying 2% minoxidil solution twice daily, versus 137 days in those applying placebo [17]. Additional applications have included stimulation of growth in hair transplants [18] and prevention of hair loss that may occur as a complication of cosmetic surgery [19].

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Nicotinamide [1]

The marked anti-inflammatory properties of topical nicotinamide, the amide derivative of vitamin B_3 (niacin), have been used to treat acne vulgaris. A 4% alcoholic gel is available. It is not yet certain by what mechanism the preparation exerts its anti-inflammatory effect. In a multicentre trial, it gave a global reduction in acne of 82% compared with 68% for 1% clindamycin gel over an 8-week period. An advantage of nicotinamide is that it avoids the problem of antibiotic resistance.

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Chapter 76

Radiotherapy and Reactions to Ionizing Radiation

M.F. Spittle & C.G. Kelly

Introduction

The clinical effects of ionizing radiation on the skin have been known since the discovery of X-rays in 1895 [1]. At first, the physical aspects of dosimetry were little understood—a fact that did not hamper the enthusiasm with which both benign and malignant diseases were irradiated. Both the dosage and indications for irradiation were initially empirical, and the dermatologist may still see the late effects on the skin and subcutaneous tissues of overdosage due to inexperience. Indications for treating benign disease by irradiation have declined since the advent of topical steroids. If the effect of irradiation is understood, this treatment still has a specific place in the dermatologist's armamentarium for patients in whom disease is otherwise refractory to treatment [2,3].

Since the introduction of supervoltage irradiation, which gives a maximum dose below the surface of the skin, the acute skin reaction is rarely seen in the treatment of deep-seated malignant disease. However, if the skin is particularly at risk from recurrence as, for example, in the primary treatment of breast cancer, it can be fully treated.

It is in the best interest of patients suffering from skin tumours to be seen in a clinic where the expertise of specialists in radiotherapy and oncology, plastic surgery and micrographic surgery, as well as dermatology, are present.

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Types of ionizing radiation

X-rays are part of the electromagnetic spectrum. They have a shorter wavelength and are more energetic and penetrating than ultraviolet (UV) radiation.

Orthovoltage radiation includes beams softer than 1 million electron volts (MeV).

Grenz (German for border) rays are the most poorly penetrating ionizing rays. At 6–15 kV, these are at the borderline with non-ionizing radiation. As 90% of this radiation is absorbed in the upper 1 mm of the skin, it is important to treat only diseases of very superficial pathology with this beam. Dose-dependent pigmentation of the skin may occur, but alopecia will not, as the energy of the beam does not reach the depth of the hair follicle. Doses of 100–300 Gy have rarely been associated with malignancy [1], but there is a wide margin of safety with Grenz rays. However, the minimum voltage consistent with the depth of pathology should be chosen.

The most commonly used forms of radiotherapy in dermatological practice are superficial X-rays and electron beams.

Superficial X-rays, up to 100 kV, are used in the management of benign skin disease. The higher voltages are used for hypertrophic disease needing treatment to a greater depth, for example keloids. Fall-off of energy below the surface of the skin occurs in an exponential manner (Fig. 76.1) and there can still be substantial dose delivered at several centimetres depth.

Beta rays are electrons and can be derived from radioactive isotopes, such as ^{90}strontium or be produced by a linear accelerator. The energy of electrons is almost totally absorbed at a depth proportional to the given voltage. A useful treatment depth in centimetres is approximately one-third of the MeV energy, so a 4.5-MeV electron beam will be useful for treating to 1.5 cm and a 9-MeV beam to 3 cm (Fig. 76.2).

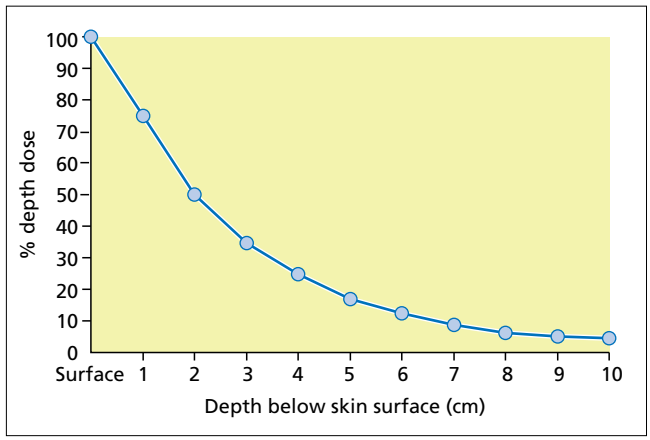

Fig. 76.1 Approximate per cent depth dose values for 90 kV superficial X-ray beam.

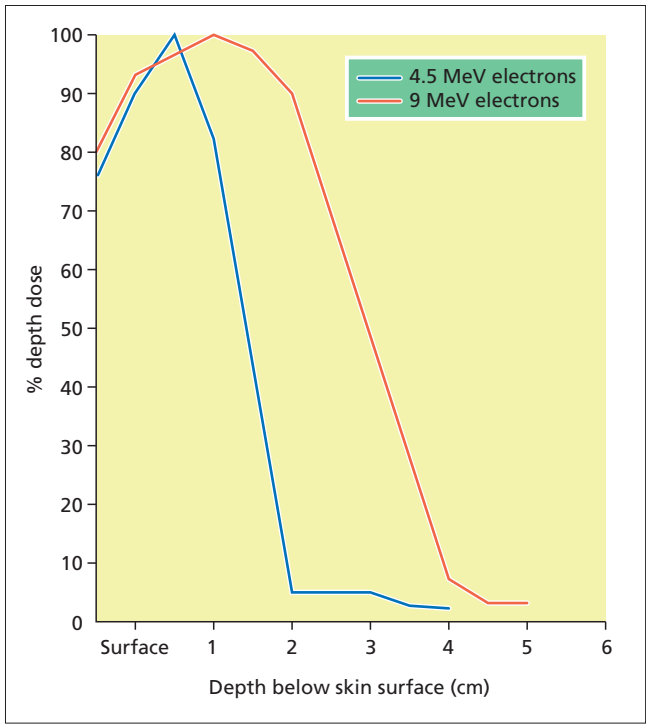

Fig. 76.2 Approximate per cent depth dose curves for 4.5 and 9 MeV electron beams.

As can also be seen in Fig. 76.2, the width of the peak of the beam also increases with electron energy. The peak can also be shifted to the left by the use of tissue equivalent material placed on the skin surface and acting as a degrader.

It is possible to irradiate the whole skin area with an electron beam. The minimal depth dose characteristics that may be achieved avoid the irradiation of subcutaneous structures which would occur if X-ray therapy that is absorbed exponentially was used. This technique is used in the treatment of mycosis fungoides [2]. Multiple radiation fields are combined to give a homogeneous dose to the whole skin down to a depth of approximately 1 cm.

Electron-beam therapy is used to irradiate skin cancers in sites where the malignant lesion to be treated is large or overlying cartilage or bone. The mode of absorption of high-energy X-rays produced from a linear accelerator or of gamma rays is relatively independent of the atomic number of the tissue irradiated. Low-voltage X-rays are absorbed disproportionately in high-atomic-number materials. If this fact is not understood, necrosis may occur in cartilage or bone underlying large superficial lesions. Therefore, superficial X-ray therapy should be avoided when treating lesions overlying the nose, ear, hand and tibia to a radical dose. Modern high-voltage electron therapy is indicated in these sites [3].

Conventional photon beams or other less commonly used forms of radiotherapy such as fast neutron beams are rarely indicated in dermatological radiotherapy.

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Dose

The SI unit of absorbed dose is 1 J/kg and is called the gray. Note that 100 rad = 1 J/kg = 1 Gy; 1 rad = 1 cGy (centigray). The dose prescription is defined by the total dose given, the energy of the beam, the number of fractions given, the total number of days over which treatment is given and the volume or area treated. For example, a typical prescription for the treatment of a small basal cell carcinoma (BCC) might be '35 Gy using 90 kV SXT beam given in five fractions over 5 days to a 3-cm area'. This time–dose relationship is crucial to understanding the biological effect.

Radiosensitivity

All radiation is destructive. Abnormal cells repair radiation damage less well than normal cells. This inability to repair is reflected in death at mitosis. Anaplastic cells and those with a high mitotic index are more radioresponsive than differentiated cells. Radioresponsiveness and radiocurability are dissimilar and are functions of differences in cell population kinetics. Radiotherapy is usually given as a fractionated course, as the intervals between doses allow for the recovery of normal cells. The effect of a dose of radiation is reduced by increasing the number of fractions in which it is given or by lengthening the total overall treatment time. The effect of irradiation can be modified by anoxia, infection, oedema, trauma and any inborn

genetic susceptibility. The face tolerates irradiation well, and radical dosages may be accompanied by good cosmetic results [1].

When benign conditions are being irradiated, the minimum dose and the lowest voltage appropriate to achieve the desired effect should be chosen. The threat of radiation carcinogenesis must clearly be seen in the context of the clinical indication for treatment. There is a threshold for somatic radiation changes which need not be breached in the treatment of benign conditions. The late radiation sequelae of treatment given many years ago are inexcusable with modern standards of dosimetry and equipment, and should not be seen in the treatment of benign diseases [2].

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Indications for radiotherapy

Benign disease

Radiotherapy is used much less now in the management of benign skin conditions than formerly and then usually only after other treatment modalities have failed or are contraindicated. In some conditions such as psoriasis and eczema there is a response to radiotherapy but this is often only temporary [1]. Coupled with the risk of late radiation-induced malignancy, this has led to a decline in its use in all but the most refractory of cases. It is also still used occasionally in the management of keratoacanthoma where the differentiation from squamous cell carcinoma cannot be made with complete confidence [2–4]. Other rare uses are in Darier's disease [5], familial benign chronic pemphigus [5] and acrodermatitis continua of Hallopeau. Radiotherapy was used in the management of acne and rosacea in the past, and there may be patients still presenting with radiation sequelae or late radiation-induced tumours resulting from treatments given years ago for these benign conditions, and others such as ringworm [6].

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Keloids

This is probably the most common benign condition now treated with radiotherapy. Keloids resistant to intralesional steroids or other conventional treatment may respond well to radiation. Excision of the keloid with early irradiation of the scar and stitch marks is more successful, but in some sites—for example, the tip of the shoulder and the upper middle chest, where surgery is inadvisable—good response of pain, itch and redness can be achieved, with some regression of the keloid itself. Relatively high doses are necessary; these will cause temporary hyperpigmentation, which will remain for many months in pigmented skin. Doornbos *et al*. [1] noted that 17 of 18 unexcised keloids that were less than a year old regressed with 1500 cGy given in three treatments over 6 days at 120 kV. Older keloids respond less well to irradiation. The most satisfactory management of keloids is postexcision irradiation, where a dose–response relationship can be seen. Total doses less than 900 cGy, irrespective of fractionation and postsurgical interval, did not prevent recurrence. Three doses of 400 cGy were given by Kovalic and Perez [2], with a 73% success rate. Using the commonly employed dose of 900 cGy, Lo *et al*. [3] described an 85% success rate and Borok *et al*. [4] a 96% response rate. No late sequelae or carcinogenesis was described by any of the previously quoted authors with follow-up in excess of 30 years.

As well as using superficial X-rays, treatment can be given using a radioactive iridium wire implant. At the time of excision a small plastic tube is inserted beneath the incision, with both ends of the tube exposed. The patient is then transferred to the radiotherapy department within 24 h, and the tube is loaded with iridium wire, and the scar irradiated to a dose of 20 Gy at 2 mm from the wire over 2 days. Escarmant *et al*. [5] describe the results of treating 783 keloid scars in 544 patients with interstitial iridium implants.

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Malignant disease

Radiotherapy for the common skin cancers

For most small BCC or squamous cell cancers without nodal involvement, surgical excision or radiotherapy will give excellent cure rates [1–4]. The decision as to which is the most appropriate modality will depend on several factors. These include the size and location of the tumour, any involvement of underlying tissues, and the likely functional and cosmetic outcome of either treatment. The patient's overall condition is important, as is the complexity of any surgery required; even the distance from the patient's home to the radiotherapy centre may play a role in determining the choice of treatment. The decision as to which modality of treatment to use should not be made solely on the basis of the patient's age.

Radiotherapy has a role to play in the treatment of almost all malignant skin conditions. Its use has been variable for several reasons. In some areas, traditional referral patterns have curtailed its use and the siting of radiotherapy departments in the larger conurbations has not given universal access to all patients. The past experience of radiation and lack of multidisciplinary meetings and clinics where the results of carefully considered fractionated radiotherapy could be seen by all attending have also reduced its use in appropriate cases [5]. Radiation damage, with skin atrophy, telangiectasia, necrosis and ulceration, occurred in the past, but this is now rare with better dosimetry, a wider range of radiotherapy modalities and more careful fractionation.

There is little difference in outcome between external beam radiotherapy with either superficial X-rays or an electron beam [6]. Locally placed moulds or applicators have also been used for malignant skin tumours, placing a radioactive source over the tumour and leaving this in position for a predetermined period [7,8].

Radiotherapy can be especially useful for tumour sites around the nose, ears and the eyelids, where surgical removal may result in a poor cosmetic result or loss of function [9]. The areas which have traditionally been considered as not suitable for radiotherapy, such as over the nose, pinna, dorsum of the hand or anterior lower leg can be treated if careful consideration is given to the volume treated, the total dose and the fractionation. It is also important to consider the general state of the patient and the condition of the skin in the site to be treated [10–13].

There are some patients who, for practical reasons, cannot have radiotherapy. If patients are unable to lie still because of confusion or neurological disease, then it can be impossible to deliver radiotherapy effectively and safely.

Radiotherapy doses for skin cancer

Radiotherapy doses have evolved empirically over a long period of time and there is a wide range in use around the UK. As a rule, the greater the fractionation employed, that is the more the total dose is broken down into smaller fractions, the better the cosmetic effect (Table 76.1). This is obviously very important to some patients, but others are content to accept a poorer cosmetic effect if it allows fewer visits to hospital.

Table 76.1 Commonly used superficial radiotherapy dosage regimens for skin basal cell carcinoma and squamous cell carcinoma.

Total dose (Gy)	No. of fractions	Fractionation interval
18	1	–
28	2	7 weeks apart
35	5	Daily (for tumours less than 4 cm in diameter)
45	10	Daily (for tumours more than 4 cm in diameter)

These fractionation regimens are only examples. Many centres will have other similar but locally derived dose fraction regimens.

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Radiotherapy for particular skin tumours

Basal cell carcinoma. Radiotherapy is useful for the primary treatment of small BCCs or larger lesions where surgery

will leave a poor functional or cosmetic result. Radiotherapy also has a role to play after primary surgery if the margins are ambiguous and further surgery is thought not to be appropriate for the patient. It should not be used for re-treating BCCs which have recurred after previous radiotherapy. The morphoeic BCC subtype and the presence of underlying bone or cartilage involvement are relative contraindications to the use of radiation treatment; but even in the latter situation, radiotherapy can be given safely and effectively [1].

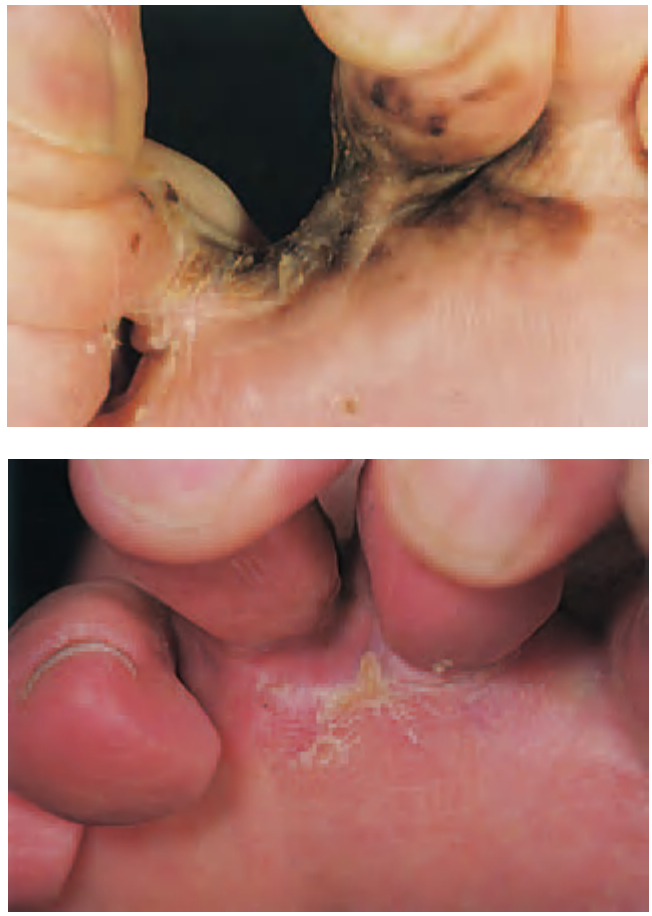
Squamous cell carcinoma. As with BCC, radiotherapy can be used as either the primary modality of treatment or as adjuvant treatment after surgery if there is a narrow surgical margin of clearance, the margin often being determined by the particular anatomical site of the tumour. The technique and dose are the same as those for treating BCC, but a wider margin is taken around the tumour and the patient is subjected to a more frequent and longer follow-up. If the squamous cell carcinoma has developed on the face, it is mandatory to check for cervical lymphadenopathy. Radiotherapy can be useful in palliation of advanced skin tumours and in some patients give long-term survival [2].

Bowen's disease. Radiotherapy can be a very effective treatment for Bowen's disease [3], but lesions on the leg have to be treated with more caution [3,4], as there is a danger of ulceration and very slow healing if large areas are treated. This condition can also be treated with a local mould, although this would be a relatively uncommon treatment modality.

Malignant melanoma. Malignant melanoma cells are not insensitive to radiotherapy, as is sometimes stated (Fig. 76.3a,b), but they do require higher dose-per-fraction regimens to overcome their ability to sustain more sublethal damage than other cell lines. Treatments may be hypofractionated, with patients receiving larger single doses in fewer fractions—for example, treatment being given three times rather than five times per week. Radiotherapy is also useful for palliation of both cutaneous and visceral metastases from melanoma [5].

There have not been any published prospective randomized controlled trials comparing surgery in melanoma with surgery and adjuvant radiotherapy, but there have been studies suggesting improved local control if post-operative radiotherapy is given [6,7].

Lentigo maligna and lentigo maligna melanoma. Radiotherapy has been used very successfully in both of these conditions. In one German study, there was no recurrence in any of 42 patients with lentigo maligna, with a mean follow-up of 15 months, and only two patients with lentigo maligna melanoma out of 22 showed local recurrence.



(a)

(b)

Fig. 76.3 A patient with malignant melanoma treated with primary radiotherapy. (a) Before treatment; (b) after treatment.

Cosmetic results were also reported as good or excellent in the majority of patients [8]. Similar complete responses for lentigo maligna were seen in studies from Australia [9] and Canada [10], again with good cosmetic results.

Merkel cell carcinoma. These tumours of neuroendocrine origin are most common on the head and neck, but can occur elsewhere on the skin. They have a tendency to recur locally after surgical removal and improved local control has been shown with a combination of wide excision and adjuvant post-operative radiotherapy [11–16].

Some authors even advocate irradiating the draining lymphatic nodes, especially if sentinal node biopsy is not performed. These are radiosensitive tumours and radiotherapy has been used as a primary treatment [16].

Cutaneous T-cell lymphoma. Radiotherapy can be used as both a localized treatment for isolated patches or plaques and for treating all of the skin by whole-body electron beam therapy [17–19]. With the latter, the patient takes up standard pre-determined poses for a number of fields allowing maximum cutaneous exposure to the beam. If

treated early in the course of the disease, the patient can remain well and disease-free for a considerable period of time, but there is still doubt as to whether patients can be cured with this technique [20]. The eyes are shielded and the patient is made aware that he or she will lose their nails with this technique. Despite its drawbacks, radiotherapy is the most effective modality in achieving a complete response to treatment in cutaneous lymphomas.

Cutaneous Kaposi's sarcoma. It is well known that these tumours are sensitive to radiotherapy. Either superficial X-rays or electron beams can be used, depending on the thickness of the lesion(s) and consequently the depth of treatment required. Radiotherapy is also used to palliate systemic disease such as pulmonary masses [21,22].

Dermatofibrosarcoma protuberans. This low-grade sarcomatous tumour has a propensity to recur after surgery alone, and local control is improved by giving adjuvant radiotherapy [23,24].

Carcinoma metastatic to the skin from other primaries. Skin metastases tend to originate from the most common parenchymal tumours such as breast, colon and lung, but occasionally isolated skin metastasis occurs from tumours originating in the thyroid or urinary system. The latter two sites should be borne in mind if a patient presents with a single bizarre metastasis with no obvious evidence of previous primary tumour.

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Acute radiodermatitis [1]

The minimal single dose that produces an observed erythema is called the 'erythema dose', and before the existence of other measurements much importance was placed on the dose needed to achieve this end. However, there is great individual variation, and field size, quality of radiation, area of skin irradiated, sex, race and age of the patient are some of the many factors affecting this parameter. The erythema dose was superseded by the roentgen and then the rad. The international unit of radiation dose is now the gray—the centigray is often used clinically.

The clinical course of the acute radiation reaction depends on the size of the dose and fractionation used. Large single fractions of irradiation are rarely given in clinical practice. An initial erythema and oedema may be seen within 24 h of irradiating the skin, and then a secondary and progressive erythema is manifest on the third to the sixth day. If the dose has been sufficiently high, vesicles and bullae may form, which subsequently dry and desquamate. The desquamated skin is usually dark. The perifollicular cells appear more resistant to radiation, and re-epithelialization is initiated in the perifollicular areas, which coalesce to cover the denuded surface. Postinflammatory pigmentation may occur at the periphery of the field and within the field in dark skins, and this pigmentation may last for many months. If the epithelium is irradi-

ated to a high dose, it will appear atrophic and smooth, it is unable to form pigment, and is devoid of hair, sweat and sebaceous glands. This thin epithelium reacts poorly to trauma and has less tolerance of further radiation. Hyperkeratosis, telangiectasia and dyspigmentation may eventually occur, and malignant lesions supervene.

Treatment. There is little which influences the natural history of the acute radiation reaction. Trauma, heat, cold, friction and infection may cause ulceration, as such skin cannot readily repair damage. Mild steroid creams may give some symptomatic relief. Vigorous and repeated washing should be avoided in the acute stage.

Chronic radiodermatitis

The skin is atrophic and shows telangiectasia due to dilatation of a reduced or poorly supported skin vasculature. Dyspigmentation occurs; pigmentation usually is reduced or absent, but there may be small islands of increased pigment production and retention. Decreased sebaceous activity is invariable. The skin is usually atrophic, but increased fibrosis occasionally causes stiffening and tethering. Radionecrotic ulceration may occur, especially in areas of moisture and trauma, and is found in the most poorly vascularized central area of the irradiation scar. Areas of ulceration often show irregular new vessel growth, and histological examination may reveal pseudoepitheliomatous hyperplasia at the edge of an area of extreme atrophy or necrosis. Where there is underlying bone sequestration, radical surgery is necessary to obtain healing.

Chronic radiation change may be confused with a recurrence of a malignant lesion, but the severe pain associated with radiation necrosis is seldom seen with the malignant disease. The effects of normal ageing and sun exposure may combine with the effects of ionizing radiation, and produce accelerated changes of atrophy, necrosis or malignant change. This may also be seen when psoralens and UVA (PUVA) are used on irradiated skin.

Late radiation changes leading to necrosis should never be seen when modern techniques of fractionation to a radical dose for skin malignancies are used. Orthovoltage irradiation of skin overlying subcutaneous bone or cartilage, as on the lower leg, nose and ear, may occasionally result in radionecrosis, as there is a disproportionate absorption of radiation in these high-density tissues, and as cartilage has a particularly poor blood supply. Thus, supervoltage irradiation should be used in these sites. Radionecrosis typically occurs approximately 1 year following complete healing of the skin after radiotherapy, and is often precipitated by trauma or infection. Excision and grafting provide the only satisfactory treatment of extensive radionecrosis. Small areas may slowly heal with conservative management.

Histopathology

In acute radiodermatitis, there is oedema and sparseness of connective tissue beneath the epidermis. There may be flattening and loss of epidermal rete ridges with separation of the elastic tissue from the basal layer. Capillary endothelium may be hypertrophic and congested capillaries a feature. Haemorrhage and thrombosis are often observed.

Special stains may show subtle changes in the DNA–RNA structure of epithelial cells as early as the third day [1,2]. During the healing phase, the patchiness of the pathology is a striking feature. Atrophy may be bordered by epidermal hyperplasia, pigmentation is very irregular, and blood vessels are of variable size and shape; deeper vessels may be fibrosed. The fundamental pathology of chronic radiodermatitis is fibrosis of the vessels, with occlusion and varying degrees of homogenization of the connective tissue. Residual vessels may be enormously dilated. Bizarre, large, stellate fibroblasts may be seen in the dermal connective tissue in some cases. Fibrosis of the deep dermis and subcutaneous tissue may occasionally occur after supervoltage radiotherapy [3].

The changes in the epidermis vary from simple atrophy to acanthosis and extreme dyskeratosis. There is usually loss of adnexa such as hair follicles.

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Radiation-induced tumours

The type of tumour induced by radiation depends on both the cellular structure and the anatomical location of the damaged tissues. Basal cell epitheliomas occur following radiation to the face, scalp and trunk, whereas on the hands squamous cell tumours may occur. These are much more rarely seen since the development of more sophisticated radiotherapy machinery and a greater knowledge of radiobiology. It has not been possible to demonstrate any precise quantitative relationship between the development of cutaneous epitheliomas and the amount of radiation received on the skin surface, nor is it known what total dose or fractionation regimen would be most carcinogenic. It has long been known that carcinomas occur more profusely in areas subjected to many small doses administered at intervals over a long period. Multiple basal cell epitheliomas on the skin over the spine following radiotherapy to the lumbar spine for ankylosing spondylitis have been reported [1]. Some may show

the histological appearances of the pre-malignant fibroepithelioma of Pinkus. Radiation-induced basal cell epitheliomas of the scalp may be seen 20–50 years following X-ray epilation for ringworm infection. Late radiation changes are not always visible on the scalps of these patients, and hair growth may be relatively normal.

The doses of radiation used to treat benign dermatological conditions should never produce late radiation damage of even mild type [2]. In general, radiation-induced cancers have occurred after inappropriate doses, often of many thousands of centigray, given over a long period, frequently by lay therapists for conditions such as hirsutism or greasy skin and large pores [3], which are not indications for treatment by radiotherapy today. Shielding of structures especially sensitive to irradiation—for example, the adolescent thyroid [4]—was not routinely carried out. Although a greater knowledge of the limitations and effectiveness of radiation should prevent the occurrence of late radiation damage including carcinogenicity, the long latent period often demonstrated in those cases warns against early complacency [5,6].

Treatment. Most radiation-induced tumours should be excised. However, where there is no radiation damage evident on the skin, a subsequent radical dose of radiotherapy can be tolerated, but this would be indicated in very limited clinical circumstances.

Atypical fibroxanthoma

SYN. PSEUDOSARCOMA OF THE SKIN

This tumour, seen particularly in fair-skinned males who have suffered actinic damage, may also follow radiation damage [7–9]. It usually occurs on the face, but occasionally on the trunk or limbs. The clinical course is benign, despite the highly anaplastic histological appearance. Twenty-one tumours initially labelled as spindle cell squamous carcinomas were found by Hudson and Winkelmann [7] to be atypical fibroxanthoma.

Fibrosarcoma

Sarcoma appears to arise in irradiated skin much less frequently than carcinoma, and many of the tumours are low grade, showing no tendency to produce distant metastases [10]. At least some of the reported sarcomas are in reality spindle cell carcinomas [11]; this may be shown by the attachment of the tumour to the epidermis or by the presence of horny pearls. Radiation fibromatosis [12] is a diffuse proliferation in which bizarre and sometimes monstrous fibroblasts appear in the dermal connective tissue; the appearance can easily be mistaken for fibrosarcoma. Only exceptionally does fibromatosis undergo malignant change. It does appear that irradiation of an already chronically inflamed skin is more likely to be followed by a fibrosarcoma than irradiation of normal skin.

The fibrosarcomas, like the carcinomas following radiation, appear usually after repeated exposures to low-voltage rays and rarely from supervoltage radiation. The latent period in one series [13] averaged 26 years.

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Chapter 77

Physical and Laser Therapies

N.P.J. Walker, C.M. Lawrence & R.J. Barlow

Cryosurgery

Various methods of freezing skin have been described [1]. These achieve the following minimum temperatures: salt–ice mixture (–20°C); carbon dioxide snow (–79°C); dimethyl ether and propane (Histofreezer; –50°C); nitrous oxide (–70°C) and liquid nitrogen (–196°C). Because of its very low temperature, liquid nitrogen works faster than other methods. It is also easy to use, inexpensive and readily available. Liquid nitrogen is therefore the most widely used cryotherapy agent. All significant studies of cryotherapy technique have used liquid nitrogen, and it is the only agent discussed in this chapter. The effectiveness and freeze times of other cryogens has not been established.

Cryotherapy is believed to cause cell death in four ways.

1 Ice crystals formed in the cell damage cellular components [2]

2 Uneven intracellular ice formation during freezing leads to osmotic differences arising during thawing, which in turn cause cell disruption

3 Cold injury to small blood vessels results in ischaemic damage

4 Immunological stimulation produced by the release of antigenic components results in cell damage.

The extent of injury is determined by the rate of freezing, the coldest temperature reached, the freeze time and the rate of thawing. Maximum damage is produced by rapid freezing and slow thawing. Repeating the freeze–thaw cycle produces much greater tissue damage than a single freeze because the greater conductivity of the previously frozen skin and the already impaired circulation both allow a greater and faster depth of cold penetration.

It is suggested that a temperature of –30°C is required to produce cell death. In practice, tissue temperatures achieved during cryotherapy do not need to be measured because clinical studies have determined the duration of liquid nitrogen spray freeze times for common skin conditions.

Clinical methods

In day-to-day use, liquid nitrogen *must* be kept in unsealed containers designed for the purpose. If containers are sealed, explosion will occur. One litre of liquid nitrogen held in an unsealed vacuum flask will last approximately 6 h. Liquid nitrogen can be applied using cotton wool swabs dipped into the liquid, but a liquid nitrogen spray is faster and more convenient.

Clinical uses

Liquid nitrogen cryotherapy has been used to treat a wide range of skin diseases (Table 77.1) [3]. The simplicity and speed of cryosurgery treatment are benefits, but cryotherapy can easily be performed incorrectly and ineffectively. The correct technique and freeze times are required to

Table 77.1 Skin conditions responsive to cryosurgery [3,13].

Naevi	Pigmented Epidermal
Lentigo	Benign
Vascular lesions	Telangiectasia Spider naevus Pyogenic granuloma Pseudopyogenic granuloma Kaposi's sarcoma Haemangioma Lymphangioma
Keratotic and preneoplastic	Viral warts Molluscum contagiosum Seborrhoeic keratosis Solar keratosis Cutaneous horn Keratoacanthoma Bowen's disease
Carcinoma [5–7]	Basal cell epithelioma Squamous cell epithelioma Lentigo maligna
Cysts	Epidermal Synovial Acne Mucous cyst
Leukoplakia	
Axillary hyperhidrosis	
Scarring	Keloid Acne (carbon dioxide snow, acetone 'slush')
Sebaceous hyperplasia	
Rhinophyma	

produce results similar to those described in published studies [4].

Cryosurgical treatment of basal cell epitheliomas gives cure rates that compare favourably with other modes of therapy [5–7], provided the correct technique is used and the treatment limited to small (less than 20 mm), well-defined, previously untreated tumours. Less favourable results are obtained with lesions on the inner canthus of the eye, nasolabial and retro-auricular folds and the hair-bearing scalp. The temperature reached and the number of freeze–thaw cycles are also critical. Debulking the tumour using curettage or electrosurgery prior to cryotherapy is advocated by some authors [8,9]. Lower leg Bowen's disease is best treated by curettage, which is superior to cryotherapy [10], which in turn is superior to radiotherapy [11].

Side effects [1]

Cryotherapy pain is significant but usually transient, and tissue swelling is common. Inflammation can be reduced with topical steroid applications [12]. Haemorrhagic blisters may occur but blister formation is not necessary for the cure of lesions such as viral warts. Sun-damaged and senile atrophic skin, and areas previously treated with topical steroids or X-irradiation, are more likely to blister or become necrotic after freezing. Skin necrosis is a desirable part of the treatment of neoplastic and many pre-neoplastic lesions, and several weeks may elapse before healing is complete. Hypopigmentation is common after liquid nitrogen cryosurgery, is particularly noticeable in dark-skinned patients and may be permanent [2,13]. Temporary post-inflammatory hyperpigmentation is to be expected following less severe freezing. Nerve damage resulting in paraesthesiae, distal anaesthesia and motor paralysis occasionally occurs [14]. Similarly, deep freezing over the lacrimal ducts may, very rarely, lead to permanent ductal obstruction [1].

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Curettage

Curettage is only possible when the curetted material is more fragile than normal skin (e.g. basal cell carcinoma; BCC), or there is a natural cleavage plane (e.g. seborrhoeic wart) between the lesion and the surrounding skin. On mobile or fragile skin areas, a starting point for curettage can be made by fulgurizing the rim. Stop bleeding using either a chemical haemostatic agent (e.g. aluminium chloride 30% in isopropyl alcohol), cautery or electrodesiccation. Do not use alcohol-based skin-cleansing solutions during cautery or electrodesiccation because of the fire

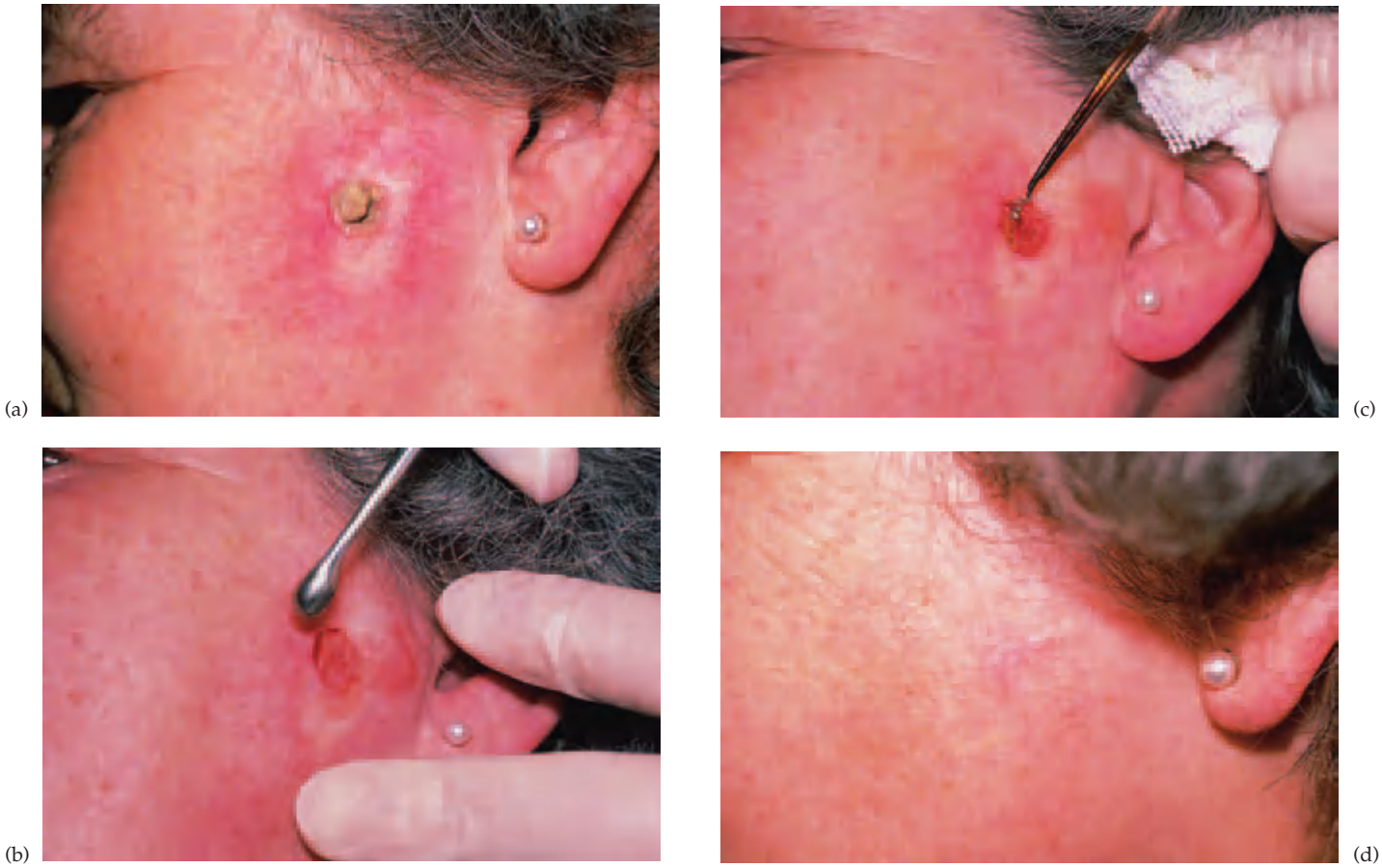

Fig. 77.1 Curettage and cautery of an actinic keratosis. (a) After local anaesthetic injection, this hyperkeratotic actinic keratosis was (b) curetted off and (c) the wound cauterized. (d) At 4 months the wound had healed leaving a barely visible scar.

risk. The resulting wound heals by re-epithelialization from the retained follicular and edge epithelium.

Benign lesions

Curettage of *viral warts* is sometimes effective. Treatment is painful and there is a risk of scarring and recurrence. Solitary warts on the face of adults can usually be removed by curettage, otherwise viral warts should only be curetted off when other methods have failed. Curettage is probably justifiable in painful plantar warts that have not responded to other therapies. Nerve block anaesthesia may be required [1]. There is a risk of painful scar formation. Peri- and subungual warts are difficult to curette off; the nail may have to be partially removed to allow adequate curettage. Genital or perianal warts that have not responded to cryotherapy, podophyllin or imiquimod can be curetted off. *Seborrhoeic warts* can be treated by cryotherapy or curetted off. In contrast, *pyogenic granulomas* and *hypertrophic* or *solitary actinic keratoses* (Fig. 77.1) are best treated using curettage, as this provides material for histological confirmation of the diagnosis.

Non-melanoma skin cancers

The technique is the same for both BCC and squamous cell carcinoma (SCC) (Fig. 77.2). Tense the anaesthetized skin around the lesion and scrape off the bulk of the tumour using a small sharp curette [2]; the curette should not be so sharp that there is a risk of it slicing through the underlying dermis. The fragmented specimen should be mounted on a small piece of filter paper, where it is allowed to congeal slightly before being dropped into formalin. In this way the pathologist receives a single sample rather than multiple small floating fragments. Cauterize, using a hot wire with a beaded tip, or electrodesiccate the wound surface. Repeat the curettage using a smaller curette to search for residual pockets of tumour. At this stage, the curette will be scraping against the normal dermis and less material will be removed. If the curette penetrates the dermis and enters fat, curettage should be abandoned as it is impossible to distinguish between the softer tumour tissue and the underlying fat. The wound will need to be excised down to and including fat. Perforation of the

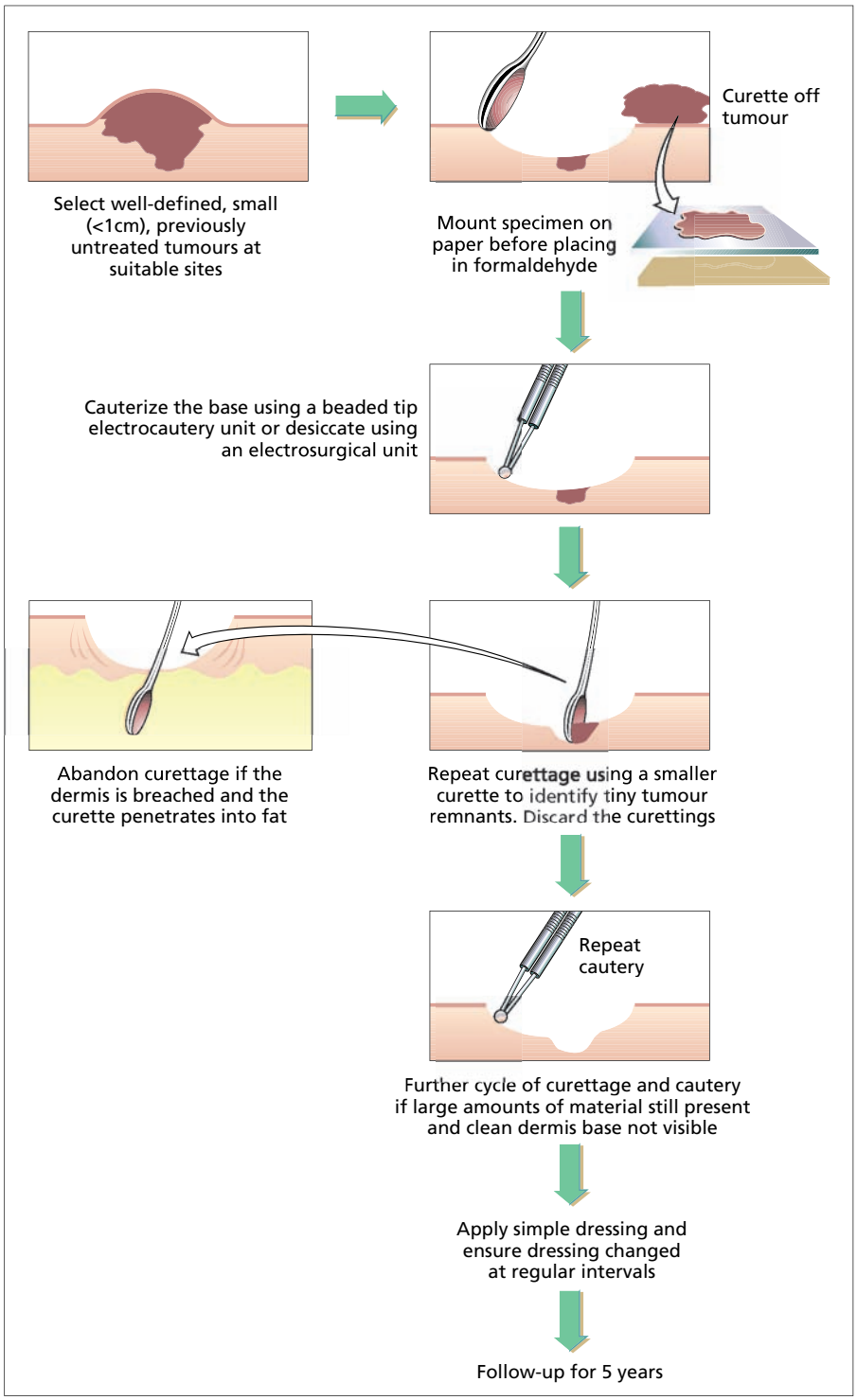

Fig. 77.2 Schematic diagram of the stages of curettage and cautery of a basal cell carcinoma. (From Lawrence [14].)

dermis is particularly likely to occur if an incisional biopsy has been taken prior to treatment. Repeat the cautery or electrodesiccation. A third cycle of curettage and cautery is required if a large amount of material is removed at the second stage. The histological specimen only confirms the diagnosis; it provides no indication about the adequacy of treatment. Do not curette recurrent tumours because of the high recurrence rates [3].

Basal cell carcinoma

Curettage of BCCs depends on the tumour being easier to scrape off than the surrounding normal tissue. Thus, if strands of fibrous tissue separate clumps of tumour (as occurs in morphoeic, recurrent or invasive BCCs) or the adjacent skin tears easily, cannot be tensed or hair roots impede curettage, the results will be poor and curettage

Table 77.2 Types of basal cell carcinoma (BCC) that should not be treated by curettage.

Large tumours (≥ 2 cm diameter)
Tumours at sites where curettage produces a poor cosmetic result, is technically difficult or is associated with a high risk of recurrence
Morphoeic, infiltrating or basisquamous BCCs
Recurrent tumours
Ill-defined tumours
Tumours penetrating muscle, fat, bone, etc.
Tumours where an incisional biopsy has been performed (risk of perforation of the dermal sling)

should be avoided. High recurrence rates occur after curettage of recurrent [3], morphoeic [4] or large tumours [4,5], or treatment by inexperienced operators (Table 77.2) [6]. When small (less than 20 mm diameter) [4–8] non-recurrent tumours [3,9,10] on suitable sites (Table 77.3) are curetted by experts [6,11], the 5-year cure rate is 95% or better (Table 77.4). Cautery and electrodesiccation can be used interchangeably and their use improves cure rates [12]. Paradoxically, despite these high cure rates, histological examination after curettage and electrodesiccation shows that some residual tumour is present in almost 30% of cases [13,14]. Thus, cure must also depend on other factors, such as residual tumour cell mass, inflammatory reaction and healing responses.

Squamous cell carcinoma

Experience shows [8,10,15] that well-differentiated, primary, slow-growing SCCs arising on sun-exposed sites can be cured by curettage and cautery (Table 77.5). However, SCCs with a higher risk of recurrence or metastasis should not be treated by curettage. These high-risk SCCs include lesions arising on scars, ears, lips, areas of radiation or thermal injury, chronic ulcers or sinuses, Bowen's disease and non-sun-exposed sites; and large (more than 20 mm), thick (more than 4 mm), poorly differentiated and recurrent SCCs, or those arising in an immunocompromised patient [16,17].

Intraepidermal carcinoma (Bowen's disease)

Intraepidermal carcinoma, especially on the lower leg, heals better after curettage than cryotherapy [18], as the extent of treatment is more predictably determined by the operator. Radiotherapy, 5-fluorouracil and excision are all alternatives.

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Table 77.3 Sites to avoid curettage and cautery of basal cell carcinomas.

Sites with a high recurrence rate after all treatment modalities	Sites where curettage is technically difficult	Sites associated with poor cosmesis after curettage
Nose	Lips	Vermilion border
Nasolabial fold	Eyelid	Ala rim
Around the eye	Hair-bearing scalp	Nose tip
Around the ear		Chin
Scalp		

Table 77.4 Cure rates following curettage and cautery and/or electrodesiccation of primary basal cell carcinoma.

Author, year of publication	Number of tumours	Duration of follow-up (years)	Number of recurrences (%)	Tumour size
Simpson [9] 1966	495	2–5	35 (7)	ns
Williamson and Jackson [11] 1962	287	3	22 (7.6)	ns
Knox *et al*. [8] 1967	282	5	4 (1.4)	< 20 mm
Sweet [4] 1963	268	≥ 3	19 (7.1)	< 20 mm
Spiller and Spiller [7] 1984	208	5	3 (1.4)	< 20 mm
Tromovitch [10] 1965	75	≥ 5	(4)	ns

ns, not stated.

Table 77.5 Cure rates following curettage and cautery of primary squamous cell carcinoma (SCC).

Author, year of publication	Number of tumours	Duration of follow-up (years)	Percentage cure rate	Metastasis?	Tumour size (number greater and smaller than 2 cm)
Knox *et al*. [8] 1967	213	5	99	No record	185 < 2 cm 28 > 2 cm
Knox *et al*. [8] 1967	545	> 1	99	1	495 < 2 cm 50 > 2 cm
Tromovitch [10] 1965	29	5	96.6	Nil	No record
Freeman *et al*. [15] 1964	407	1–5	96–100	Nil	355 < 2 cm 52 > 2 cm

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Electrosurgery

Electrosurgery includes electrodesiccation, electrofulguration, cutting diathermy (syn. electrosection, electroresection) and electrolysis [1,2]. Coagulation or tissue destruction is produced by the heat created as the electrical current passes through the tissue. Although not strictly an electrosurgical technique, electrocautery is usually also included because of its development from the established method of using heat in the form of hot oils, cautery irons, etc., to control bleeding.

Electrocautery

SYN. CAUTERY; HEAT CAUTERY; HOT-WIRE CAUTERY

The cautery machine power output should be controllable so that the tip temperature can be adjusted rather than being dependent on the battery power. A variety of tips are available. The *beaded tip* is best for haemostasis after curettage and shave biopsy; this should be just hot enough to char a cotton swab, but not red hot as the platinum tip may melt. If the beaded tip drags on the tissue as it is drawn across the wound, the tip temperature is too low. After use, any remaining debris should be burnt off the tip by briefly allowing it to become red hot. The needle-like end of the *cold point cautery tip* is heated, by conduction, via a wire coil, and is used to treat spider naevi. The *flat blade* can be used for pedunculated lesions or shave excisions, but has to be glowing red hot to cut through tissue, producing a heating artefact on the excised material. Furthermore, the red-hot blade has to be quickly passed through the skin to avoid excessive heat damage at the wound site, so the direction and depth of the cut cannot be adjusted easily and the blade may accidentally cut or burn deeper into the tissue than required.

Electrosurgery

SYN. SURGICAL DIATHERMY; COLD ELECTROCAUTERY

Waveform

Electrosurgical equipment converts domestic alternating current into high-frequency alternating current. When this passes through a high-resistance medium, such as the skin, heat is produced, resulting in tissue coagulation, desiccation or cutting, depending on the electrical waveform. A highly damped waveform (intermittent pulses of electrical discharge separated by intervals of zero voltage) results in electrodesiccation and/or fulguration. In contrast, a continuous waveform produces a cutting effect and a moderately damped or blended waveform (a

mixture of continuous and highly damped waveforms) chiefly produces coagulation [3].

Unipolar/monoterminal/bipolar diathermy

Apart from the waveform produced, electrosurgery equipment also varies in the way the current is discharged and collected. Unipolar (monopolar) current is delivered via an active electrode, usually a needle or ball tip, resulting in a high concentration of current at the electrode tip. The current disperses through the patient's body and is collected via a dispersive (syn. indifferent, passive, return, earthing, ground) electrode with a large surface area. The current density falls with increasing distance from the active electrode and there is minimal risk of tissue damage as the current is collected over the large area of the dispersive electrode. If, because of faulty application or equipment, there is only a small area of skin–electrode contact, a burn may occur at the dispersive electrode. Also, if the current is channelled at narrow points along its path (e.g. the finger), an area of high-current density leading to tissue damage can occur. Bipolar electrodes avoid these hazards by producing and collecting the current using forceps so that current only travels in the tissue held between the tips. Monoterminal electrosurgical equipment (e.g. Birtcher Hyfrecator) produces a high-voltage low-amperage current, and is designed to be used without a dispersive electrode. However, there is a risk of a small but painful discharge occurring between the patient and the operator or other earthed point (e.g. the metal edge of an electrically insulated couch) [4]. This can be prevented by maintaining a large area of skin contact between the operator and patient during use, or using a dispersive electrode.

Electrodesiccation/electrofulguration

This is produced using a monoterminal or unipolar electrode. Electrodesiccation occurs when the needle remains in contact with the skin and no spark occurs. Because the current concentration is greater at the point of contact, the tissue damage is deeper compared with electrofulguration. During the latter, the needle tip is not in contact with the skin and a spark jumps between the skin and the needle, but its energy is spread over a greater area. The resulting heat causes superficial damage to the tissues and is an effective way of stopping bleeding. Various needle tips have been developed for specific circumstances [5]. Because of the risk of virus transmission, a different clean needle must be used for each patient [6].

Pacemakers and electrosurgery

There have been reports of electrosurgery interfering with pacemaker function temporarily and causing temporary asystole if there is no underlying cardiac rhythm, or causing a demand pacemaker to switch to a fixed-rate mode [7]. The effect lasts only as long as the unit is being operated. When diathermy finishes, the pacemaker reverts to normal function. There are also anecdotal reports of the pacemaker failing shortly after electrosurgery [8]. Only older (pre-1990) pacemakers seem to be vulnerable. Modern pacemakers are considered to be resistant to these problems. All types of electrosurgical equipment, except cautery, can cause problems, although bipolar diathermy is the least hazardous. Short bursts (less than 5 s) should be used, the patient's heart rate can be monitored and resuscitation equipment should be available. Diathermy should not be performed within 15 cm of the heart, the pacemaker or its leads. If monopolar diathermy has to be used, the path from the active electrode (diathermy tip) to the dispersive electrode should be at least 15 cm from the heart, the pacemaker and its leads.

Spider naevi

Spider naevi are probably best treated using a pulsed dye laser. They can be also be destroyed using cold point cautery or electrodesiccation, but with greater risk of scarring.

Xanthelasma

Electrodesiccation and curettage of xanthelasma is relatively simple. The anaesthetized skin overlying the xanthelasma is fulgurized and disrupted. The underlying fatty deposits can be electrodesiccated, scraped off using a sharp curette and left to heal by second intention. Trichloracetic acid and ablative laser therapy can also be used.

Small seborrhoeic and plane warts

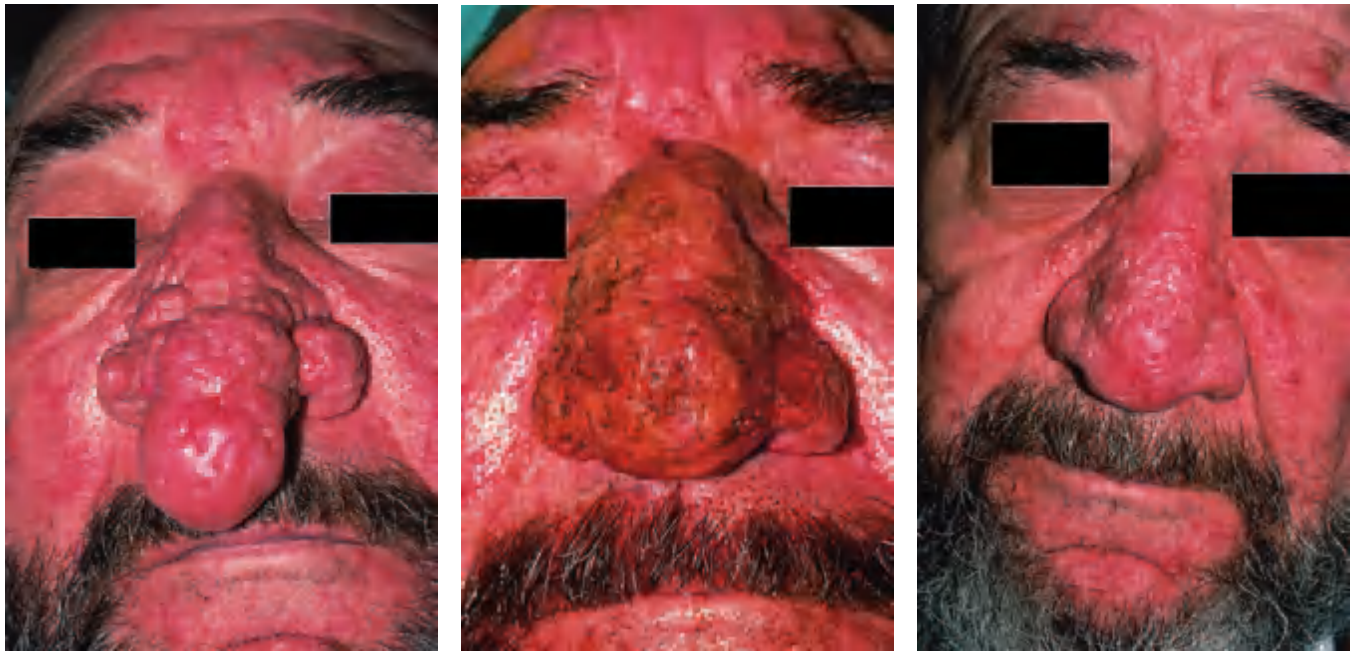
Eyelid seborrhoeic warts can be softened and removed by electrodesiccation, provided the anaesthetized eyelid margin is pulled away to prevent conjunctival damage.

Surgical paring and electrofulguration of rhinophyma

Cutting diathermy (syn. electrosection) using a unipolar diathermy and dispersive plate is particularly useful for treatment of rhinophyma, where bleeding can be a problem [9]. Re-epithelialization takes place, with surprisingly little scarring, from the abundant pilosebaceous follicles that remain in the dermis (Fig. 77.3). Carbon dioxide laser resection is also effective.

Electrolysis

Hair is not an electrical conductor and thus electronic tweezers do not produce permanent hair removal; this can only be achieved if the electrical current reaches the



(a) (b) (c)

Fig. 77.3 Shave excision and electrosurgery of a rhinophyma. (a) This disfiguring rhinophyma was reduced in size and (b) the nose shape recreated by shave excision and electrodesiccation of the bleeding surface under local anaesthetic, (c) resulting in an acceptable cosmetic result at 4 months.

germinal bulb via a needle inserted to the correct depth [10]. Galvanic electrolysis involves the use of low-voltage low-amperage direct current passed down a needle inserted into the follicle. The current causes dissolution of the follicular epithelium and hence detachment of the hair shaft. This technique is effective but time consuming. High-frequency electrodesiccation is a faster alternative, which destroys the follicle by heating. Insulated needles deliver the electrical current to the base of the follicle. Side effects of electrolysis include self-limiting redness and wealing, post-inflammatory pigmentation, and scarring. Compared with laser hair removal, electrolysis is better for sparse hairs and fair hair.

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Infrared coagulation [1–3]

The infrared coagulator produces ordinary light (non-coherent) with a spectrum of 400–2700 nm. Power is generated from a tungsten halogen bulb and is transmitted along a quartz glass light guide—at its end this has a sapphire cap, which is placed in contact with the skin. The heat imparted causes thermal injury to a depth dependent on the duration of exposure, which can be set on an automatic timer and varied from 0 to 1.5 s; for example, a 1-s exposure will remove tissue to a depth of approximately 0.75 mm.

The major characteristics are:

1 Non-laser radiation of maximum output 960 nm (near infrared)
2 Tungsten halogen bulb power source—15 V, 150 W
3 Pulsed energy
4 Solid quartz glass light guide
5 Diameter of treated area 2–10 mm, the larger diameters enabling more rapid treatment
6 Sapphire cap to light guide—sapphire is transparent to near infrared but rapidly conducts away heat generated in the upper dermis
7 Minimum optical hazard—the appearance of bright visible radiation causes aversion of the eyes if it is pointing in their direction, thus preventing infrared damage
8 It is portable, and relatively cheap.

It has been used mainly for tattoos [1], a variety of superficial vascular lesions [2], warts and myxoid cysts of the digit. Tattoos [1] can be treated with remarkably little morbidity. The area to be treated is mapped into overlapping circles similar in diameter to the sapphire tip, and each circle is treated with a pulsed exposure of approximately 1.25 s. An ice cube applied to the skin for 5 s before and after treatment is used to minimize conducted heat damage to surrounding skin. The immediate appearance of the coagulated tissue is white and slightly contracted; the eschar, which develops over several days, drops off in 2–3 weeks. Serous exudate, pain and swelling during the healing phase are generally insignificant.

Telangiectases, port-wine stains and angioma serpiginosum have been treated using short exposure times (e.g. 0.75–0.875 s, also with ice). It is evidently less specific and probably less effective, with a greater risk of scarring, than an appropriate laser.

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Caustics and chemical peeling

Caustics

In experienced hands, caustics provide a simple and readily available means of destroying many superficial skin lesions. The operator should be well acquainted with the action and degree of penetration of individual caustics, and the toxic effects that may result from absorption, especially if they are to be used on large areas, and particularly when applied to the face [1,2]. In treating individual lesions, caustics are usually applied by means of a cotton-bud applicator or a wool-tipped orange stick, pointed if necessary.

Aluminium chloride hexahydrate

A 20% solution (Driclor; Anhydrol Forte) usually applied on a cotton-bud is a very useful styptic for superficial wounds such as those following shave excision. Ferric subsulphate (Monsel's solution) is widely used, but may leave a pigmented scar.

Silver nitrate [3]

This is used in the form of a pencil or as a strong solution to suppress exuberant granulation. It is haemostatic and may be used to arrest bleeding after curettage. Repeated use tends to lead to unsightly staining of the skin.

Phenol (liquefied phenol)

This is a valuable superficial caustic, which should, however, be used cautiously. It should not be diluted as this increases its absorption and potency [4,5] and thus also its nephrotoxicity. Ochronosis may occur from prolonged absorption. It is not a haemostatic, and bleeding limits its effectiveness. When used as a treatment for ingrown toenails it is important that the phenol is applied to a 'dry' nail bed and that sufficient time is allowed for it to take effect [6].

Potential toxicity and cardiac arrhythmias remain a major concern, especially with more extensive use, and it should not be used during pregnancy. Phenol is used in a soap–croton oil–water mix for chemical face peels (see below). A glycol-spirit solution can be used for neutralization if required.

Trichloroacetic acid

This is an effective haemostatic caustic, which has many uses. The 30–50% concentration can be used as a styptic, and is frequently employed in conjunction with superficial curettage in the treatment of solar keratoses and seborrhoeic warts. The supersaturated solution can also be used on its own to treat many benign and dysplastic skin lesions. Trichloroacetic acid 50% is similar to phenol in its destructive effect on the epidermis.

Trichloroacetic acid may be a useful treatment for xanthelasmas and solar lentigos. It must be applied with great care, however, especially around the eyes. Its action is rapid, and a white 'frosting' occurs within a few seconds of application. The caustic action can be partially neutralized by applying alcohol, water or sodium bicarbonate-soaked gauze, but this is unlikely to have any effect once the acid has penetrated the skin.

Excess sebum should first be removed using detergent, ether or acetone. Trichloroacetic acid should then be applied with an 'almost dry' cotton applicator. The concentration to be used will vary according to site, the condition to be treated and whether the trichloroacetic acid is being used as a styptic or a superficial skin caustic.

Weaker solutions of trichloroacetic acid are sometimes used for treating wider areas of skin (see below). Because of deliquescence, trichloroacetic acid should be kept in a closed, coloured and corrosion-resistant bottle.

Dichloroacetic acid

This is also a powerful caustic and skin styptic.

Monochloroacetic acid

This should not be considered as a superficial caustic. It penetrates rapidly and may remove the whole epidermis

by blister formation. It may be used for mosaic warts, and can also be used for resistant periungual warts.

Alpha-hydroxyacids [7]

These acids (e.g. glycolic acid) can be used to produce superficial or freshening peels and, at high concentration, medium-depth chemical peels.

Chemical peeling [1,2,7–10]

This procedure can be used to improve the appearance of ageing, wrinkled or sun-damaged skin. It is less effective in dealing with acne scars but is a valid dermatological manoeuvre for these and other superficial lesions on the face.

Chemical face peeling is used in conjunction with or as an alternative to dermabrasion. Patients with a dry skin and a fair complexion are the best subjects. A variety of preparations in differing concentration can be used alone or in combination, depending on the desired outcome [11]. Trichloroacetic acid is probably the most commonly used agent. Weak preparations (10–15%) may be used for light 'freshening' peels, and higher concentrations for medium-depth or deep peels. Alpha-hydroxy acids (mild), Jessner's solution (mild) and phenol (deep) may also be used. The neck should only be included with caution as the skin in this area is more prone to scarring and hyperpigmentation. Weaker preparations are generally used on eyelids, and care must be taken not to cause hypertrophic scars, which may occur around the mouth or mandible. Prolonged erythema and increased sensitivity to sunlight, and pigmentary changes (both hyperpigmentation and hypopigmentation) may follow the procedure.

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Intralesional therapy

Intralesional triamcinolone [1]

Aqueous suspensions of triamcinolone acetonide (10 mg/mL [Adcortyl] and 40 mg/mL [Kenalog]) [2] are available. Intralesional hydrocortisone acetate (25 mg/mL) can also be used. Triamcinolone acetonide 10 mg/mL is sufficient for all conditions except keloids. The amount injected ranges from 0.1 to 0.5 mL of 10 mg/mL solution, depending on the size and nature of the lesion. The injection should be given using a 27–30-gauge needle, deep in the dermis when possible, to minimize the risk of collagen atrophy. The manufacturers recommend that no more than 30 mg of triamcinolone acetonide should be given in one session, with a maximum of 5 mg at any one site. (Steroid equivalence: 5 mg prednisolone = 4 mg triamcinolone = 20 mg hydrocortisone.) Plasma cortisol levels are suppressed for a few days by 20 mg of intralesional triamcinolone acetonide given into various sites; higher doses suppress cortisol levels for longer [3]. Cushing's syndrome has occurred 2–3 weeks after a single treatment with 40 mg triamcinolone acetonide injected into keloids [4]. Local side effects include collagen atrophy [5], hypopigmentation [6], skin necrosis [6], perilymphatic linear depigmented and atrophic streaks [7,8], and telangiectasia [9].

Needleless injection of steroids

Intralesional triamcinolone is also given using a needleless injector (Dermojet or Portojet). The injection is slightly less painful but is principally employed because the injections can be given quickly [10]. There is a danger of intraocular injection if this technique is used around the eye [11]. Dose-for-dose, needleless injection of steroid appears to be less effective than needle injection, probably because some steroid solution spills onto the skin.

Uses

Intralesional triamcinolone therapy is used for inflammatory acne cysts, lichen planus, lichen simplex, lupus erythematosus [12], chondrodermatitis [13], orofacial granulomatosis [14], granuloma annulare, psoriasis and nail psoriasis [15], alopecia areata and many other steroid-responsive conditions [16].

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Intralesional therapies for skin malignancies

Intralesional *methotrexate* is reported to be a painless and effective method of treating keratoacanthoma, with faster than spontaneous resolution [1,2]. Intralesional *5-fluorouracil* injections are very painful but when used for 4–6 weeks destroy small nodular BCCs [3] and some SCCs [4]. Intralesional *interferon-α2b* has been used to treat Bowenoid papulosis [5], melanoma [6], BCC [7,8] and SCC [9]. Up to 80% of small, solid or superficial BCCs injected, using high-dose therapy, appear to resolve, although adverse effects occur in 80% of patients at this dose. In contrast, only a minority of aggressive pattern, invasive BCCs respond [10]. Intralesional *interleukin 2* in 1–4 weekly doses produced complete response in eight of 12 BCC patients treated [11]. Intralesional *bleomycin* followed by electrical stimulation (electrochemotherapy) has been used for a range of skin tumours, including SCC [12].

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Sclerotherapy (see also Chapter 50) [1]

The injection of sclerosant chemicals is a useful means of obliterating dilated superficial veins, particularly on the legs. The superficial vessels should only be treated after any proximal points of reflux have been dealt with. Patients who seek treatment therefore require a thorough assessment of their vascular system, and the history and physical examination may be supplemented with non-invasive venous assessment using ultrasonography.

There are a variety of sclerosants that can be used, and some are available in different concentrations. They may be divided into detergents (sodium morrhuate, sodium tetradecyl sulphate, polidocanol) [2], osmotic solutions (hypertonic saline) and chemical irritants (chromated glycerin). Each has advantages and disadvantages.

Side effects [3] include telangiectatic matting, post-inflammatory hyperpigmentation, ulceration, thrombophlebitis and, rarely, systemic reactions (urticaria, anaphylaxis).

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Miscellaneous physical procedures

Keloid therapy

Keloids spread beyond the original wound and remain elevated, whereas hypertrophic scars are localized to the injured area and flatten spontaneously with time [1]. Both are more common in young individuals, Afro-Caribbeans

and at particular sites, especially the central chest, back and posterior neck, followed by the ears, deltoid areas, anterior chest, beard area and the rest of the neck [2,3]. Patients with one keloid, except those on the earlobe [4], are believed to be at risk of further keloids. Many treatments have been suggested, including excision, superficial X-ray therapy (although this may provoke malignant tumours [5]), cryotherapy [6,7], pressure [8,9], ultrasound, laser excision [10], intralesional steroids, interferon-α2b [11] and verapamil [12]. Most reports have claimed partial benefit, few have admitted failure. Despite systemic or local side effects [13], intralesional steroid, in the form of triamcinolone 10–40 mg/mL, injected into the scar every 2–3 weeks, is probably the most effective therapy, particularly for presternal and small keloids. High pressure is required to inject steroids into hard keloids, and a Luer-lock glass or hubless disposable syringe is recommended [14].

Pedunculated or easily excised keloids (e.g. on the earlobe) are best treated by intramarginal excision and pre- and postoperative steroid injection [15]. On the earlobe, part of the skin covering the keloid can be salvaged to cover the defect created by removal of the latter [16]. Most authorities recommend a combination of surgery and triamcinolone injections. Some suggest that triamcinolone should be given before, during and after surgery [4], others use steroids during and after surgery [17], whereas others only use steroids postoperatively, to avoid the risk of wound dehiscence [18]. All agree that triamcinolone 40 mg/mL is usually required. On balance, it seems best to give steroids both intra- and postoperatively—approximately four times at 2–3-week intervals, starting 2–3 weeks after suture removal (which should be delayed for 10–14 days because of the risk of steroid-induced wound dehiscence). Freezing the keloid with liquid nitrogen before injection is said to make triamcinolone injection easier [19]. However, this may increase the risk of hypopigmentation. With repeated injections it becomes possible to inject more triamcinolone into the keloid, which can be felt to expand slightly as the steroid is injected. Remember that both cryotherapy and triamcinolone injections may produce skin depigmentation [4]. Alternative therapies include topical clobetasol propionate cream or flurandrenolone tape. The latter carries less risk of steroid atrophy of the adjacent skin because only the keloid is covered. Intralesional interferon-α2b appears to reduce keloid size and inhibit collagen production [11]. Intralesional verapamil is said to reduce keloid size [12] by inhibiting proline incorporation into collagen [20]. Silicone gel sheeting is advocated for larger keloids but the evidence that it is effective is not conclusive [21,22].

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Minor surgical procedures

Using an orange stick, small quantities of caustic agents can be precisely applied. When 90% liquid phenol is used to treat molluscum contagiosum or small cysts, the orange stick tip may need to be sharpened so that it just fits the cavity being treated. Remember that phenol melts some plastics.

Mollusca can be squeezed to express the cellular debris from the centre of the lesion before phenol application. The tip of the orange stick is dipped into the phenol, any excess wiped off, and the stick is then placed in the centre of the lesion and gently twisted. The solution does not need to be neutralized. After initial whitening, the molluscum becomes inflamed and then resolves 7–10 days later. Treatment is painful and not usually tolerated by small children.

Xanthelasma can be treated using the blunt end of an

orange stick, dampened with trichloroacetic acid, dabbed on to the affected area. *Multiple small facial epidermoid* or *acne cysts* can be treated in a similar way. The cyst is incised, the contents expressed and phenol carefully applied to the cyst lining using an orange stick. No dressing is required, but a local anaesthetic is necessary.

Milia are tiny keratin-filled epithelial-lined cysts with no connection to the overlying skin. They can be removed via a small skin incision made with a sterile no. 21 or 19 venesection needle. No anaesthetic is required. Prick the needle tip into the skin and, by pulling the cutting edge upwards, incise the skin overlying the milium. Hook or squeeze out the cyst through the skin incision.

Comedones may be emptied using a comedone expressor—a small metal instrument with a cup-shaped end, which has a central hole.

Haemostasis

Bleeding from open wounds can be stopped readily using an absorbable haemostatic dressing such as Surgicel (glucosic copolymer), Kaltostat (calcium alginate), Oxycel (oxidized cellulose) or Gelfoam (porous gelatin matrix), although the mechanism of action of these agents is poorly understood. These materials may behave like a foreign body while dissolving in the wound and increase the risk of infection, so large pieces should be removed before wound closure.

Chemical haemostatic agents [1] are effective on oozing skin wounds (e.g. after curettage and shave excision) but are ineffective in the presence of arterial bleeding, and should not be used in sutured wounds as they cause cell death, which predisposes to infection. Application should be followed by pressure on the wound for 2–3 min to allow haemostasis to occur without the chemical being washed away. Ferric subsulphate (Monsel's) solution carries the risk of iron tattooing [2]. Silver nitrate sticks are effective but caustic, and may leave scars. Aluminium chloride, either 35% in isopropyl alcohol or 20% in ethyl alcohol, is effective; occasionally, it causes histiocytic reactions in treated skin [3].

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Soft-tissue augmentation and facial line correction

The use of biocompatible materials to augment soft-tissue defects forms an integral part of a coordinated and planned approach to the management of the ageing face and rhytides. They can be used alone or in combination with botulinum toxin injections and peels. These materials may also be used to correct scars from conditions such as acne and chickenpox. A whole variety of materials is available [1], and patients for whom this type of treatment is being considered must be carefully evaluated and the techniques available discussed. Patients must be given realistic expectations. Some of the materials are biological or naturally occurring such as those based on collagen or hyaluronic acid—although they may be subject to complex manufacturing processes to produce the final material. Autologous fat can be used, although sometimes it does not persist, and there are currently over 60 autologous and synthetic products available. The choice of material will depend on the defect being treated, and requires a thorough knowledge of the aetiology of the defect and the materials available.

As fat is an autograft, *autologous fat implantation* (*microlipoinjection*) is potentially a useful method of soft-tissue augmentation, but it can only be placed subcutaneously. Fat injected into dermis does not survive [2]. The fat is harvested under tumescent anaesthesia using a syringe, via a wide-bore needle. Any contaminating blood is washed off and the fat reinjected using a 16–18-gauge needle. Intravascular injection, and infection, must be avoided. Microlipoinjection is used to increase lip size, obliterate age-related guttering on the hands, and in breast enlargement, melelabial sulci, idiopathic fat atrophy, after lupus profundus and for some acne scars, but cannot be used for small or superficial scars. Grafted fat persists for 1–2 years, although this varies with site and the cosmetic defect treated [3].

Bovine collagen (Zyderm I (35 mg/mL collagen) and Zyderm II (65 mg/mL)) has been used to correct superficial facial scars and wrinkles. The effect is temporary; after 6 months top-up treatment is required. Glutaraldehyde cross-linked collagen (Zyplast) was introduced with the aim of prolonging the effect, but appears to be little different [4]. Approximately 3% of patients react to the test injection [5]. Late allergic reactions are rare but may occur years after collagen injections [6,7]. Soft and distensible postoperative, chickenpox and acne scars respond well [8], unlike rigid fibrotic or ice-pick scars. Hyaluronic acid is also being developed for use in soft-tissue augmentation.

The use of permanent materials such as injectable medical grade *silicon* (polymerized dimethylsiloxane), *gelatin matrix implant* (*Fibrel*) and *polytetrafluoroethylene* (*Gore-Tex*) has lost favour because of permanent imperfect results and reports of inflammatory reactions [9,10].

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Lasers and flashlamps (intense pulsed light sources)

The term 'laser' is an acronym for *l*ight *a*mplification by *s*timulated *e*mission of *r*adiation. The first laser was developed by Maiman [1] in 1959, using a ruby crystal to produce red light of wavelength 694 nm. This was followed by the development of other laser systems, notably the neodymium:yttrium-aluminium-garnet laser (Nd:YAG) in 1961 [2], the argon laser in 1962 [3] and the carbon dioxide (CO_2) laser in 1964 [4]. Goldman *et al*. [5] established a role for lasers in dermatology by reporting the use of the ruby laser in the treatment of tattoos, the argon laser in the treatment of vascular lesions [6] and the Nd:YAG laser in the treatment of tattoos, port-wine stains and cutaneous malignancies [7]. In 1983, Anderson and Parrish [8] postulated the theory of selective photothermolysis, which has been applied in lasers and flashlamps to target chromophores such as haemoglobin and melanin, and treat superficial vascular malformations, tattoos and benign pigmented lesions. More recently, observations relating to light-assisted hair removal have been explained in terms of an 'extended theory of photothermolysis' [9,10]. Flashlamp technology is relatively recent, and produces high-intensity pulsed light in the 500–1200 nm range. Filters are used to remove shorter wavelengths where necessary.

Laser safety and laser–tissue interaction

Safety

Various safety measures are required to prevent accidents resulting from exposure to direct or reflected beams. These include the ignition of inflammable materials, including anaesthetic gases, and damage to the skin or eyes. Non-beam hazards include inhalation of the 'plume' arising from tissue destruction, contact with high-voltage electricity or fluid leakage from the laser cavity.

Physics

The generic name of a laser reflects the components of the solid, liquid or gas that constitutes its active medium and determines the wavelength(s) of the radiation produced. The beam may be continuous, pulsed or quality switched (Q-switched). Continuous wave light is a constant beam and has relatively low power. This can be interrupted to produce pulses with higher peak powers than in continuous mode and to allow cooling between pulses. Q-switching is a means of creating a very short pulse (nanosecond domain) with high peak power. The pulse width is varied so that it approximates the thermal relaxation time (see below) of the target chromophore.

The energy contained within light is expressed in joules and its fluence or energy density in J/cm^2. Power is the rate at which work is performed and is measured in Watts (W) or J/s.

The concept of selective photothermolysis has been applied to the removal of superficial vascular malformations, exogenous tattoos, certain benign pigmented lesions and hair. It postulates that light can be used to selectively damage or destroy a target chromophore if the following conditions are met.

1 Its wavelength is selected so that there is as big a difference as possible between the absorption coefficient of the target and the surrounding tissue.
2 The fluence is sufficiently high.
3 The pulse duration is less than or equal to the thermal relaxation time (TRT). The TRT is the time taken for the target to dissipate half of the incident thermal energy and is largely determined by the size of the chromophore. The TRT varies from a few nanoseconds (melanosomes) to several hundred milliseconds or more (leg venules).

It is likely that damage to large targets can be maximized by means of 'thermokinetic selectivity' [10]. Structures such as the hair follicle are relatively large but contain the same chromophore as smaller targets, in this example the melanosome, which one would want to protect during photoepilation. Because large structures cool slower than small structures, it is proposed that they reach higher and potentially damaging temperatures if the light source is manipulated appropriately. This is achieved by means of a pulse that is longer than the TRT of the epidermis and shorter than that of the follicle.

Some tissue targets, notably the hair follicle, are not uniform in their absorption of light, and it is possible that light-assisted hair removal is better explained by an 'extended theory of selective photothermolysis' [9]. This distinguishes between an 'absorber' chromophore (in which heat is generated) and a distant 'target', to which heat is transmitted and which is damaged as a result.

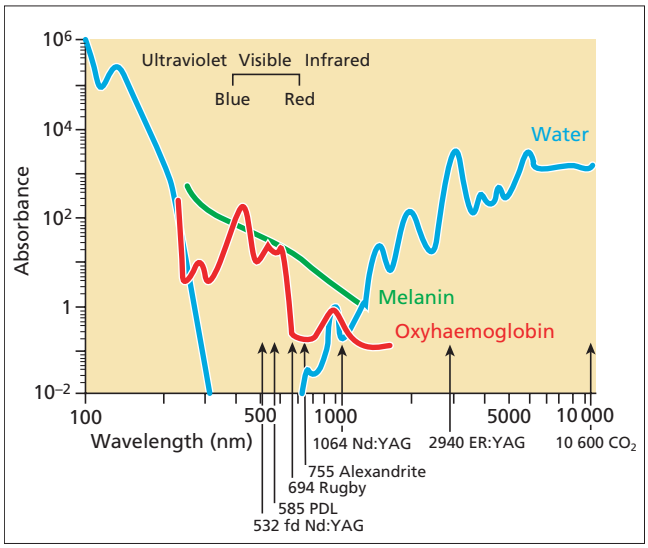

Fig. 77.4 Absorption spectra of principal tissue chromophores. (Reproduced with permission of Dr M. Waner.) Nd, neodymium; Er, erbium; YAG, yttrium-aluminium-garnet; PDL, pulsed dye laser; fd, frequency doubled.

The absorption spectra of important tissue chromophores are shown in Fig. 77.4 in relation to the wavelengths of the lasers widely used in dermatology [11]. As can be seen, haemoglobin has a number of different absorption peaks, whereas absorption by melanin diminishes in proportion to the wavelength of incident light. Consideration must also be given to the depth of the target structure and whether a long wavelength with deep penetration, albeit relatively poorly absorbed, may be preferable to a short wavelength with the opposite characteristics. In some situations, particularly in relation to melanin, a single wavelength may not be necessary and it may even be preferable to use flashlamps because of their broad emission spectrum (500–1200 nm). These are cheaper to manufacture than lasers and can be used with light filters (515–755 nm) to allow a potentially wide range of applications. It is possible to vary their pulse durations from 0.5 to 88.5 ms and to introduce intervals between pulses of 1–300 ms. At present they cannot substitute for lasers where focused high-energy beams are required.

Tissue cooling

Light wavelengths or spectra of 500–1200 nm are preferentially but not specifically absorbed by either haemoglobin or melanin, depending on the wavelengths employed. Epidermal melanin will therefore absorb both direct and back-scattered light from all such devices, whether or not it is the intended chromophore. Heat damage to the epidermis may result in blistering, dyspigmentation or scarring, and is particularly likely in pigmented skin. To reduce this risk, the wavelength should be optimized with respect to the absorption characteristics and depth of the target chromophore. Further enhancing safety in these patients is the use of long pulses [12] and cooling of the epidermis. The latter may be performed before, during or after the light pulse, or all three.

Cooling may take three forms:

1 *Cold air convection*. Air, chilled to temperatures as low as –30°C, is directed onto the area to be treated.

2 *Contact cooling*. This may involve simple application of ice-packs or more sophisticated systems that pass chilled water between colourless and transparent (usually sapphire) plates. Although a good method of cooling during light delivery, condensate on the plates can obscure the skin and require frequent wiping.

3 *Cryogen spray (dynamic) cooling*. A liquid cryogen is sprayed onto the skin immediately before the laser pulse. Evaporate cooling has a high heat transfer coefficient and this is therefore the most efficient way of precooling. With timed automated control this method is also relatively predictable and reproducible.

One important benefit of epidermal cooling has been to allow treatments at higher fluences than otherwise considered safe, and thereby to reduce the number of treatments required. It has also made possible or safer the treatment of patients with pigmented skin. Furthermore, cooling decreases the pain associated with treatment, thus reducing the need for topical or local anaesthetic. Cooling may, however, cause cryogen injury if used inappropriately.

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Laser treatment of vascular and pigmented lesions and hair removal

Vascular lesions

Light–tissue interaction

A wavelength of 577 nm was used in early pulsed dye lasers for selective photothermolysis of superficial blood vessels because of its highly selective absorption by oxyhaemoglobin [1]. This has been replaced with 585–600 nm light, which has the advantage of deeper dermal penetration, although with reduced absorption at the longer wavelengths [2]. A pulse duration of approximately 0.45 ms was included in the design of early pulsed dye lasers (PDLs), on the basis of a calculated TRT of less than 1 ms for vessel diameters of 10–50 μm. The theoretical models may have slightly underestimated the TRT, which was measured in a subsequent *in vivo* study as 1–10 ms for vessel diameters of 30–150 μm [3]. As a consequence, newer PDLs allow pulse durations of up to 40 ms. Another laser useful for vascular anomalies is the potassium titanyl phosphate (KTP) laser (532 nm), light from which is well absorbed but is most useful for very superficial vessels. The alexandrite (755 nm) and Nd:YAG (1064 nm) lasers emit light with longer wavelengths and therefore relatively deep dermal penetration, the latter absorbed by a low absorption peak at 900–1000 nm.

Devices in common use

Pulsed dye lasers (585–600 nm) 4.5 and 1.5–40 ms

These contain a rhodamine dye, which is excited by a xenon flashlamp to produce light at 585–600 nm in pulses of 4.5 ms (short pulse PDL) or 1.5–40 ms (long pulse PDL). Light penetrates the dermis to a depth of 1.2 mm [4] and photocoagulates vessels of up to 100 μm in diameter. Purpura is associated with the short pulse width, which causes cavitation and rupture of the capillary wall.

Neodymium:yttrium-aluminium-garnet laser (1064 nm)

Used with long pulses (up to several hundred milliseconds) and epidermal cooling systems, the Nd:YAG laser may have a role in treating relatively deep and large vessels, including those on the legs.

Frequency doubled Nd:YAG or potassium titanyl phosphate crystal laser (532 nm)

Nd:YAG laser emissions can be passed through a KTP crystal to double the frequency to 532 nm. They may be flashlamp or diode pumped and are characterized by trains of short pulses that summate to give a wide pulse effect which is not associated with purpura. Light produced by KTP lasers is highly absorbed by haemoglobin (and melanin) but its wavelength penetrates only superficially. They are widely used, with or without cooling devices, to treat small facial vessels and superficial hypermelanosis.

Intense pulsed light source (500–1200 nm)

This device emits non-coherent light over a broad spectrum. Filters are used to eliminate wavelengths shorter than selected thresholds. There is contact cooling and its potential advantages are the large spot size and reduced likelihood of purpura.

Superficial vascular anomalies

Haemangiomas

These almost always appear after birth and may grow for months. They are often managed conservatively because most regress, sometimes leaving redundant atrophic skin. Intervention may be warranted when functional impairment results from the site and/or size of the haemangioma or where psychological development in childhood is a major consideration. Treatment with the short pulse PDL has been reported to reduce size and colour in up to 67% of superficial haemangiomas. Early proliferative haemangiomas associated with functional impairment or surface ulceration may respond to laser treatment with a reduction in size, together with improvement in the colour and integrity of overlying skin [5]. On the other hand, a randomized controlled study of 121 infants with early haemangiomas showed no advantage to PDL treatment over observation alone [6]. Where appropriate, treatment can be attempted with systemic corticosteroids, interferon or vincristine.

Port-wine stains, or capillary malformations

These may become thickened and darker because of progressive vascular ectasia. The 585 nm short pulse PDL is probably the treatment of choice for paediatric port-wine stains because vessel diameters are relatively small [7]. At 585 nm, the absorption coefficient of haemoglobin is a factor of five higher than at 595 nm and, used in conjunction with the long pulse, may be most suitable for resistant or adult port-wine stains (Fig. 77.5) [8]. Very exophytic lesions are probably best treated with the CO_2 laser [9]. Factors favouring a good response to PDL treatment are youth as well as flat and scarlet (as opposed to purple) port-wine stains on the head and neck (excluding the cheeks or midline) [10,11]. The use of spray cooling with higher fluences in both short [12] and long pulse (1.5–4.0 ms) [13] PDL has considerably expedited treatment of

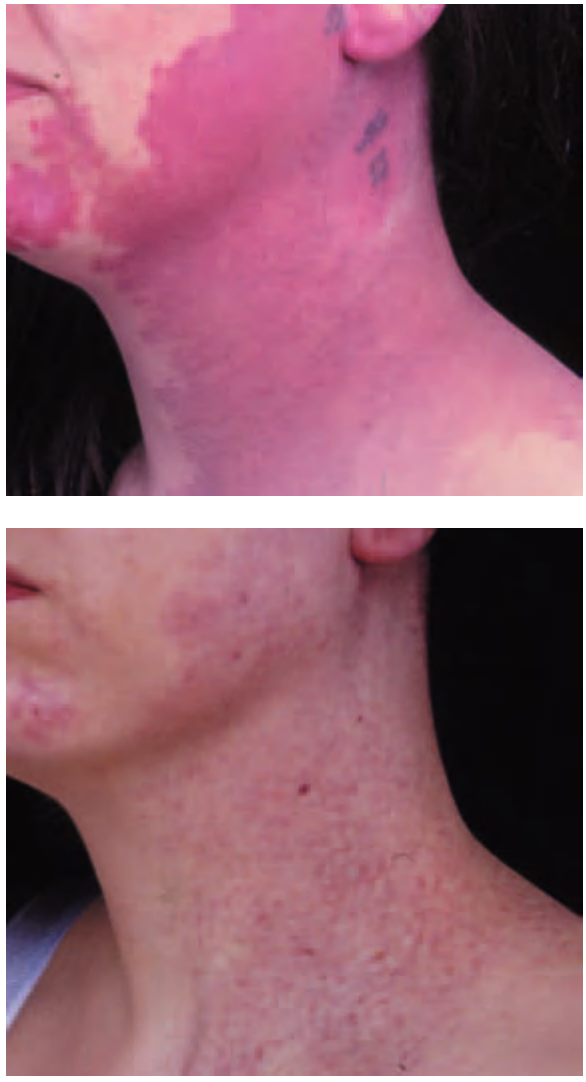

Fig. 77.5 Port-wine stain: (a) before, and (b) after treatment with a pulsed dye laser, showing considerable but incomplete lightening and polka dot patterning.

port-wine stains. Lesions immediately become purpuric if treated with adequate fluences and pulse durations of 10 ms or less. Although reduced by both cooling and long pulsing, a degree of post-treatment purpura formation is thought to be necessary for effective treatment of lesions [14]. Partial re-emergence may occur after successful treatment [15]. Flashlamps have also been used to treat port-wine stains with good effect [16].

Telangiectasiae

These are acquired capillary malformations and may occur in association with photoageing or as part of rosacea and erythrodysaesthesia. Although they respond to conventional PDL treatment [17,18], there is associated bruising and often subsequent 'polka dot' patterning. Treatments

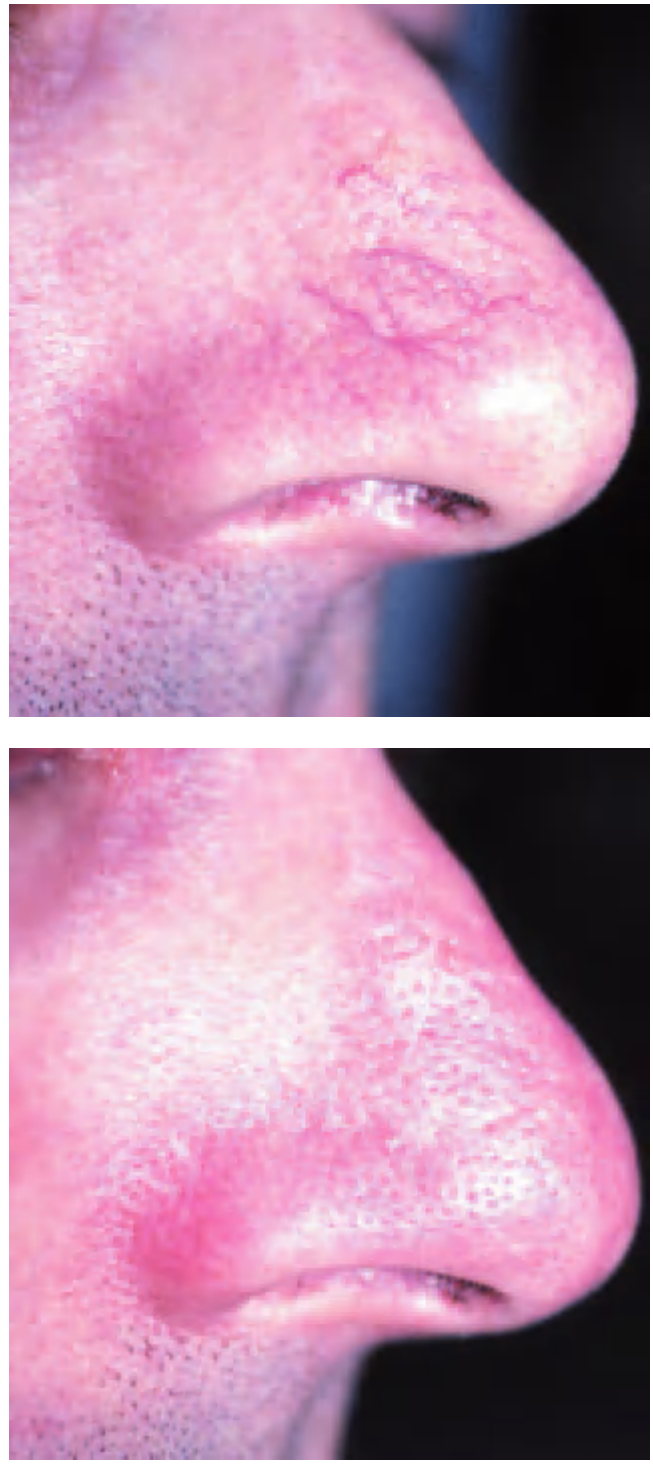

Fig. 77.6 Large nasal telangiectasiae: (a) before, and (b) immediately after KTP laser treatment, showing disappearance of vessels and absence of bruising.

with longer pulses and subpurpuric fluences are cosmetically preferable and may also be effective. Vessels can be treated individually (Fig. 77.6) or in groups, using small and large diameter KTP laser spot sizes, respectively

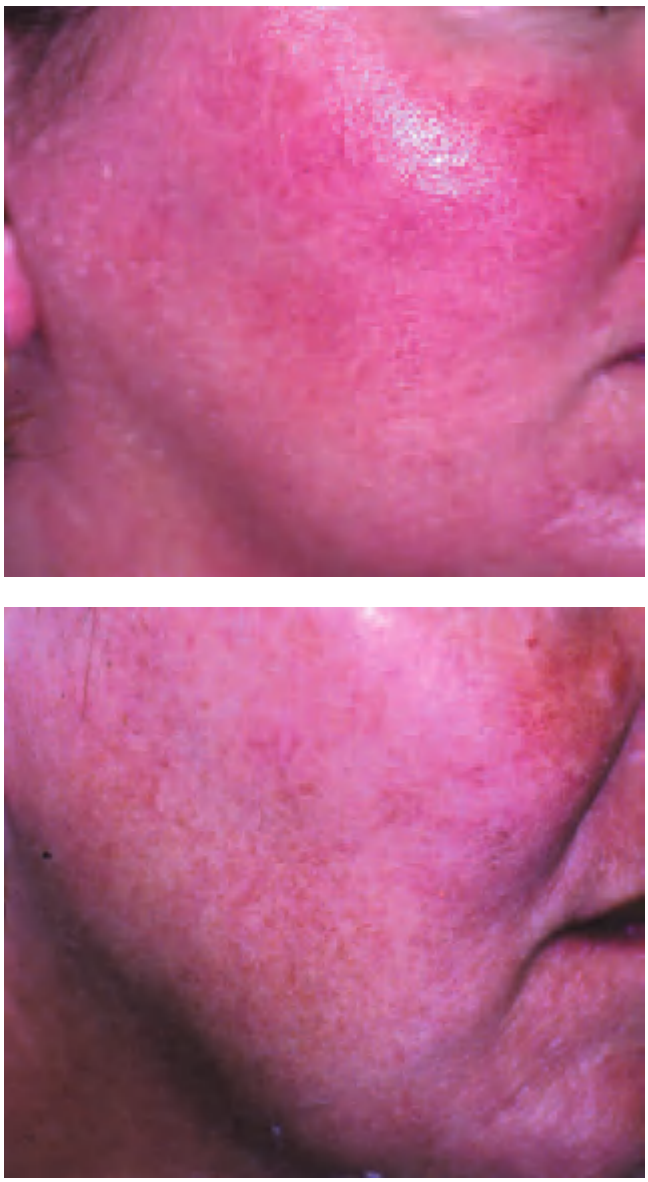

Fig. 77.7 Fine cheek telangiectasiae: (a) before, and (b) after one treatment with a flashlamp.

[19]. Flashlamps are an alternative non-bruising modality (Fig. 77.7), although several treatments may be required [20].

Leg venules

These are best treated by sclerotherapy because of their relatively high hydrostatic pressure and because of their depth and large size. If sclerotherapy is contraindicated, these vessels should respond best to large spot sizes (3–4 mm), high fluences (relative to wavelength) and long pulse durations, used in conjunction with effective cooling devices. Wavelength should be chosen according to the depth of the target vessel. Accordingly, long pulse (1.5–4.0 ms) PDLs were developed with wavelengths in the 585–600 nm range and, used with fluences of 7–9 J/cm^2 [21,22], may sometimes be useful for superficial vessels less than approximately 0.5 mm in diameter. Longer wavelengths are used to target a different absorption peak of haemoglobin and achieve deeper penetration. The 3-ms alexandrite laser (755 nm), used with a fluence of 86 J/cm^2, has been reported to clear as many as 75% of leg vessels less than 3 mm in diameter [23]. Nd:YAG lasers with fluences higher than 100 J/cm^2 and with pulse durations of up to 1 s may be useful for larger vessels [24]. However, complications are common and include ulceration, dyspigmentation and scarring. The current consensus seems to be that laser therapy should be considered for patients in whom sclerotherapy is undesirable or contraindicated and who have small superficial single vessels. There are few data on the efficacy of the intense pulsed light source in this context but its emission spectrum and large applicator head would suggest a role in treating widespread fine telangiectasiae. Other cutaneous vascular lesions that have been reported to respond to laser treatment include venous lakes, angiofibromas, angiokeratomas and pyogenic granulomas [25,26].

Topical anaesthesia is usually satisfactory for treating facial lesions in adults but local or regional anaesthesia may be required. Treatment in other anatomical sites can usually be tolerated with topical or no anaesthesia. Depending on the size and site of the lesion, children under 12 years of age may need treatment under general anaesthetic. Emollients and analgesics relieve postoperative pain, swelling and erythema. Some patients develop crusting of the treated area. Complications resulting from PDL treatment include infection, dyspigmentation and both atrophic and hypertrophic scarring. Test treatments have been reported to be poor predictors of outcome.

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Other applications

Viral warts

PDLs are used to treat viral warts [1]. The rationale for this seems to be that photocoagulation of the underlying dermal vessels may compromise the viability of the abnormal epidermis [2]. Treatment of resistant warts, particularly if on plantar surfaces, is often only partly successful [3], in which case CO_2 laser ablation may be more effective, despite the greater likelihood of pain, infection and scarring [4].

Hypertrophic scars

PDLs have been reported to improve the colour and contour of erythematous and hypertrophic scars in studies that have sometimes been supported with objective measurements such as reflectance spectrometry and silicone profilometry [5]. The mechanism of action is unknown, although it is also possible that destruction of small vessels plays a part [6].

Psoriasis

Localized and resistant plaque psoriasis has been reported to respond in 21 patients who were treated at 2-week intervals with both the short and long pulse 585 nm PDL. No significant difference was found between the two lasers and 40% of treated areas were reported to be clear of psoriasis at 6 months postoperatively [7]. Although non-toxic, treatment is often painful and can cause dyspigmentation and scarring.

Narrow-band UVB treatment can also be administered to psoriatic patients by means of a 308-nm excimer laser, the advantages of which are sparing of uninvolved skin and fewer treatments than with conventional phototherapy [8].

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Tattoos and benign pigmented lesions

Laser–tissue interaction

Melanin absorbs light in the 500–1200 nm range (Fig. 77.4). At the shorter wavelengths absorption is higher and penetration less deep than the longer wavelengths. The Q-switch is an electro-optical device that is used to produce pulses of only a few nanoseconds. These are designed to be within the estimated TRT of melanosomes (0.5–1 μs) [1], although longer than that of tattoo particles, which is in the picosecond domain. Flashlamps can pulse within a millisecond range, which is relatively long in this context. Light may fragment and disperse melanin and tattoo ink, thereby altering its optical properties. It also seems likely that some is removed by transepidermal elimination and some by lymphatic drainage [2].

Devices in common use

Q-switched Nd:YAG laser (1064 nm) and frequency doubled Nd:YAG laser (532 nm)

The Q-switched Nd:YAG laser emits light that penetrates

2–3 mm into the dermis and is therefore suitable for the removal of deeper dermal pigmentation [3]. By passing the beam through a KTP crystal, the frequency is doubled and the wavelength halved (532 nm). The shorter wavelength penetrates less deeply and is therefore more useful for the removal of epidermal pigment.

Q-switched ruby laser (694 nm)

This laser emits red light (694 nm), which penetrates less than 1 mm into skin [4] but is better absorbed by melanin than longer wavelength light.

Q-switched alexandrite (755 nm) and diode lasers (810 nm)

These also emit red light at intermediate wavelengths, allowing somewhat deeper dermal penetration, although with some loss of absorption.

Intense pulsed light source (500–1200 nm)

These emit non-coherent light over a broad spectrum, with potential advantages in terms of penetration and absorption.

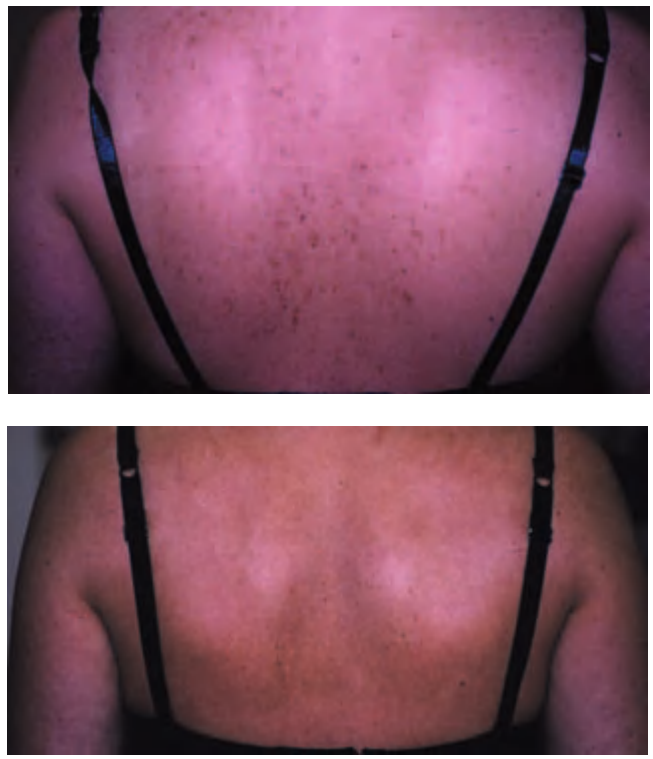
Tattoos

Q-switched treatment of tattoos is cosmetically superior to older destructive modalities [5]. Black or blue tattoo pigments absorb radiation across a broad range of wavelengths in the visible and near infrared spectrum. Green inks respond optimally to the Q-switched ruby (694 nm) [6] and Q-switched alexandrite (755 nm) lasers, but often persist [7]. Conversely, red pigments respond best to the green light emitted by the frequency doubled Nd:YAG laser (532 nm) [8]. The Nd:YAG laser is effective for blue or black tattoos but is relatively poorly absorbed by green pigments [9]. It has been successfully used to treat tattoos in pigmented skin [10]. Red, brown or flesh-toned inks may contain iron oxide or titanium oxide and can oxidize to a slate-grey or black colour during laser treatment. This may be exacerbated with subsequent treatments [11]. As these pigments may be used in cosmetic camouflage, tattoo test patches are important. Yellow and pastel colours are difficult to treat and complete resolution is unusual. Amateur tattoos usually require fewer treatments than professional tattoos [12].

Benign pigmented lesions

Epidermal pigmentation

Ephelides (freckles) and lentigines respond quickly and well to treatment with the Q-switched KTP (532 nm)



(a)

(b)

Fig. 77.8 Ephelides: (a) before, and (b) after treatment with a fd Q-switched Nd:YAG laser.

(Fig. 77.8) and Q-switched ruby laser (694 nm), although the former may bruise [13]. There are limited published data on the use of the intense pulsed light source in this context. Its emission spectrum and large beam diameter would suggest a useful role, even if the pulse width seems relatively long. Café-au-lait patches usually lighten in response to lasers, but pigmentation sometimes recurs.

Dermal pigmentation

In a study in which six patients with speckled and lentiginous naevi (naevus spilus) were treated with both a Q-switched ruby and Q-switched Nd:YAG laser, all showed 90% or greater clearance of the lesion after 1–5 treatments, the Q-switched ruby laser being the more effective. One patient is reported as showing transient hypopigmentation and another as developing hyperpigmentation peripheral to the treated lesion [14].

Naevus of Ota has been treated with the Q-switched ruby [15], alexandrite [16] and Nd:YAG lasers [17]. As might be expected, the relatively deep dermal pigmentation responds optimally and with fewer complications to treatment with the Q-switched Nd:YAG laser [18,19]. In some patients, pigmentation may re-emerge after treatment [20].

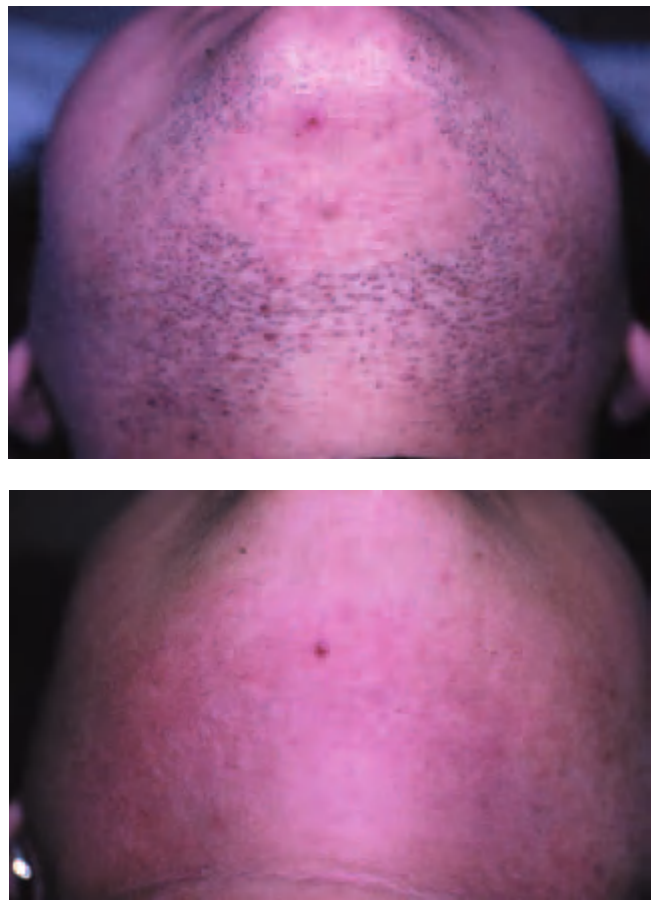
Both congenital and acquired melanocytic naevi have been treated with argon, ruby [21,22], alexandrite and

Nd:YAG lasers, although this remains controversial. The long-term effects of non-lethal laser irradiation on melanocytes are unknown, as is laser 'debulking' of congenital melanocytic naevi (CMN). Even after multiple treatments of CMN, many lesions repigment. In a study in which 31 CMN and clinically benign or atypical moles were treated with the Q-switched ruby laser, normal mode ruby laser or both, only 16 were visibly lighter 4 weeks after treatment. Subsequent excision for histological examination showed fibrosis and a decrease in melanocytes [23].

The Q-switched ruby laser appears to be ineffective in treating lentigo maligna and at least one such lesion has subsequently developed lentigo maligna melanoma [24]. It may also be relevant that *in vitro* studies of melanoma cells treated with Q-switched lasers have demonstrated an altered expression of cell surface receptors as well as altered cell migration [25]. Melasma does not in general respond to laser therapy and, as with post-inflammatory hyperpigmentation, laser therapy may darken lesions [26]. Haemosiderin seen in association with venous stasis will only occasionally respond to laser treatment [27]. Hyperpigmentation secondary to administration of minocycline [28,29] and amiodarone [30] responds readily to treatment with the Q-switched ruby, alexandrite and Nd:YAG lasers.

Light-assisted hair removal

The mechanism for light-assisted hair reduction remains incompletely understood. It is likely that the theory of selective thermolysis applies in this context. However, the targets are likely to be stem cells (mainly in the lower isthmus) and blood vessels in the papilla, whereas the absorbing chromophore is melanin in the hair shaft and matrix cells. For this reason, fair or white hair is largely resistant to treatment. Radiation in the 600–1200 nm spectrum is absorbed by melanin and penetrates the dermis further at longer wavelengths. The normal mode ruby (694 nm), alexandrite (755 nm) (Fig. 77.9) [31], diode (800 nm) [32] and Nd:YAG (1064 nm) [33] lasers have all been used with fluences of 20–60 J/cm^2, depending on spot size. The TRT of a 200–300 μm follicle is approximately 25–50 ms, but much shorter pulse durations seem to be effective. In an early study, follicular damage was demonstrated using a ruby laser (6 mm spot, 30–60 J/cm^2) with a pulse duration of only 270 μs. Six months later only four had less than 50% regrowth and five showed complete regrowth of hair [34]. These results were maintained at 2-year follow-up, suggesting that permanent loss of terminal hair is possible after one treatment with the normal mode ruby laser, albeit in a minority of patients [35]. Immediate follicular disruption has been shown to be followed by conversion of the anagen to the telogen phase with a subsequent increase in the number of miniaturized hair follicles.



(a)

(b)

Fig. 77.9 Hirsutism on the neck of a female patient: (a) after a test treatment, and (b) after four treatments with a normal mode alexandrite laser, showing sparser and finer hairs.

It has recently been demonstrated that considerably longer pulses (30–400 ms) may be more effective in damaging the stem cells and papillary vessels, neither of which contains melanin nor is in direct contact with the melanin-rich components of the follicle. This observation has been explained in terms of an 'extended theory of selective photothermolysis' [36]. By using long pulses and by limiting the power of the light source, the heat generated by the 'absorber' (melanin in the hair shaft) can be kept below levels that would alter its structural and optical properties and thus interfere with further absorption of light. On the other hand, the heat generated may be high enough to diffuse into and denature the distant 'target' (the stem cells and papillary vessels). The delay between heating of the absorber chromophore and the distant target is referred to as the thermal damage time (TDT) and is significantly longer than the TRT.

In patients with pigmented skin, long wavelengths (1064 nm) and cooling devices are particularly important in reducing the risk of epidermal damage, with subsequent dyspigmentation or scarring. A small proportion of patients seem to experience a paradoxical increase in hair growth.

Flashlamps have been used to treat hypertrichosis [37] but it seems likely that subsequent blistering and dyspigmentation is more common than after laser treatment.

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Laser resurfacing and non-ablative resurfacing

Cutaneous ablation [1,2]

Light in the mid and far infrared region of the spectrum is rapidly absorbed by water and therefore by body tissue. There is no selectivity of effect. When the light strikes the body tissue, the cells are vaporized almost instantaneously. Although vaporization is limited to those cells immediately in the path of the beam, there is a narrow band of thermal damage around the treatment site whose width depends on the laser type, the power density and the exposure times. The CO_2 laser was the first laser to be used extensively in this way. Although initially the outcome could be compromised by unwanted thermal damage and scarring, this risk has been markedly reduced by the development of a variety of scanning devices. The CO_2 laser is the archetypal surgical laser. Using a high-power density, via a focusing handpiece, the depth of an incision is controlled by the speed with which the beam is moved over the surface, enabling excisions to be performed as easily as with a scalpel. Lower densities are now achieved by using a scanner, and this allows a variety of skin lesions to be treated (Table 77.6).

Resurfacing

The development of scanning systems has allowed the

Table 77.6 Some therapeutic applications of carbon dioxide laser radiation.

Keloids
Seborrhoeic keratoses
Epidermal naevi
Tumours
Warts, condylomas
Cheilitis
Tattoos

CO_2 laser to be used to treat extensive areas of skin damaged by photoageing or scarring, with good results [3,4]. This procedure is associated with prolonged morbidity, and lasers with even higher tissue absorption (erbium:YAG, 2940 nm), and therefore even less dermal damage, may offer advantages. Initial results were often disappointing when compared with the results following CO_2 laser treatment, but the introduction of newer modulated erbium:YAG lasers has led to an improvement in clinical results [5]. Furthermore, using the erbium:YAG laser to remove the thermally damaged layer following CO_2 laser treatment speeds healing and may improve the outcome [6].

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Non-ablative skin remodelling [1,2]

Although cutaneous 'resurfacing' can produce significant improvement in sun-damaged skin and scarring, this is not without a cost in terms of discomfort, a long period of recovery and significant risks. A number of lasers, intense pulsed light sources and radiofrequency devices are being investigated for their potential to improve sun-damaged, aged and scarred skin [3]. Studies using serial treatments at intensities that induce no more than a mild erythema lasting a few hours, have shown measurable improvement in vascular and pigmentary irregularities. There are some reports of improvements in fine wrinkles, although objectively the improvement is mild. There is a vast literature on the use of lasers for biomodulation and it is interesting that some of the studies of non-ablative skin remodelling show improvement at low intensities which is absent at higher ones [4]. As these technologies develop, they may find a place in the routine management of ageing skin in communities where this is considered a worthwhile use of resources.

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Photodynamic therapy

Photodynamic therapy (PDT) is based on a mechanism whereby topical porphyrin precursors are converted by skin cells into porphyrin, and light exposure activates the porphyrin, producing oxygen radicals which cause cell death. It has been used in the treatment of non-melanoma skin cancer.

5-Aminolevulinic acid (ALA) is a porphyrin precursor. When applied to the skin, ALA is absorbed and converted by intracellular enzymes, maximally 3–5 h later, to photoactive protoporphyrin IX. Protoporphyrin generates cytotoxic singlet oxygen when irradiated with non-coherent and coherent (i.e. laser) light sources in the 400–640 nm range. Some reports suggest that protoporphyrins are concentrated in tumour cells [1], others show no difference between tumour and normal perilesional skin porphyrin fluorescence [2]. Overall it seems likely that at most the porphyrin concentration in BCC is approximately twice as great as that found in adjacent uninvolved skin. These differences could be due to enhanced absorption through a defective overlying stratum corneum, hence the use of surface débridement before porphyrin precursor application.

Currently, although ALA, a naturally occurring haem precursor, is the most promising topical sensitizer [3], it is hydrophilic and this property may limit its penetration into thick BCCs. Lipophilic esters of ALA, e.g. methyl 5-aminolaevulinate, may be better [4]. Photosensitizers can be injected, e.g. meta-tetrahydroxyphenylchlorin [5], but this renders the patient temporarily photosensitive.

The tumour surface is scraped to remove crust or scale. A thick layer of porphyrin precursor cream is applied to the affected area plus a 5-mm margin of perilesional skin and covered with an adhesive occlusive dressing for 3–6 h. The area is then irradiated using a light source that contains 630-nm red light to coincide with the maximal absorption peak of protoporphyrin IX. Red light also has the advantage of penetrating more deeply into the skin than lower wavelengths. Treatment time is around 15 min for a non-laser source. The process is painful but most

patients do not require injected local anaesthetic. The inflammatory reaction begins to appear almost immediately and discomfort may persist for 1–2 weeks. Complete healing takes 2–6 weeks. A second treatment is commonly given 2–3 months later if the first appears to have failed.

Bowen's disease and actinic keratoses

Thin *in situ* epidermal malignancies respond well with fewer side effects than are experienced after cryotherapy [6] or 5-fluorouracil (5-FU) therapy [7]. In comparison with these techniques, however, PDT is less easy to use over large areas.

BCC

In general, PDT is an unproven treatment for BCC. Most studies are small, give only 1–2-year follow-up and prefer to report cure rather than recurrence rates. PDT, using ALA, appears to work best on thin superficial BCCs, producing recurrence rates of around 10% [8–11]. Longer follow-up reveals a higher recurrence rate [12]. ALA penetrates BCCs > 2 mm thick poorly [13], resulting in high recurrence rates [14]. A recent randomized small study treating nodular BCCs showed a 10% 2-year recurrence rate after PDT compared with 2% for surgery. The poor results have led others to try two treatments 7 days apart [15], or use the lipophilic methyl 5-aminolaevulinate for PDT after first debulking the tumour by curettage [16]. These manoeuvres have not significantly improved the recurrence rates.

PDT is potentially a treatment option for large superficial BCCs or patches of Bowen's disease. However, as yet there is no convincing evidence that PDT is more cost effective than simple surgery, topical 5-FU, cryotherapy or superficial X-ray therapy for these lesions. PDT has the potential for fewer long-term side effects and better cosmesis. There is insufficient long-term cure rate evidence to justify its routine use in thick or nodular BCC.

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Chapter 78

Dermatological Surgery

C.M. Lawrence, N.P.J. Walker & N.R. Telfer

Introduction

The acquisition of basic dermatological surgery skills is an important component of dermatological training. This chapter covers simple excisional surgery and provides an introduction to more advanced techniques that dermatologists should be aware of and may practice. The reader is also referred to the specialist journal *Dermatologic Surgery*, and introductory [1–3] and intermediate textbooks [4–6]. Other books deal more specifically with cosmetic dermatological surgery [7,8] or general aspects of plastic surgery [9–11].

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Critical anatomical areas

It is essential to have a working knowledge of the important clinical anatomy of each operation site. The following is only a brief introduction to some of the critical anatomical details with which the operator must be familiar. Excisions down to superficial fat will rarely result in exposure of or potential damage to functionally important structures, except in a very thin subject. Incisions to deep fat or fascia and the removal of large cysts or lipomas may result in exposure of important structures. On the head and neck, division of larger arteries and veins will not cause vascular complications because of the extensive collateral circulation. However, it is important to be aware of the position of large arteries and veins in order to be prepared to deal with bleeding from these vessels. Division of sensory nerves may produce annoying sensory loss, but this will have little functional impact on the head and neck. Knowledge of the anatomy of the supraorbital, infraorbital and mental sensory nerves is important, as these are commonly used in peripheral nerve blocks.

Division of motor nerves is potentially disabling and thus it is essential to know the anatomy of the vulnerable superficial cranial and peripheral motor nerves.

Skin tension lines and the orientation of scars

Incisions should be designed to follow the wrinkles or relaxed skin tension lines (syn. stress lines; favourable skin tension lines; maximal skin tension lines) as the resulting scars will be stronger and less likely to stretch [1]. Relaxed skin tension lines run perpendicular to the direction of contraction of the underlying muscles and parallel to the dermal collagen bundles [2]; cutting transversely across these weakens the skin much more than a cut running parallel to the collagen bundles [3]. In the absence of wrinkles, relaxed skin tension lines can be identified by asking the patient to grimace or by skin manipulation. Langer's lines [4] (syn. resting stress lines) were mapped on cadaver skin, and differ from relaxed skin tension lines on the limbs and trunk [3]; they should not be used for identifying the elective direction of excision.

Head and neck

Cosmetic units

Cosmetic results of surgery are better if all the incisions remain within a cosmetic unit [5]. These are areas of skin that share similar characteristics (e.g. the nose, cheek and periorbital skin). The junction lines separating these areas are also important because scars placed in junction lines are usually unobtrusive whereas scars that cross a junction line (bridge two cosmetic units) are very obvious. It is thus important to try to design a repair so that the scars follow relaxed skin tension lines and remain within the same cosmetic unit, or run in the junction lines between two adjacent cosmetic units.

Blood vessels and lymphatic supply of face

Larger vessels, particularly the temporal artery, can be avoided by hydrodissection (see p. 78.32). The facial artery (Fig. 78.1) at the nasolabial fold, and its continuation into the angular artery at the medial canthus, are frequently divided when excising tumours at these sites. The external jugular vein runs under the platysma muscle but on top of the sternocleidomastoid muscle, and may be easily damaged during superficial incisions on the neck at this site (Fig. 78.2a). Emissary veins, connecting the intracranial and extracranial venous circulation, run across the subgaleal space towards the back of the scalp (parietal emissary vein) and just above the forehead (frontal emissary vein) [6]. These veins may be damaged when undermining the subgaleal space at these sites. Lymphatic drainage sites should be examined for metastases during follow-up of patients treated for squamous cell carcinoma or melanoma [7]. Division of skin lymphatics during incisions under the eye may result in temporary but unavoidable lower eyelid lymphoedema. Postoperative lymphatic leakage sometimes occurs after lower limb or axillary excision. This resolves spontaneously with conservative management.

Sensory nerves of face

Nerve blocks. Sensation to the face is supplied by the trigeminal (Vth) cranial nerve. The three branches readily blocked in skin surgical procedures on the head and neck

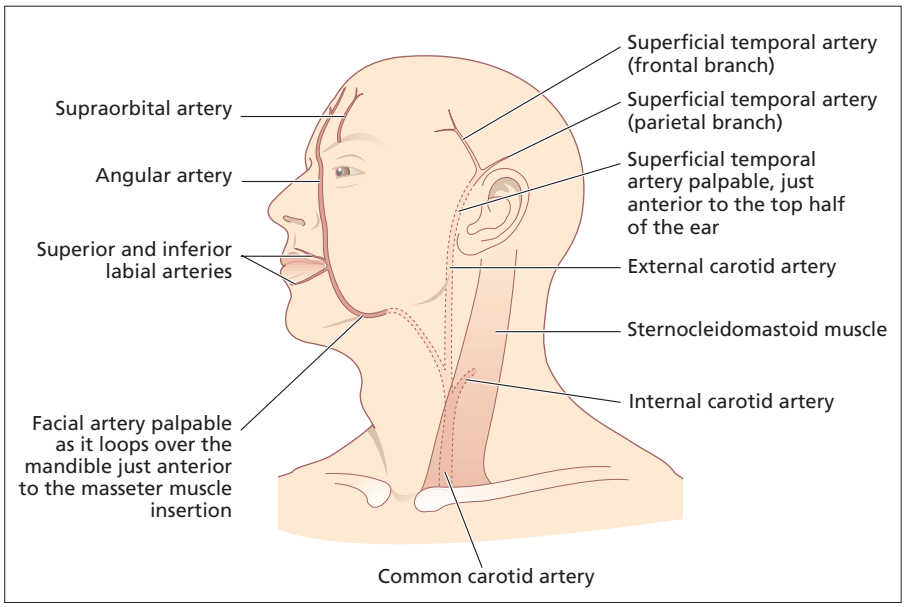

Fig. 78.1 Arteries of the head and neck encountered in skin surgery. The labial artery lies on the inside (mucosal) surface of the lip approximately 5 mm from the visible vermilion border. (---) Arteries rarely encountered; (—) arteries frequently identified during superficial skin surgery on the face.

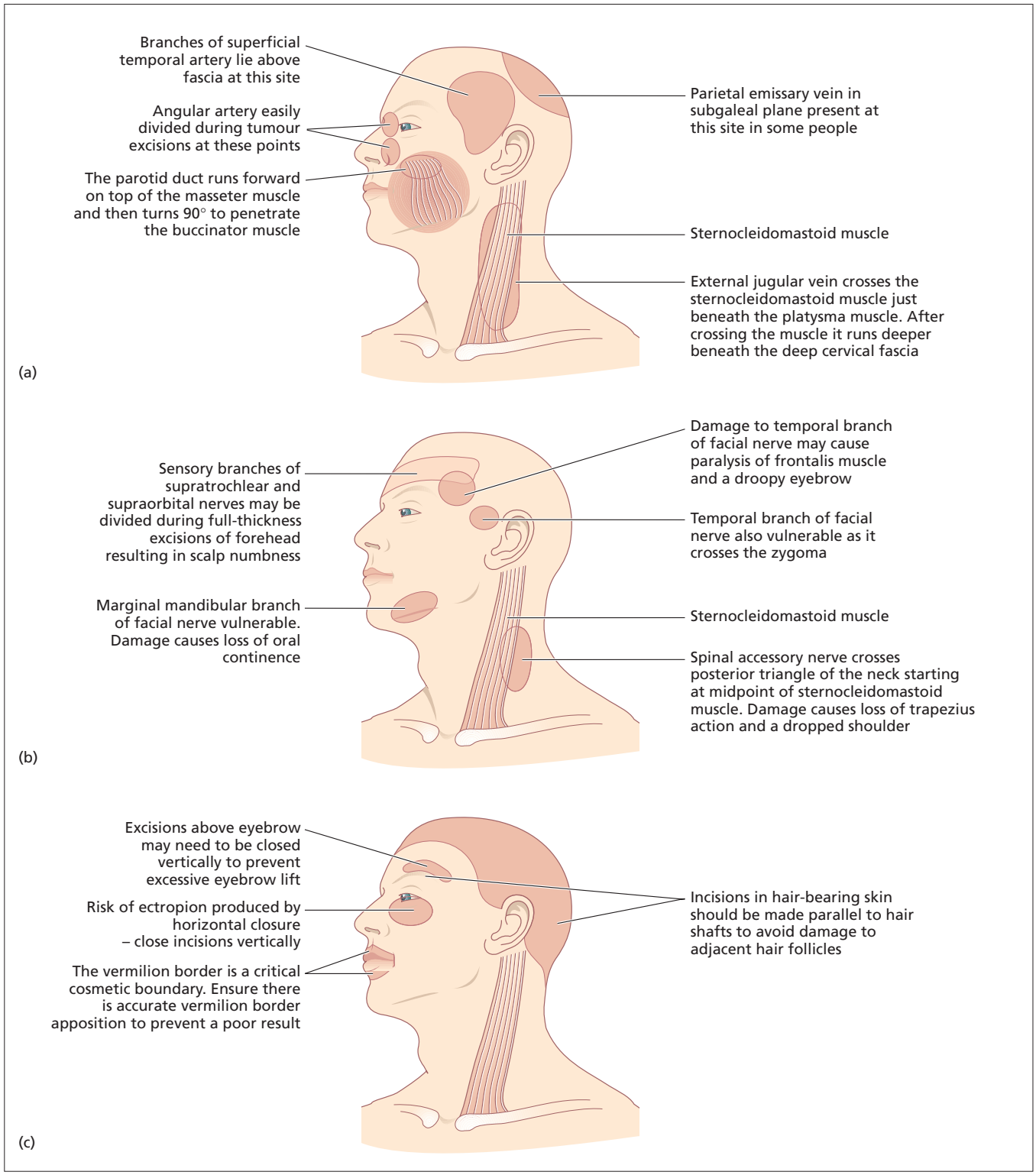

Fig. 78.2 Potential surgical hazard sites during skin surgery on the head. (a) Potential blood vessel and duct, (b) nerve and (c) cosmetic hazards on the head and neck. (From Lawrence [9].)

include the supraorbital, infraorbital and mental nerves (Fig. 78.3). These emerge from the skull via palpable foramina, which all lie in the same plane, just medial to a vertical line running through the pupil [8]. Blocking the great auricular, transverse cervical and lesser occipital

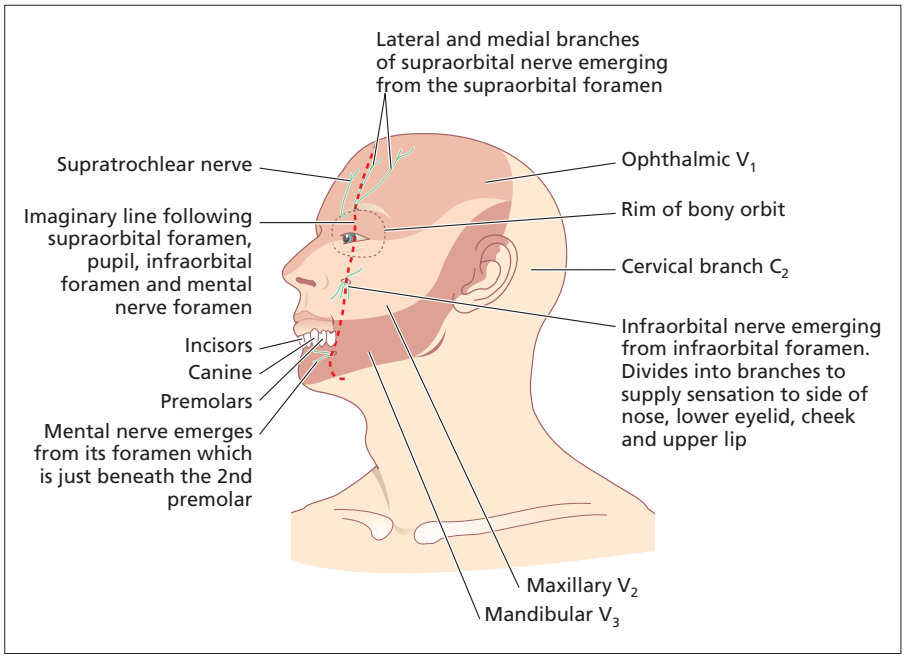

Fig. 78.3 Sensory nerves on the face used in nerve-block anaesthesia. Sensation on the face is served by the three main divisions of the trigeminal nerve: the ophthalmic, maxillary and mandibular divisions. Three important branches of these nerves—the supraorbital, infraorbital and mental nerves—emerge in the same plane along a vertical line running through the pupil.

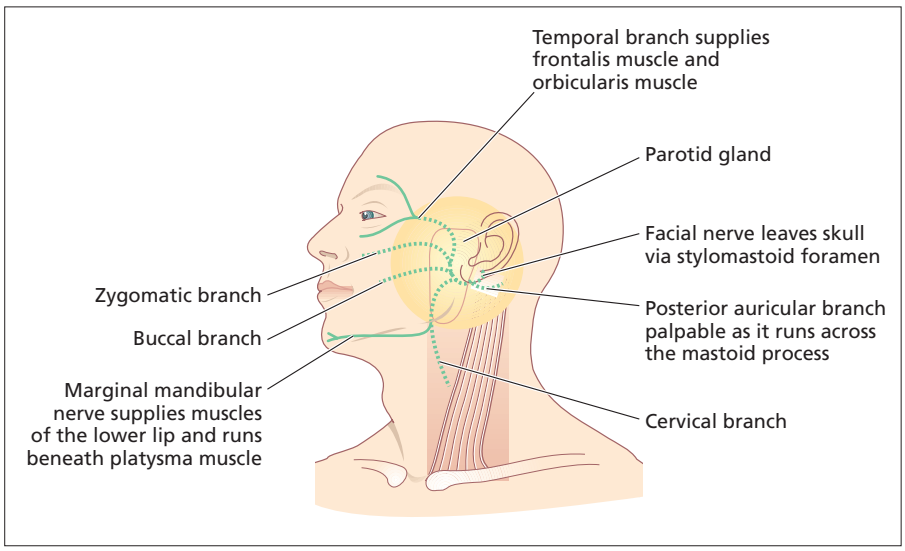

Fig. 78.4 Motor branches of the facial nerve vulnerable in skin surgery. (---) Nerves rarely encountered; (—) nerves at risk during superficial skin surgery on the face.

nerves as they emerge, approximately 10–20 mm above and below Erb's point, from the posterior border of the middle third of the sternocleidomastoid muscle [10] produces anaesthesia of a large portion of the scalp, neck and ear. Erb's point is identified by dropping a plumb line from the mid point of a line drawn between the mastoid process and the angle of the jaw. Where this line meets the posterior border of the sternocleidomastoid muscle is Erb's point. At this site, the spinal accessory (XIth) cranial nerve also emerges from behind the sternocleidomastoid muscle. This motor nerve is rarely affected by the local anaesthesia, as it lies deeper, on the floor of the posterior triangle, whereas the three named sensory branches of the cervical plexus curl round to lie on top of the sternocleidomastoid muscle [11].

Division of small sensory nerves. This is of little consequence, with the possible exception of scalp numbness following incisions on the forehead. Improvement in sensory loss can be expected for up to 1 year.

Motor nerves

Two branches of the facial (VIIth) cranial nerve, the marginal mandibular branch and the temporal branch, are vulnerable during skin surgery (Fig. 78.4). The temporal branch of the facial nerve supplies the frontalis and orbicularis muscles. Damage to the nerve supplying frontalis muscle results in difficulty raising the eyebrow, and the forehead furrows disappear. This can easily occur during excision of large tumours on the temple, lateral to the

Table 78.1 Undermining levels.

Site	Undermining level
Face	Mid-fat
Nose	Just above the periosteum and perichondrium
Forehead	Beneath the deep frontalis fascia (equivalent to the subgaleal plane)
Scalp	Subgaleal plane
Trunk and limb	
Small excisions	Deep fat
Large excisions	Just above the deep fascia

frontalis muscle, and as the nerve crosses the zygomatic arch. At both sites there is little tissue between the skin and periosteum (Fig. 78.2b). The marginal mandibular branch innervates muscles that move the lower lip. Damage can be devastating because it results in weakness of the lips, with dribbling when eating and drinking. The nerve is superficial and vulnerable as it emerges from under the parotid gland at the angle of the jaw, behind the point where the facial artery can be palpated as it crosses the mandible. More anteriorly, the nerve runs beneath the platysma muscle [12]. Variations in nerve position with age and neck position must also be considered. The remaining branches of the facial nerve are less vulnerable because they share several cross-connections and lie deeper. The other important motor cranial nerve is the accessory (XIth) nerve, which supplies the trapezius and sternocleidomastoid muscles. This may be damaged during dissection in the posterior triangle of the neck, causing weakness of the trapezius muscle and producing a dropped shoulder.

Undermining levels

When undermining to increase skin mobility, different levels are appropriate at different sites (Table 78.1).

Specific facial sites

If an incision runs across the vermilion of the *lip*, the vermilion border must be carefully marked before anaesthetic injection to avoid a poor cosmetic result (Fig. 78.2c). In older patients with poor lid elasticity, operations around the *lower eyelid* may result in ectropion if any downwards tension is applied to the lower eyelid. In a patient with poor lid elasticity, the procedure should be designed to increase rather than reduce eyelid tension; this usually means closing the wound vertically rather than horizontally. If an incision goes across the *hair line*, ensure that the scalp margin is reconstructed so that a smooth contour remains. Because hairs grow obliquely through the skin, any incision through *hair-bearing skin* should be made parallel to the hair shafts rather than vertically through the scalp so that fewer follicles are damaged.

Limbs

The only superficial motor nerve on the limbs is on the lateral aspect of the knee, where the common peroneal nerve (lateral popliteal) can be palpated against the bone as it winds round the neck of the fibula. Injury to the nerve at this site will produce a foot drop resulting from paralysis of foot dorsiflexors and elevators.

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Equipment and sterilization [1–5]

Most dermatological surgical procedures can be safely performed in well-lit dedicated outpatient units using relatively simple equipment and surgical instruments [1–3]. However, the absence of a need for either expensive equipment or a completely sterile environment does not justify cutaneous surgery being performed in inadequate facilities or using inappropriate surgical equipment.

Dermatological surgery procedures range from superficial tissue destruction and removal through to surgical excision and complex wound repair. Consequently, a range of basic surgical instruments should be available to the skin surgeon, with selection depending upon the particular procedure being performed. The basic equipment, with optional items that should be available for more specialized procedures, is shown in Table 78.2. Advanced skin surgery (e.g. the removal and complex repair of difficult tumours and Mohs' micrographic surgery) requires both dedicated facilities and specialized surgical instruments to achieve the best results.

Most wound complications are associated with closure under excessive tension, haematoma formation and the presence of either necrotic tissue or foreign material. Wound infection, an uncommon complication of dermatological

Table 78.2 Essential and optional equipment. (From Burge *et al*. [1].)

Essential	Optional
The room	
An examination couch with adjustable backrest	Theatre table
A stool for the surgeon	
Good lighting: anglepoise lights	Overhead theatre lights
Equipment—preoperative preparation	
Autoclave for steam sterilization or electric oven for dry heat sterilization	
Skin preparation	
Chlorhexidine solution	
Chlorhexidine detergent (Hibiscrub®)	
Surgical gloves	
Sterile paper towels	Re-usable drapes
A window can be cut in the centre and the towel placed over the lesion	
Skin markers	Sterile pen and Indian ink
Gentian violet and pointed orange stick	
Skin marker pen	
Indelible felt-tip pen	
Anaesthetic	
Disposable syringes 2 mL, 5 mL fine needles	Dental syringe and fine needles
	Dental syringe vials
Lidocaine (lignocaine)	
1% and 2% plain and with epinephrine (adrenaline) 1 : 100 000 or 1 : 200 000	
Instruments	
Scalpel blades	
No. 15 for excision	
No. 22 for shave biopsy	
Scalpel handle	
Forceps	
Fine-toothed (e.g. Adson–Brown)	
Non-toothed	
Skin hook	
Can easily be constructed by pushing a sterile needle onto a sterile moistened cotton wool bud on an orange stick. Bend the needle into a curve	
Scissors	
Curved pointed iris scissors	
Blunt straight scissors	
Needle holders	
Small artery clamps	
Various sizes of absorbable and non-absorbable sutures attached to needles	Skin punch for biopsies, 3 mm and 4 mm
	Sharp ring curettes in various sizes
Haemostasis	
Gauze swabs	Hyfrecator
30–50% aluminium chloride in alcohol or Monsel's solution (67.5% basic ferric sulphate)	Electrocautery
	Diathermy
	Bipolar electrocoagulation
	Cryosurgery gun
	Supply of liquid nitrogen
	Silver nitrate sticks
Dressings	
Steri-strips	Opsite
Compound Benzoin tincture BP (Friar's balsam) for sticking plaster to skin	
Elastoplast	
Micropore	
Gauze	
Jelonet®	
Histopathology	
Specimen pots	EM fixative 4% glutaraldehyde
Fixative	
10% buffered formalin	Fixative or liquid nitrogen to store specimens for immunohistology

surgery, is more commonly related to surgical technique than poor operator cleanliness or instrument sterilization. However, correct hand washing techniques are vital to the prevention of cross-infection [4]. The tradition of protracted 'scrubbing up' is not essential prior to most dermatological surgical procedures—two washes in running water using 4% chlorhexidine or 10% povidine–iodine solution are sufficient. Between cases, alcohol-based [5] skin cleaning solutions are an alternative on clinically clean hands. The use of surgical gloves is mandatory for all procedures, and wearing eye protection is strongly recommended.

Dried tissue, pus or blood on instruments may harbour potentially dangerous organisms, and all instruments should be manually or ultrasonically cleaned and placed into sealed packs prior to autoclave sterilization [6,7]. Older methods of sterilization, for example boiling in water at atmospheric pressure and the use of various chemical agents (e.g. glutaraldehyde, phenolic agents) are no longer recommended [3]. The new variant Creutzfeldt–Jakob disease (vCJD) prion cannot be destroyed by sterilization, and equipment suspected of being contaminated must be quarantined. If contact is confirmed the equipment must be destroyed.

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Safety aspects

Certain basic safety measures and protocols are essential within a dermatological surgery unit in order to minimize the risks of infection and accidental injury to both patients and staff [1].

The routine use of aseptic technique minimizes the risk of bacterial colonization at the operation site, and prevents contamination from adjacent sites. Antisepsis and sterilization are discussed elsewhere (see p. 78.5). Control of blood-borne infections, especially human immunodeficiency virus (HIV) and hepatitis, has two main components: prevention of transmission from patient to patient, and protection of the surgical team [2]. It is now mandatory for all British medical and nursing staff to be adequately vaccinated against hepatitis B, and for hospitals to have both dedicated infection control staff and protocols to ensure instrument sterility. One approach suggested by the US Centers for Disease Control and Prevention (CDC) is to treat *all* patients as if they were infected with HIV, hepatitis B or other blood-borne pathogens and to adopt 'universal precautions' [3].

Needle-stick injuries and other sharp instrument cuts are particularly important, and all members of the surgical team should take extreme care with the use and disposal of 'sharps'. It is extremely dangerous to either leave uncapped needles on the instrument tray or to attempt needle recapping by the two-handed method. Ideally, the surgeon should make a habit of both disposing of used needles and syringes *immediately* after use and removing all sharp disposable instruments (e.g. needles, scalpel blades) from the tray after the operation, placing these directly into 'sharps disposal' boxes. All relatives and those theatre personnel not directly concerned with the procedure should be excluded from the operating room. Clothing should be specific for surgery—apart from potentially introducing a variety of organisms to the procedure room, clothes may become contaminated.

At the preoperative consultation, a careful history may identify certain potential problems (e.g. diabetes, epilepsy) and the presence of cardiac pacemakers [4]. A full drug history is important—aspirin and anticoagulants promote bleeding and non-selective β-blockers (e.g. propranolol) may rarely interact with epinephrine (adrenaline) in local anaesthetics, resulting in malignant hypertension. On direct questioning, some people may admit to a tendency to faint very easily, and some patients with epilepsy may have a history of fits triggered by surgery or dental procedures. As there is always a risk of patient collapse in operating rooms, there must be adequate space available for an emergency resuscitation to be performed. Resuscitation drugs and equipment, together with both suction and an oxygen supply should be readily available [5]. All theatre personnel should be trained in advanced resuscitation techniques, including emergency electrocardiography and cardiac defibrillation [6].

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Complications [1]

All dermatological surgical procedures may result in complications [1,2], most commonly bleeding, infection and poor wound healing (Table 78.3). Although complications will always occur, most can be prevented by a combination of thorough preoperative preparation and good surgical technique.

Patients on long-term anticoagulant therapy require careful assessment regarding the potential medical risks if therapy is temporarily discontinued to facilitate surgery and the risk of significant bleeding complications if therapy is unchanged [3]. In difficult cases, discussion with other specialists involved in the patient's care will often help resolve this issue. Drugs that block platelet function (e.g. aspirin, clopidogrel, ticlopidine) potentially

Table 78.3 Complications in wound healing.

Complications	Predisposing factors	Prevention
Infection	Infected lesions Poor sterility Steroids Adjacent infectious source Occlusive dressings Poor blood supply Fat, haematoma and foreign material Sutures Poor technique Excessive devitalized tissue from careless handling or electrocoagulation	Careful preoperative and operative techniques Sutureless closure Antibiotic sprays Prophylactic antibiotics for infected or potentially infected wounds
Delay in closure	Poor blood supply Excess movement Infection Tension Steroids Debilitated patient Poor nutritional status	Layered closure Gentle tissue handling Minimize devitalization of tissues Care in decision to operate Warmth Careful postoperative dressings
'Gaping scar'	Inadequate apposition Dermal instability Excess movement Infection Tension	Careful apposition Subcutaneous or subcuticular sutures Adequate postoperative support (e.g. antitension dressings)
Painful scars	Feet and fingers especially	Avoid pressure sites if possible Dressings to reduce subsequent pressure and/or movement Careful apposition
Hypertrophic scars	Site Tension Reaction to embedded material Trauma Individual susceptibility	Avoid 'cape' area if possible Good surgical technique including undermining of edges where necessary
Keloids	Previous history Black skin Upper half of body Tension	Avoid surgery where possible Antitension measures for 3 weeks Watch and prepare to treat
'Railroad tracks'	Skin sutures under too much tension	Good suture technique Use of 'non-reactive' suture material
Stitch marks 'abscess'	Sutures left in too long	Early suture removal
Wound edge inversion	Poor technique	Good surgical technique Occlusive or semi-occlusive dressings
Bleeding and/or haematoma formation	Bleeding tendency Aspirin Clopidogrel Ticlopidine Eptifibatid Tirofiban	Preoperative screening Good haemostasis Use of epinephrine (adrenaline) in local anaesthetic

increase the risks of bleeding complications. In most instances, aspirin can be continued without resulting in a worse surgical outcome, although intraoperative bleeding may take longer to control. However, at some sites (e.g. around the eye) or in procedures involving extensive undermining or complex wound reconstruction, it may be appropriate to withhold these drugs prior to procedures. If aspirin is stopped this must be done at least 10 days before surgery to allow a sufficient number of new platelets with normal clotting responses to be produced. Non-steroidal anti-inflammatory drugs (NSAIDs) present no significant problem and can be continued in all circumstances [4].

The use of epinephrine-containing local anaesthetics results in vasoconstriction and prolongs the duration of anaesthesia. Intra-operatively, bleeding can be controlled by a combination of electrosurgery, pressure and ligation. Postoperatively, the use of appropriate wound dressings is important—ranging from simple Band Aid dressings for superficial wounds to layered dressings with pressure pads for larger wounds where there is a significant risk of haematoma formation (e.g. following cyst or lipoma excision, widely undermined wounds). All patients should be given verbal and written information regarding wound care and how to contact the dermatology unit if problems arise. Haematoma formation may occur at various times after surgery and usually results in acute pain and swelling. The clinical appearances, together with the age and size of the haematoma, will dictate whether to open the wound, evacuate the haematoma and obtain haemostasis, or to manage the complication conservatively [5].

Wound infection is a major concern, but is fortunately relatively uncommon following skin surgery. If the risk of infection is higher than normal (e.g. following excision of an ulcerated tumour from a flexural site), prophylactic antibiotic therapy may be appropriate. Postoperative infection usually presents as erythema, pain and swelling in and around the wound, 4–8 days after the procedure. Depending upon the clinical appearances, management will range from wound care, topical and systemic antibiotics, through to incision and drainage of a frank wound abscess.

Other significant problems relate to both the cosmetic and functional results of surgery. The risks of scarring must be carefully explained prior to surgery, with special attention to the possibility of distortion of facial 'free margins' (e.g. vermilion, lower eyelid) and unsightly hypertrophic scars in high-risk body sites (e.g. upper arm, shoulders, chest). Altered pigmentation in and around the wound is an additional cosmetic risk in Asian and black patients. Nerve damage is a significant concern, as both sensory and motor nerves may be damaged during cutaneous surgery, particularly at certain 'high-risk' anatomical sites (see pp. 78.2–78.5).

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Local anaesthetics [1]

Principles and types

An ideal local anaesthetic agent would be non-toxic, painless on injection, rapid in onset, highly effective and carry a low risk of sensitization. The best compromise is found in 0.5–2% lignocaine hydrochloride (lidocaine), an amide-type local anaesthetic, which is the agent of choice for most dermatological surgery. Other amide-type local anaesthetic agents include mepivacaine, bupivacaine and ropivacaine, which have a slower onset but more sustained duration than lidocaine (lignocaine) [1]. Local anaesthetics in 'multiuse' bottles generally contain parabens preservative, but those supplied in glass ampoules are often preservative-free.

Ester-type local anaesthetics, for example procaine (ester of *p*-aminobenzoic acid) are seldom used by dermatologists.

Epinephrine 1 : 80 000–1 : 200 000, when added to local anaesthetic solutions, prolongs the duration of anaesthesia and produces local vasoconstriction. By reducing absorption, it may reduce the risk of systemic lidocaine toxicity.

Toxic reactions [1,2]

Toxic reactions to lidocaine are rare, and more likely to occur with the use of high volumes of high-concentration solutions or if accidental intravascular injection occurs. Lidocaine toxicity usually presents as a sensation of numbness or tingling. Systemic reactions include vasodilatation, cardiac or respiratory depression, or central nervous system manifestations such as dizziness, drowsiness, tinnitus, slurring of speech, muscle twitching and seizures. These side effects are, to some extent, reversible with diazepam (Valium) but full resuscitation measures may be required.

Ester-type local anaesthetics should be used with caution in patients with renal impairment. They also cross-react with a number of drugs of the *p*-aminobenzoic acid ester type (e.g. sulphonamides, paraphenylenediamine)

[3,4]. Amide-type anaesthetics should be used with care in patients with hepatic impairment.

The maximum recommended dosage for lidocaine with epinephrine is 7 mg/kg or approximately 50 mL of a 1% lidocaine solution for an average adult. In practice, most dermatological procedures require substantially lower anaesthetic doses. In order to minimize the risk of accidental intravascular injection, it is a wise precaution to either aspirate prior to infiltration or, if using very fine (e.g. 30 gauge) needles, which will not aspirate blood, to keep moving the needle about in the skin while slowly infiltrating small volumes.

Systemic absorption of epinephrine may be associated with mild tachycardia and an excited state. More serious reactions are rare but, as with lidocaine toxicity, are more likely to occur with the use of high volume, high-concentration solutions or following accidental intravascular injection. The use of epinephrine in local anaesthetics should be avoided or used with caution during pregnancy, in combination with inhalation anaesthesia, or in patients suffering from severe glaucoma [5]. Interaction with non-selective β-blockers (e.g. propranolol) may rarely cause malignant hypertension [2], but this is not a risk with 'cardioselective' β-blockers (e.g. atenolol).

Patients should always be asked if they have had any untoward reactions to local anaesthetics (e.g. in dental procedures). These may have been nothing more than fainting, as vasovagal attacks are commonly associated with local anaesthesia, and should not be confused with serious toxic reactions. In cases of serious doubt, alternative methods of anaesthesia are necessary.

Methods

Local anaesthesia may be achieved *topically* using either tetracaine (amethocaine) cream (Ametop®) or a eutectic lidocaine–prilocaine cream (EMLA®) [4], or by *local infiltration*. Both EMLA® and Ametop® are applied under occlusion, 1–2 h before the procedure. Conjunctival anaesthesia is best achieved using proxymetacaine eye drops, which sting much less than tetracaine.

Other methods of anaesthesia include *field block* and *nerve block anaesthesia* [3,5], which produce temporary blockade of sensory nerve function in a given area. Field block involves infiltration of local anaesthetic at several points around surgical sites such as the nose and ear [2], and nerve block anaesthesia involves blockade of one or more major sensory nerves. The most useful facial nerve blocks in dermatological surgery involve branches of the trigeminal (Vth) cranial nerve (Fig. 78.3)—the supraorbital (forehead), supratrochlear (glabella), infraorbital (lower eyelid, nasal sidewall, upper lip) and mental (lower lip) nerves [4,5]. The choice of local anaesthetic method depends upon a number of factors, including the procedure itself, anatomical site and expected duration of the operation.

Controversy surrounds the use of epinephrine in digital nerve block ('ring block') anaesthesia because of a real or theoretical risk of digital ischaemia. Some believe it is absolutely contraindicated [6], whereas others describe routine use without incident [7,8].

In order to minimize discomfort when administering a local anaesthetic injection, consideration should be given to using a relatively fine needle, injecting slowly, and using both verbal and tactile distraction techniques. Injecting into the subcutaneous fat is less painful than intradermal infiltration, although it does take longer for the skin surface to become anaesthetic. Whenever possible, anaesthetic solutions should be at room temperature, and epinephrine avoided if not considered useful for the particular procedure. Pain on injection is less when lidocaine solutions are buffered with sodium bicarbonate immediately prior to use [9].

Other anaesthetic agents include the following:

1 *Ethyl chloride* and *liquid nitrogen* spray give short-lived periods of anaesthesia by skin refrigeration. This may be sufficient for quick superficial procedures such as the incision of small cysts and milia, abscesses or the curettage of multiple small warts.

2 The anaesthetic effect of *antihistamines* (e.g. 1% diphenhydramine hydrochloride solution) can be used when hypersensitivity to other agents is present or strongly suspected.

3 The intradermal injection of *normal saline* produces a brief anaesthetic effect [2].

4 *Hypnosis* and *acupuncture* may be useful when performed by an experienced practitioner and in a suitable subject.

5 *General anaesthesia* is rarely used in dermatological surgery. Patients requiring a general anaesthetic (e.g. children requiring treatment of large facial birthmarks) are best admitted to hospital either as a day case or overnight.

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Biopsy techniques

Incisional and excisional elliptical biopsy

Elliptical excision biopsy is used for tumour or suspect mole removal. Incisional biopsy is used to take diagnostic biopsies of rashes and tumours before treatment is started. The technique has the advantage that the entire thickness of skin down to fat is excised. An appropriate margin can be selected if required and the incision line placed in the optimum direction [1].

For lesions on the face, orientate the ellipse so that the scar runs parallel to or within an existing skin crease (wrinkle line), or follows a boundary line between two adjacent cosmetic units. Excision direction is best assessed with the patient seated rather than lying flat, to allow for the effect of gravity on the skin crease lines. Wrinkle or smile lines can be exaggerated by asking the patient to grimace or smile, or by manipulating the skin [2]. In an excisional biopsy, measure the margin to be excised and mark the optimal line of closure before injecting the anaesthetic. When drawing on the skin, use a skin marker or Bonney's blue ink (a mixture of crystal violet and brilliant green), as other inks may tattoo the skin.

The ellipse length should be approximately three times the width, to produce an ellipse angle of approximately 30°, so that buckling does not occur when the wound is sutured (Fig. 78.5) [3]. A larger angle may suffice at some sites or in older people [4]. Make the incision as a single continuous sweep rather than a series of small nicks, and hold the blade at 90° to the skin, not angled inwards, so that the ellipse sides are vertical [5]. Ensure that the incision lines meet neatly without crossing over at the tip by starting and finishing each sweep with the blade held vertically. Incise down to fat. When the ellipse sides and tips are completely separate from the surrounding skin the ellipse should be sitting on a bed of fat. The fat under the ellipse should be cut through using scissors, while the ellipse is gently pulled away from the skin using a skin hook [6]. Undermine the edge at the appropriate level if there is any tension. Close the wound using both subcutaneous and surface sutures if necessary, using the correct suture technique.

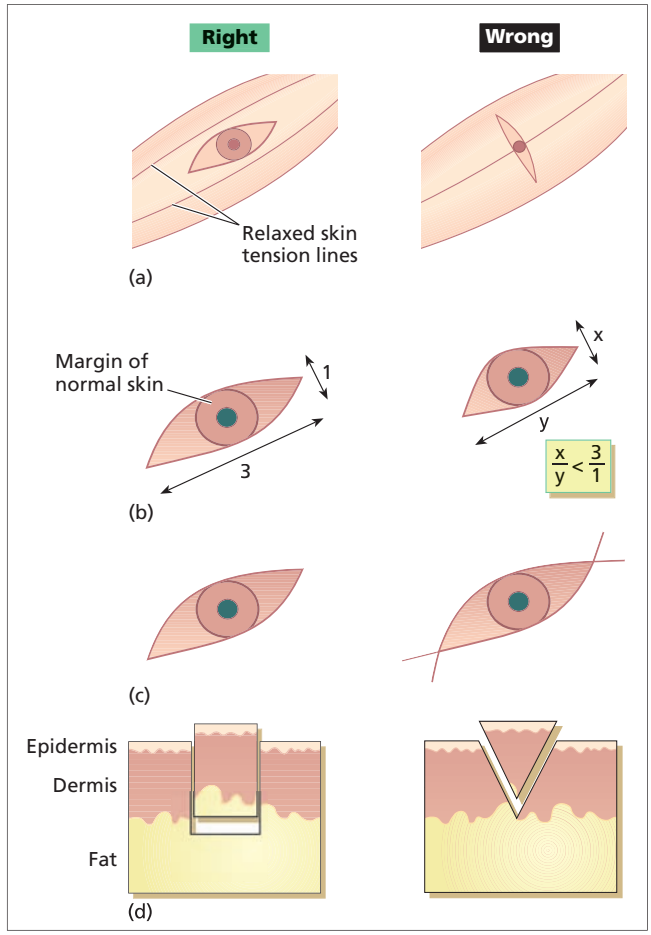


Fig. 78.5 Principles of elliptical excision. The ellipse is designed to follow skin-crease lines (a), and should be approximately three times as long as it is wide (b). Ensure that an appropriate margin of normal skin is also excised (b). At the ends of the ellipse, hold the blade vertically so that the incision lines do not cross over (c). The blade should be held at 90° to the skin when cutting the ellipse so that the wound has vertical sides down to fat. Do not bevel the blade towards the specimen as this makes the wound more difficult to close and may cut into the dermal component of the lesion (d). (From Lawrence [3].)

Punch biopsy

Punch biopsy produces a core of skin down to fat. It is quick and easy to perform, and leaves only a small wound. The disadvantages include the potential for sampling error and the difficulty in stopping bleeding if a small arteriole is punctured at the base of the wound. Punch biopsies can also be used to excise naevi on the back. At this site, wounds can be allowed to heal by second intention, with better cosmetic results than primary closure produces [7]. Subcutaneous tissue lesions can be sampled using a punch biopsy by pinching up a fold of skin to include the subcutaneous tissue before the biopsy is taken [8].

Disposable and reusable 2–8 mm diameter punches are available. When the skin is numb, drill the blade down to fat with gentle downward pressure [5]. To minimize the scar size, stretch the skin at right angles to the wrinkle lines while taking the biopsy so that, when the tension is relaxed, an oval rather than a round wound is produced, with its long axis parallel to the wrinkle lines [6]. The skin core may pop up when the surrounding skin is pressed down, or it can be hooked out using a needle. Cut through the fat at the base with scissors and remove carefully to avoid crushing the specimen. The wound can be sutured

or allowed to granulate; the latter produces an acceptable small round or oval scar. If the wound is to be allowed to heal by second intention, stopping bleeding using a collagen matrix dressing results in a better cosmetic result than using Monsel's solution [9].

Shave

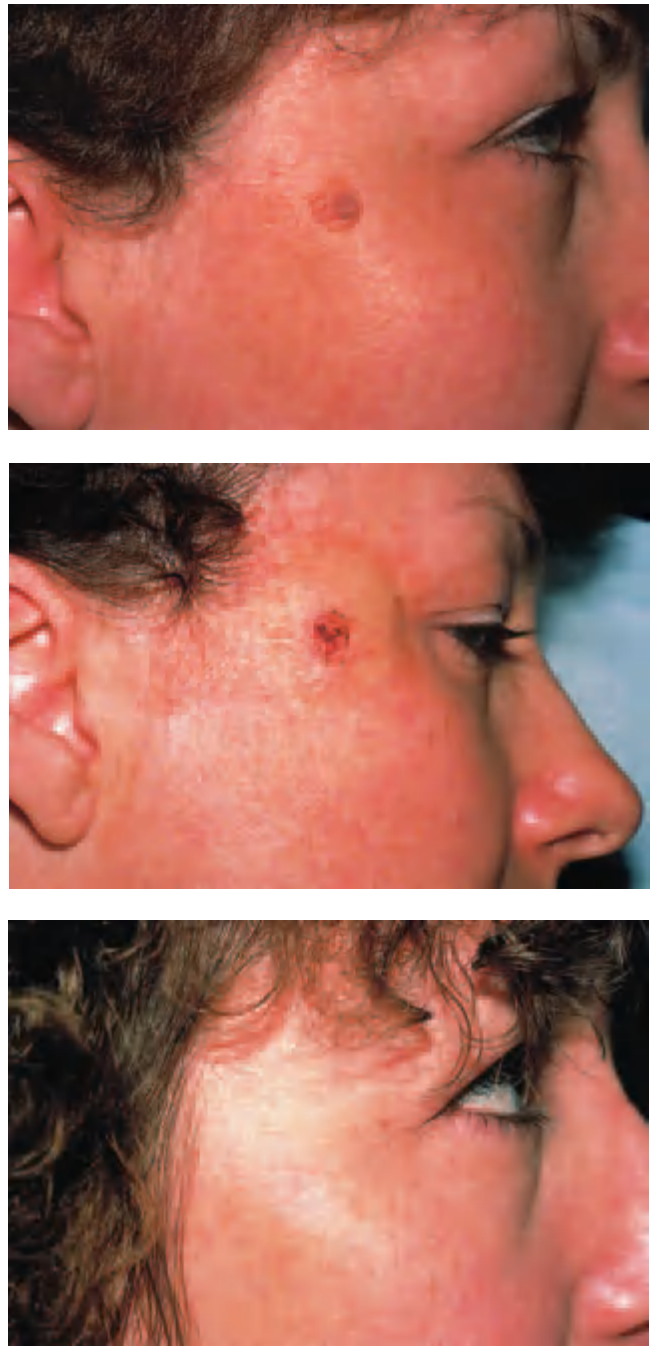
Shave excision is a simple, rapid and effective method of removing benign papular naevi. It can also be used to obtain a tissue diagnosis in protuberant nodular skin tumours. Shave biopsy of dermatoses affecting the epidermis or high dermis results in adequate tissue for diagnosis, and the subsequent re-epithelialization from follicular epithelium produces a good cosmetic result.

Naevi

Inject the local anaesthetic directly into the naevus, as this stiffens the tissue and makes it easier to slice off. Holding a No. 15 blade horizontally, shave off the naevus flush with the skin. Stop bleeding using cautery, electrodesiccation or a chemical haemostatic agent. Any remaining wound edge tissue fragments can be destroyed using cautery or electrodesiccation. The wound will take 2–3 weeks to heal. In approximately 45% of head and neck and 30% of trunk naevi, no visible scar remains (Fig. 78.6). In the remainder, the scar is smaller than the original naevus on head, neck and limb sites and a little larger than the naevus on trunk sites. Pigmentation at the scar edge or centre remains in approximately 25% of initially pigmented naevi after shave excision; non-pigmented naevi rarely, if ever, leave a pigmented scar [10]. Persistent pigmentation is even more common when aluminium chloride haemostasis is used rather than cautery [11]. Recurrent or retained pigment does not need to be excised. If a further specimen is sent, the pathologist must be given the full history in order to interpret the changes correctly. Hairs remain in 25% of initially hairy naevi; these can be destroyed by electrolysis if necessary.

Skin tumours

Shave biopsy of a solid tumour is faster and easier than an incisional biopsy, which needs to be sutured. A fragment can be shaved off to confirm the diagnosis prior to definitive treatment. This type of biopsy will not help to distinguish a keratoacanthoma from a squamous cell carcinoma, and is unsuitable if histological examination of the deep margin or edge of a tumour is required to confirm the diagnosis. Bleeding can be stopped using silver nitrate stick coagulation, as the cosmetic outcome will be determined by the subsequent treatment. The fragile specimen should be mounted on paper before being placed in formalin.



(a) (b) (c)

Fig. 78.6 Shave biopsy of benign papular naevi. (a) This patient had a benign tan-coloured naevus on the face (b) removed by shave excision followed by cautery, (c) resulting in a good cosmetic result 6 months later.

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Simple excision, suture technique and wound closure

Excision [1–3]

Skin biopsy specimens and cutaneous lesions can be removed using techniques other than elliptical excision, many of which (e.g. curettage, shave biopsy) do not result in a linear scar. Consequently, the decision to use formal surgical excision should balance the possible cosmetic advantages of other techniques (e.g. epidermal lesions and benign facial naevi) against the need to provide a full-thickness tissue specimen for histological examination (e.g. possible malignant melanoma).

Surgeon preparation

Dermatologists should be confident that they are competent to perform the proposed procedure and to manage any possible complications. If not, they should ask for a second opinion. The surgeon must be fully immunized against hepatitis B, and should observe safe practices with regard to handling sharps and tissue specimens. Surgical gloves should always be worn [4] and eye protection is strongly recommended.

Patient preparation

Patients should be fully aware of the significant risks, benefits and possible complications associated with the planned procedure. Informed consent [5] should be obtained, both verbally and in writing, for all invasive procedures. Usually, consent should be obtained from the parent or guardian in the case of minors, although some adolescents may be fully capable of both giving and withholding consent. Most patients about to undergo surgery are anxious and usually respond positively to appropriate reassurance as well as a calm and professional manner displayed by all members of the surgical team.

Examination and palpation of skin lesions will help to estimate their extent, depth and proximity to large blood vessels, nerves or other important structures. Langer's lines of skin tension [6] were previously used as a guide to incision, but the best cosmetic results are usually obtained by following the relaxed skin tension lines (RSTLs) [1,7], which tend to lie perpendicular to the major underlying muscles. Langer's lines and RSTLs often coincide, as on the neck. When they do not, as on the limbs, the choice depends on other factors. Excisions on the lower leg, for instance, close more easily along the long axis of the limb, rather than transversely. Testing for skin laxity by manipulating the skin usually clarifies the best direction in which to plan an excision. The size and type of excision made will also depend upon many factors, including the site and nature of the lesion to be excised and the nature of the planned skin closure.

The skin surface should be cleaned prior to operation with a detergent–antibacterial combination, most commonly containing either chlorhexidine [8] or povidone–iodine. This helps to reduce the risk of wound infection by removing pathogens and reducing the resident cutaneous bacterial flora [9].

Elliptical excision—general technique [2,3]

It can often be helpful to mark the planned lines of excision prior to cleaning the skin surface and infiltrating local anaesthetic. A reasonable period of time should be allowed for the anaesthetic to take full effect.

The small round-ended Gillette No. 15 blade is most commonly used to make two hemi-elliptical incisions perpendicular through the skin into the subcutaneous tissues. The length of the wound should be at least three times its breadth (the angles at the ends of the ellipse should not exceed 30°) taking care not to allow the incisions to cross each other ('fishtailing') at either end (Fig. 78.5). The skin ellipse is held firmly but gently with either fine-toothed forceps or a skin hook, and separated from its base. For both histological purposes and to facilitate wound closure the excised specimen should contain subcutaneous fat.

For standard histological processing the specimen should be placed in a formaldehyde–saline specimen bottle, clearly labelled with the patient's details. To prevent curling of small biopsy or excision samples, these may be placed on small squares of filter paper and floated into the formalin solution. When histological confirmation of tumour clearance is required, it can sometimes be helpful to 'colour code' or place a suture at the '12 o'clock' position of the surgical specimen to facilitate orientation and examination in the pathology department. For immunofluorescence or frozen section studies, specimens are placed on aluminium foil and immersed in liquid nitrogen.

Intraoperative bleeding is controlled by a combination of pressure, electrosurgery, clamping and ligation of vessels.

Depending upon the size of the defect and the body site, a variable degree of undermining of the wound edges will be necessary to facilitate the placing of subcutaneous absorbable sutures and to reduce wound tension. Finally, non-absorbable sutures are used to neatly appose and evert the wound edges [2,3].

The timing of suture removal depends upon the site and the amount of tension across the wound. With additional supporting surface tapes and buried sutures where appropriate, 4–5 days is usually sufficient for skin sutures on the face, 5–7 days for the scalp and neck and 10–14 days elsewhere.

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Sutures [1–4]

An ideal suture would have high tensile strength, handle easily, provide good knot security and cause no tissue reaction. Skin sutures are of two main types: *absorbable* and *non-absorbable*.

Now that catgut is rarely used, popular synthetic *absorbable sutures* include Vicryl™ (polyglactin-910), Dexon™ (polyglycolic acid), PDS (polydioxane sulphate), Maxon™ (polyglyconate) and Monocryl™ (poliglecaprone), all of which cause very little tissue reaction and dissolve completely in 90–120 days. Absorbable sutures are usually placed either subcutaneously in the subcutaneous fat to close off potential dead space or as subcuticular intradermal sutures to close and evert wound edges.

Non-absorbable sutures include braided silk and synthetic monofilament sutures such as nylon (Ethilon™) and polypropylene (Prolene™). Most dermatological surgeons prefer the better tensile strength and low tissue reactivity of the synthetic monofilament sutures. Braided sutures such as silk and Dacron™ have better knot-tying properties but tend to drag through tissue, and their braided nature may increase the risk of wound infection. For wounds that are likely to remain under constant tension, such as those on the back or shoulders, a non-absorbable suture such as nylon can be used to close the deep subcutaneous layer. Alternatively, a running subcuticular Prolene suture can be left in place for long periods without leaving suture marks.

In general, skin suture needles are of the reverse cutting type (the sharp edge of the needle lies on the trailing rather than the leading edge). Suture sizes usually vary from 3/0 to 6/0, with suture selection depending on the wound size, anatomical site and surgeon preference.

Suture technique [2,3,5]

The ability to perform several different suture techniques is one of the skills needed in order to become proficient in dermatological surgery. The *simple interrupted suture* is the mainstay of final skin closure, although alternatives include a *running suture*, placed either as loops through the skin (*simple running suture*) or placed entirely within the dermis (*running subcuticular suture*). They are normally 4/0–6/0 gauge, and are placed close to the skin edge for fine approximation. If the wound tends to invert, then the deeper component of the suture can be placed more laterally to help evert the edges.

If there is tension across the wound, or a significant tendency to inversion, one or two *vertical mattress* sutures can be placed initially. A modification of this suture, the *half-buried mattress*, is also useful as a corner stitch when insetting the tips of skin flaps. The *horizontal mattress* suture (with or without bolsters) [6] can also be used to approximate long wounds or wounds under tension. Any wound tension must be managed by undermining and the use of buried sutures before the insertion of skin sutures. Failure to do this will increase the risks of infection and wound dehiscence, and often leave permanent unsightly, papular or linear suture marks.

There are various forms of *buried suture*, which are used to close off 'dead space' in a deep wound. Normally, this is obliterated by the use of interrupted *deep subcutaneous* or buried absorbable dermal sutures [7], or by using a '*purse-string*' variant of the horizontal mattress suture. Running sutures, both cutaneous and subcutaneous, can be used to save time, but may be less secure than interrupted sutures and can be tricky to remove. The running subcuticular suture, although difficult to learn, is an elegant suture technique, and it can be left in place for long periods without risk of leaving permanent suture marks.

Tape closures (e.g. Steri-Strips™) may be used in conjunction with interrupted sutures or on their own if there is good approximation and adequate subcutaneous or subcuticular support. They provide additional wound support both while skin sutures are in place and for the immediate period following suture removal. Cyanoacrylate tissue glues may also be useful, especially in children [8], and for securing skin grafts [9].

Stainless steel staples are a rapid and effective way to close longer skin incisions. They are strong, incite very little tissue reaction, and can be useful for closing scalp wounds and skin graft donor sites [10].

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Particular forms of excision

Variations in detail and technique apply to particular lesions and areas of the body.

Pilar or epidermal cysts [1]

Small cysts are often deeper than they appear and may be difficult to locate after infiltration with local anaesthetic. Careful preoperative skin marking will often help in their intraoperative location. Larger, tense cysts of the scalp often extend deeply and their removal may be accompanied by significant bleeding. Many cysts can be removed by making an elliptical incision into the overlying skin (surrounding the punctum, if present) and using blunt dissection to separate the cyst from the tissues while pulling gently on the ellipse and the attached cyst. If the cyst ruptures, the remaining contents should be expressed and the whole of the cyst wall removed. Irrigation of the wound prior to closure will remove residual cyst contents which might otherwise cause a granulomatous tissue reaction. Excision of large skin cysts leaves subcutaneous dead space, which must be obliterated with deep sutures to minimize the risks of haematoma formation, infection and wound dehiscence.

Lesions on the shoulder and upper back

Surgical excision on the shoulders, upper back and deltoid areas frequently results in poor cosmetic results, with the formation of stretched and frequently hypertrophic scars. Although meticulous surgical technique, appropriate undermining and careful suture technique may minimize these problems, patients should be carefully counselled and only offered surgical excision in these areas when it is absolutely necessary. One suggested alternative to excision and repair in these areas is to excise the lesion with a narrow margin of normal skin and allow healing by secondary intention [2].

Benign naevi

Surgical excision, even by experts, leaves scars and consequently benign naevi are best either left alone or removed by shave excision when possible.

Non-melanoma skin cancer: basal cell and squamous cell carcinomas

Many different surgical and non-surgical techniques may be used to treat non-melanoma skin cancer [3,4]. The choice of treatment is based upon various factors relating to both the tumour [5] and the patient [6].

Small primary well-defined lesions in areas of skin laxity are often best excised. An adequate margin should always be obtained, and prior skin marking following careful examination in good lighting is advisable [5]. Cure rates following surgical excision of such lesions can be excellent [7–9]. Some sites, such as the lips, ear, scalp and periocular and nasolabial areas, have a higher rate of recurrence, and (for squamous cell carcinoma) metastasis. Management of lesions in these sites, particularly if recurrent, poorly defined or showing infiltrative growth patterns, is best performed by a specialist dermatological surgeon [5,10].

Mucous membranes

Excision of lesions in the mouth and on the tongue, lips and genitalia can be difficult, with restricted access and often profuse bleeding. Consequently, only simple procedures should be attempted by non-specialists, and more complex cases referred to colleagues in oral surgery, urology and gynaecology as appropriate.

Keratoacanthoma

This is often difficult to differentiate, both clinically and histologically, from squamous cell carcinoma. Small lesions are often suitable for surgical excision, and larger lesions should be subjected to a transverse incisional biopsy passing from normal adjacent skin through the centre of the lesion and extending through the subcutaneous fat [11].

Pigmented lesions (see Chapter 38)

The diagnosis and management of pigmented lesions is a key component of clinical dermatology and forms an important part of the multidisciplinary treatment of malignant melanoma, also involving pathology, plastic surgery and clinical oncology.

Blue naevi, pigmented basal cell carcinomas, seborrhoeic

keratoses and dermatofibromas are usually easily recognizable to the trained eye, although diagnostic difficulties occasionally occur. When diagnostic doubt exists, and especially when malignancy is suspected, the lesion should be excised and submitted for histopathological examination. When the lesion is too large to excise and repair directly, an incisional biopsy may be indicated (e.g. possible malignant change in a large congenital naevus or facial lentigo). In these cases, if malignant melanoma is proven on biopsy, a second procedure, possibly involving complex wound reconstruction, will often be necessary. In such cases, an initial incisional biopsy does not appear to influence the overall prognosis [12], although determination of key prognostic features (e.g. growth phase, depth of invasion, presence of vascular invasion) can only be made accurately from examination of the full excision specimen.

Hypertrophic scars

Although these may occur at any site, they are especially common in certain anatomical sites such as the upper back, shoulders and deltoid areas. Most will slowly resolve with time and regular gentle wound massage. Intralesional steroid injections can be helpful, but may cause skin and fat atrophy and should be used with caution. Hypertrophic scars may also be treated (and possibly prevented) by the use of Z-plasty techniques [13], with pressure dressings or devices [14], and silicone gel sheet dressings [15].

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Wound closure [1–3]

A significant part of dermatological surgical practice involves the repair of surgical defects. Wounds can be allowed to heal by secondary intention healing, closed primarily, or repaired using skin grafts or skin flaps. Experience and careful consideration of the various wound closure options are necessary in order to offer patients the best possible cosmetic and functional results.

The M-plasty [4]

This is occasionally useful if one end of an elliptical excision will cross an important anatomical or cosmetic line. In this situation, an M-plasty will help to reduce the overall length of excision required by bringing the apex of the excision back within the original area to be excised.

'Dog-ear' repairs [5]

'Dog-ears' (folds or humps of skin) tend to occur when the length to width ratio of an excision is insufficient to prevent the skin at the poles from bulging outwards when the opposing skin edges are brought together. They tend to occur more commonly when there is limited laxity or movement in the surrounding tissues. Excisions where the angle at the apex exceeds 30° are also liable to produce 'dog-ears'. 'Pseudo-dog-ears' occur if too much fat is left at the poles of an excision.

There are several ways in which this problem can be surmounted [3].

1 The excision can be extended and the redundant overlapping skin excised.

2 One side of the pucker can be cut back flush with the skin and the excess skin from the other side identified by drawing it across the wound; this can then be cut off.

3 The excess skin of the 'dog-ear' can be removed by converting it into a T-plasty or an M-plasty. This is a useful technique when the length of the wound cannot be extended [6].

Wound edges of unequal lengths

This problem can often be resolved by using a halving technique: a suture is placed across the centre of the wound and subsequent sutures used to divide the two resultant defects into ever smaller compartments. Because of local skin elasticity, the shorter side tends to stretch to match the longer. For more disproportionate edges, a wedge may have to be removed from the longer side in order to make the sides of the resultant ellipse more equal,

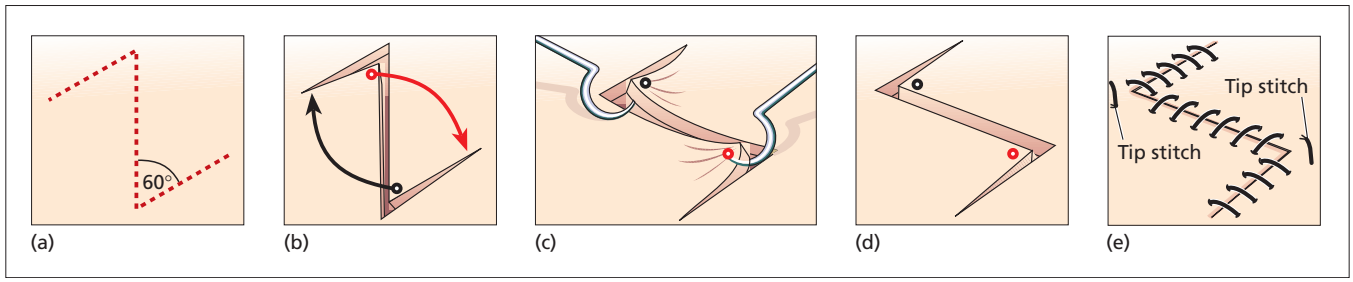

Fig. 78.7 Technique of Z-plasty. (From Eedy *et al*. [7].)

or the wound can be sutured in the normal way and a 'dog-ear' repair performed to remove the excess skin from one side.

Z-plasty

This is a technique that is used to treat scar contractures, skin 'webbing' and to break up or alter the direction of linear scars to try to improve the cosmetic or functional result. The size of the angle used determines the increase in the length of the scar that will result (Figs 78.7 & 78.8).

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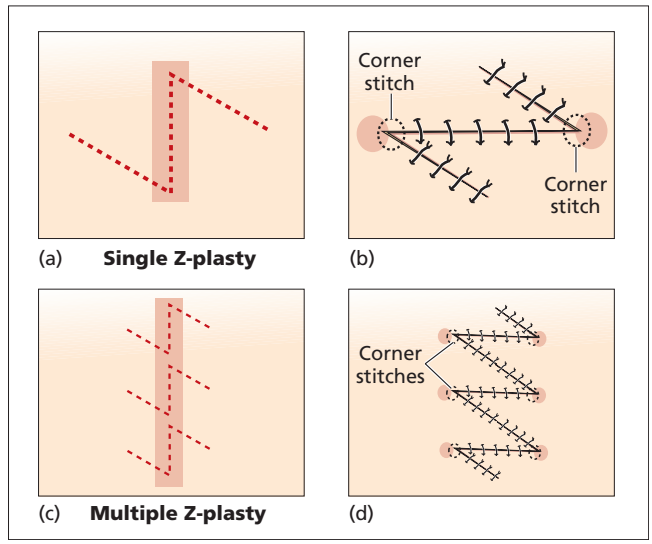

Fig. 78.8 Single and multiple Z-plasty. (a,b) Single Z-plasty. (c,d) Multiple Z-plasty. Note breaking up of zone of lateral tension (shaded areas) with multiple Z-plasty. (From Eedy *et al*. [7].)

Dressings

Wound dressings are not essential [1], although optimizing wound care by using an appropriate dressing probably produces a predictably better result. An ideal dressing should meet the following criteria.

1 Soaks up excess exudate from the wound surface, thereby reducing the risk of bacterial penetration.

2 Maintains a moist wound–dressing interface to encourage migration of epidermal cells over the granulating tissue. Covered split-thickness wounds heal faster than dry wounds [2]. A scab is a poor barrier against loss of moisture from the dermal surface because it allows the surface to dry out, thus forcing the epidermis to grow under the dry wound surface. As the epidermal cells migrate, they secrete a proteolytic enzyme which dissolves the base of the scab; migration ceases when cell–cell contact occurs [3].

3 Does not contain organisms or fibres that may contaminate the wound. Cellulose-derived dressings may shed fibre fragments into the wound [4], causing a foreign body reaction and leading to increased risk of infection.

4 Is impermeable to bacteria.

5 Causes minimal injury to healing tissue when removed.

It is often claimed that a dressing that permits increased oxygen permeability aids wound healing. Such dressings do aid healing in split-thickness wounds [5]. However, in full-thickness wounds the same synthetic wound dressings create hypoxic conditions at the healing surface [6]. Paradoxically, tissue hypoxia in full-thickness wounds appears to stimulate rather than retard granulation tissue formation [7].

Basic dressing [8]

This includes contact, absorbent and outer layers [9]. The layer in contact with the wound is non-adherent, either because it contains a greasy ointment (e.g. tulle

dressing) or because it is made from a specially designed low-adherence material (e.g. polyethylene) [10]. The absorbent layer (e.g. cotton-wool, gauze) soaks up the excess wound exudate and cushions the wound. The outer layer (e.g. tubular bandage, elasticated tape) holds the other two layers in place and applies slight pressure. The basic dressing is left in place until suture removal, but needs to be changed if it gets wet or becomes saturated with exudate [11], as this greatly increases bacterial penetration. Many proprietary dressings combine two or all three components (e.g. Melolin® contains a polyethylene non-adherent layer attached to an absorbent cellulose component). The hydrogel (e.g. Vigilon®), hydrocolloid (e.g. Granuflex®), xerogel (e.g. dextranomer starch polymer), alginate (e.g. Kaltostat®) and synthetic foam dressings are designed to provide all three components, and these can also be used on pressure sores [12,13], leg ulcers [14] and full-thickness surgical wounds [15].

Pressure dressings

These are placed over the basic dressing. Most commonly, and on suitable sites, a piece of compressible padded dressing (e.g. cotton wool, sponge, eye pad) is pressed down onto the wound with an elasticated or *crepe bandage* for 48 h. Where bandage application is difficult, a *multi-tape dressing* can be used. Dental rolls are placed over and pressed down onto the dressing by using adhesive tape strips, and additional adhesive (e.g. collodion or tinct benz co.) is used to increase the tape adhesion. A *tie-over pressure dressing* is commonly applied over skin grafts, but can be used on any wound. Paired sutures are placed around the wound and tied together to hold down a three-layered contact, absorbent and compression dressing, so that the graft is held down onto the recipient site to prevent a haematoma forming beneath it.

Suggested dressing for wound types

Small full- or *partial thickness wounds* (shave and curettage sites) require a simple low-adherent dressing or paraffin tulle held in place with a conforming adhesive tape. Unsutured punch biopsy sites do not appear to benefit from occlusive dressings [16], but heal better with a collagen matrix dressing than they do after simply applying Monsel's solution to stop bleeding [17]. *Sutured wounds* (side-to-side closures and flaps) require a greasy antiseptic ointment application and an absorbent-backed, low-adherent dressing held in place with a conforming adhesive tape. A pressure dressing may also be required. After suture removal, apply adhesive tape strips for 5 days. On a *full-thickness graft*, apply a simple contact dressing (e.g. greasy antiseptic ointment and paraffin tulle) and then a tie-over pressure dressing which includes a sponge or cotton wool compressible pad. On *full-thickness wounds*, a variety of wound management methods are used. If acceptable to the patient, the wound can be left without a dressing and simply cleaned two or three times daily, and a sterile white soft paraffin or vaseline-based antiseptic ointment applied. Alternatively, the wound can be cleaned less frequently if a combination contact/absorbent dressing is applied. During the initial exudative stage (the first 4 days) the dressing will need to be changed at least once a day. Thereafter, the dressing should be changed if the wound surface starts to dry out or the dressing becomes saturated, wet or otherwise dirty. The wound should be cleaned with a simple antiseptic (e.g. aqueous chlorhexidine, 10 vol. hydrogen peroxide) before being re-dressed using a vaseline-based antiseptic ointment (Polyfax®), and simple contact dressing (e.g. polyethylene/cellulose dressing; Melolin®) held in place with adhesive tape. Alternatively, a semi-permeable adhesive polyurethane [18] or gel, or colloid dressing can be used and changed as necessary. *Split-skin graft donor sites* heal faster with a dressing that maintains a moist wound–dressing interface; for example, a calcium alginate [19] or semi-permeable adhesive polyurethane film [20]. A pressure bandage applied over the wound is also required, but bleeding will still occur. The exudate can either be allowed to drain through puncture wounds made in the lower portion of the polyurethane film, or can be removed by changing the dressing more frequently, although this may introduce infection and is painful.

Wound healing is delayed by topical steroid application [21], tobacco smoking [22] and possibly age [23] via a decrease in skin blood flow with increasing arteriosclerosis [24].

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Secondary intention healing

Full-thickness wounds remaining after malignant [1,2] or benign [3] tumour excision can be left to heal by second intention. The cosmetic result depends on wound site and patient age. The nasolabial fold, medial canthus, scalp and pre- and postauricular skin produce particularly good results, although the technique can be used in many sites, including the fingers [4]. Almost half of the reduction in wound size occurs because of scar contraction [5] and subsequent stretching of surrounding tissues [6]. Therefore, if the wound is next to a mucocutaneous junction, such as the lip, ala nasa or eyelid, scar contraction may distort this free margin, producing poor cosmesis and function. Most other head and neck sites heal well, although in general the cosmetic results are best on concave rather than convex skin surfaces [7]. The older the patient the better the result, probably because wound contraction is aided by the availability of loose adjacent skin and because hypertrophic scarring is less common in older patients. The method can be used if there is doubt about the adequacy of excision, or closure of the defect requires a larger or more complex procedure, which the patient will not tolerate. In some situations, such as excision of naevi on the back [3] or the treatment of acne keloidalis nuchae [8] and hidradenitis [9], secondary intention healing is the preferred method as it results in a superior cosmetic result.

When a tumour is being excised, the specimen is orientated with a marking suture before complete removal, so that if further excision is required the affected margin can be identified. When bleeding is controlled, a contact dressing is applied, and this is covered by a pressure dressing for 24–48 h. Thereafter, the dressing can be changed at 2–4-day intervals, depending on the amount of exudate. At each dressing change, the wound is cleaned to remove crust or debris and a greasy antiseptic ointment (e.g. Polyfax®, Flamazine® or Betadine® ointment) and non-adherent dressing are applied. On average, a 25-mm diameter head and neck wound takes approximately 35 days to heal [10]. If histology shows that the tumour has been incompletely excised, the involved margin can be re-excised 1–2 weeks after the first excision. Because vertical sections are taken and the entire excision margin is not examined, the technique does not provide the same complete excision margin control as the horizontal sections of Mohs' surgery [1]. These wounds are surprisingly pain-free. Bacterial contamination may occur, but tissue infection is rare; when present the wound edge is tender, red and swollen. A yellow exudate is common in the first few days. Before granulation tissue appears, a yellowish fibrin clot covers the wound. Exposed periosteum and perichondrium must be kept moist and viable by using a saline-dampened alginate dressing. This encourages granulation tissue to migrate over the exposed area and also reduces the risk of bone desiccation and necrosis [11]. If the periosteum has been stripped off, the exposed bone can be fenestrated or abraded to encourage the formation of granulation tissue and hence enhance re-epithelialization [12]. When the wound first heals, the scar often contains large looped vessels, which slowly disappear as the scar thickens. A slightly elevated, red, hypertrophic scar is then present, and the cosmetic result is not optimum until approximately 1 year (Figs 78.9 & 78.10).

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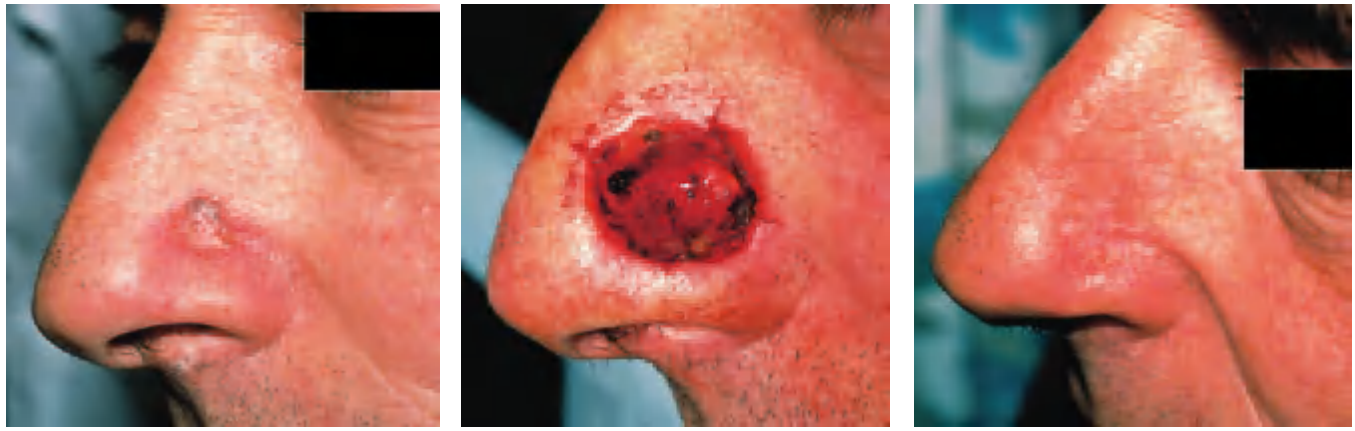
Skin grafts

Skin of varying thickness can be used for skin grafting. A

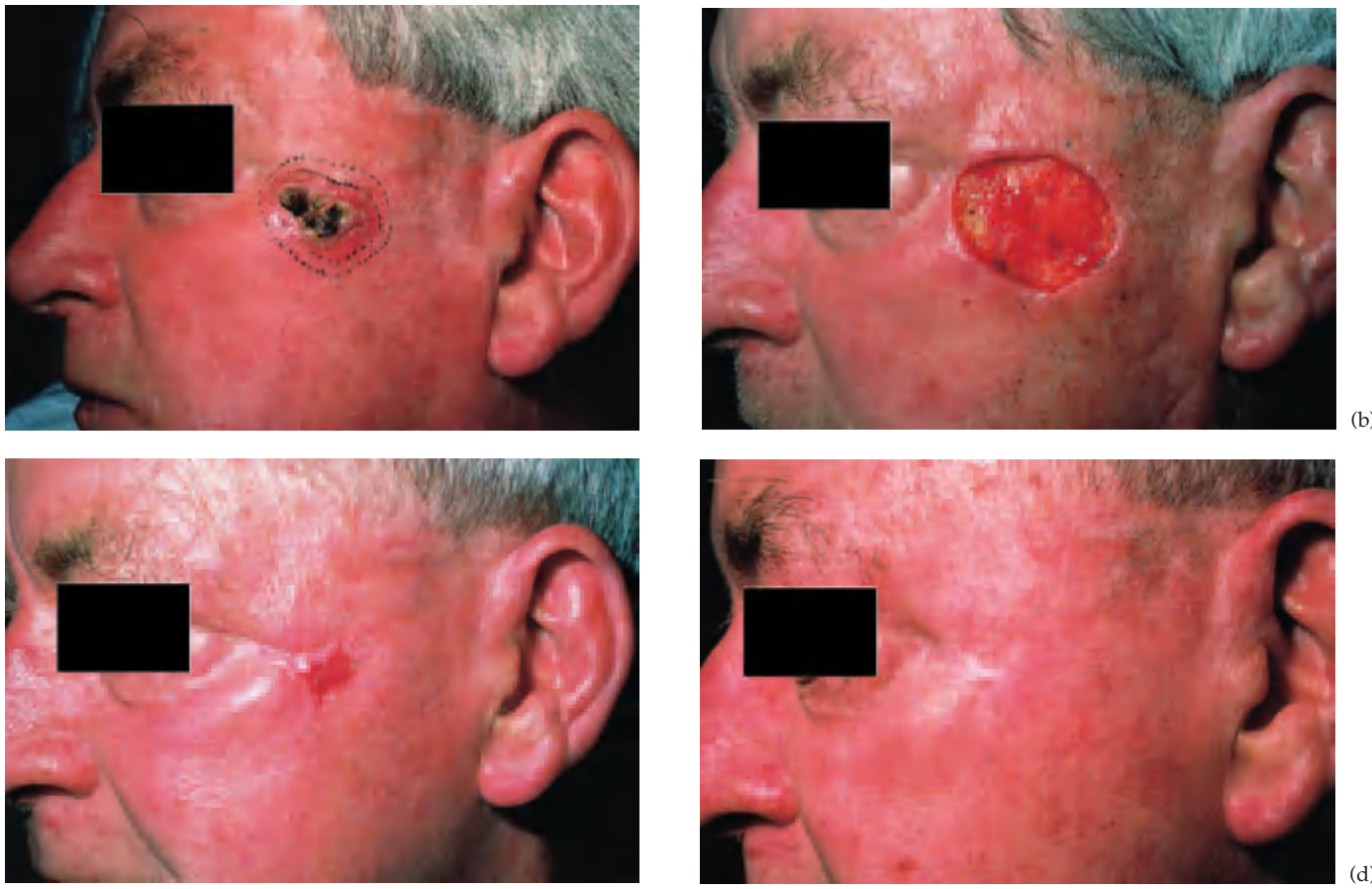


(a) (b) (c)

Fig. 78.9 (a) This man had a basal cell carcinoma on the side of the nose; (b) this was excised and the wound was allowed to heal by second intention. (c) The cosmetic result 4 months later was good.

Fig. 78.10 (a) This man had a basal cell carcinoma on the temple (b) excised. (c) Three months later the wound had healed but the scar was thick and red. (d) 15 months later this scar had become considerably less conspicuous.

split-skin graft is not limited in size, because the donor site regenerates. Full-thickness and composite skin grafts potentially produce better cosmetic results than split-skin grafts, but are limited in size by the amount of skin that can be removed from the donor site without creating problems. Compared with flaps, grafts are technically easier to perform, but generally produce inferior cosmetic results.



(a) (b) (c) (d)

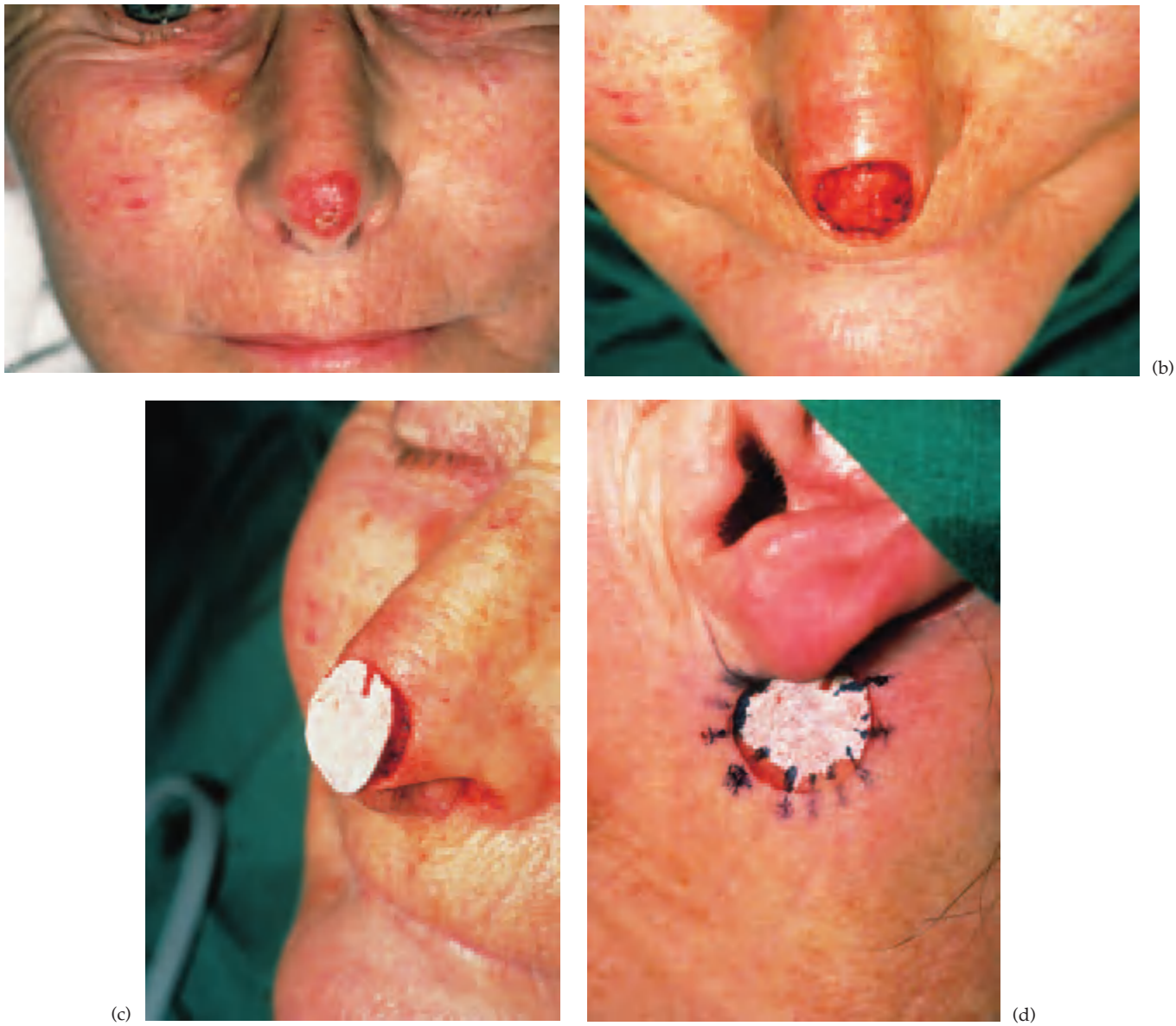
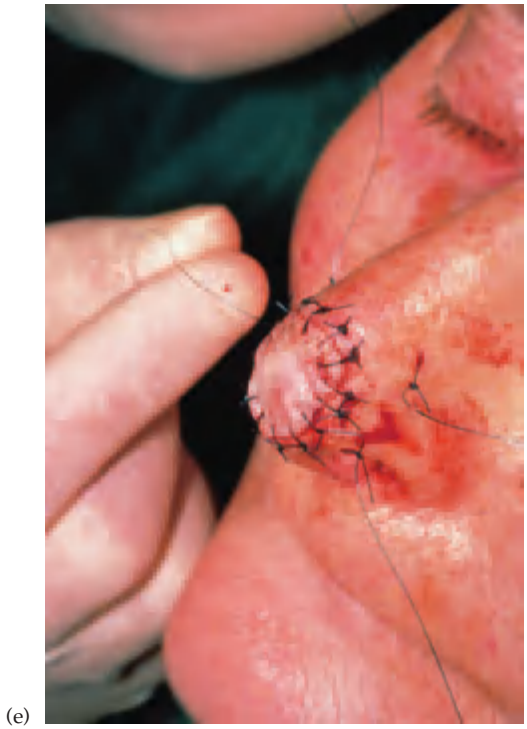


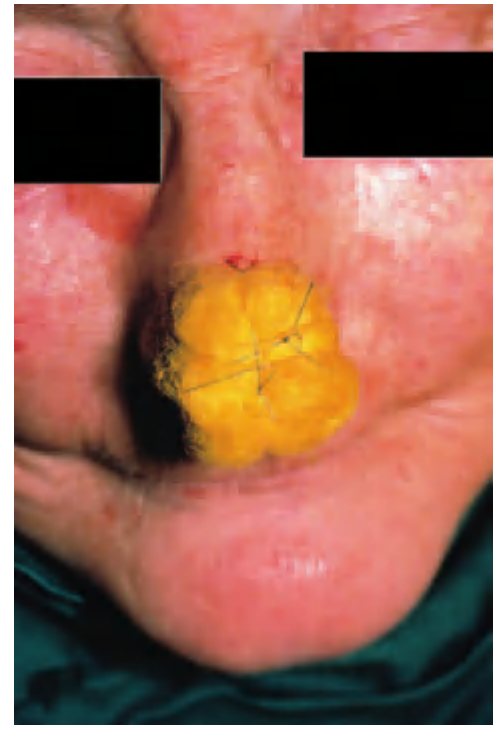
Fig. 78.11 Full-thickness graft on the nose. This basal cell carcinoma on the tip of the nose (a) was excised (b). The defect size and shape was recorded using a sterile paper template (c), the template was placed on the donor skin site (d) and the appropriate-sized piece of skin excised. The fat was trimmed off the undersurface of the donor skin, and this was sutured into place on the wound (e). A tie-over dressing was applied (f). Seven days later the dressing was removed and the graft was pink and had clearly taken (g). The subsequent cosmetic result at 3 months was excellent (h).

Full-thickness grafts

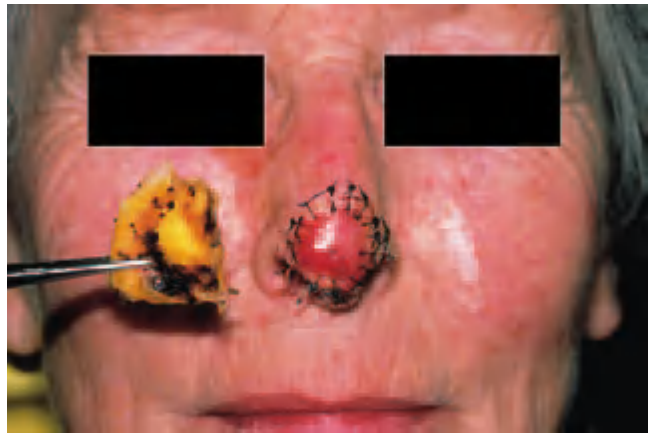
A full-thickness graft is used, in preference to a split-skin graft, when the cosmetic result and strength of the repair are important. Any site with matching and spare skin is a potential donor site [1]. Common donor sites include the skin behind and in front of the ear, nasolabial fold [2], upper eyelid, inner aspect of the upper arm, lower abdomen and supraclavicular fossa. The donor and graft sites should match for skin thickness, adnexal structures, surface markings, weathering and texture. After carefully assessing the amount and shape of skin required, the donor skin is excised down to fat [3]. The fat is then trimmed off the under surface of the graft to aid new blood-vessel penetration. Edge sutures are used to prevent shearing forces dislodging the graft, and a pressure dressing, usually held in place using tie-over sutures, is employed to prevent a haematoma lifting the graft off the recipient site (Fig. 78.11). In most instances, the donor site is chosen because there are redundant folds of skin present and the skin edges can be sutured easily after donor skin excision. At some sites (e.g. behind the ear), the donor



(e)



(f)



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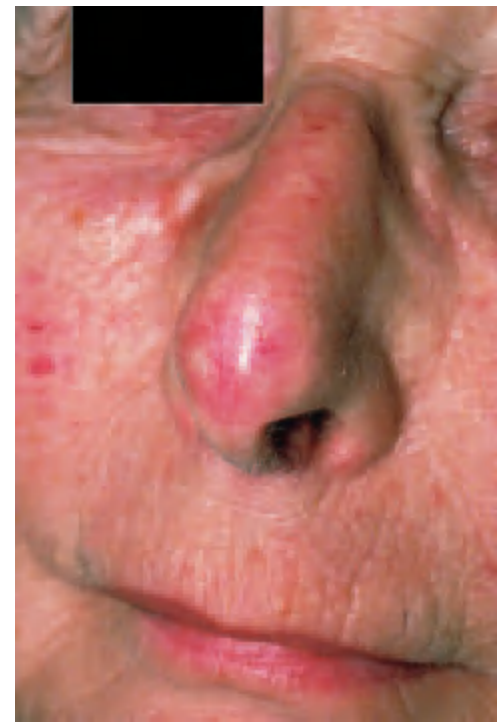

(h)

Fig. 78.11 (*cont'd*)

defect can be allowed to heal by second intention. Grafts take best on dermis and granulation tissue, will survive on fat, perichondrium and periosteum, but will perish on exposed bone or cartilage. Grafts fail because of infection or poor blood supply. The latter occurs because of faulty technique (e.g. incorrect haemostasis, suturing or wound care) or because the recipient site has an inadequate blood supply (e.g. previous radiotherapy or lower leg sites in people with compromised venous and/or arterial supply). All grafts contract, and near the lower eyelid this may lead to ectropion. Hence, at this and other critical sites, grafts should be 10–25% larger than the defect to

compensate for this. Depressed graft scars may be elevated by injection of autograft fat under the graft [4].

Composite grafts

Composite grafts are defined as those comprising two or more germ layers. In dermatology, these are grafts containing skin and cartilage components. When used to repair full-thickness ala rim defects using skin taken from the helix rim, graft survival is unpredictable [5]. In contrast, composite grafts containing skin and perichondrium, or perichondrial cutaneous grafts, are claimed to be better than full-thickness grafts for nose, ear and periocular defects, as they contract less, induce new cartilage formation, and maintain their thickness and epidermal appendages [6].

Split-skin graft

Except in extreme circumstances (e.g. extensive burns) split-skin graft size is not limited by the amount of donor skin that can be harvested, because the donor skin site will re-epithelialize by regeneration from retained follicular remnants. Split-skin grafts can therefore be used to cover very large wounds. Because the skin is thin and relatively transparent, split grafts are also sometimes used to cover tumour excision sites where the adequacy of excision is dubious, because recurrence is more easily identified through the thinner graft than it would be after full-thickness or flap closure. The disadvantages of split-skin grafts compared with full-thickness grafts are the relatively poor cosmetic result and greater graft shrinkage [1]. When a split graft is taken, skin is sliced off through the dermis, leaving behind parts of the adnexal and follicular structures from which epidermis migrates to cover the donor site. Split-skin grafts can be taken using a handheld knife or a mechanical dermatome (Fig. 78.12a). The latter is easier to use and produces a predictably good graft. *Meshing*, or cutting multiple parallel slits in the graft, allows it to expand rather like a fishnet stocking when stretched (Fig. 78.12b). The gaps are covered by epithelium migrating from the adjacent strips of the graft (Fig. 78.12c). A meshed graft will therefore cover a wider area, allow exudate to drain through the gaps (e.g. on the leg), and will conform to an uneven contour (e.g. ear). The common donor sites include the upper arm, upper thigh and abdominal wall. The donor site is best anaesthetized using EMLA® cream [7], and heals faster and painlessly with a dressing that maintains a moist wound–dressing interface (e.g. calcium alginate [8] and semi-permeable adhesive polyurethane film; Opsite®) [9].

Pinch grafts

Pinch grafts are occasionally useful for wounds of the lower leg, although the donor site heals leaving unsightly scars. The technique is simple [10], but without careful aseptic technique success rates are low [11]. The skin is elevated on a needle tip, the apex sliced off, and when multiple skin shaves have been harvested the grafts are placed at regular intervals on the clean granulating ulcer.

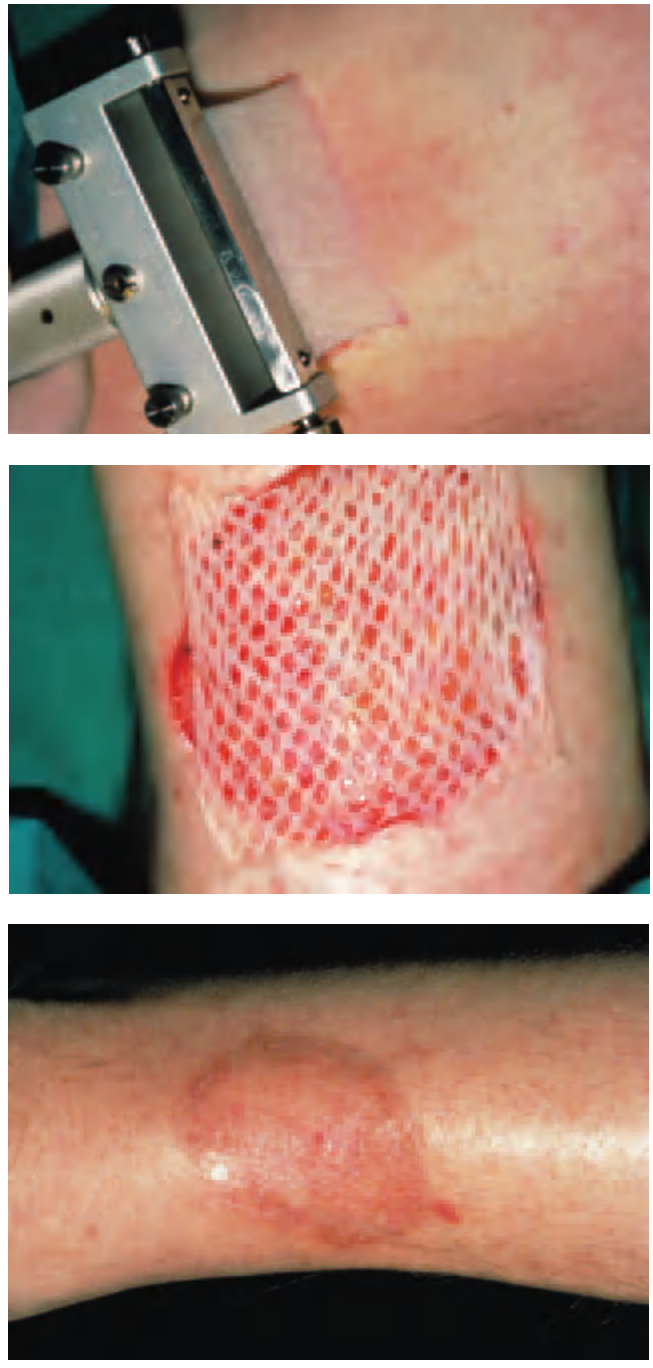

Fig. 78.12 Meshed split-skin graft. (a) A split-skin graft was harvested from the thigh skin using a power dermatome. (b) The skin was meshed on a mesher, and the meshed graft applied to the defect. (c) This was the appearance of the graft 11 months later.

As with all leg-ulcer skin grafting, if the causative factors are not eradicated before grafting, the ulcer will recur even if the graft is initially successful.

Grafting techniques used for repigmentation of inactive vitiligo

Epidermal grafts containing viable melanocytes can be harvested using suction blisters [12], or very thin split-skin grafts [13]. Before grafting, the epidermis is removed from the hypopigmented skin by freezing to create a blister [12], or by dermabrasion [13]. Alternatively, *mini-grafts*, or tiny (1.2-mm diameter) full-thickness punch grafts of normally pigmented skin are grafted, at 2-mm intervals, into similar-sized punch wounds sited in the depigmented skin [14]. Because melanocytes migrate approximately 2 mm away from the graft site, there is no need to graft the whole area, and because the punch grafts are so small there is minimal cobblestone effect at the recipient site. In both techniques, a hidden donor site, such as the upper inner thigh or lower back, is used. Grafts of cultured autologous melanocytes have also been tried [15].

Acne scar punch grafts

Ice-pick acne scars can be excised using a punch biopsy blade, and the wound filled with a slightly bigger punch biopsy-shaped piece of donor skin taken from a matching but unobtrusive site (e.g. behind the ear). Dermabrasion is usually subsequently required to reduce the cobblestone effect [16].

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Flaps (Figs 78.13–78.16)

A flap is a section of full-thickness skin in which one portion, the pedicle, remains attached to the skin while the distal portion is undermined and moved to cover the defect [1]. The blood supply of any flap is therefore, at least initially, provided principally via its pedicle, and the broader the pedicle the better the blood supply. The length to width ratio of a flap should rarely exceed 3 : 1. The more closely a flap resembles a graft (thin, defatted skin) the greater is the contribution to its blood supply from the recipient site rather than the flap pedicle. The thinner the flap, however, the greater the contraction, and this is particularly important when using thin skin around the eye. Different techniques can be used for many repairs [2], although some techniques [3] are inherently suited to the nose [4,5], chin [6], eyelid [7,8], ear [9,10], forehead [11], scalp [12], cheeks [13] and lip [14,15].

Flaps can be confusingly categorized by the direction of movement, the name of the surgeon who first described the flap, the blood supply or the type of tissue moved. The most useful method relates to how the skin was moved to cover the defect—hence the description of advancement, rotation or transposition flaps (Table 78.4). Classification according to blood supply shows that dermatologists almost exclusively use random pattern flaps (the blood supply is inherent in the skin being moved). This may come from the dermal blood supply (reticular—the type most widely used by dermatologists), or the perforating vessels from the subdermal plexus (segmental, e.g. island pedicle flaps). In contrast, axial pattern flaps are designed to obtain their blood supply from one named artery. With the exception of the midline forehead flap [4], which is based on the supratrochlear artery, axial flaps are rarely used in dermatological surgery. Island pedicle flaps do not have a skin pedicle but get their blood supply from the tissue on the underside of the flap. This may be subcutaneous tissue, muscle or a named vessel.

As skin is moved to close the primary or original defect, a secondary defect is created which in turn also has to be covered. The essence of flap repair is to design the flap so that this secondary defect is created at a site where there is sufficient spare or loose skin to permit closure. On the face, loose skin is usually present in the middle of the forehead, the glabella region and bridge of the nose, the nasolabial fold, the front of the ear and the cheek. Hence, these areas of laxity will be exploited for most flaps.

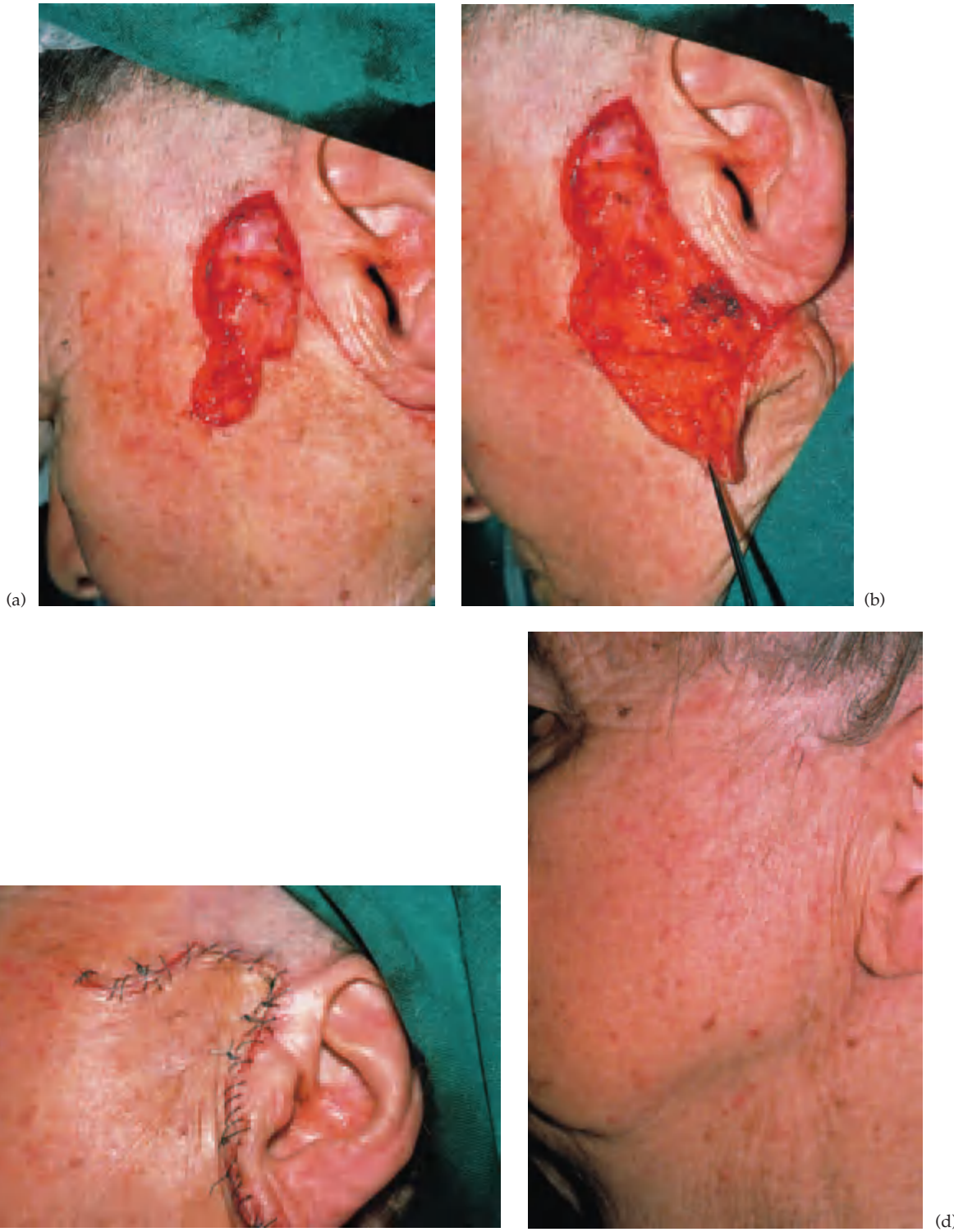

Fig. 78.13 Rotation flap on the pre-auricular skin. (a) This oddly shaped defect was closed (b) by rotating and advancing the loose skin under the chin up to cover the defect. (c) The incision line was placed in the skin crease at the anatomical boundary between the ear and the cheek, (d) and hence is inconspicuous 4 months later. The back cut was enhanced by Z-plasty under the ear (not shown).

Advancement flaps are used where skin must move in one direction from an area of laxity to cover the defect. Although simple to conceptualize they have limited use. The secondary defect is closed last, and the flaps have limited mobility. In many instances, defect coverage is only achieved by stretching the flap rather than transferring

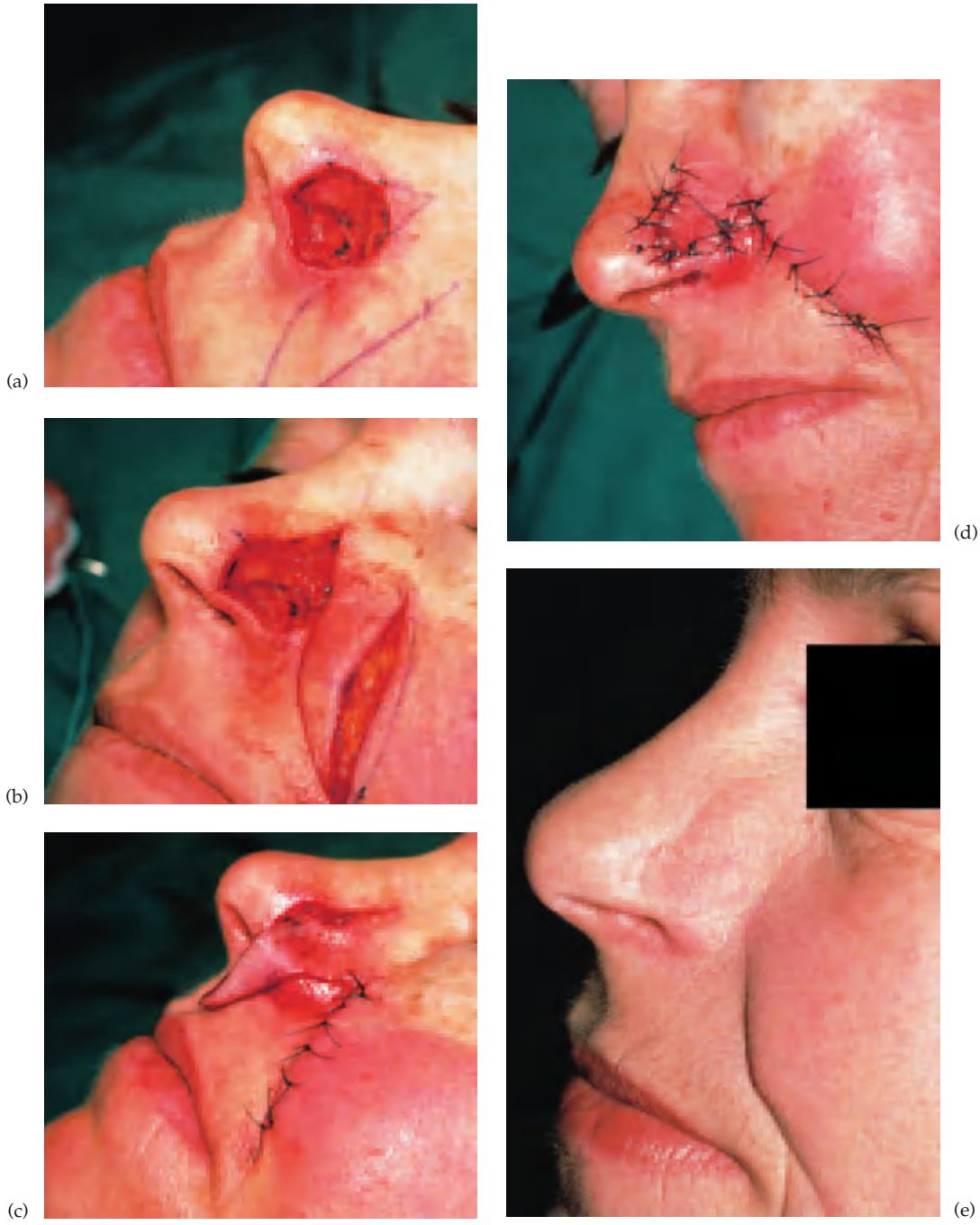

Fig. 78.14 Nasolabial fold flap. (a) This defect on the ala wall was covered by transposing a flap taken from the cheek skin (b). (c) The defect on the cheek was closed directly along the nasolabial fold, thus disguising the scar, and the flap of skin was then laid over the defect. (d) The flap was trimmed to shape and sutured into place. (e) The result 12 months later was good.

the tension to an area of lax skin. *Rotation flaps* usually require both advancement and rotation about a pivotal point on a broad pedicle (Fig. 78.13). Mobility is frequently limited, and long incisions and extensive undermining may be required to mobilize sufficient tissue; the secondary defect is closed last. *Transposition flaps* provide the greatest mobility, and the secondary defect is closed first (Fig. 78.14). As a result, the flap is pushed rather than dragged into the defect, so that if a transposition flap is designed properly virtually all the tension can be placed on the secondary defect rather than the flap, thus reducing the risk of ischaemic necrosis. These advantages make transposition flaps the most widely used (Fig. 78.15). A wide variety of flaps based on these three simple designs have been described, each with careful refinements for different sites (Table 78.4).

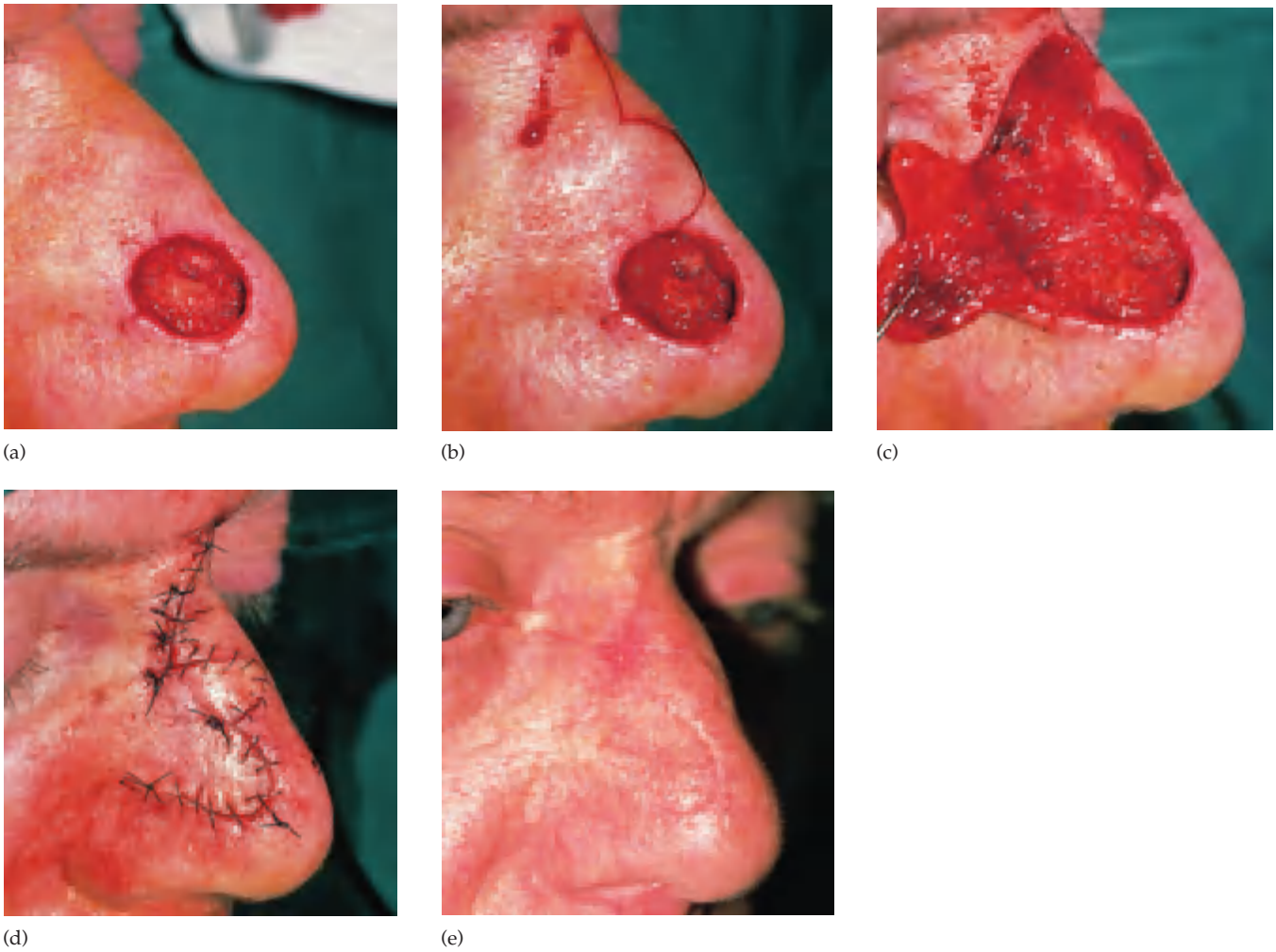

Fig. 78.15 Bilobed flap on the nose. (a) This defect near the tip of the nose was covered using a bilobed flap designed to cover the defect by exploiting the looser skin higher up on the side of the nose (b). (c) Both parts of the flap were raised together, and were transposed into the defect and the secondary defect; (d) the tertiary defect was closed directly. (e) The cosmetic result at 6 months was good.

Complications

Ischaemic necrosis of the flap usually occurs because of excessive tension resulting from poor design or mobility. Secondary infection is also more common if the flap has a poor blood supply [29]. On the head and neck, blood supply is excellent at all sites, but on the trunk, and especially on the lower limb, attempts at flap repair frequently result in failure because of relatively poor blood supply. Cigarette smokers are more likely to suffer from flap or graft necrosis than non-smokers (Fig. 78.16), although this can be reversed if smokers significantly reduce cigarette consumption 2 days before and 7 days after surgery [30]. If the flap scar is obtrusive, particularly on the nose, it can be revised by dermabrasion, which is best performed 6 weeks after surgery [31]. Manual dermabrasion [32] or scalpel sculpturing [33] may be less hazardous to the operator and equally effective.

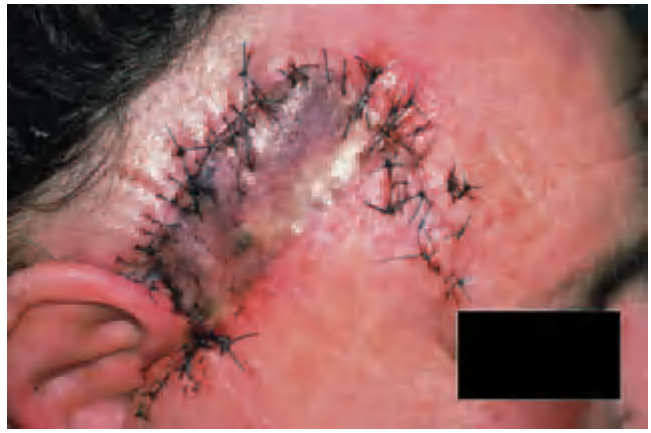

Fig. 78.16 Complications—flap necrosis in a cigarette smoker. Despite warnings, this patient continued to smoke before and after surgery. Possibly because of this, the rotation flap on her temple necrosed at 7 days.

Table 78.4 Flap types and uses.

Flap type	Random pattern flaps (synonym/s)	Uses	Comments
Advancement	Crescentic advancement flap [16]	Cheek/nose, cheek/upper lip closures	In effect side-to-side closure with special attention to cosmetic boundaries. A useful technique
	Single advancement (U-plasty)	Cheek, temple, forehead [6], upper lip [15]	If designed with a broad base can be very effective on the cheek
	Double advancement (H-plasty)	Forehead defects, eyebrow repairs	Little mobility, multiple scars, numb scalp. Conceptually easy but difficult to get right
	Bipedical advancement [17]	Forehead, nasal side wall, chin	In effect side-to-side closure with parallel or V–Y relaxing incisions
	O–T-plasty (A–T-plasty, V–T-plasty, Dieffenbach's winged V-plasty [18])	Lower eyelid, upper lip [15], forehead [6]	A bilateral advancement flap useful around the eye, lip, nose [3] and hair margin
	Midline forehead island flap [19]	Medial canthus	A variety of island pedicle flap with a random pattern blood supply. Flap is tunnelled under the skin into the defect
	Island pedicle flap [20] (kite flap of Dufourmentel)	Upper lip [14], trunk and limb	Two pedicles can be used on the trunk and limb; one is used on repairs of the upper lip. The blood supply comes from the subcutaneous tissue attached to the underside of the skin. A similar design is used in an axial flap employed for defects on the nose tip and ala. The pedicle is based on the branch of the angular artery that supplies the nasalis muscle [21]
	Single advancement (unilateral Burow's wedge flap) [3]	Upper lip, temple, cheek, forehead	A useful flap which is both advanced and rotated into position and the redundant skin removed using a Burow's triangle
Rotation	Single rotation with back-cut (hatchet flap)	Cheek, temple, medial canthus	A useful technique [1] (Fig. 78.13)
	Sliding glabella rotation flap (V–Y advancement)	Medial canthus, dorsal nose [22]	Exploits the redundant skin in the glabella area. Skin movement includes both advancement and rotation as do many rotation or advancement flaps
	Double rotation (O–Z-plasty)	Forehead, scalp, chin [6]	Large area of undermining required. Only works on lax scalp
	Multiple rotation flaps (pinwheel design)	Scalp	Variant of O–Z-plasty
Transposition	Nasolabial flap [23]	Ala rim or side wall of the nose	Good results with careful attention to detail. Pincushioning can be a problem (Fig. 78.14)
	Basic transposition/rhombic flap	Cheek, nose, chin, medial canthus, upper lip	Rarely if ever used as the true geometric rhomboid. Basic transposition flaps are very useful and generally exploit the natural elasticity of the skin so that the flap shape adapts to fit the defect [24]. A Z-plasty adaptation [25] may enhance flap mobility [26]. The glabella transposition flap (banner flap) [27] is a named variant
	Median forehead pedicle flap	Nose tip or lower third of nose	Axial flap. Two-stage procedure; the flap knuckle or pedicle has to be separated later
	30° angle transposition flap [4] (Webster flap)	Dorsum of the nose	Not difficult. Bilateral and single flaps can be used
	Bilobed [28]	Nose side wall	A double transposition flap. Not as difficult to do as might appear (Fig. 78.15)

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Micrographic (Mohs') surgery [1–4]

The concept of controlling the excision margins of infiltrative skin tumours by microscopic examination of horizontal sections cut from the periphery of an excision specimen that had previously been fixed *in vivo* was developed by Mohs in the 1940s [5]. This fixed-tissue technique, which produced excellent cure rates even in some of the most difficult of tumours, has now largely been replaced by the fresh-tissue technique [6]. There are other techniques and adaptations, which aim to achieve 100% histological margin control, that may be more appropriate for tumours with difficult morphology or because of local circumstances [7,8].

The principle of the technique is that the maximum confidence as regards tumour clearance is combined with the minimum loss of surrounding normal tissue. This is particularly important for tumours with an infiltrative growth pattern, especially in critical anatomical sites, and for recurrent lesions. Essentially, the technique involves excision of the lesion and microscopic examination of sections cut from marked, anatomically orientated, segments of tissue, so that the entire periphery of the excision specimen is examined (Fig. 78.17) [9]. Immunofluorescence or immunoperoxidase staining with cytokeratin antibodies may help in the histological interpretation of infiltrative lesions [10].

One of the major disadvantages of Mohs' original technique, other than the prolonged nature of the procedure (possibly continuing over several days) and the pain and discomfort of the *in vivo* fixative, was the presence of a postoperative eschar, which precluded immediate reconstruction and necessitated healing by secondary intention. With the fresh-tissue technique all but the most extensive lesions can be excised in one session, usually under local anaesthesia, and the area can be repaired immediately. If paraffin sections are used, repair is best delayed until the microscopic sections have been examined. This is not to deny the value of secondary-intention healing in appropriate situations [11].

The results of micrographic surgery are impressive, with a 98–99% 5-year cure rate for basal cell carcinomas and a 94.4% 5-year cure rate for squamous cell carcinomas [12]. It should be considered the treatment of choice for the management of certain lesions. Tumours with infiltrative growth patterns or morphoeic histology may extend 7–10 mm beyond the clinically defined margins [13], and if such a tumour overlies a putative anatomical fusion plane (e.g. ala base), the use of horizontal frozen sections may be crucial in ensuring complete resection. Although the main indication is for basal cell carcinoma, the technique has been used for a wide variety of cutaneous malignancies [14].

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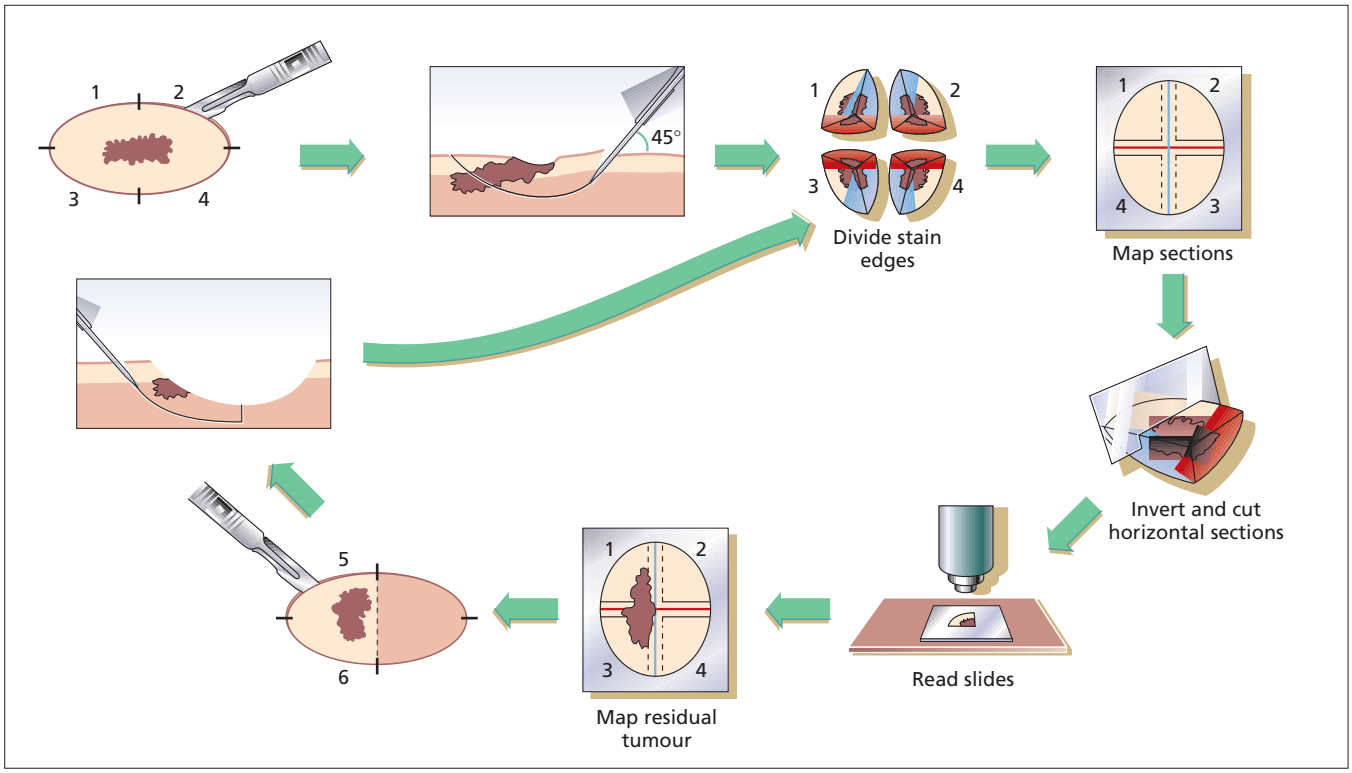

Fig. 78.17 The stages of Mohs' micrographic surgery.

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Hair transplantation [1,2]

The punch autograft, originally described in 1939, was for many years the major procedure in this field. Other surgical techniques were developed, sometimes to be used alone or as adjuncts to punch grafting. These included strip and fusiform grafting, scalp reduction of balding areas with or without tissue expansion, and a variety of scalp flaps. Although these techniques could at times produce acceptable results, often patients were uneasy with the unnatural appearance which was achieved. The development in the 1980s of mini- and micrografts has extended to its logical conclusion with the use of follicular unit transplantation. Now, with repeated sessions of 1000–1500 grafts implanted into small slit or needle tunnel recipient sites, graft counts of 60–100 hairs/cm^2 can be achieved with excellent cosmetic results. The major condition for which these techniques are used remains androgenic alopecia in its various forms. Areas of focal scarring can also be treated.

Careful preoperative assessment of the mental and physical status of the patient is crucial. It is imperative to exclude those subjects with known functional psychoses, those who are dysmorphophobic or cannot comprehend the nature of the treatment and its effects, and those with physical illness that might compromise healing or satisfactory hair regrowth (e.g. bleeding disorders, steroid therapy and previous hypertrophic or keloid scars). Every patient accepted for transplantation or other surgical corrective treatment must have received clear instructions on the details of the operation and its potential side effects, and have a realistic expectation of outcome.

The details of the techniques will not be considered here. In treating androgenic alopecia, the exact techniques used will depend on the pattern of loss. The final outcome will depend as much on the design of the hairline and appropriate patient selection as on technique. Some patients are happy with frontal density correction and less dense grafting on other more posterior vertex areas. Several sessions are usually required to achieve a satisfactory result.

In general, most patients detect early hair growth in the eighth to 12th week after treatment, good growth usually

being established at about the sixth month after graft insertion.

Complications are rare, and include arterial bleeding, arteriovenous and venous aneurysms, foreign body reactions, infection, poor graft survival and hypertrophic scarring.

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Dermabrasion (surgical skin planing) [1–4]

The abrasive (planing) technique for the removal of superficial lesions, rhinophyma, pitted or depressed scars, tattoos and foreign bodies was first clearly described by Kromayer [1]. Its main value lies in treating lesions on the face where regeneration of the epidermis proceeds rapidly, generally without scarring, because of the abundance of pilosebaceous structures from which repair occurs as long as destruction does not extend to the subcutis.

Considerable advances in the technique have taken place in the last 25 years, caused especially by the high-speed rotary drill and the use of more efficient refrigeration [2]. Care must be taken to follow details of the technique rigidly to avoid damage to the patient or operator. Briefly, the technique (allowing for many individual modifications) is as follows [2,4].

1 The patient is sedated, with, for example, 10–20 mg i.v. diazepam.
2 The area is prechilled with cold packs.
3 The skin is cleansed with spirit or some suitable substitute after washing with soap and water.
4 The ears and nostrils are plugged with ointment-impregnated gauze, and the hair and ears are carefully protected by clipped towels.
5 The eyes are carefully protected, for example by ointment and lead shields, by thick gauze held by an assistant, or by the plastic cups used by sunbathers to protect the eyes.
6 The area to be treated is frozen by a continuous stream of Freon (dichlorotetrafluoroethane), and the skin is abraded to the required depth. The degree of freezing and of abrasion necessary must be learnt by experience. The abrading wheels ('brushes') may be of stainless steel wires or diamond fraizes.

Bleeding occurs for 15–30 min after treatment. Paraffin gauze, dry dressings or non-adherent dressings are applied and removed in 1–24 h. The crusts separate in 7–10 days. Healing is usually completed within 3 weeks, particularly if the wound is left open and dry. The pain and crusting can be minimized and the rate of healing improved by the application of a biosynthetic dressing such as Opsite®, Biobrane® or Vigilon®. Preoperative topical retinoic acid may reduce the risk of postoperative milia formation and promote healing.

Infection following dermabrasion is rare, although herpes simplex can be devastating and aciclovir prophylaxis should be given to those at risk. Mild irritation or discomfort from sunlight or cosmetics may occur for a few weeks. Persistent erythema, hyperpigmentation, hypertrophic scars and dermatitis are occasional complications.

Dermabrasion can be considered as a very useful part of cosmetic dermatological practice. Its value in the minimizing of pitted acne scars of the face is undoubted (although the small 'ice-pick' scars respond less satisfactorily than coarse irregular scars). Other conditions for which it has been recommended include traumatic and surgical scars, tattoos, telangiectasia, melasma, epidermal naevi, angiofibromas in epiloia, actinic keratoses, syringomas, wrinkles, cysts and multiple milia [2]. It has been combined with topical steroids in hypertrophic lichen planus, lichen simplex and localized lichenified psoriasis.

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Botulinum toxins [1–3]

These potent neurotoxins have been used since 1979 for the treatment of strabismus and blepharospasm. They have been shown to be useful in the treatment of frown lines, disorders of the muscles of facial expression and hyperhidrosis [4]. The preparation of the toxin and its administration require great care, and although some authors advocate electromyographic guidance, most clinicians rely on clinical experience [5,6]. The effect of a single treatment may last up to 6 months, and with repeated injections the effect may become permanent. Botulinum toxin treatment is often a part of a structured approach to the management of the ageing face, which may include peels and dermal fillers.

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Miscellaneous surgical procedures

Techniques

Hydrodissection

The skin can be lifted away from underlying critical arteries and veins by hydrodissection. Approximately 20 mL of saline is injected into loose tissue below the lesion, thereby lifting the area to be excised off any underlying vital structures. The injection must be given after local anaesthesia, just before excision. The technique works best where there is a boundary that will delay the spread of the saline, for example on the temple and the ear [1].

Snip excision

Small tags can be snipped off with a pair of sharp scissors without the need for local anaesthetic [2]. The tag should be pulled away from the skin and snipped off at its base; bleeding usually stops spontaneously. Haemostasis may be a problem with larger polyps with a well-developed blood supply; hence, an anaesthetic will be required. The wounds can be left to heal by second intention, with excellent cosmetic results [3].

Relaxing incisions

Relaxing incisions are one of several techniques used to increase skin mobility. Multiple, small, full-thickness incisions are made parallel to the skin edge at the site of greatest wound tension [4]. These allow the skin to stretch like a meshed graft, resulting in small elliptical defects, which heal by second intention. The technique is particularly useful for excisions on the lower leg, where it produces surprisingly good cosmetic results with less morbidity than split- or full-thickness grafts. The technique can be used with other ways of improving skin mobility [5]. Other types of relaxing incision include the V–Y-plasty [6], which should not be confused with the V–Y island pedicle advancement flap (Table 78.4).

Wedge excision—lip, lid and ear

On the eyelid, lip and ear, a tumour can be excised and the defect readily closed by removing a full-thickness wedge with an appropriate margin of uninvolved skin. The different layers at the defect edges are then sutured, and thus the technique varies with the site. The inherent tissue elasticity of the eyelid and lip allows considerable defects to be repaired by direct closure without distorting the free margins of these structures. On the lip, defects smaller than one-third of the lip length can be closed directly following a wedge excision [7], if necessary using a W-plasty correction on the lower lip to avoid excessive distortion [8]. On the eyelid, defects of up to 50% can be closed directly, provided the correct technique is used [9]. However, a wedge excision on the ear reduces its size considerably, and buckling of the ear may occur unless the technique is modified to avoid this [10]. In most instances this type of defect is not a problem, as spectacles can still be supported by the ear and differences in ear size are rarely noticed.

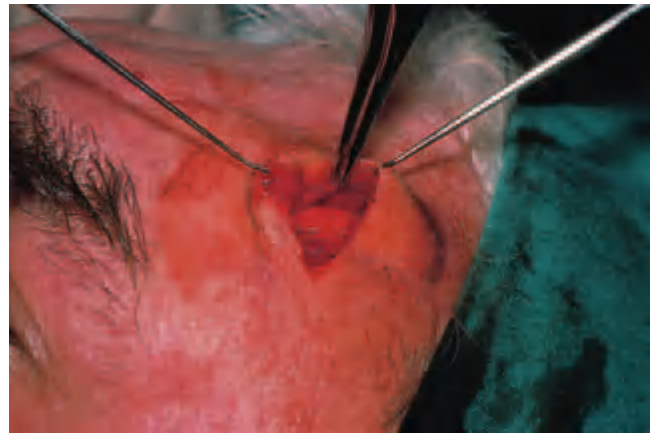

Fig. 78.18 Subfrontalis lipoma. This lipoma lies beneath the frontalis muscle. The muscle has been split vertically and is held back with forceps to reveal the lipoma.

Lipoma removal

Simple skin incision and lipoma excision ensures complete removal but produces a large scar. Scar size can be minimized by breaking up the lipoma into smaller fragments using blunt-ended forceps or a needle-holder inserted via a 4–6-mm punch biopsy wound made over the centre of the lipoma. The fragmented contents can then be squeezed out through the small wound. The fat can also be removed using liposuction [11]. A further development of this technique involves emulsification of the lipoma using an ultrasonic suction scalpel and removal of the fragments under endoscopic control [12]. A subfrontalis lipoma (Fig. 78.18) must be distinguished from a forehead epidermoid cyst. This can be particularly difficult to remove because of its site beneath the frontalis muscle of the forehead [13].

Tissue expansion

Tissue expansion may be helpful if there is insufficient local skin laxity to allow immediate closure and a graft

would produce a relatively poor cosmetic result. The skin needed to fill the defect can be stretched to the required size by steadily expanding saline-filled plastic bags placed under the skin adjacent to the proposed defect. For 8–12 weeks after insertion the bags are filled at intervals to produce a mound that stretches the overlying skin. When the defect is excised, the adjacent distended skin is then available to cover the resulting defect [14]. Because the skin used is almost identical to the piece excised, the cosmetic result is potentially excellent. Expansion does not simply stretch existing skin but actually appears to induce basal layer mitotic activity, an increase in dermal collagen, and development of an enhanced blood supply from the fibrous capsule around the implant. Atrophy of adjacent fat and muscle also occurs. By contrast, immediate tissue expansion or stretching the skin at the time of operation using skin hooks, Foley catheters [15] or sutures [16] increases available skin in the short term but appears to result in greater shrinkage and hence scar stretching.

Circumcision

This simple surgical procedure [17] may be indicated in the management of lichen sclerosus et atrophicus.

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Specific diseases

Epidermoid cysts

Epidermoid cysts (sometimes incorrectly called sebaceous cysts) are lined by a keratinizing epithelium, which produces the cheesy, keratinous contents. Epidermoid cysts require excision if they are disfiguring or repeatedly infected. The inflamed tissue around an infected epidermoid cyst is friable, making it difficult to excise without fragmenting the cyst wall. An infected cyst should therefore be drained, and the patient treated with an appropriate antibiotic. When the inflammation settles the cyst can be excised. Cysts inflamed as a result of a foreign body giant cell reaction to released keratin are best treated by triamcinolone injection followed by subsequent removal. Freely mobile cysts can be easily shelled out through the smooth tissue plane that separates the very thin cyst wall from the surrounding tissue, although at this plane the cyst wall is easily punctured and must be handled gently. In all cases the entire cyst wall and punctum should be removed, the latter at the centre of a small skin ellipse, which can also be used to manipulate the cyst during removal. If the cyst ruptures during extraction, every effort should be made to remove residual wall fragments to prevent recurrence. To avoid long scars, very large cysts can be decompressed via a 4-mm punch biopsy before excision [1]. The wound is either left to heal for 4–6 weeks before definitive removal of the shrunken cyst or an attempt can be made to pull the cyst inside out through the circular wound using artery forceps [2]. Immobile cysts are surrounded by extensive scar tissue and usually have to be excised with the surrounding fibrotic tissue and overlying skin.

Hidradenitis

If medical treatment of hidradenitis suppurativa has failed, involved areas can be excised and the defects covered with skin grafts or flaps. However, cure rates of less than 20% are reported [3] and secondary infection is a frequent problem [4]. Alternatives such as excision followed by healing by second intention are well tolerated by the patient and produce good results [5]. An even simpler procedure involves deroofing the fistula leaving the floor of the track to re-epithelialize the wounded area. Excised tissue or suspect areas should be sent for histology because of the recognized complication of malignant change [6].

Vermilionectomy

This is sometimes called a mucosal advancement [7,8]. The vermilion, usually of the lower lip, is excised, principally because of actinic damage, and replaced by lip

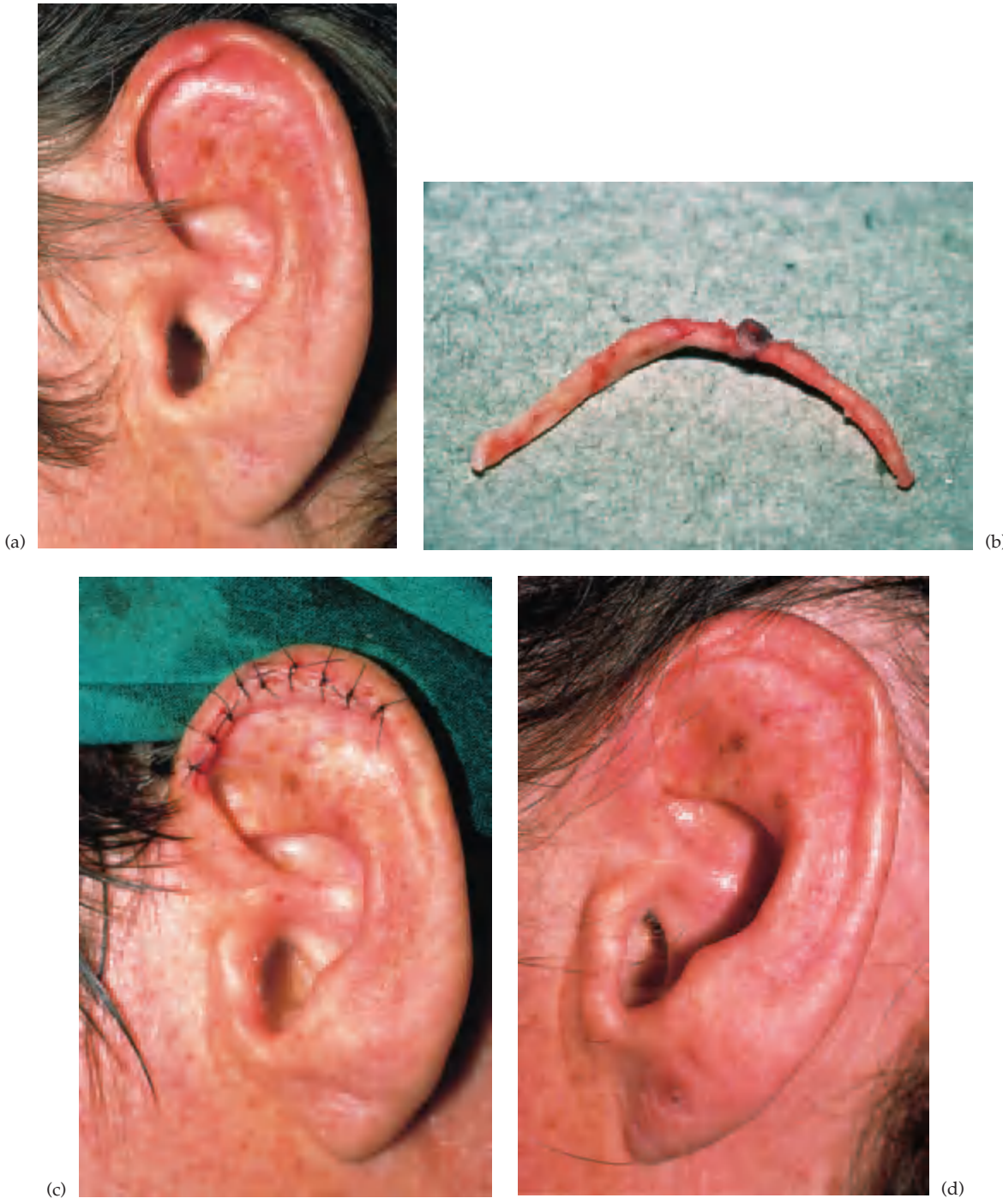

Fig. 78.19 Excision of chondrodermatitis nodularis helicis. (a) This helix nodule was treated by cartilage excision. An incision was made along the helix rim and the skin reflected to expose the cartilage. (b) A sliver of cartilage was taken to include the 3-mm punch biopsy of the skin nodule. Care was taken to ensure that the cartilage edges were smooth and gently shelving up to the uninvolved cartilage. (c) The skin edges were then sutured. (d) The result at 6 months was good.

mucosa pulled forward and sutured at the vermilion/skin border.

Split ear lobe

Split ear lobes may be congenital, or occur as a result of trauma or wearing heavy earrings. Simply de-epithelializing the sides of the cleft and suturing the exposed edges

usually results in a notch appearing at the lobe edge. A full thickness or single-sided Z-plasty correction of the cut edges, depending on lobe thickness [9], is advocated as the best way to ensure good cosmesis, although many other methods are described [10].

Partial or incomplete clefts can be repaired by excising and suturing the enlarged hole. However, if there is only a narrow band of skin separating the hole from the lower pole of the lobe, it is probably best to create a complete defect by cutting the small bridge of skin and closing the defect accordingly. Earrings can be worn again only in patients with thick lobes. Some repairs incorporate reconstruction of a new earring hole at the same time as repair of the defect [11].

Chondrodermatitis nodularis

Intralesional and topical steroids help in approximately 25% of cases. Surgical excision of the affected cartilage without removal of skin (Fig. 78.19) will result in cure in over 90% of helix lesions and 70% of those on the antihelix [12]. Recurrences will occur if rough or protuberant edges of cartilage are left at operation, but can be treated using the same technique [13]. Other methods, including cryotherapy, curettage and laser ablation, have been used, but with mixed and unpredictable results.

Myxoid cysts

Myxoid cysts are ganglia arising as a result of joint fluid leakage from the distal interphalangeal joint into the surrounding tissues. The principle of treatment is that the connection between the cyst and the adjacent joint must be disrupted to prevent the cyst refilling. This is presumably what happens after successful cryotherapy [14], intralesional steroid therapy or curettage, although the cure rate of these procedures is relatively poor. The connection between the joint and the cyst can be identified by injection of dye into the joint [15]. Dye injection, however, is difficult and not essential. The joint fluid leakage site can be assumed to lie between the proximal portion of the cyst and the joint. A proximally based flap can be raised, to include the cyst and skin between the cyst and joint. The cyst is incised and drained. The flap is then resited (Fig. 78.20). The resulting scar presumably seals off the leak from the joint capsule [16].

Axillary vault excision and other remedies for hyperhidrosis

Axilla. If medical treatments fail (see Chapter 45), botulinum toxin (see p. 78.31) can be used, and this blocks sweating for 4–6 months [17]. Axillary hyperhidrosis can also be treated by excision of the sweat-gland bearing axillary skin [18]. The operation is not difficult, but wide excision scars invariably stretch, and infections are common. Shelley described the use of a transverse excision in the centre of the hair-bearing dome of the axilla approximately 4.5×1.5 cm wide [19,20]. The sweat glands can be visualized on the undersurface of the adjacent skin and many of these can be snipped off or destroyed by electrodesiccation when the skin edges are undermined and everted. A light pressure dressing is applied for 24–48 h, and the wound is then left undressed and cleansed daily with a bactericidal antiseptic. Methods that attempt removal of the sweat glands using subcutaneous curettage [21] or liposuction [22], leaving the skin intact, are also described.

Palmar hyperhidrosis is difficult to treat. Endoscopic transthoracic sympathectomy [23] involves division of the sympathetic trunk running over the posterior wall of the chest cavity. However, side effects are significant, and over 80% of individuals develop compensatory sweating [24]. There is also a risk of Horner's syndrome and pneumothorax. In approximately 10% of cases [25], some recurrence of sweating occurs 1–2 years after surgery. The technique can also be useful in Raynaud's disease [26]. A similar approach can be used to reduce axillary sweating, when the second to sixth thoracic ganglia have to be destroyed. Access below the third thoracic ganglion is difficult, and this is believed to account for the poorer cure rate for axillary sweating [27]. Patients can also be successfully managed by repeated botulinum. Injections into the palm. The effects last about 6 months. Injections are painful. Transient weakness of the small hand muscles occurs in 40% [28].

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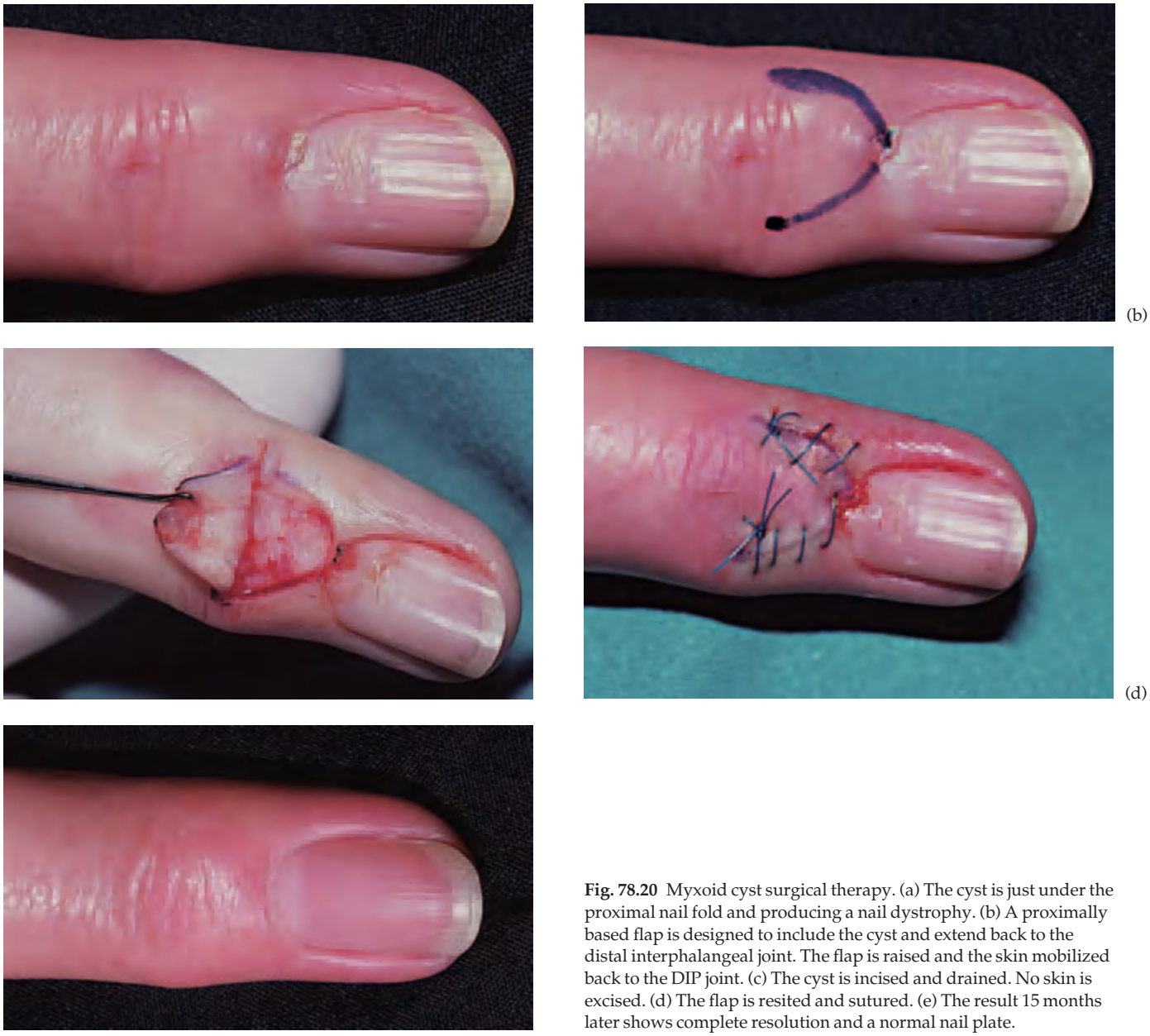

Fig. 78.20 Myxoid cyst surgical therapy. (a) The cyst is just under the proximal nail fold and producing a nail dystrophy. (b) A proximally based flap is designed to include the cyst and extend back to the distal interphalangeal joint. The flap is raised and the skin mobilized back to the DIP joint. (c) The cyst is incised and drained. No skin is excised. (d) The flap is resited and sutured. (e) The result 15 months later shows complete resolution and a normal nail plate.

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Cosmetic procedures

Scar revision including acne scar correction

Pitted or 'ice-pick' acne scars can be treated by dermabrasion [1], very deep pitted scars do well with punch grafting [2] and the wide depressed scars respond to soft-tissue augmentation techniques including collagen [3] and Fibrel injections [4]. The flat purple–pink scars are best left to improve with time. Scar revision after surgery includes dermabrasion, which is best done 6 weeks postoperatively [5], and the treatment of keloids or hypertrophic scars [6].

Liposuction (lipectomy)

This involves selective removal of subcutaneous fat using a small cannula and suction equipment to produce a slimmer body shape [7]. The technique can be used at almost any body site, and can produce impressive results when performed by an experienced physician. Tumescent anaesthesia [8] evolved from the need to do liposuction under local anaesthesia; as a consequence it has become apparent that higher maximal lidocaine doses are possible using dilute anaesthetic solutions [9]. Liposuction has also been used to treat lipomas [10] and insulin-induced fat hypertrophy [11], in flap undermining, lymphoedema [12], breast reduction, lipodystrophy [13] and axillary hyperhidrosis [14], and to remove haematomas or extravasated corrosive drugs [15].

Blepharoplasty

This involves the removal of redundant skin and orbital fat from the upper [16] and lower [17] eyelids in order to correct unsightly bags or skin folds. Selection of the correct procedure to take account of individual variations in eyelid anatomy, identification of pre-existing eye disease, meticulous technique and the ability to adapt or include other procedures depending on the coexisting abnormalities present make this an operation for the expert [18]. Complications include blindness [19], excessive sclera show or ectropion, and failure to correct the original defect.

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